HISTORICAL OVERVIEW, DEVELOPMENT AND NEW APPROACHES IN THE DESIGN OF ANGIOTENSIN CONVERTING ENZYME INHIBITORS AND ANGIOTENSIN RECEPTOR ANTAGONISTS. PART I.

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ABSTRACT

The renin-angiotensin system (RAS) plays an important role in the pathogenesis of hypertension, congestive heart failure, and chronic renal failure. In addition to a discussion of the current understanding of the chemical structures and the modes of action of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor (ATR) antagonists, this review includes their SAR analysis and a chemical modification for improving their activity. Nowadays, different modeling strategies are underway to develop tailor-made molecules with the best of properties among nonpeptide renin inhibitors, dual action receptor antagonists (e.g. angiotensin and endothelin antagonists, ACE/NEP inhibitors, AT1/TxA2 antagonists, balanced AT1/AT2 antagonists), triple inhibitors. In the first part an overview of various ACE inhibitors is given. The second part is devoted to an overview of angiotensin receptor antagonists. The advances that have been made, new opportunities, and future directions of design and development of these classes are discussed.

Keywords: renin-angiotensin system (RAS), ACE inhibitors, renin inhibitors, AT1 antagonists, AT2 antagonists, SAR analysis

Cardiovascular diseases (CVDs) are disorders of the heart and blood vessels, and include coronary heart disease, cerebrovascular disease, rheumatic heart disease and other conditions. Four out of five CVD deaths are due to heart attacks and strokes. Individuals at risk of CVD may demonstrate elevated blood pressure, glucose, and lipids as well as overweight and obesity. Identifying those at the highest risk of CVDs and ensuring they receive appropriate treatment can prevent premature deaths. CVDs are the number 1 cause of death globally: more people die annually from CVDs than from any other cause. An estimated 17.5 million people died from CVDs in 2012, representing 31% of all global deaths. Of these deaths, an estimated 7.4 million were due to coronary heart disease and 6.7 million were due to stroke. For a secondary prevention of cardiovascular disease in those with established disease, including diabetes, treatment with the following medications is necessary: aspirin, beta-blockers, statins and angiotensin-converting enzyme (ACE) inhibitors (1).

The renin-angiotensin-aldosterone system (RAAS or RAS) is one of the most important regu-
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The renin-angiotensin system blockade exerts potent antiatherosclerotic effects, which are mediated by their antihypertensive, anti-inflammatory, anti-proliferative, and oxidative-stress-lowering properties. Inhibitors of the system, ACE inhibitors and angiotensin receptor (ATR) blockers, are now first-line treatments for hypertensive target organ damage and progressive renal disease. Their effects are greater than expected by their ability to lower blood pressure alone. ATR blockers reduce the frequency of atrial fibrillation and stroke. Renin-angiotensin system blockade delays or avoids the onset of type 2 diabetes and prevents cardiovascular and renal events in diabetic patients. Thus, blockade of this system will remain a cornerstone of our strategies to reduce cardiovascular risk (2).

Although significant advances have been made in the therapeutic blockade of the RAAS using ACE inhibitors, ATR blockers and non-selective aldosterone receptor antagonists, there is a clear need for both additional blocking strategies and enhancements of current therapeutic approaches (3).

**Renin-Angiotensin-Aldosterone System**

The RAS is a complex, highly regulated pathway that is integral in the regulation of blood volume, electrolyte balance, and arterial blood pressure. It consists of two main enzymes, renin and ACE, whose primary purpose is to release angiotensin II from its endogenous precursor, angiotensinogen (Fig. 1). Angiotensin II is a potent vasoconstrictor which affects peripheral resistance, renal function and cardiovascular structure (4,5).

The history of the discovery of the renin and the elucidation of the RAS began in 1898 when the existence of a pressor substance present in crude kidney extracts was demonstrated. Later, it was established that this specific substance, which had previously been named renin, was actually an enzyme and that the true pressor substance was a peptide formed by the catalytic action of renin. In the 1950s, it was discovered that angiotensin exists as both an inactive decapeptide, angiotensin I, and an active octapeptide, angiotensin II and that the conversion of angiotensin I to angiotensin II was catalyzed by an enzyme distinct from renin (6,7). Angiotensinogen is an α₂-globulin with a molecular weight of 58,000-61,000 which consist of 452 amino acids, is abundant in the plasma, and is continually synthesized and secreted by the liver. The most important portion of this compound is the N-terminus, specifically the Leu₁₀-Val₁₁ bond. This bond is cleaved by renin and produces the decapeptide angiotensin I. The Phe₈-His₉ peptide bond of angiotensin I is then cleaved by ACE to produce the octapeptide angiotensin II. Aminopeptidase can further convert angiotensin II to the active heptapeptide angiotensin III by removing the N-terminal arginine residue (8).

Renin is a much more specific enzyme than ACE that determines the rate of angiotensin II production. Its primary function is to cleave the leucine-valine bond located at residues 10 and 11 of angiotensinogen. The stimulation of renin release is controlled very closely by hemodynamic, neurogenic and humoral signals (Fig. 2). Active renin secretion is regulated principally by 4 interdependent factors: a renal baroreceptor mechanism in the afferent arteriole that senses changes in renal perfusion pres-
sure; changes in delivery of NaCl (sensed as changes in Cl concentration) to the macula densa cells of the distal tubule; sympathetic nerve stimulation via β1-adrenergic receptors, and negative feedback by a direct action of angiotensin II on the JG cells (9,10).

ACE, also known as kininase II, is a zinc protease which removes the C-terminal dipeptide to form the octapeptide Ang II [Ang-(1-8)], a biologically active, potent vasoconstrictor. It is a relatively nonspecific dipeptidyl carboxypeptidase that requires only a tripeptide sequence as a substrate. The only structural feature required by ACE is that the penultimate amino acid in the peptide substrate cannot be proline. It is for this reason that angiotensin II, which contains a proline in the penultimate position, is not further metabolized by ACE. ACE metabolizes a number of other peptides, including the vasodilator peptides bradykinin and kallidin, to inactive metabolites. The lack of specificity and control exhibited by ACE results in its involvement in the bradykinin pathway (Fig. 3). Thus, functionally, the enzymatic actions of ACE potentially result in increased vasoconstriction and decreased vasodilation (4,11,12).

Angiotensin II is the primary active product of the RAAS, which may have significant biological activity, particularly in tissues. Angiotensins III and IV are formed by the sequential removal of amino acids from the N-terminus of Angiotensin II by the action of aminopeptidases (Fig. 1). They are most likely produced in tissues with high levels of aminopeptidases A and N, such as brain and kidney tissue. Ang

III [Ang-(2-8)], a heptapeptide formed by the removal of the first N-terminal amino acid, is present in the central nervous system, where it is thought to play an important role in tonic blood pressure maintenance and in hypertension. Ang IV [Ang-(3-8)] is a hexapeptide formed by further enzymatic degradation of Ang III. Preclinical studies have suggested a cooperative effect of Ang IV in Ang II signaling. For instance, it appears that in the brain, Ang IV increases blood pressure by cooperating with Ang II on angiotensin II type 1 (AT1)-receptor signaling, because its hemodynamic effects require the presence of both Ang II and functional AT1 receptors (13).

A link between the plasma renin activity (PRA) and the risk of cardiovascular disease has been demonstrated in several epidemiological studies. Due to the fact that the renin-angiotensin pathway is central to the maintenance of blood volume, arterial blood pressure, and electrolyte balance, abnormalities in this pathway can contribute to a variety of cardiovascular disorders, for instance, hypertension or congestive heart failure. Abnormally high levels of angiotensin II can contribute to hypertension through both rapid and slow pressor responses. Additionally, high level of angiotensin II can cause cellular hypertrophy and increase both afterload and wall tension. There are many experimental and clinical studies which provided convincing evidence that the RAS is capable of stimulating atherosclerosis by triggering basic reactions which ultimately lead to growth, instability, and rupture of atherosclerotic plaques (14,15,16,17,18).

The concept of hypertension as primarily a consequence of altered hemodynamics has changed. Many factors are now implicated in the development of hypertensive vascular disease, and the RAAS ap-
Angiotensin II, the principal effector peptide of the RAAS, has far-reaching effects on vascular structure, growth and fibrosis, and is a key regulator of vascular remodeling and inflammation. Treatments that block the pathologic effects of the RAAS at several points have been shown to limit target-organ damage in hypertension and to decrease cardiovascular morbidity and mortality. Understanding the molecular and cellular mechanisms that participate in the early development of hypertensive vascular disease may lead to more targeted treatment and improved outcomes(19).

Overview of Drug Therapy Affecting the Renin-Angiotensin Pathway

Due to the role of angiotensin II in the production of the majority of the effects connected with the renin-angiotensin pathway, compounds which can block either the synthesis of angiotensin II or the binding of angiotensin II to its receptor should affect the actions of this pathway. Indeed, enzyme inhibitors of both renin and ACE, as well as receptor antagonists of angiotensin II have all been shown to produce beneficial effects in decreasing the actions of angiotensin II. Inhibitors of ACE were the first class of compounds to be marketed. This occurred in 1981 with the FDA approval of captopril, then losartan was approved as the first angiotensin II receptor antagonist.

Attempts to develop orally active, bioavailable renin inhibitors actually predate the development of ACE inhibitors. Research in this area continues today; however one of the main attractions of renin inhibitors, specificity, has turned to be a significant hurdle to the clinical development of these agents (21).

Angiotensin-Converting Enzyme Inhibitors

The list of ACE inhibitors drugs according FDA includes: Benazepril (Lotensin), Captopril (Capoten), Enalapril/Enalaprilat (Vasotec), Fosinopril (Monopril), Lisinopril (Zestril and Prinivil), Moexipril (Univasc), Perindopril (Aceon), Quinapril (Accupril), Ramipril (Altace), and Trandolapril (Mavik)(22). These compounds can be divided into three groups based on their chemical structure: sulfhydryl-containing inhibitors exemplified by captopril, dicarboxylate-containing inhibitors exemplified by enalapril and phosphonate-containing inhibitors exemplified by fosinopril. All of these compounds effectively block the conversion of angiotensin I to angiotensin II and have similar therapeutic and physiologic effects. The compounds differ primarily in their potency and pharmacokinetic profile(4). Additionally, the sulfhydryl group in captopril is responsible for certain effects not seen with the other agent.

Development of Orally Active Direct Renin Inhibitors

Renin, a 340-amino acid protease polypeptide, is a member of the aspartyl protease superfamily, which includes pepsin, cathepsin D, and chymosin(23). The octapeptide, His-Pro-Phe-Leu-Leu-Val-Tyr, is the smallest substrate recognized by the enzyme and it is similar to the eight amino acid sequence, His$_6$-Pro$_7$-Phe$_8$-His$_9$-Leu$_{10}$-Val$_{11}$-Ile$_{12}$-His$_{13}$, which is found in angiotensinogen. Using this octapeptide, Boger and coworkers (21) replaced the labile Leu-Leu bond with the stable dipeptide mimic statin-eand replaced the two С-terminal residues (Val-Tyr) with similar hydrophobic aminoacids (Leu-Phe). The resulting compound, N-isovaleryl-His-Pro-Phe-His-Sta-Leu-Phe-NH$_2$ (aka SCRIP), was the first small molecule renin inhibitor that could maintain a lowered blood pressure for an extended period of time. However, susceptibility to proteolytic cleavage limited the therapeutic utility of SCRIP and other analogous peptides.
Structure-activity studies with SCRIP and additional changes resulted in the clinical drug candidate enalkiren, also known as A-64662 (Fig. 4). The histidine residue (His\textsubscript{6}), present in angiotensinogen and all previous inhibitors, was thought to be essential for enzyme recognition and was left unchanged. The acylated tyrosine protects the compounds from aminopeptidase enzymes and also contributes to enzyme active site recognition. The remainder of the molecule is dipeptide isostere. The cyclohexymethylene and i-butyl side chains are lipophilic and approximate the lipophilic side chains present in Leu\textsubscript{10} and Val\textsubscript{11} of angiotensinogen. Additionally, the use of C-terminal alcohol instead of C-terminal carboxylate protects enalkiren from carboxypeptidase enzymes (24,25).

However, enalkiren lacks significant bioavailability due mainly to a lack of lipid solubility. A more lipophilic analog, zankiren (A-72517, Fig. 4), demonstrated increased oral bioavailability and efficacy, but also has since been withdrawn from clinical trials for undisclosed reasons (26).

![Chemical structures of enalkiren, zankiren, and aliskiren](image)

Fig. 4. Chemical structures of enalkiren, zankiren, and aliskiren

Early attempts to develop direct renin inhibitors for the treatment of hypertension and associated CVDs were hampered by poor oral bioavailability, lack of clinical efficacy, short plasma half-lives and high cost of synthesis. However, a combination of molecular modelling techniques and crystal structure elucidation led to the development of aliskiren (Fig. 4), which will be the first orally effective direct renin inhibitor for the treatment of hypertension. Aliskiren is a highly specific inhibitor of human renin in vitro (27). Aliskiren, the direct renin inhibitor which was recently approved for treatment of hypertension, represents the most recent class of agents that block the RAAS. This compound differs from the ACE inhibitors and ATR blockers in that, by blocking the catalytic activity of renin at the point of activation of the RAAS, it blocks the synthesis of all angiotensin peptides and prevents the compensatory increase in renin activity (28).

There were some attempts to develop a potent, selective and orally active renin inhibitors based on iminopyrimidinones (29), iminotetrahydropyrimidinones (30), 3,4-diarylpiperidines (31).

Chymase, a chymotrypsin-like serine protease that is abundant in secretory granules from mast cells, has been identified to be a key enzyme in the local RAS that generates angiotensin II (Ang II) independent of ACE. The pathophysiological significance of alternative Ang II-forming pathways in human CVDs remains controversial. Although chymase inhibitors, unlike ACE inhibitors and Ang II type 1 receptor blockers, may only play a small role in the reg-
ulation of the systemic RAS, the possible applications of chymase inhibitors as new drugs that inhibit the local RAS to prevent CVDs are described in animal models. In this review, we discuss the possible application of chymase inhibitors as new drugs to inhibit the RAS mainly in cardiovascular diseases (32).

Chymase inhibitors could have the advantage of being effective even if used after injury. Several orally active inhibitors, including SUN-C8257, BCEAB, NK3201 and TEI-E548 (Fig. 5), are under development. Orally active inhibitors of chymase may have a place in the treatment of vascular diseases where injury-induced mast cell degranulation contributes to the pathology (33).

Sulfhydryl-Containing Inhibitors

The discovery of specific factors in 1965 (bradykinin potentiating factors (BPFs)) which potentiated the action of bradykinin, was a trigger of the new pattern in development ACE inhibitors. The action of these factors was subsequently linked to their ability to the enzymatic degradation of bradykinin. Later, the BPF was tested on ACE and found to be a potent inhibitor thereof. This led to Vane’s strong interest in ACE and its inhibition as a means of treating hypertension (34).

A nonapeptide, SQ 20881 (Fig. 6), isolated from the original BPFs had the greatest *in vivo* potency in inhibiting ACE and was shown to consistently lower blood pressure in patients with essential hypertension. It also exerted beneficial effects in patients with heart failure; however, due to its peptide nature and lack of oral activity, teprotide had limited activity in the therapeutic treatment of these diseases (35,36).

In further research, SQ 20881 and other peptide analogs, were used to provide an enhanced understanding of the enzymatic properties of ACE and developed a hypothetical model of the enzyme active site (37,38,39). Using the structure of carboxypeptidase A (Fig. 7) - a zinc-containing exopeptidase - were elucidated the binding of a substrate to carboxypeptidase A (Fig. 7, part A), and the binding of
substrates to ACE, which involves three major interactions (Fig. 7, part B) (40).

The role of D-2-benzylsuccinic acid as an extremely potent inhibitor of carboxypeptidase A was later found (37,38,39). Binding to carboxypeptidase A (Fig. 8, part A) it is very similar to that seen for substrates with the exception that the zinc ion binds to a carboxylate group instead of the labile peptide bond. This hypothetical model of ACE resulted in the synthesis and evaluation of a series of succinic acid derivatives (Fig. 8, part B) (41).

Later it discovered that proline was the C-terminal amino acid in SQ 20881 as well as in other potent, inhibitory snake venom peptides. Thus, this scaffold was included in the structure of the newly designed inhibitor. Using these tools the first ‘designed’ inhibitor, succinyl-L-proline was synthesized (Fig. 9). It seemed to be a specific inhibitor of ACE although of very low potency. Subsequent structural modifications of this convinced the researchers that it was the right track (42).

Therefore, further structural modifications of succinyl-proline, which included the replacement of the carboxyl group of the succinyl moiety with other atoms or group of atoms that could also function as zinc ligands. Among those tested early on were the hydroxamic acid group and the sulfhydryl group, which eventually led to captopril. All the structural modifications that were studied with captopril has been shown to be correct by studying the three-dimensional structure of a specially designed thiol-containing inhibitor with the metalloprotease thermolysin using X-ray crystallography (42).

Of course, all this potency and specificity would have been of little value without good oral absorption. Fortunately, captopril has one-fifth of the molecular size of teprotide and, strictly speaking, has no

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*Fig. 8. Molecular modeling of inhibitor binding D-2-benzylsuccinic acid to carboxypeptidase (A) and succinic acid derivatives (B) to ACE*

*Fig. 9. Chemical structures of compounds designed in the development of captopril.*
peptide bonds. It was therefore no surprise that its antihypertensive activity was equal or better by the oral route than by the parenteral route (42).

Since the advent of captopril, several other ACE inhibitors have been developed and introduced into clinical practice; each of these compounds has its own distinct chemical and pharmacological properties. Zofenopril (Fig. 10) is an ACE inhibitor with unique pharmacodynamic and pharmacokinetic properties (43).

Dicarboxylate-Containing Inhibitors

The most common adverse effects of captopril, skin rash and taste disturbance, are the same as those caused by mercapto-containing penicillamine. Therefore a group of researchers aimed at finding potent, selective ACE inhibitors that wouldn’t contain a mercapto (SH) function and would have a weaker chelating function. Compounds having the general structure shown below were designed to meet this objective (Fig. 11). All these compounds have the C-terminal (A) and penultimate (B) amino acids are retained but the third amino acid is isosterically replaced by a substituted N-carboxymethyl group (C) (44).

Enalapril is an ACE inhibitor, known as the dicarboxylate-containing ACE inhibitor, normally used in the treatment of hypertension and chronic heart failure, was developed and patented by Merck & Co., Inc (Whitehouse Station, NJ, USA) under the trade names Renitec and Vasotec (45). In comparing the activity of captopril and enalaprilat, it was found that enalaprilat was approximately 10-fold more potent than captopril.

As shown in Figure 12, enalaprilat possesses a tetrahedral carbon in place of the labile peptide bond. The secondary amine, the carboxylic acid and phenylethyl groups all contribute to the overall binding of the compound to ACE. The secondary amine is located at the same position as the labile amide nitrogen, the ionized carboxylic acid can form an ionic bond with the zinc atom, and the phenylethyl group mimics the hydrophobic side chain of the Phe amino acid which is present in angiotensin I.

Enalapril is a prodrug that is converted by deesterification to converting enzyme inhibitor, enalaprilat, with effects similar to those of captopril (Fig. 13). Enalapril itself is available only for intravenous use, primarily for hypertensive emergencies (46,47).

Lisinopril (lye-SIN-o-pril) is simply the lysine analog of enalapril. Unlike enalapril, lisinopril itself is active with a long duration of action. Historically, lisinopril was the third ACE inhibitor, after captopril and enalapril, and was introduced into therapy in the early 1990s. Lisinopril has a number of properties that distinguish it from other ACE inhibitors: it is hydrophilic, has long half-life and tissue penetration and is not metabolized by the liver. Lisinopril is the only ACE inhibitor that exhibits a linear dose-response curve. Lisinopril, along with captopril, are currently the only two ACE inhibitors which are not prodrugs (48).

Other dicarboxylate inhibitors which have been approved for various therapeutic indications are presented in Table 1; however, spirapril has never been marketed.

Studies of indoline analogs of captopril indicated that a hydrophobic pocket similar to that seen in carboxypeptidase A was also present in ACE. This led to a modification (Fig. 14) of Ondetti and Cushman’s original model and the development of inhibitors which contained larger hydrophobic ring systems (49). Even though this modified model was proposed for captopril analogs, it is readily adaptable to include enalaprilat analogs. In general, the varied ring systems seen in benazepril, moexipril, per-
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indopril, quinapril, ramipril, spirapril, and trandolapril provide enhanced binding and potency. They also lead to differences in absorption, plasma protein binding, elimination, onset of action, duration of action and dosing among the drugs.

A series of novel diethyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate embedded triazole and Mannich bases were synthesized, and evaluated for their ACE inhibitory activity (50).

**Phosphonate-Containing Inhibitors**

The quest for ACE inhibitors devoid of the sulfhydryl group also led to the evaluation of phosphorous containing compounds, on the basis of the notion that phosphinic acid is bioisosterically equivalent to sulfhydryl and carboxylate groups in terms of Zn$^{2+}$ chelation (Fig. 15) (51). Additionally, this com-

**Table 1. The dicarboxylate-containing ACE inhibitors**

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Ring</th>
<th>$R_1$</th>
<th>$R_2$</th>
<th>$R_3$</th>
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<tbody>
<tr>
<td>Lisinopril</td>
<td>(CH$_2$)$_4$NH$_2$</td>
<td>H</td>
<td></td>
<td></td>
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<tr>
<td>Moexipril</td>
<td></td>
<td>CH$_3$</td>
<td>CH$_2$CH$_3$</td>
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<table>
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<th>Inhibitor</th>
<th>Structure</th>
<th>CH&lt;sub&gt;3&lt;/sub&gt;</th>
<th>CH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;3&lt;/sub&gt;</th>
<th>CH&lt;sub&gt;3&lt;/sub&gt;</th>
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<tr>
<td>Perindopril</td>
<td><img src="image" alt="Perindopril Structure" /></td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;</td>
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<tr>
<td>Quinapril</td>
<td><img src="image" alt="Quinapril Structure" /></td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td></td>
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<tr>
<td>Ramipril</td>
<td><img src="image" alt="Ramipril Structure" /></td>
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<td>CH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;3&lt;/sub&gt;</td>
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<tr>
<td>Spirapril</td>
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<tr>
<td>Trandolapril</td>
<td><img src="image" alt="Trandolapril Structure" /></td>
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<td>CH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;3&lt;/sub&gt;</td>
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<tr>
<td>Benazepril</td>
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<tr>
<td>Cilazapril</td>
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pound is capable of forming the ionic, hydrogen, and hydrophobic bonds similar to those seen with enalapril and other dicarboxylate analogs.

This led to the development of fosinopril as a prodrug that is hydrolyzed by liver enzymes to the bioactive fosinoprilat (Fig. 16). This compound was more potent than captopril but less potent than enalaprilat. The above-mentioned differences in the spacing of the phosphinic acid and phenyl groups may be responsible for this latter difference in potency.

Similar to the dicarboxylates, fosinoprilat was too hydrophilic and exhibited poor oral activity. The prodrug fosinopril contains an (acyloxy)alkyl group which allows for better lipid solubility and improved liability (52).

A series of phosphonate analogues related to perindopril and ramipril were prepared and tested to estimate their ability to inhibit ACE. These new synthesized compounds were active ACE inhibitors with a promising activity (53).

The structural characteristics for ACE inhibitory activity are given in Table 2. ACE is a stereoselective drug target. Since currently approved ACE inhibitors act as either di- or tripeptide substrate analogs, they must contain a stereochemistry that is consistent with the L-amino acids present in the natural substrates. This was established very early in the de-
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Development of ACE inhibitors when compounds with carboxyl-terminal D-amino acids were discovered to be very poor inhibitors (6). Later work by Patchett et al. (44) reinforced this idea. They reported a 100- to 1000-fold loss in inhibitor activity whenever the configuration of either the carboxylate or the R₁ substituent (Table 1) was altered. The S,S,S configuration seen in enalapril and other dicarboxylate inhibitors meets the above stated criteria and provides for optimum enzyme inhibition (44).

To correlate the molecular properties of the most of ACE inhibitors (captopril, enalapril, perindopril, lisinopril, ramipril, trandolapril, quinapril, fosinopril, benazepril, and cilazapril) and some of their active metabolites (enalaprilat, perindoprilat, ramiprilat, trandolaprilat, quinaprilat, fosinoprilat, benazeprilat, and cilazaprilat) computational chemical methods have been used. The computed pKₐ values correlate well with the available experimental values. In the dicarboxylic ACE inhibitors, the carboxyalkyl carboxylate group of the ACE inhibitors studied is more acidic than the C-terminal carboxylate. However, at physiological pH=7.4 both carboxyl groups of ACE inhibitors are completely ionized and the dicarboxyl-containing ACE inhibitors behave as strong acids. The available experimental partition coefficients of these ACE inhibitors investigated are well reproduced by the neural network-based ALOGPs and the fragment-based KoWWiN methods.

All parent drugs (and prodrugs), with the exception of fosinopril, are compounds with low lipophilicity. Calculated pKₐ, lipophilicity, solubility, absorption, and polar surface area of the most effective ACE inhibitors for the prevention of myocardial infarction, perindopril and ramipril, were found similar. Therefore, it is probable that the experimentally observed differences in the survival benefits in the first year after acute myocardial infarction in patients 65 years of age or older correlate closely to the physicochemical and pharmacokinetic characteristics of the specific ACE inhibitor that is used (54).

Thus, a chemical overview of the compounds that influence the RAS and show cardiovascular effects, in particular ACE inhibitors, has been done in this article. Different approaches to the rational design of the new modern antihypertensive drugs have been discussed and the essential structural features of ACE inhibitors have been shown based upon the SAR analysis data. Other classes of medicines that act on RAS, namely angiotensin II receptor antagonists, will be reviewed in our future publication.

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Table 2. Structure-activity relationship of ACE inhibitors

<table>
<thead>
<tr>
<th>Zn²⁺ binding groups</th>
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a. The N-ring must contain a carboxylic acid to mimic the C-terminal of ACE substrates.
b. Large hydrophobic heterocyclic rings in the N-ring increase potency and alter pharmacokinetic parameters.
c. Groups A, B or C can serve as zinc binding groups.
d. The sulphydryl group shows superior binding to zinc (Phe in carboxylate and phosphinic acid side chain compensates for sulphydryl group).
e. Sulphydryl-containing compounds produce high, incidence of skin rash and taste disturbances.
f. Sulphydryl-containing compounds can form disulfides which may shorten duration of action.
g. Binding to zinc through either a carboxylate or phosphinate mimics the peptide hydrolysis transition state.
h. Esterification of the carboxylate or phosphinate produces an orally bioavailable prodrug.
i. X is usually methyl to mimic the side chain of alanine. Within the dicarboxylic series, when X equals n-butylamine (lysine side chain), this produces a compound which is orally active without being a prodrug.
j. Optimum activity occurs when stereochemistry of inhibitor is consistent with L-amino acid stereochemistry.
REFERENCES


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