Modern Development in ACE inhibitors

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Abstract

Ace inhibitors are one of the most active classes of molecules that lower blood pressure. This review outlines the design, discovery of some new compounds. Structure activity relations with respect to binding characteristic and pharmacodynamic properties have been described for new compound.

Keywords: Angiotensin-converting enzyme inhibitors, Captopril, Antihypertension activity, Prodrug

INTRODUCTION

Renin-angiotensin system-
The renin-angiotensin system plays an important role in an interrelated set of mechanism for the control of the volume, pressure, and electrolyte composition of blood salt homeostasis and may play a role in the pathogenesis of aspects of the metabolic syndrome [1-4].
In 1898 saline extracts of kidney were shown to contain a pressor substance (i.e. a material that increases blood pressure), which was named renin. Renin, in turn, is a proteolytic enzyme that is produced by the kidneys, and it controls the physiological functions of other organs. The secretion of renin itself is controlled by the nervous system and possibly by a recently discovered cardiac peptide hormone. Renal RAS is salt sensitive. Renal renin secretion is directly proportional to sodium excretion through kidneys. [5]

Many years later (1940) renin was shown to be an enzyme that acts on a plasma protein to catalyse the formation of the actual pressor substance. The pressor substance is called angiotensin and the plasma protein, angiotensinogen. Several forms of angiotensin have been found, the most important being angiotensin I (a decapeptide) and angiotensin II (an octapeptide). The latter, that is the more active as a pressor agent, is produced from the former by an enzyme called angiotensin-converting enzyme (ACE). [2]

Membrane receptors of smooth muscle cells of the arterioles and adrenal cortex (aldosterone secretion) are specifically stimulated by angiotensin II. As a result, peripheral resistance of vessels increases as heart rate increases, cardiac output increases, and water and sodium ion retention takes place. In turn, induced elevation of pressure by reverse binding causes a decrease in renin secretion. [2, 6] Angiotensin III was produced by action aminopeptidase enzyme from angiotensin II. Angiotensin III also has pressor activity (25-50% of that of angiotensin II). Most of the activity of angiotensin II resides in the C-terminal octapeptide. [2]

**Angiotensin converting enzyme**-
Angiotensin converting enzyme (ACE, kininase II [7], EC 3.4.15.1 or dipeptidyl carboxypeptidase) is a zinc-containing enzyme that cleaves dipeptide units from peptide substrates. It is the enzyme that converts angiotensin I to angiotensin II. [2]
responsible for conversion of the decapeptide prohormone angiotensin I into the pressor agent, angiotensin II. [8] It is known that proline must not be the penultimate amino acid and this restriction ensures that the enzyme does not degrade angiotensin II. [9]

The Angiotensin I converting enzyme, belongs to the class of zinc proteases that need zinc and chloride for its activation and increases blood pressure by converting angiotensin-I to angiotensin-II, a potent vasoconstrictor and by degrading bradykinin, a vasodilatory peptide. [10, 11]

\[
\begin{align*}
\text{Angiotensinogen} & \quad \xrightarrow{\text{Renin}} \quad \text{Angiotensin I} \\
\text{Angiotensin I} & \quad \xrightarrow{\text{Aminopeptidase}} \quad \text{Angiotensin II} \\
\text{Angiotensin II} & \quad \xrightarrow{} \quad \text{Angiotensin III}
\end{align*}
\]

**Sites of stepwise enzymatic cleavage of human angiotensionogen**

**Inhibitors of angiotensin converting enzyme**-

In the 1970s, following the brilliant work performed by Ferreira and colleagues, Ferreira in collaboration with Greene and, finally by Erdos and others investigators, two classes of inhibitors of the renin-angiotensin system were identified:

**A-** Angiotensin II antagonists, which block receptors for the natural peptide (without leading to the natural response), and

**B-** Converting enzyme inhibitors, which slow the rate of formation of angiotensin II from its inactive precursor.

Examples of the former (angiotensin II antagonists) are either modified peptides in which some of the amino acids of the natural material have been changed as saralasin or, non-peptide antagonists as DUP 753. [9] An important competitive inhibitor of ACE is captopril, which inhibits conversion of the relatively inactive angiotensin I to the angiotensin II. [2]
Classification of ACE inhibitors-
ACE inhibitors can be divided into three groups based on their molecular structure [12, 13]

1) Sulfhydryl-containing agents: Captopril (Active drug), the first ACE inhibitor, Zofenopril, Alacepril and Moveltipril

2) Dicarboxylate-containing agents: This is the largest group, including: Enalapril, Ramipril, Quinapril, Perindopril, Lisinopril (Active drug), Benazepril, Cilazapril, Delapril and Spirapril

3) Phosphonate-containing agents: Fosinopril and SQ 29852

All five newer ACE inhibitors (trandolapril, moexipril, spirapril, temocapril and imidapril) are characterised by having a carboxyl functional groups and requiring hepatic activation to form pharmacologically active metabolites. [14]

Structure activity relationship of ACE inhibitors:

1) The N-ring must contain a carboxylic acid to mimic the C-terminal carboxylate of ACE substrates.

2) Large hydrophobic heterocyclic rings (i.e., the N-ring) increase potency and alter pharmacokinetic parameters.

3) The zinc binding groups can be either sulphydryl (A), a carboxylic acid (B), or a phosphinic acid (C).

4) The sulfhydryl group shows superior binding to zinc (the side chain mimicking Phe in carboxylate and phosphinic acid compounds compensates for the lack of a sulfhydryl group).

5) Sulfhydryl-containing compounds produce high incidence of skin rash and taste disturbances.

6) Sulfhydryl-containing compounds can form dimmers and disulfides which may shorten duration of action.

7) Compounds which bind to zinc through either a carboxylate or phosphinate mimic the peptide hydrolysis transition state.

8) Esterification of the carboxylate or phosphinate produces an orally bioavailable prodrug.

9) X is usually methyl to mimic the side chain of alanine. Within the dicarboxylate series, when X equals n-butylamine (lysine side chain) this produces a compound which does not require prodrug for oral activity.

10) Optimum activity occurs when stereochemistry of inhibitor is consistent with L-amino acid stereochemistry present in normal substrates. [13]
Uses for ACE inhibitors
ACE inhibitors are widely used to prevent, treat or improve the symptoms in conditions such as high blood pressure, coronary artery disease, heart failure, diabetes, certain chronic kidney diseases, heart attacks, scleroderma and migraines. Other medications in addition to an ACE inhibitor, such as a diuretic, as part of your high blood pressure treatment. ACE inhibitors are usually taken once daily, and many people take them in the morning. [3, 6, 14, 15, 16, 58]

Side effects and cautions [17, 18]
Commonly prescribe ACE inhibitors because they don't often cause side effects. The most common side effect is a dry cough. Possible, although rare, side effects include increased blood-potassium level (hyperkalemia), rash, dizziness, lightheadedness, changes in taste and reduced appetite over long intervals. In rare cases but more commonly in blacks and in smokers ACE inhibitors can cause some areas of your tissues to swell (angioedema). If it occurs in the throat, that swelling can be life-threatening.

<table>
<thead>
<tr>
<th>Drug</th>
<th>ACE inhibitors</th>
<th>Probable mechanism</th>
<th>Result of interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allopurinol</td>
<td>Captopril</td>
<td>Unknown</td>
<td>Increased risk of hypertension</td>
</tr>
<tr>
<td>Antacids</td>
<td>All</td>
<td>-</td>
<td>Decreased bioavailability of ace inhibitors (more likely with captopril &amp; fosinopril)</td>
</tr>
<tr>
<td>Amiloride</td>
<td>-</td>
<td>Increased potassium retention secondary to lowered aldosterone levels</td>
<td>Enhanced antihypertensive effect/hyperkalemia</td>
</tr>
<tr>
<td>Capsaicin</td>
<td>All</td>
<td>-</td>
<td>Exacerbation of cough</td>
</tr>
<tr>
<td>COX 2 selective inhibitors</td>
<td>-</td>
<td>Interference with production of vasodilator and natriuretic prostaglandins</td>
<td>Decreased antihypertensive and natriuretic effects.</td>
</tr>
<tr>
<td>Digoxin</td>
<td>All</td>
<td>Deterioration of renal function</td>
<td>Either increased or decreased plasm digoxin levels</td>
</tr>
<tr>
<td>General anaesthetics</td>
<td>-</td>
<td>-</td>
<td>Marked hypotension may occur during general anaesthesia in patients receiving ACE inhibitors.</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>All</td>
<td>Vasodilation and relative intravascular volume depletion</td>
<td>Potential excessive reduction in B.P.; the effects of loop diuretics may be reduced</td>
</tr>
<tr>
<td>Iron salts</td>
<td>Captopril</td>
<td>-</td>
<td>Reduction of captopril levels unless administration is separated by at least 2 hours</td>
</tr>
<tr>
<td>Potassium preparation or Potassium-sparing diuretics</td>
<td>All</td>
<td>Lowered aldosterone levels</td>
<td>Elevated serum potassium levels</td>
</tr>
<tr>
<td>Drug</td>
<td>Interaction</td>
<td>Effect</td>
<td></td>
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<td>------------</td>
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<td>------------------------------------------------------------------------</td>
<td></td>
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<tr>
<td>Lithium</td>
<td>All</td>
<td>Increased serum lithium levels</td>
<td></td>
</tr>
<tr>
<td>NSAIDs</td>
<td>All</td>
<td>Inhibition of prostaglandin synthesis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Decreased hypotensive effects</td>
<td></td>
</tr>
<tr>
<td>Phenotheiazides</td>
<td>All</td>
<td>Diminished response to pressor amines</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Increased pharmacological effects ace inhibitors</td>
<td></td>
</tr>
<tr>
<td>Probenecid</td>
<td>Captopril</td>
<td>Decreased clearance &amp; increased blood levels of captopril</td>
<td></td>
</tr>
<tr>
<td>Rifampin</td>
<td>Enalapril</td>
<td>Decreased pharmacological effects of enalapril</td>
<td></td>
</tr>
<tr>
<td>Tetracycline</td>
<td>Quinapril</td>
<td>Decreased absorption of tetracycline(may result from high magnesium content of quinapril tablets)</td>
<td></td>
</tr>
</tbody>
</table>

Detailed accounts of various synthetic ACE Inhibitors are study below.

**Captopril**
Captopril was the first inhibitor for clinical trial. According to the mechanism proposed by Ondetti and colleagues, captopril interacts with the enzyme through several bonds, i.e. electrostatic, hydrogenic and lipophilic connections (Fig 1). Among these, a co ordinance bond formed between the free thiol group of captopril and zinc ion in the active site of ACE.

![Binding Interactions of captopril with the active side of ACE](image)

**Synthesis of Captopril**

1. HCl anhydrous
2. Cl\(_2\)CH\(_2\)COOH
3. SOCl\(_2\)
4. (L)-Proline
5. NH\(_4\)SH
6. CH\(_3\)OH

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Captopril, although is an important orally active ACE inhibitor, produces some side effects. The two most common side effects, skin rashes and taste disturbances are attributed to the presence of the sulfhydryl group. Captopril has been gained the FDA approval in June 1981. The drug went generic in the U.S. in February 1996 as a result of the end of market exclusivity for Bristol-Myers Squibb. [8, 12,13]

Enalapril
Enalaprilat, the first dicarboxylate-containing ACE inhibitor, Enalaprilic acid itself is poorly absorbed orally; it is administered orally as the monoethyl enalaprilat, which serves as a prodrug. It resembles captopril in containing a “proline surrogate,” but it differs in that it is an analogue of tripeptide rather than a dipeptide. Enalaprilat was developed partly to overcome these limitations of captopril. The sulfhydryl-moiety was replaced by a carboxylate-moiety, but additional modifications were required in its structure-based design to achieve a similar potency to captopril. Enalaprilat itself, however, was not without its problems. The consequence of the structural modifications was that it proved to have unfavourable ionisation characteristics to allow sufficient potency for oral administration (in tablets). Thus enalaprilat was only suitable for intravenous administration. This was overcome by the researchers at Merck by the esterification of enalaprilat with ethanol to produce enalapril. As a prodrug, enalapril is metabolised in vivo to the active form enalaprilat by various esterases. Enalapril plus hydrochlorothiazide and captopril tablets are indicated for the treatment of hypertension. Enalapril tablets are indicated for the treatment of hypertension and symptomatic heart failure. [3, 19, 20, 62] Angiotensin-converting enzyme (ACE) inhibitors enalapril, is prodrugs that is converted to the active metabolites, enalaprilat. Enalaprilat is mainly excreted in urine. 13-fold increase in plasma enalaprilat in patients with renal insufficiency. [21, 62]

Synthesis of Enalapril

\[
\begin{align*}
2\text{-oxo-4-phenylbutyrate} + \text{L-alanyl-L-proline} \xrightarrow{\text{Sod. cyanoborohydrate}} \text{Enalapril}
\end{align*}
\]

Lisinopril
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. [12, 13, 14, 63, 64]
Synthesis of Lisinopril

Perindopril
Another long acting ACE inhibitor with a slow onset of action: less chance of first dose hypotension. Through 66-95% of orally administered perindopril is absorbed, only about 20% is converted to the active metabolite perindoprilat. Extensive metabolism to other inactive products occurs. Studies have shown that perindopril tends to restore the reduced elastic properties of arteries & heart in hypertension. Perindopril significantly inhibits tumor growth and angiogenesis along with suppression of the VEGF level. Because perindopril is widely used in clinical practice, it may represent an effective new strategy for anticancer. [15]
Synthesis of Perindopril

\[
\text{L-norvaline} + \text{H}_2\text{COOH} + \text{H}_3\text{C-OH} \xrightarrow{\text{SOCl}_2} \text{H}_2\text{N} + \text{H}_3\text{C-OH} + \text{HCl} \quad \text{H}_2\text{N} \xrightarrow{\text{Pd-C, 30 bar}} \text{H}_2\text{N} \xrightarrow{\text{NaOH, CH}_3\text{COOH}} \text{HOOC} \xrightarrow{\text{H}_2, \text{Rh-C, 30 bar}} \text{HOOC} \xrightarrow{\text{HCl / C}_2\text{H}_2\text{OH, Sn}} \text{HOOC} \xrightarrow{\text{HCl}} \text{HOOC} \xrightarrow{\text{HO,C}_2\text{H}_5\text{OH}} \text{HOOC} \xrightarrow{\text{toluene, benzyl alcohol}} \text{HOOC} \xrightarrow{\text{1-hydroxy-benzotriazole}} \text{HOOC} \xrightarrow{\text{DCC}} \text{HOOC} \xrightarrow{\text{N(C}_2\text{H}_5)_3 \cdot \text{CH}_3\text{COOC}_2\text{H}_5} \text{HOOC} \xrightarrow{\text{1-hydroxy-benzotriazole}} \text{HOOC} \xrightarrow{\text{N(C}_2\text{H}_5)_3 \cdot \text{CH}_3\text{COOC}_2\text{H}_5} \text{HOOC} \xrightarrow{\text{DCC}} \text{HOOC} \xrightarrow{\text{N(C}_2\text{H}_5)_3 \cdot \text{CH}_3\text{COOC}_2\text{H}_5} \text{HOOC} \xrightarrow{\text{1-hydroxy-benzotriazole}} \text{HOOC} \xrightarrow{\text{N(C}_2\text{H}_5)_3 \cdot \text{CH}_3\text{COOC}_2\text{H}_5} \text{HOOC} \xrightarrow{\text{DCC}}
\]
Ramipril
Ramipril is a prodrug and is converted to the active metabolite ramiprilat by liver esterase enzymes. Ramipril, unlike enalapril, possesses high lipophilic property. This property promotes penetration of ramipril in various tissues, thereby affecting a higher degree of tissue ACE inhibitor (long acting). It shows some anti-inflammatory activity due to inhibition of PGI2 biosynthesis in vascular tissue inhibits adrenergic action in CNS & heart & inhibits enkephalinase. ACE inhibitor ramipril reduces the rates of death, myocardial infarction, stroke, revascularization, cardiac arrest, heart failure, complications related to diabetes and new cases of diabetes in a broad spectrum of high-risk patients. [5, 22]

Synthesis of Ramipril

\[
\text{Conjugation} \rightarrow \begin{array}{c}
\text{Addition} \\
\text{Diastereoisomer separation by fractional crystallisation}
\end{array}
\]

\[
H_2 \rightarrow \begin{array}{c}
\text{(A)}
\end{array}
\]
Trandolapril
Trandolapril is a prodrug that is deesterified to trandolaprilat. It is believed to exert its antihypertensive effect through the renin-angiotensin-aldosterone system. Trandolapril has a half life of about 6 hours, and trandolaprilat has a half life of about 10. Trandolaprilat has about 8 times the activity of its parent drug. Approximately 1/3 of Trandolapril and its metabolites are excreted in the urine, and about 2/3 of Trandolapril and its metabolites are excreted in the feces. Serum protein binding of trandolapril is about 80%. Trandolapril is teratogenic and can cause birth defects and even death of the developing fetus. The highest risk to the fetus is during the second and third trimester. Trandolapril require dosage reductions in patients with renal impairment. Dosage reductions of temocapril ARE recommended for elderly patients. Trandolapril was approved by the FDA in 1996. [14,23]

Benazepril
Another nonsulfhydryl prodrug ACE inhibitor is useful in patients with mild to moderate hypertension. It is a prodrug biotrasformed to active diacid metabolite benazeprilat. It is beneficial for patients with congestive heart failure & also decreased systemic & pulmonary resistance. They are useful in geriatric patients. [24]
Synthesis of Benazepril

Quinapril is a non-sulphydryl ACE inhibitor. It is the tetrahydroisoquinoline analogue of enopril & the newest ACE inhibitor of carboxylic acid class. It is prodrug & converts to the active metabolite quinaprilat. Excessive hypotension is the most common reaction & dry hacking cough is another adverse effect. It is intermediate acting ACEI with a half-life shorter than of enalapril. Quinapril inhibits the contractile and pressor effects of angiotensin I and lowers blood pressure in both high- and normal-renin animal and diuretic-treated animal models of hypertension. Quinapril treatment in
elderly patients was efficacious and well tolerated, and quinapril appears to be an effective antihypertensive drug devoid of untoward effects on metabolic risk factors for cardiovascular disease, treatment in elderly patients was efficacious and well tolerated, and quinapril appears to be an effective antihypertensive drug devoid of untoward effects on metabolic risk factors for cardiovascular disease. Quinapril also produces favorable hemodynamic changes, and improves ventricular and endothelial function in patients with various cardiovascular disorders; these effects are mediated through the binding of quinapril to both tissue and plasma ACE.[12, 25]

**Synthesis of Quinapril**

\[
\begin{align*}
\text{3-t-Butylcarboxylate-1,2,3,4-tetrahydroquinoline} + \text{HOOC} & \rightarrow \text{Quinapril} \\
\end{align*}
\]

**Cilazapril**

Cilazapril is a new pyridazine ACEI useful in the management of mild to moderate hypertension, orally administered cilazapril is a prodrug which is de-esterified to its active diacid metabolite cilazaprilat by the action of tissue esterases. Compared with enalapril & captopril, cilazapril is more potent & longer lasting. In cases of over dosage, it can be removed from circulation by dialysis. [26, 27, 28]
Synthesis of Cilazapril

\[
\text{(S)-4-(((benzyloxy)carbonyl)-2-aminobutanoic acid} \quad \text{Phthalic anhydride}
\]

\[
\text{(l)} \quad \text{Toluene, } \triangle \quad \text{PCl}_5
\]

\[
(\text{l}) + \quad \text{NaHCO}_3 \quad \text{PhthN} = \text{N} \quad \text{PhthN} = \text{N} \quad \text{PhthN} = \text{N}
\]

1. H\textsubscript{2}, Pd-C
2. Recrystallization from EtOAc/ Et\textsubscript{2}O

\[
\text{(lI)} \quad \text{PhthN} = \text{N} \quad \text{PhthN} = \text{N} \quad \text{PhthN} = \text{N}
\]

\[
\text{(lI)} \quad \text{PhthN} = \text{N} \quad \text{PhthN} = \text{N} \quad \text{PhthN} = \text{N}
\]

\[
\text{(lII)} \quad \text{PhthN} = \text{N} \quad \text{PhthN} = \text{N} \quad \text{PhthN} = \text{N}
\]

\[
\text{(lIII)} \quad \text{PhthN} = \text{N} \quad \text{PhthN} = \text{N} \quad \text{PhthN} = \text{N}
\]

\[
\text{(lIV)} \quad \text{NH}_2\text{-NH}_2
\]
Zabicipril
Zabicipril is a well tolerated, powerful and long acting inhibitor of ACE. Zabicipril is a prodrug, devoid of action per se, which is transformed by liver esterases into its active diacid form Zapiciprilate.[2]

Zofenopril
Zofenopril is a prodrug that, once absorbed, undergoes rapid and complete hydrolysis to the sulphydryl-containing active metabolite zofenoprilat. The ACE-inhibitory effects of zofenopril, via zofenoprilat, were found in vitro and in vivo to be 3 to 10 times higher on a molar basis than that of captopril. The most relevant property of zofenopril is its high lipophilicity (octanol-water distribution coefficients: zofenopril 3.5, zofenoprilat 0.22), which permits extensive and prolonged tissue penetration, and binding to tissue ACE. Zofenopril has been extensively tested in preclinical models of ischaemic heart disease (IHD). In vitro cardioprotective effects of zofenopril occur via modulation of ATP-sensitive potassium channels (K\textsubscript{ATP}), through a mechanism which differs from that of cromakalim (a classical K\textsubscript{ATP} activator). Zofenopril, like captopril, showed free-radical scavenging activity in a model of myocardial reperfusion injury. Zofenopril (also known as Zofenoprilum [Latin]) is an angiotensin converting enzyme (ACE) inhibitor with cardioprotective properties indicated for the treatment of hypertension.[29] Sulphhydryl angiotensin-converting enzyme (ACE) inhibitors inhibit oxidative stress and atherogenesis with the sulphhydrylic ACEI (ACE inhibitor) zofenopril (ZOFE), which, similar to captopril, possesses radical-scavenging capabilities.[30] In small studies, zofenopril appeared significantly more effective than the older antihypertensives atenolol and enalapril, and was associated with less adverse effects. The sulphhydryl ACE inhibitor zofenopril reduces oxidative stress and improves the NO pathway in patients with essential hypertension. [31]

Spirapril
Spirapril is a monoethyl ester prodrug which is rapidly hydrolysed to the active diacid, spiraprilat, after systemic administration. Spiraprilat is a specific inhibitor of ACE at least as potent as enalaprilat in vitro and in vivo. Spirapril hydrochloride (Renormax®) is an ACE inhibitor antihypertensive drug used to treat hypertension. Like many ACE inhibitors, this is a prodrug which is converted to the active metabolite spiraprilat following oral administration. Unlike other members of the group, it is eliminated both by renal and hepatic routes which may allow for greater use in patients with renal impairment. However data on its effect upon the renal function is conflicting. [13, 22]
Synthesis of Spirapril

Fosinopril sodium an ester prodrug of fosinopriott is in the first of a new generation of phosphinic acid ACEIs Indicated for the once-daily treatment of hypertension. Unlike captopril & lisinopril, it is reportedly effective It increases the left ventricular peak filling rates and peak ejection rate in hypertensive patients at rest. Another advantage is that fosinopril is metabolized equally by renal & hepatic routs, thereby avoiding the requirement to modify dosage in patients with renal insufficiency. The advantages of this drug over captopril are ascribed to its presence of bioisosteric anion (PO$^{3+}$) instead of the sulphydryl (SH) group which is responsible for several adverse effect of captopril.[12, 13, 61]
Synthesis of Fosinopril

1. (but-3-enyl)benzene + \( \text{Na}_2\text{HPO}_3 \) \( \xrightarrow{\text{AIBN}} \) \( \text{PO}_2\text{H}_2 \)

1. \( \text{N}((\text{C}_2\text{H}_5)_3, \text{Cl-Si(CH}_3)_3 \)

2. \( \text{BrO}_\text{O} \rightarrow \text{PO}_\text{O} \rightarrow \text{COOH} \)

\( \text{H}_3\text{C} \rightarrow \text{O} \rightarrow \text{COOH} \)

Resolution of diastereomers

1. \( \text{N}((\text{C}_2\text{H}_5)_3, \text{CH}_3\text{CN}, 0^\circ\text{C} \)

2. \( \text{N}((\text{C}_2\text{H}_5)_3, \text{trans-4-cyclohexyl-L-proline} \)

Fosinopril
A575 C
A575 C a compound which has both ACE inhibitor and beta-blocking activities, A compound that express both of these activities would has an improved therapeutic profile, considering that beta-blocker effect causes decrease in heart rate and contractility. A575C 10 was found to exhibit both effects and hence it is potentially a novel type of antihypertensive agent. [9]

RXP 40 7
A phosphinic peptide Ac-Asp\(_\text{L}\)Phe\(_\text{L}\)Phe\(_\text{L}\)Phe(PO\(_2\)-CH\(_2\))\(_\text{L}\)Ala-Ala-NH\(_2\), called RXP 407, the phosphinic peptide RXP 407 has recently been identified as the first potent selective inhibitor of the N-active site (domain) of angiotensin-converting enzyme (ACE), is able to significantly increase plasma AcSDKP levels with no effect on Ang I metabolism. with increasing doses of RXP 407 (0.1–30 mg/kg/30 min), plasma concentrations of AcSDKP, a physiological substrate of the N-domain, increased significantly and dose dependently toward a plateau 4 to 6 times basal levels. RXP 407 significantly and dose dependently inhibited ex vivo plasma ACE N-domain activity, whereas it had no inhibitory activity toward the ACE C-domain. RXP 407 (10 mg/kg) did not inhibit the pressor response to an i.v. angiotensin I bolus injection in mice. In contrast, lisinopril infusion (5 and 10 mg/kg/30 min) affected the metabolism of both AcSDKP and angiotensin I. Thus, RXP 407 is the first ACE inhibitor that might be used to control selectively AcSDKP metabolism with no effect on blood pressure regulation. [32, 33]

RXPA 380
RXPA380 was the first inhibitor that was highly selective of the C-domain of ACE; it has the formula Phe-Phe- Pro-Trp.

Delapril-
Delapril, a nonsulphydryl angiotensin converting enzyme (ACE) inhibitor, which has an indanylglycine moiety differing from the proline moiety of captopril or enalapril, is an esterified prodrug that is converted in vivo to its active metabolites(5-hydroxy derivative) and to an inactive product(Diketo-piperazine-COOH). In-vitro both Delapril diacid and 5-hydroxy delapril are between 4 and 14 times more potent than captopril in inhibiting lung ACE and angiotensin I-induced vasoconstriction in rat aorta and kidney. [28] Delapril has several characteristics that differ from captopril and enalapril, including high lipophilicity and weak bradykinin potentiating action. Delapril is a more potent inhibitor of vascular wall ACE activity than enalapril or captopril. [34] Delapril is a nonsulphydryl, nonprolinic, lipophilic ACE inhibitor, with high affinity for the C-terminal site of ACE. Delapril (also known as Alindapril or Delaprilum [Latin]) is an ACE inhibitor, in hypertensive patients with type II diabetes mellitus, the combinations delapril- manidipine and irbesartan- hydrochlorothiazide are equally effective in reducing BP levels and significantly more effective. [35]

Utibapril
Utibapril is an angiotensin-converting enzyme (ACE) inhibitor with a proposed tissue-specific inhibitory profil. Utibapril is a novel thiadiazoline that is currently under investigation as an antihypertensive agent. The major degradation product, a diacid FPL 63674XX, is biologically active. At a certain dose, utibapril should be able to inhibit tissue ACE activity without affecting plasma ACE. Moreover, if tissue ACE activity is rate limiting, functional conversion of angiotensin I should
be decreased. Accordingly the dose-dependent effect of long-term treatment occurs with utibapril on plasma and tissue ACE. [36, 37]

**Imidapril**

Imidapril hydrochloride (imidapril) is a long-acting, non-sulfhydryl angiotensin-converting enzyme (ACE) inhibitor, whose active diacid metabolite imidaprilat is responsible for the major pharmacodynamic effects of the drugs after oral administration. It has been used clinically in the treatment of hypertension, chronic congestive heart failure (CHF), acute myocardial infarction (AMI), and diabetic nephropathy. It has the unique advantage over other ACE inhibitors in causing a lower incidence of dry cough. After oral administration, imidapril is rapidly converted in the liver to its active metabolite imidaprilat and about twice as potent as captopril. The plasma levels of imidaprilat gradually increase in proportion to the dose, and decline slowly. Imidapril is a versatile ACE inhibitor. It is also sometimes known as: Tanatril. [38, 39, 40]

**Synthesis of Imidopril**

(S)-2-((S)-1-(ethoxycarbonyl)-3-phenyl(propylamino)propanoic acid

\[
\text{HOOC} \quad \text{N} \quad \text{CH}_3 \\
\text{O} \quad \text{O} \quad \text{H}_3 \text{C}
\]

DCC, THF

\[
\text{H}_3 \text{C} \quad \text{O} \quad \text{N}
\]

\[
\text{HO} \quad \text{O} \quad \text{O} \quad \text{H}_3 \text{C}
\]

KOC(CH3)3

THF, -400°C

\[
\text{H}_3 \text{C} \quad \text{O} \quad \text{N}
\]

\[
\text{HO} \quad \text{O} \quad \text{O} \quad \text{H}_3 \text{C}
\]

H2, Pd-C. Ethanol

Imidopril
Imidapril require dosage reductions in patients with renal impairment. The area under the concentration-time curve of imidapril and the peak plasma concentration of the active metabolite imidaprilat are decreased when imidapril is given together with digoxin. [14] Treatment with imidapril, a well-known long-acting ACE inhibitor, caused a significant improvement of the reduced ATP responses in both failing hearts and failing cardiomyocytes. [38, 39, 41]

Ceranapril
Ceranapril (SQ 29,852) is a new inhibitor of angiotensin I converting enzyme (ACE) belonging to the hydroxylphosphonate class. The duration of ceranapril’s inhibition of an AI pressor response was longer than an equimolar dose of captopril. Ceranapril’s blood pressure lowering effect had a longer duration than that of captopril. [42, 43]

Moexipril
Moexipril is in a group of drugs called ACE inhibitors. Moexipril is used to treat high blood pressure (hypertension). Moexipril could cause birth defects in the baby if you take the medication during pregnancy. Use an effective form of birth control. Avoid drinking alcohol. It can further lower your blood pressure and may increase some of the side effects of moexipril. Do not give this medication to a child younger than 6 years old. Moexipril requires dosage reductions in patients with renal impairment. Dosage reductions of moexipril are recommended for elderly patients, and dosages of moexipril should be lower in patients who are hepatically impaired. Moexipril should be taken 1 hour before meals. [14, 44]

Synthesis of Moexipril
Temocapril
Temocapril is prodrug that is converted to the active metabolites, temocaprilat. Temocapril (also known as Temocaprilum [Latin]; brand name Acecol) is an ACE inhibitor. Temocaprilat is eliminated by renal and biliary routes. 2- Fold increase in plasma temocaprilat in patients with renal insufficiency. Because renal function is physiologically decreased with age, it is hypothesized that, compared with temocaprilat, accumulation of enalaprilat during repeated dosing is greater and blood pressure lowering effect is enhanced in elderly hypertensive patients.[21] Temocapril, which has the 2-thienyl group at the 2-position, showed a potent and long-lasting inhibitory activity. Conformational study revealed that the 2-thienyl group of temocapril enhances the activity by restriction of the perhydrothiazepine conformation suitable for binding to ACE and by hydrophobic binding to subsite S2’ of ACE. [45]

Synthesis of Temocapril

1. H₂, Pd-C, CH₃COOH
2. diphenylphosphoryl azide, DMF

HCl, isomer separation
Idrapril

Idrapril is the prototype of a novel class of ACE inhibitors with a non-peptidomimetic structure and a hydroxamic group with zinc-binding function. The chemical structure of idrapril is (+)-(1S,2R)-2-[(N-(2-hydroxyamino-2-oxoethyl)N-methylamino)carbonyl]cyclohexane-1-carboxylic acid. Idrapril is a hydroxamic derivative of a chiral synthesis based on cis-1,2-cyclohexanedicarboxylic acid. The most active enantiomers in this series have either an S or R configuration at the C-1 position but always an R configuration at C-2. Unlike idrapril, an S configuration is essential for the activity of classical ACE inhibitors. Idrapril is a colourless powder with a bitter taste. The drug has good water, but limited lipid solubility. [36] Idrapril is approximately as potent as captopril but with longer duration of action. [46]

Pentopril

Pentopril is the prodrug ester of an active ACE inhibitor, CGS 13934, being developed for the treatment of hypertension & congestive heart failure. Pentopril, enalapril, & other similar ACE inhibitor, is hydrolysed in-vivo, to the active diacid metabolite CGS 13934. Pentopril was found to be absorbed rapidly following zero order kinetics. About 20% of the administered dose was reported to be excreted as unchanged drug while 40% was excreted in the urine as the active metabolite. [47] Pentopril (CGS 13945) is a member of a series of l-glutarylindoline-2(S) carboxylic acid derivatives. Chemically, it is 1-[4-(ethoxycarbonyl)-2-methyl-2R, 4'R-pananyloyl] 2, 3-dihydro-2S-indole-2-carboxylic acid, and it has the molecular formula C_{18}H_{23}NO_{5}. It is a no hygroscopic, very slightly
pink fine powder with a molecular weight of 333.38. In rats, pentopril was approximately 50% as potent as its dicarboxylic acid analog (CGS 13934) with respect to inhibition of A1 responses. CGS 13934 is somewhat more potent than pentopril suggests that pentopril may be endogenously hydrolyzed to the free-acid form for optimal ACE inhibition.[48, 49]

Pivalopril-
Pivalopril is a potent, orally effective ACE inhibitor and antihypertensive agent [50]. Pivalopril (RHC 3659-(S); (S)-N -cyclopentyl-N-(2-methyl-3-pivaloylthiopropionyl) glycine) is a new compound with a hindered sulfur group that has been compared to captopril for oral angiotensin-converting enzyme (ACE) inhibition and antihypertensive activity. Pivalopril produced a dose-related antagonism of angiotensin I (AngI)-induced pressor effects. The potency and duration were similar to those of captopril. [51]

Keto-ACE-
5-S-5-Benzamido-4-oxo-6-phenylhexanoyl-l-proline (ketoACE) the first of such compounds was shown to be good inhibitor of ACE with modest domain selectivity [52]. Keto ACE is C-domain selective ACE inhibitor. [53]

Rentiapril-
(2R, 4R)-2-(o-Hydroxyphenyl)-3-(3-mercaptopropionyl)-4-thiazolidinecarboxylic acid (rentiapril, SA 446), an orally active Inhibitor of angiotensin converting enzyme. [54]

Teprotide-
A parenteral ACE inhibitor is used in reducing BP for 4 months in a woman who developed severe high renin hypertension after renal transplantation. A synthetic nonapeptide (Pyr-Trp-Pro-Arg-Pro-Gln-Ile-Pro-Pro) is identical to the peptide of the snake venom. Bothrops jararaca. It inhibits kininase II and angiotensin I and has been proposed as an antihypertensive agent. [11,55]

Alacepril-
Alacepril is a novel orally active ACE inhibitor having a potent and prolonged antihypertensive activity [56]. Alacepril is a long-acting, sulfhydryl-containing angiotensin-converting enzyme inhibitor. Disposition and metabolism of orally given alacepril are responsible for the prolonged ACE inhibition and, concomitantly, for exerting the long lasting antihypertensive effect. Alacepril (1-[(S)-3-acetylthio-2-methylpropanoyl]-L-prolyl-L-phenylalanine, DU-1219) showed a dose related and long lasting antihypertensive effect in renal hypertensive treatment with alacepril improves functional status and exercise capacity in patients with mild-to-moderate CHF. Neurohormones were favorably influenced by alacepril therapy, with significant decreases in plasma aldosterone, ANP and BNP levels. The maximum hypotensive potency of alacepril after single oral administration was slightly weaker than that of captopril. [57, 58]

When orally administered, alacepril is easily metabolized to DU-1227 (desacetyl-alacepril) & further more to captopril with strong ACE inhibitor activity in intestine, liver and kidney. Alacepril is thus prodrug with a very high degree of conversion to captopril, which has been claimed to be about 3 times more potent than captopril and with a gradual onset and long lasting antihypertensive effect.
when administered orally to hypertensive animals. The antihypertensive effect by alacepril has been suggested to be mainly due to ACE inhibitor activity of the formed captopril. [28, 52]

**Synthesis of Alacepril**

MC-838 (Altiopril calcium, Moveltipril)-
Moveltipril contains a captopril moiety in its chemical structure. However, it is unclear whether, as a prodrugs, it is converted into active metabolites containing the sulfhydryl group or is converted in vivo to captopril.[28] MC-838, calcium (-)-N-[(S)-3-(N-cyclohexylcarbonyl-D-alanyl) thio]-2-methylpropionyl]-L-prolinate, is a new orally active angiotensin converting enzyme (ACE) inhibitor in which the mercapto-group is taken up in a stable thiolester linkage. The linkage was relatively resistant against enzymatic hydrolysis by liver homogenates. MC-838 was highly specific in suppressing the contractile response to angiotensin-I (A-I) an in augmenting the contractile one to bradykinin. However, the ACE inhibitory activity of MC-838 was 30-100 times less potent than that of captopril. MC-838 given orally caused a long-lasting hypotensive effect with a slow onset. The antihypertensive effect of MC-838 was comparable to that of captopril in magnitude, but the duration of action of MC-838 was approximately 2 times longer than that of captopril.[59, 60]
Table 1. Pharmacokinetic Parameters of ACE Inhibitors-

<table>
<thead>
<tr>
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<th></th>
</tr>
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<tbody>
<tr>
<td>Captopril</td>
<td>Sulfhydryl</td>
<td>Active</td>
<td>NA</td>
<td>60-75</td>
<td>R.</td>
<td>0.25-0.50</td>
<td>6-12</td>
<td>0.272</td>
<td>1</td>
<td>2</td>
<td>R.</td>
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<td>Carboxyl</td>
<td>Prodrug</td>
<td>Enalaprilat</td>
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<td>N.</td>
<td>1</td>
<td>24</td>
<td>2.426</td>
<td>4-6</td>
<td>11</td>
<td>R./F.</td>
</tr>
<tr>
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<td>Carboxyl</td>
<td>Active</td>
<td>NA</td>
<td>25-30</td>
<td>N.</td>
<td>1</td>
<td>24</td>
<td>1.188</td>
<td>6-8</td>
<td>12</td>
<td>R.</td>
</tr>
<tr>
<td>Perindopril</td>
<td>Carboxyl</td>
<td>Prodrug</td>
<td>Perindoprilat</td>
<td>65-95</td>
<td>R.</td>
<td>1</td>
<td>24</td>
<td>3.363</td>
<td>6</td>
<td>25-30</td>
<td>R.</td>
</tr>
<tr>
<td>Quinapril</td>
<td>Carboxyl</td>
<td>Prodrug</td>
<td>Quinaprilat</td>
<td>60</td>
<td>R.</td>
<td>1</td>
<td>24</td>
<td>4.318</td>
<td>-</td>
<td>-</td>
<td>R.</td>
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<tr>
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<td>Carboxyl</td>
<td>Prodrug</td>
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<td>50-60</td>
<td>S. A.</td>
<td>1-2</td>
<td>24</td>
<td>3.409</td>
<td>3-6</td>
<td>8-48</td>
<td>R., F.</td>
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<tr>
<td>Trandolapril</td>
<td>Carboxyl</td>
<td>Prodrug</td>
<td>Trandolaprilat</td>
<td>70</td>
<td>S. A.</td>
<td>0.5-1.0</td>
<td>24</td>
<td>3.973</td>
<td>-</td>
<td>-</td>
<td>F. (P.) R. (S.)</td>
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<tr>
<td>Spirapril</td>
<td>Carboxyl</td>
<td>Prodrug</td>
<td>Spiraprilat</td>
<td>50</td>
<td>-</td>
<td>1</td>
<td>24</td>
<td>3.162</td>
<td>-</td>
<td>-</td>
<td>R. (50%) H. (50%)</td>
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<tr>
<td>Benazepril</td>
<td>Carboxyl</td>
<td>Prodrug</td>
<td>Benazeprilat</td>
<td>30</td>
<td>S. A.</td>
<td>1</td>
<td>24</td>
<td>5.504</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Fosinopril</td>
<td>Phosphate</td>
<td>Prodrug</td>
<td>Fosinoprilat</td>
<td>36</td>
<td>S. A.</td>
<td>1</td>
<td>24</td>
<td>6.092</td>
<td>-</td>
<td>-</td>
<td>R.(P.) B.(S.)</td>
</tr>
<tr>
<td>Zofenopril</td>
<td>Sulfhydryl</td>
<td>Prodrug</td>
<td>Zofenoprilat</td>
<td>78</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>5.5</td>
<td>H. (35%), R. (65%)</td>
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<tr>
<td>Imidapril</td>
<td>Carboxyl</td>
<td>Prodrug</td>
<td>Imidaprilat</td>
<td>70</td>
<td>R.</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Alacepril</td>
<td>Sulfhydryl</td>
<td>Prodrug</td>
<td>Captopril</td>
<td>70</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td>Cilazapril</td>
<td>Carboxyl</td>
<td>Prodrug</td>
<td>Diacid</td>
<td>52</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>SQ 29852</td>
<td>Phosphoryl</td>
<td>Active</td>
<td>SQ 29852</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td>-</td>
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</tr>
<tr>
<td>Moveltipril</td>
<td>Sulfhydryl</td>
<td>Prodrug</td>
<td>Captopril</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pentopril</td>
<td>Carboxyl</td>
<td>Prodrug</td>
<td>CGS 13934</td>
<td>66</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>MDL 100173</td>
<td>-</td>
<td>Prodrug</td>
<td>MDL100240</td>
<td>85</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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</tr>
</tbody>
</table>

O.B. = Oral bioavailability, E.F.A. = Effects of food on absorption, O.A. = Onset of action (hours), D.A. = Duration of action (hours), T.P.A. = Time To Peak Action (hours), Elimination t ½ (hours), M.R.E. = Major Route(s) of Elimination, R. = Renal, F. = Fecal, H. = Hepatic, B. = Biliary, P. = Primary, S. = Secondary, S.A. = Slow absorption, R. = Reduced, N. = None
Table 2 Dosing Information for Orally Available ACE Inhibitors-

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>M.D.D.</th>
<th>D.R.</th>
<th>D.R.R.D.</th>
<th>A.T.S.</th>
<th>Approved Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captopril</td>
<td>Capoten</td>
<td>450</td>
<td>25-150mg b.i.d. or t.i.d.</td>
<td>Yes</td>
<td>12.5,25,50 100</td>
<td>Hypertension, Heart failure, Left ventricular dysfunction (post-MI), Diabetic nephropathy</td>
</tr>
<tr>
<td>Enalapril</td>
<td>Vasotec</td>
<td>40</td>
<td>2.5-40mg q.d. or b.i.d.</td>
<td>Yes</td>
<td>2.5,5,10 20</td>
<td>Hypertension, Heart failure, Left ventricular dysfunction (Asymptomatic)</td>
</tr>
<tr>
<td>Perindopril</td>
<td>Aceon</td>
<td>16</td>
<td>4-8mg q.d. or b.i.d.</td>
<td>Yes</td>
<td>2,4,8</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Quinapril</td>
<td>Accupril</td>
<td>80</td>
<td>10-80mg q.d. or b.i.d.</td>
<td>Yes</td>
<td>5,10,20,40</td>
<td>Hypertension, Heart failure</td>
</tr>
<tr>
<td>Ramipril</td>
<td>Altace</td>
<td>20</td>
<td>2.5-20mg q.d or b.i.d.</td>
<td>Yes</td>
<td>1.25,2.5,10</td>
<td>Hypertension, Heart failure, Reduce risk of MI, stroke &amp; death from cardiovascular causes</td>
</tr>
<tr>
<td>Trandolapril</td>
<td>Mavik</td>
<td>8</td>
<td>1-4mg q.d.</td>
<td>Yes</td>
<td>1,2,4,</td>
<td>Hypertension, Heart failure, Left ventricular dysfunction (Post-MI)</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>Prinivil</td>
<td>40</td>
<td>10-40mg q.d.</td>
<td>Yes</td>
<td>2.5,10</td>
<td>Hypertension, Heart failure, Improve survival post-MI</td>
</tr>
<tr>
<td>Moexipril</td>
<td>Univasc</td>
<td>30</td>
<td>7.5-30mg q.d or b.i.d.</td>
<td>Yes</td>
<td>7.5,15</td>
<td>Hypertension</td>
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<tr>
<td>Benazepril</td>
<td>Lotensin</td>
<td>80</td>
<td>10-40mg q.d. or b.i.d.</td>
<td>Yes</td>
<td>5,10,20,40</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>Monopril</td>
<td>80</td>
<td>10-40mg q.d.</td>
<td>No</td>
<td>10,20,40</td>
<td>Hypertension, Heart failure</td>
</tr>
<tr>
<td>Imidapril</td>
<td>Tanatril</td>
<td>5-10mg</td>
<td>5mg, 10mg, 20mg or 40mg in the 4 week</td>
<td>-</td>
<td>5 and 10</td>
<td>Angioneurotic oedema, Hereditary/Idiopathic angioedema, Pregnancy, Lactation, Renovascular hypertension, Renal Failure</td>
</tr>
</tbody>
</table>

**M.D.D.**=Maximum Daily Dose(mg), **D.R.**=Dosing Range (Treatment of Hypertention), **D.R.R.D.**=Dose Reduction with Renal Dysfunction, **A.T.S.**=Available Teblet Strengths (mg) and (-)= Not Available
The other phosphoryl containing ACE inhibitor which is expected to undergo clinical development is SQ 29852; this drug differs from fosinopril in that it is very well absorbed orally, with a 66% bioavailability in humans and practically negligible biotransformation. This compound thus seems to be the only newly developed ACE inhibitor which is not a prodrug. In vitro SQ 29852 is a potent inhibitor of isolated rabbit lung ACE and after oral administration in rats. It was slightly more effective than captopril, with a much longer lasting effect.[28]

**Current aspect and future trends**

The ACE inhibitors now constitute one of the most important classes of cardiovascular drugs. The developments of specific agents that interfere with the renin-angiotensin system have defined the contribution of this system to blood pressure regulation and to the pathogenesis of hypertension, congestive heart failure, and chronic renal failure. A major breakthrough in the treatment of blood pressure was the design of the captopril, which has spawned an entire industry. To achieve good oral bioavailability, most of the inhibitors (except captopril and lisinopril) are synthesized as ester prodrug but it also opened the door to the design of new and more targeted ACE inhibitors. Although several synthetic ACE inhibitors are now widely available for use as antihypertensive drugs, they have been known to cause some undesirable side effects such as postural hypotension, cough, renal failure and angiooedema. Currently, many studies are being done to search for more suitable antihypertensive agents, including ACE inhibitors. Findings from these studies may open up the possibilities of more alternatives with ACE inhibitory effects with better drug profiles and less adverse side effects.[1]
REFERENCES

[18] YourTotalHealth ACE Inhibitors.
[27] Patient UK cilazapril.
[29] Chapter 2; Dietary Sodium Restriction Specifically Potentiates Left Ventricular ACE Inhibition by Zofenopril, and is Associated with Attenuated Hypertrophic Response in Rats with Experimental Myocardial Infarction.