Advances in Angiotensin Converting Enzyme Inhibitors (ACEIs) and Angiotensin Receptor Blockers (ARBs)

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Abstract: Hypertension remains one of the most unmet medical needs of this century. While many drugs are available for treating hypertension, efforts are still insufficient to find potent therapeutic agents since cause for hypertension in all patients is not the same. Angiotensin-converting enzyme inhibitors (ACEIs) have emerged as an important class of drugs in the treatment of hypertension, congestive heart failure (CHF), protenuric renal disease, myocardial infarction and stroke. This class of drugs blocks the conversion of angiotensin I to angiotensin II and prevents bradykinin breakdown. However, the lack of specificity of ACEIs leads to the frequent side effects like cough and angio-oedema. Recently developed, specific non-peptide and orally active angiotensin receptor blockers (ARBs) have become the prime therapeutics as they alone or co-administration with ACE inhibitors can control the renin angiotensin disorders. This review explores recent developments in the design, synthesis, and structural modifications of ACE inhibitors as well as angiotensin receptor blockers.

Key words: ACE inhibitors, angiotensin, renin, receptors, hypertension, morbidity, mortality.

INTRODUCTION

Cardiovascular disease (CVD) remains one of the most unmet medical needs of this century. Although enormous research effort has been made, the fundamental cause of cardiovascular disease is not clearly known. Regardless of the reasons, it can be described as an epidemic. Hypertension being one of the major risk factors of CVD accompanied by high blood pressure ultimately affects and damages the heart, kidneys and other organs. Hypertension is one of the asymptomatic diseases and hence it is termed as 'silent killer'. When it is not treated in time, hypertension is going to increase the risk of myocardial infarction, cerebral haemorrhage and renal failure. The heart and vascular muscle gradually become hypertrophic and atherosclerotic changes occur in the blood vessels, which finally lead to the coronary heart disease, stroke and kidney failure. While many drugs are available for treating hypertension, approximately one-third of the hypertensive population is still not adequately treated [1]. Apart from most effective ACEIs as antihypertensive agents, recent explorations of potent vasoprotectors for treating hypertension are mainly aimed at blocking the receptor sites of angiotensin II (Ang II) or endothelin-1 (ET-1) [2].

RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM (RAAS)

In 1827, Bright at Guy's hospital in London was among the first to recognize that renal disease often accompanied by high blood pressure [3]. Then in 1898 saline extracts of kidney were shown to contain a pressor substance (i.e., a material which increases the blood pressure), which was named as *renin*. Many years later (1940) *renin* was revealed as an enzyme that acts on a plasma protein to catalyze the formation of the actual pressor substance called angiotensin. Different forms of angiotensin have been found where the most important are angiotensin I (Ang I, a decapeptide) and angiotensin II (Ang II, an octapeptide). Ang II is a more active pressor agent, which is produced from the Ang I by an enzyme called angiotensin-converting enzyme (ACE).

The *renin* degrades the angiotensinogen to release a decapeptide Ang I, which has little pharmacological activity [4,5]. ACE, an enzyme present mainly on luminal aspect of vascular endothelial cells and the blood cleaves Ang I to form an octapeptide, Ang II. Ang II has two principal pharmacological activities: it is one of the most potent vasoconstrictors known and it activates release of aldosterone from the adrenal cortex. Number of mechanisms has been proposed to explain the pressor activity of Ang II. Primarily it stimulates the vascular smooth muscles with an increase in peripheral sympathetic transmission. The peripheral action of Ang II involves the arterioles, which is the organ to determine the vascular tone and, thereby, the blood pressure. Besides this, Ang II can directly provoke aldosterone secretion from the adrenal cortex through important renal sodium reabsroption mechanism. Aldosterone controls the sodium homeostasis by enhancement of renal sodium reabsorption. As a consequence concentration of water also increase by osmotic forces. Ang II increases the blood pressure through these two separate mechanisms, arteriolar smooth muscle contraction and enhancement of sodium reabsorption.

ANGIOTENSIN CONVERTING ENZYME (ACE)

ACE is a zinc metalloprotease that catalyses the conversion of Ang I to Ang II, which is a potent

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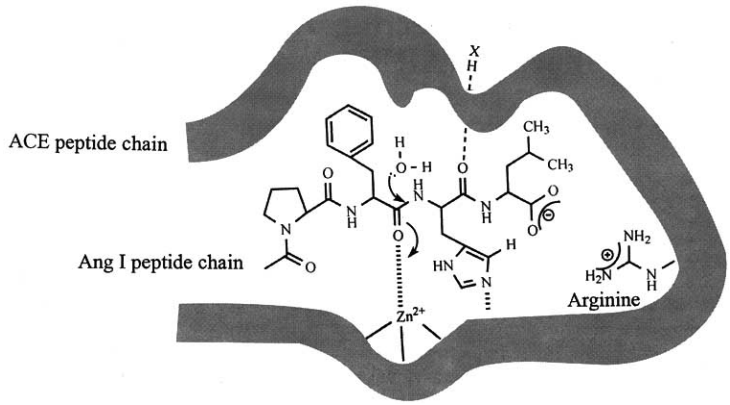


Fig (1). Schematic representation of the binding of Ang I to the active site of angiotensin converting enzyme (ACE).

vasoconstrictor (Fig.(**1**)). ACE is a nonspecific protease and also breaks bradykinin, a vasodilatory hormone and other peptides such as substance P and enkephalins [6]. ACE is found in the plasma and in a number of tissues including blood vessels, heart, kidney, brain and the adrenal gland [7]. Biochemical measurements of ACE activity shows that ACE is indeed a tissue-based enzyme, less than 10% of ACE is found circulating in the plasma [8,9]. The precise function of plasma ACE is unclear. Because it represents only a small proportion of the body's total ACE activity, its role is thought to be minimal.

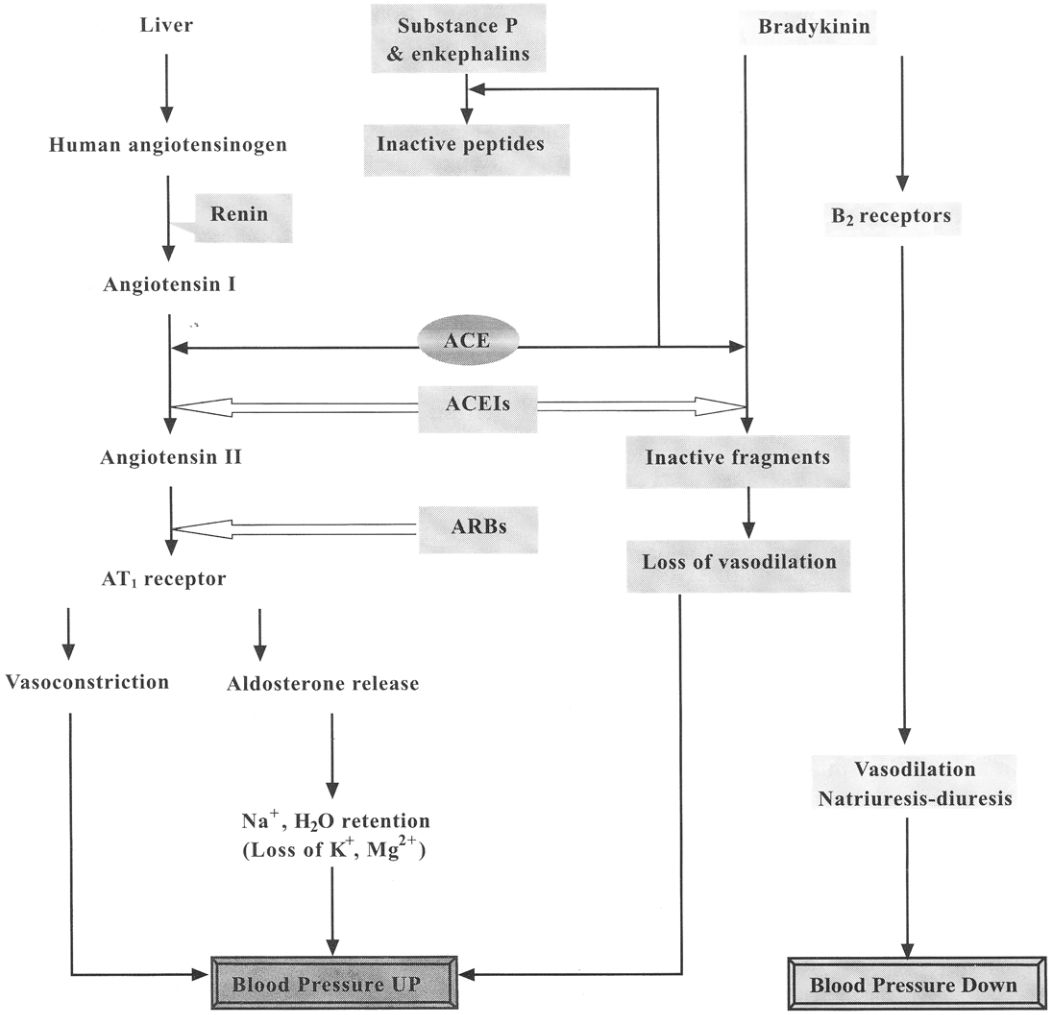
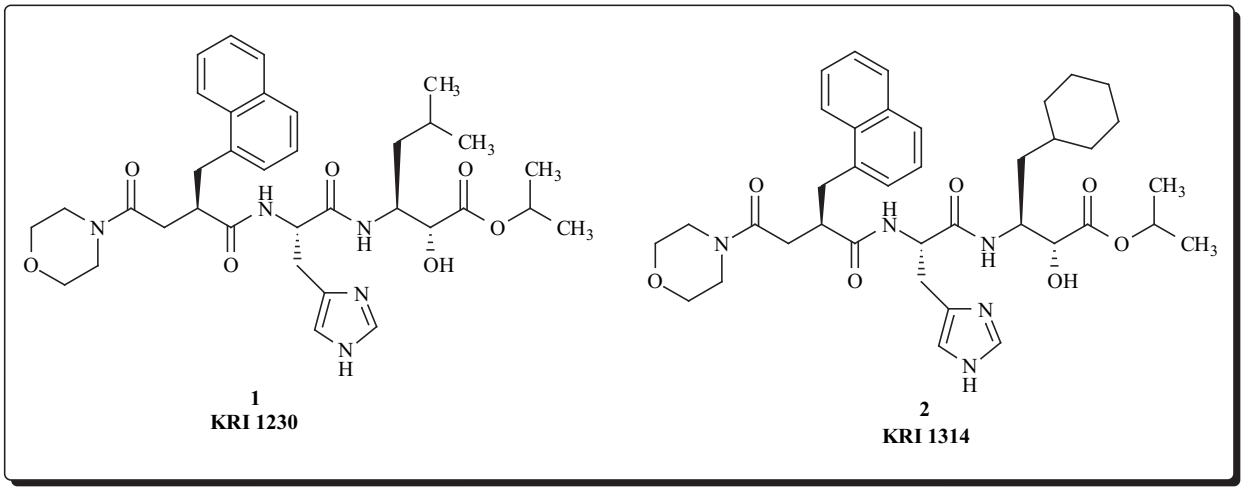


Fig (2). The renin angiotensin aldosterone system cascade.



1
KRI 1230

2
KRI 1314

ACE is also called as kininase II (the kininase responsible for the breakdown of bradykinin is identical to ACE) that cleaves the C-terminal dipeptide from Ang I and bradykinin and a number of other small peptides, which lack a penultimate proline moiety. RAAS is viewed as a cascade of proteolytic reactions under integrated controls, which produces peptides with pressor and aldosterone-producing effects. It regulates the blood pressure, blood volume, electrolytes balance and aldosterone release. The RAAS cascade reactions start with angiotensinogen, a α_2-globulin, one of the abundant group of glycoproteins in plasma produced in the liver. *Renin,* a plasma enzyme synthesized by the juxtaglomerular cells of the kidney cleaves angiotensinogen between the tenth and eleventh amino acid from the amine terminus to produce an inactive decapeptide, Ang I. The Ang I, a prohormone is then cleaved at the peptide bond between Phe^8-His^9 by the ACE to generate an octapeptide Ang II [10]. Ang II is a potent vasoconstrictor, acting directly on receptors in vascular smooth muscle cells and likewise interacts with the sympathetic nervous system both peripherally and centrally to increase the vascular tone [11]. In addition, it increases the aldosterone production and release, which promotes the tubular reabsorption of sodium ion by acting on the distal tubules of the kidney. As a result of Na^+ reabsorption, water will also retain to maintain osmolarity thereby increasing the blood volume as well as pressure. Besides catalyzing the formation of Ang II, ACE catalyzes the destruction of bradykinin. Bradykinin promotes the vasodilation by stimulating the production of arachidonic acid metabolites, nitric oxide and endothelium derived hyperpolarizing factor in vascular endothelium. In the kidney bradykinin causes natriuresis through direct tubular effects. As a whole, ACE is the regulating factor to balance between the vasodilatory/natriuretic properties of bradykinin and vasoconstrictive/salt retentive properties of Ang II [12,13].

Other enzymes like serine protease *chymase*, non-renin enzymes such as *tonin* and *cathepsin* share the ability to produce Ang II from Ang I. Both Ang I and Ang II undergoes cleavage at several sites by angiotensinases that hydrolyzes the peptide sequentially from the amino terminus (amino peptidases) or the carboxy terminus (carboxy peptidases), or cleave peptide bonds in the interior of the molecule (endopeptidases) [14]. The properties of thus produced peptide fragments may be different with that of Ang II. Most of the biological functions of RAAS are affected by Ang II, which activates the selective membrane bound receptors.

DRUGS TO TREAT RAAS DISORDERS

The most commonly used antihypertensive drugs are the thiazide diuretics, α- and β-adrenergic receptor antagonists, centrally acting antihypertensives such as α-methyldopa, calcium entry blockers and peripheral vasodilators. The important new class of drugs which principally act on RAAS are the renin inhibitors, the ACEIs, the angiotensin receptor blockers (ARBs), the aldosterone receptor antagonists, the neutral endopeptidase (NEP) inhibitors and recently developed vasopeptidase inhibitors (combined ACE and NEP inhibitors or dual inhibitors).

Since *renin* is an initiator of the RAAS cascade degradation and its active site is highly specific for angiotensinogen [15], the blockade of *renin* would be the most crucial therapeutic strategy. Both peptide mimetic compounds, KRI-1230 (**1**) and KRI-1314 (**2**) that contain the unnatural amino acid-norstatine are potent, specific and orally active *renin* inhibitors to lower the blood pressure in various experimental models of hypertension [16]. Due to overwhelming success of ACE inhibitors and ARBs, the effort to develop the drugs for renin inhibition is disregarded.

ACE INHIBITORS-RECENT PAST

Angiotensin converting enzyme inhibitors are the important antihypertensive drugs. The early development of ACEIs began with the isolation of teprotide **3**, a nonapeptide from the venom of a Brazilian pit viper; *Bothrops jararaca*, which can control raised blood pressure. Teprotide contains the unusual *pyro*-glutamic acid at the N-terminal. It was proline at C-terminal that inhibited the ACE from hydrolyzing the peptide. Due to the lack of oral bioavailability, it was precluded for further development but it gave a clue for designing drugs like ACEIs by maintaining both binding and inhibiting qualities similar to that of teprotide.

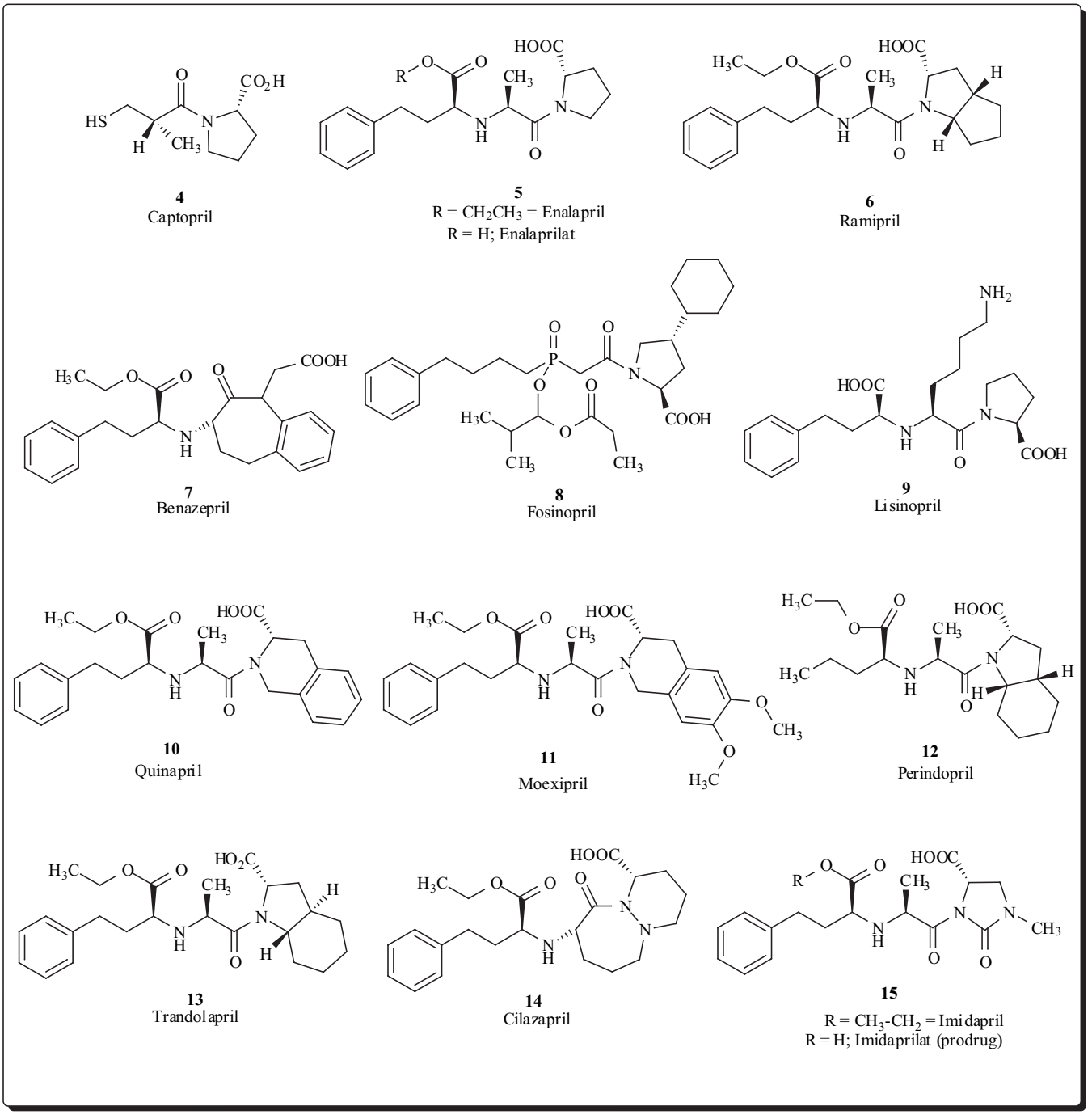
pyroGlu-Trp-Pro-Arg-Pro-Gln-Ile-Pro-Pro-OH

3

Teprotide

Using the similarities of ACE and carboxypeptidases as a basis [17,34], and utilizing the information from teprotide **3**, the prototype compound succinyl-L-proline was planed and tested. Even it was weak but its specificity towards ACE inhibition led the improvement in designing the more potent, orally active small-molecule inhibitors. Large number of dipeptides with and without zinc ligand was tested. One amongst them was a mercaptoacyl amino acid, which ultimately became captopril (**4**), 1-[(2S)-3-mercaptopropionyl]-L-proline, the most potent member of this class. Structure activity relationship studies of this class of drugs reveals that these compounds have functional groups which can bind to the zinc atom, cationic area and perfectly fit into all the subsites of ACE through the hydrogen bonding and hydrophobic interactions (Fig. (**1**)).

Several peptide mimetic compounds have been developed for the clinical use as ACEIs but only some of them were approved for the treatment of RAAS related disorders like hypertension, congestive heart failure (CHF) and left ventricular dysfunction [14]. All the ACEIs developed so far are structurally diverse (selective examples: **4-15**) and different in their potency, bioavailability, plasma half-life, ability to bind the enzyme at its active site and the route of administration/elimination. According to the chemical



structure of the active functionality, clinically approved ACEIs are classified in to three categories such as sulfhydryl group (Ex: **4**), phosphinyl group (Ex: **8**), and carboxylate group (Ex: **5-7** & **9-15**) containing drugs.

Most potent drug captopril **4** belongs to the sulfhydryl–containing ACEIs. The sulfhydryl group also associated with the properties other than ACE inhibition such as free radical scavenging and effects on prostaglandins [17,18]. FDA has approved fosinopril **8**, a phosphinyl group containing ACE inhibitor for the medicinal use. The remaining of all the approved ACEIs contains carboxyl functionality in their core structures.

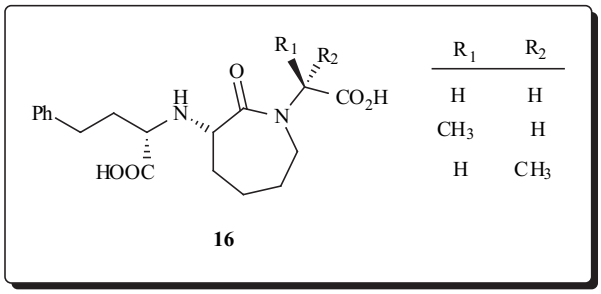
ACEIs not only are different in pharmacokinetic properties like absorption, protein binding, half-life and metabolic disorption but also in their ability to penetrate to bind tissue sites [19,20]. It has been proposed that lipophilic ACEIs like quinapril (**10**) and trandolapril (**13**) are excellent in their prolonged tissue binding properties and more effective than that of hydrophilic ACEIs in controlling the blood pressure. But clinical evidence to support this fact is unclear [19,20]. Except few lipohilics, the kidney clears mostly all other class of ACEIs. Hence a dose reduction becomes the necessary. For this reason prodrugs have been developed for majority of active ACEIs such as enalaprilat (**5**), which remain inactive until they are esterified in the liver.

ACE inhibitor therapy potentiates the bradykinin and its accumulation in the biological fluid. Bradykinin increases the synthesis and release of nitric oxide as well as vasodilatory prostaglandins like PGE_2, PGI_2 via the stimulation of B_2-receptors subtypes. Benefit of bradykinin accumulation resulted in antihypertensive, vasoprotective and antioxidant properties. Other important beneficial factor of bradykinin stimulation through ACE inhibition is that it activates the release of tissue plasminogen activator (tPA), which mediates an endogenous thrombolytic action [21]. Bradykinin receptor antagonists developed in these days are shown to attenuate the hypotensive effects of ACEIs in animal models [22,23]. However, recent B_2 antagonism studies suggest that accumulation of bradykinin during ACE inhibition therapy reduces the endothelium-dependent vasodilator effects in humans [24].

Clinical investigation found that ACE in the brain has shown to be involved in a variety of physiological functions via the generation of angiotensin II. After central application, ACE inhibitors decrease the pressor response to centrally administered angiotensin I [25]. Similarly ACE inhibition reduces thirst stimulated by water deprivation, hypovalemia and central administration of *renin* and angiotensin I [26,27]. Important function of the central RAAS is the modulation of vasopressin synthesis and secretion. ACE, Ang II receptors and *renin* were found to be highly concentrated in the vasopressin synthesizing hypothalamic nuclei, especially in the paraventricular and supraoptic nuclei [28]. To test the hypothesis that ACE inhibition may modulate the central vasopressin system, Muders [29] and co-workers measured the vasopressin content of specific microdissected brain areas in rats by chronically treating with the quinapril **10**. ACE in various brain areas was determined by *in vitro* autoradiography to assess the local inhibition of ACE in the brain after chronic treatment with quinapril. Habitual oral administration with compound **10** in rats involved in central cardiovascular control was observed to reduce central ACE concentration and vasopressin content in various brain nuclei.

Aube and his team [30] has described recently a useful synthetic methodology for obtaining seven and eight member 'Freidinger' lactams towards ACE inhibition.

Among the various strategies towards the construction of conformationally restricted peptides, incorporating backbone into a 'Freidinger' lactam structure [31] has shown to be useful in design of a variety of peptidase/protease inhibitors [32]. Like other clinically used standard ACEIs e.g., captopril (**4**) and enalapril (**5**), Freidinger-type lactams like **16** inhibit ACE well into the nanomolar range. The effectiveness of derivatives having methyl substitution at $C\alpha$ depends on the configuration of that stereocenter. The steric bulk at the $C\alpha$ adjacent to the ring nitrogen was proved to have detrimental effect on ACE inhibitory activity [30].

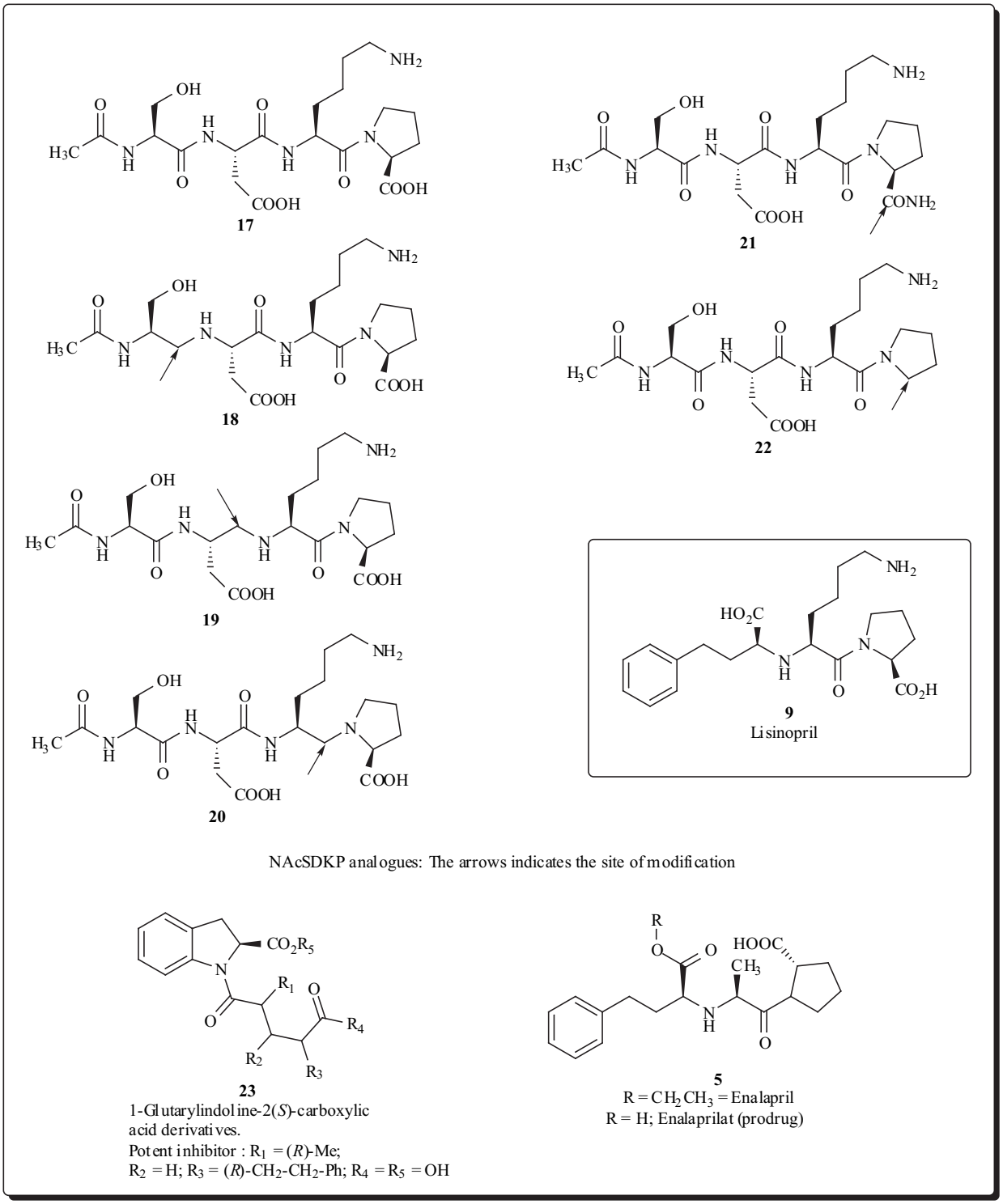


16

It is worth to note here that contribution of Thierry and his research group [33] demonstrated that N-acetyl-Ser-Asp-Lys-Pro-OH (NAcSDKP) analogues resembles with the well-known ACEIs-lisinopril **9** have ACE inhibitory activity. In order to overcome proteolysis and rapid elimination problems associated with peptides, each of the amide bonds of tetrapeptide NAcSDKP **17** was successively replaced by aminomethylene bond (by reduction) to afford the analogues **18**-**20**. As mentioned in many reports, the mechanism proposed for the hydrolysis of Ang I by ACE involves an ionic interaction between C-terminal carboxylate group of Ang I and a protonated arginine side chain in the active site of ACE (**Fig** (**1**)), [34]. Thierry [33] thought that the suppression of this ionic bond would reduce the affinity of substrate for the enzyme and therefore increase the half-life of the molecule in physiological medium. With this intention two analogues lacking the carboxylate moiety have been reported: one with a carboxamide C-terminus **21** and the other lacking the C-terminal carboxylate group **22**. Such manipulations of the peptide bond still kept the potency.

ACE inhibition study [33] of the above analogue revealed that hypothesis relying upon an ionic interaction between C-terminal carboxylate group of Ang I and a protonated arginine side chain in the active site of ACE was not valid in this case. The interaction of reported analogues with the enzyme is probably different from the one proposed for Ang I.

Some of the new sophisticated approaches were started from mid 1980s for the synthesis of ACE inhibitors. Among these, there is a very interesting design of a drug [35] in the series of glutarylindoline–2(*S*)-carboxylic acid



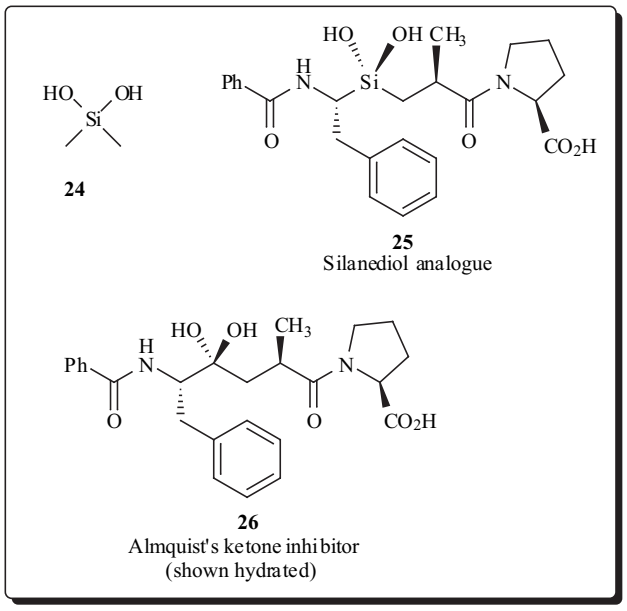
derivatives **23** that is closely related to the renowned ACE inhibitor-enalapril **5**. These glutaric acid derivatives were believed to achieve potent binding through increased interaction with several lipophilic regions of the active site instead of relying on strong binding to zinc atom of the enzyme.

Oxygen derived free radical (FR) was indicated to play an important role in myocardial ischemic-reperfusion injury in the recent discovery [36,37]. The free radical scavenging action of captopril **4** was believed due to the presence of SH-group in its structure [38]. However, Obata and Yamanaka [39] have demonstrated that all the three compounds (**4**, **5** and **15**) were able to remove •OH radical generated by the action of Iron (II), though imidaprilat **15** and enalaprilat **5** do not contain an SH-group in their structure. Imidaprilat was found to be a more potent FR scavenger than that of enalaprilat. Hence it is proved that free radical (FR) scavenging action of ACE inhibitors probably is not only related to the presence of the SH-group. This fact provides an alternative route to develop structurally diverse ACE inhibitors to replace or modify captopril.

In order to track the specific biological activities of ACE inhibitors, lisinopril **9** and enalapril **5** were made to undergo chelation with bifunctional chelating agents carrying radiometals [40]. Succinimido functionalized perfluoroarylazido(iminophosphorano)phosphine was attached to Rh(III) and Pd(III) precursors including radioactive analogues for potential *in vivo* tracking of the radiotracer. The measurement of inhibitory potency of lisinopril-metal conjugates (Rh & Pd), modified through the primary amine displayed an increase in inhibitory potency. Nevertheless, direct complexation utilizing the carboxylic groups of lisinopril with a Cu precursor resulted in the reduction of inhibition from nM to μM levels rendering it less useful as an ACE inhibitor.

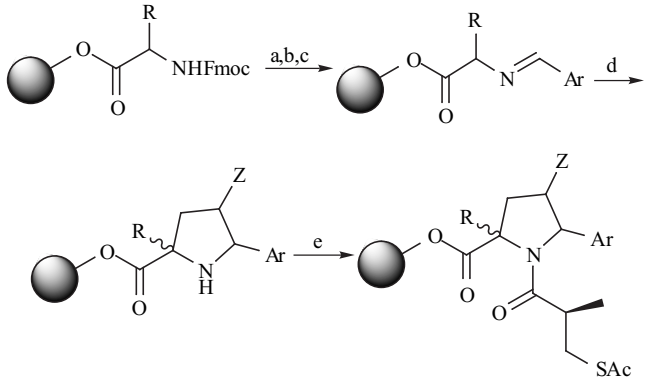
It has been realized that replacement of carbonyl group with a silanol or silanediol may create a transition state analogue as a potential enzyme inhibitor. Galardy and Kortylewicz [41], in a survey of second and third row element-based tetrahedral structures, tested aqueous solution of dimethylsilanediol **24** as an inhibitor of angiotensin-converting enzyme. Geminal diols (hydrated aldehydes and ketones) are known as enzyme inhibitors and they are expected to be effective metalloprotease inhibitors. Almquist's ketone **26** [42] is the energetically disfavored hydrate, and assumed that it may act by chelating the active site of zinc in ACE. This compound was found to be a good ACE inhibitor, with an IC_{50} value of 1.0 nM. The work described by Sieburth and coworkers [43] that illustrated the first use of silanediol **25** as a transition state analogue, anticipated to emulate the hydrated ketone **26** towards the ACE inhibition.

The silanediol tripeptide derivatives actually inhibited ACE with IC_{50} values up to 14 nM.



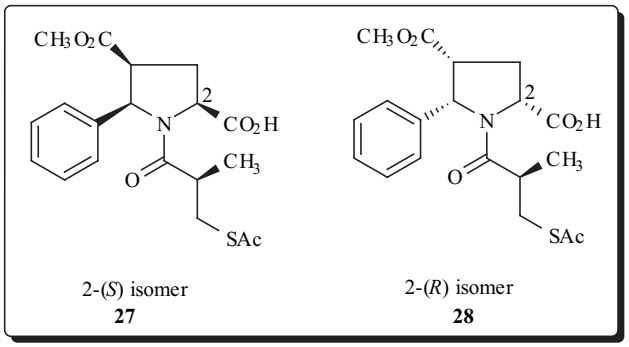
ACE INHIBITORS SYNTHESIS BY COMBINATORIAL APPROACH

Construction of small molecule library through combinatorial synthesis on polymer support promises to generate lead molecules in a considerably short time. In recent days combinatorial chemistry has gained acceptance throughout the pharmaceutical industry as a powerful tool in the identification and development of therapeutic agents [44]. Gallop *et al* [45] demonstrated the combinatorial synthesis of pyrrolidine derivatives **27** & **28** (Scheme (1)) as potent ACE inhibitors. 1,3-Dipolar cycloaddition of resin bound azomethine ylides with olefins yielded the mercaptoprolines.



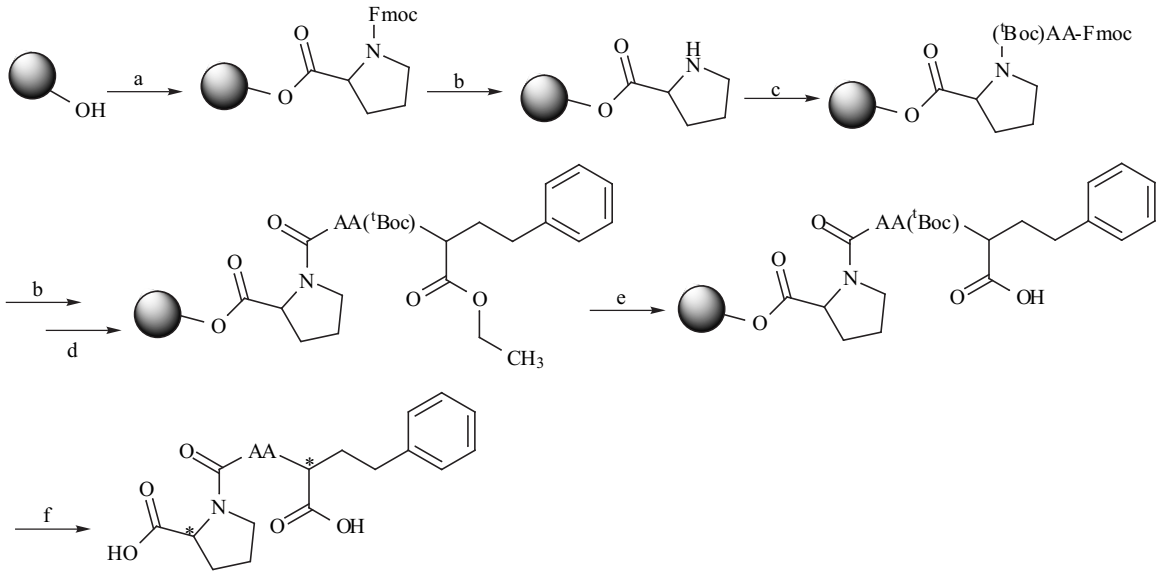
Scheme 1. Solid-phase synthesis of pyrrolidines: (a) 20% piperidine in DMF, 20 min; (b) 1 M ArCHO in $CH(OMe)_3$, 4 h; (c)Ac_2O, NEt^iPr_2, 15 min; (d) 1 M olefin, 1 M $AgNO_3$, 1 M NEt_3 in MeCN, 8 h. (e) $AcSCH_2CH(CH_3)COCl$

Biological assay [46] of the individual diastereomers (Scheme (1)) after deacetylation (assigned absolute configuration at C-2) showed that 2-*(S)* pyrrolidine isomer offered an exceedingly potent ACE inhibition, approximately 3-fold more active than captopril **4**.



In another attempt (Scheme (2)) Blackburn and co-workers [47] synthesized dipeptide libraries as ACE inhibitors using polyethylene glycol-polystyrene (PEG-PS) polymer support and 4-(1',1'-dimethyl-1'-hydroxypropyl)phenoxyacetyl (DHPP) linker. To test the feasibility of PEG-PS-DHPP support, they built up a standard method to prepare dipeptidyl ACE inhibitor-enalapril, and then applied the same strategy to synthesize various peptide libraries using mixtures of nineteen Fmoc amino acids with protective ^{t}Boc side chain except cysteine.

All the 19 amino acid coupling products (Scheme (2)) were confirmed in the reaction mixtures by ESI Mass spectrum. During the inhibition studies, unfortunately enalapril was dominated over other dipeptide components synthesized. In continuation, they prepared another set of dipeptide amide libraries in order to probe the importance of amino acid sequence and C-terminal amide substitution on ACE binding. Amongst the dipeptides synthesized Ser-Lys,

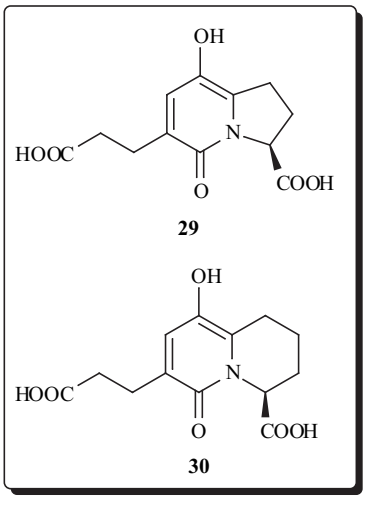


Scheme 2. Reaction conditions: (a) Fmoc-Pro-Cl, pyridine-CH_2Cl_2 (1:9), 20 h, 25°C; (b) piperidine-DMF (1:4); (c) Mixture of Fmoc-L-amino acids with ^{t}Boc side chain protection, HATU (4 equiv)/DIEA (8 equiv); (d) ethyl-2-oxo-4-phenylbutyrate in HOAc-DMF (1:99) (25 equiv), $NaBH_3CN$ (40 equiv); (e) 1N NaOH, 20 h; (f) TFA-iPr_3SiH-H_2O (95:5:5), 2 h, 25°C.

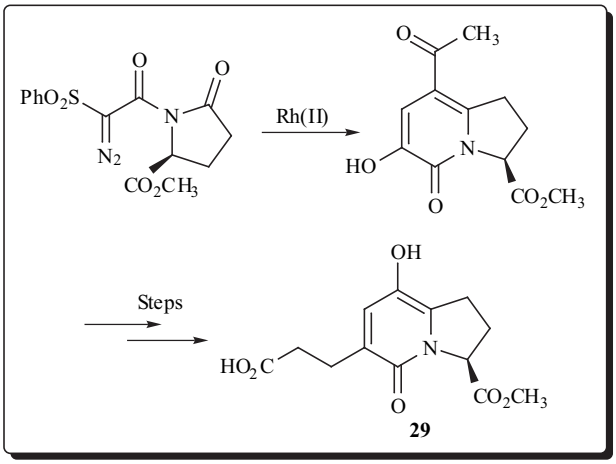
Ser-Gln, Lys-Ser and Gln-Ser were exhibited high potency towards the ACE inhibition but less active than enalaprilat and enalaprilat amide.

ACE INHIBITORS FROM NATURAL SOURCES

There are many clinically approved synthetic ACE inhibitors, which have their own side effects [48]. The search of natural products exerting ACE inhibitory activity has not yet been put much attention to the medicinal chemists. Eli Lilly laboratories isolated the 4-hydroxypyridone acids **29** and **30** from the fermentation broth of a soil bacterium *Streptomyces chromofoscus* were shown to exhibit ACE inhibitory activity at nanomolar concentrations.



Danishefsky and Fang [49] reported the total synthesis of **29** in 1989. This compound was also prepared by Moeller et al. [50] and the Clive [51] group later. Each of the synthetic routes were utilized a fundamentally different strategy. More recently (1999) Padwa and co-workers [52] established a facile route to synthesize **29** by a process based on the [3+2]-cycloaddition reaction of a phenylsulfonyl-substituted isomunchnone intermediate.



Some of the reports have shown that the fermented soybean products such as soy sauce [53] and natto [54] exhibit ACE inhibitory activity. Recently Wu and Ding [55] have reported ACE inhibitory peptides isolated from soy protein to test its hypotensive effect on spontaneously hypertensive rats (SHR) in comparison with captopril. A significant decrease in systolic blood pressure of SHR was observed. Even soy ACE inhibitory peptides were less active than synthetic drugs such as captopril. This significant finding was realized that they are contained in food taken daily and met the need for naturalness and safety. This report suggests that they could be dissolved easily in different solutions or added to other food types for functional food components since soy ACE inhibitory peptides have low molecular weight. Although the structural details regarding isolated active constituents are not clear, more interesting point to note here is the content of serum Na^+ reduced significantly with the above isolated peptide intake (tested in SHR) whereas K^+ and Ca^+ remained stable.

ANGIOTENSIN RECEPTOR BLOCKERS (ARBS)

It is evident from the clinical observations that Ang II plays an injurious role on the heart and kidney. Patients are developing higher risk of stroke or myocardial infarction with a high plasma *renin* concentration [56]. It was thought that specific blockade of RAAS might help the control on blood pressure and related diseases like CHF and chronic renal failure. This approach may overcome the drawbacks such as non-specificity and side effects (cough, angio-oedema) associated with that of ACE inhibitors. Angiotensin receptor blockers (ARBs) developed for these reasons now became the new class of drugs for the medication in hypertension and related disorder management [57]. Saralasin [^{1}Sar-^{5}Val-^{8}Ala]-Ang II **30** was the first specific peptide antagonist of Ang II and was used as a pharmacological tool. Nevertheless, the peptide has limited therapeutic value because of its poor oral bioavailability and short duration of action.

^{1}Sar-^{2}Arg-^{3}Val-^{4}Tyr-^{5}Val-^{6}His-^{7}Pro-^{8}Ala-COOH

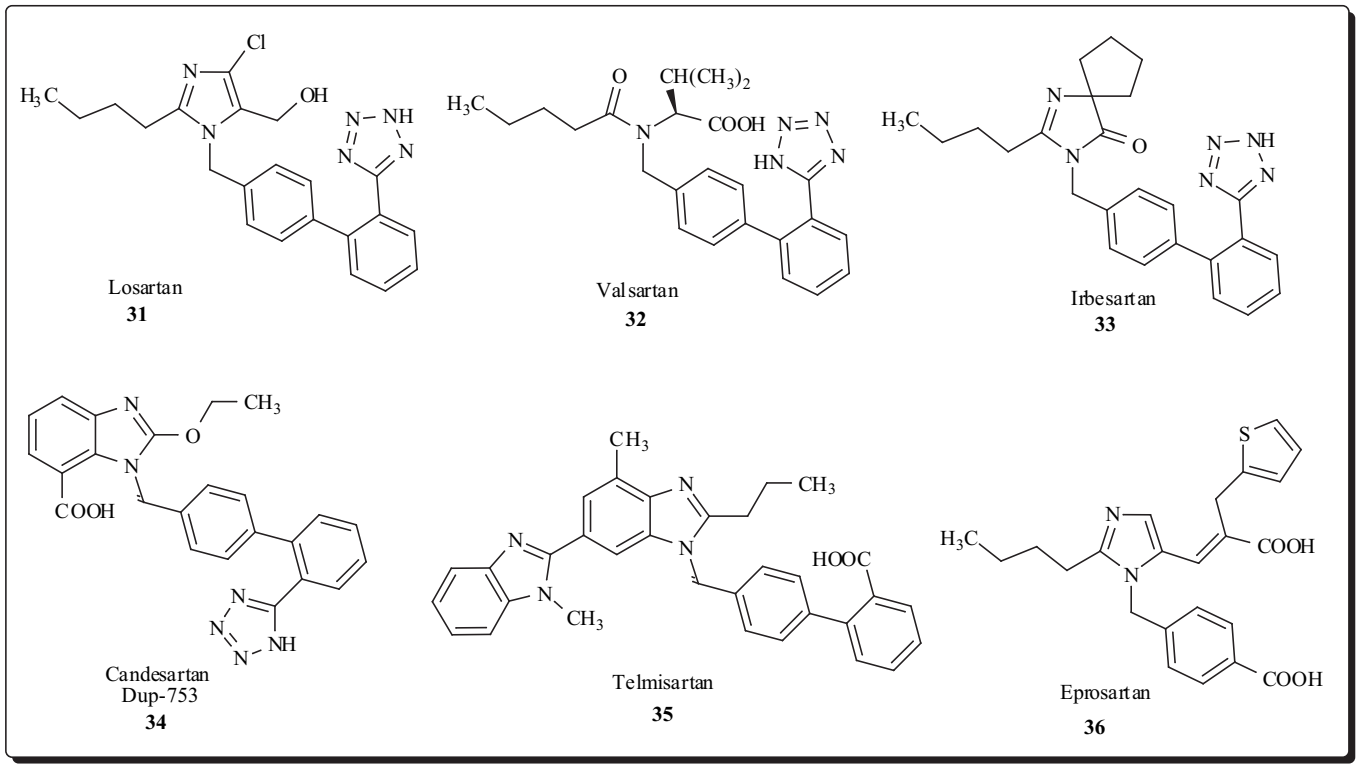
30

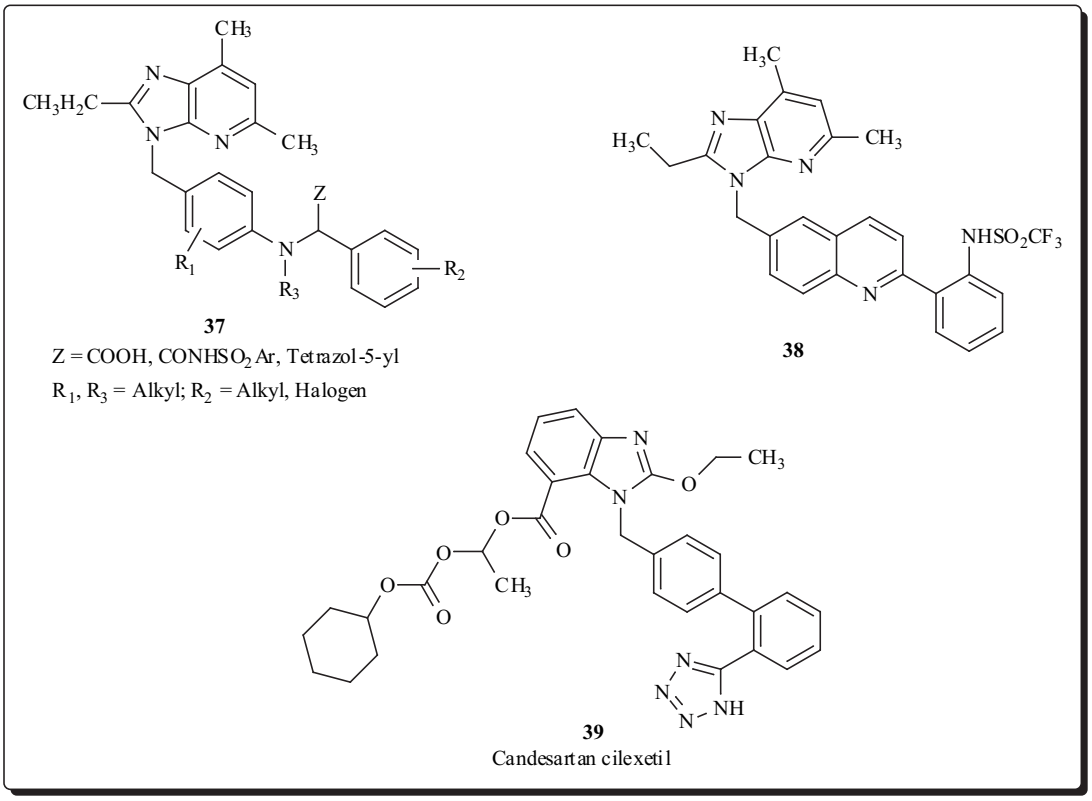
Saralasin

(Sar = Sarcosine = CH_3-NH-CH_2-CO-)

Different subtypes of Ang II receptors like AT_1, AT_2, AT_3 & AT_4 are confirmed during the development of Ang II receptor blockers [58]. A physiological function of AT_3 receptor is not clearly known and AT_2 receptor is partially understood. AT_1 receptor mediates all the known clinical effects of Ang II and physiological roles of AT_1 receptors are well documented. Various orally active ARBs have been reported up to date. FDA has already approved six of them. All these ARBs are non-peptide compounds more effectively to block the AT_1 receptor but almost no affinity towards AT_2 receptors. Development of non-peptide Ang II antagonists was considered more attraction because of lacking the disadvantages of peptide drugs. Typically, these molecules possess a nitrogen heterocycle connected to a biphenyl tetrazole by a methylene bridge as shown in losartan **31** (Dup-753) and candesartan cilexetil **38** (TCV-116) [59]. To improve the low oral bioavailability, replacement of aryl tetrazole group was an interesting route to construct effective compounds. Ang II antagonists incorporating acylsulfonamides, trifluromethane sulfonamides [60-61] and acidic heterocyclic moieties have been reported. Most of the non-peptide ARBs approved for the clinical use such as losartan **31**, valsartan **32**, irbesartan **33** and candesartan **34** are involving biphenyl-tetrazole core where as telmisartan **35** and eprosartan **36** are lacking of tetrazole moiety. These structural variations resulted in differences in their pharmacokinetic/pharmacodynamic properties, oral bioavailability, metabolism and rate of absorption and elimination. All these antagonists display a high receptor-binding property and show very slow dissociation from the receptor active site [62,63]. Irbesartan, candesartan and telmisartan are the 'insurmountable' antagonists and they associate with AT_1 receptor very firmly and dissociate from the receptor site slowly. Even under high concentration of Ang II might be unable to displace these drugs from their binding site of AT_1 receptor. Losartan, valsartan and eprosartan belong to the 'surmountable' antagonists.

The structurally distinct class of highly potent non-peptide Ang II receptor antagonists **37** were documented by Dhanoa [64]. These molecules were derived from N-substituted (phenylamino)phenyl acetic acids and acyl sulfonamides, which exhibit a high selectivity for the AT_1 receptor. This group [64] has demonstrated excellent structure-activity correlations study and revealed that the size





of the N-substitution was important for both *in vitro* and *in vivo* potency of these compounds, where as N-Et & N-Pr were found most effective. When the central and bottom phenyl rings were substituted, a loss in AT_1 and AT_2 binding affinity was observed. Replacement of carboxyl (Z = CO_2H) with acyl sulfonamide (Z = $CONHSO_2Ph$) in this series enhanced both *in vitro* and *in vivo* activity. Particularly acyl sulfonamide **39** (Z = $CONHSO_2Ph$; R_1 = R_2 = H; R_3 = Et) offers a better opportunity to develop new series of Ang II antagonists.

Morizawa and his team [65] reported a potent non-peptide, non-tetrazole Ang II receptor antagonist **38**, which carries a trifluoro sulphonamide group and a quinoline moiety as more lipophilic acidic sites. Pharmacokinetic examination demonstrated that **38** has longer $T_{1/2}$ (12.2 hr) and better bioavailability (BA) (94 %), whereas $T_{1/2}$ and BA of **39** have been reported to be 3.8 hr and 19-28 % respectively. The lipophilicity of triflamide group and a unique quinoline moiety might have increased the bioavailability of **38**.

CONCLUSION

Adequate management of blood pressure in people with hypertesion remains a major public-health challenge. It is usually achieved by the control on hypertension. Otherwise it may lead to serious cardiac failure without more intensive therapy. It generally means administration of more than one kind of antihypertensive agent. The development of individual therapeutical agents that possess the inhibition ability of angiotensin-converting enzyme (ACE) and at the same time to block the function of Ang II has been the focus of recent drug discovery program. Some of the reports claiming their success in designing the molecules with great affinity for two distinct sites called dual inhibitors (ACE/NEP inhibitors), but none of them have been replaced the existing dominating 'pril' group of ACEIs. Combinatorial drug discovery would be an ideal tool to synthesize a large number of potential potent compounds with diversity to explore their efficiency towards the hypertension. Since most of the synthetic antihypertensives accompanied with their side effects like 'save and kill,' orally active and cost effective natural product therapy such as soy bean diet is preferred in prevention or for early identified hypertesive patients. It has to be focused by pharmaceutical, food and nutrients industries.

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