IJPSR (2013), Vol. 4, Issue 2 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 30 September, 2012; received in revised form, 06 December, 2012; accepted, 18 January, 2013

ACE INHIBITORS: A COMPREHENSIVE REVIEW

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Keywords:

Hypertension, Blood pressure, Global market, Clinical trials, Recent advancements, Pharmaco-economics

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Abbreviations:

CAGR- Compound annual growth rate,
ACE- Angiotensin converting enzyme,
RAS- Renin angiotensin system,
KKS- Kallikrien system,
PCPA- Pancreatic carboxypeptidase A,
ESH- European society of hypertension,
JNC- Joint national committee,
WHO- World Health Organization,
SGO- Silicon graphics workstation,
PET- Positron emission tomography,
GPI- Glycosyl phosphatidyl inositol,
NEP- Neural endopeptidases,
COS- Chitooligosaccharides

ABSTRACT

Hypertension is a chronic increase in blood pressure, characterized as primary and secondary hypertension. The disorder is associated with various risk factors like obesity, diabetes, age, lack of exercise etc. Hypertension is being treated since ancient times by Ayurvedic, Chinese and Unani medicine. Now various allopathic drugs are available which include diuretics, calcium channel blockers, α-blockers, β-blockers, vasodilators, central sympatholytics and ACE-inhibitors. Non-pharmacological treatments include weight reduction, dietary sodium reduction, increased potassium intake and reduction in alcohol consumption. ACE-inhibitors are widely used in the treatment of hypertension by inhibiting the angiotensin converting enzyme responsible for the conversion of angiotensin I to angiotensin II (responsible for vasoconstriction). Various structure activity relationship studies led to the synthesis of ACE-inhibitors, some are under clinical development. This comprehensive review gives various guidelines on classification of hypertension, hypertension therapy including ancient, pharmacological, non-pharmacological therapies, pharmacoeconomics, historical perspectives of ACE, renin, renin angiotensin system (circulating vs local RAS), mechanism of ACE inhibitors, and development of ACE inhibitors. Review also emphasizes on the recent advancements on ACE inhibitors including drugs in clinical trials, computational studies on ACE-inhibitors, peptidomimetics, dual, natural, multi-functional ACE inhibitors, and conformational requirements for ACE-inhibitors.

HYPERTENSION: Hypertension is a chronic increase in arterial blood pressure. In general if the diastolic blood pressure is more than 80 mm/Hg and systolic blood pressure more than 120 mm/Hg the person is said to be hypertensive [1]. The Natural history of hypertension was first reported by Frederick Mahomed (1849-1884) [2]. Hypertension is categorized primarily two types viz primary hypertension and secondary hypertension.

Primary Hypertension: Primary hypertension also known as essential hypertension which is a heterogeneous disorder having different causal factors in different patients that lead to high blood pressure. It may be due to stress, high fat, high sodium diet, secondary causes such as renovascular disease, renal failure, pheochromocytoma, aldosteronism or other causes of hypertension are not present. It includes total of 95% of all cases of hypertension [3-4].

Secondary Hypertension: This is the condition of hypertension, secondary to some disorders such as renal parenchymal diseases or with disorders like pheochromocytoma, cushing's syndrome (elevated adrenal activity), primary aldosteronism, myxoedema, renal vascular disorders etc.[5].

Guidelines of Hypertension [6-7]: The hypertension is classified in accordance to ESH, JNC and WHO is listed in **Table 1**.

Etiology: Obesity, diabetes, age, race-african, americans have higher risk than caucasians, family history of high blood pressure, high normal blood pressure, high salt diet, high saturated fat diet, lack of exercise, poor physical fitness, alcoholism, stress, inactivity [8]. The pathophysiology of hypertension is shown in **figure 1**.

TABLE 1: GUIDELINES OF HYPERTENSION

GUIDELINES	ESH [27]		JNC [28]		WHO [28]	
TYPE	SYS.	DIAS.	SYS.	DIAS.	SYS.	DIAS.
Optimal	<120	<80	-	-	<120	<80
Normal optimal	120-129	80-84	<120	<80	120-129	80-84
High normal	130-139	85-89	130-139	85-89	130-139	85-89
Stage-1 Mild hypertension	140-159	90-99	140-159	90-99	140-159	90-99
Sub group borderline	-	-	-	-	140-159	90-94
Stage-2 Moderate hypertension	160-179	100-109	160-179	100-109	160-179	100-109
Stage-3 Severe hypertension	≥180	≥110	≥180	≥110	≥180	≥110
Isolated hypertension	≥140	<90	-	-	≥140	<90
Sub group border line	-	-	-	-	140-149	<90

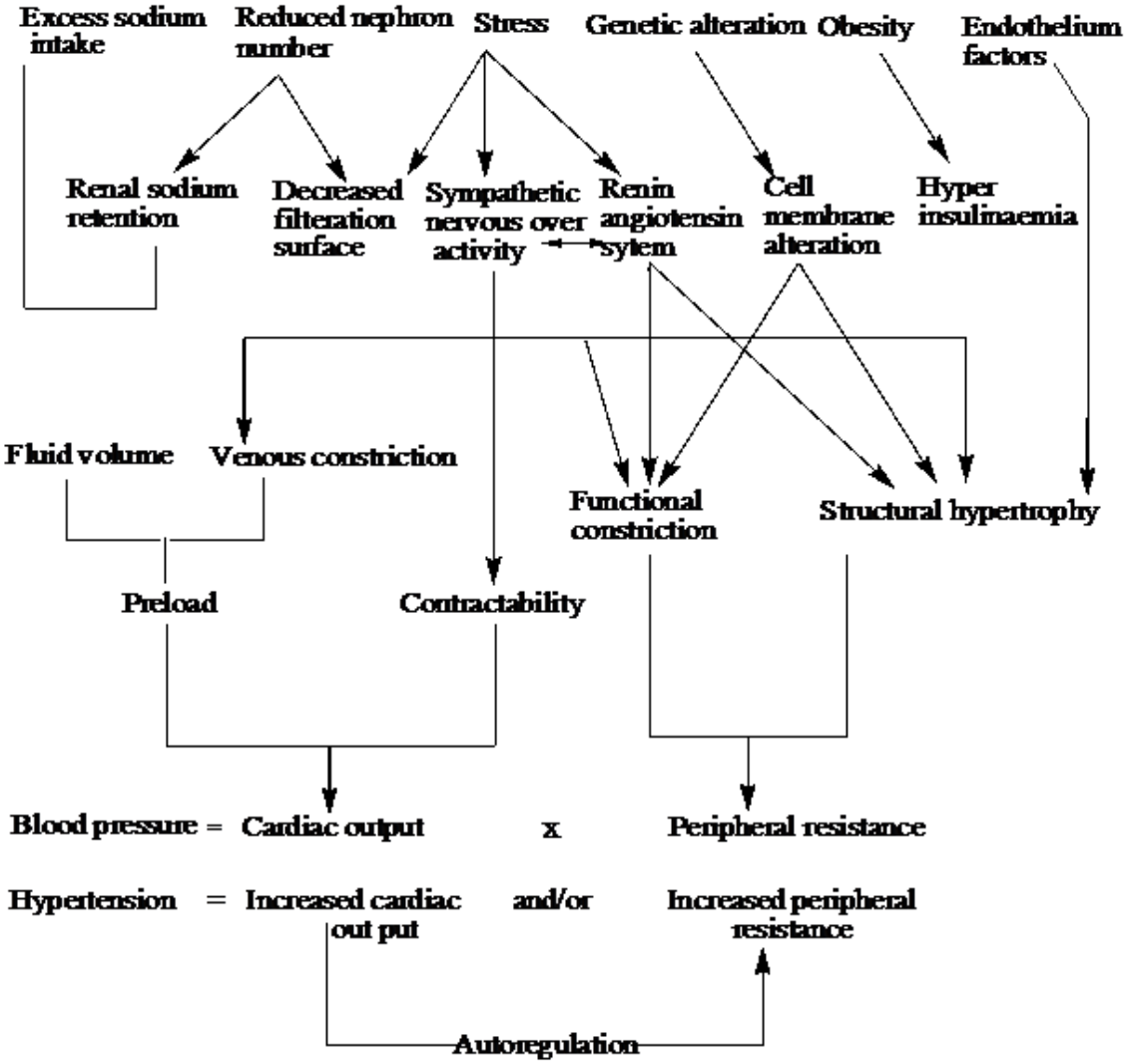


FIGURE 1: PATHOPHYSIOLOGY OF HYPERTENSION

Types of treatments available: Various types of treatments are available for hypertension:

1) Allopathic treatment
2) Ayurvedic treatment
3) Chinese treatment
4) Unani treatment

Allopathic treatment: Allopathic treatment includes various drugs belonging to different classes such as angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers, diuretics, calcium channel blockers, α-blockers, β-blockers, vasodilators, central sympatholytics [9].

Ayurvedic treatment: Various herbs reported in Ayurveda are also used for the treatment of hypertension since ancient times. Primarily herbs used for hypertension were; *Rauwolffia serpentina* (Reserpine (1)), *Ocimum gratissimum* (α-Pinene (2), Camphene (3), Myrcene (4)), *Pluchea lanceolata* (Quercetin (5)), *Terminalia chebula* (Chebulic acid (6)) [10]. Some remedies in Ayurvedic medicine are as follows:

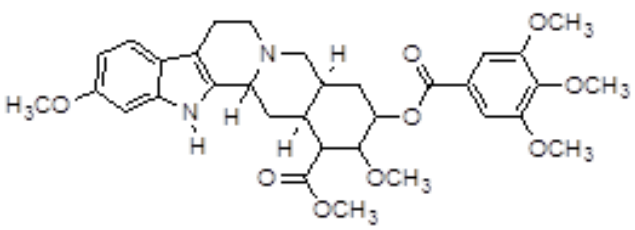
1) Including hot spices like mustard and onion in the diet.

2) Taking crushed garlic, clove with honey once or twice a week.

3) Nutmeg powder is taken with warm milk.

4) Mixture of valerian (1 part), gotu kola (1part), and 1-3g of ashwagandha taken with warm water or with ghee.

5) Other herbals include calamus, valerian, skullcap, jatamansi, black pepper, myrrh, hawthorn, berries, berryberry and cardamom used in hypertension [11].



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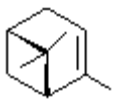

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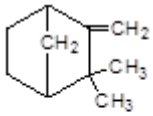

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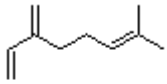

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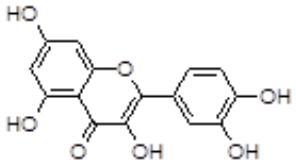

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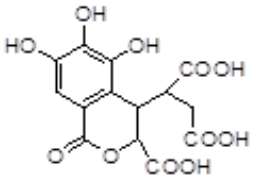

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Chinese treatment: The regimen used in chinese medicine includes tetrandra root (*Radix Stepphaniae* tetrandrae), Eucommia bark (*Cortex eucommiae*), prunella/self-heal spike (*Spica prunellae*), Chinese angelica root (*Radix angelica* sinensis) and earthworm (*Lumbricus*) [12].

Unani treatment: Different types of khamira are used for the treatment of various types of cardiovascular disorders, in particular khamira marwareed is used for hypertension. It consists of four constituents from plant origin and two constituents of animal origin [13]. The composition is given in **Table 2**.

TABLE 2: COMPOSITION OF KHAMIRA MARWAREED

INGREDIENTS	Qty.
Marwareed (*Mytilus margaritiferus*)	25g
Tabasheer (*Bambusa arundinaceae*)	25g
Sandal safaid (*Santalum album*)	25g
Ambar (*Ambra grasea*)	10g
Arq-e-gulab (*Rosa damascene*)	1Lt
Ark-e-baidmusk (*Salix caprea*)	1Lt
Quaind safaid	1.2Kg

Non-pharmacological treatment: Non pharmacological treatment include life style modifications, weight reduction, dietary sodium reduction and increase potassium intake, physical activity, reduction in alcohol consumption, a diet consist of fruits, vegetables and reduced saturated fat is suitable for the hypertensive patients. It leads to attenuate the risk of cardiovascular diseases, renal failure etc. [14].

Global Market: The share of antihypertensive drugs in the global market is $36.9 billion in 2009 with compound annual growth rate (CAGR) of 5.3% from 2001 to 2009.

The market is forecast to decline at a CAGR of -5.5% between 2009 and 2016 due to expiration of patent of some drugs [15]. The average daily cost for the consumption of antihypertensive drugs per class of medication ranges from 0.19 Ɛ for the diuretics to 0.56 Ɛ for ACE inhibitors in Germany [16].

Global market data reveals that currently there is very strong competition in the antihypertensive market. In 2009 angiotensin receptor blockers such as DIOVAN®, ATACAND®, BIOPRESS®, AVAPRO® were dominant among all the antihypertensives used. A total of 60% of global antihypertensive market was dominated by agents acting on renin angiotensin system among them angiotensin receptor blocker alone accounted for 42.6%. The second most prescribed antihypertensive drugs are β-blockers account for approximately 30% of the global antihypertensive prescription volume and the third leading therapeutic class of antihypertensives is diuretics which accounts for 17% of the total antihypertensive prescription.

Diuretics are the most cost effective drugs and are less prescribed as compared to angiotensin receptor blocker and ACE inhibitors. In 2009 diuretics covered 30-40% of the global antihypertensive market [17].

Angiotensin Converting Enzyme (ACE) Inhibitors: ACE inhibitors are the drugs which lowers the increased blood pressure by inhibiting the angiotensin converting enzyme responsible for the conversion of angiotensin I to angiotensin II. Angiotensin II is a vasoconstrictor causes to increase in blood pressure. ACE inhibitors prevent the progression of renal disease by causing a reduction in angiotensin II mediated intraglomerular pressure [18].

Therapeutic dimensions of ACE inhibitors: In 1970s, the interruption of Renin Angiotensin System (RAS) by pharmacological therapy was considered beneficial for patients with high renin hypertension due to lowering of increased blood pressure. This has led to the development of ACE inhibitors. Presently ACE inhibitors have significant role in the treatment of myocardial infarction, hypertension, diabetic and diabetic complications. These drugs can be combined safely with angiotensin receptor blockers, calcium channel blockers and thiazide diuretics with varying degree of beneficial effects [19].

The renin angiotensin system and the kallikrein system (KKS) originated in late 19th century. Skeggs et al. reported that in horse plasma renin liberates a decapeptide called angiotonin now called angiotensin I which is converted to angiotensin II in the presence of chloride ions by a factor which was later named angiotensin converting enzyme [20].

Studies of substrate and inhibitors of ACE show that ACE peptidase is a similar carboxypeptidase to pancreatic carboxypeptidase A (PCPA). Pancreatic carboxypeptidase A has two binding sites a zinc binding site and a cationic binding site. On the basis of this study ACE also have those two important binding sites although some other auxiliary binding sites may also exist [21].

Renin: Lumbers in 1971 reported that amniotic fluid at low pH in cold has renin activity. Renin is an enzyme comes under aspartic proteases. Renin shows remarkable specificity for its only substrate angiotensinogen due to monospecific nature [22]. The primary structure of renin precursor consist of 406 amino acids with a pre and pro segment carrying 20 and 46 amino acids respectively mature renin contains 340 amino acids and has a mass of 37kDa [23]. Renin includes two homologous lobes where the active site is present in the deep cleft located between the two lobes.

Seven amino acids units of the substrate (angiotensinogen) are accommodated in the active site. Renin cleaves the Leu-Val peptide bond with in substrate to form angiotensin-I. Renin is produced from an enzymatically inactive precursor prorenin after activation; activation of prorenin can be achieved by proteolytic and non- proteolytic. Proteolytic activation occurs in juxtaglomerular (J.G.) cells of kidney includes removal of pro-peptide chain [24-25].

Angiotensin Converting Enzyme: ACE is found in the microvillar structure of proximal tubules and also of small intestine placenta and choroids plexus in higher concentration [20]. It is a dipeptidylpeptidase trans membrane bound enzyme originally isolated from horse blood [26]. Proteolytic cleavage of its COOH-terminal leads to the soluble form of angiotensin converting enzyme in membrane bound form. ACE exists in two distinct forms testicular and somatic.

Both these forms are transcribed from a single gene but at different initiation sites. Testicular form of ACE is a protein (100-110 kDa) having a single catalytic domain corresponding to similar COOH-terminal of somatic ACE. Somatic form is a protein (150-180 kDa) synthesized by the vascular endothelium and by several neural and epithelial cell types having two identical catalytic domains and a cytoplasm tail [27-28].

Renin Angiotensin System: Pathogenesis of hypertension depends on the renin angiotensin system. Angiotensin II is the final product of this pathway. The whole cascade begins with renin (**figure 2**).

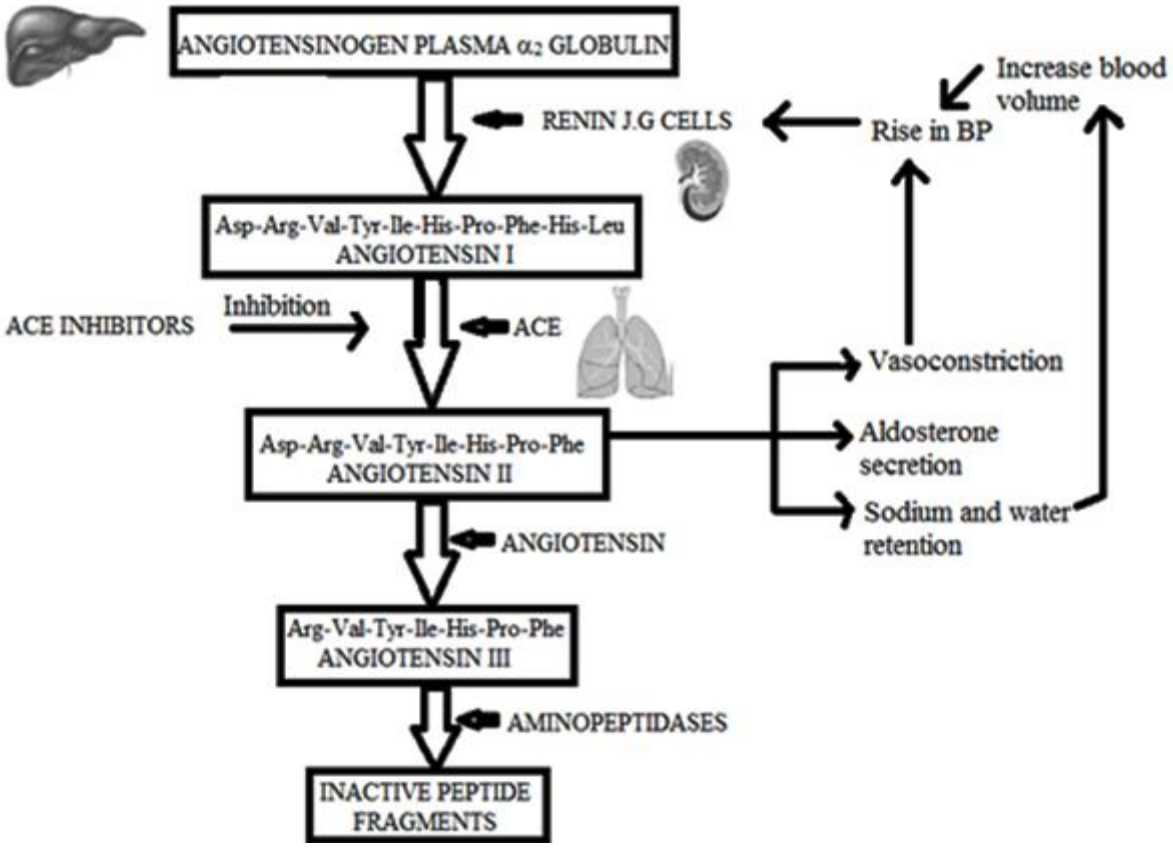


FIGURE 2: PHYSIOLOGICAL REGULATION OF ELECTROLYTE BALANCE, PLASMA VOLUME AND BLOOD PRESSURE BY THE RENIN ANGIOTENSIN SYSTEM [30-31]

Angiotensinogen is cleaved by renin into angiotensin I (Ang I). This is further acted by the angiotensin converting enzyme to produce angiotensin II (Ang II). Angiotensin binds to the different angiotensin-II receptors AT-1 and AT-2 and shows its different actions. Both these receptors when activated by angII show different significant actions.

AT-2 is responsible for most of the physiological actions like vasodilatation whereas AT-1 receptor mediate the vasoconstrictive actions. The two subtypes of angiotensin receptor-1 have been recognized in rat and mouse AT-1a and AT-1b. In humans AT-1b receptor is identified, the other two subtypes are found to be identical but produced from two distinct genes which are expressed and regulated differently [29].

Role of AT-1 Receptor: AT-1b receptor is responsible for dipsogenic response to angiotensin II in the central nervous system. Whereas vascular tone and sodium resorption is regulated by AT-1a in periphery it also regulates pressor responses to angiotensin II in the CNS. There are two types of renin angiotensin system found in human circulating and local renin angiotensin system.

Circulating vs local RAS:

1. **Circulating RAS (C-RAS):** Circulating renin angiotensin system is found in plasma and mediates the action of renin on angiotensinogen cleavage to angiotensin in plasma via systemic circulation.

Renin is originated from kidney and transported to pulmonary vasculature, angII formed is conveyed to peripheral tissues via the circulatory system.

2. **Local Renin Angiotensin System:** Tissue renin angiotensin system is a local angiotensin generating system that found in the tissue is capable of generating action of angII. Tissue RAS is found in many organs including the heart brain pancreas kidney adipose tissue gonads [29].

Classification of ACE inhibitors: The drugs of this class are divided in to five sub classes as given below:

1. Sulfhydryl (-SH) containing analogs [32].
2. Carboxyl (-COOH) containing analogs [32].
3. Phosphoryl (-PO_2) containing analogs [32].
4. Hydroxamic non amino acid derivatives [33].
5. Peptides [34- 36].
6. Peptidomimetics [37].

The potency of the drugs depends on the affinity of the various drugs towards the zinc binding site. The carboxyl group containing derivatives tends to be most potent of the five classes. Also the ACE inhibitor activity also increases with increase in the lipophillicity. On this basis ACE inhibitors may be broadly categorized into either tissue affinity or serum-affinity groups.

Structure of Angiotensin Converting Enzyme: X-ray crystallography studies of angiotensin converting enzyme and carboxypeptidase A have shown that ACE has binding site similar to that of pancreatic carboxypeptidase A and other auxiliary binding site [38] (**Fig. 3, 4**).

Ferreira *et al.,* in 1965 reported teprotide **(7)** which is isolated from venom peptide of Pit viper (*Bothrops jaraca*) [39] has the best duration of ACE inhibitory activity *in vivo*, the first ACE inhibitor to be studied was the teprotide, which shows useful blood lowering activity but its lack of oral activity limited its therapeutic use. SAR studies using synthetic venom peptide analogs improved the understanding of active site of ACE. The optimal carboxy terminal amino acid sequence of inhibitor for binding to the ACE was Phe-Ala-Pro.

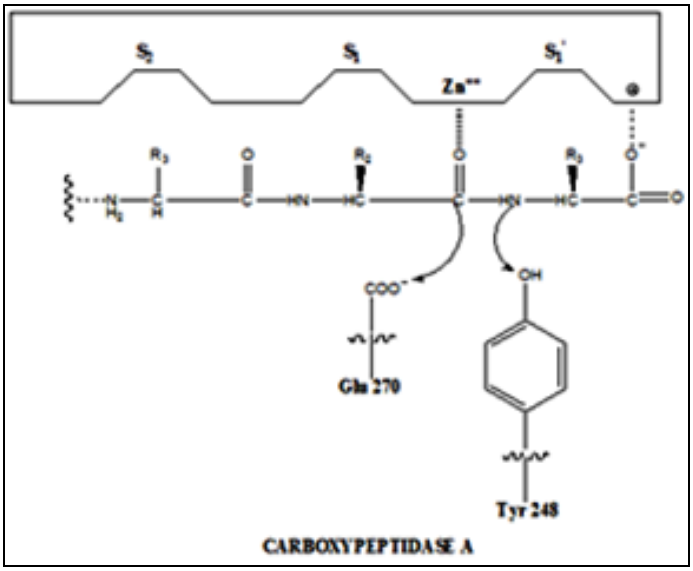


FIGURE 3: THE KNOWN ACTIVE SITE OF CARBOXYPEPTIDASE A, AND A HYPOTHETICAL MODEL OF THE ACTIVE SITE OF ACE. Sub sites S1, S2 and so on are areas or pockets in the structure of each enzyme that interact with adjacent side-chains of amino-acid residues of an enzyme-bound peptide substrate. Functional groups participate in catalysis of peptide bond cleavage. X–H is a postulated hydrogen bond donor. In the known structure of the active site of carboxypeptidase A, the carboxylate, phenolic and positively charged groups are Glu270, Tyr248 and Arg145, respectively [38]

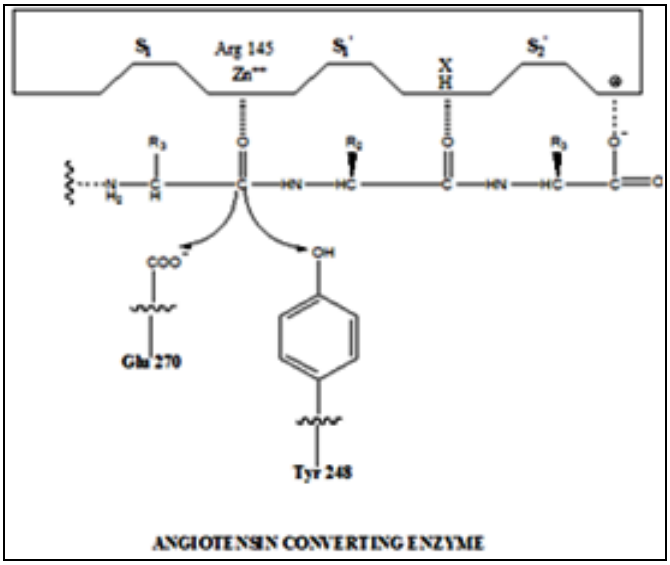
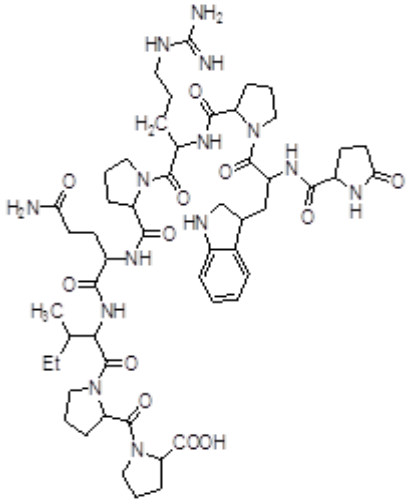


FIGURE 4: PROPOSED ACTIVE SITE BINDING OF ACE BY A VENOM PEPTIDE INHIBITOR OR BY SUBSTRATE WITH TERMINAL SEQUENCE PHE–ALA–PRO, BY SUCCINYL AMINO ACIDS, AND BY CAPTOPRIL

The side chains on these three amino acids were assumed to interact with sub sites and pockets at the active site [33]. David and Miguel proposed a new ACE inhibitor called benzylsuccinic acid **(8)**, which is not a potent inhibitor of ACE but provide important breakthrough for the further development of ACE inhibitors.



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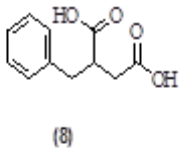

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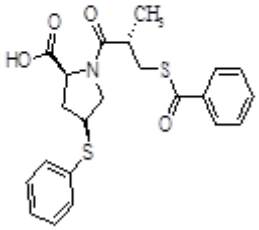

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Extensive SAR studies of ACE inhibitors suggested that 2-methylsuccinyl-l-proline (**Fig. 5**) was optimal for binding to ACE increase in the length of side chain by adding another methyl to succinic acid did not enhance the activity over the succinic acid derivative 2-*d*-D-methylglutaryl-*L*-proline.

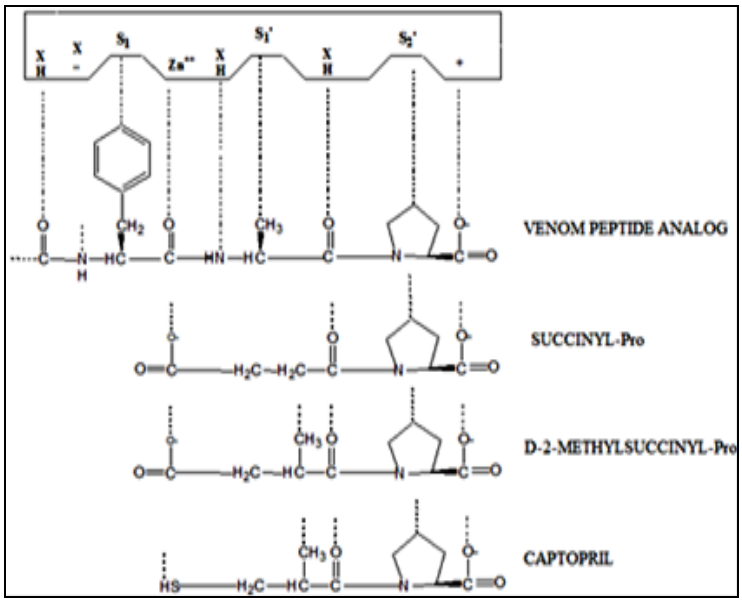
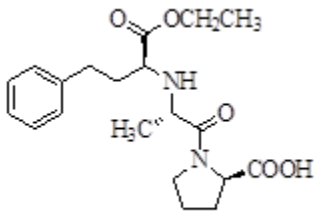


FIGURE 5: DESIGN OF CAPTOPRIL

Another modification is the replacement of the carboxyl group by a mercapto group which led to a dramatic improvement of the ACE inhibitor activity and produced the first marketed drug Captopril (IC_{50} 23nM) [40]. Another sulfhydryl drug is Zofenopril **(9)** (IC_{50} 8nM) which is more potent than Captopril [41].



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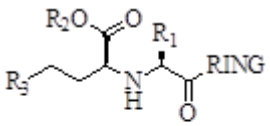

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ENALAPRIL ANALOGUES **GENERAL STRUCTURE**

SAR of Enalapril analogs (**Table 3**):

1. To enhance the potency over the captopril analogs modifications has been done that leads to the development of Enalapril **(10)** with IC_{50} 5.5nM and its analogs with general structure **(11)** (carboxyl group containing).

2. Cyclic amino acids e. g. proline gives better activity. The cyclic nature of proline provides steric hindrance to amide bond hydrolysis and allows for therapeutic utility (Lisinopril).

3. The side chain methyl group is responsible for the hydrophobic interaction and the carbonyl oxygen involved in hydrogen bonding.

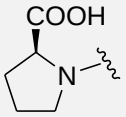
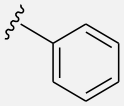
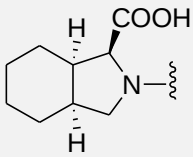
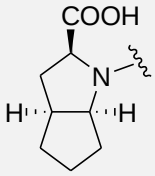
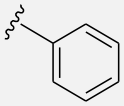
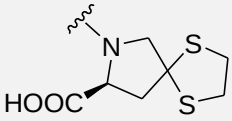
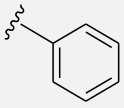
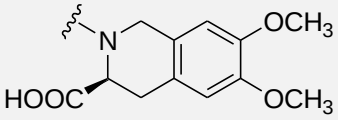
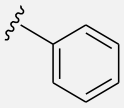
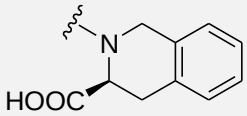
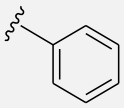
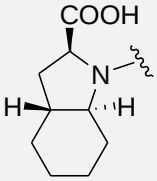
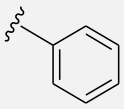
4. The substitution of amino butyl group in place of methyl group gives compound with increase oral bioavailability. e.g. Lisinopril (IC_{50} 4.7nM)

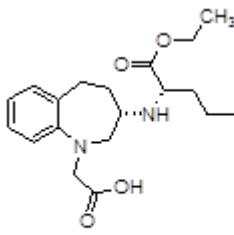
5. Ring replacement with five or six membered ring gives new compounds with increased activity. e.g. Cyclopentane (Ramipril) IC_{50} 4.0nM.[40]

6. Ring replacement with tetrahydroisoquinoline gives more potent compound than enalapril e.g. Moexepril (IC_{50} 2.6nM) [26].

7. Ring replacement with indole gives the active compound Perindopril (IC_{50} 1.44nM) [42]. Various other carboxyl containing analogs are Benazepril **(12)** (IC_{50} 1.7nM), Cilazapril **(13)** (IC_{50} 1.93nM), Delapril **(14)** (IC_{50} 40.0nM) [47], Alacepril **(15)**, Temocapril **(16)** (IC_{50} 3.6Nm) [48].

TABLE 3: STRUCTURE ACTIVITY RELATIONSHIP OF ENALAPRIL ANALOGS

DRUG	RING	R_1	R_2	R_3	IC_{50}
Lisinopril [42]		$-(CH_2)_4NH_2$	$-H$		4.7nM
Pirindopril [42]		$-CH_3$	$-CH_2CH_3$	$-CH_3$	1.44nM
Ramipril [42]		$-CH_3$	$-CH_2CH_3$		4.0nM
Spirapril [42]		$-CH_3$	$-CH_2CH_3$		16µg
Moexepril [42, 43]		$-CH_3$	$-CH_2CH_3$		2.6nM
Quinapril [44, 45]		$-CH_3$	$-CH_2CH_3$		8.3nM
Trandolapril [46]		$-CH_3$	$-CH_2CH_3$		0.9nM



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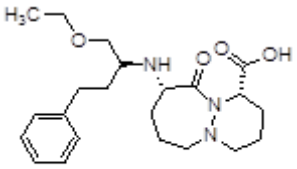

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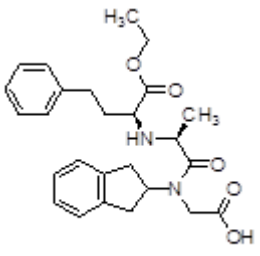

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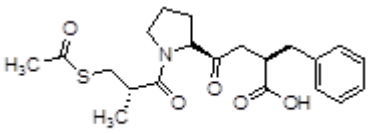
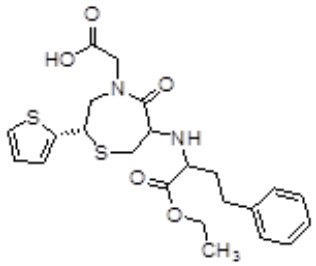


(15)



(16)

Phosphoryl containing Analogs: In phosphorous containing analogs, the zinc binding site groups has been replaced with phosphorous containing groups *i.e.* Phosphinyl group (O=P-OH). The optimal distance is maintained to both the cationic site with the carboxyl group of proline and with the anionic hydroxyl of the phosphinyl group (O=P-OH) to the zinc binding site.

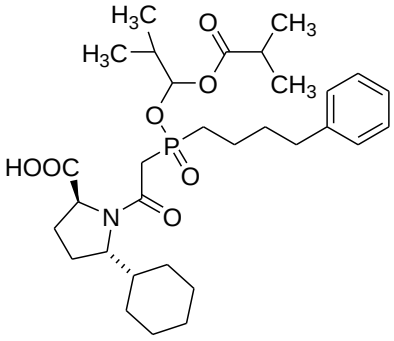
The size of the phosphorous atom is critical for maintaining the appropriate distance [40] e.g. Fosinopril **(17)**, [[Hydroxy(4-phenylbutyl)phosphinyl]acetyl]-*L*-proline **(18).**

Hydroxamic Non Amino Acid Derivatives: Idrapril **(19)** is a prototype drug of this novel class of ACE inhibitors consists of non peptidomimetic structure with a hydroxamic group and having a similar pharmaco-logical profile to Captopril. It shows short elimination half-life of 2 hours and has a much longer effect on RAS and blood pressure (12-24 hrs), without affecting heart rate [49].

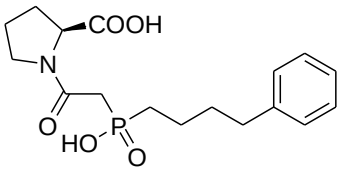
Other ACE inhibitors:

1. **RXPA 380:** RXPA 380 **(20)** is a testis ACE inhibitor. The conformation in the central backbone is much similar to the captopril than enalapril. The RXPA 380 compound occupies more active sub sites of the testis ACE than the previously determined inhibitor ACE inhibitor complexes and possess the bulkier moieties that extend in to the S_2 and S_2 [50].

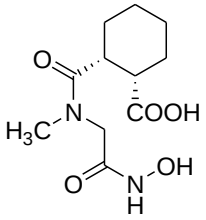
2. **RXPA 407:** RXPA 407 **(21)** is new synthetic phosphine peptides which have been tested for their ability to inhibit ACE exhibiting remarkable preference for only N-domain. RXPA 380 inhibit 3000 fold preferentially at the C-domain active site while the RXPA 407 has 1000 fold higher affinity for the N-domain active site [51-52].



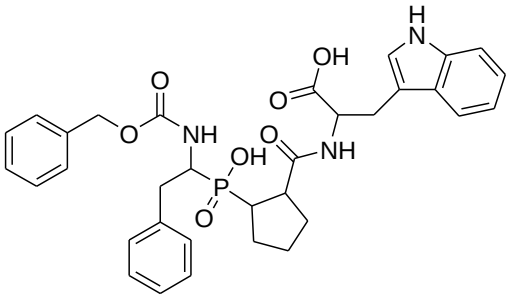
(17)



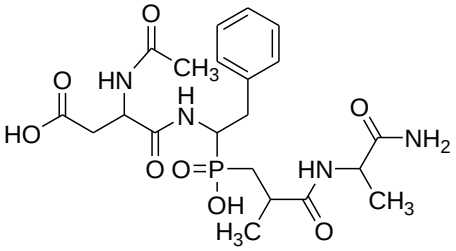
(18)



(19)



(20)

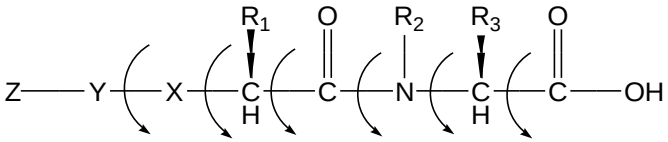


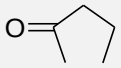
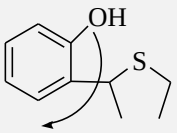
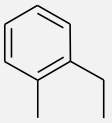
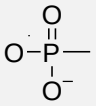
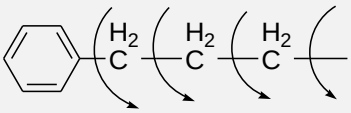
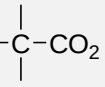
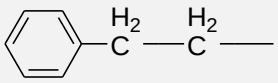
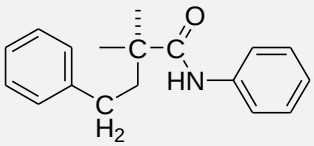
(21)

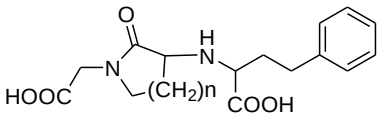
Computational studies of ACE inhibitors: Andrew *et al*., in 1985 used classical potential energy calculations using COMOL program (pairwise summation of vanderwaal's interactions between non bonded atoms together with electrostatic torsional potentials) to find the conformational analysis of few ACE inhibitors These calculations define the structurural and conformational requirements for binding to the active site of ACE (**Table 4**) which are useful for the further designing of ACE inhibitors [53]. Certain other conformational aspects for the ACE inhibitors is described by E D Thorsette, a series of ACE inhibitors in which alanylproline of enalapril was replaced by monocyclic lactam rings.

Molecular mechanics was used for investigations of model lactams. A correlation was established between inhibitor potency and computed angles (ψ) for the lowest energy conformations of model compounds. The compounds **(22-26)**, show good correlation of ring size with IC_{50} (**table 5**). More polar isomer II shows maximum inhibitory potency for the 6-7 member rings [54].

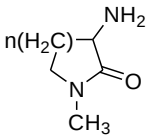
TABLE 4: STRUCTURE ACTIVITIES AND CONFORMATIONAL VARIABLES OF ACE INHIBITORS STUDIED



COMPOUND	Z	Y	X	R_1	R_2 or R_3	IC_{50} (M)
Captopril	–	–				**$2x10^{-8}$**
5-Oxocaptopril	–	–				**$9x10^{-9}$**
SA446	–	–				**$6.5x10^{-8}$**
WY44221	–	–				**$3.7x10^{-9}$**
A	–					**$1.4x10^{-9}$**
MK422						**$1.2x10^{-9}$**
B						**$0.5x10^{-9}$**
C						**$3.2x10^{-9}$**



(22-26)



(A-E)

n = 1-5

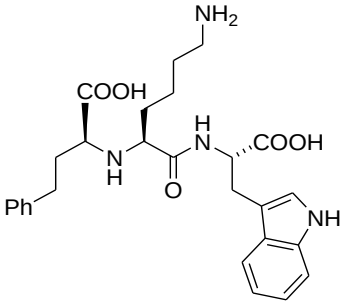
COMPOUND	n	RING SIZE	IC_{50} (iso I)[a]	IC_{50} (iso II)[a]	(MODEL)[b]	$\Psi_{CALC.}$	$\Psi_{X\text{-}RAY}$
22	1	5	$1.2x10^{-5}$	$1.9x10^{-5}$	A	-132	-
23	2	6	$4.3x10^{-7}$	$1.7x10^{-6}$	B	-138	-
24	3	7	$7.0x10^{-7}$	$1.9x10^{-8}$	C	166	166
25	4	8	$1.7x10^{-6}$	$4.8x10^{-9}$	D	145	159
25 (S,S)	4	8	-	$2.0x10^{-9}$	-	-	-
25 (R,R)	4	8	-	$9.2x10^{-8}$	-	-	-
26	5	9	$1.3x10^{-6}$	$8.1x10^{-9}$	E	135	-
ENALAPRIL	-	-	$1.2x10^{-9}$		-	140	143

[a]IC_{50} conc. In molar. Iso. I is the first diester isomer to elute from silica gel and II is the second model lactam is used to obtain Ψ_{calc}

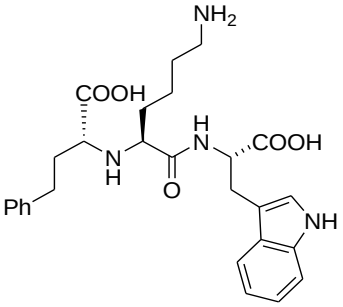
Molecular modeling study revealed that hydrophobic and hydrogen bonding interactions with residue of C-domain of S_2 subsite are found to be important for ACE inhibition activity. X-ray crystal structure of testes ACE complex with inhibitor of Lisinopril and homology model structure of N-domain were considered first. Molecular docking calculations were performed using DISCOVER module of INSIGHT II on a silicon graphics octane 1 (SGO-1) workstation. Few compounds were synthesized and bio evaluated one of the compound **(27a)** shows excellent selectivity over N/C-domain. The P_2' tryptophan moieties of compounds **(27a)** and **(27b)** demonstrated additional hydrophobic and hydrogen bonding interactions with S_2' residues Thr282,Val379, Val380 and Asp453 of the C-domain active site and may thus explain the increased C-domain selectivity of these compounds as compared with lisinopril.

Docking experiments reveals that the potential energy of the complex of compound **(27a)** with C-domain is far better than N-domain. This is in agreement with the observed biological inhibiting binding affinity i.e. selectivity of compound **(27a)** [55]. Another group of scientist considered isosteric replacement of carboxylate with phosphate functional group. Carbon phosphorous bonds were more stable and resist hydrolytic cleavage. K-26 **(28)** a phosphonotripeptide is an α-amino phosphonic acid analogue of tyrosine with IC_{50} value of 4.4nM. Eight analogues were synthesized and bio evaluated. Replacing the phosphonic acid group with carboxylic analogue leads to 1500 fold increase in activity [56].

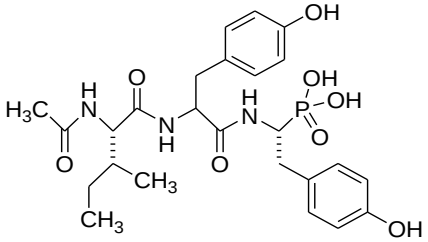
A new validated ACE inhibitors pharmacophore hypothesis developed from the biologically active (frozen) conformation of Lisinopril-Human ACE complex using stepwise technique of CATALYST module. This module was used to design a series of new 3-mercapto-2-methyl-propanoyl-pyrrolidine derivatives. Introduction of mercapto functional group, p-methoxybenzyl moiety and substituted imino functional group on to the pyrrolidine ring system gives essential lipophilic pharmacophore to the compounds, in addition to these functional groups like H-bond acceptors, hydrophobic features and negative ionization potential were used as chemical features.



(27a)



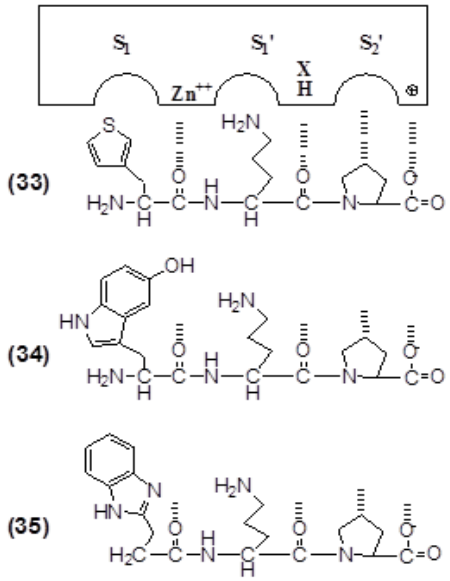
(27b)



(28)

Molecular simulation studies shows that the pyrrolidine derivatives have tendency to inhibit ACE, therefore considered as active antihypertensive hits. On these basis best pyrrolidine derivatives like **(29-32)** were selected as hit compounds for ACE inhibition [57]. Peptidomimics approaches has been used to discover new ACE inhibitor in the recent past, several groups across the globe have tried different types of peptides, consisting of non peptides moieties like unnatural amino acids or carboxylic acid derived heterocyclics conjugated with peptide moiety. Peptides containing particularly proline [58], have better bioavailability as they resist to proteolysis by digestive enzymes [59]. Two sets of libraries containing lysine and ornithine with proline as a common moiety were designed and synthesized in the designing of dipeptide motif, usual amino acid that is, proline is put at P_2' position. While P_1' position is occupied by usual (e.g. lysine) or unusual (e.g. ornithine) amino acids at the P_2' position, the $-COO^-$ group of proline is likely to interact with a positively charged side chain of arginine (or lysine) in the S_2' subsite of ACE. The S_1' subsite being hydrophobic in nature, preferentially accepts linear amino acids like lysine or ornithine for better interaction at the position P_1' unnamed amino acids and carboxylic acid derived heterocyclic moieties are incorporated to interact with S_1 subsite and Zn^{2+} ion located in the enzymes active site. ACE inhibiting potency of three peptidomimics *N*-methyl-*L*-tryptophan-orn-pro **(33)**, 5-hydroxy-*L*-tryptophan-orn-pro

(34), 2-benzimidazolepropionic acid-orn-pro **(35)** and containing heterocyclic moiety was found significant with IC_{50} values 6 x 10^{-7}, 4 x 10^{-6} and 10 x 10^{-6} M respectively [37]. The result of this study indicates that the ornithine has important role in tripeptidomimics to effectively inhibit the ACE activity.

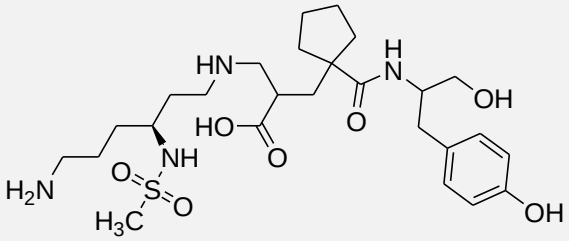
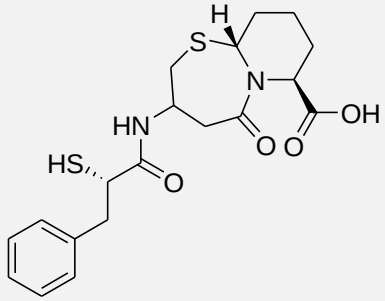
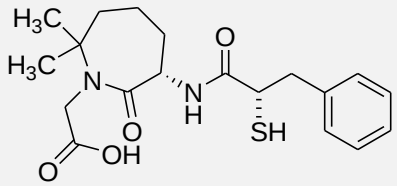


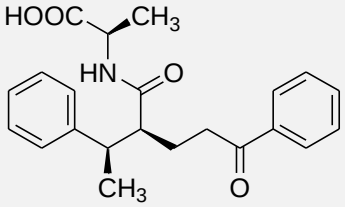
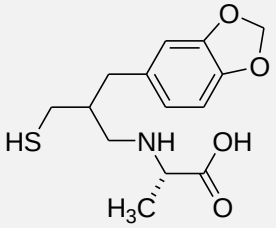
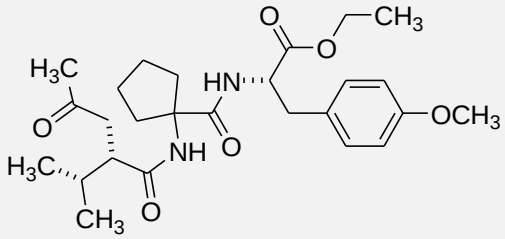
BINDING INTERACTION OF TRIPEPTIDOMIMETIC TO THE ACTIVE SITE OF ACE

Drugs In Clinical Trials (**Table 6**): Teprotide **(7)** a nonapeptide is the first ACE inhibitor isolated from viper venom rejected in clinical trial due to lack of oral bioavailability [39]. Thiorphan enantiomers **(36)** [IC_{50}(R) 860nM, IC_{50}(S) 140nM] are dual inhibitors of ACE and Neuroendopeptidases (NEP). SCH39370 **(37)** is an ACE inhibitor has (IC_{50} >1000nM). UK-69578 **(38)** (Candoxatrilat) with (IC_{50} 28nM) has discontinued from phase III clinical trials.

Fasidotril **(39)** is a dual inhibitor of ACE while its metabolite Fasidotrilat in phase III clinical trials is a potent inhibitor of ACE (K_i = 9.8nM) and NEP (K_i = 5.6nM) derived through modification of thiorphan **(36)**, Omapatrilat **(40)** having IC_{50} 5nM and 8nM for ACE and NEP activity. Omapatrilat and Sampatrilat **(41)** are in phase III and phase II clinical trials respectively. Another ACE inhibitor CGS 30440 **(42)** in clinical trials have (IC_{50} 12nM) for ACE and (IC_{50} 63nM) for NEP [60].

TABLE 6: COMPOUNDS IN DIFFERENT PHASES OF CLINICAL TRIALS

COMPOUND	STRUCTURE	IC_{50} (nM)		COMPANY	STATUS
		ACE	NEP		
Sampatrilat		**1.2**	**8**	**Pfizer**	**Halted in Phase II**
Omapatrilat		**5**	**8**	**Bristol-Myers Squibb**	**Failed in Phase III**
Gemopatrilat		**3.6**	**305**	**Bristol-Myers Squibb**	**Preclinical**

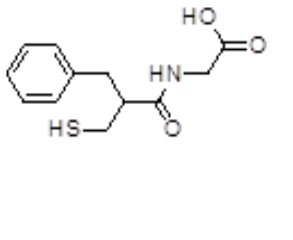
Mixanpril (S21402)		**4.5**	**1.7**	**_**	**Preclinical**
Fasidotrilat		**9.8**	**5.6**	**Eli Lilly**	**Phase II**
CGS30440		**19**	**2**	**_**	**Preclinical**

Recent Advancements: Kondoh *et al*., proposed that a novel glycosyl phosphatidyl- inositol (GPI)-anchored protein releasing activity of ACE by cleaving mannose-mannose linkage site. Tightly bound ACE inhibitors weakly inhibit the GPIase activity and not inactivated by substituting the core amino acid residue necessary for peptidase activity. Ignacio's studies suggested that neither of the both peptidase catalytic domains of ACE GPIase activity therefore in addition to its classical catalytic domain ACE may have other novel active catalytic domain [25].

Dual Inhibitors of ACE and Neural Endo Peptidase (NEP): Neural endopeptidase (NEP) is a zinc metalloproteinase which is very much similar to ACE, responsible for the degradation of angiotensin-I, bradykinin and various natriuretic peptides. Therefore, simultaneous potentiation of atrial natriuretic peptide via NEP inhibition and attenuation of angiotensin II via ACE inhibition leads to complementary effects in the control of hypertension and congestive heart failure (CHF) [51, 61].

Omapatrilat: One of the most advanced peptidomimetic of dual ACE/NEP inhibitors in development, a bicyclic thiazepinone analogue. Additional testing has been requested by FDA due to increasing angioedema [51, 61]. Various dual ACE/NEP inhibitors are Fasidotrilat **(43)** and Sampatrilat.

Chalcones and Heterocyclics: A chalcone, 3-(3-amino-4-methoxyphenyl)-1-(3,4,5-trimethoxyphenyl-prop-2-en-1-one **(44)** (IC_{50} 0.219mM) and a pyrazole derivative 4,5-dihydro-5-(4-methoxy-3-nitrophenyl)-3-(3,4,5-trimethoxyphenyl)-1-methyl-1*H*-pyrazole. **(45)** (IC_{50} 0.213mM) have been designed and synthesized. IC_{50} values shows that the following two compounds have promising ACE inhibitor activity [62].



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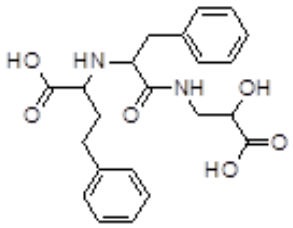

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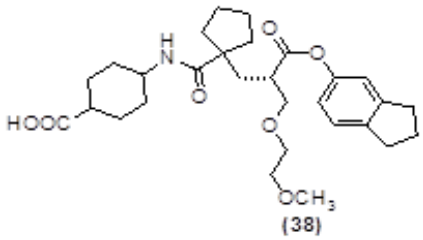

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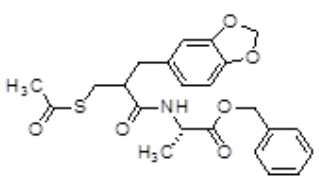

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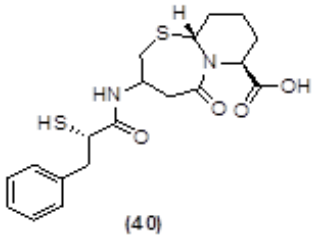

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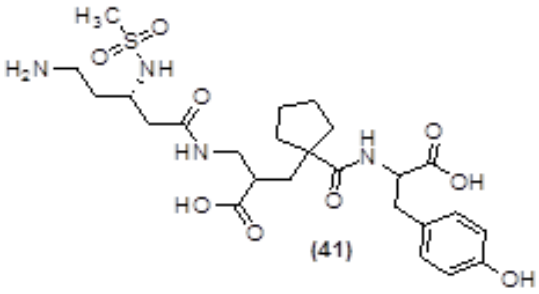
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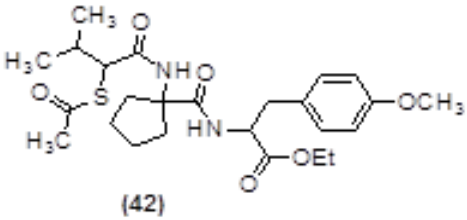
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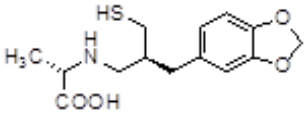
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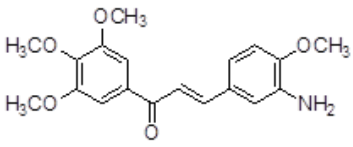
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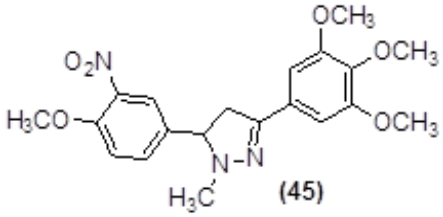
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ACE inhibitors derived from plants: Kaempferol-3-*o*-*β*-galactopyranoside, a flavanoid isolated from *Ailanthus excelsa* of family simaroubiaceae with IC_{50} value 260µM [63].

ACE inhibitors derived from Marine sources: There are various structurally diverse bioactive compounds derived from marine resources like chitooligo-saccharides derivatives (COS) and phlorotannins have potent ACE inhibitory activity [64]. The aminoethyl derivative of chitooligosaccharide (AE-COS) have IC_{50} value 0.8017 µg/ml [65].

Bioactive Peptides: Chitin is a glycan of *β* (1→4) linked *N*-acetyl glucosamine units, widely distributed in protective exoskeleton of crustaceans and insects. Chitooligisaccharides such as hetero chitooligo-saccharides, amino ethyl chitooligo-saccharides, chitin derivatives chitosan trimer oligomers and carboxylated chitooligosaccharides have been reported as possessing potent ACE inhibitor activity [66].

Phlorotannin: Phlorotannins are the phenolic compounds which are formed by the polymerization of phloroglucinol or called as 1, 3, 5-trihydroxybenzene monomer units[67]. The IC_{50} value of Phlorofucofuroeckol A (Phlorotannin) is 12.74µM, obtained from marine brown and red algae [68].

ACE inhibitory peptides: (**Table 7**)

TABLE 7: ACE INHIBITORY PEPTIDES

PEPTIDES	IC_{50}
Arg-Val-Pro-Ser-Leu **(46)**	20µM
Val-Tyr-Ala-Pro **(47)**	6.1µM
Val-Ile-Ile-Phe **(48)**	8.7µM
Met-Ala-Trp **(49)**	16.32µM
Ala-Val-Phe **(50)**	-
Ala-Gln-Gly-Glu-Arg-His-Arg **(51)**	47.01µg/ml
Leu-Gly-Pro **(52)**	0.72µM
Ala-Gly-Ser **(53)**	0.13±0.03mg/ml
Phe-Ala **(54)**	-
Leu-Arg-Pro-Val-Ala-Ala **(55)**	4.14µM
Ile-Pro-Pro **(56)**	-
Val-Pro-Pro **(57)**	-
Val-Glu-Cys-Tyr-Gly-Pro-Asn-Arg-Pro-Gln-Phe **(58)**	29.6µM
Met-Ile-Phe-Pro-Gly-Ala-Gly-Gly-Pro-Glu-Leu **(59)**	28.7µg/ml
Ala-Leu-Pro-Met-His-Ile-Arg **(60)**	77-1062µM

A new angiotensin inhibitory peptide has been isolated from egg white protein hydrolysates. The IC_{50} value of the isolated peptide RVPSL (Arg-Val-Pro-Ser-Leu) **(46)** was 20µM. On the basis of remarkable ACE inhibitory activity, RVPSL may have potential to develop as nutraceutical with hypertension lowering activity [79].

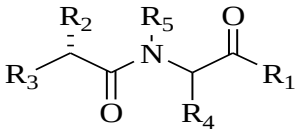
Novel peptides with angiotensin converting enzyme inhibitory activity were isolated from muscle of cuttle fish (*Sepia officinalis*). The IC_{50} value of three peptides Val-Tyr-Ala-Pro **(47)**, Val-lle-lle-Phe **(48)** and Met-Ala-Trp **(49)** are 6.1, 8.7 and 16.32 µM respectively. It is found that all three peptides act as non-competitive ACE inhibitors [34]. A tripeptide Ala-Val-Phe **(50)** was recently purified from insect protein (*Spodoptera littoralis,* Lepidoptera) shows promising ACE inhibitory activity [35]. Bioactive peptide (IKP) derived from arachin show selective ACE inhibitory activity with competitive inhibition activity. The observed IC_{50} value is obtained as 7.0 ±1 µM [36]. Peptide extracted from fresh water zooplankton (*Brachionus calyciflonus*) was screened for ACE inhibitory activity with IC_{50} 47.01 µg/ml.

The peptide is seven amino acid sequenced as Ala-Gln-Gly-Glu-Arg-His-Arg **(51)** is competitive inhibitor [70]. A tripeptide Leu-Gly-Pro **(52)** Purified from Alaskan Pollack skin gelatin hydrolysate has IC_{50} 0.72µM shows potent activity as ACE inhibitor [71]. A tripeptide isolated from smooth hound protein hydrolysates (SHPH) or mustelus mustelus and bovine trypsin with IC_{50} 0.13±0.03 mg/ml and amino acid sequence Ala-Gly-Ser (**53)** has ACE inhibitory activity [72]. Peptide coded DPC 614 obtained from bovine sodium caseinate fermentate obtained by Lactobacillus of small intestine of porcine has IC_{50} 0.8 mg/ml shows ACE inhibitor activity.[73]

Peptide Phe-Ala **(54)** incorporated with silanediol group has been synthesized and screened, shows very low IC_{50} value for ACE inhibition [74]. Peptide with sequence Leu-Arg-Pro-Val-Ala-Ala **(55)** was isolated from bovine lactoferrin hydrolysates with IC_{50} 4.14µM is non-competitive inhibitor of ACE [75, 76]. Sour milk protein Ile-Pro-Pro **(56)** and Val-Pro-Pro **(57)** was evaluated for ACE inhibitory activity in hypertensive rats and found promising results [77].

A hendeca peptide isolated from algae (*Chlorella vulgaris*) protein with sequence Val-Glu-Cys-Tyr-Gly-Pro-Asn-Arg-Pro-Gln-Phe **(58)** having IC_{50} against ACE is 29.6 µM [78]. A peptide from yellow fin sole (*Limanda aspera*) from an industrial waste is isolated and sequenced as Met-Ile-Phe-Pro-Gly-Ala-Gly-Gly-Pro-Glu-Leu **(59)** with IC_{50} 28.7 µg/ml is a non-competitive inhibitor of ACE [79]. A peptide from whey protein sequenced Ala-Leu-Pro-Met-His-Ile-Arg **(60)** show ACE inhibitory activity with IC_{50} 77-1062 µM [80].

Multifunctional ACE inhibitor: Multifunctional ACE inhibitors are capable of scavenging reactive oxygen species (ROS) and superoxide having antioxidant activity have been synthesized with the following general formula **(61)**.



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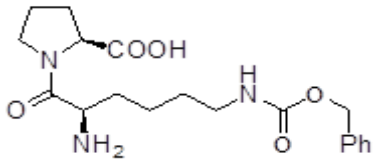
The most potent compound of the series prepared is *N*-{2-([1, 2] dithiolan-3-yl) propionyl}-pyrrolidine-2-carboxylic acid **(62)** With IC_{50} 64µM [81].



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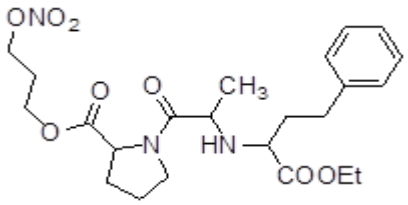

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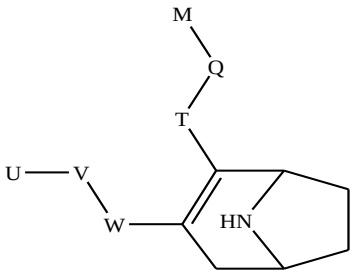
Nitro derivatives of ACE inhibitors of general formula: A-$(X_1$-$ONO_2)_S$ shows pharmacological activities like cardiovascular, renal and anti-inflammatory. One of the potent derivative is *N*-[(1*S*)-1-(ethoxycarbonyl)-3-phenylpropyl]-*L*-alanyl-*L*-proline-3-nitroxypropyl ester hydrogen maleate **(63)** is having IC_{50} 30.9±8.4µM [82].

Bezencon *et al*., proposed novel tropane derivatives as ACE inhibitors with general formula **(64)**. The synthesized and screened tropane derivatives also show activity against malaria and inhibit aspartyl proteases secreted by *Candida albicans* and therefore act as antifungal. Where W is six membered, non benzofused, phenyl or heteroaryl ring , substituted via V in meta or para position.V designated a bond $–(CH_2)_r$-A-$(CH_2)_s$-, A-$(CH_2)_v$-B- etc. A and B represent -O-, -S-, -SO-, $-SO_2$-, U represent heteroaryl or aryl, T is $-CONR_1$-, R_1 = H, lower alkyl, lower alkenyl, lower alkinyl, cycloalkyl, aryl, cycloalkyl-loweralkyl. Q is methylene, M is aryl or heteroaryl, r is 3, 4, 5 or 6, s is 2, 3, 4, 5 [83].



(64)

Dive *et al*., proposed ACE inhibitor peptide derivatives that are N-terminal site selective with amino acid sequence as follows: Asp-Phe-Ψ (PO_2CH_2)-Ala-Xaa′ Where Ψ represent that amide bond (-CONH) have been replaced by phosphonic bond (-CH_2PO_2) and Xaa′ represent amino acid residue. A peptide with amino acid sequence as follows: Ac-Asp-Phe-Ψ (PO_2CH_2)-Ala-AlaOH with Ki for N-terminal ACE is 7nM [84].

Problems associated with Hypertension: The various problems associated with hypertension are cardiovascular disease, heart failure, coronary heart disease, renal insufficiency, peripheral artery disease and stroke [85].

A New ACE: A new angiotensin converting enzyme has been found. This is angiotensin converting enzyme related carboxypeptidase. It is found that ACE 2 is a type I integral membrane protein of 805 amino acids. ACE 2 has been implicated in regulation of heart function. ACE 2 has catalytic domain which is 42% identical to that of its closest homolog, somatic ACE. The human ACE 2 has two domains in its extracellular region. The first domain is 42% identical to human somatic ACE and the second domain is present at the C-terminus and is 48% identical to human collectrin [86].

Biochemical properties of ACE 2: ACE 2 cleaves a single peptide from C-terminal residues from a range of substrate unlike ACE. ACE 2 cleaves decapeptide Ang I to Ang (1-9) and octapeptide Ang II to Ang (1-7), which antagonizes the action of Ang II and thus causes vasodilatation and antiproliferation. Despite of similar biochemical nature with ACE, ACE 2 is not sensitive to classical ACE inhibitors [87].

CONCLUSION: The data compiled in this review may be very helpful in further studies on ACE inhibitors. The comprehension in this review enlightens the evolution of ACE inhibitors, their existence and pipeline drugs of ACE inhibitors.

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How to cite this article:
Arora PK and Chauhan A: ACE Inhibitors: A Comprehensive Review. *Int J Pharm Sci Res*. 2013; 4(2); 532-549.