1. Introduction

Hypertensive disorders are the major contributors of the total global deaths; a report revealed that about 51% deaths are caused due to cardiovascular diseases only, among the noncommunicable diseases such as respiratory disorders, cancer and diabetes.[1] Since the pathophysiology of hypertension and related disorders is much complicated, there is a need of skilled treatment to control such diseases. Despite the availability of a number of drugs no single drug can effectively control the raised blood pressure, so a major part of the hypertensive population depends on the combination therapy to regulate the elevated blood pressure.[2,3] The general targets involved in the treatment of hypertension and other cardiovascular diseases, are kidney, adrenergic receptors and blood vessels.

1.1 Targets and treatments in the management of hypertension

Increased peripheral vascular resistance generally impairs the hemodynamics of body that results into hypertension. Physiologically, blood pressure is regulated through a complicated process (**Fig. 1**) and it is further associated with diseases such as renal dysfunction, diabetes and atherosclerosis[4,5]. Different systems in the body can be targeted for regulating the blood pressure and a variety of drugs are used to manage body blood pressure as discussed below.

1.1.1 Sympathetic nervous system (SNS)

To maintain the circulatory hemodynamics such as heart rate, force of contraction, vasomotor tone and ultimately the blood pressure, the role of SNS is important. It regulates the activity of α- and β-receptors. β_1 (a subtype of β) receptor blockade results in decreased cardiac output whereas peripheral vasodilatation is caused by blockade of α_1 (a subtype of α) receptor.[6]

1.1.2 Renin-angiotensin system (RAS)

RAS, one of the largest hormonal systems, plays a major role in the regulation of blood pressure and volume for a long duration. The transformation from prorenin to renin and its further circulation in the blood stream is facilitated by the juxtaglomerular cells in response to decreased renal blood flow. The formation of active angiotensin I (AI) from angiotensinogen is induced by renin which follows the production of fully active form of angiotensin II (AII). AII is a vasopresor hormone interacting with angiotensin receptors (AT_1 and AT_2). The following effects are mediated by AT_1-receptors:

- ✓ Constriction of blood vessels in the renal arterioles.
- ✓ Increase in inotropic and chronotropic effects through the secretion of noradrenaline from sympathetic nerve endings.
- ✓ Induction of sodium reabsorption.
- ✓ Release of aldosterone.
- ✓ Stimulating cellular growth rate in the arteries and heart muscles.

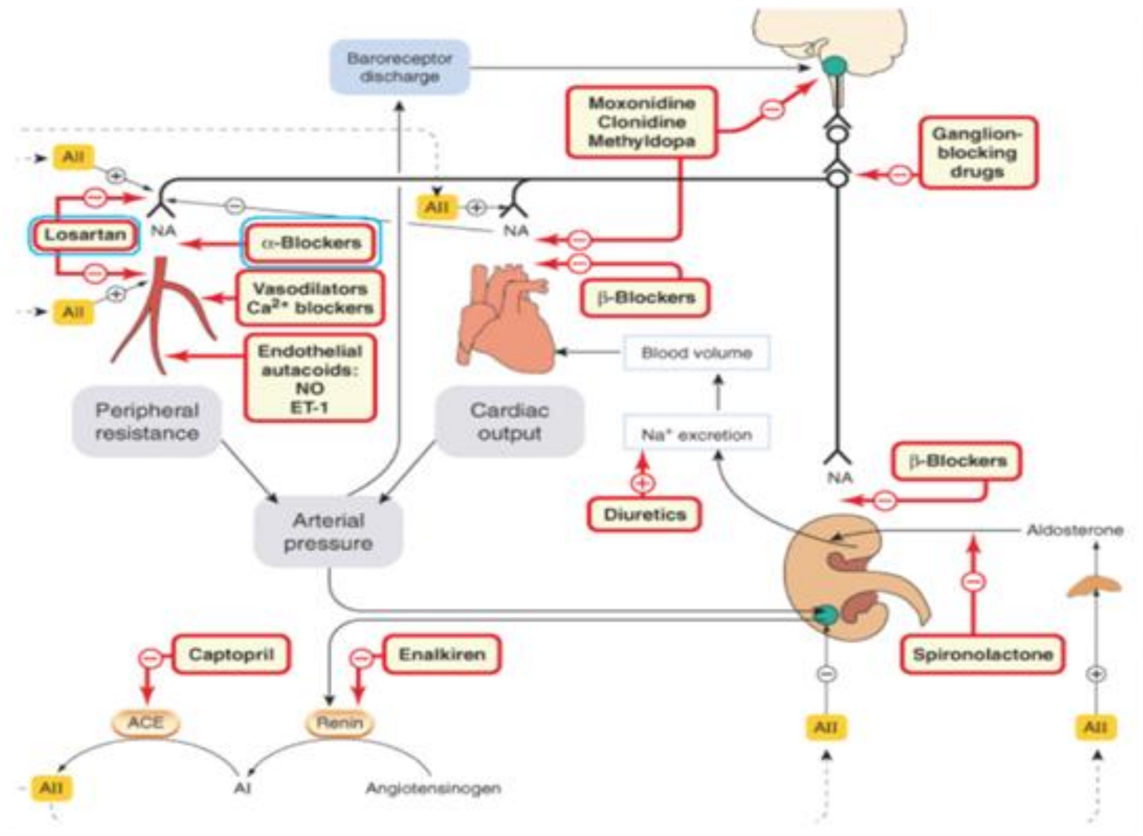


Fig. 1: Targets in the management of hypertension[7]

Adequate information is not available about AT_2-receptor and its physiological roles; probably it opposes the effects of AT_1-receptor such as renal hypertrophy and inhibition of the cell proliferation processes.[8]

1.1.3 Kidneys

To regulate the systemic blood pressure, kidneys play an important role by regulating the excretion rate of sodium. Excess of sodium intake by a normal person may cause increase in extracellular fluid (ECF), blood pressure and cardiac output. Increased sodium and water levels can be reduced by the use of diuretics. There are a number of diuretics such as thiazides, loop, potassium sparing etc.[6]

1.1.4 Calcium channels

Calcium channel blockers (CCBs) reduce blood pressure through arteriolar vasodilatation. The entry of Ca^{2+} into the cells of the smooth muscles of the blood vessels and heart is hindered by CCBs resulting in slow contractions of the heart muscles and vasodilatation, thus lowering of blood pressure. CCBs such as amlodipine, flodipine, nifedipine, diltiazem, verapamil etc. also show antiarrhythmic activity by reducing the conduction of nerve impulses in the heart.[9]

1.1.5 Aldosterone

It is a potent mineralocorticoid which stimulates sodium retention. Excess aldosterone produces adrenal hyperplasia which usually causes hypertension. Aldosterone receptor antagonists spironalactone and eplerenone competitively impede aldosterone binding to its receptor site.[10]

1.1.6 Nitric oxide (NO)

It is an arginine derived vasodilatory agent produced during increased entry of Ca^{2+} in the endothelial cells. NO exerts its vassodilating effect through relaxation of the smooth muscles via increased formation of cGMP. AII increases the activity of nicotinamide adenine dinucleotide phosphate-oxidase (NADPH-oxidase) leading to increased levels of reactive oxygen species which reduce the bioavailability of NO.[11]

1.1.7 Endothelin (EN)

Endothelial cells produce a potent twenty one amino acid vasoactive peptide EN which has both vasoconstrictory and vasodilatory properties. Through activation of EN_A receptor it stimulates vasoconstriction and cell proliferation. EN-receptor antagonists used mostly in mild to moderate essential hypertension cause reduction in blood pressure and peripheral vascular resistance.[12]

Table 1: The list of different antihypertensive agents and their targets[13]

Sr. No.	Target	Representative drugs
1	Blood vessels	Hydralazine, Minoxidil
2	α_1-Receptors	Prazosin, Terazosin, Doxazosin
3	AT_1-receptors	Losartan, Valsartan, Candesartan, Irbesartan
4	Calcium channels	Amlodipine, Nifedipine, Felodipine
5	Kidneys	Chlorothiazide, Furosemide, Triamterene
6	ACE	Captopril, Enalapril, Lisinopril, Perindopril
7	β_1-Receptors	Atenolol, Bisprolol, Metoprolol, Nadolol
8	Aldosterone	Spironolactone, Eplerenone

As discussed earlier kidneys, adrenergic receptor system and blood vessels are the major targets for the control of blood pressure. Additionally, calcium channels, ACE and angiotensin receptors also play an important role in the regulation of hypertension (**Table 1**). Due to the inefficacy of a single drug or a particular category of drugs there is the need for the use of several drug combinations (**Table 2**) for potential treatment of raised blood pressure.[14,15]

Table 2: List of some specific drug combinations[16]

Type of combination	Combination Drugs
Diuretics and AT_1 antagonists	HCTZ and Irbesartan/Losartan/Telmisartan/Valsartan
Diuretics and ACE Inhibitors	HCTZ and Captopril/Enalapril/Lisinopril/Moexipril
Diuretics and β_1 antagonists	HCTZ and Metoprolol/Propranolol
Diuretics and α_2-agonists	Chlorthalidone and Clonidine
AT_1-antagonists and ACE Inhibitors	Telmisartan and Ramipril
CCBs and ACE Inhibitors	Amlodipine and Benazepril, Verapamil and Trandolapril
CCBs and AT_1 antagonists	Amlodipine and Olmesartan/Valsartan/Telmisartan

HCTZ-Hydrochlorthiazide

1.2 Fixed dose combinations (FDCs)

FDCs are a mode of combinational drug therapy to provide an option to improve patient compliance. FDCs are formulated by uniting two or more active drug constituents in a single dosage device (**Table 3**). To increase the acceptance of such type of combinations their advantages over a single drug should be proven. These products provide patient compliance because single dosage forms with more than one active constituent are more suitable to administer than multiple drugs with one drug in one dosage form, and these are cost effective also.[17]

The following aspects are important for fixed dose combinations:[18]

- There should be different mechanisms of actions for each ingredient.
- The pharmacokinetic patterns of the drugs in combination should be nearly similar.
- There must not exist supra additive toxicities of the ingredients.

Table 3: The list of FDA approved FDCs[19,20]

FDCs	Mode of action	Year of approval
Hydrochlorothiazide with olmesartan medoxomil	Thiazide diuretic and AT_1- antagonist	2003
Amlodipine besylate with olmesartan medoxomil	CCB and AT_1- antagonist	2007
Aliskiren with hydrochlorothiazide	Direct renin inhibitor and thiazide diuretic	2008
Hydrochlorothiazide with amlodipine and valsartan	Thiazide diuretic, CCB and AT_1 antagonist	2009
Aliskiren with valsartan	Renin inhibitor and AT_1- antagonist	2009
Amlodipine besylate with telmisartan	CCB and AT_1 antagonist	2009
Hydrochlorothiazide and ramipril	ACE inhibitor and thiazide diuretic	2009
Aliskiren and amlodipine	Renin inhibitor and CCB	2010
Hydrochlorothiazide with aliskiren and amlodipine	Thiazide diuretic, renin inhibitor and CCB	2010
Chlorthalidone with azilsartan medoxomil	Diuretic and AT_1- antagonist	2011

Limitations of FDCs

- Because all constituents of the FDCs are converted in one dosage form so there is no flexibility in deciding about the dose of any one particular ingredient.

- These are not always cost effective as some FDCs might be more expensive than the single drug dosage forms.
- Since each active ingredient has its own pharmacokinetic properties so sometimes it might pose difficulties regarding the frequency of administration of the dosage form.
- FDCs may not always be safe or practicable as first-line therapy.

1.3 Development of Multiple target-directed ligands

A need was felt for the development of drugs that have the potential to act on multiple receptors synergistically with improved patient compliance.[21] Designing aspects, for the development of such a molecule that has the ability to work synergistically through different receptors are too complex in terms of metabolic stability and binding efficiency. Since the rationale, to design such type of molecules are mainly based on the fusion of the pharmacophoric features from different molecules, there are chances that such a new molecule would possess a higher molecular weight which generally would not fit in the pharmacokinetic features of the body, hence the binding efficiency of these molecules on the targeted receptors might be poor.[22,23] Thus, there are challenges for the attainment of balanced activities on the projected targets with high selectivity and improved pharmacokinetics in the designing of such multitargated drugs.[24]

1.4 Rational approaches to design multi target-directed ligands [20]

The basic rational for the design of a multiple receptor-targated ligand, is the fusion of pharmacophoric features of two or more drugs of different classes either through a chemical bonding or by overlapping of the pharmacophores with each other in a single chemical entity.[25] The resulting hybrid molecule might be capable of binding effectively to the desired receptors.[21]

There are two approaches to develop multi target-directed ligands:

- Framework combination and
- Fragment-based approach.

- **Framework combination**

The knowledge gained from structure activity relationships (SAR_S) of different classes of biologically active compounds is applied in this approach to blend the pharmacophores into one single molecule. Such as S_1 and S_2 are the two target selective molecules that bind to two different classes of receptors. Their pharmacophoric features can be incorporated to result into a new hybrid molecule M_1 (**Fig. 2**). The extent of fusion depends on the similarities between S_1 and S_2. Fusion of S_1 and S_2 would result into the formation of larger molecule M_1 which would possess poor ligand efficiency and this approach is not much advantageous.[25]

- **Fragment-based approach**

It is a screening based technique in which selected molecules are initially screened to determine a common pharmacophoric fragment (F), essential for the binding to the projected receptors. Optimization of this identified fragment would result into the molecule M_2 (**Fig. 2**) with improved efficiency. Prior screening and optimization processes minimize the chances of existence of undesired regions in the resulting molecule M_2, thus it should have greater ligand efficiency to fit the targets A and B than M_1.[25]

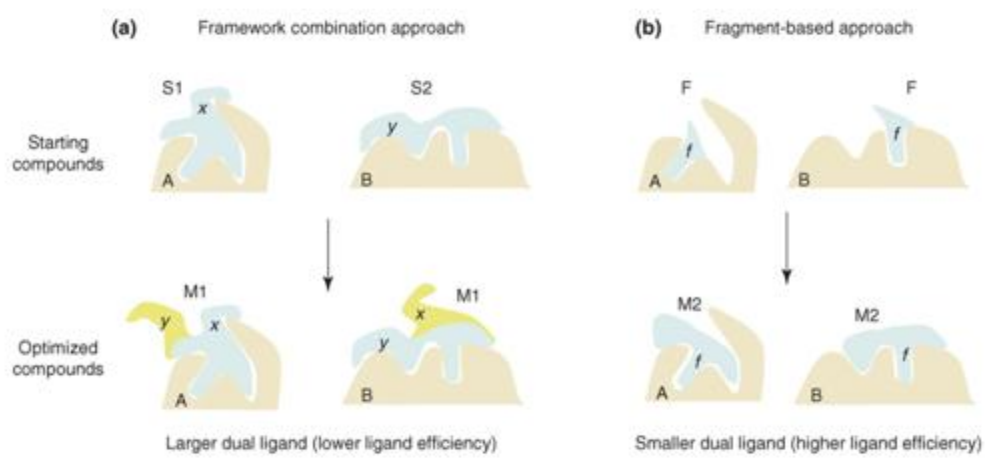


Fig. 2: Fundamental mechanistic representation of the design of multiple ligands[25]

Table 5: List of some multiple targeted ligands for hypertension[26]

Multiple receptor blockers/inhibiters	**Mechanism of action**
Bucindolol, Carvedilol, Labetalol	Antagonism of α_1- and β_1-receptors
BWA385C	ACE inhibition along with nonselective antagonism of the β-receptors
SB290670	Antagonism of AT_1, ET_A and ET_B-receptors
PS43354	Blockade of AT_1 and ET_A-receptors
LCZ696	Inhibition of NEP and AT_1-antagonism
Nevibolol	Nonselective antagonism of β-receptors with NO mediated vasodilating effect

1.4.1 Dual α_1- and β_1-antagonists

For the effective management of hypertension, dual acting α- and β-blockers are useful because they reduce the pheripheral resistance and cardiac output. There are some dual acting blockers such as bucindolol, carvedilol and labetalol (**Table 5**) which are clinically approved. A study revealed that carvedilol improved the endothelial vasodilation, anti-inflammatory functions and platelet antiaggregation activity in patients with diabetes and hypertension.[27] No adverse effect of carvedilol was observed on the left ventricular systolic function.[28] At higher concentrations it can also work as calcium channel blocker. Another molecule PP-17, evaluated as dual α_1- and β_1-adrenoceptors antagonist, reduced the heart rate and blood pressure considerably in fructose and renin induced hypertensive model of rat.

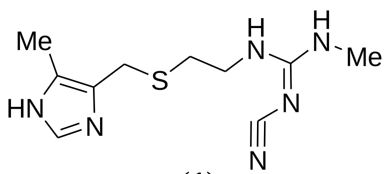
1.4.2 β_1-Blockers with NO vasodilatory effect/endothelial β_2-receptor stimulation

Hypertension with diastolic or systolic dysfunction can be effectively treated by third generation β_1 blockers. Nevibolol (approved in 2007), a selective β_1-receptor antagonist also showed some vasodilating efficacy through release of endothelial nitric oxide (NO). It proves, that the fusion of the pharmacophoric features of the selective β_1-blockers with molecules causing vasodilation through release of endothelial nitric oxide, could lower the blood pressure effectively with improved haemodynamic profile.[29-33] Endothelial β_2-receptors' stimulation improved NO mediated vasodilation and stimulation of calcium ions-mediated potassium channels are the results of navibolol induced vasodilation specially in the arteries of kidney.[34]

1.4.3 Dual CCBs and α_1-antagonists

In the designing of multitargeted drugs, the approaches based on the bioisosteric modification play a key role as was the case in the discovery of cimetidine (**1**) and pinacidil (**2**). In the designing of both **1** and **2**, *N*-cyanoguanidine, a bioisostere of thiourea moiety has been used successfully. Bioisosterism may be used as a tool to know about the interactions between the receptor and the ligand as was the case in the designing of a dopamine agonist (**3**) and selective β_1-blocker labetalol (**4**) wherein phenol-indole bioisosterism was utilized. Some indole derivatives of verapamil have also been synthesized and biologically evaluated for their dual antagonistic activity on α_1-

receptors and the calcium channels simultaneously, on the basis of phenol-indole bioisosterism. The indole congener (**5**) of verapamil showed potent antagonism in the *in vitro* study against the calcium entry but was found to be slightly less active than the parent drug. Congener (**6**) showed potent blockade against both the calcium channels and the α_1-receptors in the *in vitro* study but, it was found to be somewhat less active in the *in vivo* study than verapamil.[35]



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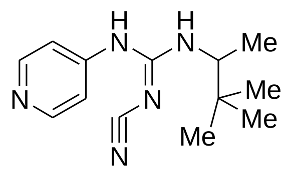

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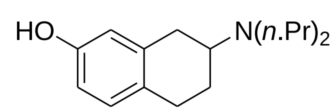

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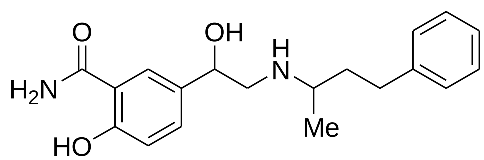

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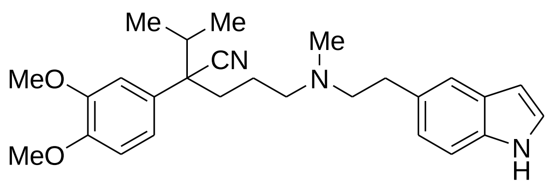

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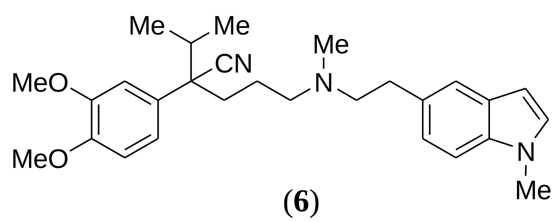

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1.4.4 Neutral endopeptidase (NEP) inhibitors

For the potential treatment of hypertension the role of natriuretic peptides are important due to their cardiovascular and renal effects.[35,37] Genetically, these peptides work through distinctively different mechanisms. These are classified as Atrial (ANP), C-type (CNP) and Brain natriuretic peptides (BNP), on the basis of their availability.[38] ANP and BNP work through natriuretic peptide receptors type A (NPR-A) and type B (NPR-B) respectively which are coupled to guanylyl cyclase. The activation of NPRs increases the level of intracellular cyclic GMP (cGMP) which results into different biological effects such as vasodilatation, natriuresis, activation of negative control of the renin-angiotensin-aldosterone system (RAAS), excess of urea formation and increased mobility of lipid, endothelin and vasopressin.[37,39]

Neprilysin, a NEP and angiotensin receptors antagonist can effectively control the condition of hypertension and heart failure. LCZ696 comprises of the pharmacophoric features of valsartan (AT_1-antagonist) and a prodrug of NEP inhibitor, AHU377. It improves the immunoreactivity of ANP through the NEP inhibition (**Fig. 3**).[40]

1.4.5 Dual inhibitors of vasopeptidases (ACE and NEP)

Inhibition of vasopeptidases such as ACE and NEP synergistically offers advantages over the inhibition of lone targets. Vasopeptidases inhibitors lower the blood pressure by reducing the vasoconstriction and enhancing the vasodilatation.[41] Inhibitors of vasopeptidases (**Table 6**) such as omapatrilat exerts its vasodilating effect through

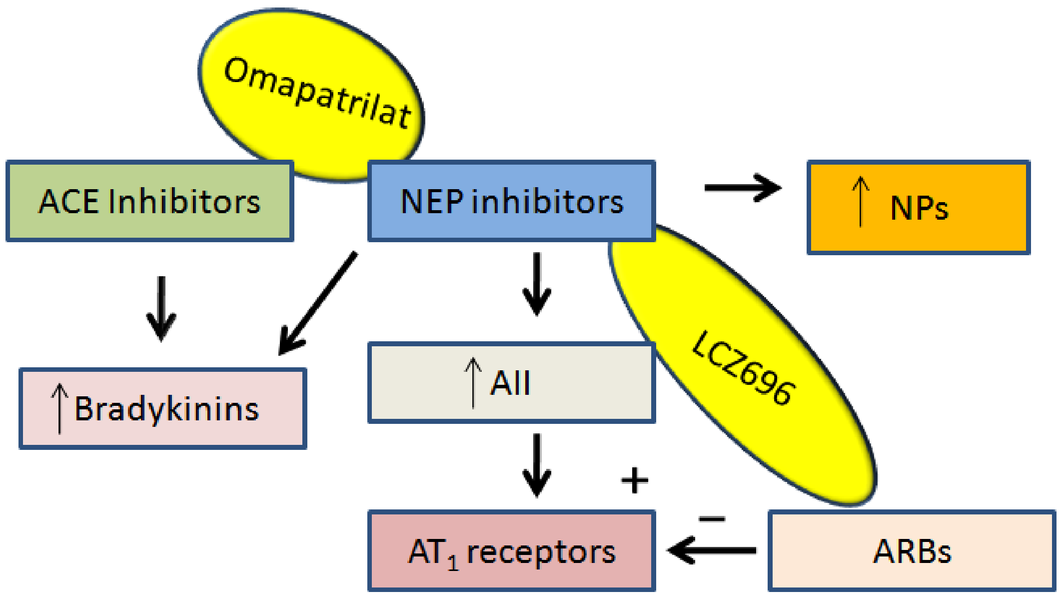


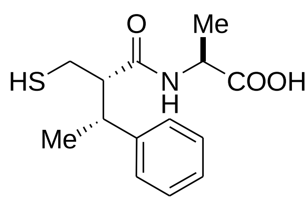
Fig. 3: Difference between AT_1 blockade-NEP inhibition and ACE-NEP inhibition

inducing the efficacy of NPRs, cGMP, and ANP in different cardiovascular conditions.[42] Omaptrilat maintains arterial pressure upto 24 hrs in different hypertensive conditions caused by lower or higher concentrations of renin.[43] Omapatrilat enhances the urinary ANP and cGMP levels through NEP inhibition and increases the activity of plasma renin through ACE inhibition in the healthy subjects (**Fig. 3**).[41] It reduces the blood pressure with improved vascular protection than others such as CCB or ACE inhibitors.[44-47] Although omapatrilat has a number of advantages, its major drawback was angioedema thus, it failed to get approval by the U.S. Food and Drug Administration (FDA).[48]

Table 6: List of some selected dual vasopeptidases (ACE and NEP) inhibitors[49,50]

Sr. No.	Drug	Company	Development status	Current status
1	Omapatrilat	Bristol Meyers Squibb	Phase III	Not approved by FDA
2	Gemopatrilat	Bristol Meyers Squibb	Phase II	--
3	Sampatrilat	Roberts	Phase I/II	--
4	MDL-100240	Aventis	Phase II/III	--
5	Fasidopril	Eli Lilly	Phase II	--
6	Z-13752A	Zambon/Glaxo Smith kline	Phase II	--

(2*S*)-2-{(2*S*,3*R*)-2-Thiomethyl-3-phenylbutanamido}propionic acid (S21402) (**7**) has been developed in order to achieve the synergistic inhibition of both, the ACE (K_i =



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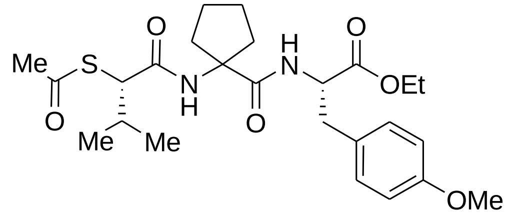

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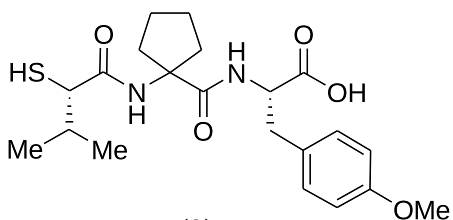

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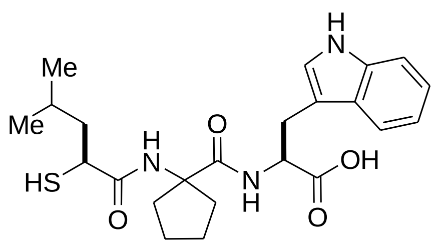
4.2 nM) and NEP (K_i = 1.7 nM).[51] It inhibits cardiac remodeling through vasodilation and natriuresis.[52-54]

Another example of such a dual inhibitor is *N*-[1-[2(*S*)-acetylthio-3-methyl-l-oxobutyl]amino]-1-cyclopentyl]carbonyl]-*O*-methyl-*L*-tyrosine ethyl ester (CGS30440) (**8**) for both, the ACE (IC_{50}: 19 nM) and NEP (IC_{50}: 2.2 nM). On biological metabolism it converts into CGS 30008 (**9**).[55]

1.4.6 Triple vasopeptidase inhibitors

The major drawback of NEP and ACE synergistic inhibition is an increased level of endothelin 1 (ET-1) in the plasma because NEP degrades plasma ET-1 that mediates similar effects as produced by AII. Additional inhibition of endothelin converting enzyme



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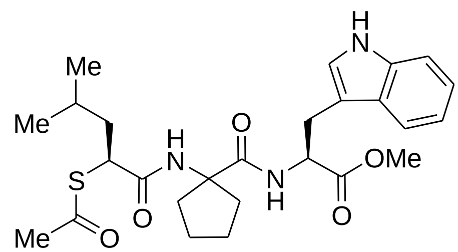

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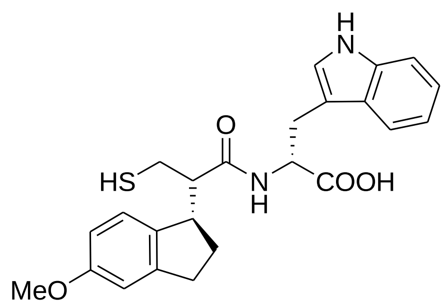

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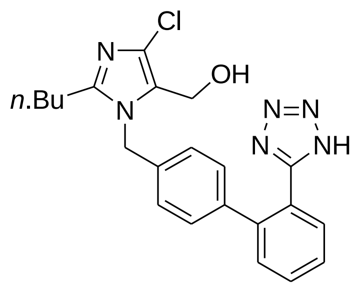
(ECE-1) can overcome this problem. CGS35601 (**10**) has been reported as a triple vasopeptidase inhibitor (VPI) which is effective in the treatment of hypertension and renal disorders. Plasma levels of NEP, ECE and ACE can be decreased simultaneously by the use of CGS35601 (**10**). In order to improve its oral bioavailability, a prodrug CGS37808 (**11**) of **10** has also been formed and biologically evaluated in the rat model. CGS37808 (**11**) offers better inhibition of ACE induced pressor response with simultaneous degradation of ANP.[56] An indanyl analog (**12**) of CGS35601 (**10**) also showed improved binding affinities for NEP, ACE and ECE-1 synergistically with IC_{50} values of 24, 1.3 and 10 nM respectively.[57]

1.4.7 Dual antagonism of AT_1- and AT_2-receptors

AII exerts its vasoconstrictory effects through RAS which is a major contributor in the regulation of blood pressure, fluid volume and electrolytes.[58] Thus RAS plays an important role in the treatment of hypertension. ACE converts the inactive angiotensin (AI) into its active (AII) form which shows vasoconstrictory effects through binding to its receptors AT_1 and AT_2.[59,60] Thus, the blockade of AII to its receptors would prove to be a more successful strategy than ACE inhibition, because angiotensin receptors antagonists prevent AII even if it has been produced through ACE-independent mechanisms.



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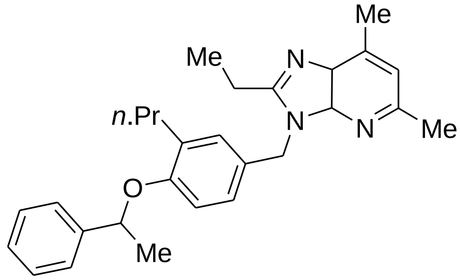

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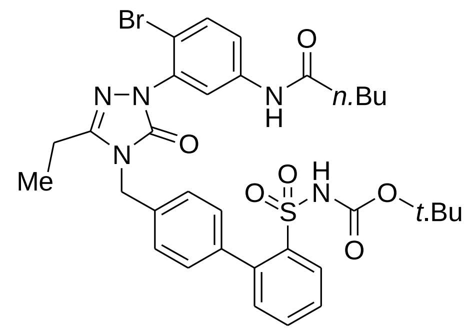

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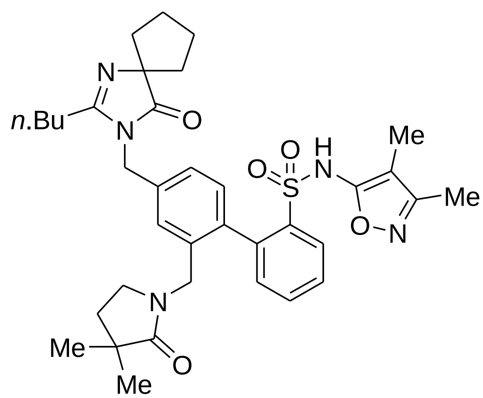
The physiological effects of AII, which are associated with kidneys and the cardiovascular system are mediated through AT_1-receptor.[61,62] Some of them, such as regulation of renal functions,[63] restricted blood flow followed by vascular injury,[64] wound healing,[65] and the synthesis of cardiac fibroblast collagen are mediated by AT_2-receptor.[66] Additionally, the processes of cell differentiation and cell proliferation are also controlled by AT_2-receptor.[62,67] Losartan (**13**) is a well known non-peptide drug which acts as AT_1-receptor antagonist[68] while some piperazinecarboxylic acid analogs have been reported as potent AT_2-receptor antagonists.[69] It is also a well known fact that renin induced AII level increases in the plasma if selective AT_1- antagonists are administered.[70,71] Thus blockade of AT_1- and AT_2-receptors might prove to be a key approach for the management of increased blood pressure and fluid volume. Several discoveries have been made in this direction that offered some of the potential lead compounds such as **14** & **15** having dual antagonistic activity on both the (AT_1- and AT_2-) receptors.

1.4.8 AII and ET-1 Inhibitors

AII and ET-1 are the two endogenous peptides which are proven potent vasoconstrictors in the cardiovascular and hypertensive pathogenesis.[72] These endogenous peptides influence the effects of each other mutually, i.e. an elevated plasma concentration of ET-1 stimulates the formation and vasoconstrictory action of AII and vice versa. Simultaneous inhibition of these two peptides would offer an improved way to regulate hypertension and related disorders.[73] Since AII and ET-1 produce vasoconstrict-



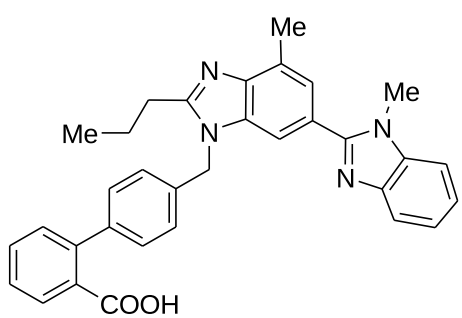
(**16**)

ory effects through their (AT_1/AT_2- and ET_A/ET_B-) receptors respectively; it has been proved that simultaneous antagonism of AT_1 and ET_A-receptors can provide better management of blood pressure than the blockade of lone receptor. A study revealed that administration of an AT_1 antagonist (losartan) and an ET_A antagonist (LU-135252) together in a hypertensive rat model would potently restore the level of elevated blood pressure and reduce the mortality rate.[74] On the basis of this study, researchers have designed and synthesized several molecules such as BMS-193884 (**16**) which could efficiently block both AT_1 and ET_A-receptors simultaneously.[75]

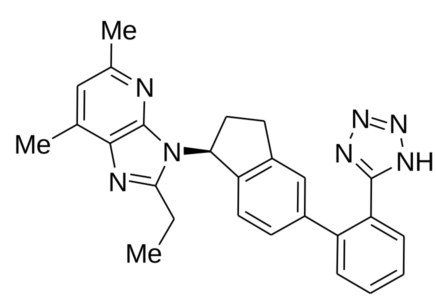
1.4.9 AII receptors antagonism along with PPAR-γ activation

Among the various metabolic syndromes, resistance for insulin uptake and hypertension, both are closely related conditions. Insulin resistance is a major contributing factor for the origin of type 2 diabetes. On the basis of reported evidences it can be concluded that the mutual correlation between different vascular diseases and blood glucose level is a prime cause for the initiation of cardiovascular diseases even in the non-diabetic population.[76] Activation of peroxisome proliferator activated receptor-γ (PPAR-γ) causes the blockade of a phosphorylation cascade resulting into decreased insulin resistance which is a helpful task for the treatment of type 2 diabetes. Drugs, related to thiazolidinediones (TZDs) are well known PPAR-γ activators. Their antidiabetic activity has been utilized for the management of type 2 diabetes.[77] On the other hand angiotensin receptor blockers (ARBs) are a widely applicable category of drugs for the treatment of hypertension.[78] If a patient suffers from insulin resistance along with hypertensive condition, he/she requires treatment with two different categories of drugs which might have different pharmacokinetic and pharmacodynamic features. Additionally, the intake of several drugs together at a time may cause drug-drug interactions and patient compliance remains a major issue. Thus, the designing of molecules which have AII receptor antagonistic activity along with PPAR-γ activation would be of a great interest.

Telmisartan (**17**) an ARB has been found to show weakly PPAR-γ agonist activity along with its strong activity on the AT_1-receptor.[79] The pharmacokinetic features of telmisartan (**17**) allow it to regulate the blood pressure upto 24 hours and also cause decrease in fluctuations as compared to other members. So, it has the potency to improve the glycemic parameters in the patients with metabolic syndrome[80] Thus, in order to achieve improved synergistic effects of telmisartan (**17**), a variety of its derivatives have been synthesized and evaluated as AT_1 antagonists with simultaneous PPAR-γ agonism.[81-83] A study has reported such a type of molecule (**18**) which has the capability for binding to both AT_1- and PPAR-γ- receptors.[84]



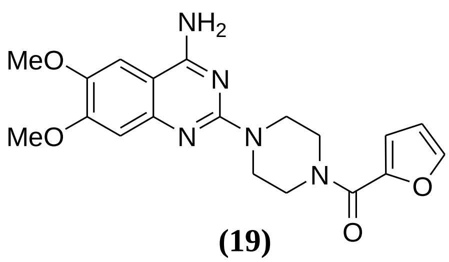
(**17**)



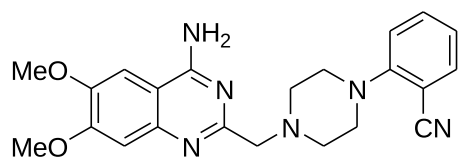
(**18**)

1.4.10 Dual antagonists for the α_1- and AT_1-receptors

SNS and RAAS both are correlated to each other in order to exert their effects on the circulatory system.[85,86] In response to a stimulus, SNS induces constriction of the blood vessels, increases myocardial contractility and heart rate. On the other hand RAAS exerts all these effects through the secretion of AII which results into increased blood pressure. Mutual interaction between SNS and RAAS plays an important role in the regulation of different metabolic, cardiovascular, renal and reflux conditions.[7,87,88] Both the systems reveal their importance in the treatment of hypertension due to synergistic control of each other. Since α_1- and AT_1-receptors work through these systems, synergistic antagonism of both these receptors might be advantageous for the treatment of hypertensive conditions.



(19)



(20)

Some earlier studies have revealed that the integration of pharmacophoric features of α_1- and AT_1- selective molecules resulted into new potent and dual acting chemical entities. Losartan (**13**) and prazosin (**19**) being typically AT_1- and α_1-receptors antagonists respectively, researchers have tried to incorporate the structural features of both these drugs to obtain a hybrid molecule (**20**) as a potent antihypertensive agent with the ability to bind to both the receptors synergistically. The designed compounds have been synthesized and evaluated for their biological activities on both the receptors. In the *in vitro* evaluation some of these compounds were found to be active on both the discussed receptors.[89] These findings have generated enough interest to work further in this direction.