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

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Keywords:

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ABSTRACT: The renin-angiotensin system (RAS) plays an important role in pathogenesis of hypertension, congestive heart failure, and chronic renal failure. In addition to a discussion of the current understanding of the chemical structures and the modes of action of angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor (ATR) antagonists, review includes their SAR analysis and chemical modification for improving their activity. Nowadays different modeling strategies are underway to develop tailor made molecules with the best of properties among nonpeptide renin inhibitors, dual action receptor antagonists (*e.g.* angiotensin and endothelin antagonists, ACE/NEP inhibitors, AT_1/TxA_2 antagonists, balanced AT_1/AT_2 antagonists), triple inhibitors. In the first part is given an overview of various ACE inhibitors. The second part is devoted to overview of angiotensin receptor antagonists. The advances that have been made, new opportunities, and future directions of design and development of these classes have been discussed.

INTRODUCTION: The angiotensin II receptor blockers (ARBs) represent a newer class of antihypertensive agents comparing with angiotensin-converting enzyme (ACE) inhibitors. Their mechanism of action differs from that of the ACE inhibitors, which also affect the renin angiotensin system (RAS). The ARBs were developed to overcome several of the deficiencies of ACE inhibitors: competitive inhibition of ACE results in a reactive increase in renin and angiotensin I levels, which may overcome the blockade effect;

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ACE is a relatively nonspecific enzyme that has substrates in addition to angiotensin I, including bradykinin and other tachykinins, and thus, inhibition of ACE may result in accumulation of these substrates; production of angiotensin II can occur through non-ACE pathways as well as through the primary ACE pathway, and these alternative pathways are unaffected by ACE inhibition; specific adverse effects are associated with ACE inhibitor effects on the enzyme; and ARBs offer more complete angiotensin II inhibition by interacting selectively with the receptor site [1]. Today, we know that more biochemical pathways are affecting the conversion of angiotensinogen to angiotensin II; although angiotensin II affects mainly two G protein–coupled receptor subtypes, namely AT_1R and AT_2R, at least four different subtypes have been identified (designated as AT_1R, AT_2R, AT_3R and AT_4R).

Also, the different metabolites of angiotensin II, which form after proteolytic degradation of the parent molecule, present biological activity. In addition, angiotensin II has high binding affinity to neurolysin which in turn may affect significantly the activity on RAS. The action of angiotensin II on AT_1R was the first to be studied in detail, while the mode of action of AT_2R remained elusive for a long time owing to the lack of ligands that selectively target this receptor as also due to its low expression. Furthermore, new functions of the two receptors have been revealed. It is now shown that AT_1R and AT_2R present opposing biological functions, *e.g.* AT_2R has anti-proliferative properties, while AT_1R facilitates angiogenesis and cellular proliferation. Besides the classical functions mediated by the AT_1R like vasoconstriction, proliferation of vascular smooth muscle and cardiac cellular growth, a direct correlation has been identified between the up-regulation of AT_1R and the immunosuppression and invasiveness state in many cancer types, establishing AT_1R as a potential cancer drug target.

There are other functions associated by AT_2R, for instance, AT_2R adopts a protective role in pathological conditions such as tissue injury and inflammation, diabetic neuropathy, stroke damage, diabetes type 2, spinal cord injury and cancer. As with renin and ACE inhibitors, extensive rational design plans had to be implemented by researchers working both in industry and academia to discover AT_1R antagonists. Initially, efforts were mainly focused on peptides, but owing to the known disadvantages that peptides encounter they could not enter clinical trials or the market as drugs [2].

Peptide Mimetics: Design of Agonists / Antagonists: The first prototypical compound was saralasin, an octapeptide. Saralasin as well as other peptide analogs demonstrated the ability to reduce blood pressure; however, these compounds lacked oral bioavailability and expressed unwanted partial agonist activity. More recent efforts have utilized peptide mimetics to circumvent these inherent problems with peptide based antagonists.

Peptide mimetics have been defined as molecules which mimic the action of peptides, have no peptide bonds, and a molecular weight less than 700 Daltons. In comparison with peptide drugs, peptide mimetics have numerous pharmaceutical advantages. Foremost among these are increased bioavailabilities and increased duration of action. The majority of known peptide mimetics have been discovered by random screening techniques; however, this process is costly, labor intensive, and unpredictable. However, these studies provided valuable SAR knowledge. From peptides, the scientists have been led to small organic molecules that mimicked the C-terminal segment of angiotensin II. The culmination of these efforts was the 1995 approval of losartan, a non-peptide angiotensin II receptor antagonist [3].

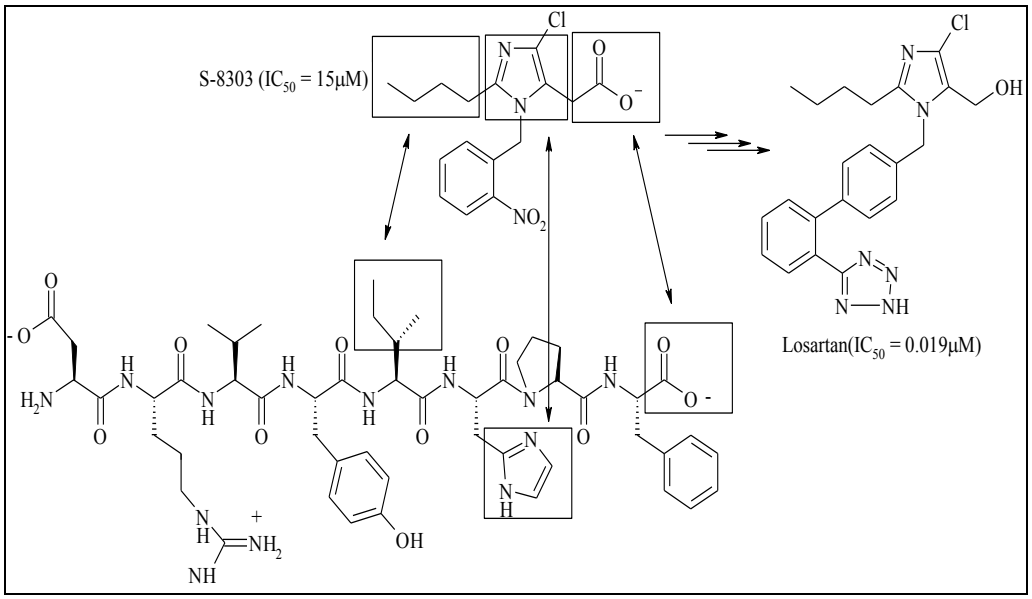


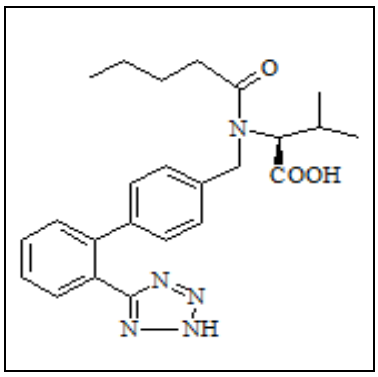
FIG. 1: COMPUTERIZED MOLECULAR MODELING OVERLAP OF ANGIOTENSIN II WITH THE STRUCTURE OF S-8308 AND MODELING OF LOSARTAN FROM S-8308

The first AT_1R antagonist that entered the market was losartan. Its development can be traced back to two 1982 patent publications [4] which described the antihypertensive effects of a series of imidazole-5-acetic acid analogs. These compounds are exemplified by S-8308 (**Fig. 1**) and were later found to specifically block the angiotensin II receptor.

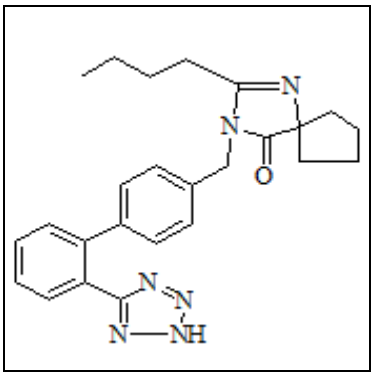
A computerized molecular modeling overlap of angiotensin II with the structure of S-8308 revealed three common structural features. The ionized carboxylate of S-8308 correlated with the C-terminal carboxylate of angiotensin II, the imidazole ring of S-8308 correlated with the imidazole side chain of the His_6 residue, and the *n*-butyl group of S-8308 correlated with the hydrocarbon side chain of the Ile_5 residue [3].

From S-8308, a number of molecular modifications were carried out in an attempt to improve receptor binding and lipid solubility. These changes resulted in preparation of losartan, a compound with high receptor affinity (IC_{50} = 0.019μM) and oral activity (**Fig. 1**).

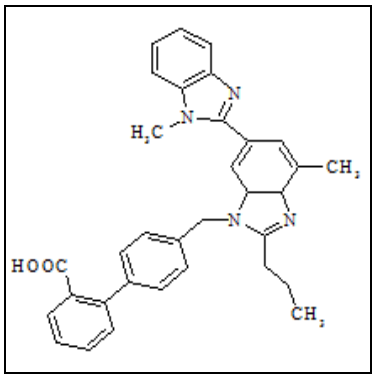
The success of losartan followed eight more derivatives constituting the class of SARTANs or ARBs (**Fig. 2**) [2].



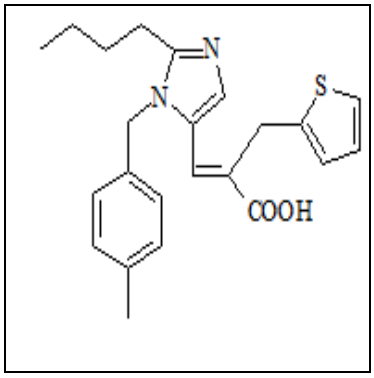
VALSARTAN



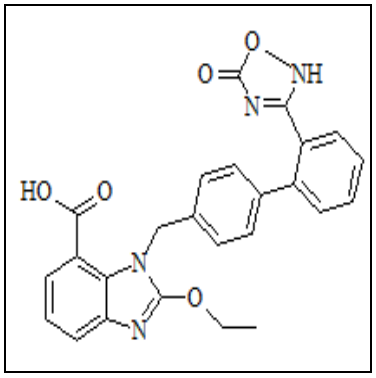
IRBESARTAN



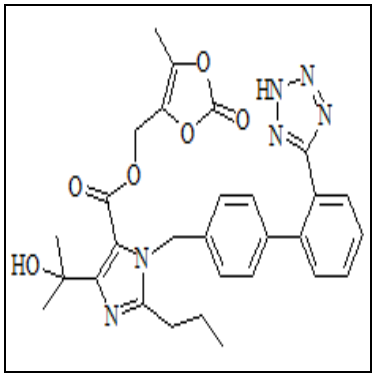
TELMISARTAN



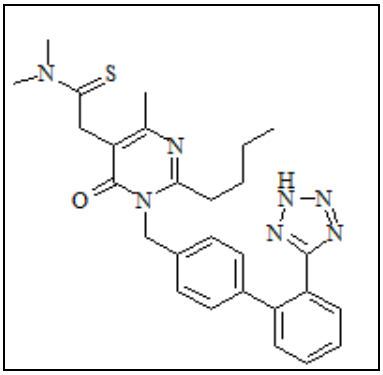
EPROSARTAN



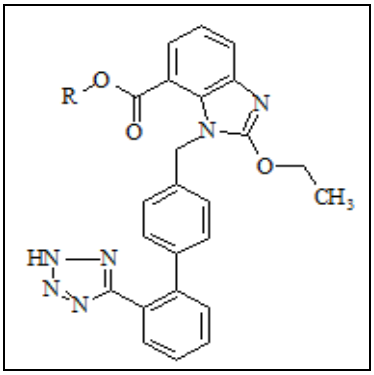
AZILARTAN



OLMESARTAN



FILMASARTAN



CANDESARTAN CILEXETIL

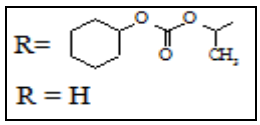


FIG. 2: CHEMICAL STRUCTURES OF LOSARTAN ANALOGS

Valsartan, irbesartan, candesartan, telmisartan, azilsartan, fimasartan and olmesartan are biphenyl analogs of losartan (**Fig. 2**). Each of these compounds has a structural feature unique from those seen in losartan. Valsartan, named for the valine portion of the compound, is the first nonimidazole containing angiotensin II antagonist, and is slightly more potent (IC_{50} = 0.0089μM) than losartan. Candesartan cilexitil and telmisartan are both contain benzimidazole rings which allow for enhanced hydrophobic binding and an increase in potency, as compared to losartan. Candesartan cilexitil is a prodrug which is rapidly and completely metabolized to the active metabolite, candesartan (**Fig. 2**).

Eprosartan was developed using a different hypothesis than that for losartan (**Fig. 3**). Similar to the rationale for losartan, the carboxylic acid of S-8308 was thought to mimic the Phe_8 (*i.e.* C-terminal) carboxylate of angiotensin II. The benzyl group of S-8308 was proposed to be an important structural feature which mimicked the aromatic side chain of Tyr_4 present in the agonist. Thus the major structural change was not extension of the N-benzyl group but enhancement of the compound's ability to mimic the C-terminal end of angiotensin II.

This was accomplished by substituting the 5-acetic acid group with an α-thienylacrylic acid. In addition, a para-carboxylate, a functional group investigated during the development of losartan, was also added. The thienyl ring isosterically mimics the Phe_8 phenyl ring of angiotensin II and along with the para-carboxylate is responsible for the excellent potency (IC_{50} = 0.0015μM) of this compound [3].

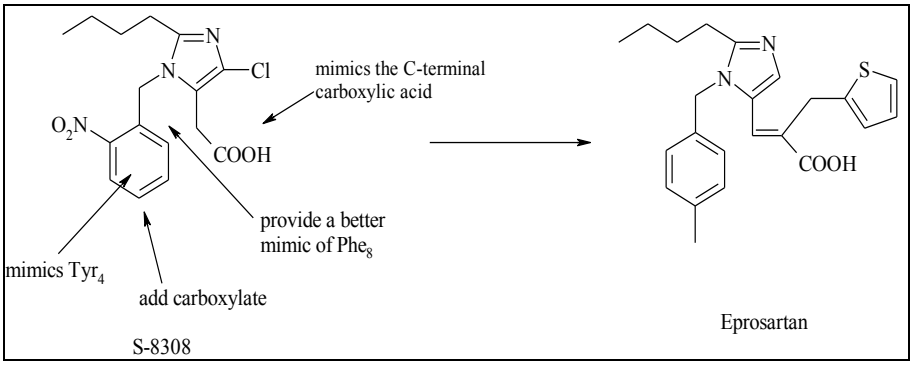
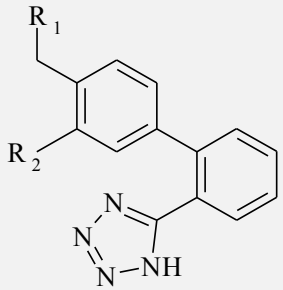
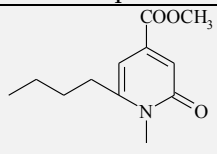
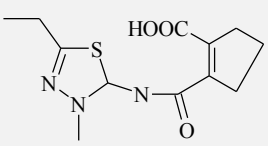
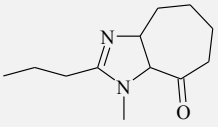


FIG. 3: STRUCTURAL MODIFICATION OF S-8308 TO DEVELOP EPROSARTAN

Amongst the other derivatives of SARTANs should mention embusartan (BAY 10-6734), with a dihydropyridinone ring, orally active AT_1 antagonist [5]; KRH-594 an acyliminothiadiazoline, selective AT_1 antagonist [6]; KT3-671 (now known as KD3-671) has a seven-membered ring fused to imidazole ring. KT3-671 is potent, competitive, selective AT_1 antagonist (**Table 1**) [7].

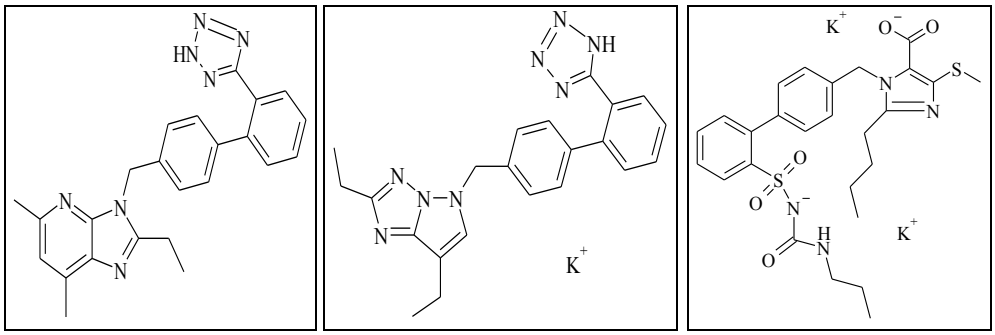
TABLE 1: CHEMICAL STRUCTURES OF NONPEPTIDE AT_1 RECEPTOR ANTAGONISTS UNDER CLINICAL TRIALS



Compound	R_1	R_2
Embursartan (BAY 10-6734)		-F
KRH - 594		-H
KT3- 671		-H

Losartan, valsartan, irbesartan, and eprosartan all show selectivity for this AT_1 subtype receptor. They prevent and reverse all of the known effects of angiotensin II, including rapid and slow pressor responses, stimulatory effects on the peripheral sympathetic nervous system, CNS effects, release of catecholamines, secretion of aldosterone, direct and indirect renal effects, and all growth-promoting effects. Replacement of the imidazole ring of losartan with heterocyclic ring also led to synthesis of many nonpeptide AT_1 antagonists. In-house 5-nitrobenzimidazole derivatives with varying substituents at 2-position, which have been designed, and synthesized have shown modest affinities for angiotensine II AT1 receptor [8].

The imidazole ring has been successfully replaced by fused heterocyclic ring systems also. Imidazo[4,5-b]pyridine derivatives *i.e.* L-158809 (**Fig. 4**) [9], which has shown highly selective AT_1 receptor antagonist activity in halothane-anesthetized *in-vivo* canine model [10]. YM 358 (**Fig. 4**) has long-lasting antihypertensive effect [11] with no rebound hypertension on discontinuation of therapy. It is 3-10 times more potent than losartan and is a competitive AT_1 antagonist as shown in *in-vitro* and *in-vivo* rat, rabbit and canine hypertension models [12]. HR 720 (**Fig. 4**), now named as fonsartan, has a sulfonylurea replacement for the tetrazole moiety and 4-alkylthio substituent at imidazole ring. It is highly potent (10 times more potent than losartan) and selective noncompetitive AT_1 antagonist in isolated rabbit aorta and human gastroepiploic arteries [13].



L158809 **YM 358** **HR 720**

FIG. 4: CHEMICAL STRUCTURES OF L-158809, YM 358, HR 720

Novel Synthetic Molecules Acting on the AT_1R: Agelis *et al.*, [14, 15] synthesized a series of symmetrically bis-substituted imidazole analogues bearing at N-1 and N-3 two biphenyl moieties ortho-substituted either with tetrazole or carboxylate groups. Among them, the imidazolium (BV6, **Fig. 5**) showed superior antagonistic activity and receptor affinity to that of losartan.

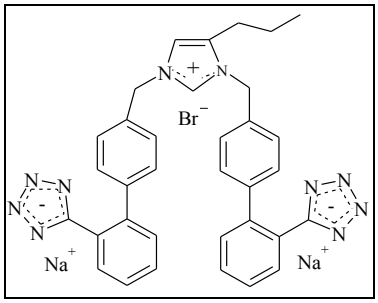
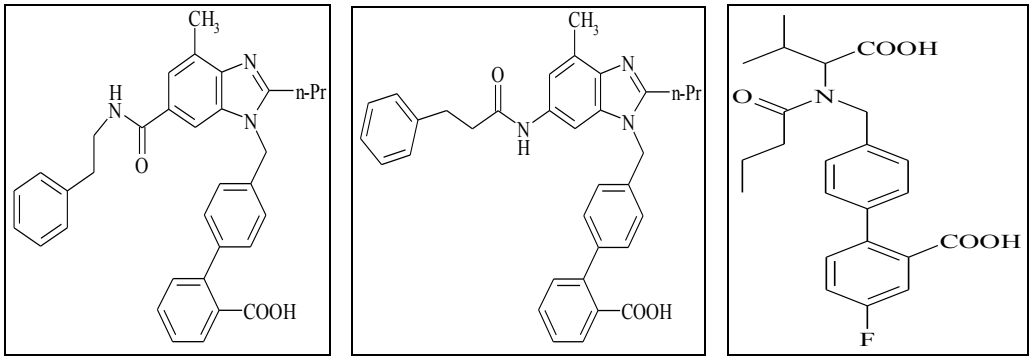


FIG. 5: CHEMICAL STRUCTURE OF BV6

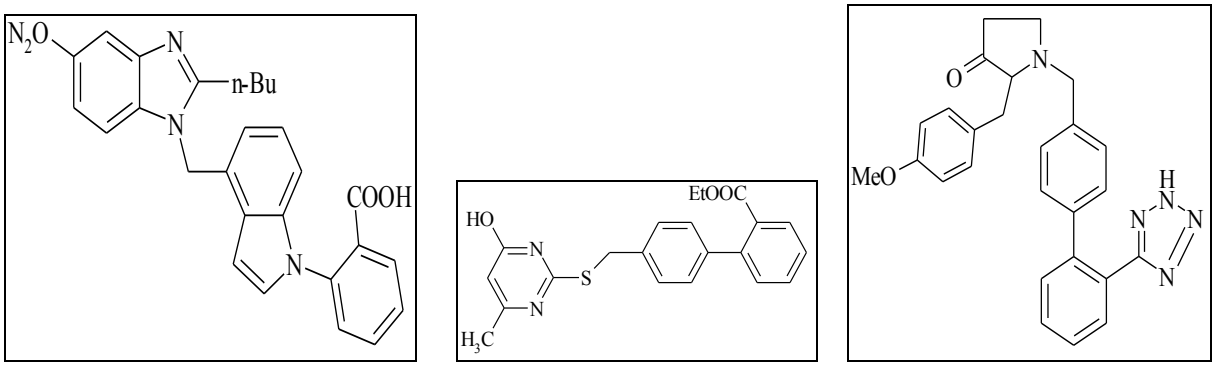
Compounds A and B (**Fig. 6**) were synthesized by Zhang *et al.*, [16], and are promising selective AT_1R antagonists. Da *et al.*, [17]synthesized fluorine substituted derivatives of losartan, valsartan and irbesartan with carboxylic acid group as replacement to the known potent tetrazole moiety at the 2'-biphenyl position. The biphenyl C (**Fig. 6**) showed an efficient and long lasting effect in reducing blood pressure which lasted more than 24 h at a dose of 10mg/kg in spontaneous hypertensive rats, which was much better than controls losartan and valsartan. In addition to antihypertensive property, the biphenyl C also inhibited prostate cancer *in vitro* and *in vivo*. The 5-nitrobenzimidazole (compound A, **Fig. 7**) exerts high nanomolar and durable activity (IC_{50} = 1.03 ± 0.26nM) in vascular smooth muscle cells. This compound bears an indole benzoic ring instead of the biphenyl scaffold with an acidic segment attached at the ortho-position, (a common feature to commercial drugs except eprosartan that contains only one phenyl ring) [18].



A **B** **C**

FIG. 6: CHEMICAL STRUCTURES OF PROMISING SELECTIVE AT_1R ANTAGONISTS

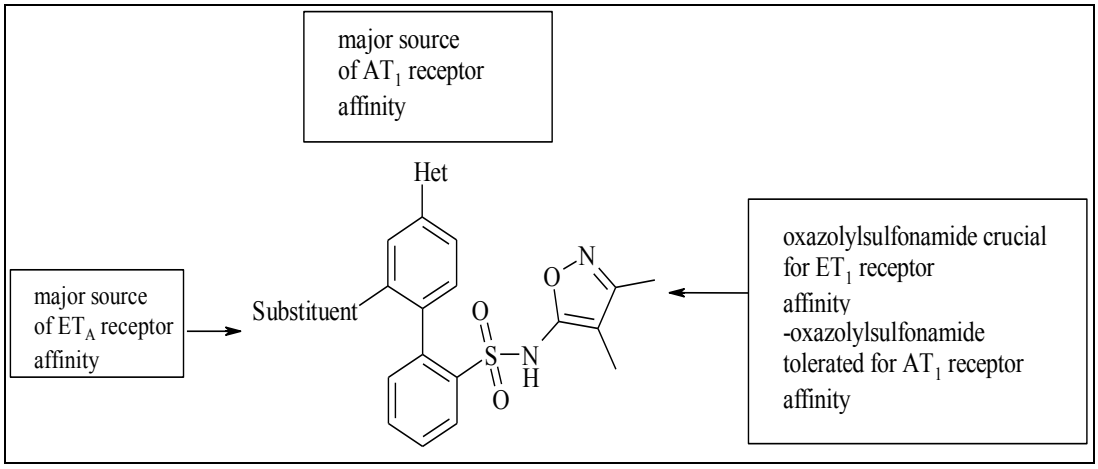
A series of compounds based on the α_1-adrenoreceptor antagonist drug urapidil and molecular modeling were synthesized. Compound B (**Fig. 7**) exhibited hypotensive activity more or less similar to losartan [19].



A **B** **C**

FIG. 7: CHEMICAL STRUCTURES OF SOME PERSPECTIVE COMPOUNDS WITH HYPOTENSIVE ACTIVITY

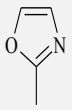
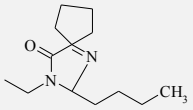
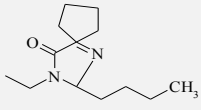
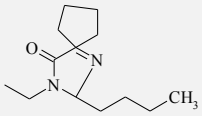
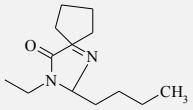
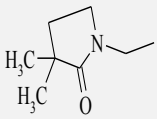
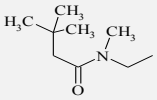
New AT_1R antagonists were designed and evaluated based on a central pyrrolidine system bearing biphenyl-tetrazoles or biphenylcarboxylic acids at the N-12, C-3 and C-4 positions. Among them compound C (**Fig. 7**) was the most promising and had 2-fold higher hypotensive activity than losartan and similar level of antihypertensive activity to losartan with LD_{50} value of 117μg/kg demonstrating in this way the high safety margin of the compound. The compound was evaluated *in vivo* for hypotensive activity on normotensive rats [20].



Multi-target Drugs: Following the molecular hybridization approach combining two discrete drugs in one molecule, numerous multi-target drug molecules, have been designed and synthesized with beneficial effects. Some such examples are outlined below.

Angiotensine II potentiates the production of endothelin (ET) and conversely endothelin augments the synthesis of angiotensine II. Thus, a combination AT_1/ET_A receptor antagonist may have a greater efficacy and broader utility compared with each drug alone. By rational drug design, a biphenyl ET_A receptor blocker was modified to acquire AT_1 recetor antagonism (**Table 2**). Out of the synthesized series of 6 compounds (A-F), compounds C and D are novel agents for treating a broad spectrum of patients with essential hypertension and other cardiovascular diseases [21]. The compound F demonstrates superiority over irbesartan (an AT_1-receptor antagonist) in the normal SHR model of hypertension in a dose-dependent manner, demonstrating the synergy of AT_1 and ET_A receptor blockade in a single molecule [22].

TABLE 2: CHEMICAL STRUCTURES AND SAR OF SOME AT_1/ET_A RECEPTOR ANTAGONISTS

Compound	A	B	C	D	E	F
Het						
Substituent	H	H		OEt		CH_2OEt

Compound BMS-1 or (butyryl-[2′-(4, 5-dimethyl-isoxazol-3- ylsulfamoyl)- biphenyl- 4- ylmethyl]- amino)-N-isopropyl-3-methyl-butyramide (**Fig. 8**) is also a potent dual acting AT_1 and ET_A receptor antagonist. As exemplified by 2-(butyryl-[2′-(4-fluoro-5-methyl-isoxazol-3-ylsulfamoyl)-biphenyl-4- ylmethyl]- amino)- *n*- isopropyl- 3- methyl-butyramide (BMS-3) (**Fig. 9**), a fluorinated analog of BMS-1, BMS-3 could be metabolized by both cytochrome P (CYP) enzymes, CYP2C9 and CYP3A4, and thus avoiding the reliance on a single CYP enzyme for metabolic clearance [23].

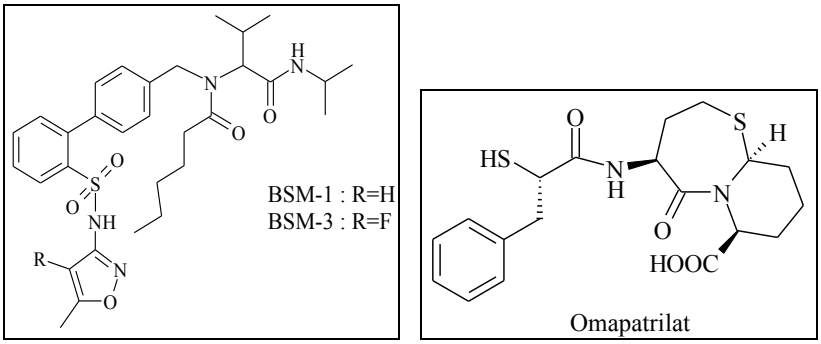
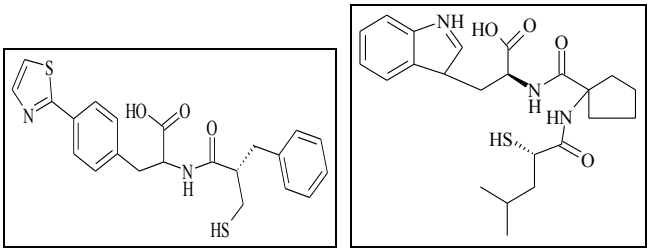


FIG. 8: CHEMICAL STRUCTURE OF THE NEW DUAL-ACTION RECEPTOR ANTAGONISTS

Earlier, losartan and EXP 3174 and recently, irbesartan have been shown to inhibit thromboxane A_2 induced contractions in canine coronary arteries by inhibiting the vascular TxA_2/PGH_2 receptor. EK112 is a new combined AT_1 and thromboxane A_2 receptor blocking agent. The antagonistic effect of these agents on the thromboxane A_2 receptor may contribute to the long-termblood pressure lowering effects of AT_1 antagonists in hypertension [24]. Omapatrilat (**Fig. 8**) is the ACE/NEP inhibitor that has been most extensively studied. Omapatrilat is a potent, long acting dual metalloproteinase inhibitor (ACE IC_{50} = 5nmol/l, NEP IC_{50} = 8nmol/l) and exerts prolonged antihypertensive effects in several experimental models of hypertension including the DOCA salt hypertensive model and the SHR [25].

Fosidotrilat, sampatrilat, Z13752A (GW660511X, **Fig. 9**) are some more novel ACE/NEP inhibitors. The latter compound has also shown efficacy against ventricular fibrillation and tachycardia in a canine model of coronary artery occlusion which is attributed to the protective effects of increased bradykinin levels [26].



Z13752A **CGS 35601**

FIG. 9: CHEMICAL STRUCTURES OF Z13752A AND CGS 35601

The concept of triple vasopeptidase inhibition has recently gained interest. In this case, ACE/NEP inhibition is supplemented by additional inhibition of endothelin converting enzyme (ECE) blocking the conversion of big ET-1 to ET-1, a vasoconstrictor and profibrotic agent acting in synergy with angionensine II. Preliminary studies in experimental settings such as the SHR have shown that triple therapy, with CGS 35601 (**Fig. 9**), dose dependently reduced blood pressure, decreased angionensine II and ET-1 concentrations as well as proANP, but increased big ET-1, ANP and bradykinin. These data suggest that CGS 35601, a triple vasopeptidase inhibitor, may represent a novel class of antihypertensive drugs and may have the potential to reduce morbidity and mortality from cardiovascular disorders, diabetes and subsequent renal complications [27].

Mojarrad *et al.*, described [28] an attempt to design and synthesize molecules that combine structural elements present in AT_1R antagonist and 1, 4-dihydropyridine calcium channel blockers. Among the synthesized molecules, eight showed both calcium channel and AT_1R blocking activities. Interestingly, the effects of compound on **Fig. 10** on AT_1R were 100000 higher than losartan (**Fig. 10**).

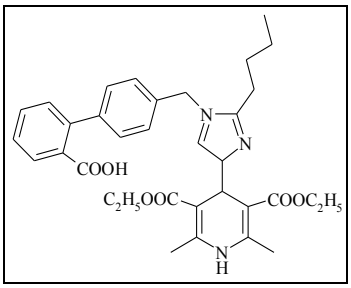


FIG. 10: DUAL CALCIUM CHANNEL AND AT1R BLOCKER

Compounds A and B (**Fig. 11**) exert potent dual activity, AT_1R antagonism and partial proliferator-activated receptor-γ (PPARγ) agonism and have desirable ADME properties [29, 30].

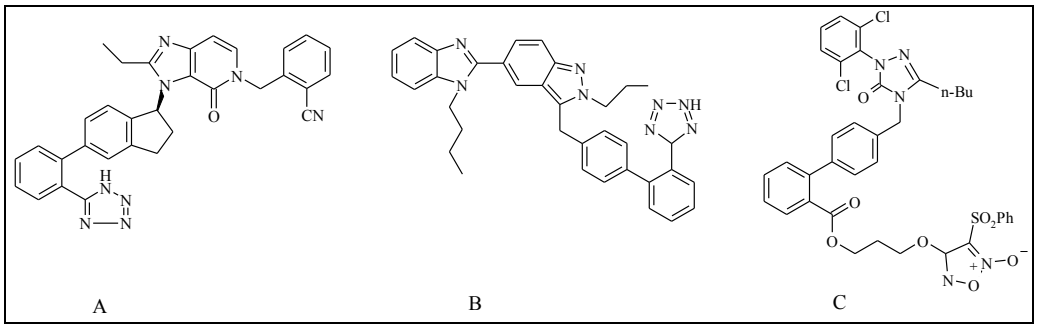


FIG. 11: THE COMPOUNDS WITH DUAL AT_1R ANTAGONISM AND PPARΓ AGONISM

A series of nitric oxide donating derivatives of [1,2,4]triazol-5(4*H*)-one exert both high AT_1R antagonist activity and good maximum NO release; compound C is the most promising amongst them (**Fig. 11**) [31].

AT_2R Agonists and Antagonists: As mentioned above, for a long time the scientific community neglected AT_2R and its major physiological role remained elusive [32-34]. However, the design and synthesis of the some selective AT_2R antagonists and agonists (PD 123,319 [35] CGP-42112A [36], M024/C21 [37], EMA401) that entered clinical trials for the treatment of neurophathic pain led to an understanding of the physiological role of this receptor and the design and synthesis of molecules possessing beneficial effects [38, 39].

Establishing ligands that will present enhanced selectivity for AT_2R *vs.* AT_1R is based on the fact that AT_2R antagonizes the functions of AT_1R. Activation of AT_2R leads to apoptosis, antiproliferation and vasodilation, whereas activation of AT_1R leads to cellular growth, proliferation and vasoconstriction [40]. Wan *et al.*, synthesized the first selective nonpeptide AT_2R agonist M024/C21 (**Fig. 12**) by stepwise simplification of the nitrogen containing

heterocyclic ring system [41, 42]. The substitution of the thienyl-phenyl to the biphenyl scaffold (resembling L162.782, **Fig. 12**) produced the equipotent C showing that the two scaffolds are bioisosteric in these compounds [43]. Compound D, a derivative of L162.782, was synthesized by Liu *et al.*, in an attempt to develop new AT_2R agonists as novel antihypertensive candidates. The compound was superior to the reference drug losartan in SHRs and it had no significant impact in heart rate [44].

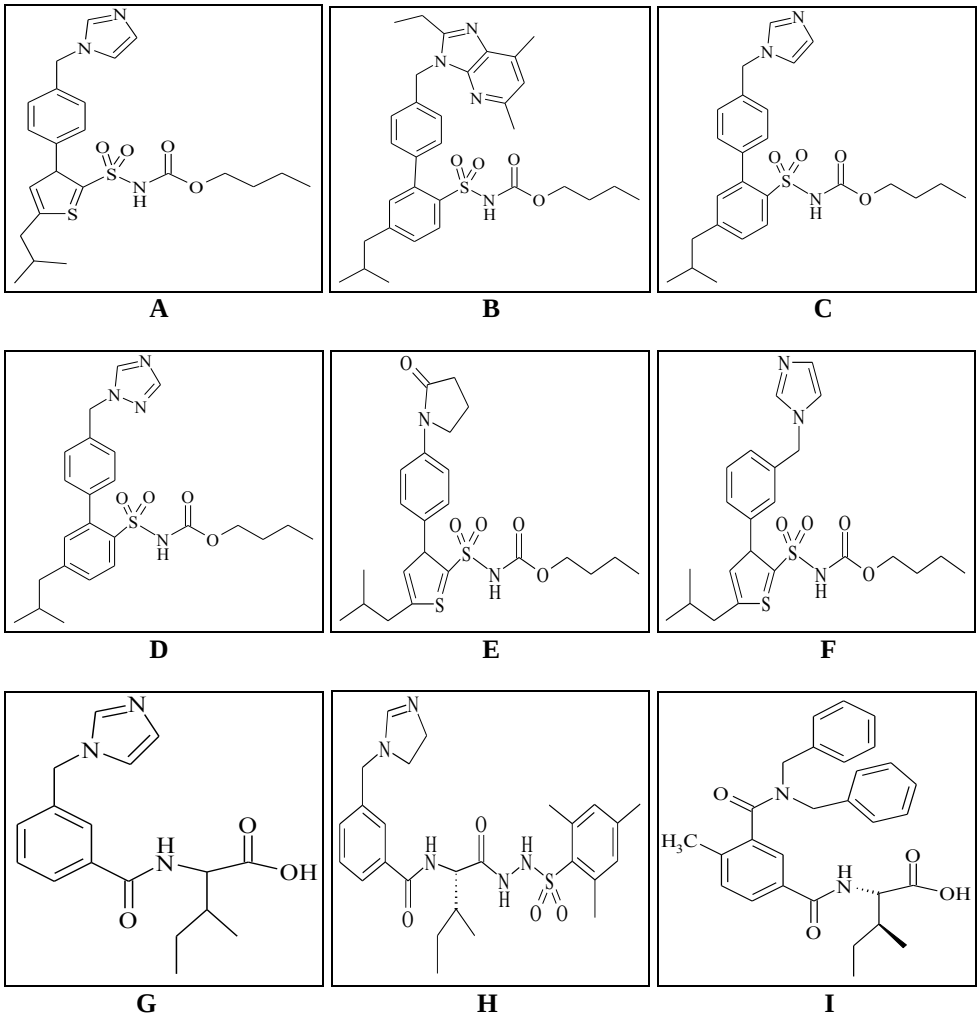


FIG. 12: CHEMICAL STRUCTURES OF THE FIRST SELECTIVE NONPEPTIDE AT_2R AGONISTS

Mahalingam *et al.*, synthesized derivatives of AT_2R agonist M024/C21 (**Fig. 12**) in an attempt to reduce the CYP450 inhibitory property. The best analogue prepared was compound E (**Fig. 12**) which induced neurite elongation in NG 108-15 cells and served as a potent and selective AT_2R agonist [45]. These scientists also synthesized another analog of MO24/C21 – compound F**,** a selective AT_2R antagonist, which is meta- rather than para-substituted on the phenyl ring [46].

Veron *et al.*, used compound G, which bears structural similarities with the C-terminal segment of angiotensine II, as a lead to synthesize sixteen new C-terminally modified analogues. Specifically, it contains a carboxylate group as Phe8, isoleucine side chain instead of benzene of Phe_8 and imidazole ring as His_6. Compound H proved the most active and was over 12-fold more potent than the lead compound G. All the synthesized compounds were evaluated for their human AT_2R affinity in a radio ligand binding assay measuring the displacement of CGP-42112A,a selective AT_2R agonist [47]. The compound G (**Fig. 12**) also was used by Behrends *et al.*, to evaluate fifteen new synthetic derivatives, most of them showed higher activity than the lead compound, for example, the substance I [48].

SAR of Angiotensine II Antagonists: There are some common scaffolds which all commercially available angiotensin II antagonist's posses (**Fig. 13**).

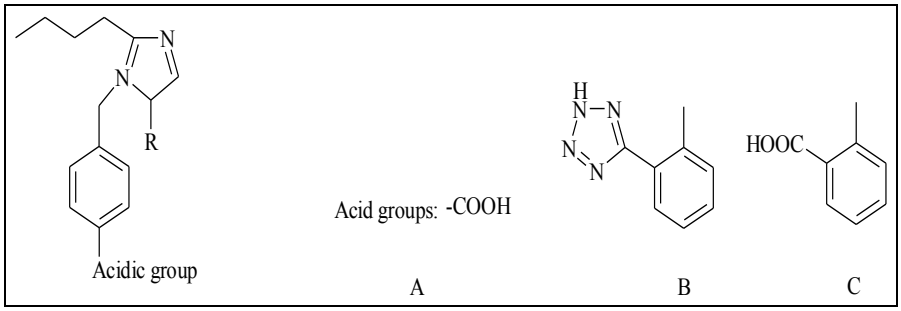


FIG. 13: COMMON SCAFFOLDS OF ANGIOTENSIN II ANTAGONISTS

1) The "acidic group" is thought to mimic either the Tyr_4 phenol or the Asp_1 carboxylate of angiotensin II. Groups capable of such a role include the carboxylic acid (A), a phenyl tetrazole (B), or a phenyl carboxylate (C).

2) In the biphenyl series, the tetrazole and carboxylate groups must be in the ortho position for optimal activity (the tetrazole group is superior in terms of metabolic stability, lipophilicity, and oral bioavailability).

3) The *n*-butyl group of the model compound provides hydrophobic binding and most likely mimics the side chain of Ile_5 of angiotensin II. As seen with candesartan and telmisartan, this *n*-butyl group can be replaced with a substituted benzimidazole ring.

4) The imidazole ring, or an isosteric equivalent, is required to mimic the His_6 side chain of angiotensin II.

5) Substitution with a variety of R groups including a carboxylic acid, methyl alcohol, an ether, or an alkyl chain is required to mimic the Phe_8 of angiotensin II.

All of these groups are thought to interact with the AT_2R, some through ionic or ion-dipole bonds and others through hydrophobic interactions [49]. Multi-target drugs will certainly continue to be an interesting and fruitful approach and potentially can lead to more beneficial drugs with fewer side effects. At the moment only the structural requirements for AT_1R antagonism are utilized.

A deeper knowledge on the molecular determinants on the AT_2R agonism and antagonism in the future will offer to medicinal chemists enhanced versatility towards the design and synthesis of new generation of more potent compounds.

This effort to synthesize more selective drugs will certainly be continued. Another research activity which appears promising in the future is the synthesis of molecular hybrids and multi-target drugs. Due to the complexity of the systems that are involved in the cardiovascular diseases and others related to AT_1R and AT_2R the use of multi-target drugs will lead to beneficial aspects for treating these diseases avoiding in the same time side-effects.

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