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Life Sciences 81 (2007) 615–639
Life Sciences
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Minireview

An update on non-peptide angiotensin receptor antagonists and related RAAS modulators

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Received 14 January 2007; accepted 20 June 2007

Abstract

The renin–angiotensin–aldosterone-system (RAAS) is an important regulator of blood pressure and fluid-electrolyte homeostasis. RAAS has been implicated in pathogenesis of hypertension, congestive heart failure, and chronic renal failure. Aliskiren is the first non-peptide orally active renin inhibitor approved by FDA. Angiotensin Converting Enzyme (ACE) Inhibitors are associated with frequent side effects such as cough and angio-oedema. Recently, the role of ACE2 and neutral endopeptidase (NEP) in the formation of an important active metabolite/mediator of RAAS, ang 1–7, has initiated attempts towards development of ACE2 inhibitors and combined ACE/NEP inhibitors. Furukawa and colleagues developed a series of low molecular weight nonpeptide imidazole analogues that possess weak but selective, competitive AT_1 receptor blocking property. Till date, many compounds have exhibited promising AT_1 blocking activity which cause a more complete RAAS blockade than ACE inhibitors. Many have reached the market for alternative treatment of hypertension, heart failure and diabetic nephropathy in ACE inhibitor intolerant patients and still more are waiting in the queue. But, the hallmark of this area of drug research is marked by a progress in understanding molecular interaction of these blockers at the AT_1 receptor and unraveling the enigmatic influence of AT_2 receptors on growth/anti-growth, differentiation and the regeneration of neuronal tissue. Different modeling strategies are underway to develop tailor made molecules with the best of properties like Dual Action (Angiotensin And Endothelin) Receptor Antagonists (DARA), ACE/NEP inhibitors, triple inhibitors, AT_2 agonists, AT_1/TxA_2 antagonists, balanced AT_1/AT_2 antagonists, and nonpeptide renin inhibitors. This abstract gives an overview of these various angiotensin receptor antagonists.

Keywords: Angiotensin; AT_1; AT_2; Antagonists; Agonists

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doi:10.1016/j.lfs.2007.06.007

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Introduction

The renin–angiotensin–aldosterone-system (RAAS) is an important regulator of blood pressure and fluid-electrolyte homeostasis (Van Epps, 2005). RAAS has been implicated in pathogenesis of hypertension (Frohlich, 2001), congestive heart failure (Opie and Sack, 2001), and chronic renal failure (Ruster and Wolf, 2006). Of particular interest is the recently identified local pancreatic renin-angiotensin system (RAS) and, perhaps more importantly, the finding that it is up-regulated in animal models of type 2 diabetes mellitus (T2DM). This putative local RAS may regulate pancreatic islet blood flow, oxygen tension, and islet (pro)insulin biosynthesis. It might also mediate the generation of reactive oxygen species, thereby causing oxidative stress-induced pancreatic beta-cell apoptosis and fibrosis. Moreover, findings that RAS blockade improved beta-cell secretory function and cell mass in experimental animal models of Type 2 diabetes indicate that inhibition of RAS activation may play a pivotal role in protecting islet cell function, and furthermore may prevent the development of overt T2DM (Leung, 2007). A recent report showed mast cells as an additional source of renin constituting a unique extrarenal renin-angiotensin system. Because of the ubiquity of mast cells, they represent local renin–angiotensin systems, not just in the heart, but in all tissues (Silver et al., 2004). Molecular cloning (Sasaki et al., 1991) and ligand binding studies (Whitebread et al., 1989) have firmly established the concept of angiotensin II (ang II) receptor heterogeneity in mammals (Smith and Timmermans, 1994). According to current nomenclature, ang II receptors are classified into AT_1 and AT_2 subtypes (de Gasparo et al., 2000). The actions of angiotensin II, an octapeptide and a mediator of RAAS, are mediated through specific surface receptors such as AT_1 and AT_2 present on the various target organs (Vinson et al., 1995) (Fig. 1). Ang II also stimulates a cellular mitogenic response via the AT_1 receptor. A recent report suggests that the ang II mitogenic effects might be mediated via ERK1/2 (Kitos et al., 2006). Although AT_1 receptors predominate in most of the tissues, AT_2 receptors are widely expressed in fetal tissue, uterus, adrenal medullary tissue and localized in discrete parts of the brain of various species, including humans (Timmermans et al., 1993; Chung et al., 1996). Majority of physiological actions of ang II such as vasoconstriction, aldosterone and vasopressin release, sodium and water retention and sympathetic facilitation, in cell proliferation, left ventricular hypertrophy, nephrosclerosis, vascular media hypertrophy, endothelial dysfunction, neointima formation and processes leading to athero-thrombosis are mediated through the AT_1 receptors (de Gasparo et al., 2000; Kaschina and Unger, 2003). AT_2 receptor fine-tunes the regulation of natriuresis, body temperature, blood pressure, reproduction, embryonic development, cell differentiation, tissue repair and programmed cell death (Steckelings et al., 2005). AT_2 receptors are upregulated in pathophysiological processes such as cardiac remodeling following hypertension and myocardial infarction, heart failure and stroke.

Renin, identified by Tigerstedt and Bergmann in 1898, is a specific and rate-limiting enzyme for ang II formation (Van Epps, 2005). Several renin inhibitors are developed (Kleinert et al., 1991) but none from the first generation has reached the clinical trials because of their poor bioavailability due to their peptide nature (Fisher et al., 1991). At present, aliskiren is the first non-peptide orally active renin inhibitor to be approved by FDA. It is the first renin inhibitor with indications for the treatment of hypertension but has potential in cardiovascular and renal disorders too (Staessen et al., 2006). Angiotensin Converting Enzyme (ACE) inhibitors are useful in the treatment of hypertension and congestive heart failure (Massie, 1998), coronary artery diseases (Brady, 2007) and to reduce proteinuria in chronic renal diseases and in diabetic nephropathy (Miyauchi and Nakamura, 2001). However, their use is associated with frequent side effects such as cough and angio-oedema due to bradykinin accumulation (Nussberger et al., 1998). Also, bradykinin release caused by ACE inhibitors might induce catecholamine release. Enzymes other than ACE such as trypsin, cathepsin G, CAGE (chymostatin sensitive ang II generating enzyme) or chymase (Kramkowski et al., 2006) are known to produce angiotensin II (ang II). Therefore, ACE inhibitors may incompletely inhibit the formation of ang II (Nussberger et al., 1989; Kramkowski et al., 2006).

Chymase is a chymotrypsin-like serine protease secreted from mast cells. Mammalian chymases are classified into two subgroups (alpha and beta) according to structure and substrate specificity; human chymase is an alpha-chymase. An important action of chymase is the ACE-independent conversion of ang I to ang II, but chymase also degrades the extracellular matrix, activates TGF (Transforming Growth Factor) -beta1 and IL-1beta, forms endothelins and is involved in lipid metabolism. In animal models of hypertension and atherosclerosis, chymase may be involved in lipid deposition and intimal and smooth muscle hyperplasia, at least in some vessels. In addition, chymase has pro-angiogenic properties. In human diseased blood vessels (e.g. atherosclerotic and aneurysmal aorta; remodeled pulmonary blood vessels), there are increases in chymase-containing mast cells and/or in chymase-dependent

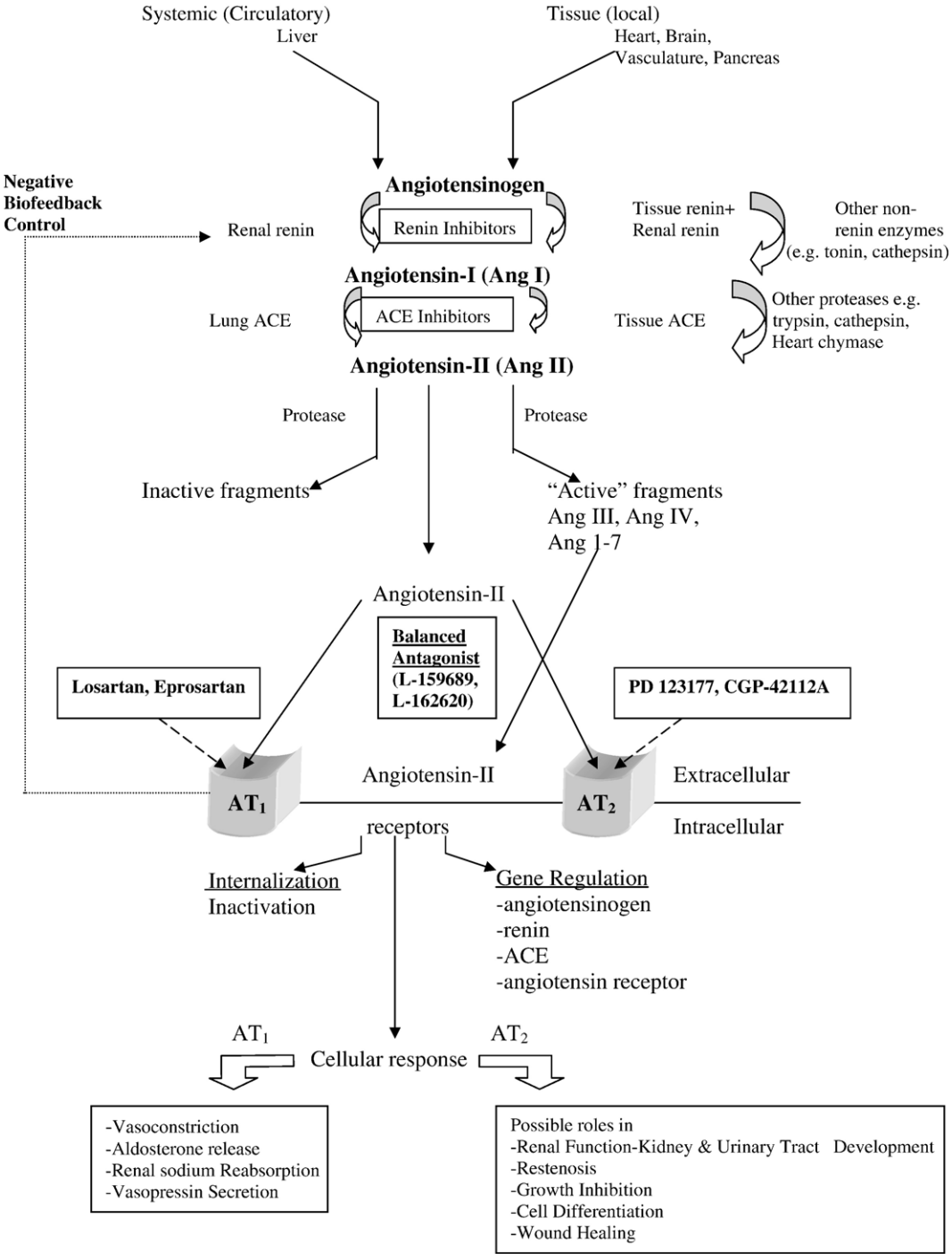

Fig. 1. Renin–angiotensin–aldosterone system: targets for intervention.

conversion of ang I to ang II. These findings have raised the possibility that inhibition of chymase may have a role in the therapy of vascular disease. The effects of chymase can theoretically be attenuated either by reducing availability of the enzyme, with a mast cell stabiliser, or alternatively with specific chymase inhibitors. Chymase inhibitors could have the advantage of being effective even if used after injury. Several orally active inhibitors, including SUN-C8257, BCEAB, NK3201 and TEI-E548, are under development. Orally active inhibitors of chymase may have a place in the treatment of vascular diseases where injury-induced mast cell degranulation contributes to the pathology (Doggrell and Wanstall, 2005).

Angiotensin-converting enzyme 2 (ACE2) has emerged as a novel regulator of cardiac function and arterial pressure by converting angiotensin II (ang II) into the vasodilator and antitrophic heptapeptide, angiotensin-(1–7) [ang (1–7)] (Brosnihan, 1998). ACE2 is more localised in its tissue expression, being found mainly in the testis, kidney, heart and intestines, in comparison to ACE which is considered to be virtually ubiquitous (19). Ang (1–7) opposes the actions of ang II by causing

vasodilation (Ueda et al., 2000), antiproliferation (Tallant et al., 1999) and apoptosis (Chappell et al., 2000). The major enzyme involved in the formation of ang (1–7) from ang I in vivo is neprilysin (NEP, neutral endopeptidase 24.11). Hence, ACE2 inhibitors and combined ACE/NEP inhibitors offer more effective strategies in search for effective antihypertensives.

Saralasin, developed as non-selective and peptide ang II receptor blocker, is reported to regulate blood pressure in hypertensive patients (Case et al., 1979) and to improve haemodynamics in congestive heart failure (Gavras et al., 1977) but it has to be administered intravenously (Turker et al., 1974) and it has behaved as a partial agonist (Streeten et al., 1975). Furukawa and colleagues (Furukawa et al., 1982a,b) have developed a series of low molecular weight nonpeptide imidazole analogues that possess weak but selective, competitive AT_1 receptor blocking property. Their bioavailability is however, limited and duration of action is short (Chiu et al., 1988). Structural modifications of these lead compounds has led to increasingly potent and orally active nonpeptide AT_1 receptor blockers i.e., losartan, eprosartan, valsartan, irbesartan, candesartan, telmisartan, zolasartan, olmesartan and saprisartan which are available for clinical treatment of mild to moderate hypertension, diabetic nephropathy, and (or at risk) heart failure following myocardial infarction (Burnier, 2001; Maggioni, 2006). Potential uses of AT_1 antagonists are in diastolic heart failure as would be decided by the I-PRESERVE (Irbesartan in Heart Failure with Preserved Systolic Function) (Bernal et al., 2006); type 2 diabetes mellitus, metabolic syndrome (Engeli, 2006; Leung, 2007), stroke (Tanahashi, 2006), prostate cancer (Uemura et al., 2006), new-onset atrial fibrillation (Anand et al., 2006), Raynaud's phenomenon (Wood and Ernst, 2006), chronic renal disease (Ruster and Wolf, 2006; Ferrari, 2007), parkinson's disease (Grammatopoulos et al., 2007), alzheimer's disease (Gard and Rusted, 2004), liver fibrosis and portal hypertension (Tox and Steffen, 2006) and aging (Basso et al., 2005).

The mode of AT_1 receptor antagonism is either competitive surmountable, competitive insurmountable or noncompetitive depending upon the dissociation rate of these antagonists from the AT_1 receptors (Lew et al., 2000; Hall and Parsons, 2001). Inverse agonist activity as shown by EXP 3174, candesartan, olmesartan is based on the constitutive expression of AT_1 receptor in certain pathological states (Miura et al., 2006). These binding characteristics may be of therapeutic relevance in management of hypertension but conclusive studies are yet to be done.

The nonpetide AT_1 antagonists have demonstrated effectiveness in preventing atheromas, improving survival in patients with heart failure caused by systolic dysfunction, decreasing endothelial dysfunction, increasing fibrinolysis, reducing proteinuria and preserving kidney function in diabetic patients (Chung and Unger, 1999).

Discovery of losartan and eprosartan

Furukawa and colleagues at Takeda Chemical Industries at Osaka in Japan (Furukawa et al., 1982a,b) are the first to discover a series of nonpeptide 1-benzylimidazole-5-acetic acid derivatives such as, S-8307 (CV 2947) and S-8308 (CV 2961), to block the responses of ang II. These compounds are shown to possess moderate potency, limited oral bioavailability and short duration of action but are selective and competitive AT_1 receptor antagonists without any partial agonistic properties (Chiu et al., 1988). Therefore, these low molecular weight imidazole compounds have served as lead compounds for further optimization of AT_1 receptor antagonists.

Losartan (Duncia et al., 1990) and eprosartan (Weinstock et al., 1991) are visualized on the basis of Dreiding models and computer aided drug designing (Smeby and Fermandjian,

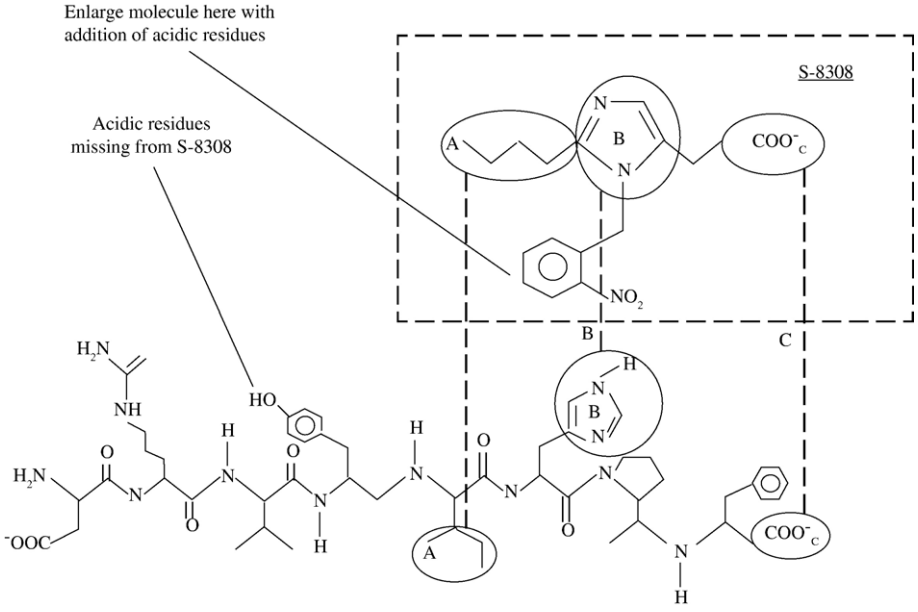

Fig. 2. Molecular modelling strategy to incorporate pharmacophoric group of angiotensin II to lead compound, S-8308.

1978), using pharmacophoric group of ang II in benzylimidazole lead compounds such as S-8308, (Fig. 2). This modelling strategy has led to the synthesis of losartan or DuP 753 or MK-954 (Timmermans et al., 1991) (Fig. 3).

Structure–activity relationships of the various compounds synthesized during the development of losartan (Duncia et al., 1990) have revealed various binding sites present on ang II AT_1 receptors (Fig. 4).

Pharmacological properties of losartan and eprosartan with important clinical data

Losartan is orally active nonpeptide ang II-AT_1 receptor (AT_1) antagonist. It exhibits competitive antagonism in guinea pig ileum (Wong et al., 1990a), rabbit aorta, rabbit juglar vein, rabbit pulmonary artery, rat portal vein, rat stomach, rat urinary bladder, human urinary bladder, human colon and human ileum (Rhaleb

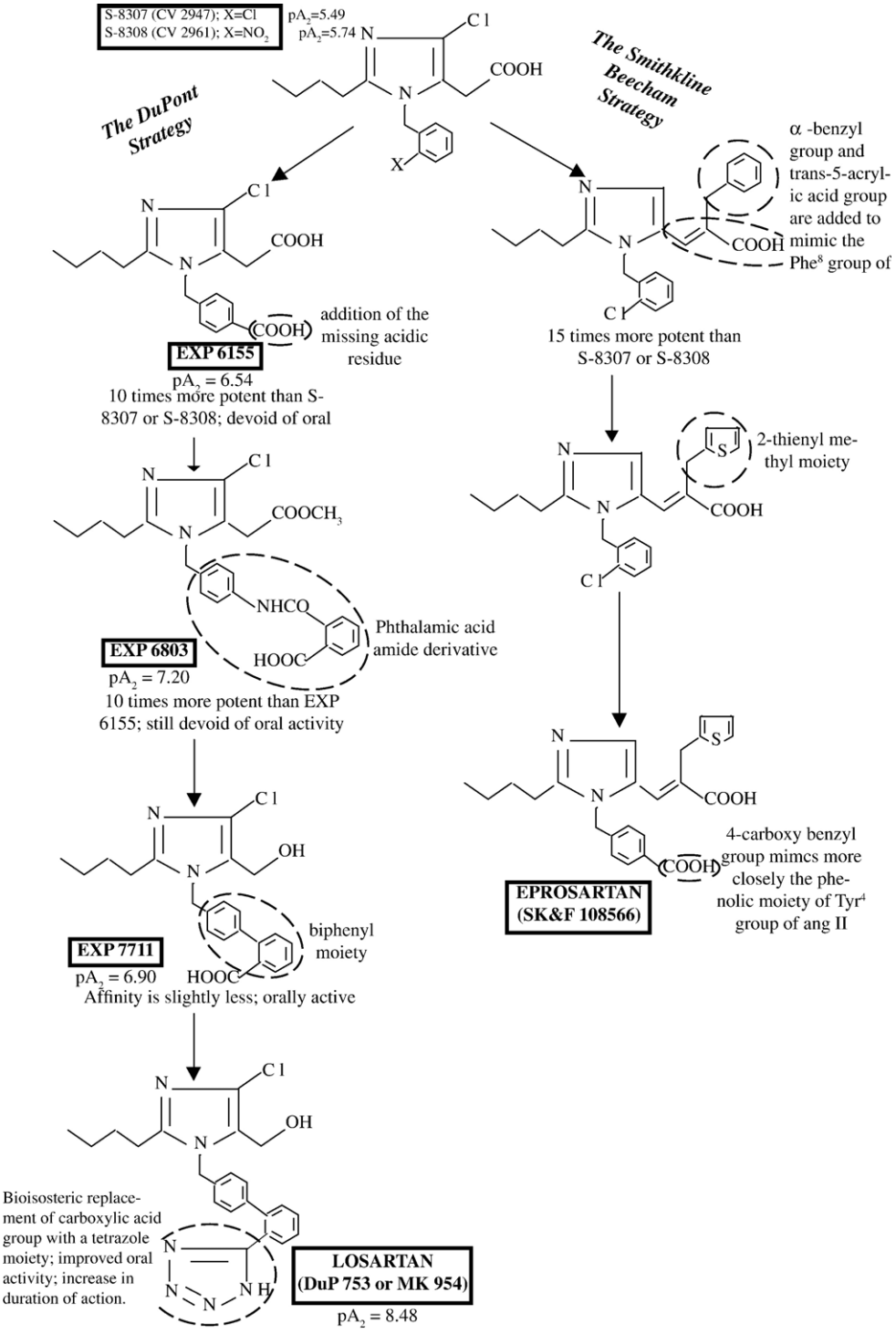

Fig. 3. Structural modification of S-8307 (CV 2947) and S-8308 (CV 2961) compounds to develop Losartan and Eprosartan; pA_2 values are obtained with ang II using isolated rabbit aorta.

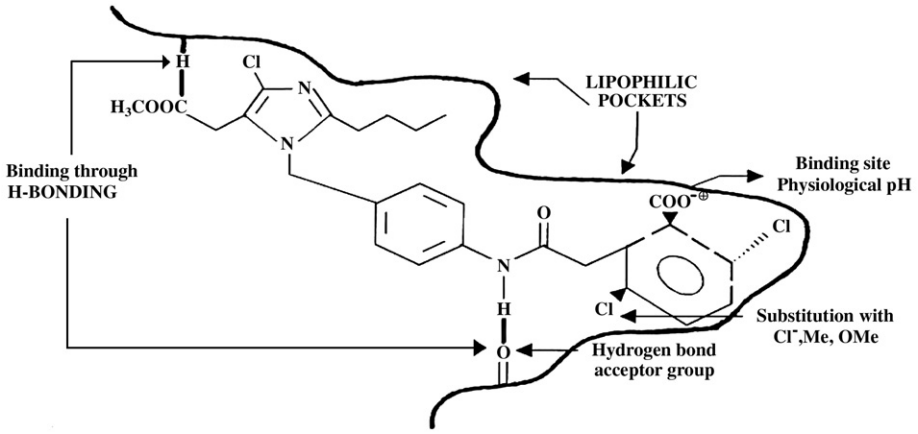

Fig. 4. Various binding sites of angiotensin II-AT_1 receptor.

et al., 1991; Tanabe et al., 1993) and noncompetitive antagonism in human subcutaneous arteries (Garcha et al., 1999). Losartan abolishes ang II-induced pressor and dipsogenic response and inhibits the release of aldosterone in rat (Wong et al., 1990a). Losartan is demonstrated to be a selective (Wong et al., 1991) and competitive antagonist of AT_1 receptors. However, the noncompetitive antagonism of losartan observed in human subcutaneous arteries is explained on the basis of two-state receptor model (Robertson et al., 1994). The two-state receptor model accounts for factors governing receptor state transitions at rest and species- or tissue-based differences in the behaviour of antagonist (Garcha et al., 1999). Losartan is not a partial agonist like saralasin (Chiu et al., 1991). Losartan is noted to decrease blood pressure in spontaneously hypertensive rats (SHR) but is ineffective in normotensive and renin independent deoxycorticosterone acetate (DOCA) hypertensive rat model (Wong et al., 1990b,c). There is a marked orthostatic cardiovascular response specific for losartan, and that it may be due, in part, to an interaction of this antagonist with ang-(1–7) receptors, probably at the cardiac level (de Moura et al., 2005). Losartan exhibits antiarrhythmic activity in simulated ventricular ischaemia and reperfusion and this action of losartan is independent of its AT_1 receptor blockade (Thomas et al., 1996). In many animal species as well as in humans, losartan is metabolized to EXP 3174 (Yun et al., 1995), which is more potent AT_1 receptor antagonist than losartan (Wong et al., 1990e). EXP 3174 has served as a template for the development of several other AT_1 receptor antagonists (Sweet and Nelson, 1993).

The ELITE clinical trial's (Evaluation of losartan in the Elderly) one-year follow-up has revealed that losartan and captopril are equally effective to provide renal safety in elderly patients with heart failure (Pitt et al., 1997). However, there were slightly, but not significantly, more deaths in the group treated with losartan (Burnier and Brunner, 1998). In ELITE II, the effects of losartan on heart failure related outcomes and quality of life were not superior to those of captopril (Konstam et al., 2005; Pitt et al., 2000). LIFE clinical trial (Losartan Hypertension Survival Study) has compared losartan with atenolol in hypertensive patients with left-ventricular hypertrophy, associated with coronary heart disease or diabetes mellitus (Dahlof et al., 1997). Losartan decreased the composite end point (cardiovascular mortality, MI, and stroke), stroke, and new-onset diabetes significantly more than atenolol for a similar reduction in blood pressure (Dahlof et al., 2002). Thus, the observed outcomes benefits favoring losartan may involve other possible mechanisms, including differential effects of losartan and atenolol on LVH regression, left atrial diameter, atrial fibrillation, brain natriuretic peptide, vascular structure, thrombus formation/platelet aggregation, serum uric acid, albuminuria, new-onset diabetes, and lipid metabolism. Sub-analyses of the LIFE study data suggest that losartan's stroke benefit may arise from a mosaic of mechanisms rather than a single action (Devereux and Dahlof, 2007). OPTIMAAL (Optimal Trial in Myocardial Infarction With the angiotensin II antagonist losartan) clinical trial compares losartan once daily monotherapy with captopril in post myocardial infarction patients with left ventricular dysfunction (Dickstein et al., 1999). Losartan was no better than captopril at preventing all-cause mortality, sudden or resuscitated cardiac death, or reinfarction; cardiovascular death was more common with losartan (Dickstein et al., 2002). RENAAL clinical trial (Losartan Renal Protection Study) is an attempt to compare losartan with standard therapy comprising of diuretics, vasodilators, and/or beta blockers in type II diabetic patients suffering from nephropathy (Burnier and Brunner, 1998; Toto, 2001). Losartan delayed progression of renal impairment, evaluated as a doubling of serum creatinine concentration or the development of end-stage renal disease (Kurokawa et al., 2006). Results of Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease (COOPERATE) trial (Kruger et al., 2003) as well as COOPERATE-ABP (ambulatory BP) trial (Nakao et al., 2004), designed to assess whether dual blockade of angiotensin-converting-enzyme (ACE), with trandolapril, and the AT_1 receptor, with losartan, was more efficacious than either ACE inhibition or AT_1 antagonism alone in non-diabetic renal disease, reveal that combination treatment should be considered in non-diabetic renal disease especially if the disease is progressing with ACE treatment alone (Doggrell, 2003). The better renoprotective effect of the combination treatment is attributed to BP-independent mechanisms by more complete renin-angiotensin system blockade.

The use of Fermandjian model has led to the synthesis of eprosartan (Weinstock et al., 1991), which is representative of one of the few AT_1 antagonists designed and derived independently of benzylimidazole lead compounds (Samanen et al., 1993) (Fig. 3). Eprosartan is a potent, selective and competitive AT_1 antagonist (Edwards et al., 1992). It is effective to reduce blood pressure in various animal models (Brooks et al., 1999). Eprosartan, alone or in combination with hydrochlorthiazide, provides an effective and well-tolerated approach to lowering blood pressure in patients with all grades of hypertension (Juan et al., 2004). Moreover, eprosartan produces AT_1 receptor independent sympathoinhibitory response (Brooks et al., 1999). It induces dual blockade of AT_1 receptors both presynaptically and postsynaptically, reducing sympathetic nerve activity to a significantly greater degree than other AT_1 receptor blockers. This dual property makes it an ideal candidate for use in chronic kidney disease (Blankestijn, 2005).

New losartan and eprosartan derivatives in clinical use

Data from important clinical trials completed/underway

Several losartan and eprosartan derivatives and related compounds have been released for clinical use (Figs. 5 and 6). Blood pressure, proteinuria, left-ventricular hypertrophy, and haemodynamics are surrogate end points and large clinical trials are complete/underway to establish the morbidity and mortality benefits of specific AT_1 receptor blockade in patients with hypertension, chronic renal failure, or heart failure (Table 1). Their results suggest that longer acting angiotensin II antagonists such as irbesartan, candesartan, and telmisartan may be more effective than losartan, particularly at trough, thus providing better 24-hour control of blood pressure (Burnier, 2001). Recent studies of the ACE inhibitor, perindopril, have revealed preservation of beneficial vascular and endothelial effects mediated by bradykinin and nitric oxide in coronary artery disease patients. The selective blockade exerted by AT_1 receptor antagonists is not associated with these effects. Whether there is an actual difference in protection from MI remains unresolved, although available data confirm the benefit and safety of ACE inhibitors, in particular perindopril, for myocardial protection (Brady, 2007).

Valsartan represents a nonheterocyclic AT_1 receptor selective antagonist in which the imidazole of losartan has been replaced by an acylated amino acid (Buhlmayer et al., 1994). VALUE clinical trial (Valsartan Antihypertensive Long-Term Evaluation) compares valsartan with amlodipine in more than 14,000 hypertensive patients on the basis of age (Burnier and Brunner, 2000). A greater blood pressure decrease was noted in the amlodipine group. The only exception was sex, in which the amlodipine-based regimen was more effective than valsartan in women, but not in men, whereas the valsartan regimen was more effective in preventing cardiac failure in men than in women (Zanchetti et al., 2006). The relative risks of heart failure and new-onset diabetes favored valsartan (Julius et al., 2006). The Val-HeFT (Valsartan Heart Failure Trial) clinical trial compares valsartan with ACE inhibitor, captopril, in various populations of heart failure patients such as ACE-inhibitor naive or ACE-inhibitor intolerant. Valsartan is administered once or twice daily as monotherapy or in combination with ACE-inhibitor, captopril (Willenheimer et al., 1999). The trial has shown unchanged rate of mortality but reduced rate of atrial fibrillation, morbidity, including hospitalization, in case of valsartan (Maggioni et al., 2005). VALIANT clinical trial is designed in post-myocardial infarction patients with left ventricular dysfunction. Valsartan is administered twice a day in combination with captopril (Cohn et al., 2001). Valsartan was as effective as captopril at decreasing all-cause mortality and a composite of cardiovascular death, MI, and heart failure hospitalization (Maggioni and Fabbri, 2005); combination of valsartan and captopril offered no additional benefit but increased the rate of adverse events (White et al., 2005). The ABCD-2V trial will evaluate the impact of valsartan in normotensive and hypertensive patients with non-insulin dependent diabetes mellitus. The goal is to compare the effect of intensive versus moderate control of blood pressure on diabetic complications and mortality (Toto, 2001). Irbesartan is a potent AT_1 receptor antagonist which incorporates an imidazolinone ring in which a carbonyl group functions as a hydrogen bond acceptor in place of the hydroxymethyl group of losartan (Christophe et al., 1995). The Irbesartan Diabetic Nephropathy Trial (IDNT) compares irbesartan with amlodipine and standard therapy comprising of diuretics, vasodilators or beta-blockers in three parallel groups (Toto, 2001). Irbesartan slowed progression of renal deterioration significantly more than amlodipine, despite comparable blood pressure reductions (Lewis et al., 2001). The benzimidazole, candesartan cilexetil (TCV 116), developed at Takeda Chemical Industries, is an ester carbonate prodrug that is rapidly converted to the corresponding 7-carboxylic acid, candesartan (CV 11974) in vivo (Shibouta et al., 1993). CV 11974 is 30- to 100-fold more potent than TCV 116 (Flesch et al., 1995). CV 11974 is a potent, long acting selective AT_1 receptor, competitive insurmountable antagonist (Nishikawa et al., 1994). The carboxyl group at the benzimidazole ring plays an important role in the interaction of CV11974 with AT_1 receptor (Noda et al., 1993). The antipressor effects of CV 11974 and TCV 116 are 12 and 48 times more than those of EXP 3174 and losartan administered intravenously and orally, respectively (Shibouta et al., 1993). 2-Alkyl benzimidazoles have comparable binding affinities with that of losartan, which suggests that chloro, and hydroxymethyl substituents in losartan are not of critical importance for receptor binding (Thomas et al., 1992). The SCOPE clinical trial (Study on Cognition and prognosis in the Elderly) compares candesartan with placebo in hypertensive patients aged 70-89. The placebo group receives diuretic to achieve a blood pressure below 160/85 mm Hg. A mini mental state examination will be used to assess the impact on cognitive function (Trenkwalder, 2000). SCOPE strongly suggests that candesartan treatment reduces cardiovascular morbidity and mortality in old and very old patients with mild to moderate hypertension. Candesartan-based antihypertensive treatment may also have positive effects on cognitive function and quality of life (Zanchetti and Elmfeldt, 2006). The Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity Program (CHARM) clinical trials, CHARM I, CHARM II and

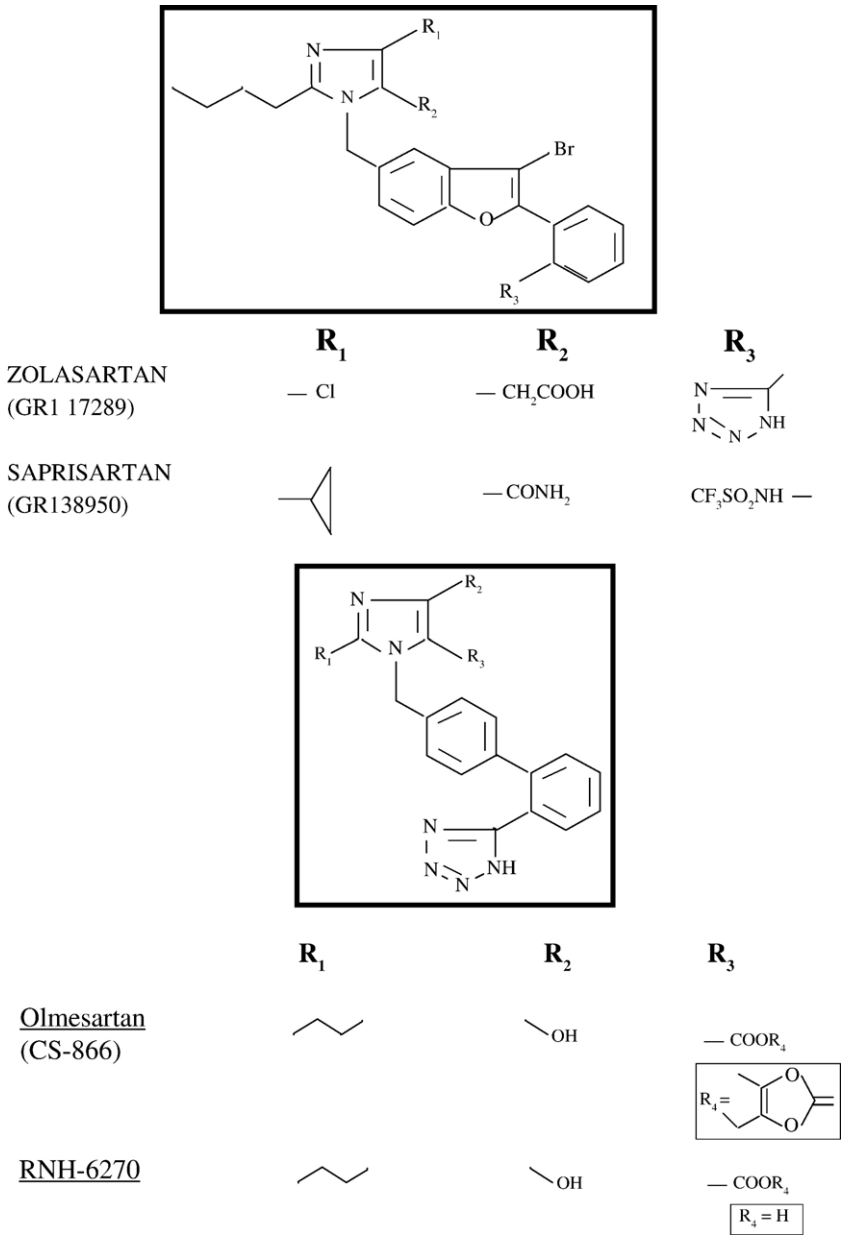

Fig. 5. Chemical structures of new AT_1 receptor antagonists in clinical use.

CHARM III, compare candesartan with ACE inhibitor, captopril in various populations of heart failure patients such as ACE-inhibitor naive or ACE-inhibitor intolerant. Candesartan significantly reduced cardiovascular deaths and hospital admissions for heart failure (Pfeffer et al., 2003). Also, candesartan appears to prevent diabetes in heart failure patients, suggesting that the renin-angiotensin axis is implicated in glucose regulation (Yusuf et al., 2005). Candesartan is administered once or twice daily as monotherapy or in combination therapy (Swedberg, 2000). Randomized evaluation of strategies for left ventricular dysfunction (RESOLVD) pilot study was initiated to investigate the effects of candesartan (an angiotensin II antagonist) alone, enalapril alone, and their combination on exercise tolerance, ventricular function, quality of life (QOL), neurohormone levels, and tolerability in congestive heart failure (CHF). Candesartan alone was as effective, safe, and tolerable as enalapril. The combination of candesartan and enalapril was more beneficial for preventing left ventricular remodeling than either candesartan or enalapril alone. (McKelvie et al., 1999). Tasosartan contains a fused six-membered heterocyclic ring and is a potent AT_1 selective antagonist (Park et al., 1994) with a long duration of action due to the formation of enol-tasosartan, an active metabolite of tasosartan (Elokdah et al., 2002). Seven placebo-controlled studies involved 2693 patients with essential hypertension; 2145 patients received olmesartan medoxomil, and 548 patients received placebo. Doses ranged from 2.5 to 80 mg once daily for six to12 weeks. Results from these trials suggest that olmesartan medoxomil can be as effective as atenolol, felodipine and atenolol and more effective than captopril, losartan, valsartan, candessartan and irbesartan in

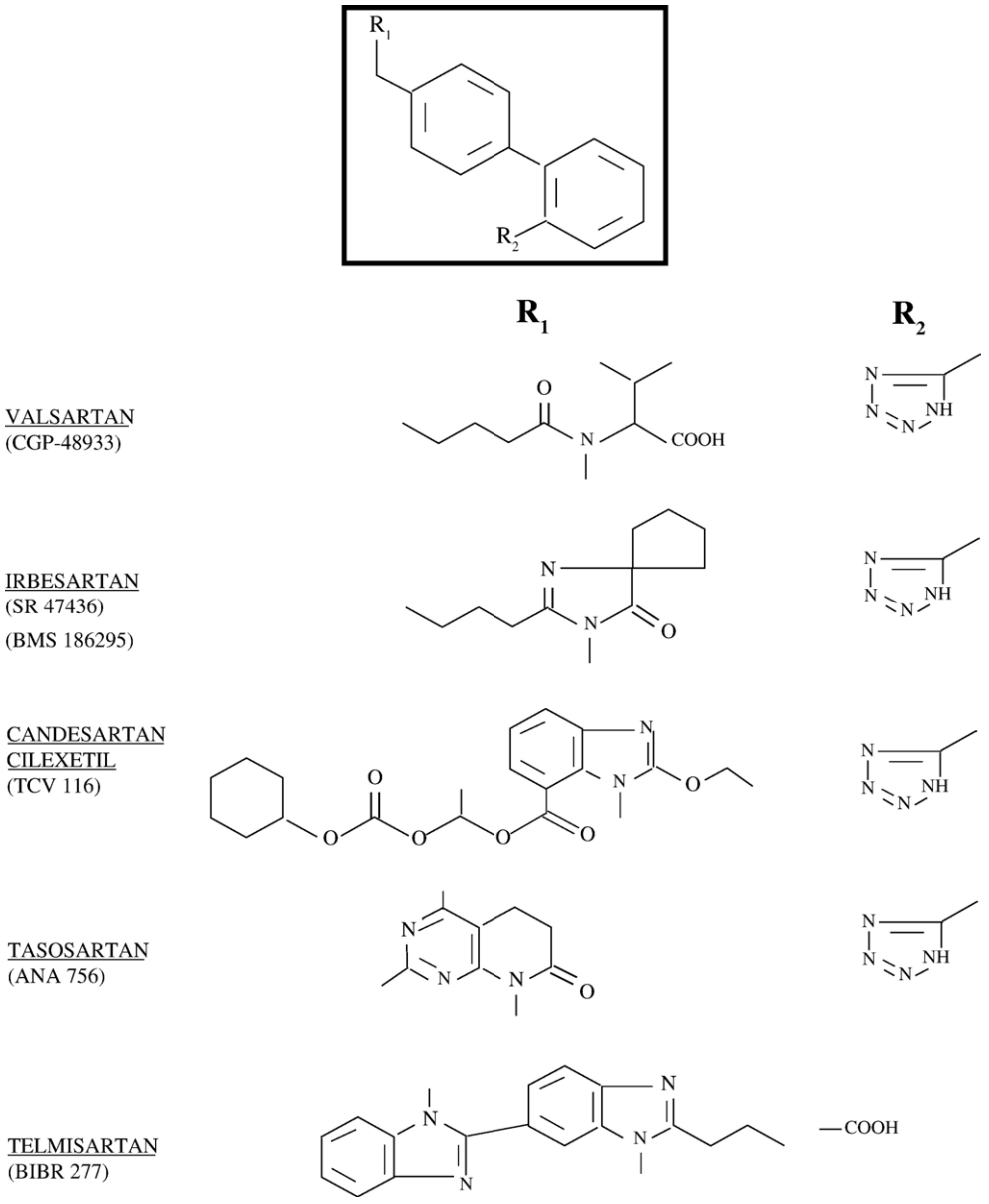

Fig. 6. Chemical structures of new AT_1 receptor antagonists in clinical use.

reducing systolic or diastolic BP. The efficacy of olmesartan medoxomil in reducing cardiovascular risk beyond BP reduction is currently being investigated in trials involving patients at high risk due to atherosclerosis or type 2 diabetes. (Brunner, 2006). Telmisartan incorporates carboxylic acid as the biphenyl acidic group and is more potent than tetrazole analogue (Ries et al., 1993). The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) is a large, long-term study (23,400 patients, 5.5 years). It will compare the benefits of ACE inhibitor treatment, AT_1 antagonists treatment, and treatment with an ACE inhibitor and AT_1 antagonists together, in a study population with established coronary artery disease, stroke, peripheral vascular disease, or diabetes with end-organ damage. Patients with congestive heart failure will be excluded. In a parallel study, patients unable to tolerate an ACE inhibitor will be randomized to receive telmisartan or placebo (the Telmisartan Randomized Assessment Study in ACE-I Intolerant Patients with Cardiovascular Disease [TRANSCEND]). The primary endpoint for both trials is a composite of cardiovascular death, MI, stroke, and hospitalization for heart failure. Secondary endpoints will investigate reductions in the development of diabetes mellitus, nephropathy, dementia, and atrial fibrillation. These two trials are expected to provide new insights into the optimal treatment of patients at high risk of complications from atherosclerosis (Yusuf, 2002).

Modifications in structure of losartan at parts other than imidazole ring has led to development of novel analogues. In zolasartan, the “spacer” phenyl ring of EXP 3174 is replaced by a bromobenzofuran ring. The 3-bromo substituent on benzofuran ring is essential for high AT_1 receptor affinity (Middlemiss et al., 1991). Zolasartan is a potent, selective antagonist possessing long-lasting antihypertensive effect (Hilditch et al., 1994). In saprisartan, the imidazole carboxylic acid of zolasartan is replaced by a neutral imidazole-5-carboxamide

Table 1
Clinical trials in progress with angiotensin II AT_1 receptor antagonists

Drug	Trial	Patient no.	Population studied
Losartan	ELITE II	3121	Heart failure
	LIFE	9194	Hypertensives with LVH
	OPTIMAAL	5000	Post-MI with LV dysfunction
	RENAAL	1520	NIDDM patients with nephropathy
Valsartan	Val-HeFT	5200	Heart failure
	VALIANT	14,500	Post-MI with LV dysfunction
	VALUE	14,400	Hypertensives with high risk
	ABCD-2V	800	NIDDM patients
Candesartan	CHARM I	1700	Heart failure, ACEI-intolerant
	CHARM II	2300	Heart failure
	CHARM III	500	Heart failure (LVEF > 0.40)
	SCOPE	4400	Elderly hypertensives
	RESOLVD	768	Heart failure
Irbesartan	IDNT	1650	NIDDM with nephropathy
	IRMA II	611	NIDDM in hypertensives
Olmesartan	OSCAR	1000	Hypertension
	BALL		Mild-moderate essential hypertension
	OPARIL	588	Hypertension
	WILLIAMS	291	Mild-moderate essential hypertension
	PUCHLER	328	Mild to moderate severe hypertension
	VAN-MIEGHEM	326	Hypertension
Telmisartan (principal trial)	ONTARGET	28,400	Cardiovascular disease patients-heart failure, newly diagnosed diabetes mellitus, atrial fibrillation
	TRANSCEND	5000	ACEI intolerant patients with cardiovascular disease

LVH = Left-ventricular hypertrophy; MI = myocardial infarction; NIDDM = non-insulin dependent diabetes mellitus; EF = ejection fraction; ACEI = ACE inhibitor.

to enhance its oral bioavailability (Judd et al., 1994) and tetrazole is replaced with triflamide (Dowle et al., 1993). Saprisartan has high affinity for the AT_1 receptors, and better bioavailability than zolasartan in experimental animals and human beings (Judd et al., 1994; Hilditch et al., 1995).

Pharmacological properties of the new AT_1 antagonists in therapeutic use

Candesartan and saprisartan possess the highest affinity for AT_1 receptors, followed by zolasartan and irbesartan. Valsartan, olmesartan, telmisartan, and EXP 3174 (active metabolite of losartan) have comparable affinities that are 10-fold less than those of candesartan and saprisartan. Losartan's affinity for the AT_1 receptors is approximately 5 times less than that of EXP 3174 whereas that of eprosartan is 100 times less than that of candesartan. The prodrug candesartan cilexetil has a moderate AT_1 receptor binding affinity. Olmesartan medoxomil exhibits more than a 12,500-fold greater affinity for the AT_1 receptor than for the AT_2 receptor, making it theoretically the second most potent agent (Herbert et al., 1994; de Gasparo et al., 1995) (Table 2).

Telmisartan, irbesartan, eprosartan and valsartan are pharmacologically active molecules, whereas losartan and tasosartan are converted to their active metabolites i.e., EXP 3174 and enol-tasosartan, respectively. Candesartan cilexetil is an inactive ester of candesartan meant for oral administration. Telmisartan can cross blood–brain barrier to inhibit centrally mediated effects of ang II and hence further contribute to the peripheral antihypertensive effect (Gohlke et al., 2001). Recently, telmisartan, an ARB, was found to act as a partial agonist of peroxisome proliferator-activated receptor-gamma (PPAR-gamma) (Yamagishi and Takeuchi, 2005). PPAR-gamma, a well-known target for insulin-sensitizing, antidiabetic drugs, influences the gene expression involved in carbohydrate metabolism (Kurtz and Pravenec, 2004). In an animal study, telmisartan administration caused a significant attenuation of weight gain and reduced glucose, insulin, and triglyceride levels in rats fed a high-fat, high-carbohydrate diet, compared with treatments of losartan. Furthermore, recently, some clinical papers also reported the insulin-sensitizing effects of telmisartan in hypertensive patients (Yamagishi et al., 2006). Some side effects reported with valsartan are fatigue, rarely diarrhoea, headache, epistaxis, thrombocytopenia, arthralgia, myalgia, taste disturbance and neutropenia. Olmesartan (CS-866), the latest AT_1 antagonist developed in Japan, is under Phase IV clinical trials. It's ester form, olmesartan medoxomil, is available as a prodrug. (Norwood et al., 2002). Olmesartan is rapidly and completely hydrolyzed to active acid i.e., RNH-6270 (Schwocho and Masonson, 2001). In bovine adrenal cortical membranes, RNH-6270 inhibits the binding of ^{125}I-angII to the AT_1 receptors at 10-fold lower concentration than losartan. Moreover, it is a noncompetitive antagonist in guinea pig aorta and is noted to inhibit ang II-induced pressor responses in conscious rats on oral administration (Mizuno et al., 1995). A single oral dose of olmesartan (10-20 mg) produces severe decrease in blood pressure, which consequently increases plasma renin activity and ang II concentration in salt-restricted hypertensive patients (Puchler et al., 1997). Preclinical study of olmesartan has demonstrated its effectiveness in diabetic nephropathy and atherosclerosis (Koike, 2001) and this effect is independent of its antihypertensive response. It is safe

Table 2
Binding Characteristics of AT_1 receptor antagonists

AT_1 receptor Antagonist	AT_1 receptor Affinity	Mode of AT_1 Receptor antagonism	AT_1 receptor Off-rate
Candesartan cilexetil	280	–	–
Candesartan	1	Noncompetitive	Slow
Saprisartan	1	Noncompetitive	N/A
Zolasartan	3	Noncompetitive	Slow
Irbesartan	5	Noncompetitive	Slow
Valsartan	10	Noncompetitive	Slow
Telmisartan	10	Noncompetitive	Slow
Tasosartan	20	Competitive	N/A
Enoltasosartan	N/A	N/A	N/A
Losartan	50	Competitive	Fast
EXP 3174	10	Noncompetitive	Slow
Eprosartan	100	Competitive	Fast
Olmesartan	–	Noncompetitive	Slow

and well-tolerated upto dose of 160 mg/kg (Schwocho and Masonson, 2001). It reduces both diastolic and systolic blood pressures and dizziness is the only adverse effect recorded with its use (Neutel, 2001). The bioavailability of the different AT_1 antagonists varies, ranging from 13% for eprosartan to around 60% for irbesartan and telmisartan. Food does not affect the clinical efficacy of AT_1 antagonists except valsartan. All AT_1 antagonists are highly plasma protein bound and thus once-daily oral administration is claimed to provide effective antihypertensive effect. Better therapeutic response is noted with twice a day administration of eprosartan (Mc Clellan and Balfour, 1998). The half-life profile of AT_1 antagonists varies significantly from each other (Csajka et al., 1997) (Table 3). The half-life of losartan, valsartan, candesartan, and eprosartan is short. Moreover, irbesartan and olmesartan have intermediate half-life of 11–15 h and 12 18 h respectively and telmisartan has a very long half-life of around 24 h (Neutel and Smith, 1998). Telmisartan inhibits the expression of the pro-inflammatory beta2-integrin MAC-1 expression in lymphocytes independently of angiotensin II, suggesting an AT_1 receptor-independent atheroprotective effect of this AT_1 receptor antagonist (Link et al., 2006). Eprosartan is the only antagonist that is competitive, surmountable and dissociates rapidly from the AT_1 receptors. Unlike losartan, it is not metabolized to produce active moieties, which block AT_1 receptors non-competitively (Brooks et al., 1999).

Like the ACE inhibitors, AT_1 receptor antagonists should be avoided in patients with renal artery stenosis and are contra-indicated in pregnancy. Losartan has been shown to increase urinary uric acid excretion. The uricosuric effect of losartan is due to a specific effect of losartan potassium on urate transport in the renal proximal tubule and is independent of angiotensin II receptor blockade. It has not been observed with other AT_1 antagonists. In the Evaluation of Losartan In the Elderly (ELITE) trial, no difference in the incidence of renal dysfunction among elderly patients receiving losartan (50 mg daily) and those treated with the ACE inhibitor captopril (50 mg TID) was found (Burnier, 2001).

Teratogenicity

Very little information is available regarding the outcome of human pregnancies in which the mother was treated with an AT1 receptor antagonist during the first trimester, but animal studies have not demonstrated teratogenic effects after maternal treatment with large doses of AT1 receptor antagonists during organogenesis. Fetal abnormalities like oligohydramnios, fetal growth retardation, pulmonary hypoplasia, limb contractures, and calvarial hypoplasia have been reported in various combinations in association with maternal losartan, candesartan, valsartan, or telmisartan treatment during the second or third trimester of pregnancy. Stillbirth or neonatal death is frequent in these reports, and surviving infants may exhibit renal damage. Pharmacological suppression of the fetal renin-angiotensin system through ACE inhibition or AT_1 receptor blockade seems to disrupt fetal vascular perfusion and renal function (Alwan et al., 2005).

Therapeutic relevance of inverse agonism toward AT_1 receptor

It has been previously reported that EXP3174, an active metabolite of losartan, but not losartan itself, can act as an inverse agonist in the inositol phosphate (IP) production assay using a constitutively active AT1-N111G mutant (Miura et al., 2003). Most AT_1 antagonists, including EXP3174 and losartan, have biphenyltetrazole and imidazole groups as common chemical moieties. In addition, EXP3174, candesartan but not losartan, has a carboxyl group in the imidazole ring. This difference in the chemical structure may be important for inverse agonist activity. Olmesartan, a potent AT_1 receptor antagonist, has a hydroxyl group in the imidazole ring in addition to the carboxyl group, and exhibits potent inverse agonist activity (Miura et al., 2006).

The extent to which inverse agonism could offer a therapeutic advantage depends on the role of constitutive G protein coupled receptor activity in the pathology. Although AT_1 receptor also has slight constitutive activity (Miura et al., 2005) and there is no evidence regarding the pharmacotherapeutic relevance of ARBs as inverse agonists, we should consider the results of two very interesting studies. Losartan, which does not contain carboxyl or hydroxyl groups, prevented Ang II-induced, but not mechanical stretch-induced, vascular endothelial growth factor (VEGF) protein secretion in human mesangial cells (de Ligt et al., 2000). Ang II and stretching can each induce VEGF production, suggesting that both ang II- and stretch-induced AT_1 receptor signals may exist. If losartan is an inverse agonist, the stretch-induced signal might be blocked. To resolve this question, Zou et al. (Gruden et al., 1999) reported

Table 3
Pharmacokinetic profile of angiotensin II at_1 receptor antagonists used clinically

Drug (active metabolite)	Bioavailability	Food effect	Active metabolite	Plasma half-life (h)	%Protein binding	Dosage (mg)
Losartan	33	Minimal	Yes	2	98.7	50–100 per day
(EXP3174) Valsartan	25	40–50% decreased by	No	(6–9) 6	(99.8) 95.0	80–320 per day
Candesartan cilexetil	42	No	Yes	3.5–4	99.5	4–32 per day
(Candesartan) Tasosartan	N/A	No	Yes	(3–11) 3–7	N/A	50–100 per day
(Enoltasosartan) Irbesartan	70	No	No	(36–72) 11–15	>90	150–300 per day
Eprosartan	13	No	No	5–9	97.0	200–400 twice daily
Telmisartan	40–60	No	No	~24	>99.5	40–120 per day
Zolasartan	20	N/A	No	N/A	N/A	N/A
Olmesartan	26	No	Yes	12–18 (8–13)	99	5–80 per day

that mechanical stress activates AT_1 receptor independent of ang II, and this activation can be inhibited by the inverse agonist candesartan. They examined pressure overload on the heart by constricting the transverse aorta of adult male angiotensinogen knockout mice. Although treatment with candesartan did not reduce blood pressure, candesartan significantly attenuated the development of cardiac hypertrophy. These results suggest that mechanical stress can induce cardiac hypertrophy *in vivo* by activating the AT_1 receptor independent of ang II. They suggested a mechanism by which mechanical stress might activate the AT_1 receptor without ang II. Stretching of the cell membrane may directly change the conformation of the AT_1 receptor, and candesartan, which contains carboxyl group, may prevent such changes as an inverse agonist.

Angioneurotic oedema with AT_1 antagonists

The use of angiotensin II receptor antagonists in people with a history of ACE inhibitor-induced angioedema is a matter of debate. Some consider that angiotensin II receptor antagonists should be contra-indicated in this group because recurrence of angioedema has been reported (Abdi et al., 2002; Chiu et al., 2001). Although angioedema has been reported with the use of angiotensin-receptor blockers, the incidence of recurrent angioedema among patients who initially had developed angioedema on ACE inhibitors is not well documented. In CHARM-Alternative, the occurrence of angioedema was infrequent, and only one of 39 patients in the candesartan group with a history of angioedema on ACE inhibitors had recurrence leading to permanent drug discontinuation. In this case, the angioedema did not lead to hospital admission and was not life threatening (Granger et al., 2003). Thus, history of angioedema or anaphylaxis on an ACE inhibitor should prompt caution but does not seem to be a contraindication to use of an angiotensin-receptor blocker.

Nonpeptide AT_1 receptor antagonists under clinical trials

An increasing number of AT_1 antagonists (Figs. 7 and 8) have demonstrated potential results during preclinical and early clinical studies. Some of them have been characterized in human subjects (Csajka et al., 1997).

Embusartan (BAY 10-6734), with a dihydropyridinone ring, is another newly developed, orally active AT_1 antagonist (Stasch et al., 1997). BAY 10-6735 is a therapeutically active moiety produced by the hydrolysis of embusartan, which is superior to losartan (Breithaupt-Grogler et al., 1997). Embusartan shows competitive whereas BAY 10-6735 exhibits a noncompetitive mode of antagonism (Knorr et al., 1996). Embusartan, administered orally to healthy male volunteers, has shifted dose dependently ang II-induced pressor response curves towards right and is well tolerated. Its duration of action is 24 h (Breithaupt-Grogler et al., 1997) and compared to losartan, it readily crosses blood brain barrier owing to its high lipophilic nature (Wang et al., 2003).

KRH-594, an acyliminothiadiazoline, is selective AT_1 antagonist and it is as potent as EXP 3174 (Tamura et al., 1997). It produces no active metabolite. KRH-594 has been reported to be orally active, noncompetitive antagonist in spontaneously hypertensive and renal hypertensive experimental animals (Inada et al., 1999). KRH-594 binds potently to rat and human AT_1 receptors in an insurmountable manner, and that at a very high dose (30 microM) it may also bind to AT_2 receptors, but in a surmountable manner. The rank order of dissociation constant values for human AT_1 receptors was KRH-594 > candesartan = Ang II (Inada et al., 2002). KRH-594 improves hypertensive complications, such as renal failure, cardiac hypertrophy and thickening of the artery wall, and prevents death in salt-loaded SHRSP/Izm spontaneously hypertensive rats (Inada et al., 2001). KRH-594 has also shown positive results in diabetic complications, such as nephropathy and hyperlipidaemia in spontaneously hypertensive rats (DM-1K-SHR) (Inada et al., 2000).

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 (Mochizuki et al., 1995). Its affinity for the AT_1 receptor in rat liver membranes is about 7-fold higher than that of losartan, and it produces parallel shift towards right of concentration-response curve of ang II in isolated rabbit aorta (KT3-671, pA_2 10.04; losartan, pA_2 8.32). KT3-671 produces sustained decrease in blood pressure and attenuates ang II-induced pressor response after oral administration to rats (Yanagisawa et al., 1993) and dogs (Takata et al., 1998). KT3-671 does not affect normal renal function and reduces hypertension-induced pathological changes in the kidney (Amano et al., 1995). KT3-671 has recently been demonstrated to produce vascular sympathoinhibitory activity (Takata et al., 2001). KD3-671 (10(−8), 10(−7), 10(−6) M) dose-dependently

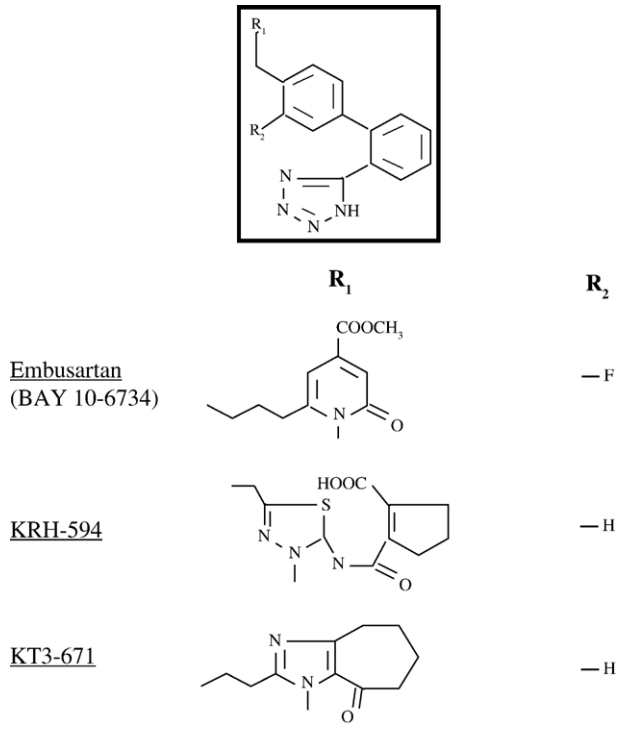

Fig. 7. Chemical structures of nonpeptide AT_1 receptor antagonists under clinical trials.

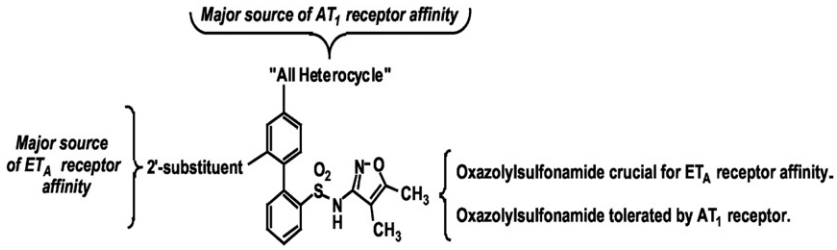

Fig. 8. Summary of the structure activity relationships of DARA compounds.

attenuated fibronectin production in isolated nephritic glomeruli from experimental rat model of mesangioproliferative glomerulonephritis. These findings suggest that KD3-671 may be an effective agent for the treatment of mesangioproliferative glomerulonephritis (Nagamatsu et al., 2003). In a citric acid-induced guinea pig coughing model, KD3-671 was not significantly different from the vehicle treatment in the ability to induce coughing, whereas enalaprilat significantly enhanced coughing compared with the vehicle treatment (Miyamoto et al., 2001). In an experimental model of membranous nephropathy (Heymann nephritis), KD3-671 had an antiproteinuric effect in rats with accelerated passive Heymann nephritis. These findings provide considerable encouragement for the clinical development of KD3-671.

Nonpeptide AT_1 receptor antagonists at pre-clinical stage of development

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 ang II AT_1 receptor (Bali et al., 2004).

The imidazole ring has been successfully replaced by fused heterocyclic ring systems also. Imidazo [4, 5-b]-pyridine derivatives i.e., L-158809 (Chang et al., 1992). L-158,809 has shown highly selective AT_1 receptor antagonist activity in halothane-anesthetized in-vivo canine model (Yoneyama et al., 2002), attenuates increased vascular endothelial growth factor (VEGF) expression in podocytes which could contribute to the renoprotective effects of AT_1 antagonists in diabetic nephropathy (Lee et al., 2004), is renoprotective as shown in chronic experimental nephritis I rats (Uhlenius et al., 2002), block bleomycin induced rat type II alveolar epithelial cells (AEC) apoptosis in situ (Li et al., 2003). Long-term inhibition of angiotensin II by olmesartan and L-158,809 restores the reduced expression of calcitonin gene-related peptide (CGRP) mRNA in dorsal root ganglia and may facilitate neurotransmission of CGRP-containing vasodilator nerves in spontaneously hypertensive rats (SHR) (Kawasaki et al., 2003). Recently, Coppey and co-workers have shown improvement in diabetes and vascular and neural dysfunction in streptozotocin-induced diabetic rats by chronic L-158,809 treatment (Coppey et al., 2006). L-158,809 may also be used as a profibrinolytic drug as it decreases plasminogen activator inhibitor-1 (PAI-1) and tissue plasminogen activator (t-PA) release (Yoshida et al., 2002). Recent data suggests that local Ang II, acting via AT_1 receptor-mediated NADPH oxidase activation, is involved in hyperglycemia-induced cardiomyocyte dysfunction, which might play a role in diabetic cardiomyopathy. Enhanced reactive oxygen species production observed in high glucose myocytes was prevented by AT_1 blockade by L-158,809 (Privratsky et al., 2003). YM 358 has long-lasting antihypertensive effect (Tokioka et al., 1994) with no rebound hypertension on discontinuation of therapy (Yamaguchi et al., 1997). 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 (Tokioka et al., 2000). YM-358 has also reduced cardiac hypertrophy and dysfunction in volume overload (Tokioka-Akagi et al., 2001) and coronary artery ligation induced rat model of heart failure after myocardial infarction (Oka-Akagi et al., 2002). HR 720, now named as Fonsartan, has a sulfonylurea replacement for the tetrazole moiety and 4-alkylthio substituent at imidazole ring. It is highly potent (ten times more potent than losartan) and selective noncompetitive AT_1 antagonist in isolated rabbit aorta and human gastroepiploic arteries (Jin et al., 1997) and reduces electrically induced sympathetic outflow (Hauser et al., 1998). Fonsartan has antiatherosclerotic effects in high-cholesterol fed Cynomolgus monkeys (Miyazaki et al., 1999) inhibits ang II-induced trophic effects, fibronectin (FN) release and FN-EIIIA$^+$ expression in rat aortic vascular smooth muscle cells in vitro (Dunn et al., 1997), reduces myocardial infarction in rats (Xia et al., 2001), doubles lifespan of hypertensive rats (Linz et al., 2000), and also prevents hypertension and renal insufficiency induced by chronic nitric oxide synthase (NOS) inhibition in rats (Hropot et al., 2003).

Dual action (angiotensin and endothelin) receptor antagonists (DARA)

Ang II potentiates the production of endothelin (ET) and conversely endothelin augments the synthesis of ang 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 (Fig. 8). Out of the synthesised series of 5 compounds, compounds C and D are novel agents for treating a broad spectrum of patients with essential hypertension and other cardiocascular diseases (Kowala et al., 2004).

2-{Butyryl-[2′-(4,5-dimethyl-isoxazol-3-ylsulfamoyl)-biphenyl-4-ylmethyl]-amino}-N-isopropyl-3-methyl-butyramide (BMS-1) is a potent dual acting AT1 and ETa 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), 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 (Zhang et al., 2007). Dual inhibition of the angiotensin and endothelin receptors has been shown to be a novel and efficacious approach to control hypertension in preclinical models (Murugesan et al., 2002; Murugesan et al., 2005). A series of 4′-[(imidazol-1-yl)methyl]biphenylsulfonamides has potent antagonist activity against both angiotensin II AT(1) and endothelin ET(A) receptors (Tellew et al., 2003). Out of a series of 2′-substituted N-3-isoxazolyl biphenylsulfonamides, Compound 7 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 (Murugesan et al., 2005).

Combined AT_1 and thromboxane A_2 receptor antagonists

Earlier, losartan and EXP 3174 and recently, irbesartan (Li et al., 2000) have been shown to inhibit thromboxane A_2 induced contractions in canine coronary arteries by inhibiting the vascular TxA_2/PGH_2 receptor (Li et al., 1997). EK 112 is a new combined AT_1 and thromboxane A_2 receptor blocking agent. The AT_1 receptor antagonizing property is revealed by its competitive antagonism of ang II-induced smooth muscle contraction in rabbit aorta (pA_2 7.63) and guinea pig ileum (pA_2 7.87). Thromboxane A_2 receptor antagonizing activity is exhibited from the competitive antagonism of aortic contractile responses elicited by U 46619 (pK_B 6.67) and $PGF_{2\alpha}$ (pK_B 6.24) in rat. EK 112 does not inhibit ACE. There is no change in cAMP or cGMP content in rat aortic rings by EK 112. Therefore, EK 112 is a selective antagonist of AT_1 and thromboxane A_2 receptor. The antagonistic effect of these agents on the thromboxane A_2 receptor may contribute to the long-term blood pressure lowering effects of AT_1 antagonists in hypertension (Li et al., 1997, 2000).

Combined ACE/NEP (neutral endopeptidase) inhibitors

Vasopeptidase inhibition is a novel therapeutic approach in the treatment of cardiovascular diseases such as hypertension and heart failure. The concept of dual inhibition of the two enzymes, angiotensin converting enzyme (ACE) and neutral endopeptidase (NEP) by a single molecule has shown major benefits and potentially superiority versus other agents in various experimental models of hypertension, heart failure and renal disease (McClean et al., 2000). The underlying presumed rationale for the combined inhibition of ACE and NEP is to block the vasoconstrictor angiotensin II (ang II) and simultaneously increase the vasodilator, atrial natriuretic peptide (ANP) by decreasing its enzymatic degradation. Furthermore, both vasoactive hormones, ang II and ANP appear to have actions beyond their haemodynamic effects. Ang II meditates proliferation, fibrosis, inflammation and oxidative stress whereas ANP has antiproliferative and antifibrotic effects. Both peptides have been postulated to act as endogenous antagonists to each other (Johnston et al., 1989). Omapatrilat is the ACE/NEP inhibitor that has been most extensively studied. Omapatrilat is a potent, long acting dual metalloproteinase inhibitor (ACE IC_{50}= 5 nmol/l, NEP IC_{50}=8 nmol/l) and exerts prolonged antihypertensive effects in several experimental models of hypertension including the DOCA salt hypertensive model and the SHR (Pu et al., 2005). The OCTAVE study investigated the effect of omapatrilat versus enalapril on cardiovascular outcomes in 5770 patients with CHF (Kostis et al., 2004). The OCTAVE study showed that omapatrilat reduced cardiovascular deaths and also had superior antihypertensive effects compared to enalapril. however, angioedema was observed in 2.17% of the population in the omapatrilat-treated groups versus 0.68% in the enalapril treated group. In Afro-American subjects the incidence was even higher (5.54 versus 1.62%, respectively). This effect has been attributed to firstly the rapid increase in bradykinin(BK) and its metabolite BK-8 by simultaneously blocking both BK degrading pathways and secondly by potentially a direct effect of the agent to promote extravasation (Sulpizio et al., 2004). Based on these findings and, in particular, the incidence of this potentially life threatening side effect it appears unlikely that omapatrilat will become routine medication for hypertension, especially in the Afro-American population. It remains controversial as to whether dual ACE/NEP inhibitors confer superior cardiovascular effects when compared to ACE inhibition alone. Fosidotrilat, sampatrilat, GW660511X, Z13752A 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 (Rastegar et al., 2000) which is attributed to the protective effects of increased bradykinin levels. Longer-term studies are needed in larger populations including patients of different ethnic backgrounds to confirm the laboratory results and to fully characterize the safety profile of these novel ACE/NEP inhibitors. Clinical data indicates towards need to develop novel dual ACE/NEP inhibitors with better safety profiles (Jandeleit-Dahm, 2006).

Triple inhibitors

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 ang II. Preliminary studies in experimental settings such as the SHR have shown that triple therapy, with CGS 35601, dose dependently reduced blood pressure, decreased ang II and ET-1 concentrations as well as proANP, but increased big ET-1, ANP and bradykinin (Daull et al., 2006, 2005). Careful evaluation of the safety profile of this promising therapeutic strategy in large-scale clinical trials is needed and mandatory

before triple vasopeptidase inhibitors may be considered an appropriate and safe option in the treatment of cardiovascular disease. In summary, based on the clinical evidence, the results are not encouraging enough for vasopeptidase inhibitors, particularly because of the adverse effect profile of these agents, to be considered for routine management of a range of cardiovascular and renal disorders. Furthermore, it remains controversial as to whether there is an incremental beneficial effect of ACE/NEP inhibition on top of ACE inhibition in hypertension or heart failure, based on the outcomes of the recent clinical trials. Nevertheless, a major impediment for recommendation of routine use of these new agents remains the potentially life threatening side effect of angioedema. Indeed, it remains unknown, if this effect is specific for omapatrilat, and if other more novel ACE/NEP inhibitors have better safety profiles. There is preliminary evidence as outlined in the present study, that novel ACE/NEP inhibitors increase bradykinin accumulation to a much lesser extent compared to omapatrilat. Thus, the therapeutic role for ACE/NEP inhibitors may be in the patients with high cardiovascular risk and atherosclerosis, potentially in the diabetic patient. Indeed, the benefits and potential risks of these agents need to be carefully evaluated in any future studies.

Nonpeptide AT_2 receptor antagonists

The first nonpeptidic compounds that have selective affinity for the AT_2 receptors are series of spinacine-derived tetrahydroimidazopyridines, such as PD-123177 (Blankley et al., 1991), PD-121981 and PD-123319 (Fig. 9) (Dudley et al., 1990). Their affinity for AT_2 receptors ($IC_{50} \approx 100$ nM) is about 50-100 times higher than their affinity for the AT_1 receptors (Blankley et al., 1991). They have no significant effect on blood pressure (Wong et al., 1990d). These compounds have served as important pharmacological tools to study ang II receptor heterogeneity in tissues and organs from various species, including humans (Whitebread et al., 1989).

Diacylpiperazine derivative, L-159686 (AT_2: $IC_{50}=1.5$ nM; AT_1: $IC_{50}>100$ nM), has 50% oral bioavailability and plasma half-life of >6 h. (Wu et al., 1993). Tetrahydroisoquinolines i.e., PD-126055 (Klutcho et al., 1994) and EXP801 (Van Atten et al., 1993) have pronounced AT_2 receptor-binding selectivity (Fig. 9). In addition, substituted quinazolinones e.g., L-161638 (Fig. 10) (AT_2: $IC_{50}=0.06$ nM; AT_1: $IC_{50}=200$ nM) (Glinka et al., 1994a) have been reported to be potent and selective AT_2 receptor antagonists.

Balanced AT_1/AT_2 receptor antagonists

Selective blockade of AT_1 receptors increases the production and release of renin by inhibiting the negative biofeedback mechanism (Fig. 1). The consequent increase in ang II formation due to increased concentration of renin activates the unblocked AT_2 receptors. The AT_2 receptors have been reported to mediate antigrowth, antihypertrophic, proapoptotic effects of ang II, promote cell differentiation, fine-tune natriuresis, body temperature, reproduction, tissue repair, and blood pressure (Stoll et al., 1995; Meffert et al., 1996; Horiuchi et al., 1999; Steckelings et al., 2005). Recently, CGP 42112, an AT_2 receptor agonist, has been shown to facilitate the antihypertensive effect of candesartan in SHR (Barber et al., 1999). Akishita et al demonstrated that the AT_2 receptor antagonist PD 123319 increased neointima formation in the cuff-induced vascular injury model in mice (Akishita et al., 2000). Furthermore, treatment with even small doses of the AT_1 receptor antagonist valsartan effectively attenuated neointima formation, whereas this effect was significantly weaker in AT_2-null mice (Wu et al., 2001). Thus, the beneficial effect of AT_1 blockade in the prevention of neointima formation seems to involve AT_2 receptor stimulation.

Although the cellular targets of the AT_2 receptor in neuronal tissue are not yet clearly identified, the findings on the neurotrophic actions of AT_2 receptor stimulation may provide a basis for the design of new therapeutic concepts for treatment of human peripheral nerve injuries, diabetic neuropathy, neurodegenerative disorders and stroke (Iwai et al., 2004; Li et al., 2005; Shanmugam et al., 1995). The inconclusiveness about the role of AT_2 receptors (Cao et al., 1999) in counterbalancing the effects of AT_1 receptors and exquisite selectivity of losartan has prompted to the design of compounds possessing equal affinity for the AT_1 and AT_2 receptors known as "balanced" AT_1/AT_2 receptor antagonists. L-162132 (Fig. 11) is a hybrid molecule (AT_1: $IC_{50}=15$ nM; AT_2: $IC_{50}=180$ nM), which combines structural parts of losartan (AT_1 receptor antagonist) and L-159686 (AT_2 receptor antagonist). It binds moderately to AT_1 and AT_2 receptors (Wu et al., 1994).

However, the most successful approach has been to modify AT_1-selective compounds to enhance their AT_2 affinity. An acylsulfonamide group, is an isosteric replacement for the tetrazole ring, to provide AT_2 affinity. L-163017, XR 510, L-163579, BIBS 39 and BIBS 222 and EXP 597 compounds (Figs. 12 and 13) have been produced by this approach. L-163017 (AT_1: $IC_{50}=0.24$ nM; AT_2: $IC_{50}=0.29$ nM), demonstrates affinity for both AT_1 and AT_2 receptors in rat adrenal

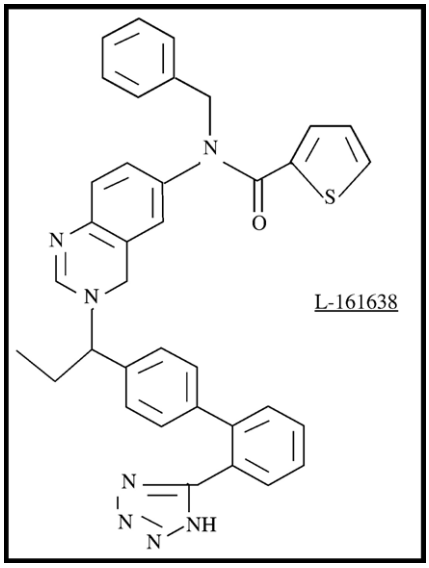

Fig. 9. Chemical structures of selective nonpeptide AT_2 receptor antagonists.

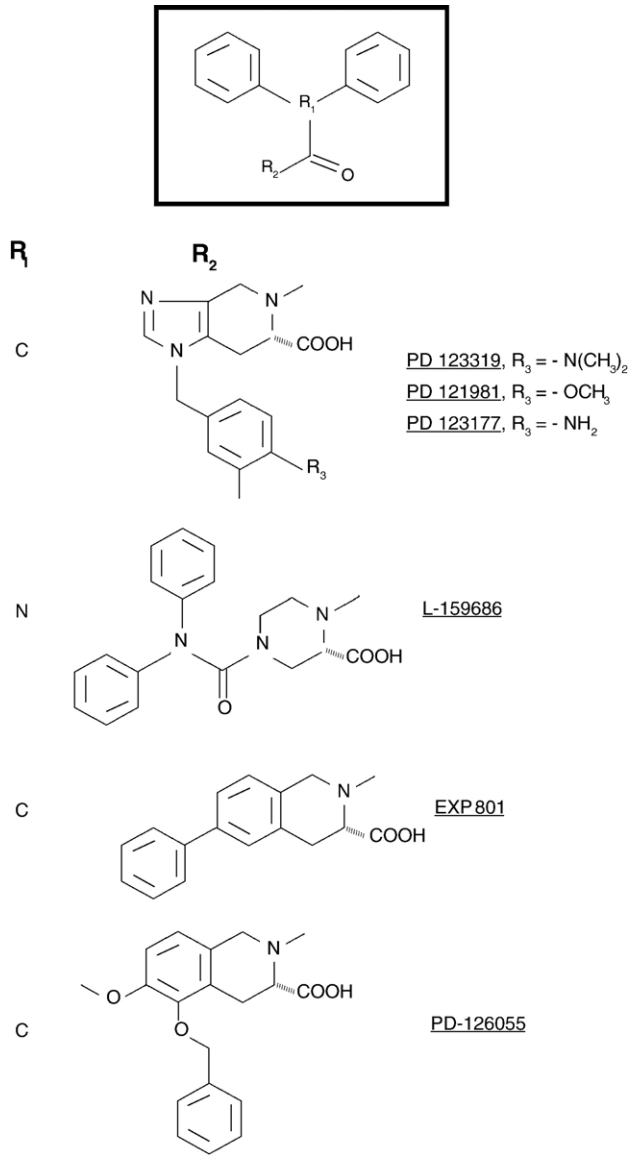

Fig. 10. Chemical structure of a substituted quinazolinone, L-161638, as a selective nonpeptide AT_2 receptor antagonist.

tissue, human tissues e.g., aorta, kidney and adrenal gland (Chang et al., 1995). L-163017 has a long duration of action (binding to receptor >6 h) after oral administration and its oral bioavailability is 45% in rats and 34% in dogs (Chang et al., 1995). XR 510 is a potent and balanced antagonist (AT_1: IC_{50}=0.26 nM; AT_2: IC_{50}=0.28 nM) and has pronounced oral antihypertensive activity in renal hypertensive rats (ED_{30}=0.27 mg/kg) with a duration of action >24 h (Wong et al., 1995). L-163579, (AT_1: IC_{50}=0.57 nM; AT_2: IC_{50}=0.39 nM) and L-163958 (AT_1: IC_{50}=0.20 nM; AT_2: IC_{50}=0.20 nM), are excellent balanced AT_1/AT_2 receptor antagonists (Glinka et al., 1994b). BIBS 39 and BIBS 222 (Zhang et al., 1992) have modest affinities for both AT_1 and AT_2 receptors (Zhang et al., 1992) and decrease blood pressure in renal hypertensive rats. Their AT_1 receptor antagonist potency is similar to losartan (Zhang et al., 1993). EXP 597 (AT_1: IC_{50}=0.5 nM; AT_2: IC_{50}=0.7 nM) is another example of balanced nonpeptide ang II receptor antagonist that demonstrates insurmountable AT_1 receptor antagonism in isolated rabbit aorta and lowers blood pressure in renal hypertensive rats (Wong et al., 1994).

Renin inhibitors

The renin–angiotensin–aldosterone system has been a highly successful pharmacologic target, as the system is strongly implicated in the development of hypertension-related target organ damage. However, 'ang II reactivation' and 'aldosterone escape' or 'breakthrough' during either ACE inhibitor or AT_1 antagonist treatment, due to compensatory increases in plasma renin levels that lead to higher angiotensin production and conversion as well as aldosterone secretion and sodium reabsorption presents limitations for existing renin–angiotensin–aldosterone system inhibitors (Athyros et al., 2007). Renin and ang I accumulate during ACE inhibition, and might overcome the ability of an ACE inhibitor to effectively suppress ACE activity. There is also data suggesting that 30–40% of ang II formation in the healthy human during RAAS activation is formed via renin-dependent, but ACE-independent, pathways. Moreover, ACE gene polymorphisms contribute to the modulation and adequacy of the neurohormonal response to long-term ACE inhibition, at least in patients with CHF (up to 45% of CHF patients have elevated ang II levels despite the long-term use of an ACE inhibitor) or diabetes. The reactivated ang II promotes aldosterone secretion and sodium reabsorption. Aldosterone breakthrough also occurs during long-term AT_1 antagonist therapy, mainly by an AT_2 dependent mechanism. This is related to target-organ damage in heart, kidney and brain viz necrosis and fibrosis of the

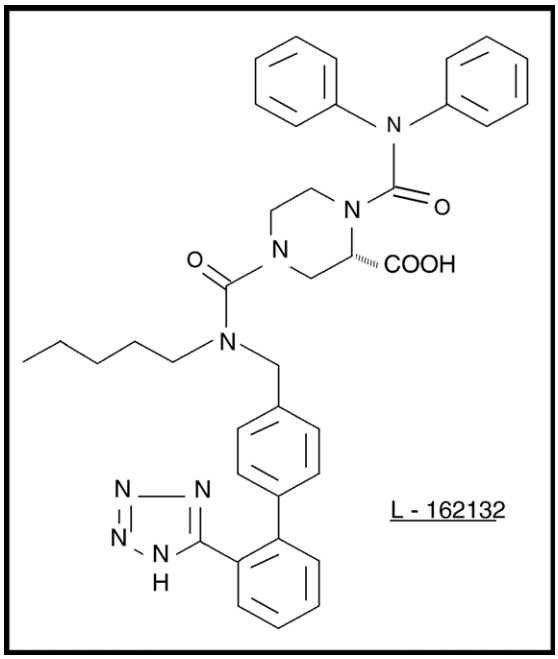

Fig. 11. L-162132, an example of hybrid molecule, which combines structural elements of the AT_1 receptor selective antagonist, losartan and AT_2 receptor selective antagonist, L-159686.

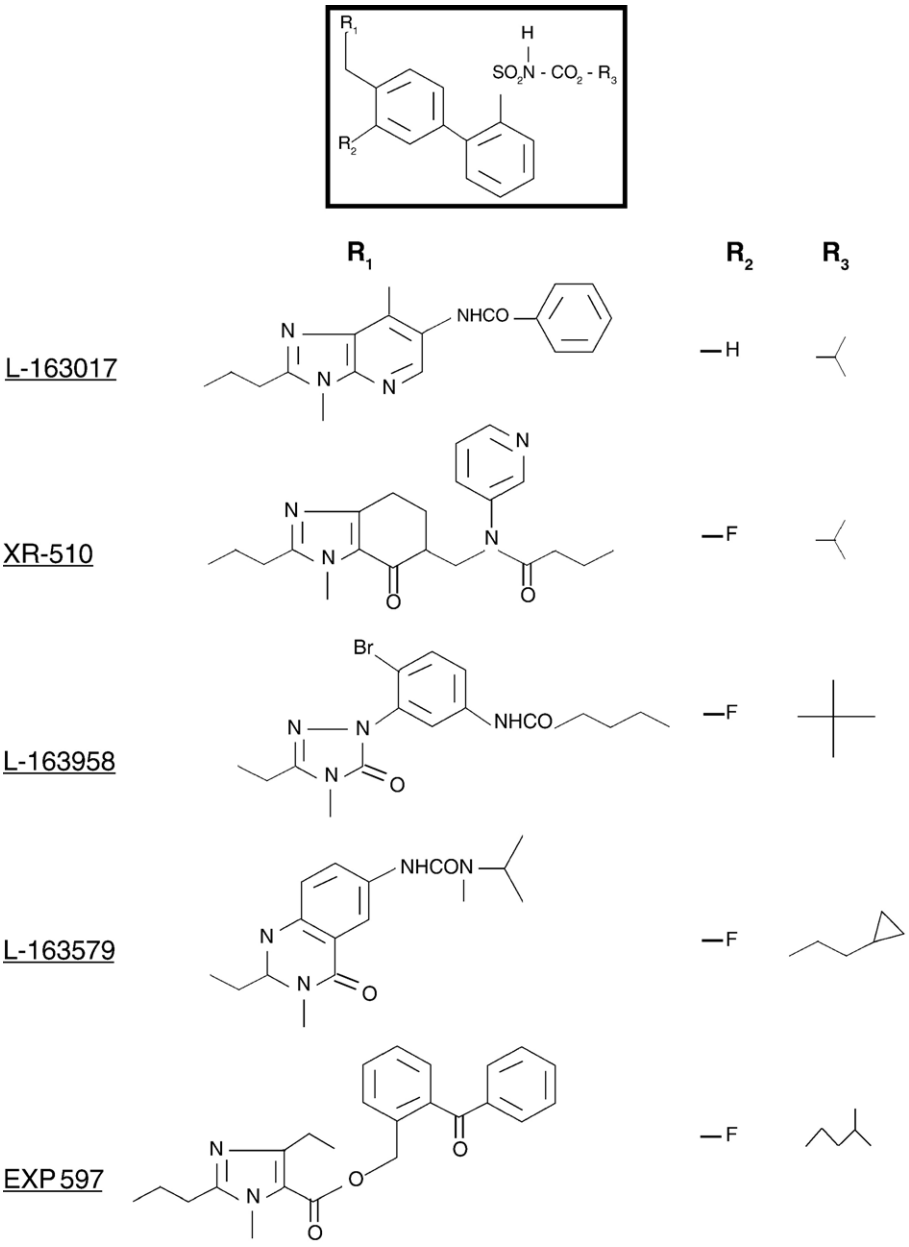

Fig. 12. Chemical structures of antagonists with equal affinity for AT_1 and AT_2 receptors, "balanced" antagonist.

vasculature and the heart, vascular stiffening and injury, reduced fibrinolysis, endothelial dysfunction, catecholamine release and production of cardiac arrhythmias in animal models (Stier et al., 2005). A 300 mg once-daily, orally effective, small-molecule renin inhibitor, aliskiren (formerly known as SPP100), is now available to address angiotensin production directly at its rate-limiting step (Athyros et al., 2007; Rump, 2007). Other second generation renin inhibitors in various phase I and phase II clinical trials are SPP1148, SPP1100, SPP 600, SPP 635 and SPP 800 series of compounds.

Aliskiren

Crystal structure analysis of renin-inhibitor complexes combined with computational methods to design inhibitors with high in-vitro affinity and specificity for renin, favorable bioavailability, and excellent oral efficacy in lowering blood pressure in primates have yielded promising renin inhibitors (Rahuel et al., 2000). One of these compounds was aliskiren (Fig. 14). In further investigations, aliskiren dose-dependently decreases systolic and diastolic BP in sodium-depleted marmosets and increased plasma immunoreactive renin levels, whereas plasma renin activity was reduced through inhibition (Wood et al., 2003). In a multicenter, randomized, placebo-controlled, 8-week trial, 1123 patients with mild-to-moderate hypertension underwent a 3 to 4 week single-blind placebo run-in and were then randomized in a modified factorial study design to receive once-daily, double-blind oral treatment with placebo, aliskiren monotherapy (75, 150, or 300 mg), valsartan monotherapy (80, 160, or 320 mg), aliskiren and valsartan in combination, or valsartan/hydrochlorothiazide

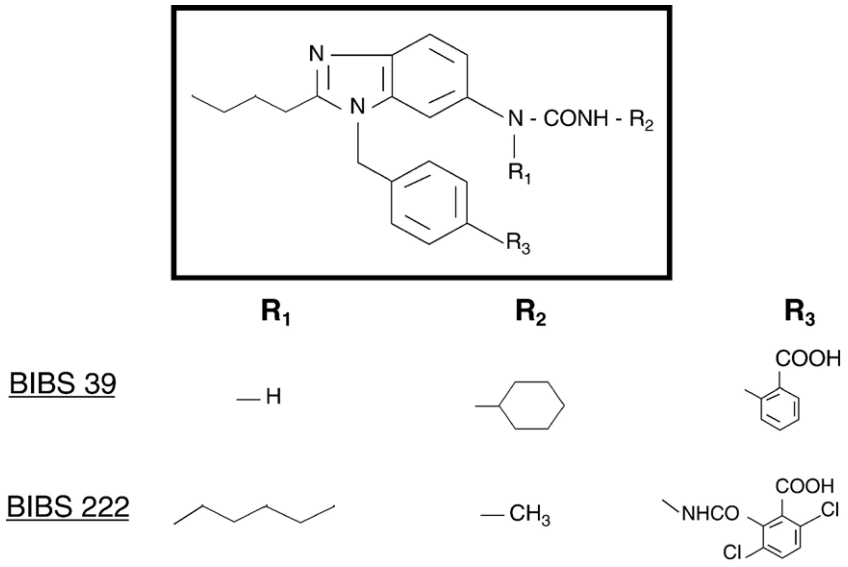

Fig. 13. Chemical structures of antagonists with equal affinity for AT_1 and AT_2 receptors, "balanced" antagonists.

(160/12.5 mg). Aliskiren monotherapy provides antihypertensive efficacy and placebo-like tolerability in patients with hypertension. Aliskiren and valsartan in combination may provide additive BP-lowering effects with maintained tolerability (Gradman and Traub, 2007; Pool et al., 2007).

In the first large-scale double-blind, placebo-controlled study to evaluate the effects of dual renin system blockade, 1797 patients of mild to moderate hypertension, were randomized to one of four treatment arms: the combination of aliskiren 150 mg plus valsartan 160 mg, aliskiren 150 mg, valsartan 160 mg, or placebo for 4 weeks, and then the doses were doubled (to their maximum recommended doses) for an additional 4 week observation period. A significant additional blood pressure reduction was obtained with the combination of aliskiren and valsartan, compared to either drug alone, headache being the only frequent side effect. "Aliskiren is advantageous as a combination drug for hypertension," as stated by Dr. S. Oparil, "and that it may be particularly advantageous in the setting of diabetes, obesity, and hypertension requiring combination therapy, and that it will not have untoward effects of a diuretic" (Oparil, 2007). Three studies (AVOID, ALOFT and ALLAY) are ongoing with aliskiren to assess end-organ protective properties (Schmieder, 2006).

A recent analysis of six clinical trials of aliskiren involving more than 5000 patients with mild to moderate hypertension indicates that aliskiren is no more effective than angiotensin-converting enzyme inhibitors, AT_1 blockers, or diuretics for lowering blood pressure. Although aliskiren suppresses plasma renin activity, it causes much greater reactive rises in plasma renin concentration than does any other antihypertensive class tested. Because aliskiren, like ACE inhibitors and AT_1 antagonists, only blocks 90% to 95% of plasma renin, the pressor consequences of its greater reactive increases in plasma renin concentration appear to offset its net ability to lower blood pressure, especially with higher doses. Patients with hyperreactive renin systems (renovascular, advanced, and malignant hypertension) were excluded from all of the trials (Sealey and Laragh, 2007).

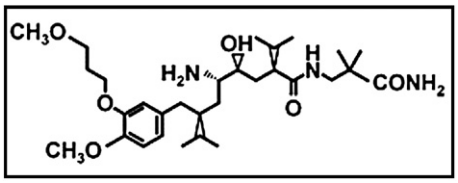

Fig. 14. Chemical structure of aliskiren- the first orally effective renin inhibitor.

After establishing the concept of renin uptake as the underling cause of tissue angiotensin generation, focus is now on the mechanism that mediates this uptake process. Several renin receptors have already been described. Importantly, these receptors also bind prorenin, and such binding results in prorenin activation, either proteolytically or nonproteolytically. Thus, for the first time, a physiological role for prorenin might be established. This is important in view of earlier observations that high prorenin levels in diabetic subjects are an indication of microvascular complications (Luetscher et al., 1985). Unexpectedly, renin and prorenin binding to their receptors not only facilitated angiotensin generation but also led to activation of second messenger pathways, thereby implying that renin and prorenin may act as agonists independently of ang II generation. Now that renin inhibitors will soon be clinically available (Gradman et al., 2005), it will be of the greatest interest to investigate how these drugs affect these mechanisms in comparison with other RAS blockers. Eventually a new class of drugs might emerge, the renin receptor blockers, which selectively block angiotensin generation at tissue sites and/or renin receptor-mediated effects (Danser and Deinum, 2005).

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