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Perspective

Angiotensin II AT1 Receptor Antagonists. Clinical Implications of Active Metabolites

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Introduction

The renin angiotensin system (RAS) is one of the most powerful regulators of blood pressure and volume homeostasis in mammals. Its effector peptide angiotensin II (ANG II) is cleaved from the decapeptide angiotensin I by the metalloprotease ACE.[2,3] ANG II mediates all the effects of RAS after binding to its G-protein-coupled angiotensin II type 1 (AT_1) receptor and thus plays a complex role in the regulation of blood pressure, fluid, and electrolyte homeostasis. More recently, ANG II was shown to regulate vascular tone by delayed effects on vascular smooth muscle via growth stimulation, aldosterone production, and release, leading to increased salt absorption in the kidney and gut and the induction of thirst and sodium appetite in the brain. It also stimulates the release of vasopressin, luteinizing hormone, oxytocin, and corticotropin. ANG II further induces vagus suppression and β-adrenergic potentiation and increases inotropy and chronotropy. Stimulation of the cardiac fibroblast matrix formation has also been described.[3−5] ANG II stimulates synthesis of prostaglandin,[6] endothelin,[7] and elicits procoagulatory effects by activating the plasminogen activator (PA) plasmin system.[8−11] Taken together, these mechanisms turn the inhibition of RAS, and especially that of the AT1 receptor, into a powerful tool to control not only blood pressure but also vascular maladaptive processes and thereby prevent cardiovascular diseases.

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The beneficial effect of a chronic RAS blockade was first shown for inhibitors of the angiotensin converting enzyme (ACE), such as captopril, quinapril, enalapril, and ramipril in patients with ischemic heart disease, congestive heart failure, postmyocardial infarct (MI) in a variety of large-scale clinical trials, e.g., SAVE, SOLVD, CONSENSUS, AIRE, and HOPE. Although ACE inhibitors were the only drugs available up to 1995 that interfered with the RAS, it was soon recognized that other enzymes such as chymase CAGE, cathepsin G, tPA, elastase tonin, and others also generate ANG II. Moreover, ACE is identical to kininase II, an enzyme that degrades bradykinin and other kinins to inactive metabolites. A blockade of ACE is therefore associated with a potentiation of endogenous kinins, a mechanism thought to contribute to desirable effects of ACE inhibitors such as the organ protection, but also associated with unwarranted effects such as dry cough (confining the use of ACE inhibitors to approximately 90% of all patients). Several well-known peptidic antagonists of Ang II had limited clinical use, but derivatives of these peptides, particularly with induced cyclic constraint and limited conformational freedom of the octapeptide, provided a starting point for peptidomimetic strategies. With the aid of NMR spectrometry, this effort finally resulted in 3D in silico models.[12−14] But prior to the availability of detailed 3D information, Takeda in the mid-1980s jump-started[15,16] the development of potent drugs that interfered with the RAS: the angiotensin receptor type 1 (AT_1) antagonists. To find a more specific blockade of ANG II at its AT_1 receptor, highly selective

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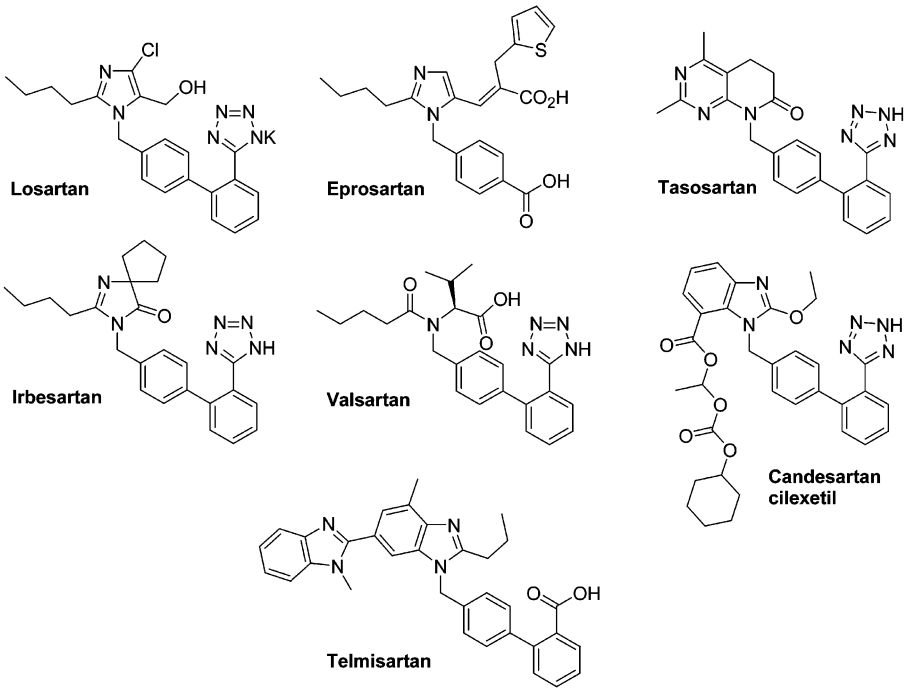

Figure 1. Sartane drug family.

non-peptidic AT_1-receptor antagonists were designed and developed as competitive antagonists with virtually no agonistic effect at the receptor level. Losartan was described as the first non-peptide AT_1 receptor antagonist, and the coined group name was sartans. The paralleling development of eprosartan by SKB (now GSK) started from the same Takeda lead and was guided by a distinctly different molecular overlay with peptide antagonists. All major pharmaceutical companies embarked on a fast follower program immediately thereafter. Today, irbesartan, candesartan, and valsartan are all established in the market, and others, e.g., tasosartan and telmisartan, are following closely (Figure 1). Some further 20 compounds are in development. Most of these compounds share the biphenyltetrazole unit or replacements thereof with the original, advanced lead losartan.[17] Some 12 000 variations of the parent biphenyltetrazole alone were reported in the meantime, excluding the obvious variation of the biphenyl spacer. The carboxylic acid, another common moiety of the sartans, appears to establish another important interaction with the receptor, but it often hampers oral absorption. Therefore, several prodrug concepts had to be realized to mask the carboxylic acid as either a labile ester or an oxidatively labile precursor that delivers the acid after absorption.

Although other ANG II receptors are known, e.g., AT2 and AT4 receptors, virtually all cardiovascular and hemodynamic effects of ANG II are mediated by the AT_1 receptor subtype, which can be blocked by the sartans.[4] Losartan was shown to be 10.000× more selective for the AT_1 receptor than for the AT_2 receptor. It does not appear to have any partial agonistic activity or to elicit any direct effect on ACE or renin, but ANG II levels increase 5- to 6-fold with chronic use. The sartans are metabolized by enzymatic oxidation by the cyctochrome P450 family and/or glucoronidation by UDP-glucoronyl transferases. Usually this metabolism results in reduced AT_1 affinity and potency. The ratio of renal to liver clearance varies significantly for the drugs, and large species-dependent differences have been observed, but liver clearance is always the dominant path for elimination. However, individual metabolism was reported for a variety of AT1 antagonists.

1. Losartan, developed as DuP753 and later as MK954, displays competitive antagonism like most of the AT_1 antagonists. However, in vivo P450 oxidation of losartan converts the hydroxy function into a carboxylic acid (Figure 2). This metabolite (EXP3174) has a 10- to 40-fold higher potency compared to losartan and is noncompetitively bound to the AT_1 receptor (insurmountable antagonism) by interaction of the tetrazole with Lys^{199} in the trans-membrane helix 5 of the AT_1 receptor.[18−21] The involvement of His^{256} in biphenyl pocket formation was confirmed by site-directed mutagenesis and found to participate Lys^{199} binding to the tetrazole moiety.[22,23] The extended half-life (6−9 h) and increased potency of EXP3174 make losartan look like a prodrug, yet the pharmacological profile is the sum of both activities.

The distribution and clearance of both compounds were established by high-performance liquid chromatography and differ significantly for losartan (V = 34 L, total clearance of 10 mL/s, CL_R = 1.1 mL/s) and EXP3174 (Vd_{ss} = 10 L, total clearance 0.78 mL/s, CL_R = 0.4 mL/s) (Table 1).[24,25] Losartan is rapidly absorbed within 30−60 min and undergoes extensive first-pass metabolism to the active metabolite EXP3174. EXP3174 is 10−40 times more potent than losartan and is responsible for most of the receptor antagonism seen with losartan.

The metabolism and clearance (Figure 2) follows one of two major pathways (pathway A or B) and involves oxidation of the benzylic imidazole substituents by P450 in liver cells,[26] which is followed or preceded by glucoronidation.[27] The rate-limiting oxidation in the major pathway gives the aldehyde EXP3179, which is rapidly oxidized [$k_{A1}C_{losartan} = 7(k_{A2}C_{EXP3179})$] to EXP3174.[28] This

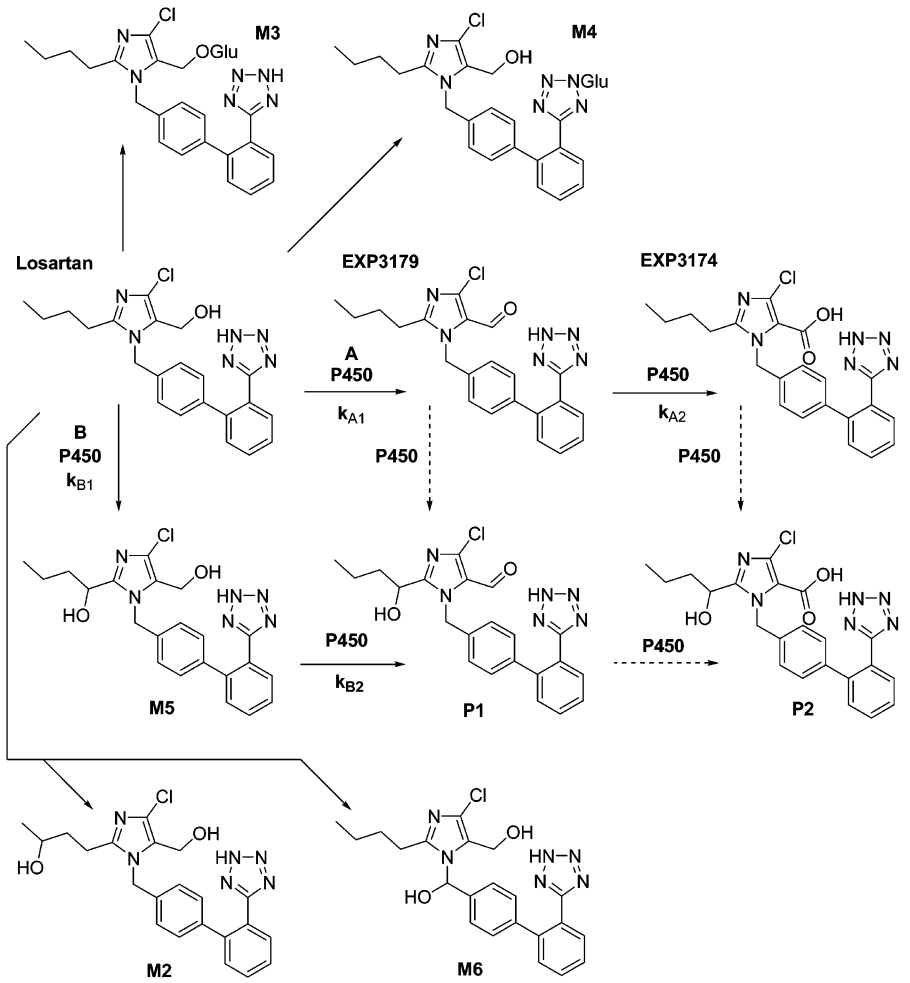

Figure 2. P450 Oxidation of losartan, reported by Stearns et al.[31,32,41]

Table 1.

substance	pK_a [92]	$\tau_{1/2}$ (h)	CL_R (mL/s)	CL_{total} (mL/s)	AT_1 affinity (10^{-9} M/L)	modification of absorbed drug (%)
losartan[24,29,93,94]	4.9	1.5−3.2	1.1−4.1	10	6.4	75
EXP3174[19,24,29,94]	2.8	4.4−6.4	0.4−1.2	0.78	1.3	
EXP3179[95]	4−5				20	
eprosartan[19,53,96,97]	4−5	5−7	0.6−0.9	2.5−18	1.5−9.2	20
irbesartan[58,98]	4.7	10−21	0.02	5.1	1.3[19,29,59,99,100]	20
valsartan[19,62,101,102]	3.1^{CO2H} 4.7^{CN4H}	6.1	4.8	37	1.4−1.7	9
candesartan[66]	3.9^{CN4H}	>9	>7	1−8	∼0.1	$^{100}/_{20}$
telmisartan[74,75]	4.5	>20	<5	∼19	∼1	16
tasosartan[63,103]	4−5	11−15			1.2	2

acid is plasma-bound to 99.8%[29] and accounts for 10% of the losartan metabolites in humans.[30] The plasma-bound percentage may explain the retarded onset of pressure reduction[31] and is not affected by the number of coadministered drugs such as cimetidine, diazepam, ibuprofen, naproxen, and warfarin.[32,33]

Losartan is transported by P-glycoprotein and other intestinal transporters, whereas the carboxylic acid metabolite, which is not a P-glycoprotein substrate, displays higher affinity for other transporter systems. This was revealed in studies on epithelial layers of Caco-2 cells and MDR1, MRP-1, and MRP-2 overexpressing cell lines.[34] Forty microorganisms were evaluated for their ability to metabolize the protonated form of losartan (DuP753 → MK954). Three of these species provided metabolites identical to rat, monkey, and human liver slices and were utilized in the up-scaled preparation of the three lead metabolites **M2**, **M4**, **M5**.[35]

The phase II glucoronidation can proceed at any hydroxy group as in **M3** or at the tetrazole unit of EXP3174. But significant *N*-glucoronidation occurs already in the duoedenum and jejenum of rat intestines.[36] The desmotropy of tetrazoles, which was proven for irbesartan,[37] may then result in two *N*-glucoronides. These were synthesized and distinguished by ^{1}H NMR NOE, and *N*2-glucoronide **M4** only was identified in human and monkey liver assays.[27,30,38,39]

A significant contribution stems from path B via side chain hydroxylation to **M2** and **M5**, the latter being oxidized to the hydroxyaldehyde **P1** and the presumed common intermediate of both pathways: **P2**. The shunt between the pathways A and B via conversion of

EXP3179 to **P1** was shown to operate in human liver microsomes.[28] The unstable hydroxyaminal **M6** was prepared by incubation of fresh liver slices (rats, monkey, human) with losartan but was not confirmed in human plasma yet.[27,30]

Drug−drug interactions via the losartan-EXP3179 to EXP3174 conversion were evaluated by incubation with isolated cytochrome P450 enzymes in the presence of $^{18}O_2$. The two-step oxidation was inhibited by antibodies raised against P4503A4 and P4502C9 but not by antibodies against 1A2, 2A6, 2C, 2D, and 2E1 or by selective inhibitors against other P450 enzymes.[28] Thus, P4503A4 and P4502C9, which were identified by fluconazole inhibition, were concluded to account for most of the oxidative metabolism, although the supposed inhibition of P4503A4 by Cimetidine proved to be negative.[26,33,40,41] On the other hand, P450 stimulation by phenobarbital resulted in a modest 20% decrease of the area under the curve (AUC) for both losartan and EXP3174. However, this is clinically less relevant.[42] Recent in vitro studies on P4502C9 and P4503A4 polymorphisms indicate P4502C9 to be the major human CYP isoenzyme responsible for losartan oxidation.[43] Grapefruit juice, a cytochrome P4503A4 inhibitor, may affect the metabolization of this drug. This was confirmed in a randomized crossover trial on nine human volunteers.[44] A recent comparison of five sartans indicated a unique affinity of losartan to P4502C19.[45] The pharmaceutical profiles of all these metabolites at AT_1 receptors were found to be diminished in comparison to that of losartan or EXP3174.[27] Additionally a detailed analysis by a radioreceptor assay in combination with HPLC monitoring indicates losartan and EXP3174 to be the only compounds responsible for Ang II antagonism.[46] A blockage of the thromboxane A2 receptor and the enhanced excretion of uric acid were observed under losartan treatment.[47,48] These known sartan interactions with non-ANG-II receptors such as TXA_2 (thromboxane A2)[49,50] put EXP3174 and the intermediates in a new perspective (Figures 2 and 9). Moreover, losartan and its metabolite E3174 modify cardiac delayed rectifier K^+ currents by different modulation of the repolarization. Losartan lengthens the duration of action, and EXP3174 slows the final stage of the repolarization.[51] New methods were developed to determine the losartan and the metabolites in urine and plasma recently.[52]

2. Eprosartan (SK&F 108566) is approved for the treatment of essential hypertension in a number of European countries. Whereas the losartan metabolism was reported in great detail, little is published for eprosartan,[53,54] although the compounds share a number of structural fragments. The effect of hepatic diseases on the metabolic clearance rates and the plasma protein binding was found to give a 40% higher AUC for protein-bound and 50% for unbound ^{14}C-eprosartan in patients with impaired hepatic function. These data suggest a minimum contribution of the oxidative metabolism to be 30%, but no metabolites were reported in this or analogue studies.[55] The simultaneous administration of fluconazole outruled a metabolism by cytochrome P4502C9,[40,41] which reduces the potential of drug−drug interactions. In a comparison of five sartans, eprosartan was the only compound lacking affinity to CYP2C9.[45] Eprosartan acts at vascular AT1 and presynaptic AT1 receptors, reducing the sympathetically stimulated noradrenaline release.[56] The differences in uric acid excretion were investigated in a double-blind study for losartan and eprosartan. While losartan increased uric acid excretion in hypertensive patients, eprosartan did not.[57]

3. Irbesartan, also known as BMS-186295 and SR 47436, was discovered by Sanofi Research and further developed jointly by Bristol Myers Squibb (BMS) and Sanofi-Winthrop. Studies on ^{14}C-labeled irbesartan indicate metabolism of irbesartan to be below 20%. A small renal and a large hepatic elimination and oxidation by P4502C9 result in a plasma half-life of 15 h.[58] A small amount of irbesartan (5%) is N-glucoronidated to **I-M8** (Figure 3), while other minor metabolites account for the remaining balance.[59] The oxidized and glucoronidated products were identified by HPLC, NMR (COSY), and MS/MS and were quantified in plasma, urine, and feces against authentic samples. The initial spiropentyl oxidation provides two diastereomeric alcohols **I-M5**/**M7**, yet only one diol **I-M1** was observed. The exact regio- and stereochemistry of the hydroxylated spiropentanes **I-M5**/**M7** was not established. Further oxidation of the side chains led to the ketones **I-M6** and **I-M2**. The dominant metabolites in urine are **I-M4** (25%) and the acid **I-M3** (15%). The imidazole N-dealkylation or hydrolytic imidazole opening was observed in monkeys or upon storage but was not confirmed in human samples. All 18 identified metabolites[60] have so far displayed lesser potency than irbesartan, with the dominant circulating **I-M3** being 1000-fold less potent as an AT_1 inhibitor. Therefore, contribution of metabolites to the AT_1 inhibition was excluded.[59] Several CYP inhibitors were coadministered to cellular essays or to purified P450 isoforms. Tolbutamide and warfarin turned out to be competitive inhibitors of irbesartan oxidation. Thus, CYP2C9 was concluded to play a major role in metabolism.[61]

4. Valsartan, also known as CGP 48933, is an AT_1-selective antagonist with high affinity to smooth muscle cells ($K_i = 2.38$ nM). ^{14}C-labeled valsartan was recovered in 96% yield from plasma, feces, and urine, and the only verified metabolite **V-M1** (Figure 4) was identified by MS and ^1H NMR and confirmed by total synthesis.[62] Two further metabolites (1.2% and 2.1%) were not elucidated, but glucoronidation was ruled out. Only one of the synthesized diastereomeric alcohols corresponded to **V-M1**. The diastereomeric mixture was tested as CGP71580 for AT_1 affinity, $IC_{50} = 0.47$ μM ($K_i = 0.37$ μM), and had a 200-fold lesser affinity than valsartan. A significant food dependency of the bioavailability is unique to valsartan and may result in up to 50% reduction.[17]

5. Tasosartan features a different heterocycle but is metabolized by the same systems. Four metabolites were found in rats and a fifth metabolite was identified in man. And again, the oxidation is very important for activity. The hydroxylation improves inhibition at AT_1 (Figure 5, tasosartan $IC_{50} = 1.2$ nM (38 nM),[65] **T4** $IC_{50} = 0.17$ nM).[63] The acidic enol in **T4** ($pK_a = 9.4$) corresponds to the acid in EXP3174 and provides the interaction with His^{256} of AT_1.[63,64] An additional four metabolites **T6**−**T9**, their affinity to AT1, their synthe-

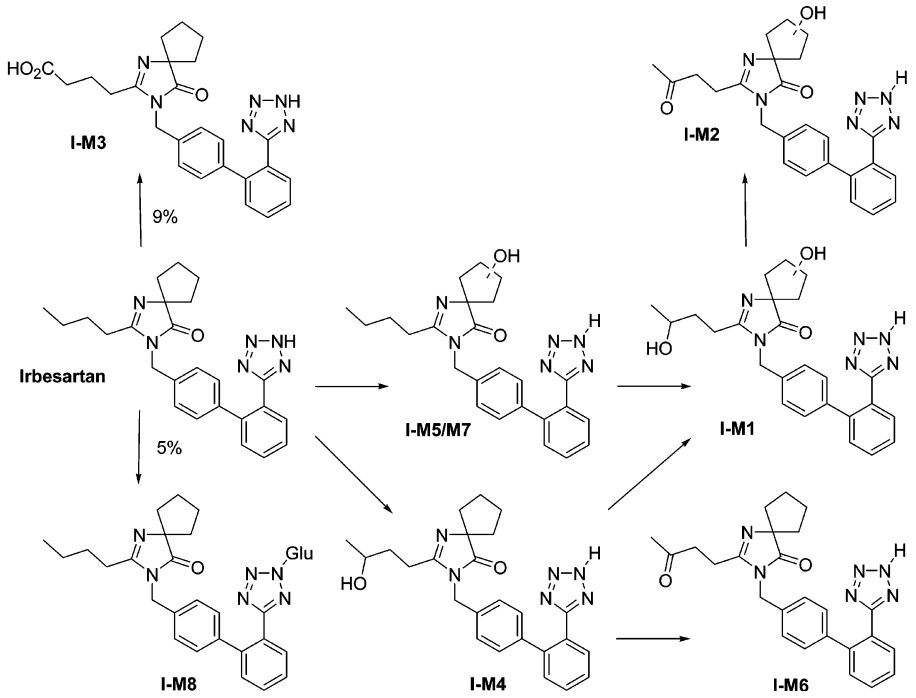

Figure 3. Irbesartan and its metabolites.

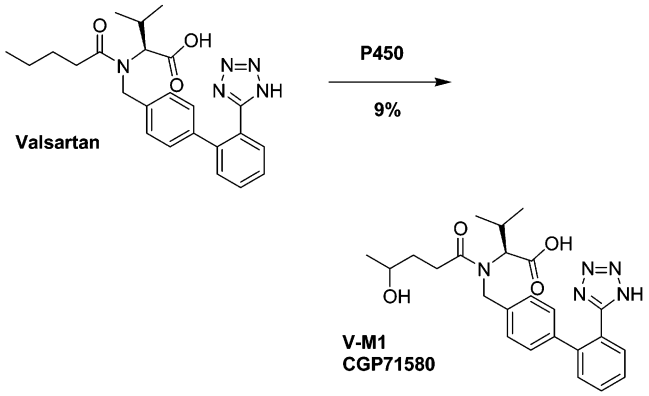

Figure 4. Valsartan and its metabolite.

sis, and their activities were reported recently.[65] Whereas previous publications emphasized the origin of the metabolites, the focus has shifted now toward activity. The intravenous administration of **T6** and **T7** to anesthetized Ang II challenged rats failed to attenuate the pressure response. However, **T8** displayed antagonistic properties, but it is much weaker than tasosartan itself. Unfortunately, the plasma levels and kinetics of these metabolites were not reported yet. Thus, clinical relevance remains to be established.

6. The less active prodrug ATACAND (candesartan cilexetil) from Takeda is hydrolyzed to candesartan (also known as CV-11974) during absorption from the gastrointestinal tract. Despite enhanced absorption of the elaborate prodrug, the total oral bioavailability is still low (<40%).[66] Finally, a cleavage of the acid-labile enolether unmasks the inactive cyclic urea CV-15959 (Figure 6) but at a slow rate and less than 20% conversion prior to excretion via urine.[67] Plasma protein binding of candesartan is almost complete, resulting in a volume of distribution of 0.13 L/kg. The relative binding affinities to the AT1 receptor (highest affinity is 1) are the following: candesartan 1, telmisartan 10, EXP3174 10, tasosartan 20, losartan 50, eprosartan 100, and the prodrug candesartan cilexetil 280.[68,69] Candesartan is further metabolized[70] by CYP2C9*3, but ^{14}C-candesartan studies did not identify further relevant metabolites.[71] A recent, detailed comparison of candesartan and losartan pharmacokinetics and pharmacodynamics included their agonistic properties.[72] The clinically relevant shift of the dose−response relationship, yet equivalent antagonistic activity and the greater pharmacodynamic effect of candesartan, may be explained by the slower off-rate from the AT1 receptor.[73]

7. ^{14}C-labeled telmisartan showed approximately 50% absorption after oral administration, with a peak plasma concentration after 0.5−1 h. The absolute bioavailability was determined to be 43%.[74] Some 16% of the radioactivity was assigned to the only metabolite in man: the telmisartan glucuronide conjugate. More than 90% of the compound is excreted within 120 h, mostly (98%) via the feces. The renal clearance accounts for less than 1% of the dose. However, this pathway is dominated by the 1-*O*-acylglucoronide (Figure 7), which turned out be one of the most stable glucoronides reported so far. There is no indication of the other 2-*O*-, 3-*O*- and 4-*O*-acylglucoronides. The rapid clearance of the 1-*O*-glucoronide was determined to be 180 mL/(min·kg) compared to 15.6 mL/(min·kg) for telmisartan.[75]

Thromboxane A2-Antagonism

Pleiotropic effects for AT_1-antagonists have been described since their early release. It has been demonstrated that thromboxane A_2 (TXA_2) and prostaglandin (PG) endoperoxides, which both stimulate the contraction of vascular smooth muscle by a common receptor[76] activation, are involved in ANG-II-dependent arterial hypertension. Moreover, early findings indicated that losartan binds to the TXA_2 receptor and thereby inhibits platelet aggregation. More recently, losartan was shown to be a functional antagonist of a specific TP receptor mediated response. TP receptors mediate the actions of thromboxane A2, a potent physiologic stimulus for

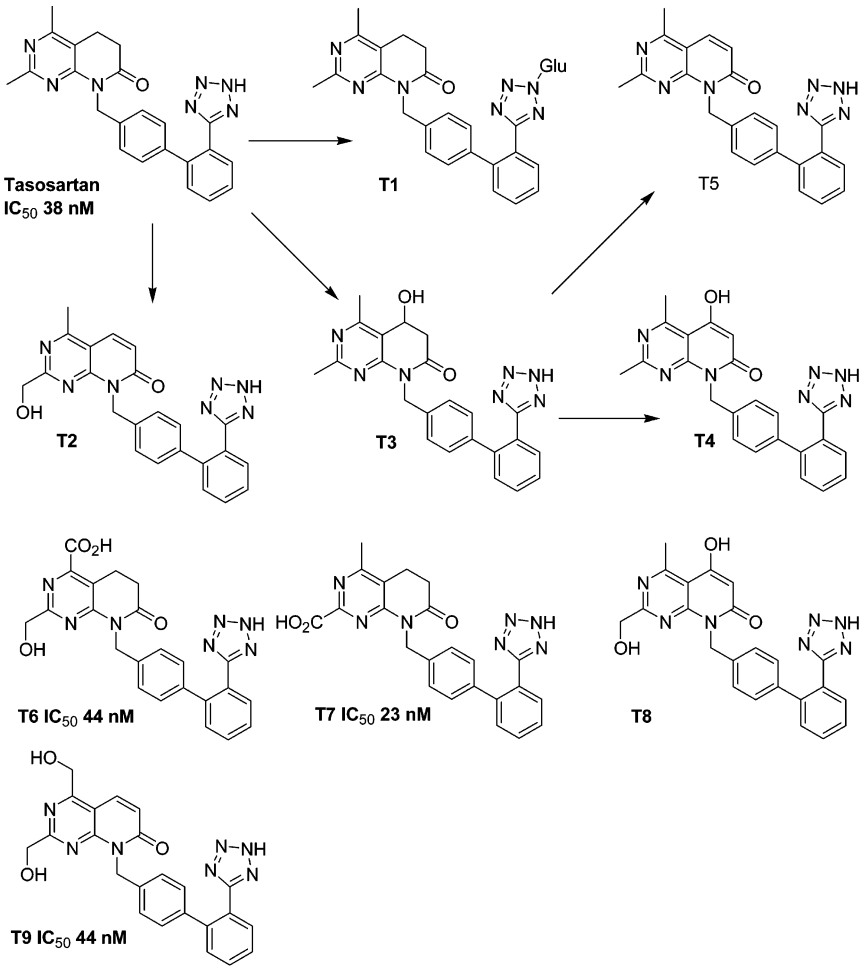

Figure 5. Tasosartan and its metabolites.

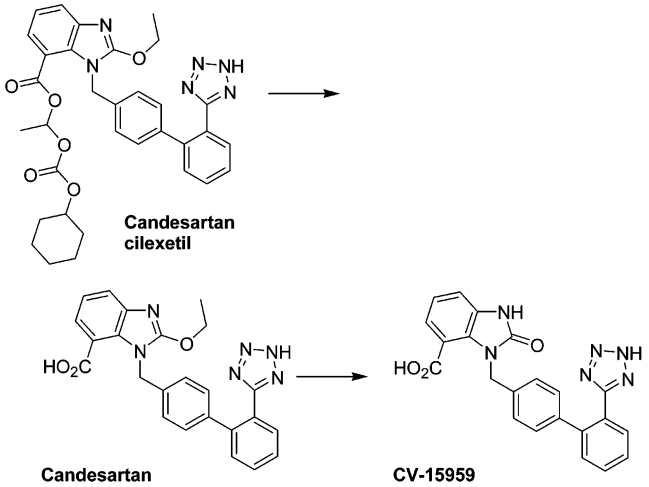

Figure 6. Candesartan and its metabolites.

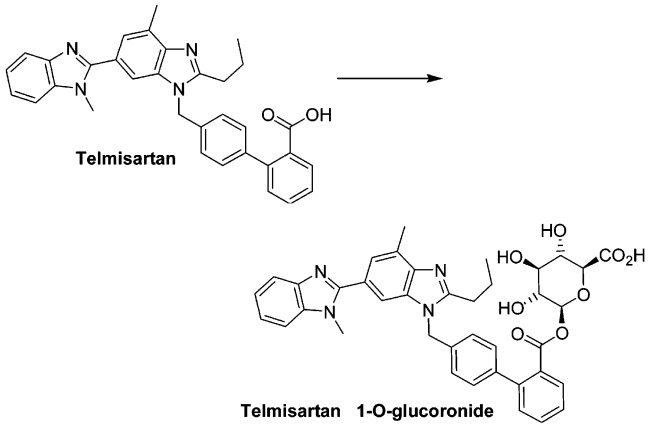

Figure 7. Telmisartan and its 1-*O*-acylglucoronide.

platelet activation, vasoconstriction, and bronchoconstriction.[18] There is also evidence of a role for this hormone TXA_2 in pathophysiologic cardiovascular and renal diseases such as acute myocardial infarction, angina pectoris, pregnancy-induced hypertension (eclampsia), and renovascular hypertension. Losartan is a competitive functional antagonist at platelet TP receptors. It is conceivable that some of the effects of losartan are mediated in part through TP receptor inhibition and that other compounds structurally related to losartan (EXP3174 or other metabolites) may bind to these receptors with higher affinity. Indomethacin and nordihydroguaiaretic acid (NDGA) do not affect losartan inhibition of [3H]S1Q 29,548 binding and platelet function, and losartan does not induce production of endogenous thromboxane or lipooxygenase products.[77]

Agonistic activity at the AT_1 was reported for a similar biphenylimidazole, which was the first example of a high-affinity, non-peptidic, non-opiate agonist at a G-protein-coupled receptor.[78] Thus, agonism by metabolites, prostaglandin and thromboxane related effects, platelet aggregation, and atherosklerotic processes are the focus of interest. The activation of cyclooxygenases

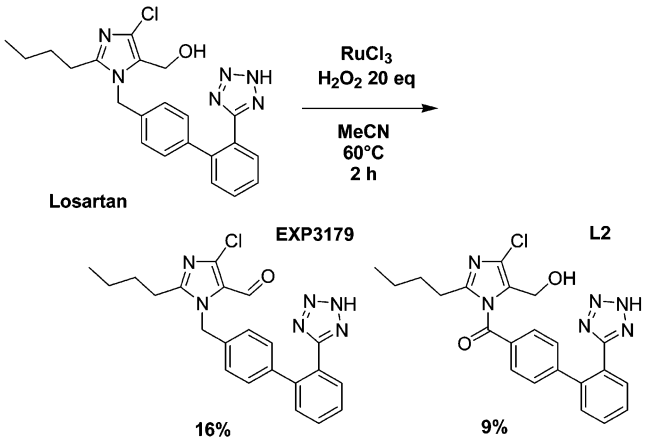

Figure 8. Cyclooxygenase inhibitor EXP3179 and **L2**.

by TxA_2-mediated pathways was ruled out by simultaneous administration of the cyclooxygenase inhibitor indomethacin.[50] A stimulation of growth hormone secretion (GHs) by circulating losartan metabolites (10−500 nM) was not reported yet, but their striking similarity to L-692,429 und L-739,943 (Figure 9), which stimulate a 300% increase of GHs (EC_{50} = 3−4 nM), awaits testing.[79−82]

Growth Hormone Analogues

Growth hormone (GH) has been shown to increase myocardial contractility by several experimental models of heart failure and human dilated cardiomyopathy. The administration of recombinant human GH to the hearts of cardiomyopathic hamsters during the development of heart failure stimulated the conclusion that GH treatment may improve cardiac function by preserving the density of cardiac sarcoplasmatic reticulum Ca^{2+} release channels (ryanodine receptors RyR).[83] Studies with a GH excess model have demonstrated improved contractile performance and a significant increase in the Ca^{2+} sensitivity of the contractile proteins. GH largely prevented the decrease of cardiac RyR in cardiomyopathic hamsters. This may change the Ca^{2+} handling and control the increase of intracellular Ca^{2+} available to activate the myofilaments, which would in turn alter cardiac contractility. An increase of protein synthesis through GH is suspected.[83] Unfortunately, a long-term effect of human GH administration could not be evaluated since the administration of GH for longer than 3 weeks leads to the formation of antibodies against human GH in hamsters. Nevertheless, it was suggested that administration of exogenous GH at an optimal dose initially seems to have favorable effects on the cardiovascular system in cardiomyopathic hamsters during the development of heart failure. If we can extrapolate from these results to humans, GH therapy might have great potential as a new therapeutic approach to the treatment of at least some form of heart failure. The stimulation of growth hormone secretion (GHs) by circulating losartan metabolites was not yet confirmed, but the similarity to L-692,429 and L-739,943 (Figure 9) is attracting our research efforts.

Should certain metabolites of losartan (Figure 2) be shown to actively stimulate endogenous GH secretion, this may help to explain the efficacy of losartan as observed in the heart failure trials ELITE I and ELITE II. Although in direct comparison with ACE inhibitors in the ELITE II and the VALHEFT trials, AT1 antagonism was less effective compared to chronic ACE inhibition. The short-term effects of excess GH on the heart produce a hyperkinetic state characterized by high cardiac output and decreased peripheral vascular resistance and in a significant increase in Ca^{2+} sensitivity of the contractile proteins. GH produces a prolonged action potential, which in turn may facilitate Ca^{2+} influx through L-type Ca^{2+} channels leading to enhanced myocardial contractility. The inhibition of bovine cAMP phosphodiesterase by losartan (IC_{50} = 139.3 μM) and EXP3174 (IC_{50} = 38.9 μM) is rather interesting, but the overall impact on cAMP-mediated signaling is blunted by typical peak concentrations of losartan of less than 2 μM (EXP3174: C_{max} < 2 μM) under standard losartan administration and the 2900-fold higher affinity of losartan to AT_1. Again, the interaction of losartan and calcium and calmodulin-dependent cGMP phosphodiesterase (PDE 1) is weak (IC_{50} = 100 μM).[84] However, inhibition of cAMP-specific PDE 4, which offers potential for asthma therapy, occurs with much higher potency (PDE 4 IC_{50} = 26 μM; PDE 3 IC_{50} = 13 μM).[85] The ligand design resulted in improved inhibition of both cAMP and cGMP (PDE 3) phosphodiesterases by compound **3-3** (PDE 4 IC_{50} = 2.9 μM, PDE 3 IC_{50} = 8 μM).

Oxidations by isolated P450 enzymes are notoriously sensitive and require isolation of P450 on a reasonably large scale.[86] State of the art biomimetic systems utilizing perhalogenated porphyrins have been developed, yet they require laborious synthesis of the ligands. For our own synthesis, we relied on the simple and catalytic oxidation of losartan by ruthenium(IV) and H_2O_2 in refluxing acetonitrile, which provides oxidation products similar to P450 (Figure 8). In addition to the expected aldehyde EXP3179, we observed the new benzamide **L2**. Both resemble indomethacin to some extent (Figure 10). The presence of the latter product was not established in human plasma yet.[87]

Conclusion

In summary, AT_1 receptor antagonists are designed compounds that elicit greater potencies and clinical

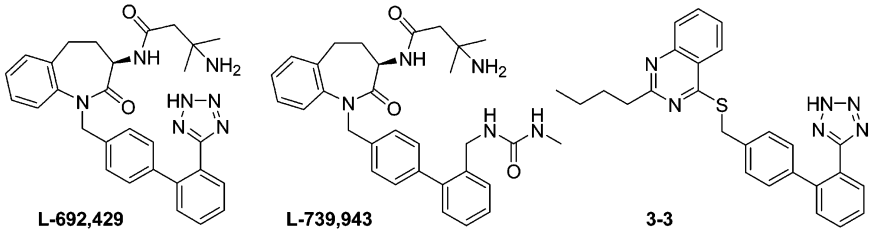

Figure 9. Non-peptidic growth hormone regulators.[82]

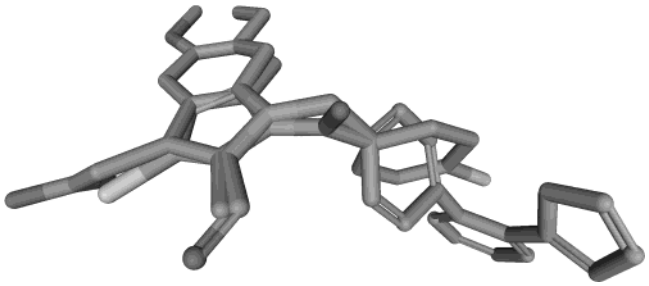

Figure 10. Overlay of EXP3179 (MM2/Mopac calculation) and indomethacin (COX1 complex).

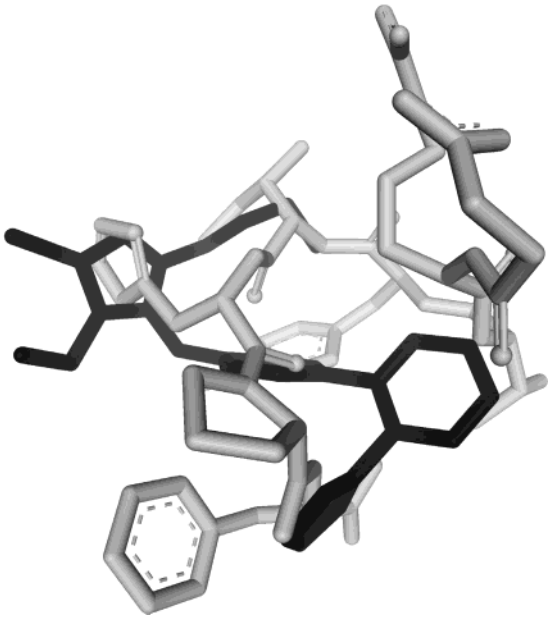

Figure 11. Losartan angiotensin II overlay in analogy to the results of Wilkes et al.[12]

potencies as initially suggested, and this may occur independent of their actions at the AT1 receptor. To prove potential independent potencies of active metabolites, further experimental and randomized clinical trials are needed to evaluate the importance of these metabolites. Significant progress was made in the determination of angiotensin II receptor antagonists in human plasma and feces, which will ease the entry into further studies.[88−90] The rapid progress in GPCR modeling after disclosure of the rhodopsin structure[91] provides detailed insight into the binding mode of Ang II. These refined homology models (Figure 11 and Wilkes et al.)[12] will fuel the design of future members of the sartan drug family.

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Biographies

Boris Schmidt, born on Trinidad in 1962, studied chemistry at the University of Hannover, Germany, and Imperial College, London (U.K.). He obtained his Ph.D. in natural product synthesis in 1991 with H. M. R. Hoffmann. He moved to the University of Uppsala, Sweden, to pursue postdoctoral studies on angiotensin II mimetics with A. Hallberg before he embarked on a grant from the Deutsche Forschungsgemeinschaft to the Scripps Research Institute, La Jolla, CA, to join K. B. Sharpless. He returned to Hannover for a habilitation on medicinal chemistry (1994−1998) and then moved on to join CNS Research at Novartis, Basel, CH, Switzerland, in 1999. Since March 2002 he holds a professorship at the Institute of Organic Chemistry and Biochemistry of the Darmstadt University of Technology.

Bernhard Schieffer, born in Kaiserslautern, Germany in 1964, started his studies in organic chemistry at the University Saarland, Saarbrücken, Germany, and switched to human medicine at the Albert Ludwigs University in Freiburg, Germany, in 1986. In 1990, he obtained his doctoral degree for his work on the role of the renin−angiotensin system in experimental congestive heart failure in the Department of Cardiology in the group of Helmut Drexler. In 1993, he moved to Atlanta, GA for a 2-year postdoctoral fellowship to work with Kenneth E. Bernstein and Mario B. Marrero on the angiotensin II− AT1-receptor signal transduction. In 1995, he returned to Freiburg and continued his AT1-receptor signaling studies with a grant from the Deutsche Forschungsgemeinschaft. In September 1996, he moved to Hannover Medical School, Department of Cardiology (Chairman, Helmut Drexler). From 1997 to 2000, he finished his habilitation on angiotensin II−AT1-receptor signaling in atherosclerosis. Since March 2001, he holds the position of an Associate Professor at the Division of Internal Medicine/Department of Cardiology at the Hannover Medical School.

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