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BALANCED ANGIOTENSIN II RECEPTOR ANTAGONISTS. II.[1,2] 4-AMINOMETHYL- and ACYLAMINOMETHYLIMIDAZOLES

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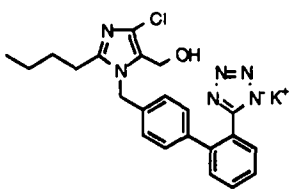
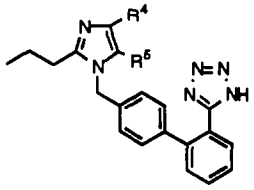
Abstract: The introduction of aminomethyl and acylaminomethyl substituents at the imidazole 4-position of 1-biphenylmethylimidazole-5-carboxylates imparts affinity for the AT_2 receptor. The highest affinity was found with the 4-(2-pyridyl)-piperazin-1-ylmethyl group and the use of hexanoylsulfonamide as a tetrazole replacement, which led to XM953 (**18d**), with an AT_2 IC_{50} of 20 nM and an AT_2/AT_1 IC_{50} ratio of 3.

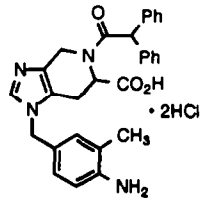
Losartan potassium (DuP 753, Cozaar™) (**1**) is a novel angiotensin II (Ang II) antagonist in Phase III clinical trials for the treatment of hypertension. The antihypertensive effects of losartan are mediated by antagonism of the Ang II AT_1 receptor subtype.[3] Losartan and other Ang II antagonists currently in clinical trials have very low affinity for a second Ang II receptor, the AT_2 site, which has been found in many tissues, including adrenal and brain.[4] We have recently become interested in designing nonselective AT_1/AT_2 nonpeptide antagonists.[1,2] Higher circulating Ang II levels have been observed after continuous treatment with losartan in animal models and in the clinic,[5] and AT_2-mediated effects could appear in the context of chronic stimulation of the AT_2 site. In addition, recent studies have indicated that the AT_2 receptor may have a role in wound healing, cardiac remodeling and cerebral blood flow.[6]



Losartan (**1**)



DMP 811 (**2**)
R^4 = Et, R^5 = CO_2H
XC331 (**3**)
R^4 = Ph, R^5 = CHO



PD123,177 (**4**)

Nonpeptide Ang II antagonists selective for AT_2, such as PD123,177 (IC_{50} = 66 nM) (**4**) have been described by workers at Parke-Davis.[7] Recently, nonpeptide AT_1 antagonists with significant affinity for the AT_2 site have been reported by Dr. Karl Thomae[8] (BIBS 39; AT_1/AT_2 K_i's = 29/480 nM) and Hoechst[9] (S0029;

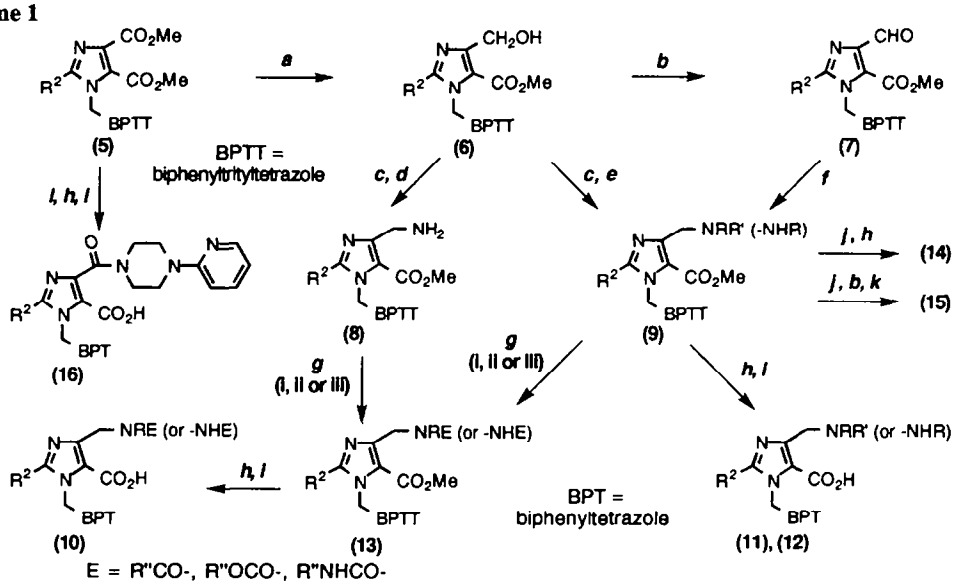
AT_1/AT_2 IC_{50}'s = 0.3/775 nM). Very recently Merck has reported nonpeptides, such as L-162,441,[10] with subnanomolar affinity for both Ang II receptor subtypes.[11,12]

Our objective was to discover orally active nonpeptide Ang II antagonists with AT_1 potency < 10 nM and AT_2/AT_1 IC_{50} ratios ≤ 1. We believed that such properties would minimize antihypertensive dosage levels, while maximizing AT_2 blockade. When the structure of losartan (**1**) was compared with that of PD123,177 (**4**), it appeared that the addition of lipophilic acylaminomethyl substituents to the imidazole ring of (**1**) might impart AT_2 affinity. Noting the excellent AT_1 affinity and *in vivo* activity of imidazole-5-carboxylates, such as DMP 811 (**2**),[13] and having found modest AT_2 affinity in certain imidazoles with large substituents at the imidazole 4-position, such as XC331 (**3**)[14] (AT_2 IC_{50} = 6.7 μM), we decided to prepare 4-(acylaminomethyl)imidazole-5-carboxylates.

Chemistry

The selective reduction of diester (**5**)[15] with DIBAL-H provided a convenient entry to the target imidazoles (Scheme 1),[16] and gave the opposite regiochemistry from that observed with lithium tri-*t*-butoxyaluminum hydride.[15,16] The protected alcohol (**6**) was converted to the mesylate and then treated with various nucleophiles. For example, treatment of the mesylate with sodium azide, followed by reduction of the azide

Scheme 1



Reagents: *a*. DIBAL-H, THF, -70°-RT; *b*. MnO_2, THF; *c*. Ms_2O, diisopropylethylamine, CH_2Cl_2, -40°-0°; *d*. NaN_3, DMSO, then Ph_3P, aq. THF; *e*. dialkyl or cyclic amines, DIEA, CH_2Cl_2, RT; *f*. amines, $NaCNBH_3$, HOAc/NaOAc, DMF, RT; *g*. i: R"COCl or $R"CO_2H$ + carbonyldiimidazole, TEA, THF or DMF; ii: Boc_2O or *i*-butylchloroformate, TEA, CH_2Cl_2; iii: R"NCO, K_2CO_3, DMF; *h*. MeOH, 65°; *i*. aq. NaOH, MeOH, then HCl; *j*. LAH, THF, 0°-RT; *k*. aq. HCl, THF; *l*. 4-(2-pyridyl)piperazin-1-yl(methyl)chloroaluminum, CH_2Cl_2, 10°-RT.

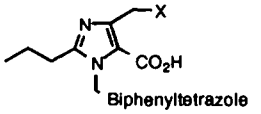
with triphenylphosphine and acylation of the resulting amine (**8**) provided the amides, ureas and carbamates (**13**), which were detritylated in hot methanol and then saponified to give (**10**). Alternatively, treatment of the mesylate with secondary and cyclic amines gave amino esters (**9**), which were deprotected to give the target

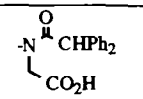
amines (**11**) or piperazines (**12**). The alcohol (**6**) was also oxidized to carboxaldehyde (**7**), which underwent reductive amination to give amines (**9**), which were converted to (**10**) as described above, or deprotected to give (**11**) or (**12**). The imidazole-5-methanol (**14**) and carboxaldehyde (**15**) were prepared from (**9**) using standard methods. Amidation of diester (5) with the aluminum amide[17] generated from 1-(2-pyridyl)piperazine gave the imidazole-4-amide, which was deprotected as above to give (**16**).[18] The acylsulfonamides and sulfonylcarbamates (**17**) and (**18**) were synthesized using the methods shown in Scheme 1 in conjunction with literature procedures.[1,12]

Discussion

The addition of nitrogen-containing substitutents at the imidazole 4-position enhanced AT_2 affinity relative to DMP 811, while generally leaving AT_1 affinity unchanged (2-20 nM). An exception is the N-diphenylacetyl-glycine (**10a**), which had relatively poor AT_2 and AT_1 affinity (10 μM and 0.1 μM, respectively). Removal, or replacement of the N-carboxymethyl group of (**10a**), and the use of other acyl groups (**10b-g**) led to improved affinity for both Ang II subtypes, with AT_2 activity ranging from 4 - 0.3 μM. An unexpected improvement in AT_2 affinity (90 nM) was found with tertiary amines (**11**).

Table 1. Binding Affinities of 4-[Acyl]aminomethylimidazoles (10) and (11)

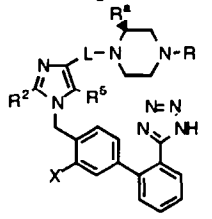


Ex. No.	X	IC_{50} (nM)[19] AT_2	AT_1
10a		7,000	100
10b	-$NHCO_2$-*t*-Bu	4,000	6
10c	-$N(CH_2Ph)CO_2$-*t*-Bu	1,000[a]	9
10d	-$N(CH_2Ph)CO_2$-*i*-Bu	800	20
10e	-$NHCOCH(Ph)_2$	600	10
10f	-$N(CH_2Ph)COCH_2Ph$	400	20
10g	-$N(CH_2Ph)CONHPh$	300	2
11a	-N(*n*-Pn)$_2$	200	2
11b	-$N(CH_2Ph)$-*n*-Bu	90	3

[a] IC_{50} estimated from biphasic displacement curve

Our attention then turned to the use of substituted piperazinylmethyl at the imidazole 4-position. An improvement in AT_2 affinity vs. (**11b**) was observed in the 2-pyridylpiperazine XH148 (**12j**) (60 nM), and in phenylpiperazine (**12h**) (50 nM), which has an AT_2/AT_1 IC_{50} ratio of 10. Modifying the length of the alkyl substituent at the 2-position of the imidazole ring, as in (**12k**) and (**12l**), resulted in lower AT_2 affinity. The use of an "ortho-fluoro"-biphenyl group, which has been shown to increase AT_2 affinity several fold in imidazoles related to DMP 811,[1] led to decreased AT_2 activity in this series (**12m**). The addition of piperazine ring substituents[20] did not change (**12n**) or decreased AT_2 affinity (**12o**).

Table 2. Binding Affinities of Piperazines (12), (14), (15) and (16)



Ex. No.	R	R^2	L	R^a	R^5	X	IC_{50} (nM)[19] AT_2	AT_1
12a	benzoyl	*n*-Pr	CH_2	H	CO_2H	H	>10000	5
12b	cyclopropylcarbonyl	*n*-Pr	CH_2	H	CO_2H	H	6000	10
12c	2-methoxyphenyl	*n*-Pr	CH_2	H	CO_2H	H	3000	2
12d	diphenylacetyl	*n*-Pr	CH_2	H	CO_2H	H	1000	10
12e	2-chlorophenyl	*n*-Pr	CH_2	H	CO_2H	H	600	2
12f	phenyl[a]	*n*-Pr	CH_2	H	CO_2H	H	400	2
12g	4-fluorophenyl	*n*-Pr	CH_2	H	CO_2H	H	80	3
12h	phenyl (XH669)	*n*-Pr	CH_2	H	CO_2H	H	50	5
12i	2-pyrimidinyl	*n*-Pr	CH_2	H	CO_2H	H	80	2
12j	2-pyridyl (XH148)	*n*-Pr	CH_2	H	CO_2H	H	60	4.2
12k	2-pyridyl	*n*-Bu	CH_2	H	CO_2H	H	700	2
12l	2-pyridyl	Et	CH_2	H	CO_2H	H	500	20
12m	2-pyridyl	*n*-Pr	CH_2	H	CO_2H	F	200	0.9
12n	phenyl	*n*-Pr	CH_2	Me	CO_2H	H	70	2
12o	phenyl	*n*-Pr	CH_2	benzyl	CO_2H	H	1000	10
14	2-pyridyl	*n*-Pr	CH_2	H	CH_2OH	H	>10000	10
15	2-pyridyl	*n*-Pr	CH_2	H	CHO	H	1000	2
16	2-pyridyl	*n*-Pr	CO	H	CO_2H	H	700[b]	2

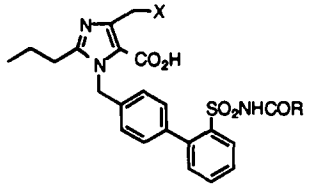
[a] **(12f)** is the piperidine (4-deaza-analog) of **(12h)**
[b] IC_{50} estimated from biphasic displacement curve

As a result of our collaboration in the Ang II area with Merck Research Laboratories, we became aware of the finding by Merck scientists that certain sulfonamide-based tetrazole replacements frequently provide increased AT_2 affinity.[11] The benzoyl- and *c*-propylcarbonylsulfonamides[21] **(18a)** and **(18b)** showed lower AT_2 affinity than tetrazole XH148 **(12j)**, however, several alkyl- and alkoxycarbonylsulfonamide based analogs of **(10)** and **(12)** were found to have ≤100 nM affinity for the AT_2 receptor, with hexanoylsulfonamide **(18d)** (XM953) having the highest AT_2 affinity (20 nM) and lowest AT_2/AT_1 ratio (3) observed in this series (Table 3). Thus, while the "ortho-fluoro" effect[1] did not enhance the AT_2 activity provided by the imidazole 4-substituent, alkyl- and alkyloxycarbonylsulfonamide tetrazole replacements provided high AT_2 affinity, while not detracting from AT_1 activity.

Consistent with their AT_1 activity, most of the 4-substituted imidazoles prepared in this study showed potent antihypertensive activity after intravenous administration to renal hypertensive rats (RHR). However, the

activity after oral administration was limited. Two compounds, (**11b**) and (**17b**), with AT_2 affinity <100 nM, but not (**12j**), (**12h**) or (**18d**) (XM953), showed significant and prolonged antihypertensive activity after oral administration at 3 mg/kg (Table 4). The apparent low bioavailability observed with this class of Ang II

Table 3. Binding Affinities of Acylsulfonamides (17) and (18)



Ex. No.	X	R	IC_{50} (nM)[19] AT_2	AT_1
17a	-N(CH_2Ph)COPh	*i*-BuO	100	8
17b	-N(*n*-Bu)CO-*n*-Pr	*n*-Pr	90	2
18a	4-(2-pyridyl)piperazinyl	*c*-Pr	600	10
18b	4-(2-pyridyl)piperazinyl	Ph	500	6
18c	4-(2-pyridyl)piperazinyl	*n*-BuO	90	6
18d (XM953)	4-(2-pyridyl)piperazinyl	*n*-Pn	20	6

antagonists may be due to their zwitterionic character. Modifying the imidazole-5-carboxy group ((**14**), (**15**)) or the basic nitrogens ((**12a**), (**12f**), (**16**)) of XH148 led to greatly decreased AT_2 affinity. However, the piperazine amide (**16**) did show improved antihypertensive activity vs. (**12j**) (XH148) after oral administration in RHR (ED_{30} ~ 3 mg/kg), as well as potent i.v. activity (ED_{30} = 0.018 mg/kg). No differences in efficacy, or effect on blood pressure and heart rate attributable to the AT_2 binding affinity were observed for the compounds in the present study as compared to losartan.

Table 4. Activity of Selected Compounds in Renal Hypertensive Rats

Ex. No.	IC_{50} (nM)[19] AT_2	AT_1	ED_{30} (mg/kg)[22] i.v.	p.o.
Losartan	10,000[4]	5.5[4]	0.78[4]	0.59
11b	90	3	0.04	~3
12j (XH148)	60	4.2	0.003	>3
12h (XH669)	50	5	0.004	>3
17b	90	2	0.18	1.65
18d (XM953)	20	6	0.13	>10

4-Substituted imidazoles (**11b**), (**12j**) (XH148), (**12h**) (XH669), (**17b**) and (**18d**) (XM953) show significant AT_2 affinity while retaining nanomolar AT_1 affinity. Two analogs, (**11b**) and (**17b**), exhibit significant antihypertensive effects upon oral administration. However, because of the low apparent oral bioavailability observed in this class of imidazoles, and the need for lower AT_2/AT_1 IC_{50} ratios, other approaches to the incorporation of AT_2 affinity in nonpeptide Ang II antagonists were pursued.

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