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POTENT TRIAZOLINONE-BASED ANGIOTENSIN II RECEPTOR ANTAGONISTS WITH EQUIVALENT AFFINITY FOR BOTH THE AT_1 AND AT_2 SUBTYPES[1]

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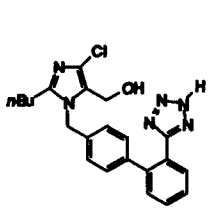
Abstract: A series of subnanomolar (IC_{50}) triazolinone-based AT_1/AT_2-balanced AII antagonists has been identified. The 70–240-fold gain in AT_2 activity relative to prototype compounds was achieved by the introduction of a 5-acylamino group on the N^2-aryl moiety and the addition of (3-F-5'-Pr)biphenyl substituents on **4**. These analogues exhibited AT_2/AT_1 IC_{50} ratios of ≤ 1 in multiple assay systems including human adrenal.

Angiotensin II (AII) is the principal effector hormone of the renin-angiotensin system (RAS).[2] This octapeptide has equivalent affinity for both of the major subtypes of the AII receptor (AT_1 and AT_2).[3] The AT_1 receptor is crucial in the regulation of blood pressure and electrolyte homeostasis, and is associated with most of the known physiological effects of AII.[3] The investigative drug Cozaar® (losartan, DuP 753, MK-954, **1**) is a nonpeptide AT_1-selective antihypertensive agent.[4] The physiological role of the AT_2 receptor has yet to be clearly defined although it has been associated with the regulation of renal function,[5] and may be involved in restenosis following vascular injury,[6] in wound healing,[7] and in cardiac fibroblast collagen synthesis.[8] In addition, it has been implicated in various cell differentiation and cell proliferation processes.[3,9] Recently, high affinity nonpeptide AT_2-selective ligands have been described also.[10] The administration of an AT_1-selective AII antagonist results in an increase in the plasma levels of AII.[11] The effect of prolonged stimulation of AT_2 receptors by elevated levels of AII is not known. Dual-action AII antagonists capable of simultaneous blockade of both receptor subtypes (AT_1/AT_2-balanced AII antagonists) would be useful as pharmacological tools and could have advantages as therapeutic agents over AT_1-selective compounds.



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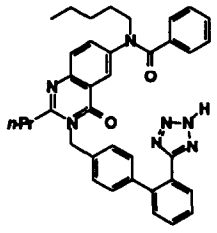
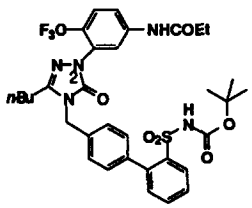
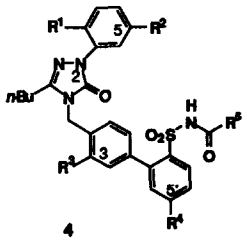


2: AT_1 IC_{50} = 1.7 nM
AT_2 IC_{50} = 0.7 nM



3: AT_1 IC_{50} = 0.29 nM
AT_2 IC_{50} = 1.0 nM



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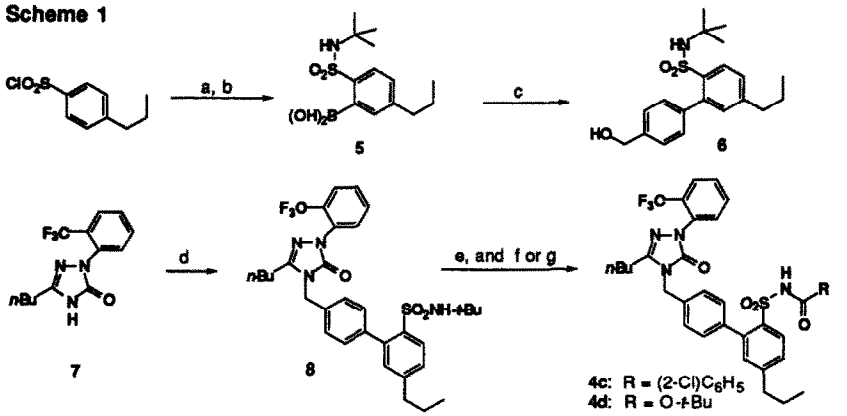
Many dual-action peptide ligands for the AII receptor are known but have unsatisfactory pharmacokinetic properties, and are of limited pharmacological value.[3,12] The discovery of a series of high affinity AT_1/AT_2-balanced (*N*-alkyl-*N*-acyl)aminoquinazolinone tetrazoles such as **2** (L-159,689),[13] paved the way towards the identification of other dual-action AII antagonists.[14] In the triazolinone series, starting from a benzoylsulfonamide (**4**, $R^1 = CF_3$, $R^2 = R^3 = R^4 = H$, $R^5 = C_6H_5$, L-159,913) with an AT_2 IC_{50} value of 300 nM (rat midbrain),[15] judicious replacement of the N-substituent of the sulfonamide, and the addition of a 5-

acylamino group on the N^2-aryl moiety resulted in compound **3** (L-163,007) which had an AT_2 IC_{50} value of 1 nM and an AT_2/AT_1 IC_{50} ratio of 3 (rat midbrain/rabbit aorta).[1] Other approaches to enhance AT_2 binding affinity include: (1) replacement of the terminal phenyl ring of the biphenyl moiety by a 5-alkyl-substituted thienyl group as shown in a series of imidazopyridine-based compounds,[16] and (2) the addition of a 3-fluoro substituent on the biphenyl moiety in a series of imidazole-based acyl (or related) sulfonamides, demonstrated by the DuPont Merck group.[17] Modifying triazolinone biphenylsulfonamides **4a** and **4b** which had modest AT_2 binding affinity[18] (see Table 1), we have prepared and evaluated compounds **4c-m** in attempts to obtain structurally diverse, potent, and fully balanced AII antagonists which show oral activity in animal models. To ensure equivalent coverage of both receptors under physiological conditions, we looked for compounds with AT_2/AT_1 IC_{50} ratios of ≤1 in three pairs of tissue preparations (rat midbrain/rabbit aorta, rat adrenal, and human adrenal).

Chemistry

Two routes were used to prepare these compounds, depending on whether R^3 in **4** is H or F. For compounds with R^3 = H (**4c,d,h,i**)[19], the requisite biarylmethyl side chain was appended onto the 4-unsubstituted triazolinone under Mitsunobu conditions. The synthesis for compounds **4c,d** is shown in Scheme 1. 4-*n*-Propylbenzenesulfonyl chloride was made into its *N*-*t*-butylsulfonamide, which was deprotonated by excess *n*-butyllithium and then treated with triisopropyl borate to furnish the boronic acid **5**.[20] Palladium(0)-catalyzed biaryl coupling between 4-bromobenzyl alcohol and **5** provided the corresponding biphenylmethanol **6**.[21a] Alkylation of the triazolinone **7**[18] using **6**, triphenylphosphine, and diisopropyl azodicarboxylate[22] provided the intermediate **8**. Removal of the *t*-butyl group followed by acylation or alkoxycarbonylation according to previously described procedures[1,18] gave target compounds **4c,d**. Analogues **4h-m** have a chloro instead of a trifluoromethyl group at R^1 since 2-chloro-5-nitrophenylhydrazine, required for the synthesis of the key intermediate **9** for these derivatives, was readily available from the corresponding aniline while 5-nitro-2-(trifluoromethyl)aniline had been synthetically elusive.[1]

Scheme 1

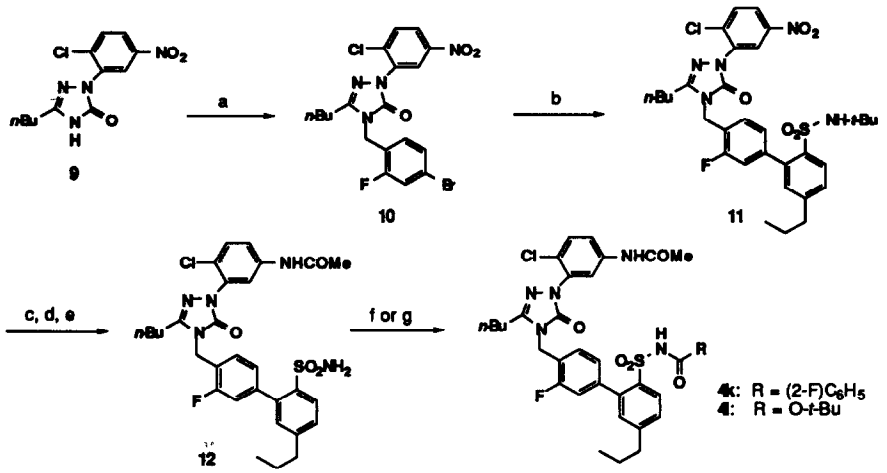


a: (i) *t*-BuNH$_2$/CH$_2$Cl$_2$, 0°C– rt, (ii) NaOH. b: (i) 2.5 eq. *n*-BuLi/THF, -40°C– rt, (ii) (*i*-PrO)$_3$B, 0°C– rt (iii) aq. HCl, 90% for a,b. c: 3 eq. (4-Br)C$_6$H$_4$CH$_2$OH, 3 mol% Pd(PPh$_3$)$_4$, NaOH, toluene/EtOH, 100°C, 3h, 62%. d: **6**, P(Ph)$_3$, DIAD/THF, -15°C– rt, 66%. e: TFA, rt, 73%. f: (2-Cl)C$_6$H$_5$C O$_2$H, Im$_2$CO, DBU/THF, 86%. g; NaH, (BOC)$_2$O/THF, 95%.

The synthesis for compounds **4k,l**, shown in Scheme 2, is typical of the route taken to prepare analogues with a 3-fluoro substituent on the biphenyl moiety (**4e-g, j-m**). Alkylation of the anion of the N^4-unsubstituted

triazolinone **9**[1] by 4-bromo-2-fluorobenzyl bromide provided the intermediate **10**. This compound underwent Pd(0)-catalyzed cross coupling reaction with boronic acid **5** to provide **11**,[21] containing the 3-fluoro-5'-propylbiaryl sulfonamide moiety. The nitro group on the N^2-aryl was reduced by stannous chloride and then acylated using acetyl chloride.[3,18] Subsequent removal of the *t*-butyl group provided the free sulfonamide **12**.[1,18] Acylation or alkoxycarbonylation furnished the desired analogues **4k,l**.[1,18]

Scheme 2



a: NaH/DMF, (4-Br,2-F)$C_6H_3CH_2Br$, 50°–90°C, 79%. b: 2 eq. **5**, 5 mol% $Pd(PPh_3)_4$, 4 eq. NaOH, toluene/EtOH, 90°C, 6 h, 68%. c: H_2/PtO_2, EtOH, 78%. d: DMAP, pyridine, ClCOMe, 88%. e: TFA, 88%. f: (2-F)$C_6H_4CO_2H$, Im_2CO, DBU/THF, 56%. g: NaH, $(BOC)_2O$/THF, 72%.

Biological Results and Discussion

The ability of compounds **4c-m** to block competitively the specific binding of the radioligand ^{125}I[Sar^1,Ile^8]AII to a rabbit aorta (for AT_1 receptor) and a rat midbrain (for AT_2 receptor) membrane preparation was assessed as previously described.[23] Compounds which showed AT_2/AT_1 IC_{50} ratios of ≤5 were further evaluated in the rat and/or human adrenal AT_1 and AT_2 receptor tissue preparations.[24] Multiple runs of the assays were conducted for each key compound to ensure consistency in the IC_{50} values obtained. For simplicity, Table 1 shows only data from the aorta/midbrain and human adrenal assays. In general, these ligands were equally potent or slightly more active at the rat adrenal AT_1 and AT_2 receptors compared to the aorta/midbrain combination. The AT_2/AT_1 IC_{50} ratios were generally very similar for these pairs.

Data from analogues **4c,d** show that, compared with **4a,b**, the added 5'-propyl group provided a 2–3-fold increase in the AT_2 binding affinity but resulted in a 10–20-fold loss in AT_1 potency. Compound **4c**, with a 2-chlorobenzoylsulfonamide moiety, was less adversely affected on AT_1 than the sulfonylcarbamate **4d**. This effect of the 5'-alkyl group in increasing the AT_2 binding affinity at the expense of AT_1 potency was also observed in other heterocyclic series.[16] Analogue **4d** was a balanced compound from the aorta/midbrain assays but was not examined further because of insufficient aorta AT_1 potency and poor IC_{50} values from the human adrenal assays. Compounds **4e,f** contain a 3-fluoro substituent on the biarylmethyl moiety. Comparing these with the unsubstituted acylsulfonamide **4a** and sulfonylcarbamate **4b**, a 3-fold increase in AT_2 binding affinity was achieved while maintaining subnanomolar AT_1 potency. From these data, we inferred that **4g**, an

acylsulfonamide containing both the 3-F and 5'-Pr substituents, could be a balanced compound. Indeed, **4g** was balanced in all pairs of tissue preparations (rat adrenal $AT_{1IC_{50}}$=1.5 nM, $AT_{2IC_{50}}$=1.1 nM). High human adrenal IC_{50} values, however, precluded further interest.

TABLE 1. *IN VITRO* SAR OF VARIOUS N^2-ARYL TRIAZOLINONE BIPHENYLSULFONAMIDES FOR THE AT_1 AND AT_2 RECEPTOR SUBTYPES OF AII

						Rabbit Aorta/Rat Midbrain[a]			Human Adrenal[a]		
						IC_{50} (nM)		AT_2/AT_1 IC_{50}	IC_{50} (nM)		AT_2/AT_1 IC_{50}
Cpd. no.	R^1	R^2	R^3	R^4	R^5	AT_1	AT_2	Ratio	AT_1	AT_2	Ratio
4a[b]	CF_3	H	H	H	(2-Cl)Ph	0.11	36	*300*			
4b[b]	CF_3	H	H	H	O-*t*-Bu	0.45	17	*39*			
4c	CF_3	H	H	n-Pr	(2-Cl)Ph	1.3	14	*11*			
4d	CF_3	H	H	n-Pr	O-*t*-Bu	10	8.1	*0.8*	150	270	*1.8*
4e	CF_3	H	F	H	(2-Cl)Ph	0.15	12	*80*			
4f	CF_3	H	F	H	O-*t*-Bu	0.31	4.2	*14*			
4g	CF_3	H	F	n-Pr	(2-Cl)Ph	3.9	3.5	*0.9*	110	140	*1.3*
4h	Cl	NHCO-n-Bu	H	Et	(2-Cl)Ph	1.0	4.9	*4.9*			
4i	Cl	NHCOEt	H	Et	(2-Cl)Ph	0.25	3.5	*14*			
4j	Cl	NHCOMe	F	n-Pr	(2-Cl)Ph	0.90	0.15	*0.2*	16 (0.48[c])	17	*1.1*
4k	Cl	NHCOMe	F	n-Pr	(2-F)Ph	0.62	0.15	*0.2*	5.9	2.4	*0.4*
4l	Cl	NHCOMe	F	n-Pr	O-*t*-Bu	0.84	0.24	*0.3*	14 (0.82[c])	12	*0.9*
4m	Cl	NHCOMe	F	n-Pr	O-Et	1.4	0.10	*0.07*	15	2.6	*0.2*
4n[d]	Cl	NHCO-n-Bu	H	H	(2-Cl)Ph	0.16	1.6	*10*			
4o[d]	Cl	NHCOEt	H	H	(2-Cl)Ph	0.17	2.5	*15*			
4p[d]	Cl	NHCOMe	H	H	(2-Cl)Ph	0.052	12	*230*			

[a] For the rabbit aorta and rat midbrain binding assays, no bovine serum albumin (BSA) was added to the assay mixtures. For the human adrenal assays, 0.2% BSA was present in the assay mixtures unless otherwise indicated. [b] This compound was reported in reference 18. [c] Data from cloned human AT_1 receptor (no BSA in assay mixture). [d] This compound was reported in reference 1.

Subsequently, we investigated compounds **4h,i** which have a 5'-ethyl substituent and an amide moiety on the 5-position of the N^2-aryl ring. The amide moiety is known to enhance AT_2 activity in the triazolinone series.[1] Compared to the 5'-propyl group, the 5'-ethyl group was expected to induce a smaller increase in AT_2 binding affinity but suffer less of a loss in AT_1 potency. Together, these modifications might result in a balanced compound more potent than **4d** or **4g**. Table 1 shows that, unfortunately, the 5'-ethyl group resulted in a decrease in AT_2 binding affinity in **4h,i** compared to **4n,o**, unsubstituted at the 5'-position, and the AT_2/AT_1 IC_{50} ratio remained unsatisfactory in the 5'-ethyl analogues.

Next, we considered using a combination of an acetylamino group at the 5-position of the N^2-aryl and 3-fluoro-5'-propylbiaryl substituents to enhance AT_2 potency. The expected loss in AT_1 potency owing to the 5'-propyl group was designed to be partially offset by the presence of the acetylamino group, which had previously provided an exceptionally potent AT_1 derivative (e.g., **4p** vs. **4o**).[1] Four analogues were synthesized in this series, **4j-m.** The first compound prepared, **4j** (rat adrenal $AT_{1IC_{50}}$=0.38 nM, $AT_{2IC_{50}}$=0.11 nM), had

subnanomolar intrinsic potency at both receptors, superior in this respect compared to a close analogue **4g**. In addition, **4j** was balanced in all 3 sets of tissue preparations. The 2-fluorobenzoylsulfonamide **4k** was slightly more favored at AT_1,[18] providing a compound with AT_2/AT_1 IC_{50} ratios consistently <1. The *t*-butyl sulfonylcarbamate **4l** (rat adrenal $AT_{1IC_{50}}$=0.70 nM, $AT_{2IC_{50}}$=0.17 nM) also met our criterion for a balanced compound (human adrenal AT_2/AT_1 IC_{50} ratio ~1). The cloned human AT_1 receptor IC_{50} values for **4j,l** were 0.48 nM and 0.82 nM, respectively.[25] These data suggest an approximate equivalence in intrinsic potency between the rabbit aorta AT_1 and the human AT_1 receptors. Finally, the ethyl sulfonylcarbamate **4m** showed a ~6–14-fold preference for the AT_2 receptor. Relative to the *t*-butyl group, the less bulky ethyl group was able to achieve greater AT_2 binding affinity but incurred a modest loss of AT_1 potency.

The inhibition of pressor response to exogenous AII challenges by **4j,l** was studied in conscious normotensive rats according to protocols described previously.[26] At 3 mg/kg i.v., **4j** showed 71% peak inhibition with a duration of 5 h and **4l** showed 41% peak inhibition. Neither **4j** nor **4l** was active orally at this dose. This contrasts dramatically with conscious rat data for compounds **4a,b** and **3**. For these compounds, which contain an acylsulfonamide or sulfonylcarbamate, with or without an acylamino moiety, excellent efficacy (generally >85% peak inhibition) and long duration of action ($6 < t < 24$ h) were observed at 1 mg/kg both i.v. and orally.[1,18] The DuPont Merck AII group has shown that the 3-F substituent on the biaryl moiety is consistent with good oral activity in rats.[17] Therefore, the present data imply that, in the triazolinone series, the 5'-propyl group on the biaryl (perhaps in conjunction with the 2-chloro substituent on the N^2-aryl) appear to reduce in vivo efficacy and adversely affect oral activity in conscious rats.

In summary, we have described triazolinone-based dual AII antagonists which showed subnanomolar binding affinity at both receptor subtypes and met goals for AT_1/AT_2 balance in multiple tissue preparations, including human adrenal. One analogue showed modest AT_2 selectivity. The 70–240-fold gain in AT_2 activity seen in **4j-m** compared to **4a,b** was primarily achieved by a 5-acetylamino group at the N^2-aryl ring of the triazolinone and 3-fluoro, 5'-propyl substituents on the biaryl moiety. This study assisted our efforts to achieve fully balanced and orally active triazolinone-based AII ligands, which will be disclosed in the near future.

Acknowledgments

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23. (a) No bovine serum albumin (BSA) was added to the assay mixtures. The standard error (expressed as percent of mean) of the IC_{50} measurement in this assay has been estimated to be <30%, based on the results of several standard compounds having 3 or more determinations. For detailed descriptions, see: (b) Chang, R. S. L.; Siegl, P. K. S.; Clineschmidt, B. V.; Mantlo, N. B.; Chakravarty, P. K.; Greenlee, W. J.; Patchett, A. A.; Lotti, V. J. *J. Pharmacol. Exp. Ther.* **1992**, *262*, 133. (c) Chang, R. S. L.; Lotti, V. J.; Chen, T. B.; Faust, K. A. *Biochem. Biophys. Res. Commun.* **1990**, *171*, 813.
24. In order to achieve a satisfactory ratio of specific to nonspecific binding, it was necessary to add BSA (2 mg/mL) to the binding buffer for the human adrenal assays, but not for the others. Since both the AT_1 and AT_2 receptors are present in the rat and human adrenal tissues, IC_{50} values on AT_1 and AT_2 were determined in the presence of 1 μM PD121981 (WL-19) or losartan to prevent binding of the radioligand to the AT_2 and AT_1 receptors, respectively. Otherwise, assay protocols were as described in 23b,c.
25. Human AT_1 receptors cloned in CHO cells were used in this assay. No BSA was present in the assay mixture.
26. At least two animals were evaluated in all cases. A ≥30% inhibition of the AII pressor response was considered significant in this assay. For details of experimental protocol, see: Siegl, P. K. S.; Chang, R. S. L.; Mantlo, N. B.; Chakravarty, P. K.; Ondeyka, D. L.; Greenlee, W. J.; Patchett, A. A.; Sweet, C. S.; Lotti, V. J. *J. Pharmacol. Exp. Ther.* **1992**, *262*, 139.

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