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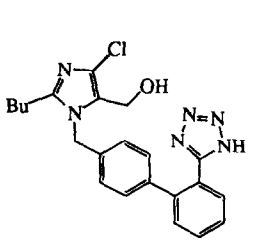
QUINAZOLINONE BIPHENYL ACYLSULFONAMIDES: A POTENT NEW CLASS OF ANGIOTENSIN-II RECEPTOR ANTAGONISTS

Prasun K. Chakravarty*,† Robert A. Strelitz,† Tsing-Bau Chen,# Raymond S. L. Chang,# Victor J. Lotti# Gloria J. Zingaro,# Terry W. Schorn,# Salah D. Kivlighn,# Peter K. S. Siegl,# Arthur A. Patchett† and William J. Greenlee†

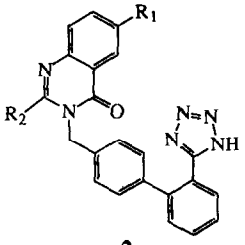
†*Exploratory Chemistry, Merck Research Laboratories, P.O. Box 2000, Rahway, New Jersey 07065 and*
#*Department of Pharmacology, Merck Research Laboratories, West Point, Pennsylvania 19486*

Abstract: A new series of quinazolinone-based AT_1 selective antagonists, bearing acylsulfonamides (-SO_2NHCOR) as the tetrazole bioisosteres, was evaluated. While AT_1 potencies remained similar to the tetrazole analogs, the AT_2 receptor affinities were significantly improved with the introduction of acylsulfonamide groups. Several of these antagonists displayed improved *in vivo* properties.

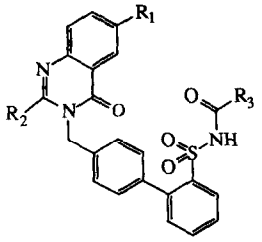
Introduction: The peptide hormone angiotensin II (AII), a potent endogenous vasoconstrictor, is the primary effector component of the renin-angiotensin system (RAS) that plays a major role in regulating the blood pressure and fluid-electrolyte balance in mammals in normal and pathophysiological conditions.[1] The biological effects of AII are mediated by the specific membrane-bound receptors that are present in various target tissues, and two subtypes of these receptors, designated as AT_1 and AT_2, have recently been identified.[2] The AT_1 receptor, the predominant AII receptor in vascular tissues and liver, is the primary mediator of many functional responses to AII (vasoconstriction, cardiac stimulation, salt-water retention by kidney, and stimulation of aldosterone biosynthesis and release), and a selective blockade of this receptor with antagonists offers an attractive approach to developing novel antihypertensive agents.[3] Since the discovery of losartan (DuP 753, MK 954) (**1**)[4], the leading non-peptide AT_1 selective antagonist, several highly potent AT_1 selective antagonists bearing novel heterocycles have been reported.[5] The tetrazole group is a common acidic function present in many of these antagonists.



1 (Losartan)



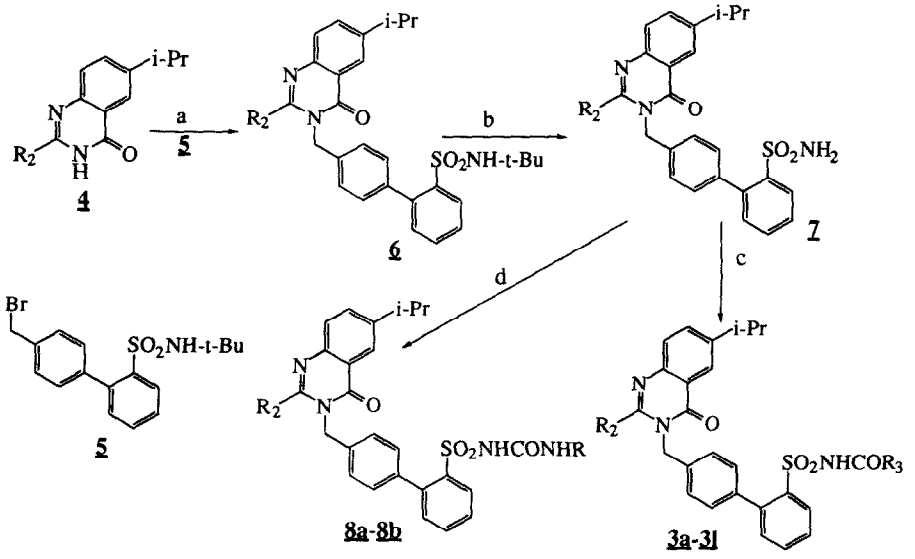
2
2a (R_1 = i-Pr)



3

Recently, quinazolinone biphenyl tetrazoles (**2**), a new series of AII antagonists, have also been reported from our laboratories.[6] Despite their good *in vitro* potency, many of these antagonists displayed short *in vivo* duration of action in conscious normotensive rats and rhesus monkeys after intravenous administration,[6b] which may be attributed to their rapid *in vivo* metabolism and/or clearance. Since the tetrazole function has been shown to be a major site for glucuronidation in losartan,[7] we envisaged that minimizing this mode of metabolism, by incorporating an alternative acidic group, might improve the pharmacological properties of these biphenyl-based antagonists. Towards this goal, the acylsulfonamide ($-SO_2NHCOR$) group was chosen as a bioisosteric replacement of the tetrazole.[8,9] Recently, in our studies with imidazole[10] and imidazo[4,5-b]pyridine[11] AII antagonists, we have demonstrated that acylsulfonamides are excellent replacements for the tetrazole function, and do not undergo rapid glucuronidation.[12] In our continued search for novel non-tetrazole AII antagonists, we exchanged the tetrazole group of quinazolinone antagonists (**2**) with acylsulfonamides. Herein we report the synthesis, the structure-activity relationships (SAR) and *in vivo* properties of quinazolinone biphenyl acylsulfonamides (**3**), a potent new series of AT_1 selective antagonists.

Chemistry: A typical synthesis of quinazolinone biphenyl acylsulfonamides (**3a-3j**; **Table I**) is outlined in **Scheme 1**. Alkylation of the quinazolinones (**4**)[6,13] with the bromomethyl biphenylsulfonamide (**5**)[10b] in the presence of aq. NaOH under phase-transfer condition gave, after chromatography, the desired N^3-alkylated product (**6**). Removal of the t-butyl group with neat trifluoroacetic acid (TFA)

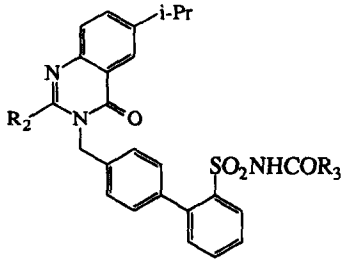


Scheme 1 Reagents: (a) 2.5 N NaOH, Triton B, toluene, 85°C, 12 h; (b) anhydrous TFA, reflux, 3 h; (c) i. R_3COOH, Carbonyldiimidazole, THF, reflux; ii.DBU, 60°C, 24 h; (d) RNCO, DBU, THF, reflux

treatment afforded the unprotected sulfonamide (7). Reaction of 7 with a mixture of an acylimidazole (prepared from a carboxylic acid R_3COOH and 1,1'-carbonyldiimidazole) and 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) provided the desired acylsulfonamides[14]. The sulfonylurea derivatives (**8a** and **8b**) were prepared by the reaction of sulfonamide 7 with an isocyanate in the presence of DBU. The compounds described in **Table II** were prepared using the chemistry reported previously.[6]

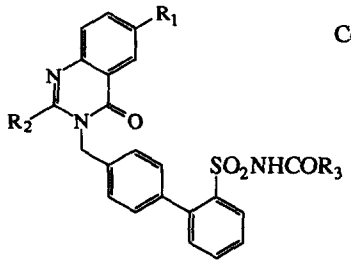
Results and discussion: The *in vitro* AII receptor binding affinities of the compounds in **Tables I** and **II** are expressed as IC_{50} values, and were determined by their ability to displace the specific binding of radio-ligand ^{125}I-[Sar^1, Ile^8]AII from the rabbit aorta membrane receptor (AT_1 receptors) and rat mid-brain receptor (AT_2 receptors) preparations as previously described.[15] The tetrazole analogue **2a** is present in **Table I** for comparison purposes.

Table I



Compd. #	R_2	R_3	AT_1 IC_{50} (nM)	AT_2 IC_{50} (nM)
3a	Bu	Ph	3.0	80
3b	Bu	(4-F)Ph	4.0	2100
3c	Bu	2-thienyl[20a]	8.0	300
3d	**Bu**	**c-Pr**	**2.6**	**390**
3e	Bu	c-pentylethyl	1.5	100
3f	Bu	(1-Me)Cyclo-Pr[20b]	1.1	549
3g	Bu	$-(CH_2)_5NH$-Boc	12	620
3h	Bu	$-(CH_2)_5NH_2$	4.4	560
3i	Pr	Cyclo-Pr	2.8	660
3j	Pr	$-(CH_2)_4COOH$	25	9500
8a	Bu	NH-i-Pr	5.6	2100
8b	Bu	NH-Ph	5.9	340
2a	Bu	Tetrazole	5.0	29,000

Table II



Compd. #	R_1	R_2	R_3	AT_1 IC_{50} (nM)	AT_2 IC_{50} (nM)
3d	i-Pr	Bu	c-Pr	2.6	390
3k	NMe_2	Bu	c-Pr	5.6	1500
3l	NMe_2	Pr	c-Pr	12	2000
3m	NMe_2	Pr	Ph	3.6	330
3n	N(Me)COOi-Bu	Bu	c-Pr	**7.4**	**120**
3o	N(Me)COOi-Bu	Pr	Ph	**0.5**	**43**

The binding data shown in **Table I** indicates that acylsulfonamides are potent AII antagonists with similar AT_1 receptor binding affinities to that of their tetrazole counterparts. A variety of acyl groups bearing aryl and alkyl substituents can be accommodated with minimal effect on AT_1 potency. However, the AT_2 receptor binding affinities are significantly improved with the incorporation of lipophilic acyl groups. Acyl groups with polar substituents (e.g. **3g**, **3h** and **3j**) are not well tolerated by either AT_1 or AT_2 receptors. As shown, the acylsulfonamide group can also be replaced with sulfonylureas (e.g, **8a** and **8b**) with minimal loss in AT_1 receptor binding affinities.

Effects of modification at the 6-position of quinazolinone ring were then examined (**Table II**). Replacing the 6-isopropyl substituent in **3d** with NMe_2 and N(Me)COOiBu groups[16] resulted in analogs **3k** and **3n** , respectively, with reduced AT_1 receptor affinity. However, AT_2 potency was enhanced in **3n**. Further structural modifications of **3n** resulted in a potent antagonist **3o** with sub-nanomolar AT_1 receptor binding affinity (IC_{50}=0.5 nM).

***In vivo* results:** Several of the acylsulfonamides were evaluated in normotensive rats.[17] The pressor responses to exogenously administered AII (0.1 μg/kg i.v. bolus) were measured before and after administration (i.v or oral) of the test antagonist. A preliminary screening led to the selection of **3d**

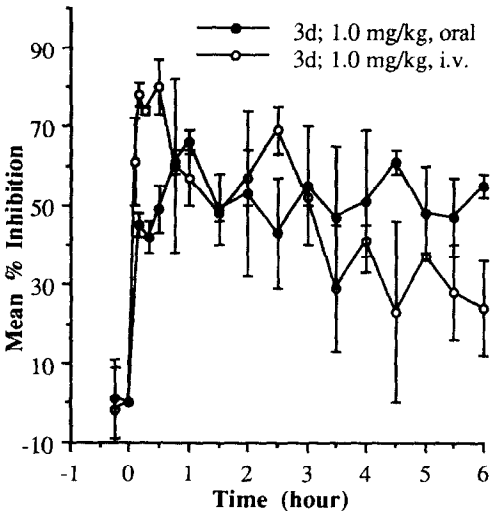


Fig.1: Inhibiton of AII induced increase in mean arterial blood pressure after administration of 3d to conscious rats (N=2)

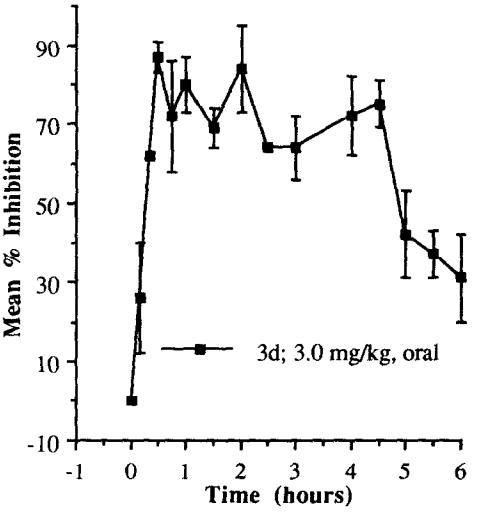


Fig. 2: Inhibition of AII induced increase in mean arterial blood pressure after oral administration of 3d (L-161,021) to conscious dogs (N=2)

(L-161,021) as a promising non-tetrazole AT_1 selective quinazolinone-based antagonist for further examination. This antagonist displayed excellent *in vivo* activity (peak effects and duration) in conscious rats after i.v. (ED_{50}=0.25 mg/kg) and oral administration (ED_{50}=0.68 mg/kg) administrations (**Fig. 1**).[18] Upon oral administration (3.0 mg/kg) to normotensive conscious dogs[19], **3d** also displayed effective blockade of AII induced pressor response with an extended duration of action (> 5 hours) (**Fig. 2**).

In conclusion, we have demonstrated that the acylsulfonamide group is an effective replacement for the tetrazole in quinazolinone-based AII antagonists. In general, incorporation of this group has resulted in improvements in *in vitro* potencies, particularly AT_2 receptor binding affinities. The acylsulfonamide L-161,021 (**3d**), a member of this new class of AT_1 selective antagonists, is potent and orally effective in blocking AII induced pressor response in both normotensive conscious rats and dogs with good duration (> 5 hours).

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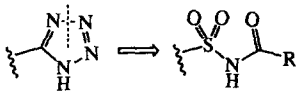
8. As shown, the acylsulfonamide group can be viewed as an isostere of tetrazole. The application of acylsulfonamides as carboxylic acid equivalents is well documented in the design of a number of therapeutic targets.[9] The pk_a value of sulphabenzamide (4.6), the antibacterial agent, is similar to that of 5-aryl-tetrazoles (5-6).



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16 The rationale for using N,N-dimethylamino and N(Me)COO-i-Bu groups as 6-position substituents has been discussed earlier (see ref. 6b).
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18. (a) At the same dose (1.0 mg/kg) level, the tetrazole analogue **2a** showed a shorter duration of action (0.3 hour) in conscious rats after i.v. administration (see ref. 6b). (b) In conscious rats, the ED_{50} values obtained for losartan were (0.28 mg/kg, i.v.) and (0.67 mg/kg, oral).
19. Female mongrel dogs were used. The protocol used was similar to the one described in ref. 17.
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