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1H-1,2,4-TRIAZOLE ANGIOTENSIN II RECEPTOR ANTAGONISTS: "C-LINKED" ANALOGS OF SC-50560

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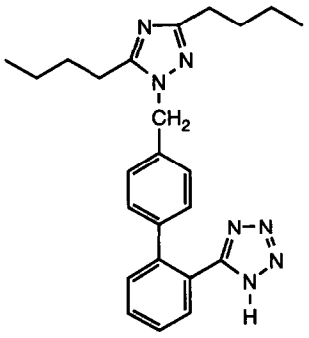
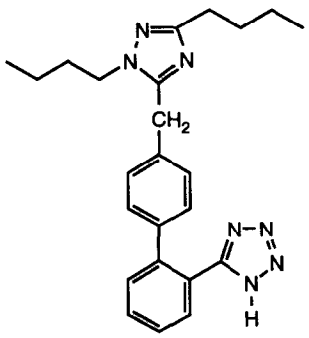
Abstract: Novel 1H-1,2,4-triazole analogs in which the biphenylmethyl group is attached to carbon and the butyl group is attached to the adjacent nitrogen were found to be potent angiotensin II receptor antagonists. Additional substitution at the carbon bearing the biphenyl group proved to be very detrimental to potency. The *in vivo* properties of the dibutyl analog SC-51757 were found to be similar to SC-50560.

N-biphenylmethyl substituted imidazoles have been shown to be good angiotensin II receptor antagonists and some analogs possess commercially interesting properties, e. g., DuP 753[1] (IC_{50}= 36 nM, pA_2= 8.1)[2]. We have reported[3] that 1H-1,2,4-triazole angiotensin II receptor antagonists in which the biphenylmethyl group is attached to the nitrogen at the 1-position and a butyl group is attached at the adjacent carbon at the 5-position are potent, orally active compounds, e. g., SC-50560[4] (IC_{50}= 5.6 nM, pA_2= 8.7). More recently, we reported[5] the effects of systematically substituting nitrogen for carbon at each position of both aromatic rings of the biphenylmethyl moiety of SC-50560. We now wish to report the results of a study in which the N^1-biphenylmethyl group and the C^5-butyl group were interchanged to give the isomeric "C-linked" 1H-1,2,4-triazole analogs, e. g., SC-51757[6], to ascertain the pharmacological properties of such "C-linked" 1H-1,2,4-triazole angiotensin II receptor antagonists[7-10]. Metalation chemistry has also been developed which provided "C-linked" analogs with substitution at the methylene that connects the triazole ring to the biphenyltetrazole.



SC-50560

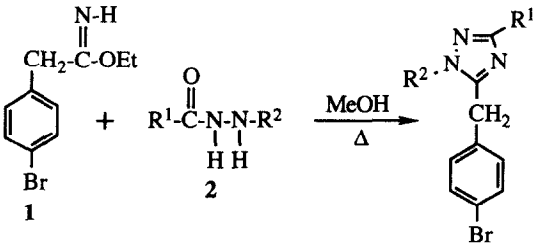


SC-51757

Synthesis:

The synthesis[11] of "C-linked"-1H-1,2,4-triazole angiotensin II receptor antagonists began with commercially available 4-bromophenylacetonitrile. A Pinner reaction gave the imidate hydrochloride which was subsequently treated with NH_3 at -78 °C to give the imidate ester **1** in 64 %. The hydrazides **2** (R^2= H) were either commercially available or were prepared from the appropriate methyl esters. Reaction of **2** (R^2= H) with butyraldehyde in CH_2Cl_2 in the presence of $MgSO_4$ followed by reduction with $NaBH_4$ in MeOH at 0 °C gave **2** (R^2= C_4H_4) in excellent yields except for **2** (R_1= $CF_2C_3H_7$)[12]. Reaction of **1** with **2** in MeOH at reflux conveniently gave the 4-bromobenzyl triazoles **3** (R= H) or **3a** (R^2= C_4H_9), as shown in Scheme 1. Apparently cyclization of the amidrazone initially formed between **1** and **2** to the corresponding 1H-1,2,4-triazole is sterically sensitive[13], as reaction times were longer and yields were lower for N^2-substituted hydrazides.

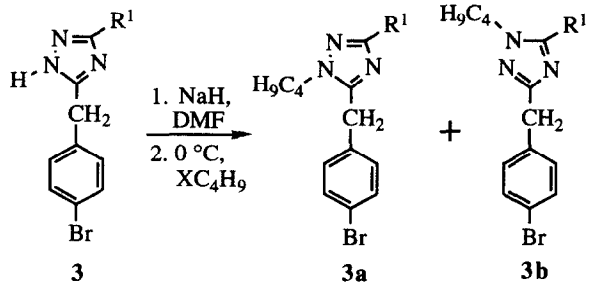
Scheme 1



R^1	R^2	Product (%)
C_4H_9	H	**3** (71)
$CF_2C_3H_7$	H	**3** (67)
C_4H_9	C_4H_9	**3a** (40)
$CH_2CH_2C_6H_5$	C_4H_9	**3a** (45)

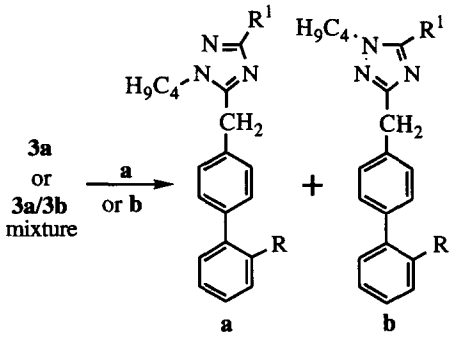
The nitrogen anion of **3**, generated by NaH in DMF, was reacted with either butyl iodide or butyl bromide to give a mixture of regioisomers **3a** and **3b**, in the yields and ratios[14] shown in Scheme 2. This mixture (R^1= C_4H_9) was reacted with (N-methyl-N-tertbutylcarboxamido)phenylboronic acid (**4**)[15] or 2-[(N^2-triphenylmethyl)-2H-tetrazol-5-yl]phenylboronic acid (**5**)[15] to give a mixture of biphenyl isomers **6a/6b** or **7a/7b**, respectively, which were subsequently separated by reverse-phase chromatography[16], as shown in Scheme 3. The **3a/3b** (R^1= $CF_2C_3H_7$) isomer mixture was separated prior to the aryl coupling procedure and **3a** (R^1=$CH_2CH_2C_6H_5$) was synthesized directly from **2** (R^2= C_4H_9); thus, subsequent reaction with **5** gave exclusively **8a** and **9a**, respectively,

Scheme 2



R^1	X	Yield (%)	Ratio (3a:3b)
$CF_2C_3H_7$	I	87	2:1
C_4H_9	Br	89	3:2

Scheme 3

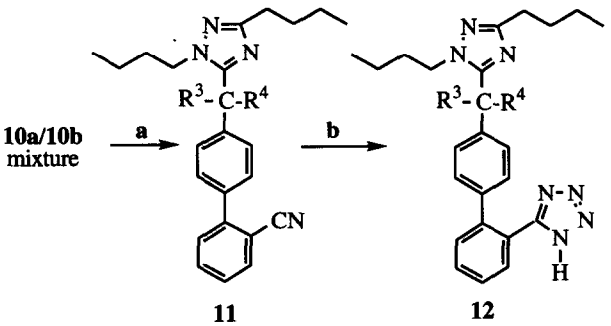


Reaction Procedure	R^1	R	Isomer (% Yield)
a	C_4H_9	CO_2H	**6a** (28), **6b** (24)
b	C_4H_9	CN_4H	**7a** (21), **7b** (19)
c	$CF_2C_3H_7$	CN_4H	**8a** (31)
c	$CH_2CH_2C_6H_5$	CN_4H	**9a** (29)

a. 1. **4**, Pd^0,Na_2CO_3, $PhCH_3$/EtOH, Δ, 2. TFA, Δ, 3. $NaNO_2$, Ac_2O, AcOH, 0 °C, 4. KOH, Δ, 5. H_3O^+; **b.** **5**, Pd^0, $PhCH_3$/EtOH, Δ.

A 1:1 mixture of 1,3-dibutyl-1H-1,2,4-triazole (**10a**) and 1,5-dibutyl-1H-1,2,4-triazole (**10b**) was prepared in 82% by reacting the nitrogen anion of 3-butyl-1H-1,2,4-triazole (generated by NaH in DMF) with butyl iodide at 0 °C. Treatment of a THF solution of this mixture at -78 °C with n-BuLi conveniently provided 5-lithio-1,3-dibutyl-1H-1,2,4-triazole, exclusively[17]. This anion reacted with 4-$CHOC_6H_4$(2-CNC_6H_4) to give the **11a** in 66% yield. The alcohol **11a** was subsequently converted to the corresponding ketone **11b** by a Swern oxidation and to the monofluoro **11c** with DAST in CH_2Cl_2 at -78 °C. Reaction of **11b** with SeF_4 in $CF_2ClCFCl_2$ at reflux provided the difluoro **11d**. Nitriles **11b**, **11c**, and **11d** were not purified. Treatment of **11a**, **11b**, and **11d** with Me_3SnN_3[1] in xylene at reflux followed by aqueous acid hydrolysis gave the corresponding tetrazole analogs **12a**, **12b**, and **12d**, respectively. Evidently, the monofluoro **12c** readily undergoes hydrolysis since only **12a** was isolated from **11c** after this two reaction sequence.

Scheme 4

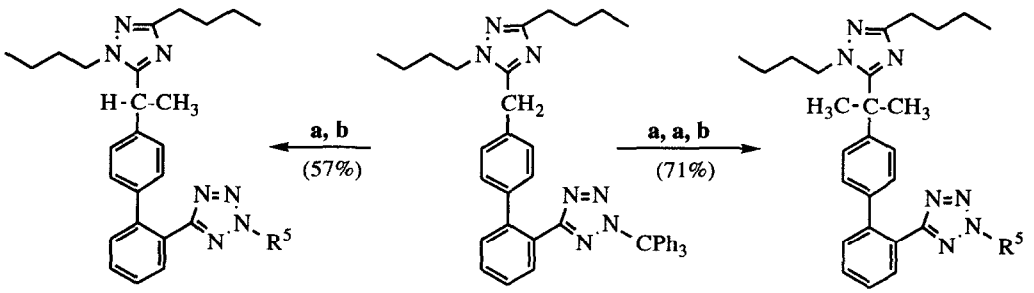


Nitrile	R^3	R^4	Tetrazole (%)
11a	H	OH	**12a** (46)
11b	C=O		**12b** (61)
11c	F	H	**12a** (19)
11d	F	F	**12d** (29)

a. 1. n-BuLi, THF, -78 °C, 2 h, 2. 4-$CHOC_6H_4$(2-CNC_6H_4) gave **11a** in 66% yield; **b.** 1. Me_3SnN_3, xylene, Δ, 2. H_3O^+.

Reaction of **7a** (SC-51757) with triphenylmethyl chloride in CH_2Cl_2 in the presence of NEt_3 gave the N^2-triphenylmethyl protected analog **13**. A THF solution of **13** at -78 °C was reacted with n-BuLi for 1h; addition of methyl iodide gave **14a** which was subsequently deprotected with AcOH/H_2O (9:1) to give after reverse-phase chromatography the monomethyl tetrazole analog **14b** in 57% overall yield. Apparently the kinetic acidity of both "C-linker" hydrogens is greater than any other hydrogens in the molecule, since a one pot sequential procedure in which a THF solution of **13** at -78 °C was treated twice with n-BuLi followed by methyl iodide provided **15a** directly. Deprotection with AcOH/H_2O (9:1) and purification by reverse-phase chromatrography gave the dimethyl tetrazole analog **15b** in 71% overall yield.

Scheme 5



a. *1. n*-BuLi, THF, -78 °C, 1h, *2.* CH_3I; **b.** ACOH/H_2O (9:1).

Results and Discussion:

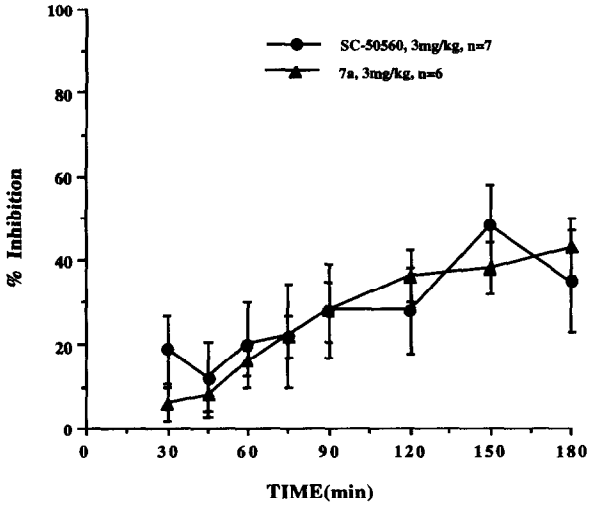
The *in vitro* properties of "C-linked" 1H-1,2,4-triazole angiotensin II receptor antagonists are shown in Table 1[18]. Comparing **6a** with **6b** and **7a** with **7b**, it is obvious that for good potency, the N-butyl group must be adjacent to the C-biphenylmethyl group and not adjacent to the C-butyl group. When the N-butyl group is adjacent to the C-butyl group, its spatial dispensation (relative to the biphenyl group) is such that it can not interact favorably with the lipophilic pocket in the receptor which has been postulated to be adjacent to the biphenyl group in the imidazole angiotensin II receptor antagonists, e. g., DuP 753[1], an interaction which can be fully taken advantage of by the SC-50560 analogs. As expected, the tetrazole analog **7a** (SC-51757) is superior to the corresponding carboxylic acid analog **6a** by a factor of 15 fold (SC-50560 is 17 fold more potent than its carboxylic analog). Table 1 also shows that substitution at the "C-linked" methylene is very detrimental to potency. It is hypothesized that this loss in potency is most likely due to conformational restriction placed on the biphenylmethyl group due to high energy steric interactions of the added functionality. Since fluorine is not much larger than hydrogen[19], the large decrease in potency found for **12d** (IC_{50}= 710 nM) relative to **7a** (IC_{50}= 16 nM) suggests that electronic effects may also play an important role.

Table 1. *In vitro* properties of "C-Linked" 1H-1,2,4-Triazole Angiotensin II Receptor Antagonists.

Analog	IC_{50} (nM)	pA_2	Analog	IC_{50} (nM)	pA_2
6a	240	7.1	**12a**	1,800	6.6
6b	12,000	5.0	**12b**	32,000	*
7a	16	8.5	**12d**	710	*
7b	6,700	5.3	**13b**	140	*
8a	40	8.0	**14b**	29,000	*
9a	9.5	7.9	**SC-50560**	5.6	8.7
				* not tested	

Figure 1[20] shows the inhibition of the angiotensin II induced pressor response by **7a** and SC-50560 in rats at a dose of 3 mg/kg. Although the binding affinity for **7a** (IC_{50}= 16 nM) is about one third the binding affinity of SC-50560 (IC_{50}= 5.6 nM), the two isomers appear to have nearly identical pharmacological profiles in rats when administered intragastrically (i.g.).

Figure 1. SC-50560 vs. 7a, i.g., in the Rat AII Pressor Assay



In summary, interchanging the N^1-biphenylmethyl group and the C^5-butyl group of the potent, orally active 1H-1,2,4-triazole angiotensin II receptor antagonist SC-50560 provided the isomeric C^5-biphenylmethyl and N^1-butyl analog **7a** (SC-51757). The *in vitro* properties of "C-linked" analogs **7a** (IC_{50}= 16 nM, pA_2=

8.5), **8a** (IC_{50}= 40 nM, pA_2= 8.0), and **9a** (IC_{50}= 9.5 nM, pA_2= 7.9) are all somewhat less than those reported[3] for the corresponding N^1-biphenylmethyl series SC-50560 (IC_{50}= 5.6 nM, pA_2= 8.7), SC-51180 (IC_{50}= 4.9 nM, pA_2= 7.9), and SC-51537 (IC_{50}= 3.2 nM, pA_2= 9.7), respectively. However, the *in vivo* properties in rats of the two isomeric dibutyl-1H-1,2,4-triazole angiotensin II receptor antagonists SC-50560 and SC-51757 are nearly identical. Substitution at the methylene which connects the 1H-1,2,4-triazole ring to the biphenyltetrazole moiety of "C-linked" analog SC-51757 was found to be very detrimental to potency. All "C-linked" analogs were found to be surmountable angiotensin II antagonists.

References and Notes

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2. In our assays, DuP 753 had an IC_{50}= 36 nM and a pA_2= 8.1, see ref. no. 18.
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11. Reaction yields were not optimized. All new compounds were fully characterized spectrally; purity was established by a combination of analytical HPLC and HRMS and/or combustion analysis. Detailed synthetic procedures with complete AII analog characterization will be published elsewhere.
12. Over reduction occurred; for the preparation of **2** (R^1= $CF_2C_3H_7$, R^2= H), see Example 10 in ref. no. 4.
13. Ethyl 4-(2-carboethoxyphenyl)phenylacetimidate reacted with **2** (R^2= C_4H_9) to give the amidrazone intermediate which on prolonged heating regenerated the hydrazide with concomitant formation of the corresponding nitrile instead of cyclizing to the 1H-1,2,4-triazole.
14. Determined by 300 mHz NMR spectroscopy; **3a** (R^1= $CF_2C_3H_7$) was assigned by analogy with **3a** (R^1 = C_4H_9) which was regiospecifically synthesized in Scheme 1, i. e., the methylene triplet of the butyl group attached to the nitrogen adjacent to R^1 is downfield from the one which is adjacent to the benzyl group.
15. Reitz, D. B., U. S. Pat. No. 1,155,177, **1992**; for the preparation of **4**, see Step 3 of Example 2 and for the preparation of **5**, see Step 5 of Example 1.
16. Regiospecifically synthesized **3a** (R_1= C_4H_9)was converted to **6a** and **7a** and subsequently used to identify **6a** and **7a** in the **6a/6b** and **7a/7b** mixtures generated in Scheme 3.
17. We have conclusively demonstrated that N-alkyl 1H-1,2,4-triazoles metalate regioselectively at the carbon adjacent to the N-alkyl group, i. e., the 5-position, see: Anderson, D. K.; Sikorski, J. A.; Reitz, D. B.; Pilla, L. T. *J. Heterocyclic Chem.* **1986**, 23, 1257.
18. Inhibition of [^{125}I] AII to rat uterine membranes (IC_{50}) had standard errors of 10% or less and antagonism of AII-contracted rabbit aortic rings (pA_2 and mode of antagonism) were the average of two aortas; the experimental procedures for both assays are described in: Olins, G. M.; Corpus, V. M.; McMahon, E. G.; Palomo, M. A.; Schuh, J. R.; Blehm, D. J.; Huang, H-C.; Reitz, D. B.; Manning, R. E.; Blaine, E. H. *J. Pharmacol. Exp. Ther.* **1992**, 261, 1037.
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