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1,3- AND 1,5-BISBIPHENYLYL SUBSTITUTED 3-MERCAPTOTRIAZOLES AS ANGIOTENSIN II RECEPTOR ANTAGONISTS

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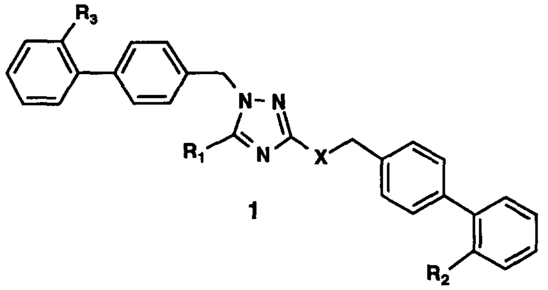
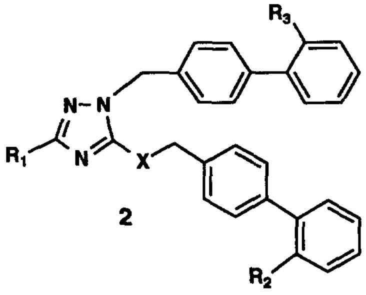
Abstract: A novel series of substituted bisbiphenylyl-3-mercaptotriazoles has been been discovered to be potent antagonists of angiotensin II. These compounds were tested in rabbit aortic rings and in a high renin rat model. The best of these compounds have pA_2 values > 8.0 and iv activity in the high renin rat at 5 mg/kg.

The role of hypertension in cardiac disfunction is continually evolving. One of the blood pressure regulating systems in man is the renin-angiotensin system. Angiotensin II (AII) is the most potent vasoconstricting agent in this pathway.[2] The discovery of nonpeptide angiotensin converting enzyme (ACE) inhibitors represented an important new step in the treatment of hypertension.[3] Direct antagonism of angiotensin II binding at the receptor is an attractive goal. By inhibiting the receptor, one would expect to have fewer side effects than inhibiting earlier steps in the pathway.[4] Losartan (DuP 753) is the most advanced AII antagonist in development.[5]

We felt that an appropriately substituted bisbiphenylylmercaptotriazole would span the distance between the acidic functions at Tyr[4] and Phe[8] of angiotensin II. We felt that the mercaptotriazole nucleus would provide a good isostere for the imidazole at His[6]. Further, the thiol group would allow for easy variations in the biphenyl substituents. Herein we report on a series of bisbiphenylyl-3-mercaptotriazoles (**1** & **2**) (X = S or SO_2) which are potent antagonists of AII contraction in rabbit aortic rings.[6] Compound **1a** also shows in vivo activity in a high renin rat model.[7]



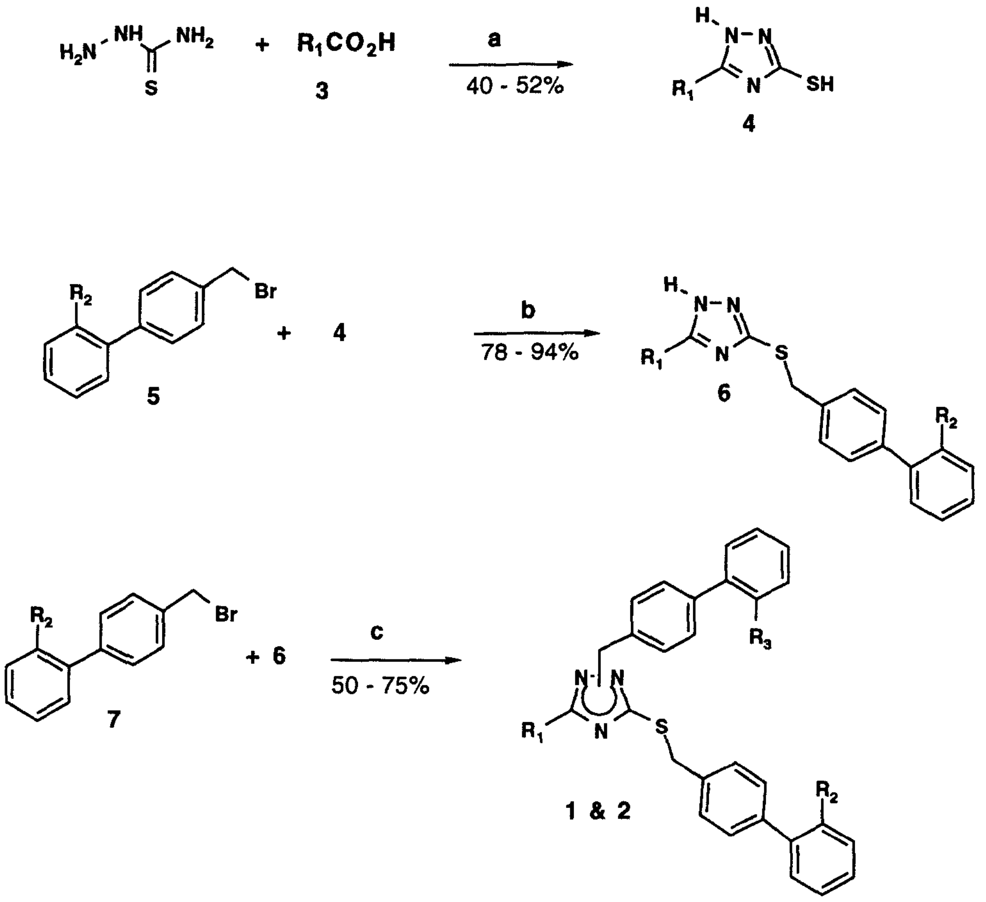
1



2

The synthesis of compounds **1** and **2** is outlined in scheme 1. Thermal reaction of **3** with N-aminothiourea affords the N-acylhydrazide which is ring closed in mild base to **4**.[8] Compound **4** is then treated with one equivalent each of sodium hydride and **5**[9] in acetonitrile. We found acetonitrile to be superior to DMF, DMSO, ether or alcoholic solvents in this reaction. Compound **6** is isolated in good to excellent yield and resubjected to the same reaction conditions.[10] This reaction afforded a mixture[11] of the 1,3 (**1**) and 1,5 (**2**) isomers which were separated by chromatography.[12,13] Compounds **1** and **2** where R_2 and/or R_3 are carboxylic acids are generated by hydrolysis of the requisite methyl ester.[14] When R_2 or R_3 is a tetrazole, **5** and **7** are protected as the trityltetrazole.

Scheme 1



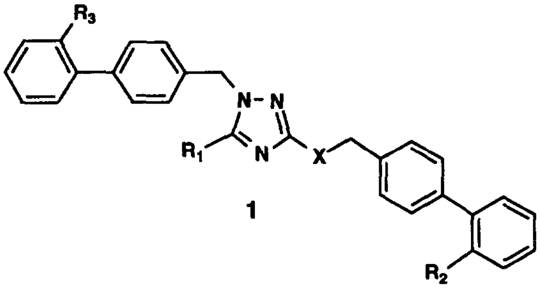
R_1 = alkyl or benzyl; R_2 = CO_2CH_3 or CN; R_3 = CO_2CH_3 or CN

a) 1) heat 2) $NaHCO_3$ b) 80% NaH, CH_3CN; c) 80% NaH, CH_3CN, Chromatography.

In these cases, the tetrazole is deprotected with wet trifluoroacetic acid. Oxidations of the substituted thio group were effected with MCPBA.[15]

The structure activity for compounds **1** and **2** is outlined in Table 1. These compounds were tested in a rat aortic ring preparation, which tests their ability to inhibit AII induced contractions.[6] In all cases **1**, the 1,3 isomer, is more potent than **2**, the 1,5 isomer. This is potentially due to a larger interacidic group distance requirement in the receptor. R_1 is best when it is either n-pentyl (**1a**) or n-butyl (**1b**). Branching in the side chain (**1d**) reduces potency. The oxidation state of X does not greatly influence activity. Diacids are favored over monoacids, but the more important acid function is R_3 as evidenced by the difference in activity between **1f** and **1g**. Esters and nitriles at R_2 and R_3 showed reduced activity in this test system. One could reason that the nitriles and esters would not show activity because the receptor requires an ionized species. The activity of **1f** could indicate that only one ionized species is necessary at R_3 while R_2 can tolerate a nonionized hydrogen bonding substituent. It is interesting, however, that the bistetrazole **1o** did not show good activity in this preparation.

Table 1



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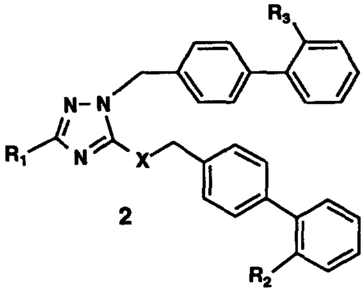

2

#	R_1	R_2	R_3	X	Substitution	pA_2
1a	n-pentyl	CO_2H	CO_2H	S	1,3	8.4
1b	n-butyl	CO_2H	CO_2H	S	1,3	8.3
1c	n-heptyl	CO_2H	CO_2H	S	1,3	6.7
1d	i-butyl	CO_2H	CO_2H	S	1,3	7.5
1e	n-hexyl	CO_2H	CO_2H	S	1,3	8.0
1f	n-pentyl	CN	CO_2H	S	1,3	6.3
1g	n-pentyl	CO_2H	CN	S	1,3	<5.0
1h	benzyl	CO_2H	CO_2H	S	1,3	7.0
1j	n-hexyl	CO_2H	CO_2H	SO_2	1,3	8.1
1k	n-heptyl	CO_2H	CO_2H	SO_2	1,3	6.5
1l	n-octyl	CO_2H	CO_2H	SO_2	1,3	6.1
1m	n-pentyl	CO_2Me	tetrazole	S	1,3	5.0
1n	n-pentyl	CN	tetrazole	S	1,3	6.6
1o	n-pentyl	tetrazole	tetrazole	S	1.3	5.0
1p	n-pentyl	CO_2Me	CO_2Me	S	1,3	<5.0
1q	n-butyl	CO_2Me	CO_2Me	S	1,3	<5.0
2a	n-pentyl	CO_2H	CO_2H	S	1,5	7.2
2b	n-heptyl	CO_2H	CO_2H	S	1,5	5.9
2c	n-butyl	CO_2H	CO_2H	S	1,5	7.0
2d	benzyl	CO_2H	CO_2H	S	1,5	6.1
DuP 753						8.8

We chose to examine compound **1a** in vivo in the high renin rat model.[7] When administered iv at 5 mg /kg it reduced blood pressure by 24 mm Hg and had a duration of ~24h. DuP 753 at 10 mg/kg po, reduced blood pressure 37 mm Hg with a duration of ~24h. To achieve oral activity doses of 100 mg/kg were required . This might be explained by poor bioavailability in this series. Efforts continue to improve the oral profile of this series.

References and notes

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7. Normotensive rats are salt depleted with furosemide causing increased renin levels. See ref.6 for details.

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9. See Ref 4b for preparations of **5**.

10. Where R_2 and R_3 are the same, 2 equivalents of **5** can be combined with **4** to afford **1** and **2**. Without intermediate purification, we obtained significantly reduced yields.
11. Mixtures ranged from 3:1 (1,3 to 1,5) to 3:2 (1,3 to 1,5).
12. Assignments were made by NOE enhancements between the methylene at R_1 and the benzylic methylene protons at N-1 in **1**. No such enhancement was seen in **2**.
13. Flash chromatography was carried out on silica gel using hexane / 20% EtOAc as mobile phase.
14. KOH / methanol at reflux.
15. Reactions were run in CH_2Cl_2 at rt.