Bioorganic & Medicinal Chemistry Letters, Vol.3, No.8, pp. 1559-1564, 1993
Printed in Great Britain

0960-894X/93 $6.00 + .00

4,5,6,7-TETRAHYDRO-8-OXO-CYCLOHEPTIMIDAZOLES: A NEW CLASS OF POTENT NON-PEPTIDE ANGIOTENSIN II RECEPTOR ANTAGONISTS

Takashi Yanagisawa, Naoto Ueyama, Tomoyuki Kawai, Motoharu Sonegawa, Hiromi Baba, Seiichiro Mochizuki, Kazukiro Kozakai and Tsuyoshi Tomiyama*

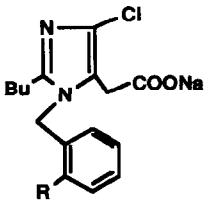
Kotobuki Research Laboratories, Kotobuki Seiyaku Company, Ltd., 6351 Sakaki-Machi, Nagano-Ken, 389-06, Japan

(*Received in USA* 25 *March* 1993)

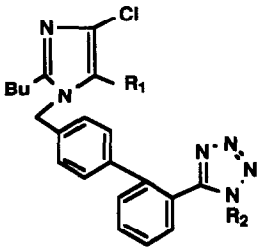
Abstract: 1,4,5,6,7,8-hexahydrocycloheptimidazoles and 4,5,6,7-tetrahydro-8-oxo-cycloheptimidazolones were synthesized as potential angiotensin-II (AII) receptor antagonists. One of these, **11c,** KT3-671, was more potent than losartan with a pA_2 value of 10.04 and AT_1 specific with an IC_{50} of 0.8 nM. In an in vivo study, it had long lasting action on blood pressure in RHR rat at a dose of 3 mg/kg.

The renin-angiotensin system (RAS) is one of the important interrelated homeostatic mechanisms that regulate hemodynamics and water and electolyte balance. The main source of renin is the kidney and renin is discharged directly to the renal arterial blood system.[1] One approach in controlling the RAS system is to use angiotensin converting enzyme (ACE) inhibitors which inhibit the conversion of angiotensin I (AI) to angiotensin II (AII). AII can also be formed in vivo by the action of enzymes other than ACE.[2] However, ACE is a non-specific dipeptidylcarboxy peptidase and will affect not only the metabolism of AI, but also the hydrolysis of bradykinin, substance P and enkephalin.[3] This might account for some of the side effects, dry cough[4] and angioedema.[5]

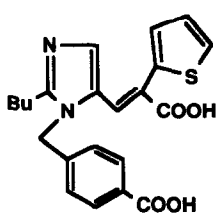
A more potentially effective approach is to block the action of AII at the AII receptor level. One of the peptide antagonists of AII receptor, saralasin,[6] was approved for limited application in



S-8307:R=Cl
S-8308:R=NO2



DuPont 753: R1=CH2OH, R2=K
Exp 3174: R1=COOH, R2=H



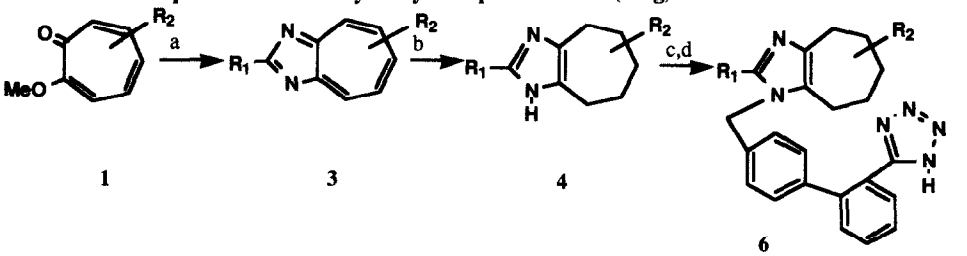
SK&F 108566

cardiovascular conditions but it has not been proven suitable as a therapeutic agent because due to partial agonist activity and lack of oral effectiveness. The concept of non-peptide AII receptor antagonists[7] which would overcome these disadvantages was reported by Takeda group.[8] Two imidazole acetic compounds from Takeda patent, S-8307 and S-8308, were studied by the Du Pont group and weak AII receptor antagonist activity of these compounds was confirmed.[11] Afterward, research groups at Du Pont and Smith Kline Beecham reported two different molecular models of non-peptide AII receptor antagonists. DuP 753[10] having a biphenyl moiety and SK&F 108566[11] with an acrylic acid moiety in the molecule. The former compound was transformed to a noncompetitive active metabolite having carboxylic acid, Exp 3174.[12] Other antagonists with 5-membered ring heterocycles include pyrazole, pyrrole, triazole, benzimidazole, imidazopyridine and other 6-membered fused imidazole have been reported.[13] No 7-membered fused imidazoles have yet been reported.[14] Since considerable interest has been shown to compounds containing 7-membered imidazole and we envisaged to prepare these compounds as AII receptor antagonists. We report, here, the synthesis of potent, orally active 7-membered fused imidazole AII receptor antagonists, 1,4,5,6,7,8-hexahydrocycloheptimidazole and 4,5,6,7-tetrahydro-8-oxo-cycloheptimidazolone analogous.

Synthesis

The initial series of compounds were prepared according to the synthesis outlined in Scheme 1. Cycloheptimidazole **3** was synthesized using with a suitable amidine **2** and the requisite methyl

Scheme I. Preparation of hexahydrocycloheptimidazoles (6a-g).

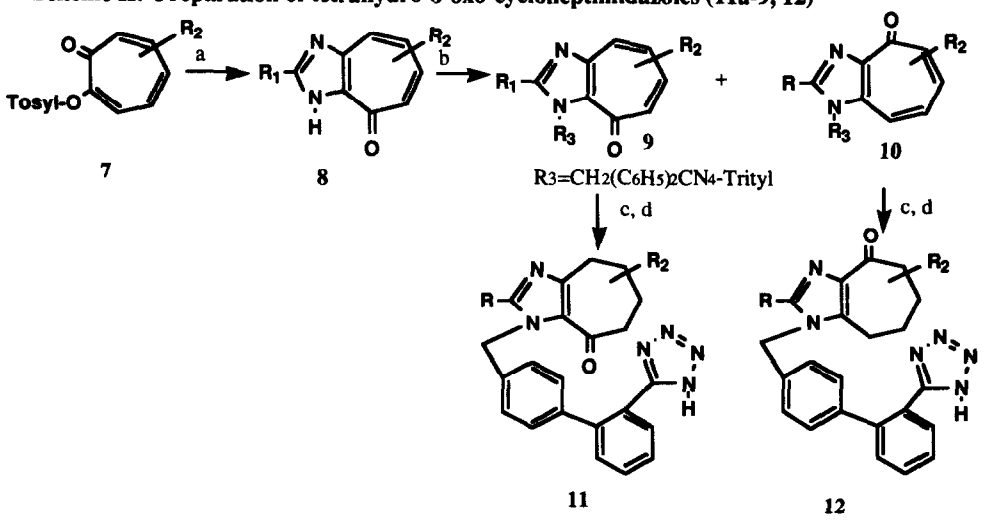


1 3 4 6

a. EtONa/EtOH, HN=C(NH2)-R1(2), reflux; b. Pd-C/H2/MeOH; c. BrCH2(C6H5)2CN4-Trityl(5)/NaOH-H2O/THF, reflux; d, 10%HCl, RT.

tropolone **1**.[15] Sequential catalytic hydrogenation of **3** over Pd-C in methanol at atmospheric pressure gave 1,4,5,6,7,8-hexahydrocycloheptimidazole **4**, followed by coupling with aralkyl bromide **5** using standard means to give 1-aralkyl compound , which was deprotected to target compound **6**. 8-Oxocycloheptimidazole **8** was readily prepared by reaction of tolopolone tosylate with **2**.[16] Benzylation of 2-methyl-8-oxocycloheptimidazole with benzyl bromide and Na_2CO_3 in methanol has been described to result in a separable 1:1 mixture of regioisomers. **8** was coupled with aralkyl bromide in this manner to give the mixtures of 8-oxo compound **9d** and 4-oxo compound **10d**. The isomers were chromatographicaly separated, hydrogenated and deprotected to give **11d** and **12d**.[17] The 8-oxo compound **11d** was found to be more active than **12d**, therefore, the regioselective

Scheme II. Preparation of tetrahydro-8-oxo-cycloheptimidazoles (11a-9, 12)



a. **2**, NaOH-H_2O/Dioxane, reflux; b.**5**/NaOH-H_2O/THF, reflux or 5/$(Bu)_4NHSO_4$/NaOH-H_2O, RT; c. Pd-C/H_2/MeOH; d. 10%HCl, RT.

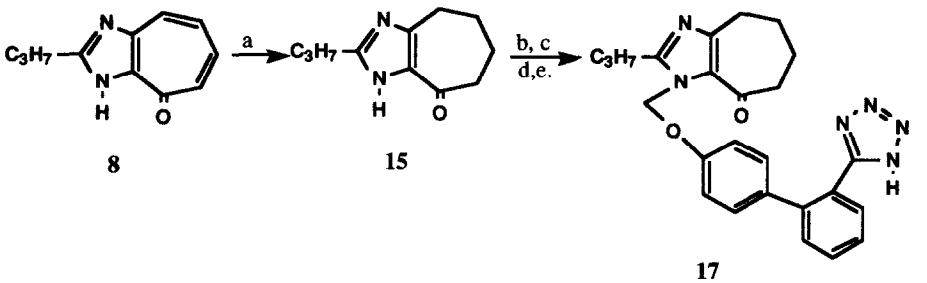
preparation was required. The regioselectivity was improved by using tetrabutylammonium hydrogensulfate as phase-transfer catalyst (PTC) in this step and no detectable 4-oxo regioisomer was observed after recrystalization. **11c** was further methylated at the 1 and 2 position of tetrazole to give a mixture of **13** and **14**.[18] Replacement of biphenyl methyl with biphenyloxymethyl was shown in Scheme III. **15**, prepared from **8** by catalytic hydrogenation, was reacted with aryloxymethylchloride **16** by standard means, followed by deprotection of the tetrazole to give **17**.

Biological Results and Discussion

The compounds described herein were tested for their AII receptor antagonistic activities. They were tested in isolated rabbit aorta precontracted by AII. pA_2 value are shown in Table I. The introduction of isopropyl at the 5 or 6 position, **6e-f**, seemed to increase the activities more than the non-substituted compound **6a**. However, their effects were not competitive since the maximal relaxations to **6e-f** were depressed. Therefore, pD_2' values were calculated in stead of pA_2 values. When the alkyl length at 2 position of **6** were varied from methyl to butyl, the maximal activity was obtained by propyl compound **6c** and the optimal alkyl length may exit for AII receptor antagonistic activity. This suggests that there is an optimal chain length of carbon atoms for the maximum biological activity.

Introduction of an oxo group at the 8 position of 1,4,5,6,7,8-hexahydrocycloheptimidazole **6a-d**, led to significant improvement of the activity (**6a-d** vs. **11a-d**), while introduction of an oxo group at the 4 position of compound **6d** showed decreased activity. Some possible explanation for this different activity may result from a specific interaction between 8-oxo group and AII receptor. This suggests that 8-oxo group may be a replaceable bioisoster for hydroxymethyl in DuP 753 and

Scheme III. Preparation of tetrahydro-1-biphenyloxymethyl-8-oxo-cycloheptimidazole



8 15 17

a. Pd-C/H_2/MeOH,RT; b. 2'CN-biphenyloxymethylchloride(**16**)/$(Bu)_4NHSO_4$/NaOH-H_2O, RT; c. Me_3SnN_3/Toluene, reflux; d. Satd. NH_4Cl, RT; e. 10%HCl, RT.

carboxylic acid in Exp 3174.

11c was the most potent compound and about 50 times more potent than Dup 753 in vitro. Therefore it was selected for further modification. Methylation of tetrazole at 1 and 2 position **13** and **14** lost the potencies. Replacement of biphenyl methyl moiety of **11c** with biphenyloxymethyl moiety yielded **17** with decreased activity.

For further characterization, **11c** was tested in radioligand binding assay using rat liver AT_1 receptor membranes[19] and inhibited the binding of [^{125}I]Sar^1, Ile^8- Angiotensin to AT_1 receptors

Table 1. Biological activities of the compounds.

Compd.	R_1	R_2	pA2±S.E.
6a	CH_3	H	7.04±0.17
6b	C_2H_5	H	7.33±0.15
6c	C_3H_7	H	8.13±0.22
6d	C_4H_9	H	7.69±0.18
6e	C_4H_9	5-i-Pro	9.48±0.14 [a]
6f	C_4H_9	6-i-Pro	8.40±0.14 [a]
11a	CH_3	H	8.31±0.12
11b	C_2H_5	H	9.04±0.18
11c	C_3H_7	H	10.04±0.12
11d	C_4H_9	H	9.66±0.2
11e	C_5H_{11}	H	9.36±0.18
11f	C_3H_7	5-i-Pro	9.01±0.19 [a]
11g	C_3H_7	6-i-Pro	9.76±0.14 [a]
12d	C_4H_9	H	7.23±0.16
13	C_3H_7	H	6.84±0.13
14	C_3H_7	H	7.41±0.14
17	C_3H_7	H	7.80±0.15
Dup753			8.32±0.11

a, pD_2' value.

with IC_{50} value of 0.8 nM and possessed high affinity for AT_1-receptor with very low affinity to AT_2-receptor (IC_{50}>10,000 nM, bovine cerebellum).[20] In an in vivo study, oral administration of

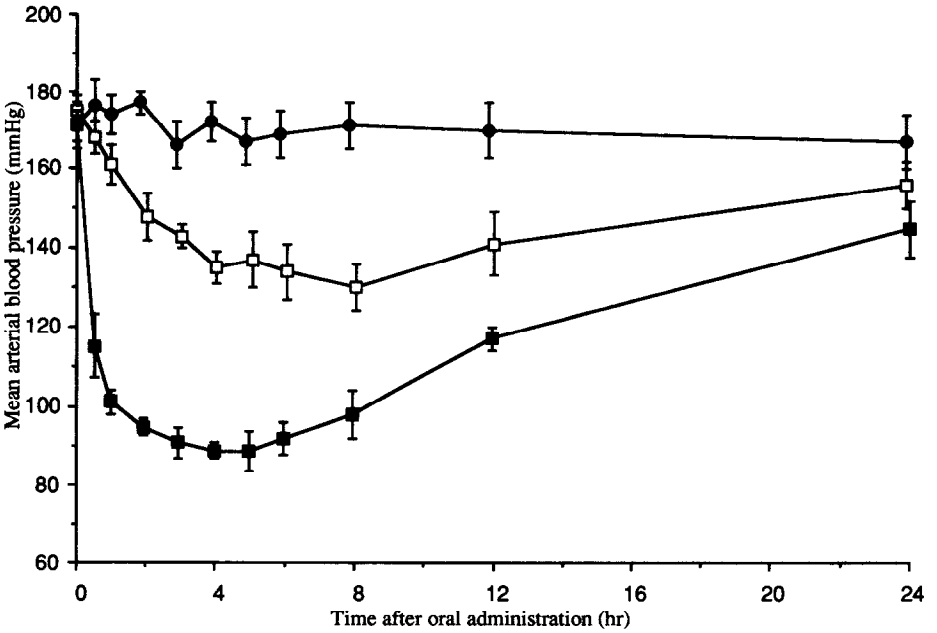


Figure I Effects of **11c**, KT3-671, on mean arterial blood pressure in conscious renal hypertensive rats. Each rat was treated with a single p.o. dose of vehicle (●), 1 mg/kg (□) and 3 mg/kg (■) of **11c**. Each point represents the mean ± S.E. of six animals.

3mg/Kg of **11c** in renal hypertension rat (RHR) lowered mean arterial blood pressure for at least 24h. and hypotensive response curve was a monophasic (Fig 1). It suggests that **11c** may not be transformed to an active metabolite which confounds individual variability in the pharmacokinetic and pharmacogenetic responsiveness in clinical use.

In summary, we have described a new class of AII receptor antagonists with high potency for AT_1, which are orally active and long lasting antihypertensive agents. Tetrahydro-8-oxo-cyclohept-imidazole **11c** (KT3-671) was selected for further investigations for the treatment of hypertension.

Acknowledgment: We would like to thank Ms. Tomoe Satoh and Mr. Kenji Hase for the biological results.

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