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CYCLOHEPTIMIDAZOLE BASED ANGIOTENSIN II RECEPTOR ANTAGONISTS. 4,5,6,7-TETRAHYDRO-8-CARBOXYMETHYLIDENE CYCLOHEPTIMIDAZOLES

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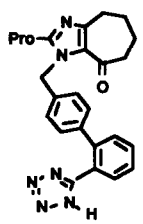
Abstract: 4,5,6,7-Tetrahydro-8-carboxymethylidene-cycloheptimidazoles were synthesized as potential angiotensin II (AII) receptor antagonists. One of these, **10b**, KT 3-866, showed a pD'2 value of 9.91 and was about 5 times more potent than KT 3-671 in an vivo study and had long lasting inhibitory action on AII-induced pressor response in rats at a dose of 0.3 mg/kg.

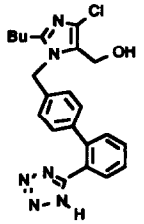
The renin-angiotensin system (RAS) is one of the important interrelated homeostatic mechanisms that regulate hemodynamic and water and electrolyte balance. The main souce of renin is the kidney and renin is discharged directly to the renal arterial blood system.[1] Angiotensin II (AII), the active hormone caused in RAS, shows a potent vasoconstrictive effect which is thought to be the etiology of hypertension and congestive heart failure. Controling of AII levels in RAS system is achieved by the use of angiotensin converting enzyme (ACE) inhibitor which inhibits the conversion of angiotensin I (AI) to AII. ACE is a non-specific dipeptidyl carboxypeptidase[2] and AII can also be formed in vivo by the action of enzymes other than ACE.[3]

Blocking the action of AII at the AII receptor level is a more effective approach and considerable effort has been expended to the search for nonpeptide AII receptor antagonists in recent year.

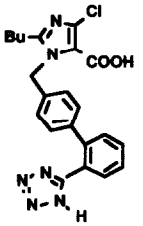
We have recently described the identification of the 4,5,6,7-tetrahydro-8-oxo-cycloheptimidazole, KT3-671,



KT 3-671



DuPont 753



Exp 3174

which is an orally active, competitive AII receptor antagonist[4] and is currently being clinically evaluated for the treatment of hypertension.

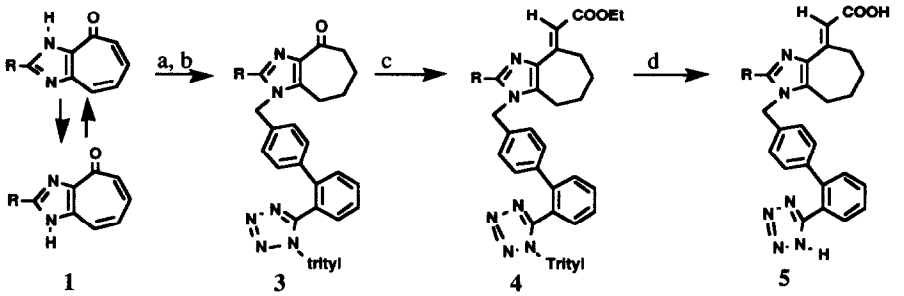
DuP 753,[5] the first example of a nonpeptide AII receptor antagonist, was reported to be transformed to a noncompetitive more potent metabolite, Exp 3174, having a carboxylic acid.[6] With this in mind, we delineated that a more highly active AII receptor antagonist may be obtained with a conversion of 8-oxo functionality of KT 3-671 to 8-carboxymethylidene functionality.

We report, here, the synthesis of potent, orally active 7-membered fused imidalole AII receptor antagonists, 4, 5, 6, 7-tetrahydro-8-carboxymethylidene cycloheptimidazole analogues.

Synthesis

Conversion of 4-oxo functionality to 4-carboxymethylidene is performed by Wittig-Horner reaction outlined in Scheme 1. 2-Propyl-4-oxo-1-((2'-trityl-tetrazolyl)-biphenyl)methyl **3**, prepared from 2-propyl-4-oxo-cycloheptimidazole **1** and the biphenylmethyl bromide **2** according to the previously reported method,[4] was treated with triethyl phosphonoacetate and NaH to give the E-ester **4**[7] which was shown to be free of

Scheme 1. Preparation of tetrahydro-4-carboxymethylidene-cycloheptimidazole



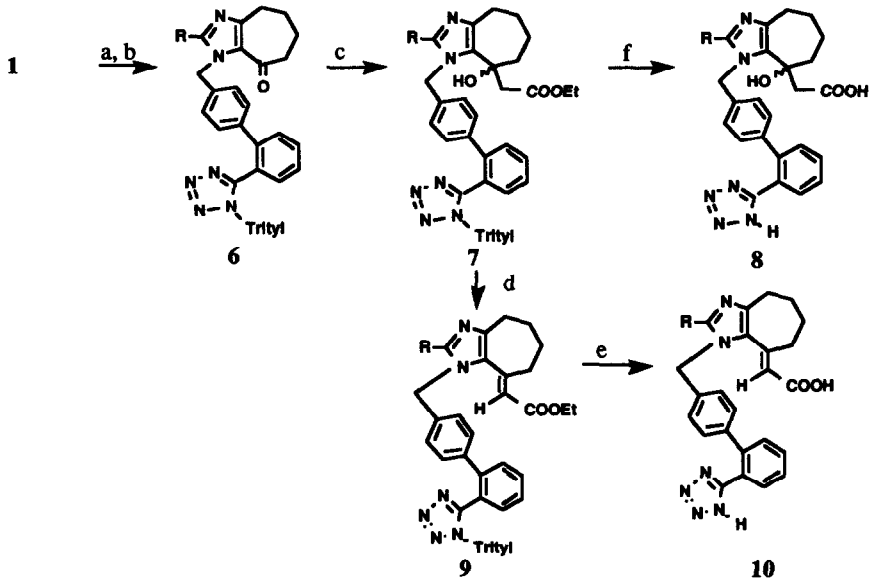
a.$BrCH_2C_6H_4C_6H_3CN_4$-Trityl (**2**)/NaOH-H_2O/THF, reflux; b. Pd-C/H_2/MeOH;
c. NaH, $(Et_2O)P(=O)CH_2COOEt$/THF, 0^oC-rt; d. 10%HCl, rt.

the Z-stereoisomer by ^1H NMR spectroscopy. Then **4** was deprotected to give the target compound **5**.

Conversion of 8-oxo-functionality to the corresponding 8-carboxymethylidene is outlined in Scheme 2. The 8-oxo compound **6** was prepared regioselectively according to the previously reported method[4] and initial attempt to convert **6** to the ester **9** using the same method described in Scheme 1 was unsuccessful. The lack of reactivity might be due to the steric hindrance surrounding 8-oxo group of **6**.

Successfully, an alternative approach involved the reaction of **6** with the acetate anion gave an inseparable 1:1 mixture of diastereomeric ethyl β-hydroxy acetates **7**,[8] followed by hydrolysis to give **8**. Additionally, subsequent dehydration of **7** gave a single compound **9** and it's trans stereochemistry was confirmed from N M R spectrum.[9] **9** was hydrolized to the target compound **10**. Further, the biphenylmethyl moiety of the compounds **10a-e** was also replaced by a pyrrolophenylmethyl to give the pyrrolophenyl analogues **21** using the standard means . Synthetic procedure for the preparation of **21** is illustrated in Scheme 3. The N-p-tolylpyrrolo-2- carbonitrile **16**,

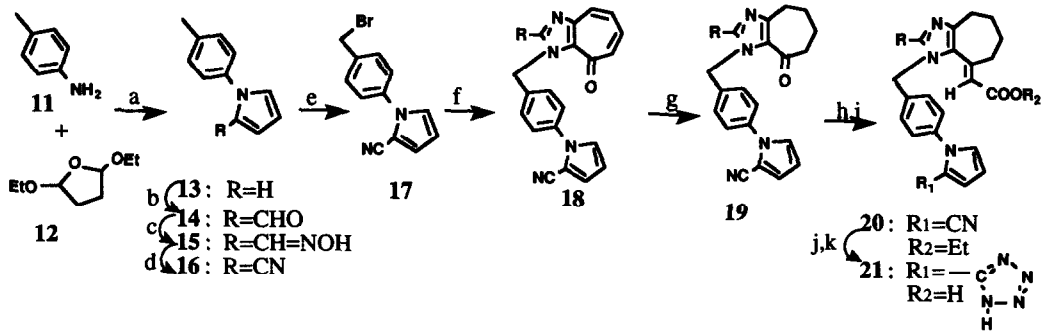
Scheme 2. Preparation of tetrahydro-8-carboxymethylidene-cycloheptimidazole



a. $BrCH_2C_6H_4C_6H_3CN_4$-Trityl (**2**)/Bu_4NHSO_4/NaOH-H_2O, rt; b. Pd-C/H_2/MeOH; c. CH_3COOEt, LiHMDS/THF, -78°C-rt; d. $SOCl_2$+pyridine/C_6H_6,rt; f, 0.6N KOH, rt.

prepared by p-methylaniline **11** and 2,5-diethoxy tetrahydrofuran **12** according to the literature method,[10] was brominated to give **17**, which was coupled with **1** to give **18**, then hydrogenated with Pd-C to give **19**. **19** converted to **21** in the same manner as outlined in Scheme 2.

Scheme 3. Preparation of pyrrolophenyl analogues



a. HOAc, reflux, 1.5h; b. $POCl_3$/DMF, 110°C; c. $NH_2OH.HCl/Na_2CO_3$/MeOH, 2h; d. Ac_2O, 130-40°C, 2h; e. NBS, AIBN/$CHCl_3$, reflux, 4h, f. 1/Bu_4NHSO_4/NaOH-H_2O, rt; g. Pd-C/H_2/MeOH; h. CH_3COOEt, LiHDMS/THF, -78°-rt; i. $SOCl_2$+pyridine/C_6H_6, rt; j. Me_3SnN_3/Toluene, reflux, 16h then Satd. NH_4Cl, 30min; k. 0.6N KOH, rt.

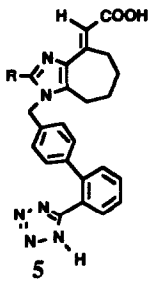
Biological Results and Discussion

The compounds reported were evaluated for antagonisms of AII induced contraction of isolated rabbit aorta and antagonist potencies were determind by pA2 or pD'2 values [12] as shown in Table 1 . In the convertion of 4-oxo functionality to 4-carboxymethylidene (Table 1A), **5a-b** showed the decreased competitive inhibitory activities as compared to the 4-oxo parent compound **3b** (R=C_3H_7), from pA2 value 7.0 to 6.31 (**5b** vs **3b**). β-Hydroxy carboxylic acid **8a-c**, the intermediates to 8-carboxymethylidene were also tested and the results are showed in Table 1B. **8a-c** had lower inhibitory activities as compared to the parent compound KT 3-671. In the biphenylmethyl anlogues **10a-e**, elongation of alkyl group at R1 from CH_3 **10a** to C_5H_{11} **10e** affected AII receptor inhibitory activity and these compounds showed noncompetitive antagonism except **10a** (Table 1C).

The optimal alkyl length at the 2 position was C_2H_5 **10b** with a pD'2 value of 9.91. These findings are consistent with the reported results that the compound having a carboxylic acid such as Exp 3174 shows noncompetitive antagonism.[6] The most active compound **10b** was found to have C_2H_5 at the 2 position as in the case of β-hydroxy carboxylic acids.

In the pyrrolophenylmethyl analogues **21a-e** (Table 1D), the optimal alkyl length at the C-2 was C_3H_7 with a pA2 value of 9.80. These compounds showed competitive antagonisms with pA2 values in contrast to the biphenyl series **10b-e** which showed noncompetitive antagonisms with pD'2 values. The reason fo the difference in the

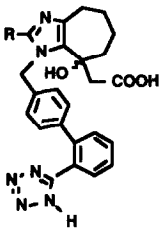
Table 1. In Vitro activities of Tetrahydro-Cycloheptimidazoles.



5

A

Compd.	R	pA2	pD'2
5a	C_2H_5	6.23	
5b	C_3H_7	6.31	
3b	C_3H_7	7.0	



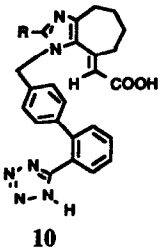
8

B

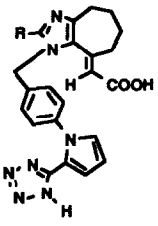
Compd.	R	pA2	pD'2
8a	CH_3	7.85	
8b	C_2H_5	9.64	
8c	C_3H_7	9.52	

C

Compd.	R	pA2	pD'2
10a	CH_3	9.80	
10b (KT3-866)	C_2H_5		9.91 (10.40) [a]
10c	C_3H_7		9.86
10d	C_4H_9		9.03
10e	C_5H_{11}		8.80
KT3-671		10.01	



10



21

D

Compd.	R	pA2	pD'2
21a	CH_3	8.90	
21b	C_2H_5	9.66	
21c	C_3H_7	9.80	
21d	C_4H_9	9.30	
21e	C_5H_{11}	8.02	

[a] pD'2 value in parenthesis was obtained by 3hr incubation time[13]

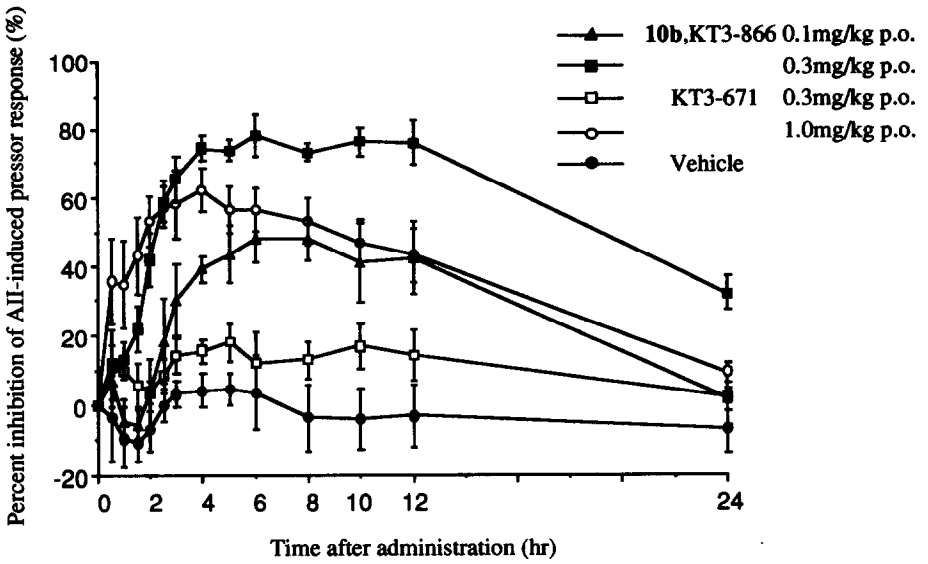


Fig. 1 The effects of **10b**,KT3-866 and KT3-671 on the angiotensin II (AII)-induced pressor response in conscious normotensive rats. AII (30ng/kg, i.v.) was injected before and at various times after the oral administration of each compound.

inhibitory patterns among the biphenylmethlyl and the pyrrolophenylmethyl series, which share the same carboxyl group, is not clear.

In the radioligand binding assay using rat liver membrane preparations, **10b** inhibited the binding of [^{125}I] Sar', Ileu^{8}-angiotensin to AT$_1$ receptor with IC$_{50}$[14] value of 5.45±0.15 nM and no agonist activity of **10b** was found at concentrations up to 10^{-5}M. In in vivo experiments, **10b** antagonised the AII-induced pressor response in rats for at least than 24h at 0.3 mg/kg p. o. (Fig 1). The inhibitory response curve of **10b** showed that the potency of **10b** was about 5 times more potent than that of KT 3-671 at 0.3 mg/kg.

In summary, we developed a new class of AII receptor antagonists with high potency for AT$_1$ by conversion of 8-oxo functionarity of KT 3-671 to 8-carboxymethylidene along with changing the inhibitory pattern from competitive to noncompetitive. **10b** (KT 3-866) was selected for further investigations.

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