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ANGIOTENSIN II RECEPTOR ANTAGONISTS: IMIDAZOLES AND PYRROLES BEARING HYDROXYMETHYL AND CARBOXY SUBSTITUENTS

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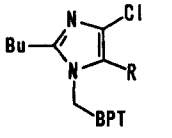
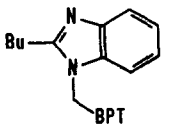
Abstract: Imidazoles and pyrroles bearing hydroxymethyl and carboxy groups were prepared, and their AII antagonistic activities were evaluated. The hydroxymethyl substituent at the 4 position and the carboxy substituent at the 5 position in the imidazole nucleus were favorable for the activity.

Since the angiotensin-converting enzyme (ACE) inhibitors,[1] captopril, enalapril and others, which block conversion of angiotensin I (AI) to angiotensin II (AII) in the renin-angiotensin system (RAS), have got a good reputation for treatment of hypertension and congestive heart failure, many medicinal chemists have been interested in the other agents that block the RAS. Though renin inhibitors,[2] which suppress the formation of AI from angiotensinogen, have not yet been successful in clinical use, because of poor bioavailability and metabolic instability in vivo, AII receptor antagonists look promising. The first potent, orally active non-peptide AII receptor antagonist, DuP753 (losartan) **1**,[3] which is converted to the more active metabolite **2** (EXP3174)[4] in vivo in rats, is undergoing clinical evaluation.

Structure-activity relationships of the imidazole antagonists have been discussed by a few research groups.[5] A linear alkyl group at the 2 position and a hydrophobic substituent such as a biphenylylmethyl group at the 1 position, both of which would bind to the hydrophobic pockets of the receptor, seem to be essential for potent antagonistic activity. Also, an acidic group, like a tetrazole group, on the hydrophobic moiety at the 1 position, which might bind to the basic region of the receptor, is required to potentiate the activity. On the other hand, the roles of the substituents at the 4 and 5 positions in biological activity have remained ambiguous. The Du Pont group[5a-c] has mentioned that a lipophilic and electron-withdrawing substituent has seemed to be favorable at the 4 position and that the 5 position would tolerate a wide variety of substituents, especially in the case of compounds bearing a carboxy group, instead of a tetrazole group, on the substituent at the 1 position. While, Thomas et al.[6] suggested that the substituents at the 4 and 5 positions were not critical to binding to the receptor, because the benzimidazole **3** had the antagonistic activity comparable to **1**.



1 : R = CH_2OH
2 : R = CO_2H



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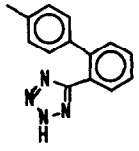


We were interested in the influence of substituents at the 4 and 5 positions on the biological activity. This paper describes the synthesis of imidazole and pyrrole antagonists having hydroxymethyl and carboxy groups on the heterocycle nuclei and their antagonist activities.

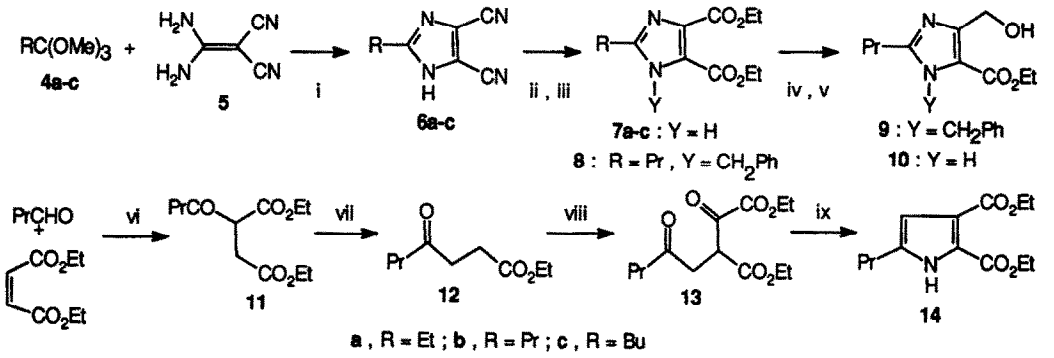
Synthetic procedure for the preparation of imidazole and pyrrole moieties is illustrated in Scheme 1. The imidazole-dicarbonitriles **6a-c**, which were easily prepared by heating the orthoesters **4a-c** with diaminomaleonitrile **5**, were hydrolyzed with 6 N HCl, followed by esterification to give the diesters **7a-c**. Protection of the nitrogen atom of the imidazole ring in **7b** with benzyl bromide, and then reduction with diisobutylaluminum hydride (DIBALH) afforded **9**, whose benzyl group was removed by hydrogenolysis to give the imidazole-methanol **10**. The pyrrole-dicarboxylate **14** was prepared using known methodologies.[7,8,9] Each step was performed with moderate or excellent yields, except the preparation step of **13** which was obtained in 14 % yield with diethyl 5-propylfuran-2,3-dicarboxylate as a by-product.

Alkylation of the heterocycles with the biphenyl **15**[5c] is depicted in Scheme 2. Alkylation of **7a-c** with **15** gave **16a-c**. Removal of the protecting groups of **16b** gave the tricarboxylic acid **18**. Alkylation of **10** with **15** furnished a mixture of the regioisomers[10] **19b** and **20** in a ratio of 3.6 : 1. The more regioselective synthesis of **19a-c** and **20** was achieved by reduction of **16a-c**. Using DIBALH as a reducing agent gave only **19a-c**, while reduction of **16b** with lithium tri-*tert*-butoxyaluminohydride (LTBALH)[11] afforded predominantly **20** (**20/19**=6.6/1). In order to investigate this selectivity, the pyrrole-diester **17**, which was prepared from **14** and **15**, was subjected to reduction. Similar results were obtained. Reduction of **17** with DIBALH gave the pyrrole-3-methanol **21** and its isomer **22** in a ratio of 20 : 1, and reduction with LTBALH afforded exclusively **22**. These results mean that selectivity on reduction may be caused by the steric effect of the bulky biphenylylmethyl group, not by the presence of the nitrogen atom at the 3 position of the imidazole ring. The final products **25a-c**, **29** and **32** were obtained by removal of the protecting groups from the corresponding esters **19a-c**, **20** and **23**. Removal of the *tert*-butyl group of **21** and **22** was troublesome, because of their instability in an acidic medium. Treatment of **21** with 4 N HCl in dioxane gave the 4-chloromethylimidazole, which was purified by silica gel flash chromatography with CH_2Cl_2 / MeOH (9:1) to give the 4-methoxymethylimidazole **26** in 58 % yield. Treatment of **22** with 4 N HCl in dioxane gave a complicated mixture, which was esterified with CH_2N_2 and then purified by flash chromatography to provide **30** in 5.7 % yield. Saponification of **26** and **30** gave **27** and **31**, respectively.

Imidazoles and pyrroles, prepared as mentioned above, were evaluated for in vitro and in vivo AII antagonistic activities. The in vitro activity (IC_{50}) was determined by displacement of [^{125}I]AII bound to the bovine adrenal cortex, and the in vivo activity (ID_{50}) was determined by suppression of the pressor response induced by infusion of AII in conscious normotensive rats at intravenous administration of the tested compounds. Results are shown in Table 1 and are compared with **1**, **2** and their carboxybiphenyl analogs **33**, **34**.[5c] The in vitro activities agreed nicely with the in vivo activities of the tested compounds.

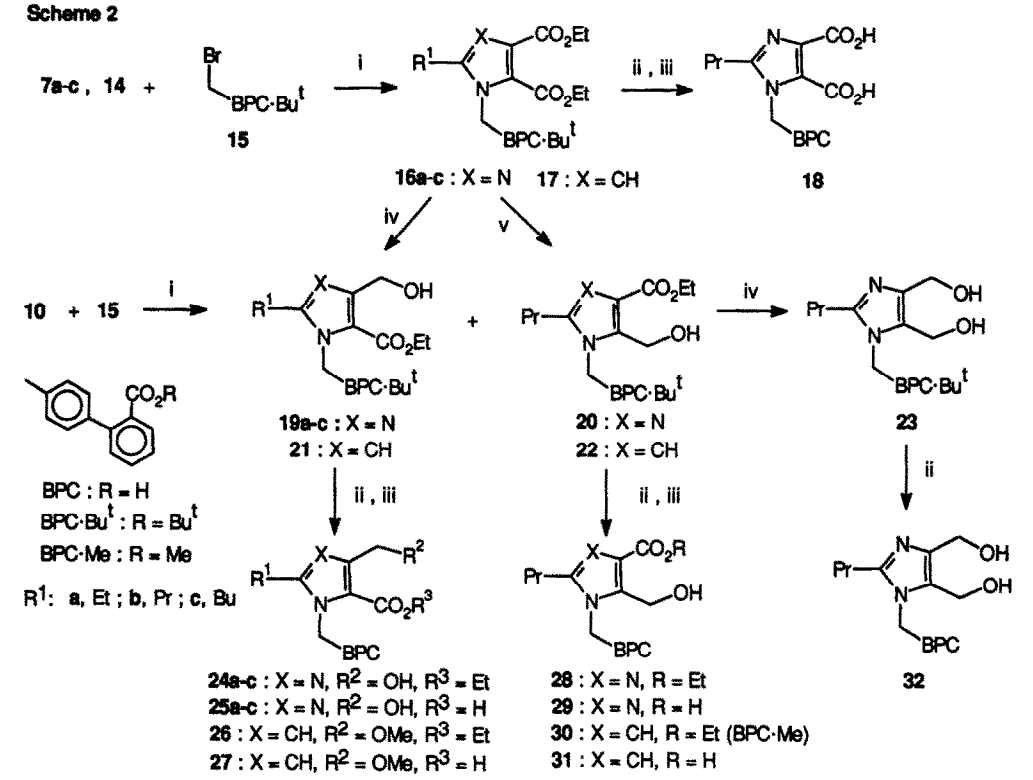
Compound **25b**, which has hydroxymethyl and carboxy groups at the 4 and 5 positions, respectively, was the most potent among the imidazole derivatives prepared. It was 8-fold more potent than **33**, twice as potent as **1** and **34**, and had one third the potency of **2** on the binding affinity. When administered intravenously, **25b** suppressed the pressor response to AII more strongly than all the reference compounds. Esterification of the

Scheme 1



i : Δ / MeCN, xylene ii : Δ / 6 N HCl then HCl / EtOH iii : $PhCH_2Br$,t-BuOK / DMA
iv : iso-Bu_2AlH / toluene-THF v : 10 % Pd-C, HCl / EtOH vi[7] : Bz_2O_2, Δ vii[8] : H_3BO_3
viii[9] : $CH(OEt)_3$-EtOH-H_2SO_4(cat) , then, NaOEt-$(CO_2Et)_2$ / Et_2O ix[9] : NH_3 / EtOH.

Scheme 2



i : t-BuOK / DMA ii : 4 N HCl / dioxane iii : LiOH / H_2O-dioxane iv : iso-Bu_2AlH / toluene-THF
v : $LiAl(OBu^t)_3H$ / THF.

carboxy group at the 5 position of **25b** reduced the activity as seen in **24b**. Also, shortening (**25a**) or elongating (**25c**) the alkyl chain at the 2 position of **25b** diminished the biological activities. Compound **25c**, which is the 2-hydroxymethyl analog of **34**, showed twice as potent as **34** on the binding affinity and had the same in vivo activity as **34**. Replacement of the hydroxymethyl substituent at the 4 position of **25b** with a carboxy group, which afforded **18**, led to 5- and 10-fold reductions in the in vitro and in vivo activities, respectively, relative to **25b**. Furthermore, **32**, which has a hydroxymethyl substituent at the 5 position instead of the carboxy group, possessed only one forty-fifth of the in vitro activity and one thirtieth of the in vivo activity of **25b**. The regioisomer **29** of **25b**, which has carboxy and hydroxymethyl substituents at the 4 and 5 positions, respectively, was the weakest antagonist in the imidazoles prepared.

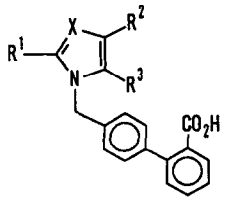
These results lead to the conclusion that a hydroxymethyl group at the 4 position and a carboxy group at the 5 position in the imidzole nucleus bring about the distinguished antagonistic activity. The advantage of a carboxy group over a hydroxymethyl group for the substituent at the 5 position was predictable from the significant activity of **2** compared to **1**.[4] The hydroxymethyl substituent at the 5 position of **1** has been supposed to contribute to the activity by forming hydrogen bonding between the substituent and the receptor.[5c] However, the remarkable enhancement of the activity by introduction of a carboxy group at the 5 position suggests that another binding mode, such as ionic bonding, may be present between the substituent and the receptor. Keenan et al.[5d-f] reported that the carboxy group on the substituent at the 5 position of SK&F108566 might be overlayed upon the C-terminal carboxy group of AII.

In contrast to the carboxy substituent at the 5 position, the potent binding affinity of the 4-hydroxymethyl derivatives **25b,c**, compared to **34**, was unpredictable as, so far, the hydrophobic and electron-withdrawing substituent has been recommended at the 4 position.[5c] The hydroxy group would affect the biological activity by means of hydrogen bonding with the receptor and/or with the carboxy group at the 5 position to lead to conformational fixation of the antagonist, which would be suitable for binding to the receptor, or by reducing lipophilicity of the molecule, which would be advantageous for approaching and/or binding to the receptor.

Both the pyrroles **27** and **31** showed weak antagonistic activities. Though **27**, which has a methoxymethyl substituent at the 3 position, is not an exact analog of the imidazole **25b**, the binding affinity of **27** was less potent than that of **25b** by two orders of magnitude. Pyrroles would be predicted to be weak antagonists compared to imidazoles, because of the lack of a nitrogen atom at the 3 position of the imidazole ring.[12] However, it is interesting that **31** had more potent in vitro and in vivo activities than the corresponding imidazole **29**.

In conclusion, imidazole and pyrrole derivatives bearing hydroxymethyl and carboxy substituents were prepared, and their in vitro and in vivo activities were evaluated. The hydroxymethyl and carboxy groups were favorable as the substituents for the 4 and 5 positions of the imidazole ring, respectively. The increase in binding affinity due to a carboxy group at the 5 position could be caused by the formation of hydrogen and/or ionic bonding between the carboxy group and the receptor. A hydroxymethyl group at the 4 position would influence in the activity by means of hydrogen bonding with the receptor and/or the carboxy group at the 5 position or by reducing lipophilicity of the molecule.

Table 1. In Vitro and In Vivo Data for Imidazole and pyrrole Derivatives



no.	R^1	R^2	R^3	X	in vitro IC_{50}, nM[a]	in vivo ID_{50}, mg/kg[b]
1					120[c]	0.30
2					22[c]	0.10
33	Bu	Cl	CH_2OH	N	490[c]	2.3
34	Bu	Cl	CO_2H	N	130[c]	0.21
18	Pr	CO_2H	CO_2H	N	320	0.67
24b	Pr	CH_2OH	CO_2Et	N	840	1.5
25a	Et	CH_2OH	CO_2H	N	150	0.27
25b	Pr	CH_2OH	CO_2H	N	58	0.069
25c	Bu	CH_2OH	CO_2H	N	65	0.22
29	Pr	CO_2H	CH_2OH	N	20000	8.8
32	Pr	CH_2OH	CH_2OH	N	2700	2.1
27	Pr	CH_2OMe	CO_2H	CH	4500	4.2
31	Pr	CO_2H	CH_2OH	CH	2100	5.9

[a] IC_{50} for inhibition of specific binding of [^{125}I]AII to bovine adrenal cortex.
[b] ED_{50} following i.v. administration to normotensive, conscious rats for inhibition of AII-induced pressor response (n=3).
[c] See Ref. 13.

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10. The structure of **19b** was determined by X-ray analysis of which details will be published elsewhere. In proton NMR spectra, the methylene protons at the 1 positions of **19b** and **21** were observed at δ 5.61 and 5.60 ppm, respectively, while ones of **20** and **22** were at δ 5.26 and 5.23 ppm, respectively. The downfield shifts observed in **19b** and **20** are caused by the anisotropic effect of the ester group at the 5 position.
11. This agrees well with the 6:1 ratio observed for the reduction of 4,5-dicarbomethoxy-2-n-propyl-1-[(2'-N-triphenylmethyl(1H-imidazol-5-yl)biphenyl-4-yl)methyl]imidazole with LTBALH reported by the Du Pont group: Carini, D.J.; Duncia, J.J.V.; Wong, P.C.B.: Example 334 in U.S. Patent 5,138,069, 1992.
12. A nitrogen atom at the 3 position has been supposed to act as a hydrogen acceptor and be required for potent activity. (Ref. 6). In fact, IC_{50} of 1-[(2'-carboxybiphenyl-4-yl)methyl]-5-n-propylpyrrole-2-carboxylic acid has been reported to be over 120 μM at rat adrenal cortical microsomes (Carini, D.J.; Duncia, J.J.V.; Wells, G.J.: Example 279 in U.S. Patent 5,043,349, 1991), whereas the corresponding imidazole, 1-[(2'-carboxybiphenyl-4-yl]methyl]-2-n-propylimidazole-5-carboxylic acid had an IC_{50} of 60 nM at bovine adrnal cortical membranes (our experiment, unpublished).
13. IC_{50} values of **1**, **33** and **34** were reported to be 19, 230 and 92 nM at rat adrenal cortical microsomes, respectively, in Ref. 5c, and IC_{50} values of **1** and **2** were 26 and 37 nM at rat adrenal cortical microsomes, respectively, in Ref. 4. The relative inhibitory potency of DuP 753 has been reported to be lower by one order of magnitude at bovine adrenal cortex than at rat adrenal cortex by Ball T.; Baukal, A.J.; Eng, S.; Catt, K.J. (*Molecular Pharmacol.* **1991**, **40**, 401) and Kubo K.; Inada, Y.; Kohara, Y.; Sugiura, Y.; Ojima, M.; Itoh, K.; Furukawa, Y.; Nishikawa, K.; Naka, T. (footnote 20 in *J. Med. Chem.* **1993**, *36*, 1772).

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