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# NONPEPTIDE ANGIOTENSIN II RECEPTOR ANTAGONISTS: THE DISCOVERY OF DMP 581 AND DMP 811

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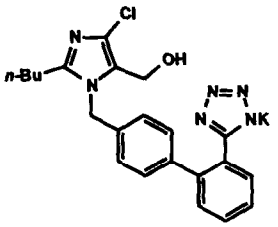
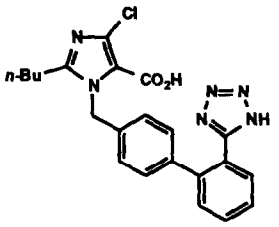
**Abstract:** A novel series of 4-alkylimidazoles have been prepared. Two of these compounds, DMP 581, 4-ethyl-2-propyl-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]imidazole-5-carboxaldehyde, and DMP 811, 4-ethyl-2-propyl-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]imidazole-5-carboxylic acid, possess among the highest oral antihypertensive potencies yet described for an angiotensin II antagonist. In addition, prodrugs of DMP 811 have been developed to further enhance the oral bioavailability of the parent diacid.

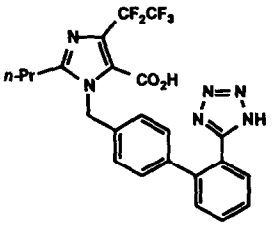
The renin-angiotensin system (RAS) is known to play an important role in cardiovascular regulation and the maintenance of blood pressure.[1] Angiotensin II (AII, AspArgValTyrIleHisProPhe) is the principal active hormone of this system and acts through the stimulation of specific receptors located on various organs.[2,3] One effect of AII production is vasoconstriction and an increase in systemic blood pressure. Interruption of the renin-angiotensin system has been shown to be an effective means of controlling hypertension as evidenced by the success of the angiotensin-converting enzyme (ACE) inhibitors.[4,5] However, an alternative and possibly superior approach to controlling the activity of the RAS is the use of specific, nonpeptide antagonists of angiotensin II.[6] This symposium represents ample proof of the high level of interest in this exciting, new approach to the treatment of hypertension.




(1) DuP 753



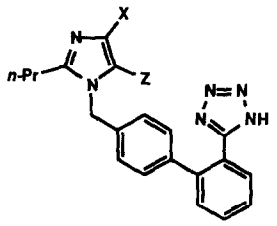

(2) EXP3174




(3) DuP 532

The early work of our group at DuPont on the discovery of selective, nonpeptide AII receptor antagonists has been reported previously.[7] These efforts led to the development of DuP 753 (1, losartan potassium) which is currently in phase III clinical trials. The major, active metabolite of DuP 753 is the corresponding imidazole-5-carboxylic acid, EXP3174 (2), and a significant portion of the antihypertensive effect of DuP 753 is believed to be due to the formation of this metabolite.[8] EXP3174 has only limited oral potency, but a more orally active analog, DuP 532 (3), was discovered.[9] However, our work on orally active AII antagonists has continued beyond the discovery of DuP 753 and DuP 532.

**Table 1.** Oral Antihypertensive Potencies of a Series of 4-Alkylimidazoles.




| No. | X | Z | Oral $ED_{30}$ (mg/kg)[10] |
|---|---|---|---|
| **4a** | Me | CHO | 0.10 |
| **4b** | Et | CHO | 0.027 |
| **4c** | *n*-Pr | CHO | 0.30 |
| **4d** | *i*-Pr | CHO | 0.13 |
| **4e** | *n*-Bu | CHO | 1.0 |
| **4f** | *i*-Bu | CHO | 0.29 |
| **4g** | *s*-Bu | CHO | 0.33 |
| **4h** | *t*-Bu | CHO | 0.048 |
| **5a** | Me | $CO_2H$ | 0.19 |
| **5b** | Et | $CO_2H$ | 0.03 |
| **5c** | *n*-Pr | $CO_2H$ | 0.63 |
| **5d** | *i*-Pr | $CO_2H$ | 0.11 |
| **5e** | *n*-Bu | $CO_2H$ | 1.3 |
| **5f** | *i*-Bu | $CO_2H$ | 0.87 |
| **5g** | *s*-Bu | $CO_2H$ | 0.46 |
| **5h** | *t*-Bu | $CO_2H$ | 0.35 |

Exploration of the structure-activity relationships (SAR) for substituents at the 4-position of the imidazole ring of our AII antagonists had already led to the discovery of the (perfluoroalkyl)imidazoles and to DuP 532.[9] The success of this earlier work seemed to confirm our original hypothesis that the 4-position of the imidazole is most appropriately substituted with a large, lipophilic, and electron-withdrawing group.[7b] In the perfluoroalkyl series pentafluoroethyl appeared to be optimal; however we had been limited by the chemistry to the examination of straight-chain perfluoroalkyl groups. To explore the effect of branched-chain substituents we returned to the simple alkyls. Our only prior work on 4-alkylimidazoles had been in the imidazole-5-methanol series.[7b] In compounds such as DuP 753 (1) the replacement of the electron-withdrawing chloro group with an alkyl had the effect of increasing the $pK_a$ of the imidazole ring to the point were the compounds became zwitterionic. Such derivatives retained most of their affinity for the AII receptor and were antihypertensive when administered intravenously, however they generally showed no oral antihypertensive activity. For this reason we chose to focus our efforts on the preparation of the imidazole-5-carboxaldehydes and imidazole-5-carboxylic acids. This approach has proven very successful. The aldehydes **4a-h** and acids **5a-h** of Table 1 all show significant oral antihypertensive activity, ranging from slightly less potent than DuP 753 to the most potent oral antihypertensives yet prepared in this program.

General trends in the SAR of the 4-alkylimidazoles are apparent from an examination of the data in Table 1. A comparison of the antihypertensive potencies of aldehydes **4a**, **4b**, **4c**, and **4e** shows that activity increases from methyl to ethyl and then falls off rapidly in the n-alkyl series with increasing chain length. This observation is consistent with the SAR observed previously for the (perfluoroalkyl)imidazoles.[9] In contrast, a comparison of the ethyl, *i*-propyl, and *t*-butyl derivatives (**4b**, **4d**, and **4h**) shows that antihypertensive activity is relatively insensitive to branching at the α-position of the alkyl group. The SAR of the acids **5a-h** parallels that of the aldehydes with one exception; in the series **5b**, **5d**, and **5h** there is a small but significant decline in activity with increased branching.

From among the compounds in Table 1 the 4-ethylimidazole derivatives **4b** and **5b** were selected for further evaluation because of their outstanding oral antihypertensive potencies. Table 2 compares the properties of DMP 581 (**4b**) and DMP 811 (**5b**) with those of our lead compounds. DMP 581, like DuP 753[7a], is a surmountable antagonist of angiotensin II, and both compounds have as major, active metabolites their corresponding imidazole-5-carboxylic acids. As described above DuP 753 is metabolized to EXP3174, while the administration of DMP 581 to either rats or dogs results in the formation of DMP 811. As in the case of DuP 753, the formation of the extremely potent DMP 811 is believed to be responsible for a significant portion of the antihypertensive effect of DMP 581. The advantages of DMP 581 over DuP 753 include its greater potency as well as an improved bioavailability. The oral bioavailability of DuP 753 in rats has been reported to be 33%.[7a] In contrast, when DMP 581 was administered in aqueous solution to either rats or dogs it was entirely absorbed. Even when dosed to dogs as a neat powder DMP 581 was 60-70% bioavailable.

DMP 811 is approximately ten-fold more potent than DuP 532 by either oral or intravenous administration, however the properties of these two imidazole-5-carboxylic acid derivatives are otherwise similar. Both DuP 532[9] and DMP 811 are insurmountable antagonists of angiotensin II, and neither compound requires metabolic activation to demonstrate full potency. In addition the $ED_{30}$(p.o.)/$ED_{30}$(i.v.) ratios and bioavailabilities of both compounds are comparable. When DuP 532 was dosed to dogs as a neat powder its oral bioavailability was determined to be 12%.[11] The bioavailability of DMP 811 administered in the same manner was 13-15%.

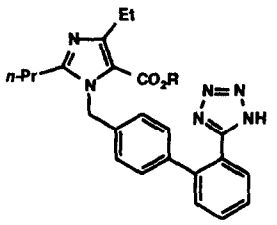
Despite the remarkable properties of DMP 581 and DMP 811, if we could combine the bioavailability of DMP 581 with the intrinsic potency of DMP 811 we would have a compound with an oral antihypertensive potency unprecedented in this program. In the hope of fulfilling this goal prodrugs of DMP 811 were examined, and the results are described in Table 3. One series of prodrugs prepared were the "linked-esters"[12] (**6-11**). In general these compounds possessed oral antihypertensive potencies comparable to that of DMP 811. However, in rats dosed with the pivaloyl ester **6** the bioavailability of DMP 811 was 47%, while in rats dosed with DMP 811 itself the bioavailability was only 11%. A second series of prodrugs prepared were the "cyclic carbonates"[13] (**12-14**), but these compounds were generally less effective.

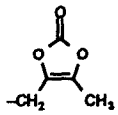
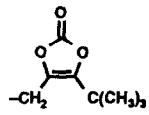
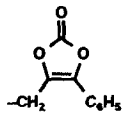
**Table 2.** Comparison of the Properties of the Lead Angiotensin II Antagonists.

| No. | I.V. $ED_{30}$(mg/kg)[10] | Oral $ED_{30}$ (mg/kg)[10] | Oral Bioavailability (%F) |
|---|---|---|---|
| DuP 753 (**1**) | 0.80 | 0.59 | 33% [a] |
| EXP3174 (**2**) | 0.038 | 0.66 | |
| DuP 532 (**3**) | 0.042 | 0.21 | 12% [b] |
| DuP 581 (**4b**) | 0.11 | 0.027 | 60-70% [b], ~100% [c] |
| DuP 811 (**5b**) | 0.005 | 0.03 | 13-15% [b] |

a) Bioavailability in rats, compound administered in solution. b) Bioavailability in dogs, compound administered as neat powder in hard gelatin capsule. c) Bioavailability in rats or dogs, compound administered in solution.

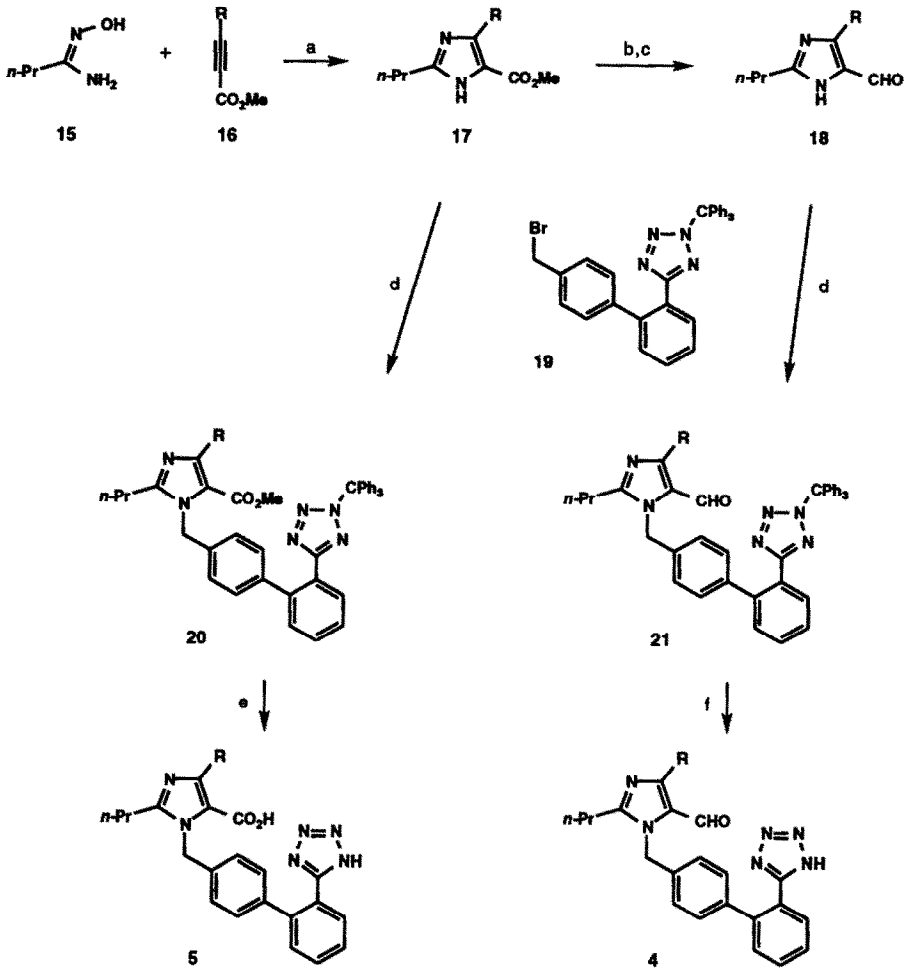
**Table 3.** Oral Antihypertensive Potencies of a Series of Prodrugs of DMP 811.




| No. | R | Oral $ED_{30}$ (mg/kg)[10] |
|---|---|---|
| **5b** | H | 0.030 |
| **6** | $CH_2O_2CC(CH_3)_3$ | 0.03 |
| **7** | $CH_2O_2CHC(CH_3)_2$ | 0.03 |
| **8** | $CH_2O_2COCH_3$ | 0.03 |
| **9** | $CH_2O_2COC(CH_3)_3$ | 0.02 |
| **10** | $CH(CH_3)O_2COCH_3$ | 0.02 |
| **11** | $CH(CH_3)O_2COC(CH_3)_3$ | 0.3 |
| **12** |  | 0.1 |
| **13** |  | 0.1 |
| **14** |  | 0.3 |

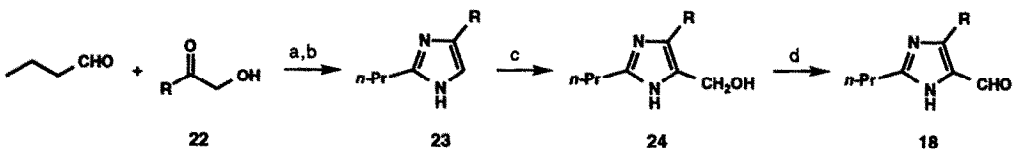
A general route to the compounds of Table 1 is shown in Scheme I. The addition of butyramidoxime (**15**) to acetylenic ester **16**, followed by thermolysis of the intermediate product, afforded imidazole ester **17**.[14] Reduction of the ester furnished an alcohol which was oxidized to aldehyde **18**. The regioselective alkylation of **17** with bromide **19**[7b] provided **20** as the major product. For example, the alkylation of **17b** (R = Et) resulted in a 4:1 mixture of **20b** and its regioisomer. The isomers were readily separated by silica gel chromatography, and the deprotection of **20** furnished acid **5**. The corresponding alkylation of **18** proceeded with high regioselectivity [20:1 for **18b** (R = Et)] to provide primarily **21**, and the deprotection of **21** afforded aldehyde **4**. In an alternative synthesis of **18** (Scheme II) a variation of the Weidenhagen synthesis[15] was employed to produce imidazole **23**. Hydroxymethylation[16] of **23** provided alcohol **24**, and the oxidation of **24** furnished **18**. The prodrugs **6-14** were prepared by selectively protecting the tetrazole ring of **5b** with triphenylmethyl followed by alkylation of the imidazole carboxylic acid group and then deprotection of the tetrazole.[17]

**Scheme I**




a) neat, 50°C; then xylenes (reflux); b) $LiAlH_4$, THF, 0°C; c) $MnO_2$, $CH_2Cl_2$, 25°C; d) $K_2CO_3$, DMF; 0-25°C; e) $HCl_{(aq)}$, THF; then $NaOH_{(aq)}$; f) $HCl_{(aq)}$, THF.

**Scheme II**




a) $Cu(OAc)_2$, $NH_{3(aq)}$, 100°C; b) $H_2S_{(g)}$; c) $HCl_{(aq)}$, $CH_2O$, Δ; d) $Ce(NH_4)_2(NO_3)_6$, HOAc.

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