Bioorganic & Medicinal Chemistry Letters, Vol.3, No.5, pp. 895-898, 1993
Printed in Great Britain

0960-894X/93 $6.00 + .00

THE PREPARATION OF (PERFLUOROALKYL)IMIDAZOLES AS NONPEPTIDE ANGIOTENSIN II RECEPTOR ANTAGONISTS

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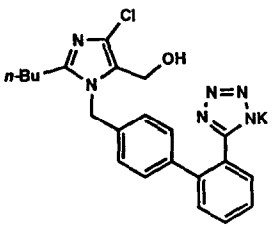
(*Received* 1 *June* 1992; *accepted* 20 *July* 1992)

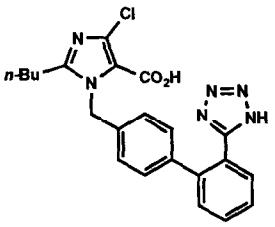
Abstract: A series of (perfluoroalkyl)imidazoles have been prepared and are potent angiotensin II antagonists. One of these compounds, DuP 532, 4-pentafluoroethyl-2-propyl-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]imidazole-5-carboxylic acid, is a selective antagonist of angiotensin II which causes a marked and long-lasting drop in blood pressure when administered orally to a renal hypertensive rat.

The renin-angiotensin system (RAS) is known to play an important role in cardiovascular regulation and the maintenance of blood pressure.[1] The active hormone of this system is angiotensin II (AII, AspArgValTyrIleHisProPhe), which acts through stimulation of specific receptors located on various organs.[2,3] AII is a powerful peripheral vasoconstrictor , and the result of AII production therefore is 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, such as Squibb's captopril[4] and Merck's enalapril.[5] However, an alternative and possibly superior approach to controlling the activity of the RAS is the use of specific antagonists of angiotensin II.[6]

The early work of our group at Du Pont 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 DuP753 is believed to be due to the formation of this metabolite.[8] Unfortunately, while EXP3174 is an antihypertensive, it has limited oral potency. Our group has sought to develop an orally active analog of EXP3174, which would not require metabolic activation to demonstrate fully potency.



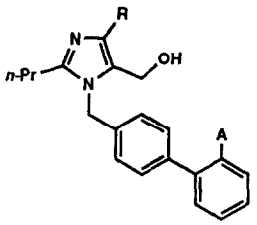
(**1**) DuP 753



(**2**) EXP3174

One of the structure-activity relationships (SAR) previously reported for our series of N-(biphenylylmethyl)-imidazole AII antagonists is the apparent preference for a large, electron-withdrawing group at the 4-position of the imidazole ring. This conclusion was based primarily upon the observation that within a given series of 4-haloimidazole derivatives the binding affinities show a small but significant increase with the increasing size of the halogen substituent (Cl < Br < I).[7b] However we desired more conclusive evidence that large lipophilic groups at the 4-position of our imidazoles would result in compounds possessing high binding affinities. To answer these questions a series of 4-(perfluoroalkyl)-imidazoles were prepared (Table 1). In both the carboxylic acid series (**3-7**) and the tetrazoles (**8-10**) binding affinities increase in going from trifluoromethyl to pentafluoroethyl and then fall off with further increases in the length of the perfluoroalkyl chain. The most potent compound in this series, **9**, demonstrates a ten-fold increase in affinity relative to DuP 753 and equals or exceeds the affinity of angiotensin II itself. Apparently there is an optimal size for this substituent; the ten-fold increase in affinity for **9** vs. DuP 753 is too great to be due to the relatively minor differences observed between n-butyl and n-propyl at the 2-position of the imidazole.[7b,d] The antihypertensive potency of **9** [ED_{30}(i.v.) = 0.25 mg/kg][9] is three-fold greater than for DuP 753, while it's oral activity [ED_{30}(p.o.) = 0.98 mg/kg][9] matches that of DuP 753.

Table 1. Effect of Chain Length on the Binding Affinities of a Series of 4-(Perfluoroalkyl)imidazoles.

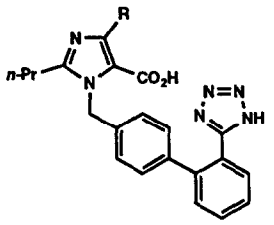


No.	A	R	IC_{50} (nM)[9]
3	CO_2H	CF_3	130
4	CO_2H	CF_3CF_2	48
5	CO_2H	$CF_3(CF_2)_2$	74
6	CO_2H	$CF_3(CF_2)_3$	290
7	CO_2H	$CF_3(CF_2)_5$	2500
1 (2-butyl)	CN_4H (K^+-salt)	Cl	19
8	CN_4H	CF_3	6.4
9	CN_4H	CF_3CF_2	1.2
10	CN_4H	$CF_3(CF_2)_2$	13
Angiotensin II			2.0

As discussed above, our primary goal was the discovery of an orally active analog of EXP3174 (**2**). For this reason, despite the considerable potencies of some of the alcohols in Table 1, the greatest interest focused on the corresponding imidazole-5-carboxylic acids (Table 2). The SAR for this series of acids, based on their intravenous antihypertensive potencies,[10] is somewhat different than that derived from the binding affinities of the above alcohols. The 4-(trifluoromethyl)imidazole **11** possesses a greater potency than EXP3174, however the antihypertensive activity drops off slightly with the 4-(pentafluoroethyl)imidazole **12**. Potency then drops sharply for the perfluoropropyl analog

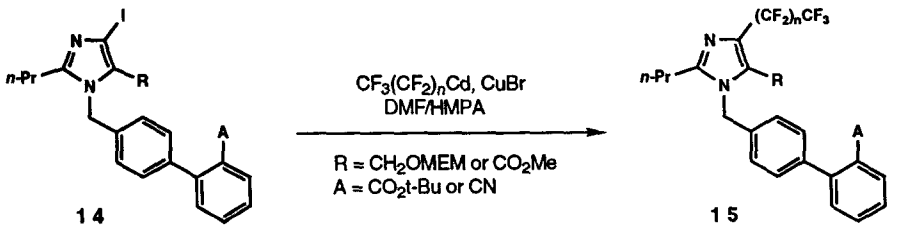
13. Remarkably, the superiority of the pentafluoroethyl group once again manifests itself when one examines the oral antihypertensive activity of these compounds. The oral potency of **12** (DuP 532) is 3-fold better than for EXP3174, and the ED_{30}(p.o.)/ED_{30}(i.v.) is improved. As with DuP 753 and EXP3174, DuP 532 is a selective angiotensin II antagonist which did not block the increase in blood pressure caused by norepinephrine or vasopressin in the pithed rat.[11] Likewise, it exerted no antagonism toward the actions of bradykinin, acetylcholine, serotonin, or histamine on the guinea pig ileum.[11] Oral doses of 0.3-3.0 mg/kg of DuP 532 produced a significant antihypertensive effect in the renal hypertensive rat which lasted for more than 24 hours.[11b]

Table 2. Effect of Chain Length on the Antihypertensive Activity of 4-(Perfluoroalkyl)imidazole-5-carboxylic acids.



No.	R	I.V. ED_{30}(mg/kg)[9]	Oral ED_{30} (mg/kg)[9]
2 (2-butyl)	Cl	0.038	0.66
11	CF_3	0.010	0.79
12	CF_3CF_2	0.042	0.21
13	$CF_3(CF_2)_2$	0.62	~10

The key step in the preparation of the (perfluoroalkyl)imidazoles is the treatment of an appropriate iodoimidazole **14** with the desired perfluoroalkylcopper reagent. In the preparation of the (trifluoromethyl)imidazoles we employed a trifluoromethylcopper reagent described Weimers and Burton[12]. This reagent is prepared by the treatment of bromochlorodifluoromethane with cadmium powder in dimethylformamide (DMF) followed by the addition of hexamethyphosphoric amide (HMPA) and then copper(I)bromide. An analogous reagent can be prepared beginning with the reaction of cadmium and trifluoromethyl iodide in DMF[13] followed, as before, by HMPA and copper(I)bromide. Extension of the later method to other perfluoroalkyl iodides permitted the preparation of the remaining required reagents. HMPA is necessary to stabilize the trifluoromethylcopper reagent against disproportionation,[12] however we have subsequently found the HMPA to be totally unnecessary when one is employing the higher-homolog reagents. In all cases the remainder of the procedure calls for the addition of the iodoimidazole to the reagent followed by heating at 65-80 °C for 1-6 hours. In general the reactions of the imidazole esters (**14**, R = CO_2Me) are faster than for the corresponding



protected alcohols (**14**, R = CH_2OMEM). The required iodoimidazoles are readily prepared employing chemistry previously described.[7] The conversion of the biphenyl esters (**15**, A = CO_2t-Bu) to the final products required only standard deprotection reactions, while the conversion of the biphenyl nitriles (**15**, A = CN) to the corresponding tetrazoles was effected employing trimethylstannyl azide.[7b]

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9. IC_{50} designates 50% inhibition of specific binding of [^{3}H]angiotensin II (2 nM) to rat adrenal cortical microsomes with intraassay and interassay variabilities of 5-10% and 15-30%, respectively. ED_{30} is the effective dose that lowers the blood pressure 30 mm Hg in renal hypertensive rats. For a more detailed discussion of these assays , see: ref 7b.
10. The binding affinities obtained for diacidic antagonists such as these imidazole-5-carboxylic acids are extremely sensitive to the assay conditions and do not generally correlate well with *in vivo* activity. For a discussion of this observation, see ref. 6a.
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