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BROMOBENZOFURANS : A NEW CLASS OF POTENT, NON-PEPTIDE ANTAGONISTS 0F ANGIOTENSIN II

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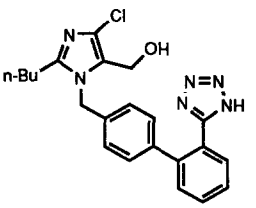
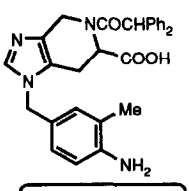
Abstract: This paper describes the synthesis and pharmacology of a novel series of benzofurans which are antagonists of angiotensin II. One of these, the bromobenzofuran **11b**, is a potent (apparent $pK_B = 9.8$) and specific antagonist of angiotensin II which, after oral administration (10mg/Kg), causes marked and long-lasting (>24h) falls in blood pressure in renal hypertensive rats.

The octapeptide angiotensin II (AngII)(AspArgValTyrIleHisProPhe) is a potent vasoconstrictor agent which is implicated in the aetiology of hypertension and congestive heart failure. Angiotensin converting enzyme (ACE) inhibitors, such as enalapril or captopril inhibit the synthesis of AngII. These compounds are well established anti-hypertensive agents in man[1]and have also been shown to be beneficial in the treatment of heart failure[2].It has been suggested[3] that a receptor antagonist of AngII would offer at least an alternative, and possibly a better, treatment of these conditions as AngII may be generated by enzymes other than ACE[4]. Furthermore, ACE is a non-specific dipeptidyl-carboxypeptidase and its inhibition will inevitably interfere with levels of other endogenous peptides (eg. bradykinin[5]). In this regard, ACE inhibitors prevent the metabolism of bradykinin and it has been suggested[6] that increased levels of this substance may cause the cough which is a significant side-effect of enalapril and captopril treatment. An angiotensin receptor antagonist ought to be devoid of these unwanted actions of the ACE inhibitors. However, until recently, only peptide antagonists of AngII were known and the poor pharmacokinetics of this class of compound has limited their clinical usefulness. They show poor oral absorption and even if administered intravenously, are short acting. Moreover, many exhibit partial agonist activity.

A series of non-peptides has now been shown to be antagonists of AngII; these are exemplified by the imidazole (**1**) (DuP753)[7]. Moreover, radioligand binding studies using imidazoles such as DuP 753 and imidazopyridines such as (**2**) (PD123177)[8] suggest the presence of two distinct populations of angiotensin binding sites, termed AT_1 (DuP753 selective) and AT_2 (PD123177 selective)[9]. At present no functional role has been attributed to AT_2 receptors and DuP753, but not PD123177, lowers blood pressure in animal models of hypertension associated with activation of the renin angiotensin system[10].



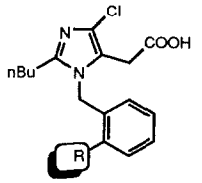
(1) DuP753



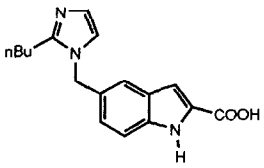
(2) PD123177

We report here our work which has led to the identification of a series of benzofurans (eg **11b**) which are potent antagonists of Ang II[11].

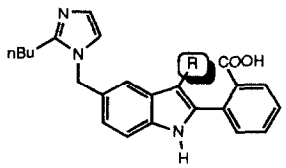
The first non-peptide antagonists of Ang II to be described were a series of weakly active imidazoles (eg **3**)[12]. Using these as a starting point we adopted a number of different strategies aimed at identifying compounds with increased potency. From one of these approaches the indole (**4**) emerged as an interesting new lead. Structural modification of this molecule, in particular by changing the vector of the carboxylic acid by introducing an aromatic ring (compound **5**) led to a small increase in potency. Further modification, by replacement of the C_3 hydrogen atom by bromine (compound **6**) surprisingly led to a twenty-fold enhancement in activity. This increase may result from an interaction of the bromine atom at the receptor, possibly with the same lipophilic pocket that has been proposed to accommodate the butyl group of DuP753 (**1**)[13], or from a decrease in the rotational freedom of the benzoic acid moiety.



(**3**) R = H,Cl,NO_2



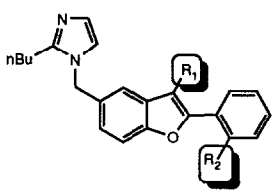
(**4**) pK_B = 5.7



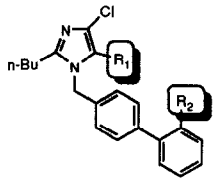
(**5**) R = **H** (pK_B = 6.3)

(**6**) R = **Br** (pK_B = 7.8)

Initially we felt that the indolic nitrogen was involved with a hydrogen-bond donor interaction at the receptor but this seems unlikely as the corresponding benzofuran analogues are also potent antagonists (**Table 1**). Again replacement of the C_3 hydrogen atom by bromine leads to a marked enhancement in potency (compare **7a** and **7b**) but, in contrast to the biphenyl antagonists, replacement of the carboxylic acid with a C-linked tetrazole has little effect on activity (compare **7b**, **7c** with **8,1**).



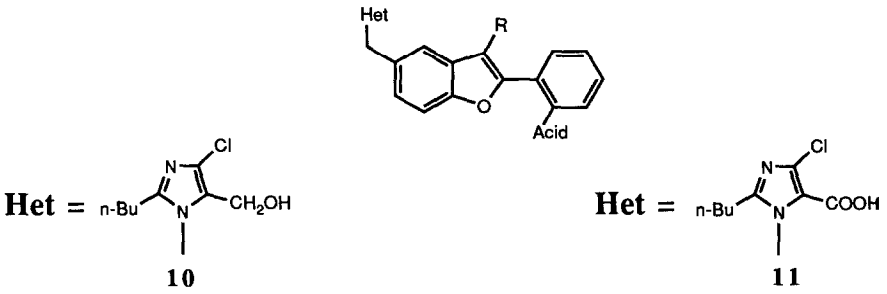
7a-c



No	R^1	R^2	pK_B	No	R^1	R^2	pK_B
a	H	COOH	6.6	**8**	CH_2OH	COOH	6.9
b	Br	COOH	8.0	**1**	CH_2OH	C_4NH	8.4
c	Br	C_4NH	8.5	**9**	COOH	C_4NH	10.6

Table 1. AT_1-receptor antagonist activity of benzofurans and biphenyls in rabbit aorta

Further modification of the benzofurans (**7**), by decreasing the basicity of the imidazole ring and incorporating substituents resulted in additional increases in potency. Thus the hydroxymethyl analogues (**10**) are slightly more potent than their unsubstituted counterparts (**Table 2**). Oxidation of these alcohols to their respective carboxylic acids (**11a-c**) resulted in further enhancements in potency which are more consistent with a hydrogen-bond rather than an additional coulombic interaction at the receptor[14]. These increases are not as marked as in the biaryls (cf. **1,9**) *suggesting a different structure-activity profile between the two series.* Further support for this difference comes from the replacement of the carboxylic acid by a tetrazole which again has little effect on potency in the benzofuran series (**10,11a** *vs* **10,11b**) compared to the biaryls (**8** *vs* **1**). *In all cases the presence of a bromine atom is crucial for high potency*.



No	R	Acid	10	11
a	Br	COOH	8.6	10.2
b	Br	CN_4H	9.1	9.8
c	H	CN_4H	7.0	8.4

Table 2. AT_1-receptor antagonist activity of substituted benzofurans in rabbit aorta (pK_B)

The bromobenzofuran GR 117289 (**11b**) was selected for further study.

In vitro using rabbit aorta[11], GR117289 is a potent antagonist of the vasoconstrictor effects of AngII (see Table 2) but unlike the biphenyl DuP753, shows insurmountable antagonism. The suppression of the AngII maximum is a common feature of many of the compounds of this class, particularly those containing a carboxylic acid in the imidazole ring[15], and may be due to the slow equilibration of the antagonist with the receptor and not irreversible antagonism (data not shown). In a variety of functional and binding assays we have been unable to demonstrate affinity for any other receptor type at concentrations below 1μM.

In vivo GR117289 antagonises the pressor response to exogenous AngII in normotensive animals (**Fig 1**) but fails to affect the response to exogenous phenylephrine (data not shown). In renal-artery ligated hypertensive rats[16] it lowers blood pressure for greater than 24h following oral administration (Fig 2).

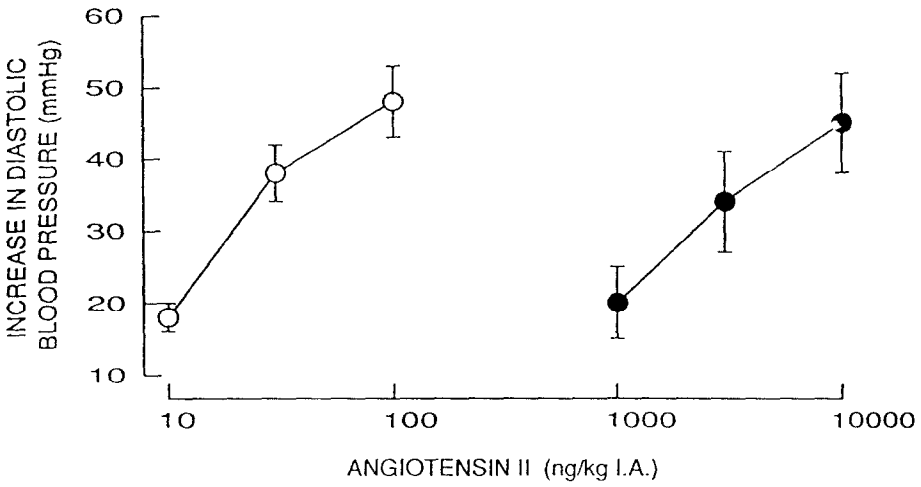


Fig 1 Increases in diastolic blood pressure produced by administration of AngII before (O) and 1h after (●) intra-arterial administration of GR117289 (1 mg/kg) to conscious normotensive rats.

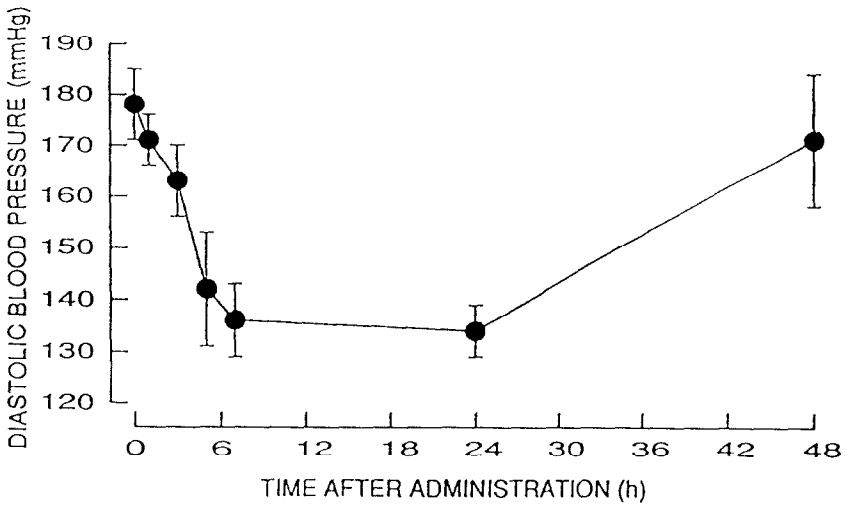
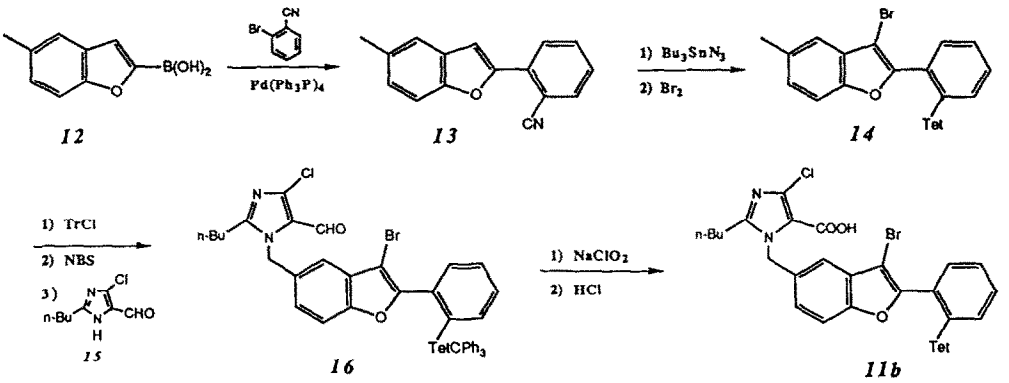


Fig 2 Effect of GR117289 (10mg/kg orally) on blood pressure in conscious hypertensive rats.

The synthesis of benzofuran (**11b**) was accomplished by the route outlined in the scheme. Palladium catalysed coupling of the boronic acid (**12**) with o-bromobenzonitrile gave the nitrile (**13**). Tetrazole formation using tributyltin azide (2 equiv, 160°C) followed by electrophilic bromination gave the tetrazole (**14**) which was protected as its trityl derivative. Activation of the 5-methyl group by free radical bromination followed by reaction with the imidazole (**15**)[18] gave the aldehyde (**16**) which was converted into the target benzofuran GR117289 (**11b**) by Pinnick oxidation[19] and deprotection of the tetrazole. Other tetrazoles were prepared by appropriate modifications to this route. Benzoic acids were prepared either by hydrolysis of the nitrile (**13**) or coupling of the boronic acid with methyl o-bromobenzoate. Indoles were prepared starting from the analogous boronic acid.



12 *13* *14* *15* *16* *11b*

In summary we have identified a novel series of potent antagonists of AngII which are orally active and long-lasting antihypertensive agents. The benzofuran GR117289 (**11b**) is currently undergoing evaluation as a potential agent for the treatment of hypertension and a more detailed account of its pharmacology will be published elsewhere.

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11) The affinities of the compounds for angiotensin AT_1 receptors were determined as a function of their abilities to antagonise the contractile effect of AngII in rabbit isolated thoracic aorta. To achieve this, the apparent pK_B value for each compound which produced a parallel displacement of the AngII concentration-response curve, was derived using a single concentration of antagonist by means of the Gaddum equation[11a]. The incubation time for each test compound was 3h. Some compounds caused insurmountable antagonism of the AngII concentration-response curve. For each of these compounds, the apparent pK_B was derived from the double reciprocal regression, as described by Kenakin [11b]. All results shown are the mean of at least three separate determinations. a).Kenakin T P, *Pharmacologic Analysis of Drug-Receptor Interaction*,1987, 212, Raven Press New York, 1987. b) Kenakin T P, *Pharmacol. Rev.*,1984, **36**, 165.

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