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BENZOFURAN BASED ANGIOTENSIN II ANTAGONISTS RELATED TO GR117289: ENHANCEMENT OF POTENCY *IN VITRO* AND ORAL ACTIVITY

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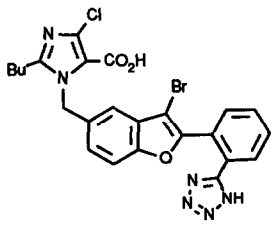
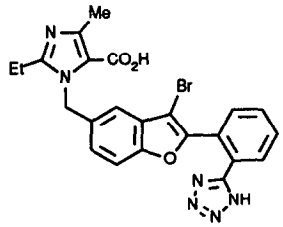
Abstract: A study of structure activity relationships based on the bromobenzofuran angiotensin II antagonist GR117289 is reported. This study led to the identification of compounds with potency *in vitro* enhanced by ca. 10 fold. Also reported is the enhancement of the oral activity of the acid analogue (1) conferred by formation of the double ester pro-drug (2). Prodrug (2) causes marked and long-lasting falls in blood pressure after oral administration at 0.3mg/kg in renal artery ligated hypertensive rats.

INTRODUCTION

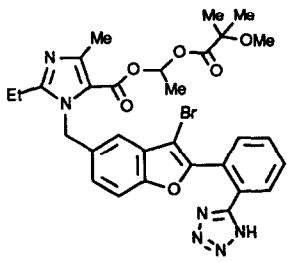
The potential role for an angiotensin II (Ang II) antagonist in the treatment of hypertension has been well documented elsewhere[1]. In this context we have previously described[2] the process which led to the identification of the bromobenzofuran GR117289, which is a potent antagonist of Ang II *in vitro* and *in vivo*, and is currently undergoing clinical evaluation. Herein we report a study of structure activity relationships which led to the identification of compounds such as the acid (1) with potency *in vitro* ca. 10 fold greater than that of GR117289. In addition we report the much enhanced oral activity of the acid (1) on formation of the double ester prodrug (2).



GR117289



(1)



(2)

STRUCTURE ACTIVITY RELATIONSHIPS

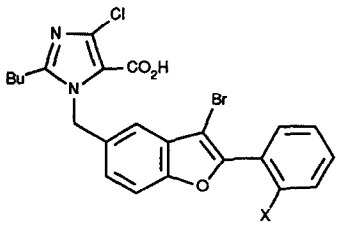
Structure activity relationships were explored for the tetrazole, the benzofuran 3-substituent and the imidazole regions of GR117289. Some modifications were found to enhance potency *in vitro* by up to ca. 10 fold, however few of the more potent compounds thus identified exhibit good oral activity in animal models of hypertension.

Replacement / Modification of the Tetrazole of GR117289

The series of compounds (3a-h) was prepared to explore the role of the tetrazole in GR117289. The compounds (3a-c) which possess an acidic replacement for the tetrazole exhibit a broad range of potency[3] *in vitro* (table 1). As each of these alternative groups has an acid strength comparable to that of a tetrazole[4] it is likely that the the differing potencies of these compounds have geometric/steric origins.

Table 1: Effect on potency *in vitro*[3] of replacing or modifying the tetrazole of GR117289

Compound	X	pK_B
3a	CO_2H	10.2
GR117289	Tetrazole	9.8
3b	CONHTetrazole	8.8
3c	$NHSO_2CF_3$	7.8
3d	CO_2Et	7.8
3e	$CONH_2$	7.2
3f	2-Me-Tetrazole	6.4
3g	1-Me-Tetrazole	7.3
3h	CN	<6



(3)

The relatively low potency of the trifluoromethanesulphonamide (3c) is noteworthy; replacement of the tetrazole with a trifluoromethanesulphonamide negates the potency enhancement conferred by the benzofuran 3-bromine atom (see below).

Methylation of the tetrazole of GR117289, or its relpacement with an amide, causes approximately a one thousand fold reduction in potency *in vitro* (compounds 3f, 3g and 3e). Replacement of the acidic tetrazole with a good hydrogen bond donor/acceptor (amide 3e) causes a fall in potency comparable to that resulting from rendering the tetrazole non-acidic (N-methyl tetrazoles 3f and 3g). Thus it can be inferred that the tetrazole of GR117289 is involved in an ionic[5], rather than a hydrogen bonded, interaction with the receptor.

Whilst replacement of the tetrazole of GR117289 with a carboxylic acid affords a more potent compound *in vitro*, this compound (3a) is only weakly orally active in the renal artery ligated hypertensive rat model of hypertension[6]. Thus in terms of both potency *in vitro* and oral activity the tetrazole of GR117289 appeared to be the optimum group for this region of the molecule.

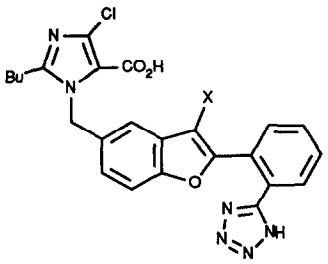
Modification of the Benzofuran 3-Substituent of GR117289

Our original studies[2] demonstrated the crucial role of the bromine atom in GR117289 in imparting high potency[3] *in vitro*, relative to the des-bromo compound (4d). The compounds of table 2 were prepared to probe the role of this benzofuran 3-substituent.

In contrast to our initial suggestions[2], it appears unlikely that the bromine atom serves to enhance potency by either reducing rotational freedom or enhancing a lipophilic interaction. Analysis of the data of table 2 suggests potency *in vitro* increases with increasing σ-electron withdrawing power (σ_I) of the benzofuran 3-substituent. This could arise from either this substituent reducing the already low Lewis basicity of the furanyl oxygen atom or, more probably, a modulation of the electron charge distribution of the furan ring. Indeed preliminary MNDO molecular orbital calculations (SYBYL version 5.32, data not shown) indicate that the increasing potency in compounds (4) parallels an increase in electron charge density on the benzofuran 3-substituent. This trend would indicate a dipolar interaction between this substituent and the receptor.

Table 2: A comparison of potency *in vitro*[3] and σ-electron withdrawing power of the 3-substituent in benzofurans (4)

Compound	X	pK_B	σ_I[7]
4a	Cl	10.5	0.47
4b	CF_3	10.0	0.42
GR117289	Br	9.8	0.46
4c	OMe	9.6	0.28
4d	H	8.4	0.00
4e	^{t}Bu	8.3	-0.07



(4)

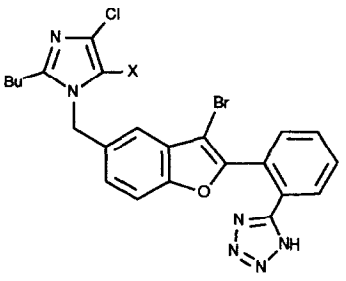
Of the compounds of table 2 only GR117289 and its chloro analogue (4a) are orally active in the renal artery ligated rat model of hypertension[6]. We chose to perform further studies with 3-bromo benzofurans as synthetically a 3-bromine atom is readily introduced[2] whereas introduction of a 3-chlorine atom is problematical.

Modification of the Imidazole Substituents of GR117289

The imidazole-5-position of GR117289 proves tolerant to a range of alternative substituents (table 3). Introduction of neutral substituents (e.g. amides (5a-c)) causes only a small potency decrease relative to GR117289. It therefore seems unlikely that the imidazole 5-carboxylic acid of GR117289 participates in a full ionic interaction with the receptor, as if this were the case the above modifications would lead to more drastic falls in potency. The observed changes in potency are more consistent with our earlier suggestion[2] of a hydrogen bonding interaction between the receptor and the imidazole 5-substituent. Furthermore the comparable potencies of the primary, secondary, and tertiary amides (5a-c) suggest that the 5-substituent serves as a hydrogen bond acceptor.

Table 3: Effect on potency *in vitro*[3] of varying the substituent at the imidazole 5-position

Compound	X	pK_B
GR117289	CO_2H	9.8
5a	CONHMe	9.2
5b	$CONH_2$	9.0
5c	$CONMe_2$	8.8
5d	CO_2Et	8.3
5e	CH_2CO_2H	9.8
5f	$CH_2NHCONH_2$	8.8

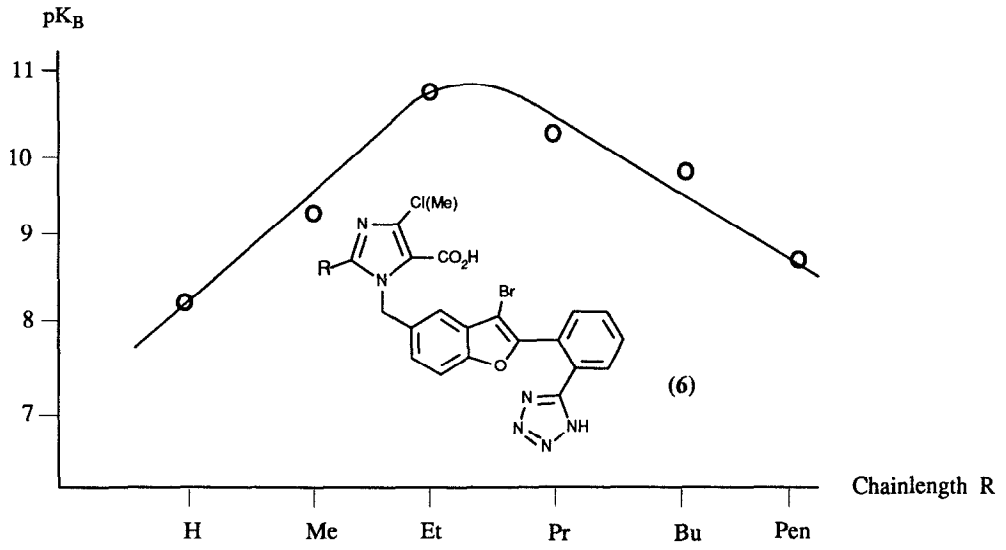


(5)

Interestingly replacement of the imidazole chlorine atom with a methyl group leaves potency *in vitro* unchanged, despite the fact that such a change would significantly enhance the basicity of the imidazole[8].

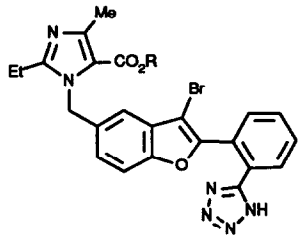
The relationship between potency *in vitro* and chainlength of the the alkyl group at the imidazole 2-position was investigated in both 4-chloro and 4-methyl imidazole analogues of GR117289. A 2-ethyl imidazole substituent was found to confer the highest potency *in vitro* in both series (Figure 1).

Figure 1: Variation in potency *in vitro*[3] with alkyl chainlength in methyl and chloro imidazole carboxylic acids (6)

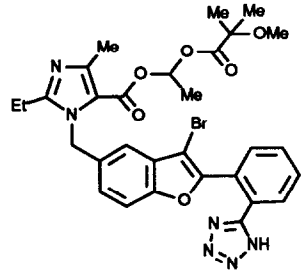


ENHANCEMENT OF ORAL ACTIVITY BY FORMATION OF ESTER PRODRUGS

Few of the new compounds described in the preceding sections display significant oral hypotensive activity in the renal-artery ligated rat model of hypertension[6]. The 2-ethyl-4-methyl imidazole (1), the most potent of these compounds *in vitro* and orally the most active, was selected for further study. The oral activity of this compound was improved by formation of the ethyl ester prodrug (7) and improved even further by formation of the double ester prodrug (2).



(1) R = H
(7) R = Et



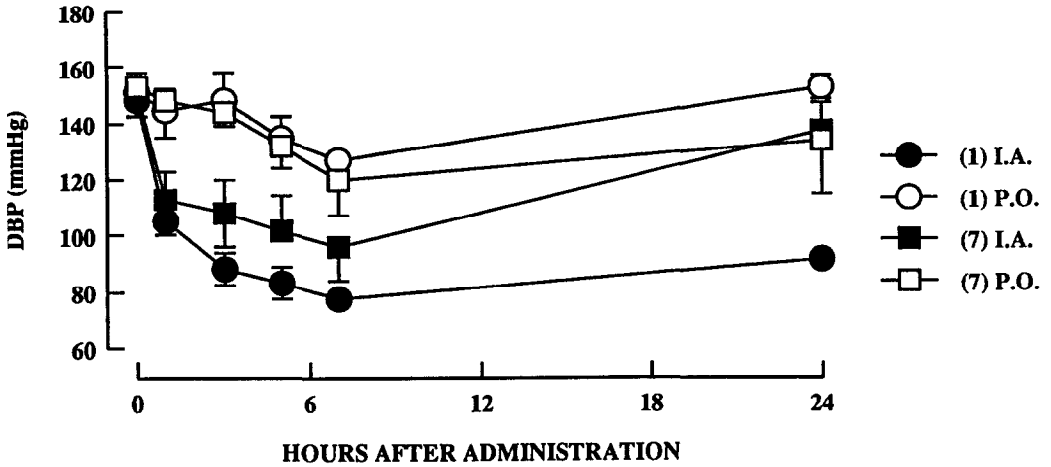
(2)

Aliphatic Ester Pro-Drugs

The acid (1) exhibits oral activity in renal hypertensive rats at low doses, however, the large difference between the hypotensive effects obtained after its oral and intra-arterial (i.a.) administration (figure 2) is indicative of poor oral absorption. A series of simple aliphatic ester prodrugs (eg ethyl, propyl, ^{i}propyl, ^{t}butyl etc) was therefore investigated with a view to enhancing oral absorption. Of these esters only the ethyl ester (7) was effective *in vivo*.

The hypotensive effects of the ester (7) and its parent acid (1) after both oral and i.a administration are compared in figure 2. After i.a. administration, the acid (1) is more effective than its ester (7), suggesting that conversion of the latter into the acid (1) is inefficient. However, despite this, after oral administration, the ester (7) is slightly more effective than the acid (1), suggesting that it is better absorbed. Consequently we proceeded to investigate other prodrugs which we anticipated would be more efficiently converted into the acid (1) *in vivo*.

Figure 2: Comparison of the hypotensive effect of the acid (1) and the ester (7) in renal artery ligated hypertensive rats after oral and intra-arterial administration (0.3mg/kg)

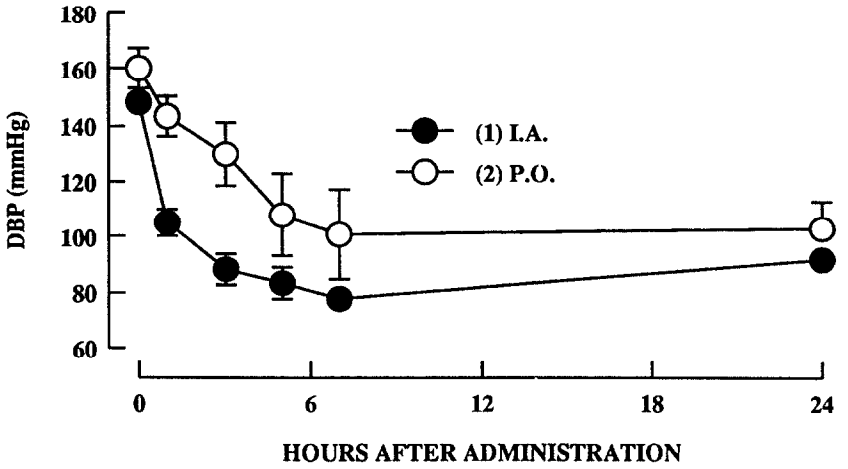


Double Ester Prodrugs

The use of double ester prodrugs of carboxylic acids has been widespread[9], typically these esters enhance oral absorption but are readily cleaved by plasma esterases to afford their parent acids.

A series of double ester prodrugs was prepared. These compounds exhibit oral efficacy much improved over that of the ethyl ester (7). Indeed oral administration of the double ester (2) to renal artery ligated hypertensive rats affords falls in blood pressure very similar to those obtained after i.a. administration of the parent acid (1) (figure 3).

Figure 3: Comparison of the hypotensive effect of the ester (2) after oral administration, and the acid (1) after i.a. administration, in renal artery ligated hypertensive rats (0.3mg/kg)



CONCLUSION

A study of structure activity relationships based on the angiotensin II antagonist GR117289 has allowed the key features of this molecule to be defined and has led to the identification of analogues with enhanced potency *in vitro*. Furthermore the oral activity of the acid analogue (1) of GR117289 has been greatly enhanced by formation of the double ester prodrug (2).

References and Notes

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