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BENZOFURAN BASED NON-PEPTIDE ANTAGONISTS OF ANGIOTENSIN II RELATED TO GR117289: PART IV; IMIDAZOPYRIDINYLBENZOFURANS.

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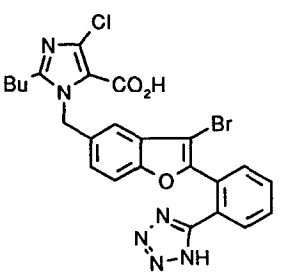
Abstract: The identification of a series of imidazopyridinylbenzofurans (1) as potent, non-peptide antagonists of angiotensin II is described. Several of these compounds cause marked falls in blood pressure in the renal artery ligated rat model of hypertension after oral administration, two of which have high bioavailability and low plasma clearance in rats.

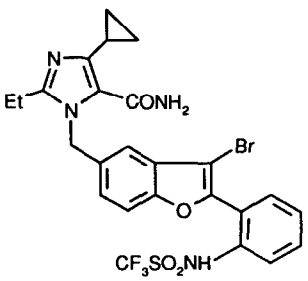
Introduction

There is good evidence that antagonists of angiotensin II will be useful in the treatment of hypertension[1] This area of research has been the focus of much effort over the last few years and many clinical candidates have been identified[2]. To compete successfully with other forms of treatment such compounds will have to be suitable for once-a-day oral administration. Consequently any clinical candidates should be well absorbed after oral administration, be metabolically stable and have low plasma clearance. Despite having good metabolic stability and low plasma clearance many of the early non-peptide antagonists of angiotensin II are only poorly absorbed. Our recent objective has been to identify antagonists of angiotensin II with improved oral absorption over that of our first clinical candidate GR117289[3].

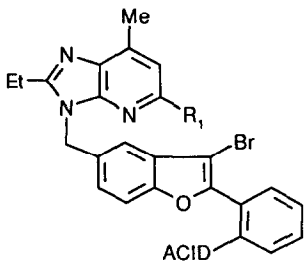
We hypothesised that the poor absorption and low bioavailability of GR117289 was a result of it being a diacid. Indeed, adopting a strategy of preparing only mono acidic compounds led to the identification of GR138950[4], a potent antagonist of angiotensin II with high bioavailability. We have further extended this strategy by replacing the imidazole moiety with other heterocycles that do not contain acidic functionality. This has resulted in the identification of a series of imidazopyridinylbenzofurans (1) two of which have high bioavailability.



GR117289



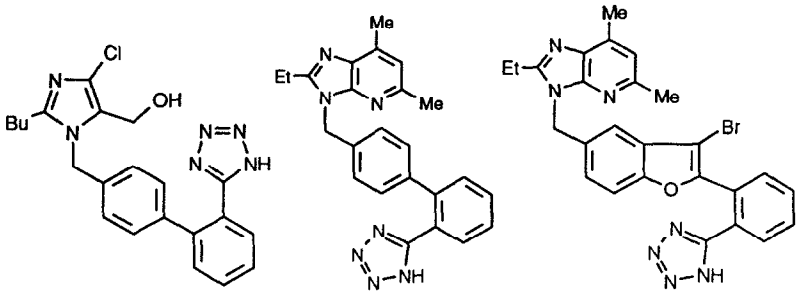
GR138950



(1)

Results And Discussion

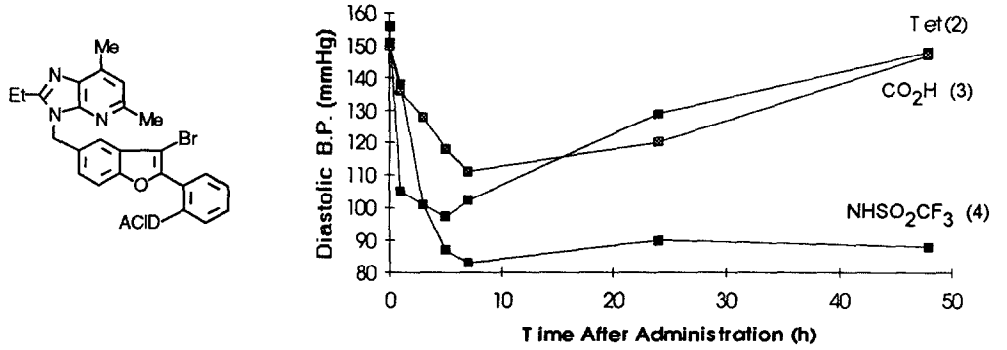
Following our strategy of enhancing oral absorption by preparing monoacidic compounds we have identified a series of imidazopyridinylbenzofurans (1), two of which have excellent pharmacodynamic and pharmacokinetic profiles. This was achieved by replacing the imidazole found in GR117289 or GR138950 by alternative heterocycles. A large number of heterocyclic replacements for the imidazole group have been reported in the biphenyl series related to DuP753[2]. We investigated a number of these alternatives in the benzofuran series and only the imidazopyridine (2) based on the biphenyl tetrazole L-158,809[5], retained any significant antihypertensive activity in the renal artery ligated rat (RALR) model of hypertension after oral administration[6a] (Fig 1)



DuP753 L-158,809 (2)

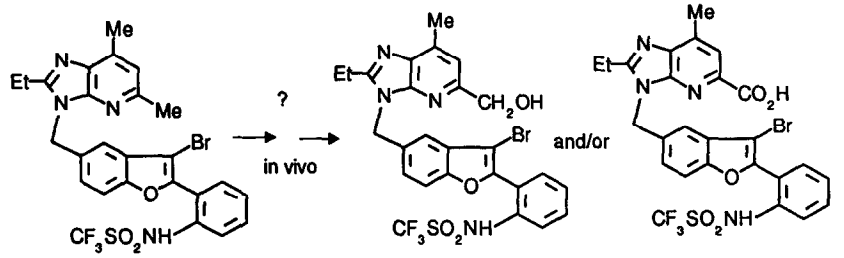
The oral activity of analogues in which the tetrazole was replaced by alternative acidic groups immediately focused our attention to the superior profile of the triflamide derivative (4) (Fig. 1) All three compounds (2-4) are potent antagonists of angiotensin II *in vitro*[7] (pK_B 8.7-9.5) but *in vivo* the triflamide has an extended duration of action compared with the carboxylic acid (3) or tetrazole (2) analogues. Interestingly, the carboxylic acid (3) and tetrazole (2) analogues possess a similar profile after oral administration, in contrast to the imidazole series related to GR117289[3], where the tetrazole is significantly more active .

Fig. 1: Data highlighting the potent and long lasting antihypertensive activity of the triflamide (4) in the RALR model of hypertension[6] after oral administration of 1mg/kg.



We were concerned that the extended duration of action of the triflamide derivative (4) may be due to the formation of an active metabolite. The formation of active metabolites is well documented in the area of antagonists of angiotensin II. For example the extended duration of action of DuP753 has been attributed at least,

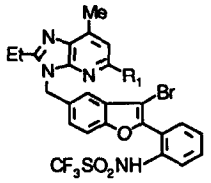
in part, to the formation of the diacidic metabolite EXP 3174[8]. In our opinion, the metabolite of the 5,7-dimethylimidazopyridine, most likely to retain significant antagonism of angiotensin II, would be the 5-carboxylic acid (6) derivative. Thus, we considered that metabolism of 4 to the corresponding 5-carboxylic acid (6) (possibly *via* the 5-hydroxymethyl derivative (5)), was the mechanism that gives extended duration of action. Therefore, it was essential to prepare these potential metabolites, to evaluate their activity *in vitro* and *in vivo*, and to determine their pharmacokinectic profiles. In addition, the 5-hydro derivative (7) was considered as an alternative target that is closely related to 4 but does not have the potential to be metabolised in this manner.



(4) (5) (6)

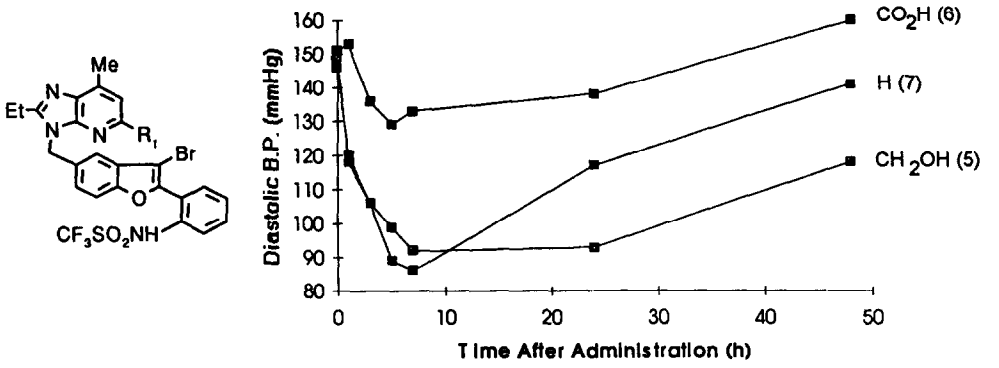
These compounds (4-7)[9] are potent antagonists of angiotensin II *in vitro* (Table 1) and all lower blood pressure in the RALR model of hypertension after oral administration (Fig. 2). The carboxylic acid (6) is the least active *in vivo*, presumably because, being a diacid, it suffers from poor oral absorption. The primary alcohol (5) has an extended duration of action in the RALR model of hypertension (Fig 2) similar to that of the 5-methyl derivative (4). The 5-hydro compound (7) which could not be oxidised to the 5-carboxylic acid (6) has a shorter duration of action.

Table 1. Potency *in vitro* of analogues of triflamide (4)



No	R_1	pK_B
4	Me	9.3
5	CH_2OH	8.6
6	CO_2H	9.3
7	H	8.3

Fig. 2: A comparison of the antihypertensive activity of 5-substituted imidazopyridine derivatives in the RALR model of hypertension[6] after oral administration of 1mg/kg.



Pharmacokinetics

In addition to the methyl analogue (4), the hydroxymethyl analogue (5) was also selected for pharmacokinetic evaluation[10] on the basis of its activity *in vitro* and profile after oral administration in the RALR model of hypertension. The oral bioavailability of 4 was high indicating good absorption. The plasma clearance was low suggesting a high degree of metabolic stability. Furthermore, HPLC analysis of the plasma samples did not show any evidence of oxidative metabolism of the 5-substituent. The 5-hydroxymethyl analogue (5) has a similar profile (Table 2) and likewise, but in sharp contrast to DuP753, is not subject to oxidative metabolism. Interestingly, there was no significant temporal relationship for 4 and 5 between the duration of their antihypertensive activity and their plasma half-lifes. This phenomenon has been observed for other antagonists of angiotensin II[11] but the reasons for this are as yet unclear.

Table 2. Pharmacokinetic parameters of selected compounds in rats.

No	R_1	F (%)	Vd (l/kg)	Clp (ml/min/kg)	$t1/_2$ (hours)
4	Me	70	1.33	5.49	2.8
5	CH_2OH	115	2.4	4.80	5.7

Conclusion

A series of imidazopyridinylbenzofurans (1) has been identified as potent, non-peptide antagonists of angiotensin II. Several of these compounds, cause marked falls in blood pressure in the renal artery ligated rat model of hypertension after oral administration. In particular, two compounds (4,5) have high bioavailability and low plasma clearance with high metabolic stability in rats

References and Notes

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6b The error bars have been removed for clarity, all values were within ±10 mm Hg except for values at 48 hours for 4 &5 which were within ±20 mm Hg.
7 Rabbit aorta; for *in vitro* test method see ref 3
8 Wong, P C , Price, W A , Chiu, A T , Duncia, J V ; Carini, D.J , Wexler, R R.; Johnson, A.L.; Timmermans, P.B W.M. , *J Pharmacol. Exp Ther* **1990,** *255*, 211-7.
9 Compounds were prepared using a similar procedure to that described for GR117289[3]. Alkylation of the requisite imidazopyridine[5] with 1,1-dimethylethyl [2-[3-bromo-5-bromomethyl-2-benzofuranyl]phenyl]carbamate(8) and further elaborations gave 4 or 7. For 5 &6. methyl 2-ethyl-7-methylimidazopyridine-5-carboxylate was prepared from 2-ethyl-7-methylimidazopyridine[5] according to the procedure of Bernardi, R.; Caronna, T.; Galli, R ; Minsci, F., Perchinunno, M., *Tet. Lett.* **1973**, *9*, 645-8 and alkylated with 8 The methyl ester of 6 was subsequently hydrolysed to give 6, or reduced with sodium borohydride to give 5
10. Plasma samples analysed by Hplc
11 Hilditch, A., Hunt, A A.H ; Gardner, C.J.; Twissell, D.J.; Polley, J.; Travers, A , Drew, G M ; Middlemiss, D., Ross, B C , Robertson, M J.; *Br J Pharmacol* , **1994**, *111*, 137-144.

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