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C-LINKED PYRAZOLE BIARYL TETRAZOLES AS ANTAGONISTS OF ANGIOTENSIN II

D. Middlemiss*, B.C. Ross, C. Eldred, J.G. Montana, P. Shah, G.C. Hirst, S.P. Watson, T.A. Panchal, J.M.S. Paton, T. Hubbard, G.M. Drew, M.J. Robertson, A Hilditch, K.L. Clark

Glaxo Group Research, Park Road, Ware, Hertfordshire SG12 0DP, U.K.

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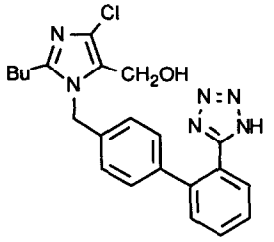
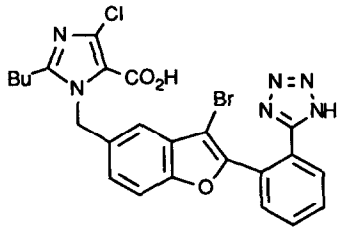
Abstract: The identification of a novel series of C-linked pyrazole biaryl tetrazole antagonists of angiotensin II is described. These compounds are highly potent *in vitro* (pK_B ca. 10) and some examples cause significant reductions in blood pressure at $1mgkg^{-1}$ p.o. in renal hypertensive rats.

Introduction

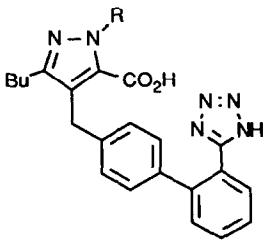
The biaryl tetrazole DuP-753[1] can be regarded as the prototype non-peptide angiotensin II (Ang II) antagonist. In the wake of its discovery a host of analagous compounds, in which an alternative "northern" heterocycle is linked through nitrogen to the "southern" biaryl tetrazole, has been reported.



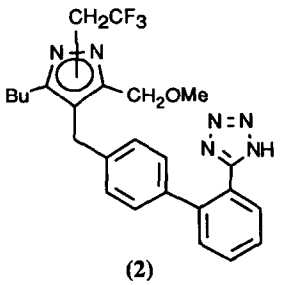
DuP 753



GR 117289



(1)



(2)

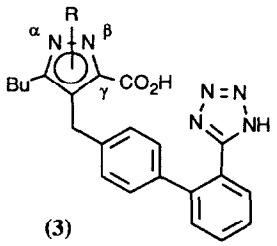
In our efforts to identify a structurally dissimilar follow-up to our Ang II antagonist, GR 117289[2], we explored the possibility of linking a northern heterocyclic unit to a biaryl tetrazole through carbon. This novel approach led to the identification of a series of C-linked pyrazoles[3] (1) which are potent orally active Ang II antagonists selective for the AT_1 receptor.

Structure-Activity Relationships

Our initial efforts to C-link a northern heterocycle to a southern biaryl tetrazole led to the two pyrazole regioisomers (2) which are moderately potent antagonists of Ang II (both pK_B ca. 7[4]). In the work leading to the identification of GR 117289[2] we found that replacement of a hydroxymethyl or methoxymethyl imidazole-5-substituent with a carboxylic acid led to a marked increase in potency. Thus in an effort to enhance the modest potency of the pyrazoles (2) the carboxylic acids (3) were prepared. This modification resulted in a substantial (ca. 1000 fold) increase in potency in the β-regioisomer[6] (3b) but only a moderate enhancement in potency in the α-isomer[6] (3a) (Table 1). These observed increases in potency may be due to either introduction of a new coulombic interaction between the γ-carboxylic acid and the receptor, or simply modulation of a hydrogen bonding interaction.

Table 1: ***In Vitro*** **Potencies[4] of Pyrazoles (3)**

Compound	R	pK_B
3a	α-CH_2CF_3	7.7
3b	β-CH_2CF_3	9.8[5]
3c	H	8.8



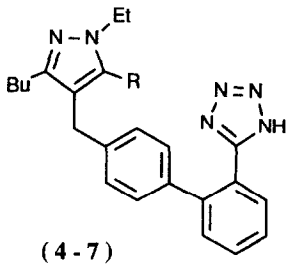
(3)

The much greater increase in potency in the β-regioisomer (3b) can be accounted for as follows in terms of a favourable interaction between the pyrazole N-substituent and a lipophilic pocket of the receptor. In the γ-methoxymethyl compounds (2) the molecules will be less tightly bound to the receptor and may allow either an α or β-substituent to be incorporated into the pocket, hence the similar potencies of the two isomers. However the enhanced receptor-ligand interactions in the γ-carboxylic acids (3) may align these molecules more rigidly such that only a β-substituent can gain access to the pocket. Furthermore, the intermediate potency of the *des*-alkyl pyrazole (3c) suggests that the α-substituent has a destabilizing interaction with the receptor.

We found that replacement of the N-β-trifluoroethyl substituent of (3b) with an ethyl group to give pyrazole (4) left potency unchanged (Table 2); further work to investigate the effects of other structural modifications on functional potency were performed with this N-substituent. Although affording some compounds of moderate functional potency, variation of the pyrazole γ-substituent failed to reveal any compounds more potent than the γ-carboxylic acid (4) (Table 2).

Table 2: ***In Vitro*** **Potencies of Pyrazoles (4-7)**

Compound	R	pK_B
4	CO_2H	9.8[5]
5	CH_2OH	8.0
6	CO_2Et	8.0
7	CONHMe	7.5

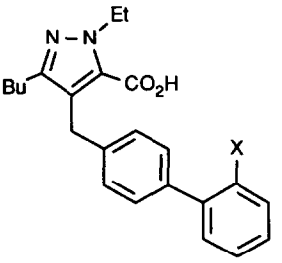


(4-7)

The nature of the acidic group of the southern biaryl region was also investigated. Replacement of the C-linked tetrazole group of pyrazole (4) with either a carboxylic acid (8) or a trifluoromethyl-sulphonamide (9) led to a ca. 100 fold potency decrease (Table 3). This effect mirrors that observed on replacement of the tetrazole of DuP-753 with either of these other acidic functions[1], but is in contrast with findings for GR 117289 where replacement of the tetrazole with a carboxylic acid causes a slight potency increase[2,7]. This suggests, not suprisingly, that the pyrazole (4) binds to the AT_1 receptor in a manner akin to DuP-753, rather than GR 117289.

Table 3: *In Vitro* Potencies of Pyrazoles (4, 8 and 9)

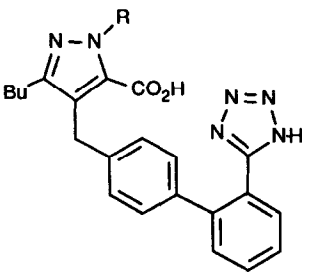
Compound	X	pK_B
4	Tet	9.8[5]
8	CO_2H	8.0
9	$NHSO_2CF_3$	8.0



Once the optimum combination of a β-N-substituent, a γ-carboxylic acid and a southern biaryl tetrazole had been established the nature of the alkyl β-substituent was examined. However, *in vitro* potency seemed largely insensitive to changes in the β-substituent (Table 4). Furthermore the relative potencies of the α and β-substituted pyrazoles (1a and b) confirm the earlier finding (see above) of superior potency in γ-acid β-regioisomers.

Table 4: *In Vitro* Potencies[5] of Pyrazoles (1)

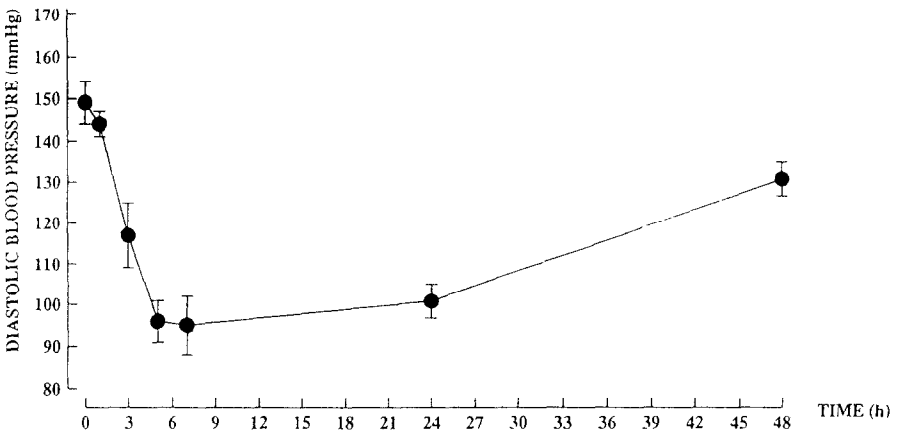
Compound	R	pK_B	
		α	β
1a	^{n}Bu	8.0	10.0
1b	^{i}Pr	8.0	10.0
1c	Me		9.8
1d	^{n}Pr		10.5
1e	$CH_2{}^t$Bu		10.6
1f	cyclo-Bu		10.9
1g	^{i}Bu		11.0
1h	CPM[9]		10.5



(1)

In contrast to their *in vitro* activity, in animal models of hypertension, the **oral** activity of the pyrazoles (1) is very sensitive to the nature of the nitrogen substituent. For example, the cyclopropylmethyl pyrazole (1h) is very effective at lowering blood pressure in renal artery ligated hypertensive rats[8] (Fig1) whereas the closely related cyclobutyl analogue (1f) is ineffective despite having superior activity *in vitro*.

Figure 1: The Effect of Pyrazole (1h) (1mgkg^{-1} p.o.) on the Diastolic Blood Pressure of Renal Artery Ligated Hypertensive Rats[8]



Conclusion

We have identified a series of C-linked pyrazole biaryl tetrazoles which are potent, orally active, AT_1 selective Ang II antagonists. Their excellent pharmacological profile suggests considerable therapeutic potential for these compounds, particularly in the area of essential hypertension.

References and Notes

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2. Middlemiss, D.; Drew, G.M.; Ross, B.C.; Robertson, M.J.; Scopes, D.I.C.; Dowle, M.D.; Akers, J.; Cardwell, K.; Clark, K.L.; Coote, S.; Eldred, C.D.; Hamblett, J.; Hilditch, A.; Hirst, G.C.; Jack, T.I.; Montana, J.; Panchal, T.A.; Paton, J.M.S.; Shah, P.; Stuart, G.; and Travers, A. *Biorg. Med. Chem. Lett.*, 1991, **1**, 711.
3. The compounds described herein were prepared via a non regiospecific synthesis affording mixtures of pyrazole α and β regioisomers which were separated chromatographically. This synthesis, and the development of a regioselective synthesis of pyrazoles (1) will be published subsequently.
4. For *in vitro* test method see Ref. 2
5. In common with some other di-acidic Ang II antagonists (e.g. GR 117289[2]) pyrazoles (1, 3d and 4) display insurmountable antagonism. For a description of the determination of pK_B under these conditions see Ref.2
6. The pyrazole ring positional nomenclature is shown on structure (3).
7. Middlemiss D.; *et. al.* forthcoming publication
8. Cagiano, J.;Rodriguez-Sargent, C.;Martinez-Maldonado, M. *J.Pharmacol. Exp Ther* ,1979, **208**, 310.
9. CPM - Cyclopropylmethyl