Bioorganic & Medicinal Chemistry Letters, Vol. 4, No. 1, pp. 151-156, 1994
Printed in Great Britain

0960-894X/94 $6.00 + .00

C-LINKED PYRAZOLE BIARYL TETRAZOLES AS ANTAGONISTS OF ANGIOTENSIN II PART II[1]: PHARMACOKINETICS AND AN EFFICIENT REGIOSELECTIVE SYNTHESIS

S.P. Watson*, D. Middlemiss, M. Pass, T. Hubbard, T.A. Panchal, N.M. Heron, J.M.S. Paton, A. Butt, A.W. Dean, M. Donnelly and M.K. Bayliss

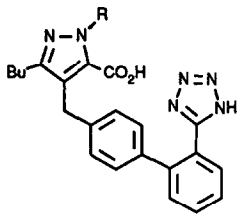
Glaxo Group Research, Park Road, Ware, Hertfordshire SG12 0DP, U.K.

Abstract: C-linked N-alkyl pyrazole biaryl tetrazoles (1) are highly potent antagonists of angiotensin II. Pharmacokinetic parameters in the rat are reported for two of these compounds. The N-cyclopropylmethyl pyrazole (1a) has an oral bioavailability of 58%. In addition an efficient regioselective synthesis of pyrazoles (1) is described.

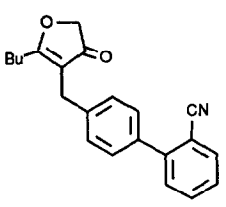
Introduction

The considerable therapeutic potential for non-peptide angiotensin II antagonists has been well documented[2a]. The search for such agents has been the focus of much effort within the pharmaceutical community of late and indeed a number of candidates are making progress in the clinic[2b]. In this journal we have reported[1] the identification of C-linked N-alkyl pyrazole biaryl tetrazoles (1), which are potent antagonists of angiotensin II both *in vitro* and *in vivo*. Furthermore a number of these pyrazoles exhibit good oral potency in the renal artery ligated rat model of hypertension[3]. Pyrazoles (1a and b) are particularly potent orally in this model and on this basis were selected for pharmacokinetic study in rats. The results of these studies are reported herein.

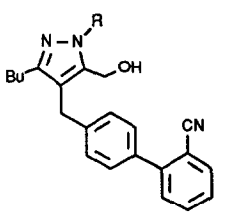
Pyrazoles (1) bear an alkyl substituent on the nitrogen atom adjacent to the pyrazole carboxylic acid (the β-nitrogen[4] atom) and are ca. 100 fold more potent *in vitro* than the regioisomeric pyrazoles bearing an alkyl substituent on the alternative pyrazole nitrogen atom (the α-nitrogen[4])[1]. Hitherto we had employed a non-regioselective pyrazole ring forming reaction (requiring tedious chromatographic separation of α and β isomers[4]) in the synthesis of pyrazoles (1). Whilst this ring synthesis was appropriate for our initial medicinal chemical investigations, a more efficient, i.e. regioselective, synthesis was required to furnish the quantities of pyrazoles (1) required for pharmacokinetic studies. Herein we report an efficient regioselective synthesis of pyrazoles (1). The key step involves the reaction of the furanone (2) with an alkyl hydrazine to regioselectively afford the corresponding β-substituted pyrazole methanol (3).



(1) R = Alkyl
(1a) R = CPM[5]
(1b) R = n-Bu



(2)



(3)

PHARMACOKINETICS

Data obtained from pharmacokinetic studies in the rat (Table) demonstrate that both pyrazoles (1a and b) exhibit a long plasma half-life, and furthermore, that this results from low plasma clearance rather than a high volume of distribution. The observation of relatively low clearances and volumes of distribution indicates that both compounds have high metabolic stability and are held largely in the blood compartment. Both of the compounds, particularly (1a), are orally well absorbed.

Table: Pharmacokinetic Parameters of Pyrazoles (1a and b) in the Rat

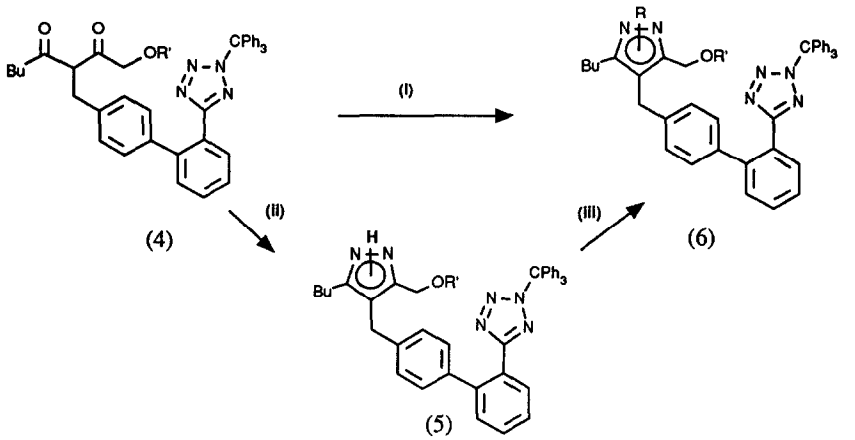
Pyrazole	$t_{1/2}$ (h)[6]	CL_p (mlmin^{-1}kg^{-1})[6]	V_d (Lkg^{-1})[6]	F (%)[6]
1a	12.3	0.20	0.20	58
1b	14.8	0.12	0.16	26

In our earlier work with di-acidic non-peptide angiotensin II antagonists[7,8] we had had to resort to formation of a pro-drug of one of the acidic functions to enhance oral absorption. Indeed for one particular series of compounds we had concluded that di-acidity was so detrimental to absorption that we adopted a strategy of working exclusively with monoacidic species[9]. Hence we found the 58% oral bioavailability of the di-acidic pyrazole (1a) particularly gratifying.

As a consequence of these pharmacokinetic data the pyrazole (1a) is currently under investigation as a potential clinical candidate.

CHEMISTRY

In our medicinal chemical investigations leading to the identification of the pyrazoles (1) we employed a non regiospecific pyrazole ring synthesis (Scheme 1). The reaction of a diketone (4) with a substituted hydrazine, or alkylation of the corresponding N-unsubstituted pyrazole (5), both typically afforded a ca. 1:1 mixture of α and β substituted[4] pyrazoles (6)



Reagents and Conditions: (i)$RNHNH_2$, (ii) NH_2NH_2, (iii) RBr / NaH

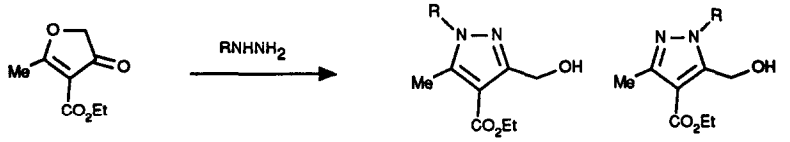
Scheme 1

For reasons outlined above we required a regioselective pyrazole ring synthesis, our initial efforts were directed at alkylation of N-unsubstituted pyrazoles. However we were unable to obtain significant selectivity for the β regioisomer using both a wide variety of substrates and conditions and a variety of

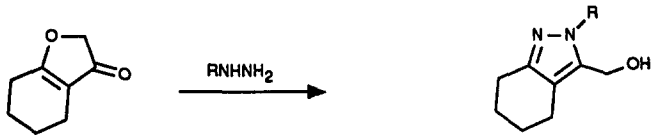
pyrazole γ-substituents[4]. Interestingly however, using n-butyl lithium and ethyl iodide, alkylation of pyrazole (5) (R' = Benzyl) gives 9:1 selectivity in favour of the undesired α regioisomer.

Having confirmed the established view[10] that regioselective pyrazole alkylation is problematical we explored the possibility of effecting a regioselective synthesis *via* substituted hydrazines.

Gelin and co-workers report[11] that the reaction of 3-oxo-dihydrofuran-4-carboxylate (7) with substituted hydrazines affords pyrazole methanols with modest regioselectivity (eqn. 1). Furthermore they report[12] an isolated example of a 4,5-dialkyl furanone (8) reacting with alkyl hydrazines to give exclusively the β substituted pyrazole methanol (9) (eqn. 2)



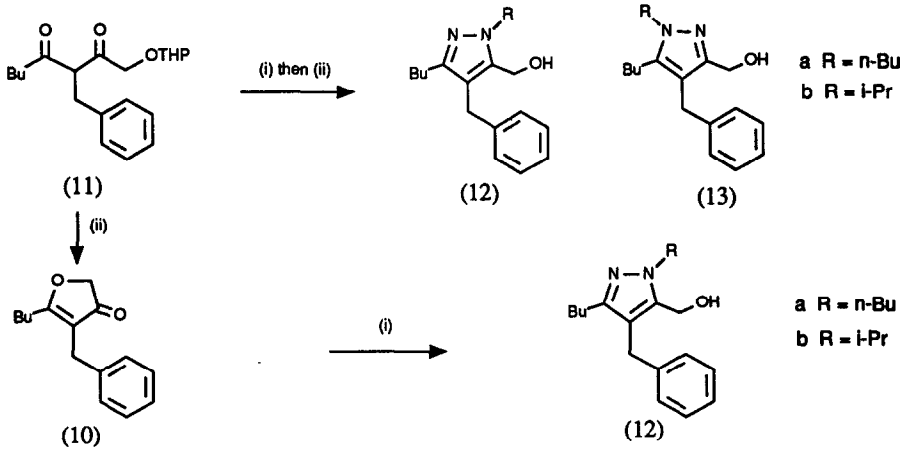
(7) 33% 66% Equation 1



(8) (9) Equation 2

We explored the possibility of applying the chemistry of Gelin and co-workers to the synthesis of pyrazoles (1). Our initial investigations were conducted using the furanone (10) as a model (scheme 2).

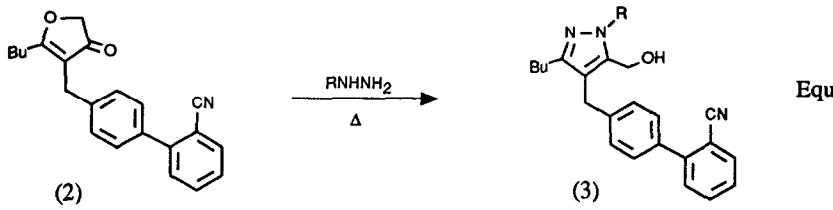
The pyrazole regioisomers (12) and (13) were prepared (ratio 1:1) via the non regiospecific reaction of the diketone (11) and n-butyl or i-propyl hydrazine. The isomer pairs were separated chromatographically and their regiochemistry unambiguously assigned through ^{1}HNMR n.O.e. experiments. The furanone (10) was prepared by treatment of the diketone (11) with acid (Dowex-50 W X 4 ion exchange resin).



Reagents and Conditions (i) $RNHNH_2$, (ii) Dowex-60 ion-exchange resin

Scheme 2

HPLC analysis of the crude reaction mixtures revealed that treatment of the furanone (10) with n-butyl or i-propyl hydrazine afforded a mixture of the β-substituted pyrazole methanols (12) and α-substituted pyrazole methanols (13) in the ratio of 40:1. Flash column chromatography (R = n-butyl) or trituration of the crude product (R = i-propyl) removed all traces of the α-substituted regioisomers to afford pyrazole methanols (12a and b) in 76% and 73% yields respectively.



(2) (3) Equation 3

(a) R = CPM[5] 68%
(b) R = n-Bu 85%
(c) R = i-Pr 92%

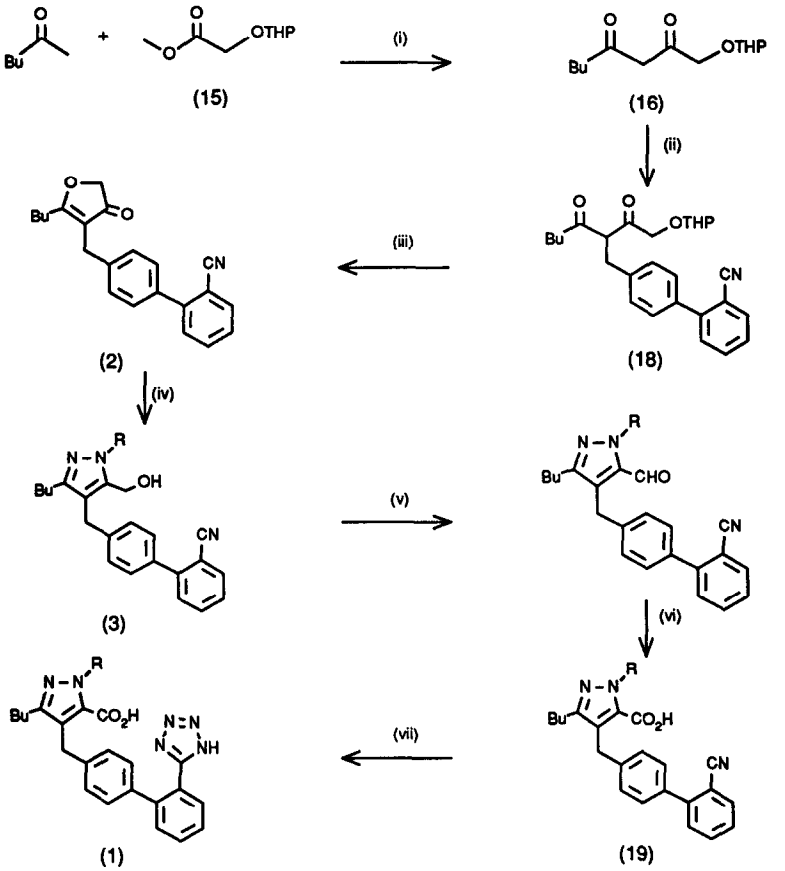
Once the high regioselectivity of the furanone-hydrazine reaction (Scheme 2) had been established it was applied to the synthesis of the pyrazole methanols (3), which we envisaged would be convenient precursors of the pyrazole carboxylic acids (1). Although the reaction was slow, the appropriate hydrazine[13] had to be used as solvent or co-solvent, we found that the furanone (2) readily afforded the β substituted pyrazole methanols (3) in good yield (eqn. 3)

The complete synthesis of pyrazoles (1), incorporating the key furanone-hydrazine reaction step, is depicted in scheme 3, the route works equally well for N-cyclopropylmethyl, N-n-butyl and N-i-propyl pyrazoles. Reaction of the kinetic enolate of hexanone with the THP protected glycolate (15) affords the diketone (16) which is readily alkylated with the known[14] alkyl bromide[15] (17) to afford the diketone (18). Treatment of the diketone (18) with Dowex 50 W X 4 ion-exchange resin in methanol affords the furanone (2) which is efficiently converted into the pyrazole methanol (3) as outlined above (eqn.3). The pyrazole methanol (3) is efficiently oxidized in two steps to give the carboxylic acid (19) which, on heating with tributyltin azide and subsequent acidic work up, affords the desired β-substituted pyrazole carboxylic acid (1).

CONCLUSION

Pyrazoles (1a and b) have good pharmacokinetic profiles in the rat. Indeed pyrazole (1a) has an oral bioavailability of 58% in the rat, this, in combination with its good oral efficacy in the renal hypertensive rat model of hypertension[2], suggests that this compound has considerable potential as an anti-hypertensive agent. An efficient regiospecific synthesis which allows the ready preparation of large quantities of pyrazoles (1) has been developed.

Scheme 3: Regioselective Synthesis of Pyrazoles (1)



Reagents and Conditions: (i) L.D.A. , 61%;(ii) NaH / R"Br[14,15](17) 74% ; (iii) Dowex 50 WX4 ion-exchange resin, 93%; (iv) $RNHNH_2$, 68-92%;, (v) MnO_2 or TPAP, 80- 85%; (vi)NaOCl / 2-methylbut-2-ene / t-BuOH / NaH_2PO_4 ,100%: (vii) Bu_3SnN_3 / Δ , 75-82%

Experimental

Pharmacokinetics: Each rat recieved a single oral or intravenous dose equivalent to 3mgkg^{-1} bodyweight. Blood was collected under anaesthesia at 0, 5, 15, 30, 45 min, and 1, 1.5, 2, 4, 6, 8, 10, 12 and 24h post dose (2 rats per time point). The blood samples were placed in heparinised tubes and centrifuged to separate the plasma. Plasma samples were extracted by solid phase extraction with certify II cartridges. The extracts were analysed by HPLC using a Supercosil LC-ABZ column with UV detection at 250nm.

Furanone (2): A suspension of Dowex-50 W X 4 ion exchange resin (15.0g) in a solution of the diketone (18) (37.1g, 90mmol) in methanol (60ml) was rapidly stirred at room temperature for 24h, further resin (15.0g) was added and stirring continued for a further 24h. The mixture was filtered through hyflo and the filtrate concentrated in vacuo to afford a yellow oil. Flash column chromatography on silica gel (hexane/ethyl acetate (4:1) as eluent) gave the furanone (2) as a yellow oil (26.6g, 93%). ^{1}H NMR ($CDCl_3$, 250MHz): 0.92(t,3H,$C\underline{H}_3CH_2CH_2CH_2$), 1.30(sex,2H,$CH_3C\underline{H}_2CH_2CH_2$), 1.55(quin,2H,$CH_3CH_2C\underline{H}_2CH_2$), 2.50(t,2H,$CH_3CH_2CH_2C\underline{H}_2$), 3.56(s,2H,$C\underline{H}_2$Ar), 4.52(s,2H,0-$C\underline{H}_2$), 7.20-7.80(m,8H,aromatics),

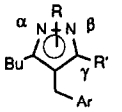
Pyrazole methanol (12b): A solution of the furanone (10) (1.00g, 4.3mmol) in i-propylhydrazine (5ml) was heated at 75^{0}C for 6h. Water (50ml) was added and the mixture extracted with ether (3x25ml). The combined extracts were washed with satd. brine (25ml), dried

($MgSO_4$),and concentrated in vacuo to afford a yellow solid (1.10g). Trituration with hexane/ether (20:1) gave the title compound as a white powder (0.90g, 73%).^{1}H NMR ($CDCl_3$,250MHz): 0.86(t,3H,$CH_3CH_2CH_2CH_2$), 1.26(bm,1H,CH_2OH), 1.31(sex,2H,$CH_3CH_2CH_2CH_2$), 1.46-1.56(m,8H,$CH_3CH_2CH_2CH_2$ + $(CH_3)_2CH$), 2.54(t,2H,$CH_3CH_2CH_2CH_2$), 3.80(s,2H,CH_2Ar), 4.48(d,2H,CH_2OH), 4.57(sept,1H,$(CH_3)_2CH$), 7.10-7.30(m,5H,aromatic)

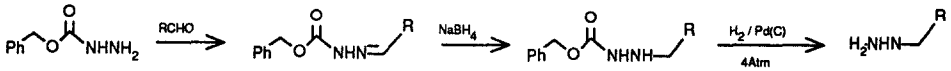
Pyrazole methanol (3a): A solution of cyclopropylmethylhydrazine (2.6g, 30mmol) and the furanone (2) (2.1g, 6.3mmol) in tetrahydrofuran (5ml) was heated at 50°C for 48h. Ethyl acetate (100ml) was added and the mixture washed with 2N hydrochloric acid (2 x 50ml) and satd. brine (50ml), dried ($MgSO_4$) and concentrated in vacuo to afford a yellow oil. Flash column chromatography on silica gel (ether/hexane (1:1) as eluent) gave the pyrazole methanol (3a) as a white solid (1.70g, 68%). ^{1}H NMR ($CDCl_3$,250MHz): 0.38-0.60(m,4H,$CHCH_2CH_2$), 0.88(t,3H,$CH_3CH_2CH_2CH_2$), 1.28-1.49(m,3H,$CH_3CH_2CH_2CH_2$ + $CHCH_2CH_2$), 1.55(quin,2H,$CH_3CH_2CH_2CH_2$), 2.55(t,2H,$CH_3CH_2CH_2CH_2$), 3.89(s,2H,CH_2Ar), 4.06(d,2H,CH_2cyclopropyl) 4.55(s,2H,CH_2OH), 7.20-7.80(m,8H,aromatics).

References and Notes

1. Part One; Middlemiss, D.; Ross, B.C.; Eldred, C.; Montana, J.G.; Shah, P.; Hirst, G.C.; Watson, S.P.; Panchal, T.A.; Paton, J.M.S.; Hubbard, T.; Drew, G.M.; Robertson, M.J.; Hilditch, A. and Clark, K.L.; *Biorg. Med. Chem. Lett.*, **1992**, 2, 1243.
2. (a) See for example; Sofer, R.L. and Sen, I. *J. Cardiovasc. Pharamacol.*, 1989, **7**(suppl. 4), S69; and Xie, M.H.; Liu, F.Y.; Wong, P.C.; Timmermans, P.B.M.W.M. and Cogan, M.G. *Kidney Int.*, **1990**, 38, 473. (b) Dudley, D.T. and Hamby, J.M., *Current Opinion in Therapeutic Patents*, **1993**, 3, 581.
3. Cagiano, J.; Rodriguez-Sargent, C. and Martinez-Maldonado, M.; *J.Pharmacol. Exp.Ther.*,**1979**, 208, 310.
4. As systematic nomenclature would be unwieldy the following pyrazole positional nomenclature is used throughout this paper.

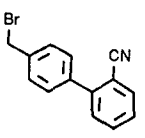


5. CPM = cyclopropylmethyl
6. $t_{1/2}$ = plasma half-life; CL_p = plasma clearance; V_d = volume of distribution; F = oral bioavailability
7. Middlemiss, D.; Watson, S.P.; Ross, B.C.; Dowle, M.D.; Scopes, D.I.C.; Montana, J.G.; Shah, P.; Hirst, G.C.; Panchal, T.A.; Paton, J.M.S.; Pass, M.; Hubbard, T.; Hamblett, J.; Cardwell, K.S.; Jack, T.I.; Stuart, G.; Coote, S.; J. Bradshaw, J.; Drew, G.M.; Hilditch, A.; Clark, K.L.; Robertson, M.J.; Bayliss, M.K.; Donnelly, M.; Palmer, E. and Manchee, G.R.M.; *Biorg. Med. Chem. Lett.*, **1993**,3,589.
8. Middlemiss, D.; Watson, S.P.; Ross, B.C.; Dowle, M.D.; Scopes, D.I.C.; Montana, J.G.; Hirst, G.C.; Panchal, T.A.; Paton, J.M.S.; Hubbard, T.; Stuart, G.; Drew, G.M.; Hilditch, A.; Travers, A.; Robertson, M.J.; Hunt, A.A.E.; Palmer, E. and Manchee, G.R., *Biorg. Med. Chem. Lett.*, in press.
9. Middlemiss, D.; presented at A.C.S. Meeting, Denver, U.S.A., March 1993, Abstract MEDI099; and,Dowle, M.D.; Judd, D.B.; Middlemiss, D.; Scopes, D.I.C.; Ross, B.C.; Pass, M.; Tranquillini, E.; Jack, T.I.; Hobson, J.E.; Panchal, T.A.; Stuart, P.G.; Drew, G.M.; Robertson, M.J.; Hilditch, A.; Clark, K.L.; Travers, A.; Hunt A.A.E.; Manchee, G.R.; Walker, D.G.; Eddershaw, P.J.; Donnelly, M. and Bayliss, M.K.; *Biorg. Med. Chem. Lett.*, in press.
10. *Comprehensive Heterocyclic Chemistry*, Vol. 4; Katritzky, A.R. and Rees, C.W.; Eds., Pergamon Press, Oxford, 1984.
11. Gelin, S.; Deshayes, C. and Chabannet, M., *J. Heterocyclic. Chem.*, **1979**, 16, 1117.
12. Gelin, S. and Dolmazon, R., *J. Heterocyclic. Chem.*, **1982**, 19, 117.
13. It was found to be of paramount importance that pure hydrazines were used in these reactions. The presence of small amounts of hydrazine (NH_2NH_2) leads to the formation of significant quantities of N-unsubstituted pyrazole. Pure hydrazines can be readily prepared as depicted below, a modification of the procedure of Gordon, M.S.; Krause, J.G.; Linneman-Mohr, M.A. and Porchue, R.R.; *Synthesis*, **1980**, 8, 244.



14. Carini, D.J.; Duncia, J.V.; Aldrich, P.E.; Chiu, A.T.; Johnson, A.L.; Pierce, M.E.; Price, W.A.; Santella J.B., III; Wells, G.J.; Wexler, R.R.; Wong, P.C.; Yoo, S.; and Timmermans, P.B.M.W.M. *J. Med. Chem.*, **1991**, 34, 2525, and references therein.
15.

R"Br =



(*Received* 2 *August* 1993; *accepted* 15 *September* 1993)