Bioorganic & Medicinal Chemistry Letters, Vol. 4, No. 1, pp. 127-132, 1994
Printed in Great Britain

0960-894X/94 $6.00 + .00

NEW NON-PEPTIDE ANGIOTENSIN II RECEPTOR ANTAGONISTS. 2: STRUCTURE - ACTIVITY RELATIONSHIPS OF A SERIES OF ANNELATED 2(1H)-PYRIDINONES

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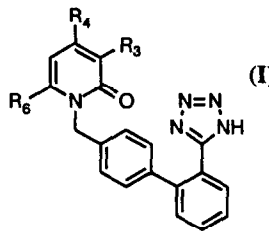
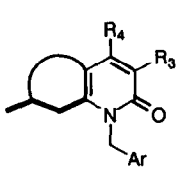
Abstract. The synthesis and angiotensin II antagonist activity of biphenyl tetrazole substituted fused bicyclic analogues of 2-pyridinone is described. Potent antagonist activity was found in the 2-quinolinone, thieno[2,3-b] pyridine and imidazo[c]pyridine series.

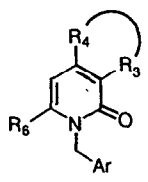
Introduction. In the previous communication in this series[1] we described the discovery of a series of novel angiotensin II antagonists based on the 4-substituted-2-pyridinone structure (I). These compounds showed very potent activity against the effects of angiotensin II both *in vitro* and *in vivo* following intravenous administration. Nevertheless, we aimed to produce compounds with increased potency and longer duration of action following oral dosing. For analogues of (I) with R_4=OH, preliminary pharmacokinetic studies suggested that although fairly well absorbed orally, such compounds are subject to relatively rapid metabolic inactivation. Hydroxylation of the 6-alkyl substituent and conjugation of the hydroxylic 4-substituent were identified as likely primary metabolic routes. As one of several approaches toward increasing the duration of action of these compounds we investigated incorporating these substituents into fused rings as in (A) and (B). Some of these bicyclic compounds have been found to be potent AII antagonists, particularly those derived by fusion of a benzo or thieno ring across the 5,6-bond or an imidazo ring across the 3,4-bond of the pyridinone.



(I) R_3 = H, alkyl, Ph;
R_4 = OH, CO_2H;
R_6 = n-Pr, n-Bu.



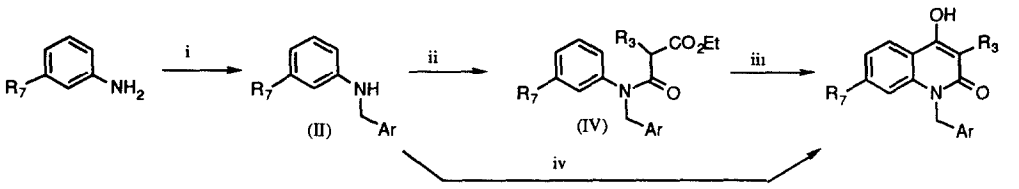
(A)



(B)

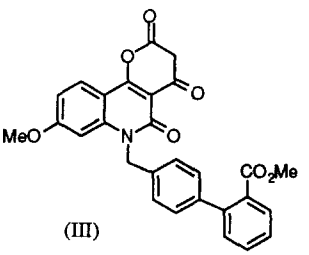
Chemistry

i. Preparation of 5,6-annelated 2-pyridinone derivatives. Two approaches to the construction of the fused bicyclic ring systems were employed. Both involved building a ring onto an existing cyclic system as the key step; the choice of approach was dependent on the nature of the existing ring. To avoid potential regiochemical complexity arising from alkylation of an N-unsubstituted pyridinone (O vs. N alkylation) it was decided to have the pendant biphenylmethyl substituent in place on its N-atom prior to formation of the pyridinone. The route in Scheme 1 was used for quinolones substituted with electron donating substituents in the benzo ring[2]:



Scheme 1. Reagents: i. $ArCH_2Br$ (Ref 3), K_2CO_3, MeCN, Δ; ii. EtO_2CCHR_3COCl, pyridine, CH_2Cl_2, r.t.; iii. heat at 200°C; iv. $R_3CH(CO_2Et)_2$, 220°C ($R_3 \neq H$); (Ar = 2'-carbomethoxy or 2'-cyanobiphenyl-4-yl).

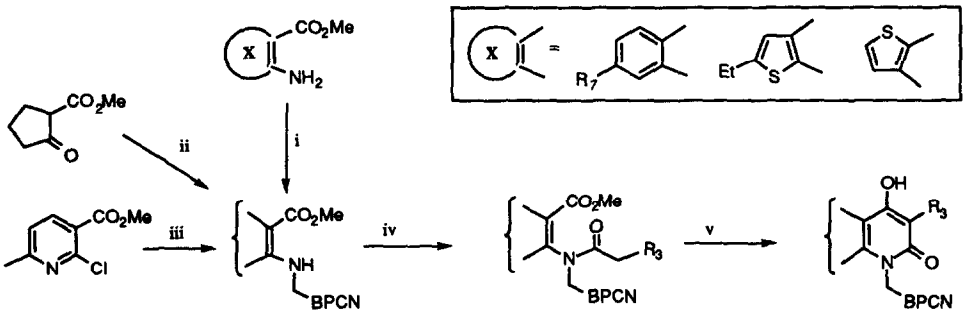
For compounds where $R_3 \neq H$, good results were obtained by the direct thermal interaction of amine (**II**) and an appropriate malonate ester. For R_3 = H complex mixtures were obtained under these conditions. Tricyclic compound (**III**), formally derived from reaction of the required 3-H quinolone (or a reaction intermediate) with excess malonate, was characterised as a major component of one such reaction. (This was an unexpected bonus, since base hydrolysis (NaOH/50% aq. MeOH) of (**III**) provided a fortuitous synthesis of the 3-acetyl analogue (**7**)[cf.2b]). Formation of products of over-reaction such as (**III**) could be suppressed by preforming and cyclizing amidoester (**IV**).



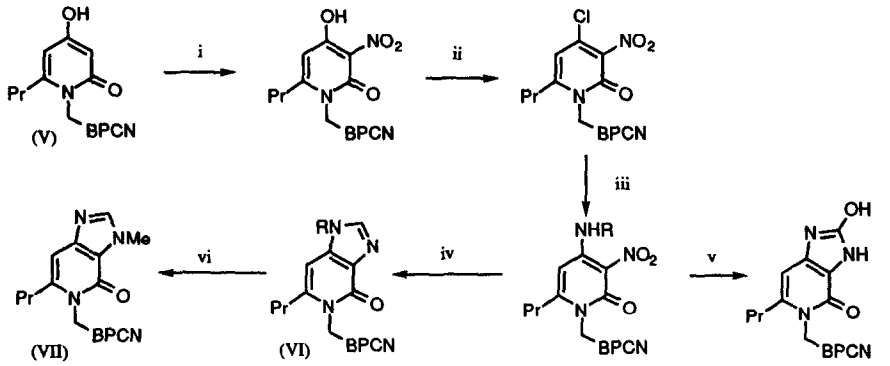
(III)

Pyrido, thieno and cyclopentano derivatives and quinolones with electron withdrawing substituents were made by base-catalyzed cyclisation of the N-acyl derivatives of the appropriate amino esters (Scheme 2)[4].

ii. Preparation of imidazo[4,5-c]pyridinones: In contrast to the 5,6-annelated compounds, these 3,4-annelated derivatives were prepared by starting with an N-substituted 4-hydroxy-2-pyridinone (**V**)[1] and building on the imidazole ring (Scheme 3)[5]. Of particular note is the observation that methylation of the intermediate (**VI**, R=H) gave an N-methylated compound which was not (**VI**, R=Me) (prepared independently by ring synthesis) and therefore must be (**VII**). For all compounds the synthesis was completed either by hydrolysis to the carboxylic acids (**1** - **7**) (for compounds where Ar is 2'-carbomethoxybiphenyl-4-yl)[3] or conversion to the tetrazoles (**8** - **25**) with trimethylstannyl azide (for compounds where Ar is 2'-cyanobiphenyl-4-yl).[3,6]



Scheme 2. Reagents: i. $BPCNCH_2Br$ (Ref 3), K_2CO_3, MeCN, Δ; ii. $BPCNCH_2NH_2$ (Ref 7), MeOH, 20°C; iii. $BPCNCH_2NH_2$, Cu, DMF, 100°C; iv. R_3CH_2COCl, propylene oxide, Bu^tOMe, 50°C; v. (a) $KOBu^t$, Bu^tOMe, 0°C. (b) AcOH, 20°C. (BPCN = 2'-cyanobiphenyl-4-yl)



Scheme 3. Reagents: i. c. HNO_3, AcOH, Δ; ii. $POCl_3$, NEt_3, Δ (Ref 5a); iii. $NH_3(g)$, N-methylpyrrolidone (for R=H) or 40% aq $MeNH_2$, THF (for R = Me); iv. (a) $Na_2S_2O_4$, aq. EtOH, 80°C. (b) $(EtO)_3CH$, Δ (Ref 5b); v. N,N'-carbonyldiimidazole, THF, 20°C (Ref 5c); vi. VI (R=H), NaH, DMF, MeI, 0°C -> 20°C. (BPCN = 2'-cyanobiphenyl-4-yl)

Biology. Results of biological tests are summarized in Tables 1 (biphenyl carboxylates) and 2 (tetrazoles).

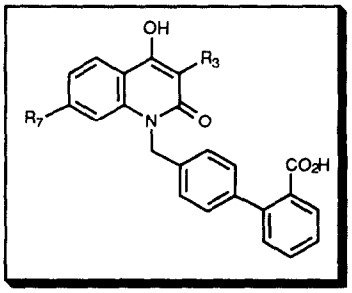
In vitro: Antagonist affinities (pK_B) were calculated using the method of Arunlakshana and Schild.[8] Concentration-response curves to cumulative doses of angiotensin II were established, either with or without preincubation with the test compound, in paired rings of rabbit aorta set up in organ baths containing oxygenated Krebs-Henseleit solution at 37°C with tension measured isometrically. The amount of rightward shift (dose ratio) produced by each of five concentrations of compound was calculated as the ratio of the A_{50} values. The dose ratios were used to calculate the pK_B (with the Schild slope constrained to unity).

In vivo potency (ID_{50}) was calculated as the dose of compound given intravenously which would produce a 50% reduction of an angiotensin II pressor response in normotensive rats. Sub-maximal doses of angiotensin II (0.1μg/kg) were given repeatedly at 5 minute intervals to urethane - anaesthetised rats to establish pressor

responses. A bolus dose of compound was administered i.v. and further doses of AII and test compound were given alternately at 5 minute intervals thereafter to establish a cumulative dose-response curve (5 determinations). Lowest and highest values obtained are quoted.

Results and Discussion. *Quinolinones:* Our initial studies concerned 2-carboxybiphenyl analogues of 2-quinolinone with R_7 substituents selected to occupy (together with the carbons of the benzo ring) roughly the same volume of space as would be occupied by an extended n-butyl group in the parent pyridinone (Table 1):

Table 1: Structures and AII antagonist activities of 2-carboxybiphenyl-4-yl substituted 2-quinolinone derivatives.

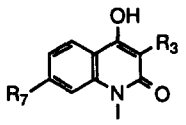
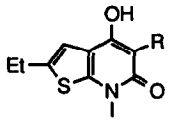
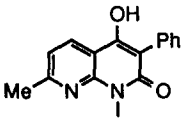
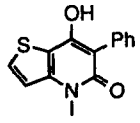
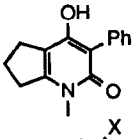
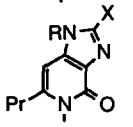
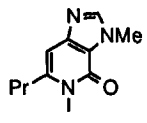


	R_3	R_7	Rabbit aorta (pK_B)*	Inhibn. of AII binding EC_{50} (μM)†
1	H	OMe	6.3	
2	Ph	OMe	6.7	9.5
3	Ph	OEt	7.7	1.8
4	Ph	Et	7.2	
5	n-Bu	OMe	6.6	
6	CH_2Ph	OEt	7.8	
7	$COCH_3$	OMe	6.6	
EXP7711			7.1	2.7

* See Biology section of disscussion for details of test procedures. † In bovine adrenal cortex. (n≥2).
EXP 7711 = 2-butyl-4-chloro-5-(hydroxymethyl)imidazole-1-ylmethyl-4'-biphenylyl-2-carboxylic acid (ref 3)

Many of these quinolones have AII antagonist potency comparable to or greater than that of the DuPont imidazole standard EXP 7711[3] *in vitro*. Some qualitative structure activity trends can be drawn from this table. For R_7 there is a substituent preference for EtO>Et>MeO. Although the 3-unsubstituted compound (**1**) appears definitely inferior to the compounds having substituents in the quinolinone 3 position, the effect of varying R_3 is otherwise practically negligible. A similar lack of sensitivity to the nature of the substituent in the 3-position was noted in the SAR of the 2-pyridinones.[1] Surprisingly, the same SAR does not appear to hold for the biphenyltetrazole substituted 2-quinolinones in respect of the requirements for substituent R_3 (Table 2, **9** - **16**). Here the presence of a phenyl or benzyl substituent in the 3-position appears to have a negative influence on AII antagonist potency in the rabbit aorta screen, while compounds with R_3 = H (**8**) and (**9**) are considerably more effective antagonists, equal or greater in potency to DuP 753. As a result there is no really significant difference in potency between the 2-carboxy and 2-tetrazolyl biphenyl analogues in the 3-phenyl substituted series, while in the 3-unsubstituted case the tetrazoles are 20 - 40 fold more potent than the carboxylic acids. For the R_7 substituent the preference EtO>MeO is also seen in (**8**) and (**9**), but for the compounds with R_3 = Ph there is little substituent preference (even H is acceptable, e.g. **15**), with the exception that SO_2Me is less good in all assays. This is presumably a steric effect since the other highly electron withdrawing substituent, 7-NO_2, does not share this property.

Table 2: Structures and activities of biphenyltetrazole substituted fused 2-pyridone derivatives.

Het			Rabbit aorta AII antagonism (pK_B)*	Anaesthetised rat i.v. (ID_{50} mg/kg)*	Inhibn. of AII binding .EC_{50} (μM)†
	**8**	R_3 = H, R_7 = OMe	8.3	0.33 - 1.08	
	9	R_3 = H, R_7 = OEt	8.9	n.t.	
	10	R_3 = Ph, R_7 = OMe	7.4	2.5	2.2
	11	R_3 = Ph, R_7 = OEt	7.1	0.37 - 1.3	0.5
	12	R_3 = Ph, R_7 = SMe	6.6	n.t.	0.6
	13	R_3 = Ph, R_7 = SO_2Me	5.9	n.t.	~30
	14	R_3 = Ph, R_7 = NO_2	7.5	n.t.	
	15	R_3 = Ph, R_7 = H	7.2	0.7 - 1.2	1.7
	16	R_3 = CH_2Ph, R_7 = H	7.5	n.t.	
	**17**	R = H	9.6	n.t.	
	18	R = Ph	n.c.	2.5 - 5.0	0.09
	**19**		7.0	n.t.	1.25
	**20**		7.4	0.34 - 3.2	6
	**21**		7.2	n.t.	2.4
	**22**	R = H, X = H	9.1	0.05 - 0.18	
	23	R = Me, X = H	7.6	n.t.	
	24	R = H, X = OH	6.4	n.t.	
	**25**		10.2	(<0.3)§	
	DuP 753		8.3	1.2	0.35

n.c. = Non competitive antagonist. n.t. = Not tested. DuP753 is 2-butyl-5-chloro-1-(2'-(5-tetrazolyl)-biphenyl-4-ylmethyl)-4-imidazolemethanol (Ref 3). * See Biology section of discussion for details of test procedures. † In bovine adrenal cortex. § Bolus injection of 0.3mg/kg (**25**) gives >50% inhibition of AII pressor responses lasting up to 90mins post dose.

Other Fused Rings: The thieno[2,3-b]pyridinone (**17**) and imidazo[c]pyridinones (**22**) and (**25**) stand out amongst the other fused rings examined on account of their exceptionally high potency (10 - 100 times that of the standard compound DuP753). The marked difference in affinity between the isomeric methyl compounds (**23**) and (**25**) is particularly significant and suggests either that a specifically directed lone pair of electrons on the heteroatom in the pyridinone 4-position is required for high antagonist potency, or that there is an unfavourable steric interaction of the methyl group in (**23**)[9]. However, none of these compounds showed sufficiently improved duration of action following i.v. dosing relative to monocycles (**I**) to justify extensive study *in vivo*.

Of the other compounds, the 3-phenyl analogue of the thieno-fused system (**18**) is unusual in showing only non-competitive antagonism against AII in the aorta screen at all concentrations tested (10^{-9}M and above). Exactly which structural feature of the molecule is responsible for this behaviour is not entirely clear, as it is not shared by several closely related compounds (the 3-H analogue (**17**), "inverted" compound (**20**) and 3-phenyl-quinolinone (**10**), for example).

Acknowledgements

The authors would like to thank Richard Carr, Lynne Fraser-Rae, Richard Kellett, Sandy Nicol, George Smith Glyn Williams, (Department of Pharmacology), John Unitt and Alan Wallace (Department of Biochemistry) at Fisons Pharmaceuticals, Loughborough for providing the biological data for the compounds described in this paper and also Kay Hallam (Biochemistry) and Dave Robinson (Chemistry) for many constructive discussions.

References and Notes

1. Part 1: J. Bantick et. al. Previous paper in this issue.
2. For similar chemistry see (a) Kappe T.; Karem A.S.; Stadlbauer W. *J. Heterocycl. Chem.*, **1988**, *25*, 857, and references cited therein. (b) Kappe C.O.; Kappe T. *J. Heterocycl. Chem.*, **1989**, *26*, 1555.
3. Carini, D.J.; Duncia, J.V.; Aldrich, P.E.; Chiu, A.T.; Johnson, A.L.; Pierce, M.E.; Price, W.A.; Santella, J.B.; Wells, G.J.; Wexler, R.R.; Wong, P.C.; Yoo, S-E.; Timmermans, P.B.M.W.M. *J. Med. Chem.* **1991**, *34*, 2525. See also E.P. 253310 (DuPont).
4. See, e.g. (a) Ashley, A.N.; Perkin, W.H. jnr.; Robinson, R.; Cromarty A.; *J. Chem. Soc.*, **1930**, 382. (b) Lutz, R.E.; Codington, J.F.; Rowlett, R.J. jnr.; Deinet, A.J.; Bailey, P.S. *J. Amer. Chem. Soc.*, **1946**, *68*, 1810. (c) Proctor, G.R.; Shabbir, M. *J. Chem. Soc. Perkin Trans. 1*, **1972**, 2012.
5. For similar chemistry see (a) Roschger, P.; Fiala, W.; Stadlbauer, W. *J. Heterocycl. Chem.* **1992**, *29*, 225. (b) Kuroda, T.; Suzuki, F. *J. Heterocycl. Chem.*. **1991**, *28*, 2029. (c) Wright W.B. jnr. *J. Heterocycl. Chem.* **1965**, 41.
6. Sisido, K.; Nabika, K.; Isida, T.; Kozima, S.; *J. Organomet. Chem.* **1971**, 337.
7. Ashton, W.T.; Cantone, C.L.; Chang, L.L.; Hutchins, S.M.; Strelitz, R.A.; MacCoss, M.; Chang, R.S.L.; Lotti, V.J.; Faust, K.A.; Chen, T-B.; Bunting, P.; Schorn, T.W.; Kivlighn, S.D.; Siegl, P.K.S. *J. Med. Chem.* **1993**, *36*, 591.
8. Arunlakshana, O.; Schild, H. O. *Br. J. Pharmacol.* **1959**, *14*, 48.
9. cf. the effect of an 8-methyl substituent in the quinazolinone derivatives as described in Allen, E.E.; deLaszlo, S.E.; Huang, S.X.; Quagliato, C.S.; Greenlee, W.J.; Chang, R.S.L.; Chen, T-B; Faust, K.A.; Lotti, V.J. *Biomed. Chem. Lett.* **1993**, *3*, 1293. We thank a referee for alerting us to this work.

(*Received* 6 *August* 1993; *accepted* 21 *September* 1993)