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SUBSTITUTED PIPERIDIN-2-ONE BIPHENYLTETRAZOLES AS ANGIOTENSIN II ANTAGONISTS

W. V. Murray*, P. Lalan, A. Gill, M. F. Addo, J. M. Lewis, D. K. H. Lee, R. Rampulla, M. P. Wachter, J. D. Hsi, D.C. Underwood

The R. W. Johnson Pharmaceutical Research Institute, P. O. Box 300, Route 202, Raritan, New Jersey 08869

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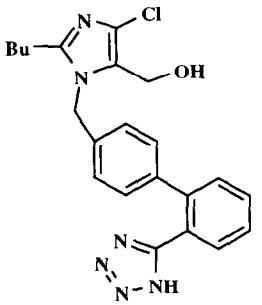
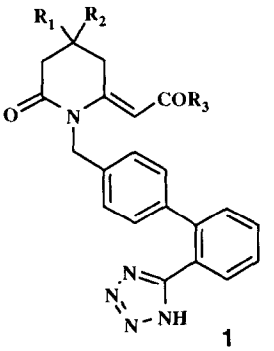
Abstract: A novel series of substituted piperidine-2-ones has been identified as antagonists of angiotensin II. These compounds showed high affinity for the receptor in bovine adrenal cortex binding assays with IC_{50}'s as low as 20nM. They are potent inhibitors of angiotensin II induced contractions in rabbit aortic rings, with pA_2 values as high as 9. A number of these compounds are also orally active as antihypertensives in spontaneously hypertensive rat preparations.

Angiotensin II (AII) is a potent vasoconstricting agent.[1] Angiotensin converting enzyme (ACE) inhibitors such as captopril and enalapril, which inhibit the formation of AII, have been shown to be effective antihypertensive drugs.[2] Receptor antagonists are potentially a more selective way to inhibit the action of AII. A number of groups have reported preparation of AII receptor antagonists.[3] One of these compounds, losartan (DuP 753), is progressing through clinical trials and is the most advanced AII antagonist.[4]

The previously reported AII receptor antagonists have been either substituted imidazoles[5] or tetrazolobiphenyl substituted aromatic heterocycles.[6] Herein we report on a series of aliphatic biphenyltetrazolopiperidinones **1** which are potent AT_1 specific antagonists of angiotensin II.



DuP 753

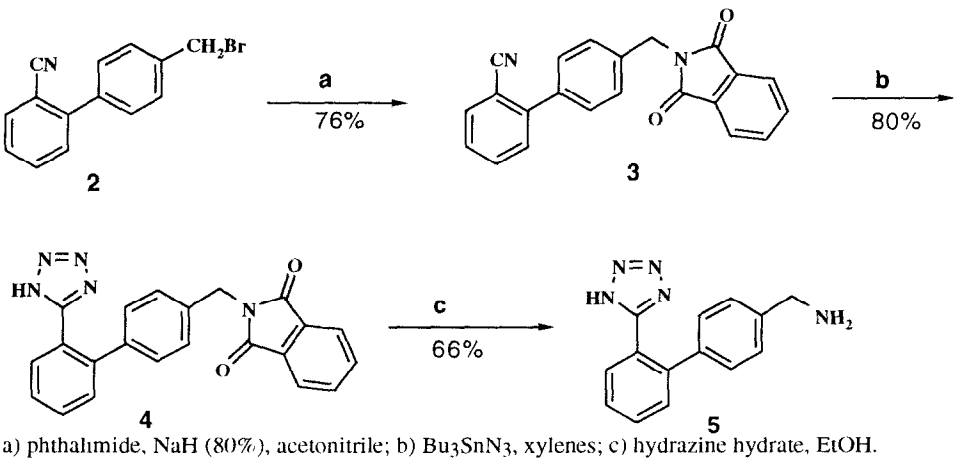


1

The lactam structure **1** requires the synthesis of the aminobiphenyltetrazole **5** (Scheme 1) and the vinylogous cyclic anhydride **8** (Scheme 2). Compound **3** is synthesized in 76% yield by the alkylkation of phthalimide by **2** in the presence of acetonitrile anion. Tetrazole formation **4**, using tributyltinazide formed in situ, is carried out in 80% yield.[7] Deprotection to **5** is achieved by treating **4** with hydrazine in ethanol. Compound **8** is synthesized by the reaction of **7** with a suitable Wittig reagent. The reaction proceeds in 44 - 77% yield and gives

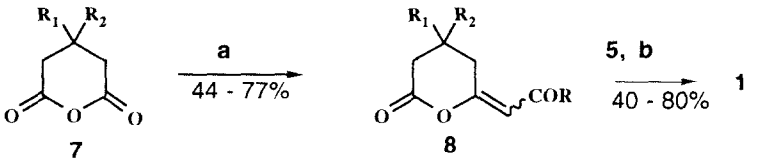
predominantly (> 4:1) the E isomer.[8] The reaction of **8** with **5** proceeds in 40 - 80 % yield and again affords predominantly the E isomer.[9]

Scheme 1



a) phthalimide, NaH (80%), acetonitrile; b) Bu_3SnN_3, xylenes; c) hydrazine hydrate, EtOH.

Scheme 2



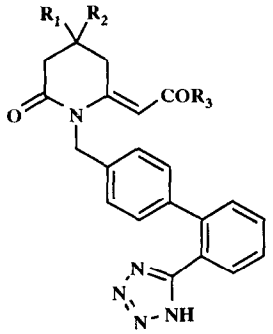
a) $Ph_3P{=}CHCO_2Et$, $CHCl_3$ reflux; b) pyidine or toluene, 40°C - reflux.

The biological data are outlined in Table 1.The pA_2 data is generated by inhibition of angiotensin II induced contaction in thoracic aortic rings from white New Zealand Rabbits. IC_{50} data are determined by displacement of ^{125}I labelled [Sar^1, $Ileu^8$] AII from bovine adrenal cortex membranes.These compounds are potent selective antagonists of AT_1 subtype receptors.[10] Most of the compounds listed have higher binding affinities to the bovine AII receptor than DuP 753.[11] A number also have pA_2's of > 8.0 in the rabbit aortic rings preparation.[12]

It is apparent that the best compounds in the bovine adrenal receptor assay require disubstitution at the 4-position of the piperidinone ring. The 4,4-diethyl (**1c**) and 4-spirocyclohexyl (**1m**) analogs have the highest affinity for the bovine AII receptor. The 4-ethyl-4-methyl (**1b**) analog is the most potent compound in the rabbit aortic rings. Compound **1b** is also an insurmountable AII antagonist in this preparation[13]. Changing R_3 to methoxy to form the methyl ester gives no advantage over the ethyl ester. The corresponding ketone (**1o**), when R_3 is methyl exibits greatly reduced activity.

Compounds **1b**, **1c** and **1m** were chosen for additional evaluation in a spontaneously hypertensive rat model.[14] Both **1b** and **1c** show blood pressure reductions of 45 mm Hg with durations of 24h in the SHR which are identical to that of DuP 753 at comparable doses.[15] Compound **1m** has comparable potency and activity to DuP 753 with half of its duration of action.

Table 1



(#)[16]	R1	R2	R3	IC50 nM[17]	pA2 (95% confidence)
1a	Me	Me	OEt	5800	7.4 (6.7 - 8.0)
1b	Me	Et	OEt	250	9.0 (7.8 - 10.1)
1c	Et	Et	OEt	20	8.1 (7.6 - 8.5)
1d	Me	H	OEt	200	6.9 (5.7 - 8.1)
1e	Me	n-butyl	OEt	470	7.5 (6.6 - 8.3)
1f	Et	n-butyl	OEt	180	7.0 (6.5 - 7.4)
1g	n-propyl	n-propyl	OEt	330	7.4 (7.2 - 7.6)
1h	Me	n-propyl	OEt	120	7.5 (7.4 - 7.6)
1i	Me	i-propyl	OEt	120	7.8 (7.2 - 8.3)
1j	Et	n-propyl	OEt	90	7.9 (7.2 - 8.6)
1k	Me	n-pentyl	OEt	680	7.0 (6.8 - 7.1)
1l	-cyclopentyl-		OEt	540	7.9 (7.1 - 8.6)
1m	-cyclohexyl-		OEt	40	8.3 (7.7 - 8.8)
1o	Et	Et	Me	3100	6.8 (6.2 - 7.4)
1p	Me	Et	OMe	320	8.6 (8.0 - 9.3)
1q	Et	Et	OMe	210	8.4 (8.3 - 8.5)
DuP 753				420	8.8 (8.5 - 9.3)

In conclusion we have discovered a novel series of potent AT_1 selective AII antagonists which are orally active antihypertensives. Compound **1b**, RWJ 46458 is undergoing expanded evaluation as a potential development candidate.

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9. In each case compound **1a-q** is isolated and tested as its pyridinium salt
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11. a)The receptor binding assay for AT-1 receptor subtype was performed using the scintillation proximity assay (SPA) technology as commercialized and described by Amersham, technical brochure NK-8981.
    b) Determination of AT_2 binding was carried out by displacement of ^{125}I labelled [Sar^1, $Ileu^8$] AII from bovine cerebellum membranes using the system purchased from DuPont NEN (brochure NED-001A). None of the

compounds described in this text showed significant binding to the AT2 receptor at 10 micromolar concentration.

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13. Insurmountable antagonists demonstrate a concentration dependent saturable depression of the upper assymtote of the AII concentration effect curve. See Wong, P. C., Timmermans, P. B. M. W. M. *J. Pharmacol. Exp. Ther.* **1991**, *258*, 49. and references there in.
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15. Doses tested were 10 and 30 mg/kg po. A maximal blood pressure reduction for AII antagonists in this preparation is between 45 and 50 mm Hg.
16. The compounds tested were the purified E isomers. Where a chiral center exists in the piperidone ring, only the racemate was tested.
17. Standard errors for triplicate assays were less than 10% in all cases.