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SUBSTITUTED PYRROLIDIN-2-ONE BIPHENYLTETRAZOLES AS ANGIOTENSIN II ANTAGONISTS

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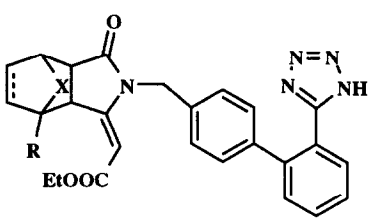
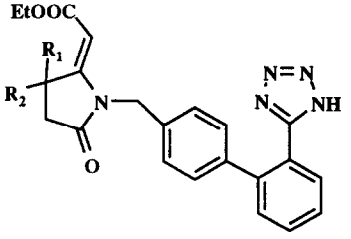
Abstract: A novel series of substituted pyrrolidin-2-ones has been identified as antagonists of the angiotensin II receptor. They are potent inhibitors of angiotensin II induced contractions in rabbit aortic rings, with pA_2 values as high as 9. A number of these compounds have been tested in rabbit adrenal cortex binding assays and exhibited IC_{50}'s as low as 60nM. Compounds **1e**, **1f** and **2e** have been found to be orally active as anti-hypertensives in spontaneously hypertensive rat preparations.

Angiotensin II (AII) is a potent vasoconstricting agent.[2] Angiotensin converting enzyme (ACE) inhibitors such as captopril and enalapril, which inhibit the formation of AII, have been shown to be effective antihypertensive drugs.[3] Receptor antagonists are potentially a more selective way to inhibit AII. A number of groups have reported the preparation of AII receptor antagonists.[4] Losartan (DuP 753) is in phase 3 clinical trials and is the most advanced AII antagonist.[5]

We have recently reported on a series of piperidine-2-one AII antagonists.[6] Herein we describe a series of biphenyltetrazolopyrrolidin-2-ones **1** and **2** which are potent antagonists of angiotensin II.[7]



1

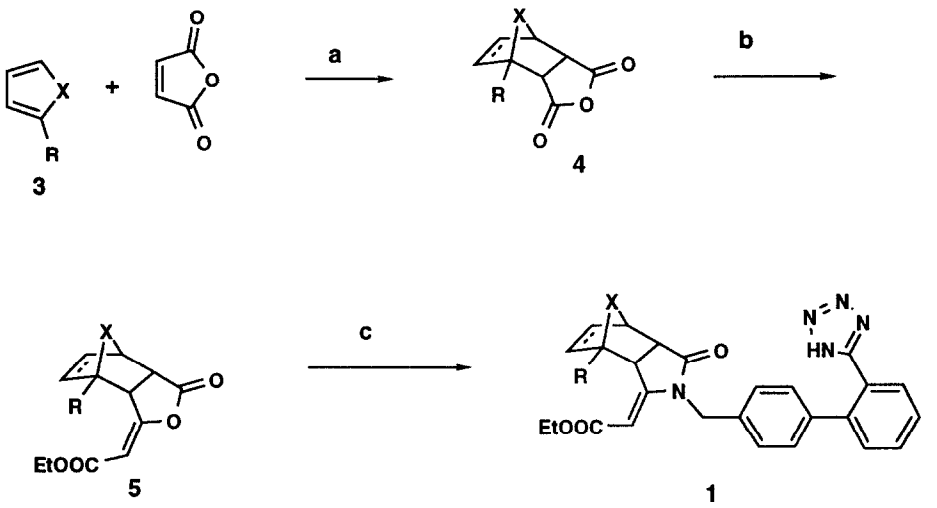


2

The synthesis of compound **1** is outlined in Scheme 1. Diels Alder reaction of an appropriate diene with maleic anhyride affords the desired cyclic anhydride **4** in good yield. All of the Diels Alder reactions with cyclic dienes yield endo addition products except when the diene is furan. In this case only the exo product is observed. Compound **5** is then formed by a Wittig reaction of **4** with (carbethoxymethylene)triphenylphosphorane. The predominant product of this reaction is the E isomer.[8] In the synthesis of **1c**, addition of the Wittig reagent occurs only at the carbon closer to the bridgehead methoxy group. This is probably due to steric hindrance in the approach of the

nucleophile.[9] The 2-[(4-aminomethyl)phenyl]phenyltetrazole used in Schemes 1 and 2 is synthesized by a route we described previously.[6] The acylation/cyclization to **1** also gives predominantly the E isomer.[10]

Scheme 1

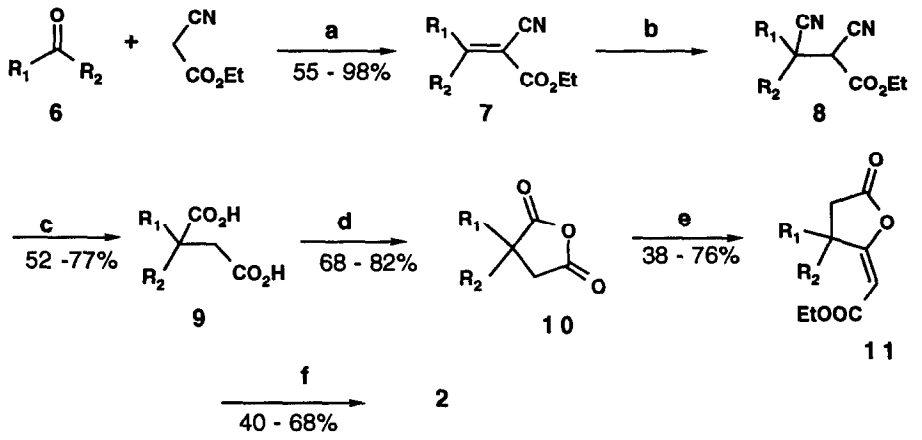


a) toluene reflux, b) (carbethoxymethylene)triphenylphosphorane, $CHCl_3$ reflux, c) 2-[(4-aminomethyl)phenyl]phenyltetrazole, pyridine 40 - 100°C, 4A sieves.

Synthesis of **2** involves preparation of nonsymmetric succinic anhydrides **10** (Scheme 2).[11] This is carried out by a Knoevenagel condensation of **6** with ethyl cyanoacetate. The condensate **7** then undergoes a Michael addition to form **8** which is hydrolyzed and decarboxylated to **9**. Dehydration with acetic anhydride affords **10** in good to excellent overall yield. Wittig reaction of **10** as above affords predominantly the E isomer of **11**.[12] No reaction takes place at the other carbonyl presumably due to steric hindrance toward the approaching nucleophile as above.[9] Acylation and cyclization afford predominantly the E isomer of **2** in good yield.[13]

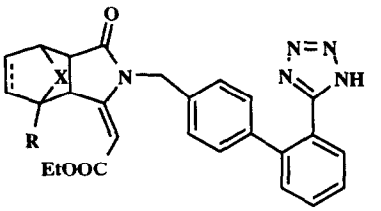
The biological activity of **1** is outlined in Table 1. The pA_2 data is generated by inhibition of AII induced contraction in rabbit aortic rings.[14] Unsaturation seems to play a minor role except when comparing **1a** and **1d**. This could be due to a destabilizing effect of the additional two sp^2 centers in the 2:2:1 fused lactam. This may accelerate either hydolysis or metabolism. It also seems that smaller bridgeheads i.e. CH_2 or $(CH_2)_2$ are favored, potentially due to an optimal lipophilicity. All of these compounds are potent surmountable inhibitors of AII induced contraction in rabbit aortic rings.Compound **1a** is equipotent to DuP 753 in this preparation.

Scheme 2



a) $NH_4OAc/HOAc$, b) $KCN/EtOH/H_2O$ c) HCl, combined yield shown for b & c, d) Ac_2O, e) carbethoxymethylidenetriphenylphosphorane, f) 2-[(4-aminomethylphenyl)phenyltetrazole, pyridine 40 - 100 °C, 4 A sieves.

Table 1

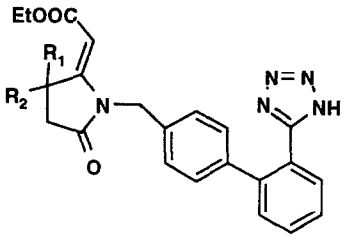


#	R	X	saturated	pA_2[14]
1a	H	CH_2	+	9.0
1b	H	CH_2CH_2	-	8.2
1c	OCH_3	CH_2CH_2	-	8.3
1d	H	CH_2	-	8.4
1e	H	CH_2CH_2	+	8.0
1f	H	$(CH_2)_3$	+	7.7
1g	H	$(CH_2)_3$	-	7.4
1h	H	O	+	8.4
1i	H	diphenylmethylidene	+	< 6.0
1j	H	dimethylmethylidene	+	6.6
1k	H	no bridgehead	+	8.4
1l	H	no bridgehead	-	7.5
DuP 753				8.8

The biological data for **2** are shown in Table 2. The binding data is generated in a bovine adrenal cortex membrane preparation specific for AT_1 antagonists.[15] Disubstitution at the 4-position of the pyrrolidin-2-one is favored. Each of these disubstituted compounds has a higher affinity for the bovine adrenal AT_1 receptor than DuP 753. It also seems that the less rigid geminial disubstituted compounds **2c**, **2d** and **2e** have better binding properties than the more rigid spirocyclopentyl **2a**.

The spirocycles **2a,b** and **c** approach the potency of DuP 753 in inhibiting AII induced contraction of rabbit aortic rings. We observed an interesting trend when testing **2a,b** and **c** in aortic rings. We found **2a** to be a competitive antagonist, **2b** was partially insurmountable and **2c** was an insurmountable AII antagonist.[16] This would suggest that there are stringent structural requirements for the internalization of receptor believed to cause the insurmountability in AII preparations.[17]

Table 2



#	R_1	R_2	pA_2[14]	IC_{50} (nM)[15]
2a	--spirocyclopentyl--		8.5	250
2b	--spirocyclohexyl--		7.9	140
2c	--spirocycloheptyl--		8.4	60
2d	Me	Et	7.6	60
2e	Et	Et	7.9	100
2f	H	Me	6.5	3100
DuP 753			8.8	425

Three analogs, **1e**,**1f** and **2c** were found to have oral antihypertensive activity in spontaneously hypertensive rat preparations.[18] Compound **1e** has similar maximal activity and duration to DuP 753 but is approximately 1/3 as potent. Compounds **1f** and **2c** have similar activity and potency to **1e** with approximatly 1/2 the duration of activity. The reduced oral activity could be due to lower bioavailability of these compounds. We are presently examining ways to improve the oral profile of these compounds.

We have discovered a novel series of AII antagonists. Three of these compounds have also shown oral antihypertensive effects in vivo. Compounds **1e** and **2c** are undergoing expanded biological profiling.

References and Notes

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   c) present address SmithKline Beecham Pharmaceuticals, P.O. Box 1539 King of Prussia Pa.
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b)General Procedure: Rabbit aortic rings are suspended from a Gould isotonic force transducer in a tissue bath. Graded angiotensin II doses are given cumulatively to achieve a maximal contraction.The test compound is then given to separate rings at different antagonist concentrations (n=2 rings/test concentration) in order to asses antagonist dose-response. The angiotensin II cumulative dose-response is then repeated in the presence of the test compound. Angiotensin II vasoconstrictor tension is expressed as a percent of maximal contraction for the before and after test compound angiotensin II dose-responses. Angiotensin II ED_{50} is determined from the angiotensin II dose-response curves generated before and after test compound. A Schild plot is constructed by plotting log (angiotensin II ED_{50} after antagonist/ED_{50} before antagonist - 1) vs. -log(antagonist concentration). A pA2 is calculated from the Schild plot regression line at y=0.
15. 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) General procedure: Drug or buffer, ^{125}I-[Sar^1,Ile^8]-angiotensin II , adrenal cortex membrane receptor preparation; assay buffer and microspheres containing scintillant (SPA beads) were introduced into miniscintillation vials. The vials were shaken (18-20 hrs) at r.t. The vials were then counted in a liquid scintillation counter. Non-specific binding was defined by at least 1000 fold excess of nonlabeled [Sar^1,Ile^8]-angiotensin or human angiotensin II, and was substracted from all other counts to obtain specific binding. Receptor binding is expressed as a ratio of specific counts bound in the presence of test compounds to the specific counts bound in the absence of test compounds. The IC_{50} value is the concentration of test compound that gives rise to 50% inhibition, and was determined from at least 8 concentration points spanning the IC_{50} value. Each value is the average of at least 5 determinations.
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