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Synthesis and *In Vitro* Evaluation of Fused Ring Heterocycle-Containing Angiotensin II Antagonists.

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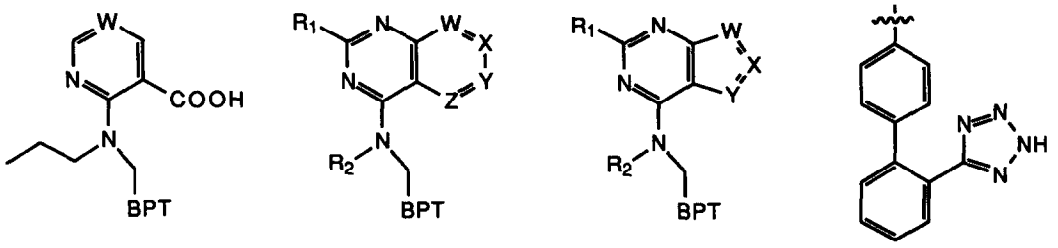
Abstract: Fused ring heterocyclic analogs of **A-81080** ($pA_2 = 9.9$) were synthesized and their activities in the rabbit aorta *in vitro* assay were measured. The best compounds ($pA_2 = 8.6$) in series **1** had R_1 = Et, R_2 = H, W = X = Z = C-H, and Y = C-OMe or C-COOH. In series **2**, the best compound ($pA_2 = 8.3$) had R_1 = Et, R_2 = H, W = N-Me, X = C-H, and Y = N.

Recently a series of orally active, non-peptide angiotensin II antagonists have been disclosed for use in the control of hypertension and related illnesses.[1] Pyrimidine **A-81080** ($pA_2 = 9.93$) and the pyridine analog **A-81988** (pA_2 = 10.3) are extremely potent antagonists of the AT_1 receptor and moreover, **A-81988** normalized blood pressure in renal artery-ligated rats at a dose of 0.3 mg/kg p.o.[1,2] Having demonstrated the importance of this new class of antagonists, we then prepared analogs in which the pyrimidine or pyridine ring was replaced with a variety of heterocycles.[3] This letter describes analogs of **A-81080** in which the six membered ring heterocycle has been expanded into a series of fused ring heterocyclic structures (Figure 1).



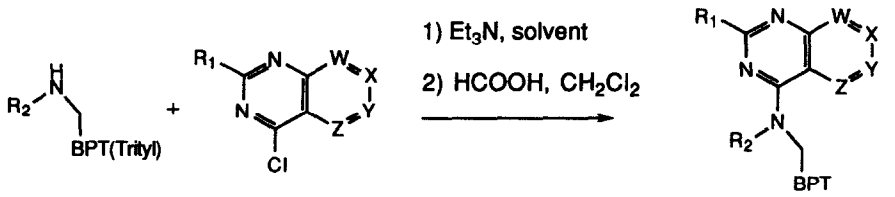
W = N: A-81080
W = CH: A-81988

1 **2** **BPT**

Figure 1

Chemistry: A general synthesis of the fused ring analogs is illustrated in Scheme 1. The condensation of trityl protected biphenyltetrazole **3** [1] with chloroheterocycle **4** [4] gave a trityl protected intermediate, which was then detritylated under acidic conditions (formic acid or HCl/THF) to provide the 6,6-fused ring analogs of general structure **1**.[5] Similar chemistry also afforded the 6,5-fused ring analogs of general structure **2**.

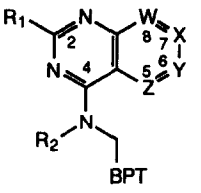
‡ This paper is dedicated to Professor Richard K. Hill on the occasion of his 65th birthday.



3 **4** **Scheme 1** **1**

***In Vitro* Pharmacology:** The pA_2 values for the final compounds were determined using rabbit aortic rings according to the method published by Chiu,et al., [6] and in all cases, duplicate determinations were made for each entry. The *in vitro* data for the 6,6-fused ring compounds are listed in Table 1. Entries 1-11 describe analogs in which the exocyclic nitrogen is substituted (as in **A-81080**) with a propyl or butyl group (R_2= n-Pr or n-Bu) and position 2 of the bicyclic ring is unsubstituted (R_1=H). Several of these analogs (entries 9 and 10) were moderately potent. However, their activity was almost 100-fold less than the best monocyclic antagonists. In this series of compounds (R_2 = alkyl), a carboxyl group at position 6 of the bicyclic ring (entries 9 and 10) was essential for activity. A carboxyl group at position 7 (entry 11) lead to a slightly less potent antagonist, and any substitution at position 5 (entries 3-5) afforded compounds that were devoid of activity.

Table 1

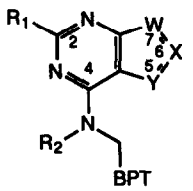


Entry	R_1	R_2	W	X	Y	Z	pA_2 (n = 2)
1	H	n-Bu	CH	CH	CH	N	6.11
2	H	n-Bu	N	CH	CH	N	6.94
3	H	n-Pr	CH	CH	CH	C-OMe	< 7
4	H	n-Pr	CH	CH	CH	C-COOMe	< 7
5	H	n-Pr	CH	CH	CH	C-COOH	< 7
6	H	n-Bu	CH	CH	C-OH	CH	7.06
7	H	n-Bu	CH	CH	C-OMe	CH	7.32
8	H	n-Bu	CH	CH	C-COOMe	CH	6.97
9	H	n-Bu	CH	CH	C-COOH	CH	8.02
10	H	n-Bu	CH	CH	C-COOH	N	8.19
11	H	n-Bu	CH	C-COOH	CH	CH	7.45
12	Et	H	CH	CH	CH	CH	8.53
13	Et	H	CH	CH	CH	C-OMe	8.07
14	Et	H	CH	CH	C-OMe	CH	8.58
15	Et	H	CH	CH	C-COOH	CH	8.59
16	Et	Me	CH	CH	C-OMe	CH	7.32
17	DUP-753						8.43

Entries 12-15 describe compounds in which the exocyclic nitrogen is unsubstituted (R_2= H) and the alkyl group is moved to position 2 (R_1= Et). These compounds are slightly more potent than those described in entries 1-11. Moreover, activity in this series of antagonists is virtually the same, regardless of the substitution pattern on the second ring. The unsubstituted analog (entry 12) is equipotent to the 6-methoxy or 6-carboxy analogs (entries 14 and 15). Entry 16 describes a compound in which the exocyclic nitrogen (R_2 = Me) and position 2 (R_1 = Et) were both substituted. In this case, the compound was greater that 10-fold less active than the corresponding NH (R_2 = H) analog (entry 14). A similar drop in activity was also seen in a related series of nitrogen linked 1,5 naphthyridines (data not shown).

The *in vitro* data for the 6,5-fused ring compounds are listed in table 2. Entries 1-19 describe analogs in which the exocyclic nitrogen is substituted with a butyl or propyl group (R_2 = n-propyl or n-butyl). This series was relatively insensitive to substitution at position 7 (entries 1-5), and for ease of synthesis most of the remaining compounds carried a methyl group at this position. Any group larger than methyl at position 6 (entries 6-13) decreased activity as did substitution at position 5 (entries 14 and 15). Heteroatom substitution (O for N) at position 7 (entry 17) or interchange (N to C and C to N) at positions 5 and 6, respectively, (entry 21) also resulted in less potent antagonists. Finally, moving the alkyl substitutent from the exocyclic nitrogen to position 2 (cf entries 3 vs. 20 and 19 vs. 21) had little effect on *in vitro* potency.

Table 2



Entry	R_1	R_2	W	X	Y	pA_2 (n = 2)
1	H	n-Pr	NH	CH	N	7.92
2	H	n-Bu	NH	CH	N	8.17
3	H	n-Bu	N-Me	CH	N	8.08
4	H	n-Pr	N-CH_2COOH	CH	N	8.14
5	H	n-Pr	N-CH_2Ph	CH	N	6.82
6	H	n-Bu	NH	C-Me	N	8.11
7	H	n-Bu	N-Me	C-Me	N	8.03
8	H	n-Bu	N-Me	C-Et	N	7.52
9	H	n-Bu	N-Me	C-Ph	N	< 7
10	H	n-Bu	N-Me	C-CN	N	7.14
11	H	n-Bu	N-Me	C-$CONH_2$	N	< 7
12	H	n-Bu	N-Me	C-SOMe	N	7.38
13	H	n-Bu	N-Me	C-SO_2Me	N	< 7
14	H	n-Pr	N	CH	N-Me	6.03
15	H	n-Pr	N	CH	N-CH_2COOH	7.13
16	H	n-Bu	N-Me	C-O	NH	7.53
17	H	n-Pr	O	C-Me	N	7.01
18	H	n-Bu	N-Me	N	N	7.97
19	H	n-Pr	NH	N	CH	6.47
20	Et	H	N-Me	CH	N	8.29
21	Et	H	NH	N	CH	6.86

Discussion: The antagonists described in this letter can be divided into two classes. The first class has an ethyl group at C-2 (R_1 = Et) and an unsubstituted exocyclic nitrogen (R_2 = H). These compounds are moderately potent (pA_2 = 8.1 to 8.6) and their potency is relatively insensitive to functional group changes in other parts of the molecule. Compounds in the pyrimidine series having the same substitution pattern (data not shown) [2] are also relatively insensitive to functional group changes and they have pA_2 values similar to the fused ring analogs. The second class of antagonists are unsubstituted at C-2 (R_1 = H) and have an alkyl substituted exocyclic nitrogen (R_2 = n-Pr or n-Bu). Several of these compounds are moderately potent (pA_2 about 8.2) and unlike the analogs described above, these compounds are extremely sensitive to changes in other parts of the molecule. A similar sensitivity to functional group changes and substitution pattern was also seen in the **A-81080** (pA_2 = 9.9) series. Therefore, the lack of potency seen in the fused ring analogs is likely due to an inability to accurately mimic the highly optimized structure presented in **A-81080** and related compounds.

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2) Winn, M. ; De, B. ; Zydowsky, T. M. ; Altenbach, R. J. ; Basha, F. Z. ; Boyd, S. A. ; Brune, M. E. ; Buckner, S. A. ; Crowell, D. ; Drizin, I. ; Hancock, A. A. ; Jae, H-S. ; Kester, J. A. ; Lee, J. Y. ; Mantei, R. A. ; Marsh, K. C. ; Novosad, E. I. ; Oheim, K. W. ;Rosenberg, S. H. ; Shiosaki, K. ; Sorensen, B. K. ; Spina, K. ; Sullivan, G. M. ;Tasker, A. S. ; von Geldern, T. W. ;Warner, R. B. ; Opgenorth, T. J. ; Kerkman, D. J. ; DeBernardis, J. F. *J. Med. Chem.*, **1993**, (in press)

3) This strategy serves to expand patent protection and in some literature examples, it has resulted in compounds with improved pharmacological profiles. For a recent literature summary see Buhlmeyer, Peter. *Current Opinion in Therapeutic Patents*, **1992**, 2, 1693.

4) After this work was completed, a patent describing AII antagonists similar to **1** was published. However, no *in vitro* data was included in the patent. Primeau, J. L. ; Garck, L. M. US Patent 5,187,168, February 16, 1993.

5) a: See Baker, B. R. ; Schaub, R. E. ; Joseph, J. P. ; McEvoy, F. J. ; Williams, J. H. *J. Org. Chem .*, ***1952***, 141, for a general synthesis of the 4-chloroquinazolones. b: See Montgomery, J. A. ; Temple, C. *J. Org. Chem.*, **1960**, 395 and Yamazaki, A. ; Kumashiro, I. ; Takenishi, T. *J. Org. Chem. , **1967***, 3258 for a general synthesis of the 2 and 6 substituted purines.

6) All final compounds were fully characterized, including elemental analysis and/or high resolution mass spectra.

7) Chiu, A. T. ; Carini, D. J. ; Johnson, A. L. ; McCall, D. E. ; Price, W. A. ; Thoolen, J. M. C. ; Wong, P. C. ; Taber, R. I. ; Timmermans, P. B. M. W. M. *Eur. J. Pharmacol.*, **1988**, 13.

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