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5-MEMBERED RING HETEROCYCLIC CARBOXYLIC ACIDS AS ANGIOTENSIN II ANTAGONISTS

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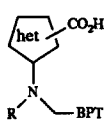
Abstract: A series of 5-membered ring heterocyclic analogs of A-81988 were synthesized in order to determine their activity as angiotensin II antagonists. The activity of these compounds in a rabbit aorta *in vitro* assay ranged from pA_2 values of <6 to 9.3, with the thiazole, thiadiazole and triazole heterocycles being more potent A-II antagonists than the imidazole and pyrazole derivatives. The best activity was seen with the triazole **9b** which had a pA_2 of 9.3.

The renin angiotensin system (RAS) is known to play a prominent role in cardiovascular regulation. The success of angiotensin converting enzyme (ACE) inhibitors as antihypertensives has led to intense research by pharmaceutical companies on angiotensin II (A-II) antagonists as alternative inhibitors of the RAS. In 1990, a group of Abbott scientists initiated an A-II project using the DuPont A-II antagonist (DUP-753)[1] as the starting point for further modifications. The result of this work was the discovery of molecules having a 6-membered heterocyclic carboxylic acid linked to the biphenyl tetrazole (BPT) by a unique aminomethylene spacer. These compounds had excellent *in vitro* activity and A-81988 was demonstrated to be an extremely potent, orally active A-II antagonist.[2]

The discovery of A-81988 spurred the investigation of a series of compounds (**1**) in which the pyridine ring, characteristic of the A-81988 class, was replaced with various 5-membered ring heterocycles. The carboxylic acid side chain of the heterocycle and the aminomethylene BPT portion of the molecule remained constant. This article describes the synthesis and biological activity of these 5-membered ring heterocyclic A-II antagonists.

Figure 1.



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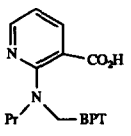
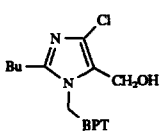
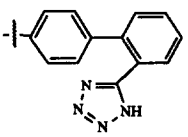


A - 81988



DUP-753



-BPT

Biology

The *in vitro* pA_2 values for the final heterocyclic carboxylic acids (Table 1) were determined by the method of Chiu et al.[3] with the exception that rabbit aortic rings were used instead of rabbit aortic strips.

Table 1 shows that the antagonists bearing two heteroatoms in the heterocycle had pA_2 values of less than 8 with the exception of select thiazole derivatives **5**, **6a** and **6e**. In the thiazole series, a comparison of the 5-aminothiazole **5** and the 2-amino counterpart **6e** indicated the 2-amino derivative to be slightly more potent. The 2-aminothiazoles were the only 5-membered ring heterocyclic systems studied in which the carboxylic acid side chain was positioned meta to the exocyclic nitrogen linkage. This meta positioning of the acid in the thiazole series had no negative effect on potency. A similar positioning of the acid in a 6-membered ring analog (4-amino-6-carboxypyrimidine) lowered the potency 15 fold. The corresponding compound in the pyridine (A-81988) series was not prepared. SAR analysis of the 2-aminothiazoles indicated that a methyl at the 4-position of the thiazole ring was preferred over a hydrogen, CF_3 or an n-propyl substituent (see **6a-d**). At the exocyclic nitrogen position, a tertiary amine was neccessary for activity (compare **6d** to **6g**). A comparison of tertiary amines indicated the n-butyl side chain was preferential to a n-propyl or n-hexyl.

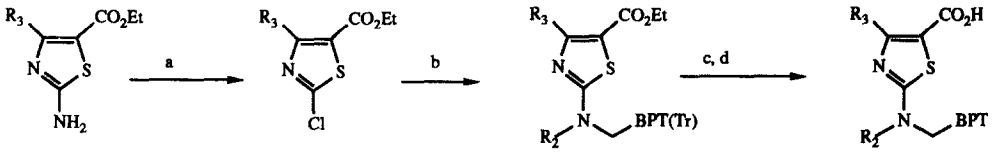
The heterocycles containing three heteroatoms had much better A-II antagonist potency with pA_2 values ranging from 8.3 to 9.3. A limited SAR of the triazole series showed that an isobutyl group was preferred over a methyl or n-butyl group at the 1-position. The N-isobutyl derivative **9b** was the most potent 5-membered antagonist prepared with a pA_2 of 9.29.

Chemistry

The compounds listed in Table 1 were prepared by linking the desired heterocycle [4] to a trityl protected biphenyl tetrazole derivative by one of two general methods. The resulting products were detritylated under acidic conditions to give the unprotected tetrazoles, and the carboxylic esters were then hydrolyzed with base to give the final acids (Table I).

The first general coupling method (illustrated in Scheme 1) involved displacing a reactive halogen on the heterocycle with the appropriate aminomethyl BPT(Tr) which, in turn was prepared from the known bromomethyl biphenyl tetrazole.[5] This coupling method was used to prepare the 5-carboxylate thiazoles **6a-6h** and the thiadiazoles **7** and **8**.

Scheme 1. [a]



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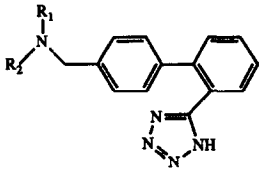
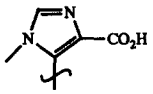
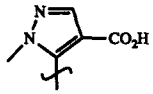
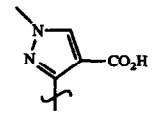
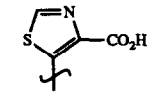
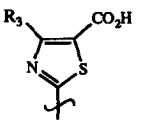
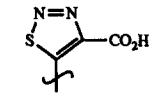
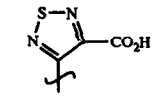
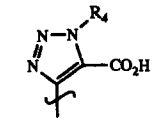
[a] Reagents: (a) t-BuONO, $CuCl_2$, MeCN, Δ; (b) R_2NH-CH_2BPT(Tr), i-Pr_2NEt, DMF, Δ; (c) p-TsOH, THF, Δ; (d) aq NaOH, 40 °C.

The second general coupling method (Scheme 2) involved a sequential alkylation of the appropriate amino heterocycle. The primary amine was first reacted with a bis(trimethylsilyl)amide base and then with an alkyl

Table 1. *In Vitro* Activity of 5-Membered Heterocycle-BPT Angiotensin II Antagonists.

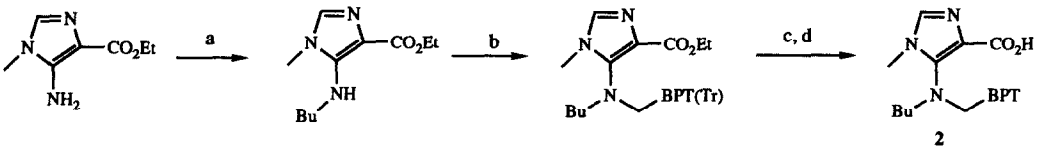


Compd	R_1	R_2	pA_2[a]	n
2		n-Bu	6.46 (0.01)	2
3		n-Bu	< 7.0 ND	2
4		n-Pr	7.94 (0.07)	2
5		n-Bu	8.20 (0.17)	2
		R_3		
6a		Me	n-Pr	8.63 (0.02)	2
6b		n-Pr	n-Pr	7.43 (0.00)	2
6c		CF_3	n-Pr	7.56 (0.06)	2
6d		H	n-Pr	7.87 (0.05)	2
6e		H	n-Bu	8.80 (0.06)	4
6f		H	n-Hex	7.34 (0.04)	2
6g		H	H	< 6.0 ND	2
6h		n-Pr	H	< 6.0 ND	2
7		n-Bu	8.36 (0.01)	2
8		n-Pr	9.00 (0.06)	2
		R_4		
9a		Me	n-Bu	8.60 (0.01)	2
9b		i-Bu	n-Bu	9.29 (0.01)	2
9c		n-Bu	n-Bu	8.86 (0.23)	4

[a] pA_2 in rabbit aorta (standard error), n = no. of determinations for estimated pA_2.
ND = not determined.

halide to give the desired secondary amine. This product was then alkylated with the bromomethyl BPT(Tr) using an amide base and DMPU to yield the tertiary amine. Detritylation followed by ester hydrolysis gave the final products. This second method was used to prepare the imidazole **2**, pyrazoles **3** and **4**, the 4-carboxylate thiazole **5** and the triazoles **9a-9c.**

Scheme 2. [a]



2

[a] Reagents: (a) $NaN(TMS)_2$, n-BuI, THF, 0 °C; (b) $LiN(TMS)_2$, $BrCH_2BPT(Tr)$, DMPU, THF, 0-25 °C; (c) AcOH/THF/H_2O(15:15:1), Δ; (d) aq KOH or NaOH, 40°C.

Summary

A series of 5-membered ring heterocyclic analogs of A-81988 were prepared to evaluate their activity as angiotensin II antagonists. The heterocycles bearing three heteroatoms in the ring were more potent antagonists than those with two heteroatoms. The *in vitro* activity of these A-II antagonists compared favorably to A-II antagonists reported in the literature.[1,6]

References and Notes

1. Duncia, J.V; Carini, D.J.; Chiu, A.T.; Johnson, A.L.; Price, W.A.; Wong, P.C.; Wexler, R.R.; Timmermans, P.B.M.W.M. *Medical Research Reviews*, **1992**, *12*, 149-191.
2. De, B.; Winn, M.; Zydowsky, T.; Kerkman, D. J.; DeBernardis, J.F; Lee, J.; Buckner, S.; Warner, R.; Brune, M.; Hancock, A.; Opgenorth, T.; Marsh, K. *J. Med. Chem.* **1992**, *35*, 3714-3717.
3. Chiu, A.T.; Carini, D.J.; Johnson, A.L.; McCall, D.E.; Proce, W.A.; Thoolen M.J.M.C.; Wong, P.C.; Taber, R.I.; Timmermans, P.B.M.W.M. *Eur. J. Pharmacology*, **1988**, *157*, 13-21.
4. For the synthesis of heterocyclic precursors see the following: precursor to **2**, Cook, A.H.; Downer, J.D.; Heilbron, Sir I. *J. Chem. Soc.* **1948**, 2028-2031; precursor to **4**, Schmidt, P.; EIchenberger, K.; Wilhelm, M; Druey, J. *Helv. Chim. Acta* **1959**, *42*, 349-359; precursor to **5**, Suzuki, M.; Moriya, T.; Matsumoto, K.; Miyoshi, M. *Synthesis* **1982**, 874-875; precursor to **6**, Grabiak, R.C.; Howe, R.K.; Lee, L.F. US Patent 5,000,775 **1991**; precursor to **7**, Demaree, P.; Doria, M.; Muchowski, J.M. *Can. J. Chem.* **1977**, *55*, 243-250; precursor to **8**, Meyer, Jr., Rich B.; Skibo, Edward B. *J. Med. Chem.* **1979**, *22*, 944-948; precursor to **9**, Albert, A.; Tratt, K. *J. Chem. Soc. (C)*, **1968**, 344-347.
5. 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*, 2525-2546.
6. Mantlo, N.B.; Chakravarty, P.K.; Ondeyka, D.L.; Siegl, P.K.S.; Chang, R.S.; Lotti, V.J.; Faust, K.A.; Chen, T.B.; Schorn, T.W.; Sweet, C.S.; Emmet, S.E.; Patchett, A.A.; Greenlee, W.J. *J. Med. Chem.* **1991**, *34*, 2919-2922.

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