Bioorganic & Medicinal Chemistry Letters, Vol. 4, No. 1, pp. 145-150, 1994
Printed in Great Britain

0960-894X/94 $6.00 + .00
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1,4-SUBSTITUTED INDOLES: A POTENT AND SELECTIVE CLASS OF ANGIOTENSIN II RECEPTOR ANTAGONISTS

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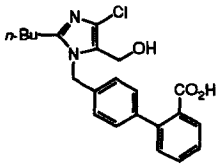
Abstract: *The syntheses and pharmacological activity of a series of 1,4-substituted indoles which function as nonpeptidic antagonists of the angiotensin II (AII) receptor are described. Compounds in this series are orally active and demonstrate long lasting antihypertensive activity.*

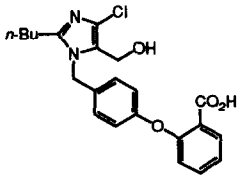
Angiotensin converting enzyme (ACE) inhibitors, such as captopril and enalapril, have been demonstrated to be clinically effective in the treatment of hypertension and congestive heart failure.[1] These compounds regulate the renin angiotensin system (RAS) by blockade of the biosynthesis of the potent endogenous vasoconstrictor angiotensin II (AII). An alternative strategy to regulate the RAS involves blockade of the action of AII at its receptor by an antagonist. Recently, the development of AII receptor antagonists has been an area of active interest and several clinical candidates have emerged.[2]

We describe here our work to develop a series of 1,4-substituted indoles which are nonpeptidic antagonists of the AII receptor. Our initial strategy to develop a novel, potent, and selective AII receptor antagonist was influenced by the data reported by workers at DuPont[2a,2e,3] for compounds **1-3**. Compounds **1-3** have nearly equal affinity for the AII receptor, but structurally have different linkers between the two 6-membered aryl rings which vary in length from one bond (**1**) to three bonds (**3**). This data suggested to us that compounds containing other linkers, particularly derivatives with more conformational constraint, might also be effective antagonists of the AII receptor.



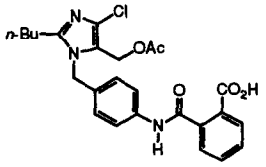
1

IC_{50} (μM) = 0.23



2

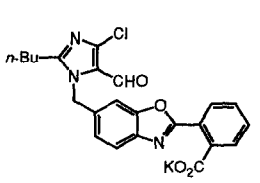
IC_{50} (μM) = 0.40



3

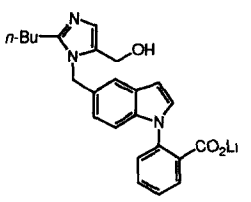
IC_{50} (μM) = 0.28

We elected to examine the [4.3.0] aromatic ring system[4] as a replacement for both the central aryl ring and the linker in compounds **2-3**. To study different substitution patterns, compounds **4-6** were prepared. From this effort, the 1,4-indole substitution pattern present in **6** emerged as superior.[5,6]



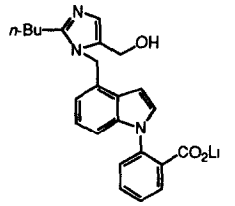
4

K_i (nM) = 6,100
K_B (nM) = 550



5

K_i (nM) = 760
K_B (nM) = 680

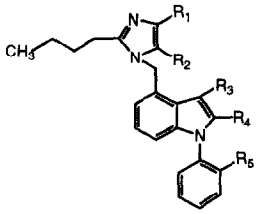


6

K_i (nM) = 79
K_B (nM) = 39

Having identified a prototype, our efforts focused next on optimization of the 1,4-substituted indole template (**Table 1**). Replacement of the carboxylic acid in **6** with a C-linked tetrazole and incorporation of chlorine at the 4-position of the imidazole[7] provided compound **7**, a derivative which was significantly more potent than our initial lead **6**. A further enhancement in potency was achieved by oxidation of the hydroxymethyl residue to a carboxylic acid (**8**).[7] Additional modification of the imidazole ring demonstrated the need for substitution of the 4-position with an electron withdrawing group. Hydrogen at the 4-position caused a dramatic decrease in potency possibly due to the attendant increased basicity of the imidazole ring (**9** vs. **8**), whereas a trifluoromethyl analog was moderately potent (**10** vs. **8**).

Table 1.

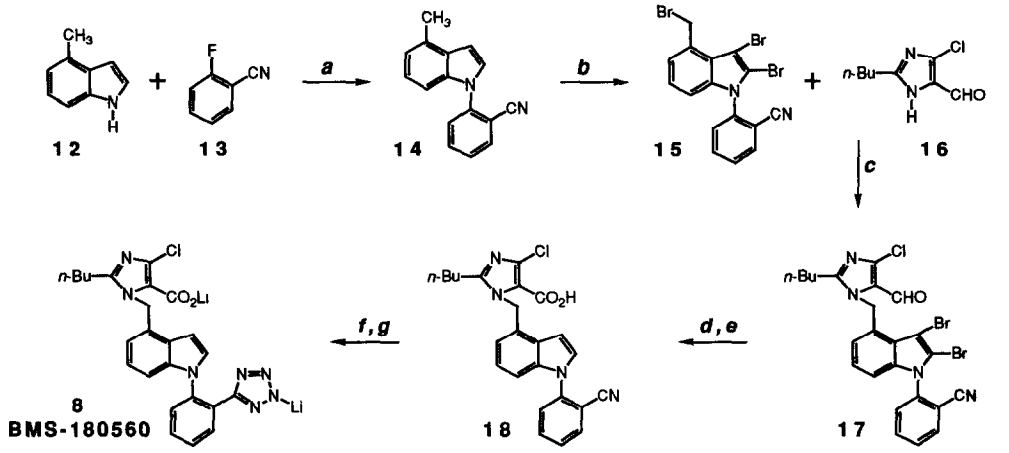


Compound	R_1	R_2	R_3	R_4	R_5	K_i (nM)	K_B (nM)
6	H	CH_2OH	H	H	CO_2Li	79	39
7	Cl	CH_2OH	H	H	CN_4Li	6.3	0.90
8 (BMS-180560)	Cl	CO_2Li	H	H	CN_4Li	0.8	0.068
9	H	CO_2H	H	H	CN_4H	3600	270
10	CF_3	CO_2Na	H	H	CN_4Na	79	0.12
11	Cl	CO_2Li	Br	Br	CN_4Li	840	300

The preparation of compound **11** was prompted by a report from Glaxo[2d] that a bromine atom at the 3-position of 2,5-substituted indole or benzofuran AII receptor antagonists was crucial for high potency. Incorporation of bromine into the 1,4-substituted indole nucleus, however, resulted in a loss of potency (**11** vs. **8**).

The compounds in **Table 1** were prepared using chemistry analogous to that outlined in **Scheme 1** which depicts the synthesis of compound **8** (**BMS-180560**). The synthesis began with SNAr coupling of 4-methylindole **12** with 2-fluorobenzonitrile **13** to provide the 1,4-substituted indole **14**. Bromination of indole **14** gave tribromide **15** which was coupled with imidazole **16**[8] to furnish **17**. Attempted monobromination of **14** led to exclusive introduction of bromine at the indole 3-position. Oxidation of **17** provided the corresponding carboxylic acid which was hydrogenated as a carboxylate salt to yield **18**. Carboxylate formation prior to hydrogenation is a prerequisite since hydrogenation of the protonated acid results in hydrogenolysis of the chlorine on the imidazole. Tetrazole formation on **18** followed by generation of the bis-salt then gave **8** (**BMS-180560**).

Scheme 1. Synthesis of Compound **8** (**BMS-180560**).

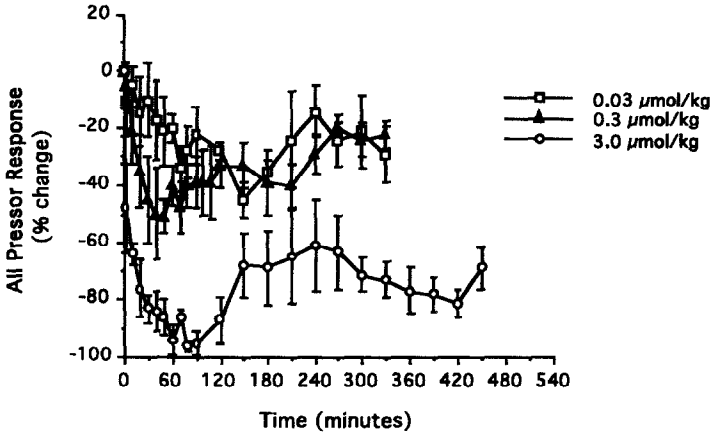


Reagents: *a*. K_2CO_3/DMF (85%); *b*. NBS/CCl_4/Benzene (72%); *c*. *t*-BuOK/*t*-BuOH/DMF (70%); *d*. $NaClO_2/NH_2SO_3H$/THF/H_2O; *e*. H_2/Pearlman's catalyst/NaOH/H_2O/EtOH (85% for 2 steps); *f*. *n*-Bu_3SnN_3/Xylene; *g*. LiOH/H_2O/CH_3OH (46% for 2 steps).

Compound **8** (**BMS-180560**) was the most potent analog identified in the series. As determined *in vitro* using strips of rabbit aorta,[5] **8** is a noncompetitive antagonist of the vasoconstrictor effects of AII (K_B = 0.068 ± 0.048 nM). Like many other AII receptor antagonists which contain a carboxylic acid in the imidazole ring,[9] **8** displays suppression of the maximum effect of AII characteristic of insurmountable antagonism. Radioligand binding studies[6] demonstrated that **8** selectively binds to the AT_1 population of angiotensin binding sites (K_i = 0.8 ± 0.2 nM for AT_1, K_i = 6,500 ± 3,600 nM for AT_2).[10]

In vivo compound **8** (**BMS-180560**) antagonizes the pressor response to exogenous AII in conscious Sprague-Dawley rats at doses as low as 0.03 μmol/kg (ED_{50} = 0.22 μmol/kg) when administered i.v. (**Figure 1**). Upon oral administration, at a dose of 30 μmol/kg to salt depleted spontaneously hypertensive rats (SHR),[11] compound **8** causes a sustained reduction in blood pressure which extends past 72 hours (**Figure 2**). The maximum percent reduction in mean arterial pressure (MAP) is 39% at the 30 μmol/kg dose.

Figure 1. Inhibition of the AII Pressor Response in Conscious Sprague-Dawley Rats upon Intravenous Administration of Compound **8** (**BMS-180560**).



Although compound **8** (**BMS-180560**) demonstrates reasonable *in vivo* efficacy, it was presumed that its highly polar diacidic character might limit its oral bioavailability. In an effort to improve oral efficacy, prodrug esters of compound **8** were prepared and evaluated in the salt depleted SHR (**Table 2**). The prodrug esters were prepared by esterification of acid **18** followed by tetrazole formation. Double esters **21-24** demonstrated either marginal or no improvement over acid **8**. The best compound in the series was ethyl ester **19** (**BMS-181688**). Oral administration of **19** at a dose of 10 μmol/kg to salt depleted SHR causes a sustained reduction in MAP which extends past 72 hours (**Figure 2**). The maximum percent reduction in MAP is 35% at the 10 μmol/kg dose.

Figure 2. Change in Mean Artial Pressure in Salt-Depleted SHR upon Oral Administration of Compound **8** (**BMS-180560**) and Compound **19** (**BMS-181688**).

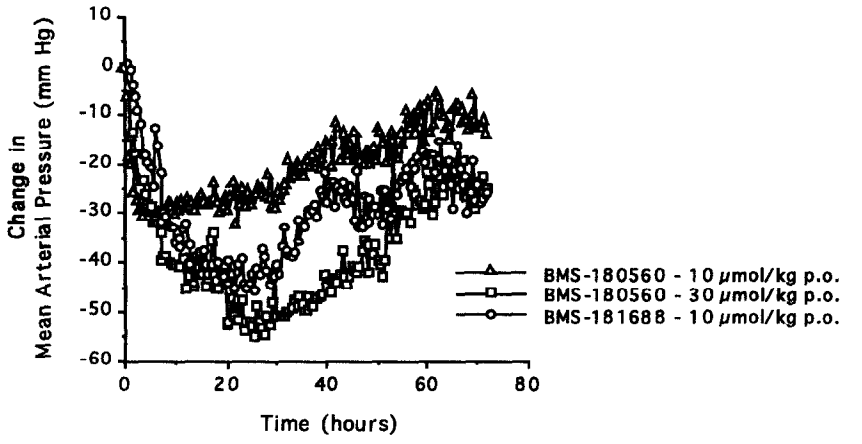
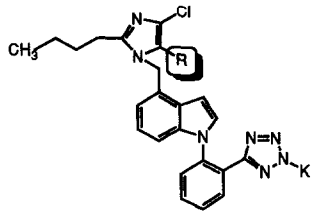
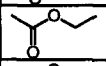
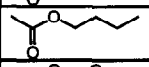
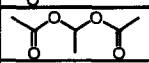
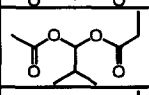
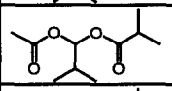
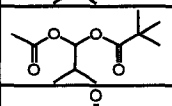
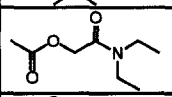
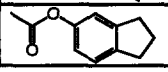


Table 2. Pro-Drug Esters of Compound **8** (**BMS-180560**).



Compound	R	K_i (nM)	K_B (nM)	Max % b.p. Fall Salt Depleted SHR 10 μmol/kg p.o.
8 (**BMS-180560**)		0.8	0.068	22% at 18 - 24 hrs
19 (**BMS-181688**)		25	5	35% at 24 - 30 hrs
20		7.3	6	22% at 18 - 24 hrs
21		4.5	4.5	26% at 6 - 24 hrs
22		30	1.2	29% at 6 - 12 hrs
23		13	4	18% at 24 - 30 hrs
24		8.9	3.6	21% at 24 - 30 hrs
25		6.3	4	15% at 18 - 24 hrs
26		39	130	18% at 24 - 30 hrs

In summary, we have identified a series of 1,4-substituted indoles which are potent, selective, noncompetitive antagonists of the vasoconstrictor effects of AII. Compounds in this series are orally active and demonstrate long lasting antihypertensive activity.

Acknowledgments: *We thank Dr. Kyoung S. Kim and Mr. Ligang Qian for the preparation of compound* ***10****, and Ms. Diane McMullen and Ms. Diane Normandin for* K_B *determinations. In addition, we thank the Bristol-Myers Squibb Department of Analytical Chemistry for microanalysis and mass spectra.*

References and Notes:

1. (a) Gomez, H. J.; Cirillo, V. J.; Smith, S. G. *J. Cardiovasc. Pharmacol.* **1990**, *15 (Suppl. 3)*, S26. (b) Giles, T. *J. Cardiovasc. Pharmacol.* **1990**, *15 (Suppl. 3)*, S6.

2. (a) Duncia, J. V.; Chiu, A. T.; Carini, D. J.; Gregory, G. B.; Johnson, A. L.; Price, W. A.; Wong, P. C.; Calabrese, J. C.; Timmermans, P. B. M. W. M. *J. Med. Chem.* **1990**, *33*, 1312. (b) 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.; Shorn, T. W.; Sweet, C. S.; Emmert, S. E.; Patchett, A. A.; Greenlee, W. J. *J. Med. Chem.* **1991**, *34*, 2919. (c) Weinstock, J.; Keenan, R. M.; Samanen, J.; Hempel, J.; Finkelstein, J. A.; Franz, R. G.; Gaitanopoulos, D. E.; Girard, G. R.; Gleason, J. G.; Hill, D. T.; Morgan, T. M.; Peishoff, C. E.; Aiyar, N.; Brooks, D. P.; Fredrickson, T. A.; Ohlstein, E. H.; Ruffolo, R. R.; Stack, E. J.; Sulpizio, A. C.; Weidley, E. F.; Edwards, R. M. *J. Med. Chem.* **1991**, *34*, 1514. (d) Middlemiss, D.; Drew, G. M.; Ross, B. C.; Robertson, M. J.; Scopes, I. C.; Dowle, M. D.; Akers, J.; Cardwell, K.; Clark, K. L.; Coote, S.; Eldred, C. D.; Hamblett, J.; Hilditch, A.; Hirst, G. C.; Jack, T.; Montana, J.; Panchal, T. A.; Paton, J. M. S.; Shah, P.; Stuart, G.; Travers, A. *Biorg. Med. Chem. Lett.* **1991**, *1*, 711. (e) 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. *Med. Res. Rev.* **1992**, *12*, 149. (f) Greenlee, W. J.; Siegl, P. K. S. *Ann. Rep. Med. Chem.* **1992**, *27*, 59. (g) Hodges, J. C.; Hamby, J. M.; Blankley, C. J.; *Drugs Future* **1992**, *17*, 575.

3. (a) Carini, D. J.; Duncia, J. V.; Johnson, A. L.; Chiu, A. T.; Price, W. A.; Wong, P. C.; Timmermans, P. B. M. W. M. *J. Med. Chem.* **1990**, *33*, 1330. (b) Wong, P. C.; Price, W. A.; Chiu, A. T.; Carini, D. J.; Duncia, J. V.; Johnson, A. L.; Wexler, R. R.; Timmermans, P. B. M. W. M. *Hypertension* **1990**, *15*, 823.

4. Subsequent to the completion of this study, workers at Glaxo described their development of 2,5-substituted indoles and bromobenzofurans as potent, nonpeptidic antagonists of AII; see reference 2d.

5. Functional antagonism (K_B) was measured by the ability of a single concentration of antagonist to block angiotensin II induced contractions in rabbit aortic smooth muscle strips employing the methods described by Wong, P. C.; Hart, S. D.; Zaspel, A. M.; Chiu, A. T.; Ardecky, R. J.; Smith, R. D.; Timmermans, P. B. M. W. M. *J. Pharm. Exp. Ther.* **1990**, *255*, 584.

6. Receptor binding affinity was determined from a competitive binding assay using ^{125}I labelled [Sar^1,Ile^8] angiotensin II in rat adrenocortical membranes employing the methods described by Chiu, A. T.; Carini, D. J.; Johnson, A. L.; McCall, D. E.; Price, W. A.; Thoden, M. J. M. C. ; Wong, P. C.; Taber, R. I.; Timmermans, P. B. M. W. M. *Eur. J. Pharmacol.* **1988**, *157*, 13. Inhibition constants (K_i) for the AT_1 receptor population were calculated by curve fitting.

7. Similar modifications of AII receptor antagonists were first described by workers at DuPont; see references 2a and 2e.

8. For the preparation of imidazole **16**, see U.S. Patent 4340598, **1982**.

9. (a) Timmermans, P. B. M. W. M.; Wong, P. C.; Chiu, A. T.; Herblin, W. F. *Trends in Pharmacol. Sci.* **1991**, *12*, 55. (b) Chiu, A. T.; Carini, D. J.; Duncia, J. V.; Leung, K. H.; McCall, D. E.; Price, W. A.; Wong, P. C.; Smith, R. D.; Wexler, R. R.; Timmermans, P. B. M. W. M. *Biochem. and Biophys. Res. Commun.* **1991**, *177*, 209.

10. The characterization of two distinct populations of angiotensin binding sites has been described by Bumpus, F. M.; Catt, K. J.; Chiu, A. T.; DeGasparo, M.; Goodfriend, T.; Husain, A.; Peach, M. J.; Taylor, D. G., Jr.; Timmermans, P. B. M. W. M. *Hypertension* **1991**, *17*, 720.

11. (a) Weeks, J. R.; Jones, J. A. *Proc. Soc. Exp. Biol. Med.* **1960**, *104*, 646. (b) Laffin, R. J.; Goldberg, M. E.; High, J. T.; Schaeffer, T. R.; Waugh, M. H.; Rubin, B. *J. Pharmacol. Exp. Ther.* **1978**, *204*, 281.

(*Received* 29 *July* 1993; *accepted* 15 *September* 1993)