cules/unit cell, d_{calcd} = 1.05 g/cm^3, space group $P2$-1. Data were collected to a maximum 2θ of 120.0°. Of a total of 1915 reflections, 1844 were unique and not systematically absent (the data was corrected for Lorentz and polarization factors, but not for absorption); 982 reflections with $F_o^2 > 3.06$ (F_o^2) were used for structural analysis. Calculation and refinement was carried out by the full-matrix least-squares method. Final anisotropic refinement of non-hydrogen atoms (hydrogen atoms not calculated) gave R = 0.107 and Rw = 0.141 where $R = (\sum||F_o|-|F_c||/\sum|F_o|$, $Rw = [\sum(|F_o| - |F_c|)^2/\sum F_o^2]_{1/2}$, and the function minimized was $(\sum|F_o| - |F_c|)^2$. The final difference map showed a highest peak of 0.14 (3) e/A^3. Tables of atomic positional parameters, bond distances and angles, useful least-square planes, and thermal parameters are available as supplementary material. The absolute configuration of (+)-**3** is *R*.

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Registry No. **1**, 88393-66-2; (*S*)-**2**, 88424-62-8; (±)-**3**, 81556-15-2; (*S*)-(−)-**3**, 106974-46-3; (*R*)-(+)-**3**, 106974-51-0; (−)-**3**((+)-ephedrine salt), 106974-49-6; (−)-**3**((−)-ephedrine salt), 106974-50-9; (*R*)-**3**-CoA ester, 92142-38-6; (*S*)-**3**-CoA ester, 106974-48-5; (±)-**4**, 92982-25-7; (*S*)-(−)-**4**, 106974-47-4; (*R*)-(+)-**4**, 106974-52-1; CPT, 9068-41-1.

Supplementary Material Available: Illustrations showing the atom-numbering system of **3** and (−)-ephedrine and tables of positional and thermal parameters, bond distances, bond angles, and torsional angels (4 pages). Ordering information is given on any current masthead.

Long-Acting Angiotensin II Inhibitors Containing Hexafluorovaline in Position 8

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An improved synthesis of hexafluorovaline (Hfv) derivatives, i.e., DL-Hfv-OBzl and Boc-DL-Hfv, is described. Incorporation of hexafluorovaline into angiotensin resulted in [Sar^1,Hfv^8]AII and [Sar^1,D-Hfv^8]AII. At the nanogram/milliliter dose range, the L congener was 20–100 times more active as either angiotensin agonist or angiotensin antagonist than its D diastereomer on isolated tissue preparations. At the microgram dose range, both [Sar^1,Hfv^8]AII and [Sar^1,D-Hfv^8]AII were significantly more effective than [Sar^1,Leu^8]AII as angiotensin II inhibitors, producing prolonged blockade of the pressor response toward angiotensin II for over 1 h.

Recent advances in recombinant biotechnology have enabled the elucidation of a variety of protein factors that may have an important role in cancer or other diseases, i.e., angiogenesis factor,[1] platelet-derived growth factor,[2,3] and atrial natriuretic hormone.[4,5] It is anticipated that further identification of their active sequences,[6] followed by the development of orally effective drugs from these peptide structures, will lead to many new therapeutic possibilities. Toward this goal, both drug design and peptide formulation have been experimented with, and metabolically stable luteinizing hormone-releasing hormone analogues[7,8] and liposome-entrapped insulin[9] have been found orally active. Nevertheless, a systematic assessment of the parameters involved in gastrointestinal absorption of peptides is needed, so that strategies generally useful for promoting their oral effectiveness can be developed. For this purpose, angiotensin II (Asp-Arg-Val-Tyr-Val-His-Pro-Phe) represents an especially stringent model, in that its many aromatic and polar side chains provide multiple foci for digestive degradations. In addition, its highly hydrophilic–ionic nature at physiological pH is contraindicative to membrane transport, such that even liposomal encapsulation did not afford orally active angiotensin II.[10]

In initial studies,[11] we incorporated the highly fluorinated $\gamma,\gamma,\gamma,\gamma',\gamma',\gamma'$-hexafluorovaline (Hfv) into angiotensin II in order to develop a probe for ^{19}F NMR conformational analysis of the hormone–receptor interaction and, possibly, for receptor localization.[12] We observed that while hexafluorovaline can substitute for valine to give the fully active [Hfv^5]angiotensin II (133% activity), its derivatives are resistant to proteolytic digestion by the enzymes carboxypeptidase A, hog renal acylase, and α-chymotrypsin. The metabolic stability of hexafluorovaline coupled with its highly lipophilic–electronegative nature makes this amino acid an especially promising candidate for further development of orally active peptide drugs. In this study, we address the need for suitably protected derivatives of hexafluorovaline that can be used in standard procedures of peptide synthesis, so that its ability to promote the oral effectiveness of peptides can be assessed in the future. In addition, the in vitro and in vivo activities of [Sar^1,Hfv^8]AII

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Table I. Relative in Vitro Effects of Angiotensin Antagonists

	agonistic activity,[a] %		antagonistic potency,[b] AII dose ratio							
			rabbit aorta, dose of inhibitors (ng/mL)			calcd	rat stomach, dose of inhibitors (ng/mL)			calcd
	rabbit aorta	rat stomach	1	10	50	pA_2	1	10	50	pA_2
AII	100	100								
[Sar[1],Leu[8]]AII						8.71[c]				8.6[c]
[Sar[1],Hfv[8]]AII (8)	1.1 ± 0.5 (3)	0.8 ± 0.4 (3)	6.1 ± 1.5 (4)	294 ± 27.5 (4)		9.08	2.2 ± 0.3 (4)	51.7 ± 8.0 (3)		9.07
[Sar[1],D-Hfv[8]]-AII (9)	0 (3)	0.03 (3)		2.1 ± 0.2 (4)	42 ± 8.2 (3)	8.10		2.0 ± 0.3 (4)	4.1 ± 0.6 (3)	8.10

[a] Agonistic activity of an analogue was expressed as the ratio of the dose of AII required to produce a 25% maximal response to that of the analogue required to produce the same response. The number of experiments is indicated in parentheses. [b] Inhibitory potency of an analogue was calculated as the ratio of the dose of AII required to produced 25% of the control maximal response in the presence and absence of the inhibitor. [c] Reviewed by: Regoli, D.; Park, W. K.; Rioux, F. *Pharmacol. Rev.* **1974**, *26*, 69.

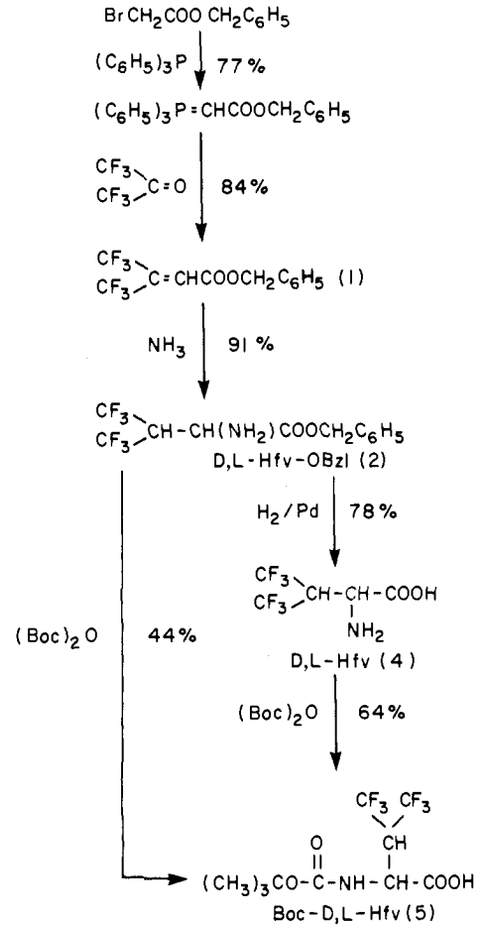

Figure 1. An improved synthesis of DL-hexafluorovaline and derivatives.

and [Sar[1],D-Hfv[8]]AII are examined.

Results and Discussion

In initial studies,[11] esterification of hexafluorovaline with benzyl alcohol proceeded slowly in an unacceptable yield (6%), and in attempts to prepare Boc-Hfv from the azide, the *tert*-butyl phenyl carbonate and *tert*-butyl *p*-nitrophenyl carbonate procedures proved unsatisfactory. For this study, benzyl bromoacetate was used as the starting material to obtain hexafluorovaline benzyl ester in an overall yield of 59% (Figure 1). Unexpectedly, this ester bond was readily susceptible to base-catalyzed hydrolysis. Thus, treatment of Hfv-OBzl with di-*tert*-butyl dicarbonate in the presence of NaOH solution[13] led to

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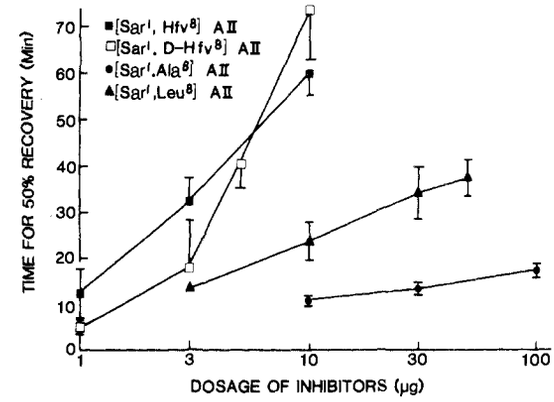

Figure 2. Time course for AII (6 ng) induced pressor response in rats (n = 4–10) to return to 50% of pretreatment level after a bolus injection of the inhibitors. Bars represent standard errors of means.

Boc-Hfv, which was independently prepared through standard reaction of Hfv with di-*tert*-butyl dicarbonate in 64% yield.

Solution coupling of Boc-Sar-Arg-Val-Tyr-Val-His-Pro with the racemic hexafluorovaline benzyl ester, followed by N- and C-terminal deprotection, gave two diastereomers. Countercurrent-distribution (CCD) separation of the diastereomer pair followed by carboxypeptidase Y digestion yielded the C-terminal Hfv from the appropriate L diastereomer only, thus permitting stereochemical assignment of the peptide fractions. Further characterization of [Sar[1],Hfv[8]]AII and [Sar[1],D-Hfv[8]]AII by fast-atom-bombardment mass spectrometry (FAB-MS) analyses indicated the correct molecular weight for each diastereomer, with its respective hydrolysate giving the appropriate amino acids at the expected ratios in amino acid analyses.

Agonistic and antagonistic activities were determined in rabbit aorta and in rat stomach preparations, and the results are tabulated in Table I. As expected, [Sar[1],Hfv[8]]AII was 20–100 times more active than its corresponding D diastereomer. Their ability to inhibit the pressor effect of angiotensin II was evaluated subsequently and compared with that for saralasin and [Sar[1],Leu[8]]AII (Figure 2). In these in vivo studies, bolus injections of the inhibitors to rats followed by angiotensin II (6 ng) at 15-min intervals permitted concurrent evaluation of the effectiveness and duration of inhibition of the antagonists, through comparison of the time periods required for the pressor response of AII to return to 50% of its pretreatment levels. Bolus injections of 1, 3, and 10 μg of [Sar[1],Hfv[8]]AII gave 50% recovery times of 12.5 ± 5.3, 32.3 ± 5.2, and 60.1 ± 4.3 min. This represents a dose ratio of antagonist/AII of 167, 500, and 1667, respectively. In comparison, 3, 10, 30, and 50 μg of [Sar[1],Leu[8]]AII (dose

ratio of 500, 1667, 5000, and 8333) gave 50% recovery times of 13.5 ± 0.5, 23.6 ± 4.5, 34.5 ± 6.7, and 37.6 ± 4.1 min, whereas 10, 30, and 100 μg of [Sar[1],Ala[8]]AII (saralasin, dose ratio of 1667, 5000, and 16667) produced a considerably weaker and transient inhibition, with the 50% recovery times of 11.0 ± 1.2, 13.7 ± 1.2, and 18.0 ± 1.5 min. Thus, to achieve a moderate inhibition of AII for 30 min, [Sar[1],Hfv[8]]AII was significantly more effective (about 7 times) than [Sar[1],Leu[8]]AII (Figure 2). For more prolonged blockade of AII, their difference in inhibitory potency would be even greater, making [Sar[1],Hfv[8]]AII one of the most effective angiotensin antagonists reported to date.

Surprisingly, [Sar[1],D-Hfv[8]]AII, which displayed very little activity as either angiotensin agonist or angiotensin antagonist in vitro, was as effective as [Sar[1],Hfv[8]]AII in inhibiting the pressor response of AII, especially at the higher dose range tested. Bolus injections of 1, 3, 5, and 10 μg of [Sar[1],D-Hfv[8]]AII gave 50% recovery times of 5.8 ± 0.5, 19.0 ± 8.8, 40.6 ± 3.7, and 73.6 ± 10.9 min. These results suggest that at the large dose ratio employed (10 μg of inhibitor/6 ng of AII, or 1667), [Sar[1],D-Hfv[8]]AII may be able to overcome its low affinity for the vascular receptor and exert prolonged blockade, partially due to the proteolytic-resistant nature of its C-terminal D-Hfv.

Experimental Section

Hexafluoroacetone was a generous gift of Dr. Joseph Lann of E. I. du Pont Co., Wilmington, DE. Benzyl bromoacetate and di-*tert*-butyl dicarbonate were obtained from Fluka AG, Tridom Chem. Inc. N^{α}-(*tert*-Butyloxycarbonyl)-L-amino acids were supplied by Bachem, Inc., Torrence, CA. Silica gel (CC-7, neutral, 100–200 μm) was from Mallinckrodt. Microgranular (carboxymethyl)cellulose (CM 52) was from Whatman Inc. and bakers' yeast carboxypeptidase Y was from Sigma, MO. All chemicals were of reagent grade. Melting points (Thomas-Hoover Uni-melt) are uncorrected. Microanalyses were performed by the Robertson Laboratory, Florham Park, NJ. Proton magnetic resonance spectra in deuteriated chloroform and/or methanol containing tetramethylsilane were obtained on a Varian T-60 (60 MHz). Infrared measurements were obtained on a Perkin-Elmer Model 237 spectrophotometer. Homogeneity of amino acid derivatives and of the synthetic peptides was assessed by thin-layer chromatography (TLC) on Merck precoated silica gel glass plates (type G60-F254) in different solvent systems: i, 1-butanol–acetic acid–water (4:1:5, upper phase); ii, 2-butanol–3% NH_4OH (100:44); iii, 1-butanol–pyridine–acetic acid–water (8:1:2:9, upper phase). The products were identified by a combination of UV, ninhydrin, Chlorox–toluidine, and Pauly sprays. Amino acid analyses were performed on a Beckman Model 119 analyzer equipped with a Beckman system AA computing integrator after hydrolysis of the peptide in 6 N HCl containing 0.2% phenol at 110 °C for 24 h in sealed tubes.

Carboxypeptidase Y (containing amidase and esterase activities) digestion of the peptide diastereomer was carried out by dissolving ca. 1 mg of peptide in 2.9 mL of pH 6.6 buffer containing 50 mM sodium phosphate and 150 mM sodium chloride, followed by incubating this solution at 37 °C with 1.5 unit of enzyme in 50 μL of balanced citrate buffer. After 24 h, another 1.5 unit of enzyme was added to the solution and the mixture was incubated for an additional 24 h. TLC analysis of the incubation mixtures at hours 24 and 40 indicated the presence of the C-terminal Hfv from the appropriate diastereomeric fraction. At the end of 48-h digestion, the incubation mixtures were boiled at 100 °C for 10 min, and 1-mL samples were withdrawn, evaporated to dryness, and examined by amino acid analysis.

Bioassay of angiotensin II analogues was performed on isolated rabbit aorta and rat stomach strips perfused with Krebs solution containing select antagonists to acetylcholine, catecholamine, serotonin, and histamine according to previously reported procedures.[14,15] Inhibitory activity of the angiotensin II antagonists in the blood pressure assay was tested in female Wistar rats, anesthetized with pentobarbital sodium (30 mg/kg body weight), vagotomized, cannulated (carotid artery and femoral vein), and treated with pentolinium tartrate (5 mg/200 g). Blood pressure was recorded on a P-1000 A pressure transducer and Narco Physiograph recorder. In order to determine the duration of action of the antagonist, the pressure response to 6 ng of angiotensin II was measured at 15-min intervals after a bolus injection of the inhibitors. None of the AII antagonists had an effect on the pressure response to norepinephrine.

Synthesis of the racemic Hfv-OBzl and Boc-Hfv is outlined in Figure 1, as described in the following.

DL-Hexafluorovaline Benzyl Ester (2; DL-Hfv-OBzl). Benzyl bromoacetate was reacted with triphenylphosphine, and the resultant triphenyl(carbobenzoxymethylene)phosphorane was suspended in anhydrous ether and saturated with hexafluoroacetone at −80 °C as described previously[11] to give as a colorless liquid benzyl 4,4,4-trifluoro-3-(trifluoromethyl)crotonate (1): bp 92 °C (3.2 mmHg). This (27 g, 0.09 mol) was dissolved in anhydrous ether (175 mL) and reacted with liquid NH_3 (12.5 g, 0.73 mol) at −80 °C for 45 min and at room temperature overnight. The mixture was filtered, the filtrate was evaporated in vacuo, and the product was distilled through a 10-cm Vigreux column to give 25.9 g (91%) of a colorless liquid, **2**: bp 84 °C (0.3 mmHg); TLC R_f (i) 0.70, (ii) 0.70; ^{1}H NMR (neat) δ 1.66 (s, 2 H, NH_2), 3.63 and 3.9 (m, 2 H, $C_{\beta}H$ and $C_{\alpha}H$), 5.07 (s, 2 H, benzylic CH_2), 7.23 (s, 5 H, benzylic C_6H_5); IR (neat) 3400 (N–H), 3000 (C–H), 1750 (CO–O), 1400 (C–F), 1340–1140 (–CO–O), 1090 (C–N).

Acidification of **2** in petroleum ether with anhydrous HCl in ether, followed by filtration and recrystallization of the precipitate in 2-propanol–ether–petroleum ether, gave hexafluorovaline benzyl ester hydrochloride salt (**3**; DL-Hfv-OBzl·HCl), mp 147–148 °C. Anal. ($C_{12}H_{11}NF_6O_2$·HCl) C, H, N, F.

Hydrogenation of **2** in methanol, followed by recrystallization of the product from methanol–ether, gave DL-Hfv (4): mp 207–207.5 °C; TLC R_f (i) 0.40, (ii) 0.30; positive to ninhydrin and Chlorox sprays. In amino acid analysis, Hfv was eluted at 18 min before Asp with a color constant equal to 1.62 that of Pro at 440 nm and a ratio of 2.42 between the values at 440 and 570 nm.

N^{α}-(*tert*-Butyloxycarbonyl)-DL-hexafluorovaline (5; Boc-DL-Hfv) was prepared from **4** (1.58 g, 7 mmol) and di-*tert*-butyl dicarbonate (1.68 g, 7.7 mmol) in 28 mL of *tert*-butyl alcohol and 14 mL of 1 N NaOH.[13] The mixture was stirred at room temperature for 48 h and evaporated to dryness in vacuo. The residue was suspended in 1 N NaOH (50 mL) and washed with EtOAc (4 × 15 mL). The NaOH solution was acidified to pH 1 with 2 N HCl and extracted with EtOAc. The organic solution was dried (Na_2SO_4) and evaporated to dryness in vacuo, and the residue was recrystallized from EtOAc–petroleum ether to give 1.9 g of precipitate: TLC R_f (i) 0.61, (ii) 0.52. This was dissolved in EtOAc and neutralized with dicyclohexylamine in ether to produce 2.5 g (70%) of N^{α}-(*tert*-butyloxycarbonyl)-DL-hexafluorovaline dicyclohexylammonium salt (**6**) upon chilling overnight: mp 165.5–167 °C. Anal. ($C_{10}H_{13}NF_6O_4$·$C_{12}H_{23}N$) C, H, N, F.

Regeneration of Boc-DL-Hfv by subjecting **6** in EtOAc to 2 N HCl washings followed by drying (Na_2SO_4), evaporation to dryness, and recrystallization from EtOAc–petroleum ether gave 1.4 g (64% overall yield): mp 131–132.5 °C; ^{1}H NMR ($CDCl_3$–CD_3OD) δ 1.47 (s, 9 H, $(CH_3)_3CO$), 3.93 (m, 1 H, $C_{\beta}H$), 4.87 (s, 3 H, $C_{\alpha}H$, NH, $COOH$).

Alternatively, when hexafluorovaline benzyl ester (**2**; 10 g, 32 mmol) was stirred with 60 mL of *tert*-butyl alcohol and 32 mL of 1 N NaOH, TLC of the mixture indicated that most of the benzyl ester was converted to hexafluorovaline within 5 min. To this solution were added di-*tert*-butyl dicarbonate (17.2 g, 78.8 mmol) and more 1 N NaOH (60 mL). The mixture was stirred at room temperature for 7 days, adjusted to pH 10 with NaOH solution, and washed with hexane. The aqueous solution was acidified to pH 2 and extracted with EtOAc and $CHCl_3$. The organic solutions were combined, dried (Na_2SO_4), and evaporated to dryness. The residue was chromatographed on a column (2

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× 50 cm) of silica gel in $CHCl_3$, washed with 200 mL of $CHCl_3$, and eluted with $CHCl_3$–CH_3OH (9:1). The appropriate fractions were combined, evaporated to dryness, and recrystallized from petroleum ether to give 4.55 g (44%) of **5**, with its ^1H NMR in $CDCl_3$–CD_3OD showing a resonance pattern identical with that of Boc-DL-Hfv regenerated from the DCHA salt **6** without any benzylic protons.

Boc-Sar-Arg-Val-Tyr-Val-His-Pro (7) was prepared by standard solid-phase procedure, with the resultant Boc-Sar-Arg(NO_2)-Val-Tyr(Bzl)-Val-His(Bzl)-Pro-resin (2.1 mmol) hydrogenated twice with palladium acetate (0.95 g, 4.2 mmol) in dimethylformamide (40 mL) at 45 °C under 60 psi of H_2 for 5 days to give 1.57 g of crude peptide.[16] Sequential purification of the peptide by countercurrent distribution in 8:1:2:9 1-butanol–pyridine–acetic acid–water for 600 transfer followed by 1000 transfers in 4:1:5 1-butanol–acetic acid–water gave 418 mg (21%) of **7**: TLC R_f (i) 0.18, (iii) 0.27. Amino acid analysis of hydrolysate gave Sar (1.02), Arg (1.04), Val (0.96), Tyr (1.00), Val (0.96), His (1.02), Pro (1.02); peptide content 89%.

Sar-Arg-Val-Tyr-Val-His-Pro-Hfv (8) and Sar-Arg-Val-Tyr-Val-His-Pro-D-Hfv (9). [Boc-Sar[1],des-Phe[8]]AII (**7**; 100 mg, 0.1 mmol), DL-Hfv-OBzl·HCl (**3**; 80 mg, 0.25 mmol), 1-hydroxybenzotriazole monohydrate (19 mg, 0.12 mmol), and dicyclohexylcarbodiimide (51 mg, 0.25 mmol) were dissolved in dimethylformamide (4 mL). The mixture was stirred at room temperature for 1 h and at 45 °C for 5 h and was evaporated to dryness. The residue was washed with chloroform and ether, followed by chromatography on a column (1 × 25 cm) of microcrystalline (carboxymethyl)cellulose (Whatman CM 52) in the upper phase of the solvent mixture of 8:1:2:9 butanol–pyridine–acetic acid–water. Elution of the column by the same solvent mixture gave 120 mg of [Boc-Sar[1],DL-Hfv-OBzl[8]]AII.

Subsequent hydrogenolysis of the peptide with 10% Pd/C (80 mg) in DMF (4 mL) under 40 psi of H_2 for 2 h, followed by treatment of the product with trifluoroacetic acid (40 mL) for 2 h, gave 111 mg of [Sar[1],DL-Hfv[8]]AII.

Separation of this diastereomeric mixture by countercurrent distribution in 8:1:2:9 1-butanol–pyridine–acetic acid–water for 800 transfers gave two fractions of K values 0.52 and 0.83. Further purification of the respective fractions by gel filtration on Sephadex G10 (2 × 96 cm) in 10% AcOH gave 24 mg (42%) of the L diastereomer (**8**: K = 0.52; TLC R_f (i) 0.17, (iii) 0.19) and 40 mg (64%) of the D diastereomer (**9**: K = 0.83; TLC R_f (i) 0.18, (iii) 0.22). The stereochemical assignments of these diastereomers were based on their susceptibilities to carboxypeptidase Y digestion, in which the L diastereomer **8** gave Val (0.59), Tyr (1.00), Val (0.59), His (0.95), Pro (0.87), Hfv (0.54), whereas the D diastereomer **9** gave only Tyr (0.16) and His (0.21) without any Hfv. FAB-MS analyses gave M + 1 of 1049 for both **8** and **9**. Amino acid analysis of a hydrolysate gave Sar (0.98), Arg (1.03), Val (0.98), Tyr (1.05), Val (0.98), His (0.98), Pro (0.95), Hfv (1.04), peptide content 91% for **8**; and Sar (1.01), Arg (1.01), Val (1.00), Tyr (1.03), Val (1.00), His (0.97), Pro (0.97), Hfv (0.96), peptide content 84% for **9**.

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Registry No. **1**, 107496-44-6; **2**, 107496-45-7; **3**, 78164-91-7; **4**, 16063-80-2; **5**, 107496-46-8; **6**, 107496-47-9; **7**, 107496-48-0; **8**, 107496-49-1; **9**, 107538-64-7; [BOC-Sar[1],DL-Hfv-OBzl[8]]AII, 107496-51-5; $BrCH_2COOCH_2Ph$, 5437-45-6; PPh_3, 603-35-0; $Ph_3P{=}CHCOOCH_2Ph$, 15097-38-8; $(CF_3)_2CO$, 684-16-2; $(BOC)_2O$, 24424-99-5; 5-L-valine angiotensin II, 58-49-1.

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Psychotropic Agents: Synthesis and Antipsychotic Activity of Substituted β-Carbolines

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A series of novel substituted β-carbolines was synthesized and tested for potential antipsychotic activity. Several compounds displayed moderate antipsychotic activity in vitro and in vivo as determined by relevant receptor binding assays and behavioral tests. The effect of substituents on antipsychotic activity was examined. The β-carbolines **10** and **19** containing 2-(2-pyridinyl)ethyl and 2-(2-quinolinyl)ethyl side chains were the most potent analogues, blocking discrete trial conditioned avoidance responding in rats with AB_{50}'s of 23 and 10 mg/kg, respectively. Both showed moderate activity at the D_2 receptor sites, but they lacked oral activity. In contrast, the β-carboline **13** containing the 4-(4-pyridinyl)butyl side chain exhibited oral activity in the discrete trial conditioned avoidance screen with an AB_{50} of 31 mg/kg. Most compounds did not antagonize apomorphine-induced stereotyped behavior, which is indicative of low potential for extrapyramidal side effect (EPS) liability.

While dopamine (DA) antagonists are used effectively in the treatment of schizophrenia,[1-3] some patients fail to respond to treatment.[4,5] Furthermore, antipsychotic therapies are known to produce extrapyramidal side effects (EPS)[5,6] such as parkinsonism, dystonia, akathisia, and tardive dyskinesia (TD).[7]

Studies have shown that neuroleptic therapy with drugs with apparent specificity for limbic as opposed to striatal regions of the brain may have a lower EPS liability.[8] Those that are potent antagonists of apomorphine-induced stereotyped behavior, on the other hand, have been asso-

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