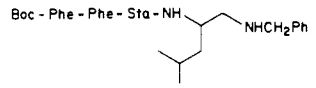
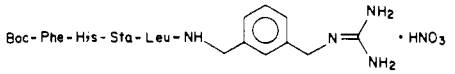
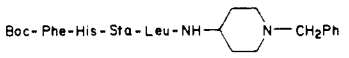
Table I. Potencies of Renin Inhibitors

no.		K_I, nM: purified human kidney renin[a]	I_{50}, nM: human plasma renin[b]	I_{50}, nM: hog kidney renin[b]
1		0.026 ± 0.008	37% I; ≈1000 nM	858 (731–1050)
2	Boc-Phe-Phe-Sta-Leu-NHCH$_2$Ph	43 ± 8.6	1900 (1750–2100)	18 (17.1–18.8)
3	Boc-Phe-Phe-Sta-Leu-Phe-NH$_2$	4.8 ± 1.0		88 (83.0–93.4)
4		3.6 ± 1.1	9.0 (7.4–10.1)	19 (17.4–21.2)
5		0.064 ± 0.020	25 (6.2–100)	269 (244–296)

[a] Values from triplicate determinations, with standard deviation. Values from duplicate or triplicate determinations, with 95% confidence limit.

related in part to the high lipophilicity of compounds such as the well-bound 1 since, in at least some cases, the effect appears to be modulated by the addition of hydrophilic functionality (cf. 4). A detailed account of these studies will be reported elsewhere.

The dramatic effect of plasma binding on the apparent potency of 1 as a renin inhibitor underscores the importance of enzyme purity in such studies. Against the crude human renin preparation, 1 appeared to be simply a weak inhibitor. It was only the high purity of the enzyme used in the human kidney renin assay that unmasked the unique potency of 1, leading in turn to discovery of the heretofore unsuspected plasma binding component. Whether the reduced potency seen in the hog renin assay was due to an actual reduction in enzyme affinity or a binding to impurities in this crude enzyme preparation was not established.

All peptides were prepared by coupling N^{α}-Boc amino acids to the appropriate amino terminal segment using 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (EDC) and 1-hydroxybenzotriazole (HBT) in dimethylformamide. N-Deprotection, where necessary, was carried out with HCl(g) in ethyl acetate at 0 °C. For preparation of compound 1, N^{α}-Boc-Leu-benzylamide was reduced with borane–THF according to the procedure of Roeske and co-workers.[14] The resulting amide was N-deprotected and further coupled as above. Extraneous coupling to the secondary amine was not significant. All final products were >95% pure by HPLC and exhibited NMR spectra consistent with the assigned structures; all gave satisfactory elemental and/or amino acid analyses. Several intermediates in the synthesis of 1 were additionally characterized by satisfactory NMR and mass spectra.

Compound 1 (0.13 mM) in reconstituted human plasma was not observed (<1%) by HPLC either at zero time or after incubation at 37 °C for 64 min. However, after precipitation of the plasma by an equal volume of acetone, 1 was observed in the supernatant at zero time (98%) and after incubation for 64 min (97%).

Compound 4 (0.12 mM) in reconstituted human plasma was observed by HPLC at zero time (87%) and after incubation at 37 °C for 64 min (83%).

For the human kidney renin assay, pure human kidney renin was prepared according to Slater and Strout.[15] The fluorimetric assay of Poe et al.[16] was used, measuring cleavage for 16–24 h of 5700 nM synthetic tetradecapeptide renin substrate at 37 °C and pH 7.2 (0.1 M citrate phosphate) by 0.5 ng/mL (10 pM) human kidney renin. Experimental data were fit to a standard competitive inhibition equation with no correction for renin-bound inhibitor.[16] Results are summarized in Table I. The K_I value obtained for 1 as an inhibitor of the cleavage of hog angiotensinogen (Sigma) by the purified human renin was identical within experimental error to the value reported in the table for inhibition of the human kidney enzyme acting upon the tetradecapeptide substrate.

The hog renin assay measured the inhibitory potency of peptides vs. hog kidney renin in accordance with the procedure of Rich et al.,[17] except that pH 7.3 was used. The results of the assay, presented in the table, are expressed as I_{50} values, which refer to the concentration of inhibitor necessary to produce 50% inhibition of renin activity. This I_{50} value was obtained typically by plotting data from four inhibitor concentrations. Pepstatin was used as an active control.

The human plasma renin assay was carried out as described in Boger et al.[7]

Acknowledgment. The authors acknowledge Dr. Leonard Oppenheimer and Nicholas Tonkonoh for aid in the analysis of experimental data and Mary Banker for assistance in preparation of the manuscript.

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Received May 13, 1985

N-(1,3,4,6,7,12b-Hexahydro-2*H*-benzo[*b*]furo[2,3-*a*]quinolizin-2-yl)-*N*-methyl-2-hydroxyethanesulfonamide: A Potent and Selective α_2-Adrenoceptor Antagonist

Sir:

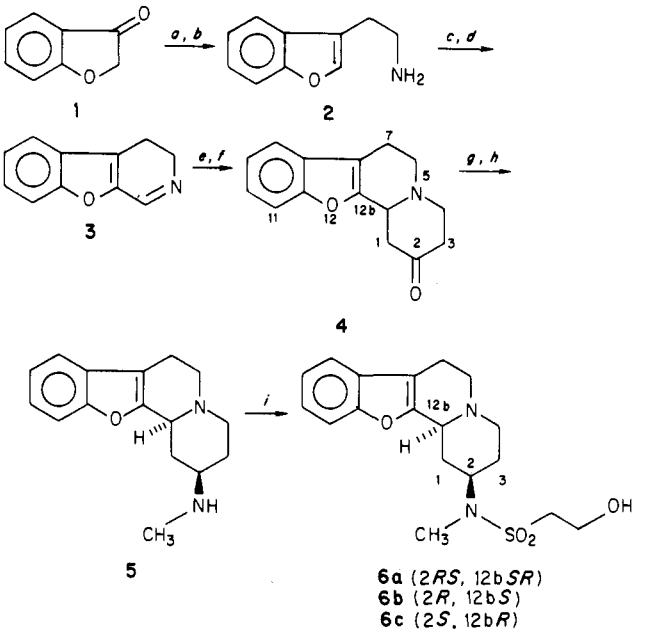
α-Adrenoceptors exist as two distinct subclasses that have been characterized both pharmacologically and functionally. The evidence for this classification has been

recently reviewed.[1-3] α_1- and α_2-adrenoceptors are generally distinguished by their selectivity toward a standard series of agonists and antagonists, irrespective of anatomical distribution.[4-6] Recent work has also provided a biochemical[7-10] and structural[11-13] basis for differentiating these receptors.

The physiological significance of α_2-adrenoceptors is currently an area of considerable interest. Stimulation of prejunctional α_2-adrenoceptors inhibits release of norepinephrine from noradrenergic nerve terminals[14-16] and thereby modulates synaptic and circulating concentrations of this neurotransmitter. Postjunctional α_2-adrenoceptors mediate contraction of vascular smooth muscle[17-19] and regulate secretion of certain hormones.[20-23] Stimulation of medullary α_2-adrenoceptors by the α_2-agonist clonidine results in reduced peripheral sympathetic tone and enhanced vagal tone. Consequently, both blood pressure and heart rate fall.[24,25]

Compounds that are selective agonists or antagonists for these receptor subtypes offer possibilities for developing novel therapeutic agents and also may serve as valuable tools for investigating the physiological roles of α-adrenoceptors. In this paper we describe the synthesis and characterization of a highly potent and selective α_2-adrenoceptor antagonist, *N*-(1,3,4,6,7,12b-hexahydro-2*H*-benzo[*b*]furo[2,3-*a*]quinolizin-2-yl)-*N*-methyl-2-hydroxyethanesulfonamide, **6**. We also report the stereoselective preference of α_2-adrenoceptors for one enantiomer of this compound.

Scheme I



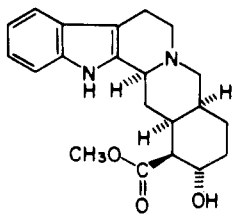
[a] NaH, $(EtO)_2P(O)CH_2CN$. [b] LAH, Et_2O. [c] HCOOEt, 80 °C. [d] PPA, 80 °C. [e] 2-[(trimethylsilyl)oxy]-1,3-butadiene, $BF_3 \cdot Et_2O$. [f] MeOH, K_2CO_3. [g] CH_3NH_2, $TiCl_4$. [h] $NaBH_4$, EtOH. [i] $HOCH_2CH_2SO_2Cl$, Et_3N.

Table I. Radioligand Binding Results

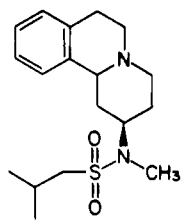
	K_i,[a] nM			
compd	[^{3}H]clonidine (α_2)	[^{3}H]rauwolscine (α_2)	[^{3}H]prazosin (α_1)	selectivity[b]
6a	1.36 ± 0.16	1.6 ± 0.5	210 ± 30	130
6b	0.77 ± 0.19	1.1 ± 0.3	110 ± 30	100
6c	100 ± 10	190 ± 7.7	8000 ± 700	42
yohimbine	49 ± 1	10.0 ± 2.1	220 ± 10	22

[a] Values are means ± SD for at least three separate determinations. [b] K_i [^{3}H]prazosin/K_i [^{3}H]rauwolscine.

Previous studies of yohimbine and diastereomerically related compounds have established that the ester substituent plays a critical role with regard to both potency and selectivity for the α_2-adrenoceptor.[26] Electronic as well as topological characteristics of the ester appear to be important. During the course of our investigation of simplified derivatives of yohimbine, the α_2-adrenoceptor antagonist properties of WY 26703 and related compounds were reported.[27] Structural comparison of these benzo[*a*]quinolizines with the yohimbine diastereomer, rauwolscine, suggested that the sulfonamide of WY 26703 acts as an ester surrogate at the α_2-adrenoceptor. Application of this concept to simplified yohimbine analogs formed the rationale for the design of the present molecules.



Rauwolscine



WY 26703

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Table II. Antagonism of Clonidine and Methoxamine in the Field-Stimulated Rat Vas Deferens

compd	clonidine		methoxamine		selectivity[b]
	pA_2[a]	slope	pA_2[a]	slope	
6a	8.77 ± 0.17	1.01 ± 0.15	6.99 ± 0.28	0.96 ± 0.12	60
6b	9.10 ± 0.23	0.94 ± 0.17	7.46 ± 0.11	0.93 ± 0.20	44
6c	7.4[c]		5.6[c]		63
yohimbine	7.65 ± 0.13	1.01 ± 0.11	6.52 ± 0.29	1.01 ± 0.08	14

[a] Values are means ± SD from Schild plot determined using at least three concentrations of antagonist and four tissues per concentration. [b] Antilog (pA_2 for clonidine − pA_2 for methoxamine). [c] Values are the mean of determinations in two tissues.

Table III. Reversal of Clonidine-Induced Mydriasis in the Rat

compd	ED_{50},[a] μg/kg, iv	compd	ED_{50},[a] μg/kg, iv
6a	43.5 (35.8–52.9)[b]	6c	5410 (4610–6350)
6b	34.6 (31.3–38.4)	yohimbine	1040 (940–1150)

[a] Dose required to reduce pupillary diameter to one-half of the maximum achieved following administration of clonidine. [b] 95% confidence limits given in parentheses.

Chemistry. Scheme I outlines the seven-step synthesis of these compounds, starting with the readily available 3-coumaranone 1.[28] Condensation of the coumaranone and diethyl cyanomethylphosphonate under Horner–Emmons conditions yielded 3-(cyanomethyl)benzofuran (66%) after distillation. Lithium aluminum hydride reduced the resulting nitrile to the corresponding amine, **2**, which was readily formylated in refluxing ethyl formate. Hot PPA effected cyclization of the formamide thus obtained to 3,4-dihydrobenzofuro[2,3-*c*]pyridine, **3**. The transformation of 3-(cyanomethyl)benzofuran to **3** was accomplished in 45% overall yield without purification of intermediates.

Ring annelation of **3**, giving rise to the required tetracyclic skeleton, represented the crucial transformation in our synthetic plan. This goal was achieved through the use of a cycloaddition reaction between the imine portion of **3** and 2-[(trimethylsilyl)oxy]-1,3-butadiene. Hydrolysis of the intermediate silyl enol ether, which could be isolated, afforded ketone **4** in 56% yield. The scope and stereochemical consequences of this reaction, which is both solvent and catalyst dependent, will be reported elsewhere.

Titanium tetrachloride mediated imine formation followed by sodium borohydride reduction afforded **5** (75%) with the relative stereochemistry indicated. Sulfonylation with 2-hydroxyethanesulfonyl chloride[29] yielded **6a** (55%): mp of the HCl salt 250 °C dec. Final corroboration of the configuration of these molecules was obtained by X-ray crystallographic analysis (vida infra).

Compound **4** formed diastereomeric salts with di-*p*-toluyl-L- or D-tartaric acid, thus allowing separation of each enantiomer of the ketone (>98% pure by NMR using shift reagents). Processing the enantiomeric ketones according to Scheme I yielded sulfonamides **6b** (HCl salt: mp 270–273 °C; $[\alpha]^{20}_D$ 13°, *c* 0.001, MeOH) and **6c** (HCl salt: mp 270–273 °C; $[\alpha]^{20}_D$ −13°; *c* 0.001, MeOH). Single crystal X-ray diffraction revealed that the absolute configuration of **6b** was 2*R*,12b*S*, analogous to that of the yohimbine alkaloids[30] and corresponding to the configuration indicated in Scheme I.

Biology. Tables I–III summarize the results of three assays that were employed to assess the potency and selectivity of these compounds as α_2-adrenoceptor antagonists. The selective α_2-adrenoceptor antagonist yohimbine has been included for reference. Relative affinities of **6a–c** for central α-adrenoceptors were determined by measuring radioligand displacement from membrane binding sites of calf and rat cerebral cortex.[31] Displacement of [^{3}H]clonidine or [^{3}H]rauwolscine was used as a measure of interaction with α_2-adrenoceptors while [^{3}H]prazosin displacement served as an assay for α_1-adrenoceptor affinity (Table I). The antagonist properties of these compounds toward presynaptic α_2- and postsynaptic α_1-adrenoceptors were characterized in the isolated, field-stimulated rat vas deferens according to previously published procedures (Table II).[32] In vivo, clonidine produces mydriasis in rats by activating postsynaptic α_2-adrenoceptors located in the central nervous system.[33] Therefore, reversal of an established clonidine-induced mydriasis reflects the ability of a compound to penetrate the blood–brain barrier and act as a central α_2-adrenoceptor antagonist (Table III).

Data in Tables I–III revealed that racemic **6a** is a potent and selective α_2-adrenoceptor antagonist. The compound exhibited high affinity for [^{3}H]rauwolscine binding sites with 130-fold selectivity vs. [^{3}H]prazosin binding sites. In the rat vas deferens low concentrations of **6a** competitively antagonized the effects of clonidine at presynaptic α_2-adrenoceptors with relatively little antagonistic effect against methoxamine at postsynaptic α_1-adrenoceptors. Finally, **6a** effectively reversed an established clonidine-induced mydriasis in rats, demonstrating that it readily crosses the blood–brain barrier to act as an α_2-adrenoceptor antagonist in the central nervous system. In all assays **6a** was substantially more potent and selective than the standard α_2-adrenoceptor antagonist yohimbine.

Hormone receptors commonly exhibit enantioselectivity in their interaction with ligands. Schmitt has reported that α_2-adrenoceptors display such stereopreference.[34] Results shown in Table I indicated that the adrenergic properties of **6a** resided primarily in one enantiomer, **6b**. This compound was 50–150-fold more potent in the three assays than the less active enantiomer, **6c**. The structural resemblance of **6a** to the yohimbine alkaloids suggested that the absolute configuration of the active enantiomer **6b** should correspond to the natural configuration of yohimbine. Subsequent X-ray crystallographic analysis confirmed the predicted (2*R*,12b*S*) stereochemistry of **6b**. This compound represents a novel class of potent and selective α_2-adrenoceptor antagonist that may serve as a useful tool for investigating the physiological role of these receptors in the periphery and central nervous system and that may have clinical utility.

Acknowledgment. We thank Dr. J. P. Springer and J. Hirshfield for carrying out the X-ray crystallography experiments, J. P. Moreau for elemental analyses, and J. Murphy for NMR studies. We are also grateful to Mary

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Banker for the preparation of this manuscript.

Registry No. 1, 7169-34-8; 2, 27404-31-5; 3, 97456-65-0; 4, 98678-87-6; 5, 98678-88-7; 6a, 98678-89-8; 6a·HCl, 98678-90-1; 6b, 98719-20-1; 6b·HCl, 98757-15-4; 6c, 98719-21-2; 6c·HCl, 98757-16-5; 3-(cyanomethyl)benzofuran, 52407-43-9; CH_2=C(OSiMe_3)CH=CH_2, 38053-91-7.

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Novel Vasopressin Analogues That Help Define a Minimum Effective Antagonist Pharmacophore

Sir:

In our attempt to ultimately design small molecules that act as vasopressin receptor antagonists, an initial goal has been to define the minimum active fragment of the class of peptide V_2-receptor antagonists first described by Manning et al. (exemplified by compound 1, Figure 1).[1] We have focused a portion of our effort on the tripeptide tail which is common to these antagonists as well as to vasopressin. This tail is postulated to contain key binding elements of the agonist pharmacophore.[2] It has recently been shown by Manning et al.[3] and independently by us[4,5] that potent octapeptide vasopressin antagonists can be obtained by deletion of the carboxyl-terminal glycine moiety, leaving a carboxyl-terminal argininamide, for example compounds **2** (SK&F 101926) and **3**. We have previously presented evidence that the pharmacophore requirements at the renal V_2-receptor differ for vasopressin agonists and antagonists.[6,7] For example, analogues of **1** (or its L-Tyr(Et)[2] congener) with either D- or L-arginine at position 8 are essentially equipotent, which is not the case with agonists.[1,6] This suggested that the terminal carboxamide group in **2** or **3** may not be essential in the antagonist pharmacophore since this situation would allow the D- and L-arginine analogues to be topochemically equivalent. This hypothesis was tested by the preparation of compound **4**, in which the lysine of **3** is replaced by an alkyldiamine.

The synthesis of **4** was dependent on proline acid **5** which was prepared by standard solid-phase synthesis techniques on Merrifield resin, cleaved from the resin with anhydrous HF, and cyclized under dilute conditions with aqueous potassium ferricyanide. Peptide **5** was then purified by flash chromatography on C-18 reverse phase using 50% aqueous acetonitrile containing 0.1% TFA[12] as eluant to afford partially purified acid. Condensation of this material with mono-Boc-cadaverine[8] using DCC/HOBT in DMF followed by deblocking with neat TFA afforded the crude peptide **4**. Purification was accomplished by ion exchange chromatography on BioRex 70 followed by preparative HPLC.[9]

The peptide was evaluated in vitro for vasopressin receptor binding and inhibition of LVP-sensitive adenylate cyclase in porcine renal medullary preparations, which have been shown to be similar to the human receptors.[5] It was also evaluated in vivo in a hydropenic rat assay.[10] The results are summarized in Table I. The aminoalkyl analogue **4** retains good activity when compared to **2**[11] or **3**, which supports our original hypothesis and suggests that

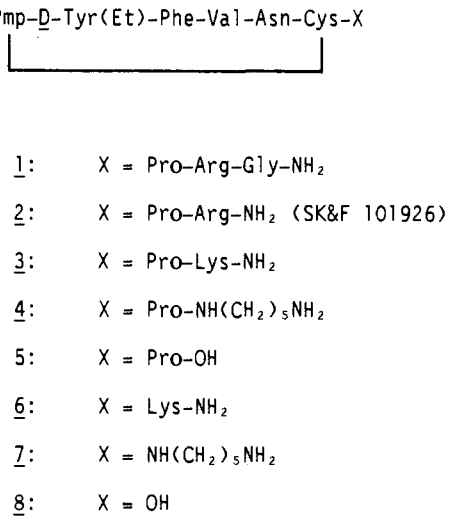

Figure 1.

Table I. Activity of Vasopressin Antagonists

compd	pig K_{bind},[a] nM	pig K_i,[b] nM	rat: ED_{300},[c] μg/kg
LVP	4.6	*b*	
1	12	6.4	11.2
2	12	3.9	9.2
3	37	9.4	22
4	30	7.2	27
6	26	5.8	59
7	19	6.8	94

[a] Inhibition constant for [^{3}H]LVP binding to medullary membranes of pig kidney (see ref 6). [b] Inhibition constant for vasopressin-stimulated adenylate cyclase of medullary membranes of pig kidney. K_{act} LVP was determined to be 1.2 nM (see ref 6). [c] Dose required to lower urine osmolality to 300 mOsm/kg (see ref 10).

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(8) Mono-Boc-cadaverine can be conveniently prepared by reacting an excess of diamine with di-*tert*-butyl dicarbonate in methylene chloride followed by an extractive workup.
(9) All new peptides were characterized by amino acid analysis and FAB mass spectrometry, and their purity was established by TLC and HPLC.
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(11) Compound **2** (SK&F 101926) is one of the most potent V_2-receptor antagonists published to date.
(12) Abbreviations: Pmp, β,β-cyclopentamethylene-β-mercaptopropionic acid; AVP, arginine vasopressin; LVP, lysine vasopressin; DCC, *N,N'*-dicyclohexylcarbodiimide; HOBT, 1-hydroxybenzotriazole; TFA, trifluoroacetic acid; DMF, dimethylformamide; Boc, *tert*-butyloxycarbonyl.

0022-2623/85/1828-1759$01.50/0