significant central dopaminergic activity. The potent and specific renal vasodilator effects of this coumpound suggest that it might be useful in reversing the increased renal vascular resistance seen in many hypertensive subjects. In addition, it could be of utility in other disease states in which renal ischemia is a prominent component.

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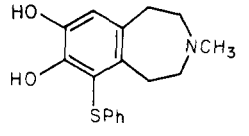
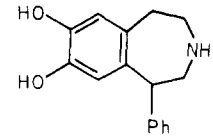
6-(Phenylthio)-Substituted 2,3,4,5-Tetrahydro-1*H*-3-benzazepines, a Novel Class of Dopamine Receptor Antagonists and Neuroleptics

Sir:

Although the activity of antipsychotic agents is generally associated with their influence on dopaminergic neurons,[1] their structural relationship[2] to the neurotransmitter is not readily apparent.[3] In this communication we describe a novel class of dopamine receptor antagonists and neuroleptics, 2,3,4,5-tetrahydro-7,8-dihydroxy-6-(phenylthio)-1*H*-3-benzazepines, e.g., 1 (SK&F 83742), that clearly incorporate the structure of dopamine within their molecular framework.



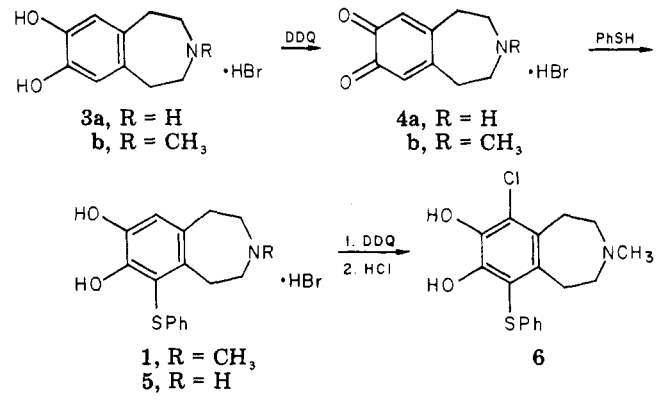
1



2

These agents were identified in an extensive study of relatives of 2,3,4,5-tetrahydro-7,8-dihydroxy-1-phenyl-1*H*-3-benzazepine (**2**, SK&F 38393), a potent agonist of both central[4] and peripheral[5] dopamine receptors. According to a recent subclassification[6] of central dopamine receptors, **2** is selective for the D-1 subtype. Conformationally, **2** differs from most dopamine receptor agonists which are analogues of dopamine constrained in an extended (anti, trans) form.[7-9] The tetrahydroazepine ring of **2**, although allowing considerable flexibility, imparts some conformational restraints. Thus, the spatial relationship of the nitrogen atom and the fused aromatic ring of **2** can vary from a nearly folded (fully eclipsed, cis) orientation[10] to a partially eclipsed (anticlinal) one; however, the extended (trans) form is prohibited.[11] This uniqueness, coupled with the partial agonism exhibited by **2** in stimulating adenylate cyclase,[4] prompted our investigation of related structures to identify potentially novel and selective dopamine receptor agonists and antagonists. Preliminary accounts of these studies are presented here and in the preceding communication.[12]

Scheme I



6-(Phenylthio)-substituted benzazepines were prepared as outlined in Scheme I.[13] Oxidation of **3a**[14] and **3b** (obtained from the corresponding dimethoxybenzazepine[14] by refluxing in 48% aqueous HBr, 47% yield, mp 230–233 °C, after recrystallization from MeOH–Et_2O) with 2,3-di-

(1) S. H. Snyder, *Am. J. Psychiatry*, **133**, 197 (1976).
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(3) A similar mode of receptor interaction has been suggested for chlorpromazine and the trans form of dopamine on the basis of possible overlap of the amino group and other structural features [A. S. Horn and S. H. Snyder, *Proc. Natl. Acad. Sci. U.S.A.*, **68**, 2325 (1971)]. Antipsychotic drugs of the butaclamol type have been employed to map the central dopamine receptor. This study has resulted in the proposal of a receptor model [A. H. Philipp, L. G. Humber, and K. Voith, *J. Med. Chem.*, **22**, 768 (1979)]. In neither chlorpromazine nor butaclamol, however, is the dopamine framework obvious.
(4) P. E. Setler, H. M. Sarau, C. L. Zirkle, and H. L. Saunders, *Eur. J. Pharmacol.*, **50**, 419 (1978).
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(10) Several catecholic tetrahydroisoquinolines, e.g., (-)-1,2-dihydroxyaporphine [R. J. Miller, P. H. Kelly, and J. L. Neumeyer, *Eur. J. Pharmacol.*, **35**, 77 (1976)] and (*S*)-(-)-salsolinol [P. Seeman, M. Titeler, J. Tedesco, P. Weinrich, and D. Sinclair, *Adv. Biochem. Psychopharmacol.*, **19**, 167–176 (1978)], in which the aromatic ring and basic nitrogen are rigidly fixed in a cis orientation apparently do not interact with dopamine receptors.
(11) J. W. Wilson, "Program and Abstracts", National Medicinal Chemistry Symposium of the American Chemical Society, 16th, Kalamazoo, MI, June 18–22, 1978, American Chemical Society, Washington, D.C., 1978, p 155.
(12) J. Weinstock, J. W. Wilson, D. L. Ladd, C. K. Brush, F. R. Pfeiffer, G. Y. Kuo, K. G. Holden, N. C. F. Yim, R. A. Hahn, J. R. Wardell, Jr., A. J. Tobia, P. E. Setler, H. M. Sarau, and P. T. Ridley, *J. Med. Chem.*, **23**, preceding communication in this issue (1980).
(13) All new compounds for which melting points are given afforded satisfactory analyses for C, H, and N. NMR and MS were determined for all compounds; they were considered consistent with the assigned structures.
(14) B. Pecherer, R. C. Sunbury, and A. Brossi, *J. Heterocycl. Chem.*, **8**, 779 (1971).

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Table I. Dopamine Antagonist and Neuroleptic Actions

compd	dopamine-sensitive adenylate cyclase blockade[a]		avoidance acquisition, naive rats: [b,c] ED_{50}, mg/kg ip	rat catalepsy production: [c,d] ED_{50}, mg/kg ip
	IC_{50}, M	K_i, M		
1	2.4×10^{-7}	2.2×10^{-8}	0.5 (0.3-1.0)	5.6 (3.6-16.0)
5	2.7×10^{-6}	2.5×10^{-7}	4.9 (1.7-20.1)[e]	64.6 (47.0-113.1)
6	3.6×10^{-7}	3.3×10^{-8}	0.08 (0.03-2.0)	3.0 (1.0-8.1)
chlorpromazine	1.3×10^{-6}	1.18×10^{-7}	1.5 (0.7-2.8)	4.2 (2.4-7.6)

[a] Obtained by a literature[19,20] procedure. [b] Obtained by a literature[22] procedure. [c] Least-squares regression analysis was used to calculate ED_{50} values, and the 95% confidence limits (in parentheses) were computed using Feiller's theorem (D. J. Finney, "Probit Analysis", Cambridge University Press, Cambridge, 1952; D. J. Finney, "Statistical Methods in Biological Assay", Hafner Publishing Co., New York, 1952). [d] Obtained by a literature[23] procedure. [e] ED_{50} = 2.1 (0.7-9.8) mg/kg sc.

Table II. Selective Antagonism of the Renal Vasodilator Activity of Dopamine by 1 (300 μg/kg, iv)

agonist	dose, μg/kg, iv	renal vascular resistance, % change: control	renal vascular resistance, % change: treated
dopamine	0.3	−8 ± 2[a]	+4 ± 2[b]
	3.0	−27 ± 8	+8 ± 4[b]
bradykinin	3.0	−14 ± 3	−19 ± 3
	15.0	−30 ± 4	−37 ± 4

[a] Mean response plus or minus standard error of four dogs. [b] Statistically significant from corresponding control response ($p < 0.05$).

chloro-5,6-dicyano-1,4-benzoquinone (DDQ) in MeOH under N_2 gave **4a** and **4b** as crystalline precipitates that were used without purification. These dione hydrobromide salts were added in portions to a MeOH solution of an excess of thiophenol to give 60% of **5**, mp 125–128 °C (EtOH–Et_2O),[15] and a quantiative yield of **1**, mp 116–118 °C dec (MeOH–Et_2O).[16] Treatment of an aqueous solution of **1**, containing about 0.1 g of ascorbic acid, with NH_3 (pH 7.0) gave the *base*, mp 174–175 °C (MeOH–EtOAc). Addition of HCl to a solution of the base in MeOH afforded the *HCl salt*, mp 232–233 °C. Oxidation of this salt with DDQ gave a dione, which was treated with HCl to give a mixture from which **6** was isolated by MeCN trituration followed by liberation of the base (as described for **1**) and recrystallization (MeOH–EtOAc), mp 173–174 °C (13% yield).

Potential dopamine receptor antagonist activity[17,18] was measured in a test for inhibition of dopamine stimulation of rat striatal adenylate cyclase.[19,20] Neuroleptic activity[21] was evaluated in tests for blockade of avoidance acquisition[22] and production of catalepsy[23] in rats. Results of these studies are tabulated in Table I. As indicated, **5** was slightly less potent than chlorpromazine in blocking both adenylate cyclase and avoidance acquisition. The *N*-methyl derivative **1** was strikingly more potent in both tests. The chloro-substituted derivative **6** was less potent than **1** in the adenylate cyclase test; however, it was more effective in the avoidance acquisition test. Potency of the neuroleptic benzazepines, **1**, **5**, and **6**, was relatively greater in the avoidance procedure than for the induction of catalepsy (see Table I). Potency in the latter test generally parallels production of extrapyramidal symptoms.[24,25]

Selective peripheral dopamine receptor antagonist activity, of utility for definition of the receptor system,[26] was established for **1**. Administration of 100–300 μg/kg antagonized the renal vasodilator activity of dopamine[27] in a dose-related manner. This antagonism was selective. Comparable decreases in renal vascular resistance produced by bradykinin were not similarly affected (Table II). Moreover, treatment with **1** did not result in large alterations of base-line hemodynamics, indicating that its inhibitory effect on renal vascular responses to dopamine was not the result of physiological antagonism.

The results presented here and in the preceding communication[12] clearly indicate that the partial agonism displayed by **2** can be separated by suitable structural modification to yield potent and selective agonists and antagonists which retain the catecholamine moiety of the natural agonist, dopamine.

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(15) This is apparently a metastable form. In another experiment, a product having identical NMR and MS, mp 184 °C, was obtained.
(16) Anal. ($C_{11}H_{20}BrNO_2S \cdot 0.25H_2O$) C, H, N.
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(27) This effect was evaluated in pentobarbital-anesthetized dogs artificially ventilated with room air. Catheters were placed in a carotid artery and femoral vein for measurement of arterial blood pressure and iv administration of drug solutions, respectively. Blood flow to one kidney was monitored electromagnetically. Renal vascular resistance was calculated as the ratio of pressure/flow.

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