(±)-3-Allyl-6-bromo-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin, a New High-Affinity D1 Dopamine Receptor Ligand: Synthesis and Structure-Activity Relationship

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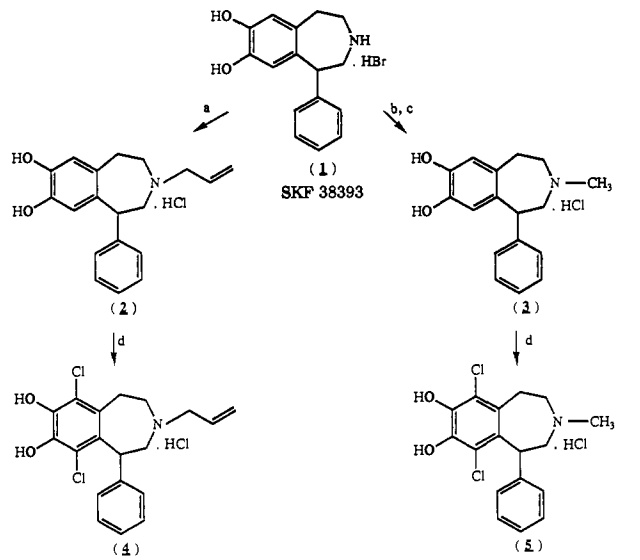
The 7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepines form a series of compounds having a high affinity at the D1 dopamine receptor. The 6-chloro derivative has been previously shown to have enhanced affinity, selectivity, and agonist activity. In an attempt to study the effect of substitution of a 6-bromo group in place of the 6-chloro, we have synthesized a series of compounds and evaluated them for their affinity for the D1 receptor. The results show that the 6-bromo derivatives have virtually identical affinities to their 6-chloro counterparts, a finding similar to that found in the D1 antagonist 7-halo-8-hydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine series. From the present work, 3-allyl-6-bromo-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (6-Br-APB) has been identified as a suitable candidate for further in vivo studies and resolution into its active and inactive enantiomers.

The involvement of dopamine (DA) and dopaminergic neurons in various physiological and pathophysiological conditions of the central nervous system (CNS) has stimulated the search for suitable therapeutic approaches utilizing dopaminergic agonists and antagonists.[1] Until recently, dopamine receptors were classified into two distinct categories, the D1 and D2 receptors, on the basis of available physiological, biochemical, and pharmacological evidence.[2-4]

The two receptors were distinguished primarily on the basis of their linkage to the second messenger generating adenylate cyclase, with the D1 receptor stimulating the enzyme and hence cAMP production and the D2 receptors inhibiting cAMP production.[2-4] Recent evidence suggests that both the D1 and D2 receptors are also linked to other second messenger systems, for example stimulation of phospholipase C, and stimulation of potassium and calcium channels.[5] Furthermore, the use of molecular biological approaches has led to the identification of a new D3 receptor as well as subtypes of the D2 receptor ($D2_{short}D2_{long}$).[6-8] These discoveries have stimulated the search for new selective agonists and antagonists for each receptor subtype. Our investigations have extended previous structure-activity relationship (SAR) studies of the D1 agonists belonging to the 1-phenyl-3-benzazepine class.[9-12]

Most of these earlier studies pertain to the peripheral effects (renal vasodilator activity) of the D1 agonists rather than their CNS effects. The 7,8-catechol substitution of such benzazepines has been shown to be essential for D1 binding affinity and agonist activity.[9,10] The 1-phenyl ring is essential in conferring both D1 affinity and D1 selectivity but has no influence on the agonist-antagonist activity of these compounds.[9,10,15] On the other hand, substitution at the 3-position can influence affinity and selectivity as well as agonist/antagonist activity.[9,10,14,15] A 3-methyl substituent leads to an increase in the affinity and selectivity for the D1 receptor but also with concomitant loss of efficacy or agonist activity.[10] A 3-substituent larger than a methyl group generally leads to a considerable loss of D1 affinity and potency.[9,10,14] However, an exception has been

Scheme I[a]



[a] (a) Allyl bromide/K_2CO_3; (b) acetic formic anhydride; (c) BH_3-THF; (d) SO_2Cl_2.

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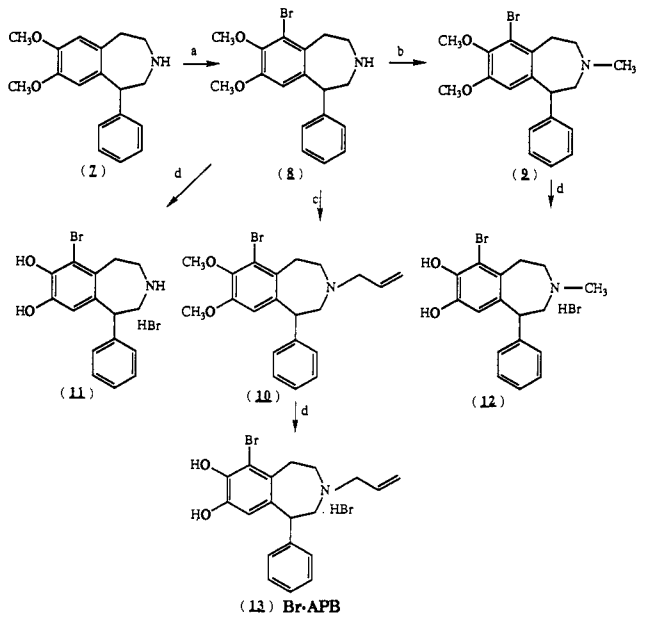
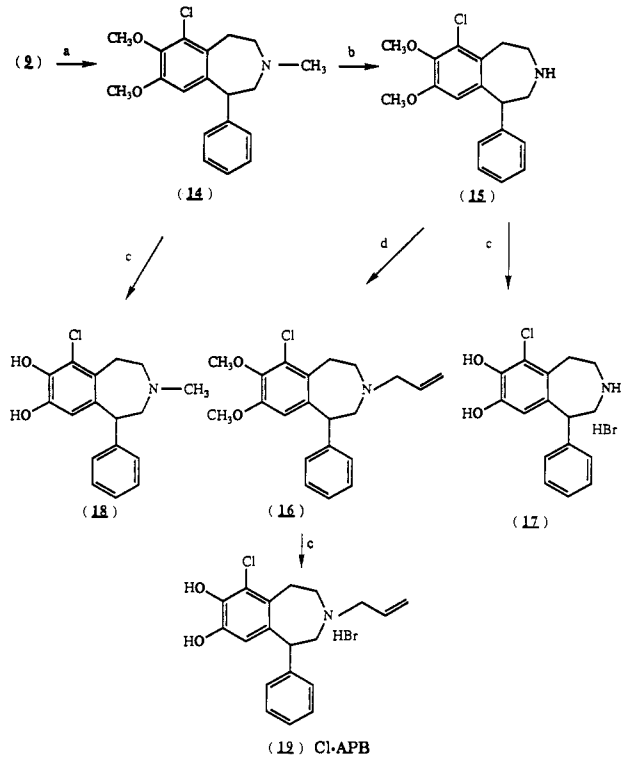
Scheme II[a]



[a] (a) Br_2/AcOH; (b) HCHO/HCOOH; (c) allyl bromide/K_2CO_3; (d) BBr_3/CH_2Cl_2.

suggested for the 3-allyl substitution which leads to the retention of both D1 affinity and efficacy.[10,14,18] 6-Chloro substitution confers a favorable influence on the affinity.[10,15,18] In order to further explore the influence of the 6-chloro substituent, we investigated the corresponding 6-bromo-substituted compounds and compared them with both the 6-chloro and 6-unsubstituted compounds. Other 6-halo substituents (6-fluoro and 6-iodo) and other 6-substituents [6-methyl, 6-carboxyl, 6-*n*-propyl, 6-hydroxy, 6-(carboxymethyl), 6-(methylthio)] have been shown to considerably lower the D1 agonist activity and hence were not considered in the present studies.[10,13,16]

Scheme III[a]



[a] (a) *n*-BuLi/Et_2O, −70 °C, C_2Cl_6; (b) BrCN/C_6H_6, HCl/AcOH; (c) BBr_3/CH_2Cl_2, −70 °C; (d) allyl bromide/K_2CO_3.

Chemistry

The 1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine skeleton was constructed by the method of Walter and Chang[17] (Scheme I). Treatment of benzazepine **1**, (SKF 38393) with allyl bromide in the presence of potassium carbonate yielded **2**, the 3-allyl derivative of SKF 38393. The corresponding 3-methyl derivative **3** could be obtained by treatment of **1** with formic acetic anhydride followed by diborane reduction of the intermediate 3-formyl derivative of **1**. Attempts to monochlorinate catechol benzazepine derivatives **2** and **3** directly with sulfuryl chloride invariably resulted in the respective 6,9-dichloro derivatives **4** and **5**. Cyclization of *N*-(2-hydroxy-2-phenethyl)homoveratrylamine (**6**)[17] was accomplished with TFA–H_2SO_4 to obtain dimethoxybenzazepine **7**, which was selectively brominated as the HCl salt, using bromine in acetic acid at room temperature (Scheme II) to obtain 6-bromo-7,8-dimethoxybenzazepine **8**. Treatment of **8** with allyl bromide in the presence of potassium carbonate gave 3-allyl derivative **10**, which was O-demethylated with boron tribromide to 3-allyl-6-bromocatechol derivative **13**. Similarly, treatment of **8** with formaldehyde and formic acid in an Eschweiler–Clarke procedure gave 3-methyl derivative **9**, which on subsequent O-demethylation with boron tribromide gave 6-bromo-3-methylcatechol derivative **12**. Direct O-demethylation of **8** with boron tribromide gave 6-bromocatechol **11**. All the catechol endproducts were crystallized as their HBr salts. The 6-chloro analogues were conveniently prepared by lithiation of 6-bromo de-

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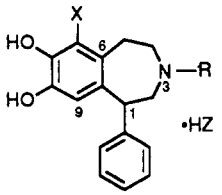
Table I. Pharmacological Characterization of D1 Probes[a]



compd[b]	X	R	HZ	K_i, nM D1	K_i, nM D2^{high}	K_i, nM D2^{low}
1 (SKF 38393)	H	H	HCl	1.1[c] 25[d]	160	8800
2	H	allyl	HCl	12		
3	H	CH_3	HCl	8.8	1900	
5	6,9-Cl_2	CH_3	HCl	2100	810000	
11	Br	H	HBr	12	39	2000
12	Br	CH_3	HBr	1.2	490	4000
13 (Br-APB)	Br	allyl	HBr	5.0	19	21000
17	Cl	H	HBr	7.0	310	8000
18	Cl	CH_3	HBr	0.9	77	2700
19 (Cl-APB)	Cl	allyl	HBr	5.5	55	1300

[a] All compounds were tested in the presence of NaCl (see methods) and all (except 1 (SKF 38393)) inhibited the binding of [^{3}H]SCH 23390 at D1 with a single dissociation constant. The dissociation constants (K_i values) of all compounds were determined from inhibition of the binding of 1 nM [^{3}H]SCH 23390. The K_i values were calculated by using the computer program LIGAND or using the Cheng–Prusoff equation (see ref 3). K_i values indicate an average of two separate experiments, the individual values agreeing to within 10% of the average. [b] All compounds are racemates unless otherwise noted. [c] The K_i value shown for 1 (SKF 38393) is from Seeman and Niznik[21] and refers to the K_i value at the high affinity state of D1, a value obtained in the absence of NaCl. [d] K_i value in the presence of NaCl, obtained by Arnt et al.[19]

rivative **9** followed by treatment with a chlorinating agent, hexachloroethane.[20] Thus 6-bromo-7,8-dimethoxy-3-methylbenzazepine derivative **9** was treated with *n*-butyllithium at −70 °C followed by hexachloroethane to obtain the corresponding 6-chloro derivative **14** (Scheme III). N-Dealkylation of **14** with cyanogen bromide yielded **15**, which on further treatment with allyl bromide in the presence of potassium carbonate gave 3-allyl derivative **16**, which was then O-demethylated with boron tribromide to 3-allyl-6-bromocatechol derivative **19**. Direct O-demethylation of both **14** and **15** with boron tribromide gave respectively 6-chloro-3-methylcatechol benzazepine derivative **18** and 6-chlorocatechol benzazepine derivative **17**.

Pharmacology

A series of nine D1 agonists, having different substitutions at the 3- and 6-positions, was synthesized and evaluated for D1 and D2 receptor affinity and D1/D2 selectivity. The D1 and D2 receptors were labeled with [^{3}H]SCH 23390 and [^{3}H]spiperone, respectively. The receptors were converted into their high-affinity state as well as their low-affinity state (absence or presence of guanine nucleotides) and the abilities of various compounds to competitively displace the respective radioligands from the receptors were determined and the *K*i values were computed for all the compounds for each affinity state of the receptor. All the compounds in this series showed only an affinity for the high-affinity state of the D1 receptor though they showed affinity for both the high- and low-affinity states of the D2 receptor. The K_i values of all these compounds are tabulated in Table I.

Results and Discussion

A study of the D1 affinity shows that at both the 3- and 6-positions, substitution results in a profound effect on the affinity of the compound. At the 3-position, in both the 6-unsubstituted and the 6-substituted series, the 3-unsubstituted compounds had the lowest affinity. In both series, substitution at the 3-position with a methyl group resulted in the highest affinity. 3-Allyl substitution in both the series resulted in compounds with an affinity intermediate between those of the 3-unsubstituted and the 3-methyl substituted compounds. Thus, the affinity order for substitution at this position in this series of compounds was methyl > allyl > H.

The 6-halogenated compounds showed a higher affinity for the D1 receptor than the 6-unsubstituted compounds, whatever the substituent at the 3-position. Both the 6-chloro- and 6-bromo-substituted compounds show very similar affinity. Thus for example, compound **12**, which has 6-bromo-3-methyl substitution (K_i = 1.2 nM), has an affinity close to that of compound **18**, which has 6-chloro-3-methyl substitution (K_i = 0.9 nM); compound **13**, which has 6-bromo-3-allyl substitution, has an affinity close to that of the compound **19**, with 6-chloro-3-allyl substitution (K_i = 5.0 vs 5.5 nM). Thus, substitution at the 6-position, the substitution in this series, resulted in the affinity order Cl = Br > H.

These results provide further evidence of the influence conferred by both the 6- and 3-substituents on the D1 affinity and selectivity as well as probable agonist activity. The higher affinity of the 6-halo-substituted compounds in comparison to the 6-unsubstituted compounds suggests that the 6-halo substituent has a favorable influence on D1 binding affinity. It can be postulated that this influence arises either through a direct interaction with a receptor functionality or through indirect effects on the lipophilicity of, or the electronic effects on, the aryl ring.

In terms of affinity alone, the best compounds are the 6-halo-3-methyl-substituted compounds **12** and **18**, which have the highest D1 affinity in this series. However, from previous studies it has been concluded that 3-methyl substitution results in a profound decrease in the in vitro efficacy of these benzazepine D1 agonists.[18,19] On the other hand, a 3-allyl substitution has been shown to result in retention of the efficacy of these compounds.[18,19] While

(19) Arnt, J.; Hyttel, J.; Meier, E. Inactivation of dopamine D1 or D2 receptors differentially inhibits stereotypes induced by dopamine agonists in rats. *Eur. J. Pharmacol.* **1988**, *155*, 37–47.
(20) SKF Co. Inc., U.S. Patent 4 352 754, 1982.

it can be argued that the 3-unsubstituted compounds show similar high efficacy, not only is their affinity considerably lower but also their in vivo CNS potency is low, owing, in part, to their relatively higher polarity (lower lipophilicity), which conceivably could hinder their passage through the blood–brain barrier.[19] Thus, the 3-allyl substitution is preferred not only on account of the retention of the efficacy but also because higher lipophilicity is conferred by the allyl substituent. Since 6-halogenated compounds had higher affinity than the corresponding 6-unsubstituted compounds, a 6-halo-3-allyl-substituted compound will likely be the best candidate as a high-affinity, high-efficacy D1 agonist with potentially high CNS potency. Of the two halo compounds, the novel 6-bromo compound (**13**, 6-BrAPB) has a slightly higher affinity than the 6-chloro compound. Thus we have designated **13** as a candidate for further pharmacological evaluation as a D1 agonist and for resolution into its active and inactive enantiomers.

In summary, our present work underscores that the substitution of bromine instead of chlorine at the 6-position leads to a retention of D1 binding affinity and selectivity.

Experimental Section

Analytical thin-layer chromatography was performed with E. Merck F-254 plastic-backed thin-layer silica gel plates. Medium-pressure column chromatography was performed with Baker flash silica gel. Melting points were obtained with a Thomas-Hoover melting point apparatus and are uncorrected. ^{1}H NMR spectra were obtained with a Varian XL-300 (300 Hz) NMR spectrometer using TMS as the internal standard. Chemical shifts are reported down-field from TMS. Spectral patterns were designated as follows: s, singlet; d, doublet; t, triplet; dd, double doublet; m, multiplet; b, broad peak. Mass spectra were determined by a Finnigan 4021 mass spectrometer under EI conditions and operated by the Department of Chemistry, Northeastern University. Microanalyses were performed by Atlantic Microlab Inc., Atlanta, GA, and were within ±0.4% of the calculated values.

3-Allyl-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine Hydrochloride (2). 7,8-Dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrobromide (**1**, 3,36 g, 0.01 mol) and anhydrous K_2CO_3 (1.38 g, 0.01 mol) were stirred to dissolution under N_2 in 100 mL of 90% EtOH. To this stirred solution was added dropwise allyl bromide (1.8 g, 0.015 mol). After addition was complete, the mixture was stirred overnight at room temperature under N_2 and filtered. The filtrate was concentrated in vacuo to a dark oil. Purification by flash chromatography (silica gel, CH_2Cl_2/MeOH, 5%) gave the pure product which was dried in vacuo to obtain a pale yellow oil. The oily free base was converted to the HCl salt with EtOH–HCl/Et_2O and the salt was recrystallized from EtOH/Et_2O to yield 1.3 g (40%) of a colorless crystalline solid. Mp: 236–238 °C. ^{1}H NMR (CD_3OD): δ 7.35–7.05 (5 H, m, C_6H_5), 6.5 (1 H, s, 6-*H*), 5.85 (1 H, s, 9-*H*), 5.95–5.75 (1 H, m, C*H*=), 5.55–5.45 (2 H, m, =CH_2), 4.4 (1 H, dd, 1-*H*), 3.8–2.7 (8 H, m, azepine *H* and NCH_2). MS: m/z = 295 (M^+). Anal. ($C_{19}H_{22}NO_2Cl$·0.25H_2O): C, H, N.

3-Allyl-6,9-dichloro-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine Hydrochloride (4). 3-Allyl-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (**2**, 1.2 g, 4 mmol) was dissolved in 60 mL of glacial acetic acid and stirred at room temperature under N_2. Sulfuryl chloride (0.81 g, 6 mmol) was added to the stirred solution dropwise (the reaction is exothermic). The mixture was allowed to stir overnight at room temperature. It was then quenched with water and concentrated in vacuo. The dark residue was purified by flash chromatography (silica gel, CH_2Cl_2/MeOH, 5%) to obtain the pure product as a pale yellow oil. The free base was converted to the HCl salt with EtOH–HCl and dried in vacuo. Recrystallization from EtOH/Et_2O yielded a total of 0.850 g of a off-white crystalline powder in two crops (60%). Mp: 233–235 °C. ^{1}H NMR (CD_3OD): δ 7.5–7.1 (5 H, m, C_6H_5), 6.1–5.9 (1 H, m, C*H*), 5.7–5.45 (2 H, m, =CH_2), 4.5 (1 H, dd, 1-*H*), 4.1–2.8 (8 H, m, azepine *H* and NCH_2). MS: m/z = 363 (M^+). Anal ($C_{19}H_{20}NO_2Cl_3$): C (calcd, 56.91; found, 56.00), H, N.

7,8-Dihydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine Hydrochloride (3). 7,8-Dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrobromide (**1**, 3.36 g, 10 mmol) and anhydrous K_2CO_3 (0.77 g, 5.5 mmol) were dissolved in 10 mL of dry DMF and stirred at room temperature under N_2. A solution of acetic formic anhydride (1.1 g, 12.5 mmol) in 2 mL of dry DMF was added to the mixture dropwise. The mixture was stirred overnight at room temperature under N_2 and then concentrated in vacuo, and the residue was purified by flash chromatography (silica gel, CH_2Cl_2/MeOH, 5%) to obtain pure 3-formyl-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine, which was dried under vacuo to yield 2.1 g (75%) of a pale yellow oil, which crystallized on standing overnight. Mp: 237–240 °C. The 3-formyl derivative (2.1 g, 7.5 mmol) was dissolved in 50 mL of dry THF and stirred at 0 °C under N_2. To this solution was added dropwise 12 mL of a 1.0 M solution of BH_3–THF. The mixture was stirred at 0 °C for 1 h and then at room temperature overnight. The reaction was quenched with 10 mL of 12 N HCl and concentrated in vacuo. The reaction mixture was made alkaline with aqueous NH_3 and extracted with CH_2Cl_2. The extracts were washed with water and brine and dried over anhydrous $CaCl_2$. The dried extract was filtered and concentrated in vacuo. The residue was dissolved in 100 mL of MeOH containing 10 mL of 12 N HCl and allowed to reflux for 2 h. The mixture was cooled and concentrated to obtain a residue which was dried under vacuo overnight. Recrystallization from isopropanol/Et_2O yielded 1.6 g of a white crystalline powder (80%). Mp: 265–267 °C. ^{1}H NMR (CD_3OD): δ 7.5–7.2 (5 H, m, C_6H_5), 6.7 (1 H, s, 6-*H*), 5.9 (1 H, s, 9-*H*), 4.5 (1 H, dd, 1-*H*), 3.8–2.9 (6 H, m, azepine *H*), 2.95 (3 H, s, NCH_3). MS: m/z = 269 (M^+). Anal ($C_{17}H_{20}NO_2Cl$·0.25H_2O): C, H, N.

6,9-Dichloro-7,8-dihydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine Hydrochloride (5). 7,8-Dihydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (**3**, 0.3 g, 4 mmol) was dissolved in 25 mL of glacial acetic acid and stirred at room temperature under N_2. Sulfuryl chloride (0.27 g, 2 mmol) was added to the stirred solution dropwise (the reaction is exothermic). The mixture was allowed to stir overnight at room temperature. It was then quenched with water and concentrated in vacuo. The dark residue was purified by flash chromatography (silica gel, CH_2Cl_2/MeOH, 5%) to obtain the pure product as a pale yellow oil. The free base was converted to the HCl salt with EtOH–HCl and dried in vacuo. Recrystallization from EtOH/Et_2O yielded a total of 0.175 g of a off-white crystalline powder in two crops (55%). Mp: 200–210 °C dec. ^{1}H NMR (CD_3OD): δ 7.5–7.0 (5 H, m, C_6H_5), 4.35 (1 H, dd, 1-*H*), 3.6–2.8 (6 H, m, azepine *H*), 2.9 (3 H, s, NCH_3). MS: m/z = 337 (M^+). Anal. ($C_{17}H_{18}NO_2Cl_3$·H_2O): C, H, N.

7,8-Dimethoxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (7). *N*-(2-Hydroxy-2-phenylethyl)homoveratrylamine[17] (**6**, 130 g, 0.43 mol) was dissolved in 520 mL of trifluoroacetic acid (anhydrous). To the stirred solution, under an atmosphere of N_2, was added dropwise 36.5 mL (0.5 mol) of concentrated H_2SO_4. The dark reaction mixture was allowed to reflux under N_2 atmosphere for 3 h. The mixture was then cooled and concentrated in vacuo. The residue was dissolved/suspended in water, and aqueus NH_3 was added to make the solution alkaline (pH 8). The mixture was extracted with CH_2Cl_2; the extracts were washed well with water and brine and dried over anhydrous $MgSO_4$. The dried extract was filtered and concentrated in vacuo to yield 116 g (95%) of a pale yellow oil. Kugelrohr distillation (180 °C; 0.2 mmHg) yielded an almost colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.4–7.21 (5 H, m, C_6H_5), 6.7 (1 H, d, 6′-*H*), 6.1 (1 H, s, 9-*H*), 4.8 (1 H, d, 1-*H*), 3.85 (3 H, s, OCH_3), 3.55 (3 H, s, OCH_3), 3.1–2.7 (6 H, m, azepine *H*).

6-Bromo-7,8-dimethoxy-2,3,4,5-tetrahydro-1-phenyl-1*H*-3-benzazepine Hydrobromide (8). 7,8-Dimethoxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride (**7**, 66 g, 0.21 mol) was dissolved in glacial acetic acid (400 mL). To the stirred solution at room temperature was added dropwise bromine (66 g, 0.42 mol). The reaction mixture was stirred at room temperature for 2 h. The yellow precipitate was filtered, washed well with anhydrous ether, and dried in vacuo. The precipitate was dissolved in MeOH and treated with an excess of acetone to remove the residual bromine. The solution was concentrated in vacuo and the residue was recrystallized from hot MeOH to yield

63 g of white crystalline solid (69%). Mp: 236–238 °C (lit.[13] mp: 236–238 °C). ^{1}H NMR (CD_3OD): δ 7.5–7.2 (5 H, m, C_6H_5), 6.45 (1 H, s, 9-*H*), 4.8 (1 H, dd, 1-*H*), 3.8 (3 H, s, OCH_3), 3.6 (3 H, s, OCH_3), 3.5–3.0 (6 H, m, azepine *H*).

6-Bromo-7,8-dimethoxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (9). 6-Bromo-7,8-dimethoxy-2,3,4,5-tetrahydro-1-phenyl-1*H*-3-benzazepine hydrobromide (8, 0.6 g, 1.5 mmol) was dissolved in a mixture of 37% formaldehyde (6.0 mL, 0.084 mol) and 90% formic acid (10 mL). The reaction mixture was allowed to reflux for 4 h and poured on ice and the resulting mixture was made alkaline (pH 8) with aqueous NH_3 and extracted with CH_2Cl_2. The extracts were washed well with water and brine and dried over anhydrous $MgSO_4$. The dried extract was filtered and concentrated in vacuo to 0.48 g (85%) of a white solid. Mp: 107–109 °C (lit.[13] mp: 108–110 °C). ^{1}H NMR ($CDCl_3$): δ 7.5–7.25 (5 H, m, C_6H_5), 6.25 (1 H, s, 9-*H*), 4.4 (1 H, d, 1-*H*), 3.8 (3 H, s, OCH_3), 3.6 (3 H, s, OCH_3), 3.4–2.8 (6 H, m, azepine *H*), 2.4 (3 H, s, NCH_3).

3-Allyl-6-bromo-7,8-dimethoxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (10). 6-Bromo-7,8-dimethoxy-2,3,4,5-tetrahydro-1-phenyl-1*H*-3-benzazepine hydrobromide (8, 12 g, 0.03 mol) was dissolved in a mixture of 60 mL of DMF and 2.5 mL of water. To this stirred solution was added anhydrous K_2CO_3 (8.4 g, 0.06 mol) followed by the dropwise addition of a solution of allyl bromide (4.2 g, 0.035 mol) in 30 mL of CH_2Cl_2. After the addition was complete, the reaction mixture was stirred at room temperature overnight, quenched by pouring into 500 mL of cold water, and extracted with CH_2Cl_2. The organic layer was separated, washed well with water and brine, and dried over anhydrous $CaCl_2$. The dried extract was filtered and concentrated in vacuo to a pale yellow oil. Purification by flash chromatography gave a pale yellow oil as the pure product (8 g, 60%). ^{1}H NMR ($CDCl_3$): δ 7.4–7.2 (5 H, m, C_6H_5), 6.2 (1 H, s, 9-*H*), 5.95–5.85 (1 H, m, C*H*=), 5.25–5.1 (2 H, m, =CH_2), 4.4 (1 H, d, 1-*H*), 3.8 (3 H, s, OCH_3), 3.6 (3 H, s, OCH_3), 3.15 (2 H, d, NCH_2), 3.0–2.4 (6 H, m, azepine *H*).

General Procedure for O-Demethylation with Boron Tribromide. Compound is dissolved in 25 mL of dry CH_2Cl_2 and the solution is stirred under N_2 at −70 °C. To the vigorously stirred solution is added dropwise a solution of boron tribromide in hexane (1.0 M solution). After the addition is complete, the reaction mixture is stirred at −70 °C for 1 h and then at room temperature for 2 h. The reaction is then quenched by again cooling to −70 °C under N_2 followed by the dropwise addition of 20 mL of anhydrous MeOH with vigorous stirring. The reaction mixture is concentrated in vacuo and the residue treated with an asddditional 50 mL of MeOH and again concentrated in vacuo. This procedure is repeated twice. Finally the residue is dried in vacuo over P_2O_5 overnight. Recrystallization yields the crystalline product.

6-Bromo-7,8-dihydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine Hydrobromide (12). 6-Bromo-7,8-dimethoxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (9, 0.48 g, 1.25 mmol) in 25 mL of dry CH_2Cl_2 was treated with boron tribromide (1.0 M solution, 3.125 g, 12.5 mmol) by using the general procedure. Recrystallization from EtOH/Et_2O yielded 300 mg of a tan crystalline solid (60%). Mp: 180–182 °C (lit.[13] mp: 181–183 °C). ^{1}H NMR (CD_3OD): δ 7.5–7.2 (5 H, m, C_6H_5), 6.05 (1 H, s, 9-*H*), 4.65 (1 H, d, 1-*H*), 3.8–3.0 (6 H, m, azepine *H*), 2.95 (3 H, s, NCH_3). MS: m/z = 347 (M^+). Anal. ($C_{17}H_{19}NO_2Br_2$·EtOH): C, H, N.

3-Allyl-6-bromo-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine Hydrobromide (13). 3-Allyl-6-bromo-7,8-dimethoxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-benzazepine (10, 8 g, 0.02 mol) in 100 mL of dry CH_2Cl_2 was treated with boron tribromide in hexane (1.0 M solution, 25 g, 100 mL, 0.1 mol) by using the general procedure. Recrystallization from EtOH/Et_2O yielded 6.0 g of an off-white crystalline solid (66%). Mp: 200–202 °C dec. ^{1}H NMR (CD_3OD): δ 7.45–7.15 (5 H, m, C_6H_5), 6.1 (1 H, s, 9-*H*), 6.05–5.85 (1 H, m, C*H*=), 5.7–5.55 (2 H, m, =CH_2), 4.7 (1 H, dd, 1-*H*), 3.9–3.0 (8 H, m, azepine *H* and NCH_2). MS: m/z = 373 (M^+). Anal. ($C_{19}H_{21}NO_2Br_2$): C, H, N.

6-Bromo-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine Hydrobromide (11). 6-Bromo-7,8-dimethoxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (8, 0.8 g, 2 mmol) in 40 mL of dry CH_2Cl_2 was treated with boron tribromide in hexane (1.0 M solution, 5.0 g, 20 mL, 20 mmol) by using the general procedure. Recrystallization from ethanol/ether yielded 0.525 g of colorless needles (65%). Mp: 190–192 °C dec. ^{1}H NMR (CD_3OD): δ 7.5–7.2 (5 H, m, C_6H_5), 6.2 (1 H, s, 9-*H*), 4.6 (1 H, d, 1-*H*), 3.8–2.8 (6 H, m, azepine *H*). MS: m/z = 333 (M^+). Anal. ($C_{16}H_{17}NO_2Br_2$·EtOH): C, H, N.

6-Chloro-7,8-dimethoxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (14). 6-Bromo-7,8-dimethoxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (9, 9.4 g, 0.025 mol) was dissolved in 75 mL of anhydrous Et_2O and the solution was stirred at −70 °C under N_2. A solution of *n*-BuLi (2.5 M solution in THF, 25.5 mL, 0.064 mol) was dissolved in 75 mL of dry Et_2O under N_2 and the solution added dropwise to the reaction mixture at −70 °C under N_2. After the addition was complete, stirring at −70 °C was continued for 10 min. Then a solution of hexachloroethane (13 g, 0.055 mol) in 75 mL of anhydrous Et_2O was added to the reaction mixture while stirring was continued at −70 °C for 5 min. The reaction was quenched by pouring into water and the organic (Et_2O) layer was drawn off. The aqueous layer was further extracted with ether, and the combined organics were washed with water and brine and then dried over anhydrous $CaCl_2$. The dried extract was filtered and concentrated in vacuo to a dark oil. Purification by flash chromatography (silica gel, CH_2Cl_2) yielded 6.3 g (75%) of a foamy product. ^{1}H NMR ($CDCl_3$): δ 7.4–7.15 (5 H, m, C_6H_5), 6.2 (1 H, s, 9-*H*), 4.435 (1 H, d, 1-*H*), 3.85 (3 H, s, OCH_3), 3.6 (3 H, s, OCH_3), 3.4–2.8 (6 H, m, azepine *H*), 2.4 (3 H, s, N-CH_3).

A small quantity of the product was converted to the HCl salt with EtOH·HCl/Et_2O. Recrystallization from MeOH/Et_2O gave an off-white crystalline solid. Mp: 232–234 °C (lit.[15] mp: 233–234 °C).

6-Chloro-7,8-dimethoxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (15). 6-Chloro-7,8-dimethoxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (14, 5.3 g, 0.016 mol) was dissolved in 60 mL of anhydrous benzene and the solution was stirred under N_2 at 55–60 °C. A solution of BrCN (1.84 g, 0.0183 mol) was added to the stirred reaction mixture at 55–60 °C. After the addition was complete, the reaction mixture was stirred at 60 °C for 3 h. It was then cooled and concentrated in vacuo and the residual oil triturated with anhydrous Et_2O. A colorless crystalline solid was obtained which was filtered, washed well with Et_2O, and dried in vacuo, yielding 3.1 g of the cyanamide intermediate. Mp: 148–150 °C (lit.[20] mp: 149–151 °C). The cyanamide was dissolved in a solution of 42 mL of acetic acid, 4.5 mL of concentrated HCl, and 23 mL of water. The solution was heated at 100 °C overnight and then concentrated in vacuo. The residue was dissolved in 100 mL of MeOH, concentrated in vacuo, and dried to obtain 3.2 g of the HCl salt. The salt was converted to the free base by suspending it in $CHCl_3$ and washing with a 10% aqueous $NaHCO_3$ solution. The organic layer was separated, washed with H_2O and brine, and dried over anhydrous $CaCl_2$. It was filtered and then concentrated in vacuo. The residual solid was purified by flash chromatography (silica gel, CH_2Cl_2/MeOH, 5%) to obtain 2.5 g of the pure product as a yellow solid (50%). Mp: 115–118 °C (lit.[20] mp: 115–121 °C). ^{1}H NMR ($CDCl_3$): δ 7.4–7.1 (5 H, m, C_6H_5), 6.2 (1 H, s, 9-*H*), 4.65 (1 H, d, 1-*H*), 3.85 (3 H, s, OCH_3), 3.55 (3 H, s, OCH_3) 3.7–2.8 (6 H, m, azepine *H*).

3-Allyl-6-chloro-7,8-dimethoxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (16). 6-Chloro-7,8-dimethoxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (15, 0.8 g, 2.5 mmol) was dissolved in a mixture of 30 mL of DMF and 2 mL of H_2O. To this stirred solution was added anhydrous K_2CO_3 (0.37 g, 2.5 mmol) followed by the dropwise addition of a solution of allyl bromide (0.42 g, 3.5 mmol) in 15 mL of CH_2Cl_2. After the addition was complete, the reaction mixture was stirred at room temperature overnight. It was then quenched by pouring into 300 mL of cold water, the solution was then extracted with CH_2Cl_2, and the organic layer was drawn off, washed well with water and brine, and dried over anhydrous $CaCl_2$. The dried extract was filtered and concentrated in vacuo to a pale yellow oil. Purification by flash chromatography gave a pale yellow oil as the pure product

(0.45 g, 50%). ^{1}H NMR ($CDCl_3$): δ 7.4–7.2 (5 H, m, C_6H_5), 6.2 (1 H, s, 9-*H*), 5.95–5.85 (1 H, m, C*H*=), 5.25–5.1 (2 H, m, =CH_2), 4.4 (1 H, d, 1-*H*), 3.8 (3 H, s, OCH_3), 3.6 (3 H, s, OCH_3), 3.4–2.4 (8 H, m, azepine *H* and NCH_2).

6-Chloro-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine Hydrobromide (17). 6-Chloro-7,8-dimethoxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (**15**, 0.8 g, 2.5 mmol) in 40 mL of dry CH_2Cl_2 was treated with boron tribromide in hexane (1.0 M solution (6.25 g, 25 mL, 25 mmol) by using the general procedure. Recrystallization from EtOH yielded 0.725 g of an off-white crystalline solid (90%). Mp: 260–261 °C dec (lit.[15] mp: 259–260 °C). ^{1}H NMR (CD_3OD): δ 7.5–7.2 (5 H, m, C_6H_5), 6.2 (1 H, s, 9-*H*), 4.6 (1 H, t, 1-*H*), 3.6–3.1 (6 H, m, azepine *H*). MS: m/z = 289 (M^+). Anal. ($C_{16}H_{17}ClNO_2Br$): C, H, N.

6-Chloro-7,8-dihydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine Hydrobromide (18). 6-Chloro-7,8-dimethoxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (**14**, 0.4 g, 1.2 mmol) in 20 mL of dry CH_2Cl_2 was treated with boron tribromide in hexane (1.0 M solution, 3.0 g, 12 mL, 12 mmol) by using the general procedure. Recrystallization from 2-propanol/Et_2O yielded 0.25 g of white needles (60%). Mp: 223–225 °C. ^{1}H NMR (CD_3OD): δ 7.5–7.2 (5 H, m, C_6H_5), 6.15 (1 H, b, 9-*H*) 4.65 (1 H, d, 1-*H*), 3.8–3.1 (6 H, m, azepine *H*), 2.95 (3 H, s, NCH_3). Anal. ($C_{17}H_{19}ClNO_2Br$): C, H, N.

3-Allyl-6-chloro-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine Hydrobromide (19). 3-Allyl-6-chloro-7,8-dimethoxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (**16**, 0.48 g, 1.1 mmol) in 20 mL of dry CH_2Cl_2 was treated with boron tribromide in hexane (1.0 M solution, 2.8 g, 11 mL, 11 mmol) by using the general procedure. Recrystallization from 2-propanol/Et_2O yielded 0.200 g of a tan crystalline solid (45%). Mp: 204–205 °C (lit.[15] mp: 203–204 °C). ^{1}H NMR (CD_3OD): δ 7.5–7.2 (5 H, m, C_6H_5), 6.15 (1 H, s, 9-*H*), 6.0–5.9 (1 H, m, C*H*=), 5.7–5.55 (2 H, m, =CH_2), 4.65 (1 H, dd, 1-*H*), 3.80–3.0 (8 H, m, azepine *H* and NCH_2). Anal. ($C_{19}H_{21}ClNO_2Br$): C, H, N.

Pharmacology Methods. The compounds were tested for their potency and D1 receptors by their ability to inhibit the binding of [^{3}H]SCH 23390 to canine striatum in vitro. The canine striata were purchased from Pel-Freez (Rogers, AR) and kept at −70 °C until used. After thawing, the tissues were suspended at 3 mg of original wet weight per mL of buffer (50 mM Tris-HCl, pH 7.4, 1 mM EDTA, 5 mM KCl, 1.5 mM $CaCl_2$, 4 mM $MgCl_2$, and 120 mM NaCl) and were homogenized in a glass homogenizer, using a Teflon piston rotating at 650 rpm (8 up–down strokes). The homogenate was washed twice by centrifugation (28000*g* for 15 min) and resuspension. The tissue was finally resuspended at 3 mg wet weight per mL. Aliquots were added to the final incubation tubes (12 × 75 mm) as follows: 0.5 mL of buffer (containing 0.1% ascorbic acid and 10 M nialamide), 0.5 mL [^{3}H]SCH 23390 (75 Ci/mMol; New England Nuclear, du Pont de Nemours & Co., Boston, MA) (the final concentration of which was between 0.9 and 1 nM), and 0.5 mL of tissue suspension. After 2 h of incubation at room temperature (21 °C), the suspensions were filtered by a Titertek cell harvester (Skatron, Lier, Norway) through a Skatron filter 11734. The filters were rinsed with 7 mL over 15 s. Nonspecific binding was that in the presence of 1 M (+)-butaclamol. The radioactivity was monitored by a liquid scintillation spectrometer (Packard Instrument Co., Chicago, IL).

The potencies of the compounds at D2 receptors were done in the same way as those at D1, except that pig anterior pituitary tissues were used (Bocknek Co., Mississauga, Ontario, Canada), the tissues were homogenized by a Polytron PT-10 (Brinkmann Co.) at setting 6 for 20 s, [^{3}H]spiperone (87 Ci/mol) was used at a final concentration of 0.15 mM, the final tissue concentration during incubation was 4 mg original weight per mL, and nonspecific binding was defined as that in the presence of either 1 μM (+)-butaclamol or 10 μM (*S*)-sulpiride. The dissociation constants, K_i values were obtained by the program LIGAND (see refs 3, 21) with a value of 0.17 nM as the dissociation constant for [^{3}H]SCH 23390 at D1 and a value of 0.06 nM as the dissociation constant for [^{3}H]spiperone at D2.

Registry No. **1**, 20012-10-6; **2**, 62751-58-0; **2** free base, 104422-04-0; **3**, 104113-96-4; **4**, 72912-32-4; **4** free base, 135974-58-2; **5**, 135974-55-9; **5** free base, 72912-31-3; **6**, 20011-97-6; **7**, 20569-49-7; **8**, 67287-40-5; **9**, 104113-80-6; **10**, 135974-56-0; **11**, 67287-42-7; **12**, 74114-95-7; **13**, 135974-57-1; **14**, 67287-58-5; **14**·HCl, 80751-60-6; **15** free base, 67287-38-1; **15**·HCl, 67287-47-2; **16**, 74115-02-9; **17**, 67287-39-2; **18**, 71636-56-1; **19**, 74115-01-8; BrCN, 506-68-3; allyl bromide, 106-95-6; 3-formyl-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine, 135974-59-3; 6-chloro-7,8-dimethoxy-3-cyano-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine, 67287-46-1.

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