(±)-3-[4′-(*N*,*N*-Dimethylamino)cinnamyl]benzazepine Analogs: Novel Dopamine D_1 Receptor Antagonists†

Jamshed H. Shah, Richard H. Kline, Beth Geter-Douglass, Sari Izenwasser, Jeffrey M. Witkin, and Amy Hauck Newman*

Psychobiology Section, National Institutes of Health, National Institute on Drug Abuse - Division of Intramural Research, Baltimore, Maryland 21224

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Neurochemical studies and structure−activity relationships of dopamine D_1 receptor ligands suggest that their intrinsic activity may depend on the conformational state or binding site at which they interact on the receptor protein. Important differences in the modes of binding of these ligands may confer their agonist, partial agonist, or antagonist properties. In an effort to develop novel dopamine D_1 antagonists and investigate the D_1 antagonist pharmacophore, a series of (±)-(*N*-alkylamino)benzazepines were prepared in which (±)-7-chloro-8-hydroxy-3-[6-(*N*,*N*-dimethylamino)hexyl]-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (**1**) demonstrated the highest binding affinity (K_i = 49.3 nM) and selectivity to dopamine D_1 receptors. This compound inhibited dopamine-stimulated adenylyl cyclase, in rat caudate, confirming a D_1 receptor antagonist profile. From this initial series of *N*-alkylamino-substituted benzazepines, structure−activity relationships suggested that the terminal amino function was necessary for optimal binding affinity and selectivity at D_1 vs D_2 sites. Further, addition of this side chain to the D_1 agonist pharmacophore (e.g., 7,8-dihydroxy-3-[4-(*N*,*N*-dimethylamino)butyl]-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine) greatly decreased binding affinity at D_1 receptors. These data suggested that a binding domain that may be unique to the D_1 antagonists may have been identified. In an attempt to exploit an apparent amine-accepting binding domain on the D_1 receptor, a series of (±)-3-[4′-(*N*,*N*-dimethylamino)cinnamyl]benzazepine analogs was designed and prepared, as D_1 antagonists. In this series, (±)-7-chloro-8-hydroxy-3-[4′-(*N*,*N*-dimethylamino)cinnamyl]-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (**6a**) showed the highest binding affinity (K_i = 60.3 nM) for dopamine D_1 receptors. Compound **6a** was a potent dopamine D_1 antagonist as evidenced by its ability to block dopamine-stimulated adenylyl cyclase activity in rat caudate (predicted K_i value = 18.4 nM). Molecular modeling studies demonstrated that the most potent and selective dopamine D_1 antagonists, in both series, contained terminal amino groups 8−9 Å away from the 3-position benzazepine nitrogen. Compounds that lacked a terminal amine function or where this moiety was less than 7 Å away from the benzazepine nitrogen demonstrated significantly lower binding affinities. Therefore, this series of (±)-3-[4′-(*N*,*N*-dimethylamino)cinnamyl]benzazepines also appears to be identifying an amine-accepting binding domain on the dopamine D_1 receptor protein that may be further explored for the development of novel dopamine D_1 antagonists.

Introduction

Central dopamine receptors are the target for pharmacotherapy in Parkinson's disease, Huntington's disease, and psychosis.[1,2] In addition, the dopaminergic system is undoubtedly involved in the reinforcing effects of drugs of abuse, particularly the psychomotor stimulants such as cocaine and amphetamine.[3−6] Dopamine receptors are classified into two major subclasses, D_1 and D_2, and the function of these receptor subtypes has largely been discerned through ligands that selectively bind to each site.[7,8] The D_1 subclass includes D_1 and D_5 receptor subtypes, whereas the D_2 subclass includes D_2, D_3, and D_4 receptor subtypes.[9−11] These receptor subtypes have been cloned, and their pattern of expression in the central nervous system has been characterized.[10] The development of highly selective ligands with which to further characterize the pharmacology of the five dopamine receptor subtypes will ultimately lead to improved understanding of the etiology of the neurodegenerative and psychiatric disorders involving the dopaminergic system as well as the development of improved medical treatments.

The prototypic partial D_1-selective agonist SKF 38393 and antagonist SCH 23390 have provided invaluable tools with which to study the function of this receptor subtype.[12−14] Intrinsic activity, as defined by the ability to stimulate dopamine-sensitive adenylyl cyclase, varies widely in this class of compounds and has been proposed to be due to different conformational states or binding sites on the receptor protein.[15,16] The structure−activity relationships derived from several structural classes of dopamine D_1-selective ligands have aided in the development of a 3-dimensional binding model of the agonist site on the receptor protein.[17,18] In addition, a model of the antagonist binding site has been proposed.[19] Elucidation and structural characterization of both agonist and antagonist pharmacophores are important for the overall understanding of the relationship of structure and function at dopamine D_1 receptors and for the ultimate development of effective therapeutics.

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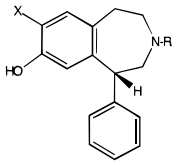


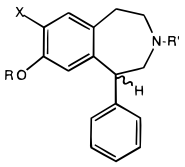
SKF 38393 R=H, X=OH
SCH 23390 R=CH_3, X=Cl
(±)1, R=$(CH_2)_6N(CH_3)_2$, X=Cl

Recently, a series of (±)-(*N*-alkylamino)benzazepine analogs were reported in which (±)-7-chloro-8-hydroxy-3-[6-(*N*,*N*-dimethylamino)hexyl]-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (**1**) showed the highest affinity (K_i = 49.3 nM) and subtype selectivity for dopamine D_1 sites.[20,21] Structure−activity relationships were derived from this series of analogs that suggested the existence of a binding domain on the dopamine D_1 receptor protein, not previously characterized, that accepts an amino function.[20] Since the compounds with highest affinity in this series demonstrated a dopamine D_1 antagonist profile, it was suggested that this binding domain may be unique to D_1 antagonists. It was, therefore, of interest to prepare analogs that had a more structurally rigid side chain to further characterize this binding domain and potentially exploit it to design more potent and selective D_1 antagonists. Thus, the following *N*-[4′-(*N*,*N*-dimethylamino)cinnamyl]benzazepines were prepared. In addition, a cinnamyl analog without a terminal amino group was prepared for comparison. Finally, replacement of the 7-Cl with a Br group was undertaken to determine whether this substitution would retain high affinity as is observed with SCH 23390 and its Br derivative SCH 24543.[14,22] All of the compounds were evaluated for binding to dopamine D_1 and D_2 sites in rat brain.

Chemistry

In Scheme 1, the benzazepines **2a**,**b** were synthesized as described previously.[20] A coupling reaction between the benzazepines **2a**,**b** and the carboxylic acids **3a**,**b** using dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole (HOBt) gave the amides **4a**−**c**. The amides **4a**−**c** were reduced with AlH_3 in THF to give the N-substituted benzazepines **5a**−**c**.[20] The use of AlH_3 instead of $LiAlH_4$ for the amide reduction was chosen to prevent dehydrohalogenation of the 7-Cl or 7-Br groups on the benzazepine ring, in intermediates **4a**−**c**. The coupling constants (J = 15−17 Hz) of the vinylic hydrogens in the ^{1}H-NMR spectra suggested the exclusive formation of the *trans* isomers. O-Demethylation of the resulting N-substituted benzazepines **5a**−**c** with BBr_3 in $CHCl_3$ yielded the target compounds **6a**−**c** in 60−70% yield. In Scheme 2, the product **7** was made first by reacting **2b** with cinnamyl bromide in the presence of K_2CO_3 in DMF[23] followed by O-demethylation with BBr_3.

Table 1. Radiolabled Binding Data for Benzazepine Analogs



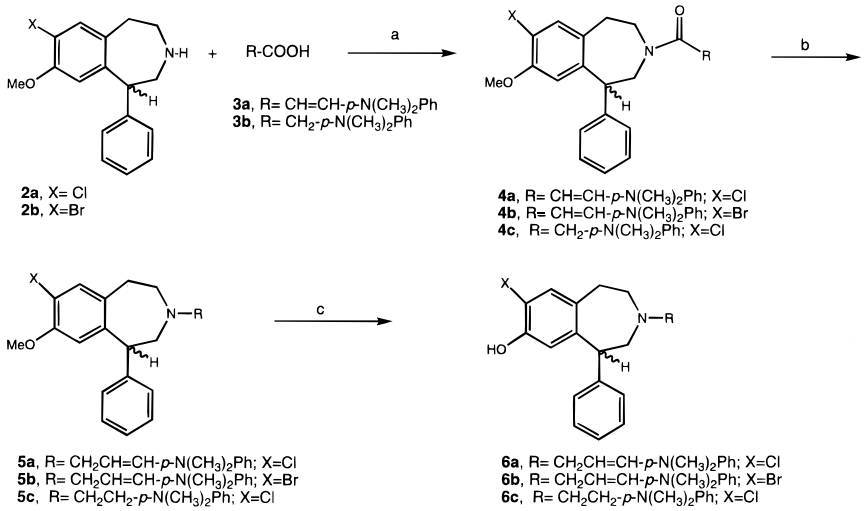
				K_i, nM (±SEM)	
compd	X	R	R′	D_1[a,b]	D_2[a,c]
5a	Cl	CH_3	CH_2CH=CH-*p*-$N(CH_3)_2Ph$	>10000	1715 ± 395
5b	Br	CH_3	CH_2CH=CH-*p*-$N(CH_3)_2Ph$	>10000	2000 ± 380
6a	Cl	H	CH_2CH=CH-*p*-$N(CH_3)_2Ph$	60.7 ± 10.9	345 ± 89.6
6b	Br	H	CH_2CH=CH-*p*-$N(CH_3)_2Ph$	120 ± 24.0	858 ± 163
6c	Cl	H	CH_2CH_2-*p*-$N(CH_3)_2Ph$	88.4 ± 31.8	NA
7	Br	H	CH_2CH=$CHPh$	209 ± 14.6	NA
1	Cl	H	$(CH_2)_6N(CH_3)_2$	49.3 ± 3.94[d]	4130 ± 1360[d]
8	Cl	H	$(CH_2)_4N(CH_3)_2$	811 ± 73.0[d]	3450 ± 1450[d]

[a] K_i values (in nM) are means (±SEM) of at least three determinations, each performed in triplicate. Affinities for dopamine D_1 and D_2 binding measured by competition against [b][^{3}H]SCH 23390 or [c][^{3}H]sulpiride, respectively, to rat striatal membranes. [d] Data from ref 20 are included for comparison. NA = due to solubility problems, these compounds could not be tested at sufficiently high doses to obtain a K_i value.

Discussion of Results

All of the compounds were evaluated for binding to dopamine D_1 and D_2 receptors in rat caudate putamen. [^{3}H]SCH 23390 was used as the radiolabeled ligand for dopamine D_1 receptors, and [^{3}H]sulpiride was used for radiolabeling dopamine D_2 receptors.[20] Results of these binding experiments are depicted in Table 1. The most

Scheme 1[a]



[a] (a) DCC/HOBt/DMF, 48 h; (b) AlH_3/THF; (c) BBr_3/$CHCl_3$.

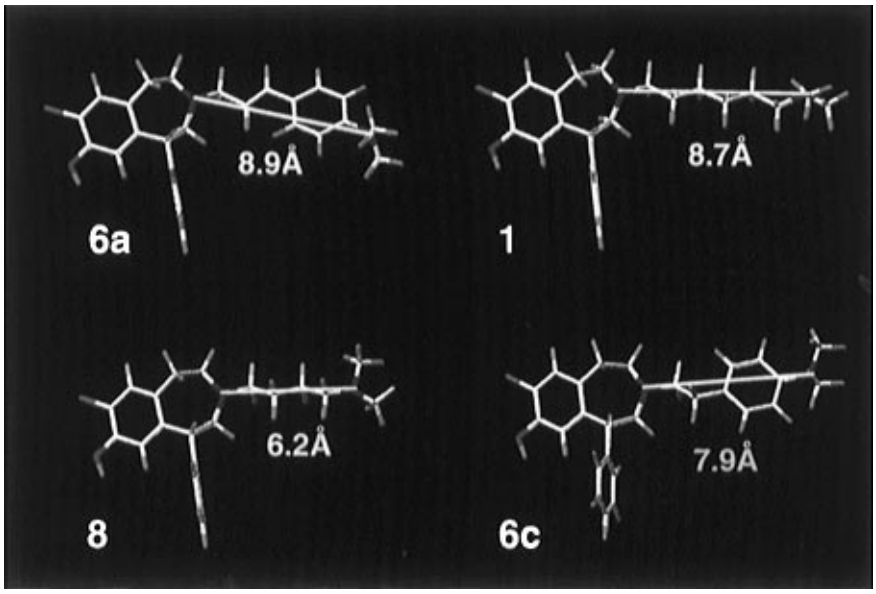
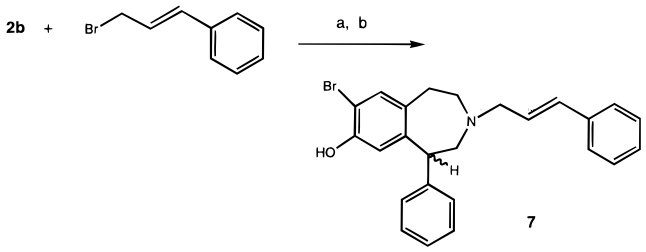


Figure 1. Energy-minimized structures of compounds **6a**,**c**, **1**, and **8** with measured distances between benzazepine and terminal nitrogen atoms (in Å).

Scheme 2[a]



[a] (a) DMF, K_2CO_3; (b) BBr_3, $CHCl_3$.

potent compound in this series was **6a** (K_i = 60.7 nM) which was found to be equipotent to compound **1**, the most potent analog in the previously reported series. The 7-Cl function of compound **6a** resulted in a 2-fold higher affinity for binding to D_1 receptors than the 7-Br substitution on the structural analog **6b**. This trend was comparable to the Br derivative of SCH 23390[22] and in the (*N*-alkylamino)benzazepine series.[20] Shortening the allylic chain of **6a** to an ethyl chain in **6c** did not significantly decrease binding affinity for dopamine D_1 receptors in this series. Compound **6b** was 2 times as potent as **7**, presumably because of the presence of the amino function at the 4′-position of the phenyl ring. The compounds that had a methoxy group at position 8 (**5a**,**b**) were inactive at dopamine D_1 receptors (K_i > 10000 nM), which corresponds to previous reports on other benzazepine analogs.[20,22]

It has been reported earlier that lengthening the alkyl side chain of the 1-phenylbenzazepines in the 3-position from a methyl group to an *n*-propyl group drastically decreased binding affinity for dopamine D_1 sites (0.3 vs 3600 nM, respectively).[14] When this alkyl chain was extended to an *n*-butyl group, the binding affinity of this analog was increased (K_i = 634 nM). Further, when a primary amine was added to the end of the 1-*n*-butyl chain, a nearly 10-fold increase in binding affinity (K_i = 75.0 nM) resulted.[20] These results suggested that the amino function may be important for increased binding affinity at the receptor. Furthermore, when a primary amine was added to the terminal carbon of a hexyl side chain, in position 1, the binding affinity was somewhat lower (K_i = 321 nM) than that of the aminobutyl analog.[20] However, potency was restored when the terminal nitrogen was derivatized to the *N*,*N*-dimethyl group (K_i = 49.3 nM).[20] These results suggested that both the length of the alkyl chain and the nature of the terminal amino function dictated the binding interactions of these compounds at D_1 sites. The binding results from the present study suggest that the 3-[4′-(*N*,*N*-dimethylamino)cinnamyl]benzazepines may also be interacting with a binding domain on the dopamine D_1 receptor that accepts an amino function, as was observed for the (*N*-alkylamino)benzazepines. The aniline nitrogen in this series of compounds is unlikely to be protonated at physiological pH. Thus, it is plausible that the interaction between the compounds and the binding site is through hydrogen bonding rather than being ionic in nature. In addition, the fact that these compounds are tertiary amines suggests that they might serve as proton acceptors in these hydrogen-bonding interactions.

In order to examine this observation further, we compared the distances between the nitrogen of the benzazepine ring system and the terminal nitrogen on the alkylamino or arylamino side chain of compounds presented in this study (**6a**,**c**) and the previously reported (*N*-alkylamino)benzazepines (**1**, **8**). The compounds studied and the distances measured are presented in Figure 1. Compounds were sketched and energy minimized as described in the Experimental Section. Clearly, the distance between the two amino nitrogens plays a significant role in the potency of these compounds. The distance of 8−9 Å between these nitrogens appears to be optimal, as indicated by the distances measured for the most potent compounds in these series (**6a**, 8.9 Å; **1**, 8.7 Å). This trend can also be seen with another potent compound (**6c**) which has a distance of 7.9 Å between the two amine functions. In contrast, the distance between the two nitrogens in the less potent butyl analog of compound **1**, (±)-7-chloro-8-hydroxy-3-[6-(*N*,*N*-dimethylamino)butyl]-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (**8**), was measured to be only 6.2 Å.

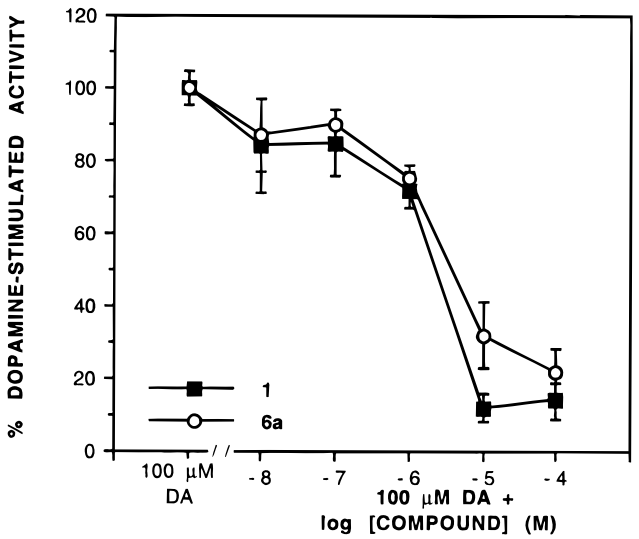


Figure 2. **1** (n = 5) and **6a** (n = 3) antagonized adenylyl cyclase activity stimulated by 100 μM dopamine. Dopamine (100 μM) stimulated adenylyl cyclase activity approximately 200% over basal levels (expressed as 100% in figure). Predicted K_i values, based on these data, are **1**, $K_i = 21 \pm 13$ nM; **6a**, $K_i = 18 \pm 15$ nM. Each data point represents mean ± SEM from n independent experiments, each performed in triplicate.

All of the compounds recognized dopamine D_2 receptors with binding affinities in the 345−2000 nM range. All of these compounds were equipotent or more potent at D_2 sites than the (*N*-alkylamino)benzazepines, with compound **6a** being the most potent. These data suggest that the *N*-[4′-(*N*,*N*-dimethylamino)cinnamyl] side chain is preferred at D_2 receptors as compared to the alkyl side chain and may be predominating the binding interaction at the receptor, for this series of compounds.

It must be noted that the compounds in this series, as in the (*N*-alkylamino)benzazepine series, are all racemic mixtures. The separation of the optical isomers (+)-**6a** and (−)-**6a** was recently achieved by HPLC with a Chiralpak-AD column (1 cm × 25 cm). However, characterization of these enantiomers was precluded by the small amounts of compounds isolated and their relative instability. Therefore, the optical resolution of an intermediate benzazepine will be pursued in order to allow the preparation of the enantiomers of interesting 3-substituted benzazepines.

Compound **6a** was further evaluated for inhibition of dopamine-stimulated adenylyl cyclase in rat caudate to confirm D_1 antagonist as opposed to D_1 agonist activity (Figure 2). This compound showed somewhat more potent inhibition of dopamine-stimulated adenylyl cyclase (predicted $K_i = 18.4 \pm 14.5$ nM) than would be anticipated by its binding affinity, as was demonstrated in the (*N*-alkylamino)benzazepine series.[20] Therefore, despite its relatively higher binding affinity at D_2 receptors, as compared to previously described 1-phenylbenzazepines, this compound demonstrated a D_1 antagonist profile.

Conclusion

A series of (±)-*N*-[4′-(*N*,*N*-dimethylamino)cinnamyl]-benzazepines were prepared that demonstrated moderate binding affinity and selectivity to dopamine D_1 receptors as compared to D_2 receptors. The most potent compound, **6a**, was equipotent to the lead compound (**1**) in a previously reported series of (*N*-alkylamino)benzazepine analogs. As with compound **1**, **6a** demonstrated a relatively potent inhibition of dopamine-stimulated adenylyl cyclase. The series of compounds described herein appear to interact with an amine-accepting binding domain on the receptor that is approximately 8−9 Å away from the site at which the pharmacophoric benzazepine nitrogen binds. Further, this binding domain may be unique to D_1 receptor antagonists. Future compounds may be designed to access this binding domain for the development of novel and potentially useful D_1 antagonists.

Experimental Section

Synthesis. Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Thin layer chromatography (silica gel GF; Analtech, Delaware) was used to detect product homogeneity. Flash column chromatography (silica gel, grade 60, 230−400 mesh; Aldrich Chemical Co., Milwaukee, WI) was used for purification. Drying refers to the use of anhydrous Na_2SO_4 followed by suction filtration. The ^{1}H-NMR data were recorded on a Bruker (Billerica, MA) AC-300 instrument. Proton chemical shifts are reported as parts per million (δ) relative to tetramethylsilane (Me_4Si; 0.0 ppm) which was used as an internal standard; J values are reported in hertz (Hz). Infrared spectra were recorded in KBr or neat (NaCl plates) with a Perkin-Elmer 1600 Series FTIR instrument. Microanalyses were performed by Atlantic Microlab, Inc. (Norcross, GA), and agree within 0.4% of calculated values. All chemicals and reagents were purchased from Aldrich Chemical Co. or Lancaster Synthesis Inc. unless otherwise indicated.

(±)-7-Chloro-8-methoxy-3-[4′-(*N*,*N*-dimethylamino)cinnamoyl]-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (4a). A mixture of 1,3-dicyclohexylcarbodiimide (DCC; 1.30 g, 6.3 mmol), 1-hydroxybenzotriazole hydrate (HOBt; 0.90 g, 6.6 mmol),[20] 4-(dimethylamino)cinnamic acid (**3a**) (0.95 g, 5.0 mmol), **2a** (1.62 g, 5.6 mmol), and triethylamine (3 mL) in 50 mL of dry DMF was stirred for 18 h at room temperature. After the completion of the reaction (assessed by TLC by loss of both starting materials), 100 mL of H_2O was added. The organic products were extracted from 3 × 100 mL portions of ethyl acetate. The combined organic layers were washed with 2 × 100 mL of H_2O and 1 × 100 mL of brine, dried, and evaporated to yield 1.60 g (70%) of a light brown viscous product. The crude product was purified by flash column chromatography and eluted with ethyl acetate to give a light yellow foamy solid: IR 3000, 1660 (NC=O) cm^{-1}.

(±)-7-Bromo-8-methoxy-3-[4′-(*N*,*N*-dimethylamino)cinnamoyl]-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (4b). Compound **4b** was prepared (2.11 g, 3.5 mmol, 65%) by a coupling reaction between **2b** and 4-(dimethylamino)cinnamic acid (**3a**) according to the procedure described for the synthesis of **4a**.

(±)-7-Chloro-8-methoxy-3-[[4′-(*N*,*N*-dimethylamino)-phenyl]acetyl]-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (4c). Compound **4c** was prepared (3.10 g, 7.1 mmol, 70%) by a coupling reaction between **2b** and 4-(dimethylamino)phenylacetic acid (**3b**) according to the procedure described for the synthesis of **4a** except for the reaction time which was extended from 18 to 48 h. The crude product was purified by flash column chromatography ($CHCl_3$/MeOH/NH_4OH, 95:4.5:0.5) to give 3.12 g (70%) of a white viscous product: IR 3000, 1645 (NC=O) cm^{-1}.

(±)-7-Chloro-8-methoxy-3-*trans*-[4′-(*N*,*N*-dimethylamino)cinnamyl]-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (5a). Into a suspension of 0.40 g (11 mmol) of $LiAlH_4$ in 100 mL of THF was carefully added 0.50 g (5.1 mmol) of 98% H_2SO_4 dropwise at 0 °C. After stirring for 30 min, product **4a** (1.40 g, 3.1 mmol) in 5 mL of anhydrous THF was added carefully. The reaction mixture was allowed to warm to room temperature and stirred for 2 h. The hydrolytic workup was performed by adding 1.6 mL of water/THF (1:1) dropwise at 0 °C. After stirring for 15 min, ether (50 mL) was added followed by 2 mL of 15% aqueous NaOH solution to form a thick

precipitate of aluminum hydroxide. The reaction mixture was diluted with 30 mL of ether while stirring continued for 15 min. The white precipitate was separated by suction filtration, and the filtrate was evaporated to give 1.21 g (90%) of a viscous white product. The crude product was passed through a silica gel column and eluted with ethyl acetate/hexanes (1:3) to give a light yellow foamy solid (1.13 g, 85%). The HBr salt was formed by bubbling HBr gas into an ether solution of the product. Upon evaporating the solvent, a light yellow solid was obtained which was recrystallized from 2-PrOH/ether to give pure **5a** (1.10 g, 77%): mp 165−168 °C dec; ^{1}H NMR ($CDCl_3$) δ 7.40−7.25 (m, $5H_{1-Ph}$), 7.15 (d, $2H_{cinnamyl-Ph}$, $J = 7$), 7.13 (s, $1H_{H9}$), 6.83 (d, $2H_{cinnamyl-Ph}$, $J = 8$), 6.40 (d, 1H, $J = 16$ for *trans* vinylic hydrogen), 6.30 (s, $1H_{H6}$), 6.15−6.01 (m, $1H_{vinylic}$), 4.30 (dd, 1H, $J = 5.3, 3.3$), 3.62 (s, 3H), 3.40−3.05 (m, 4H), 2.95 (s, 6H), 2.85−2.4 (m, 6H); IR 2990, 1590, 1490 cm^{-1}. Anal. ($C_{28}H_{33}N_2OClBr_2 \cdot H_2O$) C, H, N.

(±)-7-Bromo-8-methoxy-3-*trans*-[4′-(*N*,*N*-dimethylamino)cinnamyl]-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (5b). Compound **5b** was prepared (1.50 g, 3.1 mmol, 85%) from **4b** according to the procedure described for the synthesis of **5a**. The crude product was passed through a silica gel column and eluted with chloroform to give a light yellow foamy solid. The HBr salt was formed by bubbling HBr gas into an ether solution of the product. Upon evaporating the solvent, a light yellow solid was obtained which was recrystallized from 2-PrOH/ether to give pure **5b** (1.41 g, 82%): mp 150−153 °C; ^{1}H NMR ($CDCl_3$) δ 7.40−7.25 (m, $5H_{1-Ph}$), 7.19 (s, $1H_{H9}$), 7.15 (d, $2H_{cinnamyl-Ph}$, $J = 7$), 6.83 (d, $2H_{cinnamyl-Ph}$, $J = 8$), 6.41 (d, 1H, $J = 16$ for *trans* vinylic hydrogen), 6.11−6.00 (m, $1H_{vinylic}$), 4.30 (dd, 1H, $J = 5.2, 3.3$), 3.62 (s, 3H), 3.4−3.05 (m, 4H), 2.91 (s, 6H), 2.82−2.42 (m, 6H); IR 2995, 1580, 1495 cm^{-1}. Anal. ($C_{28}H_{33}N_2OBr_3 \cdot 1.5H_2O$) C, H, N.

(±)-7-Chloro-8-methoxy-3-[2-[4′-(*N*,*N*-dimethylamino)phenyl]ethyl]-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (5c). The reduction of the amide **4c** was performed under the same conditions as for **5a** using AlH_3 to give **5c** (2.90 g, 7.1 mmol). The crude product was purified by flash column chromatography ($CHCl_3$/MeOH/NH_4OH, 95:4.5:0.5) to give 2.11 g (60%) of a white viscous product: ^{1}H NMR ($CDCl_3$) δ 7.35 (t, $2H_{1-Ph}$, $J = 7.2$), 7.3 (t, $1H_{1-Ph}$, $J = 7.3$), 7.2 (d, $2H_{1-Ph}$, $J = 7.0$), 7.15 (s, $1H_{H9}$), 7.05 (d, $2H_{cinnamyl-Ph}$, J =7.0), 6.65 (d, $2H_{cinnamyl-Ph}$, $J = 8.0$), 6.2 (s, $1H_{H6}$), 4.15 (dd, 1H, $J = 5.2, 3.3$), 3.62 (s, 3H), 3.11−3.01 (m, 4H), 2.92 (s, 6H), 2.80−2.40 (m, 6H); IR 3010, 1595, 1480 cm^{-1}.

(±)-7-Chloro-8-hydroxy-3-*trans*-[4′-(*N*,*N*-dimethylamino)cinnamyl]-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (6a). O-Demethylation was performed starting with a 1.30 g (1.3 mmol) portion of **5a** which was dissolved in dry $CHCl_3$ (10 mL), and then 5.0 mL of BBr_3 (1 M solution in CH_2Cl_2) was added at 0 °C under an atmosphere of argon. The reaction mixture was allowed to stir for 1 h at room temperature, and then 10 mL of MeOH (anhydrous) was added dropwise at 0 °C. After refluxing the reaction mixture in an open-mouthed reaction flask for 20 min, the solvents were evaporated. The product was dissolved in 20 mL of ethyl acetate/methanol (95:5), basified with 10% aqueous NaOH solution (pH = 7.5−8.0), diluted with 20 mL of ether, and separated. The aqueous phase was extracted with ethyl acetate/ether (9:1) mixture (2 × 20 mL). The combined organic phase was washed with brine (20 mL), dried, filtered, and evaporated to give 1.10 g (80%) of a foam. The crude product was chromatographed by silica gel column and eluted with ethyl acetate/hexanes (1:2) to give a white foamy solid (1.01 g, 75%). The HBr salt was formed by bubbling HBr gas into an ether solution of the product. Upon evaporating the solvent, a white solid was obtained which was recrystallized from 2-PrOH/ether to give pure **6a** (1.01 g, 70%): mp 180−183 °C dec; ^{1}H NMR ($CDCl_3$) δ 7.40−7.25 (m, $5H_{1-Ph}$), 7.11 (d, $2H_{cinnamyl-Ph}$, $J = 7$), 7.05 (s, $1H_{H9}$), 6.65 (d, 2H, $2H_{cinnamyl-Ph}$, $J = 7.0$), 6.35 (d, 1H, $J = 18$ for *trans* vinylic hydrogen), 6.32 (s, $1H_{H6}$), 6.10−6.00 (m, $1H_{vinylic}$), 4.25 (dd, 1H, $J = 5.2, 3.0$), 3.35−3.01 (m, 4H), 2.95 (s, 6H), 2.85−2.41 (m, 6H); IR 3025, 2995, 2670 (hydrogen-bonded OH group) 1601, 1490 cm^{-1}. Anal. ($C_{27}H_{31}N_2OClBr_2 \cdot 0.5H_2O$) C, H, N.

(±)-7-Bromo-8-hydroxy-3-*trans*-[4′-(*N*,*N*-dimethylamino)cinnamyl]-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (6b). Compound **6b** was prepared (0.4 g, 1.0 mmol, 70%) from **5b** according to the procedure described for the synthesis of **6a**. The crude product was passed through a silica gel column and eluted with ethyl acetate/hexanes (1:3) to give a white foam. The HBr salt was formed by bubbling HBr gas into an ether solution of the product. Upon evaporating the solvent, a light pink solid was obtained which was recrystallized from 2-PrOH/ether to give pure **6b** (0.40 g, 70%): mp 160−163 °C dec; ^{1}H NMR ($CDCl_3$) δ 7.40−7.25 (m, $5H_{1-Ph}$), 7.21 (s, $1H_{H9}$), 7.11 (d, $2H_{cinnamyl-Ph}$, $J = 7.3$), 6.65 (d, $2H_{cinnamyl-Ph}$, $J = 7.3$), 6.42 (d, 1H, $J = 18$ for *trans* vinylic hydrogen), 6.25 (s, $1H_{H6}$), 6.11−6.01 (m, $1H_{vinylic}$), 4.25 (dd, 1H, $J = 5.0, 3.3$), 3.35−3.00 (m, 4H), 2.95 (s, 6H), 2.82−2.31 (m, 6H); IR 3000, 2675 (hydrogen-bonded OH group) 1601, 1490 cm^{-1}. Anal. ($C_{27}H_{31}N_2OBr_3 \cdot H_2O$) C, H, N.

(±)-7-Chloro-8-hydroxy-3-[2-[4′-(*N*,*N*-dimethylamino)phenyl]ethyl]-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (6c). The O-demethylation of **5c** was performed under the same conditions as for **6a** using BBr_3 to give **6c** (0.91 g, 75%). The crude product was purified by flash column chromatography ($CHCl_3$/MeOH/NH_4OH, 95:4.5:0.5) to give 0.80 g (70%) of a white viscous product. The HCl salt was formed by bubbling HCl gas into an ether solution of the product. Upon evaporating the solvent, a white solid was obtained which was recrystallized from 2-PrOH/ether to give pure **6c** (0.70 g, 65%): mp 98−100 °C; ^{1}H NMR ($CDCl_3$) δ 7.30 (t, $2H_{1-Ph}$, $J = 7.2$), 7.25 (t, $1H_{1-Ph}$, $J = 7.3$), 7.21 (d, $2H_{1-Ph}$, $J = 7.0$), 7.15 (s, $1H_{H9}$), 7.05 (d, $2H_{cinnamyl-Ph}$, $J = 7.0$), 6.65 (d, $2H_{cinnamyl-Ph}$, $J = 8.0$), 6.20 (s, $1H_{H6}$), 4.15 (dd, 1H, $J = 5.1, 3.0$), 3.10−3.00 (m, 4H), 2.9 (s, 6H), 2.80−2.41 (m, 6H); IR 3010, 2660 (hydrogen-bonded OH group) 1591, 1480 cm^{-1}. Anal. ($C_{26}H_{31}N_2OCl_3 \cdot 0.5H_2O$) C, H, N.

(±)-7-Bromo-8-hydroxy-3-cinnamyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (7). Into a solution of **2b** (0.70 g, 2.1 mmol) in 20 mL of DMF, 1 mL of H_2O, and K_2CO_3 (0.30 g, 2.2 mmol) was added dropwise a solution of cinnamyl bromide (0.44 g, 2.2 mmol) in 5 mL of DMF.[23] After the mixture stirred for 8 h, the reaction was quenched with 40 mL of H_2O and the solution was then extracted with 50 mL of ether. The ether layer was washed with H_2O (2 × 25 mL) and brine (25 mL), dried, and evaporated. The crude product was purified by flash column chromatography, eluting with $CHCl_3$/MeOH/NH_4OH (98:2:0.5) to give 0.60 g (60%) of a white viscous product as 7-chloro-8-methoxy-3-cinnamyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine: ^{1}H NMR ($CDCl_3$) δ 7.40−7.20 (m, $9H_{aromatic}$), 7.15 (d, $2H_{cinnamyl-Ph}$, $J = 7$), 6.50 (d, 1H, $J = 15$ for *trans* vinylic hydrogen), 6.25 (s, $1H_{H6}$), 6.31−6.21 (m, $1H_{vinylic}$), 4.30 (dd, 1H, $J = 5.1, 3.0$), 3.60 (s, 3H), 3.30 (dd, $2H_{allylicCH2}$, $J = 14.1, 5.0$), 3.10−2.40 (m, 6H); IR 2950 cm^{-1}.

O-Demethylation of the above product was performed as for compound **6a** using BBr_3 to give the desired phenol **7**. The crude product was purified by flash column chromatography, eluting with $CHCl_3$ to give 0.50 g (85%) of a white viscous product. The HBr salt was formed by bubbling HBr gas into an ether solution of the product. Upon evaporating the solvent, a white product was obtained which was recrystallized from 2-PrOH/ether to give pure **7** (0.4 g, 70%): mp 163−165 °C; ^{1}H NMR ($CDCl_3$) δ 7.40−7.10 (m, $9H_{aromatic}$), 7.05 (d, $2H_{cinnamyl-Ph}$), 6.5 (d, 1H, $J = 15$ for *trans* vinylic hydrogen), 6.25 (s, $1H_{H6}$), 6.31−6.22 (m, $1H_{vinylic}$), 4.2 (dd, 1H, $J = 5.1, 3.0$), 3.35−2.25 (m, 8H); IR 2995, 2690 (hydrogen-bonded OH group) 1600, 1495 cm^{-1}. Anal. ($C_{25}H_{24}NOBr_2 \cdot 0.5H_2O$) C, H, N.

Modeling Methods. Molecular modeling studies were performed using the SYBYL[24] software package (Tripos, version 6.2, R4000) installed on a Silicon Graphics IRIS Indigo XZ workstation running IRIX 5.2. The chemical structures were drawn using the SKETCH option. Optimized geometries and partial charges were obtained using the AM1[25] model Hamiltonian as implemented in the MOPAC[26] program (version 6.0) using the PRECISE convergence criteria.

Biological Evaluation. Chemicals and reagents were obtained from the following sources: [^{3}H]SCH 23390 (specific activity 71.3 Ci/mmol), [^{3}H]sulpiride (specific activity 70 Ci/

mmol), and [^{3}H]cAMP (adenosine 3′,5′-cyclic phosphate, ammonium salt; specific activity 31.4 Ci/mmol) from New England Nuclear (Boston, MA); dopamine, ATP, GTP, imidazole, theophylline, and all other buffer components from Sigma Chemical Co. (St. Louis, MO); SCH 23390 and sulpiride from Research Biochemicals International (Natick, MA).

[^{3}H]SCH 23390 and [^{3}H]sulpiride binding assays were performed as described previously.[20] Adenylyl cyclase assay was performed as described previously.[20]

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