(±)-(*N*-Alkylamino)benzazepine Analogs: Novel Dopamine D_1 Receptor Antagonists†

Jamshed H. Shah, Sari Izenwasser, Beth Geter-Douglass, 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

Received March 6, 1995®

(±)-(*N*-Alkylamino)benzazepine analogs were prepared as novel dopamine D_1 receptor antagonists to further elucidate the role of these receptor subtypes in the pharmacology and toxicology of cocaine. In the first series of compounds, (±)-7-chloro-8-hydroxy-3-[6-(*N*,*N*-dimethylamino)-hexyl]-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (**15**) showed the highest affinity (K_i = 49.3 nM) and subtype-selectivity for dopamine D_1 over dopamine D_2, 5-HT_{2a}, and 5-HT_{2c} receptors. Compounds **7a** {(±)-7-Chloro-8-hydroxy-3-[4-(*N*,*N*-dimethylamino)butyl]-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine}, **11** {(±)-7-chloro-8-hydroxy-3-[6-[(*N*,*N*-dimethylamino)hexyl]-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine–cyanoborane}, and **15** were moderately potent dopamine D_1 receptor antagonists as evidenced by their ability to block dopamine-stimulated adenylyl cyclase activity in rat caudate (predicted K_i values = 60, 34, and 21 nM, respectively). Compound **7a** appears to be unique in that, despite its relatively potent inhibition of dopamine stimulated adenylyl cyclase, it demonstrated relatively weak binding affinity at the dopamine D_1 receptors (K_i = 811 nM). Unlike previously reported *N*-alkylbenzazepines, where a significant loss in dopamine D_1 receptor binding affinity was observed when successive increases in the alkyl side chain size at the benzazepine nitrogen were made, several of these novel *N*-alkylamino analogs demonstrated high-affinity binding with an optimal chain length of six carbons. This initial series of compounds appears to be identifying another binding domain on the dopamine D_1 receptor protein that has not previously been characterized and that accepts an amino function. Further, these compounds may serve as templates for the design of peripherally active dopamine D_1 receptor antagonists.

Introduction

The neurotransmitter dopamine plays a critical role in the etiology and pharmacotherapy of a number of neurodegenerative and psychiatric disorders that include Parkinson's disease, Huntington's disease, and psychosis.[1,2] In addition, evidence suggests that the inhibition of uptake from or release of dopamine into the synapse are the primary mechanisms by which psychostimulant drugs such as cocaine and amphetamine produce their actions and are associated with the reinforcing and subjective effects of these drugs.[3–5] Dopamine receptors have been classified into two major groups, D_1 and D_2, based on the pharmacology of the compounds that selectively bind to the receptor subtypes.[6] Further, five dopamine receptor subtypes have been cloned, whereby D_1 and D_5 are in the first subclass and D_2, D_3, and D_4 belong to a second subclass.[7–10] The discovery of highly selective and potent ligands for each of the subtypes is required to further explore the physiological relevance of each of the D_1–D_5 subtypes, and these compounds may potentially be developed into novel therapeutics for treatment of dopamine-related disorders.

Dopamine D_1 antagonists have been prepared with the prototype antagonist being SCH 23390 ((*R*)-(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine), a highly potent and relatively selective ligand for the D_1 site.[11–13] The discovery of this ligand initiated dramatic and revealing investigation of dopamine D_1 receptors.[14] [^{3}H]SCH 23390 has proven to be an invaluable tool to characterize dopamine D_1 receptors and elucidate their physiological roles as well as to identify the interaction that occurs between D_1 and D_2 receptor subtypes.[15–17] Structure–activity relationships (SAR) have been described for a wide range of benzazepines, yet with few exceptions, none of these analogs have proven to be more potent than the parent drug.[13,18] Conformational analyses and molecular modeling of the benzazepine class of dopamine D_1 antagonists as well as the structurally related phenyl-substituted tetrahydroisoquinolines have been described, and a hypothetical model of the D_1 pharmacophore has been devised.[19–22] Since SCH 23390 also binds with high affinity to the 5-HT_{2a} (previously called 5-HT_2) and 5-HT_{2c} (previously called 5-HT_{1c}) receptors,[23–25] considerable effort has been directed toward synthesizing more selective D_1 antagonists.[24,26,27]

Peripheral dopamine D_1 receptors have been demonstrated to be involved in the regulation of blood flow, ganglionic neurotransmission, cardiac adrenergic transmission, and other physiological processes.[28–30] Recent studies implicated that central and particularly peripheral dopamine D_1 receptors may be mediating the lethality exhibited by high doses of cocaine.[31–33] In the absence of a peripherally-active dopamine D_1 antagonist (i.e. a compound that does not penetrate the blood–brain barrier), the role of peripheral dopamine receptors in the toxicity of cocaine could not be directly investigated.[33] Therefore, it was of interest to prepare a peripheral dopamine D_1-selective antagonist that would

† This paper has been presented in part at the 56th Annual Scientific Meeting of the College on Problems of Drug Dependence, Palm Beach, FL, June 1994, and the American Chemical Society Meeting, Washington, D.C., August 1994.

® Abstract published in *Advance ACS Abstracts*, September 1, 1995.

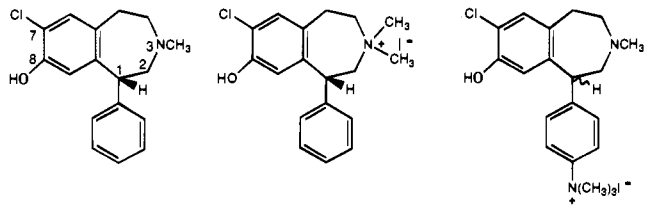


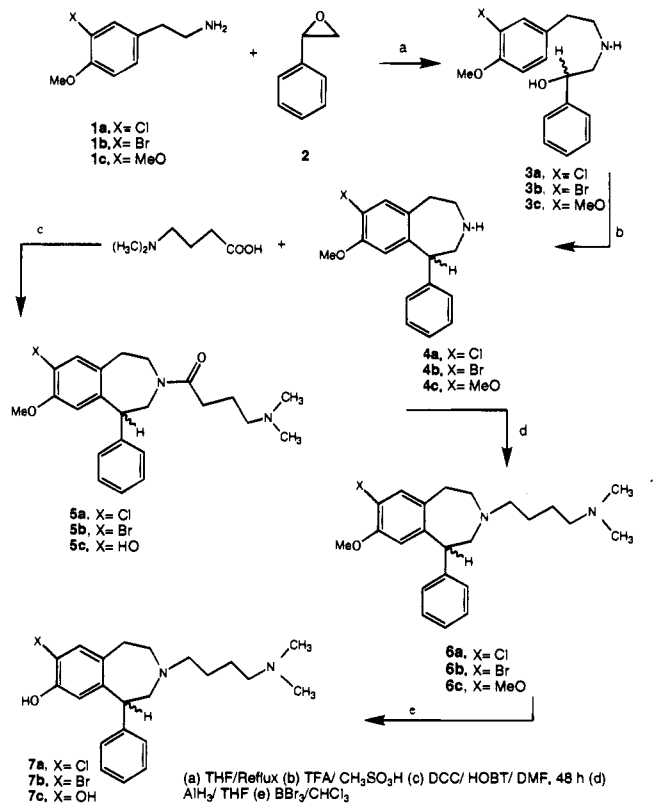
Figure 1. Chemical structures of SCH 23390 and quaternary analogs.

not penetrate the blood–brain barrier. This compound would be a useful tool for studying the relationship between cocaine toxicity and peripheral dopamine D_1 receptors and further would allow direct elucidation of the physiological functions of these receptors.

Our first attempts at preparing a peripheral dopamine D_1 receptor antagonist focused on synthesizing quaternary analogs of SCH 23390.[34] The first two compounds synthesized had a quaternary nitrogen at position 3 or at the para position of the pendant phenyl ring (Figure 1). Neither of these compounds retained high-affinity binding to dopamine D_1 sites, and therefore they were unsuitable for our purposes. It was deduced that a quaternary function on the 1-phenylbenzazepine ring was not tolerated at the receptor, and therefore, another approach was undertaken.

It was anticipated that by extending an amino function away from the pharmacophore via an alkyl chain, the pharmacophore would still be recognized by its binding site without interference from the pendant amino function. This approach has previously been successful with quaternary peripheral-type benzodiazepine receptor ligands.[35] It was apparent from previous studies that small alkyl chains at the 3-position would not be tolerated, i.e. the 3-propyl derivative of SCH 23390 has a decreased binding affinity at [^{3}H]SCH 23390-labeled D_1 binding sites (K_i = 3600 nM) as compared to the parent compound (K_i = 0.3 nM).[13] However, to our knowledge, further exploration into amino-substituted alkyl chains had not been pursued. Therefore, alkylamino analogs of SCH 23390, starting with a four-carbon methylene chain with a terminal amino group, were explored. Compounds with variable methylene chain lengths (4 and 6) were prepared to determine the optimal chain length for binding to dopamine D_1 receptors. Further, exploration of the terminal amine function was achieved by preparing the primary, secondary, and tertiary amines. Amido substitutions at either the benzazepine 3-nitrogen or at the terminal amine were evaluated to determine whether the basic nitrogen was necessary for optimal activity. 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.[13,18] The 7-OH-substituted analogs were prepared based on the prototypic dopamine D_1 agonist SKF 38393 ((*R*)-(+)-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine) to determine whether the N-alkylamino side chain would be tolerated on a dopamine D_1 agonist pharmacophore. All of the compounds were evaluated for binding to dopamine D_1 and D_2 sites in rat brain. Selected compounds were then tested for inhibition of dopamine-stimulated adenylyl cyclase and for binding at 5-HT_{2a} and 5-HT_{2c} sites to ascertain the selective dopamine D_1 antagonist actions of these compounds.

Scheme 1

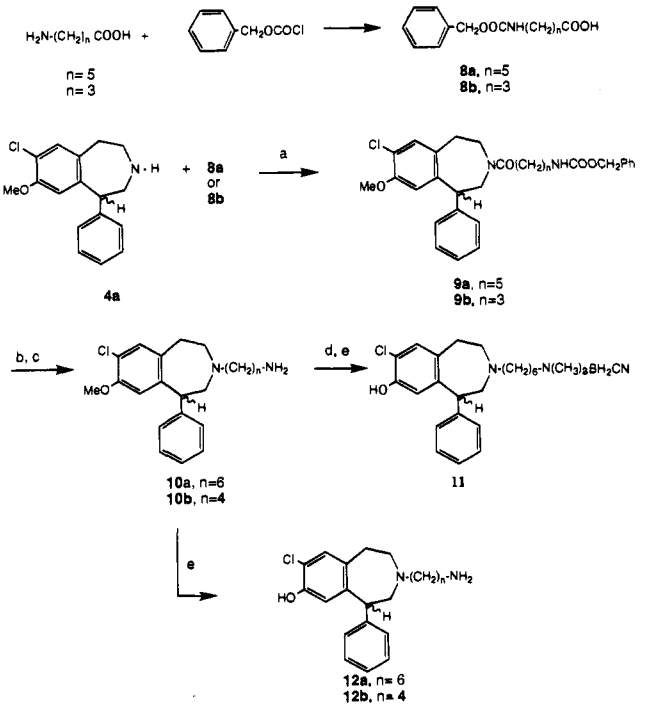


Chemistry

In Scheme 1, the benzazepines **4a–c** were synthesized by a modification of the procedure of Baindur et al.[36] The 3-substituted-4-methoxyphenylacetonitriles were reduced to the respective (3-substituted-4-methoxyphenyl)ethylamines (**1a** and **1b**; **1c** was purchased from Aldrich Chemical Co.) with alane (AlH_3) in THF according to the procedure of Yoon et al.[37] Compounds **1a–c** were condensed with styrene oxide in THF to obtain the benzyl alcohols **3a–c**. Cyclization of **3a–c** in a mixture of refluxing trifluoroacetic acid and methanesulfonic acid formed the benzazepines **4a–c** in 90–95% yield. A coupling reaction between the benzazepines **4a–c** and (*N*,*N*-dimethylamino)butyric acid using dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole (HOBt)[38] gave the amides **5a–c**. The amides **5a–c** were reduced with AlH_3 in THF to give the (*N*-alkylamino)benzazepines **6a–c** following a modification of the procedure of Yoon et al.[37] 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 **5a** and **5b**. O-Demethylation of the resulting (*N*-alkylamino)-benzazepines **6a–c** with BBr_3 in $CHCl_3$ yielded target compounds **7a–c** in 60–70% yield.

In Scheme 2, the coupling reaction of 6-aminocaproic acid and 4-aminobutyric acid with the benzazepine **4a** involved first the protection of the amino group of the amino acids with benzyl chloroformate. The resulting carbobenzoxy-protected amino acids **8a** and **8b** were reacted with benzazepine **4a** in the presence of DCC and HOBt[38] to give the amides **9a** and **9b**. The products **9a** and **9b**, after N-deprotection with iodotrimethylsilane,[39] were reduced with AlH_3 in THF to give products **10a** and **10b**.

Scheme 2[a]



[a] (a) DCC, HOBT/DMF, 48 h; (b) $ISi(Me)_3/CH_3CN$; (c) AlH_3/THF; (d) $NaBH_3CN$/HCHO 37%; (e) $BBr_3/CHCl_3$.

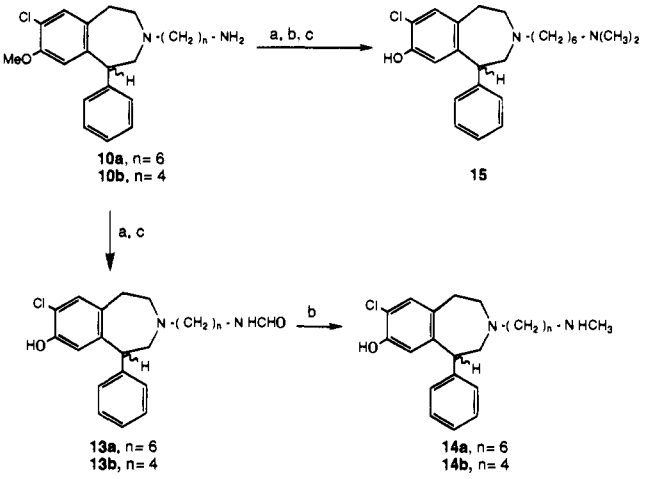
In an attempt to synthesize **15** directly from **10a** by using sodium cyanoborohydride in aqueous formaldehyde (37%) and acetonitrile,[40] the formation of **11** (60%) instead of **15** resulted. It appeared that when the acetic acid was added to the reaction mixture, the sodium cyanoborohydride generated cyanoborane which formed a stable complex with the (alkylamino)benzazepine to give compound **11**. This complex appeared to be stable under acidic and basic conditions, was purified by column chromatography, and formed a stable HCl salt. To further confirm this trend of complex formation between cyanoborane and amino compounds, (3-chloro-4-methoxyphenyl)ethylamine was reacted with sodium cyanoborohydride in the presence of formaldehyde (37%) in acetonitrile. The reaction mixture was treated with acetic acid, and after workup, the *N,N*-dimethyl(3-chloro-4-methoxyphenyl)ethylamine–cyanoborane complex, as confirmed by ^1H NMR, IR, and combustion analysis, was formed in 70% yield.

The O-demethylation of **10a** and **10b** using BBr_3 formed the primary amino derivatives **12a** and **12b**. The N-formylation of **10a** and **10b** using ethyl formate and formic acid followed by O-demethylation with BBr_3 gave compounds **13a** and **13b**, as depicted in Scheme 3. The reduction of **13a** and **13b** with AlH_3 in THF formed the secondary amines **14a** and **14b**. Compound **15** was obtained by the repeated N-formylation and reduction of **10a** followed by O-demethylation. The product **16** was made first by reacting **4a** with bromobutane in the presence of K_2CO_3 in DMF,[41] followed by O-demethylation with BBr_3 (Scheme 4). Compound **17** was prepared by first deprotecting **9b** with iodotrimethylsilane followed by O-demethylation with BBr_3 (Scheme 5).

Discussion of Results

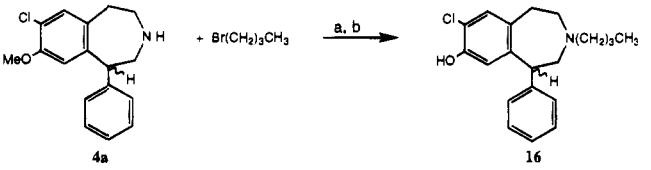
All of the compounds were evaluated for binding to dopamine D_1 and D_2 receptors in rat caudate putamen.

Scheme 3[a]



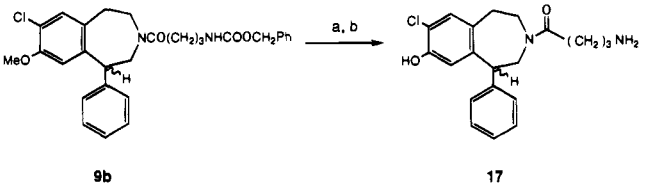
[a] (a) EtOCHO/HCOOH; (b) AlH_3/THF; (c) $BBr_3/CHCl_3$.

Scheme 4[a]



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

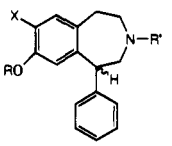
Scheme 5[a]



[a] (a) $ISiMe_3/CH_3CN$; (b) $BBr_3/CHCl_3$.

[^3H]SCH 23390 was used as the radiolabeled ligand for dopamine D_1 receptors, and [^3H]sulpiride was used for radiolabeling dopamine D_2 receptors. Results of these binding experiments are depicted in Tables 1 and 2, where all of the compounds in Table 1 have four-carbon side chains and the compounds in Table 2 have six-carbon side chains. The parent compound SCH 23390 (K_i = 0.21 nM) demonstrated the highest affinity for dopamine D_1 sites and remains one of the most potent dopamine D_1 antagonists described to date.[18] It has been reported that lengthening the side chain of the 1-phenylbenzazepines in the 3-position drastically decreases binding affinity for dopamine D_1 sites.[13] For example, the *N*-ethyl derivative of SCH 23390 has a K_i = 41 nM for dopamine D_1 sites which is a 100-fold decrease in binding affinity compared to the parent drug.[13] Further, the *N*-propyl derivative has a K_i = 3600 nM which is 10 000-fold less potent than SCH 23390.[13] Despite this trend, it was envisioned that at some further distance away from the pharmacophore, binding affinity might be restored to an acceptable level. In fact, the *N*-butyl analog, compound **16**, had a K_i = 634 nM. Although this was not a potent compound it had approximately 6-fold higher affinity than the previously reported *N*-propyl analog. Further, when a primary amine was added to the end of the *N*-butyl chain (**12b**, K_i = 75.0 nM) a nearly 10-fold increase in binding affinity was obtained as compared to the simple butyl

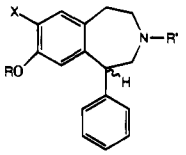
Table 1. Radiolabeled Binding Data for Benzazepine Analogs



compound	X	R	R'	K_i (nM) D_1[a,b]	K_i (nM) D_2[a,c]
SCH 23390	Cl	H	CH_3	0.21 ± 0.03	NT[d]
6a	Cl	Me	$(CH_2)_4N(CH_3)_2$	>10 000[e]	9150 ± 1920
6b	Br	Me	$(CH_2)_4N(CH_3)_2$	>10 000[e]	2490 ± 923
6c	OMe	Me	$(CH_2)_4N(CH_3)_2$	>10 000[e]	>10 000[e]
7a	Cl	H	$(CH_2)_4N(CH_3)_2$	811 ± 73.0	4130 ± 1360
7b	Br	H	$(CH_2)_4N(CH_3)_2$	1490 ± 104	>10 000[e]
7c	OH	H	$(CH_2)_4N(CH_3)_2$	4820 ± 627	>10 000[e]
12b	Cl	H	$(CH_2)_4NH_2$	75.0 ± 4.50	4280 ± 1540
14b	Cl	H	$(CH_2)_4NHCH_3$	106 ± 6.37	>10 000[e]
16	Cl	H	C_4H_9	634 ± 25.4	2360 ± 1820
17	Cl	H	$C(O)(CH_2)_3NH_2$	607 ± 24.0	7410 ± 1110

[a] K_i values (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] NT = not tested. [e] >10 000 indicates less than 50% inhibition of binding at a concentration of 10 μM.

Table 2. Radiolabeled Binding Data for Benzazepine Analogs



compound	X	R	R'	K_i (nM) D_1[a,b]	K_i (nM) D_2[a,c]
11	Cl	H	$(CH_2)_6N(CH_3)_2{\cdot}BH_2CN$	142 ± 18.0	NA[d]
12a	Cl	H	$(CH_2)_6NH_2$	321 ± 16.1	2490 ± 423
13a	Cl	H	$(CH_2)_6NH(CHO)$	553 ± 33.2	2030 ± 729
14a	Cl	H	$(CH_2)_6NHCH_3$	75.7 ± 5.30	3570 ± 893
15	Cl	H	$(CH_2)_6N(CH_3)_2$	49.3 ± 3.94	3450 ± 1450

[a] K_i values (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] NA = not available due to insolubility problems at higher concentrations of the compound.

chain. These results suggested that the amino function may be interacting at the receptor. Interestingly, in this series of butylamino analogs, by increasing steric bulk at the terminal amine to the *N*-methyl amino group (**14b**), dopamine D_1 receptor binding affinity began to slightly decrease (K_i = 106 nM). The *N,N*-dimethyl group (**7a**) further decreased binding affinity to within the range of the *N*-butyl analog (K_i = 811 nM). The amide **17** (K_i = 607) demonstrated decreased binding affinity as compared to its reduced congener **12b**, suggesting that a basic amine at position 3 of the benzazepine ring is favored. In addition, the 7-Cl function of compound **7a** showed a slightly higher binding affinity than the 7-Br substitution on the structural analog **7b**. This trend was comparable to the Br derivative of SCH 23390 ((*R*)-(+)-SCH 24543).[18] Finally, the compounds that have methoxy groups at position 8 (**6a**, **6b**, and **6c**) were totally inactive at dopamine D_1 receptors. Further, the catechol compound **7c** had a K_i = 4820 nM as compared to the prototypic dopamine D_1 agonist SKF 38393 (K_i = 1.1 nM),[42] demonstrating that addition of an alkylamino side chain to a dopamine D_1 receptor agonist significantly decreased binding affinity.

In Table 2, the six-carbon side chain series demonstrated a distinct binding pattern as compared to the four-carbon side chain series. The most potent in this series was the *N,N*-dimethyl analog, compound **15**. This compound had a K_i = 49.3 nM and thus was approximately 17-fold more potent than its analog in the four-carbon series, **7a**. Somewhat surprisingly, the *N*-methyl analog **14a** was slightly less potent (K_i = 75.7) than the tertiary amine and had a similar affinity to the *N*-methyl analog, **14b**. The unsubstituted primary terminal amine analog **12a** had a further reduced binding affinity for dopamine D_1 sites (K_i = 321 nM) and was thus less potent than the four-carbon chain analog (**12b**). The terminal *N*-formyl analog **13a** (K_i = 553 nM) was less potent than the *N*-methyl compound **14a**, suggesting that the basic terminal amine was favored for binding, as was the benzazepine 3-position amine function. The borane-complexed compound **11** demonstrated only slightly lower affinity than the non-borane-complexed analog **15**, suggesting that additional steric bulk and charge at the terminal amine may be tolerated. An alternative explanation is that under the experimental conditions the borane complex may be partly dissociated, hence resulting in some of the parent compound, **15**, at the receptor.

All of the compounds weakly recognized dopamine D_2 receptors with binding affinities in the 2 → 10 μM range of affinities, and thus the alkylamino side chains did not severely reduce or increase binding potency at these sites. As a result, within this series, binding affinity at the dopamine D_1 sites dictated selectivity, and hence the most potent dopamine D_1 compounds were the most selective for D_1 over D_2 sites.

Compounds **7a**, **11**, and **15** were selected for further evaluation of binding affinities at the 5-HT_{2a} and 5-HT_{2c} receptors since SCH 23390 binds with high affinity to both of these 5-HT receptor subtypes. Compound **15** was the most potent dopamine D_1 ligand in this series and one of the most selective (70-fold) over D_2 sites. Compound **15** demonstrated a K_i = 112 nM at 5-HT_{2a} sites[43] and a K_i = 2390 nM at 5-HT_{2c} sites.[43] Therefore this compound was only 2-fold selective for dopamine D_1 over 5-HT_{2a} sites (as compared to SCH 23390 having a 50-fold selectivity).[25] However, it was 56-fold selective over 5-HT_{2c} sites, similar to SCH 23390 (75-fold).[24] Compound **11**, which is the boron-complexed analog of **15**, demonstrated a K_i = 800 nM at 5-HT_{2a} sites[43] and was not evaluated at 5-HT_{2c} sites. Compound **7a** demonstrated a K_i = 1720 nM at 5-HT_{2a} sites[43] and a K_i = >10 000 nM at 5-HT_{2c} sites.[43] It must be noted that all of the compounds reported here are the racemic mixtures. SCH 23390 is the (*R*)-(+)-enantiomer which is far more potent and selective than its optical antipode.[12,18] Should similar enantioselectivity be observed in this series, the (*R*)-(+)-enantiomers of these compounds will demonstrate higher affinity and selectivity for dopamine D_1 sites.

These three (*N*-alkylamino)benzazepines (**7a**, **11**, and **15**) were further evaluated for the inhibition of dopamine-stimulated adenylyl cyclase in rat caudate (Figure 2). It is known that dopamine D_1 antagonists, but not D_2 antagonists or D_1 agonists, inhibit dopamine-stimulated adenylyl cyclase. SCH 23390 inhibited

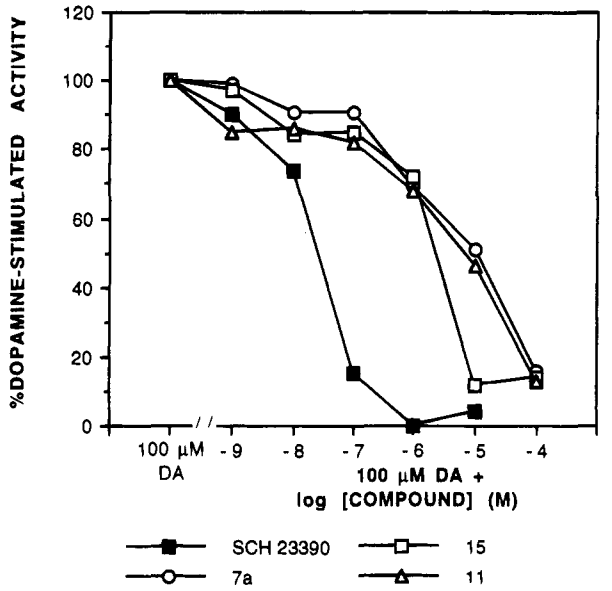


Figure 2. SCH 23390 ($n = 3$), **7a** ($n = 6$), 11 ($n = 5$), and **15** ($n = 5$) antagonize adenylyl cyclase activity stimulated by 100 μM dopamine. Dopamine (100 μM) stimulated adenylyl cyclase activity approximately 200% over basal levels (expressed as 100% in figure.) Predicted K_i values, based on these data, as described in the Experimental Section are as follows: SCH 23390, $K_i = 0.11 \pm 0.12$ nM; **7a**, $K_i = 60 \pm 39$ nM; 11, $K_i = 34 \pm 13$ nM; **15**, $K_i = 21 \pm 13$ nM. Each data point represents mean ± SEM from n independent experiments, each performed in triplicate.

dopamine-stimulated adenylyl cyclase, under these conditions, with a predicted $K_i = 0.11$ nM. Interestingly, compounds **7a**, **11**, and **15** showed somewhat more potent inhibition of dopamine-stimulated adenylyl cyclase (predicted K_i's = 60, 34, and 21, respectively) than would be anticipated by their binding affinities. This was especially apparent for compound **7a** which was >13 times more potent in the functional assay than would be predicted by its binding affinity at the dopamine D_1 receptors. One possible explanation for this difference in *in vitro* binding and function is the existence of subpopulations of dopamine D_1 receptors.[44-46]

Preliminary *in vivo* estimations of central nervous system (CNS) activity of compounds **7a**, **11**, **15**, and SCH 23390 were obtained using locomotor activity in Swiss–Webster mice. In these experiments, potency to suppress locomotor activity appeared to be consistent with affinity of the compounds for dopamine D_1 receptors suggesting that these drugs are permeable to the CNS upon systemic administration (subcutaneous administration). Evaluation of other compounds in this series as well as a terminal quaternary amino analog of compound **15** is planned.

Conclusion

A series of (*N*-alkylamino)benzazepine analogs have been prepared and evaluated as dopamine D_1 antagonists. Results of binding experiments demonstrated that several of these analogs were moderately potent and selective dopamine D_1 antagonists. Although the alkylamino side chain did decrease binding affinity relative to the *N*-methyl group of the parent compound SCH 23390, reasonably potent binding affinity ($K_i < 100$ nM) was regained when the side chain was extended to at least four carbon atoms away from the benzazepine nitrogen. The terminal amino functions appeared to be important for binding as was the 7-position Cl group in both the four- and six-carbon chain series. All of the compounds reported are the racemic mixtures, and efforts to separate and evaluate the enantiomers are underway. In addition, benzazepine analogs with different terminal amino side chains may also prove to have higher affinity and selectivity for the dopamine D_1 receptors while possessing chemical moieties that are not compatible with blood–brain barrier passage. Compounds of this nature are currently being prepared.

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, Newark, DE) 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. The solvent system used for all chromatography was $CHCl_3$/methanol/NH_4OH (90:10:1) unless otherwise specified. Drying refers to the use of anhydrous Na_2SO_4 followed by suction filtration. The ^1H NMR data were recorded on a Bruker (Billerica, Mass) AC-300 instrument. Proton chemical shifts were reported as parts per million (δ) relative to tetramethylsilane (Me_4Si; 0.0 ppm) which was used as an internal standard. Infrared spectra were recorded in KBr or neat (NaCl plates) with a Perkin-Elmer 1600 Series FTIR. Microanalyses were performed by the 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.

(3-Chloro-4-methoxyphenyl)ethylamine (1a). A 6.0 g (160 mmol) portion of $LiAlH_4$ in 250 mL of anhydrous THF was treated carefully with 7.6 g (80 mmol) of 98% sulfuric acid at 0 °C.[37] After 30 min stirring, 18.16 g (100 mmol) of 3-chloro-4-methoxyphenylacetonitrile (Parrish Chemical Co., Orem, UT) in 25 mL of THF was added dropwise at 0 °C to the reaction mixture. After 1 h stirring at room temperature, the reaction mixture was hydrolyzed by adding 25 mL of a 1:1 mixture of THF and H_2O at 0 °C. The gelatinous product was dissolved in 100 mL of ethyl ether, and then a solution of 7.0 g of sodium hydroxide in 50 mL of H_2O was added to the reaction mixture to form a thick precipitate of aluminum hydroxide. The precipitate was separated by suction filtration. The organic filtrate was dried and evaporated to yield 18.1 g (90%) of **1a** as a light brown viscous oil: ^1H NMR ($CDCl_3$) δ 7.1(s, 1H), 6.95 (d, 1H, $J = 8.3$ Hz), 6.8 (d, 1H, $J = 8.4$ Hz), 3.95 (s, 3H), 2.9 (t, 2H, $J = 6.8$ Hz), 2.65 (t, 2H, $J = 6.8$ Hz), 1.3 (broad, 2H); IR (neat) 3400, 3250 cm^{-1}.

(3-Bromo-4-methoxyphenyl)ethylamine (1b).[47] Compound **1b** was prepared (10.2 g, 45 mmol, 90%) from 3-bromo-4-methoxyphenylacetonitrile according to the procedure described for the synthesis of **1a**.

2-[*N*-[2-(3-Chloro-4-methoxyphenyl)ethyl]amino]-1-phenylethanol (3a). A solution of 6.0 g (50 mmol) of styrene oxide (**2**) and 9.3 g (50 mmol) of (3-chloro-4-methoxyphenyl)-ethylamine (**1a**) in 50 mL of dry THF was stirred at reflux for 18 h.[36] After completion of the reaction the solvent was evaporated to give a viscous crude product. Purification by flash column chromatography resulted in 8.0 g (65%) of a viscous product. Addition of anhydrous ethyl ether resulted in a white crystalline product, which was separated by suction filtration, washed with ether, and dried under reduced pressure. Alternatively, after the THF was removed, the viscous crude product was dissolved in 100 mL of ether and left to stand overnight to give a white crystalline product (50%) which was separated by suction filtration and washed with ether: mp 95–96 °C (lit.[36] mp 94–96 °C); ^1H NMR ($CDCl_3$) δ 7.4–7.25 (m, 5H, phenyl H), 7.2 (s, 1H), 7.05 (d, 1H, $J = 8.3$ Hz), 6.85 (d, 1H, $J = 8.4$ Hz), 4.7 (dd, 1H, $J = 9.0$ Hz), 3.85 (s, 3H), 3–2.6 (m, 6H); IR 3418 (OH) cm^{-1}.

2-[*N*-[2-(3-Bromo-4-methoxyphenyl)ethyl]amino]-1-phenylethanol (3b). Compound **3b** was prepared (6.9 g, 20

mmol, 45%) from **1b** and styrene oxide (**2**) according to the procedure described for the synthesis of **3a** except acetonitrile was used as a solvent instead of THF and the product was purified by flash column chromatography and recrystallized from ethyl ether to give the product as white crystals: mp 90–92 °C; ^{1}H NMR ($CDCl_3$) δ 7.4–7.2 (m, 5H, phenyl H), 7.15 (s, 1H), 7.05 (d, 1H, J = 8.5 Hz), 6.8 (d, 1H, J = 8.4 Hz), 4.7 (dd, 1H, J = 9.1 Hz), 3.85 (s, 3H), 3–2.6 (m, 6H); IR 3418 (OH) cm^{-1}.

2-[*N*-[2-(3,4-Dimethoxyphenyl)ethyl]amino]-1-phenylethanol (3c). Compound **3c** was prepared (13.9 g, 46 mmol, 50%) from (3,4-dimethoxyphenyl)ethylamine (**1c**) and styrene oxide (**2**) according to the procedure described for the synthesis of **3a**. After the THF was removed, the viscous crude product was dissolved in 100 mL of ether, and after 2 h standing white crystalline product was formed which was separated by suction filtration and washed with ether: mp 94–96 °C; ^{1}H NMR ($CDCl_3$) δ 7.38 (s, 1H), 7.35–7.25 (m, 5H), 6.8 (d, 1H, J = 8.2 Hz), 6.75 (d, 1H, J = 8.3 Hz), 4.7 (dd, 1H, J = 8.9 Hz), 3.9 (s, 3H), 3.85 (s, 3H), 3–2.6 (m, 6H), 2.4 (broad, 1H, OH); IR 3400 (OH) cm^{-1}.

(±)-7-Chloro-8-methoxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (4a). Cyclization of **3a** was performed by modifying the procedure of Baindur et al.[36] Product **3a** (3.05 g, 10 mmol) was dissolved in 30 mL of trifluoroacetic acid (99%), and then 1.0 mL (10 mmol) of methanesulfonic acid (99%) was added under an atmosphere of argon. The reaction mixture was stirred at reflux for 18 h. After completion of the reaction, the excess of trifluoroacetic acid was evaporated on the rotary evaporator and the remaining viscous mixture was poured into ice-cold H_2O (50 mL) and made alkaline with a 15% aqueous NaOH solution. Extraction with $CHCl_3$ (2 × 100 mL) followed by washing with H_2O (50 mL) and brine (50 mL), drying, filtration, and evaporation gave 2.60 g (95%) of **4a** as a viscous product: ^{1}H NMR ($CDCl_3$) δ 7.4–7.25 (m, 3H), 7.2 (s, 1H), 7.1 (d, 2H, J = 7.2 Hz), 6.45 (s, 1H), 4.2 (d, 1H, J = 8.4 Hz), 3.7 (s, 3H), 3.6–2.7 (m, 6H), 2.0 (broad, 1H, N-H); IR 3318 (NH), 3000, 1596, 1498 cm^{-1}.

(±)-7-Bromo-8-methoxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (4b). Compound **4b** was prepared (1.5 g, 4.5 mmol, 90%) from **3b** according to the procedure described for the synthesis of **4a**: ^{1}H NMR ($CDCl_3$) δ 7.35 (t, 2H, J = 7.2 Hz), 7.3 (s, 1H), 7.25 (t, 1H, J = 6.9 Hz), 7.1 (d, 2H, J = 7.2 Hz), 6.45 (s, 1H), 4.2 (d, 1H, J = 8.6 Hz), 3.7 (s, 3H), 3.6–2.7 (m, 6H), 2.0 (broad, 1H, NH); IR 3310 (NH), 3000, 1596, 1498 cm^{-1}.

(±)-7,8-Dimethoxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (4c). Compound **4c** was prepared (5.1 g, 18 mmol, 90%) from **3c** according to the procedure described for the synthesis of **4a**: ^{1}H NMR ($CDCl_3$) δ 7.4 (t, 2H, J = 7.1 Hz), 7.3 (t, 1H, J = 7.0 Hz), 7.05 (d, 2H, J = 6.9 Hz), 6.7 (s, 1H), 6.4 (s, 1H), 4.25 (d, 1H, J = 8.6 Hz), 3.8 (s, 3H), 3.65 (s, 3H), 3.6–2.8 (m, 6H), 2.5 (broad, 1H, NH); IR 3300 (NH), 3000, 1596, 1490 cm^{-1}.

(±)-7-Chloro-8-methoxy-3-[4-(*N*,*N*-dimethylamino)butanoyl]-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (5a). A mixture of 1,3-dicyclohexylcarbodiimide (DCC, 2.47 g, 12 mmol), 1-hydroxybenzotriazole hydrate (HOBT, 1.76 g, 13 mmol),[38] (dimethylamino)butyric acid hydrochloride (1.68 g, 10 mmol), **4a** (2.87 g, 10 mmol), and triethylamine (3 mL) in 150 mL of dry DMF was stirred for 48 h at room temperature. After completion of the reaction (assessed by TLC), 200 mL of H_2O was added. The reaction mixture was basified by adding a few drops of 15% aqueous NaOH solution, and the organic products were extracted from 3 × 100 mL portions of a 1:1 mixture of ethyl ether and 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 3.6 g (80%) of a light brown viscous product. The ^{1}H NMR spectra (complex spectra due to rotamers) confirmed the product to be **5a**: IR 3000, 1638 (NC=O) cm^{-1}.

(±)-7-Bromo-8-methoxy-3-[4-(*N*,*N*-dimethylamino)butanoyl]-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (5b). Compound **5b** was prepared (1.56 g, 3.5 mmol, 65%) from **4b** according to the procedure described for the synthesis of **5a**.

(±)-7,8-Dimethoxy-3-[4-(*N*,*N*-dimethylamino)butanoyl]-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (5c). Compound **5c** was prepared (1.6 g, 4 mmol, 60%) from **4c** according to the procedure described for the synthesis of **5a**.

(±)-7-Chloro-8-methoxy-3-[4-(*N*,*N*-dimethylamino)butyl]-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (6a). Into a suspension of 0.8 g (20 mmol) of $LiAlH_4$ in 150 mL of THF was added 98% H_2SO_4 (1.0 g, 10 mmol) carefully dropwise at 0 °C.[37] After 30 min of stirring, product **5a** (2.01 g, 5 mmol) in 10 mL of anhydrous THF was added carefully. The temperature of the reaction mixture was raised to room temperature and stirred for 2 h. The hydrolytic workup was performed by adding 3.2 mL of H_2O/THF (1:1) mixture dropwise at 0 °C. After stirring for 15 min, ether (100 mL) was added followed by 6 mL of 15% aqueous NaOH solution to form a thick precipitate of aluminum hydroxide. The reaction mixture was diluted with 50 mL of ether while stirring continued for 15 min. The white aluminum hydroxide precipitate was separated by suction filtration, and the filtrate was evaporated to give 1.6 g (85%) of a viscous white product. The HCl salt was formed by dissolving the product in 2 mL of 2-propanol and then adding HCl-saturated 2-propanol to pH 2. The solvents were evaporated, and the salt of **6a** was recrystallized from ethanol/2-propanol: mp 271–273 °C; ^{1}H NMR ($CDCl_3$) δ 7.35 (t, 2H, J = 7.2 Hz), 7.3 (t, 1H, J = 7.6 Hz), 7.18 (d, 2H, J = 7.1 Hz), 7.1 (s, 1H), 6.25 (s, 1H), 4.30 (d, 1H, J = 8.6 Hz), 3.6 (s, 3H), 3.2–2.2 (m, 10H), 2.15 (s, 6H), 1.45 (m, 4H); IR 2995, 1596, 1490 cm^{-1}. Anal. ($C_{23}H_{33}N_2OCl_3 \cdot {}^1/_2H_2O$) C, H, N.

(±)-7-Bromo-8-methoxy-3-[4-(*N*,*N*-dimethylamino)butyl]-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (6b). Compound **6b** was prepared (1.1 g, 2.5 mmol, 90%) from **5b** according to the procedure described for the synthesis of **6a**. The HCl salt was formed by dissolving the product in 10 mL of HCl saturated methanol solution. The solvents were evaporated, and the salt was recrystallized from methanol/2-propanol: mp 273–275 °C; ^{1}H NMR ($CDCl_3$) δ 7.35 (t, 2H, J = 7.6 Hz), 7.25 (t, 1H, J = 7.4 Hz), 7.18 (s, 1H), 7.15 (d, 2H, J = 6.9 Hz), 6.25 (s, 1H), 4.30 (d, 1H, J = 8.6 Hz), 3.6 (s, 3H), 3.2–2.2 (m, 10H), 2.2 (s, 6H), 1.40 (m, 4H); IR 2999, 1590, 1490 cm^{-1}. Anal. ($C_{23}H_{33}N_2OCl_2Br$) C, H, N.

(±)-7,8-Dimethoxy-3-[4-(*N*,*N*-dimethylamino)butyl]-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (6c). Compound **6c** was prepared (1.87 g, 4.9 mmol, 80%) from **5c** according to the procedure described for the synthesis of **6a**. The HCl salt was formed by dissolving the product in HCl-saturated methanol solution. The solvents were evaporated, and the salt was recrystallized from 2-propanol/ether: mp 260–262 °C; ^{1}H NMR ($CDCl_3$) δ 7.35 (t, 2H, J = 7.6 Hz), 7.3 (t, 1H, J = 7.3 Hz), 7.2 (d, 2H, J = 6.9 Hz), 6.7 (s, 1H), 6.25 (s, 1H), 4.30 (d, 1H, J = 8.5 Hz), 3.8 (s, 3H), 3.6 (s, 3H), 3.2–2.2 (m, 10H), 2.2 (s, 6H), 1.40 (m, 4H); IR 2990, 1560, 1490 cm^{-1}. Anal. ($C_{24}H_{36}N_2O_2Cl_2 \cdot {}^1/_4H_2O$) C, H, N.

(±)-7-Chloro-8-hydroxy-3-[4-(*N*,*N*-dimethylamino)butyl]-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (7a). O-Demethylation was performed by modifying the procedure of Baindur et al.[36] A 0.43 g (1.1 mmol) portion of **6a** was dissolved in dry $CHCl_3$ (10 mL), and then 3.5 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 methanol (anhydrous) was added dropwise at 0 °C. After the reaction mixture was refluxed in an open-mouthed reaction flask for 20 min, the solvents were evaporated. The product was dissolved in 20 mL of a 95:5 ethyl acetate and methanol mixture, basified with 10% aqueous Na_2CO_3 solution, diluted with 20 mL of ethyl acetate, and separated. The aqueous phase was extracted with ethyl acetate/methanol (9:1) (2 × 20 mL). The combined organic phase was washed with H_2O (20 mL) and brine (20 mL), dried, filtered, and evaporated to give 0.35 g (80%) of a foamy solid. Some impurities were removed by dissolving the product in ether followed by filtration. The HCl salt was formed from HCl/2-propanol saturated solution and recrystallized from 2-propanol/ether: mp 185–186 °C; ^{1}H NMR ($CDCl_3$) δ 7.35 (t, 2H, J = 7.5 Hz), 7.25 (t, 1H, J = 6.7 Hz), 7.1 (d, 2H, J = 6.9 Hz), 7.05 (s, 1H), 6.1 (s, 1H), 4.20 (d, 1H, J = 7.3 Hz),

3.2–2.2 (m, 10H), 2.1 (s, 6H), 1.4 (m, 4H); IR 2995, 2650 (hydrogen-bonded OH group) 1596, 1490 cm^{-1}. Anal. ($C_{22}H_{31}N_2OCl_3{}^3/_4H_2O$) C, H, N.

(±)-7-Bromo-8-hydroxy-3-[4-(*N,N*-dimethylamino)butyl]-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (7b). Compound **7b** was prepared (0.63 g, 1.5 mmol, 70%) from **6b** according to the procedure described for the synthesis of **7a**. The HBr salt was formed by dissolving the product in 10 mL of ether and then bubbling in HBr gas. The solvents were evaporated, and the salt was recrystallized from 2-propanol/ether: mp 180–183 °C; ^1H NMR ($CDCl_3$) δ 7.25 (t, 2H, J = 7.6 Hz), 7.15 (t, 1H, J = 7.0 Hz), 7.1 (s, 1H), 7.0 (d, 2H, J = 6.9 Hz), 6.0 (s, 1H), 4.15 (d, 1H, J = 7.7 Hz), 3.05–2.05 (m, 10H), 2.0 (s, 6H), 1.30 (m, 4H); IR 2999, 2650 (hydrogen-bonded OH group), 1590, 1490 cm^{-1}. Anal. ($C_{22}H_{31}N_2OBr_3$) C, H, N.

(±)-7,8-Dihydroxy-3-[4-(*N,N*-dimethylamino)butyl]-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (7c). Compound **7c** was prepared (1.1 g, 2.8 mmol, 70%) from **6c** according to the procedure described for the synthesis of **7a** except that after the reaction was quenched with methanol, the mixture was heated under reflux for 1 h and the HBr gas was bubbled into the reaction mixture. Finally the solvents were evaporated, and the salt was recrystallized from methanol/ethanol: mp 150–153 °C dec; ^1H NMR ($CDCl_3$) δ 7.3 (t, 2H, J = 7.5 Hz), 7.25 (t, 1H, J = 7.1), 7.05 (d, 2H, J = 7.0), 6.6 (s, 1H), 5.95 (s, 1H), 4.25 (d, 1H, J = 7.8 Hz), 3.2–2.2 (m, 10H), 2.15 (s, 6H), 1.40 (m, 4H); IR (HBr salt) 3440, 3000, 2740 (hydrogen-bonded OH group), 1600, 1490 cm^{-1}. Anal. ($C_{22}H_{32}N_2O_2Br_2{\cdot}EtOH{\cdot}{}^1/_2H_2O$) C, H, N.

***N*-Carbobenzoxy-6-aminohexanoic Acid (8a).** A 6.55 g (50 mmol) portion of 6-aminocaproic acid was dissolved in 100 mL of 3 N NaOH solution, and then 7.1 mL (50 mmol) of benzyl chloroformate was added at 0 °C. The reaction mixture was stirred at room temperature for 2 h and then neutralized by adding 50% aqueous HCl solution until acidic (pH 2). The protected amino acid was extracted from a 1:1 mixture of ether and ethyl acetate. The organic layer was dried, filtered, and evaporated to give a white viscous product (12.1 g, 90%) which solidified on standing overnight: mp 56–58 °C; ^1H NMR ($CDCl_3$) δ 7.3 (m, 5H, aromatic), 5.1 (s, 2H, benzylic), 4.95 (s, 1H, broad, NH), 3.15 (m, 2H), 2.3 (m, 2H), 1.6–1.1 (m, 6H).

***N*-Carbobenzoxy-4-aminobutyric Acid (8b).** Compound **8b** was prepared (0.63 g, 1.5 mmol, 70%) according to the procedure described for the synthesis of **8a**, mp 59–61 °C.

(±)-7-Chloro-8-methoxy-3-[6-(*N*-carbobenzoxyamino)hexanoyl]-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (9a). Into a solution of 2.47 g (12 mmol) of DCC, 1.76 g (13 mmol) of HOBT,[38] and 2.65 g (10 mmol) of *N*-carbobenzoxy-6-aminocaproic acid (**8a**) in 200 mL of dry DMF was added a solution of 2.87 g (10 mmol) of **4a** in 10 mL of DMF. After 3 mL of triethylamine was added, the reaction mixture was stirred for 48 h at room temperature. After completion of the reaction (assessed by TLC), 200 mL of H_2O was added, the reaction mixture was basified by adding a few drops of 15% NaOH solution, and the organic products were extracted from a 1:1 mixture of ethyl ether and ethyl acetate (3 × 100 mL). The combined organic layers were washed with H_2O (2 × 100 mL) and brine (1 × 100 mL), dried, and evaporated to yield 3.6 g (80%) of **9a** as a light brown viscous oil. The product was confirmed by TLC and IR spectra and used in the next reaction with out further purification.

(±)-7-Chloro-8-methoxy-3-[4-(*N*-carbobenzoxyamino)butanoyl]-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (9b). Compound **9b** was prepared (1.56 g, 3.1 mmol, 65%) by a coupling reaction between **8b** and benzazepine **4a**, according to the procedure described for the synthesis of **9a**.

(±)-7-Chloro-8-methoxy-3-(6-aminohexyl)-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (10a). Compound **9a** (1.86 g, 3.5 mmol) was deprotected[39] in 50 mL of dry acetonitrile, with 2.2 mL (15 mmol) of iodotrimethylsilane at room temperature. The color of the reaction mixture changed to red immediately. After stirring for 30 min, reaction mixture was quenched with 20 mL of methanol, the volatiles were evaporated in the rotary evaporator, and the viscous product was dissolved in 50 mL of 10% aqueous HCl. The acidic layer was washed with ethyl ether (3 × 100 mL) and separated. The aqueous layer was neutralized with 15% NaOH solution, and the product was extracted with $CHCl_3$ (2 × 100 mL), dried, filtered, and evaporated to give the deprotected intermediate (1.2 g, 79%). The product was confirmed by TLC and IR spectra and used in the next reaction without further purification. The reduction of the resulting intermediate amide to the desired amine (**10a**) was performed as described for product **6a** using AlH_3 in THF to give 1.1 g (85%) of a white foamy product: ^1H NMR ($CDCl_3$) δ 7.35 (t, 2H, J = 7.4 Hz), 7.3 (t, 2H, J = 7.1 Hz), 7.1 (d, 1H, J = 6.9 Hz), 7.0 (s, 1H), 6.2 (s, 1H), 4.25 (d, 1H, J = 7.7 Hz), 3.5 (s, 3H, OMe), 3.1–2.7 (m, 6H), 2.65 (t, 2H, J = 6.5 Hz), 2.5 (t, 2H, J = 6.6 Hz), 1.6–1.2 (m, 8H); IR 3273 (NH_2), 1480 cm^{-1}.

(±)-7-Chloro-8-methoxy-3-(4-aminobutyl)-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (10b). Compound **10b** was prepared (0.7 g, 2 mmol, 65%) according to the procedure described for the synthesis of **10a**: ^1H NMR ($CDCl_3$) δ 7.3 (t, 2H, J = 7.6 Hz), 7.25 (t, 2H, J = 7.0 Hz), 7.1 (d, 1H, J = 7.0 Hz), 7.0 (s, 1H), 6.25 (s, 1H), 4.2 (d, 1H, J = 7.7 Hz), 3.5 (s, 3H, OMe), 3.1–2.6 (m, 6H), 2.65 (t, 2H, J = 6.5 Hz), 2.5 (t, 2H, J = 6.6 Hz), 1.6–1.1 (m, 4H); IR 3270 (NH_2), 1490 cm^{-1}.

(±)-7-Chloro-8-hydroxy-3-[6-(*N,N*-dimethylamino)hexyl]-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine–Cyanoborane (11). In an attempt to synthesize **15** directly from **10a** by a known procedure,[40] compound **11** was formed instead. Aqueous formaldehyde (37%, 2.4 mL) and $NaBH_3CN$ (0.63 g, 10 mmol) were added at 0 °C to a solution of **10a** (0.77 g, 2 mmol) in 10 mL of dry MeCN. The reaction mixture (pH 12) was allowed to react at 0 °C for 5 min and then allowed to warm to room temperature. After a reaction time of 30 min, glacial HOAc (0.3 mL) was added, and the reaction mixture (pH 6) was allowed to stir at room temperature for another 45 min. The volatiles were removed *in vacuo*, and the residue was basified with 2 N NaOH (1 × 20 mL) and extracted with a 1:1 mixture of ethyl acetate/ether (2 × 20 mL). The combined organic fraction was washed with H_2O, dried and evaporated to give a viscous product. The crude product was purified by flash column chromatography ($CHCl_3$/methanol/NH_4OH, 95:4.5:0.5) to give 0.5 g (55%) of a white viscous product: ^1H NMR ($CDCl_3$) δ 7.4 (t, 2H, J = 7.2 Hz), 7.3 (t, 1H, J = 7.3 Hz), 7.2 (d, 2H, J = 7.2 Hz), 7.15 (s, 1H), 6.25 (s, 1H), 4.35 (d, 1H, J = 8.5 Hz), 3.6 (s, 3H), 3.2–2.7 (m, 6H), 2.65 (s, 6H), 2.5 (m, 4H), 1.8–1.2 (m, 8H); IR 2950, 2415 (BH_2CN), 1480 cm^{-1}. O-Demethylation of this intermediate was performed as for compound **7a** by using BBr_3 to give a white viscous product (11). The HCl salt was formed by dissolving the product in HCl-saturated 2-propanol. The solvents were evaporated, and the salt was recrystallized from CH_2Cl_2/ether: mp 140–143 °C; ^1H NMR ($CDCl_3$) δ 7.35 (t, 2H, J = 6.9 Hz), 7.3 (t, 1H, J = 7.2 Hz), 7.1 (d, 2H, J = 7.3 Hz), 7.05 (s, 1H), 6.25 (s, 1H), 4.25 (d, 1H, J = 8.6 Hz), 3.2–2.7 (m, 6H), 2.65 (s, 6H), 2.5 (m, 4H), 1.8–1.2 (m, 8H); IR 3300 (OH), 2950, 2440 (BH_2CN), 1480 cm^{-1}. Anal. ($C_{25}H_{37}N_3OBCl_2$) C, H, N.

(±)-7-Chloro-8-hydroxy-3-(6-aminohexyl)-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (12a). The O-demethylation of **10a** (0.8 g, 2 mmol) by BBr_3 was performed under the same conditions as for product **7a** to give a white foamy product **12a** (0.55 g, 70% yield). The HBr salt was formed by bubbling HBr gas in to a 2-propanol solution of the product. On evaporation of the solvent, a white solid was obtained which was recrystallized from 2-propanol/ether to give pure **12a**: mp 170 °C dec; ^1H NMR ($CDCl_3$) δ 7.4 (t, 2H, J = 7.0 Hz), 7.3 (t, 2H, J = 7.0 Hz), 7.15 (d, 1H, J = 7.2 Hz), 7.05 (s, 1H), 6.25 (s, 1H), 4.25 (d, 1H, J = 8.4 Hz), 3.1–2.7 (m, 6H), 2.65 (t, 2H, J = 6.7 Hz), 2.5 (t, 2H, J = 6.8 Hz), 1.6–1.2 (m, 8H); IR 3473 (OH), 3260 (NH_2), 1480 cm^{-1}. Anal. ($C_{22}H_{31}N_2OClBr_2{\cdot}H_2O$) C, H, N.

(±)-7-Chloro-8-hydroxy-3-(4-aminobutyl)-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (12b). Compound **12b** (0.7 g, 2 mmol, 65%) was prepared according to the procedure described for the synthesis of **10a**: mp 111–113 °C; ^1H NMR ($CDCl_3$) δ 7.4 (t, 2H, J = 6.9 Hz), 7.3 (t, 2H, J = 7.0 Hz), 7.15 (d, 1H, J = 7.2 Hz), 7.05 (s, 1H), 6.25 (s, 1H), 4.2 (d, 1H, J = 8.6 Hz), 3.1–2.7 (m, 6H), 2.6 (t, 2H, J = 6.6 Hz), 2.5 (t, 2H, J

= 6.7 Hz), 1.4–1.2 (m, 4H); IR 3470 (OH), 3265 (NH_2), 1480 cm^{-1}. Anal. ($C_{20}H_{27}N_2OClBr_2 \cdot 2H_2O$) C, H, N.

(±)-7-Chloro-8-hydroxy-3-(6-formamidohexyl)-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (13a). A 1.93 g (5 mmol) portion of product **10a** was dissolved in 20 mL of ethyl formate (dry) and then 60 μL of formic acid was added. After the reaction mixture was stirred for 18 h at room temperature, TLC showed the formation of new product with a R_f value higher than that of the starting amine. After the completion of the reaction the ethyl formate was evaporated to dryness to give a foamy solid. The O-demethylation of the resulting solid with BBr_3 as for **7a** resulted in the formation of **13a** in 70% yield (1.6 g). The HBr salt was formed by bubbling the HBr gas into an 2-propanol solution of the product. On evaporating the solvent, a white product was obtained which was recrystallized from 2-PrOH/ether to give pure product **13a**: mp 87–90 °C; ^1H NMR ($CDCl_3$) δ 8.1 (s, 1H, amide), 7.3 (t, 2H, J = 7.2 Hz), 7.25 (t, 2H, J = 7.2 Hz), 7.1 (d, 1H, J = 7.3 Hz), 7.05 (s, 1H), 6.25 (s, 1H), 4.8 (s, 1H, NH), 4.2 (d, 1H, J = 8.6 Hz), 3.25 (t, 2H, J = 6.8 Hz), 3.1–2.2 (m, 8 H), 1.6–1.2 (m, 8H); IR 3460 (OH), 1679 (NHC=O), 1500 cm^{-1}. Anal. ($C_{23}H_{30}N_2O_2ClBr \cdot 2H_2O$) C, H, N.

(±)-7-Chloro-8-hydroxy-3-(4-formamidobutyl)-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (13b). Compound **13b** (1.8 g, 5 mmol, 70%) was prepared according to the procedure described for the synthesis of **13a**, starting with **10b**.

(±)-7-Chloro-8-hydroxy-3-[6-(*N*-methylamino)hexyl]-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (14a). The reduction of the amide **13a** to the secondary amine was performed under the same conditions as for **6a** using AlH_3 to give **14a** (0.9 g, 75%). The HCl salt was formed from a saturated solution of HCl/2-propanol and recrystallized from 2-propanol/ether: mp 101–103 °C; ^1H NMR (CD_3OD) δ 7.65 (t, 2H, J = 7.0 Hz), 7.55 (t, 1H, J = 7.2 Hz), 7.5 (d, 2H, J = 7.3 Hz), 7.25 (s, 1H), 6.45 (s, 1H), 4.55 (d, 1H, J = 8.6 Hz), 3.7–2.75 (m, 10H), 2.7 (s, 3H), 1.9–1.7 (m, 8H); IR 3473 (OH), 3180 (NH), 1480 cm^{-1}. Anal. ($C_{23}H_{33}N_2OCl_3 \cdot 1.25H_2O$) C, H, N.

(±)-7-Chloro-8-hydroxy-3-[4-(*N*-methylamino)butyl]-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (14b). The reduction of the amide **13b** to the secondary amine was performed under the same conditions as described for **6a** using AlH_3 to give **14b** (0.7 g, 70%). The HCl salt was formed from a saturated solution of HCl/2-propanol and recrystallized from 2-propanol/ether: mp 181–184 °C; ^1H NMR ($CDCl_3$) δ 7.35 (t, 2H, J = 6.9 Hz), 7.25 (t, 2H, J = 7.2 Hz), 7.1 (d, 1H, J = 7.2 Hz), 7.05 (s, 1H), 6.15 (s, 1H), 4.2 (d, 1H, J = 8.5 Hz), 3.1–2.65 (m, 6H), 2.5 (m, 4H), 2.3 (s, 3H), 1.6–1.3 (m, 4H); IR 3473 (OH), 3210 (NH), 1480 cm^{-1}. Anal. ($C_{21}H_{29}N_2OClBr_2 \cdot {}^1/_2H_2O$) C, H, N.

(±)-7-Chloro-8-hydroxy-3-[6-(*N*,*N*-dimethylamino)hexyl]-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (15). A 1.93 g (5 mmol) portion of product **10a** was dissolved in 20 mL of ethyl formate (dry), and 60 μL of formic acid was added. After the reaction mixture was stirred for 18 h at room temperature, the TLC analysis showed the formation of a new product with a R_f value higher than that of the starting amine. After completion of the reaction the ethyl formate was evaporated to dryness to give a foamy solid. The crude product was purified by flash column chromatography, eluting with $CHCl_3$/methanol/NH_4OH (95:4.5:0.5) to give 1.8 g (80%) of a white viscous product: IR 3000, 1679 (amide), 1490 cm^{-1}. This intermediate amide was reduced to the secondary amine by AlH_3 under the same conditions as described for **6a** to give a white viscous product. N-Formylation of this product was conducted as above to give a foamy white solid which was reduced to the tertiary amine under the same conditions as for **6a** using AlH_3 to give the tertiary amine intermediate: ^1H NMR ($CDCl_3$) δ 7.35 (t, 2H, J = 7.1 Hz), 7.3 (t, 1H, J = 7.1 Hz), 7.2 (d, 2H, J = 7.2 Hz), 7.15 (s, 1H), 6.25 (s, 1H), 4.3 (d, 1H, J = 8.6 Hz), 3.6 (s, 3H), 3.2–2.25 (m, 6H), 2.2 (s, 6H), 1.5–1.25 (m, 12H); IR 2950, 1480 cm^{-1}. Finally, the O-demethylation of the above product was performed as for compound **7a** using BBr_3 to give the desired phenol, **15**. The HCl salt was formed from HCl/2-propanol-saturated solution and recrystallized from 2-propanol/ether: mp 245–247 °C; ^1H NMR ($CDCl_3$) δ 7.35 (t, 2H, J = 7.0 Hz), 7.25 (t, 1H, J = 7.0 Hz), 7.1 (d, 2H, J = 7.2 Hz), 7.05 (s, 1H), 6.05 (s, 1H), 4.2 (d, 1H, J = 8.5 Hz), 3.15–2.1 (m, 6H), 2.05 (s, 6H), 1.5–1.2 (m, 12H); IR 2995, 2650 (hydrogen-bonded OH group), 1600, 1495 cm^{-1}. Anal. ($C_{24}H_{35}N_2OCl_3 \cdot {}^1/_4H_2O$) C, H, N.

(±)-7-Chloro-8-hydroxy-3-butyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (16). Into a solution of **4a** (0.58 g, 2 mmol) in 20 mL of DMF was added 1 mL of H_2O.[41] To this stirring solution was added anhydrous K_2CO_3 (0.3 g, 2.2 mmol) followed by dropwise addition of bromobutane (0.22 mL, 2 mmol) in 5 mL of CH_2Cl_2. After stirring for 18 h the reaction mixture was quenched with 40 mL of H_2O, and the solution was then extracted with 50 mL of CH_2Cl_2. The CH_2Cl_2 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 $CHCl_3$/methanol/NH_4OH (95:4.5:0.5) to give (0.7 g, 70%) of a white viscous product as 7-chloro-8-methoxy-3-butyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine: ^1H NMR ($CDCl_3$) δ 7.35 (t, 2H, J = 7.2 Hz), 7.25 (t, 1H, J = 7.2 Hz), 7.15 (d, 2H, J = 7.3 Hz), 7.1 (s, 1H), 6.25 (s, 1H), 4.3 (d, 1H, J = 8.4 Hz), 3.55 (s, 3H), 3.2–2.7 (m, 4H), 2.5 (m, 4H), 2.4 (m, 2H), 1.5 (p, 2H) 1.35 (p, 2H), 0.9 (t, 3H, J = 6.6 Hz); IR 2955 cm^{-1}. Finally, O-demethylation of the above product was performed as for compound **7a** using BBr_3 to give the desired phenol, **16**. The HBr salt was formed by bubbling the HBr gas into an ether solution of the product. On evaporation of the solvent, a white product was obtained which was recrystallized from 2-PrOH/ether to give pure product (0.5 g, 70%): mp 142–144 °C; ^1H NMR ($CDCl_3$) δ 7.35 (t, 2H, J = 7.1 Hz), 7.3 (t, 1H, J = 7.2 Hz), 7.15 (d, 2H, J = 7.2 Hz), 7.1 (s, 1H), 6.25 (s, 1H), 4.2 (d, 1H, J = 8.6 Hz), 3.1–2.7 (m, 4H), 2.5 (m, 4H), 2.4 (m, 2H), 1.5 (p, 2H), 1.3 (p, 2H), 0.95 (t, 3H, J = 6.6 Hz); IR 2995, 2690 (hydrogen-bonded OH group), 1600, 1495 cm^{-1}. Anal. ($C_{20}H_{25}NOClBr \cdot {}^1/_2H_2O$) C, H, N.

(±)-7-Chloro-8-hydroxy-3-[4-aminobutanoyl]-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (17). Compound **9b** (2.02 g, 4 mmol) was deprotected[39] in 30 mL of dry acetonitrile, with 1.85 mL (13 mmol) of iodotrimethylsilane at room temperature following the same procedure as described for compound **10a**. Deprotection was directly followed by O-demethylation with BBr_3 as described for product **7a** in CH_2Cl_2 to give the desired product **17** (0.9 g, 80%). The ^1H NMR spectra was complex due to rotomers: mp 110–112 °C dec; IR 3380 (OH), 3270 (NH_2), 1670 (NHC=O),1490 (C–O) cm^{-1}. Anal. ($C_{20}H_{24}N_2O_2ClBr \cdot {}^1/_2H_2O$) C, H, N.

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. Male Sprague–Dawley rats (200–250 g, Taconic, Germantown, NY) were decapitated, their brains were removed, and caudate putamen were dissected on ice. The tissue was suspended in 100 volumes of ice-cold buffer (50 mM Tris, pH 7.4) and homogenized for 10 s with a polytron (setting 7). The homogenates were centrifuged at 35000g for 10 min at 4 °C. The supernatants were discarded, and the tissue was resuspended in buffer and centrifuged again. This was repeated, and the final pellet was resuspended in 3.75 mg/mL of binding buffer (50 mM Tris, 120 mM NaCl, 5 mM $CaCl_2$, 1 mM $MgCl_2$, pH 7.4). (This equals approximately 3 mg of tissue per assay tube, as determined by Lowry assay.)

Fresh tissue homogenate was used in all experiments. Triplicate samples of membranes were incubated in binding buffer for 30 min at 37 °C in a final volume of 1 mL. [^{3}H]SCH 23390 (final concentration 0.3 nM) or [^{3}H]sulpiride (final concentration 3 nM) was used to determine binding to dopamine D_1 or D_2 receptors, respectively. Nonspecific binding was determined as binding in the presence of 1 μM unlabeled SCH 23390 or 10 μM unlabeled sulpiride, as appropriate. The incubation was terminated by rapid filtration through What-

man GF/B glass fiber filter paper using a Brandel Cell Harvester (Gaithersburg, MD). The filters were washed with three additional 4 mL washes of buffer and transferred to scintillation vials. Absolute ethanol (0.5 mL) and Beckman Ready Value Scintillation Cocktail (2.75 mL) were added to the vials which were counted the next day at an efficiency of approximately 40%. K_D values (for the labeled ligands) and K_i values were determined using LIGAND.[48]

Adenylyl Cyclase Assays. Male Sprague–Dawley rats (200–250 g, Taconic, Germantown, NY) were decapitated, their brains were removed, and caudate putamen were dissected on ice. A crude membrane preparation was made by homogenizing the tissue in a Teflon/glass homogenizer. Dissected tissue from caudate putamen of one rat was homogenized and diluted into 25 mL of homogenization buffer (10 mM imidazole HCl (pH 7.4) and 2 mM EGTA) and centrifuged at 27000*g* for 15 min at 4 °C. The pellet was resuspended in 25 mL of fresh buffer and centrifuged again for 15 min. The supernatant was discarded, and the tissue was homogenized in 30 volumes (w/v) of ice-cold homogenization buffer containing 10% glycerol and stored at −70 °C until determination of adenylyl cyclase activity.

Tissue homogenate was thawed (20–50 μg of protein in 10 μL) and added on ice to assay tubes (final volume 0.06 mL) containing final concentrations of 10 mM imidazole hydrochloride (pH 7.4), 10 mM theophylline, 6 mM $MgSO_4$, 0.6 mM EGTA, 1.5 mM ATP, 0.01 mM GTP, and either the drug being tested or H_2O. Triplicate samples for each treatment were incubated at 30 °C for 5 min. Adenylyl cyclase activity was terminated by placing the tubes into boiling H_2O for 2 min. The amount of cAMP formed was determined by a [^{3}H]cAMP protein binding assay, as described previously.[49,50] [^{3}H]cAMP (final concentration 4 nM) was added to each test tube followed by a binding protein prepared from bovine adrenal glands. The samples were incubated on ice for 90 min, and the assay was terminated by the addition of charcoal and centrifugation to separate the free tritiated cAMP from that which was bound to the binding protein. Aliquots of the supernatant containing bound cAMP were placed into scintillation vials to which Beckman Ready Value Scintillation Cocktail was added, and radioactivity was determined by liquid scintillation spectrometry.

The amount of cAMP formed as a function of concentration of agonist was analyzed using ANOVA and linear regression techniques.[51] From this analysis, IC_{50} values and their 95% confidence limits were derived from data using the linear portion of the concentration–effect curves. Predicted K_i values were determined using the equation $K_i = IC_{50}/[1 + [^3H\text{-DA}]/DA\ K_D]$. All assays used 100 μM dopamine (DA), and the K_D for dopamine to stimulate adenylyl cyclase activity was 1023 nM.[52]

Acknowledgment. We thank Brett Heller for his technical assistance and Dr. Jonathan Katz for his editorial comments. Animals used in these studies were maintained in facilities fully accredited by the American Association for the Accreditation of Laboratory Animal Care (AAALAC), and all experimentation was conducted in accordance with the guidelines of the Institutional Care and Use Committee of the Intramural Research Program of the National Institute on Drug Abuse, NIH, and the Guide for Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council, Department of Health, Education and Welfare, Publication (NIH) 85-23, revised 1985.

References

(1) Robbins, T. W. Introduction: Milestones in dopamine research. *Semin. Neurosci.* **1992**, *4*, 93–97.
(2) Civelli, O.; Bunzow, J. R.; Grandy, D. K. Molecular diversity of the dopamine receptors. *Annu. Rev. Pharmacol. Toxicol.* **1993**, *32*, 281–307.
(3) Koob, G. F. Dopamine, addiction and reward. *Semin. Neurosci.* **1992**, *4*, 139–148.
(4) Kuhar, M. J.; Ritz, M. C.; Boja, J. W. The dopamine hypothesis of the reinforcing effects of cocaine. *Trends Neurosci.* **1991**, *14*, 299–302.
(5) Witkin, J. M. Pharmacotherapy of cocaine abuse: preclinical development. *Neurosci. Biobehav. Rev.* **1994**, *18*, 121–142.
(6) Kebabian, J. W.; Calne, D. B. Multiple receptors for dopamine. *Nature (London)* **1979**, *277*, 93–96.
(7) Schwartz, J.-C.; Giros, B.; Martres, M.-P.; Sokoloff, P. The dopamine receptor family: molecular biology and pharmacology. *Semin. Neurosci.* **1992**, *4*, 99–108.
(8) Strange, P. G. New insights into the dopamine receptors in the central nervous system. *Neurochem. Int.* **1993**, *22*, 223–236.
(9) Jarvie, K. R.; Caron, M. G. Heterogeneity of dopamine receptors. In *Advances in Neurology, Vol. 60*; Narabayashi, H., Nagatsu, T., Yanagisawa, N., Mizuno, Y., Eds.; Raven Press, Ltd.: New York, 1993; pp 325–331.
(10) Gingrich, J. A.; Caron, M. G. Recent advances in the molecular biology of dopamine receptors. *Annu. Rev. Neurosci.* **1993**, *16*, 299–321.
(11) Iorio, L. C.; Hoser, V.; Korduba, C. A.; Leitz, F.; Barnett, A. SCH 23390, a benzazepine with atypical effects on dopaminergic systems. *Pharmacologists* **1981**, *23*, 137.
(12) Iorio, L. C.; Barnett, A.; Leitz, F. H.; Houser, V. P.; Korduba, C. A. SCH 23390, a potent benzazepine antipsychotic with unique interactions on the dopaminergic systems. *J. Pharmacol. Exp. Ther.* **1983**, *226*, 462–468.
(13) Iorio, L. C.; Barnett, A.; Billard, W.; Gold, E. H. Benzazepines: structure-activity relationships between D_1 receptor blockade and selected pharmacological effects. In *Neurobiology of Central D_1 Dopamine Receptors*; Breese, G. R., Creese, I., Eds.; Plenum Press: New York, 1986; pp 1–14.
(14) Waddington, J. L.; O'Boyle, K. Drugs acting on brain dopamine receptors: A conceptual re-evaluation five years after the first selective D-1 antagonist. *Pharmac. Ther.* **1989**, *43*, 1–52.
(15) Reader, T. A.; Briere, R.; Gottberg, E.; Diop, L.; Grondin, L. Specific [^{3}H]SCH 23390 binding to dopamine D_1 receptors in cerebral cortex and neostriatum: evidence for heterogeneities in affinity states and cortical distribution. *J. Neurochem.* **1988**, *50*, 451–463.
(16) Reader, T. A.; Grondin, L.; Montreuil B.; Dewar, K. M. Dopamine D_1 receptors labeled with [^{3}H]SCH 23390 in rabbit cerebral cortex and neostriatum: equilibrium binding, kinetics and selectivity. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1989**, *340*, 617–625.
(17) Reader, T. A.; Molina-Holgado, E.; Dewar, K. M. Comparative biochemical pharmacology of central nervous system dopamine D_1 and D_2 receptors. *Mol. Neurobiol.* **1993**, *6*, 425–450.
(18) Weinstock, J.; Hieble, J. P.; Wilson, J. W. The chemistry and pharmacology of 3-benzazepine derivatives. *Drugs Future* **1985**, *10*, 646–697.
(19) Pettersson, I.; Liljefors, T.; Bogeso, K. Conformational analysis and structure-activity relationships of selective dopamine D_1 receptor agonists and antagonists of the benzazepine series. *J. Med. Chem.* **1990**, *33*, 2197–2204.
(20) Pettersson, I.; Gundertofte, K.; Palm, J.; Liljefors, T. A study on the contribution of the 1-phenyl substituent to the molecular electrostatic potentials of some benzazepines in relation to selective dopamine D-1 receptor activity. *J. Med. Chem.* **1992**, *35*, 502–507.
(21) Charifson, P. S.; Wyrick, S. D.; Hoffman, A. J.; Simmons, R. M. A.; Bowen, J. P.; McDougald, D. L.; Mailman, R. Synthesis and pharmacological characterization of 1-phenyl-, 4-phenyl-, and 1-benzyl-1,2,3,4-tetrahydroisoquinolines as dopamine receptor ligands. *J. Med. Chem.* **1988**, *31*, 1941–1946.
(22) Minor, D. L.; Wyrick, S. D.; Charifson, P. S.; Watts, V. J.; Nichols, D. E.; Mailman, R. B. Synthesis and molecular modeling of 1-phenyl-1,2,3,4-tetrahydroisoquinolines and related 5,6,8,9-tetrahydro-13bH-dibenzo[a,h]quinolizines as D1 dopamine antagonists. *J. Med. Chem.* **1994**, *37*, 4317–4328.
(23) Bischoff, S.; Heinrich, M.; Sonntag, J. M.; Krauss, J. The D-1 dopamine receptor antagonist SCH 23390 also interacts potently with brain serotonin (5-HT_2) receptors. *Eur. J. Pharmacol.* **1986**, *129*, 367–370.
(24) Taylor, L. A.; Tedford, C. E.; McQuade, R. D. The binding of SCH 39166 and SCH 23390 to 5-HT_{1c} receptors in porcine choriod plexus. *Life Sci.* **1991**, *49*, 1505–1511.
(25) McQuade, R. D.; Ford, D.; Duffy, R. A.; Chipkin, R. E.; Iorio, L. C.; Barnett, A. Serotonergic component of SCH 23390: In vitro and in vivo binding analysis. *Life Sci.* **1988**, *43*, 1861–1869.
(26) Chipkin, R. E.; Iorio, L. C.; Coffin, V. L.; McQuade, R. D.; Berger, J. G.; Barnett, A. Pharmacological profile of SCH 39166: A dopamine D_1 selective benzonaphthazepine with potential antipsychotic activity. *J. Pharmacol. Exp. Ther.* **1988**, *247*, 1093–1102.
(27) Berger, J. G.; Chang, K. W.; Clader, J. W.; Hou, D.; Chipkin, R. E.; McPhail, A. T. Synthesis and receptor affinities of some conformationally restricted analogues of the dopamine D_1 selective ligands (R)-8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1H-3-benzazepine-7-ol. *J. Med. Chem.* **1989**, *32*, 1913–1921.

(28) Amenta, F. *Peripheral dopamine pathophysiology*; CRC Press, Inc.: Boca Raton, FL, 1990.
(29) Goldberg, L. I. Cardiovascular and renal actions of dopamine: Potential clinical applications. *Pharmacol. Rev.* **1972**, *24*, 1–29.
(30) Hieble, J. P., Ed. *Cardiovascular function of peripheral dopamine receptors*; Marcel Dekker, Inc.: New York, 1989.
(31) Derlet, R. W.; Albertson, T. E.; Rice, P. The effect of SCH 23390 against toxic doses of cocaine, d-amphetamine and methamphetamine. *Life Sci.* **1990**, *47*, 821–827.
(32) Witkin, J. M.; Goldberg, S. R.; Katz, J. L. Lethal effects of cocaine are reduced by the dopamine D_1 receptor antagonist SCH 23390 but not by haloperidol. *Life Sci.* **1989**, *44*, 1285–1291.
(33) Witkin, J. M.; Newman, A. H.; Nowak, G.; Katz, J. L. Role of dopamine D_1 receptors in the lethal effects of cocaine and a quaternary methiodide analog. *J. Pharmacol. Exp. Ther.* **1993**, *267*, 266–274.
(34) Shah, J. H.; Witkin, J. M.; Tella, S. R.; Nowak, G.; George C.; Newman, A. H. Quaternary benzazepine analogs lack affinity for dopamine-D_1 receptors. *Med. Chem. Res.* **1994**, *3*, 574–588.
(35) Weissman, B. A.; Elson, H. F.; Newman, A. H. Presence of peripheral benzodiazepine binding sites on primary rat skeletal fibroblast membranes. *Eur. J. Pharmacol.* **1990**, *187*, 369–375.
(36) Baindur, N.; Tran, M.; Niznik, H. B.; Guan, H. C.; Seeman, P.; Neumeyer, J. L. 3-Allyl-7-halo-8-hydroxy-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepines as selective high affinity D_1 dopamine receptor antagonists: Synthesis and structure-activity relationships. *J. Med. Chem.* **1992**, *35*, 67–72.
(37) Yoon, N. M.; Brown, H. C. Selective reductions. XII. Exploration in some representative applications of aluminum hydride for selective reductions. *J. Am. Chem. Soc.* **1968**, *90*, 2927–2938.
(38) Allen, M. C.; Fuhrer, W.; Tuck, B.; Wade, R.; Wood, J. M. Renine inhibitors. Synthesis of transition-state analogue inhibitors containing phosphorus acid derivatives at the scissile bond. *J. Med. Chem.* **1989**, *32*, 1652–61.
(39) Lott, R. S.; Chauhan, V. S.; Stammer, C. H. Trimethylsilyl iodide as a peptide deblocking agent. *J. Chem. Soc., Chem. Commun.* **1979**, 495–496.
(40) Borch, F. R.; Hassid, I. A. A new method for the methylation of amines. *J. Org. Chem.* **1972**, *37*, 1673–1674.
(41) Neumeyer, J. L.; Kula, N. S.; Baldessarini, R. J.; Baindur, N. Stereoisomeric probes for the D_1 dopamine receptor: Synthesis and characterization of R-(+) and S-(-) enantiomers of 3-allyl-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine and its 6-bromo analogue. *J. Med. Chem.* **1992**, *35*, 1466–1471.
(42) Neumeyer, J. L.; Baindur, N.; Niznik, H. B.; Guan, H. C.; Seeman, P. (±)-3-Allyl-6-bromo-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine, a new high affinity D_1 Dopamine Receptor Ligand: Synthesis and structure-activity relationship. *J. Med. Chem.* **1991**, *34*, 3366–3371.
(43) These values were obtained through the NIMH contract with Novascreen, a division of Oceanix Biosciences Corporation, Hanover, MD. For the 5-HT_{1c} binding assay, [^{3}H]mesulergide (50.7 Ci/mmol) was used as the radiolabeled ligand and binding was performed in pig choroid plexus according to the procedure described in Pazos et al. (*Eur. J. Pharmacol.* **1985**, *106*, 539–546). For the 5-HT_2 binding assay, [^{3}H]ketanserin (60–90 Ci/mmol) was used as the radiolabeled ligand and binding was performed in rat cortical membranes according to the method described in Leyson et al. (*Mol. Pharmacol.* **1982**, *21*, 301–314).
(44) Mailman, R. B.; Schulz, D. W.; Kilts, C. D.; Lewis, M. H.; Rolleme, H.; Wyrick, S. The multiplicity of the D-1 dopamine receptor. In *Neurobiology of Central D_1 Dopamine Receptors*; Breese, G. R., Creese, I., Eds.; Plenum Press: New York, 1986; pp 53–72.
(45) Andersen, P. H.; Gingrich, J. A.; Bates, M. D.; Dearry, A.; Faldardeau, P.; Senogles, S. E.; Caron, M. G. Dopamine receptor subtypes: Beyond the D_1/D_2 classification. *Trends Pharmacol. Sci.* **1990**, *11*, 231–236.
(46) Andersen, P. H.; Braestrup, C. Evidence for different states of the dopamine D1 receptor: Clozapine and fluperlapine may preferentially label an adenylate cyclase-coupled state of the D1 receptor. *J. Neurochem.* **1986**, *47*, 1822–1831.
(47) *Chem. Abstr.* **1931**, *25*, 4552[9].
(48) Munson, P. J.; Rodbard, D. Ligand: a versatile approach for characterization of ligand-binding systems. *Anal. Biochem.* **1980**, *107*, 220–239.
(49) Izenwasser, S.; Buzas, B.; Cox, B. M. Differential regulation of adenylyl cyclase activity by mu- and delta- opioids in rat caudate-putamen and nucleus accumbens. *J. Pharmacol. Exp. Ther.* **1993**, *267*, 145–152.
(50) Cote, T. E.; Izenwasser, S.; Weems, H. B. Naltrexone-induced upregulation of μ-opioid receptors on 7315c cell and brain membranes: enhancement of opioid efficacy in inhibiting adenylyl cyclase. *J. Pharmacol. Exp. Ther.* **1993**, *267*, 238–244.
(51) Snedecor, G. W.; Cochran, W. G. In *Statistical Methods*, 6th ed.; Iowa State University Press: Ames, IA, 1967; pp 135–171.
(52) Izenwasser, S.; Katz, J. L. Differential efficacies of dopamine D_1 receptor agonists for stimulating adenylyl cyclase in squirrel monkey and rat. *Eur. J. Pharmacol.–Mol. Pharmacol. Sec.* **1993**, *246*, 39–44.

JM9501691