Evaluation of *cis*- and *trans*-9- and 11-Hydroxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridines as Structurally Rigid, Selective D_1 Dopamine Receptor Ligands

William K. Brewster,[†,‡] David E. Nichols,[*,†] Val J. Watts,[§] Robert M. Riggs,[†,∥] Dave Mottola,[§] and Richard B. Mailman[§]

Department of Medicinal Chemistry and Pharmacognosy, School of Pharmacal Sciences, Purdue University, West Lafayette, Indiana 47907, and Brain and Development Research Center, Departments of Psychiatry, Pharmacology, and Medicinal Chemistry, University of North Carolina, Chapel Hill, North Carolina 27599

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The present study reports the investigation of the D_1 structure–relationships of certain *cis*- or *trans*-9- or 11-monohydroxy analogues of (±)-*trans*-10,11-dihydroxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine (**8a**, dihydrexidine), previously identified as the first full efficacy D_1 dopamine receptor agonist. The monohydroxybenzo[*a*]phenanthridines were prepared from the appropriately substituted β-tetralones using the methods described earlier for the synthesis of their catechol analogues. The 10-bromo 11-hydroxy derivative **9e** was prepared by treatment of precursor **9c** with bromine in chloroform. The affinities of these compounds for the D_1 and D_2 dopamine receptor classes and for their effects on adenylate cyclase activity were assessed in rat striatal membranes. In addition to producing only minimal increases in adenylate cyclase activity (≤15%), these phenolic derivatives generally had significantly lower affinities for D_1 and D_2 receptors (D_1 IC_{50} ≥ 102 nM, D_2 IC_{50} ≥ 210 nM) than did their catechol analogues. Further, compounds bearing a *cis* B/C-ring fusion displayed lower affinities than those bearing a *trans* configuration, paralleling the activity differences between the catechol analogues. The data for these rigid dopamine receptor ligands from the benzo[*a*]phenanthridine class lend additional support for the hypothesis that D_1 agonist activity is optimized by a *trans* ring configuration that maintains the β-phenyldopamine substructure in the "*trans*-β-rotamer."

Introduction

In 1978, 7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (**1**, SK&F 38393) was reported as the first dopamine agonist capable of discriminating the D_1 from the D_2 receptor.[1,2] Since that time, it has been recognized as the prototypical D_1 agonist. Certain variations of the 1-phenyltetrahydrobenzazepine structure also yield very potent and selective D_1 *antagonists*. *N*-Methylation coupled with replacement of the 7-OH of **1** with chlorine yielded SCH 23390 (**2**; Chart 1), the first selective D_1 antagonist.[3,4] This compound binds to the D_1 receptor with a K_i of less than 1 nM, has nearly 1000-fold lower affinity for the D_2 receptor,[4–6] and inhibits adenylate cyclase with an IC_{50} of 10 nM.[3] It now serves as the "standard" D_1 antagonist against which other D_1 selective compounds are compared. The pharmacological profile of **2** has led some to the hypothesis that D_1 antagonists may serve as atypical antipsychotic drugs.[7,8]

The addition of an ethano bridge to **2** [connecting C(2) to C(2′)] resulted in the drug SCH 39166 (**3**), a benzonaphthazepine with slightly reduced D_1 affinity and significantly less $5HT_2$ affinity; *trans*-(−)-(6a*S*,13b*R*)-**3**, the active enantiomer, is depicted in Chart 1.[9] It may be hypothesized that the affinity of this more rigid analogue provides information about the optimal conformation of the two aromatic rings of **2** for D_1 antagonist activity. In addition, **3** "exhibits a profile of activity in several species that is indicative of potential antipsychotic activity in man, with a diminished propensity to cause undesirable neurological side effects".[9,10]

Other important structural classes that display D_1 receptor selectivity include the substituted tetrahydroisoquinolines (*e.g.*, **4a–d**, **5**)[11–15] and the structurally rigid benzergolines, represented by CY 208–243 (**6**).[16,17] A recent addition to the arsenal of selective D_1 dopamine agonists is the family of 3-substituted 1-(aminomethyl)-dihydro-1*H*-benzopyrans (*e.g.*, **7**), reported by workers at Abbott.[18–20] The importance of the phenyl substituent in **7** is made apparent by the weak activity of the 3-desphenyl analogue, another partial agonist, that was approximately 300-fold less potent.[19] In an extensive SAR study, it was shown that these (aminomethyl)-isochromans can display a high degree of D_1 selectivity and intrinsic activity, depending on the nature of the substituent at C(3).[20] It is interesting that the pharmacological assays of this series revealed that many of the compounds had lower D_1 binding affinities than would be expected, on the basis of their ability to stimulate adenylate cyclase, for reasons that remain unexplained.

Our recent efforts have been aimed at the synthesis of new selective D_1 ligands (agonists and antagonists). Many of the important structural motifs were recently incorporated into the *trans*-fused hexahydrobenzo[*a*]-phenanthridines (**8a–c**; Chart 2), of which the parent compound dihydrexidine (**8a**) is particularly noteworthy for its high intrinsic activity and affinity for the D_1

* Address all correspondence to: Dr. David E. Nichols, Department of Medicinal Chemistry and Pharmacognosy, Robert Heine Pharmacy Building, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, IN 47907. Telephone: (317) 494-1461. FAX: (317) 494-6790. Internet: drdave@sage.cc.purdue.edu.
† Purdue University.
‡ Present address: DowElanco Discovery Research, P.O. Box 68955, Indianapolis, IN 46268-1053.
§ University of North Carolina.
∥ Present address: School of Pharmacy, Samford University, Birmingham, AL 35229.
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Chart 1. Representative Selective D_1 Receptor Ligands

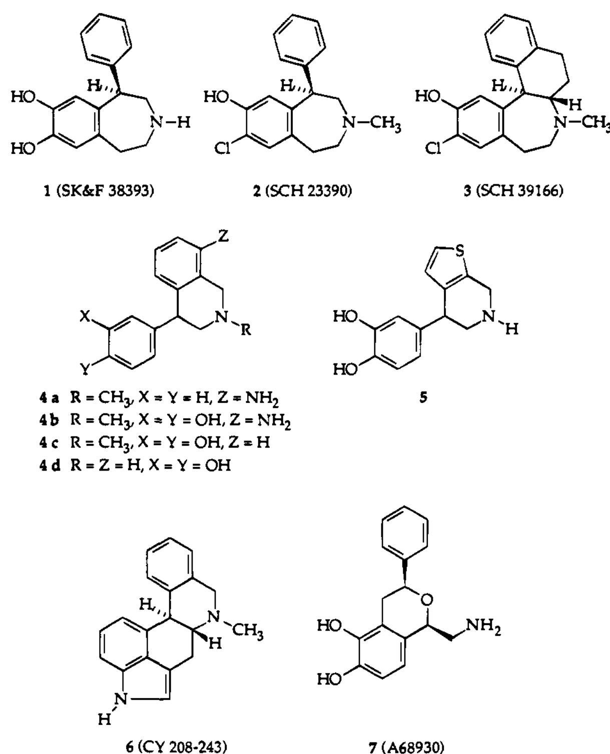
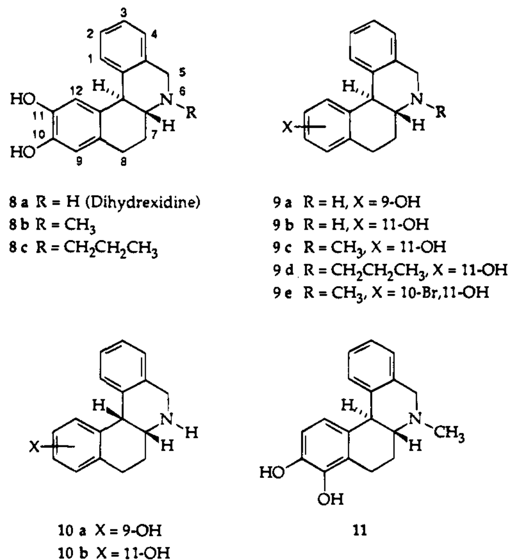


Chart 2. Hexahydrobenzo[*a*]phenanthridines under Study for Dopaminergic Effects

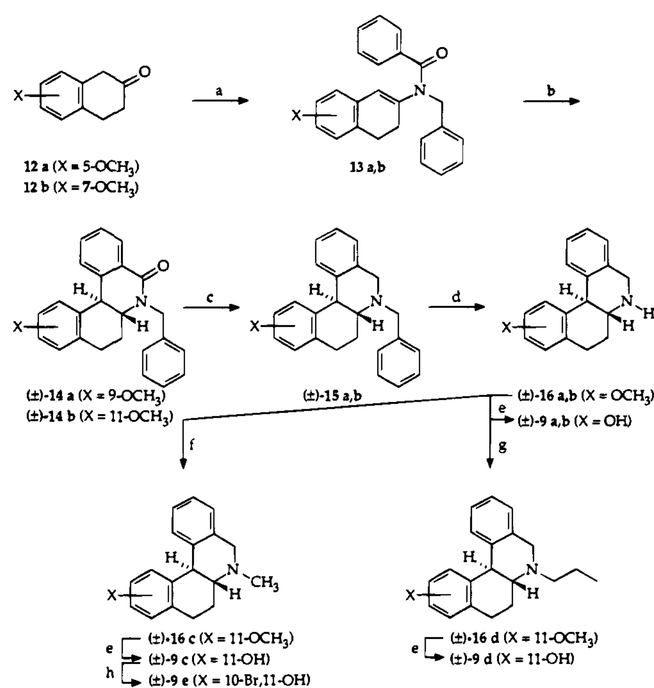


receptor.[21,22] The rigidity that the resulting hybrid structure imparts to the β-phenyldopamine pharmacophore was expected to provide a highly selective series of compounds, but in fact **8a** showed only a 10-fold selectivity for the D_1 receptor. Further evaluation of **8a** has revealed that this compound displays a novel pharmacological profile with unique overt behavioral characteristics in rats[23,24] and an acute ability to dramatically reverse MPTP-induced Parkinsonism in monkeys.[25]

We now report the results of a further inquiry into the structure–activity relationships of the benzo[*a*]phenanthridines. Various *cis*- and *trans*-monohydroxy derivatives (test compounds **9a–e** and **10a,b**; Chart 2) were prepared and pharmacologically evaluated as racemates. While the 11-hydroxy compounds (**9b–e** and **10b**) may be envisioned as phenolic derivatives of **8a**, the 9-hydroxy regioisomers (**9a** and **10a**) are analogues not only of the corresponding catechol **11** but additionally of the D_1-selective benzergoline partial agonist **6**; this may allow a comparison of the isosterism of the phenol OH and the indole NH.

It is important to mention here that the ring oxidation pattern defines the rotameric class (α or β[26]) into which these compounds fall. It is of interest to note that **11** (Ro 21-7767/001) has been reported to be inert as a dopaminergic agonist[27] while **6** is known to display D_1 agonist activity. Therefore, biological activity displayed by **9a** or **10a** might challenge the hypothesis that a *trans*-β-rotamer, and not a *trans*-α-rotamer, is the preferred dopamine conformation at the D_1 receptor. This relates closely to the work of McDermed *et al.*[28] and Seiler and Markstein[29] with the resolved enantiomers of the mono- and dihydroxy primary and tertiary amines of the tetralin series, which has shed light on the possible ways in which these compounds interact with dopamine receptors.

Scheme 1[a]



[a] (a) i. Benzylamine, toluene; ii. benzoyl chloride, triethylamine, CH_2Cl_2; (b) $h\nu$, THF; (c) BH_3, THF; (d) H_2, 10% Pd–C, 95% CH_3CH_2OH; (e) 48% HBr; (f) 37% CH_2O (aq), $NaBH_3CN$, CH_3OH; (g) CH_3CH_2CHO, $NaBH_3CN$, CH_3COOH, CH_3OH; (h) Br_2, $CHCl_3$.

Chemistry

The synthesis of the *trans*-fused series of compounds began with the conversion of 1,6- or 2,7-dihydroxynaphthalene into the β-tetralones (**12a,b**, respectively; Scheme 1) by the method of Cornforth and Robinson.[30] Condensation of the ketones with benzylamine followed by reaction of the intermediate enamines with benzoyl chloride yielded enamides **13a,b**. Photocyclization of the enamides yielded the racemic *trans*-fused tetracyclic lactams **14a,b** which were reduced with diborane in dry THF and then treated with methanol at reflux. Acidification provided the hydrochloride salts of **15a,b**. *N*-Debenzylation using catalytic hydrogenolysis provided the secondary amine hydrochlorides of **16a,b**. Reaction of **16a,b** with 48% HBr at reflux yielded the

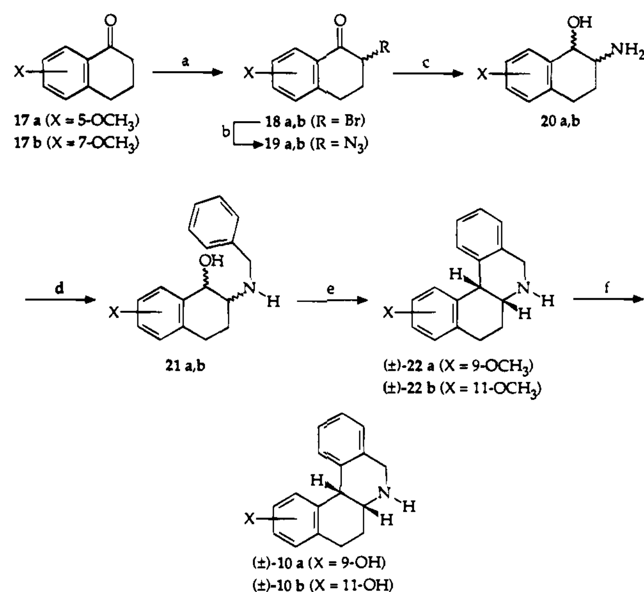
target monohydroxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]-phenanthridines **9a,b**. The tertiary amine derivatives were prepared by reaction of the secondary amine **16b** with either formaldehyde or propionaldehyde in the presence of sodium cyanoborohydride, by the method of Borch *et al.*,[31] to provide **16c,d**, respectively. Ether cleavage with 48% HBr at reflux then provided the phenolic compounds **9c,d**.

The synthesis of the potential dopamine *antagonist* **9e** was achieved by the reaction of the phenolic *N*-methyl derivative **9c** with bromine in chloroform at −78 °C. Overbrominated byproducts, which were indicated to the extent of 50−80% by mass spectrometric analysis of the other chromatography fractions, were found in the reaction mixture, even in cases in which all of the starting material was not consumed. Although these products were chromatographically separable from the desired product, the purification was complicated by the nearly identical R_f values of **9e** (the desired product) and **9c** (the unreacted starting material) in all of the solvent systems investigated. This problem was overcome, in a crude manner, by simply adding more bromine until all of **9c** had been consumed. The desired product was then isolated by chromatotron (Harrison Research, Palo Alto, CA) purification on a silica gel rotor, using 0.5% methanol/dichloromethane eluent. The separation was aided by utilizing an ammonia atmosphere, achieved by passing a stream of nitrogen gas through a solution of concentrated ammonia and then through the chromatotron. The product's identity was confirmed by the normal means, including chemical ionization mass spectrometry, in which two molecular ions were present in a ratio comparable to the natural bromine isotope ratio (~1:1). The ^{1}H NMR spectrum for **9e** was also informative since the hydrogen at the 10-position in **9c**, which had shown *ortho* and *meta* splitting, was no longer evident and the one *resolved* A-ring proton in **9e** appeared as a singlet.

The *cis*-fused analogues **10a,b** were synthesized through a cyclization of their respective *N*-benzyl-2-amino-1,2,3,4-tetrahydronaphth-1-ol precursors **21a,b** as depicted in Scheme 2. The reported procedures of Chiemprasert *et al.*[32] and Thrift[33] led to the synthesis of the *trans*-amino alcohols **20a,b**, but only in low yield. Following a modification of the method of Bowman *et al.*,[34] the bromo ketones **18a,b** were converted to the desired azido ketones **19a,b** in 69.4% and 63.4% yield, respectively. In contrast to the earlier procedures[32,33] which gave exclusively the *trans*-amino alcohol, reduction of the azido ketones with $LiAlH_4$ gave a preponderance of *cis*-amino alcohols **20a,b**, as determined by NMR analysis of the crude reduction product. In the NMR spectra, the carbinol methine is present as a doublet. The chemical shifts and coupling constants for the *cis* and *trans* diastereomers allow for unambiguous structural assignment.

The *N*-benzylations of **20a,b** were accomplished by stirring the appropriate free base with benzaldehyde in ethanol at reflux followed by reduction of the intermediate imines with sodium borohydride. The *N*-benzylamino alcohols **21a,b** were cyclized by treatment with aluminum chloride in dichloromethane at reflux, providing **22a,b**. In both cases the cyclization yielded exclusively the *cis*-hexahydrobenzo[*a*]phenanthridine. The formation of the *cis* ring fusion can be rationalized

Scheme 2[a]



[a] (a) Br_2, $CHCl_3$; (b) NaN_3, DMF, CH_3COOH; (c) $LiAlH_4$, THF; (d) i. benzaldehyde, CH_3CH_2OH; ii. $NaBH_4$; (e) $AlCl_3$, CH_2Cl_2; (f) 48% HBr.

on the basis of steric interactions and bond strain of the carbocation intermediate. Closure to the *trans*-fused system requires a transition state with two severe interactions. One interaction is between the *ortho* ring hydrogen in the benzyl group and the C(2) axial hydrogen. The second interaction is between the C(**1**) hydrogen and the aromatic ring of the benzyl moiety. In contrast, the intermediate conformation that closes to the *cis*-fused system presents only a modest steric interaction. *O*-Demethylations of **22a,b** were accomplished by stirring in 48% hydrobromic acid at reflux to provide **10a,b**, respectively.

Pharmacology

The present studies examined all compounds for their ability to compete for radioligands that label the major subpopulations of brain dopamine receptors. For the D_1 subtype, [^{3}H]-**2** was used to label the receptors. For D_2 receptors, [^{3}H]spiperone was used as the radioligand. Under the experimental conditions used, these radioligands label all members of the appropriate families. Thus, [^{3}H]-**2** labels D_1 and D_5 receptors, and [^{3}H]-spiperone labels D_2, D_3, and D_4 receptors. In rat striatum, the large majority of the receptors likely are the specific molecular forms D_1 and D_2. Table **1** presents the radioreceptor studies of the hexahydrobenzo[*a*]phenanthridines **9a−e** and **10a,b**, as well as those for other important reference compounds, including **8a** (a selective D_1 agonist), **2** (a selective D_1 antagonist), and chlorpromazine (a nonselective D_2 antagonist). In addition, the ability to stimulate adenylate cyclase from rat striatum was used to estimate functional efficacy at D_1 receptors.

Consistent with earlier reports,[22,24] the present studies demonstrate that dihydrexidine (**8a**) is a high-affinity D_1 ligand with approximately 10-fold D_1:D_2 selectivity (Table 1). Comparing the data for all of the compounds bearing a *trans* B/C-ring fusion, catechol **8a** displayed at least 14-fold higher binding affinity for the D_1 receptor than did its phenolic analogues **9b−e** while catechol **11** similarly displayed 6-fold higher affinity

Table 1. Comparison of Dihydrexidine, Its Analogues, and Prototypical Antagonists at D_1 and D_2 Receptors in Rat Striatal Membranes[a]

compd	IC_{50} (nM)	
	D_1 binding affinity	D_2 binding affinity
2	0.57	–
chlorpromazine	–	2.15
8a	7.15	107
9a	5550	532
9b	102 ± 35	631 ± 24
9c	115 ± 43	359 ± 13
9d	529 ± 177	210 ± 55
9e	322 ± 33	3000
10a	2900	2000
10b	16700	15500
11	955 ± 75[b]	121 ± 4[b]

[a] All tests were performed as described in the methods on rat striatal membranes, using [^{3}H]-**2** as the D_1 ligand and [^{3}H]spiperone as the D_2 ligand. All radioreceptor data for which SEMs are not reported represent the mean for two assays performed on different days. Other values represent three or more replications. To minimize interassay variability, at least four compounds [plus DHX (**8a**) and the prototype antagonist **2**] were run on the same day. Hill coefficients for the agonist binding curves were significantly less than 1. Therefore K_i values cannot be determined until the number of binding sites is resolved. [b] From Mottola *et al.*[24]

Table 2. Functional Activity of Dihydrexidine and Its Monohydroxy and Related Analogues on cAMP Synthesis in Rat Striatal Membranes

compd (concn)	cAMP synthesis (% increase above basal value)
dopamine (100 μM)	100
8a (10 μM)	103
8a (10 μM) + **2** (1 μM)	1
9b (10 μM)	15[a]
9c (10 μM)	8[a]
9e (10 μM)	NS[b]
10a (10 μM)	NS[b]
10b (10 μM)	NS[b]

[a] No stimulation seen at concentrations of 1 or 0.1 μM. [b] NS = no stimulation of cAMP synthesis detected.

than did phenol **9a**. Clearly, for D_1 receptor binding in this series of rigidly constrained β-phenyldopamines, the catechol is optimal relative to a phenol. Also as seen from the data in Table 1, the *trans*-**11**-oxygenated benzo[*a*]phenanthridines **9b**–**e** all bind with at least 10-fold higher affinity for the D_1 receptor than does their *trans*-9-oxygenated analogue **9a**. Clearly, within this series, compounds incorporating the *trans*-β-rotamer of dopamine are more potent. It is also of interest to note that **9e** (a compound designed as an analogue of **2**) was a rather weak competitor for D_1 receptors (IC_{50} = 322 nM, n_H = 1.08 ± 0.02). In contrast to the data for compounds bearing a *trans* B/C-ring fusion, among the *cis*-fused compounds, the 9-oxygenated compound **10a** binds with 6-fold higher affinity for the D_1 receptor than its **11**-oxygenated analogue **10b**, although both show rather poor binding. Interestingly, when the compound contains the dopamine moiety in an α-rotameric conformation, the *cis*-fused compounds have higher affinity for the D_1 receptor (compare **9a** and **10a**). This phenomenon was not observed in the 11-oxygenated series, where *trans*-**9b** bound far more tightly than did *cis*-**10b**.

The data in Table **1** reflect the propensity of these compounds to bind to D_1 receptors in rat striatal membranes. It is unclear, however, whether this represents agonist, antagonist, or mixed interactions at these receptors. To ascertain the functional characteristics of these compounds, we tested their ability to affect cAMP synthesis in striatal homogenates. This function is commonly accepted as being linked to D_1 receptors in this brain region. As can be seen in Table 2, **8a** caused the expected full efficacy stimulation relative to dopamine we have reported previously. This was completely blocked by the selective D_1 antagonist **2**. On the other hand, at 10 μM, **9b**,**c** caused 15% and 8% stimulation, respectively, whereas **9e** and **10a**,**b** caused no stimulation whatsoever. Higher concentrations were not tested because of the lack of biological relevance of such findings. Lower concentrations of all compounds (*i.e.*, 0.1 or 1 μM) caused no effects on cAMP synthesis. Moreover, 10 μM concentrations did not inhibit the increase in cAMP synthesis caused by dopamine, suggesting these compounds do not have significant antagonist effects at this receptor. Thus, these data suggest that the monohydroxy derivatives are partial agonists with lower receptor affinity than **8a**.

A rather different pattern was seen in terms of the D_2 affinity of these compounds. Again consistent with earlier reports,[22,24] the present studies demonstrate that **8a** has reasonable affinity for D_2 receptors (Table **1**). The *cis*-monohydroxyhexahydrobenzo[*a*]phenanthridines had diminished affinity for D_2 receptors when compared to the corresponding *trans* forms. It is noteworthy that both *N*-unsubstituted monohydroxy derivatives (**9a**,**b**) had only about 5-fold lower affinity for D_2 receptors than either catechol (**8a**, **11**), whereas the elimination of one hydroxyl dramatically attenuated D_1 affinity, as discussed above. As has been reported for *N*-substituted derivatives of **8a**, *N*-alkylation (**9c**,**d**) increased the D_2 affinity severalfold. Moreover, the 9,10-catechol **11** had D_2 affinity similar to **8a**. While these data are preliminary, they indicate that monohydroxyhexahydrobenzo[*a*]phenanthridines may be worthy of further study as ligands for the D_2-like family of receptors. Because the present work was focused on the D_1 nature of these compounds, it should be noted that we have not explored the functional D_2-like characteristics of these monohydroxy derivatives. It is interesting to note that preliminary data suggest that the agonist activity of catechol **8a** at D_2-like receptors may well be only at receptors located postsynaptically.[35,36]

Discussion

The *trans*-fused derivatives **9a**–**e** displayed varying potencies, depending both on the location of the hydroxy group and also on the size of the *N*-alkyl substituent. The 9-hydroxy compounds **9a** and **11**,[27] which both embody a *trans*-α-rotamer, showed at least 8-fold D_2 selectivity, with low affinity for the D_1 subtype; the catechol **11** was both more potent and more selective. In contrast to those data, the **11**-hydroxy series **9b**–**e**, which embodies a *trans*-β-rotamer, showed moderate affinity for both receptor subtypes. As previously reported,[22] **8a** displayed a pronounced selectivity for the D_1 subtype and produced a full efficacy response in stimulating adenylate cyclase (relative to dopamine). The secondary amine **9b** showed a 6-fold preference for the D_1 subtype, while **9c** showed a 3-fold preference. On the other hand, the *N*-*n*-propyl derivative **9d** displayed an approximately 2.5-fold selectivity for the D_2 subtype.

The *cis*-fused derivatives **10a**,**b** showed little D_1 affinity or intrinsic activity. The overall affinity for D_1

receptors was **8a** > **9b** ~ **9c** > **9e** > dopamine, **9d**,**a**, **11** > **10a**,**b**. These data roughly parallel the efficacy data for the stimulation of adenylate cyclase.

Many of the features required for optimal dopamine receptor complementarity and agonist activity have been schematically presented in the "cartoon" model of McDermed *et al.*[28] We[22,37] and others[20] have recently revised this model to accommodate the likely presence of a hydrophobic accessory region in the D_1 receptor subtype. Compounds **9a**–**e** and **10a**,**b** together with **8a**–**c** and **11** explore the salient features (all of which are decidedly interdependent) of this model: the degree of ring hydroxylation, the rotameric orientation of the dopamine pharmacophore, the extent of amine substitution, the geometry of the β-phenyl substituent, and the stereochemistry.

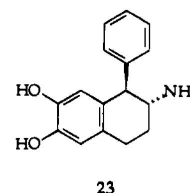
Among the new compounds, the secondary amine **9b** proved to have the greatest affinity for the D_1 receptor and the *N*-*n*-propyl analogue **9d** displayed the highest D_2 receptor affinity. This pattern agrees with the findings from other structural classes in which increasing bulk on the basic nitrogen enhances the affinity of dopaminergic ligands for the D_2 receptor.

For the ring hydroxyls, a minimal binding determinant in this structural class is the *m*-hydroxy, corresponding to the 3-position of the dopamine structure. The *p*-hydroxy, corresponding to the 4-position of the dopamine structure, appears to potentiate agonist activity. As a result of this, in direct comparison, catechols generally appear to be more potent than their phenolic analogues at both D_1 (*e.g.*, compounds **8a**–**c** vs **9b**–**d**) and D_2 sites (*e.g.*, compound **11** vs **9a**). Similar findings have previously been observed with the aminotetralins and benzo[*f*]quinolines, especially with respect to D_1 activity. Benzergoline **6**, *which bears no aromatic hydroxyl groups*, seems to lie outside the realm of this generalization.

Among our test compounds, the D_1 receptor generally favors the *trans*-β-rotamer in **9b**–**e** while the D_2 subtype appears more promiscuous in accepting compounds with either rotameric orientation. Surprisingly then, **11** was reported to display no dopaminergic activity, even though the compound contains the dopamine pharmacophore in an α-rotamer, as does apomorphine.[27] In light of the activity of the analogous benzo[*f*]quinolines,[38] this inactivity may seem incongruous; in fact, our data show **11** to have some D_2 affinity. However it is likely that **11**, and **9a** by analogy, have more of a steric demand than the benzo[*f*]quinoline because of the additional fused ring. Thus, on the basis of our recently revised schematic model of the D_1 receptor,[22] this relatively weak activity may be rationalized by the undesired projection of the unsubstituted phenyl ring into the hypothesized region of steric intolerance when other pharmacophoric elements are aligned.

The isomeric *cis*-9- and 11-hydroxybenzo[*a*]phenanthridines (**10a**,**b**) neither stimulated cAMP synthesis nor inhibited the cAMP synthesis induced by dopamine (unpublished data). These *cis* isomers, which also lacked appreciable affinity for [^{3}H]-**2** binding sites, probably suffer from the same steric problems as the structurally related *cis*-fused benzo[*f*]quinolines. The necessity for a relatively planar structure for D_2 receptor activation has been demonstrated by Cannon *et al.*[39] for the benzo[*f*]quinolines, of which the *trans*, but not the *cis*, compounds were active. The rigid, planar *trans* molecules apparently fit the receptor better than the more angular and conformationally flexible *cis* isomers. As discussed before in the case of the catechol **8a**,[22] it may be that the D_1 receptor has a similar requirement. This suggests that not only does the ethylamine moiety within the pharmacophore need to be in a *trans* extended conformation but also that the two aromatic rings should be able to approach coplanarity more nearly than is favorable in **10a**,**b**.

This is clearly the case for compound **23**[40] which embodies all of the salient features for D_1 receptor recognition. We anticipated that this compound would display moderate affinity for dopamine receptors. It displayed, however, relatively low affinity for both D_1 and D_2 receptors (IC_{50} > 1 μM). As a flexible seco



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derivative, the "pendant" phenyl group may twist in a way that disorients the molecule in regard to optimal receptor binding. Thus, the stereochemical arrangement of the B/C-ring fusion must be such that a nearly coplanar arrangement is maintained. It is clear that the two phenyl rings, in terms of the centroid distances and the relative angle of the ring planes, should have a specific orientation that may be critical both for D_1 affinity and for full agonist efficacy. Specifically, changes in the orientation of the phenyl rings may be sufficient to cause loss of affinity and intrinsic activity.

Although the test compounds in the current work did not display the potency of the catechol analogues, their pharmacological results support the concepts put forth in previous models of the dopamine D_1 receptor subtype. We have seen that, among the benzo[*a*]phenanthridines, *D_1 receptor affinity and intrinsic activity are favored by derivatives which combine a catechol and a secondary amine in the trans-β-rotameric dopamine structure and which rigidly maintain a second phenyl ring, attached at the 2-position of the ethylamine side chain, in an arrangement nearly coplanar with the catechol ring.*

Experimental Section

Chemistry. Melting points were determined on a Thomas-Hoover Meltemp melting point apparatus and are uncorrected except where indicated. ^{1}H NMR spectra were recorded on a Varian FT-80, a Chemagnetics 200-MHz, or a Varian VXR-500S 500-MHz spectrometer. Chemical shifts are reported in δ values (parts per million, ppm) relative to an internal standard of tetramethylsilane in $CDCl_3$, except where noted. Abbreviations used in NMR analysis are as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br s, broad singlet; dd, doublet of doublets. Infrared (IR) spectra were recorded on a Beckman IR-33 spectrophotometer and are reported in reciprocal centimeters (cm^{-1}). Analytical thin-layer chromatography (TLC) was performed on Baker-flex silica gel 1B2-F plastic plates. Microanalyses were obtained from the Purdue Microanalytical Laboratory or Galbraith Laboratories, Inc. The chemical ionization mass spectra (CIMS) were determined on a Finnigan 4000 quadrupole spectrometer in the Purdue University Department of Medicinal Chemistry, using ammonia or isobutane as the reagent gas, as noted, and are

reported *as m/e* (relative intensity). A low-pressure Parr apparatus was used for all hydrogenations.

Solvents and reagents were used as purchased, except as noted. THF was distilled from potassium metal/benzophenone ketyl. All other compounds (except as listed below) were purchased from commercial sources.

(±)-*trans*-9,10-Dihydroxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine Hydrobromide, 11. This compound (Ro 21-7767/001) was a generous gift from Hoffman-LaRoche, Inc., Nutley, NJ.

5-Methoxy-β-tetralone, 12a. The method of Cornforth and Robinson[30] was used to convert 1,6-dihydroxynaphthalene (20 g, 0.125 mol) into the β-tetralone **12a**. Purification by Kugelrohr distillation [110 °C, 0.5 mmHg (lit.[30] bp 120 °C, 0.5 mmHg)] provided 13.23 g (60.1%) of **12a**. IR (neat): 1705 cm^{-1}. ^1H NMR: δ 7.18 (m, 1, ArH), 6.75 (m, 2, ArH), 3.85 (s, 3, OCH_3), 3.57 (s, 2, $ArCH_2$), 3.09 (t, 2, $ArCH_2$, J = 6.7 Hz), 2.52 (t, 2, CH_2CO, J = 6.7 Hz).

7-Methoxy-β-tetralone, 12b. By the same procedure,[30] 2,7-dihydroxynaphthalene (50 g, 0.312 mol) was converted into the β-tetralone **12b**. Purification by Kugelrohr distillation [120 °C, 0.5 mmHg (lit.[41] bp 110−112 °C, 0.10 mmHg)] provided 34.43 g (62.6%) of **12b**. IR (neat): 1705 cm^{-1}. ^1H NMR: δ 7.14 (d, 1, ArH, J = 8.3 Hz), 6.77 (dd, 1, ArH, J = 2.6, 8.3 Hz), 6.68 (d, 1, ArH, J = 2.6 Hz), 3.79 (s, 3, OCH_3), 3.56 (s, 2, $ArCH_2$), 3.01 (t, 2, $ArCH_2$, J = 6.7 Hz), 2.54 (t, 2, CH_2CO, J = 6.7 Hz).

***N*-Benzoyl-*N*-benzyl-5-methoxy-3,4-dihydro-2-aminonaphthalene, 13a.** To a solution of **12a** (7.04 g, 40 mmol) in benzene (100 mL) under N_2 was added benzylamine (4.71 g, 44 mmol). The solution was heated at reflux, with stirring for 1.5 h. The water evolved was collected with a Barrett trap. The volatiles were removed *in vacuo* to yield a golden-brown oily residue. This residue was dissolved in dichloromethane (100 mL) and placed in a cool water bath, and then triethylamine (4.65 g, 46 mmol) was added. Benzoyl chloride (6.46 g, 46 mmol) was added dropwise to the enamine solution, with stirring. The solution was stirred overnight, with warming to room temperature. After the volatiles were removed *in vacuo*, the residue was taken up in ether and the insoluble triethylamine hydrochloride was removed by suction filtration. The ether filtrate was washed sequentially with 50 mL of 5% HCl, 50 mL of H_2O, 25 mL of 1 N NaOH, and 50 mL of brine. The organic fraction was then dried ($MgSO_4$), treated with silica gel (5 g) and activated carbon, and then filtered through Celite. The volatiles were removed *in vacuo*, leaving an orange solid, which was crystallized from hexane. Recrystallization from ether provided 8.155 g of **13a**, mp 103−104 °C. The second and third crops contributed to a total yield of 10.92 g (74%). IR (KBr): 1620 cm^{-1}. CIMS (isobutane): M + 1 370. ^1H NMR: δ 7.62 (m, 2, ArH), 7.33 (m, 8, ArH), 7.04 (t, 1, ArH, J = 7.8 Hz), 6.68 (d, 1, ArH, J = 8.3 Hz), 6.48 (d, 1, ArH, J = 7.2 Hz), 6.11 (s, 1, ArCH), 5.01 (s, 2, $ArCH_2N$), 3.75 (s, 3, OCH_3), 2.55 (t, 2, $ArCH_2$, J = 7.9 Hz), 2.09 (t, 2, CH_2, J = 7.9 Hz). Anal. ($C_{25}H_{23}NO_2$) C, N; H: calcd, 6.27; found, 7.59.

***N*-Benzoyl-*N*-benzyl-7-methoxy-3,4-dihydro-2-aminonaphthalene, 13b.** In the same manner as described for the synthesis of **13a**, **12b** (10.0 g, 56.7 mmol) was reacted sequentially with benzylamine (6.26 g, 58.45 mmol) and benzoyl chloride (8.46 g, 60.2 mmol) to provide **13b**. The enamide was crystallized from 100 mL of diethyl ether to provide 10.36 g (49.4%), mp 99−101 °C. The second and third crops contributed to a total yield of **13b** of 14.45 g (68.9%). IR (KBr): 1620 cm^{-1}. CIMS (isobutane): M + 1 370. ^1H NMR: δ 7.61 (m, 2, ArH), 7.33 (m, 8, ArH), 6.88 (d, 1, ArH, J = 8.3 Hz), 6.60 (dd, 1, ArH, J = 2.7 Hz, 8.3 Hz), 6.40 (d, 1, ArH, J = 2.7 Hz), 6.10 (s, 1, ArCH), 5.00 (s, 2, $ArCH_2N$), 3.71 (s, 3, OCH_3), 2.48 (t, 2, $ArCH_2$, J = 7.9 Hz), 2.11 (t, 2, CH_2, J = 7.9 Hz). Anal. ($C_{25}H_{23}NO_2$) C, H, N.

(±)-*trans*-6-Benzyl-9-methoxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridin-5-one, 14a. A solution of **13a** (5.0 g, 13.5 mmol) in THF (300 mL, 45.1 mM solution) was stirred in an Ace Glass 250-mL photochemical reactor, while irradiating with a 450-W Hanovia medium pressure, quartz, mercury vapor lamp seated in a water-cooled quartz immersion well for 2 h. The volatiles were removed to yield a solid residue. The product was crystallized from ethyl acetate and collected by suction filtration, providing 3.20 g (64%) of **14a**, mp 202−203 °C. CIMS (isobutane): M + 1 370; ^1H NMR: δ 8.19 (m, 1, ArH), 7.48 (m, 3, ArH), 7.28 (m, 6, ArH), 7.06 (d, 1, ArH, J = 7.8 Hz), 6.78 (d, 1, ArH, J = 8.1 Hz), 5.32 (d, 1, ArCHN, J = 15.8 Hz), 4.82 (d, 1, ArCHN, J = 16.1 Hz), 4.42 (d, 1, Ar_2CH, J = 11.6 Hz), 3.82 (m, 4, OCH_3, CHN), 3.01 (m, 1, ArCH), 2.27 (m, 2, CH), 1.63 (m, 1, CH). Anal. ($C_{25}H_{23}NO_2$) C, N; H: calcd, 6.27; found, 7.51.

(±)-*trans*-6-Benzyl-11-methoxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridin-5-one, 14b. A solution of **13b** (4.0 g, 10.8 mmol) in THF (500 mL, 21.6 mM solution) was stirred in an Ace Glass 500-mL photochemical reactor, while irradiating in the same manner as for the synthesis of **14a**. After 1 h, TLC analysis indicated the absence of any remaining starting material. The volatiles were removed *in vacuo*, and the oily residue was dissolved in 50 mL of dichloromethane, swirled briefly with silica gel (3 g), and filtered through Celite. Following removal of the volatiles *in vacuo*, the residual foam was dissolved in ether, filtered, and seeded. The product was obtained by suction filtration, providing 2.78 g (69.5%) of **14b**, mp 129−130 °C. An analytical sample, mp 136−138 °C, was obtained after a second crystallization from ether. IR (KBr): 1650, 1630 cm^{-1}. CIMS (isobutane): M + 1 370. ^1H NMR: δ 8.22 (m, 1, ArH), 7.46 (m, 3, ArH), 7.26 (m, 5, ArH), 7.08 (d, 1, ArH, J = 8.6 Hz), 6.98 (d, 1, ArH, J = 1.9 Hz), 6.80 (dd, 1, ArH, J = 1.9, 8.6 Hz), 5.34 (d, 1, ArCHN, J = 16.1 Hz), 4.80 (d, 1, ArCHN, J = 16.1 Hz), 4.40 (d, 1, Ar_2CH, J = 11.3 Hz), 3.83 (m, 4, OCH_3, CHN), 2.70 (m, 2, $ArCH_2$), 2.25 (m, 1, CH), 1.78 (m, 1, CH). Anal. ($C_{25}H_{23}NO_2$) C, H, N.

(±)-*trans*-6-Benzyl-9-methoxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine Hydrochloride, 15a. To a solution of **14a** (0.66 g, 1.79 mmol) in 100 mL of dry distilled THF at −78 °C was added 1 M borane−THF complex (5.4 mL, 5.4 mmol). The reaction mixture was warmed to room temperature and then heated at reflux for 6 h, after which TLC analysis indicated the absence of starting material. The reaction mixture was diluted with 10 mL of methanol, and heating was continued for 1 h. The volatiles were removed *in vacuo*, the residual free base (mp 55−58 °C) was dissolved in 20 mL of EtOH and acidified with concentrated HCl, and the solution was concentrated to dryness under reduced pressure. Recrystallization of the hydrochloride from EtOAc provided 280 mg (40%) of **15a**·HCl as a white solid, mp 231−234 °C. CIMS (NH_3): M + 1 356. ^1H NMR (free base): δ 7.43−7.15 (m, 9, ArH), 7.08 (d, 1, ArH, J = 7.04 Hz), 6.97 (d, 1, ArH, J = 7.78 Hz), 6.81 (d, 1, ArH, J = 8.06 Hz), 4.12 (d, 1, Ar_2CH, J = 11.28 Hz), 3.96 (d, 1, ArCHN, J = 13.27 Hz), 3.89 (d, 1, ArCHN, J = 15.4 Hz), 3.88 (s, 3, OCH_3), 3.52 (d, 1, ArCHN, J = 15.31 Hz), 3.32 (d, 1, ArCHN, J = 13.27 Hz), 3.23, 2.85 (m, 2), 2.42 (m, 1), 2.25 (m, 1), 1.98 (m, 1). Anal. ($C_{25}H_{26}ClNO$) C, N; H: calcd, 6.69; found, 8.49.

(±)-*trans*-6-Benzyl-11-methoxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine Hydrochloride, 15b. In the same manner as described for the synthesis of **15a**, **14b** (5.37 g, 14.5 mmol) was reacted with 1 M borane−THF complex (36 mL, 36 mmol), treated with 10 mL methanol, and then acidified to provide amine hydrochloride **15b**. After removal of the volatiles, the residual foam was crystallized from acetone to provide 4.99 g (87.5%) of **15b**·HCl as a white solid, mp 207−208 °C. Recrystallization from absolute ethanol provided 3.76 g of colorless crystals, mp 206−209 °C. Recovery of additional crops contributed to an overall 94% yield of **15b**·HCl. CIMS (NH_3): M + 1 356. ^1H NMR (free base): δ 7.43−7.01 (m, 10, ArH), 6.88 (d, 1, ArH, J = 2.5 Hz), 6.72 (dd, 1, ArH, J = 2.5, 8.3 Hz), 4.10 (d, 1, Ar_2CH, J = 10.7 Hz), 3.96 (d, 1, ArCHN, J = 13.1 Hz), 3.78 (d, 1, ArCHN, J = 15.2 Hz), 3.72 (s, 3, OCH_3), 3.46 (d, 1, ArCHN, J = 15.2 Hz), 3.28 (d, 1, ArCHN, J = 13.1 Hz), 2.86 (m, 2, CHN, ArCH), 2.40 (m, 1, ArCH), 2.20 (m, 1, CHCN), 2.00 (m, 1, CHCN). Anal. ($C_{25}H_{26}ClNO$) C, H, N.

(±)-*trans*-9-Methoxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine Hydrochloride, 16a. A suspension of **15a**·HCl (215 mg, 0.55 mmol), 10% Pd−C (50 mg), and 100 mL of 95% ethanol was placed in a Parr hydrogenation bottle. The bottle was charged with 37 psi H_2 and shaken for 15 h. The reaction mixture was filtered through Celite, and the

volatiles were removed *in vacuo* to provide 163 mg (98.5%). Recrystallization from iPrOH/EtOAc provided 125 mg (75.5%) of **16a**·HCl, mp 264–265 °C. CIMS (NH_3): M + 1 266. ^{1}H NMR (HCl salt, DMSO-d_6): δ 9.50 (br s, 2, $^+NH_2$), 7.36 (m, 4, ArH), 7.24 (m, 1, ArH), 6.93 (m, 2, ArH), 4.40 (m, 3, $ArCH_2N$, Ar_2CH), 3.82 (m, 3, OCH_3), 3.02 (m, 1, CHN), 2.85 (m, 2, $ArCH_2$), 2.22 (m, 1, CH), 1.95 (m, 1, CH). Anal. ($C_{18}H_{20}ClNO$) C, H, N.

(±)-*trans*-11-Methoxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine Hydrochloride, 16b. In the same manner as for the synthesis of **16a**, **15b**·HCl (2.92 g, 7.45 mmol) was converted to **16b**. After the product was dried azeotropically with absolute ethanol, the residual white solid was recrystallized from isopropyl alcohol/ethyl acetate to provide 2.18 g (96.9%) of **16b**·HCl, mp 232–233 °C. CIMS (NH_3): M + 1 266. ^{1}H NMR (HCl salt): δ 7.44 (m, 1, ArH), 7.34 (m, 3, ArH), 7.14 (d, 1, ArH, J = 8.2 Hz), 6.92 (d, 1, ArH, J = 2.7 Hz), 6.80 (dd, 1, ArH, J = 2.7, 8.2 Hz), 4.62–4.38 (m, 3, $ArCH_2N$, Ar_2CH), 3.80 (m, 3, OCH_3), 3.10 (m, 1, CHN), 2.90 (m, 2, $ArCH_2$), 2.51 (m, 1, CH), 2.41 (m, 1, CH). Anal. ($C_{18}H_{20}ClNO$) C, H, N.

(±)-*trans*-9-Hydroxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine Hydrobromide, 9a. A suspension of **16a**·HCl (282 mg, 0.6 mmol) in 48% HBr (5 mL) under N_2 was heated at reflux overnight, in an oil bath. The following day, the solvent was removed *in vacuo*. The residue was then dried by azeotropic distillation of absolute ethanol and finally recrystallized from ethanol to provide 300 mg (85.0%) of **9a**·HBr as a pale yellow solid, mp 240–245 °C. CIMS (NH_3): M + 1 252. ^{1}H NMR (HBr salt, DMSO-d_6): δ 9.37 (br s, 2 NH_2), 9.22 (s, 1, OH), 7.46–7.39 (m, 4, ArH), 7.04 (d, 1, ArH, J = 8.0 Hz), 6.72 (s, 1, ArH), 6.65 (d, 1, ArH, J = 8.0 Hz), 4.41 (s, 2, Ar CH_2N), 4.26 (d, 1, Ar_2CH, J = 11.3 Hz), 3.09 (m, 1, CHN), 2.82 (m, 2, $ArCH_2$), 2.22 (m, 1, CHCN), 1.94 (m, 1, CHCN). Anal. ($C_{17}H_{18}BrNO$) C, H, N.

(±)-*trans*-11-Hydroxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine Hydrobromide, 9b. In the same manner as for the synthesis of **9a**, **16b**·HCl (182 mg, 0.6 mmol) was converted to **9b**. Recrystallization from ethanol provided 132 mg (66%) of **9b**·HBr as a pale yellow solid, mp 255–256 °C. CIMS (NH_3): M + 1 252. ^{1}H NMR (HBr salt, DMSO-d_6): δ 9.37 (br s, 2, NH_2), 9.22 (s, 1, OH), 7.46–7.39 (m, 4, ArH), 7.04 (d, 1, ArH, J = 8.0 Hz), 6.72 (s, 1, ArH), 6.65 (d, 1, ArH, J = 8.0 Hz), 4.41 (s, 2, $ArCH_2N$), 4.26 (d, 1, Ar_2CH, J = 11.3 Hz), 3.09 (m, 1, CHN), 2.82 (m, 2, $ArCH_2$), 2.22 (m, 1, CHCN), 1.94 (m, 1, CHCN). Anal. ($C_{17}H_{18}BrNO$) C, H, N.

(±)-*trans*-11-Methoxy-6-methyl-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine Hydrochloride, 16c. A solution of **16b**·HCl (0.85 g, 2.82 mmol), 37% formaldehyde (1.5 mL), and sodium cyanoborohydride (0.73 g, 11.6 mmol) in methanol (25 mL) under N_2 was stirred overnight. TLC analysis the next morning indicated the absence of starting material. The volatiles were removed *in vacuo*, and the residue was stirred with 5% HCl (15 mL) and then 6 N HCl (15 mL; total volume of 30 mL) to effect solution. The acidic solution was washed with ether (2 × 10 mL). The ether washes were treated with concentrated HCl, thereby precipitating some additional amine as the hydrochloride salt, which was recovered by washing the ether layer with water. All of the aqueous fractions were then pooled and made basic with concentrated ammonia, under N_2. The free base was extracted into dichloromethane, dried ($MgSO_4$), and filtered, and the solvent was removed. The residual oil was dissolved in absolute ethanol, acidified with concentrated HCl, and filtered, and again the volatiles were removed *in vacuo*. The residue was recrystallized from absolute ethanol (10 mL) to provide 360 mg (40.4%) of **16c**·HCl, mp 219–220 °C corr. After reducing the volume, a second crop of 368 mg was obtained for an overall yield of 81.8%. CIMS (NH_3): M + 1 280. ^{1}H NMR (free base): δ 7.40 (m, 1, ArH), 7.30–7.19 (m, 4, ArH), 6.81 (br s, 1, ArH), 6.72 (dd, 1, ArH, J = 2.7, 8.0 Hz), 4.02 (d, 1, Ar_2CH, J = 9.9 Hz), 3.84 (d, 1, ArCHN, J = 14.7 Hz), 3.72 (s, 3, OCH_3), 3.50 (d, 1, ArCHN, J = 14.7 Hz), 2.89 (m, 2, CHN, ArCH), 2.39 (s, 3, NCH_3), 2.09 (m, 2, ArCH, CHCN), 1.92 (m, 1, CHCN). Anal. ($C_{19}H_{22}ClNO$) C, H, N.

(±)-*trans*-11-Methoxy-6-*n*-propyl-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine Hydrochloride, 16d. A mixture of **16b**·HCl (0.878 g, 2.91 mmol) freshly distilled propionaldehyde (0.42 mL, 5.82 mmol), and sodium cyanoborohydride (0.365 g, 5.82 mmol) in methanol (25 mL) was made acidic with acetic acid (7 drops), thereby effecting solution. After the solution was stirred overnight under N_2, TLC analysis indicated the absence of the secondary amine. The volatiles were removed, and the residue was taken up in 5% HCl. The acidic solution was washed with ether and then made basic with concentrated ammonia, under N_2. The free base was extracted into dichloromethane, and this solution was then dried ($MgSO_4$) and filtered. Following removal of the volatiles, the residual oil was dissolved in absolute ethanol, acidified with concentrated HCl, filtered, and dried azeotropically by distillation of ethanol. The product was recrystallized from ethyl acetate/hexane to provide 463 mg (46.3%) of **16d**·HCl, mp 102–108 °C. CIMS (NH_3): M + 1 308. ^{1}H NMR (free base): δ 7.37 (m, 1, ArCH), 7.32–7.16 (m, 3, ArH), 7.10 (d, 1, ArH, J = 8.0 Hz), 6.84 (d, 1, ArH, J = 2.4 Hz), 6.72 (dd, 1, ArH, J = 2.4, 8.0 Hz), 4.02 (d, 1, Ar_2CH, J = 10.4 Hz), 3.98 (d, 1, ArCHN, J = 15.0 Hz), 3.73 (s, 1, OCH_3), 3.60 (d, 1, ArCHN, J = 15.0 Hz), 2.84 (m, 2, $ArCH_2$), 2.63 (m, 1, CHN), 2.33 (m, 2, CH_2N), 2.11 (m, 1, CHCN), 1.89 (m, 1, CHCN), 1.58 (m, 2, CH_2), 0.91 (m, 3, CH_3). Anal. ($C_{21}H_{26}ClNO$) C, H, N.

(±)-*trans*-11-Hydroxy-6-methyl-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine Hydrobromide, 9c. A suspension of **16c**·HCl (1.19 g, 3.77 mmol) in 48% HBr (5 mL) under N_2 was stirred and heated at reflux, in an oil bath. The mixture quickly thickened, and an additional 20 mL of 48% HBr was added. Heating was continued overnight. The following day, the volatiles were removed *in vacuo*. The residue was then dried by azeotropic distillation of absolute ethanol, and the product was recrystallized from methanol/ethyl acetate to provide 881 mg (67.8%) of **9c**·HBr as a pale yellow solid, mp 248–249 °C. CIMS (NH_3): M + 1 266. ^{1}H NMR (free base): δ 7.37 (m, 1, ArCH), 7.26 (m, 3, ArH), 7.04 (d, 1, ArH, J = 8.1 Hz), 6.69 (s, 1, ArH), 6.64 (d, 1, ArH, J = 8.1 Hz), 3.98 (d, 1, Ar_2CH, J = 9.1 Hz), 3.84 (d, 1, ArCHN, J = 14.2 Hz), 3.50 (d, 1, ArCHN, J = 14.2 Hz), 2.87 (m, 2, CHN, ArCH), 2.38 (s, 3, NCH_3), 2.09 (m, 2, ArCH, CHCN), 1.86 (m, 1, CHCN). Anal. ($C_{18}H_{20}BrNO$) C, H, N.

(±)-*trans*-11-Hydroxy-6-*n*-propyl-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine Hydrobromide, 9d. A mixture of 250 mg (0.73 mmol) of **16d**·HCl and 5 mL of 48% HBr was heated at reflux overnight, with stirring under N_2. The volatiles were removed, and the solid residue was dissolved in hot absolute ethanol and filtered. The volume was reduced to 10 mL, and the solution was cooled to room temperature overnight. The product formed a layer of golden crystals, which were collected and dried to provide 185 mg (68.4%) of **9d**·HBr, mp 255 °C. CIMS (isobutane): M + 1 294. ^{1}H NMR (HBr salt, DMSO-d_6): δ 10.14 (s, 1, NH), 9.29 (s, 1, OH), 7.42 (m, 4, ArH), 7.07 (d, 1, ArH, J = 8.8 Hz), 6.67 (m, 2, ArH), 4.50 (m, 2, $ArCH_2N$), 4.35 (d, 1, ArCH, J = 11.4 Hz), 3.28–2.72 (m, 5, CHN, $ArCH_2$, NCH_2), 2.32 (m, 1, CHCN), 1.98 (m, 1, CHCN), 1.73 (m, 2, CH_2), 0.93 (t, 3, CH_3, J = 7.31 Hz). Anal. ($C_{20}H_{24}BrNO$) C, H, N.

(±)-*trans*-10-Bromo-11-hydroxy-6-methyl-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine Hydrochloride, 9e. A suspension of **16c**·HCl (200 mg, 0.63 mmol) in 48% HBr (10 mL) was heated at reflux under N_2 with stirring overnight. The volatiles were then removed *in vacuo*, and the residual solid **9c**·HBr was dissolved in water. The solution was cooled in an ice bath under N_2 and then made basic by the addition of excess saturated aqueous $NaHCO_3$. The resulting white precipitate was collected by suction filtration. Following repeated washes on the filter with water, the filter cake was dried under vacuum (0.3 mmHg, over Drierite) for 5 h. The aqueous filtrate was extracted with 2 × 25 mL of $CHCl_3$, which was then dried ($MgSO_4$) and filtered. The filtercake of **9c** was then suspended in this dried chloroform extract. An additional 150 mL of dry chloroform was added, with stirring, to effect solution of the free base. The solution was cooled to −78 °C, bromine (25 μL, 0.97 mmol) was added to the solution *via* a syringe, and the flask was left stirring overnight, gradually

warming to room temperature. Although the bromine color was discharged, TLC analysis (2.5% CH_3OH/CH_2Cl_2, NH_3 atm) indicated the presence of starting material (visually estimated at 30%). The solution was cooled again to −78 °C, and an additional 7.5 μL (0.29 mmol) of Br_2 was added. Subsequent TLC analysis confirmed the total consumption of starting material, so the volatiles were removed *in vacuo* and the residue was dissolved in hot water and filtered. The solution was cooled in an ice bath and basified with saturated aqueous $NaHCO_3$ under N_2. The resulting white precipitate was collected by suction filtration and washed repeatedly with water, and the aqueous filtrate was washed with 2 × 25 mL of chloroform. The solid material from above was combined with this chloroform extract, and after drying ($MgSO_4$), the product was purified using radial chromatography (Chromatotron; Harrison Research, Palo Alto, CA) over a 2-mm silica gel rotor with 0.5% CH_3OH/CH_2Cl_2 under a N_2/NH_3 atmosphere.[42] Following removal of the solvent, the free base was dissolved in absolute ethanol and acidified with concentrated HCl. The volatiles were removed, and the residue was recrystallized from methanol to provide 35 mg of **9e**·HCl as colorless crystals, mp 275 °C corr. Dilution of the filtrate with ethyl acetate provided another 17 mg of a 21.6% overall yield. CIMS (NH_3): M + 1 344, 346. ^1H NMR (free base): δ 7.30–7.06 (m, 5, ArH), 6.79 (s, 1, ArH), 3.90 (d, 1, Ar_2CH, J = 10.0 Hz), 3.80 (d, 1, ArCHN, J = 14.9 Hz), 3.48 (d, 1, ArCHN, J = 14.9 Hz), 2.99–2.67 (m, 2, CHN, ArCH), 2.35 (s, 3, NCH_3), 2.04 (m, 2, ArCH, CHCN), 1.88 (m, 1, CHCN). Anal. ($C_{18}H_{19}BrClNO$) C, H, N.

2-Bromo-5-methoxy-α-tetralone, 18a. To a solution of 2.0 g (11.4 mmol) of 5-methoxy-α-tetralone dissolved in 100 mL of chloroform was added 1.82 g (11.4 mmol) of bromine dissolved in 20 mL of chloroform. The bromine solution was added over a 30-min period, and the reaction mixture was stirred for an additional 30 min. The mixture was then washed consecutively with water (2 × 100 mL), 5% sodium bicarbonate solution (2 × 100 mL), and water (2 × 100 mL). The organic layer was dried ($MgSO_4$). After removal of the solvent, the crude bromo ketone was recrystallized from 80% hexanes/20% benzene to provide 2.0 g (68.8%) of **18a**, mp 87–88 °C [lit.[43] mp (petroleum ether) 93 °C]. ^1H NMR: δ 7.70 (dd, 1, ArH, J = 1.4, 7.3 Hz), 7.26 (m, 1, ArH), 7.05 (dd, 1, ArH, J = 1.4, 7.3 Hz), 4.70 (m, 1, CH), 3.88 (s, 3, OCH_3), 3.02 (m, 2, CH_2), 2.49 (m, 2, CH_2).

2-Bromo-7-methoxy-α-tetralone, 18b. In a procedure analogous to that for **18a**, a solution of 2 g (11.4 mmol) of 7-methoxy-α-tetralone in chloroform was treated with 1.82 g (11.4 mmol) of bromine. The crude bromo ketone was recrystallized from hexanes to yield 2.55 g (87%) of **18b**, mp 77–78 °C (lit.[44] mp 78–80 °C). ^1H NMR: δ 7.60 (d, 1, ArH), 7.11 (m, 2, ArH), 4.71 (m, 1, CH), 3.84 (s, 3, OCH_3), 2.97 (m, 2, CH_2), 2.46 (m, 2, CH_2).

***trans*-2-Amino-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ol, 20a.** A solution of bromo ketone **18a** (1.0 g, 3.92 mmol) in 15 mL of DMF and 0.26 mL of acetic acid was cooled to 0 °C. A solution of 0.633 g (9.74 mmol) of sodium azide dissolved in 2.6 mL of water was added dropwise to the bromo ketone solution; stirring was continued for 1 h at 0 °C. The reaction mixture was then poured into 75 mL of ice water and extracted with dichloromethane (2 × 10 mL). The organic layer was washed with water (2 × 30 mL) and concentrated, and the residue was redissolved in 10 mL of ether. The ether was washed with water (2 × 30 mL), dried ($MgSO_4$), and filtered.

The ethereal solution of azide **19a** prepared above was added dropwise over 5 min to a suspension of 0.5 g of $LiAlH_4$ (13 mmol) in 20 mL of dry THF at 0 °C. The mixture was then stirred at reflux for 1 h. After cooling, the excess $LiAlH_4$ was decomposed by dropwise addition of 1.5 mL of water. The alumina salts were removed by suction filtration and washed with 75 mL of ether. The filtrates were concentrated, the residue was redissolved in 20 mL of ether, and this solution was extracted with 20 mL of 1% acetic acid. The aqueous acidic solution was treated with concentrated NH_4OH (to pH 9.5) and extracted with dichloromethane (3 × 15 mL). The organic extract was dried ($MgSO_4$), filtered, and concentrated to afford 480 mg (63.4%) of **20a** as the free base, mp 113–115 °C; mp of **20a**·HCl 250–252 °C dec. CIMS: 176 (M + 1 − H_2O, 100), 194 (M + 1). ^1H NMR: δ 7.16 (m, 2, ArH), 6.64 (dd, 1, ArH, J = 7.7, 1.7 Hz), 4.52 (d, 1, *cis*-CH, J_{cis} = 3.7 Hz; the *trans*-amino alcohol comprised 25% of the mixture, J_{trans} = 8.2 Hz), 3.80 (s, 3, OCH_3), 3.08 (m, 1, CH), 2.73 (m, 2, CH_2), 2.10 (s, 2, NH, OH), 1.86 (m, 2, CH_2). Anal. ($C_{11}H_{16}ClNO_2$) H, N; C: calcd, 57.52; found, 56.48. Exact mass: calcd, 193.1103; found, 193.1108.

***trans*-2-Amino-7-methoxy-1,2,3,4-tetrahydronaphthalen-1-ol, 20b.** Bromo ketone **18b** (3.82 g, 14.9 mmol) was converted to amino alcohol **20b** using the same method as for **20a**, yielding 2.00 g (69.4%) of the free base, mp of **20b**·HCl (from ethanol/ether) 238–240 °C (lit.[32] mp for *cis*-HCl salt 239 °C). ^1H NMR: δ 6.96 (m, 3, ArH), 4.32 (d, 1, CH, J = 9 Hz), 3.79 (s, 3, OCH_3), 2.81 (m, 3, CH_2, CH), 2.11 (s, 2, NH, OH), 1.87 (m, 2, CH_2).

***trans*-2-(Benzylamino)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ol, 21a.** A solution of amino alcohol **20a** (0.45 g, 2.33 mmol) and benzaldehyde (0.28 g, 2.6 mmol) in ethanol (5 mL) was heated at reflux under a nitrogen atmosphere for 4 h. After cooling to 25 °C, sodium borohydride (67 mg, 1.7 mmol) was added. Stirring was continued for 16 h, at which time the crude product had spontaneously crystallized. To ensure complete crystallization, water (20 mL) was added to the reaction mixture. After standing for 2 h at 4 °C, the product was filtered and vacuum dried to provide 0.52 g (78.8%) of **21a**, mp 81–84 °C. CIMS: 266 (M + 1 − H_2O, 100), 284 (M + 1). ^1H NMR: δ 7.31 (m, 5, ArH), 7.12 (m, 2, ArH), 6.70 (dd, 1, ArH), 4.67 (d, 1, *cis*-CH, J = 4.84 Hz), 4.39 (d, 1, *trans*-CH, J = 6.3 Hz), 3.89 (s, 2, CH_2), 3.80 (s, 3, OCH_3), 3.09–2.54 (m, 3, CH_2, CH), 2.31 (m, 3, C_3Ha, NH, OH), 1.78 (m, 1, C_3Hb). Anal. ($C_{18}H_{21}NO_2$) C, H, N.

***trans*-2-(Benzylamino)-7-methoxy-1,2,3,4-tetrahydronaphthalen-1-ol, 21b.** Amino alcohol **20b** (0.3 g, 1.55 mmol) and benzaldehyde (0.18 g, 1.7 mmol) were converted to **21b** using the same procedure as for **21a**, yielding 0.376 g (85.6%), mp 119–120 °C. CIMS: 266 (M + 1 − H_2O, 100), 284 (M + 1). ^1H NMR δ 7.31 (m, 5, ArH), 7.10–6.76 (m, 3, ArH), 4.42 (d, 1, CH, J = 8.9 Hz), 3.90 (d, 2, CH_2, J = 8.8 Hz), 3.78 (s, 3, OCH_3), 2.79 (m, 2, CH_2), 2.20 (m, 3, CH, NH, OH), 1.79–1.27 (m, 2, CH_2). Anal. ($C_{18}H_{21}NO_2$) C, H, N.

(±)-*cis*-9-Methoxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine Hydrochloride, 22a. $AlCl_3$ (0.5 g, 3.54 mmol) was suspended in 15 mL of dry dichloromethane and stirred 40 min. A solution of *N*-benzylamine **21a** (0.5 g, 1.7 mmol) dissolved in 12.5 mL dichloromethane was then added dropwise over 5 min. The mixture was stirred at reflux under a nitrogen atmosphere for 3 h and then poured onto 100 g of ice. The mixture was adjusted to pH 9.5 with concentrated NH_4OH. The layers were separated, and the aqueous phase was carefully extracted with ethyl acetate (2 × 50 mL). The combined organic phase was washed with brine and then dried ($MgSO_4$). After filtration and removal of the solvent, the crude base was converted to the HCl salt and recrystallized from ethanol, yielding 380 mg (71%) of **22a**·HCl, mp 243–246 °C. CIMS: 266 (M + 1, 100). ^1H NMR: δ 7.24–7.00 (m, 5, ArH), 6.76 (m, 2, ArH), 4.07 (s, 2, CH_2), 3.88 (d, 1, CH, J = 3.55 Hz), 3.81 (s, 3, OCH_3), 3.50 (m, 1, CH), 2.76 (m, 2, CH_2), 2.00–1.75 (m, 2, CH_2), 1.71 (s, 1, NH). Anal. ($C_{18}H_{20}ClNO$) C, H, N.

(±)-*cis*-11-Methoxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine Hydrochloride, 22b. *Via* the same procedure as outlined for **22a**, *N*-benzylamine **21b** (0.3 g, 1.1 mmol) was treated with $AlCl_3$ (450 mg, 3.1 mmol). The HCl salt of the product was recrystallized from ethanol/ether to yield 248 mg (77.5%) of **22b**·HCl, mp 236–238 °C dec. CIMS: 266 (M + 1, 100). ^1H NMR: δ 7.11 (m, 4, ArH), 6.78–6.57 (m, 3, ArH), 4.08 (m, 2, CH_2), 3.87 (d, 1, CH, J = 4.5 Hz), 3.69 (s, 3, OCH_3), 3.54 (m, 1, CH), 2.79 (m, 2, CH_2), 2.20 (m, 1, C_7-Ha), 2.04 (s, 1, NH), 1.70 (m, 1, C_7Hb). Anal. ($C_{18}H_{20}ClNO$) C, H, N.

(±)-*cis*-9-Hydroxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine Hydrobromide, 10a. A solution of **22a**·HCl (51 mg, 0.17 mmol) in 1 mL of 48% HBr was heated at reflux for 2 h, under a nitrogen atmosphere. After removal of the solvent, the residue was recrystallized from ethanol/ether to

yield 33 mg (58.4%) of **10a**·HBr, mp 273–276 °C. ^{1}H NMR (D_2O): δ 7.35–7.04 (m, 5, ArH), 6.86–6.71 (m, 2, ArH), 4.72 (m, 1, CH), 4.36 (s, 2, CH_2), 4.12 (m, 1, CH), 2.76 (m, 2, CH_2), 2.21 (m, 1, C_7Ha), 1.90 (m, 1, C_7Hb). Anal. ($C_{17}H_{18}BrNO$) C, H, N.

(±)-*cis*-11-Hydroxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine Hydrobromide, 10b. A solution of **22b**·HCl (123 mg, 0.41 mmol) in 3 mL of 48% HBr was heated at reflux for 1 h, under a nitrogen atmosphere. After removal of the solvent, the residue was recrystallized from 90% ethanol to yield 111 mg (81.8%) of **10b**·HBr, mp 300–303 °C. CIMS: 252 (M + 1, 100). ^{1}H NMR: δ 7.15 (m, 5, ArH), 6.60 (dd, 1, ArH, J = 2, 9.1 Hz), 6.43 (d, 1, ArH, J = 2 Hz), 4.01 (m, 2, CH_2), 3.78 (d, 1, CH, J = 3.35 Hz), 3.47 (m, 1, CH), 2.75 (m, 2, CH_2), 2.23 (br s, 1, NH), 1.64 (m, 2, CH_2). Anal. ($C_{17}H_{18}BrNO$) C, H, N.

Pharmacology. Materials. SCH 23390 was a gift from Schering Corp. (Bloomfield, NJ) or, as with SK&F 38393 (**1**), was purchased from Research Biochemicals Inc. (Natick, MA). Dopamine and chlorpromazine were purchased from Sigma Chemical Co. (St. Louis, MO). Spiperone and ketanserin were gifts from Janssen Pharmaceutica (Beerse, Belgium, and New Brunswick, NJ). Dihydrexidine (**8a**) (DHX) was synthesized as described previously.[22] HEPES buffer was purchased from Research Organics, Inc. (Cleveland, OH). [^{3}H]Spiperone was purchased from Amersham Corp. (Arlington Heights, IL), and [^{3}H]-**2** was synthesized as described previously by Wyrick *et al.*[45] [α-^{32}P]ATP was supplied by New England Nuclear (Boston, MA). All other compounds were purchased from commercial sources, primarily Sigma Chemical Co. (St. Louis, MO).

Tissue Preparation. Male Sprague–Dawley rats (Charles River Breeding Laboratories, Raleigh, NC), weighing 200–400 g, were decapitated, and the brains were quickly removed and placed into ice cold saline. After a brief chilling period, brains were sliced into 1.2-mm coronal slices with the aid of a dissecting block similar to that described by Heffner *et al.*[46] The striatum was dissected from two slices containing the majority of this region, and the tissue was either used immediately or stored at −70 °C until the day of the assay.

D_1 Radioreceptor Assay. After dissection, individual rat striata were homogenized by seven manual strokes in a Wheaton Teflon–glass homogenizer with ice cold 50 mM HEPES buffer with 4.0 mM $MgCl_2$ at pH 7.4. Tissue was centrifuged at 27000*g* for 10 min (Sorvall RC-5B/SS-34 rotor; DuPont, Wilmington, DE), the supernatant was discarded, and the pellet was homogenized (five strokes), resuspended in ice cold buffer, and centrifuged again. The final pellet was suspended at a concentration of approximately 2 mg wet weight/mL.

The assay buffer was 50 mM HEPES with 4 mM $MgCl_2$ (pH 7.4). Assay tubes containing a final volume of 1.0 mL were incubated at 37 °C for 15 min. Nonspecific binding of [^{3}H]-SK&F 38393 was defined by adding unlabeled 1 μM SK&F 38393 (**1**). Incubations were filtered through glass fiber filter mats (Skatron no. 7034) with a 15-mL ice cold buffer wash using a Skatron cell harvester (Skatron Inc., Sterling, VA). Filters were allowed to dry, and 3.0 mL of Scintiverse E (Fischer Scientific) was added. After the mixture was shaken for 30 min, radioactivity was counted on an LKB 1219 betarack liquid scintillation counter. Tissue protein levels were estimated using the Folin reagent method of Lowry *et al.*[47] adapted to a Technicon autoanalyzer I (Terrytown, NY).

D_2 Radioreceptor Assay. The binding procedure and protein analysis were identical to that described above except that [^{3}H]spiperone (*ca.* 0.07 nM, the experimental K_D) was used as the radioligand. Nonspecific binding of [^{3}H]spiperone was defined by adding unlabeled 1 μM chlorpromazine. Ketanserin tartrate (50 nM) was added to mask binding of [^{3}H]spiperone to serotonin receptors.

Dopamine-Sensitive Adenylate Cyclase. The method used separates cAMP from other labeled nucleotides by automated HPLC.[48] Rat striatal tissue was homogenized at 50 mL/g of tissue in 5 mM HEPES buffer (pH 7.5) containing 2 mM EGTA. After eight manual strokes with a Wheaton Teflon–glass homogenizer, an additional 50 mL/g 100 mM HEPES–2 mM EGTA was added and mixed with one additional stroke. A 20-μL aliquot of this tissue homogenate was added to a prepared reaction mixture, yielding a final volume of 100 μL, containing 0.5 mM ATP, [α-^{32}P]ATP (0.5 μCi), 1 mM cAMP, 2 mM $MgCl_2$, 0.7 mM HEPES, 2 μM GTP, 0–100 μM dopamine and/or drug, 10 mM phosphocreatine, and 5 U of creatine phosphokinase. The reaction was initiated by placing the samples in a water bath at 30 °C and terminated 15 min later by addition of 100 μL of 3% sodium dodecyl sulfate (SDS). Proteins and much of the noncyclic nucleotides were precipitated by addition of 300 μL each of 4.5% $ZnSO_4$ and 10% $Ba(OH)_2$ (pH 2.0) to each incubation tube. The samples were centrifuged at 10000*g* for 6 min, and the supernatants were immediately removed and loaded into an ISIS (Isco Inc., Lincoln, NB) autoinjector.

HPLC separations were carried out with a Waters Z-module or RCM 8 × 10 module equipped with a C18, 10-μm cartridge, using a mobile phase of 150 mM sodium acetate–20% MeOH, adjusted to pH 5.0 with concentrated HCl prior to filtration (0.2 μm), and degassing under vacuum. A flow rate of about 4 mL/min was used for separation. The autoinjector was programmed for a 2-min injection interval, with a rinse between samples. A UV detector equipped for 254-nm detection triggered collection of the cAMP fractions *via* a FOXY fraction collector (ISCO, Inc., Omaha, NB) with a three-way diversion valve. Unlabeled cAMP added to the samples provided the source of UV absorbance and served as an internal standard. Peak areas were quantified using a Nelson analytical chromatography data system, and each fraction's radioactivity was determined with an LKB liquid scintillation counter. Percent stimulation was calculated from peak areas and radioactivity. This separation procedure is a major improvement over previously used techniques and was particularly useful when dealing with very small amounts of tissue.

Data Analysis. The data analysis for the receptor binding study involved capturing the raw data from the receptor competition binding using customized Microsoft Excel spreadsheets to calculate specific binding and provide initial graphical presentation. Specific binding was calculated by subtracting the nonspecific binding from the total binding obtained at each radioligand concentration. Preliminary estimates of affinity were made using linear-regressed Hill plots. The data were then analyzed by nonlinear regression using algorithms in the InPlot program (Graphpad, Inc., San Diego, CA) to determine IC_{50} values and Hill coefficients (n_H). In all cases, analysis of the residuals indicated an excellent fit; r values were above 0.96. Adenylate cyclase assays also were analyzed using customized Microsoft Excel spreadsheets. The radioactivity in the cAMP peak was corrected for recovery *via* the UV absorbance signal of the peak integrated by the Nelson Turbochrom III software. The corrected amount of radioactivity was then subtracted from the basal (*i.e.*, tissue only) values. Percent stimulation was calculated on the basis of the increase in cAMP synthesis caused by dopamine.

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References

(1) Setler, P. E.; Sarau, H. M.; Zirkle, C. L.; Saunders, H. L. The Central Effects of a Novel Dopamine Agonist. *Eur. J. Pharmacol.* **1978**, *50*, 419–430.
(2) Pendleton, R. G.; Samler, L.; Kaiser, C.; Ridley, P. T. Studies on Renal Dopamine Receptors with a New Agonist. *Eur. J. Pharmacol.* **1978**, *51*, 19–28.
(3) Iorio, L. C.; Barnett, A.; Leitz, F. H.; Houser, V. P.; Korduba, C. A. SCH 23390, a Potential Benzazepine Antipsychotic with Unique Interactions on Dopaminergic Systems. *J. Pharmacol. Exp. Ther.* **1983**, *226*, 462–468.
(4) Hyttel, J. SCH 23390 – The First Selective Dopamine D-1 Antagonist. *Eur. J. Pharmacol.* **1983**, *91*, 153–154.
(5) Kilpatrick, G. J.; Jenner, P.; Marsden, C. D. [^{3}H]SCH 23390 Identifies D-1 Binding Sites in Rat Striatum and Other Brain Areas. *J. Pharm. Pharmacol.* **1986**, *38*, 907–912.

(6) O'Boyle, K. M.; Waddington, J. L. [3H]SCH 23390 Binding to Human Putamen D-1 Dopamine Receptors: Stereochemical and Structure-Affinity Relationships Among 1-Phenyl-1H-3-benzazepine Derivatives As a Guide to D-1 Receptor Topography. *J. Neurochem.* **1987**, *48*, 1039–1042.
(7) Clark, D.; White, F. J.; Review: D1 Dopamine Receptor– The Search for a Function: A Critical Evaluation of the D1/D2 Dopamine Receptor Classification and its Functional Implications. *Synapse (N. Y.)* **1987**, *1*, 347–388.
(8) Waddington, J. L.; O'Boyle, K. M. Drugs Acting on Brain Dopamine Receptors: A Conceptual Re-evaluation Five Years After the First Selective D-1 Antagonist. *Pharmacol. Ther.* **1989**, *43*, 1–52.
(9) Berger, J. G.; Chang, W. K.; 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 Ligand (5R)-8-Chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1H-3-benzazepin-7-ol. *J. Med. Chem.* **1989**, *32*, 1913–1921.
(10) Chipkin, R. E.; Iorio, L. C.; Coffin, V. L.; McQuade, R. D.; Berger, J. G.; Barnett, A. Pharmacological Profile of SCH39166: A Dopamine D1 Selective Benzonaphthazepine with Potential Antipsychotic Activity. *J. Pharmacol. Exp. Ther.* **1988**, *247*, 1093–1102.
(11) Costall, B.; Kelly, D. M.; Naylor, R. J. Nomifensine: A Potent Dopaminergic Agonist of Antiparkinson Potential. *Psychopharmacologia* **1975**, *41*, 153–164.
(12) Costall, B.; Naylor, R. J. Studies on the Dopamine Agonist Properties of 8-Amino-2-methyl-4-(3,4-dihydroxyphenyl)-1,2,3,4-tetrahydroisoquinoline, a Derivative of Nomifensine. *J. Pharm. Pharmacol.* **1978**, *30*, 514–516.
(13) Jacob, J. N.; Nichols, D. E.; Kohli, J. D.; Glock, D. Dopamine Agonist Properties of N-Alkyl-4-(3,4-dihydroxyphenyl)-1,2,3,4-tetrahydroisoquinolines. *J. Med. Chem.* **1981**, *24*, 1013–1015.
(14) Riggs, R. M.; Nichols, D. E.; Foreman, M. M.; Truex, L. L.; Glock, D.; Kohli, J. D. Specific Dopamine D-1 and DA_1 Properties of 4-(Mono- and -Dihydroxyphenyl)-1,2,3,4-tetrahydroisoquinoline and Its Tetrahydrothieno[2,3-c]pyridine Analogue. *J. Med. Chem.* **1987**, *30*, 1454–1458.
(15) Brenner, L. M. (SmithKline Corp.) Renal Vasodilating 3,4-Dihydroxyphenyltetrahydrothieno-pyridines U.S. Patent 4,282,227, 1981.
(16) Markstein, R.; Seiler, M. P.; Vigouret, J. M.; Urwyler, S.; Enz, A.; Dixon, K. Pharmacologic Properties of CY 208–243, A Novel D_1 Agonist. *Neurol. Neurobiol.* **1988**, *42B*, 59–64.
(17) Seiler, M. P.; Hagenbach, A.; Wüthrich, H.-J.; Markstein, R. trans-Hexahydroindolo[4,3-ab]phenanthridines ("Benzergolines"), the First Structural Class of Potent and Selective Dopamine D_1 Receptor Agonists Lacking a Catechol Group. *J. Med. Chem.* **1991**, *34*, 303–307.
(18) Kebabian, J. W.; Briggs, C.; Britton, D. R.; Asin, K.; DeNinno, M.; MacKenzie, R. G.; McKelvy, J. F.; Schoenleber, R. A68930: A Potent and Specific Agonist for the D-1 Dopamine Receptor. *Am. J. Hypertens.* **1990**, *3*, 40S–42S.
(19) DeNinno, M. P.; Schoenleber, R.; Asin, K. E.; MacKenzie, R.; Kebabian, J. W. (1*R*,3*S*)-1-(Aminomethyl)-3,4-dihydro-5,6-dihydroxy-3-phenyl-1*H*-2-benzopyran: A Potent and Selective D_1 Agonist. *J. Med. Chem.* **1990**, *33*, 2948–2950.
(20) DeNinno, M. P.; Schoenleber, R.; Perner, R. J.; Lijewski, L.; Asin, K. E.; Britton, D. R.; MacKenzie, R.; Kebabian, J. W. Synthesis and Dopaminergic Activity of 3-Substituted 1-(Aminomethyl)-3,4-dihydro-5,6-dihydroxy-1*H*-2-benzopyrans: Characterization of an Auxiliary Binding Region in the D_1 Receptor. *J. Med. Chem.* **1991**, *34*, 2561–2569.
(21) Lovenberg, T. M.; Brewster, W. K.; Mottola, D. M.; Lee, R. C.; Riggs, R. M.; Nichols, D. E.; Lewis, M. H.; Mailman, R. B. Dihydrexidine, a Novel Selective High Potency Full Dopamine D-1 Receptor Agonist. *Eur. J. Pharmacol.* **1989**, *166*, 111–113.
(22) Brewster, W. K.; Nichols, D. E.; Riggs, R. M.; Mottola, D. M.; Lovenberg, T. W.; Lewis, M. H.; Mailman, R. B. *Trans*-10,11-Dihydroxy-5,6,6a,7,8,12b-hexahydrobenzo[a]phenanthridine: A Highly Potent Selective Dopamine D_1 Full Agonist. *J. Med. Chem.* **1990**, *33*, 1756–1764.
(23) Darney, K. J., Jr.; Lewis, M. H.; Brewster, W. K.; Nichols, D. E.; Mailman, R. B. Behavioral Effects in the Rat of Dihydrexidine, A High-Potency, Full-Efficacy D_1 Dopamine Receptor Agonist. *Neuropsychopharmacology* **1991**, *5*, 187–195.
(24) Mottola, D. M.; Brewster, W. K.; Cook, L. L.; Nichols, D. E.; Mailman, R. B. Dihydrexidine, a Novel Full Efficacy D1 Dopamine Receptor Agonist. *J. Pharmacol. Exp. Ther.* **1992**, *262*, 383–393.
(25) Taylor, J. R.; Lawrence, M. S.; Redmond, D. E., Jr.; Elsworth, J. D.; Roth, R. H.; Nichols, D. E.; Mailman, R. B. Dihydrexidine, a full dopamine D_1 agonist, reduces MPTP-induced parkinsonism in monkeys. *Eur. J. Pharmacol.* **1991**, *199*, 389–391.
(26) Cannon, J. G. Dopamine Congeners Derived from the Benzo[f]-quinoline Ring. *Adv. Biosci. (Oxford)* **1979**, *20*, 87–94.
(27) Wei, C.-C.; Teitel, S. Synthesis of a Benzo[a]phenanthridine Isomeric with Apomorphine. *Heterocycles* **1977**, *8*, 97–101.
(28) McDermed, J. D.; Freeman, H. S.; Ferris, R. M. Enantioselectivity in the Binding of (+) and (−)-2-Amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene and Related Agonists to Dopamine Receptors. In *Catecholamines: Basic and Clinical Frontiers*; Usdin, E., Kopin, I. J., Barchas, J., Eds.; Pergamon Press: New York, 1979; Vol. 1, pp 568–570.
(29) Seiler, M. P.; Markstein, R. Further Characterization of Structural Requirements for Agonists at the Striatal Dopamine D-1 Receptor Studies with a Series of Monohydroxyaminotetralins on Dopamine-Sensitive Adenylate Cyclase and a Comparison with Dopamine Receptor Binding. *Mol. Pharmacol.* **1982**, *22*, 281–289.
(30) Cornforth, J. W.; Robinson, R. Experiments on the Synthesis of Substances Related to the Sterols. Part XLVIII. Synthesis of a Tricyclic Degradation Product of Cholesterol. *J. Chem. Soc.* **1949**, 1855–1865.
(31) Borch, R. F.; Bernstein, M. D.; Durst, H. D. The Cyanohydridoborate Anion as a Selective Reducing Agent. *J. Am. Chem. Soc.* **1971**, *93*, 2897–2904.
(32) Chiemprasert, v. T.; Rimek, H.-J.; Zymalkowski, F. Zur stereospezifischen Synthese von cis-und trans-Aminotetralolen. (Stereospecific Synthesis of *cis*- and *trans*-Aminotetralols.) *Justus Liebigs Ann. Chem.* **1965**, *685*, 141–148.
(33) Thrift, R. I. Derivatives of 2-Aminotetralin. *J. Chem. Soc. C* **1967**, 288–293.
(34) Bowman, R. E.; Evans, D. D.; Guyett, J.; Nagy, H.; Weale, J.; Weyell, D. J. 1,3,4,5-Tetrahydrobenz[cd]indoles and Related Compounds. Part III. *J. Chem. Soc., Perkin Trans. I* **1973**, 438–442.
(35) Mottola, D. M.; Cook, L. L.; Jones, S. R.; Booth, R. G.; Nichols, D. E.; Mailman, R. B. Dihydrexidine, a selective dopamine receptor agonist that may discriminate postsynaptic D_2 receptors. *Soc. Neurosci. Abstr.* **1991**, *17*, 818.
(36) Nichols, N. F.; Schreur, P. J. K. D.; Smith, M. W.; Hoffman, W. E.; Nichols, D. E.; Piercey, M. F. Activation of postsynaptic but not presynaptic receptors by dihydrexidine, a potent D1 and D2 receptor ligand. *Soc. Neurosci. Abstr.* **1992**, *18*, 1170.
(37) Charifson, P. S.; Bowen, J. P.; Wyrick, S. D.; Hoffman, A. J.; Cory, M.; McPhail, A. T.; Mailman, R. B. Conformational analysis and molecular modeling of 1-phenyl-, 4-phenyl-, and 1-benzyl-1,2,3,4-tetrahydroisoquinolines as D_1 dopamine receptor ligands. *J. Med. Chem.* **1989**, *32*, 2050–2058.
(38) Cannon, J. G.; Suarez-Gutierrez, C.; Lee, T.; Long, J. P.; Costall, B.; Fortune, D. H.; Naylor, R. J. Rigid Congeners of Dopamine Based on Octahydrobenzo[f]quinoline: Peripheral and Central Effects. *J. Med. Chem.* **1979**, *22*, 341–347.
(39) Cannon, J. G.; Lee, T.; Goldman, H. D.; Long, J. P.; Flynn, J. R.; Verimer, T.; Costall, B.; Naylor, R. J. Congeners of the β Conformer of Dopamine Derived from cis- and trans-Octahydrobenzo[f]quinoline and trans-Octahydrobenzo[g]quinoline. *J. Med. Chem.* **1980**, *23*, 1–5.
(40) Tomaszewski, Z., Nichols, D. E. Unpublished results, 1990.
(41) Craig, J. C.; Torkelson, S. M.; Findell, P. R.; Weiner, R. I. Synthesis and Dopaminergic Activity of 2-Substituted Octahydrobenzo[f]quinolines. *J. Med. Chem.* **1989**, *32*, 961–968.
(42) Catalytic hydrogenation of the other chromatography fractions (overbrominated byproducts) returns some dehalogenated starting material. Thus, the yield can be improved to between 30% and 40%, based on recovered starting material.
(43) Hach, V.; Protiva, M. Synthesis in the Estrogenic Hormone Group. XVI. A Synthesis of 1,4-hydrindandione. *Chem. Listy* **1957**, *51*, 2099–2107.
(44) Mosettig, E.; May, E. L. Tetrahydroisoquinolino Alcohols Derived from Tetrahydronaphthalene. *J. Org. Chem.* **1940**, *5*, 528–543.
(45) Wyrick, S. D.; McDougald, D. L.; Mailman, R. B. Multiple Tritium Labeling of (+)-7-Chloro-8-hydroxy-1-phenyl-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (SCH23390). *J. Labelled Compd. Radiopharm.* **1986**, *23*, 685–692.
(46) Heffner, T. G.; Hartman, J. A.; Seiden, L. S. A rapid method for the regional dissection of the rat brain. *Pharmacol. Biochem. Behav.* **1980**, *13*, 453–456.
(47) Lowry, O. H.; Rosebrough, N. J.; Farr, A. L.; Randall, R. J. Protein Measurement with the Folin Phenol Reagent. *J. Biol. Chem.* **1951**, *193*, 265–275.
(48) Schulz, D. W.; Mailman, R. B. An Improved Automated Adenylate Cyclase Assay Utilizing Preparative HPLC: Effects of Phosphodiesterase Inhibitors. *J. Neurochem.* **1984**, *42*, 764–774.

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