Synthesis and Biological Evaluation of a Series of Substituted Benzo[a]phenanthridines as Agonists at D_1 and D_2 Dopamine Receptors

Timm A. Knoerzer, Val J. Watts,† David E. Nichols,* and Richard B. Mailman†

Department of Medicinal Chemistry and Pharmacognosy, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, Indiana 47907

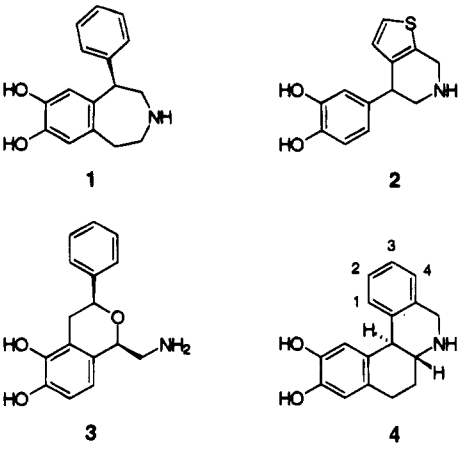
Received April 10, 1995®

Dihydrexidine [**4**; (±)-*trans*-10,11-dihydroxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine (DHX)], the first high-affinity full D_1 agonist, also is known to have significant D_2 activity. The present work reports the synthesis and pharmacological activity of a series of analogs substituted in the pendent phenyl ring (i.e., 2-, 3-, or 4-position). (±)-*trans*-2-Methyl-10,11-dihydroxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine (**5**) was a high-affinity D_1 agonist, having approximately 4-fold greater D_1 vs D_2 selectivity than DHX itself. All of the analogs containing a methyl or ethyl (but not a phenyl) substituent at the 2-, 3-, or 4-position had a pharmacological profile similar to that of the lead compound DHX (**4**). Each analog was found to be a high-affinity full agonist with moderate selectivity for the D_1 receptor. It is apparent from these results that the D_1 receptor can tolerate small substituents at the 2-, 3-, and 4-positions of the pendent phenyl ring. On the basis of earlier studies showing that *N*-alkylation increases D_2 selectivity, the 3-methyl *N*-*n*-propyl and 4-methyl *N*-*n*-propyl compounds **11** and **13** were synthesized. While these analogs exhibited much higher affinity for the D_2 receptor, surprisingly 4-methyl-*N*-propyl-DHX (**13**) exhibited high affinity for both the D_1 and D_2 receptors. It was subsequently established that this compound is a selective D_3 ligand (110-fold selectivity for the D_3 over D_2 receptor). The results from these studies demonstrate that several of the hexahydrobenzo[*a*]phenanthridine derivatives are agonists with high intrinsic activity that may serve as powerful tools to explore the structural features that determine affinity and selectivity (relative to the D_2 receptor) of drugs for D_1 receptors.

Introduction

Dopamine receptors were originally classified as D_1 and D_2 based on pharmacological and functional evidence.[1] D_1 receptors preferentially recognize the phenyltetrahydrobenzazepines and stimulate the enzyme adenylate cyclase, whereas D_2 receptors recognize the butyrophenones and benzamides and are coupled negatively (or not at all) to adenylate cyclase. Since that time, five genes coding for subtypes of dopamine receptors have been cloned, D_1, D_2, D_3, D_4, and D_5 (see refs 2 and 3 for reviews of molecular nomenclature). The traditional classification, however, remains useful, with the D_1-like class comprising the D_1 (D_{1A}) and D_5 (D_{1B}) receptors, whereas the D_2-like class consists of the D_2, D_3, and D_4 receptors.

Until the late 1980s, the primary ligands that were used as probes for the D_1 receptor were molecules from a single chemical class, the phenyltetrahydrobenzazepines such as the partial agonist SKF38393 (**1**). More recently, one or more members of several other types have been reported to be full D_1 agonists in the rat striatum. These structural classes include the phenyltetrahydrobenzazepines,[4] thienopyridines (e.g., **2**[5,6]), 3-substituted (aminomethyl)isochromans (e.g., **3**[7]), and, from our laboratories, the hexahydrobenzo[*a*]phenanthridines, the prototype of which is dihydrexidine (**4**).[8,9]



The full agonists from these structural classes share several common molecular features that include (1) a "*meta*" and (2) "*para*" hydroxyl, which comprise the catechol moiety, (3) the basic nitrogen atom, and (4) an accessory ring system. These features have been proposed to represent the pharmacophoric atoms (agonist pharmacophore) for the activation of D_1 dopamine receptors (Mottola et al., in press).

The pendent phenyl ring has been hypothesized to interact with an accessory binding region of the D_1 receptor,[9] imparting high D_1 affinity, for example, as in **4**. Other hydrophobic substituents in addition to a phenyl ring (e.g., adamantyl) also can give high D_1 affinity.[7] In addition, some studies with the phenyltetrahydrobenzazepines suggested that substitutions on the pendent phenyl ring may influence D_1:D_2 selectivity, as well as D_1 intrinsic activity.[4]

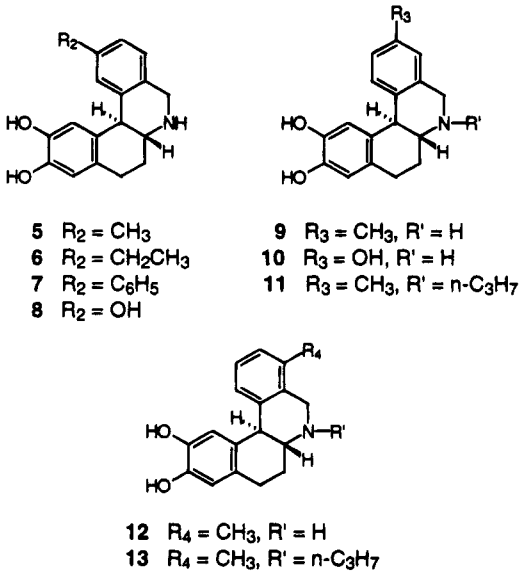
The development of the hexahydrobenzo[*a*]phenan-

* Address correspondence to this author at: Department of Medicinal Chemistry and Pharmacognosy, Robert Heine Pharmacy Building, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, IN 47907. Tel: (317)-494-1451. Fax: (317)-494-6790. Internet: drdave@sage.cc.purdue.edu.

† Brain and Development Research Center, Departments of Psychiatry, Pharmacology, and Medicinal Chemistry, University of North Carolina School of Medicine, Chapel Hill, NC 27599-7250.

® Abstract published in *Advance ACS Abstracts,* July 15, 1995.

0022-2623/95/1838-3062$09.00/0



5 $R_2 = CH_3$
6 $R_2 = CH_2CH_3$
7 $R_2 = C_6H_5$
8 $R_2 = OH$

9 $R_3 = CH_3$, R' = H
10 $R_3 = OH$, R' = H
11 $R_3 = CH_3$, R' = n-C_3H_7

12 $R_4 = CH_3$, R' = H
13 $R_4 = CH_3$, R' = n-C_3H_7

Figure 1. Structures of substituted hexahydrobenzo[*a*]-phenanthridines studied in this report.

thridines such as **4** was based upon creation of a molecule that was a hybrid between the aminotetralins and the 4-phenyltetrahydroisoquinolines.[9] The resulting structure is unique from other D_1 agonists because the accessory ring system is tethered, making the molecule relatively rigid. Molecular modeling studies of the parent compound **4** have shown that it has a limited number of low-energy conformations, in all of which the aromatic rings are held in a relatively coplanar arrangement (Mottola et al., in press). Thus, unlike the other high-affinity, high-intrinsic activity D_1 agonists, **4** provides a semirigid template with which to examine the effects of pendent phenyl ring substitutions on D_1 receptor affinity, selectivity, and intrinsic activity.

The present study examined the effects of several substitutions at the 2-, 3-, or 4-position of **4** (i.e., in the pendent phenyl ring) and also 3- and 4-substituents in combination with *N*-*n*-propyl substitution (Figure 1). In the first series of experiments, we examined how these substituents influence affinity and selectivity for D_1 and D_2 receptors. We then studied the effects of these pendent phenyl ring substitutions on the intrinsic activity at D_1 receptors by measuring activation of dopamine sensitive adenylate cyclase in the rat striatum. The results from these studies demonstrate that several of these pendent phenyl ring-substituted hexahydrobenzo[*a*]phenanthridines are high-affinity D_1 agonists with high intrinsic activity and, as such, are powerful tools to explore the structural features that affect the pharmacological properties of these ligands.

Chemistry

The methodology employed for the syntheses of the various pendent phenyl ring-substituted analogs of dihydrexidine (**4**) (Scheme 1) is based upon the approach originally utilized by Wei and Teitel.[10] The critical transformation in this series of molecules involves a stereoselective photochemical cyclization, a method exploited by Ninomiya and co-workers.[11]

The starting material for the syntheses of all of the target molecules **5**–**13** is 6,7-dimethoxy-β-tetralone. The initial step involves the conversion of the β-tetralone to the crucial enamide intermediates **16**–**22**. The ketone was first condensed with benzylamine, and the crude enamine that remained was directly used in the next reaction. The *N*-benzyl enamine was then acylated utilizing the appropriately substituted benzoyl chloride. In most cases, the enamide products were crystalline materials and could be purified by recrystallization from diethyl ether. Compounds **18** and **19** were oils, however, and were purified using flash column chromatography, requiring two passes through the column in order to obtain acceptable purity.

Once purified, solutions of the enamides in THF were photocyclized to the corresponding lactams **23**–**29** according to the Ninomiya procedure noted earlier.[11] Fastest and most efficient reactions occurred when the concentration of these enamide solutions did not exceed 5 mM. The reaction was complete when TLC analysis indicated that all of the starting material had been consumed. The length of the reaction varied, however, according to the substrate. For example, reaction of the 2-methyl enamide **16** was complete in 4 h, while the 4-phenyl derivative **19** required nearly 10 h. These variations in reaction time have a significant effect on overall yield. The longer the reaction time, the greater the formation of undesirable side products. As we have reported previously, this reaction gives *trans* fusion between the B/C rings, with a coupling constant between H6a and H12b that is typically about 11 Hz, whereas for *cis* B/C ring-fused compounds, this coupling constant is on the order of 5 Hz.[9]

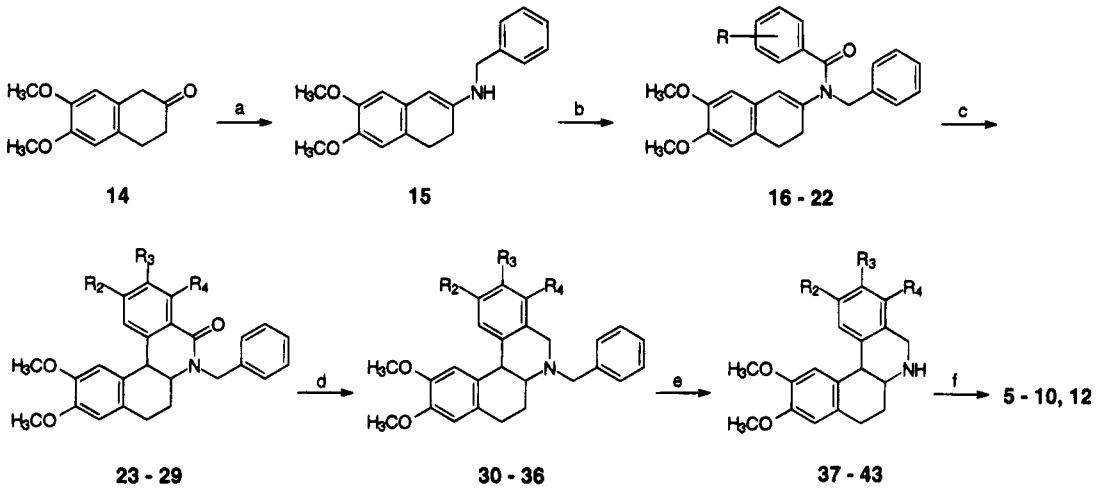
The lactams were then reduced to the *N*-benzylamines **30**–**36** with diborane in dry THF (Scheme 1), and the resulting amines were isolated as their crystalline HCl salts in excess of 75% yield. The *N*-benzyl protecting group was readily removed by catalytic hydrogenolysis. Finally, the *O*,*O*-dimethyl ethers **37**–**43** were cleaved using BBr_3 in dichloromethane to afford the target molecules **5**–**10** and **12**. All of the final compounds were converted to their HCl salts and crystallized from either methanol or methanol/ethyl acetate.

The *O*,*O*-dimethyl-*N*-*n*-propyl derivatives (**44** and **45**) of **11** and **13** were prepared by treatment of the secondary amines **38** and **39** with propionaldehyde and $NaCNBH_3$, as shown in Scheme 2. These two compounds were then *O*,*O*-demethylated with BBr_3 in CH_2Cl_2 to afford the tertiary catecholamines **11** and **13** that were also converted to their HCl salts and crystallized from methanol/ethyl acetate.

Results

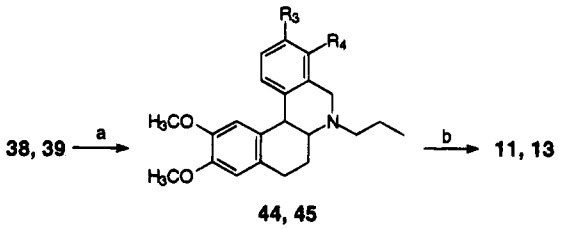
The results of the competition studies for test compounds are displayed in Table 1. Dihydrexidine (**4**) exhibited about 10-fold selectivity for D_1 versus D_2 receptors, as has been reported previously.[9] Similarly the 2-hydroxy-, 2-methyl-, and 2-ethyl-substituted analogs had similar D_1 receptor selectivity, whereas 2-phenyl-DHX (**7**) had markedly lower D_1 affinity (actually having 2-fold selectivity for the D_2 receptor). D_1 receptor affinity (relative to that of **4**) appeared to correlate with the size of the substituent at the 2-position (i.e., H > methyl > ethyl ≫ phenyl). The 3-hydroxy- or 3-methyl-substituted compounds had effects similar to the 2-substituted analogs, having only modest differences in D_1 dopamine receptor binding affinity, with the methyl substitution being 2-fold more potent than the hydroxy-substituted analog. In contrast to the 2-substitutions, substituents at the 3-position resulted in a decrease of

Scheme 1[a]



[a] Conditions: (a) benzylamine, toluene, reflux; (b) methyl-substituted benzoyl chloride, Et_3N, CH_2Cl_2, 8 h; (c) $h\nu$, THF; (d) BH_3, THF, then MeOH; (e) H_2/Pd, 95% EtOH; (f) BBr_3, CH_2Cl_2, then MeOH.

Scheme 2[a]



[a] Conditions: (a) CH_3CH_2CHO, $NaCNBH_3$; (b) BBr_3, CH_2Cl_2, then MeOH.

D_1:D_2 selectivity. Finally, the 3-methyl *N*-propyl compound **11** had affinity and selectivity similar to that of *N*-propyl-**4**, whereas the 4-methyl *N*-propyl analog **13** had increased affinity for *both* D_1 and D_2 receptors relative to that of *N*-propyl-**4**.

Adenylate Cyclase Activity in Rat Striatum. We examined the ability of these analogs to stimulate the enzyme adenylate cyclase in rat striatal homogenates as a measure of agonist intrinsic efficacy (relative to dopamine) (Table 1). Dihydrexidine (**4**) was of similar intrinsic efficacy to dopamine at stimulating adenylate cyclase in the rat striatum, whereas its *N*-propyl derivative had a significantly lower efficacy (<50%).[9] The 2-hydroxy-, 2-methyl-, and 2-ethyl-substituted analogs showed high intrinsic activity and had a rank order of potency similar to their binding affinities. In contrast, 2-phenyl-DHX (**7**) was not able to stimulate adenylate cyclase to the same extent as DA, even at very high concentrations (100 μM). Similar to the 2-substituted analogs, both the 3-methyl and 3-hydroxy compounds **9** and **10**, respectively, had high intrinsic activity and were of potency similar to **4**. In contrast, the 3-methyl *N*-propyl **11** was a very weak partial agonist. In addition, both the 4-methyl **12** and 4-methyl *N*-propyl **13** were potent D_1 agonists with high intrinsic activity (>80%).

Discussion

In our efforts to examine the structural requirements for D_1 receptor activation, we have developed a series of analogs of **4** with pendent phenyl ring substitutions. The present studies describe the D_1 dopamine receptor pharmacological properties of these novel hexahydrobenzo[*a*]phenanthridines. We assessed both the binding properties and the functional activity of these ligands at D_1 and D_2 dopamine receptors in the rat striatum.

As was noted in the Introduction, an "accessory" hydrophobic group has been hypothesized to be important for both the kinetic and functional properties of ligand interaction with D_1 receptors. In the present study we took advantage of the relatively rigid nature of the hexahydrobenzo[*a*]phenanthridines to characterize, at least in part, how changes in this accessory ring system (a phenyl ring in the present study) affected ligand interaction with the D_1 dopamine receptor. Previously, substitutions on the accessory ring of the phenyltetrahydrobenzazepines have resulted in ligands with altered D_1 affinity and intrinsic activity.[4] DeNinno et al.[7] have demonstrated the presence of a very large tolerable accessory region in the D_1 receptor, thus providing evidence that there was additional available "space" beyond that occupied by the pendent phenyl ring system. The conformational flexibility of the pharmacophoric elements (accessory ring, catechol ring, and the nitrogen) of the molecules described in that report, however, makes it difficult to predict where exactly the ligands may be interacting with the accessory binding region. Thus, the present studies represent the beginnings of a stepwise approach to examining D_1 dopamine receptor ligand and accessory binding region interactions.

In the first part of the present studies, we examined the affinity and selectivity of several pendent phenyl-substituted analogs for D_1 and D_2 receptors in the rat striatum. We have previously demonstrated that **4** binds to D_1 receptors with high affinity, and we show here that several of the pendent phenyl ring analogs also bind to D_1-like receptors with high affinity. Although there were only modest effects of small substituents on D_1 receptor affinity, when considered together with their changes in D_2 receptor affinity, these modifications led to compounds with a range of dopamine receptor selectivities. Of particular note is the fact that small 2-substituents had no deleterious effect on D_1 receptor selectivity. Indeed, 2-methyl-DHX (**5**) was the most D_1 selective analog (>30-fold) in the entire series. The results suggest that D_1 affinity is relatively insensitive to the location (e.g., 2-, 3-, or 4-position) of small substituents. These results parallel those of previous

Table 1. Apparent Affinities ($K_{0.5}$) and Receptor Selectivity of **4** and Analogs for Dopamine Receptors in Rat Striatal Homogenates[a]

drug	binding $K_{0.5}$ (nM) D_1	binding $K_{0.5}$ (nM) D_2	D_1:D_2 selectivity	adenylate cyclase activity EC_{50} (nM)	intrinsic activity (% of DA)
4 (DHX)	6.22 ± 1.07	58.1 ± 7.8	9.3	141 ± 35	95 ± 2
N-propyl-**4**	180 ± 10.9	25.7 ± 4.2	0.14	>10^5 [b]	ca. 40[b]
5	8.66 ± 2.78	302 ± 25.8	35	114 ± 16	91 ± 10
6	29.2 ± 2.40	423 ± 69	14.5	610 ± 95	103 ± 6
7	187 ± 43	90.2 ± 11.7	0.5	>10^5	ca. 60
8	18.8 ± 1.8	194 ± 27	10.3	148 ± 60	95 ± 7
9	5.06 ± 1.83	18.0 ± 3.5	3.6	134 ± 30	105 ± 15
10	12.2 ± 2.3	53.6 ± 11.1	4.4	130 ± 32	104 ± 2
11	181 ± 14	29.4 ± 4.8	0.16	>10^5	ca. 20
12	6.58 ± 0.78	18.0 ± 5.2	2.7	151 ± 19	80 ± 5
13	23.4 ± 6.9	9.01 ± 2.29	0.39	333 ± 94	89 ± 5
SKF38393[b]	17 ± 1	>500	>30	100	30–50
SCH23390[b]	0.52	>500	<1000	NA[c]	NA
domperidone[b]	>1000	1.0 ± 0.5	<1000	NA	NA

[a] Adenylate cyclase activity was measured in rat homogenates. The potency (EC_{50}) and intrinsic activity of the test compounds were estimated from dose–response curves. All results are shown as the mean ± SEM for three independent experiments completed in triplicate. [b] Taken from ref 20. [c] NA = not applicable for antagonists.

studies examining similar substitutions on the pendent phenyl ring of the phenyltetrahydrobenzazepines.[4]

These analogs were also tested for functional activity by assessing their ability to stimulate dopamine sensitive adenylate cyclase activity in rat striatum as a measure of intrinsic activity. To this end, all test analogs were able to stimulate adenylate cyclase (to varying degrees) in the rat striatum. Several analogs were of similar intrinsic activity to **4**, whereas *N*-*n*-propyl-**4**, the 3-methyl *N*-propyl **11**, and the 2-phenyl **7** were only partial agonists. These results suggest that *N*-propyl substitution or very large substituents on the pendent phenyl ring reduce efficacy. The offsetting effect of 4-methyl substitution *in combination* with an *N*-propyl (**13**) is quite interesting, however, and may indicate a different binding orientation of the drug in the ligand recognition site. It should be noted that in this striatal membrane preparation, the normal D_2-mediated inhibitory effect of agonists on adenylate cyclase is uncoupled, and these data represent action only at the D_1 receptor.[12]

Several studies have examined the importance of the catechol and the nitrogen atoms for D_1 dopamine receptor binding and activation. Recent site-directed mutagenesis studies of D_1 receptors have been aimed at determining what amino acids of the receptor interact with these atoms. These studies have provided evidence that a conserved aspartic acid residue in the third transmembrane region is critical for interaction with the nitrogen atom and that conserved serine residues in the fifth transmembrane region may be essential for hydrogen bonding to the hydroxy groups.[13,14] No site-directed mutagenesis studies of D_1 receptors have been attempted, however, to identify amino acid residues that are important for the interaction of the pendent phenyl ring (e.g., in compounds of the type studied here) with the D_1 receptor accessory binding region. Such studies, in combination with macromolecular modeling and additional structure–activity relationship studies of D_1 agonists/antagonists, may provide important clues to the molecular basis for D_1 receptor ligand recognition and activation. The present compounds would seem to be especially useful tools in this regard, since within the same structural template relatively simple structural variations can alter dopamine receptor selectivity over a 250-fold range (Table 1). Any valid receptor model must be able to explain these results.

These highly unusual results prompted the evaluation of compound **13** for D_3 activity. Both a 4-methyl substituent and an *N*-*n*-propyl group result in an increase in D_3 receptor affinity and selectivity in comparison with the unsubstituted compound (**4**). When substituted *in combination* (i.e., **13**), however, the result is a ligand with nanomolar affinity and 110-fold selectivity for the D_3 receptor over the D_2 receptor.[15] Therefore, **13** is a selective, high-affinity D_3 ligand that can be used to study this receptor. It should be noted, however, that although the present work and the study by Watts et al.[15] used the same radioligand for the D_2-like receptors (i.e., [^{3}H]spiperone), expressed cloned receptors often differ in their ligand recognition and functional characteristics from those in situ.[16]

In summary, these data demonstrate that the relatively rigid nucleus of the benzo[*a*]phenanthridines provides an important template with which to study structural features for the binding to, and activation of, dopamine D_1 receptors. These studies provide initial information on the size of the accessory binding region of the D_1 dopamine receptor and further strengthen the hypothesis that a large tolerable space exists within the ligand-binding domain of the D_1 dopamine receptor. Additional pendent phenyl ring analogs should provide further insight into the electrostatic and steric interactions of pendent phenyl ring substituents with the accessory binding region. Such analogs will be particularly useful in future molecular modeling studies of both the D_1 and D_2 pharmacophores and in the study of dopamine receptor–ligand interactions. Not only are the current findings useful in understanding structural features engendering full intrinsic activity but also certain members of this structural class could have potential research and clinical applications. The unique D_1:D_2 receptor selectivity profiles of this series of dopamine ligands also may provide important clues to the relative contributions of distinct receptor subtypes in human disease.

Experimental Section

Chemical Procedures. Melting points were determined on a Thomas-Hoover Meltemp apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Chemagnetics 200 MHz or a Varian VXR-500S 500 MHz instrument as indicated by spectrometer frequency. Chemical shifts are reported in δ values (parts per million, ppm) relative to an internal standard of tetramethylsilane. Abbreviations used in NMR analysis are as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br s, broad singlet; dd, doublet of doublets; and dt, doublet of

triplets. Infrared (IR) spectra were recorded on a Beckman IR-33 spectrophotometer and are reported in reciprocal centimeters (cm^{-1}). Analytical TLC was performed on Baker-flex silica gel 1B2-F plastic plates. Microanalyses were obtained from Galbraith Laboratories, Inc. Both the low-resolution chemical ionization mass spectra (CIMS) and high-resolution mass spectra were determined on a Finnigan 4000 quadrupole spectrometer. A Parr apparatus was used for all low-pressure hydrogenations. Solvents and reagents were used as purchased, except as noted. THF was distilled from sodium metal/benzophenone ketyl. Chloroform was washed with distilled water, to remove ethanol, and then dried over $MgSO_4$. [^{3}H]-SCH23390 was synthesized as described previously.[16] [^{3}H]-Spiperone was purchased from New England Nuclear, Boston, MA. The following drugs were obtained as gifts: SCH23390 (Schering Inc., Bloomfield, NJ), quinpirole (Eli Lilly, Indianapolis, IN), ketanserin tartrate (Janssen Pharmaceutica, New Brunswick, NJ), and SKF38393 and chlorpromazine (Smith, Kline and French, Philadelphia, PA). All other compounds were purchased from commercial sources.

General Procedure for the Preparation of Substituted Enamides. In a typical reaction, 3.0 g (14.55 mmol) of 6,7-dimethoxy-β-tetralone was stirred in 100 mL of toluene at room temperature under a nitrogen atmosphere while 1.715 g (16.0 mmol) of benzylamine was added to the solution. The reaction mixture was heated at reflux overnight under nitrogen with continuous water removal via a Dean–Stark apparatus. The reaction mixture was cooled to room temperature, and the solvent was removed in vacuo to yield the crude *N*-benzyl enamine as a brown oil.

Meanwhile, the appropriately substituted benzoic acid was converted to its acyl chloride by suspending a slight excess (~1.1 equiv with respect to the molar quantity of 6,7-dimethoxy-β-tetralone) of the starting carboxylic acid in 80 mL of benzene. To this solution, cooled to 0 °C, was added 2.0 equiv of oxalyl chloride dropwise with a pressure-equalizing dropping funnel. Three drops of DMF were added to the reaction mixture. The ice bath was then removed, and the reaction mixture was left to stir at room temperature under nitrogen for 3 h. The solvent was removed by rotary evaporation, and the reaction flask was left under high vacuum overnight.

The previously synthesized crude enamine was dissolved in 100 mL of dichloromethane, and the solution was cooled to 0 °C in an ice bath. Triethylamine (1.1 equiv) was added to the solution with stirring. The appropriately substituted benzoyl chloride (1.1 equiv) was dissolved in 20 mL of dichloromethane, and this solution was added dropwise to the cold, stirring enamine solution. After complete addition, the ice bath was removed, and the reaction mixture was left to stir overnight at room temperature under a nitrogen atmosphere. The reaction mixture was washed with 2 × 30 mL of 5% HCl, 2 × 30 mL of saturated $NaHCO_3$ solution, and brine. The organic phase was dried with $MgSO_4$, filtered, and concentrated. The crude product was passed over a silica gel flash column, eluting with 5% ether/dichloromethane. The collected fractions containing the product were combined and concentrated. Oils were not further purified. Solid products were crystallized from Et_2O.

***N*-(4′-Methylbenzoyl)-*N*-benzyl-6,7-dimethoxy-3,4-dihydro-2-naphthylamine (16):** pure recrystallized yield 69%; mp 89–90 °C; CIMS (isobutane) $(M + 1)^+$ 414; ^{1}H NMR δ 7.55 (d, 2, ArH, J = 8.2 Hz), 7.31 (m, 5, ArH), 7.11 (d, 2, ArH, J = 7.9 Hz), 6.54 (s, 1, ArH), 6.41 (s, 1, ArH), 6.08 (s, 1, ArCH), 4.99 (s, 2, $ArCH_2N$), 3.81 (s, 3, OCH_3), 3.80 (s, 3, OCH_3), 2.50 (t, 2, $ArCH_2$, J = 8.1 Hz), 2.32 (s, 3, $ArCH_3$), 2.17 (t, 2, CH_2CN, J = 8.0 Hz). Anal. ($C_{27}H_{27}NO_3$) C, H, N.

***N*-(3′-Methylbenzoyl)-*N*-benzyl-6,7-dimethoxy-3,4-dihydro-2-naphthylamine (17):** pure recrystallized yield 63%; mp 96–97 °C; CIMS (isobutane) $(M + 1)^+$ 414; ^{1}H NMR δ 7.35 (m, 4, ArH), 7.23 (m, 3, ArH), 7.11 (d, 2, ArH, J = 3.2 Hz), 6.48 (s, 1, ArH), 6.34 (s, 1, ArH), 6.00 (s, 1, ArCH), 4.92 (s, 2, $ArCH_2N$), 3.75 (s, 3, OCH_3), 3.74 (s, 3, OCH_3), 2.42 (t, 2, $ArCH_2$, J = 8.7 Hz), 2.26 (s, 3, $ArCH_3$), 2.07 (t, 2, CH_2CN, J = 8.6 Hz). Anal. ($C_{27}H_{27}NO_3$) C, H, N.

***N*-(2′-Methylbenzoyl)-*N*-benzyl-6,7-dimethoxy-3,4-dihydro-2-naphthylamine (18):** pure undistilled yield 39%; CIMS (isobutane) $(M + 1)^+$ 414; ^{1}H NMR δ 7.40 (m, 1, ArH), 7.37 (d, 1, ArH, J = 5.6 Hz), 7.31 (t, 2, ArH, J = 8.3 Hz), 7.28 (d, 1, ArH, J = 8.3 Hz), 7.17 (d, 1, ArH, J = 8.3 Hz), 7.14 (d, 1, ArH, J = 8.3 Hz), 7.08 (t, 2, ArH, J = 6.7 Hz), 6.50 (s, 1, ArH), 6.39 (s, 1, ArH), 6.06 (s, 1, ArCH), 4.98 (s, 2, $ArCH_2N$), 3.81 (s, 3, OCH_3), 3.80 (s, 3, OCH_3), 2.42 (s, 3, $ArCH_3$), 2.32 (m, 2, $ArCH_2$), 1.96 (m, 2, CH_2CN). Anal. ($C_{27}H_{27}NO_3$) C, H, N.

***N*-(4′-Phenylbenzoyl)-*N*-benzyl-6,7-dimethoxy-3,4-dihydro-2-naphthylamine (19):** pure undistilled yield 47%; CIMS (isobutane) $(M + 1)^+$ 476; ^{1}H NMR δ 7.73 (d, 2, ArH, J = 8.5 Hz), 7.56 (d, 3, ArH, J = 5.8 Hz), 7.37 (m, 8, ArH), 6.54 (s, 1, ArH), 6.41 (s, 1, ArH), 6.12 (s, 1, ArCH), 5.02 (s, 2, $ArCH_2N$), 3.81 (s, 3, OCH_3), 3.79 (s, 3, OCH_3), 2.52 (t, 2, ArCH2, J = 7.3 Hz), 2.14 (t, 2, CH_2CN, J = 8.1 Hz). Anal. ($C_{32}H_{29}NO_3$) C, H, N.

***N*-(4′-Ethylbenzoyl)-*N*-benzyl-6,7-dimethoxy-3,4-dihydro-2-naphthylamine (20):** pure recrystallized yield 74%; mp 109–110 °C; CIMS (isobutane) $(M + 1)^+$ 428; ^{1}H NMR δ 7.56 (d, 2, ArH, J = 6.5 Hz), 7.37 (d, 2, ArH, J = 7.3 Hz), 7.29 (t, 2, ArH, J = 7.1 Hz), 7.24 (m, 1, ArH), 7.12 (d, 2, ArH, J = 8.3 Hz), 6.52 (s, 1, ArH), 6.40 (s, 1, ArH), 6.08 (s, 1, ArCH), 4.98 (s, 2, $ArCH_2N$), 3.80 (s, 3, OCH_3), 3.79 (s, 3, OCH_3), 2.60 (q, 2, CH_2, J = 7.6 Hz), 2.46 (t, 2, $ArCH_2$, J = 8.9 Hz), 2.07 (t, 2, CH_2CN, J = 8.2 Hz), 1.18 (t, 3, CH_3, J = 7.6 Hz). Anal. ($C_{28}H_{29}NO_3$) C, H, N.

***N*-(4′-Methoxybenzoyl)-*N*-benzyl-6,7-dimethoxy-3,4-dihydro-2-naphthylamine (21):** pure recrystallized yield 56%; mp 128–129 °C; CIMS (isobutane) $(M + 1)^+$ 430; ^{1}H NMR δ 7.65 (d, 2, ArH, J = 8.9 Hz), 7.37 (d, 2, ArH, J = 6.9 Hz), 7.29 (t, 2, ArH, J = 7.2 Hz), 7.23 (m, 1, ArH), 6.81 (d, 2, ArH, J = 8.9 Hz), 6.53 (s, 1, ArH), 6.41 (s, 1, ArH), 6.10 (s, 1, ArCH), 4.98 (s, 2, $ArCH_2N$), 3.81 (s, 3, OCH_3), 3.79 (s, 3, OCH_3), 3.76 (s, 3, OCH_3), 2.49 (t, 2, $ArCH_2$, J = 7.9 Hz), 2.07 (t, 2, CH_2CN, J = 7.9 Hz). Anal. ($C_{27}H_{27}NO_3$) C, H, N.

***N*-(3′-Methoxybenzoyl)-*N*-benzyl-6,7-dimethoxy-3,4-dihydro-2-naphthylamine (22):** pure recrystallized yield 58%; mp 128–129 °C; CIMS (isobutane) $(M + 1)^+$ 430; ^{1}H NMR δ 7.37 (d, 2, ArH, J = 7.1 Hz), 7.30 (t, 2, ArH, J = 7.2 Hz), 7.24 (m, 1, ArH), 7.19 (d, 2, ArH, J = 5.6 Hz), 7.16 (s, 1, ArH), 6.87 (m, 1, ArH), 6.52 (s, 1, ArH), 6.39 (s, 1, ArH), 6.06 (s, 1, ArCH), 4.96 (s, 2, $ArCH_2N$), 3.80 (s, 3, OCH_3), 3.78 (s, 3, OCH_3), 3.75 (s, 3, OCH_3), 2.48 (t, 2, $ArCH_2$, J = 7.9 Hz), 2.09 (t, 2, CH_2CN, J = 8.1 Hz). Anal. ($C_{27}H_{27}NO_4$) C, H, N.

General Procedure for the Preparation of Substituted Lactams. A solution no more concentrated than 12 mM of the appropriately substituted enamide **16**–**22** was prepared in 500 mL of THF. This solution was placed into an Ace glass 500 mL photochemical reactor. The solution was stirred while irradiating with a 450 W Hanovia medium pressure, quartz, mercury-vapor lamp seated in a cold tap water-cooled, quartz immersion well. When TLC analysis had indicated the complete disappearance of the starting material (3–10 h), the solution was then concentrated via rotary evaporation. The product was purified by elution through a silica gel flash column with 5% ether/dichloromethane. The appropriate fractions were combined, and the product was crystallized from diethyl ether.

(±)-*trans*-2-Methyl-6-benzyl-10,11-dimethoxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridin-5-one (23): obtained from **16** in a recrystallized yield of 51%; mp 183–185 °C; CIMS (isobutane) $(M + 1)^+$ 414; ^{1}H NMR δ 8.09 (d, 1, ArH, J = 7.9 Hz), 7.34 (s, 1, ArH), 7.25 (m, 6, ArH), 6.93 (s, 1, ArH), 6.63 (s, 1, ArH), 5.34 (d, 1, ArCHN, J = 16.1 Hz), 4.76 (d, 1, ArCHN, J = 16.0 Hz), 4.34 (d, 1, Ar_2CH, J = 11.4 Hz), 3.89 (s, 3, OCH_3), 3.88 (s, 3, OCH_3), 3.76 (m, 1, CHN), 2.67 (t, 2, $ArCH_2$, J = 6.7 Hz), 2.37 (s, 3, $ArCH_3$), 2.25 (m, 1, CHCN), 1.62 (m, 1, CHCN). Anal. ($C_{27}H_{27}NO_3$) C, H, N.

(±)-*trans*-3-Methyl-6-benzyl-10,11-dimethoxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridin-5-one (24): obtained from **17** in a recrystallized yield of 43%; mp 156–158 °C; CIMS (isobutane) $(M + 1)^+$ 414; ^{1}H NMR δ 7.94 (s, 1, ArH), 7.34 (d, 1, ArH, J = 7.9 Hz), 7.20 (m, 7, ArH), 6.84 (s, 1, ArH), 6.54 (s, 1, ArH), 5.28 (d, 1, ArCHN, J = 16.1 Hz), 4.67 (d, 1, ArCHN, J = 16.0 Hz), 4.23 (d, 1, Ar_2CH, J = 11.4 Hz), 3.80 (s, 3, OCH_3), 3.79 (s, 3, OCH_3), 3.67 (m, 1, CHN), 2.59 (m, 2, $ArCH_2$), 2.34 (s, 3, $ArCH_3$), 2.17 (m, 1, CHCN), 1.60 (m, 1, CHCN). Anal. ($C_{27}H_{27}NO_3$) C, H, N.

(±)-*trans*-4-Methyl-6-benzyl-10,11-dimethoxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridin-5-one (25): obtained from **18** in a recrystallized yield of 20%; mp 175–176 °C; CIMS (isobutane) $(M + 1)^+$ 414; ^1H NMR δ 7.40 (m, 2, ArH), 7.29 (m, 2, ArH), 7.27 (t, 2, ArH, J = 3.9 Hz), 7.21 (t, 2, ArH, J = 6.4 Hz), 6.87 (s, 1, ArH), 6.60 (s, 1, ArH), 5.33 (d, 1, ArCHN, J = 16.4 Hz), 4.72 (d, 1, ArCHN, J = 16.0 Hz), 4.24 (d, 1, Ar_2CH, J = 11.0 Hz), 3.87 (s, 3, OCH_3), 3.85 (s, 3, OCH_3), 3.68 (m, 1, CHN), 2.73 (s, 3, $ArCH_3$), 2.63 (m, 2, $ArCH_2$), 2.20 (m, 1, CHCN), 1.72 (m, 1, CHCN). Anal. ($C_{27}H_{27}NO_3$) C, H, N.

(±)-*trans*-2-Phenyl-6-benzyl-10,11-dimethoxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridin-5-one (26): obtained from **19** in a recrystallized yield of 40%; mp 188–191 °C; CIMS (isobutane) $(M + 1)^+$ 476; ^1H NMR δ 8.18 (d, 1, ArH, J = 7.5 Hz), 7.72 (s, 1, ArH), 7.58 (d, 1, ArH, J = 7.9 Hz), 7.48 (d, 2, ArH, J = 7.3 Hz), 7.26 (m, 8, ArH), 6.92 (s, 1, ArH), 6.56 (s, 1, ArH), 5.29 (d, 1, ArCHN, J = 16.1 Hz), 4.71 (d, 1, ArCHN, J = 16.1 Hz), 4.33 (d, 1, Ar_2CH, J = 11.0 Hz), 3.80 (s, 3, OCH_3), 3.79 (s, 3, OCH_3), 3.77 (m, 1, CHN), 2.61 (m, 2, $ArCH_2$), 2.27 (m, 1, CHCN), 1.67 (m, 1, CHCN); HRMS (CI, isobutane) calcd for $C_{32}H_{29}NO_3$ 475.2147, found 475.2139.

(±)-*trans*-2-Ethyl-6-benzyl-10,11-dimethoxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridin-5-one (27): obtained from **20** in a recrystallized yield of 76%; mp 195–197 °C; CIMS (isobutane) $(M + 1)^+$ 428; ^1H NMR δ 8.10 (d, 1, ArH, J = 7.9 Hz), 7.36 (s, 1, ArH), 7.26 (m, 6, ArH), 6.92 (s, 1, ArH), 6.62 (s, 1, ArH), 5.34 (d, 1, ArCHN, J = 16.0 Hz), 4.74 (d, 1, ArCHN, J = 16.0 Hz), 4.33 (d, 1, Ar_2CH, J = 11.4 Hz), 3.87 (s, 3, OCH_3), 3.85 (s, 3, OCH_3), 3.77 (m, 1, CHN), 2.65 (m, 4, $ArCH_2$), 2.21 (m, 1, CHCN), 1.83 (m, 1, CHCN), 1.22 (t, 3, CH_3, J = 5.6 Hz); HRMS (CI, isobutane) calcd for $C_{28}H_{29}NO_3$ 428.2226, found 428.2217.

(±)-*trans*-6-Benzyl-2,10,11-trimethoxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridin-5-one (28): obtained from **21** in a recrystallized yield of 70%; mp 202–204 °C; CIMS (isobutane) $(M + 1)^+$ 430; ^1H NMR δ 8.13 (d, 1, ArH, J = 8.5 Hz), 7.27 (t, 2, ArH, J = 5.4 Hz), 7.22 (m, 3, ArH), 7.05 (s, 1, ArH), 6.89 (s, 1, ArH), 6.87 (d, 1, ArH), 6.61 (s, 1, ArH), 5.31 (d, 1, ArCHN, J = 16.1 Hz), 4.74 (d, 1, ArCHN, J = 16.0 Hz), 4.31 (d, 1, Ar_2CH, J = 11.3 Hz), 3.87 (s, 3, OCH_3), 3.86 (s, 3, OCH_3), 3.79 (s, 3, OCH_3), 3.76 (m, 1, CHN), 2.64 (m, 2, $ArCH_2$), 2.22 (m, 1, CHCN), 1.72 (m, 1, CHCN). Anal. ($C_{27}H_{27}NO_4$) C, H, N.

(±)-*trans*-6-Benzyl-3,10,11-trimethoxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridin-5-one (29): obtained from **22** in a recrystallized yield of 64%; mp 168–170 °C; CIMS (isobutane) $(M + 1)^+$ 430; ^1H NMR δ 7.76 (d, 1, ArH, J = 4.0 Hz), 7.46 (d, 1, ArH, J = 11.8 Hz), 7.30 (t, 2, ArH, J = 9.2 Hz), 7.24 (m, 3, ArH), 7.00 (dd, 1, ArH, J = 2.1 Hz), 6.92 (s, 1, ArH), 6.63 (s, 1, ArH), 5.34 (d, 1, ArCHN, J = 16.0 Hz), 4.78 (d, 1, ArCHN, J = 16.0 Hz), 4.29 (d, 1, Ar_2CH, J = 11.0 Hz), 3.90 (s, 3, OCH_3), 3.89 (s, 3, OCH_3), 3.87 (s, 3, OCH_3), 3.76 (m, 1, CHN), 2.67 (m, 2, $ArCH_2$), 2.25 (m, 1, CHCN), 1.74 (m, 1, CHCN). Anal. ($C_{27}H_{27}NO_4$) C, H, N.

General Procedure for the Preparation of Substituted *N*-Benzylamines. A solution of 1.5 g (3.76 mmol) of the individual lactams **23–29** in 100 mL of dry THF was cooled in an ice/salt bath, and 4–5 equiv (1 equiv for each nucleophilic center in the molecule plus an additional 1 equiv) of a 1.0 M solution of BH_3 in THF was added via syringe. The reaction mixture was heated at reflux until all of the starting material had been consumed (TLC, 5% Et_2O/CH_2Cl_2). Methanol (5–10 mL) was then added cautiously to the reaction mixture, and the mixture was heated at reflux for an additional 4 h. The reaction mixture was cooled to room temperature, and the solvent was removed in vacuo. Methanol (20 mL) was added to the flask and then removed on the rotary evaporator; this procedure was repeated. Likewise, two 20 mL portions of ethanol were added and removed in the same manner. The reaction flask was then left under high vacuum overnight. The residue was suspended in absolute EtOH and carefully acidified with concentrated HCl. The volatiles were removed, and the product was crystallized from ethanol.

(±)-*trans*-2-Methyl-6-benzyl-10,11-dimethoxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine hydrochloride (30): obtained from **23** in a recrystallized yield of 79%; mp 220–223 °C; CIMS (isobutane) $(M + 1)^+$ 400; ^1H NMR δ 7.37 (d, 2, ArH, J = 7.4 Hz), 7.33 (t, 2, ArH, J = 7.2 Hz), 7.27 (d, 1, ArH, J = 7.3 Hz), 7.22 (s, 1, ArH), 7.02 (d, 1, ArH, J = 7.7 Hz), 6.98 (d, 1, ArH, J = 7.6 Hz), 6.89 (s, 1, ArH), 6.72 (s, 1, ArH), 4.02 (d, 1, Ar_2CH, J = 10.9 Hz), 3.88 (s, 3, OCH_3), 3.84 (d, 1, ArCHN, J = 15.0 Hz), 3.82 (d, 1, ARCHN, J = 15.3 Hz), 3.78 (s, 3, OCH_3), 3.50 (d, 1, ArCHN, J = 15.2 Hz), 3.30 (m, 1, ArCHN), 2.83 (m, 1, ArCH), 2.81 (m, 1, ArCH), 2.33 (m, 1, CHN), 2.32 (s, 3, $ArCH_3$), 2.20 (m, 1, CHCN), 1.94 (m, 1, CHCN), 1.67 (m, 1, ArCHN). Anal. ($C_{27}H_{29}NO_2$) C, H, N.

(±)-*trans*-3-Methyl-6-benzyl-10,11-dimethoxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine hydrochloride (31): obtained from **24** in a recrystallized yield of 80%; mp 193–195 °C; CIMS (isobutane) $(M + 1)^+$ 400; ^1H NMR δ 7.37 (d, 2, ArH, J = 7.4 Hz), 7.33 (t, 2, ArH, J = 7.2 Hz), 7.28 (t, 2, ArH, J = 7.8 Hz), 7.07 (d, 1, ArH, J = 7.8 Hz), 6.90 (s, 1, ArH), 6.88 (s, 1, ArH), 6.72 (s, 1, ArH), 4.02 (d, 1, Ar_2CH, J = 10.9 Hz), 3.90 (d, 1, ArCHN, J = 13.0 Hz), 3.87 (s, 3, OCH_3), 3.80 (d, 1, ArCHN, J = 13.2 Hz), 3.77 (s, 3, OCH_3), 3.48 (d, 1, ArCHN, J = 12.9 Hz), 3.30 (m, 1, ArCHN), 2.87 (m, 1, ArCH), 2.81 (m, 1, ArCH), 2.35 (m, 1, CHN), 2.32 (s, 3, $ArCH_3$), 2.20 (m, 1, CHCN), 1.95 (m, 1, CHCN), 1.64 (m, 1, ArCHN). Anal. ($C_{27}H_{29}NO_2$) C, H, N.

(±)-*trans*-4-Methyl-6-benzyl-10,11-dimethoxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine hydrochloride (32): obtained from **25** in a recrystallized yield of 75%; mp 232–235 °C; CIMS (isobutane) $(M + 1)^+$ 400; ^1H NMR δ 7.38 (d, 2, ArH, J = 7.3 Hz), 7.33 (t, 2, ArH, J = 7.2 Hz), 7.27 (d, 1, ArH, J = 7.3 Hz), 7.24 (d, 1, ArH, J = 7.9 Hz), 7.16 (t, 1, ArH, J = 7.5 Hz), 7.06 (d, 1, ArH, J = 7.5 Hz), 6.85 (s, 1, ArH), 6.71 (s, 1, ArH), 4.05 (d, 1, Ar_2CH, J = 11.1 Hz), 3.89 (d, 1, ArCHN, J = 12.0 Hz), 3.87 (s, 3, OCH_3), 3.81 (d, 1, ArCHN, J = 14.6 Hz), 3.76 (s, 3, OCH_3), 3.55 (d, 1, ArCHN, J = 14.7 Hz), 3.31 (m, 1, ArCHN), 2.87 (m, 1, ArCH), 2.81 (m, 1, ArCH), 2.34 (m, 1, CHN), 2.20 (m, 1, CHCN), 2.16 (s, 3, $ArCH_3$), 1.94 (m, 1, CHCN), 1.68 (m, 1, ArCHN). Anal. ($C_{27}H_{29}NO_2$) C, H, N.

(±)-*trans*-2-Phenyl-6-benzyl-10,11-dimethoxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine hydrochloride (33): obtained from **26** in a recrystallized yield of 75%; mp 228–230 °C; CIMS (isobutane) $(M + 1)^+$ 462; ^1H NMR δ 7.68 (s, 1, ArH), 7.57 (m, 3, ArH), 7.47 (dd, 1, ArH, J = 20 Hz), 7.36 (m, 7, ArH), 7.17 (d, 1, ArH, J = 7.4 Hz), 6.98 (s, 1, ArH), 6.76 (s, 1, ArH), 4.14 (d, 1, Ar_2CH, J = 11.2 Hz), 3.96 (d, ArCHN, J = 12.3 Hz), 3.91 (d, 1, ArCHN, J = 15.7 Hz), 3.90 (s, 3, OCH_3), 3.79 (s, 3, OCH_3), 3.56 (d, 1, ArCHN, J = 15.7 Hz), 3.33 (d, 1, ArCHN, J = 12.3 Hz), 2.92 (m, 1, ArCH), 2.88 (m, 1, ArCH), 2.41 (dt, 1, CHCN), 2.25 (m, 1, CHN), 1.98 (m, 1, CHCN). Anal. ($C_{32}H_{31}NO_2$) C, H, N.

(±)-*trans*-2-Ethyl-6-benzyl-10,11-dimethoxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine hydrochloride (34): obtained from **27** in a recrystallized yield of 89%; mp 206–208 °C; CIMS (isobutane) $(M + 1)^+$ 414; ^1H NMR δ 7.38 (d, 2, ArH, J = 8.5 Hz), 7.34 (t, 2, ArH, J = 7.1 Hz), 7.29 (d, 1, ArH, J = 7.1 Hz), 7.27 (s, 1, ArH), 7.05 (d, 1, ArH, J = 8.5 Hz), 7.01 (d, 1, ArH, J = 7.1 Hz), 6.92 (s, 1, ArH), 6.75 (s, 1, ArH), 4.04 (d, 1, Ar_2CH, J = 11.4 Hz), 3.92 (d, 1, ArCHN, J = 16.1 Hz), 3.90 (s, 3, OCH_3), 3.83 (d, 1, ArCHN, J = 16.1 Hz), 3.79 (s, 3, OCH_3), 3.50 (d, 1, ArCHN, J = 14.6 Hz), 3.30 (d, 1, ArCHN, J = 14.6 Hz), 2.91 (m, 1, ArCH), 2.85 (m, 1, ArCH), 2.64 (q, 2, $ArCH_2$, J = 8.7 Hz), 2.37 (dt, 1, CHCN, J = 5.2 Hz), 2.23 (m, 1, CHN), 1.96 (m, 1, CHCN), 1.24 (t, 3, CH_3, J = 7.8 Hz). Anal. ($C_{28}H_{30}NO_2$) C, H, N.

(±)-*trans*-6-Benzyl-2,10,11-trimethoxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine hydrochloride (35): obtained from **28** in a recrystallized yield of 77%; mp 158–160 °C; CIMS (isobutane) $(M + 1)^+$ 416; ^1H NMR δ 7.36 (m, 4, ArH), 7.28 (d, 1, ArH, J = 7.7 Hz), 7.02 (d, 1, ArH, J = 7.4 Hz), 6.98 (d, 1, ArH, J = 3.2 Hz), 6.93 (s, 1, ArH), 6.77 (dd, 1, ArH, J = 3.2 Hz), 6.74 (s, 1, ArH), 4.05 (d, 1, Ar_2CH, J = 11.5 Hz), 3.90 (s, 3, OCH_3), 3.88 (d, 1, ArCHN, J = 13.2 Hz), 3.82 (d, 1, ArCHN, J = 14.7 Hz), 3.80 (s, 3, OCH_3), 3.77 (s, 3, OCH_3), 3.47 (d, 1, ArCHN, J = 15.0 Hz), 3.29 (d, 1, ArCHN, J = 13.1

Hz), 2.86 (m, 2, $ArCH_2$), 2.34 (dt, 1, CHCN, J = 5.2 Hz), 2.22 (m, 1, CHN), 1.94 (m, 1, CHCN). Anal. ($C_{27}H_{30}NO_3$) C, H, N.

(±)-*trans*-6-Benzyl-3,10,11-trimethoxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine hydrochloride (36): obtained from **29** in a recrystallized yield of 61%; mp 190–192 °C; CIMS (isobutane) $(M + 1)^+$ 416; ^1H NMR δ 7.36 (m, 5, ArH), 7.28 (d, 1, ArH, J = 7.5 Hz), 6.88 (s, 1, ArH), 6.83 (dd, 1, ArH, J = 2.1 Hz), 6.74 (s, 1, ArH), 6.64 (d, 1, ArH, J = 2.0 Hz), 4.00 (d, 1, Ar_2CH, J = 11.2 Hz), 3.92 (d, 1, ArCHN, J = 13.4 Hz), 3.89 (s, 3, OCH_3), 3.82 (d, 1, ArCHN, J = 15.1 Hz), 3.81 (s, 3, OCH_3), 3.80 (s, 3, OCH_3), 3.50 (d, 1, ArCHN, J = 15.1 Hz), 3.32 (d, 1, ArCHN, J = 13.4 Hz), 2.92 (m, 1, ArCH), 2.84 (m, 1, ArCH), 2.38 (dt, 1, CHCN, J = 6.5 Hz), 2.22 (m, 1, CHN), 1.96 (m, 1, CHCN). Anal. ($C_{27}H_{30}NO_3$) C, H, N.

General Procedure for *N*-Debenzylation. A solution of 0.2–3.0 g of the 6-*N*-benzyl hydrochloride salt **30–36** in 100–500 mL of 95% ethanol containing 0.04–0.60 g of 10% Pd–C catalyst was shaken at room temperature under 50 psig of H_2 overnight. The catalyst was removed by filtration through a pad of Celite. The solution was concentrated to dryness on a rotary evaporator, and the products were crystallized from acetonitrile.

(±)-*trans*-2-Methyl-10,11-dimethoxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine hydrochloride (37): obtained from **30** in a recrystallized yield of 86%; mp 238–239 °C; CIMS (isobutane) $(M + 1)^+$ 310; ^1H NMR (DMSO) δ 10.1 (s, 1, NH), 7.29 (d, 1, ArH, J = 7.6 Hz), 7.19 (s, 1, ArH), 7.14 (d, 1, ArH, J = 7.1 Hz), 6.88 (s, 1, ArH), 6.84 (s, 1, ArH), 4.31 (s, 2, $ArCH_2N$), 4.23 (d, 1, Ar_2CH, J = 10.8 Hz), 3.76 (s, 3, OCH_3), 3.70 (s, 3, OCH_3), 2.80 (m, 1, CHN), 2.71 (m, 2, $ArCH_2$), 2.30 (s, 3, $ArCH_3$), 2.19 (m, 1, CHCN), 2.04 (m, 1, CHCN). Anal. ($C_{20}H_{23}NO_2$) H, N; C: calcd, 69.54; found, 69.95.

(±)-*trans*-3-Methyl-10,11-dimethoxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine hydrochloride (38): obtained from **31** in a recrystallized yield of 78%; mp 254–256 °C; CIMS (isobutane) $(M + 1)^+$ 310; ^1H NMR δ 7.36 (d, 1, ArH, J = 7.9 Hz), 7.09 (d, 1, ArH, J = 7.9 Hz), 6.98 (s, 1, ArH), 6.92 (s, 1, ArH), 6.74 (s, 1, ArH), 4.04 (s, 2, $ArCH_2N$), 3.88 (s, 3, OCH_3), 3.79 (s, 3, OCH_3), 3.78 (d, 1, Ar_2CH, J = 10.2 Hz), 2.87 (m, 1, CHN), 2.70 (m, 2, $ArCH_2$), 2.36 (s, 3, $ArCH_3$), 2.16 (m, 1, CHCN), 1.75 (m, 1, CHCN), 1.60 (s, 1, NH). Anal. ($C_{20}H_{23}NO_2$) H, N; C: calcd, 69.45; found, 69.97.

(±)-*trans*-4-Methyl-10,11-dimethoxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine hydrochloride (39): obtained from **32** in a recrystallized yield of 87%; mp 215–216 °C; CIMS (isobutane) $(M + 1)^+$ 310; ^1H NMR (DMSO) δ 9.72 (s, 1, NH), 7.27 (t, 1, ArH, J = 2.8 Hz), 7.21 (d, 1, ArH, J = 3.2 Hz), 7.19 (d, 1, ArH, J = 3.2 Hz), 6.86 (s, 1, ArH), 6.81 (s, 1, ArH), 4.31 (s, 2, $ArCH_2N$), 4.23 (d, 1, Ar_2CH, J = 11.2 Hz), 3.75 (s, 3, OCH_3), 3.65 (s, 3, OCH_3), 2.96 (m, 1, CHN), 2.83 (m, 2, $ArCH_2$), 2.30 (s, 3, $ArCH_3$), 2.21 (m, 1, CHCN), 1.93 (m, 1, CHCN). Anal. ($C_{20}H_{23}NO_2$) C, H, N.

(±)-*trans*-2-Phenyl-10,11-dimethoxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine hydrochloride (40): obtained from **33** in a recrystallized yield of 80%; mp 262–265 °C; CIMS (isobutane) $(M + 1)^+$ 372; ^1H NMR δ 7.70 (s, 1, ArH), 7.56 (d, 2, ArH, J = 9.0 Hz), 7.48 (dd, 1, ArH, J = 2.5 Hz), 7.36 (m, 4, ArH), 6.97 (s, 1, ArH), 6.73 (s, 1, ArH), 4.18 (s, 2, $ArCH_2N$), 3.95 (d, 1, Ar_2CH, J = 11.0 Hz), 3.87 (s, 3, OCH_3), 3.76 (s, 3, OCH_3), 2.91 (m, 1, CHN), 2.80 (m, 2, $ArCH_2$), 2.24 (m, 1, CHCN), 2.03 (m, 1, CHCN), 1.83 (s, 1, NH). Anal. ($C_{25}H_{25}NO_2$) C, H, N.

(±)-*trans*-2-Ethyl-10,11-dimethoxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine hydrochloride (41): obtained from **34** in a recrystallized yield of 76%; mp 253–255 °C; CIMS (isobutane) $(M + 1)^+$ 324; ^1H NMR (DMSO) δ 9.78 (s, 1, NH), 7.32 (d, 1, ArH, J = 7.8 Hz), 7.26 (s, 1, ArH), 7.19 (d, 1, ArH, J = 7.6 Hz), 6.88 (s, 1, ArH), 6.86 (s, 1, ArH), 4.34 (dd, 2, $ArCH_2N$, J = 2.3 Hz), 4.23 (d, 1, Ar_2CH, J = 10.8 Hz), 3.77 (s, 3, OCH_3), 3.69 (s, 3, OCH_3), 2.97 (m, 1, CHN), 2.83 (m, 2, $ArCH_2$), 2.62 (q, 2, $ArCH_2$, J = 7.8 Hz), 2.20 (m, 1, CHCN), 1.97 (m, 1, CHCN), 1.16 (t, 3, CH_3, J = 7.4 Hz). Anal. ($C_{21}H_{25}NO_2$) C, H, N.

(±)-*trans*-2,10,11-Trimethoxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine hydrochloride (42): obtained from **35** in a recrystallized yield of 79%; mp 232–234 °C; CIMS (isobutane) $(M + 1)^+$ 326; ^1H NMR (DMSO) δ 9.53 (s, 1, NH),=7.35 (d, 1, ArH, J = 8.6 Hz), 6.94 (s, 1, ArH), 6.92 (d, 1, ArH, J = 6.0 Hz), 6.90 (s, 1, ArH), 6.87 (s, 1, ArH), 4.31 (dd, 2, $ArCH_2N$, J = 7.8 Hz), 4.21 (d, 1, Ar_2CH, J = 10.8 Hz), 3.77 (s, 3, OCH_3), 3.73 (s, 3, OCH_3), 3.70 (s, 3, OCH_3), 2.95 (dt, 1, CHN, J = 4.2 Hz), 2.83 (m, 2, $ArCH_2$), 2.18 (m, 1, CHCN), 1.94 (m, 1, CHCN); HRMS (CI, isobutane) calcd for $C_{20}H_{23}NO_3$ 325.1678, found 325.1668.

(±)-*trans*-3,10,11-Trimethoxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine hydrochloride (43): obtained from **36** in a recrystallized yield of 85%; mp 223–224 °C; CIMS (isobutane) $(M + 1)^+$ 326; ^1H NMR (DMSO) δ 9.63 (s, 1, NH), 7.38 (d, 1, ArH, J = 8.5 Hz), 7.03 (d, 1, ArH, J = 2.1 Hz), 6.97 (dd, 1, ArH, J = 2.1 Hz), 6.87 (s, 1, ArH), 6.84 (s, 1, ArH), 4.34 (dd, 2, $ArCH_2N$, J = 7.8 Hz), 4.15 (d, 1, Ar_2CH, J = 11.0 Hz), 3.78 (s, 3, OCH_3), 3.75 (s, 3, OCH_3), 3.68 (s, 3, OCH_3), 2.97 (dt, 1, CHN, J = 5.1 Hz), 2.83 (m, 2, $ArCH_2$), 2.18 (m, 1, CHCN), 1.92 (m, 1, CHCN); HRMS (CI, isobutane) calcd for $C_{20}H_{23}NO_3$ 325.1678, found 325.1668.

General Procedure for Cleavage of the *O*-Methyl Ethers. The *O,O*-dimethyl ether hydrochloride salts (0.200 g) **37–43** were converted to their free bases in H_2O with a saturated bicarbonate solution. The aqueous solution was extracted with 3 × 30 mL of dichloromethane. The organic fractions were dried over $MgSO_4$, filtered, and concentrated in vacuo. The free base was dissolved in 35 mL of dichloromethane, and the solution was cooled to −78 °C. A 1.0 M solution of BBr_3 in dichloromethane (4–5 equiv) was added slowly to the reaction mixture via syringe. The cooling bath was removed, and the reaction mixture was left to stir under a nitrogen atmosphere overnight, while warming to ambient temperature. Methanol (7 mL) was then added cautiously to the reaction mixture over 20 min. The solvent was removed by rotary evaporation, and the flask was left under high vacuum overnight.

The residue was dissolved in water and carefully neutralized, under nitrogen, to its free base with a saturated bicarbonate solution while cooling in an ice bath. The free base was isolated by suction filtration and washed with cold water. The filtrate was extracted with CH_2Cl_2. The CH_2Cl_2 fractions were combined, dried with $MgSO_4$, filtered, and concentrated. The precipitated free base and the organic residue were combined, dissolved in absolute ethanol, and carefully acidified with concentrated HCl. After removal of the volatiles, the hydrochloride salt was crystallized from either MeOH or MeOH/EtOAc.

(±)-*trans*-2-Methyl-10,11-dihydroxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine hydrochloride (5): obtained from **37** in a recrystallized yield of 51%; mp 208–210 °C; CIMS (isobutane) $(M + 1)^+$ 282; ^1H NMR (DMSO) δ 9.58 (s, 1, NH), 9.87 (s, 2, OH), 9.86 (s, 1, OH), 7.27 (d, 1, ArH, J = 7.7 Hz), 7.20 (s, 1, ArH), 7.14 (d, 1, ArH, J = 7.6 Hz), 6.72 (s, 1, ArH), 6.60 (s, 1, ArH), 4.30 (dd, 2, $ArCH_2N$, J = 2.4 Hz), 4.09 (d, 1, Ar_2CH, J = 11.3 Hz), 2.90 (m, 1, CHN), 2.70 (m, 2, $ArCH_2$), 2.32 (s, 3, $ArCH_3$), 2.13 (m, 1, CHCN), 1.87 (m, 1, CHCN). Anal. ($C_{18}H_{19}NO_2$) C, H, N.

(±)-*trans*-3-Methyl-10,11-dihydroxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine hydrochloride (9): obtained from **38** in a recrystallized yield of 71%; mp 219–222 °C; CIMS (isobutane) $(M + 1)^+$ 282; ^1H NMR (DMSO) δ 9.57 (s, 1, NH), 8.82 (d, 2, OH, J = 11.5 Hz), 8.82 (s, 1, OH), 7.30 (d, 1, ArH, J = 7.9 Hz), 7.20 (d, 1, ArH, J = 8.2 Hz), 7.18 (s, 1, ArH), 6.69 (s, 1, ArH), 6.60 (s, 1, ArH), 4.30 (dd, 2, $ArCH_2N$, J = 4.2 Hz), 4.07 (d, 1, Ar_2CH, J = 11.2 Hz), 2.91 (dt, 1, CHN, J = 5.8 Hz), 2.71 (m, 2, $ArCH_2$), 2.32 (s, 3, $ArCH_3$), 2.14 (m, 1, CHCN), 1.87 (m, 1, CHCN). Anal. ($C_{18}H_{19}NO_2$) C, H, N.

(±)-*trans*-4-Methyl-10,11-dihydroxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine hydrochloride (12): obtained from **39** in a recrystallized yield of 82%; mp >200 °C dec; CIMS (isobutane) $(M + 1)^+$ 282; ^1H NMR (DMSO) δ 9.57 (s, 1, NH), 8.83 (s, 1, OH), 8.80 (s, 1, OH), 7.29 (t, 1, ArH, J = 7.7 Hz), 7.26 (d, 1, ArH, J = 5.5 Hz), 7.19 (d, 1, ArH, J = 3.8 Hz), 6.65 (s, 1, ArH), 6.61 (s, 1, ArH), 4.28 (dd, 2, $ArCH_2N$, J = 12.9 Hz), 4.12 (d, 1, Ar_2CH, J = 11.6 Hz), 2.92 (m, 1, CHN), 2.72 (m, 2, $ArCH_2$), 2.29 (s, 3, $ArCH_3$), 2.17 (m, 1, CHCN), 1.87

(m, 1, CHCN); HRMS (CI, isobutane) calcd for $C_{18}H_{19}NO_3$ 280.1338, found 280.1335.

(±)-*trans*-2-Ethyl-10,11-dihydroxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine hydrochloride (6): obtained from **41** in a recrystallized yield of 67%; mp 208–209 °C; CIMS (isobutane) $(M + 1)^+$ 296; ^1H NMR (DMSO) δ 9.65 (s, 1, NH), 8.90 (s, 1, OH), 8.88 (s, 1, OH), 7.30 (d, 1, ArH, J = 7.5 Hz), 7.23 (s, 1, ArH), 7.19 (d, 1, ArH, J = 7.5 Hz), 6.72 (s, 1, ArH), 6.60 (s, 1, ArH), 4.31 (s, 2, $ArCH_2N$), 4.21 (d, 1, Ar_2CH, J = 11.0 Hz), 2.92 (m, 1, CHN), 2.82 (m, 2, $ArCH_2$), 2.61 (q, 2, $ArCH_2$, J = 7.0 Hz), 2.16 (m, 1, CHCN), 1.90 (m, 1, CHCN), 1.09 (t, 3, CH_3, J = 6.0 Hz); HRMS (CI, isobutane) $(M - H^+)$ calcd for $C_{19}H_{21}NO_2$ 294.1494, found 294.1493.

(±)-*trans*-2-Phenyl-10,11-dihydroxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine hydrochloride (7): obtained from **40** in a recrystallized yield of 49%; mp 245–248 °C; CIMS (isobutane) $(M + 1)^+$ 344; ^1H NMR (DMSO) δ 9.53 (s, 1, NH), 8.95 (s, 1, OH), 8.80 (s, 1, OH), 7.65 (m, 4, ArH), 7.48 (m, 3, ArH), 7.38 (t, 1, ArH, J = 7.0 Hz), 6.79 (s, 1, ArH), 6.63 (s, 1, ArH), 4.40 (s, 2, $ArCH_2N$), 4.20 (d, 1, Ar_2CH, J = 11.1 Hz), 3.02 (m, 1, CHN), 2.74 (m, 2, $ArCH_2$), 2.17 (m, 1, CHCN), 1.90 (m, 1, CHCN). Anal. ($C_{23}H_{21}NO_2$) C, H, N.

(±)-*trans*-2,10,11-Trihydroxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine hydrochloride (8): obtained from **42** in a recrystallized yield of 51%; mp 241–242 °C; CIMS (isobutane) $(M + 1)^+$ 284; ^1H NMR (DMSO) δ 9.62 (s, 1, OH), 9.35 (s, 1, NH), 8.90 (s, 1, OH), 8.89 (s, 1, OH), 7.17 (d, 1, ArH, J = 8.3 Hz), 6.81 (d, 1, ArH, J = 1.8 Hz), 6.73 (s, 1, ArH), 6.71 (d, 1, ArH, J = 2.0 Hz), 6.60 (s, 1, ArH), 4.22 (s, 2, $ArCH_2N$), 4.03 (d, 1, Ar_2CH, J = 11.5 Hz), 2.84 (m, 1, CHN), 2.69 (m, 2, $ArCH_2$), 2.11 (m, 1, CHCN), 1.86 (m, 1, CHCN); HRMS (CI, isobutane) calcd for $C_{17}H_{17}NO_3$ 284.1287, found 284.1280.

(±)-*trans*-3,10,11-Trihydroxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine hydrochloride (10): obtained from **43** in a recrystallized yield of 57%; mp 277–278 °C; CIMS (isobutane) $(M + 1)^+$ 284; ^1H NMR (DMSO) δ 9.6 (s, 1, OH), 9.58 (s, 1, NH), 8.93 (s, 1, OH), 8.91 (s, 1, OH), 7.20 (d, 1, ArH, J = 7.1 Hz), 6.80 (d, 1, ArH, J = 7.3 Hz), 6.73 (s, 1, ArH), 6.74 (s, 1, ArH), 6.58 (s, 1, ArH), 4.24 (s, 2, $ArCH_2N$), 4.00 (d, 1, Ar_2CH, J = 11.0 Hz), 2.84 (m, 1, CHN), 2.75 (m, 1, ArCH), 2.65 (m, 1, ArCH), 2.16 (m, 1, CHCN), 1.87 (m, 1, CHCN); HRMS (CI, isobutane) $(M - H^+)$ calcd for $C_{17}H_{17}NO_3$ 282.1130, found 282.1126.

3-Methyl-6-propyl-10,11-dimethoxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine Hydrochloride (44). A solution of 0.85 g (2.46 mmol) of the hydrochloride salt of the 3-methyl 10,11-dimethoxy-substituted secondary amine **38**, 0.912 g (15.69 mmol) of propionaldehyde, and 0.64 g (9.65 mmol) of sodium cyanoborohydride in 15 mL of MeOH was stirred overnight under a nitrogen atmosphere. The solution was concentrated in vacuo, and the residue was partitioned between 5% HCl and diethyl ether. The layers were separated, and the aqueous layer was washed once with ether. The organic fractions were discarded. The aqueous fraction was neutralized with NH_4OH, and the solution was extracted with 3 × 50 mL of dichloromethane. The organic fractions were combined, dried with $MgSO_4$, and filtered, and the volatiles were removed on a rotary evaporator. The pure free base was isolated by radial chromatography on a 2 mm silica gel plate using 5% Et_2O/CH_2Cl_2 as the eluent under an ammonia atmosphere. Product fractions were pooled and concentrated to afford the amine as an oil in 78% yield: FABMS (*m*-NBA) $(M + 1)^+$ 352; ^1H NMR δ 7.26 (d, 1, ArH, J = 7.6 Hz), 7.06 (d, 1, ArH, J = 7.5 Hz), 6.98 (s, 1, ArH), 6.83 (s, 1, ArH), 6.68 (s, 1, ArH), 4.00 (d, 1, ArCHN, J = 15.2 Hz), 3.92 (d, 1, Ar_2CH, J = 11.0 Hz), 3.87 (s, 3, OCH_3), 3.75 (s, 3, OCH_3), 3.58 (d, 1, ArCHN, J = 15.0 Hz), 2.84 (m, 1, ArCH), 2.78 (m, 1, ArCH), 2.57 (m, 1, CHN), 2.33 (s, 3, $ArCH_3$), 2.21 (m, 2, CH_2N), 2.10 (m, 1, CHCN), 1.81 (m, 1, CHCN), 1.52 (m, 2, CH_2), 1.05 (t, 3, CH_3, J = 7.1 Hz); HRMS (CI, isobutane) calcd for $C_{23}H_{29}NO_2$ 352.2277, found 352.2270.

4-Methyl-6-propyl-10,11-dimethoxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine Hydrochloride (45). Following a procedure identical to that for **44**, the hydrochloride salt of the 4-methyl 10,11-dimethoxy secondary amine **39** (385 mg, 1.11 mmol) gave 343 mg (95%) of the undistilled free base **45** as an oil: CIMS (isobutane) $(M + 1)^+$ 352; ^1H NMR δ 7.38 (d, 1, ArH, J = 7.3 Hz), 7.15 (d, 1, ArH, J = 7.4 Hz), 7.06 (d, 1, ArH, J = 7.7 Hz), 6.85 (s, 1, ArH), 6.72 (s, 1, ArH), 4.04 (d, 1, Ar_2CH, J = 10.9 Hz), 3.89 (d, 1, ArCHN, J = 12.1 Hz), 3.87 (s, 3, OCH_3), 3.79 (d, 1, CHN, J = 15.6 Hz), 3.76 (s, 3, OCH_3), 3.53 (d, 1, CHN, J = 15.6 Hz), 3.29 (d, 1, ArCHN, J = 13.4 Hz), 2.88 (m, 1, ArCH), 2.81 (m, 1, ArCH), 2.34 (m, 1, CHN), 2.21 (m, 1, CHCN), 2.33 (s, 3, $ArCH_3$), 1.92 (m, 1, CHCN), 1.60 (m, 2, CH_2), 1.05 (t, 3, CH_3, J = 7.4 Hz); HRMS (CI, isobutane) calcd for $C_{23}H_{29}NO_2$ 352.2348, found 352.2340.

3-Methyl-6-propyl-10,11-dihydroxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine Hydrochloride (11). The 3-methyl 6-propyl 10,11-dimethoxy-substituted amine free base **44** (300 mg, 0.855 mmol) was dissolved in 20 mL of dichloromethane, and the solution was cooled to −78 °C. BBr_3 (99%, 4.27 mmol) was added slowly to the reaction mixture via syringe. The cold bath was removed, and the reaction mixture was left to stir under a nitrogen atmosphere at room temperature. MeOH (6 mL) was added carefully to the reaction mixture. After 30 min, the volatiles were removed via rotary evaporation. The flask was left under high vacuum overnight. The residue was dissolved in water and carefully neutralized under nitrogen to its free base (pH 9–10) with a saturated sodium bicarbonate solution while cooling in an ice bath. The free base was isolated by suction filtration and washed on the filter with cold water. The filtrate was extracted with CH_2Cl_2. The CH_2Cl_2 fractions were combined, dried with $MgSO_4$, filtered, and concentrated. The precipitated free base and the organic residue were combined, dissolved in absolute ethanol, and carefully acidified with concentrated HCl. After removal of the volatiles, the hydrochloride salt was crystallized from MeOH/EtOAc to yield 0.218 g (71%): mp 232–234 °C; CIMS (isobutane) $(M + 1)^+$ 324; ^1H NMR δ 10.79 (s, 1, NH), 8.92 (s, 1, OH), 8.91 (s, 1, OH), 7.28 (s, 1, ArH), 7.23 (m, 2, ArH), 6.68 (s, 1, ArH), 6.61 (s, 1, ArH), 4.55 (d, 1, ArCHN, J = 16.1 Hz), 4.38 (d, 1, ArCHN, J = 16.1 Hz), 4.20 (d, 1, Ar_2CH, J = 11.3 Hz), 3.15 (m, 1, CHN), 2.86 (m, 2, $ArCH_2$), 2.73 (m, 2, CH_2N), 2.34 (s, 3, $ArCH_3$), 2.30 (m, 1, CHCN), 2.04 (m, 1, CHCN), 1.74 (m, 2, CH_2), 0.95 (t, 3, CH_3, J = 6.5 Hz). Anal. ($C_{21}H_{26}NO_2Cl$) C, H, N.

4-Methyl-6-propyl-10,11-dihydroxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine Hydrochloride (13). Following an identical procedure to that for **11**, the free base of 4-methyl 6-propyl 10,11-dimethoxy amine **45** (344 mg, 0.980 mmol) gave 208 mg (59%) of the pure recrystallized hydrochloride salt of **13**: mp 268–269 °C; CIMS (isobutane) $(M + 1)^+$ 324; ^1H NMR δ 10.85 (s, 1, NH), 8.93 (s, 1, OH), 8.90 (s, 1, OH), 7.33 (t, 1, ArH, J = 7.5 Hz), 7.23 (d, 1, ArH, J = 6.8 Hz), 7.20 (d, 1, ArH, J = 6.9 Hz), 6.64 (s, 1, ArH), 6.62 (s, 1, ArH), 4.45 (m, 2, $ArCH_2N$), 4.24 (d, 1, Ar_2CH, J = 11.0 Hz), 3.17 (m, 1, CHN), 2.97 (m, 1, ArCH), 2.86 (m, 1, ArCH), 2.74 (m, 2, CH_2N), 2.38 (s, 3, $ArCH_3$), 2.30 (m, 1, CHCN), 2.04 (m, 1, CHCN), 1.72 (m, 2, CH_2), 0.91 (t, 3, CH_3, J = 6.8 Hz); HRMS (CI, isobutane) calcd for $C_{21}H_{25}NO_2$ 324.1964, found 324.1951.

Pharmacology Methods. Materials. [^{3}H]SCH23390 (7-chloro-8-dihydroxy-3-[^{3}H]methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine) was synthesized as described by Wyrick and Mailman.[17] (*R*)-(+)-SCH23390 was purchased from Research Biochemicals, Inc. (Natick, MA). (±)-DHX (*trans*-10,11-dihydroxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine) was synthesized as previously described.[9] The analogs of DHX were synthesized as described in Brewster et al.[9] Dopamine, cAMP, and isobutylmethylxanthine (IBMX) were obtained from Sigma Chemical Co. (St. Louis, MO). [α-^{32}P]-ATP was supplied by New England Nuclear (Boston, MA).

Subjects. Adult male Sprague–Dawley rats (200–250 g) were obtained from Charles River Breeding Laboratories (Raleigh, NC). Rats were killed by decapitation and the whole brains removed, chilled briefly in ice-cold saline, and sliced into 1.2 mm coronal sections with the aid of a dissecting block similar to that described by Heffner et al.[18] Central striata were then dissected from two coronal sections containing the majority of this region. Tissue was frozen immediately on dry ice and stored at −70 °C until the day of the assay.

Radioreceptor Binding Assays with Rat Striatum. Frozen rat striata were homogenized by seven manual strokes in a Wheaton Teflon–glass homogenizer in 8 mL of ice-cold 50 mM HEPES buffer with 4.0 mM $MgCl_2$ (pH 7.4). Tissue

was centrifuged at 27000*g* for 10 min, the supernatant was discarded, and the pellet was homogenized (five strokes) and resuspended in ice-cold buffer and centrifuged again. The final pellet was suspended at a concentration of approximately 2.0 mg wet wt/mL. The amount of tissue added to each assay tube was 1.0 mg, in a final assay volume of 1.0 mL. D_1 receptors were labeled with [^{3}H]SCH23390 (0.3 nM); D_2 receptors were labeled with [^{3}H]spiperone (0.07 nM) with unlabeled ketanserin (50 nM) added to mask binding to $5HT_2$ sites. Nonspecific binding was estimated by adding unlabeled SCH23390 (1 μM) or unlabeled chlorpromazine (1 μM) for D_1 and D_2 receptor binding assays, respectively. Triplicate determinations were made for each drug concentration. Assay tubes were incubated at 37 °C for 15 min, and binding was terminated by filtering with ice-cold buffer on a Skatron 12-well cell harvester (Skatron, Inc., Sterling, VA) using glass fiber filter mats (Skatron, no. 7034). Filters were allowed to dry, and 1.0 mL of Optiphase HI-SAF II scintillation fluid was added. Radioactivity was determined on an LKB Wallac 1219 RackBeta liquid scintillation counter (Wallac, Gaithersburg, MD). Tissue protein levels were estimated using the BCA protein assay reagent (Pierce, Rockford, IL).

Dopamine Sensitive Adenylate Cyclase in Rat Striatum. The automated HPLC method of Schulz and Mailman[19] was used to measure adenylate cyclase activity by separating cAMP from other labeled nucleotides. Briefly, striatal tissue from rat (ca. 50 mg) was homogenized with eight manual strokes in a Wheaton Teflon–glass homogenizer in 5 mM HEPES buffer (pH 7.5) containing 2 mM EGTA (50 mL/g of tissue). Following the addition and mixing of 50 mL/g 50 mM HEPES buffer (pH 7.5) containing 2 mM EGTA, a 20 μL aliquot of this tissue homogenate was added to a prepared reaction mixture (final volume of 100 μL) containing 0.5 mM ATP, 0.5 mM isobutylmethylxanthine, [^{32}P]ATP (0.5 μCi), 1 mM cAMP, 2 mM $MgCl_2$, 100 mM HEPES buffer, 2 μM GTP, 10 mM phosphocreatine, 5 U of creatine phosphokinase, and various concentrations of test compounds. Triplicate determinations were performed for each drug concentration. The reaction proceeded for 15 min at 30 °C and was terminated by the 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% $Ba(OH)_2$. Samples were centrifuged (10000*g* for 9 min) and the supernatants injected onto an HPLC system (Waters Z-module or RCM 8 × 10 module equipped with a C18, 10 μm cartridge). The mobile phase was 150 mM sodium acetate (pH 5.0) with 23% methanol. A UV detector (254 nm detection) was used to quantify the unlabeled cAMP added to the samples to serve as internal standard. The radioactivity in each fraction was determined by a flow-through radiation detector (Inus Systems, Tampa, FL) using Cerenkov counting. Sample recovery was based on UV measurement of total unlabeled cAMP peak areas quantified using PE Nelson (Cupertino, CA) Model 900 data collection modules and TurboChrom software. Tissue protein levels were estimated using the BCA protein assay reagent (Pierce, Rockford, IL). Data obtained were expressed as pmol of cAMP/mg of protein/min and then normalized. Specifically, basal levels of cAMP synthesis were subtracted from the average values obtained at each drug concentration, and this value was then expressed as a percent of the stimulation produced by 100 μM dopamine.

Data Analysis for cAMP Accumulation Studies. Data were calculated for each sample and expressed initially as pmol/mg/min cAMP. Base line values of cAMP were subtracted from the total amount of cAMP produced in each drug condition. To minimize interassay variation, a reference compound (DA, 100 μM) was included in each assay to serve as an internal standard that allowed normalization of the data. Data for each drug were expressed as a percentage relative to the stimulation produced by 100 μM DA. Normalized dose–response curves were analyzed by nonlinear regression using an algorithm for sigmoid curves in the curve-fitting program InPlot (Graphpad, Inc., San Francisco, CA). For each curve, the program provided point estimates of both the EC_{50} and the maximal stimulation produced (i.e., top plateau of sigmoid curve).

Acknowledgment. This work was supported by PHS Grants MH42705 and MH40537, Center Grants HD03310 and MH33127, and Training Grant GM07040.

References

(1) Kebabian, J. W.; Calne, D. B. Multiple receptors for dopamine. *Nature* **1979**, *277*, 93–96.
(2) Civelli, O.; Bunzow, J. R.; Grandy, D. K.; Zhou, Q.-Y.; Van Tol, H. H. M. Molecular biology of the dopamine receptors. *Eur. J. Pharmacol.* **1991**, *207*, 277–286.
(3) Gingrich, J. A.; Caron, M. G. Recent advances in the molecular biology of dopamine receptors. *Annu. Rev. Neurosci.* **1993**, 299–321.
(4) Andersen, P. H.; Jansen, J. A. Dopamine receptor agonists: selectivity and dopamine D_1 receptor efficacy. *Eur. J. Pharmacol.* **1990**, *188*, 335–347.
(5) Riggs, R. M.; Nichols, D. E.; Foreman, M. M.; Truex, L. L.; Glock, D.; Kohli J. D. Specific dopamine D-1 and DA1 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.
(6) Andersen, P. H.; Nielsen, E. B.; Scheel-Kruger, J.; Jansen, J. A.; Hohlweg, R. Thienopyridine derivatives identified as the first selective, full efficacy, dopamine D_1 receptor agonists. *Eur. J. Pharmacol.* **1987**, *37*, 291–292.
(7) 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-1H-2-benzopyrans: Characterization of an auxiliary binding region in the D_1 receptor. *J. Med. Chem.* **1991**, *34*, 2561–2569.
(8) Lovenberg, T. W.; 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.
(9) 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.
(10) Wei, C.-C.; Teitel, S. Synthesis of a benzo[*a*]phenanthridine isomeric with apomorphine. *Heterocycles* **1977**, *8*, 97–101.
(11) Ninomiya, I.; Kiguchi, T.; Yamamoto, O.; Naito, T. Photocyclization of enamides. Part 13. Substituent effects in the photocyclization of N-benzoylenamines. *J. Chem. Soc., Perkin Trans. I* **1979**, 1723–1728.
(12) Cook, L. L.; Mottola, D. M.; Petitto, J. M.; Lewis, M. H.; Mailman, R. B. Functional interactions of striatal D_1 and D_2 dopamine receptors: effects of tissue preparation and lesions. *Soc. Neurosci. Abstr.* **1991**, *17*, 606.
(13) Pollock, N. J.; Manelli, A. M.; Hutchins, C. W.; Steffey, M. E.; Mackenzie, R. G.; Frail, D. E. Serine mutations in transmembrane V of the dopamine D_1 receptor affect ligand interactions and receptor activation. *J. Biol. Chem.* **1992**, *267*, 17780–17786.
(14) Tomic, M.; Seeman, P.; George, S. R.; O'Dowd, B. F. Dopamine D_1 receptor mutagenesis: role of amino acids in agonist and antagonist binding. *Biochem. Biophys. Res. Commun.* **1993**, *191*, 1020–1027.
(15) Watts, V. J.; Lawler, C. P.; Knoerzer, T.; Mayleben, M. A.; Neve, K. A.; Nichols, D. E.; Mailman, R. B. Hexahydrobenzo-[*a*]phenanthridines: Ligands with High Affinity and Selectivity for D_3 Dopamine Receptors. *Eur. J. Pharmacol.* **1993**, *239*, 271–273.
(16) Burris, K. D.; Filtz, T. M.; Chumpradit, S.; Kung, M. P.; Foulon, C.; Hensler, J. g.; Kung, H. F.; Molinoff, P. B. Characterization of [^{125}I](*R*)-trans-7-hydroxy-2-[N-propyl-N-(3′-iodo-2′-propenyl)-amino]tetralin binding to dopamine D_3 receptors in rat olfactory tubercle. *J. Pharmacol. Exp. Ther.* **1994**, *268*, 935–942.
(17) Wyrick, S.; McDougald, D. L.; Mailman, R. B. Multiple tritium labelling of (+)-7-Chloro-8-hydroxy-1-phenyl-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (SCH 23390). *J. Labelled Compd. Radiopharm.* **1986**, *23*, 685–692.
(18) 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.
(19) 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.
(20) 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.

JM9502697