Articles

Synthesis and Pharmacological Evaluation of 1-(Aminomethyl)-3,4-dihydro-5-hydroxy-1*H*-2-benzopyrans as Dopamine D1 Selective Ligands

Michael R. Michaelides,* Robert Schoenleber, Sheela Thomas, Diane M. Yamamoto, Donald R. Britton, Robert MacKenzie, and John W. Kebabian

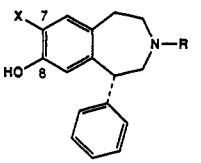
Neuroscience Research, Pharmaceutical Discovery, Abbott Laboratories, Abbott Park, Illinois 60064. *Received February 4, 1991*

A series of 3-substituted 1-(aminomethyl)-3,4-dihydro-5-hydroxy-1*H*-2-benzopyrans were prepared as potential D1 selective antagonists. The compounds were evaluated for their affinity and selectivity for the D1 receptor as well as for their functional antagonism of D1-mediated pharmacological events. The compounds show potent D1 antagonist properties in vitro. The optimum nitrogen substitution was found to be the primary amine and the observed order of potency for substitution at the 6-position is OH > Br > H > OMe. Two representative compounds, the 6-methyl and 6-bromo analogues, were also evaluated in vivo for dopaminergic activity. Interestingly, both compounds behave as potent in vivo agonists.

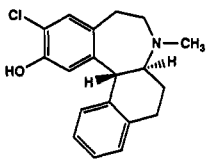
Introduction

Dopamine receptors have been divided into two classes, D1 and D2, on the basis of their pharmacological differences.[1] Recently, both receptors have been sequenced and expressed, confirming the existence of at least two distinct receptor subtypes.[2] In fact, there is growing evidence suggesting an even greater heterogeneity of dopamine receptors.[3]

Selective dopaminergic agents are potentially useful for treating neurological disorders characterized by abnormal dopamine levels, such as schizophrenia and Parkinson's Disease.[4] In order to elucidate the pharmacology of the various subtypes of dopamine receptors, more potent and selective ligands are required. A large number of structurally diverse compounds have been found to be potent and selective ligands for the D2 receptor.[5] However, a much more limited number of D1 selective agents is available. The bulk of the work in this area has been carried out with 1-phenylbenzazepines, exemplified by the prototypic D1 selective antagonist SCH 23390 (1)[6a] and agonist SKF-38393 (2).[6b]



1 X = Cl, R = Me
2 X = OH, R = H



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Recently, a number of groups have described some structurally novel dopamine D1 selective agonists. Specifically, agonists in the isochroman,[7] phenanthridine,[8] indole,[9] and thienopyridine[10] series of compounds have

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(2) D1: (a) Dearry, A.; Gingrich, J. A.; Fremeau, R. T., Jr.; Bates, M. D.; Caron, M. G. Molecular Cloning and Expression of the Gene for a Human D1 Dopamine Receptor. *Nature* **1990**, *347*, 72-76. (b) Zhou, Q. Y.; Grandy, D. K.; Thambi, L.; Kushner, J. A.; Van Tol, H. H. M.; Cone, R.; Pribnow, D.; Salon, J.; Bunzow, J. R.; Civelli, O. Cloning and Expression of Human and Rat D1 Dopamine Receptors. *Nature* **1990**, *347*, 76-80. (c) Sunahara, R. K.; Niznik, H. B.; Weiner, D. M.; Stormann, T. M.; Brann, M. R.; Kennedy, J. L.; Gelenter, J. E.; Rozmahel, R.; Yang, Y.; Israel, Y.; Seeman, P.; O'Dowd, B. F. Human Dopamine D1 Receptor Encoded by an Introless Gene on Chromosome 5. *Nature* **1990**, *347*, 80-83. D2: Bunzow, J. R.; Van Tol, H. M.; Grandy, D. K.; Albert, P.; Salon, J.; MacDonald, C.; Machida, C. A.; Neve, K. A.; Civelli, O. Cloning and Expression of a Rat D2 Dopamine Receptor cDNA. *Nature* **1988**, *336*, 783-787.

(3) The cloning of a proposed D3 receptor has been reported: Sokoloff, P.; Giros, B.; Martres, M. P.; Bouthenet, M. L.; Schwartz, J. C. Molecular Cloning and Characterization of a Novel Dopamine Receptor (D3) as a Target for Neuroleptics. *Nature* **1990**, *347*, 146-151.

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(5) Seeman, P.; Watanabe, M.; Grigoriadis, D.; Tedesco, J. L.; George, S. R.; Svensson, U.; Nilsson, J. L. G.; Neumeyer, J. L. Dopamine D2 Receptor Binding Sites for Agonists. A Tetrahedral Model. *Mol. Pharmacol.* **1985**, *28*, 391-399.

(6) (a) 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. (b) Weinstock, J.; Hieble, J. P.; Wilson, J. W. III The Chemistry and Pharmacology of 3-Benzazepine Derivatives. *Drugs Future* **1985**, *10*, 645-697.

(7) (a) 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 D1 Agonist. *J. Med. Chem.* **1990**, *33*, 2948-2950. (b) DeNinno, M. P.; Schoenleber, R.; Perner, R. J.; Lijewski, L.; Asin, K. E.; Britton, D. R.; MacKenzie, R.; Kebabian, J. W. The 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 D1 Receptor. *J. Med. Chem.*, in press.

(8) 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 D1 Full Agonist. *J. Med. Chem.* **1990**, *33*, 1756-1764.

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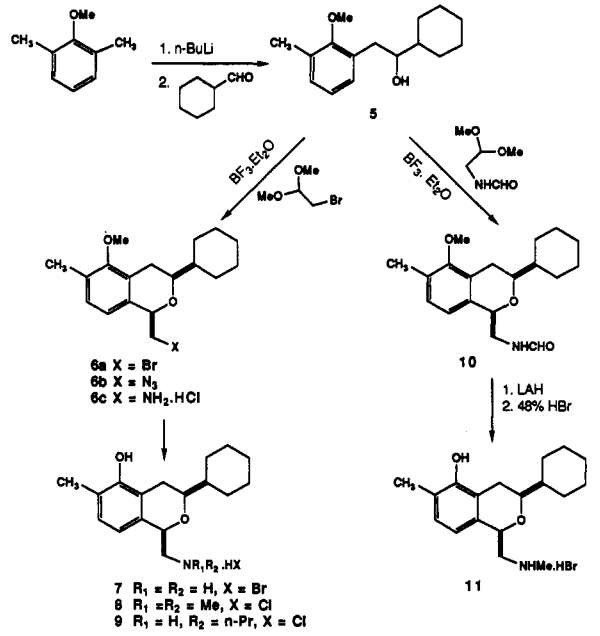
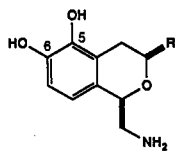
Scheme I



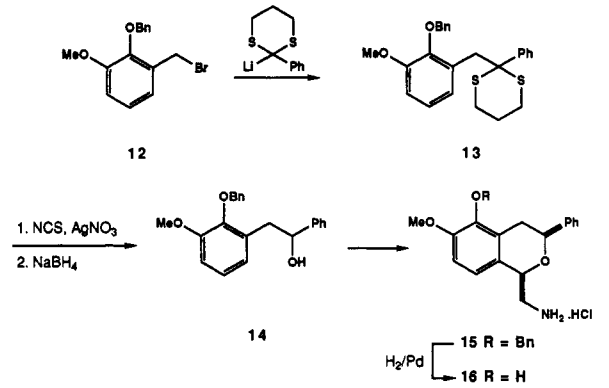
been described. There remains, however, a distinct lack of structurally diverse examples of D1 selective antagonists. Recent developments in the antagonist arena do include the preparation of the conformationally restricted analogues of the 1-phenyl benzazepines, such as SCH 39166 (3),[11a] as well as the ring-contracted derivatives such as the 1-phenyl[11b] and 1-benzyl tetrahydroisoquinolines.[11c] Unfortunately, the latter series tend to show interactions with other catecholaminergic receptors, limiting their utility as selective pharmacological probes. Thus, antagonist studies are still limited to working primarily within the benzazepine or closely related series of compounds.

As part of an ongoing program toward the development of potent and selective ligands for the D1 receptor, our group recently disclosed a series of 1-(aminomethyl)-3-substituted-3,4-dihydro-5,6-dihydroxy-1*H*-2-benzopyrans that showed potent and selective D1 agonism.[7] Two of the most potent compounds in this series are the 3-phenyl and 3-cyclohexyl compounds **4a** and **4b**. On the basis of



4a R = Ph
4b R = Cyclohexyl

Scheme II



structure–activity studies in the benzazepine class of D1 ligands, as well as our own molecular modeling, we anticipated that replacement of the catechol moiety in this isochroman series with an appropriately substituted phenol would lead to compounds with antagonist properties. Superpositioning of the isochroman pharmacophore onto the catecholic benzazepine in such a way as to maximize heteroatom lone pair overlap suggests that the 5-hydroxyl in the isochroman series would interact at the receptor surface in the same region as the 8-hydroxyl in the benzazepine series. Thus, we undertook the preparation of a series of 5-hydroxyisochromans. Our attention was focused on the preparation of 3-phenyl- or 3-cyclohexylisochromans. We further explored the comparative structure–activity relationships in this series by incorporating at the 6-position (corresponding to the 7-position in the benzazepines) those substituents most potent in the benzazepine series.[12] The synthesis and pharmacological activity of a series of 6-bromine-, methoxy-, hydrogen-, or methyl-substituted 5-hydroxyisochromans will be described.

Chemistry

Scheme I describes the synthesis of 6-methylisochromans via the Lewis acid mediated cyclization of an intermediate phenethyl alcohol. The requisite phenethyl alcohol **5** was prepared by lithiation of 2,6-dimethylanisole (*n*-BuLi, THF, 5 h) and subsequent reaction with cyclohexanecarboxaldehyde. Cyclization with bromoacetaldehyde dimethyl acetal was effected with $BF_3 \cdot Et_2O$ to afford cis isomer **6a** with greater than 95:5 diastereoselectivity, in 91% yield.[13] The presence of the *p*-methyl group is critical for the cyclization to occur. Model studies with the unsubstituted phenethyl alcohol showed that the cyclization proceeds in good yield in the absence of any aromatic substitution. However, studies with 2-methoxyphenethyl alcohol showed that the key cyclization step could not be carried out in the absence of an activating group para to the cyclization site in this system, indicating that the cyclization is hampered by the inductive deactivation of the *m*-methoxy group. To complete the synthesis, azide displacement of the bromomethyl derivative followed by LAH reduction and deprotection gave amine **7** in 43–50% overall yield. To study the effect of nitrogen substitution, amine **7** was converted to N,N-dimethyl de-

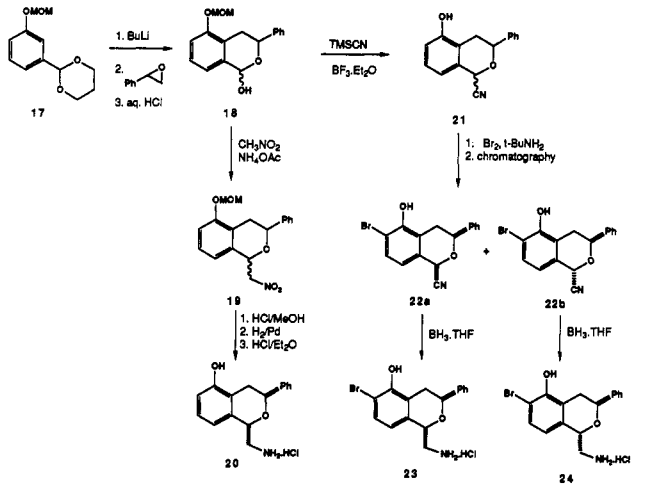
(10) Andersen, P. H.; Nielsen, E. B.; Scheel-Kruger, J.; Jansen, J. A.; Hohlweg, R. Thienopyridine Derivatives Identified as the First Selective, Full Efficacy, Dopamine D1 Receptor Agonists. *Eur. J. Pharm.* **1987**, *137*, 291–292.

(11) (a) 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 D1 Selective Ligand (5*R*)-8-Chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1*H*-3-benzazepin-7-ol. *J. Med. Chem.* **1989**, *32*, 1913–1921. (b) Charifson, P. S.; Wyrick, S. D.; Hoffman, A. J.; Ademe Simmons, R. M.; Bowen, J. P.; McDougald, D. L.; Mailman, R. B. Synthesis and Pharmacological Characterization of 1-Phenyl-, 4-Phenyl-, and 1-Benzyl-1,2,3,4-tetrahydroisoquinolines as Dopamine Receptor Ligands. *J. Med. Chem.* **1988**, *321*, 1941–1946. (b) Kerkman, D. J.; Ackerman, M.; Artman, L. D.; MacKenzie, R. G.; Johnson, M. C.; Bednarz, L.; Montana, W.; Asin, K. E.; Stampfli, H.; Kebabian, J. W. A-69024: a Non-benzazepine Antagonist with Selectivity for the Dopamine D-1 Receptor. *Eur. J. Pharmacol.* **1989**, *166*, 481–491.

(12) Iorio, L. C.; Barnett, A.; Billard, W.; Gold, E. H. Benzazepines: Structure–Activity Relationships Between D1 Receptor Blockade and Selected Pharmacological Effects. In *Neurobiology of Central D-1 Dopamine Receptors*, Advances in Experimental Medicine and Biology; Creese, I., Breese, G. R., Eds.; Plenum Press: New York, 1986; Vol. 204, pp 1–14.

(13) For discussions of the diastereoselectivity, see ref 7.

Scheme III



rivative 8 via reductive amination with formaldehyde, or to *N*-propyl derivative 9 via the propylamide. Alternatively, alcohol 5 was cyclized with *N*-formylaminoacetaldehyde dimethyl acetal in the presence of boron trifluoride etherate to give exclusively cis isomer 10. Reduction of the *N*-formyl group with LAH and deprotection of the methyl ether gave *N*-methyl derivative 11.

To effect the synthesis of the 6-methoxyisochromans, an alternate synthesis of the requisite phenethyl alcohol was carried out. The need for a phenol protecting group that could be differentiated from methoxyl, could withstand Lewis acid conditions, and yet be readily cleaved suggested the benzyl group. This choice, however, precluded an ortho-lithiation approach. Instead, we began our synthesis with the readily available 3-methoxy-2-(benzyloxy)benzyl bromide 12 (see Scheme II). Displacement of the bromide with 2-lithio-2-phenyl-1,3-dithiane afforded 13, which, after deprotection and reduction, gave alcohol 14. Alcohol 14 was then converted to amine 15 by using the methodology described for the preparation of 6c. Deprotection of the benzyl ether (H_2, Pd on carbon) proceeded smoothly to afford phenol 16.

As discussed above, the Lewis acid mediated closure to the 5-hydroxyisochroman ring system could not be applied to the 6-hydro analogues due to the absence of a para activating group. The alternate synthetic approach used is shown in Scheme III. Regioselective lithiation of 17 (*n*-BuLi, cyclohexane)[14] followed by reaction with styrene oxide and acid hydrolysis afforded lactol 18 as a mixture of isomers. The MOM group was required for effective alkylation.[15] Reaction of 18 with nitromethane in the presence of NaOH or NH_4OAc gave 19 as a 1:1 mixture of diastereomers, albeit in low yield.[16] The isomers were chromatographically separated, and the cis isomer was reduced, then deprotected to give 20. Alternatively, trimethylsilyl cyanide addition to lactol 18 under $BF_3 \cdot Et_2O$ catalysis proceeded with cleavage of the phenol protecting group to give nitrile 21 as a 4:1 mixture of trans to cis isomers. We expected kinetic selectivity for the trans isomer due to the preferred axial attack of the cyanide onto the intermediate oxonium ion.[17] Regioselective bromination ortho to the phenol was accomplished by using the procedure described by Pearson.[18] Thus, treatment of 21 with the preformed complex of bromine and *tert*-butyl amine proceeded with complete regiocontrol to give 6-bromo alcohol 22. The regiochemical assignment of the ortho bromine was confirmed (in the trans diastereomer) by an NOE study which revealed an interaction between the hydrogens at C-1 and C-8. The diastereomeric cis and trans compounds were chromatographically separated, then reduced with borane to afford amines 23 and 24. Assignment of the stereochemistry of the final products was based on NOE studies which showed a strong interaction between the C-1 and C-3 (diaxial) hydrogens in the cis isomer that was absent in the trans derivative.

Table I. In Vitro Pharmacology[a]

	K_i, nM		
	D1B	D2B	inhibn of dopamine stimulated adenylate cyclase
1	0.9 (0.8–1.0)	886 (585–1340)	1.3 (0.9–1.9)
2	64.1 (48.9–84.1)	6865 (5350–8810)	not applicable
4a	3.0 (2.1–4.3)	776 (500–1200)	not applicable
4b	5.4 (3.3–8.8)	1120 (890–1410)	not applicable
7	86.4 (80.7–92.5)	>30000	100 (77–130)
8	284 (244–330)	18000 (10700–30400)	125 (71–218)
9	2820 (2600–3050)	2630 (2440–2830)	454 (281–734)
11	263 (208–331)	4610 (3260–6510)	121 (106–139)
16	166 (164–168)	>30000	247 (203–302)
20	103 (47–228)	>30000	52.5 (20.3–135)
23	5.1 (4.1–6.3)	569 (433–746)	32.4 (20.4–51.2)
24	366 (309–433)	1960 (1180–1460)	197 (152–256)

[a] Values reported are the mean, with the range of the SEM in parentheses.

Results and Discussion

The compounds were evaluated for their in vitro affinity for both D1 and D2 receptor sites (Table I). In addition, functional antagonist activity at the D1 receptor was assayed by measuring the compounds' ability to inhibit dopamine stimulated adenylate cyclase.

The most potent compound is *cis*-6-bromo-5-hydroxy-3-phenylisochroman 23, exhibiting a D1 binding constant of 5.1 nM and K_i for inhibition of dopamine stimulated adenylate cyclase of 32 nM. The compound is 112-fold selective for the D1 over the D2 receptor. Hydrogen substitution in place of the bromine (compound 20) results in a 20-fold decrease in binding affinity, whereas methoxy substitution (compound 16) gives a 33-fold decrease. The D1 selectivity, however, is maintained in the series.

(14) Ronald, R. C.; Winkle, M. R. Regioselective Metallations of (Methoxymethoxy)Arenes. *Tetrahedron* **1983**, *39*, 2031–2042.

(15) Plaumann, H. P.; Keay, B. A.; Rodrigo, R. The Regiospecific Lithiation of Aromatic Acetals. *Tetrahedron Lett.* **1979**, 4921–4924.

(16) (a) Colonge, J.; Corbet, P. Bull. Soc. Chim. Fr. **1961**, *26*, 287–288. (b) Sowden, J. C.; Schaffer, R. The Condensation of Nitromethane with D-Mannose: Synthesis of D-Manno-D-galaheptose and D-Manno-D-talo-heptose. *J. Am. Chem. Soc.* **1951**, *73*, 1662–1664.

(17) Interestingly, attempts to convert a pure sample of the trans compound into the cis isomer via prolonged treatment with base afforded a 4:1 mixture in favor of the trans isomer, indicating that the trans isomer is the more thermodynamically favored product.

(18) Pearson, D. W.; Wysong, R. D.; Breder, C. V. The Ortho Bromination of Phenols. *J. Org. Chem.* **1967**, *32*, 2358–2360.

Table II. Binding Affinities for Selected Biogenic Amine Receptors[a]

	binding K_i, nM						
	5HT1a	5HT1c	5HT2	α1	α2	β	uptake
7	54.1 (24.7–118)	58.4 (50.1–68.1)	242 (234–249)	>30000	358 (246–519)	19200 (14500–24600)	1870 (1620–2160)
23	312 (152–638)	200 (118–339)	6360 (5560–7260)	1820 (1720–1930)	360 (324–401)	18400 (13500–25100)	>30000

[a] Values (nM) are reported as the mean, with the range of the SEM in parentheses.

Changes in the cyclase inhibition were less dramatic, showing only a 1.6-fold decrease between compounds **23** and **20** and a 7.6-fold difference between **23** and **16**. For comparison, the D1 binding constant for the corresponding catechol is 3.2 nm. The observed order of potency, that is OH > Br > H > OMe, differs from that in the 1-phenylbenzazepines, where the order of potency for substituents at the 7-position is Br > OMe > H > OH.[12] It is especially noteworthy that the catechol, while the most potent in the isochroman series, is the least potent in the benzazepine series.

A comparison of the cis and trans compounds, **23** and **24**, indicates that the cis isomer is significantly more potent in binding to the D1 receptor. Whereas the cis isomer places the substituents at the 1- and 3-positions in a pseudodiequatorial conformation, the trans compound requires one of these groups to occupy a pseudoaxial position. Previous studies on conformationally constricted analogues have consistently suggested that the amino group must be positioned near the plane of the aromatic phenol for maximal dopaminergic binding affinity. The NMR data, as well as steric considerations, suggest that the aminomethyl group is forced into the axial position and out of the plane of the aromatic group in the trans derivative, contributing to its loss of potency. Interestingly, the loss of binding affinity to the D2 receptor is not as great. The loss of functional activity is also not as large, although the process of signal transduction is too complex to rationalize on this simplistic level.

The 3-cyclohexyl-substituted derivatives do not maintain the same level of potency as the phenyl derivatives (cf. **4b** and **7**). However, the 6-methyl-3-cyclohexyl derivative is more potent than the 6-methoxy-3-phenylisochroman and similar in potency to the 6-hydro-3-phenyl analogue. The data suggest that potency due to the 6-methyl substitution in the isochroman series parallels the structure–activity relationship seen in the benzazepine series. The optimum nitrogen substitution for dopamine D1 antagonist potency in the isochroman series is determined to be the primary amine by comparison of compounds **7**–**11**. This is in direct contrast to the 1-phenylbenzazepine antagonists, where tertiary *N*-methyl substitution is clearly optimal. In addition, sequential N-methylation on the isochroman nucleus causes a decrease in D1 binding affinity upon monomethylation, but no further decrease upon dimethylation. The N-propyl derivative is virtually nonselective toward the two dopamine receptors. The same trend is seen in the D1 antagonist functional assay.

In order to assess the selectivity of these compounds toward other biogenic amines receptors, two representative compounds, **7** and **23**, were evaluated for their affinity for serotonin receptors (5HT1a, 5HT1c, 5HT2) and adrenergic receptors (α1, α2, β), as well as for the dopamine uptake site (Table II).

6-Methyl compound **7** exhibited potent binding for the 5HT1a and 5HT1c receptors, surpassing its affinity for the D1 receptor. In contrast, bromo compound **23** was very selective, showing at least a 40-fold selectivity for the D1 receptor over the other receptors tested.

Table III. In Vivo Pharmacology Rotational Behavior

no.	dose,[a,b] μmol/kg	net contralateral rotations/2 h (±SEM)[c]
2	0.43	241 (89)
	1.7	608 (294)
	1.7[d]	47 (35)
7	0.1	227 (95)
	1.0	751 (126)
	0.1[e]	4 (9)
23	0.1	1007 (202)
	1.0	748 (136)
	0.1[e]	151 (111)

[a] Vehicle treated animals show no or mild ipsilateral rotation. [b] Compounds were administered subcutaneously. [c] Number of animals was four. [d] Predosed with SCH23390 (0.05 μmol/kg sc). [e] Predosed with SCH23390 (0.1 μmol/kg sc), 40 min prior to injection of test compound.

Compounds **7** and **23** were also evaluated for their ability to act in vivo as D1 selective antagonists. Rats with unilateral 6-hydroxydopamine lesions will rotate contralaterally upon administration of either a D1 or D2 centrally acting direct dopamine agonist.[19] This behavior can be blocked by pretreatment with the corresponding dopamine antagonist. It was thought, then, that animals pretreated with one of these compounds would not rotate in response to subsequent administration of a direct-acting D1 selective agonist. However, both compounds behave as potent in vivo dopamine agonists. That is, subcutaneous injection of either compound caused immediate contralateral turning. Specifically, injection of **7** or **23** produced significant rotation in a 2-h monitoring period (Table III). Mediation through a D1 mechanism was confirmed by an experiment in which pretreatment with the known D1 selective antagonist, SCH23390, completely blocked all rotation in both cases. It is noteworthy that both compounds show no in vitro agonism, as they fail to stimulate adenylate cyclase up to a concentration of 10 μM.

There is previous evidence to suggest that the 5-hydroxy-6-methyl substitution pattern present in **7** acts as a latent dopamine agonist moiety. Cannon has suggested that 2-(di-*n*-propylamino)-5-hydroxy-6-methyltetralin is a dopamine agonist prodrug, metabolically activated through oxidation of the methyl group.[20] In ad-

(19) (a) Ungerstedt, V.; Arbuthnott, G. W. Quantitative Recording of Rotational Behavior in Rats After 6-Hydroxydopamine Lesions of the Nigrostriatial Dopamine System. *Brain. Res.* **1970**, *24*, 485–493. (b) Arnt, J.; Hyttel, J. Differential Inhibition by Dopamine D-1 and D-2 Antagonists of Circling Behaviour Induced by Dopamine Agonists in Rats with Unilateral 6-Hydroxydopamine Lesions. *Eur. J. Pharmacol.* **1984**, *102*, 349–354.

(20) Cannon, J. G.; Furlano, D. C.; Koble, D. L.; Koons, J. C.; Long, J. P. Possible Biologically Active Metabolites Of 5-Hydroxy-6-Methyl-2-di-*n*-propylaminotetralin. *Life Sci.* **1984**, *34*, 1679–1682. (b) Koons, J. C.; Long, J. P.; Koble, D. C.; Cannon, J. G.; Fischer, L. J. Effects of Metyparone on the Pharmacological Activity, Plasma Levels and Urinary Excretion of the Dopamine Receptor Agonist DK-118. *J. Pharmacol. Exp. Ther.* **1985**, *233*, 51–57. (c) Koons, J. C.; Flynn, J. R.; Cannon, J. G.; Long, J. P. Metyparone and SKF 525-A Inhibition of a Presynaptic Dopamine Agonist. Fed. Proc. **1982**, *41*, 1662.

dition, *trans*-7-hydroxy-8-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline induces rat rotation despite its in vitro profile as a dopamine D2 antagonist.[21] The mechanism for this behavior, however, was suggested to be other than dopaminergically mediated. Finally, this centrally mediated response is unique to the 5,6-like substitution in the 2-aminotetralin partial structure as the analogous 2-(di-*n*-propylamino)-7-hydroxy-6-methyltetralin, as well as other ring systems incorporating this hydroxymethyl substitution pattern, failed to show any dopaminergic effects of any kind.[22]

The reasons for these behavioral effects remain unclear. Furthermore, the in vivo agonist activity of **23** remains very puzzling, as there is no data to suggest that metabolic activation of a bromophenol in a dopaminergic series of compounds can impart agonist activity. The rapid onset of action also argues against prior metabolic activation.[23] Likewise, it would seem rather surprising that two substitution patterns as different as those in **7** and **23** would result in similar contradictory behavioral profiles. One possibility is that the discrepancy reflects biochemical pharmacological differences in the activities of the enantiomers. However, we believe this to be unlikely, as no such differences were observed with catechol isochroman **4a**. Both enantiomers of **4a** showed D1 agonist activity, with the 1*R*,3*S* isomer being predominantly responsible for activity.[7] Another possibility is that both compounds are partial agonists unable to elevate cyclic adenosine monophosphate production to determinable levels in the present assay system. This would suggest that the present in vivo assay is a more sensitive means for determining the agonist properties of these compounds, although additional in vivo and in vitro assays are required in order to substantiate this hypothesis.

Experimental Section

General. Melting points were determined with a Thomas Hoover melting point apparatus and are uncorrected. All spectral and analytical data were obtained through the Abbott analytical department. All reactions were conducted in oven-dried or flame-dried glassware under a nitrogen atmosphere. Anhydrous solvents were purchased from Aldrich Chemical Co. Analytical thin-layer chromatography was performed by using 2.5 cm × 10 cm plates coated with a 0.25-mm thickness of silica gel containing PF 254 indicator (Analtech). Flash chromatography was performed with silica gel 60 (E. Merck 9285, 230–400 mesh).

1-Cyclohexyl-2-(2′-methoxy-3′-methylphenyl)-1-ethanol (5). n-Butyllithium (14.0 mL of a 2.5 M solution in hexane, 35 mmol) was added dropwise to a solution of 4.95 mL (35 mmol) of 2,6-dimethyl anisole in 60 mL of dry THF at 0 °C and the resultant mixture was stirred at 0 °C for 1 h, and then at ambient temperature for 4 h. The reaction mixture was then cooled to 0 °C, treated with 4.2 mL (35 mmol) of cyclohexanecarboxaldehyde, allowed to warm to ambient temperature again, and poured into saturated aqueous ammonium chloride solution. The cloudy mixture was extracted with diethyl ether and the ether solution was washed with water and brine and concentrated in vacuo. The residue was purified on silica gel eluted with hexane/diethyl ether (5:1 v/v) to give 4.2 g (48% yield) of alcohol **5** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.1–6.95 (m, 3 H), 3.75 (s, 3 H), 3.57 (m, 1 H), 2.85 (dd, *J* = 3, 13 Hz, 1 H), 2.68 (dd, *J* = 10, 13 Hz, 1 H), 2.31 (s, 3 H), 2.28 (d, *J* = 3 Hz, 1 H), 1.92 (m, 1 H), 1.82–1.64 (m, 4 H), 1.5–1.05 (m, 6 H).

***cis*-1-(Bromomethyl)-3-cyclohexyl-3,4-dihydro-5-methoxy-6-methyl-1*H*-2-benzopyran (6a).** Boron trifluoride etherate (1.10 mL, 8.2 mmol) was added dropwise to a solution of 1.02 g (4.1 mmol) of alcohol **5** and 0.58 mL (4.9 mmol) of bromoacetaldehyde dimethyl acetal in 10 mL of methylene chloride at −50 °C. The reaction mixture was allowed to warm to 0 °C over a period of 1 h and then stirred at 0 °C for 7 h. The resultant mixture was diluted with 200 mL of diethyl ether and the ether solution was washed with aqueous 10% sodium carbonate solution and brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to afford 1.31 g (91% yield) of a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.03 (d, *J* = 8 Hz, 1 H), 6.77 (d, *J* = 8 Hz, 1 H), 4.93 (bd, *J* = 7.5 Hz, 1 H), 3.88 (dd, *J* = 3, 12 Hz, 1 H), 3.72 (s, 3 H), 3.56 (dd, *J* = 7.5, 12 Hz, 1 H), 3.29 (m, 1 H), 2.90 (dd, *J* = 2, 15 Hz, 1 H), 2.52 (dd, *J* = 11, 16 Hz, 1 H), 2.27 (s, 3 H), 2.15 (m, 1 H), 1.9–1.6 (m, 4 H), 1.38–1.00 (m, 6 H).

***cis*-1-(Aminomethyl)-3-cyclohexyl-3,4-dihydro-5-methoxy-6-methyl-1*H*-2-benzopyran Hydrochloride (6c).** A solution of 1.23 g (3.5 mmol) of 1-(bromomethyl)-3-cyclohexyl-3,4-dihydro-5-methoxy-6-methyl-1*H*-2-benzopyran in 20 mL of *N*,*N*-dimethylformamide (DMF) was treated with 1.03 g (21 mmol) of lithium azide. The reaction mixture was heated at 80 °C for 1.5 h, cooled to ambient temperature, and then poured into 100 mL of water. The resultant cloudy mixture was extracted with 2 × 150 mL of diethyl ether, and the combined ether extracts were washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified on a silica gel column eluted with 5% diethyl ether in hexane to give 0.565 g (51% yield) of the intermediate, 1-(azidomethyl)-3-cyclohexyl-5-methoxy-6-methyl-1*H*-2-benzopyran (**6b**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.02 (d, *J* = 8 Hz, 1 H), 6.71 (d, *J* = 8 Hz, 1 H), 4.94 (bd, *J* = 7.5 Hz, 1 H), 3.74 (s, 3 H), 3.61 (dd, *J* = 3, 14 Hz, 1 H), 3.45 (dd, *J* = 7.5, 14 Hz, 1 H), 3.33 (ddd, *J* = 3, 7.5, 11 Hz, 1 H), 2.88 (dd, *J* = 3, 16 Hz, 1 H), 2.57 (dd, *J* = 11, 16 Hz, 1 H), 2.28 (s, 3 H), 2.07 (m, 1 H), 1.9–1.6 (m, 4 H), 1.4–1.0 (m, 6 H). Azide **6b** (565 mg, 1.8 mol) was dissolved in 20 mL of diethyl ether and the resultant ether solution was cooled to 0 °C. Lithium aluminum hydride (2.2 mL of a 1.0 M solution in diethyl ether) was added and the reaction mixture was stirred at 0 °C for 1 h. The reaction mixture was allowed to warm to ambient temperature and stirred at ambient temperature for 1 h and then the reaction was quenched by the sequential addition of 95 μL of water, 95 μL of 15% aqueous sodium hydroxide solution, and 300 μL of water. The reaction mixture was filtered and the filter cake was washed with methylene chloride. The combined filtrates were concentrated, and the residue was treated with 25 mL of diethyl ether saturated with hydrogen chloride. The precipitate was collected by vacuum filtration to give 522 mg (90% yield) of the title compound as a white solid: mp 199–201 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (bs, 3 H), 7.03 (d, *J* = 9 Hz, 1 H), 6.78 (d, *J* = 9 Hz, 1 H), 5.09 (bd, *J* = 9 Hz, 1 H), 3.73 (s, 3 H), 3.66 (bd, *J* = 13 Hz, 1 H), 3.38 (m, 1 H), 3.04 (m, 1 H), 2.88 (bd, *J* = 16 Hz, 1 H), 2.54 (dd, *J* = 12, 16 Hz, 1 H), 2.27 (s, 3 H), 2.12 (bd, *J* = 12 Hz, 1 H), 1.9–1.0 (m, 10 H).

***cis*-1-(Aminomethyl)-3-cyclohexyl-3,4-dihydro-5-hydroxy-6-methyl-1*H*-2-benzopyran Hydrobromide (7).** A suspension of 1-(aminomethyl)-3-cyclohexyl-3,4-dihydro-5-methoxy-6-methyl-1*H*-2-benzopyran (467 mg, 1.43 mmol) in 10 mL of glacial acetic acid and 10 mL of 48% hydrobromic acid was heated at reflux for 2 h. The reaction mixture was then concentrated in vacuo. The residue was crystallized from ethyl alcohol/methylene chloride to afford 478 mg (94%) of **7** as a white solid: mp 217–218 °C; MS (DCI-NH_3) *m*/*z* 276 $(M + H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.40 (s, 1 H), 7.71 (bs, 3 H), 6.93 (d, *J* = 7.5 Hz, 1 H), 6.63 (d, *J* = 7.5 Hz, 1 H), 4.82 (bd, *J* = 10 Hz, 1 H), 3.51 (dd, *J* = 3, 13.5 Hz, 1 H), 3.29 (m, 1 H), 2.88 (dd, *J* = 10, 13.5 Hz, 1 H), 2.74 (dd, *J* = 2, 16 Hz, 1 H), 2.33 (dd, *J* = 11, 16 Hz, 1 H), 2.14 (s, 3 H), 2.10 (m, 1 H), 1.8–1.0 (m, 10 H). Anal. ($C_{17}H_{26}BrNO_2$) C, H, N.

***cis*-3-Cyclohexyl-3,4-dihydro-1-[(*N*,*N*-dimethylamino)methyl]-5-hydroxy-6-methyl-1*H*-2-benzopyran Hydrochloride (8).** A solution of 200 mg (0.56 mmol) of amine hy-

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(23) In contrast, 2-(di-*n*-propylamino)-5-hydroxy-6-methyltetralin shows slow onset of action with maximal effect seen 30 min after administration (ref 20c).

drobromide 7 in 3 mL of methanol was treated with 0.45 mL of a 37% aqueous formaldehyde solution (6.0 mmol), followed by 190 mg (3 mmol) of sodium cyanoborohydride, and the resultant mixture was stirred at ambient temperature for 2 days. The reaction was quenched with 5 mL of 1 M aqueous hydrochloric acid and the mixture was poured into 150 mL of saturated aqueous sodium bicarbonate solution. The cloudy mixture was extracted twice with methylene chloride. The combined organic extracts were washed with brine and concentrated in vacuo. The residue was treated with diethyl ether saturated with anhydrous hydrogen chloride and the resultant solution was concentrated under reduced pressure. The residue was recrystallized from methanol/methylene chloride/diethyl ether to afford 108 mg (57% yield) of 8 as a white solid: mp 217–219 °C; MS (DCI-NH_3) m/z 304 $(M + H)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ 9.52 (bs, 1 H), 8.47 (s, 1 H), 6.96 (d, J = 7.5 Hz, 1 H), 6.61 (d, J = 7.5 Hz, 1 H), 5.06 (bd, J = 11 Hz, 1 H), 3.77 (m, 1 H), 3.3–3.1 (m, 2 H), 2.88 (d, J = 5 Hz, 3 H), 2.85 (d, J = 5 Hz, 3 H), 2.76 (bd, J = 18 Hz, 1 H), 2.35 (dd, J = 12, 18 Hz, 1 H), 2.14 (s, 3 H), 2.07 (m, 1 H), 1.8–1.0 (m, 10 H). Anal. ($C_{19}H_{30}ClNO_2$) C, H, N.

cis-3-Cyclohexyl-3,4-dihydro-5-hydroxy-6-methyl-1-[(*N*-propylamino)methyl]-1*H*-2-benzopyran Hydrochloride (9). A suspension of amine hydrobromide 7 (404 mg, 1.13 mmol) in 8 mL of diethyl ether was treated sequentially with a 15% NaOH solution (0.81 mL, 2.95 mmol) and propionyl chloride (115 μL, 1.28 mmol). The reaction mixture was stirred at ambient temperature for 10 h. The resulting precipitate was collected by vacuum filtration to give after washing with water and ether 142 mg of the intermediate 3-cyclohexyl-3,4-dihydro-5-hydroxy-6-methyl-1-[(*N*-propionylamino)methyl]-1*H*-2-benzopyran. The intermediate amide was suspended in 2 mL of THF, cooled in an ice bath, and then treated with lithium aluminum hydride (0.6 mL of a 1.0 M solution in THF, 0.6 mmol). The reaction mixture was stirred at reflux for 5 h, and cooled to ambient temperature, and then the reaction was quenched by the sequential addition of 50 μL of water, 50 μL of 15% aqueous sodium hydroxide solution, and 150 μL of water. The reaction mixture was filtered and the filter cake was washed with methylene chloride. The combined filtrates were concentrated, and the residue was treated with 25 mL of diethyl ether saturated with hydrogen chloride. The precipitate was collected by vacuum filtration to give 97 mg (24% overall yield) of 9 as a white solid: mp 248–250 °C; MS (DCI-NH_3) m/z 318 $(M + H)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ 8.93 (bs, 1 H), 8.55 (bs, 1 H), 8.44 (s, 1 H), 6.94 (d, J = 8.5 Hz, 1 H), 6.63 (d, J = 8.5 Hz, 1 H), 4.98 (bd, J = 10 Hz, 1 H), 3.63 (m, 1 H), 3.30 (m, 1 H), 2.93 (m, 1 H), 2.76 (dd, J = 2, 17 Hz, 1 H), 2.32 (m, 1 H), 2.15 (s, 3 H), 2.10 (m, 1 H), 1.85–1.0 (m, 14 H), 0.91 (t, J = 7 Hz, 3 H). Anal. ($C_{20}H_{32}ClNO_2$) C, H, N.

cis-3-Cyclohexyl-3,4-dihydro-1-[(*N*-formylamino)methyl]-5-methoxy-6-methyl-1*H*-2-benzopyran (10). Boron trifluoride etherate (0.58 mL, 4.7 mmol) was added to a solution of 582 mg (2.3 mmol) of 1-cyclohexyl-2-(2′-methoxy-3′-methylphenyl)-1-ethanol and 245 mg (2.9 mmol) of *N*-formylaminoacetaldehyde dimethyl acetal in 5 mL of diethyl ether at 0 °C. After being stirred for 2 days at ambient temperature, the reaction mixture was poured into 150 mL of saturated aqueous sodium bicarbonate solution. The resultant cloudy mixture was extracted with ethyl acetate. The ethyl acetate solution was washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified on silica gel eluted with 40% ethyl acetate in hexane to afford 405 mg (55% yield) of 10: ^1H NMR (major rotamer) (300 MHz, $CDCl_3$) δ 8.18 (d, J = 1 Hz, 1 H), 7.03 (d, J = 8.5 Hz, 1 H), 6.85 (d, J = 8.5 Hz, 1 H), 5.97 (bs, 1 H), 4.77 (bd, J = 7.5 Hz, 1 H), 4.02 (ddd, J = 7.5, 14 Hz, 1 H), 3.72 (s, 3 H), 3.43–3.27 (m, 2 H), 2.90 (dd, J = 3, 17 Hz, 1 H), 2.51 (dd, J = 11, 17 Hz, 1 H), 2.27 (s, 3 H), 2.05 (m, 1 H), 1.9–1.0 (m, 10 H).

cis-3-Cyclohexyl-3,4-dihydro-5-hydroxy-6-methyl-1-[(*N*-methylamino)methyl]-1*H*-2-benzopyran Hydrobromide (11). A solution of 400 mg (1.27 mmol) of 3-cyclohexyl-3,4-dihydro-1-[(*N*-formylamino)methyl]-5-methoxy-6-methyl-1*H*-2-benzopyran in 4 mL of THF was treated with 2.5 mL of a 1.0 M solution of lithium aluminum hydride (2.5 mmol) in THF. The reaction mixture was heated at reflux for 12 h. The reaction was quenched by the sequential addition of 90 μL of water, 90 μL of 15% aqueous sodium hydroxide solution, and 300 μL of water. The resultant precipitate was filtered and washed with methylene chloride and ethyl acetate. The filtrate was concentrated under reduced pressure and the residue was treated with diethyl ether saturated with anhydrous hydrogen chloride. The precipitate collected by vacuum filtration was 1-(aminomethyl)-3-cyclohexyl-3,4-dihydro-5-methoxy-6-methyl-1*H*-2-benzopyran hydrochloride: ^1H NMR (300 MHz, $CDCl_3$) δ 9.93 (bs, 1 H), 9.06 (bs, 1 H), 7.02 (d, J = 8 Hz, 1 H), 7.75 (d, J = 8 Hz, 1 H), 5.24 (bd, J = 10 Hz, 1 H), 3.73 (s, 3 H), 3.64 (m, 1 H), 3.38 (ddd, J = 2.5, 7, 9 Hz, 1 H), 3.1–3.8 (m, 5 H), 2.56 (dd, J = 12, 17 Hz, 1 H), 2.27 (s, 3 H), 2.08 (m, 1 H), 1.85–1.05 (m, 10 H). This compound was dissolved in 8 mL of glacial acetic acid and 8 mL of 48% aqueous hydrobromic acid solution, and the resultant solution was heated at reflux temperature for 2 h. The solution was concentrated in vacuo to give a brown oil, which was crystallized from ethanol/methylene chloride/diethyl ether to give 250 mg (65% yield) of 11 as an off-white solid: mp 204–205 °C; MS (DCI-NH_3) m/z 290 $(M + H)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ 8.52 (bs, 1 H), 8.42 (s, 1 H), 8.28 (bs, 1 H), 6.95 (d, J = 8 Hz, 1 H), 6.62 (d, J = 8 Hz, 1 H), 4.91 (bd, J = 10 Hz, 1 H), 3.63 (m, 1 H), 3.40–3.28 (m, 4 H), 3.03 (m, 1 H), 2.76 (bd, J = 17.5 Hz, 3 H), 2.52 (t, J = 6 Hz, 3 H), 2.34 (dd, J = 12, 17.5 Hz, 1 H), 2.15 (s, 3 H), 2.10 (m, 1 H), 1.8–1.0 (m, 10 H). Anal. ($C_{18}H_{28}BrNO_2$) C, H, N.

2-(Benzyloxy)-3-(bromomethyl)-1-methoxybenzene (12). To a solution of 15.04 g (62 mmol) of 2-(benzyloxy)-3-(hydroxymethyl)-1-methoxybenzene[24] in 140 mL of diethyl ether at 0 °C was added slowly, with stirring, 2.9 mL (31 mmol) of phosphorus tribromide. The reaction mixture was stirred at 0 °C for 30 min and then allowed to warm to ambient temperature over a 4-h period. The solution phase was decanted and the reaction was quenched with aqueous sodium bicarbonate solution. The layers were separated, and the aqueous layer was extracted twice with diethyl ether. The combined organic layers were washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 12.49 g (65% yield) of the title compound as an oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.55–7.50 (m, 2 H), 7.43–7.30 (m, 3 H), 7.05 (t, J = 8 Hz, 1 H), 6.97 (dd, J = 1.5, 8 Hz, 1 H), 6.91 (dd, J = 1.5, 8 Hz, 1 H), 5.15 (s, 2 H), 4.50 (s, 2 H), 3.89 (s, 3 H).

2-(Benzyloxy)-3-[2′-(1″,3″-dithiane)-2′-phenylethyl]-1-methoxybenzene (13). To a solution of 4.38 g (23.3 mmol) of 2-phenyl-1,3-dithiane in 15 mL of THF at −78 °C under a nitrogen atmosphere was added dropwise 8.9 mL (22.3 mmol) of a 2.5 M solution of *n*-butyllithium in hexane. The resultant mixture was stirred at −78 °C for 1 h and then to it was added a solution of 6.86 g (22.3 mmol) of benzyl bromide 12 in 70 mL of THF. The reaction mixture was allowed to warm to ambient temperature and stirred at ambient temperature for 24 h. The reaction was then quenched by the addition of 125 mL of water and the resultant mixture was stirred at ambient temperature for 1 h. The mixture was then extracted three times with ethyl acetate, and the combined ethyl acetate extracts were washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to give 10.99 g (100%) of 13, which was carried on to the next step without purification: ^{1}NMR (300 MHz, $CDCl_3$) δ 7.80–7.75 (m, 2 H), 7.55–7.20 (m, 8 H), 6.85–6.78 (m, 2 H), 6.43 (dd, J = 2, 8 Hz, 1 H), 4.83 (s, 2 H), 3.80 (s, 3 H), 3.32 (s, 2 H), 3.13–3.00 (m, 2 H), 2.95–2.87 (m, 2 H), 2.20–2.11 (m, 1 H), 2.00–1.95 (m, 1 H).

2-[2′-(Benzyloxy)-3′-methoxyphenyl]-1-phenyl-1-ethanol (14). To a solution of 19.88 g (117 mmol) of silver nitrate and 13.87 g (104 mmol) of *N*-chlorosuccinimide in 250 mL of an 80% solution of acetonitrile in water was added dropwise a solution of 10.99 g (26 mmol) of 13 in acetonitrile. The reaction mixture was stirred at ambient temperature for 45 min and then quenched with 25 mL of saturated aqueous sodium hydrogen sulfite solution, 25 mL of saturated aqueous sodium carbonate solution, and 25 mL of brine. The mixture was filtered and the filtrate was washed with 1 N aqueous hydrochloric acid solution, saturated aqueous sodium bicarbonate solution, and brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue

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was purified by chromatograpy on silica gel eluted with ethyl acetate/hexane (1:5 v/v) to give 3.27 g (38% yield) of the intermediate 2-[2'-(benzyloxy)-3'-methoxyphenyl]-1-phenylethanone: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95–7.90 (m, 2 H), 7.55–7.20 (m, 8 H), 7.02 (t, J = 8 Hz, 1 H), 6.87 (dd, J = 1.5, 8 Hz, 1 H), 6.78 (dd, J = 1.5, 8 Hz, 1 H), 5.00 (s, 2 H), 4.20 (s, 2 H), 3.89 (s, 3 H). The intermediate ketone (2.3 g, 6.9 mmol) was dissolved in 20 mL of ethyl alcohol then treated with of 230 mg (6.0 mmol) of sodium borohydride. The reaction mixture was stirred for 12 h at ambient temperature and then poured into 25 mL of 10% aqueous hydrochloric acid solution. The cloudy mixture was extracted with 3 × 75 mL of diethyl ether, and the combined ether extracts were washed with aqueous sodium bicarbonate solution and brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to afford 1.89 g (82% yield) of alcohol 14: ^{1}NMR (300 MHz, $CDCl_3$) δ 7.50–7.20 (m, 5 H), 7.01 (t, J = 8 Hz, 1 H), 6.87 (dd, J = 1.5, 8 Hz, 1 H), 6.73 (dd, J = 1.5, 8 Hz, 1 H), 5.07 (d, J = 11 Hz, 1 H), 5.02 (d, J = 11 Hz, 1 H), 4.89 (m, 1 H), 3.90 (s, 3 H), 3.00 (dd, J = 4.5, 17 Hz, 1 H), 2.89 (dd, J = 9, 17 Hz, 1 H), 2.59 (d, J = 4 Hz, 1 H).

***cis*-1-(Aminomethyl)-5-(benzyloxy)-3,4-dihydro-6-methoxy-3-phenyl-1*H*-2-benzopyran Hydrochloride (15).** Following the procedures described for the conversion of alcohol 5 to amine **6c**, phenethyl alcohol 14 was converted to the title compound: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.05 (bs, 3 H), 7.54–7.28 (m, 5 H), 7.10 (t, J = 9 Hz, 1 H), 7.05 (d, J = 9 Hz, 1 H), 5.13 (bd, J = 7.5 Hz, 1 H), 4.98 (d, J = 12 Hz, 1 H), 4.92 (d, J = 12 Hz, 1 H), 4.65 (dd, J = 3, 11 Hz, 1 H), 3.87 (s, 3 H), 3.59 (m, 1 H), 3.13–2.94 (m, 2 H), 2.58 (dd, J = 11, 16.5 Hz, 1 H).

***cis*-1-(Aminomethyl)-3,4-dihydro-5-hydroxy-6-methoxy-3-phenyl-1*H*-2-benzopyran Hydrochloride (16).** A solution of 940 mg (2.28 mmol) of *cis*-1-(aminomethyl)-5-(benzyloxy)-3,4-dihydro-6-methoxy-3-phenyl-1*H*-2-benzopyran hydrochloride in 500 mL of methanol was treated with 500 mg of 10% palladium on carbon and the resultant mixture was shaken under a hydrogen atmosphere for 24 h. The reaction mixture was diluted with ethyl acetate and filtered through Celite filter aid. The filtrate was concentrated in vacuo to give an off-white solid which was crystallized from methanol/methylene chloride/ether to give 488 mg (66% yield) of **16**: mp 234 °C; MS (DCI-NH_3) m/z 286 (M + H)$^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.80 (bs, 1 H), 8.04 (bs, 3 H), 7.58 (d, J = 7.5 Hz, 2 H), 7.44–7.28 (m, 3 H), 6.91 (d, J = 9 Hz, 1 H), 6.76 (d, J = 9 Hz, 1 H), 5.13 (bd, J = 7.5 Hz, 1 H), 4.74 (dd, J = 3, 12 Hz, 1 H), 3.81 (s, 3 H), 3.56 (dd, J = 3, 13 Hz, 1 H), 3.12–3.00 (m, 2 H), 2.56 (dd, J = 12, 17 Hz, 1 H). Anal. ($C_{17}H_{20}ClNO_3 \cdot H_2O$) C, N, H: calcd, 6.52; found, 5.97.

3,4-Dihydro-1-hydroxy-5-(methoxymethoxy)-3-phenyl-1*H*-2-benzopyran (18). *n*-Butyllithium (48.8 mL of a 2.5 M solution in hexane, 122 mmol) was added dropwise to a solution of 27.5 g (122 mmol) of 2-[3'-(methoxymethoxy)phenyl]-1,3-dioxane[14] in 250 mL of cyclohexane at 0 °C. The resultant mixture was stirred at 0 °C for 1 h and then 13.67 mL (120 mmol) of styrene oxide was added and stirring was continued at ambient temperature for 3 days. The reaction mixture was then poured into 250 mL of water and the cloudy mixture was extracted with 500 mL of diethyl ether. The organic extract was washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified on silica gel eluted with 40% diethyl ether in hexane to give 18.52 g (45% yield) of the intermediate 2-[2'-[2''-(1'',3''-dioxanyl)]-6'-(methoxymethoxy)phenyl]-1-phenyl-1-ethanol as a white solid: mp 73–75 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50–7.15 (m, 8 H), 5.59 (s, 1 H), 5.28 (d, J = 6 Hz, 1 H), 5.24 (d, J = 6 Hz, 1 H), 5.04 (m, 1 H), 4.40–4.25 (m, 2 H), 4.11 (d, J = 4.5 Hz, 1 H), 4.08–3.94 (m, 2 H), 3.52 (s, 3 H), 3.39–3.33 (m, 2 H), 2.38–2.20 (m, 1 H), 1.53–1.46 (m, 1 H). A solution of 41.16 g (119 mmol) of this compound in 850 mL of acetone was mixed with 100 mL of a 1 M aqueous hydrochloric acid solution and the resultant solution was stirred at ambient temperature for 1 h. The precipitate which formed was filtered and washed with water to afford the title compound. The filtrate was concentrated in vacuo and the additional product which precipitated from the residue was recrystallized in hexane/ethyl acetate to give a total of 26.86 g (79% yield) of lactol 18 as a mixture of anomers: [higher R_f anomer (1:1 diethyl ether/hexane, SiO_2)] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64–7.35 (m, 5 H), 7.14 (t, J = 9 Hz, 1 H), 6.98 (d, J = 9 Hz, 1 H), 6.85 (d, J = 8 Hz, 1 H), 6.33 (s, 1 H), 5.37 (dd, J = 3, 12 Hz, 1 H), 5.19 (d, J = 6 Hz, 1 H), 5.15 (d, J = 6 Hz, 1 H), 3.42 (s, 3 H), 3.16 (dd, J = 3, 18 Hz, 1 H), 2.79 (dd, J = 12, 18 Hz, 1 H); [lower R_f anomer (1:1 diethyl ether/hexane, SiO_2)] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55–7.20 (m, 6 H), 7.1–7.0 (m, 2 H), 6.19 (s, 1 H), 5.25 (dd, J = 4, 13 Hz, 1 H), 5.20 (s, 2 H), 3.46 (s, 3 H), 3.13 (dd, J = 3, 18 Hz, 1 H), 2.75 (dd, J = 12, 18 Hz, 1 H).

***cis*-3,4-Dihydro-5-(methoxymethoxy)-1-(nitromethyl)-3-phenyl-1*H*-2-benzopyran (19).** A solution of 1.81 g (6.3 mmol) of lactol 18 and 488 mg (1.8 mmol) of ammonium acetate in 30 mL of nitromethane was heated at reflux for 3 days and then concentrated in vacuo. The concentrate was poured into 30 mL of a 1 M aqueous hydrochloric acid solution and the cloudy mixture was extracted with 2 × 150 mL of ethyl acetate. The organic extract was washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. NMR analysis of the crude product indicated a 1:1 mixture of diastereomers. Column chromatography on silica gel eluted with hexane/toluene/diethyl ether (6:3:1 v/v) afforded 230 mg (11% yield) of cis isomer 19 (higher R_f): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44–7.28 (m, 5 H), 7.22 (t, J = 8 Hz, 1 H), 7.05 (d, J = 8 Hz, 1 H), 6.76 (d, J = 8 Hz, 1 H), 5.73 (bd, J = 9 Hz, 1 H), 5.21 (s, 2 H), 4.90 (dd, J = 3, 13 Hz, 1 H), 4.75 (dd, J = 3, 12 Hz, 1 H), 4.70 (dd, J = 10, 12 Hz, 1 H), 3.46 (s, 3 H), 3.20 (dd, J = 3, 18 Hz, 1 H), 2.74 (dd, J = 12, 18 Hz, 1 H). **19** (trans, lower R_f): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48–7.30 (m, 5 H), 7.22 (t, J = 8 Hz, 1 H), 7.05 (d, J = 8 Hz, 1 H), 6.77 (d, J = 8 Hz, 1 H), 5.76 (dd, J = 3, 11 Hz, 1 H), 5.23 (s, 2 H), 5.03–4.93 (m, 2 H), 4.69 (dd, J = 3, 12 Hz, 1 H), 3.48 (s, 3 H), 3.22 (dd, J = 3, 17 Hz, 1 H), 2.87 (dd, J = 11, 17 Hz, 1 H).

***cis*-1-(Aminomethyl)-3,4-dihydro-5-hydroxy-3-phenyl-1*H*-2-benzopyran Hydrochloride (20).** A solution of 135 mg (0.41 mmol) of **19** in 5 mL of methanol was saturated with anhydrous hydrogen chloride. The resultant mixture was stirred at reflux temperature for 2 h and then concentrated in vacuo. The residue was purified on silica gel eluted with 5% methanol in methylene chloride to afford 75 mg (66% yield) of *cis*-3,4-dihydro-5-hydroxy-1-nitromethyl-3-phenyl-1*H*-2-benzopyran. A solution of 75 mg (0.26 mmol) of this phenol in 15 mL of ethyl acetate and 1.5 mL of isopropyl alcohol was treated with 75 mg of 10% palladium on carbon and the mixture was shaken under 4 atm of hydrogen for 1 day. The reaction mixture was diluted with ethyl acetate and filtered through Celite filter aid. The filtrate was concentrated in vacuo and the residue was purified on silica gel eluted with 5% methanol in methylene chloride to give the amine product. The amine was treated with diethyl ether saturated with anhydrous hydrogen chloride to give 52 mg (69% yield) of the title compound: mp 160–163 °C; MS (DCI-NH_3) m/z 256 (M + H)$^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.64 (s, 1 H), 8.03 (bs, 3 H), 7.58 (d, J = 7.5 Hz, 2 H), 7.42–7.29 (m, 3 H), 7.09 (t, J = 7.5 Hz, 1 H), 6.79 (d, J = 7.5 Hz, 1 H), 6.76 (d, J = 7.5 Hz, 1 H), 5.16 (bd, J = 8 Hz, 1 H), 4.77 (dd, J = 3, 12 Hz, 1 H), 3.58 (m, 1 H), 3.17–2.96 (m, 2 H), 2.56 (dd, J = 12, 18 Hz, 1 H). Anal. ($C_{16}H_{18}ClNO_2 \cdot {}^3/_4H_2O$) C, H, N.

1-Cyano-3,4-dihydro-5-hydroxy-3-phenyl-1*H*-2-benzopyran (21). A solution of 9.07 g (31.7 mmol) of lactol 18 in 150 mL of methylene chloride at −78 °C was treated sequentially with trimethylsilyl cyanide (8.5 mL, 64 mmol) and boron trifluoride etherate (6 mL, 49 mmol). After being stirred for 1.5 h at −78 °C and for 4 h at ambient temperature, 100 mL of water was added and stirring was continued for 1 h. The reaction mixture was then extracted with 2 × 300 mL of ethyl acetate and the combined organic extract was washed with 200 mL of brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified on silica gel eluted with 10% ethyl acetate in hexane to give 7.33 g (92% yield) of **21** as a 4:1 mixture of the trans and cis isomers: (major isomer, trans) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50–7.32 (m, 5 H), 7.19 (t, J = 8 Hz, 1 H), 6.87 (d, J = 8 Hz, 1 H), 6.78 (d, J = 8 Hz, 1 H), 5.86 (s, 1 H), 5.10 (dd, J = 3, 12 Hz, 1 H), 3.14 (dd, J = 4, 18 Hz, 1 H), 2.85 (dd, J = 15, 18 Hz, 1 H).

6-Bromo-1-cyano-3,4-dihydro-5-hydroxy-3-phenyl-1*H*-2-benzopyran (22a,b). Bromine (0.11 mL, 2.1 mmol) was added to a solution of 0.91 mL (8.7 mmol) of *tert*-butylamine in 15 mL of toluene at −30 °C. The resultant mixture was stirred at −30 °C for 10 min, cooled to −78 °C, and then treated with a solution

of 1.09 g (4.3 mmol) of **21** (4:1 mixture of trans to cis isomer) in 15 mL of methylene chloride. The reaction mixture was stirred at −78 °C for 3 h, allowed to slowly warm to ambient temperature over a 3-h period, and then partitioned between ethyl acetate and water. The organic extract was washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified on silica gel eluted with 1% ethyl acetate in hexane to give 0.32 g (24% yield) of **22b** (higher R_f) and 0.26 g (20% yield) of **22a** (lower R_f). **22a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50–7.32 (m, 6 H), 6.91 (d, J = 9 Hz, 1 H), 5.81 (s, 1 H), 4.75 (dd, J = 4.5, 12 Hz, 1 H), 3.18 (dd, J = 4.5, 17 Hz, 1 H), 2.93 (dd, J = 12, 17 Hz, 1 H). **22b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50–7.30 (m, 6 H), 6.78 (d, J = 9 Hz, 1 H), 5.82 (s, 1 H), 5.07 (dd, J = 3, 12 Hz, 1 H), 3.23 (dd, J = 4.5, 17 Hz, 1 H), 2.89 (dd, J = 12, 17 Hz, 1 H).

***cis*-1-(Aminomethyl)-6-bromo-3,4-dihydro-5-hydroxy-3-phenyl-1*H*-2-benzopyran Hydrochloride (23).** Borane–tetrahydrofuran complex (4 mL of a 1 M solution in THF, 4 mmol) was added to a solution of 0.29 g (0.88 mmol) of **22a** in 10 mL of THF. The resultant mixture was stirred at ambient temperature for 2 days, treated with 15 mL of methanol, and concentrated in vacuo. The residue was purified on silica gel eluted with ethyl acetate to give the amine product. The amine was treated with diethyl ether saturated with anhydrous hydrogen chloride. The precipitate which formed was collected by vacuum filtration to give 90 mg (27% yield) of the title compound: mp 207–210 °C; MS (DCI-NH_3) m/z 334 $(M + H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.98 (bs, 3 H), 7.60–7.30 (m, 6 H), 6.83 (d, J = 9 Hz, 1 H), 5.14 (bd, J = 6 Hz, 1 H), 4.78 (dd, J = 3, 12 Hz, 1 H), 3.60–3.05 (m, 3 H), 2.66 (dd, J = 12, 17 Hz, 1 H). Anal. ($C_{16}H_{17}BrClNO_2 \cdot {}^3/_4H_2O$) C, H, N.

***trans*-1-(Aminomethyl)-6-bromo-3,4-dihydro-5-hydroxy-3-phenyl-1*H*-2-benzopyran Hydrochloride (24).** Following the procedures described for **23**, nitrile **22b** was converted to the title compound: mp 255–257 °C; MS (DCI-NH_3) m/z 334 $(M + H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.35 (s, 1 H), 8.06 (bs, 3 H), 7.52–7.30 (m, 6 H), 6.75 (d, J = 9 Hz, 1 H), 5.13 (dd, J = 3, 10.5 Hz, 1 H), 4.99 (dd, J = 4, 10.5 Hz, 1 H), 3.50–3.15 (m, 2 H), 3.07 (dd, J = 4, 18 Hz, 1 H), 2.65 (dd, J = 10.5, 18 Hz, 1 H). Anal. ($C_{16}H_{17}BrClNO_2 \cdot {}^1/_2H_2O$) C, H, N.

Biological Methods. D1 and D2 Binding Assays. Homogenized rat caudate was used as the source of tissue for both assays. For the D1 assay, compounds were incubated in the presence of [^{125}I]SCH23982 according the procedures of Sidhu.[25] For the D2 assay, [^{3}H]spiperone was used as the radioligand as described by Frey.[26] In both assays, the test compounds compete with the radiolabel for occupancy of the receptors, and the affinity of the compounds for the receptors is expressed as a K_i.[27]

Biogenic Amine Receptor Binding Assays. The procedures for the binding assays used to determine affinity at the 5HT1a,[28] 5HT1c,[29] 5HT2,[30] α1,[31] α2,[31] β,[32] and dopamine uptake site[33] are known and summarized.[6] The K_i values were calculated as described above for the dopamine receptors.

Inhibition of Dopamine-Stimulated Adenylate Cyclase. Functional D1 antagonist activity of a compound was assayed by measuring the ability of the compound to block dopamine induced increases in cyclic adenosine monophosphate (cAMP) levels in cell-free homogenates of goldfish retinal tissue according to procedures previously described.[34] The values are presented as K_i's, calculated as described by Cheng and Prusoff.[27]

In Vivo Pharmacology. Dopamine agonist activity was assessed as described elsewhere[19] by monitoring the ability of the compounds to induce contralateral rotations in rats with unilateral 6-OHDA lesions of the nigrostriatal pathway.

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Registry No. **5**, 135393-52-1; **6a**, 135393-53-2; **6b**, 135393-70-3; **6c**, 135393-71-4; **7**, 135393-54-3; **7** free base, 135393-49-6; **8**, 135393-55-4; **8** free base, 135393-50-9; **9**, 135393-56-5; **9** free base, 135393-51-0; **10**, 135393-57-6; **11**, 135393-58-7; **11** free base, 135393-78-1; **12**, 58402-40-7; **13**, 135393-59-8; **14**, 135393-60-1; **15**, 135393-61-2; **16**, 135393-62-3; **16** free base, 135393-81-6; **17**, 81245-35-4; *cis*-**18**, 135393-63-4; *trans*-**18**, 135393-76-9; *cis*-**19**, 135393-64-5; *trans*-**19**, 135393-77-0; **20**, 135393-65-6; **20** free base, 135393-82-7; *trans*-**21**, 135393-66-7; *cis*-**21**, 135393-79-2; **22a**, 135393-67-8; **22b**, 135393-80-5; **23**, 135393-68-9; **23** free base, 135393-83-8; **24**, 135393-69-0; **24** free base, 135393-84-9; 2,6-dimethylanisole, 1004-66-6; cyclohexanecarboxaldehyde, 2043-61-0; bromoacetaldehyde dimethyl acetal, 7252-83-7; 3-cyclohexyl-3,4-dihydro-5-hydroxy-6-methyl-1-[(*N*-propionylamino)-methyl]-1*H*-2-benzopyran, 135393-72-5; *N*-formylaminoacetaldehyde dimethyl acetal hydrochloride, 135393-73-6; 2-(benzyloxy)-3-(hydroxymethyl)-1-methoxybenzene, 52508-44-8; 2-phenyl-1,3-dithiane, 5425-44-5; 2-[2′-(benzyloxy)-3′-methoxyphenyl]-1-phenylethanone, 135393-74-7; styrene oxide, 96-09-3; 2-[2′-[2″-(1″,3″-dioxanyl)]-6′-(methoxymethoxy)phenyl]-1-phenyl-1-ethanol, 135393-75-8; nitromethane, 75-52-5; *cis*-3,4-dihydro-5-hydroxy-1-(nitromethyl)-3-phenyl-1*H*-2-benzopyran, 135393-85-0.

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