trans-2,3-Dihydroxy-6a,7,8,12b-tetrahydro-6*H*-chromeno[3,4-*c*]isoquinoline: Synthesis, Resolution, and Preliminary Pharmacological Characterization of a New Dopamine D_1 Receptor Full Agonist

Juan Pablo Cueva, Gianfabio Giorgioni,† Russell A. Grubbs, Benjamin R. Chemel, Val J. Watts, and David E. Nichols*

Department of Medicinal Chemistry and Molecular Pharmacology, School of Pharmacy and Pharmaceutical Sciences, Purdue University, West Lafayette, Indiana 47907

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We report the synthesis of *trans*-2,3-dihydroxy-6a,7,8,12b-tetrahydro-6*H*-chromeno[3,4-*c*]isoquinoline hydrochloride **6** and the resolution of its enantiomers. This new compound is an oxygen bioisostere of the potent dopamine D_1-selective full agonist dihydrexidine. The initial synthetic approach involved, as a key step, a Suzuki coupling between a chromene triflate and a boronate ester, followed by isoquinoline formation and reduction of the resulting isoquinoline. Subsequently, a more efficient route was developed that involved conjugate addition of an aryl Grignard reagent to a 2-nitrochromene. The title compound possessed high affinity (K_i = 20−30 nM) for porcine D_1-like receptors in native striatal tissue and full intrinsic activity at cloned human dopamine D_1 receptors but had much lower affinity at dopamine D_2-like receptors (K_i = 3000 nM). The binding and functional properties of this compound illustrate again the utility of constructing dopamine D_1 agonist ligands around the β-phenyldopamine pharmacophore template.

Introduction

Dopamine mediates and modulates neurotransmission in neural pathways critical to important aspects of behavior and cognition. Its physiological and pharmacological effects are mediated by G-protein-coupled receptors that are the products of at least five distinct genes.[1] These dopamine-specific receptor proteins have been categorized into two main families. The D_1-like receptors,[2] D_1 and D_5, typically activate adenylate cyclase through coupling with $G\alpha_s/G\alpha_{olf}$ subunits, leading to increases in cAMP. D_2-like receptors, by contrast, are coupled to $G\alpha_i/G\alpha_o$ subunits and either inhibit adenylate cyclase or couple to other effector systems.[3]

Extensive research into Parkinson's disease has shown that dopaminergic projections from the substantia nigra to the striatum are vital to the initiation and control of motor movement. Degeneration of this nigrostriatal pathway leads to the classical symptoms of the disease: tremors, rigidity, and slowness of movement.[4] As such, the treatment of Parkinson's disease has been aimed at enhancing dopaminergic signaling in the central nervous system (CNS), mainly through the use of L-DOPA (a biosynthetic precursor of dopamine) and to a lesser extent the use of bioavailable D_2-like dopamine agonists such as pergolide, pramipexole, and ropinirole.[5]

It is also becoming clear that dopamine D_1 receptors are involved in a variety of crucial cognitive functions, as well as substance abuse disorders. For example, in the prefrontal cortex, working memory processes appear to depend critically on a proper level of D_1 signaling.[6] In the hippocampus, it has been shown that D_1 receptor activation strengthens the late phase of long-term potentiation of synaptic transmission,[7] believed to be a key mechanism of memory consolidation.

Dopamine D_1 receptors also are thought to be a key target for improving cognitive and working memory deficits in schizophrenia.[8] Indeed, the NIMH-sponsored MATRICS program identified D_1 receptors as the target of choice by schizophrenia researchers for treating cognitive deficits in schizophrenia. A recently completed proof-of-principle clinical trial of dihydrexidine in schizophrenia has demonstrated a significant increase in cortical blood flow, with a decrease in reaction time and improvement in working memory (George et al., unpublished results). The role of dopamine in mediating key aspects of behavioral reinforcement, conditioning, and learning has also been well documented.[9] For example, D_1 agonists have been shown to increase the latency of cocaine self-administration in rats.[10]

The accumulating evidence for the critical importance of dopamine D_1 receptors in CNS function makes it imperative that more tools be created to facilitate understanding of the role of D_1 receptors in the brain. Thus, for many years we have been pursuing the development of receptor subtype-specific ligands with the goal of understanding the physiological role that these receptors play in behavior and cognition. The successful strategy we have relied upon is based on the design of conformationally rigid analogues of dopamine that presumably mimic the geometry of dopamine when it binds to its receptors.

Early during this inquiry we discovered that attaching an aryl group to the β position of the dopamine moiety conferred D_1 selectivity and high intrinsic activity.[11] Thus, several rigid ligands containing this basic "β-phenyldopamine" pharmacophore have been developed that demonstrated both selectivity and full agonist activity at the D_1 receptor subtype. The first of these compounds, dihydrexidine[12] (**1**, Chart 1), the first high-affinity D_1-selective full agonist, demonstrated profound antiparkinsonian effects in an in vivo model of Parkinson's disease in African green monkeys,[13] establishing the importance of dopamine D_1 receptor activation in the basal ganglia for the control of motor function. Subsequent clinical trials with a structurally related compound (ABT-431) demonstrated that D_1 agonists were the only agents with efficacy in Parkinson's

* To whom correspondence should be addressed. Phone: 765-494-1461. Fax: 765-494-1414. E-mail: drdave@pharmacy.purdue.edu.

† Current Address: Department of Chemical Sciences, University of Camerino, Via S. Agostino, 1-62032 Camerino, Italy.

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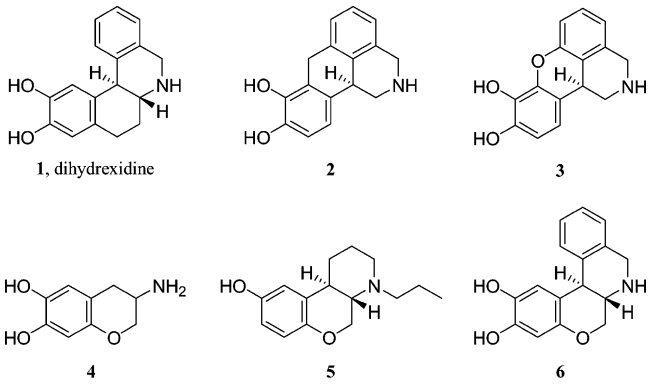
Chart 1



disease comparable to levo-dopa,[14] the current "gold standard" of treatment.

The structure of dihydrexidine, **1**, can be seen to incorporate a conformation of dopamine where its ethylamine side chain is held in the "trans-β" rotameric orientation by a tetracyclic ring system that includes the catechol and β-phenyl moieties. The trans relationship between the β-phenyl and the amino substituent establishes an energetically stable conformation in which both aromatic groups of **1** are not far from coplanarity. These basic structural features have been incorporated into a more general dopamine D_1 agonist pharmacophore that has been used as a basis for the development of subsequent dopamine D_1-selective full agonists such as dinapsoline **2**,[15] which also is a full D_1 agonist.

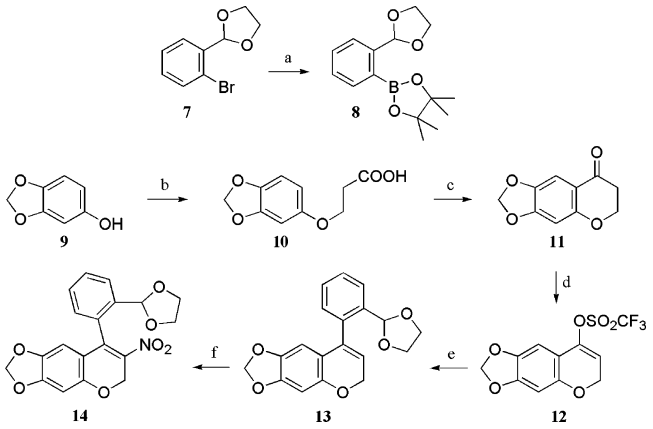
The pursuit of an oxygen bioisostere of dinapsoline yielded dinoxyline, **3**, a potent dopamine agonist at all receptor isoforms.[16] Incorporation of other heteroatoms into the tether, such as sulfur or nitrogen, did not afford active compounds.[17] We were encouraged to expand our search for other oxygen bioisosteres by the results of Horn et al.[18] and of Hutchison et al.,[19] who reported that both **4** and **5** possessed significant dopaminergic activity. Their successes using heteroatom replacement in known dopaminergic ligands, and analogies to our structural series, convinced us to prepare **6**, an analogue of **1** in which the ethyl tether between the catechol and tetrahydroisoquinoline substructures was replaced with an oxymethylene ether bridge. This new compound, *trans*-2,3-dihydroxy-6a,7,8,12b-tetrahydro-6*H*-chromeno[3,4-*c*]isoquinoline, **6**, which we have tentatively named doxanthrine, its biological properties, and those of its enantiomers are the subject of the present communication.

Chemistry

We initially approached the construction of **6** through a key Suzuki coupling between boronate ester **8** and triflate **12** as shown in Scheme 1. The synthesis of coupling partner **8** was completed in two steps from 2-bromobenzaldehyde. After preparation of the cyclic acetal **7**,[20] treatment with *n*-butyllithium was followed by addition of isopropoxypinacolborane.

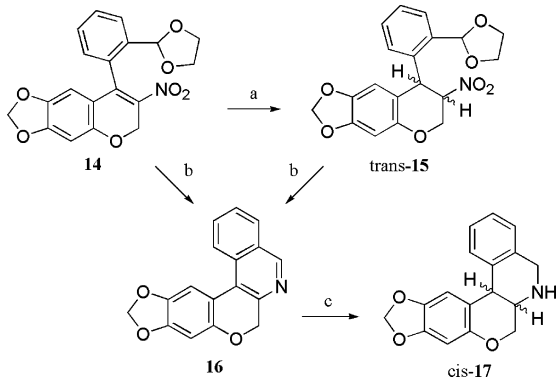
Synthesis of coupling partner **12** began with propionic acid **10**, which was obtained by O-alkylation of sesamol (**9**) with 3-bromopropionic acid. Unfortunately, this step gave extremely low yields because of base-catalyzed reverse Michael addition, which regenerates starting phenol **9**.[21,22] Treatment of **10** under Friedel−Crafts conditions gave chromanone **11** in excellent yield. Triflate **12** was then obtained from **11** following a procedure described by Pal.[20] The enolate was generated by treatment with sodium hexamethyldisilazane and was trapped with *N*-phenyltrifluoromethanesulfonimide.

Scheme 1[a]



[a] Reagents and conditions: (a) (i) THF, *n*BuLi, −78 °C; (ii) isopropoxypinacolborane, room temp, 52%; (b) NaOH, Na_2CO_3, $Br(CH_2)_2COOH$, H_2O, reflux, 11%; (c) oxalyl chloride, $SnCl_4$, benzene, 88%; (d) NaHMDS, $(CF_3SO_2)_2NPh$, THF, 80%; (e) **8**, KBr, KOH, $Pd(PPh_3)_4$, 71%; (f) $C(NO_2)_4$, pyridine, acetone, 91%.

Scheme 2[a]



[a] Reagents and conditions: (a) $NaBH_4$, EtOH, 35%; (b) Zn, CH_3COOH, 60 °C, 38%; (c) $NaBH_3CN$, MeOH, 90%.

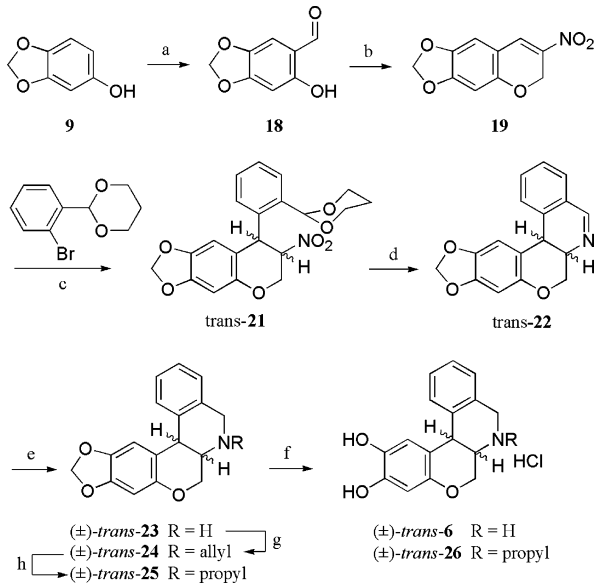
With Suzuki conditions described by Qandil et al.,[23] **8** and **12** were coupled and **13** was isolated in good yield. Treatment of **13** with tetranitromethane produced nitroalkene **14** in excellent yield.[24] After successful reduction of the olefinic bond of **14** with sodium borohydride (Scheme 2), the resulting trans product **15** was treated with zinc dust in aqueous acetic acid, as reported by Michaelides et al.[25]

Instead of producing the desired dihydroisoquinoline, however, only aromatized **16** was obtained. In view of this minor setback, the intermediate olefin reduction was abandoned, and nitroalkene **14** was reduced directly to isoquinoline **16**. To our great disappointment, however, reduction of this isoquinoline with sodium cyanoborohydride yielded cis amine **17** as the only isolable product.

Although we did not consider these difficulties insurmountable, given the very low yields of key intermediates early in this route, as well as the hardships that became evident in attaining the desired trans stereochemistry of the product, we decided to develop a new synthetic approach, prompted by awareness of the reactivity of nitroalkenes toward arylmetal reagents.[25] This more successful route is detailed in Scheme 3.

Aldehyde **18** was obtained by formylation of sesamol, **9**. Reaction conditions for this formylation had to be chosen carefully, as the reaction was prone to provide substantial amounts of a dimeric xanthydrol byproduct (Cueva and Nichols, unpublished observation). The key intermediate, nitrochromene **19**, was obtained in one step from aldehyde **18** following a very

Scheme 3[a]



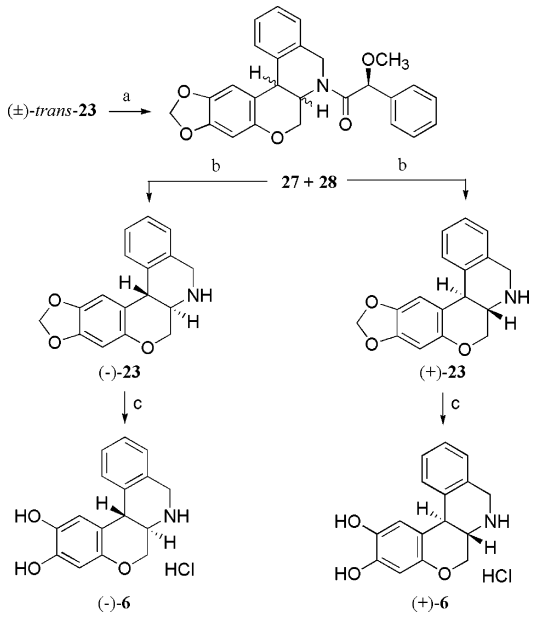
[a] Reagents and conditions: (a) Cl_2CHOCH_3, $SnCl_4$, CH_2Cl_2, reflux, 46%; (b) 2-nitroethanol, dibutylamine, phthalic anhydride, toluene, reflux, 48 h, 61%; (c) Mg, THF, −78 °C, 72%; (d) (i) Zn, AcOH, 60 °C; (ii) 2 M HCl; (iii) 2 M NaOH, 87%; (e) $NaBH_3CN$, HCl, EtOH, 79%; (f) BCl_3, CH_2Cl_2, 45%; (g) allyl bromide, K_2CO_3, acetone, 82%; (h) Pd/C, H_2, EtOH, 73%.

convenient procedure developed by Dauzonne and Royer[26] and later refined by Neirabeyeh and co-workers,[27] in which a basic solution of the aldehyde is treated with nitroethene generated in situ from nitroethanol. The concentration of this latter reagent must be kept very low to avoid base-catalyzed polymerization of nitroethene, which was nevertheless a byproduct of the process. This nitroalkene proved to be a very efficient electrophile; its reaction with the Grignard reagent formed from *o*-bromobenzaldehyde gave exclusively the more thermodynamically stable trans nitroacetal **21**. The reaction proceeded in good yield with very easy product workup. Imine **22** was then accessible by reduction of the nitro moiety of **21**, followed by acidic treatment to cleave the acetal and then basification.

The difference in outcome for the reduction of **15** and **21** with powdered Zn and acetic acid can likely be attributed to the stability of the six-membered acetal moiety under acidic conditions. The five-membered acetal **15** readily affords the aldehyde upon treatment with acetic acid, whereas the six-membered acetal **21** requires more stringent acidic conditions to effect hydrolysis. Thus, the ring closure step for the reduction of the five-membered acetal (which yields isoquinoline **16**) seems likely to have occurred by attack of a nitrogen nucleophile in an oxidation state higher than the amine. The general behavior of nitroalkenes to many reduction conditions is their transformation to oximes rather than amines.[28] This speculation is reinforced by the fact that **14** also yielded isoquinoline **16**, presumably by a ring closure step involving an oxidized nitrogen species, likely an oxime. The nitro group in acetal **21** is first reduced cleanly to the amine, and then after reaction conditions are applied to unmask the intermediate aldehyde, cyclization affords imine **22**, allowing the trans stereochemistry of the ring fusion to remain intact. Imine **22** was then reduced to yield the racemic trans amine **23**.

The resolution of (±)-**23** employed separation of diastereoisomeric amide derivatives **27** and **28**, formed by treatment of (±)-**23** with *R*-(−)-*O*-methylmandeloyl chloride (Scheme 4). The amides were separated by column chromatography, and

Scheme 4[a]



[a] Reagents and conditions: a) *R*-(−)-α-methoxyphenylacetyl chloride, CH_2Cl_2, silica column chromatography, 43% for **27**, 46% for **28**; (b) $LiEt_3BH$, THF, 94%; (c) BCl_3, CH_2Cl_2, 81%.

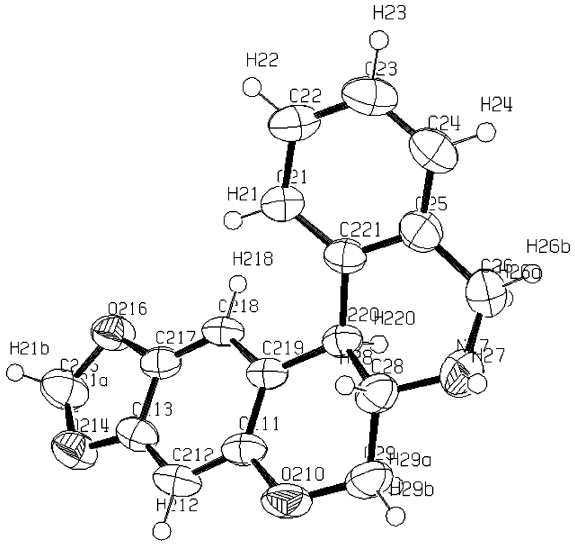


Figure 1. Crystal structure of (+)-**23**.

subsequent reductive cleavage of the amides using lithium triethylborohydride[29] afforded the enantiomers (+)-**23** and (−)-**23**.

The enantiomeric amines **23** gave crystals suitable for X-ray crystallographic analysis. The structure of a crystal of the (+)-enantiomer was determined to have the (6a*R*,12b*S*) stereochemistry (Figure 1). The catechol **6**, doxanthrine hydrochloride, was finally obtained by treatment of **23** with boron trichloride, followed by recrystallization from EtOH/EtOAc. We also prepared the *N*-propyl derivative by treatment of racemic amine **23** with allyl bromide to give **24**, followed by catalytic reduction to afford *N*-propyl compound **25** and conversion into catechol **26** by treatment with boron trichloride and crystallization as its hydrochloride salt.

Pharmacology

The dopamine D_1-like and D_2-like receptor affinities of compounds (±)-**6**, (+)-**6**, (−)-**6**, and (±)-**26** were initially

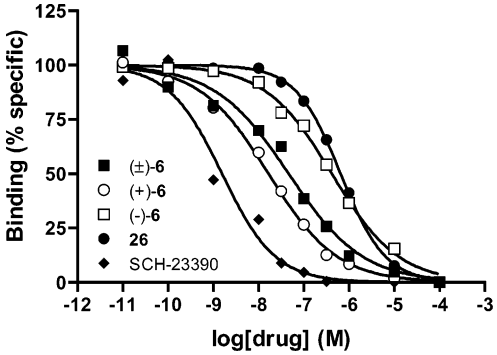


Figure 2. Representative competition binding curves for compounds **26**, **6**, and the enantiomers of **6** were obtained at D_1-like receptors in porcine striatal membranes. The prototype antagonist SCH-23390 is included for comparison.

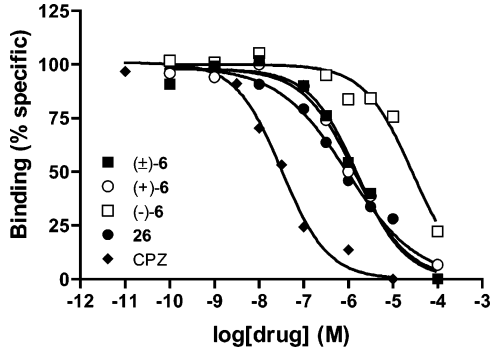


Figure 3. Representative competition binding curves for compounds **26**, **6**, and the enantiomers of **6** at D_2-like receptors in porcine striatal membranes. The prototype antagonist chlorpromazine (CPZ) is included for comparison.

evaluated by a competitive binding assay using a porcine striatal tissue preparation. Standard ligands for D_1- and D_2-type receptors, SCH 23390 and chlorpromazine, were assessed for comparison. Competitive binding at all five dopamine receptors and for adrenergic receptors was carried out by the NIMH supported Psychoactive Drug Screening Program.

To establish the functional effects of these compounds at specific receptor isoforms, we employed standard cAMP quantification assays using stably transfected cell lines expressing cloned dopamine D_1, D_2, and D_4 receptors. Full intrinsic activity was defined as the maximal activation induced by the endogenous neurotransmitter dopamine.

Results and Discussion

The receptor-binding and functional properties of these new compounds at dopamine receptors are presented in Figures 2−4 and are summarized in Tables 1 and 2. In our competition binding assays using porcine striatal preparations, we show the racemic parent compound (±)-**6** (doxanthrine) to have high affinity (K_i = 22 ± 3 nM) at D_1-like receptors (D_1 and D_5), comparable to the affinity of dihydrexidine **1**. It should be noted that cleavage of the dioxole ring of the cis ring fused isomer **17** gave a catechol that did not have measurable affinity for D_1- or D_2-like receptors (data not shown), similar to our earlier finding with *cis*-**1**.[12]

We were quite surprised to discover, however, that in this assay, (±)-**6** had only very low affinity (K_i = 3000 nM) at D_2-type receptors, in sharp contrast to the carbocyclic analogue, dihydrexidine **1**, which does possess modest D_2-like affinity (K_i = 240 nM). These observations reveal high selectivity toward D_1-type over D_2-type receptors for this new molecular template.

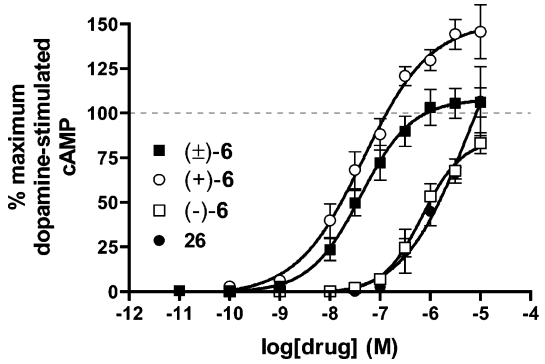


Figure 4. Stimulation of cAMP in HEK hD_1 CRE-Luc cells by compounds (±)-**6**, (+)-**6**, (−)-**6**, and **26**. The 100% represents the maximal effect produced by 10 μM dopamine. Data represent mean ± SEM from at least four experiments.

Although the basis for this difference in affinity is unclear, we note that SER107 in the D_1 receptor is located in the vicinity of the oxygen heteroatom in **6**. This residue is located approximately one turn below the critical ASP103 in transmembrane helix 3 that is thought to bind to the amine of dopamine. The cognate residue in the D_2 receptor is a cysteine, and it seems likely that hydrogen bonding of the ether oxygen atom in **6** will be more favorable with SER in the dopamine D_1 receptor than with the CYS in the dopamine D_2 receptor. Experiments to test this hypothesis are now underway.

We then submitted (±)-**6** to the NIMH sponsored Psychoactive Drug Screening Program (NIMH-PDSP). Compound (±)-**6** had no significant affinity (>10 μM) at the panel of monoamine targets, with only the few exceptions that are listed in Table 2. These assays also revealed (±)-**6** to have affinity at the dopamine D_4 receptor (K_i = 90 nM) and at the D_5 receptor, where it had affinity (K_i = 7 nM) comparable to that at the D_1 receptor. We are presently examining the dopamine D_5 properties of **6** to determine whether the high affinity reported by the NIMH-PDSP is an indication of whether **6** may have measurable selectivity for D_5 over D_1 receptors.

As anticipated, the enantiomers of **6** showed the affinity difference predicted by analogy to earlier examples of resolved β-phenyl substituted catecholamines: that is, the (6a*S*,12b*R*)-(+)-enantiomer of **6** was most potent, with more than twice the affinity of the racemate at dopamine D_1 receptors (7 nM vs 22 nM for (±)-**6**) and 40-fold higher affinity than the distomer (290 nM for (−)-**6**).

It has been consistently observed that addition of an *N*-propyl to most dopaminergic agonists tends to increase affinity and potency at D_2-like receptors while simultaneously reducing the affinity for D_1-like receptors, resulting in a net change in selectivity favoring D_2 activity.[12,16,23] With dihydrexidine **1**, for example, an *N*-propyl effectively increased the affinity of the compound for D_2 receptors by 2-fold. The net effect of the *N*-propyl in this new template was similar: although *N*-propyl analogue **26** had only modest affinity at D_2-like receptors (K_i = 300 nM), compared to its parent (±)-**6**, the increase in affinity was substantial (about 10-fold). The decrease in D_1 affinity was also considerable (from 22 nM for **6** to 340 nM for **26**), but the low D_2 affinity of the N-unsubstituted template made it impossible for N-alkylation to provide a D_2-selective compound, as is the case with structurally related molecules.

Functionally, (±)-**6** was a potent agonist at dopamine D_1 receptors, with full intrinsic activity relative to dopamine. The (+)-isomer was slightly more potent than the racemate in this assay (EC_{50} = 29 nM) but induced a very robust activation of

Table 1. Binding and Functional Properties of New Compounds at Dopamine Receptors[a]

	binding at porcine striatal homogenates, K_i (nM)		potency (nM) and intrinsic activity at cloned receptors					
			hD_1		rD_{2L}		$hD_{4.4}$	
ligand	D_1-like	D_2-like	EC_{50}	IA[b]	EC_{50}	IA[b]	EC_{50}	IA[b]
dopamine	ND[c]	ND[c]	120 ± 20	100 ± 3	5 ± 2	100 ± 2	10 ± 2	100 ± 2
1, DHX[d]	21 ± 4	240 ± 40	19 ± 8	110 ± 11	70 ± 20	70 ± 5	17 ± 3	100 ± 7
(±)-**6**	22 ± 3	3700 ± 1300	32 ± 19	95 ± 3	>10 μM	na[e]	110 ± 15	87 ± 3
(+)-**6**	8 ± 3	2500 ± 820	29 ± 11	130 ± 10	>10 μM	na[e]	95 ± 25	90 ± 4
(−)-**6**	270 ± 30	6800 ± 660	1100 ± 360	87 ± 3	>10 μM	na[e]	230 ± 90	80 ± 5
26	330 ± 50	340 ± 40	1100 ± 460	88 ± 2	1600 ± 100	92 ± 3	21 ± 8	100 ± 3
N-propyl-**1**	180 ± 11[f]	26 ± 3[f]	ND[c]	N.D	ND[c]	ND[c]	ND[c]	ND[c]
quinpirole	ND[c]	ND[c]	ND[c]	ND[c]	9 ± 2	95 ± 2	5 ± 1	100 ± 3
SCH-23390	0.5 ± 0.1	ND[c]	na[e]	na[e]	na[e]	na[e]	na[e]	na[e]
chlorpromazine	ND[c]	8 ± 2	na[e]	na[e]	na[e]	na[e]	na[e]	na[e]

[a] All results shown are the mean ± SEM for at least three independent experiments. [b] IA is intrinsic activity, the maximum stimulation observed relative to the response of dopamine, which is defined as 100% intrinsic activity. [c] Not determined by these assays. [d] Dihydrexidine. [e] Not applicable for antagonists. [f] Taken from Knoerzer et al.[29] from rat striatal homogenates.

Table 2. Affinity of (±)-**6** for Cloned Human Receptor Subtypes[a]

	receptor							
	D_1	D_2	D_3	D_4	D_5	α_{2A}	α_{2B}	α_{2C}
K_i (nM)	98	1910	390	90	7	180	10	2

[a] Screening data provided by the NIMH-sponsored PDSP. D_1 and D_5 data represent an average of two trials. All other data represent a single trial.

the D_1 receptor, with an intrinsic activity about 30% greater than that of dopamine itself! The (−)-isomer was a weak agonist (EC_{50} = 1100 nM) but still had nearly full intrinsic activity at the highest concentrations tested.

The potency of (±)-**6** and its enantiomers at dopamine D_2 receptors was negligible (EC_{50} > 10 μM). Although the *N*-propyl analogue **26** had low but nearly equal EC_{50} values for both D_1 and D_2 receptor activation, it nevertheless was a nearly full agonist at the highest concentration tested.

The functional effects of these compounds at dopamine D_4 receptors are particularly noteworthy. Racemic **6** had only modest potency at dopamine D_4 receptors (EC_{50} = 110 nM), about 10-fold lower than its isosteric predecessor, (±)-dihydrexidine (EC_{50} = 17 nM) (Table 1). But when the *N*-propyl was added to provide **26**, we observed a 5-fold increase in D_4 potency (EC_{50} = 21 nM). Combined with the marked loss of D_1 and nearly 20-fold lower D_2 potency, **26** thus appears to be a relatively selective dopamine D_4 full agonist.

Conclusions

We have devised an efficient synthesis for the construction of a new conformationally restricted version of the β-phenyldopamine pharmacophore. In doing so, we have been successful in producing a ligand that we have named doxanthrine **6**, which possesses a level of D_1/D_2 selectivity never before encountered for a conformationally rigid full agonist. In view of its pharmacological properties and its isosteric relationship with dihydrexidine **1**, it provides opportunities to identify key residues involved in the differential ligand−receptor interactions that give rise to isoform selectivity.

Experimental Section

Chemistry. General Procedures. All reagents were commercially available (Aldrich) and were used without further purification unless otherwise indicated. Dry THF and diethyl ether were obtained by distillation immediately before use from benzophenone-sodium under nitrogen. Column chromatography was carried out using silica gel 60 (230−400 mesh). J. T. Baker flexible thin layer chromatography sheets (silica gel IB2-F) were used to monitor reactions. Melting points were determined using a Thomas-Hoover apparatus and are uncorrected. ^{1}H NMR spectra were recorded using a 300 MHz Bruker ARX-300 NMR spectrometer. Chemical shifts are reported in δ values in ppm relative to an internal reference (0.03%, v/v) of tetramethylsilane (TMS) in $CDCl_3$ except where noted. All electrospray ionization analyses were carried out on a FinniganMAT LCQ Classic (ThermoElectron Corp, San Jose, CA) mass spectrometer system. The low-resolution electron impact (EI) and chemical ionization (CI) studies were carried out using a Hewlett-Packard Engine (Hewlett-Packard Company, Wilmington, DE) mass spectrometer. Elemental analyses were performed by the Purdue University Microanalysis Laboratory. All reactions were carried out under an argon atmosphere.

2-(2-[1,3]Dioxolan-2-ylphenyl)-4,4,5,5-tetramethyl[1,3,2]-dioxaborolane (8). The protected aldehyde **7**[20] (22.8 g, 0.100 mol) was dissolved in 400 mL of dry THF. After the solution was cooled to −78 °C, a 2.5 M solution of *n*-butyllithium (44.0 mL, 0.110 mol) was added. After 15 min, 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (22.4 mL, 0.110 mol) was added. The solution was allowed to warm to room temperature and was stirred for an additional 8 h. The resulting mixture was poured into 300 mL of water, extracted several times with diethyl ether (3 × 300 mL), dried (Na_2SO_4), filtered, and concentrated. The resulting oil (14.4 g, 52%) was used without further purification. ^{1}H NMR ($CDCl_3$): δ 7.71 (d, 1H, *J* = 7.2 Hz), 7.59 (d, 1H, *J* = 8.1 Hz), 7.40 (m, 2H), 6.35 (s, 1H), 4.10 (m, 2H), 4.00 (m, 2H), 1.34 (s, 12H).

3-(3,4-Methylenedioxyphenoxy)propionic Acid (10). Sesamol **9** (50 g, 0.36 mol) was treated with an aqueous sodium hydroxide solution prepared from 500 mL of H_2O and 14.5 g (0.36 mol) of NaOH pellets. To an aqueous suspension (250 mL) of 3-bromopropionic acid (55.07 g, 0.36 mol), 250 mL of an aqueous sodium carbonate (38.16 g, 0.36 mol) solution was slowly added. The two solutions were combined and the mixture was then heated at reflux for 16 h. After the mixture was cooled to room temperature, ice (200 g) was added. The solution was acidified with concentrated HCl and extracted with diethyl ether (3 × 350 mL). The organic extracts were combined and then extracted with an aqueous saturated $NaHCO_3$ solution (3 × 400 mL). The basic aqueous extracts were acidified with concnetrated HCl and extracted back into diethyl ether (3 × 400 mL). The ethereal extracts were dried (Na_2SO_4) and concentrated, and the title compound was recrystallized as tan crystals from 80% aqueous ethanol (8.16 g, 11%). The reaction was repeated several times to accumulate sufficient material to complete the synthesis. An analytical sample was prepared by dissolving the crystals in hot ethanol, treating with charcoal followed by filtration through Celite, and cooling to afford white crystals that were collected by filtration: mp 144−146 °C. ^{1}H NMR (DMSO-d_6): δ 6.78 (d, 1H, *J* = 8.4 Hz), 6.60 (d, 1H, *J* = 3 Hz), 6.34 (dd, 1H, *J* = 8.7, 3 Hz), 5.94 (s, 2H), 4.06 (t, 2H, *J* = 6 Hz), 2.63 (t, 2H, *J* = 6 Hz). Low-resolution EIMS *m*/*z*: 210. Anal. ($C_{10}H_{10}O_5$) C, H, N.

6,7-Methylenedioxychroman-4-one (11). A catalytic amount of dry DMF was added to a suspension of **10** (20.4 g, 0.097 mol) in 500 mL of dry benzene. Oxalyl chloride (16.7 mL, 0.191 mol) was then added, and the resulting solution was stirred at room temperature for 4 h. The benzene was then removed under reduced pressure, and the resulting oil was dissolved in 300 mL of dry dichloromethane. After the solution was cooled to 0 °C, $SnCl_4$ (13.58 mL, 0.12 mol) was added and the solution was stirred for 1 h while allowing it to warm to room temperature. After the reaction mixture was poured onto ice (200 g) and after dilution with water (300 mL), the aqueous layer was extracted with dichloromethane (3 × 300 mL). The organic extracts were dried (Na_2SO_4), filtered, and concentrated under vacuum. The resulting solid was dissolved in 1 L of 50% hexanes-ethyl acetate, passed through a small pad of silica gel, and concentrated to afford a tan solid that was recrystallized from ethanol (16.4 g, 88%). An analytical sample was prepared by dissolving the solid in hot ethanol, treatment with charcoal, filtration through Celite, and cooling to give white needles that were collected by filtration: mp 92−93 °C. ^{1}H NMR ($CDCl_3$): δ 7.25 (s, 1H), 6.41 (s, 1H), 5.97 (s, 2H), 4.46 (t, 2H, J = 6 Hz), 2.72 (t, 2H, J = 6 Hz). EIMS *m/z*: 192. Anal. ($C_{10}H_8O_4$) C, H, N.

6,7-Methylenedioxy-4-trifluoromethanesulfonyl-2*H*-chromene (12). With conditions described by Pal,[19] **11** (8.7 g, 0.045 mol) was dissolved in 300 mL of dry THF and cooled to −78 °C, and 50 mL of a sodium bis(trimethylsilyl)amide solution (1.0 M in THF, 0.050 mol) was added. The solution was stirred for 1 h at −78 °C. *N*-Phenyltrifluoromethanesulfonimide (17.86 g, 0.050 mol) dissolved in 50 mL of dry THF was then added to the enolate solution via syringe, and the mixture was stirred for 1 h while warming to room temperature. After the reaction was quenched with 300 mL of brine, the product was extracted into ethyl acetate (3 × 300 mL), dried (Na_2SO_4), concentrated, and purified by flash chromatography (silica gel, 95% hexanes−ethyl acetate) to yield a yellow oil (11.66 g, 80%) that was used immediately in the next step. ^{1}H NMR ($CDCl_3$): δ 6.71 (s, 1H), 6.42 (s, 1H), 5.94 (s 2H), 5.61 (t, 1H, J = 4.2 Hz), 4.86 (d, 2H, J = 4.2 Hz). EIMS *m/z*: 324.

6,7-Methylenedioxy-4-(2-[1,3]dioxolan-2-ylphenyl)-2*H*-chromene (13). Triflate **12** (11.86 g, 0.036 mol), after purification, was immediately dissolved in 100 mL of dry toluene. The pinacol boronate ester **8** (14.4 g, 0.052 mol), potassium bromide (12.85 g, 0.108 mol), potassium hydroxide (6.10 g, 0.108 mol), and tetrakis-(triphenylphosphine)palladium(0) (2.1 g, 5 mol %) were suspended in 50 mL of dry toluene and combined with the triflate solution. The mixture was degassed by bubbling argon through for 15 min and was then heated at reflux for 1 h. After the mixture had been cooled to room temperature, 200 mL of water was added and the aqueous layer was extracted with toluene (3 × 200 mL). The organic extracts were combined, dried (Na_2SO_4), filtered, and concentrated. The resulting black oil was purified by column chromatography (silica gel, 80% hexanes−ethyl acetate) to afford a white solid (8.2 g, 71%). An analytical sample was recrystallized from ethyl acetate−hexane: mp 126−127 °C. ^{1}H NMR ($CDCl_3$): δ 7.66 (dd, 1H, J = 7.5, 2.1 Hz), 7.38 (td, 2H, J = 9, 2.1 Hz), 7.14 (dd, 1H, J = 9.0, 2.1 Hz), 6.70 (s, 1H), 6.44 (s, 1H), 6.13 (s, 1H), 5.83 (s, 2H), 5.71 (s, 1H), 5.63 (t, 1H, J = 3.9 Hz), 4.80 (d, 1H, J = 3.9 Hz), 4.12 (m, 2H), 3.92 (t, 2H, J = 5.7 Hz). EIMS *m/z*: 324. Anal. ($C_{19}H_{16}O_5$) C, H, N.

6,7-Methylenedioxy-4-(2-[1,3]dioxolan-2-ylphenyl)-3-nitro-2*H*-chromene (14). Following the procedure described by Shulgin,[24] **13** (3.3 g, 102 mmol) and 0.85 mL (105 mmol) of pyridine were dissolved in 100 mL of acetone and the solution was cooled to 0 °C. Tetranitromethane (1.3 mL, 106 mmol) was then added, and the solution was stirred for 5 min. The reaction was quenched by adding 100 mL of 1.0 M KOH and stirring the resulting orange mixture for 30 min at 0 °C. The aqueous layer was extracted with ethyl ether (3 × 250 mL), dried (Na_2SO_4), filtered, and concentrated. The nitrochromene **14** was obtained by flash chromatography (silica gel, 50% hexanes−ethyl acetate) and recrystallized from methanol as bright-orange needles (3.43 g, 91%): mp 129−131 °C. ^{1}H NMR ($CDCl_3$): δ 7.64 (m, 1H), 7.45 (m, 2H), 7.10 (m, 1H), 6.50 (s, 1H), 6.07 (s, 1H), 5.91 (s, 2H), 5.61 (s, 1H), 5.22 (d, 2H, J = 6.3 Hz), 3.97 (m, 1H), 3.89 (m, 1H), 3.85 (m, 2H). EIMS *m/z*: 369. Anal. ($C_{19}H_{15}NO_7$) C, H, N.

2,3-Methylenedioxy-6*H*-5-oxa-7-aza-benzo[*c*]phenanthracene (16). Nitrochromene **14** (1.5 g, 4.10 mmol) was suspended in 80 mL of aqueous acetic acid (3:1, AcOH−H_2O). After addition of Zn dust (3.05 g, 41.0 mmol), the mixture was heated at 60 °C for 30 min. The majority of the acetic acid was then removed by rotary evaporation, and the remaining acid was neutralized by adding a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted several times with dichloromethane (3 × 350 mL), dried (Na_2SO_4), filtered, and concentrated. The amine was then purified by column chromatography (silica gel, 50% ethyl acetate−hexanes) and recrystallized from ethyl acetate as lime-colored needles (0.43 g, 38%). The same product was recovered when **15** was subjected to the Zn/HCl reduction conditions reported by Michaelides et al.:[25] mp 176−177 °C. ^{1}H NMR ($CDCl_3$): δ 9.03 (s, 1H), 8.45 (d, 1H, J = 9 Hz), 8.00 (d, 1H, J = 9 Hz), 7.74 (t, 1H, J = 3 Hz), 7.60 (t, 1H, J = 3 Hz), 7.46 (s, 1H), 6.72 (s, 1H), 6.02 (s, 2H), 5.20 (s, 2H). CIMS *m/z*: 278. Anal. ($C_{17}H_{11}NO_3$) C, H, N.

(±)-*cis*-2,3-Methylenedioxy-6a,7,8,12b-tetrahydro-6*H*-5-oxa-7-azabenzo[*c*]phenanthracene (17). Phenanthracene **16** (0.582 g, 2.1 mmol) was suspended in 100 mL of methanol. Powdered sodium cyanoborohydride (0.80 g, 12.7 mmol) was then added to the solution in a single portion, and a few crystals of bromocresol green were added. A 10% methanolic HCl solution was added dropwise to the blue solution until a yellow color persisted. Additional methanolic HCl was added periodically to maintain a slightly acidic solution. The mixture was then stirred overnight. When the reaction was complete, the methanol was removed by rotary evaporation. The resulting oil was dissolved in 250 mL of water, made basic with 2 N NaOH, extracted with dichloromethane (3 × 250 mL), dried (Na_2SO_4), filtered, and concentrated. The resulting oil was dissolved in 25 mL of diethyl ether and concentrated to afford a tan solid (0.531 g, 90%). ^{1}H NMR ($CDCl_3$): δ 7.21 (m, 3H), 7.01 (d, 1H, J = 6 Hz), 6.56 (s, 1H), 6.33 (s, 1H), 5.75 (d, 2H, J = 15 Hz), 4.21 (d, 2H, J = 3 Hz), 4.05 (q, 2H, J = 18 Hz), 3.89 (d, 1H, J = 6 Hz), 3.29 (q, 1H, J = 3 Hz). CIMS *m/z*: 282. Anal. ($C_{17}H_{15}NO_3$) C, H, N.

6-Hydroxybenzo[1,3]dioxole-5-carboxaldehyde (18). Sesamol **9** (50.98 g, 369 mmol) was dissolved in 600 mL of CH_2Cl_2, followed by 52 mL (448 mmol) of $SnCl_4$, and the solution was cooled to 0 °C. Cl_2CHOCH_3 (35 mL, 387.5 mmol) was then added dropwise as the mixture warmed to room temperature and was stirred for 3 h. The mixture was poured over ice, and the water layer was separated and extracted once with CH_2Cl_2 (30 mL). The organic extracts were pooled, washed with 2 M HCl (5 × 100 mL) to remove tin salts, brine (50 mL), and was then passed through a small column packed with $MgSO_4$, which removed color. The solvent was then removed under reduced pressure to yield 28 g (46% yield) of pure aldehyde as a cream-colored powder: mp 119 °C. ^{1}H NMR ($CDCl_3$): δ 9.63 (s, 1H, CHO), 6.87 (s, 1H, ArH), 6.47 (s, 1, ArH), 6.02 (s, 2H, $ArOCH_2O$), 1.54 (s, 1H, ArOH). Low-resolution CIMS: *m/z* (relative intensity) 167 (MH^+, 100). Anal. ($C_8H_6O_4$) C, H, N.

7-Nitro-6*H*-[1,3]methylenedioxy[4,5-*g*]chromene (19). Aldehyde **18** (6 g, 36.14 mmol) was dissolved in 300 mL of toluene containing 3.1 mL of dibutylamine (18.16 mmol) and 10.72 g (72.37 mmol) of phthalic anhydride in a two-necked flask equipped with a Dean−Stark trap, a condenser, and an addition funnel. The solution was heated to reflux, and nitroethanol (7 mL 97.69 mmol) was added very slowly over 18 h (∼1 drop every 10 min) while vigorously stirring. After addition was complete, the mixture was stirred at reflux for an additional 24 h. The flask was then cooled to room temperature, the reaction mixture was filtered through Celite, and the filtrate was washed with 2 M NaOH (3 × 300 mL), brine (100 mL), and then dried over $MgSO_4$. After filtration, the organic solution was concentrated under reduced pressure and the crude concentrated solution was passed through a short column of

silica to remove dark polar impurities. This eluate was then concentrated under vacuum, and the residue was recrystallized from methanol to afford 4.89 g (61% yield) of pure nitrochromene **19** as bright-red needles: mp 139 °C. ^{1}H NMR ($CDCl_3$): δ 5.20 (s, 2H, $ArOCH_2$), 6.02 (s, 2H, OCH_2O), 6.49 (s, 1H, ArH), 6.69 (s, 1H, ArH), 7.75 (s, 1H, ArCH). Low-resolution CIMS: *m*/*z* (relative intensity) 222 (MH^+, 100). Anal. ($C_{10}H_7NO_5$) C, H, N.

(±)-*trans*-6,7-Methylenedioxy-3-nitro-4-(2-[1,3]dioxan-2-ylphenyl)-3,4-dihydro-2*H*-chromene (21). Acetal **20**[20] (9.04 g, 37.22 mmol) was dissolved in 50 mL of dry THF under an inert atmosphere in a two-necked flask equipped with a condenser. Magnesium powder (1.8 g, 74.44 mmol) was added to the flask, and the mixture was stirred at 80 °C for 45 min to form the Grignard reagent. The flask was then cooled to room temperature, and a solution of 2.74 g (12.41 mmol) of nitrochromene **19** in 50 mL of THF was cannulated into the Grignard reagent. After stirring for 30 min, water was added to quench the reaction. The mixture was then extracted with CH_2Cl_2 (3 × 100 mL), the extracts were washed with brine (100 mL), dried over $MgSO_4$, filtered, and stripped of solvent, yielding a brown oil from which product spontaneously crystallized. The crystals were collected by filtration, rinsed on the filter with 30 mL of cold EtOAc, and dried to afford 2.91 g (61.4%) of a homogeneous cream-colored powder. Additional material was obtained from the mother liquor by flash column chromatography to provide 550 mg (72% overall yield) of product: mp 207 °C. ^{1}H NMR ($CDCl_3$): δ 7.50 (m, 1H, ArH), 7.29 (m, 2H, ArH), 6.99 (m, 1H, ArH), 6.47 (s, 1H, ArH), 6.38 (s, 1H, ArH), 5.90 (d, 2H, $ArOCH_2$), 5.70 (s, 2H, OCH_2O), 4.97 (s, 1H, O_2CHAr), 4.71 (dq, 1H, Ar_2CH, J = 10 Hz), 4.23 (m, 2H + 1H, $CH_2(CH_2O)_2$, $CHNO_2$), 3.98 (m, 2H $CH_2(CH_2O)_2$), 2.22 (m, 1H, CH_2), 1.43 (d, 1H, CH_2). Low-resolution CIMS: *m*/*z* (relative intensity) 386 (MH^+, 100). Anal. ($C_{20}H_{19}NO_7$) C, H, N.

(±)-*trans*-2,3-Methylenedioxy-6a,12b-dihydro-6*H*-chromeno-[3,4-*c*]isoquinoline (22). Acetal **21** (1.84 g, 4.77 mmol) was dissolved in a mixture of 70 mL of THF and 30 mL of AcOH. Zinc dust (1.9 g, 30 mmol) was added through a powder funnel, and the mixture was stirred for 3 h on an oil bath at 70 °C under a reflux condenser. The mixture was then cooled and filtered, and the solid metal and salts on the filter were rinsed with warm THF. The filtrate was concentrated to dryness, and the residue was stirred in 50 mL of 2 M ethanolic HCl at room temperature for 1 h to deprotect the aldehyde. The solvents were then evaporated under reduced pressure, and an amount of 100 mL of 2 M NaOH was added. The mixture was then vigorously stirred with 150 mL of CH_2Cl_2 for 1 h. The organic layer was recovered, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to dryness. The residual solid was recrystallized from EtOH to yield 1.16 g (87%) of pure imine as white needles: mp 191 °C. ^{1}H NMR ($CDCl_3$): δ 8.43 (s, 1H, NCH), 7.65 (d, 1H, ArH), 7.47−7.34 (m, 3H, ArH), 6.95 (s, 1H, ArH), 6.51 (s, 1H, ArH), 5.94 (2d, 2H, $ArOCH_2O$), 4.63 (dd, 1H, $ArOCH_2$ J_{gem} = 10.4 Hz, J_{vic} = 4.2 Hz), 4.08 (t, 1H, $ArOCH_2$, J_{gem} = 10.4 Hz), 3.80 (d, 1H, ArCH, J = 14.6 Hz), 3.45 (dt, 1H, CHN, J = 14.6 Hz, J_{vic} = 4.2 Hz). Low-resolution CIMS: *m*/*z* (relative intensity), 280 (MH^+, 100). Anal. ($C_{17}H_{13}NO_3$) C, H, N.

(±)-*trans*-2,3-Methylenedioxy-6a,7,8,12b-tetrahydro-6*H*-chromeno[3,4-*c*]isoquinoline (23). Imine **22** (1.16 g, 4.15 mmol) was dissolved in 250 mL of a 60:30 mixture of EtOH−THF. $NaBH_3CN$ (261 mg, 4.15 mmol) was then added with stirring until it dissolved. The mixture was maintained at acidic pH by addition of 2.1 mL of 2 M ethanolic HCl in four portions while the mixture was stirred for 4 h. The solution was then reduced to one-fourth its volume and made basic with NaOH. Excess water was added, and the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The extracts were washed with brine, and the organic phase was dried over $MgSO_4$. After filtration, the solvent was removed and the residual solid was recrystallized from ethanol to yield 0.922 g (79%) of the amine as colorless needles: mp 188 °C. ^{1}H NMR ($CDCl_3$): δ 7.48 (d, 1H, ArH), 7.35−7.25 (m, 3H, ArH), 6.91 (s, 1H, ArH), 6.53 (s, 1H, ArH), 5.95 (s, 2H, $ArOCH_2O$), 4.47 (dd, 1H, $ArOCH_2$, J_{vic} = 5.1 Hz, J_{gem} = 10.2 Hz), 4.24 (s, 1H, $ArCH_2N$), 4.09 (t, 1H, OCH_2, J_{gem} = 10.2 Hz), 4.03 (d, 1H, ArCHAr, J_{trans} = 11.4 Hz), 3.12 (dt, 1H, NCH, J_{trans}= 11.4 Hz, J_{vic} = 5.1 Hz). Low-resolution CIMS: *m*/*z* (relative intensity) 282 (MH^+, 100). Anal. ($C_{17}H_{15}NO_3$) C, H, N.

(±)-2,3-Dihydroxy-6a,7,8,12b-tetrahydro-6*H*-chromeno[3,4-*c*]isoquinoline hydrochloride ((±)-6). Amine **23** (570 mg, 2.03 mmol) was dissolved in 40 mL of CH_2Cl_2, and the solution was cooled to −78 °C. BCl_3 (8.1 mL of 1 M solution, 8.1 mmol) was added through a syringe, and the solution was allowed to warm to 0 °C and then stirred for 4 h. MeOH (20 mL) was added to quench the reaction, and the mixture was stirred for another hour. The solvents were then removed under vacuum, MeOH was again added, and the solution was concentrated to yield the product in quantitative yield and pure by NMR. Recrystallization from MeOH and then drying under vacuum at 70 °C yielded 280 mg of crystalline **6** as an off-white powder (45% yield): mp 185−190 °C (dec). ^{1}H NMR (D_2O): δ 7.55−7.43 (m, 4H, Ar), 7.07 (s, 1H, ArH), 6.61 (s, 1H, ArH), 4.60 (dd, 1H, $ArOCH_2$), 4.55 (2d, 2H, $ArCH_2N$, J = 7 Hz), 4.34 (d, 1H, ArCHAr, J = 11.5 Hz), 4.20 (t, 1H, $ArOCH_2$, J = 10 Hz), 3.35 (dt, 1H, NCH, J_{trans} = 11.5 Hz, J_2 = 4.2 Hz). Low-resolution ESIMS: *m*/*z* (relative intensity) 270 (MH^+, 100). Anal. ($C_{16}H_{15}NO_3 \cdot H_2O \cdot HCl$) C, H, N.

(±)-*trans*-6-Allyl-5,6a,7,13b-tetrahydro-6*H*-[1,3]methylenedioxy-[6,7]chromeno[3,4-*c*]isoquinoline (24). Amine **23** (300 mg, 1.067 mmol) was dissolved in 20 mL of dry acetone in a round-bottom flask. Allyl bromide (0.11 mL, 1.281 mmol) and 220 mg (1.60 mmol) of K_2CO_3 were added to the flask, and the mixture was stirred at room temperature for 12 h. The mixture was then filtered, the volatiles were removed under reduced pressure, and the crude material was redissolved in 20 mL of CH_2Cl_2. The organic solution was washed once with 5 mL of H_2O, dried over Na_2SO_4, and filtered, and the solvent was removed under reduced pressure. The crude material was recrystallized from EtOH to yield 281 mg (82% yield) of the free base as colorless crystals: mp 97 °C. ^{1}H NMR (DMSO-d_6): δ 7.23−7.30 (m, 4H, Ar), 6.89 (s, 1H, ArH), 6.56 (s, 1H, ArH), 5.98 (d, 2H, OCH_2O), 6.80 (m, 1H, vinylic), 5.15 (m, 2H, gem vinylic), 4.32 (dd, 1H, $ArOCH_2$, J_{gem} = 10.2 Hz, J_{vic} = 4.2 Hz), 3.99 (d, 1H, ArCHAr, J_{trans} = 11.4 Hz), 3.97 (d, 1H, $ArCH_2N$, J_{gem} =15 Hz), 3.78 (t, 1H, $ArOCH_2$, J_{gem} = 10.2 Hz), 3.64 (d, 1H, $ArCH_2N$, J_{gem} = 15 Hz), 3.18 (dd, 1H, allylic), 2.91 (dd, 1H, allylic), 2.22 (dt, 1H, NCH, J_{trans} = 11.4 Hz, J_{vic} = 4.2 Hz). Anal. ($C_{20}H_{19}NO_3$) C, H, N.

(±)-*trans*-6-Propyl-5,6a,7,13b-tetrahydro-6*H*-[1,3]dioxolo[6,7]-chromeno[3,4-*c*]isoquinoline (25). Amine **24** (100 mg, 0.311 mmol) was dissolved in 40 mL of EtOH, 10 mg of 10% Pd/C was added, and the suspension was shaken under 30 psi of H_2 for 4 h, at which point H_2 uptake had ceased. The catalyst was removed by filtration, and the filtrate was concentrated. The crude residue was recrystallized from EtOH to yield 73 mg (73% yield) of the desired *N*-propyl analogue **25** as an off-white solid: mp 119 °C. ^{1}H NMR (DMSO-d_6): δ 7.23−7.30 (m, 4, Ar), 6.89 (s, 1H, ArH), 6.56 (s, 1H, ArH), 5.98 (d, 2H, OCH_2O), 4.27 (dd, 1H, ArOCH2 J_{gem} = 10.2 Hz, J_{vic} = 4.2 Hz), 3.96 (d, 1H, $ArCH_2N$, J_{gem} =15 Hz), 3.94 (d, 1H, ArCHAr, J_{trans} = 11.4 Hz), 3.76 (t, 1H, $ArOCH_2$, J_{gem} = 10.2 Hz), 3.63 (d, 1H, $ArCH_2N$, J_{gem} = 15 Hz), 2.34 (m, 2H, NCH_2), 2.18 (dt, 1H, NCH, J_{trans} = 11.4 Hz, J_{vic} = 4.2 Hz), 1.44 (m, 2H, CCH_2C), 0.84 (t, 3H, CH_3). CIMS: *m*/*z* (relative intensity) 324 (MH^+, 100). Anal. ($C_{20}H_{21}NO_3$) C, H, N.

(±)-*trans*-2,3-Dihydoxy-7-propyl-6a,7,8,12b-tetrahydro-6*H*-chromeno[3,4-*c*]isoquinoline Hydrochloride (26). *N*-Propylamine **25** (50 mg, 0.154 mmol) was dissolved in 10 mL of CH_2Cl_2 and cooled to −78 °C. A solution of 1 M BCl_3 (0.46 mL) was then introduced through a syringe. The solution was allowed to warm to room temperature overnight and was then cooled to 0 °C and quenched with 1 mL of dry MeOH. This solution was stirred for 30 min, and the solvents were removed under reduced pressure. Dry MeOH (2 mL) was added, and the solvents were again removed under reduced pressure. This procedure was repeated once more, and the crude mixture was recrystallized from EtOH to yield 39 mg (72% yield) of the title compound as a cream-colored powder:

mp 230−245 °C (dec). ^{1}H NMR (DMSO-d_6): δ 9.21 (s br, 1H, OH), 8.41 (s br, 1H, OH), 7.53 (d, 1H, ArH), 7.47−7.37 (m, 3H, ArH), 6.82 (s, 1H, ArH), 6.40 (s, 1H, ArH), 4.67−4.47 (m, 3H, ArCHN, $ArCH_2N$, OCH_2), 4.37 (d, 1H, ArCHAr, J_{trans} = 11.4 Hz), 4.25 (t, 1H, OCH_2, J_{gem} = 10.5 Hz), 3.23−2.93 (m, 3H, NCH_2, NCH), 1.76 (m br, 2H, CH_2CH_3), 0.89 (t, 3H, CH_3). ESIMS: *m*/*z* (relative intensity) 312 (MH^+, 100). Anal. ($C_{19}H_{21}NO_3$·HCl) C, H, N.

(6a*S*,13b*R*)-(−)-6-[(2*R*)-2-Methoxy-2-phenylacetyl]-5,6a,7,-13b-tetrahydro-6*H*-[1,3]methylenedioxy[6,7]chromeno[3,4-*c*]isoquinoline ((−)-27). The procedure used by Knoerzer[28] was followed. *R*-(−)-α-Methoxyphenylacetic acid (714 mg, 4.30 mmol) was placed into a round-bottom flask containing 12 mL of $SOCl_2$. This solution was stirred for 1 h at room temperature. The solvent was then removed by rotary evaporation, followed by repeated addition of benzene and subsequent evaporation to azeotropically remove residual $SOCl_2$ to provide *R*-(−)-*O*-methylmandeloyl chloride. This acyl chloride was dissolved in 5 mL of dry CH_2Cl_2 and added to a round-bottom flask containing 930 mg (3.31 mmol) of amine **23** in a stirring suspension of 20 mL of CH_2Cl_2 and 10 mL 0.5 M NaOH. This heterogeneous mixture was vigorously stirred for 6 h, the layers were then separated, the aqueous layer was extracted with CH_2Cl_2 (30 mL), and the combined organic layer was washed with water (2 × 30 mL) and brine (50 mL). The organic layer was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was separated by silica column chromatography using 2:1 hexanes−EtOAc as the eluent to obtain 616 mg (43%) of a faster moving component, R_f = 0.32, identified as the desired amide: mp 170 °C. $[\alpha]_D$ −125.0° (CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 7.32 (d, 1H, ArH), 7.30−7.24 (m, 5, ArH), 7.20 (t, 2H, ArH), 6.98 (t, 1H, ArH), 6.93 (s, 1H, ArH), 6.51 (s, 1H, ArH), 6.22 (d, 1H, ArH), 5.93 (d, 2H, OCH_2O), 5.13 (s, 1H, OCHAr), 5.08 (m, 1H, ArOCH), 4.88 (d, 1H, $ArCH_2N$, J = 14.7 Hz), 4.17 (m, 2H, Ar_2CH, $ArCH_2N$), 3.75 (m, 2H, CHN, ArOCH), 3.60 (s, 3H, OCH_3). Low-resolution CIMS: *m*/*z* (relative intensity) 430 (MH^+, 100). Anal. ($C_{26}H_{23}NO_5$) C, H, N.

(6a*R*,13b*S*)-(+)-6-[(2*R*)-2-Methoxy-2-phenylacetyl]-5,6a,7,-13b-tetrahydro-6*H*-[1,3]methylenedioxy[6,7]chromeno[3,4-*c*]isoquinoline ((+)-28). Fractions eluting later from the chromatographic separation detailed above yielded 661 mg (46%) of a slower moving component (R_f = 0.20): mp 186 °C. $[\alpha]_D$ +197.2° (CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 7.45 (d, 1H, ArH), 7.35−7.33 (m, 5H, ArH), 7.24 (t, 1H, ArH), 7.07 (t, 1H, ArH), 6.93 (s, 1H, ArH), 6.62 (d, 1H, ArH), 6.51 (s, 1H, ArH), 5.93 (d, 2H, OCH_2O), 5.13 (m, 1H, OCH), 5.02 (s, 1H, ArCHO), 4.85 (d, 1H, ArCHN, J = 14.2 Hz), 4.15 (m, 1H, ArCHAr), 4.05 (d, 1H, ArCHN, J = 14.2 Hz), 3.76−3.71 (m, 2H, CHN, OCH), 3.42 (s, 3H, OCH_3). Low-resolution CIMS: *m*/*z* (relative intensity) 430 (MH^+, 100). Anal. ($C_{26}H_{23}NO_5$) C, H, N.

(6a*S*,12b*R*)-(−)-2,3-Methylenedioxy-6a,7,8,12b-tetrahydro-6*H*-chromeno[3,4-*c*]isoquinoline ((−)-23). The (−)-**27** diastereomeric amide (615 mg, 1.433 mmol) was dissolved in 50 mL of dry THF and stirred at 0 °C. A 1 M solution of $LiEt_3BH$ (9 mL, 9 mmol) was added through a syringe, and the solution was stirred for 12 h at 0 °C. The reaction mixture was then poured into 15 mL of ice-cooled 2 M HCl, and the aqueous layer was washed with ether (2 × 15 mL) and then basified with NH_4OH. The free amine was extracted from this aqueous suspension with CH_2Cl_2 (3 × 15 mL). The crude product was purified by column chromatography over silica gel, eluting with 1:1 hexanes−EtOAc to provide 374 mg (93%) of the chiral amine: mp 163 °C. ^{1}H NMR: identical to the data of **23**, above. $[\alpha]_D$ −35.3° (CH_2Cl_2). Low-resolution CIMS: *m*/*z* (relative intensity) 282 (MH^+, 100). Anal. ($C_{17}H_{15}NO_3$) C, H, N.

(6a*R*,12b*S*)-(+)-2,3-Methylenedioxy-6a,7,8,12b-tetrahydro-6*H*-chromeno[3,4-*c*]isoquinoline ((+)-23). The (+)-**28** diastereomeric amide was treated identically to (−)-**27** to yield the chiral amine (94% yield): mp 163 °C. ^{1}H NMR spectrum identical to that for (−)-**23**. $[\alpha]_D$ +35.3° (CH_2Cl_2). Low-resolution CIMS: *m*/*z* (relative intensity) 282 (MH^+, 100). Anal. ($C_{17}H_{15}NO_3$) C, H, N.

(6a*R*,12b*S*)-(+)-2,3-Dihydroxy-6a,7,8,12b-tetrahydro-6*H*-chromeno[3,4-*c*]isoquinoline Hydrochloride ((+)-6). A procedure identical to the one used above for (±)-**6** but starting with (+)-**23** afforded a product that had an ^{1}H NMR spectrum identical to the spectrum for (±)-**6** and that could be recrystallized from isopropanol (79% yield): mp 183−195° (dec). Low-resolution ESIMS: *m*/*z* (relative intensity) 270 (MH^+, 100). $[\alpha]_D$ +165.3° (isopropanol). Anal. ($C_{16}H_{18}ClNO_4$) C, H, N.

(6a*S*,12b*R*)-(−)-2,3-Dihydroxy-6a,7,8,12b-tetrahydro-6*H*-chromeno[3,4-*c*]isoquinoline Hydrochloride ((−)-6). A procedure identical to the one used above for (±)-**6** but starting with (+)-**23** afforded a product that had an ^{1}H NMR spectrum identical to the spectrum for (±)-**6** and that could be recrystallized from isopropanol (81% yield): mp 183−195° (dec). Low-resolution ESIMS: *m*/*z* (relative intensity) 270 (MH^+, 100). $[\alpha]_D$ −165.1° (isopropanol). Anal. ($C_{16}H_{18}ClNO_4$) C, H, N.

Pharmacology. Materials. [^{3}H]Spiperone (95 Ci/mmol) and [^{3}H]-SCH-23390 (81 Ci/mmol) were purchased from Amersham Biosciences (Piscataway, NJ). [^{3}H]Cyclic AMP (30Ci/mmol) was purchased from Perkin-Elmer (Boston, MA). Quinpirole, dopamine, chlorpromazine, SCH-23390, butaclamol, isobutylmethylxanthine, forskolin, and most other reagents were purchased from Sigma-Aldrich Chemical Co. (St. Louis, MO). Most cell culture reagents, including growth media and antibiotics, were purchased from Gibco Invitrogen Corporation (Carlsbad, CA).

Cell Lines. HEK cells stably expressing rat D_{2L} and human $D_{4.4}$ receptors were constructed as described previously.[30] HEK D_1 CreLuc cells were created by a two-step process. Briefly, HEK293 cells were cotransfected with the pBabe Puro and pGL-CreLuc vectors. Puromycin-resistant clones that expressed the functional cAMP response element-linked luciferase reporter gene were selected. Next, HEK CreLuc cells were stably transfected with pcDNA3.1(+)-D_1. Clones were assayed for dopamine D_1 receptor function by measuring cAMP accumulation and luciferase activity.

Cell Culture. All cells were maintained in DMEM with 5% fetal clone serum, 5% bovine calf serum, 0.05 μg/mL penicillin, 50 μg/mL streptomycin, and 2 μg/mL puromycin (D_{2L} and $D_{4.4}$) or 300 μg of G418 and 2 μg/mL puromycin (D_1 CRE-Luc). Cells were grown at 37 °C in a humidified incubator with 5% CO_2.

Cyclic AMP Accumulation Assay. Assays were performed on confluent monolayers of cells in 48-well plates. All drugs were diluted in Earle's balanced salt solution (EBSS) assay buffer (EBSS containing 2% bovine calf serum, 0.025% ascorbic acid, and 15 mM HEPES, pH 7.4) and added on ice. Cyclic AMP stimulation assays were performed in HEK D_1 CRE-Luc cells by incubating ligands with D_1 receptors for 15 min at 37 °C. Forskolin (5 μM) was added to stimulate cAMP production for inhibition assays performed in HEK D_{2L} and HEK $D_{4.4}$ cells. All assays were performed in the presence of 500 μM isobutylmethylxanthine (IBMX) and terminated with 3% trichloroacetic acid.

Cyclic AMP Binding Assay. cAMP accumulation assays were quantified using a previously described protocol.[31] Briefly, cellular lysate was added in duplicate to cAMP binding buffer (100 mM Tris-HCl, pH 7.4, 100 mM NaCl, 5 mM EDTA) in assay tubes containing [^{3}H]cyclic-AMP (1 nM final concentration) and bovine adrenal gland cAMP binding protein (100−150 μg in 500 μL of buffer). These were incubated on ice at 4 °C for 2−3 h and terminated by harvesting with ice cold wash buffer (10 mM Tris, 0.9% NaCl) using a 96-well Packard Filtermate cell harvester. After the samples were dried, 30 μL of Packard Microscint O was added to each well. Radioactivity was counted using a Packard Topcount scintillation counter. Standard curves ranging from 0.01 to 300 pmol of cAMP were used to determine the concentration of cAMP in each sample.

Competition Binding Experiments. Porcine striatal tissue was obtained fresh from the Purdue Butcher Block and prepared as previously described.[32] Briefly, striatal tissue was homogenized using a potter-type homogenizer, suspended in homogenization buffer (20 mM Hepes, 0.32 M sucrose, pH 7.4), and spun at 1000*g* for 10 min at 4 °C. The pellet (P1) was discarded, and the supernatant was centrifuged at 30000*g* for 10 min at 4 °C. The

resulting pellet (P2) was resuspended in 50 mM Tris buffer (pH 7.4) by briefly using a Kinematica homogenizer and then centrifuged at 30000*g* for 30 min at 4 °C. This pellet was resuspended again in 50 mM Tris buffer, dispensed into 1 mL aliquots, and centrifuged for 10 min at 13000*g* and 4 °C. A BCA protein assay was used to determine the final protein concentration of the pellets. Supernatant was aspirated and pellets were frozen at −80 °C until use.

Radioligand binding assays were performed as previously described, with only minor modifications.[33] Pellets were resuspended (1 mL/mg) in receptor binding buffer (50 mM Hepes, 4 mM $MgCl_2$, pH 7.4), and 75 μg of protein was used per assay tube. Receptor isotherms were performed with [^{3}H]SCH-23390 and [^{3}H]-spiperone to determine B_{max} and K_d for D_1-like and D_2-like receptor sites (760 fmol/mg and 0.44 nM for [^{3}H]SCH-23390; 250 fmol/mg and 0.075 nM for [^{3}H]spiperone). All D_2-like receptor binding assays were performed in the presence of 50 nM ketanserin to mask 5-HT_{2A} sites. Nonspecific binding was defined with 5 μM butaclamol. Drug dilutions for competitive binding experiments were made in receptor binding buffer and added to assay tubes containing 75 μg of protein and either 1 nM [^{3}H]SCH-23390 or 0.15 nM [^{3}H]-spiperone. All binding experiments were incubated for 30 min at 37 °C and were terminated and counted in a fashion similar to the cAMP binding assays.

Data Analysis. GraphPad Prism software was used to generate dose−response, receptor isotherm, and competition binding curves and to perform statistical analyses (GraphPad Software, San Diego, CA). Data from cAMP inhibition assays performed in HEK D_{2L} and HEK $D_{4.4}$ cells were normalized to percent maximum forskolin-stimulated cAMP accumulations defined by GraphPad Prism, and Hill slopes were fixed to generate EC_{50} values. Maximum inhibition values for D_2 and $D_{4.4}$ functional experiments were fixed to that of quinpirole in order to estimate EC_{50} values of low potency compounds. Data from D_1 cAMP stimulation assays were normalized to 10 μM dopamine. For the figures shown in this paper, data from competition binding experiments were normalized to percent of specific binding, and the bottoms of agonist curves were fixed to zero. K_i values were calculated using the Cheng−Prusoff equation.

X-ray Crystal Structure Determination. Crystals of (+)-**23** were grown from evaporating CH_2Cl_2. Preliminary examination and data collection were performed with Cu Kα radiation ($\lambda = 1.541\,84$ Å) on an Enraf-Nonius CAD4 computer-controlled κ axis diffractometer equipped with a graphite crystal and incident beam monochromator. The space group was determined to be $P2_1$ (No. 4). Data were collected to a maximum 2θ of 139.8°. The structure was solved by direct methods using SIR2002. The remaining atoms were located in succeeding difference Fourier syntheses. Refinement was performed on a LINUX PC using SHELX-97. Crystallographic rendering was done using ORTEP.

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Supporting Information Available: X-ray crystallographic data and elemental analysis results. This material is available free of charge via the Internet at http://pubs.acs.org.

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