Identification, Characterization and Pharmacological Profile of Three Metabolites of (*R*)-(+)-1,2,3,6-Tetrahydro-4-phenyl-1-[(3-phenylcyclohexen-1-yl)methyl]pyridine (CI-1007), a Dopamine Autoreceptor Agonist and Potential Antipsychotic Agent

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Liquid chromatographic–mass spectrometric (LC–MS) analysis of plasma taken from cynomolgus monkeys dosed orally with (*R*)-(+)-1,2,3,6-tetrahydro-4-phenyl-1-[(3-phenylcyclohexen-1-yl)methyl]pyridine (**1**), a dopamine (DA) autoreceptor agonist and potential antipsychotic agent, revealed several metabolites. The molecular masses of three major metabolites suggested that they were mono- and dihydroxylated derivatives of **1**. We synthesized compounds **2** and **3**, the two possible mono-*p*-hydroxyphenyl derivatives of **1**, along with the bis-*p*-hydroxyphenyl derivative **4**. These compounds coeluted by HPLC with the three hydroxylated metabolites of **1**. Compounds **2**–**4** all had high affinities for DA D2 and D3 receptors and moderate affinities for D4 receptors. Like **1**, compound **2** decreased DA synthesis and neuronal firing in rat brain, indicative of DA autoreceptor activation. Compound **2** inhibited exploratory locomotor activity in rodents and was active in the Sidman avoidance test in squirrel monkeys, predictive of antipsychotic activity in humans. Compounds **3** and **4** showed weak activity in all these tests. After squirrel monkeys were dosed with **1** orally at the ED_{100} dose of the Sidman avoidance test, the plasma concentration of **2** was below the limit of quantitation. Therefore, these metabolites are unlikely to contribute greatly to the potent activity seen with **1** in the Sidman avoidance test.

Introduction

Schizophrenia has been postulated to involve hyperactive dopamine (DA) neuronal systems.[1-3] DA antagonist antipsychotics (e.g., haloperidol) are able to attenuate this excessive neurotransmission by blocking postsynaptic DA receptors. Unfortunately, their therapeutic actions are often accompanied by severe neurological side effects such as extrapyramidal syndrome and tardive dyskinesia.[4]

DA neurotransmission is controlled in part by autoreceptors located presynaptically on DA neurons. Activation of these autoreceptors inhibits neuronal firing, synthesis, and release of DA from the neurons.[5] An agent that could activate autoreceptors without stimulating postsynaptic DA receptors could modulate dopaminergic neurotransmission.[6] This mechanism might produce antipsychotic effects without the side effects resulting from the more severe attenuation of dopaminergic neurotransmission produced by DA receptor antagonists. There is presently no evidence for a molecular difference in DA autoreceptor and postsynaptic receptor structure.[7] However, DA agonists can selectively activate autoreceptors at lower doses, suggesting that autoreceptors are more sensitive *in vivo* than postsynaptic receptors.[8] Partial DA agonists may have sufficient efficacy to activate autoreceptors while not activating postsynaptic receptors over a wider range of doses.[9]

We recently described the identification of (*R*)-(+)-1,2,3,6-tetrahydro-4-phenyl-1-[(3-phenylcyclohexen-1-yl)methyl]pyridine (**1**) as a DA partial agonist.[10] This compound activated DA autoreceptors in rat brain; it inhibited DA neuronal firing as well as synthesis and release of DA. Unlike a full DA agonist, **1** did not appear to activate postsynaptic receptors as it produced only inhibition of locomotor activity in rodents, even at high doses. In squirrel monkeys, it had comparable potency to haloperidol in the Sidman avoidance test, a predictor of antipsychotic activity in humans, but showed a reduced liability toward neurological side effects. During our studies of the metabolism of **1** in rats and monkeys, hydroxylated derivatives of **1** were seen in plasma. Inspection of the structure of **1** suggested that *para* hydroxylation of the phenyl rings might occur *in vivo* (Figure 1).[11] This process would lead to two possible monohydroxylation products **2** and **3** and a single dihydroxylation product **4**. In this paper we describe the synthesis of compounds **2**–**4**, reveal evidence that they are metabolites of **1**, and describe their pharmacology.

Chemistry

At the outset of the synthesis of compounds **2**–**4**, we assumed that their absolute configuration was *R*, the same as **1**. We considered the chiral center of **1** to be stable under metabolic conditions. While preparation of the correct enantiomer was not important for the identification of the structure of the metabolites, we had already seen for **1** and related compounds that the pharmacology of the two enantiomers was very different.

The synthesis of hydroxy derivative **2** is shown in Scheme 1. (*R*)-Ketone **5** had been prepared during the

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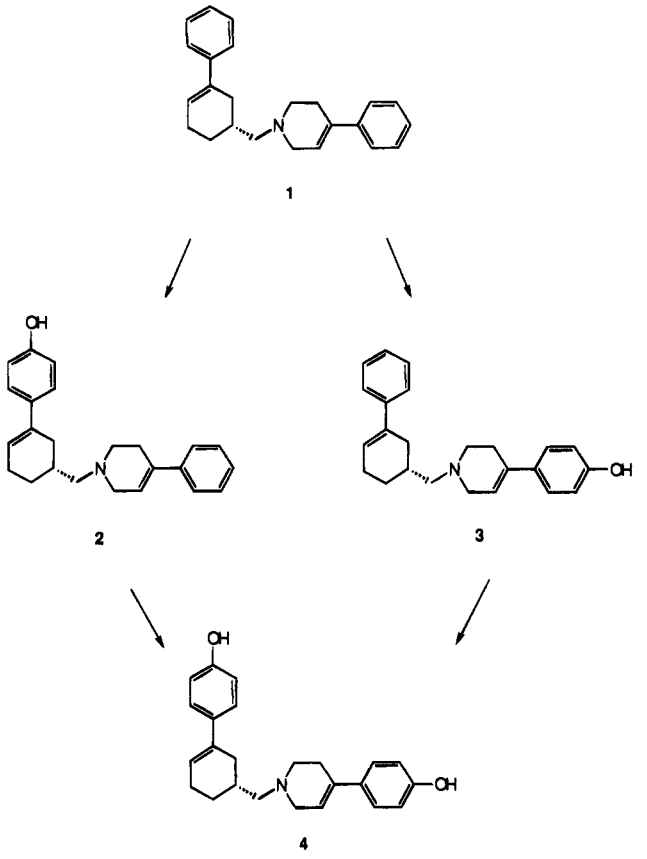


Figure 1. Proposed metabolism of 1.

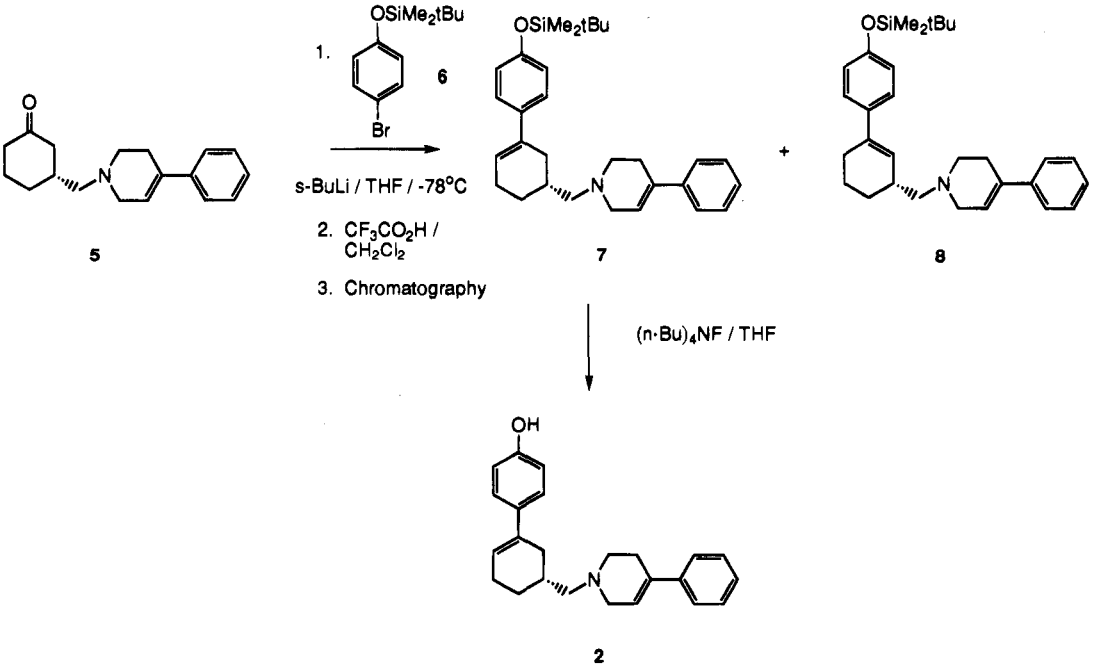
previously described studies of **1**.[10] *tert*-Butyldimethylsilyl-protected bromophenol **6**[12] was transmetalated with *s*-BuLi and added to **5**. The resulting alcohols were dehydrated by treatment with trifluoroacetic acid in dichloromethane at room temperature which avoided cleavage of the silyl ether. In contrast to the phenols, the silyl ethers were readily soluble in organic solvents which allowed separation of the double bond regioisomers **7** and **8** by chromatography. The position of the cyclohexenyl double bond was assigned using NMR spectroscopy. The carbon atom at the cyclohexenyl 3- and 5-position in **7** and **8**, respectively, was identified by ^{13}C NMR spectroscopy as the only aliphatic carbon atom coupled to one proton. A proton–carbon correlation experiment identified the proton attached to this carbon. In **8**, this proton was coupled to the cyclohexenyl vinyl proton; in **7** it was not. The silyl protecting group of the pure 1,5 isomer **7** was removed by treatment with Bu_4NF in THF to give sparingly soluble **2**.

Compound **3** was prepared by coupling the previously prepared (*R*)-acid **9**[10] (Scheme 2) to protected piperidone **10**. The resulting amide **11** was reduced with lithium aluminum hydride/aluminum chloride complex and the ketone deprotected with aqueous acid to give **12**. The anion of **6**, described above, was added to **12** and the resulting alcohol mixture dehydrated with trifluoroacetic acid to give **13**. Removal of the silyl protecting group of **13** with Bu_4NF in THF gave **3**.

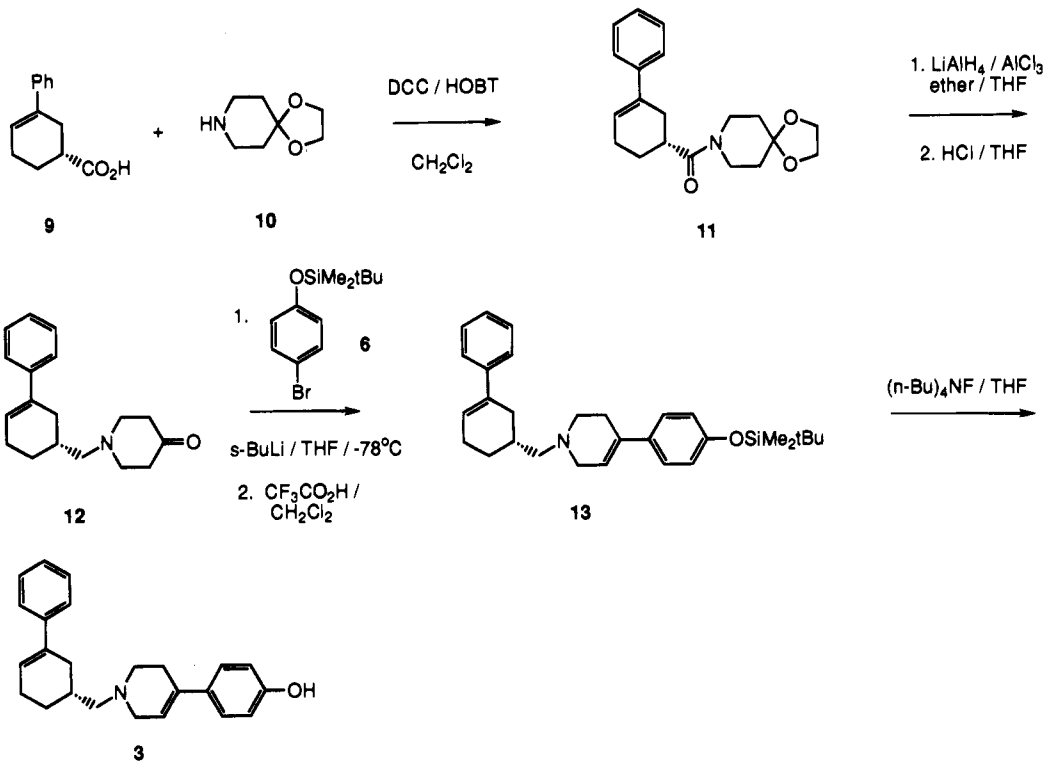
The preparation of bis-hydroxylated derivative **4** required a convergence of these routes (Scheme 3). The (*R*)-keto acid **14**[10] was coupled with **10**. The ketone of the resulting keto amide **15** was protected as the ketal to allow reduction of the amide to the amine. Both ketones were simultaneously deprotected, and the resulting diketone **16** was treated with 4 equiv of the lithium anion of **6**. The resulting alcohols were dehydrated to give a mixture of **17** and **18**. Comparison of the aliphatic region of the ^1H NMR spectra of **17** and **18** with those of **7** and **8**, respectively, confirmed the structural assignment shown. The 5-cyclohexene isomer **17** was isolated by chromatography, and treatment with Bu_4NF in THF gave pure **4**.

Compounds **2**–**4** all had much lower solubility in organic solvents than parent **1**. Once compounds **2**–**4** had been isolated as solids, they were very difficult to purify by chromatography, even using preadsorption techniques. However, the crude products isolated from the deprotection steps were sufficiently soluble to allow application onto chromatography columns. All three compounds had spectral and analytical data consistent with their assigned structures.

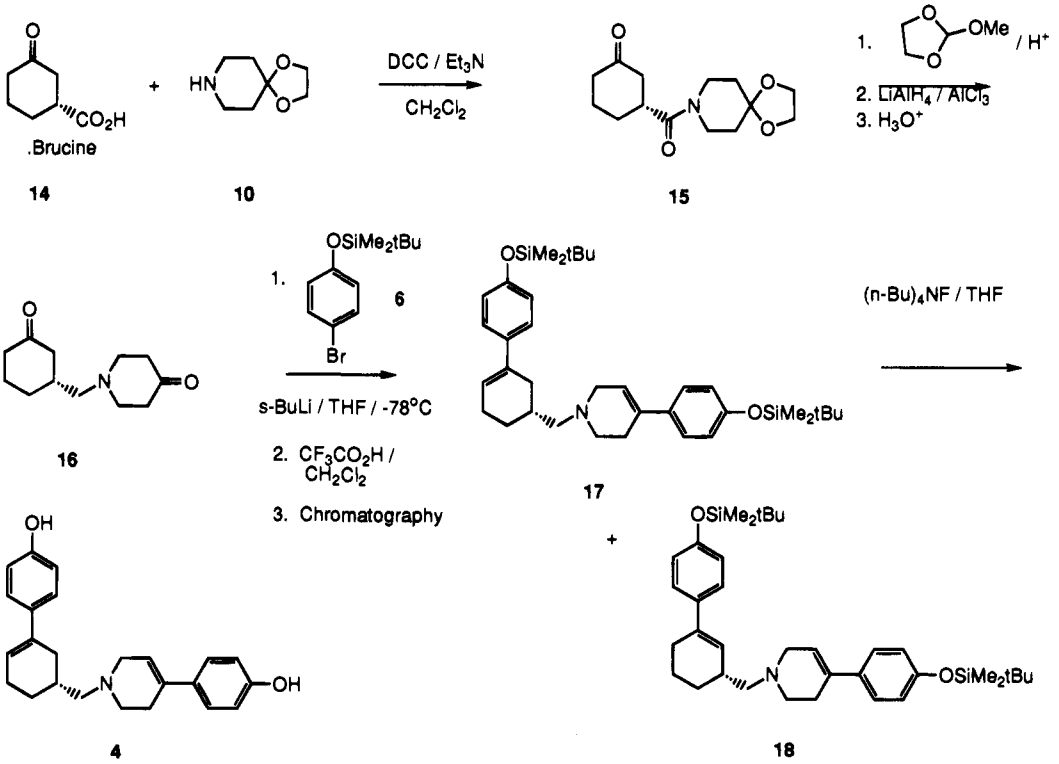
Scheme 1. Synthesis of **2**



Scheme 2. Synthesis of **3**



Scheme 3. Synthesis of **4**



Identification of Metabolites

Cynomolgus monkeys were dosed orally with 75 mg/kg of **1** as a suspension in 0.5% methylcellulose. Plasma was drawn after 3 h, and drug-derived components were isolated using reversed phase silica gel. The acid/acetonitrile eluant was evaporated and the residue analyzed by HPLC. The peaks corresponding to the proposed metabolites were analyzed by LC–MS.

Pharmacology

Brain dopamine autoreceptors are of the D2 and D3 subtype.[13] It has been suggested that certain DA antagonist antipsychotics may have some of their effects via blockade of D4 receptors.[14] Therefore, compounds were tested for their *in vitro* affinity for cloned human DA D2L receptors expressed in CHO-K1 cells using the antagonist ligand [^{3}H]spiperone to label the low-affinity

state of the receptor and the agonist ligand [^{3}H]N-0437 to label the high affinity or functional state.[15] Cloned human DA D3 receptors expressed in CHO-K1 cells exhibit mainly high-affinity states, and binding affinities of compounds to these receptors and human DA D4.2 receptors expressed in CHO-K1 cells were determined using [^{3}H]spiperone.[16] The intrinsic activities of the compounds for cloned human DA D2L and D3 receptors were determined by measuring their maximal effect on cell mitogenesis, measured via uptake of [^{3}H]-thymidine, and compared to the maximal effect caused by the full DA agonist quinpirole.[17] As an *in vivo* measure of DA autoreceptor agonist activity, the effects of compounds on γ-butyrolactone (GBL) induced increase in the rate of dihydroxy-L-phenylalanine (DOPA) synthesis in rat corpus striatum[18] were determined. In addition, they were tested for their effects on firing rate of substantia nigra DA neurons.[19] All compounds were administered intraperitoneally to mice and tested for inhibition of exploratory locomotor activity (LMA) as a behavioral measure of their ability to modulate DA neurotransmission via DA autoreceptor activation.[20] Higher doses of compound were administered to see if stimulation of LMA occurred, thus indicating postsynaptic DA receptor activation. Compounds **1**–**4** were finally evaluated in the conditioned avoidance test[21] in squirrel monkeys, a primate test which correlates well with antipsychotic activity in humans.[22]

Results and Discussion

The HPLC chromatogram of purified plasma from cynomolgus monkeys dosed orally with 75 mg/kg of **1** is shown in Figure 2. This dose is about 60-fold higher than the efficacious dose in the Sidman conditioned avoidance test in squirrel monkeys. Metabolites coeluting with monohydroxy standards **2** and **3** had matching mass spectral $(M + H)^+$ at 346; similarly, the metabolite coeluting with **4** had an $(M + H)^+$ at 362.

The affinities of compounds **1**–**4** for DA D2L, D3, and D4.2 receptors are shown in Table 1. Compounds **1**, **2**, and **4** had high affinities for DA D2L and D3 receptors but were relatively less potent at DA D4.2 receptors. Compound **3** showed weaker binding to all receptors versus [^{3}H]spiperone. As expected of full or partial DA agonists, the compounds more readily displaced the agonist ligand [^{3}H]N-0437 than the antagonist ligand

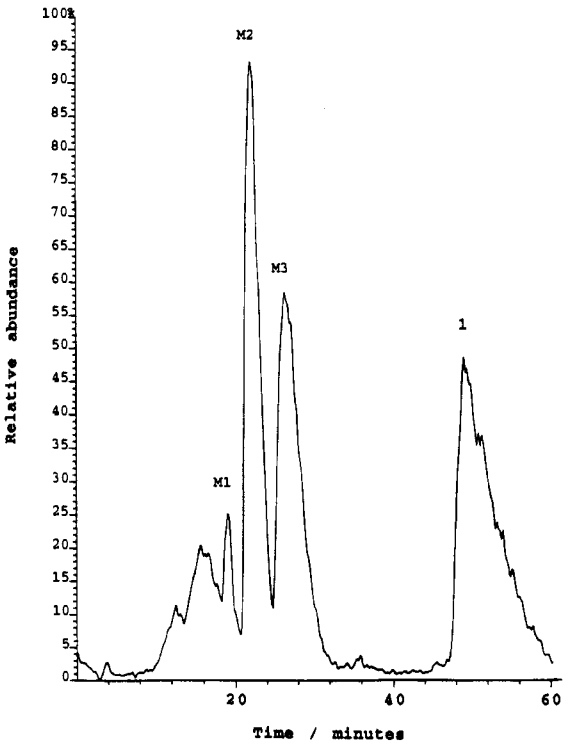


Figure 2. HPLC chromatogram of purified plasma drawn 3 h after monkeys were dosed orally with 75 mg/kg of **1**.

[^{3}H]spiperone from the DA D2L receptor. During the previously reported SAR study of **1**,[10] we discovered that *para* substitution on the phenyltetrahydropyridine produced compounds with weak DA receptor binding. In this series this was not the case; compound **3** has a *p*-hydroxyl on the phenyltetrahydropyridine and showed moderate DA D2 and D3 binding affinities. Compounds **2** and **4** contain a *p*-hydroxyl group on the cyclohexene phenyl and this group appears to enhance DA D2 and D3 binding activities compared to **1**.

The intrinsic activities of compound **2** at DA D2 and D3 receptors were similar to those of parent **1** (Table 1). Compounds **3** and **4** had less agonist activity at DA receptors. There is little correlation between the intrinsic activities of **1**–**4** at DA receptors and their relative affinities for the high-affinity versus low-affinity state of DA D2 receptors. The intrinsic activities were consistent with the effects seen on DA synthesis and

Table 1. Pharmacological Profile of Compounds 1–4

test	1	2	3	4
dopamine receptor binding (K_i, nM)[a]				
human D2L ([^{3}H]spiperone)	25.5 ± 1.6	3.5 ± 1.6	94.0 ± 10.2	10.3 ± 0.3
human D2L ([^{3}H]N-0437)	8.4 ± 1.9	0.20 ± 0.04	5.7 ± 1.0	2.2 ± 0.8
human D3 ([^{3}H]spiperone)	16.6 ± 3.8	0.52 ± 0.03	56.7 ± 19.8	3.4 ± 1.1
human D4.2 ([^{3}H]spiperone)	90.9 ± 11.0	61.4 ± 4.80	>10 000[b]	68.0 ± 12.0
intrinsic activity relative to quinpirole[c]				
human DA D2L	0.66 ± 0.01	0.62 ± 0.03	0.37 ± 0.03	0.29 ± 0.03
human DA D3	0.84 ± 0.06	0.76 ± 0.02	0.67 ± 0.02	0.54 ± 0.12
effect on DOPA accumulation in rat striatum after GBL (10 mg/kg ip)[d]	−66 ± 6%	−27 ± 7% −44 ± 7% at 3mg/kg	0%	−8 ± 14%
effect on DA neuron firing rate in rats (2.5 mg/kg ip)	−99 ± 4%	−100 ± 0%	+33 ± 13%	−10 ± 7%
inhibition of locomotor activity in mice (ED_{50}, mg/kg ip)[e]	0.7 (0.5–0.9)	0.3 (0.2–0.4)	>30	6.1 (2.9–12.8)
inhibition of conditioned avoidance in squirrel monkeys (ED_{50}, mg/kg po)[f]	0.63 (0.46–0.87)	1.34 (1.03–1.74)	>2.50	>2.50

[a] K_i values ± SEM were obtained from four to six concentrations, run in triplicate, by a nonlinear regression analysis. [b] IC_{50} >10 000 nM (<50% inhibition at 10 μM). [c] Maximal response relative to quinpirole ± SEM in the stimulation of [^{3}H]thymidine uptake in cells transfected with the human DA D2L and D3 receptor. [d] Animals were administered test compounds (10 mg/kg ip) 60 min and GBL (750 mg/kg ip), except for the control group, 30 min before sacrifice. All animals were given NSD (100 mg/kg ip) 30 min before sacrifice. Values are expressed as percent reversal of the increase in DOPA induced by GBL ± SEM. [e] LMA = locomotor activity; ED_{50} (95% confidence range) values were generated from three to six doses; 6–18 animals were used per dose. [f] ED_{50} (95% confidence range) values were generated from three doses, eight monkeys were used per dose.

DA neuronal firing, both *in vivo* measures of DA autoreceptor agonist activity.

Compounds **1** and **2** potently inhibited locomotor activity in mice. As compound **2** had intrinsic activities similar to **1** and decreased DA synthesis and firing, this activity was most likely due to DA autoreceptor activation. Compound **4** also weakly inhibited locomotor activity; however its lower intrinsic activity suggests blockade of postsynaptic DA receptors.

Compounds **1** and **2** were active in the Sidman avoidance test in monkeys. When **1** was given orally to squirrel monkeys at 1.2 **mg/kg** (the ED_{100} in the Sidman avoidance test), the maximum plasma concentrations of **1** and **2** were 34 and <5 ng/mL, respectively (below limit of quantitation for **2**).[23] Hence compound **2** is unlikely to contribute greatly to the *in vivo* effects seen after oral administration of **1**. On the basis of their high affinity for DA receptors, compounds **3** and **4** might be expected to have activity in this test. However, neither compound inhibited avoidance responding at 2.5 **mg/kg** orally. The poor solubilities of compounds **2**–**4** suggest low bioavailabilities which would compromise their effects in all these *in vivo* tests. In particular, this may explain why compound **4** is inactive orally in the Sidman avoidance test, despite its potent affinity for DA receptors.

Experimental Section

Melting points were determined on a Gallenkamp capillary melting point apparatus and are uncorrected. ^1H NMR were determined on Varian XL-300 or Unity 400 spectrometers. Mass spectra for synthesized compounds were obtained on Finnigan 4500 or VG Analytical 7070E/HF mass spectrometers. IR spectra were recorded on a Nicolet MX-1 FT spectrophotometer. Elemental analyses were performed by the Analytical Research Section at Parke-Davis, Ann Arbor, MI. TLC was performed on 0.25 mm silica gel F254 (E. Merck) glass plates. Medium-pressure liquid chromatography (MPLC) was performed on silica gel (E. Merck grade 60, 230–400 mesh, 60Å). HPLC for synthesized compounds was performed on 5 μm Beckman Ultrasphere 4.6 mm × 25 cm columns eluting at 1.5 mL/min and compounds detected using UV absorption at 254 nm. pH 3.0 buffer was prepared by mixing 28 mL of Et_3N in 4 L of HPLC-grade water and adjusting the pH to 3.0 with phosphoric acid. Ether refers to diethyl ether.

(*R*)-1,2,3,6-Tetrahydro-4-phenyl-1-[[3-[4-[(*tert*-butyldimethylsilyl)oxy]phenyl]cyclohexen-1-yl]methyl]pyridine (7) and (*R*)-1,2,3,6-Tetrahydro-4-phenyl-1-[[5-[4-[(*tert*-butyldimethylsilyl)oxy]phenyl]cyclohexen-1-yl]-methyl]pyridine (8). *s*-BuLi (17.7 mL of 1.3 M in cyclohexane, 23.0 mmol) was added to **6**[12] (6.62 g, 23.0 mmol) in ether (40 mL) at −78 °C under N_2 and stirred for 30 min. (*R*)-3-[(3,6-Dihydro-4-phenyl-1(2*H*)-pyridinyl)methyl]cyclohexanone[10] (**5**) (4.37 g, 16.2 mmol) in THF (20 mL) was added dropwise over 30 min and the mixture stirred for 4 h at −78 °C then at 25 °C overnight. Saturated NH_4Cl (100 mL) was added, and the organic layer was washed with saturated brine (100 mL), dried over $MgSO_4$, filtered, and evaporated to leave a mixture of the addition products as an oil (10.3 g). The addition product (10.3 g, 16.2 mmol) was stirred in CH_2Cl_2 (100 mL) and CF_3CO_2H (9.23 mL) at 25 °C for 2 h. The reaction mixture was washed with 2 N Na_2CO_3 (250 mL), dried over $MgSO_4$, filtered, and evaporated to leave an oil. This oil was purified by MPLC eluting with 95:5 hexane:EtOAc to give the faster-eluting isomer **8** as a colorless oil (1.59 g): ^1H NMR ($CDCl_3$) δ 7.15–7.50 (m, 7H), 6.80 (d, 2H), 6.12 (m, 1H), 3.20 (br s, 2H), 2.30–2.80 (m, 7H), 1.60–2.00 (m, 4H), 1.20–1.50 (m, 2H), 0.98 (s, 9H), 0.20 (s, 6H); MS (ES) (rel int) *m/z* 461.6 (38), 460.6 (100), 456.6 (55); HPLC (reversed-phase, 40% pH 3.0 buffer:60% MeCN) 14.33 min (98.9%); the slower isomer **7** as a colorless oil (2.25 g): ^1H NMR ($CDCl_3$) δ 7.20–7.50 (m, 7H), 6.78 (d, 2H), 6.10 (m, 1H), 3.20 (br s, 2H), 1.75–2.80 (m, 12H), 1.30 (m, 1H), 1.00 (s, 9H), 0.22 (s, 6H); MS (ES) (rel int) *m/z* 461.6 (33), 460.6 (96), 456.6 (100); HPLC (reversed-phase, 40% pH 3.0 buffer:60% MeCN) 12.98 min (100%); and a mixture of the two (0.22 g)—total yield 4.06 g (54% from ketone).

(*R*)-1,2,3,6-Tetrahydro-4-phenyl-1-[[3-(4-hydroxyphenyl)cyclohexen-1-yl]methyl]pyridine (2). A solution of **7** (2.25 g, 4.89 mmol) in THF (50 mL) was stirred with *n*-Bu_4NF (5.87 mL of 1.0 M in THF, 5.87 mmol) at 25 °C for 2 h. The THF was evaporated and the residue purified by MPLC, eluting with 95:5 CH_2Cl_2:MeOH to give the product as an off-white solid. This solid was washed with 1:1 ether:hexane to remove traces of silicon-based impurities and dried at 55 °C under high vacuum to give **2** as an off-white powder (1.36 g, 81%): mp 185–188 °C. The compound was characterized as the monooxalate salt: mp 189–191 °C (foams); IR (KBr) 3447 (broad), 3092, 3057, 1589, 1361, 1167, 1074, 810, 648, 559 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.49 (d, 2H, *J* = 7.5 Hz), 7.38 (t, 2H, *J* = 7.2 Hz), 7.31 (t, 1H, *J* = 7.2 Hz), 7.24 (d, 2H, *J* = 8.7 Hz), 6.71 (d, 2H, *J* = 8.4 Hz), 6.19 (br s, 1H), 6.02 (br s, 1H), 3.77 (br s, 2H), 3.31 (br s, 2H), 3.02 (br s 2H), 2.74 (br s, 2H), 2.58 (d, 1H, *J* = 13.7 Hz), 2.00–2.30 (m, 4H), 1.84 (br d, 1H, *J* = 11.1 Hz), 1.27 (m, 1H); HPLC (reversed-phase, 70% pH 3.0 buffer:30% MeCN) 10.73 min (99.3%); MS (ES) (rel int) *m/z* 346.4 (100), 347.4 (27); $[\alpha]^{20}_D$ +54.5° (*c* = 1.01, DMSO). Anal. ($C_{24}H_{27}NO \cdot C_2H_2O_4 \cdot 0.07H_2O$) C, H, N, water.

(*R*)-(1,4-Dioxa-8-azaspiro[4.5]dec-8-yl)(3-phenylcyclohex-3-enyl)methanone (11). Isobutyl chloroformate (3.53 mL, 27.2 mmol) was added to (*R*)-3-phenyl-3-cyclohexenecarboxylic acid[10] (**9**) (5.00 g, 24.7 mmol) and Et_3N (4.13 mL, 29.7 mmol) in CH_2Cl_2 (150 mL) at −20 °C under N_2 and stirred for 30 min. 1,4-Dioxa-8-azaspiro[4.5]decane (**10**) (3.16 mL, 24.7 mmol) was added and the mixture stirred at 25 °C overnight. The mixture was washed with saturated aqueous Na_2CO_3 (200 mL), dried over $MgSO_4$, filtered, and evaporated to leave a yellow oil (9.4 g). This was purified by MPLC, eluting with 50% EtOAc/hexanes to give **11** as a pale yellow oil (4.54 g, 56%): IR (neat) 1637, 1441, 1359, 1246, 1096, 945, 753, 697 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.18–7.38 (m, 5H), 6.08 (br s, 1H), 3.98 (s, 4H), 3.58–3.72 (m, 5H), 2.71–2.95 (m, 2H), 2.28–2.48 (m, 3H), 1.65–1.95 (m, 5H); MS (APCI) (rel int) *m/z* 328.5 (100). Anal. ($C_{20}H_{25}NO_3$) C, H, N.

(*R*)-1-[(3-Phenylcyclohex-3-enyl)methyl]piperidin-4-one (12). $AlCl_3$ (0.616 g, 4.62 mmol) in ether (10 mL) was added to $LiAlH_4$ (0.526 g, 13.9 mmol) in THF (20 mL), and the mixture was stirred for 20 min at 0 °C under N_2. A solution of **11** (4.54 g, 13.9 mmol) in THF (20 mL) was added dropwise at 0 °C and stirred for 2 h at 0 °C. Water (1 mL) and 25% NaOH (4 mL) were added, and the mixture was filtered, diluted with ether (100 mL), and washed with brine (100 mL). The organic layer was dried over $MgSO_4$, filtered, and evaporated to leave the amine as a clear colorless oil. This oil was stirred at reflux in THF (100 mL) and 2 N HCl (100 mL) for 2 h. The mixture was basified with 2 N Na_2CO_3 and extracted with EtOAc (3 × 150 mL). The extracts were washed with brine (300 mL), dried over $MgSO_4$, filtered, and evaporated. The residue was purified by MPLC, eluting with 30% EtOAc/hexanes to give **12** as a pale yellow oil (2.87 g, 79%): IR (neat) 1718, 1352, 1133, 749, 696 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.18–7.40 (m, 5H), 6.11 (br s, 1H), 1.88–2.80 (m, 16H), 1.30–1.40 (m, 1H); MS (APCI) (rel int) *m/z* 270.4 (100); HPLC (reversed-phase, 80% pH 3.0 buffer:20% MeCN) 10.39 min (100%). Anal. ($C_{18}H_{23}NO$) C, H, N.

(*R*)-1,2,3,6-Tetrahydro-4-[4-[(*tert*-butyldimethylsilyl)oxy]phenyl]-1-[(3-phenylcyclohexen-1-yl)methyl]pyridine (13). *s*-BuLi (18 mL of 1.3 M in cyclohexane, 23.4 mmol) was added to **6**[12] (6.12 g, 21.3 mmol) in THF (100 mL) at −78 °C under N_2 and the mixture stirred for 30 min at −78 °C. A solution of **12** (2.87 g, 10.7 mmol) in THF (20 mL) was added dropwise over 10 min and the mixture stirred at −78 °C for 3 h. The mixture was quenched with saturated NH_4Cl (200 mL) and extracted with EtOAc (3 × 200 mL). The extracts were washed with saturated brine (400 mL), dried over $MgSO_4$, filtered, and evaporated to give the crude alcohols as a yellow oil (6.31 g). The alcohols were stirred in CH_2Cl_2 (300 mL) and CF_3CO_2H (5.08 mL, 66 mmol) at room temperature for 1 h. The mixture was washed with 2 N Na_2CO_3 (300 mL), saturated brine (300 mL) and dried over $MgSO_4$, filtered, and evaporated

to leave a pale yellow oil. The oil was purified by MPLC, eluting with 10% EtOAc/hexanes to give **13** (3.83 g, 78%) as a pale yellow oil: IR (neat) 1509, 1250, 906, 849, 806, 776, 748, 692 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.18–7.42 (m, 7H), 6.80 (d, 2H), 6.10 (br s, 1H), 5.98 (br s, 1H), 3.18 (m, 2H), 1.85–2.75 (m, 12H), 1.22–1.42 (m, 1H), 0.98 (s, 9H), 0.20 (s, 6H); MS (APCI) (rel int) *m/z* 460.7 (100); HPLC (reversed-phase, 40% pH 3.0 buffer:60% MeCN) 9.40 min (100%). Anal. ($C_{30}H_{41}NOSi$) C, H, N.

(*R*)-1,2,3,6-Tetrahydro-4-(4-hydroxyphenyl)-1-[(3-phenylcyclohexen-1-yl)methyl]pyridine (3). A solution of **13** (3.82 g, 8.32 mmol) and Bu_4NF (16.6 mL of 1.0 M in THF, 16.6 mmol) in THF (300 mL) was stirred at room temperature for 2 h. The THF was evaporated and the residue purified by MPLC, eluting with 3% MeOH/CH_2Cl_2 to give **3** (2.46 g, 86%) as an off-white solid: mp 160–162 °C. This solid was stirred in hot EtOH (100 mL) and oxalic acid (900 mg) in EtOH (10 mL) added. The monooxalate salt precipitated; it was collected and recrystallized from EtOH to give a white powder (1.36 g): mp 204–205 °C (foams); IR (KBr) 3033 (broad), 1691, 1629, 1607, 1516, 1220, 810, 750, 703 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.43 (d, 2H, J = 8.2 Hz), 7.30–7.34 (m, 4H), 7.23 (t, 1H, J = 7.0 Hz), 6.76 (d, 2H, J = 8.7 Hz), 6.20 (br s, 1H), 6.00 (br s, 1H), 3.77 (br s, 2H), 3.33 (br s, 2H), 3.06 (br s 2H), 2.70 (br s, 2H), 2.63 (d, 1H, J = 15.2 Hz), 2.10–2.35 (m, 4H), 1.86 (br d, 1H, J = 11.3 Hz), 1.29 (m, 1H); MS (ES) (rel int) *m/z* 346.5 (100), 347.5 (29); HPLC (reversed-phase, 70% pH 3.0 buffer: 30% MeCN) 16.00 min (97.1%); $[\alpha]^{20}_D$ +58.8° (*c* = 1.04, DMSO). Anal. ($C_{24}H_{27}NO \cdot C_2H_2O_4 \cdot 0.14H_2O$) C, H, N, water.

(*R*)-3-(1,4-Dioxa-8-azaspiro[4.5]dec-8-lylcarbonyl)cyclohexanone (15). A mixture of (−)-3-oxocyclohexanecarboxylic acid, brucine salt[10] (**14**) (100 g, 0.177 mol), 1,4-dioxa-8-azaspiro[4.5]decane (**10**) (27.9 g, 0.195 mol), dicyclohexylcarbodimide (40.2 g, 0.195 mol), and 1-hydroxybenzotriazole (26.3 g, 0.195 mol) in CH_2Cl_2 (2 L) was stirred overnight at 25 °C. The mixture was filtered and the solvent evaporated. The residue was taken up in EtOAc (2 L) and filtered. The filtrate was washed with saturated aqueous $NaHCO_3$ (2 L), 5% aqueous citric acid (2 L), and saturated brine (2 L), dried over $MgSO_4$, filtered, and evaporated to leave **15** as a white solid (41.0 g): mp 105–107 °C; IR (KBr) 3430 (broad), 1708, 1630, 1442, 1233, 1104, 938, 913 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.99 (s, 4H), 3.71 (t, 2H, J = 5.8 Hz), 3.55 (t, 2H, J = 5.8 Hz), 3.06 (m, 1H), 2.71 (dd, 1H, J = 11.1, 14.5 Hz), 2.36 (m, 3H), 2.10 (m, 1H), 1.89 (m, 2H), 1.70 (m, 5H); MS (CI) (rel int) *m/z* 268 (100); $[\alpha]^{20}_D$ +5.9° (*c* = 1.05, $CHCl_3$). Anal. ($C_{14}H_{21}NO_4 \cdot 0.08H_2O$) C, H, N, water.

(*R*)-1-[(3-Oxocyclohexyl)methyl]piperidin-4-one (16). A solution of **15** (41.0 g, 0.154 mol) in CH_2Cl_2 (500 mL) was stirred with 2-methoxy-1,3-dioxolane (33.7 mL, 0.353 mol) and CH_3SO_3H (1 mL) at 25 °C overnight. The reaction mixture was washed with 2 N aqueous Na_2CO_3 (500 mL), dried over $MgSO_4$, filtered, and evaporated to leave a pale yellow oil which solidified on standing (37.0 g, 63%): mp 68–71 °C; ^1H NMR ($CDCl_3$) δ 3.85–3.95 (m, 8H), 3.63 (m, 2H), 3.52 (t, 3H, J = 5.6 Hz), 2.79 (tt, 1H, J = 3.7, 11.7 Hz), 1.30–1.80 (m, 12H). Anal. ($C_{16}H_{25}NO_5$) C, H, N.

$AlCl_3$ (7.7 g, 58 mmol) in ether (50 mL) was added to $LiAlH_4$ (6.7 g, 0.177 mol) in THF (50 mL) and the mixture stirred for 20 min at 0 °C under N_2. The oil (37.0 g, 0.177 mmol) in THF (50 mL) was added dropwise at 0 °C and stirred for 2 h at 0 °C. Water (2 mL) and 25% NaOH (10 mL) were added, and the mixture was filtered, diluted with ether (500 mL), and washed with brine (500 mL). The organic layer was dried over $MgSO_4$, filtered, and evaporated to leave a pale yellow oil. This oil was taken up in concentrated HCl (500 mL) and stirred at reflux for 2 h. The mixture was basified with 25% NaOH and extracted with EtOAc (3 × 500 mL). The extracts were washed with brine (1 L). The organic layer was dried over $MgSO_4$, filtered and evaporated to leave a pale yellow oil. This oil was purified by MPLC, eluting with EtOAc then 10% MeOH/EtOAc to give **16** (6.3 g, 27%) as a colorless oil which solidified on standing: IR (KBr) 1717, 1351, 1226, 1134, 1012, 761 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.67–2.75 (m, 4H), 2.55 (m, 1H), 2.27–2.45 (m, 8H), 1.97–2.11 (m, 4H), 1.67–1.72 (m, 1H), 1.24–1.41 (m, 1H); MS (CI) (rel int) *m/z* 210 (100), 112 (97); $[\alpha]^{20}_D$ +24.3° (*c* = 1.04, $CHCl_3$). Anal. ($C_{12}H_{19}NO_2$) C, H, N.

(*R*)-1,2,3,6-Tetrahydro-4-[4-[(*tert*-butyldimethylsilyl)oxy]phenyl]-1-[[3-[4-[(*tert*-butyldimethylsilyl)oxy]phenyl]cyclohexen-1-yl]methyl]pyridine (17) and (*R*)-1,2,3,6-Tetrahydro-4-[4-[(*tert*-butyldimethylsilyl)oxy]phenyl]-1-[[5-[4-[(*tert*-butyldimethylsilyl)oxy]phenyl]cyclohexen-1-yl]methyl]pyridine (18). *s*-BuLi (41.1 mL of 1.3 M in cyclohexane, 53.5 mmol) was added to **6**[12] (15.4 g, 53.5 mmol) in THF (300 mL) at −78 °C under N_2, and the mixture was stirred for 30 min. A solution of **16** (2.80 g, 13.4 mmol) in THF (30 mL) was added dropwise over 1 h and the mixture stirred for 2 h at −78 °C. Saturated NH_4Cl (500 mL) was added and the organic layer separated. The aqueous layer was extracted with EtOAc (2 × 200 mL); the combined organic layers were washed with saturated brine (500 mL), dried over $MgSO_4$, filtered, and evaporated to leave a yellow oil (13.3 g). The oil was stirred in CH_2Cl_2 (400 mL) and CF_3CO_2H (12 mL) at 25 °C for 2 h. The reaction mixture was washed with 2 N Na_2CO_3 (200 mL), dried over $MgSO_4$, filtered, and evaporated to leave a yellow oil. This oil was purified by MPLC on silica gel, eluting with 95:5 hexane:EtOAc to give the faster-eluting isomer **18** (1.14 g, 14%) [^1H NMR ($CDCl_3$) δ 7.25 (d, 4H, J = 8.0 Hz), 6.78 (d, 4H, J = 8.0 Hz), 6.05 (br s, 2H), 3.15 (br s, 2H), 1.60–2.80 (m, 11H), 1.30 (m, 2H), 0.98 (s, 9H), 0.20 (s, 6H); HPLC (silica gel, 3% 2-propanol:97% hexane) 12.24 min (98.6%); MS (ES) (rel int) *m/z* 590.5 (100). Anal. ($C_{36}H_{55}NO_2Si_2$) C, H, N]; the slower-eluting isomer **17** (2.34 g, 30%) [^1H NMR ($CDCl_3$) δ 7.25 (d, 4H, J = 8.0 Hz), 6.78 (d, 4H, J = 8.0 Hz), 6.05 (br s, 2H), 3.15 (br s, 2H), 1.60–2.80 (m, 11H), 1.30 (m, 2H), 0.98 (s, 9H), 0.20 (s, 6H); HPLC (silica gel, 3% 2-propanol:97% hexane) 15.00 min (99.3%); MS (ES) (rel int) *m/z* 590.7 (100). Anal. ($C_{36}H_{55}NO_2Si_2$) C, H, N]; and a mixture of the two (0.63 g, 8%), total yield 52%.

(*R*)-1,2,3,6-Tetrahydro-4-(4-hydroxyphenyl)-1-[[3-(4-hydroxyphenyl)cyclohexen-1-yl]methyl]pyridine (4). A solution of **17** (2.34 g, 3.97 mmol) in THF (100 mL) was stirred with *n*-Bu_4NF (10 mL of 1.0 M in THF, 10.0 mmol) at 25 °C for 2 h. Most of the THF was evaporated and the residue applied onto a silica MPLC column (400 g) and eluted with 95:5 EtOAc:MeOH to give **4** as an off-white solid (1.51 g): mp 206–208 °C; IR (KBr) 3170 (v broad), 1607, 1513, 1240, 822 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.40 (s, 1H), 9.33 (s, 1H), 7.23 (t, 4H), 6.72 (m, 4H), 6.20 (br s, 1H), 5.98 (br s, 2H), 3.35 (br s, 2H), 3.08 (br s, 2H), 1.70–2.80 (m, 10H), 1.22 (m, 1H); MS (CI) (rel int) *m/z* 188 (95), 362 (100). The solid was dissolved in hot EtOH (150 mL) and oxalic acid dihydrate (0.52 g, 4.14 mmol) in EtOH (10 mL) added. The monooxalate salt precipitated on cooling as an off-white powder (1.35 g, 75%): ^1H NMR (5% KOD in D_2O) δ 7.33 (t, 4H), 6.64 (dd, 4H), 6.11 (br s, 1H), 6.03 (br s, 1H), 3.19 (br s, 2H), 2.80 (br s, 2H), 2.57 (m, 3H), 2.53 (m, 2H), 2.29 (m, 2H), 2.05–2.20 (m, 2H), 1.90 (m, 1H), 1.30 (m, 1H); MS (CI) (rel int) *m/z* 188 (95), 362 (100); HPLC (reversed-phase, 70% pH 3.0 buffer:30% MeCN) 6.78 min (100%); $[\alpha]^{20}_D$ +52.5° (*c* = 1.04, DMSO). Anal. ($C_{24}H_{27}NO \cdot C_2H_2O_4$) C, H, N, water.

Pharmacological Methods. Radioligand Binding. The membrane homogenates of CHO-K1 cells expressing human DA D2L, D3, or D4.2 receptors were prepared as previously described.[10,16] Homogenate (400 μL) was incubated in triplicate with 50 μL of [^3H]N-0437 (1 nM for D2L) or [^3H]spiperone (0.6 nM for D2L, 0.2 nM for D3 and D4.2), 50 μL buffer [25 nM Tris HCl, pH 7.4 at 37 °C, EDTA (1 mM) and $MgCl_2$ (6 mM) were added to the buffer for D2L and D3; NaCl (120 nM), $CaCl_2$ (1.5 mM) and KCl (5 mM) were added for D4.2], or competing drugs where appropriate, in a final volume of 0.5 mL at 25 °C for 60 min. Specific binding was defined as binding inhibited by 1 μM haloperidol. Incubations were terminated by rapid filtration through Whatmann GF/B glass fiber filters (soaked for 1 h in 0.5% polyethylenimine) on a Brandel MB-48R cell harvester, with four washes of 5 mL of ice-cold buffer. Individual filter disks containing the bound ligand were placed in counting vials with 5 mL of scintillation fluid (Ready Gel, Beckman Instrument Inc., Fullerton, CA) and counted in a Beckman LS-6800 liquid scintillation counter at an efficiency of 45%.

Measurement of Intrinsic Activity. DA D2 and D3 receptor activation is reported by the effect of compounds on the uptake of [^3H]thymidine into CHO-10001 cells transfected

with the human DA D2L and D3 receptor. The assay was performed as described.[17] The intrinsic activities of test compounds were determined by comparing their maximal response to that obtained with the full DA D2 agonist, quinpirole.

Inhibition of GBL-Stimulated DA Synthesis.[18] Compounds were administered to male Long–Evans rats (Blue Spruce Farms, Altamont, NY) 1 h before sacrifice, and GBL (750 mg/kg ip) and NSD 1015 (100 mg/kg ip) were administered 30 min before sacrifice. Brain striatal levels of dihydroxy-L-phenylalanine (DOPA) were analyzed by HPLC with electrochemical detection.[24] DOPA control concentrations were 1.25 ± 0.07 and 4.11 ± 0.11 μg/g $\pm$ SEM for control and GBL-treated animals, respectively ($n = 10$).

Effects on the Firing Rate of Substantia Nigra DA Neurons.[19] The action potential of zona compacta DA cells was recorded in chloral-anesthetized rats by using standard extracellular recording techniques. DA cells were identified by waveform and firing pattern, and recording sites were verified histologically. Drugs were administered intraperitoneally via an indwelling catheter. Baseline firing rate was calculated by averaging the rate over 2 min prior to drug injection. Drug effects were determined by averaging the response during the 1 min period of maximal inhibition. Drug-induced inhibition of firing was reversed with the DA antagonist haloperidol to confirm a DA agonist mechanism.

Inhibition of spontaneous locomotor activity[20] was carried out according to methods described previously. Mice were treated with compounds administered ip followed immediately by a 1 h test. Rats were treated orally with compounds 1 h prior to a 30 min test. Locomotor activity was measured in darkened cylindrical photobeam chambers. Data were expressed as percentage inhibition of activity relative to vehicle-treated animals and an ED_{50} calculated from various doses.

Conditioned avoidance in squirrel monkeys was carried out according to methods described previously.[21,22] Inhibition of conditioned avoidance was measured for 6 h after oral administration of compound. Drug effects were expressed as percentage inhibition of avoidance responding relative to control performance during the 4 h of peak effect.

Identification of Compounds 2–4 as Metabolites. Cynomolgus monkeys were dosed orally with 75 mg/kg of 1 as a suspension in 0.5% methylcellulose. A 500 mg C18 Varian Sep Pak cartridge was prepared by successive washes with MeCN (2 mL), water (2 mL), and 0.05 M Na_2HPO_4 pH 7.4 buffer (2 mL). Plasma (ca. 0.5 mL) drawn 3 h postdose was applied to the cartridge followed by washes with water (2 mL) and MeCN (2 mL) and finally elution with 2% trifluoroacetic acid in MeCN (2 mL). The eluant was dried under N_2 and reconstituted in 40:60:0.1 water:MeCN:AcOH (100 μL). This mixture was injected onto a Beckman ODS 150 × 2.1 mm 5 μm HPLC column and eluted with 40:60:0.1 water:MeCN:AcOH at 200 μL/min. Compounds were detected by UV adsorption at 245 nm. A reference chromatogram of the synthesized standards was obtained by injecting a mixture of compounds 1–4 under identical conditions.

The peaks corresponding to the proposed metabolites were analyzed by LC–MS on an Autospec Ultima-Q hybrid mass spectrometer (VG Analytical Ltd., Manchester, UK) of EBEqQ geometry. Ionization was by pneumatically assisted electrospray. The HPLC conditions were identical with those described above. Samples (10 μL) were injected manually using a Rheodyne loop injector. Column effluent was monitored by UV adsorption at 245 and 252 nm using an HP 1050 diode-array detector. Scan data were acquired under the control of the VG OPUS data system.

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Supporting Information Available: Mass spectra of metabolites M1, M2, and M3 along with 1 (4 pages). Ordering information is given on any current masthead page.

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