Synthesis and Dopaminergic Activity of Pyridine Analogs of 5-Hydroxy-2-(di-*n*-propylamino)tetralin

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The pyridine analogs of 5-hydroxy-2-(di-*n*-propylamino)tetralin (5-OH-DPAT), **4**–**6**, were synthesized, and their biological activity was compared to that of 5-OH-DPAT. Compounds **4** and **6** exhibited activity similar to 5-OH-DPAT in dopamine (DA) D_2 and D_3 receptor binding and in autoreceptor activation as measured by their ability to reverse the γ-butyrolactone-induced increase in rat DA synthesis. Behaviorally, **4** and **6** decreased locomotor activity (LMA) in rats (sc) at low doses but did not increase LMA to the same extent as 5-OH-DPAT at higher doses, indicating that **4** and **6** may be more selective for the DA autoreceptor. While **4** was less active orally in rats, **6** appeared to retain most of its behavioral potency. Analog **5** showed little activity *in vivo* or *in vitro*.

Introduction

The central nervous system (CNS) activity of 2-aminotetralins has generated considerable interest in recent years. Mono- and dihydroxyaminotetralins exhibit a range of dopaminergic, serotonergic, and adrenergic effects, with the position of the hydroxyl groups important in determining the receptor preference (Figure 1). For example, 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) was found to be a very potent and selective serotonin $(5\text{-HT})_{1A}$ receptor agonist but lacking dopaminergic activity.[1] Dopamine (DA) agonist, but not serotonergic, effects appear to predominate in the 5,6-dihydroxy and 5-, 6-, and 7-monohydroxy analogs.[2] McDermed *et al.*[3] demonstrated that 5,6-di-OH-DPAT was 50 times more potent than apomorphine in producing emesis in dogs and stereotyped behavior in rats, effects consistent with a DA agonist. The 5-OH isomer was found to be only slightly less potent than the 5,6-dihydroxy analogs.[2]

Aromatic hydroxyl groups provide optimal sites for metabolism, usually via conjugation with glucuronic acid and subsequent elimination by the kidneys. This results in low oral bioavailability, a short duration of action, and, consequently, limited clinical utility for catechol- and phenol-containing compounds.[4] There has been considerable interest in the development of phenolic bioisosteres, especially heterocyclic replacements.[5] Compounds **1** and **2** (Figure 2) are two examples of heterocyclic bioisosteres of OH-DPATs; both were shown to possess DA agonist activity.[6] Cliffe *et al.*[7] prepared 5,6,7,8-tetrahydro-7-(dipropylamino)quinoline (**3**), a 5-HT_{1A} receptor ligand related to 8-OH-DPAT.

This led us to inquire whether replacing the phenolic portion of 5-OH-DPAT with pyridine and substituted pyridines would lead to compounds with similar dopaminergic properties. As a result, compounds **4**–**6** (Figure 3) were prepared and evaluated in DA receptor binding, as well as in biochemical and behavioral tests in rodents.

Chemistry

The tetrahydroquinoline **4** was synthesized as shown in Scheme 1. Reductive amination of 5,6,7,8-tetrahydro-6-oxoquinoline (**7**)[8] with propylamine and sodium triacetoxyborohydride afforded the monopropylamine **8**. Treatment of the monopropylamine with propionyl chloride under typical acylation conditions followed by reduction of the resulting propionamide with AlH_3 gave the dipropylamine **4** in good yield.

The synthesis of pyridone **10** (Scheme 2) relied on a modification of chemistry originally described by Kozikowski[9] for the preparation of hyperzine A. The pyrrolidine enamine of commercially available 1,4-cyclohexanedione monoethylene ketal was heated with methyl propiolate and methanolic ammonia in a Parr

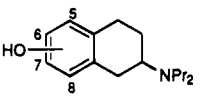


Figure 1. OH-DPATs.

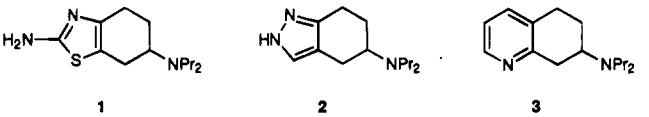


Figure 2. Heteroaromatic isosteres of OH-DPATs.

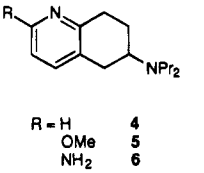
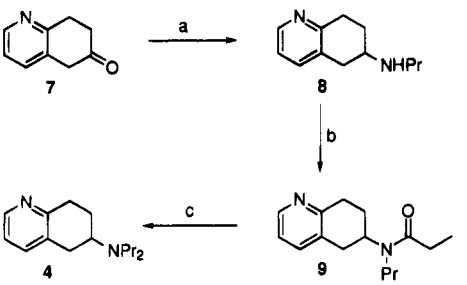


Figure 3. Pyridine analogs of 5-OH-DPAT.

Scheme 1. Synthesis of **4**[a]



[a] (a) $PrNH_2$, $NaBH(OAc)_3$, AcOH, $Cl(CH_2)_2Cl$; (b) $ClCOC_2H_5$, Et_3N, CH_2Cl_2; (c) $LiAlH_4$, $AlCl_3$, THF, Et_2O.

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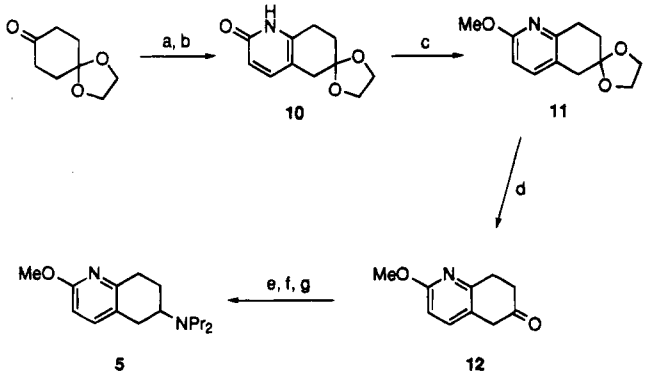
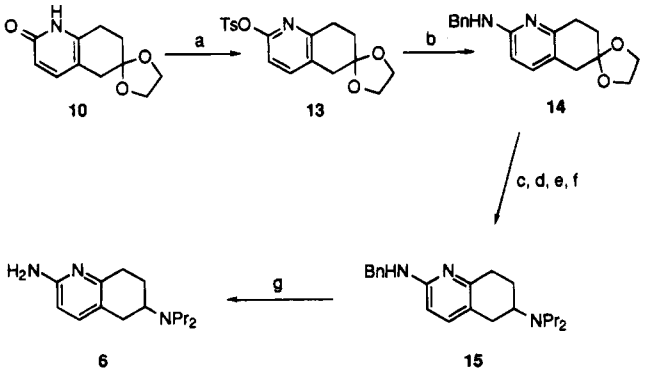
Scheme 2. Synthesis of **5**[a]



[a] (a) Pyrrolidine, C_6H_6, pTsOH; (b) methyl propiolate, NH_3, MeOH; (c) MeI, $CHCl_3$, Ag_2CO_3; (d) 5% HCl, acetone; (e) $PrNH_2$, $NaBH(OAc)_3$, AcOH, $Cl(CH_2)_2Cl$; (f) $ClCOC_2H_5$, Et_3N, CH_2Cl_2; (g) $LiAlH_4$, $AlCl_3$, THF, Et_2O.

Scheme 3. Synthesis of **6**[a]



[a] (a) TsCl, Et_3N, CH_2Cl_2, DMAP; (b) $PhCH_2NH_2$, Tol; (c) 5% HCl, acetone; (d) $PrNH_2$, $NaBH(OAc)_3$, AcOH, $Cl(CH_2)_2Cl$; (e) $ClCOC_2H_5$, Et_3N, CH_2Cl_2; (f) $LiAlH_4$, $AlCl_3$, THF, Et_2O; (g) H_2, 20% Pd/C, AcOH.

reactor at 100 °C for 5 h. The methoxypyridine **11** was obtained by methylation of the pyridone **10** with methyl iodide and silver carbonate in chloroform. Since tetrahydro-6-oxoquinolines tend to be unstable, hydrolysis of the ketal of **11** in 5% HCl in acetone was immediately followed by the same reductive amination procedure as previously described. Subsequent acylation and reduction, as shown in Scheme 1, gave the dipropylamine **5**.

Aminopyridine **6** (Scheme 3) was also obtained from the pyridone **10**. Tosylation of the pyridone followed by displacement with benzylamine gave the benzylated aminopyridine **14**. The ketal was converted to the dipropylamine as described in Schemes 1 and 2. The aminopyridine **6** was obtained by standard debenzylation conditions.

Pharmacology

All compounds were tested for their *in vitro* binding affinity for the human DA D_2 and D_3 receptors, each expressed in CHO-K1 cells[10] using the antagonist ligand [^{3}H]spiperone and the agonist ligand [^{3}H]N-0437.[11] DA autoreceptor agonist efficacy was determined by a compound's ability to reverse the γ-butyrolactone (GBL)-induced increase in DA synthesis in the corpus striatum of rats, as measured by the rate of L-dihydroxyphenylalanine (DOPA) formation following decarboxylase inhibition.[12] These compounds were also assessed behaviorally by examining their effect on exploratory locomotor activity (LMA)[13] first in mice dosed ip and, if they were sufficiently potent, in rats dosed sc (Figure 4). Compounds that produced behavioral effects in the rat sc were further tested to see if they retained their activity by an oral route of administration (Figure 5).

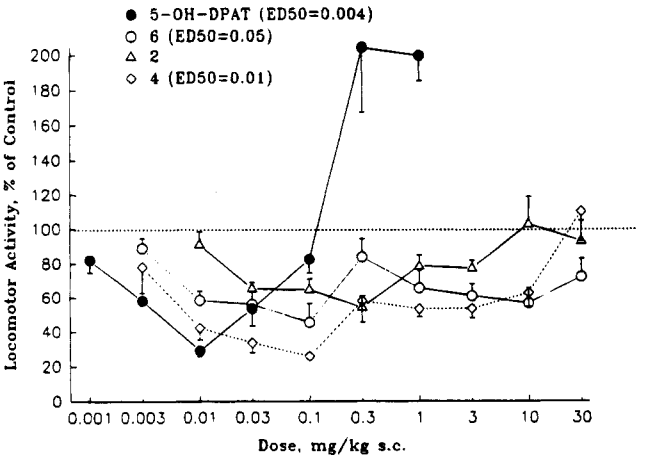


Figure 4. Effect of 5-OH-DPAT and analogs on spontaneous locomotor activity in rats dosed sc (n = 5–10).

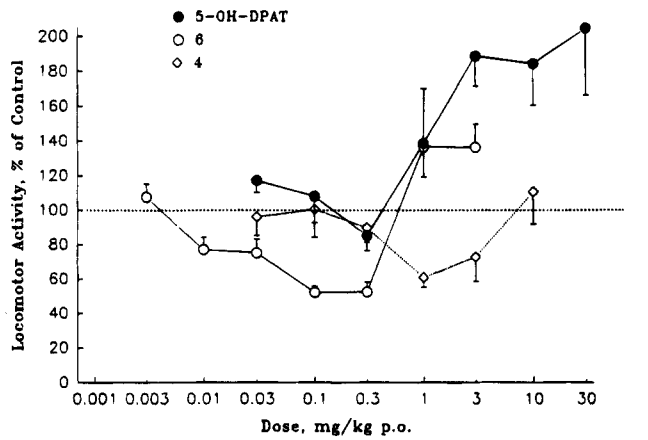


Figure 5. Effect of 5-OH-DPAT and analogs on spontaneous locomotor activity in rats dosed po (n = 5–10).

Results and Discussion

As can be seen from Table 1, 5-OH-DPAT possessed high binding affinity for the DA D_2 and D_3 receptors with approximately 10-fold selectivity for the D_3 receptor. In addition, 5-OH-DPAT decreased DOPA synthesis by 70% at 10 mg/kg, consistent with moderate activation of the DA autoreceptor. Spontaneous LMA was inhibited in mice with an ED_{50} value of 0.01 mg/kg ip and 0.004 mg/kg sc in rats. Up to a dose of 0.01 mg/kg sc, rats showed a diminution of locomotor activity; this was followed by a pronounced increase in LMA at higher doses (Figure 4). This observation, characteristic of a nonselective DA agonist that activates both pre- and postsynaptic receptors, is consistent with earlier reported results.[14] As expected of a phenolic compound, rats dosed orally with 5-OH-DPAT showed no significant effect up to 1 mg/kg, at which point LMA stimulation was observed (Figure 5).

Compound **1** displaced the agonist ligand [^{3}H]N-0437 from D_2 receptors with higher affinity than the antagonist ligand [^{3}H]spiperone. This aminothiazole, however, had even higher affinity for the DA D_3 receptor. While **1** decreased DOPA synthesis by 88% at 10 mg/kg, indicative of DA autoreceptor agonist activity, only

Table 1. Biological Data

compd	binding K_i (nM) [^{3}H]spip DA D_2[a]	[^{3}H]N-0437 DA D_2[b]	[^{3}H]spip DA D_3[a]	% decrease of striatal DOPA synthesis,[c] ip (10 mg/kg)	inhibn LMA ED_{50} (mg/kg) mouse,[d] ip	rat,[e] sc
5-OH-DPAT	26 ± 2.79	6	0.66 ± 0.20	70 ± 7.0	0.01	0.004
1	462 ± 92	57	1.90 ± 0.23	88 ± 1.3	>30	NT[f]
2	>3333	523	36 ± 3	91 ± 4.1	0.64	*g*
4	272 ± 72	466	4.97 ± 0.93	86 ± 0.7	0.08	0.01
5	>3333	1202	158 ± 19	62 ± 10.3	>30	NT
6	17.1 ± 5.50	5	0.87 ± 0.05	86 ± 2.7	0.25	0.05

[a] [^{3}H]Spiperone, antagonist ligand; human DA D_2 and D_3 receptors expressed in CHO-K1 cells, $n = 3-4$. [b] [^{3}H]N-0437, agonist ligand. [c] Percent reversal of the increase on DOPA levels in the striatum of GBL-treated rats, $n = 4$. [d] LMA = locomotor activity, ED_{50} values generated from 3–8 doses, $n = 9$ mice/dose. [e] 7–9 doses, $n = 5-10$ rats/dose. [f] NT = not tested. [g] 45% maximum inhibition of LMA, see Figure 4.

slight inhibition of LMA was observed in mice up to 30 mg/kg, with higher doses (100 mg/kg) being lethal. The pyrazole analog **2** had little affinity for the DA D_2 receptor and modest affinity for the DA D_3 receptor. Interestingly, *in vivo*, this compound decreased DOPA formation and inhibited LMA with an ED_{50} value of 0.64 mg/kg ip in mice. The maximum inhibition of LMA in rats was only 45% at 0.3 mg/kg sc (Figure 4). This difference in activity between *in vitro* and *in vivo* tests may be the result of an active metabolite.[15,16]

While the pyridine analog **4** had only modest affinity for the DA D_2 receptor, it bound to the DA D_3 receptor with a K_i of 5 nM. *In vivo*, **4** decreased DOPA formation by 88% at 10 mg/kg and inhibited LMA with an ED_{50} value of 0.08 mg/kg ip in mice and 0.01 mg/kg sc in rats, with a maximum inhibition of 74% occuring at 0.1 mg/kg sc. When tested orally in rats, the maximum effect on LMA was only 40% at 1 mg/kg.

Even though the 2-methoxypyridine analog **5** showed a moderate decrease in GBL, it was inactive in all other *in vitro* and *in vivo* tests. This inactivity is not surprising since 6-OMe-DPAT itself has very little affinity for the DA D_2 or D_3 receptor (D_2, [^{3}H]spiperone = >10 000 nM; D_2, [^{3}H]N-0437 = 3940 nM; D_3, [^{3}H]spiperone = 366 nM).

The 2-aminopyridine analog **6** was equipotent to 5-OH-DPAT in binding to the DA D_2 and D_3 receptors. *In vivo*, **6** decreased DOPA synthesis by 86% at 10 mg/kg and inhibited LMA in mice with an ED_{50} value of 0.25 mg/kg ip and 0.05 mg/kg sc in rats. When tested orally in rats, this compound retained most of its activity. At lower doses the sc and po LMA curves are very similar (Figures 4 and 5), while at higher po doses the rats exhibited more LMA stimulation than those dosed sc.

In conclusion, *in vivo* test results indicate that the pyridine analogs **4** and **6** are dopamine agonists that are nearly as potent as 5-OH-DPAT, although they do not appear to stimulate postsynaptic DA D_2 receptors to the same extent as 5-OH-DPAT. This suggests that, in contrast to 5-OH-DPAT, **4** and **6** are relatively selective DA autoreceptor agonists. While **4** was less active orally in rats, **6** retained most of its behavioral efficacy. Even though we have shown compound **6** to be active orally in behavioral tests in rodents, we can not conclude, without studying blood plasma levels, whether this is due to increased oral bioavailability or the result of active metabolites.

It has been noted with 5-OH-DPAT and other aminotetralins that their pharmacological actions are enantioselective. The *S*-enantiomer of 5-OH-DPAT is a potent DA D_2 receptor agonist, while the *R*-enantiomer is a weak antagonist.[17] In the future we would like to study the individual enantiomers of **4** and **6** to see if they exhibit a similar differentiation of pharmacological activity.

Experimental Section

Melting points were determined on a Gallenkamp capillary melting point apparatus and are uncorrected. ^{1}H NMR were determined for $CDCl_3$ or DMSO-d_6 solutions on Varian Gemini-200, XL-300, or 400 and Bruker AM 250 spectrometers. The peaks are described in ppm downfield from TMS (internal standard). IR spectra were recorded on a Nicolet MX-1 FT spectrophotometer. Mass spectra were obtained on a Finnigan 4500 or a VG analytical 7070E/HF mass spectrometer. Relative intensity values are listed in parentheses. 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, 60 Å).

Propyl(5,6,7,8-tetrahydroquinolin-6-yl)amine (8). To **7** (2.0 g, 13.6 mmol) dissolved in dichloroethane (45 mL) were added propylamine (1.2 mL, 14.9 mmol), sodium triacetoxyborohydride (3.7 g, 17.6 mmol), and acetic acid (0.78 mL, 13.6 mmol). The reaction mixture was stirred at 25 °C under N_2 for 5 h followed by careful neutralization with 5% aqueous $NaHCO_3$. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 30 mL). The organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo to give a brown oil. This oil was purified by MPLC on silica gel with 2% MeOH/CH_2Cl_2 to give **8** (2.14 g, 83%) as a light brown oil: IR ($CHCl_3$ solution) 2934, 1582, 1432, 661 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 3H, J = 7.3 Hz), 1.43–1.76 (m, 3H), 2.03–2.19 (m, 2H), 2.57–2.67 (m, 3H), 2.88–3.00 (m, 4H), 6.95–7.01 (m, 1H), 7.31 (d, 1H, J = 7.4 Hz), 8.30 (d, 1H, J = 3.7 Hz); MS (CI) *m/e* 192 (MH^+, 74), 191 (100), 190 (58), 171 (32), 170 (87), 169 (97); TLC (100% EtOAc) R_f = 0.65.

***N*-Propyl-*N*-(5,6,7,8-tetrahydroquinolin-6-yl)propionamide (9).** To a solution of **8** (1.8 g, 9.5 mmol) in CH_2Cl_2 (50 mL) and triethylamine (5.3 mL, 38.0 mmol) was added propionyl chloride (1.24 mL, 14.25 mmol) dropwise at 0 °C. The mixture was stirred for 1 h while warming to 25 °C, washed with saturated aqueous $NaHCO_3$ (30 mL), and extracted with CH_2Cl_2 (2 × 20 mL). The organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo to give a brown oil. This oil was purified by MPLC on silica gel eluting with 2% MeOH/CH_2Cl_2 to give **9** (2.3 g, 98%) as a yellow oil: IR ($CHCl_3$ solution) 2971, 1626, 1449, 1424 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 3H, J = 7.5 Hz), 1.18 (t, 3H, J = 7.4 Hz), 1.60–1.70 (m, 2H), 1.97–2.17 (m, 2H), 2.38 (q, 2H, J = 7.4 Hz), 2.78–2.90 (m, 1H), 2.98–3.27 (m, 5H), 4.03–4.67 (m, 0.34H, methine of one amide rotamer), 4.54–4.67 (m, 0.64H, methine of other amide rotamer), 7.03–7.12 (m, 1H), 7.35–7.42 (m, 1H), 8.36–8.38 (m, 1H); MS (CI) *m/e* 247 (MH^+, 100), 131 (24); TLC (50% EtOAc/hexane) R_f = 0.70.

Dipropyl(5,6,7,8-tetrahydroquinolin-6-yl)amine (4). To a suspension of lithium aluminum hydride (0.38 g, 10.1 mmol) in anhydrous THF (20 mL) at 0 °C was added a solution of aluminum chloride (0.44 g, 3.3 mmol) in anhydrous Et_2O (20

mL), and the mixture was stirred for 30 min. A solution of **9** (2.5 g, 10.1 mmol) in anhydrous THF (20 mL) was added dropwise at 0 °C, and the mixture was stirred for 3 h. The reaction was quenched by addition of water (10 mL) and 2 N NaOH (5 mL) and the mixture filtered through Celite and concentrated in vacuo to give a yellow oil. This oil was purified by MPLC on silica gel eluting with 3% MeOH/CH_2Cl_2. To the resulting oil in anhydrous Et_2O (100 mL) was added anhydrous HCl (1 M in Et_2O, 20 mL) with vigorous stirring. The yellow precipitate was recrystallized from 2-butanone and EtOH to give the dihydrochloride salt of **4** (2.35 g, 77%) as a white solid: mp 154 °C; IR (KBr)3471, 2786, 1627, 1550, 1459, 804 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.94 (t, 6H, J = 7.3 Hz), 1.82 (q, 4H, J = 7.3 Hz), 1.98–2.15 (m, 1H), 2.5 (m, 1H), 3.05–3.59 (m, 8H), 3.82 (m, 1H), 7.82–7.88 (m, 1H), 8.35 (d, 1H, J = 8.8 Hz), 8.68 (d, 1H, J = 5.5 Hz); MS (CI) *m/e* 233 (MH^+, 100), 203 (35), 85 (83). Anal. ($C_{15}H_{24}N_2$·2.0HCl·1.0H_2O) C, H, N, Cl, H_2O.

1′,5′,7′,8′-Tetrahydrospiro[1,3-dioxolane-2,6′(2′*H*)-quinolin]-2′-one (10). 1,4-Cyclohexanedione monoethylene ketal (5.0 g, 32.0 mmol) and *p*-toluenesulfonic acid (0.18 g, 0.96 mmol) in benzene (100 mL) were refluxed for 6 h with a Dean–Stark water trap. The pyrrolidine enamine was concentrated in vacuo, combined with methyl propiolate (8.1 g, 96.0 mmol) in ammonia-saturated methanol (100 mL), and heated to 100 °C in a Parr reactor for 5 h. The ammonia was carefully and thoroughly vented since the reaction mixture tended to bump vigorously on removal from the Parr reactor. The mixture was concentrated in vacuo and the resulting solid purified by MPLC on silica gel eluting with 2% MeOH/CH_2Cl_2 to give **10** (4.55 g, 68%) as a yellow solid: mp 250 °C dec; IR (KBr) 2934, 1660, 1622 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.80 (t, 2H, J = 6.6 Hz), 2.57 (s, 2H), 2.60 (t, 2H, J = 6.7 Hz), 3.91 (s, 4H), 6.11 (d, 1H, J = 9.2 Hz), 7.11 (d, 1H, J = 9.3 Hz); MS (CI) *m/e* 208 (MH^+, 64), 85 (100). Anal. ($C_{11}H_{13}NO_3$·0.11H_2O) C, H, N, H_2O.

7′,8′-Dihydro-2-methoxyspiro[1,3-dioxolane-2,6′(5′*H*)-quinoline] (11). A mixture of the pyridone **10** (8.73 g, 42.1 mmol), methyl iodide (26.2 mL, 0.42 mol), and silver carbonate (23.2 g, 84.2 mmol) in $CHCl_3$ (400 mL) was stirred in the dark at 25 °C for 72 h. The reaction mixture was filtered through Celite and concentrated in vacuo and the resulting solid purified by MPLC on silica gel eluting with 20% EtOAc/hexane to give **11** (2.76 g, 31%) as a white solid: mp 77 °C; IR (KBr) 3493, 2971, 1600, 1582, 1480, 829 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.01 (t, 2H, J = 6.7 Hz), 2.89 (s, 2H), 3.00 (t, 2H, J = 6.9 Hz), 3.88 (s, 3H), 4.03 (s, 4H), 6.51 (d, 1H, J = 8.5 Hz), 7.21 (d, 1H, J = 8.3 Hz), 11.18 (br s, 1H); MS (CI) *m/e* 222 (MH^+, 100), 149 (55), 85 (67). Anal. ($C_{12}H_{15}NO_3$) C, H, N.

2-Methoxy-7,8-dihydro-5*H*-quinolin-6-one (12). A solution of the ketal **11** (1.0 g, 4.88 mmol) in acetone (15 mL) and 5% HCl (15 mL) was heated to reflux for 15 h, cooled, neutralized with saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2 (3 × 20 mL). The organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The unstable ketone **12** (0.80 g, 94%) was obtained as a colorless solid and used immediately in the next step: ^1H NMR ($CDCl_3$) δ 2.65 (t, 2H, J = 6.8 Hz), 3.15 (t, 2H, J = 6.8 Hz), 3.50 (s, 2H), 3.93 (s, 3H), 6.61 (d, 1H, J = 8.3 Hz), 7.30 (d, 1H, J = 8.3 Hz); TLC (20% EtOAc/hexane) R_f = 0.68.

(2-Methoxy-5,6,7,8-tetrahydroquinolin-6-yl)dipropylamine (5). The monopropylamine (0.8 g, 4.51 mmol) was prepared from **12** as described in the synthesis of **8** to give 0.75 g (75%) of a yellow oil: IR ($CHCl_3$ solution) 2920, 1603, 1585, 1480, 820 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94 (t, 3H, J = 7.3 Hz), 1.48–1.80 (m, 3H), 2.02–2.19 (m, 2H), 2.40–2.59 (m, 1H), 2.63–2.71 (m, 2H), 2.85–2.94 (m, 4H), 3.88 (s, 3H), 6.49 (d, 1H, J = 8.3 Hz), 7.25 (d, 1H, J = 8.3 Hz); MS (CI) *m/e* 221 (MH^+, 100), 162 (73); TLC (20% EtOAc/hexane) R_f = 0.45.

This monopropylamine (0.75 g, 3.41 mmol) was converted to the propionamide as described in the synthesis of **9** to give 0.92 g (97%) of a yellow oil: IR ($CHCl_3$ solution) 3002, 1625, 1478 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (t, 3H, J = 7.4 Hz), 1.18 (t, 3H, J = 7.3 Hz), 1.59–1.69 (m, 2H), 1.97–2.08 (m, 2H), 2.33–2.42 (m, 2H), 2.66–2.96 (m, 4H), 3.14–3.20 (m, 2H), 3.88 (s, 3H), 3.93–4.08 (m, 0.39H, methine of one amide rotamer), 4.59–4.70 (m, 0.61H, methine of other amide rotamer), 6.48–6.56 (m, 1H), 7.20–7.27 (m, 1H); MS (CI) *m/e* 277 (MH^+, 70), 161 (100); TLC (20% EtOAc/hexane) R_f = 0.17.

This propionamide (0.90 g, 3.25 mmol) was reduced to the dipropylamine as described in the synthesis of **4** to give 0.67 g (78%) of **5** as a yellow oil. This oil was converted to the dihydrochloride salt as described in **4** to give **5** as a white solid: mp 136 °C; IR (KBr) 3443, 2932, 2606, 2517, 1633, 1618 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.93 (t, 6H, J = 7.3 Hz), 1.79 (q, 4H, J = 7.6 Hz), 1.93–2.05 (m, 1H), 2.42 (m, 1H), 2.94–3.27 (m, 8H), 3.66 (m, 1H), 3.88 (s, 3H), 6.84 (d, 1H, J = 8.5 Hz), 7.67 (d, 1H, J = 8.6 Hz); MS (CI) *m/e* 263 (MH^+, 100), 233 (45), 162 (38), 85 (67). Anal. ($C_{16}H_{26}N_2O$·1.85HCl·1.2H_2O) C, H, N, Cl, H_2O.

7′,8′-Dihydrospiro[1,3-dioxolane-2,6′(5′*H*)-quinolin]-2′-yl 4-Methylbenzenesulfonate (13). A solution of **10** (0.25 g, 1.20 mmol) in CH_2Cl_2 (10 mL), triethylamine (0.25 mL, 1.80 mmol), *p*-toluenesulfonyl chloride (0.27 g, 1.45 mmol), and a catalytic amount of 4-(dimethylamino)pyridine was stirred at 25 °C for 18 h. The reaction mixture was washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting solid was purified by MPLC on silica gel eluting with 15% EtOAc/hexane to give **13** (0.37 g, 85%) as a white solid: mp 101–103 °C; IR (KBr) 3438, 2895, 1591, 1453, 1368 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.97 (t, 2H, J = 7.0 Hz), 2.44 (s, 3H), 2.92–2.97 (m, 4H), 3.94 (s, 4H), 6.84 (d, 1H, J = 8.3 Hz), 7.32 (d, 2H, J = 8.2 Hz), 7.39 (d, 1H, J = 8.2 Hz), 7.88 (d, 2H, J = 8.2 Hz); MS (CI) *m/e* 362 (MH^+, 100), 206 (95). Anal. ($C_{18}H_{19}NO_5S$) C, H, N.

7′,8′-Dihydro-*N*-(phenylmethyl)spiro[1,3-dioxolane-2,6′-(5′*H*)-quinolin]-2′-amine (14). A mixture of **13** (1.0 g, 2.76 mmol) and benzylamine (10 mL) was heated to 130 °C for 18 h and cooled and the excess benzylamine removed in vacuo. The resulting residue was purified by MPLC on silica gel eluting with 30% EtOAc/hexane to give **14** (0.27 g, 33%) as a yellow oil: IR ($CHCl_3$ solution) 3441, 2957, 1604, 1496 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.98 (t, 2H, J = 6.7 Hz), 2.83 (s, 2H), 2.94 (t, 2H, J = 6.7 Hz), 4.01 (s, 4H), 4.44 (d, 2H, J = 5.5Hz), 5.00 (br s, 1H), 6.17 (d, 1H, J = 8.2 Hz), 7.07 (d, 1H, J = 8.4 Hz), 7.21–7.35 (m, 5H); MS (CI) *m/e* 297 (MH^+, 100), 296 (92), 224 (47), 223 (38), 133 (37), 106 (37); TLC (30% EtOAc/hexane) R_f = 0.14.

***N*²-Benzyl-*N*⁶,*N*⁶-dipropyl-5,6,7,8-tetrahydroquinoline-2,6-diamine (15).** The ketal **14** (2.08 g, 7.04 mmol) was hydrolyzed as described in the synthesis of **12** to give 1.60 g (90%) of the unstable ketone as a brown oil: ^1H NMR ($CDCl_3$) δ 2.15 (s, 2H), 2.60 (t, 2H, J = 6.7 Hz), 3.07 (t, 2H, J = 6.7 Hz), 4.48 (d, 2H, J = 5.5 Hz), 5.09 (br s, 1H), 6.24 (d, 1H, J = 8.3 Hz), 7.13 (d, 1H, J = 8.3 Hz), 7.27–7.38 (m, 5H); TLC (50% EtOAc/hexane) R_f = 0.63.

This ketone (1.60 g, 6.33 mmol) was converted to the monopropylamine as described in the synthesis of **8** to give 1.39 g (78%) of a brown oil; IR ($CHCl_3$ solution) 3280, 2925, 1603, 805, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H, J = 7.33 Hz), 1.09–1.17 (m, 1H), 1.51–1.61 (m, 2H), 1.63–1.77 (m, 1H), 2.10–2.14 (m, 1H), 2.49–2.57 (m, 1H), 2.65–2.99 (m, 6H), 4.36 (d, 2H, J = 5.82 Hz), 4.77 (t, 1H, J = 5.83 Hz), 6.08 (d, 1H, J = 8.32 Hz), 7.02 (d, 1H, J = 8.49 Hz), 7.15–7.28 (m, 5H); MS (CI) *m/e* 296 (MH^+, 100), 295 (81), 237 (40); TLC (5% MeOH/CH_2Cl_2) R_f = 0.15.

The monopropylamine (1.97 g, 7.0 mmol) was converted to the propionamide as described in the synthesis of **9** to give 1.76 g (71%) of a brown oil: IR ($CHCl_3$ solution) 2972, 1624 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (t, 3H, J = 7.2 Hz), 1.17 (t, 3H, J = 7.5 Hz), 1.60–1.66 (m, 2H), 1.95–2.04 (m, 2H), 2.33–2.42 (m, 2H), 2.65–3.24 (m, 6H), 3.95–4.05 (m, 0.5H, methine of one amide rotamer), 4.46 (br s, 2H), 4.58–4.62 (m, 0.5H, methine of other amide rotamer), 6.19 (m, 1H), 7.11 (m, 1H), 7.22–7.36 (m, 5H); MS (CI) *m/e* 352 (MH^+, 46), 279 (100), 199 (77); TLC (50% EtOAc/hexane) R_f = 0.28.

The propionamide (1.7 g, 4.87 mmol) was reduced to the dipropylamine as described in the synthesis of **4** to give 1.52 g (92%) of **15** as a brown oil: IR ($CHCl_3$ solution) 3400, 2934, 1658, 1626, 746, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (t, 6H, J = 7.3 Hz), 1.45–1.72 (m, 6H), 2.43–2.95 (m, 5H), 2.60–2.95 (m, 5H), 4.44 (d, 2H, J = 5.8 Hz), 4.88–4.95 (m, 1H), 6.18 (d, 1H,

J = 8.3 Hz), 7.12 (d, 1H, J = 8.3 Hz), 7.24–7.34 (m, 5H); MS (CI) m/e 338 (MH^+, 81), 236 (100); TLC (5% MeOH/CH_2Cl_2) R_f = 0.08.

N^6,N^6-Dipropyl-5,6,7,8-tetrahydroquinoline-2,6-diamine (6). The benzyl-protected aminopyridine **15** (1.48 g, 3.60 mmol) was stirred with 20% Pd on carbon in AcOH (75 mL) at 25 °C and 50 psi of H_2 for 36 h. The solution was filtered through Celite and the acetic acid removed in vacuo. The residue was dissolved in CH_2Cl_2 (30 mL) and washed with 2 N NaOH (3 × 30 mL). The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting oil was purified by HPLC on silica gel eluting with 2% MeOH/CH_2Cl_2 to give **6** (0.31 g, 44%) as a light brown oil: IR ($CHCl_3$ solution) 2960, 1614, 1479 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (t, 6H, J = 7.3 Hz), 1.40–1.55 (m, 4H), 1.56–1.75 (m, 2H), 2.45 (t, 4H, J = 5.6 Hz), 2.60–3.00 (m, 5H), 4.25 (br s, 2H), 6.29 (d, 1H, J = 8.3 Hz), 7.12 (d, 1H, J = 8.2 Hz); MS (CI) m/e 248 (MH^+, 100), 247 (65), 218 (91), 147 (28). Anal. ($C_{15}H_{25}N_3$·0.20H_2O) C, H, N, H_2O.

Pharmacological Methods. Cell Cultures. CHO-K1 cells (donated by Dr. J. Granneman, Wayne State University, Detroit, MI) expressing either human D_3[10] or human D_2L[18] receptors were grown in F-12 medium (GIBCO Laboratories, Grand Island, NY) supplemented with 10% fetal bovine serum (Hyclone Laboratories, Logan, UT) in T-150 culture flasks in a humidified atmosphere of 5% CO_2 and 95% air.

Dopamine Receptor Binding Assays. The affinity of compounds for brain DA receptors was determined by standard receptor binding assays,[11] according to methods described previously.[19]

Inhibition of Spontaneous Locomotor Activity.[13] Mice were treated with compounds administered ip followed immediately by a 1 h test. Rats were treated orally or subcutaneously with compounds 1 h or immediately prior to a 30 min test, respectively. Locomotor activity was measured in darkened cylindrical photobeam chambers. Data are expressed as percent inhibition of LMA relative to vehicle-treated animals, and an ED_{50} was calculated from increasing doses by regression analysis.

Inhibition of GBL-Stimulated DA Synthesis.[12] 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 DOPA were analyzed by HPLC with electrochemical detection.[20] DOPA control concentrations were 1.03 ± 0.04 and 3.76 ± 0.28 μg/g ± SEM for control and GBL-treated animals, respectively (n = 10).

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