# *Brief Articles*

## Synthesis and Dopaminergic Properties of Benzo-Fused Analogues of Quinpirole and Quinelorane

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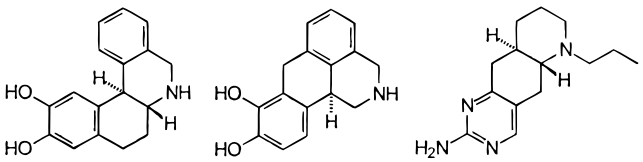
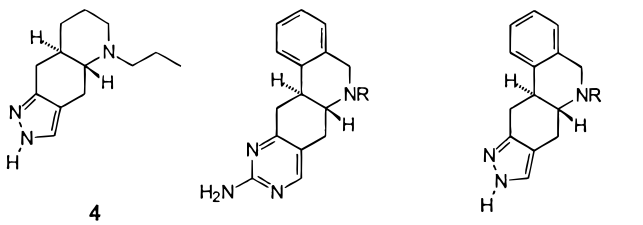
In an analogy to the potent catechol dopamine $D_1$ agonists dihydrexidine (**1**) and dinapsoline (**2**), benzo rings were fused onto the structures of the dopamine $D_2$-selective agonists quinelorane (**3**) and quinpirole (**4**). Each of the phenyl ring-substituted derivatives had significant affinity for $D_2$ receptors, albeit somewhat lower than the two parent compounds, **3** and **4**. Compounds with *N*-propyl and *N*-allyl substituents (**5b**, **5c**, **6c**, and **6d**) had higher affinity for the $D_2$ dopamine receptor than did their corresponding secondary amines (**5a** and **6a**). Slightly different effects on affinity of an *n*-propyl and an *n*-allyl group in the new analogues of **3** and **4** suggest that different binding orientations may be invoked at the receptor.

### Introduction

Dopamine-mediated neurotransmission plays a role in several psychiatric and neurological disorders and has been implicated in the action of many drugs of abuse. The development of novel ligands for brain dopamine receptors is therefore extremely important, so that appropriate pharmacological tools will be available to assist in the elucidation of the functional roles and importance of the various dopamine receptors. Classification of dopamine receptors into $D_1$ and $D_2$ subtypes was based originally on pharmacological and functional grounds, including their coupling to the enzyme adenylate cyclase.[1] Recent molecular cloning studies have led to the identification of five genes that code dopamine receptor proteins: two in the $D_1$-like family ($D_1$ and $D_5$ or $D_{1B}$) and three in the $D_2$-like family ($D_2$, $D_3$, and $D_4$).[2−4] In this paper, the use of the terms $D_1$ and $D_2$ generally will be to the respective families unless otherwise noted.

At present, no validated three-dimensional orientation of the amino acid residues at or near the ligand binding site has been elucidated. Thus, research still relies heavily on structure−activity relationship (SAR) information generated from molecules synthesized based on a lead compound. Our most important findings to date have arisen from our discovery of the high-affinity, full $D_1$ agonist activity of certain benzo[*a*]phenanthridines such as **1**[5] and naphthoisoquinoline **2**.[6] Although these molecules possess high potency at $D_1$ receptors, they nevertheless also possess significant activity at receptors of the $D_2$-type. We had reasoned initially that the pendant phenyl ring in **1** would lead to selectivity for the $D_1$ receptor. Indeed, we demonstrated that this structural feature is necessary for high affinity and agonist efficacy at the dopamine $D_1$ receptor.[5] Surprisingly, we discovered that the pendant phenyl ring does not exclude these ligands from $D_2$-like receptors. It does, however, appear to engender in these molecules functional selectivity toward specific subpopulations of dopamine $D_2$ receptors. For example both **1** and its *N*-*n*-propyl derivative proved to have selectivity for *postsynaptic* $D_2$ receptor function, with the latter having much higher affinity.[7] In addition, the 4-methyl-*N*-*n*-propyl derivative of **1** proved to be a high-affinity ($K_{0.5}$ = 2.1 nM) ligand for the dopamine $D_3$ receptor, having greater than 100-fold selectivity for the $D_3$ versus the $D_{2L}$ isoform.[8]

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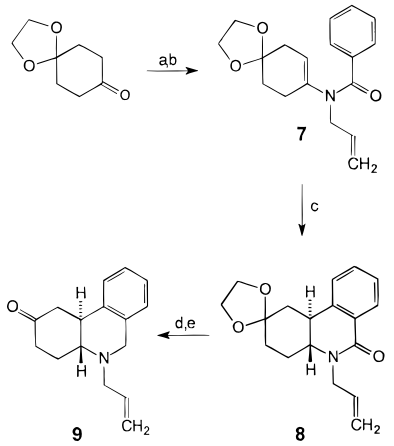
**Scheme 1**[a]




[a] Reagents and conditions: (a) allylamine/toluene, reflux; (b) benzoyl chloride/$CH_2Cl_2$, 0−25 °C, 80% (for a and b); (c) 0.025 M solution in MeOH, 24 °C, *hν*, 72%; (d) LAH/THF, reflux; (e) 1 N aq HCl/THF, 25−80 °C, 85% (for d and e).

Based on these findings, it was of interest to modify two known and highly potent ligands for $D_2$-like receptors, quinelorane (**3**) and quinpirole (**4**), by appending a phenyl ring, leading to compounds **5** and **6**. Both **3** and **4** have been previously characterized as dopamine $D_2$ ligands, with modest selectivity for the $D_3$ isoform.[9,10] It was anticipated that this strategy might lead to ligands targeted to specific subpopulations of $D_2$-like receptors that differed from those targeted by the parent molecules. This report describes the synthesis of molecules **5a**−**c** and **6a**−**d**, as well as preliminary pharmacological characterization using radioligand binding.

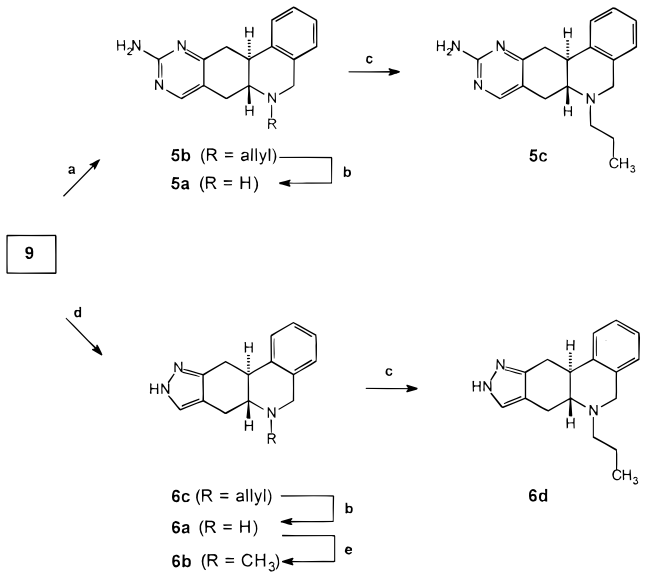
## Chemistry

For the synthesis of the two basic heterocyclic structures **5b** and **6c**, the *trans*-hexahydrophenanthridinone **9** was chosen as the common intermediate and was efficiently prepared in a three-step sequence (overall yield 49%; Scheme 1). Based on the pioneering work of Ninomiya,[11] the photocyclization of enamides proved to be a highly useful tool in alkaloid synthesis and has been extensively reviewed in the literature.[12−14] Accordingly, *trans*-4a,10b-hexahydrophenanthridines can be synthesized in good yield and with excellent diastereoselectivity from the respective benzamides.[15,16] Therefore the photochemical cyclization of **7** was chosen as the key step in the preparation of the desired intermediate **9**.

Although only a few different substituents at the amide nitrogen have been examined in the photocyclization reaction[11,17] and *N*-benzyl derivatives are usually employed, *N*-allylation in benzamide **7** seemed to be most suitable in our case. *N*-Allyl derivatives can be readily converted into both types of target compounds, the desired *N*-propyl congeners (catalytic hydrogenation) as well as into the corresponding secondary amines by deallylation procedures. In addition, in the event that the *N*-*n*-propyl compounds should prove to have pharmacological utility, the allyl moiety could be easily reduced catalytically with tritium to provide a radioligand for receptor binding studies.

Condensation of commercially available cyclohexanedione monoethylene glycol ketal with allylamine and

**Scheme 2**[a]




[a] Reagents and conditions: (a) tris(dimethylamino)methane/toluene, reflux, then guanidine carbonate/EtOH, reflux, 94%; (b) $Pd(dba)_2$/DPPB/THF, thiosalicylic acid, room temperature, 96% for **5a** and 81% for **6a**; (c) Pd−C/EtOH, ambient pressure, 86% for **5c** and 68% for **6d**; (d) *t*-BuOK/THF, $HCO_2Et$, 0 °C to room temperature, then hydrazine, pH 9, 74%; (e) $H_2CO/NaBH_3CN$ in MeOH/$H_2O$, room temperature, 77%.

subsequent acylation of the resulting enamine with benzoyl chloride provided the required precursor **7**, which was then irradiated in a 25 mM solution in MeOH to afford **8** in 72% yield. The trans ring fusion was proved unambiguously by $^1H$ NMR, showing a coupling constant of 12 Hz for the H4a/H10b spin system. Reduction of the amide carbonyl group using LAH, followed by cleavage of the ketal, was carried out as a "one-pot reaction" analogously to a procedure reported in the literature.[18] Thus, the key intermediate **9** was obtained in 85% yield. The α-enamino ketone was formed from **9** (Scheme 2) with tris(dimethylamino)-methane as the reagent and then was treated with guanidine carbonate to give the desired **5b**. Catalytic hydrogenation then afforded **5c**.

In an analogous fashion, the regioselective formylation using *t*-BuOK/ethyl formate and subsequent condensation with hydrazine[19] afforded the respective *N*-allyl intermediate **6c** in 74% yield, which was then hydrogenated to provide the target compound **6d**. The regioselectivity of the heteroannelation reaction was confirmed when it was observed in the EIMS spectra of the *N*-allyl compounds **5b** and **6c** that the base peak at *m*/*z* 170 was derived from a thermally promoted *retro*-[4+2] reaction, cleaving the tetrahydropyridine ring with generation of the *N*-allyl isoquinolinium cation (after elimination of an H radical and rearomatization of the corresponding parent ion, *m*/*z* 171). This *retro*-Diels−Alder fragmentation was observed in the CIMS spectra of all the compounds **5a**−**c** and **6a**−**d**.

Two major methods have generally been employed for *N*-deallylation reactions, based on isomerization of the allyl to a 2-propenyl group that readily undergoes in situ hydrolysis to the secondary amine and propanal.[20,21] A more recent procedure[22] relying on transfer of the allyl cation to the mercapto group of thiosalicylic acid by means of Pd(0) catalysis proved to be most successful

**Table 1.** Dopamine Receptor Affinities of Compounds **5** and **6** and Their Analogues

| | $K_{0.5}$ (nM) | | | |
|---|---|---|---|---|
| compound no. | $D_1$ affinity rat striatum | $D_2$ affinity rat striatum | $D_2$ long C-6 glioma cells | $D_3$ affinity C-6 glioma cells |
| SCH23390 | 0.4 ± 0.02 | | | |
| spiperone | | 0.21 ± 0.03 | 0.16 ± 0.02 | 0.37 ± 0.22 |
| **1** (DHX) | 6.22 ± 1.07 | 58.1 ± 7.8 | 1490 ± 270 | 170 ± 23 |
| **2** (dinapsoline) | 5.93 ± 0.45 | 31.3 ± 4.4 | 174 ± 26 | nd |
| **3** (quinelorane) | >5 μM | 4.78 ± 0.2 | 710 ± 143 | 0.67 ± 0.30 |
| **4** (quinpirole) | >5 μM | 28.8 ± 9.2 | 2250 ± 620 | 4.5 ± 1.6 |
| **5a** | >5 μM | 467 ± 115 | nd | 324 ± 109 |
| **5b** | >5 μM | 102 ± 37 | >5 μM | 15.8 ± 4.3 |
| **5c** | >5 μM | 45 ± 8.4 | >5 μM | 20.2 ± 4.6 |
| **6a** | >5 μM | 641 ± 187 | >5 μM | 955 ± 297 |
| **6b** | >5 μM | 189 ± 115 | 3090 ± 150 | 187 ± 0.75 |
| **6c** | >5 μM | 100 ±32 | 1880 ± 850 | 73.7 ± 23.5 |
| **6d** | >5 μM | 209 ± 54 | 4300 ± 1410 | 162 ± 32 |

for providing the secondary amines **5a** and **6a** in yields of 96% and 81%, respectively. The *N*-methyl derivative **6b** was additionally prepared in 77% yield using formaldehyde/$NaCNBH_3$.

## Pharmacology

**Selectivity of Compounds for Striatal $D_1$ vs $D_2$ Dopamine Receptors.** Binding affinities were assessed via competition binding assays using rat striatal membranes and with [$^3$H]SCH23390 and [$^3$H]spiperone as $D_1$ and $D_2$ radioligands, respectively (see Table 1). None of the derivatives showed significant $D_1$ affinity ($K_{0.5}$ > 5 μM). In addition, each of the phenyl ring-substituted derivatives displayed some loss of $D_2$ receptor affinity when compared to the two parent compounds, quinelorane (**3**) and quinpirole (**4**). Significant affinity at $D_2$ receptors was observed, however. Compounds with *N*-propyl and *N*-allyl substituents (**5b**, **5c**, **6c**, and **6d**) had higher affinity for the $D_2$ dopamine receptor than did their corresponding secondary amines (**5a** and **6a)**, a fact consistent with the known SAR of dopamine $D_2$ agonists.

**Selectivity of Compounds for Molecular Isoforms of $D_2$-like Receptors.** To determine the utility of these compounds as ligands to probe the $D_2$-like receptor isoforms, their affinity for the $D_{2L}$ or $D_3$ dopamine receptor was determined in C-6 glioma cells transfected with these receptors. As shown in Table 1, **5a**−**6d** did not demonstrate high affinity for the $D_{2L}$ receptor but exhibited some selectivity for the $D_3$ vs $D_2$ receptor. Those quinelorane derivatives with *N*-propyl and −allyl substituents (**5b** and **5c**) had good affinity and a high degree of selectivity for the $D_3$ vs $D_2$ receptor, much like quinpirole (**4**) and quinelorane (**3**) themselves.

The appended phenyl ring clearly lacks the effect that is seen in catechol-containing agonists such as **1** and **2**. $D_1$ receptor potency is not enhanced, and affinity for $D_2$-like receptors is attenuated significantly. Comparing quinelorane (**3**) with its benzo-fused analogue **5c**, the latter has some 30-fold lower affinity at the $D_3$ isoform. This divergence in SAR found with catechol versus non-catechol dopamine agonists suggests that different binding orientations may be invoked at the receptor. Interestingly, for the quinpirole series, the *N*-allyl **6c** had an approximately 2-fold higher affinity than did *N*-propyl **6d**, while no similar effect occurred in the quinelorane analogues. This fact would seem to suggest that perhaps even quinpirole and quinelorane bind to the receptor in different orientations. These observations imply that future attempts to carry out molecular modeling and/or receptor docking studies should carefully consider alignment of the various molecules and that the correct alignments in apparently structurally similar molecules may not be intuitively obvious.

## Experimental Section

**Chemical Procedures.** Melting points were determined on a Thomas-Hoover Meltemp apparatus and are uncorrected. Unless otherwise noted, $^1$H NMR spectra (300 MHz) were recorded on a Bruker ARX 300 instrument and the solvent ($CHCl_3$) was used as internal standard; 500-MHz spectra were performed on a Varian VXR 500 S spectrometer. Chemical shifts are reported in δ (ppm) using the common abbreviations. Elemental analysis was carried out at Purdue Microanalysis Laboratory using a Perkin-Elmer 2400 apparatus, and all of the results were within ±0.40% from the calculated values. Mass spectra were recorded on a Finnigan 4000 quadrupole mass spectrometer using isobutane as the reactant gas for chemical ionization (CI) and a −70 eV potential for the electron impact spectra (EI); all ion peaks are listed as *m*/*z* (relative intensity) values. THF was freshly distilled from Na/benzophenone ketyl. All other chemicals were used as purchased. $Pd(dba)_2$ (dba = dibenzylideneacetone) was obtained from Aldrich and DPPB (1,4-bis(diphenylphosphino)butane) from Acros Organics (Fischer Scientific). Salts were prepared either from the analytically pure bases by use of the stoichiometric amount of diluted ethanolic HCl or HBr, respectively, or from the purified bases (column chromatography) followed by recrystallization.

***N*-Allyl-*N*-(1,4-dioxaspiro[5.4]deca-7-en-8-yl)benzamide (7).** A solution of cyclohexanedione monoethylene glycol ketal (25.00 g, 160.1 mmol), and allylamine (14.5 mL, 196.2 mmol) in toluene was held at reflux for 4 h, while water was removed continuously by means of a Dean−Stark trap. Another 10 mL of allylamine was added, and reflux was continued for 2 h. The mixture then was concentrated under reduced pressure, the residue taken up into 160 mL of $CH_2Cl_2$, and $Et_3N$ (24.4 mL, 176.1 mmol) added. The solution was cooled in an ice bath, and benzoyl chloride (18.6 mL, 160.1 mmol) in $CH_2Cl_2$ (120 mL) was added dropwise with cooling. The mixture was stirred overnight at room temperature. After extraction with $H_2O$ and aqueous $NaHCO_3$ (5%), the organic layer was dried ($Na_2SO_4$) and evaporated to leave a yellow solid. Recrystallization from hexane provided **7** (38.11 g, 80%) as thick yellow crystals: mp 71 °C; CIMS *m*/*z* 300 ($[M + H]^+$, 21), 105 ($[C_6H_6CO]^+$, 100); $^1$H NMR δ 1.65−1.69 (m, 2H), 2.13 (br s, 2H), 2.25−2.27 (br m, 2H), 3.91 (s, 4H), 4.22−4.24 (d, *J* = 6.0 Hz, 2H), 5.17−5.28 (m, 3H), 5.86−5.99 (m, 1H), 7.32−7.36 (m, 3H), 7.50−7.53 (m, 2H). Anal. ($C_{18}H_{21}NO_3$) C, H, N.

***trans*-4a,10b-5-Allyl-1,2,3,4,4a,5,6,10b-octahydro-6-phenanthridone-2-spiro-2′-dioxolane (8).** A 0.025 M solution of **7** (4.64 g, 15.5 mmol) in absolute MeOH (620 mL) was

placed into an Ace glass 500-mL photochemical reactor and irradiated with a 450-W Hanovia medium pressure, quartz, mercury-vapor lamp seated in a cold tap water-cooled, quartz immersion well. Throughout the reaction time, the lamp and the solution were flushed continuously with argon and stirring was maintained using a Teflon-coated magnetic stirring bar. The reaction temperature was not allowed to exceed 24 °C while the progress of the reaction was monitored by $^1$H NMR. After 5 h the irradiation was stopped, the slightly yellow solution was evaporated, and the residue was chromatographed on silica gel, using $CH_2Cl_2-Et_2O$ (100:6) as the eluent to give **8** (3.35 g, 72%) as a colorless highly viscous oil that crystallized upon standing in the cold: mp 76−77 °C; CIMS *m*/*z* 300 ([M + H]$^+$, 100), 284 (29), 101 (21); $^1$H NMR (500 MHz) $\delta$ 1.56−1.71 (m, 2H), 1.82−1.92 (m, 2H), 2.20−2.25 (m, 1H), 2.43−2.48 (m, 1H), 3.13 (ddd, $J$ = 12.3, 12.3, 3.9 Hz, 1H), 3.39 (ddd, $J$ = 11.8, 12.0, 3.8 Hz, 1H), 3.90−4.05 (m, 5H), 4.73−4.78 (m, 1H), 5.10−5.14 (m, 2H), 5.79−5.86 (m, 1H), 7.20 (br d, $J$ = 7.7 Hz, 1H), 7,32−7.35 (br *t*-like m, 1H), 7.45 (ddd, $J$ = 7.6, 3.0, 1.5 Hz, 1H), 8.10 (dd, $J$ = 7.7, 1.4 Hz, 1H); $^{13}$C NMR (500 MHz) $\delta$ 27.34, 33.06, 36.18, 38.99, 43.85, 57.59, 64.57, 64.64, 107.74, 116.02, 122.67, 126.99, 128.73, 128.88, 131.93, 133.88, 140.39, 165.23. Anal. ($C_{18}H_{21}NO_3$) C, H, N.

***trans*-4a,10b-5-Allyl-3,4,4a,5,6,10b-hexahydro-1*H*-phenanthridin-2-one (9).** A two-necked flask (500 mL) equipped with a dropping funnel with drying tube and argon inlet was charged with a suspension of $LiAlH_4$ (3.40 g, 89.6 mmol) in THF (300 mL) and precooled to 0 °C. Over a 1-h period, a solution of **8** (5.70 g, 19.1 mmol) in THF (120 mL) was added dropwise with cooling and stirring. The dropping funnel was replaced by a condenser, and the mixture was heated at reflux for 2 h. After cooling, the flask was immersed in an ice bath, 3 N aqueous NaOH (25 mL) was added dropwise, and the resulting mixture was filtered. The filtered alumina salts were washed repeatedly with THF, the combined organic layers evaporated, and the resulting oil was dissolved in THF (100 mL). To this solution was slowly added 500 mL of 1 N aqueous HCl, and stirring was continued overnight at room temperature under argon and then at 80 °C for 1 h. The acidic solution was extracted with $CH_2Cl_2$, then basified (3 N aqueous NaOH), and extracted with $CHCl_3$. The $CHCl_3$ extract was dried ($Na_2SO_4$) and evaporated to provide 4.48 g of crude product that was chromatographed on silica gel, eluting with EtOAc−hexane−$Et_3N$ (150:100:1) affording **9** as a viscous oil (3.90 g, 85%). After standing in the cold, the pure product solidified and was recrystallized from hexane: mp 54−56 °C; CIMS *m*/*z* 242 ([M + H]$^+$, 100); $^1$H NMR $\delta$ 1.72−1.89 (m, 1H), 2.31−2.61 (m, 4H), 2.73−2.81 (m, 1H), 3.04−3.11 (m, 2H), 3.16−3.23 (m, 1H), 3.39−3.45 (m, 1H), 3.78 (d, $J$ = 15.7 Hz, 1H), 3.97 (d, $J$ = 15.7 Hz, 1H), 5.19−5.27 (m, 2H), 5.87−6.00 (m, 1H), 7.04−7.20 (m, 4H). Anal. ($C_{16}H_{19}NO$) C, H, N.

***trans*-6a,12b-7-Allyl-3-amino-1,6,6a,7,8,12b-hexahydropyrimidino[4,5-*b*]phenanthridine (5b).** To a solution of **9** (2.50 g, 10.4 mmol) in dry toluene (22 mL) was added tris(dimethylamino)methane (6.5 mL, 37.6 mmol), and the mixture was stirred under argon at 90 °C for 4 h. The solvents were removed, the residue was dissolved in EtOH (45 mL), guanidine carbonate (4.00 g, 22.2 mmol) was added, and the mixture was heated at reflux for 17 h. The solvents were evaporated, the residue was partitioned between $CHCl_3$ and $H_2O$, and the aqueous layer was repeatedly extracted ($CHCl_3$). Drying ($Na_2SO_4$) and evaporation of the organic layer left a residue that was chromatographed over silica gel, eluting with $CHCl_3$−MeOH (25:1) to yield **5b** (2.86 g, 94%) as a yellowish amorphous foam: mp (monohydrochloride salt; $H_2O$) 274−276 °C; CIMS *m*/*z* 293 ([M + H]$^+$, 100), 170 (14); EIMS *m*/*z* 292 ([M − H]$^+$, 24), 171 (45), 170 (100), 130 (11), 129 (28); $^1$H NMR $\delta$ 2.65−2.75 (m, 3H), 3.12−3.21 (m, 3H), 3.45 (dd, $J$ = 17.7, 5.0 Hz, 1H), 3.63−3.70 (m, 2H), 3.98 (d, $J$ = 15.4 Hz, 1H), 4.98 (br s, 2H), 5.23−5.32 (m, 2H), 5.92−6.05 (m, 1H), 7.07 (d, $J$ = 7.3 Hz, 1H), 7.15−7.32 (m, 3H), 8.12 (s, 1H). Anal. (monohydrochloride salt; $C_{18}H_{21}N_4Cl$) C, H, N, Cl.

***trans*-6a,12b-3-Amino-1,6,6a,7,8,12b-hexahydropyrimidino[4,5-*b*]phenanthridine (5a).** The catalyst was prepared by stirring a mixture of $Pd(dba)_2$ (9.9 mg) and DPPB (7.3 mg) in dry THF (0.5 mL) for 20 min under argon. To a solution of **5b** (100.0 mg, 0.34 mmol) stirred under argon in dry THF (6 mL) was added thiosalicylic acid (62.9 mg, 0.41 mmol). The solution of the preformed catalyst then was added dropwise. The mixture was stirred for 1 h at ambient temperature, then diluted with water, and concentrated to ca. one-third of its volume. Water was added; the solution was basified (1 N aqueous NaOH) and extracted ($CHCl_3$). The combined organic layers were washed with brine, dried ($Na_2SO_4$), and evaporated. The residue was purified on silica gel, eluting with $CHCl_3$−MeOH (8:2.5) to give **5a** (83.1 mg, 96%) as an off-white solid: mp 229 °C (sharp, decomposition; 2-propanol); mp (monohydrochloride salt) >260 °C; CIMS *m*/*z* 253 ([M + H]$^+$, 100), 131 (6), 130 (8); $^1$H NMR $\delta$ 2.54−2.72 (m, 2H), 2.91−2.95 (m, 3H), 3.46 (dd, $J$ = 18.6, 4.0 Hz, 1H), 4.09 (d, $J$ = 6.0 Hz, 1H), 4.23 (d, $J$ = 6.0 Hz, 1H), 4.87 (br s, 2H), 7.06 (d, $J$ = 7.3 Hz, 1H), 7.15−7.24 (m, 2H), 7.32 (d, $J$ = 7.3 Hz, 1H), 8.09 (s, 1H). Anal. ($C_{15}H_{16}N_4$) C, H, N.

***trans*-6a,12b-3-Amino-7-propyl-1,6,6a,7,8,12b-hexahydropyrimidino[4,5-*b*]phenanthridine (5c).** A solution of **5b** (210 mg, 0.72 mmol) in absolute EtOH (80 mL) containing 10% Pd/C (30 mg) was stirred vigorously overnight under an $H_2$ atmosphere at ambient pressure. The mixture was filtered though Celite, and the residue from evaporation was chromatographed on silica gel, eluting with $CHCl_3-CH_3CN-MeOH-NH_4OH$ (180:20:4:1) to yield **5c** (181 mg, 86%) as a yellowish resin that solidified upon standing: mp 132−136 °C dec; mp (monohydrochloride salt) 238−241 °C dec; CIMS *m*/*z* 295 ([M + H]$^+$, 100), 173 (17), 172 (32); $^1$H NMR $\delta$ 0.94 (t, $J$ = 7.3 Hz, 3H), 1.56−1.64 (m, 3H), 2.47−2.81 (m, 5H), 3.05−3.09 (m, 1H), 3.43 (dd, $J$ = 18.3, 5.2 Hz, 1H), 3.68 (d, $J$ = 15.4 Hz, 1H), 3.99 (d, $J$ = 15.3 Hz, 1H), 4.86 (br s, 2H), 7.06 (d, $J$ = 7.3 Hz, 1H), 7.14−7.24 (m, 2H), 7.29 (d, $J$ = 7.3 Hz, 1H), 8.11 (s, 1H). Anal. ($C_{18}H_{22}N_4$) C, H, N.

***trans*-5a,11b-6-Allyl-1,5,5a,6,7,11b-hexahydropyrazolo-[3,4-*b*]phenanthridine (6c).** A suspension of *t*-KOBu (0.93 g, 8.3 mmol) in THF (10 mL) was stirred under argon at 0 °C while a solution of ethyl formate (1.34 mL, 16.6 mmol) and **9** (1.00 g, 4.2 mmol) in THF (4 mL) was added via syringe over a 10-min period. The ice bath was removed, and stirring was continued for 90 min at room temperature. To this mixture was slowly added a 1 M hydrazine solution in THF (12.5 mL, 12.5 mmol) followed by a few drops of 1 N aqueous HCI to adjust the pH to ca. 9. After stirring for 20 h, the mixture was basified, diluted with twice the volume of water, and extracted ($CH_2Cl_2$). The combined organic layers were washed with brine, dried ($Na_2SO_4$), and evaporated to give an amorphous solid. Purification on silica gel, eluting with $CHCl_3$−MeOH (10:0.5), afforded **6c** (0.81 g, 74%) as a colorless foam: mp (monohydrochloride salt) >205−215 °C continuous dec; CIMS *m*/*z* 266 ([M + H]$^+$, 100), 170 (15); EIMS *m*/*z* 266 ([M + H]$^+$, 21), 265 (M$^{+\cdot}$, 28), 264 ([M − H]$^+$, 32), 171 (67), 170 (100), 129 (33); $^1$H NMR $\delta$ 2.59−2.74 (m, 3H), 3.14−3.25 (m, 3H), 3.47−3.70 (m, 3H), 3.96 (d, $J$ = 15.3 Hz, 1H), 5.21−5.30 (m, 2H), 5.92−6.06 (m, 1H), 7.07 (d, $J$ = 7.1 Hz, 1H), 7.17−7.33 (m, 3H), 7,36 (s, 1H). Anal. ($C_{17}H_{19}N_3$) C, H, N.

***trans*-5a,11b-1,5,5a,6,7,11b-Hexahydropyrazolo[3,4-*b*]-phenanthridine (6a).** The reaction was carried out as described for **5a**. For chromatography, $CHCl_3$−MeOH−$NH_4OH$ (95:5:0.5) was used as eluent, resulting in 81% of **6a** as a white solid that could be recrystallized from $CHCl_3$ as its mono-$CHCl_3$ solvate: mp 164−165 °C (light yellow needles); mp (monohydrochloride salt) >260 °C; CIMS *m*/*z* 226 ([M + H]$^+$, 100), 131 (6), 130 (9); $^1$H NMR (500 MHz) $\delta$ 2.45−2.60 (m, 2H), 2.94−3.00 (m, 3H), 3.53−3.57 (m, 1H), 4.08 (d, $J$ = 16 Hz, 1H), 4.22 (d, $J$ = 15.7 Hz, 1H), 7.06 (d, $J$ = 7.3 Hz, 1H), 7.17 (t, $J$ = 7.1 Hz, 1H), 7.21−7.24 (m, 1H), 7.34−7.36 (m, 2H). Anal. ($CHCl_3$ solvate; $C_{15}H_{16}N_3Cl_3$) C, H, N, Cl.

***trans*-5a,11b-6-Methyl-1,5,5a,6,7,11b-hexahydropyrazolo[3,4-*b*]phenanthridine (6b).** To a solution of **6a** (100 mg, 0.4 mmol) in MeOH (4 mL) and $H_2O$ (1.5 mL) were added 37% aqueous formaldehyde solution (0.18 mL, 2.4 mmol) and $NaBH_3CN$ (92.9 mg, 1.5 mmol). The mixture was stirred at

room temperature overnight under argon, then concentrated to ca. one-third, and diluted with $H_2O$. After basifying and extraction ($CHCl_3$), the organic layers were dried ($Na_2SO_4$) and evaporated. The residue was purified on silica gel, eluting with $CHCl_3$−MeOH−$NH_4OH$ (400:20:1) to give **6b** (70 mg, 77%) as a colorless glass: mp (monohydrobromide salt, acetone/$H_2O$) >225 °C dec; CIMS *m*/*z* 240 ([M + H]$^+$, 100), 145 (22), 144 (52); $^1$H NMR (500 MHz) $\delta$ 2.42−2.58 (m, 6H), 3.11−3.15 (m, 2H), 3.46 (dd, $J$ = 15.5, 5.0 Hz, 1H), 3.63 (d, $J$ = 14.5 Hz, 1H), 3.91 (d, $J$ = 15.5 Hz, 1H), 7.07 (d, $J$ = 7.5 Hz, 1H), 7.18 (t, $J$ = 7.5 Hz, 1H), 7.23 (t, $J$ = 7.5 Hz, 1H), 7.30 (d, $J$ = 8.5 Hz, 1H), 7.32 (s, 1H). Anal. ($C_{15}H_{18}N_3Br$) C, H, N, Br.

***trans*-5a,11b-6-Propyl-1,5,5a,6,7,11b-hexahydropyrazolo-[3,4-*b*]phenanthridine (6d).** Employing **6c**, the reaction procedure was identical to the one described for **5c**. The product was chromatographed on silica gel using $CHCl_3$−$CH_3CN$−MeOH−$NH_4OH$ (360:40:7:2) resulting in **6d** (68%) as a colorless foam: mp 215−220 °C (monohydrochloride salt, becomes glasslike); CIMS *m*/*z* 268 ([M + H]$^+$, 100), 173 (8), 172 (14); $^1$H NMR $\delta$ 0.92 (t, $J$ = 7.4 Hz, 3H), 1.55−1.65 (m, 2H), 2.47−2.62 (m, 3H), 2.68−2.82 (m, 2H), 3.06−3.12 (m, 2H), 3.50 (dd, $J$ = 15.8, 5.0 Hz, 1H), 3.37 (d, $J$ = 14.9 Hz, 1H), 3.96 (d, $J$ = 15.2 Hz, 1H), 7.06 (d, $J$ = 7.2 Hz, 1H), 7.13−7.21 (m, 2H), 7.31 (d, $J$ = 7.6 Hz, 1H), 7.36 (s, 1H). Anal. ($C_{17}H_{21}N_3$) C, H, N.

**Pharmacology Procedures. Striatal tissue preparation:** Adult male Sprague−Dawley rats weighing 250−400 g were obtained from Charles River Breeding Laboratories (Raleigh, NC). Rats were killed by decapitation and the brains removed rapidly and placed on ice. Striatum was dissected, and samples were placed in microcentrifuge tubes and stored frozen at −80 °C until the day of the receptor binding assays.

**Cloned receptor preparation:** C-6 glioma cells expressing rat $D_{2L}$ or $D_3$ receptors were obtained from Dr. Kim Neve (Oregon Health Sciences University) and grown in 75-cm$^2$ flasks with DMEM-H medium containing 4500 mg/L glucose, L-glutamine, 5% fetal bovine serum, and 700 ng/mL G418. Cells were grown to confluence, then rinsed and lysed with 10 mL of ice-cold lysis buffer (1 mM HEPES, 2 mM EDTA; pH 7.4) for 10 min at 4 °C. Cells were then scraped from the flasks using a sterile cell scraper obtained from Baxter (McGraw Park, IL). The combined cell suspension was spun at 24000*g* (Sorvall RC-26 Plus/SS-34, DuPont, Wilmington, DE) at 4 °C for 20 min. The pellet was resuspended in ice-cold storage buffer (50 mM HEPES, pH 8.0), homogenized with a Wheaton glass−Teflon homogenizer (5 strokes), and then stored in 1-mL aliquots to yield an estimated final concentration of ca. 1.0 mg of protein/mL. Aliquots of the final homogenate were stored in microcentrifuge tubes at −80 °C. Prior to their use for radioligand binding assays, protein levels for each membrane preparation were quantified using the bicinchoninic acid (BCA) protein assay reagent (Pierce, Rockford, IL) adapted for use with a microplate reader (Molecular Devices, Menlo Park, CA).

**Rat radioreceptor assays:** Frozen tissue samples from rat striatum were homogenized gently in 8.0 mL of ice-cold assay buffer (50 mM HEPES, 4 mM $MgCl_2$; pH 7.4) by seven strokes in a Wheaton glass−Teflon homogenizer. Tissue was pelleted by centrifugation (10 min at 15000*g*), after which the supernatant was removed. The pellet then was rehomogenized by five strokes in 8 mL of buffer, followed by repelleting. The supernatant was decanted, and the pellet was resuspended by homogenization to a final concentration of 2.0 mg/mL (estimated protein concentration of ca. 0.14−0.20 mg of protein/assay tube).

The amount of tissue added to each assay tube was ca. 0.8 mg, in a final assay volume of 1.0 mL for experiments using the Skatron harvester (Skatron, Inc., Sterling, VA) and 0.5 mL for experiments using the Packard harvester (Meridan, Connecticut). Tubes were incubated with either 0.3 nM [$^3$H]-SCH23390 ($D_1$ receptor assays) or 0.07 nM [$^3$H]spiperone ($D_2$ receptor assays) and varying concentrations of test compounds at 37 °C for 15 min. Assays with 0.07 nM [$^3$H]spiperone also included 50 nM ketanserin tartrate in all tubes to mask binding of the radioligand to serotonin sites. Total binding was defined as radioligand binding in the absence of any competing drug. Nonspecific binding of [$^3$H]SCH23390 was defined by adding 1 $\mu$M unlabeled SCH23390, whereas 1 $\mu$M chlorpromazine was used to define nonspecific binding of [$^3$H]spiperone. Triplicate determinations were performed in each assay. After incubation at 37 °C for 15 min, in some experiments tubes were filtered rapidly through Skatron glass fiber filter mats (model number 11734) and rinsed with 5 mL of ice-cold wash buffer (50 mM Hepes, 4 mM $MgCl_2$; pH 7.4) using a Skatron microcell harvester (Skatron Instruments Inc., Sterling, VA). Filters were allowed to dry and then punched into scintillation vials (Skatron Instruments Inc., Sterling, VA). OptiPhase HiSafe II scintillation cocktail (1 mL) was added to each vial. After vials were shaken for 30 min, radioactivity in each sample was determined on an LKB Wallac 1219 Rackbeta liquid scintillation counter (Wallac Inc., Gaithersburg, MD). In other experiments, 96-tube plates were filtered rapidly through Packard 96 GF/C filters and rinsed four times with 5 mL of ice-cold wash buffer (10 mM Tris, 0.9% NaCl; pH 7.4) using a Packard microcell harvester (Packard Instruments, Downers Grove, IL). Filters were allowed to dry, and then 25 $\mu$L of Microscint-20 scintillation cocktail was added to each filter well. Each plate was sealed using a microplate heat sealing film on a microplate sealer and then counted on a Packard topcount microplate scintillation counter (Packard, Downers Grove, IL). Tissue−protein levels were estimated as described for C-6 cell membranes.

**Cloned receptor assays:** Cell membranes were suspended in assay buffer (50 mM Tris, 120 mM NaCl; pH 7.4) at a concentration of 12.5 $\mu$g of wet weight/mL, in a final assay volume of 1.0 mL for experiments using the Skatron harvester (Skatron, Inc., Sterling, VA) and 0.5 mL for experiments using the Packard harvester (Meridan, CT). For competition curves, $D_{2L}$ and $D_3$ receptors were labeled with [$^3$H]spiperone (0.07 and 0.14 nM, respectively) and several concentrations of test compound. Total binding was defined as radioligand bound in the absence of any competing drug, and nonspecific binding was estimated by adding chlorpromazine (1 $\mu$M). Triplicate determinations were made for each drug concentration. Assay tubes were incubated at 37 °C for 15 min, and binding was terminated by rapid filtration as described above for assays with rat striatum.

**Analysis of radioligand competition curves:** The resulting concentration curves were analyzed by nonlinear regression using the algorithms in Prism (GraphPad, Inc.). The data were initially fit using the sigmoid model to provide a slope coefficient. All of these data are expressed as $K_{0.5}$, in which the experimental $IC_{50}$ is corrected for the radioligand concentration using the following formula: $K_{0.5} = IC_{50}/(1 + L^*/K_D^*)$, where L* is the radioligand concentration used in the assay and $K_D$* is the $K_D$ of the radioligand. In cases where the Hill slope ($n_H$) = 1, $K_{0.5} = K_I(K_D)$. Using the $K_{0.5}$ obviates the need to pick a more complex model (e.g., two vs three site) when $n_H < 1$, while allowing comparison of $IC_{50}$'s from experiments in which different [L*]'s were used.

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