Studies of the Active Conformation of a Novel Series of Benzamide Dopamine D2 Agonists

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Analogs of dopamine D2 agonist **11** were prepared in which a rigid *trans* decalin ring system was used to mimic various conformations of **11**. The four rigid analogs where compared for their ability to bind to the DA D2 receptor and to inhibit forskolin-stimulated cAMP formation, a measure of DA agonist activity. Of the four rigid analogs of compound **11**, only compound **12b** had significant activity in both assays. Molecular modeling studies of **12a-d** showed each had a single conformation with regard to the distance between the benzamide aryl-centroid and the 4-nitrogen atom of the pyridylpiperazine. Compound **12b** was shown to have a greater distance between these functionalities (11.8 Å) as compared to the other isomers (9.8–10.4 Å). The distance between these two functionalities in **12b** was similar to that of a conformer of **11** which has an extended conformation. This suggest that **11** is likely in an extended conformation when bound to the DA D2 receptor.

Introduction

A key objective in the quest for potent and selective dopamine (DA) D2 agonists has been to understand the interaction between these compounds and their target receptors on a molecular level. Applications of various hypotheses have led to a variety of novel structures which have been or continue to be evaluated as potential antipsychotic agents. Examples include quinpirole (**1**),[1] B-HT-920 (**2**),[2] 3-PPP (**3**),[3] U-68553 (**4**),[4] the ergolines SDZ-911 (**5**), and SDZ-912 (**6**) and terguride (**7**),[5] and PD 128483 (**8**).[6] All of these compound have structural elements which directly mimic DA; i.e., they contain an amino group tethered by a two-carbon spacer to an aryl of heteroaryl ring-containing moiety capable of forming hydrogen bonds with the receptor. Models of the interactions of some of these classical DA D2 agonists with the DA D2 receptor have been proposed. Experimental support for these models has come from the synthesis of more rigid analogs of **3**,[7] the ergots,[8] and the aminotetralins.[9] Through such studies a fairly detailed picture of what is necessary for the binding of this class of molecules to the DA D2 receptor is beginning to emerge.

More recently, a second broad class of DA D2 agonists has appeared which has a different pharmacophore than the prototypical DA D2 agonists mentioned above. This class is characterized by aryl or heteroaryl functionality attached via an alkyl or cycloalkyl chain to a 4-arylpiperazine or 4-phenyltetrahydropyridine structure. Examples of this type of DA D2 agonist include roxindole (**9**),[10] PD 119819 (**10**),[11] and PD 137510 (**11**).[12] The relationship between these molecules and DA is much less obvious than for prototypical DA agonists. While it has been proposed that the 4-arylpiperazine or 4-phenyltetrahydropyridine functionality mimics DA, this is not consistent with the fact that the nature of the pendant aryl or heterocyclic ring profoundly affects both the affinity of these compounds for the DA D2 receptor and their intrinsic agonist efficacy at this receptor. The interactions of these types of molecules with the DA D2 receptor is not well-understood because they have a greater amount of conformational flexibility than the prototypical DA D2 agonists. Most of the flexibility of this newer class of D2 agonists lies in the connection between the arylpiperazine or tetrahydropyridine moieties and the pendant aryl or heteroaryl functionality. Many conformers of similar energy are possible, and this complicates accurate analysis of the conformer(s) which interacts with the receptor.

Compound **11** was synthesized in these laboratories as part of a project to discover novel autoreceptor-selective DA D2 agonists.[12] As shown in Table 1, the compound had affinity for the DA D2 receptor,[13] and consistent with this activity, it was active at inhibiting spontaneous locomotor activity in the mouse.[14] Further investigations confirmed compound **11** was a DA D2 agonist as measured by its ability to inhibit forskolin-stimulated cAMP accumulation in GH_4C_1 cells transfected with the long form of the DA D2 receptor (Table 2).[15]

We considered what conformation of compound **11** might be responsible for its DA agonist activity. The amide nitrogen atom and the ethyl chain connecting the pyridylpiperazine moiety had a trans relationship across the cyclohexane ring. Thus, the lowest energy conformations of this molecule would have the two cyclohexyl substituents disposed in a diequatorial arrangement. However, the flexible ethyl chain allowed the pyridylpiperazine portion of the molecule to adopt a variety of directional orientations and spatial displacements in relation to the cyclohexylbenzamide portion of the molecule. In an effort to understand more about the active conformation of **11**, we constrained the conformational flexibility of the cyclohexylethyl spacer between the pyridylpiperazine and the benzamide by using a *trans* decalin ring system (Scheme 1). This conformationally-locked ring system serves to orient rigidly the pyridylpiperazine and benzamide portions of the molecule. By studying the DA D2 binding and second messenger properties of the set of four diastereomers of racemic **12**, we have been able to gain an

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Table 1. DA D2 Binding and Behavioral Activity

	11	12a	12b	12c	12d
DA D2 affinity[a] (IC_{50}, nM)	443	1100	72.7	7100	5800
inhib of mouse locomotor activity[b] (IP) ED_{50} (mg/kg)	0.16 (0.11; 0.23)	6.9 (5.6; 8.5)	0.10 (0.08; 0.14)	na[c]	14.3 (8.7; 23.6)

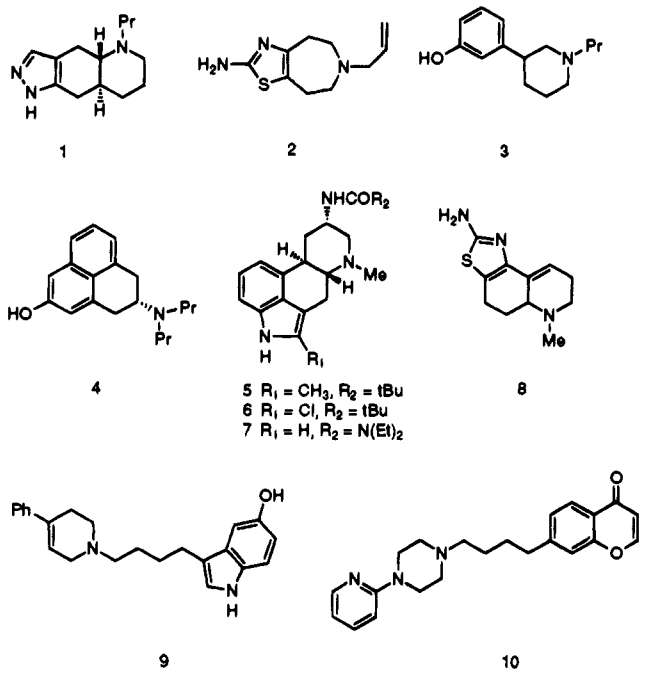
[a] Determined using displacement of [^{3}H]spiperone from rat striatal membranes by total of four to six concentrations run in triplicate by a nonlinear regression analysis.[13] [b] ED_{50} (95% confidence range) were generated from three to six doses; 6–18 animals were used per dose.[14] [c] ED_{50} >30 mg/kg.

Table 2. *In Vitro* Dopamine Agonist Efficacy[a]

compd	EC_{50}[a] (nM)	intrinsic activity
11	4.9 ± 1.5	0.83
12a	240 ± 0.37	0.63
12b	10.4 ± 0.13	0.98
12c	>1000	
12d	>1000	
quinpirole	7.6 ± 0.03	1.0

[a] Inhibition of forskolin-stimulated cAMP accumulation in GH_4C_1 cells transfected with the human DA D2 receptor. [b] Intrinsic activity relative to quinpirole.

initial insight into which conformation of compound **11** is responsible for its DA D2 agonist properties.



Chemistry

Preparation of the diastereomers of **12** proceeded via *trans* bicyclic dione monoketal **15**, which was prepared in three steps from commercially available starting materials as shown in Scheme 2.[16] Reaction of enamine **13** with methyl vinyl ketone resulted in a 42% yield of the expected Robinson annulation product **14**. Birch reduction of enone **14** provided the desired *trans* bicyclic ketone **15**. Reductive amination of **15** followed by hydrolysis of ketals **16** provided a mixture of diastereomers **17a** and **17b**. These could be easily separated by column chromatography. The relative stereochemistry of **17a** and **17b** was assigned based on the ^{13}C chemical shift differences in the decalin carbon bearing the piperazine moiety in **17a** and **17b**. These assignments were consistent with the chemical shifts and coupling constants of the protons on these carbons.

Ketone **17b** was converted to the corresponding oxime which was directly reduced and acylated to give target compounds **12a** and **12b** as a chromatographically separable mixture (Scheme 3). The relative stereochemistry of the newly introduced amide bonds could be unambiguously assigned by ^{13}C and proton NMR data in a similar manner to that outlined for **17a** and **17b**.

Similar chemistry was carried out with **17a**; however, the resulting products **12c** and **12d** could not be cleanly separated by either careful chromatography or by recrystallization. Ultimately they were prepared separately using methodology outlined in Scheme 4. Ketone **15** was converted to its oxime and reduced with Raney nickel, and the resulting amines were acylated with benzoyl chloride to give **18a** and **18b** which were separated chromatographically and then converted to the ketones **19** and **20**. Their relative stereochemistries were assigned based upon the ^{13}C shift anisotropy of the ring carbons bearing the amide nitrogen as well as the coupling patterns for the protons on those carbon atoms. Compounds **19** and **20** were converted to **12c** and **12d**, respectively. By using $Na(OAc)_3BH$ in place of $NaCNBH_3$, the isomers **12c** and **12d**, which had the piperazines in an axial orientation, became the major product in accord with previous observations.[17]

Pharmacology

The affinities of compounds for DA D2 receptors in rat striatal membranes was determined *in vitro* with the DA antagonist ligand [^{3}H]spiperone ([^{3}H]SPIP).[13] Inhibition of exploratory locomotor activity in mice was used as a behavioral index of DA autoreceptor agonist activity.[14] The ability of compounds to affect a second messenger system in GH_4C_1 cells transfected with the human D2 receptor was assessed by the inhibition of forskolin-stimulated cAMP accumulation as previously described.[15]

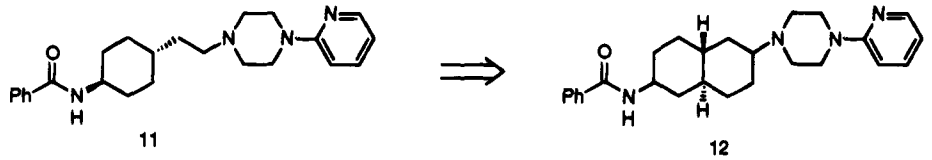
Molecular Modeling Studies

The MacroModel interactive molecular modeling system[18] was used to determine low-energy conformations of **1** and **12a–d**. Briefly, 1000 initial conformations were generated using a Monte Carlo method by varying the initial geometry about 14 dihedral angles and bond lengths. These initial conformations were minimized using the standard MacroModel force fields parameters, and their final relative energies were determined. Structures having energies within 3 kcal of the minimum were considered as being close enough in energy to warrant further consideration as low-energy conformers.

Results and Discussion

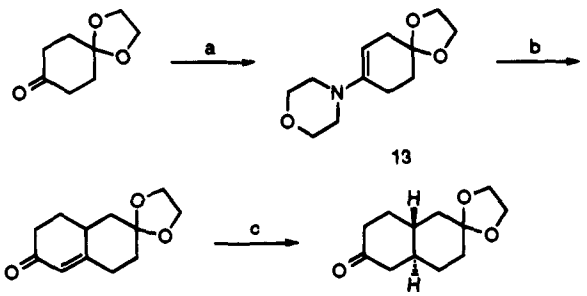
Of the four stereoisomers **12a–d** (Table 1), compound **12b** clearly had the greatest affinity for the DA D2 receptor and was most potent at inhibiting spontaneous locomotor activity in mice. To characterize the intrinsic activity of **12a–d** as DA D2 agonists, their ability to

Scheme 1



11 12

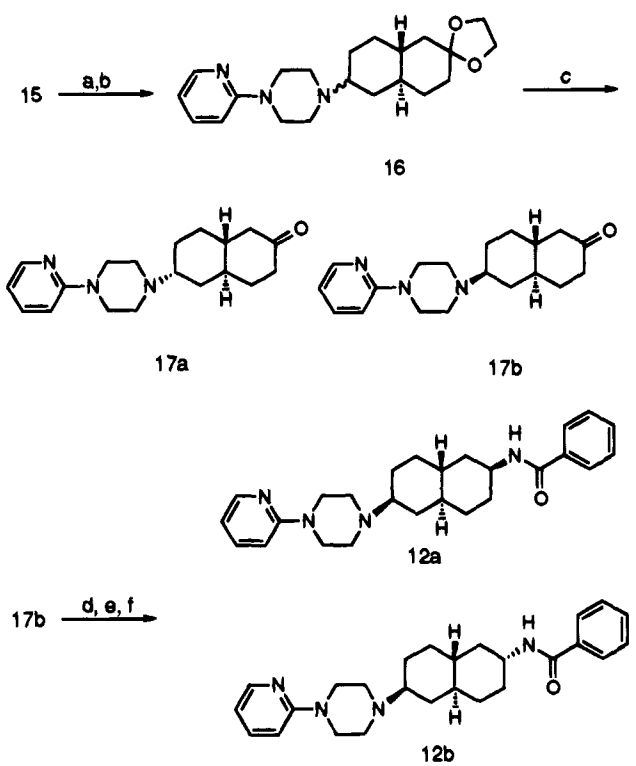
Scheme 2[a]



13 14 15

[a] (a) Morpholine, PTSA, toluene, reflux; (b) MVK, dioxane reflux then H_2O; (c) Li, NH_3, *t*-BuOH, THF.

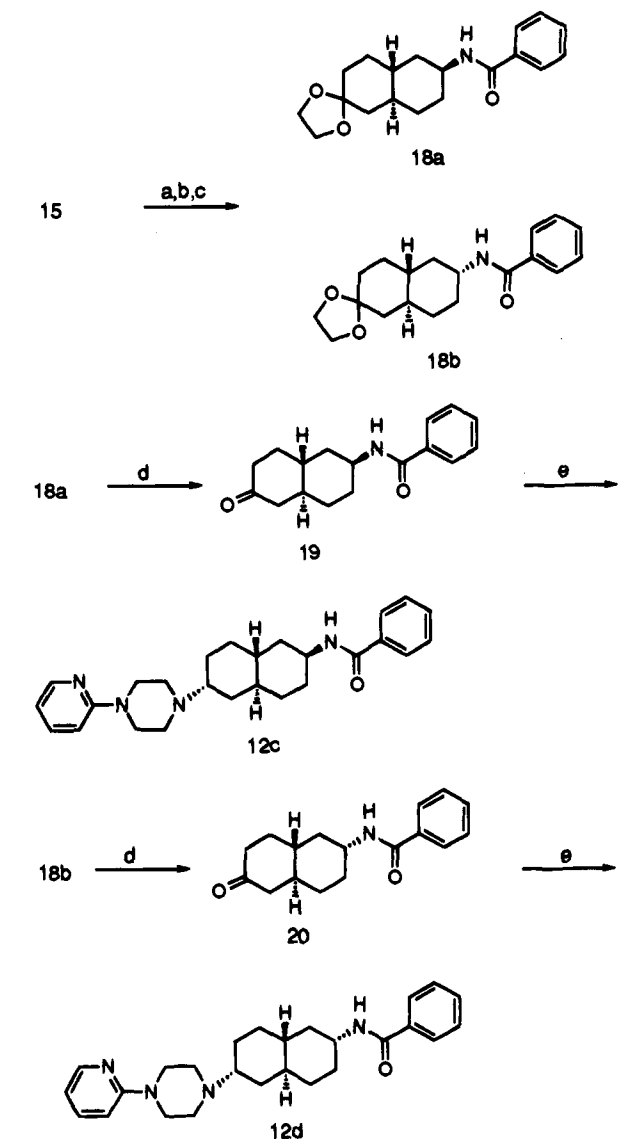
Scheme 3[a]



16 17a 17b 12a 12b

[a] (a) 1-(2-Pyridyl)piperazine, PTSA, toluene reflux; (b) $NaCNBH_3$, AcOH, MeOH; (c) HCl, H_2O, acetone; (d) NH_2OH·HCl, $NaHCO_3$, MeOH; (e) Raney nickel, H_2 (50 psi), MeOH; (f) benzoyl chloride, Et_3N, CH_2Cl_2.

Scheme 4[a]



18a 15 18b 19 12c 20 12d

[a] (a) NH_2OH·HCl, $NaHCO_3$, MeOH; (b) Raney nickel, H_2 (50 psi), MeOH; (c) benzoyl chloride, Et_3N, CH_2Cl_2; (d) HCl, H_2O, acetone; (e) 1-(2-pyridyl)piperazine, $Na(OAc)_3BH$, AcOH, MeOH.

inhibit forskolin-stimulated cAMP accumulation in GH_4C_1 cells transfected with the human DA D2 receptor was evaluated. As shown in Table 2, compound **12b** was the most potent full agonist of the series and as shown in Figure 1 had a potency and intrinsic activity comparable to that of the DA D2 agonist quinpirole. Of the four compounds, **12b** was clearly the most potent and efficacious in all three tests. Compound **12b** also had higher affinity for DA D2 receptors than **1**.

Low-energy conformers of **12a–d** generated through molecular mechanics calculations all had the *trans* decalin nucleus of the molecules in a chair–chair conformation regardless of the relative stereochemistry of the amide or piperazine substituents. Thus in compound **12a** the amide nitrogen assumes an axial orientation while the piperazine assumes an equatorial position. In compound **12b**, both substituents are found in an equatorial orientation, while in compound **12c** both substituents are forced to assume an axial position. In **12d** the piperazine functionality is oriented in an axial manner and the amide functionality in an equatorial direction. The distance between the centroid of the aromatic ring of the benzamide and the piperazine nitrogen atom attached to the *trans* decalin was measured for all four compounds. The most active analog,

compound **12b**, had a distance of 11.84 Å, while the other three analogs had significantly shorter distances between the aryl centroid and piperazine nitrogen (9.81–10.48 Å). In order to approach a displacement of at least 11.7 Å between the two nitrogens for compounds **12a**, **12c**, or **12d**, one or both of the six-membered rings in the bicyclo[4.4.0]decane ring system must be forced into a boat conformation at high energy costs (4–11 kcal).

A search for low-energy conformers of **1** produced several that were close in energy due to the flexibility of the ethylene chain connecting the cyclohexylbenzamide and pyridylpiperazine portions of the molecule. As expected, the pyridylpiperazine portion of the molecule could adopt a variety of directional orientations and spatial displacements in relation to the cyclohexylbenzamide portion of the molecule. As shown in Figure 2 the minimized structure of **12b** is similar to a low-energy conformation of compound **1** corresponding to an extended conformation of the ethylene bridge. This conformation of **1** lies only 0.28 kcal in energy above the global minimum and has a distance between the piperazine nitrogen and the aromatic centroid at 11.92 Å. On the basis of these findings we propose that the ethylene chain in **1** is in an extended conformation positioning the piperazine ring away from the cycloalkyl ring. This suggests that when binding to the DA D2 receptor, compound **1** adopts a conformation in which the benzamide and pyridylpiperazine functionalities are aligned in a coplanar, extended fashion.

These findings contrast with earlier proposals for active conformations of structurally related DA agonists.[10] It has been suggested that roxindole and other nontraditional DA agonists like PD 119819 adopt a conformation in which the phenyltetrahydropyridine and the pendant indole functionality are oriented toward each other. It is necessary to force molecules to adopt this unusual conformation in order to fit the classical McDermed model[19] for DA agonists. Such a model assumes a mode of receptor binding for all DA D2 agonists similar to that for DA, apomorphine, and aminotetralin structures. However, compound **12b** (which is clearly a DA D2 agonist) cannot adopt such a bent conformation and thus must bind in an alternative fashion to the DA D2 receptor. Thus our data may indicate, in contrast to what others have suggested,[10] that there exist alternative modes of agonist binding at the DA D2 receptor.

On the basis of amino acid sequence data obtained from the cloning of the DA D2 receptor,[20] several 3-dimensional models of the receptor have been proposed.[21] As these models are further refined, it will be important to study rigidified DA agonists such as **12b** in order to understand more about the dynamics of the interactions of DA D2 agonists with their target receptor. The advantage of the study of such rigid molecules is that the relative orientation of the spatially separated pharmacophores can be determined with great certainty, removing much ambiguity in the study of interactions between this type of agonist models of the DA D2 receptor.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Proton NMR were recorded on a Bruker 250 MHz NMR instrument.

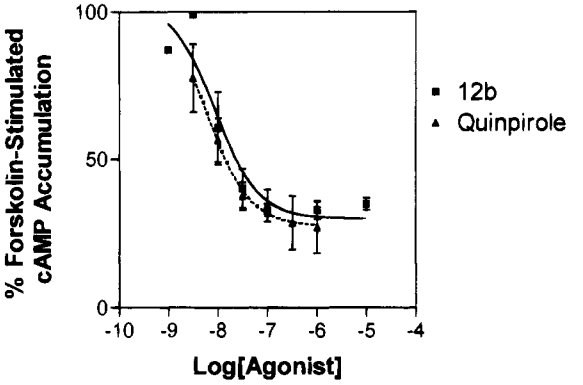


Figure 1. Dose–response curves of quinpirole (1) and **12b** in GH4C1 cells.

^{13}C spectra were recorded on the same instrument with an effective field strength of 63 MHz. The spectra recorded were consistent with proposed structures. The peaks are described in ppm downfield from TMS (internal) standard. The mass spectra were obtained on a Finnigan 4500 mass spectrometer or a VG Analytical 7070E/HF mass spectrometer; the spectra are described by the molecular peak (M) and its intensity relative to the base peak (100). Elemental analyses were performed by the Analytical Chemistry Section at Parke-Davis, Ann Arbor, MI. Where analyses are indicated by the symbols of the elements, the results are within 0.4% of the theoretical values. TLC was performed on 0.25 mm silica gel F254 (E. Merck) glass plates. Medium-pressure chromatography (MPLC) was performed on silica gel (E. Merck, grade 60, 230–400 mesh 60 Å) with a RB-SY pump (FMI).

4-(1,4-Dioxaspiro[4.5]dec-7-en-8-yl)morpholine (13). A solution of cyclohexane-1,4-dione monoethylene ketal (21.5 g, 138 mmol) and morpholine (15.7 g, 180 mmol) in 30 mL of toluene in the presence of *p*-toluenesulfonic acid (0.14 g) was refluxed under a Dean–Stark trap for 5 h. The toluene was removed under reduced pressure, and the enamine **13** was distilled (115 °C at 0.5 Torr) (18.6 g, 60% yield) and was used directly in the next reaction.

3′,4′,8′,8a′-Tetrahydrospiro[1,3-dioxolane-2,2′(1′*H*)-naphthalen]-6′(7′*H*)-one (14). A solution of enamine **13** (47.6 g, 211 mmol) and methyl vinyl ketone (17.2 g, 245 mmol) in 120 mL of anhydrous dioxane was refluxed for 10 h. Water (200 mL) was added, and the reaction mixture was refluxed for an additional 24 h. The reaction was cooled; the dioxane was removed under reduced pressure, and to the remaining residue was added water (250 mL) and brine (50 mL). The aqueous mixture was extracted with (4 × 250) mL of ether, and the combined organic extracts were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The resulting oil was eluted through a plug of silica gel using a gradient starting at 4:1 hexane–EtOAc and gradually reaching 3:1 hexane–EtOAc. The fractions enriched in the desired product were recrystallized from 600 mL of hexanes, and two crops were combined to give 19.6 g of the desired enone 14 (45% yield). Mp: 71–73 °C. Anal. ($C_{12}H_{16}O_3$) C, H. ^1H NMR (200 MHz, $CDCl_3$): 5.88 (s, 1H), 4.00 (s, 4H), 2.60 (m, 2H), 2.47 (m, 3H), 2.10 (dq, J = 13, 4 Hz, 1H), 1.88 (m, 2H), 1.69 (m, 2H), 1.48 (t, J = 13 Hz, 1H).

3′,4′,4a′,5,8′,8a′-Hexahydro-*trans*-spiro[1,3-dioxolane-2,2′(1′*H*)-naphthalen]-6′(5′*H*)-one (15). Approximately 300 mL of anhydrous NH_3 was condensed into a 1 L three-neck flask cooled to −78 °C equipped with a mechanical stirrer and a cold finger. Lithium wire (1.56 g, 229 mmol) was added portionwise and stirred to effect solution. A solution of enone **14** (14.5 g, 69.1 mmol) and *t*-BuOH (5.12 g, 691 mmol) in 200 mL of THF was added to the reaction mixture over 45 min, during which time the temperature of the reaction was maintained at −78 °C. After the addition of the substrate was complete, solid ammonium chloride (9 g) was carefully added, and the reaction was allowed to warm to room temperature overnight. The remaining THF was removed under reduced pressure, and the residue was partioned between 300 mL of

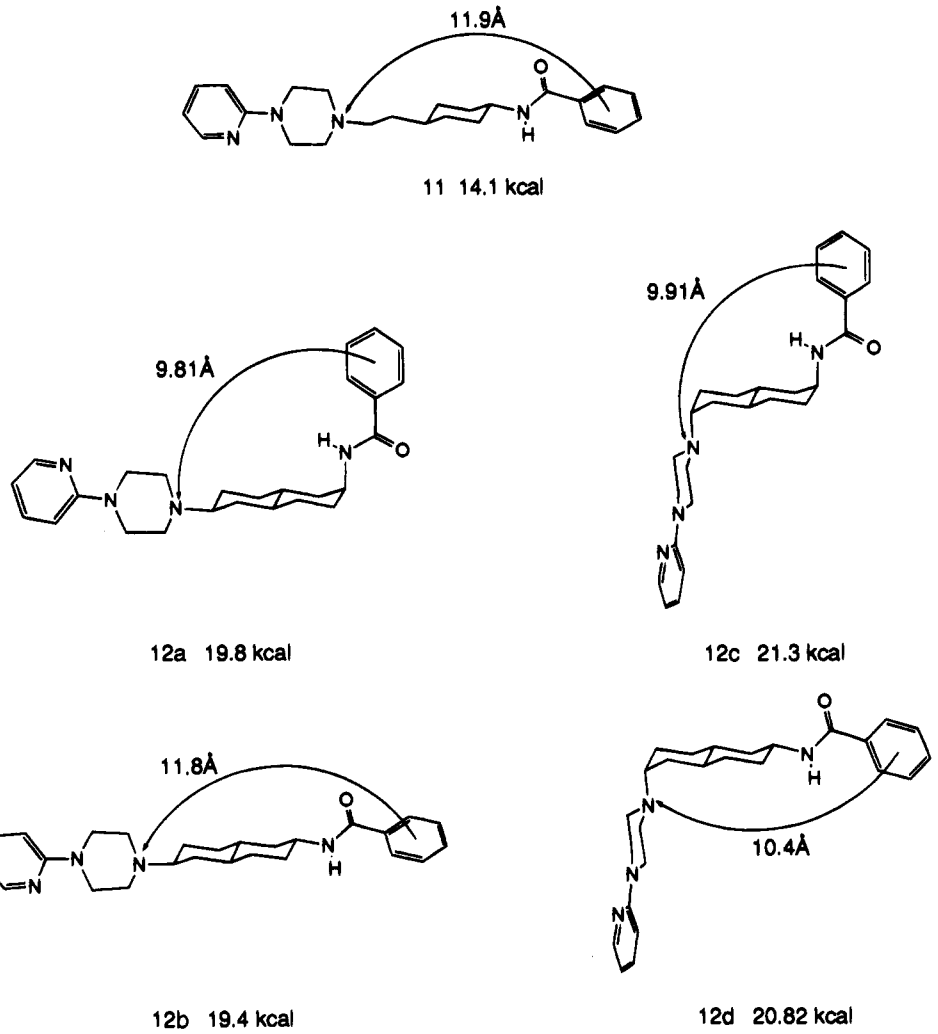


Figure 2. Aryl-centroid to piperazine nitrogen distances.

water and 300 mL of Et_2O. The ethereal layer was dried with brine and over with $MgSO_4$. The solvent was evaporated under reduced pressure. The residue was chromatographed over silica gel, using 3:1 hexane–EtOAc as the eluent, to give the desired product **15** (8.24 g, 57% yield) as an oil which solidified on standing. Mp: 66–67 °C. Anal. ($C_{12}H_{18}O_3$) C, H. Proton and ^{13}C spectra were in accord with literature data.[16] Starting material (3.3 g) eluted from the column after the desired product.

(2β,4aα,8aβ)-2-[4-(2-Pyridinyl)-1-piperazinyl]-1,2,3,4,-4a,7,8,8a-octahydronaphthalen-6(5′*H*)-one (17a) and (2α,-4aα,8aβ)-2-[4-(2-Pyridinyl)-1-piperazinyl]-1,2,3,4,4a,7,8,-8a-octahydronaphthalen-6(5′*H*)-one (17b). A solution of bicyclic ketone 14 (2.90 g, 13.8 mmol), 1-(2-pyridinyl)piperazine (2.25 g, 13.8 mmol), and a catalytic amount of PTSA (ca. 10 mg) in 10 mL of toluene was refluxed under a Dean–Stark trap for 18 h. The volatiles were removed under reduced pressure, and the residue was dissolved in 90 mL of MeOH. The resulting solution was cooled to 0 °C; sodium cyanoborohydride (1.30 g, 20.68 mmol) and a trace of the pH indicator methyl orange was added, and the reaction mixture was treated with a 1 N HCl solution (23 mL) until the reaction mixture stayed orange for 5 min. The reaction mixture was stirred at 0 °C for 1 h and was then warmed to room temperature for 2 h. The MeOH was removed under reduced pressure, and the residue was partitioned between aqueous $NaHCO_3$ (100 mL) and $CHCl_3$ (100 mL). The organic extracts were dried with sodium sulfate, and the solvent was removed under reduced pressure. The residue was treated with 120 mL of a 1:1 solution of acetone and 10% HCl. After the mixture was stirred at room temperature for 1 h, the acetone was removed under reduced pressure. The remaining aqueous solution was cooled in an ice bath and made basic with saturated ammonium hydroxide, and the resulting mixture was extracted with $CHCl_3$ (2 × 100 mL). The $CHCl_3$ extracts were dried with sodium sulfate and evaporated. The resulting residue was chromatographed on silica gel (2% MeOH in $CHCl_3$ with 0.1% NH_3). The faster moving fraction was **17a** (1.47 g, 39% yield), and the second fraction was **17b** (1.93 g, 51% yield). **17a.** Mp: 138–140 °C. Anal. ($C_{19}H_{27}N_3O$) C, H, N. ^1H NMR (200 MHz, $CDCl_3$): 8.19 (d, J = 7 Hz, 1H), 7.48 (t, J = 8 Hz, 1H), 6.67 (d, J = 8 Hz, 1H), 6.61 (dd, J = 7, 8 Hz, 1H), 3.55 (t, J = 5 Hz, 4H), 2.58 (t, J = 5 Hz, 4H), 2.41–2.22 (m, 4H), 2.19 (d, J = 12 Hz, 1H), 2.11–2.04 (m, 2H), 1.92–1.78 (m, 2H), 1.59–1.21 (m, 5H), 1.12 (t, J = 12 Hz, 1H). ^{13}C NMR ($CDCl_3$): 211.8, 160.9, 147.9, 113.2, 106.9, 59.8, 51.4, 49.7, 46.8, 45.2, 43.0, 36.4, 36.2, 34.8, 29.3, 29.2. MS: *m/e* 313 (m^+, 18), 107 (base).

17b. Mp: 170–171 °C. Anal. ($C_{19}H_{27}N_3O$) C, H, N. ^1H NMR (200 MHz, $CDCl_3$): 8.18 (d, J = 5 Hz, 1H), 7.47 (t, J = 8 Hz, 1H), 6.64 (d, J = 8 Hz, 1H), 6.61 (dd, J = 8, 5 Hz, 1H), 3.54 (t, J = 5 Hz, 4H), 2.70 (t, J = 5 Hz, 4H), 2.47 (tt, J = 11, 2 Hz, 1H), 3.34 (m, 3H), 2.0 (m, 4H), 1.79 (m, J = 12 Hz, 1H), 1.26–1.05 (m, 6H). ^{13}C NMR ($CDCl_3$): 211.5, 169.6, 147.9, 137.4, 113.2, 107.0, 63.1, 49.0, 48.0, 45.6, 42.9, 41.2, 40.7, 34.9, 33.3, 33.0, 27.6. MS: *m/e* 313 (m^+, 9), 107 (base).

(2α,4aα,6α,8aβ)-*N*-[Decahydro-6-[4-(2-pyridinyl)-1-piperazinyl]-2-naphthalenyl]benzamide (12a) and (2α,-4aα,6β,8aβ)-*N*-[Decahydro-6-[4-(2-pyridinyl)-1-piperazinyl]-2-naphthalenyl]benzamide (12b). A mixture of ketone **17b** (1.23 g, 3.9 mmol), hydroxylamine hydrochloride (0.31 g, 4.3 mmol), and triethylamine (0.82 g, 6.9 mmol) in 50 mL of EtOH was heated to reflux for 18 h. The solvent was removed under reduced pressure. The crude oxime was dissolved in 100 mL of MeOH containing 2% NH_3; Raney nickel (2 g) was added, and the reaction was placed on a Parr shaker under

50 psi of hydrogen. After 18 h the catalyst was filtered, and the filtrate was removed under reduced pressure to give the crude mixture of amines. The crude mixture was dissolved in CH_2Cl_2 (20 mL) and treated with triethylamine (0.51 g, 5 mmol) and then benzoyl chloride (0.594 g, 4.3 mmol) in 20 mL of CH_2Cl_2. After stirring at room temperature for 18 h, the reaction mixture was diluted with CH_2Cl_2 and washed with aqueous $NaHCO_3$. The organic layer was dried with Na_2SO_4, and the solvents were removed under reduced pressure to give a mixture of benzamides **2** (1.47 g, 84% yield). The mixture was separated by careful column chromatography using 1–5% MeOH in CH_2Cl_2 and 0.1% NH_3 as the eluent. The faster moving fraction **12a** was determined to be the axial amide isomer.

12a. Mp: 229 °C. Anal. ($C_{26}H_{34}N_4O$) C, H, N. ^1H NMR (200 MHz, $CDCl_3$): 8.19 (d, J = 5 Hz, 1H), 7.77 (d, J = 9 Hz, 2H), 7.47 (m, 4H), 6.67 (d, J = 8 Hz, 1H), 6.61 (t, J = 7 Hz, 1H), 6.29 (d, J = 7 Hz, 1H), 4.40 (m, J = 3 Hz, 1H), 3.54 (t, J = 5 Hz, 4H), 2.69 (t, J = 5 Hz 4H), 2.42 (m, 1H), 2.05 (m, 1H), 1.91 (m, 3H), 1.63 (m, 3H), 1.28 (m, 3H), 1.07 (m, 4H). ^{13}C NMR ($CDCl_3$): 166.71, 159.65, 147.97, 137.40, 135.29, 131.90, 128.88, 126.86, 113.13, 106.98, 63.27, 49.06, 45.61, 45.46, 41.97, 37.95, 36.85, 35.92, 32.63, 29.83, 28.90, 28.06. MS: *m/e* 419 (m + H, 6), 107 (base).

12b. Mp: 221 °C. Anal. ($C_{26}H_{34}N_4O$) C, H, N. ^1H NMR (200 MHz, $CDCl_3$) 8.18 (d, J = 5 Hz, 1H), 7.74 (d, J = 7 Hz, 2H), 7.44 (m, 4H), 6.64 (d, J = 8 Hz, 1H), 6.60 (t, J = 7 Hz, 1H), 5.99 (d, J = 7 Hz, 1H), 4.01 (br m, 1H), 3.52 (t, J = 5 Hz, 4H), 2.69 (t, J = 5 Hz, 4H), 2.39 (t, J = 12 Hz, 1H), 2.03 (m, J = 15 Hz, 3H), 1.72 (m, 2H), 1.25 (m, 4H), 1.02 (m, 5H). ^{13}C NMR ($CDCl_3$): 166.72, 159.67, 147.95, 137.40, 135.27, 131.89, 128.89, 126.85, 113.14, 106.95, 63.65, 49.06, 49.06, 45.46, 41.22, 41.19, 39.98, 35.27, 33.14, 32.56, 32.35, 28.02. MS: *m/e* 419 (m + H, 8), 107 (base).

(2α,4aβ,8aα)-*N*-[1′,2′,3′,4′,4a′,7′,8′,8a′-Octahydro-2-[spiro-1,3-dioxolane-2,6′(5′*H*)-naphthalenyl]benzamide (18a) and (2β,4aβ,8aα)-*N*-[1′,2′,3′,4′,4a′,7′,8′,8a′-Octahydro-2-[spiro-1,3-dioxolane-2,6′(5′*H*)-naphthalenyl]benzamide (18b). Hydroxylamine hydrochloride (4.17 g, 60 mmol) was slurried in MeOH (50 mL), cooled to 0 °C, and treated with sodium carbonate (3.18 g, 30 mmol). The mixture was stirred for 5 min, and a solution of ketone **15** (10.0 g, 47.5 mmol) in 40 mL of MeOH was added to the mixture. After the addition the reaction mixture was allowed to come to room temperature and stir for 4 h. The MeOH was removed under reduced pressure, and the residue was partitioned between $CHCl_3$ (250 mL) and saturated aqueous $NaHCO_3$ (100 mL). The aqueous layer was separated and washed with $CHCl_3$ (100 mL). The combined organic extracts were dried over Na_2SO_4, and the solvent was removed under reduced pressure. The resulting crude oxime was dissolved in 200 mL of MeOH containing 2% NH_3. Raney nickel (5 g) was added, and the reaction mixture was placed under 52 psi of hydrogen on a Parr shaker for 18 h. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure. The resulting residue was taken up in CH_2Cl_2 (200 mL) and treated with triethylamine (9.2 mL, 66 mmol); the solution was cooled to 0 °C, and the reaction mixture was treated with benzoyl chloride (5.62 mL, 48.4 mmol). The reaction mixture was warmed to room temperature and stirred for 2 h. The reaction mixture was extracted with dilute aqueous HCl and saturated aqueous $NaHCO_3$. The organic layer was dried over Na_2SO_4, and the solvents were removed under reduced pressure. The resulting residue was chromatographed over silica gel (4:1 $CHCl_3$–EtOAc). Isolation of the faster moving fraction gave benzamide **18a** (3.3 g, 23% yield). Mp: 211–213 °C. Anal. ($C_{19}H_{25}NO_3$) C, H, N. ^1H NMR (200 MHz, $CDCl_3$): 7.75 (d, J = 6 Hz, 2H), 7.46 (m, 3H), 6.29 (d, J = 6 Hz, 1H), 4.39 (m, 1H), 3.94 (s, 4H), 2.1–1.0 (m, 14H). MS: *m/e* 315 (m^+, 10), 99 (base).

Recrystallization of fractions enriched in the slower moving fraction from hot EtOAc gave **18b** (4.4 g, 31% yield). Mp: 183–184 °C. Anal. ($C_{19}H_{25}NO_3$) C, H, N. MS: *m/e* 419 (m + H). ^1H NMR: 7.73 (d, J = 9 Hz, 2H), 7.42 (m, 3H), 6.01 (br d, J = 8 Hz, 1H), 4.02 (m, 1H), 3.93 (s, 4H), 2.05 (m, 2H), 1.68 (m, 4H), 1.48 (dd, J = 12, 4 Hz, 1H), 1.40–1.05 (m, 6H), 0.94 (dd, J = 12, 24 Hz, 1H). MS: *m/e* 315 (m^+, 3), 105 (base).

(2α,4aβ,8aα)-*N*-(1,2,3,4,4a,7,8,8a-Octahydro-6-oxo-2-naphthalenyl)benzamide (19). A solution of ketal **18a** (3.30 g, 10.4 mmol) in 160 mL of 1:1 acetone–10% hydrochloric acid was stirred at room temperature for 12 h. The acetone was removed under reduced pressure, and the aqueous solution was extracted with $CHCl_3$ (3 × 150 mL). The combined organic extracts were dried with Na_2SO_4 and evaporated to give ketone **19** (2.8 g, 98% yield). Mp: 198–200 °C. Anal. ($C_{17}H_{21}NO_2$) C, H, N. ^1H NMR (400 MHz, $CDCl_3$): 7.79 (d, J = 7 Hz, 2H), 7.52 (t, J = 7 Hz, 1H), 7.45 (t, J = 7 Hz, 2H), 6.38 (d, J = 5 Hz, 1H), 4.44 (m, 1H), 2.40 (m, 3H), 2.11 (t, J = 12 Hz, 1H), 2.09 (m, 1H), 1.96 (m, 2H), 1.66 (m, 3H), 1.49–1.25 (m, 4H). ^{13}C NMR ($CDCl_3$) 210.5, 166.89, 134.91, 131.4, 128.6, 126.8, 48.1, 45.2, 42.6, 41.4, 36.3, 36.1, 33.1, 29.2, 28.8. MS: *m/e* 271 (m^+, 69), 105 (base).

(2α,4aα,6α,8aβ)-*N*-[Decahydro-6-[4-(2-pyridinyl)-1-piperazinyl]-2-naphthalenyl]benzamide (12c). A slurry of ketone **19** (1.00 g, 3.68 mmol) was slurried in 20 mL of dichloroethane, cooled to 0 °C, and treated with 1-(2-pyridyl)-piperazine (0.60 g, 3.68 mmol), sodium triacetoxy borohydride (1.17 g, 5.52 mmol), and acetic acid (0.22 g, 3.68 mmol). The reaction was warmed to room temperature and stirred for 2 h. The reaction mixture was partitioned between $CHCl_3$ (25 mL) and aqueous saturated sodium carbonate (50 mL). The aqueous layer was separated and extracted with $CHCl_3$ (25 mL), and the combined organic extracts were dried over Na_2SO_4. The solvents were removed under reduced pressure, and the resulting residue was chromatographed (1–2% MeOH in $CHCl_3$ with 0.1% NH_3) to obtain **12c** (0.83 g, 54%). Mp: 204–5 °C. Anal. ($C_{26}H_{34}N_4O$) C, H, N. ^1H NMR (200 MHz, $CDCl_3$): 8.19 (d, J = 5 Hz, 1H), 7.78 (d, J = 7 Hz, 2H), 7.47 (m, 4H), 6.64 (d, J = 8 Hz, 1H), 6.61 (t, J = 7 Hz, 1H), 6.34 (d, J = 7 Hz, 1H), 4.40 (m, J = 2 Hz, 1H), 3.53 (t, J = 5 Hz, 4H), 2.55 (t, J = 5 Hz, 4H), 2.27 (br s, 1H), 2.07 (d, J = 12 Hz, 1H), 1.93 (m, 2H), 1.82 (d, J = 13 Hz, 1H), 1.69 (tt, J = 14, 3 Hz, 1H), 1.50 (m, 5H), 1.17 (m, 4H). ^{13}C NMR ($CDCl_3$): 166.71, 159.65, 147.97, 137.40, 135.29, 131.29, 128.58, 126.86, 113.13, 106.98, 58.89, 50.09, 45.61, 45.53, 38.93, 37.13, 36.17, 35.98, 30.19, 28.74, 28.64, 27.50. MS: *m/e* 419 (m + H, 6), 107 (base).

(2β,4aβ,8aα)-*N*-(1,2,3,4,4a,7,8,8a-Octahydro-6-oxo-2-naphthalenyl)benzamide (20). Ketal **18b** (4.21 g, 13.34 mmol) was converted to ketone **20** as outlined above for ketone **19** (3.91 g, 97% yield). Mp: 218–219 °C. Anal. ($C_{17}H_{21}NO_2$) C, H, N. ^1H NMR (400 MHz, $CDCl_3$): 7.75 (d, J = 8 Hz, 2H), 7.50 (t, J = 7 Hz, 1H), 7.43 (t, J = 7 Hz, 2H), 6.03 (d, J = 7 Hz, 1H), 4.09 (m, 1H), 2.38 (m, 3H), 2.20 (d, J = 12 Hz, 1H), 2.13 (d, J = 1H), 2.10 (t, J = 13 Hz, 1H), 2.01 (m, 1H), 1.79 (m, 1H), 1.57 (m, 1H), 1.47–1.21 (m, 4H), 1.00 (AB q, J = 12, 12 Hz, 1H). ^{13}C NMR ($CDCl_3$): 211.0, 166.7, 134.9, 131.4, 128.5, 126.8, 48.6, 47.8, 42.4, 41.1, 40.1, 39.1, 33.0, 32.5, 32.2. MS: *m/e* 271 (m^+, 75), 105 (base).

(2α,4aβ,6β,8aα)*N*-[Decahydro-6-[4-(2-pyridinyl)-1-piperazinyl]-2-naphthalenyl]benzamide (12d). Ketone **20** (1.00 g, 3.68 mmol) was converted to piperazine **12d** as outlined above for piperazine **12c** (0.673 g, 43% yield). **12d.** Mp: 182–4 °C. Anal. ($C_{26}H_{34}N_4O$) C, H, N. ^1H NMR (200 MHz, $CDCl_3$): 8.19 (d, J = 5 Hz, 1H), 7.74 (d, J = 7 Hz, 2H), 7.44 (m, 4H), 6.65 (d, J = 8 Hz, 1H), 6.62 (t, J = 7 Hz, 1H), 5.95 (d, J = 7 Hz, 1H), 4.01 (br m, 1H), 3.52 (br s, 4H), 2.55 (br s, 4H), 2.27 (br s, 1H), 1.96 (m, 4H), 1.62 (d, J = 12 Hz, 1H), 1.37 (m, 4H), 1.21 (m, 5H). ^{13}C NMR ($CDCl_3$): 166.65, 159.66, 147.98, 137.40, 135.07, 131.25, 128.52, 126.82, 113.13, 107.00, 58.89, 50.07, 49.04, 45.55, 42.45, 40.18, 35.71, 35.51, 33.34, 32.34, 28.45, 27.48. MS: *m/e* 419 (m + H, 8.2), 107 (base).

Pharmacological Methods. DA D2 Binding. The IC_{50} of compounds were determined according to methods previously described[13] using [^3H]spiperone (0.2 nM, final concentration) binding to rat striatal membranes in the presence of (+)-butaclamol (1 μM) for nonspecific binding.

Inhibition of Spontaneous Locomotor Activity. As previously described,[14] mice were treated with compounds administered ip followed immediately by a 1 h test. Locomotor activity was measured in darkened cylindrical photobeam chambers. Data were expressed as a percentage of activity

relative to vehicle-treated animals and an ED_{50} calculated from various doses.

Inhibition of cAMP Accumulation. DA D2 receptor activation was measured by inhibition for forskolin-stimulated cAMP accumulation in GH_4C_1 cells transfected with the human D2 receptor as previously described.[15] Intrinsic activities of test compounds were determined by comparing the maximal response obtained to that of the full DA D2 agonist quinpirole.

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