Dopamine Autoreceptor Agonists as Potential Antipsychotics. 1. (Aminoalkoxy)anilines

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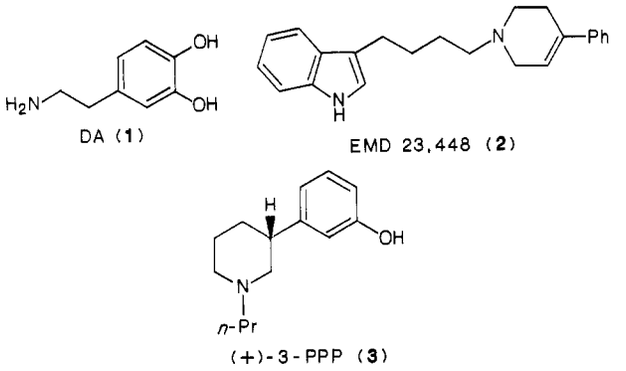
The synthesis and pharmacological properties of a novel type of [(arylpiperazinyl)alkoxy]anilines with dopaminergic properties are described. One of these compounds, 3-[3-(4-phenyl-1-piperazinyl)propoxy]benzenamine (**4c**), has been identified as a selective dopamine (DA) autoreceptor agonist in tests that include [^{3}H]haloperidol binding, inhibition of striatal DA synthesis, inhibition of DA neuronal firing, inhibition of spontaneous locomotor activity, and reversal of reserpine-induced depression in rats. In addition, **4c** possesses good oral activity in the Sidman conditioned avoidance test in squirrel monkeys, which is indicative of antipsychotic activity. In a primate model, **4c** was found to lack the liability for extrapyramidal side effects usually associated with antipsychotic drugs.

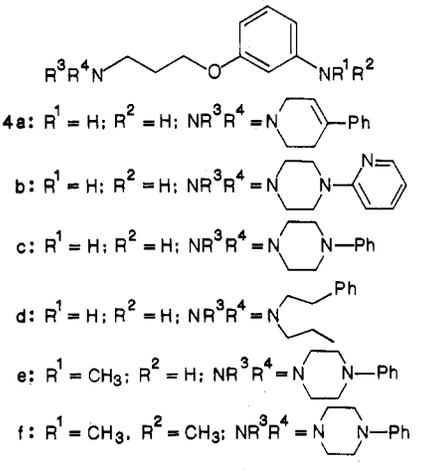
Schizophrenia appears to be associated with a functional hyperactivity of the dopamine (DA, **1**) neuronal systems of the brain.[1] All clinically available antipsychotic agents inhibit DA neurotransmission by blockade of postsynaptic DA receptors.[2] Unfortunately, DA antagonism is also responsible for the most serious side effects of these agents, namely extrapyramidal syndrome (EPS),[3] a short-term parkinsonian-like condition caused by DA receptor blockade, tardive dyskinesia (TD),[4] a syndrome of involuntary movements that has been linked to supersensitivity of brain DA receptors after long-term DA receptor blockade, and hyperprolactinaemia,[5] which is caused by blockade of pituitary DA receptors.

In the search for effective therapeutic agents that lack the side effects of available antipsychotics, attention in recent years has been directed toward developing DA agonists that are selective for presynaptic DA receptors in the brain, the so-called DA autoreceptor agonists.[6] The hypothesis underlying this approach stems from evidence that DA autoreceptors serve an inhibitory feed-back function on DA neurotransmission. Activation of DA autoreceptors results in reduced neuronal firing as well as inhibition of DA synthesis and release.[7] Thus, DA autoreceptor activation may provide functional modulation of the DA systems of the brain without the excessive reduction of neuronal activity that has been linked to the adverse effects of DA antagonists.

Prominent among several DA autoreceptor agonists described in the literature are EMD 23,448 (**2**)[8] and (+)-3-(3-hydroxyphenyl)-1-propylpiperidine [(+)-3-PPP, **3**].[9] While the DA pharmacophore is readily apparent in **3**, the structure of **2** does not resemble DA. Work on DA agonists has suggested the possibility that an indole ring can act as a bioisosteric replacement for the catechol portion of DA.[10] In this light, it seems reasonable to suggest that the indole ring of **2** might also act as a catechol bioisostere. A structural similarity between **2** and **3** is that in both compounds a meta relationship exists between the point of attachment of the basic side chain and the polar group on the aromatic ring, in agreement with the model of McDermed et al. for DA agonist activity.[11]

In search of an orally active and selective DA autoreceptor agonist, we sought to examine a simple system that would combine some features of **2** and other known DA agonists. The aniline moiety was chosen as a potential replacement for the aromatic portion of the DA pharmacophore.[12] In accordance with our understanding of the structural features required for DA autoreceptor selectivity, the basic side chain was placed meta to the amine substituent on the aromatic ring. This report describes the synthesis and pharmacology of some substituted anilines **4**.





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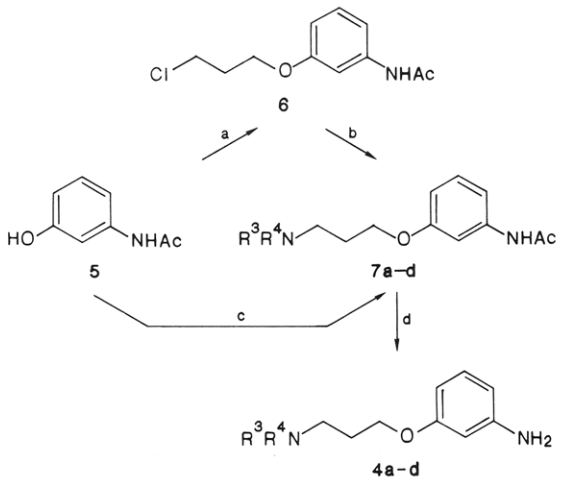
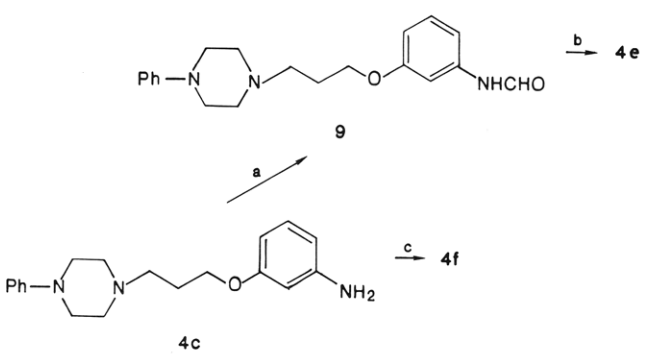
Scheme I[a]



[a] (a) $ClCH_2CH_2CH_2Br$, K_2CO_3, acetone; (b) R^3R^4NH, $NaHCO_3$, NaI, DMF; (c) $R^3R^4NCH_2CH_2CH_2Cl$ (**8**), NaO-*i*-Pr, *i*-PrOH; (d) 10% HCl.

Scheme II[a]



[a] (a) HCO_2H, Ac_2O, THF; (b) $LiAlH_4$, THF; (c) CH_2O, $NaCNBH_3$, MeOH, HCl.

Chemistry

The synthesis of compounds **4a–d** is outlined in Scheme I. Reaction of 3-acetamidophenol (**5**) with 1-bromo-3-chloropropane in acetone gave **6** in quantitative yield. Reaction of **6** with the appropriate amines gave acetamides **7a–d**. Acid hydrolysis of the amides yielded anilines **4a–d**. Alternatively, reaction of the sodium salt of **5** with an appropriate 3-chloropropylamine (i.e. **8c**) gave the intermediate amides **7a–d** in one step. To study the influence of alkyl substitution at the aniline nitrogen on dopaminergic activity, N-substituted anilines **4e** and **4f** were prepared according to the sequence shown in Scheme II. Monomethyl derivative **4e** was prepared by formylation of **4c** with formic acid and acetic anhydride, followed by reduction with lithium aluminum hydride. Dimethyl derivative **4f** was prepared by reductive alkylation of **4c** with formaldehyde and sodium cyanoborohydride in acidic methanol.

Table I. Effects of Target Compounds and Reference Agents on Rat Striatal DA Receptors

compd	[^{3}H]HAL[a,b] binding: IC_{50}, nM	% inhibn of DA neuronal firing[c] ± SEM (no. of neutrons)	inhibn of locomotor activity:[d,e] ED_{50} (95% CI), mg/kg po
2	16	100 ± 0 (4)	4.8 (0.4)
3	930	100 ± 0 (6)	>30
4a	67	89 ± 7 (4)	12.1 (0.8)
4b	1571	46 ± 13 (5)	9.2 (1.0)
4c	138	85 ± 5 (4)	10.3 (0.6)
4d	469	8 ± 2 (2)	>30
4e	359	7 ● 3 (4)	9.4 (0.5)
4f	240	21 ± 6 (3)	9.2 (0.6)
apomorphine	27	100 ± 0 (5)[f]	>30

[a] [^{3}H]Haloperidol. [b] IC_{50} values were determined from four to five concentrations by a nonlinear regression analysis. [c] All compounds were administered at 2.5 mg/kg ip, except where noted otherwise. [d] ED_{50} values were generated from four doses; 5–12 animals were used per dose. [e] No ataxia was observed up to doses of 30 mg/kg. [f] Apomorphine was dosed at 0.25 mg/kg ip.

Table II. Inhibition of DA Synthesis in Rat Striatum

compd	inhibn of DOPA accumulation:[a] ED_{50}, mg/kg ip	compd	inhibn of DOPA accumulation:[a] ED_{50}, mg/kg ip
2	2.2	**4c**	12.0
3	7.2	apomorphine	0.3
4a	7.0		

[a] Shown are the doses producing a half-maximal decrease of DOPA formation in rat striatum, estimated from dose–response curves comprising three to five dose levels with four to five animals per treatment group.

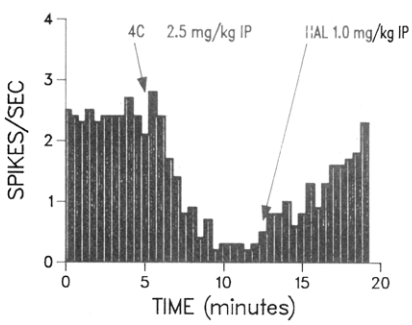


Figure 1. Histogram depicting the typical activity of **4c** on the firing rate of substantia nigra dopamine neurons. This histogram represents the results obtained in a single experiment. The value shown in Table I was obtained from combining four separate experiments (HAL = haloperidol).

Results and Discussion

The in vitro binding affinity of **4a–f** for DA receptors was measured in rat striatal membranes with [^{3}H]-haloperidol (^{3}H-HPD) as the ligand.[13] The DA autoreceptor agonist activity of these compounds was determined by their ability to inhibit spontaneous firing of DA neurons

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in the substantia nigra of anesthetized rats[14] and by their ability to decrease the γ-butyrolactone (GBL) induced increase in DA synthesis in the corpus striatum (a major brain DA projection area) of rats.[15] Inhibition of exploratory locomotor activity in rats was used as a behavioral index of DA autoreceptor agonist activity.[16] As part of this test, compounds were tested for impairment of motor coordination, since previous studies indicate that available antipsychotic drugs reduce locomotor activity at doses that do not produce ataxia.[17]

As shown in Table I, all compounds exhibited affinity for DA receptors. However, no direct correlation was found between their receptor binding affinities and their potencies as DA agonists in the neuronal firing test. Thus, while **4a** and **4c** are potent DA autoreceptor agonists, **4b** appears to be a much weaker agonist, and **4d–f** have no agonist activity. As illustrated in Figure 1 for **4c**, the inhibitory action of these compounds on DA neuron firing was reversed by the DA antagonist haloperidol, which demonstrates their DA agonist mechanism of action. The neuronal firing results obtained for **4a** and **4c** were confirmed biochemically; both compounds inhibited the accumulation of DOPA induced by GBL, which reflects a decrease in the rate of DA synthesis by activation of presynaptic DA autoreceptors (Table II).

Behaviorally, all compounds, with the exception of **3**, **4d**, and apomorphine, inhibited exploratory locomotor activity in rats at doses that did not induce ataxia (Table I). The activity of **4a–c** in this test is in agreement with their DA autoreceptor agonist properties described above. The lack of behavioral activity of **4d** is also in agreement with its inability to inhibit DA neuronal firing. Interestingly, **4e** and **4f** also inhibited exploratory locomotor activity; however, as we have shown above, these two compounds are not DA autoreceptor agonists, and thus their behavioral effects may stem from other mechanisms. Compound **2** also inhibited locomotor activity, but, as expected, **3** and apomorphine did not possess significant oral activity.

The selectivity of **4a** and **4c** for DA autoreceptor versus postsynaptic receptor sites was evaluated by determining their abilty to stimulate locomotor activity in reserpinized rats[18] and in 6-hydroxydopamine (6-OHDA) lesioned rats.[19] In both of these tests, postsynaptic DA receptors have been rendered supersensitive by drug-induced depletion of brain DA. Like **2**, neither **4a** nor **4c** caused reversal of reserpine-induced depression at doses up to 30 mg/kg sc, and **3** caused a 46% reversal at 30 mg/kg sc. In contrast, the nonselective DA agonist apomorphine caused locomotor stimulation with an ED_{50} of 0.096 mg/kg sc, a dose that is only about 4.5 times the dose required for inhibition of locomotor activity in normal rats. In 6-OHDA lesioned rats, which is one of the most sensitive models of postsynaptic DA activity, **2**, **3**, **4a**, and apomorphine all caused stimulation at doses lower than their ED_{50} values for inhibition of locomotor activity. This is reflected in values smaller than one for the presynaptic selectivity ratio *C*/*A* in Table III. However, **4c** did not cause stimulation up to a dose of 30 mg/kg sc, the highest dose tested. This is reflected in a presynaptic selectivity ratio *C*/*A* greater than 16. These results suggest that the selectivity of **4c** for DA autoreceptors is much greater than that of the reference compounds **2** or **3**.

Table III. Comparative Potency of **4a** and **4c** and Reference Agents in Rats for Behavioral Effects Mediated by Pre- and Postsynaptic Brain DA Receptors

	ED_{50} (95% CI), mg/kg sc				
	A: inhibn of locomotor activity[a]	*B*: reversal of reserpine-induced depression[b]	*C*: reversal of 6-OHDA-induced depression[a]	pre/post selectivity ratios	
compd				*B*/*A*	*C*/*A*
2	0.64 (0.04)	>30	0.4	>46	0.62
3	[8.8][c]	>30	0.6	>3.4	0.07
4a	0.35 (0.04)	>30	0.13	>85	0.37
4c	1.8 (0.1)	>30	>30	>16	>16
apomorphine	0.021 (0.001)	0.096 (0.004)	0.006	4.5	0.28

[a] ED_{50} values were generated from three or four doses; six animals were used per dose. Locomotor activity was measured immediately after dosing for a period of 30 min. [b] ED_{50} values were generated from three or four doses; five animals were used per dose. [c] Estimated value. The inhibition of locomotor activity reached a maximum at about 45%.

Table IV. Effects of **4c** and Thioridazine in the Sidman Avoidance and EPS Tests

compd	inhibn of Sidman avoid. in squirrel monkeys:[a] ED_{50} ± SEM, mg/kg po	EPS in squirrel monkeys (dose:[b] mg/kg po)
4c	8.50 ± 0.76	N[c] (42.5)
thioridazine	3.90 ± 0.02	A[c] (2.5)

[a] ED_{50} values were generated from three doses. Four animals were tested per dose. [b] Four animals were tested at each dose. [c] N, inactive; A, active.

The antipsychotic potential of **4c** was further explored in primates (Table IV). In the Sidman avoidance procedure with squirrel monkeys,[20] **4c** had an ED_{50} of 8.5 mg/kg po. The EPS liability of **4c** was examined in squirrel monkeys sensitized to haloperidol.[21] Whereas thioridazine produced dystonias and dyskinesias in sensitized monkeys near its behaviorally active dose in the Sidman avoidance test, no such signs were observed for **4c** at 42.5 mg/kg po, 5 times its behavioral ED_{50}.

In conclusion, we have identified a novel series of DA autoreceptor agonists represented by **4c**. Our results indicate that this activity is quite sensitive to structural changes. For example, the phenylpiperazine moiety found in **4c** increases the DA autoreceptor selectivity of these compounds as compared to the phenyltetrahydropyridine moiety found in **2** and **4a**. Replacement of the phenylpiperazine with a pyridylpiperazine leads to weaker compounds. Alkyl substitution at the aniline nitrogen also results in compounds that lack DA agonist activity. Our data suggest that **4c** is a more selective DA autoreceptor agonist than either **2** or **3**; **4c** also possesses good oral activity in a primate model indicative of antipsychotic efficacy, apparently without the EPS liability normally

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associated with antipsychotic drugs.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The IR spectra were obtained on a Nicolet MX-1 FT spectrometer. The proton NMR spectra were recorded on an IBM WP100SY NMR spectrometer (100 MHz) or a Varian XL200 NMR spectrometer (200 MHz) and were consistent with the 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. Where analyses are indicated by the symbols of the elements, the results are within 0.4% of the theoretical values. TLC was carried out with 0.25 mm silica gel F254 (E. Merck) glass plates.

***N*-[3-(3-Chloropropoxy)phenyl]acetamide (6).** A solution of 50.0 g (0.33 mol) of 3-acetamidophenol in 1000 mL of acetone was treated with 104.0 g (0.66 mol) of 1-bromo-3-chloropropane and 69.0 g (0.50 mol) of anhydrous K_2CO_3, and the mixture was refluxed for 16 h. An additional portion of 20.0 g (0.127 mol) of 1-bromo-3-chloropropane was added, and refluxing was continued for 6 h. The hot mixture was filtered through Celite and evaporated in vacuo to leave a light oil. The last traces of 1-bromo-3-chloropropane were removed at high vacuum to yield 75 g (100%) of **6**. An aliquot was purified by medium-pressure liquid chromatography (MPLC) to obtain an analytical sample: NMR ($CDCl_3$) δ 2.15 (3 H, s), 2.18 (2 H, m), 3.70 (2 H, t, J = 6 Hz), 4.05 (2 H, t, J = 6 Hz), 6.70 (1 H, br d, $J \simeq$ 8 Hz), 7.00 (1 H, br d, $J \simeq$ 8 Hz), 7.18 (1 H, t, $J \simeq$ 8 Hz), 7.30 (1 H, br s), 7.95 (1 H, br s, N*H*); MS, m/z 227/229 (M, 65), 109 (100). Anal. ($C_{11}H_{14}ClNO_2 \cdot 0.25H_2O$) C, H, N, Cl, H_2O.

3-[3-(3,6-Dihydro-4-phenyl-1(2*H*)-pyridinyl)propoxy]benzenamine (4a). A solution of 10.0 g (44 mmol) of **6** in 200 mL of DMF was treated with 8.8 g (45 mmol) of 1,2,3,6-tetrahydro-4-phenylpyridine dihydrochloride, 12.0 g (142 mmol) of $NaHCO_3$, and 4.5 g (30 mmol) of NaI. The mixture was heated at 80 °C for 12 h, and the volatile components were removed in vacuo. The residue was partitioned between water and CH_2Cl_2. The organic layer was dried over $MgSO_4$ and evaporated in vacuo. The residue was triturated with 200 mL of EtOAc and filtered. The filtrate was evaporated again, leaving a thick oil, which was identified by NMR as **7a**. This oil was dissolved in 150 mL of 15% HCl and was refluxed overnight. The solution was cooled, basified with concentrated NH_4OH, and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and treated with an excess of hydrogen chloride in 2-propanol. Removal of the solvent left a highly hygroscopic salt, which was recrystallized from methanol/ether: mp 230–232 °C; NMR (D_2O) δ 2.27–2.41 (2 H, m), 2.93 (2 H, br s), 3.33–3.54 (3 H, m), 3.84 (2 H, br d), 4.20 (1 H, br d), 4.25 (2 H, t, J = 5.6 Hz), 6.17 (1 H, br s), 7.01 (1 H, s), 7.05–7.13 (2 H, m), 7.42–7.58 (6 H, m); MS, m/z 308 (M, 32), 158 (100). Anal. ($C_{20}H_{24}N_2O \cdot 2HCl$) C, H, N, Cl.

3-[3-[4-(2-Pyridinyl)-1-piperazinyl]propoxy]benzenamine (4b). Via the procedure described above for the synthesis of **4a**, a solution of 10.0 g (44 mmol) of **6** in 200 mL of DMF was reacted with 7.34 g (45 mmol) of 1-(2-pyridinyl)piperazine, 9.0 g (107 mmol) of $NaHCO_3$ and 4.5 g (30 mmol) of NaI to yield 3.2 g of crude acetamide **7b**, which was hydrolyzed in 15% HCl to give 2.2 g (16% overall) of **4b** as a colorless solid: mp 109–111 °C (ether). NMR ($CDCl_3$) δ 1.80–2.10 (2 H, m), 2.43–2.63 (6 H, m), 3.50–3.70 (4 H + NH_2, m), 3.98 (2 H, t, J = 7 Hz), 6.13–6.37 (3 H, m), 6.50–6.70 (2 H, m), 6.95–7.10 (1 H, m), 7.33–7.55 (1 H, m), 8.10–8.23 (1 H, m); MS, m/z 313 (M, 43), 107 (100). Anal. ($C_{18}H_{24}N_4O$) C, H, N.

1-(3-Chloropropyl)-4-phenylpiperazine (8c). A vigorously stirred solution of 47.0 g (290 mmol) of 1-phenylpiperazine in 60 mL of acetone and 45 mL of 25% NaOH was treated dropwise with 50.0 g (320 mmol) of 1-bromo-3-chloropropane. The mixture immediately became warm. Stirring was continued at room temperature for 60 h. The organic layer was separated, diluted with 500 mL of CH_2Cl_2, dried over $MgSO_4$, and evaporated in vacuo. The residue was taken up into 300 mL of anhydrous ether, a small amount of insoluble material was gravity-filtered, and the resulting solution was treated with an excess of ethereal hydrogen chloride. A white salt formed, which was filtered and dried to give 82.5 g (92%) of the dihydrochloride salt of **8c**: mp 203–207 °C; NMR (DMSO) δ 2.10–2.50 (2 H, m), 3.00–3.45 (6 H, m), 3.50–3.70 (2 H, m), 3.70–3.95 (4 H, m), 6.60 (N*H*), 6.75–7.10 (3 H, m), 7.15–7.40 (2 H, t, J = 8 Hz); MS, m/z 238/240 (M, 67/22), 175 (80). Anal. ($C_{13}H_{19}ClN_2 \cdot 2HCl$) C, H, N.

***N*-[3-[3-(4-Phenyl-1-piperazinyl)propoxy]phenyl]acetamide (7c).** Sodium isopropoxide was prepared by refluxing 2.69 g (117 mmol) of sodium metal in 450 mL of 2-propanol under nitrogen for several hours. To this solution was added 17.78 g (117 mmol) of 3-acetamidophenol. The solution was refluxed for 10 min and cooled to room temperature. A solution of 28.0 g (117 mmol) of **8c** in 100 mL of 2-propanol was added, and the reaction mixture was refluxed overnight. The solvent was removed in vacuo, and the residue was partitioned between CH_2Cl_2 and water. The organic layer was further washed with 5% NaOH solution and brine. The solution was dried over $MgSO_4$ and evaporated in vacuo. The residue was recrystallized from EtOAc/heptane to give 30.0 g (72%) of a colorless solid: mp 112.0–113.5 °C; NMR ($CDCl_3$) δ 1.95–2.05 (2 H, m), 2.14 (3 H, s), 2.51–2.64 (6 H, m), 3.19 (2 H, t, J = 6 Hz), 3.95–4.05 (4 H, m), 6.62–6.67 (1 H, m), 6.80–6.94 (3 H, m), 7.14–7.36 (5 H, m); MS, m/z 353 (M, 76), 175 (100). Anal. ($C_{21}H_{27}N_3O_2$) C, H, N.

3-[3-(4-Phenyl-1-piperazinyl)propoxy]benzenamine (4c). A solution of 27.53 g (78 mmol) of **7c** in 500 mL of 15% HCl was refluxed for 6 h. The solution was cooled in an ice bath, basified with NH_4OH, and extracted with 500 mL of CH_2Cl_2. The organic layer was dried over $MgSO_4$ and evaporated in vacuo. The clear oil that crystallized upon trituration with 50 mL of ether yielded 22.5 g (93%) of **4c** as a colorless solid: mp 95.5–97.0 °C; NMR ($CDCl_3$) δ 1.90–2.25 (2 H, m), 2.50–2.85 (6 H, m), 3.15–3.30 (4 H, m), 3.68 (2 H, NH_2, br s), 4.00 (2 H, t, J = 7 Hz), 6.20–6.47 (3 H, m), 6.80–7.45 (6 H, m); MS, m/z 311 (M, 42), 175 (100). Anal. ($C_{19}H_{25}N_3O$) C, H, N.

***N*-[3-(3-Aminophenoxy)propyl]-*N*-propylbenzeneethanamine (4d).** A solution of 10.0 g (44 mmol) of **6**, 7.35 g (45 mmol) of *N*-propylphenethylamine, 9.0 g (107 mmol) of $NaHCO_3$, and 4.5 g (30 mmol) of NaI in 200 mL of DMF was heated at 80 °C for 6 h. The solvent was removed in vacuo, and the residue was partitioned between water and CH_2Cl_2. The organic extracts were purified by silica gel filtration to yield 6.38 g (41%) of crude **7d** as an oil, which was used without further purification. A solution of 3.15 g (8.9 mmol) of **7d** in 40 mL of 15% HCl was refluxed overnight and worked up in the usual way (vide supra). The crude reaction mixture was purified by MPLC to yield 1.50 g (54%) of the title compound as an oil: NMR ($CDCl_3$) δ 0.87 (3 H, t, J = 7.4 Hz), 1.47 (2 H, m), 1.89 (2 H, m), 2.46 (2 H, t, J = 7.5 Hz), 2.65 (2 H, t, J = 7.1 Hz), 2.72 (4 H, br s), 3.63 (2 H, NH_2, br s), 3.93 (2 H, t, J = 6.3 Hz), 6.22–6.34 (3 H, m), 7.05 (1 H, t, J = 8 Hz), 7.14–7.32 (5 H, m); MS, m/z 313 (M + 1, 7), 221 (100). Anal. ($C_{20}H_{28}N_2O$) C, H, N.

***N*-Methyl-3-[3-(4-phenyl-1-piperazinyl)propoxy]benzenamine (4e).** To 8.16 g (80 mmol) of acetic anhydride was added 4.7 g (100 mmol) of 95% formic acid dropwise under nitrogen. The mixture was cooled to room temperature, and 7 mL of anhydrous THF were added. A solution of 9.6 g (31 mmol) of **4c** in 20 mL of THF was added over a 5-min period. The mixture was heated at 50 °C for 1 h and stirred at room temperature overnight. The mixture was concentrated in vacuo, and the residue was partitioned between CH_2Cl_2 and 5% NH_4OH. The organic layer was dried and evaporated to leave 9.0 g (86%) of **9** as a thick oil, which was used without further purification. A solution of 6.7 g (19.7 mmol) of **9** in 100 mL of dry THF was added dropwise under nitrogen to a suspension of 1.68 g (44 mmol) of $LiAlH_2$ in 100 mL of dry THF. The reaction mixture was refluxed for 2 h, cooled to room temperature, and quenched by sequential addition of 8.8 mL of 10% HCl, 8.8 mL of 30% NaOH, and 8.8 mL of water. The resulting mixture was filtered through Celite, evaporated in vacuo and purified by MPLC (1% NH_4OH, 49.5% EtOAc, 49.5% heptane) to yield 4.0 g (62%) of **4e** as a crystalline solid: mp 83–86 °C; NMR ($CDCl_3$) δ 1.80–2.20 (2 H, m), 2.50–2.75 (6 H, m), 2.87 (3 H, s), 3.15–3.30 (4 H, m), 3.97–4.10 (2 H, t, J = 6.5 Hz), 6.12–6.39 (3 H, m), 6.80–7.40 (6 H, m); MS, m/z 325 (M, 72), 175 (100). Anal. ($C_{20}H_{27}N_3O$) C, H, N.

***N*,*N*-Dimethyl-3-[3-(4-phenyl-1-piperazinyl)propoxy]benzenamine (4f).** To a solution of 3.0 mL (40 mmol) of 35% aqueous formaldehyde and 2.6 mL of 3 M H_2SO_4 in 20 mL of

methanol was added dropwise a solution of 3.1 g (10 mmol) of **4c** and 2.20 g (58 mmol) of $NaBH_4$ in 20 mL of methanol. Halfway through this addition, a second portion of 2.6 mL of 6 N H_2SO_4 was added to the reaction. The resulting mixture was stirred at room temperature for about 4 h. Analysis of the reaction mixture by TLC indicated the presence of mostly starting material. The pH of the reaction was adjusted to 4 (methyl orange) with 15% HCl. Additional formaldehyde was added (3.0 mL, 40 mmol), followed by 2.51 g (40 mmol) of $NaCNBH_3$. After 30 min, excess HCl was added, and the mixture was concentrated in vacuo. The residue was partitioned between CH_2Cl_2 and 5% NH_4OH. The organic layer was dried over $MgSO_4$ and evaporated. The residue was purified by MPLC (70% heptane, 29% EtOAc, 1% NH_4OH) to yield 0.50 g (15%) of **4f**: mp 89–93 °C; NMR ($CDCl_3$) δ 1.98–2.08 (2 H, m), 2.58–2.69 (6 H, m), 2.95 (6 H, s), 3.20–3.26 (4 H, m), 4.06 (2 H, t, J = 6.4 Hz), 6.30–6.41 (3 H, m), 6.84–6.98 (3 H, m), 7.11–7.33 (3 H, m); MS, m/z 339 (M, 71), 175 (100). Anal. ($C_{21}H_{29}N_3O$) C, H, N.

Pharmacological Methods. [^{3}H]Haloperidol Receptor Binding Assay. The affinities of compounds for brain DA receptors were determined by standard receptor binding assays,[13] according to methods described previously.[22]

Effects on the Firing Rate of Substantia Nigra DA Neurons.[14] The action potential of zona compacta DA cells was recorded in chloral anesthetized rats by using standard extracellular recording techniques. DA cells were identified by waveform and firing pattern and recording sites were verified histologically. Drugs were administered intraperitoneally via an indwelling catheter. Base-line firing rate was calculated by averaging the rate over the 2 min prior to drug injection. Drug effects were determined by averaging the response during the 1-min period of maximal inhibition. Drug-induced inhibition of firing was reversed with the DA antagonist haloperidol to confirm a DA agonist mechanism.

Inhibitions of spontaneous locomotor activity and motor coordination[16] were carried out according to methods described previously.[22]

Inhibition of GBL-Stimulated DA Synthesis.[15] Compounds were administered to rats 1 h before sacrifice, and γ-butyrolactone (GBL, 750 mg/kg ip) and NSD 1015 (100 mg/kg ip) were administered 30 and 25 min, respectively, before sacrifice. Brain levels of dihydroxyphenylalanine (DOPA) were analyzed by HPLC with electrochemical detection.[23]

Effects on Spontaneous Locomotion in Reserpinized Rat vs Normal Rat.[18] Drugs were administered subcutaneously to normal rats treated with 5 mg/kg of reserpine 24 h prior to testing. Locomotor activity was measured for 30 min beginning immediately after drug administration as described previously.[17,22]

Effects on Spontaneous Locomotion in 6-OHDA Lesioned Rats.[19] Drugs were administered subcutaneously to rats treated at least one month previously with central injections of 6-hydroxydopamine (6-OHDA, 200 μg icv) and systemic injections of pargyline (50 mg/kg ip) and desmethylimipramine (25 mg/kg ip) as described previously.[24] This treatment produced large selective depletion of brain DA (approximately 90%) as described previously[24] and as determined by brain DA determinations in representative animals. Locomotor activity was measured for 30 min beginning immediately after drug administration as described previously.[17,22]

Sidman avoidance procedure[20] **and extrapyramidal side effect test**[21] in mature squirrel monkeys were performed as described previously.[22]

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Registry No. **2**, 73966-53-7; **3**, 85976-54-1; **4a**, 114597-68-1; **4a**·2HCl, 114597-69-2; **4b**, 114597-70-5; **4c**, 85868-45-7; **4d**, 114597-71-6; **4e**, 114614-34-5; **4f**, 114597-72-7; **5**, 621-42-1; **6**, 78702-97-3; **7a**, 114597-73-8; **7b**, 114597-74-9; **7c**, 78702-84-8; **7d**, 114597-75-0; **8c**, 10599-17-4; **8c**·2HCl, 93507-98-3; **9**, 78702-83-7; 1-bromo-3-chloropropane, 109-70-6; 1,2,3,6-tetrahydro-4-phenylpyridine dihydrochloride, 114597-76-1; 1-(2-pyridinyl)-piperazine, 34803-66-2; 1-phenylpiperazine, 92-54-6; *N*-propylphenethylamine, 27906-91-8.

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Synthesis, Pharmacological Action, and Receptor Binding Affinity of the Enantiomeric 1-(1-Phenyl-3-methylcyclohexyl)piperidines

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The cis and trans enantiomers of the 1-(1-phenyl-3-methylcyclohexyl)piperidines were prepared from either 3(*R*)- or 3(*S*)-methylcyclohexanone through the Bruylents reaction or a modified azide route, respectively. Separation of the intermediate amines **5** and **6** was achieved through chromatography or selective crystallization of a fumarate salt. The cis isomer **2b** had about one-third of the affinity of phencyclidine for the PCP receptor. The other isomers were less potent. There was a 40-fold difference between the binding affinity of the cis enantiomers **2a** and **2b** and a fourfold difference between the affinities of the trans enantiomers **1a** and **1b**. None of the compounds antagonized the stereotypy induced by phencyclidine in the rotorod assay in mice, after intraperitoneal introduction.

In 1981, Vincent et al.[1] examined the structure–activity relationships of various diastereomeric pairs of 1-(1-phenyl-2-methylcyclohexyl)piperidines and the 3-methyl and 4-methyl isomers. Those compounds having the methyl and phenyl group on the same side or "face" of the cyclohexyl ring were referred to as cis compounds; those with methyl and phenyl on opposite sides were called trans.[1] For the purpose of simplicity we retain these definitions when referring to the diastereomers. Potentially important differences in the receptor binding and behavioral characteristics of some of these pairs of "facial" isomers were noted. For instance, while the affinities of the 3-methylcyclohexyl "cis" and 3-methylcyclohexyl "trans" diastereomers for the phencyclidine (PCP) receptor

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