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The Discovery and Structure–Activity Relationships of 1,2,3,6-Tetrahydro-4-phenyl-1-[(arylcyclohexenyl)alkyl]pyridines. Dopamine Autoreceptor Agonists and Potential Antipsychotic Agents

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A novel dopamine (DA) autoreceptor agonist, 1,2,3,6-tetrahydro-4-phenyl-1-[(3-phenyl-3-cyclohexen-1-yl)methyl]pyridine (**14**), was identified. The structure–activity relationships surrounding this compound were studied by synthesis of analogues and evaluation of their dopaminergic activity. The cyclohexene substitution pattern was varied along with the length of the chain connecting the 1,2,3,6-tetrahydro-4-phenylpyridine to the cyclohexene. Compound **14**, having the 1,3-substitution pattern and a single methylene chain, was the most potent. The 1,2,3,6-tetrahydro-4-phenylpyridine could be replaced by other aryl-cyclic amines with a slight loss in activity. The phenyl group on the cyclohexene ring could be *para* substituted; electron-donating groups were better tolerated than electron-withdrawing groups. Finally, the enantiomers of **14** were resolved via the 1,1′-binaphthyl-2,2′-diyl hydrogen phosphate salts. Although both isomers were partial DA agonists, the (+)-enantiomer had higher intrinsic activity than the (−)-enantiomer. Syntheses were developed that allowed rapid preparation of analogues. An X-ray crystal structure determination of an intermediate identified the (+)-isomer of **14** as having *R* configuration. This compound, designated CI-1007 (PD 143188), was found to have antipsychotic-like activity in behavioral tests; in particular, it was orally active in the conditioned avoidance test in squirrel monkeys with an ED_{50} of 0.6 mg/kg. The overall profile suggests that (*R*)-(+)-**14** may be a clinically useful antipsychotic agent.

Introduction

The neurotransmitter dopamine (DA) is released upon stimulation of brain DA neurons where it can activate postsynaptic DA receptors. Released DA also stimulates presynaptic DA receptors, causing an inhibition of neuronal firing, synthesis, and release of DA.[1] This is one of several feedback mechanisms that control the level of DA in the synapse and hence the appropriate level of brain neuronal activity. It has been proposed that some of the symptoms of schizophrenia arise from DA neuronal hyperactivity.[2–4] While DA antagonists (e.g., haloperidol) are effective in the treatment of schizophrenia, their use may also be accompanied by serious neurological side effects such as extrapyramidal syndrome (EPS) and tardive dyskinesia (TD).[5] These side effects may result from excessive attenuation of brain DA neuronal activity.

This rationale has produced several approaches to discovering antipsychotic agents which may lack these side effects.[6] Stimulation of presynaptic DA autoreceptors should reduce the output of DA from the neuron without causing complete cessation of DA activity. This stimulation would have to be selective for autoreceptors as simultaneous postsynaptic stimulation may be counterproductive.[7] Indeed, DA agonists acting postsynaptically can exacerbate schizophrenic symptoms in patients.[8] There is no evidence for a structural difference between DA D2 presynaptic autoreceptors and postsynaptic receptors.[9] However it appears to be possible to selectively activate DA autoreceptors leading to the postulation that there is a difference in sensitivity between the two receptor sites. It has been proposed that DA autoreceptors have a high receptor reserve.[10] A partial DA D2 agonist may be able to selectively activate the presynaptic autoreceptors, thus modulating the level of DA in the synapse.[11] This mechanism could reduce the symptoms of schizophrenia without inducing the side effects associated with the postsynaptic blockade caused by DA antagonists.[12]

Various groups have shown that phenyltetrahydropyridines and arylpiperazines linked by a four-atom chain to an aromatic group (e.g., roxindole (**1**) and PD 120700 (**2**) in Figure **1**) possesses DA autoreceptor agonist properties.[13,14] We recently demonstrated that it was possible to incorporate this chain into a more rigid 1,4-cyclohexene system (e.g., **3**) and retain DA autoreceptor agonist activity.[15] In our search for novel DA autoreceptor agonists, we have studied additional cyclohexene systems. In this paper, we report the discovery of a 1,3-cyclohexenylmethyl series (**4**) with DA autoreceptor agonist activity.

Chemistry

The 2-substituted cyclohexene **10** (Table **1**) was prepared from commercially available ethyl 2-oxocyclohexanecarboxylate (**5**) (Scheme **1**). In this case, addition of PhMgBr to ketone **9** and elimination of the resulting

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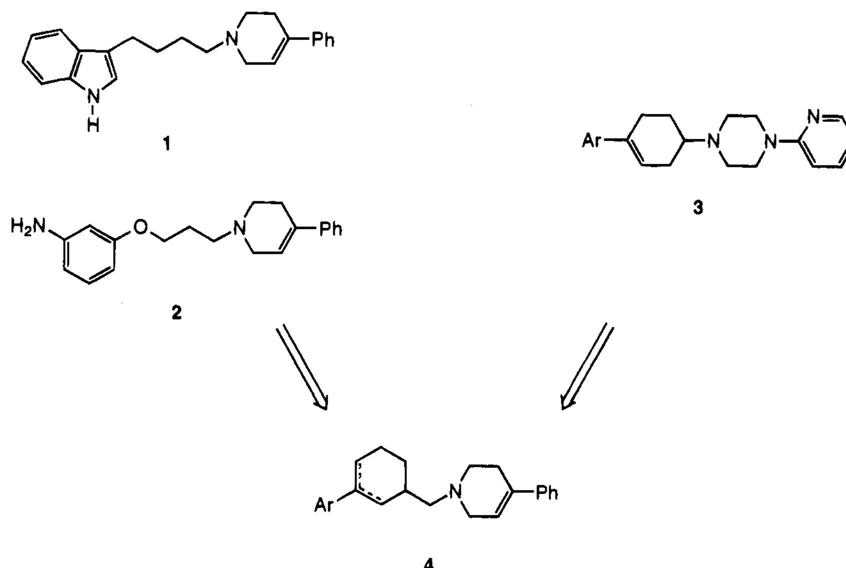


Figure 1. Derivation of the 1,3-cyclohexene series.

Table 1. DA Activity of Cyclohexene Isomers and Methylene-Bridged Homologues of 14

compd	point of attachment	n	DA D2 binding IC_{50} (nM)[a]	inhibition of mouse LMA ED_{50} (mg/kg ip)[b]	% effect on striatal DOPA synthesis after GBL[c]
10	6	1	3936	>30	NT[d]
14	5	1	112	1.1 (0.8–1.6)	−86 ± 7.9
18	4	1	1000	12.1 (9.2–16.0)	−32 ± 5.4
15	3	1	420	2.5 (1.5–4.2)	−34 ± 11.1
21	5	0	9207	≈30	NT
27	5	2	635	10.9 (6.2–19.2)	−49 ± 6.5

[a] [^{3}H]Spiperone; IC_{50} values were obtained from four to six concentrations, run in triplicate, by a nonlinear regression analysis. [b] LMA = locomotor activity; ED_{50} (95% confidence range) values were generated from three to six doses; 6–18 animals were used per dose. [c] Animals were administered test compounds (10 mg/kg) 60 min and GBL (750 mg/kg ip), except for the control group, 30 min before sacrifice. All animals were given NSD (100 mg/kg ip) 30 min before sacrifice. Values are expressed as percent reversal of the increase in DOPA induced by GBL ± SEM. For control DOPA levels in vehicle-treated and GBL-treated animals, see the Experimental Section. [d] NT = not tested.

diastereomeric alcohols led exclusively to **10**. The reaction conditions shown were typical of many of the reactions employed to synthesize other analogues.

3-Oxocyclohexanecarboxylic acid[16] (**11**) was used to prepare the 3- and 5-substituted cyclohexenes (Scheme 2). Conversion of **12** to **13** was efficient on a large scale and could be carried out without purifying the intermediates. Overall, a 63% yield of **13** was obtained based on **11**. Addition of PhLi or PhMgBr to **13** followed by elimination of the resulting alcohols gave a mixture of double-bond regioisomers. Separation using medium pressure liquid chromatography (MPLC) allowed isolation of the 5-cyclohexene **14** and its 3-isomer, **15**.

The 4-substituted cyclohexene **18** was made via coupling/reduction of the known 4-phenyl-3-cyclohexenecarboxylic acid (**16**)[17] with **7** (Scheme 3).

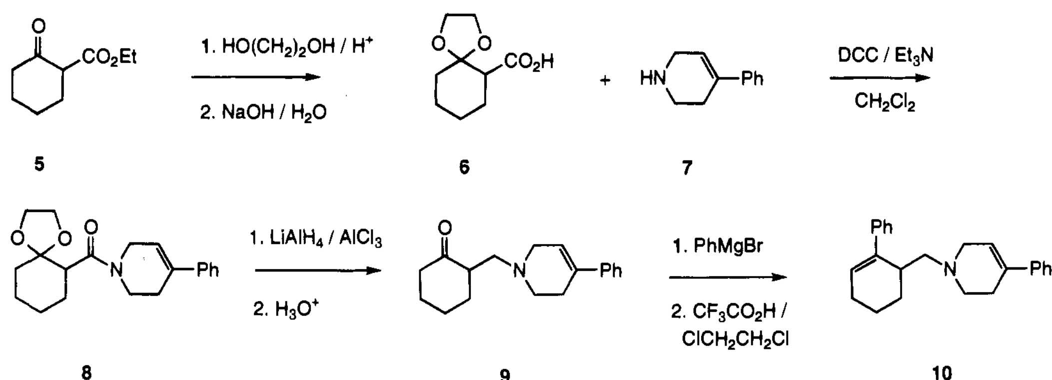
Analogue **21**, having the 5-cyclohexene directly linked to the 1,2,3,6-tetrahydro-4-phenylpyridine, was prepared using the route shown in Scheme 4. Treatment of **20** with PhMgBr or PhLi gave only the retro-Michael addition products. However, with PhLi/$CeCl_3$, addition to the carbonyl group occurred. The resulting isomeric alcohols were eliminated with CF_3CO_2H to give a 1:1 mixture of isomeric olefins. Compound **21** was isolated from this mixture by chromatography.

3-Phenyl-3-cyclohexenecarboxylic acid (**25**) was seen as a intermediate useful for the synthesis of many compounds, including an improved synthesis of **14** which avoided the concurrent production of **15**. The regiospecific synthesis of **25** is outlined in Scheme 5. δ-Valerolactone (**22**) could not be alkylated directly with α-bromoacetophenone. However, the sodium anion of lactone **23** reacted smoothly with α-bromoacetophenone. The ester was saponified/decarboxylated via heating with acid to give the cyclization precursor **24**. Treatment of **24** with triphenylphosphine hydrobromide opened the lactone, brominated the alcohol, and formed the Wittig salt. This salt was exposed to dimsyl sodium to form the betaine which undergoes intramolecular cyclization to give **25** as the sole double-bond isomer.

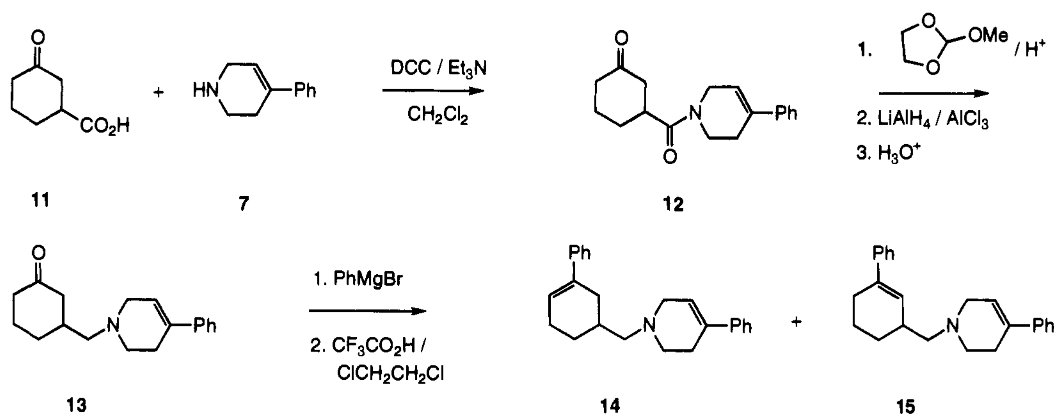
Compound **27**, the two-methylene analogue of **14**, was prepared by homologation of **25** (Scheme 5). Coupling of **25** with the corresponding amines followed by reduction allowed a convenient synthesis of compounds **28**–**31** in isomerically pure form (Table 2).

Compound **14** was initially resolved via crystallization of the diastereomeric 1,1′-binaphthyl-2,2′-diyl hydrogen phosphate salts (Scheme 6). Resolution of **11** with brucine to give (***R***)-(−)-**11** had been reported by Numata et al.[18] We repeated the resolution and confirmed the *R* assignment by single-crystal X-ray structure determination of (−)-**11**·brucine salt (Figure 2). The use of (***R***)-**11** as starting material for the route shown in Scheme 2 gave (+)-**14**, identifying it as the *R*-enantiomer. Resolution of **25** with (*S*)-α-methylbenzylamine followed by coupling with **7** and reduction also gave (***R***)-(+)-**14**. This proved that resolution of **25** with (*S*)-α-methylbenzylamine gave (***R***)-**25** and with (*R*)-α-methylbenzylamine (***S***)-**25**.

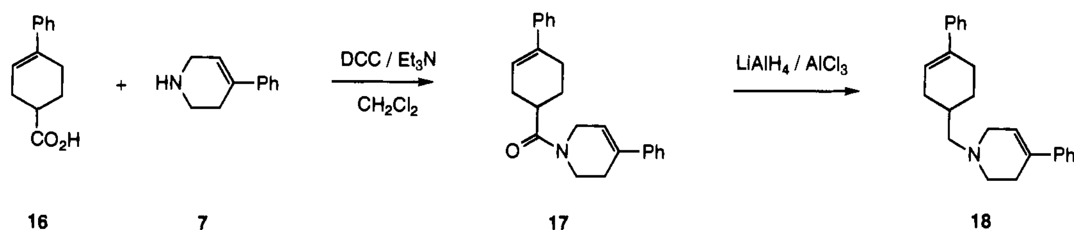
Scheme 1. Synthesis of **10**



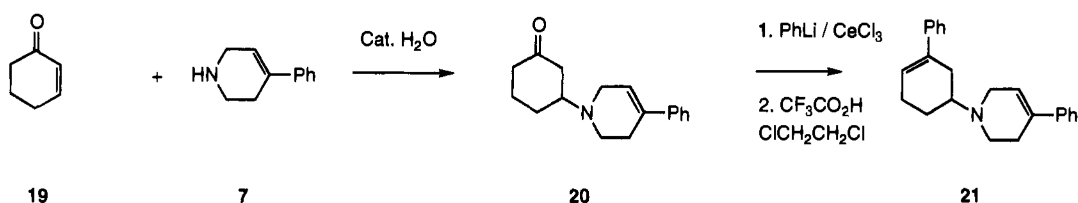
Scheme 2. Synthesis of **14** and **15**



Scheme 3. Synthesis of **18**



Scheme 4. Synthesis of **21**



Compound (***R***)-(−)-**11** was used to make compounds **32**–**36** in Table 3. Processing as described in Scheme 2 gave a mixture of double-bond isomers, from which the 5-isomers could be isolated by chromatography.

Pharmacology

All compounds were tested for their *in vitro* binding affinity for rat striatal DA D2 receptors using [^{3}H]-spiperone.[19] Compounds with significant binding affinity were tested for inhibition of exploratory locomotor activity (LMA) in mice and rats as a behavioral measure of DA autoreceptor agonist activity.[20] Higher doses of compound were tested to see if stimulation of LMA occurred, signaling postsynaptic DA receptor activation. The effect of test compounds on the γ-butyrolactone (GBL)-induced increase in the rate of L-dihydroxyphenylalanine (DOPA) synthesis in rat corpus striatum[21] was used as a neurochemical measure of DA autoreceptor efficacy.

Results and Discussion

Table 1 summarizes the effects of varying the position of attachment of the (phenyltetrahydropyridinyl)methyl group to the cyclohexenyl ring. The most active isomer in this series was the compound with the group attached to the 5-position of the cyclohexene ring. The 3-isomer, having some symmetry with the 5-isomer, showed weaker activity. Hence **14** was the most interesting compound from this series, and we explored its SAR further.

In the previously described study of the 1,4-substituted cyclohexenes, the length of the chain linking the

Scheme 5. Syntheses of **25** and **27–31**

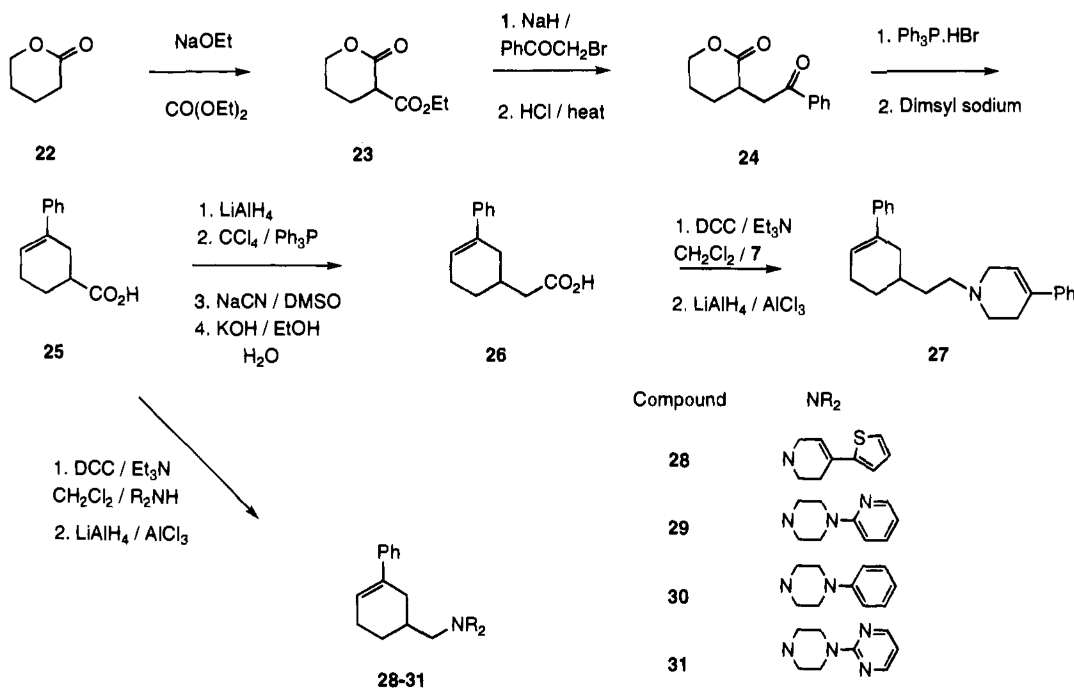


Table 2. DA Activity of 1,2,3,6-Tetrahydro-4-phenylpyridine Replacements

compd	NR	DA D2 binding IC_{50} (nM)[a]	inhibition of mouse LMA ED_{50} (mg/kg ip)[b]	% effect on striatal DOPA synthesis after GBL[c]
14		112	1.1 (0.8–1.6)	−86 ± 7.9
28		170	1.5 (0.9–2.5)	NT[d]
29		141	0.8 (0.6–1.1)	−61 ± 9
30		424	2.1 (1.2–3.5)	−7.5 ± 12.5
31		354	8.5 (3.3–21.6)	NT

[a–d] See footnotes for Table 1.

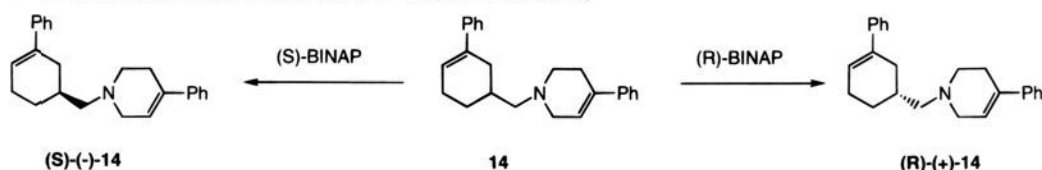
aryl-cyclic amine to the cyclohexene was critical.[15] In that series, we found that compounds containing a single methylene link were inactive but compounds with an ethylene or no link were potent DA agonists. Table 1 summarizes the effects of removing or extending the methylene link of **14**. When the nitrogen atom is attached directly to the cyclohexene ring (compound **21**), all DA receptor-binding activity was lost. The ethylene isomer **27** shows a drop in DA receptor binding and LMA potency. These results are in contrast to those seen with the **1**,4-series. However, **3** and **14** both share a four-carbon link between the aryl-cyclic amine and the cyclohexenyl aryl moiety, further suggesting that this is an important feature for DA autoreceptor activity.

In the **1**,4-series, a 2-pyridylpiperazine group attached to the phenylcyclohexene produced potent compounds.[15] We examined this and a number of other aryl-cyclic amine replacements for the 1,2,3,6-tetrahydro-4-phenylpyridine group of **14**. Table 2 shows that the replacements were well tolerated. The parent **14** and the 2-pyridylpiperazine-containing **29** were the most interesting compounds, with **14** having slightly better effects in reversing the GBL-induced increases in brain DOPA synthesis.

We had established so far that the 1,2,3,6-tetrahydro-4-phenylpyridine was best attached to the 5-position of a phenylcyclohexene unit via a methylene group. At this point we resolved **14** into its enantiomers. Table 3 shows that the DA binding and the effect on rat LMA did not change significantly for the enantiomers versus the racemate. However there were significant changes in the effects on DOPA synthesis. The *R*-enantiomer and the racemate decreased DOPA synthesis, consistent with DA autoreceptor activation. The *S*-enantiomer caused a 50% increase in DOPA levels above that seen in GBL-treated controls at 10 mg/kg ip, a DA antagonist-like effect. It was clear from these results that (***R***)-(+)-**14** was responsible for the DA agonist activity of (±)-**14**. Therefore the remaining studies were carried out on the *R*-enantiomers.

Table 3 describes the effects of *para* substituents on the phenyl ring of the phenylcyclohexene moiety. Relatively bulky groups (e.g., the methoxy in (***R***)-(+)-**35**) were tolerated, suggesting that the changes were not solely due to steric crowding. In support of this, the chloro analogue (***R***)-(+)-**33** showed virtually no DA receptor affinity. The fluoro substituent had no effect on the DA binding versus the phenyl parent (***R***)-(+)-**14** but caused a significant decrease in potency in LMA in rats. A change in physicochemical characteristics and/or an effect on metabolism could have adversely affected the bioavailability of this compound. The methyl analogue (***R***)-(+)-**32** showed moderate DA receptor affinity, and the effects in the rat LMA model were similar to those of the phenyl parent (***R***)-(+)-**14**. The trifluoromethyl analogue (***R***)-(+)-**36** lost almost all DA receptor

Scheme 6. Resolution of **14** and Confirmation of Stereochemistry



O
CO2H
11
Brucine
(R)-(-)-11
As in Scheme 2
R
N
Ph

Compound	R
(R)-(+)-14	H
(R)-(+)-32	Me
(R)-(+)-33	Cl
(R)-(+)-34	F
(R)-(+)-35	MeO
(R)-(+)-36	CF_3

BINAP = 1,1'-binaphthyl-2,2'-diyl hydrogen phosphate

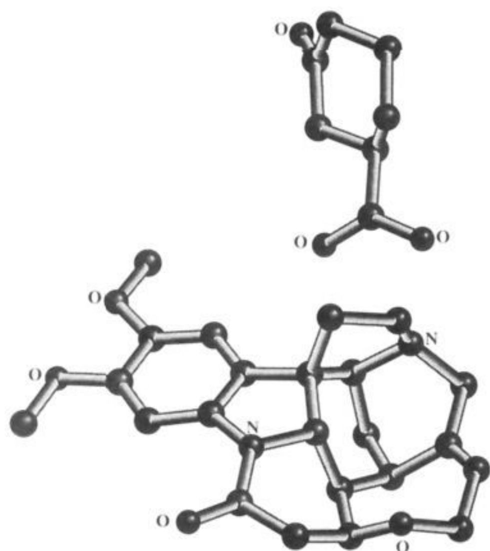
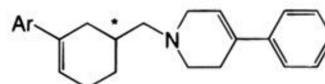


Figure 2. Perspective view of the structure of (−)-**11**·brucine salt.

Table 3. DA Activity of the Enantiomers and Aryl Analogues of **14**



compd	configuration	Ar	DA D2 binding IC_{50} (nM)[a]	inhibition of rat LMA ED_{50} (mg/kg po)[b]	% effect on striatal DOPA synthesis after GBL[c]
(±)-**14**	*R/S*	Ph	112	3.0 (1.8–5.0)	−86 ± 7.9
(+)-**14**	*R*	Ph	53 ± 3.0	2.9 (2.1–4.1)	−66 ± 7.1
(−)-**14**	*S*	Ph	113 ± 11.5	3.8 (2.9–5.1)	50 ± 10.4[e]
32	*R*	4-MePh	328	5.8 (3.2–10.4)	−42 ± 4.4
33	*R*	4-ClPh	4634	19.9 (6.9–10.4)	NT[d]
34	*R*	4-FPh	76	17.5 (12.5–24.7)	−74 ± 5.6
35	*R*	4-MeOPh	100	5.6 (2.9–10.8)	−47 ± 7.7
36	*R*	$4\text{-}CF_3Ph$	2554	NT	NT

[a–d] See footnotes for Table 1. [e] Increase above controls.

affinity. Given that the methyl analogue (***R***)-(+)-**32** was active, the strongly electron-withdrawing nature of the CF_3 group is most likely responsible for this loss of activity.

Compound (***R***)-(+)-**14** was selected for further evaluation. A summary of these tests is shown in Table 4 with a DA antagonist, haloperidol, and a full DA agonist, apomorphine, as reference compounds. These compounds were screened for their *in vitro* binding affinity for rat striatal D2 receptors using the DA agonist ligand [^{3}H]-*N*-propylnorapomorphine,[22] for rat striatal D1 receptors using [^{3}H]SCH 23390,[23] and for cloned human D2L, D3, and D4.2 receptors expressed in CHO-K1 cells using [^{3}H]spiperone.[24] These studies show that (***R***)-(+)-**14** is selective for the rat striatal DA D2 receptor versus the D1 receptor. Compound (***R***)-(+)-**14** also possesses good affinities for human DA D2, D3, and D4.2 receptors expressed in CHO-K1 cells. The DA D3/D4.2 affinities in addition to its D2 affinity may account for some of its pharmacological profile. Compound (***R***)-(+)-**14** has weak binding affinities for α_1 (K_i = 1613 ± 188 nM) and α_2 (K_i = 413 ± 95 nM) adrenergic receptors in rat cortex using [^{3}H]prazosin[25] and [^{3}H]MK-912,[26] respectively. It showed moderate affinity for 5-HT-1A receptors (K_i = 100 ± 20 nM) in rat hippocampus using [^{3}H]-8-OH-DPAT.[27] However, biochemical studies showed that (***R***)-(+)-**14** did not alter the synthesis of 5-HT in various rat brain areas, indicating lack of any *in vivo* functional activity on 5-HT neurons. Compounds were tested for their ability to inhibit cAMP accumulation in GH_4C_1 cells transfected with the human DA D2 receptor.[28] In this assay, (***R***)-(+)-**14** shows a partial agonist profile, with apomorphine showing a full agonist response and haloperidol showing no response. Compound (***R***)-(+)-**14** potently reverses GBL-stimulated accumulation of DOPA in rats and strongly

Table 4. Pharmacological Profile of (*R*)-(+)-14

test	(*R*)-(+)-14	haloperidol	apomorphine
dopamine receptor binding (K_i, nM)[a]			
rat D1 ([^{3}H]SCH 23390)	>10000	467 ± 29.9	221 ± 4.41
rat D2 ([^{3}H]spiperone)	53.0 ± 3.0	1.86 ± 0.20	17.3 ± 3.20
rat D2 ([^{3}H]NPA)	3.30 ± 0.08	NT[b]	2.20 ± 0.73
human D2L ([^{3}H]spiperone)	25.5 ± 1.63	0.50 ± 0.17	28 ± 4.8
human D3 ([^{3}H]spiperone)	16.6 ± 3.83	0.69 ± 0.14	7.8 ± 1.6
human D4.2 ([^{3}H]spiperone)	90.9 ± 11.0	NT	NT
intrinsic activity relative to quinpirole[c]	0.53 ± 0.10	0.00	1.00
reversal of DOPA accumulation in rats after GBL (ED_{50}, mg/kg ip)[d]			
striatum	3.0 (2.05–4.46)	NE[e]	0.28 (0.14–0.59)
mesolimbic	0.3 (0.19–0.47)	NE	NT
decrease of DA neuron firing rate in rats (2.5 mg/kg ip)	99 ± 4%	NE	100%[f]
inhibition of locomotor activity (ED_{50}, mg/kg)[g]			
in mice ip	1.3 (0.9–1.8)	0.3 (0.2–0.5)	0.36 (0.14–0.90)[h]
in rats po	2.9 (2.1–4.1)	0.25 (0.21–0.30)	0.03 (0.02–0.05)[i]
inhibition of conditioned avoidance in squirrel monkeys (ED_{50}, mg/kg po)[j]	0.6 (0.4–0.7)	0.5 (0.4–0.6)	stim[k]

[a] See footnote a, Table 1. [b] NT = not tested. [c] Maximal response relative to quinpirole in the reversal of forskolin-stimulated cAMP accumulation in cells transfected with the human DA D2 receptor. [d] See footnote c, Table 1. [e] NE = no effect. [f] 0.25 mg/kg ip. [g] See footnote b, Table 1. [h] Stimulation of LMA occurs at higher doses. [i] Administered sc; stimulation occurs at higher doses. [j] ED_{50} (95% confidence range) values were generated from three doses, eight monkeys were used per dose. [k] Stimulation (increase in response rate) seen at 0.156 and 0.312 mg/kg sc.

inhibits DA neuronal firing in rats. Both these effects are similar to those seen with apomorphine and are consistent with DA autoreceptor activation; haloperidol has no effect in these tests. DA agonists with selectivity for the autoreceptor inhibit spontaneous LMA in rodents. Compound (*R*)-(+)-**14** exhibits good potency in this test administered ip in mice and orally in rats. At higher doses, apomorphine causes stimulation of locomotor activity via postsynaptic receptor stimulation. Compound (*R*)-(+)-**14** showed no stimulation at doses up to 100 mg/kg in LMA, demonstrating lack of agonist effects at postsynaptic DA receptors. Compound (*R*)-(+)-**14** was evaluated in the conditioned avoidance test[29] in squirrel monkeys, a primate test which has been correlated with antipsychotic activity in humans.[30] We have previously described a number of DA autoreceptor agonists that are efficacious in this test.[14] Compound (*R*)-(+)-**14** is very potent (ED_{50} = 0.6 mg/kg) in this test when administered orally, being equivalent to the clinically effective antipsychotic haloperidol.

Conclusion

This study has identified a novel series of tetrahydro-4-phenyl-[(3-arylcyclohexen-1-yl)methyl]pyridines with DA receptor activity. As with previous series, optimal activity is obtained when the aryl group is attached to the tetrahydro-4-phenylpyridine moiety via a four-atom link. Examination of the SAR of this series has led to the identification of (*R*)-(+)-**14** (CI-1007) as a DA autoreceptor agonist and partial DA agonist. Compound (*R*)-(+)-**14** binds selectively to human D2 family receptors. It blocks GBL-stimulated brain DA synthesis and inhibits DA neuronal firing in rats, effects consistent with DA autoreceptor activation. Compound (*R*)-(+)-**14** is active in inhibition of exploratory locomotor activity in rodents and inhibits conditioned avoidance in monkeys. Thus (*R*)-(+)-**14** appears to produce antipsychotic-like effects comparable to the clinically efficacious DA antagonist haloperidol. Because of its novel mechanism, (*R*)-(+)-**14** shows potential as an antipsychotic agent with a reduced liability for DA antagonist-like side effects.

Experimental Section

Melting points were determined on a Gallenkamp or a Thomas Hoover capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were determined for $CDCl_3$ or DMSO-d_6 solutions on Varian Gemini-200, XL-300, or 400 and Bruker AM 250 spectrometers. Mass spectra were obtained on a Finnigan 4500 or VG Analytical 7070E/HF mass spectrometer. IR spectra were recorded on a Nicolet MX-1 FT spectrophotometer. Elemental analyses were performed by the Analytical Research Section at Parke-Davis, Ann Arbor, MI. TLC was performed on 0.25 mm silica gel F254 (E. Merck) glass plates. Medium pressure liquid chromatography was performed on silica gel (E. Merck grade 60, 230–400 mesh, 60 Å) or prepacked LOBAR silica gel columns (E. Merck, No. 10401,2). Column chromatography was performed on silica gel (E. Merck grade 60, 230–400 mesh, 60 Å) or TLC grade silica gel (Aldrich Chemical Co., No. 28,851-9). Reversed-phase HPLC was performed on Beckman Ultrasphere 5 μm ODS 4.6 mm × 25 cm columns eluting at 1.5 mL/min, and compounds were detected using UV detection at 254 nm, pH 3.0 buffer was prepared by mixing 28 mL of Et_3N in 4 L of HPLC grade water and adjusting the pH to 3.0 with phosphoric acid. Chiral HPLC was performed on Daicel OJ 4.6 mm × 25 cm silica gel columns eluting with hexane/2-propanol mixtures (+1% formic acid for acidic compounds) at 0.5 mL/min. Gas chromatography was performed on a Shimadzu GC-14A chromatograph using a 5 ft 3% SE-30 on 100/120 Gaschrom Q column. Helium carrier was used at 5 mL/min, and column temperature was linearly programmed from 100 to 220 °C over 18 min with flame ionization detection. Ether refers to diethyl ether.

1,4-Dioxaspiro[4.5]decan-6-oic Acid (6). Ethyl 2-cyclohexanonecarboxylate (**5**) (96.2 g, 0.565 mol), ethylene glycol (38.6 g, 0.621 mol), and *p*-toluenesulfonic acid (1.0 g) were stirred in benzene (300 mL) at reflux overnight in a flask equipped with a Dean–Stark trap. The reaction mixture was washed with saturated $NaHCO_3$ (2 × 100 mL) and water (2 × 100 mL), dried over $MgSO_4$, filtered, and evaporated to a yellow oil. This oil was dissolved in THF (575 mL) and NaOH (27.1 g, 0.678 mol) in H_2O (100 mL) added. This mixture was stirred at reflux overnight. After cooling, the mixture was acidified to pH 4 with acetic acid. The organic phase was separated and washed with water (3 × 200 mL), dried over $MgSO_4$, filtered, and evaporated to leave 72.6 g of a yellow solid. This solid was recrystallized from hexane/EtOAc to give **6** (65.7 g, 63%) as a white solid: mp 101–102.5 °C; ^{1}H NMR ($CDCl_3$) δ 4.05 (s, 4H), 2.60–2.80 (m, 1H), 1.40–2.10 (m, 8H). Anal. ($C_9H_{14}O_4$) C, H.

1-[(1,4-Dioxaspiro[4.5]decan-6-yl)carbonyl]-1,2,3,6-tetrahydro-4-phenylpyridine (8). Standard Coupling Pro-

cedure. A mixture of **6** (10.0 g, 53.7 mmol), 1,2,3,6-tetrahydro-4-phenylpyridine hydrochloride (**7**) (12.6 g, 64.4 mmol), dicyclohexylcarbodiimide (13.3 g, 64.4 mmol), 1-hydroxybenzotriazole hydrate (8.71 g, 64.4 mmol), and Et_3N (15 mL, 0.108 mol) in CH_2Cl_2 (100 mL) was stirred overnight at room temperature under N_2. The mixture was filtered and evaporated to a solid. This solid was slurried in EtOAc (200 mL) and filtered. The filtrate was washed with 5% citric acid (150 mL), 2 N Na_2CO_3 (150 mL), and saturated brine (150 mL). After drying over $MgSO_4$, the mixture was filtered and the filtrate evaporated to leave **8** as a yellow oil (17.5 g): ^1H NMR ($CDCl_3$) δ 7.20–7.42 (m, 5H), 6.08 (br s, 1H), 3.50–4.30 (m, 8H), 2.92 (m, 1H), 2.43–2.65 (m, 2H), 1.21–2.20 (m, 8H); TLC (50% EtOAc/hexane) R_f = 0.20.

2-[(3,6-Dihydro-4-phenyl-1(2*H*)-pyridinyl)methyl]cyclohexanone (9). Standard Reduction Procedure. A solution of $AlCl_3$ (2.39 g, 18.0 mmol) in ether (100 mL) was added dropwise to a stirring suspension of $LiAlH_4$ (2.04 g, 53.7 mmol) in THF (100 mL) at 0 °C under N_2. The gray suspension was stirred for 30 min, and a solution of **8** (17.5 g, 53.7 mmol) in THF (100 mL) was added dropwise. The mixture was stirred at room temperature for 12 h and cooled in an ice bath, and the reaction was quenched by dropwise addition of water (2.2 mL) followed by 25% NaOH (9.6 mL). The mixture was filtered through Celite and evaporated to leave a yellow oil which solidified on standing (16.5 g). The solid (16.5 g, 53.7 mmol) was stirred at reflux in THF (100 mL) and 1 N HCl (100 mL) for 2 h. The mixture was basified with 1 N NaOH and extracted with EtOAc (3 × 150 mL). The extracts were washed with water (300 mL) and saturated brine (300 mL), dried over $MgSO_4$, and filtered. The filtrate was evaporated to leave the ketone as a yellow oil (10.5 g). This oil was purified by column chromatography on silica gel (230–400 mesh) eluting with 50% EtOAc/hexanes to give **9** as a white solid (9.21 g, 64% from **6**) which was characterized as the hydrochloride: mp 187–188 °C; ^1H NMR ($CDCl_3$) δ 12.37 (br s, 1H), 7.32 (br s, 5H), 5.93 (br s, 1H), 1.30–4.10 (m, 17H). Anal. ($C_{18}H_{23}NO{\cdot}HCl{\cdot}0.08H_2O$) C, H, N, H_2O.

1,2,3,6-Tetrahydro-4-phenyl-1-[(2-phenyl-2-cyclohexen-1-yl)methyl]pyridine (10). Standard Addition and Elimination Procedure. Ketone **9** (4.00 g, 14.8 mmol) in THF (100 mL) was added dropwise over 20 min to PhMgBr (9.86 mL of 3.0 M in ether, 29.6 mmol) in ether (100 mL) at 0 °C under N_2 and stirred for 3 h at 0 °C. Saturated NH_4Cl (200 mL) was added; the organic layer was washed with saturated brine (200 mL), dried over $MgSO_4$, filtered, and evaporated to leave a yellow foam (5.7 g). The foam was purified by column chromatography on silica gel (230–400 mesh) eluting with 70% EtOAc/hexanes to give the alcohols as a mixture (4.18 g). This mixture (2.22 g) was stirred at reflux in 1,2-dichloromethane (25 mL) and CF_3CO_2H (2.44 mL) for 2 h. The solvent was evaporated, and the residue was treated with 2 N Na_2CO_3 (50 mL). The mixture was extracted with CH_2Cl_2 (2 × 50 mL); the extracts were washed with saturated brine (75 mL), dried over $MgSO_4$, filtered, and evaporated to leave a white solid. This solid was purified by column chromatography on silica gel (TLC grade) eluting with 25% EtOAc/hexane (loading on with a minimum of CH_2Cl_2) and recrystallized from hot EtOH to give 10 as an off-white solid (0.40 g, 25%): mp 93–95 °C; IR ($CHCl_3$ solution) 2932, 1598, 1493, 1445, 1130, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.10–7.40 (m, 10H), 5.95–6.10 (m, 2H), 2.70–3.30 (m, 4H), 2.35–2.55 (m, 4H), 2.05–2.25 (m, 4H), 1.60–1.80 (m, 3H); HPLC (reversed-phase, 60% pH 3 buffer: 40% CH_3CN) 9.98 min (100%); MS (CI) *m/z* 331 (27), 330 (100), 172 (77). Anal. ($C_{24}H_{27}N$) C, H, N.

1,2,3,6-Tetrahydro-1-[(3-oxocyclohexyl)carbonyl]-4-phenylpyridine (12). A standard coupling between 11 (25.6 g, 0.180 mol) and **7**·HCl (39.4 g, 0.200 mol) gave an orange oil (55.9 g, >100%). TLC showed the oil to be one spot with a little base line material. The oil could be used directly in the following reaction or purified by column chromatography on silica gel eluting with 50% EtOAc/hexane → 100% EtOAc to give **12** as a pale yellow oil: ^1H NMR ($CDCl_3$) δ 7.20–7.50 (m, 5H), 6.07 (d, 1H, J = 14.6 Hz), 4.23 (d, 2H, J = 15.0 Hz), 3.60–3.95 (m, 2H), 3.00–3.25 (m, 1H), 1.60–2.80 (m, 10H).

3-[(3,6-Dihydro-4-phenyl-1(2*H*)-pyridinyl)methyl]cyclohexanone (13). Crude **12** (55.9 g, 0.200 mol) was stirred in CH_2Cl_2 (150 mL) with 2-methoxy-1,3-dioxolane (40 mL) and $MeSO_3H$ (1 mL) at room temperature for 3 days. The mixture was washed with 2 N Na_2CO_3 (150 mL), dried over $MgSO_4$, filtered, and evaporated to leave the amide as a yellow oil. A standard reduction of the amide to the amine gave a yellow oil. This oil was heated to reflux in acetone (300 mL) and 2 N HCl (300 mL) for 6 h. The solvent was mostly evaporated, and the remainder was treated with 2 N Na_2CO_3 (500 mL). This mixture was extracted with CH_2Cl_2 (3 × 300 mL); the extracts were dried over $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography on silica gel eluting with 50% EtOAc/hexane to give **13** as a yellow wax (39.4 g, 80% from the acid): IR (KBr) 2826, 1703, 1141, 749, 693, 499 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.15–7.60 (m, 5H), 6.07 (br s, 1H), 3.12 (br s, 2H), 3.00–3.25 (m, 1H), 1.20–2.80 (m, 15H); HPLC (reversed-phase, 80% pH buffer:20% MeCN) 6.36 min (100%); MS (CI) *m/z* 270 (100), 172 (57). Anal. ($C_{18}H_{23}NO$) C, H, N.

1,2,3,6-Tetrahydro-4-phenyl-1-[(3-phenyl-2-cyclohexen-1-yl)methyl]pyridine (15) and 1,2,3,6-Tetrahydro-4-phenyl-1-[(3-phenyl-3-cyclohexen-1-yl)methyl]pyridine (14). A standard addition/elimination of PhMgBr with **13** gave a mixture of **14** and **15** (14.7 g). This mixture was separated using MPLC on LOBAR silica columns eluting with 5% EtOAc/hexane (loading on with a minimum of CH_2Cl_2) to give **15** (3.64 g) as a tan solid: mp 124–126 °C; IR (KBr) 2926, 746, 692 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.39–7.42 (m, 4H), 7.18–7.34 (m, 6H), 6.11 (br s, 2H), 3.20 (br s, 2H), 2.72–2.77 (m, 2H), 2.50–2.59 (m, 3H), 2.43–2.46 (m, 4H), 1.92 (m, 2H), 1.66–1.77 (m, 1H), 1.31–1.42 (m, 1H); HPLC (reversed-phase, 40% pH 3.0 buffer:60% MeCN) 11.48 min (100%); TLC (silica gel, 25% EtOAc/hexane) R_f 0.55; MS (EI) *m/z* 330 (3.6), 172 (100). Anal. ($C_{24}H_{27}N$) C, H, N.

14: 7.04 g as a yellow powder; mp 90–94 °C; IR (KBr) 3434 (br), 2910, 1135, 745, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.15–7.55 (m, 5H), 6.10 (br s, 2H), 3.20 (br s, 2H), 1.75–2.80 (m, 13H), 1.20–1.45 (m, 1H); HPLC (reversed-phase, 40% pH 3.0 buffer: 60% MeCN) 10.22 min (100%); TLC (silica gel, 25% EtOAc/hexane) R_f = 0.50; MS (CI) *m/z* 330 (100), 172 (57). Anal. $C_{24}H_{27}N$) C, H, N.

1,2,3,6-Tetrahydro-4-phenyl-1-[(4-phenyl-3-cyclohexen-1-yl)methyl]pyridine (18). A standard coupling between **16**[17] and **7**·HCl followed by a standard reduction gave **18** which was isolated as the hydrochloride salt: mp 213–215 °C; IR (KBr) 2915, 743, 694 cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.22–7.56 (m, 10H), 6.15–6.19 (m, 2H), 4.06 (d, 1H, J = 17.1 Hz), 3.78–3.82 (m, 1H), 3.63–3.66 (m, 1H), 3.21–3.30 (m, 1H), 3.10–3.20 (m, 2H), 2.96–3.01 (m, 1H), 2.74 (d, 1H, J = 17.4 Hz), 2.49–2.54 (m, 3H), 1.82–2.22 (m, 3H), 1.41–1.51 (m, 1H); MS (EI) *m/z* 330 (18), 329 (68), 328 (100), 172 (97). Anal. ($C_{24}H_{27}N{\cdot}HCl$) C, H, N.

3-(3,6-Dihydro-4-phenyl-1(2*H*)-pyridinyl)cyclohexanone (20). 2-Cyclohexenone (9.68 mL, 0.1 mol) and **7** (15.92 g, 0.1 mol) were combined with a catalytic amount of H_2O (2.5 mL). Within minutes the mixture became warm and turned solid. This solid was dissolved in EtOH (250 mL), and the solution was heated to reflux for 4 h. The reaction mixture was cooled, dried over $MgSO_4$, and concentrated to give **20** as an unstable yellow solid (24.0 g, 93%): mp 87–88 °C; IR (KBr) 2947, 1703, 1445, 755, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.23–7.39 (m, 5H), 6.06–6.08 (m, 1H), 3.25–3.38 (m, 2H), 2.76–2.95 (m, 3H), 2.56–2.69 (m, 3H), 2.28–2.49 (m, 3H), 2.09–2.13 (m, 2H), 1.76–1.81 (m, 1H), 1.53–1.68 (m, 1H); MS (EI) *m/z* 255 (64), 198 (33), 159 (100), 130 (46).

1,2,3,6-Tetrahydro-4-phenyl-1-(3-phenyl-3-cyclohexen-1-yl)pyridine (21). $CeCl_3$ (7.72 g, 31.0 mmol) was dried overnight under high vacuum. Dry THF (80 mL) was added, and the mixture was stirred at room temperature for 2 h. PhLi (17.2 mL of 1.8 M in hexanes, 31.0 mmol) was added dropwise to the slurry at −78 °C, and the mixture was stirred for 30 min. Compound **20** (5.0 g, 19.6 mmol) in dry THF (50 mL) was added dropwise to the reaction mixture, and the mixture was stirred for 3 h at −78 °C. Saturated aqueous NH_4Cl was added; the mixture was allowed to warm to room temperature

and filtered through Celite. The filtrate was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The organic extracts were dried over $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography on silica gel (230–400 mesh) eluting with 1% MeOH/CH_2Cl_2 to give a mixture of the diastereomeric alcohols. Trifluoroacetic acid (1.4 mL, 15 mmol) was added to the alcohols (1.0 g, 3.0 mmol) in 1,2-dichloroethane (30 mL), and the mixture was heated to reflux for 10 h. The reaction mixture was cooled and neutralized with saturated aqueous $NaHCO_3$. The aqueous layer was separated and extracted with CH_2Cl_2 (3 × 50 mL). The organic extracts were dried over $MgSO_4$, filtered, and evaporated. The 1:1 mixture of double-bond regioisomers was separated by MPLC on a LOBAR silica gel column eluting with 5% EtOAc/hexane to give **21** as a yellow oil which was isolated as the HCl salt (0.31 g, 30%): mp 217–218 °C; IR (KBr) 3420 (br), 2898, 2372, 1445, 749, 696 cm^{-1}; ^1H NMR (free base in $CDCl_3$) δ 7.25–7.40 (m, 10H), 6.10–6.13 (br d, 1H), 6.03 (br s, 1H), 4.02–4.20 (m, 1H), 3.22–3.81 (m, 5H), 2.87–3.12 (m, 2H), 2.70–2.78 (br d, 1H), 2.35–2.60 (m, 3H), 1.92–2.17 (m, 1H); MS (EI) *m/z* 315 (25), 185 (100), 115 (36). Anal. ($C_{23}H_{25}N{\cdot}HCl{\cdot}0.12H_2O$) C, H, N, Cl, H_2O.

Ethyl Tetrahydro-2-oxo-2*H*-pyran-3-carboxylate (23). Sodium metal (3.0 g, 0.13 mol) was dissolved in absolute EtOH (60 mL) under N_2, and the solution was concentrated under vacuum. Diethyl carbonate (50 mL, 0.41 mol) and δ-valerolactone (**22**) (11.5 g, 0.11 mol) were added to the solid sodium ethoxide, and the solution was heated on an oil bath to 130 °C. EtOH was distilled off through a 2 in. Vigreux column at 80–95 °C over 30 min (15 mL collected). The oil bath temperature was then increased to 150 °C, and distillate (11 mL) was collected up to 120 °C. A solid formed in the distillate during the distillation. The reaction mixture was cooled and diluted with ether (100 mL). The mixture was filtered, and the solid residue was washed with ether. The solid residue was stirred with water (80 mL) and AcOH (8 mL), and the mixture was extracted with ether (100 mL). The extract was dried over $MgSO_4$, filtered, and concentrated to afford an oil (13.1 g). Short path vacuum distillation gave **23** (9.1 g, 46%): bp 115–118 °C (0.5 mmHg); ^1H NMR ($CDCl_3$) δ 4.30 (t, 2H), 4.15 (q, 2H), 3.48 (t, 1H), 2.14 (m, 2H), 1.89 (m, 2H), 1.22 (t, 3H); ^{13}C NMR ($CDCl_3$) δ 169.0, 167.5, 69.4, 61.7, 47.2, 22.6, 20.8, 13.9.

Tetrahydro-3-(2-oxo-2-phenylethyl)-2*H*-pyran-2-one (24). Compound **23** (4.32 g, 25.1 mmol) in THF (10 mL) was added dropwise to NaH (1.0 g of 60% dispersion in oil, washed with hexane, 25.0 mmol) suspended in THF (10 mL) with stirring under N_2. The mixture was stirred until gas evolution almost ceased. α-Bromoacetophenone (4.98 g, Kugelrohr distilled prior to use, 25.0 mmol) in THF (10 mL) was added, and the mixture was heated on an oil bath at 65 °C for 2.5 h. (NOTE: exotherm occurred with some material boiling up into the condenser; wait for initial reaction to subside before heating.) The cooled mixture was partitioned between ether (150 mL) and 3% K_2CO_3 (100 mL). The ether layer was washed with 10% K_2CO_3, water, and saturated brine and dried over $MgSO_4$. The solvent was removed under vacuum to afford an orange-red oil (6.58 g). The oil (6.17 g) was stirred with THF (50 mL) and 1 M HCl (50 mL) and heated to reflux on an oil bath at 79 °C for 49 h. The THF was removed under vacuum, and the residue was extracted with CH_2Cl_2 (2 × 50 mL). The extract was dried over $MgSO_4$ and concentrated under vacuum to afford an oil (5.70 g) which was crystallized from 1:1 hexane:EtOAc (30 mL). The crystals were collected, washed with 1:1 hexane:EtOAc and hexane, and vacuum-dried to give **24** (2.59 g, 50%) as a white solid: mp 93–94 °C; IR (KBr) 1676, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.04 (d, 2H), 8.00 (t, 1H), 7.62 (t, 2H), 4.48 (t, 2H), 3.64 (dd, 1H), 3.28 (dd, 1H), 3.18 (m, 1H), 2.20 (m, 1H), 2.02 (m, 2H), 1.71 (m, 1H); MS (EI) *m/z* 219 (3.4), 218 (1.8), 105 (100). Anal. ($C_{13}H_{14}O_3$) C, H.

3-Phenyl-3-cyclohexenecarboxylic Acid (25). Ketone **24** (4.05 g, 18.6 mmol) and $Ph_3P{\cdot}HBr$ (6.38 g, 18.6 mmol) were thoroughly mixed and heated under N_2 with stirring on an oil bath at 170 °C for 2 h. Upon cooling, the glassy solid was powdered and dissolved in dry DMSO (50 mL), and dry THF (30 mL) was added. The solution was cooled to 10 °C and stirred under N_2 while dimsyl sodium in DMSO (18.6 mL of 2 M, prepared by dissolving NaH in DMSO at 80 °C over 1–2 h) was added dropwise at <18 °C. The solution was stirred at 25 °C for 2 h, and the DMSO was distilled off under vacuum at up to 80 °C. The residue was partitioned between CH_2Cl_2 (100 mL) and water (100 mL) containing K_2CO_3 (2 g). The aqueous layer was washed with CH_2Cl_2 (50 mL), acidified with concentrated HCl, and extracted with CH_2Cl_2 (2 × 70 mL). The extract was dried over $MgSO_4$ and concentrated under vacuum to afford an oil (3.76 g). The oil was washed through silica gel (25 g) with 1:1 $CHCl_3$:EtOAc and concentrated to give a solid (2.56 g). Trituration of this material from a minimum of THF by addition of hexane (30 mL) gave **25** (2.02 g, 54%) as a white solid, mp 111–112 °C. Additional material (0.45 g, mp 107–111 °C) was obtained upon concentrating the supernatant solution to 5 mL: IR (KBr) 1699 cm^{-1}; ^1H NMR ($CDCl_3$) δ 11.05 (br s, 1H), 7.42 (d, 2H), 7.35 (t, 2H), 7.27 (t, 2H), 6.15 (br s, 1H), 2.83 (m, 3H), 2.38 (m, 2H), 2.18 (m, 1H), 1.83 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 182.3, 141.7, 135.0, 128.3, 126.9, 125.1, 123.9, 39.7, 29.4, 25.0, 24.5; MS (EI) *m/z* 202 (53), 157 (100). Anal. ($C_{13}H_{14}O_2$) C, H.

3-Phenyl-3-cyclohexeneacetic Acid (26). Acid **25** (2.3 g, 11.4 mmol) was dissolved in THF (100 mL) and treated dropwise with a solution of $LiAlH_4$ (15 mL of 1 M in THF, 15 mmol) under N_2. The mixture was heated to reflux for 3 h and allowed to cool, and water (2.7 mL in 100 mL of THF) was added dropwise. The slurry was stirred for 1.5 h and filtered through Celite. The filter cake was washed extensively with THF (3 × 40 mL) and $CHCl_3$ (50 mL). The filtrate and washings were concentrated *in vacuo*, the residue taken up in CH_2Cl_2, dried over $MgSO_4$, filtered and evaporated to provide 3-phenyl-3-cyclohexenemethanol (2.1 g) as a yellow oil: TLC (silica gel, EtOAc) $R_f = 0.70$; ^1H NMR ($CDCl_3$) δ 7.20–7.50 (m, 5H), 6.20 (s, 1H), 3.70 (d, 2H), 1.20–2.70 (m, 9H).

A mixture of 3-phenyl-3-cyclohexenemethanol (2.10 g, 11.1 mmol), triphenylphosphine (3.07 g, 11.7 mmol), imidazole (2.20 g, 35.1 mmol), and carbon tetrachloride (12 mL) was stirred in CH_3CN (10 mL) for 2 h. TLC indicated that some starting material remained, so additional triphenylphosphine (0.3 g) was added and the mixture was stirred for 18 h. The solvents were removed *in vacuo*, and the residue was partitioned between 1 N HCl and CH_2Cl_2. The organic layer was separated, dried over $MgSO_4$, filtered, and evaporated. The residue was purified by MPLC on silica gel eluting with EtOAc to provide [3-(chloromethyl)-1-cyclohexenyl]benzene (1.7 g): TLC (silica gel, EtOAc) $R_f = 0.80$; GC $t_R = 8.80$ min (93%).

[3-(Chloromethyl)-1-cyclohexenyl]benzene (1.70 g, 8.22 mmol) in DMSO (15 mL) was added dropwise to a solution of NaCN (480 mg, 9.87 mmol) in DMSO (10 mL) at 80 °C, and the mixture was heated at 130 °C under N_2 for 1 h. The mixture was cooled, diluted with water (300 mL), and extracted with ether. The ethereal layer was washed with water, dried over $MgSO_4$, filtered, and concentrated to provide 3-phenyl-3-cyclohexeneacetonitrile (1.80 g): TLC (silica gel, 1:4 EtOAc: hexane) $R_f = 0.50$; GC $t_R = 9.53$ min (93%).

A mixture of 3-phenyl-3-cyclohexeneacetonitrile (1.80 g, 9.12 mmol), KOH (10 g), water (20 mL), and ethanol (20 mL) was heated on a steam bath for 8 h. A small amount of solid was removed by filtration. The filtrate was concentrated *in vacuo* and acidified with concentrated HCl and the mixture extracted with ether. The extracts were dried over $MgSO_4$, filtered, and evaporated to give **26** (1.28 g, 52% from **25**): mp 84–85 °C; ^1H NMR ($CDCl_3$) δ 7.20–7.40 (m, 5H), 6.10 (t, 1H), 2.60 (d, 2H), 2.40 (d, 2H), 2.20 (m, 1H), 1.80 (d, 2H), 1.30 (m, 2H).

1,2,3,6-Tetrahydro-4-phenyl-1-[2-(3-phenyl-3-cyclohexen-1-yl)ethyl]pyridine (27). Acid **26** was coupled to **7** using the standard coupling procedure. The resulting amide was reduced using the standard reduction procedure to give **27** which was isolated as the hydrochloride salt: mp 206–209 °C; IR ($CHCl_3$ solution) 2932, 1598, 1493, 1445, 1130, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.10–7.40 (m, 10H), 5.95–6.10 (m, 2H), 2.70–3.30 (m, 4H), 2.35–2.55 (m, 4H), 2.05–2.25 (m, 4H), 1.60–1.80 (m, 3H); MS (CI) *m/z* 331 (27), 330 (100), 172 (77). Anal. ($C_{25}H_{29}N{\cdot}HCl$) H, N, Cl; C: calcd, 79.03; found 76.81.

The following compounds were made via a standard coupling between **25** and the amine followed by a standard reduction.

1,2,3,6-Tetrahydro-4-(2-thienyl)-1-[(3-phenyl-3-cyclohexen-1-yl)methyl]pyridine (28): mp 238–240 °C; IR (KBr) 3412, 2924, 1597, 1497, 1445, 1428, 745, 696 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.42 (br s, 1H), 7.49 (m, 3H), 7.33 (m, 2H), 7.25 (m, 2H), 7.07 (t, 1H, J = 5 Hz), 6.21 (br s, 1H), 6.08 (br s, 1H), 4.06 (br d, 1H, J = 16 Hz), 3.90–3.68 (m, 2H), 3.28 (m, 1H), 3.21 (m, 2H), 2.95 (br d, 1H, J = 16 Hz), 3.21–2.81 (m, 2H), 2.39–2.11 (m, 4H), 1.92 (m, 1H), 1.31 (m, 1H); MS (EI) 335 (M^+). Anal. ($C_{22}H_{25}NS{\cdot}HCl{\cdot}0.33H_2O$) C, H, N, Cl, S, H_2O.

1-[(3-Phenyl-3-cyclohexen-1-yl)methyl]-4-(2-pyridinyl)piperazine (29): mp 96–98 °C; IR (KBr) 2916, 1597, 1486, 1440, 1255, 776, 751 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.18 (d, 1H, J = 4.9 Hz), 7.18–7.49 (m, 6H), 6.58–6.65 (m, 2H), 6.11 (br s, 1H), 3.54–3.57 (m, 4H), 2.56–2.58 (m, 5H), 1.87–2.38 (m, 7H), 1.23–1.39 (m, 1H); HPLC (reversed-phase, 70% pH 3.0 buffer: 30% MeCN) 6.80 min (100%); MS (EI) m/z 333 (33), 107 (100). Anal. ($C_{22}H_{27}N_3$) C, H, N.

1-[(3-Phenyl-3-cyclohexen-1-yl)methyl]-4-phenylpiperazine (30): mp 212–214 °C; IR (KBr) 3462, 2899 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.47 (d, 2H, J = 7 Hz), 7.40–7.20 (m, 5H), 7.02 (d, 2H, J = 8 Hz), 6.88 (t, 1H, J = 7 Hz), 6.15 (br s, 1H), 3.78 (br d, 2H, J = 13 Hz), 3.68 (br t, 2H, J = 6 Hz), 3.38 (m, 2H), 3.18 (m, 4H), 2.76 (d, 1H, J = 12 Hz), 2.26 (m, 4H), 1.94 (m, 1H), 1.32 (m, 1H); MS (EI) m/z 332 (M^+). Anal. ($C_{23}H_{28}N_2{\cdot}1.5HCl{\cdot}H_2O$) C, H, N, H_2O; Cl; calcd, 13.42; found, 12.48.

1-[(3-Phenyl-3-cyclohexen-1-yl)methyl]-4-(2-pyrimidinyl)piperazine (31): mp 68–70 °C; IR (KBr) 2947, 1585, 1548, 1482, 1256, 983 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.29 (d, 2H, J = 5 Hz), 7.39 (m, 2H), 7.30 (m, 2H), 7.24 (m, 1H), 6.46 (t, 1H, J = 5 Hz), 6.12 (br s, 1H), 3.84 (br t, 4H, J = 5 Hz), 2.55 (m, 5H), 2.34 (d, 2H, J = 6 Hz), 2.29 (m, 2H), 2.15 (m, 1H), 2.05 (m, 1H), 1.89 (m, 1H), 1.31 (m, 1H); MS (CI) 335 (M + 1^+). Anal. ($C_{21}H_{26}N_4$) C, H, N.

(*R*)-(+)-1,2,3,6-Tetrahydro-4-phenyl-1-[(3-phenyl-3-cyclohexen-1-yl)methyl]pyridine ((*R*)-(+)-14). Racemic **14** (5.40 g, 16.4 mmol) was dissolved in hot EtOH (500 mL) and added to (*R*)-(−)-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate (4.28 g, 12.3 mmol) in hot EtOH (500 mL). The mixture was allowed to cool slowly to room temperature and the salt crystallized. It was collected, washed with cold EtOH (200 mL), and dried at 70 °C under high vacuum to give the salt as a white microcrystalline powder (5.60 g). The salt was recrystallized twice from hot EtOH (1 L) to give a white solid (4.00 g). The solid was dissolved in CH_2Cl_2 (300 mL), washed with 1 N NaOH (300 mL), and filtered. The filtrate was washed with 1 N NaOH (300 mL) and saturated brine (300 mL) and dried over $MgSO_4$. The mixture was filtered and evaporated to leave **(*R*)-(+)-14** as a white solid (1.92 g, 36%): mp 96–99 °C; all spectral data were identical to (±)-**14**; HPLC (reversed-phase, 60% pH 3.0 buffer:40% MeCN) 10.98 min (99.4%); chiral HPLC (Daicel Chiral OJ column eluting with 40:60 2-propanol:hexane) t_R = 37.7 min, 98% ee; $[\alpha]^{20}_D$ +68.2° (c = 1.25, $CHCl_3$). Anal. ($C_{24}H_{27}N$) C, H, N.

(*S*)-(−)-1,2,3,6-Tetrahydro-4-phenyl-1-[(3-phenyl-3-cyclohexen-1-yl)methyl]pyridine ((*S*)-(−)-14). An identical procedure to the above using (*S*)-(+)-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate gave (*S*)-(−)-**14** as an off-white solid: mp 94–100 °C; all spectral data were identical to **14**; chiral HPLC (Daicel chiral OJ column eluting with 40:60 2-propanol:hexane) t_R = 14.5 min, 96.8% ee; $[\alpha]^{20}_D$ −67.5° (c = 1.39, $CHCl_3$). Anal. ($C_{24}H_{27}N$) C, H, N.

(*R*)-(+)-3-Phenyl-3-cyclohexenecarboxylic Acid ((*R*)-(+)-25). Racemic **25** (8.10 g, 40.0 mmol) was dissolved in 2-butanone (20 mL) and (*S*)-α-methylbenzylamine (4.85 g, 40.0 mmol) in 2-butanone (10 mL) added. The salt precipitated; more 2-butanone (200 mL) was added and the mixture heated to dissolve the salt. The salt recrystallized on cooling to 25 °C; it was collected and dried to give 10.02 g of the salt. The salt was recrystallized five times from 2-butanone to give 3.14 g of a white powder. The powder was slurried in EtOAc and washed with 2 N HCl. The EtOAc layer was dried over $MgSO_4$, filtered, and evaporated to give **(*R*)-(+)-25** as a white powder: mp 74–76.5 °C; all spectral data were identical to (±)-**25**; chiral HPLC (Daicel chiral OJ column eluting with 97:3 hexane:4% formic acid in 2-propanol) t_R = 12.3 min, 97% ee; $[\alpha]^{24}_D$ +28.4° (c = 1.14, $CHCl_3$). Anal. ($C_{13}H_{14}O_2$) C, H.

(*S*)-(−)-3-Phenyl-3-cyclohexenecarboxylic Acid ((*S*)-(−)-25). An identical procedure using (*R*)-α-methylbenzylamine gave **(*S*)-(−)-25** as a white powder: mp 71–73 °C; all spectral data were identical to (±)-**25**; chiral HPLC (Daicel chiral OJ column eluting with 97:3 hexane:4% formic acid in 2-propanol) t_R = 10.5 min, >95% ee; $[\alpha]^{20}_D$ −27.5° (c = 1.02, $CHCl_3$). Anal. ($C_{13}H_{14}O_2$) C, H.

The following compounds were made using the route described for **(*R*)-(+)-14** using **(*R*)-(−)-11**.

(*R*)-(+)-1,2,3,6-Tetrahydro-4-phenyl-1-[[3-(4-methylphenyl)-3-cyclohexen-1-yl]methyl]pyridine ((*R*)-(+)-32): mp 101–103 °C; IR ($CHCl_3$ solution) 2922, 1512, 1495, 1436, 1366, 1153, 1138, 967, 811, 696 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.10–7.43 (m, 9H), 6.09 (br s, 2H), 3.20 (m, 2H), 2.33 (s, 3H), 1.80–2.90 (m, 12H), 1.30 (m, 1H); MS (CI) m/z 345 (26), 344 (100), 343 (42), 342 (32), 172 (84); $[\alpha]^{20}_D$ +61.8° (c = 1.06, $CHCl_3$). Anal. ($C_{25}H_{29}N$) C, H, N.

(*R*)-(+)-1-[[3-(4-Chlorophenyl)-3-cyclohexen-1-yl]methyl]-1,2,3,6-tetrahydro-4-phenylpyridine ((*R*)-(+)-33): mp 190–193 °C; IR (KBr) 2956, 2916, 2803, 1493, 1140, 1093, 1009, 814, 747, 694 cm^{-1}; ^1H NMR (free base in $CDCl_3$) δ 7.15–7.45 9m, 9H), 6.10 (br s, 2H), 3.19 (br s, 2H), 1.80–2.85 (m, 12H), 1.20–1.50 (m, 1H); HPLC (reversed-phase, 60% pH 3.0 buffer:40% MeCN) 17.36 min (100%); MS (CI) m/z 366 (35%), 365 (35), 364 (100), 172 (68); $[\alpha]^{20}_D$ +35.0° (c = 0.986, $CHCl_3$). Anal. ($C_{24}H_{26}ClN{\cdot}HCl$) C, H, N, Cl.

(*R*)-(+)-1-[[3-(4-Fluorophenyl)-3-cyclohexen-1-yl]methyl]-1,2,3,6-tetrahydro-4-phenylpyridine ((*R*)-(+)-34): mp 130–132 °C; IR (KBr) 2910, 1597, 1509, 1224, 1135, 821, 814, 746, 692 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.20–7.45 (m, 7H), 6.98 (t, 2H, J = 8.7 Hz), 6.08 (br s, 2H), 3.19 (br s, 2H), 1.80–2.80 (m, 12H), 1.20–1.45 (m, 1H); HPLC (reversed-phase, 60% pH 3.0 buffer:40% MeCN) 11.73 min (100%); MS (CI) m/z 349 (28), 348 (100), 347 (47), 346 (33), 172 (85); $[\alpha]^{20}_D$ +60.4° (c = 0.981, $CHCl_3$). Anal. ($C_{24}H_{26}FN$) C, H, N, F.

(*R*)-(+)-1,2,3,6-Tetrahydro-1-[[3-(4-methoxyphenyl)-3-cyclohexen-1-yl]methyl]-4-phenylpyridine ((*R*)-(+)-35): mp 201–205 °C; IR (KBr) 2923, 2484 (br), 1606, 1514, 1244, 1034, 824, 745, 695 cm^{-1}; ^1H NMR (free base in $CDCl_3$) δ 7.30–7.60 (m, 7H), 6.89 (d, 2H, J = 7.6 Hz), 6.19 (s, 1H), 6.10 (s, 1H), 4.05 (m, 1H), 3.60–3.90 (m including s at 3.74, 5H), 3.15–3.40 (m, 4H), 2.97 (br s, 1H), 2.60–2.85 (m, 2H), 2.27 (br s, 4H), 1.93 (m, 1H); HPLC (reversed-phase, 60% pH 3.0 buffer: 40% MeCN) 11.73 min (100%); MS (CI) m/z 360 (100), 172 (36); $[\alpha]^{20}_D$ +39.3° (c = 1.018, $CHCl_3$). Anal. ($C_{25}H_{29}NO{\cdot}HCl$) C, H, N, Cl.

(*R*)-(+)-1,2,3,6-Tetrahydro-4-phenyl-1-[[3-[4-(trifluoromethyl)phenyl]-3-cyclohexen-1-yl]methyl]pyridine ((*R*)-(+)-36): mp 215–220 °C; IR ($CHCl_3$ solution) 2995, 2454, 2328, 1615, 1464, 1413, 1327, 1241, 1168, 1127, 1070, 828, 696 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.48–7.58 (m, 4H), 7.28–7.38 (m, 5H), 6.21 (br s, 1H), 6.00 (br s, 1H), 4.23 (m, 1H), 3.54–3.65 (m, 2H), 3.00–3.34 (m, 4H), 2.69–2.86 (m, 2H), 2.05–2.43 (m, 5H), 1.48–1.52 (m, 1H); MS (CI) m/z 399 (28), 398 (100), 397 (27), 378 (50), 172 (67); $[\alpha]^{20}_D$ +41.9° (c = 1.05, $CHCl_3$). Anal. ($C_{25}H_{26}F_3N{\cdot}HCl{\cdot}0.20H_2O$) C, H, N, Cl, F, H_2O.

Pharmacological Methods. Radioligand Binding.[31] The inhibition of binding of [^{3}H]ligand to each receptor (final concentration), brain area, nonspecific agent (final concentration), and method were carried out as follows: DA D1, [^{3}H]-SCH 23390 (0.2 nM), rat striatum, and (+)-butaclamol (0.1 μM) by the method of Billard et al.;[23] DA D2, [^{3}H]spiperone (0.2 nM), rat striatum, and (+)-butaclamol (1.0 μM) according to the method of Grigoriadis and Seeman;[19] DA D1/D2, [^{3}H]-*N*-*n*-propylnorapomorphine (0.35 nM), rat striatum, and (+)-butaclamol (2 μM) by the method of Seeman and Grigoriadis;[22] α_1 adrenergic, [^{3}]prazosin (0.1 nM), rat cortex, and phentolamine (10 μM) by the method of Morrow and Creese;[25] α_2 adrenergic, [^{3}H]MK-912 (0.5 nM), rat cortex, and yohimbine (10 μM) by the method of Pettibone et al.;[26] 5-HT-1A, [^{3}H]-8-OH-DPAT (0.4 nM), rat hippocampus, and 8-OH-DPAT (1 μM) by the method of Peroutka.[27] The membrane homogenates of CHO-K1 cells expressing human D2L or D3 receptors were prepared and receptor studies carried out as described[24] using

[^{3}H]spiperone (final concentration 0.2 and 0.6 nM for D2L and D3 receptors, respectively) and 1 μM haloperidol to define nonspecific binding. [^{3}H]Spiperone binding to human D4.2 dopamine receptor subtype in CHO-K1 cells: frozen aliquots of CHO-K1 cells stabily transfected to express the human recombinant dopamine receptor, D4.2 subtype, were purchased from Research Biochemicals International (RBI, Natick, MA). The binding protocol was carried out essentially as described by RBI. Cell pellets were suspended in 8 mL of buffer (50 mM Tris-HCl, pH 7.4, 5 mM EDTA, 1.5 mM $CaCl_2$, 5 mM KCl, and 120 mM NaCl) and homogenized in a glass/Teflon homogenizer (20 strokes). The homogenate was centrifuged at 900g for 10 min, and the supernatant fluid was removed and saved. Five milliliters of buffer was added; the pellet was rehomogenized and centrifuged as before. The second supernatant was combined with the first and the pooled supernatant centrifuged at 4000g for 30 min. The final pellet was suspended in the buffer (about 1 mg of protein/mL). Membranes were diluted in buffer to give a final concentration of 28 μg/mL. To each tube was added 140 μL of diluted membranes, 20 μL of [^{3}H]-spiperone (final concentration, 0.5 nM), 40 μL of incubation buffer, or 20 μL of unlabeled ligand in buffer. Haloperidol (1 μM) was used to define nonspecific binding which was typically less than 10–15% of total binding. After incubation at 27 °C for 1 h, the assay was terminated by rapid filtration through Whatmann GF/B filters (soaked for 1 h in 0.1% polyethylenimine) using a Brandel MB-48R cell harvester and rapid washing with 4 × 5 mL of ice-cold buffer. Filters containing the bound ligand were then counted by liquid scintillation counting.

Inhibition of Spontaneous Locomotor Activity.[20,32] This procedure was carried out according to methods described previously. Mice were treated with compounds administered ip followed immediately by a 1 h test. Rats were treated orally with compounds 1 h prior to a 30 min test. Locomotor activity was measured in darkened cylindrical photobeam chambers. Data were expressed as percentage inhibition of activity relative to vehicle-treated animals and an ED_{50} calculated from various doses.

Conditioned Avoidance in Squirrel Monkeys. This procedure was carried out according to methods described previously.[29,30] Inhibition of conditioned avoidance was measured for 6 h after oral administration of compound. Drug effects were expressed as percentage inhibition of avoidance responding relative to control performance during the 4 h of peak effect.

Effects on the Firing Rate of Substantia Nigra DA Neurons.[33] 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 wave form 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 2 min prior to drug injection. Drug effects were determined by averaging the response during the 1 min period of maximal inhibition. Drug-induced inhibition of firing was reversed with the DA antagonist haloperidol to confirm a DA agonist mechanism.

Inhibition of GBL-Stimulated DA Synthesis.[21] Compounds were administered to male Long–Evans rats (Blue Spruce Farms, Altamont, NY) 1 h before sacrifice, and GBL (750 mg/kg ip) and NSD 1015 (100 mg/kg ip) were administered 30 min before sacrifice. Brain striatal levels of L-dihydroxyphenylalanine were analyzed by HPLC with electrochemical detection.[34] DOPA control concentrations were 1.25 ± 0.07 and 4.11 ± 0.11 μg/g ± SEM for control and GBL-treated animals, respectively (n = 10).

Inhibition of cAMP Accumulation. DA D2 receptor activation is reported by inhibition of forskolin-stimulated cAMP accumulation in GH_4C_1 cells transfected with the human D2 receptor.[28] The assay was performed as previously described.[24,35] The intrinsic activities of test compounds were determined by comparing the maximal response obtained to that of the full DA D2 agonist quinpirole.

X-ray Crystal Structure Analysis. Crystals of (−)-11, brucine salt obtained from the published resolution procedure[18] were used for the determination. Intensity data were collected on an Enraf-Nonius CAD-4 automatic diffractometer. The crystal data and the data collection details are provided in Table 5. The NRCCAD programs were used for centering, indexing, and data collection. The unit-cell dimensions were obtained by least-squares fit of 24 well-centered reflections in the range 25° ≤ 2θ ≤ 35°. Reflections were measured with a constant speed of 2° min^{-1}. During data collection, the intensities of three standard reflections were monitored every 100 reflections. No decay was observed.

Table 5. Single-Crystal X-ray Crystallographic Analysis of (−)-**11**·Brucine Salt

Crystal Data	
formula	$C_7H_{10}O_3 \cdot C_{23}H_{26}N_2O_4$
formula weight	536.63
crystal size (mm)	0.20 × 0.15 × 0.10
crystal system	monoclinic
space group	$P2_12_12_1$
molecules/unit cell	4
unit-cell dimensions: a (Å)	13.0022(2)
b (Å)	13.8577(2)
c (Å)	14.2864(2)
unit-cell volume (Å^3)	2574.13(7)
density (calcd, g cm^{-3})	1.387
linear absorption coefficient (cm^{-1})	0.9
Collection Parameters	
radiation	graphite-monochromated Mo Kα (λ = 0.70930 Å)
data collected	1936
unique data	1936
unique data with $F_o^2 \geq 2.5\sigma(F_o^2)$	1623
no. of variables	464
$R(F)$	0.049
$R_w(F)$	0.026
weighting factor, w	σ_F^{-2}

The structure was solved by direct methods and refined by full matrix least squares using the NRCVAX programs.[36] No absorption correction was applied. Hydrogen positions were calculated. The final refinement included anisotropic thermal parameters for non-hydrogen atoms. The isotropic thermal parameters for the hydrogen atoms were not refined. An isotropic extinction coefficient was included in the refinement[37] to account for secondary extinction effects,[38] and its value was 1.30(5). The final discrepancy index $R(F)$ is defined as $R(F) = (\sum_i||F_{obs}|_i|F_{calc}|_i|)/\sum_i|F_{obs}|_i$; the weighted value $R_w(F)$ = SQRT-$[\sum_i[w_i(|F_{obs}|_i - |F_{calc}|_i|)]^2/\sum_i[w_i(|F_{obs}|_i)^2]]$ and the particular weighting factor w_i used are given in Table 5. The residual positive and negative electron densities in the final map were 0.36 and −0.38 eÅ^{-3}, respectively.

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Supplementary Material Available: Atomic positional parameters, intramolecular distances and angles, and anisotropic thermal parameters for non-hydrogen atoms for the X-ray structure determination of (−)-**11**·brucine salt (6 pages). Ordering information is given on any current masthead page.

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