3-[[(4-Aryl-1-piperazinyl)alkyl]cyclohexyl]-1*H*-indoles as Dopamine D2 Partial Agonists and Autoreceptor Agonists

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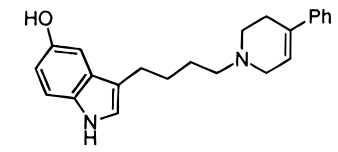
A series of arylpiperazines and tetrahydropyridines joined to indoles by semirigid cycloalkyl spacers were prepared. Target compounds were studied for their ability to bind to the DA D2 receptor in vitro and to inhibit dopamine synthesis and spontaneous locomotor activity in rats. Effects of tether length and relative stereochemistry were assessed for a series of 2-pyridylpiperazines. The cyclohexylethyl spacer was found to be the most active in the series. Further studies explored effects of changes in the arylpiperazine and indole portions of the molecule. From these studies *trans*-2-[[4-(1*H*-3-indolyl)cyclohexyl]ethyl]-4-(2-pyridinyl)piperazine (**30a**) was selected for further evaluation. It was characterized as a partial agonist of DA D2 receptors *in vitro* and caused decreases in dopamine synthesis and release as well as dopamine neuronal firing. Compound **30a** was shown to be devoid of behavioral effects associated with postsynaptic DA D2 receptor activation. Furthermore, compound **30a** was shown both to decrease DA synthesis and to inhibit Sidman avoidance responding in squirrel monkeys. These findings suggest that DA D2 partial agonists with the appropriate level of intrinsic activity can act to decrease dopamine synthesis and release and may have potential utility as antipsychotic agents.

On the basis of the success of dopamine (DA) D2 antagonists in treating the symptoms of schizophrenia, it has been proposed that hyperactive DA neurons are involved in the pathophysiology of the disease.[1] The ability of DA agonists to decrease dopamine synthesis and release and to inhibit the firing of these neurons (and therefore DA neurotransmission) via activation of presynaptic DA autoreceptors[2] has led to the suggestion of such compounds as potential antipsychotic agents. Clinical studies with low doses of the dopamine agonists apomorphine and *N*-*n*-propylapomorphine suggest that indeed this hypothesis holds merit.[3] In order for such compounds to be efficacious, they must stimulate the presynaptic DA receptors, but lack significant activity at postsynaptic receptors since stimulation of postsynaptic D2 receptors would result in exacerbation of schizophrenic symptoms.[4] Presynaptic DA receptors appear to include both the D2 and D3 receptor subtypes.[5] It has been suggested that DA D2 autoreceptors control DA synthesis and release while D3 receptors control only DA release from the presynaptic terminals.[6] However to date most of the behavioral effects seen in preclinical models used to test for possible antipsychotic activity generally have been more strongly correlated to the D2 subtype.[7] DA D2 receptors are also present postsynaptically so differentiation of these receptor populations by pharmacological means would appear to be difficult.[8] However, *in vitro* studies suggest presynaptic DA D2 receptors have a higher level of receptor reserve than postsynaptic D2 receptors[9] and therefore are more sensitive to agonists and partial agonists. Thus it is possible that partial agonists with an appropriate level of intrinsic agonist activity at DA D2 receptors would preferentially stimulate presynaptic autoreceptors while avoiding stimulation of postsynaptic receptors.[10] Such a compound would decrease the synthesis and release of dopamine as well as the firing of DA D2 neurons but would not show effects in animal models associated with stimulation of postsynaptic dopamine D2 receptors.

Two examples of DA D2 agonists which have been shown to inhibit dopamine synthesis and release via a presynaptic mechanism include roxindole[11] (**1**) and PD 119819[12] (**2**). This class of compounds is characterized by an aryl cyclic amine portion linked to a distal aryl or heterocyclic pharmacophore via an alkyl spacer. Unlike earlier DA agonists typified by apomorphine, 7-OH DPAT, and the ergots, the flexibility of the alkyl spacer between compounds **1** and **2** makes it difficult to determine the required geometric alignment of the pharmacophore units required for optimal activity.



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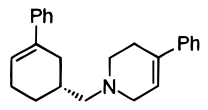

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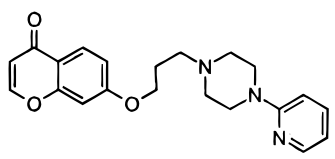

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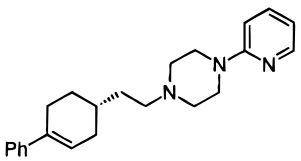

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We have designed a series of analogs which introduce constraints in the linkage of the two pharmacophores by replacing the linear alkyl linker with various cycloalkyl moieties. This work has led to the identification of CI-1007 (**3**) as a DA D2 partial agonist which is currently being developed as an antipsychotic drug.[13] In this instance the phenyl and the 4-phenyltetrahydropyridine pharmacophores are separated by the relatively rigid cyclohexenylmethyl spacer. A related series

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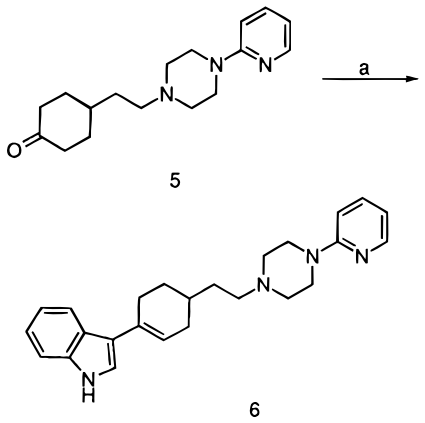
Scheme 1[a]



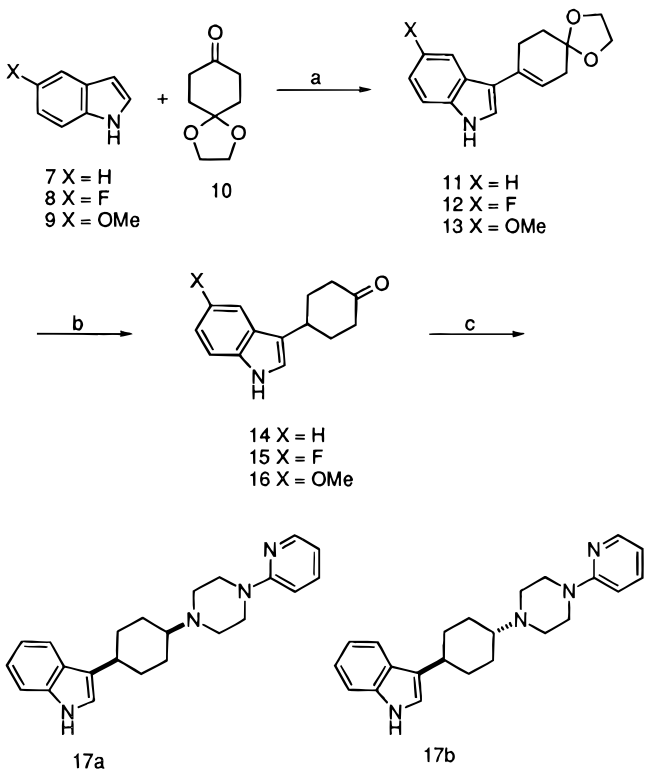
[a] (a) **7**, KOH, MeOH, 44%.

of autoreceptor agonists is represented by compound **4** where the phenyl and the 4-phenyltetrahydropyridine pharmacophores are separated by a cyclohexenylethyl spacer.[14] Replacement of the phenyl functionality resident in **4** with an indole as in **1** was contemplated because this heterocycle contained both aryl functionality and the potential for additional hydrogen bonding. It was hoped that such a feature might interact with complementary functionality in the D2 receptor binding pocket. Initially the cyclohexenylindole analog **6** was prepared, and as part of these studies, we prepared the related indole cyclohexane analogs.

Chemistry

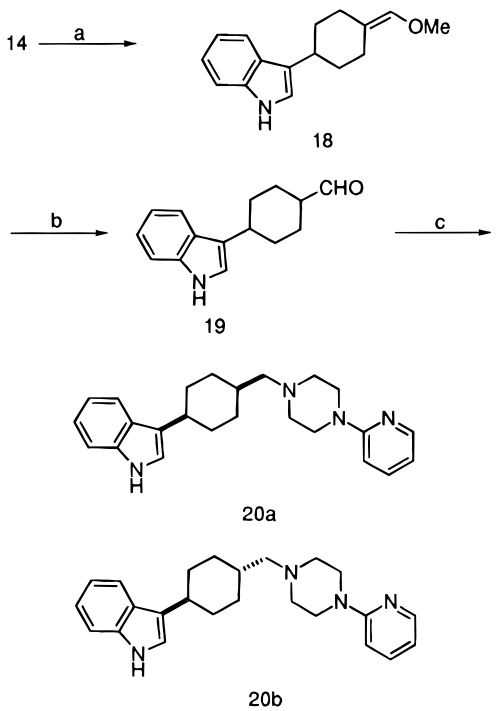
The cyclohexenylindole **6** was prepared by condensation of ketone **5**[14] with indole **7**. Attempts to prepare the cycloalkane analogs directly by hydrogenation resulted in an inseparable mixture of cis and trans isomers about the cyclohexane ring. An alternative route was developed that allowed for easier separation of the geometric isomers. Indoles **7**−**9** were condensed with cyclohexanedione monoketal **10** under basic conditions giving good yields of 4-(3-indolyl)-3-cyclohexenone ketals **11**−**13**. Reduction of the olefin and deketalization proceeded smoothly to give the 4-(3-indolyl)-3-cyclohexanones **14**−**16** as shown in Scheme 1. Ketone **14** was further elaborated via reductive amination to the corresponding pyridylpiperazines **17a** and **17b** which could be easily separated by column chromatography (Scheme 2). The corresponding one-carbon homologs were prepared as outlined in Scheme 3. Reaction of ketone **14** with the ylide derived from the reaction of (methoxymethyl)triphenylphosphonium chloride and *n*-butyllithium gave enol ether **18**, which was hydrolyzed to a mixture of aldehydes **19**. Following reductive amination of aldehydes **19**, the (cyclohexylmethyl)piperazines **20a** and **20b** were separated chromatographically. The two-carbon homologs were prepared by condensation of ketones **14**−**16** with triethyl phosphonoacetate to give the corresponding cyclohexenyl esters **21**−**23**, which were reduced and hydrolyzed to 2-[4-(3-indolyl)cyclohexyl]acetic acids **24**−**26** as approximately a 2:1 mixture of trans and cis geometric isomers. The mixtures of carboxylic acid isomers were converted to the corresponding amides using isobutyl chloroformate as the coupling agent. The amide isomers **27a,b** and **28a**−**h** were separated by column chromatography. The pure amides were then reduced to their

Scheme 2[a]



[a] (a) KOH, MeOH, 73−96%; (b) (i) H_2, Pd/C THF; (ii) HCl, 66% overall; (c) (i) 1-(2-pyridyl)piperazine, PTSA toluene, Dean-Stark; (ii) $NaCNBH_3$, 95%.

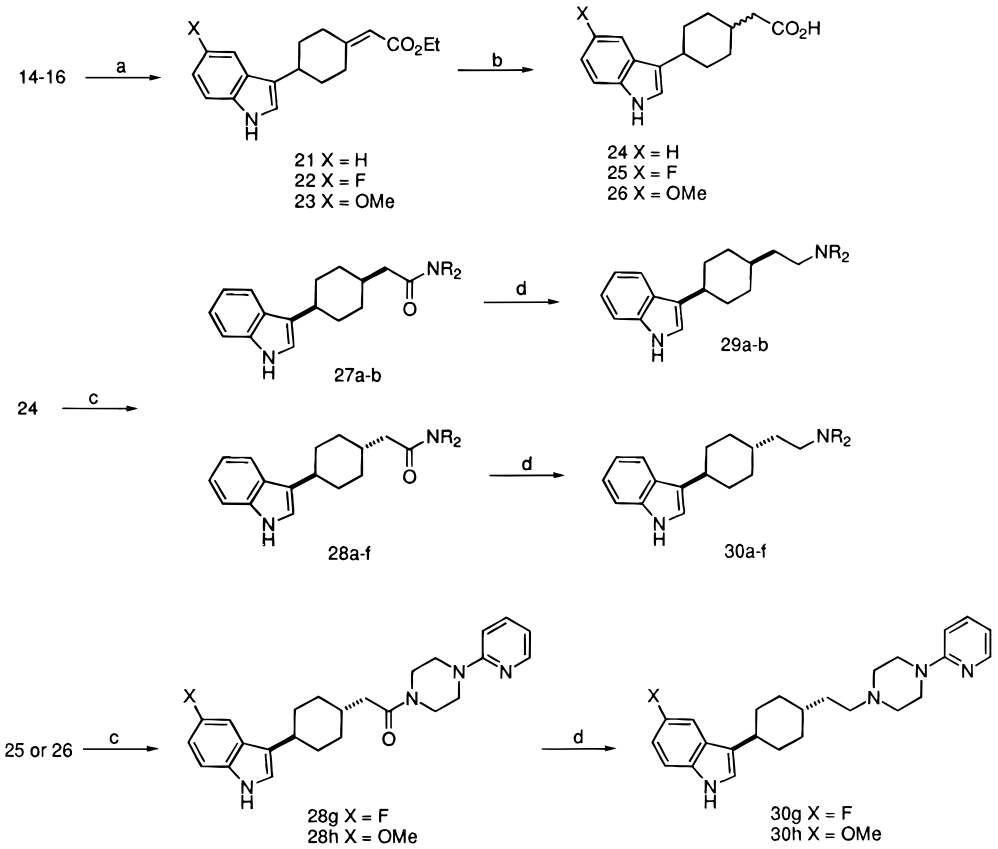
Scheme 3[a]



[a] (a) (Methoxymethyl)triphenylphosphonium chloride, *n*-BuLi, THF, −78 to 10 °C, 57%; (b) HCl, 96%; (c) 1-(2-pyridyl)piperazine, $NaCNBH_3$, 36%.

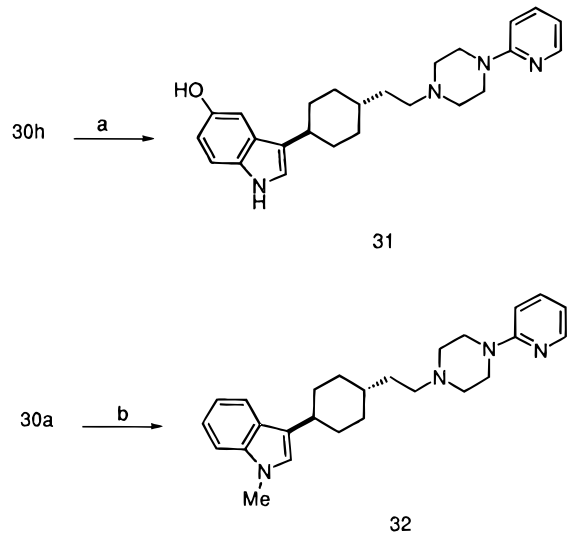
respective amines **29a,b** and **30a**−**h** with aluminum hydride. Indole **30h** could be demethylated using pyridine hydrochloride at elevated temperature to give the 5-hydroxy analog **31**. Methylation of the indole nitrogen of **30a** was accomplished following literature analogy giving compound **32**.[15] Stereochemical assign-

Scheme 4[a]



[a] (a) Triethyl phosphonoacetate, NaH, 78−83%; (b) (i) H_2, Pd/C, (ii) NaOH, 83−85%; (c) isobutyl chloroformate, Et_3N, chromatography; (d) $LiAlH_4$, $AlCl_3$, 51−83%.

Scheme 5[a]



[a] (a) Pyridine hydrochloride 130 °C, 56%; (b) KOH, MeI, DMSO, 56%.

ments were made on the basis of the chemical shifts and coupling constants of the proton attached to the carbon bearing the indole functionality.

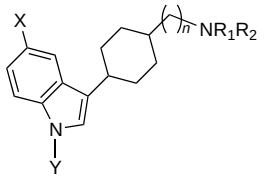
Pharmacology

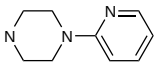
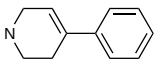
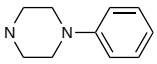
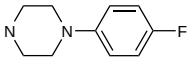
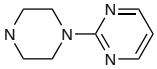
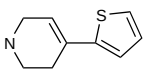
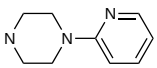
The affinities of compounds for DA D2 receptors were determined *in vitro* by measuring their ability to displace the DA D2 antagonist radio ligand [^{3}H]spiperone ([^{3}H]SPIP) from a rat striatal membrane preparation.[16] Although this radioligand labels the antagonist or "low-affinity" form of the DA D2 receptor, we used this as an initial screen for receptor binding activity because of its ready application to high throughput screening. Compounds were then screened for their ability to inhibit exploratory locomotor activity after ip injection into mice as an *in vivo* measure of the inhibition of DA neurotransmission and potential antipsychotic activity.[17] Compounds with an ED_{50} of less than 10 mg/kg in the mouse assay were then tested orally in a similar paradigm in rats in order to demonstrate oral bioavailability. Selected compounds were evaluated for their ability to reverse γ-butyrolactone (GBL)-induced synthesis of L-dihydroxyphenylalanine (DOPA)[18] in rat corpus striatum as a neurochemical measure of DA autoreceptor agonist activity.

Results and Discussion

The receptor binding screen showed that indeed the indolylcyclohexene analog **6** bound with somewhat greater affinity to the DA D2 receptor (K_i = 270 nM) than the corresponding phenyl analog **4** (K_i = 412 nM).[14] However, the corresponding indolylcyclohexane analog **30a** showed even higher affinity for the DA D2 receptor and thus became the focus of a larger study. A series of [[1-(2-pyridyl)piperazinyl]cycloalkyl]indoles **17a,b**, **20a,b**, **29a**, and **30a** were compared in order to study the effect of chain length and relative stereochemical alignment required for optimal DA D2 receptor binding (Table 1). Increasing chain length improved binding affinity for the DA D2 receptor. For each pair of geometric isomers, the *trans* isomers showed greater binding affinity than the corresponding *cis* isomers. A similar trend was observed for a pair of tetrahydropyr-

Table 1. Binding, Behavioral, and Neurochemical Activity of Target Compounds



no.	*n*	stereo	NR1R2	X	Y	[^{3}H]SPIP binding: K_i, nM[a]	inhibn LMA mouse: ED_{50}, mg/kg ip[b]	inhibn of LMA rat: ED_{50}, mg/kg po[b]	% rev of rat DA synthesis at 10 mg/kg ip[c]
17a	0	cis		H	H	2596	>30	nt[d]	nt
17b	0	trans	〃	H	H	457	1.2 (0.7; 2.2)	13.7 (7.5; 25.1)	38 ± 5.9
20a	1	cis	〃	H	H	122	1.2 (0.6; 2.2)	weak[e]	nt
20b	1	trans	〃	H	H	85	2.3 (1.4; 3.7)	8.8 (6.9; 11.1)	81 ± 5.6
29a	2	cis	〃	H	H	139	4.7 (3.5; 6.5)	12.2 (7.8; 19.2)	60 ± 9.9
30a	2	trans	〃	H	H	50	1.4 (0.7; 2.6)	4.8 (3.0; 7.6)	44 ± 4.4
29b	2	cis		H	H	28	10.5 (8.8; 12.7)	nt	5 ± 5
30b	2	trans	〃	H	H	8.7	7.2 (2.4; 21.1)	>30	inc
30c	2	trans		H	H	124	13.9 (5.7; 34.0)	nt	inc
30d	2	trans		H	H	645	>30	nt	nt
30e	2	trans		H	H	161	3.3 (2.2; 5.0)	18.6 (10.7; 32.4)	34 ± 13
30f	2	trans		H	H	630	11.6 (4.6; 29.5)	nt	nt
30g	2	trans		F	H	110	9.0 (4.9; 16.4)	stim	100 ± 3.0
30h	2	trans	〃	OMe	H	29	2.2 (1.8; 2.7)	>30	88 ± 1.3
31	2	trans	〃	OH	H	8.6	0.6 (0.4; 0.9)	>30	25 ± 11
32	2	trans	〃	H	Me	83	>30	nt	nt
1						14	0.25 (0.12; 0.52)	47.6 (15.7; 144.2)	70 ± 2.2

[a] Competition binding studies were completed in membranes form rat striatum using [^{3}H]spiperone (0.2 nM) to label D2 dopamine receptors. The K_i values were determined using the Cheng−Prusoff equation following one-site analysis using nonlinear regression analysis. [b] ED_{50} values and 95% confidence ranges were generated using from three to six doses; 6−18 animals were used per dose. [c] Shown is the per cent reversal of DOPA levels in the striatum of GBL-treated rats (n = 4−5 animals). The control values in mg/g ±SEM of the tissues for 0% (GBL + NSD 1015) 3831 ± 149 and 100% (vehicle + NSD 1015) 1181± 65. [d] Not tested. [e] 57% inhibition at 3 mg/kg ip; 1.8% inhibition at 30 mg/kg.

idine diastereomers **29b** and **30b**. Compounds in this group were screened for their ability to decrease spontaneous locomotor activity in mice when injected ip. The pyridiylpiperazine analogs were more potent in this assay, all having ED_{50} values under 5 mg/kg ip. This series also showed activity as autoreceptor agonists based upon their ability to decrease dopa levels in rats pretreated with GBL. Of the compounds which had neurochemical and behavioral activity, **30a** was the most potent at inhibiting spontaneous locomotor activity in rats when administered orally.

Having established compound **30a** with the *trans*-cyclohexylethyl spacer as the most potent member of this series, we then examined the effects of modifying the pyridylpiperazine and indole portions of compound **30a**. The 4-phenyltetrahydropyridine analog **30b** had better binding affinity for the DA D2 receptor. However, unlike **30a,** it did not decrease but rather slightly increased the DOPA levels in the striata of rats treated with GBL. A variety of other arylpiperazine and aryltetrahydropyridine ring systems (**30c**−**f**) had either decreased affinity for the DA D2 receptor or less activity in the *in vivo* assays.

Effects of substituents at the 5-position of the indole portion of **30a** were examined. Compound **30g**, having a fluorine substituent at the 5-position of the indole ring, completely reversed the GBL-induced increase in DOPA synthesis, but caused stimulation of locomotor activity in the rat. Such a profile suggests that **30a** might have high intrinsic activity and be stimulating both pre and postsynaptic DA receptors. The 5-hydroxyindole analog **31** had potent DA D2 receptor binding affinity and reduced locomotor activity when administered ip in mice; however, this compound lacked oral activity in the rat. This may be due to the poor bioavailability of the compound. Addition of a methyl substituent to the indole nitrogen (compound **32**) resulted in less than a 2-fold decrease in binding activity, suggesting the indole N-hydrogen does not play a large role in the binding affinity of **30a** for the D2 receptor. Interestingly compound **32** lacked activity in the mouse exploratory motor activity test after ip administration.

On the basis of its profile in initial biochemical, behavioral, and neurochemical tests, **30a** was selected for evaluation in a variety of secondary tests designed to understand its mechanism of action and possible

Table 2. Profile of **30a**

test	**30a**
DA D2 receptor binding [^{3}H]NPA (K_i, nM)	2.6
inhibition of 3*H*-thymidine uptake intrinsic activity DA D2 receptor[a]	72%
EC_{50} (nM)	2.8
DA D3 receptor binding [^{3}H]spiperone (K_i, nM)	29
DA D4 receptor binding [^{3}H]spiperone (K_i, nM)	73
DOPA accumulation in rats after GBL[b] (ED_{50}, mg/kg ip)	6.6
decrease of rat striatal dopamine overflow (10 mg/kg, ip)[c]	33%
decrease in DA neuronal firing rate in rats (2.5 mg/kg ip)	100%
inhibn of APO-induced climbing in mice (ED50, mg/kg/ip)	>30
stereotypy in rats (ED_{50}, mg/kg, ip)	>24
decrease in squirrel monkey striatal dopamine overflow (3 mg/kg ip)[d]	38%
inhibn of sidman avoidance in squirrel monkey (ED_{50}, mg/kg po)	1.0

[a] Data expressed relative to quinpirole (100%). [b] Graphically determined ED_{50} value, defining 50% reversal of the increase in DOPA accumulation induced by GBL. [c] Measured via *in vivo* microdialysis ($n = 4$). [d] Measured via *in vivo* microdialysis ($n = 1$)

utility as an antipsychotic agent (Table 2). Compound **30a** potently displaced the dopamine agonist ligand [^{3}H]-NPA[19] from dopamine D2 receptors in a rat brain preparation. This agonist ligand is thought to label only DA D2 receptors in the high-affinity state. The greater affinity of **30a** for DA D2 receptors using the agonist ligand suggests that the compound interacts more effectively with the high-affinity state of the DA D2 receptor as would be expected of a DA agonist. Affinities of **30a** for the human D3 and D4 receptor subtypes were also determined as previously outlined.[20,21] As the D3 receptor has been implicated in controling the neuronal release of DA, affinty for this receptor may contribute to the overall profile of the compound. The intrinsic agonist efficacy of **30a** at the DA D2 receptor was measured by its ability to stimulate [^{3}H]thymidine uptake in Chinese hamster ovary (CHO-P5) cells transfected with the human D2 receptor.[22] In this assay **30a** stimulated [^{3}H]thymidine uptake at 70% of the level observed with the full DA D2 agonist quinpriole indicating compound **30a** had partial agonist efficacy. The EC_{50} value for this functional effect was in good agreement with the K_i value obtained from the [^{3}H]NPA binding assay. This *in vitro* profile suggests **30a** to be a potent partial agonist at the DA D2 receptor.

The *in vivo* effects of compound **30a** on electrophysiological and neurochemical markers of DA D2 receptor activation were determined. Compound **30a** inhibited spontaneous firing of substantia nigra DA neurons in anesthetized rats, an effect consistent with presynaptic DA D2 receptor activation.[23] It was also effective at inhibiting GBL-induced increases of striatal DOPA synthesis with an ED_{50} of 6.6 mg/kg ip.[18] In order to determine whether compound **30a** acts to reduce DA levels in both rats and squirrel monkeys, its effects on the release of DA in the striata of both rat and squirrel monkey were measured by microdialysis experiments.[13b] In agreement with the GBL experiments, **30a** reduced extracellular dopamine overflow in the rat. Similar activity was observed in the squirrel monkey as **30a** caused a 38% decrease in DA overflow in the caudate putamen.

To determine whether the inhibitory effects on locomotor activity exhibited by **30a** were due to antagonist activity at postsynaptic DA D2 receptors, the compound was evaluated for its ability to inhibit apomorphine-induced climbing in mice.[24] DA D2 antagonists such as haloperidol potently block the climbing effects caused by the DA agonist apomorphine. Consistent with its partial agonist profile *in vitro*, compound **30a** was unable to block apomorphine-induced climbing in mice at a dose over 10 times its ED_{50} for blockade of spontaneous locomotor activity. The compound was also evaluated for its ability to cause DA agonist related stereotypy in rats by administering the test compound with the DA D1 agonist SKF 38393.[25] Administration of a dose 10 times the ED_{50} for inhibition of locomotor activity did not produce stereotypies, a property associated with postsynaptic receptor activation. Compound **30a** was then characterized for its ability to inhibit the Sidman avoidance responding in squirrel monkeys,[17c,26] a primate test which is considered to be predictive of antipsychotic efficacy. In this paradigm, compound **30a** was active after oral administration (ED_{50} 1.0 mg/kg).

Interestingly, in our hands roxindole (**1**) was inactive in this paradigm of antipsychotic efficacy.[27] Compound **1** has been shown to have a higher level of agonist activity at the D2 receptor than compound **30a** as **1** has a greater intrinsic activity in stimulating [^{3}H]thymidine uptake in CHO cells transfected with the D2 receptor (97%) compared to that observed for **30a** (72%). Taken together, these studies indicate that **30a** is a partial agonist which can stimulate presynaptic DA D2 receptors, resulting in decreases in the synthesis and release of dopamine. This inhibition in DA neurotransmission decreases the observed behavioral activity in mice, rats, and squirrel monkeys. Furthermore **30a** was not active in behavioral studies sensitive to activation of postsynaptic DA D2 receptors. Thus it would appear to be possible to prepare compounds with the appropriate level of intrinsic activity which will selectively stimulate presynaptic DA D2 autoreceptors (and thereby attenuating dopamine neurotransmission) without activating postsynaptic DA D2 receptors which could exacerbate schizophrenia.

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, a Varian 200 MHz NMR instrument, or a Bruker 400 MHz NMR instrument. The spectra recorded were consistent with the proposed structures. The mass spectra were obtained on a Finnigan 4500 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, 230−300 mesh) with an RB-SY pump (FMI).

3-[4-[2-[4-(2-Pyridinyl)-1-piperazinyl]ethyl]-1-cyclohexen-1-yl]-1*H*-indole Hydrochloride (6). A mixture of

indole **7** (0.82 g, 6.96 mmol), ketone **5**[14] (2.0 g, 6.9 mmol) and potassium hydroxide (0.194 g, 3.48 mmol) was heated to reflux in 10 mL of methanol for 18 h. The methanol was removed under reduced pressure, and the residue was partitioned between water (50 mL) and methylene chloride (50 mL). The organic layer was dried with sodium sulfate and evaporated, and the resulting residue was purified by MPLC (2% methanol 0.1% ammonia in methylene chloride) to give the free base of compound **6** (1.2 g 44% yield): EIMS *m/z* 387 (43), 386 (25), 279 (85), 107 (base); ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 8.19 (d, J = 2 Hz, 1 H), 8.09 (br s, 1 H), 7.91 (s, J = 8 Hz, 1 H), 7.47 (t, J = 8 Hz, 1 H), 7.36 (d, J = 7 Hz, 1 H), 7.25 (m, 3 H), 6.64 (d, J = 8 Hz, 1 H), 6.61 (t J = 7 Hz, 1 H), 6.25 (br s, 1 H), 3.57 (t, J = 5 Hz, 1 H), 2.59 (t, J = 5 Hz, 1 H), 2.51 (m, J = 4 Hz, 4 H), 2.38 (m, 1 H), 1.91 (m, 2 H), 1.65 (m, 1 H), 1.58 (dd, J = 9.8 Hz, 2 H), 1.21 (m, 1H). The HCl salt was formed by treating the free base (320 mg) in ethyl acetate (20 mL) with a solution of anhydrous hydrochloric acid in 2-propanol to give the product as a white precipitate. (370 mg): mp 258−60 °C. Anal. ($C_{25}H_{30}N_4$·1.25HCl·H_2O) C, H, N, water.

4-(1*H*-3-Indolyl)-3-cyclohexenone Ethylene ketal (11). Indole **7** (45.3 g, 0.38 mol), 1,4-cyclohexanedione monoethylene ketal (**10**) (45.5 g, 0.29 mol), and potassium hydroxide (9.12 g, 0.16 mol) were heated to reflux in 100 mL of methanol for 18 h. The reaction mixture was cooled, and the product was isolated by filtration and washed with water to give 4-(1*H*-3-indolyl)-3-cyclohexenone ethylene ketal (**11**) as a white solid (69.0 g, 93% yield): EIMS *m/z* 255 (47) 169 (base); IR (KBr, cm^{-1}) 3287, 2966, 2885, 1644, 1436, 1238; ^{1}H-NMR ($CDCl_3$, trace DMSO-d_6 250 MHz) δ 9.50 (br s, 1 H), 7.86 (d, J = 8 Hz, 1 H), 7.36 (d, J = 7 Hz, 1 H), 7.17 (t, J = 7 Hz, 1 H), 7.15 (s, 1H), 7.08 (t, J = 8 Hz, 1 H), 6.12 (t, J = 4 Hz, 1 H), 4.02 (s, 4 H), 2.69 (m, 2 H), 2.52 (br s, 2 H), 1.94 (t, J = 6 Hz, 1 H). Anal. ($C_{16}H_{17}NO_2$) C, H, N.

4-(5-Fluoro-1*H*-3-indolyl)-3-cyclohexenone Ethylene Ketal (12). The conversion of 5-fluoroindole **8** to 4-(5-fluoro-1*H*-3-indolyl)-3-cyclohexenone ethylene ketal (**12**) was carried out in a manner analogous to the synthesis of **11**: yield 76%; CIMS *m/z* 274 (36) 186 (base); ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 8.12 (br s, 1 H), 7.53 (dd, J = 2, 10 Hz, 1 H), 7.24 (m, 2 H), 7.17 (d, J = 2 Hz, 1 H), 6.94 (td, J = 9, 2 Hz, 1 H), 6.06 (t, J = 4 Hz, 1 H), 4.04 (s, 4 H), 2.67 (m, 2 H), 2.53 (br s, 2 H), 1.95 (t, J = 6 Hz, 1 H). Anal. ($C_{16}H_{16}FNO_2$) C, H, N.

4-(5-Methoxy-1*H*-3-indolyl)-3-cyclohexenone Ethylene Ketal (13). The conversion of 5-methoxyindole **9** to 4-(5-methoxy-1*H*-3-indolyl)-3-cyclohexenone ethylene ketal (**13**) was carried out in a manner analogous to the synthesis of **11**: yield 93%; CIMS *m/z* 285 (62) 99 (base); ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 8.05 (br s, 1 H), 7.35 (d, J = 2 Hz, 1 H), 7.24 (d, J = 9 Hz, 1 H), 7.14 (d, J = 2 Hz, 1 H), 6.87 (dd, J = 9, 2 Hz, 1 H), 6.10 (t, J = 4 Hz,1 H), 4.02 (s, 4 H), 3.88 (s, 3 H), 2.69 (m, 2 H), 2.55 (br s, 2 H), 1.97 (t, J = 6 Hz, 1 H); CIMS *m/z* 285 (62), 99 (base).

4-(1*H*-3-Indolyl)cyclohexanone (14). 4-(1*H*-3-Indolyl)-3-cyclohexenone ethylene ketal (**11**) (66.6 g, 0.26 mmol) was dissolved in 500 mL of THF and 100 mL of methanol, 1.0 g of 5% palladium on carbon was added and the mixture was placed under 60 psi of hydrogen. After 2 h the reaction mixture was filtered and concentrated to give a tan solid which was dissolved in 350 mL of acetone and 350 mL of 10% HCl and allowed to stir at room temperature for 6 h. The acetone was removed under reduced pressure, and the mixture was made basic with concentrated ammonium hydroxide. The mixture was extracted with chloroform. The organic fraction was dried with sodium sulfate, and volatiles were removed under reduced pressure. The resulting solid was taken up in hot ethyl acetate, and upon cooling and filtration 4-(1*H*-3-indolyl)cyclohexanone (**14**) was obtained as a crystalline solid (36.89 g, 66% yield): mp 124−5 °C; EIMS *m/z* 213 (63) 156 (base); ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 8.26 (br s, 1 H), 7.65 (d, J = 8 Hz, 1 H), 7.30 (d, J = 8 Hz, 1 H), 7.19 (td, J = 8, 1 Hz, 1 H), 7.11 (t, J = 8 Hz, 1 H), 6.88 (d, J = 2 Hz, 1 H), 3.29 (tt, J = 12, 3 Hz, 1 H), 2.47 (m, 4 H), 2.38 (dt, J = 13, 3 Hz, 2 H), 1.92 (ddd, J = 24, 12, 6, 2 H). Anal. ($C_{14}H_{15}NO$) C, H, N.

4-(5-Fluoro-1*H*-3-indolyl)cyclohexanone, 15. The conversion of 4-(5-fluoro-1*H*-3-indolyl)-3-cyclohexenone ethylene ketal (**12**) to 4-(5-fluoro-1*H*-3-indolyl)cyclohexanone (**15**) was carried out in a manner analogous to the synthesis of **14**: mp 117−9 °C; EIMS *m/z* 231 (62), 174 (base); IR (KBr, cm^{-1}) 3338, 1705, 1488, 1461; ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 8.13 (br s, 1 H), 7.28 (m, 2 H), 7.04 (d, J = 2 Hz, 1 H), 6.96 (td, J = 9, 2 Hz, 1 H), 3.28 (tt, J = 12, 3 Hz, 1 H), 2.53 (m, 4 H), 2.42 (m, J = 12 Hz, 2 H), 1.95 (ddd, J = 24, 12, 6 Hz, 2 H). Anal. ($C_{14}H_{14}$FNO) C, H, N, F.

4-(5-Methoxy-1*H*-3-indolyl)cyclohexanone (16). The conversion of 4-(5-methoxy-1*H*-3-indolyl)-3-cyclohexenone ethylene ketal (**13**) to 4-(5-methoxy-1*H*-3-indolyl)cyclohexanone (**16**) was carried out in a manner analogous to the synthesis of **14**: mp 118−20 °C; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 7.94 (br s, 1 H), 7.29 (d, J = 8 Hz, 1 H), 7.08 (s, 1 H), 6.99 (s, 1 H), 6.92 (dd, J = 8, 2 Hz, 1 H), 3.90 (s, 3 H), 3.32 (tt, J = 12, 3 Hz, 1 H), 2.54 (m, 4 H), 2.42 (m, J = 12 Hz, 2 H), 1.95 (ddd, J = 24, 12, 6 Hz, 2 H). Anal. ($C_{15}H_{27}NO_2$) C, H, N.

***cis*-3-[4-[4-(2-Pyridinyl)-1-piperazinyl]cyclohexyl]-1*H*-indole (17a) and *trans*-3-[4-[4-(2-Pyridinyl)-1-piperazinyl]cyclohexyl]-1*H*-indole (17b).** A solution of 4-(1*H*-3-indolyl)cyclohexanone (**14**) (5.00 g, 23.4 mmol), 1-(2-pyridyl)-piperazine (3.82 g, 23.4 mmol). and a catalytic amount of *p*-toluenesufonic acid was heated to reflux in toluene (40 mL) under a Dean−Stark trap for 8 h. The solvent was removed under reduced pressure, and the residue was dissolved in 50 mL of methanol and 30 mL of THF. The mixture was cooled to 0 °C and treated with sodium cyanoborohydride (1.61 g, 25.7 mmol) and a small amount of methyl red to act as a pH indicator. The reaction was treated with aqueous 1 N HCl (approximately 50 mL) over $^1/_2$ h until the reaction remained acidic. The reaction was stirred at 0 °C for 1 h, and the solvents were then removed under reduced pressure. The residue was partitioned between chloroform and ammonium hydroxide. The organic layer was separated, dried over sodium sulfate, and evaporated. The resulting diastereomers were separated using MPLC (2% methanol, 0.1% ammonia in chloroform) to give two fractions.

Fraction 1: *cis*-3-[4-[4-(2-pyridinyl)-1-piperazinyl]cyclohexyl]-1*H*-indole (17a) (3.66 g, 43% yield): mp 132−4 °C (ethyl acetate); EIMS *m/z* 360 (14), 241 (36), 107 (base); IR (KBr, cm^{-1}) 3248, 2920, 2807, 1595, 1411; ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 8.19 (d, J = 5 Hz, 1 H), 7.99 (brs, 1 H), 7.68 (d, J = 8 Hz, 1 H), 7.47 (dt, J = 2, 8 Hz, 1 H), 7.34 (d, J = 8 Hz, 1 H), 7.17 (t, J = 7 Hz, 1 H), 7.12 (t, J = 7 Hz, 1 H), 7.05 (d, J = 2 Hz, 1 H), 6.65 (d, J = 8 Hz, 1 H), 6.60 (t, J = 5 Hz, 1 H) 3.55 (t, J = 5 Hz, 4 H), 3.14(m, 1 H), 2.65 (m, J = 5 Hz, 4 H) 2.34 (m, 1 H), 2.15 (m, 2 H), 1.85 (m, 3 H), 1.67 (m, 3 H). Anal. ($C_{23}H_{28}N_4$) C, H, N.

Fraction 2: *trans*-3-[4-[4-(2-pyridinyl)-1-piperazinyl]-cyclohexyl]-1*H*-indole (17b) (4.51 g, 53% yield): mp 156−8 °C (ethyl acetate); EIMS *m/z* 360 (13) 241 (30), 107 (base); IR (KBr, cm^{-1}) 3156, 2926, 2852, 1596, 1455; ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 8.20 (d, J = 5 Hz, 1 H), 7.99 (brs, 1 H), 7.64 (d, J = 7 Hz, 1 H), 7.48 (dt, J = 2, 8 Hz, 1 H), 7.36 (d, J = 8 Hz, 1 H), 7.18 (t, J = 7 Hz, 1 H), 7.10 (t, J = 7 Hz, 1 H), 6.95 (d, J = 2 Hz, 1 H), 6.66 (d, J = 8 Hz, 1 H), 6.61 (t, J = 5 Hz, 1 H), 3.57 (t, J = 5 Hz, 4 H), 2.81 (m, 1 H), 2.75 (t, J = 5 Hz, 4 H), 2.46 (m, 1 H), 2.22 (m, 2 H), 2.10 (m, 2 H), 1.54 (m, 4 H). Anal. ($C_{23}H_{28}N_4$) C, H, N.

3-[4-(Methoxymethylene)cyclohexyl]-1*H*-indole (18). A mixture of (methoxymethyl)triphenylphosphonium chloride (10 g, 21.2 mmol) in tetrahydrofuran (25 mL) was cooled to −78 °C and treated with a 1.6 M solution of *n*-BuLi in hexane (13.2 mL, 21.2 mmol). After 20 min a solution of 4-(1*H*-3-indolyl)cyclohexanone (**14**) 2.25 g, 10.6 mmol) in tetrahydrofuran (25 mL) was added, and the reaction mixture was allowed to warm to 10 °C over 2 h. The reaction was quenched with saturated ammonium chloride, and the THF was removed under reduced pressure. The residue was partitioned between water and chloroform and the organic layer dried with sodium sulfate and evaporated. The residue was purified using MPLC (1:19:80 methanol−chloroform−hexanes) to give **18** as a clear oil (1.45 g, 57% yield): ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 7.99 (br s, 1 H), 7.68 (d, J = 8 Hz, 1 H), 7.37 (d, J = 8 Hz, 1 H), 7.23 (t, J = 8 Hz, 1 H), 7.13 (t, J = 8 Hz, 1 H), 6.96 (d, J = 2 Hz,

1 H), 5.86 (s, 1 H), 3.53 (t, J = 3 H), 2.97 (m, J = 2 H), 2.09 (m, 4 H), 1.86 (t, J = 12 Hz, 1 H), 1.65 (m, 2 H).

***cis*- and *trans*-4-(1*H*-Indol-3-yl)cyclohexanecarbaldehyde (19).** The enol ether **18** (1.25 g, 5.17 mmol) was heated in a refluxing solution of solution of THF (30 mL) and 10% HCl (15 mL) for 2 h. The THF was removed under reduced pressure, and the reaction mixture was partitioned between methylene chloride and water. The organic layer was dried, and solvents were evaporated under reduced pressure to obtain a 1:2 mixture of *cis*- and *trans*-aldehydes **19** by NMR (1.15 g, 98% yield): key NMR resonances ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 9.81, 9.73 (s, 1 H), 8.04, 7.99 (brs, 1 H), 6.95, 6.89 (d, J = 2 Hz, 1 H), 3.80 (m, 1 H), 2.87 (m, 1 H).

***cis*-1-[[4-(1*H*-3-Indolyl)cyclohexyl]methyl]-4-(2-pyridinyl)piperazine (20a) and *trans*-1-[[4-(1*H*-3-Indolyl)cyclohexyl]methyl]-4-(2-pyridinyl)piperazine (20b).** A mixture of *cis*- and *trans*-4-(1*H*-3-indolyl)cyclohexane-2-carboxaldehyde (**19**) (1.1 g, 4.93 mmol) and 2-pyridinylpiperazine (0.81 g, 4.9 mmol) was dissolved in 35 mL of acetonitrile, cooled to 0 °C, and treated with 0.3 mL of acetic acid. The reaction was stirred for 15 min and then treated with sodium cyanoborohydride (0.33 g, 5.3 mmol). The reaction mixture was removed from the ice bath and stirred for 3 h. The acetonitrile was removed under reduced pressure, the residue was treated with water (100 mL), and the mixture was adjusted to pH 10 with sodium hydroxide and extracted with chloroform. The chloroform extracts are dried with sodium sulfate, and the solvents are evaporated under reduced pressure. The residue was purified using MPLC (1% methanol, 99% chloroform) to give **20a** and **20b**. *cis*-1-[[4-(1*H*-3-Indolyl)cyclohexyl]methyl]-4-(2-pyridinyl)piperazine (**20a**) (0.23 g, 12% yield): mp 74−6 °C (ether); EIMS *m*/*z* (% base) 374 (M^+, 19), 280 (38), 176 (57), 107 (base); IR (KBr, cm^{-1}) 3411, 2920, 2846, 1593, 1482, 1436, 1242; ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 8.19 (d, J = 5 Hz, 1 H), 7.94 (br s, 1 H), 7.64 (d, J = 8 Hz, 1 H), 7.47 (td, J = 8, 2 Hz, 1 H), 7.35 (d, J = 8 Hz, 1 H), 7.18 (t, J = 7 Hz, 1 H), 7.09 (t, J = 7 Hz, 1 H), 7.02 (d, J = 2 Hz, 1 H), 6.65 (d, J = 8 Hz, 1 H), 6.64 (t, J = 5 Hz, 1 H), 3.54 (t, J = 5 Hz, 4 H), 3.04 (m, 1 H), 2.54 (t, J = 5 Hz, 1 H), 2.37 (d, J = 7 Hz, 1 H), 1.87 (m, 4 H), 1.68 (m 5 H). Anal. ($C_{24}H_{30}N_4$) C, H, N. *trans*-1-[[4-(1*H*-3-Indolyl)cyclohexyl]methyl]-4-(2-pyridinyl)piperazine (**20b**) (0.45 g, 24% yield): mp 169−70 °C (ethyl acetate−hexane); EIMS *m*/*z* (% base) 374 (M^+, 18), 359 (M − NH, 3), 280 (29), 267 (17), 107 (base); IR (KBr, cm^{-1}) 3404, 2919, 1595, 1483, 1245; ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 8.19 (d, J = 5 Hz, 1 H), 7.97 (brs, 1 H), 7.66 (d, J = 8 Hz, 1 H), 7.47 (td, J = 8,2 Hz, 1 H), 7.34 (d, J = 8 Hz, 1H), 7.18 (t, J = 7 Hz, 1 H), 7.12 (t, J = 7 Hz, 1 H), 6.95 (d, J = 2 Hz, 1 H), 6.65 (d, J = 8 Hz, 1 H), 6.62 (t, J = 5 Hz, 1 H), 3.59 (m, 4 H), 2.82 (t, J = 12 Hz, 1 H), 2.58 (m, 4 H), 2.29 (d, J = 7 Hz, 2 H), 2.17 (d, J = 11 Hz, 2 H), 2.00 (d, J = 11 Hz, 2 H), 1.68 (m, 1 H), 1.52 (dd, J = 20, 11 Hz, 2 H), 1.16 (dd, J = 21, 11 Hz, 2 H). The free base **20b** was converted to its maleate salt by treatment with an equimolar amount of maleic acid in methanol, removal of the solvent under reduced pressure, and recrystallization from ethanol: mp 176−7 °C. Anal. ($C_{24}H_{30}N_4 \cdot C_4H_4O_4$) C, H, N.

[4-(1*H*-Indol-3-yl)cyclohexylidene]acetic Acid Ethyl Ester (21). Sodium hydride (60% by wt in mineral oil, 13.96 g, 349 mmol) was washed with two portions of hexane (200 mL) under nitrogen. The sodium hydride was slurried in THF (200 mL) cooled to 0 °C and treated with triethyl phosphonoacetate (71.29 g, 318 mmol) in 100 mL of THF. The reaction mixture was allowed to come to room temperature over 1 h and then again cooled to 0 °C, and a solution of 4-(1*H*-3-indolyl)cyclohexanone (**14**) (33.92 g, 159 mmol) in 200 mL of THF was added. The reaction mixture was warmed to room temperature over 4 h and was quenched with 200 mL of saturated KH_2PO_4. The mixture was partitioned between chloroform and water, the combined organic extracts were washed with brine and dried over Na_2SO_4, and the solvents were removed under reduced pressure. The resulting residue was subjected to MPLC (2:1 hexane−ethyl acetate) (the compound was loaded on the column by adding a trace of methylene chloride) to obtain **21** as a white crystalline solid (35.1 g, 78% yield): mp 113−5 °C; CIMS *m*/*z* 284 (base) 283 (91), 238 (96); ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 7.92 (brs, 1 H), 7.62 (d, J = 7 Hz, 1 H), 7.32 (d, J = 7 Hz, 1 H), 7.15 (t, J = 7 Hz, 1 H), 7.08 (t, J = 7 Hz, 1 H), 6.90 (d, J = 2 Hz, 1 H), 5.66 (s, 1 H), 4.14 (q, J = 7 Hz, 2 H), 3.92 (dt, J = 17, 4 Hz, 1 H), 3.09 (tt, J = 12, 4 Hz, 1 H), 2.39 (m, 2 H), 2.28 (m, 2 H), 2.12 (td, J = 12, 3 Hz, 1 H), 1.65 (m, 2 H), 1.26 (t, J = 7 Hz, 3 H). Anal. ($C_{18}H_{21}NO_2$) C, H, N.

Similarly, esters **22** and **23** were prepared.

[4-(5-Fluoro-1*H*-indol-3-yl)cyclohexylidene]acetic acid ethyl ester (22): 78% yield; mp 149−151 °C; EIMS *m*/*z* 301 (base), 161 (95); ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 8.01 (brs, 1 H), 7.28 (m, 2 H), 6.97 (d, J = 2 Hz, 1 H), 6.91 (dd, J = 8, 2 Hz, 1 H), 5.69 (s, 1 H), 4.16 (q, J = 7 Hz, 2 H), 3.95 (d, J = 14 Hz, 1 H), 3.04 (tt, J = 12, 4 Hz, 1 H), 2.39 (m, 2 H), 2.28 (m, 2 H), 2.14 (td, J = 12, 3 Hz, 1 H), 1.67 (m, 2 H), 1.29 (t, J = 7 Hz, 3 H). Anal. ($C_{18}H_{20}FNO_2$) C, H, N.

[4-(5-Methoxy-1*H*-indol-3-yl)cyclohexylidene]acetic acid ethyl ester (23): 83% yield; mp 118−20 °C; ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 7.84 (brs, 1 H), 7.21 (d, J = 8 Hz, 1 H), 7.03 (d, J = 2 Hz, 1 H), 6.88 (d, J = 2 Hz, 1 H), 6.82 (dd, J = 8, 2 Hz, 1 H), 5.66 (s, 1 H), 4.13 (q, J = 7 Hz, 1 H), 3.92 (dt, J = 17, 4 Hz, 1 H), 3.84 (s, 3 H), 3.04 (tt, J = 12, 4 Hz, 1 H), 2.39 (m, 2 H), 2.24 (m, 2 H), 2.11 (td, J = 12, 3 Hz, 1 H), 1.62 (m, 2 H), 1.26 (t, J = 7 Hz, 3 H). Anal. ($C_{19}H_{23}NO_3$) C, H, N.

[4-(1*H*-Indol-3-yl)cyclohexyl]acetic Acid (24). A solution [4-(1*H*-indol-3-yl)cyclohexylidene]acetic acid ethyl ester **(21)** (46.4 g, 164 mmol) in 600 mL of ethanol was treated with 5% palladium on carbon (5 g) and placed under 50 psi of hydrogen gas. After the appropriate amount of hydrogen had been taken up, the mixture was filtered, and the solvents were removed under reduced pressure. The residue was redissolved in 250 mL of ethanol, and 100 mL of 10% NaOH was added. After 18 h the ethanol was removed under reduced pressure. The aqueous mixture was extracted with ethyl acetate; the aqueous layer was then was adjusted to pH 5 with potassium biphosphate and extracted with three 300 mL portions of methylene chloride. The combined methylene chloride extracts were dried over sodium sulfate and evaporated to give a cream-colored solid (35.1 g, 83% overall yield) which was a mixture of diastereomers (trans:cis; 1:1): mp 150−154 °C; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.92 (s, 1H), 7.63 (d, J = 8 Hz, 1 H), 7.35 (d, J = 8 Hz, 1 H), 7.18 (t, J = 8 Hz, 1 H), 7.10 (t, J = 8 Hz, 1 H), 7.00 (d, J = 2 Hz, $^1/_2$ H, trans isomer), 6.94 (d, J = 2 Hz, $^1/_2$ H, cis isomer), 2.96 (m, $^1/_2$ H cis isomer), 2.72 (tt, J = 3, 15 Hz, $^1/_2$ H, trans isomer), 2.44 (d, J = 8 Hz, 1 H, trans isomer), 2.33 (d, J = 7 Hz, 1 H, cis isomer), 2.26−1.21 (series of multiplets, 9 H); CIMS *m*/*z* 258 (base), 257 (50).

Similarly, acids **25** and **26** were prepared.

[4-(5-Fluoro-1H-indol-3-yl)-cyclohexyl]-acetic acid (25): mp 166−8 °C; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.92 (s, 1H), 7.19 (m, 2 H), 7.05 (d, J = 2 Hz, $^1/_2$ H trans isomer), 6.99 (d, J = 2 Hz, 1 H), 6.92 (m, 1 H), 3.07 (m, $^1/_2$ H cis isomer), 2.81 (tt, J = 4, 12 Hz, $^1/_2$ H, trans isomer), 2.45 (d, J = 8 Hz, 1 H, trans isomer), 2.32 (d, J = 7 Hz, 1 H, cis isomer), 2.26−1.21 (series of multiplets, 9 H); CIMS *m*/*z* 276 (base), 275 (58).

[4-(5-Methoxy-1*H*-indol-3-yl)cyclohexyl]acetic acid (26): mp 143−5 °C; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.80 (s, 1H), 7.25 (d, J = 8 Hz, 1 H), 7.05 (s, 1 H), 6.99 (d, J = 2 Hz, $^1/_2$ H, trans isomer), 6.93 (d, J = 2 Hz, $^1/_2$ H, cis isomer), 6.84 (d, J = 8 Hz, 1 H), 3.87 (s, 3 H), 2.98 (m, $^1/_2$ H, cis isomer), 2.75 (tt, J = 3, 15 Hz, $^1/_2$ H, trans isomer), 2.45 (d, J = 8 Hz, 1 H, trans isomer), 2.33 (d, J = 7 Hz, 1 H, cis isomer), 2.26−1.21 (series of multiplets 9H), CIMS *m*/*z* 288 (base), 287 (50).

***cis*-2-[4-(1*H*-Indol-3-yl)cyclohexyl]-1-(4-pyridin-2-ylpiperazin-1-yl)ethanone (27a) and *trans*-2-[4-(1*H*-Indol-3-yl)-cyclohexyl]-1-(4-pyridin-2-ylpiperazin-1-yl)-ethanone (28a).** A solution of the carboxylic acid **24** (5.00 g, 19.4 mmol), triethylamine (4.5 mL, 32 mmol), and methylene chloride (90 mL) was cooled in an ice bath and treated with isobutyl chloroformate (2.77 mL, 21.4 mmol). After 10 min the solution was treated with 1-(2-pyridyl)piperazine (3.49 g, 21.4 mmol), maintained at 0 °C for 3 h, and warmed to room temperature overnight. The reaction mixture was extracted with aqueous sodium bicarbonate (40 mL), the organic layer was dried over sodium sulfate and filtered, and the solvents were evaporated under reduced pressure. The mixture was purified using

MPLC (2% methanol, 0.1% ammonia, in chloroform) to obtain the following.

Cis isomer 27a: ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 8.19 (dd, J = 4, 2 Hz, 1 H), 7.98 (brs, 1 H), 7.64 (d, J = 8 Hz, 1 H), 7.53 (td, J = 8, 2 Hz, 1 H), 7.36 (d, J = 8 Hz, 1H), 7.19 (t, J = 8 Hz, 1H), 7.14(t, J = 8 Hz, 1H), 7.05 (d, J = 2 Hz, 1 H), 6.63 (m, 2H), 3.80 (t, J = 5 Hz, 4 H), 3.51 (t, J = 5 Hz, 4 H), 3.08 (m, 1 H), 2.42 (d, J = 6 Hz, 2 H), 2.42 (t, J = 5 Hz, 1 H), 1.93 (m, 4 H), 1.81 (m, 2 H), 1.71 (m, 2 H).

Trans isomer 28a: ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 8.22 (dd, J = 4, 2 Hz, 1 H), 7.98 (brs, 1 H), 7.65 (d, J = 8 Hz, 1 H), 7.53 (td, J = 8, 2 Hz, 1 H), 7.36 (d, J = 8 Hz, 1 H), 7.19 (t, J = 8 Hz, 1 H), 7.14 (t, J = 8 Hz, 1H), 6.95 (d, J = 2 Hz, 1H), 6.64 (d, J = 8 Hz, 1 H), 6.61 (t, J = 7 Hz, 1 H), 3.80 (t, J = 5 Hz, 4 H), 3.51 (t, J = 5 Hz, 4 H), 2.82 (tt, J = 12, 3 Hz, 1 H), 2.36 (d, J = 6 Hz, 2 H), 2.15 (d, J =11 Hz, 2 H), 2.03 (m, 3 H), 1.60 (dd, J = 20, 12 Hz, 2 H), 1.18 (dd, J = 20, 12 Hz, 2 H).

***cis*-1-[2-[4-(1*H*-3-indolyl)cyclohexyl]ethyl]-4-(2-pyridinyl)piperazine (29a).** Lithium aluminum hydride (0.19 g, 4.9 mmol) was slurried in 10 mL of THF and cooled in an ice bath. The mixture was treated with aluminum chloride (0.22, 1.64 mmol) in ether (10 mL) and stirred for 10 min. A mixture of the amide **27a** (0.66 g, 1.64 mmol) and 10 mL of tetrahydrofuran were added, and the reaction mixture was allowed to warm to room temperature overnight. The reaction was quenched by careful addition of 0.5 mL of water and 1 mL of 25% NaOH. After 2 h of stirring the mixture was filtered through Celite and the filtercake washed with an additional 10 mL of THF. The solvents were removed under reduced pressure, and the residue was triturated with hexanes to give **29a** as a white solid (0.51 g, 80% yield): mp 99−101 °C (hexanes); EIMS *m*/*z* 388 (21), 294 (30), 281 (21), 267 (31) 107 (base); IR (KBr, cm^{-1}) 3419, 2921, 1597, 1485, 1437 1245; ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 8.19 (dd, J = 4, 2 Hz, 1 H), 8.01 (brs, 1 H), 7.64 (d, J = 8 Hz, 1 H), 7.47 (td, J = 7, 2 Hz, 1 H), 7.34 (d, J = 8 Hz, 1H), 7.16 (t, J = 7 Hz, 1 H), 7.09 (t, J = 7 Hz, 1 H), 6.98 (d, J = 2 Hz, 1 H), 6.64 (d, J = 8 Hz, 1 H), 6.61 (t, J = 5 Hz, 1 H), 3.56 (t, J = 5 Hz, 4 H), 3.00 (m, 1 H), 2.57 (t, J = 5 Hz, 4 H), 2.42 (t, J = 8 Hz, 2 H), 1.84 (m, 4 H), 1.67 (m, 7 H). Anal. ($C_{25}H_{32}N_4$) C, H, N.

***trans*-1-[2-[4-(1*H*-3-Indolyl)cyclohexyl]ethyl]-4-(2-pyridinyl)piperazine (30a).** Using the same general methodology the amide **28a** (6.0 g, 14.9 mmol) was reduced the amine **30a**, which was purified by recrystallization from methylene chloride (2.93 g, 51%): mp 138−9 °C (methylene chloride); EIMS *m*/*z* 388 (14), 294 (23), 267 (25), 107 (base); IR (KBr, cm^{-1}) 2913, 2848, 1594, 1483, 1436, 1244; ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 8.20 (dd, J = 4, 2 Hz, 1 H), 8.10 (brs, 1 H), 7.65 (d, J = 8 Hz, 1 H), 7.47 (td, J = 8, 2 Hz, 1 H), 7.32 (d, J = 8 Hz, 1 H), 7.16 (t, J = 8 Hz, 1 H), 7.09 (t, J = 7 Hz, 1 H), 6.91 (d, J = 2 Hz, 1 H), 6.64 (d, J = 8 Hz, 1 H), 6.61 (t, J = 7 Hz, 1 H), 3.56 (t, J = 5 Hz, 4 H), 2.79 (t, J = 12 Hz, 1 H), 2.57 (t, J = 5 Hz, 4H), 2.46 (t, J = 8 Hz, 2 H), 2.13 (d, J = 11 Hz, 2 H), 1.89 (d, J = 16 Hz, 2 H), 1.4−1.3 (m, 5 H), 1.18 (dd, J = 20, 12 Hz, 2 H). Anal. ($C_{25}H_{32}N_4$) C, H, N. The maleate salt of **30a** was formed by mixing an equimolar amount of maleic acid with the free base in methanol. Evaporation and recrystallization from ethanol afforded the maleate salt: mp 167−9 °C. Anal. ($C_{25}H_{32}N_4 \cdot C_4H_4O_4$) C, H, N.

The following compounds, **29b** and **30b**−**h**, were prepared by coupling the acid precursors **24**−**26** with the appropriate amines, isolating the diastereomerically pure amides, and reducing with AlH_3 as outlined for **29a**.

***cis*-3-[4-[2-(3,6-dihydro-4-phenyl-1(2*H*)-pyridinyl)ethyl]-cyclohexyl]-1*H*-indole (29b):** mp 123−4 °C (ether); EIMS *m*/*z* 384 (24), 172 (base); IR (KBr, cm^{-1}) 3422, 3058, 2922, 1493, 1445, 742; ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 8.10 (br s, 1H), 7.64 (d, J = 8 Hz, 1 H), 7.49−7.25 (m, 5 H), 7.16 (t, J = 8 Hz, 1 H), 7.11 (t, J = 7 Hz, 1 H), 6.96 (d, J = 2 Hz, 1 H), 6.08 (s, 1 H), 3.18 (d, J = 3 Hz, 2 H), 2.99 (m, 1 H), 2.73 (t, J = 6 Hz, 2 H), 2.60 (s, 2 H), 2.50 (t, J = 6 Hz, 2 H), 1.84 (m, 4 H), 1.69 (m, 7 H). Anal. ($C_{27}H_{32}N_2$) C, H, N.

***trans*-3-[4-[2-(3,6-Dihydro-4-phenyl-1(2*H*)-pyridinyl)-ethyl]cyclohexyl]-1*H*-indole (30b):** mp 209−10 °C (ethyl acetate); EIMS *m*/*z* 384 (36), 233 (8), 172 (base); IR (KBr, cm^{-1}) 3428, 3156, 2916, 1465, 1456, 755; ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 9.38 (brs, 1 H), 7.50 (d, J = 8 Hz, 1 H), 7.49−7.28 (m, 5 H), 7.23 (d, J = 7 Hz, 1 H), 7,10 (t, J = 7 Hz, 1 H), 7.02 (t, J = 7 Hz, 1 H), 6.94 (d, J = 2 Hz, 1H) 6.08 (s, 1 H), 3.17 (m, 2 H), 2.72 (m, 1 H), 2.73 (m, 2 H), 2.54−2.44 (m, 4 H), 2.11 (d, J = 11 Hz, 2 H), 1.90 (d, J = 11 Hz, 2 H), 1.64−1.34 (m, 5 H), 1.23 (J = 24, 9 Hz, 2 H). Anal. ($C_{27}H_{32}N_2$) C, H, N.

***trans*-3-[4-[2-(4-Phenyl-1-piperazinyl)ethyl]cyclohexyl]-1*H*-indole (30c):** mp 157 °C (ethyl acetate); EIMS *m*/*z* 388 (35), 175 (base); ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 7.96 (br s, 1 H), 7.75 (d, J = 8 Hz, 1 H), 7.33 (d, J = 7 Hz, 1 H), 7.26 (t, J = 8 Hz, 2 H), 7.18 (t, J = 7 Hz, 1 H), 7.09 (t, J = 7 Hz, 1 H), 6.95 (d, J = 8 Hz, 2 H), 6.93 (s, 1 H), 6.85 (t, J = 7 Hz, 1 H), 3.23 (t, J = 5 Hz, 4 H), 2.80 (tt, J = 12, 3 Hz, 1 H), 2.64 (t, J = 5 Hz, 4 H), 2.48 (t, J = 8 Hz), 22.14 (d, J = 11 Hz, 2 H), 1.90 (d, J = 11 Hz, 1 H), 1.6−1.35 (m, 5 H), 1.20 (dd, J = 20, 12 Hz, 2 H). Anal. ($C_{26}H_{33}N_3$) C, H, N.

***trans*-3-[4-[2-[4-(4-Fluorophenyl)-1-piperazinyl]ethyl]-cyclohexyl]-1-indole (30d):** mp 163−5 °C (ethyl acetate); EIMS *m*/*z* 405 (19), 193 (base); ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 9.43 (s, 1 H), 7.35 (d, J = 8 Hz, 1 H), 6.98 (d, J = 8 Hz, 1 H), 6.85 (dd, J = 8, 7 Hz, 1 H), 6.79 (t, J = 7 Hz, 1 H), 6.67 (m, 5 H), 2.90 (t, J = 5 Hz, 4 H), 2.53 (t, J = 12 Hz, 1 H), 2.38 (t, J = 5 Hz, 4 H), 2.23 (t, J = 8 Hz, 2 H), 1.86 (d, J = 11 Hz, 2 H), 1.64 (d, J = 11 Hz, 2 H), 1.18−1.15 (m, 5 H), 0.93 (dd, J = 20, 12 Hz, 2 H). Anal. ($C_{26}H_{32}FN_3$) C, H, N, F.

***trans*-3-[4-[2-[4-(2-Pyrimidinyl)-1-piperazinyl]ethyl]cyclohexyl]-1*H*-indole monohydrochloride (30e):** mp 262 °C dec (ether−isopropyl alcohol); EIMS *m*/*z* (% base) 389 (M^+, 76), 281 (66), 177 (base); IR (KBr, cm^{-1}) 3489, 2925, 1583, 1553, 1437, 1362; ^{1}H-NMR (DMSO-d_6, 250 MHz) δ 11.12 (brs, 1 H), 10.80 (s, 1 H), 8.45 (d, J = 5 Hz, 2 H), 7.54 (d, J = 8 Hz, 1 H), 7.32 (d, J = 8 Hz, 1 H), 7.04 (m, 2 H), 6.94 (t, J = 8 Hz, 1 H), 6.77 (t, J = 5 Hz, 1 H), 4.69 (d, J = 15 Hz, 2 H), 4.26 (brs, 1 H), 3.57 (d, J = 12 Hz, 2 H), 3.43 (d, J = 12 Hz, 2 H), 3.15 (m, 2 H), 3.03 (dd, J = 18, 10 Hz, 2 H), 2.73 (t, J = 13 Hz, 1 H), 2.02 (d, J = 11 Hz, 2 H), 1.84 (d, J = 12 Hz, 2 H), 1.71 (m, 2 H), 1.47 (dd, J = 20, 11 Hz, 2 H), 1.4 (m, 1 H), 1.16 (dd, J = 20, 11 Hz, 2 H). Anal. ($C_{24}H_{31}N_5 \cdot HCl \cdot {}^1/_2H_2O$) C, H, N, Cl.

***trans*-3-[4-[2-[3,6-Dihydro-4-(2-thienyl)-1(2*H*)-pyridinyl]-ethyl]cyclohexyl]-1*H*-indole (30f):** mp 192−4 °C (EtOAc); EIMS *m*/*z* (% base) 390 (M^+, 56), 178 (base); IR (KBr, cm^{-1}) 3140, 2914, 2824, 1631, 1430, 738; ^{1}H-NMR (DMSO-d_6, 250 MHz) δ 10.69 (brs, 1 H), 7.53 (d, J = 8 Hz, 1 H), 7.37 (d, J = 7 Hz, 1 H), 7.32 (d, J = 8 Hz, 1 H), 7.04 (m, 4 H), 6.94 (t, J = 8 Hz, 1 H), 6.08 (brs, 1 H), 3.34 (s, 2 H), 3.04 (brs, 2 H), 2.72 (t, J = 12 Hz, 1 H), 2.61 (t, J = 5 Hz, 1 H), 2.44 (m, 4 H), 2.01 (d, J = 12 Hz, 2 H), 1.86 (d, J = 12 Hz, 2 H), 1.34 (m, 5 H), 1.16 (dd, J = 20, 12 Hz 2 H). Anal. ($C_{25}H_{30}N_2S$) C, H, N, S.

***trans*-1-[2-[4-(1*H*-5-Fluoro-3-indolyl)cyclohexyl]ethyl]-4-(2-pyridinyl)piperazine (30g):** mp 138−9 °C (ethyl acetate); EIMS *m*/*z* 406 (10.6), 312 (36), 299 (26), 285 (38), 107 (base); ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 8.20 (dd, J = 4, 2 Hz, 1 H), 7.98 (br s, 1 H), 7.48 (td, J = 7, 2 Hz, 1 H), 7.30−7.22 (m, 2 H), 6.98 (s, J = 2 Hz, 1 H), 6.91 (td, J = 8, 2 Hz, 1 H), 6.65 (d, J = 8 Hz, 1 H), 6.62 (t, J = 4 Hz, 1 H), 3.57 (t, J = 5 Hz, 4 H), 2.72 (t, J = 12 Hz, 1 H), 2.58 (t, J = 5 Hz, 1 H), 2.46 (t, J = 8 Hz, 2 H), 2.10 (d, J = 11 Hz, 1 H), 1.89 (d, J = 13 Hz, 2 H), 1.51 (m, 5 H), 1.19 (dd, J = 20, 13 Hz, 2 H). Anal. ($C_{25}H_{31}FN_4$) C, H, N, F.

***trans*-1-[2-[4-(1*H*-5-Methoxy-3-indolyl)cyclohexyl]ethyl]-4-(2-pyridinyl)piperazine Maleate (30h):** mp 181−2 °C (ethanol); ^{1}H-NMR (DMSO-d_6, 250 MHz) δ 10.58 (s, 1 H), 8.16 (d, J = 3 Hz, 1 H), 7.62 (t, J = 7 Hz, 1 H), 7.21 (d, J = 9 Hz, 1 H), 6.99 (dd, J = 8, 2 Hz, 1 H), 6.98 (d, J = 2 Hz, 1 H), 6.95 (d, J = 8 Hz, 1 H), 6.72 (m, 2 H), 6.03 (s, 2 H), 3.75 (s, 3 H), 3.33 (brs, 4 H), 3.15 (brs, 4 H), 2.71 (t, J = 12 Hz, 1 H), 2.02 (d, J = 12 Hz, 2 H), 1.85 (d, J = 12 Hz, 2 H), 1.62 (m, 2 H), 1.45 (m, 3 H), 1.18 (dd, J = 20, 12 Hz, 2 H. Anal. ($C_{26}H_{34}N_4O \cdot C_4H_4O_4 \cdot {}^1/_2H_2O$) C, H, N.

***trans*-3-[4-[2-(4-Pyridin-2-ylpiperazin-1-yl)ethyl]cyclohexyl]-1*H*-indol-5-ol (31).** A mixture of the free base of **30h** (1.3 g, 3.1 mmol) and pyridine hydrochloride (2.49 g, 21.5 mmol) was heated to 130 °C in a sealed tube for 72 h. The mixture was cooled and partitioned between 125 mL of concentrated aqueous ammonium hydroxide and 125 mL of chloroform. The aqueous layer was extracted with an ad-

ditional 50 mL of chloroform, and the combined organic extracts were dried over sodium sulfate. The solvent was evaporated under reduced pressure to give a brown solid which was washed with ca. 30 mL of 2% methanol in chloroform and then recrystallized from ethyl acetate to give **30** (0.70 g, 56% yield): mp 215−7 °C; EIMS *m/z* 404 (57), 389 (10), 283 (24), 107 (base); IR (KBr, cm^{-1}) 3411, 2919, 2848, 1594, 1485, 1439; ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 8.79 (brs, 1h H), 8.18 (d, J = 4 Hz, 1 H), 7.90 (brs, 1 H), 7.51 (t, J = 8 Hz, 1 H), 7.16 (d, J = 9 Hz, 1 H), 7.02 (d, J = 2 Hz, 1 H), 6.89 (d, J = 2 Hz, 1 H) 6.74 (dd, J = 8,2 Hz, 1 H), 6.67 (d, J = 9 Hz, 1 H), 6.62 (t, J = 5 Hz, 1 H), 3.56 (t, J = 5 Hz, 4 H), 2.68 (m, 1h H), 2.58 (t, J = 5 Hz, 4 H), 2.46 (t, J = 8 Hz, 2 H), 2.09 (d, J = 12 Hz, 2 H), 1.88 (d, J = 12 Hz, 2 H), 1.55−1.35 (m, 5 H), 1.16 (dd, J = 9, 25 Hz, 2 H). Anal. ($C_{25}H_{32}N_4O$) C, H, N.

1*H*-Methyl-3-[4-[2-(4-pyridin-2-ylpiperazin-1-yl)ethyl]-cyclohexyl]-1*H*-indole (32). A solution of potassium hydroxide (0.623 g, 11.1 mmol) in 6 mL of degassed DMSO (anhydrous) was treated with **30a** (1.08 g, 2.78 mmol) and stirred for 15 min. The mixture was treated with methyl iodide (0.17 mL, 2.73 mmol), and the resulting solution was stirred for 2 h at room temperature during which time a thick precipitate formed. The reaction mixture was partitioned between 50 mL of water and 50 mL of chloroform. The organic extract was dried over sodium sulfate, and the solvents were evaporated. The resulting residue was purified using MPLC (2% MeOH, 0.1% NH_3 in chloroform) to give the product which was triturated with ether and dried to give **32** (0.63 g, 56% yield): mp 78−9 °C (ether); EIMS *m/z* 402 (M^+, 17), 308 (23), 295 (27), 281 (17), 107 (base); ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 8.20 (d, J = 2 Hz, 1H), 7.63 (d, J = 8 Hz, 1 H), 7.48 (t, J = 7 Hz, 1 H), 7.25 (d, J = 8 Hz, 1 H), 7.20 (t, J = 8 Hz, 1 H), 7.08 (t, J = 7 Hz, 1 H), 6.79 (s, 1 H), 6.68 (d, J = 8 Hz, 1 H), 6.62 (t, J = 7 Hz, 1 H); 3.73 (s, 3 H), 3.57 (t, J = 5 Hz, 4 H), 2.79 (t, J = 12 Hz, 1h H), 2.58 (t, J = 5 Hz, 4 H), 2.46 (t, J = 8 Hz, 2 H), 2.12 (d, J = 12 Hz, 2 H), 1.89 (d, J = 13 Hz, 2 H), 1.40−1.26 (m, 5 H), 1.19 (dd, J = 20, 12 Hz, 2 H). Anal. ($C_{26}H_{34}N_4$) C, H, N.

Pharmacological Methods. [^{3}H]Spiperone Binding in Rat Striatal Membranes. The IC_{50} of compounds was determined according to methods previously described[16] using [^{3}H]spiperone (0.2 nM final concentration) binding to rat striatal membranes in the presence of (+)-butaclamol (1 μM) for nonspecific binding.

[^{3}H]-*N*-Propylnorapomorphine (NPA) Binding in Rat Striatal Membranes. The IC_{50} of compounds was determined according to methods previously described[19] using [^{3}H]-NPA (0.35 nM final concentration) binding to rat striatal membranes in the presence of (+)-butaclamol (2 μM) for nonspecific binding.

Binding to D3 and D4.2 Receptor Isoforms. The human DA D3 receptor cDNA cloned in the pcDNA I/Neo plasmid was obtained from Dr. K. O'Malley and stably transfected into CHO K1 cells by a modified calcium phosphate precipitation technique, and transfectants were selected in G-418, isolated, and screened for expression of human D3 receptors by radioligand binding as previously described.[20] For D4 binding, CHO K1 cells stabily transfected to express the human recombinant DA D4.2 receptor subtype as previously described[21] were used. The K_i values were determined using [^{3}H]spiperone (0.2 nM final concentration) with the appropriate cell membranes.

[^{3}H]Thymidine Uptake in D2 Transfected CHO p-5 Cells. As previously described[22] CHO p-5 cells transfected with the long form of the D2 receptor were plated and 48 h later deprived of serum and then treated 24 h later with standards or test compounds. Eighteen hours later [^{3}H]-thymidine (5 μCi/well) and then trypsin (100 μL of 0.25%) were added. The assay was terminated by filtration using a Brandel 96-well harvester. The filters were counted for radioactivity using the LKB plate counting system.

Inhibition of Spontaneous Locomotor Activity. This procedure was carried out according to methods described previously.[17] Mice were treated with compounds administered ip followed immediately by a 1 h test. Rats were treated orally with compounds 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.

Inhibition of GBL-Stimulated DA Synthesis. Compounds were administered to male Long Evans rats 1 h before sacrifice, and γ-butyrolactone (GBL) (750 mg/kg ip) and NSD 1015 (100 mg/kg ip) were administered 30 min before sacrifice. Brain striatal levels of L-dihydroxyphenylalanine (DOPA) were analyzed by HPLC with electrochemical detection. The control values in mg/g ± SEM of tissue for 0% (GBL + NSD 1015) and 100% (vehicle + NSD1015) reversal in rat striatum were 3831 ± 149 and 1181 ± 65.[18]

Effects on the Firing Rate of Substania Nigra DA Neurons.[23] The action potential of zona compacta DA cells was recorded in chloral-anesthetized rats using standard extracellular recording techniques. DA cells were identified by wave form and firing pattern, and recording sites were varied histologically. The test compound was 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 of maximal inhibition. Drug-induced inhibition of firing was reversed with the DA antagonist haloperidol to confirm a DA agonist mechanism.

Rat Striatal Microdialysis. Adult, male Sprague−Dawley rats (200−250 g) were anesthetized with urethane and placed in a stereotaxic frame. A 4 mm microdialysis probe (CMA, Inc.) was surgically implanted into the striatum and perfused with artificial cerebrospinal fluid at a flow rate of 2 μL/min. Samples were collected every 20 min and analyzed for catecholamine content by HPLC using electrochemical detection.

Inhibition of Apomorphine-Induced Climbing.[24] Mice were injected with apomorphine (1 mg/kg sc) and returned to their cages. Five minutes later the mice were removed and test compounds or vehicle were injected ip. After 10 min, climbing was scored as outlined previously.[12c]

Stereotyped Behavior in Rats.[25] Stereotyped behavior was assessed by a trained observer who rated animals for repetitive sniffing, licking, and gnawing. The duration of each observation was 30 s/rat. Stereotyped behaviors were defined by their continuous presence for a period of at least 15 s. Rats received and injection of the test compound were observed for 1 h and then injected with the DA D1 agonist SKF 383893 and observed for an additional hour.

Monkey Striatal Microdialysis Adult male squirrel monkeys, *Saimiri sciureus*, with permanent cranial guide probes were chair-restrained and had a microdialysis probe inserted through the guide into the putamen nucleus. Microdialysis samples were collected every 20 min and analyzed for catecholamine content by HPLC using electrochemical detection.

Conditioned Avoidance in Squirrel Monkeys. This procedure was carried out according to methods described previously.[26] Inhibition of conditioned avoidance was measured for 6 h after oral administration of compound. Drug effects were expressed as a percentage of avoidance responding relative to control performance during the 4 h of peak effect.

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