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Aminopyrimidines with High Affinity for Both Serotonin and Dopamine Receptors

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A series of {4-[2-(4-arylpiperazin-1-yl)alkyl]cyclohexyl}pyrimidin-2-ylamines was prepared and found to have receptor binding affinity for D2 and D3 dopamine (DA) receptors and serotonin 5-HT1A receptors. The structural contributions to D2/D3 and 5-HT1A receptor binding of the aminopyrimidine, cycloalkyl, and phenylpiperazine portions of the molecule were examined. From these studies compounds **14**, **39**, **42**, **43**, having potent affinity for both DA D2 and 5-HT1A receptors, were evaluated for intrinsic activity at these receptors, in vitro and in vivo. Compound **14** (PD 158771) had a profile indicative of partial agonist activity at both D2 and 5-HT1A receptors causing partially decreased synthesis of the neurotransmitters DA and 5-HT and their metabolites. This compound has a profile in behavioral tests that is predictive of antipsychotic activity, suggesting that mixed partial agonists such as **14** may have utility as antipsychotic agents with increased efficacy and decreased side effects.

Limbic forebrain structures associated with thought and emotion are innervated by both dopamine (DA) and serotonin (5-HT) neurons and are believed to be involved in the etiology of schizophrenia. The influence of 5-HT on midbrain DA neurons has been demonstrated by a variety of experimental techniques.[1,2] This relationship is an important tenet of the serotonergic/dopaminergic hypothesis of schizophrenia which implicates pathology of both neurotransmitter systems in the symptomology of the disease.[3,4] A variety of newer antipsychotic medications such as clozapine,[5−7] risperidone,[8] olanzapine,[9] and sertindole[10] are reported to have efficacy against positive symptoms of schizophrenia and decreased propensities for causing neurological side effects. These properties are believed to result from antagonist activity of the compounds at both DA D2 and 5-HT2 receptors.[11] In addition, the serotonergic component of such compounds has been suggested to increase their efficacy against the negative symptoms of schizophrenia.[12]

Current antipsychotic agents rely on postsynaptic DA receptor antagonism for the inhibition of DA neurotransmission; however, an alternative means to inhibit DA neurotransmission is via the action of DA partial agonists at presynaptic DA receptor sites. When activated by agonists or partial agonists, presynaptic dopamine D2 and D3 receptors have been shown to inhibit the synthesis and release of DA from DA neurons into the synapse.[13,14] Presynaptic DA D2 receptors have a higher level of receptor reserve than postsynaptic D2 receptors[15] and therefore are more sensitive to the actions of partial agonists than postsynaptic receptors. Partial agonists with an appropriate level of intrinsic activity might be expected to act as antipsychotic agents by only stimulating presynaptic DA D2 receptors causing decreased synthesis and release of DA while avoiding stimulation of postsynaptic DA D2 receptors which could exacerbate schizophrenic symptoms.[16]

Similarly agonists and partial agonists acting on somatodendritic 5-HT1A receptors decrease the synthesis and release of 5-HT.[17] Animal behavioral studies in rats,[18−20] and monkeys[21] have shown that 5-HT1A agonists and partial agonists can block catalepsy caused by DA D2 antagonists such as haloperidol. These results suggest that compounds with partial agonist activity at DA D2 and D3 receptors as well as 5-HT1A receptors would decrease both dopaminergic and serotonergic neurotransmission in a balanced manner and might have improved efficacy against schizophrenic symptomology, while having less propensity for causing extrapyramidal side effects.

Recently ziprasidone (**1**)[22,23] and 1192U90 (**2**),[24] having potent affinity for both D2 and 5HT1A receptors, were reported to be in development as antipsychotic agents. Both compounds **1** and **2** are D2 antagonists with partial agonist activity at 5-HT1A receptors. The dipropyl aminotetralin (DPAT) derivative U-67413B (**3**) was reported to have agonist activity at both 5-HT1A and D2 receptors.[25] While DPAT-related compounds have proven to be valuable research tools, they generally have low oral bioavailability properties due to poor absorption and rapid excretion. The aryl piperazine buspirone (**4**) has been shown to be a partial agonist at 5-HT1A receptors but has only moderate to weak affinity for DA D2 receptors.[26] To our knowledge no examples of compounds with potent partial agonist activity at both DA D2 and 5-HT1A receptors have been reported in the literature.

We have discovered a series of cyclohexyl-heteroaryl and cycloalkyl amides **5** which has partial agonist activity at DA D2 and D3 receptors.[27] A comparison of cis and trans isomers about the cyclohexyl ring showed the trans diastereomers had greater affinity for DA D2

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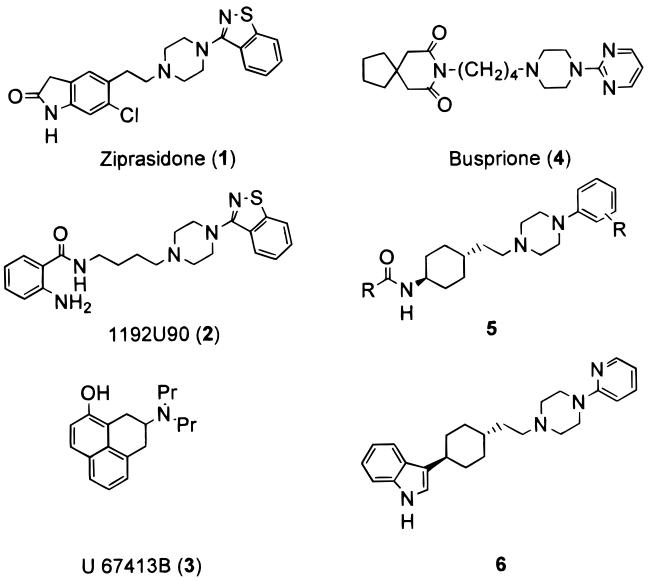
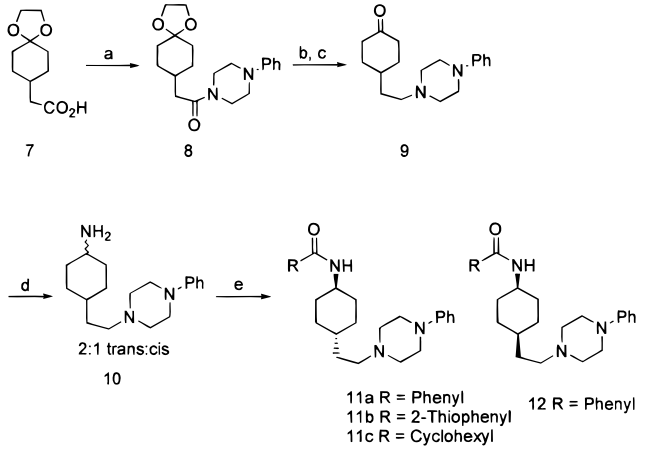


and D3 receptors than the corresponding cis isomers. In general these compounds had only moderate activity at the 5-HT1A receptor (K_i > 50 nM). In related SAR studies we have evaluated replacements to the amide functionality which retain the ability to act as hydrogen bond donors. These have included analogues such as **6** with 3-indolyl functionality attached directly to a cyclohexyl ring.[28] To further explore compounds related to cyclohexylamides **5**, we sought to prepare compounds with quinazoline and pyrimidine functionality attached directly to the cyclohexylamine nitrogen. While retaining the ability to act as hydrogen bond donors, these compounds would not be susceptible to amide bond hydrolysis and would also have a somewhat shorter molecular length than the corresponding amides.

Chemistry

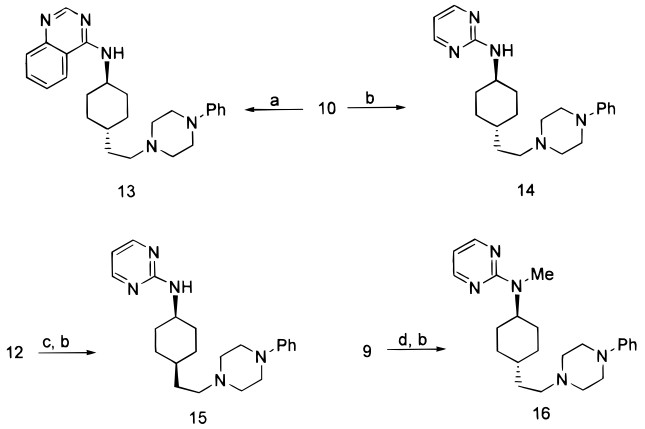
The amide analogues were prepared as outlined in Scheme 1 proceeding from the ketal acid **7**[29] which was coupled with 1-phenylpiperazine. The amide **8** was reduced and the ketal removed to give ketopiperazine **9**. The cyclohexanone **9** was converted to the cyclohexylamine **10** using reductive amination conditions, and the diastereomeric mixture of amines was acylated with various acid chlorides to prepare amides **11a**−**c** and **12**. These cis and trans isomers could be readily separated using medium-pressure liquid chromatography (MPLC) or fractional crystallization from ethyl acetate. In the case of **11b** and **11c** these cis isomers could also be isolated but had little of the desired activity. To form the amino heterocycle analogues **13** and **14**, the diastereomeric mixture of amines **10** was reacted with various chlorinated heterocycles in the presence of triethylamine in refluxing ethanol (Scheme 2). The trans aminoquinazoline analogue **13** could be separated chromatographically from the corresponding cis isomer. However isolation of the corresponding aminopyrimidine analogue **14** proved to be more difficult as the predominant trans isomers could only be obtained in low yields by fractional crystallization from ethyl acetate. The relative configuration of **14** was determined by X-ray crystallography (Figure 1) and was in agreement with the stereochemical assignment based upon NMR coupling constants and chemical shifts. The

Scheme 1[a]



[a] (a) Isobutyl chloroformate, Et_3N, CH_2Cl_2, 1-phenylpiperazine; (b) AlH_3, THF; (c) aqueous HCl; (d) NH_4OAc, $NaCNBH_3$; (e) acid chloride, Et_3N.

Scheme 2[a]



[a] (a) 4-Chloroquinazoline, Et_3N; (b) 2-chloropyrimidine, Et_3N; (c) 6 M HCl; (d) methylamine, $NaCNBH_3$.

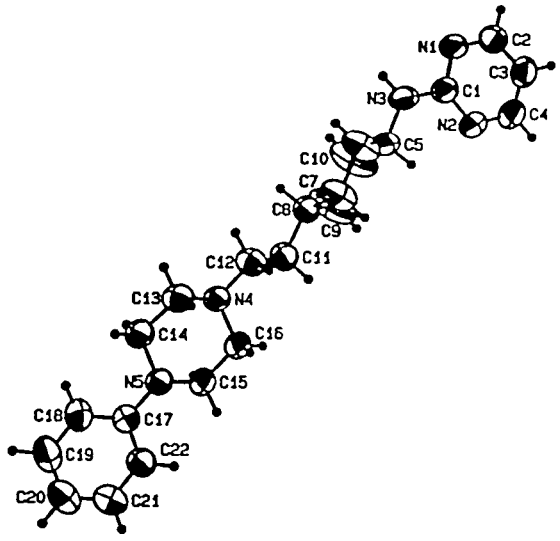
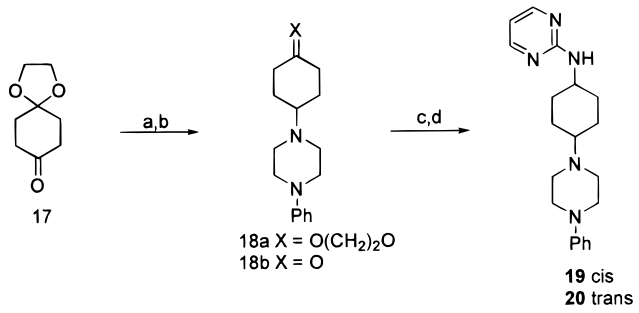


Figure 1. X-ray structure of compound **14**.

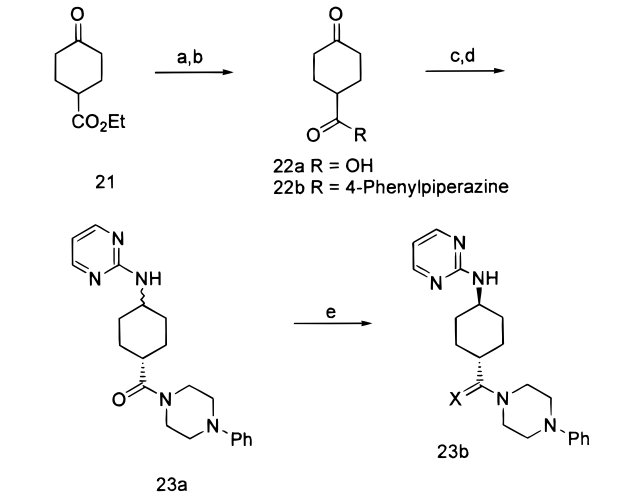
corresponding cis pyrimidine isomer **15** was prepared by hydrolysis of the pure cis benzamide analogue **12** and treatment of the intermediate cis amine with 2-chloropyrimidine. The *N*-methyl analogue **16** was prepared from ketone **9** using chemistry analogous to that employed in the synthesis of compound **14**.

Scheme 3[a]



[a] (a) Phenylpiperazine, $NaBH(OAc)_3$; (b) HCl; NH_4OAc, $NaCNBH_3$; (c) 2-chloropyrimidine, Na_2CO_3.

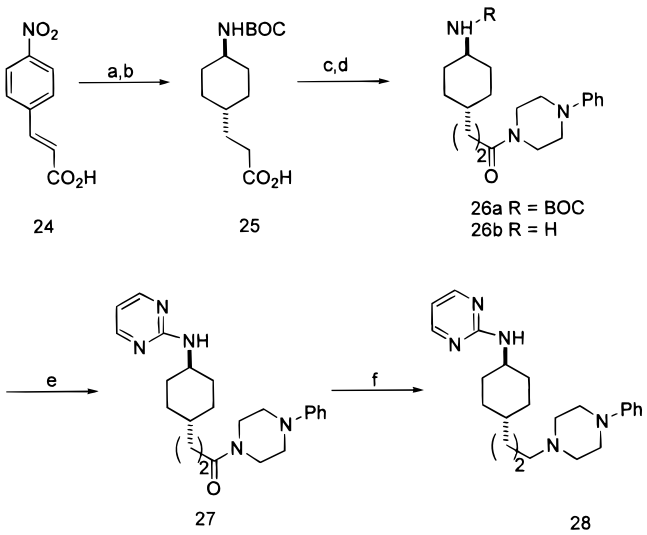
Scheme 4[a]



[a] (a) NaOH, $EtOH/H_2O$; (b) isobutyl chloroformate; Et_3N, phenylpiperazine; (c) HCl; NH_4OAc, $NaCNBH_3$; (d) 2-chloropyrimidine, Na_2CO_3; (e) $LiAlH_4$, 0 °C; chromatography.

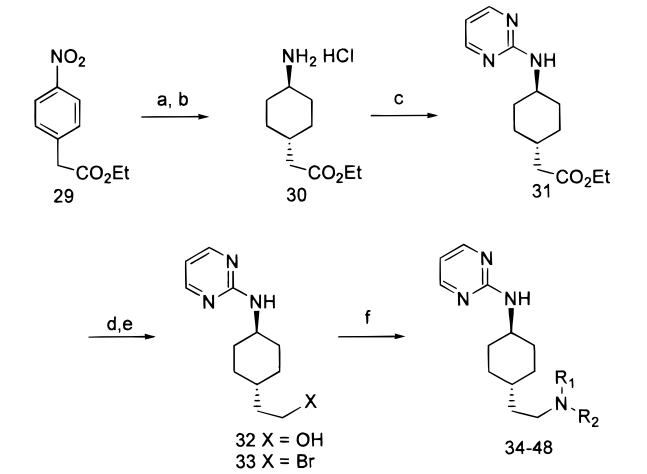
To study the effect of distance between the aminopyrimidine and the arylpiperazine functionalities on receptor affinity, compounds with varying alkyl chain lengths and cyclohexane stereochemistry were prepared. Reductive amination of cyclohexane dione monoketal **17** with 1-phenylpiperazine gave compound **18a** which was hydrolyzed to give the ketone **18b** (Scheme 3). The ketone **18b** was subjected to reductive amination with ammonium acetate as the nitrogen source, and the mixture of amines reacted with 2-chloropyrimidine to give the targets **19** and **20** which were separated chromatographically. The compound **23b** having a one-carbon link between the cyclohexane and piperazine functionality was prepared in five steps from ethyl 4-oxocyclohexanonecarboxylate **21** (Scheme 4). The carboxylic acid **22a** was converted to the corresponding amide **22b**. Using the three-step procedure previously outlined the pure trans isomer **23b** was isolated chromatographically. Hydrogenation of 4-nitrocinnamic acid (**24**) followed by protection of the amino group with the BOC protecting group allowed the isolation of the major trans amino acid isomer **25** by fractional crystallization (Scheme 5). The acid **25** was coupled with phenylpiperazine and the BOC group removed from **26a** giving the amine **26b**. Reaction of **26b** with 2-chloropyrimidine gave the amide **27** which was reduced to the target amine **28** having a three-carbon spacer between the cyclohexane and piperazine functionality.

Scheme 5[a]



[a] (a) H_2, Pd/C, aqueous NaOH; (b) $(tBuCO_2)_2O$, NaOH; (c) isobutyl chloroformate, Et_3N, phenylpiperazine; (d) TFA; (e) 2-chloropyrimidine, Na_2CO_3; (f) $LiAlH_4$, 0 °C.

Scheme 6[a]



[a] (a) H_2 Ra Ni; (b) EtOH, HCl; (c)(i) NH_4OH, $CHCl_3$, (ii) 2-chloropyrimidine, Et_3N, EtOH, reflux; (d) $LiAlH_4$, 0 °C; (e) polymer-supported PPh_3, CBr_4; (f) HNR_2R_2, K_2CO_3.

After some experimentation a more efficient route was developed for the synthesis of analogues having the trans cyclohexylethyl spacer as outlined in Scheme 6. In an adaptation of a literature procedure, exhaustive reduction of the commercially available 4-nitrophenylacetic acid **29** followed by esterification and recrystallization resulted in the preparation of pure trans amino ester hydrochloride **30**.[30] The freebase of **30** was treated with 2-chloropyrimidine giving the pyrimidinyl ester **31**, and careful reduction of ester functionality with $LiAlH_4$ at 0 °C produced the alcohol **32**. Bromination of alcohol **32** was accomplished by reaction with CBr_4 in the presence of polystyrene-supported triphenylphosphine.[31] Purification of bromide **33** was simplified because the phosphine oxide byproduct could be removed by filtration. The tertiary amines **34**−**48** were prepared through reaction of the corresponding secondary amines with bromide **33** in acetonitrile at reflux in the presence of K_2CO_3.

Pharmacology

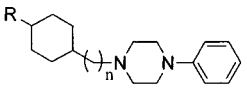
Cloned human D2 and D3 receptors expressed in CHO-K1 cells were used to determine DA receptor affinity as previously described[32,33] with the radioligands [^{3}H]N-0437 and [^{3}H]spiperone, respectively, for the D2 and D3 assays. Affinities of compounds for the 5-HT1A receptor were determined by measuring their ability to displace the radioligand [^{3}H]8-OH-DPAT from a rat hippocampal preparation.[34] Selected compounds were assessed for their intrinsic activity at DA D2 receptors in vitro by measuring their ability to increase [^{3}H]-thymidine uptake in CHO-K1 cells transfected with the hD2 receptor. In vivo, DA D2 agonist or antagonist activity was determined by measuring compounds effects on DA synthesis by observing the changes in accumulation of *l*-3,4-dihydroxyphenylalanine (DOPA) after administration of a 10 mg/kg ip dose of test compounds.[34] Similarly intrinsic agonist activity at 5-HT1A receptors could be measured in vivo by measuring changes in 5-HT levels after administration of selected compound by observing accumulation of the 5-HT metabolite 5-hydroxytryptophan (5-HTP).

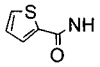
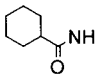
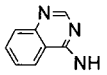
Results and Discussion

Initially a series of compounds differing only in their *N*-cyclohexyl substituents was examined for their ability to bind to DA D2, D3 and 5-HT1A receptors in vitro. Although the amides **11b** and **11c** had good affinity for D2 and D3 receptors, they had relatively weak affinity for 5-HT1A receptors (Table 1). Similarly, the quinazoline substituted analog **13** also had weak affinity for the 5-HT1A receptor relative to its potency for D2 and D3 receptors. However, aminopyrimidine analogue **14** was found to have potent affinity for both D2 and 5-HT1A receptors but was slightly weaker than the amide analogues at the D3 receptor. The good affinity of **14** for the 5HT1A and DA receptors does not appear to involve the hydrogen bond donation from the aminopyrimidine NH as the *N*-methyl analogue **16** had affinity similar to **14** at all three receptors. Thus, the aminopyrimidyl group plays a larger role for the recognition of compounds by the 5-HT1A receptor than for DA D2 or D3 receptors.

The importance of the 1,4 stereochemistry about the cyclohexane ring system was studied. While the trans isomer **14** was nearly equipotent at D2 and 5-HT1A receptors, the cis isomer **15** was nearly 10-fold weaker at D2 receptors while retaining its potency at 5-HT1A receptors. A series of analogues which probed the influence of the spacing between the aminopyrimidine and phenylpiperazine functionalities found in **14** was examined. Decreasing the chain length between the cyclohexyl and piperazinyl rings from two atoms to one (compound **23b**) caused a greater than 10-fold decrease in 5-HT1A affinity while the D2 affinity was essentially unchanged. Attachment of the phenylpiperazine ring directly to the cyclohexane ring (compound **20**) resulted in large decreases in binding for all three receptors. Increasing the chain length to three carbon atoms as in compound **28** resulted in little change in binding affinity at D2 receptors and a larger decrease at D3 and 5-HT1A receptors. These studies showed that the trans cyclohexylethyl linkage was essential for high potency at both DA D2 receptors and 5-HT1A receptors.

Table 1. Effect of Cyclohexylamine Substitution and Stereochemistry on Binding

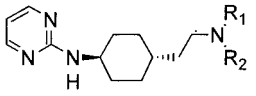


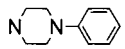
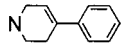
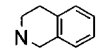
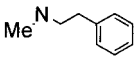
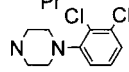
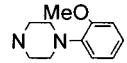
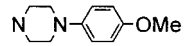
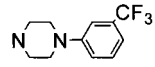
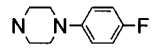
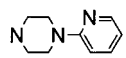
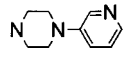
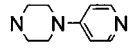
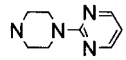
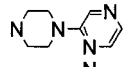
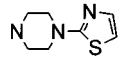
	R	n	Stereochem	Binding (Ki, nM)[a] D_2[b]	D_3[b]	5-HT_{1A}[b]
11b		2	trans	3.4	0.8	57
11c		2	trans	38	0.14	5300
13		2	trans	3.2	0.02	74
14		2	trans	5.2	13.7	3.5
15		2	cis	28	29	1.9
16		2	trans	4.8	24	4.7
19		0	cis	160	550	470
20		0	trans	320	610	83
23b		1	trans	5.7	89	41
28		3	trans	7.4	54	16

[a] Ligands: D_2, [^{3}H]N-0437; D_3, [^{3}H]spiperone; 5-HT_{1A}, [^{3}H]8-OH-DPAT. [b] K_i values were obtained from six concentrations run in triplicate by a nonlinear regression analysis, the results of which did not vary by more than 25%.

The effects of changes to the arylpiperazine functionality on DA D2 and D3 receptor affinity as well as 5-HT1A binding activity were assessed (Table 2). Analogue **34** in which the phenylpiperazine moiety was replaced with a phenyl tetrahydropyridine showed similar affinity for DA D2 and 5-HT1A receptors and somewhat improved affinity for DA D3 receptors. The *N*-methylphenethylamine analogue **36** was weaker at both D2 and 5-HT1A receptors, as was the tetrahydroisoquinoline analogue **35**. Lack of a phenyl ring in this portion of the molecule as in compound **37** resulted in an analogue that was devoid of affinity for DA D2 and D3 receptors. Having shown the importance of aromatic functionality in this portion of the molecule, we determined the effect of phenyl substituents as well as its replacement by various heterocycles. Dichloro analogue **38** had similar affinity for D2 receptors as **14** but had decreased affinity for 5-HT1A receptors. The 2-methoxyphenyl analogue **39** had somewhat increased potency for 5-HT1A receptors and similar potency for for D2 receptors as compound **14**. The 4-methoxyphenyl analogue **40** had weaker affinity for both D2 and 5-HT1A receptors. Alkylated *N*-[3-(trifluoromethyl)-phenyl]piperazines have been shown to have good affinity for 5-HT1A receptors.[35] However in this series the 3-trifluoromethyl substituted analogue **41** retained

Table 2. Structure−Activity Relationship of (Cyclohexylamino)pyrimidines



		Receptor Binding (Ki, nM)[a]		
	NR_1R_2	D_2[b]	D_3[b]	5-HT_{1A}[b]
14		5.0	14	3.5
34		4.7	3.7	3.9
35		110	40	44
36		39	ND[c]	91
37		2400	800	ND
38		11	5	76
39		3	11	0.5
40		390	52	160
41		6	32	13
42		8.5	48	4.5
43		12	26	2.2
44		25	4.7	9.5
45		4800	2300	730
46		240	590	8.6
47		180	210	29
48		46	ND	10

[a] Ligands: D_2, [^{3}H]N-0437; D_3, [^{3}H]spiperone; 5-HT_{1A}, [^{3}H]8-OH-DPAT. [b] K_i values were obtained from six concentrations run in triplicate by a nonlinear regression analysis, the results of which did not vary by more than 25%. [c] Not determined.

similar affinity to the D2 receptor as the unsubstituted analogue but was 4-fold weaker at the 5-HT1A receptor. The 4-fluorophenyl-substituted analogue **42** was found to have similar potency for both D2 and 5-HT1A receptors as the unsubstituted analogue **14**. However the potency for the D3 receptor was approximately 4-fold weaker. From this set of compounds it appears that both D2 and 5-HT1A receptors tolerate substitution in the 2 and 3 positions of the aryl ring attached to the piperazine but tolerate only small substituents such as fluorine in the 4 position of this ring.

The effects on receptor binding caused by replacement of the phenyl ring of **14** with various heterocycles were also studied. The 2-pyridyl analogue **43** had a slight (2-fold) decrease in potency at the DA D2 and D3 receptors and similar affinity for the 5-HT1A receptors.

Table 3. Functional Activity of Compounds with High Affinity for Both DA and 5HT Receptors

no.	inhibition of [^{3}H] thymidine uptake (% intrinsic activity, EC_{50} or IC_{50} in nM)[a]	% of control in limbic DOPA levels 10 mg/kg ip[b]	% of control in limbic 5-HTP levels 10 mg/kg ip[b]
14	60% EC_{50} = 29	67 ± 4	57± 5
39	8% IC_{50} = 9.9	173 ± 3	128 ± 7
42	5% IC_{50} = 79	142 ± 9	143 ± 6
43	41%, EC_{50} = 28	159 ± 3	53 ± 3

[a] Effects measured in CHO p-5 cells transfected with the h−D2 receptor. Intrinsic acvtivity measured relative to the full agonist quinpirole. In cases with less than 20% increase, blockade of quinpirole effects were measured to determine IC_{50}. [b] Test compounds were administered ip (10 mg/kg) 30 min. before the decarboxylase inhibitor NSD 1015 (100 mg/kg ip), and animals were sacrificed 30 min after the NSD 1015. Each value is a mean of 4−8 animals and is expressed as a percent of control values 974 ± 16 (ng/g ± SEM) and 469 ± 5 (mg/g ± SEM) for mesolimbic DOPA and 5-HTP levels, respectively.

The 3-pyridyl analogue **44** also showed somewhat decreased affinity for D2 and 5-HT1A receptors while having slightly improved affinity for D3 receptors. The corresponding 4-pyridyl analogue **45** had much weaker affinity for all three receptors. The 2-pyrimidinyl analogue **46** had relatively weak affinity for DA D2 and D3 receptors but good affinity for 5-HT1A receptors. A similar trend was observed with the 2-pyrazinyl analogue **47** for the DA receptor subtypes; however, **47** was somewhat weaker at 5-HT1A receptors than was the pyrimidine analogue **46**. The 2-thiazolyl analogue **27** had somewhat decreased affinity for DA D2 receptors and slightly decreased affinity for 5-HT1A receptors. Taken together these studies suggest that the DA D2 receptors and 5-HT1A receptors have differing requirements for high binding affinity which are mutually satisfied by the aryl piperazines **14, 39**, **42**, and **43**.

This subset of compounds having potent affinity for both 5-HT1A and DA D2 receptors was evaluated in more detail to characterize their intrinsic agonist activity at these two receptor sites in vitro and in vivo (Table 3). Compounds were studied in vitro for their ability to stimulate mitogenisis (as measured by [^{3}H]thymidine uptake) in CHO cells cloned with the long form of the human D2 receptor as a measure of intrinsic activity.[36] Compound **14** had partial agonist effects at DA D2 receptors exhibiting a maximal stimulation of [^{3}H]-thymidine uptake of 60% relative to the full DA D2 agonist quinpirole. In contrast, compounds **39** and **42** gave negligible increases in the [^{3}H]thymidine uptake assay and effectively antagonized the stimulation of [^{3}H]-thymidine uptake induced by the DA agonist quinpirole. Compound **43** exhibited weaker intrinsic activity (40% compared to quinpirole) at D2 receptors than the corresponding phenyl analogue **14**. Neurochemical changes in the mesolimbic region of the rat brain brought about by administration of a 10 mg/kg dose of these compounds was also studied as a measure of intrinsic activity of DA D2 receptors in vivo. The DA D2 partial agonist **14** decreased DA synthesis in the striatum when administered at 10 mg/kg ip. As expected the DA D2 antagonists **39** and **42** increased DA synthesis. The weak partial agonist **43** also increased DA synthesis, perhaps reflecting its weaker intrinsic activity at D2 receptors compared to **14**. The effect of the four compounds on 5-HTP levels after ip adminis-

Table 4. Neurochemical and Behavioral Effects of Compound **14**

test	result
% decrease of rat striatal dopamine overflow (10 mg/kg, ip)[a,b]	50 (36; 64)
% decrease of rat striatal 5-HIAA overflow (10 mg/kg, ip)[a,b]	42 (28; 56)
inhibition of spontaneous locomotor activity in mice (ED_{50} ip)[b]	0.4 (0.3; 0.5)
inhibition of spontaneous locomotor activity in rats (ED_{50} po)[b]	4.6 (3.2; 6.4)
inhibn of Sidman avoidance in squirrel monkey (ED_{50}, mg/kg po)[b]	0.28 (0.02; 0.34)

[a] Measured via in vivo microdialysis ($n = 4$). [b] 95% confidence limits in parantheses.

tration was used as an in vivo measure of intrinsic activity at 5-HT1A receptors. The DA partial agonist **14** which decreased DA synthesis also caused significantly decreased 5-HT synthesis as evidenced by decreases in 5-HTP levels, suggesting agonist or partial agonist activity at somatodendritic 5-HT1A receptors. The DA antagonists **39** and **42** which increased DA synthesis also increased 5-HT synthesis suggestive of antagonist activity at somatodendritic 5-HT1A receptors. The pyridylpiperazine analogue **43** which increased DA synthesis also caused a decrease in 5-HT1A synthesis. The contrasting effects on 5-HT1A synthesis for **43** suggest that it is acting functionally as an antagonist in vivo at presynaptic DA D2 receptors but can act as an agonist (or partial agonist) at 5-HT1A receptors.

Of these four compounds only compound **14** (PD 158771) possessed properties consistent with partial agonist activity at both DA D2 and 5-HT1A receptors. This compound was chosen for further study in neurochemical assays and behavioral models predictive of antipsychotic efficacy (Table 4). Neurotransmitter levels in the nucleus accumbens of rats were measured using microdialysis techniques following a 10 mg/kg dose (ip) of compound **14**. Parallel decreases were observed in the intracellular concentration of DA (50%), its metabolite DOPAC (50%) along with the 5-HT metabolite 5-HIAA (42%) The compound inhibited exploratory locomotor activity in mice after ip administration ($ED_{50} = 0.4$ mg/kg) and in rats after oral administration ($ED_{50} = 4.6$ mg/kg).[37] Compound **14** was also evaluated for its ability to inhibit Sidman avoidance responding in squirrel monkeys,[38] a primate test which is considered to be predictive of antipsychotic efficacy. The compound showed excellent oral potency in this paradigm ($ED_{50} = 0.28$ mg/kg po).

In summary, it has been shown that introduction of pyrimidinyl functionality to a series of [(aminocyclohexyl)ethyl]piperazines increased affinity for 5-HT1A receptors. The structure−activity relationships of both DA D2 and 5-HT1A receptors were explored. Compound **14** was identified as having a partial agonist profile at both receptors in vitro. In vivo it decreased both DA and 5-HT synthesis and release indicative of dual DA and 5-HT presynaptic receptor activation. Compound **14** was also active in three behavioral paradigms predictive of antipsychotic efficacy. These studies suggest that a compound having dual partial agonist activity at DA and 5-HT presynaptic receptors may have potential utility as an antipsychotic agent.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Proton NMR spectra were recorded on a Bruker 400 MHz NMR instrument or a Varian 200 MHz NMR instrument. The spectra recorded were consistent with the proposed structures. Chemical ionization mass spectra (CIMS) were obtained on a Micromass Trio 2A spectrometer; the spectra are described by the molecular peak (M) and its intensity relative to the base peak (100). Elemental analysis were performed by the Analytical Chemistry Section at Parke-Davis, Ann Arbor MI, and Robertson labs. 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).

2-(1,4-Dioxaspiro[4.5]dec-8-yl)-1-[4-phenyl-1-piperazinyl]ethanone (8). A solution of (1,4-dioxaspiro[4.5]dec-8-yl)-acetic acid (**7**)[29] (10.5 g, 52.5 mmol) and triethylamine (11.6 mL, 83.3 mmol) in 200 mL of methylene chloride was cooled to 0 °C in an ice bath and treated with isobutyl chloroformate (7.2 mL, 55.5 mmol). After stirring for 10 min, 1-phenylpiperazine (8.52 g, 52.5 mmol) was added in 50 mL of methylene chloride. The reaction was removed from the ice bath and stirred at room temperature for 24 h. The reaction mixture was treated with 200 mL of a saturated $NaHCO_3$ solution, and the aqueous layer was separated and extracted with an additional 150 mL of methylene chloride. The combined organic fractions were dried over magnesium sulfate, the solvent was removed under reduced pressure, and the residue was recrystallized from ethyl acetate to obtain the product **8** as white needles (12.4 g, 68% yield): mp 133−5 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.60 (m, 2 H), 6.95 (m, 3 H), 3.95 (s, 4 H), 3.80 (t, $J = 5$ Hz, 2 H), 3.63 (t, $J = 5$ Hz, 2 H), 3.25 (m, 2 H), 2.30 (d, $J = 8$ Hz, 2 H), 1.75 (m, 8 H), 1.30 (m, 2 H); CIMS *m/z* 345 (M + H), base). Anal. ($C_{20}H_{28}N_2O_3$) C, H, N.

4-[2-(4-Phenyl-1-piperazinyl)ethyl]cyclohexanone (9). A slurry of lithium aluminum hydride (3.5 g, 88.2 mmol) in 100 mL of THF was cooled to 0 °C and treated with aluminum chloride (3.92 g, 29.4 mmol) in 100 mL of ether. The reaction was stirred for 30 min at 0 °C, and the 2-(1,4-dioxaspiro[4.5]-dec-8-yl)-1-(4-phenyl-1-piperazinyl)ethanone (**8**) (10.2 g, 29.4 mmol) was added in portions over 1 h. After 18 h, the reaction was quenched with 5 mL of water and 5 mL of a 25% sodium hydroxide solution. The mixture was stirred for 1 h and filtered through a pad of Celite, and the filter cake was washed with 300 mL of ether. The combined organic extracts were concentrated to give a white solid which was dissolved in a 230 mL of a 1:1 mixture of acetone and 10% HCl. After stirring at room temperature for 60 h, the acetone was removed under reduced pressure. The pH of the aqueous reaction mixture was adjusted to pH 9 with conc NH_4OH, the aqueous mixture was extracted with two 250 mL portions of chloroform, the combined organic fractions were dried over Na_2SO_4, and the solvents were removed under reduced pressure to give 4-[2-(4-phenyl-1-piperazinyl)ethyl]cyclohexanone (7.59 g, 98%) as a white solid. Mp 94−8 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (t, $J = 8$ Hz, 2 H), 6.89 (d, $J = 8$ Hz, 2 H), 6.82 (t, $J = 8$ Hz, 1 H), 3.18 (t, $J = 5$ Hz, 4 H), 2.58 (t, $J = 5$ Hz, 4 H), 2.45 (t, $J = 8$ Hz, 2 H), 2.34 (m, 4 H), 2.04 (m, 2 H), 1.77 (m, 1 H), 1.53 (dd, $J = 15$, 7 Hz, 2H), 1.41 (ddd, $J = 24$, 11, 5 Hz, 2 H). CIMS *m/z* 287 (M + H, base). Anal. ($C_{18}H_{26}N_2O$) C, H, N.

***cis*- and *trans*-4-[2-(4-Phenyl-1-piperazinyl)ethyl]cyclohexanamine (10).** A mixture of 4-[2-(4-phenyl-1-piperazinyl)ethyl]cyclohexanone (**9**) (10 g, 36.3 mmol) and ammonium acetate (27.2 g, 360 mmol) were dissolved in 250 mL methanol, treated with sodium cyanoborohydride (1.62 g, 25.9 mmol), and stirred at room temperature for 18 h. The solvent was removed under reduced pressure and the residue partitioned between chloroform and 2 N Na_2CO_3. The organic layer was separated and dried over Na_2SO_4, and the solvent was removed under reduced pressure to give 10.0 g of a mixture

of *cis* and *trans*-4-[2-(4-phenyl-1-piperazinyl)ethyl]cyclohexanamines (**10**) as a colorless oil which was used directly in the next reactions.

***cis*- and *trans*-*N*-{4-[2-(4-Phenylpiperazin-1-yl)ethyl]cyclohexyl}benzamide (11a and 12).** A mixture of cis and trans cyclohexanamines (**10**) (4.00 g, 13.9 mmol) and triethylamine (2.92 mL, 21 mmol) in methylene chloride (80 mL) was cooled to 0 °C, treated with benzoyl chloride (1.62 mL, 14.0 mmol), and allowed to warm to room temperature and stir for 16 h. The reaction was partitioned between chloroform and aqueous $NaHCO_3$, the organic fraction was dried over Na_2SO_4, and the solvents were removed under reduced pressure. The residue was chromatographed over silica gel using a mixture of chloroform, 2−3% methanol, and 0.1% ammonia as the eluant giving the cis isomer **12** as the faster moving component (1.8 g, 33% yield). Mp 144−6 °C (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 7 Hz, 2 H), 7.50 (t, J = 7 Hz, 1 H), 7.44 (t, J = 7 Hz, 2 H), 7.26 (t, J = 7 Hz, 2 H), 6.94 (d, J = 7 Hz, 2 H), 6.84 (t, J = 7 Hz, 1 H), 6.15 (d, J = 7 Hz, 1 H), 4.23 (m, 1 H), 3.21 (t, J = 5 Hz, 4 H), 2.61 (t, J = 5 Hz, 4 H), 2.43 (t, J = 8 Hz, 2 H), 1.74 (m, 6 H), 1.53 (m, 3 H), 1.31 (m, 2 H); CIMS m/z 392 (M + H, base). Anal. ($C_{25}H_{33}N_3O$) C, H, N.

The second fraction isolated was the trans isomer **11a** (3.0 g, 55% yield). Mp 224−5 °C (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 7 Hz, 2 H), 7.48 (t, J = 7 Hz, 1 H), 7.42 (t, J = 7 Hz, 2 H), 7.26 (t, J = 7 Hz, 2 H), 6.93 (d, J = 7 Hz, 2 H), 6.85 (t, J = 7 Hz, 1 H), 5.91 (d, J = 8 Hz, 1 H), 3.92 (m, 1 H), 3.21 (t, J = 5 Hz, 4 H), 2.60 (t, J = 5 Hz, 4 H), 2.42 (t, J = 8 Hz, 2 H), 2.11 (d, J = 11 Hz, 2 H), 1.83 (d, J = 13 Hz, 2 H), 1.48 (dd, J = 11, 7 Hz, 2 H), 1.31 (m, 1 H), 1.18 (m, 4 H); CIMS m/z 392 (M + H, base). Anal. ($C_{25}H_{33}N_3O$) C, H, N.

Amides **11b** and **11c** were prepared in a similar way from intermediate **10**.

***trans*-Thiophene-2-carboxylic Acid {4-[2-(4-Phenylpiperazin-1-yl)ethyl]cyclohexyl}amide (11b).** Mp 203−4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 4 Hz, 1 H), 7.44 (d, J = 4 Hz, 1 H), 7.26 (t, J = 8 Hz, 2 H), 7.06 (t, J = 4 Hz, 1 H), 6.93 (d, J = 8 Hz, 2 H), 6.85 (t, J = 7 Hz, 1 H), 5.91 (d, J = 8 Hz, 1 H), 3.91 (m, 1 H), 3.21 (t, J = 5 Hz, 4 H), 2.60 (t, J = 5 Hz, 4 H), 2.42 (t, J = 8 Hz, 2 H), 2.10 (d, J = 12 Hz, 2 H), 1.83 (d, J = 12 Hz, 2 H), 1.47 (dd, J = 11, 7 Hz, 2 H), 1.30 (m, 1 H), 1.18 (m, 4 H); CIMS m/z 398 (M + H, base). Anal. ($C_{23}H_{31}N_3O_1S$) C, H, N.

***trans*-Cyclohexanecarboxylic Acid {4-[2-(4-Phenylpiperazin-1-yl)ethyl]cyclohexyl}amide (11c).** Mp 233−5 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (t, J = 8 Hz, 2 H), 6.92 (d, J = 8 Hz, 2 H), 6.85 (t, J = 7 Hz, 1 H), 5.22 (d, J = 8 Hz, 1 H), 3.71 (m, 1 H), 3.21 (t, J = 5 Hz, 4 H), 2.60 (t, J = 5 Hz, 4 H), 2.41 (t, J = 8 Hz, 2 H), 2.11 (d, J = 11 Hz, 2 H), 1.99 (m, 3 H), 1.79 (m, 6 H), 1.66 (m, 1H); 1.43 (m, 4 H), 1.22 (m, 4 H), 1.08 (m, 4 H); CIMS m/z 398 (M + H, base). Anal. ($C_{25}H_{39}N_3O$) C, H, N.

***trans*-{4-[2-(4-Phenylpiperazin-1-yl)ethyl]cyclohexyl}quinazolin-4-ylamine (13).** The mixture of *cis*- and *trans*-4-[2-[4-phenyl-1-piperazinyl]ethyl]cyclohexylamines (**10**) (1.1 g, 3.9 mmol), 4-chloroquinazoline (0.64 g, 3.9 mmol), and triethylamine (0.53 mL) in 10 mL of ethanol was heated to reflux for 18 h. The reaction was filtered and concentrated under reduced pressure, and the residue was chromatographed over silica gel (2% MeOH in $CHCl_3$). The appropriate fractions were concentrated and recrystallized from ethyl acetate to give the title compound as a white solid (454 mg, 28% yield). Mp 191−2 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1 H), 7.82 (d, J = 8 Hz, 1 H), 7.72(t, J = 8 Hz, 1 H), 7.67 (d, J = 8 Hz, 1 H), 7.44 (d, J = 8 Hz, 1 H), 7.26 (m, 2 H), 6.94 (d, J = 8 Hz, 2 H), 6.86 (t, J = 7 Hz, 1 H), 5.50 (d, J = 8 Hz, 1 H), 4.21 (m, 1 H), 3.23 (t, J = 5 Hz, 4 H), 2.64 (t, J = 5 Hz, 4 H), 2.47 (t, J = 8 Hz, 2 H), 2.23 (d, J = 12 Hz, 2 H), 1.88 (d, J = 12 Hz, 2 H), 1.52 (dd, J = 11, 7 Hz, 2 H), 1.31 (m, 1 H), 1.28 (m, 4 H); CIMS m/z 416 (M + H, base). Anal. ($C_{26}H_{33}N_5$) C, H, N.

***trans*-{4-[2-(4-Phenylpiperazin-1-yl)ethyl]cyclohexyl}pyrimidin-2-ylamine (14).** The mixture of *cis* and *trans*-4-[2-(4-phenyl-1-piperazinyl)ethyl]cyclohexylamines (**10**) (2.0 g, 7.0 mmol), 2-chloropyrimidine (0.92 g, 8.0 mmol), and triethylamine (2.2 mL) in 40 mL of ethanol was heated to reflux for 32 h. The reaction was cooled, and the solvents were removed under reduced pressure. The residue was partitioned between chloroform and 2 N Na_2CO_3, the organic layer was separated and dried over Na_2SO_4, and the solvents were removed under reduced pressure. The residue was chromatographed over silica gel using a mixture of chloroform, 2−3% methanol, and 0.1% ammonia as the eluants. Fractions enriched in the trans isomer were combined and recrystallized from ethyl acetate to give *trans*-{4-[2-(4-phenylpiperazin-1-yl)ethyl]cyclohexyl}-pyrimidin-2-ylamine (**14**) (0.68 g, 26% yield). Mp 162−3 °C; (400 MHz, $CDCl_3$) δ 8.21 (d, J = 5 Hz, 2 H), 7.22 (t, J = 8 Hz, 2 H), 6.89 (d, J = 8 Hz, 2 H), 6.83 (t, J = 8 Hz, 1 H), 6.44 (t, J = 5 Hz, 1 H), 4.96 (d, J = 8 Hz, 1 H), 3.72 (m, 1 H), 3.17 (t, J = 5 Hz, 4 H), 2.56 (t, J = 5 Hz, 4 H), 2.38 (t, J = 8 Hz, 2 H), 2.08 (d, J = 10 Hz, 2 H), 1.77 (d, J = 10 Hz, 2 H), 1.42 (dd, J = 11, 7 Hz, 2 H), 1.26 (m, 1 H), 1.13 (m, 4 H); CIMS m/z 366 (M + H, base). Anal. ($C_{22}H_{31}N_5$) C, H, N.

***cis*-{4-[2-(4-Phenylpiperazin-1-yl)ethyl]cyclohexyl}-pyrimidin-2-ylamine Maleate (15).** A solution of amide **12** (1.7 g, 4.3 mmol) was heated to reflux for 48 h in 50 mL of 6 N HCl. The solvents were removed under reduced pressure, and the residue was partitioned between saturated NH_4OH and chloroform. The organic fraction was dried over Na_2SO_4, the solvent was removed under reduced pressure, and the residue was treated with 2-chloropyrimidine (0.39 g, 3.5 mmol) and triethylamine in refluxing ethanol (15 mL) for 48 h. The solvent was removed under reduced pressure, and the mixture was partitioned between chloroform and 2 N Na_2CO_3. The organic fraction was dried over Na_2SO_4, and the solvents were removed under reduced pressure. The residue was chromatographed over silica gel using a mixture of chloroform, 1−2% methanol, and 0.1% ammonia as the solvents to obtain the free base of the title compound (**15**) as a clear oil (0.54 g, 43% yield). The oil was dissolved in 2-propanol and heated with 1.1 equiv of maleic acid. Upon cooling, the maleate salt was isolated as a white solid (0.56 g). Mp 157−9 °C; (400 MHz, d_6-DMSO) δ 8.21 (d, J = 5 Hz, 2 H), 7.21 (t, J = 7 Hz, 2 H), 6.5 (d, J = 7 Hz, 2 H), 6.81 (t, J = 7 Hz, 1 H), 6.48 (t, J = 5 Hz, 1 H), 5.99 (s, 2 H), 3.85 (m, 1 H), 3.28 (brs, 6 H), 3.10 (t, J = 6 Hz, 4 H), 1.59 (m, 4 H), 1.53 (m, 2 H), 1,43 (m, 5 H); CIMS m/z 366 (M + H, base). Anal. ($C_{22}H_{31}N_5 \cdot C_4H_4O_4 \cdot {}^1/_2H_2O$) C, H, N.

***trans*-Methyl-{4-[2-(4-phenylpiperazin-1-yl)ethyl]cyclohexyl}pyrimidin-2-ylamine (16).** A mixture of ketone **9** (3.0 g, 10.5 mmol) and methylamine hydrochloride (6.7 g, 100 mmol) in methanol (75 mL) was treated with sodium cyanoborohydride (0.66 g, 10.5 mmol) and stirred at room temperature for 24 h. The methanol was removed under reduced pressure, and the residue was partitioned between chloroform and 2 N Na_2CO_3. The organic fraction was dried over sodium sulfate and the solvent evaporated under reduced pressure. The resulting residue was treated with 2-chloropyrimidine (1.20 g, 10.5 mmol) and triethylamine (1.8 mL, 13.0 mmol) in refluxing ethanol (25 mL) for 48 h. Upon cooling, a solid precipitated which was filtered. The solid was partitioned between saturated ammonium hydroxide and chloroform. The organic fraction was dried over Na_2SO_4 and evaporated. The residue was recrystallized from ethyl acetate to give the product **16** as an off white solid (0.36 g, 9%). Mp 134 °C (400 MHz, $CDCl_3$) δ 8.29 (d, J = 5 Hz, 2 H), 7.26 (dd, J = 8, 7 Hz, 2 H), 6.93 (d, J = 8 Hz, 2 H), 6.85 (t, J = 7 Hz, 1 H), 6.42 (t, J = 5 Hz, 1 H), 4.61 (tt, J = 12, 4 Hz, 1 H), 3.22 (t, J = 5 Hz, 4 H), 3.00 (s, 3 H), 2.61 (t, J = 5 Hz, 4 H), 2.43 (t, J = 8 Hz, 2 H), 1.86 (d, J = 12 Hz, 2 H), 1.74 (d, J = 12 Hz, 2 H), 1.56 (dd, J = 25, 12 Hz, 2 H), 1.49 (dd, J = 11, 7 Hz, 2 H), 1.26 (m, 1 H), 1.13 (m, 2 H); CIMS m/z 380 (M + H, base). Anal. ($C_{23}H_{33}N_5$) C, H, N.

1-(1,4-Dioxaspiro[4.5]dec-8-yl)-4-phenylpiperazine (18a). 1,4-Cyclohexanedione monoethylene ketal **17** (5 g, 32 mmol), 1-phenylpiperazine (4.9 mL, 32 mmol), and glacial acetic acid (1.8 mL, 32 mmol) were mixed in 1,2-dichloroethane (100 mL). Sodium triacetoxyborohydride (8.92 g, 41.6 mmol) was added to the above mixture and was stirred at room temperature

under N_2 for 18 h. The reaction was quenched with saturated $NaHCO_3$, and the product was extracted with EtOAc (3 × 75 mL). The EtOAc extract was dried over $MgSO_4$, and the solvent was evaporated in vacuo. The resulting yellow solid was purified by MPLC on silica gel eluting with 70% EtOAc/hexane to give **18a** (9.03 g, 93%) as a white solid: mp 106−108 °C; ^{1}H NMR ($CDCl_3$) δ 7.23−7.28 (m, 2 H), 6.93 (d, J = 7.82 Hz, 2 H), 6.85 (m, 1 H), 3.94 (s, 4H), 3.17−3.21 (m, 4 H), 2.72−2.75 (m, 4 H), 2.38−2.45 (m, 1 H), 1.82−1.85 (m, 4 H), 1.52−1.70 (m, 4 H); CIMS m/z 303 (M + H). Anal. ($C_{18}H_{26}N_2O_2$) C, H, N.

4-(4-Phenyl-1-piperazinyl)cyclohexanone (18b). The ketal **18a** (9.03 g, 29.8 mmol) was heated to reflux in MeOH (200 mL) with 3 N HCl (200 mL) for 24 h. The reaction mixture was cooled and concentrated in vacuo. The residue was taken up in $CHCl_3$ (200 mL) and made basic with 6 N NaOH. The organic layer was dried over $MgSO_4$, and the solvent was evaporated in vacuo. The resulting solid was purified by MPLC on silica gel eluting with 2% MeOH/CH_2Cl_2 to give the ketone **18b** (4.66 g, 60%) as a white solid: mp 144−145 °C; ^{1}H NMR ($CDCl_3$) δ 7.24−7.30 (m, 2H), 6.94 (d, 2 H, J = 7.99 Hz), 6.87 (m, 1 H), 3.02−3.23 (m, 4H), 2.68−2.77 (m, 5H), 2.48−2.56 (m, 2H), 2.28−2.38 (m, 2 H), 2.06−2.17 (m, 2H), 1.84−1.97 (m, 2H); CIMS m/z 259 (M + H). Anal. ($C_{16}H_{22}N_2O$) C, H, N.

***cis*- and *trans*-[4-(4-Phenylpiperazin-1-yl)cyclohexyl]-pyrimidin-2-ylamine (19 and 20).** To the ketone **18b** (4.66 g, 18.0 mmol) in MeOH (200 mL) at 0 °C were added NH_4OAc (13.8 g, 180 mmol) and $NaCNBH_3$ (2.26 g, 36.0 mmol). The reaction mixture was stirred for 2 h and concentrated in vacuo. The residue was taken up in $CHCl_3$ (100 mL) and basified with saturated Na_2CO_3. The organic layer was dried over $MgSO_4$, and the solvent was evaporated in vacuo. The resulting cis/trans amine (3.15 g, 67%) was obtained as a white solid and used without purification. A mixture of this amine (3.15 g, 12.14 mmol), 2-chloropyrimidine (1.67 g, 14.57 mmol), and Na_2CO_3 (2.57 g, 24.28 mmol) was heated to reflux in EtOH (200 mL) for 48 h. The reaction mixture was concentrated in vacuo and partitioned between $CHCl_3$ (100 mL) and water (50 mL). The organic layer was separated and dried over $MgSO_4$ and the solvent evaporated in vacuo. The resulting cis/trans isomers were separated by MPLC on silica gel eluting with 2% MeOH/CH_2Cl_2 to give the cis pyrimidine **19** (0.64 g, 15%) and the trans pyrimidine **20** (0.43 g, 10%) as white solids: **19**: mp 215−217 °C; ^{1}H NMR ($CDCl_3$) δ 8.26 (d, J = 4.83 Hz, 2H), 7.24−7.29 (m, 2H), 6.94 (d, J = 8.32 Hz, 2H), 6.83−6.89 (m, 1H), 6.48−6.52 (m, 1H), 5.27 (d, J = 7.00 Hz, 1H), 4.10 (m, 1H), 3.01−3.23 (m, 4H), 2.71−2.74 (m, 4H), 2.36 (m, 1H), 1.94−1.97 (m, 2H), 1.58−1.78 (m, 6H); CIMS m/z 338 (M + H). Anal. ($C_{20}H_{27}N_5$) C, H, N.

20: mp 194−195 °C; ^{1}H NMR ($CDCl_3$) δ 8.26 (d, J = 4.83 Hz, 2H), 7.24−7.29 (m, 2H), 6.93 (d, J = 7.82 Hz, 2H), 6.83−6.88 (m, 1H), 6.48−6.51 (m, 1H),1.19−1.31 (m, 2H), 4.93 (d, J = 8.16 Hz, 1H), 3.71−3.79 (m, 1H), 3.19−3.23 (m, 4H), 2.73−2.76 (m, 4H), 2.39 (m, 1H), 2.20−2.24 (m, 2H), 2.17 (m, 2H), 1.97 (m, 2H), 1.43−1.55 (m, 2H); CIMS m/z 338 (M + H). Anal. ($C_{20}H_{27}N_5 \cdot 0.18H_2O$) C, H, N.

4-Oxocyclohexanecarboxylic Acid (22a). Ethyl 4-oxocyclohexanecarboxylate **21** (5.0 g, 29.4 mmol) was heated to reflux in EtOH (30 mL) with 10% NaOH (10 mL) for 2 h. The reaction mixture was cooled and concentrated in vacuo. The residue was washed with EtOAc, acidified with concentrated HCl, and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, and the solvent was evaporated in vacuo. The resulting pale yellow oily solid **22a** (3.9 g, 93% yield) was used without purification in the next step: ^{1}H NMR ($CDCl_3$) δ 2.78−2.85 (m, 1H), 2.46−2.53 (m, 2H), 2.20−2.42 (m, 4H), 2.00−2.12 (m, 2H); CIMS m/z 143 (M + H).

4-[(4-Phenylpiperazin-1-ylcarbonyl]cyclohexanone (22b). Triethylamine (5.3 mL, 38.04 mmol) and isobutyl chloroformate (4.2 mL, 32.18 mmol) were added to a solution of the acid **22a** (4.16 g, 29.26 mmol) in CH_2Cl_2 (75 mL) at 0 °C and stirred for 0.5 h. 1-Phenylpiperazine (4.5 mL, 29.26 mmol) in CH_2Cl_2 (25 mL) was added to the reaction mixture dropwise and stirred for 18 h with gradual warming to room temperature. The reaction mixture was washed with 3 N HCl (20 mL), 2 N NaOH, and saturated NaCl. The organic layer was dried over $MgSO_4$, and the solvent was evaporated in vacuo. The resulting oil was purified by MPLC on silica gel eluting with 2% MeOH/CH_2Cl_2 to give **22b** (4.04 g, 48% yield) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.27−7.32 (m, 2H), 6.90−6.96 (m, 3H), 3.73−3.80 (m, 4H), 3.17−3.23 (m, 4H), 2.93−3.02 (m, 1H), 2.49−2.63 (m, 2H), 2.31−2.42 (m, 2H), 2.00−2.16 (m, 4H); CIMS m/z 287 (M + H).

(4-Phenylpiperazin-1-yl)-[4-(pyrimidin-2-ylamino)cyclohexyl]methanone (23a). To the ketone **22b** (4.04 g, 14.1 mmol) in MeOH (200 mL) at 0 °C were added NH_4OAc (10.9 g, 141 mmol) and NaBHCN (1.77 g, 28.2 mmol). The reaction mixture was stirred for 2 h and concentrated in vacuo. The residue was taken up in $CHCl_3$ (100 mL) and made basic with saturated Na_2CO_3. The organic layer was dried over $MgSO_4$, and the solvent was evaporated in vacuo. The resulting cis/trans mixture of amines (3.58 g, 12.45 mmol), 2-chloropyrimidine (2.85 g, 24.9 mmol), and Na_2CO_3 (3.96 g, 37.35 mmol) were heated to reflux in EtOH (200 mL) for 48 h. The reaction mixture was concentrated in vacuo and partitioned between $CHCl_3$ (100 mL) and water (50 mL). The organic layer was separated and dried over $MgSO_4$ and the solvent evaporated in vacuo. The resulting cis/trans isomers were purified, but not separated, by MPLC on silica gel eluting with 2% MeOH/CH_2Cl_2 to give a mixture of the cis/trans pyrimidines **23a** (1.67 g, 36% yield) as a white foam: ^{1}H NMR ($CDCl_3$) δ 8.26 (d, J = 4.83 Hz, 2H), 7.28−7.31 (m, 2H), 6.88−6.95 (m, 3H), 6.48−6.52 (m, 1H), 5.37 (d, J = 7.99 Hz, 0.4 H), 4.96 (d, J = 7.49 Hz, 0.6H), 4.13−4.17 (m, 0.4H), 3.83−3.92 (m, 0.6H), 3.67−3.80 (m, 4H), 3.17 (m, 4H), 2.62−2.68 (m, 0.4H), 2.47−2.57 (m, 0.6H), 2.17−2.27 (m, 1H), 1.67−2.01 (m, 5H), 1.17−1.31 (m, 2H); CIMS m/z 366 (M + H).

***trans*-[4-[(4-Phenylpiperazin-1-yl)methyl]cyclohexyl]-pyrimidin-2-ylamine (23b).** To a suspension of lithium aluminum hydride (0.19 g, 5.01 mmol) in THF (40 mL) at 0 °C was added **23a** (1.67 g, 4.56 mmol) in THF (10 mL) dropwise and the reaction stirred 3 h. The reaction was quenched carefully with 2 N NaOH and filtered through Celite and the solvent evaporated in vacuo. The resulting cis/trans isomers were separated by MPLC on silica gel eluting with 1% MeOH/CH_2Cl_2 to give the trans pyrimidine **23b** (0.25 g, 15% yield) as a white solid: mp 194−196 °C; ^{1}H NMR ($CDCl_3$) δ 8.25 (d, 2H, J = 4.9 Hz), 7.26 (m, 2H), 6.92 (d, J = 8.0 Hz, 2H), 6.85 (m, 1H), 6.48 (m, 1H), 4.99 (m, 1H), 3.72−3.82 (m, 1H), 3.22 (m, 4H), 2.59 (m, 4H), 2.14−2.25 (m, 4H), 1.92 (m, 2H), 1.56 (m, 1H), 1.04−1.32 (m, 4H); CIMS m/z 352 (M + H). Anal. ($C_{21}H_{29}N_5 \cdot 0.10H_2O$) C, H, N.

***trans*-3-[4-(*tert*-Butoxycarbonylamino)cyclohexyl]-propionic acid (25).** 4-Nitrocinnamic acid (**24**) (24.6 g, 0.128 mol) was reduced with Ru/C (4 g) in H_2O (200 mL) and 50% NaOH (11.2 g, 0.14 mol) at 100 °C and 2000 psi for 17 h in a Parr reactor. The reaction mixture was filtered through Celite. To the filtrate were added THF (500 mL) and di-*tert*-butyl dicarbonate (35.3 g, 161.8 mol) in THF (500 mL) and stirred at room temperature for 16 h. The mixture was concentrated in vacuo, acidified to pH 6 with saturated KH_2PO_4, and extracted with $CHCl_3$. The organic layer was separated and dried over $MgSO_4$ and the solvent evaporated in vacuo. A mixture of cis/trans isomers (32.33 g, 92% yield) was obtained as a white solid. The trans isomer was isolated by recrystalization from EtOAc. **25**: mp 137 °C; H NMR ($CDCl_3$) δ 6.67 (d, J = 8.32, 1H), 3.12 (br s, 1H), 2.19 (t, J = 5.47 Hz, 2H), 1.65−1.75 (m, 4H), 1.39−1.42 (m, 1H), 1.36 (s, 9H), 1.03−1.15 (m, 4H), 0.82−0.93 (m, 2H); CIMS m/z 271 (M + H). Anal. ($C_{14}H_{25}NO_4$) C, H, N.

***trans*-{4-[3-Oxo-3-(4-phenylpiperazin-1-yl)propyl]-cyclohexyl}carbamic Acid *tert*-Butyl Ester (26a).** Triethylamine (2.05 mL, 14.74 mmol) and isobutyl chloroformate (1.15 mL, 8.84 mmol) were added to a solution of the acid **25** (2.0 g, 7.37 mmol) in CH_2Cl_2 (75 mL) at 0 °C and stirred for 0.5 h. 1-Phenylpiperazine (1.12 mL, 7.37 mmol) in CH_2Cl_2 (25 mL) was added to the reaction mixture dropwise and stirred

for 18 h with gradual warming to room temperature. The reaction mixture was washed with 3 N HCl (20 mL), 2 N NaOH, and saturated NaCl. The organic layer was dried over $MgSO_4$, and the solvent was evaporated in vacuo. The resulting oil was purified by MPLC on silica gel eluting with 50% EtOAc/hexane to give **26a** (3.00 g, 97% yield) as a white solid: mp 156−157 °C; ^{1}H NMR ($CDCl_3$) δ 7.26−7.31 (m, 2H), 6.88−6.94 (m, 3H), 4.35 (br s, 1H), 3.75−3.79 (m, 2H), 3.60−3.63 (m, 2H), 3.37 (br s, 1H), 3.13−3.19 (m, 4H), 2.39 (, J = 7.65 Hz t, 2H), 1.98−2.01 (m, 2H), 1.78−1.81 (m, 2H), 1.52−1.59 (m, 2H), 1.44 (s, 9H), 1.23 (br s, 1H), 1.00−1.15 (m, 4H); CIMS m/z 416 (M + H).

***trans*-{3-(4-Aminocyclohexyl)-1-(4-phenylpiperazin-1-yl)propan-1-one (26b).** A solution of **26a** (3.0 g, 7.22 mmol) and trifluoroacetic acid (12.2 mL, 72.2 mmol) in $CHCl_3$ (100 mL) was stirred at room temperature for 16 h. The reaction mixture was neutralized with saturated $NaHCO_3$, the organic layer separated and dried over $MgSO_4$, and the solvent evaporated in vacuo. The resulting waxy white solid **26b** (2.20 g, 96% yield) was used without purification in the next step: mp 86−87 °C; ^{1}H NMR ($CDCl_3$) δ 7.25−7.30 (m, 2H), 6.88−6.94 (m, 3H), 3.75−3.79 (m, 2H), 3.60−3.64 (m, 2H), 3.13−3.18 (m, 4H), 2.57−2.66 (m, 1H), 2.35−2.40 (m, 2H), 1.75−1.88 (m, 4H), 1.52−1.59 (m, 4H), 1.21−1.27 (m, 1H), 0.92−1.20 (m, 4H); CIMS m/z 316 (M + H).

***trans*-1-(4-Phenylpiperazin-1-yl)-3-[4-(pyrimidin-2-ylamino)cyclohexyl]propan-1-one (27).** A mixture of the amine **26b** (2.20 g, 7.00 mmol), 2-chloropyrimidine (1.20 g, 10.5 mmol), and Na_2CO_3 (2.22 g, 21.0 mmol) was heated to reflux in EtOH (100 mL) for 48 h. The reaction mixture was concentrated in vacuo and partitioned between $CHCl_3$ (500 mL) and water (25 mL). The organic layer was separated and dried over $MgSO_4$ and the solvent evaporated in vacuo. The resulting solid was purified by MPLC on silica gel eluting with 2% MeOH/CH_2Cl_2 to give **27** (1.71 g, 62% yield) as a white solid: mp 161−162 °C; ^{1}H NMR ($CDCl_3$) δ 8.25 (d, J = 4.83 Hz, 2H), 7.26−7.31 (m, 2H), 6.99−6.95 (m, 3H), 6.47−6.50 (m, 2H), 4.94 (d, J = 8.32 Hz, 1H), 3.76−3.79 (m, 3H), 3.61−3.64 (m, 2H), 3.13−3.19 (m, 4H), 2.36−2.42 (m, 2H), 2.12−2.15 (m, 2H), 1.82−1.86 (m, 2H), 1.55−1.63 (m, 2H), 1.32 (br s, 1H), 1.07−1.26 (m, 4H); CIMS m/z 394 (M + H). Anal. ($C_{23}H_{31}N_5O$) C, H, N.

***trans*-{4-[3-(4-Phenylpiperazin-1-yl)propyl]cyclohexyl}-pyrimidin-2-ylamine (28).** To a suspension of lithium aluminum hydride (0.18 g, 4.77 mmol) in THF (40 mL) at 0 °C was added **27** (1.71 g, 4.34 mmol) in THF (10 mL) dropwise and the reaction stirred 3 h. The reaction was quenched carefully with 2 N NaOH and filtered through Celite and the solvent evaporated in vacuo. The resulting solid was purified by MPLC on silica gel eluting with 2% MeOH/CH_2Cl_2 to give **28** (0.49 g, 30% yield) as a white solid: mp 123−124 °C; ^{1}H NMR ($CDCl_3$) δ 8.25 (d, J = 4.9 Hz, 2H), 7.26 (m, 2H), 6.93 (d, J = 8.0 Hz, 2H), 6.85 (m, 1H), 6.48 (m, 1H), 4.93 (m, 1H), 3.73 (m, 1H), 3.22 (m, 4H), 2.61 (m, 4h), 2.37 (m, 2H), 2.12 (m, 2H), 1.82 (m, 2H), 1.56 (m, 1H), 1.07−1.27 (m, 8H); CIMS m/z 380 (M + H). Anal. ($C_{23}H_{33}N_5$·0.11H_2O) C, H, N, H_2O.

***trans*-4-Aminocyclohexaneacetic Acid, Ethyl Ester, Hydrochloride (30).** One kilogram (5.52 mole) of 4-nitrophenylacetic acid **29** was slowly added to a stirred solution of 440 g (5.52 mole) of 50% sodium hydroxide solution in 9 L of deionized water. The clear yellow solution was then drawn by vacuum into a 5 gal stirred high-pressure autoclave. One liter of deionized water was used as a rinse. The autoclave was then charged with 400 g of water−wet sponge nickel catalyst (Activated metals A-7000), with 1 L deionized water rinse. The autoclave was sealed, flushed with nitrogen, and then pressurized to 1951 psi with hydrogen. The stirrer was started and the nitro group hydrogenated over 1 h, with a maximum temperature of 49 °C observed. When no more hydrogen uptake was noted, the reactor was heated to 130 °C with a maximum pressure of 2200 psi observed. Hydrogenation was continued 40 h with a cessation of hydrogen uptake due to catalyst deactivation. The reactor was cooled, vented, flushed with nitrogen, and charged with 125 g of the sponge nickel catalyst. The reactor was flushed with nitrogen and then pressurized with hydrogen to 1767 psi. The vessel was heated to 130 °C with stirring. The maximum pressure observed was 2508 psi. Hydrogenation was continued 21.5 h at 130 °C, with cessation of hydrogen uptake. The reactor was cooled, vented, and flushed with nitrogen, and the contents were removed and filtered through a filter aid to remove catalyst. The yellow filtrate was adjusted to pH 5.0 with concentrated hydrochloric acid. The volatiles were removed in a rotary evaporator at 50 °C/10 mm, until no more distillate was observed. Four liters of acetone were added to the thick residue, and the mixture was rotated 1 h at 50 °C without vacuum. The resulting suspension of product and sodium chloride was collected, washed with acetone, and dried under vacuum at 40 °C. Yield 1139 g. Theory with NaCl, 1188 g, NMR showed 81% trans, 19% cis, and <4% aromatic protons. Ten grams of this material was suspended in ethanol, and the mixture was treated with anhydrous HCl until the resulting mixture was saturated. After heating to reflux for 4 h, the mixture was cooled and filtered, and the filtrate was concentrated to dryness under vacuum. The residue was dissolved in 50 mL of ethanol, treated with 50 mL of ether, and cooled in an ice bath to give *trans*-4-aminocyclohexaneacetic acid ethyl ester hydrochloride as a white solid which was filtered and dried under vacuum (5.82 g, 54% overall yield). Mp 162−3 °C; ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.10 (brs, 3 H), 3.98 (q, J = 7 Hz, 2 H), 2.82 (m, 1 H), 2.11 (d, J = 7 Hz, 2 H), 1.88 (d, J = 10 Hz, 2 H), 1.65 (d, J = 10 Hz, 2 H), 1.53 (m, 1 H), 1.28 (ddd, J = 26, 13, 3 Hz, 2 H), 1.11 (t, J = 7 Hz, 3 H), 0.97 (ddd, J = 26, 13, 3 Hz, 2 H); CIMS 186 (M + H, base); Anal. ($C_{10}H_{19}NO_2$·HCl) C, H, N.

***trans*-[4-(Pyrimidin-2-ylamino)cyclohexyl]acetic Acid Ethyl Ester Hydrochloride (31).** A solution of *trans*-(4-aminocyclohexyl)acetic acid ethyl ester **30** (3.46 g, 18.7 mmol), 2-chloropyrimidine (2.14 g, 18.7 mmol), and triethylamine (5.21 mL) was heated to reflux in ethanol (10 mL) for 18 h. The reaction was cooled, and solvents were removed under reduced pressure, and the residue was partitioned between chloroform and 2 N Na_2CO_3. The organic layer was separated and dried over Na_2SO_4, and the solvents were removed under reduced pressure. The residue was chromatographed over silica gel using a mixture of 2:1 chloroform/ethyl acetate to give compound **31** as a white solid (3.49 g, 71% yield). Mp 95−97 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, J = 5 Hz, 2H), 6.44 (t, J = 5 Hz, 1 H), 5.04 (d, J = 8 Hz, 1 H), 4.08 (q, J = 7 Hz, 2 H), 3.71 (m, 1 H), 2.16 (d, J = 7 Hz 2 H), 2.07 (m, 2 H), 1.78 (m, 2 H), 1.75 (m, 1 H), 1.21 (t, J = 7 Hz, 3 H), 1.17 (m, 4 H); CIMS 264 (M + H, base). Anal. ($C_{14}H_{21}N_3$) C, H, N.

***trans*-2-[4-(Pyrimidin-2-ylamino)cyclohexyl]ethanol (32).** A suspension of lithium aluminum hydride (1.11 g, 29.2 mmol) in tetrahydrofuran (30 mL) was cooled in an ice−water bath and treated with a solution of *trans*-[4-(pyrimidin-2-ylamino)cyclohexyl]acetic acid ethyl ester (5.12 g, 19.4 mmol) in THF (30 mL) over 20 min. After stirring for 5 min, the ice bath was removed and the reaction was stirred for an additional 40 min. The reaction was quenched with water (3 mL), followed by 25% sodium hydroxide (3 mL). The mixture was stirred for 1 h and then filtered through Celite, and the filtrate evaporated to give **32** as a white solid (4.25 g, 99% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, J = 5 Hz, 2 H), 6.42 (t, J = 5 Hz, 1 H), 5.03 (d, J = 8 Hz, 1 H), 3.67 (m, 1 H), 3.63 (t, J = 6 Hz, 2 H), 2.05 (m, 2 H), 1.78 (m, 2 H), 1.43 (t, J = 6 Hz, 2 H), 1.40 (m, 1 H), 1.10 (m, J = 4 H).

***trans*-[4-(2-Bromoethyl)cyclohexyl]pyrimidin-2-ylamine (33).** A mixture of *trans*-2-[4-(pyrimidin-2-ylamino)-cyclohexyl]ethanol **(32)** (4.09 g. 18.7 mmol) was dissolved in a solution of methylene chloride (85 mL) containing polymer-supported triphenylphosphine (7.8 g, approximately 23.3 mmol). The mixture was cooled in an ice−water bath, and carbon tetrabromide (6.30 g, 19.0 mmol) was added. The reaction was stirred for 1 h, and the polymer-supported triphenylphosphine oxide was removed by filtration. The filtrate was concentrated, and the resulting residue was chromatographed on silica gel using a 3:1 mixture of chloroform and

ethyl acetate as the solvent to give the bromide **33** as an off white solid (3.56 g, 67% yield). Mp 96−7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, J = 5 Hz, 2 H), 6.44 (t, J = 5 Hz, 1 H), 4.99 (d, J = 8 Hz, 1 H), 3.72 (m, 1 H), 3.42 (t, J = 7 Hz, 2 H), 2.09 (d, J = 10 Hz, 2 H), 1.79 (d, J = 14 Hz, 2 H), 1.75 (q, J = 7 Hz, 2 H), 1.45 (m, 1 H), 1.17 (dd, J = 10, 24 Hz, 2 H), 1.08 (dd, J = 10, 24 Hz, 2 H); CIMS 284 (M + H, base). Anal. ($C_{12}H_{18}BrN_3$) C, H, N, Br.

***trans*-Pyrimidin-2-yl-(4-{2-[4-[3-(trifluoromethyl)phenyl]piperazin-1-yl]ethyl}cyclohexyl)amine (41).** A mixture of *trans*-[4-(2-Bromoethyl)cyclohexyl]pyrimidin-2-ylamine **33** (Het is 2-pyrimidinyl) (0.26 g, 0.91 mmol), 1-[3-(trifluoromethyl)phenyl]piperazine (0.21 g, 0.91 mmol), and potassium carbonate (0.21 g, 1.5 mmol) was heated in 10 mL of refluxing acetonitrile for 18 h. The reaction was diluted with methylene chloride and filtered, and the solvents were removed under reduced pressure. The residue was partitioned between chloroform and 2 N Na_2CO_3. The organic layer was dried over sodium sulfate and evaporated. The resulting residue was recrystallized from acetonitrile to give the product as a white solid (0.33 g, 83% yield). Mp 166−7 °C; 1H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, J = 6 Hz, 2 H), 7.29 (t, J = 8 Hz, 2 H), 7.03 (m, 3 H), 6.44 (t, J = 5 Hz, 1 H), 4.95 (d, J = 8 Hz, 1 H), 3.71 (m, 1 H), 3.21 (br s, 4 H), 2.56 (br s, 4 H), 2.39 (t, J = 8 Hz, 2 H), 2.08 (d, J = 9 Hz, 2 H), 1.77 (d, J = 11 Hz, 2 H), 1.42 (m, 2 H), 1.26 (m, 1 H), 1.13 (m, 4 H); CIMS *m*/*z* 434 (M + H, base). Anal. ($C_{22}H_{30}F_3N_5$) C, H, N, F.

In a similar way the following compounds were prepared from bromide **33** using the appropriate amine.

***trans*-{4-[2-(4-Phenyl-3,6-dihydro-2*H*-pyridin-1-yl)ethyl]-cyclohexyl}pyrimidin-2-ylamine (34).** Mp 146−147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.2(d, J = 5 Hz, 2 H), 7.35 (m, 2 H), 7.15 (m, 2 H), 7.10 (m, 2 H) 6.45 (t, J = 4 Hz 1 H), 6.0 (s, 1 H), 4.90 (d, J = 11 Hz, 1 H), 3.15 (br s, 2 H), 2.70 (br s, 2 H), 2.55 (br s, 2H), 2.45 (br s, 2H), 2.05 (m, 2 H), 1.80 (m, 2H), 1.30 (br s, 1H) 1.05 (m, 4H); CIMS 362 (M + H, base). Anal. ($C_{23}H_{30}N_4 \cdot 0.5H_2O$) C, H, N.

***trans*-{4-[2-(3,4-Dihydro-1*H*-isoquinolin-2-yl)ethyl]-cyclohexyl}pyrimidin-2-ylamine (35).** Mp 125−126 °C (acetonitrile); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.22 (d, J = 5 Hz, 2 H), 7.07 (m, 3 H), 6.99 (d, J = 5 Hz 1 H), 4.93 (d, J = 8 Hz, 1 H), 3.73 (m, 1 H), 3.60 (s, 2 H), 2.88 (m, 2H),6.44 (t, J = 5 Hz, 1 H), 2.71 (br s, 2 H), 2.52 (t, J = 8 Hz, 2 H) 2.08 (m, 2H), 1.82 (m, 2H), 1.51 (dt, J = 8, 7 Hz, 2 H), 1.31 (m 1 H), 1.21−1.07 (m, 4 H); CIMS 337 (M + H, base). Anal. ($C_{21}H_{28}N_4$) C, H, N.

***trans*-{4-[2-[(Methylphenethyl)amino]ethyl]cyclohexyl}-pyrimidin-2-ylamine (36).** Mp 68−9 °C (acetonitrile); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.20 (d, J = 5 Hz, 2 H), 7.24 (t, J = 8 Hz, 2H), 7.15 (m, 3H), 6.43 (t, J = 5 Hz, 1 H), 4.97 (m, 1 H), 3.70 (m, 1H), 2.73 (dd J = 9, 8 Hz, 2H), 2.55 (dd J = 9, 8 Hz, 2H), 2.38 (t, J = 8 Hz, 2H), 2.25 (s, 3H), 2.06 (d, J = 11 Hz, 2 H), 1.74 d, J = 11 Hz, 2 H), 1.36 (dd, J = 11, 7 Hz, 2 H), 1.24 (m, 1 H), 1.21−1.07 (m, 4 H); CIMS (339, M + H, 80%). Anal. ($C_{21}H_{30}N_4$) C, H, N.

***trans*-[4-(2-Dipropylaminoethyl)cyclohexyl]pyrimidin-2-ylamine (37).** Mp 71−72 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.21 (d, J = 5 Hz, 2 H), 6.44 (t, J = 5 Hz, 1 H), 4.90 (d, J = 8 Hz, 1 H), 3.70 (m, 1 H), 2.42 (m, 2 H), 2.35 (m, 4 H), 2.07 (d, J = 9 Hz, 2 H), 1.75 (d, J = 9 Hz, 2 H), 1.43 (m, 4 H), 1.34 (m, 2 H), 1.26 (m, 1 H), 1.21−1.07 (m, 4 H); CIMS (305, M + H, base). Anal. ($C_{18}H_{32}N_4$) C, H, N.

***trans*-(4-{2-[4-(2,3-Dichlorophenyl)piperazin-1-yl]ethyl}-cyclohexyl)pyrimidin-2-ylamine (38).** Mp 169−170 °C (ethyl acetate); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.26 (d, J = 5 Hz, 2 H), 7.15 (m, 2 H), 6.96 (dd, J = 3, 6 Hz, 1H), 6.48 (t, J = 5 Hz, 1 H), 4.98 (d, J = 8 Hz, 1 H), 3.75 (m, 1H), 3.07 (m, 4 H), 2.64 (m, 4 H), 2.44 (t, J = 8 Hz, 2 H), 2.13 (d, J = 9 Hz, 2 H), 1.82 (d, J = 9 Hz, 2 H), 1.46 (dt, J = 8, 7 Hz, 2 H), 1.32 (m, 2H), 1.24−1.09 (m, 4 H) CIMS (434 M + H, base). Anal. ($C_{22}H_{29}N_5Cl_2$) C, H, N, Cl.

***trans*-(4-{2-[4-(2-Methoxyphenyl)piperazin-1-yl]ethyl}-cyclohexyl)pyrimidin-2-ylamine (39).** Mp 138−139 °C (hexane, ethyl acetate); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.21 (d, J = 5 Hz, 2 H), 6.96 (d, 1 H), 6.90 (m, 2 H), 6.81 (d, J = 8 Hz, 1 H), 6.44 (t, J = 5 Hz, 1 H), 4.93 (d, J = 8 Hz, 1 H), 3.82 (s, 3 H), 3.72 (m, 1 H), 3.07 (brs, 4 H), 2.62 (brs, 4 H), 2.41 (t, J = 8 Hz, 2 H), 2.08 (d, J = 9 Hz, 2 H), 1.78 (d, J = 9 Hz, 2 H), 1.43 (dt, J = 8, 7 Hz, 2 H), 1.27 (m, 2H), 1.24−1.09 (m, 4 H); CIMS (396 M + H, base). Anal. ($C_{23}H_{33}N_5O$) C, H, N.

***trans*-(4-{2-[4-(4-Methoxyphenyl)piperazin-1-yl]ethyl}-cyclohexyl)pyrimidin-2-ylamine (40).** Mp 177−8 °C (ethyl acetate); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.21 (d, J = 5 Hz, 2 H), 6.86 (d, J = 9 Hz, 2 H), 6.79 (d, J = 9 Hz, 2 H), 6.44 (t, J = 5 Hz, 1 H), 4.96 (d, J = 8 Hz, 1 H), 3.72 (s, 3 H), 3.07 (t, J = 5 Hz, 4 H), 2.58 (t, J = 5 Hz, 4 H), 2.38 (t, J = 8 Hz, 2 H), 2.08 (d, J = 9 Hz, 2 H), 1.78 (d, J = 10 Hz, 2 H), 1.43 (dt, J = 8, 7 Hz, 2 H), 1.26 (m, 2H), 1.20−1.05 (m, 4 H); CIMS *m*/*e* 396 (M + H, base). Anal. ($C_{23}H_{33}N_5O$) C, H, N.

***trans*-(4-{2-[4-(4-Fluorophenyl)piperazin-1-yl]ethyl}-cyclohexyl)pyrimidin-2-ylamine (42).** A mixture of 4-[(2-bromoethyl)cyclohexyl]pyrimidin-2-ylamine (0.47 g, 1.64 mmol), 1-(4-fluorophenyl)piperazine (0.31 g, 1.70 mmol), and potassium carbonate (0.31 g, 2 mmol) was heated under reflux in acetonitrile (40 mL) for 18 h. After the reaction mixture was cooled, the salts were filtered off and the filtrate was concentrated to an oily solid. The residue was partitioned between chloroform (∼100 mL) and dilute Na_2CO_3 (∼100 mL), and the organic layer was dried (K_2CO_3) and then concentrated in vacuo to provide a solid. This was recrystallized in ethyl acetate (∼30 mL) to provide the title compound **42** (0.33 g, 51%). Mp 162−163 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.21 (d, J = 5 Hz, 2 H), 6.95 (m, 2 H), 6.84 (m, 2 H), 6.42 (m, 1H), 4.87 (d, J = 11 Hz, 1 H), 3.7 (m, 1 H), 3.1(s, 4 H), 2.6 (s, 4 H), 2.4 (m, 2 H), 2.1 (m, 2 H), 1.8 (m, 2 H), 1.5 (s, 2 H) 1.42 (q, J = 10 Hz, 2 H), 1.35 (br s, 1 H), 1.1 (m, 4 H); CIMS (384 M + H, base). Anal. ($C_{22}H_{30}N_5F$) C, H, N, F.

***trans*-{4-[2-(4-Pyridin-2-ylpiperazin-1-yl)ethyl]-cyclohexyl}pyrimidin-2-ylamine (43).** Mp 138−140 °C (EtOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.19 (d, J = 5 Hz, 2 H), 8.14 (d, J = 5 Hz, 1 H), 7.42 (t, J = 8 Hz, 1 H), 6.59(d, J = 8 Hz, 1 H), 6.56(t, J = 8 Hz, 1 H), 6.43 (d, J = 5 Hz, 1 H), 4.98 (d, J = 8 Hz, 1 H), 3.70 (m, 1H), 3.51 (t, J = 5 Hz, 4 H), 2.50 (t, J = 5 Hz, 4 H), 2.36 (t, J = 6 Hz, 2 H), 2.06 (dd, J = 9, 1 Hz, 2H), 1.78 (dd, J = 9, 1 Hz, 2H), 1.42 (dt, J = 8, 8 Hz, 2 H), 1.26 (m 1 H), 1.21−1.07 (m, 4 H); CIMS 367 (M + H, base). Anal. ($C_{21}H_{30}N_6$) C, H, N.

***trans*{4-[2-(4-Pyridin-3-ylpiperazin-1-yl)ethyl]-cyclohexyl}pyrimidin-2-ylamine (44).** Mp 174−5 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.27 (d, J = 2 Hz, 1 H), 8.20 (d, J = 5 Hz, 2 H), 8.05 (dd, J = 4., 2 Hz, 1 H), 7.12 (m, 2 H), 6.44 (t, J = 5 Hz, 1 H), 4.92 (d, J = 8 Hz, 1 H), 3.71 (m, 1H), 3.20 (t, J = 5 Hz, 4 H), 2.57 (t, J = 5 Hz, 4 H), 2.38 (t, J = 6 Hz, 2 H), 2.08 (d, J = 10 Hz, 2 H), 1.78 (d, J = 10 Hz, 2 H), 1.42 (dd, J = 15, 7 Hz, 2 H), 1.28 (m, 1 H), 1.21−1.07 (m, 4 H); CIMS 367 (M + H, base). Anal. ($C_{21}H_{30}N_6$) C, H, N.

***trans*-{4-[2-(4-Pyridin-4-ylpiperazin-1-yl)ethyl]-cyclohexyl}pyrimidin-2-ylamine (45).** Mp 199−200 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.21 (m, 4 H), 6.61 (d, J = 5 Hz, 2 H), 6.44 (t, J = 5 Hz, 1 H), 4.92 (d, J = 8 Hz, 1 H), 3.71 (m, 1H), 3.29 (t, J = 5 Hz, 4 H), 2.51 (t, J = 5 Hz, 4 H), 2.36 (t, J = 6 Hz, 2 H), 2.08 (d, J = 10 Hz, 2 H), 1.77 (d, J = 10 Hz, 2 H), 1.41 (dd, J = 15, 7 Hz, 2 H), 1.26 (m, 1 H), 1.21−1.07 (m, 4 H); CIMS 367 (M + H, base). Anal. ($C_{21}H_{30}N_6$) C, H, N.

Pyrimidin-2-yl-{4-[2-(4-pyrimidin-2-ylpiperazin-1-yl)-ethyl]cyclohexyl}amine (46). Mp 154−155 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (2H, m), 8.2 (2H, m), 6.4 (2H, m), 4.9 (1H, d, J = 11 Hz), 3.8 (4H, m), 3.76 (1H, m), 2.45 (4H, m), 2.38 (2H, m), 2.08 (2H, m), 1.75 (2H, m), 1.4 (2H, m), 1.35 (1H, br s),1.05 (4H, m); MS (CI/NH_3) *m*/*z* 368 (M + H). Anal. ($C_{20}H_{29}N_7$) C, H, N.

***trans*-Pyrimidin-2-yl-{4-[2-(2,3,5,6-tetrahydro-[1,2′]bipyrazinyl-4-yl)ethyl]cyclohexyl}amine (47).** Mp 162−163; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.19 (d, J = 2 Hz, 1 H), 8.07 (d, J = 1 Hz, 1 H), 7.99 (dd, J = 1, 3 Hz, 1 H), 7.77 (d, J = 3 Hz, 1 H), 6.42 (t, J = 5 Hz, 1 H), 4.92 (d, J = 8 Hz, 1 H), 3.68 (m, 1H), 3.54 (t, J = 5 Hz, 4 H), 2.48 (t, J = 5 Hz, 4 H), 2.37 (t, J = 7 Hz, 2 H), 2.05 (d, J = 10 Hz, 2 H), 1.75 (d, J = 10 Hz, 2

H), 1.40 (dd, J = 15, 7 Hz, 2 H), 1.25 (m, 1 H), 1.21−1.07 (m, 4 H); CIMS *m/e* 368 (M + H, base). Anal. ($C_{20}H_{29}N_7$) C, H, N.

***trans*-Pyrimidin-2-yl-{4-[2-(4-thiazol-2-ylpiperazin-1-yl)ethyl]cyclohexyl}amine (48).** Mp 151−2 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.19 (d, J = 2 Hz, 1 H), 7.15 (d, J = 3 Hz, 1 H), 6.51 (d, J = 3 Hz, 1 H), 6.43 (t, J = 5 Hz, 1 H), 4.99 (d, J = 8 Hz, 1 H), 3.69 (m, 1 H), 3.45 (t, J = 5 Hz, 4 H), 2.50 (t, J = 5 Hz, 4 H), 2.36 (t, J = 7 Hz, 2 H), 2.07 (d, J = 10 Hz, 2 H), 1.77 (d, J = 10 Hz, 2 H), 1.40 (dd, J = 15, 7 Hz, 2 H), 1.25 (m, 1 H), 1.21−1.07 (m, 4 H); CIMS *m/e* 372 (M + H, base). Anal. ($C_{19}H_{26}N_6S$) C, H, N, S.

X-ray Structure Determination of PD158771 (14) ($C_{22}H_{31}N_5$, FW = 365.53). 14 was crystallized as colorless rods from ethanol solutions. X-ray data were collected on an Enraf-Nonius CAD-4 diffractometer using Cu K radiation (λ = 1.54184 Å). The cell constants and an orientation matrix for data collection were determined from the centered angles of 25 reflections. X-ray diffraction data were collected at 23 °C using the ω scan technique with a variable ω scan rate from 2° to 20° per minute. The data were collected to a maximum 2θ of 148.7°. A total of 4664 reflections were collected, of which 4181 were unique and not systematically absent. Lorentz and polarization corrections were applied to the data as well as an empirical absorption correction based on a series of ψ scans. The crystal structure was determined by direct methods using SIR-92. A total of 307 reflections with E > 1.86 were used to produce a phase set with an absolute figure of merit of 1.17. All 27 heavy atoms in the structure were located from the E map calculated using this phase set. Hydrogen atom positions were located in subsequent difference Fouriers and added to the structure, but their positions were not refined. The heavy atom parameters including anisotropic temperature factors were refined by full matrix least squares using 1869 reflections with intensity greater than three times their standard deviation. The final unweighted R-factor is 0.053. The final difference Fourier was essentially featureless. The highest peak in this map had a height of only 0.16 e/Å^3.

Radioligand Binding. DA D2L and D3 Receptors. CHO K1 cells stably transfected with the genes of wild-type DA hD2L and hD3 receptors were grown and harvested as previously described.[32,33] In brief, CHO K1 cells expressing the human DA D2L and D3, receptors were removed by replacement of growth medium with PBS-EDTA (0.02% EDTA in phosphate buffered saline). After swelling for 5−10 min, the cells were scraped from the flasks and centrifuged at about 1000g for 5 min. The cells were then resuspended in TEM buffer (25 mM Tris-HCl, pH 7.4 at 37 °C, 1 mM EDTA and 6 mM $MgCl_2$) and membranes were pelleted by centrifugation at 20000g at 4 °C for 20 min. The supernatant fluid was removed, and the pellets were resuspended and homogenized with a Brinkman Polytron (setting 5 for 15 s) in the binding buffer and 1 mL aliquots stored at −80 °C until used in the binding assay.

Binding assays were carried out in duplicate in 1.4 mL microtubes (Marsh Biomedical Products, Inc.). Each tube received 50 μL of competing drug or binding buffer, 50 μL of [^{3}H]N-0437 (D2L, final concentration, 2 nM) and [3H]spiperone (D3, final concentration 0.5 nM) and 0.4 mL membranes (15−30 μg protein) to give a final volume of 0.5 mL. After 60 min incubation at 25 °C, the incubations were terminated by rapid filtration over GF/B filters presoaked in 0.5% polyethylenimine and washed rapidly with 3 × 1 mL ice-cold buffer. Filters were put in scintillation vials, 4 mL of Beckman Ready Gel Scintillation fluid was added, and the radioactive content was determined by liquid scintillation spectrophotometry. Nonspecific binding was defined in the presence of 1 μM haloperidol.

5-HT1A Receptors. A rapid filtration assay was used to characterize 5-HT1A receptors in rat hippocampal membranes as previously described.[34] In brief, the [^{3}H]8−OH-DPAT concentration was 0.4 nM, tissue concentration was 10 mg original tissue weight/mL and incubation time was for 30 min at 25 °C. Nonspecific binding was defined as the amount of [3H]8−OH-DPAT binding in the presence of 1 μM 8-OH-DPAT and represented about 20 to 25% total binding. Assays were terminated and radioactive content of filters determined as described above.

Data Analysis. Data for IC50 values were analyzed using the iterative nonlinear least-squares curve-fitting program LIGAND. The dissociation constant, K_i, was derived from the concentration, C, for 50% inhibition of binding, using $K_i = C/(1 + C^*/K_d)$ where C^* was the concentration of [^{3}H]ligand and the K_d was 0.116 nM, 0.152 nM, and 1.12 nM for DA D2L, D3, and 5-HT-1A receptors, respectively. Experimental compounds were made up as stock solutions in dimethyl sulfoxide (DMSO). The final concentration of 0.1% DMSO in the incubation mixture had no effect on specific binding.

[^{3}H]Thymidine Uptake in D2 Transfected CHO p-5 Cells. As previously described[36] CHOp-5 cells transfected with human D2l receptors were plated on 96-well plates in MEM-Alpha with 10% fetal calf serum containing penicillin (100 U/mL) and streptomycin (100 μg/mL).

Forty-eight hours later, cells were washed with serum-free media and maintained thereafter in serum-free media. After 24 h, vehicle, standards, or test compounds were added. Eighteen hours later, [^{3}H] thymidine (0.25 μCi/well) was added for 2 h, and then trypsin (100 μL of 0.25%) was added for 1 h and the assay was terminated by filtration using a Brandel 96-well harvester. The filters were counted for radioactivity using the LKB Beta-plate counting system.

Neurochemical Studies. Animals were injected with the test agents 30 min before the administration of the L-aromatic amino acid decarboxylase inhibitor NSD 1015 (100 mg/kg, ip), and the animals were sacrificed 30 min later. Control rats received the same number of injections at the corresponding time intervals. After sacrificing the rats by decapitation, the brains were quickly removed and the mesolimbic region dissected on an ice-cold glass plate. The mesolimbic region (includes the nucleus accumbens and olfactory tubercle) was frozen on dry ice until analyzed.

The concentrations of L-3,4-dihydroxyphenylalanine (DOPA) and 5-hydroxytryptophan (5 HTP) of tissue samples were determined concurrently by using HPLC equipped with electrochemical detection at a flow of 0.5 mL/min.[33] Briefly, on the day of assay, samples were thawed and homogenized in 0.5 to 1.0 mL of 0.1 M phosphate-citrate buffer (pH 2.5) containing 15% methanol and centrifuged for 1 min in a Eppendorf 5417. One to eight microliters of the supernatants and 1 ng/μL of standards were injected onto a C18 reverse-phase analytical column (3 μm spheres, 150 × 4.6 mm; IB SIL, Phenomenex, Torrance, CA) which was protected by a precolumn filter (3 μm spheres, 50 × 4.6 mm; IB-SIL). The HPLC column was coupled to an electrochemical detector (Model 464 Electrochemcial Detector, Waters, Milford, MA) equipped with a dual glassy carbon electrode set at +0.75 V, 0.2 nA and 5 nA full-scale relative to an Ag/AgCl reference electrode. The HPLC mobile phase consisted of 0.05 M sodium phosphate, 0.03 M citrate buffer, pH 2.7, 0.1 mM disodium EDTA, 0.035% sodium octyl sulfate, and 25% methanol. The concentrations of biogenic amines or metabolites in the samples were determined by Waters Millennium 2020 version 2.1 data automation system with those obtained from standards.

Data were analyzed by one-way analysis of variance and a Newman-Keuls test was used to determine significantly different group means with P < 0.05 being considered significant.

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 Spontaneous Locomotor Activity. This procedure was carried out according to methods described previously.[37] 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 dose effect curves.

Conditioned Avoidance in Squirrel Monkeys. This procedure was carried out according to methods described previously.[38] 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 6 h test. ED_{50} values were calculated at the hour of peak effect.

Supporting Information Available: Data supporting the X-ray crystallographic structure of compound **14** (18 pages). Ordering information is given on any current masthead page.

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