trans-1-[(2-Phenylcyclopropyl)methyl]-4-arylpiperazines: Mixed Dopamine D_2/D_4 Receptor Antagonists as Potential Antipsychotic Agents

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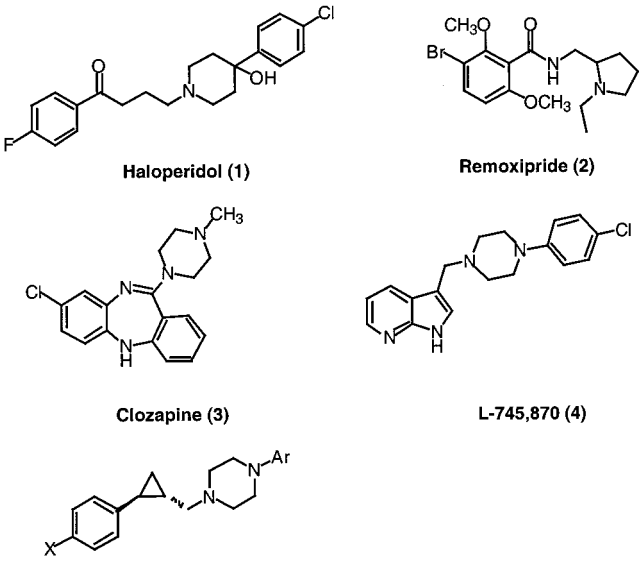
The dopaminergic receptor profile of a series of *trans*-1-[(2-phenylcyclopropyl)methyl]-4-arylpiperazines was examined. Aromatic substitution patterns were varied with the goal of identifying a compound having affinities for the D_2 and D_4 receptors in a ratio similar to that observed for the atypical neuroleptic clozapine. The compounds (1*S*,2*S*)-*trans*-1-[(2-phenylcyclopropyl)methyl]-4-(2,4-dichlorophenyl)piperazine (**5m**) and (1*S*,2*S*)-*trans*-1-[(2-phenylcyclopropyl)methyl]-4-(2,4-dimethylphenyl)piperazine (**5t**) were selected for functional antagonists at D_2 and D_4 receptors and had a D_2/D_4 ratio approximating that of clozapine; they proved inactive in behavioral tests of antipsychotic activity.

Introduction

Schizophrenia is a devastating psychiatric disorder of unknown etiology whose symptoms may include hallucinations and social withdrawal. In 1963, Carlsson and Lindquist first put forward the hypothesis that schizophrenia was linked to a malfunctioning of dopaminergic pathways in the central nervous system (CNS).[1] Since that time, many converging lines of scientific evidence have given support to this idea.[2−4] While many of the prominent antipsychotic agents bind to a wide array of CNS receptor systems, each has a significant affinity for the dopamine D_2 receptor subtype as part of its pharmacological profile. In addition, certain structural classes have been shown to be selective for dopamine D_2-like receptors. Haloperidol (**1**) and remoxipride (**2**) are representative of two structurally distinct classes of compounds, the butyrophenones and the benzamides, respectively, which are both clinically effective antipsychotic agents and antagonists at dopamine receptor subtype. Haloperidol binds with high affinity to D_2, D_3, and D_4 receptors, while most representatives of the benzamide series are mixed D_2/D_3 antagonists.

Strong support for the dopamine hypothesis of Carlsson and Lindquist is provided by a remarkable correlation between the cerebrospinal fluid concentration of antipsychotic agents determined at their clinically effective doses and the affinity of these agents for the dopamine D_2 receptor subtype.[5] An important exception to this correlation is the dibenzo[1,4]diazepine clozapine (**3**), whose cerebrospinal fluid concentration correlates best with its affinity for the D_4 receptor subtype.[6] This correlation suggests that, unlike most neuroleptic drugs, the antipsychotic effects of clozapine are a result of its interaction with the D_4 receptor population rather than D_2 receptor sites. This distinction is important in light of the observation that the neuroleptics having strong affinity for D_2 receptors also present a high risk for the development of extrapyramidal motor side effects and tardive dyskinesia, while clozapine is free of these disturbing problems.[7] The hypothesis that D_4 receptors are integrally related to schizophrenia was initially supported by the now controversial[8] finding that schizophrenics possessed a 6-fold larger number of D_4 receptors than nonschizophrenics.[9]



After these findings, a dedicated search for D_4-selective agents was carried within many laboratories resulting in the identification of a wide array of structural classes having high D_4 affinity and selectivity.[9−20] Although a number of D_4-selective compounds were advanced to clinical trials, the results of these trials have, to date, proved disappointing. In a published report from Merck, schizophrenics treated with L-745,870 (**4**) demonstrated no significant improvement in either positive or negative symptomology.[21]

These reports lead us to postulate that, while D_4 may play an important role in the actions of clozapine, some

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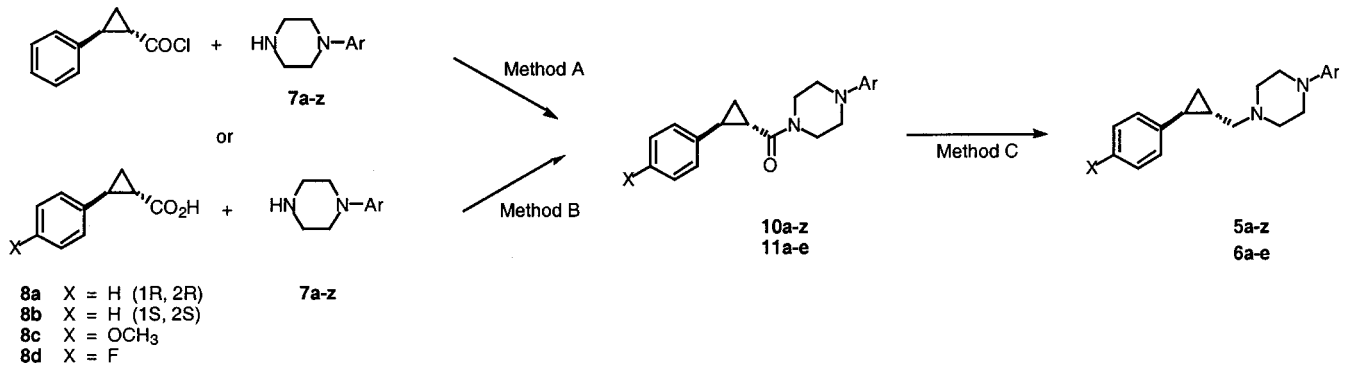
Scheme 1. Preparation of the Target Molecules[a]



[a] Reagents: Method A: NEt_3, CH_2Cl_2. Method B: EDCl, HOBT, DMAP, $CHCl_3$. Method C: AlH_3, THF.

affinity for the D_2 receptor subtype may be required for effective antipsychotic action. Therefore, a compound having a mix of high D_4 and more modest D_2 affinity might better mimic the profile of clozapine than a D_4-selective agent. Thus we set out to obtain a compound which possessed a D_2/D_4 binding ratio similar to that of clozapine. A secondary goal was to minimize α_1 binding in order to avert undesirable cardiovascular effects. In the course of our research into D_4-selective compounds, we identified a number of chemical series with such receptor pharmacology. Specifically, the 1-phenyl-4-[(*trans*-2-phenylcyclopropyl)methyl]piperazines **5** showed promise in this regard. The parent compound, *trans*-1-[(2-phenylcyclopropyl)methyl]-4-phenylpiperazine (**5a**), demonstrated an encouraging dopamine receptor profile (D_2 = 37 nM, D_4 = 48 nM) and served as a starting point for the exploration of the structure−activity relationships (SARs) within this series. We set our criteria for compound selection as a D_4 affinity of less than 10 nM and a ratio of D_2 to D_4 affinities of 2−10. Due to the asymmetric carbon at C-2 of the cyclopropyl, the results of initial receptor screens would reflect the affinities of a racemic mixture. The D_2 to D_4 ratio was therefore set in a wide range around the observed ratio of approximately 4−7 in the hopes that, upon resolution, the dopamine receptor profile of one of the enantiomers would closely resemble that of clozapine.

Chemistry

The basic synthetic route to the novel cyclopropylmethylpiperazines **5a**−**z** and **6a**−**e** prepared in this work is summarized in Scheme 1 and Table 1. Coupling of either *trans*-2-phenyl-1-cyclopropanecarbonyl chloride or *trans*-2-aryl-1-cyclopropanecarboxylic acids **8a**−**d** with various arylpiperazines **7a**−**z** provided key intermediates, the tertiary amides **10a**−**z** and **11a**−**e**. The amides were reduced by alane to elaborate the corresponding cyclopropylmethylpiperazines **5a**−**z** and **6a**−**e**. Several of the *N*-arylpiperazines used in this study were not commercially available and were prepared by several different methods according to the literature reports.[22−24] The *trans*-2-aryl-1-cyclopropanecarboxylic acids **8c**−**d** were prepared by cyclopropanation of the appropriate cinnamic acids, using the method of Friedrich.[25]

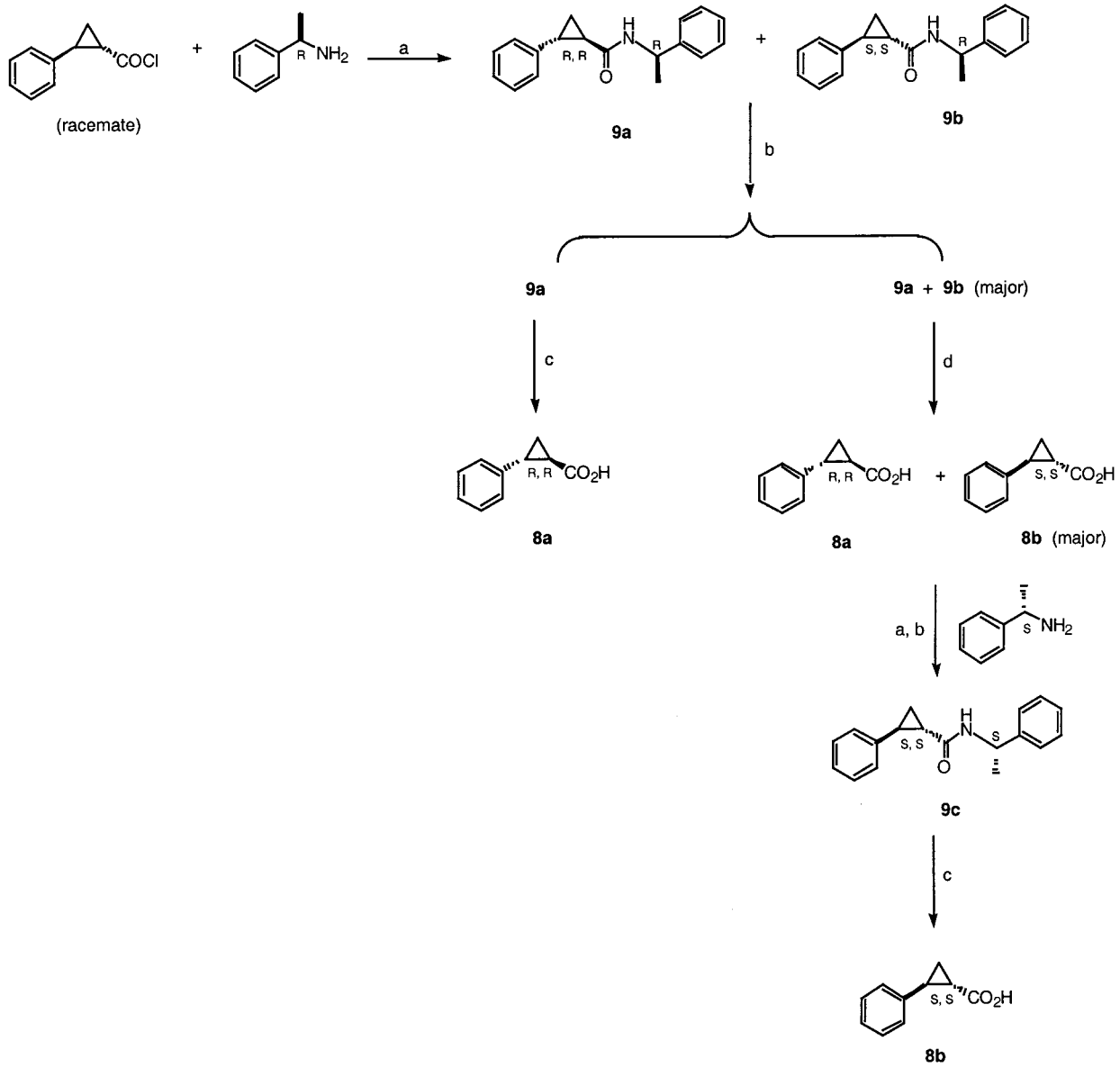
It has been reported that the chiral *trans*-2-phenyl-1-cyclopropanecarboxylic acids **8a**,**b** could be obtained by repeated fractional recrystallization of their diastereomeric salts.[26] However, we found such a procedure very time-consuming, and therefore an indirect resolution *trans*-2-phenyl-1-cyclopropanecarboxylic acid was investigated as outlined in Scheme 2. Coupling of racemic *trans*-2-phenyl-1-cyclopropanecarbonyl chloride with (*R*)-α-methylbenzylamine provided diastereomeric amides **9a**,**b**, in which **9a** could be isolated by crystallization from ethyl acetate. The mother liquid from the crystallization, containing the mixture of **9a**,**b** with **9b** as a major component, was hydrolyzed to give a mixture of **8a**,**b** with **8b** as a major component. The mixed acids were then coupled with (*S*)-α-methylbenzylamine followed by crystallization from ethyl acetate to provide **9c**, the enantiomer of **9a**. The amides **9a**,**c** were hydrolyzed to provide the chiral acids **8a**,**b**, respectively. The absolute configurations of **8a**,**b** were assigned by comparison of their optical rotation configurations with the literature values.[26] The absolute configurations of **5l**−**m**,**s**,**t** then followed the assignment of the carboxylic acid starting materials, and their optical purities were determined to be >99% by using methanol on a CHIRACEL OD chiral column. The physical properties of cyclopropylmethylpiperazines **5a**−**z** and **6a**−**e** are summarized in Table 1.

Results and Discussion

Affinity of the compounds listed in Table 1 at D_2 receptors was determined via standard competitive displacement assays using D_2 receptors cloned from human with [^{3}H]YM 09151 as the competitive ligand.[13] Affinity at D_4 receptors was determined via standard competitive displacement assays using human D_4 receptor clones with [^{3}H]YM 09151 as the competitive ligand. Affinity at α_1 receptors was determined via standard competitive displacement assays using rat brain homogenate with [^{3}H]prazosin as the competitive ligand. The results of these assays are displayed in Table 2. The reference compound remoxipride (**2**) was prepared by condensation of commercially available 3-bromo-2,6-dimethoxybenzoic acid with (−)-(*S*)-2-aminomethyl-1-ethylpyrrolidine.[27]

Our initial synthetic efforts in this series focused on the phenyl attached to the piperazine. To obtain a general sense of how the affinities for D_2, D_4, and α_1 were effected by the electronic character of this phenyl group, a representative electron-withdrawing group (chlorine) and electron-donating group (methoxy) were introduced as a single substituent at each of the three available positions (compounds **5b**−**g**). Examination of

Scheme 2. Indirect Resolution of Chiral Acid **8a**,**b**[a]



[a] Reagents: (a) Method A; (b) recrystallization in EtOAc; (c) hydrazine monohydrate, KOH, ethylene glycol, 160 °C; (d) Method B.

the data indicates that, relative to the parent compound **5a**, dopamine D_4 binding was essentially unchanged for **5c**,**f**,**g**, while significant improvement was seen for the ortho-substituted compounds **5b**,**e** and the *p*-chloro derivative **5d**. The binding of the compounds to α_1 showed a somewhat greater sensitivity to the placement of the substituents with somewhat higher affinities observed for the ortho substituents and lower affinities observed for the meta and para substituents. The finding that both electron-withdrawing and electron-donating groups at the meta and para positions lose affinity in this assay indicates that a steric interaction may be responsible for these results. Highest D_2 affinity was observed for both ortho-substituted derivatives **5b**,**e**.

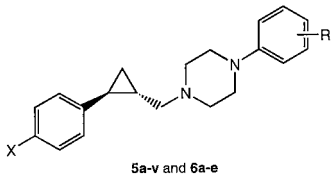
Compounds **5h**−**k** represent various dichlorinated substitution patterns of the 1-phenylpiperazine. The 3,5-dichloro derivative **5i** showed a significant loss of D_4 affinity relative to D_2, while the 2,3-dichloro and 3,4-dichloro derivatives **5h**,**j** displayed unacceptably high affinities for D_2 and α_1, respectively. The 2,4-dichloro derivative **5k** displayed an receptor profile near enough to the target profile to warrant further examination of its enantiomers.

Compounds **5n**−**p** represent various substitution patterns which were examined. The receptor profiles of these examples were found to be largely uninteresting with the exception of the 2,4-dimethyl derivative **5r** which met the desired affinity criteria.

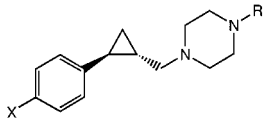
The pyridyl derivatives **5w**−**y** and the 2-pyrimidinyl **5z** were examined as examples of electron-deficient hetero aromatics. Although compounds containing the fragments 2-pyridyl- and 2-pyrimidinylpiperazine have previously been identified as D_4 antagonists,[19] their presence within the cyclopropyl series was detrimental to dopamine binding.

At this point, an examination of the effect of substitution at the para position of the phenyl attached to the cyclopropyl was undertaken. An examination of the receptor affinities for compounds **6a**−**e** indicates that while the receptors would tolerate the presence of a para substituent, it would not adversely effect α_1 binding

Table 1. Physical Data for Cyclopropylmethylpiperazines **5a**−**z** and **6a**−**e**



5a-v and **6a-e**



5w-z

compd	X	R	config	method	formula	mp (°C)
5a	H	H	racemate	A	$C_{20}H_{24}N_2$	79−80
5b	H	2-Cl	racemate	A	$C_{20}H_{23}N_2Cl$·HBr	201−202
5c	H	3-Cl	racemate	A	$C_{20}H_{23}N_2Cl$·2HBr	195−196
5d	H	4-Cl	racemate	A	$C_{20}H_{23}N_2Cl$·2HBr·0.5H_2O	229[a]
5e	H	2-OCH_3	racemate	A	$C_{21}H_{26}N_2O$·HBr·H_2O	129−130
5f	H	3-OCH_3	racemate	A	$C_{21}H_{26}N_2O$·HBr·H_2O·0.75H_2O	220[a]
5g	H	4-OCH_3	racemate	A	$C_{21}H_{26}N_2O$·2HBr	218−219
5h	H	2,3-diCl	racemate	A	$C_{20}H_{22}N_2Cl_2$·HBr	209−210
5i	H	3,5-diCl	racemate	A	$C_{20}H_{22}N_2Cl_2$·HBr	243−244
5j	H	3,4-diCl	racemate	A	$C_{20}H_{22}N_2Cl_2$·HBr·0.5H_2O	157−158
5k	H	2,4-diCl	racemate	A	$C_{20}H_{22}N_2Cl_2$·HBr	206−207
5l	H	2,4-diCl	1*R*,2*R*	B	$C_{20}H_{22}N_2Cl_2$·2HBr	197−198
5m	H	2,4-diCl	1*S*,2*S*	B	$C_{20}H_{22}N_2Cl_2$·HBr	142−143
5n	H	2-OCH_3-4-Cl	racemate	A	$C_{21}H_{25}N_2OCl$·HBr	206−207
5o	H	2-OCH_3-4-F	racemate	A	$C_{21}H_{25}N_2OF$·2HBr	208−209
5p	H	2-CH_3-4-Cl	racemate	A	$C_{21}H_{25}N_2Cl$·HBr	206−207
5q	H	2-CH_3-4-F	racemate	A	$C_{21}H_{25}N_2F$·HBr	204−205
5r	H	2,4-diCH_3	racemate	A	$C_{22}H_{28}N_2$·HBr	209−210
5s	H	2,4-diCH_3	1*R*,2*R*	B	$C_{22}H_{28}N_2$·2HBr	215−217
5t	H	2,4-diCH_3	1*S*,2*S*	B	$C_{22}H_{28}N_2$·2HBr	224−225
5u	H	2-OCH_3-5-Cl	racemate	A	$C_{21}H_{25}N_2OCl$·HBr	209−210
5v	H	3,5-diCl-4-OCH_3	racemate	A	$C_{21}H_{24}N_2OCl_2$·HBr	233−234
5w	H	2-pyridyl	racemate	A	$C_{19}H_{23}N_3$·2HCl·0.5H_2O	110
5x	H	3-pyridyl	racemate	A	$C_{19}H_{23}N_3$·2HBr	238
5y	H	4-pyridyl	racemate	A	$C_{19}H_{23}N_3$·2HBr	225
5z	H	2-pyrimidinyl	racemate	A	$C_{18}H_{21}N_4$·2HCl	172
6a	OCH_3	2,4-diCl	racemate	B	$C_{21}H_{24}N_2OCl_2$·HBr	223−224
6b	OH	2,4-diCl	racemate	*b*	$C_{20}H_{22}N_2Cl_2O$·HBr	210−211
6c	F	2-Cl	racemate	B	$C_{20}H_{22}FClN_2$·2HBr·0.5H_2O	203
6d	F	3-Cl	racemate	B	$C_{20}H_{22}FClN_2$·2HBr·0.5H_2O	215[a]
6e	F	4-Cl	racemate	B	$C_{20}H_{22}FClN_2$·2HBr·0.5H_2O	203

[a] Decomposed. [b] Prepared from **6a**.

relative to the corresponding compound lacking the substituent.

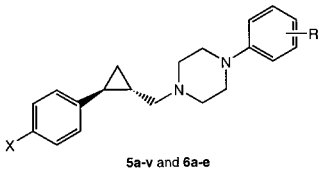
From the data obtained from this study, the racemic compounds **5k**,**r** met the initial criteria for D_2, D_4, and α_1 binding and were selected for resolution. The resolutions were carried out as described in the Experimental Section, and the absolute configurations were assigned by comparison of the optical rotation configurations of the carboxylic acid starting materials with literature values. Compounds **5l**,**m** represent the 1*R*,2*R* and 1*S*,2*S* enantiomers of the 2,4-dichloro derivative **5k**. Similarly, **5s**,**t** represent the 1*R*,2*R* and 1*S*,2*S* enantiomers of the 2,4-dimethyl derivative **5r**.

In both cases, significantly higher D_4 affinity resided within the 1*S*,2*S* enantiomers while somewhat higher D_2 affinity was observed for the 1*R*,2*R* enantiomers. Similar α_1 affinity was observed for each of the enantiomers within the racemic pair. The D_2/D_4 ratio for **5m**,**t** were thus approximately 18 and 9, respectively. Although these represented a D_2/D_4 ratio somewhat higher than that found in clozapine, **5m**,**t** were examined in behavioral tests of both antipsychotic activity and extrapyramidal symptoms.

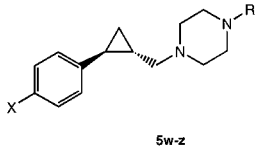
Functional assays to determine antagonist properties of **5m**,**t** at the dopamine receptors was carried out using a modification of the method of Wieland and Jakobs.[28] Both D_2 and D_4 are G-protein coupled receptors (GPCR). Stimulation of a GPCR by an appropriate agonist, in this case dopamine, will induce the binding of GTP by the G-protein. When present, the nonhydrolyzing radioligand GTP[γ-^{35}S] will also bind under these agonist stimulated conditions and thus can provide a functional measure of G-protein activation. In CHO cells stably expressing human D_2 receptors, compounds **5m**,**t** antagonized dopamine-stimulated GTP[γ-^{35}S] binding with K_i values of 181 and 61 nM, respectively. As a control, haloperidol displayed a K_i of 7 nM. Similarly, in CHO cells stably expressing human D_4 receptors, compounds **5m**,**t** antagonized dopamine-stimulated GTP[γ-^{35}S] binding with K_i values of 24 and 13 nM, respectively. In the D_4 experiment, haloperidol displayed a K_i of 2 nM.

When male Sprague−Dawley rats were injected subcutaneously with clozapine, haloperidol, and remoxipride 30 min prior to receiving amphetamine (0.5 mg/kg), the agents produced a significant and dose-dependent decline in stimulated locomotor activity ($P < 0.05$). The minimum effective doses (defined as the lowest dose tested that produced a significant effect relative to the amphetamine alone control group using a Fisher's LSD post hoc test, $P < 0.05$) were 0.5, 0.06, and 0.5 mg/kg for clozapine, haloperidol, and remoxipride, respectively. Neither **5m** nor **5t** caused a significant reduction in amphetamine-induced locomotor activity at the doses tested (4−16 mg/kg). In the catalepsy experiments, haloperidol and remoxipride displayed minimum effective doses of 0.5 and 64 mg/

Table 2. Binding Affinities of Cyclopropylmethylpiperazines **5a**−**z** and **6a**−**e**



5a-v and 6a-e



5w-z

				IC_{50} (nM ± SEM)		
compd	X	R	config	D_2	D_4	α_1
5a	H	H	racemate	37 ± 2	48 ± 4	22 ± 3
5b	H	2-Cl	racemate	5 ± 1	8 ± 2	10 ± 2
5c	H	3-Cl	racemate	146 ± 13	85 ± 17	70 ± 6
5d	H	4-Cl	racemate	246 ± 20	5 ± 2	81 ± 5
5e	H	2-OCH_3	racemate	5 ± 2	3 ± 1	5 ± 2
5f	H	3-OCH_3	racemate	171 ± 16	37 ± 4	324 ± 22
5g	H	4-OCH_3	racemate	752 ± 81	73 ± 14	633 ± 41
5h	H	2,3-diCl	racemate	2 ± 1	9 ± 3	329 ± 15
5i	H	3,5-diCl	racemate	32 ± 8	164 ± 28	1341 ± 64
5j	H	3,4-diCl	racemate	208 ± 20	10 ± 3	45 ± 9
5k	H	2,4-diCl	racemate	65 ± 4	9 ± 1	311 ± 18
5l	H	2,4-diCl	1*R*,2*R*	64 ± 2	133 ± 21	348 ± 39
5m	H	2,4-diCl	1*S*,2*S*	93 ± 7	6 ± 2	322 ± 17
5n	H	2-OCH_3-4-Cl	racemate	17 ± 1	3 ± 1	29 ± 4
5o	H	2-OCH_3-4-F	racemate	10 ± 2	6 ± 1	14 ± 3
5p	H	2-CH_3-4-Cl	racemate	128 ± 17	31 ± 11*	307 ± 86*
5q	H	2-CH_3-4-F	racemate	68 ± 14	68 ± 3	31 ± 3
5r	H	2,4-diCH_3	racemate	60 ± 2	7 ± 1	144 ± 11
5s	H	2,4-diCH_3	1*R*,2*R*	45 ± 5	17 ± 3	137 ± 21
5t	H	2,4-diCH_3	1*S*,2*S*	73 ± 2	8 ± 2	131 ± 14
5u	H	2-OCH_3-5-Cl	racemate	5 ± 2	9 ± 2	8 ± 3
5v	H	3,5-diCl-4-OCH_3	racemate	228 ± 23	16 ± 6	193 ± 16
5w	H	2-pyridyl	racemate	263 ± 15	96 ± 5	55 ± 12
5x	H	3-pyridyl	racemate	>10000	>10000	1246 ± 296
5y	H	4-pyridyl	racemate	>10000	>10000	>10000
5z	H	2-pyrimidinyl	racemate	766 ± 59*	567 ± 51*	168 ± 9
6a	OCH_3	2,4-diCl	racemate	7 ± 1	45 ± 4	61 ± 4
6b	OH	2,4-diCl	racemate	12 ± 2	43 ± 5	74 ± 8
6c	F	2-Cl	racemate	13 ± 4	10 ± 2	9 ± 2
6d	F	3-Cl	racemate	56 ± 10	29 ± 2	56 ± 8
6e	F	4-Cl	racemate	202 ± 11	30 ± 6	61 ± 4
1		(haloperidol)		4 ± 2	5 ± 1	7 ± 2
2		(remoxipride)		880 ± 17	3872	>4000
3		(clozapine)		113 ± 9	17 ± 3	4 ± 1

kg, respectively. Clozapine and **5m,t** showed no significant cataleptic effects over the dose range tested (1−40 mg/kg).

In our examination of the 2-phenylcyclopropylaminomethylpiperazines as potential antipsychotic agents, we have attempted to approximate the D_2/D_4 ratio of clozapine on the theory that this ratio might be a key to its atypical nature. A practical limitation to this approach may be found in the suggestion by other researchers that the primary behavioral assays of antipsychotic efficacy are largely D_2-mediated. With this in mind, the inability of **5m**,**t** to display significant effects in amphetamine-timulated locomotor activity as a test of antipsychotic efficacy is somewhat puzzling in light of the fact that the control compounds of haloperidol and remoxipride are effective in this assay while having greater and lesser D_2 affinity, respectively, than **5m**,**t**. It has been demonstrated that the aromatic 6-methoxy substituent of remoxipride is metabolically cleaved in rat to the corresponding 6-hydroxy. The resulting 2-hydroxybenzamide, FLA 797, displays a significantly greater D_2 affinity (12 nM)[29] than does remoxipride and thus may account for the observed behavioral profile of remoxipride.

The time course for P450 enzymatic degradation of **5m**,**t** was determined by exposure of the compounds to microsomal fractions obtained from human and rat liver homogenates. Upon exposure to human liver microsomes the half-lives ($t_{1/2}$) of **5m**,**t** were determined to be 19 and 16 min, respectively. Much shorter half-lives of 2 and 3 min, respectively, were observed upon exposure to rat liver microsomes. The short half-lives of the compounds in rat may, in part, explain the lack of observable D_2 behavioral effects, although clozapine also shows a fairly short (5 min) half-life in rat. Alternatively, the D_2/D_4 hypothesis may be flawed. Proper testing of the hypothesis will require a series of D_2/D_4 antagonists having a more favorable pharmacokinetic profile.

In conclusion, a series of *trans*-1-[(2-phenylcyclopropyl)methyl]-4-arylpiperazines were prepared and tested for their ability to bind to adrenergic α_1 and dopamine D_2 and D_4 receptor subtypes in order to identify candidates with both D_2/D_4 ratios similar to that of clozapine and a low propensity to produce untoward cardiac responses. Two compounds having the 1*S*,2*S* absolute configuration and a 2,4-dimethyl or 2,4-dichloro substitution pattern on the 4-aryl were selected. While the compounds had D_2/D_4 ratios approximating that of clozapine and, in functional assays, were found to be antagonists at the dopamine subtypes, behavioral effects observed in rats for both typical and atypical antipsy-

chotic agents were absent. Thus, while these or similar compounds might prove to be effective antipsychotics in humans, the short $t_{1/2}$ in rat leaves the hypothesis that a compound with the proper D_2/D_4 ratio will display an atypical behavioral profile untested at this time.

Experimental Section

Chemistry. Melting points were determined on a Thomas-Hoover capillary melting-point apparatus and are uncorrected. Elemental analyses were obtained for all compounds tested for binding. Elemental analysis were performed at Robertson Microlabs, Madison, NJ, and the results were within ±0.4% of the theoretical values unless otherwise indicated. ^{1}H NMR spectra were recorded in $CDCl_3$ (unless otherwise noted) with tetramethylsilane (TMS) as the internal standard on a Varian Unity 400 spectrometer. Electron ionization mass spectra (MS) were recorded on a Hewlett-Packard 5890 mass spectrometer.

General Procedure for the Preparation of *trans*-1-[(2-Phenylcyclopropyl)methyl]-4-arylpiperazines from *trans*-2-Phenyl-1-cyclopropanecarbonyl Chloride (Method A). *trans*-1-[(2-Phenylcyclopropyl)methyl]-4-(2-chlorophenyl)-piperazine Hydrobromide. (5b) To a solution of 1-(2-chlorophenyl)piperazine hydrochloride (0.59 g, 3.0 mmol) in 10 mL of dichloromethane was added triethylamine (0.61 g, 6.0 mmol) followed by the addition of *trans*-2-phenyl-1-cyclopropanecarbonyl chloride (0.54 g 3.0 mmol) at 0 °C. The mixture was stirred at room temperature for 3 h and then quenched by the addition of 10 mL of water. The aqueous layer was extracted with chloroform (10 mL × 2) and the combined organics were washed with brine, dried over Na_2SO_4 and evaporated to dryness to give 1.0 g (98%) of **10b** as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31−1.34 (m, 1H), 1.67−1.73 (m, 1H), 1.99−2.05 (m, 1H), 2.48−2.55 (m, 1H), 3.03−3.06 (m, 4H), 3.81−3.85 (m, 4H), 6.98−7.03 (m, 2H), 7.12−7.18 (m, 2H), 7.20−7.29 (m, 4H), 7.31−7.39 (m, 1H); MS (LC−MS) *m/e* 341 (MH^+). This crude product was used in the next step without further purification.

To a 10-mL solution of alane (AlH_3; 0.5 M in THF) was added a solution of **10b** in 5 mL of THF at 0 °C. The mixture was stirred at room temperature for 3 h, then carefully quenched with NaOH (10%). The aqueous layer then was extracted with EtOAc (30 mL × 2). The combined organics were washed with brine, dried over Na_2SO_4 and concentrated. The free base was dissolved in 2-propanol and then treated with HBr (48%). Crystallization of the salt from *i*-PrOH/*i*-Pr_2O provided the desired product (1.0 g, 82%) as white crystals: mp 201−202 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 1.14−1.28 (m, 2H), 1.45−1.50 (m, 1H), 2.07−2.10 (m, 1H), 3.18−3.29 (bs, 4H), 3.39−3.71 (bd, 6H), 7.08−7.28 (m, 5H), 7.30−7.34 (m, 3H), 7.41 (dd, J = 1.37, 7.96 Hz, 1H); MS (LC−MS) *m/e* 327 (free base, MH^+). Anal. ($C_{20}H_{23}N_2Cl$·HBr) C, H, N.

Compounds **5a**−**k**,**n**−**r**,**u**−**z** were prepared according to Method A.

***trans*-1-[(2-Phenylcyclopropyl)methyl]-4-phenylpiperazine (5a).** 50% yield from *trans*-2-phenyl-1-cyclopropanecarbonyl chloride and 1-phenylpiperazine: mp 79−80 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84−0.89 (m, 1H), 0.97−1.01 (m, 1H), 1.26−1.31 (m, 1H), 1.68−1.73 (m, 1H), 2.38−2.43 (m, 1H), 2.59−2.67 (m, 1H), 2.70−2.75 (m, 4H), 3.18−3.23 (m, 4H), 6.86 (t, J = 7.2 Hz, 1H), 6.92 (d, J = 8.0 Hz, 2H), 7.06 (d, J = 7.2 Hz, 2H), 7.15 (t, J = 8.0 Hz, 1H), 7.24−7.28 (m, 4H); MS (LC−MS) *m/e* 293 (free base, MH^+). Anal. ($C_{20}H_{24}N_2$) C, H, N.

***trans*-1-[(2-Phenylcyclopropyl)methyl]-4-(3-chlorophenyl)piperazine Dihydrobromide (5c).** 38% yield from *trans*-2-phenyl-1-cyclopropanecarbonyl chloride and 1-(3-chlorophenyl)piperazine: mp 195−196 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.11−1.16 (m, 2H), 1.40−1.42 (m, 1H), 2.00−2.04 (m, 1H), 3.04 (t, J = 11.6 Hz, 2H), 3.13−3.22 (m, 2H), 3.26 (d, J = 6.5 Hz, 2H), 3.56 (d, J = 11.6 Hz, 2H), 3.91 (bs, 2H), 6.86 (d, J = 8 Hz, 1H), 6.95−6.97 (m, 1H), 7.05 (s, 1H), 7.12−7.18 (m, 4H), 7.23−7.29 (m, 2H); MS (LC−MS) *m/e* 327 (free base, MH^+). Anal. ($C_{20}H_{23}N_2Cl$·2HBr) C, H, N.

***trans*-1-[(2-Phenylcyclopropyl)methyl]-4-(4-chlorophenyl)piperazine Dihydrobromide (5d).** 37% yield from *trans*-2-phenyl-1-cyclopropanecarbonyl chloride and 1-(4-chlorophenyl)piperazine: mp 229 °C dec; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.05−1.16 (m, 2H), 1.40−1.42 (m, 1H), 2.00−2.04 (m, 1H), 3.04 (t, J = 11.6 Hz, 2H), 3.13−3.22 (m, 2H), 3.26 (d, J = 6.5 Hz, 2H), 3.56 (d, J = 11.6 Hz, 2H), 3.91 (bs, 2H), 7.01 (d, J = 8.4 Hz, 2H), 7.13 (d, J = 7.6 Hz, 2H), 7.26−7.30 (m, 5H); MS (LC−MS) *m/e* 327 (free base, MH^+). Anal. ($C_{20}H_{23}N_2Cl$·2HBr·0.5H_2O) C, H, N.

***trans*-1-[(2-Phenylcyclopropyl)methyl]-4-(2-methoxyphenyl)piperazine Hydrobromide (5e).** 91% yield from *trans*-2-phenyl-1-cyclopropanecarbonyl chloride and 1-(2-methoxyphenyl)piperazine: mp 129−130 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.05−1.15 (m, 2H), 1.39−1.41 (m, 1H), 2.01−2.06 (m, 1H), 2.93 (t, J = 11.6 Hz, 2H), 3.20−3.29 (m, 4H), 3.50−3.59 (m, 4H), 3.77 (s, 3H, OCH_3), 6.87−6.99 (m, 4H), 7.13−7.18 (m, 3H), 7.27 (t, J = 7.6 Hz, 2H); MS (LC−MS) *m/e* 323 (free base, MH^+). Anal. ($C_{21}H_{26}N_2O$·HBr·H_2O) C, H, N.

***trans*-1-[(2-Phenylcyclopropyl)methyl]-4-(3-methoxyphenyl)piperazine Hydrobromide (5f).** 91% yield from *trans*-2-phenyl-1-cyclopropanecarbonyl chloride and 1-(3-methoxyphenyl)piperazine: mp 220 °C dec; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.05−1.15 (m, 2H), 1.41−1.44 (m, 1H), 2.01−2.06 (m, 1H), 3.01 (t, J = 11.6 Hz, 2H), 3.14−3.30 (m, 4H), 3.55−3.66 (m, 2H), 3.71 (s, 3H, OCH_3), 3.81−3.86 (m, 2H), 6.43 (dd, J = 2.4, 8.0 Hz, 1H), 6.52 (t, J = 2.4 Hz, 1H), 6.56 (dd, J = 2.4, 8.2 Hz, 1H), 7.13−7.18 (m, 4H), 7.25−7.29 (m, 2H); MS (LC−MS) *m/e* 323 (free base, MH^+). Anal. ($C_{21}H_{26}N_2O$·HBr·H_2O) C, H, N.

***trans*-1-[(2-Phenylcyclopropyl)methyl]-4-(4-methoxyphenyl)piperazine Dihydrobromide (5g).** 90% yield from *trans*-2-phenyl-1-cyclopropanecarbonyl chloride and 1-(4-methoxyphenyl)piperazine: mp 218−219 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.06−1.15 (m, 2H), 1.42−1.44 (m, 1H), 2.01−2.05 (m, 1H), 2.92 (t, J = 11.6 Hz, 2H), 3.14−3.28 (m, 4H), 3.55−3.66 (m, 4H), 3.68 (s, 3H, OCH_3), 6.83 (d, J = 9.2 Hz, 2H), 6.94 (d, J = 9.2 Hz, 2H), 7.13−7.18 (m, 3H), 7.25−7.29 (m, 2H); MS (LC−MS) *m/e* 323 (free base, MH^+). Anal. ($C_{21}H_{26}N_2O$·2HBr) C, H, N.

***trans*-1-[(2-Phenylcyclopropyl)methyl]-4-(2,3-dichlorophenyl)piperazine Hydrobromide (5h).** 28% yield from *trans*-2-phenyl-1-cyclopropanecarbonyl chloride and 1-(2,3-dichlorophenyl)piperazine: mp 209−210 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.01−1.16 (m, 2H), 1.40−1.43 (m, 1H), 2.02−2.07 (m, 1H), 3.07 (t, J = 12.4 Hz, 2H), 3.23−3.29 (m, 4H), 3.46 (bd, J = 13.6 Hz, 2H), 3.61 (bd, J = 11.2 Hz, 2H), 7.13−7.18 (m, 3H), 7.21−7.29 (m, 3H), 7.32−7.39 (m, 2H); MS (LC−MS) *m/e* 361 (free base, MH^+). Anal. ($C_{20}H_{22}N_2Cl_2$·HBr) C, H, N.

***trans*-1-[(2-Phenylcyclopropyl)methyl]-4-(3,5-dichlorophenyl)piperazine Hydrobromide (5i)**. 21% yield from *trans*-2-phenyl-1-cyclopropanecarbonyl chloride and 1-(3,5-dichlorophenyl)piperazine: mp 243−244 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.04−1.10 (m, 1H), 1.12−1.17 (m, 1H), 1.39−1.42 (m, 1H), 1.99−2.02 (m, 1H), 3.09−3.16 (m, 2H), 3.25−3.29 (m, 4H), 3.53−3.55 (m, 2H), 3.99−4.02 (m, 2H), 6.95 (s, 1H), 7.04 (s, 2H), 7.12−7.18 (m, 3H), 7.25−7.29 (m, 2H); MS (LC−MS) *m/e* 361 (free base, MH^+). Anal. ($C_{20}H_{22}N_2Cl_2$·HBr) C, H, N.

***trans*-1-[(2-Phenylcyclopropyl)methyl]-4-(3,4-dichlorophenyl)piperazine Hydrobromide (5j).** 33% yield from *trans*-2-phenyl-1-cyclopropanecarbonyl chloride and 3,4-dichlorophenyl piperazine: mp 157−158 °C; ^{1}H NMR (free base, 400 MHz, $CDCl_3$) δ 0.84−0.89 (m, 1H), 0.98−1.02 (m, 1H), 1.25−1.29 (m, 1H), 1.68−1.73 (m, 1H), 2.36−2.41 (m, 1H), 2.59−2.64 (m, 1H), 2.66−2.71 (m, 4H), 3.17−3.20 (m, 4H), 6.73 (dd, J = 2.8, 9.0 Hz, 1H), 6.95 (d, J = 3.2 Hz, 1H), 7.05−7.07 (m, 2H), 7.14−7.18 (m, 1H), 7.25−7.29 (m, 3H); MS (LC−MS) *m/e* 361 (free base, MH^+). Anal. ($C_{20}H_{22}N_2Cl_2$·HBr·0.5H_2O) C, H, N.

***trans*-1-[(2-Phenylcyclopropyl)methyl]-4-(2,4-dichlorophenyl)piperazine Hydrobromide (5k).** 75% yield from *trans*-2-phenyl-1-cyclopropanecarbonyl chloride and 2,4-dichlo-

rophenylpiperazine: mp 206−207 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.06−1.15 (m, 2H), 1.43−1.45 (m, 1H), 2.02−2.07 (m, 1H), 3.05 (t, J = 12.0 Hz, 2H), 3.21−3.27 (m, 4H), 3.42−3.45 (m, 2H), 3.60−3.62 (m, 2H), 7.13−7.18 (m, 3H), 7.23−7.29 (m, 2H), 7.40 (dd, J = 2.4, 8.0 Hz, 2H), 7.60 (d, J = 2.4 Hz, 1H). Anal. ($C_{20}H_{22}N_2Cl_2$·HBr) C, H, N.

***trans*-1-[(2-Phenylcyclopropyl)methyl]-4-(4-chloro-2-methoxyphenyl)piperazine Hydrobromide (5n).** 63% yield from *trans*-2-phenyl-1-cyclopropanecarbonyl chloride and 1-(4-chloro-2-methoxyphenyl)piperazine: mp 206−207 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.00−1.15 (m, 2H), 1.40−1.42 (m, 1H), 2.01−2.04 (m, 1H), 2.93 (t, J = 12.4 Hz, 2H), 3.22−3.27 (m, 4H), 3.47−3.55 (m, 4H), 3.79 (s, 3H, OCH_3), 6.94 (s, 2H), 7.02 (s, 1H), 7.12−7.18 (m, 3H), 7.25−7.29 (m, 2H); MS (LC−MS) *m/e* 357 (free base, MH^+). Anal. ($C_{21}H_{25}N_2OCl$·HBr) C, H, N.

***trans*-1-[(2-Phenylcyclopropyl)methyl]-4-(4-fluoro-2-methoxyphenyl)piperazine Dihydrobromide (5o).** 29% yield from *trans*-2-phenyl-1-cyclopropanecarbonyl chloride and 1-(4-fluoro-2-methoxyphenyl)piperazine: mp 208−209 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.06−1.15 (m, 2H), 1.40−1.43 (m, 1H), 2.00−2.03 (m, 1H), 2.90 (t, J = 11.2 Hz, 2H), 3.22−3.28 (m, 2H), 3.43 (12.8, 2H), 3.56 (d, J = 10.4 Hz, 2H), 3.79 (s, 3H, OCH_3), 6.68−6.73 (m, 1H), 6.89−6.97 (m, 2H), 7.13−7.18 (m, 3H), 7.25−7.29 (m, 2H); MS (LC−MS) *m/e* 341 (free base, MH^+). Anal. ($C_{21}H_{25}N_2OF$·2HBr) C, H, N.

***trans*-1-[(2-Phenylcyclopropyl)methyl]-4-(4-chloro-2-methylphenyl)piperazine Hydrobromide (5p).** 90% yield from *trans*-2-phenyl-1-cyclopropanecarbonyl chloride and 1-(4-chloro-2-methylphenyl)piperazine: mp 206−207 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.08−1.17 (m, 2H), 1.40−1.43 (m, 1H), 2.03−2.05 (m, 1H), 2.25 (s, 3H, CH_3), 2.96 (t, J = 10.2 Hz, 2H), 3.20−3.30 (m, 6H), 3.55−3.57 (m, 2H), 7.07 (d, J = 8.8 Hz, 2H), 7.14−7.24 (m, 4H), 7.26−7.30 (m, 2H); MS (LC−MS) *m/e* 341 (free base, MH^+). Anal. ($C_{21}H_{25}N_2Cl$·HBr) C, H, N.

***trans*-1-[(2-Phenylcyclopropyl)methyl]-4-(4-fluoro-2-methylphenyl)piperazine Hydrobromide (5q).** 44% yield from *trans*-2-phenyl-1-cyclopropanecarbonyl chloride and 1-(4-fluoro-2-methoxyphenyl)piperazine: mp 204−205 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.06−1.15 (m, 2H), 1.42−1.44 (m, 1H), 2.02−2.06 (m, 1H), 2.25 (s, 3H, CH_3), 2.97 (t, J = 12.0 Hz, 2H), 3.14−3.26 (m, 6H), 3.54−3.58 (m, 2H), 6.96−7.00 (m, 1H), 7.03−7.18 (m, 5H), 7.25−7.29 (m, 2H); MS (LC−MS) *m/e* 325 (free base, MH^+). Anal. ($C_{21}H_{25}N_2F$·HBr) C, H, N.

***trans*-1-[(2-Phenylcyclopropyl)methyl]-4-(2,4-dimethylphenyl)piperazine Hydrobromide (5r).** 77% yield from *trans*-2-phenyl-1-cyclopropanecarbonyl chloride and 2,4-dimethylphenylpiperazine: mp 209−210 °C; ^{1}H NMR (free base, 400 MHz, $CDCl_3$) δ 0.86−0.90 (m, 1H), 0.94−1.01 (m, 1H), 1.28−1.31 (m, 1H), 1.69−1.72 (m, 1H), 2.26 (s, J = 6 Hz, 6H, 2CH3), 2.43−2.47 (m, 1H), 2.57−2.62 (m, 1H), 2.71 (bs, 4H), 2.91−2.94 (m, 4H), 6.92−7.00 (m, 3H), 7.06−7.08 (m, 2H), 7.15−7.16 (m, 1H), 7.24−7.27 (m, 2H); MS (LC−MS) *m/e* 321 (free base, MH^+). Anal. ($C_{22}H_{28}N_2$·HBr) C, H, N.

***trans*-1-[(2-Phenylcyclopropyl)methyl]-4-(5-chloro-2-methoxyphenyl)piperazine Hydrobromide (5u).** 51% yield from *trans*-2-phenyl-1-cyclopropanecarbonyl chloride and 1-(4-chloro-2-methylphenyl)piperazine: mp 209−210 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.06−1.14 (m, 2H), 1.40−1.42 (m, 1H), 2.01−2.03 (m, 1H), 2.93 (t, J = 12.0 Hz, 2H), 3.22−3.29 (m, 6H), 3.56 (bd, J = 10.4 Hz, 2H), 3.77 (s, 3H, OCH_3), 6.94−6.99 (m, 2H), 7.04 (dd, J = 2.4, 8.0 Hz, 1H), 7.12−7.18 (m, 3H), 7.25−7.29 (m, 2H); MS (LC−MS) *m/e* 357 (free base, MH^+). Anal. ($C_{21}H_{25}N_2OCl$·HBr) C, H, N.

***trans*-1-[(2-Phenylcyclopropyl)methyl]-4-(3,5-dichloro-4-methoxyphenyl)piperazine Hydrobromide (5v).** 81% yield from *trans*-2-phenyl-1-cyclopropanecarbonyl chloride and 1-(3,5-dichloro-4-methoxyphenyl)piperazine: mp 233−234 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.04−1.07 (m, 1H), 1.13−1.14 (m, 1H), 1.39−1.41 (m, 1H), 1.99−2.03 (m, 1H), 3.03 (t, J = 12.0 Hz, 2H), 3.10−3.20 (m, 2H), 3.24−3.25 (m, 2H), 3.54 (bd, J = 11.6 Hz, 2H), 3.72 (s, 3H, OCH_3), 3.88−3.90 (m, 2H), 7.12−7.19 (m, 5H), 7.25−7.29 (m, 2H); MS (LC−MS) *m/e* 391 (free base, MH^+). Anal. ($C_{21}H_{24}N_2OCl_2$·HBr) C, H, N.

***trans*-1-[(2-Phenylcyclopropyl)methyl]-4-(pyridin-2-yl)piperazine Dihydrochloride (5w).** 25% yield from *trans*-2-phenyl-1-cyclopropanecarbonyl chloride and 1-(pyridin-2-yl)piperazine: mp 110 °C; ^{1}H NMR (free base, 400 Hz, $CDCl_3$) δ 0.86 (dt, J = 8.4 and 5.6 Hz, 1H), 1.00 (dt, J = 8.4 and 4.8 Hz, 1H), 1.27 (m, 1H), 1.70 (dt, J = 8.4 and 4.8 Hz, 1H), 2.40 (dd, J = 12.8 and 6.8 Hz, 1H), 2.60 (dd, J = 12.4 and 6.0 Hz, 1H), 2.66 (m, 4H), 3.57 (m, 4H), 6.62 (dd, J = 7.6 and 5.2 Hz, 1H), 6.64 (d, J = 8.4 Hz, 1H), 7.07 (m, 2H), 7.16 (tt, J = 7.6 and 1.2 Hz, 1H), 7.26 (t, J = 7.2 Hz, 2H), 7.47 (ddd, J = 9.2, 7.6 and 2.0 Hz, 1H), 8.19 (dd, J = 4.8 and 2.0 Hz, 1H). Anal. ($C_{19}H_{23}N_3$·2HCl·0.5H_2O) C, H, N.

***trans*-1-[(2-Phenylcyclopropyl)methyl]-4-(pyridin-3-yl)piperazine Dihydrobromide (5x).** 63% yield from *trans*-2-phenyl-1-cyclopropanecarbonyl chloride and 1-(pyridin-3-yl)piperazine: mp 238 °C; ^{1}H NMR (free base, 400 Hz, $CDCl_3$) δ 0.86 (dt, J = 8.8 and 5.2 Hz, 1H), 1.00 (dt, J = 8.8 and 4.8 Hz, 1H), 1.27 (m, 1H), 1.71 (dt, J = 8.4 and 4.8 Hz, 1H), 2.40 (dd, J = 12.4 and 6.8 Hz, 1H), 2.61 (dd, J = 12.4 and 5.6 Hz, 1H), 2.70 (m, 4H), 3.24 (t, J = 5.2 Hz, 4H), 7.06 (d, J = 7.6 Hz, 2H), 7.16 (m, 3 H), 7.26 (t, J = 8.0 Hz, 2 H), 8.08 (dd, J = 3.6 and 1.6 Hz, 1H), 8.30 (d, J = 1.6 Hz, 1H). Anal. ($C_{19}H_{23}N_3$·2HBr) C, H, N.

***trans*-1-[(2-Phenylcyclopropyl)methyl]-4-(pyridin-4-yl)piperazine Dihydrobromide (5y).** 75% yield from *trans*-2-phenyl-1-cyclopropanecarbonyl chloride and 1-(pyridin-4-yl)piperazine: mp 225 °C; ^{1}H NMR (free base, 400 Hz, $CDCl_3$) δ 0.86 (dt, J = 9.2 and 4.8 Hz, 1H), 1.00 (dt, J = 8.8 and 4.8 Hz, 1H), 1.26 (m, 1H), 1.70 (dt, J = 9.2 and 4.0 Hz, 1H), 2.37 (dd, J = 12.4 and 6.8 Hz, 1H), 2.60 (dd, J = 12.0 and 5.6 Hz, 1H), 2.64 (m, 4H), 3.34 (m, 4H), 6.64 (dd, J = 4.8 and 2.0 Hz, 2H), 7.05 (d, J = 8.0 Hz, 2H), 7.16 (m, 1H), 7.27 (t, J = 7.6 Hz, 2H), 8.26 (dd, J = 5.6 and 1.2 Hz, 2H). Anal. ($C_{19}H_{23}N_3$·2HBr) C, H, N.

***trans*-1-[(2-Phenylcyclopropyl)methyl]-4-(pyrimidin-2-yl)piperazine Dihydrochloride (5z).** 54% yield from *trans*-2-phenyl-1-cyclopropanecarbonyl chloride and 1-(pyrimidin-2-yl)piperazine: mp 172 °C; ^{1}H NMR (free base, 400 Hz, $CDCl_3$) δ 0.85 (dt, J = 8.8 and 5.2 Hz, 1H), 1.00 (dt, J = 8.4 and 4.8 Hz, 1H), 1.27 (m, 1H), 1.69 (dt, J = 9.2 and 4.8 Hz, 1H), 2.40 (dd, J = 12.4 and 6.8 Hz, 1H), 2.58 (dd, J = 11.6 and 6.4 Hz, 1H), 2.60 (m, 4H), 3.85 (m, 4H), 6.47 (t, J = 4.8 Hz, 1H), 7.05 (dd, J = 6.8 and 1.6 Hz, 2H), 7.15 (t, J = 7.6 Hz, 1H), 7.26 (t, J = 8.0 Hz, 2H), 8.29 (d, J = 4.4 Hz, 2H). Anal. ($C_{18}H_{21}N_4$·2HCl) C, H, N.

General Procedure for the Preparation of *trans*-1-[(2-Phenylcyclopropyl)methyl]-4-arylpiperazines from *trans*-2-Aryl-1-cyclopropanecarboxylic Acids (Method B). (1*S*,2*S*)-*trans*-1-[(2-Phenylcyclopropyl)methyl]-4-(2,4-dichlorophenyl)piperazine Hydrobromide (5m). (Dimethylamino)pyridine (DMAP; 0.73 g, 6 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI; 1.15 g, 6.0 mmol) and 1-hydroxybenzotriazole (HOBT; 0.81 g, 6.0 mmol) were successively added to a solution of (1*S*,2*S*)-*trans*-2-phenyl-1-cyclopropanecarboxylic acid (**8b**; 0.95 g, 5.8 mmol) and 1-(2,4-dichlorophenyl)piperazine (1.35 g, 5.8 mmol) in 40 mL of CH_2Cl_2 at 0 °C with stirring. After being stirred overnight, the reaction was quenched by the addition of 50 mL of water. The aqueous layer was extracted with chloroform (40 mL × 2) and the combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated to dryness to give 1.2 g (55%) of **10m** as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29−1.34 (m, 1H), 1.69−1.71 (m, 1H), 1.99−2.03 (m, 1H), 2.49−2.54 (m, 1H), 3.01−3.12 (m, 4H), 3.80−3.83 (m, 4H), 6.92 (d, J = 8.4 Hz, 1H), 7.12 (d, J = 7.6 Hz, 2H), 7.19−7.22 (m, 2H), 7.28−7.31 (m, 3H); MS (LC−MS) *m/e* 375 (MH^+). The crude product was used in the second step without further purification.

To a 20-mL solution of AlH_3 (0.5 M in THF) was added a solution of **10m** in 10 mL of THF at 0 °C. The mixture was stirred at room temperature for 3 h, then carefully quenched with NaOH (10%). The aqueous layer was then extracted with EtOAc (30 mL × 2). The combined organics were washed with brine, dried over Na_2SO_4 and concentrated. The free base was

dissolved in 2-propanol and then treated with HBr (48%) to adjust the pH to 3. Crystallization of the salt in *i*-PrOH/*i*-Pr_2O provided the desired product (1.25 g, 88%) as white crystals: mp 142−143 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.06−1.15 (m, 2H), 1.43−1.45 (m, 1H), 2.02−2.07 (m, 1H), 3.05 (t, J = 12.0 Hz, 2H), 3.21−3.27 (m, 4H), 3.42−3.45 (m, 2H), 3.60−3.62 (m, 2H), 7.13−7.18 (m, 3H), 7.23−7.29 (m, 2H), 7.40 (dd, J = 2.4, 8.0 Hz, 2H), 7.60 (d, J = 2.4 Hz, 1H); MS (LC−MS) *m/e* 361 (free base, MH^+); $[\alpha]_D^{20}$ +94.0° (free base, c = 0.436, CH_3Cl). Anal. ($C_{20}H_{22}N_2Cl_2$·HBr) C, H, N. The optical purity was shown to be >99% by HPLC analysis (CHIRACEL OD, 1.0 mL/min, methanol). The approximate retention time was 6.45 min.

Compounds **5l**,**m**,**s**,**t** and **6a**−**e** were prepared according to Method B.

(1*R*,2*R*)-*trans*-1-[(2-Phenylcyclopropyl)methyl]-4-(2,4-dichlorophenyl)piperazine Dihydrobromide (5l). mp 197−198 °C; ^{1}H NMR (free base, 400 MHz, $CDCl_3$) δ 0.85−0.89 (m, 1H), 0.97−1.01 (m, 1H), 1.25−1.31 (m, 1H), 1.69−1.74 (m, 1H), 2.42−2.47 (m, 1H), 2.58−2.63 (m, 1H), 2.74 (bs, 4H), 3.06 (bs, 4H), 6.96 (d, J = 8.4 Hz, 1H), 7.06−7.08 (m, 2H), 7.15−7.20 (m, 2H), 7.28−7.31 (m, 3H); MS (LC−MS) *m/e* 361 (free base, MH^+); $[\alpha]_D^{20}$ −89.4° (free base, c = 0.4675, $CHCl_3$). Anal. ($C_{20}H_{22}N_2Cl_2$·2HBr) C, H, N. The optical purity was shown to be >99% by HPLC analysis (CHIRACEL OD, 1.0 mL/min, methanol). The approximate retention time was 7.38 min.

(1*R*,2*R*)-*trans*-1-[(2-Phenylcyclopropyl)methyl]-4-(2,4-dimethylphenyl)piperazine Dihydrobromide (5s). 19% yield from (1*R*,2*R*)-*trans*-2-phenyl-1-cyclopropanecarboxylic acid (**8a**) and 1-(2,4-dimethylphenyl)piperazine: mp 215−217 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 1.14−1.19 (m, 1H), 1.22−1.28 (m, 1H), 1.16−1.49 (m, 1H), 2.06−2.09 (m, 1H), 2.25 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 3.02−3.10 (m, 2H), 3.22−3.30 (m, 6H), 3.67−3.72 (m, 2H), 6.98 (d, J = 1.1 Hz, 2H), 7.03 (s, 1H), 7.14−7.20 (m, 3H), 7.26−7.30 (m, 2H); MS (LC−MS) *m/e* 321 (MH^+); $[\alpha]_D^{20}$ −58.5° (c = 0.582, CH_3OH). Anal. ($C_{22}H_{28}N_2$·2HBr) C, H, N. The optical purity was shown to be >99% by HPLC analysis (CHIRACEL OD, 1.0 mL/min, methanol).

(1*S*,2*S*)-*trans*-1-[(2-Phenylcyclopropyl)methyl]-4-(2,4-dimethylphenyl)piperazine Dihydrobromide (5t). 29% yield from (1*S*,2*S*)-*trans*-2-phenyl-1-cyclopropanecarboxylic acid (**8b**) and 1-(2,4-dimethylphenyl)piperazine: mp 224−225 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 1.14−1.19 (m, 1H), 1.22−1.28 (m, 1H), 1.16−1.49 (m, 1H), 2.06−2.09 (m, 1H), 2.25 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 3.02−3.10 (m, 2H), 3.22−3.30 (m, 6H), 3.67−3.72 (m, 2H), 6.98 (d, J = 1.1 Hz, 2H), 7.03 (s, 1H), 7.14−7.20 (m, 3H), 7.26−7.30 (m, 2H); MS (LC−MS) *m/e* 321 (MH^+); $[\alpha]_D^{20}$ +60.7° (c = 0.594, CH_3OH). Anal. ($C_{22}H_{28}N_2$·2HBr) C, H, N. The optical purity was shown to be >99% by HPLC analysis (CHIRACEL OD, 1.0 mL/min, methanol).

***trans*-1-[(2-(4-Methoxyphenyl)cyclopropyl)methyl]-4-(2,4-dichlorophenyl)piperazine Hydrobromide (6a).** 60% yield from *trans*-2-(4-methoxyphenyl)-1-cyclopropanecarboxylic acid[28] and 1-(2,4-dichlorophenyl)piperazine: mp 223−224 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.00−1.08 (m, 2H), 1.33−1.34 (m, 1H), 1.97−1.99 (m, 1H), 3.01−3.07 (m, 3H), 3.20−3.29 (m, 3H), 3.44 (d, J = 12.8 Hz, 2H), 3.60 (d, J = 9.6 Hz, 2H), 3.70 (s, 3H, OCH_3), 6.83 (d, J = 8.4 Hz, 2H), 7.06 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 8.8 Hz, 1H), 7.40 (dd, J = 2.4, 8.6 Hz, 1H), 7.60 (2.4, 1H); MS (LC−MS) *m/e* 391 (free base, MH^+). Anal. ($C_{21}H_{24}N_2OCl_2$·HBr) C, H, N.

***trans*-1-[(2-(4-Fluorophenyl)cyclopropyl)methyl]-4-(2-chlorophenyl)piperazine Dihydrobromide (6c).** 67% yield from *trans*-2-(4-fluorophenyl)-1-cyclopropanecarboxylic acid[29] and 1-(2-chlorophenyl)piperazine: mp 203 °C; ^{1}H NMR (free base, 400 Hz, $CDCl_3$) δ 0.86 (dt, J = 5.0, 8.5 Hz, 1H), 0.96 (dt, J = 5.0, 8.5 Hz, 1H), 1.20−1.26 (m, 1H), 1.71 (dt, J = 5.0, 9.0 Hz, 1H), 2.42 (dd, J = 7.0, 12.5 Hz, 1H), 2.61 (dd, J = 7.0, 12.5 Hz, 1H), 2.69−2.72 (m, 4H), 3.22−3.25 (m, 4H), 6.93−7.06 (m, 6H), 7.20 (t, J = 8.0 Hz, 1H), 7.35 (dd, J = 1.0 and 8.0 Hz). Anal. ($C_{20}H_{22}FClN_2$·2HBr·0.5H_2O) C, H, N.

***trans*-1-[(2-(4-Fluorophenyl)cyclopropyl)methyl]-4-(3-chlorophenyl)piperazine Dihydrobromide (6d).** 74% yield from *trans*-2-(4-fluorophenyl)-1-cyclopropanecarboxylic acid and 1-(3-chlorophenyl)piperazine: mp 215 °C dec; ^{1}H NMR (free base, 400 Hz, $CDCl_3$) δ 0.88 (dt, J = 5.0, 8.5 Hz, 1H), 0.97 (dt, J = 5.0, 8.5 Hz, 1H), 1.21−1.26 (m, 1H), 1.68 (dt, J = 5.0, 9.0 Hz, 1H), 2.39 (dd, J = 7.0, 13.0 Hz, 1H), 2.59 (dd, J = 7.0, 13.0 Hz, 1H), 2.63−2.68 (m, 4H), 3.12−3.22 (m, 4H), 6.76−6.81 (m, 2H), 6.87 (s, 1H), 6.97−7.02 (m, 2H), 7.15 (t, J = 8.5 Hz, 1H), 7.21−7.30 (m, 2H). Anal. ($C_{20}H_{22}FClN_2$·2HBr·0.5H_2O) C, H, N.

***trans*-1-[(2-(4-Fluorophenyl)cyclopropyl)methyl]-4-(4-chlorophenyl)piperazine Dihydrobromide (6e).** 79% yield from *trans*-2-(4-fluorophenyl)-1-cyclopropanecarboxylic acid and 1-(4-chlorophenyl)piperazine: mp 203 °C; ^{1}H NMR (free base, 400 Hz, $CDCl_3$) δ 0.85 (dt, J = 5.0, 8.5 Hz, 1H), 0.94 (dt, J = 5.0, 8.5 Hz, 1H), 1.21−1.23 (m, 1H), 1.70 (dt, J = 5.0, 9.0 Hz, 1H), 2.41 (dd, J = 7.5, 13.0 Hz, 1H), 2.60 (dd, J = 7.5, 13.0 Hz, 1H), 2.68−2.70 (m, 4H), 3.16−3.20 (m, 4H), 6.82−6.85 (m, 2H), 6.94 (t, J = 8.8 Hz, 1H), 7.00−7.04 (m, 3H), 7.18−7.21 (m, 2H). Anal. ($C_{20}H_{22}FClN_2$·2HBr·0.5H_2O) C, H, N.

***trans*-1-[(2-(4-Hydroxyphenyl)cyclopropyl)methyl]-4-(2,4-dichlorophenyl)piperazine Hydrobromide (6b).** To a solution of **6a** (free base, 0.5 g 1.3 mmol) in 12 mL of CH_2Cl_2 was added 5 mL of BBr_3 solution (1.0 M in CH_2Cl_2) at −78 °C. The mixture was warmed to room temperature and then quenched with 15 mL of CH_3OH. The volatile was removed under reduced pressure. The residue was partitioned between $CHCl_3$ (30 mL) and saturated $NaHCO_3$ solution and the pH of the aqueous was carefully adjusted to 10 by 10% NaOH. The aqueous layer was extracted with $CHCl_3$ (20 mL × 2) and the combined organics were washed with brine, dried over Na_2SO_4 and concentrated. The crude product was purified by chromatography to provide 0.35 g (73%) of colorless oil, which was then converted to hydrobromide salt: mp 210−211 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.96−1.02 (m, 2H), 1.27−1.28 (m, 1H), 1.91−1.97 (m, 1H), 3.03 (t, J = 11.2 Hz, 2H), 3.22−3.29 (m, 4H), 3.43 (bd, J = 12.0 Hz, 2H), 3.59 (bd, J = 10.8 Hz, 2H), 6.66 (d, J = 8.4 Hz, 2H), 6.93 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 9.2 Hz, 1H), 7.40 (dd, J = 9.2, 2.8 Hz, 1H), 7.60 (d, J = 2.8 Hz, 1H); MS (LC−MS) *m/e* 377 (free base, MH^+). Anal. ($C_{20}H_{22}N_2Cl_2O$·HBr) C, H, N.

Indirect Resolution of *trans*-2-Phenyl-1-cyclopropanecarboxylic Acid (8a,b). To a solution of (*R*)-α-methylbenzylamine (17.6 g, 145 mmol) in 200 mL of dichloromethane was added 20 mL of triethylamine followed by the addition of *trans*-2-phenyl-1-cyclopropanecarbonyl chloride (25.0 g 138.4 mmol) at 0 °C. The mixture was stirred at room temperature for 3 h and then quenched by the addition of aqueous HCl (5%, 100 mL). The aqueous layer was extracted with chloroform (100 mL × 2) and the combined organic layers was washed with brine, dried over Na_2SO_4 and evaporated to dryness to give 36 g of crude product as an off-white solid. The crude product was dissolved in 350 mL of EtOAc at reflux and then cooled to room temperature. After filtration, 9.0 g of crystals were obtained and it was recrystallized from 180 mL of EtOAc to provide the amide **9a** (5.5 g, 15%) as white needles: mp 180−181 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21−1.28 (m, 1H), 1.51 (d, J = 9.2 Hz, 3H, CH_3), 1.59−1.67 (m, 2H), 2.45−2.52 (m, 1H), 5.11−5.21 (m, 1H, CH), 5.83 (bd, J = 9.6 Hz, 1H, NH), 7.05−7.08 (m, 2H), 7.15−7.20 (m, 1H), 7.25−7.31 (m, 4H), 7.34−7.37 (m, 3H); MS (LC−MS) *m/e* 265 (MH^+); $[\alpha]_D^{20}$ −207° (c = 0.50, $CHCl_3$). The mother liquid of the crystallization was concentrated to give 16.0 g of a mixture of **9a**,**b** (**9b** major component), which was utilized in the next step.

The mixed amide **9a**,**b** (16.0 g, 60 mmol) was suspended in 300 mL of ethylene glycol and mixed with 15 g of KOH and 9 mL (180 mL) of hydrazine monohydrate. The mixture was stirred at 160 °C for 30 h and then quenched by the addition of 200 mL of water at room temperature. The aqueous layer was extracted with Et_2O (200 mL) and the ether layer was discarded. The aqueous layer was acidified carefully with concentrated HCl to pH ∼ 1, then extracted with EtOAc (300 mL × 3). The extracts were washed with brine, dried over Na_2SO_4 and concentrated to give 9.5 g (98%) of gummy oil, which is a mixture of *trans*-2-phenyl-1-cyclopropanecarboxylic acid (**8a**,**b**) (**8b** major component). This acid was coupled with (*S*)-

α-methylbenzylamine (7.10 g, 59 mmol) with EDCI (11.31 g, 59 mmol), HOBT (7.97 g, 59 mmol) and 10 mL of trimethylamine in 100 mL of CH_2Cl_2 at room temperature. The crude product was crystallized twice in EtOAc to provide the amide **9c** (3.96 g, 26%) as long-needle cystals: mp 175−176 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21−1.28 (m, 1H), 1.51 (d, J = 9.2 Hz, 3H, CH_3), 1.59−1.67 (m, 2H), 2.45−2.52 (m, 1H), 5.11−5.21 (m, 1H, CH), 5.83 (bd, J = 9.6 Hz, 1H, NH), 7.05−7.08 (m, 2H), 7.15−7.20 (m, 1H), 7.25−7.31 (m, 4H), 7.34−7.37 (m, 3H); MS (LC−MS) *m/e* 265 (MH^+); $[\alpha]_D^{20}$ +216° (c = 0.73, $CHCl_3$).

(1*R*,2*R*)-*trans*-2-Phenyl-1-cyclopropanecarboxylic Acid (8a). 93% yield from **9a** following the procedure described above: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40−1.45 (m, 1H), 1.64−1.70 (m, 1H), 1.88−1.94 (m, 1H), 2.58−2.64 (m, 1H), 7.10−7.19 (m, 2H), 7.27−7.32 (m, 3H); $[\alpha]_D^{20}$ −425° (c = 0.725, $CHCl_3$) [lit.[26] $[\alpha]_D^{20}$ −410° (c = 1.0, $CHCl_3$)].

(1*S*,2*S*)-*trans*-2-Phenyl-1-cyclopropanecarboxylic Acid (8b). 99% yield hydrolyzed from **9c** following the same procedure as described above: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40−1.45 (m, 1H), 1.64−1.70 (m, 1H), 1.88−1.94 (m, 1H), 2.58−2.64 (m, 1H), 7.10−7.19 (m, 2H), 7.27−7.32 (m, 3H); $[\alpha]_D^{20}$ +453° (c = 0.9, $CHCl_3$) [lit.[26] $[\alpha]_D^{20}$ +405° (c = 1.0, $CHCl_3$)].

Biological Methods. 1. Expression of Recombinant Dopamine Receptors. The recombinant human $D_{4.2}$ receptor was prepared from the $D_{4.2}$ minigene expression construct by replacement of the *Not*I-*Kas*I fragment containing two introns with a synthetic DNA fragment encoding the intron-deleted sequence (Genbank #HSD4DOP). Stable clones expressing each receptor were isolated under G418 selection after calcium phosphate transfection of CHO-K1 cells (the human $D_{4.2}$ plasmid was cotransfected with pSV2Neo; Clontech). The membranes prepared from cell pellets were stored at −80 °C.

2. Membrane Preparation. Pellets containing selected cloned dopamine receptor membrane were thawed on ice and resuspended in ice cooled 50 mM Tris buffer (pH 7.4 at 25 °C) containing 120 mM NaCl, 1 mM EDTA and 5 mM $MgCl_2$. All subsequent work was performed on ice. The membranes were homogenized on a Brinkmann polytron (10 s, setting 5). The homogenate was centrifuged at 48000*g* and 4 °C for 10 min (DuPont Sorvall RC5B). The pellet was resuspended in fresh buffer and centrifugation was repeated. The pellet was again resuspended in fresh buffer and centrifuged a final time at 48000*g* and 4 °C for 10 min. The pellet was resuspended to a final concentration of 100 mg protein/mL with 50 mM Tris buffer (pH 7.4 at 25 °C) containing 120 mM NaCl, just prior to addition to the assay tubes. The protein content was determined using the Bio-Rad assay (Hercules, CA), with bovine plasma γ-globulin as a standard.

3. Binding Assay. For D_2 and D_4 binding, each sample was tested in triplicate in a final volume of 0.5 mL in polypropylene microtube strips containing 0.1 nM [^{3}H]YM 09151 (81.4 Ci/mmol; NEN DuPont) and CHO cell homogenate (40 μg protein) in 50 mM Tris buffer (pH 7.4 at 25 °C) containing 120 mM NaCl. After a 2-h incubation at 25 °C at room temperature the samples were rapidly filtered through 1% PEI-treated GF/C filters using a Tomtec harvester 96. The filters were rinsed with two washes of assay buffer. After air-drying, bound radioactivity was then quantitated via the BetaPlate scintillation counter at an efficiency of 65%. Nonspecific binding was defined with 1 mM spiperone.

For α_1 binding, each sample was tested in triplicate in a final volume of 0.5 mL in polypropylene microtube strips containing 0.2 nM [^{3}H]prazosin and rat cortex homogenate in 50 mM Tris buffer (pH 7.4 at 25 °C) containing 0.01% ascorbate. After a 30-min incubation at 25 °C at room temperature the samples were rapidly filtered through untreated GF/C filters using a Tomtec harvester 96. The filters were rinsed with two washes of assay buffer. After air-drying, bound radioactivity was then quantitated via the BetaPlate scintillation counter at an efficiency of 65%. Nonspecific binding was defined with 1 μM phentolamine.

4. Data Analysis. Binding data were analyzed with the nonlinear curve-fitting program RS/1 (BBN Software Products, Cambridge, MA). Calculated IC_{50} values were then converted to K_i values using the Cheng−Prusoff correction[30] with the following equation: $K_i = IC_{50}/(1 + [L]/K_d)$, where [L] is the radioligand concentration and K_d is the previously determined dissociation constant for [^{3}H]YM 09151 at the cloned human D_2 receptor (0.070 nM) and cloned human D_4 receptor (0.37 nM).

5. Dopamine Functional Assays. CHO cells stably expressing either human $D_{4.2}$ or D_2 receptor were grown to confluency in Ham's media supplemented with 10% fetal calf serum, harvested, and then stored as pellets at −80 °C. Thawed cells were homogenized using a Polytron (30 s, setting 5) in 50 mM Tris pH 7.4, 10 mM $MgCl_2$ and 2 mM EGTA. Membrane homogenates were centrifuged at 14000*g* for 10 min and the pellet washed one time in cold PBS. The final pellet was resuspended in homogenization buffer and stored at −80 °C. On the day of the assay, thawed membrane homogenates were resuspended in assay buffer (50 mM Tris pH 7.4, 120 mM NaCl, 10 mM $MgCl_2$, 2 mM EGTA, 0.1% BSA, 0.1 mM bacitracin, 100 KIU/mL aprotinin, 5 μM GDP) and added to reaction tubes at a concentration of 25 μg/0.200 mL. Reactions were initiated by the addition of 100 pM GTP[γ-^{35}S], dopamine (0.01 nM−10 μM) and individual compounds ranging in concentration from 0.1 nM to 10 μM. Following a 30-min incubation at 22 °C, the reaction was terminated by vacuum filtration over GF/C filters with ice-cold wash buffer (50 mM Tris pH 7.4, 5 mM $MgCl_2$). Bound GTP[γ-^{35}S] was determined by liquid scintillation spectrometry. Nonspecific binding was defined by 10 μM GTP[γ-^{35}S] and represented less than 10% of total binding.

6. Behavioral Assays. Male Sprague−Dawley rats weighing 200−350 g served as subjects. The animals were housed in groups of three in a temperature-controlled (21 ± 1 °C) animal facility on a 12-h light-dark cycle (lights on at 0630 h) and had free access to food and water.

Locomotor activity was measured in eight computerized Digiscan-16 animal activity monitors (Omnitech Electronics, Columbus, OH) equipped with 48 infrared photocell emittors and detectors (2.5 cm between sensors). Each box (41 × 41 × 30 cm^3) was constructed of Plexiglass sides and floor.

Rats were pretreated with clozapine (0.125−8.0 mg/kgsc), haloperidol (0.0075−0.25 mg/kg sc), **5m** (4−16 mg/kg sc) or **5t** (4−16 mg/kg sc) 30 min prior to an injection of 0.5 mg/kg d-amphetamine (ip). Immediately following the amphetamine administration, the rats were placed into the Omnitech activity boxes where horizontal (total distance traveled) and vertical activity (rearing) were measured for 1 h.

7. Microsomal Metabolism Assays. Into a 5-mL deep well microtiter plate was placed a microsomal reaction preparation containing the following: microsomal protein (50 μL, having a P450 content of ∼0.5 nmol/mg protein), test compound solution (10 μL of 10 mmol solution in DMSO), 0.1 M phosphate buffer (798 μL). The plate was preincubated at 39° C for 10 min. A cofactor mixture was prepared by dissolving NADP (16.2 mg) and glucose-6-phosphate dehydrogenase (45.4 mg) in 4 mL of 100 mM $MgCl_2$ solution. The enzyme reaction was then initiated by the addition of 142 μL of the cofactor mixture to the microsomal reaction preparation followed by shaking. At each time point (0, 1, 3, 5 and 10 min), 175 μL of the reaction mixture was transferred via pipet to be quenched with 175 μL of ice-cold acetonitrile. After the final sample was collected, the samples were centrifuged at 6000 rpm for 10 min. HPLC analysis of the samples was then carried out with UV detection. Concentrations were determined using a standard concentration curve.

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