Synthesis and Biological Characterization of α-(4-Fluorophenyl)-4-(5-fluoro-2-pyrimidinyl)-1-piperazinebutanol and Analogues as Potential Atypical Antipsychotic Agents

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A series of 1-(pyrimidin-2-yl)piperazine derivatives were prepared and evaluated in receptor binding assays and in in vivo behavioral paradigms as potential atypical antipsychotic agents. Compound **16** (BMS 181100 (formerly BMY 14802)) emerged as the lead compound from within the series on the basis of its good activity and duration of action in the inhibition of both conditioned avoidance responding and apomorphine-induced stereotopy in the rat. Compound **16** not only failed to induce catalepsy in the rat but was quite effective in reversing the cataleptic effect of neuroleptic agents, thus indicating a low propensity for causing extrapyramidal side effects. In comparison to reference antipsychotic agents, **16** appeared to be less sedating and was relatively weaker in causing muscle incoordination. The compound was essentially inactive in binding to dopamine D_2 receptors and its chronic administration to rats did not result in dopamine receptor supersensitivity. It exhibited modest to weak affinity for 5-HT_{1A} and α_1 receptors but was found to be a fairly potent ligand for σ binding sites (IC_{50} vs (+)-[^{3}H]-3-PPP = 112 nM). Although the resolved enantiomers of racemic **16** did not show dramatic differences from racemate or from each other in most tests, the *R*(+) enantiomer was up to 11-fold more potent than its antipode in binding to σ sites. Several studies have indicated that **16** may be a limbic-selective agent which may modulate dopaminergic activity by an indirect mechanism. The compound has been selected for clinical evaluation in the treatment of psychosis.

Schizophrenia, a major psychiatric disorder, is believed to involve an aberration of central dopaminergic neurotransmission. The drugs used to treat the symptoms of schizophrenia function as dopamine (DA) receptor antagonists and the DA receptor blockade hypothesis of antipsychotic drug action has remained essentially unchanged since first proposed by Carlsson and Lindquist nearly three decades ago.[1] In support of this hypothesis is the empirical observation that the clinical potencies of antipsychotic drugs parallel their affinity for binding to DA D_2 receptors.[2] Unfortunately, the DA antagonist properties of neuroleptic agents of the phenothiazine and butyrophenone types are also responsible for the serious extrapyramidal side effects (EPS) commonly associated with this class of drugs. Tardive dyskinesia, a debilitating and often irreversible syndrome, can occur following prolonged neuroleptic usage.[3]

In our quest to discover novel and safer antipsychotic agents, we chose to diverge from the traditional approach of designing yet more potent D_2 antagonists. We have focussed instead upon compounds having in vivo behavioral activity suggestive of both antipsychotic efficacy and minimal side effect liability but which lack strong affinity for DA receptors. A drug having such a profile could, if effective in man, represent a major advance in the therapy of psychosis. An atypical antipsychotic might attenuate abnormal informational processing via a multiplicity of subtle neuronal interactions including an indirect modulation of dopaminergic pathways and have a favorable selectivity of action within relevant (limbic) brain regions.

Our earlier research on heteroarylpiperazine derivatives as central nervous system (CNS) drugs has resulted in the clinically efficacious anxiolytic/antidepressants buspirone (**1**, Buspar)[4] and gepirone (**2**)[5] and the potential antipsychotic tiospirone (**3**),[6] which despite its high affinity for D_2 receptors was viewed as having atypical properties. Unfortunately, the encouraging results of open clinical studies of **3**[7] were not corroborated by subsequent double-blind evaluation. Compounds such as **1** and **2** that bear the 1-(pyrimidin-2-yl)piperazine (1-PP) pharmacophore not only have psychotherapeutic utility but are also void of serious side effects including EPS. Moreover, we have found that blocking the metabolically-labile 5-position of the pyrimidine ring by a fluorine substituent affords compounds having potent in vivo activity, extended

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(2) Creese, I.; Burt, D. R.; Snyder, S. H. Dopamine Receptor Binding Predicts Clinical and Pharmacological Potencies of Antipsychotic Drugs. *Science* **1976**, *192*, 481-483.

(3) Jenner, P.; Marsden, C. D. Neuroleptics and Tardive Dyskinesia. In *Neuroleptics: Neurochemical, Behavioral, and Clinical Perspectives*; Coyle, J. T., Enna, S. J., Eds.; Raven Press: New York, 1983; pp 223-253.

(4) Tunnicliff, G.; Eison, A. S.; Taylor, D. P. *Buspirone, Mechanisms and Clinical Aspects*. Academic Press: New York, 1991.

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(7) Moore, N. C.; Kurtz, N. M.; Owen, P. Q.; Gershon, S.; O'Brien, C. P.; Henn, F. A.; Saxena, B. M. BMY 13859: Summary of Results from Initial Clinical Trials. *ACNP Meeting Abstr.* 1985, 149.

(8) Temple, D. L.; Yevich, J. P.; New, J. S. Buspirone: Chemical Profile of a New Class of Anxioselective Agents. *J. Clin. Psychiatry* **1982**, *43*, 4-9.

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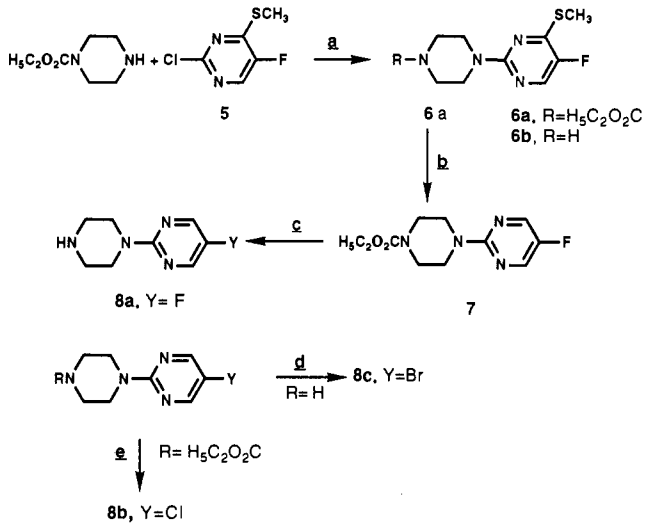
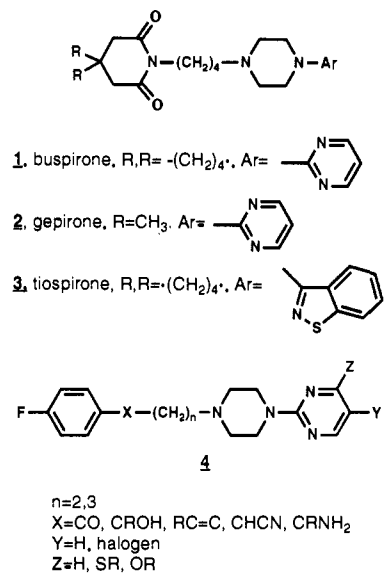
Scheme I



(a) K_2CO_3, MeCN, reflux; (b) Raney Ni, EtOH, reflux
(c) 1. 6NHCl, reflux 2. 50% NaOH; (d) Br_2, 1N HCl, 0-100°C
(e) 1. Cl_2, IN HCl, r.t. 2. 6NHCl, reflux 3. 50% NaOH

duration of action, and a lack of D_2 receptor interaction.[8] We thus reasoned that the coupling of 1-PP pharmacophores to appropriate side chains might provide nondopaminergic agents having useful antipsychotic activity without neuroleptic-like side effects. This paper describes the syntheses and biological characterization of a series of compounds[9] of general formula **4** in which the 1-PP (or 5-substituted 1-PP) moiety is appended to butyrophenone or structurally-related side chains.

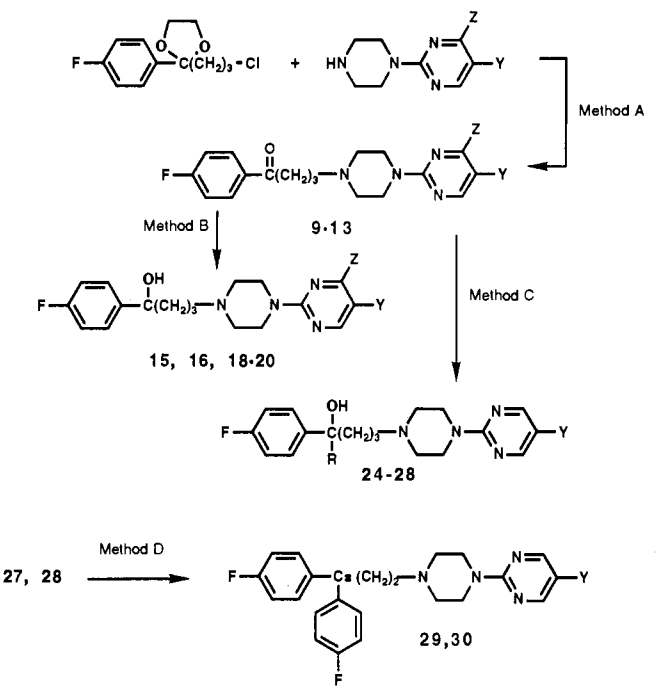


n=2,3
X=CO, CROH, RC=C, CHCN, $CRNH_2$
Y=H, halogen
Z=H, SR, OR

Chemistry

Compounds of the general formula **4** were obtained via elaboration of 1-PP or its substituted derivatives. The preparations of 1-PP analogues bearing a 5- or 4,5-substituted pyrimidine ring are depicted in Scheme I. Heating 2-chloro-5-fluoro-4-(methylthio)pyrimidine (**5**),[10] which was prepared by literature methods from 5-fluorouracil, with *N*-(ethoxycarbonyl)piperazine in acetonitrile afforded **6a**. The latter was converted to 5-F-1-PP (**8a**) by Raney nickel desulfurization followed by acid hydrolysis of the carbamate moiety. Hydrolysis of **6a** gave **6b**. The 5-chloro (**8b**) and 5-bromo (**8c**) intermediates were prepared by halogenation of 1-PP or an N-protected derivative.

Scheme II



Method A: 1. K_2CO_3, KI, MeCN, reflux 2. 3N HCl
Method B: $NaBH_4$, EtOH
Method C: RMgX, THF, reflux
Method D: CF_3CO_2H, room temp.

As shown in Scheme II, alkylation of the piperazines with the ketal derivative of 4-chloro-4′-fluorobutyrophenone gave, upon aqueous acidic workup, the ketones **9–13** (Table I). Use of the chloro ketone itself in the alkylation procedure resulted in significantly lower yields. The secondary carbinols, **15**, **16**, **18–20**, were obtained in good yield via sodium borohydride reduction of their ketone precursors. Analogous procedures afforded the propiophenone **14** and the corresponding carbinol **23**. Reaction of butyrophenones **9** and **10** with alkyl or aryl Grignard reagents led to the tertiary carbinols **24–28**; olefins **29** and **30** were derived by acid-catalyzed dehydration of the appropriate carbinol.

Further transformations of ketone **10**, illustrated in Scheme III, include conversion to the cyano compound **31** with tosylmethyl isocyanide and reaction with hydroxylamine to give the oxime **32**, which was catalytically reduced to the amino compound **33**. Compounds **21** and **22** resulted from displacement of the methylthio group of **20** by heating in aqueous and methanolic KOH, respectively.

Following unsuccessful attempts to resolve the racemic carbinol **16** into its enantiomers by salt formation with various chiral resolving acids, the resolution was achieved by derivatization with either (*R*)-(+)-α-methylbenzyl isocyanate (**34**) as shown in Scheme IV or the (*S*)-(−)-isocyanate. The utilization of such reagents for the resolution of racemic alcohols and amines has been

(9) Yevich, J. P.; Lobeck, W. G. Antipsychotic 1-Fluorophenylbutyl-4-(2-Pyrimidinyl)Piperazine Derivatives. U.S. Patent 4,605,655, August 12, 1986.

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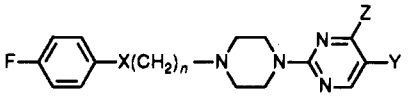
Table I. 1-(Pyrimidin-2-yl)piperazine Derivatives



compd	X	n	Y	Z	yield, %[a]	mp, °C	prep method	formula
9	CO	3	H	H	50	111–113	A	$C_{18}H_{21}FN_4O$
10	CO	3	F	H	50	234–236	A	$C_{18}H_{20}F_2N_4O$·HCl
11	CO	3	Cl	H	45	115–117	A	$C_{18}H_{20}ClFN_4O$
12	CO	3	Br	H	33	129–131	A	$C_{18}H_{20}BrFN_4O$
13	CO	3	F	SCH_3	58	195–197	A	$C_{19}H_{22}F_2N_4OS$·HCl
14	CO	2	F	H	70	126–128	A	$C_{17}H_{18}F_2N_4O$
15	CHOH	3	H	H	56	204–206	B	$C_{18}H_{23}FN_4O$·HCl
16	CHOH	3	F	H	81	236–238	B	$C_{18}H_{22}F_2N_4O$·HCl
16a	CHOH	3	F	H	69	228–230	J	$C_{18}H_{22}F_2N_4O$·HCl
16b	CHOH	3	F	H	88	228–230	J	$C_{18}H_{22}F_2N_4O$·HCl
17a	CHOCONHCH(CH_3)Ph	3	F	H	72	115–116	I	$C_{27}H_{31}F_2N_5O_2$
17b	CHOCONHCH(CH_3)Ph	3	F	H	88	113–114	I	$C_{27}H_{31}F_2N_5O_2$
18	CHOH	3	Cl	H	50	230–232	B	$C_{18}H_{22}ClFN_4O$·HCl·H_2O
19	CHOH	3	Br	H	56	204–206	B	$C_{18}H_{22}BrFN_4O$·HCl
20	CHOH	3	F	SCH_3	72	251–253	B	$C_{19}H_{24}F_2N_4OS$·HCl
21	CHOH	3	F	OH	50	205–207	H	$C_{18}H_{22}F_2N_4O_2$
22	CHOH	3	F	OCH_3	36	235–237	H	$C_{19}H_{24}F_2N_4O_2$·HCl
23	CHOH	2	F	H	59	103–105	B	$C_{17}H_{20}F_2N_4O$
24	CH_3COH	3	F	H	59	192–194	C	$C_{19}H_{24}F_2N_4O$·HCl
25	C_2H_5COH	3	H	H	30	203–205	C	$C_{20}H_{27}FN_4O$·HCl
26	C_2H_5COH	3	F	H	24	208–210	C	$C_{20}H_{28}F_2N_4O$·HCl
27	4-F-C_8H_4COH	3	H	H	42	219–221	C	$C_{24}H_{26}F_2N_4O$·HCl
28	4-F-C_6H_4COH	3	F	H	17	153–155	C	$C_{24}H_{25}F_3N_4O$·HCl
29	4-F-C_6H_4CH=CH	2	H	H	52	251–253	D	$C_{24}H_{24}F_2N_4$·HCl
30	4-F-C_6H_4CH=CH	2	F	H	38	213–215	D	$C_{24}H_{23}F_3N_4$·HCl
31	CHCN	3	F	H	23	234–236	E	$C_{19}H_{21}F_2N_5$·HCl
32	C=NOH	3	F	H	67	147–149	F	$C_{18}H_{21}F_2N_5O$
33	$CHNH_2$	3	F	H	74	298–300	G	$C_{18}H_{23}F_2N_5$·2HCl

[a] All compounds were recrystallized from ethanol.

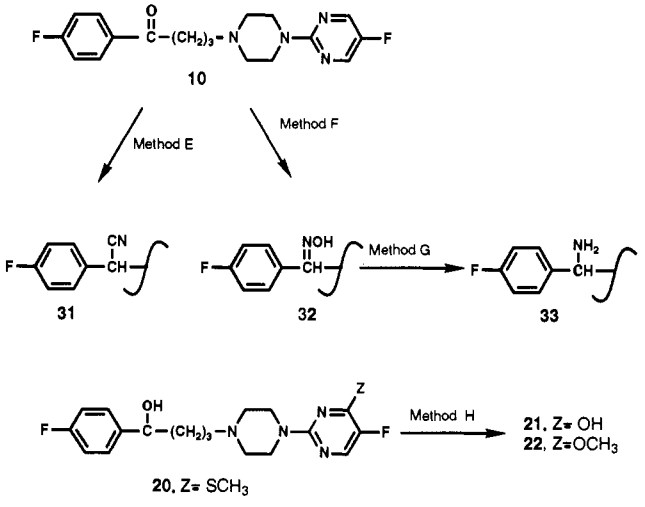
Table II. Biological Activity in Primary CNS Screens

compd	inhibn of [^{3}H]spiperone binding: IC_{50}, nM[a,b]	inhibn of [^{3}H]WB-4101 binding: IC_{50}, nM[b]	inhibn of (+)[^{3}H]-3-PPP binding: IC_{50}, nM[c]	inhibn of CAR: ED_{50}, mg/kg, po[b]	inhibn of apomorphine-induced stereotypy: ED_{50}, mg/kg, po[b]	induction of catalepsy: ED_{50}, mg/kg, po[b]
9	679	6	430	25.3 (19.6–32.7)[d]	21.6 (15.6–30.0)	>100
10	494	29	130	36.3 (27.0–48.9)	58.9 (47.7–72.8)	144
11	817	51	57	>100	NT[e]	NT
12	2190	72	85	>100	NT	NT
13	396	95	120	>100	>100	NT
14	>1000	523	69	>100	>100	NT
15	1380	162	130	25.0 (19.4–32.2)	32.3 (27.0–32.7)	>100
16	6430	520	112	26.4 (19.9–35.0)	33.0 (22.7–47.8)	>100
18	5660	1420	22	87.1 (51.0–148.7)	>100	148.0 (94.7–231.1)
19	>1000	1500	26	50.0 (40.9–61.1)	>65	108.1 (76.1–153.5)
20	>1000	305	26	>100	>100	NT
21	>1000	>1000	>1000	>100	>100	NT
22	3940	180	24	40.8 (31.0–53.7)	54.0 (38.0–76.8)	79.2 (60.0–104.8)
23	>1000	814	160	>100	>100	NT
24	2120	NT	110	>25	>50	>100
25	415	230	NT	>100	>100	NT
26	3750	>1000	370	48.5 (32.0–73.5)	>50	>100
27	200	400	>1000	52.9 (40.8–68.6)	>50	NT
28	940	1140	>1000	>100	NT	NT
29	1700	375	>1000	>100	NT	NT
30	8800	756	>1000	>100	NT	NT
31	1880	266	190	19.8 (12.9–30.6)	>100	>100
32	1860	22	81	>100	NT	NT
33	>1000	446	~1000	>100	NT	NT
haloperidol	7	130	1.4	2.8 (2.5–3.5)	0.5 (0.4–0.7)	0.58 (0.34–1.02)
thioridazine	60	65	750[f]	126 (102.2–156)	280.0 (212–369)	45.2 (27.5–74.3)
clozapine	440	62	>1000[f]	24.1 (20.5–28.2)	49.2 (33.4–72.3)	>200

[a] In Tables II and V the reported receptor binding data are based on single experiments in which the displacement of tritiated ligand by test drug was measured at five different concentrations of test drug. IC_{50} values are reported as >1000 nM for determination in which data analysis failed to generate a discrete value. [b] Test performed as previously described.[41] [c] Test performed as previously described.[42] [d] In this and subsequent tables, 95% confidence limits are shown in parentheses. [e] Not tested. [f] K_i values vs. (+)NAN.[22b]

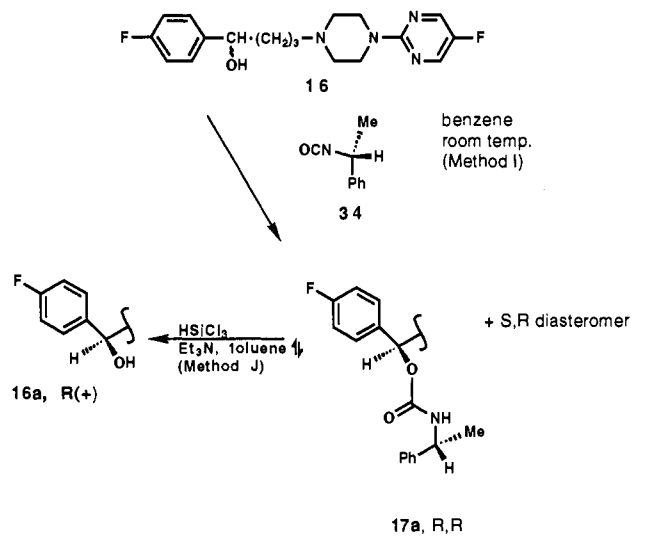
previously described.[11] Reaction of **16** and **34** resulted in a mixture of diastereomeric carbamates from which the *R,R*-diastereomer **17a** crystallized in >98% purity. Recrystallization gave pure **17a**, which underwent cleavage of the carbamate moiety upon treatment with $HSiCl_3$[12] to provide the optically-pure *R*-(+)-enantiomer **16a**. Sim-

Scheme III



Method E: $TOSCH_2NC$, t-BuOK, 1,2-dimethoxyethane
Method F: NH_2OH·HCl, NaOH, EtOH, reflux
Method G: Raney Ni, H_2, EtOH
Method H: KOH, H_2O, MeOH, reflux (**21**), KOH, MeOH, reflux (**22**)

Scheme IV



ilarly, the use of (*S*)-(−)-isocyanate resulted in the isolation of pure (*S*,*S*)-carbamate which upon cleavage gave the (*S*)-(−)-carbinol **16b**. Ideally, both enantiomers of **16** would have been obtained via separation and cleavage of the carbamates derived from either isocyanate. However, purification of the *S* (**16**), *R* (**34**) and *R* (**16**), *S* (**34**) diastereomers proved to be tedious and inefficient and resulted in very poor recovery of the desired **16** enantiomers. Thus, for the practical expedient of obtaining multi-gram quantities of **16a** and **16b** for biological evaluation, separate reaction sequences employing (*R*)- and (*S*)-isocyanate, respectively, were conducted.

The *R* chirality of the (+)-enantiomer **16a** was established by single-crystal X-ray structure of **17a** as shown in Figure 1.

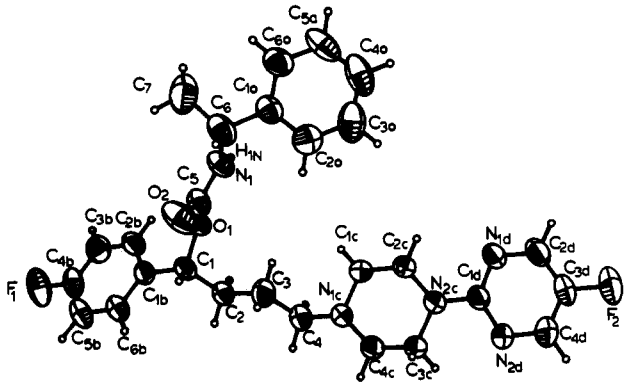


Figure 1. Drawing of a single molecule of **17a** showing 50% probability ellipsoids.

Biology

All compounds were tested for their in vitro binding to rat striatal D_2 receptors labeled with [^{3}H]spiperone and cortical α_1-adrenergic receptors labeled with [^{3}H]WB-4101. Snyder has suggested that the affinity of various typical and atypical antipsychotic agents for σ binding sites may be relevant to their antipsychotic activity.[13] Thus, we also evaluated compounds for their displacement of [^{3}H]3-PPP from rat cortical σ sites. Tranquilizer activity was assessed by measuring the ability of compounds to attenuate the response of rats trained to avoid an electric shock (inhibition of conditioned avoidance response, CAR). Other primary in vivo screening included inhibition of apomorphine (APO)-induced stereotypy and induction of catalepsy in rats, the latter a test predictive of potential EPS. Compounds were administered orally in all in vivo tests. By our own criteria, test values >1000 nM in the binding assays or >100 mg/kg in the behavioral paradigms are regarded as inactive.

Results and Discussion

Table III lists the biological test results in primary screens for both the title compounds and the following clinically-effective reference agents: haloperidol, a potent typical antipsychotic agent of the butyrophenone type having a high incidence of neuroleptic side effects; thioridazine, a phenothiazine having a somewhat lower incidence of EPS than other typical agents; clozapine, an atypical antipsychotic having little, if any EPS liability. Those test compounds that displayed activity in the CAR and stereotypy tests were considerably less potent than haloperidol but were more potent than thioridazine and comparable in potency to clozapine.

The butyrophenones **9** and **10** bearing a 1-PP and 5-F-1-PP moiety, respectively, exhibited good activity in inhibiting both the CAR and APO-induced stereotypy. Activity was lost by introduction of a 4-methylthio substituent on the pyrimidine ring (**13**), by replacement of F by either Cl (**11**) or Br (**12**), or by shortening the side chain to three carbons (**14**). Several of the butyrophenones (**9**–**11**, **13**) had modest activity at displacement of [^{3}H]-spiperone from dopaminergic binding sites but were

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(12) Pirkle, W. H.; Hauske, J. R. Trichlorosilane-Induced Cleavage. A Mild Method for Retrieving Carbinols from Carbamates. *J. Org. Chem.* **1977**, *42*, 2781–2782.

(13) (a) Snyder, S. H. Psychotogenic Drugs as Models for Schizophrenia. *Neuropsychopharmacology* **1988**, *1*, 197–199. (b) Snyder, S. H.; Largent, B. L. Receptor Mechanisms in Antipsychotic Drug Action. Focus on Sigma Receptors. *J. Neuropsyciatry* **1989**, *1*, 7–15.

Table III. Side-Effect Profile of 16 and Reference Antipsychotic Agents

test[a]	16	haloperidol	thioridazine	clozapine
reversal of trifluoperazine-induced catalepsy (rat)[b]	16.9 (11.9–25.6)	I	I	I
inhibition of spontaneous motor activity (rat)[c,d]	87.3	0.73	33.0	17.5
motor incoordination, rotarod method (rat)[d]	43.5 (37.4–50.6)	5.2	20.0	7.9
ethanol potentiation (rat)[d]	20.1 (13.8–29.9)	0.28 (0.17–0.45)	56.0 (37.2–84.3)	3.23 (2.15–4.85)
inhibition of norepinephrine lethality (mouse)[d]	>100	26.0 (17.0–39.8)	2.2 (1.5–3.1)	3.5 (1.8–6.9)
inhibition of physostigmine lethality (mouse)[d]	>100	>80	45.0 (28–71)	5.4 (4.0–7.3)

[a] Activities reported as ED_{50} values, mg/kg, po (95% confidence limits); I = inactive. [b] Performed by previously described method.[19] [c] 95% confidence limits not determined. [d] Performed by methods previously described or referenced.[6]

somewhat weaker D_2 ligands than azaperone, for which we determined an IC_{50} value of 360 nM vs [^{3}H]spiperone and which differs structurally only in having a 2-pyridinyl rather than a 2-pyrimidinyl ring. All of the ketones except 14 are fairly potent α_1-adrenergic antagonists as evidenced by their having IC_{50} values <100 nM in α_1 receptor binding and the fact that several (9, 10) were effective in attenuating norepinephrine-induced lethality in the rat (data not shown). The ketones displayed good to moderate binding to σ sites with the potency of the 5-halogenated pyrimidine derivatives ranging from 3 to 8 times that of the des-halo compound 9.

While the *sec*-butanols 15–20 showed much weaker affinity for both D_2 and α_1 receptors than did the corresponding ketones, they remained very good ligands for the σ site. The loss of D_2 receptor recognition did not impact upon the in vivo activity of the butanols as they were, for the most part, equivalent or superior to their ketone congeners in blocking conditioned avoidance responding. What is at best an ambiguous relationship between in vivo activity and σ binding is illustrated by the 4-substituted-5-fluoropyrimidine analogues 20–22. Compound 22, which bears a 4-methoxy substituent, was among the more potent σ ligands in the series (IC_{50} = 24 nM) and was active in both the CAR and stereotypy tests. In contrast, neither the 4-methylthio derivative 20, which has σ site affinity equivilant to that of 22, nor the 4-hydroxy compound 21, which lacks σ binding, showed in vivo activity. Perhaps the inactivity of compound 20 in the behavioral tests is due to its in vivo oxidation to a polar sulfoxide metabolite that does not permeate the blood–brain barrier. The absence of not only in vivo activity but also receptor binding affinity of 21 may be attributable to the fact that its 4-hydroxypyrimidine ring prefers the lactam tautomeric form as evidenced by both its infrared and NMR spectra (see Experimental Section). Disruption of the aromaticity of the pyrimidine ring could render it a poor ligand for the aromatic ring binding sites of neuroreceptors.

Since hydroxylation at the pyrimidine 5-position is among the major metabolic pathways of buspirone,[8] it was of interest to determine whether blocking this metabolically-labile site would effect the in vivo activity of the title compounds. The 5-fluoro compound 16 was found to have at least twice the duration of action of its desfluoro analogue 15 in inhibition of both CAR (7 vs 3 h) and APO-induced stereotypy (4 vs 2 h). These results suggest that suitable substituents at the pyrimidine 5-position can retard metabolic deactivation. Compound 16 has also been shown to be active in a lever-release version of the CAR test.[14]

In general, the other compounds in the series (24–33) failed to show interesting activity profiles although the primary amine 31 had the lowest ED_{50} value of any compound in the CAR. The CAR activity of the *tert*-butyl alcohols 26 and 27 was accompanied by signs of toxicity.

On the basis of the results of the primary screening, compound 16 was selected for further study. None of the compounds evaluated in the catalepsy test approached the potency of the typical antipsychotics haloperidol and thioridazine and in fact, like clozapine, most were inactive. Only one compound (22) caused catalepsy at doses <100 mg/kg and several others (10, 18, 19) had ED_{50} values >100 mg/kg. As will be subsequently discussed, several compounds, most notably 16, reversed the cataleptic effect caused by prior administration of a neuroleptic agent.

Compound 16 (BMS 181100, Formerly BMY 14802). To further probe the potential antipsychotic activity and side effect profile of 16, the compound was evaluated vs reference agents in a number of additional tests. Table III summarizes a comparison of 16 with haloperidol, thioridazine, and clozapine in several behavioral tests indicative of side effect liability. While both 16 and clozapine failed to cause catalepsy, only 16 was capable of reversing the cataleptic effect of a neuroleptic agent (trifluoperazine); this is a property shared by buspirone[15] and gepirone,[5] neither of which produce EPS in man. Compound 16 appeared less sedating than the reference drugs based on its lower potency in decreasing spontaneous motor activity and potentiating ethanol hypnosis and was also relatively weaker in causing muscle incoordination. Its inactivity in the inhibition of norepeniphrine and physostigmine lethality indicates that it should not induce the peripheral side effects caused by α-adrenergic and cholinergic antagonists.

Chronic administration of neuroleptics to laboratory animals has been shown to promote D_2 receptor proliferation,[16] an effect that may correlate with the ability of such drugs to cause tardive dyskinesia in man.[3] As shown in Table IV, 29-day administration of haloperidol and two dose levels of 16 to rats resulted in a decrease in D_2 receptor affinity but only the haloperidol treatment increased receptor number (B_{max}) relative to control. The failure of 16 to produce D_2 supersensitivity suggests that it should not be likely to cause tardive dyskinesia.

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Table IV. Effect of Chronic Administration of Compound **16** and Haloperidol on D_2 Receptor Binding in Rat Striata[a]

treatment (mg/kg, po, qd, 29 days)	B_{max}, fmol/mg of protein[b]	K_D, pM[b]
vehicle	228 ± 5 (5)	153 ± 10 (5)
16 (15)	233 ± 7 (4)	121 ± 7 (4)
16 (30)	212 ± 7 (5)	101 ± 5 (5)[c]
haloperidol (3)	290 ± 9 (5)[c]	125 ± 5 (5)[c]

[a] Performed by previously described methods.[6] [b] Values are mean ± SEM for the number of preparations in parentheses. [c] $p < 0.05$ vs vehicle (Student's t-test).

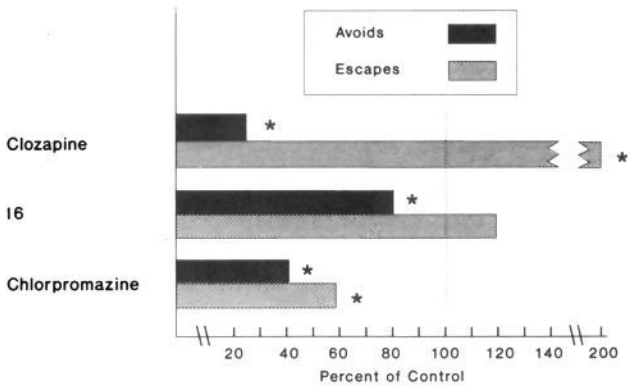

Figure 2. Comparative effects of **16**, clozapine, and chlorpromazine on discriminated avoidance and escape behavior of rats. All drugs administered at 100 mg/kg, po to groups of eight male Sprague-Dawley rats per drug dose. Statistically significant difference from control denoted an asterisk. Testing was conducted as previously described.[6]

Figure 2 depicts the results of an evaluation of **16** vs clozapine and chlorpromazine at common doses of 100 mg/kg, po, in a modification of the Sidman avoidance paradigm. Like clozapine, **16** reduced the avoid response to aversive stimulus (electric footshock) while tending to enhance escapes, although the latter effect of **16** did not achieve statistical significance. Typical antipsychotics, such as chlorpromazine, are found to attenuate both the avoid and escape responses. Perhaps the most compelling in vivo evidence of the antipsychotic activity (and possible limbic selectivity) of **16** was afforded by a study of the drug by Schlemmer in a model of amphetamine-induced psychosis in monkeys.[17] The compound was found to significantly inhibit those components of the amphetamine syndrome that may approximate psychosis in man and that may be mediated by the limbic system, while having minimal effect upon stereotypy which is believed to be a striatally-mediated behavior. Although this finding may appear to be inconsistent with the blockade of APO stereotypy in the rat by **16**, the discrepancy may be attributable to differences in species[17b] and/or inducing agents. The inhibition of APO stereotypy by **16** may seem a bit puzzling since such activity is generally associated with DA antagonists and **16** does not bind to DA receptors. However, Garattini found certain serotonergic agents lacking dopaminergic activity to be effective in blocking drug-induced stereotypies,[18] and we have reported similar findings.[19] Thus, the inhibition of stereotypy in the rat by **16** may be due to the compound's interaction with the 5-HT_{1A} receptor subtype as discussed later.

Further empirical support for the limbic selectivity of **16** is the work of Wachtel and White who studied the effects of the compound upon the electrophysiological activity of nigrostriatal (A9) and mesolimbic (A10) DA neurons.[20] Like clozapine, repeated sc administration of **16** to rats reduced the number of spontaneously active A10 cells in a dose-responsive manner without altering the activity of A9 cells. Chronic dosing with typical antipsychotic drugs results in the inhibition of both A9 and A10 neurons. Again, because of its lack of direct interaction with DA receptors, the mechanism of action of **16** upon A10 cells is uncertain. Other apparently indirect effects of **16** on rat brain dopaminergic function have been described.[21]

Table V lists the results of the evaluation of racemic **16** in a variety of neuroreceptor binding assays as well as a comparison of the racemate with the (+)- and (−)-enantiomers in several of the binding tests. Of the binding tests in which it has been screened, **16** showed submicromolar activity only in the 5-HT_{1A}, α_1, and σ tests with its highest affinity, as previously reported,[22] being for σ sites.

Measurement by published methodology[23] of the compound's inhibition of forskolin-stimulated adenylate cyclase activity characterized it as a partial agonist at the 5-HT_{1A} receptor subtype with an intrinsic activity of 0.28 (relative to 5-HT = 1.0). This finding was substantiated by electrophysiological studies that showed **16** to cause a dose-related inhibition of the firing of dorsal raphe 5-HT neurons after iv administration.[24] The ED_{50} of **16** for dorsal raphe inhibition is 0.19 mg/kg, iv, and it is thus about 10-fold less potent than buspirone and gepirone, both of which are 5-HT_{1A} partial agonists. Serotonergic activity may be an important pharmacological component of certain atypical antipsychotics such as clozapine, ritanserin, and risperidone, but these drugs act as antagonists at the 5-HT_2 receptor subtype.[25] Although the

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Table V. Receptor Binding Profile of 16 and Comparison with Enantiomers 16a and 16b in Several Binding and Behavioral Tests

test	16, racemate	16a, R-(+)	16b, S-(-)
α_2-adrenergic binding (clonidine, rat cortex)[a,b]	>1000		
β-adrenergic binding (dihydroalprenolol, rat cortex)[c]	>1000		
serotonin$_2$ (5-HT$_2$) binding (spiperone, rat cortex)[b]	1700		
GABA binding (muscimol, rat cerebellum)[b]	>1000		
glutamate binding (kainic acid, rat cortex)[b]	>1000		
glycine binding (strychnine, rat medulla pons)[b]	>1000		
benzodiazepine binding (diazepam, rat cortex)[d]	>1000		
serotonin uptake site binding (imipramine, rat hippocampus)[b]	>1000		
dopamine D$_1$ binding (SCH 23390, rat striatum)[e]	>1000		
dopamine D$_2$ binding (spiperone, rat striatum)	6430	>1000	>1000
α_1-adrenergic binding (WB 4101, rat cortex)	460	610	570
serotonin$_{1A}$ (5-HT$_{1A}$) binding (8-OH-DPAT, rat hippocampus)[f]	320	210	340
haloperidol-sensitive sigma binding (3-PPP, whole guinea pig brain)	112	28	310
haloperidol-sensitive σ-binding ((+)-NAN, whole guinea pig brain)[g]	83	43	420
haloperidol-sensitive σ binding (DTG, whole guinea pig brain)[h]		32	140
catalepsy reversal[i]	16.9 (11.9–25.6)	11.4 (6.9–18.8)	38.1 (26.9–34.0)
inhibition of apomorphine-induced stereotypy	33.0 (22.7–47.8)	44.0 (38.4–50.4)	25.4 (17.3–27.4)

[a] Binding test ([^{3}H] ligands, tissue); data reported as IC$_{50}$ values, nM. [b] Performed by methods described in previously-cited references.[6] [c–h] Performed by methods described in indicated references (footnote, reference): c, 43; d, 44; e, 45; f, 46; g, 22a; h 47. [i] Behavioral test data reported as ED$_{50}$ values in mg/kg, po (±95% confidence limits).

observation of altered 5-HT$_{1A}$ receptor density in schizophrenic brain may have therapeutic implications,[26] it is likely that the 5-HT$_{1A}$ properties of 16 are more pertinent to its anticipated lack of serious side effects than to its potential antipsychotic utility. A number of 5-HT$_{1A}$ receptor-mediated pharmacological effects of 16 have been described elsewhere.[27]

No striking differences were observed among the affinities of 16 and its enantiomers for 5-HT$_{1A}$, α_1, or D$_2$ receptors nor between racemate and enantiomers in in vivo tests. Even though the affinity of **16a** was determined to be several fold greater than that of 16 or **16b** in the D$_2$ binding assay, it is unlikely that this is of consequence since its IC$_{50}$ is still well in excess of 2 μM. Relative to its antipode, the *R*(+) isomer is somewat more potent in the catalepsy reversal test and less potent in the inhibition of APO stereotypy. The ED$_{50}$ values for the enantiomers lie slightly outside each other's 95% confidence limits. The greatest difference between the enantiomers was seen in σ binding; the eudismic ratio for σ binding of the stereoisomers ranged fron 4.4 to 11.1 depending upon the tritiated ligand being displaced. Although even the larger value is not high for a eudismic ratio,[28] it is of sufficient magnitude to conclude that the σ site shows a predilection for the *R*(+) enantiomer.

Whether the σ binding of 16 is relevant to its possible antipsychotic activity is, at this time, a matter of intriguing speculation. The physiological role of the σ binding site in mammalian brain and whether or not it can be elevated to the status of a true biological receptor remain to be elucidated. The characterization, current understanding, and ambiguities of σ "receptors" have recently been discussed in considerable detail in an excellent review.[29] Despite the uncertainty regarding the functional significance of σ binding sites, the observation that various typical and atypical antipsychotics have a high propensity for σ binding has elicited the suggestion that the design of agents as σ antagonists may be a novel approach to the drug therapy of schizophrenia.[13] The rationale for σ ligands as antipsychotics may be strengthened by the finding of significant reductions in the density of cerebral cortical σ binding sites in the postmortem brains of schizophrenic patients.[30]

Although compound 16 has been referred to as a σ antagonist,[31] this remains a moot point in the absence of an unequivocal functional assay for agonist/antagonist activity. The compound has undergone extensive investigation in a number of disparate biochemical and behavioral tests in which other known σ ligands show activity.[31a,32-36] All that can be concluded from such studies, for now, is that 16 also shows activity thus corroborating its observed interaction at σ binding sites. In a summary of these findings,[37] it was observed that 16 mimics the effects of other σ agents in some tests, whereas in other tests it blocks, reverses, or is opposite to the effects of reference σ agents; in certain cases, 16 was similar to or different from the very same reference agent depending on the biological endpoint being measured. Perhaps this disparity of results can be ascribed to a heterogeneity of

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σ binding sites. There is recent evidence that different tritiated σ ligands (e.g., (+)-[^{3}H]-3-PPP and [^{3}H]DTG) label pharmacologically distinct sites[38] which differ in their sensitivity to chronic drug exposure[39] and that the same ligand ([^{3}H]DTG) labels several dissimilar high-affinity sites.[40]

In summary, compound **16** has been found to possess in vivo behavioral activity indicative of possible antipsychotic utility with minimal side effect liability. It is encouraging that several pieces of empirical evidence point toward the compound having limbic vs striatal selectivity. On the basis of preclinical findings, compound **16** has been entered into clinical trials to evaluate its efficacy and safety in the treatment of schizophrenia. Since it does not bind to DA receptors, the demonstration of its antipsychotic activity in man could render **16** a breakthrough drug that may challenge the DA hypothesis of schizophrenia. Positive clinical findings would also do much to establish the viability of σ-selective ligands as useful antipsychotic drugs.

Experimental Section

Chemistry. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The spectra of all reported compounds were consistent with the assigned structures. The IR spectra were recorded on either a Nicolet MX-1FTIR or a Perkin-Elmer 1800 FTIR spectrometer using KBr pellets. All ^{1}H NMR spectra were recorded on a Bruker AM300 spectrometer in either deuteriochloroform with 2% (v/v) tetramethylsilane as the internal reference or perdeuteriodimethyl sulfoxide. The X-ray determination of compounds **17a** was performed by the Crystalytics Company, Lincoln, NE. Mass spectra were obtained on a Finnegan 4023 GC/MS instrument. Elemental C, H, N analyses were run on a Perkin-Elmer 240B analyzer, and Karl Fischer water determinations were made with an Aquatest II apparatus. Analytically pure compounds showed a single spot on Analatech silica gel plates of 0.25-mm thickness and were visualized with UV or I_2. Modifications of the described procedures were used to prepare the bulk (kilogram) quantities of **16**. All other target compounds were prepared on scales of no greater than 0.02 mol. In most cases, no efforts were made to optimize yields.

Ethyl 4-[5-Fluoro-4-(methylthio)-2-pyrimidinyl]-1-piperazinecarboxylate (6a). A mixture of 2-chloro-5-fluoro-4-(methylthio)pyrimidine (28.3 g, 0.159 mol), *N*-carbethoxypiperazine (25.26 g, 0.159 mol), anhydrous K_2CO_3 (66.0 g), and a catalytic amount of KI in acetonitrile (400 mL) was stirred and heated under reflux for 18 h. The hot reaction mixture was filtered and concentrated in vacuo, and the residue recrystallized from ethanol to give 29.84 g (62%) of product.

5-Fluoro-4-(methylthio)-2-(1-piperazinyl)pyrimidine (6b). A solution of **6a** (6.22 g, 0.02 mol) in 6 N HCl (50 mL) was stirred and heated under reflux for 18 h. The cooled solution was made alkaline by addition of 50% NaOH and extracted with ether. The dried ($MgSO_4$) extract was evaporated to provide 4.1 g (86%) of product as a viscous oil that was used without further purification.

5-Fluoro-2-(1-piperazinyl)pyrimidine (8a). Ethyl 4-(5-Fluoro-2-pyrimidinyl)-1-piperazinecarboxylate (7). A mixture of ethyl 4-[5-fluoro-4-(methylthio)-2-pyrimidinyl]-1-piperazinecarboxylate (**6a**, 29.8 g, 0.1 mol) and Raney nickel catalyst (15 tsp) in ethanol (550 mL) was stirred and heated under reflux for 48 h. The reaction mixture was filtered and concentrated in vacuo, and the residue recrystallized twice from ethanol to provide 11.2 g (45%) of product, mp 104–107 °C. A solution of this intermediate (**7**, 11.2 g, 0.04 mol) in 6 N HCl (100 mL) was stirred and heated under reflux overnight. The cooled reaction mixture was made alkaline by addition of 50% NaOH and extracted with ether, and the extract was dried (MgSO4) and concentrated in vacuo to provide 7.23 g (100%) of product as a viscous oil which was treated with ethanolic HCl in ethanol to yield the hydrochloride salt: mp 250–252 °C. Anal. ($C_8H_{11}FN_4$·HCl) C, H, N.

5-Chloro-2-(1-piperazinyl)pyrimidine (8b). Chlorine gas was bubbled into a solution of ethyl 4-(2-pyrimidinyl)-1-piperazinecarboxylate (31.4 g, 0.133 mol) in 1 N HCl (150 mL) for 15 min. The reaction mixture was cooled in ice and the solid product collected by filtration and dried to afford 19.3 g (54%) of the 5-chloro-*N*-carbethoxy intermediate compound, mp 80–83 °C. This intermediate was hydrolyzed under acidic conditions as described for the 5-fluoro analog. From 19.3 g (0.07 mol) of the *N*-carbethoxy intermediate compound was obtained 10.7 g (77%) of product as a viscous oil.

5-Bromo-2-(1-piperazinyl)pyrimidine (8c). To an ice-cooled solution of 1-(2-pyrimidinyl)piperazine (16.4 g, 0.1 mol) in 1 N HCl (100 mL) was added dropwise bromine (15.98 g, 0.1 mol). After stirring at 0 °C for 0.5 h, the mixture was heated to 100 °C until dissipation of the red color had occurred. The mixture was filtered, cooled, made alkaline with 50% NaOH, and extracted with ether. The dried extract ($MgSO_4$) was concentrated in vacuo to provide 14.5 g (62%) of product: mp 73–75 °C.

γ-Chloro-*p*-fluorobutyrophenone Ethylene Ketal. A solution of γ-chloro-*p*-fluorobutyrophenone (50 g, 0.24 mol), ethylene glycol (50 mL), and *p*-toluenesulfonic acid (0.1 g) in 300 mL of benzene was refluxed for 18 h with water of reaction being removed by means of a Dean–Stark water trap. Upon cooling to room temperature, the reaction mixture was washed with dilute $NaHCO_3$, dried ($MgSO_4$), and filtered and the benzene was removed by concentration in vacuo. The residual oil was distilled to give 57.7 g (93%) of product: bp 107–112 (0.01 Torr).

Method A. 1-(4-Fluorophenyl)-4-[4-(5-fluoro-2-pyrimidinyl)-1-piperazinyl]butanone Hydrochloride (10). A mixture of the piperazine **8a** (7.3 g, 0.04 mol), γ-chloro-*p*-fluorobutyrophenone ethylene ketal (14.5 g, 0.06 mol), anhydrous K_2CO_3 (24.8 g), and a catalytic amount of KI in acetonitrile (100 mL) was stirred and heated under reflux for 36 h. The hot mixture was filtered and concentrated in vacuo, and the residue was treated with 20 mL of 3 N HCl and 100 mL of ethanol. After cooling in ice, the product was collected by filtration and dried to give 7.6 g (50%) of product as a white solid: mp 234–236 °C; NMR (DMSO-d_6) δ 210 (2H, m), 3.20 (6H, m), 3.54 (4H, m), 4.58 (2H, m), 7.34 (2H, m), 8.08 (2H, m), 8.55 (2H, s), 11.60 (1H, bs); IR (KBr) 960, 1235, 1245, 1365, 1510, 1560, 1600, 1680, 2550, and 2910 cm^{-1}. Anal. ($C_{18}H_{20}F_2N_4O$·HCl) C, H, N.

Method B. (±)-α-(4-Fluorophenyl)-4-(5-fluoro-2-pyrimidinyl)-1-piperazinebutanol Hydrochloride (16). A mixture of **10** (7.6 g, 0.02 mol) and sodium borohydride (2.3 g, 0.06 mol) in ethanol (650 mL) was stirred overnight. The mixture was

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treated with ethanolic HCl, stirred at room temperature for 1.5 h, and then heated to reflux. Solvent was removed in vacuo, and to the residue were added 1 N NaOH and methylene chloride. The organic layer was separated, dried ($MgSO_4$), and concentrated in vacuo. This residue was dissolved in ethanol, treated with ethanolic HCl, and cooled. The hydrochloride salt was collected by filtration and dried to afford 6.2 g (81%) of product: mp 236–238 °C; NMR (DMSO-d_6) δ 1.71 (2H, m), 3.10 (4H, m), 3.47 (4H, m), 4.59 (3H, m), 5.30 (1H, bs), 7.11 (2H, m), 7.40 (2H, m), 8.53 (2H, s), 11.50 (1H, bs); IR (KBr), 955, 1220, 1235, 1370, 1440, 1455, 1480, 1510, 1560, 1605, 2600, and 2920 cm^{-1}. Anal. ($C_{18}H_{22}F_2N_4O$·HCl) C, H, N.

Method C. α,α-Bis(4-fluorophenyl)-4-(5-fluoro-2-pyrimidinyl)-1-piperazinebutanol Hydrochloride (28). To a Grignard reagent prepared in the usual manner from 4-bromofluorobenzene (6.3 g, 0.03 mol) and magnesium turnings (0.73 g, 0.03 mol) in dried tetrahydrofuran (40 mL) was added a solution of **10** (7.87 g, 0.023 mol) in tetrahydrofuran (40 mL). The mixture was stirred and heated under reflux for 18 h, cooled, and treated with NaCl solution. The decanted tetrahydrofuran solution was concentrated in vacuo to remove solvent and the oily residue was flash chromatographed on silica gel using hexane–ethyl acetate, 3:7, as eluent. Fractions containing a single component (R_f 0.45 in hexane–ethyl acetate, 3:7) were combined and concentrated in vacuo to provide 5.2 g of a viscous oil. An ethanol solution of the latter was treated with ethanolic HCl following which the ethanol was removed in vacuo and the residue was azeotroped in 100 mL of benzene. Concentration of this resulting solution at atmospheric pressure to half volume resulted in separation of a solid. The solid product was collected by filtration and dried to afford 1.9 g (17%) of the tertiary carbinol product: mp 153–155 °C; NMR (DMSO-d_6) δ 1.66 (2H, m), 2.34 (2H, m), 3.08 (4H, m), 3.42 (4H, m), 4.50 (2H, m), 5.82 (1H, bs), 7.07 (4H, m), 7.46 (4H, m), 8.50 (2H, s), 11.30 (1H, bs); IR (KBr) 835, 950, 1220, 1235, 1365, 1450, 1490, 1510, 1560, 1605, 2590, 2930 cm^{-1}. Anal. ($C_{24}H_{25}F_3N_4O$·HCl) C, H, N.

Method D. 1-[4,4-Bis(4-fluorophenyl)-3-butenyl]-4-(5-fluoro-2-pyrimidinyl)piperazine Hydrochloride (30). A solution of the carbinol **28** (2.0 g, 0.004 mol) in trifluoroacetic acid (20 mL) was stirred for 18 h. The TFA was removed in vacuo, and the residue was treated with dilute NH_4OH and extracted with ether. The dried ($MgSO_4$) extract was freed of solvent and treated with ethanolic HCl. THe resulting salt was collected by filtration and dried to yield 0.72 g (38%) of **30**: mp 213–215 °C. Anal. ($C_{24}H_{23}F_3N_4$·HCl) C, H, N.

Method E. α-(4-Fluorophenyl)-4-(5-fluoro-2-pyrimidinyl)-1-piperazinepentanenitrile Hydrochloride (31). To a stirred suspension of *t*-BuOK (1.76 g, 0.014 mol) in 15 mL of 1,2-dimethoxyethane at −4 °C was added dropwise under N_2 a solution of ketone **10** (2.07 g, 0.006 mol) and tosylmethyl isocyanide (1.56 g, 0.008 mol) in dimethoxyethane (25 mL) and ethanol (5 mL). After stirring for 30 min at ambient temperature, the mixture was heated at 45 °C for 18 h and flash chromatographed on silica gel using ethyl acetate as eluant. Appropriate fractions were combined and concentrated in vacuo to a viscous oil which was dissolved in ethanol and treated with ethanolic HCl. The precipitated salt was collected by filtration and recrystallized from ethanol to afford 0.54 g (23%) of product as a white solid: mp 234–236 °C. Anal. ($C_{19}H_{21}F_2N_5$·HCl) C, H, N.

Method F. 1-(4-Fluorophenyl)-4-[4-(5-fluoro-2-pyrimidinyl)-1-piperazinyl]butanone Oxime (32). A mixture of ketone **10** (6.97 g, 0.02 mol), hydroxylamine hydrochloride (1.39 g, 0.02 mol), and 50% NaOH (3.5 mL) in ethanol (50 mL) and water (20 mL) was stirred and heated under reflux for 1 h. The cooled mixture was partially concentrated and extracted with ether. The dried ($MgSO_4$) extracts were concentrated in vacuo, and the residual solid was recrystallized twice from ethanol to provide 4.82 g (67%) of product: mp 147–149 °C. Anal. ($C_{18}H_{21}F_2N_5O$) C, H, N.

Method G. α-(4-Fluorophenyl)-4-(5-fluoro-2-pyrimidinyl)-1-piperazinebutanamine Dihydrochloride (33). A mixture of Raney nickel catalyst (2 tsp) in a solution of oxime **32** (3.61 g, 0.01 mol) in ethanol (100 mL) was shaken on a Parr apparatus until the theoretical amount of hydrogen was consumed. The mixture was filtered and concentrated in vacuo, and the residue was redissolved in ethanol (30 mL) and treated with ethanolic HCl. The resulting salt was collected by filtration and recrystallized from ethanol to afford 1.78 g (42%) white solid: mp 298–300 °C. Anal. ($C_{18}H_{23}F_2N_5$·2HCl) C, H, N.

Method H. α-(4-Fluorophenyl)-4-(5-fluoro-4-hydroxy-2-pyrimidinyl)-1-piperazinebutanol (21). A solution of the methylthio compound **20** (5 g, 0.0127 mol) and KOH (10 g, 0.178 mol) in water (25 mL) and methanol (25 mL) was heated under reflux for 18 h. The methanol was removed in vacuo and the aqueous solution neutralized with glacial acetic acid. The resulting precipitate was collected by filtration and recrystallized from ethanol to give 2.31 g (50%) of a white crystalline solid: mp 205–207 °C; ^{13}C NMR (DMSO-d_6) δ 22.5, 37.2, 44.6, 52.1, 57.5, 71.5, 114.6, 114.7, 127.6, 136.0, 141.3, 142.5, 142.6, 144.5, 152.1, 157.4, and 157.7 (amide carbon, doublet due to F–C coupling), 159.4 162.6; IR (KBr) 1680; IR (MeOH) 1684 (amide C=O). Anal. ($C_{18}H_{22}F_2N_4O_2$) C, H, N.

Method I. (*R,R*)-4-[4-(5-Fluoro-2-pyrimidinyl)-1-piperazinyl]-1-(4-fluorophenyl)butyl (1-Phenethyl)carbamate (17a). A suspension of the free base of the racemic carbinol **16** (81.1 g, 0.233 mol) in benzene (3.4 L) was heated under reflux for 4–5 h with an attached Dean–Stark trap for azetropic removal of any water of hydration. The solution was cooled to room temperature, treated by addition of (*R*)-α-methylbenzyl isocyanate (38.8 mL, 0.271 mol) and stirred for 6 days. The solvent was removed in vacuo, the residue was dissolved in hot ethanol, and the hot solution was filtered and refrigerated. The resulting crystalline precipitate was collected by filtration, washed with cold ethanol (50 mL) and hexane (50 mL), and dried to provide 45 g of solid. Recrystallization from ethanol gave 41.4 g (72%) of the pure *R,R*-diastereomer: mp 115–116 °C; $[\alpha]^{25}_D$ = +32.4 ($CHCl_3$, *c* 0.57); HPLC (chiracel OD, mobile phase 10% IPA–hexane) retention time = 9.97 min (100% purity); ^1H NMR ($CDCl_3$) δ 1.43 (3H, d), 1.3–2.1 (7H), 2.2–2.6 (6H, m), 3.6–3.9 (4H, m), 4.65–4.9 (1H, m), 4.9–5.1 (1H, m), 5.6 (1H, t), 6.6–7.5 (9H, m), 8.18 (2H, s); IR (KBr) 1358, 1442, 1462, 1507, 1540, 1604, 1717, 3200 cm^{-1}. Anal. ($C_{27}H_{31}F_2N_5O_2$), C, H, N. X-ray data: single crystals of $C_{27}H_{31}F_2N_5O_2$ (formula wt 495.57) are at 20 + 1 °C, monoclinic, space group $P2_1$–C^2_2 (No. 4) with a = 6.330 (1) Å, b = 17.836 (2) Å, c = 11.409 (2) Å, β = 94.68 (1)°, V = 1283.7 (3) Å^3, and Z = 2 [d_{calcd} = 1.283 g cm^{-3}; μ_a(Cu Kα) = 0.73 mm^{-1}). A total of 1971 independent reflections having 2q (Cu Kα) < 120° (the equivalent of 0.65 limiting Cu Kα spheres) were collected on a computer-controlled four-circle Nicolet autodiffractometer using θ–2θ scans and Nickel-filtered Cu Kα radiation. The structure was solved using direct methods techniques with Nicolet SHELXTL software package as modified at Crystalytics Co. A structural model which utilized anisotropic thermal parameters for all F, C, N, and O atoms and isotropic thermal parameters for all H atoms has been refined to convergence [R_1 (unweighted, based on F) = 0.032 for 1697 independent reflections having 2θ(Cu Kα) < 120° and $I > 3\sigma(I)$] using counter-weighted cascade block diagonal least-squares techniques. The methyl group was included in the refinement as an idealized sp^3-hybridized rigid rotor. Hydrogen atom H1N was located from a difference Fourier map and refined as an independent isotropic atom. The remaining hydrogen atoms were fixed at idealized sp^2- or sp^3-hybridized positions with a C–H bond length of 0.96 Å. The correctness of the enantiomeric description was verified by a series of refinement cycles in which the multiplier of Df″ was varied; this multiplier refined to a value of 1.3 (5). Data for final atomic positional and thermal parameters as well as a complete compilation of bond distances and angles have been submitted as supplementary material.

Method J. (*R*)-(+)-α-(4-Fluorophenyl)-4-(5-fluoro-2-pyrimidinyl)-1-piperazinebutanol Hydrochloride (16a). A mixture of **17a** (41.0 g, 0.0827 mol) and triethylamine (15.1 mL, 0.108 mol) in toluene (525 mL) was heated to 40–45 °C to dissolve the carbamate and then cooled to 10 °C and treated by the dropwise addition of $SiHCl_3$ (10.1 mL, 0.1 mol) in toluene (100 mL). The resulting mixture was mechanically stirred for 72 h under argon and then treated with cold, saturated NH_4Cl solution (900 mL), stirred for 0.5 h, and filtered. The solid was suspended in saturated NH_4Cl solution (400 mL) and toluene (375 mL), and the suspension was magnetically stirred for 0.5 h and filtered. The filtrates were combined, and the aqueous layer was separated, washed with toluene (50 mL), basified to pH 9.5 with solid Na_2

CO_3, and twice extracted with CH_2Cl_2 (1.2 L, 240 mL). The extract was washed with brine, dried ($MgSO_4$), and filtered through a silica gel pad which was then washed with ethyl acetate (1 L). The solvents were evaporated in vacuo to afford a solid residue which was recrystallized from ethanol to afford 21.59 (75%) of optically-pure **16a** free base: mp 114.5–115.5 °C. $[\alpha]^{25}_D = +14.3°$ (MeOH, *c* 0.53); HPLC (resolvosil BSA-7, 4 × 150 mm, mobile phase IPA–0.2 M phosphate buffer, 3.5:96.5) retention time = 4.51 min (>99.9% ee). Anal. ($C_{18}H_{22}F_2N_4O$) C, H, N.

The HCl salt was prepared as follows: acetyl chloride (4.8 mL, 0.67 mol) was added dropwise to cold (5 °C) ethanol (85 mL) stirring at 5 °C for 0.75 h. The solution was treated by dropwise addition of **16a** free base (21.5 g, 0.062 mol) in methylene chloride (310 mL). The mixture was stirred 1 h and filtered, and the collected solid was rinsed with methylene chloride. The filtrate was concentrated in vacuo until formation of a heavy precipitate which was collected by filtration, combined with the initial solid, and dried to provide 21.8 g (69% based on **17a**, 49% based on **16**) of white solid: mp 228–230 °C; $[\alpha]^{25}_D = +19.6°$ (MeOH, *c* 0.51). Anal. ($C_{18}H_{22}F_2N_4$·HCl) C, H, N.

Biological Tests. All biological tests were performed according to methods described in our earlier contributions to this journal, in references cited therein, or in other references as indicated in footnotes to Tables II–V.

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Supplementary Material Available: Data for final atomic positional and thermal parameters and a complete compilation of bond distances and angles (18 pages). Ordering information is given on any current masthead page.