N-Aryl-N'-Benzylpiperazines as Potential Antipsychotic Agents

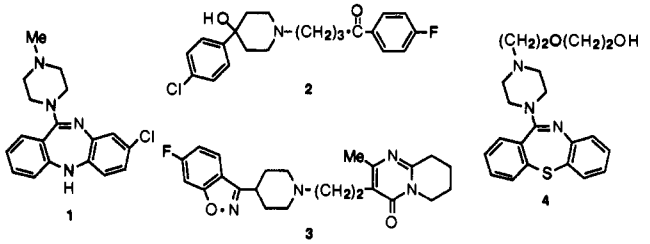
Allen B. Reitz,*,† Ellen W. Baxter,† Debra J. Bennett,‡ Ellen E. Codd,‡ Alfonzo D. Jordan,† Elizabeth A. Malloy,§ Bruce E. Maryanoff,† Mark E. McDonnell,† Marta E. Ortegon,‡ Michael J. Renzi,‡ Malcolm K. Scott,† Richard P. Shank,‡ Ronald G. Sherrill,†,∥ Jeffry L. Vaught,‡,⊥ and David J. Wustrow§,▽

Drug Discovery, The R. W. Johnson Pharmaceutical Research Institute, Spring House, Pennsylvania 19477, and Raritan, New Jersey 08869

Received October 24, 1994®

N^1-(2-Alkoxyphenyl)piperazines additionally containing an N^4-benzyl group bearing alcohol, amide, imide, or hydantoin functionalities were prepared and evaluated in the conditioned avoidance response (CAR) test predictive of clinical antipsychotic activity and in in vitro receptor-binding assays. Certain of the compounds display high affinity for the D_2, 5-HT_{1A}, and α_1-adrenergic receptors. Structures bearing acyclic amide, lactam, and imide fuctionalities display good biological activity, with a preference for the 1,3-disubstituted phenyl ring relative to the 1,4- and 1,2-congeners (**7** vs **10** and **12**). Every possible position of hydantoin attachment was investigated (e.g., substitution at N^1, N^3, and C^5). The hydantoin involving attachment to N^1 (**24**) was found to have good biological activity, whereas those hydantoins with attachment to N^3 or C^5 (**22**, **23**, and **25**) were inactive. Several of the smaller acetylated derivatives (**30** and **33**) have fair in vivo activity, which was lost in the case of the larger benzoyl analog **31**. Uracil congener **34** had modest affinity for the D_2 receptor (65 nM) as well as excellent in vivo activity. Benzylamino compounds display (viz. **27** and **35–38**) moderate CAR activity but have surprising receptor affinity, often greater than those of comparable structures bearing a carbonyl (**36** vs **7**). Benzyl and benzhydryl alcohol compounds **40–48** are more active than amino structures **27** and **35–38** and also exhibit excellent in vivo activity in the CAR test with modest D_2 and 5-HT_{1A} receptor binding.

Drug treatment of schizophrenia has advanced significantly with the discovery of clozapine (**1**), which lacks the side effects of Parkinsonism and akathesia classified as extrapyramidal symptoms (EPS) and tardive dyskinesias found with standard antipsychotic drug therapy such as haloperidol (**2**).[1] Unfortunately clozapine causes a ca. 1% incidence of agranulocytosis, which is an effect peculiar to this drug and not generally found with antipsychotic drugs as a class.[2] Removing EPS and agranulocytosis is the goal of current antipsychotic drug research. In addition, drug candidates which ameliorate both the positive (hallucinations, delusions) and negative (apathy, withdrawal) symptoms of the disease are widely sought after.[1] Considerable success has been achieved with risperidone (**3**), a compound recently introduced into clinical use which antagonizes both D_2 and serotonin-2 (5-HT_2) receptors[3] and is the forerunner of a significant number of compounds which act at both of these receptors.[4] Seroquel (**4**, ICI 204,636) is one of a class of clozapine analogs with increased 5-HT_2 affinity relative to clozapine and possibly a lower potential for causing agranulocytosis.[4] Haloperidol (**2**) is a classic D_2 blocker, although it also shows affinity for 5-HT_2 and so-called σ-receptor sites.[5,6] Serotonin 5-HT_{1A} agonists reverse the production of catalepsy by antipsychotic agents in rats,[7] an effect which is predictive of EPS in humans, suggesting that a combination of dopaminergic and 5-HT_{1A}-binding activity may afford an antipsychotic agent with minimal EPS liability. Thus a suitable mix of dopaminergic and serotonergic binding appears to offer many advantages, such as those seen for risperidone and related compounds.

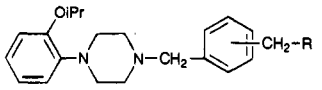


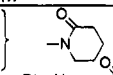
Our search for potential antipsychotic agents containing a favorable combination of dopaminergic and serotonergic binding began with a series of arylpiperazines that inhibit conditioned avoidance response (CAR), show little or no binding activity at dopamine receptors (D_1, D_2), have high affinity for serotonin receptors (5-HT_{1A}, 5-HT_{1B}), and do not cause catalepsy in rats.[8,9] When the piperazines were additionally extended with pyrrole-containing groups prepared via a Mannich reaction, we obtained a series of methylenepyrrole compounds from which **5** was chosen for further evaluation.[10] This compound exhibited potent binding to D_2, 5-HT_{1A}, and α_1-adrenergic receptors (K_i's < 4 nM) and displayed a favorable in vivo profile. Since administration of **5** caused the deposition of red-colored bodies in the fundus region of dog stomachs, probably related to rapid decomposition (reverse Mannich reaction) in the pres-

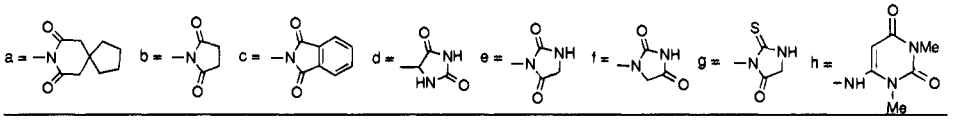
† Medicinal Chemistry Department, Spring House.
‡ Central Nervous System Research, Spring House.
§ Medicinal Chemistry Department, Raritan.
∥ Present affiliation: Glaxo Wellcome, Inc., 5 Moore Dr., Research Triangle Park, NC 27709.
⊥ Present affiliation: Cephalon, Inc., 145 Brandywine Parkway, West Chester, PA 19380.
▽ Present affiliation: Parke-Davis Research Division, Warner-Lambert Co., 2800 Plymouth Rd., Ann Arbor, MI 48105.
® Abstract published in *Advance ACS Abstracts*, September 15, 1995.

0022-2623/95/1838-4211$09.00/0

Table 1. Methylene Amides, Imides, Hydantoins, and Related Structures

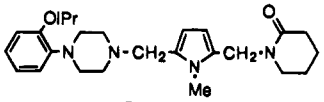


Compd	Substitution Pattern	R	% Yield	Rxn. Solv.	M.p. (°C)	Formula[a]	Analysis
7	1,3		44	iPrOH/Et_2O	206-208	$C_{26}H_{35}N_3O_2$•1.5HCl	C,H,N
10	1,4		30	CH_2Cl_2/Et_2O	196-206	$C_{26}H_{35}N_3O_2$•2HCl	C,H,N[b]
12	1,2		61	MeOH/Et_2O	249.5-252.5	$C_{26}H_{35}N_3O_2$•1.5HCl0.3H_2O	C,H,N,Cl,H_2O[c]
14	1,3	R' = H	70	iPrOH/Et_2O	103-105	$C_{26}H_{33}N_3O_3$•$C_4H_4O_4$	C,H,N
15	1,3	R' = Me	40	Et_2O	196-200	$C_{27}H_{35}N_3O_3$•2HCl•0.25H_2O	C,H,N,H_2O[d]
16	1,3	a	25	Et_2O	212-216	$C_{30}H_{39}N_3O_3$•2HCl	C,H,N,Cl
17	1,3	b	87	iPrOH/Et_2O	105-108	$C_{25}H_{31}N_3O_3$•$C_4H_4O_4$	C,H,N
18	1,3	c	88	iPrOH/Et_2O	143-145	$C_{28}H_{31}N_3O_3$•$C_4H_4O_4$	C,H,N
22	1,3	d	94	H_2O	178-181	$C_{24}H_{30}N_4O_3$	C,H,N
23	1,3	e	45	H_2O	144-146	$C_{24}H_{30}N_4O_3$	C,H,N
24	1,3	f	18	iPrOH	218-221	$C_{24}H_{30}N_4O_3$•2HCl•0.25H_2O	C,H,N,H_2O[e]
25	1,3	g	29	H_2O	202-205	$C_{24}H_{30}N_4SO_2$•2HCl•0.25H_2O	C,H,N,H_2O[f]
30	1,3	NHAc	72	Et_2O/pentane	199-201	$C_{23}H_{31}N_3O_2$•$C_4H_4O_4$	C,H,N
31	1,3	NHC(O)Ph	27	Et_2O/pentane	142-144	$C_{28}H_{33}N_3O_2$•$C_4H_4O_4$	C,H,N
32	1,3	$NHSO_2Me$	40	EtOH	162.5-164	$C_{22}H_{31}N_3O_3S$•0.5$C_4H_4O_4$	C,H,N
33	1,3	N(Me)Ac	27	iPrOH/Et_2O	154-156	$C_{24}H_{33}N_3O_2$•1.5$C_4H_4O_4$	C,H,N
34	1,3	h	40	iPrOH	143-147	$C_{27}H_{35}N_5O_3$	C,H,N

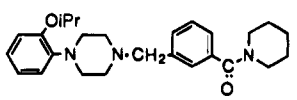


[a] Where the formula is given as symbols of elements in Tables 1–3, the elemental analyses for those elements were within ±0.4% of the calculated values except where indicated. [b] C: calcd, 63.15; found, 63.60. [c] Cl: calcd, 11.02; found, 13.40. [d] H_2O: calcd, 0.90; found, 1.90. [e] H_2O: calcd, 0.90; found, 2.13. [f] H_2O: calcd, 0.87; found, 2.64.

ence of dilute acid ($t_{1/2}$ ca. 80 min at pH 2), it was dropped from further drug development.[11]



5; RWJ-25730



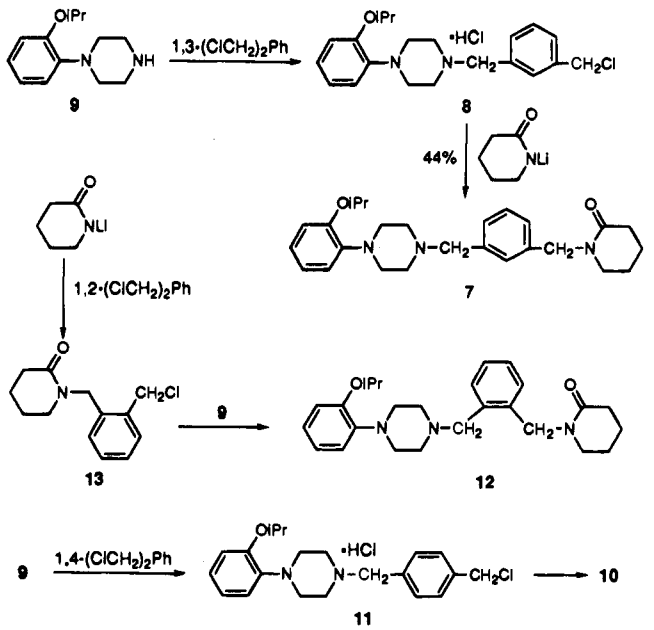
6; RWJ-37796

In order to improve the stability of compounds related to **5**, we prepared benzamide **6** (RWJ-37796, mazapertine succinate) which binds with high affinity to D_2, D_3, 5-HT_{1A}, and α_1-adrenergic receptors (K_i's < 3 nM), displays potent in vivo activity, and was found to be stable under the conditions described above.[11,12] One of the key aspects of the biological profiles of **5** and **6** is that both compounds exhibit a very low tendency to produce catalepsy in rats, a predictor of their liability for EPS in man.[11-13] Also, the combination of dopaminergic and 5-HT_{1A} affinity in a series of compounds with antipsychotic activity is generally unique, although there are several other series which have been reported to have this combination.[14] In this paper we describe structure–activity relationships (SAR) of compounds related to **6** in which the benzamide moiety has been replaced with a variably substituted phenyl ring bearing a methylene group having appended functionalities such as imides, hydantoins, amines, and alcohols. For many of the antipsychotic compounds reported in the literature,[15] the suitable positioning of a carbonyl group relative to a basic nitrogen appears to be a key to activity, and the hydantoin and imide structures incorporate these features.

Results and Discussion

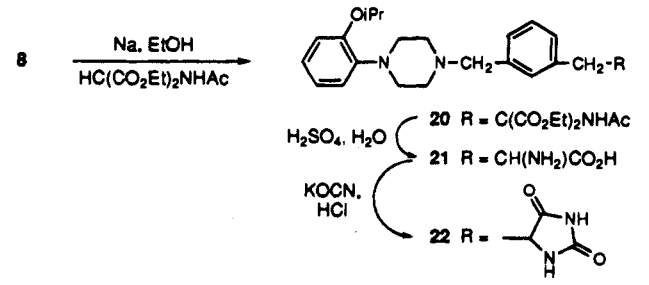
Synthetic Chemistry. Compound **7**, the direct phenyl replacement analog of **5**, and related structures were prepared by displacement of the anion of δ-valerolactam with chloromethyl compound **8** (Table 1, Scheme 1). Intermediate **8** was itself readily obtained by treatment of *N*-(2-isopropoxyphenyl)piperazine (**9**) with an excess of 1,3-bis(chloromethyl)benzene (α,α'-dichloro-*m*-xylene). In the case of the 1,4-disubstituted methylene lactam analog **10**, a similar protocol was followed involving 1,4-bis(chloromethyl)benzene to afford key intermediate **11**. For 1,2-disubstituted congener **12**, reaction of 1,2-bis(chloromethyl)benzene with **9** proved to be unsuitable as competing quaternization of the product ensued, and the 2-chloromethyl derivative was not obtained. An alternative approach was employed in which the anion of δ-valerolactam was first reacted with 1,2-bis(chloromethyl)benzene to give **13** followed by reaction with **9** to afford target **12**.

Scheme 1

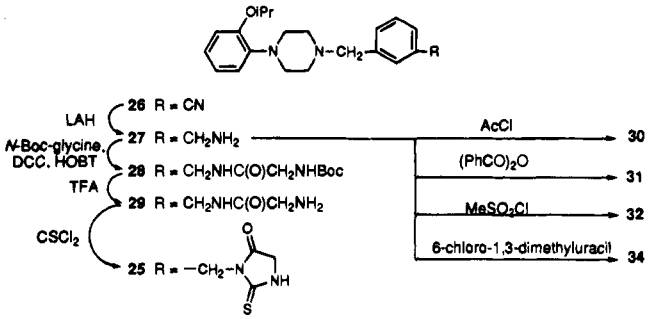


Imides **14**–**18** were prepared from **8** by displacement reactions of the appropriate imide anions. Hydantoin

Scheme 2



Scheme 3



22 was prepared by treatment of **8** with 2-acetamidodiethyl malonate to give **20** followed by hydrolysis to amino acid **21** and reaction with potassium cyanate to afford **22** (Scheme 2). Reaction of **8** with the monoanion of hydantoin afforded derivative **23**. Isomeric congener **24** was synthesized from reaction of 3-(morpholinylmethyl)hydantoin with **8** followed by hydrolysis of the morpholinylmethyl protecting group. Alternatively, thiohydantoin **25** was prepared by a multistep sequence shown in Scheme 3 first involving preparation of 3-cyanobenzyl compound **26** by reaction of **9** with 3-cyanobenzyl bromide and reduction to afford benzylamine **27**. This compound was then coupled with *N*-Boc-glycine to give **28** followed by cleavage of the Boc protecting group to provide **29** and cyclization with $CSCl_2$ to give congener **25**. Benzylic amine **27** was also acylated for the preparation of amides **30** and **31** and sulfonamide **32**. *N*-Methylacetamide **33** was prepared from **8** by treatment with the anion of *N*-methylacetamide. Dimethyluracil derivative **34**, structurally related to the α-adrenergic vasodilator urapidil,[16] was synthesized from amine **27** followed by reaction with 6-chloro-1,3-dimethyluracil.

In addition to benzylamine **27**, additional amines **35**–**38** were prepared (Table 2, Scheme 4). Aldehyde **39** was prepared by a Kornblum oxidation of **8** with $NaHCO_3$ in DMSO,[17] which then underwent a reductive amination with 4-$FPhNH_2$ ($NaCNBH_3$, MeOH) to yield **35**. Derivative **36** was synthesized by reaction of **8** with piperidine. In a similar manner, amines **37** and **38** were prepared by reaction of **11** with pyrrolidine and butylamine, respectively.

Benzyl and benzhydryl alcohols **40**, **41**, and **43**–**50** and acetate **42** were prepared by the steps outlined in Schemes 4–6. Benzophenone **51** was obtained by reaction of **9** with 3-(bromomethyl)benzophenone; **51** was then reduced with $NaBH_4$ to give **40** (Scheme 5). Carbinol **41** was prepared by reaction of aldehyde **39** with MeMgBr (Scheme 4). A displacement reaction of **8** with potassium acetate afforded compound **42**, which was then hydrolyzed with KOH/MeOH to give **43**. 3-[[4-(2-Methoxyphenyl)-1-piperazinyl]methyl]benzenenitrile (**52**) was prepared from *N*-(2-methoxyphenyl)-piperazine in the same manner as **26** and then reacted with Grignard reagents to afford intermediate ketones, which were reduced with $NaBH_4$ to give **44**, **46**, and **47** (Scheme 6). Treatment of 3-[[4-(2-methoxyphenyl)-1-piperazinyl]methyl]benzenenitrile with MeMgBr to give the corresponding acetophenone followed by reaction with EtMgBr afforded carbinol **45** (Scheme 6). The isomeric 1,2- and 1,4-compounds **48**–**50** were prepared in a directly analogous manner from the appropriate benzonitrile intermediate.

Pharmacology. The compounds prepared herein were evaluated in a series of receptor-binding assays involving D_2, 5-HT_{1A}, and α_1-adrenergic sites, as described in the Experimental Section, the results of which are shown in Table 4. Also included in Table 4, for comparitive purposes, are reference compounds RWJ-25730 (**5**),[10] mazapertine (**6**), haloperidol (**2**), and clozapine (**1**). The primary in vivo assay that we have employed is the CAR test, which measures the ability of a drug to ameliorate the conditioned response to a disagreeable stimulus.[9] As part of the CAR test, the percentage of animals failing to escape the shock (percent escape loss) was measured and affords a rough index for nonspecific sedation.[18]

The direct phenyl replacement analog of **5** is compound **7**, which displays good in vivo CAR activity but only moderate D_2 affinity. The considerable in vivo biological activity of compound **7** suggests that the *N*-methylpyrrole unit of **5** acts primarily as a spacer orienting the lactam and arylpiperazine moieties in a suitable orientation for optimal receptor interactions.

Scheme 4

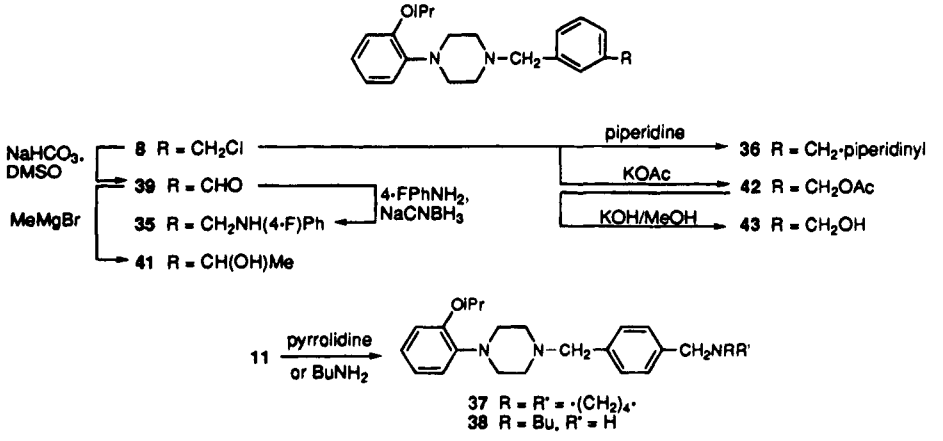
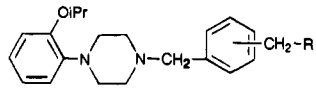


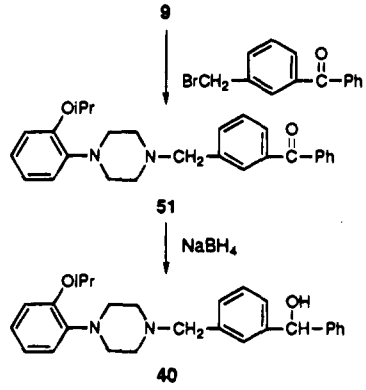
Table 2. Benzylic Amines



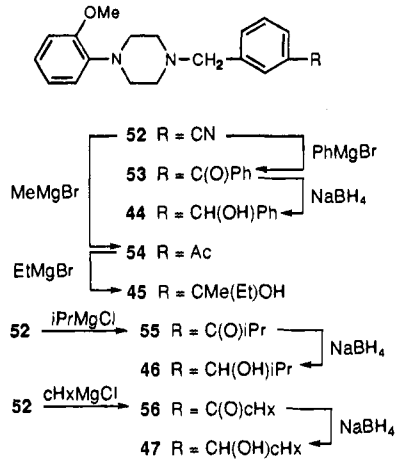
compd	substitution pattern	R	yield (%)	recrystn solv	mp (°C)	formula	anal.
27	1,3	NH_2	53	EtOH	131–133	$C_{21}H_{29}N_3O{\cdot}(E)C_4H_4O_4$	C,H,N
35	1,3	NH(4-F)Ph	26	MeOH/Et_2O	117–165	$C_{27}H_{32}FN_3O_2{\cdot}2HClO_4{\cdot}1.3H_2O$	C,H,N,H_2O
36	1,3	*N*-piperidinyl	10	MeOH/Et_2O	129–131	$C_{26}H_{37}N_3O{\cdot}2HClO_4{\cdot}0.2H_2O$	C,H,N,Cl[a]
37	1,4	*N*-pyrrolidinyl	80	*i*-PrOH	280–300 dec	$C_{25}H_{35}N_3O{\cdot}2HCl{\cdot}0.75H_2O$	C,H,N,Cl[b]
38	1,4	NHBu	53	MeOH/Et_2O	124–125.5	$C_{25}H_{37}N_3O{\cdot}1.5C_2H_3O_4{\cdot}0.1H_2O$	C,H,N,H_2O

[a] H_2O: calcd, 0.59; found, 1.21. [b] H_2O: calcd, 2.81; found, 1.21. H: calcd, 7.87; found, 8.19.

Scheme 5



Scheme 6



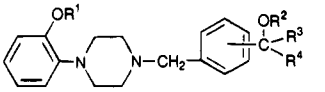
Although 1,4- and 1,2-disubstituted compounds **10** and **12** have higher affinities for the D_2 receptor, they are less potent in vivo. 1,4-Isomer **10** has particularly high affinity for the α_1-adrenergic receptor (0.7 nM). The comparison of **7**, **10**, and **12** suggests that every mode of disubstitution is allowed but that the 1,3-pattern (e.g., **7**) is preferred for in vivo activity. Therefore, imides, amides, and related structures (**14–18**, **22–25**, and **30–34**) were prepared and evaluated incorporating the 1,3-disubstituted benzene middle portion. Some of these compounds were weakly active or inactive, but others such as imides **15** and **17**, hydantoin **23**, thiohydantoin **25**, amides **30** and **33**, sulfonamide **32**, and uracil **34** displayed at least 65% inhibition of CAR activity at the screening dose (5 mg/kg ip), although compounds **17** and **34** may suffer sedative liability due to their significant escape loss. Apparently a large bulky imide group causes a loss of CAR inhibitory activity as can be seen in the comparison of imide **16**, succinimide **17**, and phthalimide **18**. For these compounds, and the others of similar structure, there is generally good affinity at the three receptors shown, indicating that poor oral absorption, poor blood–brain barrier penetration, or rapid metabolism had prevented distribution into the brain. Uracil congener **34** had a high level of in vivo activity, with a large degree of loss of escape (70%).

Amines **27** and **35–38** were also evaluated and found to have moderate in vivo and in vitro activity. Structure **36** is the desoxy analog of **7**, and it actually has a 6-fold *greater* affinity for the D_2 receptor than does **7**, although the in vivo activity is lower and it does exhibit significant escape loss. This suggests, unexpectedly, that the amide carbonyl of **7** is not required for receptor recognition as much as it is for eventual transport into the central nervous system.

Among alcohols or esters **40–48** bearing either a 1,3- or 1,4-disubstituted middle phenyl ring, alcohols **41** and **43–48** and ester **42** have a fairly high degree of in vivo activity in the CAR test. The escape loss of compounds **42** and **48** suggests that they may be sedating. Compounds **41–48** have relatively modest D_2 binding but stronger 5-HT_{1A} affinity. For example, compound **43** has −89% inhibition of CAR at the screening dose, with only 302 nM D_2 affinity and 6.2 nM 5-HT_{1A} binding. It could be that 5-HT_{1A} binding contributes to the CAR activity, as had been seen for the earlier phenylpiperazines.[8] We do not know if the 5-HT_{1A} affinity is agonist or antagonist in character, as we have not done the raphe cell-firing experiments to differentiate this effect.[19] 1,2-Disubstituted analogs **49** and **50** have essentially no biological activity.

Blockade of dopaminergic neurotransmission is the traditional means of effecting antipsychotic activity.[15,20] As mentioned earlier, it has been shown that 5-HT_{1A} agonists reverse antipsychotic-induced catalepsy, so that it may be that a 5-HT_{1A} component in the binding profile of a series of mixed D_{2-4} and serotonergic ligands would impart a lower propensity to induce EPS in humans.[7] Supporting this view is the finding that **7** produced ca. 50% catalepsy at a dose of 50 mg/kg (ip) with a 1 h pretreatment time and ca. 25% catelepsy at 50 mg/kg (ip) with a 4 h pretreatment time, which are significantly lower values than those observed with standard drugs such as **2** under the same conditions. The relevance of the α_1-adrenergic binding in this series is unknown, although no untoward cardiovascular effects have been seen. There is evidence that antagonism of α_1-adrenergic receptors may contribute to the therapeutic effect of antipsychotic drugs when this type of activity is part of an overall receptor-binding profile.[21]

Table 3. Benzyl and Benzhydryl Alcohols as Potential Antipsychotic Agents



compd	substitution pattern	R^1	R^2	R^3	R^4	yield (%)	recrystn solv	mp (°C)	formula	anal.
40	1,3	*i*-Pr	H	Ph	H	75	Et_2O	139–142	$C_{27}H_{32}N_2O_2$	C,H,N[a]
41	1,3	*i*-Pr	H	Me	H	60	MeOH/Et_2O	184–194	$C_{22}H_{30}N_2O_2 \cdot 2HCl \cdot 0.1H_2O$	C,H,N,Cl[b]
42	1,3	*i*-Pr	Ac	H	H	90	Et_2O	174	$C_{23}H_{30}N_2O_3 \cdot 2HCl \cdot 0.5H_2O$	C,H,N,Cl
43	1,3	*i*-Pr	H	H	H	70	Et_2O	201	$C_{21}H_{28}N_2O_2 \cdot 2HCl$	C,H,N
44	1,3	Me	H	Ph	H	31	MeOH/Et_2O	198–210	$C_{25}H_{28}N_2O_2 \cdot 2HClO_4 \cdot H_2O$	C,H,N,Cl[c]
45	1,3	Me	H	Et	Me	30	Me_2CO/Et_2O	178.5–179.5	$C_{22}H_{30}N_2O_2 \cdot 0.5C_4H_4O_4$	C,H,N
46	1,3	Me	H	*i*-Pr	H	19	Me_2CO/Et_2O	160–161	$C_{22}H_{30}N_2O_2 \cdot 0.5(E)C_4H_4O_4 \cdot 0.5H_2O$	C,H,N,H_2O
47	1,3	Me	H	*c*-Hx	H	43	MeOH/Et_2O	230–240	$C_{25}H_{34}N_2O_2 \cdot 2HClO_4$	C,H,N
48	1,4	Me	H	Ph	H	28	Me_2CO	195–196	$C_{25}H_{28}N_2O_2 \cdot C_4H_4O_4$	C,H,N
49	1,2	Me	H	Me	H	37	MeOH/Et_2O	174–199	$C_{20}H_{26}N_2O_2 \cdot 1.4HClO_4 \cdot 0.2H_2O$	C,H,N,Cl,H_2O
50	1,2	Me	H	Ph	H	20	MeOH/Et_2O	150–157	$C_{25}H_{28}N_2O_2 \cdot 1.2HClO_4 \cdot 0.1H_2O$	C,H,N,Cl,[d] H_2O

[a] C: calcd, 77.85; found, 77.35. [b] H_2O: calcd, 0.42; found, 1.67. [c] H_2O: calcd, 2.97; found, 0.35. [d] Cl: calcd, 8.32; found, 7.49.

Table 4. Receptor Affinity and Conditioned Avoidance Response (CAR) Activity

compd	CAR (5 mg/kg ip)		receptor affinity (K_i, nM)[a]		
	inhibtn (%)	esc loss (%)	D_2 [^{3}H]spiperone	5-HT_{1A} [^{3}H]WB4101	α_1-adrenergic [^{3}H]prazosin
clozapine (1)	9.6[b]		53.6	38.5	23.2
haloperidol (**2**)	0.17[b]		1.4	401	23.5
RWJ-25730 (**5**)	−87 2.2[b]	8	0.8	3.3	8.2
mazapertine (**6**)	−92 (at 1 mg/kg) 0.66[b]	8	2.2	1.7	1.3
7	−89	12	120	10	4.0
10	−29	1	23	5.9	0.7
12	6	0	46	1.6	32
14	−17	0	63	8.6	2.6
15	−71	15	17	1.2	1.7
16	0	0	20	0.13	1.4
17	−68	29	94	8.0	5.0
18	−8	1	57	2.6	2.8
22	−1	0	280	19	5.5
23	−83	21	23	7.8	1.9
24	−2	0	90	12	6.1
25	−82	1	31	12	5.8
27	1	0	32	31	13
30	−74	6	28	20	9.1
31	−4	0	20	3.7	4.0
32	−35	1	31	12	5.8
33	−95	8	22	17	5.7
34	−100	70	65	5.1	7.1
35	−14	0	117	29	12
36	−68 (at 15 mg/kg)	25	20	41	5.3
37	−38 (at 15 mg/kg)	11	23	29	6.2
38	**1**	0	32	31	13
40	−18 (at 15 mg/kg)	15	5.0	4.5	1.8
41	−67	0	56	25	8.5
42	−86	38	51	11	3.7
43	−89	13	302	6.2	3.4
44	−65	2	87	4.1	18
45	−87	21	198	10	47
46	−100	13	90	39	8.6
47	−93	2	16	3.7	2.7
48	−100 (at 15 mg/kg)	32	53	9.2	6.2
49	0	0	>1000	460	>1000
50	0.5	0	>1000	25	52

[a] D_2, 5-HT_{1A}, and α_1-adrenergic data were obtained using rat brain synaptosomal preparations as described in the Experimental Section. [b] ED_{50}, mg/kg ip.

Conclusions

Activity of the amino- and hydroxy-containing compounds described here indicate that a carbonyl positioned at a remote site in arylpiperazine antipsychotics, as in **6**, is not required for activity. For example, the descarbonyl analog of **6** and **7** is **36** which actually has pronounced D_2 receptor affinity although with a lesser degree of in vivo CAR activity. Among those compounds bearing a carbonyl, certain of the imides, hydantoins, and amides as shown in Table 1 display activity. One of the more promising compounds is **7**, which is the direct phenyl replacement analog of **5**. The activity with **7** indicates that the *N*-methylpyrrole moiety of **5** acts primarily as a spacer, properly orienting the aryl piperazine and lactam rings. Compound **7** had greater

in vivo activity than either the 1,4- (**10**) or 1,2- (**12**) disubstituted derivatives. The activity of benzyl alcohols **40**–**48** opens a new avenue for SAR analysis in the antipsychotic area.

Experimental Section

General Procedures. ^{1}H NMR spectra were recorded on either a Bruker AC-300 (300 MHz), AM-360WB (360 MHz), or AM-400 (400 MHz) or Varian 390 (90 MHz) spectrometer. For NMR work, DMSO-d_6 was used as the solvent unless otherwise noted and tetramethylsilane (TMS) was used as an internal standard. Elemental analyses were mainly conducted by the Analytical Services group at Raritan, NJ; those samples requiring water analysis were evaluated by Robertson Microlit, Madison, NJ. Melting points were determined in open capillary tubes with a Thomas-Hoover apparatus and are corrected. Infrared spectra were recorded on a Perkin-Elmer 1420 IR spectrometer. Chemical ionization mass spectra (CI-MS) were recorded on a Finnigan 3300-6100 system with methane as the reagent gas unless otherwise noted. Fast-atom-bombardment mass spectra (FAB-MS) were obtained on a VG 7070E spectrometer. An Ion Tech saddlefield gun, which generated a primary beam of argon atoms at 8 keV and 2 mA, was used for the FAB analysis. Where elemental analyses are reported by symbols of elements, the results are within 0.4% of the calculated values. Most reagents and solvents were purchased and used without further purification.

1-[[3-[[1-[2-(1-Methylethoxy)phenyl]-4-piperazinyl]-methyl]phenyl]methyl]piperidin-2-one Hydrochloride (2:3) (7). A solution of *N*-(2-isopropoxyphenyl)piperazine (11.95 g, 54.3 mmol) in THF (250 mL) was treated with α,α′-dichloro-*m*-xylene (23.7 mL, 0.163 mol) and refluxed. After 4 h, diisopropylethylamine (10.4 mL, 55 mmol) was added, and the solution was refluxed an additional 1.5 h. Treatment with 1 N HCl (120 mL), water (50 mL), and ether (200 mL) caused **8** to form as a white solid which was collected by filtration: ^{1}H NMR ($CDCl_3$) δ 7.70–7.50 (br m, 4H, phenyl H), 6.90 (m, 4H, phenyl H), 4.62 (m, 1H, $CHMe_2$), 4.31 (s, 2H, phenyl CH_2Cl), 3.70–3.00 (br m, 8H, piperazine H), 1.40 (d, J = 6 Hz, 4H, $C(CH_3)_2$).

The compound thus obtained (**8**·HCl) was relatively insoluble in both ethyl acetate and water and could be directly isolated from the reaction mixture. This material (7.40 g, 18.73 mmol) was partitioned into saturated aqueous $NaHCO_3$ to give 6.0 g of an oil, which was dissolved in THF (10 mL) and added to a solution of γ-valerolactam (1.74 g, 17.5 mmol) in THF (80 mL) which had been treated at 0 °C with 2.5 M *n*-BuLi/hexane (7.0 mL, 1 mol equiv). The resulting solution was heated at reflux for 1.5 h, treated with a suspension of γ-valerolactam (500 mg, 5.05 mmol) and 2.5 M *n*-BuLi/hexane (2.0 mL) in THF (10 mL), and refluxed an additional 1 h. The solution was cooled and partitioned between water and ether; the ether layer was separated, dried, filtered, and concentrated to give a yellow oil. This material was purified on two Waters Prep-500 silica gel columns (EtOAc/hexane, 8:2) affording **7** as an oil (4.80 g). A solution of this oil in *i*-PrOH (30 mL) was treated with concentrated HCl (1.15 mL) followed by ether (ca. 500 mL). A white solid was collected by filtration and recrystallized from *i*-PrOH/ether affording **7** hydrochloride (2:3) as a white crystalline solid (3.74 g, 44%): mp 206–208 °C; ^{1}H NMR ($CDCl_3$) δ 7.68–7.60 (br s, 2H, phenyl H), 7.46–7.32 (m, 2H, phenyl H), 7.20–7.00 (m, 2H, phenyl H), 6.92–6.83 (m, 2H, phenyl H), 4.70–4.58 (m, 1H, $CHMe_2$), 4.62 (s, 2H, piperidinone CH_2), 4.25–4.15 (m, 2H, piperazine CH_2), 3.90–3.60 (br m, 2H, piperidinone 6H), 3.55–3.05 (br m, 8H, piperazinyl H), 2.55–2.40 (br s, 2H, piperidinone 3H), 1.90–1.78 (br s, 4H, piperidinone 4- and 5H), 1.42–1.30 (d, 6H, J = 6 Hz, $C(CH_3)_2$). Anal. ($C_{26}H_{35}N_3O_2$·1.5HCl) C, H, N.

1-[[4-[[1-[2-(1-Methylethoxy)phenyl]-4-piperazinyl]-methyl]phenyl]methyl]piperidin-2-one Dihydrochloride (10). **10** was prepared as for **7** using α,α′-dichloro-*p*-xylene and proceeding through intermediate **11**. **10**: ^{1}H NMR (Me_2SO-d_6) δ 7.75–7.68 (m, 2H, phenyl H), 7.57–7.50 (m, 2H, phenyl H), 7.00–6.82 (m, 4H, phenyl H), 4.82 (s, 2H, phenyl CH_2Cl), 4.67–4.57 (p, 1H, J = 6 Hz, $CHMe_2$), 4.42–4.35 (s, 2H, piperazinyl CH_2), 3.58–3.00 (br m, 8H, piperazinyl H), 1.30–1.21 (d, 6H, J = 6 Hz, $C(CH_3)_2$).

10·2HCl: 2.45 g, 30%; mp 196–206 °C; ^{1}H NMR ($CDCl_3$) δ 7.80–7.60 (br m, 2H, phenyl H), 7.48–7.20 (br m, 4H, phenyl H), 7.02–6.90 (m, 2H, phenyl H), 4.78–4.65 (m, 1H, $CHMe_2$), 4.62 (s, 2H, piperidinone CH_2), 4.60–3.40 (br m, 8H, piperazinyl H), 4.28–4.20 (m, 2H, piperazine CH_2), 3.28–3.18 (br m, 2H, piperidinone 6H), 2.52–2.42 (br s, 2H, piperidinone 3H), 1.90–1.75 (br s, 4H, piperidinone 4- and 5H), 1.55–1.40 (d, 6H, J = 6 Hz, $C(CH_3)_2$). Anal. ($C_{26}H_{35}N_3O_2$·2.0HCl) C, H, N.

1-[[2-[[1-[2-(1-Methylethoxy)phenyl]-4-piperazinyl]-methyl]phenyl]methyl]piperidin-2-one Hydrochloride (2:3) (12). A solution of γ-valerolactam (7 g, 70.5 mmol) in THF (150 mL) and DMSO (20 mL) was treated with NaH (2.83 g of a 60% oil dispersion) at 0 °C under a nitrogen atmosphere. After a total of 15 min, α,α′-dichloro-*o*-xylene (25 g, 140 mmol) was added and the solution was allowed to warm and stir at room temperature. After 4 h, 100 mL of ether and 100 mL of 0.2 N HCl were added. The water was withdrawn, and the organic layer was washed twice more with water, dried ($MgSO_4$), filtered, and concentrated. This material was purified on ca. 400 g of silica gel (flash chromatography, EtOAc/hexane, 7:3) to yield **13** (6.6 g, 40%): ^{1}H NMR ($CDCl_3$) δ 7.40–7.10 (br m, 4H, phenyl H), 4.82 (s, 2H, phenyl CH_2N), 4.72 (s, 2H, phenyl CH_2Cl), 3.10 (m, 2H, piperidinone 6H), 2.50 (m, 2H, piperidinone 3H), 1.80–1.70 (br s, 4H, piperidinone 4- and 5H).

A solution of **13** (5.0 g, 21.09 mmol), *N*-(2-isopropoxyphenyl)-piperazine fumarate (6.38 g, 18.99 mmol), and triethylamine (8.82 mL, 62.37 mmol) in DMF (75 mL) was heated for 3 h at 50–60 °C. After 3 h, the solution was added to a 3:1 solution of ether/ethyl acetate (ca. 100 mL), extracted three times with water, dried ($MgSO_4$), filtered, and concentrated. The residual oil was purified on ca. 400 g of silica gel (flash chromatography, EtOAc/hexane, 6:4) to give 5.41 g of white semisolid, pure by thin layer chromatography. It was then dissolved in *i*-PrOH, filtered through a Millipore filter, treated with 2.44 mL of concentrated aqueous HCl (ca. 26 mmol), and then triturated out of solution by the addition of ether. The resultant white solid was recrystallized in MeOH/ether to give **12**·HCl (2:3) as a white powder (5.50 g, 61%): mp 249.5–252.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.92–7.15 (br m, 6H, phenyl H), 6.99–6.90 (br m, 2H, phenyl H), 4.87 (s, 2H, piperidinone CH_2), 4.75–4.65 (m, 1H, $CHMe_2$), 4.60 (s, 2H, piperazine CH_2), 4.50–3.50 (br m, 8H, piperazinyl H), 3.37–3.28 (br s, 2H, piperidinone 6H), 2.47–2.37 (br s, 2H, piperidinone 3H), 1.85–1.75 (br s, 4H, piperidinone 4- and 5H), 1.50–1.40 (d, 6H, J = 6 Hz, $C(CH_3)_2$). Anal. ($C_{26}H_{35}N_3O_2$·1.5HCl) C, H, N.

1-[[3-[[1-[2-(1-Methylethoxy)phenyl]-4-piperazinyl]-methyl]phenyl]methyl]piperidine-2,6-dione (*Z*)-2-Butenedioate (1:1) (14). A mixture of NaH (0.224 g, 7.48 mmol) and DMF (10 mL) was treated slowly with 2,6-piperidinedione (0.846 g, 7.48 mmol) at room temperature. After the addition was complete, the mixture was cooled to 0 °C and a solution of **8** prepared as above (2.46 g, 7.12 mmol) and DMF (10 mL) was added dropwise. The cooling bath was removed, and the reaction mixture was stirred at room temperature overnight. A small portion of water was added, and the reaction mixture was concentrated under vacuum. The residue was partitioned between CH_2Cl_2 and water, and the organic layer was separated, dried, and evaporated to give **13** as an oil, 3.25 g. This material was dissolved in *i*-PrOH (13 mL) and treated with maleic acid (0.83 g, 7.15 mmol). Trituration with ether, filtration, and drying afforded **14** (*Z*)-2-butenedioate (1:1) as a white solid (2.73 g, 70%): mp 103–105 °C; ^{1}H NMR (Me_2SO-d_6) δ 7.50–7.24 (m, 4H, phenyl H), 7.02–6.85 (m, 4H, phenyl H), 6.06 (s, 2H, maleate H), 4.86 (br s, 2H, piperidine-2,6-dionyl CH_2), 4.67–4.58 (p, 1H, J = 6 Hz, $CHMe_2$), 4.40–4.15 (s, 2H, piperazinyl CH_2), 3.60–2.80 (br m, 8H, piperazinyl H), 2.72–2.65 (t, 4H, J = 6 Hz, piperidine-2,6-dione 3- and 5H), 1.93–1.85 (q, 2H, J = 6 Hz, piperidine-2,6-dione 4H), 1.30–1.22 (d, 6H, J = 6 Hz, $C(CH_3)_2$). Anal. ($C_{26}H_{33}N_3O_3$·$C_4H_4O_4$) C, H, N.

4-Methyl-1-[[3-[[1-[2-(1-methylethoxy)phenyl]-4-piperazinyl]methyl]phenyl]methyl]piperidine-2,6-dione Dihydrochloride (15). A solution of benzylamine **27** (2.32 g, 6.84 mmol), 3-methylglutaric anhydride (0.88 g, 6.84 mmol), and THF (20 mL) was stirred at room temperature for 3 h and then concentrated to an oily residue. This material was dissolved in acetic anhydride (25 mL), heated at 100 °C for 4 h, cooled, and added slowly to saturated aqueous $NaHCO_3$. Extraction with CH_2Cl_2, separation of the organic layer, drying, filtration, and evaporation afforded an oil. This material was chromatographed on flash grade silica gel using 97:3 CH_2Cl_2/MeOH to give **15** as an oil, which was dissolved in ether and added to ethereal HCl causing a solid to form. Filtration afforded **15**·2HCl (1.43 g, 40%): mp 196–200 °C; ^{1}H NMR (Me_2SO-d_6) δ 7.55–7.25 (m, 4H, phenyl H), 7.02–6.83 (m, 4H, phenyl H), 4.88 (s, 2H, piperidine-2,6-dionyl CH_2), 4.66–4.55 (p, 1H, J = 6 Hz, $CHMe_2$), 4.36 (s, 2H, piperazinyl CH_2), 3.60–3.07 (br m, 8H, piperazinyl H), 2.78–2.50 (m, 4H, piperidine-2,6-dione 3- and 5H), 2.33–2.20 (m, 2H, piperidine-2,6-dione 4H), 1.32–1.23 (d, 6H, J = 6 Hz, $C(CH_3)_2$), 1.00–0.92 (d, 6H, J = 7 Hz, CH_3). Anal. ($C_{27}H_{35}N_3O_3$·2HCl·0.25H_2O) C, H, N, H_2O.

8-[[3-[[1-[2-(1-Methylethoxy)phenyl]-4-piperazinyl]methyl]phenyl]methyl]-8-azaspiro[4.5]decane-7,9-dione Dihydrochloride (16). A solution of **27** (2.50 g, 7.37 mmol) and 3,3-tetramethyleneglutaric anhydride (1.12 g, 6.66 mmol) in toluene (30 mL) was heated to reflux, cooled slightly, and treated with thionyl chloride (9.72 mL, 13.3 mmol). The resulting slurry was refluxed for 30 min and cooled and the solid collected by filtration. This material was partitioned between CH_2Cl_2 and 3 N NaOH, and the organic layer was separated, dried, filtered and evaporated giving **16** as a crude oil. Chromatography of this material on flash silica gel using EtOAc/hexane (2:8) gave an oil which was dissolved in ether and added to ethereal HCl causing formation of a solid which was filtered affording **16**·2HCl (0.94 g, 25%): mp 212–216 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 7.53–7.25 (m, 4H, phenyl H), 7.00–6.84 (m, 4H, phenyl H), 4.88 (s, 2H, azaspiro[4.5]decane-7,9-dionyl CH_2), 4.65–4.57 (p, 1H, J = 6 Hz, $CHMe_2$), 4.35 (s, 2H, piperazinyl CH_2), 3.58–3.00 (br m, 8H, piperazinyl H), 2.23 (s, 4H, azaspiro[4.5]decane-7,9-dione 6- and 10H), 1.68–1.58 (m, 2H, azaspiro[4.5]decane-7,9-dione 1- and 4H), 1.48–1.38 (m, 2H, azaspiro[4.5]decane-7,9-dione 2- and 3H), 1.30–1.22 (d, 6H, J = 6 Hz, $C(CH_3)_2$). Anal. ($C_{30}H_{39}N_3O_3$·2HCl) C, H, N.

1-[[3-[[1-[2-(1-Methylethoxy)phenyl]-4-piperazinyl]methyl]phenyl]methyl]pyrrolidine-2,5-dione (*Z*)-2-Butenedioate (1:1) (17). This compound was prepared as described for compound **14** using succinimide in place of 2,6-piperidinedione (3.54 g, 87%): mp 105–108 °C; ^{1}H NMR (Me_2SO-d_6) δ 7.55–7.35 (m, 4H, phenyl H), 7.08–6.83 (m, 4H, phenyl H), 6.35 (s, 2H, maleate H), 4.67 (s, 2H, pyrrolidine-2,5-dionyl CH_2), 4.62–4.55 (p, 1H, J = 6 Hz, $CHMe_2$), 4.20 (s, 2H, piperazinyl CH_2), 3.65–2.88 (br m, 8H, piperazinyl H), 2.72 (s, 4H, pyrrolidine-2,5-dione 3- and 4H), 1.32–1.23 (d, 6H, J = 6 Hz, $C(CH_3)_2$). Anal. ($C_{25}H_{31}N_3O_3$·$C_4H_4O_4$) C, H, N.

2-[[3-[[1-[2-(1-Methylethoxy)phenyl]-4-piperazinyl]methyl]phenyl]methyl]-1*H*-isoindole-1,3(2*H*)-dione (*Z*)-2-Butenedioate (1:1) (18). This compound was prepared as described for compound **14**, using phthalimide in place of 2,6-piperidinedione (3.89 g, 88%): mp 143–145 °C; ^{1}H NMR (Me_2SO-d_6) δ 7.97–7.85 (m, 4H, phenyl H), 7.52–7.38 (m, 4H, phenyl H), 7.01–6.86 (m, 4H, phenyl H), 6.06 (s, 2H, maleate H), 4.82 (s, 2H, 1H-isoindole-1,3(2*H*)-dionyl CH_2), 4.68–4.55 (p, 1H, J = 6 Hz, $CHMe_2$), 4.40–4.10 (s, 2H, piperazinyl CH_2), 3.65–2.65 (br m, 8H, piperazinyl H), 1.32–1.20 (d, 6H, J = 6 Hz, $C(CH_3)_2$). Anal. ($C_{29}H_{31}N_3O_3$·$C_4H_4O_4$) C, H, N.

5-[[3-[[1-[2-(1-Methylethoxy)phenyl]-4-piperazinyl]methyl]phenyl]methyl]imidazolidine-2,4-dione (22). Sodium metal (0.192 g, 8.34 mmol, 1.1 mol equiv) was dissolved in EtOH (25 mL) at reflux under argon. After dissolution, the alkoxide solution was cooled to room temperature, a solution of diethyl acetamidomalonate (1.65 g, 7.59 mmol, 1.0 mol equiv) was added, and the solution was further cooled to 0–5 °C with an ice/water bath. A solution of **8** (2.73 g, 7.59 mmol, 1.0 equiv) in EtOH (12 mL) was then added, and the reaction mixture was heated to reflux for ca. 3.0 h and then allowed to cool to room temperature. The resulting slurry was filtered, and the filtrate was concentrated in vacuo to a residue and chromatographed on flash grade silica gel using an EtOAc/hexane mixture as eluent. The appropriate fractions were combined and concentrated in vacuo to an oil, which was dissolved in Et_2O and added dropwise to a solution of ethereal HCl. The resulting slurry was filtered, washed with Et_2O, and dried under reduced pressure at room temperature overnight to provide 2.06 g (43%) of **20** as a hydrochloride salt.

To a mixture of crude **20** (10.37 g, 19.21 mmol, 1.0 mol equiv) and H_2O (40 mL) was cautiously added concentrated H_2SO_4 (10.0 mL, 198 mmol, 10.3 mol equiv) with agitation. The reaction mixture was heated to reflux for 14 h. The solution was then cooled to 0–5 °C with an ice/water bath, basified by the addition of concentrated NH_4OH, diluted with Et_2O, and transferred to a separatory funnel. The aqueous layer was extracted again with Et_2O and then concentrated to a residue and purified by reverse-phase chromatography (C-18 column, H_2O/MeOH, 85:15). The appropriate fractions were concentrated to a residue and triturated with CH_3CN. The product was filtered, washed with cold MeCN, and then dried overnight at 65 °C under reduced pressure to afford **21** (3.06 g, 40%).

A mixture of **21** (1.80 g, 4.53 mmol) and potassium cyanate (0.73 g, 9.06 mmol, 2.0 mol equiv) was combined in H_2O (18 mL) and heated at 100 °C for 1.0 h followed by the addition of concentrated HCl (34.6 mL, 0.83 mol, 92 mol equiv) as quickly as possible. After stirring for ca. 30 min, the reaction mixture was cooled to 0–5 °C and neutralized by the dropwise addition of saturated aqueous $NaHCO_3$. The product precipitated directly from the mixture on neutralization and was filtered, washed with water, and dried under vacuum at 6 °C for 24 h to provide **22** directly (1.81 g, 94%): mp 178–181 °C; ^{1}H NMR (Me_2SO-d_6) δ 10.40 (s, 1H, imidazolidine-2,4-dione 3-NH), 7.92 (s, 1H, imidazolidine-2,4-dione 5-NH), 7.27–7.17 (m, 4H, phenyl H), 6.95–6.85 (m, 4H, phenyl H), 4.63–4.53 (p, 1H, J = 6 Hz, $CHMe_2$), 4.35–4.31 (m, 1H, imidazolidine-2,4-dione 4H), 3.47 (s, 2H, piperazinyl CH_2), 3.10–2.95 (br m, 4H, piperazinyl 2- and 6H), 2.95–2.89 (m, 2H, imidazolidine-2,4-dione CH_2), 2.56–2.41 (br m, 4H, piperazinyl 3- and 5H), 1.30–1.23 (d, 6H, J = 6 Hz, $C(CH_3)_2$). Anal. ($C_{24}H_{30}N_4O_3$) C, H, N.

3-[[3-[[1-[2-(1-Methylethoxy)phenyl]-4-piperazinyl]methyl]phenyl]methyl]-2,5-imidazolidinedione (23). To a slurry of sodium hydride (300 mg, 10.0 mmol, 1.1 mol equiv) in DMF (30 mL) under argon was added 1.00 g (10.01 mmol, 1.1 mol equiv) of hydantoin. The mixture was allowed to stir at room temperature for 30 min at which time **8** (31.23 g, 8.7 mmol) in DMF (10 mL) was added. The reaction mixture was heated to 70 °C for 16 h and then concentrated to a residue and partitioned between CH_2Cl_2 and H_2O. The layers were separated, and the aqueous phase was back-extracted with CH_2Cl_2. The organic layers were combined, extracted with saturated aqueous NaCl, separated, dried over $MgSO_4$, filtered, and finally concentrated. The resultant residue was purified using chromatography on flash grade silica gel (MeOH/CH_2Cl_2, 4:96). The product was then recrystallized from *i*-PrOH and subsequently dried under reduced pressure at 65 °C to afford 1.89 g (49%) of **23**: mp 144–146 °C; ^{1}H NMR (Me_2SO-d_6) δ 8.17 (s, 1H, 2,5-imidazolidinedione 3-NH), 7.32–7.10 (m, 4H, phenyl H), 6.90–6.80 (m, 4H, phenyl H), 4.62–4.55 (p, 1H, J = 6 Hz, $CHMe_2$), 4.52 (m, 2H, 2,5-imidazolidinedione 4H), 4.00 (s, 2H, piperazinyl CH_2), 3.50 (s, 2H, 2,5-imidazolidinedione CH_2), 3.10–2.45 (br m, 8H, piperazinyl H), 1.30–1.21 (d, 6H, J = 6 Hz, $C(CH_3)_2$). Anal. ($C_{24}H_{30}N_4O_3$) C, H, N.

1-[[3-[[1-[2-(1-Methylethoxy)phenyl]-4-piperazinyl]methyl]phenyl]methyl]-2,4-imidazolidinedione Dihydrochloride (24). 3-(*N*-Morpholinomethyl)-2,4-imidazolidinedione[22] (1.750 g, 8.8 mmol, 1.1 mol equiv) and sodium hydride (0.26 g, 8.8 mmol, 1.1 mol equiv) were combined in DMF (25 mL) at room temperature under argon. After hydrogen evolution had ceased, a solution of **8** (2.87 g, 8.0 mmol, 1.0 mol equiv) in DMF (15 mL) was added, and the reaction mixture was allowed to stir at room temperature for ca. 16 h. The reaction mixture was then concentrated to an oily residue, which was combined with 3 N NaOH (40 mL) under argon

and stirred at room temperature for 30 min. The reaction mixture was neutralized with acetic acid, diluted with CH_2Cl_2 and H_2O, and transferred to a separatory funnel. The layers were separated, and the aqueous layer was back-extracted with CH_2Cl_2. The organic layers were combined, extracted with saturated aqueous NaCl, separated, dried over $MgSO_4$, and then concentrated to a residue. The crude product was purified by chromatography on flash grade silica gel using a $MeOH/CH_2Cl_2$ mixture as an eluent. The appropriate fractions were combined and concentrated in vacuo to an oil, which was dissolved in ethyl ether and added dropwise to a solution of Et_2O/HCl. The product was filtered, washed with Et_2O, and then dried under reduced pressure for 14 h to afford 0.74 g (18%) of **24**·2HCl·0.25H_2O: mp 218–221 °C; ^{1}H NMR (Me_2SO-d_6) δ 10.91 (s, 1H, 2,4-imidazolidinedione 3-NH), 7.60–7.35 (m, 4H, phenyl H), 7.02-6.86 (m, 4H, phenyl H), 4.67–4.58 (p, 1H, J = 6 Hz, $CHMe_2$), 4.50 (s, 2H, piperazinyl CH_2), 4.40 (m, 2H, 2,4-imidazolidinedione 5H), 3.95 (s, 2H, 2,4-imidazolidinedione CH_2), 3.60–2.95 (br m, 8H, piperazinyl H), 1.32–1.22 (d, 6H, J = 6 Hz, $C(CH_3)_2$). Anal. ($C_{24}H_{30}N_4O_3$·2HCl·0.25H_2O) C, H, N, H_2O.

3-[[3-[[1-[2-(Methylethoxy)phenyl]-4-piperazinyl]-methyl]phenyl]methyl]-4-oxoimidazolidine-2-thione (25). A solution of **27** (1.71 g, 5.04 mmol) prepared as described below, 0.88 g (5.04 mmol) of *N*-Boc-glycine, dicyclohexylcarbodiimide (1.04 g, 5.04 mmol), and *N*-hydroxybenzotriazole (1.36 g, 10.1 mmol) in THF (40 mL) under argon was allowed to stir at room temperature overnight. The reaction mixture was filtered and the filtrate concentrated to an oil and partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was back-extracted. The combined organics were extracted with saturated aqueous NaCl, dried over $MgSO_4$, and then concentrated to an oil (2.74 g). Impure *N*-Boc-glycine amide **28** was then dissolved in TFA (15 mL) at 0–5 °C and allowed to react for 1 h under argon. The reaction was neutralized with 3.0 N NaOH and the mixture extracted with CH_2Cl_2. The aqueous layer was back-extracted, and then the organic layers were combined, extracted with saturated aqueous NaCl, dried over $MgSO_4$, and concentrated to an oil (2.12 g). Crude amide **29** was then dissolved in CH_2Cl_2 (30 mL) and cooled under argon to 0–5 °C. A solution of thiophosgene (0.394 mL, 5.04, 1.0 mol equiv) in CH_2Cl_2 (5 mL) was added followed by triethylamine (0.70 mL). The reaction mixture was diluted with saturated aqueous $NaHCO_3$, the layers were separated, and the aqueous layer was back-extracted with CH_2Cl_2. The organic layers were combined, extracted with saturated aqueous NaCl, dried over $MgSO_4$, and then concentrated to an oil, which was purified by chromatography on silica gel. The product was added to ethereal HCl, and the resulting slurry was filtered and washed with Et_2O. The product was dried under reduced pressure at room temperature to provide compound **25** as a dihydrochloride salt (0.81 g, 29%): mp 202–205 °C; ^{1}H NMR (Me_2SO-d_6) δ 10.35 (s, 1H, 4-oxoimidazolidine-2-thione 1-NH), 7.61–7.35 (m, 4H, phenyl H), 7.02–6.82 (m, 4H, phenyl H), 4.90 (s, 2H, piperazinyl CH_2), 4.68–4.57 (p, 1H, J = 6 Hz, $CHMe_2$), 4.37 (m, 2H, 4-oxoimidazolidine-2-thione 5H), 4.28 (s, 2H, 4-oxoimidazolidine-2-thione CH_2), 3.58–3.02 (br m, 8H, piperazinyl H), 1.32–1.22 (d, 6H, J = 6 Hz, $C(CH_3)_2$). Anal. ($C_{24}H_{30}N_4O_2S$·2HCl·0.25H_2O) C, H, N, H_2O.

3-[[1-[2-(Methylethoxy)phenyl]-4-piperazinyl]methyl]-benzylamine (*E*)-2-Butenedioate (27). A solution of 3-cyanobenzyl bromide (10.0 g, 0.051 mol) and acetonitrile (250 mL) was added to a mixture of **9** fumarate (13.10 g, 0.051 mol), K_2CO_3 (21.15 g, 0.153 mol), and acetonitrile (250 mL), and the resulting mixture was stirred at reflux under nitrogen for 6.8 h. The reaction mixture was cooled and concentrated to dryness and the residue partitioned between CH_2Cl_2 and aqueous $NaHCO_3$. The organic layer was separated, dried over anhydrous Na_2SO_4, and evaporated to give a gummy residue. This material was chromatographed on silica gel (CH_3OH/CH_2Cl_2, 2:98) to produce nitrile **26** as a yellow gum (10.86 g).

A solution of this material (10.36 g, 0.031 mol) and anhydrous ether (500 mL) was added dropwise to a slurry of $LiAlH_4$ (1.17 g, 0.031 mol) in anhydrous ether (500 mL) under N_2 at room temperature. The reaction mixture was stirred at reflux for 5.5 h, at which point additional $LiAlH_4$ (1.17 g, 0.031 mol) was added. After stirring at reflux for 12 h, the reaction mixture was cooled in an ice bath and treated slowly with H_2O (100 mL), 20% aqueous NaOH (100 mL), and H_2O (100 mL), in that order, followed by extraction with diethyl ether. The ether layer was separated, dried over anhydrous Na_2SO_4, filtered, and evaporated to give a pale yellow gum. Treatment of a solution of this material (0.53 g, 1.3 mmol) in ethanol (10 mL) with fumaric acid (0.15 g, 1.3 mmol) afforded **27** fumarate (0.49 g): mp 131–133 °C; ^{1}H NMR (DMSO-d_6) δ 4.47–4.67 (m, 1H, $CHMe_2$), 3.97 (s, 2H, phenyl CH_2), 3.51 (s, 2H, piperazinyl CH_2), 1.24 (d, 6H, J = 6.0 Hz, $2CH_3$). Anal. ($C_{21}H_{29}N_3O$·$C_4H_4O_4$) C, H, N.

3-[[1-[2-(1-Methylethoxy)phenyl]-4-piperazinyl]methyl]-1-[(acetylamino)methyl]benzene (*E*)-2-Butenedioate (30). A solution of **27** (2.00 g, 0.0059 mol) in diethyl ether (250 mL), under N_2, was cooled in an ice bath, and triethylamine (0.99 mL, 0.0071 mol) was added followed by the addition of acetyl chloride and diethyl ether (50 mL), causing a white precipitate to form immediately. The reaction mixture was stirred at 0–5 °C for 0.5 h and filtered, and the insoluble material was washed with ether. The ether washings were evaporated to a yellow oil which was purified by chromatography on silica gel (2–5% CH_3OH in CH_2Cl_2) to give **30** as a pale yellow oil (2.09 g). A solution of this material (1.0 g, 0.0026 mol) and ethanol (10 mL) was treated with fumaric acid (0.24 g, 0.0021 mol) and allowed to stand at room temperature for 0.5 h. The solvent was evaporated and the residue triturated with Et_2O followed by pentane. Filtration afforded **30** (*E*)-2-butenedioate (1.05 g, 72%): mp 199–201 °C; ^{1}H NMR (DMSO-d_6) δ 4.53–4.68 (m, 1H, OCH), 4.25 (d, 2H, J = 5.8 Hz, phenylCH_2NHCO), 3.53 (s, 2H, piperazinyl CH_2), 1.87 (s, 3H, $COCH_3$), 1.24 (d, 6H, J = 6.0 Hz, $2CH_3$). Anal. ($C_{23}H_{31}N_3O_2$·$C_4H_4O_4$) C, H, N.

3-[[1-[2-(1-Methylethoxy)phenyl]-4-piperazinyl]methyl]-1-[(benzoylamino)methyl]benzene (*E*)-2-Butenedioate (31). A solution of **27** (2.01 g, 0.0059 mol) and diethyl ether (100 mL) was cooled in an ice bath and treated with a solution of benzoic anhydride (1.34 g, 5.9 mmol) and diethyl ether (100 mL). The resulting mixture was stirred at 0 °C for 0.5 h and at room temperature for 0.5 h. The solvent was evaporated, and the product was purified by chromatography on silica gel (CH_3OH/CH_2Cl_2, 1:49) to give **31** as a white solid. A solution of this material (1.49 g, 3.4 mmol) and ethanol (30 mL) was treated with fumaric acid (0.31 g, 2.7 mmol) in ethanol (10 mL) and allowed to stand at room temperature for 0.5 h. The solvent was evaporated and the residue triturated with diethyl ether/pentane. A white solid separated and was filtered to give **31** (*E*)-2-butenedioate (0.90 g, 27%): mp 142–144 °C; ^{1}H NMR (DMSO-d_6) δ 4.50–4.65 (m, 1H, OCH), 4.49 (d, 2H, J = 5.9 Hz, phenylCH_2NHCO), 3.54 (s, 2H, piperazinyl CH_2), 1.23 (d, 6H, J = 6.0 Hz, $C(CH_3)_2$). Anal. ($C_{28}H_{33}N_3O_2$·$C_4H_4O_4$) C, H, N.

3-[[1-[2-(1-Methylethoxy)phenyl]-4-piperazinyl]methyl]-1-[[(methylsulfonyl)amino]methyl]benzene (*E*)-2-Butenedioate (32). A solution of **27** (2.09 g, 6.23 mmol) in CH_2Cl_2 (150 mL) was cooled in an ice bath and treated with triethylamine (1.26 g, 12.46 mmol) followed by the addition of methanesulfonyl chloride (1.178 g, 10.28 mmol). After stirring for 0.5 h at 0 °C, the reaction mixture was poured into ice water (300 mL). The organic layer was washed with saturated NaCl solution, separated, dried (Na_2SO_4), filtered, and concentrated to give a yellow gum (2.88 g), which was purified by chromatography on silica gel (CH_2Cl_2/MeOH, 98:2, as eluant) to give **32** as a pale yellow gum (1.45 g). A solution of this material (1.43 g, 3.43 mmol) in ethanol (20 mL) was treated with fumaric acid (0.32 g, 2.74 mmol) and ethanol (10 mL). On standing at room temperature, a white solid formed which was collected by filtration to give **32** (*E*)-2-butenedioate (1.18 g, 40%): mp 162.5–164 °C; ^{1}H NMR (DMSO-d_6) δ 4.52–4.68 (m, 1H, OCH), 4.16 (d, 2H, J = 6.2 Hz, phenylCH_2NHSO_2), 3.54 (s, 2H, piperazinyl CH_2), 2.84 (s, 3H, SO_2CH_3), 1.24 (d, 6H, J = 6.0 Hz, $C(CH_3)_2$). Anal. ($C_{21}H_{31}N_3O_2$·1.5$C_4H_4O_4$) C, H, N.

***N*-Methyl-*N*-[[3-[[4-[2-(1-methylethoxy)phenyl]-1-piperazinyl]methyl]phenyl]methyl]acetamide (*E*)-2-Butene-**

dioate (2:3) (33). A mixture of NaH (0.250 g, 8.35 mmol) in DMF (15 mL) was treated slowly with *N*-methylacetamide (0.610 g, 8.35 mmol) at room temperature. After the addition was complete, a solution of **8**·HCl prepared as above (3.00 g, 7.59 mmol) and DMF (10 mL) was added dropwise, and the reaction mixture was stirred at room temperature overnight. The reaction mixture was concentrated and the residue partitioned between CH_2Cl_2 and water. The organic layer was separated, dried, and evaporated to give a crude oil which was chromatographed twice on flash grade silica gel (CH_2Cl_2/MeOH, 98:2, and hexane/acetone, 60:40) to give **33** as an oil (1.28 g). This material was dissolved in *i*-PrOH and treated with fumaric acid (0.38 g, 3.27 mmol). Trituration with ether, filtration, and drying afforded **33**·1.5[(*E*)-2-butenedioate] (1.04 g, 27%): mp 154–156 °C; ^{1}H NMR (Me_2SO-d_6) δ 7.40–7.08 (m, 4H, phenyl H), 6.90–6.80 (m, 4H, phenyl H), 6.62 (s, 2H, fumarate vinyl H), 4.62–4.52 (p, 1H, J = 6 Hz, $CHMe_2$), 4.49 (s, 2H, piperazinyl CH_2), 3.60–3.51 (br s, 2H, acetamido CH_2), 3.10–2.92 (br m, 4H, piperazinyl 2- and 6H), 2.79 (s, 1H, acetamido NH), 2.60–2.45 (br m, 4H, piperazinyl 3- and 5H), 2.10–2.00 (d, 3H, J = 10 Hz, NCH_3), 1.29–1.20 (d, 6H, J = 6 Hz, $C(CH_3)_2$). Anal. ($C_{24}H_{33}N_3O_2$·1.5$C_4H_4O_4$) C, H, N.

6-[*N*-[[3-[[4-[2-(1-Methylethoxy)phenyl]-1-piperazinyl]-methyl]phenyl]methyl]amino]-1,3-dimethyl-2,4-pyrimidinedione (34). A mixture of benzylamine **27** (2.35 g, 5.89 mmol), 6-chloro-1,3-dimethyluracil (1.20 g, 6.90 mmol), and triethylamine (1.1 mL, 7.89 mmol) in *N*-methylpyrrolidinone (20 mL) was stirred in an oil bath (85 °C) for 3 h. The reaction mixture was diluted with Et_2O (100 mL) and washed with H_2O (5 × 100 mL). The aqueous phase was back-extracted with additional Et_2O (2 × 50 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated to provide 3.24 g of a tacky brown solid. The crude product was chromatographed on silica gel (MeOH/$CHCl_3$, 3:97) and subsequently recrystallized from *i*-PrOH to provide **34** as a buff-colored powder (1.16 g, 40%): mp 143–147 °C; ^{1}H NMR (Me_2SO-d_6) δ 7.53–7.47 (m, 1H, benzyl NH), 7.35–7.18 (m, 4H, phenyl H), 6.90–6.83 (m, 4H, phenyl H), 4.62–4.54 (p, 1H, J = 6 Hz, $CHMe_2$), 4.52 (s, 1H, vinyl H), 4.37–4.32 (m, 2H, amino CH_2), 3.50 (s, 2H, piperazinyl CH_2), 3.39 (s, 3H, NCH_3), 3.05 (s, 3H, NCH_3), 3.00–2.90 (br m, 4H, piperazinyl 2- and 6H), 2.55–2.45 (br m, 4H, piperazinyl 3- and 5H), 1.28–1.21 (d, 6H, J = 6 Hz, $C(CH_3)_2$). Anal. ($C_{25}H_{37}N_5O_3$) C, H, N.

***N*-[[3-[[1-[2-(1-Methylethoxy)phenyl]-4-piperazinyl]-methyl]phenyl]methyl]-4-fluoroaniline Diperchlorate Hydrate (35).** To a solution of sodium bicarbonate (15.9 g, 190 mmol) in dimethyl sulfoxide (100 mL) at 110 °C was added a solution of **8**·HCl (10.0 g, 25.3 mmol) in dimethyl sulfoxide (50 mL). The reaction mixture was heated at 110 °C for 25 h. After cooling, the reaction mixture was partitioned between ether and water. The ether layer was separated, washed with brine, dried ($MgSO_4$), and concentrated to afford an oil. After the addition of ethereal HCl, the resulting solid was filtered and the filtrate was partitioned between methylene chloride and saturated aqueous bicarbonate solution. The aqueous layer was extracted with methylene chloride. The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated to afford aldehyde **39** as an oil which was purified by flash silica gel chromatography (hexane/acetone, 9:1–87:13).

A solution of this material (1.70 g, 5.02 mmol), 4-fluoroaniline (0.59 g, 5.02 mmol), and glacial acetic acid (0.302 g, 5.02 mmol) in 1,2-dichloroethane (15 mL) was treated with $NaCNBH_3$ (1.49 g, 5.02 mmol) and stirred at room temperature for 2 days. The reaction mixture was concentrated to a brown semisolid and partitioned between saturated aqueous sodium bicarbonate and $CHCl_3$. The organic layer was separated, dried (Na_2SO_4), filtered, and evaporated to an oil, which was purified on flash silica gel ($CHCl_3$/MeOH, 100:0–98:2) to give **35** as an oil. A solution of this material (1.75 g, 4.03 mmol) was dissolved in MeOH (25 mL) and treated with 70% $HClO_4$ (0.86 mL). On the addition of ether, a white crystalline solid formed which was collected by filtration to give **35**·2$HClO_4$·1.3H_2O (0.71 g, 26%): mp 117–165 °C; ^{1}H NMR (Me_2SO-d_6) δ 7.48–7.74 (m, 4H, phenyl H), 7.00–6.80 (m, 6H, phenyl H), 6.62 (br m, 2H, phenyl H), 4.61 (p, 1H, J = 6 Hz, $CHMe_2$), 4.40 (d, J = 4.7 Hz, 2H, $NHCH_2$), 4.32 (s, 2H, piperazinyl CH_2), 3.53–2.86 (br m, 8H, piperazinyl H), 1.27 (d, 6H, J = 6 Hz, $C(CH_3)_2$). Anal. ($C_{27}H_{32}FN_3O_2$·2$HClO_4$·1.3H_2O) C, H, N, H_2O.

1-[3-[[4-(2-Isopropoxyphenyl)piperazinyl]methyl]-benzyl]piperidine Perchlorate Hydrate (36). A solution of **8** (16.67 g, 4.66 mmol) was treated with piperidine (3.95 g, 46 mmol) and sodium carbonate (7.39 g, 70 mmol) in a biphasic system (water/EtOAc, 125 mL, 4:1) to 50 °C for 3 h. The organic layer was separated, dried, filtered, and concentrated. Purification of the residue on a silica gel column ($CHCl_3$) resulted in the isolation of an oil which was the converted to **36**·2.0$HClO_4$·0.2H_2O (1.92 g, 10%) and recrystallized from MeOH/Et_2O: mp 129–131 °C; ^{1}H NMR ($CDCl_3$) δ 8.0 (s, 1H, phenyl), 7.7 (dd, 2H, phenyl), 7.6 (t, 1H, phenyl), 7.05 (m, 1H, phenyl), 4.6 (p, 1H, $CHMe_2$), 6.9 (d, 3H, phenyl), 4.4 (s, 2H, piperidine CH_2), 4.3 (s, 2H, butyl CH_2), 3.2–3.6 (m, 8H, piperazine CH_2, 1H, piperidine CH_2), 3.05 (s, 2H, piperidine CH_2), 1.9 (m, 6H, piperidine CH_2), 1.5 (s, 1H, piperidine CH_2), 1.35 (d, 6H, $C(CH_3)_2$). Anal. ($C_{26}H_{37}N_3O$·2.0$HClO_4$·0.2H_2O) C, H, N, Cl, H_2O.

General Procedure for the Preparation of Compounds 37 and 39. This procedure is illustrated for the preparation of 1-[(butylamino)methyl]-4-[[1-[2-(1-methylethoxy)phenyl]-4-piperazinyl]methyl]benzene oxalate (2:3) hydrate (10:1) (**38**). A solution of α,α′-dichoro-*p*-xylene (30.40 g, 0.174 mol), **9** (12.70 g, 0.058 mol), triethylamine (6.08 g, 0.06 mol), and THF (200 mL) was refluxed for 4 h. Ether (100 mL) and 1 N HCl (100 mL) were added producing a white suspension which was filtered to give **11**.

A solution of **11** (4.0 g, 11.6 mmol), butylamine (15.44 g, 211 mmol), and *N*-methylpyrrolidone (100 mL) was stirred at room temperature for 5 h. The reaction mixture was then diluted with water and partitioned between 1 N NaOH and $CHCl_3$. The organic layer was separated, dried, filtered, and evaporated, and the residue was chromatographed on silica gel (CH_2Cl_2/MeOH, 95:5) to give **38** as an oil (4.07 g, 93%). This material (2.0 g, 5.06 mmol) was dissolved in ether and treated with oxalic acid (0.48 g, 5.33 mmol). The resulting solid was collected by filtration to give **38** oxalate (2:3) hydrate (10:1) (1.50 g, 53%): mp 124–125.5 °C; ^{1}H NMR (DMSO-d_6) δ 7.5 (m, 4H, phenyl), 6.9 (m, 4H, phenyl), 4.6 (m, 1H, $CHMe_2$), 4.2 (s, 2H, butyl CH_2), 3.8 (s, 2H, N-butyl CH_2), 3.1 (s, 4H, piperazine CH_2), 2.9 (t, 2H, butyl CH_2), 2.7 (s, 4H, piperazine CH_2), 1.6 (m, 2H, butyl CH_2), 1.3 (q, 2H, butyl CH_2), 1.2 (d, 6H, $C(CH_3)_2$), 0.9 (t, 3H, butyl CH_3). Anal. ($C_{25}H_{37}N_3O$·1.5$C_2H_3O_4$·0.1H_2O) C, H, N, H_2O.

3-[[4-[2-(1-Methylethoxy)phenyl]-1-piperazinyl]methyl]-α-phenylbenzenemethanol (40). Compound **9** (7.28 g, 33.0 mmol) in THF (75 mL) was treated with a solution of 3-(bromomethyl)benzophenone (10.0 g, 3.63 mmol) in THF (75 mL) and triethylamine (5.53 mL, 39.6 mmol). The solution was refluxed for 19 h and then cooled to ambient temperature and poured into 1 N HCl. After washing with ether, the aqueous layer was basified with solid K_2CO_3 and extracted with chloroform (three times). The chloroform extracts were combined, dried (Na_2SO_4), and concentrated to provide a dark brown oil which was purified by preparative liquid chromatography (hexanes/$CHCl_3$, 1:99) to afford **51** (9.09 g) as a brown oil. This oil was dissolved in acetone and treated with concentrated HBr (2.5 mL). Diethyl ether was added, and a fine white precipitate fell out of solution, which was recrystallized from acetone/ether to provide benzophenone **51**·HBr (7.94 g, 46%): mp 193–197 °C; ^{1}H NMR ($CDCl_3$) δ 8.40–8.30 (m, 1H, phenyl H), 7.98–7.47 (m, 8H, phenyl H), 7.30–6.80 (m, 4H, phenyl H), 4.75–4.55 (br s, 1H, $CHMe_2$), 4.35 (s, 1H, piperazinyl CH_2), 3.70–3.40 (br m, 8H, piperazine H), 1.60–1.40 (br s, 6H, $C(CH_3)_2$). Anal. Calcd for $C_{27}H_{30}N_2O_2$·1.4HBr: C, 61.44; H, 6.00; N, 5.31; Br, 21.19. Found: C, 61.02; H, 5.99; N, 5.17; Br, 20.63.

The free base of **51** was prepared by treatment with aqueous sodium bicarbonate followed by extraction into chloroform, giving a brown oil (3.30 g, 7.96 mmol) which was dissolved in ethanol (125 mL) followed by the addition of $NaBH_4$ (0.36 g, 9.55 mmol). After stirring under nitrogen (6 h), the reaction mixture was cooled in ice, and cold 1 N HCl (15 mL) was added. After 1 min of stirring, the reaction mixture was basified with solid K_2CO_3 and extracted with chloroform. The chloroform

extracts were combined, dried (Na_2SO_4), and concentrated to provide a waxy white solid. Recrystallization from diethyl ether afforded benzhydryl alcohol **40** (2.50 g, 75%) as white crystals: mp 139–142 °C; ^{1}H NMR ($CDCl_3$) δ 7.41–7.29 (m, 9H, phenyl H), 6.95–6.84 (m, 4H, phenyl H), 5.86 (br s, 1H, phenyl CHO-), 4.59 (p, 1H, J = 6 Hz, $CHMe_2$), 3.55 (s, 2H, piperazinyl CH_2), 3.09–2.60 (br m, 8H, piperazinyl H), 2.31 (br s, 1H, OH), 1.33 (d, 6H, J = 6 Hz, $C(CH_3)_2$). Anal. ($C_{27}H_{32}N_2O_2$) C, H, N.

3-[[4-[2-(1-Methylethoxy)phenyl]-1-piperazinyl]methyl]-α-methylbenzenemethanol Dihydrochloride Hydrate (41). Aldehyde **39** (1.90 g, 5.61 mmol) was dissolved in ether (120 mL) and cooled to 0 °C. To this mixture was added dropwise a solution of methylmagnesium bromide in ethyl ether (2.30 mL, 2.9 M). The reaction mixture was kept at 0 °C for 1 h and then warmed to ambient temperature. After 15 h of stirring under nitrogen, the reaction mixture was cooled in an ice bath, and saturated aqueous ammonium chloride was added. After neutralization with solid sodium bicarbonate, the mixture was extracted with chloroform (three times). The chloroform extracts were combined, dried (Na_2SO_4), and concentrated to provide a light brown oil, which was dissolved in methanol, and concentrated aqueous HCl (1.0 mL) was added. When ethyl ether was added, a cream-colored precipitate came out of solution. Recrystallization from methanol/ether provided alcohol **41**·2HCl·0.1H_2O (1.33 g, 60%) as cream-colored granules: mp 184–194 °C; ^{1}H NMR (D_2O) δ 7.54–7.47 (m, 4H, phenyl H), 7.15–7.00 (m, 4H, phenyl H), 4.97 (q, J = 6.5 Hz, 1H, phenyl CHO-), 4.72 (p, 1H, J = 6 Hz, $CHMe_2$), 4.44 (s, 2H, piperazinyl CH_2), 3.59–3.02 (br m, 8H, piperazinyl H), 1.50 (d, 6H, J = 6.4 Hz, CCH_3), 1.34 (d, 6H, J = 6 Hz, $C(CH_3)_2$). Anal. ($C_{22}H_{30}N_2O_2$·2HCl·0.1H_2O) C, H, N, Cl.

1-[[3-(Acetoxymethyl)phenyl]methyl]-4-[2-(1-methylethoxy)phenyl]piperazine Dihydrochloride Hemihydrate (42). Compound **8** (5.50 g, 13.9 mmol) dissolved in acetonitrile (70 mL) was treated with potassium acetate (2.73 g, 27.8 mmol) and 18-crown-6 (0.18 g, 0.70 mmol). The reaction mixture was refluxed under argon for 4 h and concentrated in vacuo, and the residue was partitioned between methylene chloride and water. The layers were separated, and the aqueous layer was extracted with methylene chloride. The organic extracts were combined, washed with brine, and dried ($MgSO_4$). The organic layer was concentrated, and the residue was taken up in ethyl ether. This solution was added to ethereal HCl. The resulting precipitate was collected, washed with ethyl ether, and dried under vacuum to provide 5.3 g (90%) of **42**·2HCl·0.5H_2O: mp 174 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 7.67–7.45 (m, 4H, phenyl H), 7.02–6.83 (m, 4H, phenyl H), 5.13 (s, 2H, CH_2OAc), 4.68–4.58 (p, 1H, J = 6 Hz, $CHMe_2$), 4.40–4.30 (m, 2H, piperazinyl CH_2), 3.60–2.98 (br m, 8H, piperazinyl H), 2.10 (s, 3H, $COCH_3$), 1.33–1.24 (d, 6H, J = 6 Hz, $C(CH_3)_2$). Anal. ($C_{23}H_{30}N_2O_3$·2HCl·0.5H_2O) C, H, N, Cl, H_2O.

1-[[3-(Hydroxymethyl)phenyl]methyl]-4-[2-(1-methylethoxy)phenyl]piperazine Dihydrochloride (43). To a solution of 85% KOH (0.5 g, 7.57 mmol) in methanol (50 mL) was added **42** (2.50 g, 5.97 mmol). After overnight stirring, the reaction mixture was refluxed under argon for 5 min. Additional KOH (0.53 g) was added, and refluxing was continued another 15 min. The reaction mixture was concentrated, and the residue was partitioned between methylene chloride and water. The layers were separated, and the aqueous layer was further extracted with methylene chloride. The organic extracts were combined, washed with brine, and dried ($MgSO_4$). The organic extract was concentrated to provide an oil which was dissolved in *i*-PrOH and filtered through $MgSO_4$. To the filtrate was added maleic acid (0.725 g), and the resulting mixture was concentrated to provide an oil which was partitioned between 3 N NaOH and methylene chloride. The layers were separated, and the aqueous layer was extracted with methylene chloride. The organic extracts were combined, washed with brine, and dried ($MgSO_4$). The resulting oil was purified on TLC mesh silica gel (methylene chloride/methanol, 97:3). The purified material was dissolved in ethyl ether and added to ethereal HCl. The resulting precipitate was collected by suction filtration and washed with ether. The sample was dried to provide **43**·2HCl (1.72 g, 70%): mp 201 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 10.72–10.62 (br s, 1H, benzyl OH), 7.60–7.38 (m, 4H, phenyl H), 7.02–6.83 (m, 4H, phenyl H), 4.67–4.60 (p, 1H, J = 6 Hz, $CHMe_2$), 4.53 (s, 2H, CH_2OH), 4.41–4.37 (m, 2H, piperazinyl CH_2), 3.57–2.97 (br m, 8H, piperazinyl H), 1.32–1.25 (d, 6H, J = 6 Hz, $C(CH_3)_2$). Anal. ($C_{21}H_{28}N_2O_2$·2HCl) C, H, N.

General Procedure for the Preparation of Carbinols 44 and 46–50. This procedure is illustrated for the preparation of 3-[[4-(2-methoxyphenyl)-1-piperazinyl]methyl]-α-phenylbenzenemethanol diperchlorate hydrate (**44**). *N*-(2-Methoxyphenyl)piperazine (58.0 g, 302 mmol) was dissolved in THF (650 mL) and treated with 3-cyanobenzyl bromide (70.8 g, 0.362 mol) and triethylamine (54.7 mL, 0.362 mol). The reaction mixture was refluxed for 20 h, cooled, and poured into 1 N HCl. The resulting solution was washed with ether, basified with solid K_2CO_3, and extracted with chloroform. The chloroform extracts were combined, dried (Na_2SO_4), and concentrated to provide a golden brown oil which was purified by preparative liquid chromatography (chloroform/hexanes, 95:5) to afford 3-[[[4-(2-methoxyphenyl)-1-piperazinyl]methyl]-phenyl]benzenenitrile (89.3 g, 93%) as a golden brown solid; ^{1}H NMR (DMSO-d_6) δ 7.87–7.55 (m, 4H, phenyl H), 7.00–6.83 (m, 4H, phenyl H), 4.65–4.52 (m, 1H, OCH), 3.61 (s, 2H, piperazine-CH_2), 3.12–2.92 (m, 4H, piperazine H), 2.65–2.45 (m, 4H, piperazine H), 1.24 (d, 6H, J = 6.0 Hz, $2CH_3$).

To an ice-cooled solution of this material (16.5 g, 53.7 mmol) in THF (800 mL) was added a solution of PhMgBr in ether (53.6 mL, 3.0 M) under nitrogen. The solution was slowly warmed to 25 °C and then brought to reflux. After 8 h, the reaction mixture was cooled to 0 °C and ice cold 6 N HCl (650 mL) was added. The reaction mixture was then stirred at ambient temperature for 8 h. After cooling, the reaction mixture was poured into a separatory funnel and washed with ether. The aqueous layer was then basified with K_2CO_3 and extracted with chloroform (three times). The organic extracts were combined, dried (Na_2SO_4), and concentrated to provide a dark brown oil which was purified by preparative liquid chromatagraphy (hexanes/chloroform, 1:9) to afford [3-[[4-(2-methoxyphenyl)-1-piperazinyl]methyl]phenyl]phenylmethanone as a brown oil (19.4 g, 93%): ^{1}H NMR ($CDCl_3$) δ 7.87–6.90 (m, 9H, phenyl H), 7.04–6.78 (m, 4H, phenyl H), 3.85 (s, 3H, OCH_3), 3.67 (s, 1H, piperazinyl CH_2), 3.18–3.00 (br s, 4H, piperazine H), 2.75–2.60 (m, 4H, piperazine H).

To a solution of this material (3.00 g, 7.76 mmol) in ethanol (75 mL) was added sodium borohydride (0.35 g, 9.31 mmol). After 36 h, additional sodium borohydride (0.07 g) was added and stirring was continued for another 18 h. After cooling in an ice bath, 1 N HCl (11 mL) was added, and the resulting suspension was basified with solid K_2CO_3. This mixture was extracted with chloroform; the organic extracts were combined, dried (Na_2SO_4), and concentrated to provide **44** as a white foam (2.84 g). This material was dissolved in methanol and perchloric acid (1.2 mL) was added. The solution was triturated with ethyl ether, and the resultant solid was recrystallized from methanol/ethyl ether to afford **44**·2$HClO_4$·H_2O (1.45 g, 31%) as a cream-colored powder: mp 198–210 °C; ^{1}H NMR (D_2O) δ 7.41–7.27 (m, 9H, phenyl H), 7.08–6.87 (m, 4H, phenyl H), 5.82 (br s, 1H, phenyl CHO-), 4.26 (s, 2H, piperazinyl CH_2), 3.73 (s, 3H, OCH_3), 3.28 (br m, 8H, piperazinyl H). Anal. ($C_{25}H_{28}N_2O_2$·2$HClO_4$·H_2O) C, H, N, Cl.

3-[[4-(2-Methoxyphenyl)-1-piperazinyl]methyl]-α-methyl-α-ethylbenzenemethanol Hemifumarate (45). To an ice-cooled solution of **52** (20.0 g, 0.0649 mol) in THF (750 mL) was added a solution of methylmagnesium bromide in ether (65.0 mL, 3.0 M) under nitrogen. The solution was slowly warmed to 25 °C and then brought to reflux. After 8 h of reflux, the reaction mixture was cooled to 0 °C, 6 N HCl solution (600 mL) was added, and the reaction mixture was stirred at ambient temperature for 15 h. The reaction mixture was washed with ether, and the aqueous layer was basified with K_2CO_3 and then extracted with chloroform. The organic extracts were combined, dried (Na_2SO_4), and concentrated to provide a dark brown oil, which was purified by liquid chromatography (hexanes/chloroform, 1:9) to afford methyl ketone **54** (16.0 g, 76%) as a brown oil: ^{1}H NMR ($CDCl_3$) δ

7.97–7.40 (m, 4H, phenyl H), 7.02–6.83 (m, 4H, phenyl H), 3.85 (s, 3H, OCH_3), 3.62 (s, 1H, piperazinyl CH_2), 3.19–3.00 (br s, 4H, piperazine H), 2.72–2.60 (br s, 4H, piperazine H), 2.61 (s, 3H, CH_3CO).

A solution of **54** (4.20 g, 12.9 mmol) in THF (150 mL) was cooled to −78 °C under nitrogen, and a solution of ethylmagnesium bromide in ether (8.6 mL, 3.0 M) was added. After stirring at −78 °C for 2 h, the reaction mixture was slowly warmed to 25 °C. After 15 h of reflux, the reaction mixture was then cooled to 0 °C, and saturated aqueous sodium bicarbonate was added. The resulting solution was then extracted with chloroform (three times); the organic extracts were combined, dried (Na_2SO_4), and concentrated. The residue was purified on flash silica gel (hexanes/chloroform, 1:10–1:25) to afford a brown oil which was repurified by flash column chromatography on silica gel (hexanes/chloroform, 1:10, to MeOH/chloroform, 1:30) to provide a brown oil (2.35 g). This material was dissolved in MeOH, and fumaric acid (0.66 g) was added followed by trituration with ethyl ether. The resultant solid was recrystallized from acetone/ethyl ether to afford **45**·0.5fumarate (1.62 g, 30%) as a white powder: mp 178.5–179.5 °C; ^1H NMR (CD_3OD) δ 7.55–7.34 (m, 4H, phenyl H), 7.05–6.91 (m, 4H, phenyl H), 6.66 (s, 2H, fumarate vinyls), 4.09 (s, 2H, piperazinyl CH_2), 3.84 (s, 3H, OCH_3), 3.19–3.11 (br m, 8H, piperazinyl H), 1.83 (q, J = 7.4 Hz, 2H, CH_2Me), 1.53 (s, 3H, CH_3), 0.77 (t, J = 7.4 Hz, 3H, CH_3). Anal. ($C_{22}H_{30}N_2O_2$·0.5$C_4H_4O_4$) C, H, N.

Binding Studies. All assays were carried out in duplicate with one to five concentration–response curves determined for each agent as previously described.[10] The variability was generally <10%. The membrane preparations and binding studies followed the method of Shank et al.[23]

Preparation of Membranes from Rat Brain Cortex and Striatum. Rats (Charles River, male, Wistar) were received at 5–6 weeks of age (110–140 g body wt) in filtered crates from Kingston, NY. The rats were group-housed for 1–4 weeks in a temperature- and humidity-controlled room and given food (Wayne Lab Blox) *ad libitum*. Water was given *ad libitum* through an automatic water system. Animals had equal hours (12–12) of dark and light. Each rat (150–200 g body wt, 7–12 weeks of age) was killed by cervical dislocation, and the brain was immediately excised. The cerebral cortex and corpus striatum were dissected out, weighed, and homogenized separately in 20 or 40 vol of 5 mM Na-HEPES-buffered sucrose (0.3 M) solution (pH 7.5 at 37 °C), using a motor-driven Teflon pestle fitted to a glass tube with a tolerance of 0.25 mm. The homogenate was centrifuged (4–8 °C) at 1000*g* for 10 min, and the resulting supernatant was centrifuged at 48000*g* for 10 min. The pellet that formed (P_2 fraction) was resuspended in 20 vol of 3 mM K_2PO_4–KH_2PO_4 solution (pH 7.5 at 23 °C, used in all assays) with an Ultra-turrax (Janke & Kunkel) homogenizer and then incubated for 30 min at 25 °C. Each suspension was centrifuged at 42000*g* for 10 min, and the resulting sediment was resuspended in either 30 vol (cerebral cortex) or 50 vol (corpus striatum) of the 3 mM phosphate-buffered solution.

D_2 Affinity. Binding was determined using membranes prepared from rat striatum. The receptor was labeled with 0.05 nM [^3H]spiperone by incubation at 37 °C for 45 min. Nonspecific binding was determined using 1 μM haloperidol. Under these conditions, specific binding constituted 75% of total binding, and the K_i values for some known drugs were 0.37 nM for haloperidol and 82 nM for clozapine. The data from this assay were analyzed by calculating the percent inhibition of the tritiated ligands by given concentrations of the test compound. K_i values were obtained from the logit analysis of concentration–inhibition curves. The results of the logit analysis (ED_{50}) were converted to K_i values using the Cheng–Prusoff equation.[24]

5-HT_{1A} Affinity. Binding was determined using membranes prepared from rat cerebral cortex. The receptor was labeled with 3 nM [^3H]-8-hydroxydipropylaminotetralin (8-OH-DPAT) by incubation at 25 °C for 20 min. Nonspecific binding was determined using 1 μM serotonin.

α_1-Adrenergic Affinity. Binding was determined using membranes prepared from rat cerebral cortex. The receptor was labeled with 0.06 nM [^3H]prazosin by incubation at 25 °C for 20 min. Nonspecific binding was determined using 10 μM norepinephrine.

Conditioned Avoidance Response. This test was modified from that described by Martin et al.[8] Trained rats were run in a 1 h session on two consecutive days. Animals had access to food and water up until being placed in the test chambers. The test consisted of 60 discrete trials spaced at 1/min, with four animals being used for each compound. The conditioned stimuli (paired light and tone) were presented for 15 s followed by 5 s of foot shock (0.7 mA delivered via the metal grid floor) in the absence of a lever press. The animal could also escape the shock by pressing the lever during the 5 s shock interval. Only animals that exhibited >90% CAR on day 1 were given the test compound on day 2.

References

(1) (a) Tamminga, C. A., Schulz, S. C., Eds. *Advances in Neuropsychiatry and Psychopharmacology, Volume I: Schizophrenia Research*; Raven Press: New York, 1991. (b) Meltzer, H. Y. *Psychopharmacology: The Third Generation of Progress*; Raven Press: New York, 1987. (c) Reynolds, G. P. Developments in the Drug Treatment of Schizophrenia. *Trends Pharmacol. Sci.* **1992**, *13*, 116–121. (d) Tricklebank, M. D.; Bristow, L. J.; Hutson, P. H. Alternative Approaches to the Discovery of Novel Antipsychotic Agents. *Prog. Drug Res.* **1992**, *38*, 299–336.

(2) (a) West, S. A.; Nemeroff, C. B. Atypical Antipsychotic Drugs: Current Status and Future Directions. *Drugs Today* **1993**, *29*, 183–188. (b) Meltzer, H. Y.; Gudelsky, G. A. *Arzneim.-Forsch.* **1992**, *42*, 268–272. (c) The toxicity of clozapine can be ameliorated by the addition of ascorbic acid; see: Fischer, V.; Haar, J. A.; Greiner, L.; Lloyd, R. V.; Mason, R. P. *Mol. Pharmacol.* **1991**, *40*, 846.

(3) (a) Janssen, P. A. J.; Niemegeers, C. J. E.; Awouters, F.; Schellekens, K. H. L.; Megens, A. A. H. P.; Meert, T. F. Pharmacology of Risperidone (R 64766), a New Antipsychotic With Serotonin-S_2 and Dopamine-D_2 Antagonistic Properties. *J. Pharmacol. Exp. Ther.* **1988**, *244*, 685–693. (b) Leysen, J. E.; Gommeren, W.; Eens, A.; De Chaffoy De Courcelles, D.; Stoof, J. C.; Janssen, P. A. J. Biochemical Profile of Risperidone, A New Antipsychotic. *J. Pharmacol. Exp. Ther.* **1988**, *247*, 661–670. (c) Staff. Risperidone. *Drugs Future* **1988**, *13*, 1052–1055.

(4) Lowe, J. A., III. Atypical Antipsychotics Based on the D_2/5-HT_2 Ratio Hypothesis. *Curr. Med. Chem.* **1994**, *1*, 50–61 and references cited therein.

(5) Abou-Gharbia, M.; Ablordeppey, S. Y.; Glennon, R. A. Sigma Receptors and Their Ligands: The Sigma Enigma. *Annu. Reps. Med. Chem.* **1993**, *28*, 1–10.

(6) Meltzer, H. Y.; Nash, J. F. Effects of Antipsychotic Drugs on Serotonin Receptors. *Pharmacol. Rev.* **1991**, *43*, 587–604.

(7) (a) Neal-Beliveau, B. S.; Joyce, J. N.; Lucki, I. Serotonergic Involvement in Haloperidol-Induced Catalepsy. *J. Pharmacol. Exp. Ther.* **1993**, *265*, 207–217. (b) Wadenberg, M. L.; Ahlenius, S. Antipsychotic-Like Profile of Combined Treatment With Raclopride and 8-OH-DPAT in the Rat: Enhancement of Antipsychotic-Like Effects Without Catalepsy. *J. Neural Transm.* **1991**, *83*, 43–53. (c) Hicks, P. B. The Effect of Serotonergic Agents on Haloperidol-Induced Catalepsy. *Life Sci.* **1990**, *47*, 1609–1615. (d) McMillen, B. A.; Scott, S. M.; Davanzo, E. A. Reversal of Neuroleptic-Induced Catalepsy by Novel Aryl-Piperazine Anxiolytic Drugs. *J. Pharm. Pharmacol.* **1988**, *40*, 885–887.

(8) Martin, G. E.; Elgin, R. J., Jr.; Mathiasen, J. R.; Davis, C. B.; Kesslick, J. M.; Baldy, W. J.; Shank, R. P.; DiStefano, D. L.; Fedde, C. L.; Scott, M. K. Activity of Aromatic Substituted Phenylpiperazines Lacking Affinity for Dopamine Binding Sites in a Preclinical Test of Antipsychotic Efficacy. *J. Med. Chem.* **1989**, *32*, 1052–1056.

(9) Martin, G. E.; Elgin, R. J., Jr.; Kesslick, J. M.; Baldy, W. J.; Mathiasen, J. R.; Shank, R. P.; Scott, M. K. Block of Conditioned Avoidance Responding in the Rat by Substituted Phenylpiperazines. *Eur. J. Pharmacol.* **1988**, *156*, 223–229.

(10) Scott, M. K.; Martin, G. E.; DiStefano, D. L.; Fedde, C. L.; Kukla, M. J.; Barrett, D. L.; Baldy, W. J.; Elgin, R. J., Jr.; Kesslick, J. M.; Mathiasen, J. R.; Shank, R. P.; Vaught, J. L. Pyrrole Mannich Bases as Potential Antipsychotic Agents. *J. Med. Chem.* **1992**, *35*, 552–558.

(11) Reitz, A. B.; Scott, M. J. Novel Antipsychotics with Unique D_2/5-HT_{1A} Affinity and Minimal Extrapyramidal Side-Effect Liability. In *Advances in Medicinal Chemistry*; Maryanoff, B. E., Maryanoff, C. A., Eds.; Jai Press: New York, 1995; in press.

(12) Reitz, A. B.; Bennett, D. J.; Blum, P. S.; Codd, E. E.; Maryanoff, C. A.; Ortegon, M. E.; Renzi, M. J.; Scott, M. K.; Shank, R. P.; Vaught, J. L. A New Arylpiperazine Antipsychotic with High D_2/D_3/5-HT_{1A}/α_{1A}-Adrenergic Affinity and a Low Potential for Extrapyramidal Effects. *J. Med. Chem.* **1994**, *37*, 1060–1062.

(13) Clineschmidt, B. V.; McKendry, M. A.; Papp, N. L.; Pflueger, A. B.; Stone, C. A.; Totaro, J. A.; Williams, M. Stereospecific Antidopaminergic and Anticholinergic Actions of the Enantiomers of (+/-)-1-Cyclopropylmethyl-4-(3-trifluoromethylthio-5H-dibenzo[a,d]cyclo-hepten-5-ylidene)piperidine (CTC), a Derivative of Cyproheptadine. *J. Pharmacol. Exp. Ther.* **1979**, *208*, 460–476.

(14) For other examples of antipsychotics with combined D_2 and 5-HT_{1A} affinity, see: (a) Lowe, J. A., III; Seeger, T. F.; Nagel, A. A.; Howard, H. R.; Seymour, P. A.; Heym, J. H.; Ewing, F. E.; Newman, M. E.; Schmidt, A. W.; Furman, J. S.; Vincent, L. A.; Maloney, P. R.; Robinson, G. L.; Reynolds, L. S.; Vinick, F. J. 1-Naphthylpiperazine Derivatives as Potential Atypical Antipsychotic Agents. *J. Med. Chem.* **1991**, *34*, 1860–1866. (b) Perrone, R.; Berardi, F.; Colabufo, N. A.; Tortorella, V.; Fiorentini, F.; Olgiati, V.; Vanotti, E.; Govoni, S. Mixed 5-HT_{1A}/D_2 Activity of a New Model of Arylpiperazines: 1-Aryl-4-[3-(1,2-dihydronaphthalene-4-yl)-*n*-propyl]piperazines. 1. Synthesis and Structure-Activity Relationships. *J. Med. Chem.* **1994**, *37*, 99–104.

(15) (a) Howard, H. R.; Seeger, T. F. Novel Antipsychotics. In *Annual Reports in Medicinal Chemistry*; Bristol, J. A., Ed.; Academic Press: San Diego, CA, 1993; Vol. 28, Chapter 5, pp 39–47. (b) Cipollina, J. A. *Curr. Opin. Ther. Pat.* **1992**, *2*, 485. (c) Horn, A. S. In *Comprehensive Medicinal Chemistry*; Emmett, J. C., Ed.; Pergamon Press: New York, 1990; Vol. 3, p 229. (d) Kane, J.; Honigfeld, G.; Singer, J.; Meltzer, H. *Arch. Gen. Psychiatry* **1988**, *45*, 789–796. (e) Honigfeld, G.; Patin, J.; Singer, J. *Adv. Ther.* **1984**, *1*, 77–97. (f) Kaiser, C.; Setler, P. E. In *Burger's Medicinal Chemistry*; Wolff, M. E., Ed.; John Wiley & Sons: New York, 1980; Part III, p 859. (g) McDonnell, M. E.; Reitz, A. B. Recent Advances in Antipsychotic Research. *Exp. Opin. Ther. Pat.* **1994**, in press.

(16) Schoetensack, W.; Bruckschen, E. G.; Zech, K. Urapidil. In *New Drugs Annual: Cardiovascular Drugs*; Scriabine, A., Ed.; Raven Press: New York, 1983; Vol. 1, pp 19–48.

(17) Kornblum, N.; Jones, W. J.; Anderson, G. J. A New and Selective Method of Oxidation: The Conversion of Alkyl Halides and Alkyl Tosylates to Aldehydes. *J. Am. Chem. Soc.* **1959**, 4113–4114.

(18) Davidson, A. B.; Weidly, E. Differential Effects of Neuroleptic and Other Psychotropic Agents on Acquisition of Avoidance in Rats. *Life Sci.* **1976**, *18*, 1279–1284.

(19) (a) Cliffe, I. A.; Brightwell, C. I.; Fletcher, A.; Forster, E. A.; Mansell, H. L.; Reilly, Y.; Routledge, C.; White, A. C. (*S*)-*N*-*tert*-Butyl-3-(4-(2-methoxyphenyl)piperazin-1-yl)-2-phenylpropanamide [(*S*)-WAY-100135]: A Selective Antagonist at Presynaptic and Postsynaptic 5-HT_{1A} Receptors. *J. Med. Chem.* **1993**, *36*, 1509–1510. (b) Cliffe, I. A.; Fletcher, A. Advances in 5-HT_{1A} Antagonist Research. *Drugs Future* **1993**, *18*, 631–642.

(20) (a) Seeman, P. Dopamine Receptor Sequences: Therapeutic Levels of Neuroleptics Occupy D_2-Receptors, Clozapine Occupies D_4. *Neuropsychopharmacology* **1992**, *7*, 261–284. (b) Sibley, D. R.; Monsma, F. J., Jr. Molecular Biology of Dopamine Receptors. *Trends Pharmacol. Sci.* **1992**, *7*, 61–69. (c) Seeman, P.; Guan, H.-C.; Van Tol, H. H. M. Dopamine D_4 Receptors Elevated in Schizophrenia. *Nature* **1993**, *365*, 441–445. (d) Sokoloff, P.; Martres, M.-P.; Giros, B.; Bouthenet, M.-L.; Schwartz, J.-C. The Third Dopamine Receptor (D_3) as a Novel Target for Antipsychotics. *Biochem. Pharmacol.* **1992**, *43*, 659–666.

(21) Cortizo, L.; Santana, L.; Ravina, E.; Oralla, F.; Fontenla, J. A.; Castro, E.; Calleja, J. M.; de Ceballos, M. L. Synthesis and Antidopaminergic Activity of Some 3-(Aminomethyl)tetralones as Analogues of Butyrophenone. *J. Med. Chem.* **1991**, *34*, 2242–2247 and references cited therein.

(22) Orazi, O. O.; Corral, R. A. Substitution in the Hydantoin Ring. I. Aminomethylation. *Tetrahedron* **1961**, *15*, 93–99.

(23) Shank, R. P.; Gardocki, J. F.; Schneider, C. R.; Vaught, J. L.; Setler, P. E.; Maryanoff, B. E.; McComsey, D. F. Preclinical Evaluation of McN-5707 as a Potential Antidepressant. *J. Pharmacol. Exp. Ther.* **1987**, *242*, 74.

(24) Cheng, Y.-C.; Prusoff, W. H. Relationship Between the Inhibition Constant (K_i) and the Concentration of Inhibitor Which Causes 50% Inhibition of an Enzymatic Reaction. *Biochem. Pharmacol.* **1973**, *22*, 3099–3108.

JM9407062