Journal of
Medicinal
Chemistry

Volume 41, Number 12 June 4, 1998

Articles

Orally Active Benzamide Antipsychotic Agents with Affinity for Dopamine D_2, Serotonin 5-HT_{1A}, and Adrenergic α_1 Receptors

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Received March 12, 1997

New antipsychotic drugs are needed because current therapy is ineffective for many schizophrenics and because treatment is often accompanied by extrapyramidal symptoms and dyskinesias. This paper describes the design, synthesis, and evaluation of a series of related (aminomethyl)benzamides in assays predictive of antipsychotic activity in humans. These compounds had notable affinity for dopamine D_2, serotonin 5-HT_{1A}, and α_1-adrenergic receptors. The arylpiperazine 1-[3-[[4-[2-(1-methylethoxy)phenyl]-1-piperazinyl]methyl]benzoyl]piperidine (mazapertine, **6**) was chosen because of its overall profile for evaluation in human clinical trials. The corresponding 4-arylpiperidine derivative **67** was also highly active indicating that the aniline nitrogen of **6** is not required for activity. Other particularly active structures include homopiperidine amide **14** and *N*-methylcyclohexylamide **31**.

Schizophrenia is a debilitating disease which inflicts great emotional distress and financial loss on those who suffer from it.[1,2] The first effective antipsychotic drugs such as chlorpromazine (**1**) (Chart 1), introduced in the early 1950s, also produced undesirable effects such as extrapyramidal symptoms and dyskinesias.[3] Eliminating these unwanted effects has been a continuing goal of antipsychotic drug research. The ideal drug would treat both positive (hallucinations, delusions) and negative (apathy, withdrawal) symptoms of the disease.[1c−g] Safer and more effective medication is expected to improve the relatively low rate of patient compliance observed with current therapy.[4]

Marketed antipsychotics antagonize dopamine receptors in the brain, particularly those of the dopamine D_2−D_4 subtypes,[1,5] and there are many different chemical series that have been investigated as putative antipsychotics.[6] Many compounds with antipsychotic activity on the market or in development modulate serotonin (5-HT) receptors.[7,8] Clozapine (**2**) binds with greatest affinity to D_4 receptors at physiologically relevant concentrations,[5a] and risperidone (**3**) displays high affinity for both D_2 and 5-HT_2 receptors.[9] Haloperidol (**4**) is a D_2 blocker that also shows affinity for 5-HT_2 receptors and σ binding sites.[10] Newer antipsychotics such as olanzepine, sertindole, and ziprasidone are useful because of their atypical biological profile

We had reported an earlier series of arylpiperazines which showed affinity for both D_2 and 5-HT_{1A} receptors, from which compound **5** (RWJ-25730) was chosen for further evaluation.[11,12] However, administration of **5** caused deposition of red-colored bodies in the fundus region of dog stomachs, probably due to rapid decomposition via a reverse-Mannich reaction in the presence of aqueous acid ($t_{1/2}$ ca. 80 min at pH 2).[13] Therefore, we embarked on a program involving replacement of the pyrrole ring in **5** with a variety of alternatives, maintaining roughly the same overall relationship of the

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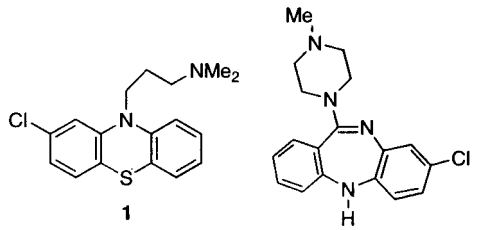
S0022-2623(97)00164-7 CCC: $15.00
Published on Web 05/01/1998

Chart 1



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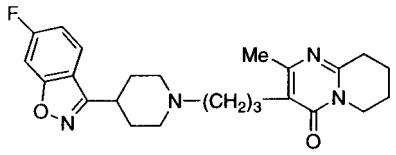

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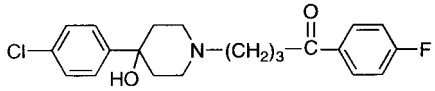

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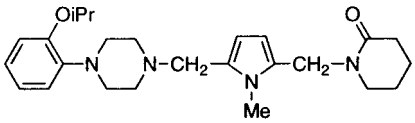
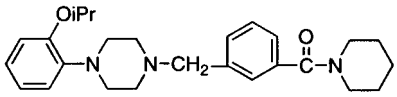


5; RWJ-25730



6; mazapertine, RWJ-37796

amide and arylpiperazine functionalities.[14] During the course of this effort, benzamide **6** (RWJ-37796, mazapertine) was identified. It binds with high affinity to D_2, D_3, D_4, 5-HT_{1A}, and α_1-adrenergic receptors (K_i values < 3 nM) and has potent in vivo activity in animal tests predictive of antipsychotic efficacy in humans.[15] The combination of dopaminergic and 5-HT_{1A} affinity is relatively unique and has been observed in certain other chemical series as well.[16] Both **5** and **6** exhibit a low tendency to produce catalepsy in rats, a measure of their liability for side effects in humans.[17] In this paper we describe new structure−activity studies on compounds related to benzamide **6**, systematically varying each portion of the molecule in order to gain insight into the structural requirements for biological activity.

Synthetic Chemistry

2- and 3-Substituted benzamides were prepared by the method shown in Scheme 1 via reaction of (halomethyl)benzoyl halides with amines to give (halomethyl)benzamides, followed by reaction with the requisite piperazines. The compounds prepared in this manner are listed in Table 1. For the preparation of compound **7**, piperazine itself (10 mol equiv) was used in the reaction sequence. Methyl ether **10** was prepared by reaction of alcohol **9** with methyl iodide. The preparation of 4-fluoro derivative **33** was conducted because the 4-position on the aryl ring was found to be a major site of oxidation during metabolism.[18] The necessary piperazine intermediate to prepare **33** was synthesized as shown in Scheme 2. Commercially available phenol **34** was alkylated with isopropyl bromide to give isopropyl ether **35**. Catalytic reduction of **35** then afforded aniline **36**, which was reacted with bis(chloroethyl)amine yielding piperazine **37**.

Since substituted bicyclic arylpiperazines have consistently exhibited potent serotonergic binding,[16,19] we prepared and evaluated several derivatives of this structural type (viz. **39**−**41** and **43**). The benzodioxane eltoprazine (**38**) (Chart 2) has been reported to have strong 5-HT_{1A} affinity and is a member of a group of compounds investigated as "serenics",[19c,d] which was the reason we prepared derivative **39**. The benzofuranylpiperazine used in the preparation of compound **40** was obtained by a literature procedure.[19b] Since *N*-(1-naphthyl)piperazine has excellent 5-HT_1 receptor affinity,[19a] and substituted derivatives such as compound **42** also have a dopaminergic component to their binding profile,[16g] we synthesized naphthylpiperazine **43**. The *N*-(2-pyrimidinyl)piperazinyl moiety is associated with 5-HT_{1A} receptor affinity mainly because of the anxiolytic buspirone (**44**),[20] and we prepared corresponding congener **45** in our series as well.

Remoxipride (**46**) is an antipsychotic which has a benzamide functionality in its structure.[21] Since we also have a benzamide in lead compound **6**, we incorporated the remoxipride pyrrolidine amide substructure in the design and preparation of derivative **47**. 4-Fluorophenylamide **48** was synthesized as a representative example of *N*-arylamide substitution.

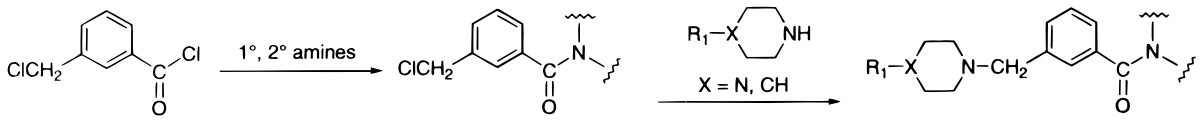
Since the benzyl C−N bond was another major site of metabolism,[18] we attempted to block this metabolism by inserting methyl substitution as shown in Scheme 3. Reductive amination of 3-acetylbenzonitrile with (2-isopropoxyphenyl)piperazine gave **52**, which was then hydrolyzed (NaOH/EtOH) to afford acid **53**. Coupling of **53** with piperidine using dicyclohexylcarbodiimide (DCC) produced α-methyl derivative **54**.

Chain-extended analogues of 4-substituted benzamides were prepared in order to investigate the effects of increasing the distance between the amide carbonyl and the arylpiperazine upon biological activity (Scheme 4). 4-Bromophenethyl bromide was reacted with (2-isopropoxyphenyl)piperazine to give **55**. A palladium-mediated amidation reaction[22] then produced two-carbon spacer derivative **56**. Reaction of 4′-chloro-4-bromobutyrophenone with (2-isopropoxyphenyl)piperazine yielded **57** which was then subjected to the carbonylation reaction to afford **58**. Reduction of **58** sequentially led to alcohol **59** and alkane **60** as shown.

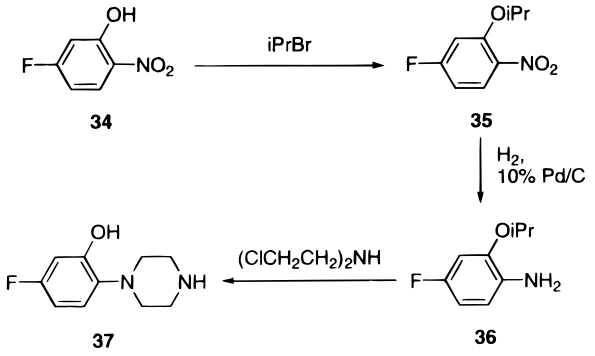
We examined the effects of amide modification by preparing thioamide **61** (Chart 2) from **6** upon treatment with Lawesson's reagent and sulfonamide **62** which was prepared by the standard route (viz. Scheme 1) using 3-($BrCH_2$)$PhSO_2Br$.[23]

4-Arylpiperidine variants were prepared as shown in Scheme 5. 2-Bromophenol was reacted with isopropyl bromide to give ether **63**, which was then converted to the corresponding Grignard reagent and treated with *N*-carbethoxy-4-piperidone to afford **64**. The hydroxyl group of **64** was removed by treatment with 10% Pd/C to give piperidine **65**. Removal of the carbethoxy group under basic conditions afforded **66** which was converted to **67** upon reaction with the appropriate benzyl chlo-

Scheme 1



Scheme 2



ride. Since haloperidol (**4**) has 4-aryl-4-hydroxypiperidine substitution, we wanted to prepare **69** and examine its biological activity. Intermediate **64** was deprotected with KOH/DMSO to give benzyl alcohol **68**, which was then converted to target alcohol **69**.

Structure–Activity Relationships (SAR)

The test compounds were evaluated in the conditioned avoidance response (CAR) assay in rats as the primary in vivo screen for antipsychotic activity (Table 2).[24] This test measures the ability of a compound to lessen the conditioned response to a disagreeable stimulus. CAR testing results are reported as either ED_{50} values for a few selected compounds or percent inhibition at a fixed dose. The animals were either allowed free access to food prior to the experiment or deprived of food for the evening before. The CAR activity (ED_{50} values) for **6** in Table 2 is given both ip and po so that the activity of the other target compounds can be directly compared. The catalepsy test in rats was used as a measure of EPS liability,[17] and data for 13 of the target compounds are given in Table 3. Binding affinity at the D_2, 5-HT_{1A}, and α_{1A}-adrenergic receptors was evaluated in competition experiments against standard radioligands in synaptosomal membrane preparations as described in the Experimental Section.

The need for the aryl moiety of the arylpiperazine found in **6** was demonstrated by the inactivity of derivatives **7**–**10**. The NH compound (**7**) had no in vivo or receptor binding activity, and neither did N-Me congener **8**. Alcohol **9** and ether **10**, which have an oxygen two atoms removed from the piperazine in a manner similar to **6**, were also inactive, clearly establishing the need for the aryl ring for activity. Unsubstituted phenyl derivative **11** had no observed binding at the D_2 receptor but did have 5-HT_{1A} and α_1-adrenergic affinity.

Among the aryl substitutions examined, 2-alkoxyphenyl was the most active. In a homologous series 2-methoxy (**12**), 2-ethoxy (**13**), and 2-isopropoxy (**14**) substitution revealed that increasing the size of the alkoxy group had little effect upon 5-HT_{1A} or α_1 binding but did have a pronounced effect upon D_2 binding and catalepsy production. The series **12**–**14** showed a progression of 201, 57, and 6.3 nM D_2 K_i's and 70.0%, 47.5%, and 27.8% catalepsy at 50 mg/kg ip (60-min pretreatment time). Compounds **12**–**14** were very active in the CAR test. Indeed, the oral activity of **14** is comparable to that of **6**, and **14** even displays greater activity at the longer pretreatment time (120 min). Our SAR program focused primarily on 2-isopropoxyphenyl substitution, although we did examine other 2-substituents as well (**15**–**19**). The electron-withdrawing CF_3, F, Cl, and CN derivatives all showed pronounced binding to the 5-HT_{1A} receptor (<20 nM K_i), but the D_2 affinity was considerably lower (>60 nM K_i) except for **15** which had a 16 nM D_2 receptor K_i. The in vivo activity in CAR for these compounds was less than that seen for **6** or **14**. The 2-propyl derivative (**19**) is noteworthy because it is an analogue of ethoxy compound **13** with the ethoxy oxygen being exchanged for a methylene group. Even though **13** and **19** have somewhat comparable affinities at the three receptors, **19** is devoid of in vivo CAR activity. 3-Substituted arylpiperazines (**20**–**22**) had fair affinity for the 5-HT_{1A} receptor (<25 nM K_i) but very little activity elsewhere. 4-Chlorophenyl analogue **23** had very little activity in any of the tests except for a 121 nM K_i at the 5-HT_{1A} receptor.

The effect of amide modifications was systematically examined. Primary amide **24** had modest activity which was increased upon conversion to cyclic amide structures such as **25** and **26**. As the size of the ring increased from four- to eight-membered (**25**, **26**, **6**, **14**,

Chart 2

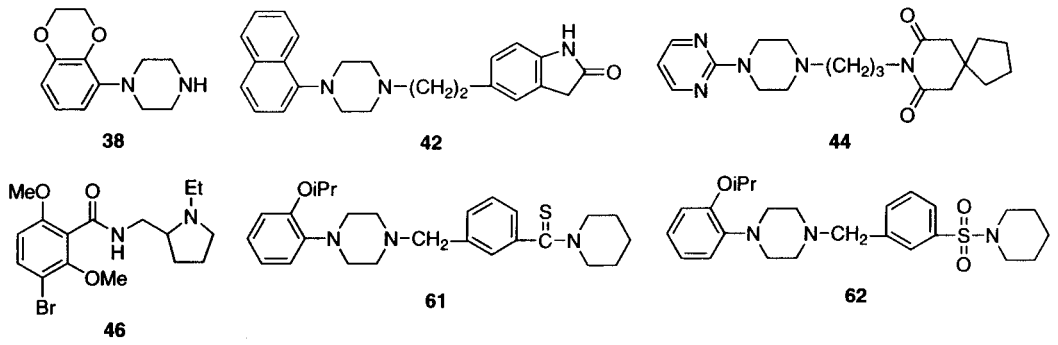
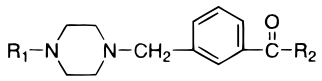
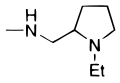


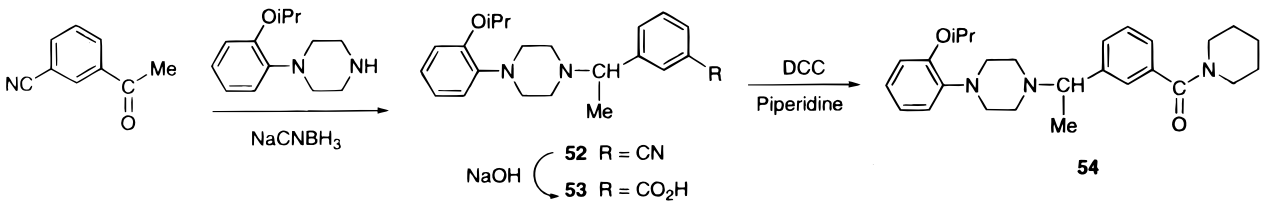
Table 1. 3-(Piperazinylmethyl)benzamides



compd[a]	R_1	R_2	% yield	recrystn solvent	mp (°C)	formula[b]	anal.
6	IPP	*N*-piperidinyl	45	iPrOH/Et_2O	222−227	$C_{26}H_{33}N_3O_2$·1.5HCl	C,H,N,Cl
7	H	*N*-piperidinyl	68	MeOH/Et_2O	189.5−192	$C_{17}H_{25}N_3O$·1.65$C_2H_2O_4$·0.35HCl	C,H,N,H_2O
8	Me	*N*-piperidinyl	21	MeOH/EtOAc	151−152	$C_{18}H_{37}N_3O$·2HNO_3	C,H,N
9	$HO(CH_2)_2$	*N*-homopiperidinyl	37	iPrOH/MeOH	175.5−177.5	$C_{20}H_{31}N_3O_2$·1.8$C_4H_4O_4$(f)·0.3H_2O	C,H,N,H_2O
10	$MeO(CH_2)_2$	*N*-homopiperidinyl	10	iPrOH/MeOH	184−188	$C_{21}H_{33}N_3O_2$·$C_4H_4O_4$(f)·0.25H_2O	C,H,N,H_2O
11	Ph	*N*-piperidinyl	19	MeCN	134−136	$C_{23}H_{29}N_3O$·HCl	C,H,N
12	MPP	*N*-homopiperidinyl	14	iPrOH	196−198	$C_{25}H_{33}N_3O_2$·HCl·1.5H_2O	C,H,N,Cl,H_2O
13	EPP	*N*-homopiperidinyl	30	MeOH/EtOAc	188−190	$C_{26}H_{35}N_3O_2$·HCl	C,H,N,H_2O
14	IPP	*N*-homopiperidinyl	32	iPrOH/Et_2O	212−214	$C_{27}H_{37}N_3O_2$·HCl	C,H,N,Cl
15	2-CF_3Ph	*N*-piperidinyl	48	iPrOH/Et_2O	210−211.5	$C_{24}H_{28}F_3N_3O$·HCl	C,H,N,Cl,F
16	2-FPh	*N*-piperidinyl	82	MeOH/Et_2O	192.5−194.5	$C_{23}H_{28}FN_3O$·$C_2H_4O_2$·0.14H_2O	C,H,N,F,H_2O
17	2-ClPh	*N*-piperidinyl	46	iPrOH/Et_2O	170−174	$C_{23}H_{28}ClN_3O$·HCl	C,H,N,Cl
18	2-CNPh	*N*-piperidinyl	30	MeOH/Et_2O	182−184	$C_{24}H_{28}N_4O$·0.85$C_4H_4O_4$(f)	C,H,N
19	2-PrPh	*N*-piperidinyl	59	MeCN/Et_2O	190.5−192.5	$C_{26}H_{35}N_3O$·HCl	C,H,N,Cl
20	3-CF_3Ph	*N*-piperidinyl	24	iPrOH/Et_2O	207−209	$C_{24}H_{28}F_3N_3O$·HCl·0.3H_2O	C,H,N,H_2O
21	3-ClPh	*N*-piperidinyl	55	EtOAc	183−184	$C_{23}H_{28}ClN_3O$·HCl	C,H,N[c]
22	3-NO_2Ph	*N*-piperidinyl	42	iPrOH	194−197	$C_{23}H_{28}N_4O_3$·$C_4H_4O_4$(f)	C,H,N[d]
23	4-ClPh	*N*-piperidinyl	66	MeOH/Et_2O	172−175	$C_{23}H_{28}ClN_3O$·HCl·0.5H_2O	C,H,N,Cl,H_2O
24	IPP	NH_2	68	CH_2Cl_2	172−175	$C_{21}H_{27}N_3O_2$	C,H,N
25	IPP	*N*-azetidinyl	18	iPrOH/Et_2O	122−124	$C_{24}H_{31}N_3O_2$·$C_4H_4O_4$(m)	C,H,N
26	IPP	*N*-pyrrolidinyl	35	iPrOH/Et_2O	197−199	$C_{25}H_{33}N_3O_2$·1.5HCl	C,H,N,Cl
27	IPP	*N*-heptamethyl-enimine	30	MeOH-Et_2O	172−174	$C_{26}H_{39}N_3O_2$·$C_2H_2O_4$	C,H,N
28	IPP	NEt_2	12	EtOAc	175.5−180	$C_{25}H_{35}N_3O_2$·1.5HCl	C,H,N,Cl
29	IPP	NBu_2	24	iPrOH/Et_2O	163−167	$C_{29}H_{43}N_3O_2$·1.4HCl	C,H,N,Cl
30	IPP	NH(cC_6H_{11})	38	CH_2Cl_2/Et_2O	170−175	$C_{27}H_{37}N_3O_2$·2HCl·H_2O	C,H,N,H_2O[e]
31	IPP	NMe(cC_6H_{11})	10	iPrOH/Et_2O	170−172.5	$C_{26}H_{39}N_3O_2$·$C_4H_4O_4$(f)·0.5C_3H_8O	C,H,N
32	IPP	*N*-morpholinyl	16	MeOH/Et_2O	145−148	$C_{25}H_{33}N_3O_3$·1.85HCl·H_2O	C,H,N,Cl,H_2O
33	4-F-2-(OiPr)Ph	*N*-piperidinyl	32	iPrOH/Et_2O	204−206.5	$C_{26}H_{35}FN_3O_2$·1.5HCl	C,H,N,Cl,F[f]
39	3-benzodioxanyl	*N*-piperidinyl	49	iPrOH/MeOH/Et_2O	150−156	$C_{25}H_{31}N_3O_3$·1.4$HClO_4$	C,H,N,Cl[g]
40	6-benzofuranyl	*N*-piperidinyl	40	iPrOH/Et_2O/hexane	155−158	$C_{25}H_{29}N_3O_2$·HCl·H_2O	C,H,N,Br,H_2O
41	3-(1,2-benzoiso-thiazolyl)	*N*-piperidinyl	52	MeOH/EtOAc	243.5−244	$C_{24}H_{28}N_4OS$·1.1HCl	C,H,N
43	1-naphthyl	*N*-piperidinyl	63	iPrOH/Et_2O	137−140	$C_{27}H_{31}N_3O$·0.8$C_4H_4O_4$(m)	C,H,N
45	2-pyrimidinyl	*N*-piperidinyl	11	iPrOH	107−108	$C_{21}H_{27}N_5O$	C,H,N
47	IPP		10	EtOH/Et_2O	192−195	$C_{28}H_{40}N_4O_2$·2.6HBr·1.5H_2O·0.5EtOH	C,H,N,Br
48	IPP	NH(4-F)Ph	17	MeOH/iPrOH/pentane	149−151	$C_{27}H_{30}FN_3O_2$·1.5HCl	C,H,N,F,Cl[h]
49	IPP		28	MeCN/MeOH	198−199	$C_{29}H_{33}N_3O_2$·$C_2H_2O_4$·0.1H_2O	C,H,N,H_2O
50	IPP		30	EtOH	159−161	$C_{24}H_{31}N_3O_3$·$C_2H_2O_4$	C,H,N
51	IPP		13	iPrOH	131.5−133	$C_{26}H_{33}N_3O_2$·$C_4H_4O_4$(f)	C,H,N

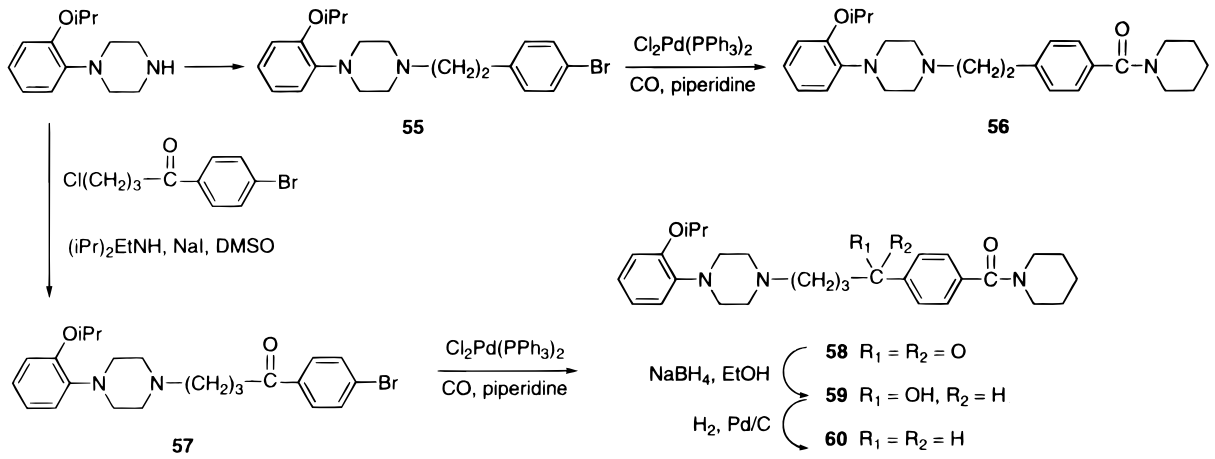
[a] Abbreviations: IPP, (2-isopropoxyphenyl)piperazine; MPP, (2-methoxyphenyl)piperazine; EPP, (2-ethoxyphenyl)piperazine. [b] $C_4H_4O_4$(m) represents maleic acid, $C_4H_4O_4$(f) represents fumaric acid, and $C_2H_2O_4$ represents oxalic acid. Where the formula is given as symbols of elements, the analytical data for the designated elements were within ±0.4% of the calculated values except where otherwise indicated. [c] C: calcd, 63.59; found, 64.22. [d] C: calcd, 61.82; found, 62.40. [e] C: calcd, 61.58; found, 61.07. [f] C: calcd, 63.18; found, 62.59. [g] N: calcd, 7.47; found, 7.03. [h] N: calcd, 8.37; found, 7.95.

Scheme 3

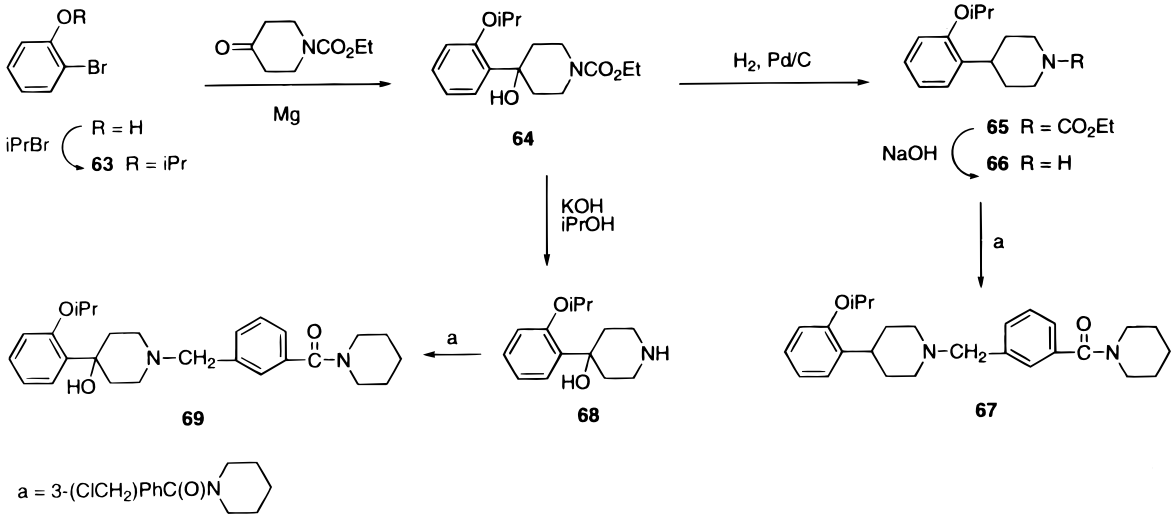


and **27**), there were several trends that became evident. Although all of the compounds have potent in vivo activity, the six-membered ring analogue (**6**) has the greatest D_2 receptor affinity (2.2 nM). As the ring size

Scheme 4



Scheme 5



increases, 5-HT_{1A} affinity increases with a maximum K_i value of 0.13 nM for eight-membered ring congener **27**. There was a large degree of lethality for **26** in the catalepsy test, which precluded its further consideration as a drug candidate. When the ring was opened to afford diethylamide **28** and dibutylamide **29**, good receptor affinity was retained. Surprisingly, **29** is basically inactive in vivo whereas **28** has good activity, but **28** also shows a large induction of catalepsy (76.9% at 50 mg/kg ip). Cyclohexylamide **30** was less active than **6**, whereas much of the activity was restored along with no observed catalepsy when *N*-methyl substitution was added in **31**. However, when administered ip in the CAR test, **31** had little activity at 1 mg/kg, suggesting that it is less active than **6** in that test. Morpholine amide **32** had good in vivo activity at the screening dose but lesser D_2 receptor binding (95 nM K_i). As mentioned earlier, the 4-fluoro derivative of **6** (i.e., **33**) was prepared in order to potentially increase biological duration by retarding metabolism. Compound **33** was somewhat less active in the in vivo test when compared with **6** and had ca. 8 times less D_2 receptor affinity.

Bicycles **39**, **40**, **41**, and **43** all have pronounced 5-HT_{1A} activity, anticipated to some degree by the reported activities of **38** and **42**.[19a–d] The in vivo CAR activity is good except for **43**, which shows very little in vivo activity. An especially intriguing compound is **39** because it displays in vivo activity (−94% at 5 mg/kg ip) with only modest catalepsy but has no D_2 receptor affinity (>1000 nM K_i) and excellent 5-HT_{1A} receptor affinity (0.34 nM K_i). Benzoisothiazolyl congener **41** had a 74.0% level of catalepsy at 50 mg/kg ip. Pyrimidinyl derivative **45** exhibited a 12 nM K_i for the 5-HT_{1A} receptor but was devoid of in vivo activity.

Analogue **47** resembles the antipsychotic benzamides such as remoxipride, but **47** had very little activity. 4-Fluorophenylamide **48** had receptor affinity K_i's in the range of 10−30 nM but had no in vivo activity. Indoline **49** displayed in vivo activity and <4 nM K_i's at 5-HT_{1A} and α_1-adrenergic receptors without observed D_2 receptor affinity. Imide functionality is found in buspirone (**44**) and related derivatives, so we had prepared imides **50** and **51**, both of which were only modestly active in the various tests in which they were examined.

α-Methyl derivative **54** showed considerably less activity than **6** and was not pursued further. Chain-extended analogues **56** and **60** were both active in vivo and in vitro, but less so than the other more active members of the series such as **6**. Thioamide **61** was somewhat less active than amide **6**. Sulfonamide **62** had no in vivo activity but had excellent receptor affinities with K_i's all <10 nM.

Table 2. Conditioned Avoidance Response (CAR) Activity and Receptor Binding Affinity[a]

compd	CAR activity, ED_{50} or inhibition (dose, mg/kg)	route of admin	pretreatment time (min)	fasted/fed	receptor affinity (K_i, nM)		
					D_2	5-HT_{1A}	α_1
5	34.72 mg/kg [31.40, 38.25]	po	60	fed	0.8	3.3	8.2
haloperidol	0.31 mg/kg [0.26, 0.39]	po	60	fed	0.37	>1000	1.0
clozapine	32.5 mg/kg [24.8, 54.3]	po	30	fed	82.0	111	1.4
	9.3 mg/kg [7.4, 11.5]	po	30	fasted			
risperidone				fed	3.1	253	0.81
6	0.66 mg/kg [0.55, 0.78]	ip	30	fed	2.2	1.7	1.3
	14.54 mg/kg [10.22, 20.95]	po	30	fed			
	10.96 mg/kg [8.64, 14.07]	po	60	fed			
	3.35 mg/kg [2.55, 4.76]	po	60	fasted			
	25.99 mg/kg [23.18, 44.37]	po	120	fed			
7	−30.2% (15)	ip	30	fed	>1000	>1000	>1000
8	0.4% (15)	ip	30	fed	>1000	>1000	>1000
9	−2.1% (5)	ip	30	fed	>1000	>1000	>1000
10	ND				>1000	>1000	>1000
11	−2.2% (5)	ip	30	fed	>1000	7.2	44
	−82.1% (15)	ip	30	fed			
12	−94.6% (5)	ip	30	fed	201	0.46	4.7
13	1.26 mg/kg [1.00, 1.55]	ip	30	fed	57	0.71	8.2
14	0.85 mg/kg [0.70, 1.12]	ip	30	fed	6.3	0.6	2.1
	3.32 mg/kg [2.04, 4.89]	po	30	fasted			
	11.86 mg/kg [9.74, 14.74]	po	60	fed			
	15.39 mg/kg [4.04, 31.16]	po	120	fed			
15	−5.5% (5)	ip	30	fed	16	0.8	3.3
	−59.7% (15)	ip	30	fed			
16	−84.3% (15)	ip	30	fed	263	16	27
17	−68.6% (15)	ip	30	fed	77	8.2	16
	−67.9% (5)	ip	30	fed			
18	−5.3% (1)	ip	30	fed	63	2.5	19
	−73.9% (5)	ip	30	fed			
	−5.4% (20)	po	60	fed			
19	−0.7% (15)	ip	30	fed	38	9.1	16
20	−3.7% (5)	ip	30	fed	682	2.3	562
	−71.6% (15)	ip	30	fed			
21	−36.1% (5)	ip	30	fed	347	1.2	11.4
	−27.9% (20)	po	60	fed			
22	−1.3% (5)	ip	30	fed	>1000	24	>1000
	−77.7% (15)	ip	30	fed			
23	−4.7% (15)	ip	30	fed	>1000	121	486
24	−3.0% (1)	ip	30	fed	146	18	11.4
	−88.5% (5)	ip	30	fed			
	−1.1% (20)	po	60	fed			
25	−87.0% (15)	ip	30	fed	13	3.4	1.2
26	−44.8% (1)	ip	30	fed	35	3.6	1.9
	−98.3% (7.5)	ip	30	fed			
	−79.4% (13.4)	ip	30	fed			
27	−24.5% (1)	ip	30	fed	5.3	0.6	1.9
	−90.4% (5)	ip	30	fed			
	−84.7% (20)	po	60	fed			
28	−65.1% (1)	ip	30	fed	14	2.1	4.4
	−60.0% (2.5)	ip	30	fed			
	−44.4% (2.5)	ip	240	fed			
	−96.2% (5)	ip	30	fed			
	−94.5% (15)	ip	30	fed			
	−93.4% (20)	po	60	fed			
	−44.6% (20)	po	240	fed			
29	−5.6% (15)	ip	30	fed	16	0.8	3.3
30	−86.2% (15)	ip	30	fed	47	4.1	3.4
	−17.6% (5)	ip	30	fed			
31	−9.3% (1)	ip	30	fed	5.4	1.2	1.2
	−98.9% (5)	ip	30	fed			

Table 2. (Continued)

compd	CAR activity, ED_{50} or inhibition (dose, mg/kg)	route of admin	pretreatment time (min)	fasted/fed	receptor affinity (K_i, nM) D_2	$5\text{-}HT_{1A}$	α_1
32	−94.5% (1)	ip	30	fed	95	3.2	29
	−95.4% (5)	ip	30	fed			
	−96.2% (20)	po	60	fed			
33	−22.6% (1)	ip	30	fed	19	4.2	6.0
	−82.6% (5)	ip	30	fed			
39	−2.6% (1)	ip	30	fed	>1000	0.34	21
	−93.8% (5)	ip	30	fed			
	−68.2% (20)	po	30	fed			
40	−82.4% (5)	ip	30	fed	15	0.21	13
41	−89.6% (5)	ip	30	fed	41	2.5	2.7
43	−18.8% (15)	ip	30	fed	124	1.8	57
45	−17.9% (5)	ip	30	fed		12	
	−6.8% (15)	ip	30	fed			
47	−19.4% (5)	ip	30	fed	>1000	121	486
	−74.9% (15)	ip	30	fed			
48	−2.5% (15)	ip	30	fed	30	11	11
49	−1.6% (1)	ip	30	fed	>1000	3.4	1.7
	−1.4% (10)	po	60	fed			
	−95.8% (15)	ip	30	fed			
50	−9.6% (1)	ip	30	fed	158	3.3	388
	−94.5% (5)	ip	30	fed			
	−1.6% (20)	po	60	fed			
51	−11.2% (5)	ip	30	fed	39	3.9	6.4
	−92.4% (15)	ip	30	fed			
54	−7.1% (15)	ip	30	fed	122	>1000	87
56	−1.1% (1)	ip	30	fed	24	2.5	2.1
	−98.2% (15)	ip	30	fed			
60	−95.3% (15)	ip	30	fed	16	16	284
61	−71.6% (5)	ip	30	fed	20	1.1	2.3
62	−6.7% (5)	ip	30	fed	1.1	1.1	6.7
67	0.75 mg/kg [0.48, 1.18]	ip	30	fed	0.9	0.9	2.2
	7.69 mg/kg [5.50, 10.30]	po	60	fed			
	7.93 mg/kg [4.30, 16.63]	po	240	fed			
69	0.9% (5)	ip	30	fed	37	>1000	110

[a] Conditioned avoidance response (CAR) testing in rats was performed as described in the Experimental Section, and the 95% confidence limits for ED_{50} values are listed in brackets. Data listed for **5** and the reference compounds were taken from refs 9 and 15.

Arylpiperidine **67** was essentially as active as **6** and had slightly greater D_2 and $5\text{-}HT_{1A}$ receptor affinity (0.95 nM K_i's) with a relatively low level of catalepsy. This finding demonstrates that the arylpiperazine nitrogen of **6** is not needed for biological activity. Corresponding hydroxypiperidine **69** was not active in vivo, with only moderate D_2 receptor binding and no $5\text{-}HT_{1A}$ affinity. Unlike haloperidol (**4**), hydroxypiperidine substitution had greatly reduced activity in this series.

As a result of our ongoing evaluation of putative antipsychotics described in this paper, compound **6** was chosen for clinical evaluation as the succinate salt (mazapertine succinate). In addition to the data reported elsewhere for **6**,[15] it has a 7.6 nM K_i for the D_4 receptor, with no detectable binding (>5000 nM K_i's) at α-adrenergic, $GABA_A$, $GABA_B$, norepinephrine, and serotonin uptake sites and the NMDA ion channel.

There was 32.4% catalepsy when **6** was administered at 50 mg/kg ip, a dose 75 times higher than that required for activity in the CAR test in rat (0.66 mg/kg ED_{50} ip). It is reasonable to propose that this separation between efficacy and the undesired catalepsy may be due to the $5\text{-}HT_{1A}$ receptor affinity, as it has been reported that $5\text{-}HT_{1A}$ agonists reverse neuroleptic-induced rat catalepsy production.[25] Further, $5\text{-}HT_{1A}$ partial agonists are known to improve the extrapyramidal symptoms and tardive dyskinesias induced by haloperidol (**4**) and other typical neuroleptics in humans.[26] Even though **6** inhibited reciprocal forepaw treading,[15] it is possible that the compound is a $5\text{-}HT_{1A}$ partial agonist since very few structures act as antagonists at both pre- and postsynaptic $5\text{-}HT_{1A}$ receptors.[27] The α_1-adrenergic binding component of the profile of clozapine may contribute to its favorable separation of therapeutic from extrapyramidal effects.[28] In the same manner, the α_1-adrenergic affinity seen for **6** may play a role in its favorable therapeutic index in preclinical models.

The log *P* of compound **6** was experimentally determined to be 3.85 at pH 7.3 which suggests reasonable blood−brain barrier penetration.[29] The first pK_a was found to be 6.95, so that slightly less than half would be expected to be protonated in the blood. Compound **6** was evaluated by X-ray structure analysis and found to be in an extended, bent conformation in the solid state (Figure 1). The piperazine ring resides in a chair conformation, and the amide functionality is skewed with respect to the middle aromatic ring. The 2-isopropoxyphenyl ring is ca. 35° out of plane with respect to the adjacent piperazine ring.[30] The monosuccinate salt adopts the unusual crystal habit of one dianionic succinate and one succinate in the fully protonated form associated in a 1:1 complex with mazapertine by hydrogen bonding.

Table 3. Catalepsy Data[a]

compd	dose (mg/kg)	route of admin	pretreatment time (min)	catalepsy (%)
6	50	ip	60	32.4
	50	ip	240	47.9
12	50	ip	60	70.0
13	50	ip	60	47.5
14	50	ip	60	27.8
	50	ip	240	24.1
	100	ip	240	0 (3.5L)
	250	po	60	32.5
	250	po	240	15.5
21	50	ip	60	21.8
	50	ip	240	33.9
26	50	ip	60	0 (3/5L)
	50	ip	240	0 (4/5L)
27	50	ip	60	34.4
	50	ip	240	17.6
28	50	ip	60	76.9
	50	ip	240	36.8
31	50	ip	60	0.0
	50	ip	240	58.1
33	50	ip	60	45.2
	50	ip	240	50.0
39	50	ip	60	29.0
41	50	ip	60	74.0
67	50	ip	60	26.3 (1/5L)

[a] Catalepsy was evaluated in rats as described in the Experimental Section. Lethality, where observed, is indicated in the catalepsy (%) column. For example, (3/5L) means that three out of five rats died during the course of the experiment.

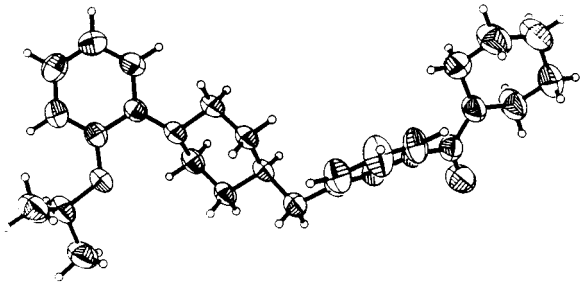


Figure 1. X-ray crystal structure of mazapertine (**6**) succinate (salt not shown).

Summary

The compounds described here provide the basis for direct comparison of a large number of related derivatives directed toward the discovery of new and safer antipsychotic drugs for clinical use. Certain compounds in the series show notable selectivity for the 5-HT_{1A} receptor such as the benzodioxanyl derivative **39**. 2-Alkoxyphenyl substitution on the arylpiperazine was preferred, such as in compounds **12**−**14**. There is a large tolerance for amide substitution, with homopiperidine **14** showing a high level of in vivo (ip and po) activity. The *N*-methylcyclohexylamide **31** was also very active. Larger amide derivatives, such as in **27**, resulted in a higher 5-HT_{1A} affinity. The significant lack of catalepsy for **6** could be due to its unusual receptor binding profile which includes large 5-HT_{1A} and α_{1A} binding components. Since modulation of the serotonergic system (e.g., 5-HT_{1A}) has been shown to ameliorate the motor discoordination associated with current neuroleptics in rats and humans, it is reasonable to imagine that having both D_{2-4} and 5-HT_{1A} affinities in a compound such as mazapertine would be beneficial.

Experimental Section

General Procedures. ^{1}H NMR spectra were recorded on either a Varian 390 (90 MHz), Bruker AC-300 (300 MHz), or Bruker AM-400 (400 MHz) spectrometer. For the NMR work, DMSO-d_6 was used as solvent unless otherwise noted, and tetramethylsilane (TMS) was used as an internal standard. Elemental analyses were obtained primarily by Galbraith Laboratories (Knoxville, TN) and Robertson Microlit, Madison, NJ. Melting points were determined in open capillary tubes with a Thomas-Hoover apparatus and are corrected. 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) 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 nA, was used for the FAB analysis. Where elemental analyses are reported by symbols of elements in the Experimental Section, the results are within 0.4% of the calculated values. The X-ray crystal structure analysis was obtained by the Crystalytics Co. of Lincoln, Nb. Most reagents and solvents were purchased and used without further purification.

1-[3-[[4-(2-Isopropoxyphenyl)-1-piperazinyl]methyl]-benzoyl]piperidine 1.5Hydrochloride (6). A solution of 3-(chloromethyl)benzoyl chloride (6 mL, 42.3 mmol) in 70 mL of THF was treated with diisopropylethylamine (33.1 mL, 0.19 mol). This solution was cooled to −78 °C and treated with piperidine (4.18 mL, 42.3 mmol) over a period of 2 min. After 5 min, the ice bath was removed, and the solution was allowed to warm to ambient temperature. After a total of 1 h, (2-isopropoxyphenyl)piperazine fumarate (14.45 g, 43 mmol) was added. The solution was stirred at ambient temperature overnight and then at reflux for 7 h and cooled to ambient temperature, followed by the addition of water and methylene chloride. The organic layer was withdrawn, dried ($MgSO_4$), and filtered. The product was purified on silica gel (EtOAc/hexane, 6:4), dissolved in ^{i}PrOH, treated with concentrated HCl (ca. 2.5 mL), and then triturated with ethyl ether. The resultant solid was recrystallized from ^{i}PrOH/ethyl ether to give 9.1 g (45%) of **6** as a white powder: mp 222−227 °C; FAB-MS (thioglycerol) *m/e* 422 (MH^+); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (d, 6H), 1.58 (br s, 2H), 1.70 (br s, 4H), 3.32 (br s, 2H), 3.4−3.6 (m, 5H), 3.7 (br s, 3H), 4.2 (br s, 4H), 4.68 (m, 1H), 6.92 (m, 2H), 7.18 (m, 1H), 7.48 (m, 3H), 7.60 (s, 1H), 7.96 (d, 1H). Anal. ($C_{26}H_{35}N_3O_2$·1.5HCl) C, H, N, Cl.

Other compounds listed in Table 1 were prepared in a like manner from the appropriate amine component and the piperazine or piperidine counterpart. The requisite piperazines were either commercially available or prepared as described in the literature. In addition to the sesquihydrochloride salt of **6**, a variety of other salt forms of this compound have been prepared. The X-ray crystal structure determination was conducted on **6** as the succinate salt (Figure 1).

4-Fluoro-2-isopropoxy-1-nitrobenzene (35). A suspended orange mixture of 5-fluoro-2-nitrophenol (**34**; 10.0 g, 63.6 mmol), potassium carbonate (8.84 g, 64.0 mmol), and 2-bromopropane (6.00 mL, 63.6 mmol) in dimethylformamide (63.0 mL) was stirred at 22 °C under argon. After 1 day, an additional 2.0 mL of 2-bromopropane was added and the resultant mixture was heated at 60 °C for 1 day. The reaction mixture was then partitioned between methylene chloride and 3 N NaOH. The organic layer was separated, and the basic aqueous layer was extracted with additional methylene chloride. The combined organic solution was washed with water (5 × 200 mL), dried ($MgSO_4$), filtered, and concentrated to provide 12.02 g (95%) of an orange oil, 95% pure by GC, which was carried on without further purification: FAB-MS *m/e* 200 (MH^+); ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.30 (d, J = 6.0 Hz, 6H), 4.60 (septet, J = 6.0 Hz, 1H), 6.50−6.90 (m, 2H), 7.70−8.00 (m, 1H).

4-Fluoro-2-isopropoxyaniline (36). A solution of **35** (9.50 g, 45.3 mmol) and 10% palladium on carbon (0.50 g) in absolute ethanol (100 mL) was shaken on a Parr apparatus under 53 psig of hydrogen at 22 °C for 2 h. The reaction was then

filtered over Celite, diluted with chloroform, dried ($MgSO_4$), filtered, and concentrated to afford 8.37 g of **36** as a purple oil, 97% pure by GC, which was carried on without further purification: EI-MS *m/e* 169 (M^+); ^1H NMR (90 MHz, $CDCl_3$) δ 1.30 (d, J = 6.0 Hz, 6H), 3.50−3.70 (br s, 2H), 4.50 (septet, J = 6.0 Hz, 1H), 6.30−6.70 (m, 3H).

1-(4-Fluoro-2-isopropoxyphenyl)piperazine (37). A crude solution of **36** (8.35 g, 47.9 mmol) prepared as described above, bis(2-choroethyl)amine hydrochloride (12.83 g, 71.9 mmol), and triethylamine (10.00 mL, 71.7 mmol) in chlorobenzene (70 mL) was heated at reflux for 25 h. The dark-brown reaction mixture was then partitioned between 3 N NaOH and methylene chloride. The organic layer was separated, dried ($MgSO_4$), filtered, and concentrated to yield 15.9 g of **37** as a brown oil. This crude free base was dissolved in MeOH, treated with fumaric acid (5.25 g), and diluted with ether. The monofumarate salt precipitated, was collected by filtration, and was dried in a vacuum oven at 60 °C to furnish 11.38 g of a brown solid of **37**, which was used without further purification: CI-MS *m/e* 239 (MH^+); ^1H NMR (90 MHz, CD_3OD) δ 1.30 (d, J = 6.0 Hz, 6H), 3.00−3.40 (m, 8H), 4.60 (septet, J = 6.0 Hz, 1H), 6.50−7.00 (m, 5H).

1-[3-[[4-(2-Isopropoxyphenyl)-1-piperazinyl]methyl]-benzoyl]-2-piperidone Fumarate (51). A solution of 2-piperidinone (10.0 g, 0.101 mol) and pyridine (16.35 g, 0.207 mol) in benzene (300 mL) was cooled in an ice bath and treated dropwise over 5 min with 3-(chloromethyl)benzoyl chloride (19.2 g, 0.102 mol). The resulting mixture was stirred overnight at ambient temperature. Water (300 mL) was then added, and the organic layer was separated, washed with 1 N HCl (200 mL) and three 200-mL portions of water, dried ($NaSO_4$), filtered, and concentrated to give 16.5 g of a yellow oil. Addition of ether with cooling afforded 7.25 g of a cream-colored crystalline solid. The ^1H NMR was consistent with the structure being *N*-[3-(chloromethyl)benzoyl]-2-piperidone. A mixture of the intermediate prepared above (6.25 g, 0.025 mol), (2-isopropoxyphenyl)piperazine fumarate (8.40 g, 0.025 mol), potassium iodide (4.50 g, 0.027 mol), triethylamine (9.57 g, 0.095 mol), and *N*-methyl-2-pyrrolidinone (50 mL) was stirred for 5.5 h at ambient temperature, treated with water (250 mL), and extracted into ethyl ether (100 mL). The organic layer was separated, dried (Na_2SO_4), filtered, and concentrated to give 6.3 g of an orange oil. This material was purified on 200 g of flash silica gel (1:1 EtOAc/methylene chloride) to give 3.40 g of **51** (free base) as a clear oil. Treatment of the oil with fumaric acid (0.90 g) in ^{i}PrOH (20 mL) produced a white solid which was recrystallized from ^{i}PrOH affording 1.80 g (13%) of **51** as a white powder: mp 131.5−133 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 1.25 (d, 6H), 1.89 (m, 4H), 2.50 (m, 2H), 2.60 (s, 4H), 3.00 (s, 4H), 3.66 (s, 2H), 3.71 (m, 2H), 4.58 (q, 1H), 6.90 (d, 4H), 7.40 (m, 1H), 7.46 (m, 2H), 7.52 (s, 1H). Anal. ($C_{26}H_{33}N_3O_3 \cdot C_4H_4O_4$) C, H, N.

3-[[4-(2-Isopropoxyphenyl)-1-piperazinyl]-1-ethyl]benzonitrile (52). A mixture of (2-isopropoxyphenyl)piperazine (7.28 g, 33 mmol), 3-acetylbenzonitrile (4.80 g, 33 mmol), and titanium isopropoxide (11.74 g, 41 mmol) was stirred at room temperature for 2 h, heated to 80 °C for several minutes, and then cooled to room temperature. Methanol (150 mL) was added, and the mixture was heated to dissolve most of the solids. After cooling to room temperature, sodium borohydride (2.27 g, 60 mmol) was added in portions and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated on a rotary evaporator, and the residue was partitioned between 3 N NaOH and CH_2Cl_2. The organic layer was separated, dried (K_2CO_3), filtered, and evaporated to an oily residue which was passed through flash grade silica gel using 4:1 hexane/EtOAc as eluant to give **52** as an oil (1.55 g, 13.5%): ^1H NMR (300 MHz, $CDCl_3$) δ 1.30−1.36 (d, 6H), 1.36−1.42 (d, 3H), 2.47−2.58 (m, 2H), 2.60−2.75 (m, 2H), 3.00−3.20 (br s, 4H), 3.40−3.50 (q, 1H), 4.51−4.68 (p, 1H), 6.80−7.00 (m, 4H), 7.40−7.70 (m, 4H).

3-[[4-(2-Isopropoxyphenyl)-1-piperazinyl]-1-ethyl]benzoic Acid (53). A solution of **52** (1.55 g, 4.4 mmol), 10 N NaOH (10 mL), and EtOH (10 mL) was refluxed for 8 h and stirred overnight at room temperature. The reaction was concentrated by evaporation, and the residue was dissolved in water (50 mL). Addition of acetic acid (5 mL) caused a white precipitate to form which was filtered to give **53** as a white solid (1.26 g, 77%): CI-MS *m/e* 369 (M^+).

1-[3-[[4-(2-Isopropoxyphenyl)-1-piperazinyl]-1-ethyl]-benzoyl]piperidine Oxalate Hydrate (54). Compound **53** was dissolved in DMF (11 mL) and treated portionwise at room temperature with 1,1′-carbonyldiimidazole (0.32 g, 2.0 mol). The reaction was stirred at room temperature for 1.5 h and then treated with piperidine (0.314 g, 3.7 mmol). After stirring for an additional 2 h, water (105 mL) was added and the mixture was extracted with ether. The ether layer was washed with saturated NaCl solution, separated, dried (K_2CO_3), filtered, and evaporated to give **54** (free base) as a yellow oil (0.60 g). This material was dissolved in EtOH and treated with oxalic acid (0.17 g, 1.9 mmol). Addition of ether caused a solid to precipitate which was collected by filtration, affording **54** (oxalate salt) as a white solid (0.123 g, 14%): mp 124−130 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 1.22 (d, 6H), 1.55 (d, 3H), 1.35−1.70 (m, 6H), 2.75−3.65 (m, 12H), 4.08−4.20 (m, 1H), 4.50−4.60 (m, 1H), 6.80−6.85 (m, 4H), 7.30−7.60 (s, 4H). Anal. C, H, N.

1-[4-[2-[4-(2-Isopropoxyphenyl)-1-piperazinyl]ethyl]-benzoyl]piperidine Oxalate (56). *N*-(2-Isopropoxyphenyl)-piperazine (30.6 g, 139 mmol), 4-bromophenethyl bromide (44.0 g, 167 mmol), sodium iodide (4.85 g, 37.5 mmol), and *N*,*N*-diisopropylethylamine (73.6 g, 570 mmol) were dissolved in 200 mL of anhydrous DMSO, and the solution was stirred under argon for 3 days. The reaction mixture was then poured into saturated aqueous sodium bicarbonate and extracted several times with ether. The ether extracts were combined, washed successively with aqueous sodium bicarbonate solution and brine, dried ($MgSO_4$), and concentrated to provide a sticky brown solid. This material was purified on a Waters Delta Prep 3000 LC apparatus (35:65−0:100 hexanes/dichloromethane) to afford 34.9 g (62%) of aralkylpiperazine **55** as a light-brown solid. A mixture of this material (5.0 g, 12.4 mmol), piperidine (3.17 g, 37.2 mmol), and $Cl_2Pd(PPh_3)_2$ (0.39 g, 0.558 mmol) under 1 atm of carbon monoxide was heated at 100 °C for 3 days. An additional 0.39 g of palladium catalyst was added to the reaction mixture which was heated for an additional 4 days. The reaction mixture was cooled, and chloroform and water were added to the resultant black solid. The layers were separated, and the aqueous layer was extracted with chloroform several times. The chloroform extracts were combined, dried (Na_2SO_4), and concentrated to provide a dark-brown oil which was purified on flash silica gel (10:90−0:100 hexanes/chloroform) to provide 1.13 g of pure **56** (free base) as a green solid. This material was dissolved in acetone, and oxalic acid (0.33 g) was added; upon treatment with diethyl ether and hexanes, a cream-colored solid precipitated, which was recrystallized from methanol/ether to provide 0.69 g (13%) of compound **56**: mp 202−205.5 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 1.27 (d, J = 6.0 Hz, 6H), 1.33−1.68 (m, 6H), 2.85−3.05 (m, 2H), 3.05−3.33 (m, 10H), 3.40−3.70 (br s, 2H), 4.62 (pentet, J = 6.0 Hz, 1H), 6.85−7.00 (m, 4H), 7.30 (s, 4H). Anal. ($C_{27}H_{37}N_3O_2 \cdot C_2H_2O_4$) C, H, N.

1-[4-[4-[4-(2-Isopropoxyphenyl)-1-piperazinyl]-4-oxobutyl]benzoyl]piperidine Fumarate (58). (2-Isopropoxyphenyl)piperazine (41.0 g, 186 mmol), 4′-bromo-4-chlorobutyrophenone (58.4 g, 223 mmol), sodium iodide (6.49 g, 50.2 mmol), and *N*,*N*-diisopropylethylamine (98.6 g, 763 mmol) were dissolved in 435 mL of anhydrous DMSO. After 7 days the reaction mixture was poured into saturated aqueous bicarbonate solution and then extracted into ether. The ether extracts were combined, washed successively with aqueous sodium bicarbonate and brine, dried ($MgSO_4$), and concentrated to provide a sticky brown solid. This material was purified on a Waters Delta Prep 3000 LC apparatus (45:55−0:100 hexanes/dichloromethane) to afford 19.0 g (23%) of the desired halobutyrophenone piperazine **57** as a light-brown solid. A mixture of this material (5.0 g, 11.2 mmol), piperidine (2.87 g, 33.7 mmol), and $Cl_2Pd(PPh_3)_2$ (0.35 g, 0.505 mmol) was

heated at 100 °C for 20 h under 1 atm of carbon monoxide. An additional 0.35 g of palladium catalyst was added to the reaction mixture which was then heated for an additional 20 h, cooled, and treated with chloroform and water. The layers were separated, and the aqueous layer was extracted with chloroform several times. The chloroform extracts were combined, dried (Na_2SO_4), and concentrated to provide a dark-brown oil which was purified on flash silica gel (0:100−1:99 methanol/chloroform) to give 1.25 g of pure **58** (free base) as a golden-brown oil. This material was dissolved in acetone, and fumaric acid (0.30 g) was added. Upon addition of diethyl ether and hexanes a fluffy white solid precipitated, which was recrystallized from acetone/ether to provide 0.74 g (11%) of **58**: mp 154−155.5 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.23 (d, J = 6.0 Hz, 6H), 1.40 (br s, 2H), 1.48−1.68 (br s, 4H), 1.87 (pentet, J = 6.8 Hz, 2H), 2.45 (t, J = 6.9 Hz, 2H), 2.55 (br s, 4H), 2.88 (br s, 4H), 3.05 (t, J = 6.8 Hz, 2H), 3.20 (br s, 2H), 3.58 (br s, 2H), 4.57 (pentet, J = 6.0 Hz, 1H), 6.61 (s, 2H), 6.77−6.95 (m, 4H), 7.49 (d, J = 8.1 Hz, 2H), 8.02 (d, J = 8.1 Hz, 2H). Anal. ($C_{29}H_{39}N_3O_3 \cdot 1.1C_2H_2O_4$) C, H, N.

1-[4-[4-[4-(2-Isopropoxyphenyl)-1-piperazinyl]-4-hydroxybutyl]benzoyl]piperidine Bisoxalate (59). To a solution of compound **58** (4.98 g, 10.4 mmol) described above in 200 mL of EtOH was added $NaBH_4$ (0.47 g, 12.5 mmol). The reaction mixture was stirred for 20 h under argon and then was cooled in ice. Cold 1 N HCl (20 mL) was added dropwise, and the reaction mixture was stirred for 1 min and then basified with solid potassium carbonate. The resulting mixture was extracted with chloroform; the organic extracts were combined, dried (Na_2SO_4), and concentrated to provide a green foam which was purified on flash silica gel (1:99−5:95 methanol/chloroform) to give 1.25 g of **59** (free base) as a yellow foam. This compound was dissolved in hot methanol, and oxalic acid (0.33 g) was added. When ether and hexanes were added, a white precipitate formed. This solid was recrystallized from methanol/ether to afford 0.44 g (9%) of **59**: mp 141−144.5 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.27 (d, J = 6.0 Hz, 7H), 1.40−1.82 (br m, 11H), 2.85−3.75 (br m, 13H), 4.55−4.70 (m, 2H), 6.83−7.02 (m, 4H), 7.34 (d, J = 8.0 Hz, 2H), 7.41 (d, J = 8.0 Hz, 2H). Anal. ($C_{29}H_{41}N_3O_3 \cdot 2C_2H_2O_4$) C, H, N.

1-[4-[4-[4-(2-Isopropoxyphenyl)-1-piperazinyl]butyl]-benzoyl]piperidine Dihydrobromide (60). A solution of **59** (3.20 g, 6.67 mmol), 20% palladium hydroxide on charcoal (1.00 g), and concentrated HCl (1.7 mL, 20.0 mmol) in 100 mL of 95% ethanol was shaken under 60 psig of hydrogen at 50 °C for 8 days. The reaction mixture was cooled, filtered through Dicalite, and concentrated to provide an olive-green foam. To this material was added saturated aqueous sodium bicarbonate and chloroform. The resulting mixture was passed through Dicalite, and the layers were separated. The aqueous layer was extracted with chloroform; the organic extracts were combined, dried (Na_2SO_4), and concentrated to provide a light-brown oil which was purified on flash silica gel (1:99 methanol/chloroform) to give 2.46 g of **60** (free base) as a golden-brown oil. This compound was dissolved in hot methanol, and concentrated HBr (1.1 mL) was added. A tan precipitate formed when ether and hexanes were added. This solid was recrystallized from methanol/ether to afford 1.36 g (32%) of **60**: mp 197.5−198.5 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.28 (d, J = 6.1 Hz, 6H), 1.35−1.78 (m, 10H), 2.67 (br t, 2H), 2.90 (br t, J = 11.7 Hz, 2H), 3.06−3.40 (m, 6H), 3.56 (br d, J = 10.8 Hz, 6H), 4.62 (pentet, J = 6.0 Hz, 1H), 6.00−6.70 (br s, 1H), 6.82−7.05 (m, 4H), 7.29 (s, 4H), 9.25−9.45 (br s, 1H). Anal. ($C_{29}H_{41}N_3O_2 \cdot 2HBr$) C, H, N; Br: calcd, 25.55; found, 24.68.

1-[3-[[4-(2-Isopropoxyphenyl)-1-piperazinyl]methyl]-thiobenzoyl]piperidine Hydrochloride (61). A solution of **6** (3.86 g, 9.2 mmol) and toluene (50 mL) was treated with 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (2.22 g, 5.5 mmol), and the resulting mixture was heated at 90 °C for 1 h. The reaction was cooled followed by the addition of toluene (50 mL) and then thoroughly mixed with excess 3 N NaOH. The organic layer was separated, washed with saturated aqueous NaCl, dried ($MgSO_4$), and concentrated to an oily residue. Chromatography of this material on flash silica (1.1:98.5−2.5:97.5 methanol/methylene chloride) afforded **61** which was converted to its hydrochloride salt in ethereal HCl (3.61 g, 77%): mp 221−224 °C dec (uncorrected); FAB-MS m/e 438 (MH^+); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.28 (d, 6H), 1.52 (m, 2H), 1.68 (m, 4H), 3.00−3.20 (m, 4H), 3.38 (m, 2H), 3.50 (q, 4H), 4.20−4.40 (m, 2H), 4.42 (s, 2H), 4.60 (m, 1H), 6.80−7.00 (m, 4H), 7.32 (m, 1H), 7.40−7.55 (m, 2H), 7.67 (m, 1H). Anal. ($C_{26}H_{35}N_3O_2 \cdot HCl$) C, H, N.

1-[3-[[4-(2-Isopropoxyphenyl)-1-piperazinyl]methyl]-phenylsulfonyl]piperidine Hydrate (62). *N*-Bromosuccinimide (6.27 g, 35 mmol), *m*-toluenesulfonyl chloride (6.72 g, 35 mmol), and benzoyl peroxide (0.67 g, 1.9 mmol) were combined in CCl_4 (40 mL) and heated at reflux for 2 h. The reaction mixture was filtered and washed with CCl_4. The filtrate was concentrated to give 3-(bromomethyl)benzenesulfonyl chloride (9.74 g) as a viscous yellow oil. A mixture of this material (4.68 g, 17.4 mmol) in THF (100 mL) was cooled to 0−5 °C in an ice−water bath and treated with a solution of piperidine (1.72 g, 20.2 mmol), triethylamine (3.08 g, 30.5 mmol), and THF (40 mL) over 20 min. The resulting mixture was warmed to ambient temperature and filtered, and the solution was concentrated. A solution of the resulting oil (3.12 g, 9.81 mmol), (2-isopropoxyphenyl)piperazine (3.30 g, 9.81 mmol), and triethylamine (1.27 g, 12.5 mL, 10 mmol) in THF (50 mL) was heated to reflux for 4.5 h and then stirred at ambient temperature overnight. The reaction mixture was filtered and concentrated to a residue which was partitioned between methylene chloride and 3 N NaOH. The organic layer was separated, dried ($MgSO_4$), filtered, and evaporated to yield an oil which was purified by chromatography on flash silica gel (9:1 hexane/ethyl acetate) to give **62** (free base). This material was triturated with Et_2O/HCl, affording **62** as a tan, crystalline solid (0.65 g, 12%): mp 189−191 °C; FAB-MS m/e 458 (MH^+); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.27 (d, 6H), 1.37 (m, 2H), 1.57 (m 4H), 2.95 (m, 4H), 3.05 (m, 2H), 3.20 (q, 2H), 3.32 (m, 2H), 3.55 (m, 2H), 4.52 (m, 2H), 4.65 (m, 1H), 6.80−7.00 (m, 4H), 7.72 (m, 1H), 7.82 (m, 1H), 8.05 (m, 2H). Anal. ($C_{25}H_{35}N_3O_4S \cdot 0.75C_4H_8O \cdot H_2O$) C, H, N, H_2O.

1-Bromo-2-isopropoxybenzene (63). A mixture of 2-bromophenol (23.2 mL, 0.20 mol), potassium carbonate (33.2 g, 0.24 mol), and 2-bromopropane (28.0 mL, 0.30 mol) in DMF (200 mL) was stirred in a preheated oil bath (60 °C) for 5 h. The cooled reaction mixture was then partitioned between ether and water. The layers were separated, and the aqueous phase was extracted with ether. The combined organic solution was washed with copious amounts of water and 3 N NaOH, dried ($MgSO_4$), filtered, and concentrated in vacuo to furnish 39.3 g (91%) of **63** as a pale-yellow oil which was carried on without further purification. The structure was supported by GC/MS and 90-MHz ^{1}H NMR.

1-Carbethoxy-4-(2-isopropoxyphenyl)-4-piperidinol (64). To a suspended solution of Mg chips (10.07 g, 0.414 mol) in anhydrous ether (150 mL) at 22 °C under argon was added 1,2-dibromoethane (ca. 0.15 mL), and **63** (43.7 g, 0.20 mol) in 200 mL of ether was added dropwise. After 50% of the aryl halide was added, the reaction began to reflux vigorously, and the flask was cooled in an ice bath. After the refluxing had subsided somewhat, the ice bath was removed and the remaining aryl halide was added over a 1.5-h period. The resultant Grignard reagent was cooled in a dry ice/ether bath for 2 h and then treated with 34.0 mL (0.221 mol) of 1-carbethoxy-4-piperidone. Upon complete addition of ketone, the reaction mixture was allowed to warm to 22 °C and stirred for 2 h. The reaction was then quenched with cold aqueous ammonium chloride resulting in an emulsion which was separated by addition of 1 M HCl. The aqueous phase was extracted with additional ether, and the combined organic solution was washed with 10% aqueous sodium bisulfite, 1 M HCl, and saturated aqueous $NaHCO_3$ and dried (K_2CO_3). Filtration and concentration yielded 56.36 g of **64** as a yellow viscous oil which was carried on without further purification:

CI-MS (CH_4) *m/e* 308 (MH^+), 290 (M − 18), 248 (M − ^{i}PrO); ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.1−1.5 (m, 9H), 1.8−2.2 (m, 4H), 3.1−3.5 (m, 2H), 3.9−4.3 (m, 4H), 4.35 (s, 1H, exchangeable), 4.45−4.85 (septet, 1H), 6.8−7.0 (m, 2H), 7.1−7.4 (m, 2H).

1-Carbethoxy-4-(2-isopropoxyphenyl)piperidine (65). A solution of **64** (36 g), 10% palladium on carbon (1.80 g), 5 mL of concentrated HCl, and 125 mL of MeOH was shaken on a Parr apparatus under 55.5 psig of hydrogen at 22 °C for 3 days. The reaction was filtered through Celite and concentrated to a residue. This material was partitioned between ether and water. The organic solution was dried ($MgSO_4$), filtered, and concentrated to yield 29.34 g of **65** as a light-yellow oil which was carried forward without further purification: CI-MS (CH_4) *m/e* 292 (MH^+); ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.1−1.4 (m, 9H), 1.5−1.9 (m, 3H), 2.6−3.1 (m, 3H), 3.9−4.6 (septet, 6H), 6.7−6.9 (m, 2H), 7.0−7.2 (m, 2H).

4-(2-Isopropoxyphenyl)piperidine Hydrochloride (66). A mixture of crude **65** (29.3 g) and sodium hydroxide pellets (6.12 g, 0.106 mol) in DMSO (100 mL) was stirred in a preheated oil bath at 100 °C for 4 days. The reaction mixture was then poured into water (200 mL), and the crude product was extracted into methylene chloride. The methylene chloride extracts were dried over $MgSO_4$, filtered, and concentrated to afford 21.34 g of a crude dark-brown oil. This oil was dissolved in 1 N HCl and washed with ether. The acidic aqueous solution was basified with 3 N NaOH, and the product was extracted into methylene chloride. The combined methylene chloride extracts were dried ($MgSO_4$), filtered, and concentrated to yield 13.34 g of a semisolid which was dissolved in ^{i}PrOH and acidified to pH 3 with concentrated HCl. The acidified solution was treated with ether resulting in precipitation of the hydrochloride salt of **66** which was collected by filtration and dried under vacuum to provide 11.21 g of a beige powder: CI-MS (CH_4) *m/e* 220 (MH^+); ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.1−1.4 (d, 6H), 1.6−2.2 (m, 3H), 2.8−3.6 (m, 6H), 4.4−4.8 (septet, 1H), 6.7−7.2 (m, 4H), 9.0−9.5 (m, 2H).

1-[3-[[4-(2-Isopropoxyphenyl)-1-piperidinyl]methyl]-benzoyl]piperidine Hydrochloride (67). A suspended mixture of **66** (3.75 g, 14.6 mmol), *N*-[3-(chloromethyl)benzoyl]-piperidine (3.45 g, 14.5 mmol), and triethylamine (4.50 mL, 32.2 mmol) in *N*-methylpyrrolidinone (15 mL) was stirred in a preheated oil bath (80 °C) for 18 h. The reaction mixture was partitioned between methylene chloride and water. The organic layer was separated, washed with water, dried ($MgSO_4$), filtered, and concentrated to afford 5.90 g of a brown oil. Flash chromatography of this material over silica gel (4: 96 MeOH/chloroform) and conversion to the corresponding HCl salt provided **67** (2.66 g, 47%) as off-white needles: FAB-MS *m/e* 421 (MH^+); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.30 (d, J = 6.0 Hz, 6H), 1.40−1.70 (m, 6H), 1.9−2.1 (m, 4H), 3.10−3.20 (m, 3H), 3.35−3.45 (m, 2H), 3.55−3.65 (m, 2H), 3.85−3.95 (m, 2H), 4.35−4.40 (m, 2H), 4.60 (septet, J = 6.0 Hz, 1H), 6.90 (t, J = 8.0 Hz, 1H), 7.00 (d, J = 8.0 Hz, 1H), 7.10 (d, J = 8.0 Hz, 1H), 7.20 (t, J = 8.0 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.55 (t, J = 8.0 Hz, 1H), 7.60 (s, 1H), 7.75 (d, J = 8.0 Hz, 1H). Anal. ($C_{27}H_{36}N_2O_2$·HCl) C, H, Cl; N: calcd, 6.13; found, 5.71.

4-(2-Isopropoxyphenyl)-4-piperidinol (68). A suspended solution of **64** (18.52 g, 60.3 mmol) and sodium hydroxide pellets (4.82 g, 120.5 mmol) in DMSO (100 mL) was stirred in a preheated oil bath (105 °C) for 1 day. The cooled reaction mixture was poured into a beaker containing 200 mL of aqueous NaCl and extracted with CH_2Cl_2 (3 × 200 mL). The combined CH_2Cl_2 solution was then washed with H_2O (3 × 200 mL), dried over Na_2SO_4, filtered, and concentrated to yield 10.50 g of a brown viscous oil. This crude free base was dissolved in ^{i}PrOH (100 mL), and the solution was filtered and acidified with concentrated HCl to a pH of 3. The acidified solution was diluted with Et_2O and a brown crystalline solid precipitated. The HCl salt was collected by filtration and dried in a vacuum oven at 50 °C for 20 h to give **68** (8.60 g, 61%): CI-MS (CH_4) *m/e* 235 (MH^+), 218 (M − 18); ^{1}H NMR (90 MHz, DMSO-d_6) δ 1.1−1.5 (m, 8H), 2.3−3.2 (m, 7H), 4.3−4.7 (septet, 1H), 6.6−7.2 (m, 3H), 7.3−7.5 (m, 1H), 8.7−9.0 (m, 1H), 9.1−9.5 (m, 1H).

1-[3-[[4-[2-(1-Methylethoxy)phenyl]-4-hydroxy-1-piperidinyl]methyl]benzoyl]piperidine Hydrochloride 0.25Hydrate (69). A suspended solution of **68** (2.61 g, 9.6 mmol), *N*-[3-(chloromethyl)benzoyl]piperidine (2.43 g, 10.2 mmol), and triethylamine (3.0 mL, 21.5 mmol) in *N*-methylpyrrolidinone (9 mL) was stirred in a preheated oil bath (80 °C) for 20 h. Upon cooling to room temperature, the reaction mixture was diluted with ether (200 mL) and washed once with water. The aqueous phase was extracted with additional ether (2 × 100 mL). The combined ethereal solution was washed with water (3 × 150 mL), dried over $MgSO_4$, filtered, and concentrated to provide an oil which was purified by flash chromatography on silica gel (3:97 methanol/chloroform) to give **69** as a light-yellow oil. This oil was dissolved in 2-propanol and acidified to pH 3 with concentrated HCl. The acidified solution was treated with hexane and ether resulting in precipitation of the hydrochloride salt which was collected by filtration and dried under high vacuum to provide **69** hydrochloride (1.95 g, 43%) as a white powder (mp 148−154 °C): IR (KBr) cm^{-1} 3387 (OH stretch), 1618 (CO stretch); CI-MS (CH_4) *m/e* 437 (MH^+), 418 (M − 18); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.4 (d, 6H), 1.6−1.8 (m, 4H), 2.2 (d, 2H), 3.25−3.45 (m, 6H), 3.2−3.3 (m, 2H), 4.15−4.20 (m, 2H), 4.20−4.30 (m, 2H), 4.65−4.75 (m, 1H), 4.85 (s, 1H), 6.9−7.0 (m, 2H), 7.2−7.3 (m, 2H), 7.4−7.6 (m, 3H), 8.0 (s, 1H), 12.5 (br s, 1H). Anal. ($C_{27}H_{36}N_2O_3$·HCl·0.25H_2O) C, H, N, Cl, H_2O.

Pharmacological Methods. 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 of body weight) 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 of body weight, 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 23 °C), using a motor-driven Teflon pestle fit 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. All radioligands were purchased from New England Nuclear.

D_2 Affinity. Binding was determined using membranes prepared from rat striatum. The receptor was labeled with 0.05 nM [^{3}H]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.[31]

D_4 Affinity. Binding was determined by Cerep (France) using membranes from a human recombinant $D_{4.4}$ receptor. The receptor was labeled with 0.5 nM [^{3}H]spiperone, and 10 mM (+)-butaclamol was used for determination of nonspecific binding.

5-HT_{1A} Affinity. Binding was determined using membranes prepared from rat cerebral cortex. The receptor was labeled with 3 nM [^{3}H]-8-OH-dipropylaminotetralin (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 [^{3}H]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.[11] Trained rats (N = 4) 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 for that data indicated as fed, or the animals were not allowed access to food overnight prior to the experiment. Test sessions consisted of 60 trials, 1/min. Only animals that exhibited greater than 90% CAR on day 1 were given the test compound on day 2.

Catalepsy Test in the Rat. Male, Sprague−Dawley rats were obtained from Charles River Laboratories (Kingston, NY) ranging in weight between 170 and 240 g on the day of the test. The experiment was conducted in a quiet room with the experimenter unaware of the drug or dose level administered. Groups of five rats were treated with drug. In each test session, two control groups were used for the production of catalepsy; animals treated with saline (or vehicle) served as a negative control, and animals treated with haloperidol (2 mg/kg) were a positive control. If 2 mg/kg haloperidol failed to produce greater than 80% catalepsy, data from that session were not used. To begin a test session, the rat's forepaw was gently placed on a black cork (3.5 cm high) and the time until the forepaw was removed was recorded. Each rat was given three trials with a maximum time of 60 s on the cork for each trial. The sum of the three trials was taken as the score for each rat. Percent catalepsy was defined as the percent of 3 min (maximum time) that a rat permitted its forepaw to rest on the cork.

Acknowledgment. We wish to acknowledge the assistance of our colleagues listed as follows during the course of this project: A. Abdel-Magid, D. J. Bennett, P. S. Blum, R. E. Boyd, K. R. Jacobs, E. Malloy, M. E. Ortegon, C. R. Rasmussen, R. G. Sherrill, F. J. Villani, N. Yim, W.-N. Wu, and D. Wustrow.

Supporting Information Available: X-ray crystallographic data for mazapertine succinate (**6**), including unit cell parameters, standard errors, tables of atomic coordinates, thermal parameters, and bond lengths (32 pages); table of structure factors (10 pages). Ordering information is given on any current masthead page.

References

(1) (a) Frankenburg, F. R.; Hegarty, J. D. Cost Considerations in the Treatment of Schizophrenia. *CNS Drugs* **1996**, *5*, 75−82. (b) Lindstrom, E. The Hidden Cost of Schizophrenia. *J. Drug Dev. Clin. Pract.* **1996**, *7*, 281−288. (c) Tamminga, C. A., Schulz, S. C., Eds. *Advances in Neuropsychiatry and Psychopharmacology, Volume I: Schizophrenia Research*; Raven Press: New York, 1991. (d) Meltzer, H. Y. *Psychopharmacology: The Third Generation of Progress;* Raven Press: New York, 1987. (e) Reynolds, G. P. Developments in the Drug Treatment of Schizophrenia. *Trends Pharmacol. Sci.* **1992**, *13*, 116−121. (f) 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. (g) Owens, D. G. C. Adverse Effects of Antipsychotic Agents. *Drugs* **1996**, *51*, 895−930.

(2) Murray, R. M., Turner, T. H., Eds. *Lectures on the History of Psychiatry*; Alden Press: London, 1990.

(3) (a) Swazey, J. P. *Chlorpromazine in Therapy: A Study of Therapeutic Intervention*; The MIT Press: Cambridge, MA, 1974. (b) Courvoisier, S.; Fournel, J.; Ducrot, R.; Kolsky, M.; Koetschet, P. Proprietes Pharmadynamiques Du Chlorhydrate De Chloro-3-(dimethylamino-3′-propyl)-10 Phenothiazine (4.560 R.P.). *Arch. Int. Pharmacodyn. Ther.* **1953**, *92*, 305−361.

(4) Frances, A. J.; Weiden, P. Promoting Compliance With Outpatient Drug Treatment. *Hosp. Community Psychiatry* **1987**, *38*, 1158−1160.

(5) (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. (e) Civelli, O.; Bunzow, J. R.; Grandy, D. K.; Zhou, Q.-Y.; Van Tol, H. H. M. Molecular Biology of the Dopamine Receptors. *Eur. J. Pharmacol. − Mol. Pharmacol. Sect.* **1991**, *207*, 277−286. (f) Thurkaff, A.; Yuan, J.; Chen, X.; Wasley, J. W. F.; Paneitz, G.; Meade, R.; Woodruff, K. H.; Huston, K.; Ross, P. C. 3-Aminomethylbiphenyls. A New Class of Dopamine Receptor Ligands. *Med. Chem. Res.* **1996**, *6*, 69−80 and references therein.

(6) (a) McDonnell, M. E.; Reitz, A. B. Recent Advances in Antipsychotic Research. *Expert Opin. Ther. Pat.* **1994**, *4*, 1221−1231. (b) Howard, H. R.; Seeger, T. F. Novel Antipsychotics. In *Annual Reports in Medicinal Chemistry*; Bristol, J. A., Ed.; Academic Press: San Diego, 1993; Vol. 28, Chapter 5, pp 39−47. (c) Cipollina, J. A. New Antipsychotic Agents: A Patent Overview − 1991. *Curr. Opin. Ther. Pat.* **1992**, *2*, 485. (d) Horn, A. S. Dopamine Receptors. In *Comprehensive Medicinal Chemistry*; Emmett, J. C., Ed.; Pergamon Press: New York, 1990; Vol. 3, p 229. (e) Kane, J.; Honigfeld, G.; Singer, J.; Meltzer, H. Clozapine for the Treatment-Resistant Schizophrenic. *Arch. Gen. Psychiatry* **1988**, *45*, 789−796. (f) Honigfeld, G.; Patin, J.; Singer, J. *Adv. Ther.* **1984**, *1*, 77−97. (g) Kaiser, C.; Setler, P. E. Antipsychotic Agents. In *Burger's Medicinal Chemistry*, Wolff, M. E., Ed.; John Wiley & Sons: New York, 1980; Part III, p 859.

(7) For reviews on the multiplicity of serotonin subtypes, see: (a) Saudou, F.; Hen, R. 5-HT Receptor Subtypes: Molecular and Functional Diversity. *Med. Chem. Res.* **1994**, *4*, 16−84. (b) Gothert, M. 5-Hydroxytryptamine Receptors. *Arzneimforsch* **1992**, *42*, 238−249.

(8) (a) Meltzer, H. Y.; Nash, J. F. Effects of Antipsychotic Drugs on Serotonin Receptors. *Pharmacol. Rev.* **1991**, *43*, 587−604. (b) Abi-Dargham, An.; Laruelle, M.; Charney, D.; Krystal, J. Serotonin and Schizophrenia: A Review. *Drugs Today* **1996**, *32*, 171−185.

(9) (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) Risperidone. *Drugs Future* **1988**, *13*, 1052−1055.

(10) For an early comparison of the pharmacological activity of dopamine antagonists, see: Niemegeers, C. J. E.; Janssen, P. A. J. A Systematic Study of the Pharmacological Activities of Dopamine Antagonists. *Life Sci.* **1979**, *24*, 2201−2216.

(11) 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.

(12) 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.

(13) Reitz, A. B.; Scott, M. K. 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: Greenwich, CT, 1995; Vol. 3, pp 1−56.

(14) (a) Scott, M. K.; Baxter, E. W.; Bennett, D. J.; Boyd, R. E.; Blum, P. S.; Codd, E. E.; Kukla, M. J.; Malloy, E.; Maryanoff, B. E.; Maryanoff, C. A.; Ortegon, M. E.; Rasmussen, C. R.; Reitz, A. B.; Renzi, M. J.; Schwender, C. F.; Shank, R. P.; Sherrill, R. G.; Vaught, J. L.; Villani, F. J.; Yim, N. Piperazinylalkyl Heterocycles as Potential Antipsychotic Agents. *J. Med. Chem.* **1995**, *38*, 4198−4210. (b) Reitz, A. B.; Baxter, E. W.; Bennett, D. J.; Codd, E. E.; Jordan, A. D.; Malloy, E. A.; Maryanoff, B. E.; McDonnell, M. E.; Ortegon, M. E.; Renzi, M. J.; Scott, M. K.; Shank, R. J.; Sherrill, R. G.; Vaught, J. L.; Wustrow, D. J. *N*-Aryl-*N*′-Benzylpiperazines as Potential Antipsychotic Agents. *J. Med. Chem.* **1995**, *38*, 4211−4222.

(15) 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.

(16) See also: (a) Kuipers, W.; Kruse, C. G.; van Wijngaarden, I.; Standaar, P. J.; Tulp, M. Th. M.; Veldman, N.; Spek, A. L.; IJzerman, A. P. 5-HT_{1A}- versus D_2-Receptor Selectivity of Flexinoxan and Analogous N^4-Substituted N^1-Arylpiperazines. *J. Med. Chem.* **1997**, *40*, 300−312. (b) Hrib, N. J.; Jurcak, J. G.; Bregna, D. E.; Burgher, K. L.; Hartman, H. B.; Kafka, S.; Kerman, L. L.; Kongsamut, S.; Roehr, J. E.; Szewczak, M. R.; Woods-Kettelberger, A. T.; Corbett, R. Structure−Activity Relationships of a Series of Novel (Piperazinylbutyl)thiazolidinone Antipsychotic Agents Related to 3-[4-[4-(6-Fluorobenzo[*b*]thien-3-yl)-1-piperazinyl]butyl]-2,5,5-trimethyl-4-thiazolidinone Maleate. *J. Med. Chem.* **1996**, *39*, 4044−4057. (c) Norman, M. H.; Rigdon, G. C.; Hall, W. R.; Navas, F., III. Structure−Activity Relationships of a Series of Substituted Benzamides: Potent D_2/5-HT_{1A} Antagonists and 5-HT_{1A} Agonists as Neuroleptic Agents. *J. Med. Chem.* **1996**, *39*, 1172−1188. (d) Kuroita, T.; Ikebe, T.; Murakami, S.; Takehara, S.; Kawakita, T. *N*-(2-Pyrrolidinylmethyl)benzoxazine-8-carboxamides Exhibiting High Affinities for All of D_2, 5-HT_{1A}, and 5-HT_2 Receptors. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1245−1250. (e) Perregaard, J. K.; Moltzen, E. K. WO9533729-A1, 1995, assigned to Lundbeck AS. (f) 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. (g) 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. (h) Ikebe, T.; Murakami, S.; Takehara, S.; Sakamori, M. *N*-[(1-Long Alkyl-2-pyrrolidinyl)methyl]benzamides With Potent Serotonin and 5-HT_{1A} Receptor Affinities. *Chem. Pharm. Bull.* **1991**, *39*, 3370−3372.

(17) 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*]cyclohepten-5-ylidene)piperidine (CTC), a Derivative of Cyproheptadine. *J. Pharmacol. Exp. Ther.* **1979**, *208*, 460−476.

(18) Reitz, A. B.; McDonnell, M. E.; Baxter, E. W.; Codd, E. E.; Wu, W.-N. The Synthesis and Evaluation of the Major Metabolites of Mazapertine. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1927−1930.

(19) (a) Glennon, R. A.; Slusher, R. M.; Lyon, R. A.; Titeler, M.; McKenney, J. D. 5-HT_1 and 5-HT_2 Binding Characteristics of Some Quipazine Derivatives *J. Med. Chem.* **1996**, *29*, 2375−2380. (b) van Wijngaarden, I.; Kruse, C. G.; van der Heyden; Tulp, M. Th. M. 2-Phenylpyrroles as Conformationally Restricted Benzamide Analogues. A New Class of Potential Antipsychotics. *J. Med. Chem.* **1988**, *31*, 1934−1940. (c) Olivier, B.; Mos, J.; Hartog, J.; Rasmussen, D. Serenics. *Drug News Perspect.* **1990**, *3*, 261−271. (d) Sijbesma, H.; Schipper, J.; de Kloet, E. R. Eltoprazine, a Drug Which Reduces Aggressive Behaviour, Binds Selectively to 5-HT_1 Receptor Sites in the Rat Brain: an Autoradiographic Study. *Eur. J. Pharmacol.* **1990**, *177*, 55−66. (e) van Steen, B. J.; van Wijngaarden, I.; Tulp, M. Th. M.; Soudijn, W. A Series of N^4-Imidoethyl Derivatives of 1-(2,3-Dihydro-1,4-benzodioxin-5-yl)piperazine as 5-HT_{1A} Receptor Ligands: Synthesis and Structure-Affinity Relationships. *J. Med. Chem.* **1995**, *38*, 4303−4308.

(20) (a) Yevich, J. P. Drug Development: From Discovery to Marketing. In *A Textbook of Drug Design and Development*; Krogsgaard-Larsen, P., Bundgaard, H., Eds.; Harwood Academic Publishers: Philadelphia, 1991; pp 606−630. (b) Traber, J.; Glaser, T. 5-HT_{1A} Receptor-Related Anxiolytics. *Trends Pharmacol. Sci.* **1987**, *8*, 432−437.

(21) (a) de Paulis, T.; Kumar, Y.; Johansson, L.; Ramsby, S.; Hall, H.; Sallemark, M.; Angeby-Moller, K.; Ogren, S.-O. Potential Neuroleptic Agents. 4. Chemistry, Behavioral Pharmacology, and Inhibition of [^{3}H]Spiperone Binding of 3,5-Disubstituted *N*-[(1-Ethyl-2-pyrrolidinyl)methyl]-6-methoxysalicylamides. *J. Med. Chem.* **1986**, *29*, 61−69. (b) de Paulis, T.; Kumar, Y.; Johansson, L.; Ramsby, S.; Florvall, L.; Hall, H.; Angeby-Moller, K.; Ogren, S.-O. Potential Neuroleptic Agents. 3. Chemistry and Antidopaminergic Properties of Substituted 6-Methoxysalicylamides. *J. Med. Chem.* **1985**, *28*, 1263−1269.

(22) Schoenberg, A.; Heck, R. F. Palladium-Catalyzed Amidation of Aryl, Heterocyclic, and Vinylic Halides. *J. Org. Chem.* **1974**, *37*, 3327−3331.

(23) Levy, L. A. Synthesis of *N*-Methoxybenzisothiazole Derivatives. *J. Heterocycl. Chem.* **1971**, *8*, 873−874.

(24) 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.

(25) (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 Trans.* **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.

(26) (a) Goff, D. C.; Midha, K. K.; Brotman, A. W.; McCormick, S.; Waites, M.; Amico, E. T. An Open Trial of Buspirone Added to Neuroleptics in Schizophrenic-Patients. *J. Clin. Psychopharmacol.* **1991**, *11*, 193−197. (b) Moss, L. E.; Neppe, V. M.; Crevets, W. C. Buspirone in the Treatment of Tardive Dyskinesia. *J. Clin. Psychopharmacol.* **1993**, *13*, 204−209. (c) Neal Beliveau, B. S.; Joyce, J. N.; Lucki, I. Serotonergic Involvement in Haloperidol-Induced Catalepsy. *J. Pharmacol. Exp. Ther.* **1993**, *265*, 207−217. (d) D′Mello, D. A.; McNeil, J. A.; Harris, W. Buspirone Suppression of Neuroleptic-Induced Akathesia: Multiple Case Reports. *J. Clin. Psychopharmacol.* **1989**, *9*, 151−152.

(27) 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.

(28) Lane, R. F.; Blaha, C. D.; Rivet, J. M. Selective Inhibition of Mesolimbic Dopamine Release Following Chronic Administration of Clozapine: Involvement of α_1−Noradrenergic Receptors Demonstrated by In vivo Voltammetry. *Brain Res.* **1988**, *460*, 398−401.

(29) (a) Hansch, C.; Bjorkroth, J. P.; Leo, A. Hydrophobicity and Central Nervous System Agents: On the Principle of Minimal Hydrophobicity in Drug Design. *J. Pharm. Sci.* **1987**, *76*, 663−687. (b) Hansch, C.; Leo, A.; Hoekman, D. *Exploring QSAR Hydrophobic, Electronic, and Steric Constants;* ACS Professional Reference Book; American Chemical Society: Washington, DC, 1995.

(30) For computational analysis of arylpiperazine conformation, see: Dijkstra, G. D. H. Conformational Analysis of 1-Arylpiperazines and 4-Arylpiperidines. *Recl. Trav. Chim. Pays-Bas* **1993**, *112*, 151−160.

(31) 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.

JM970164Z