Piperazinylalkyl Heterocycles as Potential Antipsychotic Agents

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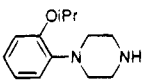
We recently reported on a series of pyrrole Mannich bases orally active in inhibiting the conditioned avoidance response (CAR) in rats. These compounds exhibit affinity for both D_2 and 5-HT_{1A} receptors, and some are noncataleptogenic. Such a profile suggests that they may be potential antipsychotic agents which lack the propensity for causing extrapyramidal side effects and tardive dyskinesias in humans. One of these compounds, 1-[[1-methyl-5-[[4-[2-(1-methylethoxy)phenyl]-1-piperazinyl]methyl]-1*H*-pyrrol-2-yl]methyl]-2-piperidinone (RWJ 25730, **1**), was chosen for further development but found to be unstable in dilute acid. In order to improve stability, we replaced the pyrrole methylene linkage to the piperazine ring with ethylene, employed ethylene and dicarbonyl as linkers between the lactam and the pyrrole ring, placed electron-withdrawing groups on the pyrrole ring, and substituted acyclic amide for lactam. In addition, we replaced the pyrrole segment with other heterocycles including thiophene, furan, isoxazole, isoxazoline, and pyridine. Generally, replacement of the *N*-methylpyrrole segment with thiophene, furan, isoxazoline, or pyridine afforded compounds equipotent with **1** in CAR, which were more stable in dilute acid. In the case of side chain or lactam modifications, CAR activity was significantly decreased or abolished, with the exception of **6**. For the most part, the modifications to **1** resulted in the decrease or loss of D_2 receptor binding. However, within this series, 5-HT_{1A} receptor binding was greatly increased, with thiophene **40** exhibiting an IC_{50} of 0.07 nM. The CAR activities of pyrroles **6** and **12**, thiophene **40**, furans **44**–**47**, isoxazolines **49** and **50**, and pyridine **54** coupled with their weak or nonexistent D_2 binding and strong 5-HT_{1A} binding suggest that they may be acting via a nondopaminergic mechanism or that dopaminergic active metabolites are responsible. Pyrrole **6** and furans **44** and **47** show promise as antipsychotic agents based on their CAR activity, receptor-binding profile, and solution stability.

As part of our research in the antipsychotic area, we discovered a series of arylpiperazines, exemplified by 1-[2-(methylethoxy)phenyl]piperazine (Figure 1), which inhibited the conditioned avoidance response (CAR) in the rat, a test predictive of antipsychotic activity in humans, and had high affinity for the serotonin 5-HT_{1A} and 5-HT_{1B} binding sites but had little or no affinity for the D_2 binding site.[1, 2] In addition, the aryl piperazines did not cause catalepsy in rats, indicative of a lack of propensity for the production of extrapyramidal side effects (EPS) in humans.[3] The lack of catalepsy seen with these compounds may be due to their 5-HT_{1A}-binding activity since it has been reported that 5-HT_{1A} agonists reverse the catalepsy induced by antipsychotic agents in rats.[4] Compared with the clinically proven antipsychotic drugs clozapine, which binds to many receptors including the D_4 and 5-HT_2 binding sites,[5–9] and risperidone, selective for D_2 and 5-HT_2 binding sites,[10–12] these compounds represent potentially unique antipsychotic agents by virtue of their activity in inhibiting CAR, lack of catalepsy, and novel receptor-binding profile. However, they did not display oral efficacy in the CAR assay. The conversion of these arylpiperazines to "pyrrole Mannich bases" afforded a series of compounds orally active in CAR which exhibited affinity for both D_2 and 5-HT_{1A} receptors.[13] This combination of potential antipsychotic activity with D_2- and 5-HT_{1A}-binding affinity has been reported only twice before.[14] Some of the pyrrole Mannich bases were determined to be noncataleptogenic in rats, suggesting that the combination of dopaminergic and 5-HT_{1A} binding may provide an antipsychotic agent with a low liability for the production of EPS or tardive dyskinesias (TD) in humans.

Figure 1.



Out of the pyrrole Mannich base series, 1-[[1-methyl-5-[[4-[2-(1-methylethoxy)phenyl]-1-piperazinyl]methyl]-1*H*-pyrrol-2-yl]methyl]-2-piperidinone (RWJ 25730, **1**) was found to be the best compound in terms of oral efficacy in CAR and lack of catalepsy. Although this compound is more selective for the dopamine D_2 receptor (K_i = 1.2 nM), it also has high affinity for the serotonin 5-HT_{1A} receptor (K_i = 4.2 nM). Compound **1** also blocked apomorphine-induced emesis in beagle dogs and, despite high affinity for the α_1-adrenergic receptor, did not significantly lower blood pressure in the spontaneously hypertensive rat at high doses (50 mg/kg, po).[13]

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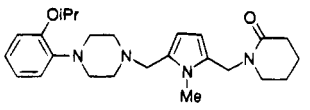
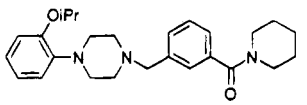


1 (RWJ 25730)

At this point, **1** was considered a candidate for further development and underwent evaluation of its solubility, pharmaceutical formulation, and stability characteristics. Unfortunately, stability studies in aqueous media revealed that **1** at pH 2 was unstable with a $t_{1/2}$ of 82 min, possibly because the compound suffers a retro-Mannich reaction or pyrrole hydrolysis to a 1,4-diketone.

In order to improve stability, phenyl was substituted for *N*-methylpyrrole to afford 1-[3-[[4-[2-(1-methylethoxy)phenyl]-1-piperazinyl]methyl]benzoyl]piperidine monosuccinate (mazapertine succinate, RWJ 37796), a compound of superior potency in CAR which is noncataleptogenic, displays a receptor-binding profile similar to that of **1**, and is stable in solution at pH 2.[15] This compound is currently being evaluated in humans as an antipsychotic agent.



Mazapertine Succinate (RWJ 37796)

In addition to employing phenyl as a replacement for *N*-methylpyrrole, in a vast collection of analogues,[15] we undertook other modifications of the pyrrole segment of **1**, which are described in this paper. Our goal was to prepare compounds which had a combination of D_2- and 5-HT_{1A}-binding activity and inhibited CAR. Thus we set a criteria for selecting further lead compounds as having a K_i < 50 nM at both receptors and CAR inhibition (ip) > 80% (5 mg/kg) or > 90% (15 mg/kg), in addition to being acid-stable. We prepared derivatives which had a piperazinylethyl, versus a piperazinylmethyl, linkage to the pyrrole ring, thereby eliminating the possibility of a retro-Mannich reaction (compounds **2**–**7**, Table 1). Additionally, the effects of employing an ethylene linkage between the lactam and pyrrole rings (compounds **8** and **9**, Table 1), changing the lactam group to an acyclic amide (compounds **10**–**22**, Table 2) or a sulfonamide (compounds **23**–**30**, Table 3), and placing an electron-withdrawing group on the pyrrole ring (compounds **31**–**34**, Table 4) were explored. Since the acid instability may also be due to the π-deficient nature of the pyrrole ring, a series of analogues was prepared where the pyrrole ring had been replaced by thiophene (compounds **35**–**41**, Table 5), furan (compounds **42**–**48**, Table 6), isoxazoline (compounds **49**, **50**, and **53**, Table 7), isoxazole (compounds **51** and **52**, Table 7), and pyridine (compound **54**, Table 7). In addition, the preparation of these compounds, shown in Schemes 1–6, enabled us to explore the effect of further structural changes on CAR activity and on the balance of D_2 and 5-HT_{1A} receptor binding. The results of these studies are shown in Table 8.

Synthetic Chemistry

Extended chain pyrroles **2**–**5** were obtained from (piperazinylethyl)pyrroles **56** by treatment with oxalyl chloride and a cyclic amine, as shown in Scheme 1. Intermediate **56** was prepared via the borane reduction of glyoxamide **55**, the product of *N*-methylpyrrole, an arylpiperazine, and oxalyl chloride. Amidomethylation of **56** gave direct piperazinylethyl analogues of **1**, compounds **6** and **7**.[16] Treatment of *N*-methyl-2-(2-aminoethyl)pyrrole with methylbromovalerate afforded **57** which was converted to **8** and **9** under Mannich conditions.

The synthesis of the (amidomethyl)-, (sulfonamidomethyl)-, and amidopyrroles is outlined in Scheme 2 and converges on intermediates **58a,b** which arose from the reaction of *N*-methylpyrrole, triphosgene, and an appropriate amine as shown. Mannich reaction of **58a,b** with arylpiperazines gave compounds **31**–**34**. Sulfonamides **23**–**30** were obtained from **58a** by reduction to **59**, conversion to sulfonamide **60**, and subsequent Mannich reaction with an arylpiperazine. Treatment of **59** with an acid chloride afforded amides **61** which were converted to amides **10**–**22** under Mannich conditions.

Construction of the 5-thiophene analogues of **1**, depicted in Scheme 3, originated from commercially available 5-(bromomethyl)thiophene carboxylic acid and involved two divergent syntheses. In one case, treatment of 5-(bromomethyl)thiophene carboxylic acid with thionyl chloride followed by amination with piperazine or azepine afforded intermediates **62** which were converted to the corresponding thiophene Mannich bases **37**–**39**. Alternatively, amidation of 5-(bromomethyl)thiophene carboxylic acid with 2-piperidinone gave acid **63** which was reduced to carbinol **64**. Subsequent oxidation of **64** to aldehyde **65** followed by reductive amination using an appropriate piperazine afforded **40** and **41**. The 4-thiophene analogues **35** and **36** were prepared by reductive amination of 4-bromo-2-thiophenecarboxaldehyde to give **66** followed by aminocarbonylation.

Furans **42**–**47** were obtained as shown in Scheme 4 from the Mannich reaction of furans **69** and an appropriate aryl piperazine. Compounds **69** were prepared by amidomethylation of furan with the corresponding hydroxy lactams **68**, obtained from lactams **67**. Phthalimide analogue **48** was synthesized by treating 2-(aminomethyl)furan with phthalic anhydride to give **70** followed by treatment with 4-(2-methoxyphenyl)-piperazine under Mannich conditions.

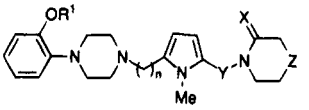
Isoxazoline **49** and isoxazole **51** were obtained by treatment of the respective allyl- and propargylpiperazines **71a,b** with the nitrile oxide derived from tetrahydropyranyl-protected nitroethanol,[17] as shown in Scheme 5. These carbinols were converted to their respective chlorides which underwent displacement with piperidinone anion to give **50** and **52**. A variation of this sequence, where carbinol **73** was formed from piperidine **72**, converted to chloride **74**, and treated with 4-(2-isopropoxyphenyl)piperazine, afforded isoxazoline **53**.

The synthesis of pyridine **54** from intermediate **75** is depicted in Scheme 6. Treatment of 4-(2-methoxyphenyl)piperazine with 2,6-bis(chloromethyl)pyridine[18] gave chloride **75** which was converted to **54** with the anion of 2-piperidone.

Biological Results and Discussion

Compounds **2**–**54** were examined for potential antipsychotic activity by determining their propensity to block the conditioned avoidance of a foot shock (CAR).[1,2]

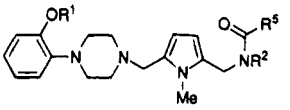
Table 1. Extended Pyrroles **2–9**



compd	R^1	n	Y	X	Z	yield (%)	mp (°C)	recryst solvent	formula[a]
2	Me	2	COCO	H_2	CH_2	28	(197 sinter) 204–205.5	MeOH/Et_2O	$C_{25}H_{34}N_4O_3 \cdot C_2H_2O_4 \cdot 0.3H_2O$
3	*i*-Pr	2	COCO	H_2	$(CH_2)_2$	41	(sinter 168) 171.5–174	EtOH	$C_{28}H_{40}N_4O_3 \cdot C_2H_2O_4 \cdot 0.3C_2H_5OH$
4	*i*-Pr	2	COCO	H_2	O	28	(199 sinter) 201–203	95% EtOH	$C_{26}H_{36}N_4O_4 \cdot C_2H_2O_4 \cdot 0.1C_2H_5OH$
5	*i*-Pr	2	COCO	H_2	CH_2	29	(189 sinter) 193–195.5	MeOH/Et_2O	$C_{27}H_{38}N_4O_3 \cdot C_4H_2O_4 \cdot 0.2C_4H_{10}O \cdot 0.4H_2O$
6	*i*-Pr	2	CH_2	O	CH_2	6	(161 sinter) 169.5–172.5	EtOH	$C_{26}H_{38}N_4O_2 \cdot C_2H_2O_4 \cdot 0.4H_2O$
7	Me	2	CH_2	O	CH_2	4	(146 sinter) 155.5–157	EtOH	$C_{24}H_{34}N_4O_2 \cdot C_2H_2O_4 \cdot 0.5H_2O$
8	Me	1	$(CH_2)_2$	O	CH_2	36	173	*i*-PrOH/Et_2O	$C_{24}H_{34}N_4O_2 \cdot HCl$
9	*i*-Pr	1	$(CH_2)_2$	O	CH_2	15	177	*i*-PrOH/Et_2O	$C_{26}H_{38}N_4O_2 \cdot HCl \cdot 0.5C_3H_8O$

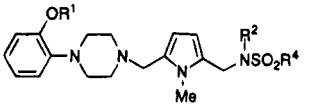
[a] All compounds in Tables 1-7 were analyzed within ±0.4% of the calculated value for C, H, N, Cl, or H_2O except as indicated.

Table 2. Acyclic (Amidomethyl)pyrroles **10–22**



compd	R^1	R^2	R^5	yield (%)	mp (°C)	recrsyt solvent	formula
10	*i*-Pr	Me	Me	19	140–141	*i*-PrOH	$C_{23}H_{34}N_4O_2 \cdot C_4H_4O_4$
11	*i*-Pr	Me	*i*-Pr	73	155–157	*i*-PrOH	$C_{25}H_{38}N_4O_2 \cdot C_4H_4O_4$
12	Me	Me	Me	81	100–102	*i*-PrOH	$C_{21}H_{30}N_4O_2 \cdot C_4H_4O_4 \cdot 0.5H_2O$
13	Me	Me	*i*-Pr	81	129–132	*i*-PrOH	$C_{23}H_{34}N_4O_2 \cdot C_4H_4O_4$
14	Me	Me	*n*-Bu	32	109–112	*i*-PrOH	$C_{24}H_{36}N_4O_2 \cdot C_4H_4O_4$
15	*i*-Pr	Me	*n*-Bu	26	133–135	*i*-PrOH	$C_{26}H_{40}N_4O_2 \cdot 1.5C_4H_4O_4$
16	Me	*i*-Pr	*c*-Hex	25	121–123	*i*-PrOH/hexane	$C_{28}H_{42}N_4O_2 \cdot C_4H_4O_4$
17	*i*-Pr	*i*-Pr	*c*-Hex	67	139–142	*i*-PrOH	$C_{30}H_{46}N_4O_2 \cdot C_4H_4O_4$
18	*i*-Pr	*i*-Pr	*i*-Pr	57	107–110	*i*-PrOH	$C_{27}H_{42}N_4O_2 \cdot C_4H_4O_4 \cdot 0.5H_2O$
19	Me	Bn	Me	19	(soften 65) 78–80	Et_2O	$C_{27}H_{34}N_4O_2 \cdot C_4H_4O_4 \cdot H_2O$
20	Me	*i*-Pr	Me	72	82–84	Et_2O	$C_{23}H_{34}N_4O_2 \cdot C_4H_4O_4 \cdot 0.25H_2O$
21	Me	Bn	Ph	29	95–98	Et_2O	$C_{32}H_{36}N_4O_2 \cdot C_4H_4O_4 \cdot 0.5H_2O$
22	Me	H	Me	35	(soften 68) 88–91	Et_2O	$C_{20}H_{28}N_4O_2 \cdot C_4H_4O_4 \cdot 0.5H_2O$

Table 3. (Sulfonamidomethyl)pyrroles **23–30**

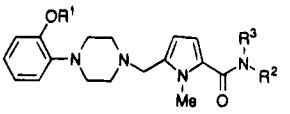


compd	R^1	R^2	R^4	yield (%)	mp (°C)	recryst solvent	formula
23	Me	Me	Me	76	142–144	*i*-PrOH	$C_{20}H_{30}N_4O_3S \cdot C_4H_4O_4$
24	*i*-Pr	Me	Me	53	142–144	*i*-PrOH	$C_{22}H_{34}N_4O_3S \cdot C_4H_4O_4$
25	*i*-Pr	Me	*n*-Bu	76	140–142	*i*-PrOH	$C_{25}H_{40}N_4O_3S \cdot C_4H_4O_4$
26	Me	Me	*i*-Pr	66	140–141	*i*-PrOH	$C_{22}H_{34}N_4O_3S \cdot C_4H_4O_4$
27	Me	Me	*n*-Bu	87	137–138 dec	*i*-PrOH	$C_{23}H_{36}N_4O_3S \cdot 1.5C_4H_4O_4$
28	*i*-Pr	Me	*i*-Pr	84	152–155 dec	*i*-PrOH	$C_{24}H_{38}N_4O_3S \cdot 1.5C_4H_4O_4$
29	Me	Pr	Ph		142–144	MeOH/Et_2O	$C_{27}H_{36}N_4O_3S$
30	Me	*i*-Pr	Me	18	108–110	*a*	$C_{22}H_{34}N_4O_3S$

[a] Purified by chromatography on silica gel, elution with 2% MeOH–CH_2Cl_2.

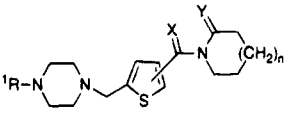
The binding affinities of these compounds for the dopamine D_2 and serotonin 5-HT_{1A} receptors were determined as described earlier.[1] Table 8 shows the results of these studies as percent inhibition of CAR and K_i's for receptor binding and contains data on mazapertine succinate, clozapine, haloperidol, and buspirone for comparison. 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.[19] Any compound inhibiting CAR with an escape loss >20% is considered to have a potential for sedation. In addition, Table 8 shows the stability half-lives for some of the compounds which were evaluated at pH 2 in a citric acid–phosphate buffer

Table 4. Amidopyrroles **31–34**



compd	R^1	R^2	R^3	yield (%)	mp (°C)	recrsyt solvent	formula
31	*i*-Pr	*i*-Pr	H	81	168–170	*i*-PrOH	$C_{23}H_{34}N_4O_2 \cdot C_4H_4O_4$
32	Me	Me	H	26	187–189 dec	EtOH	$C_{19}H_{26}N_4O_2 \cdot C_4H_4O_4$
33	*i*-Pr	Me	H	32	183–185 dec	EtOH	$C_{21}H_{30}N_4O_2 \cdot C_4H_4O_4$
34	*i*-Pr	$-(CH_2)_5-$		43	208–210	*i*-PrOH/Et_2O	$C_{25}H_{36}N_4O_2 \cdot HCl \cdot 0.25H_2O$

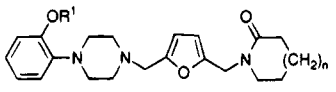
Table 5. Thiophenes **35–41**



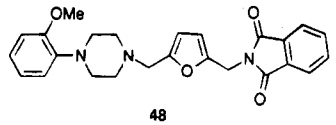
compd	R^1	isomer	X	Y	*n*	yield %	mp (°C)	recryst solvent	formula
35	2-*i*-PrOPh	3	O	H_2	1	53	210.5–212.5	*i*-PrOH	$C_{24}H_{33}N_3O_2S \cdot HCl$
36	2-*i*-PrOPh	3	O	H_2	2	25	199–201 dec	MeOH/*i*-PrOH	$C_{25}H_{35}N_3O_2S \cdot HCl \cdot H_2O$
37	2-*i*-PrOPh	2	O	H_2	1	40	147.5–148.5	*i*-PrOH/Et_2O	$C_{24}H_{33}N_3O_2S \cdot C_4H_4O_4$
38	2-*i*-PrOPh	2	O	H_2	2	40	212–215.5 dec	CH_3CN	$C_{25}H_{35}N_3O_2S \cdot HCl \cdot 0.5H_2O$
39	7-benzofuran	2	O	H_2	1	7	215–220 dec	Et_2O	$C_{23}H_{27}N_3O_2S \cdot HCl \cdot 0.25H_2O$
40	7-benzofuran	2	H_2	O	1	24	*a*	Et_2O	$C_{25}H_{35}N_3O_2S \cdot 1.5C_4H_4O_4 \cdot H_2O$
41	2-*i*-PrOPh	2	H_2	O	1	21	205–209	*i*-PrOH/Et_2O	$C_{24}H_{33}N_3O_2S \cdot HCl$

[a] Amorphous solid.

Table 6. Furans **42–48**



42–47



48

compd	R^1	*n*	yield (%)	mp (°C)	recryst solvent	formula
42	*i*-Pr	1	21	150–151	*i*-PrOH/Et_2O	$C_{24}H_{33}N_3O_3 \cdot C_2H_2O_4 \cdot 0.25H_2O$
43	Me	1	31	155–156	*i*-PrOH/Et_2O	$C_{22}H_{29}N_3O_3 \cdot C_2H_2O_4$
44	Me	2	28	(130 sinter) 135–138	EtOH	$C_{23}H_{31}N_3O_3 \cdot C_2H_2O_4$
45	*i*-Pr	2	37	160–163	EtOH	$C_{25}H_{35}N_3O_3 \cdot C_2H_2O_4$
46	*i*-Pr	3	17	(165 sinter) 168.5–170	*i*-PrOH	$C_{26}H_{37}N_3O_3 \cdot C_2H_2O_4$
47	Me	3	18	(135 sinter) 136.5–138	*i*-PrOH/EtOH	$C_{24}H_{33}N_3O_3 \cdot C_2H_2O_4 \cdot 0.4H_2O$
48			10	(143 sinter) 146.5–148.5	Et_2O/CH_2Cl_2	$C_{25}H_{25}N_3O_4 \cdot C_4H_{10}O \cdot 0.05CH_2Cl_2$

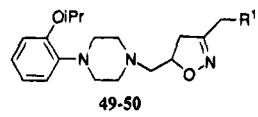
at 22 °C . Compounds which had zero slope for a plot of percent compound remaining versus time were considered stable.

Replacement of the piperazinemethyl of **1** with piperazineethyl provided a stable compound (**6**) at pH 2, which retains comparable activity with **1** in CAR, whereas 2-(methoxyphenyl)piperazine analogue **7** is weakly active (see Table 8). Other related extended pyrroles (**2–5**) which contain a glyoxamide segment, although more stable than **1** in solution, are essentially inactive. Pyrroles **8** and **9**, which contain an ethylene chain connecting the piperidinone to the pyrrole ring, are slightly less active than **1** in CAR but much less stable in acid solution. Compounds **2–7** exhibit significant selectivity (> 10-fold) for the 5-HT_{1A} binding site as opposed to the D_2 receptor, with **5–7** being fairly potent in 5-HT_{1A} binding (K_i < 3 nM).

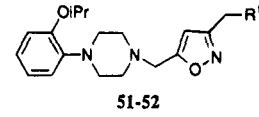
Alteration of the cyclic amide group of **1** to produce either amides **10–22** or sulfonamides **23–30** resulted in decreased (**10** and **12**) or abolished CAR activity with stability half-lives slightly less than that of **1** for the amides and ca. 2 times as long for the sulfonamides. Only sulfonamides **29** and **30** have D_2 binding IC_{50}'s of ca. 10 nM, whereas the remainder of the amides and sulfonamides are much less active. However, both series of compounds bind well to the 5-HT_{1A} receptor, with the most potent compound being amide **15** which has a K_i value of 0.25 nM.

When the amidomethyl group of **1** is replaced by a piperidinecarbonyl group (compound **34**), CAR activity and D_2 receptor binding are significantly decreased. Replacement of the piperidine with an acyclic amine segment, as in **31–33**, abolished both CAR and D_2 activity while affording weak 5-HT_{1A} binding. These

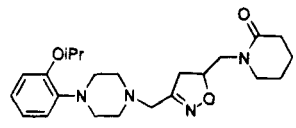
Table 7. Isoxazolines **49**, **50**, and **53**, Isoxazoles **51** and **52**, and Pyridine **54**



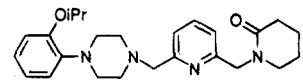
49-50



51-52



53

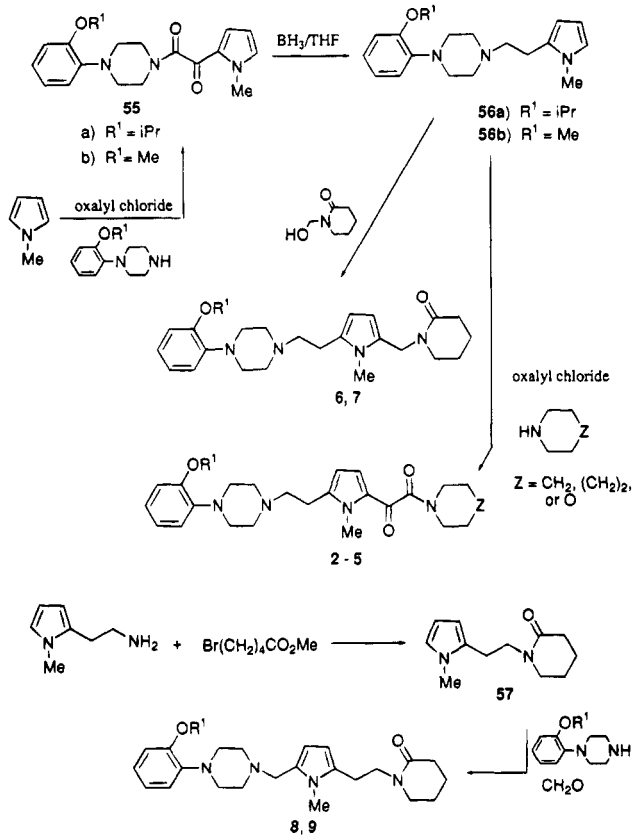


54

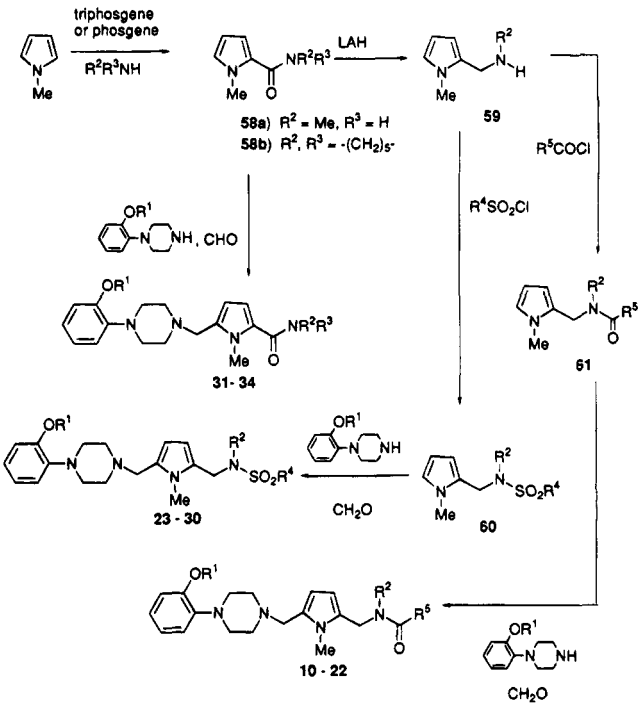
compd	R^1	yield (%)	mp (°C)	recryst solvent	formula
49	OH	52	99–102	CH_2Cl_2/hexane	$C_{18}H_{27}N_3O_3$
50	2-piperidinone	16	161–165 dec	MeOH/Et_2O	$C_{23}H_{34}N_4O_3 \cdot 2HClO_4 \cdot 0.75H_2O$
51	OH	72	102–103	chromatographed	$C_{18}H_{25}N_3O_3$
52	2-piperidinone	27	(softens 110–115) 191–196	Et_2O/CH_2Cl_2	$C_{23}H_{32}N_4O_3 \cdot H_2O \cdot HCl$[a]
53		14	(bubbling 92) 141 dec	MeOH/Et_2O	$C_{23}H_{34}N_4O_3 \cdot HCl \cdot H_2O$[b]
54		23	180–183	*i*-PrOH/Et_2O	$C_{25}H_{34}N_4O_3 \cdot 2.6HCl$

[a] C: calcd, 59.15; found, 58.63. H: calcd, 6.91; found, 7.50. H_2O: calcd, 3.06; found, 4.16. [b] C: calcd, 58.90; found, 59.23. N: calcd, 11.95; found, 12.40. H_2O: calcd, 3.84; found, 5.39.

Scheme 1



Scheme 2

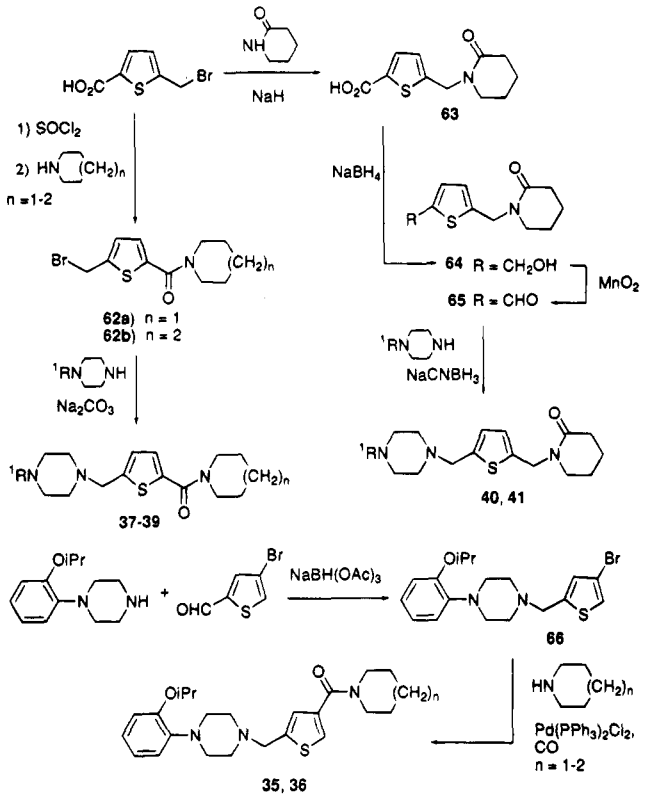


compounds were found to be significantly more stable in solution than **1** at pH 2.

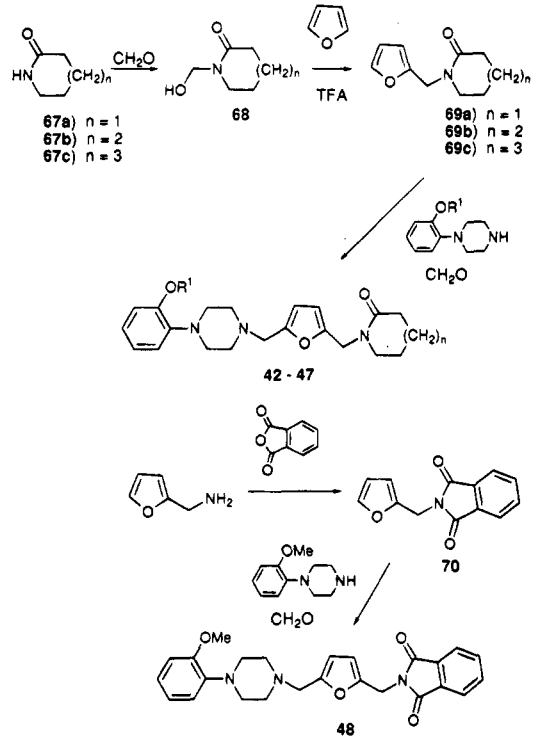
Thus, among the pyrrole analogues of **1**, extended pyrrole **6** appears to be the best compound regarding CAR activity and stability. In addition, **6** possesses an interesting receptor-binding profile in that it has weak D_2-binding activity but is active in CAR and is both selective for and potent at the 5-HT_{1A} binding site.

Two types of thiophene analogues of **1** were prepared. These consist of 2- and 3-aminocarbonyl derivatives **35**–**39** and 2-(amidomethylene)thiophenes **40** and **41**. Within the aminocarbonyl series, piperidinecarbonyl is better than azepinecarbonyl for CAR activity with 3-substitution slightly better than 2-substitution but not as effective compared with **1**. Data from a published series of pyrroles which inhibit CAR suggest that replacement of 2-methoxyphenyl with 7-benzofuran, to give **76**, increases potency in CAR.[20] More recently, the parent piperazine of **76** was found to have good binding affinity at the 5-HT_{1A} receptor.[20] When this structural change was applied to the thiophene Mannich base series, we found that the benzofuran modification abolishes CAR activity, as demonstrated with **39**. However, for amidocarbonyl analogues **40** and **41**, CAR activity is retained with benzofuran but is significantly less compared to **1**. Thiophenes **35**–**41** display high selectivity

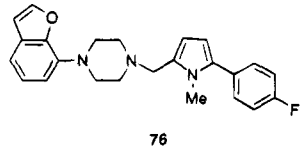
Scheme 3



Scheme 4

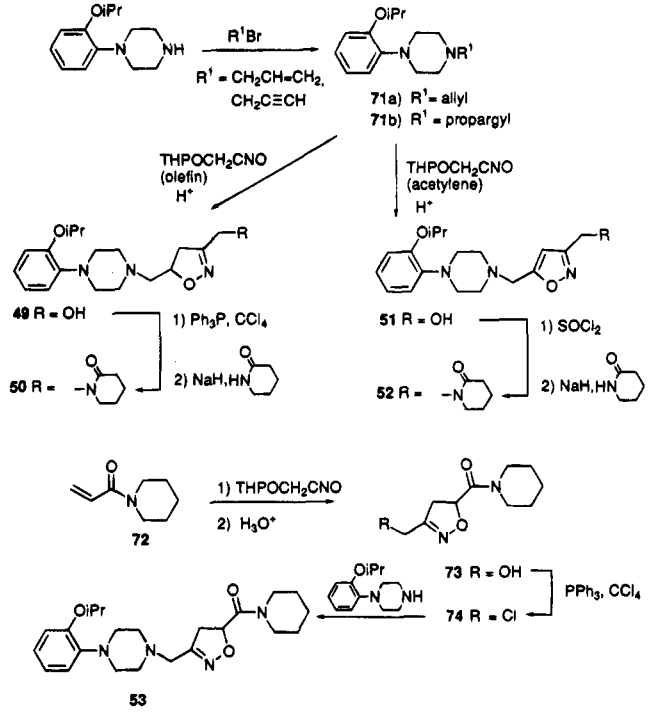


and affinity for the 5-HT_{1A} receptor. The most striking of these is compound **40** which has an exceedingly low IC_{50} of 0.07 nM.

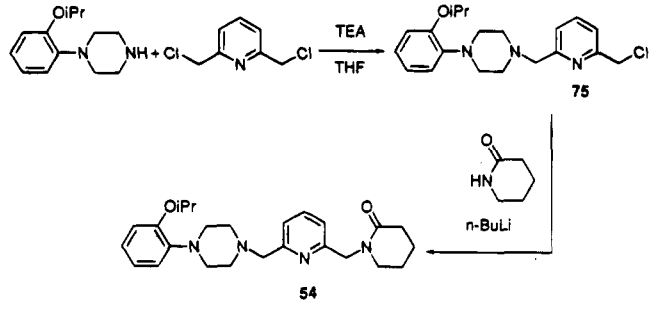


76

Scheme 5



Scheme 6



Furan **42**, the direct analogue of **1**, displays significantly less CAR activity than **1**, while methoxyphenyl analogue **43** is devoid of activity. However, increasing the lactam ring size to 7- and 8-membered rings afforded **44**–**47**, which were roughly as active as **1** in inhibiting CAR. All four compounds are stable in acid solution. Replacing the lactam segment with phthalimide, as in **48**, abolishes CAR activity but provides a compound highly selective for the 5-HT_{1A} receptor. The remaining furans range from moderately active to inactive in D_2 binding and moderately active at the 5-HT_{1A} receptor.

Replacement of the pyrrole segment of **1** with a 5-isoxazoline affords **50** which is less active in CAR, whereas the isomeric 3-isoxazoline **53** and isoxazole **52** are inactive. Interestingly, hydroxymethyl analogue **49**, which represents a marked departure in structure from **1** and is more stable in solution at pH 2, is highly active in CAR, while the corresponding isoxazole **51** is inactive. None of these compounds bind at the D_2 or 5-HT_{1A} sites with the exception of **50** which has a moderately high affinity for the 5-HT_{1A} binding site. The strong CAR activity of **49** coupled with its lack of D_2 binding is in contrast to the profiles observed with classical antipsychotic agents.[21–23] However, this compound may cause sedation because of its significant escape loss

Table 8. Action of Piperazinylalkyl Heterocycles in Blocking CAR and at Selected Binding Sites and Acid Stability of Selected Compounds

	CAR (5 mg/kg, ip)		receptor affinity (K_i, nM)		
compd	inhibtn (%)	esc loss (%)	D_2 [^{3}H]spiperone	5-HT_{1A} [^{3}H]WB4101	$t_{1/2}$ (min)[a]
1	87 98[b] 2.2 mg/kg[c]	8	1.2	4.2	82
2	45	26	≫1000	25	
3	1	0	~100	12	stable
4	2	0	~300	9.4	5103
5	16	1	~300	2.3	stable
6	82	19	26	1.5	stable
7	23	4	~100	1.4	stable
8	75	9	>30	NT	<7
9	77	27	~3	NT	<13
10	63	2	~300	12	70
11	3	0	~100	0.84	64
12	52	2	>1000	39	
14	2	1	~300	4.5	
15	4	0	~50	0.25	
16	36	26	~100	11	
17	13	0	~50	4.7	
18	0	0	81	1.9	
19	3	0	>30	NT	
20	8	0	30	16	
21	8	0	>30	NT	
22	14	3	≫30	NT	
23	23	4	>1000	11	172
24	8	0	NT	4.6	222
25	2	0	~100	18	150
26	6	0	>1000	39	130
27	7	1	~1000	7.1	222
28	0	0	72	5.7	
29	0[b]	0	1–10	NT	
30	1[b]	0	1–10	NT	
31	1	0	~1000	48	22907
32	22	0	>1000	248	stable
33	15	0	>1000	57	4345
34	56[b]	5	1–10	NT	
35	72	34	24	2.5	
36	45	4	28	0.41	
37	56	18	33	4.2	
38	8	3	30	3.2	
39	3	0	>1000	0.63	
40	63	5	333	0.07	
41	58	3	68	3.1	
42	46	0	~100	21	stable
43	10[b]	0	>1000	38	
44	93[b]	11	167	27	stable
45	83[b]	1	122	51	629
46	76[b]	1	130	29	stable
47	99[b]	19	1431	32	stable
48	3b	0	>1000	1.9	
49	96	26	≫1000	120	3652
50	69	20	1841	10	
51	29	1	≫1000	~1000	3463
52	0	0	>1000	94	1098
54	85	15	2415	829	4221
clozapine	9.6 mg/kg[c]		53.6	39	
haloperidol	0.17 mg/kg[c]		0.2	401	
buspirone	4.5 mg/kg[c]		367	5.0	
mazapertine	98 0.66 mg/kg[c]		2.2	1.7	

[a] Stability half-lives at pH 2, concentration ~3×10^{-3} M in citric acid–phosphate buffer at 22 °C. [b] Tested at 15 mg/kg. [c] ED_{50}, ip.

(26%). Compounds **51** and **52** were found to be more stable than **1** in solution at pH 2.

Finally, substitution of a pyridine ring for the pyrrole segment of **1** afforded **54**. This compound, similar to some of the other heterocyclic analogues of **1**, displayed good CAR activity but lacked D_2 and 5-HT_{1A} binding. In addition, **54** was more stable than **1** in acid solution.

Conclusions

Replacement of the *N*-methylpyrrole nucleus of **1** with thiophene, furan, isoxazoline, or pyridine afforded some compounds (**44**, **45**, **47**, **49**, and **54**) which are equipotent with or slightly less potent than **1** in inhibiting CAR and are stable in aqueous solution at pH 2. Modification of the lactam and side chain segments of **1** resulted in compounds where activity was weaker or abolished, with the exception of **6** which retained comparable activity and was acid-stable. The modifications of **1** have, for the most part, led to a decrease or abolishment of D_2 binding while giving rise to compounds which have a high affinity for the 5-HT_{1A} receptor. This receptor-binding profile is similar to that of the non-benzodiaz-

epine anxiolytics buspirone[24] and tandospirone,[25] which interact at both the 5-HT_{1A} and D_2 receptors. Since most known antipsychotic agents show a correlation between D_2-blocking activity and potency in CAR, the observed 5-HT_{1A}-binding selectivity of compounds **6**, **12**, **40**, **44**–**47**, **49**, **50**, and **54** in conjunction with their relatively weak D_2 binding suggests that they are acting to inhibit CAR via a mechanism that is different from D_2 dopaminergic blockade or that dopaminergic active metabolites are responsible. Of these compounds, furans **44** and **47** and pyrrole **6** show considerable promise as candidates for further development as potential antipsychotic agents by meeting our criteria, based on their CAR activity, relatively low escape loss, receptor-binding profile, and stability in acidic solution.

Experimental Section

Chemistry. All melting points are uncorrected and were taken on a Thomas-Hoover Uni-Melt or Laboratory Devices melting point apparatus in capillary melting point tubes. The ^{1}H NMR spectra were obtained on either a 90 MHz Varian EM-390 NMR spectrometer or a 360 MHz Bruker AM-360 NMR spectrometer with Me_4Si as an internal standard. The spectral data for each compound supported the assigned structure, and all elemental and Karl-Fischer analyses were within 0.4% of the calculated values, except as indicated.

General Procedure for the Preparation of Extended Pyrroles 2–5. This procedure is illustrated for the preparation of hexahydro-1-[2-[1-methyl-5-[2-[4-[2-(1-methylethoxy)-phenyl]-1-piperazinyl]ethyl]-1H-pyrrol-2-yl]-1,2-dioxo-1,2-ethanediyl]-1*H*-azepine (**3**). A solution of **56a** (5.00 g, 0.015 mol) and CH_2Cl_2 (15 mL) was added dropwise to an ice-cooled solution of oxalyl chloride (1.96 g, 0.015 mol) and CH_2Cl_2 (15 mL) over 0.5 h. After addition was complete, the resulting mixture was stirred at 25 °C for 0.75 h, cooled in an ice bath, and treated dropwise with a solution of hexamethyleneimine (1.49 g, 0.015 mol) and CH_2Cl_2 (15 mL). The reaction mixture was stirred for 0.5 h after which 3 N NaOH solution (50 mL) was added with thorough mixing. The organic layer was separated, dried over anhydrous K_2CO_3, filtered, and evaporated to 9.60 g of a brown oil. This material was chromatographed on a column of flash silica gel (elution with ether) affording 5.20 g of clear oil. Treatment of this oil (4.20 g) in ethanol with oxalic acid (1.25 g) gave a yellow solid which was recrystallized from ethanol (50 mL) to give 3.70 g (41%) of **3** as a light yellow crystalline solid: mp (sinter 168 °C) 171.5–174 °C; ^{1}H NMR (Me_2SO-d_6) δ 7.00–6.85 (br m, 4H, phenyl H), 6.79 (d, 1H, J = 4.1 Hz, 3H pyrrole), 6.18 (d, 1H, J = 4.1 Hz, 4H pyrrole), 4.64 (p, 1H, J = 6Hz, $CHMe_2$), 3.90 (s, 3H, NCH_3), 3.50 (t, 2H, J = 5.8 Hz, piperazine-NCH_2), 3.30 (t, 2H, J = 5.8 Hz, 5-CH_2 pyrrole), 3.25–2.95 (m, 12H, piperazinyl H, 2- and 7-azepine H), 1.75–1.40 (m, 8H, remaining methylenes), 1.28 (d, 6H, J = 6 Hz, $C(CH_3)_2$). Anal. ($C_{28}H_{40}N_4O_3 \cdot C_2H_2O_4 \cdot 0.3\ C_2H_6O$) C, H, N.

General Procedure for the Preparation of Extended Pyrroles 6 and 7. This procedure is illustrated for the synthesis of 1-[[1-methyl-5-[2-[4-[2-(1-methylethoxy)phenyl]-1-piperazinyl]ethyl]-1*H*-pyrrol-2-yl]methyl]-2-piperidone (**6**). To an ice-cooled solution of *N*-(hydroxymethyl)-2-piperidone (5.08 g, 0.039 mol), **56a** (9.40 g, 0.029 mol), and CH_2Cl_2 (160 mL) was added saturated anhydrous HCl/Et_2O solution in one portion, causing a gummy brown residue to precipitate. The reaction was decanted, and the residue was partitioned between 3 N NaOH and CH_2Cl_2. The organic layer was separated, dried over anhydrous K_2CO_3, filtered, and evaporated to give 15.0 g of brown oil. This material was chromatographed on flash silica gel (elution with 9:1 CH_2Cl_2:Et_2O) yielding 4.76 g of clear oil which was dissolved in *i*-PrOH (20 mL) and treated with oxalic acid (1.36 g). The resulting solid was filtered and recrystallized from *i*-PrOH and EtOH (charcoal), respectively, affording 0.89 g (6%) of **6** as a tan solid: mp (sinter 161 °C) 169.5–172.5 °C; ^{1}H NMR (Me_2SO-d_6) δ 7.03–6.82 (m, 4H, phenyl H), 5.97–5.87 (d, 1H, J = 3.1 Hz, 3H pyrrole), 5.82–5.73 (d, 1H, J = 3.1 Hz, 4H pyrrole), 4.68–4.56 (p, 1H, J = 6 Hz, $CHMe_2$), 4.52–4.43 (s, 2H, 5-CH_2 pyrrole), 3.47–3.37 (s, 3H NCH_3), 3.36–3.11 (m, 8H, piperazine H), 3.11–3.02 (s, 2H, 6H piperidone), 2.99–2.81 (m, 2H, CCH_2 pyrrole), 2.32–2.117 (s, 2H, 3H piperidone), 1.75–1.56 (s, 4H, remaining methylene H), 1.37–1.18 (d, 6H, J = 6 Hz, $C(CH_3)_2$). Anal. ($C_{26}H_{38}N_4O_2 \cdot C_2H_2O_4 \cdot 0.4H_2O$) C, H, N, H_2O.

General Procedure for the Preparation of Pyrroles 8 and 9. This procedure is illustrated for the preparation of 2-[[4-(2-methoxyphenyl)piperazin-1-yl]methyl]-1-methyl-5-[2-(2-oxopiperidin-1-yl)-1-ethyl]pyrrole (**8**). A solution of 2-(2-aminoethyl)-*N*-methylpyrrole (4.96 g, 0.04 mol) and TEA (5.6 mL, 0.04 mol) in toluene (60 mL) was treated with 5-bromovaleric acid methyl ester (7.89 g, 0.04 mol) in toluene (20 mL) and stirred at 70 °C overnight. The reaction mixture was cooled and treated with H_3PO_4/$NaHPO_4$ solution and Et_2O with thorough mixing. The organic layer was separated, and the aqueous layer was extracted with Et_2O. The organic layers were combined, dried over anhydrous K_2CO_3, filtered, and evaporated to a light yellow oil. This material was crystallized from CH_2Cl_2 and hexane to give **57** as a white solid.

Compound **57** (2.06 g, 0.01 mol) in MeOH (8.0 mL) was added to a solution of 1-(2-methoxyphenyl)piperazine acetate (2.52 g, 0.01 mol), acetic acid (2 drops), 37% formalin (0.8 mL, 0.01 mol), and MeOH (8.0 mL) at 25 °C. After stirring overnight, the solution was diluted with CH_2Cl_2 (80 mL) and mixed thoroughly with 1 N NaOH (30 mL). The organic phase was separated, washed with 1 N HCl, dried over $MgSO_4$, filtered, and evaporated. The solid residue was recrystallized twice from *i*-PrOH and Et_2O, using charcoal, and triturated with acetone to give 1.60 g (36%) of **8** as a light pink crystalline solid: mp 173 °C; ^{1}H NMR ($CDCl_3$) δ 7.29–6.86 (m, 4H, phenyl H), 6.33 (d, 1H, J = 6.4 Hz, pyrrole 3H), 5.96 (d, 1H, J = 3.5 Hz, pyrrole 4H), 4.24 (s, 2H, piperazinyl CH_2), 3.86 (s, 3H, OCH_3), 3.76 (s, 3H, NCH_3), 3.57–3.47 (m, 8H, piperazine H), 3.27–3.25 (m, 2H, 5-pyrrolyl CH_2), 2.86–2.82 (t, 2H, J = 7.6 Hz, piperidinone 6H), 2.34 (t, 2H, J = 6 Hz, piperidinonyl CH_2), 1.79–1.78 (s, 4H, piperidinone 3- and 5H), 1.22–1.20 (m, 2H, piperidinone 4H). Anal. ($C_{24}H_{34}N_4O_2 \cdot HCl$) C, H, N.

General Procedure for the Preparation of (Amidomethyl)pyrroles 10–22. This procedure is illustrated for the preparation of *N*-methyl-*N*-[[1-methyl-5-[[4-[2-(1-methylethoxy)phenyl]-1-piperazinyl]methyl]-1*H*-pyrrol-2-yl]methyl]acetamide (**10**). An ice-cooled solution of *N*-methylpyrrole (85.93 g, 1.06 mol) and Et_2O (400 mL) was treated dropwise with a solution of triphosgene (104.78 g, 0.353 mol) in Et_2O (400 mL) over 40 min and stirred at 25 °C overnight. The reaction mixture was then added slowly to 40% aqueous CH_3NH_2 (500 mL) and Et_2O (250 mL) with ice bath cooling. After 1 h, the organic layer was separated, washed with water (150 mL) followed by saturated $NaHCO_3$ solution (150 mL), dried over anhydrous $MgSO_4$, filtered, and evaporated to give 117.06 g of **58a** as a light green solid.

A solution of **58a** (25.0 g, 0.181 mol) in dioxane (275 mL) was added to a suspension of LAH (10.31 g, 0.272 mol) in dioxane (250 mL) at 25 °C under argon. The reaction mixture was slowly heated to reflux and maintained at that temperature for 2 h. After cooling, the reaction mixture was treated with successive portions of water (10.31 mL), 3 N NaOH (10.31 mL), water (20.0 mL), and $MgSO_4$, filtered, and evaporated to give 13.97 g of **59** as an oil.

Pyrrole **59** (4.66 g, 0.038 mol), TEA (7.85 mL, 0.056 mol), and CH_2Cl_2 (75 mL) were combined, cooled in an ice bath, and treated with acetyl chloride (3.20 mL, 0.045 mol) in CH_2Cl_2 (20 mL). After stirring for 17 h, water (50 mL) and CH_2Cl_2 (50 mL) were added, the organic layer was separated, washed with saturated $NaHCO_3$ solution and saturated NaCl solution, dried over $MgSO_4$, filtered, and evaporated to give 6.38 g of **61** as an oil.

A solution of 1-[2-(1-methylethoxy)phenyl]piperazine fumarate[1] (12.27 g, 0.037 mol), 37% formalin (2.74 mL, 0.037 mol), and MeOH (75 mL) at 25 °C was treated with **61** (6.00 g, 0.036 mol) in MeOH (25 mL) and stirred for 2 h. The reaction mixture was concentrated on a rotary evaporator to an oil which was partitioned between saturated $NaHCO_3$ solution and CH_2Cl_2. The organic layer was separated, washed with

saturated NaCl solution, dried over $MgSO_4$, filtered, and evaporated to a reddish oil. This material was chromatographed on flash silica gel (elution with 6% EtOH–CH_2Cl_2) to give an oil (4.12 g) which was treated with fumaric acid (1.20 g) in 2-propanol (25 mL) affording 3.71 g (20%) of **10** as white solid: mp 140–141 °C; ^{1}H NMR (Me_2SO-d_6) δ 6.92–6.81 (br s, 4H, phenyl H), 6.61 (s, 2H, fumarate vinyl H), 5.90–5.85 (m, 2H, 3- and 4-pyrrole H), 4.62–4.53 (m, 1H, $CHMe_2$), 4.45 (s, 2H, $2CH_2$ pyrrole), 3.48 (s, 3H, pyrrole NCH_3), 3.08–2.87 (s, 4H, piperazinyl H), 2.80 (s, 3H, NCH_3), 2.60–2.42 (s, 4H, piperazinyl H), 2.01 (s, 3H, CH_3), 1.30–1.18 (d, 6H, $C(CH_3)_2$). Anal. ($C_{23}H_{34}N_4O_2 \cdot C_4H_4O_4$) C, H, N.

General Procedure for the Preparation of (Sulfonamidomethyl)pyrroles 23–30. This procedure is illustrated for *N*-methyl-*N*-[[5-[[4-[2-(1-methylethoxy)phenyl]-1-piperazinyl]methyl]-1-methyl-1*H*-pyrrol-2-yl]methyl]methylsulfonamide (**24**). An ice-cooled solution of **59** (4.66 g, 0.038 mol), Et_3N (5.70 g, 0.056 mol), and CH_2Cl_2 (75 mL) was treated dropwise with a solution of methanesulfonyl chloride (5.15 g, 0.045 mol) in CH_2Cl_2 (20 mL) and stirred overnight at 25 °C. A further 50 mL of CH_2Cl_2 was added followed by water (50 mL). The organic layer was separated, washed successively with saturated $NaHCO_3$ solution and saturated NaCl solution, dried over $MgSO_4$, filtered, and evaporated to give 7.59 g of **60a** as an oil.

This material (3.50 g, 0.018 mol) was added as a solid to a mixture of 1-[2-(1-methylethoxy)phenyl]piperazine fumarate (6.12 g, 0.018 mol), 37% formalin (1.37 mL, 0.018 mol), and MeOH (40 mL) at 25 °C. After stirring for 16 h, the reaction mixture was concentrated on a rotary evaporator to an oil which was dissolved in CH_2Cl_2 and mixed thoroughly with saturated $NaHCO_3$ solution; gas evolution ceased. The organic layer was separated, dried over $MgSO_4$, filtered, and evaporated to give an oil. Trituration of this material afforded a white solid (5.06 g) which was dissolved in *i*-PrOH (100 mL) and treated with fumaric acid (1.29 g) to yield 5.23 g (53%) of **24** as a white solid: mp 142–144 °C; ^{1}H NMR (Me_2SO-d_6) δ 6.95–6.80 (s, 4H, phenyl H), 6.61 (s, 2H, fumarate vinyl H), 6.00–5.97 (d, 1H, J = 3 Hz, 4H pyrrole), 5.92–5.89 (d, 1H, J = 3 Hz, 3H pyrrole), 4.62–4.50 (p, 1H, J = 6 Hz, $CHMe_2$), 4.18 (s, 2H, 2-CH_2 pyrrole), 3.57 (s, 3H, pyrrole NCH_3), 3.48 (s, 2H, 5-CH_2 pyrrole), 3.10–2.90 (s, 4H, piperazinyl H), 2.91 (s, 3H, SO_2CH_3), 2.57 (s, 3H, NCH_3), 2.50 (s, 4H, piperazinyl H), and 1.30–1.17 (d, 6H, J = 6 Hz, $C(CH_3)_2$). Anal. ($C_{22}H_{34}N_4O_3S \cdot C_4H_4O_4$) C, H, N.

General Procedure for the Preparation of Amidopyrroles 31–33. This procedure is illustrated for compound 5-[[4-[2-(1-methylethoxy)phenyl]-1-piperazinyl]methyl]-*N*,1-dimethyl-1*H*-pyrrole-2-carboxamide (**33**). Pyrrole **58a** (3.50 g, 0.025 mol), 37% formaldehyde solution (2.20 mL, 0.027 mol), 1-[2-(1-methylethoxy)phenyl]piperazine fumarate (8.61 g, 0.026 mol), and EtOH (84 mL) were combined, refluxed for 3.5 h, and stirred overnight at 25 °C. A white solid was filtered from the reaction mixture and recrystallized from EtOH (40 mL) affording 3.91 g (32%) of **33** as a white crystalline solid: mp 183–185 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 7.92–7.84 (s, 1H, NH), 6.93–6.80 (s, 4H, phenyl H), 6.62 (s, 3H, pyrrole 3H, fumarate vinyl H), 6.00–5.93 (d, 1H, J = 3.79 Hz, pyrrole 4H), 4.64–4.51 (p, 1H, J = 6 Hz, $CHMe_2$), 3.87 (s, 3H, pyrrole NCH_3), 3.50 (s, 2H, 5-CH_2 pyrrole), 3.05–2.88 (s, 4H, piperazinyl H), 2.70 (s, 3H, NCH_3), 2.60–2.45 (s, 4H, piperazinyl H), 1.30–1.20 (d, 6H, J = 6 Hz, $C(CH_3)_2$). Anal. ($C_{21}H_{30}N_4O_2 \cdot C_4H_4O_4$) C, H, N.

2-[[4-[1-(Methylethoxy)phenyl]piperazin-1-yl]methyl]-1-methyl-5-(piperidin-1-ylcarbonyl)pyrrole Monohydrochloride Hydrate (34). A solution of *N*-methylpyrrole (8.1 g, 0.10 mol), phosgene (9.80 g, 0.10 mol), and Et_2O (200 mL) was stirred at 25 °C overnight. The Et_2O was removed to give a yellow oil. This material (4.20 g, 0.03 mol) in Et_2O (10 mL) was added to a solution of piperidine (2.80 g, 0.033 mol), Et_3N (3.03 g, 0.03 mol), and CH_2Cl_2 (40 mL) and stirred overnight at 25 °C. Water was added with thorough mixing, and the organic layer was separated. The aqueous layer was washed with Et_2O, and the organic layer was separated and combined with the original organic layer. After washing with 1 N NaOH, the organic phase was dried over Na_2SO_4, filtered, and evaporated to give **58b** as a thick oil.

A solution of **58b** (1.92 g, 0.01 mol) in MeOH (10 mL) was added to a solution of 1-[2-(1-methylethoxy)phenyl]piperazine dihydrochloride (2.93 g, 0.01 mol), NaOAc (1.64g, 0.02 mol), 37% formalin (0.80 mL, 0.01 mol), and MeOH (20 mL) at 0 °C and stirred overnight at 25 °C. An additional amount of formalin (0.30 mL) was added, and stirring was continued for another 24 h. The reaction mixture was diluted with water (40 mL), made basic with 1 N NaOH, and extracted with CH_2Cl_2. The organic layers were combined, washed with 1 N HCl, dried over $MgSO_4$, filtered, and evaporated. The residual oil was crystallized from *i*-PrOH. This material was recrystallized from *i*-PrOH–Et_2O to give 2.00 g (43%) of **34** as a white crystalline solid: mp 208–210 °C; ^{1}H NMR ($CDCl_3$) δ 7.05–6.95 (m, 4H, phenyl H), 6.53 (s, 1H, pyrrole 3H), 6.34 (s, 1H, pyrrole 4H), 4.66 (p, 1H, J = 6 Hz, $CHMe_2$), 4.33 (s, 2H, piperazinyl CH_2), 3.91 (s, 3H, NCH_3), 3.80–3.68 (m, 10H, piperazine H, piperidinone 2- and $6H_{ax}$), 3.18 (br s, 2H, piperidinone 2- and $6H_{eq}$), 1.58–1.77 (m, 6H, piperidinone 3-, 4-, and 5H), 1.44 (d, 6H, J = 6 Hz, $C(CH_3)_2$). Anal. ($C_{25}H_{36}N_4O_2 \cdot HCl \cdot 0.25H_2O$) C, H, N.

General Procedure for the Preparation of Thiophenes 35 and 36. This procedure is illustrated for the synthesis of 1-[[5-[[4-[1-(methylethoxy)phenyl]-1-piperazinyl]methyl]-3-thienyl]carbonyl]piperidine (**35**). A mixture of **66** (3.0 g, 0.0076 mol) as the free base, piperidine (6.45 g, 0.0076 mol), and Pd(PPh_3)$_2Cl_2$ (100 mg) was placed in a bomb, purged with CO, and heated at 100 °C for 3 h. An additional amount of piperidine (6.45 g, 0.0076 mol) was added, and heating was continued overnight. The reaction mixture was purified using HPLC (gradient elution, 99:1–98:2 of $CHCl_3$:10% NH_4OH/MeOH) to give a clear syrup, 2.6 g. This material was converted to the monohydrochloride salt in 2-propanol, using Et_2O/HCl. Recrystallization from 2-propanol produced **35** (1.82 g, 53%): mp 210.5–212.5 °C; ^{1}H NMR (Me_2SO-d_6) δ 7.91 (s, 1H, thiophene 2H), 7.48 (s, 1H, thiophene 4H), 7.0–6.82 (m, 4H, phenyl H), 4.65 (s, 2H, piperazinyl CH_2), 4.65–4.58 (m, 1H, J = 6 Hz, $CHMe_2$), 3.60–3.40 (m, 8H, piperazine H), 3.25–2.95 (m, 4H, piperidine 2- and 6-H), 1.70–1.50 (m, 6H, remaining piperidine H), 1.30–1.22 (d, 6H, J = 6 Hz, $C(CH_3)_2$). Anal. ($C_{24}H_{33}N_3O_2S \cdot HCl$) C, H, N.

General Procedure for the Preparation of Thiophenes 37–39. This procedure is illustrated for the preparation of 1-[[5-[[4-[2-(1-methylethoxy)phenyl]-1-piperazinyl]methyl]-2-thienyl]carbonyl]piperidine fumarate (**37**). A mixture of 5-(bromomethyl)-2-thiophenecarboxylic acid (13.00 g, 0.059 mol) and thionyl chloride (20 mL) were refluxed 1 h. The excess thionyl chloride was evaporated, and the residue was dissolved in CH_2Cl_2 (25 mL). After cooling in an ice bath, the solution was treated dropwise with a solution of piperidine (5.51 g, 0.065 mol), NEt_3 (6.50 g, 0.064 mol), and CH_2Cl_2 (25 mL) over 20 min. After stirring for 15 min at 0 °C, the reaction mixture was poured onto ice, and the organic layer was separated and washed with dilute HCl, 10% Na_2CO_3, and water. The organic layer was dried over $MgSO_4$, filtered, and evaporated to a brown oil which was purified using HPLC (elution with 4:1 hexane:EtOAc) affording 8.10 g of **62a** as a solid.

This material (2.88 g, 0.01 mol), 1-[2-(methylethoxy)phenyl]-piperazine fumarate (3.20 g, 0.095 mol), and *N*-methylpyrrolidinone (20 mL) were combined and stirred at 25 °C for 4 h. At this point, Na_2CO_3 (2.10 g, 0.19 mol) was added, and the mixture was stirred overnight and then heated on a steam bath for 1 h. The reaction mixture was poured into water and extracted with Et_2O. The organic layer was washed with saturated NaCl solution, dried over Na_2SO_4, filtered, and evaporated to give 3.36 g of **37** as a crude oil. This material was chromatographed on flash silica gel (elution with 98:2 $CHCl_3$:10% NH_4OH) to give an oil (2.10 g) which was treated with fumaric acid (0.57 g) in *i*-PrOH (40 mL). A crystalline solid formed which was collected and recrystallized from *i*-PrOH–Et_2O affording **37** as a fumarate salt (2.08 g, 40%): mp 147.5–148.5 °C; ^{1}H NMR (Me_2SO-d_6) δ 7.22 (s, 1H, thiophene 3H), 6.99 (s, 1H, thiophene 4H), 6.92–6.82 (m, 4H, phenyl H), 4.62–4.53 (m, 1H, J = 6 Hz, $CHMe_2$), 3.75 (s, 2H, piperazinyl CH_2), 3.62–3.55 (m, 4H, 2- and 6-piperazine H),

3.09–2.95 (m, 4H, piperazine 3- and 5H), 2.65–2.50 (m, 4H, piperidine 2- and 6 H), 1.70–1.50 (m, 6H, remaining piperidine H), 1.28–1.20 (d, 6H, J = 6 Hz, $C(CH_3)_2$). Anal. ($C_{24}H_{33}N_3O_2S \cdot C_4H_4O_4$) C, H, N.

General Procedure for the Preparation of Thiophenes 40 and 41. The general procedure is illustrated for 1-[[5-[[4-[2-(1-methylethoxy)phenyl]-1-piperazinyl]methyl]-2-thienyl]-methyl]-2-piperidinone (**41**). To a mixture of NaH (1.95 g, 0.065 mol) in toluene (100 mL) was added 2-piperidinone (6.40 g, 0.065 mol), and the resulting mixture was stirred for 0.5 h. After cooling in an ice bath, the mixture was treated dropwise with a solution of 5-(bromomethyl)-2-thiophenecarboxylic acid (11.8 g, 0.05 mol) and toluene (50 mL). The resulting blood-red mixture was stirred for 1 h, poured into ice water, and extracted with Et_2O. The ether layer was washed with dilute HCl, 10% Na_2CO_3, water, and brine. The ether layer was dried over $MgSO_4$, filtered, treated with charcoal, filtered, and evaporated to give **63** as a yellow semisolid (5.6 g).

This material (4.40 g, 0.017 mol) and sodium borohydride (6.40 g, 0.017 mol) were combined in EtOH (100 mL) and refluxed for 8 h. Water was added, and the reaction mixture was extracted with $CHCl_3$. The organic layer was separated, dried over $MgSO_4$, filtered, and evaporated. The residue was chromatographed on flash silica gel (2:1 hexane:acetone eluant) to give 2.0 g of a yellow oil. This material was dissolved in CH_2Cl_2, washed with 10% Na_2CO_3, separated, dried over $MgSO_4$, filtered, and evaporated affording carbinol **64** as a yellow oil, 1.8 g.

This yellow oil (1.70 g, 0.0075 mol) and MnO_2 (8.50 g, 0.097 mol) were combined in CH_2Cl_2 (70 mL) and stirred at room temperature for 1 h. The reaction mixture was filtered through diatomaceous earth and evaporated to give aldehyde **65** as a yellow oil, 1.45 g.

A solution of **65** (1.45 g, 0.0065 mol), 1-[2-(methylethoxy)-phenyl]piperazine (1.40 g, 0.0065 mol), glacial acetic acid (0.39 g, 0.0065 mol), and MeOH (20 mL) was treated with sodium cyanoborohydride (0.44 g, 0.007 mol), and the resulting mixture was stirred overnight at room temperature. The solvent was evaporated, and the residue was slurried in 3 N NaOH. Extraction with Et_2O, drying over Na_2SO_4, treatment with charcoal, and filtration produced a clear oil. The material was chromatographed on flash silica gel (98:2 CH_2Cl_2:10% NH_4OH) to give 0.65 g of a solid. The HCl salt was prepared in Et_2O and recrystallized from i-PrOH–Et_2O affording **41** (0.64 g, 21%): mp 205–209 °C; ^{1}H NMR (Me_2SO-d_6) δ 7.25 (s, 1H, thiophene 3H), 7.05 (s, 1H, thiophene 4H), 7.00–6.83 (m, 4H, phenyl H), 4.63 (s, 2H, piperazinyl CH_2), 4.62–4.55 (m, 1H, J = 6 Hz, $CHMe_2$), 4.60 (s, 2H, piperidinone 2H), 3.60–2.92 (m, 10H, piperazine H, piperidinone 6H), 2.28 (m, 2H, piperidinone 3H), 1.77–1.64 (m, 4H, remaining piperidine H), 1.32–1.22 (d, 6H, J = 6 Hz, $C(CH_3)_2$). Anal. ($C_{24}H_{33}N_3O_2S \cdot HCl$) C, H, N.

General Procedure for the Preparation of Furans 42–47. This procedure is illustrated for the preparation of hexahydro-1-[[5-[[4-[2-(1-methylethoxy)phenyl]-1-piperazinyl]-methyl]-2-furanyl]methyl]-1*H*-azepin-2-one (**45**). A mixture of 2-oxohexamethyleneimine (**67b**; 50.0 g, 0.44 mol) and paraformaldehyde was heated at 100–110 °C for 3 h and cooled to give 59.45 g of **68** as a clear syrup.

Trifluoroacetic acid (23.95 g, 0.21 mol) was added to an ice-cooled mixture of **68** (30.0 g, 0.21 mol) and furan (14.29 g, 0.21 mol), and the resulting solution was stirred at 25 °C for 4 h. The reaction mixture was dissolved in CH_2Cl_2 (100 mL) and mixed thoroughly with 3 N NaOH (80 mL). The organic layer was separated, dried over anhydrous K_2CO_3, filtered, and evaporated to give 37.0 g of a yellow oil. This material was chromatographed on flash silica gel (elution with Et_2O) affording 19.40 g of **69b** as a yellow oil.

A solution of 1-[2-(methylethoxy)phenyl]piperazine fumarate (8.70 g, 0.026 mol), 37% formalin (2.50 mL, 0.031 mol), and water (140 mL) was treated with **69b** (5.00 g, 0.026 mol) and refluxed overnight. The reaction mixture was cooled, decanted from a dark residue which had formed, and treated with 3 N NaOH (20 mL). The basic mixture was extracted twice with CH_2Cl_2 (175 mL). The organic layers were combined, dried over anhydrous K_2CO_3, filtered, and evaporated to give a brown oil. Chromatography of this material on flash silica gel gave a light brown oil (7.32 g) which was treated with oxalic acid (2.17 g) in EtOH (45 mL), yielding a white solid. This was recrystallized from EtOH, affording 4.68 g (37%) of **45** as a white solid: mp 160–163 °C; ^{1}H NMR (Me_2SO-d_6) δ 6.99–6.79 (br s, 4H, phenyl H), 6.42 (s, 1H, furan 4H), 6.32 (s, 1H, furan 3H), 4.65–4.53 (p, 1H, J = 6 Hz, $CHMe_2$), 4.47 (s, 2H, piperazinyl CH_2), 3.96 (s, 2H, piperidinone CH_2), 3.46–3.31 (d, 2H, J = 8 Hz, piperidinone 6H), 3.26–2.97 (br s, 4H, piperazine 2- and 6H), 2.96–2.72 (br s, 4H, piperazine 3- and 5H), 2.48–2.35 (m, 2H, piperidinone 3H), 1.71–1.33 (m, 6H, remaining methylenes), 1.33–1.13 (d, 6H, J = 6 Hz, $C(CH_3)_2$). Anal. ($C_{25}H_{35}N_3O_3 \cdot C_2H_2O_4$) C, H, N.

2-[[5-[[4-(2-Methoxyphenyl)-1-piperazinyl]methyl]-2-furanyl]methyl]-1*H*-isoindole-1,3(2*H*)-dione (48). A mixture of 2-(aminomethyl)furan (11.99 g, 0.124 mol) and phthalic anhydride (20.0 g, 0.135 mol) was heated at 120–130 °C for 45 min, cooled, and dissolved in EtOH. On cooling a white precipitate formed which was filtered to give 21.50 g of **70** as a white crystalline solid. A solution of **70** (6.00 g, 0.026 mol) in n-PrOH (48 mL) was added to a solution of 1-(2-methoxyphenyl)piperazine hydrochloride (6.00 g, 0.026 mol), 37% formalin (3.20 mL, 0.039 mol), and water (12.0 mL). After the addition of more n-PrOH (24 mL), the reaction mixture was stirred at reflux for 48 h. The reaction mixture was cooled and concentrated, and the residue was dissolved in CH_2Cl_2 and mixed thoroughly with 3 N NaOH. The organic layer was separated, dried over K_2CO_3, filtered, and evaporated, yielding a brown oil. Chromatography of this material on flash silica gel (elution with Et_2O) gave a yellow crystalline solid which was recrystallized from CH_2Cl_2–Et_2O, affording 1.10 g (10%) of **48** as a white crystalline solid: mp (sinter 143 °C) 146.5–148.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.88 (m, 2H, isoindoledione 3- and 6H), 7.72 (m, 2H, isoindoledione 4- and 5H), 7.01–6.82 (m, 4H, phenyl H), 6.27 (d, 1H, J = 2.94 Hz, furan 3H), 6.17 (d, 1H, J = 2.94 Hz, furan 4H), 4.85 (s, 2H, isoindoledionyl CH_2), 3.83 (s, 3H, OCH_3), 3.58 (s, 2H, piperazinyl CH_2), 3.08 (br s, 4H, piperazine H), 2.68 (br s, 4H, piperazine H). Anal. ($C_{25}H_{25}N_3O_4 \cdot 0.1C_4H_{10}O \cdot 0.05CH_2Cl_2$) C, H, N.

4,5-Dihydro-5-[[4-[2-(1-methylethoxy)phenyl]-1-piperazinyl]methyl]-3-isoxazolemethanol (49). A solution of 1-[2-(methylethoxy)phenyl]piperazine (57.0 g, 0.26 mol) in THF (700 mL) was treated with allyl bromide (37.60 g, 0.31 mol) and TEA (34.0 g, 0.34 mol) and then stirred at reflux for 18 h. The reaction mixture was cooled, poured into 1 N HCl solution, and washed with Et_2O. The aqueous layer was separated, made basic with Na_2CO_3, and extracted with $CHCl_3$. The organic layers were combined, dried over anhydrous K_2CO_3, filtered, and evaporated to give an oil. This material was purified by HPLC (elution with 99:0.75:0.25 $CHCl_3$:MeOH:NH_4OH) affording 50.0 g of **71a** as an orange oil.

Compound **71a** (17.15 g, 0.065 mol) was dissolved in dry toluene (67 mL), and the resulting solution was treated successively with $THPOCH_2CH_2NO_2$[17] (17.31 g, 0.099 mol), PhNCO (31.4 g, 0.26 mol), and Et_3N (0.67 g, 0.0065 mol) and heated at 30 °C. After 12 h the temperature was raised to 55 °C, and after 40 h an additional 28.6 mL of PhNCO was added. The reaction mixture was maintained at 55 °C for another 52 h and was then cooled to 25 °C and filtered. The filtrate was treated with water (5 mL), filtered, dried over anhydrous Na_2SO_4, filtered, and evaporated on a rotary evaporator. The residue was slurried with Et_2O and filtered, and the filtrate was washed successively with 1 N HCl solution and saturated $NaHCO_3$ solution. The HCl wash was made basic with solid Na_2CO_3 and extracted with $CHCl_3$. The organic layer was separated, dried over anhydrous Na_2SO_4, filtered, and evaporated yielding a dark red-brown oil which was chromatographed by HPLC (elution with 1% MeOH–$CHCl_3$) affording 11.35 g (52%) of **49** as a golden-brown crystalline solid: mp 99–102 °C; ^{1}H NMR ($CDCl_3$) δ 6.99–6.82 (m, 4H, phenyl H), 4.90–4.80 (m, 1H, 4,5-dihydrooxazole 5H), 4.67–4.58 (p, 1H, J = 6 Hz, $CHMe_2$), 4.41 (s, 2H, piperazinyl CH_2), 3.20–3.05 (m, 4H, piperazine H), 2.95–2.85 (m, 1H, 4,5-dihydrooxazole 4H), 2.80–2.62 (m, 4H, piperazine H), 2.61–2.47 (m, 1H, 4,5-dihydrooxazole 4H), and 1.39–1.30 (d, 6H, J = 6 Hz, $C(CH_3)_2$). Anal. ($C_{18}H_{27}N_3O_3$) C, H, N.

1-[[4,5-Dihydro-5-[[4-[2-(1-methylethoxy)phenyl]-1-piperazinyl]methyl]-3-isoxazolyl]methyl]-2-piperidinone Perchlorate Hydrate (50). A solution of carbinol **49** (9.50 g, 0.029 mol) in CCl_4 (50 mL) at 25 °C was treated with PPh_3 (9.72 g, 0.037 mol) and refluxed for 18 h. The reaction mixture was cooled and filtered, and the filtrate was concentrated to a dark residue. This material was dissolved in CCl_4 and slowly concentrated in stages, filtering off triphenylphosphine oxide at each stage. The last concentrate was evaporated to a dark oil. A solution of this oil (7.40 g) in DMF (500 mL) was added to a solution of an 80% dispersion of NaH (1.01 g, 0.042 mol) and γ-valerolactam (4.17 g, 0.042) in THF (250 mL) at 25 °C. After stirring for 50 h, the reaction mixture was poured into an ice–water mixture and extracted several times with ethyl acetate. The organic layers were combined, washed with water several times, dried over anhydrous Na_2SO_4, filtered, and evaporated to an oil. HPLC purification (elution with 99:1 $CHCl_3$:MeOH) of this material followed by flash chromatography on silica gel (elution with 98.5:1.5 $CHCl_3$:MeOH) afforded 1.60 g of a brown oil. A solution of this oil in MeOH (50 mL) was treated with $HClO_4$ (0.49 mL) and concentrated on a hot plate followed by addition of Et_2O to give a beige solid which was recrystallized from MeOH–Et_2O affording 2.15 g (16%) of **50** as a tan powder: mp 161–165 °C dec; ^1H NMR (D_2O) δ 7.22–7.01 (m, 4H, phenyl H), 5.21 (m, 1H, 4,5-dihydrooxazole H), 4.74 (p, 1H, J = 6 Hz, $CHMe_2$), 4.29 (s, 2H, pyrrolidinone CH_2), 3.58 (br s, 4H, piperazine H), 3.60–3.30 (m, 5H, piperazine H, 4,5-dihydrooxazole 4H), 2.87 (m, 1H, 4,5-dihydrooxazole 4H), 2.39 (t, 2H, J = 6.1 Hz, 3-piperidinone H), 1.81 (m, 4H, 3- and 4-piperidinone H), 1.34 (d, 6H, J = 6.0 Hz, $C(CH_3)_2$). Anal. ($C_{23}H_{37}ClN_4O_8 \cdot 2HClO_4 \cdot 0.75H_2O$) C, H, N.

5-[[4-[2-(1-Methylethoxy)phenyl]-1-piperazinyl]methyl]-3-isoxazolemethanol (51). A solution of 1-[2-(methylethoxy)-phenyl]piperazine (22.0 g, 0.10 mol) in THF (750 mL) was treated with propargyl bromide (14.30 g, 0.12 mol) and TEA (13.20 g, 0.13 mol) and then stirred at reflux for 48 h. The reaction mixture was cooled, poured into 1 N HCl solution (300 mL), and washed with Et_2O. The aqueous layer was separated, made basic with Na_2CO_3, and extracted with 5 × 50 mL portions of $CHCl_3$. The organic layers were combined, dried over anhydrous K_2CO_3, filtered, and evaporated to give an oil. This material was purified by HPLC (elution with 97:2.6:0.4 $CHCl_3$:MeOH:NH_4OH) affording 15.77 g of **71b** as a golden-brown solid.

Compound **71b** (5.17 g, 0.020 mol) was dissolved in dry toluene (19 mL), and the resulting solution was treated successively with $THPOCH_2CH_2NO_2$ (5.26 g, 0.030 mol), PhNCO (9.53g, 0.080 mol), and Et_3N (0.202 g, 0.0002 mol) and heated at 50 °C. After 12 h the temperature was raised to 55 °C, and after 16 h an additional 8.0 mL of PhNCO was added. The reaction mixture was maintained at 55 °C for another 24 h and then cooled to 25 °C and filtered. The filtrate was treated with water (3 mL), filtered, dried over anhydrous Na_2SO_4, filtered, and evaporated on a rotary evaporator. The residue was slurried with Et_2O and filtered, and the filtrate was washed successively with 1 N HCl solution and saturated $NaHCO_3$ solution. The HCl wash was made basic with solid Na_2CO_3 and extracted with $CHCl_3$. The organic layer was separated, dried over anhydrous Na_2SO_4, filtered, and evaporated yielding a dark red oil which was chromatographed by HPLC (elution with 1% MeOH–$CHCl_3$) affording 5.02 g (72%) of **51** as a golden-brown solid: mp 102–103 °C; ^1H NMR ($CDCl_3$) δ 6.99–6.81 (m, 4H, phenyl H), 6.29 (s, 1H, 4H isoxazole), 4.73 (s, 2H, piperazinyl CH_2), 4.63–4.53 (p, 1H, J = 6 Hz, $CHMe_2$), 3.72 (s, 2H, CH_2O), 3.20–3.06 (br s, 4H, piperazinyl 2H), 2.74–2.66 (br s, 4H, piperazinyl 3H), 2.53 (s, 1H, OH), 1.38–1.30 (d, 6H, J = 6 Hz, $C(CH_3)_2$). Anal. ($C_{18}H_{25}N_3O_3$) C, H, N.

1-[[5-[[4-[2-(1-Methylethoxy)phenyl]-1-piperazinyl]-methyl]-3-isoxazolyl]methyl]-2-piperidinone Monohydrochloride Monohydrate (52). Carbinol **51** (6.40 g, 0.019 mol) was dissolved in $SOCl_2$ (60 mL) and stirred at 25 °C for 6 h. The reaction was neutralized with saturated $NaHCO_3$ solution, and the mixture was extracted with EtOAc. The organic layer was separated, washed with saturated $NaHCO_3$ solution, dried over anhydrous Na_2SO_4, filtered, and evaporated on a rotary evaporator to give 2.59 g of a dark brown oil. A solution of this material (2.50 g, 0.0072 mol) in DMF (150 mL) was added to a solution of γ-valerolactam (1.42 g, 0.014 mol) and NaH (0.34 g, 0.014) in DMF (150 mL), and the resulting mixture was stirred at 25 °C for 29 h. The reaction mixture was poured into ice water and extracted with EtOAc. The EtOAc layers were combined, washed with water, dried over Na_2SO_4, filtered and evaporated yielding 2.68 g of an oil which was chromatographed twice on flash silica gel (elution with 95:4.5:0.5 $CHCl_3$:MeOH:NH_4OH and 99:1 $CHCl_3$:MeOH) to give an orange oil. This material (2.30 g) was dissolved in CH_2Cl_2 (30 mL)/Et_2O (5 mL) and treated with 12 N HCl (0.46 mL). The solvent was allowed to evaporate overnight, leaving a red-brown oil which was taken up in CH_2Cl_2/hexane. An amorphous solid was collected and recrystallized from Et_2O/CH_2Cl_2 affording 0.87 g (27%) of **52** as a cream-colored solid: mp (softens 110–115 °C) 191–196 °C; ^1H NMR (Me_2SO-d_6) δ 7.05–6.82 (m, 4H, phenyl H), 6.80–6.62 (br s, 1H, 4H isoxazole), 4.68–4.58 (p, 1H, J = 6 Hz, $CHMe_2$), 4.59 (s, 2H, 3-isoxazole CH_2), 3.42–3.32 (s, 8H, piperazine H), 3.32–3.27 (m, 2H, pyrrolidinone 6H), 2.33–2.27 (m, 2H, pyrrolidinone 3H), 1.80–1.68 (br s, 4H, pyrrolidinone 4- and 5H). Anal. ($C_{23}H_{32}N_4O_3 \cdot HCl \cdot H_2O$) C, H, N.

4,5-Dihydro-1-[[3-[[4-[2-(1-methylethoxy)phenyl]-1-piperazinyl]methyl]isoxazol-5-yl]carbonyl]piperidine Monohydrochloride Monohydrate (53). A solution of piperidine (100.0 g, 1.17 mol) and CH_2Cl_2 (830 mL) at 0 °C was treated dropwise with acryloyl chloride (35.4 g, 0.39 mol), stirred overnight at 25 °C, and poured into water (500 mL). The organic layer was separated and washed successively with 1 N HCl and saturated $NaHCO_3$ solution. The organic layer was separated, dried over anhydrous Na_2SO_4, filtered, and evaporated to give **72** as an oil which was purified by Kugelrohr distillation.

A toluene solution (96 mL) of **72** (14.0 g, 0.105 mol) was treated with $THPOCH_2CH_2NO_2$ followed by PhNCO (47.92 g, 0.402 mol) and Et_3N (1.02 g, 0.01 mol) and stirred at ambient temperature for 64 h. The reaction mixture was filtered, and the filtrate was stirred with water (10 mL) for 2 h at 25 °C. The resulting suspension was filtered, dried over Na_2SO_4, filtered, and evaporated. The residue was taken up in Et_2O and extracted several times with 1 N HCl solution. The acid washes were combined, neutralized with $NaHCO_3$, and extracted with $CHCl_3$. The organic extracts were combined, dried over Na_2SO_4, filtered, and evaporated to a dark red oil which was purified by chromatography on flash silica gel (elution with 1–5% MeOH–$CHCl_3$) to give carbinol **73** as a cream-colored solid.

This material (4.87 g, 0.023 mol) was dissolved in CCl_4 (20.5 mL) and treated with PPh_3. The reaction mixture was refluxed for 31 h, cooled to ambient temperature, treated with pentane (23 mL), stirred 5 min, and filtered. The filtrate was concentrated to a yellow oil containing a semisolid. This material was dissolved in CCl_4 and concentrated in stages removing Ph_3PO to afford **74** as a crude oil.

A solution of this material (4.99 g, 0.022 mol) in THF (50 mL) was added to a solution of 1-[2-(methylethoxy)phenyl]-piperazine (4.33 g, 0.020 mol), Et_3N (2.39 g, 0.024 mol), and THF (50 mL). The reaction mixture was refluxed for 34 h, cooled, and poured into 1 N HCl solution. The aqueous mixture was neutralized and extracted several times with $CHCl_3$. The organic extracts were combined, dried over Na_2SO_4, filtered, and evaporated to an oil. This material was chromatographed on flash silica gel (elution with 1% MeOH–$CHCl_3$) to give 3.17 g of a yellow-brown oil which was converted to an HCl salt by treatment with 12 N HCl (0.8 mL) in i-PrOH (90 mL). The resulting solid was recrystallized (MeOH–Et_2O) affording 1.28 g (14%) of **53** as a tan powder: mp (92 °C bubbling) 141 °C dec; ^1H NMR (CD_3OD) δ 7.15–6.88 (m, 4H, phenyl H), 5.62 (dd, 1H, J = 11.1, 6.3 Hz, 4,5-dihydrooxazole 5H), 4.67 (p, 1H, J = 6.0 Hz, $CHMe_2$), 4.26 (br s, 2H, piperazine CH_2), 3.90–3.10 (br m, 14 H, piperazine H, piperidine 2H, 4,5-dihydrooxazole 4H), 1.68 (br m, 4H, piperidine 3- and 5H), 1.58 (br m, 2H, piperidine 5H), 1.34 (d, 6H, J = 6 Hz, $C(CH_3)_2$). Anal. ($C_{23}H_{34}N_4O_3 \cdot HCl \cdot H_2O$) C, H, N.

1-[[6-[[1-[2-(Methylethoxy)phenyl]-4-piperazinyl]-methyl]pyridinyl]methyl]-2-piperidinone Hydrochloride (54). A solution of of 2-(isopropoxyphenyl)piperazine fumarate (20.0 g) in a minimal volume of water was treated with saturated aqueous $NaHCO_3$ until pH 8 was achieved and then extracted twice with CH_2Cl_2. The combined organics were dried ($MgSO_4$), filtered, and concentrated to give 12.4 g (56.6 mmol) of the free base as an oil. This was then treated with 2,6-bis(chloromethyl)pyridine[18] (29.8 g, 0.170 mol) and triethylamine (97.89 mL, 56.6 mmol). The brownish solution was heated at reflux in THF (200 mL). After 3 h, the solution was cooled and treated with 5.7 mL of concentrated HCl, ether, and ca. 50 mL of water. The product was extracted into the aqueous phase. It was then basified (saturated aqueous $NaHCO_3$), extracted into ether, and concentrated to give 19 g of 6-[[1-[2-(1-methylethoxy)phenyl]-4-piperazinyl]methyl]-2-(chloromethyl)pyridine (19 g, **75**). The chemical ionization MS was consistent with the assigned structure.

A solution of γ-valerolactam (3.86 g, 38.9 mmol) in 50 mL of THF was treated with *n*-BuLi (15.57 mL of 2.5 M hexane, 38.9 mmol) at 9 °C under a nitrogen atmosphere. The resultant suspension was treated with **75** (10 g, 27.8 mmol) dissolved in DMF (50 mL). The solution was heated at reflux, whereupon the lactam anion went entirely into solution. After 2 h, the solution was cooled and treated with water, and the product was extracted twice into ether. The combined ether layers were dried ($MgSO_4$), filtered, and concentrated. The resultant oil was washed with water and then purified on two Waters Prep 500 columns, first with $CHCl_3$:MeOH:NH_4OH (96:3.5:0.5) and then with CH_2Cl_2:MeOH:NH_4OH (94.3:5.0:0.7). A pure fraction of 5.84 g of material was obtained. This was dissolved in *i*-PrOH, filtered through a Millipore filter, and treated with 2.72 mL of concentrated HCl. Trituration with ether caused a voluminous precipitate to emerge, which was recrystallized from *i*-PrOH–ether. This solid was dried at 65 °C overnight under vacuum to give 3.3 g (23%) of **54**: mp 180–183 °C; ^{1}H NMR (Me_2SO-d_6) δ 8.39–8.31 (m, 1H, pyridine 5H), 7.90–7.85 (m, 1H, pyridine 3H), 7.78–7.72 (m, 1H, pyridine 4H), 7.60–7.15 (m, 4H, phenyl H), 5.05–4.90 (m, 1H, $CHMe_2$), 4.56 (s, 2H, piperazinyl CH_2), 3.90–3.80 (m, 4H, piperazine 2- and 6H), 3.70–3.54 (m, 6H, piperazine 3- and 5H, piperidinone 6H), 2.63–2.57 (m, 2H, piperidinone 3H), 2.05–1.90 (m, 4H, remaining piperidinone H), 1.56–1.47 (d, 6H, J = 6 Hz, $C(CH_3)_2$). Anal. ($C_{25}H_{34}N_4O_2$·2.6HCl) C, H, N, Cl.

General Procedure for the Preparation of 55a,b. This procedure is illustrated for the preparation of 1-[2-(1-methyl-1*H*-pyrrol-2-yl)-1,2-dioxo-1,2-ethanediyl]-4-[2-(1-methylethoxy)phenyl]piperazine (**55a**). A solution of *N*-methylpyrrole (16.20 g, 0.20 mol) and Et_2O (50 mL) was added to an ice-cooled solution of oxalyl chloride (25.40 g, 0.20 mol) and Et_2O (150 mL) over 10 min. After stirring at 25 °C for 2 h, the solvent was evaporated and replaced with benzene (100 mL), and the reaction mixture was poured into a 3-neck flask with a mechanical stirrer and cooled with an ice bath to 0 °C. A solution of 1-[2-(1-methylethoxy)phenyl]piperazine (63.30 g, 0.29 mol) and benzene (100 mL) was added followed by stirring for 15 min. Water was added (400 mL) with vigorous stirring, and the organic layer was separated, dried over anhydrous K_2CO_3, filtered, and evaporated to give 70.50 g of a dark oil. This material was dissolved in benzene (70 mL) followed by the addition of Et_2O (200 mL), and subsequent cooling in an ice bath causing a tan-colored crystalline solid to form. The solid was taken up in CH_2Cl_2 (200 mL) and washed with 3 N NaOH (200 mL), and the organic layer was separated, dried over anhydrous K_2CO_3, and filtered. The filtrate was treated with charcoal, filtered, and evaporated to give a light-colored oil which was dissolved in Et_2O (200 mL) and cooled, affording 27.40 g (27%) of **55a** as a peach-colored solid: mp 113–115 °C; ^{1}H NMR (Me_2SO-d_6) δ 7.34 (s, 1H, 5H-pyrrole), 7.00–6.82 (m, 5H, phenyl, 3H-pyrrole), 6.24 (s, 1H, 4H-pyrrole), 4.61 (p, 1H, J = 6 Hz, $CHMe_2$), 3.95 (s, 3H, NCH_3), 3.72 (m, 2H, piperazine), 3.46 (m, 2H, piperazine), 3.06 (m, 2H, piperazine), 2.95 (m, 2H, piperazine), 1.28 (d, 6H, J = 6 Hz, $C(CH_3)_2$). Anal. ($C_{20}H_{25}N_3O_3$) C, H, N.

General Procedure for the Preparation of 56a,b. This procedure is illustrated for the preparation of 1-[2-(1-methyl-1*H*-pyrrol-2-yl)ethyl]-4-[2-(1-methylethoxy)phenyl]piperazine (**56a**). An ice-cooled solution of BH_3·THF (105 mL, 0.105 mol) was treated dropwise with a solution of **55a** (15.0 g, 0.042 mol) and THF (100 mL), and the resulting mixture was stirred at reflux for 4 h. The reaction mixture was cooled in an ice bath and treated with 3 N HCl (150 mL) and water (120 mL), and the THF was removed on a rotary evaporator to give a white solid. This material was dissolved in water (200 mL) with heating and made basic with 3 N NaOH. Extraction with CH_2Cl_2, separation of the organic layer, drying over anhydrous K_2CO_3, filtration, and evaporation gave 14.20 g of a clear orange oil. This material (2.00 g) was dissolved in 2-propanol and treated with oxalic acid (0.77 g) to give a white solid. Recrystallization from EtOH–Et_2O afforded 1.20 g (17%) of **56a** as white crystalline solid: mp (sinter 180 °C) 185.5–187 °C; ^{1}H NMR (Me_2SO-d_6–$CDCl_3$) δ 7.00–6.80 (m, 4H, phenyl), 6.60 (s, 1H, 5H pyrrole), 5.90 (s, 1H, 3H pyrrole), 5.85 (s, 1H, 4H pyrrole), 4.60 (p, 1H, J = 6 Hz, $CHMe_2$), 3.55 (s, 3H, NCH_3), 3.55–3.15 (m, 10H, piperazine H, piperazine CH_2), 3.00 (m, 2H, 2-pyrrole CH_2), 1.30 (d, 6H, J = 6Hz, $C(CH_3)_2$). Anal. ($C_{20}H_{29}N_3O$·$C_2H_2O_4$) C, H, N.

General Procedure for the Preparation of 1-[(4-bromo-2-thienyl)methyl]-4-[2-(1-methylethoxy)phenyl]piperazine Monohydrochloride (66). A mixture of 1-[2-(methylethoxy)phenyl]piperazine (6.30 g, 0.029 mol), 4-bromo-2-thiophenecarboxaldehyde (5.50 g, 0.029 mol), $NaBH(OAc)_3$ (8.00 g, 0.038 mol), acetic acid (1.70 g, 0.029), and dichloroethane was stirred for 2 h at room temperature. The reaction mixture was then partitioned between diethyl ether and aqueous 10% Na_2CO_3, and the ether layer was separated, washed with saturated NaCl solution, dried over anhydrous K_2CO_3, filtered, and evaporated to give 11.33 g of a crude oil. Treatment of this material with diethyl ether–2-propanol gave a crystalline solid which was recrystallized from methanol to give 1-[(4-bromo-2-thienyl)methyl]-4-[2-(1-methylethoxy)phenyl]piperazine (10 g, 77%).

A 2.0 g sample of this was recrystallized twice from methanol and chromatographed on flash silica gel (99:1 $CHCl_3$:MeOH with 1% NH_4OH as eluant). The resulting oil was converted to the hydrochloride salt, as described previously, recrystallized from methanol, dried to give **66**: mp (darkens 240 °C) 243–249.5 °C; ^{1}H NMR (Me_2SO-d_6) δ 7.89 (s, 1H, thiophene 5H), 7.50 (s, 1H, thiophene 3H), 7.03–6.87 (m, 4H, phenyl H), 4.68–4.57 (m, 3H, $CHMe_2$ and piperazinyl CH_2), 3.59–2.99 (s, 8H, piperazine H), 1.32–1.25 (d, 6H, J = 6 Hz, $C(CH_3)_2$). Anal. ($C_{18}H_{23}BrN_2OS$·1.5HCl·0.5H_2O) C, H, N, H_2O; Cl: calcd, 11.58; found, 12.05.

Block of Conditioned Avoidance Responding (CAR). Block of CAR was determined at a time of peak effect in a single-lever discrete trial lever response, as described previously.[1,2] Male Fischer 344 rats (Charles River Farms), weighing 300–500 g and trained to perform a CAR task consisiting of a lever press in order to avoid an impending shock, were employed in this assay. 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.

Binding Studies. All assays were carried out in duplicate with one to five concentration-response curves determined for each agent as previously described.[13] The variability was generally <10%.

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 Receptor. 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 mM 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.[26]

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

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