and buffered with 20 mM Tris to pH 7.85. The suspension was shown by fluorometric assay[42] to contain 83 μg of DNA/mL. In the nuclear receptor displacement assay, carried out according to the procedure of Samuels and Tsai,[43] the assay tubes contained 0.8 mL of hepatic nuclear fraction, 0.1 mL of [^{125}I]-L-T_3 (10 nCi diluted with unlabeled T_3 to a final concentration of 0.075 nM), and 0.1 mL of test compounds (dissolved in a minimum volume of 0.25 N NaOH and diluted to volume with saline) in concentrations varying from 0.025 to 100 nM. Total binding to the receptor was determined by incubation in the absence of unlabeled T_3 and nonspecific binding by incubation in the presence of 1 μM unlabeled T_3. Each compound was tested at five to eight different concentrations and each test point was assayed in quadruplicate.

For the enzyme-induction assays thyroidectomized male rats (180–200 g) were injected intramuscularly for 3 consecutive days with vehicle or with solutions of compounds at doses varying from 10^{-4} to 10^{-6} mol/kg. Each compound was injected in six test doses and two animals were used at each dose. Twenty-four hours after the last injection the animals were sacrificed and their livers excised and homogenized in 9 volumes of 0.25 M sucrose containing 1 mM EDTA and buffered with 100 mM Tris to pH 7.5. The cytoplasmic fraction of each homogenate was obtained by centrifuging the homogenate (2000g for 10 min and 40000g for 15 min). Total GPD activity was assayed by following the reduction of 2-(4-iodophenyl)-3-(4-nitrophenyl)-5-phenyltetrazolium in the whole homogenate.[20,44] ME activity was assayed in the cytoplasmic fraction by following the reduction of NADP+ at 340 nm. The protein content of homogenates and cytoplasmic fractions was assayed by the method of Bradford.[45]

To test for hypocholesteremic effect, rats (in groups of five) were injected daily for 7 days with doses of test compounds varying from 4 to 16 nmol/kg per day while receiving a diet containing 2% cholesterol and 1% cholic acid.[23] At the end of that period the animals were fasted for 18 h and their trunk blood collected in heparinized tubes. Total plasma cholesterol was assayed by a cholesterol-esterase cholesterol-oxidase peroxidase method.

(42) Labarca, C.; Paigen, K. *Anal. Biochem.* **1980**, *102*, 344–352.
(43) Samuels, H. H.; Tsai, J. S. *Proc. Natl. Acad. Sci. U.S.A.* **1973**, *70*, 3488–3492.
(44) Fried, G. H.; Greenberg, N.; Antopol, W. *Proc. Soc. Exp. Biol. Med.* **1961**, *107*, 523–525.
(45) Bradford, M. *Anal. Biochem.* **1976**, *72*, 248–254.
(46) Allain, C. C.; Poon, L. S.; Chan, C. S. G.; Richmond, W.; Pu, P. C. *Clin. Chem.* **1974**, *20*, 470–475.

Pyrrole Mannich Bases as Potential Antipsychotic Agents

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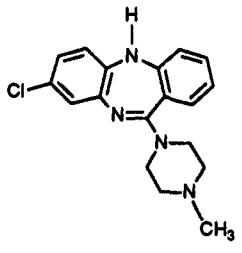
Recently, we reported on a series of arylpiperazines 4 which exhibit high affinity for the serotonin 5-HT-1A and 5-HT-1B binding sites. Although these compounds interact weakly with dopamine D-1 and D-2 receptors, they are reasonably potent in inhibiting conditioned avoidance responding (CAR) in the rat, an indication of potential antipsychotic activity. Conversion of these arylpiperazines to pyrrole Mannich bases has provided a series of compounds (10–44) which exhibit potent inhibition of CAR when given po and have strong affinity for both the D-2 and 5-HT-1A binding sites. Some of these agents also fail to produce catalepsy. The D-2 binding data and the block of CAR suggest that they are potential antipsychotic agents and the lack of cataleptogenic potential suggests some might possess less liability for producing extrapyramidal side effects and tardive dyskinesias in man.

In the quest for an antipsychotic agent superior to clozapine (1) which does not cause extrapyramidal side effects (EPS), recent efforts have focused on compounds which interact with the serotonin receptor. Examples of such agents are ritanserin (2)[1] and risperidone (3),[2] which are potent serotonin-2 receptor (5-HT-2) blockers. Although the blockade of 5-HT-2 receptors has been inferred as a mechanism for reducing EPS,[2] it is not known whether this action contributes to antipsychotic efficacy. Previously, we reported on a series of aryl substituted phenylpiperazines (4) with an in vivo profile of activity predictive of antipsychotic activity in man.[3] These compounds are unique, however, insofar as they block conditioned avoidance responding (CAR) in the rat, but do not demonstrate high affinity for the dopamine D-2 binding site in ligand



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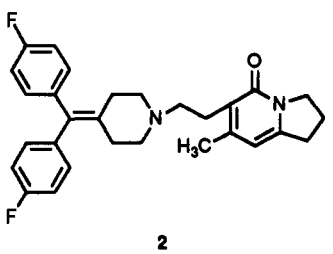

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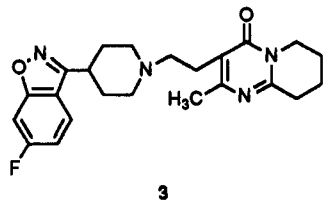

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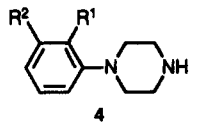

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(1) Reyntjens, A.; Gelders, Y. G.; Hoppenbrouwers, M. L. J. A.; Van Den Bussche, G. Thymosthenic effects of ritanserin (R 55667), a centrally acting serotonin-S_2 receptor blocker. *Drug Dev. Res.* **1986**, *8*, 205–211.
(2) Janssen, P. A. J.; Niemegeers, C. J. E.; Awouters, F.; Schellekens, K. H. L.; Megens, A. A. H. P.; Meert, T. F. Pharmacology of risperidone (R 64 766), a new antipsychotic with serotonin-S_2 and dopamine-D_2 antagonistic properties. *J. Pharmacol. Exp. Ther.* **1988**, *244*, 685–693.
(3) 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.

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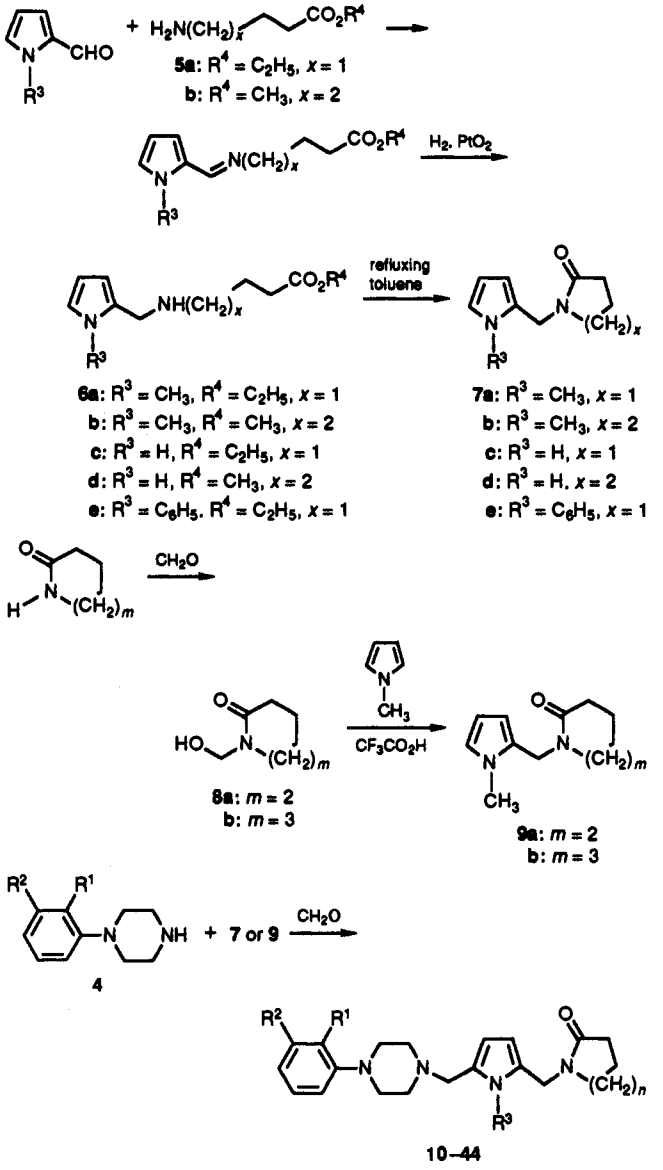
binding studies. With the exception of (-)-sulpiride, all known antipsychotic agents block CAR and D-2 dopamine receptors with a potency directly proportional to their clinical efficacy,[4-6] but these phenylpiperazines interacted with high affinity only with 5-HT-1A and 5-HT-1B binding sites.[3] Hence, these phenylpiperazines differ from presently known antipsychotic agents which both block CAR in vivo[4,5] and displace ligands for the D-2 binding sites in vitro.[6] Moreover, these agents did not produce catalepsy when given to the rat.[7] This is a significant finding since potency in producing catalepsy in the rat is highly correlated with a compound's tendency to produce EPS[8] and tardive dyskinesias in man[9] and blockade of dopamine neurons ascending from the brain stem is involved in the production of catalepsy.[10,11]

The preclinical profile of the phenylpiperazines, therefore, was that of an effective antipsychotic agent, since they block CAR, which might possibly lack the debilitating EPS of most of the presently marketed antipsychotic agents since they do not produce catalepsy in rats. A similar profile of activity is produced by clozapine, the only antipsychotic agent reported to lack the potential for EPS and tardive dyskinesia (TD) in man.[12,13] Clozapine differs from the phenylpiperazines in exhibiting moderate affinity for D-2 dopamine receptors (see Table V below).

Although arylpiperazines **4** might be novel antipsychotic agents with a unique nondopaminergic mechanism of action, they suffer from poor activity when given orally.[3] Because these agents lack D-2 dopaminergic blocking properties, a property shared by all antipsychotic agents, we cautioned that the CAR data for the phenylpiperazines might be an indication of a false positive response in this test.[3,7] Our continuing research program focused on finding compounds with better oral activity. In this paper, we describe a series of pyrrole Mannich bases (**10–44**) incorporating this arylpiperazine structural moiety. These agents are slightly more potent inhibitors of CAR in rats than the parent arylpiperazines. Furthermore, the pyrrole Mannich bases possess high affinity for D-2 receptors and yet some agents in this series still lack cataleptogenic activity. Hence, these compounds have a clozapine-like profile of activity. Data will be presented to show that the pyrrole Mannich bases differ from arylpiperazines by displaying high affinity for the D-2 binding sites in rat brain and by demonstrating more robust pharmacological activity when given po. On the basis of their preclinical profile, pyrrole Mannich bases should prove to be effective antipsychotic agents which may have low potential for EPS and tardive dyskinesia.

Scheme I

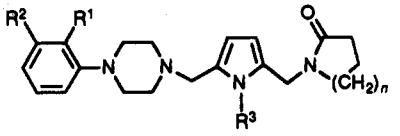


Chemistry

The compounds shown in Table I were obtained from the Mannich reaction of the requisite piperazines **4**[3] with the corresponding 1-(1-methylpyrrol-2-ylmethyl) 2-lactams **7** or **9**, as depicted in Scheme I. Two different approaches were used for the preparation of lactams **7a–e** and **9a–b**. In the case of pyrrolidinones **7a**, **7c**, and **7e** and piperidinones **7b** and **7d**, condensation of the appropriate amino ester **5** with the corresponding pyrrole-2-carboxaldehyde afforded imines which were reduced catalytically to amines **6** and subsequently cyclized. Alternatively, amidomethylation of *N*-methylpyrrole with methanols **8a,b**, prepared from formaldehyde and either the 7- or 8-membered lactam, gave **9a,b**, which were purified by column chromatography.

(4) Kuribara, H.; Tadokoro, S. Correlation between antiavoidance activities of antipsychotic drugs in rats and daily clinical doses. *Pharmacol. Biochem. Behav.* 1981, *14*, 181–192.
(5) Arnt, J. Pharmacological specificity of conditioned avoidance response inhibition in rats: inhibition of neuroleptics and correlation of dopamine receptor blockade. *Acta Pharmacol. Toxicol.* 1982, *51*, 321–329.
(6) Seeman, P. Brain Dopamine Receptors. *Pharmacol. Rev.* 1981, *32*, 229–313.
(7) 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.
(8) Julou, L. Palpebral ptosis as an index of neuroleptic activity. In *Modern Problems of Pharmacopsychiatry, The Neuroleptics*; Bobon, D. P., Janssen, P. A. J., Bobon, J., Eds.; Basel: Karger, 1970; Vol. 5, pp 50–54.
(9) Vinick, F. J.; Heym, J. H. Antipsychotic agents. *Annu. Rep. Med. Chem.* 1987, *22*, 1–10.
(10) Costall, B.; Naylor, R. J. The importance of ascending dopaminergic systems to the extrapyramidal and mesolimbic brain areas for the cataleptic action of neuroleptic and cholinergic agents. *Neuropharmacology* 1974, *13*, 353–364.
(11) Costall, B.; Naylor, R. J. Is there a relationship between the involvement of extrapyramidal and mesolimbic brain areas with the cataleptic action of neuroleptic agents and their clinical antipsychotic effect? *Psychopharmacologia* 1973, *32*, 161–170.
(12) Simpson, G. M.; Varga, E. Clozapine—a new antipsychotic agent. *Curr. Ther. Res.* 1974, *16*, 679–686.
(13) Griffith, R. W.; Saameli, K. Clozapine and agranulocytosis. *Lancet* 1975, *2*, 657.

Table I. Pyrrole Mannich Bases



compd	R_1	R_2	R_3	n	formula[a]	method	% yield	mp, °C	recryst solv	analysis
10	H	H	H	1	$C_{20}H_{26}N_4O$	A	6	142–144	ethyl acetate	C, H, N
11	H	H	CH_3	1	$C_{21}H_{28}N_4O{\cdot}0.5C_4H_4O_4{\cdot}0.1H_2O$	A	15	174–175	MeOH/Et_2O	C, H, N, H_2O
12	CH_3	H	CH_3	1	$C_{22}H_{30}N_4O{\cdot}C_2H_2O_4{\cdot}0.5H_2O$	A	24	146–149	iPrOH	C, H, N, H_2O
13	C_2H_5	H	CH_3	1	$C_{23}H_{32}N_4O{\cdot}1.5C_4H_4O_4$	A	38	150–152	EtOH	C, H, N
14	$(CH_2)_2CH_3$	H	CH_3	1	$C_{24}H_{34}N_4O{\cdot}C_4H_4O_4{\cdot}0.16H_2O$	A	38	152.5–153	iPrOH	C, H, N, H_2O
15	$(CH_2)_3CH_3$	H	CH_3	1	$C_{25}H_{36}N_4O{\cdot}C_4H_4O_4$	B	55	150.5–152	iPrOH	C, H, N
16	$CH(CH_3)_2$	H	CH_3	1	$C_{24}H_{34}N_4O{\cdot}1.5C_4H_4O_4$	A	34	159.5–160.5	iPrOH	C, H, N
17	OCH_3	H	H	1	$C_{21}H_{28}N_4O_2{\cdot}C_2H_2O_4{\cdot}0.2H_2O$	A	44	150–152.5	MeOH	C, H, N, H_2O
18	OCH_3	H	CH_3	1	$C_{22}H_{30}N_4O_2{\cdot}C_4H_4O_4$	A	19	140–142	iPrOH	C, H, N, H_2O
19	OCH_3	H	C_6H_5	1	$C_{27}H_{32}N_4O_2{\cdot}C_4H_4O_4{\cdot}0.1C_2H_6O{\cdot}0.3H_2O$	A	8	149–152	EtOH	C, H, N, H_2O
20	OC_2H_5	H	CH_3	1	$C_{23}H_{32}N_4O_2{\cdot}C_2H_2O_4{\cdot}0.7H_2O$	A	57	145.5–150	EtOH	C, H, N, H_2O
21	$OCH(CH_3)_2$	H	CH_3	1	$C_{24}H_{34}N_4O_2{\cdot}C_4H_4O_4$	A	23	148–149	iPrOH	C, H, N
22	OH	H	CH_3	1	$C_{21}H_{28}N_4O_2{\cdot}0.5C_4H_4O_4{\cdot}0.2H_2O$	A	41	186–188	EtOH/H_2O	C, H, N, H_2O
23	Cl	H	CH_3	1	$C_{21}H_{27}ClN_4O{\cdot}C_2H_2O_4{\cdot}0.1H_2O$	A	16	135–139	EtOH	C, H, N, H_2O
24	CN	H	CH_3	1	$C_{22}H_{27}N_5O{\cdot}C_2H_2O_4{\cdot}0.4H_2O$	A	30	150–153	EtOH	C, H, N, H_2O
25	H	Cl	CH_3	1	$C_{21}H_{27}ClN_4O{\cdot}1.5C_4H_4O_4$	B	16	172–174	iPrOH	C, H, Cl, N
26	H	F	CH_3	1	$C_{21}H_{27}FN_4O{\cdot}1.5C_4H_4O_4$	A	45	167–168	MeOH	C, H, N
27	H	CF_3	CH_3	1	$C_{22}H_{27}F_3N_4O{\cdot}0.5C_4H_4O_4$	A	56	151–153	EtOH	C, H, N
28	H	NO_2	CH_3	1	$C_{21}H_{27}N_5O_3{\cdot}0.8C_4H_4O_4$	A	20	142–143	iPrOH	C, H, N
29	H	OCH_3	CH_3	1	$C_{22}H_{30}N_4O_2{\cdot}C_2H_2O_4$	A	66	157–158.5	iPrOH	C, H, N
30	C_2H_5	H	CH_3	2	$C_{24}H_{34}N_4O{\cdot}1.35C_4H_6O_6{\cdot}0.7H_2O$	B	43	70 (dec)	EtOH/Et_2O	C, H, N, H_2O
31	$CH(CH_3)_2$	H	CH_3	2	$C_{25}H_{36}N_4O{\cdot}C_4H_4O_4$	B	68	141.5–144	iPrOH	C, H, N
32	OCH_3	H	CH_3	2	$C_{23}H_{32}N_4O_2{\cdot}C_4H_4O_4$	B	52	141.5–143.5	iPrOH	C, H, N
33	$OCH(CH_3)_2$	H	H	2	$C_{24}H_{34}N_4O_2{\cdot}C_2H_2O_4{\cdot}0.5H_2O$	B	15	156–157.5	MeOH/H_2O	C, H, N, H_2O
34	$OCH(CH_3)_2$	H	CH_3	2	$C_{25}H_{36}N_4O_2{\cdot}C_2H_2O_4$	B	37	139–140	EtOH/Et_2O	C, H, N
35	$OCH(CH_3)(C_2H_5)$	H	CH_3	2	$C_{26}H_{38}N_4O_2{\cdot}C_4H_6O_6{\cdot}0.2H_2O$	B	21	153–154	EtOH/Et_2O	C, H, N, H_2O
36	H	Cl	CH_3	2	$C_{22}H_{29}ClN_4O{\cdot}C_2H_2O_4{\cdot}0.4H_2O$	B	35	130 (dec)	iPrOH	C, H, N, H_2O
37	H	NO_2	CH_3	2	$C_{22}H_{28}N_5O_3$	B	13	140–141.5	b	H, N; C[c]
38	$CH(CH_3)_2$	H	CH_3	3	$C_{26}H_{36}N_4O{\cdot}C_4H_4O_4{\cdot}0.1H_2O$	B	55	146.5–148	iPrOH	C, H, N, H_2O
39	OCH_3	H	CH_3	3	$C_{24}H_{34}N_4O_2{\cdot}C_4H_4O_4$	A	36	146–148	iPrOH	C, H, N
40	$OCH(CH_3)_2$	H	CH_3	3	$C_{26}H_{38}N_4O_2{\cdot}2.0C_4H_4O_4$	A	23	147.5–148.5	iPrOH	C, H, N
41	$O(CH_2)_3CH_3$	H	CH_3	3	$C_{27}H_{40}N_4O_2{\cdot}C_4H_4O_4$	A	13	148 sinter 149.5–150.5	EtOH/Et_2O	C, H, N
42	$CH(CH_3)_2$	H	CH_3	4	$C_{27}H_{40}N_4O{\cdot}C_4H_4O_4$	A	19	162–163.5	EtOH	C, H, N
43	OCH_3	H	CH_3	4	$C_{25}H_{36}N_4O_2{\cdot}1.75C_2H_2O_4{\cdot}0.1H_2O$	A	25	146–148	EtOH	C, H, N, H_2O
44	$OCH(CH_3)_2$	H	CH_3	4	$C_{27}H_{40}N_4O_2{\cdot}1.5C_4H_6O_6$	A	14	85.5–106.5	d)	C, H, N

[a] $C_4H_4O_4$ represents fumaric acid, $C_2H_2O_4$ represents oxalic acid, $C_4H_6O_6$ represents tartaric acid, C_2H_6O represents ethanol. [b] Purified by flash chromatography, 1:9 EtOH/hexane. [c] C: calcd, 64.21; found 63.78. [d] Purified by flash chromatography, 2:98 EtOH/hexane.

Pharmacological Results and Discussion

The Mannich reaction of piperazines 4 with pyrroles 7 and 9 produced compounds with a most interesting pharmacological profile of activity. The antipsychotic potential of these agents will first be discussed. Then the pharmacological activity of the pyrrole Mannich bases will be contrasted with the analogous phenylpiperazines. The 35 pyrrole Mannich bases shown in Table I were synthesized and examined for blockade of CAR in the rat as an indicator of antipsychotic potential (Table III). Active agents were then examined at a dose 10 times the ED_{50} value for CAR block for production of catalepsy in the rat, a sign of EPS liability.[9] Compounds active in blocking CAR were also examined in receptor binding assays for interactions with dopamine D-1 and D-2, serotonin(5-HT)-1 and -2, and adrenergic α_1 binding sites in rat brain tissue. For selected agents which interacted with the 5-HT-1 receptor, binding to 5-HT-1A and 5-HT-1B binding sites was also examined. The radioligands and tissue used are shown in Table II.

Given intraperitoneally, 16 of the 35 agents had ED_{50} values of less than 11 mg/kg in blocking CAR in the rat (Table III). In fact, six agents, 18, 20, 21, 32, 34, and 39, had ED_{50} values of less than 2.5 mg/kg. A comparison of these agents after po administration revealed that 32 and 34 had the lowest ED_{50} values for CAR blockade with po/ip ED_{50} ratios determined to be 4.2 and 4.6, respectively. Given po, compounds 18, 21, and 44 did not produce a 50% block of CAR at dose levels 7.5–9.5 times their respective ip ED_{50} values.

Table II. Radioligands Used and Tissue Source for Ligand Binding Assays

receptor	radioligand	tissue source
D-2 dopamine	[^{3}H]spiperone	rat striatum
5-HT-1	[^{3}H]serotonin	rat cerebral cortex
5-HT-1A	[^{3}H]WB4101[a]	rat hippocampus
5-HT-1B	[^{3}H]serotonin[b]	rat cerebral cortex
5-HT-2	[^{3}H]ketanserin	rat cerebral cortex
α_1 adrenergic	[^{3}H]WB4101	rat cerebral cortex

[a] Prazosin (0.1 mL, 30 μM) was added to each test tube to prevent binding to α_1 adrenergic receptors. [b] 8-OH-DPAT in a final concentration of 100 nM was added to the incubation medium to prevent binding to the 5-HT-1A binding site.

Pyrrole Mannich bases 18, 31, 33, 34, 35, 36, 38, 40, 43, and 44 all produced a relatively low amount of catalepsy (Table IV), viz. less than 32% of the maximum catalepsy score when given in a dose ~10 times the ED_{50} for CAR block. Compound 34 was given at a dose 24.5 times its ED_{50} value for CAR block and yet produced only 12% catalepsy. This profile compares favorably with that of clozapine (1), which produced 10% catalepsy given in a dose 10 times its ED_{50} value for CAR block (Table IV). On

Table III. Action of Pyrrole Mannich Bases in Blocking CAR and at Selected Binding Sites

compound	CAR ED_{50}, mg/kg ip (95% CL)	receptor binding data; K_i values, nM (95% CL)					
		D-2	5-HT-1	5-HT-1A	5-HT-1B	5-HT-2	α_1
10	>15	ND[a]	ND	ND	ND	ND	ND
11	>15	>1000	ND	ND	ND	>1000	436
12	>15	167	~1000	ND	ND	ND	136 (117, 162)
13	~15	22.5 (17, 29)	304 (259, 359)	ND	ND	227 (170, 314)	38.2 (26, 59)
14	>30	12.8 (9.3, 17.9)	283 (179, 415)	ND	ND	317 (201, 634)	26.6 (24, 30)
15	>15	ND	ND	ND	ND	ND	ND
16	5.8 (3.8, 7.0)	4.6 (3.6, 5.8)	76.0 (56, 102)	ND	ND	409 (242, 835)	20.0 (17, 23)
17	>15	53.7 (48, 60)	148 (107, 202)	ND	ND	~1000	43.1 (22.7, 79.2)
18	2.1 (1.2, 3.0)	54.9 (44, 68)	185 (147, 232)	17.2 (9, 36)	ND	>1000	44.9 (37, 58)
19	>15	≥80	ND	ND	ND	ND	~100
10	1.8 (1.5, 2.2)	9.3 (7.5, 11.4)	76 (72, 160)	ND	ND	455 (320, 711)	27.5 (23.8, 31.9)
21	2.2 (1.8, 2.9)	3.3 (2.6, 4.0)	120 (77, 184)	ND	ND	386 (288, 819)	7.3 (5.6, 9.4)
22	>15	>1000	ND	ND	ND	ND	~140
23	>15	≥80	ND	ND	ND	ND	53.1
24	≥15	~1000	140 (114, 172)	ND	ND	>1000	63.7 (40, 116)
25	12.3	101 (63, 159)	196 (155, 251)	ND	ND	256 (143, 564)	264 (222, 299)
26	>15	>100	~1000	ND	ND	>100	>100
27	5.8 (4.8, 7.6)	65.5 (48, 88)	156 (135, 178)	ND	ND	~1000	>1000
28	~15	>100	>1000	ND	ND	>100	>100
29	>7.5	>1000	>1000	ND	ND	ND	~1000
30	>15	6.7 (4, 10)	27.3 (14, 61)	30 (17, 57)	100 (36, 154)	355 (113, 258)	11.3 (2.7, 58.1)
31	8.9 (7.4, 11.3)	1.4 (1.1, 1.7)	41.3 (35, 49)	ND	ND	137 (69, 299)	ND
32	2.3 (1.9, 2.7)	9.5 (7.7, 11.5)	139 (113, 172)	ND	ND		166.0 (132, 211)
33	4.0 (32, 4.8)	1.6 (1.4, 1.7)	33.1 (18.4, 56.8)	5.4	ND	55.3 (48.2, 63.8)	5.2 (2.4, 11.2)
34	2.2 (1.2, 3.0)	0.8 (0.6, 0.9)	57 (40, 87)	3.3 (1.8, 5.8)	85.2 (43, 213)	1006 (793, 1560)	8.2 (6.5, 10.3)
35	3.7 (2.7, 4.6)	1.1 (0.8, 1.4)	29.3 (19.2, 42.2)	1.8 (1.3, 2.5)	45 (28, 82)	267 (146, 544)	17.4 (2, 24)
36	10.4 (8.3, 13.0)	35.2 (19, 72)	ND	34.3 (28, 42)	95.0 (39, 369)	ND	
37	>15	ND	ND	ND	ND	669	ND
38	10.0 (7.0, 14.5)	2.3 (1.7, 3.0)	82.1 (62, 110)	ND	ND	110 (86, 141)	53.9 (31, 136)
39	2.1 (1.8, 2.9)	7.0 (3.2, 12.4)	120.0 (97, 150)	ND	ND	669 (526, 871)	43.7 (36, 53)
40	5.7 (3.8, 10.9)	0.45 (0.06, 1.47)	68.8 (32, 180)	ND	ND	~1000	16.3 (9.4, 27.5)
41	>15	3.1 (1.7, 5.4)	58.9 (18.1, 19.5)	ND	ND	237 (131, 502)	15.7 (9.5, 27.2)
42	>15	3.3 (2.7, 3.95)	50.2 (26, 133)	ND	ND	196 (144, 271)	35.9 (23, 57)
43	8.2 (7.1, 15.4)	5 (2.3, 11.2)	41 (22.5, 83)	ND	ND	~1000	23.1 (14.9, 36)
44	4.0 (3.1, 4.7)	0.65 (0.46, 0.91)	18.1 (13.6, 24.6)	1.7 (0.8, 2.8)	~75	260 (190, 395)	20.8 (15, 30)

[a] ND = not done.

the basis of its good activity in blocking CAR following po administration and the lack of cataleptic response, **34** shows promise of being a superior antipsychotic agent with fewer EPS than existing agents.

The receptor binding data for compound **34** revealed high-affinity interactions with binding sites (K_i (nM) in parentheses) for D-2 (0.8), 5-HT-1A (3.3), and α_1 adrenergic (8.2) receptors (Table III). Interestingly, there is no high-affinity interaction with 5-HT-2 binding sites. The data are not shown, but all of the pyrrole Mannich bases tested had K_i values of greater than 1000 nM in the assay for dopamine-1 binding sites. We assume the affinity for D-2 receptors reflects dopamine receptor blocking properties since the pyrrole Mannich bases blocked stereotypy induced by either apomorphine or amphetamine with potency directly related to its affinity for D_2 binding sites (data not shown).[15] The specific ED_{50} values for **34** for block of amphetamine (2 mg/kg, ip) or apomorphine (1.25 mg/kg, sc) induced stereotypy were 0.4 (0.3, 0.7) and 2.8 (2.4, 3.2) mg/kg ip, respectively (95% CL). **34** also blocked apomorphine (0.31 mg/kg sc) induced emesis in beagles with an ED_{50} value of 96 (55, 222) μg/kg sc.

Table IV. Action of Pyrrole Mannich Bases in Blocking CAR in the Rat, via Oral or Intraperitoneal Routes of Administration, and in Producing Catalepsy in the Rat

compd	ED_{50} values; CAR block ip	po	po/ip	catalepsy dose,[b] mg/kg ip	catalepsy % catalepsy[c] ($N \geq 6$)
16	5.8	NT		NT	NT
18	2.1	>20	>14	25	31
20	1.8	32	17.8	20	97
21	2.2	>20	9.1	27	52
27	5.8	NT		58	56
31	8.9	>30	>3.4	90	19
32	2.3	9.7	4.2	25	39.8
33	4.0	NT		40	10.0[a]
34	2.2	10.4	4.7	54[b]	12.1
35	3.7	NT		37	17.0[a]
36	10.4	NT		50[b]	28
38	10	>30	>3.0	100	17[a]
39	2.1	30.5	14.5	25	51
40	5.7	18.9	3.4	57	26[a]
43	8.2	>27	>3.3	25[b]	16.3
44	4.0	>30	>7.5	40	4.2
(1) clozapine	9.6	32.5	4.8	70	10
(3) risperidone	0.32	2.20	6.9	4	50

[a] Mean of two experiments. [b] This dose was usually ≃10 times the ED_{50} value for CAR block. The *b* superscript denotes a significant departure from that norm. [c] Agents producing less than 30% catalepsy at 10 times the ED_{50} level for CAR block were considered low in EPS potential. NT = not tested.

Despite the high affinity for α1 adrenergic receptors, **34** produced no significant fall in mean arterial pressure of conscious spontaneously hypertensive rats when given in doses as high as 50 mg/kg po.[14]

In contrasting the structure–activity of the pyrrole Mannich bases with the analogous phenylpiperazines, several trends are clear. For the 5-membered ring lactam analogues, alkyl substitution in the ortho position of the phenyl ring of the pyrrole Mannich base rendered only one agent, the isopropyl analogue **16**, active at less than 15 mg/kg ip in blocking 50% of CAR. Both propyl analogue **14** and compound **16** were relatively potent in interacting with the D-2 dopamine binding sites. **14**, however, was inactive in vivo. As was seen with the phenylpiperazines, replacement of alkyl by alkoxy at the ortho position of the phenyl ring produced pyrrole Mannich bases **18**, **20**, and **21**, which were active in blocking CAR. Each of these agents, however, had po ED_{50} values greater than 10 times their ip values. Moreover, **18** and **21** produced a significant amount of catalepsy when given ip in doses ≃10 times their ED_{50} for CAR block. Although **17** differs from **18** only in the methyl group on the pyrrole ring and each had similar activity at D-2 binding sites, **17** was inactive in blocking CAR. In contrast to the analogous phenylpiperazines in which 64 nM was the lowest K_i value vs D-2 binding, many of the 5-membered ring analogues demonstrated high affinity (<15 nM, $n = 17$) for D-2 binding sites. Most meta (R2) and ortho (R1) phenyl substituted compounds in the 5-membered ring lactam series failed to produce inhibition of CAR. The *m*-(trifluoromethyl) analogue **27** had an ED_{50} value of 5.8 mg/kg, but displayed no high affinity interactions with any binding site.

Compounds **30–36** feature various ortho or meta phenyl substitutions in a pyrrole Mannich base with a 6-membered lactam. Compounds **32–35** were about equipotent in blocking CAR with ED_{50} values (ip) ranging from 2.2 to 4.0 mg/kg. All four agents demonstrated high affinity for D-2 binding sites and three also displaced ligands for the 5-HT-1 binding site with high affinity. Clearly the transformation of phenylpiperazine **4** to pyrrole Mannich bases somehow results in the appearance of D-2 activity whereas this property is lacking in the phenylpiperazine itself. Unlike ritanserin (**2**) or risperidone (**3**) (Table V), **34** (Table IV) is almost inactive at the 5-HT-2 binding site. Hence it is not possible to infer that the 5-HT-2 receptor mediates the lack of cataleptic response incurred by this agent. It is not clear whether the affinity for the 5-HT-1A binding site shown by **34** reflects 5-HT-1A antagonism or agonism. Neither 5-HT-1A agonists nor antagonists block CAR.[15] Perhaps the 5-HT-1A receptor property of **34** contributes to the low cataleptic potential of this agent. In this regard, compounds **33**, **35**, and **44** also had K_i values of ≤5.4 nM in the 5-HT-1A binding assay and produced low levels of catalepsy (Table IV). Each of these agents also had K_i values of <10.0 nM at the α adrenergic receptor, and the role of this receptor in the behavioral profile of these agents remains to be determined.

Looking at the reference data in Table V, **34** is not as potent as the standard agents haloperidol, trifluoperazine, or chlorpromazine in blocking CAR, but **34** did not produce catalepsy at any dose tested. Risperidone, an experimental drug with low EPS potential in phase III clinical trials, shows a 10-fold separation between the ED_{50} value required for producing 50% catalepsy and 50% block of CAR. A representative phenylpiperazine, N-(*o*-methoxyphenyl)piperazine, is shown in Table V to possess no affinity for D-2 receptors. Clozapine, the prototypic atypical antipsychotic agent with proven low potential for EPS, is less potent than **34** in blocking CAR and in displacing the tritiated ligand from D-2 binding sites, but like **34** fails to produce catalepsy. **34** differs from clozapine (**1**) in displaying no affinity for 5-HT-2 binding sites. (–)-Sulpiride is a weak antipsychotic agent with low side-effect potential primarily due to the fact that it penetrates poorly into the brain. Buspirone is a novel anxiolytic agent with weak D-2 blocking properties. Although not the most potent agent in blocking CAR when compared to standard antipsychotic medications, the lack of catalepsy produced by **34** together with its bioavailability when given po suggests it may be an atypical antipsychotic agent with low side-effect potential.

Conclusions

A series of pyrrole Mannich bases is described that incorporates, as a structural feature, a previously reported series of phenylpiperazines. These novel agents are active in blocking D-2 dopamine receptors and in blocking CAR responding in the rat, suggesting that they might be effective antipsychotic agents. Moreover, compound **34** was active in blocking CAR when given po and produced little or no catalepsy even when given in a dose 20 times its ED_{50} value. Compound **34** also demonstrated high affinity for 5-HT-1A binding sites and α_1 adrenergic binding sites, while exerting little or no activity at D-1 or 5-HT-2 binding sites. The preclinical profile of activity suggests that these compounds will be effective antipsychotic agents with the potential for fewer extrapyramidal side effects than presently marketed agents.

Experimental Section

Chemistry. All melting points were uncorrected and were taken on a Thomas-Hoover Uni-Melt or Laboratory Devices Mel-Temp melting point apparatus in capillary melting point tubes. The ^1H NMR spectra were obtained on either a 90-MHz

(14) Gill, A., unpublished results.

(15) Vaught, J. L.; Martin, G. E.; Raffa, R. B.; Shank, R. P.; Dubinsky, B.; Bowden, C.; Scott, M. The pharmacological profile of RWJ 25730: a potential antipsychotic agent with reduced EPS liability. *FASEB. J.* **1990**, *4*, A618.

Table V. Radioligand Binding Data and in Vivo Pharmacology for Reference Serotonergic Agents and Antipsychotic Agents

compound	ED_{50} values, mg/kg ip (95% CL)		receptor binding data; K_i values, nM (95% CL)				
	CAR[a]	catalepsy[b]	D-2	5-HT-1	5-HT-1A	5-HT-2	α_1
(1) clozapine	9.6 (6.5, 20.2)	>70	53.6 (32, 94)	210 (179, 244)	39 (28, 53)	1.8 (1.6, 2.1)	23.2 (18.8, 28.4)
(2) ritanserin	>3.0	>3.0	53.2 (35.6, 40.6)	842 (747, 953)	ND[a]	0.26 (0.11, 1.23)	49.5 (24.8, 147)
(3) risperidone	0.32 (0.27, 0.38)	35 (2.3, 7.4)	2.8 (2.0, 3.9)	339 (189, 689)	ND	0.2 (0.1, 0.3)	3.0 (2.0, 4.5)
N-(*o*-methoxyphenyl)piperazine	5.6 (4.6, 7.3)	>45	>1000	28 (23, 52)	9.5 (5.4, 17.5)	>100	510 (416, 562)
chlorpromazine	1.9 (1.7, 2.0)	9.4 (3.8, 5.0)	7.8 (6.7, 9.1)	>1000	179 (119, 280)	0.7 (0.5, 1.1)	5.5 (3.7, 8.8)
haloperidol	0.17 (0.13, 0.27)	0.36 (0.34, 0.38)	0.2 (0.1, 0.4)	>1000	401 (190, 1020)	10.6 (7.7, 15.3)	23.5 (16.6, 31.7)
trifluoperazine	0.5 (0.4, 0.6)	1.7 (1.2, 2.0)	2.2 (1.7, 2.8)	>1000	411 (172, 1287)	5.2 (3.1, 10.4)	29.3 (17.4, 50.6)
(−)-sulpiride	>40	>40	20.6 (16.3, 35.7)	>1000	>1000	>1000	>1000
buspirone	4.5 (2.9, 6.6)	ND	367 (147, 914)	ND	5.0 (4.3, 5.9)	174 (11, 2250)	138 (98, 192)

[a] Conditioned avoidance responding blockade. [b] Dose required to produce a 50% of maximum catalepsy score, or highest dose tested at which less than 50% of catalepsy was observed. ND = not done.

Varian EM-390 NMR spectrometer or a 360-MHz Bruker AM-360 wide-bore NMR spectrometer with Me_4Si as an internal standard. GC analyses were performed on a Perkin-Elmer Sigma 3B gas chromatograph equipped with a 1.83 m X 2 mm glass Chromosorb Q column with 3% SE-30 as the liquid phase. All GC runs were carried out at 90–280 °C at a rate of 32 °C/min. 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.

General Procedure for the Preparation of Amino Esters 6a–d. This procedure is illustrated for the preparation of **6b**. A slurry of *N*-methylpyrrole-2-carboxaldehyde (8.55 g, 0.078 mol), 5A molecular sieves (31.37 g), and $CHCl_3$ (78 mL), under N_2, was treated with a solution of **5b**[14] (12.0 g, 0.071 mol) and $CHCl_3$ (78 mL). After 5 min, Et_3N (21.93 g, 0.22 mL) was added causing an exotherm. The resulting mixture was stirred for 4 h at 25 °C, filtered through diatomaceous earth, and evaporated on a rotary evaporator to a yellow semisolid. This material was slurried with Et_2O and filtered, and the filtrate was evaporated, affording 19.6 g of an orange oil. Hydrogenation of this material in EtOH (200 mL) using PtO_2 (0.50 g) as catalyst on a Paar shaker at 35–39 psig gave, after filtration and concentration, an orange-yellow semisolid which was mixed with Et_2O and filtered, affording 8.00 g of a cream-colored solid, **6b**·HCl: mp (sinter 140 °C) 143–145 °C after recrystallization from MeOH–Et_2O; ^1H NMR ($CDCl_3$) δ 6.66 (m, 1 H, 5H-pyrrole), 6.38 (m, 1 H, 3H-pyrrole), 6.09 (m, 1 H, 4H-pyrrole), 4.10 (s, 2 H, pyrrolyl methylene), 3.80 (s, 3 H, NCH_3), 3.65 (s, 3 H, OCH_3), 2.50–3.00 (br m, 2 H, $HNCH_2$), 2.33 (t, J = 6 Hz, 2 H, $CH_2C{=}O$), and 2.10–1.40 (br m, 4 H, CH_2CH_2). Anal. ($C_{12}H_{20}N_2O_2HCl$) C, H, N, Cl. **6b**·HCl (8.00 g) was converted to the free base using CH_2Cl_2/3 N NaOH to give 7.30 g of **6b** as a yellow oil. Evaporation of the filtrate of **6b**·HCl afforded 7.00 g of orange oil (60% pure by GC, t_R = 4.62 min, identical with **6b** by GC).

Similarly prepared were the following esters: **6a** (HCl salt, mp 105–106 °C, in 80% yield), **6c** (HCl salt, mp 93–95 °C, in 40% yield), and **6d** (succinic acid salt, mp 105–106.5 °C, in 28% yield). **6e** was not isolated but was converted under the reaction conditions to **7e**.

General Procedure for the Preparation of Lactams 7a–e. This procedure is illustrated for the preparation of **7b**. A solution of **6b** (98.04 g, 0.438 mol) and toluene (980 mL) was refluxed with stirring under N_2 for 8 h. The solvent was evaporated and the residue was distilled to give 60.24 g (72%) of **7b**, bp 125–130 °C (0.35 mm), which slowly crystallized. Two recrystallizations of a small sample of **7b** from Et_2O–hexane afforded a white crystalline solid: mp 44.5–47.5 °C; ^1H NMR ($CDCl_3$) δ 6.50 (m, 1 H, 5H-pyrrole), 5.96 (m, 2 H, 3- and 4H-pyrrole), 4.53 (s, 2 H, pyrrole–CH_2–piperidinone), 3.49 (s, 3 H, NCH_3), 3.25–2.95 (br m, 2 H, NCH_2), 2.50–2.20 (br m, 2 H, $O{=}CCH_2$), and 1.90–1.50 (br m, 4 H, remaining methylenes). Anal. ($C_{11}H_{16}N_2O$) C, H, N.

Prepared similarly were the following lactams: **7a** [in 45% yield, bp 111–113 °C (0.45 mm), mp 40–42 °C. Anal. ($C_{10}H_{12}N_2O$) C, H, N], **7c** [in 78% yield, bp 120 °C (0.5 mm), 96% by GC], **7d** [in 55% yield, purified by chromatography on flash silica (elution with ether), 96% by GC, t_R = 4.49 min], and **7e** [in 22% yield, bp 148 °C (0.1 mm)].

1-[(1-Methylpyrrol-2-yl)methyl]perhydro-2*H*-azepin-2-one (9a). To a stirred solution of **8a**[15] (5.50 g, 0.039 mol) and 1-methylpyrrole (3.12 g, 0.039 mol) cooled in an ice bath was added, dropwise, trifluoroacetic acid (2.96 mL, 0.039 mol) over 45 min. After stirring for 2.0 h at 0 °C, the reaction was diluted with CH_2Cl_2 (10 mL) and mixed thoroughly with 3 N NaOH solution until basic. THe organic layer was separated, dried over anhydrous K_2CO_3, filtered, and evaporated to give 6.0 g of a light brown oil. The material was chromatographed on a column of flash silica gel (elution with ether). Evaporation of the product fractions afforded 1.84 g (23%) of **9a** as a crystalline solid (94% by GC, t_R = 5.07 min): ^1H NMR ($CDCl_3$) δ 6.50 (m, 1 H, 5H-pyrrole), 6.00 (br s, 2 H, 3- and 4H-pyrrole), 4.50 (s, 2 H, pyrrolyl methylene), 3.50 (s, 3 H, NCH_3), 3.35–3.15 (m, 2 H, $O{=}CNCH_2$), 2.70–2.35 (m, 2 H, $O{=}CCH_2$), and 1.85–1.20 (m, 6 H, remaining methylenes).

1-[(1-Methylpyrrol-2-yl)methyl]-2-perhydroazocinone (9b). A mixture of 2-azacyclooctanone (10.0 g, 0.079 mol) and paraformaldehyde (2.36 g, 0.079 mol) was heated at 95 °C for 3 h. After cooling to room temperature, the reaction mixture was chromatographed on a column of flash silica (elution with 5:1 CH_2Cl_2/acetone) to give 3.43 g of **8b** (70% by GC, t_R = 8.07 min). This material (71.32 g) and 1-methylpyrrole (25.77 g, 0.318 mol) were cooled in an ice bath and treated with trifluoroacetic acid over 0.5 h. After stirring for 1 h at 0 °C, the mixture was worked up as in **9a** to give 113.85 g of a dark brown oil which was chromatographed by HPLC (elution with 50:1 CH_2Cl_2/acetone), affording **9b** as a brown crystalline solid (9.78 g, 5%, 99% by GC, t_R = 5.69 min): ^1H NMR ($CDCl_3$) δ 6.52 (m, 1 H, 5H-pyrrole), 6.00 (m, 2 H, 3- and 4H-pyrrole), 4.52 (s, 2 H, pyrrolyl methylene), 3.50 (s, 3 H, NCH_3), 3.40–3.20 (m, 2 H, $O{=}CNCH_2$), 2.60–2.40 (m, 2 H, $O{=}CCH_2$), and 1.90–1.30 (m, 8 H, remaining methylenes).

General Procedure for the Preparation of Compounds 10–44. This procedure is illustrated for the preparation of 1-[[1-methyl-5-[[4-[2-(1-methylethoxy)phenyl]-1-piperazinyl]-methyl]-1*H*-pyrrol-2-yl]methyl]-2-piperidinone (**34**). An ice-cooled solution of 1-[2-(1-methylethoxy)phenyl]piperazine[3] (6.32 g, 0.029 mol), acetic acid (1.71 mL), and methanol (18 mL) was treated

(16) Oelofson, W.; Li, C. H. Synthesis of a protected C-terminal δ-aminovaleric acid analog of the peptide sequence occurring at positions 11–19 in adrenocorticotropins. *J. Org. Chem.* **1968**, *33*, 1581–1583.

(17) Bohme, H.; Driesen, G.; Schunemann, D. *Arch. Pharm.* **1961**, *294*, 344–348.

with 37% formaldehyde solution (2.14 mL) and stirred for 5 min at 25 °C. To this was added a solution of **7b** (5.50 g, 0.029 mol) and the resulting solution was stirred overnight at 25 °C. The reaction mixture was evaporated on a rotary evaporator to give an oily residue which was dissolved in CH_2Cl_2 and mixed thoroughly with 3 N NaOH solution until the aqueous layer was basic. The organic layer was separated, dried over anhydrous K_2CO_3, filtered, and evaporated to 12.5 g of a thick oil. This material was chromatographed on a column of flash silica (elution with ether), giving 8.00 g of light yellow oil which was dissolved in ethanol and treated with oxalic acid (2.50 g). Addition of ether until slightly cloudly and cooling in ice afforded 6.25 g of a cream-colored solid which was recrystallized from ethanol (20 mL) and ether (15 mL) to give 5.50 g (37%) of **34** as a white solid: mp 139–140 °C; ^1H NMR ($CDCl_3$) δ 6.80 (s, 4 H, phenyl H), 6.10 (d, J = 3 Hz, 1 H, 4H-pyrrole), 6.03 (d, J = 3 Hz, 1 H, 3H-pyrrole), 4.53 (s, 2 H, 5-CH_2 pyrrole), 4.22 (s, 2 H, 2-CH_2 pyrrole), 3.53 (s, 3 H, NCH_3), 3.45-3.00 (s, 11 H, piperazinyl H, $(CH_3)_2HC$, O=$CNCH_2$), 2.38 (br m, 2 H, NO=CCH_2), 1.75 (m, 4 H, remaining methylenes), and 1.30 (d, J = 6 Hz, 6 H, $(CH_3)_2CH$). Anal. ($C_{25}H_{36}N_4O_2 \cdot C_2H_2O_4$) C, H, N.

Binding Studies. All assays were carried out in duplicate with one to five concentration–response curves determined for each agent as described previously.[3]

Block of Conditioned Avoidance Responding (CAR). As described previously,[3,7] block of CAR was determined at time of peak effect in a single-lever discrete trial lever response. ED_{50} values and 95% confidence limits were determined by regression analysis.

Catalepsy Measurement. The test agent was given ip to male rats and the rat's forepaw was gently placed on a black cork (3.5 cm high) at the time of the drug's peak effect, which was generally 30 min after dosing. The time the forepaw remained on the cork was recorded. Each rat was given three trials on the cork with a maximum time of 60 s allowed per placement. The sum of the three trials was the rat's catalepsy score. Percent catalepsy was defined as a percent of the 180 s (maximum) the rat left its paw on the cork. The experiment was carried out in a quiet room with the evaluator unaware of the drug treatment. A vehicle-treated control group was always run concomitantly. Controls rarely remained on the cork for more than a total of 10 s.

Blockade of Amphetamine Sulfate- or Apomorphine Hydrochloride-Induced Stereotypy. Stereotyped behavior in the rat consists of persistent gnawing, biting, licking, and/or sniffing. It was scored using the system indicated below:

score	behavior
0	inactive or asleep
1	active or grooming
2	discontinuous sniffing
3	continuous sniffing
4	continuous sniffing and licking
5	continuous sniffing and biting

To determine whether **34** blocks amphetamine sulfate (2.0 mg/kg, free base, ip) induced stereotypy, male Sprague–Dawley rats obtained from Charles River (Kingston, NY), weighing 150–220 g, were housed in individual cages with a grid floor. Amphetamine sulfate was given ip to groups of six animals per dose. At 10-min intervals for 2 h after dosing, each animal was rated for stereotypy. There were three dose levels of the test drug administered ip as a pretreatment (30 min) prior to amphetamine. Also, a group was given only vehicle as pretreatment and another group was given vehicle as both treatment and pretreatment. All dose levels of the drug were administered in a random fashion with the rater unaware of the test treatment given to each animal. The 60-min period (six consecutive scoring period) of peak activity for the vehicle-pretreated control group (viz., demonstrating the greatest scores) was taken as the comparison period for blockade of stereotypy. The time period for peak effect of amphetamine sulfate was invariably 30–90 min after dosing. The pretreatment time prior to amphetamine sulfate was determined by time of peak effect observed for **34** in the CAR test.

Stereotypy-induced by apomorphine hydrochloride (1.25 mg/kg, free base, sc), was measured for the 60-min period following administration, since this is its period of peak activity. The dose was selected since it produces about 50% of the maximal stereotypy score in control animals. **34** was given 30 min prior to apomorphine hydrochloride.

The maximal stereotypy score possible for any rat was 6 × 5 = 30. The blockade of amphetamine sulfate-induced stereotypy was deduced by determining the reduction in stereotypy scores below the group score tabulated for the vehicle–amphetamine or apomorphine control group. A dose of amphetamine sulfate (2 mg/kg, calculated as free base, ip) was selected which would be expected to produce a stereotypy score of 60%–70% of the maximum. A percent deviation from the control value was determined for each animal using the formula:

$$[[(\bar{x}\text{ control group score}) - (\text{individual score of rat given test drug})]/(\bar{x}\text{ control group score})] \times 100 = \%\ I\text{ of stereotypy}$$

ED_{50} values (95% confidence limits) for blockade of amphetamine sulfate- or apomorphine hydrochloride-induced stereotypy were determined using linear regression analysis.

Block of Apomorphine Hydrochloride-Induced Emesis in the Beagle. Male and female beagles obtained from Marshal Research Animals (North Rose, NY) or White Eagle Labs, Inc. (Doylestown, PA) weighing 7.8–14.5 kg were used. **34** was dissolved in distilled water and given in a dose range of 30–300 μg/kg sc 30 min prior to apomorphine hydrochloride (0.31 mg/kg sc). The animals were observed for 30 min following dosing with apomorphine hydrochloride for bouts of emesis. An ED_{50} value for blockade of emesis, viz. the dose required to block emesis in 50% of the dogs treated, was determined using log probit analysis.

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Registry No. **4** (R_1, R_2 = H), 92-54-6; **4** (R_1 = CH_3, R_2 = H), 39512-51-1; **4** (R_1 = C_2H_5, R_2 = H), 40224-10-0; **4** (R_1 = $(CH_2)_2CH_3$, R_2 = H), 119695-81-7; **4** (R_1 = $(CH_2)_3CH_3$, R_2 = H), 100861-48-1; **4** (R_1 = $CH(CH_3)_2$, R_2 = H), 119695-82-8; **4** (R_1 = OCH_3, R_2 = H), 35386-24-4; **4** (R_1 = OC_2H_5, R_2 = H), 13339-01-0; **4** (R_1 = $OCH(CH_3)_2$, R_2 = H), 54013-91-1; **4** (R_1 = OH, R_2 = H), 1011-17-2; **4** (R_1 = Cl, R_2 = H), 39512-50-0; **4** (R_1 = CN, R_2 = H), 111373-03-6; **4** (R_1 = H, R_2 = Cl), 6640-24-0; **4** (R_1 = H, R_2 = F), 3801-89-6; **4** (R_1 = H, R_2 = CF_3), 15532-75-9; **4** (R_1 = H, R_2 = NO_2), 54054-85-2; **4** (R_1 = H, R_2 = OCH_3), 16015-71-7; **4** (R_1 = $OCH(CH_3)(C_2H_5)$, R_2 = H), 123547-55-7; **4** (R_1 = $O(CH_2)_3CH_3$, R_2 = H), 106476-37-3; **5a**, 5959-36-4; **5b**, 63984-02-1; **6a**, 137965-43-6; **6a**·HCl, 137965-44-7; **6b**, 123547-54-6; **6b**·HCl, 137965-45-8; **6c**, 137965-46-9; **6c**·HCl, 137965-47-0; **6d**, 137965-48-1; **6d**·succinic acid, 137965-49-2; **6e**, 137965-50-5; **7a**, 138008-44-3; **7b**, 123547-52-4; **7c**, 137965-51-6; **7d**, 137965-52-7; **7e**, 137965-53-8; **8a**, 137965-54-9; **8b**, 137965-55-0; **9a**, 137965-56-1; **9b**, 137965-57-2; **10**, 137965-58-3; **11**, 137965-59-4; **11**·fumarate, 137965-60-7; **12**, 137965-61-8; **12**·oxalate, 137965-62-9; **13**, 137965-63-0; **13**·fumarate, 137965-64-1; **14**, 137965-65-2; **14**·fumarate, 137965-66-3; **15**, 137965-67-4; **15**·fumarate, 137965-68-5; **16**, 137965-69-6; **16**·fumarate, 137965-70-9; **17**, 137965-71-0; **17**·oxalate, 137965-72-1; **18**, 137965-73-2; **18**·fumarate, 137965-74-3; **19**, 137965-75-4; **19**·fumarate, 137965-76-5; **20**, 137965-77-6; **20**·oxalate, 137965-78-7; **21**, 137965-79-8; **21**·fumarate, 137965-80-1; **22**, 137965-81-2; **22**·fumarate, 137965-82-3; **23**, 137965-83-4; **23**·oxalate, 137965-84-5; **24**, 137965-85-6; **24**·oxalate, 137965-86-7; **25**, 137965-87-8; **25**·fumarate, 137965-88-9; **26**, 137965-89-0; **26**·fumarate, 137965-90-3; **27**, 137965-91-4; **27**·fumarate, 138008-45-4; **28**, 137965-92-5; **28**·fumarate, 137965-93-6; **29**, 137965-94-7; **29**·oxalate, 137965-95-8; **30**, 123547-36-4; **30**·tartrate, 137965-96-9; **31**, 123547-31-9; **31**·fumarate, 137965-97-0; **32**, 123547-32-0; **32**·fumarate, 137965-98-1; **33**, 123547-35-3; **33**·oxalate, 123547-46-6; **34**, 123547-30-8; **34**·oxalate, 123547-42-2; **35**, 123547-37-5; **35**·tartrate, 137965-99-2; **36**, 123547-34-2; **36**·oxalate, 123547-45-5; **37**, 123547-33-1; **38**, 137966-00-8; **38**·fumarate, 137966-01-9; **39**, 137966-02-0; **39**·fumarate, 137966-03-1; **40**, 137966-04-2; **40**·fumarate, 137966-05-3; **41**, 137966-06-4; **41**·fumarate, 137966-07-5; **42**, 137966-08-6; **42**·fumarate, 137966-09-7; **43**, 137966-10-0; **43**·oxalate, 137966-11-1; **44**, 137966-12-2; **44**·tartrate, 137966-13-3; 1-methylpyrrole, 96-54-8; *N*-methylpyrrole-2-carboxaldehyde, 1192-58-1; pyrrole-2-carboxaldehyde, 1003-29-8; *N*-phenylpyrrole-2-carboxaldehyde, 30186-39-1; 2-azacyclooctanone, 78411-28-6.