Activity of Aromatic Substituted Phenylpiperazines Lacking Affinity for Dopamine Binding Sites in a Preclinical Test of Antipsychotic Efficacy

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Generally, antipsychotic agents are dopamine receptor blocking agents that also block conditioned avoidance responding (CAR) in the rat. Recently, however, both (*o*-methoxyphenyl)piperazine (OMPP, **1h**) and (*m*-chlorophenyl)piperazine (MCPP, **1o**) have been reported to block conditioned avoidance responding in the rat although neither has dopamine receptor blocking properties. The present paper examines the behavioral and biochemical profile of a number of additional substituted phenylpiperazines. None of the phenylpiperazines tested demonstrated high affinity for either dopamine D-1 or D-2 receptor sites, yet many were effective in blocking CAR. The results suggest that the phenylpiperazines may be effective antipsychotic agents without blocking dopamine receptors. Moreover, the active compounds did demonstrate activity in displacing ligand binding to serotonin receptors. Receptor binding profiles were determined for 5-HT-1A and 5-HT-1B binding sites as well as for 5-HT-2 sites. The data from this preclinical test suggest these phenylpiperazines might be effective antipsychotic agents acting via a nondopaminergic mechanism of action.

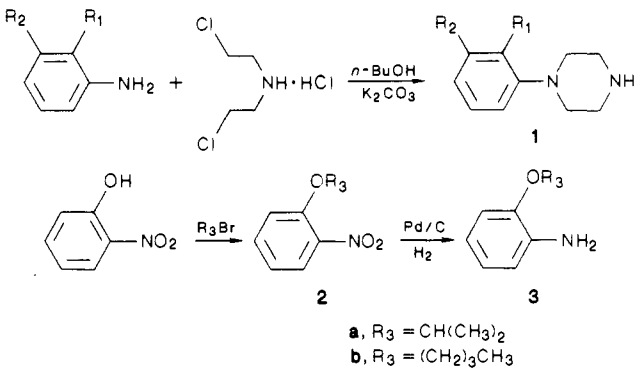
(*m*-Chlorophenyl)piperazine (MCPP, **1o**) and (*o*-methoxyphenyl)piperazine (OMPP, **1h**) both block conditioned avoidance responding (CAR) in the rat despite the fact that neither has demonstrated affinity for dopamine binding sites.[1,2] This finding is of interest since, in general, dopamine receptor antagonists, which act as antipsychotic agents in man,[3] reliably block conditioned avoidance responding in a specific and dose-related manner.[4] Furthermore, an agent's antipsychotic potency is proportional both to its potency in blocking CAR[5] and to its affinity for the dopamine D-2 binding site.[6] These phenylpiperazines, therefore, are unique since the only sites they bind to with high affinity are serotonin sites.[1] In addition, **1o** and **1h** have different binding profiles with regard to subclasses of serotonin receptor binding sites. Specifically, **1h** is relatively selective for 5-HT-1A binding sites, and its action in blocking CAR is not reduced by the serotonin antagonist metergoline.[1] MCPP (**1o**), on the other hand, is equipotent in displacing ligands for 5-HT-1 and 5-HT-2 binding sites[1] (Table III) and is thought to be selective for the 1B subclass of 5-HT binding sites.[7] The blockade of CAR produced by **1o** can be reduced by metergoline.[1,8] Since these phenylpiperazines block CAR, they raise the question of whether or not they might be effective antipsychotic agents. This is especially interesting since neither piperazine interacts with dopamine receptors,[1,2] raising the additional question of serotonin's role in blocking CAR.

The primary purpose of the present experiments, therefore, was to synthesize and evaluate a series of aromatic substituted phenylpiperazines for activity in blocking CAR in the rat. In addition, in an effort to determine the possible site of action for CAR block, specific binding to various transmitter binding sites was also ascertained for these compounds.

Chemistry

N-Arylpiperazines (Table I) **1c**,[9] **1d**, **1e**,[9] **1f**, **1i**,[9,10] **1k**,[11] **1m**,[12] **1p**,[13] and **1q**[13] were prepared via condensation of the requisite aniline with bis(2-chloroethyl)amine as shown in Scheme I. Anilines **3a**[14] and **3b**,[15] precursors for **1j** and **1k**, were obtained by alkylation of 2-nitrophenol followed by reduction of the resulting 2-alkoxynitrobenzenes **2a**[14] and **2b**.[16] Treatment of **1h** with hydrobromic acid afforded **1g**[12] while **1n**[17] was prepared from 2-cyanobromobenzene and piperazine, as shown in Scheme II.

Scheme I



Scheme II

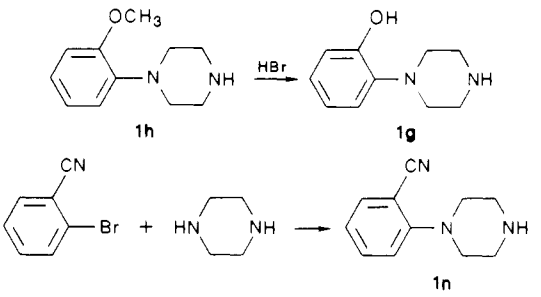


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Table I. 1-Arylpiperazines

compd	R_1	R_2	formula[a]	mp, °C	recrystallization solvent	% yield	anal.
1a	H	H					
1b	CH_3	H					
1c	CH_2CH_3	H	$C_{12}H_{18}N_2 \cdot HCl$	dec above 252	ethanol	26	C, H, N
1d	$(CH_2)_2CH_3$	H	$C_{13}H_{20}N_2 \cdot C_4H_4O_4$	170.5–171.5	methanol	26	C, H, N, H_2O
1e	$(CH_2)_3CH_3$	H	$C_{14}H_{22}N_2 \cdot 1.05C_4H_6O_6 \cdot 0.15H_2O$	dec 100	2-propanol	14	C, H, N, H_2O
1f	$CH(CH_3)_2$	H	$C_{13}H_{20}N_2 \cdot C_4H_4O_4$	188–189	methanol	21	C, H, N, H_2O
1g	OH	H	$C_{10}H_{14}N_2O \cdot 2HBr$	dec 278	methanol	49	C, H, N
1h	OCH_3	H					
1i	OCH_2CH_3	H					
1j	$O(CH_2)_3CH_3$	H	$C_{14}H_{22}N_2O \cdot C_4H_4O_4$	134.5–135.5	2-propanol	10	C, H, N, H_2O
1k	$OCH(CH_3)_2$	H	$C_{13}H_{20}N_2O \cdot C_4H_4O_4$	166.5–168.5	2-propanol	38	C, H, N, H_2O
1l	H	CF_3					
1m	F	H	$C_{10}H_{13}FN_2 \cdot HCl$	185–186	2-propanol	27	C, H, N
1n	CN	H	$C_{11}H_{13}N_3 \cdot 0.6C_4H_4O_4 \cdot 0.1C_3H_8O$	199.5–200.5	2-propanol	32	C, H, N
1o	H	Cl					
1p	H	F	$C_{10}H_{13}FN_2 \cdot C_4H_4O_4$	188–188.5	methanol	51	C, H, N, H_2O
1q	H	NO_2	$C_{10}H_{13}N_3O_2 \cdot C_4H_4O_4$	178–178.5	2-propanol	44	C, H, N, H_2O
1r	Cl	H					

[a] $C_4H_4O_4$ represents fumaric acid, $C_4H_6O_6$ represents tartaric acid, and C_3H_8O represents 2-propanol.

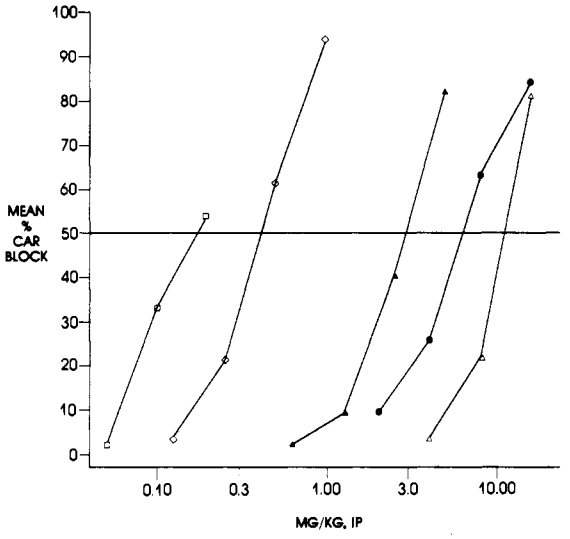

Figure 1. Dose–response curves for the block of CAR produced by standard antipsychotic agents: (□) haloperidol; (●) clozapine; (◇) trifluoperazine; (△) thioridazine; (▲) chlorpromazine. Each data point represents the mean of 12 rats. See Table II for the ED_{50} values derived from these data.

Pharmacological Results and Discussion

The dose–response curves produced by standard antipsychotic agents are shown in Figure 1. As is true for clinically effective dose levels, haloperidol was the most potent agent tested, whereas clozapine and thioridazine were the weakest. ED_{50} values for CAR blockage are shown in Table II. Also shown in the table are inactive dose levels of agents which have been reported to possibly produce block of CAR in other paradigms. The present paradigm seems quite selective for antipsychotic drugs.

Data for blockade of CAR are also presented for alkyl- and alkoxy-substituted phenylpiperazines as well as for selected substituted phenylpiperazines in Table II. Dose–response curves for *o*-alkyl-substituted compounds are shown in Figure 2. The simple phenylpiperazine (**1a**) as well as those with ethyl (**1c**) or isopropyl (**1f**) substitution at the ortho position of the phenyl ring were active in blocking CAR in the rat (Table II). Methyl (**1b**), propyl (**1d**), or butyl (**1e**) substitution, at the ortho position, on the other hand, resulted in agents that failed to block 50% of CAR when given in dose levels as great as 15–20 mg/kg ip (Figure 2).

Every *o*-alkoxy-substituted compound was active in blocking CAR (Table II, Figure 3). The ethoxy- (**1i**) and isopropoxy- (**1k**) substituted compounds had the lowest ED_{50} values.

The ED_{50} values determined for 3-Cl- and 3-F-substituted derivatives (**1o** and **1p**) were lower than the ED_{50} values determined for the compounds with analogous substitutions in the ortho position of the phenyl ring

Table II. ED_{50} Values in Blocking Conditioned Avoidance Responding in the Rat[a]

compd	CAR ED_{50}, mg/kg ip, [95% CL]	% loss of escape at ED_{50}
1a	2.7 [2.1, 4.1]	6.0
1b	>20	
1c	6.8 [5.4, 9.9]	2.5
1d	>15	
1e	>15	
1f	5.9 [4.9, 8.0]	0.1
1g	26.2 [17, 66]	ND
1h	5.6 [4.6, 7.3]	1.8
1i	3.4 [2.2, 6.4]	~1.0
1j	11.2 [9.3, 13]	0.2
1k	4.8 [3.6, 8.6]	0.4
1l	2.6 [2.2, 3.2]	0.6
1m	5.1 [4.4, 6.1]	1.6
1n	5.7 [4.3, 9.2]	4.3
1o	2.4 [1.9, 2.9]	1.5
1p	3.2 [ND[b]]	ND
1q	5.6 [4.2, 7.3]	4.3
1r	10.2 [7.2, 17.3]	3.1
MK-212	2.8 [1.8, 5.1]	19
haloperidol	0.17 [0.13, 0.27]	1.7
chlorpromazine	1.8 [1.1, 2.0]	0.2
clozapine	9.6 [6.5, 20.2]	12.6
trifluoperazine	0.52 [0.44, 0.63]	1.2
thioridazine	9.7 [7.5, 13.7]	7.3

[a] Scopolamine (1), phencyclidine (1.0), LSD (0.32), cocaine (10), atropine (3), desmethylimipramine (20), 8-OHDPAT (0.5), and diazepam (10) all failed to block 20% or more of CAR (doses given in mg/kg ip are shown in parentheses). [b] ND = not done.

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Table III. Action of Phenylpiperazines in Radioreceptor Binding Assays[a]

compd	K_i [95% CL]						
	α-1	D-1	D-2	5-HT-1A	5-HT-1B	5-HT-1	5-HT-2
1a	794 [745, 847]	>1000	>1000	149.0 [1.90, 192]	63.3 [31.2, 165]	149.0 [95, 256]	668 [269, 3980]
1b	108 [51, 293]	>1000	>1000	27.4 [17, 45.7]	44.6 [21.3, 119]	62.4 [36, 120]	558 [ND[b]]
1c	96 [73, 128]	>1000	449 [438, 460]	22.7 [14.8, 35.4]	8.2 [6.2, 10.8]	17.1 [11, 27]	124 [53, 286]
1d	117 [81, 197]	>1000	379 [314, 476]	19.4 [11.1, 30.2]	15.9 [8.1, 33.7]	34.9 [26, 45]	232 [113, 530]
1e	31.8 [18, 59]	>1000	841 [635, 1150]	19.1 [13.8, 26.6]	8.4 [5.8, 12.0]	64.8 [34, 140]	204 [180, 234]
1f	168 [84, 282]	>1000	111 [89, 142]	12.5 [10.7, 14.7]	3.98 [1.2, 11.5]	23.4 [16, 32]	190 [96, 402]
1g	516 [392, 673]	>1000	>1000	35.3 [25.8, 47.7]	74.20 [ND]	117.0 [88, 155]	>1000
1h	510 [416, 652]	>1000	>1000	9.5 [5.4, 17.5]	17.3 [10.9, 28.4]	29.0 [26, 33]	>1000
1i	70 [29, 230]	>1000	144 [86, 289]	9.1 [6, 13.4]	13.8 [9.8, 19.6]	42.6 [25, 78]	774 [ND]
1j	139 [42, 263]	>1000	244 [194, 323]	11.1 [7.2, 17.3]	4.0 [2.9, 5.5]	19.3 [14, 25]	277 [165, 678]
1k	84 [67, 103]	>1000	64 [55, 75]	7.6 [4.7, 12.4]	6.9 [4.8, 9.6]	19.0 [14, 26]	235 [189, 310]
1l	337 [123, 1760]	>1000	530 [338, 1080]	80.6 [ND]	2.25 [0.7, 5.3]	19.8 [12, 33]	31.1 [15, 74]
1m	373 [187, 1140]	>1000	>1000	43.0 [31, 61]	28.9 [13.1, 79.3]	57.9 [29.2, 133]	>1000
1n	214 [149, 330]	>1000	>1000	25.5 [17.6, 37.6]	21.8 [12.9, 39.6]	26.1 [20, 36]	>1000
1o	236 [182, 297]	>1000	>1000	23.0 [13.6, 40.2]	4.4 [2.7, 6.7]	25.0 [13, 67]	40 [33, 48]
1p	670 [465, 963]	>1000	>1000	114.0 [70.6, 205]	30.8 [12.2, 109]	86.5 [65, 120]	>1000
1q	>1000	>1000	>1000	~322 [ND]	33.6 [18, 72.4]	250.0 [206, 312]	419 [ND]
1r	261 [106, 500]	>1000	>1000	19.5 [8.8, 44.2]	11.7 [6.7, 20.7]	24.3 [18.5, 31]	>1000
MK-212	913 [404, 3660]	>1000	>1000	202 [83, 648]	178.00 [ND]	844.00 [727, 1003]	>1000

[a] All data are expressed in nM. [b] ND = not done.

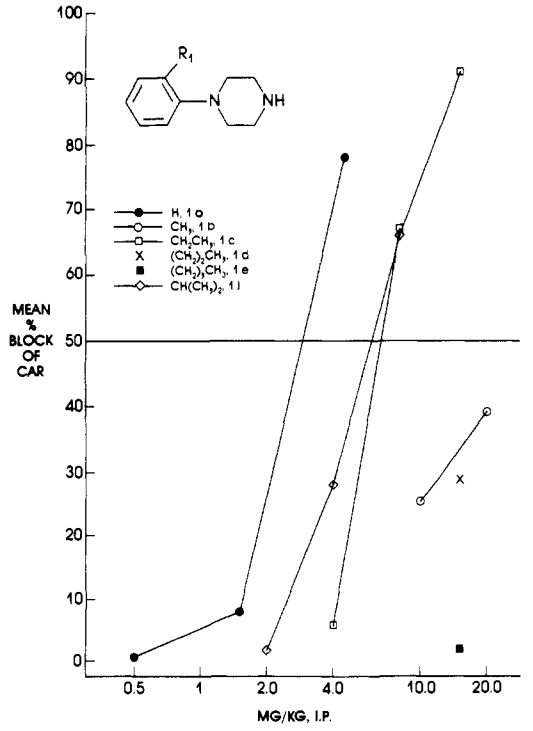

Figure 2. Dose–response curves for the block of CAR produced by *o*-alkyl substitutions on the phenyl ring of the indicated phenylpiperazines. Each data point represents the mean of 6–12 rats. See Table II for the ED_{50} values derived from these data.

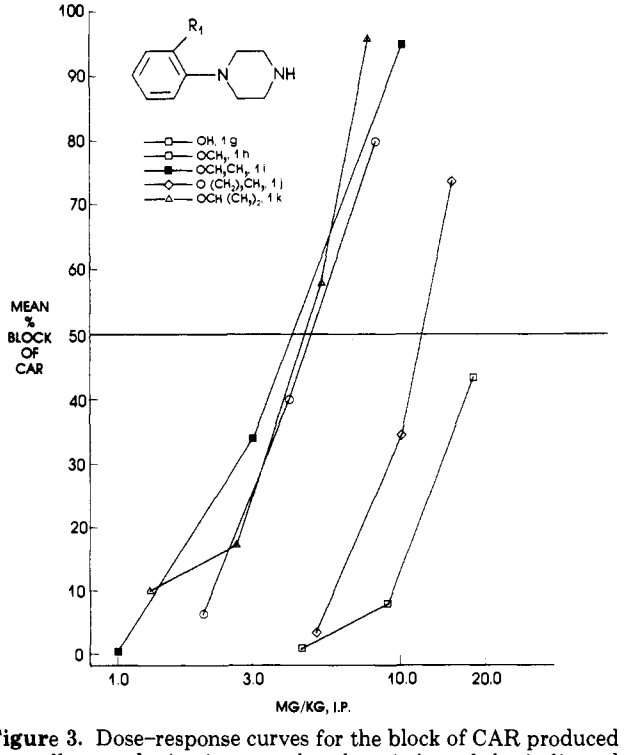

Figure 3. Dose–response curves for the block of CAR produced by *o*-alkoxy substitutions on the phenyl ring of the indicated phenylpiperazines. Each data point represents the mean of 6–12 rats. See Table II for the ED_{50} values and 95% confidence limits for block of CAR.

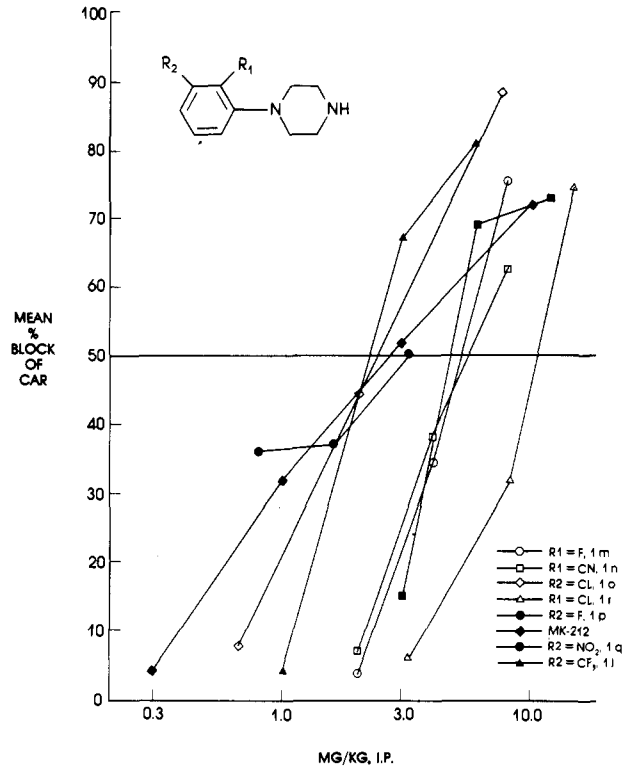

Figure 4. Dose–response curves for the block of CAR produced by ortho- or meta-substituted phenylpiperazines. The data are presented as in Figures 1 and 2. Data are also presented for MK-212, a piperazinylpyrazine.

(Table II). Also shown in Table II are data for MK-212, a piperazinylpyrazine with serotonergic properties,[18] and the *o*-(trifluoromethyl)- (CF_3-) substituted compound (**1l**, TFMPP), a known serotonergic agonist.[19] Both of these compounds also blocked CAR (Table II, Figure 4).

The phenylpiperazines demonstrated no affinity for the D-1 dopamine binding site and little affinity to the D-2 dopamine binding site, the site at which all antipsychotic agents act as an antagonist.[5] As shown in Table III, only the isopropoxy compound (**1k**) had a K_i value of less than 100 nM in displacing radiolabeled ligand from the D-2 binding site. All but three of the phenylpiperazines synthesized did interact somewhat with the α-1 adrenergic receptor with K_i values ranging from 31.8 to 794 nM. Although these data suggest a mild interaction with the α-1 receptor, none of these K_i values indicate a high-affinity interaction.

With no exception, each phenylpiperazine had a lower K_i value for displacing [^{3}H]5HT binding (5-HT-1 site) than for displacing [^{3}H]ketanserin (5-HT-2 site) (Table III). Only **1o** and **1l** had K_i values for the 5-HT-1 binding site that were not markedly lower than the K_i values for the 5-HT-2 site. It is not clear that this difference in affinities for 5-HT-1 vs 5-HT-2 receptors has any bearing on CAR block, but it seems to be a reliable finding for phenylpiperazines.

In general, the most potent ligand binding interactions were observed for subtypes of the 5-HT-1 binding site. Both *o*-methoxy (**1h**) and isopropoxy (**1k**) phenylpiperazine had K_i values of less than 10 nM for 5-HT-1A sites and *o*-butoxy (**1j**) and *m*-chloro (**1o**) phenylpiperazine had K_i values of less than 10 in the 5-HT-1B binding assay.

Although each of the phenylpiperazines did interact with one or all of the 5-HT binding sites, there was no strong correlation between affinity for any receptor and activity in blocking CAR. Computing the Spearman rank order correlation coefficient by using K_i values derived in 5-HT-1, -2, -1A, and -1B and dopamine D-1 and D-2 binding assays vs potencies in blocking CAR failed to generate a significant correlation for any single correlation.

Previously, phenylpiperazines have been shown to possess serotonergic activity both in vivo and in vitro.[20-23] Indeed, **1h** and **1o** have been tested in the clinic for the treatment of hypertension[24] and anxiety,[25] respectively. The data in the present paper extend the observation that phenylpiperazines, lacking affinity for dopamine binding sites and possessing activity at serotonin binding sites, can exert activity in an animal model that indicates antipsychotic potential in man. It does not seem likely that the interaction with specific serotonin receptor subtypes can explain the observed effects in blocking CAR since potency in these binding assays does not correlate highly with potency in the block of CAR.

Since **1h** demonstrates high affinity for 5-HT-1A binding sites, it was tempting to postulate 5-HT-1A receptor activation as the basis for the block of CAR, but pilot studies using the prototypic 5-HT-1A agonist, 8-hydroxy(dipropylamino)tetralin (8-OH-DPAT), have failed to demonstrate a correlation between 5-HT-1A receptor activation and CAR block (Table II).

Although the present data fail to reveal an interaction with dopamine receptors for the phenylpiperazines in vitro, there are reports that suggest **1h** may be a dopamine receptor antagonist in vivo.[1,26] MCPP (**1o**), however, has been shown to be devoid of dopamine receptor blocking properties in vivo.[1] In vivo antidopaminergic properties of the remaining phenylpiperazines, however, remain to be determined.

The present data raise the question of whether or not the phenylpiperazines that display activity in the blockade of CAR might be effective antipsychotic agents. Alternatively, they may simply be a class of agents that provides a false positive result in this screening assay. It should be pointed out that anticholinergic agents (scopolamine, atropine), benzodiazepines (diazepam), hallucinogenic agents (LSD, PCP, or cocaine), and antidepressant drugs (demethylimipramine) all fail to block CAR responding in the present test situation which utilizes a colony of well-trained animals in a discrete lever-press paradigm (Table II). The resolution of these questions will come only with further research.

Conclusions

A series of phenylpiperazines are described that have affinity for 5-HT-1A and/or 5-HT-1B binding sites but minimal activity at dopamine sites. Many of these agents block CAR responding, an activity usually associated with dopamine receptor blockade and antipsychotic activity in man. These agents may be novel antipsychotic agents or

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simply false positives in the CAR test.

Experimental Section

Chemistry. All melting points are uncorrected and were taken on Thomas-Hoover Uni-Melt or Laboratory Devices Mel-Temp melting point apparatuses in capillary melting point tubes. The ^{1}H NMR spectra were obtained on a 90-MHz Varian EM-390 NMR spectrometer with Me_4Si as an internal standard. IR spectra were taken on Perkin-Elmer 283B infrared spectrophotometer. GC analyses were performed on a Perkin-Elmer Sigma 3B gas chromatograph equipped with a 1.83 m × 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 Piperazines 1c–f, 1i–1k, 1m, 1p, and 1q. This procedure is illustrated for the preparation of **1f**. A mixture of 19.78 g (0.111 mol) of bis(2-chloroethyl)amine hydrochloride and 1-butanol (200 mL) was treated slowly with 2-isopropylaniline at room temperature. After addition was complete, the mixture was refluxed for 48 h and then cooled. Sodium carbonate was added and the mixture was refluxed for another 48 h, after which the reaction was cooled in ice and a white solid was collected by filtration. This material was partitioned between 3 N NaOH and CH_2Cl_2. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The organic layers were combined, dried over anhydrous K_2CO_3, filtered, and evaporated, affording 6.82 g of **1f**, as an oil. A hot solution of **1f** and 2-propanol–methanol was treated with fumaric acid (3.87 g) to give a white solid on cooling. Recrystallization from methanol gave the fumaric acid salt of **1f**: yield 7.38 g (21%); mp 188–189 °C; ^{1}H NMR (Me_2SO-d_6) δ 3.35 [m, 1 H, C*H*(CH_3)], 3.20 (m, 8 H, piperazine methylenes), 1.13 [d, J = 6 Hz, 6 H, CH(C*H*$_3$)].

1-(2-Cyanophenyl)piperazine (1n). This compound was prepared by using a modification of the method in reference 15. A mixture of 2-bromobenzonitrile (10.25 g, 0.056 mol) and anhydrous piperazine (24.52 g, 0.285 mol) was heated at 100 °C with stirring overnight. After cooling, the reaction mixture was partitioned between 3 N NaOH and CH_2Cl_2. The aqueous layer was reextracted with CH_2Cl_2, and the organic layers were combined and washed with brine. The organic portion was dried over anhydrous K_2CO_3, filtered, and evaporated to a dark oil, 11.87 g. A solution of this material in 50 mL of 2-propanol was treated with fumaric acid (6.53 g) in 100 mL of 2-propanol, cooled in ice, and filtered to give the fumaric acid salt of **1n**: yield 4.85 g (46%); mp 199.5–200.5 °C; IR (KBr) ν_{max} 2210 cm^{-1} (C≡N).

1-(2-Hydroxyphenyl)piperazine (1g).[12] A solution of **1h** (22.91 g, 0.119 mol) and 230 mL of 48% hydrobromic acid was refluxed 90 h and cooled in an ice bath. The brown crystalline solid that precipitated was collected and recrystallized by dissolving it in 500 mL of hot methanol, reducing the volume to 350 mL, and cooling overnight in a refrigerator. Trituration of the resulting material in boiling 2-propanol, followed by filtration and drying, afforded **1g** as a white crystalline solid: yield 14.97 g (49%); mp dec 278 °C.

2-(1-Methylethoxy)benzenamine (3a). Compound **3a** was prepared by the method of Muller.[14]

2-Butoxybenzenamine (3b).[15] A solution of 2-butoxynitrobenzene[16] (12.12 g, 0.062 mol) and 100 mL of ethanol was hydrogenated in the presence of 10% Pd/C at 43 psig. The reaction mixture was filtered and evaporated to give 9.27 g of **3b** as a brown oil, 99% pure by GC (retention time 3.84 min).

Binding Studies. Many of the radioligand studies have been described in detail elsewhere.[27] For the dopamine D-1 binding assay tissue was taken from rat striata and suspended in 20 mM NaHepes (no sucrose) so that the volume was 250 times the initial tissue weight. The radioligand used was 0.1 mL of 3 nM [^{3}H]-SCH-23390 (Amersham, specific activity ~85 Ci/mmol). For determination of nonspecific binding, 0.1 mL of aqueous 30 μM SCH-23390 maleate was substituted for the 0.1 mL of water. Samples were incubated for 20 min and treated like the other assays. For the 5-HT-1A assay the method of Norman et al.[28] was modified. A synaptic membrane fraction was prepared from the hippocampus of rat brains. The membrane pellet was resuspended in 50 volumes of the 20 mM NaHepes-buffered solution. The binding reaction was initiated by combining 0.5 mL of this crude synaptic membrane suspension with 2.2 mL of 20 mM NaHepes buffer, 0.1 mL of 15 nM [^{3}H]WB4101 (NEN Products, specific activity ~18 Ci/mmol), and 0.1 mL of water or 0.1 mL of 30 mM 5-HT. In addition, 0.1 mL of 30 μM prazosin hydrochloride was added to prevent binding of WB4101 to the α-1 receptor. For the 5-HT-1B binding assay, cortical tissue of the rat was the tissue used and [^{3}H]serotonin was the ligand as in the 5-HT-1 assay.[27] The assay was carried out as for the 5-HT-1 assay with the exception that 8-OH-DPAT in a final concentration of 100 nM was added to the incubation medium. All assays were carried out in duplicate and one to five concentration–response curves were determined for each compound.

Block of Conditioned Avoidance Responding (CAR). The CAR test was carried out at time of peak effect in trained rats as described previously.[1] The animals had been trained to perform a discrete trail single-lever conditioned avoidance response. In short, each rat served as its own control, having a sixty session trial run during a 1-h testing period the day prior to drug testing. A total of 6–12 rats was given each dose of each compound, and reduction in CAR responding as well as loss of escape responding were recorded. Linear regression was used to determine the values at which CAR performance was reduced by 50% (ED_{50} value) with 95% confidence intervals from the control levels. A minimum of three doses of each active drug was used to determine the ED_{50} values. The loss of escape responding was determined for the estimated ED_{50} value for CAR block.

Registry No. **1a**, 92-54-6; **1b**, 39512-51-1; **1c**, 40224-10-0; **1c**·HCl, 119720-84-2; **1d**, 119695-81-7; **1d** fumarate, 119695-83-9; **1e**, 100861-48-1; **1e** fumarate, 119695-84-0; **1f**, 119695-82-8; **1f** fumarate, 119695-85-1; **1g**, 1011-17-2; **1g**·2HBr, 58260-69-8; **1h**, 35386-24-4; **1i**, 13339-01-0; **1j**, 106476-37-3; **1j** fumarate, 119695-86-2; **1k**, 54013-91-1; **1k** fumarate, 119695-87-3; **1l**, 15532-75-9; **1m**, 1011-15-0; **1m**·HCl, 1011-16-1; **1n**, 111373-03-6; **1n** fumarate, 119695-88-4; **1o**, 6640-24-0; **1p**, 3801-89-6; **1p** fumarate, 119695-89-5; **1q**, 54054-85-2; **1q** fumarate, 119695-90-8; **1r**, 39512-50-0; **2b**, 7252-51-9; **3a**, 643-28-7; **3b**, 4469-81-2; piperazine, 110-85-0; bis(2-chloroethyl)amine, 334-22-5; 2-bromobenzonitrile, 2042-37-7.

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