determined by nonlinear regression analysis and expressed as the mean ± standard error of the mean (SEM) for 5–6 separate experiments.

Determination of Cyclic AMP Accumulation in Glioma Cells. The C6 glioma cells were cultured as previously described.[4] One day prior to the experiment the cells were subcultured in multidish trays, incubated overnight at 37 °C, the media removed and the cells washed twice with buffer made with the following components (mM): NaCl 118, KCl 4.7, $CaCl_2$ 3, $MgSO_4$ 1.2, KH_2PO_4, EDTA 0.5, glucose 10, and HEPES 20, pH 7.4. Fresh buffer (1 mL) containing the phosphodiesterase inhibitor rolipram (30 μM) was added to each well. Following a 10-min preincubation the test compounds were added and the incubation continued for an additional 10 min. Incubations were stopped by the removal of buffer and the addition of 0.1 N HCl (1.0 mL) to each well. After 30 min, the media was neutralized by the addition of 0.1 N NaOH, and cyclic AMP levels determined with a commercial kit (Amersham, Arlington Heights, IL). Results were expressed as picomole of cyclic AMP formed per 10 min. EC_{50} values were determined graphically.

Synthesis and Biological Evaluation of a Series of Substituted *N*-Alkoxyimides and -amides as Potential Atypical Antipsychotic Agents[1]

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In a continuing program to discover antipsychotic agents with a reduced propensity toward extrapyramidal side-effects, a series of *N*-alkoxyimides and -amides was prepared. Evaluation of these compounds in vitro revealed affinities for D_2, $5HT_2$ and $5HT_{1A}$ receptors. Several members of the series displayed a profile indicative of potential antipsychotic activity in preclinical assays. The most potent compound in these assays, **7**, also displayed possible effectiveness for the negative symptoms of schizophrenia. The synthesis of these compounds and details of their structure–activity relationships are described.

The inhibition of postsynaptic dopaminergic neurotransmission is traditionally assumed to be the mode of action of clinically available antipsychotic agents.[2] While treatment with these agents can be effective, it is often accompanied by the development of extrapyramidal side-effects (EPS),[3] and chronic treatment may result in tardive dyskinesia.[4]

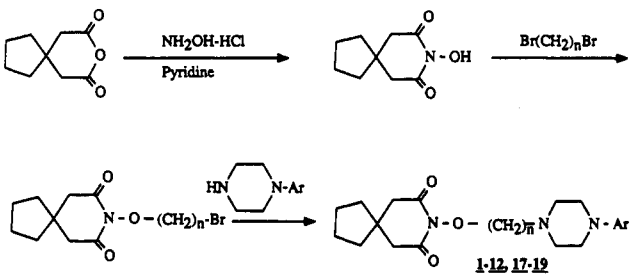
In research toward the development of a more selective therapeutic agent for schizophrenia, one emerging strategy is that the dopaminergic system can be more sensitively modulated through pharmacological manipulation of the serotonergic system. Consistent with this theory, clinical evidence exists for the involvement of the serotonergic receptor system in the pathology of schizophrenia. For example, in addition to its dopaminergic and α-adrenergic antagonist properties the atypical neuroleptic clozapine displays serotonergic antagonism at the $5\text{-}HT_2$ receptor site.[5] Another putative atypical neuroleptic, risperidone, also possesses both D_2 and $5\text{-}HT_2$ antagonist properties.[6] In addition to their reduced propensity to produce EPS, both compounds have been reported to improve type II (negative syndrome) schizophrenia, characterized by apathy and social withdrawal. Classical neuroleptics such as haloperidol are generally less effective against negative symptoms.[7]

We have prepared a series of compounds which would incorporate a $5HT_2$ antagonist component of action with dopamine D_2 antagonist activity and submitted them to a battery of tests predictive of antipsychotic activity. Several members of this series displayed a profile of activity indicative of potential antipsychotic efficacy with a reduced propensity for EPS liability. The standard neuroleptic agents haloperidol, clozapine, tiospirone and risperidone were assayed for comparison.

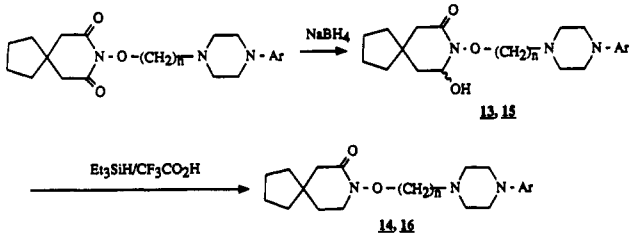
Chemistry

The target compounds reported here were synthesized according to the routes outlined below. The azaspiro[4.5]decane-7,9-dione derivatives were prepared via treatment of 8-oxaspiro[4.5]decane-7,9-dione with hydroxylamine hydrochloride and pyridine to provide 8-hydroxy-8-azaspiro[4.5]decane-7,9-dione. This compound

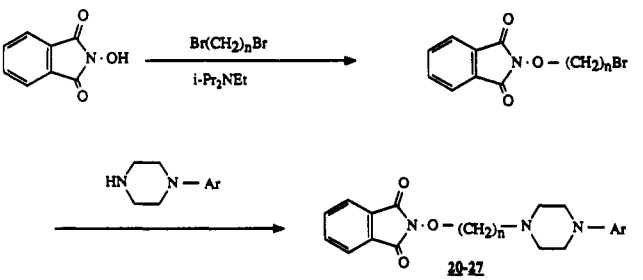
Scheme I



Scheme II



Scheme III



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(1) Presented in part in poster form at the 197th American Chemical Society Meeting, Dallas, Tx, April 1989; Abstract MEDI 37.
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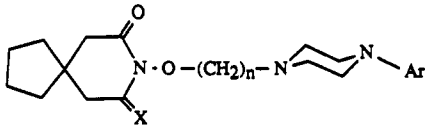
Table I. Azaspiro[4.5]decane-7,9-dione and Azaspiro[4.5]decan-7-one Derivatives



compd no.	Ar	X	n	mp, °C	formula[a]
1	*m*-trifluorotolyl	O	3	200–203	$C_{23}H_{30}F_3N_3O_3$·HCl
2	2-pyrimidyl	O	3	204–206	$C_{20}H_{29}N_5O_3$·HCl·0.5H_2O
3	*m*-tolyl	O	3	173–175	$C_{22}H_{33}N_3O_3$·HCl·0.5H_2O
4	*m*-chlorophenyl	O	3	165–168	$C_{22}H_{30}ClN_3O_3$·HCl·0.5H_2O
5	2,3-xylyl	O	3	188–191	$C_{24}H_{35}N_3O_3$·HCl·0.5H_2O[b]
6	*o*-chlorophenyl	O	3	206–209	$C_{22}H_{30}ClN_3O_3$·HCl
7	1,2-benzisothiazol-3-yl	O	3	207–210	$C_{23}H_{30}N_4O_3S$·HCl·0.5H_2O
8	*o*-methoxyphenyl	O	3	192–194	$C_{23}H_{33}N_3O_4$·HCl·0.5H_2O
9	(*m*-methylthio)phenyl	O	3	86–88	$C_{22}H_{33}N_3O_3S$
10	2-benzothiazolyl	O	3	120–123	$C_{23}H_{30}N_4O_3S$
11	2-quinolyl	O	3	103–106	$C_{25}H_{32}N_4O_3$
12	1,1-dioxo-1,2-benzisothiazol-3-yl	O	3	163–165	$C_{23}H_{30}N_4O_5S$
13	1,2-benzisothiazol-3-yl	H,OH	3	135–137	$C_{23}H_{32}N_4OS$
14	1,2-benzisothiazol-3-yl	H_2	3	194–197	$C_{23}H_{32}N_4O_2S$·HCl[c]
15	*o*-methoxyphenyl	H,OH	3	107–110	$C_{23}H_{35}N_3O_4$
16	*o*-methoxyphenyl	H_2	3	140–142	$C_{23}H_{35}N_3O_3$·HCl·1.5H_2O
17	1,2-benzisothiazol-3-yl	O	2	150–152	$C_{22}H_{28}N_4O_3S$
18	*o*-methoxyphenyl	O	2	176–179	$C_{22}H_{31}N_3O_4$·2HCl
19	2-pyrimidyl	O	2	98–100	$C_{19}H_{27}N_5O_3$

[a] All compounds were analyzed for C, H, and N to within ±0.4%, except where noted. [b] Calcd 62.79 C, found 62.32 C. [c] Calcd 59.39 C, found 58.93 C.

was alkylated with dibromoalkenes to give the bromoalkoxy intermediates which were then treated with various arylpiperazines to provide the compounds **1–12** and **17–19** (Scheme I).

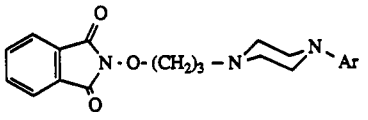
The azaspiro[4.5]decan-7-one derivatives were synthesized by reducing the appropriate azaspiro[4.5]decane-7,9-dione derivative with sodium borohydride to provide the carbinolamides **13** and **15**. These compounds could be further reduced by triethylsilane and trifluoroacetic acid to provide azaspiro[4.5]decan-7-ones **14** and **16** (Scheme II).

The phthalimido derivatives were prepared by alkylation of commercially available *N*-hydroxyphthalimide with dibromoalkanes to give bromoalkoxy intermediates, which were then treated with arylpiperazines to provide the [(piperazinylalkyl)oxy]phthalimides **20–27** (Scheme III). The targets prepared by these routes are listed in Tables I and II.

Pharmacological Results and Discussion

The target compounds were screened for dopaminergic D_2 receptor binding in vitro and for antagonism of apomorphine-induced climbing in mice (CMA) in vivo (Table III). These screening assays are predictive of potential antipsychotic activity since all clinically effective neuroleptics antagonize climbing and possess dopamine D_2 antagonist properties.[8-10] Several of the compounds were then chosen to be tested for their affinity for the 5-HT_2 and/or 5-HT_{1A} receptor binding site.

Table II. Phthalimide Derivatives



compd no.	Ar	mp, °C	formula
20	*m*-trifluorotolyl	161–164	$C_{22}H_{22}F_3N_3O_3$·HCl
21	*o*-methoxyphenyl	141–143	$C_{22}H_{25}N_3O_4$
22	*m*-tolyl	127–128	$C_{22}H_{23}N_3O_3$
23	*m*-chlorophenyl	140–142	$C_{21}H_{22}ClN_3O_3$
24	1,2-benzisothiazol-3-yl	143–144.5	$C_{22}H_{22}N_4O_3S$
25	2-quinolyl	158–160	$C_{24}H_{24}N_4O_3$
26	*o*-tolyl	174–176	$C_{22}H_{25}N_3O_3$
27	(*m*-methylthio)phenyl	103–106	$C_{22}H_{25}N_3O_3S$

[a] All compounds were analyzed for C, H, and N to within ±0.4%.

As shown in Table III, only those compounds which possessed a nonaromatic imide or amide, linked by a four-atom tether to the piperazine moiety, showed in vivo activity in the CMA assay. The most active target in the CMA, compound **7** (ED_{50} = 5.7 mg/kg ip), showed the most potent dopamine D_2 binding (0.14 μM). Dopamine D_2 antagonist effects were confirmed in the measurement of turnover of the dopamine metabolites DOPAC and HVA in an acute study (unpublished results). Compound **7** also binds to both the serotonin 5-HT_2 and 5-HT_{1A} receptor binding sites. The ratio of D_2/5HT_2 receptor binding has been proposed to be predictive of potential atypicality, e.g. clozapine-like antipsychotics show a ratio >1 whereas typical neuroleptics show a ratio <1.[11,12] Compound **7**, with a ratio of 8.75, resembles clozapine (ratio = 31.25) and risperidone (ratio = 41.66) rather than haloperidol (ratio 0.13) in its in vitro profile. Also, 5-HT_{1A} agonists have been reported to possess a pharmacological profile suggesting potential antipsychotic effects with a lack of EPS liability.[13] Compound **7** shows an affinity for

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Table III. Structure–Activity Relationships

compd	inhibition of apomorphine-induced mouse climbing: ED_{50}, mg/kg ip (95% confidence limits)[a]	effects on receptor binding: IC_{50}, μM		
		$5HT_{1A}$ receptor[c]	$5HT_2$ receptor[d]	D_2 receptor[e]
1	>20[b]	0.03	3.10	2.90
2	>20	0.38		2.00
3	26.5 (25.5–27.6)	0.09	0.39	3.70
4	>20	0.04		2.80
5	39.7 (34.9–46.3)	0.17	0.25	2.00
6	>20	0.22		0.68
7	5.7 (5.4–6.1)	0.11	0.02	0.14
8	11.0 (10.2–11.8)	0.11	1.19	0.93
9	>20	0.05		4.09
10	>20	2.20	8.10	>20.00
11	>20			>20.00
12	>20	>20.00	>20.00	>20.00
13	>20	0.08	0.01	0.27
14	17.8 (15.3–21.8)	0.03	0.01	0.17
15	>20	0.06		1.00
16	>20	0.07	2.70	0.72
17	>20	0.97	0.24	2.70
18	>20	0.37	3.20	0.74
19	>20	2.76	>20.00	>20.00
20	>20	5.30		>20.00
21	>20	6.90		>20.00
22	>20	>20.00		>20.00
23	>20	>20.00		>20.00
24	>20	>20.00	>20.00	>20.00
25	>20			>20.00
26	>20	>20.00		>20.00
27	>20	>20.00		>20.00
haloperidol	0.25 (0.23–0.26)	6.21	0.13	0.02
clozapine	8.10 (7.6–8.7)	0.58	0.03	1.00
risperidone	0.06 (0.047–0.077)	0.82	0.005	0.03
tiospirone	0.84 (0.76–0.92)	0.018	0.002	0.022

[a] Pretreat time was 30 min. [b] ED_{50} was not determined but is greater than screening dose (20 mg/kg ip). [c] Versus ^{3}H-8-OH-DPAT. [d] Versus ^{3}H-spiroperidol in cortical tissue. [e] Versus ^{3}H-spiroperidol in striatal tissue.

Table IV. In Vitro Profile of Compound 7

receptor	ligand/tissue	inhibition of ligand binding: IC_{50}, μM
$5HT_{1A}$	^{3}H-8-OH-DPAT/hippocampus	0.11
$5HT_{1B}$	^{3}H-5HT/striatum	5.53
$5HT_2$	^{3}H-spiroperidol/cortex	0.02
D_2	^{3}H-spiroperidol/striatum	0.14
alpha-1	^{3}H-WB4101/whole brain	0.01
sigma	^{3}H-SKF 10,047/slide-mounted slices	1.10
D_1	^{3}H-SCH 23390/striatum	6.60

the $5\text{-}HT_{1A}$ binding site in vitro and was shown to be an agonist at this site based on its generalization to the $5\text{-}HT_{1A}$ agonist 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) in a drug-discrimination paradigm (at 0.3–1 mg/kg sc, compound 7 showed partial to full generalization in 11 rats). On the basis of these results, this compound was selected for further evaluation. In addition to its dopaminergic and serotonergic binding properties compound 7 showed potent α_1-adrenergic receptor binding and less affinity for dopamine D_1, σ, and $5\text{-}HT_{1B}$ sites (Table IV). Despite its potent α_1-adrenergic binding, compound 7 showed no cardiovascular liability as evidenced by inactivity in the indirect hypotensive assay in the rat (at 5 mg/kg po, after 3 days daily dosing, an increase in blood pressure of 11 mmHg, and an increase in heart rate of 3 beats/min was observed).

The in vivo profile of compound 7 is presented in Table V, along with reference antipsychotic agents. As mentioned above, compound 7 showed the most potent inhibition of apomorphine-induced mouse climbing (ED_{50} = 5.7 mg/kg, ip) in this series, with a potency comparable

Table V. In Vivo Profile of Compound 7 and Reference Antipsychotic Agents

assay	7	haloperidol	clozapine	tiospirone	risperidone
inhibition of apomorphine-induced climbing (mouse), ED_{50}[b]	5.7 (5.4–6.1)	0.08 (0.07–0.09)	8.1 (7.6–8.7)	0.84 (0.76–0.92)	0.062 (0.047–0.077)
inhibition of apomorphine-induced stereotypy (rat), ED_{50}[c]	35.4 (21.8–57.5)	0.31 (0.21–0.45)	33% at 40	3.7 (2.1–6.5)	3.2 (2.1–4.8)
inhibition of amphetamine-induced stereotypy (rat), ED_{50}[c]	17% at 20	0.215 (0.149–0.309)	0% at 50	nt[g]	nt
intracranial self-stimulation (rat), ED_{50}[c]	0.92 (0.641–1.33) 12.49 (11.73–13.18)[d]	0.077 (0.073–0.081)	9.1 (8.5–9.7)	0.124 (0.1–0.148)	0.13 (0.11–0.15)
pole-climb avoidance (rat):					
ED_{50}, avoidance	2.5 (1.9–3.0)[b]	0.53 (0.44–0.64)[e]	13.06 (11.66–14.67)[c]	0.93 (0.83–1.04)[f]	0.48 (0.48–0.52)[c]
ED_{50}, escape failures	>20	7.3 (6.1–9.7)	>80	2.77 (2.61–2.97)	1.3 (1.1–1.4)
induction of catalepsy (rat), ED_{50}[c]	33% at 30, 83% at 40	0.659 (0.396–1.09)	0% at 80	67% at 20	5.7 (3.7–8.6)
social interaction (rat)	+24% at 1.0	−45% at 0.25	+44% at 5.0	+34% at 1.0	+27% at 0.5

[a] ED_{50} + 95% confidence limits (or dose administered and percent activity), mg/kg ip unless otherwise noted. [b] Pretreat time was 30 min. [c] Pretreat time was 60 min. [d] ED_{50} mg/kg po. [e] Pretreat time was 240 min. [f] Pretreat time was 120 min. [g] nt = not tested.

to that of clozapine (ED_{50} = 8.1 mg/kg ip). The potential antipsychotic activity of compound 7 was confirmed in a number of animal models. In the rat intracranial self-stimulation model, compound 7 dose dependently attenuated bar pressing for electrical stimulation of the medial forebrain bundle (ED_{50} = 0.92 mg/kg ip). Also, compound 7 antagonized conditioned avoidance responding in the pole-climb avoidance assay and furthermore provided a favorable separation between ED_{50} values for avoidance (2.5 mg/kg ip) vs escape failures (>20 mg/kg, ip), suggesting a neuroleptic agent with reduced sedative liability.

Compound 7, similar to clozapine, was less efficacious in the inhibition of apomorphine- or amphetamine-induced stereotypy models as well as in the induction of catalepsy. The behaviors induced in these assays have been shown to be primarily mediated by the nigrostriatal dopaminergic system, and antagonism in this system has been linked to potential EPS liability.[14-16] On the basis of the results in these assays, compound 7 may, like clozapine, have a reduced propensity to produce extrapyramidal side-effects.

Clozapine[17,18] and risperidone[19,20] have been reported to attenuate some of the negative symptoms of schizophrenia in the clinic, while haloperidol is reported to be less effective.[21] Table V shows that compound 7 increases social interaction behavior in rats similarly to clozapine and risperidone while haloperidol attenuates this behavior, suggesting that compound 7 may be efficacious for the negative symptom of social withdrawal.

Conclusions

Several members of the series of compounds presented here have demonstrated potential antipsychotic activity, as evidenced in vivo by activity in the climbing mouse model. In vitro, the active compounds bind to the dopamine D_2 as well as $5HT_{1A}$ and $5HT_2$ receptors. The lead target in this series, compound 7, demonstrated the best activity in preclinical tests such as inhibition of apomorphine-induced climbing, rat self-stimulation, and pole-climb avoidance behavior.

In addition, compound 7 may possess a reduced propensity for EPS liability as indicated by its lack of potency in catalepsy induction, and also in the wide separation between inhibition of apomorphine-induced climbing vs stereotyped behaviors, indicative of potential selectivity for mesolimbic vs striatal dopaminergic systems. Its activity in the social interaction test may be predictive of efficacy in the social withdrawal aspect of the negative symptomatology of schizophrenia. Compound 7 is currently undergoing further preclinical evaluation.

Experimental Section

All structures are supported by their IR (Perkin-Elmer 547) and ^1H NMR (Varian XL-200) spectra. Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Mass spectra were determined on a Finnigan 4000 GC-MS equipped with an INCOS data system. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, IL.

8-Hydroxy-8-azaspiro[4.5]decane-7,9-dione. A solution of 8-oxaspiro[4.5]decane-7,9-dione (5.0 g) and hydroxylamine hydrochloride (2.1 g) in 75 mL of anhydrous pyridine was heated to 80 °C with stirring under nitrogen. After 18 h the mixture was cooled to room temperature. The solids were filtered off, and the filtrate was concentrated in vacuo. The residue was triturated exhaustively with Et_2O. The Et_2O was concentrated in vacuo to provide 3.2 g of product as a white solid, homogeneous by TLC, mp 69–71 °C. NMR ($CDCl_3$): δ 8.46 (br, 1 H), 2.74 (s, 4 H), 1.74 (m, 4 H), 1.58 (m, 4 H).

8-[(2-Bromoethyl)oxy]-8-azaspiro[4.5]decane-7,9-dione. To a solution of 8-hydroxy-8-azaspiro[4.5]decane-7,9-dione (30 g) in 600 mL of anhydrous acetonitrile were added diisopropylethylamine (57 mL) and 1,2-dibromoethane (42.4 mL). The mixture was heated to 70 °C with stirring. After 7 h, heating was discontinued and the mixture was stirred at room temperature for 48 h. The volatiles were removed in vacuo, and the residue was taken up in EtOAc and filtered. The filtrate was concentrated in vacuo, and the residue chromatographed on silica with CH_2Cl_2 as eluent. The fractions containing desired product were combined and concentrated to provide a solid which was recrystallized from Et_2O to provide 25.57 g of white crystals, mp 75–77 °C. NMR ($CDCl_3$): δ 4.28 (t, J = 8 Hz, 2 H), 3.58 (t, J = 8 Hz, 2 H), 2.50 (s, 4 H), 1.75 (m, 4 H), 1.54 (m, 4 H). IR ($CHCl_3$): 1755 (sm), 1710 cm^{-1}. Anal. ($C_{11}H_{16}BrNO_3$) C, H, N.

***N*-[(3-Bromopropyl)oxy]phthalimide.** To a solution of *N*-hydroxyphthalimide (2.0 g) and 1,3-dibromopropane (2.49 mL) in 50 mL of dry acetonitrile was added diisopropylethylamine (4.27 mL). The mixture was stirred at room temperature. After 4 h the volatiles were removed in vacuo. The residue was triturated with Et_2O to provide 2.53 g of white solid, homogeneous by TLC, mp 81–83 °C. NMR ($CDCl_3$): 7.90 (m, 4 H), 4.40 (t, J = 6 Hz, 2 H), 3.76 (t, J = 6 Hz, 2 H), 2.34 (m, 2 H). IR ($CHCl_3$): 1740 (sm), 1700 cm^{-1}. Anal. ($C_{11}H_{10}BrNO_3$) C, H, N.

8-[(3-Bromopropyl)oxy]-8-azaspiro[4.5]decan-7,9-dione. A mixture of 8-hydroxy-8-azaspiro[4.5]decane-7,9-dione (5.22 g), 1,3-dibromopropane (5.8 mL), K_2CO_3 (3.9 g) and NaI (200 mg) in 100 mL of anhydrous acetonitrile was heated to 80 °C with stirring under nitrogen. After 6 h the mixture was cooled to room temperature, filtered, and concentrated in vacuo. The residue was chromatographed on silica with CH_2Cl_2 as eluent to provide 3.7 g of product, homogeneous by TLC. NMR ($CDCl_3$): δ 4.14 (t, J = 6 Hz, 2 H), 3.66 (t, J = 6 Hz, 2 H), 2.68 (s, 4 H), 2.26 (m, 2 H), 1.74 (m, 2 H), 1.58 (m, 2 H). IR ($CHCl_3$): 1750 (sm), 1708 cm^{-1}. Anal. ($C_{12}H_{18}BrNO_3$) C, H, N.

8-[[3-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl]propyl]oxy]-8-azaspiro[4.5]decane-7,9-dione Hydrochloride Hemihydrate (7). To a mixture of 8-[(3-bromopropyl)oxy]-8-azaspiro[4.5]decane-7,9-dione (5.26 g) and 1-(1,2-benzisothiazol-3-yl)piperazine (3.8 g) in 100 mL of anhydrous acetonitrile were added K_2CO_3 (4.8 g) and NaI (200 mg). The mixture was heated to 80 °C with stirring under nitrogen. After 18 h the mixture was cooled to room temperature and filtered, and the filtrate concentrated in vacuo. The residue was chromatographed on silica with EtOAc as eluent. The fractions containing desired product were combined, concentrated, and taken up in Et_2O. The HCl salt of the free amine was precipitated by the addition of ethereal HCl, collected, and dried to provide 3.42 g of product as a white solid, mp 207–210 °C. NMR ($CDCl_3$): δ 12.18 (br, 1 H), 7.88 (d, J = 10 Hz, 1 H), 7.86 (d, J = 10 Hz, 1 H), 7.56 (t, J = 6 Hz, 1 H), 7.42 (t, J = 6 Hz, 1 H), 4.14 (m, 7 H), 3.60 (br d, J = 12 Hz, 2 H), 3.48 (m, 2 H), 3.20 (m, 2 H), 2.68 (s, 4 H), 2.38 (m, 2 H), 1.74 (m, 4 H), 1.54 (m, 4 H). IR (KBr): 1750 (sm), 1708 cm^{-1}. Anal. ($C_{23}H_{30}N_4O_3S \cdot HCl \cdot 0.5H_2O$) C, H, N, Cl. Compounds 1–6, 8–12, and 17–19 were prepared in an analogous manner.

***N*-[[3-[4-(3-Trifluorotolyl)-1-piperazinyl]propyl]oxy]phthalimide Hydrochloride (20).** To a solution of *N*-[(3-bromopropyl)oxy]phthalimidie (3.0 g) and 1-(3-trifluorotolyl)-piperazine (2.4 g) in 100 mL of anhydrous acetonitrile was added diisopropylethylamine (3.7 mL). The solution was stirred at room temperature under nitrogen. After 18 h the volatiles were removed in vacuo, and the residue chromatographed on silica with EtOAc as eluent. The fractions containing the desired product were

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combined, concentrated, and taken up in Et_2O. The HCl salt of the free amine was precipitated by the addition of HCl in Et_2O, collected, and recrystallized from CH_2Cl_2/Et_2O to provide 1.92 g of white solid, mp 161–164 °C. NMR ($CDCl_3$): δ 7.70 (br, 1 H), 7.64 (m, 4 H), 7.26 (br d, J = 12 Hz, 2 H), 7.16 (d, J = 8 Hz, 2 H), 3.88 (t, J = 4 Hz, 2 H), 3.68 (m, 6 H), 3.34 (m, 8 H), 2.26 (m, 2 H). IR (KBr): 1650, 1605 (sm) cm^{-1}. Anal. ($C_{22}H_{22}F_3N_3O_3$·HCl) C, H, N, Cl. Compounds **21–27** were prepared in an analogous fashion.

8-[[3-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl]propyl]oxy]-7-hydroxy-8-azaspiro[4.5]decan-7-one (13). To a solution of compound **7** (4.25 g) in 80 mL of CH_3OH and 20 mL of CH_2Cl_2 was added with stirring $NaBH_4$ (1.52 g) in one portion. The mixture was stirred at room temperature for 1 h and then quenched with a solution prepared from 2 mL of 20% aqueous KOH and 50 mL of H_2O. The mixture was partitioned between CH_2Cl_2/H_2O and the organic phase was dried over $MgSO_4$ and concentrated in vacuo to 3.92 g of a yellow foam. This crude material was chromatographed on silica with 95:5 EtOAc/CH_3OH as eluent to provide first 360 mg of unreacted starting material followed by the desired product. This was recrystallized from Et_2O to provide 2.34 g of white solid, mp 135–137 °C. NMR ($CDCl_3$): δ 7.96 (d, J = 8 Hz, 1 H), 7.84 (d, J = 8 Hz, 1 H), 7.42 (m, 2 H), 4.2 (t, J = 6 Hz, 2 H), 3.40 (m, 6 H), 2.72 (m, 6 H), 2.34 (s, 2 H), 1.96 (m, 2 H), 1.84 (m, 2 H), 1.68 (m, 4 H), 1.46 (m, 4 H). IR ($CHCl_3$): 3000, 1670 cm^{-1}. Anal. ($C_{23}H_{32}N_4OS$) C, H, N. Compound **15** was prepared analogously.

8-[[3-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl]propyl]oxy]-8-azaspiro[4.5]decan-7-one Hydrochloride (14). To a solution prepared from compound **13** (4.7 g), 80 mL of CH_2Cl_2, and 40 mL of trifluoroacetic acid was added triethylsilane (1.8 mL) dropwise. The mixture was stirred at room temperature. After 1.5 h, the volatiles were removed in vacuo. The residue was taken up in EtOAc, washed with saturated aqueous Na_2CO_3 and then with brine, dried over $MgSO_4$, filtered, and concentrated. Chromatography on silica with 95:5 EtOAc/CH_3OH as eluent provided the desired product as an unrecrystallizable solid. The HCl salt of this amine was prepared through addition of ethereal HCl to an Et_2O solution and recrystallized from CH_2Cl_2/EtOAc/hexane to provide 1.36 g of needles, mp 194–197 °C. NMR ($CDCl_3$): δ 12.08 (br, 1 H), 7.84 (d, J = 8 Hz, 2 H), 7.46 (m, 2 H), 4.08 (m, 6 H), 3.58 (m, 4 H), 3.46 (m, 2 H), 3.28 (m, 2 H), 2.32 (br s, 4 H), 1.84 (m, 2 H), 1.68 (m, 4 H), 1.46 (m, 4 H). IR ($CHCl_3$): 1660, 1500 cm^{-1}. Anal. ($C_{23}H_{32}N_4O_2S$·HCl) H, N; C: calcd 59.39; found 58.93. Compound **16** was prepared in an analogous manner.

In Vitro Studies. Receptor binding assays were performed according to previously reported procedures.[22]

Apomorphine-Induced Climbing in Mice. This method is a modification of Protais et al.[9] and Costall et al.[10] Male CD-1 mice (18–30 g) were individually placed in wire-mesh stick cages (4 × 4 × 10 in.) and were allowed 1 h for adaptation. Animals (eight per dose group) received either distilled water or test drugs ip 30 or 60 min prior to apomorphine challenge (1.5 mg/kg sc). Animals were then observed for climbing behavior for 30 min. ED_{50} values were calculated by linear regression analysis.

Apomorphine-Induced Stereotypy in Rats. The procedure is a modification of Janssen et al.[23] Male Wistar rats (150–250 g) were dosed ip with distilled water or test compounds (6–10 per dose group). After 50 min, apomorphine (1.5 mg/kg sc) was administered and the rats were placed in individual opaque plastic cages (40 × 22 × 18 cm). After 10 min, the rats were observed for the presence of continuous stereotyped licking or sniffing behavior.

Catalepsy in Rats. The procedure is a modification of Costall and Naylor.[24] Male Wistar rats (150–250 g) were dosed ip with distilled water or test compounds (6–10 per dose group). Every hour for 6 h after dosing, each rats' forepaws were placed on an elevated wooden bar mounted in an opaque plastic cage. If the forepaws remained on the bar for 60 s, the animal was considered to be cataleptic at that time.

Pole-Climbing Avoidance in Rats. The procedure is similar to that described by Cook and Weidley.[25] Male Long Evans rats were trained in a discrete trial, signaled avoidance paradigm. A tone and light (CS) signaled the onset (4 s) of foot shock delivered through the grid floor of a test cage. A jump onto a steel pole suspended in the center of the test cage during the CS prevented the onset of shock and an avoidance response was recorded. Pole climbing after the onset of shock terminated the shock and an escape response was recorded. Rats failing to pole climb after the onset of shock could receive a maximum of 26 s of shock per trial. There were 25 trials per 50-min test session. Rats were trained to 80% avoidance prior to use. Distilled water or test compounds were administered ip to rats (six per dose group) at the pretreatment times listed in Table V. Individual rat avoidance responses and escape failures were compared with the corresponding distilled water controls. ED_{50} values were calculated by linear regression analysis.

Intracranial Self-Stimulation in Rats. Male Wistar rats (300–400 g) were stereotaxically implanted with chronic electrodes aimed at the medial forebrain bundle at the level of the preoptic nucleus as described by Ornstein.[26] Following a 2-week surgical recovery period, they were trained to lever-press for a train of biphasic square-wave pulses. After stable baseline responding for electrical stimulation was established, drugs were administered ip (3–6 per dose group) and compared to nondrug controls. ED_{50} values were calculated by linear regressioin analysis by using percent change from controls.

Social Interaction in Rats. The procedure is a modification of that used by File[27] and Gardner and Guy.[28] Pairs of male Wistar rats (200–275 g) were placed in an arena (45 × 45 × 40 cm) and allowed to acclimate for 8 min on two consecutive days. On the third day, rats naive to one another were assigned to treatment groups, six pairs per treatment group, and the rats received test drug or vehicle. After 30 or 60 min, the appropriate rats were paired and placed in the test arena for observation of social interaction behavior (time spent sniffing partner, climbing over partner, following partner, mutual grooming, etc.) for 5 min. Social interaction time (in seconds) and total activity (counts per body length of movement) for the test groups were compared to control, and statistical significance was determined by a one-way ANOVA and Duncan's multiple range test.

Hypotensive Activity in Spontaneously Hypertensive Rats. Compound **7** was screened for hypotensive activity in spontaneously hypertensive rats of the Okamoto-Aoki strain. Systolic blood pressures were determined at the following times by tail-cuff plethysmography: day 1, predose and 2 h postdose; day 3, predose and 2 h postdose; day 5, predose and 2 and 4 h postdose. Details of the method are described by Buggy et al.[29] Animals (n = 4) were dosed every day.

Drug Discrimination Assay. Male Fischer rats (200–300 g) were trained to discriminate between 8-OH-DPAT (0.1 mg/kg sc) and 0.9% saline in a two-choice discrete trial avoidance paradigm as described by Shannon and Holtzman.[30] Experimental sessions ended after 20 trials or 30 min, whichever came first. Training sessions were conducted 5 days per week. Either 8-OH-DPAT or saline was administered 30 min before each training session. Training continued until rats would complete at least 18 of 20 trials at the appropriate choice lever. For generalization studies, compound **7** was administered sc 30 min before testing. Animals were considered to show generalization when they bar pressed at the appropriate 8-OH-DPAT lever.

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