Atypical Antipsychotic Agents: Patterns of Activity in a Series of 3-Substituted 2-Pyridinyl-1-piperazine Derivatives

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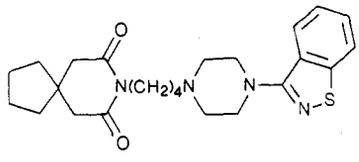
A series of 3-substituted 2-pyridinyl-1-piperazine derivatives have been appended to cyclic imide groups and evaluated for their potential antipsychotic activity. The dopamine receptor affinities of these target molecules, as well as their ability to block apomorphine-induced stereotypy or reverse neuroleptic-induced catalepsy, was dependent on the lipophilic and electronic characteristics of the substituent situated on the pyridine ring. Groups with $+\sigma$ and $-\pi$ values were most consistent with the desired biological profile of the target molecules, the cyano moiety being the optimum choice. Evaluation of compound **12** in a monkey model of amphetamine psychosis, and the regional selectivity it expresses for the A10 dopaminergic cell bodies in electrophysiological experiments, suggest this compound would be an atypical antipsychotic agent with few side effects.

Advances in our understanding of the brain and how the integrated neurochemistry of this complex organ controls our thought processes, emotions, and moods continually provides us with new therapeutic strategies to treat the disruption of these various functions. The basic thrust in the discovery of new antipsychotic drugs is the development of compounds that lack the extrapyramidal symptoms and tardive dyskinesia side effects frequently induced by the commonly used neuroleptic agents. In addition, while many modalities exist to treat the delusions, hallucinations, or paranoia known collectively as the positive symptoms of schizophrenia, the flattening of affect and social withdrawal, which characterize the negative symptoms of this disease, are refractive to drug treatment.[1-5]

An improved pharmacotherapy for the treatment of schizophrenia may spring from the discovery that some atypical antipsychotic agents demonstrate a regional selectivity for the various population subsets of dopamine neurons they antagonize.[6] While typical antipsychotic drugs affect the mesolimbic, mesocortical, and nigrostriatal dopamine (DA) systems, some atypical agents are observed to antagonize only the mesolimbic and mesocortical areas. The high incidence of side effects associated with the typical antipsychotic agents may be derived from their interference with the nigrostriatal system, since only the mesocortical and mesolimbic systems are thought to be primarily involved in the pathophysiology of schizophrenia.[7-9] A new generation of more efficacious antipsychotic drugs thus appears feasible if their development strategies incorporate a targeted specificity for the mesocortical and mesolimbic DA structures. We have previously reported the medicinal chemistry of tiospirone (**1**), a clinical antipsychotic candidate whose reduced side effect profile may be related to its strong serotonergic antagonist effects.[10] Here, we detail the pharmacology of a prototype originating from the same *N*-[(4-heteroaryl-1-piperazinyl)alkyl]-substituted imide chemical class, which features several atypical antipsychotic characteristics in its profile.



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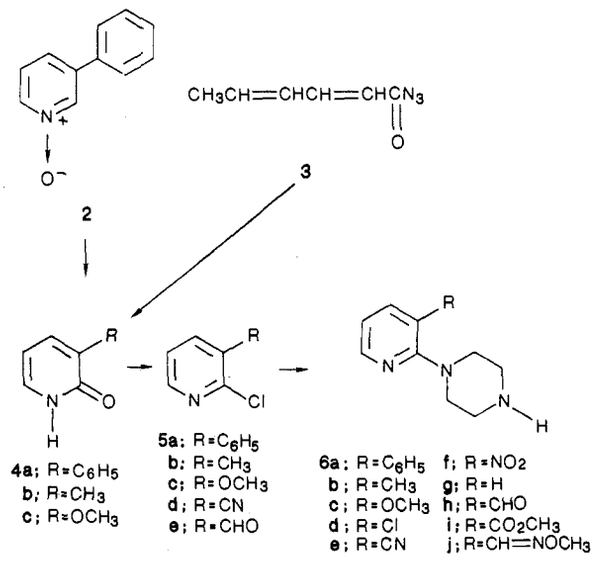
Scheme I



Chemistry. The variety of 1-(3-substituted-2-pyridinyl)piperazine derivatives required in the target compounds left little convergence in their synthetic elaborations. The 2(1*H*)-pyridone intermediates represented in **4** (Scheme I) either were obtained from Curtius rearrangement of the acyl azide derived from sorbic acid, with subsequent cyclization of the isocyanate to 3-methyl-2-(1*H*)-pyridone (**4b**) according to a published procedure,[11]

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‡ Illinois State Psychiatric Institute. Present address: Department of Pharmacodynamics, University of Illinois at Chicago, Chicago, IL 60612.

(1) Meltzer, H. Y.; Sommers, A. A.; Luchins, D. J. *J. Clin. Psychopharmacol.* **1986**, *6*, 329.
(2) Rosen, W. G.; Mohs, R. C.; Johns, C. A.; Small, N. S.; Kendler, K. S.; Horvath, T. B.; Davis, K. L. *Psychiatry Res.* **1984**, *13*, 277.
(3) Crow, T. J. *Psychopharmacol. Bull.* **1982**, *18*, 22.
(4) Angrist, B.; Rotrosen, J.; Gershon, S. *Psychopharmacology (Berlin)* **1980**, *72*, 17.
(5) Kendler, K. S. *Drug. Dev. Res.* **1986**, *9*, 3.
(6) White, F. J.; Wang, R. Y. *Science (Washington, D. C.)* **1983**, *221*, 1054.
(7) Morris, R. G. M. *Trends Neurosci. (Pers. Ed.)* **1983**, *6*, 479.
(8) Chiodo, L. A.; Bunney, B. S. *J. Neurosci.* **1983**, *3*, 1607.
(9) Bunney, B. S. *Trends Neurosci. (Pers. Ed.)* **1984**, *7*, 212.
(10) Yevich, J. P.; New, J. S.; Smith, D. W.; Lobeck, W. G.; Catt, J. D.; Minielli, J. L.; Eison, M. S.; Taylor, D. P.; Riblet, L. A.; Temple, D. L., Jr. *J. Med. Chem.* **1986**, *29*, 359.

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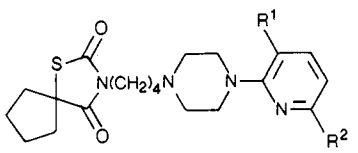
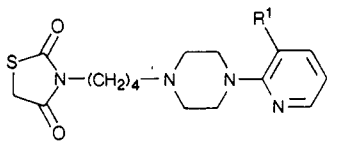
Table I. Compounds Containing the Thiazolidinedione Imide, 11–24

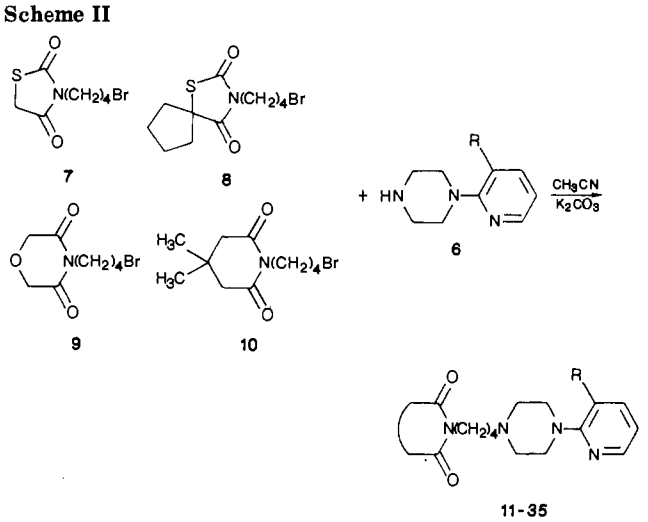
compd	R^1	R^2	recrystn solvent	mp, °C	yield[a]	formula[b]
						
11	H	H	CH_3CN	168–171	58	$C_{20}H_{28}N_4O_2S \cdot C_7H_8O_3S$
12	CN	H	EtOH	207–208	64	$C_{21}H_{27}N_5O_2S \cdot HCl$
13	CHO	H	CH_3CN	183–185	37	$C_{21}H_{28}N_4O_3S \cdot HCl$
14	NO_2	H	CH_3CN	190–194	63	$C_{20}H_{27}N_5O_4S \cdot 2HCl$
15	CO_2CH_3	H	*i*-PrOH	193–195	40.8	$C_{22}H_{30}N_4O_4S \cdot 2HCl$
16	CL	H	EtOH	185–188	30	$C_{20}H_{27}ClN_4O_2S \cdot HCl$
17	OCH_3	H	EtOAc	125–128	20	$C_{21}H_{30}N_4O_3S \cdot C_7H_8SO_3$
18	H	OCH_3	*i*-PrOH	194–196	40	$C_{21}H_{30}N_4O_3S \cdot HCl$
19	C_6H_5	H	EtOAc	125–127	42	$C_{26}H_{32}N_4O_2S \cdot C_4H_4O_4 \cdot 0.4H_2O$
20	$CH{=}NOCH_3$	H	*i*-PrOH	168–170	39.1	$C_{22}H_{31}N_5O_3S \cdot HCl$
21	CH_3	H	*i*-PrOH	175–182	57	$C_{21}H_{30}N_4O_2S \cdot HCl$
22	NH_2	H	EtOH	170–173	60	$C_{20}H_{29}N_5O_2S \cdot 2C_7H_8O_3S \cdot H_2O$
						
23	H		CH_3CN	232.5–236.5	79.8	$C_{16}H_{22}N_4O_2S \cdot 2HCl \cdot H_2O$
24	CN		EtOH	233–235 dec	51.2	$C_{17}H_{21}N_5O_2S \cdot 2HCl$

[a] Based on analytically pure sample. [b] All compounds gave satisfactory C, H, N analysis within ±0.4% of the theoretical values.

Polonovski rearrangement of the *N*-oxide derived from 3-phenylpyridine to yield 3-phenyl-2(1*H*)-pyridone (**4a**), or were commercially available (**4c**). Treatment of **4** with phosphorus oxychloride generated intermediates **5a–c**.[12] Alternatively, **5c** is available from the iodomethane alkylation of the sodium salt of 2-chloro-3-pyridinol in dry dimethyl sulfoxide.[13] Compound **5d** is derived from the phosphorus pentachloride and phosphorus oxychloride treatment of nicotinamide *N*-oxide,[14] DIBAH reduction of **5d** and hydrolysis of the resultant imine affords **5e**.[13] The 1-(3-substituted-2-pyridinyl)piperazine derivatives **6a–c** are obtained by reaction of the corresponding 2-chloropyridine precursors represented in **5** with an excess of piperazine in a bomb at 165 °C for varying periods of time or under reflux conditions in 2-propanol.

Compounds **6d–g** are commercially available or their synthesis has been previously reported.[15] The intermediate **6h** can also be generated by DIBAH reduction of **6e**. Compound **6i** is generated by the diazomethane esterification of 2-chloronicotinic acid, and **6j** is synthesized by the condensation of **6h** with methoxylamine. The target compounds **11–35** were formed by reaction of the 1-(3-substituted-2-pyridinyl)piperazine intermediates **6** with the *N*-(4-bromobutyl)imide derivatives represented by structures **7–10** (Scheme II); the synthesis of these latter intermediates has also been reported.[16–19] The synthesis of

Scheme II

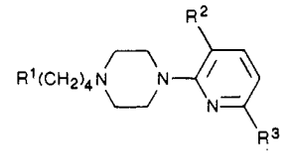


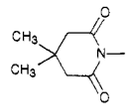
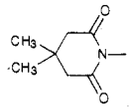
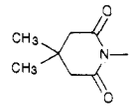
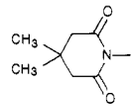
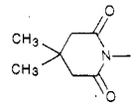
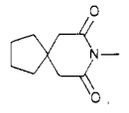
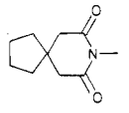
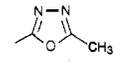
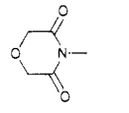
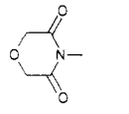
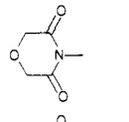
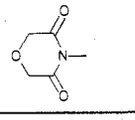
the oxadiazole substituent appended to the pyridine ring in **31** was achieved through a published procedure.[20] The synthesis of all previously undisclosed intermediates, as well as representative examples of the various target structures, is reported in the Experimental Section. Tables I and II further summarize the physical chemical data associated with these compounds.

Biology. All target compounds were evaluated in vitro for their binding affinity to rat cortical α_1-adrenergic receptors vs [^{3}H]WB-4101 and to rat DA D_2 receptors labeled with [^{3}H]spiperone. The tranquilizing activity of these compounds is measured by the ability of various doses of an orally administered compound to block the response of rats trained to avoid an electric shock (inhibition of the conditioned avoidance response, CAR). Activity in this

(11) Derijckere, A. M.; Eloy, F. G. F. German Patent DE 2052536, 1971.
(12) Temple, D. L., Jr.; Yevich, J. P.; Lobeck, W. G., Jr. U.S. Patent 4305944, 1981.
(13) New, J. S.; Lobeck, W. G., Jr.; Yevich, J. P. U.S. Patent 4619930, 1986.
(14) Taylor, E. C.; Crovetti, A. J. *J. Org. Chem.* **1954**, *19*, 1633.
(15) Saari, W. S.; Halczenko, W.; King, S. W.; Huff, J. R.; Guare, J. P. Jr.; Hunt, C. A.; Randall, W. C.; Anderson, P. S.; Lotti, V. J.; Taylor, D. A.; Clineschmidt, B. V. *J. Med. Chem.* **1983**, *26*, 1696.
(16) Temple, D. L., Jr.; Yeager, R. E. U.S. Patent 4456756, 1984.
(17) Temple, D. L., Jr.; Yevich, J. P. U.S. Patent 4411901, 1983.
(18) Yevich, J. P.; Temple, D. L.; New, J. S.; Taylor, D. P.; Riblet, L. A. *J. Med. Chem.* **1983**, *26*, 194.
(19) New, J. S.; Yevich, J. P.; Eison, M. S.; Taylor, D. P.; Eison, A. S.; Riblet, L. A.; VanderMaelen, C. P.; Temple, D. L., Jr. *J. Med. Chem.* **1986**, *29*, 1476.
(20) Ponticello, G. L.; Engelhardt, E. L.; Ponticello, G. S. *J. Heterocycl. Chem.* **1980**, *17*, 425.

Table II. Compounds **25–35** with Piperdinedione and Morpholinedione Imides



compd	R^1	R^2	R^3	recrystn solvent	mp, °C	yield	formula
25		CO_2CH_3	H	CH_3CN	168–170	39.1	$C_{22}H_{32}N_4O_4 \cdot HCl$
26		H	OCH_3	CH_3CN	212–214	61	$C_{21}H_{32}N_4O_3 \cdot HCl$
27		Cl	H	CH_3CN	217–221	67	$C_{20}H_{29}ClN_4O_2 \cdot 1.2HCl$
28		C_6H_5	H	CH_3CN	230–235	36.7	$C_{26}H_{34}N_4O_2 \cdot 1.2HCl \cdot 0.8H_2O$
29		CH_3	H	*i*-PrOH	195–200	47.5	$C_{21}H_{32}N_4O_2 \cdot 1.1HCl$
30		CH_3	H	CH_3CN	145–147	32	$C_{23}H_{34}N_4O_2 \cdot 2HCl \cdot 1.3H_2O$
31			H	EtOH	185–187	51	$C_{25}H_{34}N_6O_3 \cdot HCl \cdot 0.5H_2O$
32		CHO	H	CH_3CN	184–186	52	$C_{18}H_{24}N_4O_4 \cdot HCl$
33		NO_2	H	*i*-PrOH	199–203	52	$C_{17}H_{23}N_5O_5 \cdot HCl$
34		Cl	H	CH_3CN	217–220	46	$C_{17}H_{23}ClN_4O_3 \cdot 2HCl$
35		C_6H_5	H	*i*-PrOH	225–235 dec	27.9	$C_{23}H_{28}N_4O_3 \cdot 2.1HCl \cdot H_2O$

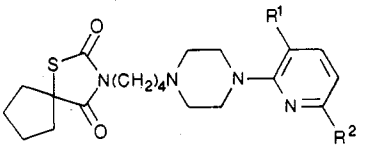
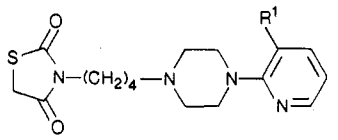
test is described by the dose inhibiting the CAR in half the animals tested. The compounds were also screened in vivo for their inhibition of apomorphine (APO) induced stereotypy in rats, a test predictive of potential dopamine antagonist effects. The ability of the test compounds to reverse a neuroleptic-induced catalepsy suggests they would have little propensity to induce the tardive dyskinesia or the extrapyramidal side effects frequently associated with neuroleptic agents. The amphetamine-induced psychosis model in monkeys was also employed as an evaluation of the potential antipsychotic activity of these compounds in primates. Antipsychotic agents have been shown to be effective in attenuating certain amphetamine-induced behaviors in monkeys, a model whose primary features are correlative with symptoms observed in human amphetamine-induced psychosis.[21] The biological activity of tested compounds is reported in Tables III and IV. Pertinent pharmacologic methodologies are presented in the Experimental Section.

Results and Discussion

The antipsychotic potential of the target compounds **11–35** is largely determined by the nature of the substituent at the 3-position of the pyridine ring. Compound **11**, which lacks substitution at this position, supports only marginal affinity for the dopamine receptor and fails to antagonize apomorphine-induced stereotypies (Table III). The function of a cyano group oriented meta to the pyr-

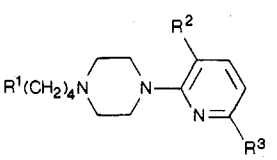
(21) Schlemmer, R. F.; Davis, J. M. In *Ethopharmacology: Primate Models of Neuropsychiatric Disorders*; Miczek, K. A., Eds.; Alan R. Liss: New York, 1983; pp 33–78.

Table III. Biological Activity of Thiazolidinedione Compounds 11–24

compd	binding at dopamine D_2 receptor–rat corpus striatum (vs [^{3}H]spiperone): IC_{50}, nM	rat conditioned avoidance response: ED_{50}, mg/kg, po	reversal of trifluoperazine-induced catalepsy: ED_{50}, mg/kg, po	blockade of apomorphine-induced stereotypy: ED_{50}, mg/kg, po	binding at α_1-adrenergic receptors (vs [^{3}H]WB-4101): IC_{50}, nM
					
11	620	20.8[a] (16.7–26.0)	IA[b]	>95.0	
12	34	38.0 (30.6–47.8)	9.2 (6.0–14.0)	29.3 (20.7–41.5)	35.0
13	130	60.0 (37.6–95.5)	12.9 (8.6–19.4)	48.0 (35.5–64.9)	9.6
14	69	25.3 (18.8–34.1)	44.2 (26.9–72.7)	43.6 (32.9–57.7)	34.1
15	138	29.8 (21.2–42.0)	5.05 (0.79–32.06)	50.2 (39.0–64.6)	7.8
16	160	66.9 (51.2–87.4)	IA	50.0 (39.0–64.1)	19.9
17	79	18.8 (15.0–23.8)	IA	<57.0	
18	>1000	35.9 (27.5–46.9)	IA	>100	
19	236	>100	IA	>100	
20	428	71.3 (49.4–102.8)	IA[b]	IA	67.4
21	630	46.4 (35.6–60.4)	IA	>50	
22	>1000	>100	IA		
					
23	>1000	45.8 (35.5–59.1)	IA		
24	>1000	15.8 (10.0–24.7)	IA[b]	>100	39.0
clozapine	400	24.1 (20.5–28.2)	IA	49.2 (33.4–72.3)	62

[a] In both Tables III and IV, the 95% fiducial limits are given in parentheses. [b] Compound induced catalepsy.

Table IV. Biological Activity of Compounds 25–35



compd	binding at dopamine D_2 receptor–rat corpus striatum (vs [^{3}H]spiperone): IC_{50}, nM	rat conditioned avoidance response: ED_{50}, mg/kg, po	induction of catalepsy: ED_{50}, mg/kg, po	blockade of apomorphine-induced stereotypy: ED_{50}, mg/kg, po	binding at α_1-adrenergic receptors (vs [^{3}H]WB-4101): IC_{50}, nM
25	>1000	57.0 (50.1–64.8)	≃228[a]	69.2 (50.7–94.5)	36.9
26	>1000	11.9 (10.0–14.2)	≃48[b]	76.2 (53.8–108.0)	68.0
27	360	25.9 (20.4–32.9)	≃104[a]		
28	109	67.6 (48.4–94.6)	90.8 (59.6–138.3)		
29	>1000	42.1 (31.4–56.5)	>200	>100	
30	476	46.4 (36.4–59.1)	>186		
31	610	70.9 (53.1–94.6)			
32	>1000	>100			
33	>1000	55.0 (39.8–76.0)	≃220[b]		38.3
34	>1000	59.8 (46.2–77.4)		>63	16.0
35	>41	>100			

[a] Toxic dose. [b] Maximum dose examined.

idinyl nitrogen, as in **12**, increases the dopaminergic receptor affinity 1 order of magnitude and restores an effective blockade of the apomorphine stereotypy syndrome to the molecule's biological profile. However, the most significant biological effect resulting from this seemingly minor structural change is observed in the catalepsy-induction properties of the two molecules; while **11** induced catalepsy and therefore would be predicted to cause extrapyramidal symptoms in humans, **12** lacks this property and is actually effective in reversing a prior neuroleptic-induced catalepsy in rats. This suggests that **12** would have a greatly reduced risk of inducing the debilitating extrapyramidal symptoms commonly associated with chronic neuroleptic therapy. Both **11** and **12** have appreciable activity in the CAR test, but the profound substituent effects that fashion the desired antipsychotic profile in **12** led to a broader structure-activity relationship (SAR) evaluation of this result.

A systematic construct to evaluate the full gamut of electronic and lipophilic properties from a panel of synthetically feasible substituent choices was derived from a Craig plot.[22] Although the data set is limited, the observed biological results supported our prediction that substituents that had $+\sigma$ and $-\pi$ characteristics, similar to that of the CN group of **12**, would best model the desired phar-

(22) Craig, P. N. *J. Med. Chem.* 1971, *14*, 680.

macological profile of that structure. The carboxaldehyde, nitro, and carbomethoxy moieties of compounds **13–15**, respectively, are the only substituents that meet these electronic and lipophilic criteria and confer on their parent structures a pattern of biological activity strictly analogous to the profile of **12** (Table III). However, none of these modifications offered a consistent potency advantage relative to the test parameters observed with **12**, except in their blockade of α_1-adrenergic receptors. The latter is actually a negative associated with the profiles of these derivatives because of its implications in the occurrence of orthostatic hypotension. The evaluation of substituents that have $+\sigma$ and $+\pi$ characteristics in congeners **16–19** led to their abrupt loss of activity in the reversal of trifluoperazine-induced catalepsy. The additional reductions in both dopamine D_2 receptor affinity and the blockade of apomorphine-induced stereotypies for compounds **16–19** compromised their potential as viable antipsychotic leads.

Similar to the pattern observed with **12** and its descyano derivative **11**, compound **17** loses its D_2 receptor affinity through translocation of its 3-methoxy group to the 6-position of the pyridine ring, as in isomer **18**. The minimum pharmacophore requirements for the potent D_2 receptor affinity in this series are then accordingly described by an electron-withdrawing group regiospecifically fixed at the 3-position of the pyridine ring. The degree of coplanarity existing between the pyridine and piperazine rings would also be directly influenced by the steric demands of this substituent, which, if significant, may favor an orientation of the pyridine ring that is twisted relative to the average plane of the piperazine ring. Such a conformation would also hinder any delocalization of the proximal piperazinyl nitrogen lone pair of electrons into the π-deficient 3-substituted pyridine system. The role of this delocalization in mediating the biological activity of the general arylpiperazine class has been the subject of previous investigations but still is not fully defined.[23,24] The loss of dopaminergic receptor affinity found to accompany the phenyl and methoxyimine substituents in compounds **19** and **20** could result from their steric perturbation of a relatively coplanar conformation of the pyridylpiperazine system, which may be preferred for optimum fit to the D_2 receptor. The out-of-plane skewing of this bicyclic system would also negate any participation of the electron-withdrawing group at the 3-position of the pyridine ring in facilitating a more extended delocalization of this nitrogen lone pair of electrons. A precipitous loss in catalepsy-reversing activity and the blockade of apomorphine-induced stereotypy is observed for all substituents other than those possessing $+\sigma$ and $-\pi$ characteristics. The electron-donating effects the substituents expressed in compounds **21** and **22** also disrupt the dopaminergic affinity of the pyridinylpiperazine pharmacophore in these molecules.

Modification to the Imide Group. Removal of the spirally fused cyclopentane ring of **12** leading to **24** results in a loss of both dopaminergic receptor affinity and catalepsy-reversing activity; a similar result is observed for the analogous transformation involving the descyano derivatives **11** and **23**. The tethering of the imide substructure through a four-carbon chain to the pyridylpiperazine pharmacophore obviously plays an important complement toward maximizing the affinity these prototypes display for the dopamine receptor. A variety of imide structures coupled to substituted pyridines in compounds **25–35** (Table IV) served to expand the scope of allowable imide modifications within this series. None of these modifications offered significant antipsychotic potential nor did the pattern of their biological results parallel the empirical SAR observations which were formulated for the thiazolidinedione imides **11–22**. A trend toward cataleptic properties with low dopaminergic receptor affinity in this subgrouping of molecules suggested the optimum imide substructure had been formulated in the spirally fused thiazolidinedione ring of **12**.

Atypical Antipsychotic Activity of 12 (BMY 13980). The promising antipsychotic efficacy of **12** led to an extensive preclinical profiling of this drug's activity. The acute iv administration (0.1–1.0 mg/kg) of **12** in rats was found to only partially reverse the APO-induced suppression of cell firing for the A9 DA neurons that project to the nigrostriatal DA system, but it elicited a complete reversal of the suppression in the A10 DA neuronal system; the latter projects to the mesolimbic and mesocortical DA systems.[25] A 28-day daily dosing regimen of **12** (5.0 or 10.0 mg/kg per day) via sc injection also produced a significant dose-dependent reduction in the number of spontaneously active A10 DA neurons but failed to exert a similar effect on the number of spontaneously active A9 DA neurons. The selectivity **12** expresses for the A10 DA neurons vs the A9 system, in both the acute and chronic treatment time frames, parallels the pharmacology of the atypical antipsychotic agents thioridazine and clozapine;[7,8] it is therefore predicted to share the reduced side effect risks of these agents. Since antagonism of the nigrostriatal DA system by typical antipsychotic agents may contribute little to their efficacy, but instead is linked with their propensity to induce extrapyramidal symptoms, this component of an antipsychotic profile is of dubious value. Presumably, the selective antagonism of only the mesolimbic and mesocortical dopaminergic systems, which may be complemented by other aspects of their profiles, is sufficient for the antipsychotic effects of the atypical agents.

Antagonism of Amphetamine-Induced Psychosis in Monkeys. A model of human amphetamine-induced psychosis was established in macaque monkeys by chronic administration of amphetamine to selected members of two small social colonies. Several behavioral changes result in the drug treated animals, which correlate with both the positive and negative symptoms of human amphetamine-induced psychoses. Known antipsychotic drugs can prevent or reverse major features of the amphetamine syndrome in monkeys, providing a model to evaluate the potential efficacy of preclinical antipsychotic drug candidates.

Daily nasogastric administration of **12** (60 mg/kg) was found effective in blocking the inappropriate submissive gesturing and scratching behavior observed in the amphetamine-treated monkeys. The submissive gesturing may model the paranoia or fear component of amphetamine-induced human psychosis, while the scratching behavior may be a correlate of the human tactile hallucinatory experiences.[26] The blocking or reversal of these amphetamine-induced changes by **12**, which are associated with the positive symptoms of schizophrenia, suggest that this atypical prototype would be an efficacious antipsychotic agent in man. The attenuation of the social withdrawal behavior of the amphetamine-treated monkeys,

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(24) Huff, J. R.; King, S. W.; Saari, W. S.; Springer, J. P.; Martin, G. E.; Williams, M. *J. Med. Chem.* **1985**, *28*, 945.
(25) White, F. J.; Wang, R. Y. *Neuropharmacology* **1986**, *25*, 995.
(26) Schlemmer, R. F.; Davis, J. M. *Pharmacol. Biochem. Behav.* **1981**, *14* (Suppl 1), 95.

which may be affiliated with the negative symptoms of schizophrenia, was less effectively treated by the administration of **12**.

Conclusions

Compound **12** has been identified as a novel antipsychotic candidate demonstrating possible mesolimbic-mesocortical selectivity in its mechanism of action. It emerges from a pyridinylpiperazine structural class whose affinity for the D_2 receptor requires an electron-withdrawing group be located at the 3-position of the pyridine ring. This substituent confers not only dopaminergic receptor affinity on the molecule but is also correlated with the compound's ability to block apomorphine-induced stereotypy and to reverse neuroleptic-induced catalepsy. The thiazolidinedione substructure of compounds **11–22** is the optimum imide group for lending the desired profile to these antipsychotic agents. The novel substituent effects observed in this family of compounds has stimulated further research pursuing this concept, which will be the subject of future reports.

Experimental Section

Biology. Procedures for the CAR, inhibition of apomorphine stereotypy, and evaluation of ligand affinities for DA D_2 and α_1-adrenergic receptors have been previously described.[10,18]

Reversal of Trifluoperazine-Induced Catalepsy. Fasted male rats are dosed with trifluoperazine (15 mg/kg, po) and placed in individual animal cages (10 × 26 × 43 cm) located in a quiet room. At 1 and 2 h, the animals are checked for catalepsy by carefully picking them up and placing their front paws on the top edge of the cage side. If the animal remains motionless in this position for 30 s, catalepsy is considered to be present. At a time interval $2^1/_2$ h after the trifluoperazine administration, the test compound is administered orally. Thirty minutes after the test compound administration (3 h after trifluoperazine), the animals are checked for a reversal of their catalepsy. Normally, at 3 h, 15 mg/kg (po) of trifluoperazine would produce catalepsy in 100% of the animals.

Determination of Effects on the Amphetamine Model of Psychosis in Nonhuman Primate Social Colonies. The chronic administration of amphetamine to selected members of primate social colonies is used to induce behavioral changes that resemble features of amphetamine-elicited psychosis as well as symptoms of schizophrenia in humans. These features are prevented or reversed by known antipsychotic drugs. In these studies, a stable social colony consisted of a male adult stumptail macaque (*Macaca arctoides*) and four females. The male in two such colonies did not receive drug at any time, whereas the females in each colony were divided into groups of two. Animals were observed initially for undrugged behavior. Then, one group in each colony received *d*-amphetamine for 12 days and was observed. Essentially, each colony was then crossed over; after 1–2 weeks off drug, the other group received an identical course of *d*-amphetamine. In the next part of the study, one colony had one group receive BMY 13980-1 only for 7 days followed by BMY 13980-1 plus *d*-amphetamine for 12 days. Two weeks later, after an observation of undrugged behavior, the other group of the same colony received a similar series of treatments with BMY 13980-1 and *d*-amphetamine. In the other colony, an observation period was followed by a treatment for each group that was different from the first colony; the first group received *d*-amphetamine only for 4 days followed by *d*-amphetamine plus BMY 13980-1 for 8 days. Drugs were given by nasogastric tube: 1.6 mg/kg amphetamine base in time-release form, twice a day and/or 60 mg/kg BMY 13980-1 once a day. Animals were rated for various behaviors by two experienced observers who were blind to the treatment. Two 1-h observation sessions were held each day.

Chemistry. All IR spectra were recorded on a Nicolet MX-1 FT-IR spectrometer, and the ^{1}H NMR spectra were recorded on a Perkin-Elmer R-32 spectrometer. Melting points were recorded on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental C, H, N analyses were run on a Perkin-Elmer 240B analyzer and Karl Fischer water determinations were made with an Aquatest II apparatus. Flash chromatography was used for all chromatographic purification with Woelm silica gel 230–400-mesh size as the absorbent.

Methyl 2-[4-[4-(2,4-Dioxo-1-thia-3-azaspiro[4.4]nonan-3-yl)butyl]-1-piperazinyl]pyridine-3-carboxylate Dihydrochloride (15). A stirred solution of potassium hydroxide (22.6 g, 0.4 mol), ethanol (45.3 mL), and water (36 mL) is treated with *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (22.6 g, 0.1 mol; Diazald, Aldrich) in ether (204 mL) at 65 °C. The rate of addition of the solution is regulated so as to maintain a steady ethereal diazomethane distillation rate. A diazomethane generation kit containing all polished glass surfaces is employed for the distillation; the distillate is received in two collection vessels connected in tandem, the first cooled to 0 °C and the second to −78 °C. The diazomethane preparation is treated dropwise with a solution of 2-chloronicotinic acid (4.7 g, 0.03 mol) in methanol at −15 °C. After being stirred for 4 h at this temperature, the solution is slowly brought to room temperature and concentrated in vacuo to a yellow solid which is partitioned between aqueous sodium carbonate and methylene chloride. The organic layer is isolated, dried ($MgSO_4$), and concentrated yielding 5.2 g (100%) of methyl 2-chloronicotinate as a crude oil.

A mixture of methyl 2-chloronicotinate (3.8 g, 0.02 mol) and piperazine (9.7 g, 0.11 mol) is refluxed in 2-propanol (125 mL) for 24 h. The solution is concentrated in vacuo and partitioned between dichloromethane and water, and the organic layer is isolated, dried ($MgSO_4$), and concentrated in vacuo to an oil. Flash chromatography (CH_2Cl_2–10% CH_3OH–1% NH_4OH) of this material affords 1.7 g (35%) of **6i** as a golden oil.

A mixture of 3-(4-bromobutyl)thiazolidine-5-spirocyclopentane-2,4-dione (**8**) (3.5 g, 0.01 mol), methyl 2-(1-piperazinyl)-3-pyridinecarboxylate (**6i**) (2.5 g, 0.01 mol), and 3.1 g (0.022 mol) of potassium carbonate is refluxed in acetonitrile (300 mL) for 24 h. The solution is filtered and concentrated in vacuo to a dark viscous oil, which is flash chromatographed ($CHCl_3$–5% EtOH), affording a golden oil. The oil is dissolved in hot acetonitrile (60 mL) and treated with 2 equiv of ethanolic hydrochloric acid to generate the hydrochloride salt (2.04 g, 40.8%): mp 195 °C; NMR (Me_2SO-d_6) δ 1.76 (m, 8 H), 2.20 (m, 4 H), 3.10 (m, 4 H) 3.55 (m, 6 H), 3.83 (s, 2 H), 3.90 (m, 2 H), 7.00 (dd, J = 4.8, 7.4 Hz, 1 H), 8.11 (dd, J = 1.6, 7.4 Hz, 1 H), 8.16 (br s, 2 H), 8.35 (dd, J = 1.6, 4.8 Hz, 1 H), 11.70 (br s, 1 H); IR (KBr) 770, 1270, 1350, 1600, 1670, 1725, 2370, 2950 cm^{-1}. Anal. ($C_{22}H_{30}N_4O_4S$·2HCl) C, H, N.

2-[4-[4-(2,4-Dioxo-1-thia-3-azaspiro[4.4]nonan-3-yl)butyl]-1-piperazinyl]pyridine-3-carboxaldehyde Hydrochloride (13). A solution of 2-chloro-3-cyanopyridine (**5d**) is treated dropwise with a 1 M solution of DIBAH in methylene chloride (0.03 mol, 33 mL) at −78 °C. The colorless solution turns a bright yellow-orange color during the addition while it is stirred for 3 h at −78 °C. The mixture is treated with 3 N HCl (75 mL) while warming the mixture to −10 °C, and further reaction with 10% NaOH solution affords a bright yellow emulsion, which is filtered through sintered glass. The collected aluminum salts are exhaustively washed with methylene chloride, and the filtrate is dried ($MgSO_4$). Concentration of the organic solution in vacuo yields a yellow solid, which is purified by Kugelrohr distillation [60 °C/(0.4 torr)], affording 0.46 g (33%) of 2-chloro-3-pyridinecarboxaldehyde (**5e**) as a white solid, mp 48 °C.

A solution of **5e** (6.4 g, 0.05 mol) and piperazine (19.4 g, 0.23 mol) is refluxed for 5 h in 2-propanol (250 mL). The mixture is concentrated in vacuo to a syrup, which is partitioned between methylene chloride and water. The organic phase is isolated, washed with water (3 × 500 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to a syrup, which is flash chromatographed (10% methanol–methylene chloride). Treatment of the purified product in acetonitrile with 1 equiv of ethanolic hydrochloric acid yields 8.8 g (87%) of the crude hydrochloride salt **6h**. An alternative preparation of this compound is realized by DIBAH reduction of **6e** (43%).

A mixture of **8** (5.5 g, 0.018 mol), **6h** (3.4 g, 0.018 mol), and potassium carbonate (4.9 g, 0.036 mol) is refluxed in acetonitrile (100 mL) for 24 h. The solution is filtered, concentrated in vacuo, and flash chromatographed (CH_2Cl_2–5% CH_3OH) to yield a brown oil. The brown oil is dissolved in hot acetonitrile and treated with 1 equiv of ethanolic hydrochloric acid, affording 2.8 g (37%) of

a white solid after chilling and filtration: mp 187–189 °C; NMR ($CDCl_3$) δ 2.04 (m, 2 H), 3.35 (m, 6 H), 3.69 (t, J = 6.7 Hz, 2 H), 3.95 (m, 4 H), 7.06 (dd, J = 4.5, 7.7 Hz, 1 H), 8.07 (dd, J = 1.8, 7.7 Hz, 1 H), 8.41 (dd, J = 1.8, 4.5 Hz, 1 H), 10.02 (s, 1 H), 11.80 (br s, 1 H); IR (KBr) 940, 1350, 1365, 1390, 1435, 1580, 1675, 1745, 2590, 2950 cm^{-1}. Anal. ($C_{21}H_{28}N_4O_3S$·HCl) C, H, N.

1-(3-Phenyl-2-pyridinyl)piperazine (6a). A neat mixture of **5a** (28.8 g, 0.15 mol) and piperazine (65.7 g, 0.76 mol) is heated for 24 h at 165 °C in a sealed bomb. The cooled mixture is partitioned between methylene chloride and water, and the separated organic phase is further extracted with water (3 × 300 mL), isolated, dried ($MgSO_4$), filtered, and concentrated in vacuo producing an oil. Flash chromatography (15% EtOH–$CHCl_3$) and concentration in vacuo of this purified material yields an oil, which is dissolved in ethanol and treated with 1 equiv of ethanolic hydrochloric acid. Upon cooling, the hydrochloride salt crystallizes to afford 19.8 g (48.2%) of white hydrochloride salt **6a**: mp 185–187 °C; NMR (Me_2SO-d_6) δ 3.02 (m, 4 H), 3.27 (m, 4 H), 7.09 (dd, J = 7.0, 5.0 Hz, 1 H), 7.55 (m, 6 H), 8.25 (dd, J = 5.0, 2.0 Hz), 9.66 (s, 2 H); IR (KBr) 710, 770, 945, 1245, 1375, 1425, 1445, 1590, 2460, 2770, 2800, 2940 cm^{-1}. Anal. ($C_{15}H_{17}N_3$·2HCl) C, H, N.

2-Chloro-3-phenylpyridine (5a). A solution of 3-phenyl-2-(1*H*)-pyridone (**4a**) (20.0 g, 0.12 mol) and phosphorus oxychloride (300 mL) is refluxed for 6 h and then slowly poured over crushed ice (300 mL). The resulting solution is made basic with ammonium hydroxide, leading to formation of a precipitate. This mixture is extracted with ethyl ether (3 × 500 mL), and the combined organic extracts are dried ($MgSO_4$), filtered, and concentrated in vacuo to a solid, which is recrystallized from ethyl acetate yielding 7.0 g (31%) of **6a**: mp 52–56 °C; NMR ($CDCl_3$) δ 7.22 (dd, J = 7, 5 Hz, 1 H), 7.38 (s, 5 H), 7.57 (dd, J = 7, 2 Hz, 1 H), 8.32 (dd, J = 5, 2 Hz, 1 H); IR (KBr) 700, 760, 1390, 1440, 1555, 1575, 3040 cm^{-1}. Anal. ($C_{11}H_8ClN$) C, H, N.

2-Chloro-3-methylpyridine (5b). By employment of the phosphorus oxychloride methodology reported for the preparation of **5a**, 2-chloro-3-methylpyridine is isolated from 3-methyl-2-(1*H*)-pyridone in 65% yield. This material is used crude in the following preparation without further purification.

1-(3-Methyl-2-pyridinyl)piperazine (6b). By a procedure similar to that reported for the preparation of **6a**, 2-chloro-3-methylpyridine **5b** is reacted with piperazine in a sealed bomb for 24 h to afford a 50% yield of the white hydrochloride salt of **6b**: mp 221–234 °C; NMR (Me_2SO-d_6) δ 2.34 (s, 3 H), 3.23 (m, 4 H), 3.62 (m, 4 H), 7.20 (dd, J = 8, 5 Hz, 1 H), 7.96 (d, J = 8 Hz, 1 H), 8.16 (d, J = 5 Hz, 1 H), 9.87 (s, 2 H); IR (KBr) 945, 1150, 1235, 1330, 1440, 1540, 1605, 2480, 2720, 2780, 2920 cm^{-1}. Anal. ($C_{10}H_{15}N_3$·2HCl) C, H, N.

1-[3-[(Methoxyimino)methyl]-2-pyridinyl]piperazine (6j). A mixture of **6h** (2.7 g, 0.014 mol), methoxyamine hydrochloride (1.8 g, 0.02 mol), and pyridine (1.7 g, 0.02 mol) is refluxed 48 h. The reaction mixture is concentrated in vacuo and partitioned between water and ether. The isolated water phase is concentrated in vacuo, yielding a pale yellow solid. Recrystallization from ethanol affords 0.3 g (53%) of **6j**: mp 225 °C; NMR (D_2O) δ 3.61 (s, 8 H), 4.12 (s, 3 H), 4.8 (s, 1 H), 7.27 (dd, J = 8, 5.5 Hz, 1 H), 8.02 (dd, J = 8, 2 Hz, 1 H), 8.17 (s, 1 H), 8.33 (dd, J = 5.5, 2 Hz, 1 H); IR (KBr) 920, 1045, 1240, 1430, 1455, 1560, 1595, 2480, 2720, 2760, 2930, cm^{-1}. Anal. ($C_{11}H_{16}N_4O_1$·1.7HCl) C, H, N.

3-[4-[4-(3-Amino-2-pyridinyl)-1-piperzinyl]butyl]-1-thia-3-azaspiro[4.4]nonane-2,4-dione (22). A mixture of **14** (6 g, 0.014 mol) and Raney nickel (0.03 g) in ethanol (100 mL) is hydrogenated (50 psi) at room temperature until the uptake of hydrogen is complete. The reaction mixture is filtered, concentrated in vacuo, dissolved in a minimum volume of ethanol, and treated with 1 equiv of tosic acid, leading to crystallization of 6.5 g (60%) of **22** as an off-white solid: mp 170–173 °C; NMR (Me_2SO-d_6) 1.72 (m, 8 H), 2.24 (m, 4 H), 2.28 (s, 6 H), 3.40 (m, 12 H), 6.04 (br s, 4 H), 7.12 (d, J = 8 Hz, 4 H), 7.27 (d, J = 5.0 Hz, 1 H), 7.52 (m, 5 H), 7.70 (d, J = 5 Hz, 1 H), 9.60 (br s, 1 H); IR (KBr) 565, 680, 1005, 1030, 1120, 1180, 1220, 1560, 1615, 1680, 1745, 2740, 2870, 2650, cm^{-1}. Anal. ($C_{20}H_{29}N_5O_2S$·2$C_7H_8O_3S$·H_2O) C, H, N.

Registry No. **2**, 1131-48-2; **3**, 104813-89-0; **4a**, 24228-13-5; **4c**, 20928-63-6; **5a**, 31557-57-0; **5b**, 18368-76-8; **5c**, 52605-96-6; **5d**, 6602-54-6; **5e**, 36404-88-3; **6a**, 104813-87-8; **6a**·2HCl, 111960-10-2; **6b**, 104396-10-3; **6b**·HCl, 111960-11-3; **6c**, 80827-67-4; **6d**, 87394-55-6; **6e**, 84951-44-0; **6f**, 87394-48-7; **6g**, 34803-66-2; **6h**, 104842-73-1; **6h**·HCl, 104813-90-3; **6i**, 104813-92-5; **6j**·HCl, 111960-12-4; **7**, 85073-21-8; **8**, 85581-61-9; **9**, 106261-31-8; **10**, 84951-42-8; **11**, 111960-13-5; **11**·$C_7H_8O_3S$, 111960-14-6; **12**, 85581-64-2; **12**·HCl, 85581-65-3; **13**, 104813-48-1; **13**·HCl, 104813-47-0; **14**, 104813-45-8; **14**·2HCl, 104813-46-9; **15**, 104813-50-5; **15**·2HCl, 104813-49-2; **16**, 104813-59-4; **16**·HCl, 104813-60-7; **17**, 104813-51-6; **17**·$C_7H_8SO_3$, 104813-52-7; **18**, 104813-69-6; **18**·HCl, 104813-70-9; **19**, 104813-61-8; **20**, 104813-81-2; **20**·HCl, 104813-82-3; **21**, 104813-53-8; **21**·HCl, 104813-54-9; **22**, 111960-15-7; **22**·2$C_7H_8O_3S$, 111960-16-8; **23**, 85073-41-2; **23**·2HCl, 85073-49-0; **24**, 85089-90-3; **24**·2HCl, 85073-25-2; **25**, 104813-79-8; **25**·HCl, 104813-80-1; **26**, 104813-71-0; **26**·HCl, 104813-72-1; **27**, 104813-57-2; **27**·xHCl, 111960-17-9; **28**, 104813-67-4; **28**·xHCl, 111960-18-0; **29**, 104813-55-0; **29**·xHCl, 111960-19-1; **30**, 104813-65-2; **30**·2HCl, 104813-66-3; **31**, 104813-85-6; **31**·HCl, 104813-86-7; **32**, 104813-75-4; **32**·HCl, 104813-76-5; **33**, 104813-77-6; **33**·HCl, 104813-78-7; **34**, 104813-73-2; **34**·2HCl, 104813-74-3; **35**, 104813-63-0; **35**·xHCl, 111960-20-4; 2-chloro-3-pyridinol sodium salt, 104813-91-4; nicotinamide *N*-oxide, 1986-81-8; 2-chloronicotinic acid, 2942-59-8; methyl 2-chloronicotinate, 40134-18-7; piperazine, 110-85-0; 3-methyl-2(1*H*)-pyridone, 1003-56-1; methoxyamine hydrochloride, 593-56-6.