Summarily, 1 demonstrates activity in a number of models of inflammation and seems a likely candidate for clinical trials to test the hypothesis that a LTB_4 receptor antagonist may have therapeutic value in the treatment of inflammatory bowel disease and other conditions where LTB_4 is a putative mediator such as psoriasis and ankylosing spondylitis.

(14) O'Donnell, et al. (O'Donnell, M.; Welton, A. F.; Crowley, H.; Brown, D.; Garippa, R.; Cohen, N.; Weber, G.; Banner, B.; Lapresti, R. J. *Adv. Prostaglandin, Thromboxane Leukotriene Res.* **1987**, *17*, 512) describe a related LTC_4/D_4 antagonist that antagonizes LTB_4-induced bronchospasm in guinea pigs. No receptor binding data was reported however.

Stevan W. Djuric,* Paul W. Collins, Peter H. Jones Robert L. Shone, Bie Shung Tsai, Donald J. Fretland Gregory M. Butchko, Doreen Villani-Price Robert H. Keith, Jeanne M. Zemaitis Linda Metcalf, Raymond F. Bauer

Gastrointestinal Diseases Research G.D. Searle and Co. Skokie, Illinois 60077

Received December 7, 1988

Articles

The Thieno[3,2-*c*]pyridine and Furo[3,2-*c*]pyridine Rings: New Pharmacophores with Potential Antipsychotic Activity

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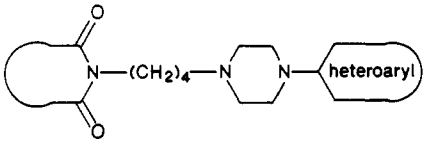
Two new arylpiperazine derivatives, the 4-(1-piperazinyl)thieno- and -furo[3,2-*c*]pyridine ring systems, have been synthesized and appended via tetramethylene chains to various imide rings. Target compounds from each series were found to have significant activity in the blockade of apomorphine stereotypy and apomorphine-induced climbing, the Sidman avoidance response, and the conditioned avoidance response. In addition, while potent affinity for serotonin 5-HT_1 and 5-HT_2 receptors was observed for both the thieno- and furo[3,2-*c*]pyridine derivatives, the interaction of these molecules with the dopamine D2 receptor was weak. Electrophysiological studies of the lead prototypes from each series, involving compounds **22** and **33**, indicate these two molecules have distinctively different effects on dopamine neurons in areas A9 and A10. Despite the similarity these molecules share in their behavioral indices of antipsychotic activity, it is likely that the thieno- and furo[3,2-*c*]pyridine rings employ different mechanisms to achieve this convergence of biological effects.

The family of chemical structures generically described as the *N*-[(4-heteroaryl-1-piperazinyl)alkyl]-substituted imides (**1**) has generated clinical candidates with anti-



1

psychotic or anxiolytic properties. Noteworthy alumni in this class of psychotropic molecules are the anxiolytic agents buspirone and gepirone and the antipsychotic agent tiospirone.[1-3] The pharmacological profile of these molecules is largely determined by the dominant influence of the heteroarylpiperazine moiety that is common to each of their structures. In the case of buspirone and gepirone, the serotonin agonist properties that mediate the anxiolytic effects of these compounds can be attributed to their 1-(2-pyrimidinyl)piperazine substructure. In tiospirone, the blend of dopamine and serotonin antagonist properties, which arise from its 1-benzisothiazol-3-ylpiperazine moiety, contribute to the antipsychotic activity of the molecule. The function of the imide group in these molecules is less well understood, but its modification in lead optimization studies is commonly pursued toward the fine-tuning of the molecule's biological expression.

Recently, we reported an extension of this structural family in a series of 3-substituted 2-pyridinyl-1-piperazine derivatives.[4] The desired antipsychotic profile of these molecules was shown to be strictly dependent on the electronic and lipophilic properties of the substituent located at the 3-position of the pyridine ring. Inspired by the specificity of this effect and the promising biological activity that resulted from it, we embarked on the synthesis of several hetero-ring-fused pyridine compounds.

The design of the target molecules stemmed from the observation that the lead prototypes in the 3-substituted pyridinylpiperazine study were formulated with X = ni-

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(1) Yevich, J. P.; Temple, D. L., Jr.; New, J. S.; Taylor, D. P.; Riblet, L. A. *J. Med. Chem.* **1983**, *26*, 194.
(2) 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.
(3) 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.
(4) New, J. S.; Yevich, J. P.; Temple, D. L., Jr.; New, K. B.; Gross, S. M.; Schlemmer, R. F., Jr.; Eison, M. S.; Taylor, D. P.; Riblet, L. A. *J. Med. Chem.* **1988**, *31*, 618.

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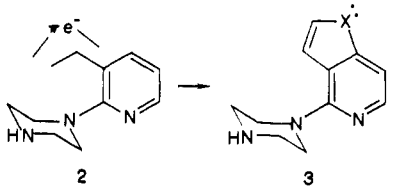


Figure 1.

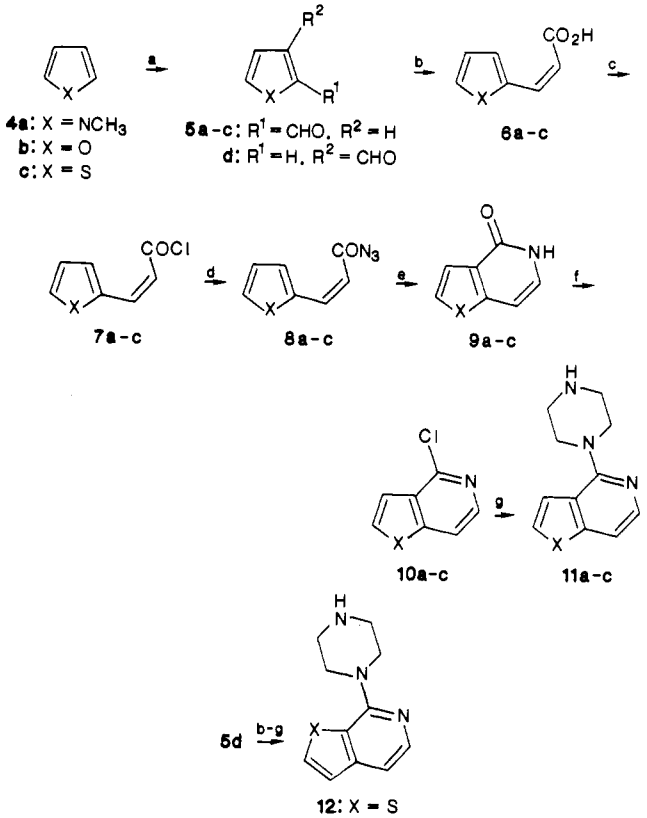
trogen or oxygen (**2**, Figure 1); the most active compounds have a CHO, CO_2CH_3, or C≡N function at this position. Annulation of a hetero-ring across the 3- and 4-positions of the pyridine ring was seen to serve as a conformationally restrained elaboration of this substituent effect (**3**, Figure 1). The resulting bicyclic heteroaromatic system and its expanded π-electron density surface would also probe new regions of receptor space left uncharted by the 3-substituted pyridines. To that end, we now report the synthesis and biological activity of several furo[3,2-*c*]-, thieno[3,2-*c*]-, and pyrrolo[3,2-*c*]pyridine derivatives, whose preclinical evaluation has demonstrated that significant antipsychotic-like activity is associated with the target compounds.

Chemistry

Synthesis of the pyrrolo[3,2-*c*]pyridines, as well as the thieno- and furo[3,2-*c*]pyridines, is accomplished through one common methodology. Vilsmeier–Haack formylation of *N*-methylpyrrole (**4a**) yielded **5a** (X = NCH_3); 2-furaldehyde (**5b**), 2-thiophenecarboxaldehyde (**5c**), and 3-thiophenecarboxaldehyde (**5d**) are commercially available. Condensation of these derivatives with malonic acid at 100 °C, usually in pyridine as a solvent with piperidine as a catalyst, for approximately 12 h, followed by a short reflux period to enhance decarboxylation, yields the corresponding acrylic acid intermediates **6** (Scheme I). NMR indicates the *E* isomer predominates in the *E*/*Z* product mixture of **6**. Thermally induced isomerization of the *E* to *Z* isomer apparently occurs later in step e (Scheme I), enabling the cyclization of **8** to **9**. Chlorination of these acids with thionyl chloride in chloroform and a catalytic amount of dimethylformamide affords the acid chlorides **7**, which are not purified but can be used directly in the preparation of the azides **8**. Compound **8** can be prepared either in a biphasic mixture of acetone and water at 5 °C through the agency of sodium azide or with trimethylsilyl azide in refluxing benzene. Crude preparations of **8** in methylene chloride solutions are added portionwise to either diphenyl ether, biphenyl, or diphenylmethane heated to 230 °C, which facilitates the Curtius rearrangement to the isocyanates that undergo subsequent electrophilic cyclization to the fused 6–5 bicyclic systems **9**. Chlorination of **9** to generate the imidoyl chloride derivatives **10** is possible with phosphorus oxychloride or a phosphorus pentachloride–phosphorus oxychloride mixture. Reaction of **10** with an excess of piperazine in a bomb at 120–140 °C for varying periods of time affords compound **11**. This general synthesis of pyrrolo-, furo-, and thieno[3,2-*c*]pyridines has been reported from several sources.[5-8]

The synthesis of various derivatives of **11** with substitution at the 2-position of the bicyclic system, as in several of the target compounds, was accomplished by incorporating this substituent in the starting material **4**. The

Scheme I[a]



[a] Reagents: (a) DMF, $POCl_3$, $C_2H_4Cl_2$, −5 °C; (b) $CH_2(CO_2H)_2$, C_5H_5N, $C_5H_{11}N$, 90 °C; (c) $SOCl_2$, DMF, $CHCl_3$; (d) NaN_3, H_2O–acetone; (e) 240 °C, $(C_6H_5)_2O$; (f) 1. $POCl_3$, 5 °C, 2. reflux; (g) $C_4H_{10}N_2$, 120 °C, bomb, 20 h.

efficiency of applying this same methodology to the synthesis of the thieno[2,3-*c*]pyridine system **12** from **5d** was compromised by the propensity of the isocyanate, derived from the analogous intermediate **8**, to undergo intermolecular cyclization affording 2,4,6-trisubstituted triazines rather than intramolecular electrophilic cyclization.

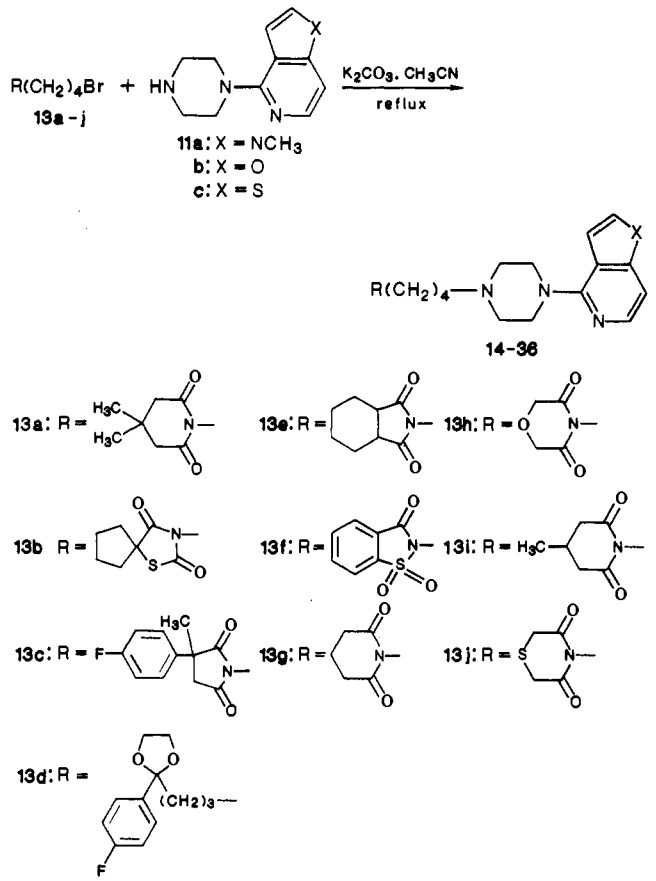
Synthesis of target compounds **14–36** involved the coupling of compounds **11a–c** with the imide derivatives **13a–j** (Scheme II). Examples detailing synthetic preparations of representative intermediate and target compounds are reported in the Experimental Section. The physical data for all target compounds are listed in Table I.

Biology

The potential antipsychotic activity of the target compounds was assessed in the conditioned avoidance response, the blockade of apomorphine-induced climbing and stereotypy, and the Sidman avoidance test. A methodological description of the Sidman avoidance test and the inhibition of spontaneous motor activity is available as supplementary material. Evaluation of the catalepsy-induction properties of the target compounds was investigated as a predictor of the neuroleptic-induced side effect of extra pyramidal symptoms (EPS) in humans. If a compound did not induce catalepsy, it was further examined for catalepsy-reversing properties. Activity in the latter may suggest the compound would have little or no tendency to induce the side effects typically found in neuroleptics that possess catalepsy activity. With the exception of the blockade of apomorphine-induced climbing, which was evaluated in mice, each of the preceding tests were run in rats. The potential antipsychotic efficacy of **33** was also examined in the antagonism of amphetamine-induced psychoses in monkeys. The pharmaco-

(5) Eloy, F.; Deryckere, A. *Helv. Chim. Acta* **1970**, *53*, 645.
(6) Eloy, F.; Deryckere, A. *J. Heterocycl. Chem.* **1971**, *8*, 57.
(7) Eloy, F.; Deryckere, A. *Bull. Soc. Chim. Belges.* **1970**, *79*, 301.
(8) Bisagni, E.; Bourzat, J.-D.; Andrē-Louisfert, J. *Tetrahedron* **1970**, *26*, 2087.

Scheme II[a]



[a] Compound **13d** does not contain the tetramethylene chain as indicated in the generic formulas above.

logical basis of these various in vivo tests has been previously discussed.[1-4]

The in vitro affinity of these compounds for rat dopamine (DA) receptors labeled with [^{3}H]spiperone or for α_1 receptors labeled with [^{3}H]WB-4101 was also evaluated. Affinity for the serotonin 5-HT$_1$ site employed [^{3}H]serotonin as the competitive radioligand, and affinity for the 5-HT$_{1A}$ subpopulation of receptors used [^{3}H]-8-OH-DPAT as the radioligand. [^{3}H]Spiperone was used to label 5-HT$_2$ receptors. The biological activity of tested compounds is reported in Tables II–V. Pertinent pharmacologic methodologies are presented in the Experimental Section.

Results and Discussion

The unsubstituted arylpiperazines **11b** and **11c** were evaluated for their CNS effects before elaboration to the target structures. Limited compound supply for **11a** and **12** precluded a similar evaluation of these structures. The most potent in vitro receptor affinities of **11b** and **11c** were recorded for the 5-HT$_1$ and α_2 receptors. The thiophene derivative **11c** was consistently more potent than **11b** at these receptors, with neither compound demonstrating any affinity for dopamine (DA) D2 receptors (Table II). The furan derivative **11b** had greater in vivo potency than **11c**, in both the conditioned avoidance response (CAR) and the inhibition of spontaneous motor activity. The significant sedative activity of these compounds indicates both derivatives readily cross the blood–brain barrier.

Derivatization of **11c** through attachment of a thiomorpholine group via a tetramethylene chain to its secondary piperazinyl nitrogen, as in **14** (Table III), leads to a significant increase in affinity for the α_1 and 5-HT$_{1A}$ receptor. These potent receptor affinities made little difference in the CAR activity of **14** relative to the unsubstituted precursor **11c** nor was this in vivo parameter affected by interchange of the thieno[3,2-*c*]pyridine ring with the furo analogue, as evidenced in **27**. Subnanomolar affinities at the 5HT$_{1A}$ receptor for **15**, and at the α_1 receptor for **16**, were observed when saccharin and phthalimide groups were appended to the thieno[3,2-*c*]-pyridinylpiperazine group. The in vitro receptor affinities for **15** and **16** are nearly identical, with the phthalimide derivative **16** having slightly greater potency in the CAR. The thiazolidinedione imide was selected next for evaluation because of our previous studies indicating the salutory effect this group conveyed to the antipsychotic activity of 1-(3-substituted-pyridin-2-yl)piperazine derivatives. Compound **17**, which contains this imide, does demonstrate enhanced potency in the CAR and greater affinity for D2 receptors relative to compounds **14–16**. The effectiveness of **17** in the blockade of the Sidman avoidance serves to strengthen its promising antipsychotic indications (Table IV). Compound **18**, the thieno[2,3-*c*]pyridine isomer of **17**, has less activity in both the conditioned avoidance response and in its affinity at the D2 receptor. Interestingly, the 5-HT$_1$ and 5-HT$_2$ receptor affinities of **18** are not substantially different from compounds **14–17**, suggesting that either isomeric configuration of the thienopyridine is capable of expressing potent in vitro serotonergic receptor affinity. The relative potencies of **17** and **18** in the blockade of apomorphine (APO) induced stereotypy corresponded to their respective affinities for the D2 receptor (Table IV).

The effect of bromine substitution at the 2-position of the thienopyridine system in **19** eliminated the in vivo effects observed in the unsubstituted analogue **17**. A significant loss in 5-HT$_2$ receptor affinity also accompanies this halogen substitution, which was similarly observed for methyl substitution at this same position of the ring as in compound **20**, although CAR activity was retained in the latter. The only constancy associated with each of the thienopyridines substituted at the 2-position of the ring in **19–21** was their potency at the 5-HT$_1$ receptor. A 10-fold increase in the CAR activity for the desbromo compound **22** was observed relative to that of **21**. This potency trend was observed not only in the CAR but also in the 5-HT$_1$ (or 5-HT$_{1A}$) and 5-HT$_2$ receptor affinity for each of the substituted glutarimides **22–24**. While only modest affinity for the D2 receptor was manifest in compounds **22** and **23**, they were found to be weakly effective in the blockade of APO-induced stereotypy (Table IV). The low dose effects of **22** in the blockade of APO-induced climbing presents a desirable selectivity ratio favoring the attenuation of climbing behavior versus stereotypy. This selectivity index frequently portends a lower side-effect liability for neuroleptic agents that possess it.[9] The higher effective dose associated with **22** in the Sidman avoidance (MED = 50 mg/kg, po) is unexpected and difficult to reconcile with the activity of **24** (MED = 20 mg/kg, po), which does not block APO-induced climbing. Since the primary neural substrates that mediate the behavioral responses in these paradigms are poorly understood, these results cannot be taken as inconsistent.

The most potent affinity for the DA receptor within this family of compounds was observed in the butyrophenone derivative **25**. The promising antipsychotic potential of **25** is distinguished by its uniformly potent activity in each of the in vivo tests predictive of antipsychotic activity. However, the APO climbing/stereotypy ratio of **25** is not

(9) Costall, B.; Naylor, R. J.; Nohvia, V. *Eur. J. Pharmacol.* **1978**, *50*, 39.

Table I. Physical Data for Compounds 11b, 11c, and 14–36

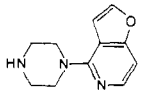
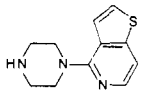
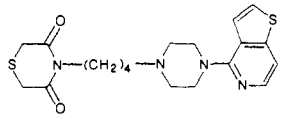
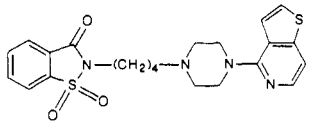
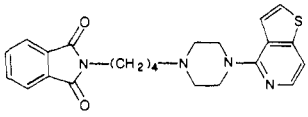
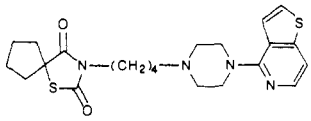
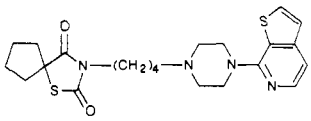
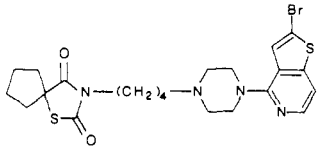
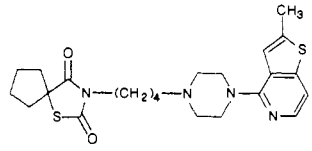
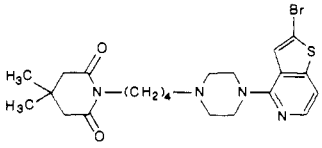
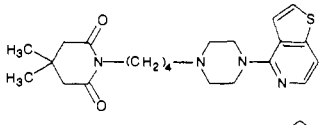
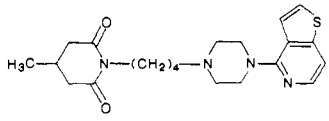
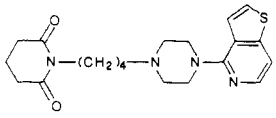
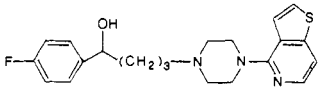
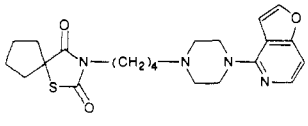
compd	structure	recrystn solvent	yield, %	mp, °C	formula
11b		MeOH	83	>250	$C_{11}H_{13}N_3O\cdot HCl$
11c		EtOH	54	>250	$C_{11}H_{13}N_3S\cdot HCl$
14		CH_3CN	48	186–188	$C_{19}H_{24}N_4O_2S_2\cdot 1.1C_7H_8O_3S\cdot 0.5H_2O$
15		EtOH	62	229–230	$C_{22}H_{24}N_4O_3S_2\cdot HCl$
16		EtOH	98	226–227	$C_{23}N_{24}N_4O_2S\cdot HCl\cdot 0.5H_2O$
17		CH_3CN	76	180–182	$C_{22}H_{28}N_4O_2S_2\cdot 1.4HCl$
18		CH_3CN	60	120–122	$C_{22}H_{28}N_4O_2S_2\cdot 2HCl\cdot 1.8H_2O$
19		CH_3CN	89	203–205	$C_{22}H_{27}BrN_4O_2S_2\cdot HCl$
20		CH_3CN	67	195–197	$C_{23}H_{30}N_4O_2S_2\cdot HCl$
21		CH_3CN	73	216–219	$C_{22}H_{29}BrN_4O_2S\cdot HCl\cdot 0.5H_2O$
22		CH_3CN	33	195–197	$C_{22}H_{30}N_4O_2S\cdot HCl$
23		*i*-PrOH	86	173–175	$C_{21}H_{28}N_4O_2S\cdot HCl$
24		*i*-PrOH	66	199–201	$C_{20}H_{26}N_4O_2S\cdot HCl$
25		CH_3CN	77	115–118	$C_{23}H_{24}FN_3OS$
26		CH_3CN	40	251–253	$C_{22}H_{28}N_4O_3S\cdot 2HCl\cdot C_2H_6O$

Table I (Continued)

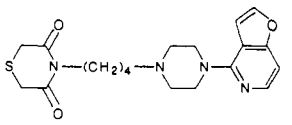
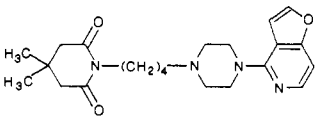
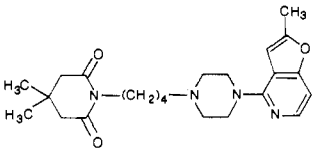
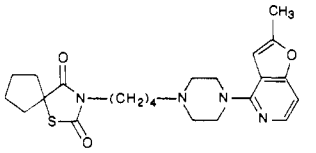
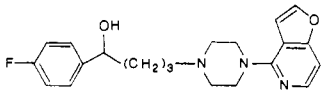
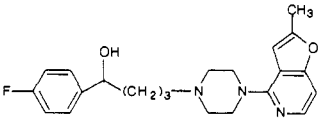
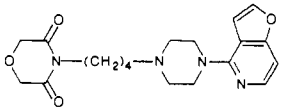
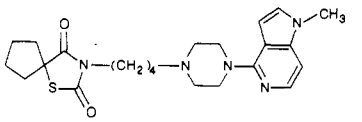
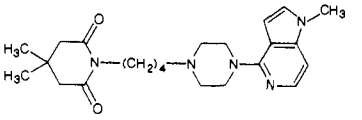
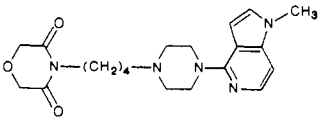
compd	structure	recrystn solvent	yield, %	mp, °C	formula
27		EtOAc/EtOH	31	245–250	$C_{19}H_{24}N_4O_3S\cdot 2HCl\cdot 0.5H_2O$
28		MeOH/EtOH	23	>250	$C_{22}H_{30}N_4O_3\cdot 1.4HCl$
29		*i*-PrOH/EtOH	53	221–223	$C_{23}H_{32}N_4O_3\cdot 1.2HCl\cdot 0.5H_2O$
30		*i*-PrOH	54	176–177	$C_{23}H_{30}N_4O_3S\cdot 1.2HCl$
31		CH_3CN	80	205–207	$C_{21}H_{24}FN_3O_2\cdot HCl$
32		MeOH	99	121–122	$C_{22}H_{26}FN_3O_2\cdot HCl$
33		*i*-PrOH	76	109–110	$C_{19}H_{24}N_4O_4$
34		*i*-PrOH/CH_3CN	73	148–150	$C_{23}H_{31}N_5O_2S\cdot 2HCl\cdot 1.6H_2O$
35		EtOH	49	192–194	$C_{23}H_{33}N_5O_2\cdot 2.1HCl\cdot 2.6H_2O$
36		EtOH	78	144–146	$C_{20}H_{27}N_5O_3\cdot 2.3HCl\cdot 0.4H_2O$

Table II. Biological Activity of the 4-(1-Piperazinyl)thieno- and -furo[3,2-*c*]pyridine Derivatives

	11b	11c
binding at dopamine D_2 receptors, rat corpus striatum: (vs [^{3}H]spiperone) IC_{50}, nM	>1000	>1000
binding at α_1-adrenergic receptors: (vs [^{3}H]WB-4101) IC_{50}, nM	426	139
binding at serotonin 5-HT_1 receptors, rat hippocampus: (vs [^{3}H]serotonin) IC_{50}, nM	150	71.3
binding at serotonin 5-HT_2 receptors, rat cortex: (vs [^{3}H]spiperone) IC_{50}, nM	377	141
rat conditioned avoidance response: ED_{50}, mg/kg, po	7.3 (5.0–10.8)[a]	28.6 (16.0–51.2)
binding at α_2-adrenergic receptors: (vs [^{3}H]clonidine) IC_{50}, nM	144	113
inhibition of spontaneous motor activity: AED, mg/kg, po[b]	10.7	20.9

[a] In this and subsequent tables, 95% fiducial limits are given in parentheses. [b] AED = approximate effective dose.

as attractive as that observed for **22**. It is noteworthy that the potent CAR values associated with compounds **22–25** are expressed in the absence of any catalepsy-induction properties.

Furo- and Pyrrolo[3,2-*c*]pyridine Derivatives. A dramatic change in the biological profiles of the target compounds results when furo[3,2-*c*]pyridine rings are evaluated in place of the thieno[3,2-*c*]pyridines. An example of this effect is seen in comparing the thienopyridine compounds **17** and **22** with the analogously derived imide formulations involving **26** and **28**, respectively, in the furopyridine series. While comparable activity in the CAR is retained for the imide-matched comparisons involving this heteroatom interchange, the furopyridines have a lower affinity for the D2 receptor. This is in contrast to the greater potency the furopyridines display in blocking

Table III. Biological Activity of Compounds 14–36

no.	rat conditioned avoidance response: ED_{50}, mg/kg, po	binding at α_1-adrenergic receptors: (vs [^{3}H]WB-4101) IC_{50}, nM	binding at dopamine D_2 receptors, rat corpus striatum: (vs [^{3}H]spiperone) IC_{50}, nM	binding at serotonin 5-HT_1 receptors, rat hippocampus: (vs [^{3}H]serotonin) IC_{50}, nM	binding at serotonin 5-HT_{1A} receptors, rat hippocampus: (vs [^{3}H]8-OH-DPAT) IC_{50}, nM	binding at serotonin 5-HT_2 receptors, rat cortex: (vs [^{3}H]spiperone) IC_{50}, nM
14	31.9 (25.2–40.4)	1.1	608	*a*	1.15	6.7
15	≥62.5	1.2	320	2.3	0.68	5.7
16	38.9 (22.8–66.4)	0.69	306	5.3	2.7	2.8
17	11.6 (9.8–13.7)	30.5	88.3	8.1	–	3.9
18	43.1 (32.9–56.4)	36.8	418	3.7	–	20.2
19	>100	–	440	25.3	–	116
20	35.4 (24.7–50.5)	–	279	3.6	–	43.4
21	65.3 (42.9–99.3)	27.2	228	3.7	–	70.9
22	6.0 (4.6–7.9)	18.8	115[b]	5.7	–	3.0
23	2.9 (1.8–4.4)	–	663	8.8	1.3	4.2
24	5.4 (4.2–7.0)	–	–	–	2.5	19.1
25	9.9 (8.0–12.3)	22.8	71.7	3.8	–	5.8
26	9.2 (7.1–11.7)	23.5	331	–	–	–
27	35.8 (26.6–48.2)	–	>1000	–	–	–
28	4.2 (3.3–5.2)	47	626	–	8.64	–
29	13.8 (10.7–17.9)	–	708	–	4.90	–
30	28.4 (20.5–39.2)	27.5	751	–	2.2	–
31	3.1 (2.6–3.7)	23.8	339	–	12.4	55.2
32	23.2 (17.7–30.4)	–	–	–	6.2	–
33	11.2 (9.6–13.0)	40.9	>1000	33.5	–	55.2
34	59.5 (46.1–76.8)	–	517	–	245.6	–
35	67.2 (44.0–102.8)	–	>1000	–	–	–
36	>100	–	>1000	–	–	–
clozapine	24.1 (20.5–28.2)	62	440	587	–	21
chlorpromazine	38.7 (32.6–46.0)	31	40	>1000	372	8.8

[a] A dash indicates the compound was not tested. [b] Binds to D1 receptors; IC_{50} = 28 nM.

Table IV. In Vivo Indications of Potential Antipsychotic Activity for Selected Compounds

compd	blockade of apomorphine-induced stereotypy: ED_{50}, mg/kg, po	blockade of apomorphine-induced climbing: MED, mg/kg, po[a,b]	blockade of Sidman-avoidance activity: MED, mg/kg, po	induction of catalepsy: ED_{50}, mg/kg, po	reversal of trifluoperazine-induced catalepsy: ED_{50}, mg/kg, po
17	35.2 (30.3–41.1)	–	5.0	–	–
18	46.7 (36.1–60.3)	–	IA	–	IA
22	39.7 (27.9–56.5)	10.0	50.0	IA[c]	IA
23	39.5 (32.4–48.1)	IA	–	IA	–
24	55.6 (42.4–73.0)	IA	20.0	IA	–
25	9.0 (6.6–12.3)	10.0	10.0	IA	–
33	34 (27.4–42.0)	5.0	25.0	IA	2.2
clozapine	49.2 (33.4–72.3)	10.0	50.0	>200	IA[d]
chlorpromazine	9.6 (7.1–13.0)	6.0	25.0	4.1 (2.4–7.1)	IA

[a] The blockade of apomorphine-induced climbing was evaluated in mice. The remaining in vivo tests reported in this table were evaluated in rats. [b] A description of the MED value is provided in the Experimental Section. [c] Maximum dose examined was 4 times the ED_{50} value established in the CAR. [d] Maximum dose examined was 20 mg/kg.

Table V. Electrophysiological Responses of Different Cell Populations in Rat Brain to Compounds 22 and 33

compd	A9 DA cells substantia nigra neurons: ED_{25}, mg/kg, iv		A10 DA cells ventral tegmentum neurons: ED_{25}, mg/kg, iv		dorsal raphe firing: ED_{50}, mg/kg, iv	locus coeruleus firing: ED_{25}, mg/kg, iv
22	0.086 (excitatory)	-	0.05 (excitatory)		0.042 (inhibitory)	0.06 (excitatory)
33	no effect[a]	small increase[b] in the number of DA cells per track	no effect[a]	no effect[b]	0.010 (inhibitory)	0.017 (excitatory)
time course	acute	chronic	acute	chronic	acute	acute

[a] Dose = 0.1–6.3 mg/kg, iv. [b] Dose = 5.0 mg/kg per day, sc.

APO stereotypy relative to the thienopyridine examples.[10] The catalepsy induction properties of **26** and **28**, which was also found in two other compounds evaluated for this indication, **29** and **31**, renders this portion of the series uninteresting as antipsychotic leads.[11] The diminution in CAR potency that results from further interchange of the furopyridine for a *N*-methylpyrrolo[3,2-*c*]pyridine ring in compounds **34–36** also left the pyrrolo isostere an untenable alternative.

Compound **33** (BMY 20661) failed to follow the cataleptogenic trend of its furopyridine congeners but instead exhibited the unique property of potently reversing a neuroleptic-induced catalepsy. We have made previous note of this trait in the antipsychotic candidates BMY 13980 and BMY 14802, structurally dissimilar compounds disclosed in earlier work.[4,12] The pharmacologic mechanism for this effect remains unknown, but an antipsychotic prototype that features this activity would have a minimum potential to induce EPS or tardive dyskinesia. This assumption hinges on the generally accepted correlation of the catalepsy-induction properties of various antipsychotic agents in animals with their tendency to induce EPS in humans. It is tempting to speculate that the catalepsy reversing properties of **33** arise from its activating effects on the locus coeruleus (LC) as observed in electrophysiological extracellular in vivo recording experiments (Table V). Excitation of the LC neurons is thought to be involved in the "fight or flight" response, which is associated with an increased release of norepinephrine in the brain.[13] Yohimbine, an α_2 antagonist that excites LC neurons, also reversed catalepsy in our studies. The lack of catalepsy-reversing activity in **22** (BMY 20551), which possesses LC-activating properties, therefore appears to be contradictory (Table V). However, the in vitro DA receptor affinity of **22** and its DA antagonist-like effects on A9 neurons are antipodal to the lack of activity observed for **33** in these dimensions. It is proposed that a cataleptic response derived from potent DA antagonist effects can mute the LC-activating property of an antipsychotic agent, or, alternatively, the LC-activating property of an antipsychotic agent may blunt a cataleptogenic potential in the molecule that may arise from a weak DA antagonist effect. The net biological expression of a prototype possessing both LC-activating and DA-antagonist properties would depend on the balance of the two opposing forces.

Table III indicates this family of molecules has varying degrees of affinity for the DA D_2 receptor. Compounds that potently bind to this receptor are more likely to possess dopaminergic antagonist effects, and therefore potential antipsychotic activity, than those compounds that lack this affinity. Nondopaminergic antipsychotics may be accordingly defined as agents that express DA-antagonist effects without involving the direct blockade of DA receptors. Because of this unconventional profile, such a prototype should minimally meet some behavioral endpoints predictive of antipsychotic activity. Compound **33** fulfills this criterion by demonstrating the desired selectivity in low-dose blockade of APO-induced climbing versus its weaker effects in the blockade of APO-induced stereotypy. It is also active in the blockade of Sidman avoidance activity. The electrophysiological data suggests these behavioral effects result from mechanisms unlike those of typical neuroleptic drugs since **33**, when administered alone in either acute or chronic time frames, had minimal effect on dopaminergic neuronal activity in areas A9 and A10[14] (Table V). Compound **22**, which excites A9 cells (acute administration) in a manner similar to typical antipsychotic agents, offers no superiority relative to **33** in any of the behavioral indices of antipsychotic activity and actually suffers a loss of potency in the Sidman avoidance (Table IV). Both **22** and **33** potently inhibit the firing of serotonergic neurons in the dorsal raphe, suggesting these compounds express serotonin agonist-like activity in this nucleus.

The Efficacy of 33 in the Antagonism of Amphetamine-Induced Psychosis in Monkeys. Chronic administration of *d*-amphetamine to selected members of nonhuman primate social colonies provides a model of human amphetamine psychosis where behavioral correlates of positive and negative symptoms of psychosis are induced.[15] In addition, these behavioral changes are reversed by antipsychotic agents. Compound **33** was tested in this model for corroborating evidence of its antipsychotic properties that were demonstrated in several of the rodent models. The drug was administered nasogastrically, twice a day (5 mg/kg) for 19 days, to three amphetamine-treated members of a stumptail macaque social colony of five monkeys. Compound **33** significantly reduced *d*-amphetamine-induced stereotyped behavior in each treated monkey. Large increases in checking (visual scanning) induced by amphetamine were also antagonized to a similar extent by compound **33**, although scores still remained elevated from base-line levels.

Several behavioral changes induced in monkeys by amphetamine are particularly relevant to the study of psychosis. These include increases in unprovoked submissive gestures, which have been suggested as a model of paranoia,[16] intense scratching similar to that which accompanies tactile hallucinations in human amphetamine psychosis, and behaviors suggestive of social withdrawal

(10) The ED_{50} values for compounds **26** and **28** in blocking APO stereotypy are 17.7 (13.0–24.0) and 6.7 (5.2–8.6) mg/kg, po, respectively.
(11) The catalepsy-induction properties of compounds **26**, **28**, **29**, and **31** are not reported in any of the tables.
(12) Yocca, F. D.; Yevich, J. P.; New, J. S. *Drugs Future* **1987**, *12*, 752.
(13) Lal, H.; Fielding, S.; Eds. *Psychopharmacology of Clonidine*; Alan R. Liss: New York, 1981.
(14) Henry, D. J.; White, F. J. *Drug. Dev. Res.* **1988**, *12*, 211.
(15) Schlemmer, R. F., Jr.; Davis, J. M. *Pharmacol. Biochem. Behav.* **1981**, *14* (Suppl 1), 95.
(16) Schlemmer, R. F., Jr.; Davis, J. M. In *Ethopharmacology: Primate Models of Neuropsychiatric Disorders*; Miczek, K. A., Ed.; Alan R. Liss: New York, 1983; pp 33–78.

such as a decrease in initiated social grooming and increased distancing from other colony members. Increases in submissive gestures that were induced by amphetamine in two monkeys were blocked by **33**. On the other hand, **33** antagonized the intense scratching in only one of the three treated animals. Compound **33** partially restored initiated social grooming in all treated monkeys during the latter days of amphetamine treatment, but did not alter the increased distancing induced by amphetamine.

In summary, compound **33** partially reversed some components of the amphetamine-induced model of psychosis in monkeys. As is the case with antipsychotic agents, the behavioral changes modeling positive symptoms of psychosis (e.g., increased submissiveness, increased checking) are antagonized better than those that model negative symptoms.

Conclusions

Two new arylpiperazine pharmacophores with significant CNS activity have been discovered in the thieno[3,2-*c*]pyridine and furo[3,2-*c*]pyridine systems. The pharmacological profiles of the target molecules indicates an atypical antipsychotic-like activity, coupled with potent affinity for serotonin 5-HT_1 and 5-HT_2 receptors, is associated with the lead compounds in each series. In the thieno[3,2-*c*]pyridine system, compounds **22** and **25** are active in several behavioral paradigms predictive of antipsychotic activity and lack catalepsy induction properties. Compound **33**, which is the only furo[3,2-*c*]pyridine derivative that does not induce catalepsy, is also the only compound in either series that potently reverses a neuroleptic-induced catalepsy. The potent in vivo antipsychotic-like activity of **33** does not appear to be derived from any direct antagonism of the dopaminergic system. Both compounds **22** and **33** were found to inhibit the firing of dorsal raphe neurons and stimulate the firing of locus coeruleus neurons. The biological activity of the pyrrolo[3,2-*c*]pyridine ring was vastly inferior to that of the furo- or thienopyridine analogues.

The potential antipsychotic efficacy of **22** and **33** requires further study, but the dichotomy in their biological profiles fires the on-going polemics concerning what combination of preclinical parameters most reliably predict clinical antipsychotic efficacy. The abyss existing between currently inadequate drug treatment therapies for schizophrenia and our poor comprehension of the disease state offers ample challenge for refinement in drug design approaches and screening strategies that more effectively target this disease.

Experimental Section

Chemistry. All IR spectra were recorded on a Nicolet MX-1 FT-IR spectrometer. The ^1H NMR spectra were recorded on a Varian FT-80 or a Bruker AM300 spectrometer in either deuteriochloroform with 2% (v/v) tetramethylsilane as the internal reference or perdeuteriodimethyl sulfoxide. Melting points were determined with a Thomas-Hoover capillary apparatus and are uncorrected. All compounds gave satisfactory C, H, and N analyses (±0.4%), which were determined on a Perkin-Elmer 240B analyzer. Karl Fischer water determinations were made with an Aquatest 2 apparatus.

3-(2-Thienyl)acrylic Acid (6c). A mixture of 2-thiophenecarboxaldehyde (100 g, 0.89 mol), pyridine (446 mL), and piperidine (8.9 mL) was heated at 100 °C for 12 h. The solution was then refluxed for 20 min, allowed to cool, and poured into water (1 L), and the resulting aqueous mixture was acidified with concentrated HCl. The resulting off-white precipitate was collected by filtration and recrystallized from ethanol–water (1:1), yielding 109 g (80%) of product, mp 145–148 °C.

The yields for products **6a** and **6b** were 62% and 82%, respectively. The yield for the 3-(3-thienyl)acrylic acid derived from thiophene-3-carboxaldehyde was approximately 67%. No attempts were made to optimize yields.

3-(2-Thienyl)acryloyl Chloride (7c). A stirred suspension of 3-(2-thienyl)acrylic acid (118.9 g, 0.77 mol) and dimethylformamide (12 mL) in chloroform (600 mL) was treated dropwise with thionyl chloride (110.1 g, 0.93 mol) at room temperature. The reaction was then refluxed for 2 h, cooled, and concentrated in vacuo to a brown oil, which solidified upon further standing. A low-melting solid (131 g, 99%) was collected and used without further purification in the next reaction step.

The yields for products **7a**, **7b**, and 3-(3-thienyl)acryloyl chloride were quantitative.

4-Oxo-4,5-dihydrothieno[3,2-*c*]pyridine (9c). A stirred suspension of sodium azide (168.6 g, 2.6 mmol) in a mixture of *p*-dioxane (400 mL) and water (400 mL) was treated dropwise with a solution of 3-(2-thienyl)acryloyl chloride (223.9 g, 1.3 mol) in dioxane at 5 °C. The dioxane layer resulting from this biphasic mixture was isolated, concentrated in vacuo, dissolved in methylene chloride (500 mL), dried ($MgSO_4$), and filtered. This methylene chloride filtrate was added dropwise to refluxing diphenyl ether (400 mL) in a three-neck flask equipped with two air condensers. The solution was refluxed an additional hour, cooled, and concentrated in vacuo to a dark syrup, which was crystallized in acetonitrile to afford a brown solid. Recrystallization of the solid from water (650 mL) yielded 106 g (54%) of a pale yellow solid, mp 213–214 °C.

The yields for intermediates **9a** and **9b** were 22% and 34%, respectively. Only a trace amount of 7-oxo-6,7-dihydrothieno[2,3-*c*]pyridine was obtained from the cyclization of 3-(3-thienyl)acryloyl chloride, the major product being the trimerized derivative 1,3,5-tris[2-(3-thienyl)ethenyl]-1,3,5-triazine-2,4,6-(1*H*,3*H*,5*H*)-trione. The NMR data of this triazine are as follows: (DMSO-d_6) δ 7.00 (d, J = 15 Hz, 1 H), 7.12 (d, J = 15 Hz, 1 H), 7.42 (m, 1 H), 7.60 (m, 2 H).

4-Chlorothieno[3,2-*c*]pyridine (10c). Finely divided 4-oxo-4,5-dihydrothieno[3,2-*c*]pyridine (105.6 g, 0.69 mol) was stirred while being treated dropwise with phosphorus oxychloride (321.5 g, 2.1 mol) at 0 °C. The reaction mixture was then refluxed for 2.5 h, cooled, and cautiously poured onto crushed ice (1 L). The resulting solution was stirred for 30 min and extracted with dichloromethane (3 × 400 mL). The organic portions were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo to a solid, which was recrystallized from acetonitrile (400 mL), affording 101 g (85%) of light yellow solid, mp 91 °C (lit.[7] mp 96 °C).

The yield of **10a** was 57%, and it was used directly in the next step without further purification (lit.[8] mp 91 °C). The yield for **10b** was 82%; bp ca. 85 °C (0.5 mmHg) (lit.[6] bp 117 °C (16 mmHg), mp 41 °C). The yield of 7-chlorothieno[2,3-*c*]pyridine was 74% (lit.[7] bp 106 °C (5 mmHg), mp 38 °C).

4-(1-Piperazinyl)furo[3,2-*c*]pyridine (11b). 4-Chlorofuro[3,2-*c*]pyridine (25.0 g, 0.16 mol) was combined with piperazine (69 g, 0.8 mol) in the minimum volume of ethanol required to form a loose slurry in a Parr bomb. The bomb was flushed with nitrogen, sealed, and heated to 120 °C for 24 h. The bomb contents were dissolved in ethanol and concentrated to dryness in vacuo. The isolated aqueous layer was back-extracted with dichloromethane, and the organic fractions were combined, dried ($MgSO_4$), filtered, and concentrated to 31 g of a gold oil. Flash chromatography (1% NH_4OH, 10% MeOH, CH_2Cl_2) yielded 27.4 g (83%) of an oil. Treatment of an ethanol solution of the oil with 1 equiv of ethanolic hydrochloric acid afforded the hydrochloride salt, which was recrystallized from methanol, yielding brown crystals: mp >250 °C; NMR (Me_2SO-d_6) δ 3.44 (m, 4 H), 4.19 (m, 4 H), 7.44 (br s, 1 H), 7.56 (m, 1 H), 8.08 (d, J = 5.2 Hz, 1 H), 8.30 (br s, 1 H), 9.83 (br s, 2 H); IR (KBr) 1456, 1600, 2775, 3425 cm^{-1}. Anal. ($C_{11}H_{13}N_3O$·HCl) C, H, N.

An identical methodology was used in the synthesis of **11c**. The spectral data for 11c is as follows: NMR (D_2O) δ 3.73 (m, 8 H), 5.21 (br s, 2 H), 7.36 (m, 2 H), 7.72 (d, J = 5.2 Hz, 1 H), 7.90 (d, J = 5.6 Hz, 1 H); IR (KBr) 1440, 1535, 1570, 2775, 3440 cm^{-1}. Anal. ($C_{11}H_{13}N_3S$·HCl) C, H, N.

The yields of **11a** and 7-(1-piperazinyl)thieno[2,3-*c*]pyridine (**12**) were approximately 60%.

Synthesis of *N*-(4-Bromobutyl)imides. The preparation of the *N*-(4-bromobutyl)imides **13a–d** has been previously re-

ported.[17-20] Derivatives **13e**, **13f**, and **13g** were obtained by alkylation of phthalimide, saccharin, or glutarimide, with 1,4-dibromobutane by using similar methodologies. Compound **13h** was synthesized from the 2,6-morpholinedione which was obtained from diglycolic anhydride. Imides **13i** and **13j** were synthesized from 3-methylglutaric acid and thiodiglycolic acid.

4,4-Dimethyl-1-[4-[4-(1-methyl-1*H*-pyrrolo[3,2-*c*]pyridin-4-yl)-1-piperazinyl]butyl]-2,6-piperidinedione (35). A mixture of 4-(1-piperazinyl)-1-methyl-1*H*-pyrrolo[3,2-*c*]pyridine (**11a**) (2.9 g, 0.01 mol), *N*-(4-bromobutyl)-3,3-dimethylglutarimide (**13a**) (2.7 g, 0.01 mol), and potassium carbonate (5.5 g, 0.04 mol) was refluxed in acetonitrile (150 mL) for 24 h. The reaction mixture was filtered, concentrated in vacuo, and partitioned between methylene chloride and water. The organic layer was isolated, dried ($MgSO_4$), concentrated to an oil, and flash chromatographed (10% EtOH–$CHCl_3$). Two grams (48.7%) of an oil was recovered, which was dissolved in ethanol and treated with 1 equiv of ethanolic hydrochloric acid to yield the hydrochloride salt: mp 192–194 °C; NMR (DMSO-d_6) δ 1.00 (s, 6 H), 1.60 (br m, 4 H), 2.54 (s, 4 H), 3.18 (br m, 2 H), 3.57 (br m, 8 H), 3.88 (s, 3 H), 4.53 (m, 2 H), 7.04 (m, 1 H), 7.39 (m, 1 H), 7.68 (m, 2 H); IR (KBr) 1350, 1612, 1669, 2960, 3440 cm^{-1}. Anal. ($C_{23}H_{33}N_5O_2 \cdot 2.1HCl \cdot 2.6H_2O$) C, H, N.

α-(4-Fluorophenyl)-4-(thieno[3,2-*c*]pyridin-4-yl)-1-piperazinebutanol (25). A mixture of 2-(3-chloropropyl)-2-(4-fluorophenyl)-1,3-dioxolane (**13d**) (3.9 g, 0.016 mol), 4-(1-piperazinyl)thieno[3,2-*c*]pyridine (**11c**) (3.5 g, 0.016 mol), and potassium carbonate (6.6 g, 0.048 mol) in acetonitrile (150 mL) was refluxed 72 h. The reaction mixture was filtered and partitioned between methylene chloride and water, and the organic layer was isolated, dried ($MgSO_4$), and concentrated in vacuo to a golden-orange oil. This product was purified by flash chromatography (5% EtOH–$CHCl_3$), affording 4.9 g (72%) of the ketal intermediate. This material was dissolved in 1 N hydrochloric acid and gently heated for 40 min. The solution was basified with 0.1 N sodium hydroxide and extracted with methylene chloride (3×), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo to 3.9 g (89%) of a white solid.

4-[4-(Thieno[3,2-*c*]pyridin-4-yl)-1-piperazinyl]-1-(4-fluorophenyl)-1-butanone (3.8 g, 9 mmol) was added portionwise to a stirring solution of sodium borohydride (1.9 g, 0.05 mol) in methanol (100 mL) at room temperature. The reaction mixture was stirred 1 h and concentrated in vacuo to a white foam, which was partitioned between dichloromethane and water. The organic layer was isolated, dried ($MgSO_4$), filtered, and concentrated in vacuo to a white foamy solid, which was recrystallized from acetonitrile to afford 2.8 g (73.6%) of a white solid: mp 115–118 °C; NMR ($CDCl_3$) δ 1.79 (br m, 4 H), 2.47 (m, 2 H), 2.70 (m, 4 H), 3.62 (m, 4 H), 4.67 (m, 1 H), 6.73 (br s, 1 H), 6.98 (m, 2 H), 7.34 (m, 5 H), 8.05 (d, J = 5.2 Hz, 1 H); IR (KBr) 1430, 1540, 2815, 3450 cm^{-1}. Anal. ($C_{21}H_{24}FN_3OS$) C, H, N.

4-[4-[4-(4-Furo[3,2-*c*]pyridinyl)-1-piperazinyl]butyl]-3,5-morpholinedione (33). A mixture of 4-(1-piperazinyl)furo[3,2-*c*]pyridine (**11b**) (4.5 g, 0.022 mol), 4-(4-bromobutyl)-3,5-morpholinedione (**13h**) (5.5 g, 0.022 mol), and potassium carbonate (9.1 g, 0.066 mol) was refluxed in acetonitrile for 24 h. The reaction mixture was filtered, concentrated in vacuo, and partitioned between methylene chloride and water. The organic layer was isolated, dried ($MgSO_4$), and concentrated in vacuo to a yellow oil, which was flash chromatographed. The appropriate chromatographic fractions were combined, concentrated in vacuo, and crystallized from 2-propanol, yielding 6.2 g (69%) of the free base: mp 109–110 °C; NMR ($CDCl_3$) δ 1.60 (m, 4 H), 2.40 (m, 2 H), 2.57 (m, 4 H), 3.74 (m, 6 H), 4.31 (s, 4 H), 6.78 (d, J = 2 Hz, 1 H), 6.89 (d, J = 5.8 Hz, 1 H), 7.49 (d, J = 2 Hz, 1 H), 8.01 (d, J = 5.8 Hz, 1 H); IR (KBr) 760, 780, 1250, 1285, 1440, 1460, 1570, 1595, 1690, 1735, 2830 cm^{-1}. Anal. ($C_{19}H_{24}N_4O_4$) C, H, N.

4,4-Dimethyl-1-[4-[4-(thieno[3,2-*c*]pyridin-4-yl)-1-piperazinyl]butyl]-2,6-piperidinedione (22). A mixture of 4-(1-piperazinyl)thieno[3,2-*c*]pyridine (**11c**) (2.79 g, 0.012 mol), *N*-(4-bromobutyl)-3,3-dimethylglutarimide (**13a**) (3.3 g, 0.012 mol), and potassium carbonate (3.3 g, 0.024 mol) was refluxed in acetonitrile (150 mL) for 24 h. The reaction mixture was filtered, concentrated in vacuo, and partitioned between methylene chloride and water. The organic layer was isolated, dried ($MgSO_4$), and concentrated in vacuo to a gold oil, which was flash chromatographed (5% ethanol–chloroform). The chromatographed material was dissolved in acetonitrile and treated with ethanolic hydrochloric acid to yield 1.3 g (24%) of the hydrochloride salt: mp 195–197 °C; NMR (DMSO-d_6) δ 1.08 (s, 6 H), 1.71 (m, 4 H), 2.60 (s, 4 H), 3.40 (m, 10 H), 4.00 (m, 2 H), 7.65 (m, 2 H), 7.87 (m, 1 H), 8.08 (d, J = 5 Hz, 1 H), 11.74 (br s, 1 H); IR (KBr) 715, 965, 1425, 1535, 1670, 1720, 2580, 2960 cm^{-1}. Anal. ($C_{22}H_{30}N_4O_2S \cdot 2HCl \cdot 1.5H_2O$) C, H, N.

Biology. Procedures for the CAR, inhibition of APO stereotypy, and induction or reversal of catalepsy have been previously described.[1-4] In vitro binding assays for DA, α_1, 5-HT_1, and 5-HT_2 receptors have also been recently disclosed.[1-4] The procedure for the 5-HT_{1A} binding assay is analogous to the published methodology.[21] The calculation of the IC_{50} value was performed in the standard way by using a log-probit analysis with n = 5; where "n" equals five different test ligand concentrations used to calculate the IC_{50}. Each assay was performed in duplicate. Several compounds, such as **22** and **33**, had IC_{50} values in the various receptor binding assays determined four times (in duplicate). In these cases, the reported IC_{50} value represents a mean IC_{50} result. The high degree of reproducibility in these binding assays indicates a variability of 20% can be expected between independent IC_{50} determinations for a particular compound in each binding assay. This same variability applies to the IC_{50} values determined for the less potent compounds, which were run only in duplicate.

The approximate effective dose (AED) in the inhibition of spontaneous motor activity was determined from evaluation of the compound in three groups of five animals, each run at different doses of test compound. The mean log activity count for each test compound group is compared to the control group. This difference from the control value of the mean log activity counts is plotted on a two-cycle semi-log graph paper. The approximate effective dose ± 0.3 (AED ± 0.3) is determined. This level is considered to be a significant difference from controls in that 0.3 is the approximate log of 2. A 2-fold deviation in most cases would be considered significant.

In the Sidman avoidance test, groups of rats are trained with once daily sessions in the paradigm until they are performing stably. Animals who fail to learn the paradigm in 3 days are replaced with other trainable animals. Twelve animals are dosed with each test compound for 30 min prior to the initiation of the Sidman session. Data are analyzed by comparing each rat's performance in the test to the mean of its previous three drug-free days, in a paired-comparison t test. Thus, each rat serves as its own control. Testing of an active compound continues until a minimally effective dose is determined. The maximum dose examined is usually 100 mg/kg. The MED represents the mean value calculated from trials of the drug in 12 animals.

Electrophysiology. Extracellular single-unit recordings were made from chloral hydrate anesthetized male Sprague-Dawley rats according to standard procedures described previously.[22] Glass microelectrodes filled with 1.0 or 2.0 M NaCl and 0.5% Pontamine Sky Blue were used to record the spontaneous discharge activity of individual serotonergic neurons in the dorsal raphe (DR) nucleus,[22] noradrenergic neurons in the locus coeruleus (LC),[23] dopaminergic neurons in the substantia nigra (area A9),[24] and dopaminergic neurons in the ventral tegmental area (area A10).[25] Drugs were dissolved in saline and infused gradually over a period of 0.5–3.0 min intravenously via a tail vein. Increases or decreases in discharge rates following drug administration were expressed as percent changes from base-line firing rates and calculated over a 1-min period at peak effect. ED_{50} and ED_{25} values in these experiments were defined as the estimated doses

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that produced changes in spontaneous discharge rates of 50 and 25%, respectively, in the indicated directions (excitation or inhibition). These values were determined by graphical log-probit analysis or computerized curve-fitting programs.

Blockade of Apomorphine-Induced Climbing. Male mice were weighed and placed into individual cages (10 × 10 × 13 cm) where they were habituated for 30 min. After the habituation period, drug was administered orally (dissolved in distilled H_2O or suspended in 0.5% Methocel) at volumes of 10 mL/kg body weight. Control groups were administered an equal volume of vehicle at this time. Thirty minutes post drug or vehicle administration, animals were injected subcutaneously with 1.5 mg/kg apomorphine (dissolved in distilled H_2O). For accurate assessment of climbing behavior, three readings were taken at 10, 20, and 30 min following administration of apomorphine (40, 50, and 60 mins post drug or vehicle). Climbing behavior was rated according to the following scale: four paws on the bottom of the cage (no climbing) = 0; two paws on the wall (rearing) = 1; four paws on the wall (full climbing) = 2. Climbing scores were then totaled (maximal score: 6/mouse over three readings), and an average was taken for each group. The dose–response relationship was usually evaluated in a minimum of five animals with 100 mg/kg being the maximum dose examined. A MED value is the minimum dose of the test compound that produces a response statistically different from that of control animals. The control group (vehicle–apomorphine) value was set to 100%. The mean, standard error, and 95% confidence limits were calculated and compared to controls. A compound was considered active if it blocked the development of apomorphine-induced climbing behavior. Activity is reflected in the drugs group's mean score (for three rated observations) being significantly lower than those of the controls. The reported MED value represents the mean result from five different trials with the drug. This methodology is essentially identical with previously published procedures.[26] The pharmacologic specificity of this test has also been discussed.[9,26-28]

Determination of Effects on the Amphetamine Model of Psychosis in Nonhuman Primate Social Colonies. The determination of the effects of compound **33** in the amphetamine model of psychosis in a nonhuman primate social colony was conducted by using methods similar to those previously described.[4] Briefly, compound **33** was tested in three female members of a stable, adult stumptail macaque (*Macaca arctoides*) social colony consisting of one dominant male and four females. Initially, the amphetamine psychosis model was established by first observing the colony behavior prior to drug treatment (base line) followed by administration of amphetamine for 12 consecutive days. Dextroamphetamine, 1.6 mg (base)/kg in time-release form (Dexedrine Spansules), was administered nasogastrically every 12 h for 12 days. Compound **33** was then tested several weeks later. Following another base-line observation period, compound **33**, 5 mg/kg, was administered nasogastrically twice a day for 19 days. *d*-Amphetamine treatment identical with that given previously was added to the treatment regimen on day 8 for the remaining 12 treatment days. Animals were rated by experienced primate observers during the 1-h observations on designated days of the experiment with a rating scale of over 40 behaviors of this species.

Registry No. **5a**, 1192-58-1; **5b**, 98-01-1; **5c**, 98-03-3; **5d**, 498-62-4; (*E*)-**6a**, 119924-13-9; (*Z*)-**6a**, 119924-20-8; (*E*)-**6b**, 15690-24-1; (*Z*)-**6b**, 25129-65-1; (*E*)-**6c**, 15690-25-2; (*Z*)-**6c**, 51019-83-1; (*E*)-**6c** 3-thienyl analogue, 102696-71-9; (*Z*)-**6c** 3-thienyl analogue, 119924-21-9; (*E*)-**7a**, 119924-14-0; (*Z*)-**7a**, 119924-23-1; (*E*)-**7b**, 63485-67-6; (*Z*)-**7b**, 79148-89-3; (*E*)-**7c**, 73186-06-8; (*Z*)-**7c**, 119924-24-2; (*E*)-**7c** 3-thienyl analogue, 119924-22-0; (*Z*)-**7c** 3-thienyl analogue, 119924-25-3; (*E*)-**8a**, 119924-15-1; (*Z*)-**8a**, 119924-29-7; (*E*)-**8b**, 119924-26-4; (*Z*)-**8b**, 119924-30-0; (*E*)-**8c**, 119924-27-5; (*Z*)-**8c**, 119924-31-1; **9a**, 27381-99-3; **9b**, 26956-43-4; **9c**, 27685-92-3; **10a**, 27382-01-0; **10b**, 31270-80-1; **10c**, 27685-94-5; **11a**, 119924-16-2; **11b**, 81078-84-4; **11b**·HCl, 119924-32-2; **11c**, 106261-27-2; **11c**·HCl, 119945-89-0; **12**, 106261-29-4; **13a**, 84951-42-8; **13b**, 85581-61-9; **13c**, 119924-17-3; **13d**, 39899-01-9; **13e**, 5394-18-3; **13f**, 103564-59-6; **13g**, 62966-92-1; **13h**, 106261-31-8; **13i**, 119924-18-4; **13j**, 119924-19-5; **14**, 106260-99-5; **15**, 106261-01-2; **15**·HCl, 106261-02-3; **16**, 106261-03-4; **16**·HCl, 106261-04-5; **17**, 106260-92-8; **17**·1.4HCl, 106260-93-9; **18**, 106261-05-6; **18**·2HCl, 106261-06-7; **19**, 106260-95-1; **19**·HCl, 106260-96-2; **20**, 113316-33-9; **20**·HCl, 106260-98-4; **21**, 106286-49-1; **21**·HCl, 106260-97-3; **22**, 106260-89-3; **22**·HCl, 106260-90-6; **23**, 106261-20-5; **23**·HCl, 119924-33-3; **24**, 106261-21-6; **24**·HCl, 119924-34-4; **25**, 106260-94-0; **25** (ketone, ethylene ketal), 119924-11-7; **25** ketone, 119924-12-8; **26**, 106261-07-8; **26**·2HCl, 106261-08-9; **27**, 106261-16-9; **27**·2HCl, 106261-17-0; **28**, 106261-09-0; **28**·1.4HCl, 106261-10-3; **29**, 106261-14-7; **29**·1.2HCl, 106261-15-8; **30**, 106261-13-6; **30**·1.2HCl, 106286-48-0; **31**, 106261-11-4; **31**·HCl, 106261-12-5; **32**, 106261-18-1; **32**·HCl, 106261-19-2; **33**, 106260-91-7; **34**, 106261-22-7; **34**·2HCl, 106261-23-8; **35**, 106261-25-0; **35**·2.1HCl, 119924-37-7; **36**, 106261-24-9; **36**·2.3HCl, 119924-38-8; malonic acid, 141-82-2; 7-oxo-6,7-dihydrothieno[2,3-*c*]pyridine, 28981-13-7; 1,3,5-tris[2-(3-thienyl)ethenyl]-1,3,5-triazine-2,4,6(1*H*,3*H*,5*H*)-trione, 119924-28-6; 7-chlorothieno[2,3-*c*]pyridine, 28948-58-5; piperazine, 110-85-0; alimide, 85-41-6; saccharin, 81-07-2; glutarimide, 1121-89-7; 1,4-dibromobutane, 110-52-1; 2,6-morpholinedione, 4385-40-4; diglycolic anhydride, 4480-83-5; 3-methylglutaric acid, 626-51-7; thiodiglycolic acid, 123-93-3; 7-(1-piperazinyl)-5-methylthieno-[3,2-*c*]pyridine, 119924-36-6; 4-(1-piperazinyl)-5-methylfuro[3,2-*c*]pyridine, 119924-39-9; 2-bromo-4-(1-piperazinyl)thieno[3,2-*c*]-pyridine, 119924-35-5.

Supplementary Material Available: Procedures for both the Sidman avoidance and inhibition of spontaneous motor activity (2 pages). Ordering information is given on any current masthead page.

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