7-[3-(1-Piperidinyl)propoxy]chromenones as Potential Atypical Antipsychotics

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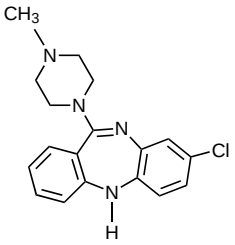
Compound **1** (1-benzyl-3-methyl-4-[4-(4-fluorophenyl)-4-oxobutyl]piperazine), a synthetic intermediate identified as a potential atypical antipsychotic, was selected as the starting point for pharmacological improvement. From **1**, sequential structural variations were conducted in order to improve its potency and oral bioavailability. These variations included a series of piperazine, ethanediamine, and piperidine derivatives. The piperidine series afforded some orally potent compounds in the inhibition of apomorphine-induced climbing and hyperactivity in mice, which are regarded as behavioral models predictive of antipsychotic efficacy. Further optimization of these structures led to the highly potent 7-[3-(1-piperidinyl)propoxy]chromenones. Inhibition of stereotypies and induction of catalepsy in rats at doses substantially higher than required for inhibition of climbing suggest an atypical antipsychotic profile, which is assumed to predict a reduced induction of extrapyramidal side effects in humans.

Introduction

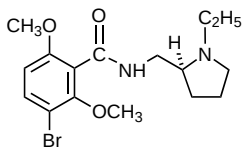
For many years, treatment of schizophrenia and psychoses has relied on conventional neuroleptics, such as chlorpromazine, fluphenazine, and haloperidol. However, their application is limited by the frequent appearance of adverse neurological effects,[1] mainly involuntary movement disorders and extrapyramidal side effects. For some time, these side effects have been regarded as inherent to the same mechanism of action of the antipsychotic drugs. Thus, the term neuroleptic (that is a drug producing neurological side effects) was considered a synonym of antipsychotic drug. Nevertheless, the efforts to discover more effective antipsychotic medications introduced some compounds characterized by minimal induction of extrapyramidal effects. Clozapine[2] (Chart 1) was the prototype of these new drugs, which were classified as "atypical antipsychotics". This compound proved to be effective in the treatment of psychoses without essentially any tendency to produce extrapyramidal side effects. Unfortunately, clozapine is not devoid of other severe undesirable effects,[3] such as agranulocytosis and seizures in a significant number of cases. For this reason, its use has been restricted to a small population of closely monitored patients, who have been resistant to other drugs. In the recent years several potential atypical antipsychotics have been developed, among them, remoxipride[4] and risperidone[5] have been launched; however, remoxipride was withdrawn from the market in 1993 due to some cases of induction of aplastic anemia.[6] Thus, the discovery of novel atypical antipsychotics as safe substitutes for clozapine still remains a primary goal in the research for the therapy of schizophrenia.

The most accepted model to explain the biochemical basis of schizophrenia postulates that dopaminergic activity is increased in the mesolimbic system of the brain.[7] In accordance with this, the pharmacological potencies of classical antipsychotics correlate with their affinities for D_2 receptors.[8] On the other hand, the extrapyramidal effects have been attributed to dopamine antagonism at nigrostriatal regions.[9] However, at present, although several models have been proposed, there is not a theory that satisfactorily explains the atypical antipsychotic profile. Selective binding to certain subtypes of dopaminergic receptors,[10] preferential 5-HT_2 in relation to D_2 antagonism,[11] σ receptor blockade,[12] and neurotensin agonism[13] are among the proposed theories to account for their mechanism of action. In animal models, it is widely accepted that atypical antipsychotics are identified by inhibition of apomorphine-induced stereotyped behavior (characteristic of dopamine antagonism at nigrostriatal system) at doses significantly higher than those required for inhibition of apomorphine-induced climbing response (indicative of antagonism in the mesolimbic dopamine system).[14]

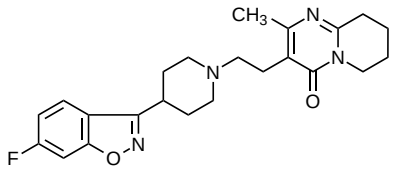
Chart 1. Some Atypical Antipsychotics



clozapine



remoxipride



risperidone

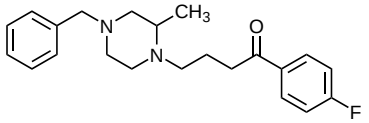


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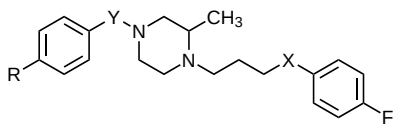
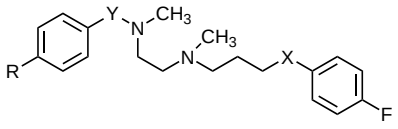
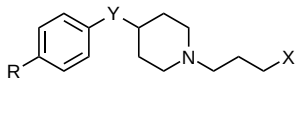
Table 1. Physicochemical Data of Compounds **1**−**34**



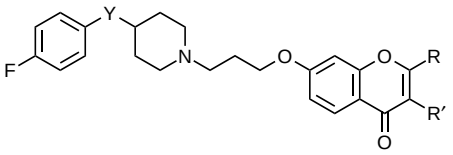
I



II



III



IV

compd	structure type	X	Y	R	R′	method[a]	yield, %	mp, °C (cryst solvent)	formula[b]
1	I	C=O	CH_2	H		B	72	207−209 (iPrOH)	$C_{22}H_{27}FN_2O\cdot 2HCl$
2	I	CHOH	CH_2	H		C	33	189−192 (iPrOH)	$C_{22}H_{29}FN_2O\cdot 2HCl$
3	I	C=O	CH_2	F		B	55	210−212 (EtOH)	$C_{22}H_{26}F_2N_2O\cdot 2HCl$
4	I	CHOH	CH_2	F		C	67	205−207 (iPrOH)	$C_{22}H_{28}F_2N_2O\cdot 2HCl$
5	I	C=O	C=O	F		A	59	131−133 (iPrOH)	$C_{22}H_{24}F_2N_2O_2\cdot HCl$
6	I	CHOH	C=O	F		C	72	153−156 (iPrOH−Et_2O)	$C_{22}H_{26}F_2N_2O_2\cdot HCl$
7	I	C=O	SO_2	CH_3		B	83	148−149 (iPrOH−Et_2O)	$C_{22}H_{27}FN_2O_3S\cdot HCl$
8	I	CHOH	SO_2	CH_3		C	60	141−143 (EtOH)	$C_{22}H_{29}FN_2O_3S\cdot HCl$
9	II	C=O	CH_2	H		B	54	212−215 (iPrOH)	$C_{21}H_{27}FN_2O\cdot 2HCl$
10	II	CHOH	CH_2	H		C	74	208−209 (iPrOH)	$C_{21}H_{29}FN_2O\cdot 2HCl$
11	II	C=O	CH_2	F		B	83	227−229 (EtOH)	$C_{21}H_{26}F_2N_2O\cdot 2HCl$
12	II	CHOH	CH_2	F		C	88	219−222 (EtOH)	$C_{21}H_{28}F_2N_2O\cdot 2HCl$
13	II	O	CH_2	F		A	67	237−239 (EtOH)	$C_{20}H_{26}F_2N_2O\cdot 2HCl$
14	II	CH(4-FC_6H_4)	CH_2	F		A	69	204−206 (EtOH)	$C_{27}H_{31}F_3N_2\cdot 2HCl$
15	III	CO(4-FC_6H_4)	CH_2	H		B	86	182−184 (EtOH−Et_2O)	$C_{22}H_{26}FNO\cdot HCl$
16	III	CHOH(4FC_6H_4)	CH_2	H		C	66	186−188 (EtOH−Et_2O)	$C_{22}H_{28}FNO\cdot HCl$
17	III	CO(4-FC_6H_4)	CH_2	F		B	44	170−172 (EtOH−iPrOH)	$C_{22}H_{25}F_2NO\cdot HCl$
18	III	CHOH(4FC_6H_4)	CH_2	F		C	66	188−190 (EtOH−iPrOH)	$C_{22}H_{27}F_2NO\cdot HCl$
19	III	O(4-FC_6H_4)	CH_2	F		A	36	144−147 (EtOH−iPrOH)	$C_{21}H_{25}F_2NO\cdot HCl$
20	III	CH(4-FC_6H_4)$_2$	CH_2	F		A	39	98−100 (iPrOH−Et_2O)	$C_{28}H_{30}F_3N\cdot HCl$
21	III	CH_2-DOAD[c]	CH_2	F		A	41	192−194 (EtOH−Et_2O)	$C_{25}H_{35}FN_2O_2\cdot HCl$
22	IV		CH_2	H	H	A	30	78−80 (EtOH−Et_2O)	$C_{24}H_{26}FNO_3\cdot HCl$
23	III	O(4-FC_6H_4)	C=O	F		A	42	190−192[d] (EtOH−Et_2O)	
24	III	O(4-FC_6H_4)	CHOH	F		C	77	116−117 (iPrOH−Et_2O)	$C_{21}H_{25}F_2NO_2$
25	III	O(4-FC_6H_4)	CH(OCH_3)	F		A	49	109−111 (acet-Et_2O)	$C_{22}H_{27}F_2NO_2\cdot HCl$
26	IV		C=O	H	H	A	38	236−238 (iPrOH)	$C_{24}H_{24}FNO_4\cdot HCl$
27	IV		C=O	CH_3	H	A	77	251−253 (MeOH−Et_2O)	$C_{25}H_{26}FNO_4\cdot HCl$
28	IV		C=O	CF_3	H	A	41	248−250 (MeOH−Et_2O)	$C_{25}H_{23}F_4NO_4\cdot HCl$
29	IV		C=O	C_6H_5	H	A	53	259−262 (MeOH−Et_2O)	$C_{30}H_{28}FNO_4\cdot HCl$
30	IV		C=O	H	CH_3	A	50	224−227 (MeOH−Et_2O)	$C_{25}H_{26}FNO_4\cdot HCl$
31	IV		C=O	H	CH_2CH_3	A	59	173−176 (MeOH−Et_2O)	$C_{26}H_{28}FNO_4\cdot HCl$
32	IV		C=O	H	CH_2OH	A	38	217−218 (MeOH−Et_2O)	$C_{25}H_{26}FNO_5\cdot HCl$
33	IV		C=O	H	Cl	A	39	240−243 (MeOH−Et_2O)	$C_{24}H_{23}ClFNO_4\cdot HCl$
34	IV		C=O	H	F	A	22	234−237 (MeOH−Et_2O)	$C_{24}H_{23}F_2NO_4\cdot HCl$

[a] See the Experimental Section for details. [b] All compounds gave satisfactory elemental analyses (±0.4%) for C, H, N, and Cl. [c] DOAD = 7,9-dioxo-8-azaspiro[4.5]decan-8-yl. [d] Lit.[18] mp 186−188.5 (iPrOH).

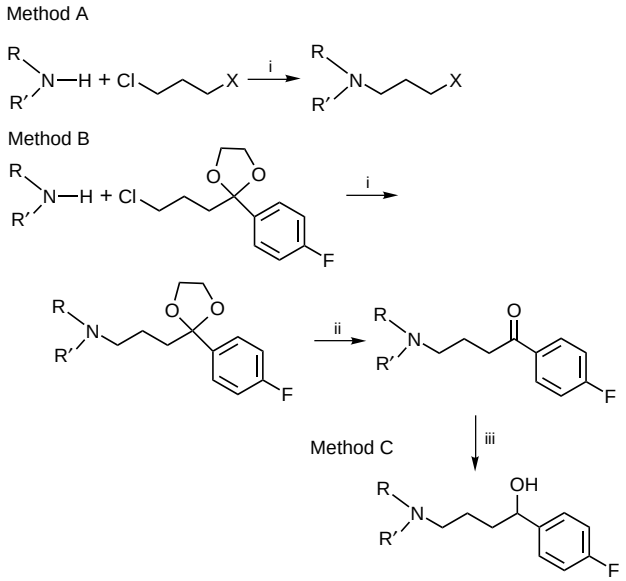
As a part of a research program aimed at the discovery of novel antipsychotic drugs, from a preliminary screening process, we had selected compound **1** as a structural starting point. This compound, formerly obtained as a synthetic intermediate in the preparation of other antipsychotic entities,[15] was found to possess a potentially atypical antipsychotic profile, showing a difference between doses for inhibition of apomorphine-induced climbing and for inhibition of stereotypies. Unfortunately, it displayed only moderate intraperitoneal activity and was not active on oral administration. This fact encouraged us to explore several structural variants of **1** that could give rise to novel therapeutically useful antipsychotics. We report here the results in our efforts in the chemical improvement of this structure, which have led to the discovery of new potent and orally active atypical antipsychotic compounds.

Chemistry

The target compounds **1**−**34** (see Table 1) were prepared by alkylation of the corresponding secondary amines (piperazines, piperidines or ethanediamines) with the appropriate chlorides in the presence of potassium iodide (method A), as indicated in Scheme 1. Similarly, introduction of the butyrophenone moiety was accomplished by alkylation with the protected chloroketal, followed by acidic hydrolysis of the crude product (method B). The corresponding phenylbutanols were prepared by sodium borohydride reduction of butyrophenones (method C).

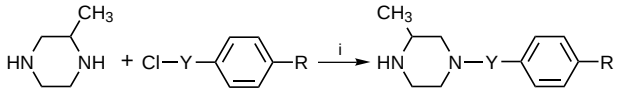
The required *N*-benzylpiperazine precursors **35** and **36** (Scheme 2) were obtained by selective monoalkylation of 2-methylpiperazine at the less hindered position in a variant of the method reported for 1-benzyl-3-methylpiperazine (**35**).[16] Similarly, *N*,*N*′-dimethyl-

Scheme 1.[a] Synthesis of Target Compounds



[a] Reagents and conditions: (i) K_2CO_3, CH_3CN, reflux; (ii) 6 M HCl, 70 °C; (iii) $NaBH_4$, EtOH, room temperature.

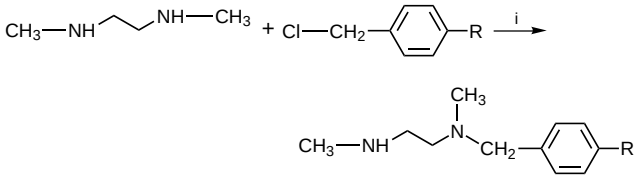
Scheme 2.[a] Synthesis of Piperazine Precursors



35: Y = CH_2; R = H
36: Y = CH_2; R = F
39: Y = CO; R = F
40: Y = SO_2; R = CH_3

[a] Reagents: (i) $NaHCO_3$, EtOH or H_2O−acetone.

Scheme 3.[a] Synthesis of Ethanediamine Precursors

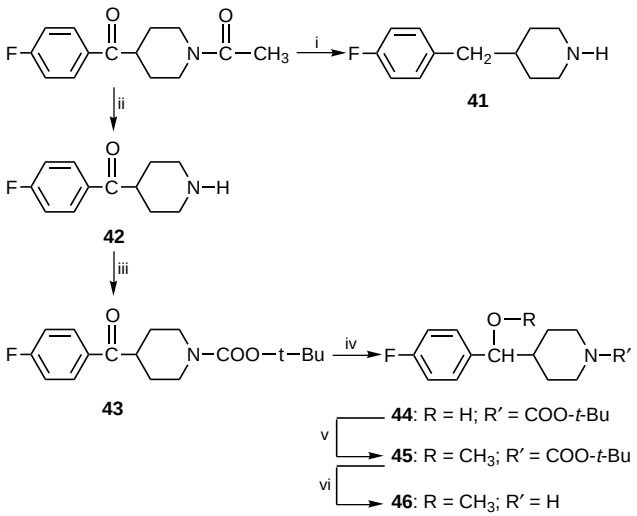


37: R = H
38: R = F

[a] Reagents: $NaHCO_3$, EtOH.

ethanediamine was monoalkylated with the appropriate benzyl chlorides to afford **37**[17] and **38** (Scheme 3). In a related procedure, monoacylation of 2-methylpiperazine with the corresponding acid chlorides afforded benzamide **39** and sulfonamide **40**.

Scheme 4.[a] Synthesis of Piperidine Precursors



[a] Reagents: (i) (1) NH_2NH_2, EtOH; (2) NaOH, diglyme; (ii) 6 M HCl; (iii) $(t\text{-BuOCO})_2O$, Et_3N, THF; (iv) $NaBH_4$, EtOH; (v) (1) CH_3I, NaH, THF; (2) 4 M HCl, EtOH.

Piperidines were either commercial or easily synthesized from the common intermediate *N*-acetyl-4-(4-fluorobenzoyl)piperidine[18] (see Scheme 4). Simultaneous amide hydrolysis and ketone reduction under Wolff−Kishner conditions afforded 4-(4-fluorobenzyl)-piperidine (**41**).[19] On the other hand, amide hydrolysis under acidic conditions provided 4-(4-fluorobenzoyl)-piperidine (**42**).[18] Alternatively, compound **42** was protected as the *N*-*tert*-butoxycarbonyl derivative (**43**), reduced to alcohol **44**, O-alkylated with methyl iodide, and deprotected to yield the 4-(methoxymethyl)piperidine **46**. The smoothly removable *tert*-butoxycarbonyl protecting group avoided methanol elimination during hydrolysis.

Most alkylating reagents were commercially available. The (3-chloropropoxy)chromenones (see Table 2) were prepared from the adequate 2,4-dihydroxyphenyl ketones through two different sequences, as shown in Scheme 5.

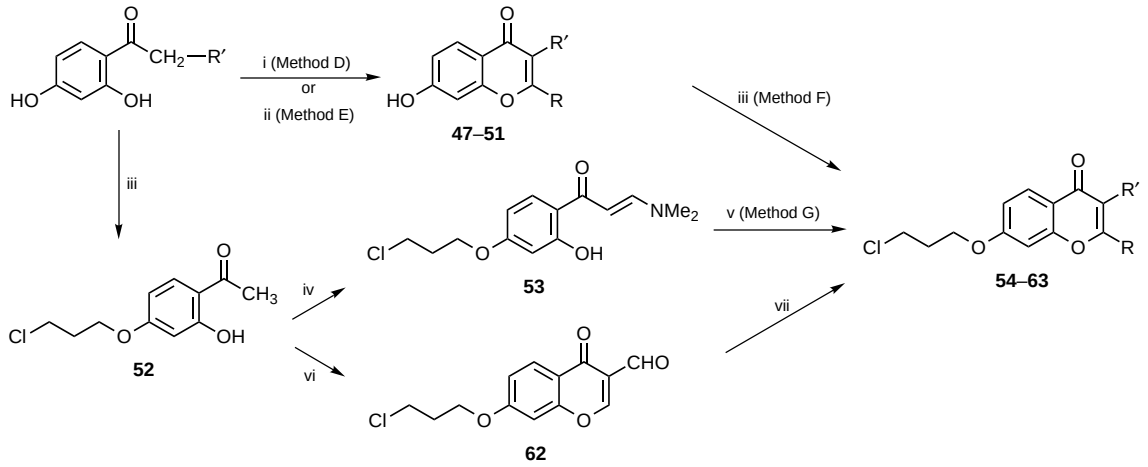
Conversion of 2,4-dihydroxyphenyl ketones into the corresponding 7-hydroxychromenones was effected according to published procedures for some of the simpler analogues. Thus, 7-hydroxy-2-(trifluoromethyl)chromen-4-one (**47**) was prepared by the Kostanecki−Robinson procedure, by heating 2′,4′-dihydroxyacetophenone with trifluoroacetic anhydride and sodium trifluoroacetate

Table 2. Physicochemical Data for Novel Chromen-4-ones

compd	R	R′	R″	method	yield, %	mp, °C	formula[a]
47	CF_3	H	H	D	68	208−10	$C_{10}H_5F_3O_3$
50	H	CH_3	H	E	88	231−34[b]	
51	H	C_2H_5	H	E	23	179−81	$C_{11}H_{10}O_3$
54	H	H	$(CH_2)_3Cl$	*c*	70	76−8[d]	
55	CH_3	H	$(CH_2)_3Cl$	F	85	113−15	$C_{13}H_{13}ClO_3$
56	CF_3	H	$(CH_2)_3Cl$	F	69	77−9	$C_{13}H_{10}ClF_3O_3$
57	C_6H_5	H	$(CH_2)_3Cl$	F	96	119−21	$C_{18}H_{15}ClO_3$
58	H	CH_3	$(CH_2)_3Cl$	F	63	83−5	$C_{13}H_{13}ClO_3$
59	H	C_2H_5	$(CH_2)_3Cl$	F	86	oil	
60	H	Cl	$(CH_2)_3Cl$	G	67	101−3	$C_{12}H_{10}Cl_2O_3$
61	H	F	$(CH_2)_3Cl$	G	66	89−91	$C_{12}H_{10}ClFO_3$
62	H	CHO	$(CH_2)_3Cl$	*c*	51	105−8	$C_{13}H_{11}ClO_4$
63	H	CH_2OH	$(CH_2)_3Cl$	*c*	40	102−4	$C_{13}H_{13}ClO_4$

[a] Compounds were analyzed for C, H, and, where present, for Cl, and were within ±0.4% of theoretical values. [b] Lit.[23] mp 222−224 °C. [c] See the Experimental Section for details. [d] Lit.[22] mp 70−74 °C.

Scheme 5.[a] Synthetic Routes to 7-(3-Chloropropoxy)chromenones



[a] Reagents: (i) $(RCO)_2O$, RCOONa; (ii) $HC(OEt)_3$, $HClO_4$; (iii) $Cl(CH_2)_3Br$, K_2CO_3, acetone; (iv) $Me_2NCH(OMe)_2$; (v) *t*-BuOCl or 1-F-2,4,6-Me_3Pyr; (vi) $POCl_3$, DMF; (vii) $NaBH_4$, MeOH, CH_2Cl_2.

(method D) in a procedure related to that reported for the 2-methyl (**48**)[20] and the 2-phenyl (**49**)[21] derivatives. Some of the 2-unsubstituted chromenones were prepared from the appropriate ketones by reaction with triethyl orthoformate in the presence of perchloric acid following a procedure similar to that described for 7-hydroxychromen-4-one[22] (method E). Further, the hydroxychromenones obtained by one of these methods were in turn O-alkylated with 1-bromo-3-chloropropane (method F). Alternatively, some (3-chloropropoxy)-chromenones could be obtained from 1-[4-(3-chloropropoxy)-2-hydroxyphenyl]ethanone (**52**) on formation of a pyran ring by means of formylating reagents. Thus, reaction with dimethylformamide dimethyl acetal afforded keto enamine **53**. Acidic cyclization of this compound provided an alternative access to unsubstituted chromenone **54**,[22] whereas treatment with appropriate halogenating reagents afforded in a one-pot procedure the 3-halochromenones **60** and **61** (method G). If formylation was effected with dimethylformamide−phosphoryl chloride reagent, the corresponding 3-formylchromenone **62** was obtained, which was converted into the 3-hydroxymethyl derivative **63** by sodium borohydride reduction. The chromenones prepared are summarized in Table 2.

Biological Results and Discussion

Structural optimization of the compounds was conducted on the basis of pharmacological profiles in animal models, instead of a definite binding pattern to selected receptors. Efforts were focused upon compounds possessing a pharmacological profile suggestive of high oral antipsychotic activity and minimal induction of extrapyramidal side effects. The antipsychotic potential of compounds was evaluated by testing their ability to antagonize climbing behavior[25] and hyperactivity[26] in apomorphine-dosed mice. Propensity to cause extrapyramidal side effects was assessed by the ability to antagonize stereotypy[27] produced by subcutaneous administration of apomorphine in rats, and for some compounds, also by the induction of catalepsy.[28]

Our initial approaches to structural variants of compound **1** were started with modifications of the benzyl moiety. Thus, a series of substituted piperazines (**1**−**8**) was synthesized and tested. The results are shown in Table 3. Benzyl derivatives **1** and **4** were moderately active on intraperitoneal administration, although all compounds lacked appreciable oral activity. Benzoyl and arylsulfonyl amides were essentially inactive.

In an attempt to improve oral bioavailability of our compounds, we turned our attention to the modification

Table 3. Biological Activity of Piperazine (**1**−**8**) and Ethanediamine (**9**−**14**) Derivatives

	climbing[a]		hyperactivity[b]		
compd	ip	po	ip	po	stereotypy[c]
1	28.2 (22.0−35.1)	>200	30	>200	30
2	>50	>200	35	>200	16
3	>50	>200	45	>200	19
4	30.0 (23.4−40.1)	>200	50	>200	48
5	>50	>200	>50	>200	22
6	>50	>200	>50	>200	0
7	>200	>200	>200	>200	8
8	>200	>200	>200	>200	0
9	38.2 (25.9−56.3)	>200	50	>200	33
10	>50	>200	>50	>200	NT[d]
11	15.2 (10.3−22.8)	48.4 (33.6−69.7)	15.2 (10.5−21.8)	33.6 (24.7−45.7)	35
12	40.0 (28.8−56.8)	>200	32	>200	38
13	35.0 (25.9−47.2)	>200	25.0 (17.3−31.8)	>200	NT
14	>50	>200	30	>200	NT

[a] Inhibition of apomorphine-induced climbing behavior in mice. Results are expressed as ED_{50} values in mg/kg; 95% confidence limits are shown in parentheses. [b] Inhibition of apomorphine-induced hyperactivity in mice. Results are expressed as ED_{50} values in mg/kg. [c] Inhibition of apomorphine-induced stereotypy in rats. Results are expressed in percent inhibition at 50 mg/kg ip dose. [d] NT = not tested.

Table 4. Biological Activity of Piperidine Derivatives

	climbing[a]		hyperactivity[b]		
compd	ip	po	ip	po	stereotypy[c]
15	2.85 (0.9−8.3)	15.2 (7.2−21.2)	12.3 (6.8−22.2)	NT[e]	46
16	20.0 (12.0−33.2)	>200	12.6 (7.3−21.6)	>200	48
17	6.6 (4.5−9.6)	23.0 (4.6−113.8)	4.7 (2.3−6.8)	13.7 (6.1−30.8)	25
18	8.0 (4.6−13.8)	15.6 (11.7−20.8)	5.5 (2.3−13.6)	15.6 (12.3−19.7)	20
19	12.7 (8.7−18.4)	35.9 (26.5−48.7)	7.6 (5.7−9.9)	13.1 (4.0−42.5)	45
20	45.3 (36.2−54.1)	>100	8.6 (5.7−13.5)	12.0 (11.7−12.2)	23.0[d] (17.0−30.7)
21	>50	>200	12.5 (9.3−16.7)	>200	43.1[d] (30.3−61.2)
22	>50	>200	NT	>200	0
23	1.82 (0.7−4.4)	4.3 (2.0−9.1)	1.15 (0.6−1.9)	4.9 (2.2−8.4)	12.4[d] (10.8−14.1)
24	11.3 (7.6−16.6)	16.8 (10.7−26.4)	12.9 (9.1−18.3)	21.3 (12.3−36.8)	48
25	11.6 (7.2−18.6)	34.6 (27.9−42.9)	11.1 (8.0−15.1)	25.7 (18.7−35.4)	15
26	3.6 (2.4−5.4)	6.4 (4.4−9.2)	1.65 (1.4−1.9)	2.9 (2.7−3.1)	18.6[d] (15.5−22.3)
clozapine	7.7 (5.1−11.6)	14.5 (9.8−21.3)	7.8 (2.5−23.6)	11.0 (8.2−14.5)	85.3[d] (68.0−106.0)
remoxipride	5.2 (2.9−9.1)	16.0 (9.0−28.3)	4.2 (2.0−8.6)	11.1 (7.4−16.3)	48.7[d] (37.0−64.2)
haloperidol	0.21 (0.07−0.60)	1.6 (0.8−3.1)	0.20 (0.08−0.40)	0.56 (0.5−0.6)	1.95[d] (1.6−2.2)
risperidone	0.20 (0.09−0.40)	0.74 (0.5−1.2)	0.14 (0.09−2.30)	0.26 (0.16−0.40)	3.80[d] (3.1−4.5)

[a] Inhibition of apomorphine-induced climbing behavior in mice. Results are expressed as ED_{50} values in mg/kg; 95% confidence limits are shown in parentheses. [b] Inhibition of apomorphine-induced hyperactivity in mice. Results are expressed as ED_{50} values in mg/kg; 95% confidence limits are shown in parentheses. [c] Inhibition of apomorphine-induced stereotypy in rats. Results are expressed in percent inhibition at 50 mg/kg ip dose, unless where noted. [d] Stereotypy ED_{50} in mg/kg ip. [e] NT = not tested.

Table 5. Biological Activity of (Piperidinylpropoxy)chromenones

compd	climbing[a] (ED_{50}, po)	hyperactivity[b] (ED_{50}, po)	stereotypy[c] (ED_{50}, po)	catalepsy[d] (ED_{50}, po)
26	6.4 (4.4−9.2)	2.9 (2.7−3.1)	63.4 (22.0−179.0)	35.2 (28.0−44.3)
27	28.0 (13.7−59.3)	4.6 (3.5−5.8)	>100	94.8 (65.0−137.7)
28	60.0 (31.1−115.8)	10.9 (5.0−23.7)	>100	>100
29	>100	48.4 (35.8−65.3)	>100	>100
30	5.7 (4.4−7.3)	1.65 (1.3−2.0)	77.3 (49.0−120.0)	37.5 (30.7−45.7)
31	11.3 (7.9−15.9)	6.9 (3.2−19.4)	NT[e]	NT
32	3.2 (2.4−4.1)	1.32 (0.6−4.1)	35.9 (10.0−126.0)	14.0 (11.2−17.3)
33	11.2 (9.1−13.9)	7.0 (2.6−18.5)	>100	21.2 (15.6−29.7)
34	23.5 (4.6−117.7)	20.0 (6.4−65.7)	NT	18.0 (6.0−53.5)
clozapine	14.5 (9.8−21.3)	11.0 (8.2−14.5)	85.3 (68.0−106.0)	107.3 (88.6−129.8)
remoxipride	16.0 (9.0−28.3)	11.1 (7.4−16.3)	48.7 (37.0−64.2)	64.3 (36.1−114.4)
haloperidol	1.6 (0.8−3.1)	0.56 (0.5−0.6)	1.95 (1.6−2.2)	2.5 (2.2−2.8)
risperidone	0.74 (0.5−1.2)	0.26 (0.16−0.40)	3.8 (3.1−4.5)	5.0 (4.8−5.3)

[a] Inhibition of apomorphine-induced climbing behavior in mice. Results are expressed as ED_{50} values in mg/kg po; 95% confidence limits are shown in parentheses. [b] Inhibition of apomorphine-induced hyperactivity in mice. Results are expressed as ED_{50} values in mg/kg po; 95% confidence limits are shown in parentheses. [c] Inhibition of apomorphine-induced stereotypy in rats. Results are expressed as ED_{50} values in mg/kg po. [d] Induction of catalepsy. Results are expressed as dose required to produce a 50% of maximum catalepsy score in mg/kg, po; 95% confidence limits are shown in parentheses. [e] NT = not tested.

of the piperazine nucleus, while maintaining the benzyl moiety. Thus, a series of benzylethanediamines and a series of benzylpiperidines were designed. The results for the ethanediamine compounds (**9**−**14**) are shown in Table 3. The most active compounds on intraperitoneal administration were ketone **11** and ether **13**, but only **11** showed appreciable oral activity. This compound, at doses required for inhibition of climbing and hyperactivity, retained a small inhibition of stereotypies. Our next efforts were then focused on the substitution of the piperazine by a piperidine ring. In the 4-benzylpiperidine series (**15**−**22**), a number of compounds displayed good oral activity in the climbing and hyperactivity tests (Table 4). For most compounds, it was not possible to calculate the ED_{50} for the inhibition of stereotypies due to poor activity in this assay, and thus, results are expressed as percent inhibition at the maximum practicable dose of 50 mg/kg ip. This difference is in agreement with the suggested potentially atypical antipsychotic profile of these compounds. Particularly, compounds **17** and **18**, with a ketone or an alcohol function, showed a high potency in the climbing and hyperactivity tests and an appreciable difference with doses required for inhibition of stereotypies. Unfortunately, they displayed other important side effects, such as motor incoordination, hypothermia, and tremors in the Irwin test,[24] even at doses lower than the ED_{50} in the climbing assay. With a similar oral potency, ether **19** possessed a broader margin for the above side effects. Thus, the structural framework of [(aryloxy)propyl]-piperidine was selected as the target for further improvement.

On the basis of the structure of compound **19**, we devised again the introduction of some modifications on the benzyl group. Thus, the corresponding derivatives hydroxy-, methoxy-, and keto-substituted at the benzyl position were synthesized. Alcohol **24** and ketone **23** can be regarded as the "reversed piperidine" analogues of phenylbutanol **18** and butyrophenone **17**. For these compounds, the climbing and hyperactivity potencies were similar to those of their analogues; however, the reversed derivatives showed lesser motor incoordination and hypothermia side effects. The greater potency corresponded to compound **23**, with a ketone function. An additional improvement was achieved by substitution of the *p*-fluorophenyl group for a chromenone ring (**26**), which afforded a similarly potent compound, but with a somewhat broader margin for inhibition of stereotypies and devoid of motor incoordination, hypothermia, and tremors. All analogues in the piperidine

series displayed appreciable oral activities, as shown in Table 4. Also, the corresponding data for some representative standard antipsychotics are included for comparison.

Finally, we explored the chemical modification of the chromenone ring of compound **26** with the introduction of some substituents at positions 2 and 3. The biological results for the substituted chromene derivatives are indicated in Table 5. Evaluation of stereotypies was effected on oral administration, due to high oral potency of most of these compounds. Assessment of potential induction of extrapyramidal effects is complemented with the catalepsy assay. All of the 2-substituted derivatives prepared were less active in the climbing and hyperactivity tests, but some of the 3-substituted analogues showed a higher potency than the parent compound **26**. Thus, the 3-(hydroxymethyl)chromenone **32** is the most active compound, whereas the 3-methyl derivative **30** shows the broader margin for induction of catalepsy and stereotypy in the conditions of the test.

As a conclusion, compounds **26**, **30**, and **32** stand for the most potent members of this interesting family of 7-[3-(1-piperidinyl)propoxy]chromenones. They possess in vivo pharmacological profiles predictive of possible atypical antipsychotic activity, with high potency on oral administration. On the basis of these pharmacological profiles, an oral potency for these compounds higher than that of clozapine or remoxipride and a lesser induction of extrapyramidal effects than haloperidol and at least similar to that of risperidone can be suggested. Compounds **26**, **30**, and **32** have been selected as candidates for further studies in order to evaluate their therapeutic potential as antipsychotic drugs.

Experimental Section

Chemistry. General Methods. Melting points were determined in open capillary tubes on a Büchi apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini 300 spectrometer. Chemical shifts are expressed in parts per million downfield from TMS as internal standard. IR spectra were registered with a Perkin-Elmer 1710 apparatus. Microanalyses were obtained using a Perkin-Elmer 2400 elemental analyzer. Where analyses are indicated with the symbols of the elements, the results are within ±0.4% of the theoretical values. Column chromatography separations were carried out using Merck silica gel 60 (70−230 mesh ASTM). Prior to concentration, under reduced pressure, all organic extracts were dried over anhydrous Na_2SO_4 powder.

The general methods of synthesis exemplified are illustrative of those of the analogous compounds.

Method A: 7-[3-[4-(*p*-Fluorobenzoyl)-1-piperidinyl]-propoxy]chromen-4-one (26). A mixture of 3.9 g (18.8 mmol) of 4-(*p*-fluorobenzoyl)piperidine (**42**), 4.5 g (18.8 mmol) of 7-(3-chloropropoxy)chromen-4-one (**54**), 2.7 g (18.8 mmol) of anhydrous potassium carbonate, and a trace of potassium iodide in 250 mL of acetonitrile was heated to reflux for 24 h. The resulting suspension was filtered, and the filtrates were evaporated, then redissolved in CH_2Cl_2, washed with brine, and concentrated. The residue was dissolved in 2-propanol and precipitated by addition of an isopropanolic solution of hydrogen chloride. The solid was collected and recrystallized from methanol−ether to afford 2.2 g (26%) of **26**: mp 235−238 °C; IR (KBr) 3200−3600, 2300−2800, 1680, 1650, 1630 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.01 (m, 4H, piper-3H and -5H), 2.30 (m, 2H, OCH_2CH_2), 3.13 (m, 2H, piper-2H$_{ax}$ and -6H$_{ax}$), 3.24 (br t, J = 6 Hz, 2H, NCH_2), 3.61 (br d, J = 10.2 Hz, 2H, piper-2H$_{eq}$ and -6H$_{eq}$), 3.75 (m, 1H, piper-4H), 4.25 (br t, J = 6 Hz, 2H, OCH_2), 6.29 (d, J = 6.3 Hz, 1H, 3-H), 7.08 (dd, J = 9 and 2 Hz, 1 H, 6-H), 7.16 (d, J = 2 Hz, 1H, 8-H), 7.40 (t, J = 9 Hz, 2H, Ph-3H and -5H), 7.96 (d, J = 9 Hz, 1H, 5-H), 8.11 (dd, J = 9 and 6 Hz, 2H, Ph-2H and -6H), 8.25 (d, J = 6.3 Hz, 1H, 2-H); ^{13}C NMR (DMSO-d_6) δ 22.93 (OCH_2CH_2), 25.46 (piper-3C and -5C), 40.03 (piper-4C), 50.85 (piper-2C and -6C), 53.18 (NCH_2), 65.77 (OCH_2), 101.77 (8-C), 111.91 (3-C), 114.62 (6-C), 115.65 (d, J = 21.7 Hz, Ph-3C and -5C), 117.90 (4a-C), 126.13 (5-C), 131.04 (d, J = 9.2 Hz, Ph-2C and -6C), 131.52 (d, J = 3.5 Hz, Ph-1C), 156.16 (2-C), 157.34 (8a-C), 162.31 (7-C), 164.78 (d, J = 250.4 Hz, Ph-4C), 175.25 (4-C), 199.09 (PhC=O). Anal. ($C_{24}H_{24}FNO_4$.HCl) C, H, N, Cl.

Method B: 4-(*p*-Fluorobenzyl)-1-[4-(*p*-fluorophenyl)-4-oxobutyl]-2-methylpiperazine (3). A mixture of 75 g (0.36 mol) of 1-(*p*-fluorobenzyl)-3-methylpiperazine (**36**), 90 g (0.36 mol) of 2-(3-chloropropyl)-2-(*p*-fluorophenyl)-1,3-dioxolane, 175 g (1.27 mol) of anhydrous potassium carbonate, and 3 g of potassium iodide in 500 mL of acetonitrile was stirred at reflux for 24 h. The insoluble residue was removed by filtration, and the solution was concentrated to give 42 g (30%) of crude **4-(*p*-fluorobenzyl)-1-[4,4-(ethylenedioxy)-4-(*p*-fluorophenyl)butyl]-2-methylpiperazine** as an oil, which was used in the next step without further purification: IR (film) 1600, 1520, 1240 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.50 (d, 3H, CH_3), 2.20 (m, 4H, $NCH_2CH_2CH_2$), 3.10 (m, 2H, NCH_2), 3.50−4.00 (m, 7H, piperazine), 4.00−4.20 (2 m, 4H, OCH_2CH_2O), 4.50 (s, 2H, CH_2Ar), 7.00 (t, J = 9 Hz, 4H, Ar-H), 7.60 (m, 4H, Ar-H).

The crude ketal was dissolved in 300 mL of ethanol and 100 mL of aqueous 6 M HCl, and the resulting solution was heated at 70 °C for 2 h. Then, the solvent was evaporated under vacuum, and the residue was crystallized from absolute ethanol to afford 25.6 g (55%) of **3**: mp 210−212 °C; IR (KBr) 2560, 2480, 1680, 1600, 1230 cm^{-1}; ^{1}H NMR (CD_3OD) δ 1.67 (d, 3H, CH_3), 2.25 (m, 2H, NCH_2CH_2), 3.40 (m, 4H, NCH_2 and CH_2C=O), 3.50−4.00 (m, 7H, piperazine), 4.55 (s, 2 H, CH_2-Ph), 7.20 (t, J = 9 Hz, 4H, Ar-H), 7.70 (dd, J = 9 and 5 Hz, 2H, benzyl-2H and -6H), 8.10 (dd, J = 9 and 5 Hz, 2H, benzoyl-2H and -6H). Anal. ($C_{22}H_{26}F_2N_2O$·2HCl) C, H, N, Cl.

Method C: 1-[4-(*p*-Fluorophenyl)-4-hydroxybutyl]-4-(*p*-fluorobenzyl)-2-methylpiperazine (4). Sodium borohydride (3.2 g, 85 mmol) was added portionwise to a solution of 11.5 g (27 mmol) of ketone **3** in 1 L of absolute EtOH, and the mixture was stirred at room temperature for 24 h. Then, the solution was acidified with 6 M HCl and concentrated. The residue was dissolved in CH_2Cl_2, washed with diluted NaOH solution and with water, and evaporated. The resulting oil was dissolved in 2-propanol and precipitated by dropwise addition of an isopropanolic solution of HCl. The solid was collected and recrystallized from isopropanol to afford 7.7 g (67%) of **4**: mp 204−207 °C; IR (KBr) 3390, 2440, 1510, 1220 cm^{-1}; ^{1}H NMR (CD_3OD) δ 1.55 (d, 3H, CH_3), 1.90 (m, 4H, $NCH_2CH_2CH_2$), 3.45 (m, 2H, NCH_2), 3.55−4.00 (m, 7H, piperazine), 4.52 (s, 2H, CH_2Ph), 4.70 (m, 1H, C*H*OH), 7.08 (t, J = 9 Hz, 2H, Ph-3H and −5H), 7.20 (t, J = 9 Hz, 2H, Ph′-3H and -5H), 7.44 (dd, J = 9 and 5 Hz, 2H, Ph-2H and 6-H), 7.70 (dd, J = 9 and 5 Hz, 2H, Ph′-2H and 6-H). Anal. ($C_{22}H_{28}F_2N_2O$·2HCl) C, H, N, Cl.

1-(4-Fluorobenzyl)-3-methylpiperazine (36). A mixture of 60 g (0.6 mol) of 2-methylpiperazine, 87 g (0.6 mol) of 4-fluorobenzyl chloride, and 150 g (1.8 mol) of $NaHCO_3$ in 500 mL of EtOH was heated to reflux for 24 h. The cooled solution was filtered and evaporated under vacuum. The residue was dissolved in 500 mL of 1 M HCl and washed with CH_2Cl_2. The aqueous solution was then basified to pH 13 with NaOH and extracted with CH_2Cl_2. Evaporation gave 80 g (64%) of crude **36**. A sample was purified by distillation at 75−77 °C/0.1 mmHg: IR (neat) 1610, 1510, 1230 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.08 (d, J = 6 Hz, 3H, CH_3), 1.49 (s, 1H, NH), 1.70 (t, J = 10.5 Hz, 1H, 3-H$_{ax}$), 2.02 (dt, J = 11 and 7 Hz, 1H, 5-H$_{ax}$), 2.60−3.00 (m, 5H, piperazine), 3.49 (s, 2H, $PhCH_2$), 7.00 (t, J = 9 Hz, 2H, Ph-3H and -5H), 7.30 (dd, J = 9 and 6.5 Hz, 2H, Ph-2H and -6H). Anal. ($C_{12}H_{17}FN_2$) C, H, N.

***N*-(4-Fluorobenzyl)-*N*,*N*′-dimethylethanediamine (38).** Operating as above, from 50 g (0.57 mol) of *N*,*N*′-dimethylethanediamine and 72 g (0.57 mol) of 4-fluorobenzyl chloride was obtained the title compound, which was purified by distillation at 65−67 °C/ 0.01 mmHg to afford 47 g (42%) of pure **38**: IR (neat) 1610, 1510, 1220 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ

1.45 (s, 1H, NH), 2.11 (s, 3H, NCH_3), 2.27 (s, 3H, NCH_3), 2.41 (t, J = 6 Hz, 2H, NCH_2), 2.57 (t, J = 6 Hz, 2H, NCH_2), 3.44 (s, 2H, $PhCH_2$), 7.12 (t, J = 9 Hz, 2H, Ph-3H and -5H), 7.32 (dd, J = 9 and 6.5 Hz, 2H, Ph-2H and -6H). Anal. ($C_{11}H_{17}FN_2$) C, H, N.

1-(4-Fluorobenzoyl)-3-methylpiperazine (39). A solution of 40 g (0.4 mol) of 2-methylpiperazine and 150 g (1.79 mol) of $NaHCO_3$ in 500 mL of H_2O was diluted with 300 mL of acetone and cooled in an ice bath. Then, a solution of 70.5 g (0.44 mol) of 4-fluorobenzoyl chloride in 200 mL of acetone was added dropwise at a temperature lower than 10 °C, and the mixture was allowed to warm to room temperature and stirred for further 1.5 h. The reaction mixture was concentrated under vacuum to a volume of 500 mL and was extracted with three portions of CH_2Cl_2. The crude product was purified on column chromatography (1:9 MeOH−$CHCl_3$) to give 46 g (48%) of **39** as an oil: IR (neat) 3100−3500, 1630, 1510, 1440, 1280, 1220 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10 (d, J = 6 Hz, 3H, CH_3), 2.10 (s, 1H, NH), 2.50−3.10 (m, 5H, piperazine), 3.60 (m, 1H, 6-H_{eq}), 4.55 (m, 1H, 2-H_{eq}), 7.11 (t, J = 9 Hz, 2H, Ph-3H and -5H), 7.41 (dd, J = 9 and 6.5 Hz, 2H, Ph-2H and -6H). Anal. ($C_{12}H_{15}FN_2O$) C, H, N.

1-[(4-Methylphenyl)sulfonyl]-3-methylpiperazine (40). Operating as above, from 22.6 g (0.22 mol) of 2-methylpiperazine and 50 g (0.26 mol) of *p*-toluenesulfonyl chloride was obtained 35 g (57%) of **40** as a solid of mp 112−114 °C: IR (KBr) 1620, 1470, 1340, 1170 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.02 (d, J = 6 Hz, 3H, piper-CH_3), 1.42 (s, 1H, NH), 1.88 (t, J = 10.6 Hz, 1H, 3-H_{ax}), 2.25 (td, J = 11 and 4 Hz, 1 H, 5-H_{ax}), 2.43 (s, 3H, $PhCH_3$), 2.84−3.04 (m, 3H, piperazine), 3.60 (br d, J = 11 Hz, 2H, piper), 7.35 (d, J = 8 Hz, 2H, Ph-3H and -5H), 7.62 (d, J = 8 Hz, 2H, Ph-2H and -6H). Anal. ($C_{12}H_{18}N_2O_2S$) C, H, N, S.

4-[1-(4-Fluorophenyl)-1-methoxymethyl]piperidine (46). A mixture of 4-(4-fluorobenzoyl)piperidine (**42**) (10 g, 48 mmol), di-*tert*-butyl dicarbonate (10.5 g, 48 mmol), and triethylamine (10 mL) in tetrahydrofuran (50 mL) was stirred overnight at room temperature. Then, the solvent was evaporated and the residue was dissolved in benzene, washed with diluted HCl and water, and evaporated to afford 12 g (83%) of **1-(*tert*-butoxycarbonyl)-4-(4-fluorobenzoyl)piperidine (43)** as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.47 (s, 9H, *t*-Bu), 1.60−1.80 (m, 2H, 3-H_{ax} and 5-H_{ax}), 1.80−1.90 (m, 2H, 3-H_{eq} and 5-H_{eq}), 2.88 (br t, J = 11 Hz, 2H, 2-H_{ax} and 6-H_{ax}), 3.39 (tt, J = 11 and 3 Hz, 1H, 4-H), 4.18 (br d, J = 11 Hz, 2H, 2-H_{eq} and 6-H_{eq}), 7.15 (t, J = 9 Hz, 2H, Ph-3H and -5H), 7.98 (dd, J = 9 and 6.5 Hz, 2H, Ph-2H and -6H).

To a solution of **43** (10 g, 33 mmol) in 100 mL of ethanol was added 2 g of sodium borohydride, and the mixture was stirred for 2 h at room temperature. The solution was evaporated, and the residue was redissolved in benzene, poured onto ice water, and acidified with HCl to pH 5−6. The organic extract was washed with water and evaporated to give 5.9 g (59%) of **1-(*tert*-butoxycarbonyl)-4-[1-(4-fluorophenyl)-1-hydroxymethyl]piperidine (44)** as an oil which was used without further purification: ^1H NMR ($CDCl_3$) δ 1.00−1.20 (m, 1H, 4-H), 1.20−1.30 (m, 2H, 3-H_{ax} and 5−H_{ax}), 1.43 (s, 9H, *t*-Bu), 1.70 (m, 1H, 3-H_{eq}), 1.92 (br d, J = 11 Hz, 1H, 5-H_{eq}), 2.50−2.70 (m, 2H, 2-H_{ax} and 6-H_{ax}), 4.00−4.20 (m, 2H, 2-H_{eq} and 6-H_{eq}), 4.36 (d, J = 6 Hz, 1H, C*H*OH), 7.02 (t, J = 9 Hz, 2H, Ph-3H and -5H), 7.26 (dd, J = 9 and 6.5 Hz, 2H, Ph-2H and -6H).

Sodium hydride (0.8 g of 80% dispersion in paraffin), previously washed with hexane, was suspended in 25 mL of anhydrous tetrahydrofuran, and 5 g (16 mmol) of **44** was added. The mixture was stirred for 30 min at room temperature, and then 2 mL (32 mmol) of iodomethane was added. After further stirring for 16 h, the solvent was evaporated, and the residue was dissolved in chloroform. The solution was poured into ice−water and neutralized by addition of HCl. Evaporation of the organic extract afforded 5 g (96%) of crude **1-(*tert*-butoxycarbonyl)-4-[1-(4-fluorophenyl)-1-methoxymethyl]piperidine (45):** ^1H NMR ($CDCl_3$) δ 1.00−1.30 (m, 3H, 3-H_{ax}, 5-H_{ax}, and 4-H), 1.44 (s, 9H, *t*-Bu), 1.70 (m, 1H, 3-H_{eq}), 1.92 (br d, J = 11 Hz, 1H, 5-H_{eq}), 2.45−2.65 (m, 2H, 2-H_{ax} and 6-H_{ax}), 3.16 (s, 3H, OCH_3), 3.78 (d, J = 6 Hz, 1H, C*H*OCH_3), 3.95−4.15 (m, 2H, 2-H_{eq} and 6-H_{eq}), 7.03 (t, J = 9 Hz, 2H, Ph-3H and -5H), 7.20 (dd, J = 9 and 6.5 Hz, 2H, Ph-2H and -6H).

A solution of **45** (5 g, 15 mmol) in 35 mL of ethanol and 35 mL of 4 M HCl was stirred at room temperature for 1 h, and the ethanol was removed in vacuo. The aqueous solution was washed with benzene and then was basified to pH 14 by addition of NaOH and extracted with chloroform. The chloroform extracts were dried and evaporated to give 2.4 g (69%) of **4-[1-(4-fluorophenyl)-1-methoxymethyl]piperidine (46)** as an oil which solidified on standing: mp 73−76 °C; IR (KBr) 3270, 1610, 1510, 1230, 1090 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00−1.30 (m, 3H, 3-H_{ax}, 5-H_{ax}, and 4-H), 1.62 (m, 1H, 3-H_{eq}), 2.00 (br d, J = 11 Hz, 1H, 5-H_{eq}), 2.18 (br s, 1H, NH), 2.40−2.60 (2 overlapped t, 2H, 2-H_{ax} and 6-H_{ax}), 2.98 (br d, J = 12 Hz, 1 H, 2-H_{eq}), 3.10 (br d, J = 12 Hz, 1H, 6-H_{eq}), 3.16 (s, 3H, OCH_3), 3.78 (d, J = 6 Hz, 1H, C*H*OCH_3), 7.02 (t, J = 9 Hz, 2H, Ph-3H and -5H), 7.20 (dd, J = 9 and 6.5 Hz, 2H, Ph-2H and -6H); ^{13}C NMR ($CDCl_3$) δ 29.36 and 30.06 (3-C and 5-C), 43.02 (4-C), 46.29 and 46.36 (2-C and 6-C), 56.70 (OCH_3), 87.78 (C*H*OCH_3), 114.84 (d, J = 22 Hz, Ph-3C and -5C), 128.65 (Ph-2C and -6C), 135.90 (Ph-1C), 161.93 (d, J = 260 Hz, Ph-4C). Anal. ($C_{13}H_{18}FNO$) C, H, N.

Method D: 7-Hydroxy-2-(trifluoromethyl)chromen-4-one (47). A mixture of 1-(2,4-dihydroxyphenyl)ethanone (10 g, 66 mmol), sodium trifluoroacetate (16.6 g, 122 mmol), and trifluoroacetic anhydride (39 mL, 277 mmol) was heated in an oil bath, allowing excess trifluoroacetic anhydride to distill off until the internal temperature was about 125 °C, and then stirred at this temperature for 40 h. The cooled solution was treated with 100 mL of 3 M HCl, and the resulting suspension was stirred for 2 h at room temperature. The solid was collected, suspended in H_2O, warmed at 40 °C, and dissolved by addition of a solution of NaOH to pH 9. The solution was filtered and then precipitated by dropwise addition of HCl. The solid was collected by filtration, washed with water, and vacuum-dried to afford pure **47** (10.3 g, 68%): mp 208−210 °C; IR (KBr) 3400−3600, 1665, 1560, 1250 cm^{-1}; ^1H NMR (CD_3COCD_3) δ 3.60 (br, 1H, OH), 6.75 (s, 1H, 3-H), 7.03 (d, J = 2.3 Hz, 1H, 8-H), 7.10 (dd, J = 8.8 and 2.3 Hz, 1H, 6-H), 8.01 (d, J = 8.8 Hz, 1H, 5-H); ^{13}C NMR (CD_3COCD_3) δ 103.33 (8-C), 111.11 (3-C), 116.65 (6-C), 117.58 (4a-C), 119.61 (q, J = 271 Hz, CF_3), 127.87 (5-C), 151.68 (q, J = 37.5 Hz, 2-C), 158.06 (8a-C), 164.26 (7-C), 175.64 (4-C). Anal. ($C_{10}H_5F_3O_3$) C, H.

Method E: 7-Hydroxy-3-methylchromen-4-one (50). To an ice bath cooled suspension of 1-(2,4-dihydroxyphenyl)-1-propanone (75 g, 0.45 mol) in 750 mL (4.5 mol) of triethyl orthoformate was added dropwise over a 30 min period 66 mL of 70% perchloric acid (0.77 mol). The mixture was heated for 5 h at 50 °C, and then the resulting solution was concentrated to a volume of 500 mL and poured dropwise on 2500 mL of ice−water. The suspension that resulted was stirred while allowing to warm to room temperature, and the solid was collected by filtration, washed with water, and vacuum-dried to afford 77 g (97%) of pure **50**. A sample was crystallized from EtOH−H_2O: mp 231−234 °C (lit.[23] mp 222−24 °C).

Method F: 7-(3-Chloropropoxy)-3-methylchromen-4-one (58). A mixture of 30 g (0.17 mol) of 7-hydroxy-3-methylchromen-4-one (**51**), 25 mL (0.25 mol) of 1-bromo-3-chloropropane, and 35 g (0.25 mol) of anhydrous potassium carbonate in 200 mL of acetone was stirred at reflux for 24 h. After removal of the insoluble solids by filtration, the solution was evaporated under vacuum. The residue was stirred with diethyl ether, and the resulting solid was filtered and vacuum-dried to afford 27 g (63%) of **58**.

A sample was recrystallized from Et_2O: mp 83−85 °C. IR (KBr) 1640, 1600, 1240 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.00 (s, 3H, CH_3), 2.28 (quint, J = 6 Hz, 2H, OCH_2CH_2), 3.76 (t, J = 6 Hz, 2H , CH_2Cl), 4.19 (t, J = 6 Hz, 2H, OCH_2), 6.80 (d, J = 2.3 Hz, 1H, 8-H), 6.93 (dd, J = 9 and 2.3 Hz, 1H, 6-H), 7.71 (d, J = 0.9 Hz, 1H, 2-H), 8.12 (d, J = 9 Hz, 1H, 5-H); ^{13}C NMR ($CDCl_3$) δ 11.08 (CH_3), 31.81 (OCH_2CH_2), 41.12 (CH_2Cl), 64.69 (OCH_2), 100.48 (8-C), 114.32 (6-C), 117.55 (4a-C), 120.34 (3-C), 127.00 (5-C), 151.12 (2-C), 158.11 (8a-C), 162.58 (7-C), 177.42 (4-C). Anal. ($C_{13}H_{13}ClO_3$) C, H, Cl.

1-[4-(3-Chloropropoxy)-2-hydroxyphenyl]-1-ethanone (52). A mixture of 50 g (0.33 mol) of 2′,4′-dihydroxyacetophenone, 50 mL (0.50 mol) of 1-bromo-3-chloropropane, and 65 g (0.47 mol) of anhydrous potassium carbonate in 700 mL of acetone was heated at reflux for 16 h. The cooled solution was filtered to remove the insoluble solids, and the solvent was evaporated under vacuum. The residue was suspended in MeOH, filtered, and vacuum-dried to afford 52 g (69%) of **52** as a white solid. A sample was recrystallized from EtOAc−hexane (1:2): mp 73−74 °C; IR (KBr) 3200−3600, 1650, 1590, 1285, 1160 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.25 (quint, J = 6 Hz, 2H, OCH_2CH_2), 2.56 (s, 3H, CH_3), 3.73 (t, J = 6 Hz, 2H, CH_2Cl), 4.15 (t, J = 6 Hz, 2H, OCH_2), 6.42 (m, 2H, 3-H and 5-H), 7.63 (d, J = 8.1 Hz, 1H, 6-H), 12.73 (s, 1H, OH). Anal. ($C_{11}H_{13}ClO_3$) C, H, Cl.

(*E*)-1-[4-(3-Chloropropoxy)-2-hydroxyphenyl]-3-(dimethylamino)-1-propenone (53). A mixture of **52** (6 g, 26 mmol) and 5.2 mL (39 mmol) of dimethylformamide dimethyl acetal was heated at reflux for 3.5 h. The resulting solution was evaporated under vacuum, and the residue was suspended in 40 mL of ether. The solid that formed was filtered and dried to afford 5.6 g (75%) of **53**: mp 119−121 °C; IR (KBr) 3200−3600, 1620, 1530, 1350, 1235, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.24 (quint, J = 6 Hz, 2H, OCH_2CH_2), 2.96 (br s, 3H, NCH_3), 3.18 (br s, 3H, NCH_3), 3.73 (t, J = 6 Hz, 2H, CH_2Cl), 4.13 (t, J = 6 Hz, 2H, OCH_2), 5.68 (d, J = 12 Hz, 1H, =CH−N), 6.38 (d, J = 8.6 Hz, 1H, Ph-5H), 6.41 (s, 1H, Ph-3H), 7.61 (d, J = 8.6 Hz, 1H, Ph-6H), 7.84 (d, J = 12 Hz, 1H, =CH−CO); ^{13}C NMR ($CDCl_3$) δ 31.96 (OCH_2CH_2), 37.28 (NCH_3), 41.25 (CH_2Cl), 45.20 (NCH_3), 64.15 (OCH_2), 89.59 (=CHN), 101.48 (Ph-3C), 106.31 (Ph-5C), 113.81 (Ph-1C), 129.45 (Ph-6C), 153.73 (CO−CH=), 163.04 (Ph-2C), 165.13 (Ph-4C), 190.17 (C=O). Anal. ($C_{14}H_{18}ClNO_3$) C, H, Cl, N.

7-(3-Chloropropoxy)chromen-4-one (54). To a cooled solution of 3 g (11 mmol) of **53** in 60 mL of chloroform were added 2 mL of a 5.6 M solution of HCl in ethanol, and the mixture was stirred at room temperature for 15 min. The chloroformic solution was washed with water and with a saturated solution of $NaHCO_3$. Evaporation of the dried extracts gave a solid, which was suspended in ether, filtered, and dried to afford 2 g (70%) of **54**: mp 76−78 °C (lit.[22] mp 70−74 °C).

Method G: 3-Chloro-7-(3-chloropropoxy)chromen-4-one (60). To a solution of 4.5 g (16 mmol) of **53** in 60 mL of chloroform was added at 0−5 °C a solution of 1.9 g (16 mmol) of *tert*-butyl hypochlorite in 40 mL of chloroform. Then, the mixture was stirred for 4 h at room temperature and evaporated. The residue was washed with diisopropyl ether to afford 2.9 g (67%) of **60**: mp 101−103 °C; IR (KBr) 1635, 1610, 1255, 1220 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.30 (quint, J = 6 Hz, 2H, OCH_2CH_2), 3.77 (t, J = 6 Hz, 2H, CH_2Cl), 4.23 (t, J = 6 Hz, 2H, OCH_2), 6.87 (d, J = 2.4 Hz, 1H, 8-H), 7.02 (dd, J = 9 and 2.4 Hz, 1H, 6-H), 8.10 (s, 1H, 2-H), 8.16 (d, J = 9 Hz, 1H, 5-H); ^{13}C NMR ($CDCl_3$) δ 31.81 (OCH_2CH_2), 41.08 (CH_2Cl), 65.00 (OCH_2), 100.72 (8-C), 115.38 (6-C), 117.20 (4a-C), 120.61 (3-C), 127.50 (5-C), 151.53 (2-C), 157.58 (8a-C), 163.25 (7-C), 171.51 (4-C). Anal. ($C_{12}H_{10}Cl_2O_3$) C, H, Cl.

7-(3-Chloropropoxy)-3-fluorochromen-4-one (61). A solution of 1 g (3.5 mmol) of **53** and 1.2 g (3.5 mmol) of 85% 1-fluoro-2,4,6-trimethylpyridinium triflate in 10 mL of dichloromethane and 10 mL of acetonitrile was heated at reflux for 1 h. After cooling to room temperature, an additional 0.5 g (1.5 mmol) of fluoropyridinium triflate was added, and the solution was stirred for 2 h at room temperature. Then, the solution was poured onto diluted hydrochloric acid and was stirred for 15 min. The organic extract was washed with diluted HCl and evaporated to give 1 g of crude **61**, which was purified on column chromatography (3:1 C_6H_6−Et_2O) to afford 0.6 g (66%) of title compound: mp 89−91 °C; ^1H NMR ($CDCl_3$) δ 2.30 (quint, J = 6 Hz, 2H, OCH_2CH_2), 3.77 (t, J = 6 Hz, 2H, CH_2Cl), 4.22 (t, J = 6 Hz, 2H, OCH_2), 6.88 (d, J = 2.4 Hz, 1H, 8-H), 7.00 (dd, J = 9 and 2.4 Hz, 1H, 6-H), 8.08 (d, J = 3.6 Hz, 1H, 2-H), 8.16 (d, J = 9 Hz, 1H, 5-H). Anal. ($C_{12}H_{10}ClFO_3$) C, H, Cl.

7-(3-Chloropropoxy)-3-formylchromen-4-one (62). Phosphoryl chloride (30 mL, 214 mmol) was added dropwise to a cooled solution (0 °C) of **52** (20 g, 87 mmol) in 80 mL of *N*,*N*-dimethylformamide. The solution was stirred at 0 °C for 30 min, and for 16 h at room temperature. Then, it was poured onto ice, extracted with $CHCl_3$, washed with water, and evaporated to give crude **62**, which was purified by column chromatography ($CHCl_3$) to afford the title compound (12 g, 51%) as an oil which solidified on standing: mp 105−108 °C dec; IR (KBr) 1695, 1650, 1620 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.31 (quint, J = 6 Hz, 2H, OCH_2CH_2), 3.78 (t, J = 6 Hz, 2H, CH_2Cl), 4.25 (t, J = 6 Hz, 2H, OCH_2), 6.94 (d, J = 2 Hz, 1H, 8-H), 7.04 (dd, J = 9 and 2 Hz, 1 H, 6-H), 8.18 (d, J = 9 Hz, 1H, 5-H), 8.47 (s, 1H, 2-H), 10.35 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$) δ 31.73 (OCH_2CH_2), 41.02 (CH_2Cl), 65.07 (OCH_2), 101.55 (8-C), 115.53 (6-C), 118.72 (4a-C), 120.01 (3-C), 127.31 (5-C), 157.58 (8a-C), 160.01 (2-C), 163.64 (7-C), 174.88 (4-C), 188.45 (CHO). Anal. ($C_{13}H_{11}ClO_4$) C, H, Cl.

7-(3-Chloropropoxy)-3-(hydroxymethyl)chromen-4-one (63). To an ice−salt bath cooled solution of 2.5 g (9.4 mmol) of **62** in 15 mL of $CHCl_3$ and 15 mL of absolute EtOH was added portionwise 0.2 g (5.3 mmol) of sodium borohydride. The solution was stirred for 15 min at −10 °C and for a further 1 h at 0 °C, poured on ice−water, neutralized with HCl, and extracted with $CHCl_3$. The crude product was purified by column chromatography (MeOH−$CHCl_3$, 2:98) to afford 1 g (40%) of the title compound: mp (Et_2O) 102−104 °C; IR (KBr) 3330, 1638, 1625, 1590, 1445, 1270 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.30 (quint, J = 6 Hz, 2H, OCH_2CH_2), 3.24 (t, J = 6.4 Hz, 1H, OH), 3.77 (t, J = 6 Hz, 2H, CH_2Cl), 4.22 (t, J = 6 Hz, 2H, OCH_2), 4.56 (d, J = 6.4 Hz, 2H, CH_2OH), 6.85 (d, J = 2.4 Hz, 1H, 8-H), 6.98 (dd, J = 9 and 2.4 Hz, 1H, 6-H), 7.87 (s, 1H, 2-H), 8.11 (d, J = 9 Hz, 1H, 5-H); ^{13}C NMR ($CDCl_3$) δ 31.77 (OCH_2CH_2), 41.02 (CH_2Cl), 58.55 (CH_2OH), 64.17 (OCH_2), 100.65 (8-C), 114.75 (6-C), 117.60 (4a-C), 122.81 (3-C), 126.75 (5-C), 151.94 (2-C), 158.01 (8a-C), 162.98 (7-C), 177.42 (4-C). Anal. ($C_{13}H_{13}ClO_4$) C, H, Cl.

Pharmacological Methods. General. Subjects were either male Swiss Albino mice (20−24 g) or male Sprague−Dawley rats (180−200 g), and 8−12 individuals were used per dose group. Animals were placed in cages and allowed for adaptation two hours before each assay. Test compounds were administered as suspensions in 0.25% agar in water, and dosing volume was 1 mL/100 g of body weight.

Inhibition of Apomorphine-Induced Climbing Behavior in Mice. A modification of the method of Protais et al.[25] was used. Mice received either the test drug or the vehicle alone 30 min (for ip administration) or 60 min (for po administration) prior to apomorphine challenge (1 mg/kg, sc) and were individually placed in transparent vertical polymethacrylate boxes (11 × 7.5 × 4.5 cm) with one of the broad lateral walls formed by a wire reticle of 3 mm mesh. Animals were then observed for climbing behavior at 10, 20, and 30 min. Climbing was scored as follows: all four feet on the floor cage, 0; three feet on the floor, 1; two feet on the floor, 2; one foot on the floor, 3; and all four feet off the cage floor, 4. Percent inhibition of apomorphine was calculated by the difference from total score of treated subjects to total score of control animals, and referring it to total score of control group set to 100%. ED_{50} values, with 95% confidence limits, were calculated by linear regression analysis.

Inhibition of Apomorphine-Induced Hyperactivity in Mice.[26] Animals were either dosed with vehicle or with test compounds, and after 30 min (for ip administration) or 60 min (for po administration), mice were challenged with 1 mg/kg (sc) of apomorphine. Then, animals were placed in groups of three per cage on a Panlab Actisystem D. A. S. 16 v. 1 activity meter, and the motility was recorded through a 90 min period. The percent inhibition of treated groups was recorded with respect to control group.

Inhibition of Apomorphine-Induced Stereotypy in Rats. The procedure is a modification of Puech et al.[27] Rats were dosed with vehicle or with test compounds 30 min prior to apomorphine (1.5 mg/kg, sc) and were placed individually in transparent observation cages. At 10, 20, and 30 min, animals were observed for the presence of stereotyped behavior, which was scored as follows: any abnormal movement, 0;

slight head rotation movements and intermittent sniffing, 1; intense head movements, mild licking, and continuous sniffing, 2; and intense sniffing, licking, and gnawing, 3. Results are expressed as percent inhibition of treated groups with respect to controls.

Catalepsy in Rats.[28] Rats were dosed with vehicle or with test compounds. At 30, 60, 90, 120, 180, and 300 min after dosing, each rat's forepaws were elevated by placing them on a wooden bar 9 cm high, and then, on a bar 3 cm high. It was scored 1 for each forepaw that remained on the 9 cm bar for 10 s and 0.5 for each forepaw on the 3 cm bar. Additionally, a homolateral leg crossing was effected, and was scored 1 if position was maintained for 10 s. For each dosage group, scores were totaled, and results are expressed as percent with respect to maximum possible score (4 for each animal).

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