7-[3-(1-Piperidinyl)propoxy]chromenones as Potential Atypical Antipsychotics. 2. Pharmacological Profile of 7-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-piperidin-1-yl]propoxy]-3-(hydroxymethyl)chromen-4-one (Abaperidone, FI-8602)

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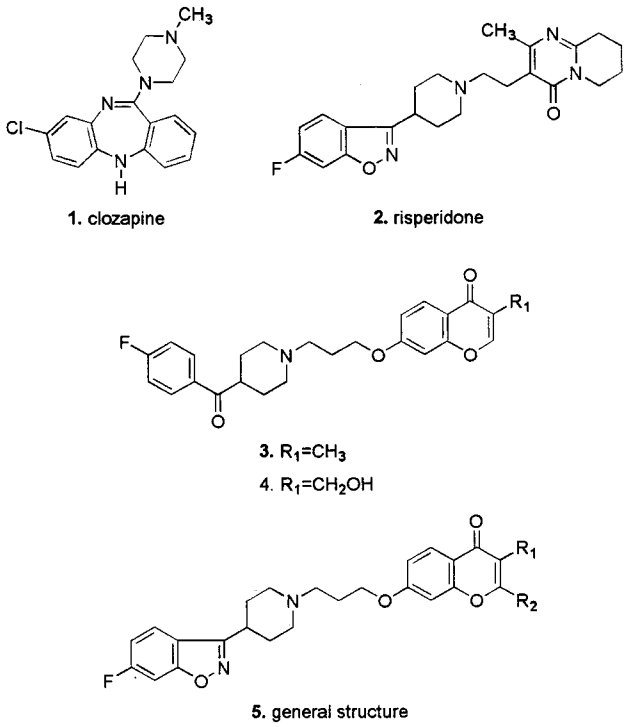
Received May 29, 1998

A series of novel 7-[3-(1-piperidinyl)propoxy]chromenones was synthesized and tested as potential antipsychotics in several in vitro and in vivo assays. The compounds possessed good affinity for D_2 receptors, together with a greater affinity for 5-HT_2 receptors, a profile which has been proposed as a model for atypical antipsychotics. Several agents also displayed a high potency in the climbing mice assay on oral administration, suggesting a potent antipsychotic effect as compared to reference standards. Compound **23** was selected for further pharmacological evaluation. Induction of catalepsy and inhibition of stereotypies weaker than standards, along with a lower increase in serum prolactin levels, were indicative of a potential atypical profile for this compound. From these results, 7-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]propoxy]-3-(hydroxymethyl)chromen-4-one (**23**, abaperidone) has been proposed for clinical evaluation in humans as a potential atypical antipsychotic.

Introduction

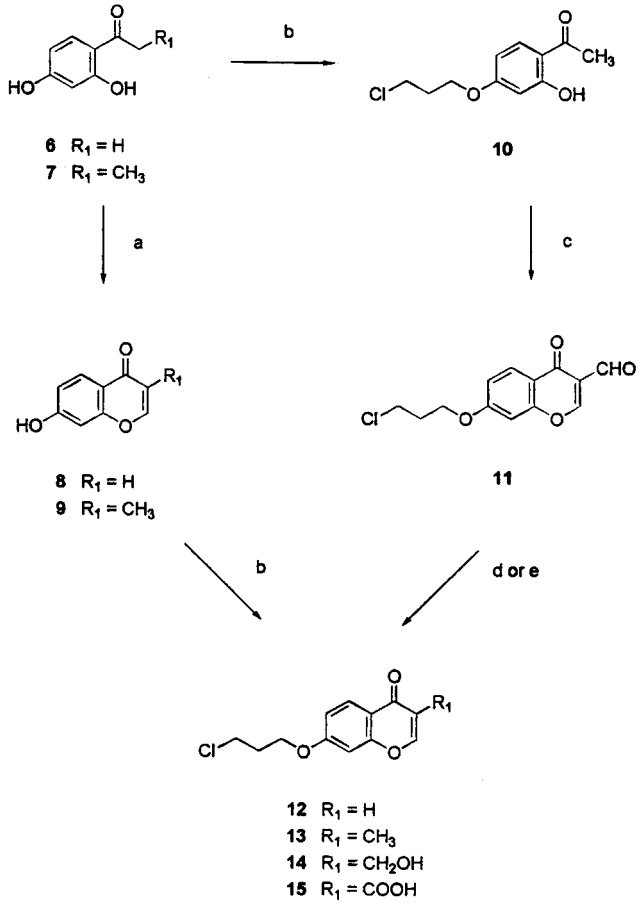
Conventional neuroleptics such as chlorpromazine, fluphenazine, and haloperidol are recognized as effective agents in the treatment of positive symptoms of schizophrenia, namely hallucinations and delusions. However, they show poor or no efficacy against negative symptoms[1] (apathy, social withdrawal), and their use is frequently associated with serious side effects, such as extrapyramidal syndrome,[2] tardive dyskinesia,[3] and hyperprolactinemia.[4] A common feature of these compounds is antagonism at dopamine D_2 receptors, which has been correlated with the pharmacological potencies of the drugs.[5] This fact constitutes one of the supports of the hypothesis that postulates an increase in dopaminergic activity at the mesolimbic system of the brain as the biochemical basis of schizophrenia.[6] On the other hand, many side effects of classical antipsychotics are also associated with dopamine antagonism,[7] in particular extrapyramidal effects (dopamine blockade at the nigrostriatal system) and hyperprolactinemia (dopamine blockade at the pituitary dopamine receptors). The so-called "atypical antipsychotics" have been effective against positive and negative symptoms of schizophrenia while showing a reduced propensity to induce extrapyramidal effects.[8] Clozapine (**1**), the prototype of these drugs, has other severe undesirable effects, such as agranulocytosis and seizures, that have restricted its therapeutic application.[9] At present, the need for novel antipsychotic drugs as safe substitutes for clozapine still remains a challenge in the pharmacological research of schizophrenia. Attempts to explain the particular mechanism of action of clozapine are hampered by the binding of this drug to a variety of central nervous system receptors,[10] and thus, a number of theories have been proposed to explain the atypical antipsychotic profile. Serotonin antagonism at 5-HT_{2A} receptors has been reported to improve the negative symptoms of schizophrenia and to reduce the occurrence of extrapyramidal side effects.[11] According to this, one of the most accepted theories proposes that an affinity for 5-HT_{2A} higher than for D_2 receptor accounts for the atypical antipsychotic profile,[12] and compounds possessing this property are being developed as potential atypical antipsychotics. Among them, risperidone (**2**) has been launched. Other atypical antipsychotics, chemically related to clozapine, include olanzapine and quetiapine. In recent years, the discovery of new subtypes of dopamine receptors has

Chart 1. Some Typical and Atypical Antipsychotics



10.1021/jm9810396 CCC: $15.00
Published on Web 12/11/1998

Scheme 1. Synthesis of 3-Substituted Chromenones[a]

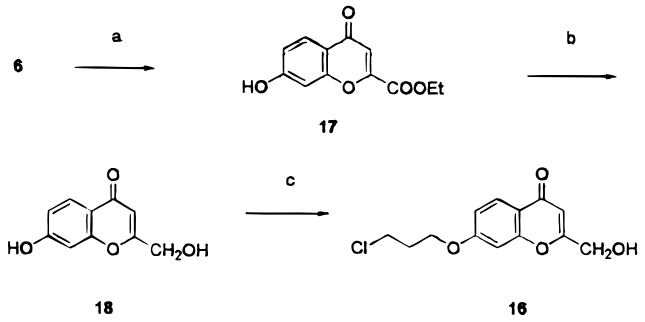


[a] Reagents: (a) $HC(OEt)_3$, $HClO_4$; (b) $Br(CH_2)_3Cl$, K_2CO_3, acetone; (c) $POCl_3$, DMF; (d) for **14**, $NaBH_4$, MeOH, CH_2Cl_2; (e) for **15**, $NaClO_2$, NH_2SO_3H, H_2O, CH_2Cl_2.

received considerable interest as possible targets for novel antipsychotic drugs.[13] Thus, preferential affinities for D_3[14] or D_4[15] receptors have been proposed as models for atypical antipsychotics. In vivo assays in animal behavioral models are assumed to predict a potential atypical profile. Thus, induction of catalepsy and inhibition of apomorphine-induced stereotyped behavior (characteristics 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) are recognized as a means to identify novel atypical antipsychotics.[16]

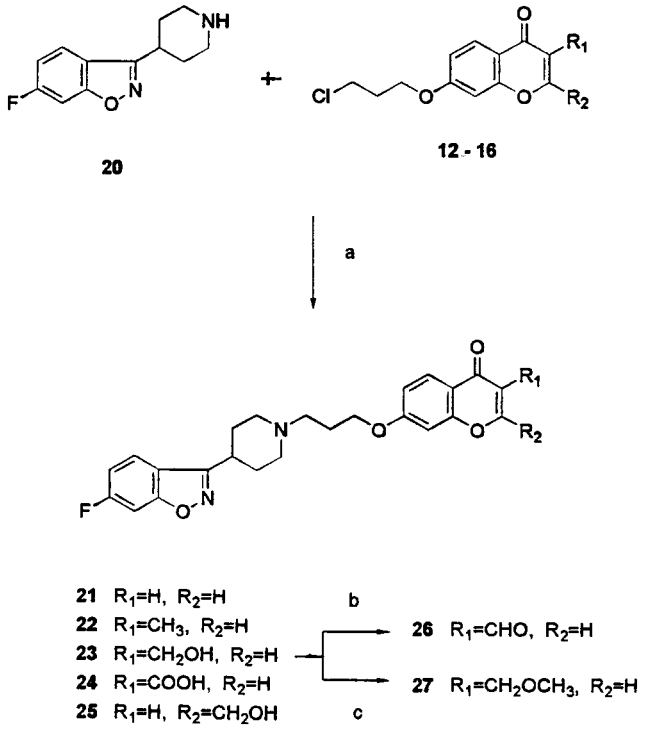
In a previous paper, we described the discovery of potential atypical antipsychotics possessing a 7-[3-(1-piperidinyl)propoxy]chromenone framework.[17] The most potent compounds in this series were the 3-substituted chromenones **3** and **4** (Chart 1), which in behavioral models demonstrated activities suggestive of high oral antipsychotic efficacy, along with a minimal induction of extrapyramidal side effects. In the search for more potent and safer drugs, we decided to extend our investigations to the benzisoxazolyl piperidine derivatives as a structural modification for the benzoyl piperidine moiety. Bioisosterism between both groups has been proved in this[18] and other[19] therapeutic areas. Here, we report the synthesis and biological evaluation of a series of benzisoxazolyl piperidines with the general structure **5**. This research has resulted in the discovery

Scheme 2. Synthesis of 2-Substituted Chromenones[a]



[a] Reagents: (a) (1) $(COOEt)_2$, NaOEt, EtOH, (2) HCl, EtOH; (b) $NaBH_4$, $CaCl_2$, EtOH; (c) $Br(CH_2)_3Cl$, K_2CO_3, $(CH_3)_2CO$.

Scheme 3. Synthesis of Target Compounds[a]



[a] Reagents and conditions: (a) K_2CO_3, CH_3CN, reflux; (b) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, −70 °C to rt; (c) HCl, MeOH, reflux.

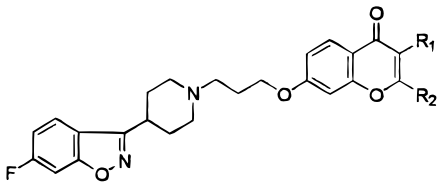
of some very active compounds, with high receptor binding affinities and excellent in vivo profiles on oral administration. Compound **23** (abaperidone, FI-8602) has been selected for clinical development as a putative atypical antipsychotic drug.

Chemistry

The 7-(3-chloropropoxy)chromenones **11**−**16** were the key intermediates for the synthesis of the target compounds. Compounds **11**−**14** were synthesized from 2,4-(dihydroxyphenyl)ketones, as previously reported.[17] From formyl chromenone **11**, alcohol **14** was obtained by sodium borohydride reduction, whereas carboxylic acid **15** was prepared by oxidation of **11** with sodium chlorite (Scheme 1). The 2-substituted chromenone **16** was prepared by calcium borohydride reduction of chromenone-2-carboxylate **17**,[20] followed by alkylation with 1-bromo-3-chloropropane (Scheme 2).

The synthetic methods used in the preparation of the target compounds are shown in Scheme 3. Compounds **21**−**25** were prepared by alkylation of 6-fluoro-3-(4-

Table 1. In Vitro and in Vivo Antipsychotic Activity of 7-[3-(1-Piperidinyl)propoxy]chromenones and Reference Compounds



			binding affinities, IC_{50} (nM)[a]		inhibition of climbing, ED_{50} (mg/kg, po)[b]	induction of catalepsy, ED_{50} (mg/kg, po)[c]
compd	R_1	R_2	D_2 receptor	5-HT_{2A} receptor		
21	H	H	28.1	8.6	1.08 (0.56−1.92)	12.58 (9.40−16.83)
22	CH_3	H	16.6	11.3	0.40 (0.27−0.59)	2.85 (2.19−3.71)
23	CH_2OH	H	17.0	6.2	0.24 (0.22−0.26)	8.48 (7.05−10.18)
24	COOH	H	12.8	0.6	>10	>50
25	H	CH_2OH	31.0	7.2	5.88 (2.19−15.81)	>100
26	CHO	H	13.1	2.1	3.32 (2.57−4.29)	15.93 (9.40−26.99)
27	CH_2OCH_3	H	48.1	1.4	0.27 (0.10−0.65)	6.88 (3.72−12.72)
3			211	25.3	3.01 (1.31−6.42)	38.21 (32.02−45.69)
4			190	32.9	2.02 (0.60−6.80)	13.03 (12.01−14.09)
haloperidol			13.7	104	0.31 (0.14−0.69)	2.0 (1.30−2.61)
clozapine			130	13.0	15.40 (10.13−23.36)	>100
risperidone			27.4	1.4	0.29 (0.24−0.36)	5.0 (4.10−6.25)

[a] IC_{50} values for inhibition of [^{3}H]methylspiperone binding to rat striatal membranes, using unlabeled haloperidol for nonspecific binding (D_2 receptor), and of [^{3}H]ketanserin binding to rat frontal cortex membranes, using unlabeled mianserin for nonspecific binding. IC_{50} values were determined from concentration−response curves of 11-point logarithmic concentrations of the test compounds, each concentration done in duplicate. The SEM for all values was <15%. [b] Inhibition of apomorphine-induced climbing behavior in mice, via oral administration 30 min (see note 22) before apomorphine challenge. Results are expressed as ED_{50} values in mg/kg; 95% confidence limits are shown in parentheses. [c] Induction of catalepsy in rats. Results are expressed as the dose required to produce a 50% of maximum catalepsy score in mg/kg, po; 95% confidence limits are shown in parentheses.

piperidinyl)-1,2-benzisoxazole (**20**)[18a] with the appropriate chloropropoxy chromenones. However, aldehyde **26** could not be obtained by direct alkylation of piperidine **20** with **11**, due to instability of the formyl chromenone in the basic reaction medium. Instead, this compound was prepared by Swern oxidation of alcohol **23** with dimethyl sulfoxide−oxalyl chloride reagent. Alternatively, alcohol **23** was converted into the methyl ether **27** on treatment with methanol and hydrochloric acid.

Results and Discussion

Several different assays were used to evaluate the potency and the atypical antipsychotic profile of the target compounds. All compounds were tested in vitro for their affinity at dopamine D_2 and serotonin 5-HT_{2A} receptors. Concurrently, targets were screened for potential atypical antipsychotic profile by oral administration in some in vivo assays. For comparative purposes, benzoyl piperidines **3** and **4** from our prior work and some representative standards are also included. Results are shown in Table 1. All compounds displayed a high affinity for D_2 receptors, which is similar to the most potent standards haloperidol and risperidone and about 1 order of magnitude higher than clozapine and our previous benzoyl piperidine analogues **3** and **4**. Also, all compounds had a greater affinity for 5-HT_{2A} than for D_2 receptors, a common feature with the atypical antipsychotics clozapine and risperidone. This fact provides additional support for the predicted atypical antipsychotic profile of the compounds.

The antipsychotic potential of compounds by oral administration was evaluated by testing their ability to antagonize climbing response[21] induced by apomorphine in mice. Inhibition of this response, a characteristic of dopamine antagonism in the limbic dopamine system, is regarded as a measure of antipsychotic potency. Although all compounds were highly potent in the in vitro assays, there were substantial differences in the oral activities. Pharmacological data for benzisoxazole compounds **22** and **23** in comparison to their benzoyl counterparts **3** and **4** reveal a significant increase in oral potency,[22] which can be correlated with their D_2 receptor affinities. Substitution patterns on the chromenone ring were designed according to our previous results on the chromenone series.[17] Thus, the introduction of a methyl (**22**) or a substituted methyl group (**23** and **27**) on position 3 of the chromenone gave, as expected, more potent derivatives than the parent compound **21**. However, oxidation of alcohol **23** to the aldehyde **26** appreciably reduced oral activity, and further oxidation to the acid **24** rendered the compound virtually inactive. Since these compounds show binding profiles similar to **21**−**23**, a poor absorption or penetration into the central nervous system can be assumed. Our previous work on chromenones had given indications that C_2-substituted derivatives had lesser oral potencies compared to the C_3-substituted compounds. As a confirmation of this, the corresponding 2-substituted hydroxymethyl compound (**25**) showed a dramatic reduction in the oral activity. Since **25** was extremely insoluble in water, the reduced oral effect of this compound was attributed to a poor bioavailability by this route of administration. Thus, the intraperitoneal ED_{50} in the climbing assay for **25** was about 1 mg/kg, and also induction of catalepsy was observed by this route.

As an assessment of the proposed atypical antipsychotic profile, induction of catalepsy[23] in rats was included as a measure of the potential for induction of extrapyramidal side effects. The target compounds displayed an appreciable difference between doses required for inhibition of apomorphine-induced climbing and those that induced catalepsy, thus showing a mesolimbic selectivity, which is consistent with the

Table 2. Comparison of Receptor Binding Affinities of **23** and Reference Compounds at Several Neurotransmitter Receptors (K_i, nM)[a]

receptor	tissue	[^{3}H]radioligand	nonspecific	**23**	haloperidol	clozapine	risperidone
D_1	rat striatum	SCH-23390	apomorphine	239	145	235	251
D_2	rat striatum	methylspiperone	haloperidol	12	9.8	93	19
D_3	human recombinant CCL 1.3 cells	YM-09151−2	7-OH-DPAT	5.4[b]	ND	513[b]	31[b]
D_4	human recombinant CHO cells	spiperone	haloperidol	179	4.3	36	6.2
5-HT_{1A}	rat cortex	8-OH-DPAT	buspirone	94	8400	247	491
5-HT_{2A}	rat cortex	ketanserin	mianserin	1.9	75	9.4	0.7
α_1	rat cortex	prazosin	WB-4101	2.4	ND	22	13
α_2	rat cortex	clonidine	NA bitartrate	169	ND	19	25
β	rat cortex	DHA	isoprenalin	2990	ND	26000	22000
muscarinic	guinea pig cerebellum	pyrilamine	tripolidine	1130	ND	ND	6300
σ	guinea pig cerebellum	3-PPP	3-PPP	490	1.5	8500	4300

[a] The SEM for all values was <10%). [b] IC_{50} values.

Table 3. Additional Pharmacological Assays of **23** and Reference Compounds

	23	haloperidol	clozapine	risperidone
hyperactivity[a]	0.16 (0.11−0.22)	0.30 (0.15−0.58)	6.41 (4.82−8.51)	0.20 (0.11−0.38)
head twitches[b]	0.08 (0.06−0.11)	0.56 (0.35−0.89)	0.85 (0.35−2.05)	0.03 (0.02−0.04)
grooming[c]	0.31 (0.20−0.46)	0.28 (0.15−0.50)	0.33 (0.24−0.45)	0.41 (0.32−0.52)
stereotypies[d]	18.60 (13.24−25.56)	1.75 (0.90−2.85)	>100	9.70 (8.30−11.40)

[a] Inhibition of *p*-chloroamphetamine-induced hyperactivity in mice. [b] Inhibition of head twitches induced by 2,5-dimethoxy-4-iodoamphetamine (DOI) in mice. [c] Inhibition of grooming induced by SKF 38393 in mice. [d] Inhibition of apomorphine-induced stereotypy in rats. Results are expressed as ED_{50} values in mg/kg, po; 95% confidence limits are shown in parentheses.

expected atypical profile. Comparison with standard drugs suggested that the most active compounds **22**, **23**, and **27** would exhibit a reduced propensity to induce extrapyramidal effects, similar to the atypical antipsychotics clozapine and risperidone. Notably, the broader margin for the induction of catalepsy also corresponds to the most potent compound, **23**, in the climbing mice assay. On the basis of this assessment, **23** was advanced for further in vitro and in vivo assays in comparison to standards, to acquire complementary evidences for the proposed potent atypical antipsychotic activity of this compound. Table 2 shows additional receptor binding data for **23** in comparison with representative standards. Compound **23** displays a higher affinity for D_3 receptor than stardards. Since D_3 receptors have been found to be more abundant in some areas of the limbic system while being scarce or even absent in the pituitary gland and striatum,[14,24] antagonism at D_3 receptor has been proposed as a target for newer atypical antipsychotics. The higher preference of **23** for this receptor could explain, at least in part, its atypical profile. In contrast, although D_4 antagonism has been proposed to explain the atypical profile of clozapine,[15] our compund displays only weak affinity for this receptor, which cannot be correlated to its high potency in vivo. A potent α_1 affinity has been postulated by some authors as one of the determinants of the atypical antipsychotic profile,[25] but this could also be associated with some cardiovascular side effects. A study in rats at iv doses of 0.01−1 mg/kg showed no alteration in the heart rate and only a mild and transient hypotensive effect at the highest doses (results not shown). However, the therapeutical relevance of this remains to be disclosed in the clinical studies. Table 3 includes some additional pharmacological results. Inhibition of stereotypies[26] is regarded as indicative of the tendency to induce extrapyramidal side effects, whereas inhibition of *p*-chloroamphetamine-induced hyperactivity,[27] SKF-38393-induced grooming,[28] and DOI-induced twitches[29] are related to D_2, D_1, and 5-HT_2 antagonism, respectively. A comparison of the effects of **23** and risperidone

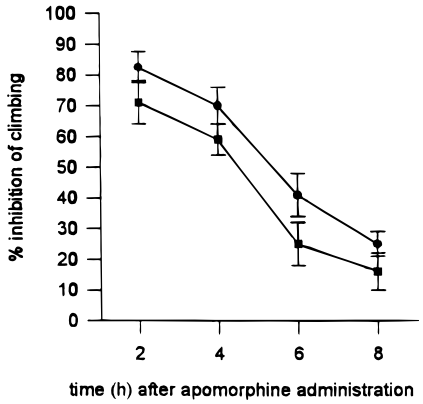


Figure 1. Time course of the inhibitory effect of **23** and risperidone on climbing response induced by subcutaneous administration of apomorphine at several time intervals after oral administration of the drugs in mice. Each point represents the mean response of 10−15 animals at each time after drug dosage (± standard error): (●) **23**, 0.5 mg/kg, po; (■) risperidone, 0.5 mg/kg, po.

along time is shown in Figures 1 and 2. Figure 1 shows the time course of the inhibition of climbing behavior for a period of several hours after oral administration of either 0.5 mg/kg of **23** or risperidone in mice. Also is included a comparative test of catalepsy induced by **23** and risperidone along several hours following oral administration at several doses in rats (Figure 2). A somewhat lesser induction of catalepsy is observed for compound **23**. Figure 3 includes a study of serum prolactin levels after oral administration of **23**, haloperidol, and risperidone at 5 mg/kg for either 1 or 3 days in rats. Increases in prolactin levels after oral administration of **23** were smaller than those for reference drugs. Since some hyperprolactinemia is also observed in laboratory animals for the atypical antipsychotics at high doses,[30] our results compare favorably with standards. The above results thus provide further evidences for the atypical profile of compound **23**. Moreover, preliminary toxicological assays have shown the absence

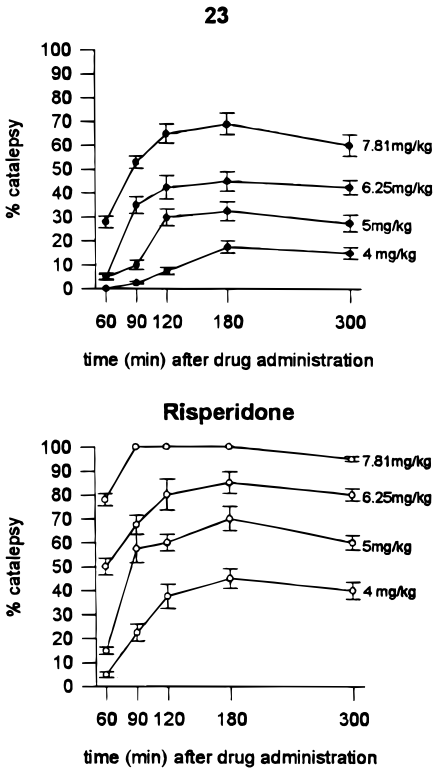


Figure 2. Time course of the catalepsy induced by oral administration of **23** and risperidone in rats. Each point represents the mean response of 10−15 animals (± standard error) at each time after drug dosage.

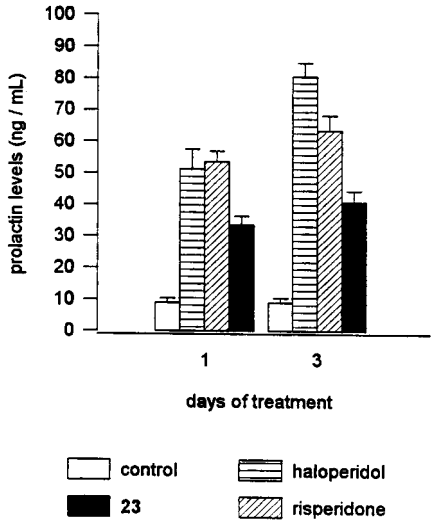


Figure 3. Serum prolactin levels 3 h after last oral administration of **23** and some reference compounds (5 mg/kg/day) for 1 or 3 consecutive days in rats. Each value represents the mean ± standard error of 5 animals. Significant differences at $P < 0.05$ for control vs haloperidol, risperidone, and **23**, risperidone vs haloperidol and **23**, and haloperidol vs risperidone and **23** at both time points.

of significant toxicological properties, thus giving indications of the safety of its study in humans.

Conclusions

Compund **23** was selected from a series of 7-[3-(1-piperidinyl)propoxy]chromenones. The pharmacological and biochemical profile of **23** suggest that this compound will display a potent antipsychotic activity in humans, together with a reduced propensity for the induction of extrapyramidal effects or hyperprolactinemia associated to classical antipsychotics. According to these results, compound **23** (abaperidone, FI-8602) has been selected for clinical development.

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.

7-(3-Chloropropoxy)-4-oxochromen-3-carboxylic Acid (15). To a solution of 0.49 g (1.84 mmol) of **11**[17] in 50 mL of dichloromethane was added a solution of 0.3 g (3.09 mmol) of sulfamic acid in 5 mL of water, and the mixture was cooled in an ice−water bath. A solution of 0.26 g (2.30 mmol) of sodium chlorite in 10 mL of water was added dropwise at a temperature not higher than 5 °C to the cooled mixture, and then the cooling bath was removed and the mixture was stirred for 30 min. To this, additional water (25 mL) was added, and the organic layer was separated and washed with 25 mL of 0.1 M HCl. The organic extracts were dried over Na_2SO_4 and evaporated, and the residue was purified on column chromatography (dichloromethane−methanol 9:1 as eluent) to afford 380 mg (73%) of acid **15**. An analytical sample was crystallized from acetone−diethyl ether: mp 106−108 °C; IR (KBr) 3300−3700, 2500−2800, 1750, 1618, 1442 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.34 (m, 2 H, OCH_2CH_2), 3.79 (t, J = 6.1 Hz, 2 H, CH_2Cl), 4.29 (t, J = 5.7 Hz, 2 H, OCH_2), 7.03 (d, J = 2 Hz, 1 H, 8-H), 7.14 (dd, J = 9 and 2.4 Hz, 1 H, 6-H), 8.22 (d, J = 9 Hz, 1 H, 5-H), 8.93 (s, 1 H, 2-H), 13.7 (s, 1 H, COOH); ^{13}C NMR ($CDCl_3$) δ 31.7 (OCH_2CH_2), 41.0 (CH_2Cl), 65.4 (OCH_2), 101.4 (8-C), 112.7 (3-C), 116.6 (4a-C), 116.9 (6-C), 158.6 (8a-C), 163.3 (2-C), 164.4 and 165.0 (7-C and COOH), 178.4 (4-C). Anal. ($C_{13}H_{11}ClO_5$) C, H, Cl.

7-Hydroxy-(2-hydroxymethyl)chromen-4-one (18). To an ice-bath-cooled suspension of 10 g (43 mmol) of ethyl 7-hydroxy-4-oxochromen-2-carboxylate (**17**)[20] and 4.8 g (43 mmol) of anhydrous calcium chloride in 200 mL of absolute ethanol was added sodium borohydride (6 g, 167 mmol) portionwise, and the mixture was stirred while warming to room temperature. After 2 h, the suspension was cooled again, and an additional amount of 2 g (56 mmol) of sodium borohydride was added and stirred overnight at room temperature. Then, the solvent was removed in vacuo, a volume of 300 mL of water was cautiously added, and the solution was acidified by dropwise addition of HCl. Ice was added to the suspension, and after stirring for 30 min, the resulting precipitate was filtered. The solid was washed with water and vacuum-dried to afford 5.2 g (63%) of **18**: mp 252−254 °C (MeOH); IR (KBr) 2600−3300, 1651, 1634, 1619, 1570, 1249 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.50 (br s, 1 H, OH), 4.40 (s, 2 H, CH_2O), 6.20 (s, 1 H, 3-H), 6.82 (d, J = 2.4 Hz, 1 H, 8-H), 6.90 (dd, J = 8.7 and 2.4 Hz, 1 H, 6-H), 7.86 (d, J = 8.7 Hz, 1 H, 5-H), 10.80 (s, 1 H, OH); ^{13}C NMR (DMSO-d_6) δ 60.0 (CH_2O), 102.5 (8-C), 107.2 (3-C), 115.1 (6-C), 116.4 (4a-C), 126.9 (5-C), 157.8 (8a-C), 162.9 (7-C), 169.1 (2-C), 176.5 (4-C). Anal. ($C_{10}H_8O_4$) C, H.

7-(3-Chloropropoxy)-2-(hydroxymethyl)chromen-4-one (16). A mixture of 6 g (31 mmol) of **17**, 6 mL (61 mmol) of 1-bromo-3-chloropropane and 4.3 g (31 mmol) of anhydrous potassium carbonate in 100 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 4.2 g (50%) of **16**: mp 110−112 °C (Et_2O); IR (KBr) 2800−3600, 1651, 1638, 1628, 1592, 1448, 1246 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.28 (quint, J = 6 Hz, 2 H,

OCH_2CH_2), 3.76 (d, 2 H, CH_2Cl), 4.16 (t, $J = 6$ Hz, 2 H, OCH_2), 4.51 (m, 3 H, CH_2OH + OH), 6.44 (s, 1 H, 2-H), 6.78 (d, $J =$ 2.4 Hz, 1 H, 8-H), 6.90 (dd, $J = 8.7$ and 2.4 Hz, 1 H, 6-H), 7.99 (d, $J = 8.7$ Hz, 1 H, 5-H). Anal. ($C_{13}H_{13}ClO_4$) C, H, Cl.

7-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]-propoxy]-3-(hydroxymethyl)chromen-4-one Hydrochloride (23). A mixture of 2.0 g (7.5 mmol) of 7-(3-chloropropoxy)-3-(hydroxymethyl)chromen-4-one (**14**),[17] 1.9 g (7.5 mmol) of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (**20**),[18a] 2.1 g (15 mmol) of anhydrous potassium carbonate, and a trace of potassium iodide in 30 mL of acetonitrile was heated to reflux for 18 h. The reaction mixture was cooled and poured onto 100 mL of water and 100 mL of chloroform. The organic layer was separated, washed with 50 mL of water, dried over Na_2SO_4, and vacuum-dried. The product was crystallized from *N*,*N*-dimethylformamide to afford 1.27 g (37%) of 7-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]propoxy]-3-(hydroxymethyl)-chromen-4-one: mp 200−202 °C; IR (KBr) 3300−3600, 1634, 1603, 1444, 1272, 1242 cm^{-1}; ^1H NMR ($CDCl_3-CD_3OD$) δ 2.10−2.35 (m, 8 H), 2.68 (t, $J = 7.5$ Hz, 2 H, $OCH_2CH_2CH_2$), 3.13−3.18 (d + m, 3 H, piper-2H_{eq}, -4H and -6H_{eq}), 4.18 (t, $J = 6.3$ Hz, 2 H, OCH_2), 4.57 (s, 2 H, CH_2OH), 6.96 (d, $J = 2.7$ Hz, 1 H, 8-H), 7.03 (dd, $J = 9$ and 2.4 Hz, 1 H, 6-H), 7.12 (td, $J = 8.7$ and 2.1 Hz, 1 H, benzisox-7H), 7.53 (s, 1 H, 2-H), 7.81 (dd, $J = 9$ and 5 Hz, 1 H, benzisox-4H), 8.09 (d, $J = 9$ Hz, 1 H, 5-H).

By addition of the stoichiometric amount of a methanolic solution of hydrogen chloride to a solution of this compound in methanol, hydrochloride **23** was precipitated as white crystals: mp 244−246 °C; IR (KBr) 3200−3600, 2500−2750, 1640, 1607, 1445, 1274, 1240 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.21−2.33 (m, 4 H, piper-3H and -5H), 2.35 (m, 2 H, OCH_2CH_2), 3.15 (m, 2 H, piper-2H_{ax} and -6H_{ax}), 3.30 (m, 2 H, OCH_2-CH_2CH_2), 3.48 (br t, 1 H, piper-4H), 3.67 (br d, $J = 10$ Hz, 2 H, piper-2H_{eq} and -6H_{eq}), 4.26 (t, $J = 6$ Hz, 2 H, OCH_2), 4.35 (d, $J = 4.5$ Hz, 2 H, CH_2OH), 5.09 (t, $J = 4.5$ Hz, 1 H, OH), 7.07 (dd, $J = 9$ and 1.5 Hz, 1 H, 6-H), 7.16 (d, $J = 1.5$ Hz, 1 H, 8-H), 7.33 (td, $J = 9$ and 1 Hz, 1 H, benzisox-5H), 7.72 (dd, $J = 9$ and 1 Hz, 1 H, benzisox-7H), 7.97 (d, $J = 9$ Hz, 1 H, 5-H), 8.14 (s, 1 H, 2-H), 8.20 (dd, $J = 9$ and 5 Hz, 1 H, benzisox-4H), 10.80 (br s, 1 H, NH); ^{13}C NMR (DMSO-d_6) δ 23.2 (OCH_2CH_2), 26.9 (piper-3C and -5C), 31.1 (piper-4C), 51.45 (piper-2C and -6C), 53.3 ($OCH_2CH_2CH_2$), 55.2 (CH_2OH), 65.9 (OCH_2), 97.5 (d, $J = 27$ Hz, benzisox-7C), 101.2 (8-C), 112.7 (d, $J = 25$ Hz, benzisox-5C), 114.8 (6-C), 116.7 (benzisox-3aC), 117.2 (4a-C), 123.8 (d, $J = 11$ Hz, benzisox-4C), 123.8 (3-C), 126.3 (5-C), 153.1 (2-C), 157.7 (8a-C), 160.0 (benzisox-3C), 162.6 (7-C), 163.2 (d, $J = 14$ Hz, benzisox-7aC), 163.7 (d, $J =$ 248 Hz, benzisox-6C), 175.2 (4-C). Anal. ($C_{25}H_{25}FN_2O_5$·HCl) C, H, N, Cl.

Operating as above, the following compounds were obtained.

7-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]-propoxy]chromen-4-one (21): (18%) mp 132−134 °C (MeOH). Anal. ($C_{24}H_{23}FN_2O_4$) C, H, N.

7-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]-propoxy]-3-methylchromen-4-one (22): (43%) mp 157−158 °C (EtOAc). Anal. ($C_{25}H_{25}FN_2O_4$) C, H, N.

7-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]-propoxy]-2-(hydroxymethyl)chromen-4-one Hydrochloride (25): (28%) mp 248−251 °C (MeOH). Anal. ($C_{25}H_{25}FN_2O_5$·HCl) C, H, N.

7-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]-propoxy]-4-oxochromen-3-carboxylic Acid Hydrochloride (24) was prepared as above in *N*,*N*-dimethylformamide as solvent at 90 °C for 24 h. The reaction mixture was poured onto water and was neutralized to pH 7 with HCl. The precipitated solid was redissolved in an aqueous solution of NaOH and precipitated again by addition of hydrochloric acid to pH 1−2 to afford **24** as a solid (40% yield). Anal. ($C_{25}H_{23}$-FN_2O_6·HCl) C, H, N.

7-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]-propoxy]-3-formylchromen-4-one (26). A solution of 2 mL (23 mmol) of oxalyl chloride in 35 mL of dry dichloromethane was cooled to −70 °C, then a solution of 3 mL (42 mmol) of dimethyl sulfoxide in 10 mL of dichloromethane was added dropwise, and it was sitrred at this temperature for 5 min. To this were added 5 g of **23** (11 mmol) portionwise for 15 min, and the solution was stirred for further 30 min at −70 °C. Then, 15 mL (107 mmol) of triethylamine were added dropwise, and the mixture was allowed to warm to room temperature and stirred overnight. The solution was cooled again to −20 °C, and 50 mL of water were slowly added. After the mixture warmed to room temperature, the organic layer was separated, dried over anhydrous sodium sulfate, and vacuum-evaporated. The solid residue was purified by column chromatography on silica gel with 98:2 chloroform/methanol as eluent, to afford 2.12 g (43%) of **26** as a white solid: mp 163−165 °C; IR (KBr) 1691, 1652, 1619, 1441 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.10 (m, 6 H, piper-3H, -5H, and OCH_2CH_2), 2.20 (m, 2 H, piper-2H_{ax} and -6H_{ax}), 2.60 (t, $J = 7.2$ Hz, 2 H, $OCH_2CH_2CH_2$), 3.10 (d + m, 3 H, piper-2H_{eq}, -4H, and -6H_{eq}), 4.19 (t, $J = 6.5$ Hz, 2 H, OCH_2), 6.96 (d, $J = 2.4$ Hz, 1 H, 8-H), 7.05 (m, 2 H, benzisox-5H and -7H), 7.24 (dd, $J = 8.7$ and 2.4 Hz, 1 H, 6-H), 7.69 (dd, $J = 8.7$ and 5 Hz, 1 H, benzisox-4H), 8.19 (d, $J = 8.7$ Hz, 1 H, 5-H), 8.47 (s, 1 H, 2-H), 10.37 (s, 1 H, CHO); ^{13}C NMR ($CDCl_3$) δ 26.5 (OCH_2CH_2), 30.5 (piper-3C and -5C), 34.4 (piper-4C), 53.5 (piper-2C and -6C), 54.9 ($OCH_2CH_2CH_2$), 67.1 (OCH_2), 97.3 (d, $J = 27$ Hz, benzisox-7C), 101.4 (8-C), 112.1 (d, $J = 26$ Hz, benzisox-5C), 115.6 (6-C), 117.1 (benzisox-3aC), 118.5 (4a-C), 120.0 (3-C), 122.2 (d, $J = 11$ Hz, benzisox-4C), 127.2 (5-C), 157.7 (8a-C), 159.9 (2-C), 160.7 (benzisox-3C), 163.5 (d, $J = 14$ Hz, benzisox-7aC), 163.7 (d, $J = 248$ Hz, benzisox-6C), 164.1 (7-C), 174.9 (4-C), 188.5 (CHO). Anal. ($C_{25}H_{23}FN_2O_5$) C, H, N.

7-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]-propoxy]-3-(methoxymethyl)chromen-4-one Hydrochloride (27). A solution of 2 g (4.4 mmol) of **23** in 20 mL of a 2 M methanolic solution of hydrogen chloride was heated to reflux for 2 h. After evaporation of the solvent, the residue was dissolved in dichloromethane and washed with a saturated solution of $NaHCO_3$. The organic layer was evaporated, and the residue was dissolved in acetonitrile and then precipitated by addition of an ethereal solution of hydrogen chloride. The solid was recrystallized from methanol to afford 0.75 g (34%) of **27** as a solid: mp 219−221 °C; IR (KBr) 1659, 1615, 1443, 1273, 1244 cm^{-1}; ^1H NMR ($CDCl_3-CD_3OD$) δ 2.25 (m, 2 H), 2.50 (m, 2 H), 2.90 (m, 2 H), 3.05 (m, 2 H, piper-2H_{ax} and -6H_{ax}), 3.35 (m, 2 H, $OCH_2CH_2CH_2$), 3.48 (s, 3 H, OCH_3), 3.60 (m, 1 H, piper-4H), 3.80 (br d, 2 H, piper-2H_{eq} and -6H_{eq}), 4.20 (m, 2 H, $ArOCH_2$), 4.39 (s, 2 H, CH_2OCH_3), 6.90 (d, 1 H, 6-H), 6.97 (d, 1 H, 8-H), 7.16 (td, 1 H, benzisox-5H), 7.66 (dd, 1 H, benzisox-7H), 7.95 (s, 1 H, 2-H), 8.10 (d, 1 H, 5-H), 8.20 (dd, 1 H, benzisox-4H). Anal. ($C_{26}H_{27}FN_2O_5$·HCl) C, H, N.

Pharmacological Methods. General. Subjects were either male Swiss Albino mice (20−24 g) or male Sprague−Dawley rats (180−200 g), and 10−15 individuals were used per dose group. Animals were individually placed in transparent cages and allowed for adaptation 2 h 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.[21] was used. Mice received orally either the test drug or the vehicle alone 30 min (for the screening tests) or 2, 4, 6, and 8 h (for the time course assay) prior to apomorphine challenge (1 mg/kg, sc) and were individually placed in transparent vertical polymethacrylate boxes (11 × 7.5 × 4.5 cm^3) 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.

Catalepsy in Rats.[23] 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 3 cm high and then on a bar 9 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 time point, scores were totaled, and results are expressed as the highest percent value with respect to maximum possible score (4 for each animal).

Inhibition of Apomorphine-Induced Stereotypy in Rats. The procedure is a modification of that of Puech et al.[26] Rats were dosed with vehicle or with test compounds 30 min prior to apomorphine (1,5 mg/kg, sc). 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.

Inhibition of *p*-Chloroamphetamine-Induced Hyperactivity in Mice.[27] Animals were either orally dosed with vehicle or with test compounds, and after 60 min, mice were challenged with 5 mg/kg (sc) of *p*-chloroamphetamine. 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 reference to control group.

(±)-1-(2,5-Dimethoxy-4-iodophenyl)-2-aminopropane-Induced Head Twitches in Mice.[28] Mice were dosed with 3 mg/kg ip of (±)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane·HCl (DOI) 60 min after po administration of the test drug or the vehicle alone. Then, the number of head twitches induced by DOI was counted between 5 and 10 min after dosing. ED_{50} values were calculated by linear regression analysis.

SKF-38393-Induced Grooming in Mice.[29] Mice were dosed with SKF-38393 (2.5 mg/kg, ip) 60 min after po administration of the test drug or the vehicle alone. After 15 min, the total time of grooming was measured during a period of 15 min. ED_{50} values were calculated by linear regression analysis.

Receptor Binding Assays. Receptor binding assays were performed by inhibition of radioligand binding according to reported procedures for D_1,[31] D_2,[32] D_3,[33] D_4,[15a] 5-HT_{1A},[34] 5-HT_{2A},[35] α_1,[36] α_2,[37] β,[38] muscarinic,[39] and σ[40] receptors. IC_{50} values were calculated from concentration−response curves at 11 different concentrations of the test compound, each done in duplicate.

Determination of Serum Prolactin Levels. Sprague−Dawley rats (220−240 g) were assigned to 8 groups of 5 animals each, and were orally dosed with either **23** (5 mg/kg/day), haloperidol (5 mg/kg/day), risperidone (5 mg/kg/day), or the vehicle for 1 or 3 consecutive days. The animals were killed by decapitation 3 h after last dosing, blood samples of 2 mL were collected, and prolactin levels were determined by means of an EIA kit from Amersham.

Acknowledgment. We thank Mr. Joan Nieto for accurate synthetic work and Mr. Josep M. Fernández for the analytical determinations.

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JM9810396