Synthesis and Atypical Antipsychotic Profile of Some 2-(2-Piperidinoethyl)benzocycloalkanones as Analogues of Butyrophenone†

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Four new 2-(2-piperidinoethyl)benzocycloalkanone derivatives, **20–23**, were prepared and evaluated as potential antipsychotic agents in receptor binding assays for dopamine (DA) and 5-HT_{2A} receptors and in functional and behavioral screens. Their affinities for D_2 receptors (K_i's in the nanomolar range: 46.7–70.7) and D_1 receptors (K_i's in the micromolar range: 1.09–2.81) were slightly lower than that showed by haloperidol (K_i's in the nanomolar range: 5.01 and 97.72 for D_2 and for D_1 receptors, respectively). The ratio of pK_i's values D_1/D_2 showed that the new molecules are more D_2-selective than haloperidol. In contrast, in the [^{3}H]-ketanserin binding assays the new compounds had greater affinity for 5-HT_{2A} receptors (pK_i's 7.89–8.60) than haloperidol (pK_i 7.70) and in functional studies, endothelium-stripped aorta rings, the pA_2 values (6.75–8.12) were slightly lower than that of ketanserin (8.87) in suppresing serotonin-induced contractions. The pK_i's for D_2 binding (and to a lesser extent pK_i's for D_1 binding) tend to be greater among typical (classical) than among atypical antipsychotics, while these two classes of antipsychotics exhibit no difference with regard to pK_i's for 5-HT_{2A} receptors. The ratios of pK_i's for 5-HT_{2A}/D_2 receptors may be useful for rapid screening of new compounds, and its potential induction of extrapyramidal symptoms (ratio values >1.12 were predictive of an atypical antipsychotic profile). The new molecules had a ratio value in the range 1.08–1.20, while haloperidol showed a ratio of 0.93. In the behavioral screening tests, the new molecules showed antagonist activity of amphetamine-inducing hyperactivity and apomorphine-induced climbing (predictive tests for antipsychotic activity). In the catalepsy test (predictive test for induction of extrapyramidal symptoms), the values obtained were in accordance with an atypical antipsychotic drugs profile.

Introduction

Administration of neuroleptics such as chlorpromazine or haloperidol is still the only effective treatment of a variety of psychiatric disorders (schizophrenia, the manic phase of manic-depressive psychosis). However, most neuroleptics (also called "classical antipsychotics") have two major drawbacks. First, they can induce extrapyramidal symptoms (sometimes at the start of treatment or following months/years of therapy). Second, negative symptoms (such as blunted affectivity, emotional withdrawal, apathy, and motor retardation) respond poorly in most patients. Since the 1970s, atypical (nonclassical) antipsychotics which have no extrapyramidal side effects and are effective against negative symptoms have been available. The prototype of this group, clozapine, whose atypical activity has been attributed classically to its anticholinergic activity, was withdrawn because of its ability to induce agranulocytosis, but in view of the lack of alternatives has since been reintroduced into clinical practice, with the restriction that its use must be accompanied by rigorous blood monitoring.[1–3]

Seeman[4–6] reported that antipsychotic activity is closely correlated with the ability to block D_2 dopamine receptors but not with D_1 receptor blockade, although the subsequent development of D_1-selective agonists and antagonists indicated that D_1 receptors may also be involved in the clinical response to antipsychotics.[7–9] For 10 years or more, the two subtype classification could accommodate most of the activities attributed to the dopaminergic system. However, this has changed and the dopamine receptors have been reviewed recently.[10,11] Molecular cloning techniques have permitted the identification of several dopamine receptors called D_1, D_2 (D_{2L} and D_{2S}), D_3, D_4, and D_5/D_{1B}, recently grouped together into two subfamilies: D_1-like (D_{1A} and D_5/D_{1B}) and D_2-like (D_2, D_3 and D_4) subfamilies.

The D_1-like receptors exhibit very similar ligand binding properties: high affinity for benzazepines (SCH 23390, SKF 38393) and low affinity for butyrophenones (spiperone, haloperidol) and substituted benzamides (sulpiride). An interesting difference between the D_1-like receptors is that the D_5/D_{1B} receptor binds dopamine with a higher affinity than does the D_{1A} receptor.

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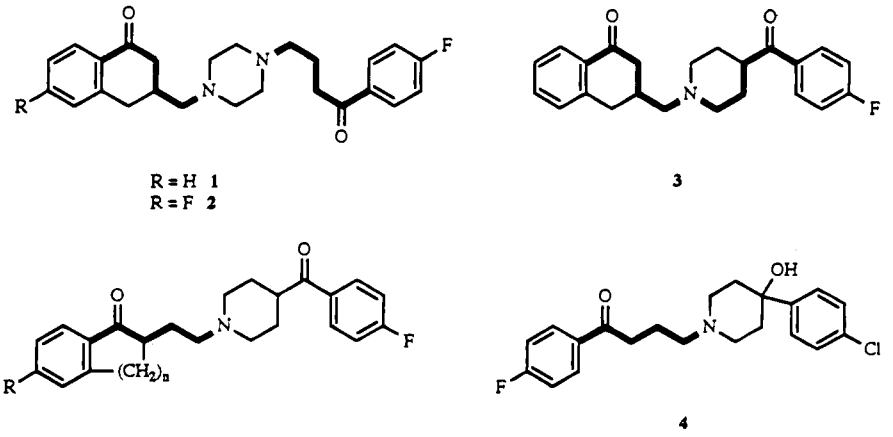


Figure 1.

All three D_2-like receptors possess high affinity for butyrophenones such as spiperone and haloperidol and low affinity for benzazepines such as SKF 38393. The D_4 receptor exhibits relatively high affinity for the atypical neuroleptic clozapine; this has led to speculation that the D_4 receptor might be the relevant target of this atypical neuroleptic (for a review of DA receptors, see ref 12 and 13).

Clozapine blocks not only dopamine receptors but also 5-HT_{2A} serotonin receptors, and recent findings suggest that its atypical activity may be due to this latter feature.[14] This hypothesis is supported by clinical evidence that the 5-HT_{2A}-blocking capacity of certain antipsychotics reduces extrapyramidal side effects and improves the outcome of negative symptoms. An example is setoperone, a drug with potent 5-HT_{2A}-blocking and moderate D_2-blocking activity which has proved effective in the treatment of negative symptoms in schizophrenics and also causes few extrapyramidal effects.[15]

In previous papers[16,17] we have reported the synthesis and antidopaminergic and antiserotoninergic activities of 3-(aminomethyl)tetralones **1**–**3**, which are conformationally restricted butyrophenone structures analogous to haloperidol, **4**. As a continuation of that work we have now prepared the 2-(2-aminoethyl)benzocycloalkanones **20**–**23**, which also possess the essential requirements for interaction with DA and serotonin (5-HT) receptors. These compounds have two butyrophenone pharmacophores, the (aminoethyl)cycloalkanone moiety and the 4-(*p*-fluorobenzoyl)piperidine fragment. This latter, which has been described as a neuroleptic pharmacophore of similar potency to the butyrophenone portion,[18] is also an important feature for 5-HT_{2A} binding.[19]

On the other hand, it is known that ketanserin **5** is the prototypic 5-HT_{2A} receptor antagonist. In the ketanserin molecule is necessary to consider two structural aspects: (a) the quinazolinone moiety is not essential and may be replaced by a pyrimido pyrimidine (e.g., pirenperone **6**) or a thienopyrimidine nucleus (e.g., setoperone **7**) or abbreviated to a simpler structural aroyl ketone or amide and (b) there is an aromatic binding site that accommodates the aryl portion of the heterocyclic ring.[19] It is evident that the design of molecules under study satisfy these requirements because they have an aroyl portion that binds the *p*-fluorobenzoyl fragment across an aminoethyl side chain partially incorporated in a conformationally restricted cycloalkanone structure.

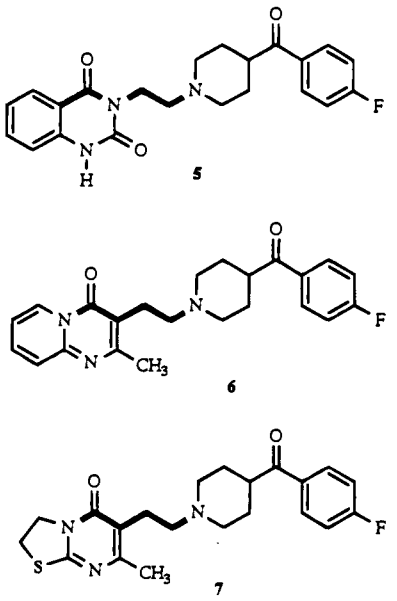


Figure 2.

Chemistry

Compounds **20**–**23** were synthesized via the sequence of reactions outlined in Scheme 1. Literature procedures for the preparation of tetralone- and indanoneacetic acids involve condensation with glyoxylic acid in alkaline medium and subsequent reduction with zinc and acetic acid of the resulting alkene acid.[20,21] Other synthetic routes have been described for preparing these compounds.[22–26]

In this paper, indanone, 5-fluoroindanone, tetralone, and benzosuberone-2-acetic acids **12**–**15** were prepared by one of the following methods: (A) aldol condensation with glyoxylic acid in alkaline medium to give 1-oxo-2,3-dihydro-indanylidene acetic acid **8** and their 5-fluoro derivative **9**, (1-oxo-1,2,3,4-tetrahydro-2-naphthylidene)-acetic acid **10**, and (1-oxo-1,2,3,4-tetrahydro-5*H*-2-benzocycloheptenylidene)acetic acid **11** in variable yields and (B) thermal condensation with glyoxylic acid at 160 °C in quantitative yields (Table 1). Subsequent reduction of the alkene acids with zinc and acetic acid gave the saturated acids **12**–**15** also in quantitative yields (Table 2). 1-Tetralone-2-acetic acid, **12**, was also prepared with an overall yield of 75% by hydrolysis of the

Scheme 1

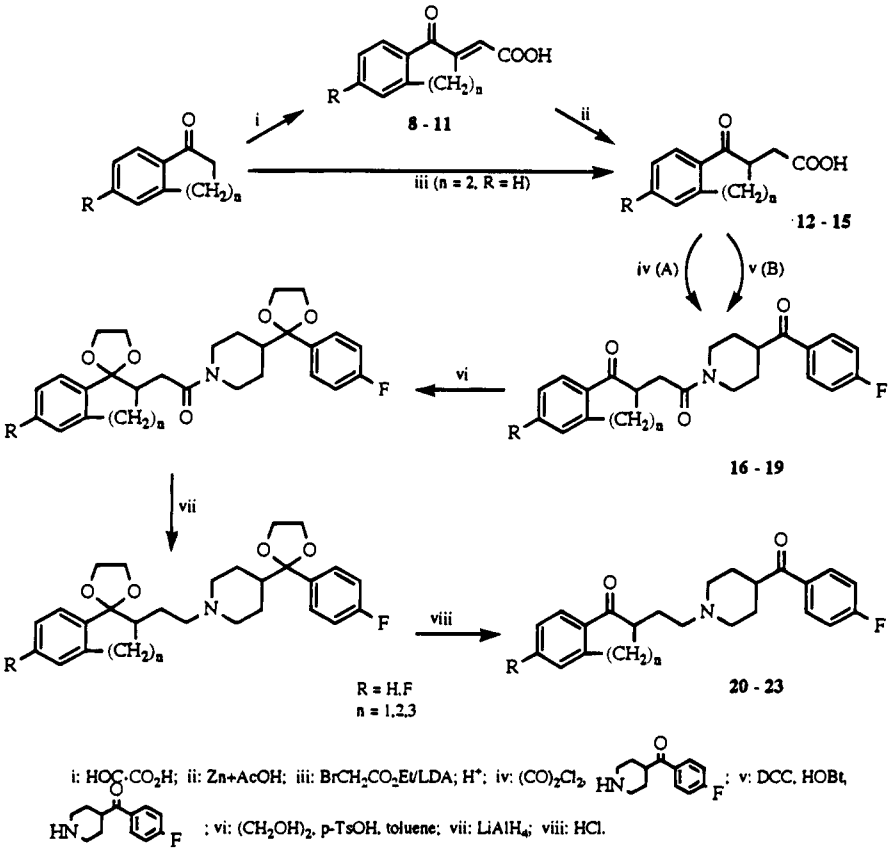
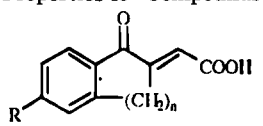


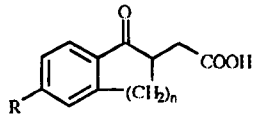
Table 1. Physical Properties for Compounds **8–11**



compd	n	R	method	yield, %	mp, °C	recrystn solv	formula
8	1	H	A	22	201–202	EtOH	$C_{11}H_9O_3$
			B	57			
9	1	F	B	69	210–212	EtOH	$C_{11}H_8O_3F$
10	2	H	A	74[a]	188–190[b]	EtOH	$C_{12}H_{10}O_3$
			B	95			
11	3	H	B	70	229–231[c]	EtOH	$C_{13}H_{11}O_3$

[a] As reported in ref 20, 67%. [b] mp 184.5–185.5 °C.[20] [c] mp 232 °C (AcOH).[36]

Table 2. Physical Properties for Compounds **12–15**

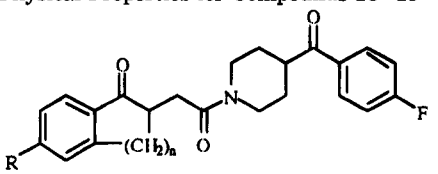


compd	n	R	yield, %	mp, °C	recrystn solv	formula
12	1	H	66	147–149[a]	AcOEt	$C_{11}H_{10}O_3$
13	1	F	92	130–133	toluene	$C_{11}H_9O_3F$
14	2	H	95	107–109[b]	AcOEt	$C_{12}H_{12}O_3$
15	3	H	87	123–127	AcOEt	$C_{13}H_{14}O_3$

[a] Lit.[21] 144–146 °C; lit.[24] 147–148 °C; lit.[26] 147–149 °C. [b] Lit.[23] 106–108 °C; lit.[25] 104–105 °C; lit.[37] 108 °C; lit.[38] 107–109 °C.

corresponding ethyl ester, in turn obtained by alkylation of tetralone with ethyl bromoacetate in the presence of lithium diisopropylamide. The synthesis of amides **16–19** (Table 3) was accomplished in good to excellent yields

Table 3. Physical Properties for Compounds **16–19**

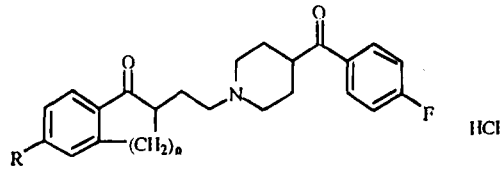


compd	n	R	method	yield, %	mp, °C	recrystn solv	formula
			A	85			
16	1	H			oil[a]		$C_{23}H_{22}NO_3F$
			B	80			
			A	75			
17	1	F			127–128	*i*-PrOH	$C_{23}H_{21}NO_3F_2$
			B	72			
			A	85			
18	2	H			oil[b]		$C_{24}H_{24}NO_3F$
			B	81			
			A	90			
19	3	H			117–118	AcOEt	$C_{25}H_{26}NO_3F$
			B	78			

[a] Bis(2,4-dinitrophenyl)hydrazone, mp 180–181 °C (MeOH). Anal. ($C_{35}H_{30}N_9O_9F$) C, H, N. MS (FAB) M + 1: 740. [b] Bis(2,4-dinitrophenyl)hydrazone, mp 207–208 °C (AcOEt). Anal. ($C_{36}H_{32}N_9O_9F$) C, H, N. MS (FAB) M + 1: 754.

by reaction of the acid chlorides with 4-(*p*-fluorobenzoyl)-piperidine (route A) or by direct acid amine coupling with carboxylate activation by dicyclohexylcarbodiimide in the presence of 1-hydroxybenzotriazole (HOBt) (route B). Ketalization of both the carbonyl groups with ethylene glycol and *p*-TsOH in toluene gave the bis-(ethylene ketals) with variable yields. Later, lithium aluminum hydride reduction and subsequent deketalization then afforded to the amino ketones **20–23** in good to excellents yields (Table 4).

Table 4. Physical Properties for Compounds **20**–**23**



compd (code number)	*n*	R	yield, %	mp, °C	recrystn solv	formula
20 (QF 0307B)	1	H	91	264–266	MeOH	$C_{23}H_{24}NO_2F$·HCl
21 (QF 0313B)	1	F	55	270–272	MeOH–Et_2O	$C_{23}H_{23}NO_2F_2$·HCl
22 (QF 0303B)	2	H	85	176–179	MeOH	$C_{24}H_{26}NO_2F$·HCl
23 (QF 0311B)	3	H	80	224.5–226	MeOH–Et_2O	$C_{25}H_{28}NO_2F$·HCl

Table 5[a]

drug	pK_i values			pK_i ratios			pA2 5-HT_{2A}
	D_1	D_2	5-HT_{2A}	D_1/D_2	5-HT_{2A}/D_1	5-HT_{2A}/D_2	
haloperidol	7.01	8.30	7.70	0.85	1.10	0.93	–
20	5.55	7.15	8.60	0.78	1.55	1.20	8.12 ± 0.4
21	5.96	7.32	8.42	0.81	1.41	1.15	8.12 ± 0.7
22	5.81	7.32	8.11	0.79	1.40	1.11	7.45 ± 0.2
23	5.89	7.33	7.89	0.80	1.34	1.08	6.75 ± 0.1
ketanserin	–	–	–	–	–	–	8.87 ± 0.1
methysergide	–	–	8.84	–	–	–	–

[a] pK_i's were obtained from the inhibition of [^{3}H]ketanserin binding to rat frontal cortex membranes (5-HT_{2A}) and [^{3}H]spiperone or [^{3}H]SCH 23390 binding to striatal membranes (D_2 or D_1) by new compounds. Results are means ± SEM of three or four separate experiments. D_1/D_2, pK_i value of D_1 binding/D_2 binding; 5-HT_{2A}/D_1, pK_i value of 5-HT_{2A} binding/D_1 binding; 5-HT_{2A}/D_2, pK_i value of 5-HT_{2A} binding/D_1 binding. pA_2 values were obtained against serotonin-induced contractions in rat aorta rings. (–) not evaluated.

Results and Discussion

Pharmacology. Dopamine and 5-HT_{2A} antagonist activity of the compounds was evaluated by *in vivo* and *in vitro* experiments.

***In Vitro* Results.** In [^{3}H]spiperone binding assays, all the new compounds exhibited pK_i values of 7.15–7.33, slightly lower than that of haloperidol, 8.3 (Table 5). In [^{3}H]SCH 23390 binding assays, the new molecules again had very similar pK_i values (5.55–5.96) which were again lower than that of haloperidol (7.01). These results indicate that the new compounds are more D_2-selective than haloperidol.

In [^{3}H]ketanserin binding experiments, the new molecules showed greater affinity for 5-HT_{2A} receptors (pK_i 7.89–8.60) than haloperidol (pK_i 7.70). The new compounds exhibited pA_2 values of 6.75–8.12,[27] slightly lower than that of ketanserin (8.87) in suppressing serotonin-induced contractions in rat aorta rings stripped of endothelium (Table 5).

pK_i's for D_2 binding (and to a lesser extent pK_i's for D_1 binding) tend to be greater among typical (classical) than atypical antipsychotics, whereas these two classes of antipsychotic exhibit no difference as regards pK_i's for 5-HT_{2A} binding.[28,29]

***In Vivo* Results.** All the substances tested caused statistical significant reductions in spontaneous motor activity (SMA) at a dose of 2 mg/kg (Figure 3). Haloperidol and compounds **20**, **23**, and **21** were effective immediately after their administration, and **22**, 40 min later.

Depending on the reductions of SMA obtained with 2 mg/kg doses, the substances were next assayed at doses 4 times greater or smaller. The percent reduction in SMA measured 60 min after administration of 8 mg/kg

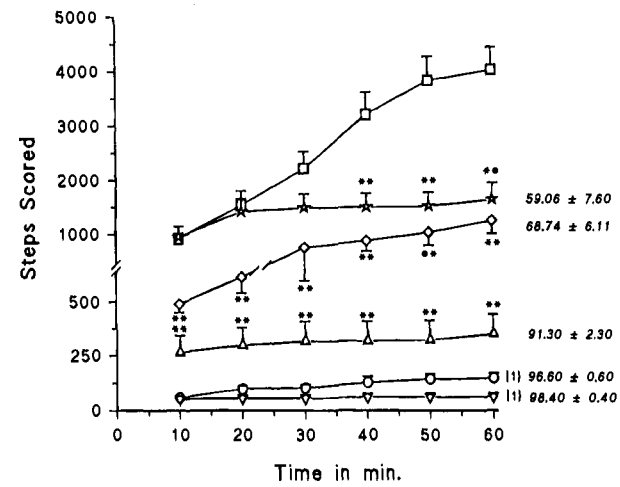


Figure 3. Spontaneous locomotor activity in mice treated with vehicle (□), haloperidol (○), **20** (◇), **21** (▽), **22** (☆), or **23** (△) at a dose of 2 mg/kg. The data shown are means ± SEM (accumulated data). Significant differences with respect to control indicated by *p < 0.05 or **p <0.01. (1) All values showed significant differences with respect to control (p < 0.01). Numerical values at the end of each curve show percent reduction in SMA 60 min after administration of the drugs.

of compound **20** or 0.5 mg/kg of **23** or **21** was in all three cases very similar to that caused by 0.5 mg/kg of haloperidol, and **22** (8 mg/kg) was slightly less active (Figure 4).

The new compounds were also tested for activity against amphetamine-induced hyperactivity at doses which had caused at least 75% inhibition of SMA 60 min after their administration. Haloperidol (ED_{50} = 0.098 mg/kg ip) or compound **21** at dosages of 0.5 mg/kg, **23** at 0.5 or 2 mg/kg, and **20** or **22** at 8 mg/kg all inhibited

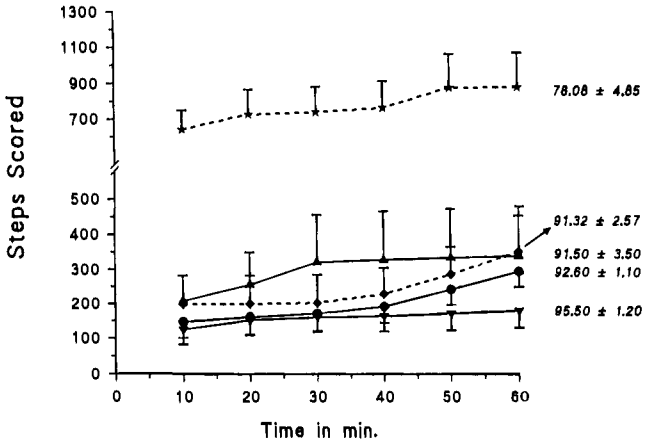


Figure 4. Spontaneous locomotor activity in mice treated with haloperidol (●), **21** (▼), or **23** (▲) at a dose of 0.5 mg/kg, or **20** (◆) or **22** (☆) at a dose of 8 mg/kg. The data shown are means ± SEM (accumulated data). All values showed significant differences with respect to control ($p < 0.01$). Numerical values at the end of each curve show percent reduction in SMA 60 min after administration of the drugs.

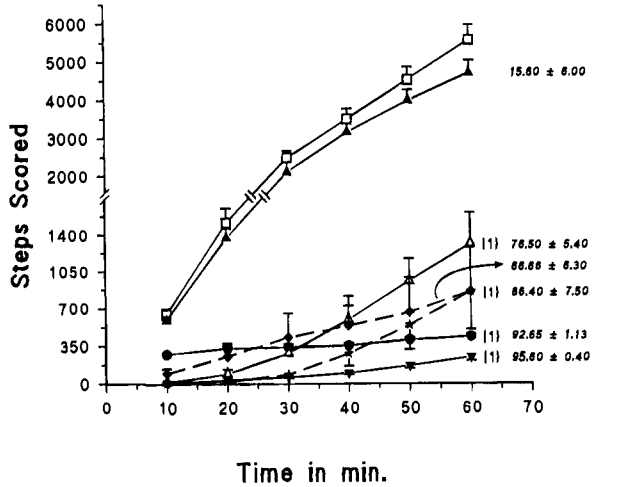


Figure 5. Antagonism of *d*-amphetamine-induced hypermotility in mice treated with vehicle (□), haloperidol (●), or **21** (▼) at a dose of 0.5 mg/kg, **23** at doses of 0.5 (▲) or 2 mg/kg (△), or **20** (◆) or **22** (☆) at a dose of 8 mg/kg. All values are means ± SEM (1) Significant differences ($p < 0.01$) with respect to control throughout the experiment. Numerical values at the end of each curve show the percent reduction in hyperactivity 60 min after administration of the drugs.

amphetamine-induced hyperactivity throughout the experiment (Figure 5).

Apomorphine-induced climbing was strongly inhibited by haloperidol (ED_{50} = 0.15 mg/kg ip) and by all the new compounds at the highest dose used (Figure 6). If it is assumed, following Ferris et al.,[30] that climbing is caused by activation of limbic dopamine receptors, and since antipsychotic activity is the result of blockade of DA receptors in the limbic system, then these results suggest that the compounds tested can be classified as antipsychotics.

The potency of the compounds under study to inhibit spontaneous locomotor activity, amphetamine-induced hyperactivity, and apomorphine induced climbing (at the highest dose used) was similar. Thus, the indanone derivative **21** was the most potent in reducing all behaviors, followed by the benzosuberone **23**, being the least potent **20**, analogue of **21**, but lacking a fluorine atom in position 5, and **22**, bearing a tetralone moiety. Differences in the affinity for either D_1 or D_2 receptors cannot account for the relative potencies of the compounds, since their K_i's were almost identical. It appears that the existence of two complete butyrophenone groups, such as in **21**, is necessary to show a similar profile to haloperidol in behavioral tests.

Certain experimental results suggest that D_2 selectivity may be a sign that a drug will induce catalepsy in experimental animals (and hence that it may cause extrapyramidal symptoms in human beings).[31,32] Since our binding results showed that all the new substances are more D_2 selective than haloperidol, we hypothesized that they would be more cataleptogenic than haloperidol *in vivo*. Somewhat to our surprise, this was not so. Whereas haloperidol, as expected, was markedly cataleptogenic (ED_{50} = 0.67 mg/kg ip, confidence limits 0.5–0.9) and induced an average increase in position retention time of 28.8 s ($p < 0.01$) when the larger dose was used, the new compounds, in general, exhibited a much lower propensity to produce catalepsy. Compounds **20** and **22** produced, at dosages of 2–8 mg/kg, a slight increase (no more than 5 s) in the time for which the imposed position was maintained and induced no catalepsy, while the molecules **21** and **23** (dosages of 0.5–8 mg/kg) increased the time in initial imposed posture (in the range 10–20 s) and catalepsy was induced in only 13.3–33.3% and 6.7–16.7% of the tested animals, respectively; however, these percentages are much lower than those obtained with haloperidol (Figure 7). Furthermore, the effects of **21** and **23** in the catalepsy test differed qualitatively from those of haloperidol: whereas animals treated with the new molecules showed reduced muscle tone (appeared flaccid), the animals treated with haloperidol appeared rigid with high level of muscle tone.

Bruhwyler et al.[33] suggested that the induction of extrapyramidal symptoms by neuroleptics may be due to an imbalance between their effects on dopaminergic and cholinergic systems, and that atypical antipsychotics, such as clozapine, may lack extrapyramidal effects because they have both antidopaminergic and anticholinergic activity. To determine whether the weak cataleptogenic activity exhibited by our new compounds might be due to anticholinergic activity, we evaluated the protection they afforded against eserine (physostigmine)-induced lethality. Since none of the new compounds afforded such protection, even at the highest dose used (results not shown), their weak cataleptogenic activity cannot, in fact, be attributed to concomitant anticholinergic activity.

Recent studies have suggested that 5-HT_{2A}-blocking activity can reduce the cataleptogenic activity of neuroleptics while enhancing their antipsychotic activity.[3,15,34] Setoperone and ritanserin, for example, both of which are more active as 5-HT_{2A} blockers than as D_2 blockers, have been reported to be more effective than selective DA receptors blockers in reducing the negative symptoms of schizophrenia and induce few extrapyramidal side effects. In view of such reports, other compounds with both 5-HT_{2A}-blocking and D_2-blocking activity have also been developed.[35]

According to the binding studies the new compounds interacted with both D_1 and D_2 receptors like haloperidol, although they had less affinity. However, they were slightly more D_2 selective compared to haloperidol, as

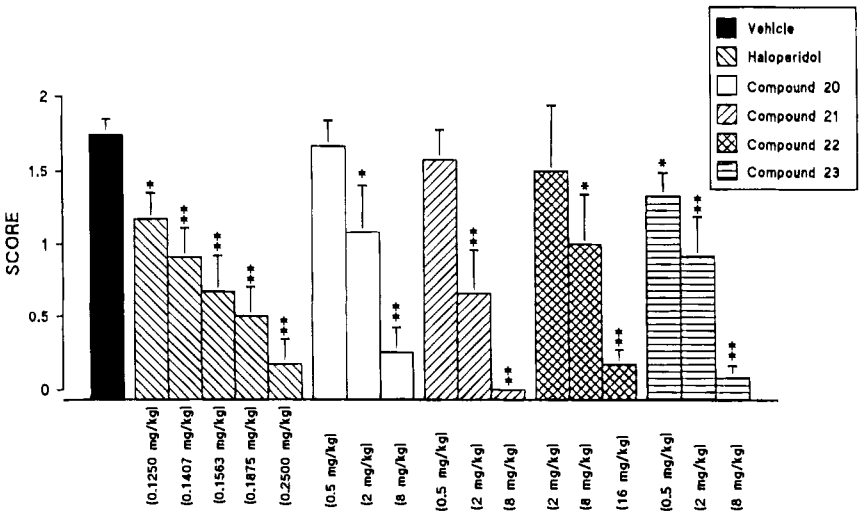


Figure 6. Climbing behavior induced by administration of apomorphine (2 mg/kg sc) 30 min after administration of vehicle, haloperidol, **20**, **21**, **22**, or **23**. All values show means ± SEM of the scores obtained between 20–30 min postapormorphine administration. Significant differences with respect to control indicated by $*p < 0.05$ or $**p < 0.01$.

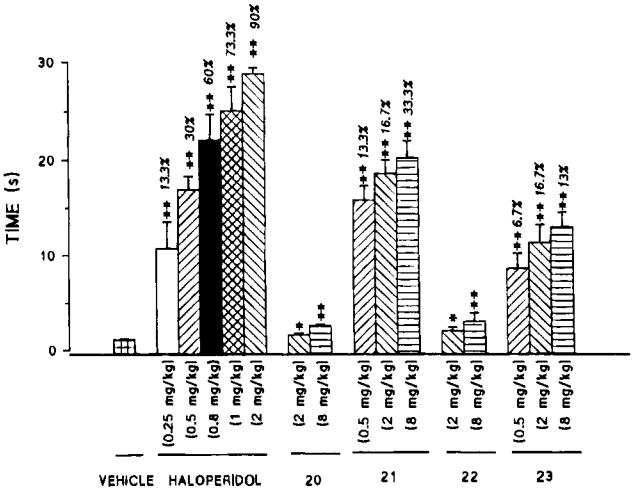


Figure 7. Results of catalepsy test, showing the time for which initial posture was maintained (mean ± SEM) by mice treated with vehicle, haloperidol, **20**, **21**, **22**, or **23**. Times in excess of 30 s were recorded as 30 s. Significant differences with respect to control indicated by $*p < 0.05$ or $**p < 0.01$. Numerical values at column heads represent the percentage of cataleptics.

shown by the D_1/D_2 ratio. In contrast, all the new molecules displayed higher affinity for 5-HT_{2A} receptors than haloperidol. Interestingly, in this case the relative affinity for serotonin receptors appears to be related to the chemical structure of the compounds. **21** and **20**, both bearing an indanone moiety, but the latter lacking the fluorine atom, showed the highest affinity for 5-HT_{2A}; the compound having a tetralone fragment (**22**) exhibited an affinity slightly lower, while **23** with the least affinity bore a benzosuberone. In summary, increasing the size of the ring which bears the carbonyl group diminishes the affinity for serotonin receptors.

In keeping with the above hypotheses regarding the combination of 5-HT_{2A}-blocking and D_2-blocking activities, Meltzer et al.[28,29] suggested that atypical antipsychotic drugs might be characterized by having a pK_i 5-HT_{2A}/D_2 ratio no smaller than 1.12. The pK_i 5-HT_{2A}/D_1 and pK_i 5-HT_{2A}/D_2 ratios of our new compounds were all greater than those of haloperidol; only **20** (hereafter designed as QF 0307B) and **21** (QF 0313B) have pK_i 5-HT_{2A}/D_2 ratios strictly higher than 1.12, while **22** (QF 0303B) may be considered as a borderline case (Table 5). Our results with QF 0303B, QF 0307B, and QF 0311B are in accordance with Meltzer et al. In addition, QF 0313B having an appropriate pK_i 5-HT_{2A}/D_2 ratio induced weak catalepsy in a small percentage of animals.

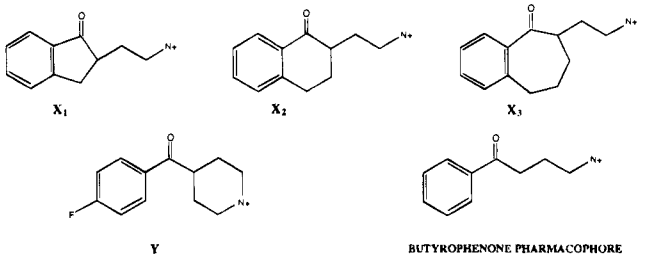


Figure 8. Molecular fragments considered in the molecular modeling analysis.

In summary, these new synthetic molecules had pharmacological properties compatible with a profile of atypical antipsychotics.

Molecular Modeling. Structures of the compounds (**20**, **22**, **23**) were represented as X-Y (Figure 8) where Xs are the fused cyclic moieties (indanone, tetralone, and benzosuberone; X_1, X_2 and X_3 in Figure 8) and Y is the 4-(*p*-fluorobenzoyl)piperidine fragment common to all the compounds.

Structural fittings of X and Y fragments and the butyrophenone pharmacophore of haloperidol were performed by starting from their most stable conformations, superimposing the carbonyl groups, effecting torsions bringing the terminal nitrogen as close as possible to this of the template molecule, and then optimizing with these contraints. All the torsions affected only linear aliphatic chains and involved very little change in energy.

Fitting the butyrophenone pharmacophore of haloperidol to Y as above resulted in almost perfect overlap, with N atoms at only 0.09 Å (Figure 9). Since both structures block dopamine receptors (see Pharmacology section), this suggests that the active conformation of haloperidol fragment may not be its minimum-energy conformation (Figure 9a) but a more twisted for closer to Y (Figure 9b). In this specific case, the energetic cost to acquire this final conformation is only 0.85 kcal/mol; that it to say, nearly a free rotation.

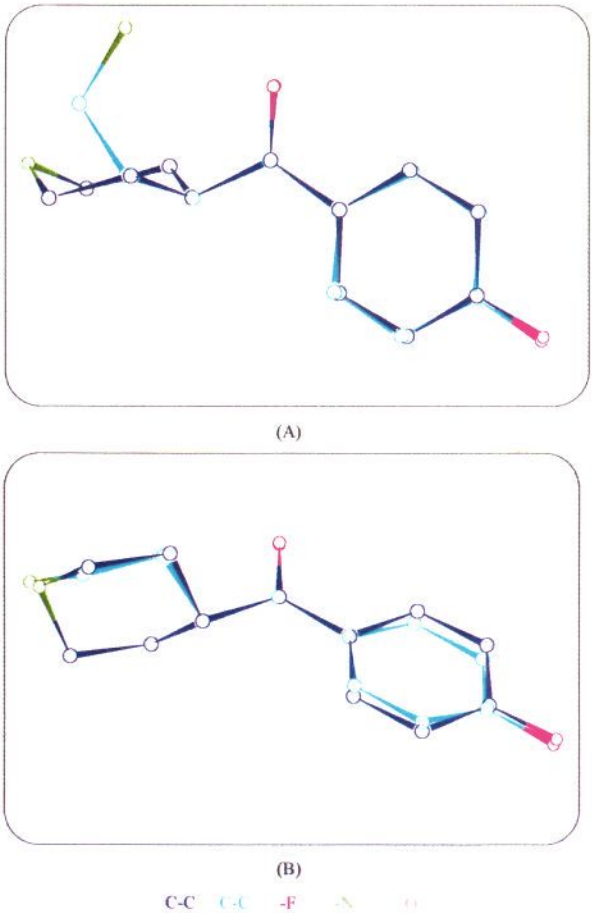


Figure 9. Structural fitting of the haloperidol pharmacophore on the 4-(*p*-fluorobenzoyl)piperidine fragment (Y). (a) Both molecules in minimum-energy conformation. (b) Haloperidol pharmacophore twisted to match fragment Y.

Following the same previously described procedure, the rigid 4-(*p*-fluorobenzoyl)piperidine fragment (Y) was used as a template to which the three X fragments were fitted (Figure 10). Since the goodness of the fit was unaffected by the size of the rings, and since all the X fragments appear to be pharmacologically effective, planarity of the aryl systems related to their size seems not to influence the dopamine-blocking activity of these structures. This finding contrasts with those of a parallel study of their 5-HT_{2A}-blocking activity.[27]

Experimental Section

Chemistry. Melting points were determined with a Kofler hot-stage instrument or a Gallenkamp capillary melting points and are uncorrected. Infrared spectra were recorded with a Perkin-Elmer 1600 FTIR spectrophotometer; main bands are given in cm^{-1}. Proton magnetic resonance spectra were obtained with a Brucker WM-250 (250 MHz) with tetramethylsilane as an internal standard. Mass spectra (FAB) were performed with a Kratos MS-50 mass spectrometer using 2-hydroxyethyl disulfide as a matrix. Elemental analyses were performed in a Perkin-Elmer 240B apparatus at the Microanalyses Service of the University of Santiago de Compostela (Spain); all reported values are within ±0.4% of the theoretical compositions.

The general method of synthesis described are illustrative of those analogous compounds.

The progress of the reactions was monitored by the thin-layer chromatography.

1-Oxo-1,2,3,4-tetrahydro-2-naphthylideneacetic Acid (10) (Table 1). Method B. A stirred mixture of 2.2 g (15 mmol) of α-tetralone and 1.48 g (16 mmol) of glyoxylic acid monohydrate was heated in a Dean–Stark apparatus at 160 °C for 40–45 min. After cooling, the solid which formed was thoroughly triturated with ethyl acetate (2 × 50 mL). After filtration to separate undissolved materials, the liquid filtrate was washed several times with water and dried (Na_2SO_4), and the solvent was evaporated to give 2.90 g (95%) of **10**. A sample for analysis was obtained by recrystallization from EtOH. Mp: 188–190 °C. IR (KBr): 3400–2500 (OH), 1700 (COOH), 1670 (CO), 1640–1600 (C=C). ^1H NMR ($CDCl_3$): δ 8.11–8.08 (d, 1H, H-8), 7.63–7.57 (dt, 1H, H-6), 7.44–7.38 (t, 1H, H-7), 7.35–7.31 (d, 1H, H-5) 6.92 (s, 1H, =CHCOO), 3.48–3.42 (m, 2H, $PhCH_2$), 3.17–3.00 (m, 2H, $PhCH_2CH_2$).

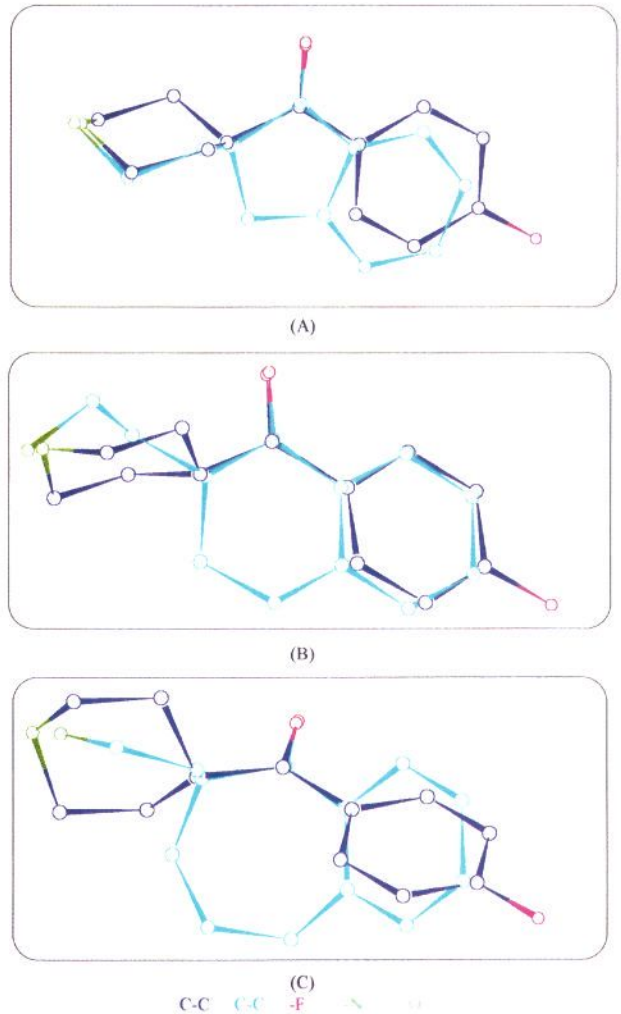


Figure 10. Structural fitting of X fragments on the 4-(*p*-fluorobenzoyl)piperidine fragment (Y) taken as template. (a) Indanone (X_1); (b) tetralone (X_2); and (c) benzosuberone (X_3).

1-Oxo-1,2,3,4-tetrahydro-2-naphthaleneacetic Acid (14) (Table 2). 14 was prepared by reduction of **10** with zinc dust and acetic acid as previously described.[38] Mp: 107–109 °C.

The acetic acid **14** was also prepared by hydrolysis of the corresponding ethyl ester as indicated below.

A solution of 1.06 mL (7.5 mmol) of diisopropylamine in 40 mL of dried THF was cooled to −20 °C under N_2 with stirring. *n*-Butyllithium (3.06 mL of a 2.5 M solution in *n*-C_6H_{14}; 7.5 mmol) was added, and stirring was continued for 0.5 h between −20 and −10 °C. The solution was then cooled to −70 °C and stirred 1 h more. A solution of 1.10 g (7.5 mmol) of α-tetralone in 8 mL of THF was added dropwise over 5–10 min. After 15 min at −70 °C the cooling bath was removed and the reaction mixture was allowed to warm to room temperature under N_2 over 18 h. The THF was evaporated off, and the residue was dissolved in AcOEt/H_2O. The solution was washed with 5% $NaHCO_3$ and 5% HCl and dried (Na_2SO_4), and the AcOEt was evaporated off to give 1.71 g of crude product, which was purified by chromatography on silica gel with CH_2Cl_2 as eluent,

yielding 1.34 g (77%) of the desired 1-oxo-1,2,3,4-tetrahydro-2-naphthaleneacetic acid, ethyl ester. Mp: 47–49 °C. IR (KBr): 1730 (COO), 1682 (CO), 1600 (C=C). ^{1}H-NMR ($CDCl_3$): δ 8.04–8.01 (dd, 1H, H-8), 7.50–7.44 (dt, 1H, H-6), 7.33–7.23 (m, 2H, H-5, H-7), 4.23–4.12 (m, 2H, $COOCH_2CH_3$), 3.20–2.92 (cm, 4H, CH_2AR, CH_2COO), 2.47–2.35 (m, 1H, 2H, H-5, H-7, =CH), 2.30–1.88 (m, 2H, HCHCH=), 1.31–1.22 (dt, 3H, CH_3).

Acid hydrolysis of this ethyl ester with concentrated HCl gave **14** in quantitative yield. Mp: 107–109 °C (EtOH). IR (KBr): 3100–2500 (OH), 1710 (COOH), 1680 (CO) (see Table 2).

1-Oxo-1,2,3,4-tetrahydro-2-naphthaleneacetic Acid Chloride. A solution of 76.2 g (0.6 mol) of oxalyl chloride in 40 mL of anhydrous toluene was added dropwise to a stirred solution of 12.02 g (0.06 mmol) of **13** in 260 mL of anhydrous toluene under an atmosphere. The resulting reaction mixture was allowed to stir overnight at room temperature. The solvent was removed under reduced pressure, and the orange solid residue was used in the next step without further purification. IR: strong band at 1794 cm^{-1} (O=CCl). Quantitative yield.

***N*-[(1-Oxo-1,2,3,4-tetrahydro-2-naphthyl)acetyl]-4-(*p*-fluorobenzoyl)piperidine (18). Route A.** A solution of 1.91 g (22 mmol) of (*p*-fluorobenzoyl)piperidine in 30 mL of anhydrous toluene was slowly added to a stirred solution of 1.97 g (8.9 mmol) of acid chloride in 130 mL of anhydrous toluene under argon atmosphere. The resutling mixture was allowed to stir for 1 h and then heated under reflux for 24 h. After cooling, the solvent was removed under reduced pressure to give a brown oil which was dissolved in dichloromethane, the resulting solution washed with 10% Na_2CO_3 and H_2O and dried (Na_2SO_4), and the solvent was removed in vacuo. The resulting orange oil was purifed by flash chromatography (silica gel, AcOEt/hexane, 1:1) to give 1.1 g (95%) of a yellow oil that does not crystallize on standing. Attempted Kugelrohr distillation caused decomposition. IR (film): 1715 (CO cycloalkanone), 1678 (CO benzoyl), 1643 (CO-N). The *bis*(2,4-dinitrophenyl)hydrazone melted at 207–208 °C (AcOEt) (see Table 3).

Route B. Under an argon atmosphere, a solution of 0.61 g (2.94 mmol) of 4-(*p*-fluorobenzoyl)piperidine, *N*-hydroxybenzotriazole (0.80 g, 5.88 mmol), and 0.60 g (2.94 mmol) of the acid **14** was stirred at room temperature for 1 h; 1.21 g (5.88 mmol) of *N*,*N*-dicyclohexylcarbodiimide was then added to the cooled mixture (0 °C) which was stirred at 0 °C for 1 h and then for 16 h at room temperature. After removal of the DMF in vacuo, the residue obtained was dissolved in CH_2Cl_2 (150 mL), and the resulting solution was washed with 5% $NaHCO_3$ (2 × 25 mL) and H_2O (2 × 40 mL) and dried (Na_2SO_4), and the solvent was removed under reduced pressure. The oil residue was purified by flash chromatography (silica gel, AcOEt/hexane 1:1) to give 0.94 g (81%) of a yellow oil that was identified by IR and as 2,4-dinitrophenylhydrazone, mp 207–208 °C (EtOH) (see Table 3).

***N*-[β-(1-Oxo-1,2,3,4-tetrahydro-2-naphthyl)ethyl]-4-(*p*-fluorobenzoyl)piperidine Bis(ethylene ketal).** A stirred solution of 1.76 g (46 mmol) of the amide **18**, 17.27 g (0.28 mmol) of ethylene glycol, and 54 mg of *p*-TsOH in 55 mL of anhydrous toluene was refluxed in a Dean–Stark apparatus for 22.5 h with azeotropic distillation of water. After cooling, the toluene solution was washed with 10% Na_2CO_3 (2 × 30 mL) and H_2O (2 × 30 mL) and dried (Na_2SO_4), and the solvent was removed under reduced pressure. The resulting crude bisketal (2.05 g, 95%) was an orange oil with only one IR band (1650, CO–N) and was used in the next step without further purification.

***N*-[β-(1-Oxo-1,2,3,4-tetrahydro-2-naphthyl)ethyl]-4-(*p*-fluorobenzoyl)piperidine (22).** A solution of 0.83 g (0.003 mol) of **18** bis(ethylene ketal) in 25 mL of ether was added dropwise to a stirred suspension of 0.47 g (0.012 mol) of $LiAlH_4$ in 16 mL of anhydrous ether under an argon atmosphere. The reaction mixture was heated under reflux for 8 h, cooled at 0 °C in an ice bath, and quenched by the sequential dropwise addition of H_2O (0.5 mL), 10% NaOH (0.7 mL), and H_2O (3 mL). The coarse precipitate formed was filtered off and thoroughly washed with ether. The combined filtrates were treated with 10% HCl and stirred vigorously at 35–40 °C for 1 h. On cooling, the aqueous layer was made alkaline with 10% NaOH and extracted with ether (3 × 50 mL), the combined ether extracts were dried (Na_2SO_4), and the solvent was partially removed under reduced pressure. To the resulting concentrated solution was cautiously added ether-saturated HCl gas. The white precipitate that formed was recovered and kept overnight in a vacuum desiccator; recrystallization from MeOH afforded 0.61 g (85%) of white crystals. Mp: 279–281 °C. Spectral data for the free base follows. IR (film): 1710 (CO cycloalkanone), 1678 (CO benzoyl). ^{1}H-NMR ($CDCl_3$): δ 8.04–7.93 (m, 1H, H-8), 7.49–7 42 (dt, 1H, H-6), 7.337.21 (m, 2H, H-5, H-7), 7.16–7.09 (dd, 2H *o*-Ph-F), 3.06–2.98 (m, 4H, CH_2CH_2N), 2.62–1.62 (complex multiplet). Anal. ($C_{24}H_{26}NO_2F$·HCl) C, H, N.

Pharmacology. Drugs and Chemicals. All compounds were administered in 0.01 mL/g injections (apomorphine subcutaneously and all others intraperitoneally). Compound **20** was administered as a suspension in 0.5% (w/v) sodium carboxymethylcellulose (Merck); haloperidol (Sigma) and compounds **21** and **23** were dissolved in 1% lactic acid in water; dextroamphetamine sulfate (Sigma), atropine hydrochloride (Sigma), eserine (physostigmine) hemisulphate (Sigma), and compound **22** were prepared in saline; and apomorphine hydrochloride (Sigma) was dissolved in 0.9% saline solution with 1% ascorbic acid (w/v) to prevent oxidation. Chemicals used for physiological solutions were of analytical grade.

Experimental Animals and Conditions. Male Charles River CD1 albino mice weighing 25 ± 2 g, male Wistar rats (275 ± 25 g), and male Sprague–Dawley rats (275 ± 25 g) were used. *"In vivo"* assays was carried out in a quiet room thermostated at 22 ± 1 °C with a 12-h light/dark cycle (08.00–20.00) and always at the same time of day (so as to avoid variation due to circadian rhythms). Food and tap water were free available in the home cage.

***"In Vivo"* Experiments. Locomotor Activity.** Spontaneous locomotor activity was monitored in six groups of five mice during 1 h following administration of haloperidol, **21**, or **23** at doses of 0.5 or 2.0 mg/kg, **20** or **22** at doses of 2 or 8 mg/kg, or vehicle alone. In experiments to determine amphetamine-induced hyperactivity, 5 mg/kg of dextroamphetamine sulfate was administered to 4–10 groups of three mice 30 min after administration of vehicle, haloperidol (0.063, 0.094, 0.125, or 0.5 mg/kg), compound **23** at doses of 0.5 or 2 mg/kg, **21** at a dose of 0.5 mg/kg, or **20** or **22** at a dose of 8 mg/kg. Both spontaneous and amphetamine-induced motor activity were recorded during the following hour in an activity cage (Panlab Actisystem D.A.S. 16 V.1), which contains an electromagnetic field that is sensitive to any motion within it.

Catalepsy. This was tested in mice (n = 15–30) 60 min after administration of vehicle, haloperidol (0.25, 0.5, 0.8, 1, or 2 mg/kg), compounds **21** or **23** (0.5, 2 or 8 mg/kg), or **20** or **22** (2 or 8 mg/kg). The mice were placed with their forepaws on one horizontal wire and their hindpaws on another 6 cm away and 2 cm lower. The time during which the mouse maintained this position was recorded, and more than 30 s was considered to indicate catalepsy.

Eserine (Physostigmine)-Induced Mortality. Groups of 10 mice (two groups per compound and dosage level) were treated, 30 min before eserine injection (2 mg/kg), with vehicle, atropine (4 mg/kg), haloperidol, compounds **21** or **23** (2 mg/kg), or **20** or **22** (8 mg/kg). The mice were placed in cages and deaths were counted 60 min after injection of eserine.

Apomorphine-Induced Climbing. The method of Protais[39] was used with a minor modification. The climbing behavior of mice was observed in individual cylindrical stainless-steel wire cages (diameter, 12 cm; height, 14 cm). Mice (six per compound and dosage, except for the control group, for which 12 animals were used) were treated with vehicle, haloperidol (0.125–0.25 mg/kg), or compounds **20**, **21**, or **23** (0.5, 2, or 8 mg/kg) or compound **22** (2, 8, or 16 mg/kg), and 30 min later with 2 mg/kg of apomorphine (subcutaneously). During the next 30 min, climbing activity was recorded every 10 min using the following scale: 0, four paws were on the floor; 1, one or two paws were against the grid wall; and 2,

the mouse clung to the grid wall with three or four paws. The scores recorded 20 and 30 min postapomorphine were added, and the mean of this sum was calculated for each group.

***"In Vitro"* Experiments.** Male Wistar rats were killed by cervical dislocation and decapitation. Both striata and the frontal cortex were quickly dissected out on a cold plate, weighed, and stored at −20 °C until assay.

D_2 Binding. For [^{3}H]spiperone binding assays, paired striata were homogenized in 50 volumes of ice-cold 50 mM Tris-HCl with a Polytron (setting 6 for 5 s) and then centrifuged at 40000*g* for 10 min in a Sorvall centrifuge at 4 °C. The pellet was resuspended and the process repeated. The final pellet was resuspended in 200 volumes of 50 mM Tris-HCl buffer containing 120 mM NaCl. Samples (200 μL) of the final suspension were incubated for 10 min at 37 °C with 25 μL of displacing agent or its vehicle (10% methanol) and 25 μL of a solution of [^{3}H]spiperone; the reaction was terminated by rapid vacuum filtration through Watman GF/C filters, which were washed with 3 × 5 mL of cold buffer. For equilibrium saturation analysis, six ligand concentrations from 0.05−1 nM were used. Nonspecific binding was determined by addition of 10^{-5} M (+)-sulpiride. For determination of the IC_{50} values of drugs displacing [^{3}H]spiperone (0.25 nM) binding, at least six ascending concentrations of each drug were used (10^{-9}–10^{-4} M). Assays were carried out in triplicate at each ligand or displacing drug concentration.

D_1 Binding. For [^{3}H]SCH 23390 binding assays, paired striata were homogenized in 200 volumes of 50 mM Tris-HCl buffer and centrifuged at 1000*g* for 10 min, and the supernatant was centrifuged at 20000*g* for 10 min. The pellet was resuspended and the process repeated. The final pellet was resuspended in 50 mM Tris-HCl containing 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, and 1 mM $MgCl_2$. Saturation curves were constructed with six ligand concentrations from 0.15 to 2.5 nM. Nonspecific binding was determined by addition of unlabeled SCH 23390 (10^{-6} M). Samples were incubated at 25 °C for 30 min.

5-HT_{2A} Binding. Frontal cortex tissue was homogenized (Ultraturrax 5, s at 20 000 rpm) in 50 volumes of 50 mM Tris-HCl, pH 7.4, and centrifuged at 30000*g* for 10 min at 4 °C. The pellet was rehomogenized and centrifuged again. The final pellet was reconstituted in 200 volumes of buffer. Aliquots of membrane preparations (200 μL) were incubated with 25 μL of 1 nM [^{3}H]ketanserin (NEN 60 Ci/mmol). Specific binding was defined by incorporation of 25 μL of methysergide (final concentration 1 μM). Samples were incubated for 15 min at 37 °C, and incubation was terminated by vacuum filtration.

Aorta Ring Experiments. Endothelium-stripped aorta rings from Sprague−Dawley rats were mounted under a resting tension of 1.5 g in a 20-mL organ bath containing Krebs solution (composition (mM): NaCl, 118.07; KCl, 4; $CaCl_2H_2O$, 2.5; $MgSO_4{\cdot}7H_2O$, 1.2; KH_2PO_4, 1.2; $NaHCO_3$, 25; glucose, 11) at 37 °C bubbled with carbogen (95% O_2, 5% CO_2). Isometric contraction forces were measured using a CPUL 0−25-g transducer connected to a Celaster IOS-1 apparatus. After stabilization for 60 min, cumulative concentration−response curves were constructed as per Van Rossum,[40] increasing serotonin concentrations from 30 nM to 10 mM in the absence or in the presence of increasing concentrations of ketanserine or new compounds.

Expression of Results and Statistical Analysis. Pharmacological calculations were obtained by PCS program (Pharmacologic Calculation System).[41] The statistical significance of differences between means was determined by Student's test for unpaired data, the differences with probabilities lower than 0.05 were considered statistically significant. Percentage change in locomotor activity (% LC) was calculated as: % LC = [(mean no. of movements by control animals) − (mean no. of movements by treated animals)]/(mean no. of movements by control animals) × 100. The percentage of animals showing catalepsy (% C) was calculated as (no. of animals showing catalepsy)/(total no. of animals) × 100. ED_{50} values were calculated by Litchfield and Wilcoxon's method in the catalepsy test.

Inhibition constant (K_i) values were calculated from the Cheng−Prussof equation: $K_i = IC_{50}/[1 + (F/K_D)]$, where F is the total concentration of ^{3}H-ligand used, K_D is the equilibrium dissociation constant, and IC_{50} is the drug concentration required to inhibit 50% of specific binding.[42] Percentage specific binding was calculated as [(dpm sample) − (dpm nonspecific binding)]/[(dpm total binding) − (dpm nonspecific binding)] × 100. Competitive antagonism was quantified as pA_2, which was calculated from a Schild plot of log (dose ratio − 1) for three antagonist concentrations; six replicate experiments were performed.

Molecular Modeling. The geometries of molecular fragments were optimized by the AM1 method[43] as implemented in the program MOPAC.[44] For both these computations and structural fitting, the molecular modeling package BIOSYM Inc., San Diego, CA, was used.

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