Synthesis and Antidopaminergic Activity of Some 3-(Aminomethyl)tetralones as Analogues of Butyrophenone

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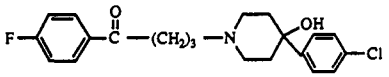
Starting from β-benzoylpropionic acid we synthesized 3-(aminomethyl)tetralones in which the amino substituent was 4-(*N*-piperazinyl)-*p*-fluorobutyrophenone (**14**), 4-benzoylpiperidine (**15**), 4-hydroxy-4-phenylpiperidine (**16**) or 4-(*o*-methoxyphenyl)piperazine (**17**). The possible dopamine antagonist activity of these compounds was investigated in both "in vitro" and "in vivo" experiments. These compounds potently inhibited [^{3}H]spiperone binding to D_2 striatal receptors and moderately inhibited [^{3}H]SCH-23390 binding to D_1 striatal receptors (K_is in the nanomolar and micromolar ranges, respectively). Apomorphine-induced stereotypies and amphetamine group toxicity were antagonized, to different extents, by the compounds under study, with a potency similar to that of haloperidol. Interestingly, no catalepsy was observed after administration of the new compounds (2–8 mg/kg). The most active compounds "in vivo" **14** and **15** possessed two butyrophenone pharmacophores. However, the tetralone moiety appeared not critical for their antidopaminergic activity, since all target compounds were less active than haloperidol. These studies provide a pharmacological basis for future research on these new compounds devoid of cataleptogenic activity.

Introduction

Since the discovery of chlorpromazine as an effective antipsychotic agent, large numbers of potential neuroleptics have been synthesized. Despite this intense research activity, there are still relatively few structurally distinct classes of drugs with clinically confirmed antipsychotic activity. The butyrophenones, whose prototype is haloperidol (**1**),[1] are perhaps the most important such group.



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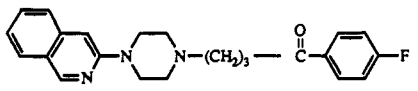

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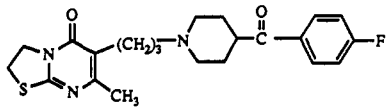

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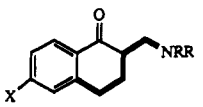
While neuroleptic drugs continue to be the best form of treatment for schizophrenia, they possess two major disadvantages. First, one-third of patients suffering from this disorder do not respond to neuroleptic treatment. Second, almost all existing neuroleptics produce extrapyramidal side effects (EPS a short-term parkinsonismlike condition caused by dopamine receptor blockade), tardive dyskinesia (a syndrome of involuntary movements that has been linked to hypersensitivity of brain dopamine receptors after long blockade), and hyperprolactinaemia (caused by blockade of pituitary dopamine receptors). Efforts have therefore been made to find drugs with greater clinical efficacy and/or reduced propensity to produce EPS. Drugs which possess this clinical profile have been termed "atypical antipsychotics". Cinuperone (**2**)[2] and setoperone (**3**)[3] are two atypical antipsychotics belonging to the butyrophenone group which have been developed in the last years.

In earlier papers[4,5] we have reported the potential neuroleptic activity of 2- and 3-(aminomethyl)tetralones **4** and **5**, where the Rs represent simple amine substituents. These compounds are semirigid variants of the general neuroleptic structure Ar-C_4-N.



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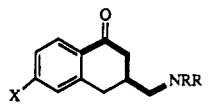

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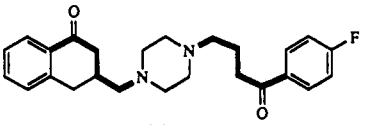
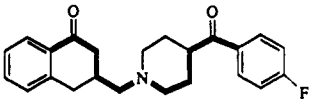
We have also studied the α-blocking and antidopaminergic activity of compounds **5** in isolated rat vas deferens, finding that pA_2 values increase with the size of the amine moiety.[6] These results have prompted us to synthesize derivatives **14–17** and to investigate their potential antidopaminergic activity.

Interestingly, compounds **14** have two butyrophenone pharmacophores, one semirigid and the other flexible, while compound **15** combines a semirigid 3-(aminomethyl)tetralone fragment with a benzoylpiperidine moiety.[7]



14a



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‡Department of Pharmacology, University of Santiago de Compostela.
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(1) Janssen, P. A. J. *Psychopharmacological Agents*; Academic Press: New York, 1974; Vol. III, p 129.
(2) Su, T. P. *Neurosci. Lett.* **1986**, *71*, 224.
(3) Leysen, J. E.; Van Gompel, P.; Gommeren, W.; Woestenborghs, P., Janssen, P. A. J. *Psychopharmacology* **1986**, *88*, 434.
(4) Eirin, A.; Ravina, E.; Montanes, J. M.; Calleja, J. M. *Eur. J. Med. Chem.* **1976**, *11*, 29.
(5) Eirin, A.; Santana, L.; Ravina, E.; Fernandez, F.; Sanchez-Abarca, E.; Calleja, J. M. *Eur. J. Med. Chem.* **1978**, *13*, 533.
(6) Santana, L.; Ravina, E.; Cortizo, L.; Orallo, F. *An. R. Acad. Farm.* **1989**, *55*, 461.
(7) The benzoyl piperidine moiety is a potent neuroleptic pharmacophore comparable to butyrophenone group. See: Boswell, R. F., Jr.; Welstead, W. J., Jr.; Duncan, R. L., Jr.; Johnson, D. N.; Funderburk, W. H. *J. Med. Chem.* **1978**, *21*, 136.

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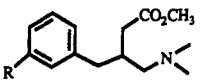
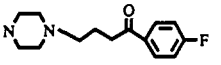
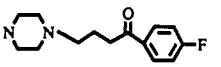
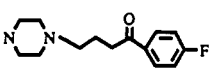
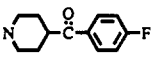
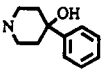
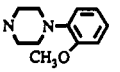
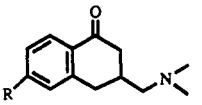
Table I. β-(Aminomethyl)-γ-phenylbutyric Acids, Methyl Esters

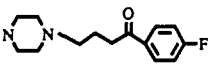
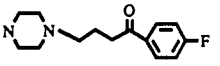
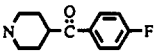
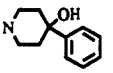
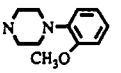


compd	R	N	method	% yield	mp, °C	solvent
10a	H		A	51	179–183[a]	EtOH anhyd
10a	H		B	73	179–183[a]	EtOH anhyd
10b	F		B	85	200–202[b]	MeOH–Et_2O[c]
11	H		B	70	167.5–170[a]	EtOH–Et_2O
12	H		B	53	149–151[a]	AcOEt–EtOH
13	H		B	77	190–192[a]	*n*-PrOH

[a] Hydrochloride. [b] Oxalate. [c] Washed.

Table II. 3-(Aminomethyl)-1-tetralones



compd	R	N	% yield	mp, °C	solvent	formula
14a	H		37	165–166[a]	EtOH anhyd	$C_{25}H_{29}FN_2O_2 \cdot C_8H_8O_8$
14b	F		43	260.4–262[b]	*n*-PrOH-H_2O	$C_{25}H_{28}F_2N_2O_2 \cdot C_3H_8O_2 \cdot 2HBr$
15	H		50	135–136[c]	cyclohexane	$C_{23}H_{24}FNO_2$
16	H		33	154–156[d]	Et_2O[d]	$C_{22}H_{25}NO_2 \cdot HCl$
17	H		65	217–218.8	*i*-PrOH	$C_{22}H_{26}N_2O_2 \cdot 2HCl$

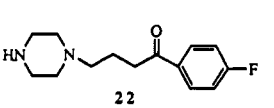
[a] Maleate. [b] Hydrobromide. [c] Base. [d] Washed.

Results and Discussion

Chemistry. The general synthetic strategy followed in preparation of these compounds is shown in Scheme I. Arylbutyrolactones **7a,b** were prepared by a method previously described for the unsubstituted compound,[8] hydroxymethylation of the β-aroylpropionic acids followed by lactonization to aroylbutyrolactones **6a,b** and subsequent reduction of the carbonyl group. Reaction of **7a,b** with hydrogen bromide in acetic acid afforded unstable bromo acids **8a,b**, which upon ring closure with polyphosphoric acid were converted to 3-(bromomethyl)-1-tetralones **18a,b**, whose structures were established by ^1H NMR. In the nucleophilic reactions with amines, compound **18a** invariably gave the elimination product 3,4-benzobicyclo[4.4.0]heptan-2-one (**19a**) instead of the desired substituted derivative. The structure of cyclopropyltetralone **19a**, which has been prepared by van Tamelen et al.[9] and Julia et al.[10] by alkaline treatment of the tosylate of 3-(hydroxymethyl)-1-tetralone, was confirmed by analytical and spectral data.

Several attempts were made to block the carbonyl group of (bromomethyl)tetralones **18**. It was not possible to obtain the ethylene ketals, and though the ethylene dithioketals **20** were obtained by standard procedures in 70% yield, subsequent attempts at nucleophilic substitution were unsuccessful. In the end, the final products **14–17** (Table II) were obtained in good yields by substitution with methyl esters **9** and subsequent cyclization of the resulting amino esters **10–13** with PPA (Table I).

p-Fluoro-4-(*N*-piperazinyl)butyrophenone (**22**) was prepared by direct alkylation of piperazine with a large excess of ω-chloro-*p*-fluorobutyrophenone in methyl isobutyl ketone or, better, by alkylation with the ethylene ketal of ω-chloro-*p*-fluorobutyrophenone and subsequent acidic hydrolysis.[11]



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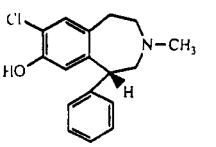

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(8) Rothe, J.; Zimmer, H. *J. Org. Chem.* **1959**, *24*, 586.
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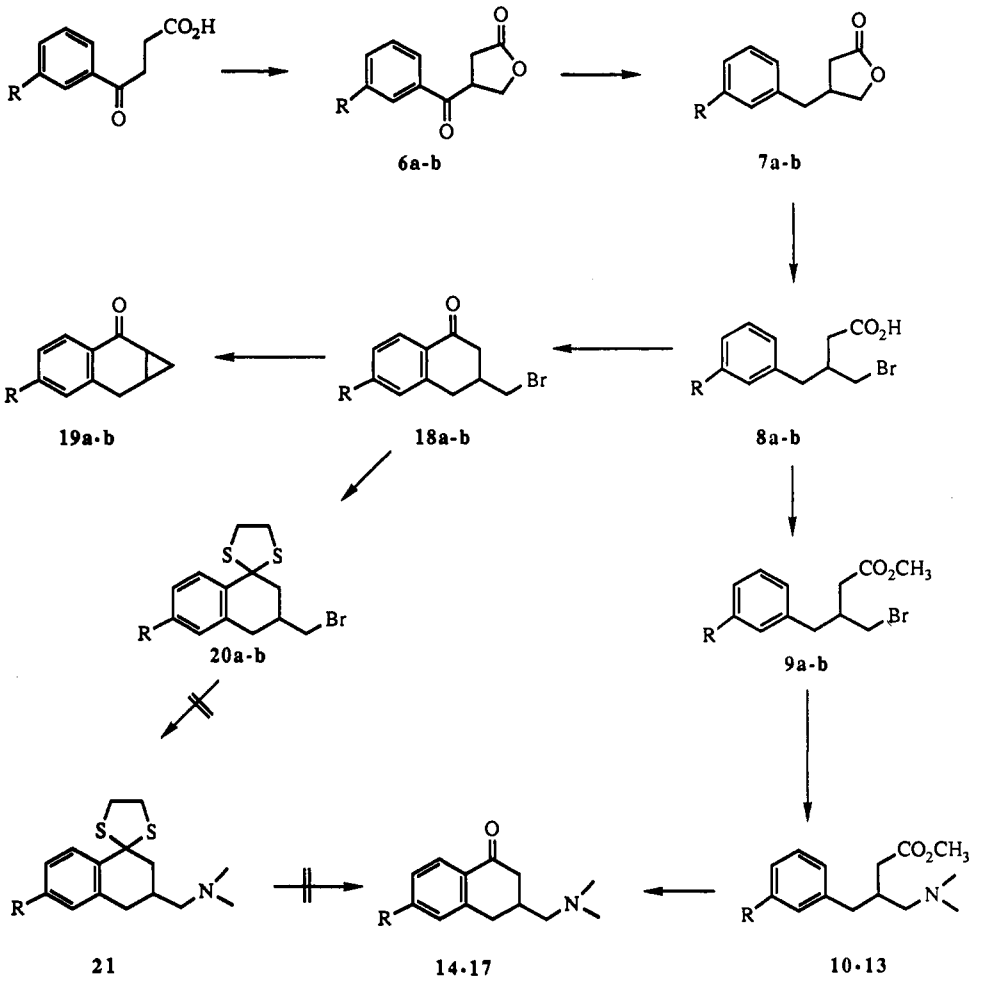
Scheme I



a (R=H)

b (R=F)

Table III. Inhibition Constants (pK_i) at D_1 and D_2 Receptors and Group Toxicity Antagonism

compd	pK_i,[a] M		D_2[b] selectivity	group[c] toxicity antagonism	confidence limit
	[^{3}H]spiperone	[^{3}H]SCH-23390			
halop	8.30	7.01	1.29	0.020	0.005–0.085
14a	7.60	6.42	1.18	0.251	0.133–0.473
14b	7.11	6.04	1.07	0.053	0.016–0.181
15	7.68	6.49	1.19	0.055	0.014–0.215
16	7.13	6.13	1.00		
17	8.19	5.87	2.32	0.349	0.137–0.892

[a] Results represent the mean of at least four inhibition curves constructed with each drug. The mean standard error of K_i values was 10–18%. [b] D_2 selectivity: values were calculated as pK_i[^{3}H]spiperone minus pK_i[^{3}H]SCH-23390. [c] Results correspond to ED_{50} expressed in mg/kg.

Pharmacology

The existence of two types of dopamine receptors is widely accepted.[12] D_1 receptor stimulation leads to increased adenylate cyclase activity, while D_2 receptors are either not coupled or are negatively coupled to this enzyme.[13-15] The antipsychotic activity of neuroleptic drugs has usually been ascribed to their relatively well-known D_2-mediated effects, though it has recently been reported that a selective D_1 antagonist, SCH-23390 (**23**), also has antipsychotic activity.[16]

In the work described here possible interaction of the compounds synthesized with DA receptors and α-receptors

(11) The alkylation of *N*-(ethoxycarbonyl)piperazine and ω-chloro-*p*-fluorobutyrophenone and subsequent decarbethoxylation in an alkaline medium gives *p*-ethoxy-4-(*N*-piperazinyl)butyrophenone in accordance with the results obtained by Rajsner et al.: Rajsner, M.; Metysova, J.; Nemec, J.; Protiva, M. *Collect. Czech. Chem. Commun.* **1975**, *40*, 1218.

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(16) Iorio, L. C.; Barnett, A.; Leitz, F. H.; Houser, V. P.; Korduba, C. A. *J. Pharmacol. Exp. Ther.* **1983**, *226*, 462.

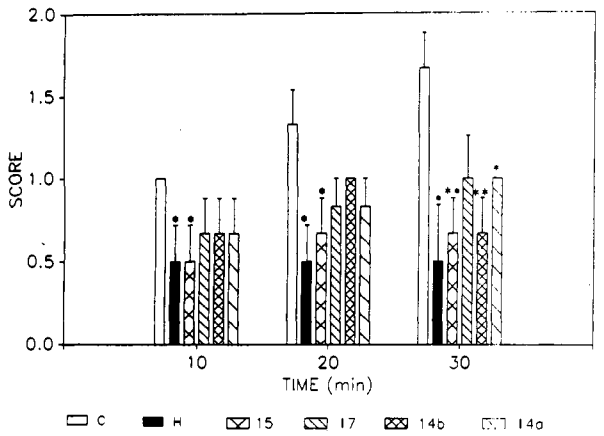

Figure 1. Apomorphine (1 mg/kg sc) was injected into the animals 30 min after the administration of the vehicle (C), haloperidol (H), or compounds (2 mg/kg ip). Stereotyped behavior was monitored every 10 min for 30 min, after the injection of apomorphine. Results are means ± SEM of the scores of six animals. Significant difference vs controls: $*p < 0.05$, $**p < 0.01$ (Student's t test).

was investigated "in vivo" by studying their antagonism of (+)-amphetamine group toxicity and apomorphine-induced stereotyped behavior and catalepsy in mice and "in vitro" by studying ligand binding and their effects on dopamine- and norepinephrine-induced contractions of isolated rat vas deferens.

Blockade of (+)-amphetamine lethality in aggregated mice (group toxicity) is a recognized measure of neuroleptic activity.[17-19] In this study compounds **14b** and **15** afforded greatest protection against group toxicity, though with ED_{50}'s greater than that of haloperidol (Table III).

In the antagonism to apomorphine the activity of compound **15** was at all times postadministration (p.a.) similar to just slightly less than that of haloperidol. None of the compounds studied induced catalepsy at dosages in the range 2–8 mg/kg i.p. (data not shown), and since at this dosage level they failed to protect against eserine (data not shown), this absence of cataleptogenic activity cannot have been due to concomitant anticholinergic activity. Their effects in these assays designed to test activity in the striatum (the catalepsy test and possibly the antistereotyping test) are nevertheless somewhat contradictory when considered in the light of previous studies, for while their lack of cataleptogenic activity suggests that they do *not* block striatal dopaminergic receptors, whose blockade by neuroleptics has been reported to cause catalepsy in experimental animals[20,21] and extrapyramidal symptoms in man,[22] their antagonism of apomorphine suggests that they *may*, the induction of stereotyped activity by apomorphine having been related by several authors to the striatal dopaminergic system.[23-27] This possible contradiction would be resolved either if the dopaminergic mesolimbic system as well as the nigrostriatal pathway were involved in the induction of stereotyped behavior by apomorphine (indeed, McKenzie[28] claimed that only the nucleus accumbens was involved in this response) or if the tetralone dosages used in this study, though sufficient to antagonize apomorphine, were insufficient to elicit a cataleptic response. Whether or not higher tetralone dosages would be cataleptogenic, the existence of a dosage range for which their neuroleptic effects are not associated with catalepsy in mice suggests that it might be possible to use them in man as selective antipsychotics lacking extrapyramidal side effects (Figure 1).

Table IV. Effects of (Aminomethyl)tetralones on NE- and DA-Induced Contraction of Isolated Rat Vas Deferens

compd	pA_2 values ± SEM against NE	pA_2 values ± SEM against DA
haloperidol	6.99 ± 0.08	7.40 ± 0.15
14a	6.75 ± 0.12	7.27 ± 0.28
15	7.08 ± 0.11	7.45 ± 0.14
17	6.76 ± 0.18	7.18 ± 0.21

Table III summarizes the results on binding to striatal dopamine receptors. All the new compounds potently displaced [^{3}H]spiperone binding to striatal D_2 receptors and moderately inhibited the binding of [^{3}H]SCH-23390 to striatal D_1 receptors, with K_i values in the nanomolar and micromolar ranges, respectively. Compound **17** has the greatest affinity for D_2 receptors and the least for D_1 receptors, and was thus the most D_2 selective.

Antidopaminergic activity was also investigated by measuring the inhibition of dopamine-induced contractions of isolated rat vas deferens which may be mediated by postsynaptic D_2 or α_1-receptor activation.[29,30] The fact that for every antagonist (haloperidol or the new compounds) the pA_2 values for norepinephrine and dopamine were practically the same (a result also reported for haloperidol by Leedham and Pennefather,[31] though not by Simon and Van Maanen[32]) strongly suggests that both agonists bind to the same receptors in rat vas deferens. Since for haloperidol the pA_2 values are unchanged under experimental conditions blocking β-adrenoceptors (by addition of propranolol), reuptake of catecholamines by neutrons (by addition of cocaine), and extraneuronal uptake (by addition of β-estradiol),[33] it seems likely that norepinephrine and dopamine both bind to the α_1-receptors to which norepinephrine is already[30] known to bind in this tissue. The pharmacological activity of the new compounds in rat vas deferens would thus consist in adrenergic blocking activity; the hypothesis that the therapeutic effects of antipsychotic drugs are mediated largely through noradrenergic blockade has been reassessed, and several lines of evidence now suggest that antagonism of α_1-noradrenergic receptors may contribute to the thera-

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peutic effects of antipsychotic drugs[34] (Table IV).

The antipsychotic activity of neuroleptics correlates well with their ability to block D_2 receptors,[35] but not with D_1 blockade;[36,37] the performance of neuroleptics in behavioral tests is accordingly generally attributed solely to their D_2-blocking ability,[38] though research carried out since the discovery of selective D_1 agonist and antagonist[16,39-42] suggests that D_1 receptors too may mediate the effects of neuroleptics on behavior, and possibly their clinical effect also.[43-45] This may explain the differences between the relative potencies of the compounds studied in the "in vivo" and binding experiments; compound **17**, the most D_2 selective, was the least effective "in vivo", indicating *the* possible contribution of both D_1 and D_2 receptors to the antipsychotic activity.

In conclusion, all the tetralones tested in this study proved to possess antipsychotic activity at dosages at which no cataleptic effects were observed. The most active were compounds **14b** and **15**, both of which have two butyrophenone pharmacophores, one the semirigid (aminomethyl)tetralone moiety and the other a flexible linear butyrophenone moiety (**14b**) or a semirigid benzoylpiperidine fragment (**15**). However, since all the new compounds were less active than haloperidol, their tetralone moiety may not be essential for their neuroleptic activity.

Experimental Section

Chemistry. Melting points were determined with a Kofler hot-stage instrument and with a Gallemkamp capillary melting point apparatus and are uncorrected. Proton magnetic resonance spectra were obtained with a Varian FT-80 (80 MHz) or a Bruker WM-250 (250 MHz) with tetramethylsilane as an internal standard. Infrared spectra were recorded with a Perkin-Elmer 297 spectrometer. Mass spectra were obtained with a Varian MAT-711 (70 eV) apparatus. Elemental analyses were performed in a Perkin-Elmer 240 apparatus at the Micronalyses Service of the University of Santiago de Compostela (Spain), and values are within 0.4% of the theoretical compositions.

4-(*N*-Piperazinyl)-*p*-fluorobutyrophenone (22). Method A. To a solution of 12.87 g (149 mmol) of anhydrous piperazine in 75 mL of methyl isobutyl ketone was added 5.0 g (25 mmol) of ω-chloro-*p*-fluorobutyrophenone dropwise. The solution was refluxed for 12 h. The solvent was removed under reduced pressure, the solid residue was treated with 10% HCl, and the resulting acidic solution was washed with ethyl acetate, made alkaline with aqueous sodium hydroxide solution, and extracted with methylene chloride. The organic extract was washed with water and dried (Na_2SO_4) and the solvent was removed "in vacuo" to yield 5.38 g (86%) of **22** as an oil which solidified on standing. Mp: 90–93 °C. ^{1}H NMR ($CDCl_3$): δ 7.95–7.91 (d, 2 H, *o*-PhCO), 6.93–6.90 (d, 2 H, *o*-PhF), 2.99–2.91 (m, 6 H, piperazino C-2 and C-6, CH_2CO), 2.58–2.56 (m, 4 H, piperazino C-3 and C-5), 2.47–2.42 (t, 2 H, CH_2N), 1.96–1.90 (t, 2 H, CCH_2C). Anal. ($C_{14}H_{19}FN_2O$): C, H, N.

Method B. To a solution of 2.10 g (24 mmol) of anhydrous piperazine in 7 mL of methyl isobutyl ketone was added 1.0 g (4 mmol) of 4-chloro-1,1-(ethylenedioxy)-1-(4-fluorophenyl)butane in 3 mL of methyl isobutyl ketone dropwise. The solution was refluxed for 12 h. The solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2, washed with water to neutral pH, and dried (Na_2SO_4). The solvent was removed to leave 1.1 g (92%) of 4-piperazinyl-1,1-(ethylenedioxy)-1-(4-fluorophenyl)butane, which was used for the following reaction without further purification.

A solution of 1.1 g (3.4 mmol) of the ethylene ketal and concentrated HCl (2 mL) in methanol (30 mL) was refluxed for 2 h. The methanol was removed under reduced pressure and the residue was dissolved in water, made alkaline with aqueous ammonia, and extracted with CH_2Cl_2. The organic layer was washed with water and dried (Na_2SO_4). The solvent was removed by evaporation under reduced pressure to yield 0.77 g (83%) of **22**.

β-(Bromomethyl)-γ-phenylbutyric Acid, Methyl Ester (9a). To a stirred solution of 11.05 g (0.062 mol) of **7** in 17 mL of glacial acetic acid at 0 °C was added 20 mL of 33% HBr–AcOH dropwise. After 15 min at room temperature, the solution was heated at 80 °C for 4 h. After cooling, the reaction mixture was poured into ice–water and extracted with chloroform. The chloroform solution was washed several times with water and dried (Na_2SO_4), and the solvent evaporated to afford 15.16 g (94%) of **8**.

Methyl ester **9a** (R = H) was obtained as usual using a solution of CH_2N_2 in ether. Bp: 116–120 °C (0.2 mmHg). ^{1}H NMR ($CDCl_3$): δ 7.32–7.21 (m, 5 H, Ar), 3.68 (s, 3 H, OCH_3), 3.53–3.40 (m, 2 H, CH_2-Br), 2.72–2.45 (m, 5 H, aliphatic). Anal. ($C_{12}H_{15}BrO_2$): C, H.

Compound **9b** (R = F) was prepared by the same procedure as **9a**, using the appropriate lactone, to give quantitative yields. Bp 130–135 °C (0.15 mmHg). Anal. ($C_{12}H_{14}BrFO_2$): C, H.

3-(Bromomethyl)-1-tetralone (18a). To 196.5 g of well-stirred polyphosphoric acid at 60 °C was slowly added 13.10 g (0.05 mol) of crude **8a**, after which the temperature was increased to 120 °C. After 2 h, the reaction mixture was poured into ice–water and extracted with ether. The organic extracts were washed several times with water and dried (Na_2SO_4), and the solvent evaporated "in vacuo". The oily residue was distilled (bp 146 °C, 0.5 mmHg) to yield the desired product, which solidified immediately and was recrystallized from heptane to afford **18a** (9.25 g, 76%). Mp: 45–47 °C. ^{1}H NMR ($CDCl_3$): δ 8.02 (dd, $J_{7,61}$ = 1.38 Hz, 1 H, C-8), 7.54–7.48 (dt, $J_{7,46}$ = 1.47 Hz, 1 H, C-6), 7.36–7.28 (m, 2 H, C-5 and C-7), 3.55–3.43 (m, 2 H, CH_2Br), 3.15–2.99 (m, 1 H, *H*CHPh), 2.57–2.46 (m, 2 H, *H*CHCO, CH). MS: *m/z* (relative intensity) 238–240 M^+ (100). Anal. ($C_{11}H_{11}BrO$): C, H.

Compound **18b** was prepared similarly to **18a**, using **8b** as starting product (80%). Bp: 150 °C (0.1 mmHg). ^{1}H NMR ($CDCl_3$) aromatic ^{1}H: δ 8.07–8.01 (m, 1 H, C-8), 7.07–6.95 (m, 2 H, C-5 and C-7). Anal. ($C_{11}H_{10}BrFO$): C, H.

β-(Aminoethyl)-γ-phenylbutyric Acids, Methyl Esters (10–13). General Procedures: Method A. To a solution of the appropriate amine (1.9 mmol) in anhydrous benzene (3 mL) was added β-(bromoethyl)-γ-phenylbutyric acid methyl ester (0.95 mmol), in anhydrous benzene (1 mL). After 14 h of refluxing the resulting precipitate was removed by filtration and discarded, and the solvent was removed from the filtrate under reduced pressure. The resulting oil was dissolved in ether and treated with a solution of HCl in ether to precipitate the salt, which was collected by filtration and recrystallized (Table I).

Method B. To a solution of the appropriate amine (8.4 mmol) in methyl isobutyl ketone (80 mL) were added anhydrous Na_2CO_3 (2.96 g) and KI (0.046 g) followed by β-(bromomethyl)-γ-phenylbutyric acid methyl ester (8.4 mmol) in methyl isobutyl ketone. This mixture was refluxed for 20 h. Inorganic salts were filtered, and the solvent was removed under reduced pressure. The resulting oil was dissolved in chloroform, washed several times with water, and dried (Na_2SO_4). The chloroform was removed under reduced pressure to afford the desired aminomethyl ester (Table I). Anal.: C, H, N.

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3-(Aminomethyl)-1-tetralones (14–17). General Procedure. To the appropriate aminomethyl ester was slowly added (3.6 mmol) 32 g of well-stirred polyphosphoric acid at 90 °C and the temperature was raised to 130 °C. After 5 h the reaction mixture was poured into ice–water and stirred to obtain a total solution, which was then made alkaline with 5 N NaOH and extracted with Cl_2CH_2. The organic phase was washed several times with water to neutral pH and dried (Na_2SO_4), and the Cl_2CH_2 was removed "in vacuo" to afford the desired 3-(aminomethyl)-1-tetralone (Table II). Anal.: C, H, N.

^1H NMR ($CDCl_3$) data for **14a**: δ 8.03–7.97 (m, 3 H, C-8, *o*-PhCO), 7.71–7.44 (m, 1 H, C-6), 7.33–7.25 (m, 2 H, C-5 and C-7), 7.17–7.09 (m, 2 H, *o*-PhF), 3.11–2.31 (m, 19 H), 1.96–1.91 (m, 2 H, CH_2CH_2CO). **14b** (aromatic ^1H): δ 8.04–7.99 (m, 3 H, C-8, *o*-PhCO), 7.38–6.92 (m, 4 H, C-5, C-7, *o*-PhF). **15**: δ 8.07–7.94 (m, 3 H, C-8, *o*-PhCO), 7.49–7.45 (m, 1 H, C-6), 7.34–7.26 (m, 2 H, C-5 and C-7), 7.17–7.10 (m, 2 H, *o*-PhF), 3.20–2.67 (m, 6 H, aliphatic), 2.45–2.11 (m, 6 H, $(CH_2)_3N$), 1.89–1.81 (m, 4 H, piperidino, C-3 and C-5). **16**: δ 8.04–8.01 (m, 1 H, C-8), 7.48–7.19 (m, 8 H, aromatic), 3.16–2.29 (m, 15 H, aliphatic). **17**: δ 8.07–8.01 (m, 1 H, C-8), 7.52–7.49 (m, 1 H, C-6), 7.34–7.27 (m, 2 H, C-5 and C-7), 7.26–6.84 (m, 4 H), 3.86 (s, 3 H, OCH_3), 3.16–2.34 (m, 15 H, aliphatic).

Pharmacology. "In Vivo" Experiments. These experiments were peformed in a thermostated room (22 ± 1 °C) with a 12/12 h light/dark cycle (8.00–20.00). All were carried out at the same time of day in order to avoid variations caused by circadian rhythms. Male albino mice (Charles River CD.1) weighing 26 ± 3 g were used throughout. Doses of test compounds, haloperidol, apomorphine, (+)-amphetamine, and eserine were prepared immediately before administration.

In the *group toxicity antagonism* test, the new compounds or haloperidol (0.25, 0.5, 1, and 2 mg/kg) were injected ip 30 min prior to (+)-amphetamine (dose 15 mg/kp ip) in volumes of 0.01 mL/body weight; control groups were administered an equal volume of vehicle. After the first administration, the mice were placed into groups of 10 in circular cages 20 cm in diameter, without food or water; the death rate 24 h after administration of (+)-amphetamine was recorded. Group toxicity antagonism is expressed as ED_{50} (mg/kg), which was calculated as per Litchfield and Wilcoxon.[46]

Catalepsy was tested in five-mice groups 30 and 60 min after administration of saline solution, haloperidol, or one of the compounds under investigation (six groups for each substance). The mice were placed with their forepaws on one horizontal wire and their hindpaws on another 6 cm away and 2 cm lower; those remaining in this position for over 30 s were considered cataleptic.

In the test of antagonism to *apomorphine-induced stereotyped behavior* six-mice groups were treated with 1 mg/kg (sc) of apomorphine 30 min after administration of 2 mg/kg (ip) of the compounds, haloperidol, or saline solution, and during the following $^1/_2$ h stereotypes were scored every 10 min with the following scale: 0, absence of stereotypes; 1, some stereotyped movement shown; 2, intense smelling, with mastication and licking periods, and 3, large periods of mastication and licking, usually with mice climbing on the wall of the cage.[47]

To test ability to *protect against a lethal dose of eserine* (2 mg/kg ip), groups of 10 mice were treated ip 30 min before eserine injection, with vehicle, atropine (4 mg/kg), haloperidol, or the new compounds (2–8 mg/kg). The mice were placed in individual cages and the dead were counted 24 h after injection of eserine.

Vas Deferens Assays. Male Sprague–Dawley rats (250–300 g) were killed by a blow on the head. The vas deferens was dissected free from adhering tissue, removed, and suspended in a 10-mL tissue bath containing Krebs solution (composition in mM: NaCl, 118; KCl, 4.7; $MgSO_4 \cdot 7H_2O$, 1.2; $CaCl_2 \cdot 2H_2O$, 2.5; KH_2PO_4, 1.2; $NaHCO_3$, 25; glucose, 11) maintained at 37 °C and gassed with a mixture of 95% O_2 and 5% CO_2. After an equilibration period of at least 1 h under 0.8 g of resting tension, cumulative concentration–response curves of isotonic contractions induced by an agonist (norepinephrine or dopamine) were obtained by the method of Van Rossum[48] before and after 5 min of exposure to the test compounds. All values were expressed as mean ± SEM. pA_2 values were calculated as per Arunlakshana and Schild,[49] log(dose ratio − 1) being calculated at three antagonist concentrations, with four replicate experiments performed.

(−)-Norepinephrine bitartrate and 3-hydroxytyramine hydrochloride were obtained from stock solutions (10 mM) in distilled water containing sodium bisulfite (1%) and kept frozen (−20 °C). Solutions of haloperidol and the test compounds were prepared in distilled water immediately before use. The chemicals used for the preparation of the Krebs solution were of analytical grade.

Binding Assays. Male Wistar rats weighing 250–300 g were killed by cervical dislocation and decapitation. Both striata were quickly dissected on a cold plate, weighed, and stored at −20 °C until assayed.

For determination of [^3H]spiperone binding to membrane preparations, tissue was homogenized with a Polytron (setting 6 for 5 s) in 50 vol of ice-cold 50 mM Tris HCl (pH 7.4) and 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 vol of 50 mM Tris HCl buffer containing 120 mM NaCl. Aliquots (200 μL) of the final suspension were incubated with 25 μL of displacing agent or its vehicle and 25 μL of a solution of [^3H]spiperone. For equilibrium saturation analysis, six ligand concentration from 0.05 to 1 nM were used. Nonspecific binding was defined by addition of 10^{-5} M of (+)-sulpiride. For determinations of the IC_{50} values of drugs to displace [^3H]spiperone (0.25 nM) binding at least six ascending concentrations of each drug were included in the assay (10^{-9}–10^{-4} M). All samples were examined in triplicate at each ligand or displacing drug concentration. Samples were incubated for 10 min at 37 °C. The reaction was terminated by rapid vacuum filtration through Whatman GF/C filters, which were washed with 3 × 5 mL of cold buffer.

For the determination of [^3H]SCH-23390 binding to membrane preparations, paired striata were homogenized in 200 vol 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 mM. Nonspecific binding was determined by addition of unlabeled SCH-23390 (10^{-6} M). Samples were incubated at 25 °C for 30 min. Inhibition constant (K_i values) were calculated by using the Cheng–Prussof equation

$$K_i = IC_{50}/(1 + (F/K_d))$$

where F is the free concentration of [^3H]ligand used, K_d is the equilibrium dissociation constant, and IC_{50} is the drug concentration required to inhibit 50% of specific binding, defined as follows:

$$\frac{\text{dpm sample} - \text{dpm nonspecific binding}}{\text{dpm total binding} - \text{dpm nonspecific binding}} \times 100$$

Registry No. **7a**, 22530-98-9; **7b**, 133496-49-8; **8a**, 133496-51-2; **8b**, 133496-50-1; **9a**, 133496-52-3; **9b**, 133496-74-9; **10a**, 133496-53-4; **10a**·*x*HCl, 133496-64-7; **10b**, 133496-63-6; **10b**·$C_2H_2O_4$, 133496-65-8; **11**, 133496-54-5; **11**·HCl, 133496-66-9; **12**, 133496-55-6; **12**·HCl, 133496-67-0; **913**, 133496-56-7; **13**·*x*HCl, 133496-68-1; **14a**, 133496-57-8; **14a**·$C_4H_4O_4$, 133496-70-5; **14b**, 133496-69-2; **14b**·2HBr, 133496-71-6; **15**, 133496-58-9; **16**, 133496-59-0; **16**·HCl, 133496-72-7; **17**, 133496-60-3; **17**·2HCl, 133496-73-8; **18a**, 133496-61-4; **18b**, 133496-62-5; **22**, 2560-31-8; piperazine, 110-85-0; ω-chloro-*p*-fluorobutyrophenone, 3874-54-2; 4-chloro-1,1-(ethylenedioxy)-1-(4-fluorophenyl)butane, 3308-94-9; 4-piperazinyl-1,1-(ethylenedioxy)-1-(4-fluorophenyl)butane, 55846-41-8.

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