Piperazinomethyl Tetralines: Synthesis and Affinities for D_1, D_2 and 5-HT_{2A} Receptors

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Starting from the methyl ester of β-(bromomethyl)-γ-phenylbutyric acid and its *m*-fluoro derivative, we have prepared 2-[4-[3-(*p*-fluorobenzoyl)-1-propyl]piperazin-1-ylmethyl]tetraline (QF0105B) and the corresponding 7-fluoro derivative (QF0106B). The affinities of these compounds for D_1 and D_2 dopamine and 5-HT_{2A} receptors was evaluated *in vitro*. The affinities of QF0105B and QF0106B for D_2 receptors are less than that of haloperidol (pK_i's for inhibition of [^{3}H]spiperone binding: 7.72, 7.06 and 8.30, respectively) but all three compounds have similar affinities for 5-HT_{2A} receptors (pK_i's for inhibition of [^{3}H]ketanserine binding: 7.70, 7.36 and 7.70, respectively).

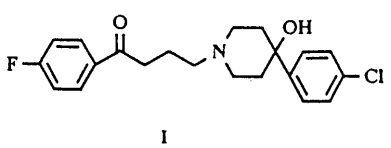
Key words piperazino tetraline; butyrophenone; D_1 receptor; D_2 receptor; 5-HT_{2A} receptor; antipsychotic activity

Since the discovery of chlorpromazine as an effective antipsychotic agent, many potential neuroleptics have been synthesized. Haloperidol (I) is the prototype of a group of butyrophenone derivatives with a very potent and specific antipsychotic activity.[1] The clinical efficacy of traditional, or classical, antipsychotics in the treatment of schizophrenia and other psychotic disorders is directly related to their ability to block D_2 dopamine receptors in the brain.[2-5] Unfortunately, dopamine receptor blockade (in the striatum) is also intimately associated with extrapyramidal side effects (EPS).[6-10] Furthermore, the classical antipsychotics are ineffective against the negative symptoms of schizophrenia, such as apathy, motor retardation, flat affectivity, poverty of speech and others.

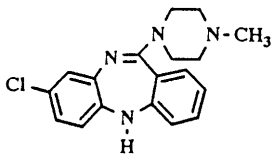
The discovery of clozapine (II) in the 1960s gave rise to a new group of "atypical" or "non classical" antipsychotics which have no EPS and are effective against negative symptoms. Clozapine blocks not only dopamine receptors but also 5-HT_{2A} receptors, and it is to this mixed activity that its atypical antipsychotic profile has been attributed: Meltzer *et al.*[11,12] suggested that the efficacy against negative symptoms and lack of EPS of atypical antipsychotic drugs are determined by their relative affinities for D_2 and 5-HT_{2A} receptors, clozapine and clozapine-like antipsychotics having a pK_i(5-HT_{2A})/pK_i(D_2) ratio ≥ 1.12 whereas typical neuroleptics have a ratio < 1.09.

Clinical studies with setoperone (III) and ritanserine (IV) have provided evidence that blockade of 5-HT_{2A} receptors may ameliorate EPS associated with D_2 dopamine receptor blockade. More recently, another two putative antipsychotics with both D_2 and 5-HT_{2A} blocking activity, risperidone (V) and ocaperidone (VI), have been reported to improve both positive and negative symptoms of schizophrenia while showing little propensity to produce EPS.[13-17]

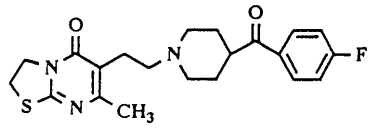
In previous papers[18-20] we have reported the synthesis and antidopaminergic (D_1 and D_2) and antiserotoninergic (5-HT_{2A}) activity of the 3-piperazinomethyl tetralones **1a** and **1b**. These compounds, in which a piperazine bridge links two butyrophenone pharmacophores (the semirigid aminomethyl tetralone moiety and the flexible linear butyrophenone fragment) may be considered as conformationally restricted butyrophenone structures analogous to haloperidol. Compounds **1a** and **1b** potently inhibit



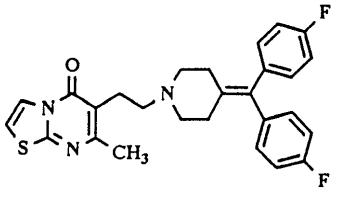
I



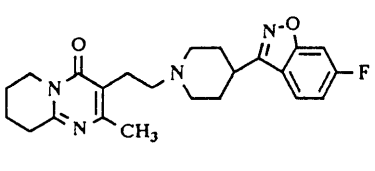
II



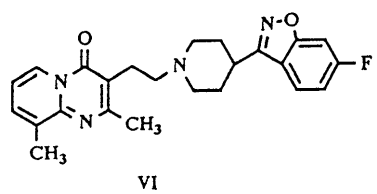
III



IV



V



VI

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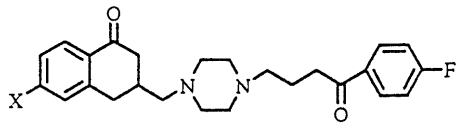
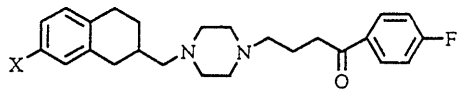


X=H **1a** QF 0102B

X=F **1b** QF 0103B



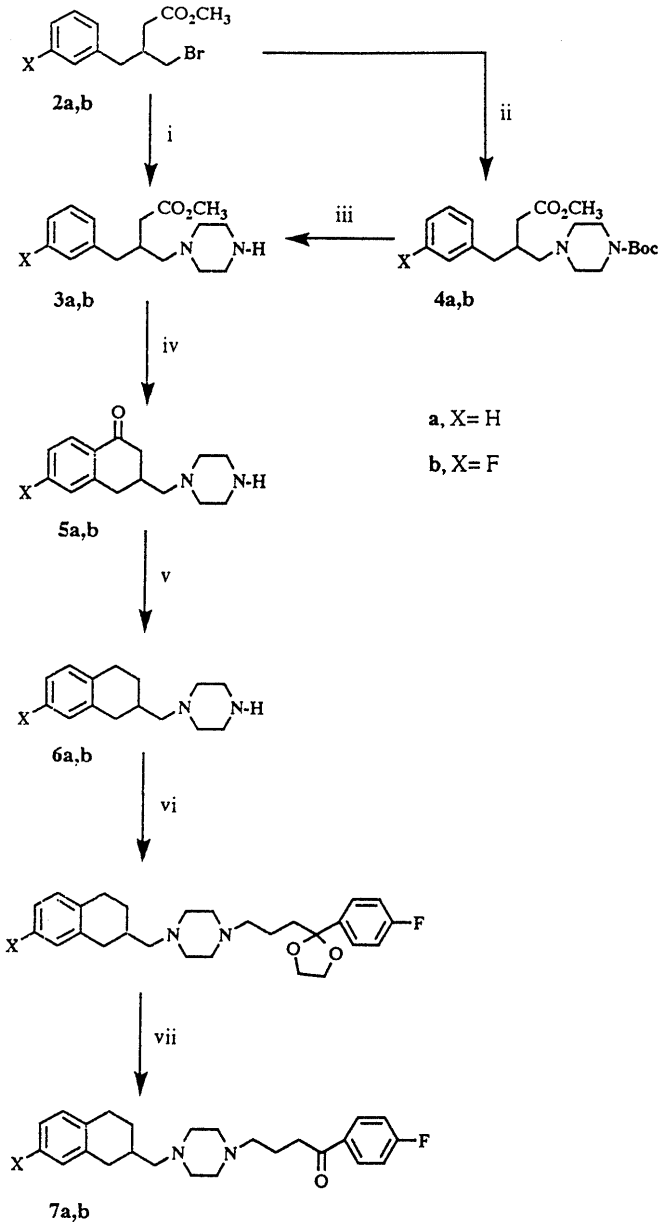
X=H **7a** QF 0105B

X=F **7b** QF 0106B

the binding of [^{3}H]spiperone to striatal D_2 receptors (pK_i's = 7.60 for **1a**, 7.11 for **1b** and 8.30 for haloperidol) and moderately inhibit the binding of [^{3}H]SCH-23390 to D_1 receptors (pK_i's = 6.42 for **1a**, 6.04 for **1b** and 7.01 for haloperidol).[18] Compounds **1a** and **1b** also have significant affinity for 5-HT_{2A} receptors with pK_i's of 7.25 and 7.29 respectively (8.84 for methylsergide) for inhibition of the binding of ^{3}H-ketanserine to frontal cortex membrane preparations; and both compounds show inhibitory activity against serotonin-induced contractions in rat aorta stripped of endothelium, though with pA_2 values lower than that of ketanserine, a classical 5-HT_{2A} antagonist (7.25 for **1a**, 7.29 for **1b** and 8.87 for ketanserine).

To investigate the influence of the tetralone moiety on the antidopaminergic and antiserotoninergic activities of the above mentioned compounds, we have now synthesized and characterized the receptor-binding properties of their tetraline analogues, the novel products **7a** and **7b** (QF0105B and QF0106B respectively), which have only one linear butyrophenone fragment. They were prepared as outlined in Chart 1.

The key methyl esters of β-(bromomethyl)-γ-phenylbutyric acid and its *m*-fluoro derivative, **2a** and **2b**, were prepared from β-benzoyl and 6-fluoro-β-benzoylpropionic acids as previously described.[11,21] The corresponding β-(piperazine-1-ylmethyl)-γ-phenylbutyric acid methyl esters, **3a** and **3b** were directly prepared in moderate yields (50—60%) by alkylation of the bromoesters with a large excess of anhydrous piperazine in refluxing methyl isobutyl ketone (method A). Alternatively, alkylation with piperazine–BOC in refluxing ethanol and subsequent deprotection afforded **3a** and **3b** in quantitative yields (method B). Ring closure with polyphosphoric acid gave the tetralones **5a** and **5b** in yields of 60—70%. Removal of the keto group was achieved by the Wolf–Kishner Huang–Minlon procedure for **5a**, giving **6a** and **6b** in 45—50% yield; and by catalytic reduction over Pd–C in acetic acid at 90 °C for **5b**, giving **6b** in 75% yield. Finally, the best yields (50%) of the 2-[4-(3′-*p*-fluorobenzoylpropyl)piperazin-1-ylmethyltetralines **7a** and **7b** were obtained by prolonged refluxing of tetralines **6a** and **6b** in basic methyl isobutyl ketone with 4-chloro-1,1-ethylenedioxy-1-(4-fluorophenyl)butane after addition of potassium iodide.



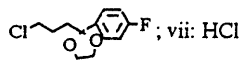
i: piperazine; ii: piperazine-Boc; iii: TFA; iv: PPA;
v: Wolf-Kishner for X= H, Pd/C-MeOH/90°C for X= F;
vi:  ; vii: HCl

Chart 1

Table 1. Results of Receptor Binding and Functional Studies

	pK_iD_1	pK_iD_2	pK_i5-HT_{2A}	pK_is5-HT_{2A}/D_2	pA_2
Haloperidol	7.01	8.30	7.70	0.93	—
Clozapine	6.8[11]	7.0[11]	8.3[11]	1.19[11]	9.16
QF0105B	6.60	7.72	7.70	1.00	7.12
QF0106B	—	7.06	7.36	1.04	7.20
Methysergide	—	—	8.84	—	7.97[23]
Ketanserine	—	—	—	—	8.87

Table 1 lists the results of dopamine and serotonin receptor binding experiments and of functional experi-

Table 2. Behavioral Effects

Test	Compound	Dose (mg/kg)	% variation
Spontaneous motor activity	Haloperidol	$ED_{50}=0.65$	50
	Clozapine	—	—
	QF0105B	2	30.9 ($p<0.01$)
	QF0102B	2	6.9 (n.s.)
Hypermotility	Haloperidol	$ED_{50}=0.1$	50
	Clozapine	$ED_{50}=1.7$	50
	QF0105B	2	9.1 (n.s.)
		8	36.5 ($p<0.01$)
	QF0102B	2	0.76 (n.s.)
Stereotyped behaviour	Haloperidol	2	70 ($p<0.01$)
	Clozapine[a]	$ED_{50}=2.23$	50
	QF0105B	2	40 ($p<0.01$)
	QF0102B	2	40 ($p<0.01$)
Conditioned avoidance response	Haloperidol	0.1	45.8 ($p<0.01$)
	Clozapine	5	50.85
	QF0105B	2	4.5 (n.s.)
	QF0102B	2	18.4 ($p<0.05$)
Catalepsy	Haloperidol	$ED_{50}=0.7$	50
	Clozapine	$ED_{50}>50$	—
	QF0105B	2	No effect
		8	No effect
	QF0102B	2	No effect
		8	3.3 (n.s.)
Rota-rod	Haloperidol	$ED_{50}=0.15$	50
	Clozapine	$ED_{50}=2.28$	50
	QF0105B	2	6 (n.s.)
	QF0102B	2	10 (n.s.)
Traction	Haloperidol	$ED_{50}=1$	50
	Clozapine	$ED_{50}=3.8$	50
	QF0105B	1	16.6 ($p<0.05$)
		2	20 ($p<0.05$)
	QF0102B	1	13.4 (n.s.)
		2	20 ($p<0.01$)

a) ED_{50} in climbing behavior.

ments using rat aorta. In [^{3}H]spiperone binding assays the new compounds exhibited pK_i values that were similar to those of tetralones **1a** and **1b**, lower than that of haloperidol and slightly higher than that of clozapine. In [^{3}H]ketanserine-binding assays, the affinities of the tetralines for 5-HT_{2A} receptors were similar to those of the tetralones, the same as (QF0105B) or slightly less than (QF0106B) that of haloperidol, and about 1 unit lower than that of methylsergide or clozapine. The pK_i(5-HT_{2A})/pK_i(D_2) ratios are lower than 1.12 (1.19 for clozapine), and according to Meltzer's classification[11] the new compounds may be considered as typical antipsychotics. In the rat aorta experiments, both compounds showed competitive antagonism of serotonin, shifting the serotonin concentration–response curve dose dependently to higher concentrations with no significant depression of the maximum effect; their Schild plot slopes did not differ significantly from one, and their pA_2 values did not differ significantly from each other.

QF0105B was less active than haloperidol in behavioral screening test (Table 2, QF0106B was not evaluated). The new compound was more active than its analog QF0102B in the locomotor activity,[22] showed similar activity in amphetamine-induced hypermotility (only high doses of QF0105B show significative reduction), catalepsy,[18] apomorphine-induced stereotypes and traction tests, and was less active in the conditioned avoidance test. Values of a so-called atypical antipsychotic drug, clozapine in binding experiments, functional experiments using rat aorta and behavioral experiments are included for comparison.

These results suggest that the loss of the carbonyl group in the tetralone moiety of **1a** and **1b** does not significantly modify the activities.

Experimental

Chemistry Melting points were determined with Köfler hot stage and Gallenkamp capillary instruments 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. Elemental analyses were performed on a Perkin–Elmer 240B apparatus at the Microanalysis Service of the University of Santiago de Compostela; all values were within $\pm 0.4\%$ of the theoretical compositions. Unless otherwise stated, hydrochlorides were prepared by dropwise addition, until cessation of salt formation, of a saturated solution of HCl in anhydrous Et_2O to a solution of the amine in anhydrous Et_2O or absolute MeOH/Et_2O.

***β*-(1-Piperazinylmethyl)-*γ*-phenylbutyric Acid Methyl Ester (3a). Method A** The methyl ester of *β*-bromomethyl-*γ*-phenylbutyric acid (5 g, 0.018 mol) in methyl isobutyl ketone (10 ml) was cautiously added to a solution of anhydrous piperazine (9.51 g, 0.110 mol) in methyl isobutyl ketone (45 ml) was cautiously added with stirring. The mixture was refluxed with stirring for 7 h, then the resulting precipitate was removed by vacuum filtration and dissolved in CH_2Cl_2. The resulting solution was washed with water and dried (Na_2SO_4) and the solvent was removed by distillation under reduced pressure. The resulting brown oil was distilled in a Kugelrohr apparatus to give 3.17 g (62%) of a colorless oil of bp 150—153 °C (0.5 mmHg). IR (KBr): 1735 (COO). ^{1}H-NMR ($CDCl_3$) δ: 7.18—7.19 (5H, d, aromatics), 3.58 (3H, s, $COOCH_3$), 2.85—2.21 (complex multiplet, aliphatic protons). Picrate: yellow needles, mp 196—198 °C (ethanol). *Anal.* Calcd for $C_{16}H_{24}N_2 \cdot 2C_6H_3N_3O_7$: C, 45.78; H, 4.11; N, 15.24. Found: C, 46.05; H, 4.25; N, 15.01. Hydrochloride: white prisms, mp 198—200 °C.

A similar reaction starting from the methyl ester of *β*-bronomethyl-*γ*-(*m*-fluorophenyl)butyric acid gave the methyl ester of *β*-(1-piperazinylmethyl)-*γ*-(*m*-fluorophenyl)butyric acid (**3b**), in a yield no higher than 30%, as a colorless oil of bp 150—152 °C (0.5 mmHg). IR (KBr): 1740 (COO). ^{1}H-NMR ($CDCl_3$) δ: 7.28 (1H, dd, H_4), 6.88—6.95 (3H, m, H_2, H_5, H_6), 3.69 (3H, s, $COOCH_3$), 3.15—2.83 (complex multiplet, aliphatic protons). Hydrochloride: mp 205—206 °C (MeOH). *Anal.* Calcd for $C_{16}H_{23}FN_2O_2 \cdot 2HCl$: C, 52.32; H, 6.86; N, 7.63. Found: C, 52.38; H, 6.75; N, 7.63.

Method B *β*-(4-BOC-piperazin-1-ylmethyl)-*γ*-phenylbutyric Acid Methyl Ester (4a) Piperazine-BOC (1.22 g, 1.7 mmol) in ethanol (15 ml) was added to a solution of the bromoester **2a** (2.23 g, 0.077 mol) in ethanol (15 ml). The mixture was refluxed with stirring for 18 h, then the solvent was removed under vacuum and the resulting residue was partitioned between CH_2Cl_2 and 10% $NaHCO_3$. The organic extracts were combined and dried (Na_2SO_4), and the solvent was removed by distillation under reduced pressure. The oil gave a white crystalline solid on standing. Chromatography on a silica gel column (AcOEt : hexane = 1 : 4) afforded 2.71 g (90%) of a white solid, mp 69—70 °C. IR (KBr): 1732 (COO), 1694 (COO-BOC). ^{1}H-NMR ($CDCl_3$) δ: 7.18—7.19 (5H, d, aromatics), 3.58 (3H, s, $COOCH_3$), 2.12—2.49 (complex multiplet, aliphatic protons), 1.44 (9H, s, $OC(CH_3)_3$).

***β*-(4-BOC-piperazin-1-yl-methyl)-*γ*-(*p*-fluorophenyl)butyric Acid Methyl Ester (4b)** Compound **4b** was prepared similarly. White needles, mp 74—75 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.22 (1H, dd, H_4), 6.86—6.94 (3H, complex multiplet, H_2, H_5, H_6), 3.62 (3H, s, $COOCH_3$), 3.36 (4H, t, *p*-F-Ph-C$\underline{H}_2$, C$\underline{H}_2$N(CH_2CH_2)$_2$N-BOC), 2.71—2.12 (complex multiplet, aliphatic protons), 1.44 (9H, s, $OC(CH_3)_3$).

BOC Removal: A solution of **4b** in trifluoroacetic acid (7.86 g, 0.069 mol) was stirred at room temperature for 20 min. After removal of the acid under vacuum, the residue was dissolved in CH_2Cl_2, the resulting solution was washed with 10% $NaHCO_3$ and water and dried (Na_2SO_4), and the solvent was distilled off under reduced pressure to give **3b** as a white oil. Hydrochloride, mp 205—206 °C (MeOH).

3-(1-Piperazinylmethyl)tetralone (5a) Well-stirred polyphosphoric acid (55.2 g) (Fluka) was slowly added at 90 °C to 1.84 g (6.6 mol) of **3a**. Under vigorous stirring the temperature was raised to 130—140 °C. After 5 h, the reaction mixture was poured into ice-water and stirred to obtain a solution which was made alkaline with 0.5 N NaOH and then extracted with CH_2Cl_2. The organic phase was washed with water to neutral pH and dried (Na_2SO_4) and the solvent was removed *in vacuo* to afford 1.12 g (69%) of **5a** as a brown oil that decomposed after attempted distillation in a Kugelrohr apparatus. Chromatography on a silica gel column (AcOEt : hexane = 1 : 4) gave pure **5a** IR (KBr): 1680 (CO). ^{1}H-NMR ($CDCl_3$) δ: 7.08 (4H, s, aromatics), 2.95—2.00 (complex multiplet, aliphatic protons). Oxalate: white prisms, mp 204—206 °C (EtOH). 2,4-Dinitrophenylhydrozone: fine orange needles, mp 204—205 °C (*n*-PrOH). *Anal.* Calcd for $C_{21}H_{24}N_6O_4$: C, 59.40; H, 5.71; N, 19.80. Found: C, 59.22; H, 5.42; N, 19.55. Oxalate; mp 204—205 °C (EtOH).

6-Fluoro-3-(1-piperazinylmethyl)tetralone (5b) Compound **5b** was obtained similarly as a white oil. IR (KBr): 1680 (CO). ^{1}H-NMR ($CDCl_3$) δ: 8.05 (1H, dd, H_8), 6.94—7.01 (2H, m, H_5, H_7), 2.66—3.10 (6H, complex multiplet, $H_4N(CH_2CH_2)_2NH$), 2.30—2.39 (complex multiplet, remaining aliphatic protons), 2,4-dinitrophenylhydrazone: orange needles, mp 308—310 °C (AcOEt). Hydrochloride: white prisms, mp 192—195 °C. *Anal.* Calcd for $C_{15}H_{19}FN_2O \cdot 2HCl$: C, 53.74; H, 6.31; N, 8.36. Found: C, 53.70; H, 6.26; N, 8.38.

2-(Piperazinylmethyl)tetraline (6a) Hydrazine hydrate (1.43 g, 0.028 mol) and KOH (1.63 g) were cautiously added to a solution of 3-(1-piperazinylmethyl)tetralone (**5a**, 3.5 g, 14 mmol) in diethyleneglycol (14 ml). The mixture was heated first for 1 h at 120 °C, then for 2 h at 230 °C (for decomposition of the hydrazone) and finally for 6 h at 360 °C. It was cooled, then water was added and the resulting mixture was extracted with ether. The organic phase was washed with water to neutral pH and dried (Na_2SO_4), and the solvent was removed under reduced pressure to give a brown oil which was distilled in a Kugelrohr apparatus to afford 2.07 g (63%) of a white oil, bp 130—135 °C (0.5 mmHg). This oil, on treatment with anhydrous ether, gave aciculate crystals of mp 72—73 °C (acetone–chloroform). Hydrochloride: white prisms, mp 99—100 °C (AcOEt). *Anal.* Calcd for $C_{15}H_{22}N_2 \cdot HCl$: C, 78.00; H, 9.60; N, 12.13. Found: C, 77.83; H, 9.55; N, 12.40.

7-Fluoro-3-(1-piperazinylmethyl)tetraline (6b) A solution of tetralone **5b** (0.14 g, 0.53 mmol) in glacial acetic acid (34.4 ml) containing 0.3 g of 10% Pd–C was shaken at 90 °C and 50 psi in a Parr hydrogenation apparatus. Reduction was complete in about 8 h and no further absorption occurred on continued shaking. The catalyst was removed by filtration, the filtrate was washed with acetic acid, and the solvent was removed under reducted pressure to give 0.10 g (75%) of a colorless oil that did not crystallize either on standing or after treatment with anhydrous ether. Hydrochloride: white prisms, mp 156—158 °C (MeOH). *Anal.* Calcd for $C_{15}H_{21}FN_2 \cdot 2HCl$: C, 56.08; H, 7.22; N, 8.72. Found: C, 56.11; H, 7.17; N, 8.37.

2-{4-[3-(*p*-Fluorobenzoyl)propyl]piperazin-1-ylmethyl}tetraline (7a) A solution of 4-chloro-1,1-ethylenedioxy-1-(4-fluorophenyl)butane (1.43 g, 5.9 mmol) in methyl isobutyl ketone (15 ml) was added to a mixture of **6a** (1.38 g, 5.9 mmol), anhydrous Na_2CO_3 (1.65 g) and potassium iodide (0.032 g) in methyl isobutyl ketone (45 ml), with stirring. After having been refluxed with vigorous stirring for 10 h, the mixture was allowed to stand at room temperature overnight. The precipitate was filtered off and the solvent was removed from the filtrate under reduced pressure to give a white oil, that, on standing evolved to afford 1.11 g (47%) of white prisms of mp 99—101 °C (acetone). IR (KBr): 1680 (CO). ^{1}H-NMR ($CDCl_3$) δ: 8.01—8.03 (2H, dd, *o*-Ph-CO), 7.07—7.97 (6H, m, aromatics), 3.00—2.79 (6H, complex multiplet, 4H benzylic protons and CH_2CO), 2.46—1.91 (complex multiplet, remaining aliphatic protons). *Anal.* Calcd for $C_{25}H_{31}FN_2O$: C, 76.14; H, 7.86; N, 7.10. Found: C, 76.01; H, 7.77; N, 7.31. Hydrochloride: white flakes, mp 200 °C (dec.) (AcOEt : EtOH).

7-Fluoro-2-{4-[3-(*p*-fluorobenzoyl)propyl]piperazin-1-ylmethyl}tetraline (7b) Compound **7b** was prepared similarly as a colorless syrup (30%). IR (KBr); 1682 (CO). ^{1}H-NMR ($CDCl_3$) δ: 7.91 (2H, dd, *o*-CO-Ph), 7.12 (2H, t, *o*-F-Ph), 6.98 (1H, t, H_6), 6.76 (2H, d, H_5, H_8), 2.97—1.94 (complex multiplet, aliphatic protons). Hydrochloride: white flakes, mp 172—173 °C (MeOH–ether). *Anal.* Calcd for $C_{25}H_{30}F_2N_2O_2 \cdot 2HCl$: C, 61.86; H, 6.64; N, 5.77. Found: C, 61.89; H, 6.66; N, 5.82.

Pharmacology The pharmacological methods for the *in vitro* receptor assays and for *in vivo* tests have been published in detail elsewhere.[18-20,22] The conditioned avoidance response test,[24] the traction test[25] and the rota-rod test[26] were conducted as described.

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