Synthesis and Affinities for Dopamine (D_2) and 5-Hydroxytryptamine ($5\text{-}HT_{2A}$) Receptors of 1-(Benzoylpropyl)-4-(1-oxocycloalkyl-2-ethyl)-piperazines as Cyclic Butyrophenone Derivatives

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Starting from benzo- or thienocycloalkaneacetic acids, we have prepared a series of 1-(3-*p*-fluorobenzoylpropyl)-4-(1-oxo-benzo- or thienocycloalkyl-2-ethyl)piperazines 8a—e containing both semirigid and linear butyrophenones pharmacophores. The affinities of these compounds for dopamine (D_2) and 5-hydroxytryptamine ($5\text{-}HT_{2A}$) receptors were evaluated *in vitro* in receptor-binding assays and in functional experiments. The ratios of pK_i's for $5\text{-}HT_{2A}/D_2$ receptors may be useful for rapid screening of new compounds and assessing potential induction of extrapyramidal symptoms; ratio values ≥ 1.12 (Meltzer's ratio) are predictive of an atypical antipsychotic profile. The new molecules had a ratio in the range of 0.96—1.11 while haloperidol showed a ratio of 0.93. The 2-piperazinoethyl thiotetralone derivative 8d (QF 0506B) with a ratio of 1.11 was the most active compound.

Key words benzocycloalkanone; thienocycloalkanone; piperazine derivative; D_2 receptor; $5\text{-}HT_{2A}$ receptor; butyrophenone pharmacophore

Haloperidol[1] (I) is the prototype of a group of butyrophenone derivatives with a very potent antipsychotic activity, including the potent neuroleptics spiperone and fluanisone, which are 4-amino-*p*-fluorobutyrophenone derivatives. 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 dopamine (D_2) receptors in the brain.[2—5] Unfortunately, dopamine receptor blockade (in the striatum) is also intimately associated with their extrapyramidal side effects (EPS).[6—9] 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" antypsychotics which have no EPS and are effective against negative symptoms. Clozapine blocks not only dopamine receptors but also 5-hydroxytryptamine ($5\text{-}HT_{2A}$) receptors, and it is to this mixed activity that its atypical antipsychotic profile has been attributed. Clozapine[10,11] does, however, have side effects of its own, such as agranulocytosis and seizures. The shortcomings of all current antipsychotic drugs have led to an urgent need for better therapies. Meltzer *et al.*[12,13] suggested that the efficacy of atypical antipsychotic drugs against negative symptoms and their lack of EPS are determined by their relative affinities for D_2 and $5\text{-}HT_{2A}$ receptors; clozapine and clozapine-like antipsychotics have pK_i ($5\text{-}HT_{2A}/D_2$ ratios) ≥ 1.12 whereas for typical antipsychotics this ratio is <1.09. A number of mixed $5\text{-}HT_{2A}/D_2$ antagonists which may be considered as belonging to the butyrophenone group are now available, *e.g.* cinuperone III, setoperone IV, risperidone V; clinical studies with risperidone have supported the theory that blockade of $5\text{-}HT_{2A}$ receptors may ameliorate the EPS associated with D_2 dopamine receptor blockade.[14]

In previous papers[15—17] we have reported the synthesis and antidopaminergic and antiserotoninergic activities of 3-(aminomethyl)tetralones VI, VII and 2-(2-piperidinoethyl)-benzocycloalkanones VIII, which are conformationally restricted butyrophenone structures analogous to haloperidol.

As a continuation of that work we have now prepared the compounds **8a—e**, which also possess the essential requirements for interaction with dopamine and serotonin receptors. These compounds have two butyrophenone pharmacophores, a semirigid aminoethyl cyclanone moiety and a flexible linear butyrophenone fragment. Both pharmacophores are linked by a piperazine bridge.

Initially, to synthesize the final compounds **8a—e**, we tried a route *via* acylation of the 4-piperazino-1-(4-fluorophenyl)-1-butanone with acid chlorides **3a—e** and subsequent ketalization and reduction of the resulting amide. However, although **9c** was obtained in very good yield (86%), the ketalization of both carbonyl groups was not possible. Thus, we prepared the piperazinylamines **7a—e** and the alkylation was done in the final step.

Compounds **8a—e** were prepared *via* the sequence of reactions outlined in Chart 1. Synthesis of benzo- or thienocycloalkaneacetic acids (1-indanone-2-acetic acid **2a**, 5-fluoro-1-indanone-2-acetic acid **2b**, 1-tetralone-2-acetic acid **2c**, 4-oxo-4*H*-5,6-dihydrocyclopenta[*b*]thiophen-5-yl acetic acid **2d**, and 4-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophen-5-yl acetic acid **2e**) was accomplished by thermal condensation of the corresponding cycloalkanones (indanone, 5-fluoro indanone, tetralone, 5,6-dihydro-4*H*-cyclopenta[*b*]thiophene-4-one[18] and 4,5,6,7-tetrahydrobenzo[*b*]thiophene-4-one[19]) with glyoxylic acid at 160 °C, in quantitative yields followed by reduction

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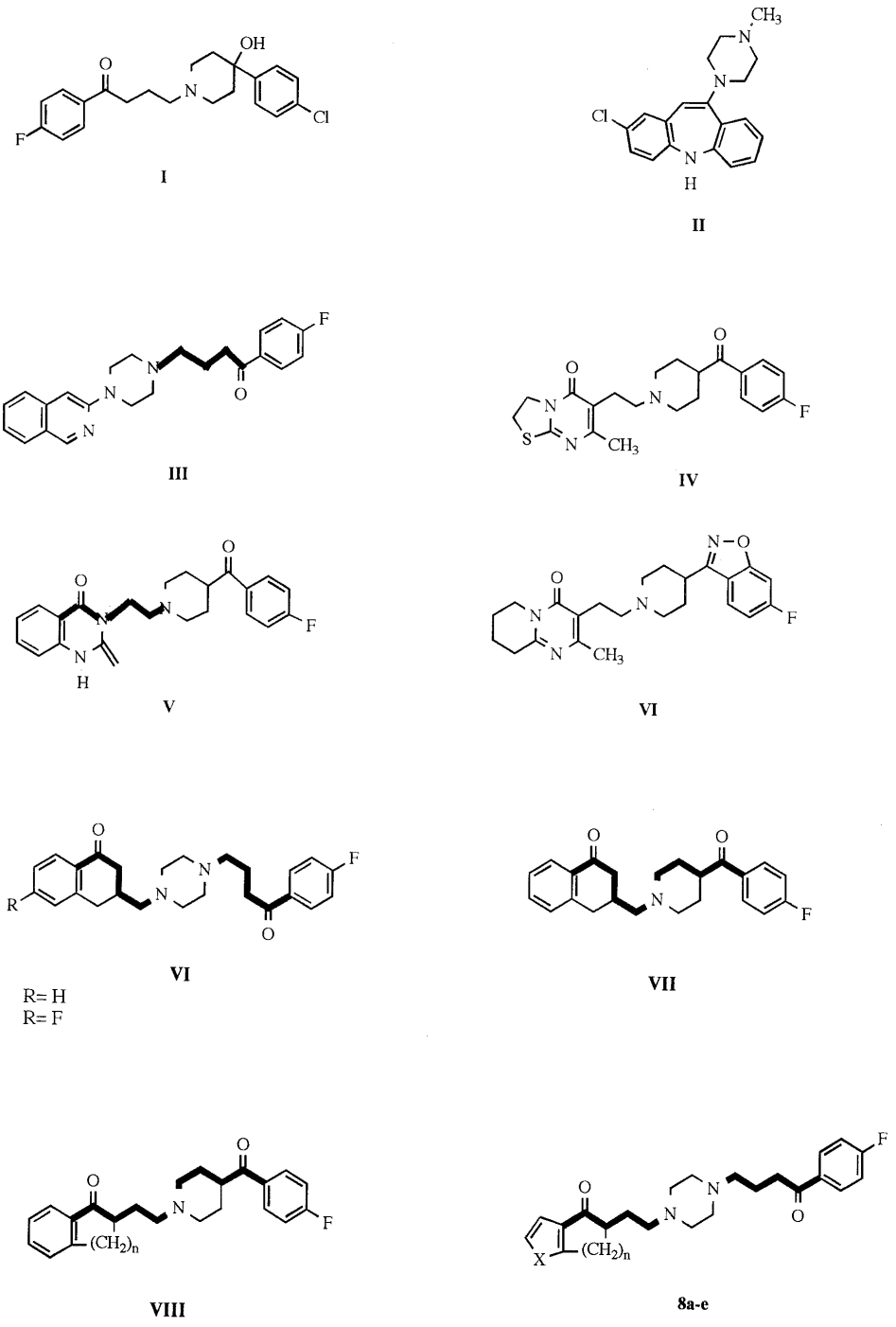


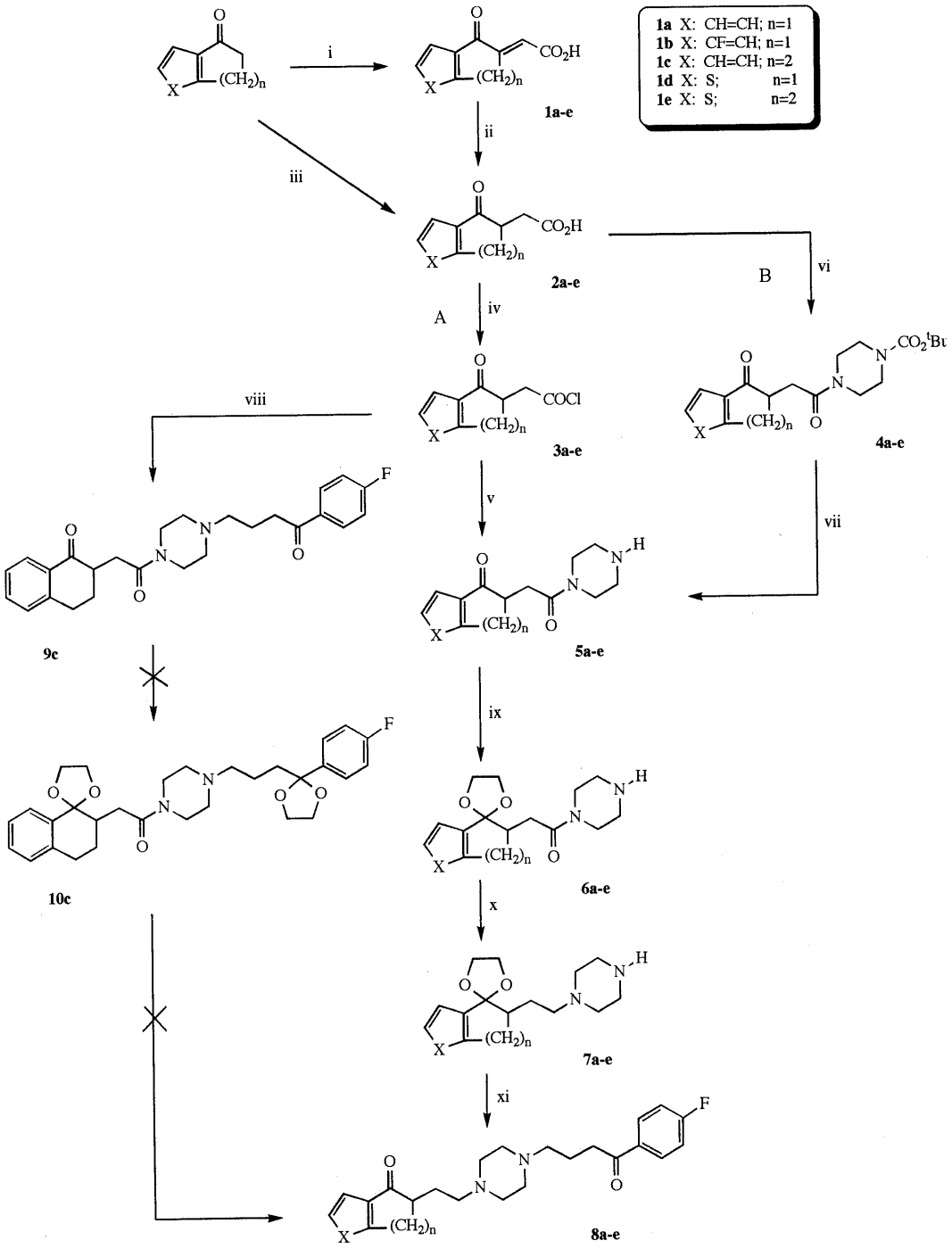
Fig. 1

with zinc and acetic acid of the resulting alkanylidene acetic acids **1a—e**, also in quantitative yields.[20] Tetralone, thiaindanone and thiatetralone acetic acids **2c**, **2d**, **2e** respectively were also prepared in overall yields of 30—35% by hydrolysis of the corresponding ethyl ester, in turn obtained by alkylation of cycloalkanones with ethyl bromoacetate in the presence of lithium diisopropylamide.

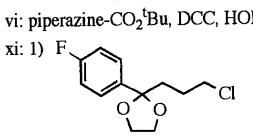
Two alternatives routes were considered for the preparation of the piperazinylamides **5a—e**. In route A, acid chlorides **3a—e** were submitted to reaction with an excess of piperazine to give **5a—e** in quantitative yields. In route B, the acids **2a—e** were coupled to the piperazine protected as the *tert*-butoxycarbonyl derivative with carboxylate activation by dicyclohexylcarbodiimide in the presence of 1-hydroxybenzotriazole to give BOC-piperazinyl derivatives **4a—e** in quantitative yields (Table 1). Subsequent BOC-removal with trifluoroacetic acid afforded the amides **5a—e** in overall yields of 55—60% (Table 2).

Ketalization of both carbonyl groups with ethyleneglycol and catalytic amounts of *p*-TsOH or pyridinium tosylate in anhydrous toluene with azeotropic distillation of water in a Dean–Stark apparatus gave the ethylene ketals **6a—e** in yields of 50—90%; they were isolated as colorless oils and used in the next step without further purification (Table 3).

Lithium aluminum hydride reduction afforded the amines **7a—e** in quantitative yields. Later, the final



i: HOOC-CHO; ii: Zn+AcOH; iii: 1) $BrCH_2CO_2Et$/LDA, 2) KOH/EtOH, 3) HCl conc.; iv: $COCl_2$; v: piperazine; vi: piperazine-$CO_2{}^tBu$, DCC, HOBt; vii: TFA; viii: 2) HCl. ix: $(CH_2OH)_2$/p-TsOH; x: $LiAlH_4$; xi: 1)



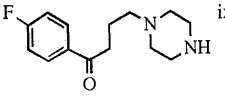
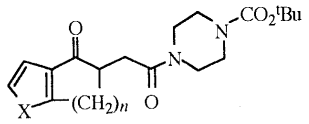


Fig. 1

products **8a**—**e** were obtained by alkylation of the amines with 4-chloro-1,1-ethylenedioxy-1-(4-fluorophenyl)butane in methyl isobutyl ketone after addition of a catalytic amount of potassium iodide, followed by acidic hydrolysis of the ethylene ketals, in yields not higher than 50% (Table 4).

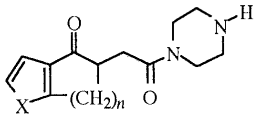
All five compounds were active (Table 5). The affinities of the indanone derivatives **8a** and **8b** were practically the same in both D_2 and 5-HT_{2A} receptors (pK_i $D_2 = 7.17$ and 7.0 and pK_i 5-$HT_{2A} = 6.91$ and 7.14, respectively). The substitution of the indanone moiety by a thioindanone fragment resulted in a decrease in affinity for D_2 receptors and in an increase for 5-HT_{2A} receptors, so the ratio pK_i (5-HT_{2A})/pK_i (D_2) of **8d** was close to the boundary of

Table 1. BOC Piperazinyl Amides **4a—e**



Compound	*n*	X	Yield (%)	mp (°C)	Recrystn. solvent	Formula
4a	1	CH=CH	71	106—107	iso-PrOH	$C_{20}H_{26}N_2O_4$
4b	1	CF=CH	85	136—137	Cyclohexane	$C_{20}H_{25}FN_2O_4$
4c	2	CH=CH	74	103—105	Cyclohexane	$C_{21}H_{28}N_2O_4$
4d	1	S	92	116—118	iso-PrOH	$C_{18}H_{24}N_2O_4S$
4e	2	S	90	114—116	iso-PrOH	$C_{19}H_{26}N_2O_4S$

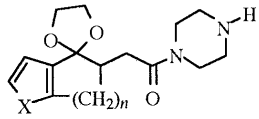
Table 2. Piperazinyl Amides **5a—e**



Compound	*n*	X	Yield (%)	mp (°C)	Recrystn. solvent	Formula
5a	1	CH=CH	72	228—230	MeOH–Et_2O	$C_{15}H_{18}N_2O_2 \cdot HCl$
5b	1	CF=CH	73	243—245[a]	MeOH–Et_2O	$C_{15}H_{17}FN_2O_2 \cdot HCl$
5c	2	CH=CH	74	209—212[b]	MeOH–Et_2O	$C_{16}H_{20}N_2O_2 \cdot HCl$
5d	1	S	78	264—266	MeOH–Et_2O	$C_{13}H_{16}N_2O_2S \cdot HCl$
5e	2	S	89	226—228	MeOH–Et_2O	$C_{14}H_{18}N_2O_2S \cdot HCl$

a) Base mp 106—108 °C (2-propanone). *b*) Base mp 118—120 °C (2-propanone).

Table 3. Ethyleneketals **6a—e**



Compound	*n*	X	Yield (%)	Reflux time (h)	Catalyst.	Formula
6a	1	CH=CH	95	20	*p*-TsOH	$C_{17}H_{22}N_2O_3$
6b	1	CF=CH	48	22	*p*-TsOH	$C_{17}H_{21}FN_2O_3$
6c	2	CH=CH	95	22	*p*-TsOH	$C_{18}H_{24}N_2O_3$
6d	1	S	95	96	*p*-TsOH	$C_{15}H_{20}N_2O_3S$
6e	2	S	94	90	Pyridinium tosylate	$C_{16}H_{22}N_2O_3S$

the values which Meltzer *et al.*[12] correlated with typical or atypical character, 1.11 and 1.12, respectively. In contrast, the affinity of the thiotetralone derivative **8e** was low for both D_2 and 5-HT_{2A} receptors (pK_i $D_2 = 6.44$, pK_i 5-$HT_{2A} = 6.54$), while those of the tetralone compound **8c** were similar to those of the fluoro-indanone **8b** (pK_i $D_2 = 7.04$ and 7.0 respectively; pK_i 5-$HT_{2A} = 7.14$ for both).

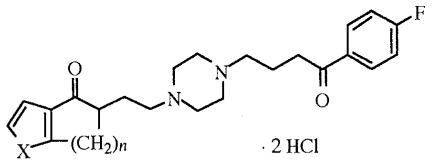
The new compounds exhibited pA_2 values of 6.67—7.84, *i.e.*, slightly lower than that of ketanserin (8.87) in suppressing serotonin-induced contractions in rat-aorta rings stripped of endothelium. The more active compounds were **8b** and **8d**, with pA_2 values of 7.84 and 7.63, respectively.

In summary, these results show that, according to Meltzer's classification, the best pharmacophoric approach to an atypical antipsychotic activity would be a structure carrying a piperazinyl linear butyrophenone moiety linked to a 2-ethylthiotetralone fragment. Moreover, the results of this study do not rule out activity of the compounds at non-D_2 dopaminergic, non-5-HT_{2A} serotoninergic and other receptors that can contribute to the eventual atypical antipsychotic profile of the compounds.

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 give in cm^{-1}. Proton magnetic resonance (^{1}H-NMR) 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 ±0.4% of theoretical compositions. Unless otherwise stated, hydrochlorides were prepared by cautious dropwise addition, until cessation of salt formation, of a saturated solution of dry HCl in anhydrous Et_2O to a solution of the amine in anhydrous Et_2O or absolute

Table 4. Piperazinyl Amines **8a**—**e** Hydrochlorides



Compound	*n*	X	Yield (%)	mp (°C)	Recrystn. solvent	Formula
8a (QF 0309B)	1	CH=CH	47	238—240	MeOH	$C_{25}H_{29}FN_2O_2 \cdot 2HCl$
8b (QF 0315B)	1	CF=CH	15	239—241	MeOH–Et_2O	$C_{25}H_{28}F_2N_2O_2 \cdot 2HCl$
8c (QF 0304B)	2	CH=CH	38	259—262[a]	iso-PrOH	$C_{26}H_{31}FN_2O_2 \cdot 2HCl$
8d (QF 0506B)	1	S	38	244—246[b]	iso-PrOH	$C_{23}H_{25}FN_2O_2S \cdot 2HCl$
8e (QF 0602B)	2	S	30	234—235	iso-PrOH	$C_{22}H_{29}FN_2O_2S \cdot 2HCl$

a) Base mp 85—87 °C (cyclohexane). *b*) Base mp 89—90 °C (cyclohexane).

Table 5. Results of Dopamine and Serotonin Receptor Binding Experiments and of Functional Experiments Using Rat Aorta

	pK_i[a]		pK_i ratio	pA_2[b]
	D_2	5-HT_{2A}	5-HT_{2A}/D_2	5HT_{2A}[21]
Haloperidol	8.30	7.70	0.93	
Clozapine	7.0	8.3	1.19	9.16
8a	7.17	6.91	0.96	7.30
8b	7.0	7.14	1.02	7.84
8c	7.04	7.14	1.01	7.35
8d	6.65	7.35	1.11	7.63
8e	6.44	6.54	1.02	6.83
Methysergide		8.84		
Ketanserine		8.65		8.87

a) pK_i values for inhibition of [^{3}H]spiperone binding to striatal membranes (D_2 receptor) and [^{3}H]ketanserine binding to rat frontal cortex membranes (5-HT_{2A} receptor). *b*) pA_2 values for inhibition of concentration–response cumulative curves of serotonin. Results are means of three or four separate experiments (s.e.m. less than 10%) and slopes were not significantly different from unity.

MeOH–Et_2O. The progress of the reactions was monitored by thin-layer chromatography.

4-Oxo-4*H*-5,6-dihydrocyclopenta[*b*]thiophen-5-ylideneacetic Acid (1d) A stirred mixture of 5,6-dihydro-4*H*-cyclopenta[*b*]thiophen-4-one (2 g, 14.5 mmol), glyoxylic acid (40%, 2 g, 27.6 mmol) and sulfuric acid (80%, 0.5 ml) in dioxane (20 ml) was refluxed for 3 h. After cooling, the precipitated solid was collected by filtration and washed with ether. 2.25 g (90%), mp 224—226 °C (benzene). IR (KBr): 3100—2800 (OH), 1719 (COOH), 1674 (CO), 1629 (C=C). ^{1}H-NMR (DMSO) δ: 7.68 (1H, d, J=5.1 Hz, H_3), 7.26 (1H, d, J=5.1 Hz, H_2), 6.39 (1H, t, J=2.0 Hz, =CHCOO), 4.13 (2H, d, J=1.5 Hz, H_6). *Anal.* Calcd for $C_9H_6O_3S$: C, 55.66; H, 3.11; S, 16.51. Found: C, 55.72; H, 3.25; S, 16.32.

4-Oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophen-5-ylideneacetic Acid (1e) This was prepared similarly to **1d**, 60%, mp 162—164 °C (AcOEt). IR (KBr): 3100—2800 (OH), 1696 (COOH), 1674 (CO), 1612 (C=C). ^{1}H-NMR (DMSO) δ: 7.48 (1H, d, J=5.2 Hz, H_3), 7.14 (1H, d, J=5.2 Hz, H_2), 6.90 (1H, t, J=1.6 Hz, =CHCOO), 3.55 (2H, dd, J=1.6, 6.2 Hz, H_7, $H_{7'}$), 1.74 (2H, t, J=6.2 Hz, H_6, $H_{6'}$). *Anal.* Calcd for $C_{10}H_8O_3S$: C, 57.68; H, 3.87; S, 15.39. Found: C, 57.73; H, 3.95; S, 15.21.

4-Oxo-4*H*-5,6-dihydrocyclopenta[*b*]thiophen-5-ylacetic Acid (2d) A vigorously stirred suspension of **1d** (2 g, 10.3 mmol) and zinc dust (0.83 g, 12.7 mmol) in AcOH (23.2 ml) and water (8.6 ml) was heated under reflux at 100 °C for 1 h. After cooling, the inorganic material was removed by filtration and the filtrate was extracted several times with AcOEt. The combined organic extracts were distilled under reduced pressure. The residue was recrystallized from cyclohexane, 1.64 g (80%), mp 137—138 °C (cyclohexane). IR (KBr): 3200—2800 (OH), 1719 (COOH), 1653 (CO). ^{1}H-NMR (DMSO) δ: 7.34 (1H, d, J=5.1 Hz, H_3), 7.16 (1H, d, J=5.1 Hz, H_2), 3.53 (1H, dd, $J_{gem.}$=17.4 Hz, $J_{vic.}$=7.1 Hz, –HCH–COO), 3.05 (1H, dd, $J_{gem.}$=17.2 Hz, $J_{vic.}$=4.2 Hz, H_6), 2.96 (1H, dd, $J_{gem.}$=17.4 Hz, $J_{vic.}$=3.3 Hz, HCH–COO), 2.65 (1H, dd, $J_{gem.}$=17.2 Hz, $J_{vic.}$=9.3 Hz, H_6). *Anal.* Calcd for $C_9H_8O_3S$: C, 55.09; H, 4.11; S, 16.34. Found: C, 55.13; H, 4.23; S, 16.28.

4-Oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophen-5-ylacetic Acid (2e) 85%, mp 113—115 °C (water). IR (KBr): 3000—3200 (OH), 1702 (COOH), 1684 (CO). ^{1}H-NMR ($CDCl_3$), δ: 7.38 (1H, d, J=5.2 Hz, H_3), 7.08 (1H, d, J=5.2 Hz, H_2), 2.95—3.19 (4H, m, H_7, $H_{7'}$, H_5, HCH–COO), 2.32—2.50 (2H, m, H_6, HCH–COO), 2.05—2.16 (1H, m, H_6). *Anal.* Calcd for $C_{10}H_{10}O_3S$: C, 57.13; H, 4.79; S, 15.25. Found: C, 57.23; H, 4.89; S, 15.41.

The acids **2a**, **2b** and **2e** were also prepared by hydrolysis of the corresponding ethyl esters as indicated below, in quantitative yields.

A solution of diisopropylamine (1.06 ml, 7.5 mmol) in dry tetrahydrofuran (THF, 40 ml) was cooled to −20 °C under N_2 with stirring. *n*-Butyllithium (3.06 ml of a 2.5 M solution in *n*-hexane, 7.5 mmol) was added and stirring continued for 0.5 h between −20 and −10 °C. The solution was then cooled to −70 °C for 1 h more. A solution of 5,6-dihydro-4*H*-cyclopenta[*b*]thiophen-4-one (1 g, 7.5 mmol) in dry THF (8 ml) was added dropwise over 5—10 min. 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 AcOEt extract was washed with 5% $NaHCO_3$ and 5% HCl, then dried (Na_2SO_4) and the solvent was evaporated to give 1.65 g of a crude, product which was purified by chromatography on silica gel with CH_2Cl_2 as the eluent, yielding 1.33 g (81%) of 4-oxo-5,6-dihydrocyclo-penta[*b*]thiophen-5-ylacetic acid ethyl ester.

A solution of this ester (1.68 g, 7.5 mmol) in ethanol (7.64 ml) and 10% ethanolic KOH (9.3 ml, 38.5 mmol) was heated at reflux for 2 h. After cooling, the solution was concentrated, and the residue was dissolved in water. This solution was washed with CH_2Cl_2 and the aqueous layer was acidified to pH 3 with concentrated HCl. The resulting precipitate was filtered off and recrystallized from cyclohexane, mp 137 °C, 0.80 g (55%).

1-Oxo-2-indanylacetyl Chloride (3a) Route A: Under an argon atmosphere, a solution of oxalyl chloride (76.2 g, 0.6 mol) in anhydrous toluene (40 ml) was added dropwise to a stirred solution of **2a** (11.46 g, 0.06 mol) in anhydrous toluene (260 ml). The resulting reaction mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure, and the resulting orange solid residue was used in the next step without further purification. Quantitative yield. IR (KBr): strong band at 1794 cm^{-1} (COCl). The rest of the acid chlorides (**3b**—**e**) were obtained similarly, also in quantitative yields.

***N*-[(1-Oxo-2-indanyl)acetyl]piperazine (5a)** A solution of piperazine

(1.9 g, 22 mmol) in anhydrous toluene (30 ml) was slowly added to a stirred solution of **3a** (1.85 g, 8.9 mmol) in anhydrous toluene (130 ml) under an argon atmosphere. The resulting mixture was stirred 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, and the resulting solution was washed with 10% Na_2CO_3 and H_2O, and dried (Na_2SO_4). After removal of the solvent *in vacuo*, the resulting orange oil was purified by flash chromatography (silica gel, AcOEt–hexane, 1 : 1) to give 1.66 g (72%) of a yellow oil that did not crystallize on standing. Attempted Kugelrohr distillation caused decomposition. Hydrochloride, mp 227—230 °C (MeOH–Et_2O). IR (film): 1715 (CO), 1645 (CON). ^{1}H-NMR (D_2O) δ: 7.47—7.52 (2H, m, H_5, H_7), 7.35 (1H, d, J=7.7 Hz, H_4), 7.24 (1H, t, J=7.5 Hz, H_6), 3.62—3.66 (2H, m, piperazine), 3.44—3.59 (2H, m, piperazine), 3.21 (1H, dd, $J_{gem.}$=17.4 Hz, $J_{vic.}$=6.4 Hz, HCH–CON), 3.12 (2H, t, J=5.3 Hz, piperazine), 3.02 (2H, t, J=5.5, piperazine), 2.80—2.98 (3H, m, H_2, H_3), 2.64 (dd, $J_{gem.}$=17.3 Hz, $J_{vic.}$=3.3 Hz, HCH–CON). *Anal.* Calcd for $C_{15}H_{18}O_2N_2$: C, 69.74; H, 7.02; N, 10.84. Found: C, 69.85; H, 7.26; S, 10.95.

Compounds **5b**—**e** were obtained similarly.

***N*-[(5-Fluoro-1-oxo-2-indanyl)acetyl]piperazine (5b)** 73%, mp 106—108 °C (EtOH). Hydrochloride, mp 243—245 °C (MeOH–Et_2O). IR (KBr): 1715 (CO), 1645 (CON). ^{1}H-NMR ($CDCl_3$) δ: 7.77 (1H, q, J=5.3 Hz, H_7), 7.08 (2H, m, H_4, H_6), 3.47 (9H, m, rest of aliphatic protons), 3.04 (2H, m, H_2, HCH–CON), 2.92 (1H, dd, $J_{gem.}$=17.2 Hz, $J_{vic.}$=4.3 Hz, H_3), 2.7 (1H, dd, $J_{gem.}$=17.2 Hz, $J_{vic.}$=8.5 Hz, HCH–CON). *Anal.* Calcd for $C_{15}H_{17}N_2O_2F$: C, 65.20; H, 6.20; N, 10.14. Found: C, 65.18; H, 6.25; N, 10.32.

***N*-[(1-Oxo-1,2,3,4-tetrahydro-2-naphthyl)acetyl]piperazine (5c)** 74%, mp 118—120 °C (2-propanone). Hydrochloride, mp 209—212 °C (MeOH–Et_2O). IR (KBr): 1678 (CO), 1646 (CON). ^{1}H-NMR ($CDCl_3$) δ: 8.01 (1H, dd, J=7.8, 1.3 Hz, H_8), 7.46 (1H, dt, J=7.4, 1.4 Hz, H_6), 7.26 (2H, m, H_5, H_7), 3.58 (4H, m, N(CH$_2$–CH$_2$)$_2$NH), 3.15 (3H, m, H_2, H_4, HCH–CON), 2.98 (1H, m, H_4), 2.88 (4H, m, N(CH$_2$–CH$_2$)$_2$NH), 2.32 (2H, m, H_3, HCH–CON), 1.92 (1H, dc, J=12.7, 4.4 Hz, H_3). *Anal.* Calcd for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.29. Found: C, 70.62; H, 7.29; N, 10.35.

***N*-[4-Oxo-4*H*-5,6-dihydrocyclopenta[*b*]thiophen-5-ylacetyl]piperazine (5d)** 78%. Hydrochloride, mp 264—266 °C (MeOH–Et_2O). IR (KBr): 2920 (N–H), 1694 (CO), 1633 (CON). ^{1}H-NMR ($CDCl_3$) δ: 7.25 (1H, d, J=5.1 Hz, H_3), 7.08 (1H, d, J=5.1 Hz, H_2), 3.49 (1H, dd, $J_{gem.}$=17.5 Hz, $J_{vic.}$=9.1 Hz, HCH–CON), 3.28—3.59 (5H, m, –N(CH$_2$–CH$_2$)$_2$NH, H_5), 2.96 (1H, dd, $J_{gem.}$=16.7 Hz, $J_{vic.}$=3.1 Hz, H_6), 2.86 (1H, dd, $J_{gem.}$=17.5 Hz, $J_{vic.}$=3 Hz, HCH–CON), 2.73—2.79 (4H, m, N(CH$_2$–CH$_2$)NH), 2.53 (1H, s, N–H), 2.50 (dd, $J_{gem.}$=16.7 Hz, $J_{vic.}$=9.6 Hz, H_6). *Anal.* Calcd for $C_{13}H_{16}N_2O_2S$: C, 51.91; H, 5.70; N, 9.31; S, 10.66. Found: C, 52.23; H, 5.91; N, 9.27; S, 10.72.

***N*-[4-Oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophen-5-ylacetyl]piperazine (5e)** 89%. Hhydrochloride, mp 226—228 °C (MeOH–Et_2O). IR (KBr): 2900 (N–H), 1678 (CO), 1636 (CON). ^{1}H-NMR ($CDCl_3$) δ: 7.36 (1H, d, J=5.3 Hz, H_3), 7.04 (1H, d, J=5.3 Hz, H_2), 3.47—3.68 (m, 4H, –N(CH$_2$–CH$_2$)$_2$NH), 3.16 (1H, dd, $J_{gem.}$=16.0 Hz, $J_{vic.}$=3.8 Hz, HCH–CON), 3.06—3.12 (3H, m, H_7, $H_{7'}$, H_5), 2.82—2.89 (4H, m, –N(CH$_2$–CH$_2$)$_2$NH), 2.37—2.43 (1H, m, $H_{6'}$), 2.27 (1H, dd, $J_{gem.}$= 16.0 Hz, $J_{vic.}$=7.7 Hz, HCH–CON), 2.86 (1H, dd, $J_{gem.}$=17.5 Hz, $J_{vic.}$=3 Hz, HCH–CON), 2.73—2.79 (4H, m, N(CH$_2$–CH$_2$)$_2$NH), 1.97—2.04 (1H, m, H_6). *Anal.* Calcd for $C_{14}H_{18}N_2O_2S$: C, 60.41; H, 6.52; N, 10.06; S, 11.52. Found: C, 60.37; H, 6.71; N, 9.98; S, 11.72.

1-*tert*-Butoxycarbonyl-4-[(1-oxo-2-indanyl)acetyl]piperazine (4a) Route B: Under an argon atmosphere, a solution of *N*-(*tert*-butoxycarbonyl)piperazine (1.1 g, 5.9 mmol), *N*-hydroxybenzotriazole (0.54 g, 5.9 mmol) and **2a** (1.12 g, 5.9 mmol) in CH_2Cl_2 (25 ml) was stirred at room temperature for 1 h; *N*,*N*′-dicyclohexylcarbodiimide (1.23 g, 5.9 mmol) 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. The 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, 3 : 1) to give 1.60 g (71%) of **4a**, mp 106—107 °C (iso-PrOH). IR (KBr): 1715 (CO), 1696 (carbamate), 1645 (CON). ^{1}H-NMR ($CDCl_3$) δ: 7.76 (1H, d, J=7.6 Hz, H_7), 7.57 (1H, t, J=7.4 Hz, H_5), 7.44 (1H, d, J= 7.6 Hz, H_4), 7.36 (1H, t, J=7.4 Hz, H_6), 3.60—3.37 (9H, m, H_2, –N(CH$_2$– CH$_2$)$_2$N–BOC), 3.04 (1H, dd, $J_{gem.}$=17.0 Hz, $J_{vic.}$=3.3 Hz, H_3), 3.05—2.99 (1H, m, HCH–CON), 2.90 (1H, dd, $J_{gem.}$=17.1 Hz, $J_{vic.}$=4.3 Hz, HCH–CON), 2.63 (1H, dd, $J_{gem.}$=17.1, $J_{vic.}$=9.2, H_3), 1.46 (9H, s, –C(CH$_3$)$_3$). *Anal.* Calcd. for $C_{20}H_{26}N_2O_4$: C, 67.02; H, 7.31; N, 7.82; S, 11.52. Found: C, 67.21; H, 7.27; N, 7.71.

1-*tert*-Butoxycarbonyl-4-[(5-fluoro-1-oxo-2-indanyl)acetyl]piperazine (4b) 85%, mp 136—137 °C (iso-PrOH). IR (KBr): 1703 (CO and carbamate), 1647 (CON). ^{1}H-NMR ($CDCl_3$) δ: 7.77 (1H, dd, J=5.4, 8.4 Hz, H_7), 7.03—7.12 (2H, m, H_4, H_6), 3.61—3.37 (9H, m, H_2, –N(CH$_2$–CH$_2$)$_2$N–BOC), 2.99—3.08 (2H, m, H_3, –HCH–CON), 2.91 (1H, dd, $J_{gem.}$=17.2 Hz, $J_{vic.}$=4.4 Hz, –HCH–CON), 2.70 (1H, dd, $J_{gem.}$=17.1 Hz, $J_{vic.}$=8.7 Hz, H_3), 1.46 (9H, s, –C(CH$_3$)$_3$). *Anal.* Calcd for $C_{20}H_{25}FN_2O_4$: C, 63.82; H, 6.69; N, 7.44. Found: C, 63.71; H, 6.87; N, 7.35.

1-*tert*-Butoxycarbonyl-4-[(1-oxo-1,2,3,4-tetrahydro-2-naphtyl)acetyl]-piperazine (4c) 85%, mp 103—105 °C (cyclohexane). IR (KBr): 1703 (CO), 1696 (carbamate), 1647 (CON). ^{1}H-NMR ($CDCl_3$) δ: 8.00 (1H, dd, J=7.8, 1.2 Hz, H_8), 7.46 (dt, J=7.4, 1.2 Hz, H_6), 7.30 (1H, d, J=7.6 Hz, H_5), 7.23 (1H, d, J=7.6 Hz, H_7), 3.72—3.36 (8H, m, piperazine), 3.23—3.10 (3H, m, H_2, H_4, HCH–CON), 2.96 (1H, dd, $J_{gem.}$=16.8 Hz, $J_{vic.}$=3.5 Hz, –HCH–CON), 2.37—2.27 (2H, m, H_3, H_4), 1.94 (1H, dc, J=12.8, 4.3 Hz, H_3), 1.47 (9H, s, C(CH$_3$)$_3$). *Anal.* Calcd for $C_{21}H_{28}N_2O_4$: C, 67.72; H, 7.58; N, 7.5. Found: C, 67.51; H, 7.77; N, 7.41.

1-*tert*-Butoxycarbonyl-4-[(4-oxo-5,6-dihydro-4*H*-cyclopenta[*b*]thiophen-5-yl)acetyl]piperazine (4d) 92%, mp 116—118 °C (iso-PrOH). IR (KBr): 1697 (carbamate), 1694 (CO), 1645 (CON). ^{1}H-NMR ($CDCl_3$) δ: 7.33 (1H, d, J=5.1 Hz, H_3), 7.16 (1H, d, J=5.1 Hz, H_2), 3.52—3.60 (1H, m, H_5), 3.56 (1H, dd, $J_{gem.}$=17.4 Hz, $J_{vic.}$=7.1 Hz, HCH–CON), 3.36—3.49 (8H, m, –N(CH$_2$–CH$_2$)$_2$N–BOC), 3.05 (1H, dd, $J_{gem.}$=16.7, $J_{vic.}$=3.2, H_6), 2.94 (dd, $J_{gem.}$=17.4 Hz, $J_{vic.}$=3 Hz, HCH–CON), 2.59 (1H, dd, $J_{gem.}$=16.7 Hz, $J_{vic.}$=9.6 Hz, H_6), 1.46 (9H, s, C(CH$_3$)$_3$). *Anal.* Calcd for $C_{18}H_{24}N_2O_4S$: C, 59.32; H, 6.64; N, 7.69; S, 8.80. Found: C, 59.33; H, 6.60; N, 7.58; S, 8.83.

1-*tert*-Butoxycarbonyl-4-[(4-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophen-5-yl)acetyl]piperazine (4e) 90%, mp 114—116 °C (iso-PrOH). IR (KBr): 1697 (carbamate), 1673 (CO), 1638 (CON). ^{1}H-NMR ($CDCl_3$) δ: 7.37 (1H, d, J=5.4 Hz, H_3), 7.06 (1H, d, J=5.1 Hz, H_2), 3.44—3.71 (8H, m, N(CH$_2$–CH$_2$)$_2$NH), 3.11—3.21 (3H, m, H_7, $H_{7'}$, H_5), 3.12 (1H, dd, $J_{gem.}$=16.0 Hz, $J_{vic.}$=4.0 Hz, HCH–CON), 3.12 (1H, dd, $J_{gem.}$= 16.0, $J_{vic.}$=3.2, HCH-CON), 2.28—2.44 (1H, m, $H_{6'}$), 2.36 (1H, dd, $J_{gem.}$=16.0 Hz, $J_{vic.}$=7.9 Hz, HCH–CON), 2.03—2.10 (1H, m, H_6), 1.47 (9H, s, C(CH$_3$)$_3$). *Anal.* Calcd for $C_{19}H_{26}N_2O_4S$: C, 60.29; H, 6.92; N, 7.49; S, 8.47. Found: C, 60.19; H, 6.85; N, 7.53; S, 8.39.

***N*-[(1-Oxo-2-indanyl)acetyl]piperazine (5a)** A solution of **4a** (2.3 g, 6.5 mmol) in trifluoroacetic acid (5 ml, 6.6 mmol) was stirred at room temperature for 20 min. After removal of the acid under vacuum, the residue was dissolved in CH_2Cl_2 and the resulting solution was washed with 10% $NaHCO_3$ and water, then dried (Na_2SO_4). The solvent was evaporated off under reduced pressure to give 1.43 g (87%) of **5a** as a white oil. Hydrochloride, mp 227—230 °C (MeOH–Et_2O).

Compounds **5b**—**e** were prepared similarly.

1-[(1,1-Ethylenedioxyindan-2-yl)acetyl]piperazine (6a) A stirred solution of the amide **5a** (1 g, 3.9 mmol), ethyleneglycol (17.27 g, 0.28 mmol) and *p*-TsOH (54 mg) in anhydrous toluene (55 ml) 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). The solvent was removed under reduced pressure. The resulting crude ketal (1.10 g, 95%) was an orange oil which showed only one IR band (1645, CON) and was used in the next step without further purification.

Similarly, **5b**—**e** afforded **6b**—**e**, also in quantitative yields.

1-[2-(1,1-Ethylenedioxyindan-2-yl)ethyl]piperazine (7a) A stirred solution of the amide **6a** (1.3 g, 4.3 mmol) in anhydrous Et_2O (25 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (0.74 g, 0.019 mol) also in anhydrous Et_2O (16 ml) 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 to give 1.02 g of **7a** (83%) as a colorless oil, which was used in the next step without further purification.

The rest of the amines **7b**—**e** were obtained similarly.

1-[3-(*p*-Fluorobenzoyl)-1-propyl]-4-[*β*-(1-oxo-2-indanyl)ethyl]piperazine (8a) A solution of 4-chloro-1,1-ethylenedioxy-1-(4-fluorophenyl)butane (1.17 g, 4.8 mmol) in methyl isobutyl ketone (15 ml), was added to a mixture of **7a** (1.38 g, 4.8 mmol), anhydrous Na_2CO_3 (1.65 g)

and KI (0.032 g) in methyl isobutyl kenone (45 ml) with stirring. After refluxing with vigorous stirring for 10 h, the mixture was allowed to stand at room temperature overnight, then filtered. The filtrate was evaporated under reduced pressure to give 1.12 g (45%) of a white oil. This was treated with 10% HCl and the resulting suspension was vigorously stirred at 35—40 °C for 1 h. After 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 dry HCl gas. The white precipitate that formed was recovered and kept overnight in a vacuum desiccator; recrystallization from MeOH–Et_2O afforded 0.92 g of white crystals, mp 238—240 °C (MeOH). IR (KBr): 1688 (CO indanone), 1682 (CO butyrophenone), 1597 (C=C aromatics). ^{1}H-NMR ($CDCl_3$) δ: 7.98 (2H, dd, J=5.5, 8.8 Hz, *m*-F-Ph), 7.73 (1H, d, J=7.6 Hz, H_7), 7.55 (1H, t, J=7.3 Hz, H_5), 7.43 (1H, d, J=7.6 Hz, H_4), 7.35 (1H, t, J=7.4 Hz, H_6), 7.11 (2H, t, J=8.6 Hz, *o*-F-Ph), 3.31 (1H, dd, $J_{gem.}$=17.1 Hz, $J_{vic.}$=7.9 Hz, H_3), 2.94 (2H, t, J=7.1 Hz, –C$\underline{H}_2$CO), 2.82 (1H, dd, $J_{gem.}$=17.2 Hz, $J_{vic.}$=4.0 Hz, $H_{3'}$), 2.70 (1H, m, H_2), 2.27—2.59 (12H, m, C_2–CH_2–C$\underline{H}_2$–N(C$\underline{H}_2$–C$\underline{H}_2$)$_2$N–C$\underline{H}_2$-), 2.07—2.18 (1H, m, C_2–H$\underline{C}$H–CH_2–N), 1.90 (3H, q, J=7.1 Hz, H_2, N–CH_2–C$\underline{H}_2$–CH_2–CO), 1.66—1.76 (1H, m, C_2–HC$\underline{H}$–CH_2–N). *Anal.* Calcd for $C_{25}H_{29}N_2FO_2\cdot$2HCl: C, 62.37; H, 6.49; N, 5.82. Found: C, 62.40; H, 6.60; N, 5.99.

1-[3-(*p*-Fluorobenzoyl)-1-propyl]-4-[β-(5-fluoro-1-oxo-2-indanyl)ethyl] piperazine (8b) 15%. Hydrochloride, mp 239—241 °C (MeOH–Et_2O). IR (KBr): 1705 (CO indanone), 1678 (CO butyrophenone), 1593 (C=C aromatics). ^{1}H-NMR ($CDCl_3$) δ: 7.97 (2H, dd, J=8.9, 5.4 Hz, *m*-F-Ph), 7.72 (1H, dd, J=8.3, 5.4 Hz, H_7), 7.15—7.02 (4H, m, H_4, H_6, *o*-F-Ph), 3.29 (1H, dd, $J_{gem.}$=17.2 Hz, $J_{vic.}$=7.8 Hz, H_3), 2.94 (2H, t, J=7.1 Hz, –N–CH_2–CH_2–C$\underline{H}_2$–CO), 2.81 (1H, dd, $J_{gem.}$=17.8 Hz, $J_{vic.}$=4.0 Hz, H_3), 2.77—2.70 (1H, m, H_2), 2.45—2.33 (12H, m, –C$\underline{H}_2$–N(C$\underline{H}_2$–C$\underline{H}_2$)$_2$N–C$\underline{H}_2$–), 2.16—2.07 (1H, m, >CH–H$\underline{C}$H–CH_2–N<), 1.90 (2H, q, J=7.1 Hz, >N–CH_2–C$\underline{H}_2$–CH_2–CO), 1.75—1.68 (1H, m, >CH–HC$\underline{H}$–CH_2–N–). *Anal.* Calcd for $C_{25}H_{28}N_2F_2O_2\cdot$2HCl: C, 60.12; H, 6.05; N, 5.61. Found: C, 60.31; H, 6.14; N, 5.48.

1-[3-(*p*-Fluorobenzoyl)-1-propyl]-4-[β-(5-fluoro-1-oxo-2-indanyl)ethyl] piperazine (8c) 58%, mp 85—87 °C (cyclohexane). Hydrochloride, mp 259—262 °C (iso-PrOH). IR (KBr): 1688 (CO tetralone and butyrophenone), 1596 (C=C aromatics). ^{1}H-NMR ($CDCl_3$) δ: 8.03—7.97 (3H, m, H_8, *m*-F-Ph), 7.45 (1H, dt, J=7.4, 1.6 Hz, H_6), 7.31—7.21 (2H, m, H_5, H_7), 7.12 (2H, t, J=8.6 Hz, 2H, *o*-F-Ph), 2.94—3.01 (4H, m, N–CH_2–CH_2–C$\underline{H}_2$–CO, 2H$_4$), 2.38—2.56 (13H, m, –N(C$\underline{H}_2$–C$\underline{H}_2$)$_2$N–, C_2–CH_2–C$\underline{H}_2$–N–, N–C$\underline{H}_2$–CH_2–CH_2–CO, H_2), 2.20—2.22 (2H, m, H_3), 1.95—1.90 (3H, m, –N–CH_2–C$\underline{H}_2$–CH_2–CO, C_2–H$\underline{C}$H–CH_2–N–), 1.60—1.72 (1H, m, C_2–HC$\underline{H}$–CH_2–N). *Anal.* Calcd for $C_{26}H_{31}N_2FO_2\cdot$2HCl: C, 63.03; H, 6.71; N, 5.65. Found: C, 63.09; H, 6.68; N, 5.89.

1-[3-(*p*-Fluorobenzoyl)-1-propyl]-4-[β-(4-oxo-4*H*-5,6-dihydrocyclopenta[*b*]thiophen-5-yl)ethyl]piperazine (8d) 58%, mp 89—90 °C (cyclohexane). Hydrochloride, mp 244—246 °C (iso-PrOH). IR (KBr): 1706 (CO thiaindanone), 1685 (CO butyrophenone), 1590 (C=C aromatics). ^{1}H-NMR ($CDCl_3$) δ: 7.98 (2H, dd, J=8.8, 5.4 Hz, *m*-F-Ph), 7.30 (1H, d, J=5.2 Hz, H_3), 7.12 (1H, d, J=5.2 Hz, H_2), 7.09 (2H, d, J=8.8 Hz, *o*-F-Ph), 3.35 (1H, dd, $J_{gem.}$=17.3 Hz, $J_{vic.}$=6.9 Hz, H_6), 2.98—3.05 (1H, m, H_5), 2.95 (2H, t, J=7.1 Hz, N–CH_2–CH_2–C$\underline{H}_2$–CO), 2.87 (1H, dd, $J_{gem.}$=17.3 Hz, $J_{vic.}$=2.8 Hz, H_6), 2.27—2.45 (12H, m, C_2–CH_2–C$\underline{H}_2$–N(C$\underline{H}_2$–C$\underline{H}_2$)$_2$–N–C$\underline{H}_2$–), 2.06—2.19 (1H, m, C_2–H$\underline{C}$H–CH_2–N), 1.91 (2H, q, J=7.1 Hz, N–CH_2–C$\underline{H}_2$–CH_2–CO), 1.63—1.70 (1H, m, C_2–HC$\underline{H}$–CH_2–N). *Anal.* Calcd. for $C_{23}H_{27}N_2FO_2S$: C, 66.64; H, 6.57; N, 5.76; S, 7.73. Found: C, 66.65; H, 6.63; N, 6.52; S, 7.75.

1-[3-(*p*-Fluorobenzoyl)-1-propyl]-4-[β-(4-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophen-5-yl)ethyl]piperazine (8e) 30%. Hydrochloride, mp 234—235 °C (iso-PrOH). IR (KBr): 1684 (CO butyrophenone), 1670 (CO thiotetralone), 1596 (C=C aromatics). ^{1}H-NMR ($CDCl_3$) δ: 7.99 (2H, dd, J=4.9, 1.7 Hz, *m*-F-Ph), 7.36 (1H, d, J=5.1 Hz, H_3), 7.07—7.11 (2H, m, *o*-F-Ph), 7.05 (1H, d, J=5.1 Hz, H_2), 3.43—3.59 (1H, m, H_5), 2.93—3.15 (2H, m, H_7, $H_{7'}$), 2.97 (2H, t, J=7 Hz, N–CH_2–CH_2–C$\underline{H}_2$–CO), 2.27—2.50 (12H, m, –C$\underline{H}_2$–N(C$\underline{H}_2$–C$\underline{H}_2$)$_2$N–C$\underline{H}_2$–), 1.64—2.20 (4H, m, H_6, $H_{6'}$, C_5–C$\underline{H}_2$–CH_2–N–), 1.96 (2H, q, J=7.1 Hz, N–CH_2–C$\underline{H}_2$–CH_2–CO). *Anal.* Calcd for $C_{24}H_{29}N_2FO_2S\cdot$2HCl: C, 57.48; H, 6.23; N, 5.59; S, 6.39. Found: C, 55.31; H, 6.48; N, 5.62; S, 6.23.

***In Vitro* Experiments** Male Sprague–Dawley 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 −80 °C until assay.

D_2 Binding[12,17]: 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 was 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 Whatman 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 for 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.

5-HT_{2A} Binding[12,17]: Frontal cortex tissue was homogenized (Ultraturrax, 5 s at 20000 rpm) in 50 volumes of 50 mM Tris–HCl, pH 7.4, and centrifuged at 30000 ***g*** for 10 min at 4C. 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]ketanserine (NEN 60 Ci/mmol). Specific binding was defined as incorporation of 25 μl of methysergide (final concentration 1 mM). Samples were incubated for 15 min at 37 °C, and incubation was terminated by vacuum filtration. 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, percentage specific binding being calculated as (dpm sample-dpm non specific binding/dpm total-dpm non specific binding) × 100.[22]

5-HT_{2A} Functional Experiments: Aorta rings from 275±25 g male Sprague–Dawley rats stripped of endothelium 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; $CaCl_2\cdot H_2O$, 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 60 min stabilization, cumulative concentration–response curves were recorded as per Van Rossum, increasing the serotonin concentration from 30 nM to 10 mM in the absence and in the presence of increasing concentrations of ketanserine or the new compounds. Competitive antagonism was quantified as pA_2 (-log concentration of antagonist required to maintain a constant response when agonist concentration is doubled), which was calculated from a Schild plot of log(dose ratio-1) for three antagonist concentrations; six replicate experiments were performed.

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