Conformationally Restricted Butyrophenones with Mixed Dopaminergic (D_2) and Serotoninergic (5-HT_{2A}) Affinities. Synthesis of 5-Aminoethyl- and 6-Aminomethyl-4-oxotetrahydroindoles as Potential Atypical Antipsychotics

Christian F. Masaguer, Isabel Casariego, and Enrique Raviña*

Dpto. Química Orgánica, Laboratorio de Química Farmacéutica, Facultad de Farmacia, Universidad de Santiago, 15706-Santiago de Compostela, España/Spain. Received November 24, 1998; accepted January 25, 1999

We describe the synthesis of 5-aminoethyl- and 6-aminomethyl-4-oxotetrahydroindoles as butyrophenone derivatives in the indole series, as potential atypical antipsychotics. The affinities of these compounds for serotonin (5-HT_{2A}) and dopamine (D_2) receptors were evaluated *in vitro*. The ratios of pK_i's for 5-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. Compounds 26e (QF 0408B) and 26f (QF 0409B) showed high affinity for both D_2 and 5-HT_{2A} receptors, and their Meltzer's ratios were 1.32 and 1.17 respectively, while haloperidol showed a ratio of 0.93.

Key words aminoalkyl-4-oxotetrahydroindole; D_2 affinity; 5-HT_{2A} affinity; antipsychotic

Schizophrenia is a complex disorder affecting approximately 1% of the population.[1] Classical neuroleptics, such as haloperidol (Fig. 1), are currently used for the treatment of this disease, but their use is associated with severe mechanism-related side effects, including induction of acute extrapyramidal symptoms (EPS).[2] Several aminoketones also possess potent antipsychotic (neuroleptic) activity: molindone,[3] first marketed in the U.S.A. in l974, has been used in the treatment of schizophrenia and psychosis, but its associated incidence of EPS is significant; the pyrrolo[2,3-g]isoquinoline piquindone (Ro 22-13l9)[4] is an antipsychotic with a low propensity to induce EPS. The clinical efficacy of 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;[5—7] however, it has been reported that dopamine receptor blockade in the striatum is closely associated with their extrapyramidal side effects.[8—10] Furthermore, the classical antipsychotics are ineffective against negative symptoms of schizophrenia such as apathy, motor retardation, flat affectivity and poverty of speech.

The introduction of clozapine for treatment–resistant schizophrenia gave rise to a new group of atypical or non-classical antipsychotics which have no EPS and are effective against negative symptoms.[11—13] Clozapine blocks not only dopamine receptors but also 5-HT_{2A} serotonin receptors, and its atypical activity may be due to this latter feature; this focused attention on the interaction between the serotonin and dopamine systems as an avenue for superior therapeutics in schizophrenia, and demonstrated the implication of the serotoninergic system in this pathology.[14—16] Meltzer *et al*.[17,18] suggested that in the efficacy of clozapine and other atypical antipsychotics as risperidone, olanzapine and quetiapine (Chart 1),[19] the most important factor is their relative affinities for D_2 and 5-HT_{2A} receptors.[20] Clozapine and other atypical antipsychotics have a pK_i (5-HT_{2A}/D_2) ratio >1.12, whereas for typical antipsychotics this ratio is <1.09.

Current works based on experimental and clinical studies seem to confirm the major role of the 5-HT_{2A} receptor for the atypical profile of the antipsychotics.[21—24] In fact, MDL 100907 (Fig. 2), a 5-HT_{2A} receptor selective antagonist, is being developed as a new atypical antipsychotic drug on the bases of data obtained in a wide-range of neurochemical, electrophysiological and behavioural models.[25—27]

The study of the serotonin–dopamine interaction from a basic and clinical viewpoint promises a certain and substantial change in the pharmacotherapy of schizophrenia. The 5-HT_{2A}/D_2 concept has contributed to the development of com-

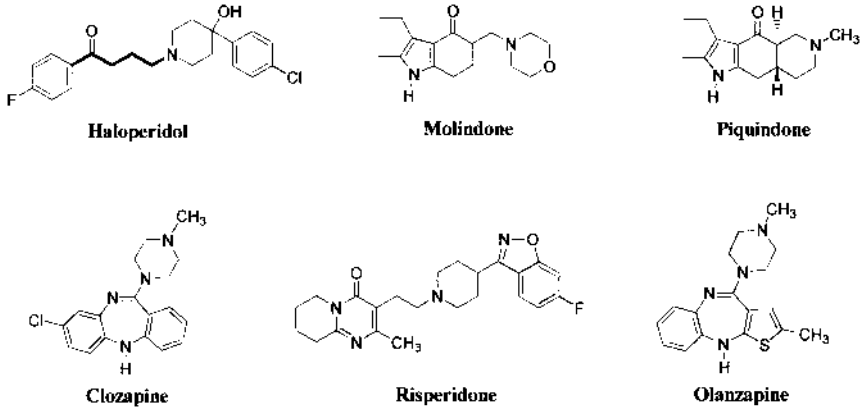


Fig. 1

* To whom correspondence should be addressed.

pounds such as cinuperone, risperidone,[28] ocaperidone,[29] sertindole,[30] which are mixed 5-HT_{2A}/D_2 antagonists. Nevertheless, clozapine remains the prototype of atypical antipsychotic drugs and no currently available agents appear to have the spectrum of efficacy of clozapine. However, treatment with clozapine is associated with an increased risk of agranulocytosis,[31] which strongly limits its therapeutic use. Therefore, the discovery of a more effective side effects free therapy for the treatment of schizophrenia remains a challenging research goal.

As part of a program aimed at developing dopamine D_2 receptors, we have reported in previous papers[32—35] the synthesis and atypical antipsychotic activity of 3-aminomethyl tetralones and 2-aminoethyl benzocycloalkanones which are conformationally restricted butyrophenone analogues of haloperidol with the aminobutyl side chain partially incorporated in a semirigid framework. As a continuation, we wish to report here on convenient methodologies for the preparation of 5-aminoethyl- and 6-aminomethyl-4,5,6,7-tetrahydroindol-4-ones (**12a**—**e** and **26a**—**f**) as cyclic butyrophenone derivatives in the indole series (Fig. 3), as well as the results of studies of the affinities of the most active compounds for D_2 and 5-HT_{2A} receptors. Some preliminary results from this work have been published in communication form.[36,37] Some of these compounds have two butyrophenone pharmacophores: the semirigid aminoalkyl indolone moiety and the 4-(*p*-fluorobenzoyl)piperidine fragment. The 4-(*p*-fluorobenzoyl)piperidine fragment may be considered as a butyrophenone pharmacophore constrained in a six membered ring; this fragment is also an important feature for 5-HT_{2A} binding. Moreover, the bioisosteric relationships between benzoyl and 1,2-benzisoxazol moieties are noteworthy.[38]

In Charts 1, 2 and 3 are outlined the synthesis of 5-aminomethylindolones **12a**—**e**. Knorr condensation of 2-isonitroso-3-pentanone with 1,3-cyclohexadione in 70% acetic acid afforded the 3-ethyl-2-methyl-1*H*-4,5,6,7-tetrahydroindol-4-one **1** with 60% yield. The conjugation between the pyrrole nitrogen and the carbonyl group deactivates both functions. Furthermore, the methylene group adjacent to this carbonyl group does not participate in base catalyzed condensations. However, if the nitrogen is substituted with a strong electron-withdrawing group such as benzenesulfonyl, the pyrrole ring is deactivated and consequently the carbonyl group activated by inhibiting electron release to it. The 1-benzenesulfonyl derivative **2** was readily prepared and could be alkylated with ethyl bromoacetate to afford the ester **3** according to our previously reported procedure.[39] Alternatively, the general strategy of malonic synthesis allowed the acid **4** to be obtained with overall yields of 40%. The benzenesulfonyl group so deactivates the pyrrole ring that bromination in the 5 position is favoured. Thus, treatment of **2** with cupric bromide afforded the 5-bromo ketone **5** in high yields (80%). The bromoderivative **5** was allowed to react with diethyl malonate in NaH/dimethylformamide (DMF) to give the ketodiester **6** (70%). One step cleavage of both ester and benzenesulfonyl groups with ethanolic sodium hydroxide afforded in very high yields (85%) the N-unprotected diacid **7**, which was decarboxylated in the presence of cupric oxide to give the required monoacid **4** in quantitative yield.

The protected amides **9a**—**d** were prepared as white crystalline solids in 65—85% yield by reaction of ketoester **3** with the appropriate dimethylaluminum amide (prepared *in situ* from a solution 2 M of trimethyl aluminum in hexane) followed by hydrolysis of the resulting complex (route A, Chart 2). Alternatively (route B, Chart 2), from the N-unprotected acid **4** by acid amine coupling with carboxylate activation by dicyclohexylcarbodiimide (DCC) in the presence of 1-hydroxybenzotriazole (HOBt) in DMF afforded the amides **8a**—**d** in 55—80% yields. In order to avoid the formation of intractable tars and salts during the reduction due to the acidic NH group, it was protected as benzenesulfonyl derivative by reaction with benzenesulfonyl chloride in the presence of sodium hydride. Reduction of the ketonic group in 4-oxotetrahydroindoles with lithium aluminum hydride (LAH) or $NaBH_4$ has been reported to afford the methylene group.[40] However, we successfully reduced the N-protected amides **9a**—**d** with AlH_3 in tetrahydrofuran (THF) to give the aminoalcohols **10a**—**d** in quantitative yields which were oxidised to aminoketones **11a**—**d** with pyridinium dichromate in 50—60% overall yield. Finally, the synthesis of the target compounds **12a**—**d** was accomplished by removing the benzenesulfonyl protecting group with a) ethanolic sodium hydroxide (58—74%), or b) with the recently described[41] tetrabutyl ammonium fluoride (TBAF) in refluxing THF (70—75%).

In order to prepare the target compound **12e**, the presence of two carbonyl groups is troublesome following the above procedure. Amide **9e** was obtained similarly to the rest of amides described in this work. Reduction of ketoamide **9e**

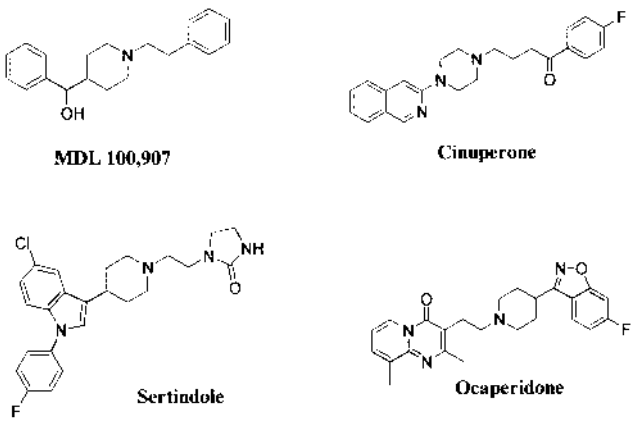


Fig. 2

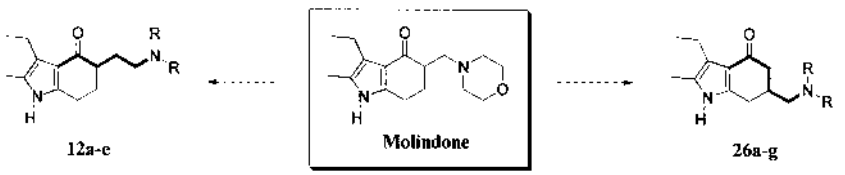
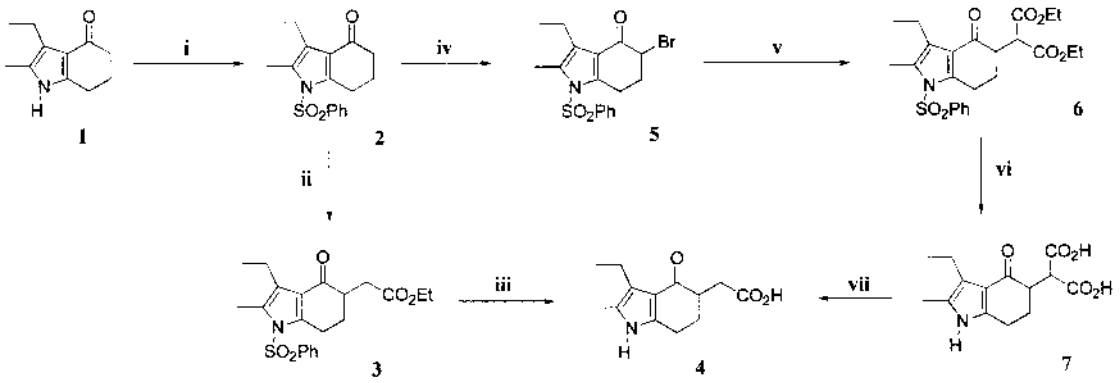
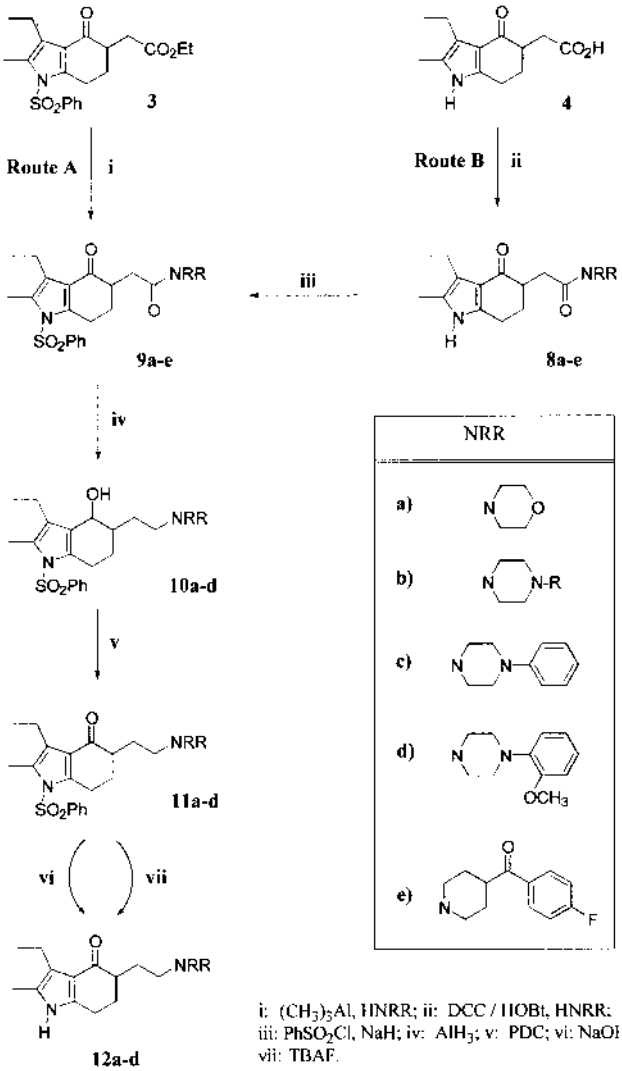


Fig. 3



i: $PhSO_2Cl$, NaH; ii: $BrCH_2CO_2Et$, LDA; iii: NaOH; iv: $CuBr_2$; v: $H_2C(CO_2Et)_2$, NaH; vi: NaOH; vii: Cu_2O

Chart 1



i: $(CH_3)_3Al$, HNRR; ii: DCC / HOBt, HNRR; iii: $PhSO_2Cl$, NaH; iv: AlH_3; v: PDC; vi: NaOH; vii: TBAF.

Chart 2

with boro or aluminum hydrides took place with secondary reactions to give by-products. The crude alcohol underwent oxidation slowly, and only amorphous solid was obtained. According to these results, we explored another strategy which involved the protection of both ketonic groups. The synthesis was carried out from the ketoacid **4** with an overall yield of 7% as outlined in Chart 3. Most attempts to convert **9e** into the corresponding ethylene ketal left the ketoamide unaffected. Ketalyzation of both carbonyl groups with ethylene glycol and pyridinium tosylate in anhydrous toluene with azeotropic distillation of water in a Dean–Stark apparatus proceeded very slowly and partially to afford bis ethylene ketal **13** in moderate yields (50%); it was isolated as a yellow foam which partially decomposes after attempted purification by column chromatography. The severe conditions which were necessary for ketal formation of **9e** are probably a consequence of the increased steric hindrance.

A number of attempts were made to reduce the carbonyl amide group of **13** to the corresponding amine. According to the reductive agent and reaction conditions, the results were as follows:

a) LAH in Refluxing THF: Under these vigorous conditions, the reaction proceeds with cleavage of the benzenesulfonyl protecting group (related reductions of benzenesulfonyl groups have been reported[42]) as well as reductive cleavage of the indolone ketal and reduction of the amide carbonyl group. The more stable ketal of benzoyl carbonyl group remain unaffected. After chromatographic purification, compound **16** was obtained as a foam and characterized by spectroscopic data.

b) LAH in Refluxing Diethyl Ether: In these conditions only reduction of the amide group took place. The resulting crude foam which also partially decomposes after attempted chromatographic purification, was allowed to react with HCl–MeOH to cleavage both ketals. Protected aminoketone **15** was obtained (55%) as a yellow oil which was identified by the usual spectroscopic measurements. Despite the facile removing of the benzenesulfonyl group in the previous examples, it was difficult to remove it in this compound either in strong alkaline conditions or by reduction (magnesium in MeOH). However, reductive cleavage with sodium in ammonia was successful. In these mild conditions, amine **12e** was obtained in 50—60% yield.

c) Aluminum Hydride in THF: The reaction proceeds with reductive cleavage of the indolone ketal and reduction of the amide carbonyl group. The benzoyl and benzenesulfonyl groups remain unaffected. Acidic hydrolysis of the resulting crude foam **17** give the protected pyrrol ketone **18** (14%

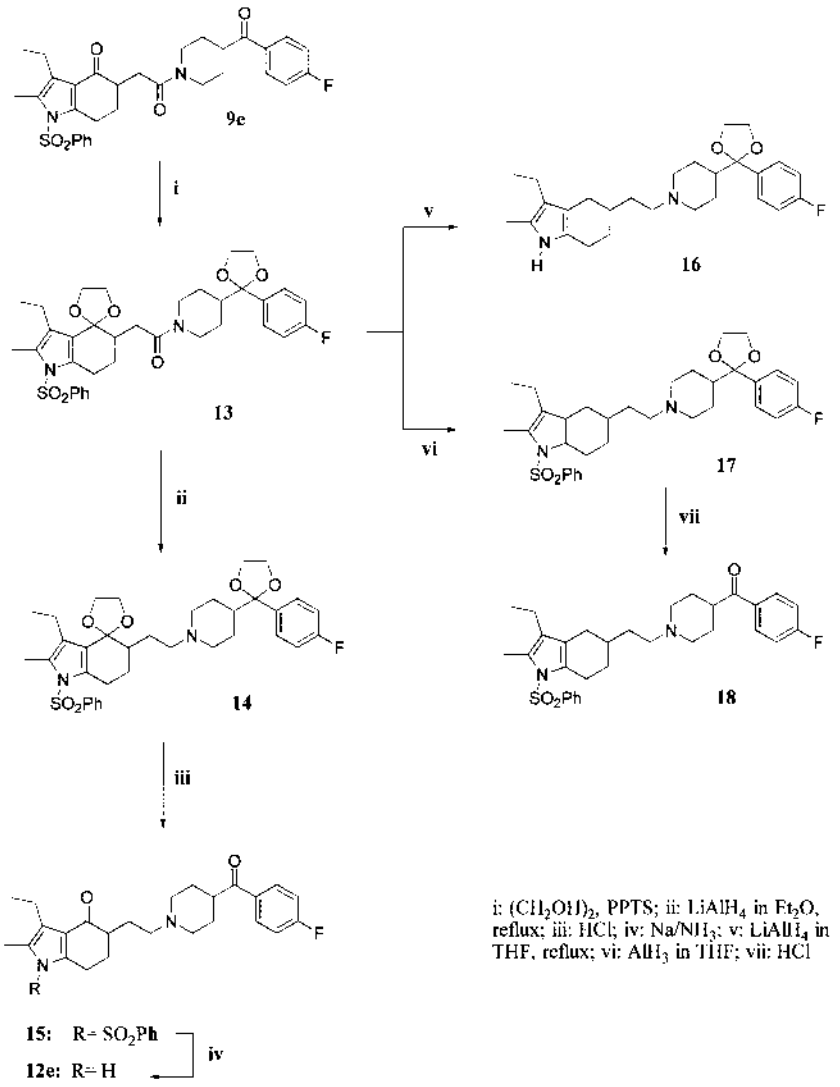


Chart 3

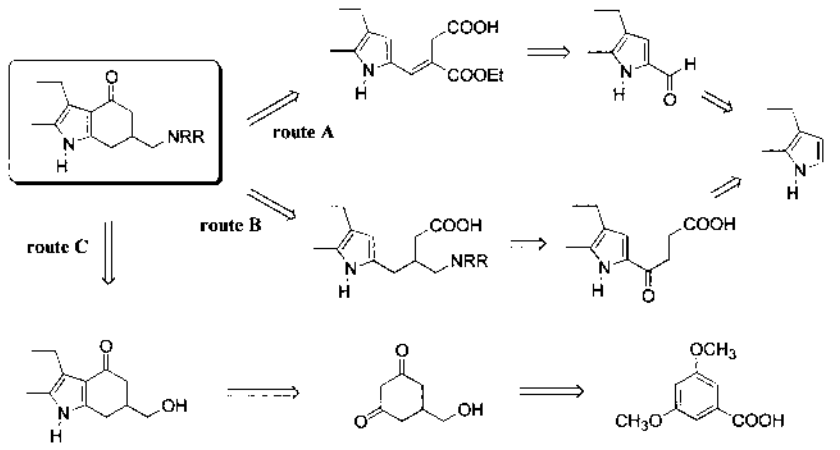
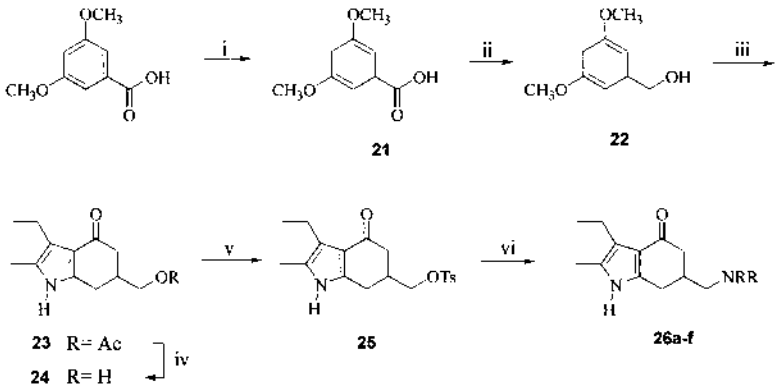


Chart 4

from **13**) isolated as a crystalline oxalate.

For the synthesis of 6-aminomethyl indolones **26a**—**f**, several retrosynthetic strategies (Chart 4) are possible by using the pyrrole ring previously formed (A and B) or generating it at the last steps of the procedure (C). In route A, Wilsmeier-Haak formylation of 2-methyl-3-ethylpyrrol and Stobbe condensation are the key steps. Alternatively (route B), succinoylation, aminomethylation and ring closure would lead to the desired compounds. In cases A and B, the procedures have a high number of steps and according to our experience



i: Li/NH_3; ii: $LiAlH_4$; iii: $CH_3CNOHCOCH_2CH_3$, Zn, AcOH 70%; iv: KOH; v: Ts-Cl/Py; v: HNRR, NMP

Chart 5

in the benzene and thiophene series,[32,43] the final ring closure would likely proceed with only moderate yields. In route C, the key step is a Knorr pyrrole formation upon the 5-hydroxymethyl-1,3-cyclohexanedione. Accordingly, we considered and successfully explored case C, where the number of steps is lower, the reactions, surprisingly for pyrrole chemistry, are clean and overall yields are good.

In Chart 5 is shown the procedure followed for preparation of final compounds **26a**—**f** with overall yields from 15% to 25%. Birch reduction of 3,5-dimethoxybenzoic acid with lithium-ammonia in methanol afforded 1,4-dihydro-3,5-dimethoxybenzoic acid **21**.[44] Treatment of this compound with LAH in THF gave the hydroxymethyl alcohol **22**[45] in 85% yield over two steps. Pyrrole ring formation was achieved by Knorr methodology with 2-isonitroso-3-pentanone refluxing in 70% acetic acid in the presence of zinc powder to yield a mixture of 3-ethyl-2-methyl-6-acetoxymethyl-4,5,6,7-tetrahydroindol-4-one **23** (30%) and 3-ethyl-2-methyl-6-hydroxymethyl-4,5,6,7-tetrahydroindol-4-one **24** (30%). After chromatographic separation, the acetyl ester **23** on treatment with 10% ethanolic potassium hydroxide gave **24** (60%) as a white crystalline solid. Reaction of the alcohol **24** with *p*-toluenesulfonyl chloride in pyridine afforded the tosylate **25** (75%), which underwent subsequent nucleophilic displacement with heterocyclic amines in *N*-methyl-2-pyrrolidone, providing the amines **26a**—**f** as white crystalline solids with yields ranging 40—75% (Table 1). Linear butyrophenone **26g** was prepared from the corresponding piperazine-free derivative **26b** with a yield of 51%, by alkylation of the piperazine-free nitrogen with 4-chloro-1,1-ethylenedioxy-1-(4-fluorophenyl)butane in methyl isobutyl ketone after addition of catalytic amounts of potassium iodide as previously reported by us,[34] followed by acidic hydrolysis of the resulting ethylene ketal.

Table 2 lists the results of experiments to evaluate the affinities of the most active compounds for dopamine D_2 and serotonin 5-HT_{2A} receptors. These compounds inhibited the binding of ^{3}H-spiperone to D_2 receptors (pK_i=6.20 to 7.55), but less than haloperidol (pK_i=8.30); the pK_i of compound **12d** was similar to that of molindone (pK_i=7.48). All compounds also inhibited the binding of ^{3}H-ketanserine to 5-HT_{2A} receptors: the seven compounds tested displayed higher affinity for 5-HT_{2A} receptors than molindone (pK_i=5.85). In keeping with the hypotheses suggested by Meltzer *et al.*[15,17]

Table 1. 5-Aminoethyl- and 6-Aminomethyl-4,5,6,7-tetrahydroindol-4-ones (Fig. 3)

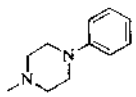
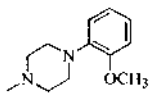
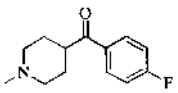
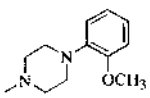
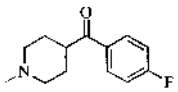
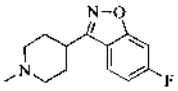
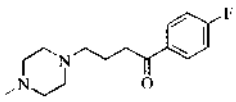
Compound	-NRR	mp (°C)	Recr. solvent	Yield
12a		127—128	Hexane	74%
12b		135—137	Hexane	58%
12c		122—123	H_2O	61%
12d		182—184	H_2O	60%
12e		168—170	AcOEt/hexane	60%
26a		127—130	AcOEt/hexane	75%
26b		176—178	iso-Propanol	70%
26d		219—221	Acetone	64%
26e		162—164	AcOEt/hexane	40%
26f		203—205	*n*-Butanol	65%
26g		170—172	iso-Propanol	51%

Table 2. Inhibition Constants (pK_i) at D_2 and 5-HT_{2A} Receptors of 5-Aminoethyl- and 6-Aminomethyl-4,5,6,7-tetrahydroindol-4-ones[a)]

Compound	pK_i (D_2)	pK_i (5-HT_{2A})	pK_i (5-HT_{2A})/pK_i (D_2)
12a (QF 0400B)	6.23	6.04	0.97
12d (QF 0402B)	7.55	7.04	0.97
12e (QF 0405B)	6.70	6.65	0.99
26d (QF 0407B)	6.02	6.55	1.08
26e (QF 0408B)	6.20	8.21	1.32
26f (QF 0409B)	7.04	8.30	1.17
26g (QF 0410B)	6.55	6.40	0.97
Haloperidol	8.30	7.70	0.93
Molindone	7.48	5.85	0.78
Clozapine	7.00	8.30	1.19

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). Results are means of three or four separate experiments (s.e.m. less than 10%) and slopes were not significantly different from unity.

regarding the combination of 5-HT_{2A}-blocking and D_2-blocking activities, our compounds would have a more atypical profile than molindone.

The most interesting compounds in this series are **26e** and **26f**. Compound **26e** has two butyrophenone pharmacophores: the semirigid aminomethylindolone moiety and the 4-(*p*-fluorobenzoyl)piperidine fragment, and, in compound **26f**, this latter fragment has been substituted by a 4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidine moiety. These two compounds show high affinity for the 5-HT_{2A} receptor, as potent as clozapine. Comparing clozapine with **26e**, a significant loss in D_2 affinity is observed, which results in much improved 5-HT_{2A}/D_2 selectivity. Hence, the Meltzer's ratio (pK_i 5-HT_{2A}/D_2=1.32) for this compound is the highest of our compounds.

Replacement of the benzoyl group of **26e** by its bioisoster, the 1,2-benzisoxazol-3-yl group, to give **26f**, significantly increases the affinity at both D_2 and 5-HT_{2A} receptors. The pK_i 5-HT_{2A}/D_2 for this compound is 1.17, similar to that of the atypical antipsychotic clozapine.

In conclusion, we have developed a practical and efficient synthetic approach for obtaining butyrophenone derivatives in the indole series as atypical antipsychotics. Modification of the amine substituent of molindone and the increase of the β-aminoketone chain to give a butyrophenone structure have given compounds with high affinities for the serotonin 5-HT_{2A} and the dopamine D_2 receptors. The promising affinity for both D_2 and 5-HT_{2A} receptors showed by compounds **26e** (QF 0408B) and **26f** (QF 0409B) together with their high Meltzer's ratio has prompted us to choose these compounds for further development.

Experimental

Chemistry Melting points were determined with a Kofler's hot stage instrument or a Gallenkamp capillary melting point apparatus and are uncorrected. Infrared spectra were recorded with a Perkin Elmer 1600 FTIR spectrophotometer; main bands are given in cm^{-1}. Proton NMR spectra (^{1}H-NMR) and ^{13}C-NMR spectra were recorded with a Bruker WM AMX (300 MHz). Chemical shifts are recorded in parts per million (δ) downfield from tetramethylsilane (TMS). Mass spectra were performed on a Kratos MS-50 or Varian Mat-711 mass spectrometer in a fast atom bombardment (FAB) mode (2-hydroxyethyl disulphide as a matrix) or by electronic impact (EI). Silica gel used for flash column chromatography was Kieselgel 60 (60—200 mesh) (E. Merck AG, Darmstadt, Germany). The progress of reaction was monitored by thin layer chromatography (TLC) on Merck 60 GF_{254} chromatogram sheets and the purified compounds each showed a single spot; unless otherwise stated iodine vapour and/or UV light were used for detection. Elemental combustion analyses were performed on a Perkin Elmer 240B apparatus at the Microanalyses Service of our University; unless otherwise stated all reported values were within ±0.4% of theoretical compositions. The solvents used were purified by distillation over a drying agent under argon atmosphere and used immediately. The following drying agents were used: Na/benzophenone for THF, ether, toluene; P_2O_5 for CH_2Cl_2; K_2CO_3 for acetone and ethyl acetate; KOH for pyridine and triethylamine; $CaSO_4$/4 Å molecular sieves for DMF. Unless otherwise stated, salts were prepared by the following general procedure: (a) oxalates, by the dropwise addition of a molar equivalent solution of oxalic acid in anhydrous ether to a solution of the amine in anhydrous ether, (b) hydrochlorides, by the dropwise addition, under cooling, until cessation of salt formation of a saturated solution of HCl in anhydrous ether to a solution of the amine in anhydrous ether or absolute ethanol/ether. 2,4-Dinitrophenylhydrazones were obtained by dropwise addition of a solution 2,4-dinitrophenylhydrazine sulphate in absolute MeOH to a molar solution of carbonyl derivative in absolute MeOH.

3-Ethyl-2-methyl-4,5,6,7-tetrahydroindol-4-one (1) To a solution of 1,3-cyclohexanedione (18.5 g, 0.165 mol) and α-oxyiminodiethylketone (19.0 g, 0.165 mol) in 70% AcOH (240 ml), powder Zn (21.57 g, 0.33 mol) was added in small portions. Then, the mixture was stirred at reflux temperature for 45 min. After this time, the mixture was quenched with ice/water and the precipitate was filtered and crystallized from methanol/water to give 17.13 g (60%) of the desired compound, mp 178—179 °C. IR (KBr) cm^{-1}: 3217—3179 (N–H), 1620 (C=O), 1472 (pyrrole). ^{1}H-NMR ($CDCl_3$) δ: 1.12 (t, 3H, J=7.4 Hz, –CH_2–C$\underline{H}_3$), 2.09 (q, 2H, J=6.2 Hz, –CH_2–C$\underline{H}_2$–CH_2–), 2.15 (s, 3H, CH_3–Ar), 2.43 (m, 2H, –CO–CH_2–), 2.65 (q, 2H, J=7.4 Hz, –C$\underline{H}_2$–CH_3), 2.74 (t, 2H, J=6.2 Hz, –CH_2–C$\underline{H}_2$–Ar), 8.06 (s, 1H, NH).

1-Benzenesulfonyl-3-ethyl-2-methyl-4,5,6,7-tetrahydroindol-4-one (2) To a suspension of 55% NaH (3.7 g, 0.084 mol) in dry DMF (50 ml), a solution of ketone **1** (15.0 g, 0.084 mol) in dry DMF (50 ml) was added dropwise. The mixture was stirred at room temperature for 1 h, and then benzenesulfonyl chloride (10.7 ml, 0.084 mol) was added. The mixture was stirred at 65 °C for 12 h. The solvent was removed *in vacuo* and the residue was dissolved in CH_2Cl_2, washed with water and brine, dried (Na_2SO_4), filtered and concentrated at reduced pressure to give an oil which was purified by flash chromatography (AcOEt/hexane 1 : 1) to afford 15.34 g (60%) of **2**, mp 86—87 °C (hexane). IR (KBr) cm^{-1}: 1675 (C=O), 1378 and 1174 (SO_2). ^{1}H-NMR ($CDCl_3$) δ: 1.03 (t, 3H, J=7.4 Hz, –CH_2–C$\underline{H}_3$), 2.09 (q, 2H, J=6.5 Hz, –CH_2–C$\underline{H}_2$–CH_2–), 2.28 (s, 3H, CH_3–Ar), 2.44 (t, 2H, J=6.5 Hz, –CO–CH_2–), 2.63 (q, 2H, J=7.4 Hz, –C$\underline{H}_2$–CH_3), 3.13 (t, 2H, J=6.2 Hz, CH_2–C$\underline{H}_2$–Ar), 7.55 (dt, 2H, J_{ortho}=7.5 Hz, J_{meta}=1.6 Hz, *m*-Ph), 7.65 (dt, 1H, J_{ortho}=7.3 Hz, J_{meta}=1.5 Hz, *p*-Ph), 7.73 (dd, 2H, J_{ortho}=6.9 Hz, J_{meta}=1.5 Hz, *o*-Ph). *Anal*. Calcd for $C_{17}H_{19}NO_3S$: C, 64.33; H, 6.03; N, 4.41. Found: C, 64.51; H, 6.11; N, 4.50.

Ethyl 1-Benzenesulfonyl-3-ethyl-2-methyl-4-oxo-4,5,6,7-tetrahydro-5-indolylacetate (3) To a stirred mixture of diisopropylamine (2.98 ml, 0.021 mol) in dry THF (200 ml) at −20 °C, a 2.5 M solution of *n*-BuLi in hexane (8.53 ml, 0.021 mol) was added. The mixture was stirred for 30 min at −20 °C and a further 30 min at −70 °C. After this time, a solution of ketone **2** (6.65 g, 0.021 mol) in dry THF (60 ml) was added dropwise. After stirring 1 h at −70 °C, ethyl bromoacetate (2.0 ml, 0.021 mol) was added, and the mixture was stirred for 30 min at −70 °C and then 18 h at room temperature. The solvent was removed *in vacuo* and the residue was dissolved in AcOEt, washed with water, 5% $NaHCO_3$ and 5% HCl. The organic extracts were dried (Na_2SO_4) and concentrated to give a residue which was purified by column chromatography (CH_2Cl_2) to yield 7.5 g (45%) of **3** as a pale yellow oil. IR (film) cm^{-1}: 1732 (C=O ester), 1670 (C=O ketone), 1374 and 1176 (SO_2). ^{1}H-NMR ($CDCl_3$) δ: 1.01 (t, 3H, J=7.4 Hz, –CH_2–C$\underline{H}_3$), 1.26 (t, 3H, J=7.1 Hz, C$\underline{H}_3$-CH_2–O–), 1.90 (dq, 1H, J=11.8 and 5.1 Hz, –CH_2–$\underline{H}$CH–HC<), 2.16—2.24 (m, 1H, –CH_2–HC$\underline{H}$–HC<), 2.27 (s, 3H, CH_3–Ar), 2.29 (m, 1H, HC$\underline{H}$–COO), 2.61 (q, 2H, J=7.4 Hz, CH_3–C$\underline{H}_2$–Ar), 2.85—3.06 (m, 3H, $\underline{H}$CH–COO, >CH–CO, Ar–HC$\underline{H}$–CH_2), 3.40 (ddd, 1H, J=18.2, 5.0 and 2.8 Hz, Ar–$\underline{H}$CH–CH_2), 4.16 (q, 2H, J=7.1 Hz, CH_3–C$\underline{H}_2$–O–), 7.51—7.74 (m, 5H, Ph).

3-Ethyl-2-methyl-4-oxo-4,5,6,7-tetrahydro-5-indolylacetic acid (4) To a solution of ester **3** (2.25 g, 5.5 mmol) in methanol (6 ml), a 15% solution of NaOH in methanol (4.4 ml, 16.5 mmol) was added. The mixture was stirred at reflux temperature for 2 h. After this time, the solvent was removed under reduced pressure; the residue was dissolved in water, washed with CH_2Cl_2 and acidified with conc. HCl. The solid precipitate was collected by filtration and crystallized from methanol to give 0.95 g (75%) of the acid **4**, mp 231—232 °C (MeOH). IR (KBr) cm^{-1}: 3263 (N–H), 1711 (C=O acid) 1618 (C=O ketone). ^{1}H-NMR ($CDCl_3$–TFA) δ: 1.07 (t, J=7.4 Hz, 3H, C$\underline{H}_3$–CH_2–Ar), 2.03—2.20 (m, 1H, >CH–HC$\underline{H}$–CH_2), 2.16 (s, 3H, CH_3–

Ar), 2.27—2.35 (m, 1H, >CH–HCH–CH_2), 2.57 (q, 2H, J=7.4 Hz., CH_3-CH_2–Ar), 2.75 (dd, 1H, J=4.4, 16.8 Hz, HCH–COOH), 2.89—3.03 (m, 3H, Ar–CH_2–CH_2, HCH–COOH), 3.18—3.24 (m, 1H, >CH–CO). *Anal*. Calcd for $C_{13}H_{17}NO_3$: C, 66.37; H, 7.28; N, 5.95. Found: C, 66.73; H, 6.95; N, 6.19.

1-Benzenesulfonyl-5-bromo-3-ethyl-2-methyl-4-oxo-4,5,6,7-tetrahydroindole (5) A solution of ketone **2** (1.69 g, 5.3 mmol) and $CuBr_2$ (2.39 g, 10.7 mmol) in AcOEt (20 ml) was stirred under Ar at reflux temperature for 1 h. After this time, the solution was filtered and washed with water, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (CH_2Cl_2/hexane 1 : 1) to give 1.75 g (82%) of **5** as a colourless oil. IR (film) cm^{-1}: 1667 (C=O), 1375 and 1172 (SO_2). ^{1}H-NMR ($CDCl_3$) δ: 1.02 (t, 3H, J=7.4 Hz, CH_3–CH_2), 2.26 (s, 3H, CH_3–Ar), 2.44 (m, 2H, CH_2–CH_2–CH), 2.60 (q, 2H, J=7.4 Hz, CH_3–CH_2–), 3.27 (m, 2H, Ar–CH_2–CH_2), 4.50 (t, 1H, J=4.1 Hz, CHBr), 7.53—7.75 (m, 5H, Ph).

Diethyl 1-Benzenesulfonyl-3-ethyl-2-methyl-4-oxo-4,5,6,7-tetrahydro-5-indolyl-malonate (6) To a stirred suspension of 50% NaH (0.19 g, 7.72 mmol) in anhydrous benzene (15 ml) and DMF (5 ml) at 0—5 °C, a solution of diethyl malonate (0.67 g, 4.16 mmol) in benzene (5 ml) was added dropwise. After 15 min, a solution of compound **5** (1.50 g, 3.79 mmol) in benzene (5 ml) and DMF (1 ml) was added, and then, the mixture was stirred at 90 °C for 3 h. After cooling, water (50 ml) was added; the aqueous phase was extracted with AcOEt and the combined organic extracts were dried and concentrated under reduced pressure. The residue was purified by column chromatography (CH_2Cl_2) to afford 1.3 g (72%) of diester **6** as a colourless oil. IR (film) cm^{-1}: 1752 and 1735 (C=O ester), 1672 (C=O ketone), 1370 and 1178 (SO_2). ^{1}H-NMR ($CDCl_3$) δ: 0.98 (t, 3H, J=7.4 Hz, CH_3-CH_2–Ar), 1.21—1.32 (m, 6H, 2×CH_3–CH_2–O–), 2.12—2.23 (m, 2H, CH_2–CH_2–CH-), 2.25 (s, 3H, CH_3–Ar), 2.57 (q, 2H, J=7.4 Hz, CH_3–CH_2–Ar), 2.98 (m, 1H, Ar–CH_2–CH_2), 3.17 (m, 1H, Ar–CH_2–CH_2), 3.38—3.50 (m, 1H, CO–CH–), 3.94 (d, 1H, J=6.8 Hz, –CH(COOEt)$_2$), 4.14—4.26 (m, 4H, 2×–O–CH_2–CH_3), 7.50—7.73 (m, 5H, Ph).

3-Ethyl-2-methyl-4-oxo-4,5,6,7-tetrahydro-5-indolylmalonic acid (7) A 15% solution of NaOH in ethanol (3.6 ml, 13.5 mmol, 4 eq) was added to a solution of diester **6** (1.6 g, 3.4 mmol) in ethanol (25 ml). The mixture was stirred at 80 °C for 20 h. After this time, the solid was collected by filtration, dissolved in water, acidified with 6 N HCl and extracted with AcOEt. The organic phase was dried (Na_2SO_4), filtered and concentrated under reduced pressure to give 0.80 g (85%) of diacid **7**, mp 228—230 °C (CH_3CN). IR (KBr) cm^{-1}: 3378, 1734 (C=O acid), 1674 (C=O ketone). ^{1}H-NMR ($CDCl_3$–TFA) δ: 1.03 (t, 3H, J=7.4 Hz, CH_3–CH_2–Ar), 2.15 (s, 3H, CH_3–Ar), 2.22—2.43 (m, 2H, CH–CH_2), 2.50—2.60 (m, 2H, CH_3–CH_2–), 2.89—2.94 (m, 2H, –CH_2–CH_2–Ar), 3.39 (dd, 1H, J=4.4, 12.4 Hz, CO–CH), 4.02 (d, 1H, J=4.4 Hz, CH-(COOH)$_2$), 8.62 (s, 1H, NH). *Anal*. Calcd for $C_{14}H_{17}NO_5$: C, 60.21; H, 6.13; N, 5.02. Found: C, 59.88; H, 5.91; N, 5.39.

3-Ethyl-2-methyl-4-oxo-4,5,6,7-tetrahydro-5-indolylacetic acid (4) Copper(I) oxide (0.38 g, 2.6 mmol) was added to a solution of diacid **7** (2.20 g, 7.9 mmol) in dry acetonitrile (50 ml), and the mixture was stirred at reflux temperature for 20 h. After this time, the solvent was removed *in vacuo*, the residue was dissolved in 0.5% NaOH, filtered and acidified with 6 N HCl to pH 4. The solid precipitate was collected by filtration to give 1.76 g (95%) of a yellow solid, identical to the previously described acid **4**.

***N*-(3-Ethyl-2-methyl-4-oxo-4,5,6,7-tetrahydro-5-indolylacetyl)morpholine (8a) General procedure** A solution of morpholine (0.36 ml, 5.9 mmol), 1-hydroxybenzotriazole (1.61 g, 11.9 mmol) and the acid **4** (1.40 g, 5.9 mmol) in DMF (15 ml) was stirred at room temperature for 15 min. Then, the mixture was cooled to 0 °C and dicyclohexylcarbodiimide (2.45 g, 11.9 mmol) was added. After stirring for 20 h at room temperature, the precipitate was filtered off and the filtrate was diluted with AcOEt and washed with 5% $NaHCO_3$. The organic layer was dried (Na_2SO_4) and evaporated; the residue was purified by column chromatography (AcOEt) to give 1.45 g (80%) of the amide **8a**, mp 165—166 °C (AcOEt). IR (KBr) cm^{-1}: 3291 (N–H), 1625 (C=O amide and ketone). ^{1}H-NMR ($CDCl_3$) δ: 1.10 (t, 3H, J=7.4 Hz, –CH_2–CH_3), 1.88 (dq, 1H, J=11.9, 5.3 Hz, CH_2–HCH–HC<), 2.14 (s, 3H, CH_3-pyrrole), 2.32 (m, 1H, –CH_2–HCH–HC<), 2.29—2.36 (m, 1H, –HCH–CON<), 2.63 (q, 2H, J=7.4 Hz, CH_3–CH_2), 2.71—2.97 (m, 3H, –CH_2–CH_2–pyrrole, –CH–CO–), 3.28 (dd, 1H, J=16.0 Hz, –HCH–CON<), 3.54—3.68 (m, 8H, morpholine), 8.12 (s, 1H, NH). *Anal*. Calcd for $C_{17}H_{24}N_2O_3$: C, 67.08; H, 7.95; N, 9.20. Found: C, 67.50; H, 7.67; N, 9.66.

***N*-(*tert*-Butyloxycarbonyl)-*N′*-(3-ethyl-2-methyl-4-oxo-4,5,6,7-tetrahydro-5-indolylacetyl)piperazine (8b)** Yield: 70%, mp 179—180 °C (AcOEt). IR (KBr) cm^{-1}: 3264 (N–H), 1691 (C=O BOC), 1630 (C=O ketone). ^{1}H-NMR ($CDCl_3$) δ: 1.10 (t, 3H, J=7.4 Hz, –CH_2–CH_3), 1.47 (s, 9H, $C(CH_3)_3$), 1.88 (dq, 1H, J=12.1, 5.3 Hz, CH_2–HCH–HC<), 2.14 (s, 3H, CH_3–pyrrole), 2.17 (dd, 1H, J=16.1, 8.8 Hz, –HCH–CON<), 2.28—2.43 (m, 1H, –CH_2–HCH–HC<), 2.63 (q, 2H, J=7.4 Hz, CH_3–CH_2–), 2.73 (ddd, 1H, J=16.3, 5.0, 3.2 Hz, –CH_2–HCH–pyrrole), 2.82—3.06 (m, 2H, –CH_2–HCH–pyrrole, >CH–CO–), 3.30 (dd, 1H, J=16.0, 3.5, –HCH–CON<), 3.36—3.76 (m, 8H, piperazine), 7.87 (s, 1H, NH). *Anal*. Calcd for $C_{22}H_{33}N_3O_4$: C, 65.48; H, 8.24; N, 10.41. Found: C, 65.99; H, 8.73; N, 10.20.

***N*^{1}-(3-Ethyl-2-methyl-4-oxo-4,5,6,7-tetrahydro-5-indolylacetyl)-*N*^{4}-phenylpiperazine (8c)** Yield: 55%, mp 174—175 °C (AcOEt). IR (KBr) cm^{-1}: 3291 (N–H), 1624 (C=O amide and ketone). ^{1}H-NMR ($CDCl_3$) δ: 1.11 (t, 3H, J=7.4 Hz, –CH_2–CH_3), 1.90 (dq, 1H, J=12.1, 5.1 Hz, CH_2–HCH–HC<), 2.15 (s, 3H, CH_3-pyrrole), 2.22 (m, 1H, J=16.0, 9.1 Hz, –HCH–CON<), 2.32—2.40 (m, 1H, –CH_2–HCH–HC<), 2.64 (q, 2H, J=7.4 Hz, CH_3–CH_2–), 2.75 (ddd, 1H, J=16.4, 4.9, 3.1 Hz, CH_2–HCH–pyrrole), 2.83—2.99 (m, 2H, –CH–CO–, –CH_2–HCH–pyrrole), 3.15—3.20 (m, 4H, $(CH_2)_2$NPh), 3.36 (dd, 1H, J=16.0, 3.3 Hz, –HCH–CON<), 3.71—3.86 (m, 4H, $(CH_2)_2$NCO), 6.68—6.95 (m, 3H, *o*-Ph, *p*-Ph), 7.29—7.31 (m, 2H, *m*-Ph), 7.92 (s, 1H, NH). *Anal*. Calcd for $C_{23}H_{29}N_3O_2$: C, 72.79; H, 7.70; N, 11.07. Found: C, 72.48; H, 7.29; N, 10.93.

***N*^{1}-(3-Ethyl-2-methyl-4-oxo-4,5,6,7-tetrahydro-5-indolylacetyl)-*N*^{4}-(*o*-methoxyphenyl)piperazine (8d)** Yield: 57%, mp 146—147 °C (AcOEt). IR (KBr) cm^{-1}: 3325 (N–H), 1635 (C=O amide), 1618 (C=O ketone). ^{1}H-NMR ($CDCl_3$) δ: 1.11 (t, 3H, J=7.4 Hz, –CH_2–CH_3), 1.89 (dq, 1H, J=12.0, 5.2 Hz, –CH_2–HCH–HC<), 2.14 (s, 3H, CH_3–pyrrole), 2.22 (m, 1H, J=16.0, 9.3 Hz, –HCH–CON<), 2.32—2.44 (m, 1H, –CH_2–HCH–HC<), 2.64 (q, 2H, J=7.4 Hz, CH_3–CH_2–), 2.75 (ddd, 1H, J=16.3, 5.0, 3.3 Hz, CH_2–HCH–pyrrole), 2.83—2.99 (m, 2H, –CH–CO–, –CH_2–HCH–pyrrole), 3.01—3.07 (m, 4H, $(CH_2)_2$NPh), 3.37 (dd, 1H, J=16.0, 3.2 Hz, –HCH–CON<), 3.71—3.85 (m, 4H, $(CH_2)_2$NCO), 3.88 (s, 3H, CH_3O–), 6.68—7.06 (m, 4H, Ph), 8.01 (s, 1H, NH). *Anal*. Calcd for $C_{24}H_{31}N_3O_3$: C, 70.39; H, 7.63; N, 10.26. Found: C, 69.97; H, 7.81; N, 10.04.

***N*^{1}-(1-Benzenesulfonyl-3-ethyl-2-methyl-4-oxo-4,5,6,7-tetrahydro-5-indolylacetyl)morpholine (9a)** To a suspension of 55% NaH (0.15 g, 3.3 mmol) in dry DMF (15 ml), a solution of amide **8a** (1.0 g, 3.3 mmol) in dry DMF (10 ml) was added dropwise. The mixture was stirred at room temperature for 1 h, and then benzenesulfonyl chloride (0.41 ml, 3.3 mmol) was added. The mixture was stirred at 65 °C for 12 h. The solvent was removed *in vacuo* and the residue was dissolved in CH_2Cl_2, washed with water and brine, dried (Na_2SO_4), filtered and concentrated at reduced pressure to give an oil which was purified by flash chromatography (AcOEt/hexane 2 : 1), to yield 1.22 g (84%) of the amide **9a** as a white solid, mp 140—141 °C (iso-PrOH). IR (KBr) cm^{-1}: 1660 (C=O ketone), 1648 (C=O amide), 1360 and 1178 (SO_2). ^{1}H-NMR ($CDCl_3$) δ: 1.02 (t, 3H, J=7.4 Hz, CH_3–CH_2), 1.88 (dq, 1H, J=12.0, 5.0 Hz, >CH–HCH–CH_2–), 2.19 (dd, 1H, J=16.1, 7.5 Hz, >NCO–HCH–), 2.28 (s, 3H, CH_3–pyrrole), 2.31—2.36 (m, 1H, >CH–HCH–CH_2–), 2.61 (q, 2H, J=7.4 Hz, CH_3–CH_2–), 2.95—3.06 (m, 2H, CO–CH<, CH_2–HCH–pyrrole), 3.12 (dd, 1H, J=16.1, 4.2 Hz, >NCO–HCH–), 3.41 (ddd, 1H, J=18.2, 5.0, 2.7 Hz, CH_2–HCH–Ar), 3.51—3.71 (m, 8H, morpholine), 7.51—7.74 (m, 5H, Ph). *Anal*. Calcd for $C_2{}_3H_{28}N_2O_5S$: C, 62.14; H, 6.35; N, 6.30. Found: C, 62.47; H, 6.88; N, 6.01.

***N*^{1}-(1-Benzenesulfonyl-3-ethyl-2-methyl-4-oxo-4,5,6,7-tetrahydro-5-indolylacetyl)-*N*^{4}-(*tert*-butoxycarbonyl)piperazine (9b)** Yield: 82%, mp 112—113 °C (AcOEt). IR (KBr) cm^{-1}: 1698 (C=O carbamate), 1670 (C=O ketone), 1654 (C=O amide), 1365 and 1174 (SO_2). ^{1}H-NMR ($CDCl_3$) δ: 1.01 (t, 3H, J=7.4 Hz, CH_3–CH_2), 1.47 (s, 9H, –$C(CH_3)_3$), 1.88 (dq, 1H, J=12.2, 5.1 Hz, >CH–HCH–CH_2–), 2.20 (dd, 1H, J=16.1, 7.4 Hz, >NCO–HCH–), 2.27 (s, 3H, CH_3–pyrrole), 2.29—2.32 (m, 1H, >CH–HCH–CH_2–), 2.60 (q, 2H, J=7.4 Hz, CH_3–CH_2–), 2.94—3.04 (m, 2H, >CH–CO, –CH_2–HCH–pyrrole), 3.12 (dd, 1H, J=16.1, 4.3 Hz, >NCO–HCH–), 3.36—3.63 (m, 9H, –CH_2–HCH–pyrrole, piperazine), 7.51—7.73 (m, 5H, Ph). *Anal*. Calcd for $C_{28}H_{37}N_3O_6S$: C, 61.86; H, 6.86; N, 7.73. Found: C, 61.33; H, 6.82; N, 7.65.

***N*^{1}-(1-Benzenesulfonyl-3-ethyl-2-methyl-4-oxo-4,5,6,7-tetrahydro-5-indolylacetyl)-*N*^{4}-phenylpipe-razine (9c)** Yield: 79%, mp 97—98 °C (iso-PrOH). IR (KBr) cm^{-1}: 1660 (C=O ketone), 1647 (C=O amide), 1373 and 1176 (SO_2). ^{1}H-NMR ($CDCl_3$) δ: 1.02 (t, 3H, J=7.3 Hz, CH_3–CH_2), 1.89 (dq, 1H, J=12.6, 5.1 Hz, >CH–HCH–CH_2–), 2.21—2.35 (m, 5H, CH_3-pyrrole, >NCO–HCH–, >CH–HCH–CH_2–), 2.61 (q, 2H, J=7.3 Hz, CH_3–CH_2–), 2.96—3.07 (m, 3H, >CH–CO, –CH_2–HCH–pyrrole, >NCO–HCH–), 3.15—3.21 (m, 4H, $(CH_2)_2$NPh), 3.41 (d, 1H, J=16.4 Hz, –CH_2–HCH–pyrrole), 3.69—3.80 (m, 4H, $(CH_2)_2$NCO), 6.88—6.94 (m, 3H, *o*-Ph, *p*-Ph), 7.29—7.31 (m, 2H, *m*-Ph), 7.53—7.74 (m, 5H, –SO_2–Ph). *Anal*. Calcd for $C_{29}H_{33}N_3O_4S$: C, 67.03; H, 6.40; N, 8.09. Found: C, 67.28; H,

6.13; N, 8.31.

***N*^{1}-(1-Benzenesulfonyl-3-ethyl-2-methyl-4-oxo-4,5,6,7-tetrahydro-5-indolylacetyl)-*N*^{4}-(*o*-methoxy-phenyl)piperazine (9d)** Yield: 74%, mp 126—127 °C (iso-PrOH). IR (KBr) cm^{-1}: 1666 (C=O ketone), 1647 (C=O amide), 1370 and 1176 (SO_2). ^{1}H-NMR ($CDCl_3$) δ: 1.03 (t, 3H, J=7.4 Hz, C<u>H</u>$_3$–CH_2), 1.88 (dq, 1H, J=12.0, 5.1 Hz, >CH–HC<u>H</u>–CH_2–), 2.20—2.37 (m, 2H, >NCO–<u>H</u>CH–, >CH–<u>H</u>CH–CH_2–), 2.29 (s, 3H, CH_3–pyrrole), 2.62 (q, 2H, J=7.4 Hz, CH_3–C<u>H</u>$_2$–), 2.97—3.06 (m, 6H, $(CH_2)_2$NPh, >C<u>H</u>–CO, –CH_2–<u>H</u>CH–pyrrole), 3.20 (d, 1H, J=16.7 Hz, >NCO–HC<u>H</u>–), 3.41 (d, 1H, J=16.4 Hz, –CH_2–HC<u>H</u>–pyrrole), 3.69—3.80 (m, 4H, $(CH_2)_2$NCO), 6.88—6.94 (m, 3H, *o*-Ph, *p*-Ph), 7.29—7.31 (m, 2H, *m*-Ph), 7.53—7.74 (m, 5H, –SO_2–Ph). *Anal*. Calcd for $C_{30}H_{35}N_3O_5S$: C, 65.55; H, 6.42; N, 7.64. Found: C, 65.27; H, 6.15; N, 7.51.

***N*-(1-Benzenesulfonyl-3-ethyl-2-methyl-4-oxo-4,5,6,7-tetrahydro-5-indolylacetyl)morpholine (9a) General procedure** A 2 M solution of Me_3Al in hexane (1.30 ml, 2.57 mmol) was added to a mixture of morpholine (0.22 ml, 2.57 mmol) in dry $CHCl_3$ (10 ml). After stirring at room temperature under argon for 15 min, a solution of the compound **3** (0.49 g, 1.28 mmol) in $CHCl_3$ (10 ml) was added dropwise. The mixture was refluxed for 12 h, cooled and acidified with 10% HCl (5 ml), the organic layer was washed with water, dried (Na_2SO_4) and concentrated to give a residue which was purified by column chromatography (AcOEt/hexane 2 : 1) to afford 0.47 g (85%) of the amide **9a** as a white solid.

***N*^{1}-(1-Benzenesulfonyl-3-ethyl-2-methyl-4-oxo-4,5,6,7-tetrahydro-5-indolylacetyl)-*N*^{4}-(*tert*-butoxycarbonyl)piperazine (9b)** Yield: 47%.

***N*^{1}-(1-Benzenesulfonyl-3-ethyl-2-methyl-4-oxo-4,5,6,7-tetrahydro-5-indolylacetyl)-*N*^{4}-phenylpiperazine (9c)** Yield: 65%.

***N*^{1}-(1-Benzenesulfonyl-3-ethyl-2-methyl-4-oxo-4,5,6,7-tetrahydro-5-indolylacetyl)-*N*^{4}-(*o*-methoxyphenyl)piperazine (9d)** Yield: 69%.

***N*-(1-Benzenesulfonyl-3-ethyl-2-methyl-4-oxo-4,5,6,7-tetrahydro-5-indolylacetyl)piperazine (9e)** A solution of amide **9b** (3.0 g, 5.5 mmol) and trifluoroacetic acid (40 ml) was stirred under Ar at room temperature for 45 min Then, the solvent was removed *in vacuo*. The residue was dissolved in CH_2Cl_2 and washed with 0.1 M NaOH. The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (AcOEt) to give 2.0 g (82%) of the amide **9e** as a pale yellow solid, mp 128—129 °C (AcOEt). IR (KBr) cm^{-1}: 3420 (N–H), 1662 (C=O ketone), 1654 (C=O amide), 1368 and 1175 (SO_2). ^{1}H-NMR ($CDCl_3$) δ: 0.99 (t, 3H, J=7.4 Hz, C<u>H</u>$_3$–CH_2), 1.93 (dq, 1H, J=12.5, 5.1 Hz, >CH–HC<u>H</u>–CH_2–), 2.16—2.27 (m, 5H, >NCO–<u>H</u>CH–, CH_3–pyrrole, >CH–<u>H</u>CH–CH_2–), 2.47 (q, 2H, J=7.4 Hz, CH_3–C<u>H</u>$_2$–), 2.96—3.47 (m, 7H, $(CH_2)_2$NH, >C<u>H</u>–CO, –CH_2–<u>H</u>CH–pyrrole, >NCO–HC<u>H</u>–), 3.78—4.14 (m, 5H, $(CH_2)_2$NCO, –CH_2–HC<u>H</u>–pyrrole), 7.53—7.74 (m, 5H, Ph). *Anal*. Calcd for $C_{23}H_{29}N_3O_4S$: C, 62.28; H, 6.59; N, 9.47. Found: C, 62.57; H, 6.16; N, 9.31.

***N*-[β-(1-Benzenesulfonyl-3-ethyl-2-methyl-4-hydroxy-4,5,6,7-tetrahydro-5-indolyl)ethyl)]morpholine (10a)** A 1 M solution of AlH_3 in THF (11.3 ml, 11.3 mmol, 5 eq) was added dropwise to a solution of amide **9a** (1.0 g, 2.2 mmol) in anhydrous THF (25 ml), the mixture was stirred under Ar at room temperature for 12 h. After this time, the mixture was poured into 10% NaOH (35 ml) and extracted with CH_2Cl_2. The organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was subjected to column chromatography (AcOEt) to give 0.78 g (80%) of the aminoalcohol **10a** as a colourless oil. IR (film) cm^{-1}: 3418 (OH), 1360 and 1178 (SO_2). ^{1}H-NMR ($CDCl_3$) δ: 1.08 (t, 3H, J=7.4 Hz, C<u>H</u>$_3$–CH_2), 1.54—1.76 (m, 4H, >N–CH_2–C<u>H</u>$_2$–CH, CHOH–C<u>H</u><, –HC<u>H</u>–CH_2–Ar), 2.28 (s, 3H, CH_3–Ar), 2.49—2.71 (m, 10H, 3×N–CH_2–, CH_3–C<u>H</u>$_2$–, CH_2–HC<u>H</u>–Ar, –<u>H</u>CH–CH_2–Ar), 3.00 (dd, 1H, J=17.4, 3.6 Hz, –<u>H</u>CH–Ar), 3.70—3.76 (m, 4H, 2×–CH_2–O–), 4.42 (d, 1H, >C<u>H</u>–OH), 7.42—7.67 (m, 5H, Ph).

A sample of **10a** was dissolved in ether and a 5% solution of oxalic acid in ether was added dropwise. The solid precipitate was collected by filtration, mp 202—203 °C (AcOEt). *Anal*. Calcd for $C_{23}H_{32}N_2O_4S\cdot C_2H_2O_4$: C, 57.46; H, 6.56; N, 5.36. Found: C, 57.12; H, 6.83; N, 5.10.

***N*-[β-(1-Benzenesulfonyl-3-ethyl-2-methyl-4-hydroxy-4,5,6,7-tetrahydro-5-indolyl)ethyl)]piperazine (10b)** Yield: 72%. IR (film) cm^{-1}: 3402 (OH), 1364 and 1185 (SO_2). ^{1}H-NMR ($CDCl_3$) δ: 1.05 (t, 3H, J=7.5 Hz, C<u>H</u>$_3$–CH_2), 1.60—1.75 (m, 4H, >N–CH_2–C<u>H</u>$_2$–<u>H</u>C<, HC<u>H</u>–CH–Ar), 2.27 (s, 3H, CH_3–Ar), 2.32—3.02 (m, 15H, 5×N–CH_2, CH_3–C<u>H</u>$_2$–, –<u>H</u>CH–C<u>H</u>$_2$–Ar), 4.32—4.48 (ds, 1H, >C<u>H</u>–OH), 7.43—7.73 (m, 5H, Ph). Oxalate: mp 211—213 °C (iso-PrOH). *Anal*. Calcd for $C_{23}H_{33}N_3O_3S\cdot C_2H_2O_4$: C, 57.57; H, 6.76; N, 8.06. Found: C, 57.21; H, 7.13; N, 7.85.

***N*-[β-(1-Benzenesulfonyl-3-ethyl-2-methyl-4-hydroxy-4,5,6,7-tetrahydro-5-indolyl)ethyl)]-*N*^{4}-phenylpiperazine (10c)** Yield: 81%. IR (film) cm^{-1}: 3241 (OH), 1372 and 1173 (SO_2). ^{1}H-NMR ($CDCl_3$) δ: 1.07 (t, 3H, J=7.5 Hz, C<u>H</u>$_3$–CH_2), 1.52—1.87 (m, 4H, >N–C<u>H</u>$_2$–CH_2–HC<, HC<u>H</u>–C<u>H</u>$_2$–Ar), 1.91—3.23 (m, 18H, 5×N–C<u>H</u>$_2$, CH_3–C<u>H</u>$_2$–, HC<u>H</u>–C<u>H</u>$_2$–Ar, C<u>H</u>$_3$–Ar), 4.37—4.53 (ds, 1H, >C<u>H</u>–OH), 6.85—6.95 (m, 3H, *o*-Ph, *p*-Ph), 7.21—7.29 (m, 2H, *m*-Ph), 7.42—7.76 (m, 5H, –SO_2–Ph). Oxalate: mp 205—207 °C (AcOEt). *Anal*. Calcd for $C_{29}H_{37}N_3O_3S\cdot C_2H_2O_4$: C, 62.29; H, 6.58; N, 7.03. Found: C, 62.71; H, 6.12; N, 6.82.

***N*-[β-(1-Benzenesulfonyl-3-ethyl-2-methyl-4-hydroxy-4,5,6,7-tetrahydro-5-indolyl)ethyl)]-*N*^{4}-(*o*-methoxyphenyl)piperazine (10d)** Yield: 82%. IR (film) cm^{-1}: 3394 (OH), 1364 and 1186 (SO_2). ^{1}H-NMR ($CDCl_3$) δ: 1.09 (t, 3H, J=7.5 Hz, C<u>H</u>$_3$–CH_2), 1.57—1.95 (m, 4H, >N–CH_2–C<u>H</u>$_2$–<u>H</u>C<, HC<u>H</u>–CH_2–Ar), 2.24—3.12 (m, 18H, 5×N–C<u>H</u>$_2$, CH_3–C<u>H</u>$_2$–, –HC<u>H</u>–C<u>H</u>$_2$–Ar, C<u>H</u>$_3$-Ar), 3.86 (s, 3H, CH_3–O–), 4.37—4.53 (ds, 1H, >C<u>H</u>–OH), 6.85—7.03 (m, 4H, Ph–N<), 7.43—7.67 (m, 5H, Ph–SO_2–). Oxalate: mp 212—214 °C (AcOEt). *Anal*. Calcd for $C_{30}H_{39}N_3O_4S\cdot C_2H_2O_4$: C, 61.23; H, 6.58; N, 6.69. Found: C, 60.81; H, 6.92; N, 6.40.

***N*-[β-(1-Benzenesulfonyl-3-ethyl-2-methyl-4-oxo-4,5,6,7-tetrahydro-5-indolyl)ethyl)]morpholine (11a)** PDC (2.6 g, 6.9 mmol) was added to a solution of aminoalcohol **10a** (1.0 g, 2.3 mmol) in dry CH_2Cl_2 (50 ml). The mixture was stirred at room temperature for 20 h, diluted with ether, filtered through Celite, eluted with ether and AcOEt, and concentrated. The residue was purified by column chromatography (AcOEt) to give 0.49 g (50%) of the amine **11a**. IR (film) cm^{-1}: 1665 (C=O), 1373 and 1176 (SO_2). ^{1}H-NMR ($CDCl_3$) δ: 1.01 (t, 3H, J=7.4 Hz, C<u>H</u>$_3$–CH_2–), 1.51 (m, 1H, >CH–HC<u>H</u>–CH_2–N<), 1.77—1.92 (m, 1H, Ar–CH_2–HC<u>H</u>–), 2.04—2.23 (m, 2H, >CH–<u>H</u>CH–CH_2–N<, Ar–CH_2–HC<u>H</u>–CH<), 2.26 (s, 3H, CH_3–Ar), 2.35—2.49 (m, 7H, 3×N–CH_2–, >CO–CH), 2.60 (q, 2H, J=7.4 Hz, CH_3–C<u>H</u>$_2$), 3.00 (ddd, 1H, J=18.2, 9.6, 5.0 Hz, Ar–<u>H</u>CH–CH_2–), 3.29 (dt, 1H, J=18.2, 5.0 Hz, Ar–<u>H</u>CH–CH_2–), 3.69 (t, 4H, J=4.7 Hz, –CH_2–O–CH_2–), 7.50—7.75 (m, 5H, Ph). Oxalate: mp 169—170 °C (AcOEt). *Anal*. Calcd for $C_{23}H_{30}N_2O_4S\cdot C_2H_2O_4$: C, 57.68; H, 6.20; N, 5.38. Found: C, 57.40; H, 6.51; N, 5.12.

***N*-[β-(1-Benzenesulfonyl-3-ethyl-2-methyl-4-oxo-4,5,6,7-tetrahydro-5-indolyl)ethyl)]piperazine (11b)** Yield: 41%. IR (film) cm^{-1}: 1681 (C=O), 1372 and 1178 (SO_2). ^{1}H-NMR ($CDCl_3$) δ: 0.95 (t, 3H, J=7.4 Hz, C<u>H</u>$_3$–CH_2–), 1.41—1.55 (m, 1H, >CH–HC<u>H</u>–CH_2–N<), 1.71—1.92 (m, 1H, Ar–CH_2–<u>H</u>CH–CH<), 2.02—2.17 (m, 2H, >CH–<u>H</u>CH–CH_2–N<, Ar–CH_2–HC<u>H</u>–CH<), 2.20 (s, 3H, CH_3–Ar), 2.24—2.50 (m, 7H, 3×N–CH_2–, >CO–CH), 2.54 (q, 2H, J=7.4 Hz, CH_3–C<u>H</u>$_2$), 2.90—3.01 (m, 1H, Ar–<u>H</u>CH–CH_2–), 3.25 (dt, 1H, J=18.7, 4.9 Hz, Ar–HC<u>H</u>–CH_2–), 3.28—3.49 (m, 4H, –CH_2–NH–CH_2–), 7.45—7.67 (m, 5H, Ph). Oxalate: mp 190—192 °C (AcOEt). *Anal*. Calcd for $C_{23}H_{31}N_3O_3S\cdot C_2H_2O_4$: C, 57.79; H, 6.40; N, 8.09. Found: C, 57.42; H, 6.72; N, 7.82.

***N*-[β-(1-Benzenesulfonyl-3-ethyl-2-methyl-4-oxo-4,5,6,7-tetrahydro-5-indolyl)ethyl)]-*N*^{4}-phenylpiperazine (11c)** Yield: 44%. IR (film) cm^{-1}: 1674 (C=O), 1365 and 1178 (SO_2). ^{1}H-NMR ($CDCl_3$) δ: 1.03 (t, 3H, J=7.3 Hz, C<u>H</u>$_3$–CH_2–), 1.35—1.52 (m, 1H, >CH–HC<u>H</u>–CH_2–N<), 1.81—1.96 (m, 1H, Ar–CH_2–<u>H</u>CH–HC<), 2.18—2.50 (m, 6H, >CH–HC<u>H</u>–CH_2–N<, Ar–CH_2–HC<u>H</u>–CH<, CH_3–Ar, >CO–CH), 2.60 (q, 2H, J=7.3 Hz, CH_3–C<u>H</u>$_2$–), 2.71—2.85 (m, 2H, >CH–CH_2–C<u>H</u>$_2$–N<), 2.96—3.18 (m, 4H, –CH_2–N(C<u>H</u>$_2$)$_2$), 3.22—3.57 (m, 6H, CH_2–C<u>H</u>$_2$–Ar, $(CH_2)_2$–N–Ph), 6.87—6.91 (m, 3H, *o*-Ph, *p*-Ph), 7.28—7.32 (m, 2H, *m*-Ph), 7.51—7.75 (m, 5H, Ph). Oxalate: mp 185—187 °C (AcOEt). *Anal*. Calcd for $C_{29}H_{35}N_3O_3S\cdot C_2H_2O_4$: C, 62.50; H, 6.29; N, 7.05. Found: C, 62.39; H, 6.75; N, 7.51.

***N*-[β-(1-Benzenesulfonyl-3-ethyl-2-methyl-4-oxo-4,5,6,7-tetrahydro-5-indolyl)ethyl)]-*N*^{4}-(*o*-methoxyphenyl)piperazine (11d)** Yield: 47%. IR (film) cm^{-1}: 1674 (C=O), 1371 and 1183 (SO_2). ^{1}H-NMR ($CDCl_3$) δ: 1.03 (t, 3H, J=7.3 Hz, C<u>H</u>$_3$–CH_2–), 1.34—1.57 (m, 1H, >CH–HC<u>H</u>–CH_2–N<), 1.83—1.98 (m, 1H, Ar–CH_2–<u>H</u>CH–HC<), 2.17—2.49 (m, 6H, >CH–HC<u>H</u>–CH_2–N<, Ar–CH_2–HC<u>H</u>–CH<, CH_3–Ar, >CO–CH), 2.59 (q, 2H, J=7.4 Hz, CH_3–C<u>H</u>$_2$–), 2.65—2.71 (m, 2H, >CH–CH_2–C<u>H</u>$_2$–N<), 2.91—3.20 (m, 4H, –CH_2–N(C<u>H</u>$_2$)$_2$), 3.26—3.56 (m, 6H, CH_2–C<u>H</u>$_2$–Ar, $(CH_2)_2$–N–Ph), 3.86 (s, 3H, CH_3–O–), 6.84—7.09 (m, 4H, >N–Ph), 7.50—7.74 (m, 5H, Ph). Oxalate: mp 172—174 °C (AcOEt). *Anal*. Calcd for $C_{30}H_{37}N_3O_4S\cdot C_2H_2O_4$: C, 61.43; H, 6.28; N, 6.72. Found: C, 61.09; H, 6.61; N, 6.47.

***N*-[β-(3-Ethyl-2-methyl-4-oxo-4,5,6,7-tetrahydro-5-indolyl)ethyl)]morpholine (12a) General Procedure** A 15% solution of NaOH in ethanol (1.2 ml, 4.6 mmol, 2 eq) was added dropwise to a solution of the amine **11a** (1.0, 2.3 mmol) in ethanol (50 ml). The mixture was refluxed for 12 h and then concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2, washed with water, dried (Na_2SO_4) and concentrated to give a grey solid which was purified by column chromatography (AcOEt) to afford 0.50 g (74%) of the amine **12a** as a white solid, mp 127—128 °C (hexane). IR (KBr) cm^{-1}: 3266 (N–H), 1617 (C=O), 1116 (C–O–C). ^{1}H-NMR ($CDCl_3$) δ: 1.11 (t, 3H,

J=7.4 Hz, C$\underline{H}_3$–CH_2), 1.55 (m, 1H, >CH–HC$\underline{H}$–CH_2–N<), 1.82—1.97 (m, 1H, Ar–CH_2–$\underline{H}$CH–), 2.13 (s, 3H, CH_3–Ar), 2.10—2.25 (m, 2H, >CH–HC$\underline{H}$–CH_2–N<, Ar–CH_2–HC$\underline{H}$–), 2.33—2.49 (m, 7H, 3×N–CH_2, >CO–CH), 2.64 (q, 2H, J=7.4 Hz, CH_3–C$\underline{H}_2$–), 2.74—2.79 (m, 2H, –CH_2–C$\underline{H}_2$–Ar), 3.70 (t, 4H, J=4.7 Hz, –CH_2–O–CH_2–), 7.85 (s, 1H, NH). ^{13}C-NMR ($CDCl_3$): δ: 10.23 (C$\underline{H}_3$–CH_2–), 15.40 (CH_3–pyrrole), 17.98 (CH_3–C$\underline{H}_2$–), 21.95 (>CH–C$\underline{H}_2$–CH_2–pyrrole), 26.40 (>CH–C$\underline{H}_2$–CH_2–N<), 29.31 (–CH_2–C$\underline{H}_2$–pyrrole), 44.98 (CO–H$\underline{C}$<), 53.67 (–N(C$\underline{H}_2$–CH_2)$_2$O), 56.99 (>CH–CH_2–C$\underline{H}_2$–N<), 66.96 (–N(CH_2-C$\underline{H}_2$)$_2$O), 118.10 (C=C–CO), 121.15 (CH_3–CH_2-C=C), 123.69 (CH_3–C=C), 140.80 (HN–C=C), 196.26 (C=O). MS m/z: 290 (M^+, 7.6%), 177 (100%). *Anal*. Calcd for $C_{17}H_{26}N_2O_2$: C, 70.31; H, 9.02; N, 9.64. Found: C, 69.80; H, 9.23; N, 9.08.

***N*-[*β*-(3-Ethyl-2-methyl-4-oxo-4,5,6,7-tetrahydro-5-indolyl)ethyl)]-piperazine (12b)** Yield: 58%, mp 135—137 °C (hexane). IR (KBr) cm^{-1}: 3290 (N–H), 1620 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.10 (t, 3H, J=7.4 Hz, C$\underline{H}_3$–CH_2), 1.35—1.50 (m, 1H, >CH–HC$\underline{H}$–CH_2–N<), 1.75—1.90 (m, 1H, –HC$\underline{H}$–CH_2–Ar), 1.93—2.11 (m, 2H, >CH–HC$\underline{H}$–CH_2–N<, Ar–CH_2–HC$\underline{H}$), 2.15 (s, 3H, CH_3–Ar), 2.36—2.57 (m, 7H, 3×N–CH_2, >CO–CH), 2.63 (q, 2H, J=7.4 Hz, CH_3–C$\underline{H}_2$–), 2.73—2.81 (m, 2H, Ar–CH_2–CH_2–), 2.92—2.99 (m, 4H, –$(CH_2)_2$NH), 7.83 (s, 1H, NH). *Anal*. Calcd for $C_{17}H_{26}N_2O_2$: C, 70.311; H, 9.02; N, 9.64. Found: C, 69.80; H, 9.23; N, 9.08.

***N*-[*β*-(3-Ethyl-2-methyl-4-oxo-4,5,6,7-tetrahydro-5-indolyl)ethyl)]-N^4-phenylpiperazine (12c)** Yield: 61%, mp 122—123 °C (H_2O). IR (KBr) cm^{-1}: 3244 (N–H), 1618 (C=O), 1602 (C=C). ^{1}H-NMR ($CDCl_3$) δ: 1.11 (t, 3H, J=7.4 Hz, C$\underline{H}_3$–CH_2), 1.58—1.76 (m, 1H, >CH–HC$\underline{H}$–CH_2–N<), 1.85—2.02 (m, 1H, –HC$\underline{H}$–CH_2–Ar), 2.13 (s, 3H, C$\underline{H}_3$–Ar), 2.17—2.30 (m, 2H, >CH–$\underline{H}$CH–CH_2–N<, –$\underline{H}$CH–CH_2–Ar), 2.40—2.99 (m, 11H, CO–HC<, CH_3–C$\underline{H}_2$–, –C$\underline{H}_2$–N(C$\underline{H}_2$–CH_2)$_2$N, –CH_2–C$\underline{H}_2$–Ar), 3.18—3.44 (m, 4H, –N(CH_2–C$\underline{H}_2$)$_2$N–Ph), 6.64—6.71 (m, 3H, *o*-Ph, *p*-Ph), 7.21—7.23 (m, 2H, *m*-Ph), 8.16 (s, 1H, NH). *Anal*. Calcd for $C_{23}H_{31}N_3O$: C, 75.58; H, 8.55; N, 11.50. Found: C, 75.12; H, 8.91; N, 11.13.

***N*-[*β*-(3-Ethyl-2-methyl-4-oxo-4,5,6,7-tetrahydro-5-indolyl)ethyl)]-N^4-(*o*-methoxyphenyl)piperazine (12d)** Yield: 60%, mp 182—184 °C (H_2O). IR (KBr) cm^{-1}: 3178 (N–H), 1615 (C=O), 1596 (C=C), 1238 (C–O–). ^{1}H-NMR ($CDCl_3$) δ: 1.09 (t, 3H, J=7.4 Hz, C$\underline{H}_3$–CH_2), 1.35—1.69 (m, 1H, >CH–HC$\underline{H}$–CH_2–N<), 1.78—1.94 (m, 1H, –HC$\underline{H}$–CH_2–Ar), 1.98—2.38 (m, 8H, C$\underline{H}_3$–Ar, >CH–$\underline{H}$CH–, –CH_2–N<, –$\underline{H}$CH–C$\underline{H}_2$–Ar, CO–HC<), 2.58—2.76 (m, 8H, CH_3–C$\underline{H}_2$–, –CH_2–N(CH_2)$_2$–), 3.11 (s, 2H, C$\underline{H}_2$–N–Ph), 3.44—3.53 (m, 2H, CH_2–N–Ph), 3.83 (s, 3H, CH_3–O–), 6.82—7.07 (m, 4H, Ph–N<), 8.91 (s, 1H, NH). ^{13}C-NMR ($CDCl_3$) δ: 10.52 (C$\underline{H}_3$–CH_2–), 15.84 (CH_3–pyrrole), 18.33 (CH_3–C$\underline{H}_2$–), 22.15 (>CH–C$\underline{H}_2$–CH_2–pyrrole), 26.73 (>CH–C$\underline{H}_2$–CH_2–N<), 29.70 (–CH_2–C$\underline{H}_2$–pyrrole), 45.11 (CO–H$\underline{C}$<), 50.40 (–N(C$\underline{H}_2$–CH_2)$_2$N–Ph), 53.43 (–N(CH_2–C$\underline{H}_2$)$_2$N–Ph), 55.60 (>CH–CH_2–C$\underline{H}_2$–N<), 55.83 (CH_3–O–), 111.43 (C_3 Ph), 117.89 (C_4 Ph), 118.50 (C=C–CO), 120.94 (C_5 Ph), 121.24 (CH_3–CH_2–C=C), 123.35 (C_6 Ph), 124.29 (CH_3–C=C), 141.20 (HN–C=C), 141.68 (C_2 Ph), 152.45 (C_1 Ph), 196.57 (C=O). *Anal*. Calcd for $C_{24}H_{33}N_3O_2$: C, 77.88; H, 8.41; N, 10.62. Found: C, 77.29; H, 8.68; N, 11.33.

***N*-(2-Methyl-3-ethyl-4-oxo-4,5,6,7-tetrahydro-5-indolylacetyl)-4-(*p*-fluorobenzoyl)piperidine (8e)** A solution of 4-(*p*-fluorobenzoyl)piperidine (2.87 g, 13.86 mmol), 1-hydroxybenzotriazole (1.88 g, 13.86 mmol) and acid **4** (2.17 g, 9.23 mmol) in DMF (20 ml) was stirred at room temperature under Ar for 15 min. *N*,*N*-Dicyclohexylcarbodiimide (2.86 g, 13.86 mmol) was then added to the mixture at 0 °C and stirred for 1 h and then at room temperature for 16 h. After removal of the dicyclohexylurea formed by filtration, the DMF was distilled *in vacuo*, the resulting oil dissolved in ethyl acetate and the solution washed several times with 5% $NaHCO_3$, and water, dried (Na_2SO_4) and the solvent removed at reduced pressure. The oil residue was purified by column chromatography (AcOEt/hexane 2 : 1) to give 3.31 g (85%) of **8e** as a foam solid. IR (KBr) cm^{-1}: 3264 (N–H), 1682 (C=O benzoyl), 1623 (C=O), 1116 (C–O–C). ^{1}H-NMR ($CDCl_3$) δ: 1.08 (t, 3H, J=7.4 Hz, C$\underline{H}_3$–CH_2–), 1.62—1.91 (m, 5H, –N(CH_2–C$\underline{H}_2$)$_2$CH–, pyrrole–CH_2–HC$\underline{H}$–), 2.11 (s, 3H, CH_3–pyrrole), 2.15—2.33 (m, 2H, pyrrole–CH_2–$\underline{H}$CH–C$\underline{H}$–), 2.60 (q, 2H, J=7.4 Hz, CH_3–C$\underline{H}_2$–), 2.68—2.98 (m, 4H, –N($\underline{H}$CH–CH_2)$_2$CH–, pyrrole–C$\underline{H}_2$–CH_2–), 3.17—3.33 (m, 2H, –N(HC$\underline{H}$–CH_2)$_2$CH–), 3.41—3.51 (m, 1H, >C$\underline{H}$–CO–Ph), 4.07 (d, 1H, J=13.4 Hz, –$\underline{H}$CH–CO–N<), 4.58 (d, 1H, J=13.3 Hz, –HC$\underline{H}$–CO–N<), 7.14 (t, 2H, J=8.5 Hz, *o*-F-Ph), 7.93—7.99 (m, 2H, *m*-F-Ph). ^{13}C-NMR ($CDCl_3$) δ: 10.6 (C$\underline{H}_3$–CH_2–), 15.9 (C$\underline{H}_3$–pyrrole), 18.4 (CH_3–C$\underline{H}_2$–pyrrole), 23.1 (C_6), 28.9 (–N(CH_2–C$\underline{H}_2$)$_2$CH–), 33.5 (–N(CH_2–CH_2)$_2$C$\underline{H}$–), 41.6 (C_5), 43.5 (–N(C$\underline{H}_2$–CH_2)$_2$CH–), 44.3 (C_7), 45.3 (–C$\underline{H}_2$–CO–N<), 116.3 (d, J=21.8 Hz, *o*-F-Ph), 117.9 (C_{3a}), 121.1 (C_3), 124.4 (C_2), 131.3 (d, J=9.4 Hz, *m*-F-Ph), 132.4 (d, J=2.2 Hz, *p*-F-Ph), 142.2 (C_{7a}), 166.2 (d, J=253.3 Hz, >C–F), 171.2 (–CO–N<), 195.4 (–CO– indol), 200.5 (–CO– benzoyl). *Anal*. Calcd for $C_{25}H_{29}FN_2O_3$: C, 70.73; H, 6.88; N, 6.59. Found: C, 70.61; H, 8.82; N, 6.73.

***N*-(1-Benzenesulfonyl-3-ethyl-2-methyl-4-oxo-4,5,6,7-tetrahydro-5-indolylacetyl)-4-(*p*-fluoroben-zoyl)piperidine (9e)** Under an argon atmosphere, a solution of the amide **8e** (2.3 g, 5.56 mmol) in DMF (10 ml) was added dropwise to a suspension of 55% NaH (0.28 g, 6.4 mmol) in DMF (15 ml) at 0—5 °C with vigorous stirring. The resulting mixture was stirred at room temperature for 1 h and the DMF distilled under reduced pressure. The solid residue was dissolved in CH_2Cl_2 and the resulting solution washed several times with water, dried and the solvent distilled *in vacuo*. The solid residue was subjected to column purification on silica gel using AcOEt–hexane 2 : 1 to elute 2.31 g (75%) of **9e** as a yellow foam solid. IR (KBr) cm^{-1}: 1675 (C=O benzoyl), 1638 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 0.97 (t, 3H, J=7.4 Hz, C$\underline{H}_3$–CH_2–), 1.59—1.89 (m, 5H, –N(CH_2–C$\underline{H}_2$)$_2$)CH–, pyrrole–CH_2–HC$\underline{H}$–), 2.23 (s, 3H, CH_3–pyrrole), 2.11—2.29 (m, 2H, pyrrole–CH_2–$\underline{H}$CH–CH–), 2.56 (q, 2H, J=7.4 Hz, CH_3–C$\underline{H}_2$–), 2.79—3.01 (m, 3H, –N($\underline{H}$CH–CH_2)$_2$CH–, pyrrole–$\underline{H}$CH–CH_2–), 3.08—3.21 (m, 2H, –N(HC$\underline{H}$–CH_2)$_2$CH–), 3.33—3.46 (m, 2H, pyrrole–HC$\underline{H}$–CH_2–, –C$\underline{H}$–CO–Ph), 4.00 (d, 1H, J=13.3 Hz, –$\underline{H}$CH–CO–N<), 4.55 (d, 1H, J=13.3 Hz, –HC$\underline{H}$–CO–N<), 7.10 (t, 2H, J=8.5 Hz, *o*-F-Ph), 7.50 (t, 2H, J=7.5 Hz, *m*-Ph–SO_2–), 7.60 (t, 1H, J=7.3 Hz, *p*-Ph–SO_2–), 7.69 (d, 2H, J=7.4 Hz, *o*-Ph–SO_2–), 7.94 (dd, 2H, J=7.6 Hz, J=5.5 Hz, *m*-F-Ph). ^{13}C-NMR ($CDCl_3$) δ: 11.7 (C$\underline{H}_3$–CH_2–pyrrole), 15.2 (C$\underline{H}_3$–pyrrole), 18.2 (CH_3–C$\underline{H}_2$–), 24.9 (C_6), 29.7 (–N(CH_2–C$\underline{H}_2$)$_2$CH–), 32.9 (–C$\underline{H}$–CO–Ph), 41.6 (C_5), 43.52 (C_7), 44.2 (–N(C$\underline{H}_2$–CH_2)$_2$CH–), 45.2 (–C$\underline{H}_2$–CO–N<), 116.4 (d, J=21.9 Hz, *o*-F-Ph), 121.6 (C_{3a}), 125.6 (C_3), 126.8 (*o*-Ph–SO_2–), 128.4 (C_2), 130.6 (*m*-Ph–SO_2–), 131.3 (d, J=9.21 Hz, *m*-Ph-F), 132.4 (d, J=2.41 Hz, *p*-Ph-F), 134.5 (*p*-Ph–SO_2–), 139.7 (C_{7a}), 144.9 (C–SO_2–), 166.1 (d, J=255 Hz, >C–F), 170.2 (CO–N<), 196.4 (C=O indol), 200.4 (C=O benzoyl). 2,4-Dinitrophenylhydrazone: A saturated solution of 2,4-dinitrophenylhydrazine sulfate in abs. MeOH was added to a solution of a sample of amide **9e** in abs. MeOH. After a slight heating, the hydrazone precipitated as a crystalline solid which was recovered by filtration, washed with MeOH and recrystallized from ethyl acetate. Red crystals, mp 141—142 °C.

***N*-(1-Benzenesulfonyl-3-ethyl-2-methyl-4-oxo-4,5,6,7-tetrahydro-5-indolylacetyl)-4-(*p*-fluorobenzoyl)piperidine, Bis Ethylene Ketal (13)** A stirred solution of amide **9e** (3.5 g, 6.4 mmol) in ethyleneglycol (222.6 g, 3.59 mol) and freshly prepared pyridinium tosylate (0.5 g) in anhydrous toluene (100 ml) was refluxed in a Dean–Stark apparatus for 200 h with azeotropic distillation of water. After cooling, the toluene solution was washed with 10% NaOH (2×50 ml), water (2×50 ml), dried and the solvent distilled *in vacuo* to give 2 g (50%) of a yellow foam solid which was used in the next step whithout further purification. IR (film) cm^{-1}: 2962 (C–H), 1639 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.01 (t, 3H, J=7.3 Hz, C$\underline{H}_3$–CH_2–), 1.04—1.39 (m, 3H, –N(CH_2–HC$\underline{H}$)$_2$CH–, $1H_6$), 1.57—2.08 (m, 5H, –N(CH_2–HC$\underline{H}$)$_2$C$\underline{H}$–, $1H_6$, $1H_5$), 2.28 (s, 3H, C$\underline{H}_3$–pyrrole), 2.23—3.24 (m, 8H, CH_3–C$\underline{H}_2$–, $2H_7$, –N(CH_2–CH_2)$_2$CH–), 3.35—3.41 (m, 1H, –HC$\underline{H}$–CO–N<), 3.61—4.18 (m, 8H, 2 –O–CH_2–CH_2–O–), 4.62—4.66 (m, 1H, –$\underline{H}$CH–CO–N<), 7.01 (t, 2H, J=8.7 Hz, *o*-F-Ph), 7.33—7.38 (m, 2H, *m*-Ph–SO_2–), 7.44—7.58 (m, 2H, *o*-Ph–SO_2–), 7.59—7.73 (m, 3H, *m*-Ph–SO_2–, *p*-Ph–SO_2–). MS m/z: 653 (M+1, 30%), 609 (49%), 358 (100%), 217 (53%), 123 (35%).

***N*-(1-Benzenesulfonyl-3-ethyl-2-methyl-4-oxo-4,5,6,7-tetrahydro-5-indolylethyl)-4-(*p*-fluorobenzoyl)piperidine (15)** Under an argon atmosphere, a stirred solution of amide **13** (1 g, 1.53 mmol) in anhydrous ether (20 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (0.3 g, 7.8 mmol) in anhydrous ether. Under vigorous stirring, the resulting suspension was heated under reflux for 2 h. After cooling in an ice bath, the reaction mixture was quenched by cautious addition of a saturated solution of sodium potassium tartrate. The white coarse precipitate formed was filtered off and thoroughly washed with ether. The combined filtrates were dried and the solvent distilled *in vacuo*. The crude bis ethylene ketal **14** (0.70 g, 70%) was dissolved in abs. MeOH and acidified with MeOH–HCl saturated. After 15—20 min on standing at room temperature, 20% HCl was added and the resulting solution heated under reflux with vigorous stirring for 2 h. After cooling, the solution was made alkaline with 10% NaOH and then extracted into ethyl acetate, the organic layer was dried and the solvent was removed *in vacuo* to give 0.45 g of a brown oil which was subjected to column chromatographic purification using AcOEt to elute 0.35 g (50%) of **15** as a colorless oil which decomposed after attempted ball to ball distillation.

***N*-(3-Ethyl-2-methyl-4-oxo-4,5,6,7-tetrahydro-5-indolylethyl)-4-(*p*-fluorobenzoyl)piperidine (12e)** Under an argon atmosphere, to a solution of sulfonamide **15** (0.24 g, 0.50 mmol) in anhydrous THF (0.4 ml) at −78 °C was distilled about 6 ml of ammonia. Sodium (0.03 g, 3 at-g) was added until a blue coloration persisted for 25 min after which the reaction was quenched

with ammonium chloride (0.30 g). Ammonia was allowed to evaporate and the resulting residue partitioned between water (2 ml) and CH_2Cl_2 (10 ml). The water layer was washed with CH_2Cl_2 and the combined organic layers, dried (Na_2SO_4) and concentrated to give 140 mg (60%; 10% from **8e**) of a yellow oil which was purified by flash chromatography (AcOEt as eluent) to give a colorless oil which slowly crystallized on standing, mp 168—170 °C.

***N*-(3-Ethyl-2-methyl-4,5,6,7-tetrahydro-5-indolylethyl)-4-(*p*-fluorobenzoyl)piperidine, Ethylene Ketal (16)** The experimental procedure was similar to that described for **14** (*vide supra*) but using THF (70 °C) instead ether. After chromatographic purification an amorphous solid (70%) was obtained from which a satisfactory elemental analysis could not be obtained.

***N*-(1-Benzenesulfonyl-3-ethyl-2-methyl-4,5,6,7-tetrahydro-5-indolylethyl)-4-(*p*-fluorobenzoyl)piperidine, Ethylene Ketal (17)** Under an argon atmosphere, a 1 M solution of AlH_3 in THF (1.5 ml, 1.5 mmol, 5 eq) was added slowly by syringe to a solution of amide **13** (0.2 g, 0.31 mmol) in anhydrous THF (6 ml). The resulting mixture was stirred at room temperature for 15 h, after which the solution was made basic with 10% NaOH (35 ml) and extracted into CH_2Cl_2. The combined organic layers were washed with water, dried (Na_2SO_4) and the solvent removed *in vacuo*. After chromatographic purification (silica gel, ethyl acetate) **17** was obtained as an amorphous solid foam (0.12 g, 70%) which was directly used in the next step. A sample was subjected to spectroscopic measurement. A sample of **17** (200 mg, 0.34 mmol) was dissolved in abs. MeOH (1.5 ml) and the solution acidified with MeOH–HCl saturated until pH 1—2. After 15—30 min of standing at room temperature, 20% HCl (20 ml) was added and the resulting solution heated at 60—65 °C under vigorous stirring for 2 h. After cooling, the solution was made basic with 10% NaOH and then extracted into ethyl acetate which was washed with water, dried and the solvent distilled off. The residue was subjected to column chromatographic purification using AcOEt as eluent to give 0.11 g (55%) of **18** as a colorless oil from which crystalline oxalate and oxime were obtained. Spectral data of free base follows. IR (film) cm^{-1}: 1680 (C=O benzoyl), 2928 (C–H). $_1$H-NMR ($CDCl_3$) δ: 0.98 (t, 3H, J=7.5 Hz, C$\underline{H}_3$–CH_2–), 1.23—1.59 (m, 3H, $1H_5$, >CH–C$\underline{H}_2$–CH_2–N<), 1.82—2.11 (m, 5H, –N(CH_2–C$\underline{H}_2$)$_2$CH–, $1H_6$), 2.15—2.38 (m, 8H, $1H_6$, C$\underline{H}_3$–pyrrole, $2H_7$, $2H_4$), 2.43—2.68 (m, 4H, CH_3–C$\underline{H}_2$–, >CH–CH_2–C$\underline{H}_2$–N<), 2.92—3.23 (m, 5H, –N(C$\underline{H}_2$–CH_2)$_2$C$\underline{H}$–), 7.13 (t, 2H, J=8.6 Hz, *o*-Ph-F), 7.40—7.74 (m, 5H, Ph–SO_2–), 7.96 (dd, 2H, J=5.4 Hz, J=8.9 Hz, *m*-Ph-F).

Oxalate: A saturated solution of oxalic acid in ethyl ether was slowly added to a sample of oil also in ether. Inmediately a crystalline white solid precipitated which was recovered by filtration and recrystallized from ethyl acetate, mp 186—187.5 °C. *Anal*. Calcd for $C_{33}H_{39}FN_2O_7S$: C, 63.24; H, 6.27; N, 4.47. Found: C, 62.89; H, 6.33; N, 4.58.

Oxime: A solution of amine **18** (1.3 g, 0.056 mmol), NH_2OH (0.3 g, 6.38 mmol) in EtOH (1.5 ml) and pyridine (1.5 ml, 0.018 mol) was heated to 100 °C for 2 h. Then, the solvent was removed *in vacuo* and H_2O (1.5 ml) was added. The oxime crystallized on cooling to give a white solid of mp 213—214 °C (iso-PrOH). MS *m/z*: 552 (M+1, 87%), 410 (41%), 235 (100%), 188 (57%), 162 (27%), 96 (27%).

1,4-Dihydro-3,5-dimethoxybenzoic Acid (21) To a solution of 3,4,5-trimethoxybenzoic acid (8.0 g, 37 mmol) in methanol (50 ml) and liquid ammonia (180 ml) was added lithium (4.5 g) in small pieces. When the addition was complete, ammonium chloride (20 g) was added, and the ammonia was allowed to evaporate at room temperature. The residue was dissolved in ice-water and the solution was acidified at 0 °C with 2 M HCl to congo red. The solution was extracted with methylene chloride and the combined organic phases were washed with water, dried (Na_2SO_4) and evaporated under reduced pressure giving 6.5 g (93%) of **21** as a white solid, mp 99—104 °C (hexane).

1,4-Dihydro-3,5-dimethoxybenzyl Alcohol (22) A solution of 1,4-dihydro-3,5-dimethoxybenzoic acid **21** (3.45 g, 18.7 mmol) in dry ether (100 ml) was added to a suspension of $LiAlH_4$ (2.85 g, 75.1 mmol) in dry ether (150 ml). The reaction mixture was stirred for 18 h under argon atmosphere, and then water (4.2 ml), 2 M NaOH (4.2 ml) and water (18 ml) were added. White aluminium hydroxides were filtered off and the filtrate was dried (Na_2SO_4) and the solvent was removed *in vacuo* to give 2.90 g (90%) of **22** as a colourless oil which crystallized on cooling, mp 41—43 °C.

3-Ethyl-2-methyl-6-hydroxymethyl-4,5,6,7-tetrahydroindol-4-one (24) A solution of bis(enol ether) **22** (1.37 g, 8 mmol) in 70% aqueous acetic acid (25 ml) was refluxed for 15 min, then removed from the heating bath and Zn powder (1.16 g, 24 mol) was added in portions over 15 min with stirring. The mixture was heated to reflux and a solution of 2-isonitroso-3-pentanone (1.12 g, 9 mmol) in 70% aqueous acetic acid (10 ml) was added. The resulting mixture was refluxed for 4 h and then cooled to room temperature. The solvent was evaporated, and the residue was dissolved in water (30 ml) and extracted with CH_2Cl_2 (3×25 ml). The aqueous solution was evaporated and the residue was treated with CH_2Cl_2 (50 ml), the zinc acetate was removed by filtration and the filtrate was dried (Na_2SO_4). The combined organic extracts were concentrated to give 1.54 g of yellow solid which was purified by column chromatography (silica gel, AcOEt/hexane 2 : 1) to afford 0.60 g (30%, *Rf*= 0.40) of 3-ethyl-2-methyl-6-acetoxymethyl-4,5,6,7-tetrahydroindol-4-one (**23**) and 0.50 g (30%, *Rf*=0.07) of 3-ethyl-2-methyl-6-hydroxymethyl-4,5,6,7-tetrahydroindol-4-one (**24**).

23: mp 147—149 °C (benzene). IR (KBr) cm^{-1}: 3232 (H–N), 1731 (C=O ester), 1625 (C=O ketone), 1604 (C=C), 1475. ^{1}H-NMR ($CDCl_3$) δ: 7.97 (s, 1H, >NH), 4.09 (d, 2H, J=5.8 Hz, –C$\underline{H}_2$OCO), 2.86—2.79 (m, 1H, H_7), 2.63 (q, 2H, J=7.4 Hz, CH_3C$\underline{H}_2$–), 2.59—2.49 (m, 3H, H_5, H_6, H_7), 2.36—2.27 (m, 1H, H_5), 2.15 (s, 3H, C$\underline{H}_3$–C=), 2.07 (s, 3H, CH_3–COO–), 1.11 (t, 3H, J=7.4 Hz, C$\underline{H}_3$–CH_2–). MS *m/z*: 207 (M^+, 100%). *Anal*. Calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.80; H, 7.60; N, 5.39.

24: mp 178—180 °C (hexane/AcOEt). IR (KBr) cm^{-1}: 3423 (O–H), 3232 (H–N), 1624 (C=O), 1480. ^{1}H-NMR ($CDCl_3$–TFA) δ: 8.34 (s, 1H, >NH), 4.49—4.33 (m, 2H, –C$\underline{H}_2$OH), 3.02—2.53 (m, 7H, CH_3C$\underline{H}_2$–, H_5, H_6, H_7), 2.16 (s, 3H, C$\underline{H}_3$–C=), 1.08 (t, 3H, J=7.4 Hz, C$\underline{H}_3$–CH_2–). MS *m/z*: 249 (M^+, 90%). *Anal*. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.91; H, 8.12; N, 6.41.

The acetyl derivative **23** (0.55 g, 2.2 mmol) was dissolved in ethanol (5 ml) and a 10% solution of KOH in ethanol (6.2 ml) was added. The mixture was refluxed for 12 h. Solvent was evaporated at reduced pressure and the residue dissolved in CH_2Cl_2 and washed with water. The organic layer was dried (Na_2SO_4), filtered and the solvent was evaporated *in vacuo* to give 0.58 g of a brown solid which was purified by column chromatography (silica gel, AcOEt/hexane 2 : 1) to afford 0.28 g (60%) of **24**.

3-Ethyl-2-methyl-6-(*p*-tolylsulfonyl)oxymethyl-4,5,6,7-tetrahydroindol-4-one (25) *p*-Toluenesulfonyl chloride (3.3 g, 17.4 mmol) was added to a cooled solution of the alcohol **24** (1.8 g, 8.7 mmol) in dry pyridine (50 ml) and the mixture stirred at 0 °C for 24 h. Ice water was then added to the reaction mixture, and the resultant solid was collected by filtration and washed with water to give 1.57 g (50%) of **25** as a white solid, mp 153—154 °C (toluene). IR (KBr) cm^{-1}: 3226 (H–N), 1625 (C=O), 1601 (C=C), 1362, 1171 (S=O). ^{1}H-NMR ($CDCl_3$) δ: 7.83 (s, 1H, >NH), 7.78 (d, 2H, J=8.3 Hz, H_2 and H_6 of Ts), 7.36 (d, 2H, J=8.1 Hz, H_3 and H_5 of Ts), 4.03—3.96 (m, 2H, C$\underline{H}_2$OTs), 2.93—2.83 (m, 1H, H_7), 2.68—2.57 (m, 4H, CH_3C$\underline{H}_2$–, H_6, H_7), 2.46 (s, 3H, TsC$\underline{H}_3$), 2.37 (dd, 1H, J=3.7, 15.6 Hz, H_5), 2.26—2.17 (m, 1H, H_5), 2.14 (s, 3H, C$\underline{H}_3$–C=), 1.08 (t, 3H, J=7.4 Hz, C$\underline{H}_3$–CH_2–). *Anal*. Calcd for $C_{19}H_{23}NSO_4$: C, 63.14; H, 6.41; N, 3.88. Found: C, 62.90; H, 6.60; N, 3.98.

3-Ethyl-2-methyl-6-morpholinylmethyl-4,5,6,7-tetrahydroindol-4-one (26a). General procedure: A solution of the tosylate **25** (0.20 g, 0.55 mmol) and morpholine (0.10 g, 1.1 mmol) in 1-methyl-2-pyrrolidone (NMP, 6 ml) was stirred at 85 °C for 16 h. The solvent was evaporated under reduced pressure and the residue was purified by chromatography on silica with ethyl acetate as eluant to give 0.11 g (75%) of **26a** as white solid, mp 127—130 °C.

3-Ethyl-2-methyl-6-piperazin-1-ylmethyl-4,5,6,7-tetrahydroindol-4-one (26b) mp 176—178 °C. IR (KBr) cm^{-1}: 3260 (H–N), 1635 (C=O), 1478. ^{1}H-NMR ($CDCl_3$) δ: 8.12 (s, 1H, >N–H), 2.92—2.83 (m, 5H, –N(CH_2–C$\underline{H}_2$)$_2$N–Ph, H_7), 2.68—2.60 (m, 2H, CH_3–C$\underline{H}_2$–), 2.58—2.25 (m, 9H, H_5, H_6, H_7, –C$\underline{H}_2$–N(CH_2–C$\underline{H}_2$)$_2$N–), 2.22—2.17 (m, 1H, H_5), 2.14 (s, 3H, CH_3–C=), 1.12 (t, 3H, J=7.4 Hz, C$\underline{H}_3$–CH_2–). *Anal*. Calcd for $C_{16}H_{25}N_3O$: C, 69.78; H, 9.15; N, 15.26. Found: C, 69.52; H, 9.34; N, 15.44.

3-Ethyl-2-methyl-6-[4-(*o*-methoxyphenyl)piperazinyl]methyl-4,5,6,7-tetrahydroindol-4-one (26d) mp 219—221 °C (acetone). IR (KBr) cm^{-1}: 3176 (H–N), 1621 (C=O), 1597 (C=C), 1240 (C–O–C). ^{1}H-NMR ($CDCl_3$) δ: 7.86 (s, 1H, >N–H), 7.03—6.85 (m, 4H, Ph), 3.86 (s, 3H, –O–CH_3), 3.07 (s, 4H, –N(CH_2–C$\underline{H}_2$)$_2$N–Ph), 2.95—2.87 (m, 1H, H_7), 2.71—2.36 (m, 11H, H_5, H_6, H_7, CH_3–C$\underline{H}_2$–, –C$\underline{H}_2$–N(CH_2–C$\underline{H}_2$)$_2$N–), 2.26—2.17 (m, 1H, H_5), 2.15 (s, 3H, CH_3–C=), 1.12 (t, 3H, J=7.4 Hz C$\underline{H}_3$–CH_2–). *Anal*. Calcd for $C_{23}H_{31}N_3O_2$: C, 72.41; H, 8.19; N, 11.01. Found: C, 71.61; H, 8.35; N, 10.90.

3-Ethyl-2-methyl-6-[4-(*p*-fluorobenzoyl)piperidinyl]methyl-4,5,6,7-tetrahydroindol-4-one (26e) mp 162—164 °C (AcOEt/hexane). IR (KBr) cm^{-1}: 3274 (H–N), 1679 (C=O benzoyl), 1618 (C=O indole), 1598 (C=C), 1475. ^{1}H-NMR ($CDCl_3$) δ: 7.99—7.94 (m, 3H, H_2 and H_6 of Ph, >N–H), 7.13 (t, 2H, J=8.6 Hz, H_3 and H_5 of Ph), 3.25—3.15 (m, 1H, –N(CH_2–CH_2)$_2$C$\underline{H}$–), 3.00—2.83 (m, 3H, H_7, –N(C$\underline{H}$CH–CH_2)$_2$CH–), 2.68—2.60 (m, 2H, CH_3–C$\underline{H}_2$–), 2.58—2.30 (m, 5H, –C$\underline{H}_2$–N(HC$\underline{H}$–CH_2)$_2$CH–, H_7),

2.23—2.12 (m, 5H, CH_3–C=, H_5, H_6), 2.08—1.89 (m, 1H, H_5), 1.85—1.80 (m, 4H, N(CH_2–CH_2)$_2$CH–), 1.11 (t, 3H, J=7.4 Hz, CH_3–CH_2–). *Anal*. Calcd for $C_{24}H_{29}FN_2O_2$: C, 72.70; H, 7.37; N, 7.07. Found: C, 72.40; H, 7.89; N, 7.22.

3-Ethyl-2-methyl-6-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidinyl]-methyl-4,5,6,7-tetrahydroin-dol-4-one (26f) mp 203—205 °C (*n*-butanol). IR (KBr) cm^{-1}: 3253 (H–N), 1619 (C=O), 1474. ^{1}H-NMR ($CDCl_3$) δ: 7.90 (s, 1H, >N–H), 7.67 (dd, 1H, J=5.1, 8.7 Hz, H_4 benzisoxazole), 7.24 (dd, 1H, J=2.0, 8.7 Hz, H_7 benzisoxazole), 7.05 (dt, 1H, J=2.1, 8.8 Hz, H_5 benzisoxazole), 3.10—2.89 (m, 4H, H_7, –N(HCH–CH_2)$_2$CH–), 2.69—2.60 (m, 2H, CH_3–CH2–), 2.57—2.33 (m, 5H, –CH_2–N(HCH–CH_2)$_2$C–, H_7), 2.26—2.17 (m, 2H, H_6, H_5), 2.15 (s, 3H, CH_3–C=), 2.09—2.02 (m, 5H, H_5, –N(CH_2–CH_2)$_2$CH–), 1.12 (t, 3H, J=7.4 Hz, CH_3–CH_2–). *Anal*. Calcd for $C_{24}H_{28}FN_3O_2$: C, 70.39; H, 6.89; N, 7.81. Found: C, 69.97; H, 7.08; N, 7.74.

3-Ethyl-2-methyl-6-[4-[3-(*p*-fluorobenzoyl)-1-propyl]piperazinyl]-methyl-4,5,6,7-tetrahydroindol-4-one (26g) A solution of 4-chloro-1,1-ethylenedioxy-1-(4-fluorophenyl)butane (0.08 g, 0.33 mmol) in methyl isobutyl ketone (5 ml) was added to a mixture of **26b** (0.09 g, 0.33 mmol), anhydrous K_2CO_3 (0.10 g) and KI (0.02 g) in methyl isobutyl kenone (5 ml) with stirring. After refluxing with vigorous stirring for 69 h, the mixture was allowed to stand at room temperature overnight, then filtered. The filtrate was evaporated under reduced pressure to give 0.20 g of a yellow oil. This was dissolved in a mixture of ether (15 ml) and methanol (5 ml), treated with 20% HCl (15 ml) 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 (3×15 ml). The combined ether extracts were dried (Na_2SO_4), and the solvent was removed under reduced pressure to give 0.18 g of a yellow solid, which was purified by flash chromatography (silica gel, methanol) to give 0.12 g (83%) of **26f** as a white solid, mp 170—172 °C (iso-PrOH). IR (KBr) cm^{-1}: 3256 (H–N), 1684 (C=O benzoyl), 1623 (C=O indole), 1598 (C=C), 1474. ^{1}H-NMR ($CDCl_3$) δ: 7.99 (dd, 2H, J=5.4, 8.9 Hz, H_2 and H_6 of Ph), 7.88 (s, 1H, >N–H), 7.12 (t, 2H, J=8.6 Hz, H_3 and H_5 of Ph), 2.97 (t, 2H, J=7.1 Hz, >N–CH_2–CH_2–CH_2–CO), 2.90—2.82 (m, 1H, H_7), 2.68—2.59 (m, 2H, CH_3–CH_2–), 2.57—2.23 (m, 15H, –CH_2–N(CH_2–CH_2)$_2$–N–CH_2–, H_5, H_6, H_7), 2.21—2.11 (m, 4H, CH_3–C=, H_5), 1.93 (q, 2H, J=7.1 Hz, >N–CH_2–CH_2–CH_2–CO), 1.11 (t, 3H, J=7.4 Hz, CH_3–CH_2–). *Anal*. Calcd for $C_{26}H_{34}FN_3O_2$: C, 71.04; H, 7.80; N, 9.56. Found: C, 69.86; H, 7.43; N, 9.73.

***In Vitro* Experiments** Detailed methods for D_2 and 5-HT_{2A} binding assays have been published elsewhere.[34)]

Acknowledgements This work was supported by the Spanish Interministerial Commission for Science and Technology (CICYT) under grant SAF 95-1081 and by Xunta de Galicia grant 20312 B95. We also thank Dr. Jose Angel Fontenla and Dr. M. Isabel Loza for pharmacological results.

References

1) Reynolds G. P., *Trends Pharmacol. Sci*., **13**, 116—121 (1992).
2) Martin A. R., "Antipsychotic Agents," in *Burger's Medicinal Chemistry*, 5th ed.; ed. by Wolf M. E., Wiley-Interscience, New York, 1997, Vol. 5, p. 195.
3) *a*) Lednicer D., Mitscher L. A., "The Organic Chemistry of Drug Synthesis," Vol. 2, Wiley Interscience, New York, 1980, p. 4559; *b*) Horu A. S, "Dopamine Receptors," in *Comprehensive Medicinal Chemistry*, Vol. 3, ed. by Hansch C., Sammes P. G., Taylor J. B., Pergamon Press, Oxford, 1990, p. 133.
4) Olson G. L., Ho-Chuen C., Morgan D. K., Blount J. F., Todaro L., Berger L., Davidson A. B., Boff E., *J. Med. Chem*., **24**, 1026—1034 (1981).
5) Seeman P., Chou-Wong M., Tadesco J., Wong K., *Nature* (London), **261**, 717—719 (1976).
6) Seeman P., Lee T., *Science*, **188**, 184—189 (1975).
7) Peroutka S. J., Snyder S. H., *Am. J. Psychiatry*, **173**, 1518—1522 (1980).
8) Sanberg P. R., *Nature* (London), **284**, 472—473 (1980).
9) Seeman P., Bzowej N. H., Guan H. C., Bergeron C., Becker L. E., Reynols G. P., Bird E. D., Riedeger P., Jelliger K., Watanabe S., Tourtellote W. W., *Synapse*, **1**, 399—404 (1987).
10) Nowak K., Welsch-Kunze S., Kuschinsky K., *Naunyn-Schmiedeberg's Arch. Pharmacol*., **337**, 385—391 (1988).
11) Fitton A., Heel R. C., *Drugs*, **40**, 722—747 (1990).
12) Schwarz J. T., Brotman A. W., *Drugs*, **44**, 981—985 (1992).
13) Rosenheck R., Cramer J., Xu W., Thomas J., Henderson W., Frisman L., Fye C., Charney D., *N. Engl. J. Med*., **337**, 809—815 (1997).
14) Sanders-Buch E., Mayer S. E, "Agonistas y antagonistas de los receptores de 5-hidroxitriptamina," in Goodman & Gilman. Las bases farmacológicas de la terapeutica., 9th ed., Molinoff P. B., Ruddon R. W., eds., McGraw-Hill Interamericana, México, 1996, pp. 265—280.
15) Meltzer H. Y., Matsubara S., Lee J. C., *J. Pharmacol. Exp. Ther.*, **251**, 238—246 (1989).
16) Roth B. L., Meltzer H. Y., "The role of Serotonin in Schizophenia," in Psychopharmacology: The Fourth Generation of Progress, Bloom F. E., Kupfer D. J., eds., Raven Press, Ltd., New York, 1995, pp. 1215—1227.
17) Meltzer H. Y., Matsubara S., Lee J. C., *Psychopharmacol. Bull.*, **25**, 390—392 (1989).
18) Roth B. L., Tandra S., Burgess L. H., Sibley D. R., Meltzer H. Y., *Psychopharmacology*, **120**, 365—368 (1995).
19) *a*) Megens A. H. P., Kennis L. E. J., "Risperidone and Related 5-HT2/D2 Antagonists: a New Type of Antipsychotic Agent," in Progress in Medicinal Chemistry, Ellis G. P., Luscombe D. K., eds., Elsevier Sci., 1996, Vol. 33, p. 186; *b*) Beasley C. M., Tollefson G., Tran P., Satterlee W., Sanger T., Hamilton S., *Neuropsychopharmacol*., **14**, 111—123 (1996); *c*) Conley R. R., Buchanan R. W., *Schizophrenia Bull*., **23**, 663—674 (1997).
20) Lowe III J. A., *Curr. Med. Chem*., **1**, 50—60 (1994).
21) Gleason S. D., Shannon H. E., *Psychopharmacology. Berl.*, **129**, 79—84 (1997).
22) Sipes T. E., Geyer M. A., *Brain Res*., **761**, 97—104 (1997).
23) Okuyama S., Chaki S., Kawashima N., Suzuki Y., Ogawa S., Kumagai T., Nakazato A., Nagamine M., Yamaguchi K., Tomisawa K., *Brit. J. Pharmacol.*, **121**, 515—525 (1997).
24) Green M. F., Marshall B. D., Jr., Wirshing W. C., Ames D., Marder S. R., McGurk S., Kern R. S., Mintz J., *Am. J. Psychiat*., **154**, 799—804 (1997).
25) Martin P., Waters N., Carlsson A., Carlsson M. L., *J. Neural. Transm*., **104**, 561—564 (1997).
26) Padich R. A., McCloskey T. C., Kehne J. H., *Psychopharmacology*, **124**, 107—116 (1996).
27) Schmidt C. J., "Development of a Selective 5-HT_{2A} Receptor Antagonist for the Treatment of Schizophrenia," IBS's International Conference on: Serotonin receptors. Central Nervous System. Targets for New Therapeutic Agents, Philadelphia, 1996.
28) Janssen P. A. J., Niemegeers C. J. E., Awouters F., Schelekens K. H. L., Megens A. A. H. P., Meert T. F., *J. Pharmacol. Exp. Ther*., **244**, 685—693 (1988).
29) Megens A. A. H. P., Niemegeers C. J. E., Awouters F. H. L., *J. Pharmacol. Exp. Ther*., **260**, 160—167 (1992).
30) Hyttel J., Arnt J., Costall B., Domeney A., Dragsted N., Lembol H. L., Meier E., Naylor R. J., Nowak G., Sanchez C., Starsfeldt T., *Clin. Neuropharmacol.*, **15** (Suppl.1 PtA), 267A—268A (1992).
31) Lieberman J. A., Hohn C. A., Mikane J., Rai K., Pisciotta A. V., Salz B. L., Howard A., *J. Clin. Psychiat*., **49**, 271—277 (1988).
32) Cortizo L., Santana L., Raviña E., Orallo F., Fontenla J. A., Castro E., de Ceballos M., *J. Med. Chem*., **34**, 2242—2247 (1991).
33) Fontenla J. A., Osuna J. A., Rosa E., Castro E., Loza I., G-Ferreiro T., Calleja J. M., Sanz F., Rodriguez J., Fueyo J., Raviña E., Masaguer C. F., Vidal A., de Ceballos M., *J. Med. Chem*., **37**, 2564—2573 (1994).
34) Raviña E., Fueyo J., Masaguer C. F., Negreira J., Cid J., Loza I., Honrubia H., Tristan H., Ferreiro T. G., Fontenla J. A., Rosa E., Calleja J. M., de Ceballos M. L., *Chem. Pharm. Bull.*, **44**, 534—541 (1996).
35) Loza I., Verde I., Orallo F., Fontenla J. A., Calleja J. M., Raviña E., Cortizo L., de Ceballos M., *Bioorg. Med. Chem. Lett.*, **1**, 717—720 (1991).
36) Raviña E., Masaguer C. F., Cid J., Casariego I., Fontenla J. A., Ferreiro T. G., Cadavid I., Loza I., de Ceballos M. L., *Bioorg. Med. Chem. Lett*., **5**, 579—584 (1995).
37) Masaguer C. F., Raviña E., Fontenla J. A., Loza I., *Bioorg. Med. Chem. Lett.*, **7**, 913—918 (1997).
38) *a*) Shustke G. M., Setescak L. L., Allen R. C., Davis L., Effland R. E., Ranbom K., Kitzen J. M., Wilker J. C., Novick W. J., *J. Med. Chem*., **25**, 36—44 (1982); *b*) Strupczewski J. T., Allen R. C., Gardner B. A., Schmid B. L., Stache U., Glamkowski E. J., Jones M. C., Ellis D. B., Huger F. P., Dunn R. W., *ibid*., **28**, 761—769 (1985).
39) Masaguer C. F., Raviña E., Fueyo J., *Heterocycles*, **34**, 1303—1309 (1994).
40) Remers W. A., Roth R. H., Gibs G. J., Weiss M. J., *J. Org. Chem*., **36**,

1232—1240 (1971).
41) Yasuhara A., Sakamoto T., *Tetrahedron Lett.*, **39**, 595—596 (1998).
42) Fuji M., Muratake H., Natsume M., *Chem. Pharm. Bull*., **40**, 2338—2343 (1992).
43) Raviña E., Negreira J., Cid J., Masaguer C. F., Rosa E., Rivas M. E., Fontenla J. A., Loza M. I., Tristán H., Cadavid M. I., Sanz F., Lozoya E., Carotti A., Carrieri A., "Conformationally Constrained Butyrophenones with Mixed Dopaminergic (D2) and Serotoninergic (5-HT2A, 5-HT2C) Affinities. Synthesis, Pharmacology, 3D-QSAR and Molecular Modelling of Aminoalkyl Benzo and Thienocycloalkanones as Putative Atypical Antipsychotics," *J. Med. Chem.* (in press)
44) Kuehne M. E., Lambert B. F., *J. Am. Chem. Soc.*, **81**, 4278—4287 (1959).
45) Chapmann O. L., Fitton P., *J. Am. Chem. Soc*., **85**, 41—47 (1963).