Conformationally Constrained Butyrophenones with Mixed Dopaminergic (D_2) and Serotoninergic (5-HT_{2A}, 5-HT_{2C}) Affinities: Synthesis, Pharmacology, 3D-QSAR, and Molecular Modeling of (Aminoalkyl)benzo- and -thienocycloalkanones as Putative Atypical Antipsychotics[▽]

Enrique Raviña,*[,†] Jesús Negreira,[†] José Cid,[†] Christian F. Masaguer,[†] Elizabeth Rosa,[‡] M. Emilia Rivas,[‡] José A. Fontenla,[‡] M. Isabel Loza,[‡] Helena Tristán,[‡] M. Isabel Cadavid,[‡] Ferran Sanz,[§] Estrella Lozoya,[§] Angelo Carotti,[||] and Antonio Carrieri[||]

Departamento de Química Orgánica, Laboratorio de Química Farmacéutica, and Departamento de Farmacología, Facultad de Farmacia, Universidad de Santiago, E-15706 Santiago de Compostela, Spain, Departamento d'Informàtica Mèdica, Institut Municipal d'Investigació Mèdica, Universitat Pompeu Fabra, Dr. Aiguader 80, E-08003 Barcelona, Spain, and Dipartimento Farmaco Chimico, Università di Bari, I-70126 Bari, Italy

Received October 11, 1998

A series of novel conformationally restricted butyrophenones (2-(aminoethyl)- and 3-(aminomethyl)thieno- or benzocycloalkanones bearing (6-fluorobenzisoxazolyl)piperidine, (*p*-fluorobenzoyl)piperidine, (*o*-methoxyphenyl)piperazine, or linear butyrophenone fragments) were prepared and evaluated as atypical antipsychotic agents by in vitro assays of affinity for dopamine receptors (D_1, D_2) and serotonin receptors (5-HT_{2A}, 5-HT_{2C}) and by in vivo assays of antipsychotic potential and the risk of inducing extrapyramidal side effects. Potency and selectivity depended mainly on the amine fragment connected to the cycloalkanone structure. As a group, compounds with a benzisoxazolyl fragment had the highest 5-HT_{2A} activities, followed by the benzoylpiperidine derivatives; in general, α-substituted cycloalkanone derivatives were more active than the corresponding *β*-substituted congeners. CoMFA (comparative molecular field analysis) and docking studies showed electrostatic, steric, and lipophilic determinants of 5-HT_{2A} and D_2 affinities and 5-HT_{2A}/D_2 selectivity. The in vitro and in vivo pharmacological profiles of *N*-[(4-oxo-4*H*-5,6-dihydrocyclopenta[*b*]thiophene-5-yl)ethyl]-4-(6-fluorobenzisoxazol-3-yl)piperidine (**23b**, QF 0510B), *N*-[(4-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-5-yl)ethyl]-4-(6-fluorobenzisoxazol-3-yl)piperidine (**24b**, QF 0610B), and *N*-[(7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-6-yl)ethyl]-4-(6-fluorobenzisoxazol-3-yl)piperidine (**29b**, QF 0902B) suggest that they may be effective antipsychotic drugs with low propensity to induce extrapyramidal side effects.

Introduction

Schizophrenia is a complex psychological disorder of unclear aetiology which to some degree affects 0.5−1.5% of the world's population.[1] It is widely accepted that the dopaminergic system plays a key role in schizophrenic illness. Affected individuals may exhibit a wide spectrum of behavioral and other symptoms, ranging from social withdrawal, catatonia, and affective flattening of the personality ("negative" symptoms thought to be associated with dopaminergic hypoactivity in the prefrontal cortex) to hallucinations, paranoia, and disorganized behavior ("positive" symptoms thought to be associated with hyperactive dopaminergic transmission in the mesolimbic region of the brain).[1,2]

The cell-borne receptors with which dopamine interacts are broadly classified as D_1-like or D_2-like. Only the D_2-like family, which includes receptors D_2, D_3, and D_4, appears to be involved in schizophrenia. The activity of classical antipsychotics such as haloperidol (Chart 1) and the intensity of their undesirable side effects (prolactin release and extrapyramidal symptoms (EPS)) are closely correlated with their ability to block dopamine receptor D_2.[2−4] It has also been suggested that receptors D_3[5] and D_4 may be involved in antipsychotic activity (the atypical antipsychotic clozapine has high affinity for D_4), but clinical assays have shown selective D_4 blockers to be ineffective as antipsychotics.[6]

Haloperidol and other classical butyrophenone-based antipsychotics, such as spiperone and fluanisone, not only have the side effects mentioned above but are also ineffective against negative symptoms. Clozapine (Chart 1) was the prototype of a new group of "atypical" (nonclassical) antipsychotics that cause no EPS and are effective against negative as well as positive symptoms.[7−9] This superior activity profile of clozapine and other atypical antipsychotics, such as risperidone, olanzapine, and quetiapine (Chart 1),[10] may be due to their blocking not only dopamine receptors but also serotonin receptor 5-HT_{2A},[11−13] and Meltzer and co-workers[14,15] have accordingly suggested that it is reflected by the ratio between the pK_i's of these agents at receptors 5-HT_{2A} and D_2, which appears to be >1.12 for atypical antipsychotics and <1.09 for classical antipsychotics.

[▽] Presented, in part, at the XIVth International Symposium on Medicinal Chemistry, Maastricht, The Netherlands, September 1996 (*Book of Abstracts*, P-6.51). 20th paper in the series "Synthesis and CNS Activity of Conformationally Restricted Butyrophenones"; for preceding papers, see ref 47.

* For correspondence and reprints: Prof. Enrique Raviña. Phone: + 34-981-594628. Fax: + 34-981-594912. E-mail: qofara@usc.es.
[†] Departamento de Química Orgánica.
[‡] Departamento de Farmacología.
[§] Departamento d'Informàtica Mèdica.
[||] Dipartimento Farmaco Chimico.

10.1021/jm981094e CCC: $18.00
Published on Web 07/13/1999

Chart 1

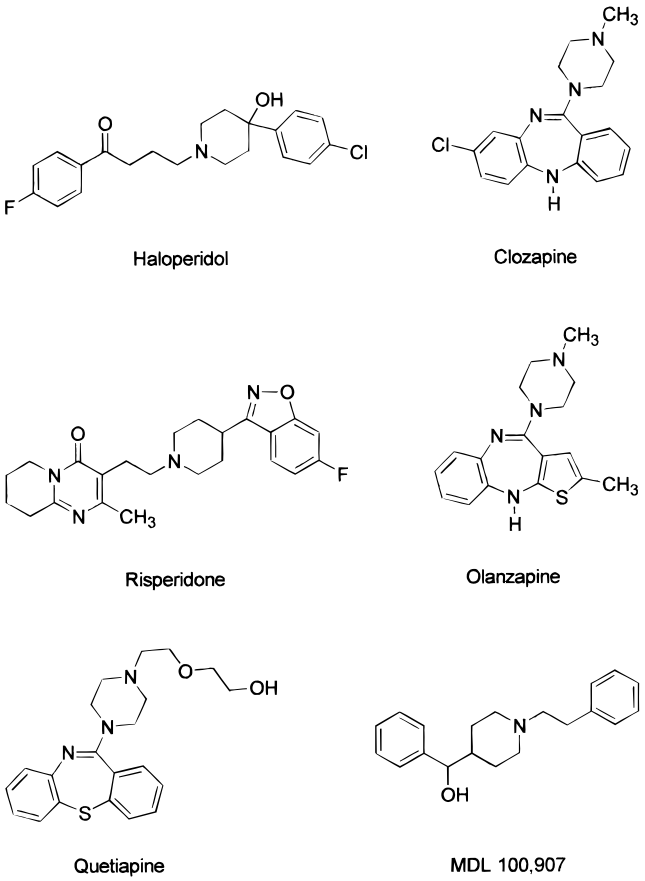


Chart 2

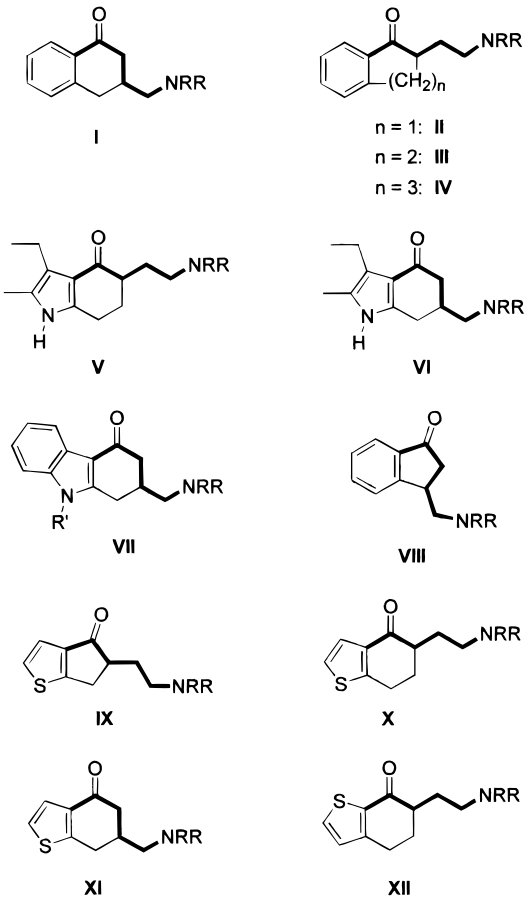
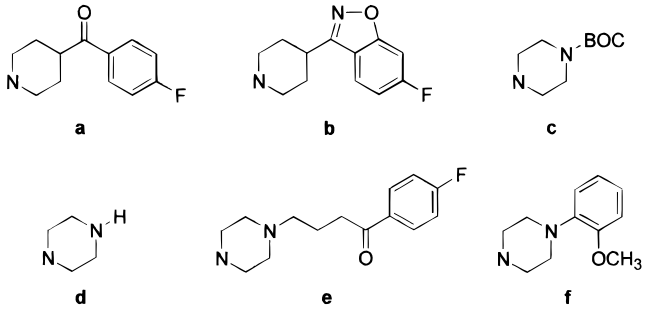


Chart 3. NRR of Structures in Chart 2



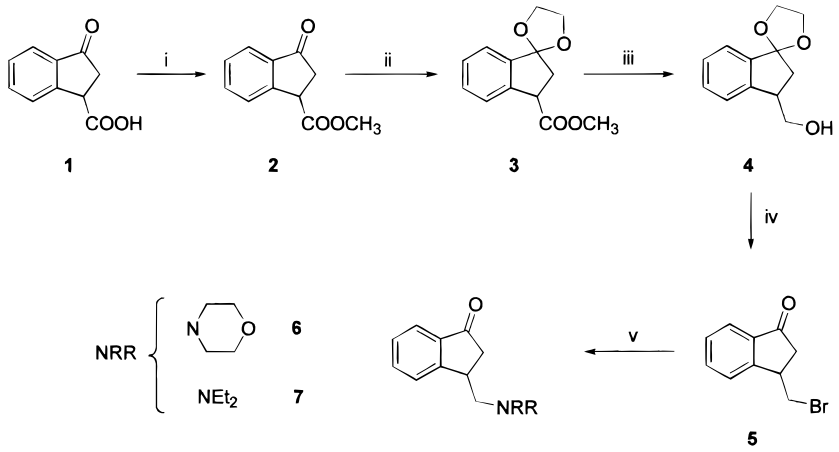
Currently there are two main hypotheses as to the mechanism by which serotonin receptor blockage may prevent the EPS that are otherwise induced by dopamine receptor blockage. According to one, 5-HT receptor blockage may lead to disinhibition of the nigrostriatal dopaminergic pathway and hence to enhancement of striatal dopaminergic release and competitive displacement of the drug from postsynaptic striatal dopamine receptors, i.e., to partial deblockage of this pathway. According to the other, 5-HT_2 blockage may raise the threshold for EPS by modulating cholinergic or GABAergic mechanisms. These two possibilities are not necessarily mutually exclusive. In either case, the improvement in negative symptoms caused by 5-HT_2 blockers is thought to be due to disinhibition of dopaminergic transmission in the frontal cortex.[16]

Recent experimental and clinical studies appear to confirm the importance of 5-HT_{2A} for the activity profile of atypical antipsychotics.[17−21] Indeed, even the 5-HT_{2A}-selective serotonin antagonist MDL 100907 (Chart 1), which has no activity at dopamine receptors, has shown antipsychotic potential in experiments with neurochemical, electrophysiological, and behavioral models.[22−24] Atypical antipsychotics also bind to 5-HT_{2C}, 5-HT_6, and 5-HT_7 serotonin receptors.[25−29] In the case of the last two recombinant receptors, new supplementary studies are necessary in order to clarify their role as pharmacological receptors and their pathophysiological involvements.[30] In any case, 5-HT_7 receptors are thought not to be involved in schizophrenia.[31]

The development of drugs such as cinuperone,[32] risperidone,[33] ocaperidone,[34] or sertindol,[35] which like clozapine block both 5-HT_{2A} and D_2, has been prompted in part by the finding that clozapine increases the risk of agranulocytosis.[36] However, since none of these drugs has proved to be as broadly effective as clozapine, the discovery of effective antipsychotics with no side effects is still a major research goal.

In previous papers[37,38] we have reported the synthesis of the 3-(aminomethyl)tetralones **Ia**,**d**−**f** (Charts 2 and 3) and their affinities for D_1, D_2, and 5-HT_{2A}. Compounds **Ia**,**e** showed high affinity for 5-HT_{2A} and D_2 (pK_i(5-HT_{2A}, **Ia**) = 8.80, pK_i(5-HT_{2A}, **Ie**) = 7.75, pK_i(D_2, **Ia**) = 7.68, pK_i(D_2, **Ie**) = 7.60) and in conventional behavioral tests on laboratory animals exhibited antipsychotic potential similar to that of haloperidol but much lower cataleptogenicity. Both **Ia**,**e** have two butyrophenone pharmacophores: the common semirigid 3-(aminomethyl)tetralone fragment and either a flexible linear butyrophenone moiety linked to the cycloalkanone by a piperazine bridge (**Ie**) or a 4-(*p*-fluorobenzoyl)piperidine

Scheme 1[a]



[a] Reagents: (i) MeOH, H^+; (ii) $CH(OCH_3)_3$, $(CH_2OH)_2$/*p*-TsOH; (iii) $LiAlH_4$; (iv) CBr_4, Ph_3P; (v) HNRR, KI, Na_2CO_3, Me^iBuCO.

moiety in which carbons 2−4 of the butyrophenone form part of a six-membered ring (**Ia**). As early as 1970, this latter structure was described as an antipsychotic pharmacophore of similar potency to linear butyrophenones,[39] and a SAR study of ketanserin analogues has suggested that the benzoyl carbonyl (present in both **Ia**,**e**) may play a prominent role in anchoring or orienting these compounds at receptor 5-HT_2.[40]

We subsequently extended our SAR study to the 2-(aminoethyl)benzocycloalkanones **IIa**,**d**−**f**, **IIIa**,**d**−**f**, and **IVa**,[41−43] the 5-(aminoethyl)-4,5,6,7-tetrahydroindol-4-ones **Vd**,**f**,[44] (butyrophenone homologues of the antipsychotic molindone), the 6-aminomethyl analogues **VIa**−**f**,[45,46] and the 2-(aminomethyl)-1,2,3,9-tetrahydro-4*H*-carbazol-4-ones **VIIa**,**b**,**f**.[47] In all these series, the conformation of the butyl chain is restricted by its partial incorporation in a cycloalkanone ring fused to a benzene ring or a heterocycle (Chart 2).

In continuation of our previous work, we have now synthesized and pharmacologically evaluated a number of members of the indanone series **10** and the approximately isosteric thiophene series **23**, **24**, **29**, and **35**, whose activity at receptors D_2 and 5-HT_{2A} was suggested by the similarity of their structures to those of previously synthesized active compounds such as **Ia**,**e**; we have used these structures and the pharmacological results in a 3D-QSAR study. Like compounds **I**−**VII**, most of the new target compounds (all except **24f** and **35f**) have two butyrophenone pharmacophores, one being the common semirigid (aminoalkyl)cycloalkanone moiety and the other either a flexible, linear butyrophenone fragment (**e** in Chart 3), a 4-(*p*-fluorobenzoyl)-piperidine moiety (**a**), or a 4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidine moiety (**b**). The NRR fragment **b** was included because 1,2-benzisoxazole is bioisosteric to benzoyl[48] and in view of recent results on 3-(4-piperazinyl)-6-hydroxybenzisoxazoles as potential atypical antipsychotics.[49]

Chemistry

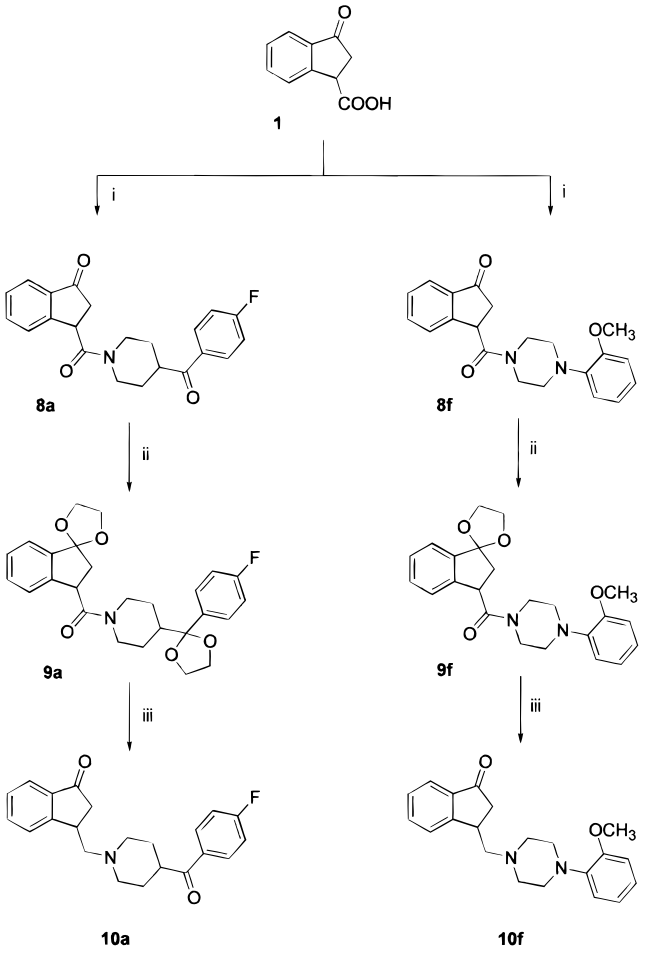
We initially attempted to prepare target compounds **10a**,**b**,**e**,**f** via 3-(bromomethyl)-1-indanone (**5**; Scheme 1). 3-Carboxy-1-indanone (**1**) was prepared by Friedel−Crafts cyclization of phenylsuccinic anhydride[50] and esterified to obtain the methyl ester **2**. Reaction of **2** with ethylene glycol in the presence of catalysts (*p*-toluenesulfonic acid, pyridinium tosylate, or acid ion-exchange resins) failed to afford significant yields of the ethylene ketal, but Delepine's method (acid-catalyzed reaction of the ketone with ethylene glycol and trimethyl orthoformate) furnished ketal **3** in virtually quantitative yield (80% from **1**). Reduction of the ester with lithium aluminum hydride then gave alcohol **4**, which was brominated with carbon tetrabromide/triphenylphosphine to obtain a 70% yield of the bromo derivative **5**. However, all attempts to replace the bromine atom of **5** with the substituted piperidines or piperazines required by the target compounds were unsuccessful (although it was found possible to obtain 45−50% yields of compounds **6** and **7** by this method; see Experimental Section).

Target compounds **10**, **23**, **24**, and **29** containing as their NRR fragment either **a**, **b**, or **f** (Chart 3) were eventually prepared by amide-linking the two moieties, protecting non-amide carbonyls as ketals, reducing the amide carbonyl, and deprotection (Schemes 2, 4, and 5). For compound **10e** and the previously reported[43] compounds **23e** and **24e**, the Chart 2 moiety was amide-linked to piperazine-Boc (fragment **c**), Boc was removed, and the rest of fragment **e** was added after reduction of the amide carbonyl (Schemes 3 and 4). For compounds **35**, the cycloalkanone ring was constructed after the thiophene ring was linked as shown in Schemes 6 and 7 to a Chart 3 amine (**a**, **b**, or **f** for **35a**,**b**,**f**, respectively; piperazine-Boc for **35e**, in which the remainder of fragment **e** was incorporated after construction of the cycloalkanone ring). Details of the operations involved in these strategies are given in what follows. The melting points of all the target compounds are listed in Tables 1−4 and 7 together with the yields of the final step(s) of their synthesis.

Alkylation of the thienocycloalkanones **11**, **12**, and **25** with lithium diisopropylamide at −70 °C, followed by quenching with ethyl bromoacetate, gave ethyl esters[42] that were then hydrolyzed to the thienocycloalkanone acetic acids **17**, **18**, and **26**, with yields of 50−55% from the thienocycloalkanones. Compound **18** was also prepared by condensation of thiatetralone with glyoxylic acid in acidic medium to obtain 1-oxo-1,2,3,4-benzo[*b*]-thiophene-5-ylideneacetic acid (**14**) and then subsequent reduction of the alkene acid with zinc and acetic acid.

The amides listed in Table 5 were prepared in good yields by direct acid−amine coupling, with carboxylate

Scheme 2[a]



[a] Reagents: (i) HNRR, DCC/HOBt; (ii) $(CH_2OH)_2$/*p*-TsOH or PPTS; (iii) (1) $LiAlH_4$, (2) HCl (dilute).

activation by dicyclohexylcarbodiimide (DCC) in the presence of 1-hydroxybenzotriazole (HOBt) or by bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl)[51] (which gave clean reactions with excellent yields). Direct conversion of the keto ester to the amide with trimethylaluminum amide (prepared in situ) was attempted for **20a**,**c**,**f** but only gave an acceptable yield in the case of **20f**.

Table 1. 3-(Aminomethyl)-1-indanone Hydrochlorides

compd (code no.)	mp (°C)	recryst solv	yield (%)	formula
6	174−175[a]	EtOH−Et_2O	45 (A) 45 (B)	$C_{14}H_{19}NO$·HCl
7 (QF 0500B)	162−165[b]	EtOH−Et_2O	50 (A) 45 (B)	$C_{14}H_{17}NO_2$·HCl
10a (QF 0501B)	229−231	*i*-PrOH	75	$C_{22}H_{22}FNO_2$·HCl
10e (QF 0502B)	216−217	*i*-PrOH	50	$C_{24}H_{27}N_2O_2$·2HCl
10f (QF 0503B)	220−222	*i*-PrOH	85	$C_{21}H_{23}N_2O_2$·2HCl

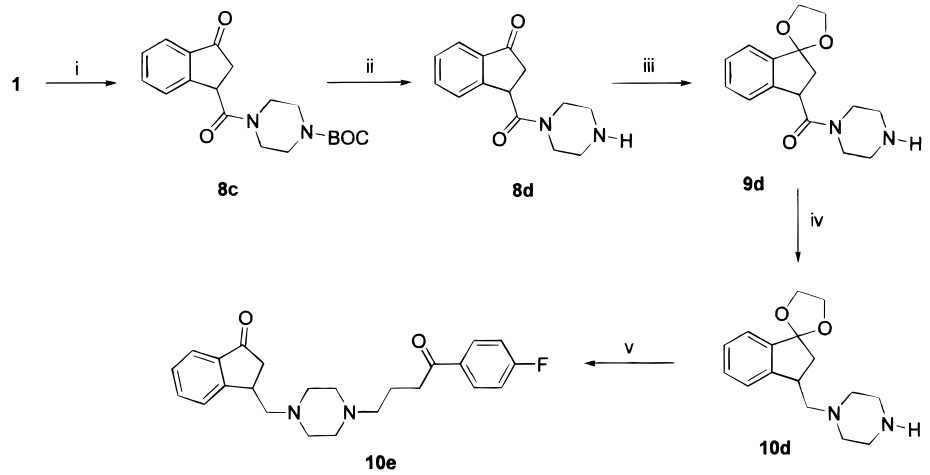
[a] Base, mp 69−71 °C. [b] Base, mp 72−73 °C (AcOEt); 2,4-dinitrophenylhydrazone, mp 240−243 °C (EtOH). [c] Base, mp 99−102 °C (AcOEt).

Ketalization of carbonyl groups with ethylene glycol and *p*-toluenesulfonic acid or pyridinium tosylate (PPTS) in anhydrous toluene, with azeotropic distillation of water in a Dean−Stark apparatus, provided the ethylene ketals listed in Table 6 in yields of 80−95%. Attempts to shorten the reaction times by using other catalysts (amberlyst and boron trifluoride etherate) and/or other conditions (e.g., by using 2,2-dimethyl-1,3-propanediol[52] instead of ethylene glycol or Noyori's conditions[53]) were unsuccessful. The ethylene ketals were isolated as colorless oils and used in the next step without further purification.

Deketalization to restore carbonyl groups was initially attempted by cautious dropwise addition of a saturated solution of dry HCl in anhydrous ether to a solution of aminoketone ketal. However, in the case of bis(ketals) it was found that only one carbonyl was restored. According to the results of NOE experiments showing significant interaction between the protons of the phenyl ring and ethylene ketal in the product obtained from *N*-[(4-oxo-4*H*-5,6-dihydrocyclopenta[*b*]thiophene-5-yl)-ethyl]-4-(*p*-fluorobenzoyl)piperidine bis(ethylene ketal) (Figure 1), the nondeprotected carbonyl was that of the benzoyl group.

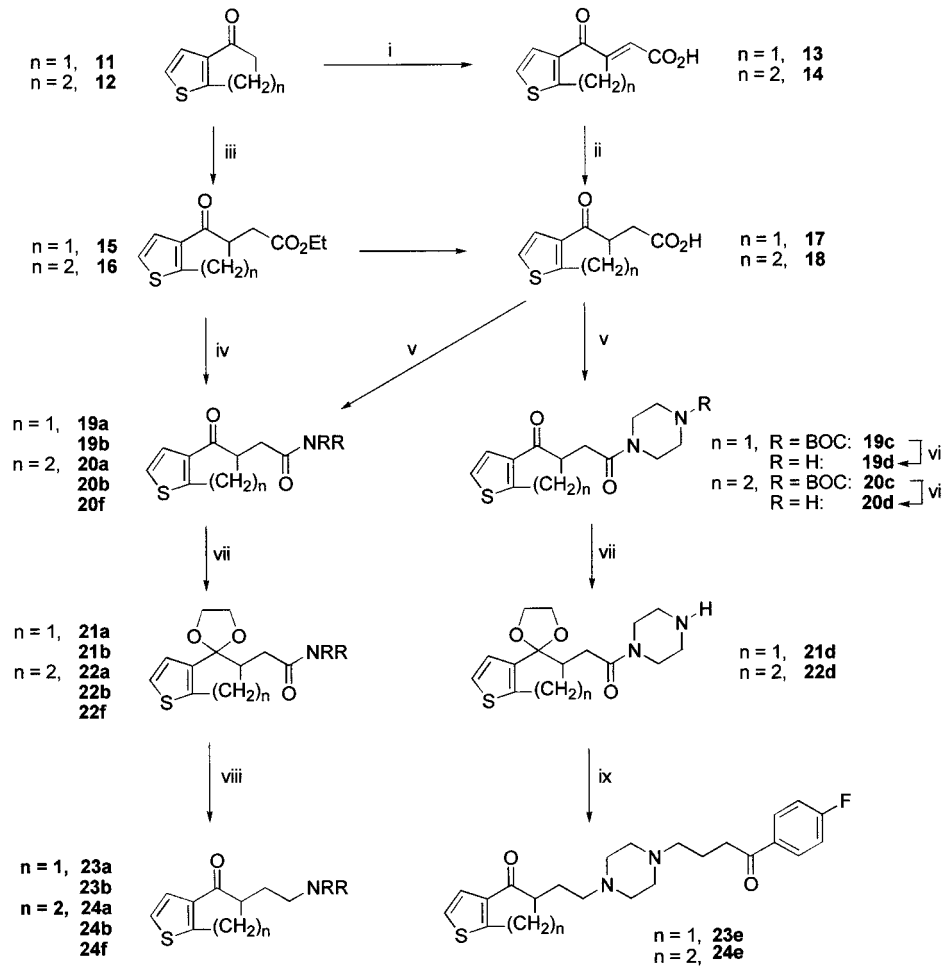
The piperazine-Boc derivatives **8c**, **19c**, and **20c** were transformed into the desired compounds **10e**, **23e**, and **24e** by removal of Boc with trifluoroacetic acid, reduction of the amide carbonyl, alkylation of the piperazine NH group with 4-chloro-1,1-(ethylenedioxy)-1-(4-fluorophenyl)butane in methyl isobutyl ketone containing catalytic amounts of potassium iodide,[43] and cleavage of the resulting bis(ethylene ketal) (overall yields of 35−40% from **8d**, **19d**, and **20d**).

Scheme 3[a]



[a] Reagents: (i) *N*-(*tert*-butyloxycarbonyl)piperazine, DCC/HOBt; (ii) CF_3CO_2H; (iii) $(CH_2OH)_2$/*p*-TsOH; (iv) $LiAlH_4$; (v) (1) 4-chloro-1,1-(ethylenedioxy)-1-(4-fluorophenyl)butane, KI, Na_2CO_3, (2) HCl (dilute).

Scheme 4[a]



[a] Reagents: (i) HOOC−CHO; (ii) Zn/AcOH; (iii) (1) $BrCH_2CO_2Et$/LDA, (2) KOH/EtOH; (iv) HNRR, $(CH_3)_3Al$ (only for benzo[*b*]thiophene series); (v) HNRR, DCC/HOBt or BOP-Cl; (vi) TFA; (vii) $(CH_2OH)_2$/*p*-TsOH or PPTS; (viii) (1) $LiAlH_4$, (2) HCl (dilute); (ix) (1) $LiAlH_4$, (2) 4-chloro-1,1-(ethylenedioxy)-1-(4-fluorophenyl)butane, KI, Na_2CO_3, (3) HCl (dilute).

Table 2. 5-(Aminoethyl)-4-oxo-5,6-dihydrocyclopenta[*b*]-thiophenes

compd (code no.)	mp (°C)	recryst solv	yield (%)	formula
23a (QF 0505B)	172−173[a]	AcOEt	70	$C_{21}H_{22}FNO_2S\cdot C_2H_2O_4$
23b (QF 0510B)	230−232[b]	*i*-PrOH	75	$C_{21}H_{21}FN_2O_2S\cdot 2HCl$
23e (QF 0506B)	244−246[c]	*i*-PrOH	58	$C_{23}H_{27}FN_2O_2S$

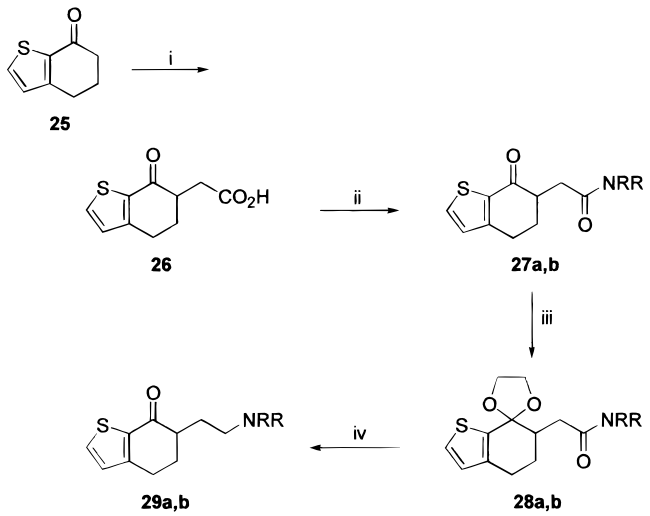
[a] Oxalate. [b] Hydrochloride. [c] Hydrochloride; base crystallized on standing, mp 89−90 °C; 2,4-dinitrophenylhydrazone, mp 198−199 °C (MeOH).

Table 3. 5-(Aminoethyl)-4-oxo-4,5,6,7-tetrahydrobenzo[*b*]-thiophene Hydrochlorides

compd (code no.)	mp (°C)	recryst solv	yield[a]	formula
24a (QF 0601B)	278−280	MeOH−Et_2O	85	$C_{22}H_{24}FNO_2S\cdot HCl$
24b (QF 0610B)	248−249	AcOEt	75	$C_{22}H_{23}FN_2O_2S\cdot HCl$
24e (QF 0602B)	234−236	MeOH−Et_2O	50	$C_{24}H_{29}FN_2O_2S\cdot 2HCl$
24f (QF 0603B)	233−235	MeOH−Et_2O	85	$C_{21}H_{26}N_2O_2S\cdot 2HCl$

[a] Overall yield for amide reduction + ketal cleavage.

Scheme 5[a]



[a] Reagents: (i) (1) $BrCH_2CO_2Et$/LDA, (2) KOH/EtOH; (ii) HNRR, DCC/HOBt or BOP-Cl; (iii) $(CH_2OH)_2$/PPTS; (iv) (1) $LiAlH_4$, (2) HCl (dilute).

The general synthetic strategy used for the 6-(aminomethyl)thiatetralone derivatives **35** (Schemes 6 and 7) parallels the approach used previously for the benzene series.[37] Thienylbutyrolactone **32** was prepared by hydroxymethylation of *β*-thenoylpropionic acid **30** followed by lactonization of thenoylbutyrolactone **31** and subsequent Clemmensen reduction.[54] Reaction of **32** with hydrogen bromide in acetic acid afforded unstable

Table 4. 6-(Aminomethyl)-7-oxo-4,5,6,7-tetrahydrobenzo[*b*]-thiophene Hydrochlorides

compd (code no.)	mp (°C)	recryst solv	yield[a] (%)	formula
29a (QF 0901B)	262−264	*i*-PrOH	65	$C_{22}H_{24}FNO_2S$·HCl
29b (QF 0902B)	246−248	*i*-PrOH	80	$C_{22}H_{23}FN_2O_2S$·2HCl

[a] Overall yield for amide reduction + ketal cleavage.

(bromomethyl)-γ-(2-thenoyl)propionic acid, which was immediately esterified to afford the bromo ester **33**. Subsequent nucleophilic substitution with amine **a**, **b**, **c**, or **f** in basic methyl isobutyl ketone led to the β-amino esters **34a**−**c**,**f** in good to excellent yields (Table 8). Finally, acid-catalyzed ring closure with polyphosphoric acid[55] gave the final thiatetralones in yields of up to 50%.[56]

As a step toward currently incomplete studies of receptor binding by the pure enantiomers of our compounds, we obtained those of compound **35b**. Attempts to resolve racemic **35b** using chiral columns failed, but resolution of its β-amino ester precursor **34b** was successful, affording (+)**34b** and (−)**34b** with high optical purity (ee > 95%).[57] Subsequent ring closure of each enantiomer (Scheme 8) gave (+)**35b** and (−)**35b** with no loss of enantiomeric purity.[58]

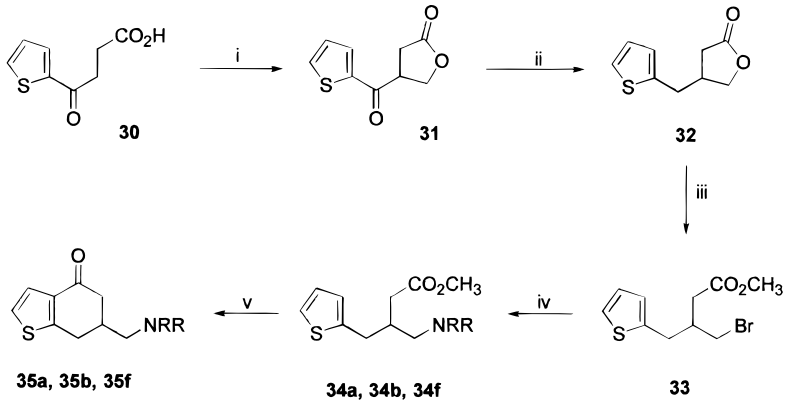
Results and Discussion

In Vitro Studies of New Compounds. Details of the in vitro assays performed are described in the Experimental Section. In none of the binding assays did the slope of the corresponding curve of specific radioligand binding against competitor concentration differ significantly from unity at the $p = 0.05$ level, and in none of the experiments on serotonin-induced contraction of rat aorta did the slope of the Schild plot differ significantly from unity at the $p = 0.05$ level. Table 9 lists affinities for D_1, D_2, 5-HT_{2A}, and 5-HT_{2C}, together with pA_2 values and the 5-HT_{2A}/D_2 and 5-HT_{2A}/5-HT_{2C} selectivity ratios.

The new compounds all showed greater affinity for D_2 than for D_1. The most active at D_1 were **23b**, **24b**, **29b**, and **35b**, which had pK_i's ranging from 6.53 for **24b** to 6.90 for **23b**. For D_2, pK_i's ranged from 5.98 for **10a** to 7.70 for **23b**. Figure 2 shows the radioligand-binding curves recorded with **23b** and **24b** as competitors at receptors D_1 and D_2, respectively.

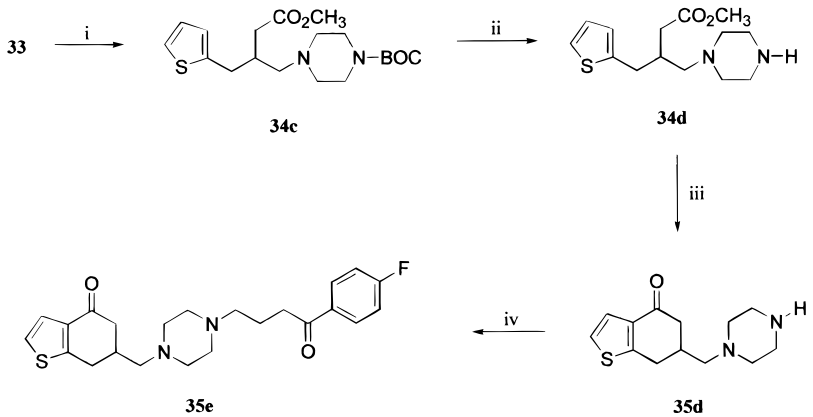
The affinities of the new compounds for 5-HT_{2A} in rat cerebral cortex, calculated as pK_i using [^{3}H]ketanserin as the competing radioligand, ranged from <6 for **35f** to 8.84 for **24a** (Figure 3A shows the radioligand-binding curves recorded with **24b** and risperidone as competitors). The pK_i of the 5-HT_{2A}-specific agent ketanserin (8.49 ± 0.11) was exceeded by **23b** and **24a**,**b**, that of the atypical antipsychotic clozapine (8.30) by **23b**, **24a**,**b**, and **35b**, and that of the classical antipsychotic haloperidol (7.70) by **23a**,**b**, **24a**,**b**, **29a**,**b**, and **35b**. The pK_i values agree well with the pA_2 values obtained measuring inhibition of the 5-HT-induced contraction

Scheme 6[a]



[a] Reagents: (i) (1) HCHO/NaOH, (2) HCl; (ii) Zn−Hg/HCl; (iii) (1) HBr−AcOH, (2) CH_2N_2; (iv) HNRR, KI, Na_2CO_3; (v) PPA.

Scheme 7[a]



[a] Reagents: (i) *N*-(*tert*-butyloxycarbonyl)piperazine, KI, Na_2CO_3; (ii) HCl/CH_3OH; (iii) PPA; (iv) (1) 4-chloro-1,1-(ethylenedioxy)-1-(4-fluorophenyl)butane, KI, Na_2CO_3, (2) HCl (dilute).

Table 5. Ketoamides

compd	mp (°C)	recryst solv	coupling reagent	yield (%)	formula
8a	146−149	AcOEt	DCC/HOBt	80	$C_{22}H_{20}FNO_3$
8c	146−147	*i*-PrOH	DCC/HOBt	85	$C_{19}H_{24}N_2O_4$
8d[a]	142−143[b]	*i*-PrOH		85	$C_{14}H_{16}N_2O_2$.HCl
8f	165	AcOEt	DCC/HOBt	80	$C_{21}H_{22}N_2O_3$
19a	*c*		DCC/HOBt	78	$C_{21}H_{20}FNO_3S$
19b	155−157	*i*-PrOH	DCC/HOBt	75	$C_{21}H_{19}FN_2O_3S$
			BOP-Cl	85	
19c	116−118	*i*-PrOH	DCC/HOBt	90	$C_{18}H_{24}N_2O_4S$
19d[a]	264−266[b]	MeOH−Et_2O		78	$C_{13}H_{16}N_2O_2S$·HCl
20a	143−145	*i*-PrOH	DCC/HOBt	85	$C_{22}H_{22}FNO_3S$
			Me_3Al	15	
20b	161−163	*i*-PrOH	DCC/HOBt	90	$C_{22}H_{21}FN_2O_3S$
20c	113−115	*i*-PrOH	DCC/HOBt	90	$C_{19}H_{26}N_2O_4S$
			Me_3Al	15	
20d[a]	226−228[b]	MeOH−Et_2O		80	$C_{14}H_{18}N_2O_2S$·HCl
20f	135−137	AcOEt	DCC/HOBt	80	$C_{21}H_{24}N_2O_3S$
			Me_3Al	65	
27a	163−165	cyclohexane	DCC/HOBt	70	$C_{22}H_{22}FNO_3S$
			BOP-Cl	90	
27b	148−150	cyclohexane	DCC/HOBt	75	$C_{22}H_{21}FN_2O_3S$
			BOP-Cl	90	

[a] Obtained by BOC removal with TFA. [b] Hydrochloride. [c] Bis(2,4-dinitrophenylhydrazone), mp 223−225 °C (*i*-PrOH). Anal. ($C_{33}H_{28}FN_9O_9S$) C, H, N. From the ester **16**.

Table 6. Ethylene Ketals

compd	catalyst	reaction time (h)	yield (%)
9a[a]	*p*-TsOH	96	93
9d	pyridinium tosylate	144	82
9f	*p*-TsOH	96	93
21a[b]	*p*-TsOH	120	87
21b	pyridinium tosylate	168	90
21d	*p*-TsOH	96	95
22a[b]	*p*-TsOH	48	90
22b	*p*-TsOH	120	90
22d	pyridinium tosylate	90	94
22f	*p*-TsOH	24	95
28a[b]	pyridinium tosylate	190	90
28b	pyridinium tosylate	144	90

[a] Bis(ethylene ketal), crystallized on standing, mp 138−139 °C. [b] Bis(ethylene ketals).

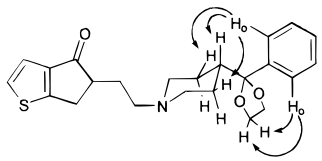


Figure 1. NOE interactions in *N*-[(4-oxo-4*H*-5,6-dihydrocyclopenta[*b*]thiophene-5-yl)ethyl]-4-(*p*-fluorobenzoyl)piperidine monoethylene ketal.

Table 7. 3-(Aminomethyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophene Hydrochlorides

compd (code no.)	mp (°C)	recryst solv	yield (%)	formula
35a (QF 0605B)	243−244	*i*-PrOH	25	$C_{21}H_{22}FNO_2S$·HCl
35b (QF 0609B)	258−260	AcOEt	40	$C_{21}H_{21}FN_2O_2S$·2HCl
35e (QF 0606B)	236−237	MeOH−Et_2O	55	$C_{23}H_{27}FN_2O_2S$·2HCl
35f (QF 0607B)	215−217	AcOEt	35	$C_{20}H_{24}N_2O_2S$·2HCl

of rat aorta (Figure 3B shows dose−response curves for **35b**), which supports the accuracy of both parameters and attests to the similarity between cortical and peripheral 5-HT receptors of type 2A.

The affinities of the new compounds for 5-HT_{2C}, calculated as pK_i using [^{3}H]mesulergine as the competing radioligand, ranged from <5 for **10e** to 7.09 for **24f** (Figure 3C shows the radioligand-binding curves recorded with **24f** and risperidone as competitors). Only **23b** and **24b**,**f** exhibited affinity similar to that of clozapine (7.00), and none of the new compounds had a pK_i approaching that of haloperidol (8.30).

Table 8. γ-Amino-β-(2-thenyl)butyric Acid Methyl Ester Hydrochlorides

compd	mp (°C)	recryst solv	yield (%)	formula
34a	190−191	AcOEt	90	$C_{22}H_{26}FNO_3S$·HCl
34b	162−164	AcOEt	85	$C_{22}H_{25}FN_2O_3S$·HCl
34c	133−135	MeOH−Et_2O	90	$C_{23}H_{27}FN_2O_2S$·HCl
34d[a]	130−131	AcOEt	95	$C_{14}H_{22}N_2O_2S$·2HCl
34f	191−192	AcOEt	90	$C_{21}H_{28}N_2O_3S$·2HCl

[a] From **34c** by BOC removal (HCl/MeOH).

SAR Studies. The pK_i's listed in Table 9 for the compounds synthesized in our laboratory show a fair spread of values for 5-HT_{2A} (2.84 units if the lowest pK_i is taken to be 6; $n = 25$) and rather smaller spreads for D_2 (2.21; $n = 25$), 5-HT_{2C} (2.09; $n = 14$), and D_1 (1.9; $n = 25$). Highest affinities are shown for 5-HT_{2A} (range: <6−8.84), followed by D_2 (5.98−8.19), 5-HT_{2C} (<5−7.09), and D_1 (<5−6.90).

The highest 5-HT_{2A} affinities are those of the α-substituted cycloalkanones with a piperidine NRR fragment (**23a**,**b**, **24a**,**b**, **29a**,**b**, **Ia**, **IIa**, **IIIa**, all with pK_i > 7.9), while most of the lowest affinities correspond to (*o*-methoxyphenyl)piperazine derivatives (**10f**, **35f**, **If**, all with pK_i < 6.5). Isosteric substitution of thiophene for the benzo ring fused to the cycloalkanone generally reduces interaction with 5-HT_{2A} somewhat (compare compounds **I** with compounds **35**, **II** with **23**, **III** with **24** and **29**; the exceptions are the pairs **IIIa**/**24a** and **IIe**/**23e**). Moving the thiophene sulfur as close as possible to the exocyclic oxygen of the cycloalkanone also reduces 5-HT_{2A}-blocking activity slightly (compare **24a**,**b** with **29a**,**b**).

Among the β-substituted cycloalkanones, replacing the six-membered cycloalkanone ring with a five-membered ring dramatically reduces D_2-blocking activity (compare **Ia**,**e**,**f** with **10a**,**e**,**f**). Replacement of the fused benzo ring with thiophene generally gives rise to a much more modest reduction in activity.

There are no significant pairwise correlations among the pK_i's for the various receptors ($r^2 \leq 0.35$), presum-

Scheme 8

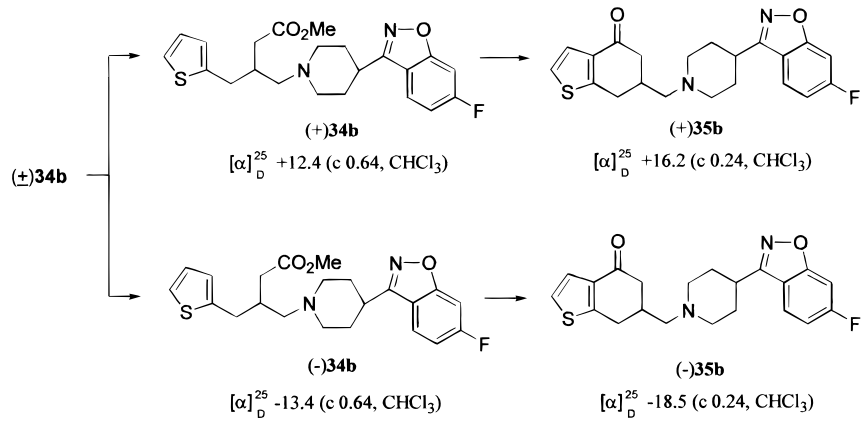


Table 9. In Vitro Assays

		pK_i				pK_i ratios		pA_2
compd	structure[a]	D_1	D_2	5-HT_{2A}	5-HT_{2C}	5-HT_{2A}/D_2	5-HT_{2A}/5-HT_{2C}	5-HT_{2A}
10a (QF 0501B)	**VIII**	5.81 ± 0.06	5.98 ± 0.10	7.58 ± 0.14	5.96 ± 0.07	1.27	1.27	8.13 ± 0.09
10e (QF 0502B)	**VIII**	5.15 ± 0.07	6.49 ± 0.13	7.34 ± 0.10	<5	1.10	>1.47	7.20 ± 0.20
10f (QF 0503B)	**VIII**	5.43 ± 0.09	6.19 ± 0.09	6.05 ± 0.21	6.44 ± 0.07	0.98	0.94	6.21 ± 0.10
23a (QF 0505B)	**IX**	5.60 ± 0.08	6.39 ± 0.14	8.15 ± 0.13	6.38 ± 0.06	1.27	1.28	8.92 ± 0.04
23b (QF 0510B)	**IX**	6.90 ± 0.14	7.70 ± 0.31	8.76 ± 0.20	7.06 ± 0.06	1.14	1.24	
23e (QF 0506B)	**IX**	6.49 ± 0.04	6.58 ± 0.19	7.37 ± 0.15	5.90 ± 0.11	1.12	1.25	7.63 ± 0.08
24a (QF 0601B)	**X**	5.86 ± 0.03	6.68 ± 0.08	8.84 ± 0.17	6.48 ± 0.06	1.32	1.36	9.02 ± 0.04
24b (QF 0610B)	**X**	6.53 ± 0.11	7.34 ± 0.20	8.56 ± 0.20	6.90 ± 0.05	1.17	1.24	9.87 ± 0.40
24e (QF 0602B)	**X**	5.51 ± 0.07	6.65 ± 0.12	6.54 ± 0.13	6.40 ± 0.70	0.98	1.02	6.83 ± 0.20
24f (QF 0603B)	**X**	5.27 ± 0.12	6.79 ± 0.16	6.84 ± 0.12	7.09 ± 0.17	1.01	0.96	6.95 ± 0.02
29a (QF 0901B)	**XII**	6.25 ± 0.20	6.76 ± 0.40	7.95 ± 0.09		1.18		
29b (QF 0902B)	**XII**	6.87 ± 0.28	7.36 ± 0.33	8.17 ± 0.80		1.11		
35a (QF 0605B)	**XI**	6.37 ± 0.03	6.50 ± 0.13	7.24 ± 0.12	6.03 ± 0.04	1.11	1.20	7.82 ± 0.16
35b (QF 0609B)	**XI**	6.89 ± 0.09	7.26 ± 0.10	8.33 ± 0.11	6.69 ± 0.12	1.15	1.24	9.13 ± 0.70
35e (QF 0606B)	**XI**	5.87 ± 0.10	6.57 ± 0.09	6.97 ± 0.13	5.40 ± 0.12	1.06	1.29	7.79 ± 0.06
35f (QF 0607B)	**XI**	<5	6.49 ± 0.13	5.82 ± 0.06	6.04 ± 0.06			5.90 ± 0.01
Ia (QF 0104B)[b]	**I**	6.49	7.68	8.80 ± 0.80		1.15		7.86 ± 0.86
Ie (QF 0102B)[b]	**I**	6.42	7.60	7.75 ± 0.60		1.02		7.27 ± 0.70
If (QF 0100B)[b]	**I**	5.87	8.19	6.29 ± 0.60		0.77		6.48 ± 0.50
IIa (QF 0307B)[d]	**II**	5.55	7.15	8.60 ± 0.80		1.20		8.12 ± 0.11
IIe (QF 0309B)[e]	**II**	5.88	7.17	6.91 ± 0.60		0.96		7.30 ± 0.70
IIIa (QF 0303B)[d]	**III**	5.81	7.32	8.11 ± 0.80		1.11		7.47 ± 0.81
IIIe (QF 0304B)[e]	**III**	5.87	7.04	7.14 ± 0.70		1.01		7.35 ± 0.11
IIIf (QF 0301B)[c]	**III**	5.83	7.64	7.39 ± 0.70		0.97		6.72 ± 0.06
IVa (QF 0311B)[d]	**IV**	5.89	7.33	7.88 ± 0.70		1.08		6.75 ± 0.60
haloperidol		6.80 ± 0.03	8.48 ± 0.25	7.70	5.60	0.91	1.37	
clozapine		6.77 ± 0.13	6.58 ± 0.10	8.30	7.80	1.30	1.10	9.16
risperidone			8.09 ± 0.63	9.70	7.04 ± 0.7	1.20	1.29	
SCH23390		9.27 ± 0.23						

[a] See Charts 2 and 3. [b] See ref 36. [c] See ref 40. [d] See ref 41. [e] See ref 42.

ably due to differences among the binding sites of the receptors and the ways in which the compounds bind to them. The best 5-HT_{2A}/D_2 selectivity ratio, 1.32, is that of **24a**, which combines the highest pK_i for 5-HT_{2A} (8.84) with a moderate pK_i for D_2 (6.68); good ratios are also shown by all the (*p*-fluorobenzoyl)piperidine derivatives except **35a** (1.11) and by the benzisoxazolyl derivatives **23b** (1.14), **24b** (1.17), and **35b** (1.15), despite their high pK_i's for D_2 (7.26−7.70). Borderline selectivity between Meltzer and co-workers' limits of 1.09 and 1.12 is shown by the new compounds **10e** (1.10), **29b** (1.11), and **35a** (1.11). Selectivity for D_2 versus 5-HT_{2A} was shown by the (*o*-methoxyphenyl)piperazine derivatives **10f**, **35f**, **If**, and **IIIf** and by the (*p*-fluorobenzoyl)-propylpiperazine **24e**.

24a also had the highest 5-HT_{2A}/5-HT_{2C} selectivity ratio, 1.36. In fact, all the new compounds had good selectivity for 5-HT_{2A} versus 5-HT_{2C} except, once again, the (*o*-methoxyphenyl)piperazines and **24e**.

3D-QSAR Studies. Since its introduction in 1988,[59] comparative molecular field analysis (CoMFA) has proved to be a useful tool in 3D-QSAR studies of biologically active substances.[60] Traditional CoMFA correlates the biological activity of a series of molecules with their steric and electrostatic fields sampled at grid points in a 3D box around the aligned molecules. Unfortunately, these two fields alone are not able to describe all binding forces appropriately.[61] Moreover, CoMFA describes only the enthalpy component of ligand−receptor interactions. Introducing the molecular lipophilicity potential (MLP)[62] as an additional field significantly improves the descriptive, predictive, and interpretative powers of CoMFA in many cases. The MLP encodes hydrogen-bonding and hydrophobic interactions, which are not sufficiently described by the steric and electrostatic fields, and also includes an entropy component.[63] The preferred regression method for analysis of the dependence of biological activity on the large

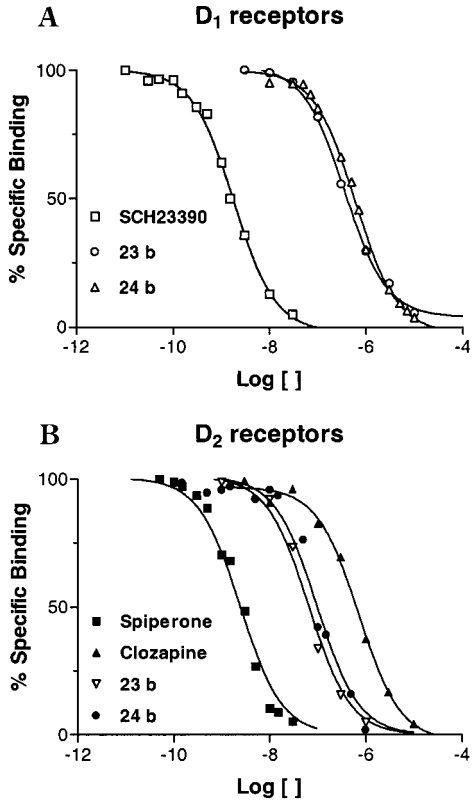


Figure 2. Inhibition by reference drugs and selected new compounds of [^{3}H]SCH23390 binding by striatal D_1 (A) and [^{3}H]spiperone binding by striatal D_2 (B).

number of structure-related variables (steric, electrostatic, and lipophilic potentials at the grid points) is partial least squares (PLS).[64] The optimal number of components (ONC) is determined by cross-validation, and the predictive ability of the model is assessed as the cross-validated r^2 (r^2_{cv}, q^2).[65] Graphical representations of CoMFA results (coefficient isocontour maps) indicate the regions where the variation in the steric, electrostatic, and lipophilic properties of the molecules in the data set is correlated with the variation in biological activity.

In this work, the molecules synthesized in our laboratory that are listed in Table 9 were subjected to CoMFA using steric, electrostatic, and/or lipophilic potentials and the binding data for 5-HT_{2A} and D_2 (the only receptors for which affinities were sufficiently high and the number, spread, and distribution of the data adequate).[66,67] In accordance with Holtje and Folkers' pharmacophore model for 5-HT_{2A} blockers,[68] molecular alignment was carried out with reference to the centroid(s) of the aromatic system(s), the oxygen atoms of carbonyl and methoxy groups, and the charged amino group; isoxazolyl nitrogens were treated as oxygens. The compounds were initially considered in their most extended conformations, which were optimized by energy minimization using the PM3 Hamiltonian of MOPAC.[69] At this stage both enantiomers of chiral molecules were considered, but further analyses used only the better-aligning enantiomer, which was the *S* form for all the chiral compounds except **23a**,**b**,**e**. We note that although the affinities of Table 9 refer to racemic mixtures, preliminary data on some resolved enantiomers[58] seem to indicate that their pK_i values are quite

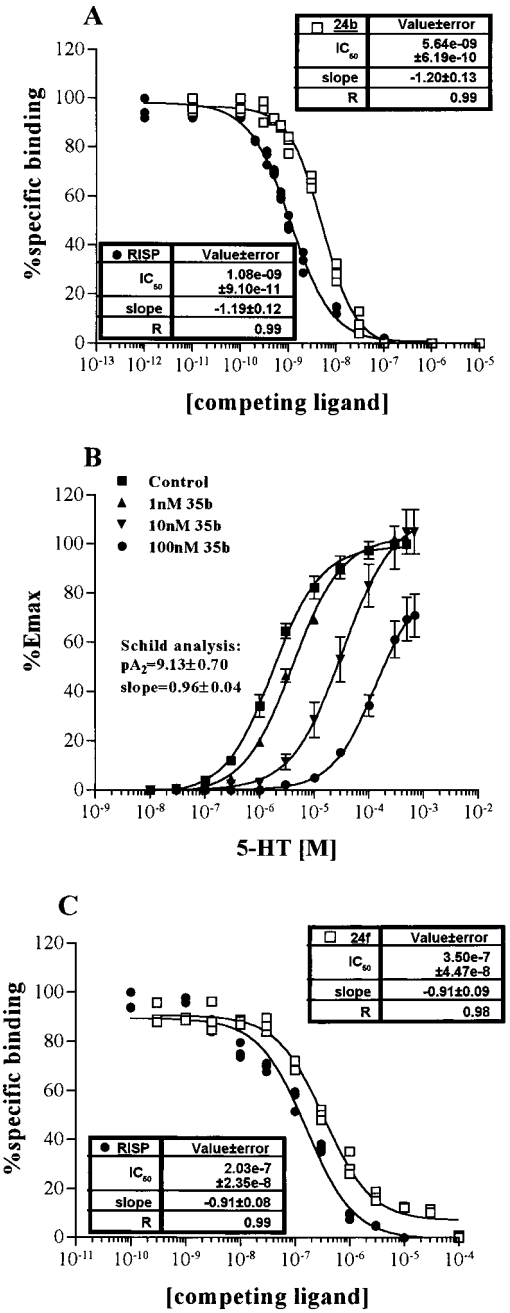


Figure 3. (A) Inhibition by **24b** (○) and risperidone (●) of [^{3}H]ketanserin binding by 5-HT_{2A} receptors in murine frontal cortex membrane preparations. (B) Inhibition by **35b** of serotonin-induced contractions of denuded rat aorta (curves from a single representative of six replicate experiments; vertical bars indicate SEM). (C) Inhibition by **24f** (○) and risperidone (●) of [^{3}H]mesulergine binding by 5-HT_{2C} receptors in murine frontal cortex membrane preparations. Graphs A and C show triplicate points from a single experiment; a total of two replicate experiments were performed in each case.

similar, which justifies our exclusive use of the better-aligning enantiomer.

To improve matching, the structures selected as described above were rotated about single bonds and replaced with the best-aligning resulting conformation if the energy cost of the change was less than 8 kcal/mol.[70] The validity of this apparently high limit was investigated by importing these conformers and the minimum-energy structures from which they were derived into Macromodel and reoptimizing (without

Table 10. Statistical Results[a] of CoMFA for Receptor Ligands[b]

receptor(s)	model	field(s)	*n*	q^2	*nc*	r^2	*s*	*F*
5-HT_{2A}	S_1	ste	25	0.505	4			
	S_2		24[c]	0.617	4			
	E_1	ele	25	0.486	4			
	E_2		24[c]	0.624	4			
	L_1	lipo	25	0.493	4			
	L_2		24[c]	0.619	4			
	SE_1	ste + ele	25	0.519	4			
	SE_2		24[c]	0.615	4	0.865	0.352	30.364
	SL_1	ste + lipo	25	0.504	4			
	SL_2		24[c]	0.637	4	0.878	0.335	34.045
	EL_1	ele + lipo	25	0.530	4			
	EL_2		24[c]	0.642	4	0.876	0.337	33.682
	SEL_1	ste + ele + lipo	25	0.521	4			
	SEL_2		24[c]	0.630	4			
D_2	S_3	ste	25	0.714	5			
	E_3	ele	25	0.604	5			
	L_3	lipo	25	0.721	4			
	SE_3	ste + ele	25	0.688	4			
	SL_3	ste + lipo	25	0.743	4	0.928	0.161	64.601
	EL_3	ele + lipo	25	0.720	4	0.914	0.177	52.849
5-HT_{2A}/D_2[d]	S_4	ste	25	0.583	3			
	E_4	ele	25	0.640	3			
	L_4	lipo	25	0.601	3			
	SE_4	ste + ele	25	0.626	3	0.823	0.380	32.650
	SL_4	ste + lipo	25	0.606	3	0.823	0.381	32.492
	EL_4	ele + lipo	25	0.613	3	0.836	0.366	35.700
	SEL_4	ste + ele + lipo	25	0.625	3			

[a] *n*, q^2, *nc*, r^2, *s*, and *F* are the number of data points, the squared cross-validated correlation coefficient, the chosen number of components (see text), the squared correlation coefficient, the standard deviation of regression equation, and the *F* ratio, respectively. [b] See ref 65. [c] Excluding compound **IIIf** (QF 0301B). [d] Selectivity expressed as pK_i(5-HT_{2A}) − pK_i(D_2).

changing torsion angles) using the solvent continuum approximation;[71] the results suggest that the solvent effect may substantially reduce the energy difference between the two conformers.

For each combination of fields, the number of components to be used in a final CoMFA model was identified by leave-one-out cross-validation of models with up to five components.[72] Since in several cases the model with the highest value of q^2 had a relatively large number of components, the associated risk of overfitting[73] was avoided by taking, for the final model, the number corresponding to the first maximum of a plot of q^2 against the number of components. Final non-cross-validated models were only actually calculated for two-field combinations chosen on the basis of the q^2 results.

CoMFA results for 5-HT_{2A} and D_2 affinities and 5-HT_{2A}/D_2 selectivity are summarized in Table 10. Most models had fairly high predictive power ($q^2 > 0.5$); no significant improvements were achieved by changing the standard CoMFA settings for grid size and minimum σ. For 5-HT_{2A} affinity, all three single-field models had similar predictive power, especially when the flagrant outlier **IIIf** was excluded from the analyses (models S_2, E_2, and L_2). Combining two or three fields afforded, at most, moderate improvement in predictive power. The good performance of the pure electrostatic model E_2 is in keeping with the excellent correlation between electrostatic potential similarity and 5-HT_{2A} affinity recently reported by some of us for a subset of the compounds considered in the present study.[74] For D_2 affinity, the best models are those in which the lipophilic field is considered, either alone (model L_3) or in combination with the electrostatic field (EL_3) or the steric field (SL_3).

Graphical representations of the most significant two-field models for 5-HT_{2A} affinity (SL_2 and EL_2) and D_2 affinity (SL_3 and EL_3) are shown in Figure 4 together with representations of the corresponding models for 5-HT_{2A}/D_2 selectivity (SL_4 and EL_4) and, to aid interpretation, representations of both highly active or selective ligands and poorly active or selective ligands. These color maps (the color code is defined in Table 11) show the regions of space in which variation of the field considered has most effect on the dependent variable.

For the model of 5-HT_{2A} affinity SL_2, the map of Figure 4 (which includes representations of the active ligands **23b** and **24a** and the low-activity ligands **24e**,**f**) shows, in yellow, regions in which affinity is favored by high MLPs and which chiefly correspond to those associated with the cycloalkanone fragment, the alkyl part of piperidine rings, and benzoyl-borne fluorine atoms; in cyan, regions in which affinity is favored by high hydrophilicity and which chiefly correspond to the neighborhood of the carbonyl oxygens of α-substituted cycloalkanone rings; in green, a sterically favorable region around the aromatic systems opposite the benzo- or thienocycloalkanone moiety; and in red, sterically unfavorable regions associated with the methoxy groups of (*o*-methoxyphenyl)piperazines and the carbonyl groups of their butyrophenone congeners. The map for model EL_2, which depicts the low-activity compound **10f** as well as those shown in the SL_2 map, shows the same lipophilic (yellow) and hydrophilic (cyan) regions as the SL_2 map (as expected); in magenta, regions in which affinity is favored by high electron density, which mainly correspond to the aromatic systems of the piperidine compounds or the thieno sulfur; and in white, a region in which affinity is disfavored by high electron density and which corresponds to methoxy oxygen atoms or the piperazine nitrogen farthest from the cycloalkanone (this unfavorable interaction in this region may suffice by itself to explain the low affinities of the (*o*-methoxyphenyl)piperazines).

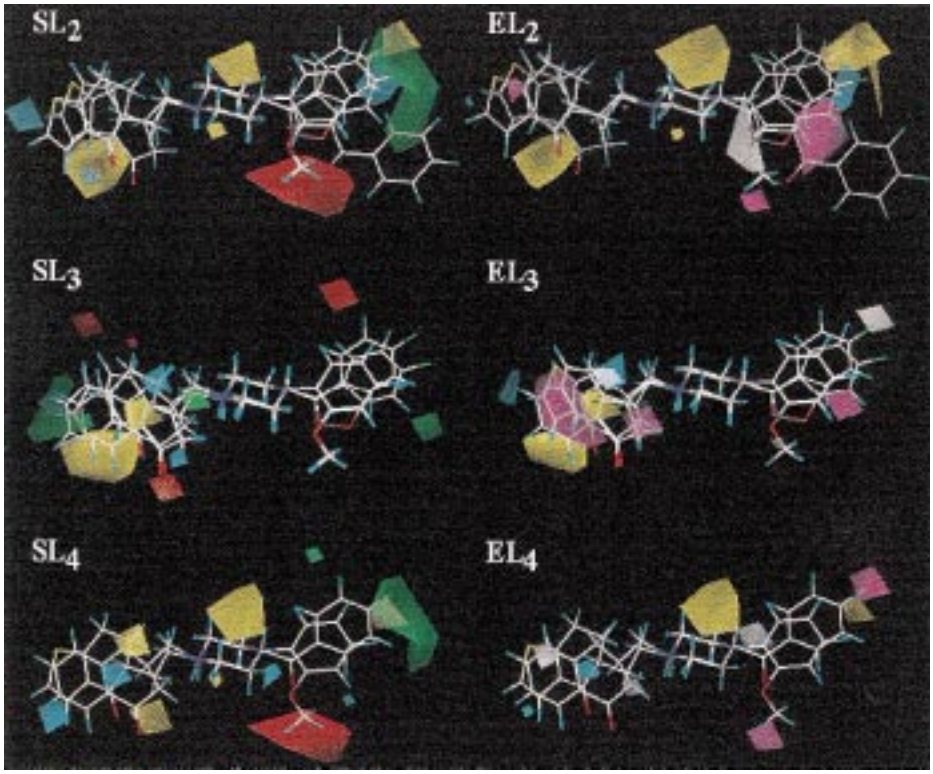


Figure 4. STDEV×COEFF isocontour plots for models SL_2, EL_2, SL_3, EL_3, SL_4, and EL_4 (for the color code, see Table 11). Model SL_2 levels: red, −0.039; green, 0.030; cyan, −0.023; yellow, 0.020. EL_2: magenta, −0.027; white, 0.034; cyan, −0.032; yellow, 0.020. SL_3: red, −0.018; green, 0.021; cyan, −0.027; yellow, 0.035. EL_3: magenta, −0.035; white, 0.022; cyan, −0.021; yellow, 0.035. SL_4: red, −0.028; green, 0.020; cyan, −0.020; yellow, 0.010. EL_4: magenta, −0.017; white, 0.030; cyan, −0.029; yellow, 0.018. Compounds shown: for SL_2, **23b**, **24a**,**e**,**f**; for EL_2, **10f**, **23b**, **24a**,**e**,**f**; for SL_3, **If**, **IIIf**, **10a**,**f**, **29b**; for EL_3, **Ia**,**f**, **10f**, **23b**; for SL_4 and EL_4, **If**, **24a**.

Table 11. Color Code of CoMFA Isocontour Maps in Figure 4

field component	increased affinity	decreased affinity
steric field	green	red
electrostatic field (positive charge)	white	magenta
electrostatic field (negative charge)	magenta	white
lipophilic field (lipophilic component)	yellow	cyan
lipophilic field (hydrophilic component)	cyan	yellow

For the model of D_2 affinity SL_3, the map of Figure 4 (which includes representations of the active ligands **If**, **IIIf**, and **29b** and the low-affinity ligands **10a**,**f**) shows sterically favorable regions associated with the thieno moiety and the aromatic ring opposite the cycloalkanone of some active ligands; sterically unfavorable regions associated with the benzo ring of benzocycloalkanones and benzoyl moieties; regions in which affinity is favored by high MLPs (which appear to be most fully occupied by the high-MLP zones around the most active ligands); and hard-to-interpret regions in which affinity is disfavored by high MLP. The map for model EL_3, which depicts compounds **Ia**,**f**, **10f**, and **23b**, shows the same lipophilic and lipophobic regions as the SL_3 map (as expected); the regions in which affinity is favored or disfavored by high electron density are not easy to interpret, but the former seem to correspond to the aromatic systems of the most active compounds and the latter to the benzo ring of benzocycloalkanones and the fluorine atoms of compounds with low affinity.

Even though careful visual comparison of the maps for SL_2, EL_2, SL_3, and EL_3 might suggest structural elements favoring selectivity for 5-HT_{2A} rather than D_2, we preferred to model 5-HT_{2A}/D_2 selectivity directly by means of a PLS analysis. Single-field and two-field models had similar q^2 values (Table 10) and other statistical parameters. The map of Figure 4 for SL_4, which includes representations of the most and least selective ligands (**If** and **24a**, respectively), shows regions in which selectivity is favored by high MLPs, corresponding to the cycloalkyl part of piperidine rings; a sterically favorable region around the fluorine atom of piperidine compounds; and a sterically unfavorable region associated with the methoxy groups of the D_2-selective (methoxyphenyl)piperazines. The importance of the electrostatic field for 5-HT_{2A}/D_2 selectivity is shown by the map for model EL_4, which shows the *p*-fluorophenyl groups of 5-HT_{2A}-selective compounds in regions in which high electron density favors selectivity and the phenyl group of compounds with low 5-HT_{2A}-selectivity in the region in which high electron density discourages selectivity.

Docking of 24a,b into Receptor 5-HT_{2A}. The docking of two of the most active 5-HT_{2A} ligands, **24a**,**b**, was simulated using a receptor model with the same seven-transmembrane α-helices and topology as were deduced by Baldwin[75] for bovine rhodopsin from electron density projection maps (Figure 5). The model was geometrically optimized using the program AMBER 4.1[76] and successfully passed the PROCHECK[77] and WHATCHECK[78] quality tests. It has a possible binding site that includes all the residues that have been described as critical for receptor−ligand interactions in site-directed mutagenesis experiments (Asp155 and Ser159 in helix III, Ser239 in helix V, and Phe340 in helix VI).[79,80] Furthermore, it has the hydrogen bond

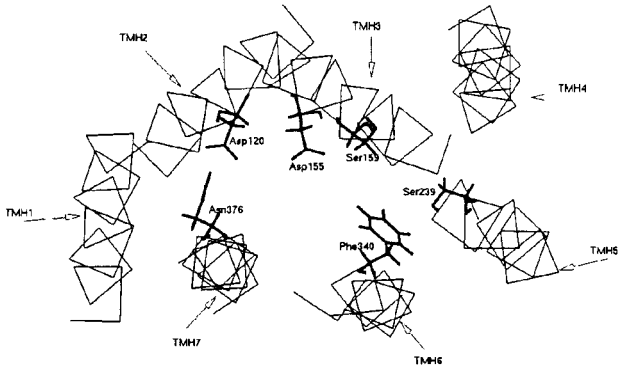


Figure 5. Model of the 5-HT_{2A} showing important amino acids in the binding site and the hydrogen bond between Asp120 in helix II and Asn376 in helix VII.

between Asp120 in helix II and Asn376 in helix VII that has been reported to be crucial for maintenance of the functional receptor structure.[81] Ligand binding was automatically explored using the Affinity module of BIOSYM,[82] which takes into account the conformational flexibility of both ligand and receptor. Molecular dynamics simulations supported the stability of the most interesting complexes obtained. Two of the most significant and stable complexes are shown in Figure 6. Both are stabilized by two hydrogen bonds, one of which involves the amino group of the ligand and Asp155 in helix III. The other hydrogen bond of the **24b** complex involves Asn343 in helix VI, while that of the **24a** complex involves Ser239 in helix V. Lipophilic or $\pi-\pi$ aromatic−aromatic interactions also contribute to stabilization of the complexes; they include the interactions between Trp336 in helix VI and the 6-fluorobenzisoxazole moiety of **24b** or the aromatic ring fused to the cycloalkanone of **24a**. Note that lipophilic interactions involving the same fragments are clearly suggested by the CoMFA results (Figure 4).

It must be pointed out that although all the complexes obtained share the hydrogen bond between Asp155 in helix III and the protonated amino group, the cycloalkanone moiety appears to one side of Asp155 in some complexes and to the other side in others (Figure 6 shows an example of each orientation). This is coherent with the presence of the same pharmacophore on both sides of the protonated amino group (aryl−CO−CH_2−CH_2−CH_2−NRH^+−CH_2−CH_2−CH_2−CO−aryl′) and hints at the possibility of multiple binding modes.

Table 12. In Vivo Assays

compd	ED_{50} (mg/kg) climbing (CL 95%)	ED_{50} (mg/kg) catalepsy
10a (QF 0501B)	>7.0	>4.0
10e (QF 0502B)	>8.0	>8.0
10f (QF 0503B)	>8.0	>8.0
23a (QF 0505B)	2.65 (2.30−3.06)	>16.0
23b (QF 0510B)	0.47 (0.31−0.70)	>20
23e (QF 0506B)	3.34 (2.04−5.46)	>15.0
24a (QF 0601B)	2.03 (1.19−3.46)	>4.0
24b (QF 0610B)	0.79 (0.62−0.99)	>2.0
24e (QF 0602B)	>15.0	>10.0
24f (QF 0603B)	>8.0	>8.0
29a (QF 0901B)	1.98 (0.98−4.00)	>4.0
29b (QF 0902B)	0.50 (0.38−0.66)	>2.0
35a (QF 0605B)	1.25 (0.48−3.3)	>16.0
35b (QF 0609B)	1.46 (0.91−2.32)	>8.0
35e (QF 0606B)	>8.0	>2.0
35f (QF 0607B)	>8.0	>8.0
haloperidol	0.14 (0.13−0.15)	0.67
clozapine	2.21 (2.03−2.41)	>50.0
risperidone	0.09 (0.08−0.09)	>2.0

In Vivo Studies. Potential for antipsychotic activity was quantified in terms of inhibition of apomorphine-induced climbing by mice and potential for causing EPS in terms of induction of catalepsy in mice (Table 12).

Apomorphine-induced climbing by mice was strongly inhibited by haloperidol and risperidone (ED_{50} < 0.2 mg/kg), closely followed by the α-ethylbenzisoxazolyl derivatives **23b** (0.47), **24b** (0.79), and **29b** (0.50): see Figure 7. Changing the size of the cycloalkanone ring had relatively little effect on climbing inhibition among the more active thiophene derivatives (compare **23a**,**b**

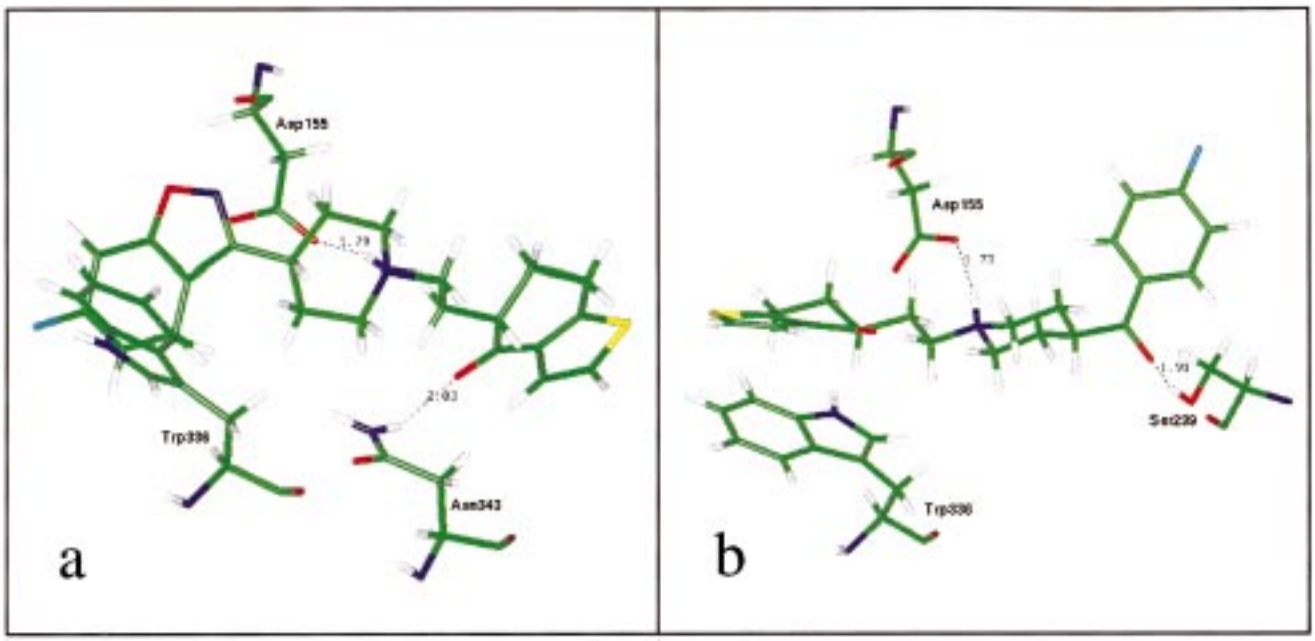


Figure 6. Feasible complexes of **24b** (a) and **24a** (b) with the binding site of rat 5-HT_{2A}, showing hydrogen bonds and the interaction with Trp336.

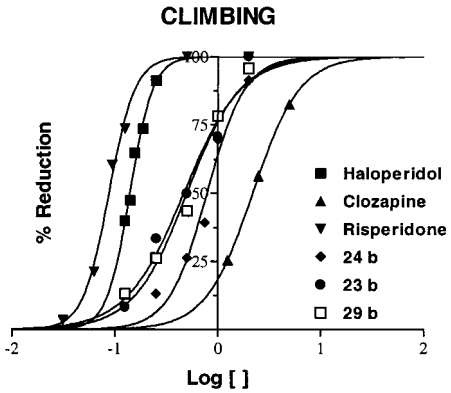


Figure 7. Dose−effect curves for inhibition of induced climbing by mice by reference drugs and selected new compounds.

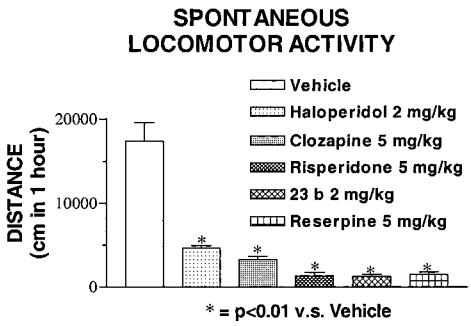


Figure 8. Spontaneous locomotor activity in mice treated with vehicle, haloperidol (2 mg/kg), clozapine (5 mg/kg), risperidone (5 mg/kg), **23b** (2 mg/kg), or reserpine (5 mg/kg).

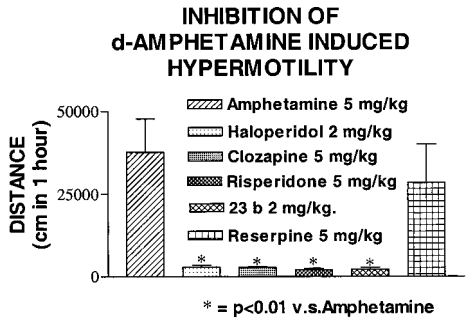


Figure 9. Inhibition of *d*-amphetamine-induced hypermotility in mice treated with haloperidol (2 mg/kg), clozapine (5 mg/kg), risperidone (5 mg/kg), **23b** (2 mg/kg), or reserpine (5 mg/kg).

with **24a**,**b**), and moving the position of the thiophene sulfur also had little effect, although such change as there was paralleled the slight changes in 5-HT_{2A}-blocking activity observed in the binding experiments (compare **24a**,**b** with **29a**,**b**). The three α-ethylbenzisoxazolyl derivatives were all more active than the *β*-methylbenzisoxazolyl **35b** (ED_{50} = 1.46 mg/kg), but the reverse was true among the (*p*-fluorobenzoyl)piperidinyl compounds (**23a**, 2.65; **24a**, 2.03; **29a**, 1.98; **35a**, 1.25), although none of these latter exhibited marked activity. The difference in activity between the benzisoxazolyl and (*p*-fluorobenzoyl)piperidinyl compounds was greater in the α-ethyl than in the *β*-methyl series (compare the difference between **35a** and **35b** with those between **23a** and **23b**, **24a** and **24b**, and **29a** and **29b**). All the (*o*-methoxyphenyl)piperazine derivatives were completely devoid of activity (ED_{50} > 8 mg/kg), as were all the compounds with the linear butyrophenone moiety **e** (except **23e** did have very slight activity: ED_{50} = 3.34 mg/kg).

None of the new compounds induced catalepsy at the doses assayed. In particular, the compound showing most activity in the climbing test, **23b**, failed to induce catalepsy at a dose of 20 mg/kg, more than 40 times its ED_{50} for climbing inhibition (among the new compounds, **23b** also had the highest or near-highest activity at all the receptors considered). The fact that **10f**, **24e**,**f**, and **35e** were not cataleptogenic despite their pK_i(5-HT_{2A})/pK_i(D_2) ratios being similar to those of classical antipsychotics (<1.09) may be due to their affinities for both 5-HT_{2A} and D_2 being low (which is in keeping with the climbing test results), to insufficient dosage in the catalepsy trials, or to unevaluated factors such as anticholinergic activity or α_1 blockage. Haloperidol was markedly cataleptogenic, as expected (ED_{50} = 0.67 mg/kg).

Statistical analysis of pairwise correlations between in vivo and in vitro test results found best Pearson correlation between climbing inhibition (ED_{50}) and pK_i at 5-HT_{2A} ($r = -0.640$, $p < 0.001$ for $n = 22$).

In view of its good performance in all the in vitro and in vivo tests described above, compound **23b** was subjected to supplementary in vivo trials. At a dosage of 2 mg/kg, its marked inhibition of spontaneous locomotor activity in mice was similar to that exerted by 5 mg/kg risperidone or 5 mg/kg reserpine (the latter administered, as usual, 24 h prior to observation of the response) and rather greater than that exerted by 2 mg/kg haloperidol or 5 mg/kg clozapine (Figure 8). In addition, 2 mg/kg **23b**, like 2 mg/kg haloperidol, 5 mg/kg clozapine, or 5 mg/kg risperidone, completely inhibited *d*-amphetamine-induced hyperlocomotion, which was not inhibited by reserpine (Figure 9). Hence **23b** seems likely to inhibit *d*-amphetamine-induced hyperlocomotion by the same specific mechanism as haloperidol, clozapine, and risperidone, which are assumed to act by blocking dopaminergic receptors in the nucleus accumbens.

Conclusion

Several conformationally restricted butyrophenones (α- and *β*-(aminoalkyl)cycloalkanones bearing (*p*-fluorobenzoyl)piperidine, (6-fluorobenzisoxazolyl)piperidine, (*o*-methoxyphenyl)piperazine, or linear butyrophenone fragments) were synthesized and evaluated in vitro for affinity for dopamine receptors (D_1, D_2) and serotonin receptors (5-HT_{2A}, 5-HT_{2C}). Most had good D_2 and 5-HT_{2A} affinities and a high 5-HT_{2A}/D_2 pK_i ratio, thus showing potential for atypical antipsychotic activity. 3D-QSAR (CoMFA) analyses identified the most significant steric, lipophilic, and electrostatic interactions involved in 5-HT_{2A} and D_2 binding and 5-HT_{2A}/D_2 selectivity. A study of docking into a 5-HT_{2A} model constructed by computer-assisted modeling techniques gave results consistent with the CoMFA and furnished further information on hydrogen bonds and $\pi-\pi$ or hydrophobic interactions involved in 5-HT_{2A} binding. The newly synthesized compounds were also subjected to in vivo behavioral tests of antipsychotic potential and risk of EPS. The pharmacological profiles of thiaindanone **23b** (QF 0510B) and thiatetralones **24b** (QF 0610B) and **29b** (QF 0902B), all of which bear a benzisoxazolylpiperidine

fragment, suggest that they may be effective atypical antipsychotic drugs with little propensity to produce EPS.

Experimental Section

Chemistry. Melting points were determined with a Kofler hot stage instrument or a Gallenkamp capillary melting point apparatus and are uncorrected. Infrared spectra were recorded with a Perkin-Elmer 1600 FTIR spectrophotometer; the main bands are given, in cm^{-1}. ^1H and ^{13}C NMR spectra were recorded with a Bruker WM AMX spectrometer (300 MHz); chemical shifts are recorded in parts per million (δ) downfield from tetramethylsilane (TMS), and J values are given in hertz (Hz). Mass spectra were performed on Kratos MS-50 or Varian Mat-711 mass spectrometers in fast atom bombardment (FAB) mode (with 2-hydroxyethyl disulfide as matrix) or by electron impact (EI). Optical rotations at the sodium D-line were determined in MeOH solutions of the indicated concentrations using a Perkin-Elmer 241 polarimeter. Flash column chromatography was performed using Kieselgel 60 (60−200 mesh, E. Merck AG, Darmstadt, Germany). Reactions were monitored by thin-layer chromatography (TLC) on Merck 60 GF_{254} chromatogram sheets using iodine vapor and/or UV light for detection; unless otherwise stated the purified compounds each showed a single spot. Elemental combustion analyses were performed on a Perkin-Elmer 240B apparatus at the Microanalysis Service of the University of Santiago de Compostela; unless otherwise stated all reported values are within ±0.4% of the theoretical compositions. Solvents were purified as per Vogel[83] by distillation over the drying agent under an argon atmosphere and were used immediately. The drying agents used were Na/benzophenone for THF, ether, and toluene; P_2O_5 for CH_2Cl_2; K_2CO_3 for acetone and ethyl acetate; KOH for pyridine and TEA; and $CaSO_4$/4 Å molecular sieves for DMF. Unless otherwise stated salts were prepared by the following general procedures: (a) *oxalates*, by dropwise addition of a 1 mol equiv solution of oxalic acid in anhydrous ether to a solution of the amine in anhydrous ether; (b) *hydrochlorides*, by dropwise addition, with cooling, 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 sulfate in absolute MeOH to a 1 M solution of carbonyl derivative in absolute MeOH.

3-Carboxy-1-indanone (1) was prepared by Friedel−Crafts cyclization of phenylsuccinic anhydride as per Hashimoto and Takatsuka.[50]

4-Oxo-4,5-dihydro-6*H*-cyclopenta[*b*]thiophene (**11**, thiaindanone) was synthesized by ring closure of β-(2-thienyl)-acrylic acid as per Sam and Thompson.[84] 2,4-Dinitrophenylhydrazone: mp 152−154 °C (EtOH).

4-Oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene (12) was synthesized by ring closure of γ-(α-thienyl)butyric acid as per Nishimura et al.[85] 2,4-Dinitrophenylhydrazone: mp 252−255 °C (AcOEt).

7-Oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene (25) was prepared by Wolf−Kishner reduction of the 4-oxo derivative **12** and subsequent cerium ammonium nitrate (CAN) oxidation of the resulting thiatetraline, as per Cagniant[86] and Conjat et al.[87]

4-Oxo-4*H*-5,6-dihydrocyclopenta[*b*]thiophene-5-ylideneacetic acid (13), 4-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-5-ylideneacetic acid (14), 4-oxo-4*H*-5,6-dihydrocyclopenta[*b*]thiophene-5-ylacetic acid (17), and 4-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-5-ylacetic acid (18) were prepared as previously described.[43]

7-Oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-5-ylacetic acid (26) was obtained similarly to its regioisomer **18** by alkylation of the enolate of thiatetralone **25** with ethyl bromoacetate (50% yield) and subsequent ester hydrolysis (95%): white crystalline solid of mp 70−72 °C (H_2O). IR: 1710, 1659. ^1H NMR ($CDCl_3$): δ 1.98−2.12 (m, 1H, H_5); 2.27−2.35 (m, 1H, $H_{5'}$); 2.47 (dd, J_{gem} = 18.1, J_{vic} = 8.5, *H*CH-COOH); 2.86−3.12 (m, 4H, -HC*H*-COOH, H_4, $H_{4'}$, H_6); 6.96 (d, J = 4.9, H_3); 7.61 (d, J = 4.9, H_2). ^{13}C NMR ($CDCl_3$): δ 26.2, 30.9, 34.9 (C_4, C_5, -*C*H_2-COOH); 44.2 (C_6); 128.5, 135.0 (C_2, C_3); 136.2 (C_{3a}); 152.9 (C_{7a}); 178.1 (-*C*OOH); 192.6 (C_7). MS (FAB, *m*/*z*): 211 (MH^+). Anal. ($C_{10}H_{10}O_3S$) C, H.

3-Carboxy-1-indanone Methyl Ester (2). A solution of **1** (10 g, 0.057 mol) in methanol (40 mL) with a few crystals of *p*-TsOH was refluxed with stirring for 5 h. After cooling, the solvent was distilled off under reduced pressure. The residue was dissolved in CH_2Cl_2, and the resulting solution was washed with 10% $NaHCO_3$ and water and then dried (Na_2SO_4). After removal of the solvent in vacuo the resulting orange oil was ball-to-ball distilled (130−133 °C/0.4 mmHg) to give **2** (9.90 g, 92%) as a colorless oil which on standing soon crystallized as white crystals of mp 119−120 °C (*i*-PrOH). IR: 3200, 1737, 1713. ^1H NMR ($CDCl_3$): δ 2.83 (dd, 1H, J_{gem} = 19.1, J_{vic} = 8, H_2); 3.10 (dd, 1H, J_{gem} = 19.1, J_{vic} = 3.6, H_2); 3.74 (s, 3H, CO_2CH_3); 4.26 (m, 1H, J_{3-2} = 8, J_{3-2} = 3.6, H_3); 7.41 (t, 1H, J = 7.3, H_6); 7.56−7.62 (dt, 1H, J_{5-4} = 7.7, H_5); 7.67 (d, 1H, J_{4-5} = 7.7, H_4); 7.71 (d, 1H, J_{7-6} = 7.6, H_7). Anal. ($C_{11}H_{10}O_3$) C, H.

3-Carboxy-1-indanone Methyl Ester, Ethylene Ketal (3). Ketal **3** was prepared in a flask fitted with a Liebig condenser and a water aspiration pump. The reaction was monitored by TLC (ethyl acetate/benzene, 4:1). A vigorously stirred mixture of keto ester **2** (5 g, 0.056 mol), trimethyl orthoformate (5 mL, 0.26 mol), and *p*-TsOH (20 mg) in dry benzene (25 mL) was held at 50 °C (bath temperature), and methyl formate was distilled off under moderately low pressure. Two 40-mg portions of *p*-TsOH were added at 1-h intervals. After a total of 4 h, keto ester **2** had disappeared. The bath temperature was raised to 70−80 °C, and volatile components, including benzene, were distilled off in vacuo. The resulting residue was dissolved in ether, the solution was washed with 10% $NaHCO_3$ (3×) and water (3×) and dried (Na_2SO_4), and the ether was distilled off. The residue, a pale-yellow oil, was purified by ball-to-ball distillation (140−145 °C/0.4 mmHg) to give **3** (5.37 g, 87%) as a colorless oil which was used in the next step without further purification. IR: 2800, 1739. ^1H NMR ($CDCl_3$): 2.55 (dd, 1H, J_{gem} = 13.7, J_{vic} = 8.1, H_2); 2.70 (dd, 1H, J_{gem} = 13.7, J_{vic} = 6.5, H_2); 3.76 (s, 3H, -CO_2CH_3); 4.06−4.25 (m, 5H, H_3, -O-CH_2CH_2-O-); 7.32−7.42 (m, 4H, aromatic H).

3-(Hydroxymethyl)-1-indanone Ethylene Ketal (4). A stirred solution of ester **3** (2 g, 8 mmol) in anhydrous 1:1 ether/benzene was added dropwise to a vigorously stirred suspension of $LiAlH_4$ (0.9 g, 24 mmol) in anhydrous ether (75 mL) under argon. The reaction mixture was heated under reflux for 8 h, cooled to 0 °C in an ice bath, and quenched by the sequential dropwise addition of H_2O (2 mL), NaOH (2 mL), and H_2O (2 mL). The coarse precipitate formed was filtered off and thoroughly washed with ether. The organic extracts were washed with water several times and dried (Na_2SO_4), and the solvent was distilled off in vacuo. The crude brown oily residue was purified by ball-to-ball distillation to give **4** (1.2 g, 85%) as a colorless oil of bp 160−165 °C/0.5 mmHg. IR: 3300−3400. ^1H NMR ($CDCl_3$): δ 1.8 (s, 1H, -CH_2OH); 2.17 (dd, 1H, J_{gem} = 13.8, J_{vic} = 4.3, H_2); 2.49 (dd, 1H, J_{gem} = 13.8, J_{vic} = 8.1, H_2); 3.4 (m, 1H, J_{3-2} = 4.5, J_{3-2} = 8, H_3); 3.85 (m, 2H, -CH_2OH); 4.06−4.21 (m, 4H, -O-CH_2CH_2-O-); 7.30−7.40 (m, 4H, aromatic H). Anal. ($C_{12}H_{14}O_3$) C, H. 2,4-Dinitrophenylhydrazone: red crystals, mp 230−231 °C (AcOEt). ^1H NMR ($CDCl_3$): δ 2.9 (dd, 1H, J_{gem} = 18, J_{vic} = 3.2, H_2); 3.12 (dd, 1H, J_{gem} = 18, J_{vic} = 8.05, H_2); 3.72−3.75 (m, 1H, H_3); 3.94 (t, 2H, J = 5.3, -CH_2-OH); 7.40−7.49 (m, 3H, H_4, H_5, H_6); 7.90 (d, 1H, J = 7.1, H_7); 8.13 (d, 1H, $J_{6'-5'}$ = 9.6, $H_{6'}$); 8.36 (dd, 1H, $J_{5'-6'}$ = 9.6, $J_{5'-3'}$ = 2.6, $H_{5'}$); 9.16 (d, 1H, $J_{3'-5'}$ = 2.6, $H_{3'}$); 11.27 (s, 1H, -N*H*-). MS (EI, *m*/*z*): 342 (M^+). Anal. ($C_{16}H_{14}O_5N_4$) C, H, N.

3-(Bromomethyl)-1-indanone (5). A stirred solution of alcohol **4** (2.06 g, 10 mmol), carbon tetrabromide (15 g, 12.5 mmol), and triphenylphosphine (3.93 g, 15 mmol) in CH_2Cl_2 (50 mL) was refluxed for 20 h under argon. After cooling, the reaction mixture was washed with 5% $NaHCO_3$ and water, the organic phase was dried (Na_2SO_4), and the solvent was

distilled off. Purification of the residue by flash chromatography (AcOEt/hexane, 3:1) gave **5** (1.84 g, 82%) as a pale-brown oil which on standing gave white crystals of mp 224−225 °C (*i*-PrOH). IR: 1715. ^{1}H NMR ($CDCl_3$): δ 2.65 (dd, 1H, J_{gem} = 19.2, J_{vic} = 3.1, H_2); 2.93 (dd, 1H, J_{gem} = 19.2, J_{vic} = 7.1, H_2); 3.84 (c, 1H, J = 8.5, H_3); 3.81−3.87 (m, 2H, -CH_2Br); 7.46 (t, 1H, J = 7.6, H_6); 7.57 (d, 1H, J = 7.5, H_4); 7.66 (t, 1H, J = 7.7, H_5); 7.77 (d, J = 7.6, H_7). MS (FAB, *m*/*z*): 226 (MH^+). Anal. ($C_{10}H_9BrO$) C, H.

3-(*N*-Morpholinomethyl)-1-indanone (6). Method A. A solution of (bromomethyl)indanone **5** (1 g, 4.45 mmol) in 20 mL of methyl isobutyl ketone (MIK) was added dropwise under argon to a stirred suspension of morpholine (0.77 g, 8.9 mmol), Na_2CO_3 (0.94 g, 8.9 mmol), and KI (50 mg) in MIK (50 mL). After refluxing with vigorous stirring for 12 h, the mixture was allowed to stand at room temperature overnight and then filtered. The filtrate was condensed under reduced pressure to give a brown oil which was purified by flash chromatography (AcOEt). The resulting colorless oil crystallized on standing. Recrystallization from ethyl acetate gave **6** (0.51 g, 50%) as white crystals of mp 72−73 °C (AcOEt). IR: 1708. ^{1}H NMR ($CDCl_3$): δ 2.44−2.53 (m, 4H, -N(CH_2CH_2)$_2$O); 2.45 (dd, 1H, J_{gem} = 12.4, J_{vic} = 8.5, -HC*H*-NRR); 2.57 (dd, 1H, J_{gem} = 19.25, J_{vic} = 3.1, H_2); 2.68 (dd, 1H, J_{gem} = 12.4, J_{vic} = 6.4, -*H*CH-NRR); 2.82 (dd, 1H, J_{gem} = 19.25, J_{vic} = 7.4, H_2); 3.55 (m, 1H, J_{3-2} = 3.1, J_{3-2} = 7.2, J = 8.5); 3.73 (t, 4H, -N-(CH_2CH_2)O, J = 4.66); 7.4 (t, 1H, J = 7.7, H_6); 7.58 (dd, 1H, J_{4-5} = 7.8, J_{4-6} = 1.1, H_4); 7.61−7.66 (m, 1H, H_5); 7.74 (d, 1H, J = 7.6, H_7): ^{13}C NMR ($CDCl_3$) δ 35.93; 42.12; 54.17; 64.65; 67.24 (O(CH_2-CH_2)$_2$N-); 123.85 (C_4); 126.59 (C_7); 128.10 (C_6); 134.79 (C_5); 137.24 (C_{7a}); 157.32 (C_{3a}); 206.42 (C_1). MS (FAB, *m*/*z*): 232 (MH^+). Anal. ($C_{14}H_{17}NO_2$) C, H, N. 2,4-Dinitrophenylhydrazone: red needles, mp 240−243 °C (AcOEt).

Method B. A solution of (bromomethyl)indanone **5** (0.5 g, 2.2 mmol) and morpholine (0.39 g, 4.4 mmol) in absolute ethanol (30 mL) was heated in a Parr reactor for 2 h. After cooling, the mixture was vacuum-filtered to recover morpholinium bromide, and the filtrate was condensed under reduced pressure. The oily residue was purified by flash chromatography (AcOEt) to give **6** (0.21 g, 47%) as a colorless oil which soon crystallized on standing: mp 72−73 °C (AcOEt).

3-(*N*,*N*-Diethylaminomethyl)indan-1-one (7) was prepared by method B. Hydrochloride: mp 162−165 °C (EtOH). Anal. ($C_{14}H_{19}NO$·ClH) C, H, N. 2,4-Dinitrophenylhydrazone: red crystalline powder, mp 240−243 °C (AcOEt).

General Procedure for Synthesis of Ketoamides (Table 5) Using DCC and HOBt as Coupling Reagents. *N*-[(1-Oxoindan-3-yl)carbonyl]-4-(*p*-fluorobenzoyl)piperidine (8a). A solution of (*p*-fluorobenzoyl)piperidine (2.35 g, 11.36 mmol), 1-hydroxybenzotriazole (HOBt) (1.54 g, 11.36 mmol), and 3-carboxy-1-indanone (**2**) in anhydrous CH_2Cl_2 (30 mL) was stirred under argon at room temperature for 15 min and then cooled to 0 °C. At this temperature, dicyclohexylcarbodiimide (DCC) (2.34 g, 11.36 mmol) was added, and the reaction mixture was kept at 0−5 °C for 1 h and then allowed to reach room temperature and left overnight. The precipitated dicyclohexylurea was filtered off, and the filtrate was washed several times with 5% $NaHCO_3$ and water, dried (Na_2SO_4), and condensed to dryness. The oily residue was purified by flash chromatography (AcOEt/hexane, 1:1) to give the amide **8a** (3.32 g, 80%) as a white crystalline solid of mp 146−149 °C (AcOEt). IR: 2933, 1716, 1678, 1628. ^{1}H NMR ($CDCl_3$): δ 1.97−2.03 (m, 4H, -N(CH_2CH_2)$_2$-CH-); 2.89 (dd, 1H, J_{gem} = 13.6, J_{vic} = 7.1, H_2); 2.98 (dd, 1H, J_{gem} = 13.6, J_{vic} = 3.7, H_2); 2.96−3.01 (m, 1H, H_3); 3.45−3.59 (m, 2H, -N(*H*CHCH$_2$)$_2$-CH-); 4.27−4.31 (m, 1H, -N(CH_2CH_2)$_2$-C*H*-); 4.55−4.59 (m, 2H, -N(HC*H*CH$_2$)$_2$-CH-); 7.17 (t, 2H, J = 8.4, *o*-F-Ph); 7.43 (t, 1H, J = 7.3, H_6); 7.59−7.61 (m, 1H, H_5); 1.17−1.78 (m, 1H, H_7); 1.98−8.01 (m, 2H, *o*-CO-Ph). ^{13}C NMR ($CDCl_3$): δ 25.86; 28.98; 34.19; 43.46; 49.40; 116.32 (d, 2C, J_{C-F} = 21.8, *o*-F-Ph); 118.00 (C_4); 124.30 (C_7); 126.49 (C_6); 128.77 (C_5); 131.24 (d, 2C, J_{C-F} = 9.1, *m*-F-Ph); 135.20; 137.08 (C_{7a}); 153.10 (C_{3a}); 164.47; 167.85; 170.55; 170.90; 200.27 (CO-Ph); 204.63 (C_1). MS (FAB, *m*/*z*): 366 (MH^+). Anal. ($C_{22}H_{20}FNO_3$) C, H, N.

The amides **8c**,**f** were obtained similarly from **1**, **19a**−**c** from **17**,[42] **20a**−**c**,**f** from **18**,[42] and **27a**−**b** from **26**, as white crystalline solids (Table 5); their data follow.

***N*^{1}-[(1-Oxoindan-3-yl)carbonyl]-*N*^{4}-(*tert*-butoxycarbonyl)piperazine (8c):** yield 85%, mp 146−147 °C (*i*-PrOH). IR: 2930, 1716, 1696, 1641. ^{1}H NMR ($CDCl_3$): δ 1.49 (s, 9H, -C(C*H*$_3$)$_3$); 2.89 (dd, 1H, J_{gem} = 18.5, J_{vic} = 7.6, H_2); 2.99 (dd, 1H, J_{gem} = 18.5, J_{vic} = 4.2, H_2); 3.63−3.74 (m, 8H, piperazine); 4.54 (m, 1H, J_{3-2} = 7.6, J_{3-2} = 4.2, H_3); 7.40−7.47 (m, 2H, H_4, H_5); 7.62 (dt, 1H, J = 7.5−1.2, H_6); 7.78 (d, 1H, J = 7.6, H_7). MS (FAB, *m*/*z*): 345 (MH^+). Anal. ($C_{19}H_{24}O_4N_2$) C, H, N.

***N*^{1}-[(1-Oxoindan-3-yl)carbonyl]-*N*^{4}-(*o*-methoxyphenyl)-piperazine (8f):** yield 81%, mp 165 °C (AcOEt). IR: 1706, 1638. ^{1}H NMR ($CDCl_3$): δ 3.07 (dd, 1H, J_{gem} = 18.5, J_{vic} = 7.5, H_2); 3.21 (dd, 1H, J_{gem} = 18.5, J_{vic} = 4.1, H_2); 3.26−3.45 (m, 4H, CO-N(CH_2C*H*$_2$)$_2$N-); 4.03−4.23 (m, 4H, CO-N(C*H*$_2$CH$_2$)$_2$-N-); 4.12 (s, 3H, -OC*H*$_3$); 7.02−7.3 (m, 4H, $H_{3'}$, $H_{4'}$, $H_{5'}$, $H_{6'}$); 7.57−7.79 (m, 3H, H_4, H_5, H_6); 7.95 (d, 1H, J = 5.3, H_7). Anal. ($C_{21}H_{22}N_2O_3$) C, H, N.

***N*-[(4-Oxo-4*H*-5,6-dihydrocyclopenta[*b*]thiophene-5-yl)acetyl]-4-(*p*-fluorobenzoyl)piperidine (19a):** yield 78%. IR: 1701, 1680, 1643. ^{1}H NMR ($CDCl_3$): δ 1.88−1.93 (m, 4H, -N(CH_2CH_2)$_2$-CH); 2.51−2.68 (m, 1H, H_5); 2.77−2.89 (m, 2H, -N(HCHCH$_2$)$_2$-CH); 3.07 (dd, 1H, J_{gem} = 16.6, J_{vic} = 3.1, H_6); 3.15−3.26 (m, 1H, -N(CH_2CH_2)$_2$-CH); 3.33−3.49 (m, 2H, -N(H-CHCH$_2$)$_2$-CH); 3.55 (dd, 1H, J_{gem} = 16.6, J_{vic} = 4.4, H_6); 3.94 (dd, 1H, J_{gem} = 13.5, J_{vic} = 3.9, HCH-CON<); 4.54 (dd, 1H, J_{gem} = 13.5, J_{vic} = 4.4, HCH-CON<); 7.11−7.17 (m, 3H, $1H_2$, 2H: *o*-F-Ph); 7.31 (d, 1H, J = 5.2, H_3); 7.97 (dd, 2H, J = 8.9, 5.4, *o*-CO-Ph). Anal. ($C_{21}H_{20}FNO_3S$) C, H, N. 2,4-Dinitrophenylhydrazone: mp 223−225 °C (*i*-PrOH). Anal. ($C_{33}H_{28}FN_9O_9S$) C, H, N.

***N*-[(4-Oxo-4*H*-5,6-dihydrocyclopenta[*b*]thiophene-5-yl)acetyl]-4-(6-fluorobenzisoxazol-3-yl)piperidine (19b):** yield 85%, mp 155−157 °C. IR: 1698, 1640, 1616. ^{1}H NMR ($CDCl_3$): δ 1.89−2.16 (m, 4H, -N(CH_2-C*H*$_2$)$_2$C-); 2.60−2.68 (m, 1H, H_5); 2.91−3.00 (m, 2H, -N(*H*CH-CH$_2$)$_2$-); 3.10 (dd, 1H, J_{gem} = 16.6, J_{vic} = 2.9, H_6); 3.23−3.46 (m, 3H, -N(HCH-CH$_2$)$_2$C*H*-, -N(HC*H*-CH$_2$)$_2$-, HC*H*-CONRR); 3.57 (dd, 1H, J_{gem} = 17.4, J_{vic} = 7.0, $H_{6'}$); 4.05 (dd, 1H, J_{gem} = 13.6, J_{vic} = 7.1, -HC*H*-CONRR); 4.57−4.66 (m, 1H, -N(HC*H*-CH$_2$)$_2$-); 7.08−7.11 (m, 1H, $H_{5''}$); 7.16 (d, 1H, J = 5.1, H_2); 7.25 (dd, 1H, $J_{7'-F}$ = 8.2, $J_{7'-5'}$ = 2.1, $H_{7'}$); 7.32 (d, 1H, J = 5.3, H_3); 7.63 (dd, 1H, $J_{4'-5'}$ = 8.7, $J_{4'-F}$ = 4.3, $H_{4'}$). ^{13}C NMR ($CDCl_3$): δ 30.7, 32.4, 35.0, 41.9, 45.6, 50.3 (C_5, C_6, -CH_2-CONRR, -N(*C*H$_2$-*C*H$_2$)$_2$*C*-); 97.9 (d, J_{C-F} = 26.8, $C_{7'}$); 113.1 (d, J_{C-F} = 25.3, $C_{5'}$); 117.4 ($C_{3'a}$); 120.0, 131.1 (C_2, C_3); 122.5 (d, J_{C-F} = 11.0, $C_{4'}$); 145.4 (C_{6a}); 160.5 ($C_{3'}$); 164.2 (d, J_{C-F} = 13.5, $C_{7'a}$); 164.6 (d, J_{C-F} = 251, $C_{6'}$); 167.5 (C_{3a}); 169.5 (-*C*ONRR); 199.7 (C_4). MS (FAB, *m*/*z*): 398.7 (MH^+). Anal. ($C_{21}H_{19}FN_2O_3S$) C, H, N.

***N*^{1}-[(1-Oxo-4*H*-5,6-dihydrocyclopenta[*b*]thiophene-5-yl)acetyl]-*N*^{4}-(*tert*-butoxycarbonyl)piperazine (19c):** yield 91%, mp 116−118 °C (*i*-PrOH). IR: 1697, 1645. ^{1}H NMR ($CDCl_3$): δ 1.46 (s, 9H, -C(CH_3)$_3$); 2.59 (dd, 1H, J_{gem} = 16.7, J_{vic} = 9.6, H_6); 2.94 (dd, 1H, J_{gem} = 17.4, J_{vic} = 3.0, -*H*CH-CON<); 3.05 (dd, 1H, J_{gem} = 16.7, J_{vic} = 3.2, H_6); 3.36−3.49 (m, 8H, -N(CH_2-CH_2)$_2$N-); 3.56 (dd, 1H, J_{gem} = 17.4, J_{vic} = 7.1, -HC*H*-CON<); 3.52−3.60 (m, 1H, H_5); 7.16 (d, 1H, J = 5.1, H_2); 7.33 (d, 1H, J = 5.4, H_3). MS (FAB, *m*/*z*): 365 (MH^+). Anal. ($C_{18}H_{24}N_2O_4S$) C, H, N.

***N*-[(4-Oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-5-yl)-acetyl]-4-(*p*-fluorobenzoyl)piperidine (20a):** yield 85%, mp 143−145 °C (*i*-PrOH). IR:1677, 1663, 1635, 1594. ^{1}H NMR ($CDCl_3$): δ 1.74−1.91 (m, 4H, -N(CH_2-C*H*$_2$)$_2$CH-); 2.00−2.17 (m, 1H, H_6);2.23−2.33 (m, 1H, H_6); 2.41 (dd, 1H, J_{gem} = 16.3, J_{vic} = 9.8, *H*-CH-CONRR); 2.81−2.94 (m, 1H, -CO-N(*H*-CH-CH$_2$)$_2$CH-); 3.02−3.31 (m, 5H, H_5, H_7, H_7, H-C*H*-CONRR, -CO-N(H-C*H*-CH$_2$)$_2$CH-); 3.43−3.52 (m, 1H, RRC*H*-CO-Phe); 4.04−4.15 (m, 1H, -CON(*H*-CH-CH$_2$)$_2$CH-); 4.57−4.61 (m, 1H, -CON(H-C*H*-CH$_2$)$_2$CH-); 7.06 (d, J = 5.2, 1H, H_2); 7.16 (t, 2H, J = 8.4, *o*-F-Ph); 7.37 (d, 1H, J = 5.2, H_3); 7.98 (dd, 2H, J = 8.4, 5.7, *m*-F-Ph). ^{13}C NMR ($CDCl_3$): δ 25.6, 28.7, 41.5, 43.5, (C-5, C-6, C-7, -CH_2-CONRR); 31.1 (-CH_2)$_2$CH-CO-); 44.0, 45.1 (-N(*C*H$_2$-CH$_2$)$_2$*C*H-); 116.15 (d, 2C, J_{C-F} = 22.6, *o*-F-Ph); 123.6,

125.2 (C_2, C_3); 131.2 (d, 2C, J_{C-F} = 9.8, *m*-F-Ph); 137.1, 155.6 (C_{3a}, C_{7a}); 132.7 (*p*-F-Ph); 165.0 (d, J_{C-F} = 251, F-*C*); 170.5 (-*C*ONRR); 194.3 (C-4); 200.6 (-*C*O-Ph). MS (FAB, *m*/*z*): 400 (MH^+). Anal. ($C_{22}H_{22}FNO_3S$) C, H, N.

***N*-[(4-Oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-5-yl)-acetyl]-4-(6-fluorobenzisoxazol-3-yl)piperidine (20b):** yield 85%, mp 161−163 °C (*i*-PrOH). IR: 1665, 1643. ^{1}H NMR ($CDCl_3$): δ 1.93−2.15 (m, 5H, H6, -N(CH$_2$-CH$_2$)$_2$C-); 2.33 (dd, 1H, J_{gem} = 15.5, J_{vic} = 7.2, HCH-CONRR); 2.32−2.46 (m, 1H, H_6); 2.89−2.98 (m, 1H, -CON(HCH-CH$_2$)$_2$-); 3.01−3.39 (m, 6H, H_5, H_7, H_7, HCH-CONRR, -CON(HCH-CH$_2$)$_2$-, -CH$_2$)CH-); 4.06−4.13 (m, 1H, -N(HCH-CH$_2$)$_2$-); 4.62−4.75 (m, 1H, -N(HCH-CH$_2$)$_2$-); 7.08−7.11 (m, 2H, H_2, $H_{5'}$); 7.26 (dd, 1H, $J_{7'-F}$ = 8.3, $J_{7''-5'}$ = 2.0, H7′); 7.38 (d, 1H, J = 5.3, H_3); 7.68 (2dd, 1H, $J_{4''-5''}$ = 8.7, $J_{4''-F}$ = 5.1, H4′). ^{13}C NMR ($CDCl_3$): δ 25.8, 30.8, 31.5, 34.6, 34.9, 44.2 (C_5, C_6, C_7, -*C*H$_2$CONRR, -N(*C*H$_2$-*C*H$_2$)$_2$*C*-); 97.8 (d, J_{C-F} = 26.7, $C_{7'}$); 112.7 (d, J_{C-F} = 25.3, $C_{5'}$); 117.7 ($C_{3\acute{a}}$); 123.1 (d, J = 11.1, $C_{4'}$); 123.7, 125.4 (C_2, C_3); 137.1, 155.6 (C_{3a}, C_{7a}); 160.6 ($C_{3'}$); 164.2 (d, J_{C-F} = 13.5, $C_{7\acute{a}}$); 164.4 (d, J_{C-F} = 251, $C_{6'}$); 170.5 (-*C*ONRR); 194.5 (C_4). MS (FAB, *m*/*z*): 413 (MH^+). Anal. ($C_{22}H_{21}FN_2O_3S$) C, H, N.

***N*^{1}-[(4-Oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-5-yl)-acetyl]-*N*^{4}-(*tert*-butoxycarbonyl)piperazine (20c):** yield 90%, mp 114−116 °C (*i*-PrOH). IR: 1693, 1673 (CO); 1638. ^{1}H NMR ($CDCl_3$): δ 1.47 (s, 9H, -C(CH$_3$)$_3$); 2.03−2.10 (m, 1H, H_6); 2.36 (dd, J_{gem} = 16.0, J_{vic} = 7.9, 1H, *H*CH-CONRR); 2.28−2.44 (m, 1H, $H_{6'}$); 3.12 (dd, J_{gem} = 16.0, J_{vic} = 4.0, 1H, H-C*H*-CONRR); 3.11−3.21 (m, 3H, H_7, $H_{7'}$, H_5); 3.44−3.71 (m, 8H, -N(C*H*$_2$-C*H*$_2$)$_2$N-); 7.06 (d, J = 5.4, 1H, H_2); 7.37 (d, J = 5.4, 1H, H_3). ^{13}C NMR ($CDCl_3$): δ 25.7, 31.5, 33.2, 42.0, 44.2, 45.7 (C_5, C_6, C_7, -*C*H$_2$-CONRR, -N(*C*H$_2$-*C*H$_2$)$_2$N-); 28.7 (-COO-C(*C*H$_3$)$_3$); 80.6 -COO-*C*(CH$_3$)$_3$); 123.7, 125.4 (C_2, C_3); 137.1, 155.6 (C_{3a}, C_{7a}); 156.4 (N-*C*O-O-); 170.5 (-*C*ONRR); 194.3 (C_4). MS (FAB, *m*/*z*): 379 (MH^+). Anal. ($C_{19}H_{26}N_2O_4S$) C, H, N.

***N*^{1}-[(4-Oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-5-yl)-acetyl]-*N*^{4}-(*o*-methoxyphenyl)piperazine (20f):** yield 80%, mp 135−138 °C (AcOEt). IR: 1668, 1644. ^{1}H NMR ($CDCl_3$): δ 2.02−2.08 (m, 1H, H_6); 2.34 (dd, 1H, J_{gem} = 16.1, J_{vic} = 8.04, *H*CH-CONRR); 2.41−2.49 (m, 1H, J = 12.8, 8.0, 4.1, H_6); 3.02−3.17 (m, 7H, H_7, H_7, H_5, -CON(CH$_2$-C*H*$_2$)$_2$N-); 3.25 (dd, 1H, J_{gem} = 16.1, J_{vic} = 3.8, HC*H*-CONRR); 3.67−4.12 (m, 4H, -CON-(C*H*$_2$-CH$_2$)$_2$N-); 3.88 (s, 3H, -OCH$_3$); 6.87−6.94 (m, 3H, $H_{4'}$, $H_{5'}$, $H_{6'}$); 7.03 (dd, 1H, J_o = 5.6, J_m = 3.6, $H_{3'}$); 7.06 (d, 1H, J = 5.3, H_2); 7.38 (d, 1H, J = 5.3, H_3). ^{13}C NMR ($CDCl_3$): δ 26.1, 33.1, 34.3, 43.8, 44.8, 52.4 (C_5, C_6, C_7, -*C*H$_2$-CON(*C*H$_2$-*C*H$_2$)$_2$N-); 56.5 (-OCH$_3$); 113.8 ($C_{6'}$); 118.6 ($C_{3'}$); 120.6 ($C_{5'}$); 122.6, 124.3, 125.3 (C_2, C_3, $C_{4'}$); 153.1 ($C_{2'}$); 156.4 (C_{3a}); 171.0 (-*C*ONRR); 195.4 (C_4). Anal. ($C_{21}H_{24}N_2O_3S$) C, H, N.

***N*-[(7-Oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-6-yl)-acetyl]-4-(*p*-fluorobenzoyl)piperidine (27a):** yield 70%, mp 162−164 °C (cyclohexane). IR: 1682, 1646. ^{1}H NMR ($CDCl_3$): δ 1.62−2.16 (m, 5H, -N(CH$_2$-C*H*$_2$)$_2$CH-, H_5); 2.27−2.44 (m, 2H, -*H*CH-CONRR, H_5); 2.80−2.98 (m, 3H, -CON(*H*CH-CH$_2$)$_2$CH-, H_4, H_4); 3.08−3.31 (m, 3H, HC*H*-CONRR, -CON(HC*H*-CH$_2$)$_2$-CH-, H_6); 3.45−3.52 (m, 1H, C*H*-CO-Ph); 4.03−4.12 (m, 1H, -CON(HC*H*-CH$_2$)$_2$CH-); 4.56−4.63 (m, 1H, -CON(HC*H*-CH$_2$)$_2$-CH-); 6.95 (d, 1H, J = 4.9, H_3); 7.15 (t, 2H, J = 8.4, *o*-F-Ph); 7.60 (d, 1H, J = 4.9, H_2); 7.98 (dd, 2H, J = 5.7, *m*-F-Ph). ^{13}C NMR ($CDCl_3$): δ 26.3 (C_5); 28.9 (-N(CH$_2$-*C*H$_2$)$_2$C-); 31.3 (C_4); 33.2 (-*C*H$_2$-CONRR); 43.6 (-N(CH$_2$-CH$_2$)$_2$*C*H-); 44.7 (C_6); 45.5 (-N(*C*H$_2$-CH$_2$)$_2$CH-); 116.30 (d, 2C, J_{C-F} = 21.8, *o*-F-Ph); 128.5, 134.4 (C_2, C_3); 131.2 (d, 2C, J = 9.0, *m*-F-Ph); 132.5 (*p*-F-Ph); 136.5 (C_{3a}); 152.8 (C_{7a}); 165.9 (d, J = 251, F-*C*); 170.1 (-*C*ONRR); 193.7 (C_7); 200.4 (-*C*O-Phe-F). MS (FAB, *m*/*z*): 399 (MH^+). Anal. ($C_{22}H_{22}FNO_3S$) C, H, N.

***N*-[(7-Oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-6-yl)-acetyl]-4-(6-fluorobenzisoxazol-3-yl)piperidine (27b):** yield 75%, mp 148−150 °C (cyclohexane). IR: 1678, 1642. ^{1}H NMR ($CDCl_3$): δ 1.92−2.19 (m, 5H, -N(CH$_2$-C*H*$_2$)$_2$CH-, H_5); 2.30−2.40 (m, 2H, -*H*CH-CON<, H_5); 2.95−3.03 (m, 3H, -N(*H*CH-CH$_2$)$_2$CH-, H_4, H_4); 3.20−3.39 (m, 4H, HC*H*-CON<, -N(HC*H*-CH$_2$)$_2$CH-, H_6, -CH$_2$)$_2$C*H*-); 4.08−4.15 (m, 1H, -N(HC*H*-CH$_2$)$_2$-CH-); 4.62−4.76 (m, 1H, -N(HC*H*-CH$_2$)$_2$CH-); 6.95 (d, 1H, J = 4.9, H_3); 7.08 (t, 1H, J = 8.7, $H_{5'}$); 7.24 (s, 1H, $H_{7'}$); 7.60 (d, 1H, J = 4.9, H_2); 7.81 (dd, 1H, J_{4-5} = 8.7, J_{4-F} = 5.1, $H_{4'}$). ^{13}C NMR ($CDCl_3$): δ 26.3 (C_5); 30.6 (-N(CH$_2$-CH$_2$)$_2$C-); 31.5 (C_4); 33.3 (-*C*H$_2$-CONRR); 42.2 (-N(CH$_2$-CH$_2$)$_2$*C*H-); 44.7 (C_6); 45.8 (-N(*C*H$_2$-CH$_2$)$_2$CH-); 97.9 (d, J_{C-F} = 27.0, $C_{7'}$); 113.0 (d, J = 25.1, $C_{5'}$); 117.3 ($C_{3\acute{a}}$); 123.1 (d, J_{C-F} = 11.1, $C_{4'}$); 128.5, 134.4 (C_2, C_3); 136.5 (C_{3a}); 152.8 (C_{7a}); 160.7 ($C_{3'}$); 164.2 (d, J_{C-F} = 13.7, $C_{7\acute{a}}$); 164.5 (d, J_{C-F} = 250.7, $C_{6'}$); 170.2 (-*C*ONRR); 193.6 (C_7). MS (FAB, *m*/*z*): 413.7 (MH^+). Anal. ($C_{22}H_{21}FN_2O_3S$) C, H, N.

General Procedure for Synthesis of Ketoamides 19b and 27a,b (Table 5) Using BOP-Cl as Coupling Reagent. *N*-[(4-Oxo-4*H*-5,6-dihydrocyclopenta[*b*]thiophene-5-yl)-acetyl]-4-(6-fluorobenzisoxazol-3-yl)piperidine (19b). A solution of carboxylic acid **17** (0.45 g, 2.27 mmol) and 4-(6-fluorobenzisoxazol-3-yl)piperidine (0.5 g, 2.27 mmol) in CH_2Cl_2 (15 mL) was stirred under argon until dissolution was complete (10 min at 25 °C). TEA (0.61 mL, 4.5 mmol) and *N*,*N*-bis(2-oxo-3-oxazolidinyl)phosphoroamidic chloride (0.57 g, 2.27 mmol) were added, followed after 2 h by H_2O (15 mL), and the solution was then acidified to pH 1 with 6 N HCl. The organic phase was washed with H_2O (2 × 20 mL) and $NaHCO_3$, decantated, and dried with Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (AcOEt−hexane, 1:1) to give **16** (0.70 g, 85%) as a white solid of mp 154−156 °C (*i*-PrOH). IR: 1698, 1640. ^{1}H NMR ($CDCl_3$): δ 1.89−2.16 (m, 4H, -N(CH$_2$-C*H*$_2$)$_2$C); 2.60−2.68 (m, 1H, H_5); 2.91−3.00 (m, 2H, -N(*H*CH-CH$_2$)$_2$-); 3.10 (dd, 1H, J_{gem} = 16.6, J_{vic} = 2.9, H_6); 3.23−3.46 (m, 3H, -N(HCH-CH$_2$)$_2$C*H*-, -N(HC*H*-CH$_2$)$_2$-, HC*H*-CONRR); 3.57 (dd, 1H, J_{gem} = 17.4, J_{vic} = 7.0, H_6); 4.05 (dd, 1H, J_{gem} = 13.6, J_{vic} = 7.1, -HC*H*-CONRR); 4.57−4.66 (m, 1H, -N(HC*H*-CH$_2$)$_2$-); 7.08−7.11 (m, 1H, $H_{5'}$); 7.16 (d, 1H, J = 5.1, H_2); 7.25 (dd, 1H, $J_{7'-F}$ = 8.2, $J_{7'-5'}$ = 2.1, $H_{7'}$); 7.32 (d, 1H, J = 5.3, H_3); 7.63 (dd, 1H, $J_{4'-5'}$ = 8.7, $J_{4'-F}$ = 4.3, $H_{4'}$). ^{13}C NMR ($CDCl_3$): δ 30.7, 32.4, 35.0, 41.9, 45.6, 50.3 (C_5, C_6, -*C*H$_2$-CONRR, -N(*C*H$_2$-*C*H$_2$)$_2$*C*-); 97.9 (d, J_{C-F} = 26.8, $C_{7'}$); 113.1 (d, J_{C-F} = 25.3, $C_{5'}$); 117.4 ($C_{3'a}$); 120.0, 131.1 (C_2, C_3); 122.5 (d, J_{C-F} = 11.0, $C_{4'}$); 145.4 (C_{6a}); 160.5 ($C_{3'}$); 164.2 (d, J_{C-F} = 13.5, $C_{7\acute{a}}$); 164.6 (d, J_{C-F} = 251, $C_{6'}$); 167.5 (C_{3a}); 169.5 (-*C*ON<); 199.7 (C_4). MS (FAB, *m*/*z*): 398.7 (MH^+). Anal. ($C_{21}H_{19}FN_2O_3S$) C, H, N.

Compounds **27a** (yield 90%) and **27b** (yield 90%) were prepared similarly.

BOC Removal. *N*^{1}-[(1-Oxoindan-3-yl)carbonyl]piperazine (8d). A solution of amide **8c** (4 g, 11.63 mmol) in trifluoroacetic acid (TFA; 27 mL) was stirred under argon at room temperature for 20 min. Evaporation of the solvent under N_2 gave an oil which was dissolved in CH_2Cl_2. The resulting solution was washed several times with 0.1 N NaOH and water and dried (Na_2SO_4), and the solvent was distilled off. The oily residue was purified by flash chromatography (AcOEt) to give **8d** (86%) as a colorless oil. IR: 2925, 1712, 1640. ^{1}H NMR ($CDCl_3$): δ 2.88 (dd, 1H, J_{gem} = 18.5, J_{vic} = 7.8, H_2); 3.00 (dd, 1H, J_{gem} = 18.5, J_{vic} = 4.1, H_2); 2.83−3.04 (m, 4H, -N(C*H*$_2$-CH$_2$)$_2$NH); 3.61−3.75 (m, 4H, -N(CH$_2$C*H*$_2$)$_2$NH); 4.52 (m, 1H, J_{3-2} = 7.7, J_{3-2} = 4.1, H_3); 7.42−7.46 (m, 2H, H_4, H_5); 7.62 (t, 1H, J = 7.5, H_6); 7.78 (d, 1H, J = 7.6, H_7). Hydrochloride: mp 142−143 °C (*i*-PrOH). Anal. ($C_{14}H_{16}N_2O_2$·HCl) C, H, N.

The following piperazines were prepared similarly.

***N*^{1}-[(4-Oxo-4*H*-5,6-dihydrocyclopenta[b]thiophene-5-yl)acetyl]piperazine (19d):** yield 78%. IR: 2923, 1694, 1633. ^{1}H NMR ($CDCl_3$): δ 2.50 (dd, 1H, J_{gem} = 16.7, J_{vic} = 9.6, H_6); 2.53 (s, 1H, NH); 2.73−2.79 (m, 4H, -N(C*H*$_2$-CH$_2$)$_2$NH); 2.86 (dd, 1H, J_{gem} = 17.5, J_{vic} = 3.0, *H*CH-CON<); 2.96 (m, 1H, J_{gem} = 16.7, J_{vic} = 3.1, $H_{6'}$); 3.28−3.59 (m, 5H, -N(CH$_2$-C*H*$_2$)$_2$-NH, H_5); 3.49 (dd, 1H, J_{gem} = 17.5, J_{vic} = 9.1, HC*H*-CONRR); 7.08 (d, 1H, J = 5.1, H_2); 7.25 (d, 1H, J = 5.3, H_3). MS (FAB, *m*/*z*): 265 (MH^+). Hydrochloride: mp 264−266 (MeOH/ether). Anal. ($C_{13}H_{16}N_2O_2S$·HCl) C, H, N.

***N*^{1}-[(4-Oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-5-yl)-acetyl]piperazine (20d):** yield 80%. IR: 2947, 1667, 1633. ^{1}H NMR ($CDCl_3$): δ 1.97−2.04 (m, 1H, H_6); 2.27 (dd, 1H, J_{gem} = 16.0, J_{vic} = 7.7, *H*-CH-CON<); 2.37−2.43 (m, 1H, $H_{6'}$); 2.82−2.89 (m, 4H, -N(CH$_2$-C*H*$_2$)$_2$NH); 3.06−3.12 (m, 3H, H_7, $H_{7'}$, H_5); 3.16 (dd, 1H, J_{gem} = 16.0, J_{vic} = 3.8, H-C*H*-CONRR); 3.47−3.68 (m, 4H, -N(C*H*$_2$-CH$_2$)$_2$NH); 7.04 (d, 1H, J = 5.3, H_2); 7.36

(d, $J = 5.3$, 1H, H_3). ^{13}C NMR ($CDCl_3$): δ 25.7, 31.4, 33.0, 43.2, 44.1, 46.3 (C_5, C_6, C_7, -CH_2-CON(CH_2-CH_2)$_2$NH); 123.7, 125.4 (C_2, C_3); 137.1, 155.8 (C_{3a}, C_{7a}); 170.2 (-CON<); 194.5 (C_4). MS (FAB, *m*/*z*): 279 (MH^+). Hydrochloride: mp 226.5−228.5 °C (MeOH/ether). Anal. ($C_{14}H_{18}N_2O_2S$·HCl) C, H, N.

Synthesis of Amides 20a,c,f from Ester 16 Using Trimethylaluminum. *N*-[(4-Oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-5-yl)acetyl]-4-(*p*-fluorobenzoyl)piperidine (20a). A 2 M solution of trimethylaluminum in hexane (3 mL, 6 mmol) was added at 0 °C under argon to a solution of *N*-(*tert*-butoxycarbonyl)piperazine in anhydrous CH_2Cl_2 (3 mL). After stirring at room temperature for 15 min, a solution of ester **16** (0.7 g, 3 mmol) in anhydrous CH_2Cl_2 (5 mL) was added dropwise, and the resulting mixture was refluxed for 48 h. After cooling, 10% HCl was added until cessation of gas release. The organic layer was separated and dried (Na_2SO_4), and the solvent was distilled off. The oily residue was purified by flash chromatography (hexane/AcOEt, 1:1) to give **20a** (15%): mp 143−145 °C (*i*-PrOH).

Compounds **20c**,**f** (Table 5) were prepared similarly.

General Procedure for Synthesis of Ethylene Ketals 9a,d,f, 21d, 22a,b,f, and 28a,b (Table 6). *N*-[(1-Oxoindan-3-yl)carbonyl]-4-(*p*-fluorobenzoyl)piperidine Bis(ethylene ketal) (9a). A stirred solution of amide **8a** (3 g, 8.2 mmol), ethylene glycol (50.84 g, 0.82 mol), and *p*-TsOH (50 mg) in anhydrous toluene (75 mL) was refluxed in a Dean−Stark apparatus for 96 h with azeotropic distillation of water. After cooling, the toluene solution was washed several times with 10% Na_2CO_3 and water and dried (Na_2SO_4), and the solvent was removed under reduced pressure. The resulting crude dioxolane (3.46 g, 93%), an orange oil with only one carbonyl band in its IR spectrum (at 1641 cm^{-1}), was used in the next step without further purification. A sample crystallized slowly on standing: mp 138−139 °C. MS (FAB, *m*/*z*): 454 (MH^+).

All the other ethylene ketals listed in Table 6 were prepared similarly as crude oils, checked by IR and ^{1}H NMR spectroscopy, and used in the following step without further purification.

General Procedure for Synthesis of Aminoketones 10a,f (Table 1), 23a,b (Table 2), 24a,b,f (Table 3), and 29a,b (Table 4). N^1-[(1-Oxoindan-3-yl)methyl]-4-(*p*-fluorobenzoyl)piperidine (10a). A solution of amide bis(ethylene ketal) **9a** (2.08 g, 4.6 mmol) in anhydrous ether (20 mL) was added dropwise under argon to a stirred suspension of $LiAlH_4$ (0.70 g, 18.5 mmol) in anhydrous ether (40 mL). The reaction mixture was heated under reflux for 8 h, cooled to 0 °C in an ice bath, and then quenched by sequential dropwise addition of H_2O (1 mL), NaOH 10% (2 mL), and H_2O (4 mL). The coarse precipitate formed was filtered out and thoroughly washed with ether. The combined filtrates were treated with 10% HCl and heated under reflux for 1−2 h. On cooling, the aqueous phase was made alkaline with 10% NaOH and extracted with CH_2Cl_2 three times, the combined organic extracts were dried (Na_2SO_4), and the solvent was removed in vacuo. The residue was dissolved in anhydrous ether, and ether-saturated HCl gas was cautiously added to the resulting solution. The white precipitate formed was recovered and kept overnight in a vacuum desiccator. Recrystallized from isopropyl alcohol, the hydrochloride melted at 229−231 °C. Anal. ($C_{22}H_{22}FNO_2$·HCl) C, H, N. Data for free base: ^{1}H NMR ($CDCl_3$): δ 1.83−1.90 (4H, -N(CH_2CH_2)$_2$-CH-); 2.14−2.25 (m, 2H, -N(*H*CHCH$_2$)-CH-); 2.47 (dd, 1H, $J_{gem} = 12.2$, $J_{vic} = 8.2$, -*H*CH-NRR); 2.50 (dd, 1H, $J_{gem} = 19.3$, $J_{vic} = 3.1$, H_2); 2.65 (dd, 1H, $J_{gem} = 12.3$, -HC*H*-NRR); 2.82 (dd, 1H, $J_{gem} = 19.3$, $J_{vic} = 7.5$, H_2); 2.99−3.05 (m, 2H, -N(HC*H*CH$_2$)$_2$-CH-); 3.22 (m, 1H, H_3); 3.55 (m, 1H, -N(CH_2-CH_2)$_2$-C*H*-); 7.13 (t, 2H, $J = 8.6$, *o*-F-Ph); 7.38 (t, 1H, $J = 7.3$, H_6); 7.55−7.60 (m, 1H, H_5); 7.69 (d, 1H, $J = 7.5$, H_4); 7.73 (d, 1H, $J = 7.6$, H_7); 7.97 (dd, 2H, $J = 8.8$, 5.5, *o*-CO-Ph). ^{13}C NMR ($CDCl_3$): δ 29.04; 36.28; 42.22; 43.89; 53.75; 64.51; 116.05 (d, 2C, $J_{C-F} = 21.89$, *o*-F-Ph); 123.74 (C_4); 126.91 (C_7); 128.03 (C_6); 131.14 (d, 2C, $J_{C-F} = 9.8$, *m*-F-Ph); 132.63 (CO-$C_{aromatic}$); 134.77 (C_5); 137.17 (C_{7a}); 157.65 (C_{3a}); 164.21; 167.58; 201.40 (*C*O-Ph); 206.58 (C_1). MS (FAB, *m*/*z*): 352 (MH^+).

The following amines were prepared similarly.

***N*^{1}-(*o*-Methoxyphenyl)-*N*^{4}-[(1-oxoindan-3-yl)methyl]piperazine (10f):** yield 85%, mp 100−102 °C (AcOEt). IR: 2936, 2813, 1716. ^{1}H NMR ($CDCl_3$): δ 2.50 (dd, 1H, $J_{gem} = 12.4$, $J_{vic} = 8.4$, *H*CH-NRR); 2.65 (dd, 1H, $J_{gem} = 19.2$, $J_{vic} = 3.1$, H_2); 2.61−2.77 (m, 4H, -CH_2-N(CH_2CH_2)$_2$-N-); 2.74 (dd, 1H, $J_{gem} = 12.4$, $J_{vic} = 6.6$, -HC*H*-NRR); 2.82 (dd, 1H, $J_{gem} = 19.2$, $J_{vic} = 7.4$, H_2); 3.02−3.19 (m, 4H, -CH_2-N(CH_2CH_2)$_2$-N-); 3.49−3.62 (m, 1H, H_3); 3.83 (s, 3H, -OCH_3); 6.81−7.01 (m, 4H, $H_{3'}$, $H_{4'}$, $H_{5'}$, $H_{6'}$); 7.38 (t, 1H, $J = 7.2$, H_6); 7.59 (t, 1H, $J = 7.5$, H_5); 7.67 (d, 1H, $J = 7.6$, H_4); 7.72 (d, 1H, $J = 7.6$, H_7). ^{13}C NMR ($CDCl_3$): δ 36.37; 42.50; 51.12; 54.09; 55.76; 64.56; 111.53 ($C_{6'}$); 118.61 ($C_{3'}$); 121.38 ($C_{5'}$); 123.94 (C_5); 137.41 (C_{7a}); 141.67 ($C_{1'}$); 152.65 ($C_{2'}$); 157.75 (C_{3a}); 206.77 (C_1). MS (FAB, *m*/*z*): 337 (MH^+). Hydrochloride: mp 220−222 °C (*i*-PrOH). Anal. ($C_{21}H_{23}N_2O_2$·2HCl) C, H, N.

***N*-[(4-Oxo-4*H*-5,6-dihydrocyclopenta[*b*]thiophene-5-yl)ethyl]-4-(*p*-fluorobenzoyl)piperidine (23a):** yield 70%. IR: 1712, 1685. ^{1}H NMR ($CDCl_3$): δ 1.75−1.85 (m, 6H, -CH_2-CH_2-NRR, -CH_2)$_2$CH-); 1.88−2.19 (m, 4H, -N(CH_2-CH_2)$_2$CH-); 2.21−2.23 (m, 1H, H_5); 2.52 (t, 2H, $J = 7.3$, -CH_2-NRR); 2.93 (dd, 1H, $J_{gem} = 17.4$, $J_{vic} = 2.7$, H_6); 3.06−3.11 (m, 1H, -CH_2)$_2$-C*H*-CO-); 3.40 dd, 1H, $J_{gem} = 17.3$, $J_{vic} = 6.9$, H_6); 7.12−7.18 (m, 3H, $J = 5.3$, H_2, *o*-F-Ph); 7.34 (d, 1H, $J = 5.2$, H_3); 7.97 (dd, 2H, $J = 8.9$, 5.4, *m*-F-Ph). ^{13}C NMR ($CDCl_3$): δ 28.9(2C, -N(CH_2CH_2)$_2$CH); 30.1 (C_6); 31.3, 43.9, 52.0, 53.4 (2C, -N(*C*H_2-CH_2)$_2$CH-); 53.5, 56.4, 116.1 (d, 2C, $J_{C-F} = 21.8$, *o*-F-Ph); 120.0 (C_2); 131.0 (C_3); 131.2 (d, 2C, $J_{C-F} = 9.4$, *m*-F-Ph); 132.8 (d, $J_{C-F} = 3.0$, *p*-F-Ph); 145.8 (C_{6a}); 166.02 (d, $J_{C-F} = 251$, *C*-F); 169.3 (C_{3a}); 200.5 (C_4); 201.4 (-*C*O-Ph). MS (FAB, *m*/*z*): 372 (MH^+). Oxalate: mp 172−173 °C (AcOEt). Anal. ($C_{21}H_{22}$-FNO_2S·$C_2O_4H_2$) C, H, N.

***N*-[(4-Oxo-4*H*-5,6-dihydrocyclopenta[*b*]thiophene-5-yl)ethyl]-4-(6-fluorobenzisoxazol-3-yl)piperidine (23b):** yield 75%. IR: 2924, 1698, 1615. ^{1}H NMR ($CDCl_3$): δ 1.77−2.25 (m, 9H, H_5, -N(*H*CH-CH_2)$_2$-, -CH_2-CH_2N<); 2.54 (t, 2H, $J = 7.3$, -CH_2N<); 2.93 (dd, 1H, $J_{gem} = 17.3$, $J_{vic} = 2.8$, H_6); 3.02−3.13 (m, 3H, -N(HC*H*-CH_2)$_2$C*H*-); 3.39 (dd, 1H, $J_{gem} = 17.3$, $J_{vic} = 6.9$, $H_{6'}$); 7.04 (dt, 1H, $J = 8.8$, 2.1, $H_{5''}$); 7.15 (d, 1H, $J = 5.1$, H_2); 7.22 (dd, 1H, $J_{7''-F} = 8.5$, $J_{7''-5''} = 2.1$, $H_{7''}$); 7.32 (d, 1H, $J = 5.1$, H_3); 7.67 (dd, 1H, $J_{4''-5''} = 8.7$, $J_{4''-F} = 5.1$, $H_{4''}$). ^{13}C NMR ($CDCl_3$): δ 29.0, 30.7, 31.2, 34.9 (C_5, C_6, -CH_2-CH_2-NRR, -CH_2)$_2$-); 51.9 (-CH_2)$_2$C*H*-); 53.8 (-CH_2N<); 56.4 (-N(*C*H_2-CH_2)$_2$-); 97.8 (d, $J_{C-F} = 26.7$, $C_{7'}$); 112.7 (d, $J_{C-F} = 25.2$, $C_{5'}$); 117.6 ($C_{3a'}$); 123.0 (d, $J_{C-F} = 11.0$, $C_{4'}$); 120.0, 131.1 (C_2, C_3); 161.4 ($C_{3'}$); 164.2 (d, $J_{C-F} = 13.7$, $C_{7a'}$); 165.0 (d, $J_{C-F} = 250$, $C_{6'}$); 200.4 (C_4). MS (FAB, *m*/*z*): 385 (MH^+). Hydrochloride: mp 230−232 °C (*i*-PrOH). Anal. ($C_{21}H_{21}FN_2O_2S$·HCl) C, H, N.

***N*-[(4-Oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-5-yl)ethyl]-4-(*p*-fluorobenzoyl)piperidine (24a):** yield 85%. IR: 1678, 1680. ^{1}H NMR ($CDCl_3$): δ 1.59−1.85 (m, 6H, -CH_2-CH_2-NRR, -CH_2)$_2$CH-); 1.91−2.36 (m, 5H, H_6, -N(CH_2-CH_2)$_2$-CH-); 2.49 (t, 2H, $J = 8.0$, -CH_2-NRR); 2.45−2.58 (m, 1H, H_6); 2.96−3.10 (m, 3H, H_7, $H_{7'}$, -CH_2)$_2$-C*H*-CO-); 3.14−3.20 (m, 1H, H_5); 7.05 (d, 1H, $J = 5.3$, H_2); 7.13 (t, 2H, $J = 8.7$, *o*-F-Phe); 7.32 (d, 1H, $J = 5.2$, H_3); 7.95 (dd, 2H, $J = 8.7$, 5.5, *m*-F-Ph). ^{13}C NMR ($CDCl_3$): δ 24, 26, 29, 30 (C_6, C_7, -CH_2-CH_2NRR, -CH_2)$_2$CH-); 43, 44 (C_5, -CH_2)$_2$CH-); 53, 56 (-CH_2-N(*C*H_2-CH_2)$_2$-CH-); 116.0 (d, 2C, $J_{C-F} = 21.8$, *o*-F-Ph); 123.4, 125.3 (C_2, C_3); 131.1 (d, 2C, $J_{C-F} = 9.0$, *m*-F-Ph); 132.6 (d, $J_{C-F} = 3.0$, *p*-F-Ph); 137, 155 (C_{3a}, C_{7a}); 167.3 (d, $J_{C-F} = 254$, *C*-F); 195.3 (C_4); 201.3 (-*C*O-Ph). MS (FAB, *m*/*z*): 386 (MH^+). Hydrochloride: white crystals, mp 278−280 °C (MeOH/ether). Anal. ($C_{22}H_{24}$-FNO_2S·HCl) C, H, N.

***N*-[(4-Oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-5-yl)ethyl]-4-(6-fluorobenzisoxazol-3-yl)piperidine (24b):** yield 75%. IR: 2922, 1668, 1615. ^{1}H NMR ($CDCl_3$): δ 1.59−1.85 (m, 6H, -CH_2-CH_2-NRR, -CH_2)$_2$CH-); 1.91−2.36 (m, 5H, H_6, -N(CH_2-CH_2)$_2$CH-); 2.49 (t, 2H, $J = 8.0$, -CH_2-NRR); 2.45−2.58 (m, 1H, H_6); 2.96−3.10 (m, 3H, H_7, H_7, -CH_2)$_2$-C*H*-CO-); 3.14−3.20 (m, 1H, H_5); 7.05 (d, 1H, $J = 5.3$, H_2); 7.13 (t, 2H, $J = 8.7$, *o*-F-Ph); 7.32 (d, 1H, $J = 5.2$, H_3); 7.95 (dd, 2H, $J = 8.7$, 5.5, *m*-F-Ph). ^{13}C NMR ($CDCl_3$): δ 24, 26, 29, 30 (C_6, C_7, -CH_2-CH_2NRR, -CH_2)$_2$CH-); 43, 44 (C-5, -CH_2)$_2$CH-); 53, 56 (-CH_2-N(*C*H_2-CH_2)$_2$-CH-); 116.0 (d, 2C, $J_{C-F} = 21.8$, *o*-F-Ph); 123.4, 125.3 (C_2, C_3);

131.1 (d, 2C, J_{C-F} = 9.0, *m*-F-Ph); 132.6 (d, J_{C-F} = 3.0, *p*-F-Ph); 137, 155 (C_{3a}, C_{7a}); 167.3 (d, J_{C-F} = 254, *C*-F); 195.3 (C_4); 201.3 (-*C*O-Ph). MS (FAB, *m*/*z*): 399 (MH^+). Hydrochloride: mp 248−249 °C (AcOEt). Anal. ($C_{22}H_{23}FN_2O_2S$·HCl) C, H, N.

***N*¹-[(4-Oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-5-yl)ethyl]-*N*⁴-(*o*-methoxyphenyl)piperazine (24f):** yield 85%. IR: 1670. ^{1}H NMR ($CDCl_3$): δ 1.65−1.78 (m, 2H, -CH_2-CH_2-NRR); 1.96−2.18 (m, 2H, H_6, H_6); 2.50−2.71 (m, 7H, -CH_2-N(CH_2-CH_2)$_2$N-, H_7); 3.03−3.17 (m, 6H, H_5, H_7, -CH_2-CH_2)$_2$N-); 3.86 (s, 3H, -OCH_3); 6.84−7.02 (m, 4H, Ph); 7.05 (d, 1H, J = 5.2, H_2); 7.38 (d, 1H, J = 5.2, H_3). ^{13}C NMR ($CDCl_3$): δ 24.9, 26.7, 30.3 (C_6, C_7, -CH_2-CH_2N<); 45.0 (C_5); 50.9, 53.8 (-N(CH_2-CH_2)$_2$N-); 55.7 (-OCH_3); 61.7 (-CH_2-NRR); 111.5 ($C_{6'}$); 118.6 ($C_{3'}$); 121.3 ($C_{5'}$); 123.3, 123.7, 125.0 (C_2, C_3, $C_{4'}$); 137.6 (C_{7a}); 141.6 ($C_{1'}$); 152.6 ($C_{2'}$); 155.6 (C_{3a}); 195.4 (C_4). MS (FAB, *m*/*z*): 371 (MH^+). Hydrochloride: mp 233.5−235.5 °C (MeOH−ether). Anal. ($C_{21}H_{26}N_2O_2S$·2HCl) C, H, N.

***N*-[(7-Oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-6-yl)ethyl]-4-(*p*-fluorobenzoyl)piperidine (29a):** yield 65%. IR: 1678, 1653, 1596. ^{1}H NMR ($CDCl_3$): δ 1.59−2.03 (m, 7H, -CH_2-CH_2NRR, -N(CH_2-CH_2)$_2$CH-, H_5); 2.08−2.32 (m, 4H, -N(CH_2-CH_2)$_2$CH-); 2.52 (t, 2H, J = 7.9, -CH_2NRR); 2.47−2.67 (m, 1H, H_5); 2.79−3.04 (m, 3H, H_4, H_4, -CH_2)$_2$C*H*-); 3.14−3.24 (m, 1H, H_6); 6.94 (d, 1H, J = 4.9, H_3); 7.13 (t, 2H, J = 8.7, *o*-F-Ph); 7.58 (d, 1H, J = 4.9, H_2); 7.96 (dd, 2H, J = 8.8, 5.5, *m*-F-Ph). ^{13}C NMR ($CDCl_3$): δ 25.4 (-CH_2-CH_2NRR); 26.9 (C_5); 29.1 (-N(CH_2-CH_2)$_2$CH-); 30.2 (C_4); 44.0 (C_6); 45.5 (-CH_2)$_2$-*C*H-); 53.5 (-CH_2NRR); 56.6 (-N(CH_2-CH_2)$_2$CH-); 116.15 (d, 2C, J = 21.8, *o*-F-Ph); 128.5, 134.1 (C_2, C_3); 131.2 (d, 2C, J = 9.0, *m*-F-Ph); 132.8 (*p*-F-Ph); 136.9 (C_{3a}); 152.1 (C_{7a}); 165.5 (d, J = 251, F-C); 194.6 (C_7); 201.4 (-*C*O-Ph-F). MS (FAB, *m*/*z*): 386 (MH^+). Hydrochloride: mp 262−264 °C (*i*-PrOH). Anal. ($C_{22}H_{24}FNO_2S$·HCl) C, H, N.

***N*-[(7-Oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-6-yl)ethyl]-4-(6-fluorobenzisoxazol-3-yl)piperidine (29b):** yield 80%. IR: 1636. ^{1}H NMR ($CDCl_3$): δ 1.57−2.00 (m, 7H, H_5, -CH_2-CH_2NRR, -N(CH_2-CH_2)$_2$CH-); 2.04−2.32 (m, 4H, -N(CH_2-CH_2)$_2$CH-); 2.47−2.69 (m, 3H, -CH_2NRR, H_5); 2.80−3.11 (m, 4H, H_4, H_4, H_6, -CH_2)$_2$C*H*-); 6.95 (d, 1H, J = 4.9, H_3); 7.04 (dt, 1H, J = 8.8, 2.1, $H_{5'}$); 7.21−7.25 (m, 1H, $H_{7'}$); 7.59 (d, 1H, J = 4.9, H_2); 7.68 (dd, 1H, $J_{4'-5'}$ = 8.7, $J_{4'-F}$ = 5.1, $H_{4'}$). ^{13}C NMR ($CDCl_3$): δ 25.4, 27.0, 28.3, 30.2 (C_4, C_5, -CH_2-CH_2NRR, -CH_2)$_2$-CH-); 41.6, 45.5 (C_6, -CH_2)$_2$C*H*-); 53.8 (-CH_2NRR); 56.7 (-N(CH_2-); 97.8 (d, J_{C-F} = 26.6, $C_{7'}$); 112.7 (d, J_{C-F} = 25.5, $C_{5'}$); 117.7 ($C_{3á}$); 123.0 (d, J_{C-F} = 11.0, $C_{4'}$); 128.5, 134.1 (C_2, C_3); 137.0 (C_{3a}); 152.1 (C_{7a}); 161.5 ($C_{3'}$); 164.2 (d, J_{C-F} = 13.4, $C_{7a'}$); 165.0 (d, J_{C-F} = 250, $C_{6'}$); 194.5 (C_7). MS (FAB, *m*/*z*): 399 (MH^+). Hydrochloride: mp 246−248 °C (*i*-PrOH). Anal. ($C_{22}H_{23}FN_2O_2S$·HCl) C, H, N.

General Procedure for Preparing *N*¹-[(Oxocycloalkanyl)alkyl]-*N*⁴-[3-(*p*-fluorobenzoyl)propyl]piperazines 10e (Table 1), 23e (Table 2), and 24e (Table 3). *N*¹-[(1-Oxoindan-3-yl)methyl]-*N*⁴-[3-(*p*-fluorobenzoyl)propyl]piperazine (10e). A solution of 4-chloro-1,1-(ethylenedioxy)-1-(4-fluorophenyl)butane (0.52 g, 21 mmol) in MIK (15 mL) was added under argon with stirring to a mixture of ethylene ketal **10d** (0.62 g, 2 mmol), anhydrous Na_2CO_3 (1.65 g, 56 mmol), and a few crystals of KI (0.032 g, 0.2 mmol) in MIK (45 mL). After refluxing with vigorous stirring for 20 h, the mixture was allowed to stand at room temperature overnight before filtration. The filtrate was condensed under reduced pressure to give 0.25 g of a white oil. This product was treated with 10% HCl, and the resulting suspension was vigorously stirred at 35−40 °C for 2 h. After cooling, the aqueous layer was made alkaline with 10% NaOH and extracted several times with ether. 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 dry ether-saturated HCl gas. The white precipitate formed was recovered and kept overnight in a vacuum desiccator. Recrystallization from MeOH/ether afforded 0.18 g (35%) of amine **10e** hydrochoride as white crystals, mp 216−217 °C (*i*-PrOH). Anal. ($C_{24}H_{27}FN_2O_2$·2HCl) C, H, N. Data for the free base: IR: 2813, 1715, 1680. ^{1}H NMR ($CDCl_3$): δ 1.88 (c, 2H, J = 7.1, >N-CH_2C$H_2$$CH_2$-CO-); 2.23−2.52 (m, 12H, RRN-C$H_2$$CH_2$-$CH_2$-CO-, -N(C$H_2CH_2$)$_2$-N-, -*H*CH-NRR, 1H$_2$); 2.58 (dd, 1H, J_{gem} = 12.2, J_{vic} = 6.6, -HC*H*-NRR); 2.74 (dd, 1H, J_{gem} = 19.3, J_{vic} = 7.4, H_2); 2.91 (t, 2H, J = 7.1, -N-$CH_2$$CH_2CH_2$-CO-); 3.42−3.49 (m, 1H, H_3); 7.06 (t, J = 8.6, 2H, *o*-F-Ph); 7.31 (t, 1H, J = 7.2, H_6); 7.49−7.58 (m, 2H, H_4, H_5); 7.66 (d, 1H, J = 7.6, H_7); 7.93 (dd, 2H, J = 5.4−8.8, *o*-CO-Ph). ^{13}C NMR ($CDCl_3$): δ 21.79; 36.21; 36.44; 42.27; 53.35; 53.56; 57.91; 64.26; 115.71; 115.86 (d, 2C, J_{C-F} = 21.9, *o*-F-Ph); 123.78 (C_4); 126.70 (C_7); 128.02 (C_6); 130 (d, 2C, J_{C-F} = 9.8, *m*-F-Ph); 134.75 (C_5); 137.21 (C_{7a}); 157.56; 198.67 (CO-Ph); 206.61 (C_1). MS (FAB, *m*/*z*): 395 (MH^+).

***N*¹-[(4-Oxo-4*H*-5,6-dihydrocyclopenta[*b*]thiophene-5-yl)ethyl]-*N*⁴-[3-(*p*-fluorobenzoyl)propyl]piperazine (23e)** [yield 58%, mp 89−90 °C (cyclohexane); hydrochloride, mp 244−246 °C (*i*-PrOH); 2,4-dinitrophenylhydrazone, mp 198−199 °C (MeOH)] and ***N*⁴-[3-(*p*-fluorobenzoyl)propyl]-*N*¹-[(4-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-5-yl)ethyl]piperazine (24e)** [yield 50%; hydrochloride, 234−236 °C (MeOH/ether)] were prepared as previously reported.[42]

***β*-(2-Thenoyl)-*γ*-butyrolactone (31).** To a stirred solution of *β*-(α-thenoyl)propionic acid (**30**; 10 g, 54.3 mmol) in 0.5 N NaOH (120 mL) was added 37% CH_2O (5.2 mL). After 1 h at room temperature, the mixture was brought to pH 1 with 6 N HCl, and stirring was continued for 24 h. The white precipitate formed was recovered and washed with ether, and recrystallization from *i*-PrOH afforded **31** (9.05 g, 85%) as white crystals: mp 99−100 °C. IR: 1765 (COO), 1646 (CO). ^{1}H NMR ($CDCl_3$): δ 2.78 (dd, 1H, J_{gem} = 17.8, J_{vic} = 9.4, -H-C*H*-COO-), 3.03 (dd, 1H, J_{gem} = 17.8, J_{vic} = 7.9, -*H*-CH-COO-); 4.23−4.31 (m, 1H, Ar-CO-C*H*-); 4.48 (dd, 1H, J = 9.2, 7.0, HC*H*-OCO-); 4.61 (t, 1H, J = 8.9, *H*CH-OCO-); 7.20 (dd, 1H, J = 4.9, 3.9, H-4); 7.74 (dd, 1H, J = 3.9, 1.1, -C*H*=CH-); 7.76 (dd, 1H, J = 5.0, 1.0, -CH=CH-). ^{13}C NMR ($CDCl_3$): δ 31.3 (-*C*-COO-); 43.6 (Ar-CO-*C*); 69.5 (-*C*-O-CO-); 128.9; 133.1; 135.9; 142.5 (-CH=*C*-); 175.4 (-*C*OO-); 189.4 (Ar-*C*O-C). Anal. ($C_9H_8O_3S$) C, H.

***β*-(2-Thienyl)-*γ*-butyrolactone (32).** A suspension of Zn wool (21 g) and Hg_2Cl_2 (2.1 g) in a mixture of 6 N HCl (1 mL) and H_2O (31 mL) was stirred under argon for 5 min. After decantation, H_2O (15.6 mL), 6 N HCl (34.6 mL), toluene (21 mL), ketone **31** (10.5 g, 533.5 mmol), and glacial acetic acid (1 mL) were added. The reaction mixture was heated under reflux with continuous stirring for 48 h, during which time additional 6 N HCl (1 mL) and glacial acetic acid were added every 12 h. After cooling, the organic phase was dried (Na_2SO_4), and the solvent was removed under reduced pressure. The oily residue was purified by flash chromatography (silica gel, AcOEt/hexane, 1:3) to give **32** (4.7 g, 50%) as a colorless oil. IR: 1774. ^{1}H NMR ($CDCl_3$): δ 2.29 (dd, 1H, J_{gem} = 17.6, J_{vic} = 6.7, HC*H*-COO-); 2.63 (dd, 1H, J_{gem} = 17.6, J_{vic} = 8.2, *H*CH-COO-); 2.82−2.87 (m, 1H, Ar-CH_2-C*H*-); 2.97 (d, 2H, J = 7.5, Ar-CH_2-); 4.03 (dd,1H, J_{gem} = 9.2, J_{vic} = 6.0, *H*CH-O-CO-); 4.36 (dd, 1H, J_{gem} = 9.2, J_{vic} = 7.0, -H-C*H*-O-CO-); 6.80 (dd, 1H, J_{3-4} = 3.4, J_{3-5} = 1.0, H_3); 6.92 (dd, 1H, J_{4-5} = 5.1, J_{4-3} = 5.1, H-4); 7.15 (dd, 1H, J_{5-4} = 5.1, J_{5-3} = 1.1, H-5). ^{13}C NMR ($CDCl_3$): δ 33.4, 34.5, 37.7 (Ar-*C*-, Ar-C-*C*-, -*C*-COO-); 72.9 (-*C*-OCO-); 124.6; 126.1; 127.5; 140.9 (-CH=*C*H-CH_2-); 177.1 (-*C*OO-). MS (EI, *m*/*z*): 182 (M^+). Anal. ($C_9H_{10}O_2S$) C, H.

***γ*-Bromo-*β*-(2-thenyl)butyric Acid Methyl Ester (33).** HBr−AcOH (33%, 3.1 mL) was added dropwise under argon to a stirred solution of *β*-(2-thienyl)-*γ*-butyrolactone (**32**; 2.64 g, 15.9 mmol) in glacial acetic acid (35 mL) at 0 °C. After 15 min at room temperature the solution was heated at 80 °C for 4 h. After cooling, the reaction mixture was poured into ice−water and extracted with CH_2Cl_2 (3 × 25 mL). The organic phase was washed several times with water and dried (Na_2SO_4), and the solvent was distilled off to provide the *γ*-bromo-*β*-(2-thenyl)butyric acid (3.35 g, 75%), which was immediately esterified with CH_2N_2/ether as usual. IR: 1734. ^{1}H NMR ($CDCl_3$): δ 2.46−2.56 (m, 3H, -CH_2-COO-, -C*H*-CH_2-Br); 2.95−2.98 (m, 2H, Ar-CH_2-C); 3.45 (dd, 1H, J_{gem} = 10.4, J_{vic} = 4.3, *H*CH-Br); 3.54 (dd, 1H, J_{gem} = 10.4, J_{vic} = 3.9, HC*H*-Br); 3.69 (s, 3H, -COO-CH_3); 6.86 (dd, 1H, J_{3-4} = 3.4, J_{3-5} = 0.9, H_3); 6.93 (dd, 1H, J_{4-3} = 3.4, J_{4-5} = 5.1, H_4); 7.16 (dd, 1H, J_{5-4} =

5.1, $J_{5-3} = 1.2$, H_5). ^{13}C NMR ($CDCl_3$): δ 33.0, 36.9, 38.1, 38.9 (Ar-*C*-*C*-, -*C*-COO-, -*C*-Br); 52.2 (-COO-*C*H_3); 124.5, 126.6, 127.4 (-*C*H=*C*H-, -*C*H=*C*-); 141.1 (-CH=*C*-); 172.8 (-*C*OO-). MS (FAB, *m*/*z*): 277.9 (MH^+). Anal. ($C_{10}H_{13}BrO_2S$) C, H.

General Procedure for the Synthesis of γ-Amino-β-(2-thenyl)butyric Acid Methyl Ester Hydrochlorides 34a−c,f. To a solution of amine (9 mmol) and γ-bromo-β-thenylbutyric acid methyl ester (9 mmol) in MIK (35 mL) were added K_2CO_3 (2.5 g) and KI (0.045 g). This mixture was refluxed for 12 h. Inorganic salts were then filtered out, and the solvent was removed under reduced pressure. The resulting oil was dissolved in CH_2Cl_2, washed several times with water, and dried (Na_2SO_4). The CH_2Cl_2 was removed under reduced pressure to afford the desired aminomethyl ester in quantitative yields. After dissolution in anhydrous ether, ether-saturated HCl gas was cautiously added. The white precipitates formed were recovered and kept overnight in a vacuum desiccator; recrystallization from various solvents afforded **34a−c**,**f** as white crystals.

4-[(*p*-Fluorobenzoyl)piperidin-1-yl]-β-(2-thenyl)butyric acid methyl ester hydrochloride (34a): mp 190−191 °C (AcOEt). Anal. ($C_{22}H_{26}FNO_3S$·HCl) C, H, N. Spectral data for the free base: IR: 1732, 1678. ^1H NMR ($CDCl_3$): δ 1.76−1.81 (m, 4H, -N(CH_2-CH_2)$_2$CH-); 1.96−2.30 (m 6H, -CH_2-COO-, -N(*H*-CH-CH_2)$_2$CH-, -CH_2NRR); 2.42−2.49 (m, 1H, -C*H*-CH_2-NRR); 2.84−2.95 (m, 4H, -N(H-C*H*-CH_2)$_2$-, thienyl-CH_2-C-); 3.13−3.18 (m, 1H, -CH_2)$_2$-C*H*-CO); 3.65 (s, 3H, -COOCH_3); 6.78 (d, 1H, $J_{3-4} = 3.4$, H_3); 6.91 (dd, 1H, $J_{4,3} = 3.4$, $J_{4,5} = 5.1$, H_4); 7.09−7.16 (m, 3H, H_5, -CH=C*H*)$_2$-CF); 7.94 (dd, 2H, $J = 8.7$, 5.5, -C*H*=CH)$_2$CF). ^{13}C NMR ($CDCl_3$): δ 29.1, 29.2 (-N(CH_2-*C*H_2)$_2$C-); 32.8, 35.3, 37.7 (thienyl-*C*H_2-*C*H-*C*H_2-COO-); 44.0 (-N(CH_2-CH_2)$_2$*C*-); 51.9 (-COO*C*H_3); 53.5, 54.2 (-N(*C*H_2-CH_2)$_2$-C-); 62.6 (-*C*H_2-NRR); 116.15 (d, 2C, $J_{C-F} = 21.8$, *o*-F-Ph); 124.1, 126.1, 127.3 (C-3, C-4, C-5); 131.25 (d, 2C, $J_{C-F} = 9.44$, *m*-F-Ph); 123.8 (CO-*C* aromatic); 165.0 (d, $J_{C-F} = 251$, F-*C*); 173.9 (-*C*OO-CH_3); 201.6 (-*C*O-Ph).

γ-[4-(6-Fluorobenzisoxazol-3-yl)piperidin-1-yl]-β-(2-thenyl)butyric acid methyl ester hydrochloride (34b): mp 162−163 °C (AcOEt). Anal. ($C_{22}H_{25}FN_2O_3S$·HCl) C, H, N. Spectral data for the free base: IR: 1732. ^1H NMR ($CDCl_3$): δ 2.0−2.37 (m, 10H, -N(CH_2-CH_2)$_2$CH-, -CH_2-COO-, -N(*H*-CH-CH_2)$_2$CH-, -CH_2NRR); 2.43−2.53 (m, 1H,-C*H*-CH_2-NRR); 2.84−3.04 (m, 5H, thienyl-CH_2-, -N(*H*-CH-CH_2)$_2$CH-, -N(CH_2-CH_2)$_2$C*H*-); 3.67 (s, 3H, -COOCH_3); 6.79 (d, 1H, $J_{3-4} = 3.2$, H_3); 6.92 (dd, 1H, $J_{4-5} = 5.1$, $J_{4-3} = 3.4$, H_4); 7.05 (dt, 1H, $J_{5'-4'} = J_{5'-F} = 8.8$, $J_{5'-7'} = 2.1$, $H_{5'}$); 7.14 (dd, 1H, $J_{5-4} = 5.1$, $J_{5-3} = 1.1$, H_5); 7.23 (dd, 1H, $J_{7'-F} = 8.6$, $J_{7'-5'} = 2.1$, $H_{7'}$); 7.66 (dd, 1H, $J_{4'-5'} = 8.7$, $J_{4'-F} = 5.1$, $H_{4'}$). ^{13}C NMR ($CDCl_3$): δ 31.02, 31.08 (-N(CH_2-*C*H_2)$_2$C-); 32.8; 35.3; 37.7; 34.9 (-N(CH_2-CH_2)$_2$-*C*-); 51.8 (-COO*C*H_3); 53.9; 54.5; 62.5 (-*C*H_2NRR); 97.8 (d, $J = 26.7$, $C_{7'}$); 112.7 (d, $J_{CF} = 25.3$, $C_{5'}$); 117.7 ($C_{3'a}$); 129.9 (d, $J_{C-F} = 11$, $C_{4'}$); 124.1; 126.2; 127.1; 142.2 (C_2); 161.6 ($C_{3'}$); 164.2 (d, $J_{C-F} = 3.5$, $C_{7'a}$); 164.4 (d, $J_{C-F} = 251$, $C_{6'}$); 173.8 (-*C*OOCH$_3$).

γ-[4-(*tert*-Butoxycarbonyl)piperazin-1-yl]-β-(2-thenyl)-butyric acid methyl ester hydrochloride (34c): mp 133−134 °C (MeOH/Ether). Anal. ($C_{19}H_{30}N_2O_4S$·HCl) C, H, N. Spectral data for the free base: IR: 1736, 1695. ^1H NMR ($CDCl_3$): δ 1.44 (s, 9H, -OCO-C(CH_3)$_3$); 2.12−2.49 (m, 9H, -CH_2-COO-, -C*H*-CH_2NRR, -N(CH_2-CH_2)$_2$N-COO-); 2.83 (dd, 1H, $J_{gem} = 14.8$, $J_{vic} = 6.8$, thienyl-*H*CH-); 2.89 (dd, 1H, $J_{gem} = 14.9$, $J_{vic} = 6.0$, thienyl-HC*H*-); 3.36 (t, 4H, $J = 4.7$, -N(CH_2-CH_2)$_2$N-COO-); 3.63 (s, 3H, -OCH_3); 6.77 (d, 1H, $J_{3-4} = 3.1$, H_3); 6.90 (dd, 1H, $J_{4-5} = 5.1$, $J_{43} = 3.4$, H_4); 7.12 (dd, 1H, $J_{5-4} = 5.1$, $J_{5-3} = 0.7$, H_5). ^{13}C NMR ($CDCl_3$): δ 28.8 (3C, -OC-(*C*H_3)$_3$); 32.7, 35.0, 37.6 (thienyl-*C*H_2-*C*H-*C*H_2-COO-); 44.2 (2C, -N(CH_2-*C*H_2)$_2$N-COO-); 51.8 (-COO*C*H_3); 53.6 (2C, -N(*C*H_2-CH_2)$_2$N-COO-); 62.4 (-*C*H_2NRR); 79.8 (-O*C*(CH$_3$)$_3$); 124.1; 126.2; 127.1; 142.0 (C_2); 155.1 (-*C*OOC(CH$_3$)$_3$); 173.7 (-*C*OOCH$_3$).

γ-[4-(*o*-Methoxyphenyl)piperazinyl]-β-(2-thenyl)butyric acid methyl ester hydrochloride (34f): mp 190−192 °C (AcOEt). Anal. ($C_{21}H_{28}N_2O_3S$·2HCl) C, H, N. Spectral data for the free base: IR: 1732 (COO). ^1H NMR ($CDCl_3$): δ 2.21−2.36 (m, 4H, -CH_2-NRR, -N(*H*-CH-CH_2)$_2$N-Ph); 2.38−2.68 (m, 5H, -N(H-C*H*-CH_2)$_2$N-Ph, -CH_2-COOCH$_3$, -C*H*-CH_2NRR); 2.85 (dd, 1H, $J = 14.8$, 6.8, thienyl-H-C*H*-); 2.95 (dd, 1H, $J = 14.8$, 5.6, thienyl-*H*CH-); 3.05 (s.a., 4H, -N(H-CH-CH_2)$_2$N-Ph); 3.65 (s, 3H, -COOCH$_3$); 3.85 (s, 3H, Ph-OCH$_3$); 6.81 (d, 1H, $J = 3.4$, H_3); 6.81−7.02 (m, 5H, $H_{3'}$, H_4, $H_{4'}$, $H_{5'}$, $H_{6'}$); 7.14 (dd, 1H, $J_{5-3} = 1.1$, $J_{5-4} = 5.2$, H_5). ^{13}C NMR ($CDCl_3$): δ 32.8, 35.1, 37.6 (thienyl-*C*H_2-*C*H-*C*H_2-COO-); 51.1 (2C, -N(CH_2-CH_2)$_2$N-Ph); 51.9 (-COO*C*H_3); 54.0 (2C, -N(*C*H_2-CH_2)$_2$N-Ph); 55.7 (-O*C*H_3); 62.6 (-*C*H_2-NRR); 111.5 ($C_{6'}$); 118.5 ($C_{3'}$); 121.3 ($C_{5'}$); 123.2 ($C_{4'}$); 124.1; 126.2; 127.1; 141.8 ($C_{1'}$); 142.2 (C_2); 152.6 ($C_{2'}$); 173.9 (-*C*OOCH$_3$).

BOC Removal. γ-(Piperazin-1-yl)-β-(2-thenyl)butyric Acid Methyl Ester Hydrochloride (34d). A solution of BOC derivative **34c** base (1.25 g, 3.2 mmol) in MeOH (15 mL) was brought to pH 1 by addition of dry MeOH-saturated HCl gas under argon and then stirred at room temperature for 24 h. The solvent was removed under reduced pressure, and the residue was dissolved in 10% $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was dried and the solvent removed in vacuo to provide **34d** (0.87 g, 95%) as a colorless oil which was subjected to ring closure without further purification. IR: 1734. ^1H NMR ($CDCl_3$): δ 2.11−2.43 (m, 9H, -C*H*-CH_2-COOCH$_3$, -CH_2NRR, -N(CH_2-CH_2)$_2$NH); 2.75−2.89 (m, 6H, thienyl-CH_2-, -N(CH_2-CH_2)$_2$NH); 3.60 (s, 3H, -COOCH_3); 6.83 (dd, 1H, $J_{4-5} = 5.1$, $J_{4-3} = 3.5$, H_4); 7.07 (dd, 1H, $J_{5-4} = 5.1$, $J_{5-3} = 0.8$, H_5). ^{13}C NMR ($CDCl_3$): δ 32.6, 34.8, 37.5 (thienyl-*C*H_2-*C*H-*C*H_2-COO-); 46.3 (-N(CH_2-*C*H_2)$_2$NH); 51.7 (-COO*C*H_3); 54.9 (2C, -N(*C*H_2-CH_2)$_2$NH); 63.0 (-*C*H_2NRR); 124.0; 126.1; 127.0; 142.1 (C_2); 173.7 (-*C*OO-). MS (FAB, *m*/*z*): 283 (MH^+). Hydrochloride: mp 130−131 °C (AcOEt). Anal. ($C_{14}H_{22}N_2O_2S$·2HCl) C, H, N.

General Procedure for Synthesis of 6-(Aminomethyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophen-4-one Hydrochlorides 35a,b,d,f (Table 7). To 110 g of polyphosphoric acid (Fluka) stirring under argon at 90 °C was slowly added the appropriate crude aminomethyl ester (9 mmol), after which the temperature was increased to 130 °C. After 5 h the reaction mixture was poured into ice−water, stirred, made alkaline with 5 N NaOH, and extracted with CH_2Cl_2. The organic phase was washed several times with water to neutral pH and dried (Na_2SO_4), and the CH_2Cl_2 was removed in vacuo to afford the desired 6-(aminomethyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-4-one. The oily residue was dissolved in anhydrous ether to obtain the hydrochloride salt as usual.

1-[(4-Oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-6-yl)-methyl]-4-(*p*-fluorobenzoyl)piperidine hydrochloride (35a): yield 25%, mp 243−244 °C (*i*-PrOH). Anal. ($C_{21}H_{22}FNO_2S$·HCl) C, H, N. Spectral data for the free base: IR: 1681, 1674. ^1H NMR ($CDCl_3$): δ 1.80−1.87 (m, 4H, -N(CH_2-CH_2)$_2$C-); 2.04−2.42 (m, 4H, -CH_2NRR, -N(*H*CH-CH_2)$_2$-); 2.46−2.99 (m, 5H, H_5, H_5, H_7, -N(HC*H*-CH_2)$_2$C-); 3.17−3.30 (m, 2H, H_7, -CH_2)$_2$-C*H*-CO-); 7.07 (d, 1H, $J = 5.3$, H_2); 7.13 (t, 2H, $J = 8.6$, *o*-F-Ph); 7.37 (d, 1H, $J = 5.3$, H_3); 7.96 (dd, 2H, $J = 8.8$, 5.4, *m*-F-Ph). ^{13}C NMR ($CDCl_3$): δ 29.0, 29.1 (-N(CH_2-*C*H_2)$_2$C-); 30.4 (C_7); 35.3; 43.0; 44.0 (-N(CH_2-CH_2)$_2$*C*-); 53.5, 54.6 (-N(*C*H_2-CH_2)$_2$C-); 63.4 (-*C*H_2NRR); 116.18 (d, 2C, $J_{C-F} = 21.8$, *o*-F-Phe); 123.7; 125.0; 131.27 (d, 2C, $J_{C-F} = 9.13$, *m*-F-Ph); 132.8 (-CO-*C*aromatic); 137.5 (C-$_{7a}$); 155.7 (C_{3a}); 165.9 (d, $J = 251$, F-*C*); 193.1 (C_4); 201.4 (-*C*O-Ph). MS (FAB, *m*/*z*): 372 (MH^+).

1-[(4-Oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-6-yl)-methyl]-4-[3-(6-fluorobenzisoxazolyl)]piperidine hydrochloride (35b): yield 40%, mp 258−260 °C. Anal. ($C_{21}H_{21}FN_2O_2S$·HCl) C, H, N. Spectra data for the free base: IR: 1682. ^1H NMR ($CDCl_3$): δ 2.02−2.37 (mc, 11H, H_6, -CH_2NRR, -N(CH_2-CH_2)$_2$CH-); 2.76 (dd, 1H, $J_{gem} = 16.6$, $J_{vic} = 9.8$, H_7); 2.95−3.16 (m, 3H, H_5, H_5, -N(CH_2-CH_2)$_2$C*H*-); 3.28 (dd, 1H, $J_{gem} = 16.6$, $J_{vic} = 3.9$, H_7); 7.01 (dt, 1H, $J_{5'-4'} = J_{5'-F} = 8.8$, $J_{5'-7'} = 2.5$, $H_{6'}$); 7.02 (d, 1H, $J = 5.2$, H_2); 7.16−7.23 (m, 1H, $H_{7'}$); 7.39 (d, 1H, $J = 5.2$, H_3); 7.69 (dd, 1H, $J_{4'-5'} = 8.7$, $J_{4'-F} = 5.1$, $H_{4'}$). ^{13}C NMR ($CDCl_3$): δ 30.5; 31.0; 34.9; 35.4; 43.0 (-CH_2)$_2$-*C*H-); 54.0, 54.8 (-N(*C*H_2-CH_2)$_2$-); 63.6 (-*C*H_2NRR); 97.8 (d, $J_{C-F} = 26.7$, $C_{7'}$); 112.7 (d, $J_{C-F} = 25.2$, $C_{5'}$); 117.6 (C_{3a}); 122.9 (d, $J_{C-F} = 11.0$, $C_{4'}$); 133.7; 125.0; 137.6; 155.6; 161.4 ($C_{3'}$); 164.2 (d, $J_{C-F} = 13.4$, $C_{7'a}$); 165.0 (d, $J_{C-F} = 250$, $C_{6'}$); 193.2 (C_4). MS (FAB, *m*/*z*): 385 (MH^+).

1-[(4-Oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-6-yl)-methyl]piperazine (35d): Acid-catalyzed ring closure of **34d** was carried out with PPA as previously described, yield 45%. IR: 1670. ^{1}H NMR ($CDCl_3$): δ 2.23−2.67 (m, 10 H, H_5, H_5, H_6, -CH_2NRR, -N(CH_2-CH_2)$_2$NH); 2.72 (dd, 1H, J_{gem} = 16.6, J_{vic} = 9.8, H_7); 2.95 (t, 4H, J = 4.9, -N(CH$_2$-CH_2)$_2$NH); 3.23 (dd, 1H, J_{gem} = 16.6, J_{vic} = 3.9, H_7); 7.06 (d, 1H, J = 5.2, H_2); 7.36 (d, 1H, J = 5.2, H_3). ^{13}C NMR ($CDCl_3$): δ 30.5 (C_7); 35.1; 42.9; 45.8 (2C, -N(CH$_2$-CH$_2$)$_2$NH); 54.0 (2C, -N(CH$_2$-CH$_2$)$_2$NH); 63.7 (-CH$_2$NRR); 123.7; 125.0; 137.6 (C_{7a}); 155.6 (C_{3a}); 193.0 (C_4). Hydrochloride: mp 108−110.5 °C (MeOH−ether). Anal. ($C_{13}H_{18}N_2OS$·2HCl) C, H, N.

1-[(4-Oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-6-yl)-methyl]-4-(*o*-methoxyphenyl)piperazine hydrochloride (35f): yield 35%, mp 215−217 °C (AcOEt). Anal. ($C_{20}H_{24}N_2O_2S$·2HCl) C, H, N. Spectra for the free base: IR: 1669. ^{1}H NMR ($CDCl_3$): δ 2.31 (dd, 1H, J = 16.4, 11.0, H_5); 2.44−2.78 (m, 7H, H_6, -CH_2NRR, -N(CH_2-CH$_2$)$_2$N-Ph); 2.60 (dd, 1H, J = 16.5, 4.0, H_5); 2.75 (dd, 1H, J = 16.5, 9.4, H_7); 3.08 (s.a., 4H, -N(CH$_2$-CH_2)$_2$N-Ph); 3.28 (dd, 1H, J = 16.5, 3.8, H_7); 3.86 (s, 3H, -OCH_3); 6.85−7.03 (m, 4H, $H_{3'}$, $H_{4'}$, $H_{5'}$, $H_{6'}$); 7.07 (d, 1H, J = 5.3, H_2); 7.39 (d, 1H, J = 5.3, H_3). ^{13}C NMR ($CDCl_3$): δ 30.5 (C_7); 35.1; 43.0; 51.0 (2C, -N(CH$_2$-CH$_2$)$_2$N-); 54.2 (2C, -N(CH$_2$-CH$_2$)$_2$N-); 55.7 (-OCH$_3$); 63.5 (-CH$_2$NRR); 111.5 ($C_{6'}$); 118.6 ($C_{3'}$); 121.3 ($C_{5'}$); 123.3; 123.7; 125.0; 137.6 (C_{7a}); 141.6 ($C_{1'}$); 152.6 ($C_{2'}$); 155.6 (C_{3a}); 193.2 (C_4). MS (FAB, *m*/*z*): 357 (MH^+).

***N*^{1}-[(4-Oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-6-yl)-methyl]-*N*^{4}-[3-(*p*-fluorobenzoyl)propyl]piperazine (35e).** A solution of 4-chloro-1,1-(ethylenedioxy)-1-(4-fluorophenyl)-butane (0.24 g, 1 mmol) in MIK (10 mL) was added with stirring to a mixture of **35d** (0.25 g, 1 mmol), anhydrous Na_2CO_3 (0.25 g), and KI (0.025 g) in MIK (20 mL). After refluxing with vigorous stirring for 10 h, the mixture was allowed to stand at room temperature overnight. The precipitate formed was filtered out, and the solvent was removed under reduced pressure to give **35e** (0.23 g, 55%) as a white oil which on standing crystallized as white prisms of mp 110−112 °C (*i*-PrOH). IR: 1682, 1669. ^{1}H NMR ($CDCl_3$): δ 2.95 (q, 2H, J = 7.1, -CH$_2$-CH_2-CH$_2$-CO-); 2.23−2.65 (m, 15H, H_5, H_5, H_6, -CH_2-NRR, -N(CH_2-CH_2)$_2$N-CH_2-); 2.71 (dd, 1H, J_{gem} = 16.6, J_{vic} = 9.8, H_7); 2.97 (t, 2H, J = 7.1, -CH$_2$-CH_2-CO-Ph); 3.23 (dd, 1H, J_{gem} = 16.6, J_{vic} = 3.9, H_7); 7.07 (d, 1H, J = 5.4, H_2); 7.12 (t, 2H, J = 3.8, *m*-F-Ph); 7.37 (d, 1H, J = 5.4, H_3); 7.99 (dd, 2H, J = 8.9, 5.3, *m*-F-Ph). ^{13}C NMR ($CDCl_3$): δ 22.0 (-CH$_2$-CH_2-CH$_2$-CO-); 30.4 (C_7); 35.1; 43.0; 36.6 (-CH$_2$-CO-Ph); 53.5, 53.8 (4C, -N(CH_2-CH_2)$_2$N-); 58.0 (RRNCH_2-); 63.3 (-CH$_2$NRR); 115.9 (d, 2C, J_{C-F} = 21.8, *o*-F-Ph); 1123.6; 125.0; 131.1 (d, 2C, J_{C-F} = 9.2, *m*-F-Ph); 137.6 (C_{7a}); 155.5 (C_{3a}); 165.9 (d, J_{C-F} = 251, F-C); 193.1 (C_4); 198.6 (-CO-Ph). Hydrochloride: mp 236−237.5 °C (MeOH−ether). Anal. ($C_{23}H_{27}FN_2O_2S$·2HCl) C, H, N.

Pharmacological Test Methods. Behavioral studies (general): Male Charles River CD1 albino mice weighing 27 ± 3 g were kept in a quiet room thermostated at 22 ± 1 °C with a 12/12-h light/dark cycle (08:00−20:00). Assays were always carried out at the same time of day so as to avoid variation due to circadian rhythms. Food and tap water were freely available in the home cage. All compounds were administered in 0.01 mL/g injections (apomorphine subcutaneously and all others intraperitoneally). Haloperidol (Sigma) was dissolved in 1% lactic acid in water and apomorphine hydrochloride (RBI) in 0.9% saline solution with 1% ascorbic acid (w/v) to prevent oxidation.

Apomorphine-induced climbing: The method of Protais et al.[88] was used, with a minor modification. The climbing behavior of mice was observed in individual cylindrical stainless steel wire cages (diameter, 12 cm; height, 14 cm). Mice (6 per compound and dosage except for the control group, for which 12 animals were used) were treated with vehicle, haloperidol, clozapine, or new compounds and 30 min later with 2 mg/kg apomorphine. During the next 30 min, climbing activity was recorded every 10 min using the following scale: 0, four paws on the floor; 1, one or two paws against the wall; 2, the mouse clung to the wall with three or four paws. The scores recorded 20 and 30 min post-apomorphine were added, and the mean of this sum was calculated for each group. ED_{50} values were calculated by nonlinear curve fitting.

Catalepsy: Catalepsy was tested in 6−12 mice 30 min after administration of vehicle, haloperidol, clozapine, or new compounds. The mice were placed with their forepaws on one horizontal wire and their hindpaws on another 6 cm away and 2 cm lower. The time during which the mouse maintained this position was recorded, and more than 30 s was considered to indicate catalepsy. ED_{50} values were calculated by Litchfield and Wilcoxon's method.[89]

Locomotor activity: Spontaneous locomotor activity and *d*-amphetamine-induced hyperlocomotion were monitored using a motion analysis system (EthoVision v.1.90, Noldus Information Technology, Wageningen, The Netherlands). Mice (4 per treatment) were placed in individual 50- × 50- × 30-cm test arenas, and their activity was recorded for 1 h by a videocamera fixed to the ceiling above the arenas and connected to a videomonitor and to the computer running the motion analysis system, which were located in a separate room. Activity was determined by the analysis system as total distance traveled, in cm.

In spontaneous activity assays, the mice were placed in the arenas immediately after administration of vehicle, haloperidol (2 mg/kg), risperidone (2 mg/kg), clozapine (5 mg/kg), or **23b** (2 mg/kg) or 24 h after administration of reserpine (5 mg/kg). In amphetamine-induced hyperlocomotion assays, the mice were placed in the arenas immediately after administration of *d*-amphetamine sulfate (5 mg/kg), which was effected 30 min after administration of vehicle, haloperidol, risperidone, clozapine, or **23b** or 24 h after administration of reserpine (all at the same dosage levels as in the spontaneous activity assays).

Binding assays (special reagents): [^{3}H]Spiperone (95 Ci/mmol), [^{3}H]SCH23390 (81 Ci/mmol), and [^{3}H]mesulergine (76 Ci/mmol) were obtained from Amersham International (England), and [^{3}H]ketanserin (60.08 Ci/mmol) was from DuPont NEN (Boston, MA). Unlabeled *R*(+)SCH23390·HCl, ketanserin, mianserine, and methysergide were supplied by Research Biochemicals Inc. (Natick, MA), and sulpiride·HCl by Sigma (St. Louis, MO). The new compounds and reference drugs were stored in 1 mM solutions at −20 °C and diluted to the required concentration on ice immediately before use in binding assays.

D_1 and D_2 receptor binding assays: Male Sprague−Dawley rats were killed by decapitation, and their brains were rapidly removed and dissected on an ice-cold plate. Striatal membrane preparations were obtained by homogenization (Polytron homogenizer, setting 6, 10 s) in 50 mM Tris-HCl (pH 7.7 at 25 °C; about 100 μL/mg of tissue) containing 5 mM EDTA; the homogenates were centrifuged (49 000*g* for 15 min at 4 °C; Sorvall RC-26 plus), resuspended in 50 mM Tris-HCl buffer (pH 7.4 at 25 °C), and centrifuged again (same conditions), and the final pellets were stored at −80 °C pending use. Just before binding assays, the pellets were resuspended (1.25 mg original wet weight/750 μL for D_2 assays, 1.00 mg/750 μL for D_1) in 50 mM Tris-HCl buffer (pH 7.4 at 25 °C) containing 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, and 1 mM $MgCl_2$. For D_2 binding assays, 750-μL aliquots of striatal membrane preparation were added to ice-cold tubes containing (a) 100 μL of [^{3}H]spiperone, (b) 50 μL of ketanserin (final concentration 50 nM) to block 5-HT_{2A} receptors, and either (c) 100 μL of buffer (for total binding assay) or (d) 100 μL of sulpiride (final concentration 10 μM) to allow quantification of unspecific binding by [^{3}H]spiperone, or (e) 100 μL of the compounds to be tested. For D_1 binding assays, the same procedure was followed except that [^{3}H]spiperone was replaced by [^{3}H]SCH23390, ketanserin by buffer, and sulpiride by nonradiolabeled SCH23390 (final concentration 1 μM) to allow quantification of nonspecific binding by [^{3}H]SCH23390. The final assay volume was thus 1 mL in all cases. All assays were performed in duplicate. Incubations (15 min at 37 °C) were stopped by rapid vacuum filtration through GF-52 glass fiber filters (Schleicher and Schuell) in a Brandel M-30 cell harvester. The filters were rinsed three times with 3 mL of ice-cold 50 mM Tris-HCl buffer (pH 7.4), and radioactivity was

determined by liquid scintillation counting in a Beckman LS-6000LL apparatus (counting efficiency approximately 50%). Competition analyses were carried out with the aid of the Prism program (GraphPad); K_i values were calculated as $K_i = IC_{50}/(1 + D/K_d)$, where D is the concentration and K_d the apparent dissociation constant of the ligand.

5-HT$_{2A}$ receptor binding assays: Male 200−250-g Sprague−Dawley rats were asphyxiated with CO_2 and decapitated. The frontal cortex, containing 5-HT$_{2A}$ receptors,[90,91] was dissected free on ice, frozen on dry ice, and stored at −70 °C until use (generally less than 1 week later). All membrane preparation procedures were carried out at 4 °C. The tissue was thawed on ice and homogenized with 10 volumes of 0.32 M sucrose in a Polytron homogenizer (Brinkmann Instruments, Westbury, NY). The homogenate was centrifuged twice at 4 °C (900*g* for 10 min followed by 40 000*g* for 30 min). The supernatant was discarded and the pellet resuspended in Tris-HCl buffer (pH 8.07) in a Teflon/glass homogenizer (10 strokes by hand). The homogenate was incubated at 37 °C for 15 min to remove endogenous 5-HT and centrifuged for 30 min at 40 000*g*. The final pellet was resuspended in Tris-HCl buffer of pH 8.07 containing 4 mM $CaCl_2$ and 0.1% ascorbic acid. Competition at [^{3}H]ketanserin binding sites was assayed in triplicate in assay mixtures consisting of 750 μL of membrane homogenate, 50 μL of [^{3}H]ketanserin, 50 μL of either buffer or the compound under test, 50 μL of masking ligand solution (1 μM methysergide) as required, and buffer to a final volume of 1 mL. Mixtures were incubated for 30 min at 37 °C. The assay was terminated by rapid filtration through Whatman GF/C filter strips (presoaked in 3% poly(ethylenimine)) in a Brandel cell harvester (Gaithersburg, MD) followed by washing with ice-cold Tris-HCl buffer (pH 6.6) to remove unbound radioligand. The radioactivity retained on filters was determined by liquid scintillation counting in a beta counter (Beckman, LS-1800).

The nonlinear curve-fitting program Kaleidagraph (Synergy Software, Reading, PA) was used to fit the equation $E = E_{max} - [E_{max} - E_{min}/(1 + (IC_{50}/C)^n)]$, where E_{max} and E_{min} are dpm at the beginning and end of the competition experiment, respectively, IC_{50} is the drug concentration required to inhibit binding by 50%, C is the concentration of the inhibitor, and n is the slope of the decay. Nonspecific binding was determined independently in the presence of unlabeled methysergide. pK_i values were estimated from IC_{50} values using the equation $K_i = IC_{50}/(1 + D/K_d)$, where K_d is the equilibrium dissociation constant for [^{3}H]radioligand determined by saturation binding studies and D is the concentration of [^{3}H]ligand used.

5-HT$_{2C}$ receptor binding assays: Bovine choroid plexus containing 5-HT$_{2C}$ receptors[92] was treated as described in the previous assay. A suspension of the resulting pellet in the same buffer was stored on ice while not being manipulated. Competition at [^{3}H]mesulergine binding sites was determined by a protocol analogous to that described above for the 5-HT$_{2A}$ binding assay, using a final [^{3}H]mesulergine concentration of 2 nM and 1 mM mianserine as a 5-HT$_{2A}$ receptor masking ligand. The mixtures were incubated for 1 h at room temperature. Membranes were harvested on Whatman GF/B filter. Nonspecific binding was determined in the presence of unlabeled mianserine. IC_{50} and pK_i values were calculated as for 5-HT$_{2A}$ receptors.

Functional experiments: Antagonism of serotonin at 5-HT$_{2A}$ receptors[30,90] was assayed using thoracic aorta from male 250−350-g Sprague−Dawley rats killed by cervical dislocation. The descending aorta was removed, cleaned, stripped of endothelium, and cut into rings 4 mm in length[41] that were then mounted under a tension of 2 g in a CELASTER-IOS 1 computerized organ bath containing 20 mL of Krebs solution of the following composition (mM): NaCl, 119; KCl, 4.7; $MgSO_4 \cdot 7H_2O$, 1.2; $CaCl_2 \cdot 2H_2O$, 1.5; KH_2PO_4, 1.2; $NaHCO_3$, 25; glucose, 11. Clorpheniramine (1 μM) was added to block uptake of serotonin.[93,94] The bath solution was maintained at 37 °C and aerated with carbogen (95% O_2, 5% CO_2). Isometric contraction force was monitored via a CPOL 0−25 g transducer. Following equilibration for 60 min under a load of 2 g, the rings were sensitized by addition of 10 μM 5-HT for 8 min. Equilibration periods (60 min)[95] were then alternated with the construction of cumulative 5-HT concentration−effect curves (from 30 nM to 100 μM). Two control runs giving identical curves were followed by test runs with ketanserin or the new compounds, which were added to the bath solution 20 min before the end of the preceding equilibration period. Antagonist potency was measured, following Arunlaksana and Schild, in terms of pA_2 (−log concentration of antagonist required to maintain a constant response when agonist concentration is doubled).

5-Hydroxytryptamine·HCl was supplied by Sigma and ketanserin by RBI. All other drugs and chemicals were reagent grade products from Sigma. Aqueous solutions of all drugs as their hydrochlorides were prepared daily using distilled water. All drug concentrations mentioned above are final molar concentrations in the tissue bath.

Molecular modeling and CoMFA: Molecular models of the protonated ligands were constructed with standard bond distances and angles using SYBYL (ver. 6.4) software (Tripos Assoc., St. Louis, MO) running on a Silicon Graphics Indigo2 R4400 workstation. Full geometry optimization was performed with the PM3 Hamiltonian using the parameter set included in the MOPAC (ver. 6.0)[69] suite of programs. The Mulliken partial atomic charges given by PM3 calculations were used in the CoMFA study. Molecular alignment for CoMFA was performed with the RIGIDFIT option of SYBYL. The CoMFA study was carried out using the QSAR module of SYBYL with default settings, except that the "drop-electrostatic" option was set to "NO". Steric and electrostatic interaction energies were calculated at the points of a regular 3D lattice using an sp^3 carbon atom probe with a charge of +1 and a van der Waals radius of 1.52 Å. The MLP was calculated by the method of Gaillard et al.[62] The grid had a resolution of 2 Å, and the region dimensions were defined automatically using the "molecular volume" mode. For each combination of fields, the number of components to be used in a final model was determined on the basis of calculations of q^2 for PLS models of five or fewer components ($q^2 = (SD - PRESS)/SD$, where SD is the sum of squares of deviations of the observed values from their mean and PRESS is the prediction error sum of squares). PLS was then carried out without cross-validation using the number of components so determined. The results of this latter analysis were used to produce the final 3D-QSAR models with which the coefficient isocontour maps of Figure 4 were constructed. The predictive and fitting capabilities of the models were assessed by q^2 and by r^2 and s, respectively.

Acknowledgment. This research was supported by Spanish Comisión Interministerial de Ciencia y Tecnología (CICYT) under Grants SAF 92-0957-C02-01, SAF 94-0593-C04, and SAF 95-1081 and by the Xunta de Galicia under Grants XUGA 20308 B93, XUGA 20308B94, and XUGA 20308B96. Thanks are given to Prof. Alexandros Makriyannis (School of Pharmacy, University of Connecticut) for generous assistance with enantiomer separation during visits to his laboratory by J. Negreira. We also thank José González Parga for his enthusiastic technical assistance. J. Negreira, J. Cid, E. Rosa, and M. E. Rivas were aided by predoctoral grants from Xunta de Galicia, and E. Lozoya was aided by a predoctoral grant from CIRIT. The molecular modeling studies were supported by CESCA grants (TMR fellowship for A. Carrieri and computational facilities). We are grateful to Sandoz and Janssen Laboratories for generous gifts of clozapine and risperidone, respectively.

References

(1) For reviews, see: (a) Howard, H. R.; Seeger, T. F. Novel Antipsychotics. In *Annual Reports in Medicinal Chemistry*; Bristol, J. A., Ed.; Academic Press: New York, 1993; Vol. 28, p

39. (b) Schaus, J. M.; Bymaster, F. P. Dopaminergic Approachesto Antipsychotic Agents. In *Annual Reports in Medicinal Chemistry*; Bristol, J. A., Ed.; Academic Press: New York, 1998; Vol. 33, p 1.
(2) Seeman, P. Dopamine receptors and dopamine hypothesis of schizophrenia. *Synapse* **1987**, *192*, 481−483.
(3) Sitsen, A. Current trends in antipsychotic agents. *Script Report*; PJB Publications: Richmond, U.K., 1990; p 57.
(4) Seeman, P.; Chou-Wong, M.; Tadesco, J.; Wong, K. Antipsychotic drug doses and neuroleptic/dopamine receptors. *Nature* **1976**, *261*, 717−719.
(5) Kennedy, J. L.; Billett, E. A.; Macciardi, F. M.; Verga, M.; Parsons, T. J.; Meltzer, H. Y.; Lieberman, J.; Buchanan, J. A. Association study of dopamine D3 receptor gene and schizophrenia. *Am. J. Med. Genet.* **1995**, *60*, 558−562.
(6) Bristow, L. J.; Kramer, M. S.; Kulagowski, J.; Patel, S.; Ragan, C. I.; Seabrook, G. R. Schizophrenia and L-745,870, a novel dopamine D4 receptor antagonist. *Trends Pharmacol. Sci.* **1997**, *18*, 186−187.
(7) Filton, A.; Heel, R. C. Clozapine. A review of its pharmacological properties and therapeutic use in schizophrenia. *Drugs* **1990**, *40*, 722−747.
(8) Schwarz, J. T.; Brotman, A. W. A clinical guide to antipsychotic drugs. *Drugs* **1992**, *44*, 981−992.
(9) Rosenheck, R.; Cramer, J.; Xu, W.; Henderson, W.; Frismann, L. A comparison of clozapine and haloperidol in hospitalized patients. *N. Engl. J. Med.* **1997**, *337*, 809−815.
(10) (a) Megens, A. H. P.; Kennis, L. E. J. Risperidone and related 5-HT_2/D2 Antagonists: a new type of antipsychotic agent. In *Progress in Medicinal Chemistry*; Ellis, G. P., Luscombe, D. K., Eds.; Elsevier Sci.: Amsterdam, 1996; Vol. 33, p 186. (b) Beasley, C. M.; Tollefson, G.; Tran, P.; Satterlee, W.; Sanger, T.; Hamilton, S. Olanzapine versus placebo and haloperidol: Acute phase results of the North American Double-Blind Olanzapine Trial. *Neuropsychopharmacology* **1996**, *14*, 111−123. (c) Conley, R. R.; Buchanan, R. W. Evaluation of treatment-resistant schizophrenia. *Schizophrenia Bull.* **1997**, *23*, 663−674.
(11) Sanders-Bush, E.; Mayer, S. E. 5-Hydroxytryptamine (Serotonin) Receptor Agonists and Antagonists. In *The Pharmacological Basis of Therapeutics*, 9th ed.; Hardman, J. G., Limbird, L. E., Molinoff, P. B., Ruddon, R. W., Goodman, A., Eds.; McGraw-Hill: New York, 1996; pp 249−263.
(12) Meltzer, H. Y.; Matsubara, S.; Lee, J. C. Classification of typical and atypical antipsychotic drugs on the basis of dopamine D-1, D-2 and serotonin2 p*K*i values. *J. Pharmacol. Exp. Ther.* **1989**, *251*, 238−246.
(13) 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: New York, 1995; pp 1215−1227.
(14) Meltzer, H. Y.; Matsubara, S.; Lee, J. C. The ratios of serotonin2 and dopamine2 affinities differentiate atypical and typical antipsychotic drugs. *Psychopharmacol. Bull.* **1989**, *25*, 390−392.
(15) Roth, B. L.; Tandra, S.; Burgess, L. H.; Sibley, D. R.; Meltzer, H. Y. D_4 receptor binding affinity does not distinguish between typical and atypical antipsychotic drugs. *Psychopharmacology* **1995**, *120*, 365−368.
(16) Kapur, S.; Remington, G. Serotonin-Dopamine Interaction and Its Relevance to Schizophrenia. *Am. J. Psychiatry* **1996**, *153*, 466−476.
(17) Lowe III, J. A. Atypical Antipsychotics based on the D_2/5-HT_2 Ratio Hypothesis. *Curr. Med. Chem.* **1994**, *1*, 50.
(18) Gleason, S. D.; Shannon, H. E. Blockade of phencyclidine-induced hyperlocomotion by olanzapine, clozapine and serotonin receptor subtype selective antagonists in mice. *Psychopharmacology (Berlin)* **1997**, *129*, 79−84.
(19) Sipes, T. E.; Geyer, M. A. DOI disrupts prepulse inhibition of startle in rats via 5-HT_{2A} receptors in the ventral pallidum. *Brain Res.* **1997**, *761*, 97−104.
(20) Okuyama, S.; Chaki, S.; Kawashima, N.; Suzuki, Y.; Ogawa, S.; Kumagai, T.; Nakazato, A.; Nagamine, M.; Yamaguchi, K.; Tomisawa, K. The atypical antipsychotic profile of NRA0045, a novel dopamine D4 and 5-hydroxytryptamine2A receptor antagonist, in rats. *Br. J. Pharmacol.* **1997**, *121*, 515−25.
(21) Green, M. F.; Marshall, B. D., Jr.; Wirshing, W. C.; Ames, D.; Marder, S. R.; McGurk, S.; Kern, R. S.; Mintz, J. Does risperidone improve verbal working memory in treatment-resistant schizophrenia? *Am. J. Psychiatry* **1997**, *154*, 799−804.
(22) Martin, P.; Waters, N.; Carlsson, A.; Carlsson, M. L. The apparent antipsychotic action of the 5-HT2A receptor antagonist MDL 100907 in a mouse model of schizophrenia is counteracted by ritanserin. *J. Neural. Transm.* **1997**, *104*, 561−564.
(23) Padich, R. A.; McCloskey T. C.; Kehne, J. H. 5-HT modulation of auditory and visual sensorimotor gating: II. Effects of the 5-HT2A antagonist MDL 100, 907 on disruption of sound and light prepulse inhibition produced by 5-HT agonists in Wistar rats. *Psychopharmacology* **1996**, *124*, 107−116.
(24) 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, PA, 1996.
(25) Meltzer, H. Y. Atypical antipsychotic drugs: which receptors are relevant? IBS's International Conference on Serotonin Receptors. Central Nervous System. Targets for New Therapeutic Agents, Philadelphia, PA, 1996.
(26) Meltzer, H. Y. Multiple serotonin/dopamine receptor interactions contribute to atypical antipsychotic drug action. *Eur. Neuropsychopharmacol.* **1996**, *6*, S-32−2.
(27) Roth, B. L.; Craigo, S. C.; Choudhary, S.; Uluer, A.; Monsma, F. J., Jr.; Shen, Y.; Meltzer, H. Y.; Sibley, D. R. Binding of typical and atypical antipsychotic agents to 5-hydroxytryptamine-7 receptors. *J. Pharmacol. Exp. Ther.* **1994**, *268*, 1403−1410.
(28) Monsma, F. J.; Shen, Y.; Ward, R. P.; Hamblin, M. W.; Sibley, D. R. Cloning and expression of a novel serotonin receptor with high affinity for tricyclic psychotropic drugs. *Mol. Pharmacol.* **1992**, *43*, 320−327.
(29) Ward, R. P.; Hamblin, M. W.; Lachowicz, J. E.; Hoffman, B. J.; Sibley, D. R.; Dorsa, D. M. Localization of serotonin subtype 6 receptor messenger RNA in the rat brain by in situ hybridization histochemistry. *Neuroscience* **1995**, 1105−1111.
(30) (a) Hoyer, D.; Martin, G. R. Classification and nomenclature of 5-HT receptors: a comment on current issues. *Behav. Brain Res.* **1996**, *73*, 263−268. (b) Hoyer, D.; Clarke, D. E.; Fozard, J. R.; Hartig, P. R.; Martin, G. R.; Mylecharane, E. J.; Saxena, P. R.; Humphrey, P. P. A. VII International Union of pharmacology classification of receptors for 5-hydroxytryptamine (serotonin). *Pharmacol. Rev.* **1994**, *46*, 157−203.
(31) Erdmann, J.; Nothen, M. M.; Shimron-Abarbanell, D.; Rietschel, M.; Albus, M.; Borrmann, M.; Maier, W.; Frankzek, E.; Korner, J.; Weigelt, B.; Fimmers, R.; Propping, P. The human serotonin 7 (5-HT7) receptor gene: genomic organization and systematic mutation screening in schizophrenia and bipolar affective disorder. *Mol. Psychiatry* **1996**, *1*, 392−397.
(32) Largent, B. L.; Wikstrom, H.; Snowman, A. M.; Snyder, S. H. Novel antipsychotic drugs share high affinity for sigma receptors. *Eur. J. Pharmacol.* **1988**, *155*, 345−347.
(33) Janssen, P. A. J.; Niemegeers, C. J. E.; Awouters, F.; Schelekens, K. H. L.; Megens, A. A. H. P.; Meert, T. F. Pharmacology of Risperidone (R 64 766). A new antipsychotic with serotonin S_2 and dopamine D_2 antagonistic properties. *J. Pharmacol. Exp. Ther.* **1988**, *244*, 685−693.
(34) Megens, A. A. H. P.; Niemegeers, C. J. E.; Awouters, F. H. L. Behavioral disinhibition and depression in amphetaminized rats: A comparison of risperidone, ocaperidone and haloperidol. *J. Pharmacol. Exp. Ther.* **1992**, *260*, 160−167.
(35) Hyttel, J.; Arnt, J.; Costall, B.; Domeney, A.; Dragsted, N.; Lembol, H. L.; Meier, E.; Naylor, R. J.; Nowak, G.; Sanchez, C.; Starsfeldt, T. Pharmacological profile of the atypical neuroleptic Sertindol. *Clin. Neuropharmacol.* **1992**, *15* (Suppl. 1 Pt A), 267A−268A.
(36) Lieberman, J. A.; Hohn, C. A.; Mikane, J.; Rai, K.; Pisciotta, A. V.; Salz, B. L.; Howard, A. Clozapine-induced agranulocytosis: non cross-reactivity with other antipsychotic drugs. *J. Clin. Psychiatry* **1988**, *49*, 271−277.
(37) Cortizo, L.; Santana, L.; Raviña, E.; Orallo, F.; Fontenla, J. A.; Castro, E.; Calleja, J. M.; de Ceballos, M. L. Synthesis and antidopaminergic activity of some 3-(aminomethyl)tetralones as analogues of butyrophenone. *J. Med. Chem.* **1991**, *34*, 2242−2247.
(38) Loza, M. I.; Verde, I.; Castro, E.; Orallo, F.; Fontenla, J. A.; Calleja, J. M.; Raviña, E.; Cortizo, L. 5-HT_2 antagonist activity of 3-aminomethyl tetralones. *Bioorg. Med. Chem. Lett.* **1991**, *1*, 717−720.
(39) Duncan, R. L., Jr.; Helsey, G. C.; Welstead, W. J., Jr.; Da Vanzo, J. P.; Funderburk, W. H.; Lunsford, C. D. Aroylpiperidines and pyrrolidines. A new class of potent central nervous system depressants. *J. Med. Chem.* **1970**, *13*, 1−6.
(40) Ismaiel, A. M.; Arruda, K.; Teitler, M.; Glennon, R. A. Ketanserin analogues: the effect of structural modifications on 5-HT_2 serotonin receptor binding. *J. Med. Chem.* **1995**, *38*, 1196−1202.
(41) Loza, I.; Ferreiro, T. G.; Sanz, F.; Lozoya, E.; Rodriguez, J.; Manaut, F.; Verde, I.; Castro, E.; Fontenla, J. A.; Cadavid, I.; Honrubia, M.; Fueyo, J.; Raviña, E. Antiserotoninergic activity of 2-aminoethyl benzocyclanones in rat aorta: Structure−activity relationships. *J. Pharm. Sci.* **1993**, *82*, 513−517.
(42) Fontenla, J. A.; Osuna, J.; Rosa, E.; Castro, E.; Ferreiro, T. G.; Loza García, I.; Calleja, J. M.; Sanz, F.; Rodriguez, J.; Raviña, E.; Fueyo, J.; Masaguer, C. F.; Vidal, A.; de Ceballos, M. L. Synthesis and atypical antipsychotic profile of some 2-(2-piperidinoethyl) benzocycloalkanones as analogues of butyrophenone. *J. Med. Chem.* **1994**, *37*, 2564−2573.
(43) Raviña, E.; Fueyo, J.; Masaguer, C. F.; Negreira, J.; Cid, J.; Loza, I.; Honrubia, A.; Tristan, H.; Ferreiro, T. G.; Fontenla, J. A.; Rosa, E.; Calleja, J. M.; de Ceballos, M. L. Synthesis and

affinities for dopamine (D_2) and 5-hydroxytryptamine (5-HT_{2A}) receptors of 1-(benzoylpropyl)-4-(1-oxocycloalkyl-2-ethyl)piperazines as cyclic butyrophenone derivatives. *Chem. Pharm. Bull.* **1996**, *44*, 534−541.

(44) Raviña, E.; Masaguer, C. F.; Cid, J.; Fontenla, J. A.; Ferreiro, T. G.; Cadavid, M. I.; Loza, I.; de Ceballos, M. L. Butyrophenone analogues: Synthesis of 2-methyl-3-ethyl-5-aminomethyl-4,5,6,7-tetrahydroindol-4-ones and their affinities for D_1, D_2 and 5-HT_{2A} receptors. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 579−584.

(45) Masaguer, C. F.; Raviña, E. A practical and efficient route for synthesis of 6-aminomethyl-4-oxo-4,5,6,7-tetrahydroindoles as new CNS precursors. *Tetrahedron Lett.* **1996**, *37*, 5171−5174.

(46) Masaguer, C. F.; Casariego, I.; Raviña, E. 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. *Chem. Pharm. Bull.* **1999**, *47*.

(47) Masaguer, C. F.; Formoso, E.; Raviña, E.; Tristán, H.; Loza, I.; Rivas, E.; Fontenla, J. A. Butyrophenone analogues in the carbazole series: synthesis and determination of affinities at D_2 and 5-HT_{2A} receptors. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3571−3576.

(48) For benzisoxazole−benzoyl bioisosterism see: (a) Shutske, G. M.; Setescak, L. L.; Allen, R. C.; Davis, L.; Effland, R. C.; Ranbom, K.; Kitzen, J. M.; Wilker, J. C.; Novick, W. J., Jr. [(3-Aryl-1,2-benzisoxazol-6-yl)oxy]acetic acids. A New Diuretic Series. *J. Med. Chem.* **1982**, *25*, 36−44. (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. Synthesis and neuroleptic activity of 3-(1-substituted-4-piperidinyl)-1,2-benzisoxazoles. *J. Med. Chem.* **1985**, *28*, 761−769. (c) Mewshaw, R. E.; Silversman, L. S.; Mathew, R. M.; Kaiser, C.; Sherrill, R. G.; Cheng, M.; Tiffanny, C. W.; Karbon, E. W.; Bailey, M. A.; Borosky, S. A.; Ferkany, J. W.; Abreu, M. E. Bridged γ-carbolines and derivatives possessing selective and combined affinity for 5-HT_{2A} and D_2 receptors. *J. Med. Chem.* **1993**, *36*, 1488−1495.

(49) Palermo, M. G.; Corbett, R.; Hartman, H. B.; Hrib, N. J.; Kafka, S.; Kongsamut, S.; Nmeoto, P. A.; Schilp, D. E.; Tseng, H.; Woods-Kettelberger, A.; Martin, L. L. Synthesis and evaluation of 3-(4-piperazinyl)-6-hydroxy-benzisoxazoles and depot analogues as potential atypical neuroleptic compounds. *Abstracts of Papers*; 214th National Meeting of the American Chemical Society, Division of Medicinal Chemistry, Las Vegas, NV, 1997.

(50) Hashimoto, I.; Takatsuka, R. Friedel−Crafts Reaction of Benzene with 2-Phenylbutanedioic Anhydride. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2495−2496.

(51) Diago-Meseguer, J.; Palomo-Coll, A. L.; Fernández-Lizarbe, J. R.; Zugaza-Bilbao, A. A new reagent for activating carboxyl groups; preparation and reactions of N,N-bis[2-oxo-3-oxazolidinyl]phosphorodiamidic chloride. *Synthesis* **1980**, 547−551.

(52) Waldmann, H. Der Phenylacetyl-(PhAc-)Rest als enzymatisch ablösbare Schutzgruppe für Peptide und Kohlenhydrate: Selektrive Schutzgruppenabspaltungen mit Penicillin-Acylase. *Liebigs Ann. Chem.* **1998**, 1175−1180.

(53) Tsunada, T.; Suzuki, M.; Noyori, R. A facile procedure for acetalization under aprotic conditions. *Tetrahedron Lett.* **1980**, *21*, 1357−1358.

(54) The Clemmenssen reaction is clean and does not affect the lactone ring. Attempted catalytic and Et_3Si/TFA reductions were unsuccessful.

(55) Attempted ring closure with TFA−acetic anhydride invariably gave the 2-acetylthiophene derivative in quantitative yield.

(56) With the exception of **35b**, all chiral compounds described in this work are racemic mixtures.

(57) Chromatography was performed using a Beckman System Gold HPLC system with a column containing cellulose-based chiral stationary phase (Chiracel, OD 250 × 10 mm), *i*-PrOH−hexane (20:80) as solvent, and a flow rate of 0.5 mL/min.

(58) The enantiomers differed little in receptor affinity. (+)**35b**: pK_i(D_2) = 7.24, pK_i(5-HT_{2A}) = 7.91. (−)**35b**: pK_i(D_2) = 7.82, pK_i(5-HT_{2A}) = 7.83.

(59) Cramer, R. D.; Patterson, D. E.; Bunce, J. D. Comparative Molecular Field Analysis (CoMFA). 1. Effects of shape on binding of steroids to carrier protein. *J. Am. Chem. Soc.* **1988**, *110*, 5959−5967.

(60) Cramer, R. D.; De Prierst, S. A.; Patterson, D. E.; Hect, P. The developing practice of Comparative Molecular Field Analysis. In *Drug Design: Theory, Methods and Applications*; Kubinyi, H., Ed.; Escom: Leiden, 1993; pp 443−485.

(61) Thibaut, U. Applications of CoMFA and Related 3D-QSAR Approaches. In *Drug Design: Theory, Methods and Applications*; Kubinyi, H., Ed.; Escom: Leiden, 1993; pp 661−696.

(62) Gaillard, P.; Carrupt, P.-A.; Testa, B.; Boudon, A. Molecular lipophilicity potential, a tool in 3D-QSAR: Method and applications. *J. Comput.-Aided Mol. Des.* **1994**, *8*, 83−96.

(63) Testa, B.; Carrupt, P.-A.; Gaillard, P.; Tsai, R. S. Intramolecular Interactions Encoded in Lipophilicity. In *Lipophilicity in Drug Action and Toxicology*; Pliska, V., Testa, B., van der Waterbeemd, H., Eds.; VCH: Weinheim, 1997; pp 49−71.

(64) Wold, S.; Johansson, E.; Cocchi, M. PLS − Partial Least Squares Projections to Latent Structures. In *Drug Design: Theory, Methods and Applications*; Kubinyi, H., Ed.; Escom: Leiden, 1993; pp 523−549.

(65) Cramer, R. D., III; Bunce, J. D.; Patterson, D. E. Crossvalidation, bootstrapping and Partial Least Squares compared with Multiple Regression Analysis. *Quant. Struct.-Act. Relat.* **1988**, *7*, 18−25.

(66) For the present CoMFA study we used the compounds listed in Table 9 together with the following compounds of our earlier butyrophenone series: **Ia**,[36] **Ie**,[36] **If**,[36] **IIa**,[41] **IIIa**,[41] **IVa**,[41] **IIe**,[42] **IIIe**,[42] and **IIIf**.[40]

(67) The pK_i(5-HT_{2A}) value for compound **35f** was estimated by linear regression of pK_i vs pA_2 for the congeneric (*o*-methoxyphenyl)-piperazine derivatives **If**, **IIIf**, **10f**, and **24f**.

(68) Holtje, H. D.; Folkers, G. In *Molecular Modeling, Basic Principles and Applications*; Mannhold, R., Kubyi, H., Timmerman, H., Eds.; VCH: Weinheim, 1996; Chapter 3.

(69) Stewart, J. J. P. MOPAC: A semiempirical molecular orbital program. *J. Comput.-Aided Mol. Des.* **1990**, *4*, 1−103.

(70) Carrieri, A.; Brasili, L.; Leonetti, F.; Pigini, M.; Giannella, M.; Bousquet, P.; Carotti, A. 2-D and 3-D Modeling of Imidazoline Receptor ligands: Insights into Pharmacophore. *Bioorg. Med. Chem.* **1997**, *5*, 843−856.

(71) Still, W. C.; Tempczyk, A.; Hawley, R. C.; Hendrickson, T. Semianalytical treatment of solvation for molecular mechanics and dynamics. *J. Am. Chem. Soc.* **1990**, *112*, 6127−6129.

(72) Wold, S.; Eriksson, L. Statistical Validation of QSAR Results. In *Chemometric Methods in Molecular Design*; van de Waterbeemd, H., Ed.; VCH: Weinheim, 1996; pp 309−318.

(73) Folkers, G.; Merz, A.; Rognan, D. CoMFA scope and limitations. In *Drug Design: Theory, Methods and Applications*; Kubinyi, H., Ed.; Escom: Leiden, 1993; pp 583−618.

(74) Lozoya, E.; Berger, M.; Rodríguez, J.; Sanz, F.; Loza, M. I.; Moldes, V.; Masaguer, C. F. Comparison of electrostatic similarity approaches applied to a series of ketanserin analogues with 5-HT_{2A} antagonist activity. *Quant. Struct.-Act. Relat.* **1998**, *17*, 199−204.

(75) Baldwin, J. M. The probable arrangement of the helices in G protein-coupled receptors. *EMBO J.* **1993**, *12*, 1693−1703.

(76) Pearlman, D. A.; Case, D. A.; Caldwell, J. W.; Ross, W. S.; Cheatham, T. E.; Ferguson, D. M.; Seibel, G. L.; Singh, C.; Weiner, P. K.; Kollman, P. A. AMBER 4.1; University of California: San Francisco, CA, 1995.

(77) Laskowski, R. A.; MacArthur, M. W.; Moss, D. S.; Thornton, J. M. Procheck: a program to check the stereochemical quality of protein structures. *J. Appl. Crystallogr.* **1993**, *26*, 283−291.

(78) Hooft, R. W. W.; Vriend, G.; Sander, C.; Abola, E. E. Errors in protein structures. *Nature* **1996**, *381*, 272.

(79) Fraser, C. M.; Wang, C. D.; Robinson, D. A.; Gocayne, J. D.; Venter, J. C. Site-directed mutagenesis of m1 muscarinic receptors: conserved aspartic acids play important roles in receptor function. *Mol. Pharmacol.* **1989**, *36*, 840−847.

(80) Strader, C. D.; Sigal, I. S.; Dixon, R. A. F. Structural basis of α-adrenergic receptor function. *FASEB J.* **1989**, *3*, 1825−1832.

(81) Zhou, W.; Flanagan, C.; Ballesteros, J. A.; Konvicka, K.; Davidson, J. S.; Weinstein, H.; Millar, R. P.; Sealfon, S. C. A. Reciprocal Mutation Supports Helix 2 and Helix 7 Proximity in the Gonadotropin-Releasing Hormone Receptor. *Mol. Pharmacol.* **1994**, *45*, 165−170.

(82) Molecular Simulations Inc., San Diego, CA.

(83) Vogel, A. I. *Vogel's Textbook of Practical Organic Chemistry*, 5th ed.; Longman: Harlow, U.K., 1989.

(84) Sam, J.; Thompson, A. C. Thiaindanones. Thiophene isosters of indanone. *J. Pharm. Sci.* **1963**, *52*, 898−901.

(85) Nishimura, S.; Nakamura, M.; Suzuki, M.; Imoto, E. Some reactions of 4-oxo-4,5,6,7-tetrahydrothianaphthene. *Nippon Kagaku Zasshi* **1962**, *83*, 343−347; *Chem. Abstr.* **1963**, *59*, 3862c.

(86) Cagniant, M. P.; Cagniant, P. Contribution a l'etude des hétérocycles soufrés condensés. V. Substitution dans le noyau du tétrahydro-4-5-6-7 thionaphtène au moyen de la réaction de Friedel−Crafts. *Bull. Soc. Chim. Fr.* **1953**, *20*, 62−69.

(87) Conjat, J. P.; Cagniant, P.; Cagniant, D.; Mirjolet, M. Syntheses dans le domaine des methoxy oxo-4 et oxo-7 tetrahydro-4,5,6,7 benzo[*b*]thiophenes. *Tetrahedron Lett.* **1975**, 2885−2888.

(88) Protais, P.; Costentin, J.; Schwartz, J. C. Climbing behavior induced by apomorphine in mice: A simple test for the study of dopamine receptors in striatum. *Psychopharmacology* **1976**, *50*, 1−6.

(89) Tallarida, R. J.; Murray, R. B. *Manual of Pharmacologic Calculations with Computer Programs*, 2nd ed.; Springer-Verlag: New York, 1987; pp 153−158.

(90) Bradley, P. B.; Engel, G.; Feniuk, W.; Fozard, J. R.; Humphrey, P. P. A.; Middlemiss, D. N.; Mylecharane, E. J.; Richardson, B. P.; Saxena, P. R. Proposals for the classification and nomenclature of functional receptors for 5-hydroxytryptamine. *Neuropharmacology* **1986**, *25*, 563−576.
(91) Pazos, A.; Cortes, R.; Palacios, J. M. Quantitative autoradiographic mapping of serotonin receptors in the rat brain II. Serotonin-2 receptors. *Brain Res.* **1985**, *346*, 231−245.
(92) Wong, D. T.; Threlkeld, P. G.; Robertson, D. W. Affinities of fluoxetine, its enantiomers, and other inhibitors of serotonin uptake for subtypes of serotonin receptors. *Neuropsychopharmacology* **1991**, *5*, 43−47.
(93) Fukuda, S.; Su, C.; Lee, T. J. F. Mechanisms of extraneuronal serotonin uptake in the rat aorta. *J. Pharmacol. Exp. Ther.* **1986**, *239*, 264−269.
(94) Gruetter, C. A.; Lemke, S. M.; Anestis, D. K.; Szarek, J. L.; Valentovic, M. A. Potentiation of 5-hydroxytryptamine-induced contraction in rat aorta by chlorpheniramine, citalopram and fluoxetine. *Eur. J. Pharmacol.* **1992**, *217*, 109−118.
(95) Cohen, M. L.; Fuller, R. W.; Wiley, K. S. Evidence for 5-HT_2 receptors mediating contraction in vascular smooth muscle. *J. Pharmacol. Exp. Ther.* **1981**, *218*, 421−425.

JM981094E