Synthesis and Molecular Modeling of New 1-Aryl-3-[4-arylpiperazin-1-yl]-1-propane Derivatives with High Affinity at the Serotonin Transporter and at 5-HT_{1A} Receptors

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It has been proposed that 5-HT_{1A} receptor antagonists augment the antidepressant efficacy of selective serotonin (5-HT) reuptake inhibitors. In a search toward new and efficient antidepressants, 1-(aryl)-3-[4-arylpiperazin-1-yl]-1-propane molecular hybrids were designed, synthesized, and evaluated for 5-HT reuptake inhibition and 5-HT_{1A} receptor affinity. The design was based in coupling structural moieties related to inhibition of serotonin reuptake, such as benzo[*b*]-thiophene derivatives to arylpiperazines, typical 5-HT_{1A} receptor ligands. In binding studies, several compounds showed affinity at the 5-HT transporter and at 5-HT_{1A} receptors. Molecular modeling studies predicted the pharmacophore elements required for high affinity binding and the features that enable to discriminate between agonist, partial agonist, or antagonist action at 5-HT_{1A} receptors and 5-HT transporter inhibition. Solvent interactions in desolvation prior to the binding step along with enthalpy and enthropy compensations might be responsible to explain agonist, partial agonist, and antagonist character. Hydrogen-bonding capability seems to be important to break hydrogen interhelical hydrogen bonds or alternatively to form other bonds upon ligand binding. Partial agonists and antagonists are unable to do this as the full agonist, which interacts closely by long-range forces or directly. The compounds showing the higher affinity at both the 5-HT transporter (K_i < 50 nM) and the 5-HT_{1A} receptors (K_i < 20 nM) were further explored for their ability to stimulate [^{35}S]GTPγS binding or to antagonize 8-hydroxy-2-di-*n*-propylamino-tetralin (8-OH-DPAT)-stimulated [^{35}]GTPγS binding to rat hippocampal membranes, an index of agonist/antagonist action at 5-HT_{1A} receptors, respectively. Compound **8g** exhibited agonist activity (EC_{50} = 30 nM) in this assay, whereas compounds **7g** and **8h**,**i** behaved as weak partial agonists and **7h**−**j** and **8j**,**l** antagonized the *R*(+)-8-OH-DPAT-stimulated GTPγS binding. Functional characterization was performed by measuring the antagonism to 8-OH-DPAT-induced hypothermia in mice.

Introduction

The selective 5-HT reuptake inhibitors (SSRIs) are effective in major depression. However, there are two serious problems in the pharmacological treatment of depression, the 2−6 week delay in the onset of therapeutic benefit after antidepressant administration and the lack of a consistent response to treatment in aproximately 30% of patients.[1] SSRIs are thought to have a delayed onset partly because of the need to overcome the inhibitory influence of 5-HT_{1A} somatodendritic autoreceptors, which inhibit the firing rate of serotonergic neurons.[2] Pindolol, a 5-$HT_{1A/1B}$ and β-adrenoreceptor antagonist, accelerates and in some cases enhances the onset of antidepressant effects when given in combination with SSRIs. The effect of pindolol has been related to an antagonist effect on somatodendritic 5-HT_{1A} autoreceptors, although the partial agonist properties of pindolol at 5-HT_{1A} and β-adrenoceptors suggest that other mechanisms of action are still posible.[3]

In previous studies,[4−6] we have reported the synthesis of a series of 1-aryl-3-[4-arylpiperazin-1-yl]propane, which showed moderate to high affinity at 5-HT transporter and 5-HT_{1A} receptors (general structure A, Chart 1). The benzo[*b*]thiophene derivatives **1**[5] and **2**[6] (Chart 1) showed the higher affinity. As a continuation of our research program, we have analyzed a new set of derivatives (general structure B, Chart 2) with the aim of obtaining efficacious 5-HT transporter blockers with high antagonist potency at 5-HT_{1A} autoreceptors. We considered two series of benzo[*b*]thiophen derivatives

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Chart 1. Structures of the Investigated Compounds

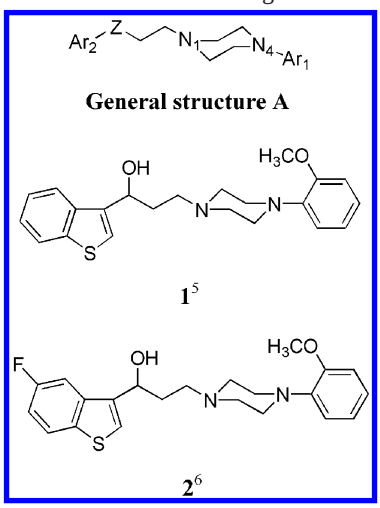
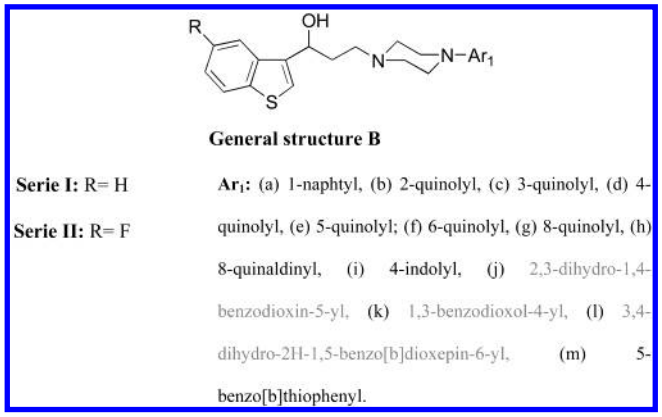


Chart 2. General Structure of the Presented Compounds



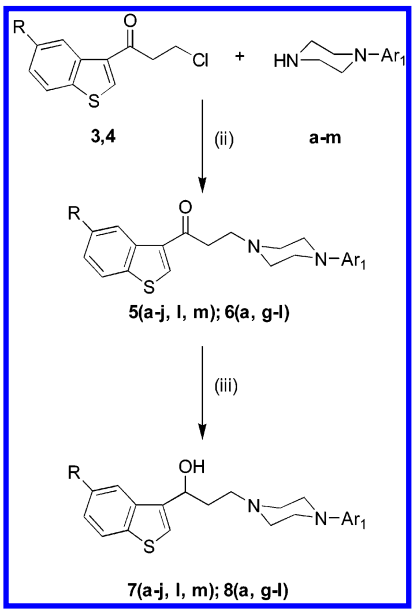
(series **I** and **II**) (Chart 2) in which we explored the influence of different benzocondensed arylpiperazines.

Chemistry

The general strategy for the synthesis of the target compounds is summarized in Scheme 1. An aliphatic nucleophilic substitution in tetrahydrofurane (THF) and K_2CO_3 affords the corresponding 1-(3-benzo[*b*]thiophenyl)-3-[4-arylpiperazin-1-yl]propanone derivatives **5a**−**j**,**l**,**m** and **6a**,**g**−**l**. The reduction of these ketones with sodium borohydride in methanol at 0 °C gave the corresponding alcohol derivatives **7a**−**j**,**l**,**m** and **8a**,**g**−**l**. 1-(3-Benzo[*b*]thiophenyl)-3-chloropropan-1-one derivatives (**3** and **4**) were synthesized by a Friedel−Craft acylation of the corresponding benzo[*b*]thiophene precursors (Scheme 2). Benzo[*b*]thiophene is commercially available while 5-fluorobenzo[*b*]thiophene was prepared as described.[7]

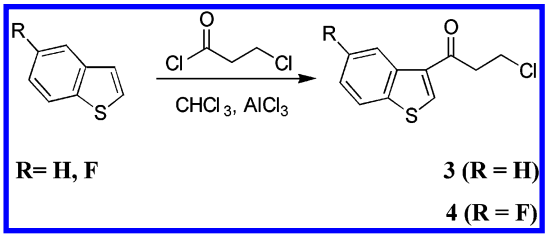
For the synthesis of the piperazines **11a**−**m**, two synthetic strategies were followed via amino precursors **11a**,**c**,**e**−**m** (Scheme 3) or via chloro precursors **11b**,**d** (Scheme 4). In the first synthetic route, in the cases in which the amino precursor was not commercially available, the nitro precursor was reduced with hydrazine monohydrate and Ni−Raney in methanol. The bibliographic references for the synthesis of the nitro precursors are depicted in Scheme 3. The preparation of the 4-nitro-1,3-benzodioxolpiperazine was carried out from 3-nitrocatechol with dibromomethane by the method

Scheme 1[a]



[a] Reagents: (ii) THF, K_2CO_3, room temperature. (iii) Methanol, BH_4Na, 0 °C. R = H, F. Ar_1: (a) 1-Naphthyl, (b) 2-quinolyl, (c) 3-quinolyl, (d) 4-quinolyl, (e) 5-quinolyl, (f) 6-quinolyl, (g) 8-quinolyl, (h) 8-quinaldinyl, (i) 4-indolyl, (j) 2,3-dihydro-1,4-benzodioxin-5-yl, (k) 1,3-benzodioxol-4-yl, (l) 3,4-dihydro-2H-1,5-benzo[*b*]dioxepin-6-yl, and (m) 5-benzo[*b*]thiophenyl.

Scheme 2

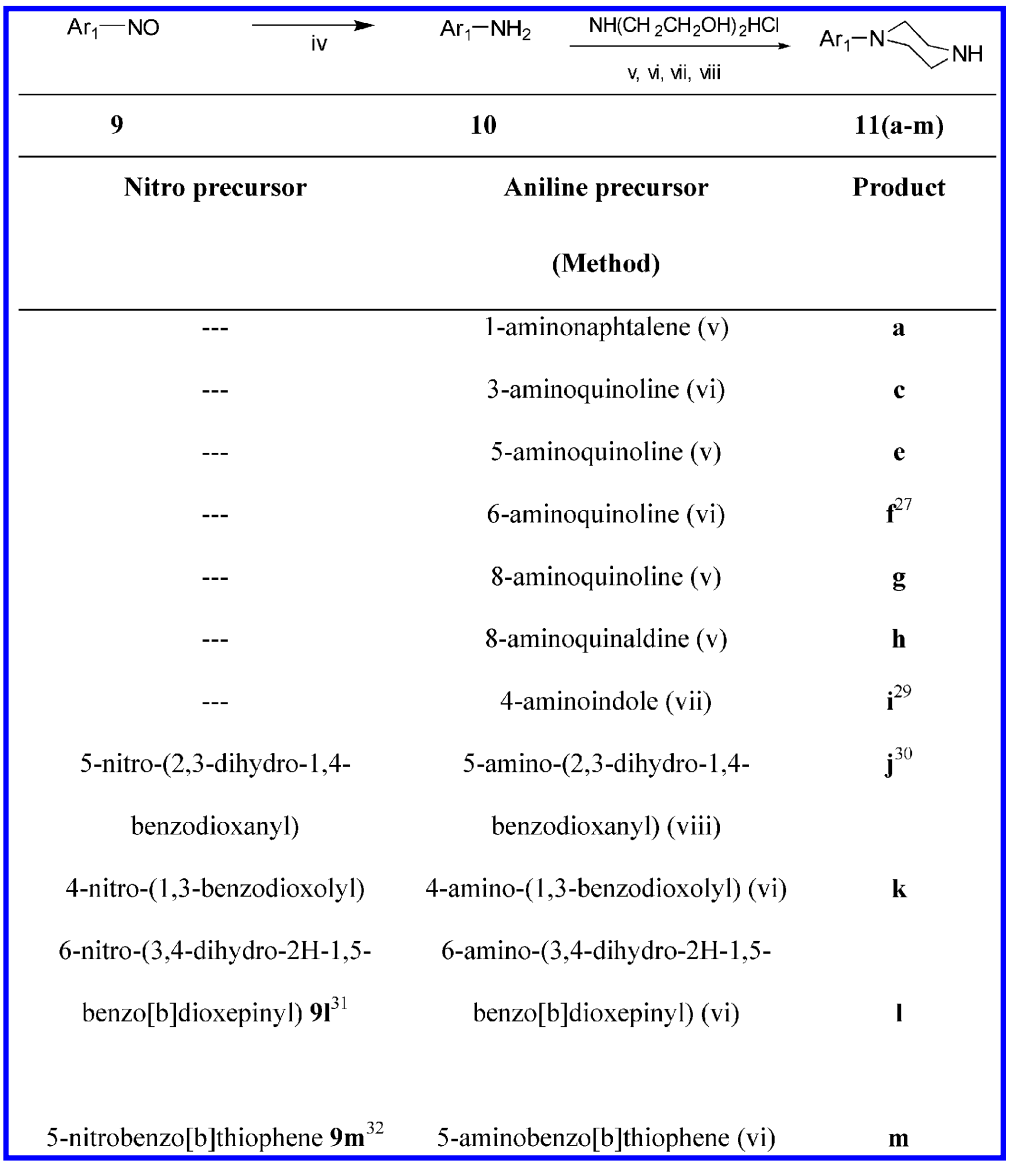


described for its analogue 3,4-dihydro-2H-6-nitro-1,5-benzo[*b*]dioxepinpiperazine in ref 30 (see Experimental Section).

The second strategy started with the chloro precursors, which react with the piperazine in an aromatic nucleophilic substitution (Scheme 4). This route was chosen for 2-quinolylpiperazine[8] (quipazine) **11b** and 4-quinolylpiperazine[9] **11d**. All compounds were characterized by physical constants, elemental analysis, IR, and ^{1}H NMR.

Molecular Modeling. To determine the pharmacophore elements required to discriminate functional effect at 5-HT_{1A} receptors and 5-HT transporter inhibition, a molecular modeling study using the CATALYST[10] software package was undertaken. The automatic identification of pharmacophoric pattern based on atomistic comparison has been extensively described (e.g., Disco, Compair, Family).[11] Another promising approach for defining alignment rules focuses on the consideration of chemical features rather than explicit atoms.[12,13] Within the program CATALYST, feature-based alignments are produced in a three step procedure: (i) for each molecule, a conformational model is generated using a quasi random sampling approach with sequential poling,[14] which has been shown to produce a good coverage of the conformational space;[15−16] (ii) each conformer is examined for the presence of

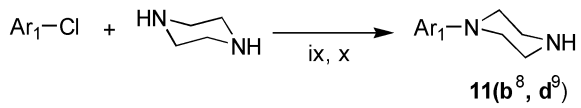
Scheme 3[a]



9	10	11(a-m)
Nitro precursor	**Aniline precursor (Method)**	**Product**
---	1-aminonaphtalene (v)	**a**
---	3-aminoquinoline (vi)	**c**
---	5-aminoquinoline (v)	**e**
---	6-aminoquinoline (vi)	**f**[27]
---	8-aminoquinoline (v)	**g**
---	8-aminoquinaldine (v)	**h**
---	4-aminoindole (vii)	**i**[29]
5-nitro-(2,3-dihydro-1,4-benzodioxanyl)	5-amino-(2,3-dihydro-1,4-benzodioxanyl) (viii)	**j**[30]
4-nitro-(1,3-benzodioxolyl)	4-amino-(1,3-benzodioxolyl) (vi)	**k**
6-nitro-(3,4-dihydro-2H-1,5-benzo[b]dioxepinyl) **9l**[31]	6-amino-(3,4-dihydro-2H-1,5-benzo[b]dioxepinyl) (vi)	**l**
5-nitrobenzo[b]thiophene **9m**[32]	5-aminobenzo[b]thiophene (vi)	**m**

[a] Reagents: (iv) Methanol, $NH_2-NH_2 \cdot H_2O$, Ni—Raney. (v) K_2CO_3, C_6H_5Cl, △. (vi) C_6H_5Cl, △. (vii) Diisopropylethylamine, C_6H_5Cl, △. (viii) *p*-TosOH, C_6H_5Cl, △.

Scheme 4[a]



11(b[8]**, d**[9]**)**

Ar_1: 2-quinoline (**b**)
4-quinoline (**d**)

[a] Reagents: (ix) △ (**b**). (x) Toluene, △ (**d**).

chemical features; and (iii) a set of chemical features common to the input molecules that correlates best with biological activity is determined. Global minimum energy conformation is not always the bioactive conformation, above all in the case of ionizable or charged structures where hydrophobic interactions are not structural determinants by strong intramolecular packings.

This three-dimensional (3D) array of chemical features (called a hypothesis) provides a relative alignment for each input molecule. In CATALYST, the chemical features considered can be H bond acceptors and donors, aliphatic and aromatic hydrophobes, positive and negative charges, positive and negative ionizable groups, and aromatic planes.[17] Multiple hypotheses are produced and ranked according to how well they explain the biological activity of the input molecule set. In a hypothesis, each pharmacophoric function is characterized by points defined by the location constraint (*x*,*y*,*z* coordinates in Cartesian space) surrounded by a tolerance sphere.

In a first step, a model describing the common feature pharmacophore of all 19 5HT transport inhibitors was generated using the HipHop algorithm within CATALYST. The highest ranking resulting model (Hypo-1.01-1, Figure 1) was obtained when the maximum miss of one function was allowed to consist of six features (one hydrophobic and three hydrophobic aromatic functions, one positive ionizable, and one H bond acceptor function). All compounds of the training set except one of

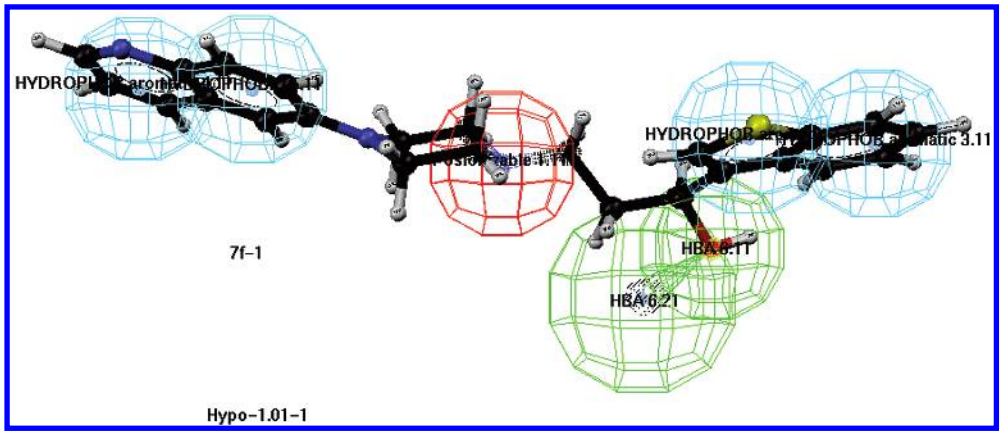
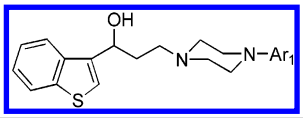


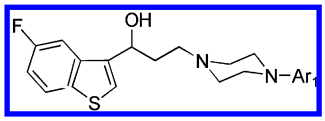
Figure 1. Mapping of the most potent 5HT transporter inhibitor (**7f**, K_i = 2.2 nM, fit value = 6.0) fitted onto common feature pharmacophore model Hypo-1.01-1 obtained for inhibitors of the 5HT transporter. Pharmacophore features are color-coded (cyan, hydrophobic; blue, hydrophobic aromatic; red, positive ionizable; green, H bond acceptor).

Table 1. Compounds of Series I: Structure and Affinity for 5-HT_{1A} Receptors and for 5-HT Transporter



		K_i (nM)	
compd	Ar_1	5-HT_{1A} receptor	5-HT transporter
7a	1-naphthyl	66.7	81.7
7b	2-quinolyl	377	6.4
7c	3-quinolyl	995	4.2
7d	4-quinolyl	301	19.4
7e	5-quinolyl	36.8	32.5
7f	6-quinolyl	546	2.2
7g	8-quinolyl	6.3	24
7h	8-quinaldinyl	10.2	9.9
7i	4-indolyl	5.5	4.1
7j	2,3-dihydro-1,4-benzodioxin-5-yl	5.7	50
7l	3,4-dihydro-2H-1,5-benzo[*b*]dioxepin-6-yl	1.9	77
7m	5-benzo[*b*]thiophenyl	913	3.2

Table 2. Compounds of Series II: Structure and Affinity for 5-HT_{1A} Receptors and for 5-HT Transporter



		K_i (nM)	
compd	Ar_1	5-HT_{1A} receptor	5-HT transporter
8a	1-naphthyl		62
8g	8-quinolyl	2.7	7.5
8h	8-quinaldinyl	2.5	9.4
8i	4-indolyl	5.9	7.3
8j	2,3-dihydro-1,4-benzodioxin-5-yl	6	16
8k	1,3-benzodioxol-4-yl	9.4	58
8l	3,4-dihydro-2H-1,5-benzo[*b*]dioxepin-6-yl	3	21.2

the less active molecules (**8k**, K_i = 58 nM) are able to map all functions of this model. If all of the active compounds retrieved from a 3D structural database using the CATALYST pharmacophore hypothesis should map all of the features of a model, our best model for 5-HT transporters was able to retrieve more than 94% (18 out of 19) of the active compounds in Tables 1 and 2.

When no miss of features was allowed during model generation, a slightly modified model was obtained containing one hydrophobic feature less than the previously calculated hypothesis (Hypo-4.01, Figure 2). Moreover, in this model, which is able to retrieve all compounds of the training set, the hydroxy groups of the compounds are represented as H bond donors.

In a second step, the generation of pharmacophore models permitting the discrimination between 5HT_{1A} receptor antagonistic and partial agonistic activity was envisaged. Therefore, we calculated common feature models starting both from the four potent antagonists **8j** and **7h**−**j** and from the five partial agonists **2222**[5] (1-(benzo[*b*]thiophen-3-yl)-3-[4-(2-methoxyphenyl)piperazin-1-yl]1-propanol) (Chart 1, Figure 1), **8422**[6] (1-(5-fluorobenzo[*b*]thiophen-3-yl)-3-[4-(2-methoxyphenyl)piperazin-1-yl]1-propanol) (Chart 1, Figure 2) (compounds previously synthesized in our department with the same aim), **7g**, and **8h**,**i**. As all compounds exhibit affinity values in the low nanomolar range, no feature misses were allowed. The best model obtained for receptor antagonists (Hypo-3.01, represented in Figure 3 with compound **7i**) consists of six features (two hydrophobic functions, one positive ionizable, one H bond donor, one lipophilic H bond acceptor, and one aromatic ring with direction constraint). In contrast to the models described before for 5-HT transporter inhibition, the "right" part of the pharmacophore consists of an aromatic system containing a directed H bond acceptor function. When using this model for in silico filtering of compounds described in this study, only receptor antagonists are found exhibiting fit values for the model in a range of 3.0−6.0. The fit values are calculated for comparing a compound and a hypothesis. The quality of the mapping is indicated by the fit value. A higher fit value represents a better fit. The computed fit value depends on two parameters: how close the features in the molecule are to the centers of the corresponding location constraints in the hypothesis and the weights assigned to the hypothesis features (in our case, a value of one per feature, giving a total fit of 6.0 for a compound perfectly fitting to all features of the model).

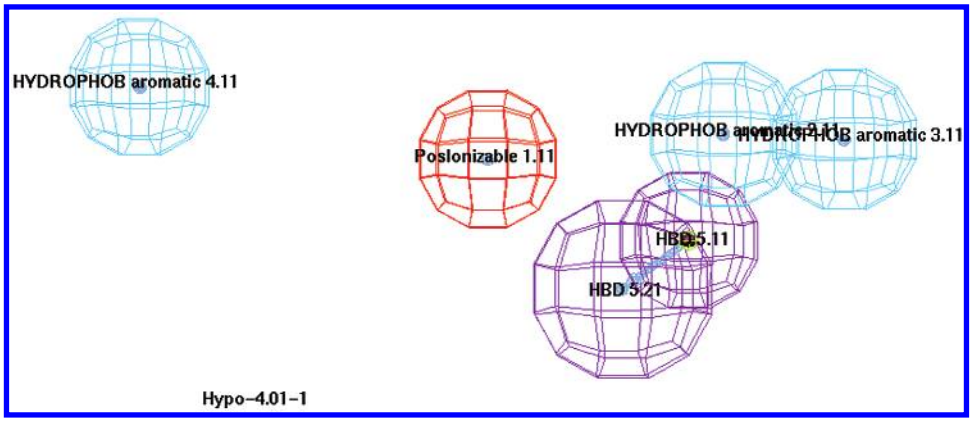


Figure 2. Common feature pharmacophore model Hypo-4.01-1 obtained for inhibitors of the 5HT transporter. Pharmacophore features are color-coded (blue, hydrophobic aromatic; red, positive ionizable; green, H bond acceptor).

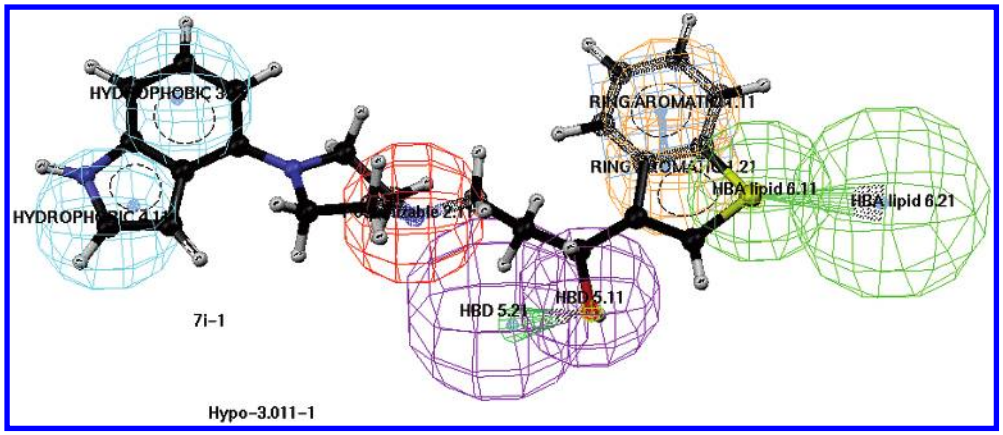


Figure 3. Mapping of compound **7i** on the best common feature pharmacophore model obtained for receptor antagonists (Hypo-3.01). Pharmacophore features are color-coded (cyan, hydrophobic; red, positive ionizable; magenta, H bond donor; brown, aromatic ring; green, H bond acceptor).

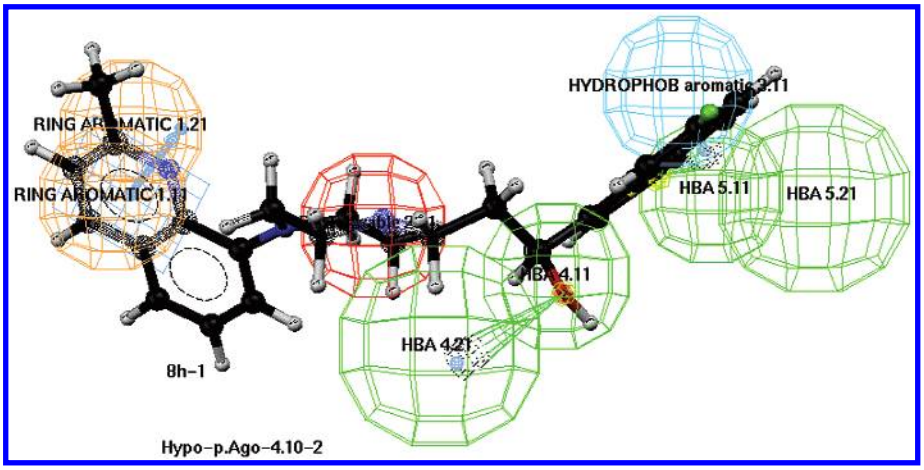


Figure 4. Compound **8h** mapped on common feature pharmacophore model obtained for partial agonists (Hypo-p.Ago-4.10-2). Pharmacophore features are color-coded (blue, hydrophobic aromatic; red, positive ionizable; brown, aromatic ring; green, H bond acceptor).

On the other hand, when using the partial agonists for model generation, a hypothesis containing five features was obtained (Hypo-p.Ago-4.10-2, represented in Figure 4 with compound **8h**). This hypothesis is also different from those calculated from the 5-HT transporter inhibitors.

In contrast to the model for antagonists, the "left" part of the partial agonist pharmacophore (Figure 4) consists now of a directed aromatic ring function and the right part contains both a hydrophobic function (mapping the fluoro-substituted aromatic ring) and another H bond acceptor. Moreover, the hydroxyl group in these compounds is recognized as acting as a H bond acceptor too. When using this hypothesis as a 3D query for database search of the compounds under investigation, partial agonists are retrieved with fit values in a range of 3.6−5.0, which is somehow less selective than the model for antagonists.

Biological Results and Discussion

All of the synthesized compounds (19 piperazine derivatives) were evaluated for their affinity at 5-HT_{1A} receptors and the 5-HT transporter. Structure and binding data of the compounds are shown in Tables 1 and 2. The inhibition constant (K_i) was obtained from the IC_{50} by the Cheng−Prusoff equation.[21]

The inspection of binding data with compounds from series **I** and **II** (benzothiophene and 5-fluorobenzo[*b*]-thiophene derivatives) permitted the assessment of the following structure−activity relationships (SARs):

All of the compounds showed affinity for both receptors. The best results were obtained with nine of them (**7g**−**j** and **8g**−**j**,**l**). The presence of fluoro at the benzo[*b*]thiophene (series **I** or **II**) did not appear to influence decisively in the affinity of the synthesized compounds, suggesting that the aromatic system in terms of electronic structure and π clouds is not directly involved in the recognition and binding process for these chemotypes at the 5-HT_{1A} receptor whether electronic factors play a substantial role in the trasporter recognition and binding process. Conformational changes due to a different folding of the molecule as a consequence of the fluorine withdrawn effects may account for the reduced selectivity at the receptor. Nevertheless, the presence of a heteroatom and its position appear to be critical for the affinity at 5-HT_{1A} receptors, with the compounds derived from 8-quinolyl showing the best results. Heteroatoms may lead to additional cooperative noncovalent interactions finally increasing the "ligand valency"[18] in terms of contacting points in the recognition and binding process, i.e., extending the pharmacophore capability. The methyl group of the quinaldine ring does not significantly affect the affinities suggesting that no strict steric constrains are in the binding process, which might be mainly governed by electronic more than steric factors. Modification of the distance between the heteroatoms in the piperazines **j**−**l** affects the affinity to the 5-HT transporter. Changing the heteroatoms arrangement may lead to their improper location, therefore repulsive interactions, or their exclusion from advantageous binding interactions.

The compounds that exhibited high affinity at 5-HT_{1A} receptors (K_i < 20 nM) and the 5-HT transporter (K_i < 50 nM) were selected to determine the agonist or antagonist action at 5-HT_{1A} receptors by means of [^{35}S]GTPγS binding assays in hippocampal membranes.

For agonist activity, the effects of nine compounds were compared with the selective 5-HT_{1A} receptor agonist *R*(+)-8-hydroxy-2-di-*n*-propylamino-tetralin (8-OH-DPAT) for stimulation of [^{35}S] GTPγS binding (Table 3). Compound **8g** produced a significant stimulation (% increase = 71.38%) in a concentration-dependent manner (EC_{50} = 31 nM), whereas the compounds **7g** and **8h**,**i** only partially stimulated GTPγS binding by 31, 27.7, and 33.5%, respectively. The data suggest that **8g** is a 5-HT_{1A} receptor full agonist while **7g** and **8h**,**i** only show a partial agonist action.

Hydrogen-bonding capability seems to be important to break the hydrogen-bonding network, i.e., interhelical hydrogen bonds (presumably at amino acids in TMH1, -2, -3, and -7 with their constrain relative to each other) or to attenuate them as recently reported at Asn54(TMH1)−Asp82(TMH2) or alternatively to form other bonds upon ligand binding followed by rigid body movements of TMH4 and -6 relative to each other and to the other TMHs, switching on the conversion to an active receptor structure.[19−20]

Table 3. Effect of Selected Compounds on [^{35}S]GTPγS Binding in Isolated Rat Hippocampal Membranes[a]

compds	basal fmol GTPγS bound/mg protein	maximal fmol GTPγS bound/mg protein	increase (%)
R(+)-8-OH-DPAT	13.50 ± 0.8	25.9 ± 1.6	91.85**
7g	11.87 ± 1.12	15.55 ± 1.71	31.00*
7h	11.20 ± 1.21	12.48 ± 1.54	11.42
7i	13.36 ± 3.32	16.87 ± 3.12	26.3
7j	15.57 ± 4.31	16.10 ± 1.91	3.4
8g	13.87 ± 1.31	23.87 ± 2.21	71.38**
8h	14.43 ± 0.90	18.43 ± 1.10	27.7*
8i	10.08 ± 0.81	13.66 ± 2.90	35.5*
8j	11.87 ± 1.70	14.00 ± 0.32	17.94
8l	14.41 ± 1.43	17.70 ± 1.62	22.83

[a] Compounds tested at concentrations from 10^{-10} to 10^{-5}. Values represent the mean ± SEM from three separate experiments. Significant increase, *p < 0.05; **p < 0.01 (one way ANOVA followed by Student−Newman−Keuls test).

The piperazine ring of the ligands whether protonated[19,20] may interact with the aspartic acid in TMH3 or that highly conserved closer to intracellular end of the TMHs intracellular end. A negative area outside the Asp116, which is a key residue in the ligand binding, might be a guide region for the interaction.[18−20] Considering the ambiguous character of the piperazine ring, an uncharged form of it may exist allowing for a different binding mode or representing a silent state of the ligand before binding.[19−21]

Compounds with no agonistic activity in this system were then tested in antagonism studies (Table 4). The selective 5-HT_{1A} receptor antagonist WAY 100635 did not alter GTPγS binding by itself but fully prevented the 8-OH-DPAT-induced effect, a result in keeping with previous studies. All other compounds in Table 4 exhibited antagonist activity at 5-HT_{1A} receptors, as inferred from the inhibition of *R*(+)-8-OH-DPAT-stimulated [^{35}S]GTPγS binding. The compounds **8j** and **7h**−**j** exhibited antagonist activity with minimal or not detectable agonist effect.

In vivo, pharmacological evaluation of the antagonist activity at 5-HT_{1A} receptors was assessed by measuring mouse rectal temperature (Table 5). All of the compounds antagonizing (+)-8-OH-DPAT-stimulated GTPγS binding were assayed. The 5-HT_{1A} receptor agonist 8-OH-DPAT, 0.5 mg/kg s.c., produced a marked decrease in rectal temperature, an effect probably mediated through activation of somatodendritic 5-HT_{1A} receptors. This study also showed that the compounds **7g**,**i**,**j** and **8i**,**j** at 10 mg/kg i.p. significantly antagonized the hypothermic response to 8-OH-DPAT at different times after administration. Consequently, in vitro and in vivo studies for 5-HT_{1A} receptor function rather appear to reflect an antagonist profile of compounds **7h**−**j** and **8j**,**l** at this 5-HT receptor subtype. According to current theories (see Introduction), 5-HT uptake blockers with an additional antagonist activity at somatodendritic 5-HT_{1A} receptors may be efficacious antidepressants with quicker onsets of action.

Conclusions

In this study, we synthesized two series of benzo[*b*]-thiophene (**I** and **II**) derivatives with different arylpip-

Table 4. Inhibition of (+)-8-OH-DPAT-Stimulated [^{35}S]GTPγS Binding in Hippocampal Membranes[a]

compd	basal fmol GTPYγS bound/mg protein	maximal fmol GTPγS bound/mg protein	inhibition (%)	IC_{50} (nM)
control (*R*(+)-8-OH-DPAT)	12.98 ± 0.9	23.83 ± 1.41**		
WAY 100635	16.34 ± 1.00	15.89 ± 0.98	104	5.7 ± 2.2
7g	16.37 ± 2.33	19.69 ± 3.06	69	18.03 ± 1.5
7h	12.28 ± 3.64	12.47 ± 3.03	98	31.47 ± 14
7i	12.84 ± 1.09	13.92 ± 1.34	90	31.19 ± 16
7j	18.53 ± 0.80	19.09 ± 0.43	90	56.21 ± 10
8h	19.29 ± 3.38	21.38 ± 2.45	80	3.80 ± 1.8
8i	11.22 ± 1.60	10.06 ± 1.23	110	16.12 ± 45
8j	19.07 ± 2.16	18.90 ± 6.2	101	31.16 ± 6.4
8l	18.69 ± 1.08	20.42 ± 2.40	84	360 ± 82

[a] Values represent the mean ± SEM from three separate experiments. *P < 0.05 vs basal. *R*(+)-8-OH-DPAT used at a single 1 μM concentration. All other compounds tested at concentrations from 10^{-12} to 10^{-5} M in the presence of the above indicated 8-OH-DPAT concentration.

Table 5. Time-Dependent Effects of WAY 100635 and Selected Compounds on 8-OH-DPAT-Induced Hypothermia in Mice[a]

compds	dose (mg/kg)	change in body temp (°C) 15 min	30 min	60 min
control (*R*(+)-8-OH-DPAT)		−3.05 ± 0.12	−2.85 ± 0.15	−2.07 ± 0.13
WAY 100635	1	−0.71 ± 0.21**	−0.95 ± 0.15**	0.35 ± 0.09**
7g	1	−2.38 ± 0.34	−1.86 ± 0.37	−1.09 ± 0.10
	10	−0.80 + 0.30**	−0.52 ± 0.24**	−0.20 ± 0.19**
7h	1	−2.10 ± 0.27	−2.46 ± 0.41	−1.76 ± 0.26
	10	−2.19 ± 0.45	−2.31 ± 0.22	−1.62 ± 0.09
7i	1	−2.08 ± 0.24*	−1.59 ± 0.25	−1.13 ± 0.22
	10	−1.03 ± 0.32**	0.84 ± 0.22**	−0.80 ± 0.22**
7j	1	−2.90 ± 0.27	−2.47 ± 0.26	−1.94 ± 0.35
	10	−1.38 ± 0.37**	−1.03 ± 0.28**	−0.50 ± 0.09**
8h	1	−2.85 ± 0.14	2.45 ± 0.40	1.92 ± 0.22
	10	−2.50 ± 0.36	1.71 ± 0.44	1.48 ± 0.25
8i	1	−3.28 ± 0.46	−3.61 ± 0.34	−2,72 ± 0.84
	10	−0.95 ± 0.17**	−0.89 ± 0.19**	−0.95 ± 0.16**
8j	1	−1.49 ± 0.19*	−1.04 ± 0.16*	−1.04 ± 0.13*
	10	−1.33 ± 0.40**	−0.72 ± 0.16**	−0.84 ± 0.10**

[a] 8-OH-DPAT was given always at a single dose of 0.5 mg/kg, s.c. All other drugs were given 30 min before 8-OH-DPAT. Values (means + SEM) correspond to changes in rectal temperature measured immediately before first drug injection and at different times after 8-OH-DPAT. *p < 0.05; **p < 0.01 vs 8-OH-DPAT group (one way ANOVA followed by Student−Newman−Keuls test).

erazines in order to obtain new compounds with affinity at both the 5-HT_{1A} receptor and the 5-HT transporter. All of the compounds showed high affinity for both sites. From GTPγS binding assays, it could be concluded that **8g** exhibited agonist activity, whereas compounds **7g** and **8h**,**i** behaved as weak partial agonists and **7h**−**j** and **8j**,**l** antagonized the 8-OH-DPAT-stimulated GTPγS binding. Body temperature studies in mice revealed also an antagonist activity at this 5-HT receptor subtype. Using ligand-based modeling techniques, we established chemical features based on pharmacophore models. Elements required for high affinity binding and the features that enable one to discriminate between optimal 5-HT_{1A} receptor agonist, partial agonist, or antagonist activity were determined. Our models particularly emphasize the role of the hydrogen-bonding capability of the ligands in affecting the receptor operating as well as the inhibition of the 5-HT transporter. By calculating the fit values of compounds to the different models obtained, it is possible to predict in silico the biological effect of molecules to the targets under investigation.

High affinity ligands are assumed to adopt energetically favorable conformations in the receptor orienting their molecular features toward the target in a more optimal way than the low affinity compounds. Binding of full agonists seems to induce larger conformational changes into helices 3 and 6 than into the other transmembrane helices. Receptor activation induces rigid body movements of these transmembrane helices relative to other transmembrane helices. Partial agonists and antagonists are unable to do this as the full agonist, which interacts closely by long-range forces or directly at amino acids in transmembrane helix 4 for inducing the above rigid body movements of transmembrane helices 3 and 6 relative to each other. Agonist binding (largest changes into transmembrane helices 2, 4, and 5) has stronger effects on the helical packing and overall structure of the receptor than binding of the antagonist. The binding of agonist might constrain the movements of the third intracellular loop more than did the partial agonist and the antagonist.[19,20] Solvent interactions in desolvation prior to the binding step along with enthalpy/entropy compensations might be responsible to explain agonist/partial agonist and antagonist character.[21−23] Conversion into a proper structure for G-protein interactions has also been reported by conformational−structural changes at TMHs I2 and I3.[20]

Experimental Section

Chemistry. Melting points were determined using a Mettler FP82+FP80 apparatus and are uncorrected. Elemental analyses were obtained from vacuum-dried samples (over phosphorus pentoxide at 3−4 mmHg, 24 h, at ca. 80−100 °C) with a Leco CHN-900 instrument and are within ±0.4% of the calculated values except where otherwise stated. Infrared spectra were recorded on a Perkin-Elmer 681 apparatus, using potassium bromide tablets for solids products and sodium chloride plates for oil products; the frequencies are expressed

in cm^{-1}. ^1H NMR spectra were recorded on a Brucker AC-200E (200 MHz) instrument, with tetramethylsilane (TMS) as the internal reference, at a concentration of ca. 0.1 g/mL and with dimethyl sulfoxide-d_6 (DMSO-d_6) or chloroform ($CDCl_3$) as solvents; chemical shifts are expressed in parts per million (ppm) relative to internal TMS in δ units, and the coupling constants (J) values are in hertz (Hz). The mass spectra were recorded on a Hewlett-Packard 5988-A instrument at 70 eV.

Thin-layer chromatography (TLC) was run on Merck silica gel 60 F-254 plates with the indicated solvents and revealed with iodine, and the plates were scanned under ultraviolet light at 254 and 366 nm. Column chromatography was carried out with Merck silica gel 60 (70−230 mesh ASTM).

Synthesis of 4-Nitro-(1,3-benzodioxolyl) (9k). A mixture of 6.2 mmol of nitrocathecol, 18.6 mmol of K_2CO_3, 9.3 mmol of 1,2-dibromomethane, and 0.62 mmol of tetrabutylammonium bromide in toluene (30 mL) was refluxed for 24 h under N_2 atmosphere. Once the reaction mixture was cooled, the solvent was removed under reduced pressure. The obtained product was purified by flash chromatography (SP: silica gel), eluting with toluene; yield 40%; mp 118 °C. IR (KBr): 1546, 1358 cm^{-1}. ^{1} NMR (DMSO-d_6) δ (free base): 6.16 (s, 2H, O−CH_2−O); 6.87 (t, 1H, H_6); 7.01 (d, 1H, H_7); 7.55 (d, 1H, H_5). Anal. ($C_7H_5NO_4$) C, H, N.

General Procedure for Preparation of the Amine Precursors 10i,k,m. Ni−Raney and hydrazine monohydrate (1 mol) were added to a well-stirred solution of the corresponding nitro derivative **9i,k,m** (1 mol) in methanol at 0 °C. The stirring was continued for 2−3 h. The reaction mixture was filtered over Celite, and the solvent was removed under reduced pressure. The obtained product was purified by flash chromatography (SP: silica gel), eluting with dichloromethane.

4-Aminoindole (10i). Yield 67%; mp 106−108 °C. IR (KBr): 3368 cm^{-1}. ^{1} NMR (DMSO-d_6) δ (free base): 5.09 (s, 2H, NH_2); 6.48 (s, 1H, H_6); 6.60 (d, 2H, $H_5 + H_7$, $J = 8.04$); 6.76 (t, 1H, H_3); 7,06 (t, 1H, H_2); 10.71 (s, 1H, NH). Anal. ($C_8H_8N_2$) C, H, N.

4-Amino-(1,3-benzodioxolyl) (10k). Yield 90%; mp 136−138 °C. IR (KBr): 3348 cm^{-1}. ^{1} NMR (DMSO-d_6) δ (free base): 3.42 (b.s., 2H, NH_2); 5.83 (d, 2H, O−CH_2−O); 6.26 (t, 1H, $H_5 + H_7$); 6.60 (t, 1H, H_6). Anal. ($C_7H_7NO_2$) C, H, N.

5-Aminobenzo[*b*]thiophene (10m). Yield 66%; mp 270−272 °C. IR (KBr): 3412 cm^{-1}. ^{1} NMR ($CDCl_3$) δ (free base): 6.70 (dd, 1H, H_6); 7.02 (d, 1H, H_4); 7.07 (d, 1H, H_3); 7.30 (d, 1H, H_2); 7.56 (d, 1H, H_7). Anal. (C_8H_7NS) C, H, N.

General Procedure for Preparation of the Piperazines (a,e,g,h). A suspension of the corresponding amino precursor **10a,e,g,h** (0.12 mmol), bis(chloroethyl)amine hydrochloride (0.12 mmol), and K_2CO_3 (0.12 mmol) in chlorobenzene (250 mL) was stirred under reflux for 24 h. Once the reaction mixture was cooled, the solvent was removed under reduced pressure. The residue was treated with 2 N NaOH (75 mL) and extracted with AcOEt (3 × 75 mL). The extracts were dried (Na_2SO_4), and after it was evaporated, the residue was purified by flash chromatography (SP: silica gel), eluting with dichloromethane/MeOH (90:10) (V:V). In some cases, the hydrochloride salt of the product was formed by adding some drops of concentrated hydrochloric acid to a solution of the piperazine free base in acetone.

1-(1-Naphthyl)piperazine Hydrochloride (a). Yield 35%; mp 235−237 °C. IR (KBr): 3375 cm^{-1}. ^{1} NMR (DMSO-d_6) δ (free base): 2.14 (s, 4H, $N^4(CH_2)_2$); 3.07 (s, 4H, $N^1(CH_2)_2$); 7.19 (d, 1H, H_2 $J = 7.2$); 7.28−7.50 (m, 4H, $H_3 + H_4 + H_6 + H_7$); 7.94 (dd, 1H, H_8 $J_{56} = 7.2$ $J_{57} = 3.6$); 8.18 (dd, 1H, H_5 $J_{78} = 7.2$ $J_{68} = 3.7$). Anal. ($C_{14}H_{16}N_2$·HCl) C, H, N.

1-(5-Quinolyl)piperazine (e). Yield 23%. IR (KBr): 3368 cm^{-1}. ^{1} NMR (DMSO-d_6) δ (free base): 2.96 (s, 8H, $N(CH_2)_4$); 7.15 (c, 1H, H_4); 7.33 (c, 1H, H_7); 7.44−7.54 (m, 1H, H_3); 7.61−7.73 (m, 1H, H_2); 8.53 (dd, 1H, H_6); 8.77−8.93 (m, 1H, H_8). Anal. ($C_{13}H_{15}N_3$) C, H, N.

1-(8-Quinolyl)piperazine (g). Yield 17%. IR (KBr): 3296 cm^{-1}. ^{1} NMR (DMSO-d_6) δ (free base): 3.03 (d, 4H, $N^4(CH_2)_2$); 3.31 (t, 4H, $N^1(CH_2)_2$); 7.09−7.15 (m, 1H, H_7); 7.45−7.51 (m, 2H, $H_3 + H_6$); 8.28 (dd, 2H, $H_4 + H_5$); 8.84 (c, 1H, H_2). Anal. ($C_{13}H_{15}N_3$) C, H, N.

1-(8-Quinaldinyl)piperazine (h). Yield 30%. IR (KBr): 3414 cm^{-1}. ^{1} NMR (DMSO-d_6) δ (free base): 2.85 (s, 3H, CH_3), 3.54 (d, 4H, $N^4(CH_2)_2$); 3.69 (t, 4H, $N^1(CH_2)_2$); 7.19−7.41 (m, 4H, $H_3 + H_4 + H_5 + H_6$); 7.94 (d, 1H, H_7, $J = 8.47$). Anal. ($C_{14}H_{17}N_3$) C, H, N.

General Procedure for Preparation of the Piperazines (c,f,k,m). A suspension of the corresponding amino precursor **10c,f,k,m** (0.12 mmol) and bis(chloroethyl)amine hydrochloride (0.12 mmol) in chlorobenzene (250 mL) was stirred under reflux for 24 h. Once the reaction mixture was cooled, the solvent was removed under reduced pressure. The residue was treated with 2 N NaOH (75 mL) and extracted with AcOEt (3 × 75 mL). The extracts were dried (Na_2SO_4), and after it was evaporated, the residue was purified by flash chromatography (SP: silica gel), eluting with dichloromethane/MeOH (90:10) (V:V). In some cases, the hydrochloride salt of the product was formed by adding some drops of concentrated hydrochloric acid to a solution of the piperazine free base in acetone.

1-(3-Quinolyl)piperazine (c). Yield 17%. IR (KBr): 3485 cm^{-1}. ^{1} NMR (DMSO-d_6) δ (free base): 3.57 (d, 4H, $N^4(CH_2)_2$); 3.83 (t, 4H, $N^1(CH_2)_2$); 7.31 (d, 1H, H_4, $J = 1.9$ Hz); 7.37−7.53 (m, 2H, $H_6 + H_8$); 7.65 (dd, 1H, H_5, $J = 6$ Hz; $J = 2$ Hz); 7.86 (d, 1H, H_7); 8.74 (s, 1H, H_2). Anal. ($C_{13}H_{15}N_3$) C, H, N.

1-(6-Quinolyl)piperazine (f). Yield 63%. IR (KBr): 3423 cm^{-1}. ^{1} NMR (DMSO-d_6) δ (free base): 3.23 (d, 4H, $N^4(CH_2)_2$); 3.80 (t, 4H, $N^1(CH_2)_2$); 7.24−7.54 (m, 2H, $H_2 + H_7$); 7.80−8.04 (m, 3H, $H_3 + H_4 + H_5$); 8.38 (s, 1H, H_8). Anal. ($C_{13}H_{15}N_3$) C, H, N.

1-(1,3-Benzodioxol-4-yl)piperazine Hydrochloride (k). Yield 25%; mp 225−228 °C. IR (KBr): 3373 cm^{-1}. ^{1} NMR (DMSO-d_6) δ: 3.28 (d, 8H, piperazine), 6.00 (s, 2H, O−CH_2−O), 6.58 (t, 1H, $H_5 + H_7$), 6.83 (t, 1H, H_6), 9.14 (bs, 1H, HCl). Anal. ($C_{11}H_{17}N_2O_2$·HCl) C, H, N.

1-(5-Benzo[*b*]thiophenyl)piperazine (m). Yield 36%. IR (KBr): 3455 cm^{-1}. ^{1} NMR (DMSO-d_6) δ (free base): 2.85 (s, 3H, CH_3); 3.54 (d, 4H, $N^4(CH_2)_2$); 3.69 (t, 4H, $N^1(CH_2)_2$); 7.17 (dd, 1H, H_6); 7.32−7.41 (m, 3H, $H_2 + H_4 + H_6$); 7.70 (d, 1H, H_3, $J = 5.4$ Hz); 7.86 (d, 1H, H_7). Anal. ($C_{12}H_{14}N_2S$) C, H, N.

General Procedure for Preparation of the 1-(3-Benzo[*b*]thiophenyl)-3-[4-(aryl)piperazin-1-yl]propanone Derivatives 5a−m and 6a,g−l. A suspension of 1-(benzo[*b*]-thiophenyl)-3-chloropropanone **(3)** or 3-chloro-1-(5-fluorobenzo[*b*]thiophenyl)propanone **(4)** (depending on series **I** or **II**), the corresponding arylpiperazine **(a−m)**, and K_2CO_3 in THF was stirred during 72 h at room temperature. After the solvent was evaporated, the obtained residue was purified by flash chromatography (SP: silica gel), eluting with hexane/AcoEt (50:50) (V:V). In some cases, the hydrochloride salt of the product was formed by adding some drops of concentrated hydrochloric acid to a solution of the compound in acetone.

1-(Benzo[*b*]thiophen-3-yl)-3-[4-(naphth-1-yl)piperazin-1-yl]propan-1-one Hydrochloride (5a). Yield 25%; mp 223−226 °C. IR (KBr): 1668 cm^{-1}. ^{1} NMR (DMSO-d_6) δ: 3.33−3.86 (b.s., 12H, CH_2); 7.18 (d, 1H, H_2, $J = 7.2$); 7.41−7.54 (m, 4H, $H_{3'} + H_{5'} + H_5 + H_6$); 7.67 (d, 1H, H_4, $J = 8.00$); 7.90−7.94 (m, 1H, $H_{7'}$); 8.11 (d, 1H, H_4); 8.23 (d, 2H, $H_{6'} + H_8$, $J = 7.2$); 8.64 (d, 1H, H_7, $J = 7.5$); 9.19 (s, 1H, H_2), 9.42 (bs, 1H, HCl). Anal. ($C_{25}H_{24}N_2OS$·HCl·0.5H_2O) C, H, N.

1-(Benzo[*b*]thiophen-3-yl)-3-[4-(quinol-2-yl)piperazin-1-yl]propan-1-one (5b). Yield 38%; mp 92−96 °C. IR (KBr): 1664 cm^{-1}. ^{1} NMR ($CDCl_3$) δ (free base): 2.66 (t, 4H, $N^4(CH_2)_2$); 2.94 (t, 2H, $COCH_2CH_2$); 3.25 (t, 2H, $COCH_2$); 3.76 (t, 4H, N^1-$(CH_2)_2$); 6.96 (d, 1H, H_3, $J = 7.9$); 7.21−7.25 (m, 1H, $H_{6'}$); 7.41−7.56 (m, 4H, $H_5 + H_6 + H_{5'} + H_{7'}$); 7.68 (d, 1H, $H_{4'}$); 7.85−7.90 (m, 2H, $H_7 + H_{8'}$); 8.33 (s, 1H, H_2); 8.74 (d, 1H, H_4). Anal. ($C_{24}H_{23}N_3OS$) C, H, N.

1-(Benzo[*b*]thiophen-3-yl)-3-[4-(quinol-3-yl)piperazin-1-yl]propan-1-one (5c). Yield 38%; mp 112−114 °C. IR (KBr): 1665 cm^{-1}. ^{1} NMR ($CDCl_3$) δ (free base): 2.75 (t, 4H, $N^4(CH_2)_2$); 2.96 (t, 2H, $COCH_2$); 3.21−3.36 (m, 6H, $N^1(CH_2)_3$); 7.31 (d, 1H, H_4, $J = 1.9$ Hz); 7.37−7.53 (m, 4H, $H_5 + H_6 + H_{6'} + H_{8'}$); 7.65 (dd, 1H, H_5, $J = 6$ Hz; $J = 2$ Hz); 7.86 (d, 1H, $H_{7'}$);

7.97 (d, 1H, H_7, J = 8 Hz); 8.32 (s, 1H, H_2); 8.74 (s, 1H, $H_{2'}$); 8.78 (d, 1H, H_4). Anal. ($C_{24}H_{23}N_3OS$) C, H, N.

1-(Benzo[*b*]thiophen-3-yl)-3-[4-(quinol-4-yl)piperazin-1-yl]propan-1-one (5d). Yield 43%; mp 134−136 °C. IR (KBr): 1615 cm^{-1}. ^{1} NMR ($CDCl_3$) δ (free base): 2.81−2.85 (m, 4H, $N^4(CH_2)_2$); 3.02 (t, 2H, CO−CH_2); 3.24−3.32 (m, 6H, $N^1(CH_2)_3$); 6.84 (d, 1H, H_3, J = 4.9 Hz); 7.43−7.51 (m, 3H, H_5 + H_6 + $H_{6'}$); 7.65 (t, 1H, $H_{7'}$);7.85 (t, 1H, H_7); 7.99−8.06 (m, 2H, $H_{5'}$ + $H_{8'}$); 8.35 (s, 1H, H_2); 8.71−8.79 (m, 2H, $H_{2'}$ + H_4). Anal. ($C_{24}H_{23}N_3OS$) C, H, N.

1-(Benzo[*b*]thiophen-3-yl)-3-[4-(quinol-5-yl)piperazin-1-yl]propan-1-one Dihydrochloride (5e). Yield 28%; mp 212−214 °C. IR (KBr): 1689 cm^{-1}. ^{1} NMR (DMSO-d_6) δ: 3.26 (s, 4H, $N^1(CH_2)_2$); 3.38 (b.s., 6H, $COCH_2$ + $N^4(CH_2)_2$); 3.77 (d, 2H, $COCH_2CH_2$); 7.29 (t, 1H, $H_{3'}$); 7.49−7.59 (m, 2H, $H_{4'}$ + $H_{6'}$); 7.61−7.81 (m, 2H, $H_{2'}$ + $H_{7'}$); 8.13 (d, 1H, H_4, J_{45} = 7.94); 8.64 (c, 2H, H_5 + H_6); 8.93 (d, 1H, $H_{8'}$); 9.13 (d, 2H, H_7 + H_2); 10.88 (b.s., 1H, HCl). Anal. ($C_{24}H_{23}N_3OS$·2HCl) C, H, N.

1-(Benzo[*b*]thiophen-3-yl)-3-[4-(quinol-6-yl)piperazin-1-yl]propan-1-one (5f). Yield 32%; mp 208−210 °C. IR (KBr): 1672 cm^{-1}. ^{1} NMR (DMSO-d_6) δ (free base): 2.78 (bs, 4H, $N^4(CH_2)_2$); 2.98 (t, 2H, $COCH_2CH_2$); 3.22−3.40 (m, 6H, $COCH_2$ + $N^1(CH_2)_2$); 7.24−7.56 (m, 4H, H_5 + H_6 + $H_{2'}$ + $H_{7'}$); 7.82−8.04 (m, 3H, $H_{3'}$ + $H_{4'}$ + $H_{5'}$); 8.28 (d, 1H, H_4); 8.38 (s, 1H, $H_{8'}$); 8.70−8.80 (m, 2H, H_7 + H_2). Anal. ($C_{24}H_{23}N_3OS$) C, H, N.

1-(Benzo[*b*]thiophen-3-yl)-3-[4-(quinol-8-yl)piperazin-1-yl]propan-1-one Dihydrochloride (5g). Yield 39%; mp 150−152 °C. IR (KBr): 1658 cm^{-1}. ^{1} NMR (DMSO-d_6) δ: 3.38 (b.s., 12H, CH_2); 7.24 (t, 1H, $H_{3'}$); 7.41−7.63 (m, 4H, $H_{4'}$ + $H_{5'}$ + $H_{6'}$ + $H_{7'}$); 8.35−8.55 (m, 2H, H_5 + H_6); 8.68 (d, 1H, H_4, J_{45} = 7.15); 8.70 (d, 1H, H_7, J_{67} = 8.7); 8.71 (dd, 1H, $H_{2'}$); 9.15 (s, 1H, H_2); 9.35 (s, 1H, HCl). Anal. ($C_{24}H_{23}N_3OS$·2HCl) C, H, N.

1-(Benzo[*b*]thiophen-3-yl)-3-[4-(quinaldin-8-yl)piperazin-1-yl]propan-1-one Dihydrochloride (5h). Yield 45%; mp 199−200 °C. IR (KBr): 1663 cm^{-1}. ^{1} NMR (DMSO-d_6) δ: 2.86 (s, 3H, CH_3); 3.28−3.96 (m, 12H, CH_2); 7.41−7.73 (m, 6H, $H_{3'}$ + $H_{5'}$ + H_5 + H_6 + $H_{6'}$ + $H_{7'}$); 8.11 (c, 1H, $H_{4'}$); 8.50 (d, 1H, H_4, J_{45} = 8.04); 8.61 (t, 1H, H_7); 9.15 (s, 1H, H_2); 11.39 (bs, 1H, HCl). Anal. ($C_{25}H_{25}N_3OS$·2HCl) C, H, N.

1-(Benzo[*b*]thiophen-3-yl)-3-[4-(indol-4-yl)piperazin-1-yl]propan-1-one (5i). Yield 20%; mp 83−85 °C. IR (KBr): 3397; 1661 cm^{-1}. ^{1} NMR (DMSO-d_6) δ (free base): 2.69 (bs, 4H, $N^4(CH_2)_2$); 2.83 (t, 2H, $COCH_2CH_2$); 3.10 (bs, 4H, N^1-$(CH_2)_2$); 3.31 (t, 2H, $COCH_2CH_2$); 6.41 (t, 2H, $H_{3'}$ + $H_{5'}$); 6.91−7.04 (m, 2H, H_5 + H_6); 7.24 (t, 1H, $H_{2'}$); 7.43−7.56 (m, 2H, $H_{6'}$ + $H_{7'}$); 8.10 (dd, 1H, H_4, J_{45} = 8.3, J_{46} = 1.7); 8.65 (d, 1H, H_7, J_{76} = 8.1); 9.06 (s, 1H, H_2); 11.03 (s, 1H, NH). Anal. ($C_{23}H_{23}N_3$-OS) C, H, N.

1-(Benzo[*b*]thiophen-3-yl)-3-[4-(2,3-dihydro-1,4-benzodioxin-5-yl)piperazin-1-yl]propan-1-one Dihydrochloride (5j). Yield 23%; mp 183−185 °C. IR (KBr): 1664 cm^{-1}. ^{1} NMR (DMSO-d_6) δ: 3.11 (t, 6H, $N^1(CH_2)_3$); 3.55 (t, 4H, N^4-$(CH_2)_2$) 3.76 (d, 2H, $COCH_2$); 4.28 (d, 4H, $O(CH_2)_2$); 6.53 (d, 2H, $H_{6'}$ + $H_{8'}$); 6.76 (t, 1H, $H_{7'}$); 7.43−7.57 (m, 2H, H_5 + H_6); 8.10 (dd, 1H, H_4, J_{45} = 8.3, J_{46} = 1.4); 8.61 (dd, 1H, H_7, J_{67} = 8.90, J_{57} = 1.5); 9.13 (s, 1H, H_2); 11.38 (bs, 1H, HCl). Anal. ($C_{23}H_{24}N_2O_3S$·2HCl·H_2O) C, H, N.

1-(Benzo[*b*]thiophen-3-yl)-3-[4-(3,4-dihydro-2H-1,5-benzo[*b*]dioxepin-6-yl)piperazin-1-yl]propan-1-one (5l). Yield 28%; mp 195−197 °C. IR (KBr): 1664 cm^{-1}. ^{1} NMR (DMSO-d_6) δ (free base): 2.10 (t, 6H, $N^1(CH_2)_3$); 2.98 (t, 4H, $N^4(CH_2)_2$); 3.08 (d, 2H, $COCH_2$); 4.20−4.34 (m, 6H, benzodioxepine); 6.58−6.70 (m, 2H, $H_{7'}$ + $H_{9'}$); 6.82 (t, 1H, $H_{8'}$); 7.38−7.56 (m, 2H, H_5 + H_6); 7.84 (d, 1H, H_4); 8.37 (s, 1H, H_2); 8.79 (d, 1H, H_7). Anal. ($C_{24}H_{26}N_2O_3S$) C, H, N.

1-(Benzo[*b*]thiophen-3-yl)-3-[4-(benzo[*b*]thiophen-5-yl)piperazin-1-yl]propan-1-one (5m). Yield 54%; mp 140−142 °C. IR (KBr): 1668 cm^{-1}. ^{1} NMR ($CDCl_3$) δ (free base): 2.78 (b.s., 6H, $N^1(CH_2)_3$); 3.00 (t, 2H, $COCH_2$) 3.26 (b.s., 4H, $N^4(CH_2)_2$); 7.07 (d, 1H, $H_{4'}$); 7.21−7.30 (m, 4H, $H_{2'}$ + $H_{3'}$ + $H_{6'}$ + $H_{7'}$); 7.68−7.75 (m, 2H, H_5 + H_6); 7.70 (d, 1H, H_4); 8.35 (s, 1H, H_2); 8.77 (d, 1H, H_7). Anal. ($C_{23}H_{23}N_2O_3S_2$) C, H, N.

1-(5-Fluorobenzo[*b*]thiophen-3-yl)-3-[4-(naphth-1-yl)-piperazin-1-yl]propan-1-one Hydrochloride (6a). Yield 28%; mp 236−238 °C. IR (KBr): 1667 cm^{-1}. ^{1} NMR (DMSO-d_6) δ (free base): 3.24−3.44 (b.s., 12H, CH_2); 7.17 (d, 1H, $H_{2'}$, J = 7.2); 7.33−7.54 (m, 3H, $H_{3'}$ + $H_{5'}$ + H_6); 7.64 (d, 1H, $H_{4'}$, J = 8.00); 7.89 (t, 1H, $H_{7'}$); 8.16 (t, 1H, H_4); 8.29 (d, 2H, $H_{6'}$ + $H_{8'}$, J = 7.2); 8.32 (dd, 1H, H_7, J = 7.5); 9.19 (s, 1H, H_2). Anal. ($C_{25}H_{23}FN_2OS$·HCl·0.5H_2O) C, H, N.

1-(5-Fluorobenzo[*b*]thiophen-3-yl)-3-[4-(quinol-8-yl)-piperazin-1-yl]propan-1-one Hydrochloride (6g). Yield 38%; mp 215−217 °C. IR (KBr): 1673 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ (free base): 3.38 (b.s., 12H, CH_2); 7.19 (d, 1H, $H_{3'}$, J = 7.02); 7.36−7.60 (m, 4H, $H_{5'}$ + $H_{6'}$ + $H_{7'}$ + H_6); 8.18 (c, 2H, H_4 + H_7); 8.33 (d, 1H, $H_{4'}$, J = 8.27); 8.88 (d, 1H, $H_{2'}$, J = 2.95); 9.22 (s, 1H, H_2). Anal. ($C_{24}H_{22}FN_3OS$·HCl) C, H, N.

1-(5-Fluorobenzo[*b*]thiophen-3-yl)-3-[4-(quinaldin-8-yl)piperazin-1-yl]propan-1-one Dihydrochloride (6h). Yield 23%; mp 230−232 °C. IR (KBr): 1662 cm^{-1}. ^{1} NMR (DMSO-d_6) δ: 2.63 (s, 3H, CH_3); 2.72 (d, 4H, $N^1(CH_2)_2$); 2.82 (d, 2H, $COCH_2CH_2$); 3.29 (t, 6H, $N^4(CH_2)_2$+$COCH_2$); 7.36−7.88 (m, 5H, quinaldine); 8.16−8.28 (m, 1H, H_6); 8.32 (dd, 1H, H_7, J_{F7} = 5.84); 8.71 (d, 1H, H_4, J_{F4} = 7.94); 9.27 (s, 1H, H_2); 11.56 (b.s., 1H, HCl). Anal. ($C_{25}H_{24}FN_3OS$·2HCl·H_2O) C, H, N.

1-(5-Fluorobenzo[*b*]thiophen-3-yl)-3-[4-(indol-4-yl)piperazin-1-yl]propan-1-one (6i). Yield 27%; mp 76−78 °C. IR (KBr): 3397; 1661 cm^{-1}. ^{1} NMR (DMSO-d_6) δ (free base): 2.69 (b.s., 4H, $N^1(CH_2)_2$); 2.83 (t, 2H, $COCH_2CH_2$); 3.10 (b.s., 4H, $N^4(CH_2)_2$); 3.31 (t, 2H, $COCH_2CH_2$); 6.41 (t, 2H, $H_{3'}$ + $H_{5'}$); 6.97 (q, 2H, $H_{6'}$ + $H_{7'}$); 7.33 (c, 1H, $H_{2'}$); 7.80 (d, 1H, H_6, J_{67} = 8.00); 8.12 (c, 1H, H_7), 8.30 (d, 1H, H_4, J_{F4} = 10.7); 9.13 (s, 1H, H_2); 10.98 (s, 1H, NH). Anal. ($C_{23}H_{22}FN_3OS$·0.5H_2O) C, H, N.

1-(5-Fluorobenzo[*b*]thiophen-3-yl)-3-[4-(2,3-dihydro-1,4-benzodioxin-5-yl)piperazin-1-yl]propan-1-one Hydrochloride (6j). Yield 23%; mp 191−193 °C. IR (KBr): 1668 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ: 3.05 (t, 4H, $N^1(CH_2)_2$); 3.23 (t, 2H, $COCH_2CH_2$); 3.60 (t, 4H, $N^4(CH_2)_2$) 3.72 (t, 2H, $COCH_2$); 4.24 (b.s., 4H, $O(CH_2)_2$); 6.55 (d, 2H, $H_{6'}$ + $H_{8'}$); 6.76 (t, 1H, $H_{7'}$); 7.40 (dd, 1H, H_6, J_{67} = 8.94, J_{46} = 2.5); 8.18 (c, 1H, H_7); 8.30 (dd, 1H, H_4, J_{F4} = 10.7); 9.20 (s, 1H, H_2); 10.83 (bs, 1H, HCl). Anal. ($C_{23}H_{23}FN_2O_3S$·HCl) C, H, N.

1-(5-Fluorobenzo[*b*]thiophen-3-yl)-3-[4-(1,3-benzodioxol-4-yl)piperazin-1-yl]propan-1-one (6k). Yield 28%; mp 84−86 °C. IR (KBr): 1667 cm^{-1}. ^{1} NMR (DMSO-d_6) δ (free base): 2.68 (t, 4H, $N^1(CH_2)_2$); 2.92 (t, 2H, $COCH_2CH_2$); 3.19 (t, 6H, $COCH_2$ + $N^4(CH_2)_2$); 5.91 (s, 2H, O−CH_2−O), 6.46 (c, 2H, $H_{5'}$ + $H_{7'}$), 6.75 (t, 1H, $H_{6'}$), 7.20 (dd, 1H, H_6, J_{67} = 8.44, J_{46} = 2.5); 7.77 (c, 1H, H_7); 8.37 (s, 1H, H_2); 8.46 (dd, 1H, H_4 J_{F4} = 10.76). Anal. ($C_{22}H_{23}FN_2O_3S$) C, H, N.

1-(5-Fluorobenzo[*b*]thiophen-3-yl)-3-[4-(3,4-dihydro-2H-1,5-benzo[*b*]dioxepin-6-yl)piperazin-1-yl]propan-1-one (6l). Yield 30%; mp 195−196 °C. IR (KBr): 1670 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ (free base): 2.20 (q, 2H, CH_2); 2.73 (t, 4H, $N^1(CH_2)_2$); 2.95 (t, 2H, $COCH_2CH_2$); 3.09 (t, 4H, $N^4(CH_2)_2$); 3.25 (t, 2H, $COCH_2$); 4.25 (q, 4H, O−$(CH_2)_2$−O); 6.63 (t, 2H, $H_{9'}$ + $H_{7'}$); 6.84 (t, 1H, $H_{8'}$); 7.20 (dd, 1H, H_6, J_{67} = 8.44, J_{46} = 2.5); 7.79 (c, 1H, H_7); 8.41 (s, 1H, H_2); 8.48 (dd, 1H, H_4, J_{F4} = 10.76). Anal. ($C_{24}H_{21}FN_2O_3S$) C, H, N.

General Procedure for Preparation of the 1-(3-Benzo[*b*]thiophenyl)-3-[4-(aryl)piperazin-1-yl]-propanol Derivatives 7a−m and 8a,g−l. An excess of sodium borohydride was added to a well-stirred suspension of the corresponding 1-(3-benzo[*b*]thiophenyl)-3-[4-(aryl)piperazin-1-yl]propanone **5a−m** and **6a,g−l** (3 mmol) in methanol, over a period of 15 min at 0 °C. The reaction mixture was stirred over a period of 1 h and after the solvent was evaporated. The obtained product was washed with plenty of water and extracted with ethyl acetate (3 × 20 mL) and dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and in the cases in which the hydrochloride was formed, this was carried out by dissolving the free base in AcoEt and by adding an equimolar quantity of HCl(c).

1-(Benzo[*b*]thiophen-3-yl)-3-[4-(naphth-1-yl)piperazin-1-yl]propan-1-ol Dihydrochloride (7a). Yield 48%; mp 95−97 °C. IR (KBr): 3414 cm^{-1}. ^{1} NMR ($CDCl_3$) δ (free base): 2.10

(c, 2H, CHOHCH_2); 2.71−2.87 (t, 6H, N^1(CH$_2$)$_3$); 3.17 (bs, 4H, N^4(CH$_2$)$_2$); 5.35 (t, 1H, C*H*OH); 6.94−7.18 (m, 2H, H_6 + H_5); 7.18−7.56 (m, 7H, naphthyle); 7.76−7.86 (m, 2H, H_4 + H_7); 8.15 (s, 1H, H_2). Anal. ($C_{25}H_{26}N_2OS$·2HCl) C, H, N.

1-(Benzo[*b*]thiophen-3-yl)-3-[4-(quinol-2-yl)piperazin-1-yl]propan-1-ol (7b). Yield 53%; mp 192−196 °C. IR (KBr): 3410 cm^{-1}. ^{1} NMR ($CDCl_3$) δ (free base): 2.12 (t, 2H, CH_2-CHOH); 2.64−2.76 (m, 6H, N^1(CH$_2$)$_3$); 3.82 (t, 4H, N^4(CH$_2$)$_2$); 5.37 (t, 1H, C*H*OH), 6.98 (d, 1H, $H_{3'}$, J = 7.8 Hz); 7.24−7.92 (m, 10H, aromatic). Anal. ($C_{24}H_{25}N_3OS$) C, H, N.

1-(Benzo[*b*]thiophen-3-yl)-3-[4-(quinol-3-yl)piperazin-1-yl]propan-1-ol (7c). Yield 27%; mp 98−100 °C. IR (KBr): 3392 cm^{-1}. ^{1} NMR ($CDCl_3$) δ (free base): 2.13 (t, 2H, CH_2-CHOH); 2.67−2.91 (m, 6H, N^1(CH$_2$)$_3$); 3.36 (t, 4H, N^4(CH$_2$)$_2$); 5.34 (t, 1H, C*H*OH), 7.29−7.52 (m, 5H, H_2 + H_5 + H_6 + $H_{6'}$ + $H_{8'}$); 7.68 (d, 1H, $H_{5'}$, J = 6 Hz); 7.77−7.86 (m, 2H, H_4 + $H_{4'}$); 7.98 (d, 1H, H_7, J = 8 Hz); 8.78 (d, 1H, $H_{2'}$). Anal. ($C_{24}H_{25}N_3$-OS) C, H, N.

1-(Benzo[*b*]thiophen-3-yl)-3-[4-(quinol-4-yl)piperazin-1-yl]propan-1-ol Hydrochloride (7d). Yield 62%; mp 174−176 °C. IR (KBr): 3277 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ: 2.02 (t, 2H, CH_2CHOH); 2.50−2.60 (m, 6H, N^1(CH$_2$)$_3$); 3.19 (bs, 4H, N^4(CH$_2$)$_2$); 5.08 (t, 1H, C*H*OH), 6.55 (s, 1H, OH); 6.98 (d, 1H, $H_{3'}$, J = 4.7 Hz); 7.35−7.44 (m, 2H, H_6 + H_5); 7.50−7.57 (m, 2H, $H_{6'}$ + H_2); 7.69 (t, 1H, $H_{7'}$); 7.93−8.03 (m, 4H, H_4 + H_7 + $H_{8'}$ + $H_{5'}$); 8.62 (d, 1H, $H_{2'}$, J = 4.6 Hz); 10.07 (bs, 1H, HCl). Anal. ($C_{24}H_{25}N_3OS$·HCl) C, H, N.

1-(Benzo[*b*]thiophen-3-yl)-3-[4-(quinol-5-yl)piperazin-1-yl]propan-1-ol (7e). Yield 48%; mp 127−129 °C. IR (KBr): 3368 cm^{-1}. ^{1} NMR (DMSO-d_6) δ (free base): 2.00 (d, 2H, CH_2-CHOH); 2.60 (t, 6H, N^1(CH$_2$)$_3$); 3.02 (s, 4H, N^4(CH$_2$)$_2$); 5.08 (t, 1H, C*H*OH), 5.62 (b.s., 1H, OH); 7.15 (d, 1H, $H_{4'}$); 7.21−7.43 (m, 3H, H_5 + H_6 + $H_{7'}$); 7.46−7.88 (m, 3H, $H_{2'}$ + $H_{3'}$ + $H_{6'}$); 7.89−7.98 (m, 2H, H_7 + H_4); 8.44 (d, 1H, $H_{8'}$, J = 8.39); 8.87 (s, 1H, H_2). Anal. ($C_{24}H_{25}N_3OS$) C, H, N.

1-(Benzo[*b*]thiophen-3-yl)-3-[4-(quinol-6-yl)piperazin-1-yl]propan-1-ol (7f). Yield 77%; mp 156−158 °C. IR (KBr): 3335 cm^{-1}. ^{1} NMR ($CDCl_3$) δ (free base): 2.02 (t, 2H, CH_2-CHOH); 2.50−2.68 (m, 6H, N^1(CH$_2$)$_3$); 3.19 (b.s., 4H, N^4(CH$_2$)$_2$); 5.08 (t, 1H, C*H*OH), 6.62 (bs, 1H, OH); 7.01 (d, 1H, $H_{7'}$); 7.24−7.54 (m, 4H, H_5 + H_6 + $H_{2'}$ + $H_{7'}$); 7.80−8.04 (m, 3H, $H_{3'}$ + $H_{4'}$ + $H_{5'}$); 8.28 (d, 1H, H_4); 8.38 (s, 1H, $H_{8'}$); 8.70−8.80 (m, 2H, H_7 + H_2). Anal. ($C_{24}H_{25}N_3OS$) C, H, N.

1-(Benzo[*b*]thiophen-3-yl)-3-[4-(quinol-8-yl)piperazin-1-yl]propan-1-ol Dihydrochloride (7g). Yield 19%; mp 169−171 °C. IR (KBr): 3314 cm^{-1}. ^{1} NMR (DMSO-d_6) δ (free base): 2.13 (t, 2H, CH_2CHOH); 3.39 (bs, 12H, CH_2); 5.11 (t, 1H, C*H*OH), 7.40 (q, 2H, $H_{3'}$ + $H_{4'}$); 7.58 (d, 1H, $H_{5'}$, J = 7.34); 7.72 (t, 2H, $H_{6'}$ + $H_{7'}$); 7.86 (t, 2H, H_5 + H_6); 8.04 (q, 2H, H_7 + H_4); 9.08 (d, 1H, $H_{2'}$); 9.33 (s, 1H, H_2); 11.19 (b.s., 1H, OH). Anal. ($C_{24}H_{25}N_3OS$·2HCl) C, H, N.

1-(Benzo[*b*]thiophen-3-yl)-3-[4-(quinaldin-8-yl)piperazin-1-yl]propan-1-ol Dihydrochloride (7h). Yield 48%; mp 138−142 °C. IR (KBr): 3358 cm^{-1}. ^{1} NMR (DMSO-d_6) δ (free base): 2.37 (t, 2H, CHOHCH_2); 2.94 (s, 3H, CH_3); 3.38 (bs, 6H, N^1(CH$_2$)$_3$); 3.76 (t, 4H, N^4(CH$_2$)$_2$); 5.11 (t, 1H, C*H*OH); 7.37−7.45 (m, 2H, $H_{6'}$ + $H_{7'}$); 7.54−7.85 (m, 5H, H_6 + H_5 + $H_{5'}$ + $H_{4'}$ + H_2); 7.97−8.07 (m, 2H, H_4 + H_7); 8.67 (d, 1H, H_3, J = 8.22); 12.21 (bs, 1H, OH). Anal. ($C_{25}H_{27}N_3OS$·2HCl) C, H, N.

1-(Benzo[*b*]thiophen-3-yl)-3-[4-(indol-4-yl)piperazin-1-yl]propan-1-ol Dihydrochloride (7i). Yield 53%; mp >300 °C. IR (KBr): 3396 cm^{-1}. ^{1} NMR (DMSO-d_6) δ (free base): 2.00 (t, 2H, CHOHCH_2); 2.55 (t, 6H, N^1(CH$_2$)$_3$); 3.28 (bs, 4H, N^4-(CH$_2$)$_2$); 5.33 (t, 1H, C*H*OH); 5.62 (bs, 1H, OH); 6.42 (t, 2H, $H_{3'}$ + $H_{5'}$); 6.99 (q, 2H, H_6 + H_5); 7.23−7.43 (m, 3H, $H_{2'}$ + $H_{6'}$ + $H_{7'}$); 7.57 (s, 1H, H_2); 7.96 (q, 2H, H_4 + H_7); 11.03 (bs, 1H, NH). Anal. ($C_{23}H_{25}N_3OS$·2HCl) C, H, N.

1-(Benzo[*b*]thiophen-3-yl)-3-[4-(2,3-dihydro-1,4-benzodioxin-5-yl)piperazin-1-yl]propan-1-ol Dihydrochloride (7j). Yield 45%; mp 151−153 °C. IR (KBr): 3414 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ (free base): 2.08 (b.s., 2H, CHOHCH_2); 2.73 (bs, 6H, N^1(CH$_2$)$_3$); 3.12 (bs, 4H, N^4(CH$_2$)$_2$); 4.26 (d, 4H, O−CH_2−CH_2−O); 5.33 (bs, 1H, C*H*OH); 6.54 (t, 2H, $H_{6'}$ + $H_{8'}$); 6.77 (t, 1H, $H_{7'}$); 7.33 (t, 2H, H_5 + H_6); 7.41 (s, 1H, H_2); 7.78 (d, 1H, H_4 + H_7, J = 7.60). Anal. ($C_{23}H_{26}N_2O_3S$·2HCl) C, H, N.

1-(Benzo[*b*]thiophen-3-yl)-3-[4-(3,4-dihydro-2H-1,5-benzo[*b*]dioxepin-6-yl)piperazin-1-yl]propan-1-ol (7l). Yield 59%; mp 184−186 °C. IR (KBr): 3365 cm^{-1}. ^{1} NMR ($CDCl_3$) δ (free base): 2.02 (t, 2H, CH_2CHOH); 2.50−2.68 (m, 6H, N^1-(CH$_2$)$_3$); 3.19 (bs, 4H, N^4(CH$_2$)$_2$); 5.08 (t, 1H, C*H*OH), 4.22−4.32 (m, 6H, benzodioxepine); 6.58−6.70 (m, 2H, $H_{7'}$ + $H_{9'}$); 6.82 (t, 1H, $H_{8'}$); 7.38−7.56 (m, 2H, H_5 + H_6); 7.84 (d, 1H, H_4); 8.37 (s, 1H, H_2); 8.79 (d, 1H, H_7). Anal. ($C_{24}H_{29}N_2O_3S$) C, H, N.

1-(Benzo[*b*]thiophen-3-yl)-3-[4-(benzo[*b*]thiophen-5-yl)piperazin-1-yl]propan-1-ol (7m). Yield 36%; mp 181−183 °C. IR (KBr): 3412 cm^{-1}. ^{1} NMR ($CDCl_3$) δ: 2.23−2.32 (m, 2H, CH_2CHOH); 3.18−3.35 (m, 6H, N^1(CH$_2$)$_3$); 3.60−83 (bs, 4H, N^4(CH$_2$)$_2$); 5.08 (dd, 1H, C*H*OH), 7.17 (dd, 1H, $H_{4'}$); 7.32−7.41 (m, 4H, H_5 + H_6 + $H_{2'}$ + $H_{6'}$); 7.65 (s, 1H, H_2); 7.70 (d, 1H, $H_{3'}$, J = 5.4 Hz); 7.86 (d, 1H, $H_{7'}$); 7.97−8.01 (m, 2H, H_4 + H_7); 10.99 (bs, 1H, HCl). Anal. ($C_{23}H_{25}N_2O_3S_2$) C, H, N.

1-(5-Fluorobenzo[*b*]thiophen-3-yl)-3-[4-(naphth-1-yl)-piperazin-1-yl]propan-1-ol Dihydrochloride (8a). Yield 36%; mp 197−198 °C. IR (KBr): 3410 cm^{-1}. ^{1} NMR (DMSO-d_6) δ (free base): 2.31 (t, 2H; CH_2CHOH); 3.33 (q, 6H, N^1(CH$_2$)$_3$); 3.65 (d, 4H, N^4(CH$_2$)$_2$); 5.07 (t, 1H, C*H*OH); 7.16 (d, 1H, H_2, J = 7.2); 7.27 (t, 2H, H_6 + H_7); 7.28−7.55 (m, 4H, $H_{3'}$ + $H_{4'}$ + $H_{5'}$ + $H_{6'}$); 7.66 (d, 1H, H_8, J = 8.16); 7.81−8.00 (m, 2H, $H_{7'}$); 8.03−8.10 (m, 2H, H_2 + H_4). Anal. ($C_{25}H_{25}FN_2$-OS·2HCl) C, H, N.

1-(5-Fluorobenzo[*b*]thiophen-3-yl)-3-[4-(quinol-8-yl)-piperazin-1-yl]propan-1-ol Hydrochloride (8g). Yield 15%; mp 89−91 °C. IR (KBr): 3102 cm^{-1}. ^{1} NMR (DMSO-d_6) δ (free base): 2.52 (t, 2H, CH_2CHOH); 3.37 (b.s., 12H, CH_2-s); 5.03 (t, 1H, C*H*OH), 5.66 (bs, 1H, OH); 7.09 (t, 2H, H_6 + H_7); 7.19 (t, 1H, $H_{3'}$); 7.23−7.28 (m, 3H, $H_{5'}$ + $H_{6'}$ + $H_{7'}$); 7.68 (s, 1H, H_2); 7.97 (c, 1H, $H_{4'}$); 8.26 (d, 1H, H_4, J = 7.40); 8.82 (d, 1H, $H_{2'}$). Anal. ($C_{24}H_{24}FN_3OS$·H_2O·HCl) C, H, N.

1-(5-Fluorobenzo[*b*]thiophen-3-yl)-3-[4-(quinaldin-8-yl)piperazin-1-yl]propan-1-ol Dihydrochloride (8h). Yield 48%; mp 148−150 °C. IR (KBr): 3375 cm^{-1}. ^{1} NMR ($CDCl_3$) δ (free base): 2.11 (t, 2H, CHOHCH_2); 2.75 (s, 3H, CH_3); 2.82 (b.s., 6H, N^1(CH$_2$)$_3$); 2.91 (t, 4H, N^4(CH$_2$)$_2$); 5.31 (t, 1H, C*H*OH); 7.10 (c, 2H, $H_{6'}$ + $H_{7'}$); 7.27 (c, 2H, $H_{5'}$ + $H_{3'}$); 7.39 (d, 1H, H_4, J = 2.33); 7.52 (s, 1H, H_2); 7.55 (d, 1H, H_6, J_{46} = 2.2); 7.78 (c, 1H, H_4); 7.99 (d, 1H, H_7). Anal. ($C_{25}H_{26}FN_3OS$·2HCl) C, H, N.

1-(5-Fluorobenzo[*b*]thiophen-3-yl)-3-[4-(indol-4-yl)piperazin-1-yl]propan-1-ol Hydrochloride (8i). Yield 26%; mp 171−173 °C. IR (KBr): 3414 cm^{-1}. ^{1} NMR (DMSO-d_6) δ (free base): 1.99 (d, 2H, CHOHCH_2); 2.55 (d, 6H, N^1(CH$_2$)$_3$); 2.55 (bs, 4H, N^4(CH$_2$)$_2$); 5.02 (s, 1H, C*H*OH); 5.64 (bs, 1H, OH); 6.41 (t, 2H, $H_{3'}$ + $H_{5'}$); 6.98 (t, 3H, $H_{2'}$ + $H_{6'}$ + $H_{7'}$); 7.29 (s, 1H, H_2); 7.69 (d, 1H, H_4, J_{F7} = 4.92); 7.76 (d, 1H, H_6, J_{46} = 2.48); 8.01 (t, 1H, H_7). Anal. ($C_{23}H_{24}FN_3OS$·HCl·H_2O) C, H, N.

1-(5-Fluorobenzo[*b*]thiophen-3-yl)-3-[4-(2,3-dihydro-1,4-benzodioxin-5-yl)piperazin-1-yl]propan-1-ol Dihydrochloride (8j). Yield 40%; mp 147−150 °C. IR (KBr): 3360 cm^{-1}. ^{1} NMR ($CDCl_3$) δ (free base): 2.05 (q, 2H, CHOHCH_2); 2.64−2.88 (m, 6H, N^1(CH$_2$)$_3$); 3.13 (bs, 4H, N^4(CH$_2$)$_2$); 4.24 (d, 2H, 2H**e**, J = 5.6); 4.30 (d, 2H, H**a**, J = 13.6); 5.25 (t, 1H, C*H*OH); 6.55 (c, 2H, $H_{6'}$ + $H_{8'}$); 6.77 (t, 1H, $H_{7'}$); 6.98−7.13 (m, 2H, H_6 + H_4);7.44 (s, 1H, H_2); 7.75 (c, 1H, H_7). Anal. ($C_{23}H_{25}FN_2O_3S$·2HCl) C, H, N.

1-(5-Fluorobenzo[*b*]thiophen-3-yl)-3-[4-(1,3-benzodioxol-4-yl)piperazin-1-yl]propan-1-ol (8k). Yield 39%; mp 147−149 °C. IR (KBr): 3415 cm^{-1}. ^{1} NMR ($CDCl_3$) δ (free base): 2.00−2.09 (m, 2H, CHOHCH_2); 2.64−2.87 (m, 6H, N^1(CH$_2$)$_3$); 3.24 (t, 4H, N^4(CH$_2$)$_2$); 5.24 (t, 1H, C*H*OH); 5.92 (s, 2H, O−CH_2−O), 6.47 (c, 2H, $H_{5'}$ + $H_{7'}$), 6.77 (t, 1H, $H_{6'}$), 7.09 (dd, 1H, H_6, J_{67} = 8.44, J_{46} = 2.5); 7.44−7.50 (m, 2H, H_2 + H_7); 7.75 (c, 1H, H_4). Anal. ($C_{22}H_{23}FN_2O_3S$) C, H, N.

1-(5-Fluorobenzo[*b*]thiophen-3-yl)-3-[4-(3,4-dihydro-2H-1,5-benzo[*b*]dioxepin-6-yl)piperazin-1-yl]propan-1-ol (8l). Yield 52%; mp 125−127 °C. IR (KBr): 3414 cm^{-1}. ^{1} NMR ($CDCl_3$) δ (free base): 2.03 (q, 2H, CH_2); 2.17 (t, 2H, CHOHCH_2); 2.64−2.80 (m, 6H, N^1(CH$_2$)$_3$); 3.09 (bs, 4H, N^4-

$(CH_2)_2$); 4.23 (q, 4H, O−$(CH_2)_2$−O), 5.23 (t, 1H, C*H*OH); 6.55−6.66 (m, 2H, $H_{9'} + H_{7'}$); 6.81 (t, 1H, $H_{8'}$); 7.06 (dd, 1H, H_6, J_{67} = 8.44, J_{46} = 2.5); 7.42−7.48 (m, 2H, $H_2 + H_7$); 7.73 (c, 1H, H_4). Anal. ($C_{24}H_{23}FN_2O_3S$) C, H, N.

Molecular Modeling. All calculations were performed using the molecular Modeling package Catalyst 4.6 10 installed on Silicon Graphics O2 desktop workstations equipped with a 200 MHz MIPS R5000 processor (128 or 256 MB RAM) running the Irix 6.5 or 6.5+ operating system. The compounds used in this study were built using the Catalyst 2D-3D sketcher, and representative families of conformations were generated for each molecule using the following parameters for conformational analysis: maximum number of conformers, 255; generation type, best quality; energy range, 15.00 kcal/mol beyond the calculated potential energy minimum. For hypothesis generation, the default parameters were used.

Binding to 5-HT Transporter. Binding studies to 5-HT transporter were performed using rat frontal cortex homogenates according to the procedure described by Marcusson.[24] Briefly, rat cortical tissue was homogenized in Tris-HCl buffer (50 mM, pH 7.4) and centrifuged at 4 °C for 10 min at 50 000*g*. The supernatant was discharged, and the pellet was resuspended in Tris buffer and preincubated at 37 °C for 10 min. The suspension was then washed twice by centrifugation and resuspended in the same conditions as above. For displacement assays, cortical membranes (4 mg tissue/mL) were incubated with 0.1 nM [^{3}H]paroxetine in Tris buffer, pH 7.4, containing NaCl 120 mM and KCl 5 mM, for 60 min at 23 °C. The final incubation volume was 2 mL, and nonspecific binding was determined using 10 μM fluoxetine as the cold displacer. The inhibition constants (K_i) were calculated using the equation of Cheng and Prussof from the displacement curves analyzed with the Receptor Fit Competition LUNDON program.

Binding to 5-HT$_{1A}$ Receptors. Binding studies to 5-HT$_{1A}$ receptors were performed using rat frontal cortex homogenates according to the procedure described by Hoyer et al.[25] Briefly, rat cortical tissue was homogenized in Tris−HCl buffer 50 mM, pH 7.7, and centrifuged at 4 °C for 15 min at 50 000*g*. The supernatant was discharged, and the pellet was suspended in Tris buffer and preincubated at 37 °C for 10 min. The suspension was then centrifuged in the same conditions, and the final pellet was resuspended in assay buffer (Tris-HCl 50 mM, pH 7.4, containing $CaCl_2$ 4 mM). For displacement assays, cortical membranes (5 mg tissue/mL) were incubated with 2.5 nM [^{3}H] 8-OH-DPAT in buffer assay for 15 min a 37 °C. The final incubation volume was 0.4 mL, and nonspecific binding was determined using 10 μM 8-OH-DPAT as the cold displacer. The inhibition constants (K_i) were calculated as above.

Functional Characterization at 5-HT$_{1A}$ Receptors. [^{35}S] GTPγS Binding Assay. Membranes were prepared from rat hippocampus according to the method described by Alper and Nelson.[26] The tissue was homogenized in 50 mM Tris buffer (Tris base 50 mM, pH 7.4) and centrifuged at 4 °C for 10 min at 40 000*g*. The pellet was suspended in fresh Tris buffer, and the homogenate was preincubated at 37 °C for 10 min. The suspension was washed twice by centrifugation and resuspension. After the last centrifugation, the homogenate was frozen at −70 °C for later use. Defrosted aliquots were resuspended in Tris buffer and centrifuged as above. This final membrane pellet was suspended in assay buffer (4 mM Mg_2-Cl, 160 mM NaCl, 0.267 mM EGTA, 67 mM Tris base, pH 7.4). For binding assays, hippocampal membranes (30−50 mg/protein/tube) were incubated with 0.1 nM [^{35}S] GTPγS in a final incubation volume of 0.8 mL for 20 min at 37 °C and the reaction was terminated by filtration through Whatman GF/B filters presoaked with 20 mM $Na_4P_2O_7 \cdot 10H_2O$ solution. After they were filtered, the samples were placed in vials with scintillation cocktail for 2 h before counting. Binding was expresed as femtomoles [^{35}S] GTPγS bound per milligram of protein. The agonist activity of increasing concentration of the compounds was determined by stimulation of [^{35}S] GTPγS binding whereas the antagonist activity was evaluated by inhibition of 8-OH-DPAT-stimulated [^{35}S] GTPγS binding. The percentage of inhibition of [^{35}S] GTPγS binding elicited by a fixed 8-OH-DPAT concentration (1 μM) by the assayed compounds was calculated according to the formula: $\%I = [(B_{DPAT} - B_C) - (B_T - B_C)]/(B_{DPAT} - B_C) \times 100$, where B_C is basal binding in absence of 8-OH-DPAT, B_{DPAT} is binding elicited by 1 μM 8-OH-DPAT, and B_T is binding elicited by 8-OH-DPAT in the presence of increasing drug concentrations. Linear regression analysis was used in order to estimate the IC_{50} values of the tested compounds.

8-OH-DPAT-Induced Hypothermia in Mice. The procedures used for these studies were based on previously described methods.[27] Briefly, male Swiss mice (23−28 g) were housed in groups of five and body temperature was measured with a lubricated digital thermometer probe (pb0331, Panlab, Barcelona) inserted to a depth of 2 cm into the rectum of the mice. The temperature was recorded at 15, 30, and 60 min, after injection of 8-OH-DPAT or the compound to be tested. To study the antagonism to 8-OH-DPAT-induced hypothermia, compounds or vehicle (control) were administered ip 30 min before the injection of 8-OH-DPAT (0.5 mg/kg s.c.). The hypothermic response to 8-OH-DPAT was measured as the maximum decrease in body temperature recorded in this period. The results were expressed as change in body temperature (Δt) with respect to basal temperature, measured at the beginning of the experiment. The obtained data were analyzed by analysis of variance (ANOVA) followed by Student−Newman−Keuls test.

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