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BRIEF ARTICLE

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Novel Benzo[*b*]thiophene Derivatives as New Potential Antidepressants with Rapid Onset of Action

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Supporting Information

ABSTRACT: We report benzo[*b*]thiophene derivatives synthesized according to a dual strategy. **8j**, **9c**, and **9e** with affinity values toward 5-HT$_7$R and 5-HTT were selected to probe their antidepressant activity in vivo using the forced swimming text (FST). The results showed significant antidepressant activity after chronic treatment. **9c** was effective in reducing the immobility time in FST even after acute treatment. These findings identify these compounds as a new class of antidepressants with a rapid onset of action.

INTRODUCTION

The most widely used treatment for depression is based on selective serotonin reuptake inhibitors (SSRIs, e.g., citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline). However, antidepressant treatments require several weeks for the onset of action and exhibit limited efficacy. In this sense, new directions for antidepressant treatment have been developed, and dual action drugs could represent an advance over SSRIs.

Some years ago, dual action compounds (Figure 1), with affinity for the 5-HT$_{1A}$ receptor and able to inhibit serotonin transporter, synthesized in our laboratory showed good antidepressant activity.[1−3] A pharmacophore study was carried out, and the inhibition of serotonin reuptake was related to the benzo[*b*]thiophene moiety and the affinity to 5-HT$_{1A}$ receptors to the arylpiperazine group.[4]

Advances in the neurobiology of depression have suggested a number of novel targets for antidepressant treatment, such as 5-HT$_7$ receptors (5-HT$_7$R),[5] the most recent serotonin receptor cloned in 1993.[6−9] The fact that clinical effective antipsychotic and antidepressant drugs present affinity for 5-HT$_7$R[10] and that chronic administration of antidepressants down-regulates 5-HT$_7$ receptor mediated responses and receptor binding in limbic areas[10,11] leads to the prediction that these receptors are likely involved in depressive states and antidepressant responses. Abbas et al.[12] suggest that amisulpride exerts its antidepressant activity through 5-HT$_7$R. Pure 5-HT$_7$ receptor antagonists could be effective in the treatment of depression and might have advantages over currently available options.[13] The 5-HT$_7$ receptor antagonism seems capable of producing diverse antidepressant-like behavioral effects, affecting hippocampal neuronal morphology, and enhancing hippocampal neurogenesis.[14]

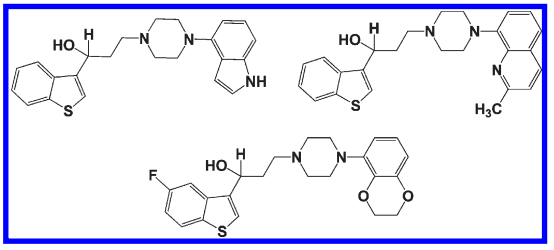

Figure 1. Compounds with dual action, 5HT$_{1A}$ antagonists, and serotonin reuptake inhibitors.

SB-269970 and SB-656104-A are 5-HT$_7$ receptor antagonists that exhibit antidepressant-like activity.[17] Moreover, recent studies suggest that selective blockade of 5-HT$_7$R may have a synergistic effect with the inhibition of 5-HT reuptake in animal model of depression.[16] Therefore, compounds inhibiting serotonin reuptake and blocking the 5-HT$_7$R could open new horizons in the treatment of this disease. Other studies have shown the antidepressant efficacy of dual 5-HT1/SSRIs compounds.[17] One of the most important advantages of these compounds is that they may behave as novel antidepressant-like agents with a faster onset of action.[18]

CHEMISTRY

To obtain new dual compounds, 5-HT$_7$ receptor antagonists and serotonin reuptake inhibitors, a bibliographic revision was carried out and it was observed that structures such as

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arylsulfonamides[19−24] and arylamines[22,23,25] presented high affinity toward 5-HT$_7$R. Therefore, two new molecules were synthesized (Figure 2) in which the benzo[*b*]thiophene ring[4] was fused with an arylsulfonamide for the compounds of series I (**6** and **7** of the Scheme 1) and with an arylamine for the compounds of series II (**8** and **9** of the Scheme 1).

The structures of the investigated compounds and their synthesis are presented in Scheme 1. 1-(3-Benzo[*b*]thiophenyl)-3-chloropropan-1-one precursor was synthesized by a Friedel−Craft acylation of the corresponding benzo[*b*]thiophene precursor as previously described.[2] Benzo[*b*]thiophene is commercially available, and 5-fluorobenzo[*b*]thiophene was prepared as reported.[26] The synthesis of the sulfonamides **2** was carried out by a nucleophilic attack of the amine over different sulfonyl chlorides via S_N2 mechanism. BOC-arylamines **3** were obtained by an Ar S_N reaction via Meisenheimer complex[27] between a monoprotected diamine and an aryl fluoride. Removal of the BOC group from **2** and **3** with HCl and acetic acid yielded **4** and **5**. Compounds **6** and **8** were synthesized by a nucleophilic attack of the nitrogen atom on the carbon carrying the chlorine atom via S_N2 mechanism. The hydroxyl derivatives **7** and **9** were obtained by reduction of the carbonyl groups of **6** and **8** with $NaBH_4$ in methanol. The effect of the newly created stereogenic center in **7** and **9** on the pharmacological profile should be evaluated in future studies.

The influence of the structural modifications on the affinity for the targets was investigated, and the most interesting compounds were pharmacologically evaluated in the forced swimming test (FST), a pharmacological model for anxiety and depression.[28]

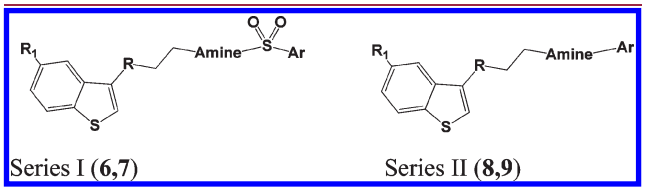
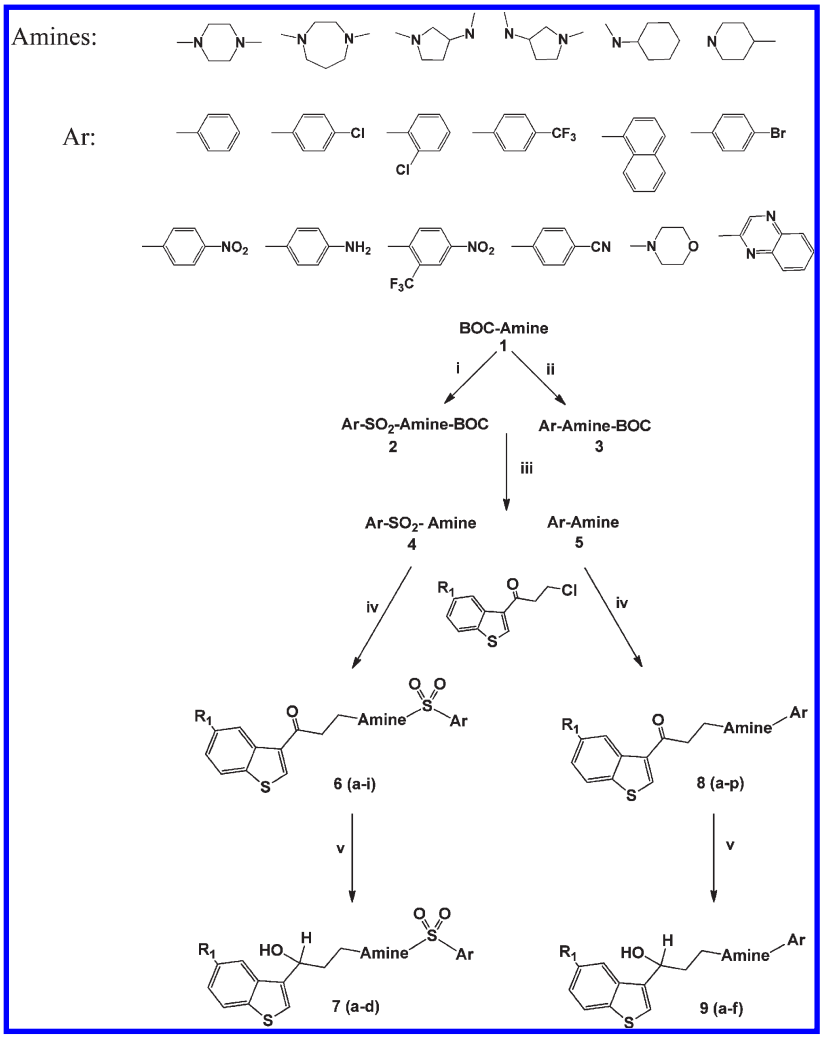


Figure 2. General structures of the new arylsulfonamides and arylamines synthesized.

RESULTS AND DISCUSSION

All synthesized compounds were tested in competition binding experiments for the evalutation of their affinity for the 5-HT$_7$R and SERT (Table 1).

Scheme 1. Synthesis of New Sulfonamides and Arylamines, Benzo[*b*]thiophene Derivatives[a]



[a] (i) Cl-SO_2-Ar, CH_2Cl_2, EtN_3; (ii) F-Ar, K_2CO_3, CH_3CN, reflux 48 h; (iii) HCl, acetic acid, 2 h; (iv) THF, K_2CO_3, 72 h; (v) methanol, $NaBH_4$, 0 °C, 2 h.

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Table 1. Series II: Arylamine Derivative Affinity toward 5-HT$_7$ Receptor and 5-HTT (Serotonin Transport Protein)[a]

					5-HT$_7$		5-HTT affinity, % displacement of [^{3}H]5-HT	
compd	R_1	R	amino	Ar	pK_i	agonism	10 μM	1 μM
8a	H	C=O	piperazine	*p*-nitrophenyl	<4.00	ND	33.2	2.1
8b	H	C=O	piperazine	*p*-aminophenyl	4.85	ND	ND	ND
8c	H	C=O	piperazine	*p*-cyanophenyl	<4.00	ND	38.2	5.4
8d	F	C=O	piperazine	*p*-nitrophenyl	4.04	ND	16.3	0
8e	H	C=O	homopiperazine	*p*-nitro-*o*-trifluoromethylphenyl	<4.00	ND	ND	ND
8f	H	C=O	homopiperazine	*p*-cyanophenyl	4.82	ND	63.1	1.2
8g	H	C=O	homopiperazine	2-quinoxaline	5.02	ND	58.0	23.8
8h	H	C=O	(*R*)-pyrrolidin-3-amine	*p*-nitrophenyl	<4.00	ND	76.5	17.9
8i	H	C=O	3-amine-(*S*)-pyrrolidine	*p*-nitrophenyl	<4.00	ND	36.6	0
8j	H	C=O	3-amine- (*S*)-pyrrolidine	*p*-nitro-*o*-trifluoromethylphenyl	<4.00	ND	97.9	28.4
8k	H	C=O	3-amine-(*S*)-pyrrolidine	*p*-cyanophenyl	<4.00	ND	45.6	0
8l	H	C=O	3-amine-(*R*)-pyrrolidine	*p*-nitrophenyl	<4.00	ND	45.4	9.0
8m	H	C=O	4-amine-piperidine	*p*-nitro-*o*-trifluoromethylphenyl	5.04	A/PAg	62.8	26.9
8n	H	C=O	4-amine-piperidine	*p*-cyanophenyl	5.14	PAg	ND	ND
8o	F	C=O	4-amine-piperidine	*p*-nitrophenyl	5.32	A/PA	35.0	3.1
8p	H	C=O	piperidine	Morpholine	4.27	ND	30.2	11.1
9a	H	C−OH	piperazine	*p*-cyanophenyl	4.90	A/IAg	57.7	43.5
9b	H	C−OH	homopiperazine	*p*-nitro-*o*-trifluoromethylphenyl	5.06	PAg	36.0	0
9c	H	C−OH	homopiperazine	*p*-cyanophenyl	6.58	A/IAg	36.7	19.7
9d	H	C−OH	3-amine-(*R*)-pyrrolidine	*p*-nitrophenyl	<4.00	ND	49.2	28.1
9e	H	C−OH	4-amine-piperidine	*p*-cyanophenyl	5.78	A/IAg	80.4	53.1
9f	H	C−OH	piperidine	morpholine	4.56	ND	63.6	2.2

[a] ND, no data; A, antagonist; Ag, agonist; PAg, partial agonist; IAg, inverse agonist.

Binding Assay to the 5-HT$_7$R. Compounds from series I, containing the arylsulfonamide moiety, showed in general low affinity toward 5-HT$_7$R, whereas the arylamine derivatives of series II displayed the most interesting results of affinity toward this receptor (Table 1).

The 5-HT$_7$ receptor affinity values revealed that the alcohol derivatives **9** are the most suited compounds for interacting with this target, especially the homopiperazinyl and aminopiperidinyl compounds (**9b**,**c**,**e**). The influence of the different substituents in the aromatic ring is not very clear, but it appears that products containing a *p*-cyano group (**9c**,**e**) have more affinity toward this target than those that hold any other residue. Accordingly, **9c**, containing a homopiperazine as central diamine and a *p*-cyano group as substituent of the phenyl ring, is the most potent compound, behaving as a 5-HT$_7$R antagonist in adenylyl cyclase assays and displaying pK_i = 6.58 in 5-HT$_7$ receptor binding assays. For this reason, these compounds were chosen for the study of antidepressant activity in vivo.

Binding Assay to the SERT. To evaluate the duality of our compounds, we assessed their affinity for SERT. The displacement of the radioligand [^{3}H]5-HT by fluoxetine and our compounds was compared. Some molecules from series I presented relevant affinity for SERT (see Table 1 in Supporting Information), but the arylamine derivatives from series II displayed the highest affinity for this target (Table 1). As opposed to 5-HT$_7$ receptor data, the ketones **8** showed higher affinity for SERT than the alcohol derivatives. Activity toward SERT was further studied for **8j**, **9c**, and **9e**. IC$_{50}$ was 8.3 ± 2.24 μM for fluoxetine, 7.02 ± 3.05 μM for **8j**, 3.66 ± 1.29 μM for **9e**, and 57.81 ± 16.15 μM for **9c**. On the basis of the affinity values toward both targets, **9e** was chosen as one of the most interesting products because it showed dual affinity. This compound might be considered as prototypical for the design of new antidepressant agents.

In Vivo Assays. Three compounds were selected for testing antidepressant activity in the FST, which has predictive value for antidepressant-like activity.[28] **8j** was chosen because of its affinity for SERT. **9c** was found to be the best 5-HT$_7$ receptor antagonist, while **9e** was one of the most interesting compounds because it showed dual affinity. All compounds were tested at a dose of 10 mg/kg. For comparative purposes, fluoxetine (10 and 20 mg/kg, ip) was also included in the experiment.

After acute administration, **9c** (10 mg/kg, ip) but not fluoxetine (10 or 20 mg/kg) was able to significantly reduce the immobility time compared to controls (Figure 3). After chronic treatment, **8j**, **9c**, and **9e** showed antidepressant activity comparable to that of chronic fluoxetine (20 mg/kg, ip) treatment (Figure 3).

The FST must be validated by testing the influence of the compounds on motor behavior because an increase in motor activity might account for changes in the immobility time in the test. The results in the present study do not appear to be related to unspecific effects of any of the drugs in motor activity because no differences were found in total path length traveled in the locomotor activity test (data not shown).

Binding Assay to 5-HT$_{1A}$ Receptor. The affinity for 5-HT$_{1A}$ receptors was also checked because this receptor is known to have a pharmacological profile similar to the 5-HT$_7$ receptor and it also plays a role in the antidepressant response. The pK_i for the reference 8-OH-DPAT was 8.9. The pK_i values obtained for **9c**, **9e**, and **8j** were 5.5, 6.8, and 7.3 respectively. These results show that the affinity of these compounds for the 5-HT$_{1A}$ receptor does not seem to be related to their antidepressant-like activity.

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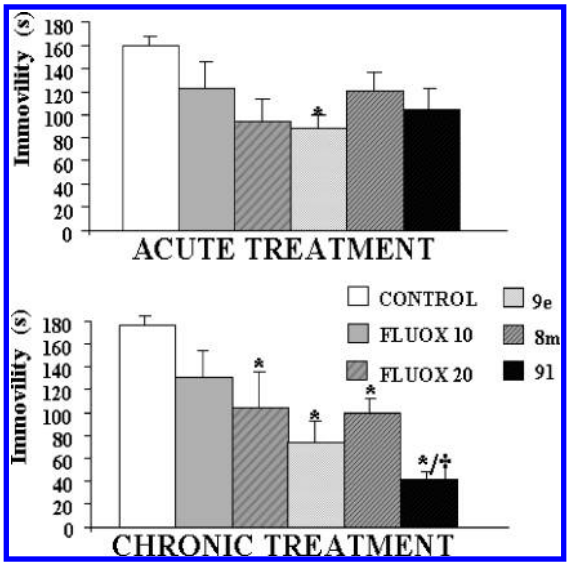

Figure 3. Antidepressant effect, measured as immobility time in the Porsolt swimming test, after acute or chronic treatment with fluoxetine (10 or 20 mg/kg) for **9c**, **9e**, **8j** (all 10 mg/kg): acute treatment, one-way ANOVA ($F_{5,75} = 4217$, $p < 0.01$) followed by Scheffe post hoc test, (∗) $p < 0.05$ vs control; chronic treatment, one-way ANOVA ($F_{5,73} = 11\,029$, $p < 0.001$) followed by Scheffe posthoc test, (∗) $p < 0.001$ vs control, (†) $p < 0.05$ vs fluxetine (10 mg/kg).

Compounds with higher affinity for this receptor do not show great antidepressant effects in this test.

■ CONCLUSIONS

The thorough research carried out on new compounds with antidepressant profiles resulted in the synthesis of 35 new benzo[*b*]thiophene derivatives. Some of them have shown acceptable affinity toward 5-HT$_7$R, one of the serotonin receptors that has been purportedly described as being involved in the development of depression. The affinity for this target and for SERT was studied, and three products were selected for performing in vivo assays.

The FST revealed that all three compounds possessed antidepressant activity after chronic treatment (15-day treatment) and that one of them showed activity even after acute administration.

The results of this study indicate that 5-HT$_7$ receptor antagonists have properties that are common to classical antidepressants in the FST, suggesting that they may be of interest for the treatment of depression. However, a note of caution should be considered at this point, as dual activity of these compounds on SERT and 5HT$_{1A}$ receptors cannot be completely excluded as being purportedly involved in the biological effects of these compounds.

In addition, considering that SSRIs such as fluoxetine often require several weeks to achieve clinical benefits in depressed patients, the rapid onset of action of **9c** suggests that 5-HT$_7$ receptor antagonists may represent a new class of antidepressants with beneficial effects over classical SSRIs.

■ EXPERIMENTAL SECTION

All the compounds were chemically characterized by TLC, melting point, IR, and ^{1}H NMR spectra. To determine the purity of the compounds, we used elemental microanalysis. The analytical results for C, H, and N were within ±0.4 of the theoretical values.

Synthesis of 1-Benzo[*b*]thiophen-3-yl-3-[1-(4-nitro-2-trifluoromethylphenyl-(*S*)-pyrrolidin-3-ylamino)propan-1-one (8j). A mixture of 1-(benzo[*b*]thiophen-3-yl)-3-chloropropan-1-one (1.24 g, 4.61 mmol), 1-(4-nitro-2-trifluoromethylphenyl)-(*S*)-pyrrolidin-3-amine (1.52 g, 5.53 mmol), and K_2CO_3 (0.68 g, 6.91 mmol) was stirred in THF for 72 h at room temperature. The solvent was removed under reduced pressure, and the residue was dissolved in CH_2Cl_2 (40 mL), and washed with water (3 × 30 mL). After evaporating to dryness under reduced pressure, the residue was purified by column chromatography (SP, silica gel), eluting with CH_2Cl_2/methanol 99:1 v/v. Yield: 18%. Mp 122−124 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.74(s, 1H, N**H**); 1.93−2.00 (m, 1H, H_{4ec} pyrrolidine); 2.21−2.28 (m, 1H, H_{4ax} pyrrolidine); 3.04−3.10 (q, 1H, C**H**$_2$-NH); 3.14−3.20 (m, 1H, CO-CH$_2$-C**H**$_2$); 3.26 (t, 2H, CO-C**H**$_2$, J = 5.9 Hz); 3.40 (dd, 1H, H_{2ec} pyrrolidine, $J_{2ec,2ax}$ = 10.3 Hz, $J_{2ec,3}$ = 4.9 Hz,); 3.54−3.62 (m, 2H, H_5); 3.68−3.74 (m, 1H, H_3 pyrrolidine); 3.78 (dd, 1H, H_{2ax} pyrrolidine, $J_{2ax,2ec}$ = 10.3 Hz, $J_{2ax,3}$ = 5.7 Hz,); 6.79 (d, 1H, $H_{6'}$, $J_{6',5'}$ = 9.5 Hz); 7.45 (ddd, 1H, H_5, $J_{5,4}$ = 8.0 Hz, $J_{5,6}$ = 7.1 Hz, $J_{5,7}$ = 1.1 Hz); 7.51 (ddd, 1H, H_6, $J_{6,7}$ = 8.3 Hz, $J_{6,5}$ = 7.1 Hz, $J_{6,4}$ = 1.2 Hz); 7.89 (ddd, 1H, H_4, $J_{4,5}$ = 8.0 Hz, $J_{4,6}$ = 1.1 Hz, $J_{4,7}$ = 0.7 Hz); 8.12 (dd, 1H, $H_{5'}$, $J_{5',6'}$ = 9.5 Hz, $J_{5',3'}$ = 2.8 Hz); 8.33 (s, 1H, H_2); 8.54 (d, 1H, $H_{3'}$, $J_{3',5'}$ = 2.8 Hz); 8.75 (ddd, 1H, H_7, $J_{7,6}$ = 8.0 Hz, $J_{7,5}$ = 1.2 Hz, $J_{7,4}$ = 0.6 Hz) ppm. Anal. Calcd for $C_{22}H_{20}N_3F_3O_3S$: C, 57.01%; H, 4.35%; N, 9.07%. Found: C, 56.72%; H, 4.31%; N, 8.82%.

Synthesis of 4-[4-(3-Benzo[*b*]thiophen-3-yl-3-hydroxypropyl)[1,4]diazepan-1-yl]benzonitrile (9c). Sodium borohydride (0.14 g, 3.84 mmol) was added little by little to a precooled suspension (0 °C, 5 min) of 4-[4-(3-benzo[*b*]thiophen-3-yl-3-oxopropyl)[1,4]diazepan-1-yl]benzonitrile (0.50 g, 1.28 mmol) in methanol (20 mL) over 30 min. The mixture was stirred until TLC proved that the reaction did not go on (∼1 h). The solvent was removed under reduced pressure, and the residue dissolved in dichloromethane (40 mL) was washed with water (3 × 30 mL). The organic phase was dried with anhydrous Na_2SO_4 and filtered. After evaporation of the solvent to dryness under reduced pressure, the compound was purified by preparative chromatography (SP, silica gel), eluting with CH_2Cl_2/methanol 95:5 v/v.Yield: 61%. Mp 41−43 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.04−2.15 (m, 4H, CHOH-C**H**$_2$ and H_6 diazepane); 2.68−2.99 (m, 6H, CHOH-CH$_2$-C**H**$_2$ and H_2 + H_7 diazepane); 3.54−3.63 (m, 2H, H_5 diazepane); 3.70 (bs, 2H, H_3 diazepane); 5.35−5.38 (dd, C**H**OH, $J_{H,CH2}$ = 7.7 Hz, $J_{H,OH}$ = 3.0 Hz); 6.68 (d, 2H, $H_{2'}$ + $H_{6'}$, $J_{2',3'} = J_{6',5'}$ = 8.8 Hz); 7.34−7.41 (m, 2H, H_6 + H_5); 7.42 (s, 1H, H_2); 7.49 (d, 1H, $H_{3'}$ + $H_{5'}$, $J_{3',2'} = J_{5',6'}$ = 8.8 Hz); 7.79 (dd. 1H, H_4, $J_{4,5}$ = 7.1 Hz, $J_{4,6}$ = 1.5 Hz); 7.88 (dd, 1H, H_7, $J_{7,6}$ = 7.0 Hz, $J_{7,5}$ = 1.5 Hz) ppm. Anal. Calcd for $C_{23}H_{25}N_3OS$: C, 70.56%; H, 6.44%; N, 10.73%. Found: C, 70.58%; H, 6.78%; N, 10.44%.

Synthesis of 4-[4-(3-Benzo[*b*]thiophen-3-yl-3-hydroxypropylamino)piperidin-1-yl]benzonitrile (9e). Sodium borohydride (0.51 g, 13.32 mmol) was added little by little to a precooled suspension (0 °C, 5 min) of 4-[4-(3-benzo[*b*]thiophen-3-yl-3-oxopropylamino)piperidin-1-yl]benzonitrile (1.19 g, 4.44 mmol) in methanol (30 mL) over 30 min. The mixture was stirred until TLC proved that the reaction did not go on (∼1 h). The solvent was removed under reduced pressure, and the residue dissolved in dichloromethane (40 mL) was washed with water (3 × 30 mL). The organic phase was dried with anhydrous Na_2SO_4 and filtered. After evaporation of the solvent to dryness under reduced pressure, the compound was purified by column chromatography (SP, silica gel), eluting with CH_2Cl_2/methanol 99:1. Yield: 56%. Mp 150−151 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.59−1.69 (m, 2H, H_{3ax} + H_{5ax} piperidine); 2.16−2.19 (bs, 2H, H_{3ec} + H_{5ec} piperidine); 2.92−2.98 (m, 3H, H_{2ax} + H_{6ax} + H_4 piperidine); 3.25 (t, 2H, CHOH-C**H**$_2$, J = 6.1 Hz); 3.41 (t, 2H, CHOH-CH$_2$-C**H**$_2$, J = 6.1 Hz); 3.87 (d, 2H, **H**$_{2ec}$ + **H**$_{6ec}$ piperidine, $J_{2ec,2ax} = J_{6ec,6ax}$ = 13.1 Hz); 5.51 (bs, 1H, N**H**); 6.87 (d, 2H, $H_{2'}$ + $H_{6'}$, $J_{2',3'} = J_{6',5'}$ = 9.1 Hz); 7.42−7.53 (m, 4H, H_5 + H_6 + $H_{3'}$ + $H_{5'}$); 7.88 (ddd, 1H, H_4,

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$J_{4,5}$ = 7.8 Hz, $J_{4,6}$ = 1.2 Hz, $J_{4,7}$ = 0.7 Hz); 8.39 (s, 1H, H_2); 8.73 (ddd, 1H, H_7, $J_{7,6}$ = 8.2 Hz, $J_{7,5}$ = 1.3 Hz, $J_{7,4}$ = 0.7 Hz) ppm. Anal. Calcd for $C_{23}H_{25}N_3OS$: C, 70.56%; H, 6.44%; N, 10.73%. Found: C, 70.27%; H, 6.51%; N, 10.44%.

■ ASSOCIATED CONTENT

Supporting Information. Synthesis methods and characterization data of all compounds and details of biological assay procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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