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Original article

New 3-[4-(aryl)piperazin-1-yl]-1-(benzo[b]thiophen-3-yl)propane derivatives with dual action at 5-HT_{1A} serotonin receptors and serotonin transporter as a new class of antidepressants

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Abstract – A series of new 3-[4-(aryl)piperazin-1-yl]-1-(benzo[b]thiophen-3-yl)propane derivatives were synthesized in an attempt to find a new class of antidepressant drugs with dual activity at 5-HT_{1A} serotonin receptors and serotonin transporter. Title compounds were evaluated for in vitro activity on 5-HT_{1A} receptor and 5-HT transporter. They show high nanomolar affinity for both activities, and in particular, compounds 1-(5-chlorobenzo[b]thiophen-3-yl)-3-[4-(2-methoxyphenyl)piperazin-1-yl]propan-1-ol (**7**) and 1-(5-fluorobenzo[b]thiophen-3-yl)-3-[4-(2-methoxyphenyl)piperazin-1-yl]propan-1-ol (**8**) show values (nM) of $K_i = 30$ and 2.3 for 5-HT_{1A} receptors and $K_i = 30$ and 12 for serotonin transporters, respectively. In GTPγS binding assays, compound **8** revealed antagonist properties to 5-HT_{1A} receptors. Such a pharmacological profile could lead to potent antidepressant agents with new dual mechanism of action. © 2001 Éditions scientifiques et médicales Elsevier SAS

arylpiperazines / antidepressant / 5-HT_{1A} antagonist / serotonin reuptake inhibitor

1. Introduction

Selective serotonin (5-hydroxytriptamine, (5-HT)) reuptake inhibitors (SSRIs) are effective in the treatment of depression. With these and other antidepressants, several weeks of treatment are, however, required before their therapeutic effects become apparent [1, 2]. It has been hypothesized that this delay can be explained by the initial elevation in the raphe nuclei of extracellular 5-HT, which reduces the firing of serotoninergic neurons by activating somatodendritic 5-HT_{1A} autoreceptors [3]. After repeated antidepressant treatment, somatodendritic 5-HT_{1A} receptors become desensitized, firing activity of serotoninergic neurons is restored and the increase in extracellular 5-HT in forebrain areas coincides with the onset of antidepressant effect [4, 5]. This hypothesis is supported by the augmentation of extracellular 5-HT concentration in terminal fields of serotoninergic system observed after concomitant administration of a 5-HT_{1A} receptor antagonist such as pindolol or the silent antagonist WAY 100635 with different SSRIs [6–9]. Recent clinical trials indicate, on the other hand, that a combination of the 5-HT_{1A} receptor antagonist pindolol and a SSRI such as fluoxetine, paroxetine or citalopram may shorten the onset of action and improve the efficacy of antidepressant treatment [10–15]. Conceivably, new agents with 5-HT_{1A} receptor antagonist and 5-HT transporter inhibitor properties could produce the same therapeutic benefits observed with the combination of a SSRI and a 5-HT_{1A} antagonist. However, few pharmacological

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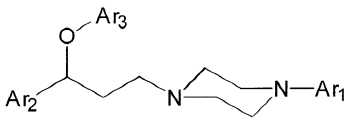


Figure 1. General structure I.

data of compounds with both activities have been reported to date [16].

We synthesized compounds with the general structure shown in *figure 1* where there is an arylpiperazine and a γ-phenoxypropylamine moiety, which may provide 5-HT_{1A} receptor affinity and 5-HT reuptake inhibition, respectively. Some structurally related compounds endowed with either pharmacological action are shown in *figure 2*. Preliminary studies revealed, however, not only γ-phenoxypropylamine derivatives but compounds without the aromatic ring Ar_3 showed too the dual pharmacological activity [17]. Consequently we synthesized new compounds of general structure II (*figure 3*) in which Z represents the different functional groups indicated [17]. The best pharmacological results were obtained when there was a hydroxyl group on Z, Ar_2 was a benzo[b]thiophene ring and Ar_1 a 2-methoxyphenyl moiety. Accordingly, we synthesized new derivatives of general structure III (*figure 4*) in which substitution at position 5 of benzo[b]thiophene ring appeared to be the most interesting from the biological point of view due to the presence of this substitution in molecules with biological activity such as 5-HT. Compounds that exhibited high affinity at 5-HT_{1A} receptor and 5-HT transporter (**6**, **7** and **8**) were studied for their agonist/antagonist activity to 5-HT_{1A} receptors using a 5-HT_{1A} receptor-mediated GTPγS binding assay in rat hippocampal membranes.

2. Chemistry

Chemical data of 3-[4-(aryl)piperazin-1-yl]-1-(benzo[b]thiophen-3-yl)propane derivatives synthesized in this work are shown in *table I*. *Figures 5* and *6* illustrate the procedures used to synthesize 1-(5-halogenbenzo[b]thiophen-3-yl)-3-[4-(2-methoxyphenyl)-

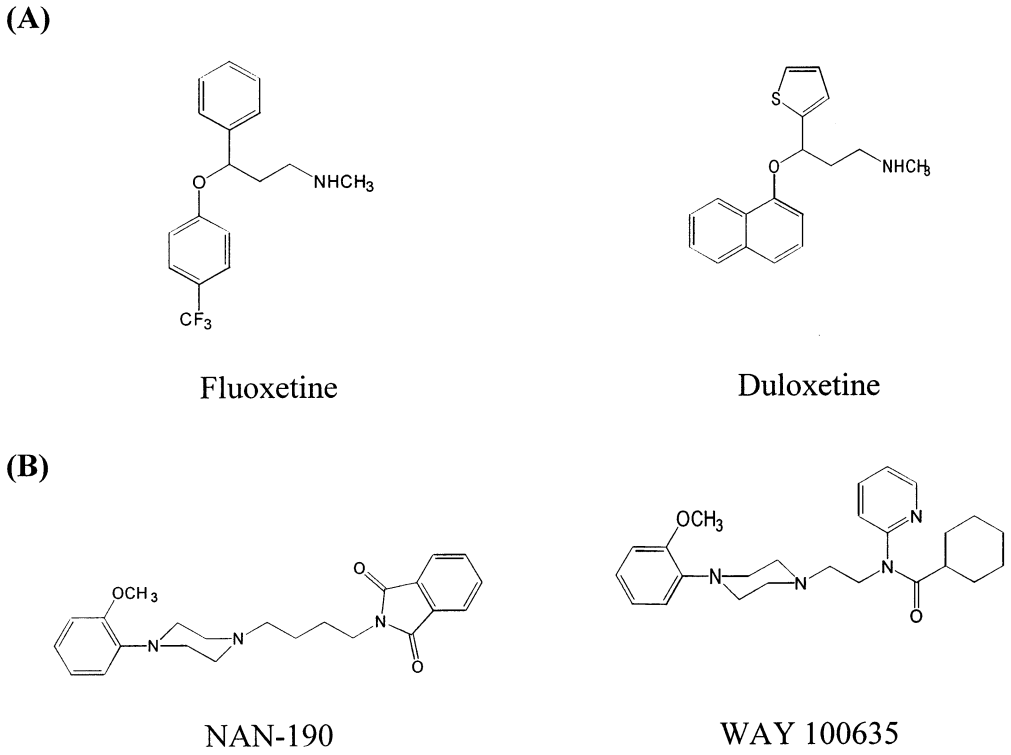
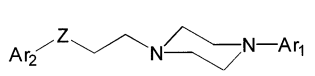


Figure 2. Serotonin reuptake inhibitors derived from γ-phenoxypropylamine (**A**) and 5-HT_{1A} receptor antagonist derived from arylpiperazine (**B**).



Z = CO, CHOH, CNOH, CHOAr, $CHOC(CH_3)_3$, $CHOCONHCH(CH_3)_2$

Figure 3. General structure II.

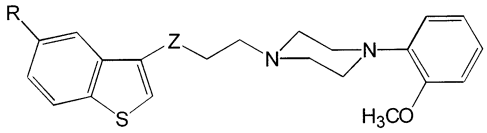
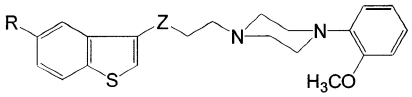


Figure 4. General structure III.

piperazin-1-yl] propan-1-one derivatives (**5** and **6**), and *figure 7* illustrates the general procedure followed to synthesize 1-(5-halogenbenzo[b]thiophen-3-yl)-3-[4-(2-methoxyphenyl) piperazin-1-yl]propan-1-ol derivatives (**7** and **8**). Hydroxyl derivatives were synthesized by reduction of the corresponding carbonyl derivatives **5** and **6** with sodium borohydride in methanol at 0 °C. Compound **5** was synthesized by the Mannich reaction of the corresponding 3-acetyl-5-chlorobenzo-[b]thiophene (**3**) and 1-(2-methoxyphenyl)piperazine with paraformaldehyde and concentrated hydrochloric acid in refluxing ethanol. Compound **6** was synthesized by nucleophylic substitution of 1-(2-methoxyphenyl)piperazine and 3-chloro-1-(5-fluorobenzo[b]thiophen-3-yl)propan-1-one (**4**) in tetrahydrofurane with potassium carbonate. Compound **4** was synthesized from 5-fluorobenzo[b]thiophene (**2**) by classical Friedel–Craft acylation with 3-chloropropionyl chloride and aluminum chloride in dry chloroform. Compound **3** was synthesized following an adaptation of the procedures described in the litera-

Table I. Chemical data of 1-(benzo[b]thiophene)-3-[4-(2-methoxyphenyl) piperazin-1-yl)propane derivatives **5**–**8**.



Compound	R	Z	m.p. (°C)	% Yield	Purification[a]	Formula
5·HCl	Cl	CO	238	35	A	$C_{22}H_{23}N_2ClO_2S$
6·2HCl	F	CO	197	62	A	$C_{22}H_{23}FN_2O_2S$
7·2HCl	Cl	CHOH	187	42	A	$C_{22}H_{25}N_2ClO_2S$
8	F	CHOH	125	60	B	$C_{22}H_{25}FN_2O_2S$

[a] A = column chromatography on silica gel: light petroleum/AcOEt 1:1; B = recrystallization from light petroleum/*i*-PrOH.

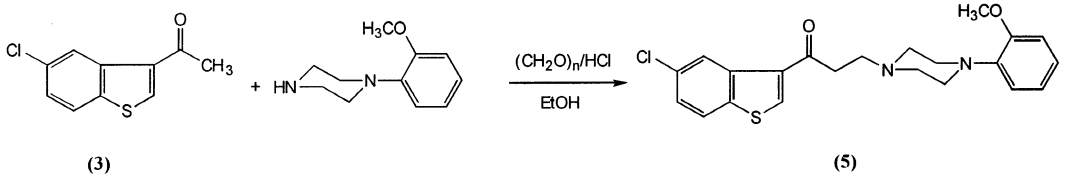


Figure 5. Synthesis of 1-(5-chlorobenzo[b]thiophen-3-yl)-3-[4-(2-methoxyphenyl)piperazin-1-yl]propan-1-one.

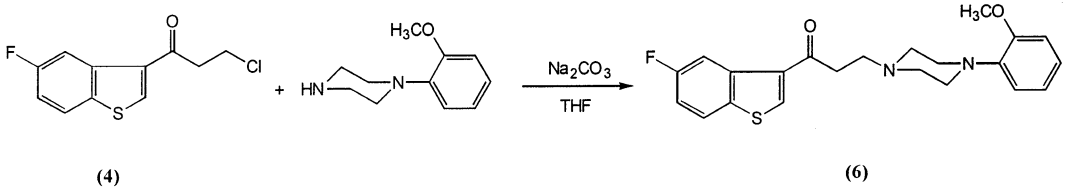
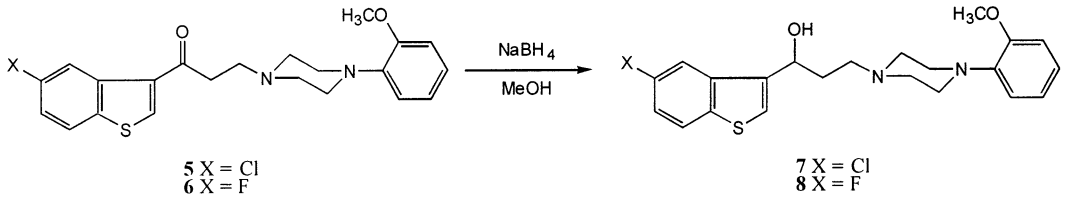


Figure 6. Synthesis of 1-(5-fluorobenzo[b]thiophen-3-yl)-3-[4-(2-methoxyphenyl)piperazin-1-yl]propan-1-one.



5 X = Cl
6 X = F

7 X = Cl
8 X = F

Figure 7. Synthesis of 1-(5-halogenbenzo[b]thiophen-3-yl)-3-[4-(2-methoxyphenyl)piperazin-1-yl]propan-1-ol derivatives.

ture [18]; the use of aluminum trichloride and acetyl chloride slightly improved the yield. The starting reagents for compounds **1** and **2** (5-chlorobenzo[b]thiophene and 5-fluorobenzo[b]thiophene) were synthesized from 1-(2-diethoxyethilthio)-4-chlorobenzene and 1-(2-diethoxyethilthio)-4-fluorobenzene following a previously described procedure [19]. 1-(2-diethoxyethylthio)-4-chlorobenzene and 1-(2-diethoxyethylthio)-4-fluorobenzene were synthesized following an adaptation of the method described in literature which facilitates the work procedure [20].

3. Pharmacology

Binding affinity to 5-HT_{1A} receptor and 5-HT transporter were determined for **5**–**8**. The affinity for 5-HT_{1A} receptors was determined by studying the displacement of binding of [^{3}H]-8-hydroxy-2-(di-*n*-propylamino)tetralin ([^{3}H]-OH-DPAT) to rat cerebral cortex homogenates according to procedures reported previously [21, 22]. The affinity for 5-HT transporter was determined by studying the competition in [H^3]-paroxetine bindings to rat cerebral cortex homogenates, as described [22, 23]. Compounds were studied for their agonist/antagonist activity to 5-HT_{1A} receptors using a 5-HT_{1A} receptor-mediated GTPγS binding assay in rat hippocampal membranes. This assay was carried out by studying the competition in [^{35}S]GTPγS binding to rat hippocampal homogenates following the method described [24].

4. Results and discussion

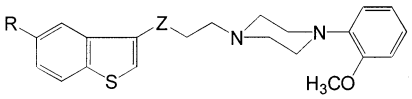
The results of binding studies for compounds **5**–**8** are summarized in *table II*. All of the compounds showed a moderate to high affinity at both the 5-HT_{1A} receptor and the 5-HT transporter.

The introduction of an alkyl-benzo[b]thiophene moiety attached to the arylpiperazine enhanced the affinity at the 5-HT transporter of synthesized compounds. This result confirms previous findings of our group in which it was shown that arylpiperazine derivatives with a benzene or thiophene ring attached at the end of the alkyl chain could yield the desired activities without the presence of the third aromatic ring Ar_3 [17]. The present results also confirm that the substitution of a thiophene ring by a benzocondensed ring, such as benzo[b]thiophene, clearly improves the affinity.

Observation of the results shows better pharmacological results for hydroxylic derivatives than for carbonylic derivatives in both activities. These results are in agreement with previous work carried out in our laboratory in which hydroxylic derivatives present the best results among the different functional groups introduced, which include carbonyl, hydroxyl, arylether, alkylether, oxime and carbamate [17].

The results of affinity of the analogues of compounds synthesized in which there is no substituent at benzo[b]thiophene ring (R = H in general structure III, in *figure 4*) were obtained in previous work of our group: 1-benzo[b]thiophen-3-yl-3-[4-(2-methoxyphenyl) piperazin-1-yl]propan-1-one (K_i = 45 nM and K_i = 110 nM affinity at the 5-HT_{1A} receptors and

Table II. Binding affinity (K_i, nM) at 5-HT_{1A} receptors and 5-HT transporter of compounds **5**–**8**.[a]



Compound	R	Z	5-HT_{1A} receptor	5-HT transporter
5	Cl	CO	250 ± 10	260 ± 15
6	F	CO	15 ± 2.1	100 ± 5.6
7	Cl	CHOH	30 ± 2.2	30 ± 1.5
8	F	CHOH	2.3 ± 0.3	12 ± 0.8

[a] Values are means ± S.E.M. from at least 3 experiments.

Table III. Effect of WAY 100635 and compounds **5**–**8** on 8-OH-DPAT-stimulated GTPγS binding in hippocampus.[a]

Compound	Basal fmol GTPγS /mg protein	Maximal fmol GTPγS /mg protein[b]	IC_{50} (nM)
Control + 8-OH-DPAT 10^{-6}	17.9 ± 0.5	32.8 ± 4.2	
WAY 100635 + DPAT 10^{-6}	18.5 ± 2.4	20.2 ± 1.6	5.7 ± 0.6
6 (10^{-10}–10^{-5}) + DPAT 10^{-6}	15.9 ± 1.2	30.1 ± 1.8	> 10000
7 (10^{-10}–10^{-5}) + DPAT 10^{-6}	18.9 ± 1.6	26.0 ± 1.4	10000
8 (10^{-10}–10^{-5}) + DPAT 10^{-6}	17.3 ± 1.5	21.5 ± 1.2	14 ± 2.1

[a] Hippocampal homogentates were incubated in the presence of graded concentrations of either WAY 100635 or compounds **6–8**, and 1 μM of 8-OH-DPAT. IC_{50} were calculated as measures of the potencies of these compounds as 5-HT_{1A} receptor antagonist. Values represent the mean ± S.E.M. from at least 3 experiments.
[b] The maximal response is the GTPγS binding observed at the highest concentration of the ligand that was varied.

5-HT transporter respectively), and 1-benzo-[b]thiophen-3-yl-3-[4-(2-methoxyphenyl)piperazin-1-yl]propan-1-ol ($K_i = 20$ nM and $K_i = 20$ nM affinity at the 5-HT_{1A} receptors and 5-HT transporter, respectively) [17]. These results were improved by 5-fluorobenzo[b]thiophene derivatives (compounds **6** and **8**), but no by 5-chlorobenzo[b]thiophene derivatives (compounds **5** and **7**). Therefore, introduction of fluor in the 5 position of benzo[b]thiophene ring improves the affinity result when comparing with no-substituted benzo[b]thiophene derivatives. On the other hand, the change of chloro by fluor in the benzo[b]thiophene ring improves the affinities at both 5-HT_{1A} receptor and 5-HT transporter. This impairment can be observed for both carbonyl (**5** and **6)** and hydroxyl derivatives (**7** and **8**).

Compounds **6**, **7** and **8** were selected to study their agonist/antagonist activity to 5-HT_{1A} receptors in GTPγS binding assays. As expected, the 5-HT_{1A} agonist 8-OH-DPAT produced a concentration-dependent decrease of the GTPγS binding with an $EC_{50} = 81 \pm 9$ nM. The selective 5-HT_{1A}-receptor antagonist WAY 100635 did not alter the binding by itself. Compound **5** and **6** did not alter the GTPγS binding, but compound **8** produced an stimulation of 50% at 10 μM. In antagonism studies WAY 100635 (0.1–10 μM) abolished the effect of 8-OH-DPAT 1 μM showing a $IC_{50} = 5.7 \pm 0.2$ nM. Compound **8** showed a moderate antagonist activity to 5-HT_{1A} receptor since it concentration-dependently reduced the 8-OH-DPAT-stimulated GTPγS binding ($IC_{50} = 140 \pm 12$ nM). Compound **7** produced a small reduction of the 8-OH-DPAT-stimulated GTPγS binding (44% of inhibition at 10 μM). See results in *table III*.

5. Conclusion

We have synthesized new arylpiperazine derivatives with affinity at both 5-HT_{1A} receptors and 5-HT transporter of potential use in the treatment of depression. The alkyl benzo[b]thiophene moiety in which there is a polar group like carbonyl or hydroxyl, adds affinity towards the 5-HT transporter to the arylpiperazine. From GTPγS binding assays, compound **8** appears to be the most interesting compound since it shows antagonist activity at 5-HT_{1A} receptors.

At this point, the introduction of new substituents in the benzo[b]thiophene ring in position 5 and in other positions such as 4, 7 or 2, seems to be very interesting in order to obtain new compounds with potent affinity for both pharmacological activities. Further pharmacological evaluation of the compounds herein described is in progress.

6. Experimental protocols

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 4 mm Hg, 24 h, at ca. 80–100 °C). Infrared spectra were recorded on a Perkin-Elmer 1600 series FTIR apparatus, using potassium bromide tablets for solid products and sodium chloride plates for liquid products, the frequencies are expressed in cm^{-1}. The ^{1}H-NMR spectra (*table IV*) were obtained on a Brucker AC-200E (200 MHz) instrument with tetramethylsilane as the internal reference, at a concentration of ca. 0.1 g mL^{-1} and with dimethyl solfoxide-d_6 (DMSO-d_6) or chloroform

($CDCl_3$) as the solvent; the chemical shifts are reported in parts per million (PPM) of tetramethylsilane in d units, and the *J* values are given in hertz (Hz) (*table IV*). The mass spectra were recorded on a Hewlett-Packard 5988-A instrument at 70 eV.

Thin layer chromatography (TLC) was carried out on silica gel (DSF-5, Cammaga 0.3 mm thickness) with the indicated solvents, 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).

Elemental analyses were performed on a Carlo-Erba 1106 Instrumentazione and the experimentally determined values are within ± 0.4% of the theoretical values.

6.1. Synthesis of 3-acetyl-5-chlorobenzo[b]thiophene ***3***

A solution of 5-chlorobenzo[b]thiophene (1.00 g, 5.90 mmol) and acetyl chloride (0.49 g, 6.24 mmol) was added dropwise to a well stirred solution of 0.86 g of aluminum trichloride in dry dichloromethane (10 mL) at 0 °C. The temperature was allowed to rise to 25 °C and the mixture was stirred overnight. Then, the reaction mixture was refluxed for 1 h, and after cooling, diluted sulfuric acid was added. The aqueous portion was extracted with dichloromethane and the combined organic portions were washed with water and dried with sodium sulfate. The solvent was evaporated at reduced pressure. The product was purified by flash chromatography (SP: silica gel), eluting with toluene (60%) m.p. 80–82 °C.

6.2. Synthesis of 3-chloro-1-(5-fluorobenzo[b]thiophen-3-yl)propan-1-one ***4***

A solution of 5-fluorobenzo[b]thiophene (0.80 g, 5.26 mmol) and 3-chloropropionyl chloride (0.49 mL, 6,32 mmol) in dry chloroform (35 mL) was added dropwise to a well-stirred solution of aluminum trichloride (0.58 g) in dry chloroform (18 mL) at 0 °C. After 24 h the reaction was quenched with 1.5 N hydrochloric acid (100 mL), the organic layer washed with 5% sodium bicarbonate, water, 'brine' and dried with sodium sulfate. It was then evaporated at reduced pressure. The product was purified by flash chromatography (SP: silica gel), eluting with light petroleum/toluene (25:75) (43%) m.p. 80–81 °C.

6.3. Synthesis of 1-(5-chlorobenzo[b]thiophen-3-yl)-3-[4-(2-methoxyphenyl) piperazin-1-yl]propan-1-one ***5·HCl***

A mixture of 3-acetyl-5-chlorobenzo[b]thiophene (1.7 g, 8.08 mmol) and hydrochloride of 2-meth-

Table IV. ^{1}H-NMR and IR data for new compounds.

Ref.	^{1}H-NMR. δ (ppm) (*J* in Hz)	IR (cm^{-1}, KBr)
4	3.46 (t; 2H, $CH_2C=O$); 3.96 (t; 2H, CH_2Cl); 7.19 (dd; 1H, H_6, $J_{46}=2.6$, $J_{67}=8.4$); 7.77 (dd; 1H, H_7, $J_{F7}=4.7$); 8.38 (s; 1H, H_2); 8.47 (d; 1H, H_4, $J_{F4}=10.3$).	1672
5	3.06–3.12 (m; 4H, N^1CH_2's); 3.54 (br; 6H, N^4CH_2's $+COCH_2$); 3.75 (t; 2H, COCH2C*H2*); 3.80 (s; 3H, OCH_3); 6.91–7.00 (m; 4H, Ph); 7.55 (dd; 1H, H_6, $J_{46}=1{,}8$ and $J_{67}=8.2$); 8.19 (d; 1H, H_7); 8.61 (d; 1H, H_4); 9.19 (s; 1H, H_2).	1669; 1241
6	3.16 (br; 4H, N^1CH_2's); 3.38–3.57 (br; 6H, N^4CH_2's $+COCH_2$); 3.73 (t; 2H, $COCH_2CH_2$); 3.78 (s; 3H, OCH_3); 6.85–6.98 (m; 4H, Ph); 7.39 (dd; 1H, H_6,$J_{46}=2.5$, $J_{67}=8.3$); 8.16 (dd; 1H, H_7, $J_{F7}=5.2$); 8.28 (d; 1H, H_4, $J_{F4}=10.7$); 9.20 (s; 1H, H_2).	1669; 1241
7	1.93 (t; 2H, CHOHC*H2*); 2.65–2.88 (m; 6H, N^1CH_2's); 3.14 (br; 4H, N^4CH_2's); 3.85 (s; 3H, OCH_3); 5.29 (t; 1H, C*H*OH); 5.83 (br; 1H, OH); 6.74–6.96 (m; 4H, Ph); 7.18 (dd; 1H, H_6, $J_{46}=1.5$, $J_{67}=8.7$); 7.36 (s; 1H, H_2); 7.63 (d; 1H, H_7); 7.70 (d; 1H, H_4).	1241
8	2.02–2.11 (m; 2H, CHOHC*H2*); 2.68–2.87 (m; 6H, N^1CH_2's); 3.15 (br; 4H, N^4CH_2's); 3.86 (s; 3H, O–CH_3); 5.26 (t; 1H, C*H*OH); 6.84–7.01 (m; 4H, Ph); 7.08 (dd; 1H, H_6, $J_{46}=2.2$, $J_{67}=8.8$); 7.49 (s; 1H, H_2); 7.50 (d; 1H, H_7, $J_{F4}=10.0$); 7.75 (d; 1H, H_4, $J_{F7}=4.8$).	3401; 1241

oxyphenylpiperazine (1.86 g, 8.08 mmol) dissolved in isopropanol (40 mL) with concentrated hydrochloric acid (pH 2–3) was refluxed, and paraformaldehyde (0.67 g) was added. After 24 h the reaction was cooled, poured over crushed ice and extracted with ethyl acetate. The organic layer was washed with water and dried with sodium sulfate. The solvent was evaporated at reduced pressure. The product was purified by flash chromatography (SP: silica gel), eluting with light petroleum/ethyl acetate (1:1). The hydrochloride was obtained adding concentrated hydrochloric acid to a solution of the product in ethanol/diethyl ether (35%).

6.4. Synthesis of 1-(5-fluorobenzo[b]thiophen-3-yl)-3-[4-(2-methoxyphenyl) piperazin-1-yl]propan-1-one ***6·2HCl***

A mixture of 2-methoxyphenylpiperazine hydrochloride (1.30 g, 6.78 mmol) and sodium carbonate (0,24 g, 2.26 mmol) were added to a solution of (5-fluorobenzo[b]thiophen-3-yl)-3-chloropropan-1-one (0.50 g, 2.26 mmol) in tetrahydrofurane (30 mL).The reaction mixture was stirred for 72 h. The solvent was evaporated at reduced pressure and the residue was poured over water and extracted with ethyl acetate. After washing the organic layer with water it was dried with sodium sulfate and the solvent was evaporated at reduced pressure. The product was purified by flash chromatography (SP: silica gel), eluting with light petroleum/ethyl acetate (1:1). The dihydrochloride was obtained by adding concentrated hydrochloric acid to a solution of the product in ethanol/diethyl ether (62%).

6.5. General procedure for compounds ***7*** *and* ***8***

Sodium borohydride, in excess, was added to a well stirred solution or suspension of the corresponding 3-(4-arylpiperazin-1-yl)-1-(5-halobenzo[b]thiophen-3-yl)-1-propanone derivative (2.0 mmol) in methanol at 0 °C over a period of 30 min. The stirring was further continued for 2 h. The reaction mixture was poured over water and stirred at room temperature overnight. The product was obtained by filtration and purified by recrystallization from light petroleum/isopropanol (**8**) (60%) or by flash chromatography (SP: silica gel), eluting with *n*-hexane/ethyl acetate 1:1 (V/V) (**7**) (42%). The dihydrochloride of compound **7** was obtained by adding concentrated hydrochloric acid to a solution of the product in acetone.

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References

[1] Asberg M., Eriksson B., Martensson B., Traskman-Bendz L., Wagner A., J. Clin. Psychiatry 47 suppl (1986) 23–35.

[2] Schatzberg A.F., Dessain E., O'Neil P., Katz D.L., Cole J.O., J Clin. Psychopharmacol. 7 (1987) 44S–49S.

[3] Rutter J.J., Gundlah C., Auerbach S.B., Synapse 20 (1995) 225–233.

[4] Chaput Y., De Montygny C., Blier P., Naunyn Schmeidebergs Arch. Pharmacol. 333 (1986) 342–348.

[5] Moret C., Briley M., Eur. J. Pharmacol. 180 (1990) 351–356.

[6] Hjorth S., J. Neurochem. 60 (1993) 776–779.

[7] Gartside S.E., Umbers V., Hajos M., Sharp T., Br. J. Pharmacol. 115 (1995) 1064–1070.

[8] Dreshfield L.J., Wong D.T., Perry K.W., Engleman E.A., Neurochem. Res. 21 (1996) 557–562.

[9] Sharp T., Umbers V., Gartside S.E., Br. J. Pharmacol. 121 (1997) 941–946.

[10] Artigas F., Perez V., Alvarez E., Arch. Gen. Psychiatry 51 (1994) 248–251.

[11] Tome M.B., Cloninger C.R., Watson J.P., Isaac M.T., J. Affective Disord. 44 (1997) 101–109.

[12] Perez V., Gilaberte I., Faries D., Alvarez E., Artigas F., Lancet 349 (1997) 1594–1597.

[13] Zanardi R., Artigas F., Franchini L., Sforzini L., Gasperini M., Smeraldi E., Perez J., J. Clin. Psychopharmacol. 17 (1997) 446–450.

[14] Puzantian T., Kawase K., Pharmacotherapy 19 (1999) 205–212.

[15] Perez V., Soler J., Puigdemont D., Alvarez E., Artigas F., Arch. Gen. Psychiatry. 56 (1999) 375–379.

[16] Evrard D.A., Harrison B.L., Recent approaches to novel antidepressant therapy, Ann. Rep. Med. Chem. 34 (1999) 1–10.

[17] A. Monge Vega, J. del Rio Zambrana, B. Lasheras, J.A. Palop, A. Bosch, J.C. del Castillo, J. Roca, (Vita Farma) WO 9902516A1.

[18] M.S. Shanta, R.M. Scrowston, J. Chem. Soc. (C) (1967) 2084–2089.

[19] Février B., Dupas G., Bourguignon J., Queginer G., J. Heterocyclic Chem. 30 (1993) 1085–1088.

[20] O. Noboru, M. Hideyoshi, S. Tadashi, K. Aritsune, Synthesis (1980) 952–954.

[21] Gozlan H., El Mestikawy S., Pichat L., Glowinski J., Hamon M., Nature 305 (1983) 140–142.

[22] Aguirre N., Galbete J.L., Lasheras B., Del Rio J., Eur. J. Pharmacol. 281 (1995) 101–105.

[23] Habert E., Graham D., Tehraqui L., Claustre I., Langer S.Z., Eur. J. Pharmacol. 118 (1989) 107–114.

[24] Alper R.H., Nelson D.L., Eur. J. Pharmacol. 343 (1998) 303–312.