Department of Medicinal Chemistry and Centro de Investigación en Farmacobiología Aplicada (CIFA[1]), and Department of Pharmacology[2], Universidad de Navarra, Pamplona, Spain

New 3-[4-(2,3-dihydro-1,4-benzodioxin-5-yl)piperazin-1-yl]-1-(5-substituted benzo[*b*]thiophen-3-yl)propanol derivatives with dual action at 5-HT_{1A} serotonin receptors and serotonin transporter as a new class of antidepressants

S. Pérez Silanes[1], L. Orús[1], A.M. Oficialdegui[1], J. Martínez Esparza[1], B. Lasheras[2], J. del Río[2], A. Monge[1]

Received August 13, 2003, accepted October 29, 2003

Prof. Antonio Monge, Centro de Investigación en Farmacobiología Aplicada (CIFA), Universidad de Navarra, C/ Irunlarrea s/n, 31080, Pamplona, Spain
amonge@unav.es

Pharmazie 59: 499–501 (2004)

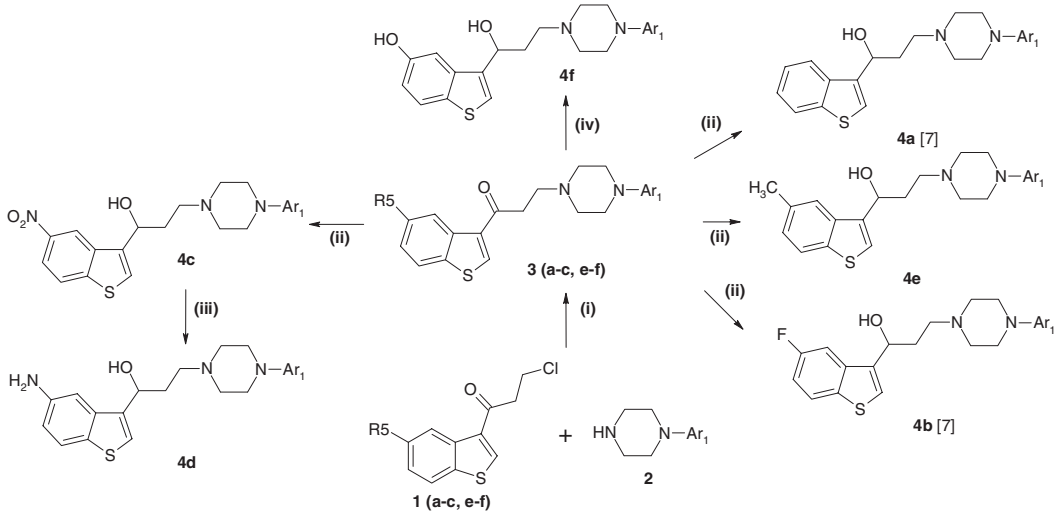
Compounds derived from 2,3-dihydro-(1,4-benzodioxin-5-yl)piperazine and benzo[*b*]thiophene with different substituents in 5 position (H, F, NO_2, NH_2, CH_3 and OH) have been synthesized in order to obtain new dual antidepressant drugs. The final compounds were evaluated for *in vitro* 5-HT_{1A} receptor affinity and serotonin reuptake inhibition by radioligand assays. Compounds 1-(5-nitrobenzo[*b*]thiophen-3-yl)-3-[4-(2,3-dihydro-1,4-benzodioxin-5-yl)piperazin-1-yl]propan-1-ol (**4c**) ($K_i = 6.8$ for 5-HT_{1A} receptor and $K_i = 14$ for 5-HT transporter) and 1-(5-hydroxybenzo[*b*]thiophen-3-yl)-3-[4-(2,3-dihydro-1,4-benzodioxin-5-yl)piperazin-1-yl] propan-1-ol (**4f**) ($K_i = 6.2$ for 5-HT_{1A} receptor and $K_i = 18.2$ for 5-HT transporter) showed the best results for both activities.

1. Introduction

It has been proposed that 5-HT_{1A} receptor antagonists augment the antidepressant efficacy of selective serotonin (5-HT) reuptake inhibitors.

Previous work of our group have dealt with the synthesis of 1-aryl-3-(4-arylpiperazin-1-yl)propanol derivatives (Cheng and Prussof 1973; Hoyer et al. 1985; Marcusson et al. 1988; Martinez et al. 2001a,b; Oficialdegui et al. 2000; Orús et al. 2002a) in the search for new and effi-

Scheme



R_5 = H (a), F (b), NO_2 (c), CH_3 (e), OAc (f); Ar_i = 2,3-dithydro-(1,4-benzodioxane). Reagents: (i): THF, K_2CO_3, r.t.; (ii): menthol, BH_4Na, 0 °C; (iii): Ni-Raney, NH_4H_2O, EtOH; (iv): $NaBH_4$, DME; H_2O

cient antidepressants with a dual mode of action: serotonin reuptake inhibition and 5-HT_{1A} receptor antagonism. From these studies we concluded that the 3-[4-(2,3-dihydro-1,4-benzodioxin-5-yl)piperazin-1-yl]-1-(benzo[b]thiophen-3-yl)propanol derivatives led to the best results. As a continuation of our research program we have prepared some new 5-substituted benzo[*b*]thiophenes with the mentioned piperazine.

2. Investigations, results and discussion

2.1. Chemistry

Scheme 1 illustrates the procedure used to synthesize **4** (**a**: H; **b**: F; **c**: NO_2, **d**: NH_2; **e**: CH_3; **f**: OH) compounds. Compounds **3** (**a–c, e–f**) were synthesized by nucleophylic substitution of the corresponding 3-chloro-1-(5-substitutedbenzo[*b*]thiophen-3-yl)propanone **1** (**a–c, e–f**) and (2,3-dihydro-1,4-benzodioxin-5-yl)piperazine (**2**) (Orus et al. 2002b). Some of the hydroxyl derivatives were synthesized by reduction of the corresponding carbonyl derivative (**3a–c, e**) with sodium borohydride in methanol at 0 °C. Compound **4d** is obtained by reaction of **4c** with Ni-Raney and hidrazine monohydrate. Compound **4f** is by reduction of ketone **3f** with sodium borohydride in 1,2-dimethoxyethane. Reduction of the ketone and the acethoxy group carries in only one step. Chemical data of these compounds are shown in Table 1.

All of the hydroxyl derivatives **4** (**a–f**) were evaluated for their affinity for 5-HT_{1A} receptors and 5-HT transporter. Structure and binding data of the compounds are shown in Table 2. The inhibition constant (Ki) was obtained from the IC_{50} by the Cheng-Prusoff equation (Orus et al. 2002c).

The affinity for 5-HT_{1A} receptors was determined by studying displacement of the binding of [^{3}H]-8-hydroxy-2-(di-n-propylamino)tetralin ([^{3}H]-OH-DPAT) to rat cerebral cortex homogenates according to previously reported procedures (Peglieu et al. 1995). The affinity for 5-HT transporter was determined by studying the competition in [^{3}H]-paroxetine bindings to rat cerebral cortex homogenates, as described (Pérez et al. 2001).

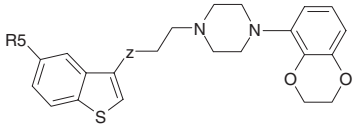
From these binding assays, compounds 1-(5-nitrobenzo[*b*]thiophen-3-yl)-3-[4-(2,3-dihydro-1,4-benzodioxin-5-yl)piperazin-1-yl]propan-1-ol **(4c)** ($K_i = 6.8$ for 5-HT_{1A} receptor and $K_i = 14$ for 5-HT transporter) and 1-(5-hydroxybenzo[*b*]thiophen-3-yl)-3-[4-(2,3-dihydro-1,4-benzodioxin-5-yl)piperazin-1-yl]propan-1-ol dihydrochloride **(4f)** ($K_i = 6.2$ for 5-HT_{1A} receptor and $K_i = 18.2$ for 5-HT transporter) appear to be the most interesting.

As we expected, the introduction of different substituents in 5 position of the benzo[*b*]thiophene ring maintains high affinity (nM) for both activities.

These results suggest that the substitution in the benzo[*b*]thiophene ring is important for the activity. Compounds **4c** ($R_5 = NO_2$) and **4f** ($R_5 = OH$) show activities similar to products previously described **4a** (R_5= H) and **4b** ($R_5 = F$) (Orus et al. 2002a).

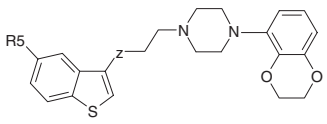
At this moment we are carrying out further research on pharmacologic, pharmacokinetic and toxicology profiles of the new compounds, and the results will lead to the most interesting candidate for clinic use.

Table 1: Formula and physical data of propanone derivatives



Compd.	R_5	Z	Fw	M.p. (°C)	Yield (%)	Formula
3c	NO_2	CO	453	168–171	72	$C_{23}H_{23}N_3O_5S$
3e	CH_3	CO	422	132–133	62	$C_{24}H_{26}N_2O_3S$
3f	OAc	CO	466	112–114	34	$C_{25}H_{26}N_2O_5S$
4c	NO_2	CHOH	454	105–107	43	$C_{23}H_{24}N_3O_5S$
4d	NH_2	CHOH	424	122–125	27	$C_{23}H_{26}N_3O_3S$
4e	CH_3	CHOH	423	144–147	57	$C_{24}H_{27}N_2O_3S$
4f	OH	CHOH	428	168–170	16	$C_{23}H_{28}N_2O_4S$

Table 2: Binding affinity (Ki, nM) for 5-HT_{1A} receptors and for 5-HT transporter of the propanol derivatives



Compd.	R_5	Ki (nM)	
		5-HT_{1A} receptor	5-HT transporter
8-OH-DPAT		1.5	–
Fluoxetine		–	3.75
4a*	H	5.7	50
4b*	F	6	16
4c	NO_2	6.8	14
4d	NH_2	379	–
4e	CH_3	70.6	3.4
4f	OH	6.2	18.2

* Orus et al. (2002b)

3. Experimental

Melting points (°C) were determined on a Mettler FP82+FP80 apparatus (Grifense, Switzerland) and are uncorrected. Elemental analyses were performed on a Carlo Erba Elemental Analyzer Mod. 1106 and agreed with calculated values within ± 0.4%. IR spectra were recorded on a Perkin-Elmer 681 apparatus (ν_{max} in cm^{-1}), using potassium bromide tablets. ^{1}H NMR spectra were determined in DMSO-d_6 or $CDCl_3$ solutions and TMS was an internal reference with a Brucker AC-200E Spectrometer (Rheinstetten, Germany). Chemicals shifts are given in ppm (δ-scale) and coupling constants (J) values are given in Hertz (Hz). Signal multiplicity is represented by: s (singlet), ws (wide singlet), d (doublet), dd (double doublet), t (triplet), m (multiplet). Merck silica gel 60 (70–230 mesh) was used for CC. TLC (Merck silica gel 60 F_{254} analytical plates) was used to monitor reactions, and revealed with iode. The plates were scanned under UV light at 254 and 366 nm. Organic solutions were dried over anh. Na_2SO_4.

3.1. General procedure for the preparation of the propanone derivatives 3c, 3e, 3f

A suspension of 3-chloro-1-(5-R-benzo[*b*]thiophen-3-yl)propan-1-one **1** (**c, e** or **f**) prepared according to a previously described method (Martinez et al.2001a), 2,3-dihydro-1,4-benzodioxinpiperazine (**2**) and K_2CO_3 in THF was stirred for 72 h at room temperature. After evaporation of the solvent, the obtained residue is purified by flash chromatography (SP: silica gel), eluting with hexane/AcoEt (40 : 60) (V : V).

3.1.1. 1-(5-Nitrobenzo[b]thiophen-3-yl)-3-[4-(2,3-dihydro-1,4-benzodioxin-5-yl)piperazin-1-yl]propan-1-one (**3c**)

^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm): 2.71 (t, 4 H, $N^1(CH_2)_2$); 2.93 (t, 2 H, $COCH_2CH_2$); 3.06 (t, 4 H, $N^4(CH_2)_2$) 3.23 (t, 2 H, $COCH_2$); 4.20 (dd, 4 H, $O(CH_2)_2$); 6.47–6.57 (dd, 2 H, $H_6' + H_8'$); 6.73 (t, 1 H, H_7', $J_{7'6'} = 8.2$, $J_{7'8'} = 7.9$); 7.33 (d, 1 H, H_7, $J_{76} = 8.8$); 8.22 (dd, 1 H, H_6, $J_{67} = 8.8$, $J_{64} = 2.0$); 8.46 (s, 1 H, H_2), 9.59 (d, 1 H, H_4, $J_{46} = 1.9$).

3.1.2. 1-(5-Methylbenzo[b]thiophen-3-yl)-3-[4-(2,3-dihydro-1,4-benzodioxin-5-yl)piperazin-1-yl]propan-1-one (**3e**)

IR (KBr, cm^{-1}): 1673. ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm): 2.46 (s, 3H, CH_3); 2.70 (w.s., 4 H, $N^1(CH_2)_2$); 2.93 (d, 2 H, $COCH_2CH_2$); 3.06 (w.s., 4 H, $N^4(CH_2)_2$) 3.18 (d, 2 H, $COCH_2$); 4.20–4.28 (m, 4 H, $O(CH_2)_2$); 6.47–6.57 (m, 2 H, $H_6' + H_8'$); 6.73 (t, 1 H, H_7', $J_{7'6'} = 8.3$, $J_{7'8'} = 7.8$); 7.21 (s, 1 H, H_6); 7.69 (d, 1 H, H_7, $J_{76} = 8.1$); 8.26 (s, 1 H, H_2); 8.54 (s, 1 H, H_4).

3.1.3. 1-(5-Acetoxybenzo[b]thiophen-3-yl)-3-[4-(2,3-dihydro-1,4-benzodioxin-5-yl)piperazin-1-yl]propan-1-one (**3f**)

IR (KBr, cm^{-1}): 1673. ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm): 2.35 (s, 3 H, CH_3); 2.70 (w.s., 4 H, $N^1(CH_2)_2$); 2.81 (w.s., 6 H, $N^1(CH_2)_3$); 3.00 (w.s., 4 H, $N^4(CH_2)_2$); 3.18 (d, 2 H, $COCH_2$); 4.20–4.28 (m, 4 H, $O(CH_2)_2$); 6.47–6.57 (m, 2 H, $H_{6'} + H_{8'}$); 6.73 (t, 1 H, $H_{7'}$, $J_{7'6'} = 8.2$, $J_{7'8'} = 7.8$); 7.21 (s, 1 H, H_6, $J_{67} = 8.7$); 7.69 (d, 1 H, H_7, $J_{76} = 8.7$); 8.26 (s, 1 H, H_2); 8.54 (s, 1 H, H_4).

3.2. Synthesis of the propanol derivatives 4 c–f

3.2.1. 1-(5-Nitrobenzo[b]thiophen-3-yl)-3-[4-(2,3-dihydro-1,4-benzodioxin-5-yl)piperazin-1-yl]propan-1-ol (**4c**)

An excess of sodium borohydride was added to a well-stirred solution of 1-(5-nitrobenzo[*b*]thiophen-3-yl)-3-[4-(2,3-dihydro-1,4-benzodioxin-5-yl)piperazin-1-yl]propan-1-one (**3c**) (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 that the solvent was evaporated. The obtained product was washed with plenty of water and extracted with ethyl acetate (3 × 20 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the product **4c** was obtained in analytically pure form.
IR (KBr, cm^{-1}): 3360. RMN-^1H ($CDCl_3$, 200 MHz) δ (ppm): 2.05 (t, 2 H, $CHOHCH_2$), 2.71–2.96 (m, 6 H, $N^1(CH_2)_3$); 3.15 (w.s., 4 H, $N^4(CH_2)_2$); 4.28 (d, 4 H, $O(CH_2)_2$); 5.37 (c, 1 H, $CHOH$); 6.52–6.56 (d, 1 H, $H_{6'}$, $J_{6'7'} = 7.5$); 6.58–6.62 (d, 1H, $H_{8'}$, $J_{8'7'} = 8.4$); 6.78 (t, 1 H, $H_{7'}$, $J_{7'6'} = 8.4$, $J_{7'8'} = 7.7$); 7.59 (s, 1 H, H_2); 7.94 (d, 1 H, H_7, $J_{76} = 8.9$); 8.18 (dd, 1 H, H_6, $J_{67} = 8.9$, $J_{46} = 2.0$); 8.76 (d, 1 H, H_4, $J_{46} = 1.9$).

3.2.2. 1-(5-Aminobenzo[b]thiophen-3-yl)-3-[4-(2,3-dihydro-1,4-benzodioxin -5-yl)piperazin-1-yl]propan-1-ol (**4d**)

Ni-Raney and hidrazine monohydrate (1 mol) was added to a well stirred solution of 1-(5-nitrobenzo[*b*]thiophen-3-yl)-3-[4-(2,3-dihydro-1,4-benzodioxin-5-yl)piperazin-1-yl]propan-1-ol (**4c**) (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.
1 H NMR ($CDCl_3$, 200 MHz) δ (ppm): 2.22 (t, 2 H, $CHOHCH_2$), 2.71–2.81 (m, 6 H, $N^1(CH_2)_3$); 3.12 (w.s., 4 H, $N^4(CH_2)_2$); 4.24 (m, 4 H, $O(CH_2)_2$); 5.25 (t, 1 H, CHOH); 6.60 (d, 1 H, $H_{6'}$, $J_{6'7'} = 8.2$); 6.67 (d, 1 H, $H_{8'}$, $J_{8'7'} = 8.4$); 6.84 (t, 1 H, $H_{7'}$); 7.09 (dd, 1 H, H_7); 7.24 (s, 1 H, H_2); 7.45–7.51 (m, 1 H, H_6); 7.76 (m, 1 H, H_4).

3.2.3. 1-(5-Methylbenzo[b]thiophen-3-yl)-3-[4-(2,3-dihydro-1,4-benzodioxin -5-yl)piperazin-1-yl]propan-1-ol (**4e**)

An excess of sodium borohydride was added to a well-stirred solution of 1-(5-methylbenzo[*b*]thiophen-3-yl)-3-[4-(2,3-dihydro-1,4-benzodioxin-5-yl)-piperazin-1-yl]propan-1-one (**3e**) (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 that 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 the product 4e was obtained in analytically pure form.
IR (KBr, cm^{-1}): 3414. ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm): 2.13 (t, 2 H, CH_2CHOH); 2.5 (s, 3 H, CH_3); 2.70–2.84 (m, 8 H, piperazine); 3.18 (d, 2 H, $CHOHCH_2CH_2$); 4.28–4.37 (m, 4 H, $O(CH_2)_2$); 5.35 (t, 1 H, CHOH); 6.56 (d, 1 H, $H_{6'}$, $J_{6'7'} = 9.1$); 6.63 (d, 1 H, $H_{8'}$, $J_{8'7'} = 8.4$); 6.82 (t, 1 H, $H_{7'}$, $J_{7'6'} = 8.2$, $J_{7'8'} = 8.0$); 7.19 (d, 1 H, H_6, $J_{67} = 8.1$); 7.43 (s, 1 H, H_4); 7.61 (s, 1 H, H_2); 7.76 (d, 1 H, H_7, $J_{76} = 8.3$ H_6, $J_{67} = 8.9$, $J_{46} = 2.0$).

3.2.4. 1-(5-Hydroxybenzo[b]thiophen-3-yl)-3-[4-(2,3-dihydro-1,4-benzo dioxin-5-yl)piperazin-1-yl]propan-1-ol dihydrochloride (**4f**)

An excess of sodium borohydride was added to a well-stirred of 1-(5-acetoxybenzo[*b*]thiophen-3-yl)-3-[4-(2,3-dihydro-1,4-benzodioxin-5-yl)piperazin-1-yl]propan-1-one (**3f**) (1.2 g) in 1,2-dimethoxyethane, over a period of 20 min at 45 °C. The reaction mixture was stirred over a period of 18 h and after that 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. After the evaporation of the solvent, the obtained residue was purified by flash chromatography (SP: silica gel), eluting with hexane/AcoEt (90 : 10) (V : V).
IR (KBr, cm^{-1}): 3413. ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm): 1.23 (t, 2 H, $CHOHCH_2$); 2.71–2.81 (m, 6 H, $N^1(CH_2)_3$); 3.00 (w.s., 4 H, $N^4(CH_2)_2$); 4.27 (d, 2 H, $O\text{-}(CH_2)_2\text{-}O$); 5.16 (t, 1 H, CHOH); 6.45 (d, 1 H, $H_{6'}$, $J_{6'7'} = 7.9$); 6.55 (d, 1 H, $H_{8'}$, $J_{8'7'} = 8.3$); 6.74 (t, 1 H, $H_{7'}$, $J_{7'6'} = 7.9$, $J_{7'8'} = 8.2$); 6.87 (d, 1 H, H_6, $J_{67} = 8.6$); 7.22 (d, 1 H, H_4, $J_{46} = 4.0$); 7.35(s, 1 H, H_2); 7.60 (d, 1 H, H_7, $J_{76} = 8.7$).

References

Cheng YC, Prussof WH (1973) Relationship between the inhibition constant (Ki) and the concentration of inhibitor witch causes 50% inhibition (IC_{50}) of an enzymatic reaction. Biochem Pharmacol 22: 3099–3108.

Hoyer D, Engel G Kalhman HO (1985) Molecular pharmacology of 5-HT_1 and 5-HT_2 recognition sites in rat and pig brain membranes radioligand binding sites with [^{3}H]-ketanserin. Eur J Pharmacol 118: 13–23.

Marcusson JO, Bergstrom M, Eriksson K et al. (1988) Characterisation of [^{3}H]-paroxetine binding in rat brain. J Neurochem 50: 1783–1790.

Martínez J, Oficialdegui AM, Pérez S et al. (2001a) New 1-(aryl)-3-[4-(aryl)piperazin-1-yl]-propane derivatives with dual action at 5-HT_{1A} serotonin receptors and serotonin transporter as a new class of antidepressants. J Med Chem 44: 418–428.

Martínez J, Pérez S, Oficialdegui AM et al. (2001b) 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. Eur J Med Chem 36: 55–61.

Oficialdegui AM, Martínez J, Pérez S et al. (2000) Design, synthesis and biological evaluation of new 3-[(4-aryl)piperazin-1-yl]-1-arylpropane derivatives as potential antidepressants with a dual mode of action: serotonin reuptake inhibition and 5-HT1A receptor antagonism. Farmaco 55: 345–353.

Orús L, Martínez J, Pérez S et al. (2002a) New 3-[4-(aryl)piperazin-1-yl]-1-(benzo[*b*]thiophen-2-yl)propane derivatives with dual action at 5-HT_{1A} serotonin receptors and serotonin transporter as a new class of antidepressants. Pharmazie 57: 505–518.

Orús L, Pérez S, Oficialdegui AM et al. (2002b) Synthesis and molecular modeling of new 1-aryl-3-[4-arylpiperazin-1-yl]-1-propane derivatives with high affinity at the serotonin trasporter and at 5-HT_{1A} receptors. J Med Chem 19: 4128–4139.

Orús L, Sáinz Y, Pérez S et al. (2002c) New 3-[4-(3-substituted phenyl)piperazin-1-yl]-1-(benzo[*b*]thiophen-3-yl)propanol derivatives with dual action at 5-HT_{1A} serotonin receptors and serotonin transporter as a new class of antidepressants. Pharmazie 57: 355–357.

Peglion JL, Canton H, Bervoets K et al. (1995) Characterization of potent and selective antagonists at postsynaptic 5-HT_{1A} receptors in a serie of N^4-substutuued arylpiperazines. J Med Chem 38: 4044–4055.

Pérez S, Martínez J, Oficialdegui AM et al. (2001) Synthesis of New 5-Substitutedbenzo[*b*]thiophene derivatives. J Het Chem 38: 1025–1030.