Department of Medicinal Chemistry and Centro de Investigación en Farmacobiología Aplicada[1], Department of Pharmacology[2], Universidad de Navarra, Pamplona, and Vita Invest S.A.[3], Barcelona, Spain

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

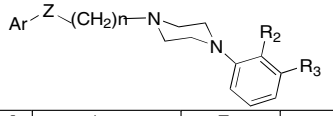
L. Orús[1], J. Martínez[1], S. Pérez[1], A. M. Oficialdegui[1], J.-C. Del Castillo[3], M. Mourelle[3], B. Lasheras[2], J. del Río[2] and A. Monge[1]

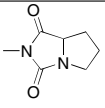
In this paper a series of new 3-[4-(3-substituted phenyl)piperazin-1-yl]-1-(benzo[*b*]thiophen-3-yl)propanol derivatives is presented as a new class of antidepressant drugs with dual activity at 5-HT_{1A} serotonin receptors and serotonin transporter. The 5-HT_{1A} receptor and 5-HT transporter binding affinities of hydroxylic compounds **4 a–e** have been determined. The new compounds present nanomolar affinity for both activities, and 1-(benzo[*b*]thiophen-3-yl)-3-[4-(3-methoxyphenyl)piperazin-1-yl]propan-1-ol (**4d**) shows values (nM) of $K_i = 86$ for 5-HT_{1A} receptors and $K_i = 76$ for the serotonin transporter, respectively.

1. Introduction

The use of serotonin selective reuptake inhibitors (SSRI) in the treatment of depression has become a very effective pharmacotherapy for many patients. However, the onset of therapeutic action of an SSRI can be very delayed, taking anywhere from 2–4 weeks [1, 2]. With the aim of improving the delayed onset of the therapeutic response and following the research carried out in our laboratory [3–5], we now present new 3-[4-(3-substituted phenyl)piperazin-1-yl]-1-(benzo[*b*]thiophen-3-yl)propanol derivatives with a dual mode of action: serotonin reuptake inhibition and 5-HT_{1A} receptor antagonism. In our laboratory, the best results have been obtained for compound **1.I**. It has high nanomolar affinity (nM) for both activities ($K_i = 20$ for 5-HT transporter and $K_i = 20$ for 5-HT transporter) [4].

Now, we synthetized new compounds with the general structure **1.II**. This was done in order to explore the *meta* position in the phenyl ring united with the piperazine in our model structure. We based this approach on the fact that López-Rodriguez et al. [6] had obtained a compound with high affinity for 5-HT_{1A}/D_2 receptors (EF-7412) in structures with a substituent aminosulphonamide in *meta* position (EF-7412).



Compd.	Ar	Z	n	R_2	R_3
1.I		CHOH	2	CH_3O	H
1.II		CHOH	2	H	$NHSO_2CH_2CH_3$, $NHSO_2CH_3$, CH_3, Cl, OCH_3
EF-7412		CH_2	3	H	$NHSO_2CH_2CH_3$

The substituents selected for the phenyl ring united with the piperazine are CH_3, Cl and OCH_3; this selection was based on the fact that in previous work, they had demonstrated considerable activity and, sulphonamide substituents were used following the work of López-Rodriguez et al.

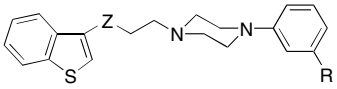
2. Investigations and results

2.1. Chemistry

Scheme 1 illustrates the procedure used to synthesize carbonylic **3 a–e** and hydroxylic derivatives **4 a–e**. Compounds **3 a–e** were synthesized by nucleophylic substitution of 1-(3-substitutedphenyl)piperazines **a–e** and 1-(benzo[*b*]thiophen-3-yl)propan-1-one (**2**) in tetrahydrofurane with potassium carbonate. Compound **2** was synthesized from benzo[*b*]thiophene [ACROS, 13862-0050] (**1**) by classical Friedel-Craft acylation with 3-chloropropionyl chloride [ALDRICH, 14,744-3] and aluminum chloride [ALDRICH, 44,959-8] in dry chloroform. Hydroxyl derivatives were synthesized by reduction of the corresponding carbonyl derivatives **3 a–e** with sodium borohydride [ALDRICH, 45,288-2] in methanol at 0 °C. Chemical data of 3-[4-(3-substitutedphenyl)piperazin-1-yl]-1-(benzo[*b*]thiophen-3-yl)propane derivatives synthesized in this work are shown in Table 1.

Three of the piperazines (**a** [ACROS, 34595-0010], **d** [ALDRICH, 47,168-2] and **e** [ALDRICH, 12,518]) were available commercially. At first, the synthesis of the piperazines **b** and **c** were aborded as shown in Scheme 2. But, in the case of the substituent methanosulphonamide, we did not isolate the final compound and therefore, we planned a new route depicted in Scheme 3. The 1-(3-ethanosulphonamidephenyl)piperazine (**c**) was obtained in three steps. In the first, the treatment of 3-nitroaniline [ALDRICH, N982-9] with ethylsulphonylchloride in basic medium formed by triethylamine [ALDRICH, 47,128-3] and dimethylaminopyridine led to the *N*-(3-nitrophenyl)ethylsulphonamide (**c.2**). In the next step, the nitro group is reduced to amino with Ni-Raney [FLUKA, 83440] and hydrazine [ALDRICH, 22,581-9] and, in the

Table 1: Chemical data of 1-(benzo[b]thiophene)-3-[4-(3-substitutedphenyl) piperazin-1-yl)propane derivatives 3, 4 a–e

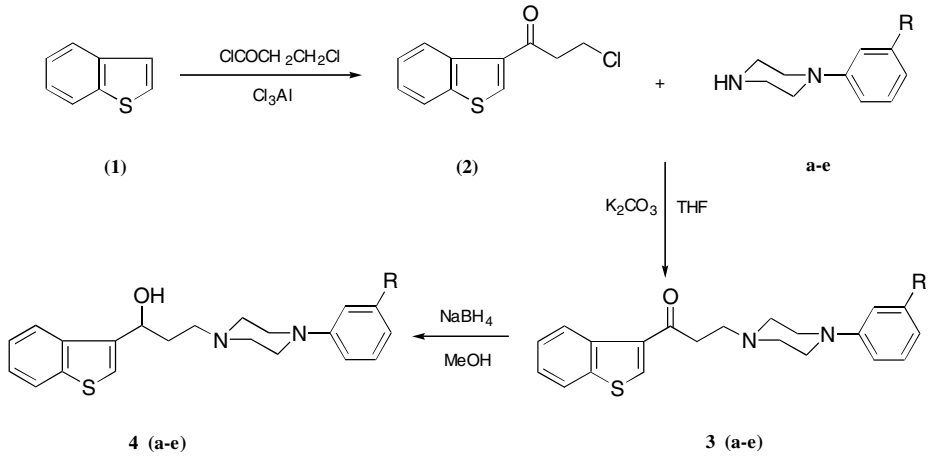


Compd.	Z	R	Fw	M.p. (°C)	Yield (%)	Formula
3a (· 2 HCl)	CO	CH_3	437	202–203	35	$C_{22}H_{24}N_2OS$
3b (· HCl)	CO	$NHSO_2CH_3$	479.5	212–214	38	$C_{22}H_{25}N_3O_3S_2$
3c (· 2 HCl)	CO	$NHSO_2CH_2CH_3$	530	149–152	45	$C_{23}H_{27}N_3O_3S_2$
3d (· 2 HCl)	CO	OCH_3	453	194–196	57	$C_{22}H_{24}N_2O_2S$
3e (· HCl)	CO	Cl	421	189–192	28	$C_{21}H_{21}ClN_2OS$
4a (· 2 HCl)	CHOH	CH_3	439	191–193	23	$C_{22}H_{26}N_2OS$
4b	CHOH	$NHSO_2CH_3$	445	69–71	42	$C_{22}H_{27}N_3O_3S_2$
4c (· 2 HCl)	CHOH	$NHSO_2CH_2CH_3$	532	132–134	55	$C_{23}H_{29}N_3O_3S_2$
4d	CHOH	OCH_3	382	102–106	34	$C_{22}H_{26}N_2O_2S$
4e (· 2 HCl)	CHOH	Cl	459.5	160–162	15	$C_{21}H_{23}ClN_2OS$

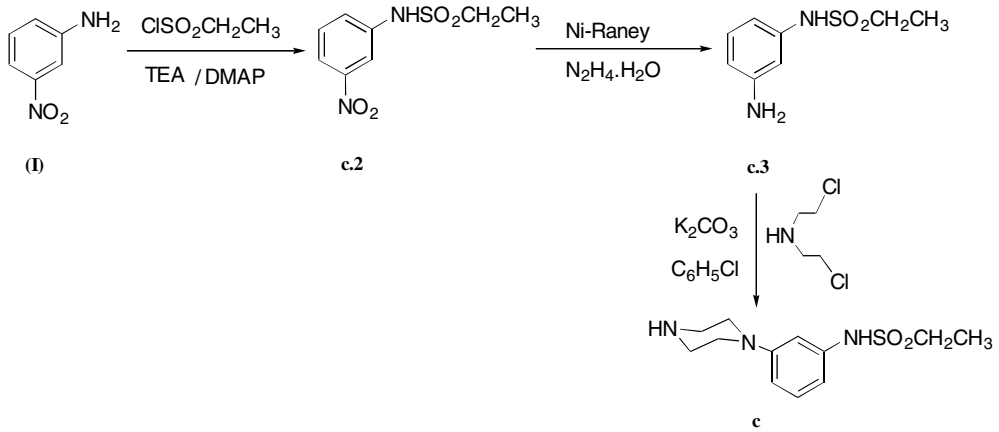
last step, the 1-(3-ethanosulphonamidephenyl)piperazine (**c**) was obtained by condensation of *N*-(3-aminophenyl)ethylsulphonamide (**c.3**) with bis-chloroethylamine [ALDRICH, B3,850-3] in basic medium (Scheme 2).

The synthesis of 1-(3-methanosulphonamidephenyl)piperazine (**b**) starts with the formation of 1-(3-nitrophenyl)piperazine (**b.2**). The nitrogen of the piperazine is protected with acetic acid and acetic anhydride. The compounds **b.4** and **b.5** were obtained in the same manner as described for **c.3** and **c.2**. The piperazine (**c**) was formed by hydrolysis in basic medium with 0.1M NaOH (Scheme 3). Chemical data of these intermediate compounds are shown in Table 2.

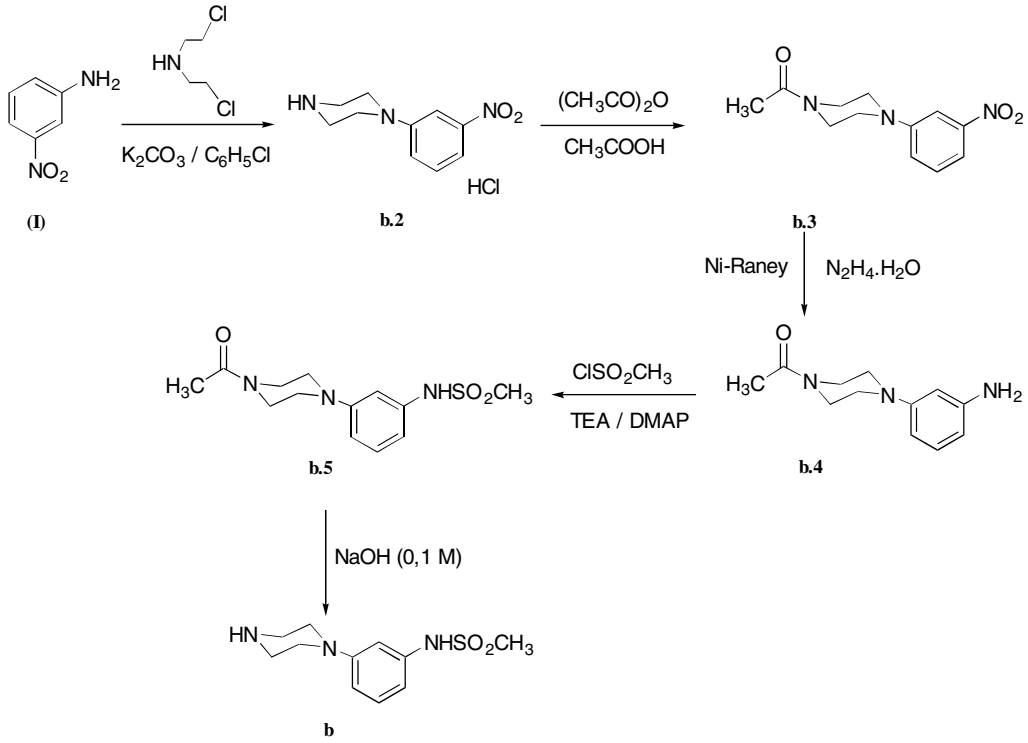
Scheme 1



Scheme 2



Scheme 3



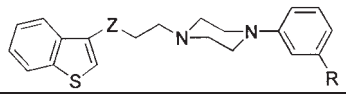
2.2. Pharmacology

Binding affinity to 5-HT_{1A} receptor and 5-HT transporter were determined for **4 a–e**. 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 [7]. The affinity for 5-HT transporter was determined by studying the competition in [^{3}H]-paroxetine bindings to rat cerebral cortex homogenates, as described [8].

Table 2: Chemical data of intermediate compounds

Compd.	M.p. (°C)	FW	Yield (%)	Formula
c.2	139–141	230	83	$C_8H_{10}N_2O_4S$
c.3	oil	200	69	$C_8H_{12}N_2O_2S$
c	165–167	269	33	$C_{12}H_{19}N_3O_2S$
b.2 (· HCl)	>300	243.5	76	$C_{10}H_{13}N_3O_2$
b.3	90–92	249	99	$C_{12}H_{15}N_3O_3$
b.4	127–129	219	85	$C_{12}H_{17}N_3O$
b.5 (· HCl)	148–150	315.5	20	$C_{12}H_{19}N_3O_3S$
b	190–193	255	20	$C_{11}H_{17}N_3O_2S$

Table 3: Binding affinity (K_i, nM) at 5-HT_{1A} receptors and 5-HT transporter of compounds 4 a–e[a]



Compd.	R	5-HT_{1A} receptor	5-HT transporter
4a (· 2 HCl)	CH_3	>5.000	60 ± 15
4b (free base)	$NHSO_2CH_3$	278 ± 2.1	143 ± 5.6
4c (· 2 HCl)	$NHSO_2CH_2CH_3$	422 ± 2.2	73 ± 1.5
4d (free base)	OCH_3	86 ± 2.6	76 ± 1.3
4e (· 2 HCl)	Cl	161 ± 0.3	56 ± 0.8

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

3. Discussion

The results of binding studies for compounds **4 a–e** are summarized in Table 3. All of the compounds showed a moderate to high affinity at both the 5-HT_{1A} receptor and the 5-HT transporter.

As we expected, the introduction of a methoxy substituent in *meta* position of the phenyl ring united to the piperazine gives high affinity (nM) for both activities ($K_i = 86$ for 5-HT_{1A} receptor and $K_i = 76$ nM for 5-HT transporter). However, if we compare these results with the same product but with a methoxy substituent in *ortho* position (previously synthesized in our department), these last results are not as good ($K_i = 20$ and $K_i = 20$ nM, respectively).

When we change an ethylsulphonamide group for a methylsulphonamide, the results do not change and in fact, are worse than with the methoxy substituent.

From the binding assays it can be concluded that 1-(benzo[*b*]thiophen-3-yl)-3-[4-(3-methoxyphenyl)piperazin-1-yl] propan-1-ol (**4d**) is the most interesting compound.

The new compound presents a fairly good activity profile, but does not improve the results obtained previously with related structures.

4. Experimental

Melting points were determined with 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). R 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 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, 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).

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. CC 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.

4.1. 1-(3-Benzo[b]thiophenyl)-3-[4-(3-substituted phenyl)piperazin-1-yl] propanone derivatives **3 a–e**

A suspension of 1-(benzo[*b*]thiophenyl)-3-chloropropanone (7 mmol) (**2**), the corresponding arylpiperazine (7 mmol) (**a–e**) and K_2CO_3 (7 mmol) in THF (50 ml) was stirred for 72 h at room temperature. After evaporation of the solvent, the hydrochloride salt of the product was formed by adding some drops of concentrated HCl to a solution of the compound in acetone.

4.2. 1-(3-Benzo[b]thiophenyl)-3-[4-(3-substituted phenyl)piperazin-1-yl] propanol derivatives **4 a–e**

An excess of sodium borohydride (5 mmol) was added to a well-stirred or suspension of the corresponding 1-(3-benzo[*b*]thiophenyl)-3-[4-(aryl)-piperazin-1-yl]-propanone **3 a–e** (3 mmol) in methanol, over a period of 15 min at 0 °C. The reaction mixture was stirred over a period of 1 h, after which the solvent was evaporated. The obtained product was washed with H_2O (200 ml), extracted with ethyl acetate (3 × 20 ml), and dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The product was purified by flash chromatography (SP: silica gel), eluting with light petroleum/ethyl acetate (1 : 1). In the cases in which the hydrochloride was formed, elution was carried out by dissolving the free base in EtOAc and by adding and equimolar quantity of HCl (**c**).

4.3. N-(3-Aminophenyl)ethylsulphonamide **(c.3)** *and 1-acetyl-4-(3-aminophenyl)piperazine* **(b.4)**

Ni-Raney and hydrazine monohydrate (1 mol) was added to a well-stirred solution of the corresponding nitro derivative *N*-(3-nitrophenyl)ethylsulphonamide (**c.2**) or 1-acetyl-4-(3-nitrophenyl)piperazine (**b.3**) (1 mol) in methanol at 0 °C. Stirring was continued for 2–3 hours. 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.

4.4. N-(3-Nitrophenyl)ethylsulphonamide **(c.2)** *and 1-acetyl-4-(3-methanosulphonamidophenyl)piperazine hydrochloride* **(b.5)**

A solution of the corresponding amino precursor 3-nitroaniline (**I**) or 1-acetyl-4-(3-aminophenyl)piperazine (**b.4**) (3.6 mmol) in dry dichloromethane (100 ml) was stirred at 0 °C. Next, triethylamine (3.6 mmol) and dimethylaminopyridine were added (0.7 mmol). The corresponding sulphonylchloride (5.4 mmol) was added dropwise. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (SP: silica gel), eluting with dichloromethane/MeOH (90 : 10) (V : V).

4.5. 1-(3-Nitrophenyl)piperazine hydrochloride **(b.2)** *and 1-(3-ethanosulphonamidophenyl)piperazine* **(c)**

A suspension of the corresponding amino precursor 3-nitroaniline (**I**) or *N*-(3-aminophenyl)ethylsulphonamide (**c.3**) (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 EtOAc (3 × 75ml). The extracts were dried (Na_2SO_4) and after evaporation, the residue was purified by flash chromatography (SP: silica gel), eluting with dichloromethane/MeOH (90 : 10) (V : V). In the case of compound **b.2,** the hydrochloride salt of the product was formed by adding some drops of concentrated to a solution of the piperazine free base in acetone.

4.6. 1-Acetyl-4-(3-nitrophenyl)piperazine **(b.3)**

A solution of 1-(3-nitrophenyl)piperazine hydrochloride (**b.2**) (0.24 mmol) in methanol (100 ml) was stirred at room temperature. Next, acetic acid (1.38 ml) and acetic anhydride (2.27 ml) were added. The residue was treated with 2 N NaOH (75 ml) and extracted with EtOAc (3 × 75 ml). The extracts were dried (Na_2SO_4) and after evaporation, the residue was purified by flash chromatography (SP: silica gel), eluting with dichloromethane/MeOH (90 : 10) (V : V).

4.7. 1-(3-Methanosulphonamidephenyl)piperazine **(b)**

A solution of 1-acetyl-4-(3-methanosulphonamidephenyl)piperazine (**b.5**) (0.14 mmol) in 0.1 N NaOH (50 ml) was stirred under reflux for 1 h. Once the reaction mixture was cooled, the residue was extracted with EtOAc (3 × 75 ml). The extracts were dried (Na_2SO_4) and after evaporation, the residue was purified by flash chromatography (SP: silica gel), eluting with dichloromethane/MeOH (90 : 10) (V : V).

References

1 Asberg, M.; Eriksson, B.; Martensson, B.; Traskman-Bendz, L.; Wagner, A. J.: Clin. Psychiatry **47**, suppl, 23 (1986)

2 Schatzberg, A. F.; Dessain, E.; O'Neil, P.; Katz, D. L.; Cole, J. O.: J. Clin. Psychopharmacol. **7**, 44S (1987)

3 Martínez, J.; Pérez, S.; Oficialdegui, A. M.; Heras, B.; Orús, L.; Villanueva, H.; Palop, J. A.; Roca, J.; Mourelle, M.; Bosch, A.; Del Castillo, J. C.; Tordera, R.; Lasheras, B.; Del Río, J.; Monge, A.: Eur. J. Med. Chem. **6**, 55 (2001)

4 Martínez, J.; Oficialdegui, A. M.; Pérez, S.; Heras, B.; Orús, L.; Palop, J. A.; Lasheras, B.; Roca, J.; Mourelle, M.; Bosch, A.; Del Castillo, J. C.; Tordera, R.; Del Río, J.; Monge, A. J.: Med. Chem. **44**, 418 (2001)

5 Oficialdegui, A. M.; Martínez, J.; Pérez, S.; Irurzun, M.; Palop, J. A.; Tordera, R.; Lasheras, B.; Del Río, J.; Monge, A.: Pharmaco **55**, 345 (2000)

6 López Rodriguez, M. L. et al.: Bioorg. Med. Chem. Lett. **9**, 1679 (1999)

7 Hoyer, D.; Engel, G.; Kalkman, H. O.: Eur. J. Pharmacol. **118**, 13 (1985)

8 Habert, E.; Graham, D.; Tehraqui, L. Y.; Claustre, S. Z.: Langer, S. Z.: Eur. J. Pharmacol. **118**, 107 (1985)

Received January 21, 2002
Accepted March 27, 2002

Prof. Dr. Antonio Monge
Department of Medicinal Chemistry
Cento de Investigación en
Farmacobiología Aplicada (CIFA)
Universidad de Navarra
C/Irunlarrea s/n, 31080
Pamplona
Spain
amonge@unav.es