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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

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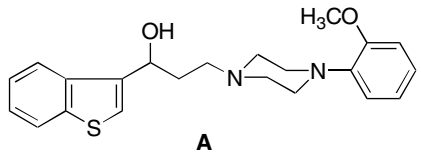
Some benzo[*b*]thiophene derivatives with different substituents in positions 3 and 5 have been synthesized in order to obtain new dual antidepressant drugs. Compounds derived from 2-acetyl-3-methylbenzo[*b*]thiophene or 2-acetyl-3,5-dimethylbenzo[*b*]thiophene were prepared with two different phenylpiperazines (2-methoxy and 2-hydroxyphenylpiperazine) and evaluated for *in vitro* 5-HT_{1A} receptor affinity and serotonin reuptake inhibition by radioligand assays. Compound 1-(3,5-dimethylbenzo[*b*]thiophen-2-yl)-3-[4-(2-methoxyphenyl)piperazin-1-yl]propan-1-ol (**II.2.a**) shows good values (nM) for both activities: $K_i = 85$ for 5-HT_{1A} receptor and $K_i = 120$ for serotonin transporter.

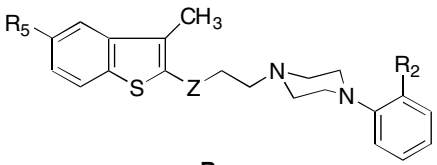
1. Introduction

Major depression is one of the most frequent psychiatric disorders, with an incidence of about 5% and a life time prevalence of 17%. The mainstay for the treatment of depression is pharmaco-therapy. Extensive research is being carried out in our laboratory [1–3] to find new antidepressants with a dual mode of action: serotonin reuptake inhibition and 5-HT_{1A} receptor antagonism, with the aim of improving the delayed onset of the therapeutic response. This mechanism of action is based on the observation that the administration of a 5-HT_{1A} antagonist, such as WAY 100635 or pindolol, in addition to a selective serotonin reuptake inhibitor (SSRI) increases extracellular 5-HT levels in terminal regions of the serotoninergic system because of a prevention of the attenuation by the SSRI of the firing activity of 5-HT neurones [4–8]. Accordingly, when major depression patients are treated with a SSRI and pindolol, a reduction in the latency period for the therapeutic effect is observed [9–13].

In our laboratory, the best results have been obtained for compound **A**. It has high nanomolar affinity (nM) for both activities ($K_i = 20$ for 5-HT transporter and $K_i = 20$ for 5-HT transporter) [2]. We have now synthesized new compounds with the general structure **B**.



A



B

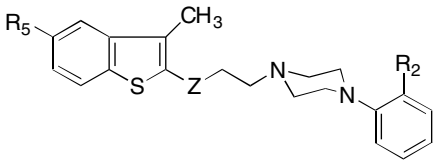
2. Investigations, results and discussion

The Scheme illustrates the procedures used to synthesize 3-[4-(aryl)piperazin-1-yl]-1-(benzo[*b*]thiophen-2-yl)propane derivatives presented in this work (**I.1.a–b**; **II.1.a**). The synthesis of the ketone derivatives was carried out by the condensation of the corresponding acetophenones (**I** or **II**) with the different phenylpiperazine hydrochlorides (**a** or **b**) and paraformaldehyde, in ethanol and acid medium (Mannich reaction). The reduction of ketones with sodium borohydride in methanol afforded the corresponding alcohols (**I.2.a–b**; **II.2.a**). The oximes (**I.3.a–b**; **II.3.a**) were prepared from ketones with hydroxylamine hydrochloride in basic medium.

All of the compounds were characterized by physical constants, elemental analysis, IR, ^{1}H NMR, and MS spectra (Table 1).

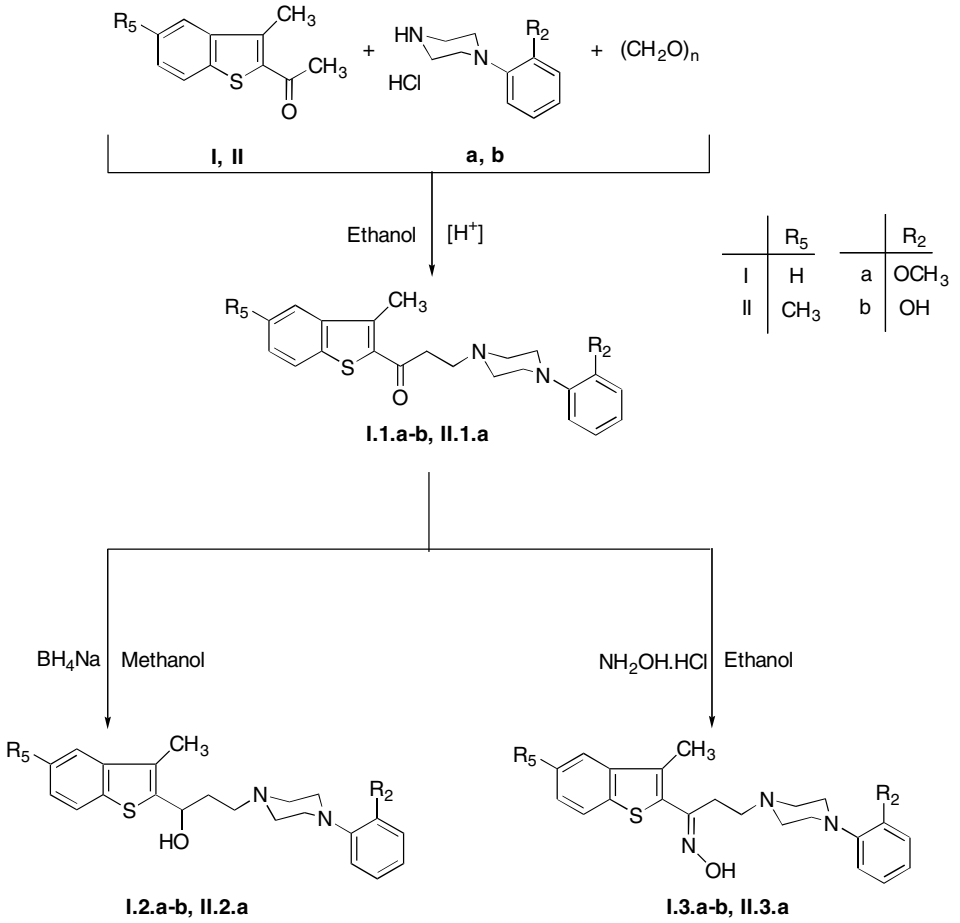
The results of the binding studies for all of the compounds are summarized in Table 2. The affinity for 5-HT_{1A} receptors was determined by studying the displacement of binding of [^{3}H]-8-hydroxy-2-(di-n-propylamino)tetralin ([^{3}H]-OH-DPAT) to rat cerebral cortex homogenates according to previously reported procedures [14]. The affinity for the 5-HT transporter was determined by

Table 1: Formula and physical data of benzo[*b*]thiophene derivatives



Compd.	Z	R_5	R_2	Formula	M.p. (°C)	Yield (%)
I.1.a	CO	H	OCH_3	$C_{23}H_{26}N_2O_2S \cdot HCl \cdot 0.5\ H_2O$	190–193	40
I.2.a	CHOH	H	OCH_3	$C_{23}H_{28}N_2O_2S$	145–147	37
I.3.a	CNOH	H	OCH_3	$C_{23}H_{27}N_3O_2S$	82–84	51
I.1.b	CO	H	OH	$C_{22}H_{24}N_2O_2S \cdot HCl \cdot 0.5\ H_2O$	207–210	52
I.2.b	CHOH	H	OH	$C_{22}H_{26}N_2O_2S$	149–151	51
I.3.b	CNOH	H	OH	$C_{22}H_{25}N_3O_2S$	151–153	29
II.1.a	CO	CH_3	OCH_3	$C_{24}H_{28}N_2O_2S \cdot HCl \cdot 0.5\ H_2O$	86–87	48
II.2.a	CHOH	CH_3	OCH_3	$C_{24}H_{30}N_2O_2S$	79–80	42
II.3.a	CNOH	CH_3	OCH_3	$C_{24}H_{29}N_3O_2S$	72–74	57

Scheme



studying the competition in [^{3}H]-paroxetine bindings to rat cerebral cortex homogenates, as described [15].

We have synthesized nine new compounds derived from 3-[4-(aryl)piperazin-1-yl]-1-(benzo[*b*]thiophen-2-yl)propane. All of them showed moderate affinity at both the 5-HT_{1A} receptor and the 5-HT transporter sites. The results showed better pharmacological results for hydroxylic derivatives than for carbonylic and oximes derivatives in both activities. The change of 1-(2-methoxyphenyl)piperazine (Serie **I**, **a**) by the other piperazine 1-(2-hydroxyphenyl)-piperazine (Serie **I**, **b**) showed similar activities in all of the compounds except the oxime derivative (**I.3.b**). Introduction of CH_3 in position 5 (Serie **II**) of the benzo[*b*]-thiophene ring improves the affinity result when comparing with disubstituted benzothiophene derivatives (Serie **I**). However, if we compare these results with the same product without substituents in the benzo[*b*]thiophene ring (**A**), the result is not as good ($K_i = 20$ and $K_i = 20$ nM, respectively).

Table 2: Binding affinity (Ki, nM) at 5-HT_{1A} receptors and 5-HT transporter sites of the reference and final compounds [a, b]

Compound	5-HT_{1A} Ki(nM)	Uptake Ki(nM)
8-OH-DPAT	1.5 ± 3.5	–
Fluoxetine	–	3.75 ± 2.1
I.1.a	200 ± 2.3	1000 ± 125
I.2.a	220 ± 1.5	400 ± 120
I.3.a	380 ± 3.5	1000 ± 110
I.1.b	280 ± 8.2	5000 ± 50
I.2.b	200 ± 10	55 ± 105
I.3.b	>5000	500 ± 95
II.1.a	105 ± 2.3	150 ± 110
II.2.a	85 ± 2.1	120 ± 13
II.3.a	435 ± 2.2	2750 ± 1.5

[a] Values are means ± S.E.M. from at least 3 experiments.
[b] For experimental conditions see references [14–15].

3. Experimental

Melting points (°C) were determined on a Mettler FP82 + FP80 apparatus 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 solutions and TMS was an internal reference with a Brucker AC-200E spectrometer. Chemical shifts are given in ppm (δ-scale). Merck silica gel 60 (70–230 mesh) was used for CC. MS were recorded on a Hewlett-Packard 5988-A instrument at 70 eV. TLC (Merk 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. Synthesis of 1-aryl-3-(4-arylpiperazin-1-yl)-propan-1-one (I.1.a-b. II.1.a) (general procedure)

A mixture of the appropiated benzo[*b*]thiophene (30 mmol), arylpiperazine hydrochloride (30 mmol) and concentrated HCl in absolute ethanol (40 ml) was heated at reflux. Paraformaldehyde (90 mmol) was added in four equal portions over a period of 40 min. The reaction mixture was refluxed for another 48 h (**I.1.a**, **II.1.a**) or 24 h (**I.1.b**), cooled and poured onto crushed ice. The separated solid was filtered, dried and recrystallized from 1-propanol (**I.1.a**, **II.1.a**) or 1-propanol/dioxane/ethanol (**I.1.b**).

3.1.1. 1-(3-Methylbenzo[b]thiophen-2-yl)-3-[4-(2-methoxyphenyl)piperazin-1-yl]propan-1-one hydrochloride (**I.1.a**)

IR (KBr): 1671, 1247 cm^{-1}. ^1H NMR (DMSO-d_6): 2.63 (s, 3 H, CH_3), 2.77–3.11 (m, 8 H, $N^1(CH_2)_3 + CH_2CO$), 3.35–3.52 (b.s., 4 H, $N^4(CH_2)_2$), 3.79 (s, 3 H, CH_3O), 6.78–7.10 (m, 4 H, H-Ar), 7.50–7.58 (m, 2 H, $H_5 + H_6$), 8.05 (d, 2 H, $H_4 + H_7$), 10.90–11.11 (b.s., 1 H, HCl). MS: m/z (%) = 394 (1) [M^+, 150 (100).

3.1.2. 1-(3-Methylbenzo[b]thiophen-2-yl)-3-[4-(2-hydroxyphenyl)piperazin-1-ylpropan-1-one hydrochloride (**I.1.b**)

IR (KBr): 3406, 1668, 1256 cm^{-1}. ^1H NMR (DMSO-d_6): 2.77 (s, 3 H, CH_3), 3.06–3.77 (m, 12 H, CH_2), 6.71–7.91 (m, 4 H, H-Ar), 7.47–7.62 (m, 2 H, $H_5 + H_6$), 8.03 (d, 2 H, $H_4 + H_7$), 9.36 (s, 1 H, OH), 10.10–10.33 (b.s., 1 H, HCl). MS: m/z (%) = 380 (5) [M^+, 120 (100).

3.1.3. 1-(3,5-Dimethylbenzo[b]thiophen-2-yl)-3-[4-(2-methoxyphenyl)-piperazin-1-ylpropan-1-one hydrochloride (**II.1.a**)

IR (KBr): 1671, 1247 cm^{-1}. ^1H NMR (DMSO-d_6): 2.42 (s, 3 H, CH_3[5]), 2.67 (s, 3 H, CH_3[3]), 2.97–3.21 (m, 8 H, $N^1(CH_2)_3 + CH_2CO$), 3.34–3.62 (m, 4 H, $N^4(CH_2)_2$), 3.78 (s, 3 H, CH_3O), 6.81–7.02 (m, 4 H, H-Ar), 7.36 (d, 1 H, H_6, H_{67} = 8.1 Hz), 7.75 (s, 1 H, H_4), 7.85 (d, 1 H, H_7, J_{67} = 8.2 Hz),10.65–10.80 (b.s., 1 H, HCl). MS: m/z (%) = 408 (1) [M^+, 189 (42).

3.2. Synthesis of 1-aryl-3-(4-arylpiperazin-1-yl)-propan-1-ol (**I.2.a-b**. **II.2.a**) *(general procedure)*

An excess of sodium borohydride was added to a well-stirred solution or suspension of the corresponding 1-substituted 3-(4-arylpiperazin-1-yl)-1-propanone (3 mmol) in methanol, over a period of 15 min at 0 °C. The stirring was continued for another 4 to 8 h. The reaction mixture was poured into water. The separated solid was filtered, dried and recrystallized from 1-propanol (**I.2.a**, **II.2.a**) or 1-propanol/dioxane/ethanol (**I.2.b**)

3.2.1. 1-(3-Methylbenzo[b]thiophen-2-yl)-3-[4-(2-methoxyphenyl)piperazin-1-yl]propan-1-ol (**I.2.a**)

IR (KBr): 3405, 1240 cm^{-1}. ^1H NMR (DMSO-d_6): 1.82–1.95 (m, 2 H, CHOH-CH_2), 2.33 (s, 3 H, CH_3-Ar), 2.38 (b.s., 6 H, $N^1(CH_2)_3$), 2.90 (b.s., 4 H, $N^4(CH_2)_2$), 3.75 (s, 3 H, CH_3O), 5.12 (b.s., 1 H, C*H*–OH), 5.91 (s, 1 H, OH), 6.90 (d, 4 H, H-Ar), 7.26–7.40 (m, 2 H, $H_5 + H_6$), 7.69 (d, 1 H, H_4, J_{45} = 7.4 Hz), 7.88 (d, 1 H, H_7, J_{67} = 7.0 Hz). MS: m/z (%) = 396 (68) [M^+, 205 (100).

3.2.2. 1-(3-Methylbenzo[b]tiophen-2-yl)-3-[4-(2-hydroxyphenyl)piperazin-1-yl]propan-1-ol (**I.2.b**)

IR (KBr): 3398 cm^{-1}. ^1H NMR (DMSO-d_6): 1.79–1.96 (m, 2 H, CHOH-CH_2), 2.34 (s, 3 H, CH_3), 2.43 (b.s., 6 H, $N^1(CH_2)_3$), 2.90 (b.s., 4 H, $N^4(CH_2)_2$), 5.19 (t, 1 H, C*H*–OH), 6.66–6.87 (m, 5 H, 4H-Ar + OH), 7.27–7.41 (m, 2 H, $H_5 + H_6$), 7.70 (d, 1 H, H_4, J_{56} = 7.8 Hz), 7.90 (d, 1 H, H_7, J_{67} = 3.7 Hz). MS: m/z (%) = 382 (77) [M^+, 134 (100).

3.2.3. 1-(3,5-Dimethylbenzo[b]thiophen-2-yl)-3-[4-(2-methoxyphenyl)-piperazin-1-yl]propan-1-ol (**II.2.a**)

IR (KBr): 3415, 1240 cm^{-1}. ^1H NMR: (DMSO-d_6): 1.77–1.97 (m, 2 H, CHOH-CH_2), 2.29 (s, 3 H, CH_3[5]), 2.42 (s, 3 H, CH_3[3]), 2.44 (b.s., 6 H, $N^1(CH_2)_3$), 2.88 (b.s., 4 H, $N^4(CH_2)_2$), 3.75 (s, 3 H, CH_3O), 5.12 (b.s., 1 H, C*H*OH), 5.80 (b.s., 1 H, OH), 6.85 (d, 4 H, H-Ar), 7.15 (d, 2 H, H_6, J_{67} = 8.1 Hz), 7.45 (s, 1 H, H_4), 7.70 (d, 1 H, H_7, J_{67} = 8.1 Hz). MS: m/z (%) = 410 (76) [M^+, 200 (100).

3.3. Synthesis of oximes from 1-aryl-3-(4-arylpiperazin-1-yl)-propan-1-ol (I.3.a-b. II.3.a) (general procedure)

A mixture of the appropiated 1-substituted 3-(4-arylpiperazin-1-yl)-1-propanone (30 mmol), in absolute ethanol (40 ml), was heated at reflux and hydroxylammonium hydrochloride (40 mmol) was added. The reaction mixture was refluxed for another hour. A solution of 2N NaOH (20 ml) was added. Once the reaction mixture was cooled, the solvent was removed under reduced pressure. The residue was washed with water.

3.3.1. Oxime from 1-(3-methylbenzo[b]thiophen-2-yl)-3-[4-(2-methoxyphenylpiperazin-1-yl]propan-1-one (**I.3.a**)

IR (KBr): 3652 cm^{-1}. ^1H NMR (DMSO-d_6): 2.48 (b.s., 9 H, $N^1(CH_2)_3$ + CH_3), 2.85 (b.s., 4 H, $N^4(CH_2)_2$), 3.77 (s, 3 H, CH_3O), 6.85–7.02 (d, 4 H, H-Ar), 7.35–7.50 (m, 2 H, $H_5 + H_6$), 7.79–7.85 (m, 1 H, H_4), 7.90–7.99 (m, 1 H, H_7), 11.52–11.82 (b.s., 1 H, N-OH). MS: m/z (%) = 409 (13) [M^+, 205 (100).

3.3.2. Oxime from 1-(3-methylbenzo[b]thiophen-2-yl)-3-[4-(2-hydroxyphenylpiperazin-1-yl]propan-1-one (**I.3.b**)

IR (KBr): 3413 cm^{-1}. ^1H NMR (DMSO-d_6): 2.28 (s, 3 H, CH_3), 2.50 (b.s., 6 H, $N_1(CH_2)_3$), 2.83 (b.s., 4 H, $N^4(CH_2)_2$), 6.84–7.70 (m, 4 H, H-Ar), 7.36–7.41 (m, 2 H, $H_5 + H_6$), 7.76–7.87 (m, 1 H, H_4), 7.88–7.92 (s, 1 H, H_7), 11.50–11.62 (b.s., 1 H, N-OH). MS: m/z (%) = 188 (100).

3.3.3. Oxime from 1-(3,5-dimethylbenzo[b]thiophen-2-yl)-3-[4-(2-methoxyphenylpiperazin-1-yl]propan-1-one (**II.3.a**)

IR (KBr): 3421 cm^{-1}. ^1H NMR (DMSO-d_6): 2.42 (b.s., 14 H, $N^1(CH_2)_3$ + $2CH_3$[3 + 5] + CH_2-CNOH), 2.80 (b.s., 4 H, $N_4(CH_2)_2$), 3.73 (s, 3 H, CH_3O), 6.88 (d, 4 H, H-Ar), 7.19 (d, 1 H, H_6), 7.57 (s, 1 H, H_4), 7.71–7.80 (m, 1 H, H_7), 11.40–11.80 (b.s., 1 H, N-OH). MS: m/z (%) = 423 (13) [M^+, 205 (100).

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References

1 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)
2 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)
3 Oficialdegui, A. M.; Martínez, J.; Pérez, S.; Irurzun, M.; Palop, J. A.; Tordera, R.; Lasheras, Del Río, J.; Monge, A.: Farmaco **55**, 345 (2000)
4 Dreshfield, L. J.; Wong, D. T.; Perry, K.W.; Engleman, E.A.: Neurochem. Res. **21**, 557 (1996)
5 Sharp, T.; Umbers, V.; Gartside, S. E.: Br. J. Pharmacol. **121**, 941 (1997)
6 Artigas, F.; Perez, V.; Alvarez, E.: Arch. Gen. Psychiatry **51**, 248 (1994)
7 Dawson, L. A.; Nguyen, H. Q.: Eur. J. Pharmacol. **345**, 41 (1998)
8 Dawson, L. A.; Nguyen, H. Q.; Smith, D. I.; Schechter, L. E.: Br. J. Pharmacol. **130**, 797 (2000)
9 Tome, M. B.; Cloninger, C. R.; Watson, J. P.; Isaac, M. T.: J. Affective Disord. **44**, 101 (1997)
10 Perez, V.; Gilaberte, I.; Faries, D.; Alvarez, E.; Artigas, F.: Lancet **349**, 1594 (1997)
11 Zanardi, R.; Artigas, F.; Franchini, L.; Sforzini, L.; Gasperini, M.; Smeraldi, E.; Perez J.: J. Clin. Psychopharmacol. **17**, 446 (1997)
12 Puzantian, J.; Kawase, K.: Pharmacotherapy **19**, 205 (1999)
13 Perez, V.; Soler, J.; Puigdemont, D.; Alvarez, E.; Artigas, F.: Arch. Gen. Psychiatry **56**, 375 (1999)
14 Hoyer, D.; Engel, G.; Kalhman, H. O.: Eur. J. Pharmacol. **118**, 13 (1985)
15 Marcusson, J. O.; Bergstrom, M.; Eriksson, K.; Ross, S. V.: J. Neurochem. **50**, 1783 (1988)

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