SYNTHESIS OF CONFORMATIONALLY RESTRICTED *N*-{4-[4-(4,7-DIMETHOXY-BENZO[*b*]THIOPHENE–2–CARBONYL)-1-PIPERAZINYL]–PHENYL}-ARYLCARBOXAMIDES POTENTIAL LIGANDS WITH 5-HT$_{1A}$ BINDING AFFINITY

HERNÁN PESSOA-MAHANA, CHRISTIAN GONZÁLEZ L., RAMIRO ARAYA- MATURANA, CLAUDIO SAITZ B., C. DAVID PESSOA-MAHANA.*

Department of Organic and Physical Chemistry. Faculty of Chemical and Pharmaceutical Sciences. University of Chile. Casilla 233. Santiago 1. Chile. Department of Pharmacy. Faculty of Chemistry. Pontificia Universidad Católica de Chile. P.O.Box 306. Santiago 22. Chile.

ABSTRACT

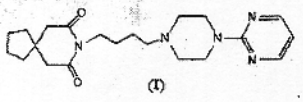
New benzothiophene arylpiperazine derivatives 7 (a-f) were synthesized as potential serotoninergic agents with 5-HT$_{1A}$ receptor affinity. Preparation of the derivatives was performed by reaction of 1-(4-aminophenyl)-4-[(4,7-dimethoxy-1-benzothien-2-yl)carbonyl] piperazine (6) with a series of substituted aroyl chlorides.

Keywords: Secotonine, arylpiperazines, 5-HT$_{1A}$ binding affiniy.

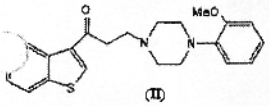
INTRODUCTION

Serotonine (5HT) is a neurotransmitter that mediates a wide range of physiological functions including sleep, feeding, aggression, sexual and parental behavior. Numerous studies have also implicated the impaired function of the 5-HT system in the pathogenesis of depression[1-3]. The Arylpiperazines family are compounds of great importance to many different biological targets, especially central nervous system receptors. In the case of serotonin, (5-HT) receptors, compounds containing this moiety represent the biggest and thoroughly examined class of 5-HT$_{1A}$ receptor ligands[4,5].

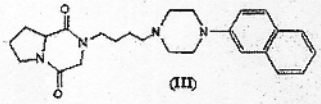
The discovery that the anxiolytic agent buspirone (I), binds with high affinity to 5-HT$_{1A}$ receptor as partial agonist[6], has encouraged the development of new arylpiperazine derivatives acting as pharmacophores with improved pharmacological profiles.



(I)



(II)

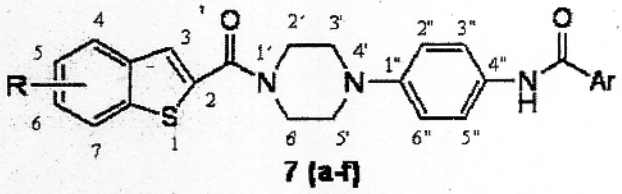


(III)

Monge *et-al* have reported the synthesis of a series of benzothiophene arylpiperazines which displayed a dual mode of action[7,8] (II). López-Rodríguez *et-al* characterized new long chain aryl piperazines exhibiting high affinity for 5-HT$_{1A}$ receptor along with an interesting receptorial selectivity [9,10] (III). The majority of the arylpiperazinic compounds contain a flexible aliphatic chain of different length, which connects this fragment with a second pharmacophoric group. Structural modification within long-chain arylpiperazines occurs mainly at the two opposite ends of a molecule, and with the aliphatic chain length.

Although a number of synthetic approaches to molecules with potential antidepressant activity have been reported, the preparation of arylpiperazinil derivatives conformationally constrained, to the best of our knowledge, has not yet been investigated excepting the works reported by Kossakowski *et-al*[11] carried out on a series of imides and the rigid and highly potent constrained cyclohexylarylpiperazines reported by Nowak *et-al*[12]. Hence, our general strategy was to generate more rigid amide analogues of well-known 5-HT$_{1A}$ receptor ligands by elimination in this case of the aliphatic chain. This approach was based on previous theoretical studies obtained with a series of amide benzothiophene analogues, using autodock studies.

In this article, we report the synthesis of a series of 4,7-dimethoxy-benzo[*b*]thiophene-2-carbonyl)-1-piperazinyl]–phenyl}arylcarboxamides of general structure 7(a-f) as new arylpiperazine derivatives, conformationally restricted (Figure 1).

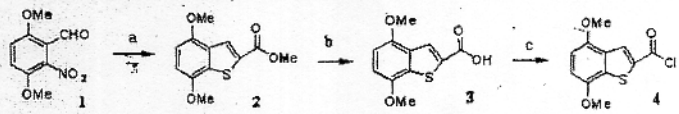


7 (a-f)

Figure 1 .- R = 4,7-Dimethoxy ; **Ar** = phenyl; 4-chloro-phenyl; 4-fluoro-phenyl; 2-methoxy-phenyl; 2,5-dimethoxy-4-nitrophenyl; and 4,7-dimethoxy-2-benzo[*b*]thiophenyl.

RESULTS AND DISCUSSION

The synthesis of *N*-{4-[4-(4,7-dimethoxy-benzo[*b*]thiophene-2-carbonyl)-1-piperazinyl]–phenyl}arylcarboxamides **7(a-f)** is outlined in Scheme 1 and 2.



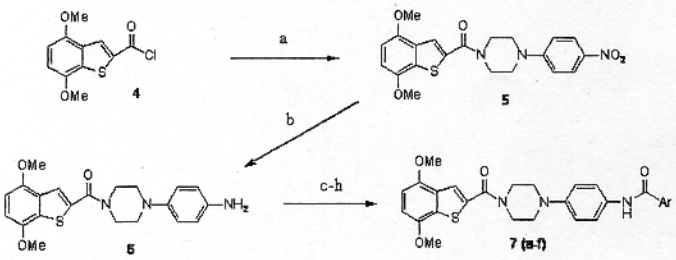
Scheme I.

Reagents and conditions: a) Methyl thioglycolate / K_2CO_3 / DMF, 65-70 °C 4 h. b) KOH – CH_3OH 3 h, r.t., H_3O^+; d) $SOCl_2$ –reflux 3 h.

The preparation of aroyl benzothiophene (**4**) was carried out in three steps from the previously described 2,5-dimethoxy-6-nitro-benzaldehyde[13,14] (**1**) (Scheme I). The benzothiophene ester (**2**) was obtained in good yield (85%), by treating nitrobenzaldehyde (**1**) with methyl thioglycolate in basic medium. The mechanism of the cyclization of the 2-nitrobenzaldehyde derivative is unknown. However, a reasonable mechanism probably involves thiol anion displacement of the activated nitro group followed by a base-catalyzed aldolic-condensation[5,15]. The structure of the ester (**2**) was mainly confirmed by ^{1}H NMR, and their subsequent basic hydrolysis, followed by acidification provided the carboxylic acid (**3**) in a 90% yield.

The aroylchloride (**4**), was easily obtained by reaction of the carboxylic acid (**3**) with thionyl chloride under reflux conditions to provide a yellow solid, which was purified and subsequently treated with 1-(4-nitro-phenyl)-piperazine, under inert atmosphere to afford the expected benzothiophene carboxamide (**5**) as a yellow solid in 98% yield.

e-mail: hpessoa@ciq.uchile.cl



Scheme 2

Reagents and conditions : a) anhydrous THF/ 4-nitroarylpiperazine / N_2 atmosphere / dry pyridine 3 h, r.t.; b) Fe° / HOAc/ EtOH / H_2O (1:1:1), 45-50 °C 1 h.; c-h) anhydrous THF ArCOCl dry pyridine / N_2 atmosphere : c) : 3-OMe-C_6H_4COCl ; d) C_6H_5COCl; e) 4-F-C_6H_4COCl; f) 4-Cl-C_6H_4COCl; g) 2,5-di-OMe-4-NO_2-C_6H_2COCl; h) 4,7-di-OMe-2-$C_{10}H_9O_2SCOCl$./ N_2 atmosphere / 2 h, r.t.

In ^{1}H NMR this compound showed the characteristic pair of double doublets at δ: 6.69 and 6.76 ppm (J= 8.5 Hz) assigned to 5-H and 6-H protons, along with the AX pattern for protons of the nitrophenyl moiety at δ: 6.83 and 8.15 ppm (J= 9.4 Hz). It is also interesting to note the highfield shift observed with the H-3 signal of amide (**5**) (δ: 7.69 ppm), in comparison with the same signal observed for compounds (**2**), (**3**) and (**4**) : (δ: 8.20, 8.24 and 8.38 ppm respectively), such difference can be attributed in the case of amide (**5**), to the major donor effect of the nitrogen, which disfavours the α,β-carbonylic conjugation shielding the H-3 signal.

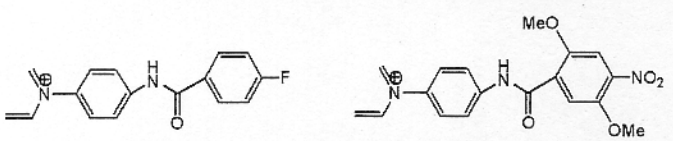
The nitroamide (**5**) was selectively reduced with Fe° in a mixture of EtOH /H_2O/ HOAc to afford the benzothiophene amino piperazine (**6**) in 90 % yield .The ^{1}H NMR spectrum of aminopiperazine (**6**) exhibited an AB pattern at δ: 6.66 and 6.82 ppm for the aromatic protons of the aniline moiety, while the NH_2 group appeared as a broad singlet at δ: 3.48 ppm. The IR spectrum showed the expected two absorption bands at 3424 and 3339 cm^{-1}.

Compound (**6**) was finally reacted with a series of six aroyl chlorides under inert atmosphere, to provide the corresponding diamides **7(a-e)** in good yields, with the exception of **7-f**, which showed solubility problems.

Products	HRMS (M^+) Calculated / Experimental	m.p. °C	Yield %
7-a	531.18280 / 531.181242	183-184	71
7-b	501.17221 / 501.17295	180-182	82
7-c	519.16278 / 519.16114	168-169	87
7-d	535.13324 / 535.132301	203-204	78
7-e	606.17844 / 606.17903.	215-216	66
7-f	617.16547 / 617.161358	212-214	30

We also analysed, the mass spectrum for two compounds of the series, the bis-amides **7-c** and **7-e,** they showed fragments (m/z) at 269.1 and 356.1 respectively for the base peaks (100%), which may arise from the piperazinic ring cleavage, with loss of the neutral fragment ($C_{12}H_{11}NO_3S$).

It is worthy to mention, that an oxidative deprotection assay with the



269.1 356.1

amides 7(a,b), focused to obtain the corresponding quinines, employing cerium ammonium nitrate (CAN) gave a complex mixture of products which were not purified. In conclusion we have synthesized new piperazinobenzothiophene derivatives **7(a-f)**, for developing potential bioactives ligands in 5-$HT1_A$ receptors. Biological screening will be carried out in a near future.

EXPERIMENTAL

Melting points were determined on a hot-stage apparatus and are uncorrected. The IR spectra were recorded on a FT-IR Bruker IFS 55 spectrophotometer for KBr disc, and wave numbers are reported in cm^{-1}. The ^{1}H NMR and ^{13}C NMR spectra were performed on a Bruker DRX-300 spectrometer (300 and 75 MHz) in $CDCl_3$, or DMSO-d_6. Chemical shifts were recorded in ppm (δ) relative to TMS as an internal standard. J values are given in Hz. Microanalyses were carried out on a Fisons EA 1108 analizer. High resolution mass spectrum (HRMS) were recorded on a Thermo Finnigan model MAT 95XP Mass spectrometer. Silica gel Merck 60 (70-230mesh) and DC-alufolien 60 F_{254} were used for column and TLC chromatography respectively.

4,7-Dimethoxy-2-methoxycarbonyl-benzo [*b*] thiophene (2).

To a solution of nitrobenzaldehyde **1**[5] (1000 mg, 4.74 mmol) in DMF(15 mL) anhydrous K_2CO_3 (654 mg, 4.74 mmol) and methyl thioglycolate (503 mg,4.74 mmol) were added. The suspensión was stirred at 75-80 °C for 4h, then poured onto crushed ice, and vigorously stirred for 15 min. The resultant precipitate was filtered and washed with water (3x40 mL) to afford crude benzothiophene ester (**2**) as a pale yellow solid, which was purified by column chromatography (CH_2Cl_2) to provide pure 4,7-dimethoxy-2-methoxycarbonyl-benzo[*b*] thiophene (**2**), (1000 mg, 85 %) mp: 124-125 °C.IR (cm^{-1}): 3010 (C-H, Aromatic), 1702 (C=O), 1260 (C-O). Anal.Calcd. for $C_{12}H_{14}O_4S$:C (57.13%), H (4.80%), S (12.69%). Found : C (56.78%), H (4.90%), S (12.42%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.91 (s,3H,OCH_3), 3.93 (s,3H, Ar- OCH_3), 3.94 (s,3H, Ar- OCH_3), 6.66 (d,1H, 5-H, J=8.5 Hz), 6.76 (d,1H, 6-H, J = 8.5 Hz), 8.20 (s,1H, 3-H). ^{13}C NMR (75 MHz, $CDCl_3$): 52.4, 55.8, 56.0, 104.6, 106.8, 128.0, 131.1, 132.4, 132.9, 148.4, 150.5, 163.2.

4,7-Dimethoxy-benzo[*b*]thiophene-2-carboxylic acid (3).

A solution of the methyl ester (**2**) (1000 mg, 3.96 mmoles) in KOH 0.5 N: EtOH (1:1 v/v 60 mL) was stirred at room temperatura for 4h. The mixture was then concentrated in vacuo and acidified with HCl (concd.) at 0 °C. The resulting precipitate was filtered, washed with small amount of cold water and dried to provide a pure yellow pale solid (**3**) (850 mg, 90%). mp : 129-130 °C, IR (cm^{-1}): 3650-2800 (O-H), 1670 (C=O), 1529 (C=C Ar). Anal.Calcd. for $C_{11}H_{10}O_4S$: C (55.45%), H (4.23%), S (13.46%). Found: C (55.45%), H (4.50%), S (13.10 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.91 (s,3H,OCH_3); 3.94 (s,3H,OCH_3); 6.86 (d,1H, 5-H, J=8.5 Hz); 6.95 (d,1H, 6-H, J = 8.5 Hz); 8.24 (s,1H, 3-H); 12.7 (s,1H, COOH). ^{13}C-NMR (75 MHz, $CDCl_3$): 56.2, 56.4, 105.9, 107.3, 122.6, 130.7, 131.4, 135.4, 148.3, 150.0, 171.6.

4,7-Dimethoxy-benzo[*b*]thiophene-2-carbonyl chloride (4).

A solution of carboxylic acid (**5**) (850 mg, 3.6 mmoles) in thionyl chloride (50 mL) was heated under reflux for 4h. Once the reaction proceeded the excess of thionyl chloride was removed under pressure, to give the crude acyl halide (**4**) as a yellow solid. The crude residue was immediately chromatographed on silica gel column (CH_2Cl_2) to provide pure compound (**4**) (825 mg, 90%) yield. mp: 84-85 °C ; IR (cm^{-1}): 1730 (COCl), 1600 (C=C Ar). Anal.Calcd. for ($C_{11}H_9ClO_3S$): C (51.47%), H (3.53%), S (12.49%). Found: C (51.44%), H (3.60%), S (12.46 %). ^{1}H NMR (300MHz, $CDCl_3$) δ: 3.93 (s,3H,OCH_3); 3.95 (s,3H,OCH_3); 6.68 (d,1H, 5-H, J=8.5 Hz); 6.84 (d,1H, 6-H, J = 8.5 Hz); 8.38 (s,1H, 3-H). ^{13}C NMR (75 MHz, $CDCl_3$): 55.8, 56.1, 104.9,108.6, 130.6, 133.5,134.8, 135.5, 148.1, 151.1, 161.1.

1-(4-Nitrophenyl)-4-[(4,7-dimethoxy-1-benzothien-2-yl)carbonyl] piperazine (5).

To a solution of aroyl halide (**5**) (478 mg, 1.86 mmol) in anhydrous THF (60 mL) was added 1-(4-nitrophenyl)-piperazine (386 mg, 1.86 mmoles) and dry pyridne (147 mg,1.86 mmoles) under nitrogen atmosphere . The mixture was stirred for 4h, then diluted with water (30 mL) and extracted with EtOAc (3x50 mL), the organic layers were dried over $MgSO_4$, and concentrated in vacuo to afford crude amide (**7**) which was purified by silica gel column chromatography EtOAc / CH_2Cl_2 (1:2) to afford pure amide (**7**) (675 mg, 85%). mp: 192-193 °C; (EtOH). IR (cm^{-1}): 1625 (C=O) , 1598 (NO_2), 1485 (C=C Aromátic), 1335 (NO_2). Anal.Calcd. for ($C_{21}H_{21}N_3O_5S$): C (58.95%), H (4.91%), N (9.83%), S (7.50%). Found : C (58.66%), H (5.00 %), N (9.48%), S (7.96%). ^{1}H NMR ($CDCl_3$): δ 3.53 (t, 4H, 2'-H and 6'-H , J= 5.1 Hz,), 3.92 (s,3H, OMe, C-7), 3.96 (s,3H, OMe, C-4), 3.98 (t, 4H, 3'-H and 5'-H , J = 5.1 Hz), 6.69 (d,1H, 5-H, J = 8.5Hz,), 6.76 (d, 1H, 6-H , J = 8.5 Hz), 6.83 (d, 2H, 2"-H and 6"-H , J = 9.4 Hz), 7.69 (s,1H, 3-H), 8.15(d, 2H, 3"-H and 5"-H , J = 9.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) : δ 44.6, 47.6, 56.3 , 56.6, 105.4, 106.6, 113.5 (2C), 123.8, 126.5 (2C), 131.4, 131.5, 135.8, 139.7, 149.0, 150.5, 154.9,

164.6.

1-(4-Aminophenyl)-4-[(4,7-Dimethoxy-1-benzothien-2-yl)carbonyl] piperazine. (6)

To a solution of 4-nitrophenyl piperazine benzothiophenamide (**5**) (500 mg, 1.17 mmol) in a mixture (EtOH / H_2O / HOAc) (1:1:1), was added powder iron (327 mg, 5.84 mmol) . After stirring at 45 °C for 45 min, water was added (50mL). The reaction mixture was neutralized with sodium hydrogencarbonate and extracted with EtOAc (3x 50 mL). The combined organic layers were dried overMgSO_4 and evaporated to dryness in vacuo to give a crude mixture which was purified by column chromatography (EtOAc) to afford pure aminobenzothiophene **(6)** (357 mg, 77%). mp : 193-194.5 °C. IR (cm^{-1}) : 3424 and 3339 (Ar-NH_2), 3007 (C-H Ar), 1597(C=O), 1517 (C=C). ^{1}H NMR (300 MHz, $CDCl_3$) δ : 3.07 (t,4H, 2'-H and 6'-H, *J* = 5.0 Hz), 3.48 (s, 2H, Ar-NH_2), 3.91-3.95 (m,6H, 2x Ar-OCH_3 and 4H-Pip; 3'-H and 5'-H), 6.66 (d, 2H, 3''-H and 5''-H, *J*= 8.6 Hz), 6.68 (d,1H, 5-H, *J*= 8.3 Hz), 6.73 (d,1H,6-H, *J* =8.3 Hz), 6.82 (d,2H, 2''-H and 6''-H, *J* = 8.6 Hz). 7.65 (s,1H,3-H). ^{13}C NMR (75 MHz,$CDCl_3$): 44.4(2C), 52.0(2C), 55.7, 56.0, 104.8, 105.7, 116.1(2C), 119.3 (2C), 122.6, 130.8, 130.9 135.8, 140.9, 143.9, 148.4, 149.9, 163.8. HRMS (EI) Calcd for $C_{21}H_{23}N_3O_3S$ (M^+) : 397.14601. Found: 397.14532.

General procedure for the preparation of *N*-{4-[4-(4,7-Dimethoxy-benzo[*b*]thiophene–2–carbonyl)-1-piperazinyl]–phenyl}-arylcarboxamides. 7(a-f).

***N*-{4-[4-(4,7-Dimethoxy-benzo[*b*]thiophene-2-carbonyl)-1-piperazinyl]–phenyl}-3-methoxy-benzamide. 7(a)**

To a solution of aminophenylpiperazinyl benzothiophene (**6**) (200 mg; 0.5 mmol) in dry THF (25 mL) was slowly added 3-methoxy-benzoyl chloride, (85.3 mg; 0.5 mmol) and dry pyridine (0.04 ml, 0.5 mmol) at 0°C under nitrogen atmosphere. After stirring for 10 min, the mixture was allowed to warm at room temperature and maintained for 2 h. The mixture was then diluted with water (100 mL), extracted with EtOAc (3x50 mL) and dried over anhydrous $MgSO_4$. Concentration of the solvent in vacuo afforded the crude product as a brown pale solid, which was purified by silica-gel column chromatography (EtOAc) to afford pure benzamide **7(a)** (188 mg, 71%). mp : 183-184.5 °C ; IR ν_{max} : 3410 (ArCONH), 1668 (NHC=O),1637 (Pip-NC=O). ^{1}H NMR (300 MHz, $CDCl_3$) δ : 3.22 (t,4H, 2x-CH_2-Pip, 2'H and -6'-H, *J*= 5.0 Hz), 3.87 (s, 3H, 3'''-H, Ar-OMe), 3.92 (s, 3H, 7-H, Ar-OMe), 3.93 (m, 4H,2x-CH_2-Pip, 3'H and 5'-H), 3.96 (s, 3H, 4-H, Ar-OMe), 6.69 (d,1H, 5-H, *J* = 8.5 Hz), 6.75 (d, 1H, 6-H , *J* = 8.5 Hz), 6.96 (d, 2H, 2''-H and 6''-H , *J* = 9.0 Hz), 7.08 (m,1H, 4'''-H), 7.38 (d,2H, 5'''-H and 6'''-H, *J*= 5.2 Hz), 7.44 (d,1H, 2'''-H, J_m = 1.5 Hz), 7.56 (d, 2H, 3''-H and 5''-H, *J* = 9.0 Hz), 7.67 (s,1H, 3-H), 7.77 (s,1H, NHCO). ^{13}C NMR (75 MHz,$CDCl_3$): 46.7(2C) , 55.0 (2C), 55.7, 56.1, 56.3, 105.1, 106.1, 112.7, 117.6 (2C), 118.1, 118.9, 121.9 (2C), 123.1, 130.0, 131.1, 131.2, 131.4, 135.9, 136.8, 148.3, 148.7, 150.2, 160.2, 164.2, 165.6. HRMS (EI) Calcd for $C_{29}H_{29}N_3O_5S$ (M^+) : 531.18280 . Found: 531.181242.

***N*-{4-[4-(4,7-Dimethoxy-benzo[*b*]thiophene-2-carbonyl)-1-piperazinyl]–phenyl}-benza-mide 7(b).**

Prepared from 4-aminophenylpiperazinyl benzothiophene **6** (220 mg; 0.54 mmol), dry pyridine (0.05 ml, 0.5 mmol), and benzoyl chloride (80 mg; 0.54 mmol) in dry THF (20 ml). The crude was purified by silica-gel column chromatography (EtOAc), to provide pure **7(b)** (222 mg, 82%). mp : 180-182 °C IR ν_{max} : 3424(ArCONH), 1641 (-NHC=O), 1619 (Pip-NC=O). ^{1}H NMR (300 MHz,$CDCl_3$): δ 3.22 (t,4H, 2x-CH_2-Pip, 2'H and -6'-H, *J*= 4.8 Hz), 3.92 (s, 3H, 3'''-H, Ar-OMe), 3.93 (m, 4H,2x-CH_2-Pip, 3'H and 5'-H), 3.96 (s,3H,4-H, Ar-OMe), 6.69 (d,1H, 5-H, *J* = 8.5 Hz), 6.75 (d, 1H, 6-H , *J* = 8.5 Hz), 6.95 (d, 2H, 2''-H and 6''-H , *J* = 9.0 Hz), 7.43-7.52 (m,3H, 3'''-H 4'''-H, and 5'''-H).7.56 (d, 2H, 3''-H and 5''-H, *J* = 9.0 Hz), 7.67 (s,1H,3-H), 7.80 (s,1H,NHCO), 7.87 (d,2H, 2'''-H and 6'''-H, *J*= 6.9 Hz). ^{13}C NMR (75 MHz,$CDCl_3$): δ 45.6 (2C), 50.1 (2C), 55.8, 56.0, 104.8, 105.7, 117.4 (2C), 121.6 (2C), 122.8, 127.0 (2C), 128.8 (2C), 130.7, 130.8, 131.2, 131.7 , 135.0, 135.6, 148.0, 148.4, 149.9, 163.9, 165.6 . HRMS (EI) Calcd for $C_{28}H_{27}N_3O_4S$ (M^+) : : 501.17221. Found : 501.17295.

***N*-{4-[4-(4,7-Dimethoxy-benzo[*b*]thiophene-2-carbonyl)-1-piperazinyl]–phenyl}-4-fluoro-benzamide. 7(c).**

Prepared from 4-aminophenylpiperazinyl benzothiophene **6** (100 mg; 0.25 mmol), dry pyridine (0.05 ml, 0.5 mmol) and 4-fluoro-benzoyl chloride (40.0 mg; 0.25 mmol) in anhydrous THF (20 ml). The crude was purified by silica-gel column chromatography (AcOEt), to provide (113mg, 87%) of pure (**7c**) as a white solid mp : 168-170 °C IR ν_{max} : 3441(ArCONH), 1636 (NHC=O), 1615 (Pip-NC=O). ^{1}H NMR (300 MHz,$CDCl_3$): δ 3.20 (m,4H, 2x-CH_2-Pip, 2'H and -6'-H), 3.92-3.97 (m,10 H, 2xOMe and 2x-CH_2-Pip, 3'H and -5 '-H), 6.67 (d,1H, 5-H, *J* = 8.4 Hz), 6.74 (d, 1H, 6-H, *J* = 8.4 Hz), 6.93 (d,2H, 2''H and -6''-H, *J* = 8.9 Hz), 7.13 (t,2H, 3'''H and -5'''-H, J = 8.6 Hz), 7.53 (d,2H, 3''H and -5''-H, *J* = 8.9 Hz), 7.66 (s,1H, 3-H), 7.85-7.90 (m, 3H, 2'''H , 6'''-H and NHCO). ^{13}C NMR (75 MHz,$CDCl_3$): δ 45.5(2c), 50.1(2c), 55.8, 56.0, 104.8, 105.8, 115.7(d, 2C, ^2J= 22.0 Hz), 117.3, (2c), 117.4, 121.9 (2C), 122.8, 129.4 (d, 2C, ^3J= 8.9 Hz), 130.9, 131.1, 131.2 (d, ^4J= 3.3 Hz), 135.6, 148.1, 148.5, 149.9, 163.9, 164.6, 164.8 (d,^1J=2 53 Hz). HRMS (EI) Calcd for $C_{28}H_{26}N_3O_4SF$ (M^+) : 519.16278. Found : 519.16114.

4-Chloro-*N*-{4-[4-(4,7-dimethoxy-benzo[*b*]thiophene-2-carbonyl)-1-piperazinil]–phenyl}-benzamide. 7(d).

Prepared from **6** (100 mg; 0.25 mmol) and 4-chloro-benzoyl chloride (44.0 mg; 0.25 mmol), dry pyridine (0.1ml,1.27 mmol) in anhydrous THF (25 ml). The crude mixture, was subjected to column cromatography (EtOAc) to afford pure (**7d**) (104 mg, 78%) mp : 203-204 °C IR ν_{max} : 3431(ArCONH), 1651 (NHC=O), 1614 (Pip-NC=O). ^{1}H NMR (300 MHz,$CDCl_3$): δ 3.22 (m,4H, 2x-CH_2-Pip, 2'H and -6'-H), 3.93-3.96 (m,10 H, 2xOMe and 2x-CH_2-Pip, 3'H and -5 '-H), 6.70 (d,1H, 5-H, *J* = 8.5 Hz), 6.75 (d, 1H, 6-H, *J* = 8.5 Hz), 6.95 (d,2H, 2''H and -6''-H, *J* = 9.0 Hz), 7.44 (d,2H, 3'''H and-5'''-H, *J* = 8.9 Hz), 7.54 (d,2H, 3''H and-5''-H, *J* = 8.9 Hz), 7.66 (s,1H, 3-H), 7.80-7.84 (m, 3H, 2'''H ,-6'''-H and NHCO). ^{13}C NMR (75 MHz,$CDCl_3$): δ 46.5 (2C), 50.0 (2C), 55.8, 56.1, 104.8, 105.8, 117.3 (2C), 121.8 (2C), 122.8, 128.5 (3C), 129.0 (2C), 130.9 (2C) 133.4, 135.8, 137.9, 148.1, 148.5, 150.0, 163.9, 164.5. HRMS (EI) Calcd for $C_{28}H_{26}N_3O_4SCl$ (M^+): 535.13324 . Found : 535.132301.

***N*-{4-[4-(4,7-Dimethoxy-benzo[*b*]thiophene-2-carbonyl)-1-piperazinyl]–phenyl}-2,5-dimethoxy.-4-nitrobenzamide. 7(e).**

Prepared from **6** (484 mg; 1.22 mmol), 2,5-dimethoxy 4-nitrobenzoyl chloride (300 mg; 1.22 mmol) and dry pyridine (0.1 ml 1.22 mmol) in anhydrous THF (40 ml). The crude mixture was column chromatographed (CH_2Cl_2 / AcOEt 3:1) and recristallized (ethanol) to afford **7-e** (475mg, 66%). mp : 214.5-216 °C. IR ν_{max} : 3437 (ArCONH), 1668 (-NHC=O), 1613 (Pip-NC=O). ^{1}H NMR (300 MHz,$CDCl_3$): δ 3.25 (m,4H, 2x-CH_2-Pip, 2'H and -6'-H), 3.92-3.96 (m,10 H, 2xOMe and 2x-CH_2-Pip, 3'H and -5 '-H), 4.02 (s, 3H, OMe 2'''-H or 5'''–H), 4.09 (s, 3H, OMe 5'''-H or 2'''–H), 6.69 (d, 1H, 5-H, *J* = 8.5 Hz), 6.75 (d, 1H, 6-H, *J*= 8.5 Hz), 6.97 (d, 2H, 2''H and -6''-H, *J* = 9.0 Hz), 7.56 (s, 1H, 6'''-H), 7.59 (d, 2H, 3''H and -5''-H, *J*= 9.0 Hz), 7.67 (s, 1H, 3'''H), 8.09 (s, 1H, 3-H), 9.72 (s, 1H, NHCO). ^{13}C NMR (75 MHz,$CDCl_3$): δ 46.6 (2C), 50.2 (2C), 56.1, 56.3, 57.3, 57.5, 105.1, 106.1, 109.6, 117.5 (2C), 118.1, 122,1 (2C), 122.2, 123.1, 127.2, 131.1, 135.9, 140.8, 142.6, 147.7, 148.4, 148.7, 150.2 (2C), 160.9, 164.2. HRMS (EI) Calcd. for $C_{30}H_{30}N_4O_8S$ (M^+): 606.17844 . Found : 606.17903.

4-[4-(4,7-Dimethoxy-benzo[*b*]thiophene-2-carbonyl)-1-piperazinyl]–phenyl}-4,7-dimethoxy-benzo[*b*]thiophene-2-carboxamide. 7(f).

Prepared from **6** (400 mg; 1.0 mmol), 4,7-dimethoxy-benzo[*b*]thiophene-2-carbonyl chloride **6** (256 mg; 1.0 mmol) and dry pyridine (0.08 ml 1.0 mmol) in anhydrous THF (40 ml). The crude was column chromatographed (CH_2Cl_2 / AcOEt 3:1) and recristallized (ethanol) to afford **7-f** (185 mg, 30%). mp : 212-214 °C. IR ν_{max} : 3421(ArCONH), 1655 (NHC=O), 1615 (Pip-NC=O). ^{1}H NMR (300 MHz,$CDCl_3$): δ 3.22 (m,4H, 2x-CH_2-Pip, 2'H and -6'-H), 3.92-3.96 (m, 16 H, 4x OMe and 2x-CH_2-Pip, 3'H and -5 '-H), 6.67 – 6.77 (m, 4H, 5-H, 6-H, 5'''-H and 6'''-H), 6.92 (d, 2H, 2''-H and 6''-H, *J*= 8.9 Hz), 7.55 (d, 2H, 3''H and -5''-H, *J* = 8.9 Hz), 7.66 (s, 1H, 3-H), 7.91 (s, 1H, NHCO), 7.98 (s, 1H, 3'''-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 46.0 (2C), 50.2 (2C), 56.0 (2C), 56.3 (2C), 105.1(2C), 106.1, 106.6, 117.5 (2C), 121.8 (2C), 122.4, 123.1, 131.1, 131.2, 131.6, 135.9 (2C), 138.7 (2C), 148.3, 148.7, 148.8, 150.2, 150.4, 160.5, 164.2. HRMS (EI) Calcd. for $C_{32}H_{31}N_3O_6S_2$ (M^+) : 617.16547 . Found : 617.161358.

ACKNOWLEDGEMENTS

We thank to **PROYECTO FONDECYT 1050289** for the financial support and **PROYECTO MECESUP 0116.** Red nacional de Doctorado en Química for providing access to the HRMS equipment.

REFERENCES

1. Caliendo,G. ; Santagada,V.; Perissutti,E.; Fiorino,F. Derivatives as 5-HT_{1A} Receptor Ligands –Past and Present. *Curr. Med. Chem.* **12**, 1721, (2005).

2. Pessoa-Mahana, H. ; Araya-Maturana, R. ; Saitz B.C.; Pessoa-Mahana, C.David. A Synthetic Overview of Antidepressants with 5-HT_{1A} Binding Affinities. *Minirev. Med. Chem.* **3**, 77, (2003).
3. López-Rodríguez,M.L.; Ayala,D.; Benhamú,B.; Morcillo, M.J. Arylpiperazine Derivatives Acting at 5-HT_{1A} Receptors. *Curr. Med. Chem.* **9**, 443, (2002).
4. Zlatovic, M.V.; Sukalovic,V.V.; Schneider,Ch.; and Roglic,G.M. Interactions of arylpiperazine ligands with the hydrophobic part of the 5-HT_{1A} receptor binding site. *Bioorg.& Med.Chem.* **14**, 2994, (2006).
5. Pessoa-Mahana, H.; Rodrigo Acevedo R. , Ramiro Araya- Maturana, Claudio Saitz B. Pessoa-Mahana,C.David. Synthesis of Benzo[*b*] thiophene carboxamides connected to 4- arylpiperazines through a benzylic spacer. Potential ligands with 5-HT_{1A} binding affinity. *Synth Commun.* **37**, 3559, (2007).
6. Sato,H.; Skelin,I.; Debonnel,G.; Diksic,M. Chronic Buspirone treatment normalizes open field behavior in olfactory bulbectomized rats: Assessment with a quantitative autoradiographic evaluation of the 5-HT_{1A} binding sites. *Brain Res. Bull.* **75**, 545, (2008).
7. 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.; Lasheras,B.; Tordera,R.; Del Río,J.; Monge, A. New 3-[4-(aryl)piperazin-1-yl]-1-(benzo[*b*]thiophen-3-yl) propane Derivatives with Dual Action at 5-HT_{1A}. Serotonin Transporter as a New Class of Antidepressants. *Eur.J. Med. Chem.* **36**, 55, (2001).
8. Orús,L.; Pérez,-Silanes.; Oficialdegui, A. M.; Martínez-Esparza, J.; Del Castillo,J.C.; Mourelle, M.; Langer,T.; Guccione,S.; Doncella,G.; Krovat,E.M.; Poptodorov,K.; Lasheras,B.; Ballaz,S.; Hervías,I.; Tordera,R.; Del Río,J.; Monge, A. Synthesis and Molecular Modeling of New 1-Aryl-3-[4-arylpiperazin-1-yl]-1-propane Derivatives with High affinity at the Serotonin Transporter and at 5-HT_{1A} receptors. *J.Med.Chem.* **45**, 4128, (2002).
9. López-Rodríguez, M.L.; Morcillo,M.J.; Fernández,E.; Benhamú,B.; Tejada,I.; Ayala,D.; Viso,A.; Olivella,L,; Pardo,L.; Delgado,M.; Manzanares,J.; Fuentes,J.A. Design and Synthesis of S-(-)-2[(4-(Napht-1-yl)piperazin-1-yl] methyl]-1,4-dioxoperhydro-pyrrolo[1,2-α]pyrazine (CSP-2503) Using Computational Simulation. A 5-HT_{1A} Receptor Agonist. *Bioorg. & Med. Chem. Lett.* **13**, 1429, (2003).
10. López-Rodríguez, M; Morcillo, M; Fernández, E; Benhamu, B; Tejada, I; Ayala, D; Viso, A; Campillo, M; Pardo, L; Delgado, M; Manzanares, J; Fuentes, J. A.; Synthesis and Structure-Activity Relationships of a New Model of Arylpiperazines. 8.1 Computational Simulation of Ligand-Receptor Interaction of 5-$HT1_{AR}$ Agonists with Selectivity over r1-Adrenoceptors. *J. Med. Chem.* **48**, 2548, (2005).
11. Kossakowski, Jerzy; Krawiecka, Mariola; Kuran, Bozena. Synthesis of conformationally constrained aryl- or heteroaryl-piperazinyl derivatives of selected imides as 5 - HT_{1A} receptor ligands. *Molecules* **11**, 615, (2006).
12. Paluchowska,M.; Mokrosz, M.J.; Bojarski, A.J.; Wesolowska, A.; Borycz, J.; Charakchieva-Wójcik, E. On the bioactive conformation of NAN-190 (1) and MP 3022 (2),5-HT (1a) receptor antagonists. *J. Med. Chem.* **42**, 4952, (1999).
13. Valderrama,J.A.; Valderrama,C.; Studies on Quinones. Part 30.Synthesis of benzo[*b*]thiophene –4,7-quinones. *Synth. Commun.* **27**, 2143, (1997).
14. Pessoa-Mahana, C.D.; Valderrama, J.A.; Olmos, M.G.; Espinoza, O.A.; Pessoa-Mahana, H.; Rojas de Arias, A.; Nakayama, H.; Torres, S.; Miret, J. Studies on Quinones. Part 36. Synthesis and Trypanocidal Activity of 2-Alkoxy carbonylbenzo[*b*]thiophene-4,7-quinones. *Heterocycl. Commun.* **8**, 135, (2002).
15. Pessoa-Mahana, H.; Kosche, C.J.; Ron, H.,N.; Recabarren-Gajardo,G.; Saitz,B.C.;Araya-Maturana,R.; and C.David Pessoa-Mahana. Solvent-Free Microwave Synthesis of 3-(4-benzo[*b*]thiophene-2-carbonyl)-1-piperazinyl-1-benzo[*b*]thiophene-2-yl-1-propanones. New hetero bis-ligands with potential 5-HT_{1A} serotonergic activity. *Heterocycles* **75**, 1913, (2008).