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

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ABSTRACT

New benzothiophene arylpiperazine derivatives **7** (a-f) were synthesized as potential serotonergic 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 aryl chlorides.

Keywords: Secotonine, arylpiperazines, 5-HT_{1A} binding affinity.

INTRODUCTION

Serotonin (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 depression¹⁻³. 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 agonist⁶, has encouraged the development of new arylpiperazine derivatives acting as pharmacophores with improved pharmacological profiles.

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 arylpiperazine 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 arylpiperazine 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 cyclohexylaryl piperazines 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).

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 1.

Reagents and conditions: a) Methyl thioglycolate / K₂CO₃ / DMF, 65-70 °C 4 h. b) KOH – CH₃OH 3 h, r.t., H₃O⁺; c) SOCl₂–reflux 3 h.

The preparation of aryl benzothiophene (**4**) was carried out in three steps from the previously described 2,5-dimethoxy-6-nitro-benzaldehyde^{13,14} (**1**) (Scheme 1). 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 ¹H NMR, and their subsequent basic hydrolysis, followed by acidification provided the carboxylic acid (**3**) in a 90% yield.

The arylchloride (**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.

Scheme 2

Reagents and conditions : a) anhydrous THF/ 4-nitroarylpiperazine / N₂ atmosphere / dry pyridine 3 h, r.t.; b) Fe⁰ / HOAc/ EtOH / H₂O (1:1:1), 45-50 °C 1 h.; c-h) anhydrous THF ArCOCl dry pyridine / N₂ atmosphere : c) : 3-OMe-C₆H₄COCl ; d) C₆H₅COCl; e) 4-F-C₆H₄COCl; f) 4-Cl-C₆H₄COCl; g) 2,5-di-OMe-4-NO₂-C₆H₃COCl; h) 4,7-di-OMe-2-C₁₀H₇O₂SCoCl./ N₂ atmosphere / 2 h, r.t.

In ¹H NMR this compound showed the characteristic pair of doublet 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 Fe⁰ in a mixture of EtOH / H₂O / HOAc to afford the benzothiophene amino piperazine (6) in 90 % yield. The ¹H 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 NH₂ 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 aryl 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 (C₁₂H₁₁NO₂S).

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

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-HT_{1A} 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 ¹H NMR and ¹³C NMR spectra were performed on a Bruker DRX-300 spectrometer (300 and 75 MHz) in CDCl₃, 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 analyzer. 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 F₂₅₄ were used for column and TLC chromatography respectively.

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

To a solution of nitrobenzaldehyde 1⁵ (1000 mg, 4.74 mmol) in DMF (15 mL) anhydrous K₂CO₃ (654 mg, 4.74 mmol) and methyl thioglycolate (503 mg, 4.74 mmol) were added. The suspension 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 (CH₂Cl₂) 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 C₁₂H₁₄O₄S : C (57.13%), H (4.80%), S (12.69%). Found : C (56.78%), H (4.90%), S (12.42%). ¹H NMR (300 MHz, CDCl₃) δ: 3.91 (s, 3H, OCH₃), 3.93 (s, 3H, Ar-OCH₃), 3.94 (s, 3H, Ar-OCH₃), 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). ¹³C NMR (75 MHz, CDCl₃): 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 C₁₁H₁₀O₄S : C (55.45%), H (4.23%), S (13.46%). Found: C (55.45%), H (4.50%), S (13.10 %). ¹H NMR (300 MHz, CDCl₃) δ: 3.91 (s, 3H, OCH₃); 3.94 (s, 3H, OCH₃); 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). ¹³C-NMR (75 MHz, CDCl₃): 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 (CH₂Cl₂) 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 (C₁₁H₉ClO₃S): C (51.47%), H (3.53%), S (12.49%). Found: C (51.44%), H (3.60%), S (12.46 %). ¹H NMR (300MHz, CDCl₃) δ: 3.93 (s, 3H, OCH₃); 3.95 (s, 3H, OCH₃); 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). ¹³C NMR (75 MHz, CDCl₃): 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 aryl 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 pyridine (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 MgSO₄, and concentrated in vacuo to afford crude amide (7) which was purified by silica gel column chromatography EtOAc / CH₂Cl₂ (1:2) to afford pure amide (7) (675 mg, 85%). mp: 192-193 °C; (EtOH). IR (cm⁻¹): 1625 (C=O), 1598 (NO₂), 1485 (C=C Aromatic), 1335 (NO₂). Anal. Calcd. for (C₂₁H₂₁N₃O₅S): 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%). ¹H NMR (CDCl₃) 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* = 8.5 Hz), 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). ¹³C NMR (75 MHz, CDCl₃) : 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 / H₂O / HOAc) (1:1:1), was added powder iron (327 mg, 5.84 mmol). After stirring at 45 °C for 45 min, water was added (50 mL). The reaction mixture was neutralized with sodium hydrogencarbonate and extracted with EtOAc (3x 50 mL). The combined organic layers were dried over MgSO₄ 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-NH₂), 3007 (C-H Ar), 1597(C=O), 1517 (C=C). ¹H NMR (300 MHz, CDCl₃) δ : 3.07 (t, 4H, 2'-H and 6'-H, *J* = 5.0 Hz), 3.48 (s, 2H, Ar-NH₂), 3.91-3.95 (m, 6H, 2x Ar-OCH₃ 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). ¹³C NMR (75 MHz, CDCl₃) : 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 C₂₁H₂₃N₃O₃S (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}-arylcaboxamides. 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 MgSO₄. 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 v_{max} : 3410 (ArCONH), 1668 (NHC=O), 1637 (Pip-NC=O). ¹H NMR (300 MHz, CDCl₃) δ : 3.22 (t, 4H, 2x-CH₂-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-CH₂-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* = 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). ¹³C NMR (75 MHz, CDCl₃) : 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 C₂₉H₂₉N₃O₅S (M⁺) : 531.18280. Found: 531.181242.

N-{4-[4-(4,7-Dimethoxy-benzo[b]thiophene-2-carbonyl)-1-piperazinyl]-phenyl}-benzamide 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 v_{max} : 3424(ArCONH), 1641 (-NHC=O), 1619 (Pip-NC=O). ¹H NMR (300 MHz, CDCl₃) : δ 3.22 (t, 4H, 2x-CH₂-Pip, 2'-H and -6'-H, *J* = 4.8 Hz), 3.92 (s, 3H, 3'''-H, Ar-OMe), 3.93 (m, 4H, 2x-CH₂-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). ¹³C NMR (75 MHz, CDCl₃) : 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 C₂₈H₂₇N₃O₄S (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 v_{max} : 3441(ArCONH), 1636 (NHC=O),

1615 (Pip-NC=O). ¹H NMR (300 MHz, CDCl₃) : δ 3.20 (m, 4H, 2x-CH₂-Pip, 2'-H and -6'-H), 3.92-3.97 (m, 10H, 2xOMe and 2x-CH₂-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). ¹³C NMR (75 MHz, CDCl₃) : δ 45.5(2c), 50.1(2c), 55.8, 56.0, 104.8, 105.8, 115.7(d, 2C, ³*J* = 22.0 Hz), 117.3, (2c), 117.4, 121.9 (2C), 122.8, 129.4 (d, 2C, ³*J* = 8.9 Hz), 130.9, 131.1, 131.2 (d, ⁴*J* = 3.3 Hz), 135.6, 148.1, 148.5, 149.9, 163.9, 164.6, 164.8 (d, ¹*J* = 2.53 Hz). HRMS (EI) Calcd for C₂₈H₂₆N₃O₄SF (M⁺) : 519.16278. Found : 519.16114.

4-Chloro-N-{4-[4-(4,7-dimethoxy-benzo[b]thiophene-2-carbonyl)-1-piperazinyl]-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 (0.1 mL, 1.27 mmol) in anhydrous THF (25 mL). The crude mixture, was subjected to column chromatography (EtOAc) to afford pure (**7d**) (104 mg, 78%) mp : 203-204 °C IR v_{max} : 3431(ArCONH), 1651 (NHC=O), 1614 (Pip-NC=O). ¹H NMR (300 MHz, CDCl₃) : δ 3.22 (m, 4H, 2x-CH₂-Pip, 2'-H and -6'-H), 3.93-3.96 (m, 10H, 2xOMe and 2x-CH₂-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). ¹³C NMR (75 MHz, CDCl₃) : 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 C₂₈H₂₆N₃O₄SCl (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 (CH₂Cl₂ / AcOEt 3:1) and recrystallized (ethanol) to afford **7-e** (475mg, 66%). mp : 214.5-216 °C. IR v_{max} : 3437 (ArCONH), 1668 (-NHC=O), 1613 (Pip-NC=O). ¹H NMR (300 MHz, CDCl₃) : δ 3.25 (m, 4H, 2x-CH₂-Pip, 2'-H and -6'-H), 3.92-3.96 (m, 10H, 2xOMe and 2x-CH₂-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). ¹³C NMR (75 MHz, CDCl₃) : 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 C₃₀H₃₀N₄O₈S (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 (CH₂Cl₂ / AcOEt 3:1) and recrystallized (ethanol) to afford **7-f** (185 mg, 30%). mp : 212-214 °C. IR v_{max} : 3421(ArCONH), 1655 (NHC=O), 1615 (Pip-NC=O). ¹H NMR (300 MHz, CDCl₃) : δ 3.22 (m, 4H, 2x-CH₂-Pip, 2'-H and -6'-H), 3.92-3.96 (m, 16H, 4x OMe and 2x-CH₂-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). ¹³C NMR (75 MHz, CDCl₃) : 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 C₃₂H₃₁N₃O₆S₂ (M⁺) : 617.16547. Found : 617.161358.

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