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SOLVENT-FREE MICROWAVE SYNTHESIS OF 3-(4-BENZO[*b*]-THIOPHENE-2-CARBONYL)-1-PIPERAZINYL-1-BENZO[*b*]THIOPHEN-2-YL-1-PROPANONES. NEW HETERO BIS-LIGANDS WITH POTENTIAL 5-HT$_{1A}$ SEROTONERGIC ACTIVITY

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Abstract – A novel series of 2-benzothiophenealkylpiperazine derivatives **11**(**a-d**) with potential affinity at 5-HT$_{1A}$ serotonin receptors have been synthesized *via* solvent-free, microwave-promoted Michael addition of benzo[*b*]thiophene piperazine derivatives **6**(**a-c**) to substituted benzo[*b*]thiophen-2-yl propenones **10**(**b,c**).

INTRODUCTION

Serotonin (5-hydroxytryptamine, 5-HT) represents a major target for neurobiological research because of its involvement in numerous (phato) physiological processes.[1,2] The development of drugs that alter 5-HT neurotransmission is thus an area of intense research because of the potential to find new therapeutic agents. During last 18 years, seven distinct families of 5-HT receptors (5-HTRs) have been identified (5-HT$_1$-5-HT$_7$) and at least 15 subpopulations have been described. Among 5-HTRs, the 5-HT$_{1A}$ is involved in psychiatric disorders such as depression anxiety and memory loss.[3] A large number of agonist and antagonist for 5-HT$_{1A}$ receptors are reported in the literature among these, the long chain arylpiperazine derivatives represent one of the most important classes of 5-HT$_{1A}$Rs ligands.[4-6]

In view of the high prevalence of major depression (second leading cause of disease by 2020), and the

inadequacies of current medication (low selectivity with undesirable side effects), there remains an urgent need to discover novel antidepressants with improved pharmacological profiles. Although most of the conventional methods are useful for the synthetic goals, the microwave irradiation has been used to improve many organic syntheses as an efficient and environmentally friendly technique.[7-9]

Microwave-assisted reactions have become increasingly important in chemical synthesis in the last 20 years due to the advantages they provide over conventional heating methods. Significant reduction in reaction times, side reactions, increased yields, ease of purification, and minimization of the amount of solvent used are only a few of these desirable qualities.[10-13] Shorter reaction times (usually <15 min) allow rapid investigation into new methodologies and reaction optimisation. Microwave-assisted reactions are believed to facilitate polarization of the substrates thereby promoting the reactions.[14]

Given our interest in the synthesis of bioactive heterocycles at 5-HT_{1A} serotonin receptor, the present study describes the synthesis of new 3-[4-(benzo[*b*]thiophene-2-carbonyl)piperazin-1-yl]-1-benzo[*b*]thiophen-2-yl-propan-1-one derivatives **11**(**a-d**), by heating functionalised benzothiophene piperazines **6**(**a-c**) and benzo[*b*]thiophen-2-yl propenones **10**(**b,c**) under solvent free microwave irradiation. (Figure 1).

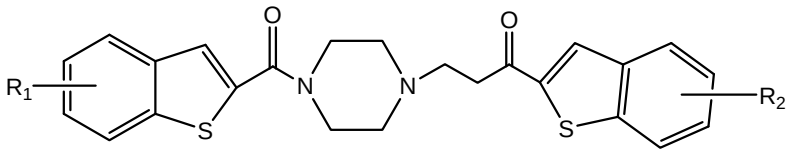
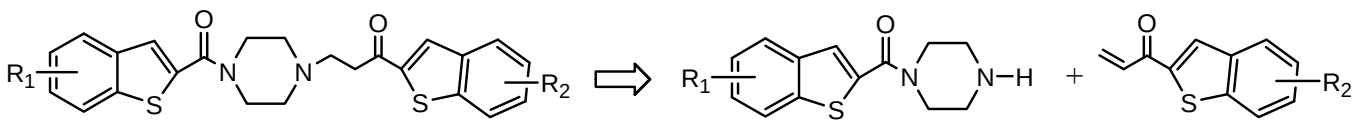


Figure 1

11(a): R_1 = 5-NO_2; R_2 = 4',7'-OMe; **11**(b): R_1 = 4,7-OMe; R_2= 4',7'-OMe; **11**(c): R_1 = H; R_2= 4',7'-OMe; **11**(d): R_1 = 5-NO_2; R_2= H

RESULTS AND DISCUSSION

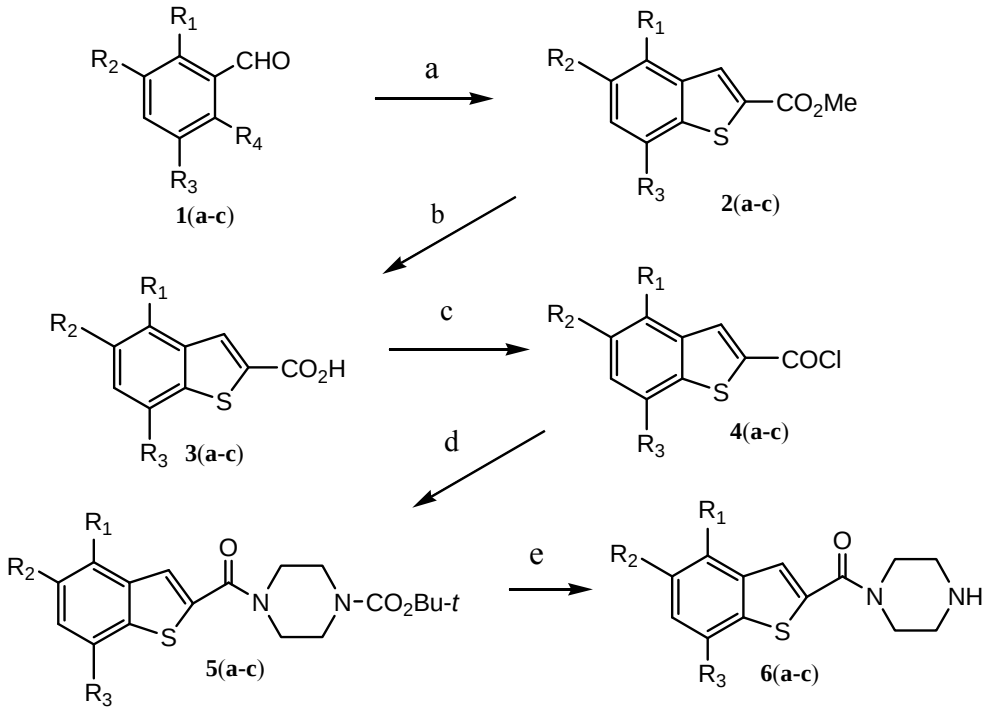
As shown in Scheme 1, compounds **11**(**a-d**) were prepared according the retrosynthetic strategy based on a Michael reaction disconnecting the target molecules in the benzothiophenamides **6**(**a-c**) and the benzothiophen propenone derivatives **10**(**b,c**).



11(**a-d**) **6** (**a-c**) **10** (**b-c**)

Scheme 1

The required units **6**(**a-c**) and **10** (**b-c**) were prepared according the synthetic sequences showed in Schemes 2 and 3. The preparation of benzothiophen amide derivatives **6** (**a-c**) was carried out as follows (Scheme 2). Treatment of the starting benzaldehydes **1**(**a-c**) with methyl thioglycolate in basic medium at 65-70 °C provided the corresponding benzo[*b*]thiophene esters **2**(**a-c**)[15,16] in (67%, 70% and 67%) respectively. The esters were purified and subsequently hydrolyzed at room temperature in a methanolic potassium hydroxide solution to afford the carboxylic acid derivatives **3**(**a-c**) in good yield: 100% **3**(**a**), 65% **3**(**b**) and 82% **3**(**c**). The aroyl chlorides **4**(**a-c**) were obtained by reaction of the carboxylic acid derivatives **3**(**a-c**) with thionyl chloride under reflux conditions, and subsequently treated with *N*-Boc-piperazine under inert atmosphere to afford the benzothiophene carboxamide derivatives **5**(**a-c**) in good yields 75% **5**(**a**), 83% **5**(**b**) and 73% **5**(**c**). Finally the *N*-Boc removal was carried out under hydrochloric acidic medium[17] to provide the 1-(1-benzothien-2-ylcarbonyl)piperazines **6**(**a-c**) with yields over 70%.



1 (a): R_1=H; R_2=NO_2 ; R_3=H; R_4=Cl
(b): R_1=OMe; R_2=H ; R_3=OMe; R_4=NO_2
(c): R_1=R_2=R_3=H ; R_4=NO_2

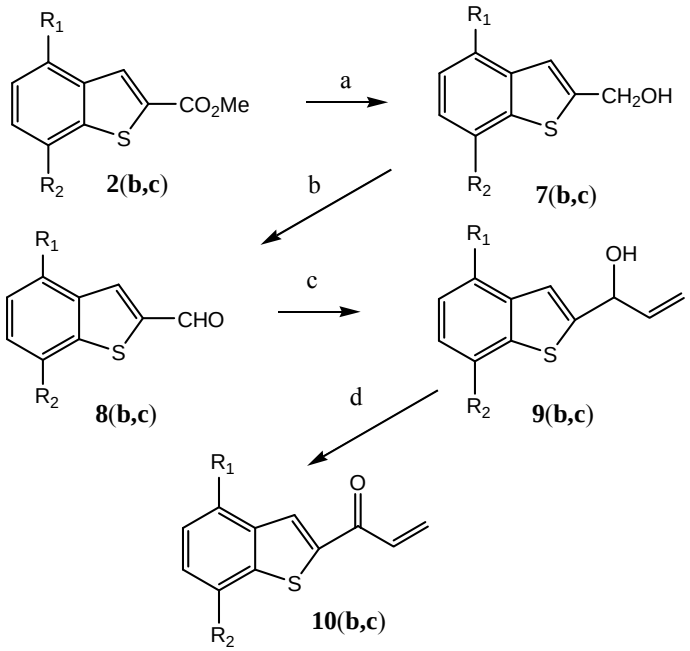
2-6 (a): R_1=H; R_2=NO_2 ; R_3=H
(b): R_1=OMe; R_2=H ; R_3=OMe
(c): R_1=R_2=R_3=H

Scheme 2

Reagents and conditions : a) Methyl thioglycolate/K_2CO_3/DMF, 65-70 °C, 4 h; b) KOH-MeOH, 3 h, rt, H_3O^+; c) $SOCl_2$-reflux 3 h; d) *N*-Boc-piperazine, dry pyridine/anhydrous THF/N_2 atmosphere; e) HCl (concd.)/THF/EtOH, 24 h, rt

Once synthesized the corresponding donor Michael derivatives, our second objective was to prepare the 1-(1-benzothien-2-yl)-2-propenones **10**(**b-c**) (Scheme 3). The esters **2**(**b,c**) were reduced with $LiAlH_4$ to

afford the alcohols **7**(**b,c**) with yields of 65% and 67%. The obtained compounds showed disappearance of the carbonylic signals in the IR at 1702 and 1725 cm^{-1}, the ^1H NMR showed a singulet at δ: 4.87 and a doublet at δ: 4.92 ppm for the methylenic protons. Subsequent oxidation to the benzothiophene aldehydes **8**(**b,c**) was carried out using pyridinium chlorochromate (PCC) in 92% and 87% yields respectively.



Scheme 3

Reagents and conditions: a) $LiAlH_4$-anhydrous THF/N_2 atmosphere, 50 °C, 3 h; b) PCC/dry CH_2Cl_2, 3 h; c) vinylmagnesium bromide, THF, microwave/600W, 4 min; d) MnO_2-CH_2Cl_2, 4 h, 25 °C.

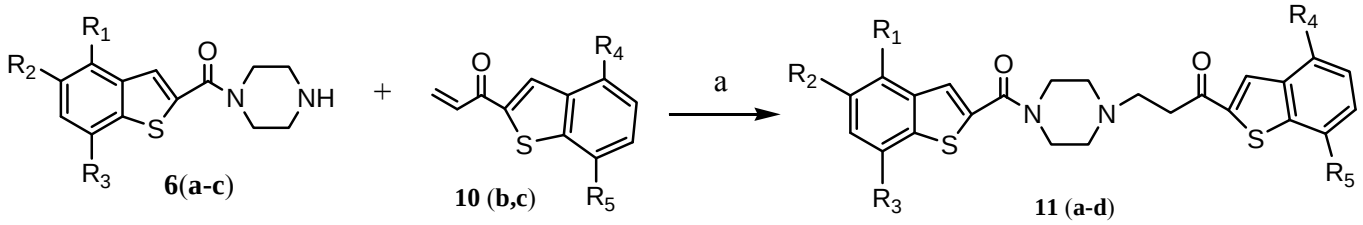
The IR of compounds **8**(**b,c**) exhibited the characteristic carbonylic absorption at 1667 (**b**) and 1673 (**c**) cm^{-1} and their ^1H NMR spectrum showed the expected singlets at downfield δ: 9.98 ppm **8**(**b**) and δ: 9.92 ppm **8**(**c**).

The Grignard reaction of vinylmagnesium bromide on aldehydes **8**(**b,c**) was not successful under conventional heating, probably due to the low reactivity of the formyl group, bonded to the large aromatic character of the π-donor benzothiophene moiety. To overcome this problem we decided to carry out the assay in a microwave-assisted organic synthesizer. The absorption of microwave energy by the polar reactants, generated enough heat energy to promote the reaction. In general 600 W, 4 min of microwave irradiation was enough to complete the reaction between aldehydes **8**(**b,c**) and vinyl magnesium bromide. The obtained alcohols **9**(**b,c**) were purified by column chromatography and subsequently oxidized with MnO_2 to the corresponding 2-propenones **10**(**b,c**) in (58% and 62%) respectively. It should be noted that

an oxidation assay of **9**(**b,c**) with pyridinium chlorochromate (PCC) provided a complex mixture of products which were not purified.

The crude enones **10**(**b,c**) were purified by column chromatography (CH_2Cl_2) to afford pure ketones **10**(**b,c**), which displayed typical unsaturated carbonylic signals in the IR at 1665 and 1661 cm^{-1}. In the ^1H NMR spectra we observed the disappearance of signals at δ: 5.45 and δ: 5.46 ppm (methyne protons) and the appearance of signals in ^{13}C NMR at δ: 184.0 **10**(**b**) and 183.9 ppm **10**(**c**).

Finally, a Michael addition assisted by solvent free microwave irradiation,[18-20] between piperazine derivatives **6**(**a-c**) and 1-(1-benzothien-2-yl)-2-propenones **10**(**b,c**) conducted to give the expected 2-benzothiophenealkylpiperazine derivatives **11**(**a-d**) in good yield, **11**(**a**): 73%; **11**(**b**): 65%; **11**(**c**): 75%; and **11**(**d**): 75%. (Scheme 4).



Scheme 4

11 (**a**): R_1=H; R_2=NO_2; R_3=H; R_4=OMe; R_5=OMe
11 (**b**): R_1=OMe; R_2=H; R_3=OMe; R_4=OMe; R_5=OMe
11 (**c**): R_1=R_2=R_3= H; R_4=OMe; R_5=OMe
11 (**d**): R_1=H; R_2=NO_2; R_3=H; R_4=H; R_5=H

Reagents and conditions: a) microwave irradiation at 600 W for 4 min in an inorganic support of MnO_2/SiO_2 (4:1).

Formation of series **11**(**a-d**) was mainly supported in ^1H NMR by the presence of two triplets at δ: 2.93 and 3.22 ppm **11**(**a**), δ: 2.93 and 3.24 ppm **11**(**b**), δ: 2.93 and 3.23 ppm **11**(**c**) and δ: 2.96 and 3.24 ppm **11**(**d**), the expected two carbonylic absorptions in the IR: **11**(**a**): 1676(C=O) - 1623(CON) cm^{-1}; **11**(**b**): 1660(C=O) - 1620(CON) cm^{-1}; **11**(**c**): 1673(C=O) - 1612(CON) cm^{-1}; and **11**(**d**): 1660(C=O) - 1612 (CON) $cm.^{-1}$ Finally the M^+ peaks obtained with HRMS confirmed the proposed structures.

In conclusion we have synthesized new piperazinobenzothiophene derivatives **11**(**a-d**) in good yield using microwave-assisted Michael addition, to develop potential bioactives ligands in 5-HT_{1A} receptors. Biological screening is currently under study.

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 deuterochloroform, 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 were recorded on a Thermo Finnigan model MAT 95XP Mass spectrometer. The microwave-assisted procedures were carried out in a Milestone Mega 240 microwave oven operating at 600 watts. Manganese (IV) dioxide was prepared by our reported procedure.[20] The solid support was preparing by heating a 4:1 mixture of silica gel (70-230 mesh) and manganese (IV) dioxide at 300 ºC for 2h. Silica gel Merck 60 (70-230 mesh) and DC-alufolien 60 F_{254} were used for column and TLC chromatography respectively.

Synthesis of 1-[(5-Nitro-1-benzo[*b*]thien-2-yl)carbonyl]piperazine 6(a).

5-Nitrobenzo[*b*]thiophene-2-carboxylic acid methyl ester 2(a).

To a mixture of 2-chloro-5-nitrobenzaldehyde **1**(**a**) (700 mg, 3.8 mmol), and anhydrous K_2CO_3 (507 mg, 3.8 mmol) in dry DMF (10 mL) was added methyl thioglycolate (0.34 mL, 3.8 mmol) and heated at 70 ºC for 4 h. The reaction mixture was poured into an ice-water solution and the precipitate was filtered to provide crude **2**(**a**) (670mg). The crude product was purified by column chromatography (CH_2Cl_2) to provide pure ester **2** (**a**) (603 mg, 67%). mp 199-200 ºC. IR ν_{max}: 1703 (CO_2Me), 1529 (NO_2), 1346 (NO_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.99 (s, 3H, CO_2Me), 8.00 (d, 1H, 7-H, *J* = 9.0 Hz), 8.19 (s, 1H, 3-H), 8.31 (dd, 1H, 6-H, *Jo* = 9.0 Hz, *Jm* = 2.2 Hz), 8.78 (d, 1H, 4-H, *Jm* =2.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 53.0, 121.0, 121.2, 123.6, 130.7, 137.2, 138.3, 145.9, 147.4, 162.3. HRMS (EI) Calcd for $C_{10}H_7NO_4S$ (M^+): 237.00958. Found: 237.00841.

5-Nitrobenzo[*b*]thiophene-2-carboxylic acid 3(a).

A solution of the 5-nitromethyl ester **2**(**a**) (800 mg, 3.38 mmol) in KOH (0.5 N): EtOH (1:1 v/v, 80 mL) was stirred at rt for 3 h. The mixture was then concentrated in vacuo and acidified with concd. HCl at 0 °C. The solution was extracted with EtOAc (3 x 50 mL) and the organic layers dried over anhydrous $MgSO_4$. Concentration of the solvent in vacuo afforded a residue (quantitative) which was purified by silica gel column chromatography (CH_2Cl_2/MeOH 1:1) to give the benzothiophene carboxylic acid **3**(**a**) as a yellow pale solid (750 mg, 100%). mp 211-213 °C. IR ν_{max}: 3610-3300 (O-H), 1695 (CO), 1536 (NO_2), 1350 (NO_2). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 4.98(bs, 1H, CO_2H), 8.23 (m, 3H, 4-H, 6-H and 7-H), 8.92 (s, 1H, 3-H). ^{13}C NMR (75 MHz, DMSO-d_6): 121.0, 121.9, 124.9, 131.3, 138.9, 139.1, 145.8, 147.5, 163.4. HRMS (EI) Calcd for $C_9H_5NO_4S$ (M^+): 222.99393. Found: 222.99474.

5-Nitrobenzo[*b*]thiophene-2-carbonyl chloride 4(a).

A solution of carboxylic acid **3**(**a**) (600 mg, 2.69 mmol) in thionyl chloride (50 mL) was heated under reflux for 4 h. Once the reaction proceeded the excess of the thionyl chloride was removed under reduced pressure, to give **4**(**a**) as an unstable pale yellow solid, which was immediately reacted. mp 159-160 °C. IR: 1768 (COCl), 1525 (NO_2), 1392 (NO_2). HRMS (EI) Calcd for $C_9H_4ClNO_3S$ (M^+): 240.96004. Found: 240.96102.

4-(5-Nitrobenzo[*b*]thiophene-2-carbonyl)-1-piperazine-1-carboxylic acid *tert*-butyl ester 5(a).

Aroyl chloride **4**(**a**) (649 mg, 2.69 mmol) in dry THF (25 mL) was slowly added to a stirred solution at 0 °C of piperazine-1-carboxylic acid *tert*-butyl ester (500 mg, 2.69 mmol), dry triethylamine (292 mg, 2.89 mmol) in dry THF (25 mL) under nitrogen atmosphere. The mixture was maintained with stirring for 6 h at room temperature and then diluted with water (100 mL). The solution was extracted with EtOAc (3 x 50 mL) and the organic layers dried over $MgSO_4$. Concentration of the solvent in vacuo afforded a residue (quantitative yield), which was purified by recristallization (EtOH) to give pure benzothiophene piperazine carbamate **5**(**a**) (748 mg, 71%). mp 170-171 °C. IR ν_{max}: 1704 (NCO_2-*tert*-Bu), 1612 (NC=O), 1532 (NO_2), 1347(NO_2). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.41 (s,9H,$(Me)_3$-), 3.44 (bs, 4H, 2'-H and 6'-H), 3.33 (bs, 4H, 3'-H and 5'-H), 7.98 (s, 1H, 3-H), 8.23 (bd, 1H, 6-H, J = 9.0 Hz), 8.30 (d, 1H, 7-H, J = 9.0 Hz), 8.84 (s, 1H, 4-H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 27.0 (3C), 42.0 (2C), 46.2 (2C), 78.2, 118.7, 119.5, 122.9, 125.3, 137.5, 139.3, 144.2, 144.3, 152.7, 160.8. HRMS (EI) Calcd for $C_{18}H_{21}N_3O_5S$ (M^+): 391.12019. Found: 391.12002.

1-[(5-Nitro-1-benzo[*b*]thien-2-yl)carbonyl]piperazine 6(a).

To a solution of carbamate **5**(**a**) (536 mg, 1.37 mmol) in THF-EtOH (1:1, 40 ml), was added HCl (concd.) (37% w/v, 6 mL, 72 mmol) and the mixture stirred at rt during 12 h. After this time the solution was basified (NH_4OH) to pH 9.0 and extracted with EtOAc (3 x 50 mL), the organic layers dried over anhydrous $MgSO_4$. Concentration of the solvent in vacuo provided a crude residue (387 mg), which was purified by silica gel column chromatography (CH_2Cl_2-MeOH = 1:1) to give 1-[(5-nitro-1- benzo[*b*]thien-2-yl)carbonyl]piperazine **6**(**a**) (331 mg, 83%). mp 172-173 ºC. IR ν_{max}: 3300 (N-H), 1626 (NC=O), 1531 (NO_2), 1344 (NO_2). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.74 (bs, 4H, 3'-H and 5'-H), 3.31 (bs., 1H, NH), 3.59 (bs, 4H, 2'-H and 6'-H), 7.96 (s, 1H, 3-H), 8.23 (bd, 1H, 6-H, J = 9.0 Hz), 8.31 (d, 1H, 7-H, J = 9.0 Hz), 8.86 (s,1H, 4-H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 44.8 (2C), 53.5 (2C), 118.6, 119.5, 122.9, 124.8, 137.6, 139.7, 144.1, 144.2, 160.4. HRMS (EI) Calcd for $C_{13}H_{13}N_3O_3S$ (M^+): 291.06776. Found: 291, 06699.

Synthesis of 1-[(4,7-dimethoxy-1-benzo[*b*]thien-2-yl)carbonyl]piperazine 6(b).

4,7-Dimethoxy-2-methoxycarbonylbenzo[*b*]thiophene 2(b).[15]

To a solution of dimethoxy nitrobenzaldehyde **1**(**b**) (552 mg, 2.61 mmol) in DMF (10 mL) was added anhydrous K_2CO_3 (436 mg, 2.61 mmol) and methyl thioglycolate (0.3 mL, 2.61 mmol). The suspension was stirred at 70 °C during 4 h and then poured onto crushed ice and vigorously stirred for 15 min. The resultant precipitate was filtered and washed with water (3 x 25 mL) to afford crude benzothiophene ester as a pale yellow solid (562 mg), which was purified by column chromatography (CH_2Cl_2) to afford pure benzothiophene ester **2**(**b**) (462 mg, 70 %) mp 124-125 ºC. Anal. Calcd for $C_{12}H_{12}O_4S$: C, 57.13; H, 4.80; S, 12.69. Found: C, 56.78; H, 4.90; S, 12.52 %. IR ν_{max}: 3010 (C-H, Ar), 1702 (C=O), 1260 (C-O). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.91 (s, 3H, OMe), 3.93 (s, 3H, Ar- OMe), 3.94 (s, 3H, Ar- OMe), 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-Dimethoxybenzo[*b*]thiophene-2-carboxylic acid 3(b).

A solution of the methyl ester **2**(**b**) (562 mg, 2.23 mmol) in KOH 0.5 N: EtOH (1:1 v/v, 60 mL) was stirred at room temperature for 3 h. 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**(**b**) (345 mg, 65%). mp 129-130 ºC. 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, 13.21 %. IR ν_{max}: 3650-2800 (O-H), 1670 (C=O), 1529(ArC=C). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.91 (s, 3H, OMe), 3.94 (s, 3H, OMe), 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, CO_2H). ^{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-1-benzo[*b*]thiophene-2-carbonyl chloride 4(b).

A solution of carboxylic acid **3**(**b**) (1.30 g, 5.50 mmol) in thionyl chloride (50 mL) was heated under reflux for 4 h. Once the reaction proceeded the excess of the thionyl chloride was removed under reduced pressure, to give the crude acyl halide **4**(**b**) as a yellow solid. The crude residue was immediately chromatographed on silica gel column (CH_2Cl_2) to give pure compound **4**(**b**) (1.30 g, 92%) yield. mp 84-85 ºC. Anal. Calcd for $C_{11}H_9ClO_3S$: C, 51.47; H, 3.53; S, 12.49. Found: C, 50.54; H, 3.64; S, 12.45 %. IR ν_{max}: 1730 (ArCOCl), 1600 (Ar C=C). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.93 (s, 3H, OMe), 3.95 (s, 3H, OMe), 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, 148.0, 151.1, 161.1.

1-[(4,7-Dimethoxy-1-benzo[*b*]thiophene-2-carbonyl)-1-piperazine-1-carboxylic acid *tert*-butyl ester 5(b).

To a solution of aroyl halide **4**(**b**) (1.07 g, 4.17 mmol) in anhydrous THF (60 mL) was added piperazine-1-carboxylic acid *tert*-butyl ester (778 mg, 4.17 mmol) and dry pyridine (330 mg, 4.17 mmol)

under nitrogen atmosphere. The mixture was stirred for 4 h, then diluted with water (50 mL) and extracted with EtOAc (3 x 50 mL), the organic layers were dried over $MgSO_4$ and concentrated in vacuo to afford crude amide **5**(**b**) (1.54 g, 91%) which was purified by silica gel column chromatography (CH_2Cl_2/EtOAc 3:1) (1.41 g, 83%). mp 100-101 °C. IR: 1694 (NCO_2), 1630(CON), 1484 (ArC=C). ^{1}H -NMR (300 MHz, $CDCl_3$) δ: 1.35 (s, 9H, *tert*-butyl), 3.39 (bs, 4H, Piper. 3"-H and 5"-H), 3.61 (bs, 4H, Piper. 2"-H and 6"-H), 3.74 (s, 3H, C-4 or C-7, OMe), 3.77 (s, 3H, C-7 or C-4, OMe), 6.50 (d, 1H, 5-H, *J* = 8.5 Hz), 6.56 (d, 1H, 6-H, *J* = 8.5 Hz), 7.49 (s, 1H, 3-H). ^{13}C NMR (75 MHz, $CDCl_3$): 28.5 (3C), 43.9 (2C), 45.2 (2C) 55.8, 56.0, 80.3, 105.0, 106, 123.0, 130.8, 130.9, 135.7, 148.5, 150.0, 154.6, 164.1. HRMS (EI) Calcd for $C_{20}H_{26}N_2O_5S$, (M^+): 406.15624. Found: 406.15643.

1-[(4,7-Dimethoxy- 1-benzo[*b*]thien-2-yl)carbonyl]piperazine 6(b).

To a solution of carbamate **5**(**b**) (1.37 g, 3.37 mmol) in THF-EtOH (1:1, 50 ml), was added HCl (concd.) (37% w/v. 6 ml, 72 mmol) and the mixture stirred at rt during 20 h. After this time the solution was basified (NH_4OH) to pH 9.0 and extracted with EtOAc (3 x 50 mL), the organic layers were dried over $MgSO_4$. Concentration of the solvent in vacuo provided a crude residue (830 mg), which was purified by silica gel column chromatography (CH_2Cl_2-MeOH = 1:1) to afford pure **6**(**b**) (763 mg, 74.0%). mp 108-108.5 ºC. IR ν_{max}: 3480 (N-H), 1597 (NHCO), 1488 (Ar C=C). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.95-2.15 (bs, 1H, NH), 2.91 (bs, 4H, Piper. 3"-H and 5"-H), 3.73 (bs, 4H, Piper. 2"-H and 6"-H), 3.89 (s, 3H, Ar-OMe, C-7 or C-4), 3.92 (s, 3H, Ar-OMe, C-4 or C-7), 6.65 (d, 1H, 5-H, *J* = 8.4 Hz), 6.70 (d, 1H, 6-H, *J* = 8.4 Hz), 7.59 (s, 1H, 3-H). ^{13}C NMR (75 MHz, $CDCl_3$): 46.2 (2C), 53.0 (2C), 55.7, 56.0, 104.7, 105.6, 122.4, 130.6, 130.8, 135.8, 148.4, 149.8, 163.8. HRMS (EI) Calcd for $C_{15}H_{18}N_2O_3S$, (M^+): 306.10381. Found : 306.10321.

Synthesis of 1-(1-benzothien-2-ylcarbonyl)piperazine 6(c).

2-Methoxycarbonyl benzo[*b*]thiophene 2(c).

To a solution of nitrobenzaldehyde **1**(**c**) (700 mg, 4.63 mmol) in DMF (10 mL) was added anhydrous K_2CO_3 (639 mg, 4.63 mmol) and methyl thioglycolate (0.42 mL, 4.63 mmol). The suspension was stirred at 70 °C for 4 h and then poured onto crushed ice and vigorously stirred for 15 min. The resultant precipitate was filtered and washed with water (3 x 25 mL) to afford crude benzothiophene ester **2**(**c**) (615 mg) as a pale yellow solid, which was purified by column chromatography (CH_2Cl_2) to afford pure benzothiophene ester **2**(**c**) (594 mg, 67%) mp 62-63 ºC. IR ν_{max}: 1725 (CO_2Me), 1524 (ArC=C), 1252 (C-O). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.98 (s, 3H, CO_2Me), 7.46 (m, 2H, 5-H and 6-H), 7.88-7.92 (m, 2H, 4-H and 7-H), 8.10 (s, 1H, 3-H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 52.5, 122.8, 124.9, 125.6, 127.0, 130.7, 133.3, 138.7, 142.2, 163.3. HRMS (IE) Calcd for $C_{10}H_8O_2S$, (M^+): 192.02450. Found: 192.02343.

Benzo[*b*]thiophene-2-carboxylic acid 3(c).

A solution of the methyl ester **2**(**c**) (800 mg, 4.17 mmol) in KOH 0.5 N: MeOH (1:1 v/v, 60 mL) was stirred at rt for 3 h. 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 yellow pale solid **3**(**c**) (721 mg, 97%) which was purified by column chromatography (CH_2Cl_2: MeOH =1:1), to afford (609 mg, 82%). mp 224-225 °C. IR ν_{max}: 3220-2574 (O-H), 1664 (C=O), 1520(ArC=C). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 3.50 (s, 1H, CO_2H), 7.38-7.46 (m, 2H, 5-H and 6-H), 7.94 (d, 1H, 4-H or 7-H, J = 7.8 Hz), 7.98 (d, 1H, 7-H or 4-H, J = 7.8 Hz), 8.10 (s, 1H, 3-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 123.4, 125.5, 126.2, 127.5, 130.7, 135.2, 139.2, 141.8, 164.0. HRMS (IE) Calcd for $C_9H_6O_2S$, (M^+): 178.00885. Found: 178.00877.

Benzo[*b*]thiophene-2-carbonyl chloride 4(c).

A solution of carboxylic acid **3**(**c**) (600 mg, 3.37 mmol) in thionyl chloride (50 mL) was heated under reflux for 4 h. Once the reaction proceeded the excess of the thionyl chloride was removed under reduced pressure, to give **4**(**c**) as a brown yellow solid (662 mg). mp 76-77 ºC. IR ν_{max}: 1744 (COCl), 1509 (ArC=C), 1497 (ArC=C). ^{1}H NMR (DMSO-d_6) δ: 7.39 (t, 1H, 5-H or 6-H, J = 7.6 Hz), 7.44 (t, 1H, 6-H or 5-H, J = 7.6 Hz), 7.94 (d, 1H, 4-H or 7-H, J = 7.6 Hz), 7.97 (d, 1H, 7-H or 4-H, J = 7.6 Hz), 8.10 (s, 1H, 3-H). ^{13}C NMR (DMSO-d_6) δ: 123.4, 125.5, 126.2, 127.4, 130.6, 135.2, 139.2, 141.8, 163.9. HRMS (IE) Calcd for C_9H_5ClOS (M^+): 195.97496. Found: 195.97458.

***tert*-Butyl 4-(1-benzothien-2-yl-carbonyl)piperazine-1-carboxylate 5(c).**

Aroyl chloride **4**(**c**) (662 mg, 3.37 mmol) in dry THF (25 mL) was slowly added to a stirred solution at 0 °C of piperazine-1-carboxylic acid *tert*-butyl ester (627 mg, 3.37 mmol), 0.46 mL of dry triethylamine (340 mg, 3.37 mmol) in dry THF (25 mL) under nitrogen atmosphere. The mixture was stirred for 6 h at rt and then diluted with water (100 mL). The solution was extracted with EtOAc (3 x 50 mL) and the organic layers were dried over $MgSO_4$. Concentration of the solvent in vacuo afforded a residue in quantitative yield, which was purified by recristallization (EtOH) to give (852 mg, 73%) of pure *tert*-butyl 4-(1-benzothien-2-yl-carbonyl)piperazine-1-carboxylate **5**(**c**). mp 140-141 ºC. IR ν_{max}: 1689 (NCO_2R), 1618 (NCO). ^{1}H NMR (DMSO-d_6) δ: 1.37 (s,9H,(-CH_3)$_3$), 3.38 (broad s., 4H, -CH_2-Piper-NCO), 3.62 (broad s., 4H,-CH_2-Piper -NCO_2), 7.36-7.43 (m, 2H, 4-H, 7-H), 7.70 (s, 1H, 3-H), 7.86 (m, 1H, 5H or 6-H), 7.97 (m, 1H, 6H or 5-H). ^{13}C NMR (DMSO-d_6) δ: 28.1(3C), 43.6(2C), 45.8(2C), 80.0, 123.0, 125.4, 126.4, 126.6, 137.1, 138.1, 139.1, 140.1, 154.2, 163.1. HRMS (IE) Calcd for $C_{18}H_{22}N_2O_3S$ (M^+): 346.13511. Found: 346.13245.

1-(1-Benzothien-2-ylcarbonyl)piperazine 6(c).

To a solution of carbamate **5**(**c**) (400 mg, 1.26 mmol) in THF-EtOH (1:1, 40 ml), was added HCl (concd.) (37% w/v, 6 mL, 72 mmol) and the mixture stirred at rt for 12 h. After this time the solution was basified (NH_4OH) to pH 9.0, extracted with EtOAc (3 x 50 mL), and the organic layers were dried over $MgSO_4$. Concentration of the solvent in vacuo provided a crude residue in quantitative yield, which was purified by silica gel column chromatography (CH_2Cl_2-MeOH, 1:1) to give 1-(1-benzothien-2-ylcarbonyl)-piperazine **6**(**c**) as viscous liquid (260 mg, 84%). IR ν_{max}: 3475 (N-H), 1620 (NHCO). ^{1}H NMR: (DMSO-d_6) δ: 1.98 (s, 1H, NH), 2.75 (broad s., 4H, -CH_2-Pip), 3.60 (broad s., 4H,-CH_2-Pip-CO), 7.44 (m, 2H, 4H and 7-H), 7.70 (s, 1H, 3-H), 7.91 (m, 1H, 5-H or 6-H), 8.00 (m, 1H, 6-H or 5-H). ^{13}C NMR (DMSO-d_6) δ: 44.5 (2C), 48.5 (2C), 122.5, 123.8, 124.9, 125.1, 125.8, 137.0, 138.6, 139.2, 162.4. HRMS (IE) Calcd for $C_{13}H_{14}N_2OS$ (M^+): 246.08268. Found: 246.08060.

Synthesis of 1-(benzo[*b*]thiophen-2-yl)-2-propen-1-one derivative 10(b).

(4,7-Dimethoxy-2-benzothiophen-2yl)methanol 7(b).

To a solution of benzothiophene ester. **2**(**b**) (540 mg, 2.14 mmol) in anhydrous THF (50 mL) was added $LiAlH_4$ (325 mg, 8.6 mmol) at 0 °C and the mixture stirred under nitrogen atmosphere for 10 min. The suspension was then heated at 45 °C for 1 h, the reaction mixture was then quenched with AcOEt/H_2O (2:1, 40 mL). The resulting precipitate was filtered and washed with EtOAc (60 mL). The combined filtrates were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude alcohol **7**(**b**) as a yellow pale solid (413 mg). The residue was purified by column chromatography on silica gel (CH_2Cl_2/EtOAc 1:1), to give pure **7**(**b**) (320 mg, 65%). mp 125-126 °C (H_2O/EtOH 3:1). IR ν_{max}: 3356 (O-H), 3017 (C-H Ar),1262 (C-O). Anal. Calcd for $C_{11}H_{12}O_3S$: C, 58.91; H, 5.39; S,14.30. Found: C,58.63; H,5.48; S,14.28 %. ^{1}H NMR ($CDCl_3$) δ: 1.35(broad t, 1H, OH), 3.92 (s, 3H, Ar-OMe), 3.95 (s, 3H, ArOMe), 4.87 (s, 2H, -CH_2-OH), 6.68 (s, 2H, 5-H y 6-H), 7.38 (s, 1H, 3-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 55.8, 55.9, 66.6, 104.3, 104.6, 116.8, 130.3, 131.6, 144.0, 148.7, 149.3.

4,7-Dimethoxybenzo[*b*]thiophene-2-carbaldehyde 8(b).

A solution of alcohol **7**(**b**) (327 mg, 1.46 mmol) in CH_2Cl_2 50 (mL) was added pyridinium chlorochromate (948 mg, 4.4 mol), and the suspension stirred at rt for 3 h. After that TLC showed the disappearance of the starting material, the solution was concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel using CH_2Cl_2 as the eluent to give **8**(**b**) (298 mg, 92%). Anal. Calcd for $C_{11}H_{10}O_3S$: C, 59.44; H, 4.53; S, 14.43. Found: C, 59.65; H, 4.68; S, 14.43. mp 109-110 °C (EtOH). IR ν_{max}: 2910 and 2840 (C-H), 1667 (C=O), 1603 and 1526 (ArC=C). ^{1}H NMR ($CDCl_3$) δ: 3.86 (s, 3H, OMe), 3.88 (s, 3H, OMe), 6.61 (d, 1H, 5-H, J = 8.4 Hz), 6.75 (d, 1H, 6-H, J = 8.4 Hz), 8.10 (s, 1H, 3-H), 9.98 (s, 1H, CHO). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 55.8, 56.0, 104.8, 108.2, 131.1, 132.0, 133.6, 142.5, 148.6, 151.0, 184.6.

1-(4,7-Dimethoxybenzo[*b*]thiophen-2-yl)-2-propen-1-ol 9(b).

To a solution of aldehyde **8**(**b**) (356 mg, 1.42 mmol) in anhydrous THF (30 mL) was added vinyl-magnesium bromide (1 M solution in THF 1.5 mL, 1.5 mmol) and irradiated at 600 W in a microwave reactor until TLC showed that the starting product had disappeared (5 min). The resulting mixture was poured into water (50 mL) and extracted with EtOAc (2 x 50 mL). The combined extracts were dried over anhydrous Na_2SO_4 and evaporated to dryness. The crude residue was purified by column chromatography on silica gel (CH_2Cl_2-AcOEt 1:2) to afford (249 mg, 62%) of **9**(**b**) as a pure yellow oil, which solidified by petroleum ether addition. mp 105-106 °C IR ν_{max}: 3183 (O-H), 2966 (C-H Aliph.), 1600 (C=C), 1485 (ArC=C). ^{1}H NMR ($CDCl_3$) δ: 2.21 (d, 1H, OH, *J* = 3.2 Hz), 3.93 (s, 3H, Ar-OMe), 3.95 (s, 3H, Ar-OMe), 5.28 (d, 1H, 3-H, *J* = 10.3 Hz), 5.45 (d, 2H, 3-H and 1-H, *J* = 17.2 Hz), 6.16 (m, 1H, 2-H), 6.65 (s, 2H, 5'-H_{BT}, and 6'-H_{BT}), 7.35 (s, 1H, 3'-H_{BT}). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 55.9, 56.0, 71.7, 104.4, 104.7, 118.0, 116.3, 130.1, 131.6, 138.9, 146.6, 148.7, 149.3. HRMS (EI) Calcd for $C_{13}H_{14}O_3S$ (M^+): 250.06637. Found: 250.06437.

1-(4,7-Dimethoxy benzo[*b*]thiophen-2-yl)-2-propen-1-one 10(b).

To a solution of alcohol **9**(**b**) (242 mg, 0.97 mmol) in CH_2Cl_2 (50 mL) was added MnO_2 (252 mg, 2.91 mmol), anhydrous $MgSO_4$ (117 mg, 0.97 mmol), and the mixture stirred at rt for 3 h. The reaction mixture was filtered off and the solvent removed under reduced pressure to give (151 mg) of crude enone **10**(**a**). The organic residue was purified by column chromatography on silica gel (CH_2Cl_2) and recrystallized from (EtOH/cyclohexane 2:1) to afford **10**(**b**) pure (140 mg, 58%) of a yellow-orange solid. mp 99-100 °C. IR ν_{max}: 3054 (C-H Ar), 2968 (C-H Aliph.), 1665 (C=O), 1556 (C=C). ^{1}H NMR ($CDCl_3$) δ: 3.94 (s, 3H, Ar-OMe), 3.96 (s, 3H, Ar-OMe), 5.92 (dd, 1H, 3-H, *J* =10.4 Hz and *J* = 1.6 Hz), 6.55 (dd, 1H, 3-H, *J* = 17.0 Hz and *J* = 1.6 Hz), 6.67 (d, 1H, 5'-H_{BT}, *J* = 8.5 Hz), 6.80 (d, 1H, 6'-H_{BT}, *J* = 8.5 Hz), 7.22 (dd, 1H, 2-H, *J* = 17.0 Hz and *J* = 10.4 Hz), 8.16 (s, 1H, 3'-H_{BT}). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 55.8, 56.0, 104.6, 107.6, 127.0, 129.6, 131.4, 131.6, 133.7, 143.6, 148.6, 150.8, 183.8. HRMS (EI) Calcd for $C_{13}H_{12}O_3S$ (M^+): 248.05071. Found: 248.05001.

Synthesis of 1-(benzo[*b*]thiophen-2-yl)-2-propen-1-one derivative 10(c).

Benzo[*b*]thiophene-2-carboxylic acid methyl ester 2(c).

To a mixture of 2-nitrobenzaldehyde **1**(**c**) (755 mg, 5.0 mmol), and anhydrous K_2CO_3 (690 mg, 5.0 mmol) in dry DMF (9.0 mL) was added methyl thioglycolate (530 mg, 5.0 mmol) and heated at 70 ºC during 4 h. After this time the reaction mixture was poured into an ice-water solution and the precipitate filtered to provide **2**(**c**) in (706 mg). The crude was purified by column chromatography (CH_2Cl_2) providing the pure ester (500 mg, 52%) yield. m.p. 62-63 ºC. IR ν_{max}: 1725 (C=O), 1522 (ArC=C), 1252 (C-O). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.97 (s, 3H, CO_2Me), 7.46 (qt, 2H, 5-H and 6-H, *J* = 8.9 Hz), 7.91 (d, 1H, 4-H or

7-H, *J* = 4.4 Hz), 7.88 (d, 1H, 7-H or 4-H, *J* = 4.4 Hz), 8.10 (s, 1H, 3-H). ^{13}C NMR (75 MHz, $CDCl_3$): 52.5, 122.8, 124.9, 125.6, 126.9, 130.7, 133.3, 138.7, 142.2, 163.3. HRMS (EI) Calcd for $C_{10}H_8O_2S$ (M^+): 192.02450. Found: 192.02343.

1-Benzo[*b*]thiophen-2-yl-2-methanol 7(c).

To a solution of benzothiophene ester **2**(**c**) (500 mg, 2.6 mmol) in anhydrous THF (50 mL) was added $LiAlH_4$ (706 mg, 18.6 mmoles) at 0 °C and the mixture stirred under nitrogen atmosphere for 10 min. After this time the reaction mixture was heated at 45 °C for 1 h and then quenched with AcOEt/H_2O (2:1, 30 mL). The resulting precipitate was filtered and washed with EtOAc (60 mL). The combined filtrates were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give alcohol **7**(**c**) (397 mg), which was purified by column chromatography on silica gel (CH_2Cl_2/EtOAc 1:1) to give pure alcohol **7**(**c**) (286 mg, 67%). mp 97-98 ºC. IR ν_{max}: 3580-3250 (O-H), 1456 (ArC=C), 1034 (C-O). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.04 (t, 1H, OH, *J* = 5.8 Hz), 4.92 (d, 2H, -CH_2- *J* = 5.8 Hz), 7.21 (s, 1H, 3-H), 7.26-7.36 (m, 2H, 5-H and 6-H), 7.72 (dd, 1H, 4-H or 7-H, *Jo* = 6.5 Hz, *Jm* = 2.1 Hz), 7.82 (dd, 1H, 7-H or 4-H, *Jo* = 7.6 Hz, *Jm* = 2.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 60.9, 121.5, 122.5, 123.6, 124.3 (2C), 139.5, 139.9, 144.8. HRMS (EI) Calcd for C_9H_8OS (M^+): 164.02959. Found: 164.02929.

1-Benzo[*b*]thiophene-2-carbaldehyde 8(c).

To a solution of alcohol **7**(**c**) (794 mg, 4.84 mmol) in CH_2Cl_2, (50 mL), was added pyridinium chlorochromate (2.60 g, 12.1 mmol) and the solution stirred for 4 h, the mixture was then concentrated under vacuum condition and purified by column chromatography using (CH_2Cl_2) as the eluent to give **8** (**c**) as a pink liquid (683 mg, 87%). IR ν_{max}: 1673 (CHO), 1589 (ArC=C), 1515 (ArC=C). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.32 (td, 1H, 5-H or 6-H, *Jo* = 7.3 Hz ; *Jm* =1.3 Hz), 7.39 (td, 1H, 6-H or 5-H, J_o = 7.3 Hz ; J_m =1.3 Hz), 7.77 (dd, 1H, 7-H or 4-H, *Jo* =8.1 Hz ; *Jm* = 0.6 Hz), 7.82 (dd, 1H, 4-H or 7-H, *Jo* = 8.1; *Jm* = 0.6 Hz), 7.90 (s, 1H, 3-H), 9.98(s, 1H, CHO). ^{13}C NMR (75 MHz,$CDCl_3$): 123.3, 125.3, 126.3, 128.2, 134.6, 138.6, 142.7, 143.3, 184.8. HRMS (EI) Calcd for C_9H_6OS (M^+): 162.01394. Found: 162.01468.

1-Benzo[*b*]thiophene-2-yl-2-propen-1-ol 9(c).

To a solution of aldehyde **8**(**c**) (500 mg, 3.1 mmol) in anhydrous THF (40 mL) was added vinyl-magnesium bromide (3.1 mL, 3.1 mmol, 1.0 M solution in THF), and irradiated at 600 W in a microwave equipment until TLC showed that the starting product had disappeared (5 min). The resulting mixture was poured into water (60 mL) and extracted with EtOAc (3 x 50 mL). The combined extracts were dried over anhydrous Na_2SO_4 and evaporated to dryness to afford (537 mg). The crude residue was purified by column chromatography on silica gel (CH_2Cl_2) to afford **9**(**c**) (277 mg, 47%). mp 60-61 ºC. IR ν_{max}: 3240

(O-H), 2917 (C-H), 1655 (C=C). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.10-2.20 (broad s., 1H, OH), 5.29 (d, 1H, 3'-H_{cys}, J = 10.0 Hz), 5.42 -5.5 (m, 2H, 3'-H $_{trans}$ and 1'-H), 6.16 (m, 1H, 2'-H), 7.19 (s, 1H, 3-H), 7.26-7.36 (m, 2H, 5-H and 6-H), 7.70 (dd, 1H, 4-H, *Jo* = 6.6 Hz, *Jm* = 1.9 Hz), 7.77-7.82 (m, 1H, 7-H). ^{13}C NMR (75 MHz, $CDCl_3$): 72.2, 116.9, 121.3, 123.0, 124.1, 124.8(2C), 139.3, 140.0, 140.2, 147.7. HRMS (EI) Calcd for $C_{11}H_{10}OS$ (M^+): 190.04523. Found: 190.04538.

1-Benzo[*b*]thiophene-2-yl-propenone 10(c).

To a solution of alcohol **9**(**c**) (430 mg, 2.28 mmol) in CH_2Cl_2 (50 mL) was added MnO2 (991 mg, 11.4 mmol), anhydrous $MgSO_4$ (275 mg, 2.28 mmol) and the mixture stirred at rt for 6 h. The crude residue was then filtered off and concentrated in vacuo, to afford (321 mg), which was purified by column chromatography (CH_2Cl_2) to provide pure **10**(**c**) (265 mg, 62%). mp 45-46 C°. IR ν_{max}: 3032 (C-H Arom), 1661 (C=O), 1601 (C=C). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.92 (dd, 1H, 3'-H_{cys}, J_{cys} = 10.4 Hz ; J_{gem} = 1.5 Hz), 6.54 (dd, 1H, 3'-H_{trans}, J_{trans} = 17.0 Hz ; J_{gem} = 1.5 Hz), 7.18 (dd, 1H, 2'-H, J_{trans} = 17.0 Hz ; J_{cys} = 10.4 Hz), 7.41 (td, 1H, 6-H or 5-H, J_o = 7.5 Hz ; J_m =1.25 Hz), 7.47 (td, 1H, 5-H or 6-H, J_o = 7.5 Hz; *Jm* = 1.25 Hz), 7.87 (t, 2H, 4-H and 7-H, J_o =7.1 Hz), 8.0 (s, 1H, 3-H). ^{13}C NMR (75 MHz, $CDCl_3$): 123.0, 125.3, 126.1, 127.6, 128.7, 128.8, 131.4, 139.2, 142.8, 144.2, 183.7. HRMS (EI) Calcd for $C_{11}H_8OS$ (M^+): 188.02959. Found: 188.02904.

General procedure for the preparation of 3-[4-(benzo[*b*]thiophene-2-carbonyl)piperazin-1-yl]-1-benzo[*b*]thiophen-2-yl-propan-1-one derivatives 11(a-d).

1-(4,7-Dimethoxybenzo[*b*]thiophen-2-yl)-3-[4-(5-nitrobenzobenzo[*b*]thiophene-2-carbonyl)-piperazin-1-yl]-1-propanone 11(a).

To a solution of 1-(4,7-dimethoxybenzo[*b*]thiophen-2-yl)-2-propen-1-one **10**(**b**) (253 mg, 1.02 mmol) and 5-nitro-2-piperazinocarboxamide **6**(**a**) (300 mg, 1.03 mmol), in dichloromethane (20 mL) was added a mixture of the inorganic support SiO_2- MnO_2 (5.0 g, 4:1) and the suspension was vigorously stirred for 15 min at rt. The solvent was removed *in vacuo* and the solid was irradiated in a microwave equipment at 600 W for 4 min, until TLC showed that the starting product had disappeared. The solid was thoroughly washed with EtOAc followed by remotion of the solvent, to afford **11**(**a**) as a crude in quantitative yield. The solid residue was purified by chromatographic column (EtOAc/CH_2Cl_2 4:1), and recrystallized (THF) to give (405 mg, 73%). mp 163-164 °C. IR ν_{max}: 3032 (Ar C-H), 1676 (C=O), 1623 (NC=O), 1524 (NO_2), 1340 (NO_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.60 (broad s, 4H, Piper. 3"-H and 5"-H), 2.93 (t, 2H, 3"'-H, *J*= 7.0 Hz), 3.22 (t, 2H, 2"'-H, *J*= 7.0 Hz), 3.77 (broad s, 4H, Piper. 2"-H and 6"-H), 3.92 (s, 3H, Ar-OMe, C-7 or C-4), 3.93 (s, 3H, Ar-OMe, C-4 or C-7), 6.66 (d, 1H, 5-H, *J* = 8.5 Hz), 6.77 (d, 1H, 6-H, *J* = 8.5 Hz), 7.58 (s, 1H, 3-H), 7.98 (d, 1H, 7′-H, *J* = 8.9 Hz), 8.10 (s, 1H, 3'-H), 8.22 (dd, 1H, 6'-H, *Jo* = 8.9, *Jm* = 2.2 Hz), 8.68 (d, 1H, 4'-H, *J* = 2.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 36.5, 46.3 (2C), 53.2 (3C), 55.7,

56.0, 104.6, 117.4, 119.9, 120.2, 123.1, 125.2, 126.5, 131.3, 133.2, 138.3, 140.5, 142.7, 145.6, 145.7, 148.5, 150.6, 162.4, 193.0. HRMS (EI) Calcd for $C_{26}H_{25}N_3O_6S_2$ (M^+): 539.11848. Found: 539.11513.

3-[4-(4,7-Dimethoxybenzo[*b*]thiophene-2-carbonyl)piperazin-1-yl]-1-(4,7-dimethoxybenzo[*b*]-thiophen2-yl)-1-propanone 11(b).

Prepared from 1-(4,7-dimethoxybenzo[*b*]thiophen-2-yl)-2-propen-1-one **10**(**b**) (60 mg, 0.24 mmol) and 4,7-dimethoxy-2-piperazinecarboxamide **6**(**b**) (74.0 mg, 0.24 mmol), to afford crude **11**(**b**) (133 mg) yield. Purified by chromatographic column (EtOAc/CH_2Cl_2 4:1), (87.0 mg, 65%). mp 193-194 °C .IR ν_{max}: 1660 (C=O), 1620 (CONH), 1260 (C-O). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.61 (bs, 4H, Piper. 3"-H and 5"-H), 2.93 (t, 2H, 3"'-H, *J* = 7.0 Hz), 3.24 (t, 2H, 2"'-H, *J* = 7.0 Hz), 3.80 (bs, 4H, Piper. 2"-H and 6"-H), 3.92 (s, 3H, Ar-OMe), 3.95 (s, 3H, Ar-OMe), 3.96 (s, 6H, 2x Ar-OMe), 6.69 (t, 2H, 5-H and 6-H or 5'-H and 6`-H, *J* = 8.0 Hz), 6.79 (t, 2H, 5'-H and 6'-H or 5-H and 6-H, *J* = 8.4 Hz), 7.72 (s, 1H, 3-H), 8.14 (s, 1H, 3'-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 36.6, 45.1 (2C), 53.0 (3C), 55.7 (2C), 56.0 (2C), 104.6, 104.7, 105.6, 107.4, 122.5, 126.5, 130.7, 130.9, 131.4, 133.3, 135.8, 142.8, 148.4, 148.5, 149.9, 150.7, 163.7, 193.1. HRMS (EI) Calcd for $C_{28}H_{30}N_2O_6S_2$ (M^+): 554.15453. Found: 554.15625.

1-Benzo[*b*]thiophen-2-yl-3-[4-(4,7-dimethoxybenzo[*b*]thiophene-2-carbonyl)piperazin-1-yl]-1-propanone 11(c).

Prepared from 1-(4,7-dimethoxybenzo[*b*]thiophen-2-yl)-2-propen-1-one **10**(**b**) (207 mg, 8.35 mmol) and benzothiophen-2-piperazinecarboxamide **6**(**c**) (206 mg, 8.35 mmol) to afford crude **11**(**c**) in quantitative yield. Purified by chromatographic column (EtOAc/CH_2Cl_2, 4:1) to afford (310 mg). mp 128.0-128.5 °C. IR ν_{max}: 1673 (C=O), 1612 (CO-N), 1260 (C-O). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.60 (bs, 4H, Piper. 3"-H and 5"-H), 2.93 (t, 2H, 3"'-H, *J* = 6.5 Hz), 3.23 (t, 2H, 2"'-H, *J* = 6.5 Hz), 3.79 (bs, 4H, Piper. 2"-H and 6"-H), 3.95 (s, 3H, Ar-OMe), 3.96 (s, 3H, Ar-OMe), 6.68 (d, 1H, 5'-H, *J* = 8.5 Hz), 6.80 (d, 1H, 6'-H, *J* = 8.5 Hz), 7.39-7.42 (m, 2H, 5-H and 6-H), 7.48 (s, 1H, 3'-H), 7.81 -7.88 (m, 2H, 4-H and 7-H), 8.14 (s, 1H, 3-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 36.1, 45.1(2C), 52.6 (3C), 55.3, 55.6, 104.1, 106.9, 121.9, 124.1, 124.3, 124.7, 125.3, 126.0, 130.9, 132.8, 136.0, 138.1, 139.7, 142.4, 148.0, 150.2, 163.3, 192.7. HRMS (EI) Calcd for $C_{26}H_{26}N_2O_4S_2$ (M^+): 494.13340. Found: 494.13175.

1-Benzo[*b*]thiophen-2-yl-3-[4-(5-nitrobenzobenzo[*b*]thiophene-2-carbonyl)piperazin-1-yl]-1-propanone 11(d).

Prepared from 1-(benzo[*b*]thiophen-2-yl)-2-propen-1-one **10**(**c**) (60 mg, 0.3mmol) and 5-nitro-2-piperazinocarboxamide **6**(**a**) (93 mg, 0.32 mmol), to afford crude **11**(**d**) in quantitative yield. Purified by chromatographic column (EtOAc/CH_2Cl_2 4:1), (114 mg, 75%). mp 160-161 °C (THF). IR ν_{max}: 3030 (Ar C-H), 1660 (C=O), 1612 (CO-N),1526 (NO_2), 1350 (NO_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.62 (bs, 4H,

Piper. 3”-H and 5”-H), 2.96 (t, 2H, 3”’-H, *J*= 7.0 Hz), 3.24 (t, 2H, 2”’-H, *J*= 7.0 Hz), 3.76 (bs, 4H, Piper. 2”-H and 6”-H), 7.39-7.49 (m, 2H, 4-H and 7-H), 7.59 (s, 1H, 3-H), 7.89 (t, 2H, 5-H and 6-H, *J* = 7.1 Hz), 7.97 (d, 1H, 7’-H, *J* = 9.0 Hz), 8.0 (s, 1H, 3’-H), 8.25 (dd, 1H, 6’-H, *Jo* = 8.9, *Jm* = 2.1 Hz), 8.71(d, 1H, 4’-H, *J* =1.9Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 36.7, 46.3 (2C), 53.1(3C), 120.1, 120.3, 123.1, 123.3, 125.3, 125.3, 126.1, 127.8, 129.2, 138.5, 139.2, 140.7, 142.6, 143.6, 145.8, 146, 163.6, 193.2. HRMS (EI) Calcd for $C_{24}H_{21}N_3O_4S_2$ (M^+): 479.09735 . Found: 479.09803.

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