

## Solvent-free microwave-promoted Michael addition of aza-nucleophiles to benzo[*b*]thiophen-2-yl-2-propenone

Hernán Pessoa-Mahana,<sup>1\*</sup> Marcos González,<sup>1</sup> Marcelo González,<sup>2</sup> David Pessoa-Mahana,<sup>2</sup> Ramiro Araya-Maturana,<sup>1</sup> Nadia Ron,<sup>1</sup> and Claudio Saitz<sup>1</sup>

<sup>1</sup>*Department of Organic and Physical Chemistry, Faculty of Chemical and Pharmaceutical Science, University of Chile, Casilla 233, Santiago 1, Chile*

<sup>2</sup>*Department of Pharmacy, Faculty of Chemistry, Pontificia Universidad Católica de Chile, Casilla 306, Santiago 22, Chile*  
*E-mail: [hpessoa@ciq.uchile.cl](mailto:hpessoa@ciq.uchile.cl)*

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### Abstract

A series of Michael adducts (**5-11**) have been synthesized with good yields under solvent-free microwave conditions. Aliphatic and aromatic amines utilized as Michael donors reacted with 1-(4,7-dimethoxybenzo[*b*]thiophen-2-yl)-2-propen-1-one (**4**), to produce  $\beta$ -aminoketones and azaheterocyclic compounds of potential biological interest.

**Keywords:** Aza-nucleophiles, microwave irradiation, Michael addition, bis-adduct.

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### Introduction

$\beta$ -amino ketones are useful synthetic intermediates used in the synthesis of biologically active natural products and pharmaceuticals.<sup>1,2</sup> Classical methods for the synthesis of  $\beta$ -aminoketones include the Mannich reaction of methylketones with amines in the presence of paraformaldehyde, alkylation of amines with  $\beta$ -haloalkyl ketones, and 1,4-conjugate addition reactions with vinyl ketones and amines.<sup>3</sup>

The Mannich reaction has serious disadvantages, including drastic reaction conditions and long reaction times. The Michael addition as one of the most important C-C bond-forming reactions, has attracted much attention toward the development of enantioselective catalytic procedures<sup>4</sup>. Aza-Michael addition of a nitrogen-centered nucleophile is a convenient way to introduce amine-based functionality to a  $\beta$ -carbon attached to an electron-withdrawing group,<sup>5-7</sup> although this route usually requires acid or base-catalyst to activate one of the substrates. Hetero-Michael addition of amines to  $\alpha,\beta$ -unsaturated carbonyl compounds gives  $\beta$ -amino ketones, which are attractive for their use as synthetic intermediates of anticancer agents, and

antibiotics.<sup>8,9</sup> The addition of thiols to  $\alpha,\beta$ -unsaturated carbonyl compounds results in the synthesis of biologically active compounds, such as the calcium antagonist diltiazem.<sup>10,11</sup>

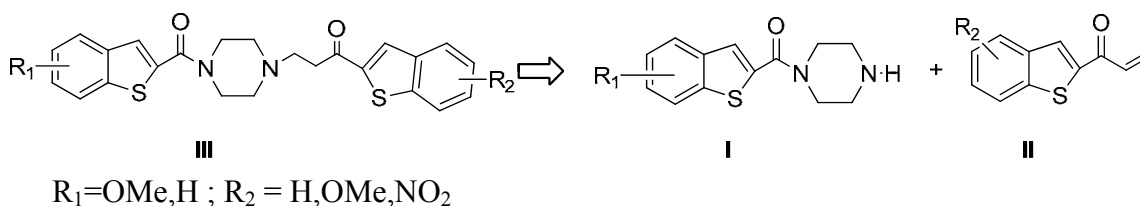
Gomtsyan et al.<sup>12,13</sup> reported the synthesis of  $\beta$ -aminoketones from N-methoxy amides (Weinreb amides) through a novel sequential transformation consisting of nucleophilic substitution with vinyl-Grignard reagents, followed by a Michael-type reaction with a number of amines. The reaction proceeds in good yields for a variety of amides, vinyl Grignard reagents, and N-nucleophiles. It is interesting to note that aza-Michael reactions have also provided an easy and direct route to  $\beta$ -amino esters<sup>14</sup> and  $\beta$ -amino amides.<sup>15</sup>

Many organic reactions proceed much faster and with higher yields under microwave irradiation compared to conventional heating. It was found that microwave irradiation and solid support in solventless conditions considerably shortens reaction time and greatly reduces waste production.<sup>16-18</sup>

In this paper we report the synthesis in good yield of a variety of  $\beta$ -aminoketones of potential biological interest under environmentally friendly conditions, using microwave-supported Michael-addition. This protocol includes reactions that can be conducted without solvent and in absence of metal catalysts, a highly desirable experimental condition.

## Results and Discussion

In a previous communication<sup>19</sup> we described that 2-piperazinobenzothiophene derivatives (**I**) were allowed to react with benzothiophen-2-propenone (**II**) in a Michael reaction microwave supported under solventless conditions, to yield a series of benzothiophene (**III**) in the search for potential neurobioactive compounds, as shown in the retrosynthetic scheme 1.

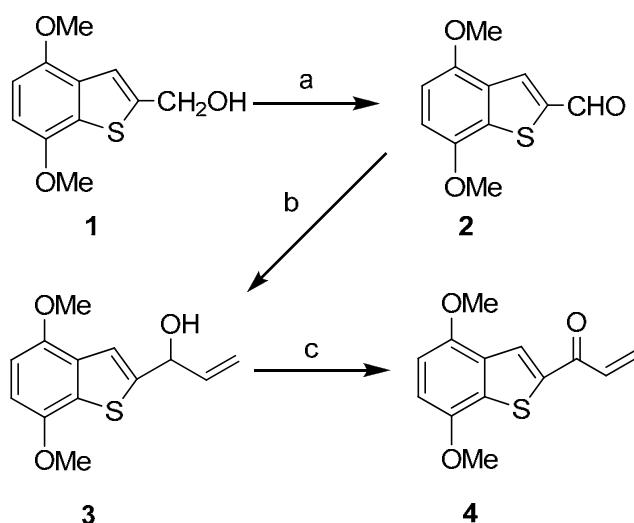


### Scheme 1

As an extension of this work, the scope of this approach was explored for a variety of aza-nucleophiles **1-7** of pharmacological interest,<sup>20-22</sup> reacting with 1-(4,7-dimethoxybenzo[*b*]thiophen-2-yl)-2-propen-1-one **4**, as Michael acceptor under microwave conditions (Table 1).

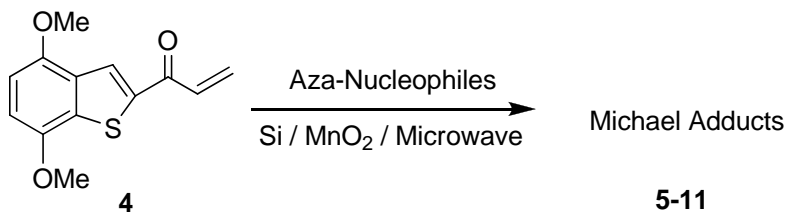
The synthesis of 2-propenone **4**, was carried out<sup>19</sup> in three steps from the benzothiophene alcohol **1** which was oxidized with pyridinium chlorochromate (PCC) in  $\text{CH}_2\text{Cl}_2$  to give

aldehyde **2** in good yield. Further reaction with vinyl magnesium bromide, afforded allyl alcohol **3** which was finally converted in the 2-propenone **4** (Scheme 2).



**Scheme 2**

In a model reaction, benzothiophen-2-propenone **4** and the corresponding aza-nucleophile were impregnated on a 95:5 mixture of silica gel-manganese dioxide as solid inorganic support, and irradiated in a microwave-assisted organic synthesizer during short periods of time (Scheme 3).

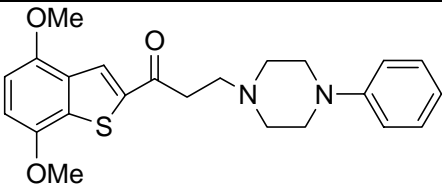
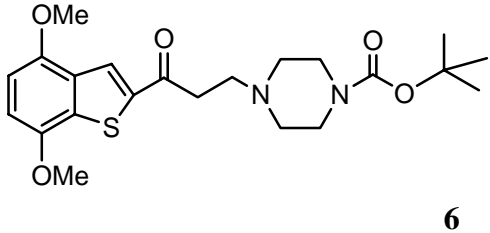
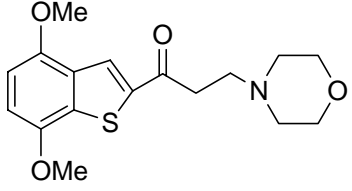
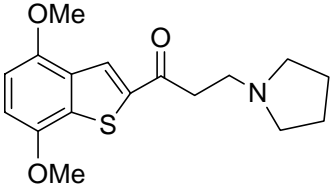
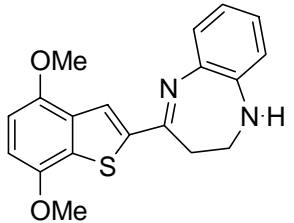
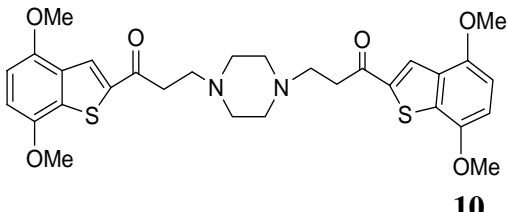


**Scheme 3**

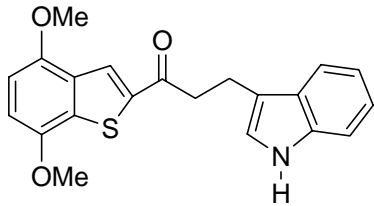
In general, the reactions proceeded efficiently with relatively good yields of the desired products (Table 1, entries **1-7**). Michael addition and cyclodehydration in a single synthetic step occurred for compound **9**. An interesting reaction was carried out using the carbo-nucleophile 1(H)-indole as a Michael-donor. The product was the 3-indolyl adduct **11** because of the known electron-rich nature of the C-3 position of 1(H)-indoles.

In table 1 it is seen that products were obtained in relatively good yields (63-90%) and with short reaction times. The bis-adduct **6** needed the longest time, which may be due to a major steric hinderance present in the second addition step.

**Table 1.** Synthesis of products **5-11** by reaction of nitrogenated nucleophiles with the Michael acceptor 1-(4,7-dimethoxybenzo[*b*]thiophen-2-yl)-2-propen-1-one **4**.

Entry	Nucleophile	Compound N°	Yield (%)	Time (min)
1	1-Phenylpiperazine	 <b>5</b>	88	4
2	N-Boc piperazine	 <b>6</b>	90	4
3	Morpholine	 <b>7</b>	87	4
4	pyrrolidine	 <b>8</b>	63	6
5	o-phenyldiamine	 <b>9</b>	68	7
6	piperazine	 <b>10</b>	78	9

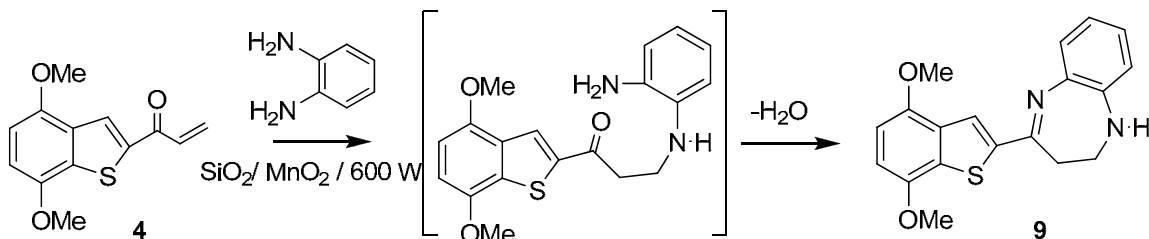
**Table 1.** Continued

Entry	Nucleophile	Compound N°	Yield (%)	Time (min)
7	1[H]-Indole	 <b>11</b>	70	7

It is important to note that when the reaction of thiophene **4**, with the azanucleophiles was carried out under conventional heating conditions, long times (over 7h ) were required and the reactions did not go to completion, which may be attributed to the high stability of propenone **4**, due to the great aromatic character of the  $\pi$ -donor benzothiophene moiety.

When a mixture of benzothiophene propenone **4** and 1-phenylpiperazine (as nucleophile) was irradiated at 600 W, the conjugated product **5** was obtained efficiently (88% yield). The IR spectrum showed bands at 1655(C=O), and 1600 (Aromatic,C=C). The  $^1\text{H}$  NMR displayed signals at  $\delta$ : 2.95 (t,2H, 3-H,  $J = 7.4$  Hz) ppm, and 3.24 (t, 2H, 2-H,  $J = 7.4$  Hz) ppm for the methylenic chain and signals at  $\delta$ : 2.71 (t, 4H, 2'-H<sub>Pip</sub> y 6'-H<sub>Pip</sub>,  $J = 5.0$  Hz) ppm , and 3.22 (t,2H, 3'-H<sub>Pip</sub>,5'-H<sub>Pip</sub>,  $J = 5.0$  Hz) assigned to the piperazinic ring protons. Compound **5** has been recently screened on 5-HT<sub>1A</sub> receptors, showing an interesting binding affinity with potential antidepressant effect (unpublished results). Cyclic secondary aliphatic amines (N-Boc-piperazine, morpholine and pyrrolidine,) also underwent the conjugate addition successfully (Table 1, entries 6,7,8).

We next moved to binucleophiles by reaction of 1-(4,7-Dimethoxy benzo[*b*]thiophen-2-yl)-2-propen-1-one **4** with 1,2-diaminobenzene. The solid mixture was irradiated at 600W for 7 min, to give an orange solid characterized as 1,5-benzodiazepine **9**. The reaction takes place in two steps involving the previous formation of the Michael Adduct as an intermediate, which readily undergoes a dehydrative cyclization to give **9** as described in Scheme 3.

**Scheme 3**

The  $^1\text{H}$  NMR spectrum of **9** was clean and exhibited two triplets at  $\delta$ : 3.22 and 3.78 ppm derived from methylene groups. The IR (KBr) spectrum exhibited absorptions at 3386  $\text{cm}^{-1}$  (N-

H), and a weak band at  $1611\text{ cm}^{-1}$  (C=N), along with the disappearance of the strong carbonylic absorption at  $1665\text{ cm}^{-1}$ , which indicated the nature of the cyclization. The final confirmation came with the HRMS analysis  $M^{+}_{(\text{Theoric} / \text{Experimental})}$  (338.10890 / 338.10868).

The bis-aza-Michael reaction between piperazine and Michael acceptor **4**, followed a similar procedure, although in this case a 2:1 mole ratio of piperazine (1 mmol), and 2-propenone (2 mmol) was used forming a bis-addition product, leading to dimeric benzothiophene piperazine **10** in 78% yield. The  $^1\text{H}$  NMR displayed a singlet at  $\delta$ : 2.73 ppm, for the eight equivalent piperazine hydrogens, along with two triplets at  $\delta$ : 2.97 and 3.29 ppm for the methylene protons. The homo bis-adducts have been recognized in medicinal chemistry as compounds which usually enhance the potency and selectivity relative to their monomeric lead, through a more thermodynamically favourable binding interaction with a biological receptor<sup>23</sup>.

Finally, we were interested in the reaction of **4** with 1(H)-indole since it often gives rise to rather complicated reactions (e.g., dimerization and polymerization). As stated previously, the C-3 alkylation proceeded regioselectively (N-alkylation product was not observed), giving the adduct **11** in relatively good yield. The IR band at  $3414\text{ cm}^{-1}$  (N-H), along with singlets in  $^1\text{H}$  NMR at  $\delta$ : 7.96 (s, 1H, NH) ppm, and  $\delta$ : 8.06 (s, 1H, 2'-H) ppm for the C-2 indole position confirmed this addition.

## Conclusions

The procedure presented here provides a simple, efficient and rapid method for the preparation of  $\beta$ -aminoketones and benzothiophene propenone bis-adducts of biological interest using an aza-Michael microwave-assisted protocol. Further efforts focused on the synthesis of new skeletons with potential biological relevance, along with a neurobiological screening of the synthesized compounds are in progress.

## Experimental Section

**General.** 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  $\text{cm}^{-1}$ . The  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were performed on a Bruker DRX-300 spectrometer (300 and 75 MHz) in deuteriochloroform, or DMSO- $d_6$ . Chemical shifts were recorded in ppm ( $\delta$ ) 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 were recorded on a Thermo Finnigan model MAT 95XP Mass Spectrometer. The microwave-assisted procedures were carried out in a Milestone, Lavis 1000. Multiquant<sup>®</sup>, operating at 600-watts. Manganese (IV) dioxide was obtained by our reported procedure<sup>14</sup>. The solid support was prepared by heating a 4:1 mixture of silica gel (70-230mesh) and manganese (IV) dioxide at 300

°C for 2h. Silica gel Merck 60 (70-230mesh) and DC- alufolien 60 F<sub>254</sub> were used for column and TLC chromatography respectively.

**1-(4,7-Dimethoxy benzo[*b*]thiophen-2-yl)-2-propen-1-ol (3).**<sup>19</sup> To a solution of aldehyde **2** (356mg, 1.42 mmol) in anhydrous THF (30 mL) was added vinyl magnesium bromide (1.5mL 1.5 mmol, 1M solution in THF) 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 (50mL) and extracted with EtOAc (2x 50 mL). The combined extracts were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and evaporated to dryness. The crude residue was purified by column chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>-AcOEt 1:2) to afford (249 mg, 62%) of **(3)** as a pure yellow oil, which solidified by addition of petroleum ether. mp 105-106 °C IR<sub>vmax</sub> (KBr) : 3183 (O-H), 2966(C-H Aliph.), 1600 (C=C), 1485(ArC=C)cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 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<sub>BT</sub> and 6'-H<sub>BT</sub>), 7.35 (s, 1H, 3'-H<sub>BT</sub>). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>) : 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<sub>13</sub>H<sub>14</sub>O<sub>3</sub>S (M<sup>+</sup>): 250.06637, found: 250.06549.

**1-(4,7-Dimethoxybenzo[*b*]thiophen-2-yl)-2-propen-1-one (4).**<sup>19</sup> To a solution of alcohol **3** (242 mg, 0.97 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) was added MnO<sub>2</sub> (252 mg, 2.91 mmol), anhydrous MgSO<sub>4</sub> (117mg, 0.97 mmol), and the mixture stirred at room temperature for 3 h. The reaction mixture was filtered off and the solvent removed under reduced pressure to give 151 mg, 63% of crude enone **4**. The crude residue was purified by column chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>) and recrystallized from (EtOH / Cyclohexane 2:1) to afford (139 mg, 58%) of pure **4** as a yellow-orange solid. mp 99-100 °C IR<sub>vmax</sub> (KBr) : 3054 (C-H Ar), 2968 (C-H Aliph.), 1665 (C=O), 1556 (C=C)cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 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 Hz and *J* = 1.6 Hz), 6.67 (d, 1H, 5'-H<sub>BT</sub>, *J* = 8.5 Hz), 6.80(d, 1H, 6'-H<sub>BT</sub>, *J* = 8.5 Hz), 7.22 (dd, 1H, 2-H, *J* = 17 Hz and *J* = 10.4 Hz), 8.16 (s, 1H, 3'-H<sub>BT</sub>). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>) : 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<sub>13</sub>H<sub>12</sub>O<sub>3</sub>S (M<sup>+</sup>): 248.05072, found :248.05001.

### General Procedure for the synthesis of the Michael Adducts 5-11

**1-(4,7-Dimethoxybenzo[*b*]thiophen-2-yl)-3-(4-phenylpiperazin-1-yl)propan-1-one (5).** To a solution of 1-(4,7-dimethoxy benzo[*b*]thiophen-2-yl)-2-propen-1-one **4** (100 mg, 0.40 mmol) and 1-phenylpiperazine (93 mg, 0.57 mmol), in CH<sub>2</sub>Cl<sub>2</sub> (20 mL), a mixture of the inorganic support MnO<sub>2</sub> / SiO<sub>2</sub> was added (5.0g, 1: 4). The suspension was vigorously stirred for 15 min at room temperature and the solvent removed *in vacuo*, the remnant solid was irradiated in a microwave equipment at 900 W for 4 min. The solid mixture was thoroughly washed with EtOAc (3x25 mL), and the solvent removed to afford **5** as a crude in quantitative yield. The solid residue was purified by recrystallization (EtOH / CH<sub>3</sub>CN 5:1), to give **5** (138 mg, 88%) as pale yellow crystals. mp 169-170 °C. IR<sub>vmax</sub> (KBr) : 3032 (C-H Ar), 2934, (C-H Aliph.), 1655(C=O), 1600

(C=C)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 2.71 (t, 4H, 2'-H<sub>Pip</sub> y 6'-H<sub>Pip</sub>,  $J = 5.0$  Hz), 2.95 (t, 2H, 3-H,  $J = 7.4$  Hz), 3.22 (t, 4H, 3'-H<sub>Pip</sub>, 5'-H<sub>Pip</sub>,  $J = 5.0$  Hz), 3.24 (t, 2H, 2-H,  $J = 7.4$  Hz), 3.95 (s, 3H, Ar-OMe 4'-HBt or 7'-HBt), 3.96 (s, 3H, Ar-OMe 7'-HBt or 4'-HBt), 6.68 (d, 1H, 5'-H<sub>BT</sub>,  $J = 8.4$  Hz), 6.8 (d, 1H, 6'-H<sub>BT</sub>,  $J = 8.4$  Hz), 6.87 (t, 1H, 4''-H<sub>Ph</sub>,  $J = 7.4$  Hz), 6.94 (d, 2H, 2''-H<sub>Ph</sub>, 6''-H<sub>Ph</sub>,  $J = 8.5$  Hz), 7.27 (t, 2H, 3''-H<sub>Ph</sub> and 5''-H<sub>Ph</sub>,  $J = 8.3$  Hz), 8.15 (s, 1H, 3'-H<sub>BT</sub>).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$ : 36.7, 49.1(2C), 53.1(2C), 53.3, 55.8, 56.1, 104.6, 107.4, 116.1 (2C), 119.73, 129.1 (2C), 126.5, 131.5, 133.4, 142.8, 148.6, 150.7, 151.3, 193.3. HRMS:(EI) Calcd for  $\text{C}_{23}\text{H}_{26}\text{N}_2\text{O}_3\text{S}$  ( $\text{M}^+$ ): 410.16641, found: 410.16618.

**tert-butyl-4-(3-(4,7-dimethoxybenzo[*b*]thiophen-2-yl)-3-oxopropyl)piperazine-1-carboxylate (6).** Prepared from 1-(4,7-dimethoxy benzo[*b*]thiophen-2-yl)-2-propen-1-one **4**, (85 mg, 0.34 mmol) and N-Boc-piperazine, (63 mg, 0.34 mmol), to yield crude **6** (142 mg). The residue was purified by column chromatography ( $\text{CH}_2\text{Cl}_2$  / EtOAc 1:1) to yield **6** (133 mg, 90 %) as yellow crystals. mp 118-119 °C. IR  $\nu_{\text{max}}$  (KBr): 2972 (C-H aliph.), 1702 (NCOO *t*-Bu), 1665 (C=O), 1599 and 1583 (C=C Ar), 1182 (C-O).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ): 1.5 (s, 9H, *ter*-but), 2.50 (t, 4H, 2'-H<sub>Pip</sub> and 6'-H<sub>Pip</sub>,  $J = 4.8$  Hz), 2.91 (t, 2H, 3-H,  $J = 7.3$  Hz), 3.24 (t, 2H, 2-H,  $J = 7.3$  Hz), 3.47 (t, 4H, 3'-H<sub>Pip</sub>, 5'-H<sub>Pip</sub>,  $J = 4.8$  Hz), 3.97 (s, 3H, Ar-OMe 4'-HBt or C-7'-HBt), 3.98 (s, 3H, Ar-OMe 7'-HBt or C-4'-HBt), 6.71 (d, 1H, 5'-HBt,  $J = 8.5$  Hz), 6.82 (d, 1H, 6'-HBt,  $J = 8.5$  Hz), 8.15 (s, 1H, 3'-HBt).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$ : 28.4 (3C), 36.6, 42.8 (2C), 53.4, 53.6 (2C), 55.8, 56.1, 79.6, 104.7, 107.5, 126.4, 131.5, 132.3, 143.0, 148.6, 150.8, 154.7, 193.2. Anal. Calcd. for  $\text{C}_{22}\text{H}_{30}\text{N}_2\text{O}_5\text{S}$ : C, 60.81; H, 6.96; N, 6.45; S, 7.38. Found: C, 60.71; H, 6.97; N, 6.43; S, 7.39 %.

**1-(4,7-Dimethoxybenzo[*b*]thiophen-2-yl)-3-morpholinopropan-1-one (7).** Prepared from 1-(4,7-dimethoxybenzo[*b*]thiophen-2-yl)-2-propen-1-one **4**, (80 mg, 0.32 mmol) and morpholine, (28 mg, 0.32 mmol), to provide crude **7** (105 mg), which was purified by column chromatography ( $\text{CH}_2\text{Cl}_2$  / EtOAc 1:1), yielded (93 mg, 87%). mp 115-116 °C. IR  $\nu_{\text{max}}$  (KBr): 3067 (C-H Ar.), 2939 (C-H aliph.), 1656 (C=O), 1520 (C=C Ar).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  2.56 (t, 4H, 2-H'-Morph. and 6-H'-Morph.,  $J = 4.6$  Hz), 2.90 (t, 2H, 3-H,  $J = 7.3$  Hz), 3.24 (t, 2H, 2-H,  $J = 7.3$  Hz), 3.75 (t, 4H, 3-H'-Morph. and 5-H'-Morph.,  $J = 4.6$  Hz), 3.97 (s, 3H, Ar-OMe, 4'-HBt or C-7'-HBt), 3.98 (s, 3H, Ar-OMe, 7'-HBt or 4'-HBt), 6.71 (d, 1H, 5'-HBt,  $J = 8.5$  Hz), 6.82 (d, 1H, 6'-H<sub>BT</sub>,  $J = 8.5$  Hz), 8.15 (s, 1H, 3'-HBt).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  36.6, 53.6 (2C), 53.8, 55.8, 56.1, 67.0 (2C), 104.7, 107.5, 126.3, 131.5, 133.3, 143.0, 148.6, 150.8, 193.2. HRMS: (EI) Calcd for  $\text{C}_{17}\text{H}_{21}\text{NO}_4\text{S}$  ( $\text{M}^+$ ): 335.11913, found: 335.11707.

**1-(4,7-Dimethoxybenzo[*b*]thiophen-2-yl)-3-(pyrrolidin-1-yl)propan-1-one (8).** Prepared from 1-(4,7-dimethoxybenzo[*b*]thiophen-2-yl)-2-propen-1-one **4** (100mg, 0.40 mmol) and pyrrolidine (28.7 mg, 0.40 mmol), to produce crude **8** (114 mg). Purified by column chromatography ( $\text{CH}_2\text{Cl}_2$  / EtOAc 1:1), to yield (87 mg, 63%) as a yellow crystals. mp 54-55 °C. IR  $\nu_{\text{max}}$  (KBr): 2934 (C-H aliph.), 1658 (C=O), 1599 (C=C), 1262 (C-O).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.68 (m, 4H, 2xCH<sub>2</sub>-Pyrrol.), 2.51 (m, 4H, 2x CH<sub>2</sub>-Pyrrol.), 2.68-2.91 (m, 2H, 3-H), 3.43 (t, 2H, 2-H,  $J = 7.1$  Hz), 3.92 (s, 3H, Ar-OMe), 3.94 (s, 3H, Ar-OMe), 6.68 (d, 1H, 5-H,  $J = 8.4$  Hz), 6.77 (d, 1H, 6'-HBt,  $J = 8.4$  Hz), 8.16 (s, 1H, 3-H).  $^{13}\text{C}$ -NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$ : 23.5 (2C), 32.0,

50.6, 53.8 (2C), 55.8, 56.0, 104.6, 107.4, 126.1, 131.5, 133.2, 142.6, 148.5, 150.7, 192.7. Anal. Calcd. for  $C_{17}H_{21}NO_3S$  : C, 63.92; H, 6.63; N, 4.39; S, 10.04. Found : C, 63.81; H, 6.68; N, 4.32; S, 10.09 %.

**2,3-Dihydro-4-(4,7-dimethoxybenzo[*b*]thiophen-2-yl)-1*H*-benzo[*b*][1,5]-diazepine (9).** Prepared from 1-(4,7-dimethoxy benzo[*b*]thiophen-2-yl)-2-propen-1-one **4** (85 mg, 0.34 mmol) and *o*-phenylenediamine, (37 mg, 0.34 mmol), to give crude **9** (105 mg). Purified by column chromatography (EtOAc), yield **9** (78 mg, 68%) as orange needles. mp 69-70 °C. (EtOH) IR  $\nu_{\max}$  (KBr): 3386 (N-H), 1611 (C=N), 1580 (C=C).  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$ : 1.68 (s, 1H, NH), 3.22 (t, 2H, 3-H,  $J = 5.3$  Hz), 3.78 (t, 2H, 2-H,  $J = 5.3$  Hz), 3.96 (s, 3H, Ar-OMe 4'-HBt or 7'-HBt), 3.98 (s, 3H, Ar-OMe 7'-HBt or 4'-HBt), 6.67 (d, 1H, 5'-HBt,  $J = 8.5$  Hz), 6.72 (d, 1H, 9-H,  $J = 8.2$  Hz), 6.74 (d, 1H, 6'-HBt,  $J = 8.5$  Hz), 6.93 (t, 1H, 7-H or 8-H,  $J = 7.5$  Hz), 7.03 (td, 1H, 8-H or 7-H,  $J_o = 7.5$  Hz,  $J_m = 1.4$  Hz), 7.45 (dd, 1H, 6-H,  $J_o = 7.8$  Hz,  $J_m = 1.3$  Hz), 7.76 (s, 1H, 3'-HBt).  $^{13}C$ -NMR (75 MHz,  $CDCl_3$ )  $\delta$ : 33.6, 48.5, 55.7, 56.1, 104.4, 106.1, 116.3, 118.7, 120.0, 121.0, 127.3, 132.3, 132.4, 135.6, 141.5, 147.5, 148.7, 149.8, 161.0. HRMS : (EI) Calcd for  $C_{19}H_{18}N_2O_2S$  ( $M^+$ ) : 338.10890, found : 338.10868.

**1-(4,7-Dimethoxybenzo[*b*]thiophen-2-yl)-3-{4-[3-(4,7-dimethoxybenzo[*b*]thiophen-2-yl)-3-oxo-propyl]-piperazin-1-yl}-propan-1-one (10).** Prepared from 1-(4,7-dimethoxybenzo[*b*]thiophen-2-yl)-2-propen-1-one **4** (100 mg, 0.41 mmol) and 1-piperazine (18 mg, 0.20 mmol), to afford crude bis-addition product **10** quantitatively. The solid residue was purified by column chromatography ( $CH_2Cl_2$  / MeOH) (10:1) to yield pure **10** (91 mg, 78%) as a yellow solid, together with traces of its monoadduct. mp 183-184 °C. IR: 2930 (C-H aliph.), 1656 (C=O), 1522 (C=C), 1263 (C-O).  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$ : 2.73 (br.s, 8H, Pip.), 2.97 (br.s, 4H,  $-CH_2-$  3-H and 3'-H), 3.29 (br.s, 4H,  $-CH_2-$  2-H and 2'-H), 3.94 (s, 6H, OMe), 3.95 (s, 6H, OMe), 6.67 (d, 2H, 5-H and 5'-H,  $J = 6.3$  Hz), 6.79 (d, 2H, 6-H and 6'-H,  $J = 6.3$  Hz), 8.14 (s, 2H, 3-H and 3'-H).  $^{13}C$  NMR (75 MHz,  $CDCl_3$ )  $\delta$ : 36.7 (2C), 53.0 (4C), 53.2 (2C), 55.8 (2C), 56.0 (2C), 104.6 (2C), 107.4 (2C), 126.5 (2C), 131.5 (2C), 133.4 (2C), 142.9 (2C), 148.6 (2C), 150.8 (2C), 193.3 (2C). Anal. Calcd. for  $C_{30}H_{34}N_2O_6S_2$  : C, 61.83; H, 5.88; N, 4.81; S, 11.01. Found: C, 61.79; H, 5.84; N, 4.75; S, 11.07 %.

**1-(4,7-Dimethoxybenzo[*b*]thiophen-2-yl)-3-(1*H*-indol-3-yl)propan-1-one (11).** Prepared from 1-(4,7-dimethoxy benzo[*b*]thiophen-2-yl)-2-propen-1-one **4** (100 mg, 0.40 mmol) and 1(*H*)-indole (47 mg, 0.40 mmol) to produce crude **11**. Purification by column chromatography, (EtOAc / Hexane) (1:2) yielded (102mg, 70%) of pure product. mp: 148-150 °C. IR  $\nu_{\max}$ : 3414 (N-H), 3089 (C-H Arom.), 2899 (C-H aliph.), 1664 (C=O), 1264 (C-O).  $^1H$  NMR (300 MHz,  $CDCl_3$ ): 3.28 (t, 2H,  $CH_2$   $J = 7.9$  Hz), 3.42 (t, 2H,  $CH_2$   $J = 7.9$  Hz), 3.89 (s, 3H, Ar-OMe), 3.93 (s, 3H, Ar-OMe), 6.63 (d, 1H, 5'-HBt,  $J = 8.5$  Hz), 6.76 (d, 1H, 6'-HBt,  $J = 8.5$  Hz), 7.05 (d, 1H, 2''-H  $J = 2.0$  Hz), 7.14 (t, 1H, 5''-H or 6''-H,  $J = 7.5$  Hz), 7.20 (t, 1H, 6''-H or 5''-H,  $J = 7.5$  Hz), 7.35 (d, 1H, 7''-H  $J = 7.7$  Hz), 7.65 (d, 1H, 4''-H  $J = 7.7$  Hz), 7.96 (s, 1H, NH), 8.06 (s, 1H, 2'-H).  $^{13}C$  NMR (75 MHz,  $CDCl_3$ ): 20.0, 39.7, 55.7, 56.0, 104.5, 107.3, 111.2, 115.2, 118.7, 119.4, 121.6, 122.0, 126.3, 127.2, 131.5, 133.3, 136.3, 143.0, 148.6, 150.7, 194.3. HRMS : (EI) Calcd for  $C_{21}H_{19}NO_3S$  ( $M^+$ ): 365.10856, found: 365.10781.

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