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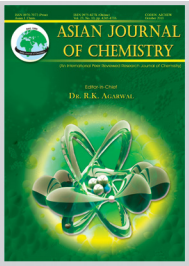

Synthesis and Dual 5-HT$_{1A}$/SSRI Activities of Some Novel Arylpiperazine Derivatives of Duloxetine

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A series of novel arylpiperazine derivatives of duloxetine were designed and synthesized from the key intermediate **5** by acylation, alkylation and reduction based on 5-HT$_{1A}$/SSRI drugs design strategies. Compound **5** was obtained through the reaction sequence including condensation, reduction, O-etherification, Von Braun reaction, hydrolysis reaction. Structures of the synthesized compounds were confirmed by MS, ^{1}H NMR and HRMS. Furthermore, these compounds were evaluated for their dual 5-HT^{1A}/5-HTT activities. The results indicated that all the compounds exhibited certain affinity to 5-HTT and 5-HT$_{1A}$ receptor.

Key Words: Antidepressants, Duloxetine, 5-HT$_{1A}$/5-HTT activities, Arylpiperazines.

INTRODUCTION

Selective serotonin (5-HT) reuptake inhibitors (SSRIs) are the most widely used antidepressants. But they have a delayed onset of action of 2-6 weeks[1]. To solve this problem, it is necessary to search and develop new drugs. The drugs design strategies focussing on incorporating a 5-HT$_{1A}$ pharmacophore into a SSRI pharmacophore have been proposed. These dual 5-HT$_{1A}$/ SSRI agents show a more immediate and complete antidepressant effect[2-17].

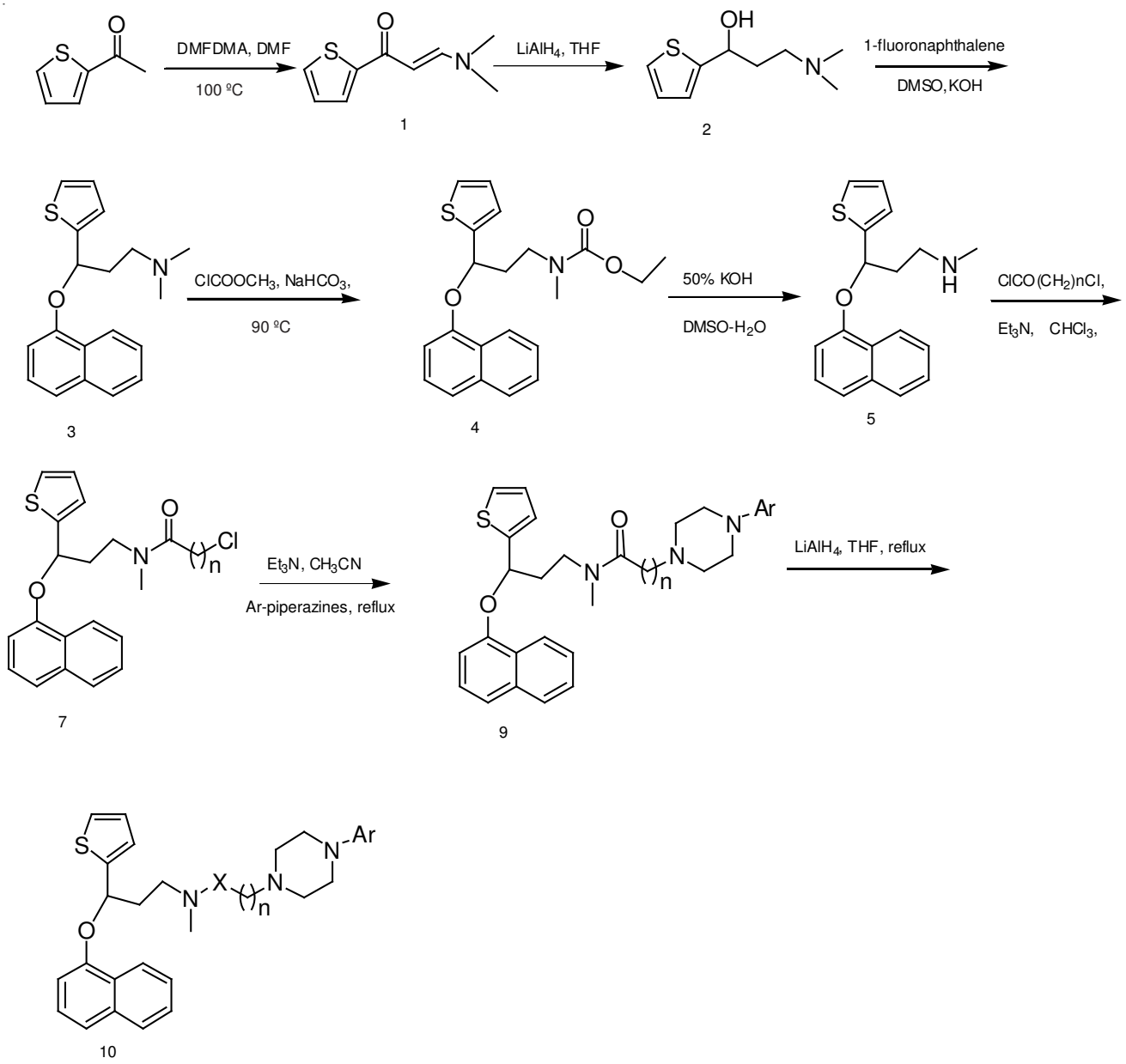
Duloxetine is a dual inhibitor of serotonin (SSRIs) and norepinephrine reuptake as an antidepressant drug. It can also be used for treating obsessive compulsive disorder and urinary incontinence[18]. Low affinities for neuronal receptors and dual inhibiting nature give duloxetine an edge over other existing antidepressants. On the other hand, arylpiperazines have also attracted attention because of their promising biological activities[19,20]. Furthermore, previous researches on diphenylsulfide-arylpiperazines derivatives for dual 5-HT$_{1A}$/SSRI activities have shown that they have potential dual activities of 5-HT$_{1A}$ receptor and 5-HT reuptake inhibition *in vitro* based on drugs design strategies of 5-HT$_{1A}$/SSRI[20-24]. Motivated by these facts, we introduced arylpiperazines to duloxetine with the aim at testing novel componds for dual 5-HT$_{1A}$/SSRI activities. In this paper, nine novel compounds were designed and synthesized according to the routes in **Scheme-I** and dual activities of 5-HT$_{1A}$ receptor and 5-HT reuptake inhibition *in vitro* were evaluated.

EXPERIMENTAL

All the reagents and solvents were purchased from common commerial suppliers and were used without further purification. Melting points were measured on a X4 apparatus and were uncorrected. ^{1}H NMR spectra was recorded using 500 MHz spectrometer in DMSO as the solvent with TMS as internal standard. MS were performed on a VGZAB-HS spectrometer (EI at 70 eV). HRMS was reporded on a microTOF-Q-10204 spectrometer.

Synthesis of 3-dimethylamino-1-(2-thienyl)-2-propenone (1): The mixture of acetyl thiophene (5.1 g, 0.04 mol), N,N-dimethyl formamide (25 mL) and N,N-dimethyl formamide dimethyl acetal (DMFDMA, 9.5 g, 0.08 mol) was heated to100 ºC for 3 h, then the mixture was evaporated to remove solvent. The residue was collected and recrystallized from ethyl acetate, to give compound **1** (6.7 g) as pale yellow powder, yield 92.1 %. m.p. 117-119 ºC; EI-MS, m/z: 180.9 (M^+), 148.0, 110.9, 98.0, 55.0, 42.0; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75 (d, J = 12.5 Hz, 1H), 7.60 (m, 1H, Th-H), 7.44 (m, 1H, Th-H), 7.05 (m, 1H, Th-H), 5.60 (d, J = 12.5 Hz, 1H), 3.08 (bs, 3H, N-CH_3), 2.88 (bs, 3H, N-CH_3).

Synthesis of N,N-dimethyl-3-hydroxy-3-(2-thienyl)-propylamine (2): To a suspension of lithium aluminium hydride (3.8 g, 0.1 mol) in THF (30 mL) was added compound **1** (3.6 g, 0.02 mol) at room temperature, then the mixture was refluxed for 8 h. After cooling, water (12 mL) and 15 % sodium hydroxide solution were added and stirred for 0.5 h. Filtrated



6a: $ClCH_2COCl$; **6b**: $ClCH_2CH_2COCl$; **6c**: $ClCH_2CH_2CH_2COCl$. **7a**: n = 1; **7b**: n = 2; **7c**: n = 3;
8a: Ar=2-OMe-phenyl; **8b**: Ar=3-F_3C-phenyl; **8c**: Ar=2-pyrimidyl

Scheme-I: Synthetic route of title compounds

and extracted with methylene chloride (40 mL × 3), the organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporated *in vacuo*. The residue was purified by recrystallization to afford **2** (3.4 g) as white powder, yield 95.6 %. m.p. 71-73 ºC (lit[23] 72-74 ºC); EI-MS, m/z: 185.1 (M^+), 139.1, 113.0, 85.0, 58.1, 30.1; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26-7.20 (m, 1H, Th-H), 6.98-6.90 (m, 2H, Th-H), 5.20-5.16 (m, 1H, CH), 2.69-2.51 (m, 2H, CH_2N), 2.29 (s, 6H, $N(CH_3)_2$), 1.97-1.90 (m, 2H, CH_2).

Synthesis of N,N-dimethyl-3-(1-naphthyloxy)-3-(2-thienyl)-propylamine (3): A suspension of **2** (2.2 g, 12 mmol) and potassium hydroxide (3.4 g, 0.06 mol) in a mixture of water (1 mL) and dimethyl sulfoxide (DMSO, 10 mL) was stirred at room temperature for 0.5 h, then 1-fluoronaphthalene (2.1 g, 14.4 mmol) was added and heated to 90 ºC for 12 h. After cooling to room temperature, the resulting mixture was poured into 10 mL water and extracted with methylene chloride (20 mL × 3), the organic layer was washed sequence with 2N hydrochloride and water, dried over anhydrous sodium sulfate, evaporated *in vacuo* and give compound **3** (3.1 g) as pale yellow oil[25], yield 82.8 %. EI-MS, m/z: 311.0, 255.0, 238.9, 201.0, 168.0, 144.0, 115.0, 58.1, 42.0; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.19 (m, 1H, Nap-H), 7.58 (m, 1H, Nap-H), 7.51 (m, 2H, Nap-H), 7.43 (m, 1H, Nap-H), 7.29 (m, 1H, Nap-H), 7.19 (m, 1H, Nap-H), 7.07 (m, 1H, Th-H), 6.92 (m, 1H, Th-H), 6.83 (m, 1H, Th-H), 5.01 (m, 1H, OCH), 2.41 (m, 2H, CH_2N), 2.30 (s, 6H, $N(CH_3)_2$), 2.10 (m, 2H, CH_2).

Synthesis of N-methyl-N-ethyloxyacyl-3-(1-naphthyloxy)-3-(2-thienyl)-propylamine (4): To a mixture of compound **3** (3.1 g, 10 mmol) and sodium bicarbonate (3.4 g, 0.4 mol) in toluene (20 mL) was added ethyl chloroformate (1.2 g, 12 mmol), the reaction mixture was heated to 90 ºC for 10 h,

then saturated sodium hydroxide solution (10 mL) was added and stirred 1 h. After cooling to room temperature, the organic layer was separated and the water layer was extracted with tolune (10 mL × 3), then the organic layer was combined and washed sequence with 1N hydrochloride and water, decoloured with activated carbon, dried by anhydrous sodium sulfate and evaporated *in vacuo* to give compound **4** (3.0 g) as pale yellow oil[25], yield 81.3 %. EI-MS, m/z: 369.2 (M^+), 315.1, 226.1, 116.1, 57.1, 44.1; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.42-8.39 (m, 1H, Nap-H), 7.82 (m, 1H, Nap-H), 7.55-7.50 (m, 2H, Nap-H), 7.43 (m, 1H, Nap-H), 7.31-7.27 (m, 1H, Nap-H), 7.19 (m, 1H, Nap-H), 7.10 (m, 1H, Th-H), 6.95 (m, 1H, Th-H), 6.86 (m, 1H, Th-H), 5.73-5.68 (m, 1H, OCH), 4.09-3.93 (m, 2H, OCH_2), 3.65-3.50 (m, 2H, NCH_2), 2.93 (s, 3H, NCH_3), 2.50-2.35 (m, 2H, CH_2), 1.24-1.03 (m, 3H, CH_3).

Synthesis of N-methyl-3-(1-naphthyloxy)-3-(2-thienyl)-propylamine (5): The mixture of compound **4** (3.7 g, 10 mmol), 50 % potassium hydroxide solution (4.8 g, 60 mmol) and DMSO (40 mL) was heated to 80 ºC for 6 h, after cooling to room temperature, the resulting mixture was poured into 40 mL water, extracted with ethyl acetate (40 mL × 3) and the organic layer was combined. Then, the solution of oxalic acid (1.3 g, 10 mmol) in methanol (20 mL) was added dropwise to the organic layer, then the resulting white precipitate was collected by filtration. The precipitate was dissloved in the mixture of water (20 mL) and methylene chloride (20 mL) and 10 % sodium hydroxide solution was added to adjust the pH value of the mixture to 9, extracted with methylene chloride (40 mL × 3), washed with water (40 mL × 3), dried by anhydrous sodium sulfate and evaporated *in vacuo* to give compound **5** (2.3 g) as brown oil[26], yield 77.4 %. EI-MS, m/z: 297.0 (M^+), 266.0. 239.0, 187.1, 144.0, 115.0, 44.0, 39.0; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.31 (m, 1H, Nap-H), 7.78 (m, 1H, Nap-H), 7.46 (m, 2H, Nap-H), 7.38 (m, 1H, Nap-H), 7.26 (m, 1H, Nap-H), 7.19 (m, 1H, Nap-H), 7.07(m, 1H, Th-H), 6.92 (m, 1H, Th-H), 6.83 (m, 1H, Th-H), 5.79 (m, 1H, OCH), 3.01 (m, 2H, CH_2N), 2.58 (s, 3H, NCH_3), 2.10 (m, 2H, CH_2).

General synthetic procedure for compounds 9a-i: To a stirred mixture of compound **5** (0.86 g, 2.9 mmol) in methylene chloride (40 mL) was added triethylamine (0.6 mL, 4.4 mmol) followed by one of compounds **6a-c** (3.2 mmol). The reaction mixture was stirred for 1.5 h at room temperature, poured into water (50 mL), extracted with methylene chloride (40 mL × 3), washed with water, dried by anhydrous sodium sulfate and evaporated *in vacuo* to give compound **7a-c**, yield 81.3-99.3 %. Without further purification, compound **7** were used directly in the next step.

To the mixture of compound **7** (0.45 g, 1.4 mmol), triethylamine (0.37 mL, 2.7 mol) and catalyst sodium iodide in acetonitrile (40 mL) was added one of compounds **8a-c** (1.2 mmol). The reaction mixture was heated to 80 ºC for 4 h, poured into water (50 mL), extracted with methylene chloride (40 mL × 3), washed with water, dried by anhydrous sodium sulfate and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel with ethyl acetate/ethanol (volume ratio from 1:0.8) to afford compound **9** as pale yellow oil.

N-[4-(2-Methoxy-phenyl-piperazinyl)acetyl]-N-methyl-3-(1-(1-naphthyloxy)-3-(2-thienyl)-propylamine (9a): yield 47.6 %; ESI-MS, m/z: 530.2 (M + H); ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.17-8.10 (m, 1H, Nap-H), 7.75 (m, 1H, Nap-H), 7.51-7.41 (m, 3H, Ar-H), 7.35-7.24 (m, 2H, Ar-H), 7.06-6.81 (m, 7H, Ar-H), 5.07 (m, 1H, OCH), 3.87(s, 3H, OCH_3), 3.59-3.52 (m, 4H, CH_2), 3.23-2.98 (m, 10H, CH_2), 2.99 (m, 3H, NCH_3), 2.43-2.30 (m, 2H, CH_2). HRMS (ESI) calcd. (%) for $C_{31}H_{36}N_3O_3S$ $[M + H]^+$ 530.2479. Found (%) 530.2497.

N-[4-(3-Trifluoromethyl-phenyl-piperazinyl)acetyl]-N-methyl-3-(1-(1-naphthyloxy)-3-(2-thienyl)-propylamine (9b): Yield 52.7 %; ESI-MS, m/z: 568.2 (M + H); ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.19-8.11 (m, 1H, Nap-H), 7.81 (m, 1H, Nap-H), 7.51-7.41 (m, 4H, Ar-H), 7.37-7.27 (m, 3H, Ar-H), 7.17 (m, 1H, Ar-H), 7.10-7.02 (m, 2H, Ar-H), 6.98-6.91 (m, 2H, Ar-H), 5.07 (m, 1H, OCH), 4.50-4.25 (m, 2H, CH_2), 3.94 (m, 2H, CH_2), 3.59-3.52 (m, 2H, CH_2), 3.43-3.21 (m, 6H, CH_2), 2.99-2.89 (m, 3H, NCH_3), 2.43-1.91 (m, 2H, CH_2). HRMS (ESI) calcd. (%) for $C_{31}H_{33}N_3O_2SF_3$ $[M + H]^+$ 568.2147. Found (%) 568.2279.

N-[4-(2-Pyrimidinyl-piperazinyl)acetyl]-N-methyl-3-(1-(1-naphthyloxy)-3-(2-thienyl)-propylamine (9c): Yield 55.3 %; ESI-MS, m/z: 502.2 (M + H); ^{1}H NMR (500 MHz, DMSO-d_6); δ 8.78 (m, 1H, Pm-H), 8.45 (m, 2H, Pm-H), 8.17-8.10 (m, 1H, Nap-H), 7.61-7.21 (m, 5H, Ar-H), 7.07-7.02 (m, 1H, Ar-H), 6.96-6.91 (m, 2H, Ar-H), 6.77 (m, 1H, Ar-H), 4.98 (m, 1H, OCH), 3.56-3.01 (m, 9H, CH_2, CH_3), 2.47-2.31 (m, 10H, CH_2); HRMS (ESI) calcd. (%) for $C_{28}H_{32}N_5O_2S$ $[M+H]^+$ 502.2298. Found (%) 502.2313.

N-[4-(2-Methoxy-phenyl-piperazinyl)propionyl]-N-methyl-3-(1-(1-naphthyloxy)-3-(2-thienyl)-propylamine (9d): yield 25.0 %; FAB-MS, m/z: 544.1 (M + H); ^{1}H NMR (500 MHz, DMSO-d_6); δ 8.18-8.09 (m, 1H, Nap-H), 7.81 (m, 1H, Nap-H), 7.52-7.41 (m, 3H, Ar-H), 7.36-7.26 (m, 2H, Ar-H), 7.09-6.88 (m, 7H, Ar-H), 5.05-4.95 (m, 1H, OCH), 3.89 (s, 3H, OCH_3), 3.55-2.78 (m, 17H, NCH_3, CH_2), 2.47-2.33 (m, 2H, CH_2); HRMS (ESI) calcd. (%) for $C_{31}H_{36}N_3O_3S$ $[M+H]^+$ 544.2634. Found (%) 544.2657.

N-[4-(3-Trifluoromethyl-phenyl-piperazinyl)propionyl]-N-methyl-3-(1-(1-naphthyloxy)-3-(2-thienyl)-propylamine (9e): Yield 25.0 %; FAB-MS, m/z: 582.1 (M + 1), 372.1, 307.1, 154.1, 80.2; ^{1}H NMR (500 MHz, DMSO-d_6); δ 8.19-8.11 (m, 1H, Nap-H), 7.81 (m, 1H, Nap-H), 7.51-7.41 (m, 4H, Ar-H), 7.37-7.27 (m, 4H, Ar-H), 7.17 (m, 1H, Ar-H), 6.98-6.91 (m, 3H, Ar-H), 5.07 (m, 1H, OCH), 3.64-3.45 (m, 4H, CH_2), 3.31-2.78 (m, 11H, CH_2, NCH_3), 2.45-2.21 (m, 4H, CH_2). HRMS (ESI) calcd. (%) for $C_{32}H_{35}N_3O_2SF_3$ $[M + H]^+$ 582.2402. Found (%) 582.2415.

N-[4-(2-Pyrimidinyl-piperazinyl) propionyl]-N-methyl-3-(1-(1-naphthyloxy)-3-(2-thienyl)-propylamine (9f): Yield 23.0 %; FAB-MS, m/z: 516.1 (M + H), 372.1, 307.1, 154.1, 80.2; ^{1}H NMR (500 MHz, DMSO-d_6); δ 8.80 (m, 1H, Pm-H), 8.47 (m, 2H, Pm-H), 8.19-8.09 (m, 1H, Nap-H), 7.50-7.41 (m, 3H, Ar-H), 7.36-7.27 (m, 2H, Ar-H), 7.08-7.00 (m, 1H, Ar-H), 6.99-6.92 (m, 2H, Ar-H), 6.80 (m, 1H, Ar-H), 5.01-4.93 (m, 1H, OCH), 3.56-2.97 (m, 9H, CH_2, CH_3), 2.47-2.17 (m, 12H, CH_2). HRMS (ESI) calcd. (%) for $C_{29}H_{34}N_5O_2S$ $[M+H]^+$ 516.2433. Found (%) 516.2457.

N-[4-(2-Methoxy-phenyl-piperazinyl)butyryl]-N-methyl-3-(1-(1-naphthyloxy)-3-(2-thienyl)-propylamine

(9g): Yield 62.6 %; FAB-MS, m/z: 558.1 (M +H), 452.1, 366.0, 299.1, 154.1, 76.3; ^{1}H NMR (500 MHz, DMSO-d_6); δ 8.18-8.09 (m, 1H, Nap-H), 7.81 (m, 1H, Nap-H), 7.52-7.41 (m, 4H, Ar-H), 7.36-7.25 (m, 2H, Ar-H), 7.07-6.68 (m, 6H, Ar-H), 4.99-4.93 (m, 1H, OCH), 3.89 (s, 3H, OCH_3), 3.48 (m, 4H, CH_2), 3.38-3.05 (m, 8H, CH_2), 2.96-2.83 (m, 3H, NCH_3), 2.45-1.78 (m, 6H, CH_2). HRMS (ESI) calcd. (%) for $C_{33}H_{40}N_3O_3S$ $[M + H]^+$ 558.2790. Found (%) 558.2811.

N-[4-(3-Trifluoromethyl-phenyl-piperazinyl)butyryl]-N-methyl-3-(1-(1-naphthyloxy)-3-(2-thienyl)-propylamine (9h): Yield 68.1 %; FAB-MS, m/z: 596.1 (M +H), 386.0, 233.1, 123.1, 66.3; ^{1}H NMR (500 MHz, DMSO-d_6); δ 8.18-8.09 (m, 1H, Nap-H), 7.81 (m, 1H, Nap-H), 7.45-7.41 (m, 4H, Ar-H), 7.36-7.27 (m, 4H, Ar-H), 7.17 (m, 1H, Ar-H), 6.97-6.90 (m, 3H, Ar-H), 5.01 (m, 1H, OCH), 3.94-3.48 (m, 4H, CH_2), 3.31-3.08 (m, 8H, CH_2), 2.92-2.78 (m, 3H, NCH_3), 2.35-1.68 (m, 6H, CH_2); HRMS (ESI) calcd. (%) for $C_{33}H_{37}N_3O_2SF_3$ $[M + H]^+$ 596.2559. Found (%) 596.2571.

N-[4-(2-Pyrimidinyl-piperazinyl)butyryl]-N-methyl-3-(1-(1-naphthyloxy)-3-(2-thienyl)-propylamine (9i): Yield 51.2 %; FAB-MS, m/z: 530.1 (M+H), 414.0, 307.0, 288.9, 154.0, 136.0, 58.3; ^{1}H NMR (500 MHz, DMSO-d_6); δ 8.76 (m, 1H, Pm-H), 8.43 (m, 2H, Pm-H), 8.17-8.09 (m, 1H, Nap-H), 7.52-7.43 (m, 3H, Ar-H), 7.36-7.25 (m, 2H, Ar-H), 7.07-7.02 (m, 1H, Ar-H), 6.97-6.91 (m, 2H, Ar-H), 6.78 (m, 1H, Ar-H), 4.98-4.94 (m, 1H, OCH), 3.54-2.80 (m, 15H, CH_2, CH_3), 2.47-1.81 (m, 6H, CH_2); HRMS (ESI) calcd. (%) for $C_{30}H_{36}N_5O_2S$ $[M + H]^+$ 530.2590. Found (%) 530.2616.

General synthetic procedure for compounds 10d-i

The mixture of lithum aluminium hydride ($LiAlH_4$, 0.2 g, 5.4 mmol) in tetrahydrofurane (THF, 20 mL) was added to solution of compound **9** (1.8 mmol) in THF (30 mL) and heated to reflux 12 h. After cooling to room temperature, the resulting mixture was added water (4 mL), 15 % sodium hydroxide solution (2 mL) and stirred for 0.5 h. The mixture was poured into water (50 mL), extracted with methylene chloride (40 mL × 3), washed with water, dried by anhydrous sodium sulfate and evaporated *in vacuo* to give compound **10** as pale yellow oil.

N-[4-(2-Methoxy-phenyl-piperazinyl)propyl]-N-methyl-3-(1-(1-naphthyloxy)-3-(2-thienyl)-propylamine (10d): Yield 37.7%; ESI -MS, m/z: 516.0 (M + H); ^{1}H NMR (500 MHz, DMSO-d_6); δ 8.19-8.10 (m, 1H, Nap-H), 7.81 (m, 1H, Nap-H), 7.50-7.42 (m, 3H, Ar-H), 7.38-7.24 (m, 2H, Ar-H), 7.08-6.89 (m, 7H, Ar-H), 5.10-5.01 (m, 1H, OCH), 3.86 (s, 3H, OCH_3), 3.56-2.74 (m, 17H, NCH_3, CH_2), 21-1.68 (m, 4H, CH_2); HRMS (ESI) calcd. (%) for $C_{31}H_{38}N_3O_2S$ $[M + H]^+$ 516.2685. Found (%) 516.2697.

N-[4-(3-Trifluoromethyl-phenyl-piperazinyl)propyl]-N-methyl-3-(1-(1-naphthyloxy)-3-(2-thienyl)-propylamine (10e): Yield 49.8 %; ESI -MS, m/z:554.4 (M + H); ^{1}H NMR (500 MHz, DMSO-d_6); δ 8.19-8.13 (m, 1H, Nap-H), 7.81 (m, 1H, Nap-H), 7.51-7.42 (m, 4H, Ar-H), 7.38-7.24 (m, 4H, Ar-H), 7.17 (m, 1H, Ar-H), 6.97-6.90 (m, 3H, Ar-H), 5.10 (m, 1H, OCH), 3.64-3.45 (m, 4H, CH_2), 3.29-2.80 (m, 8H, CH_2), 2.78-2.74 (m, 5H, NCH_3, $NCHCH_2$), 2.21-1.61 (m, 4H, CH_2); HRMS(ESI) calcd. (%) for $C_{31}H_{35}F_3N_3OS$ $[M + H]^+$ 554.2453. Found (%) 554.2461.

N-[4-(2-Pyrimidinyl-piperazinyl)propyl]-N-methyl-3-(1-(1-naphthyloxy)-3-(2-thienyl)-propylamine (10f): Yield 59.8 %; ESI -MS, m/z: 488.1 (M + H); ^{1}H NMR (500 MHz, DMSO-d_6); δ 8.80 (m, 1H, Pm-H), 8.47 (m, 2H, Pm-H), 8.19-8.13 (m, 1H, Nap-H), 7.50-7.42 (m, 3H, Ar-H), 7.38-7.24 (m, 2H, Ar-H), 7.08-6.98 (m, 1H, Ar-H), 6.97-6.80 (m, 3H, Ar-H), 5.06-4.97 (m, 1H, OCH), 3.51-3.00 (m, 9H, CH_2, CH_3), 2.78-2.74 (m, 5H, NCH_3, $NCHCH_2$), 2.47-2.31 (m, 5H, CH_2), 2.21-1.67 (m, 2H, CH_2); HRMS (ESI) calcd. (%) for $C_{28}H_{34}N_5OS$ $[M + H]^+$ 488.2484. Found (%) 488.2491.

N-[4-(2-Methoxy-phenyl-piperazinyl)butyl]-N-methyl-3-(1-(1-naphthyloxy)-3-(2-thienyl)-propylamine (10g): Yield 49.8 %; ESI-MS, m/z: 530.4 (M + H); ^{1}H NMR (500 MHz, DMSO-d_6); δ 8.18-8.09 (m, 1H, Nap-H), 7.79 (m, 1H, Nap-H),7.53-7.40 (m, 4H, Ar-H), 7.38-7.21 (m, 2H, Ar-H), 7.01-6.68 (m, 6H, Ar-H), 5.06 (m, 1H, OCH), 3.91 (m, 3H, CH_3), 3.54-3.48 (m, 4H, CH_2), 3.31-3.08 (m, 8H, CH_2), 2.92-2.78 (m, 3H, NCH_3), 2.32-1.43 (m, 8H, CH_2); HRMS (ESI) calcd. (%) for $C_{321}H_{40}N_3O_2S$ $[M + H]^+$ 530.2841. Found (%) 530.2850.

N-[4-(3-Trifluoromethyl-phenyl-piperazinyl)butyl]-N-methyl-3-(1-(1-naphthyloxy)-3-(2-thienyl)-propylamine (10h): Yield 68.9 %; ESI -MS, m/z:568.2 (M + H); ^{1}H NMR (500 MHz, DMSO-d_6); δ 8.19-8.11 (m, 1H, Nap-H), 7.81 (m, 1H, Nap-H), 7.45-7.41 (m, 4H, Ar-H), 7.36-7.27 (m, 4H, Ar-H), 7.11-7.07 (m, 1H, Ar-H), 6.97-6.89 (m, 3H, Ar-H), 4.98 (m, 1H, OCH), 3.96-3.48 (m, 4H, CH_2), 3.34-3.04 (m, 8H, CH_2), 2.93 (s, 3H, NCH_3), 2.31-1.42 (m, 8H, CH_2); HRMS (ESI) calcd. (%) for $C_{32}H_{37}N_3OSF_3$ $[M + H]^+$ 568.2609 found (%) 568.2618.

N-[4-(2-Pyrimidinyl-piperazinyl)butyl]-N-methyl-3-(1-(1-naphthyloxy)-3-(2-thienyl)-propylamine (10i): Yield 90.2 %; ESI -MS, m/z: 502.4 (M + H); ^{1}H NMR (500 MHz, DMSO-d_6); δ 8.76 (m, 1H, Pm-H), 8.45 (m, 2H, Pm-H), 8.19-8.11 (m, 1H, Nap-H), 7.53-7.41 (m, 3H, Ar-H), 7.38-7.31 (m, 2H, Ar-H), 7.11-7.06 (m, 1H, Ar-H), 6.97-6.89 (m, 2H, Ar-H), 6.77 (m, 1H, Ar-H), 4.94 (m, 1H, OCH_3), 3.57-3.43 (m, 4H, CH_2), 3.17-3.04 (m, 10H, CH_2), 2.75 (m, 3H, NCH_3), 2.63 (m, 2H, $OCHCH_2$), 1.61-1.39 (m, 4H, CH_2); HRMS (ESI) calcd. (%) for $C_{29}H_{36}N_5OS$ $[M + H]^+$ 502.2641. Found (%) 502.2648.

Biological activities: The assays were performed by the method reported by Orús *et al.*[3]. Fluoxetine and 8-OH-DPAT were used as reference compounds. The experimental results of binding to 5-HT transporter and 5-HT_{1A} receptor were shown in Table-1. As can be seen, all of the target compounds exhibited low to moderate affinity to 5-HT transporter and 5-HT_{1A} receptor. Compounds **10f** and **10i** showed moderate dual 5- HT_{1A}/SSRI activities(5-HTT 69 and 65 % inhib. And 5-HT1A 64 and 72 %, respectively). Change of the space length in the arylpiperazine component has a little effect on the binding affinity for 5-HTT and 5-HT_{1A} receptor. In most case, a 4-carbon chain resulted in slightly higher 5-HTT affinity than a 2-carbon or a 3-carbon chain. The highest 5-HTT activity was obtained when 2-pyrimidylpiperazine (**10f**) was introduced in 2-carbon chain derivatives. In each series of target compounds, the 2-methoxy-phenyl derivatives displayed the best 5-HT_{1A} affinity (**9a, 10d, 10g**). In conclusion, these synthesized

TABLE-1
BIOLOGICAL DATA FOR TARGET COMPOUNDS **9a-c** AND **10d-i**

Compound	x	n	Ar	5-HTT % inhib@ 1 μM	5-HT_{1A} % inhib@ 1 μM
Fluoxetine	–	–	–	100	–
8-OH-DPAT	–	–	–	–	100
9a	C=O	1	2-OCH_3-Phenyl	24	62
9b	C=O	1	3-CF_3-Phenyl	30	53
9c	C=O	1	2-Pyrimidyl	51	34
10d	CH_2	2	2-OCH_3-Phenyl	15	87
10e	CH_2	2	3-CF_3-Phenyl	28	56
10f	CH_2	2	2-Pyrimidyl	69	64
10g	CH_2	3	2-OCH_3-Phenyl	50	66
10h	CH_2	3	3-CF_3-Phenyl	56	35
10i	CH_2	3	2-Pyrimidyl	65	72

compounds showed certain affinity to 5-HT transporter and 5-HT_{1A} receptor.

RESULTS AND DISCUSSION

The general synthetic route of compounds **10d-i** was outlined in **Scheme-I**. Compound **2** was obtained by reduction β-enaminoketone using lithium aluminium hydride (LAH) with the yield of 82.4 %, to our knowledge, which was not reported in the literature. Using O-etherification reaction, compound **3** could be prepared in good yield in the presence of KOH at 90 ºC. Compound **3** reacted with ethyl chloroformate in tolune in the presence of sodium bicarbonate as a base through Von Braun reaction to give compound **4** with the yield of 81.3 %. During this process, ethyl chloroformate was used instead of the expensive reagents such as phenyl chloroformate and trichloroethyl chloroformate. Reaction of compound **4** with 50 % potassium hydroxide in DMSO furnished compound **5** in good yield (77.4 %). Subsequently, intermediate **5** was reacted with various substituted acyl chloride to afford **7a-c** in methylene chloride with triethylamine as acid binding reagent. Compounds **10** were prepared from compound **7** *via* N-alkylation, followed by reduction of carbonyl to methylene using $LiAlH_4$. The structures of compounds **10d-i** and intermediates were confirmed using MS, ^1H NMR and HRMS.

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