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New 3-(4-arylpiperazin-1-yl)-1-(benzo[*b*]thiophen-3-yl)-2-methylpropanol derivatives: Synthesis and evaluation for dual 5-HT_{1A}/SSRI activities

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Abstract

A series of 3-(4-arylpiperazin-1-yl)-1-(benzo[*b*]thiophen-3-yl)-2-methylpropanol derivatives were designed and synthesized based on 5-HT_{1A}/SSRI drugs design strategies. The synthesized compounds were evaluated for their dual 5-HT_{1A}/5-HTT activities.

Keywords: Antidepressants; Arylpiperazines; 5-HT_{1A}/SSRI; 5-HT transporter; 5-HT_{1A} receptor

Selective serotonin (5-HT) reuptake inhibitors (SSRIs) are effective in major depression. However, there are two serious problems in the pharmacological treatment of depression such as side effects and a delayed onset of action of 2–6 weeks [1]. Therefore, the drugs design strategies focusing on incorporating a 5-HT_{1A} antagonist pharmacophore into a SSRI pharmacophore have been proposed [2–18]. This dual 5-HT_{1A}/SSRI agent shows a more immediate and complete antidepressant effect.

Long chain arylpiperazines are important compounds which possess potent and selective affinity to 5-HT_{1A} receptor. Their general chemical structure consists of an alkyl chain attached to the N4 atom of the piperazine moiety. Monge group reported that a new series of 3-(4-arylpiperazin-1-yl)-1-(benzo[*b*]thiophen-3-yl)propanol derivatives showed moderate to high affinity at 5-HT transporter (5-HTT) and 5-HT_{1A} receptor [2–5]. Their design strategies were based on the coupling of benzo[*b*]thiophene derivatives with long arylpiperazines. But branched chain arylpiperazines derivatives coupling benzo[*b*]thiophene have not been studied for their dual 5-HT_{1A}/5-HTT activities so far. So we think this work were important for our series of researchment.

With above-mentioned knowledge, we hypothesized that add a branched methyl group on alkyl chain of 3-(4-arylpiperazin-1-yl)-1-(benzo[*b*]thiophen-3-yl)propanol derivatives could improve the affinity at 5-HTT and 5-HT_{1A} receptor and represent a new class of compounds with dual 5-HT_{1A}/SSRI activities (Fig. 1). Furthermore, we have synthesized several 3-(4-arylpiperazin-1-yl)-1-(thiophen-2-yl)propanol derivatives which are not reported by Monge's

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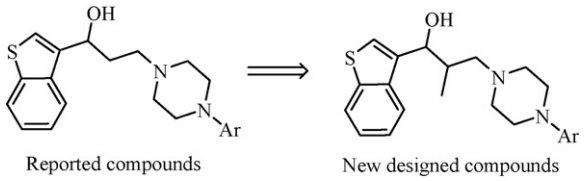
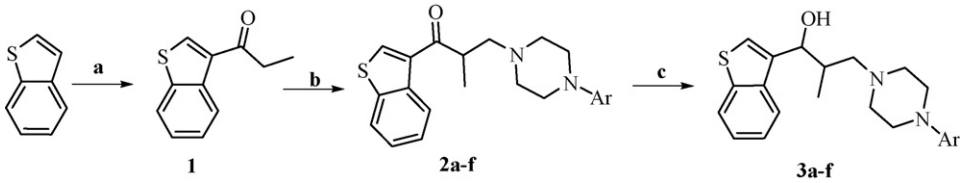


Fig. 1. Designed 3-(4-arylpiperazin-1-yl)-1-(benzo[*b*]thiophen-3-yl)-2-methylpropanol derivatives.



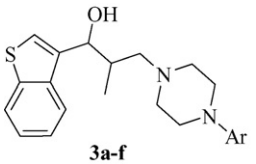
Scheme 1. Reagents and conditions: (a) BF3, propanoic anhydride, 114 °C, 1 h, 80%; (b) CH_2O, arylpiperazines, ethanol, reflux; 60% (c) ethanol, NaBH4, rt. 75%.

group [2–5]. In this letter, we disclosed our initial investigation of 3-(4-arylpiperazin-1-yl)-1-(benzo[*b*]thiophen-3-yl)-2-methylpropanol derivatives and 3-(4-arylpiperazin- 1-yl)-1-(thiophen-2-yl)propanol derivatives on synthesis and evaluation for their dual activity at the 5-HTT and 5-HT_{1A} receptor.

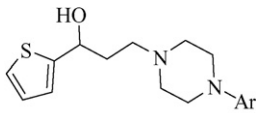
Scheme 1 showed the synthesis of target compounds. Compound **1** was synthesized from benzo[*b*]thiophene by classical Friedel–Craft acylation with propanoic anhydride and BF_3, and compounds **2a–f** were synthesized by the Mannich reaction of **1** and arylpiperazines with paraformaldehyde in refluxing ethanol. Latter, reduction of the corresponding carbonyl derivatives **2a–f** with sodium borohydride in ethanol to give the target compounds 3**a–f** [4]. 3-(4-Arylpiperazin-1-yl)-1-(thiophen-2-yl)propanol derivatives **4–8** were prepared from thiophene by the similar synthesized methods of **2a–f**. The simple spectroscopic data of selected compounds were shown in references [4,19].

The affinities to 5-HTT and 5-HT_{1A} receptors of synthesized compounds were evaluated using a protocol similar to that of Orús et al. [5]. Fluoxetine and 8-OH-DPAT were used as reference compounds. The biological results of target compounds were summarized in Table 1. All of the target compounds exhibited lower affinity to 5-HTT but moderate

Table 1
Biological data for target compounds and reference compounds



3a-f



4-8

Compound	Ar	5-HTT %inhib@1 μM	5-HT_{1A} %inhib@1 μM
Fluoxetine		100	
8-OH-DPAT			100
3a	2-OCH_3-phenyl	35	92
3b	2,3-Di-Cl-phenyl	58	96
3c	2,3-Di-CH_3-phenyl	44	91
3d	4-OCH_3-phenyl	62	55
3e	3-Cl-phenyl	2	90
4	2-OCH_3-phenyl	7	88
5	2,3-Di-Cl-phenyl	24	91
6	2,3-Di-CH_3-phenyl	23	89
7	Phenyl	43	53
8	3-CF_3-phenyl	7	95

to high affinity to 5-HT_{1A} receptor. Although both series of compounds all showed lower affinity to 5-HTT benzo[*b*]thiophene derivatives are more potent than the corresponding thiophene derivatives (**3a–c** vs. **4–6**). This conclusion explained that benzo[*b*]thiophene structure was important ligand for the 5-HTT. At this point, the introduction of different functional groups in the benzo[*b*]thiophene ring seemed to be needed to obtain a higher 5-HTT affinity. For affinity to 5-HT_{1A} receptor, benzo[*b*]thiophene derivatives and corresponding thiophene derivatives all showed good results except compounds **3d** and **7**. Results showed arylpiperazines structure were important for affinity at the 5-HT_{1A} receptor. Theses findings suggested that structural optimization is needed for obtaining new compounds with potent affinity to both receptors.

In conclusion, we have designed and synthesized a novel class of 3-(4-arylpiperazin-1-yl)-1-(benzo[*b*]thiophen-3-yl)-2-methylpropanol derivatives with affinity to both 5-HT_{1A} and 5-HTT receptors. All of the target compounds exhibited low affinity to 5-HTT but moderate to high affinity to 5-HT_{1A} receptor. More studies are currently underway in our laboratory to create molecules which are expected to have more potent to both 5-HTT and 5-HT_{1A} receptor.

Acknowledgments

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[19] Spectroscopic data of selected compounds: **3a**: ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.91–7.71 (m, 3H), 7.42–7.27 (m, 3H), 7.30 (m, 1H), 7.00 (m, 2H), 5.75 (bs, 1H), 4.13 (s, 3H), 3.81–2.65 (m, 10H), 2.03 (m, 1H), 1.20 (m, 3H). MS (*m*/*z*): 43.0 (19), 91.1 (22), 163.0 (60), 205.1 (100), 233.1 (5), 396.2 (M+, 27). **3b**: ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.88 (m, 1H), 7.76 (m, 1H), 7.56 (m, 1H), 7.35 (m, 2H), 7.33–7.0 (m, 3H), 5.71 (bs, 1H), 3.89–3.69 (m, 5H), 3.54 (m, 1H), 3.42 (m, 1H), 3.20 (m, 2H), 2.81–2.72 (m, 2H), 1.83 (m, 1H), 1.26 (m, 3H). MS (*m*/*z*): 27.0 (73), 56.1 (28), 161.1 (20), 174.0 (7), 243.1 (100), 434.2 (M+, 100). **3c**: ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.86 (m, 1H), 7.77 (m, 1H), 7.54 (s, 1H), 7.39–7.34 (m, 3H), 7.26–7.19 (m, 2H), 5.77 (bs, 1H), 4.69–4.49 (m, 4H), 3.87 (m, 2H), 3.71–3.66 (m, 2H), 3.45 (m, 1H), 3.03(m, 2H), 2.64–2.54 (m, 6H), 2.02 (m, 1H), 1.25 (m, 3H). MS (*m*/*z*): 28.0 (12), 70.0 (16), 132.0 (10), 203.1 (100), 394.0 (M+, 18). **3d**: ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.86 (m, 1H), 7.70–7.27 (m, 5H), 6.95 (m, 3H), 5.72 (bs, 1H), 4.10 (s, 3H), 3.81–2.65 (m, 10H), 2.10 (m, 1H), 1.25 (m, 3H). MS (*m*/*z*): 43.0 (50), 57.1 (44), 150.1 (100), 192.1 (48), 234.1 (9), 396.1 (M+, 10). **3e**: ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.92 (m, 2H), 7.38 (m, 2H), 7.15 (m, 2H), 6.91–6.76 (m, 3H), 5.74 (d, 1H), 3.85–2.71 (m, 10H), 1.93 (m, 1H), 1.28 (m, 3H). MS (*m*/*z*): 91.0 (32), 163.0 (100), 209.0 (74), 223.0 (6), 400.0 (M+, 14). **4**: ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.26–7.22 (m, 1H), 7.03–6.97 (m, 2H), 6.94–6.88 (m, 3H), 6.88 (d, 1H), 5.23 (t, 1H), 3.87 (s, 3H), 3.16 (m, 4H), 2.81 (m, 6H), 2.06 (m, 2H). MS (*m*/*z*): 42.1 (40), 56.1 (44), 120.1 (38), 205.2 (100), 219.2 (43), 332.2 (M+, 86). **5**: ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.29–7.27 (m, 1H), 7.23–7.19 (m, 2H), 7.05–6.99 (m, 3H), 5.29 (t, 1H), 3.17 (m, 4H), 2.86 (m, 6H), 2.11 (m, 2H). MS (*m*/*z*): 43.0 (32), 56.1 (30), 111.0 (9), 173.9 (10), 243. (100), 370.0 (M+, 44). **6**: ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.31–7.27 (m, 1H), 7.14 (t, 1H), 7.04 (t, 1H), 6.96 (m, 3H), 5.29 (t, 1H), 3.02 and 2.86 (m, 10H), 2.32 (s, 3H), 2.27 (s, 3H), 2.11 (m, 2H) **7**: ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.35–7.27 (m, 3H), 7.04–6.92 (m, 5H), 7.32–7.26 (m, 5H), 5.29 (t, 1H), 3.35 (m, 4H), 2.92–2.82 (m, 6H), 2.13 (m, 2H). MS (*m*/*z*): 28.0 (8), 70.0 (24), 105.0 (25), 132.0 (17), 175.0 (100), 302.0 (M+, 62). **8**: ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.77–7.59 (m, 5H), 7.22–7.04 (m, 2H), 5.45 (bs, 1H), 3.76–3.45 (m, 10H), 2.40 (m, 2H). MS (*m*/*z*): 43.0 (14), 70.1 (20), 145.0 (10), 188.1 (14), 243.1 (100), 370.1 (M+, 44).