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Design, synthesis, and biological evaluation of arylpiperazine–benzylpiperidines with dual serotonin and norepinephrine reuptake inhibitory activities

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ABSTRACT

The limitations of established serotonin (5-hydroxytryptamine, 5-HT) and norepinephrine (NE) reuptake inhibitors necessitate the development of safer and more effective therapeutic agents. Based on the structures of 4-benzylpiperidine carboxamides and trazodone, arylpiperazine–benzylpiperidines with chemical scaffolds different from those of marketed drugs were designed, synthesized, and evaluated for their neurotransmitter reuptake inhibitory activities. The majority of the synthesized compounds showed greater NE than 5-HT reuptake inhibition. The activities were even greater than those of the standard drug, venlafaxine hydrochloride were. The derivatives with a three-carbon linker showed better activities than the derivatives with a two-carbon linker. Among the newly synthesized compounds, **2d** exhibited the strongest reuptake inhibition of the neurotransmitters (IC_{50} = 0.38 μM for NE and 1.18 μM for 5-HT). The biological activity data demonstrate that arylpiperazine–benzylpiperidines have the potential to be developed as a new class of therapeutic agents to treat neuropsychiatric and neurodegenerative disorders.

1. Introduction

Serotonin and norepinephrine transporters regulate synaptic cleft concentrations of the corresponding neurotransmitters, serotonin (5-hydroxytryptamine, 5-HT) and norepinephrine (NE), via a reuptake mechanism.[1–5] 5-HT and NE are involved in the control of human behaviors such as mood, sleep, pain, appetite, aggression, and sexual activity.[6,7] Reduction in the synaptic levels of 5-HT and NE is associated with various neuropsychiatric and neurodegenerative disorders, such as attention deficit hyperactivity disorder, anxiety, and depression.[8–15] One of the attractive approaches to the treatment of these disorders is inhibition of reuptake of the neurotransmitters to increase their concentrations in the synaptic cleft.[16–21]

Dual 5-HT and NE reuptake inhibitors such as duloxetine, venlafaxine, and milnacipran (Fig. 1) have been used for the treatment of disorders, including depression, anxiety, and painful peripheral neuropathy.[22–27] However, these drugs have several limitations and cause side effects. Suicidal risk is high in patients prescribed duloxetine and venlafaxine. Duloxetine can cause hepatotoxicity and severe cutaneous hypersensitivity reactions. Treatment with venlafaxine can exacerbate or trigger migraines, and the patients may develop potentially life-threatening serotonin syndrome. Moreover, all of these dual reuptake inhibitors may cause cardiac disorders such as arterial hypertension, tachycardia, and arrhythmias.[28–32]

A common strategy to avoid drug-related side effects is to design molecules with a different chemical scaffold. With this fact in mind, we successfully developed 4-benzylpiperidine carboxamides as dual reuptake inhibitors.[33] Inspired by the initial success of the 4-benzylpiperidine carboxamides and the quest to identify safe and effective dual reuptake inhibitors, we designed a series of arylpiperazine–benzylpiperidines (Fig. 2). An arylpiperazine–benzylpiperidine derivative is a hybrid structure of 4-benzylpiperidine carboxamide and trazodone. Trazodone, a 5-HT reuptake inhibitor, was considered for the design of new dual reuptake inhibitors since it has structural similarity with 4-benzylpiperidine carboxamides (Ar1–linker–Ar2) and exhibits a reduced onset of action with no side effects commonly displayed by conventional selective 5-HT reuptake inhibitors.[34–41] The details of the synthetic pathways employed, biological evaluation, and structure–activity relationship of these compounds are discussed in the following sections.

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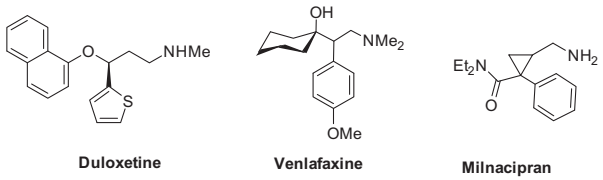


Figure 1. Some of the marketed dual serotonin (5-hydroxytryptamine, 5-HT) and norepinephrine (NE) reuptake inhibitors.

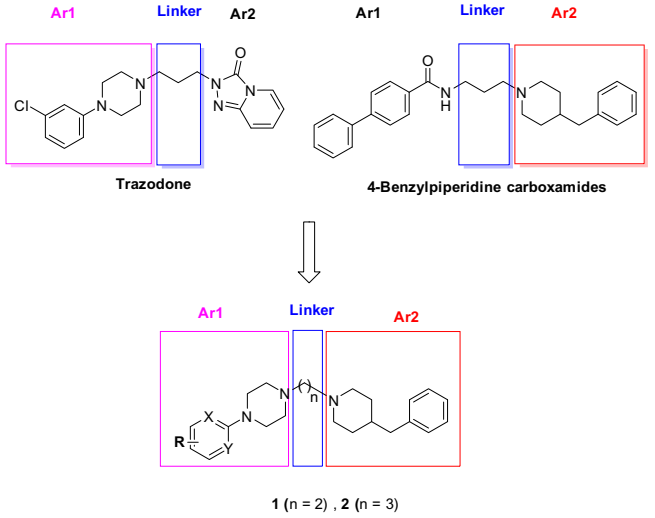


Figure 2. Design of arylpiperazine–benzylpiperidines **1** and **2**.

2. Chemistry

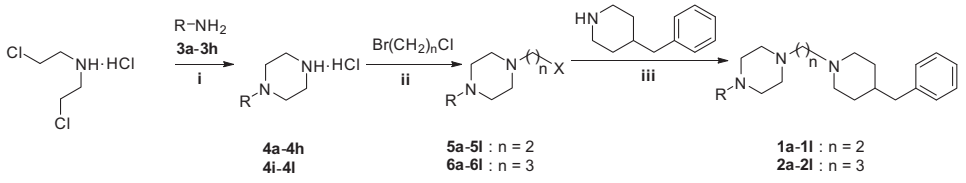
The detailed synthetic procedures for obtaining arylpiperazine–benzylpiperidines are shown in Scheme 1. Various aromatic amines, **3a–3h**, were reacted with bis(2-chloroethyl)amine hydrochloride to obtain 4-phenylpiperazine hydrochloride salts **4a–4h** (**4i–4l** were commercially available). Substitution reactions between 4-phenylpiperazines **4a–4l** and 1-bromo-2-chloroethane or 1-bromo-3-chloropropane gave various haloalkyl-4-phenylpiperazines, **5a–5l** ($n = 2$) and **6a–6l** ($n = 3$). Finally, arylpiperazine–benzylpiperidines **1a–1l** and **2a–2l** were obtained by substitution reactions of **5a–5l** and **6a–6l** with 4-benzylpiperidine, respectively.

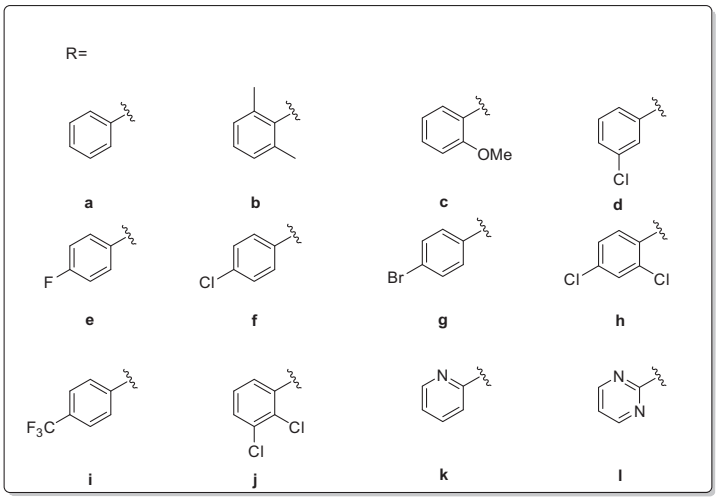
3. Results and discussion

3.1. Biological assay

Inhibition of 5-HT and NE reuptake was assessed using a neurotransmitter uptake assay. Human embryonic kidney 293 (HEK-293) cells transfected with human serotonin transporter (hSERT) or human norepinephrine transporter (hNET) were used in this assay. The 5-HT and NE reuptake-inhibiting activities of the arylpiperazine–benzylpiperidines are presented in Table 1.

The 5-HT reuptake-inhibiting activities of the arylpiperazine–benzylpiperidine derivatives, measured relative to that of venlafaxine·HCl, were 0.08–2.83. Consistent with our previous results,[33] most of the arylpiperazine–benzylpiperidines with three carbon units in the linker displayed better 5-HT reuptake inhibition than the derivatives with two carbon units. Interestingly, the activity of 2-Me compound **1c** increased significantly (9-fold) when the length of the linker was extended from two to three carbons. However, compounds **1a**, **1f**, and **1l** with shorter linkers were more effective than their longer-linker analogs **2a**, **2f**, and **2l**. The 5-HT reuptake inhibitory activities of the derivatives with mono–halogen substitution were in the following order: 3-Cl (**1d**) = 4-F (**1e**) < 4-Cl (**1f**) < 4-Br (**1g**) for the compounds with two-carbon-unit linkers and 4-Br (**2g**) > 3-Cl (**2d**) > 4-Cl (**2f**) > 4-F (**2e**) for the compounds with three-carbon-unit linkers. The derivatives with





Scheme 1. Synthesis of arylpiperazine–benzylpiperidines **1** and **2**. Reagents and conditions: (i) diethylene glycol monomethyl ether, 150 °C; (ii) K_2CO_3, acetone, room temperature (rt); (iii) dimethyl sulfoxide (DMSO), triethylamine (TEA), 100 °C.