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Research paper

Synthesis and antidepressant-like activity of novel aralkyl piperazine derivatives targeting SSRI/5-HT$_{1A}$/5-HT$_7$

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ABSTRACT

A series of novel aralkyl piperazine derivatives were synthesized, and evaluated for their serotonin reuptake inhibitory and 5-HT$_{1A}$/5-HT$_7$ receptors affinities activity. Antidepressant activities *in vivo* of the compounds were screened using the forced swimming test (FST) and tail suspension test (TST). The results indicated that compounds **21k** (RUI, $IC_{50} = 31$ nM; 5-HT$_{1A}$, 5-HT$_7$, $k_i = 62$, 12 nM) and **21n** (RUI, $IC_{50} = 25$ nM; 5-HT$_{1A}$, 5-HT$_7$, $k_i = 28$, 3.3 nM) exhibited high affinities for the 5-HT$_{1A}$/5-HT$_7$ receptors coupled with potent serotonin reuptake inhibition. Specifically, the most promising compound **21n** possessed a good oral pharmacokinetic properties and an acceptable hERG profile, and showed potent antidepressant-like effect in the FST and TST models.

1. Introduction

Depression is a debilitating disease that is characterized by low mood, slow thought and mental disorder [1]. According to the World Health Organization (WHO), depression, especially major depression disorder, would be the second leading cause of disability worldwide by the year 2020 [2]. Over the past six decades, about six major classes of monoamine based drugs have been developed in the therapy of depression [3]. Despite the extensive use of antidepressant drugs, there are still significant unmet needs in the treatment of depression, including a long onset of action, moderate patient response, and numerous adverse effects such as nausea/emesis, weight gain, insomnia and sexual dysfunction [4,5]. Recently, there has been important achievement of antidepressant development, which interacts with dual or multiple targets. The combination of serotonin transporter (SERT) inhibition with various 5-HT receptor subtypes seems to be one of the most valuable approach to antidepressive therapy [6]. Recent clinical research has demonstrated that pindolol could accelerate antidepressants onset time and enhance SSRIs beneficial effects by affecting 5-HT$_{1A}$ receptor [7]. Similarly, the approved antidepressant vilazodone with high affinity and selectivity for 5-HT transporter and 5-HT$_{1A}$ receptor displayed fast antidepressant efficacy with minimal adverse effects [8]. Moreover, the combined administration of low doses of an SSRI with selective 5-HT$_7$ receptor antagonist (SB-269970) was also found active in behavioral models of depression [9]. Additionally, recent research has indicated that the vortioxetine showed obvious cognitive enhancement effects through blockade of 5-HT$_7$ receptor [10]. Hence, it stands to reason that agents with dual or multiple binding affinities to SERT/5-HT$_{1A}$/5-HT$_7$ may be beneficial as treatment options for depression and other cognitive impairment disorders (Fig. 1).

Earlier study by Mewshaw et al. showed that aryloxylethylindolealkylamine derivative **I** displayed high affinities for the SERT and 5-HT$_{1A}$ receptor [11]. Venkatesan et al. reported that the benzofuran derivative **II** exhibited potent binding affinity for the 5-HT$_{1A}$ receptor and SERT [12]. Moreover, our previous research reported that the aryl piperazine benzo[b] [1,4]oxazine derivative **III** exhibited high affinities for 5-HT$_{1A}$ receptor coupled with moderate serotonin reuptake inhibitory [13] (Fig. 2). Meanwhile, considerable research efforts have also been directed toward the identification of novel compounds targeting 5-HT$_{1A}$ and 5-HT$_7$ receptor. Leopoldo et al. disclosed that 2-biphenyl piperazine derivatives **IV-VI** showed high affinity for 5-HT$_{1A}$ and 5-HT$_7$ receptors [14–16] (Fig. 2). Brasili et al. focused on the development of novel potent 5-HT$_{1A}$ ligands [17], and reported that 1,4-dithiaspiro[4.5] decane derivative **VII** and 1-(2-methoxyphenyl)piperazine

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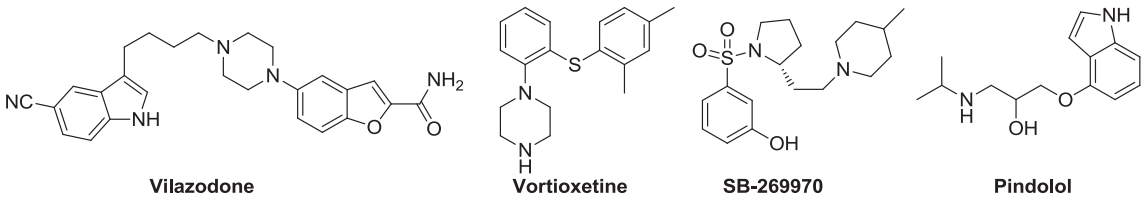

Fig. 1. Chemical structures of representative antidepressant compounds.

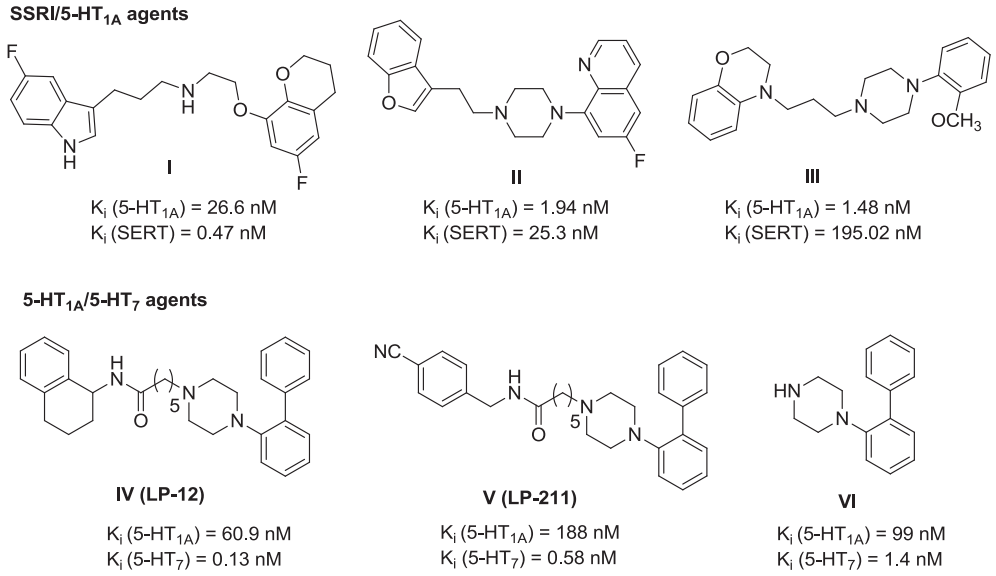

Fig. 2. Structures of SSRI/5-HT_{1A} agents and 5-HT_{1A}/5-HT_7 agents.

derivatives **VIII-X** exhibited high affinity and moderate to good selectivity for 5-HT_{1A}R (Fig. 3) [18–21].

Our lab has been engaged in multiple receptor-targeting in order to extend the scope and utility of CNS agents. Herein we designed and synthesized a series of novel aralkyl piperazine derivatives by modifying the scaffold of compound **II**. As shown in Fig. 4, we first explored the effect of different aromatic ring substituents at the N1 position on the affinity for 5-HT_{1A} and 5-HT_7 receptors. Additionally, we examined whether serotonin reuptake inhibition was improved by replacing the benzofuran moiety with indole moiety. From these studies, we have discovered a new series of compounds that exhibited high binding affinities at 5-HT_{1A}/5-HT_7 receptors coupled with potent 5-HT reuptake inhibitory activity, and also demonstrated excellent oral bioavailability and marked antidepressant-like activity in animal behavioral models.

2. Results and discussion

2.1. Chemistry

The synthetic routes of target compounds were outlined in Schemes 1–5. In scheme 1, a series of benzofuran-3-yl piperazine derivatives (**6a-d**) were prepared. The starting material benzofuran-3(2H)-one **1** was converted into ethyl ester **2** via the

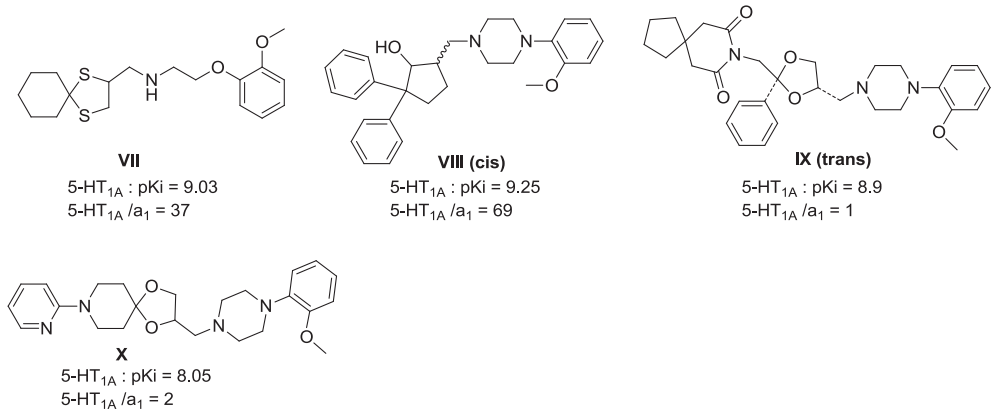

Fig. 3. Structures of 5-HT_{1A}R/α1-adrenoceptor ligands.