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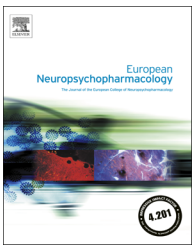

Antidepressant-like effects of 071031B, a novel serotonin and norepinephrine reuptake inhibitor

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Abstract
SNRIs (serotonin and norepinephrine reuptake inhibitors) have been proposed to exert increased therapeutic efficacy or be faster acting compared to commonly used antidepressants. In this study, we performed in vitro binding and uptake assays and in vivo behavioral tests to assess the pharmacological properties and antidepressant-like efficacy of the compound 071031B; we also performed cytotoxicity tests using HepG2 cells and SH-SY5Y cells to predict the toxicity of 071031B. In vitro, 071031B had high affinity for both serotonin transporters and norepinephrine transporters prepared from rat cortex tissue (K_i=2.68 and 1.09 nM, respectively) and recombinant cells (K_i=1.57 and 0.36 nM, respectively). Moreover, 071031B also potently inhibited the uptake of serotonin (5-HT) and norepinephrine (NE) into rat cortical synaptosomes (K_i=1.99 and 1.09 nM, respectively) and recombinant cells (K_i=3.23 and 0.79 nM, respectively). In vivo, acute administration of 071031B dose-dependently reduced the immobility time in the tail suspension test in mice and the forced swimming test in mice and rats with higher efficacy than duloxetine and showed no stimulatory effect on the locomotor activity. Chronic 071031B treatment (5 or 10 mg/kg) significantly reversed depressive-like behaviors in chronically stressed rats, including reduced sucrose preference, decreased

Abbreviations: MDD, major depressive disorder; TCAs, tricyclic antidepressants; MAOIs, monoamine oxidase inhibitors; 5-HT, serotonin; NE, norepinephrine; SSRIs, selective serotonin reuptake inhibitors; NRIs, norepinephrine reuptake inhibitors; SNRIs, serotonin and norepinephrine reuptake inhibitors; SERTs, serotonin transporters; NETs, norepinephrine transporters; DATs, dopamine transporters; DA, dopamine; TST, tail suspension test; FST, forced swimming test; CUS, chronic unpredictable stress; SP, sucrose preference; NSF, novelty-suppressed feeding; ANOVA, one-way analysis of variance; CNS, central nervous system

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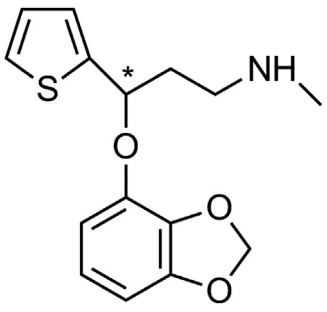
locomotor activity, and prolonged latency to begin eating. Furthermore, 071031B also exhibited lower cytotoxicity in HepG2 cells and SH-SY5Y cells in vitro than duloxetine. These findings suggest that 071031B is a novel, balanced serotonin and norepinephrine reuptake inhibitor, with more potent antidepressant effects and lower hepatotoxicity and neurotoxicity in vitro than duloxetine.

1. Introduction

Major depressive disorder (MDD) is a common and severe psychiatric disorder with a lifetime prevalence of 10–20% (Wong and Licinio, 2001). MDD is becoming one of the most prevalent public health problems due to its high rate of morbidity, recurrence, and suicide, producing a serious burden to the patients and society. Unfortunately, the current therapy for MDD is not satisfactory. Although the antidepressants have been in development for more than 50 years, they remain inadequate. The tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs), also known as the first generation antidepressants, were discovered by chance more than 50 years ago (Davis, 1958; Kuhn, 1958). TCAs and MAOIs are indeed effective in antidepressant treatment, but they also have unfavorable side effects due to their high affinity for other receptors, e.g., adrenergic, muscarinic, and histamine receptors (Klerman and Cole, 1967). Then, research began to focus on the selective serotonin reuptake inhibitors (SSRIs) or norepinephrine reuptake inhibitors (NRIs). The successful introduction of SSRIs was indeed a milestone in the history of pharmacotherapy for depression; however, despite major improvements in side effects and their extensive use in the clinic, SSRIs did not offer greater efficacy or faster onset than TCAs (Anderson, 1998, 2001; Steffens et al., 1997). It has been suggested that antidepressants targeting selectively at 5-HT or NE system may be effective in managing differential symptoms or subtype of depression, which means that SSRIs may be not effective for all the depressed patients, at least not all the symptoms (Nutt, 2002; Shelton and Tomarken, 2001). Therefore, novel antidepressants capable of treating a broad set of symptoms associated with depression, including emotional and physical symptoms, may be more effective.

Given the complicated etiology of MDD, the important role of 5-HT and NE in antidepressant therapy, and the cross-talk between these neurotransmitters, it has been suggested that drugs that simultaneously increase the levels of 5-HT and NE may exert increased therapeutic efficacy or be faster acting (Millan, 2006; Wong and Bymaster, 2002). Clinical research indicated that combination therapy of fluoxetine (SSRIs) and desipramine (NRIs) results in an earlier onset of action than the therapy of fluoxetine or desipramine alone (Nelson et al., 1991). Furthermore, TCAs with dual reuptake profile, such as chlorimipramine, showed superior efficacy than paroxetine or citalopram (SSRIs), especially in severely depressed patients (Danish University Antidepressant Group, 1986, 1990). Recently, SNRIs (serotonin and norepinephrine reuptake inhibitors), a new class of antidepressants that includes venlafaxine, duloxetine, milnacipran, and desvenlafaxine, hit the market. Their successful introduction and extensive use in the clinic further validate the feasibility of this strategy. Clinical evidence demonstrates that SNRIs display superior efficacy to SSRIs in the treatment of depression, as demonstrated by the higher rates of response and/or remission (Anderson 2001; Goldstein et al., 2004; Stahl et al., 2005; Thase et al., 2001, 2007b). In addition, compared to the TCAs, the SNRIs are better tolerated because of their increased selectivity (Millan, 2009). Notably, in addition to improvements in mood, SNRIs also produce strong relief on painful physical symptoms associated with depression, whereas SSRIs are generally not effective in the treatment of chronic pain (Fishbain, 2000; Staiger et al., 2003). It is not surprising, since depression and pain may share similar etiology and rely on common monoamine transmitters, especially that for NE (Delgado, 2004). SNRIs have been the first-line antidepressants and produced huge economic benefit. Therefore, the development of novel SNRIs with greater efficacy and lower toxicity is promising for both patients and pharmaceutical companies.

Given all the factors abovementioned, we designed and synthesized a series of compounds with novel structures. 071031B [(±)-3-(benzo[*d*] [1,3]dioxol-4-yloxy)-*N*-methyl-3-(thiophen-2-yl) propan-1-amine, Fig. 1] was screened as the final candidate because of its strong antidepressant effects (Zhang et al., 2010). In the present study, we performed detailed investigation of the pharmacological characteristics of 071031B in vivo and in vitro. First, we determined the binding profile of 071031B, i.e., its affinity for rat and human 5-HT transporters (SERTs), NE transporters (NETs), and dopamine transporters (DATs); then, we evaluated the inhibitory activity of 071031B on the uptake of 5-HT, NE, and dopamine (DA) into the rat synaptosomes and recombinant cells. We also investigated the antidepressant-like activity of 071031B in various mouse and rat models; finally, to predict the hepatotoxicity and neurotoxicity of 071031B,



071031B

Fig. 1 Chemical structure of 071031B.