European Journal of Medicinal Chemistry 54 (2012) 123–136

Contents lists available at SciVerse ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Synthesis and antidepressant activity of arylalkanol-piperidine derivatives as triple reuptake inhibitors

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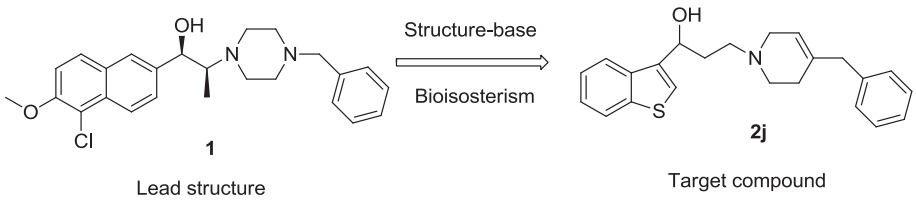
HIGHLIGHTS

- A series of arylalkanol-piperidine derivatives (**2a**–**y**) were synthesized.
- Synthesized compounds were tested for triple reuptake inhibition and antidepressant activities.
- 5 compounds exhibited high potency for 5-HT, NA and DA transporters.
- Some compounds showed antidepressant activities in TST and displayed desirable pharmacokinetic properties.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 11 February 2012
Received in revised form
23 April 2012
Accepted 24 April 2012
Available online 30 April 2012

Keywords:
Arylalkanol-piperidine derivatives
Triple reuptake inhibitor
Antidepressant

ABSTRACT

A series of arylalkanol-piperidine derivatives was synthesized, and their triple reuptake inhibition and in vivo activities have been evaluated. Among them, compounds **2a**, **2j**, **2k**, **2m** and **2n** exhibited high potency for 5-HT, NA and DA transporters. Optimized compounds **2j** and **2m** showed significant reduction of immobility time compared to that of vehicle in the mouse tail suspension test (TST) test at doses ranging from 10 to 50 mg/kg po, and were not generally motor stimulants at 50 mg/kg dose. In addition, compounds **2j** and **2m** displayed desirable pharmacokinetic properties in SD rats.

1. Introduction

Depression has received considerable attention in the last decades. Notoriously, it is involved in people's thought, feeling and behavior, which can eventually lead to suicide [1]. Various chemical drugs have been developed to treat patients with depression by interfering with either the uptake or metabolism of aminergic neurotransmitters [2]. Specifically, drugs that selectively block the neurotransmitter reuptakes of either serotonin (5-HT) (SSRI, e.g., fluoxetine) or noradrenalin (NA) (SNRI, e.g., reboxetine) have established as effective antideprssants. Furthermore, drugs which block reuptake at both 5-HT and NA transporters (e.g., venlafaxine and duloxetine, Fig. 1) or at both NA and dopaminergic (DA) neurons (e.g., bupropion, Fig. 1), also known as dual reuptake inhibitors, provide good efficacy and tolerability too [3–5].

Recent research showed that triple reuptake inhibitors are promising chemical entities for the treatment of depression. New structures of some triple reuptake inhibitors [6] were revealed to be DOV-21947 (EB-1010) [7], PRC200-SS [8], and GSK1360707F [9,10] (Fig. 1), which block the reuptake of 5-HT, NA and DA

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doi:10.1016/j.ejmech.2012.04.030

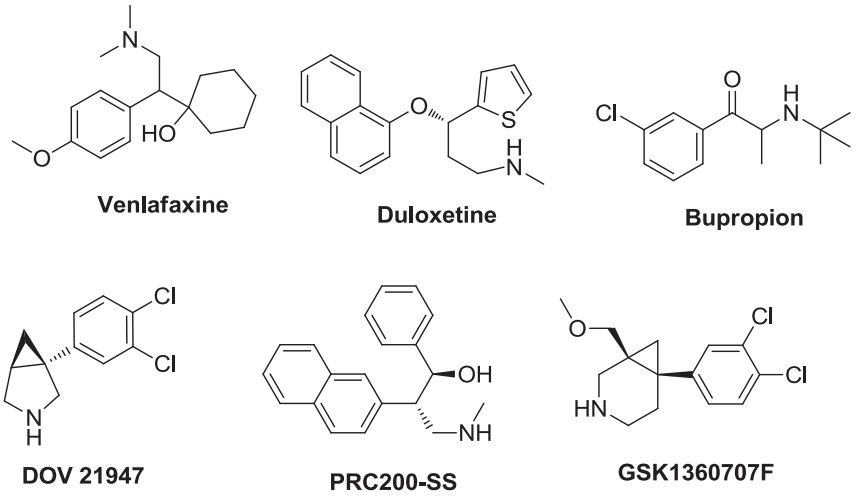

Fig. 1. Molecular structures of known clinical and preclinical antidepressants.

transporters. The effectiveness of this class of compounds was further supported by both preclinical [11] and clinical studies. It is known that DA agonists themselves (e.g., pergolide, bromocriptine) showed efficacy as augmenting agents with antidepressant in clinical studies [7]. It is hypothesized [12,13] that the increase of DA levels in triple reuptake inhibitors may address the anhedonic component of depression as well as shorten the time to onset. Therefore, the triple reuptake inhibitors might result in improved efficacy toward a broader range of the depressed population [14].

In our previous studies on monoamine transporters, we disclosed a series of arylalkanol-piperazine compounds (Fig. 2, Compound **1**) and reported the biological evaluation of their antidepressant activity [15–17]. We have extended our research to the alternate isostere of piperazine since then.

Herein we reported our synthesis of the arylalkanol-piperidine derivatives where piperazine in compound **1** was substituted by piperidine (**2j**), and investigations of their antidepressant activities by focusing on both in vitro effect of different arylalkanol substitution on reuptake inhibition and in vivo activity. The results demonstrate that the arylalkanol structure has great impact on the antidepressant activity.

2. Results and discussion

2.1. Chemistry

The synthetic routes of all target compounds were outlined in two schemes. In Scheme 1, a series of linear-chain arylalkanol-piperidine derivatives (**2a**–**o**) was prepared. Briefly, a commercially available aryl ketone **3** with 4-benzylpiperidine derivatives **4** in the presence of paraformaldehyde by the Mannich reaction afforded the intermediate arylalkaneone-piperidine derivatives **5a**–**j** in good yields (71–89%). Finally, the compounds **5a**–**j** were reduced by sodium borohydride provided the series of target compounds **2a**–**j** in excellent yields (85–92%). An alternative synthesis was employed for those linear-chain analogs of **2k**–**o**, where the corresponding aryl ketone is unavailable. In this case, ketone derivatives **7a**–**c** were prepared with 3-chloropropanoyl chloride and aromatic ring in the presence of aluminum choride and dichloromethane in 75–87% yields. The resulting compounds **7a**–**c** were then treated with 4-benzylpiperidine derivatives **4** via S_N2 mechanism, yielding **5k**–**o** in good yields (76–86%).

According to Scheme 2, target compounds with two chiral carbon centers on the side-chain analogs, erythro and threo conformations, were prepared. The relative threo or erythro configuration were determination by ^{1}H NMR as Solladie reported [18]. In general, intermediate **9a**–**c** were synthesized by Friedel-Craft acylation of the corresponding aromatic ring in 61–84% yields, and **9d**–**9e** were obtained from commercial suppliers. Bromination of compounds **9a**–**e** with $CuBr_2$ provided compounds **10a**–**e** in good yields (74–83%), which were then coupled with **4** to yield **5p**–**t** by nucleophilic substitution in good to excellent yields (72–90%). Final reduction of ketone **5p**–**t** with $NaBH_4$ in methanol gave a mixture, which were further separated by column chromatography to give threo- and erthro-compounds **2p**–**2y** in 27–38% yields. All final products were characterized by ^{1}H NMR, MS(ESI) and elemental analysis.

2.2. Biology

The novel compounds described above were test for their inhibition of functional uptake of serotonin, noradrenalin and dopamine. The plasmids were transfected into CHO cells, which encoded the human serotonin transporter (hSERT), noradrenalin

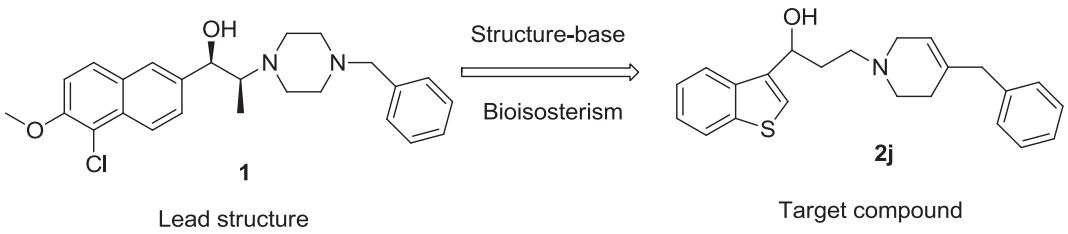

Fig. 2. Rational design of novel triple reuptake inhibitors.