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Original article

Synthesis and pharmacological investigation of aralkyl diamine derivatives as potential triple reuptake inhibitors

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ABSTRACT

A series of aralkyl diamine derivatives were designed, synthesized, and evaluated for their triple reuptake inhibitory abilities. Compounds **18c** (5-HT, NE, DA, IC_{50} = 389, 69, 238 nM), **36a** (5-HT, NE, DA, IC_{50} = 378, 477, 247 nM), and **36d** (5-HT, NE, DA, IC_{50} = 501, 206, 357 nM) showed *in vivo* activities in the rat forced swim test at 5, 10, and 20 mg/kg PO. **36a** was identified as the most promising candidate in this study. Specifically, **36a** exhibited high selectivity for monoamine transporters over a number of CNS-related targets. Furthermore, **36a** showed a good pharmacokinetic properties and acceptable safety profile in preclinical studies.

1. Introduction

Depression is increasing as a global mental health issue, and this condition can disturb thoughts, feelings, behaviors, and can sometimes lead to suicide [1]. Thus, antidepressants to treat these concerns is of enormous scientific interest [2–5]. Current hypotheses suggest that depression is related to deficiencies of certain neurotransmitters such as serotonin, (5-HT) and norepinephrine (NE) [6].

In particular, onset of action and side effects appear to be a general hurdle, even for the dual reuptake inhibitors. For instance, 5-HT/NE transporters (SNRIs, e.g., venlafaxine, duloxetine and milnacipran, Fig. 1) were reported to exhibit more benign side effect profiles than those of mono-reuptake inhibitors, although they have not been shown to be more efficacious or to have more rapid onset of antidepressant response [7]. Therefore, high efficacy drugs with few side effects should be intensively pursued to identify new therapeutics for treating depression.

To enhance drug efficacy while suppressing unwanted effects, different strategies have been developed, such as the monoamine hypothesis and non-monoamine-based antidepressants [3,8]. Reports suggest that the addition of dopamine (DA) reuptake to 5-HT and NE reuptake may improve efficacy and reduce the time to onset of antidepressant response [9]. In particular, recent experiments suggest that the triple reuptake inhibitors (TRIs), *i.e.* DOV-21947 (EB-1010) [10], PRC200-SS [11], and GSK1360707F [12,13] (Fig. 1), which block the reuptake of 5-HT, NE and DA transporters, offer more rapid onset of action and possess greater efficacy than traditional antidepressants. Therefore, TRIs may be applicable for a broader range of the depressed population [14].

Inspired by these works, reuptake of DA with NE and 5-HT was thought to be a possible solution for producing potent antidepressants. In our previous studies of monoamine transporters, a series of arylalkanol-piperdine derivatives was identified and their triple reuptake inhibition and antidepressant activities were reported [15]. In this study, we designed and synthesized a new series of compounds (Fig. 2) by changing the arylalkanol-piperdine scaffold. We then examined whether monoamine transporter reuptake inhibition was improved by replacing the hydroxyl group at the C1 position in arylalkanol-piperdine derivatives with heterocycles (such as cyclic amines). Subsequently, we replaced the 3-benzo[*b*]thiophene moiety at the C1 position with other aromatic substituents to understand the effect of different aromatic ring substitutions on the affinity and selectivity for different monoamine transporters. Finally, we explored the role of different substituents at the C3 position to produce aralkyl diamine compounds. From

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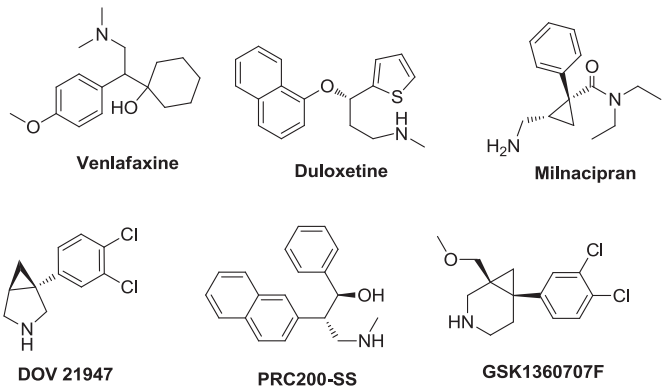

Fig. 1. Molecular structures of selected clinical and preclinical antidepressants.

these studies, we have discovered a series of compounds that potently inhibit the reuptake of 5-HT, NE, and DA transporters.

2. Results and discussion

2.1. Chemistry

Synthetic access to the novel aralkyl diamine derivatives was achieved by seven synthetic routes as illustrated in Schemes 1–7. The synthesis of 4-benzyl-1,2,3,6-tetrahydropyridine derivatives **6** and **12** are depicted in Scheme 1. Briefly, a commercially available 4-benzyl-1,2,3,6-tetrahydropyridine **1** with 3-acetylbenzo[b]thiophene in the presence of paraformaldehyde by the Mannich reaction afforded the intermediate aryl alkaneone amine derivatives **2** (73% yield). Then compound **2** was reduced with sodium borohydride into the corresponding alcohol **3** (89% yield). A strategy to introduce a heterocycle at the C1 position was then applied. Activation of alcohol **3** with 4-toluenesulfonyl chloride in the presence of *N*,*N*-diisopropylethylamine at room temperature provided compound **4**, which was immediately coupled with cyclic amines **5** to yield **6a**–**d** by nucleophilic substitution in moderate yields (47–60% yield). An alternative synthesis was employed for analogs of **12a**–**b**, for which the corresponding aryl ketone was unavailable. In this case, ketone **8** was prepared through Friedel–Crafts acylation reactions. The acylation of the aromatic ring with 3-chloropropanoyl chloride **7** was catalyzed by aluminum chloride. Then **8** was treated with **1** via the SN2 mechanism, yielding **9** (77–82% yield), which were then treated successively with sodium borohydride, 4-toluenesulfonyl chloride and pyrrolidine provided the target compounds **12a**–**b**.

The C3 cyclic amine substituted compounds **18a**–**e** (Scheme 2) were obtained by substitution of aryl ketone **13** with cyclic amines **5** in the C3 position, and subsequent reduction, activation, and substitution with cyclic amines **17**. Synthesis of the corresponding C3 *N*-methyl-1-phenylmethanamine substitution compounds **23a**–**b** and **27a**–**b** is shown in Schemes 3 and 4. Treating aryl ketone **19** or **8** with N-methyl-1-phenylmethanamine resulted in C3 substitution. Furthermore, the target compounds **23a**–**b** and **27a**–**b** were obtained by reduction, activation and substitution. Then the N-methylamine derivative **28** was obtained through *N*-debenzylation of **23b** (81% yield).

Finally, the preparation of the desired *N*,*N*-dimethylamine derivatives **32a**–**m** is outlined in Scheme 5. The key precursors **30** were obtained via a Mannich reaction of aryl ketone **19** with dimethylamine, and then reduction. Then, **30** could be activated with 4-toluenesulfonyl chloride and substituted with cyclic amines **5** to provide target compounds **32a**–**m**. The desired compounds **36a**–**e** and **40** were offered by substitution, reduction, activation, and substitution with cyclic amines (Schemes 6 and 7).

2.2. Biology

All synthesized compounds were tested for their inhibition of 5-HT, NE and DA reuptake. The plasmids were transfected into CHO cells, which encoded the human 5-HT transporter (hSERT), NE transporter (hNET), and DA transporter (hDAT). Then, the stably expressed cell strains were selected and used for the uptake test. ^{3}H-5-HT, ^{3}H-DA, ^{3}H-NE were obtained from PerkinElmer Life Sciences (LesUlis, France). All compounds were initially screened at 10 μM concentration, and selective compounds (inhibition >90%) were then assayed to obtain their IC_{50} values. The triple reuptake inhibitor DOV-21947 was used as a reference. Detailed results are summarized in Table 1.

For the C3 substituent 4-benzyl-1,2,3,6-tetrahydropyridine derivatives, inhibition of 5-HT, NE and DA reuptake were explored (Table 1, **6a**–**d**, **12a**–**b**). Compound **6a** bearing pyrrolidine and 3-benzo[b]thiophene moieties exhibited high potency for all three monoamine transporters, whereas piperidine (**6b**), morpholine (**6c**) and piperazine (**6d**) analogs were moderately inhibitory for 5-HT, DA and NE, respectively. When the pyrrolidine feature remained, the replacement of the 3-benzo[b]thiophene moiety with the 5-chloro-6-methoxynaphthalen moiety (compound **12a**) dramatically decreased inhibition of the three transporters. Data show that the 3,4-dichlorophenyl is a preferred substituent. Thus, **12b** was prepared.

In our next series, we investigated the effects of replacing the C3 substituent 4-benzyl-1,2,3,6-tetrahydropyridine moiety with piperidine and morpholine moieties (Table 1, compounds **18a**–**e**). None of these C3 piperidine or morpholine substituted compounds were potent except the C1 pyrrolidine substituted compound **18c**. Compound **18c** exhibited interesting triple reuptake potency (5-HT, IC_{50} = 389 nM; NE, IC_{50} = 69 nM; DA, IC_{50} = 238 nM), however the C1 substituent with morpholine (**18a** and **18b**), 3-methylpiperidine (**18d**) and ethyl piperidine-3-carboxylate (**18e**) were weak reuptake inhibitors of all three transporters.

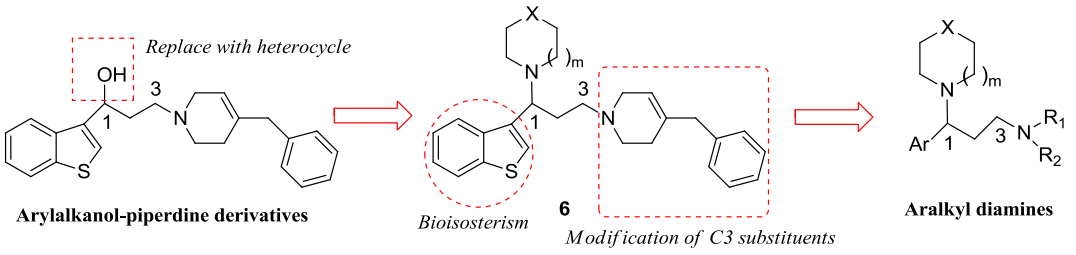

Fig. 2. Rational design of novel triple reuptake inhibitors.