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Synthesis and biological evaluation of novel 3,4-diaryl lactam derivatives as triple reuptake inhibitors

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This article is dedicated to Professor Jahyo Kang for his lifelong commitment to mentoring graduate students

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ABSTRACT

A series of 3,4-diarylpyrrolidin-2-one was designed, prepared and evaluated as triple reuptake inhibitors for antidepressant. Most compounds exhibited comparable in vitro efficacy as norepinephrine and dopamine transporter reuptake inhibitors. Especially, **2i** showed better potency than GBR-12909 (IC_{50} = 14 - nM) which was used as reference compound for dopamine transporter. In addition, **2a** and **2b** showed inhibition (5.17 μM–85.6 nM) for three transporters.

In general, the most powerful hypothesis of depression is regarded as the lack of monoaminergic neurotransmitters such as serotonin, norepinephrine and dopamine in the synapses of central nervous system. Most of antidepressants maintain the concentration of monoamine neurotransmitters by blocking reuptake of monoamine neurotransmitters.[1]

Currently selective serotonin reuptake inhibitor (SSRI) like fluoxetine (Prozac)[2] and selective serotonin and norepinephrine reuptake inhibitor (SNRI) like duloxetine (Cymbalta)[1,3] are the most prevalent drugs for major depression. These drugs have less side effects than tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) such as lack of histamine, acetylcholine, and alpha-adrenergic receptor antagonism.[1a,3]

However SSRI[4] and SNRI still have side effects such as sexual dysfunction, weight loss or gain, and drug–drug interaction.[5] The biggest problems of these drugs are that only 65% of patients showed efficacy with antidepressants therapy and 15% of patients had no response to all known types of therapy.[6] In addition, the therapeutic efficacy showed only after 2–4 weeks from antidepressant therapy. In other words, the clinical unmet needs of SSRIs and SNRIs were low remission rate and therapeutic lag associated with their use.[6]

In order to overcome these problems, the researchers tried to develop drugs with new mode of action (MOA) such as triple monoamine reuptake inhibition.[7] Our first approach began to have a similar pharmacophore suggested from leading candidate compounds such as DOV216303 (Merck, phase II),[8] SEP225289 (Sepracor, phase I),[9] PRC025 (Mayo clinic, preclinical)[10] for depression with triple reuptake inhibition as a MOA (Fig. 1).

First series of phenethylamine compounds (**1**) were designed from DOV 216303 by insertion of an ethylene group to increase rigidity, changing nitrogen position from beta to gamma, and addition of a chiral aryl group. The number and positions of the two chlorines in DOV 216303 was altered to different position such as 2-chloro, 3-chloro, 4-chloro and 3,4-dichloro on the phenyl ring. The nitrogen and ethyl group were dissociated due to the low potency of series **1** (not published results: binding affinity of 4 derivatives of structure **1** at 10 μM: *h*SERT = 9.0–61.0, *h*NET = 10.0–69.0, *h*DAT = 5.0–54.0). Then, γ-lactam scaffold (**2**) was designed from structure of compounds **1** and JZAD-IV-22 (Figure 2) via ethylene removal and carbonyl group insertion.

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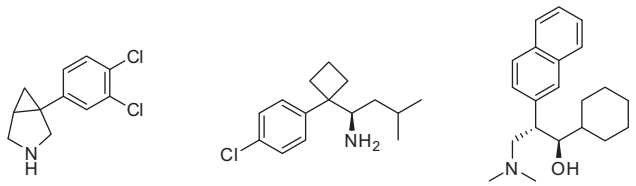


Figure 1. Representative leading candidate compounds as triple reuptake inhibitor.

Syntheses of initial set of biaryl γ-lactam (Scheme 1) began with commercially available benzaldehydes **3** which involved the nitroaldol reaction using Henry condition[11] and dehydration in one-pot. Various phenyl acetic acids **5** were esterified to give methyl esters **6**. Michael addition of β-nitrostyrenes **4** with methyl esters **6** under basic conditions gave diarylbutanoates **7**. Reduction of the diarylbutanoates **7** with Raney nickel gave intermediate amines and the subsequent intramolecular cyclization using sodium hydride lead lactam **2**.

The synthesized compounds **2** were evaluated for serotonin, norepinephrine, and dopamine neurotransmitters uptake activities using the Neurotransmitter Transporter Uptake Assay Kit (Molecular Devices, Sunnyvale, CA, USA)[13] with the FDSS6000 96-well fluorescence plate reader (Hamamatsu Photonics, Hamamatsu, Japan, Table 1).[14] First approach was to contain the 3,4-dichlorophenyl group (R_2 = 3,4-dichlorophenyl) and to change various substituents on the R^1 groups (**2a**, **2e**, **2i**, **2m**, **2p**) like DOV 216303. But most compounds showed better activities in norepinephrine transporter (NET) and dopamine transporter (DAT) than serotonin transporter (SERT).

The results of R^1 group derivatization in the reuptake activities of SERT showed good activities when the R^1 group was 4-chlorophenyl group (**2a**–**2c**) than other substituents (Table 1). Compounds, 2-chlorophenyl (**2i**–**2l**) or 3-chlorophenyl (**2m**–**2o**) on R^1 groups, showed lower inhibitory activities regardless of R^2 group.

In the reuptake activities of NET, naphthyl compounds on R^1 (**2t**–**2v**) showed low inhibitory activities while 2-chlorophenyl (**2i**–**2l**) or phenyl (**2p**–**2s**) on R^1 group showed good activities. The results showed different structure–activity relationship (SAR) with reuptake activities of SERT in R^1 derivatization. In the case where R^2 was derivatized, they showed same SAR with SERT inhibitory activities.

Most compounds in this series showed above 80% inhibitory activities in DAT without 2-chlorophenyl in R^2 group.

The compounds (**2a**–**v**) were also evaluated for their binding affinities of serotonin, norepinephrine, or dopamine transporters using human recombinant transporters expressed in HEK293, MDCK or CHO-K1 cells (Table 2).[15]

In the binding affinities of SERT, 4-chlorophenyl (**2a**–**d**) or naphthyl (**2t**–**v**) on R^1 group showed good activities than other substituents (**2e**–**s**). All of 2-chlorophenyl on R^1 (**2i**–**2l**) had low affinities regardless of R^2. On the other hand, 3-chlorophenyl (**2c**, **2g**, **2k**, **2o**) on R^2 showed that reversed tendency with other substituents.

And those of NET and DAT showed similar trend as in the reuptake activities. In the binding affinities of NET showed good po-

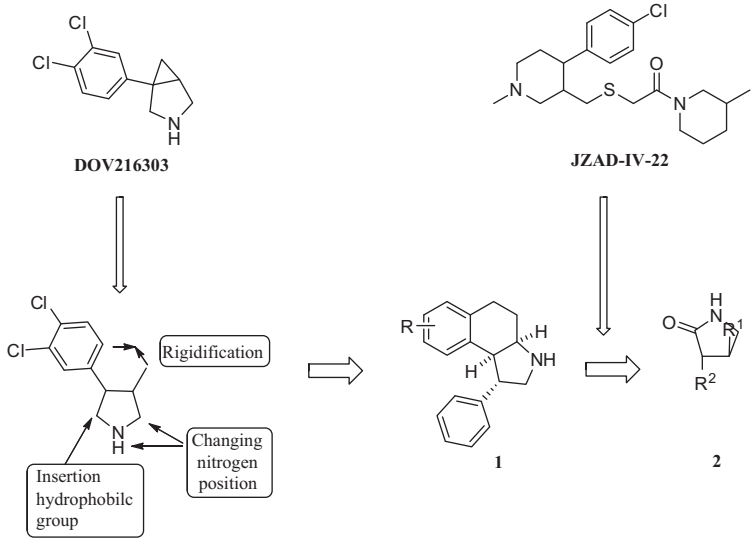
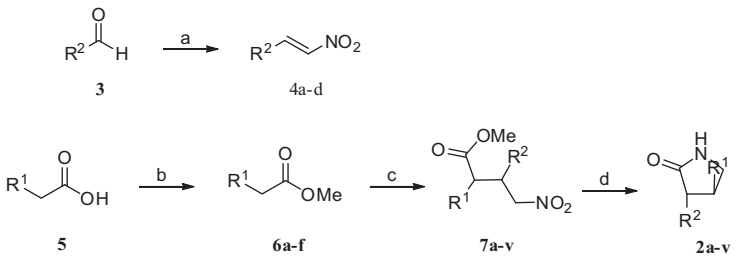


Figure 2. Design strategy of compound **2**.



Scheme 1. Reagents and conditions: (a) nitromethane (3 equiv), ammonium acetate (2.5 equiv), acetic acid, reflux, 49.5–76.7%;[11] (b) $SOCl_2$ (3 equiv), MeOH, 0 °C to rt, 95–98%; (c) LDA (2 equiv), **4**, THF, −78 °C,[12] 40–69%; (d) (i) H_2, Raney Ni, EtOH/Et_2O (1/1); (ii) NaH (2 equiv), toluene, 90 °C,[12] 34–53%.