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Novel 3,3-disubstituted pyrrolidines as selective triple serotonin/norepinephrine/dopamine reuptake inhibitors

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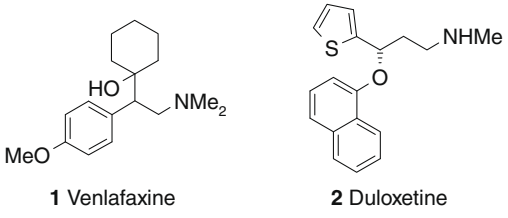
ABSTRACT

A series of 3,3-disubstituted pyrrolidine monoamine triple reuptake inhibitors were discovered. Analogues with low nanomolar potency, good human in vitro microsomal stability and in vitro permeability, and low drug–drug interaction potential are described. One example showed in vivo anti-depressant-like effects in the mouse tail suspension assay with a minimum effective dose of 30 mg/kg ip.

Nearly all clinical antidepressants act by elevating levels of one or more of the monoamine neurotransmitters serotonin (5-HT), norepinephrine (NE) and dopamine (DA).[1] Selective inhibitors of 5-HT and NE reuptake (SNRIs) have been shown to be effective in the treatment of major depressive disorders (MDD). Venlafaxine (Effexor®) **1** and duloxetine (Cymbalta®) **2** are both Food and Drug Administration (FDA) approved SNRI drugs for the treatment of MDD. Venlafaxine **1** has been shown to have a higher remission rate than the class of selective serotonin reuptake inhibitors (SSRIs) (Fig. 1).[2]



1 Venlafaxine **2** Duloxetine

Figure 1. Marketed SNRIs.

While the SSRI/SNRI classes of drugs have been shown to provide a safe and effective treatment for depression there is still a need for improvement. Triple reuptake inhibitors (TRIs) increase DA levels in addition to 5-HT and NE.[3] Elevating CNS levels of dopamine through inhibition of the dopamine transporter (DAT) may address the anhedonic component of depression as well as shorten the time to onset. This could result in improved efficacy toward a broader range of the depressed population.[4] Duloxetine has also been approved for the treatment of diabetic neuropathic pain and preclinical data suggest that dopamine transporter (DAT) inhibition may bring additional efficacy.[5] Thus, TRIs have the potential to be more effective in the management of depression and neuropathic pain, and to clearly differentiate from the current treatments. Our aim, therefore, was to generate novel small molecule inhibitors of all three monoamine transporters that would address the need for improved therapies and also act as tool compounds to permit greater understanding of the role of the DAT in MDD.

We recently disclosed a series of indolyl phenyl propylamines as SNRIs, exemplified by **3**.[6] Our knowledge of the structure–activity relationships (SAR) around this template combined with that of DOV-21947 **4**, a weakly active TRI that is currently undergoing Phase II clinical trials by DOV Pharmaceuticals for the treatment of depression,[7] led us to design a series of novel inhibitors based

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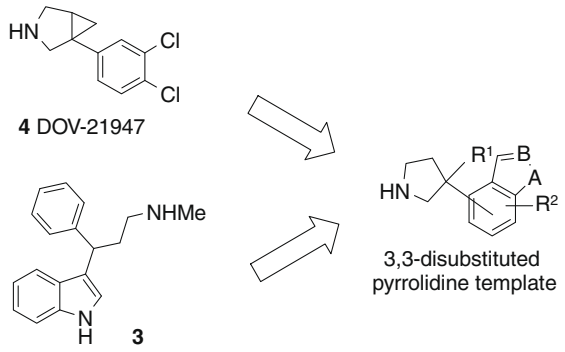


Figure 2. Design of novel triple reuptake inhibitors.

Table 1
In vitro inhibition of monoamine reuptake.[a]

Compd	SERT	K_i(nM) NET	DAT
3	9	89	>1400
4	63	63	251

[a] Monoamine reuptake K_i values are the geometric mean of at least three experiments.

on a 3,3-disubstituted pyrrolidine motif (Fig. 2 and Table 1). Herein we describe the synthesis and SAR for this series of triple reuptake inhibitors.

The target compounds were all prepared using rhodium catalyzed conjugate-addition of aryl boronic acids to maleimides as the key bond forming step.[8] Representative synthetic schemes are shown (Schemes 1–7).[9] Thus, the appropriate boronic acid **5** was coupled with *N*-benzylmaleimide to generate 1-benzyl-3-substituted pyrrolidine-2,5-diones **6** as outlined in Scheme 1. Protection of the indole under phase transfer conditions, followed by alkylation under mild conditions furnished the 3,3-disubstituted pyrrolidine-2,5-diones **7**. Deprotection of **7** followed by reduction with lithium aluminum hydride yielded the corresponding 1-benzylpyrrolidine **9**. Finally, a hydrogenolysis yielded the desired pyrrolidines **10** and **11**.

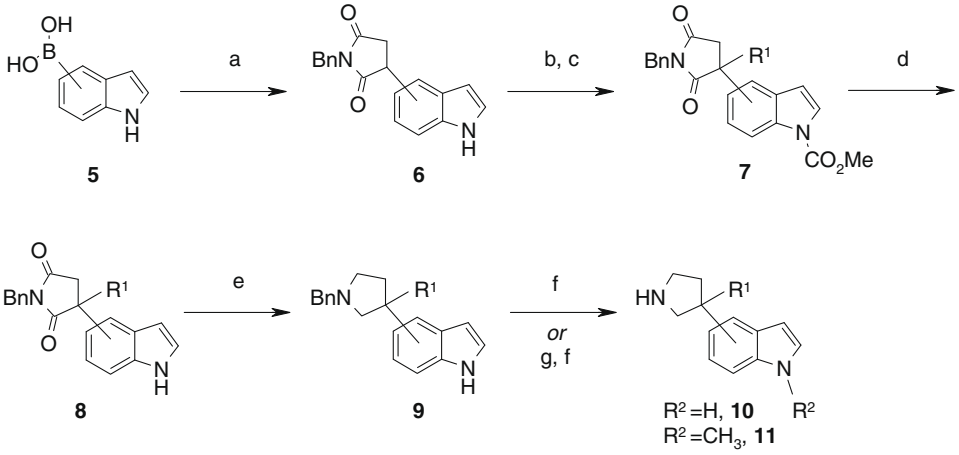
The first compound synthesized, **16**, was a potent inhibitor at all three of the monoamine reuptake transporters (Table 2). We were excited to find that it exhibited significantly higher potency than DOV-21947.[10] In addition, it showed favorable in vitro permeability and hERG inhibition (Table 6).[11,12] Liabilities included low human in vitro microsomal stability and strong CYP2D6 inhibition. When the enantiomers were separated most of the potency was found to reside in a single enantiomer, (+)-**16**. When tested in vivo in the mouse tail suspension assay, an assay used to evaluate anti-depressant agents, activity was observed at 30 mg/kg, ip.[13] Comparative data for Duloxetine showed anti-depressant like activity in the same assay with a minimum effective dose of 10 mg/kg ip.

Initial SAR investigations focused on replacing the indole ring (Table 2 and Schemes 2, 6 and 7). Many of the replacements were essentially equipotent with the indole, but maintaining acceptable microsomal stability,[14] permeability, and CYP2D6[15] and hERG inhibition levels proved challenging (Table 6). Indole regioisomer **20** retained similar potency but offered no notable benefits. Benzothiophene **18** was balanced and potent at all three SERT/NET/DAT transporters but unfortunately also showed poor in vitro stability. Introduction of polarizing groups to increase polar surface area resulted in stabilization towards microsomal clearance. Indazole **17** showed a threefold improvement in metabolic stability but remained a potent CYP2D6 inhibitor. 7-Azaindole **19** gave only a moderate improvement to stability and lost significant potency.

We next studied the SAR around the hydrophobic aromatic group (Table 3). In general, substitution was tolerated for potency but there was no improvement in stability towards human liver microsomes (Table 6). Replacement of the phenyl ring with a pyridyl group (e.g., **22**) did result in an improved CYP2D6 and hERG profile, but the additional hydrogen bond acceptor also resulted in P-gp mediated efflux.[16] Since minor modifications of the benzyl group appeared unlikely to yield metabolically stable compounds, we turned our focus back to the indole ring (Schemes 3–5).

Introduction of substituents in the 2- or 3-position of the indole ring reduced microsomal clearance and therefore increased metabolic stability (Tables 4 and 6). Inhibition of the hERG channel was notably worse in the case of 2-cyanoindole **28** despite its increased polar surface area, and CYP2D6 inhibition remained high. Amide **29** was potent and quite balanced at all three transporters, and showed a marked reduction in affinity to CYP2D6 and hERG. However, the two additional hydrogen bond donors resulted in strong P-gp mediated efflux. The efflux ratio was reduced by successive replacement of the hydrogen atoms with methyl groups, but could not be entirely avoided (see **30** and **31**). 3-Cyanoindole **32** lost potency and also suffered high P-gp mediated efflux.

We next investigated replacement of the aromatic hydrophobe portion of our pharmacophore with an aliphatic one (Tables 5 and 6). Increasing metabolic stability by the introduction of polarizing



Scheme 1. Reagents and conditions: (a) *N*-benzylmaleimide, [RhOH(cod)]$_2$ Et_3N], dioxane, H_2O, rt, 99%; (b) $BnNEt_3Br$, $ClCO_2Me$, 30% NaOH, 0 °C, 80%; (c) RX, K_2CO_3, DMF, rt, 77%; (d) LiOH, THF, 80 °C, 91%; (e) $LiAlH_4$, THF, 80 °C, 90%; (f) H_2, 20% $Pd(OH)_2$/C, MeOH, 60 psi, 54%; (g) NaH, DMF, rt, then MeI, rt, 62%.