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N-Benzyl-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrrolidin-3-amines as selective dual serotonin/noradrenaline reuptake inhibitors

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Abstract—A series of *N*-benzyl-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrrolidin-3-amine monoamine reuptake inhibitors are described. Selective dual 5-HT and NA reuptake inhibition was achieved, and analogues with weak CYP2D6 inhibition, good human in vitro metabolic stability and wide ligand selectivity, such as **12b**, were identified.

Selective inhibition of serotonin (5-HT) and noradrenaline (NA) reuptake (SNRI) has been shown to be an attractive dual pharmacology approach for the treatment of a number of diseases. For example, venlafaxine **1** and duloxetine **2** are approved drugs for the treatment of depression.[1,2] Efficacy in clinical trials for neuropathic pain[3,4] and stress urinary incontinence (SUI)[5] has also been demonstrated for dual 5-HT/NA reuptake inhibitors.

We recently described the discovery of *N*-substituted piperazine derivatives, for example, **3** and **4**, that acted as dual inhibitors of 5-HT and NA reuptake with good selectivity over dopamine (DA) reuptake (Fig. 1).[6]

Scaffold-hopping from the piperazine template led to a series of amino-pyrrolidines, and we investigated this area for selective dual 5-HT/NA reuptake inhibitors (SNRI's) with attractive drug-like properties (Fig. 2).[7]

The target compounds were readily prepared in a 3-step sequence from enantiomerically pure BOC-protected 3-amino-pyrrolidine **5** (Scheme 1). Standard reductive alkylation conditions introduced R^1 (via $NaBH(OAc)_3$ for aldehyde substrates and hydrogenation conditions [H_2, Pd/C catalyst] for ketone substrates). The benzylic group was then installed by alkylation with a benzylic halide. Finally BOC deprotection with trifluoroacetic acid gave the required pyrrolidines **8**–**21**.

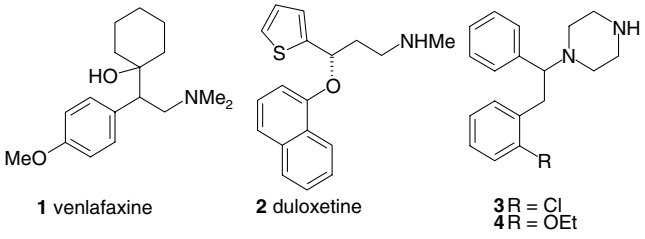

Figure 1.

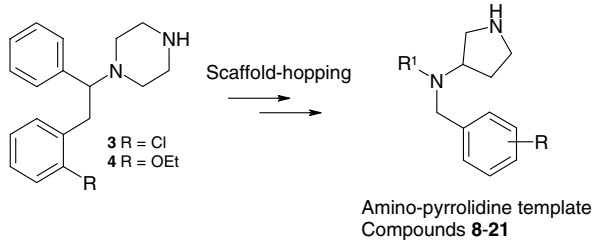

Figure 2.

Initial SAR investigations focused on variation of the R^1 group, with the benzylic R substitution as 2,3 di-Cl or 2,3 di-Me (Table 1). Cyclopropyl methyl and pyridylmethyl analogues **8a**,**b** and **9a**,**b** gave balanced and potent SNRI activity with moderate selectivity over dopamine transport. Replacement with a more polar

Keywords: Serotonin reuptake; Noradrenaline reuptake; Metabolic stability; hERG; SNRI.
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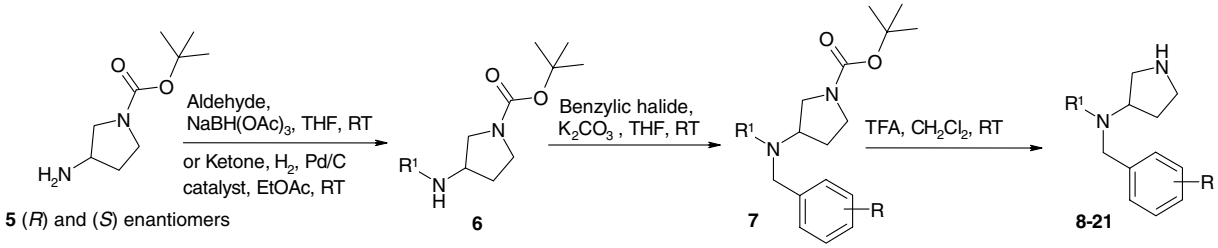
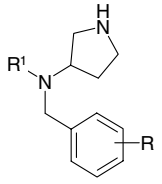
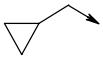
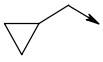
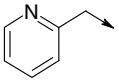
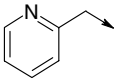
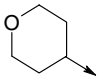
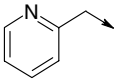
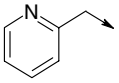
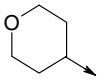
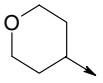


Scheme 1. Synthesis of amino-pyrrolidine target compounds.

Table 1. In vitro inhibition of monoamine reuptake,[a,b] human microsomal stability[c] and CYP2D6 inhibition for compounds **8**–**12**



Compound	R	R^1	Stereochemistry	5-HT IC_{50} (nM)	NA IC_{50} (nM)	DA IC_{50} (nM)	HLM $T_{1/2}$ (min)	CYP2D6 IC_{50} (μM)
8a	2,3 di-Cl		(*R*)	4	15	44	>120	NT
8b	2,3 di-Cl		(*S*)	6	9	206	>120	0.03
9a	2,3 di-Cl		(*R*)	3	5	125	NT	0.5
9b	2,3 di-Cl		(*S*)	5	3	122	61	0.1
10	2,3 di-Cl		(*S*)	10	5	89	NT	4.8
11a	2,3 di-Me		(*R*)	15	8	1470	24	NT
11b	2,3 di-Me		(*S*)	8	12	1600	14	NT
12a	2,3 di-Me		(*R*)	43	144	>4000	>120	9.4
12b	2,3 di-Me		(*S*)	9	7	727	>120	5.9
Duloxetine	—	—		6	19	870	NT	NT

NT denotes not tested.
[a] See Ref. 8 for description of assay conditions.
[b] Monoamine reuptake IC_{50} values are geometric means of at least three experiments.
[c] Maximum measurable half-life was 120 min.

branched 4-tetrahyropyranyl (4-THP) group in **10** retained very potent SNRI activity and similar selectivity. It was found that by replacing 2,3 di-Cl with 2,3 di-Me, dopamine selectivity could be improved, for example, compound **12b** had dopamine selectivity of 80- to 100-fold compared to **10** with 8- to 18-fold window.

Conscious of the fact that CYP2D6 inhibition was prevalent in the monoamine reuptake inhibition area,[9] we collated in vitro CYP2D6 inhibition data and human in vitro metabolic stability data in parallel with primary pharmacology and selectivity screening.

Compounds **8** and **9** gave very potent CYP2D6 inhibition, whereas the 4-THP analogues **10** and **12** had significantly reduced activity. By following this parallel screening approach we quickly showed the 4-THP analogues **12** combined excellent metabolic stability with weak P450 inhibition. An assessment of stereochemistry showed that both enantiomers possessed SNRI activity, with the (*S*) enantiomer exhibiting slightly better potency.

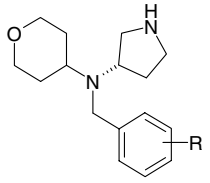
Having identified the 4-THP as a key group, we then investigated substitution on the benzylic aryl ring in more detail in the (*S*) enantiomeric series (Table 2). A range of different substitution patterns were investigated, with 2,3 and 2,4 disubstitution affording excellent dual serotonin/noradrenaline reuptake inhibition, with good selectivity over dopamine reuptake activity. Interestingly, a single 2-Ph substituent, that is, compound **20**, demonstrated the series could also deliver selective inhibitors of the noradrenaline transporter.[10] The majority of 4-THP analogues had excellent metabolic stability, the exception being compound **16** which had a half-life of less than 120 min. This may be due to *O*-dealkylation of the 3-alkoxy group resulting in more rapid metabolic turnover. The 4-THP series generally exhibited weak CYP2D6 inhibition, the exception being the 2-Ph analogue **20** which was a potent CYP2D6 inhibitor.

In order to rank compounds which had human liver microsomal half-lives of >120 min still further, a number of analogues were assessed in a human hepatocyte assay (Table 2).[11] This assay demonstrated that compounds could indeed be differentiated in human hepatocytes, with examples **12b** and **15** being the most metabolically robust. It was also interesting to note that replacement of the 3-Me of **12b** with a CF_3 group in **15** improved stability, again indicating that the 3-position may be a site of metabolism. This trend was also seen when comparing regioisomers **13** and **14**, with the 2-Me 3-Cl isomer conferring more stability than 2-Cl 3-Me.

We also assessed the series for its potential to block the hERG channel, as activity at this ion channel has been linked to QT prolongation and cardiac arrhythmia in man.[12] We were pleased to see that the 4-THP aminopyrrolidine series, in general, possessed weak affinity for the hERG channel (Table 2),[13] however some interesting SAR trends were observed. It was found that hERG activity appeared to be more sensitive to structural changes on the aromatic ring rather than lipophilicity.[14] For example, the 2,3 di-methyl substituted example **12b** showed the weakest hERG activity, whereas the more polar 2-methyl analogue **18** had a greater than 5-fold increase in hERG potency. In another example, the 2-CF_3 analogue **19** had the most potent hERG activity, even though it was isolipophilic with example **12b**.

With the optimal balance of pharmacological and ADME properties, example **12b** was assessed in a panel of 150 receptors and enzymes, including adrenergic, dopaminergic, nicotinic and opiate receptors, CYP450's and a range of sodium/calcium/potassium channels. We were pleased to find that **12b** demonstrated >200-fold selectivity for serotonin and noradrenaline reuptake inhibition over all targets.

Table 2. In vitro inhibition of monoamine reuptake,[a,b] human microsomal stability,[c] CYP2D6 inhibition, human hepatocyte stability,[d] hERG channel activity[e] and clog *P* calculations for compounds **12b**–**21**



Compound	R	5-HT IC_{50} (nM)	NA IC_{50} (nM)	DA IC_{50} (nM)	HLM $T_{1/2}$ (min)	CYP2D6 IC_{50} (μM)	Hepatocyte $T_{1/2}$ (min)	hERG IC_{50} (μM)	clog *P*
12b	2,3 di-Me	9	7	727	>120	5.9	144	14.4	2.4
13	2-Cl 3-Me	5	4	115	>120	15.7	71	NT	2.7
14	2-Me 3-Cl	11	5	196	>120	NT	104	NT	2.7
15	2-Me 3-CF_3	13	20	>4000	>120	5.5	>240	2.9	2.9
16	2-Me 3-OMe	11	11	968	94	8.2	NT	NT	1.9
17	2-CF_3 3-F	24	13	>4000	>120	30	NT	1.6	2.6
18	2-Me	29	7	1200	>120	30	NT	2.4	2.0
19	2-CF_3	21	9	>4000	>120	30	NT	1.1	2.4
20	2-Ph	400	12	>4000	>120	0.1	83	NT	3.1
21	2,3,4 tri-F	15	40	1190	NT	6.8	NT	1.2	1.8

NT denotes not tested.

[a] See Ref. 8 for description of assay conditions.

[b] Monoamine reuptake IC_{50} values are geometric means of at least three experiments.

[c] Maximum measurable half-life was 120 min.

[d] Maximum measurable half-life was 240 min.

[e] Values are geometric means of at least two experiments.

In summary, scaffold-hopping from piperazines **3** and **4** to the amino-pyrrolidine structure has delivered a series of compounds with excellent dual serotonin and noradrenaline reuptake inhibition and 100-fold selectivity over dopamine reuptake inhibition. By determining potency, selectivity, CYP2D6 inhibition and human metabolic stability in parallel we were quickly able to optimize the drug-like properties of the series. Example **12b** was found to have a large selectivity window over hERG channel activity, and showed greater than 200-fold selectivity for 5-HT and NA activity over a wide panel of receptors, enzymes and ion channels. This investigation has also shown that small substitution changes can have subtle effects on the ratio of 5-HT to NA reuptake inhibition. This may prove useful in determining the optimal ratio of activities in a number of disease areas such as depression, neuropathic pain and stress urinary incontinence. Further information on this series, including pharmacokinetic and in vivo efficacy data, will be reported in the near future.

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10. This is in contrast to the piperazine series described in Ref. 6, in which a 2-substituent delivers potent dual 5-HT and NA reuptake inhibition.
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