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4-Piperidines and 3-pyrrolidines as dual serotonin and noradrenaline reuptake inhibitors: Design, synthesis and structure–activity relationships

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ABSTRACT

Single enantiomer [(aryloxy)(pyridinyl)methyl]piperidine and pyrrolidine derivatives **5**–**9** are inhibitors of monoamine reuptake. Structure–activity relationships established that monoamine reuptake inhibition are functions of amine, pyridine isomer, aryloxy ring substitution and stereochemistry. Consequently, selective NRIs, selective SRIs, dual SNRIs and triple SNDRIs were all identified. Dual SNRIs **5l**–**a** and **9c** were evaluated in additional pharmacology and pharmacokinetic studies as representative examples from this series.

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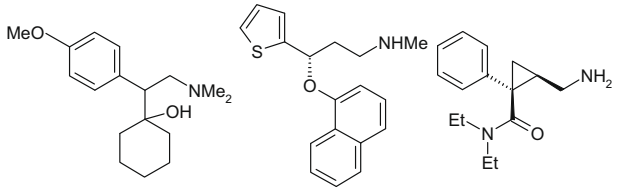
Dual serotonin (5-HT) and noradrenaline (NA) reuptake inhibitors (SNRI) have proven to be an effective treatment for a number of indications including depression, anxiety disorders, fibromyalgia, painful peripheral neuropathy and stress urinary incontinence.[1,2] The search for potent and selective SNRIs has identified venlafaxine (**1**),[3] duloxetine (**2**)[4] and milnacipran (**3**)[5] which are all marketed drugs. Furthermore, several small molecule SNRIs have been reported to be in early clinical development or undergoing preclinical optimization and evaluation.[6] Hence, the discovery of new SNRIs with enhanced properties continues to be an attractive target for the pharmaceutical industry.



1: venlafaxine **2**: duloxetine **3**: milnacipran

We have reported several new templates that inhibit monoamine reuptake and some of these compounds have now progressed to clinical trials.[7] As part of our research efforts to identify potential new SNRI drug candidates, we adopted a strategy of exploring multiple chemical templates in order to increase our chances of having compounds survive to become advanced clinical candidates.

In this Letter, we disclose derivatives of 4-[(aryloxy)(pyridinyl)methyl]piperidines (**5**–**7**) and 3-[(aryloxy)(pyridinyl)methyl]pyrrolidines (**9**) as potent dual SNRIs with selectivity over dopamine (DA) reuptake inhibition (DRI). In addition, we discuss some factors that modulate SRI–NRI–DRI activity and present additional pharmacology and pharmacokinetic data on representative examples from this series.

Investigation of the 3-(aryloxy)-3-phenylpropanamine template has identified a number of monoamine reuptake inhibitors including fluoxetine, nisoxetine, atomoxetine and duloxetine (**2**) (Fig. 1).[8] Modification of this template by cyclization into a piperidine ring to furnish 4-[(aryloxy)(phenyl)methyl]piperidines **4** has been reported by Orjales et al. (e.g., **10**).[9] Our own limited exploration of this template furnished potent dual SNRI **11** (Table 1). However, **11** had some degree of liver microsomal instability and carried ion channel activity; these properties could be attributed to the highly lipophilic nature of this amine template (clog*P* 5; cpK_a 10).

We proposed that a new SNRI template would benefit from a significant decrease in lipophilicity as this was likely to improve

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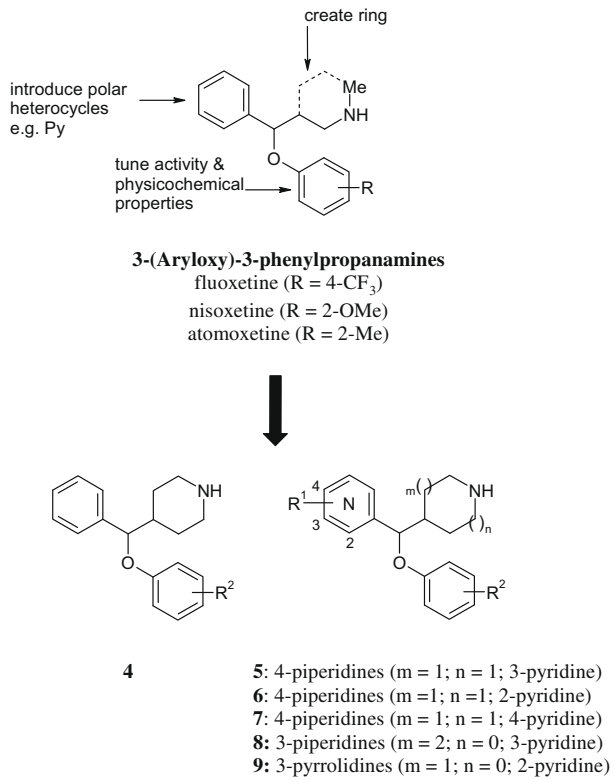
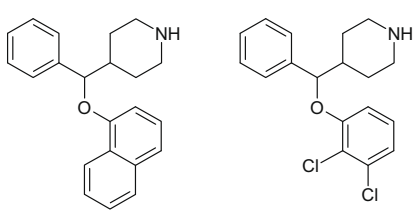


Figure 1. Design of 4-piperidines **5**–**7**, 3-piperidines **8** and 3-pyrrolidines **9** derived from 3-(aryloxy)-3-phenylpropanamines.

Table 1
Physicochemical properties, in vitro inhibition of monoamine reuptake, and ion channel affinities of racemic **10** and **11**[a,b,c]



10 **11**

	10[d]	**11**[e]
M.wt.	317	336
clog*P*	5.0	5.1
TPSA (Å^2)	21	21
5-HT, IC_{50} (nM)	15	8
NA, IC_{50} (nM)	120	16
DA, IC_{50} (nM)	370	200
HLM, $T_{1/2}$ (min)	NT	87
K^+ hERG, IC_{50} (nM)	NT	950
Na^+ TTX-S, IC_{50} (nM)	NT	840

[a] See Ref. 14 for details of assay conditions and Ref. 16 for definition of terms.
[b] Monoamine reuptake IC_{50} values are geometric means of at least two experiments. Differences of <2-fold should not be considered significant.
[c] NT denotes not tested.
[d] Compound **10** was first disclosed by Orjales et al., see: Ref. 9. Data is presented for comparison in a common assay format.
[e] Compound **11** is novel. This work.

metabolic stability, decrease ion channel activity and reduce the risk of potential toxicological outcomes;[10] this reduction in lipophilicity would need to be balanced with retaining good central nervous system (CNS) permeability.[11] A suitable modification of this template would be exchanging the phenyl ring for a pyridine ring (i.e., **4**→**5**–**9**) as this would significantly reduce lipophilicity compared to **4** (Δclog*P* −1.5 to −2.0) whilst retaining a pharmacophore with potential for inhibition of monoamine reuptake (Fig. 1). Hence, a detailed investigation of the structure–activity relationships (SAR) of the 4-piperidines **5–7**, 3-piperidines **8** and 3-pyrrolidines **9** was undertaken with the primary objective of optimizing dual SNRI activity in these more polar templates.

4-Piperidines **5–7** (Table 2) were conveniently prepared in a three-step sequence as described in Scheme 1. Bromopyridines **12a–c** were converted to the corresponding Grignard reagents and then reaction with aldehyde **13** gave racemic alcohols **14**. Treatment of **14** with phenols ArOH under Mitsunobu conditions gave aryloxy ethers **15** and deprotection of the *N*-Boc amine with TFA afforded the target compounds **5–7**. The two pairs of single enantiomers of **5l–a/b** and **5m–a/b** (Table 3) were prepared by separation of the corresponding racemic *N*-Boc aryloxy ethers **15** by chiral HPLC followed by deprotection with TFA.

The synthesis of (3*R*)-piperidines **8a**,**b** (Table 4) is illustrated in Scheme 2. Resolution of (±)-ethyl nipecotate (**16**) with L-(+)-tartaric acid by the method of Gollamudi[12] gave (*R*)-**17** (>99% ee) and (*S*)-**18** (>99% ee). 3-Piperidine **17** was then protected as the *N*-Boc amine **19**. Reduction of **19** with DIBAL gave alcohol **20** and oxidation under Swern conditions gave aldehyde **21** which was converted through to (3*R*)-piperidines **8a**,**b** by the three-step sequence as described for 4-piperidines in Scheme 1. The (3*S*)-piperidines **8c**,**d** were prepared by an identical sequence but starting with (*S*)-ethyl nipecotate **18**.

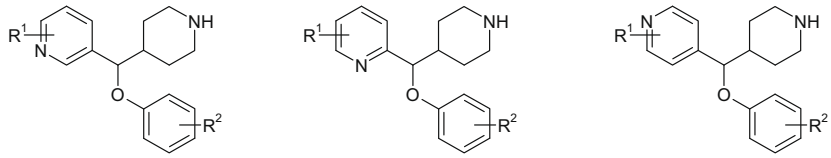
The synthesis of (3*R*)-pyrrolidines **9a**,**b** (Table 4) is shown in Scheme 3. The chiral (3*R*)- and (3*S*)-pyrrolidine rings were constructed by Michael addition and cyclization of (*R*)-α-methylbenzylamine (**23**) with dimethyl itaconate (**22**) to give an equal mixture of lactams **24** and **25** as described by Domagala;[13] this mixture of lactams was separated by chromatography to give (*R*,*R*)-**24** (>99% de) and (*R*,*S*)-**25** (>99% de). Reduction of **24** with $LiAlH_4$ gave alcohol **26** and the *N*-benzyl chiral auxiliary/protecting group was exchanged for the *N*-Boc amine **27** by transfer hydrogenation in the presence of $(Boc)_2O$. Oxidation of **27** under Swern conditions gave aldehyde **28** which was converted through to (3*R*)-pyrrolidines **9a**,**b** by the three-step sequence as described for 4-piperidines in Scheme 1. The (3*S*)-pyrrolidines **9c**,**d** were prepared by an identical sequence but starting with (*R*,*S*)-lactam **25**.

Target compounds **5–9**, **10** and **11** (Tables 1–4) were tested for their ability to inhibit the uptake of [^{3}H]-5-HT, [^{3}H]-NA and [^{3}H]-DA in HEK293 cells expressing a single human transporter.[14] Compound lipophilicity was assessed by calculation of partition coefficients (clog*P*). Selected compounds were then screened for metabolic stability in human liver microsomes (HLM), for CYP2D6 inhibition, and binding to the potassium hERG channel as a measure of ion channel activity.

The SAR of the aryloxy ring (R^2) was initially explored in the 3-Py isomer **5**. Introduction of lipophilic groups at the 2-position (**5a**–**e**) gave SNRIs with the 2-Cl **5a** having the most potent dual activity. Appropriate monosubstitution also gave selective NRIs and selective SRIs: **5f** (R^2 = 2-Ph) was a very potent NRI with good selectivity over SRI and DRI activity (>50-fold); **5j** (R^2 = 4-Et) and **5k** (R^2 = 4-SMe) were potent SRIs with excellent selectivity over both NRI and DRI (>600-fold). The combination of 2- and 3-disubstitution gave potent dual SNRIs **5l**, **5n**, **5o** and the introduction of a 6-Me group onto the Py ring, compound **5m**, was tolerated and marginally reduced DRI activity (**5l** vs **5m**). The corresponding 2,4-dichloro analogue **5p** was a selective SRI and so NRI activity had been lost by inclusion of a 4-Cl group (**5p** vs **5a**).

The SAR of the 2-Py isomer **6** generally mimicked that of **5** as an NRI **6a** was again achieved with bulky R^2 = 2-Ph, and **6b** (R^2 = 2-Cl; 3-Cl) was a potent dual SNRI. The 2-Py template was also used to further explore the SAR of methyl substitution (R^1 = Me). The 2-

Table 2
In vitro inhibition of monoamine reuptake for racemic 4-piperidines **5**, **6** and **7**[a,b,c]



5: 3-Py **6**: 2-Py **7**: 4-Py

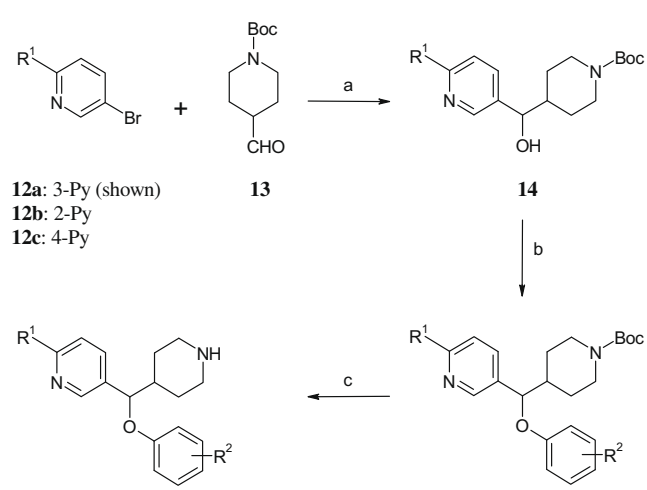
Compound	R^1	R^2	clog*P*	5-HT IC_{50} (nM)	NA IC_{50} (nM)	DA IC_{50} (nM)
Duloxetine (**2**)[d]	–	–	4.3	4	5	590
5a	H	2-Cl	3.0	9	30	400
5b	H	2-Et	3.4	61	91	>4000
5c	H	2-OEt	2.6	80	13	>2920
5d	H	2-CF_3	3.5	77	106	ND
5e	H	2-OCF_3	3.2	95	45	>40,000
5f	H	2-Ph	3.7	109	2	>40,000
5g	H	2-OPh	4.1	76	23	>4000
5h	H	3-Cl	3.2	3	23	1600
5i	H	3-Et	3.4	7	404	ND
5j	H	4-Et	3.4	5	4850	7830
5k	H	4-SMe	2.9	7	5850	>30,000
5l	H	2-Cl; 3-Cl	3.6	11	7	150
5m	6-Me	2-Cl; 3-Cl	4.1	14	14	590
5n	H	2-F; 3-F	2.6	3	24	1070
5o	H	2-Me; 3-Me	3.3	3	42	1270
5p	H	2-Cl; 4-Cl	3.7	5	>400	480
5q	H	2-Cl; 5-Cl	3.7	7	84	>4000
5r	H	3-Cl; 5-Cl	4.0	10	>400	ND
5s	H	2-Cl; 3-Cl; 5-Cl	4.3	10	215	ND
6a	H	2-Ph	3.7	>400	33	ND
6b	H	2-Cl; 3-Cl	3.6	6	23	353
6c	3-Me	2-Cl; 3-Cl	4.1	11	>400	ND
6d	4-Me	2-Cl; 3-Cl	4.1	8	35	644
6e	5-Me	2-Cl; 3-Cl	4.1	16	48	3470
6f	H	2-Cl; 4-Cl	3.7	7	>400	ND
7a	H	2-Cl; 3-Cl	3.6	8	8	60
7b	H	2-Cl; 4-Cl	3.7	7	>400	ND

[a] See Ref. 14 for complete details of assay conditions.
[b] Monoamine reuptake IC_{50} values are geometric means of at least two experiments. Differences of <2-fold should not be considered significant.
[c] ND denotes not determined.
[d] Data is presented for comparison in a common assay format.

Py ring could accommodate a Me group at the 4- and 5-positions to give SNRIs (**6b** vs **6d**, **6e**) although the 3-Me isomer **6c** retained SRI activity but NRI activity was lost. The 4-Py **7a** also gave dual SNRI activity but with the most significant DRI activity of the three pyridine isomers (**5l** vs **6b** vs **7a**).

In summary, an emerging understanding of the SAR within these 4-piperidine scaffolds **5**–**7** showed that the aryloxy ring played an important role in modulating NRI and SRI activity; that is, appropriate substitution at the 2-position conferred capricious NRI activity whereas substitution at the 3/4-position gave robust SRI activity. The NRI activity was sensitive to both the position and the nature of the R^2 group whereas SRI activity was less sensitive to these factors and more tolerant of groups at other positions on the ring. From this analysis, **5l** and **5m** emerged as examples with a combination of superior dual SNRI activity and selectivity over DRI.

Caution must be exercised when evaluating SAR from the biological activities of racemic compounds as the contribution to the observed effects may not be equal for each enantiomer; this is further complicated when seeking dual activities at two biological targets.[15] Hence, compound **5l** and **5m** were then prepared as the two single enantiomers **5l–a**,**b** and **5m–a**,**b** so as to determine the influence of absolute stereochemistry on SRI, NRI and DRI activity (Table 3).

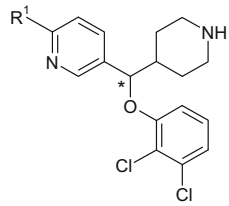


12a: 3-Py (shown) **13** **14**
12b: 2-Py
12c: 4-Py

5: 3-Py (shown) **15**
6: 2-Py
7: 4-Py

Scheme 1. General synthesis of 4-piperidines **5**–**7**. Reagents and conditions: (a) *i*-PrMgCl, THF, 0 °C→rt; (b) ArOH, $Me_2NCON{=}NCONMe_2$, *n*-Bu_3P, toluene, 85 °C; (c) TFA, CH_2Cl_2, rt.

Table 3
In vitro inhibition of monoamine reuptake,[a,b] human liver microsomal stability,[c] CYP2D6 inhibition and hERG binding activity for single enantiomer 4-piperidines **5**[d]



5

Compound	R^1	stereochemistry[d] *	5-HT IC_{50} (nM)	NA IC_{50} (nM)	DA IC_{50} (nM)	HLM $T_{1/2}$ (min)	CYP2D6-i IC_{50} (nM)	K^+, hERG IC_{50} (nM)
Duloxetine[e]	–	–	4	5	590	>120	1,000	
5l-a	H	Enantiomer 1	7	6	71	>120	20,000	5180
5l-b	H	Enantiomer 2	3	128	375	>120	2000	1970
5m-a	Me	Enantiomer 1	16	17	270	>120	30,000	
5m-b	Me	Enantiomer 2	37	220	820	>120	5500	

[a] See Ref. 14 for details of assay conditions.
[b] Monoamine reuptake IC_{50} values are geometric means of at least two experiments. Differences of <2-fold should not be considered significant.
[c] Maximum measurable half-life was 120 min.
[d] Compounds are single enantiomers of undetermined absolute stereochemistry.
[e] Data is presented for comparison in a common assay format.

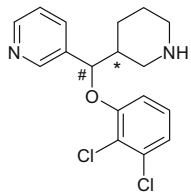
Screening of the separate enantiomers showed one isomer possessed more SRI, NRI and DRI activity combined with weaker activity for CYP2D6 and hERG inhibition (Table 3). Compounds **5l–a** and **5m–a** were potent dual SNRIs with selectivity over DRI (10- and 15-fold, respectively), excellent metabolic stability consistent with low predicted clearance, and minimal CYP2D6 inhibition.

Compound **5l–a** was then evaluated in additional pharmacology and pharmacokinetic screens as a representative example from this series. Compound **5l–a** had reduced ion channel activity compared to **11** as measured by binding to sodium (TTX-S: IC_{50} 2530 nM) and potassium (hERG: IC_{50} 5180 nM) channels, and minimal off-target activity against a panel of representative aminergic receptors (5-HT_{1A}, 5-HT_3, α_2, H_3: <15% @ 200 nM; 5-HT_{2A}: 30% @ 200 nM).

Additional pharmacokinetic data for **5l–a** was generated in vitro and in vivo in rat (Table 5). Screening in rat liver microsomes showed **5l–a** to have low metabolic stability (RLM, $T_{1/2}$ 5 min) consistent with high predicted clearance. Following single intravenous administration in rat, plasma clearance of **5l–a** was high relative to liver blood flow resulting in an elimination half-life of 2.0 h. Compound **5l–a** distributes extensively into tissues as shown by the high volume of distribution. Furthermore, it was encouraging that **5l–a** had physicochemical properties predicted to be consistent with CNS target space.[11,16,17]

The next phase of analogue design was to investigate 3-piperidines **8** and 3-pyrrolidines **9** where the relative positions of the amine N-atom and the distal aromatic groups could more closely mimic the spatial arrangement of duloxetine (**2**). 3-Piperidines **8** had significant activity at all three transporters with isomer **8a**

Table 4
In vitro inhibition of monoamine reuptake,[a,b] human liver microsomal stability,[c] CYP2D6 inhibition and hERG binding activity for single enantiomer 3-piperidines **8** and 3-pyrrolidines **9**[d]



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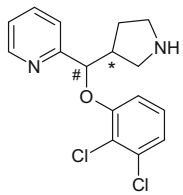
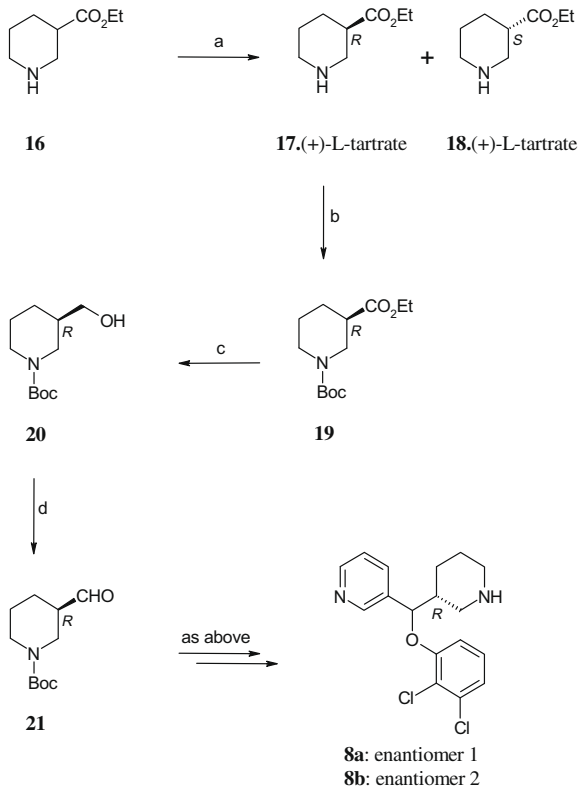


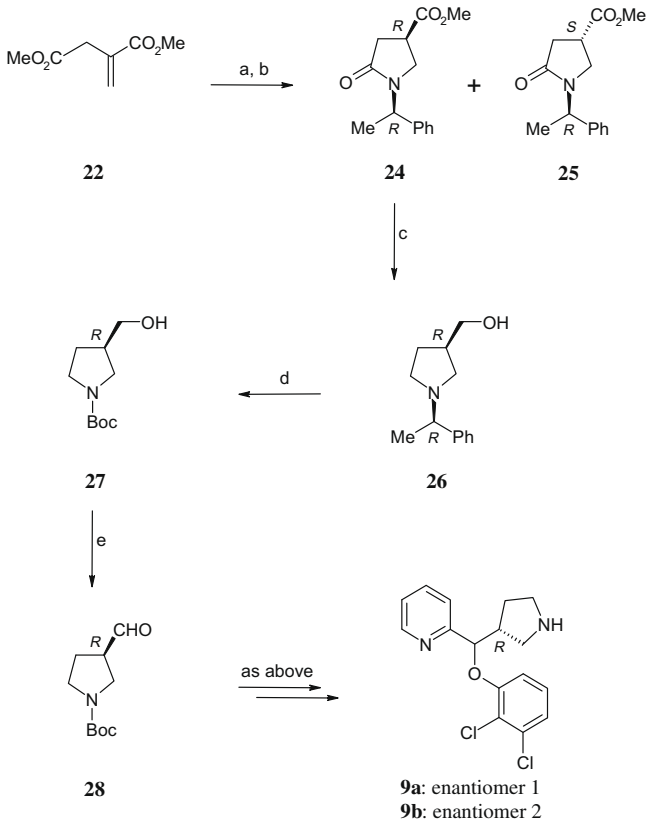
9

Compound	Stereochemistry[d] *	#	5-HT IC_{50} (nM)	NA IC_{50} (nM)	DA IC_{50} (nM)	HLM $T_{1/2}$ (min)	CYP2D6-i IC_{50} (nM)	K^+, hERG IC_{50} (nM)
8a	*R*	Enantiomer 1	4	9	6		2400	6610
8b	*R*	Enantiomer 2	16	35	99			
8c	*S*	Enantiomer 1	54	3	53			
8d	*S*	Enantiomer 2	3	13	36			
9a	*R*	Enantiomer 1	18	44	720			
9b	*R*	Enantiomer 2	17	9	330			
9c	*S*	Enantiomer 1	36	14	1060	>120	5300	10,000
9d	*S*	Enantiomer 2	13	43	1530	>120	600	>10,000

[a] See Ref. 14 for details of assay conditions.
[b] Monoamine reuptake IC_{50} values are geometric means of at least two experiments. Differences of <2-fold should not be considered significant.
[c] Maximum measurable half-life was 120 min.
[d] Compounds are single enantiomers with one chiral center of undetermined absolute stereochemistry.



Scheme 2. Synthesis of (3*R*)-piperidines **8a**,**b**. Reagents and conditions: (a) L-(+)-tartaric acid, EtOH; (b) $(Boc)_2O$, $NaHCO_3$, CH_2Cl_2, rt, 24 h; (c) DIBAL, CH_2Cl_2, 0 °C→rt, 18 h; (d) $(COCl)_2$, Me_2SO, $EtN(iPr)_2$, −78 °C.



Scheme 3. Synthesis of (3*R*)-pyrrolidines **9a**,**b**. Reagents and conditions: (a) (*R*)-α-methylbenzylamine (**23**), PhMe, molecular sieves 4 Å, 110 °C, 2d; (b) separation by chromatography; (c) $LiAlH_4$, THF, 0 °C→65 °C, 18 h; (d) 10% Pd/C, 2,5-dihydrotoluene, $(Boc)_2O$, EtOH, 85 °C, 2 h; (e) $(COCl)_2$, Me_2SO, $EtN(iPr)_2$, CH_2Cl_2, −78 °C.

Table 5
Pharmacokinetic parameters of **5l**–**a** after single intravenous administration to rat

	Rat (n = 2)
Intravenous dose (mg/kg)	5
Elimination half-life, $T_{1/2}$ (h)	2.0
Plasma clearance, Cl (ml/min/kg)	180
Volume of distribution, V_d (l/kg)	33

being a potent triple SNDRI (Table 4).[18] 3-Pyrrolidines **9** proved to be some of the most potent and selective dual SNRIs identified in this work (Table 4). Both compounds **9c** and **9d** had good selectivity over DRI (>30-fold), excellent HLM stability and weak hERG activity, however **9c** offered an advantage of weaker CYP2D6 inhibition.

Cerebrospinal fluid (CSF) concentrations were then used as a surrogate measure of CNS availability for **9c**.[19] Administration of **9c**[17] (3.1 mg/kg iv bolus, followed by 2.0 mg/kg iv infusion over 60 min, $n = 2$) showed a CSF-free plasma ratio of 0.36 ± 0.05 (mean ± sem) confirming reasonable CNS exposure.[20]

In conclusion, we have designed and evaluated a new series of 4-piperidine **5**–**7**, 3-piperidine **8** and 3-pyrrolidine **9** derivatives as inhibitors of monoamine reuptake. Structure–activity relationships established that monoamine reuptake inhibition are functions of amine, pyridine isomer, aryloxy ring substitution and stereochemistry. Consequently, selective NRIs (**5f**), selective SRIs (**5k**), dual SNRIs (**5l**–**a**, **5m**–**a**, **9c**) and triple SNDRIs (**8a**) were all identified. Furthermore, selected examples had excellent HLM stability, weak CYP2D6 inhibition, modest ion channel activity, and reasonable CNS penetration. The next phase of evolution of these templates will be reported in future publications.

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17. For suggested physicochemical property ranges for increasing the potential for CNS penetration, see Ref. 11. Physicochemical properties for **5l–a**: m.wt. 337; clog*P* 3.61; Log$D_{7.4}$ 1.2; pK_a 9.9 and 4.4; HBD 1; HBA 3; TPSA 34 Å^2. **9c**: m.wt. 323; clog*P* 3.05; log$D_{7.4}$ 0.9; HBD 1; HBA 3; TPSA 34 Å^2.
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