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Discovery and structure–activity relationships of novel selective norepinephrine and dual serotonin/norepinephrine reuptake inhibitors

John Boot,[a] Manuel Cases,[a] Barry P. Clark,[a] Jeremy Findlay,[a] Peter T. Gallagher,[a] Lorna Hayhurst,[a] Teresa Man,[a] Christian Montalbetti,[b] Richard E. Rathmell,[a] Hélène Rudyk,[a] Magnus W. Walter,[a,*] Maria Whatton[a] and Virginia Wood[a]

[a]*Eli Lilly & Co. Ltd, Lilly Research Centre, Erl Wood Manor, Windlesham, Surrey GU20 6PH, UK*
[b]*Evotec OAI, 151 Milton Park, Abingdon, Oxon OX14 4SD, UK*

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Abstract—Novel arylthiomethyl morpholines are potent selective norepinephrine reuptake inhibitors (NERIs) and dual serotonin/norepinephrine reuptake inhibitors (SRI/NERIs). The target compounds were prepared using a stereochemically versatile synthesis featuring an aldol condensation as the key step. One enantiomer of the 2-methoxy-substituted analogue was found to be a potent and selective norepinephrine reuptake inhibitor, whereas the opposite enantiomer was a potent dual serotonin/norepinephrine reuptake inhibitor.

1. Introduction

Monoamine reuptake inhibition is an important neuropharmacological strategy for the treatment of major affective disorders.[1] Selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine **1** (Prozac™), are widely used in the treatment of depression.

Only two selective norepinephrine reuptake inhibitors (NERIs) are currently in clinical use. Lilly recently introduced atomoxetine (Strattera™) **2** for the treatment of attention-deficit/hyperactivity disorder (ADHD).[2] Reboxetine (Edronax™) **4**, another selective NERI, is marketed in Europe for the treatment of depression.[3] The combination of multiple mechanisms of action in a single active ingredient is an important concept in psychopharmacology. Combination of serotonin and norepinephrine reuptake inhibition for example in duloxetine **3** (Cymbalta™) has been shown to improve potency and accelerate onset of action of antidepressant activity.[4] Thus, there is continued interest in biogenic amine reuptake inhibitors with both selective and mixed activity profiles (Fig. 1).

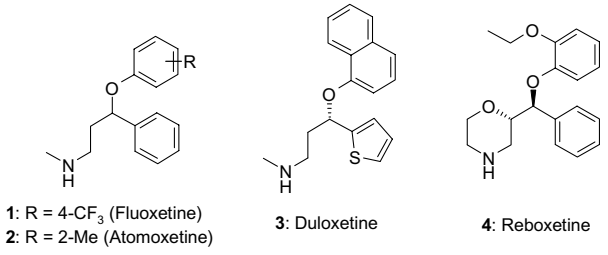

Figure 1. Selective and dual monoamine reuptake inhibitors.

2. Target design

Atomoxetine **2**, fluoxetine **1**, and duloxetine **3** contain a 3-aryloxypropylamine scaffold. This privileged structural motif has the potential for high affinity binding to biogenic amine transporters. The same motif can also be found in reboxetine **4** where it is constrained in a morpholine ring system. The nature of the aromatic substituent R in fluoxetine and atomoxetine has a

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* Corresponding author. Tel.: +44 1276 484786; fax: +44 1276 483305; e-mail: magnus.walter@lilly.com

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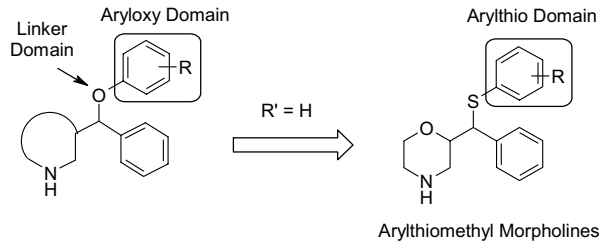


Figure 2. Arylthiomethyl morpholine targets.

significant influence on the activity and selectivity of compounds as inhibitors of the serotonin transporter (SERT) and/or the norepinephrine transporter (NET).

The objective of this study was to investigate biogenic amine reuptake inhibition (activity against NET, SERT and the dopamine transporter, DAT) of compounds with a sulfur atom in the linker domain (Fig. 2).

3. Chemistry

The target design outlined above required the development of a flexible and stereoselective synthetic approach to arylthiomethyl morpholines. Existing routes to reboxetine **4** and analogues thereof introduce the aryloxy domain early with closure of the morpholine ring occurring at a late stage in the synthetic scheme.[5,6]

We envisaged the approach shown in Figure 3 in which a suitable intermediate, such as an activated arylmethyl morpholine **A**, would allow variation of the arylthio domain through introduction of a variety of thiophenols at a late stage in the synthetic scheme. The morpholine ring would be derived from readily available *N*-benzyl protected morpholinone **5**.[7]

Reaction between benzaldehyde and the enolate derived from readily available *N*-benzyl-2-morpholinone **5** gave an acceptable yield of the two diastereomeric benzylalcohols **6** and **7** in a ratio of 2.2/1 (Scheme 1).[7] The aldol products could be separated by chromatography on silica gel. The assignment of relative stereochemistry was based on the coupling constants between the proton at

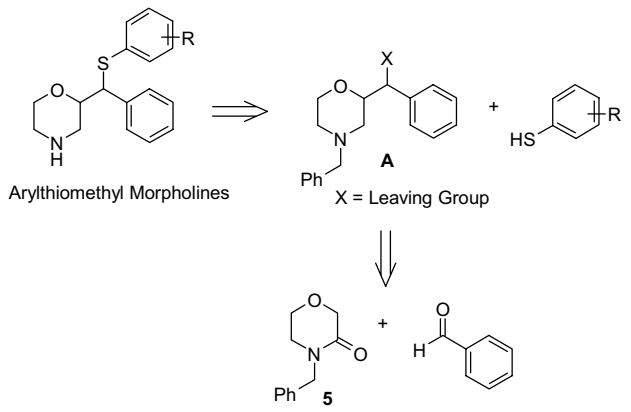
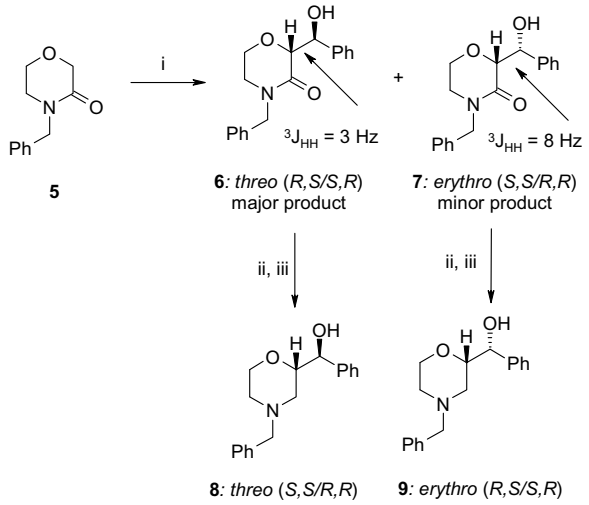


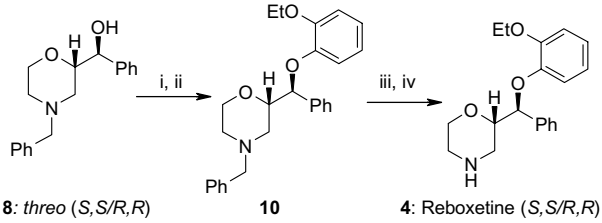
Figure 3. Retrosynthetic analysis of arylthiomethyl morpholines.



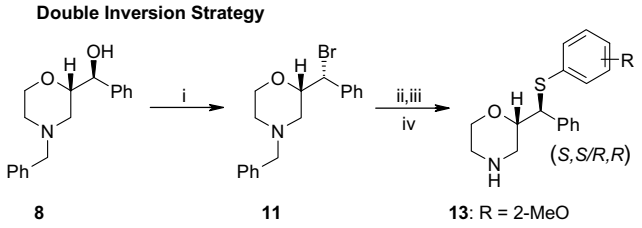
Scheme 1. (i) LDA (1.5 equiv), THF, −78 °C, 30 min; PhCHO (1 equiv) −78 °C, 1 h (inverse addition: anion to aldehyde) 56%; (ii) BH_3, THF, 60 °C, 2 h followed by MeOH; (iii) HCl (aq), 60 °C, 1 h, 68% (major ds **8**), 60% (minor ds **9**).

C-2 of the morpholine ring and the benzylic hydrogen. The initial assignment of the relative stereochemistry was later confirmed by X-ray crystallographic analysis.[8] Diborane-mediated reduction of the lactam gave morpholine benzyl alcohols **8** and **9** in good yield.

The stereochemical assignment of aminoalcohol **8** derived from the major aldol product was confirmed by conversion to 2-ethoxyaryloxy analogue **4** which was compared to an authentic sample of reboxetine (Scheme 2). Reboxetine is marketed as a mixture of the (*S*,*S*) and (*R*,*R*) form. Aminoalcohol **8** was converted to the corresponding benzyl bromide using polymer-supported triphenylphosphine and carbon tetrabromide with inversion of configuration at the benzylic position. Bromide displacement with 2-ethoxy phenol gave *N*-protected arylether **10**. Due to the presence of the hydrogenolytically labile benzyl group a two-step deprotection procedure was adopted.[9] Treatment of **10** with α-chloroethyl chloroformate followed by methanolysis of the intermediate α-chloroethyl carbamate removed the protecting group. After conversion into the hydrochloride salt the sample obtained via this route from *threo*-alcohol **8** was found to be identical to an authentic sample of commercial (*S*,*S*/*R*,*R*) reboxetine **4**. Attempts to introduce the aryloxy group before reduction of the



Scheme 2. (i) PS–PPh_3, CBr_4, $CHCl_3$, reflux, 62%; (ii) 2-EtO–C_6H_4OH, KOtBu, *t*-BuOH, 80 °C, 80%; (iii) α-chloroethyl chloroformate, Et_3N, DCM, 40 °C; (vi) MeOH, reflux, 43% over two steps.



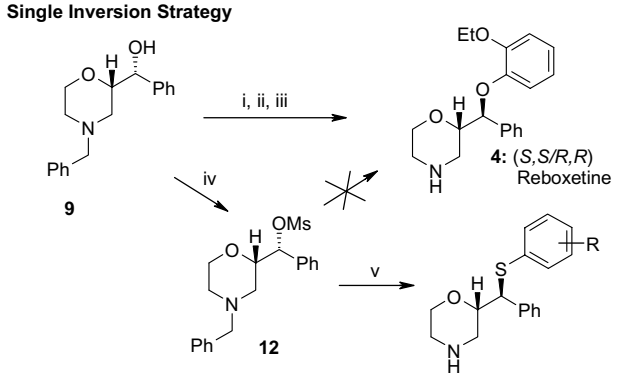
Scheme 3. (i) PPh_3, CBr_4, $CHCl_3$, reflux, 62%; (ii) arylthiol, Cs_2CO_3, DMF, 95 °C, 74% (R = 2-MeO); (iii) α-chloroethyl chloroformate, Et_3N, DCM, 40 °C; (iv) MeOH, reflux, 75% over two steps.

lactam moiety in **6** and **7** led to formation of significant amounts of eliminated product and were abandoned. This double inversion strategy was successfully employed in the synthesis of the target arylthiomethyl morpholines (Scheme 3).

To complement this efficient route to the desired *threo* (*S*,*S*/*R*,*R*) products from the major aldol product **6** we also investigated a single inversion approach (Scheme 4). This would then allow us to use the minor diastereomer **9** in the preparation of the target molecules.

Formation of an oxy-phosphonium intermediate under Mitsunobu-type conditions employing 1,1-(azodicarbonyl)dipiperidine (ADDP)[10] followed by displacement with 2-ethoxyphenol gave the expected (*S*,*S*/*R*,*R*) diastereomer mixture of reboxetine after standard deprotection with α-chloroethyl chloroformate. In an alternative approach, mesylate **12** could be obtained under standard conditions, but displacement with 2-ethoxyphenol did not lead to the desired product. Displacement of mesylate **12** with arylthiols using caesium carbonate as base in DMF was successful and gave access to the desired arylthiomethyl morpholine targets in similar yields to the double inversion strategy.

Figure 4 gives a summary of our stereochemical strategies to the target arylthiomethyl morpholines. Using either a double or a single inversion strategy both the *threo* product **6** and the *erythro* product **7** of the key



Scheme 4. (i) ADDP, 2-EtO–C_6H_4OH, PBu_3, THF 40 °C, 56%; (ii) α-chloroethyl chloroformate, Et_3N, DCM, 40 °C; (iii) MeOH, reflux, 45% over two steps; (iv) MsCl, pyridine, DCM, room temperature; (v) arylthiol, Cs_2CO_3, DMF, 95 °C.

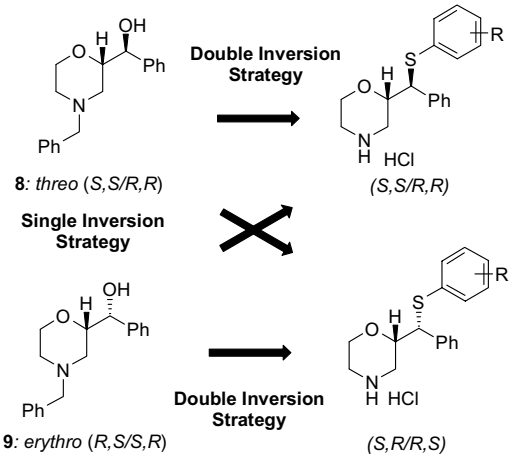


Figure 4. Stereochemical strategies to (*S*,*S*/*R*,*R*) arylthiomethyl morpholines.

aldol condensation could be used as starting material for the synthesis of the target molecules.

4. Stereochemistry and SAR

All target compounds were tested as *S*,*S*/*R*,*R* racemates for reuptake inhibition at the norepinephrine (NET), serotonin (SERT) and dopamine transporter (DAT).[8]

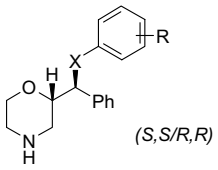
Table 1 shows the inhibitory activity of a limited set of 2-substituted-thioaryl morpholines compared with (*R*,*R*/*S*,*S*) reboxetine (**4**).

Replacement of oxygen in reboxetine by sulfur in arylthiomethyl morpholines **13** to **16** maintained potent levels of norepinephrine reuptake inhibition. Whilst thioarylmethyl morpholines **13** to **17** did not inhibit dopamine reuptake, compounds **13** to **16** were potent serotonin reuptake inhibitors. The methoxy analogue of reboxetine (corresponding to **14**) had been reported to give poor serotonin reuptake inhibition.[5,10] NET and SERT inhibition of methyl substituted morpholines **15** to **17** appeared to decrease in the order *ortho* > *meta* > *para*. To investigate the interesting possibility of dual activity against both the serotonin and norepinephrine transporter in single compounds racemic 2-methoxy analogue **14** was separated into its enantiomers **14a** and **14b** using chiral HPLC (Table 2). The faster eluting isomer 1 was found to be a potent selective norepinephrine reuptake inhibitor whereas the slower eluting isomer showed potent inhibition (NET and SERT $K_i \leqslant 20$ nM) of both norepinephrine and serotonin reuptake.

5. Summary

We have developed an efficient and highly versatile route to arylthiomethyl morpholine analogues of reboxetine. Selective norepinephrine reuptake inhibition and dual norepinephrine/serotonin reuptake inhibition was found to reside in different enantiomers of a member of this series. More detailed SAR studies of both series and

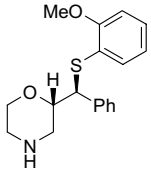
Table 1. Inhibition of monoamine reuptake for norepinephrine, serotonin and dopamine



Compound	X	R	K_i (nM)[a]		
			NET	SERT	DAT
13	S	H	17.6 ± 2.4	36 ± 0.3	522.1 ± 48.7
14	S	2-OMe	10.7 ± 2.2	1.2 ± 1.1	>200 (9.7 ± 3.0%)[c]
15	S	2-Me	8.3 ± 1.0	0.2 ± 0.1	226.9 ± 34.9
16	S	3-Me	108.6 ± 7.4	3.2 ± 1.2	>200 (51 ± 0.2%)[c]
17	S	4-Me	364.3 ± 19.3	>100 (19.3 ± 2.3)[b]	>200 (8 ± 1.1%)[c]
Reboxetine 4	O	2-OEt	1.9 ± 0.2	>100 (25 ± 18%)[b]	>200 (2 ± 1.7%)[c]

[a] Values are means of at least three experiments.
[b] %-displacement at 100 nM.
[c] %-displacement at 1000 nM. For experimental details of assay conditions see Ref. 8. Minimum significant ratio (MSR): NET:2.5; SERT:3.0; DAT:1.6. NET, SERT and DAT binding data for fluoxetine **1**, atomoxetine **2**, and duloxetine **3** has recently been published.[11]

Table 2. Inhibition of monoamine reuptake for norepinephrine, serotonin and dopamine



Compound	Stereochemistry	K_i (nM)[a]		
		NET	SERT	DAT
14	(*SS*/*RR*)	10.7 ± 2.2	1.2 ± 1.1	>200 (9.7 ± 3.1%)[b]
14a	Isomer 1	1.7 ± 0.4	66.2 ± 3.0	>200 (2.8 ± 1.8%)[b]
14b	Isomer 2	24.6 ± 2.3	1.5 ± 0.2	>200 (19.0 ± 3.4%)[b]

[a] Values are means of at least three experiments.
[b] %-displacement at 1000 nM.

assignment of absolute stereochemistry will be communicated in due course.

6. Selected experimental data

Compound **6**: MW 297.36; $C_{18}H_{19}NO_3$: ^{1}H NMR ($CDCl_3$): δ 7.36–7.41 (2H, m), 7.16–7.31 (6H, m), 6.86–6.91 (2H, m), 5.14 (1H, d, 3 Hz), 4.71 (1H, d, 14 Hz), 4.48 (1H, d, 3 Hz), 4.25 (1H, d, 14 Hz), 4.20 (1H, br, s), 3.89 (1H, ddd, 11 Hz, 3 Hz, 2 Hz), 3.67 (1H, dt, 11 Hz, 3 Hz), 3.16 (1H, dt, 12 Hz and 4 Hz), 2.86 (1H, br, d, 12 Hz); LCMS: *m*/*z* 298 $[M + H]^+$.

Compound **7**: MW 297.36; $C_{18}H_{19}NO_3$: ^{1}H NMR ($CDCl_3$): δ 7.55–7.61 (2H, m), 7.36–7.50 (6H, m), 7.25–7.31 (2H, m), 5.21 (1H, d, 2 Hz), 5.09 (1H, d, 8 Hz and 2 Hz), 4.73 (2H, s), 4.37 (1H, d, 8 Hz), 4.01 (1H, ddd, 12 Hz, 3 Hz, 2 Hz), 3.77 (1H, dt, 11 Hz, 4 Hz), 3.50 (1H, dt, 12 Hz, 4 Hz), 3.16 (1H, br, d, 12 Hz); LCMS: *m*/*z* 298 $[M + H]^+$.

Compound **14**: MW 315.44; $C_{18}H_{21}NO_2S$: ^{1}H NMR ($CDCl_3$): δ 7.14–7.34 (7H, m), 6.74–6.84 (2H, m), 4.50 (1H, d, 8 Hz), 4.10 (1H, d, 11 Hz), 3.85–4.00 (4H, m), 3.74 (1H, dt, 1 Hz, 11 Hz), 2.82–3.02 (2H, m), 2.66–3.02 (3H, m); *m*/*z* 316 $[M + H]^+$. Compound **14a** was obtained after separation by chiral HPLC on a Chiralcel-OJ(3624) semi-preparative column using a gradient of heptane/isopropyl alcohol as eluent (ee >95%, sample concentration 0.2 mg/ml 1.0 ml/min, sample solvent: 50% heptane, 50% ethanol, 0.2 dimethylethyl amine), t_R = 9.32 min. Compound **14b** was obtained after separation by chiral HPLC using the same conditions; t_R = 11.45 min (ee >95%).

Acknowledgements

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