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Design and synthesis of reboxetine analogs morpholine derivatives as selective norepinephrine reuptake inhibitors

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ABSTRACT

As part of a discovery effort aimed at identifying novel norepinephrine reuptake inhibitors (NRIs), a number of substituted morpholines were designed and synthesized. The target compounds contain vicinal stereogenic centers, and the program was greatly facilitated by the adoption of efficient synthetic routes which allowed for the late stage incorporation of structural and physicochemical diversity into the targets. Structure–activity relationships were developed by optimizing individual ring components of the structure for NRI potency and for selectivity against other monoamine reuptake transporters. Several novel morpholine derivatives with a potent and selective NRI profile are described.

Modulating central norepinephrine (NE) levels via its reuptake transporter (NET) has been shown to be an effective pharmacotherapy strategy for treating a variety of illnesses including ADHD,[1–4] depression,[5] fibromyalgia,[6] peripheral neuropathy, and other types of pain.[7] Consequently, there is much interest in developing agents which selectively inhibit the norepinephrine reuptake transporter (NRI's). The precise mechanism by which an NRI might have beneficial effects on each of these disease states varies – for instance, atomoxetine (**1**, Strattera™), a relatively selective NRI recently approved for the treatment of ADHD, is proposed to provide efficacy for ADHD symptoms by increasing synaptic NE and DA levels via blockade of the NET in cortical regions associated with attention and memory.[8] Similarly, elevated concentration of NE in the synaptic cleft is considered to increase or maintain the activity of the descending inhibitory bulbospinal pathway, which is compromised in chronic pain conditions, thereby leading to analgesic effects in some patients.[9] Previous work in the area of small molecule monoamine reuptake inhibitors has shown that it is challenging to identify molecules with high affinity for inhibition of NET which simultaneously exhibit high selectivity (>100×) versus the related serotonin reuptake transporter (SERT) and dopamine reuptake transporter (DAT). In this paper, we describe elements of a program which was aimed at identifying centrally acting NRI's with the potential for treating disease, specifically, the synthesis and structure–activity relationships of a series of morpholine-based NRIs with general structure **3**.

Certain substituted morpholines such as **2** have been shown to exhibit excellent binding selectivity for NET versus SERT and continue to attract attention to their synthesis and biological activity.[10–12] We developed an interest in evaluating structures of general form **3** (Fig. 1) for NRI potency, with the aim to access compounds with varied physicochemical properties while retaining selectivity and NRI activity. Initially, we looked to literature describing the preparation of related morpholine derivatives for synthetic inspiration.[13] The first published route to **2** is highly reliable, but lengthy. It requires a 10-step linear sequence where the desired diversity at R_1 and R_2 (**3**, Fig. 1) is incorporated into the molecules at the very beginning of the synthesis and R_2 is primarily limited to phenyl. Despite its excellent utility, this route did not incorporate suitable speed or design flexibility to allow for a rapid and complete exploration of the broader chemical space embodied within generic structure **3**. Our first attempt at a general synthesis of some target morpholines is outlined in Scheme 1. We expected

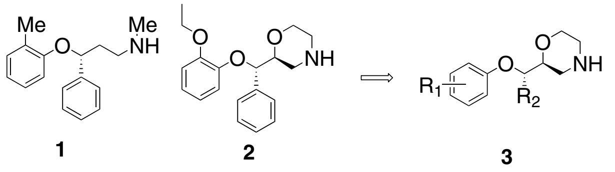

Figure 1. General structure of compounds targeting selective NRI activity.

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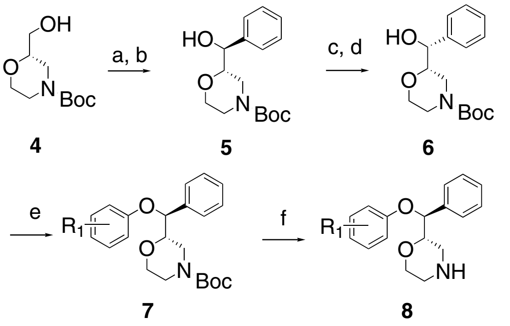
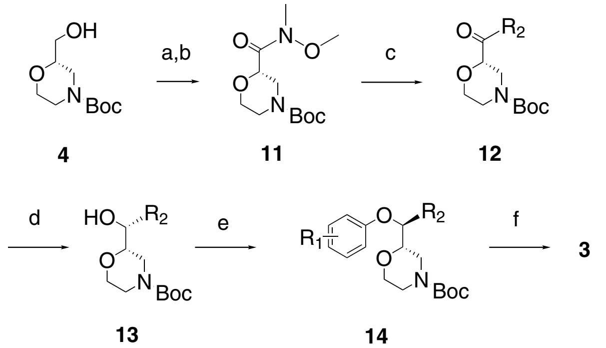


Scheme 1. Reagents and conditions: (a) IBX; (b) C_6H_5MgBr, −78 °C, 67% for two steps; (c) C_6H_5COOH, PPh_3, DIAD; (d) 5% NaOH, 60 °C, 81% for two steps; (e) C_6H_5OH, PPh_3, DIAD, 70–85%; (f) CF_3COOH or 4 M HCl in Dioxane, 0 °C, 80–90%.



Scheme 2. Reagents and conditions: (a) NaOCl, TEMPO, KBr, TBACl; (b) 1-propanephosphonic acid cyclic anhydride, 91% for two steps; (c) C_6H_5Li, −78 °C–rt, 45–80%; (d) H_2, *trans*-$RuCl_2$[(*R*)-xylbinap][(*R*)-daipen], 85%; (e) C_6H_5OH, PPh_3, DIAD, 70–85%; (f) CF_3COOH or 4 M HCl in Dioxane, 0°C, 80–90%.

that hydroxymorpholine **4** would be a useful common intermediate from which to access our targets. This important starting material was prepared in high optical purity according to a literature procedure.[14] In this approach, IBX was used to oxidize (*S*)-hydroxymorpholine **4** to deliver its aldehyde derivative in high yield.[15,16] For R_2 = phenyl (Fig. 1), Grignard addition of phenyl magnesium bromide to this sensitive aldehyde afforded a 6:1 mixture of diastereoisomeric secondary alcohols **5** which were chromatographically separated. A purified single isomer was subjected to a two-step inversion procedure consisting of Mitsunobu reaction with benzoic acid followed by benzoate hydrolysis. This process effectively converged the mixture to a single isomer (either one as desired) and provided a common intermediate for exploring the SAR of phenoxy ring substitution. Mitsunobu conditions were employed to couple the appropriate phenol with **6** (Scheme 1, (*S*,*S*) series shown), affording the Boc-protected targets **7** which were deprotected upon exposure to HCl in dioxane, providing the products **8** as their corresponding HCl salts in good yield. In order to verify the stereochemical identity of the chromatographically separated intermediates **5**, each isomer was carried independently through the outlined sequence to **2** and co-injected with standards of the same on chiral HPLC. This procedure indicated that the (2*S*,3*S*) alcohol (**5**) was the major isomer arising from the addition of phenyl magnesium bromide to the aldehyde. For most nucleophiles, the substrate-based stereocontrol of addition to the aldehyde was between 3:1 and 8:1 favoring the (2*S*, 3*S*) isomer. The new route had certain advantages, however, the addition of lithium-based organometallic nucleophiles to the aldehyde resulted in moderate to poor yields of the desired adducts; some Grignard reagents were also problematic. With benzyl magnesium bromide, we observed rearrangement to the scrambled toluene adducts (**9** → **10**, Fig. 2).

As a result of these and other issues with the generality and reliability of this route, we chose to seek an alternative method for generating diverse morpholine derivatives (**3**, Fig. 1), in particular, an approach which would be more amenable to generating non-phenyl substitutions at R_2 and allow isolation of single isomers at the R_2 stereocenter. Weinreb amide **11** was deemed to be a good alternate intermediate from which the target morpholine derivatives might be readily accessed.

This key compound was obtained in a two-step procedure wherein hydroxymorpholine **4** was oxidized by exposure to buffered bleach,[17] and the derived acid subsequently converted to the desired intermediate N,O dimethyl amide **11** via cyclic phosphinic acid anhydride promoted amidation (Scheme 2).[18] With the target electrophile (**11**) in hand, various organometallic reagents were added to the amide, typically affording the functionalized ketone **12** in moderate to good yield. The next task, namely reduction of ketone **12** in a stereocontrolled fashion, was critical to the success of this synthetic route, and several approaches were adopted to successfully address the stereocontrol in subclasses of these molecules.[19–21] Some substitutions required chromatography at this stage to upgrade the diastereoisomeric purity of the products. After establishing the required stereocenters, Mitsunobu coupling of selected substituted phenols with the secondary alcohols **13** proceeded without event, affording the Boc-protected ethers **14**. Removal of the carbamate protecting group was smoothly effected by treatment with HCl in dioxane as before, affording the morpholine products **3** in good yield.

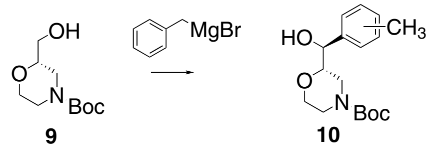
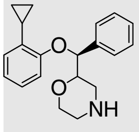
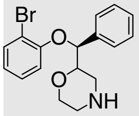


Figure 2. Undesired rearrangement observed during Grignard addition.

Catalytic hydrogenation was initially effective in setting the second stereocenter adjacent to the morpholine ring for $R_2 \neq$ phenyl, however, one drawback of this method was that a small amount (<10%) of racemization was sometimes observed at the morpholine center during the chiral reduction (**12** → **13**). Additionally, in some of the later cases, the resultant isomeric mixture of heterocyclic alcohol isomers (**13**) was not separable by flash chromatography.

An inelegant, but workable solution to this problem was found by carrying these mixtures through the remaining steps of the synthesis and separating the final target isomers by chiral preparatory HPLC. For such compounds, lacking positive proof of the stereochemical identity of the separated isomers, both isomers were screened for activity. The binding affinities for some of the more potent morpholine derivatives are given in Tables 1–4.

Table 1
Monoamine transporter binding of compounds with (R,S) and (S,S) configurations

Structures	Entry	Stereo chem	NET (nM)	SERT (nM)
	1	(2*S*,3*S*)	2	482
	2	(2*R*,3*S*)	35	75
	3	(2*S*,3*S*)	3	477
	4	(2*R*,3*S*)	17	105