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Identification of 1*S*,2*R*-milnacipran analogs as potent norepinephrine and serotonin transporter inhibitors

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Abstract—A series of milnacipran analogs were synthesized and studied as monoamine transporter inhibitors, and several potent compounds with moderate lipophilicity were identified from the 1*S*,2*R*-isomers. Thus, **15l** exhibited IC_{50} values of 1.7 nM at NET and 25 nM at SERT, which were, respectively, 20- and 13-fold more potent than 1*S*,2*R*-milnacipran **1**–**II**.

The antidepressant milnacipran (**1**, Fig. 1),[1] marketed as a racemic mixture, is a hydrophilic molecule ($\log D \sim 0$), and in this respect, differs from many CNS drugs such as atomoxetine **2** ($\log D = 0.8$).[2] Because of its low molecular weight and low lipophilicity, milnacipran exhibits almost ideal pharmacokinetics in humans, such as high oral bioavailability of ~85%, low inter-subject variability, limited liver enzyme interaction, moderate tissue distribution, and a reasonably long elimination half-life of ~8 h.[3] Its lack of potential for drug–drug interaction via cytochrome P450 enzymes is quite attractive because many CNS drugs are highly lipophilic and rely heavily on liver enzymes for elimination.[4]

The mechanism of action of milnacipran is believed to inhibit the monoamine uptake by the norepinephrine transporter (NET) and the serotonin transporter (SERT),[5] and milnacipran has a negligible activity at the dopamine transporters (DAT) and many monoamine receptors.[6] However, milnacipran has only a moderate potency at both human NET and SERT (Fig. 1), and its ratio at these two transporters is reported to be about 3:1.[7] Milnacipran is currently in phase III clinical trials for fibromyalgia, and recent reports have suggested a significant efficacy.[8] The SAR of milnacipran and its analogs based on in vivo efficacy was reported by Bonnaud and coworkers in 1987.[9] We have described the SAR of a series of *N*-alkyl and dialkyl amides, and potent analogs such as **3a** and **3b** were discovered.[10] Very recently, Roggen et al. reported the synthesis and SAR studies of a series of milnacipran analogs as single stereoisomers with a variation in the aromatic moiety.[11] Here, we report our continued efforts to discover potent 1*S*,2*R*-milnacipran analogs without a significant change in lipophilicity.

The milnacipran derivatives **6**–**8** were synthesized by a cyclization of the allyl esters **4**[12] to give the lactones **5**, which were elaborated to the desired products as a pair of enantiomers using a procedure similar to that for milnacipran (Scheme 1).[13]

The amide analogs of milnacipran **9**–**15** were prepared from phenylacetonitriles **16** and (*R*)-(−)-epichlorohydrin using a reported stereo-selective synthesis[11,13] or a modified procedure (NaHMDS/THF, Scheme 2).[14]

The target compounds **6**–**15** were tested in functional transport assays evaluating the inhibition of human

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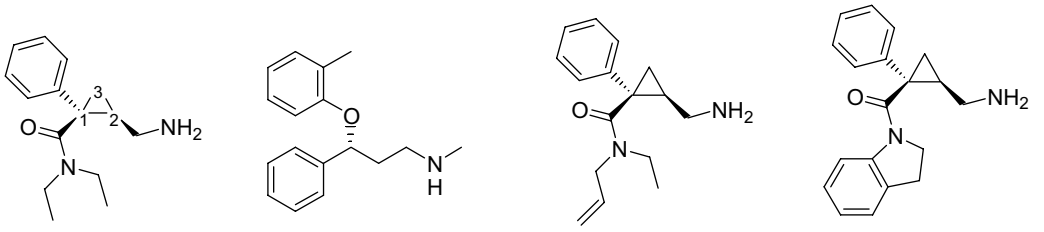
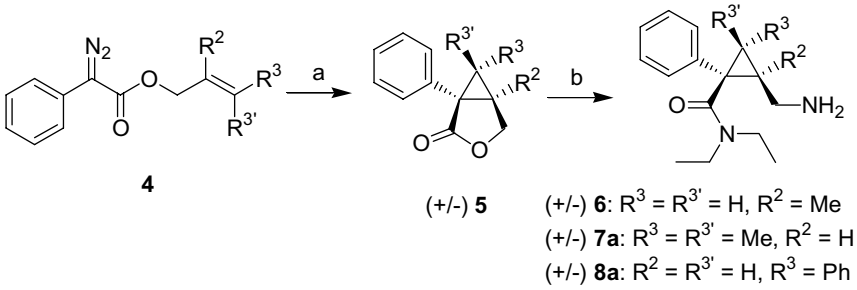
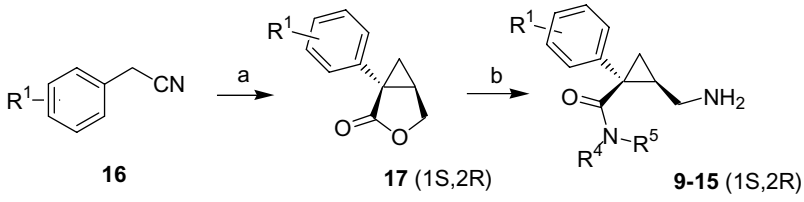


Figure 1. Chemical structures of atomoxetine, milnacipran and its potent analogs.

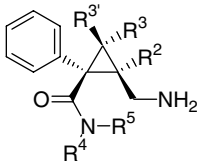


Scheme 1. Reagents and conditions: (a) $Rh(OAc)_2/CH_2Cl_2$/reflux, 3 h; (b) i—potassium phthalimide/DMF/140 °C, 16 h; ii—$SOCl_2/CH_2Cl_2$/rt, 2 h; iii—Et_2NH/CH_2Cl_2/0 °C to rt, 16 h; iv—NH_2NH_2/EtOH/rt, 16 h.



Scheme 2. Reagents and conditions: (a) i—$NaNH_2$/toluene or NaHMDS/THF/0 °C; ii—(*R*)-(−)-epichlorohydrin/0 °C to rt, 16 h; iii—KOH/EtOH/reflux, 8 h; iv—12N HCl/0 °C to rt, 2.5 h; (b) i—potassium phthalamide/DMF; ii—$SOCl_2$/reflux; iii—R^4R^5NH/CH_2Cl_2/0 °C to rt, 16 h; iv—NH_2NH_2/EtOH/rt, 16 h.

Table 1. Inhibition (IC_{50}, nM) of monoamine transporters by the cyclopropane-substituted milnacipran analogs **6**–**8**[a]



(+/-) **1**: $R^2 = R^3 = R^{3'} = H$
(+/-) **6**: $R^2 = Me$, $R^3 = R^{3'} = H$
(+/-) **7**: $R^2 = H$, $R^3 = R^{3'} = Me$
(+/-) **8**: $R^2 = R^{3'} = H$, $R^3 = Ph$

Compound	R^4NR^5	NET	SERT	DAT
1	NEt_2	77	420	6100
6	NEt_2	>10,000	6900	>10,000
7a	NEt_2	>10,000	>10,000	4500
7b	$EtNCH_2CH{=}CH_2$	6400	>10,000	>10,000
7c	Indolin-1-yl	>10,000	>10,000	>10,000
8a	NEt_2	>10,000	6400	>10,000
8b	$EtNCH_2CH{=}CH_2$	>10,000	3400	>10,000
8c	Indolin-1-yl	>10,000	560	4300

[a] Data are the average of two or more independent measurements.

NET, SERT, and DAT using a procedure similar to that described by Owens et al.[7,15] These results are summarized in Tables 1 and 2.

Since the conformation of milnacipran (**1**) is an important part of its pharmacophore, we first examined the substitution at the cyclopropane. Introducing a 2-methyl group (compound **6**) to milnacipran almost abolished its potency at both NET and SERT (Table 1). This result was somewhat of a surprise since the active pharmacophore based on our previous studies showed that the amino nitrogen is located under the cyclopropane ring,[10] and this additional methyl group might favor this conformation. One possible explanation is that this *cis*-2-methyl group limits the rotation of the 1-phenyl ring to a preferred orientation (Fig. 2). The 3,3-dimethyl derivative of milnacipran (**7a**) also possessed poor potency at the two transporters. In this case, the 3′-methyl group might prevent the *N*-alkyl group of **7** from getting close to the 1-phenyl