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Synthesis and structure–activity relationships of selective norepinephrine reuptake inhibitors (sNRI) with a heterocyclic ring constraint

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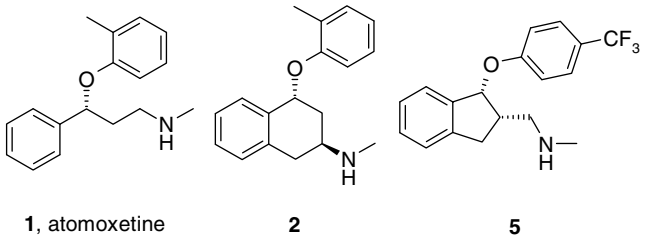
ABSTRACT

The design, synthesis and SAR of a series of heterocyclic ring-constrained norepinephrine reuptake inhibitors are described. As racemates, the best compounds compare favorably with atomoxetine (IC_{50}'s < 10 nM) in potency at the transporter.

Monoamine reuptake inhibition has been an effective therapeutic intervention in a variety of CNS diseases, starting with depression and recently expanding to include chronic pain, ADHD, and stress urinary incontinence.[1–4] We were interested in multiple indications in the therapeutic spectrum of selective norepinephrine reuptake inhibitors (sNRI), and initiated work directed toward finding potent and selective compounds with good pharmaceutical properties and minimal risk of drug–drug interactions. In the previous paper NBI 80532 (compound **2**), a rigid and potent sNRI with a significant risk of drug–drug interactions was discovered.[5] Further work toward improving the drug-like properties of active compounds is reported here.

The previous paper described a new ring constraint for the 3-aryloxypropylamine scaffold of atomoxetine that maintained potency and selectivity for NET but was significantly more rigid than atomoxetine **1**.[5] However, in compound **2** (Fig. 1), potent inhibition of CYP2D6 was also observed. In an effort to separate the two activities, other ring connectivities were explored. Our attention was drawn to the SSRI MDL 28618 (compound **5**),[6] an additional isomer of the indane core described previously.[5] Compound **5** had similar activity to fluoxetine, but the series selectivity profile had not been published. In order to determine the scope and selectivity of this ring constraint, both carbocyclic and heterocyclic cores were synthesized and studied.



1, atomoxetine **2** **5**

Figure 1. Structures of atomoxetine **1**, NBI 80532 **2**, and the SSRI MDL 27777A (racemic) **5**. MDL 28618A (*R*,*S*) is the active enantiomer.[17]

Synthesis of the indane compounds followed the literature procedure.[7,8] Synthesis of other core structures was generalized as shown in Scheme 1. All bicyclic ketones are commercially available except for isochromanone **12**, which was made in three steps from 2-iodobenzyl alcohol **30**. In all cases, Mannich reactions generated the tertiary amine ketones **15**–**19** that could then be converted predominantly to the *cis* amino alcohols **20**–**24** with L-selectride (~9:1 *cis*:*trans*) or to a mixture favoring the *trans* alcohols **25**–**29** with sodium borohydride (1:2–5 *cis*:*trans*). The two diastereomers were readily distinguishable by ^{1}H NMR coupling constant of the benzyloxy proton. When X was a heteroatom, selectivities with L-Selectride® decreased to 2:1 but could be restored with the more bulky reducing agent LS-Selectride®. In general, **15**–**29** were dimethyl substituted because the Mannich reactions gave high yields of crystalline products, and demethylation was accomplished in good yield.

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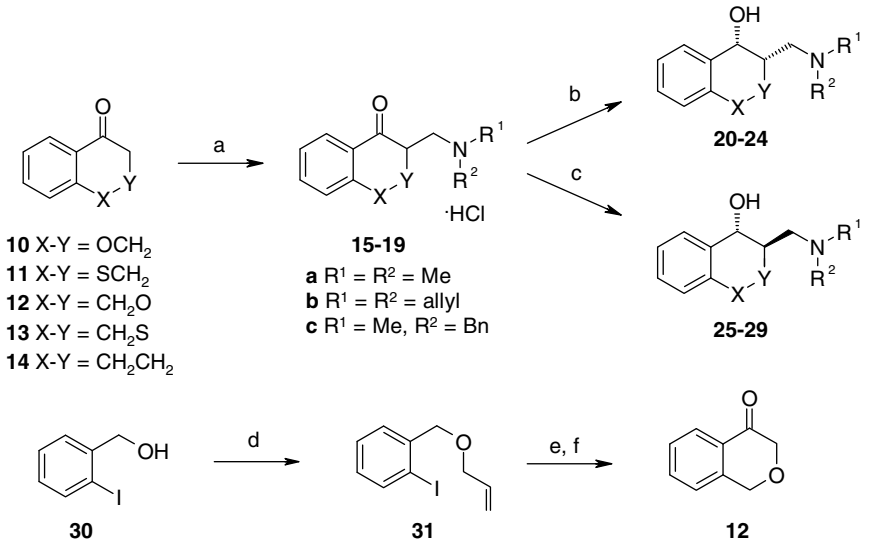
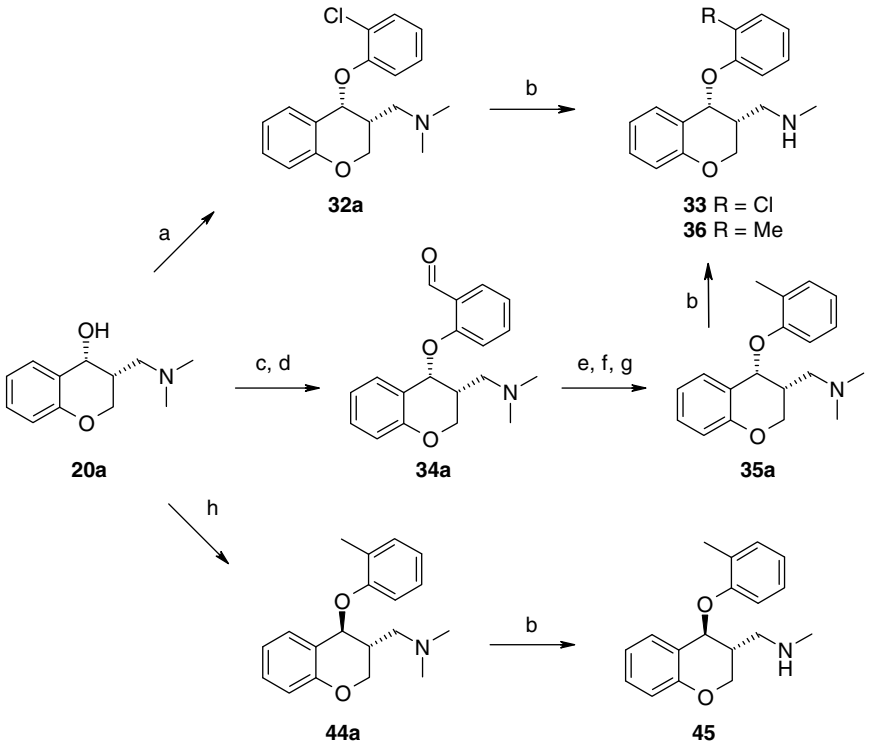


Scheme 1. Reagents and conditions: (a) R^1R^2NH, paraformaldehyde, concd HCl, EtOH or IPA, 16 h, 70 °C, 50–75%; (b) L-selectride, THF, −30 °C, 60–80%; (c) $NaBH_4$, MeOH, −15 °C, 60–90%; (d) allyl bromide, NaH, THF, 16 h, rt, quant; (e) $Pd(OAc)_2$, PPh_3, Et_3N, CH_3CN, 2 h, Δ_R; (f) O_3, pyr., DCM, MeOH, 5 h, −78 °C then DMS, rt, 3 h, 78% (3 steps).

Formation of final compounds followed the sequence shown in Scheme 2 for the chromane example. Starting from the *cis* alcohol **20a**, S_NAr substitution with an aryl fluoride[9] followed by deprotection with 1-chloroethyl chloroformate generated the target secondary methyl amines predominantly with retention of the *cis* configuration. Higher temperatures and extended reaction times led to epimerization as has been observed with **1**.[10] Conversely, a Mitsunobu reaction starting with either *cis* or *trans* alcohols generated predominantly the *trans* product, for example, **44a**. When X or Y is a heteroatom, the product was almost exclusively *trans*, probably due to neighboring group participation by the aminomethyl side chain in the more stabilized intermediate.[11] This was consistent with the expectation that the *trans* isomer, having only pseudoequatorial substitution, was more stable thermodynamically.

For the key 2-methyl substitution, generation of the *cis* product **35a** using 2-fluorotoluene was extremely low yielding, so the alternative literature method was employed.[12] S_NAr with the *tert*-butyl imine of 2-fluorobenzaldehyde followed by hydrolysis to the alde-



Scheme 2. Reagents and conditions: (a) aryl fluoride, for example, 2-chlorofluorobenzene for **32a**, NaH and potassium benzoate or KOtBu, DMSO or DMA, 16 h, 70 °C, 30–80%; (b) ACE-Cl, diisopropylethylamine, 1,2-DCE, 1 h, 45 °C, then MeOH, rt, 32–75%; (c) *tert*-butyl-[1-(2-fluoro-phenyl)-meth-(*Z*)-ylidene]-amine, NaH, potassium benzoate, DMSO, 2.5 h, 70 °C; (d) AcOH, THF, H_2O, 3 h, rt, 57% (2 steps); (e) $NaBH_4$, MeOH, 30 min, 0 °C, 97%; (f) $SOCl_2$, DCM, 30 min, 0 °C; (g) Zn, AcOH, H_2O, 3 h, rt, 86% (2 steps); (h) substituted phenol, for example, o-cresol for **44a**, TMAD, *n*-Bu_3P, THF, 16 h, 0 °C–rt, 25–80%.

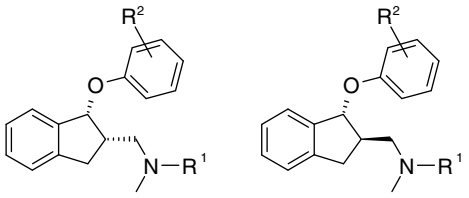
hyde **34a** proceeded in reasonable yield. Conversion to the methyl in the reduction, alcohol to chloride, reduction sequence, then demethylation under the standard conditions gave **36**. This alternative route was used to produce the other *cis* 2-methyl aryl substituted products **37**, **39**, **41**, and **43** as well as to control substitution of the asymmetric difluoroaromatic used to produce **61**. More electron rich 2-substituents gave even lower yields of the nucleophilic substitution product. Fortunately, the ethyl derivatives **52** and **64** could be generated by S_NAr with the appropriate 2-fluorovinylbenzene followed by reduction with hydrazine.[13] In this manner, the thiomethyl compound **57** could be generated using 2-fluorophenyl methyl sulfoxide followed by reduction with dimethylsulfide/trimethylsilyl chloride.[14] The 2-methoxy and 2-ethoxy substitutents were synthesized only in the *trans* diastereomer.

Several other compounds in the tables required additional synthetic steps. The primary amines **37** and **41** were best generated using diallylamine in the Mannich reaction to produce **15b** and **17b**. After installation of the aryloxy ring, the allyl groups were removed by palladium mediated deprotection.[15] Compound **47** was generated by oxidation of Boc protected **46** with *m*CPBA followed by acidic deprotection.[16]

All compounds were tested for their ability to inhibit norepinephrine, serotonin, and dopamine uptake in HEK cell lines that had been stably transfected with the human transporters.[16] Compounds were initially tested in two independent dose response experiments, and those with reasonable potency at NET were retested multiple times. Atomoxetine was included on all assay plates as a standard control, and assay variability was reasonable for a functional assay with SEM values typically below 0.2 log units. A table of SEM values at all three transporters is included as Supplementary material. Potency values are reported as IC_{50}, though with the neurotransmitter concentrations in each assay well below their respective K_m values, little difference would be expected between the measured IC_{50} and K_i of the compounds. Active compounds were further tested in transporter binding assays by competition with the appropriate radioligand.

Compound **5** has been described in the literature as an analog of fluoxetine,[6] and the active enantiomer is known.[17] However, the available literature does not describe the SAR of the series. As this ring structure represents an alternate ring connection to our previous work,[5] it presented a possible starting point for a new series of

Table 1
SAR of indanes[a]

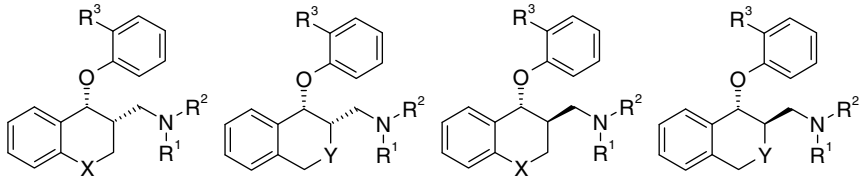


3-7 **8, 9**

Compound	R^1	R^2	NET[b]	SERT[b]	DAT[b]
3	H	2-Me	10	1600	5300
4	Me	2-Me	5000	6500	>10,000
5	H	4-CF_3	880	190	>10,000
6	Me	4-CF_3	4500	230	>10,000
7	H	Naphthyl	30	140	5700
8	H	2-Me	35	1500	>10,000
9	H	Naphthyl	400	90	4000
Atomoxetine, **1**			5	180	3000
Nisoxetine			15	1400	2400
Fluoxetine			2000	47	6000

[a] Data are the average of two or more independent measurements.
[b] IC_{50} (nM) for monoamine uptake.

Table 2
SAR of six-membered ring hetereocycles with 2 substitution[a]

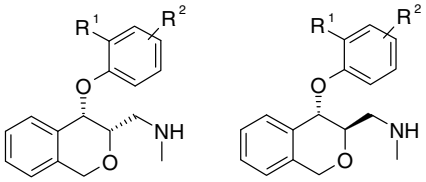


33-38 **39-43** **45-47** **48-50**

Compound	X	Y	R^1	R^2	R^3	NET[b]	SERT[b]	DAT[b]
33	O		Me	H	2-Cl	36	6000	>10,000
35a	O		Me	Me	2-Me	700	1100	>10,000
36	O		Me	H	2-Me	26	1400	>10,000
37	O		H	H	2-Me	46	3800	>10,000
38	S		Me	H	2-Cl	145	3600	>10,000
39		O	Me	H	2-Me	18	2500	>10,000
40		O	Me	H	2-Cl	17	1800	>10,000
41		O	H	H	2-Me	95	6000	>10,000
42		S	Me	H	2-Cl	140	2700	>10,000
43		C	Me	H	2-Me	40	2600	>10,000
45-I[c]	O		Me	H	2-Me	200	1200	4200
46	S		Me	H	2-Me	430	3100	7500
47	SO_2		Me	H	2-Me	8000	10,000	>10,000
48		O	Me	H	2-Cl	140	3500	>10,000
49		O	Me	H	2-Me	100	1100	4100
50		C	Me	H	2-Me	180	2700	>10,000

[a] Data are the average of two or more independent measurements.
[b] IC_{50} (nM) for monoamine uptake.
[c] Active enantiomer, racemic not tested.

Table 3
SAR of the aryloxy ring in the isochromanes[a]



51-52, 57-65 **53-56**

Compound	R^1	R^2	NET[b]	SERT[b]	DAT[b]
51	F	H	75	3100	>10,000
52	Et	H	15	4500	>10,000
53	Et	H	36	3000	>10,000
54	OMe	H	480	>10,000	>10,000
55	OEt	H	240	>10,000	>10,000
56	SMe	H	45	640	4000
57	SMe	H	14	6000	>10,000
58	CF_3	H	6	5600	>10,000
59	Me	3-F	8	1100	>10,000
60	Me	3-Cl	9	100	1400
61	Me	4-F	13	150	>10,000
62	Me	5-F	11	4000	>10,000
63	Me	6-F	7	3100	>10,000
64	Et	6-F	8	1400	>10,000
65	CF_3	6-F	4	3200	>10,000

[a] Data are the average of two or more independent measurements.
[b] IC_{50} (nM) for monoamine uptake.

sNRI compounds. Synthesis of the minimal set of analogs was undertaken to determine the correlation with the atomoxetine/fluoxetine (Lilly) series. As shown in Table 1, the activity of this series correlated well with the Lilly compounds. 2-Substitution on the aromatic ring produced compound **3**, a potent and selective NET inhibitor with properties very similar to atomoxetine. The dimethyl tertiary amine **4** was much less active at NET. Naphthyl substitution generated significant activity at both transporters, see **7** and **9**. Comparing *cis* and *trans* diastereomers, the *cis* was more potent at NET and more selective for NET. As was observed with NBI 80532 (**2**), the more potent compounds have one of the aryloxy or aminomethyl substituents in a pseudoaxial orientation. Thus this ring connection produced compounds with the desired primary potency and selectivity. Additionally, this series was more flexible than **2** but less flexible than the Lilly series.

Characterization of the active enantiomer of **3** revealed that it was also similar to atomoxetine in both CYP2D6 inhibition and oxidative stability as described in the following paper. Accordingly, a number of ring variants were tested with the objective of modifying the shape and geometry enough to improve these properties without losing potency or selectivity at NET. As shown in Table 2, the tetralin analog **43** was 4-fold less potent than the similar indane. Again the *cis* diastereomer **43** was more potent than the *trans* **50**. Replacement of the benzylic carbon to generate the chromane **36** gave about a 2-fold improvement, and at this stage the isochromane **39** was similar though generally trended toward higher potency. As with the indanes, the *trans* diastereomer was less potent and less selective for NET. The same trends were observed for 2-chloro substitution. Replacement with sulfur was less successful, generally resulting in a 10-fold drop in potency, and conversion of thio to sulfone (**47**) resulted in a 20-fold loss of activity. Overall, the results are consistent with potency increasing as the ring size decreases.

Selectivity was further explored with the most potent heterocycle, the isochromane, as shown in Table 3. Potency was correlated with the size and hydrophobicity of the aryloxy substitution, 2-CF_3 > 2-ethyl = 2-SMe > 2-F. As had been observed in the previous series, 2-methoxy and 2-ethoxy were significantly less active.[5] A combination of 2-methyl and fluoro substitution to modify the hydrophobicity of the ring gave compounds with single digit nM activity. Selectivity was found to be a function of the fluorine position, with 4-F the least selective at 10-fold (**61**), and the other isomers more selective. Increasing the size of the 2-substituent also improved the selectivity of the *trans* diastereomer, so that compounds like **53** had encouraging profiles. However, increasing the size of the 3-substituent from fluorine to chlorine led to a greater than 10-fold drop in selectivity (compare **59** and **60**, Table 3).

Overall, this series produced a number of potent and selective compounds. Further development required characterization in safety and in vivo efficacy studies as separate enantiomers. To determine whether these compounds could have improved profiles over atomoxetine, multiple racemic compounds were tested for inhibition of CYP2D6 and CYP3A4, and their oxidative stability in human liver microsomes was measured. Multiple compounds, including **40** and **49**, exhibited inhibition of CYP2D6 in the micromolar range and low oxidative clearance. Because it was possible that both enantiomers contributed to the observed selectivity profile (see Boot et al. for an example[18]), further characterization was reserved for the separate individual enantiomers. Results will be reported in the next publication in this series.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2008.07.050.

References and notes

1. Jann, M. W.; Slade, J. H. *Pharmacotherapy* **2007**, *27*, 1571.
2. Babu, R. P. K.; Maiti, S. N. *Heterocycles* **2006**, *69*, 539.
3. Zhou, J. *Drugs Future* **2004**, *29*, 1235.
4. Wernicke, J. F.; Iyengar, S.; Ferrer-Garcia, M. D. *Curr. Drug Ther.* **2007**, *2*, 161.
5. Wu, D.; Pontillo, J.; Ching, B.; Hudson, S.; Gao, Y.; Fleck, B. A.; Gogas, K.; Wade, W. S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4224.
6. Olivier, B.; Soudijn, W.; van Wijngaarden, I. *Prog. Drug Res.* **2000**, *54*, 59.
7. Cregge, R. J.; Wagner, E. R.; Freedman, J.; Margolin, A. L. *J. Org. Chem.* **1990**, *55*, 4237.
8. Freedman, J.; Dudley, M. W. Preparation and formulation of (aryloxy)indanamines and related compounds useful as antidepressants and as inhibitors of synaptic norepinephrine and serotonin uptake. US 5149714.
9. Berglund, R. A. *Org. Process Res. Dev.* **1997**, *1*, 328.
10. Koenig, T. M.; Mitchell, D. *Tetrahedron Lett.* **1994**, *35*, 1339.
11. Okuda, M.; Tomioka, K. *Tetrahedron Lett.* **1994**, *35*, 4585.
12. Heath, P. C.; Ratz, A. M.; Weigel, L. O. Preparation of tomoxetine. WO 2000058262.
13. Hu, T.; Stearns, B. A.; Campbell, B. T.; Arruda, J. M.; Chen, C.; Aiyar, J.; Bezverkov, R. E.; Santini, A.; Schaffhauser, H.; Liu, W.; Venkatraman, S.; Munoz, B. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2031.
14. Samanen, J. M.; Brandeis, E. *J. Org. Chem.* **1988**, *53*, 561.
15. Garro-Helion, F.; Merzouk, A.; Guibe, F. *J. Org. Chem.* **1993**, *58*, 6109.
16. Kiankarimi, M.; Hudson, S.; Dwight, W. J.; Wade, W. S. Preparation of benzofuranylmethylamines, chromanylmethylamines, and thiochromanylmethylamines as monoamine reuptake inhibitors. US 2006252818.
17. Michals, D.; Smith, H. E. *Chirality* **1993**, *5*, 20.
18. Boot, J.; Cases, M.; Clark, B. P.; Findlay, J.; Gallagher, P. T.; Hayhurst, L.; Man, T.; Montalbetti, C.; Rathmell, R. E.; Rudyk, H.; Walter, M. W.; Whatton, M.; Wood, V. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 699.