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1-Naphthyl and 4-indolyl arylalkylamines as selective monoamine reuptake inhibitors

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ABSTRACT

A series of enantiomerically pure 1-naphthyl and 4-indolyl arylalkylamines were prepared and evaluated for their binding affinities to the monoamine transporters. The two series of enantiomers displayed considerable differences in binding selectivity between the monoamine transporters, leading to the design of (*S*)-4-(3,4-dichlorophenyl)-4-(1*H*-indol-4-yl)-*N*-methylbutan-1-amine as a potent inhibitor for the dopamine and serotonin transporters.

3-Aryloxy-3-arylpropanamines can be designed to be selective monoamine reuptake inhibitors and have become one of the most widely used classes of antidepressants. The most established member of this class is the selective serotonin transporter (SERT) inhibitor, fluoxetine[1] (**1**). More recently, it has been recognized that compounds with different selectivities at the monoamine transporters can also show beneficial antidepressant efficacy. A range of newer analogs have been developed such as nisoxetine[2] (**2**) and atomoxetine[3] (**3**) that are norepinephrine transporter (NET) inhibitors and (+)-*S*-duloxetine[4] (**4**), which is a mixed SERT/NET inhibitor. In addition to the antidepressant utility of selective monoamine transporter inhibitors, interest has been shown in developing potential medications for cocaine addiction using long acting dopamine transporter (DAT) inhibitors or less selective monoamine transporter inhibitors.[5] In many of the studies, the use of bicyclic aromatic ring systems, particularly naphthyl, has resulted in significantly more potent inhibitors than analogs containing a monocyclic aromatic ring[6] (Table 1).

For some time, we have been engaged in a research program directed towards the development of novel asymmetric methods for the synthesis of the most common classes of monoamine reuptake inhibitors. These have included 3β-aryltropanes,[6c,e] 4-arylindanamines,[7] as well as commercial therapeutic agents, such as sertraline,[8] ritalin[9] and venlafaxine.[10] We have developed an effective method for the synthesis of 1,1-diarylbutenoates, and due to our interest in the incorporation of bicyclic aromatic rings into CNS agents, we have extended the chemistry to the synthesis of 1-naphthyl[11] and 4-indolyl derivatives.[12] The 4-indolyl system is especially worth exploring because normally functionalization at the 4-position in indoles is quite challenging.[12] In this letter, we use these transformations to generate enantioselectively 1-naphthyl and 4-indolyl arylalkylamines (**5** and **6**, Fig. 1) and demonstrate that selective monoamine reuptake inhibitors can be generated using these scaffolds.

The key step for the asymmetric synthesis of the 1-naphthyl and 4-indolyl arylalkylamines is the combined C–H activation/Cope rearrangement using 4-acetoxy-1,2-dihydronaphthalene (**8**) or 4-acetoxy-6,7-dihydroindole (**10**) as substrates (Scheme 1). A subsequent elimination of acetic acid generates directly 1,1-diarylbutenoates with very high asymmetric induction (>98% ee). In this study, the second aryl group was chosen to be either 2-thiophenyl, in analogy to the structure of duloxetine, and 3,4-dichlorophenyl, which has been shown to be a useful pharmacophore for generating potent dopamine transporter inhibitors.[5c,6a] The reaction of the aryldiazoacetate **9** with **8**, catalyzed by the chiral dirhodium catalyst Rh_2(*S*-DOSP)$_4$ generated a diarylbutenoate that was directly hydrogenated with Wilkinson's catalyst to form the butanoate **11b**. A representative example of the synthesis of **11** is shown in Scheme 1. In this case of the 2-thiophenyl derivative the reaction

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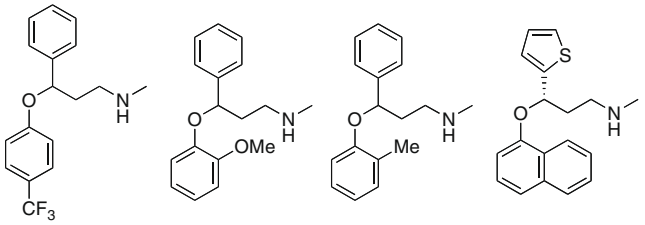
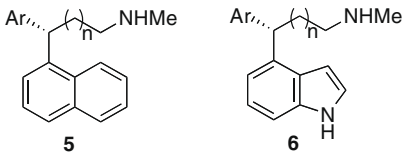
Table 1
Monoamine transporter binding affinities of **1**–**4**



1 (Fluoxetine) **2** (Nisoxetine) **3** (Atomoxetine) **4** (*S*-Duloxetine)

Compound	SERT K_i (nM)	NET K_i (nM)	DAT IC_{50} (nM)
(±)-**1**	48	2000	6000
(±)-**2**	277	6	—
(±)-**3**	1500	4	2000
S-**4**	4.6	16	370
R-**4**	8.8	16	660

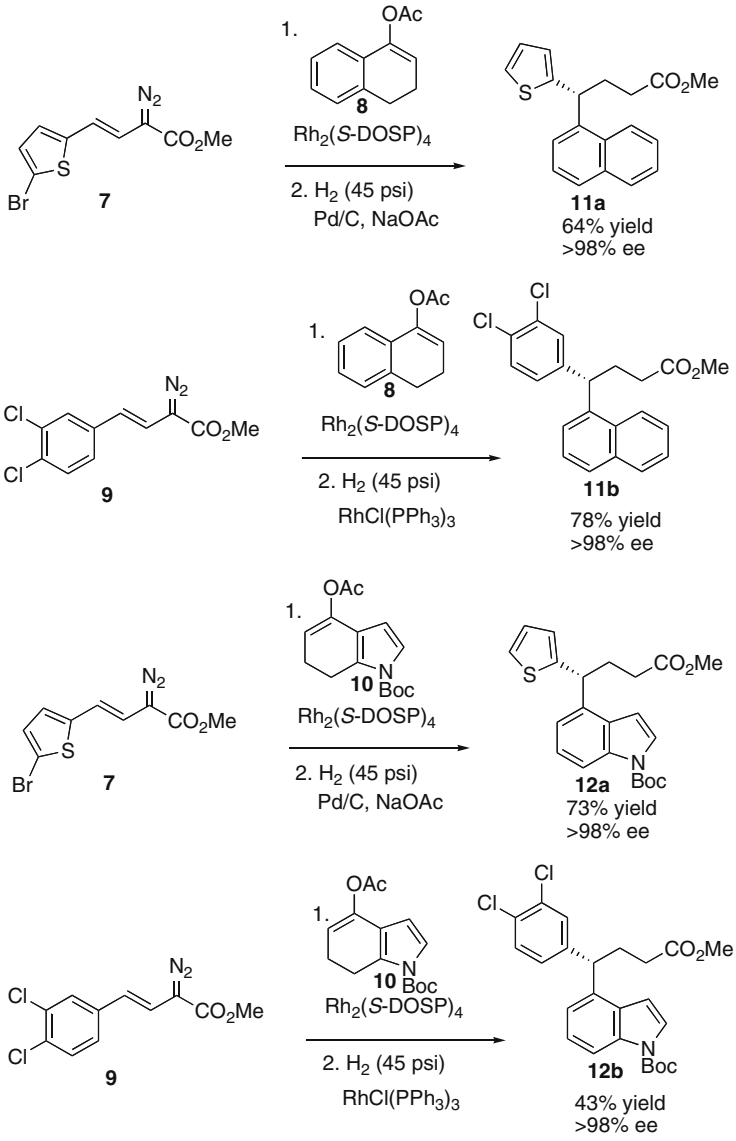


5 **6**

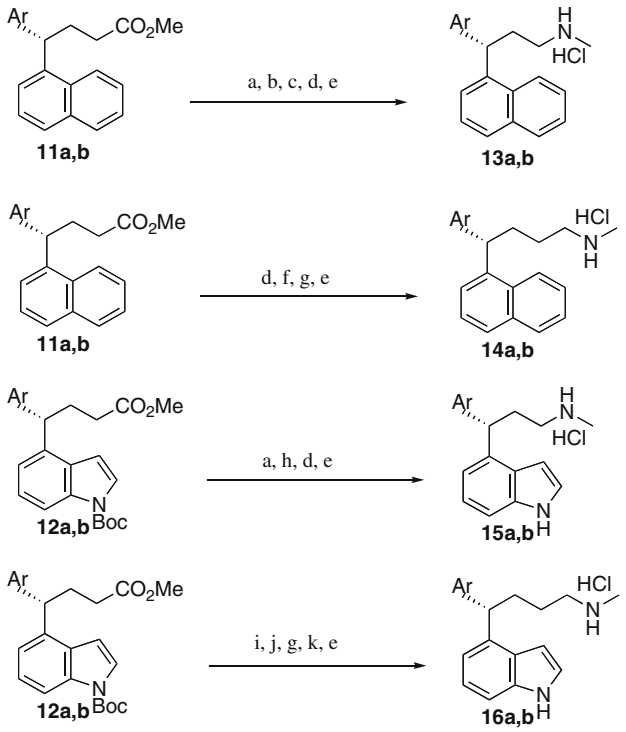
Figure 1. 1-Naphthyl and 4-indolyl derivatives (**5** and **6**).

is best conducted with the 5-bromothiophenylvinyldiazoacetate **7** followed by removal of the bromine during the hydrogenation by using a more reactive catalyst, palladium on charcoal, to form the butanoate **11a**. Similar reactions starting from **10** generated the indole derivatives **12a** and **12b**. The opposite enantiomeric series of **11–12** (**ent-11–12**) were obtained by conducting the first reactions with Rh_2(*R*-DOSP)$_4$ as catalyst.[13]

The resulting diarylbutenoates **11a,b** and **12a,b** were readily converted to diarylalkylamines **13–16a,b** using standard synthetic methods as illustrated in Scheme 2. The diarylpropylamines **13a,b**



Scheme 1. Asymmetric synthesis of naphth-1-ylbutanoates and indol-4-ylbutanoates **11–12**.



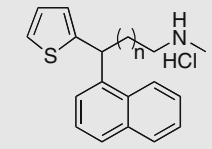
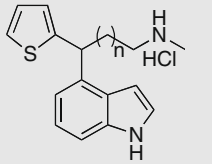
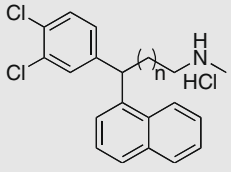
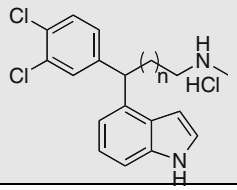
Scheme 2. Synthesis of **13–16**. Reagents and condition: (a) LiOH, THF/H_2O; (b) DPPA, Et_3N, CH_3CN; H_3O^+; (c) $ClCO_2Me$, K_2CO_3, DCM/H_2O; (d) LAH, THF; (e) 1.0 M HCl in Et_2O; (f) PCC, DCM; (g) Ti(O*i*Pr)$_4$, $MeNH_2$; $NaBH_4$; (h) DPPA, Et_3N, CH_3CN; MeOH; (i) DIBAL-H, THF; (j) for Ar = thiophen-2-yl, Dess–Martin; for Ar = 3,4-dichlorophenyl, f; (k) for Ar = thiophen-2-yl, d; for Ar = 3,4-dichlorophenyl, TFA.

and **15a,b** were obtained by using a Curtius rearrangement[14] to decrease the carbon chain, while the diarylbutylamines **14a,b** and **16a,b**, were obtained by a reductive amination procedure.[15] The enantiomeric series of these eight compounds, **ent-13–16a,b**, was also prepared.

The 16 diarylalkylamine derivatives were evaluated for their binding affinities at the three monoamine transporters.[16] A considerable difference was seen between the 2-thiophenyl- (entries 1–8) and the 3,4-dichlorophenyl series (entries 9–16). In the case of the naphthyl-thiophenyl alkylamines, the DAT binding was not very strong (230–466 nM) and not especially influenced by which enantiomer was bound. The binding affinities were also not greatly influenced by the tether length as the diarylpropylamines were roughly equipotent to the diarylbutylamines (compare entries 1 and 2 with entries 3 and 4). In contrast, the enantiomers had significantly different SERT and NET binding affinities in which **13a** and **14a** had the greatest binding affinity for SERT (12.1 and 9.3 nM, respectively), while the enantiomers **ent-13a** and **ent-14a** have the greatest binding affinities to NET (52.1 and 7.92 nM, respectively). Consequently **13a** and **14a** are moderately selective for SERT (by a factor of about 10) while **ent-13a** has roughly equal binding affinities towards both SERT and NET and **ent-14a** is moderately selective for NET. In the case of the indolyl thiophenylalkylamines **15a** and **16a**, the selectivity trends were slightly different as the **ent** series (**ent-15a** and **ent-16a**) was 2–14 times more potent a binder than the enantiomeric series at all of the transporters (entries 5–8) Table 2.

The 3,4-dichlorophenyl moiety is well known to enhance binding to the dopamine transporter[5c,6a] and this was very much the trend that was observed in entries 9–16. In the case of the 3,4-dichlorophenyl naphthyl series **13b** and **14b**, the NET binding

Table 2
Monoamine transporter binding affinities of compounds **13–16**

Entry	Structure	Compound	*n*	SERT K_i[a] (nM)	NET K_i[a] (nM)	DAT IC_{50}[a] (nM)
1		**13a**	1	12.1 (±2.3)	139 (±20)	230 (±27)
2		**Ent-13a**	1	30.2 (±8.6)	52.1 (±6.8)	309 (±26)
3		**14a**	2	9.5 (±1.7)	109 (±10)	405 (±40)
4		**Ent-14a**	2	39.7 (±6.2)	7.9 (±1.1)	466 (±69)
5		**15a**	1	166 (±15)	102 (±23)	572 (±103)
6		**Ent-15a**	1	31.9 (±3.6)	13.8 (±2.5)	292 (±89)
7		**16a**	2	271 (±70)	79.7 (±8.5)	957 (±85)
8		**Ent-16a**	2	72.9 (±7.9)	9.0 (±1.6)	318 (±43)
9		**13b**	1	86 (±25)	1630 (±240)	35.8 (±4.5)
10		**Ent-13b**	1	5.3 (±1.7)	1640 (±320)	9.7 (±1.3)
11		**14b**	2	49.9 (±6.9)	>10000	209 (±41.0)
12		**Ent-14b**	2	4.1 (±1.8)	2480 (±590)	61.2 (±6.9)
13		**15b**	1	3.63 (±0.41)	35.4 (±1.9)	14.9 (±0.77)
14		**Ent-15b**	1	1.68 (±0.18)	95 (±12)	7.21 (±0.53)
15		**16b**	2	2.72 (±0.51)	360 (±96)	14.3 (±3.6)
16		**Ent-16b**	2	0.82 (±0.31)	4840 (±540)	3.8 (±1.2)

[a] Values are means of three experiments, standard deviation is given in parentheses.

was not influenced by the enantiomers but for DAT and SERT, the **ent** series was considerably more potent (about 3–4 times more potent at DAT and 12–16 times more potent at SERT. The trends were slightly different for the 3,4-dichlorophenyl indolyl alkylamine series because the **ent** series was most potent for DAT and SERT binding while the opposite is seen for NET binding. As a consequence of these trends, **ent-16b** has strong binding to DAT and SERT (3.83 and 0.815 nM, respectively) and a 1000-fold selectivity compared to the NET binding affinity.

In summary these studies illustrate the subtle differences in selectivities between enantiomeric series for binding to the monoamine transporters. The 4-substituted indoles, **15** and **16**, represent an interesting series of compounds because they are relatively potent and contain a substitution pattern that has not been previously greatly explored.

Acknowledgments

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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.2008.11.022.

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16. *Transporter binding studies:* Affinities of analogs at dopamine transport sites are determined by displacement of [125I]RTI-55 binding in membranes from rat striatum.[17] Frozen brains from Sprague–Dawley rats are obtained commercially and striata are dissected on ice. Tissue is homogenized in 10 vol of RTI-55 assay buffer (0.32 M sucrose, 10 mM sodium phosphate buffer, pH 7.4) with a Polytron, and centrifuged three times at 48,000*g* for 10 min, with fresh buffer resuspension for each centrifugation. Assay tubes contain 0.5 mg (original wet weight) of membranes, 0.01 nM [125I]RTI-55, and various concentrations of unlabeled drugs dissolved in RTI-55 assay buffer in a final volume of 2 ml. Tubes are incubated for 50 min at 25 °C, and the reaction is terminated by rapid filtration with 3× 5 ml of cold Tris buffer through Whatman GF/B glass fiber filters pre-soaked in Tris buffer containing 0.1% BSA for at least 1 h. Non-specific binding is determined in the presence of 1 μM WF-23.Affinities of analogs at 5-HT transport sites are determined by displacement of [3*H*]citalopram binding in membranes from rat frontal cortex.[18] Tissue is obtained from frozen rat brains as described above, homogenized in 10 vol of citalopram assay buffer (50 mM Tris–HCl, 120 mM NaCl, 5 mM KCl, pH 7.4) with a Polytron, and centrifuged two times at 48,000*g* for 10 min, with fresh buffer resuspension for each centrifugation. Assay tubes contain 50 mg (original wet weight) of membranes, 0.4 nM [3*H*]citalopram, and various concentrations of unlabeled drugs dissolved in citalopram assay buffer in a final volume of 2 ml. Tubes are incubated for 60 min at 25 °C, and the reaction is terminated by rapid filtration with 3× 4 ml of cold Tris buffer through Whatman GF/B glass fiber filters pre-soaked in Tris buffer containing 0.1% BSA for at least 1 h. Non-specific binding is determined in the presence of 10 μM fluoxetine.Binding of analogs at NE transport sites is determined by displacement of [3*H*]nisoxetine binding.[19] Whole rat brains (minus cerebellum) are homogenized in 30 vol of 120 mM NaCl, 5 mM KCl, 50 mM Tris–HCl, pH 7.4, and centrifuged at 48,000*g* for 10 min. The membranes are resuspended in nisoxetine assay buffer (300 mM NaCl, 5 mM KCl, 50 mM Tris–HCl, pH 7.4) and centrifuged again before final resuspension in volumes of buffer. Assay tubes contain 750 μl of brain membranes, [3*H*]nisoxetine (0.7 nM) together with unlabeled drugs dissolved in nisoxetine assay buffer to a final volume of 1 ml. Tubes are incubated for 40 min at 25 °C, and the reaction is terminated by rapid filtration with 3× 4 ml of cold Tris buffer through Whatman GF/B glass fiber filters which have been pre-soaked in Tris buffer containing 0.1% BSA for at least 1 h. Non-specific binding is determined in the presence of 1 μM desipramine.In [3*H*]citalopram and [3*H*]nisoxetine binding assays, radioactivity is determined by liquid scintillation spectrophotometry (efficiency: 50%) after eluting filters overnight in 5 ml of Ecolite scintillation fluid (ICN). IC_{50} values are calculated from displacement curves using 7–10 concentrations of unlabeled analogs. Because binding of tropanes at dopamine transporter sites is generally regarded as multiphasic,[20] potencies in inhibiting [125I]RTI-55 binding are reported as IC_{50} values. For [3*H*]paroxetine and [3*H*]nisoxetine binding assays, K_i values are calculated using the Cheng–Prusoff equation.[21] All data are mean values ± SEM of at least three separate experiments, each of which is conducted in triplicate.
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