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Rational Design and Synthesis of Novel 2,5-Disubstituted *cis*- and *trans*-Piperidine Derivatives Exhibiting Differential Activity for the Dopamine Transporter

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Abstract—Herein, we report the rational design and synthesis of novel 2,5-disubstituted piperidine derivatives in the *cis* and *trans* isomeric forms. Out of these two isomers, the *cis*-isomer, **7a**, was found to exhibit the most potent activity and selectivity for the dopamine transporter. These novel derivatives represent conformationally constrained version of piperidine analogue of GBR compounds.

Widespread abuse of cocaine has become a national and international problem and discovery of pharmacotherapeutic agents for potential treatment of cocaine addiction is urgent.[1] Cocaine binds to all three monoamine transporter molecules in the central nervous system (CNS): the dopamine transporter (DAT), serotonin transporter (SERT), and norepinephrine transporter (NET). But the binding of cocaine to the DAT is implicated strongly in its reinforcing effects.[2,3] Thus, significant effort has been directed towards development of drugs for the DAT.[4a–h]

Our ongoing structure–activity relationship (SAR) studies of piperidine analogues of GBR 12909 resulted in the development of many molecules with high affinity and selectivity for the DAT.[5a–c] In our goal of converting flexible piperidine analogues into more rigid structures, we designed a general structural representation of molecule **II** resulting from a transformation of molecular structure of our previous lead compound, 4-[2-(diphenyl)ethyl]-aminomethyl]-1-[(4-fluorophenyl)-methyl]-piperidine **I** which is shown in Figure 1.[5c] Thus, formation of a new piperidine ring from the secondary amine and opening up of the existing piperidine ring of **I** led to the formation of a general structure **II**. As a result, the structural complexity of the newly designed compound increases due to introduction of the two asymmetric centers relative to the parent molecule **I**. Our current targets, the *cis*- and *trans*-derivatives (**7a**,**b**) are derived from this structural representation and are shown in Figure 2. These novel 2,5-disubstituted compounds are conformationally constrained compared to the parent lead **I** (Fig. 1). In this report, we describe the rational design, synthesis and biological characterization of these molecules.

The synthesis of our target molecules is shown in Scheme 1 in a linear six-step process. The starting 2-chloro-5-nitropyridine reacted with diphenylacetonitrile

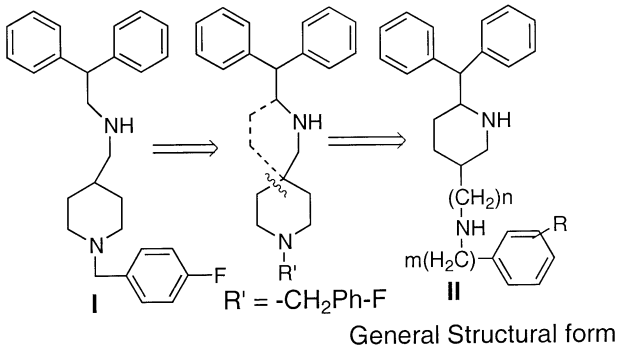

Figure 1. Structural transformation of **I** into relatively conformationally constrained 2,5-disubstituted piperidine derivatives.

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under phase-transfer condition consisting of toluene, tetrabutylammonium fluoride and 50% NaOH to furnish 2-(diphenyl-cyanomethyl)-5-nitropyridine **2** in very good yield.[6] Acidic hydrolysis of nitrile **2** by brief treatment with aqueous sulfuric acid produced amide intermediate **3** in good yield.[7] In our initial effort, this intermediate was hydrolyzed and decarboxylated to **5** in one step by reaction with sulfuric acid and sodium nitrite but only in fair yield. We found an alternative two-step route that improved the yield of **5**. The nitro group of **3** was first reduced by hydrogenation in presence of 10% Pd/C as a catalyst producing amino-amide **4** in almost quantitative yield. Then **4** was hydrolyzed and decarboxylated to **5** by refluxing 37% HCl in excellent yield.

In the key step, hydrogenation (60 psi) of **5** in the presence of PtO_2 (IV) yielded *cis*- and *trans*-isomers **6** in approximately 3:2 ratio (by NMR), respectively. This mixture was too difficult to separate using preparative column chromatography. The reductive alkylation of **6** with less than one equivalent of 4-fluorobenzaldehyde resulted in *cis*- and *trans*-isomers mixture, **7a**,**b**, respectively, which could then be separated by column chromatography.[8,9] The mixture **6** was also converted into amide mixtures **8a**,**b** by reaction with 4-fluorobenzoyl chloride as shown in Scheme 2 and was separated by column chromatography to isolate pure **8a** and **8b**.

The assignment of structures of **7a**,**b** and **8a**,**b** was determined by 1-D and 2-D NMR (400 MHz) experiments (Table 1).[8,9] In these compounds, the assumption that the diphenylmethyl moiety would assume the equatorial position was borne out by the data. The compound **7a** eluted first from the column. The multiplet at δ 2.7 ppm attributed to H-5 is 13 Hz broad (overlapping with one half of the H-6 doublet) composed of Σ ($^3J_{5,4} + {}^3J_{5,6}$). This small Σ^3J for H-5 is consistent with H-5_{eq} orientation having two $^3J_{axeq}$ and two $^3J_{eqeq}$ couplings. The signal attributed to H-2, δ 3.28 ppm, is a

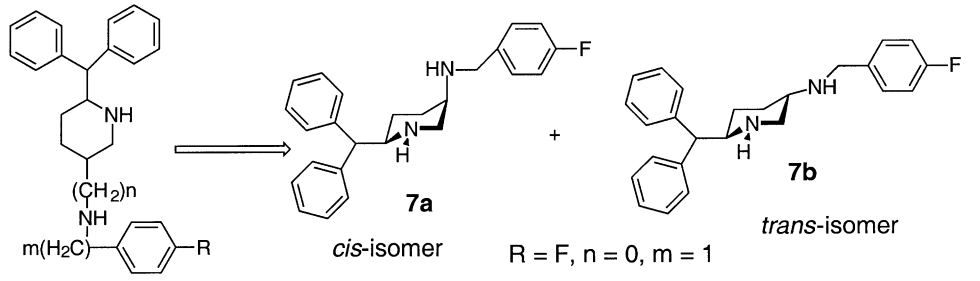
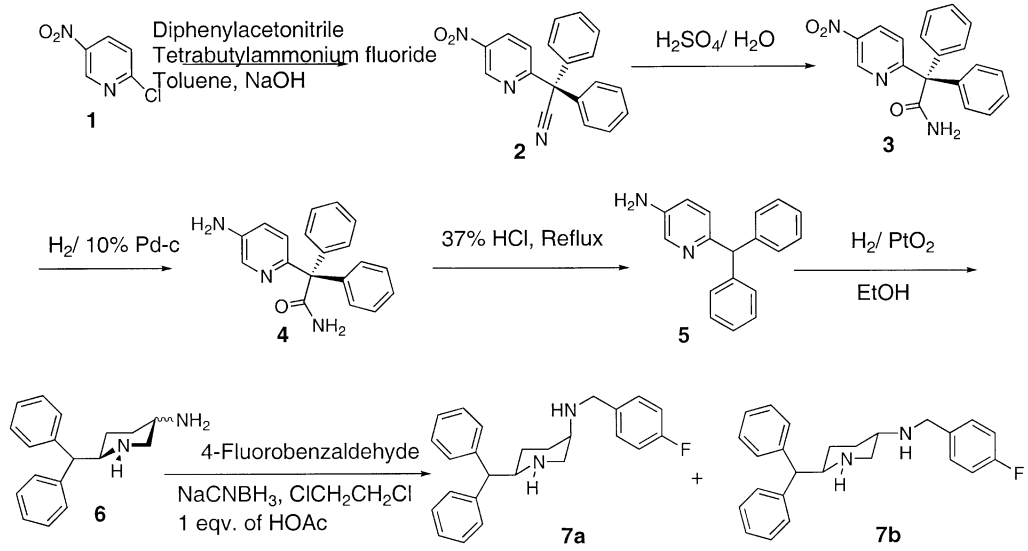
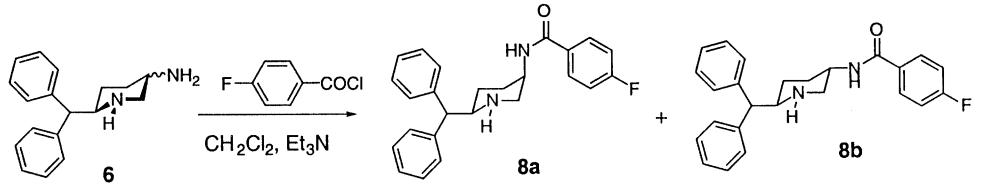


Figure 2. Two geometrical isomers of our target compounds.



Scheme 1.



Scheme 2.

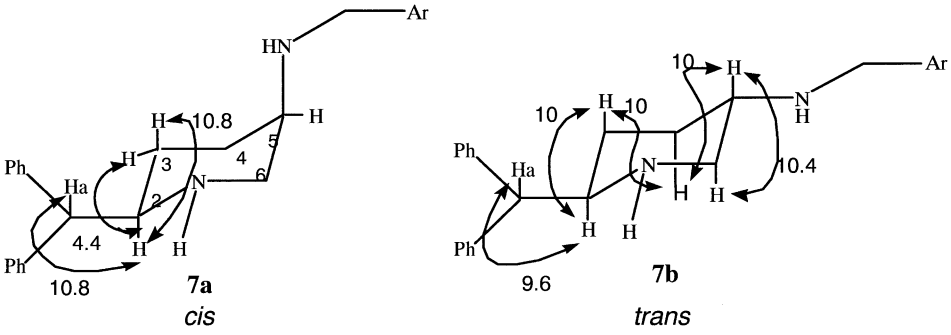
doublet of triplets (^3J 4.4 and 10.8 Hz) where $^3J_{2,3ax} = {}^3J_{2,CH(Ph)_2}$. The large coupling of H-2 and H-3_{ax} is consistent with H-2_{ax} orientation (Table 1).

The compound, **7b**, eluting last has the *trans* configuration. The multiplet at δ 2.65 ppm attributed to H-5 is 36 Hz broad. The H-6_{ax} signal, δ 2.33, appears as a triplet ($^2J_{6ax6eq}$ and $^3J_{6ax5}$) with $^3J = 10.4$ Hz indicating that H-5 is axially oriented. The Σ^3J for H-5 is consistent with axial orientation having two $^3J_{axeq}$ and two large $^3J_{axax}$ couplings. Unfortunately, the signal attributed to H-2, δ 3.2, overlaps with H-6_{eq} and the expected triplet ($^3J_{2a3a} = {}^3J_{2aCH(Ph)2}$) could not be confirmed. However, the peakwidth of H-2 signal is 20 Hz broad indicating H-2 in an axial position. In addition, in a nuclear Overhouser experiment, irradiation of H-6_{ax} resulted in an enhancement of (H2,H6eq) peak. Therefore, H-2 must be axially oriented in order to have this interaction.

Our previous SAR studies in piperidine analogues of GBR compounds developed 1,4-disubstituted piperidine compounds showing selective affinity for the DAT. These substituted piperidine analogues are also quite flexible and it is not clear at this point the extent of contribution of their flexibility in their high affinity binding activity for the DAT. Recently in another study, 2,3-disubstituted analogues of piperidine were developed which exhibited good affinity for the DAT and the activity resided mainly in the *cis*-isomeric form of these compounds.[10a] In another recent study, 3- and 4-amino derivatives of piperidine molecules were developed which showed potent affinities for both the DAT and NET.[10b]

The binding affinity of **7a**,**b** and **8a** for monoamine transporter systems was evaluated by measuring their potency in inhibiting binding of [^{3}H]WIN 35,428 to DAT, [^{3}H]citalopram to SERT, and [^{3}H]nisoxetine to NET in rat brain tissue (Table 2). Binding results demonstrated more activity for the *cis* isomer (±)-**7a** compared to the *trans* (±)-**7b** (IC_{50} of 30 nM vs 212 nM). Thus the *cis* isomer was 7 times more potent than the *trans* isomer for the DAT. The selectivity of the *cis* isomer for the DAT was 93 when compared against SERT and was 45 when compared against NET (Table 3). Furthermore, the *cis* compound (±)-**7a** was much more potent at DAT than cocaine (IC_{50} of 30 nM vs 266 nM; Table 2) and was also much more selective at the DAT than cocaine when compared against either SERT or NET. In addition, the more active *cis* compound also turned out to be more selective than our

Table 1. Selected NMR data of **7a**,**b**



Compd	Chemical shifts	Multiplicity	Coupling constants
7a			
H_{2ax}	3.28	dt	$J_{2ax,3ax} = J_{2ax,a} = 10.8$ Hz, $J_{2ax,3eq} = 4.4$ Hz
H_{5eq},H_{6ax}	2.65–2.72	m	Peak width = 13 Hz
H_{6eq}	2.99	dd	$J_{6eq,6ax} = 12.9$ Hz, $J_{6eq,5eq} = 6$ Hz
7b			
H_{2ax},H_{6eq}	3.15–3.25	m	Peak width = 20 Hz
H_{5ax}	2.60–2.70	m	Peak width = 36 HZ
H_{6ax}	2.33	t	$J_{6ax,5ax} = 10.4$ Hz, $J_{6ax,6eq} = 10.4$ Hz

Table 2. Binding activity of **7a**,**b** and **8a** at the dopamine, serotonin and norepinephrine transporters in rat brain tissue

Compd	DAT, IC_{50} (nM) [^{3}H]WIN 35, 428[a]	SERT, IC_{50} (nM) [^{3}H]citalopram[a]	NET, IC_{50} (nM) [^{3}H]nisoxetine[a]	[^{3}H]DA uptake Inhibition, IC_{50} (nM)[a]
Cocaine	266±37	737±160	3520±554	191±28
I	19.7±1.4[b]	137±46	1110±120	49.6±7.2
(±)-**7a**	30.0±0.5	2810±411	1349±190	28.9±2.5
(±)-**7b**	212±20	1330±102	4470±1,180	106±10
(±)-**8a**	87.0±8.8	6210±822	5610±445	

[a]The DAT was labeled with [^{3}H]WIN 35, 428, the SERT with [^{3}H]citalopram and the NET with [^{3}H]nisoxetine (see ref 5a for procedure). Results are average±SEM of three independent experiments assayed in triplicate.
[b]See ref 5c.

Table 3. Selectivity of various ligands for their binding to the monoamine transporters

Compd	SERT/DAT	NET/DAT
Cocaine	2.7	6.36
I	6.9	56
(±)-**7a**	93.7	44.9
(±)-**7b**	6.28	21
(±)-**8a**	71.4	64.4

previous lead **I** for binding to the DAT (93 vs 6.9; Table 3). Interestingly, the *cis* amide (±)-**8a** was moderately potent and quite selective at the DAT which might indicate relative less importance of a basic N-atom at the 5-position in binding interaction. This result is in contrast to our earlier findings where we have demonstrated both exocyclic and piperidine N-atoms are important for binding interactions with the DAT.[5b,c]

To the best of our knowledge, these newly designed molecules represent a novel structural class of compounds evaluated for activity for the monoamine transporter systems in the CNS. It is evident from these results that the stereochemistry at the 5-position played a significant role in activity. Our ongoing work is looking into extensive SAR studies of these newly developed molecules to understand more about the dynamics of interaction of these molecules with the monoamine transporter systems.

Acknowledgements

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8. Racemic *cis*-2-diphenylmethyl-5-(4-fluorobenzylamino)-piperidine, **7a**, ^{1}H NMR ($CDCl_3$; 400 MHz) δ 1.3–1.4 (2H, m, H-3), 1.49 (1H, tt, ^2J and $^3J_{3a} = 13.6$ Hz; $^3J_{3e}$ and $^3J_{5e} = 4.0$ Hz, H-4ax), 1.65–1.85 (3H, m, H-4eq, 2NH), 2.65–2.72 (2H, m, H-5eq, H-6ax), 2.99 (1H, dd, $^3J = 12.9$ Hz, $J_{5eq} = 6$ Hz, H-6eq), 3.28 (1H, dt, $^3J = 4.4$ and 10.8 Hz, H-2ax), 3.71 (2H, s, $CH_2C_6H_4F$), 3.81 (1H, d, $^3J = 9.6$ Hz, $CH(C_6H_5)_2$), 6.99 (2H, t, $^3J = 8.4$ Hz, ArH *ortho* F), 7.12–7.39 (12H, m, ArH). Precipitated as bis-hydrochloride salt. Mp 240–261 °C. EA calcd for $C_{25}H_{29}N_2FCl_2 \cdot 0.5\ H_2O$: C, 65.93; H, 6.59; N, 6.15. Found: C, 65.62; H, 6.78; N, 6.49.
9. Racemic *trans*-2-diphenylmethyl-5-(4-fluorobenzylamino)-piperidine, **7b**, ^{1}H NMR ($CDCl_3$; 400 MHz) δ 1.17 (2H, qm, $^3J = 10$ Hz, H-3ax and H-4ax), 1.57–1.65 (1H, m, H-3eq), 1.4–1.7 (bs, NH), 1.9–1.96 (1H, m, H-4eq), 2.33 (1H, t, ^2J and $^3J = 10.4$ Hz, H-6ax), 2.65 (1H, m, $\Sigma^3J = 36$ Hz, H-5ax), 3.15–3.25 (2H, m, H-2ax, H-6eq), 3.68 (1H, d, $^2J = 9.6$ Hz, $CH(C_6H_5)_2$), 3.76 (2H, s, $CH_2C_6H_4F$), 6.97 (2H, t, $^3J = 8.8$ Hz, ArH *ortho* F), 7.1–7.3 (10H, m, ArH), 7.36 (2H, d, $^3J = 7.6$ Hz, ArH *meta* F). Precipitated as bis-hydrochloride salt, mp 291–295 °C. EA calcd for $C_{25}H_{29}N_2FCl_2 \cdot 0.5\ H_2O$: C, 65.93; H, 6.59; N, 6.15. Found: C, 65.56; H, 6.89; N, 6.14.
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