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Conformationally restricted homotryptamines. Part 5: 3-(trans-2-aminomethylcyclopentyl)indoles as potent selective serotonin reuptake inhibitors

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ABSTRACT

A series of racemic 3-(*trans*-2-aminomethylcyclopentyl)indoles was synthesized and found to have potent binding to the human serotonin transporter (hSERT). The most active analog was synthesized stereospecifically and the active enantiomer was shown to have high affinity binding to hSERT.

Serotonin (5-hydroxytryptamine or 5-HT) is an important neurotransmitter and alterations in its signaling are implicated in affective disorders. The selective serotonin reuptake inhibitors (SSRIs) block the serotonin transporter (SERT) and prevent reuptake into presynpatic neuron.[1]

The SSRIs are widely used antidepressants, and are relatively safe despite some recognized issues.[2] Some recent SSRI research has sought to discover compounds with more rapid onset of action as well as discovering compounds that increase the number of patients who respond to treatment. Among other approaches, some investigations have attempted to combine SERT inhibition with 5-HT_{1A}, 5-HT_{1B}, or NK1 antagonism.[3]

The conformational restriction of ligands or inhibitors is a well-precedented way to improve binding and selectivity of these agents. We have previously reported SERT binding results with homotryptamines **1**[4] and conformationally-restricted homotryptamine analogs **2**[5] and **3**[6] (Fig. 1).

In this report we discuss methods to vary the ring size from the cyclopropyl in **3** to cyclopentyl and the effect this modification has on SERT binding and the physical properties of the 3-cyclopentylindole derivatives. The 5-cyanoindole core (Fig. 1, X = CN) was maintained based on SAR from the indole cyclopropane series discovered previously.[6]

The synthesis of the racemic *cis* and *trans* 3-(2-aminomethylcyclopentyl)indoles is shown in Scheme 1 5-cyanoindole **4** is converted into iodoindole **5** and then subjected to a Stille coupling with **6** to provide olefin **7**.[7] Tosyl removal and hydrogenation provided racemic *cis* compound **8**. Base equilibration followed by functional group conversion produced racemic *trans* aldehyde **9**

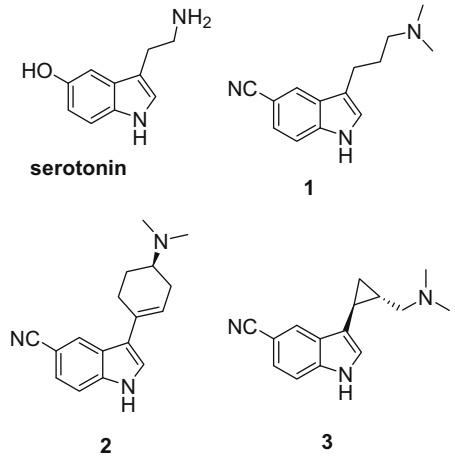

Figure 1. Previously reported indole SERT ligands.

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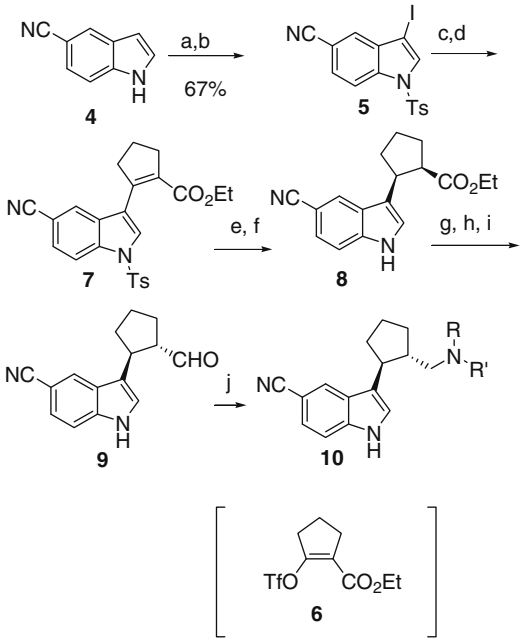
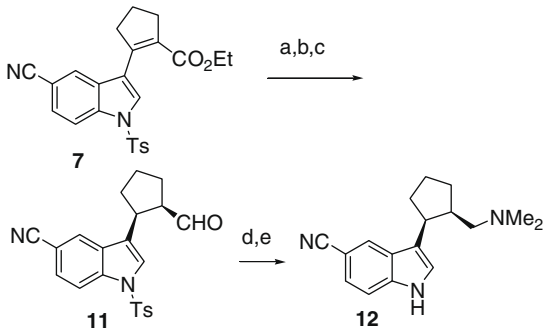


Scheme 1. Synthesis of *trans* racemic cyclopentanes. Reagents and conditions: (a) I_2. KOH; (b) TsCl, DIPEA (67%); (c) $(Bu_3Sn)_2$, $Pd(OAc)_2$, PPh_3 (82%); (d) 6, Pd_2dba_3, Ph_3As (73%); (e) NaOH, H_2O (94%); (f) H_2, Pd/C, (89%); (g) LiOH, H_2O, EtOH, reflux; (h) MeONHMe–HCl, EDCI, Et_3N (41%); (i) LAH, −38 °C (68%); (j) R-NH-R′, $NaBH(OAc)_3$.



Scheme 2. Synthesis of *cis* cyclopentane **10**. Reagents and conditions: (a) H_2, Pd/C; (b) $LiAlH_4$, −40 °C; (c) $(COCl)_2$, DMSO, then ROH, then Et_3N; (d) Me_2N, $NaBH(OAc)_3$; (e) NaOH, EtOH.

which was then reductively aminated to provide a variety of amines **10**.

The data for the racemic *trans* compounds are shown in Table 1. This series provided several highly potent SERT[8] inhibitors, most notably the dimethylamine **10b**. The data show a clear preference for small alkyl groups, exemplified by the potent binding of **10a–c** contrasted with the drop in activity for the diethylamine **10f**. These SAR trends are similar to what was observed for the previously reported 3-cyclopropylindole series.[6]

To test the effects of bond orientation about the cyclopentane ring, we desired to test the enantiomers of both *trans* and *cis* cyclopentane dimethylamines. The racemic *trans* **10b** could be separated into (1*S*,2*S*) **(+)-10b** and (1*R*,2*R*) **(−)-10b** using chiral HPLC. Alternatively, larger amounts of these *trans* enantiomers could be synthesized by an asymmetric Michael addition as previously reported.[9] The synthesis of racemic *cis* compounds is shown in Scheme 2. The previously synthesized **7** was hydrogenated and subjected to careful ester reduction followed by Swern oxidation[10] to provide racemic *cis* aldehyde **11**. Reductive amination followed by tosyl removal gave desired racemic *cis* amine **12**. This racemic mixture was separated into **(+)-12** and **(−)-12** using chiral HPLC.

As can be seen from the data in Table 2, the most potent compound was the *trans*-(1*S*,2*S*) enantiomer **(+)-10b** with a hSERT binding IC_{50} of 0.13 nM. The *cis* compounds (+)-**12** and (−)-**12** were several fold less active than the *trans* analogs. The most active *cis* enantiomer was the (1*R*,2*S*) (+)-**12** with an IC_{50} of 1.2 nM. The absolute configurations of active enantiomers were as expected based on the indole cyclopropane series reported previously.[2]

In Table 3 can be seen data on the binding potency of **(+)-10b** and the previously reported compounds **2** and **3** to the major biogenic amine transporters SERT, DAT (dopamine) and NET (norepinephrine).[11] The cyclo pentyl compound **(+)-10b** is the most potent at binding to SERT, with the cyclohexene compound **2** being the least potent (although still subnanomolar in IC_{50}). Both compounds **2** and **3** show binding to DAT which is at least 5000 fold weaker than its binding to SERT, and binding to NET which is at least 25,000 fold weaker than SERT. Compound **2** is significantly less selective than **3** and **(+)-10b**.

In vivo microdialysis studies with **(+)-10b** are shown in Figure 2.[12] Compound **(+)-10b** given orally caused a robust increase in extracellular serotonin concentrations in the frontal cortex of awake, freely moving rats. The maximal response was achieved at 1 mg/kg (po), and this increased serotonin levels to greater than 300% of baseline. This effect was similar to that produced by the SSRI paroxetine given at 5 mg/kg.

In conclusion, the 3-(2-aminomethylcyclopentyl)indole series provided a compound (+)-10b which was a picomolar potent and selective inhibitor of the hSERT transporter. Future studies are ongoing to fully appreciate the therapeutic potential of such a compound.

Table 1
Binding affinities of racemic *trans* compounds **10a–g**[a]

Compound	R	R'	SERT IC_{50}[a] (nM)
10a	Me	H	7.0 ± 1.1
10b	Me	Me	0.32 ± 0.04
10c	Me	Et	10 ± 0.50
10d	Me	CH_2Ph	85 ± 12
10e	Et	H	170
10f	Et	Et	240
10g		$-(CH_2)_4-$	22 ± 4.2

[a] Where indicated with ± SEM, n >= 3 for the reported IC_{50} values. Otherwise, n = 2.

Table 2
hSERT binding affinities of stereoisomers of **10b** and **12**[a]

Compound	*cis*/*trans*	SERT IC_{50}[a] (nM)
10b	*trans*	0.32 ± 0.04
(+)-10b	*trans*	0.13
(-)-10b	*trans*	58
12	*cis*	2.6 ± 0.34
(+)-12	*cis*	130 ± 16
(-)-12	*cis*	1.2 ± 0.21

[a] Where indicated with ± SEM, n >= 3 for the reported IC_{50} values. Otherwise, n = 2.

Table 3
Binding affinities (IC_{50} in nM) versus selected receptors for **2**, **3**, and **(+)-10b**

Compound	SERT	DAT	NET
2	0.72	290	390
3	0.36	4200	9200
(+)-10b	0.13	690	7900

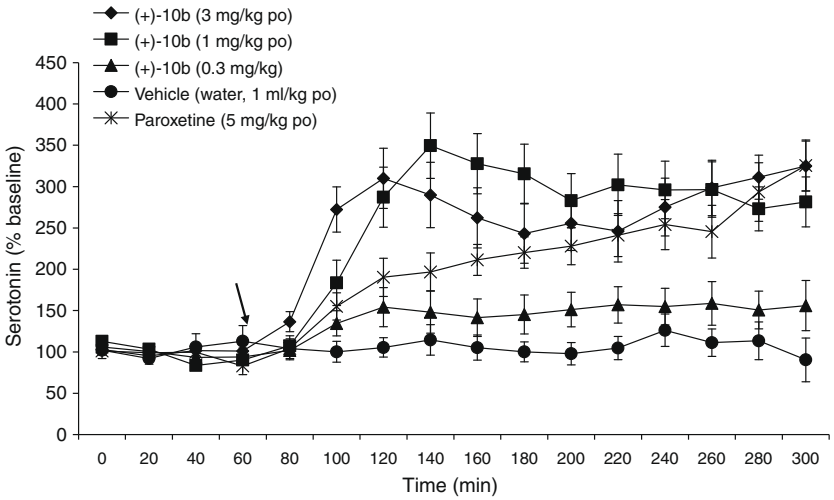


Figure 2. Dose-reponse curves for compound **(+)-10b** given po.

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