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Conformationally Restricted Homotryptamines. Part 7: 3-*cis*-(3-Aminocyclopentyl)indoles As Potent Selective Serotonin Reuptake Inhibitors

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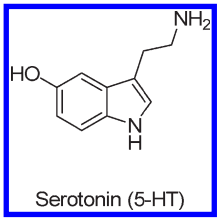
A series of conformationally restricted homotryptamines has been synthesized and shown to be potent inhibitors of hSERT. Conformational restriction of the homotryptamine side chain was attained by the insertion of a cyclopentyl ring, with the indole ring and the terminal dialkylamino group occupying the 1- and 3-positions, respectively. Nitrile and fluoro substitutions at the indole 5-position gave highest hSERT potency. Preferred cyclopentane ring stereochemistry in both series was cis (1*S*,3*R* for 5-CN compound **8a**, 1*R*,3*S* for 5-F compound **9a**). High hSERT binding affinity was observed for **8a** and **9a** (0.22 and 0.63 nM, respectively). The corresponding trans isomers were 4−9 times less potent. **8a**, dosed at 1 and 3 mg/kg po, produced a robust, dose-dependent increase in extracellular serotonin in the frontal cortex of rats, similar to that induced by paroxetine at 5 mg/kg, po. By contrast, **9a** did not produce a significant increase in extracellular serotonin in rat frontal cortex at 3 mg/kg po due to relatively low brain and plasma levels.

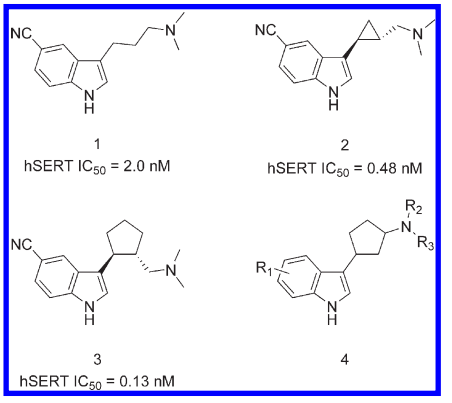
Introduction

The serotonergic system constitutes an important target for psychoactive drugs. The human serotonin transporter (hSERT[a]) is responsible for the regulation of synaptic serotonin (5-hydroxytryptamine, 5-HT) levels. Selective serotonin reuptake inhibitors (SSRIs) act by blocking the reuptake of serotonin into the presynaptic neuron, thus increasing the effective concentration of this neurotransmitter to enervate the postsynaptic 5-HT receptors. SSRIs have found utility primarily in depression disorders, although other indications including anxiety have been developed as well.[1]



Although many clinically useful SSRIs have been discovered,[2] the development of compounds with higher affinity and target selectivity continues to be an area of interest.[3] Our own efforts to achieve this have concentrated on a number of homotryptamine analogues of serotonin.[4−10] Ranging from analogues with simple flexible side chains[4,5] to those with conformationally restricted elements,[6−10] homotryptamines have been shown to be potent inhibitors of hSERT. In these series, conformational restriction of the C3 spacer, which separates the indole nucleus and the terminal amino group, was accomplished via the incorporation of a 1,2-substituted cyclopropyl[6] or cyclopentyl group[10] as represented by **2** and **3**, respectively. In these examples, the conformationally restricted analogues were more potent in vitro than the corresponding straight chain homotryptamine **1** by 4−15-fold. In vivo, both **2** and **3** produced dose-dependent increases in cortical serotonin levels consistent with serotonin reuptake inhibition.[11]

In an effort to further refine the conformational and stereochemical requirements of the most potent homotryptamine SSRI's, several alternate conformationally restricted homotyptamine side chains were considered. We now report the 1,3-cyclopentane series **4**, in which the amino group is directly attached to the ring, unlike **2** and **3**, which utilized the exocyclic aminomethyl group.



Results

To enable a rapid assessment of R_1 substituent effects on hSERT affinity, we initially synthesized the racemic/diastereomeric mixtures **6**−**17** (Table 1). Previous experience

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[a] Abbreviations used: hSERT, human serotonin transporter; 5-HT, serotonin or 5-hydroxytryptamine; SSRI, selective serotonin reuptake inhibitor; hDAT, human dopamine transporter; hNET, human norepinephrine transporter.

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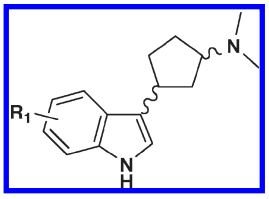
with other homotryptamine analogues suggested that this approach would provide adequate guidance concerning overall SAR trends. We chose to concentrate on compounds with alkyl groups R_2 and R_3 = CH_3, knowing that these would likely yield compounds with relatively high hSERT potency.[5,6,10]

Michael addition of R_1-substituted indoles to cyclopent-2-enone in the presence of the Lewis acid $Yb(OTf)_3$ yielded racemic ketone **5** (Scheme 1).[12] In the case of R_1 = 5-CN, longer reaction times were necessary because of the presence of the strong electron withdrawing group. Reductive amination of **5** with dimethylamine then afforded **6**−**17** in quantitative yields.

Confirming a trend we have observed in other homotryptamine analogues,[5,6,10] 5-CN substitution yielded **8**, a sub-nM inhibitor of hSERT and the most potent analogue examined (Table 1). Halogen substitution at alternate indole positions (**6**−**7**, **9**−**17**) failed to improve on this result, although appreciable potency was maintained. On the basis of these results, we decided to explore analogues of both **8** and **9** in an effort to further improve hSERT potency via optimization of the dialkylamino side chain.

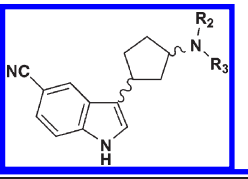
A representative group of side chain alkyl group substitutions (R_2 and R_3) in the 5-CN and 5-F series was synthesized as shown in Scheme 1. Results for the racemic/diastereomeric mixtures are listed in Tables 2 and 3, respectively. Relative to **8**, removal of both methyl groups in **18** and a single methyl group in **19** resulted in a significant decrease in hSERT potency. Increasing the size of the R_2 and/or R_3 substituents beyond methyl in compounds **20**−**32** also decreased potency relative to **8** (Table 2). Although we examined a more limited set of R_2 and R_3 substituents in the similar 5-fluoro series **33**−**35** (Table 3), the same trend was observed relative to **9**. Therefore, in both series, dimethyl substitution (i.e., R_2 = R_3 = Me) of the terminal side chain amine was optimal for

Table 1. hSERT Binding Affinities of Racemic 3-(3-Dimethylaminocyclopentyl)-indole Diastereomers



compd	R_1	hSERT IC_{50} (nM ± SEM)
6	4-F	31 ± 4
7	4-Br	5.3 ± 1.2
8	5-CN	0.48 ± 0.18
9	5-F	1.7 ± 0.2
10	5-Cl	3.0 ± 0.4
11	5-Br	4.3 ± 1.4
12	6-F	5.1 ± 1.1
13	6-Cl	6.5 ± 3.0
14	6-Br	9.6 ± 4.4
15	7-F	3.3 ± 1.5
16	7-Cl	1.4 ± 0.3
17	7-Br	1.6 ± 0.7

Table 2. hSERT Binding Affinities of Racemic 5-Cyano-3-(3-dialkylaminocyclopentyl)-indole Diastereomers



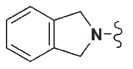
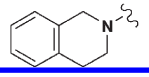
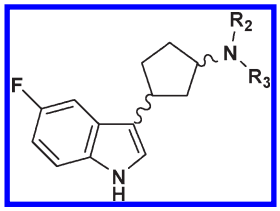
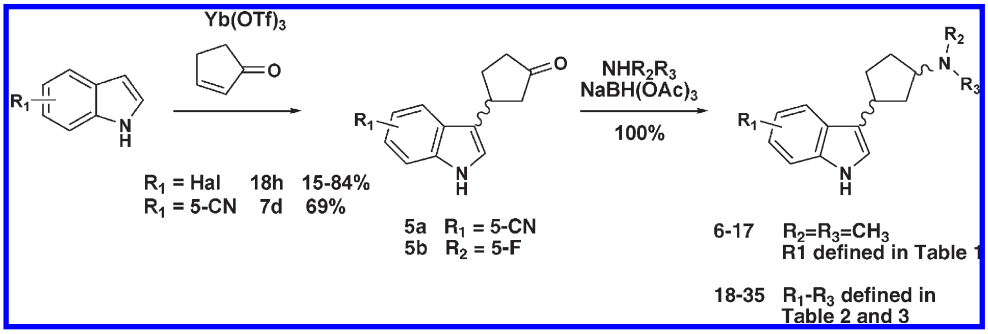
Cmpd	R2	R3	hSERT IC50 (nM +/- SEM)
8	Me	Me	0.48±0.18
18	H	H	32±7
19	H	Me	8.5±5.1
20	H	Et	6.6±3.4
21	H	Pr	30±16
22	H	Bn	15±2
23	H	CH2CH2Ph	10±5
24	Me	Et	1.6±0.7
25	Et	Et	6.2±1.9
26	Me	Bn	5.3±2.0
27	Me	CH2CH2Ph	6.2±3.7
28	-(CH2)4-		3.0±1.2
29	-(CH2)5-		65±20
30	-CH2CH2-O-CH2CH2-		110±27
31			6.8±4.5
32			6.5±5.1

Table 3. hSERT Binding Affinities of Racemic 5-Fluoro-3-(3-dialkylaminocyclopentyl)-indole Diastereomers



compd	R2	R3	hSERT IC_{50} (nM ± SEM)
9	Me	Me	1.7 ± 0.2
33	Me	Et	3.7 ± 1.4
34	Et	Et	7.3 ± 1.2
35	−((CH2)4)−		2.9 ± 0.9

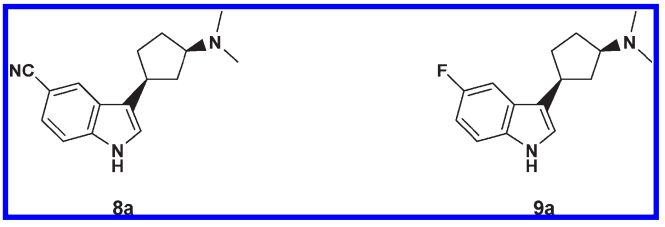
Scheme 1. Racemic Synthesis of Diastereomeric 3-(3-Dialkylaminocyclopentyl)-indoles



hSERT potency, as has been the case in the other homotryptamine series we have reported.[5,6,10]

On the basis of our prior experience with other stereoisomeric homotryptamines,[6,10] we believed that one of the various stereoisomers of **8** and **9** would preferentially bind to hSERT. To obtain all four possible stereoisomers of **8**, we initially obtained working quantities of the ketones *S*- and *R*-**5a** (compd **5**, R_1 = 5-CN) by chiral preparative HPLC resolution of *racemic*-**5a** (Scheme 1). After standard reductive amination of *S*- and *R*-**5a** with dimethylamine, the two sets of diastereomers were resolved by chiral preparative HPLC to give **8a**−**d** (Table 4). An identical procedure was followed starting with *racemic*-**5b** (compd **5**, R_1 = 5-F) to give the fluoro-series **9a**−**d**. A slight potency advantage was observed in the 5-CN series for isomer **8a**, which inhibited hSERT with an IC_{50} of 0.22 nM (Table 4). In the 5-fluoro series, **9a** was the most potent stereoisomer of the 5-fluoro series, although still 3-fold less potent than **8a** in the 5-CN series.

Table 4. hSERT Binding Affinities of Stereoisomers of **8** and **9**



8a **9a**

compd	cis/trans	configuration	hSERT IC_{50} (nM ± SEM)
8a	cis	1*S*,3*R*	0.22 ± 0.10
8b	trans	1*S*,3*S*	0.97 ± 0.22
8c	cis	1*R*,3*S*	0.38 ± 0.07
8d	trans	1*R*,3*R*	1.3 ± 0.7
9a	cis	1*R*,3*S*	0.63 ± 0.21
9b	trans	1*S*,3*S*	5.9 ± 1.2
9c	cis	1*S*,3*R*	2.4 ± 0.4
9d	trans	1*R*,3*R*	2.8 ± 0.5

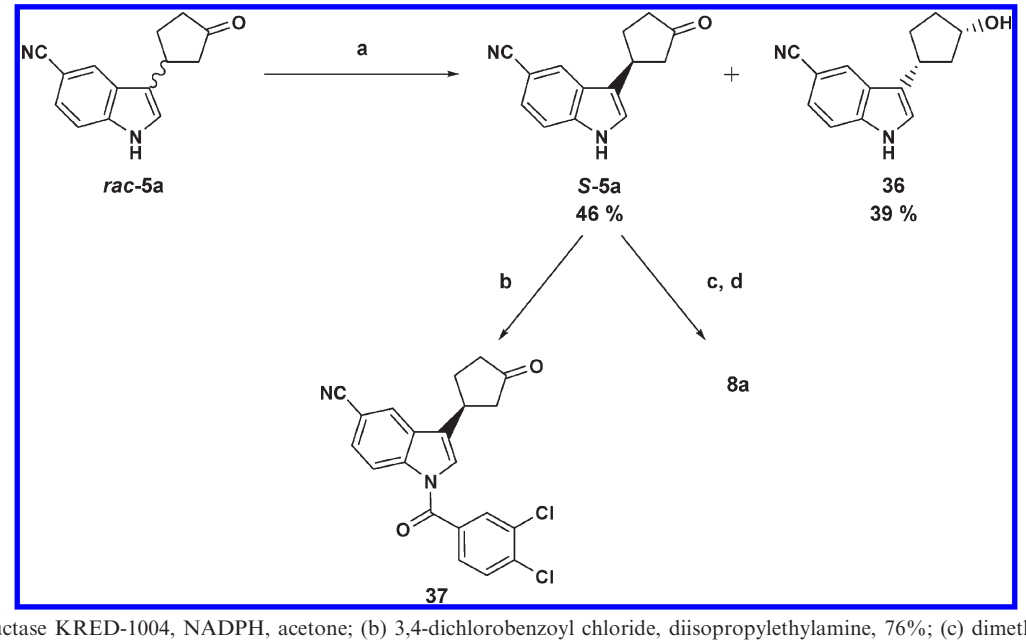
To determine the absolute stereochemistry of **8a** and **9a** and to produce larger quantities for in vivo testing than available via the chiral preparative HPLC method, it was necessary to devise a stereospecific synthesis of each. We were unable to find a general method applicable to both compounds, therefore, the individual approaches are outlined in the following section.

Synthesis and Absolute Stereochemistry of 8a. Large-scale synthesis of **8a** was accomplished by the method outlined in Scheme 2. Racemic ketone *racemic*-**5a** (compd **5**, R_1 = 5-CN) was resolved by partial enzymatic reduction using ketoreductase KRED-1004 to yield multigram quantities of the easily separable mixture of chiral ketone *S*-**5a** and alcohol **36**.[13] The absolute configuration of the chiral ketone was determined by X-ray crystallography of its *N*-3,4-dichlorobenzoyl derivative **37** (Figure 1). Chiral ketone *S*-**5a** was then subjected to reductive amination with dimethylamine and the mixture of diastereomers now efficiently separated by chiral preparative HPLC. The cis isomer was determined by NMR, and its correlation to the original isolate **8a** was confirmed by all analytical methods. Thus, the configuration of the most potent isomer **8a** was determined as 1*S*,3*R*. By analogy, the other isomers of **8** were identified as shown in Table 4.

An alternate synthetic approach which avoids preparative chiral HPLC is outlined in Scheme 3. Starting from chiral ketone *S*-**5a**, the mixture of diastereomers **38** and **39** obtained by reductive alkylation with *N*-methyl-*N*-benzylamine followed by N_1-BOC protection was separated by silica gel chromatography. **38** was then debenzylated and realkylated with formaldehyde/sodium cyanoborohydride under reductive conditions and deprotected to yield **8a** in good yield, identical in all respects to that obtained by the other methods.

Synthesis and Absolute Stereochemistry of 9a. In the 5-F series, we found it most convenient to obtain working quantities of chiral ketone *S*-**5b** via the procedure outlined in Scheme 4. Condensation of (1*S*,2*S*)-1,2-diphenylethane-1,2-diol with *racemic*-**5b** (compd **5**, R_1 = F) yielded a mixture

Scheme 2. Stereospecific Synthesis of **8a**[a]



[a] (a) Ketoreductase KRED-1004, NADPH, acetone; (b) 3,4-dichlorobenzoyl chloride, diisopropylethylamine, 76%; (c) dimethylamine, sodium triacetoxyborohydride; (d) preparative chiral LC.

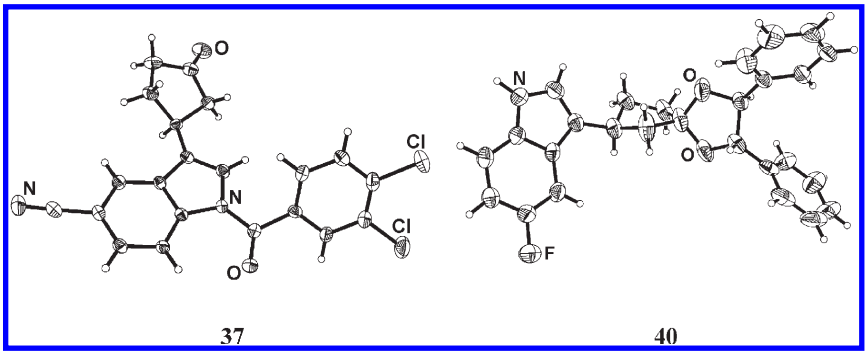
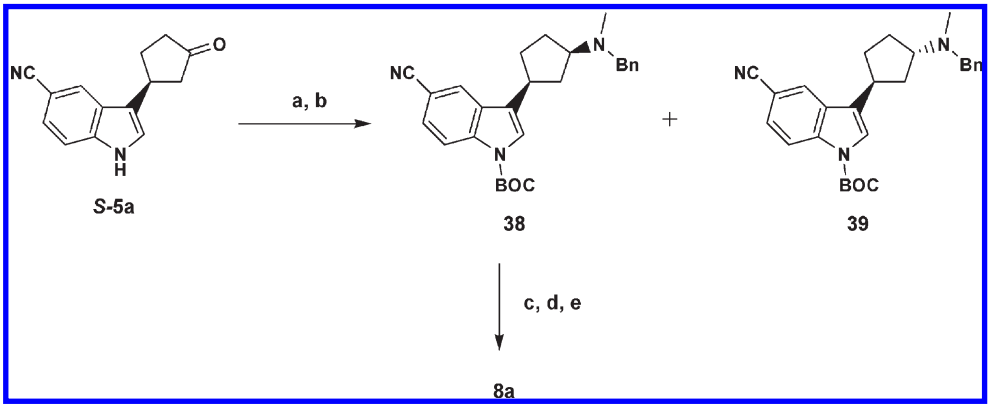


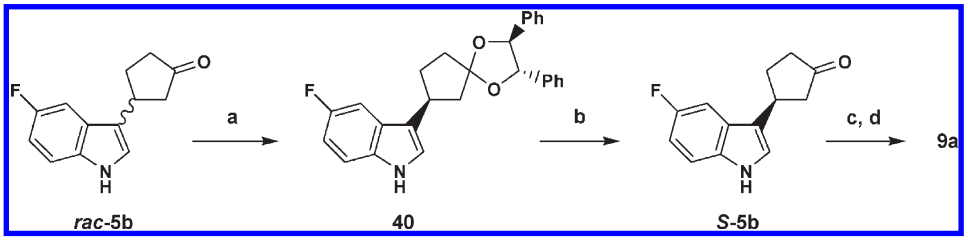
Figure 1. ORTEP drawing of **37** and **40** with thermal ellipsoids at 30% (**37**) and 25% (**40**) probability for non-H atoms and open circles for H-atoms.

Scheme 3. Alternate Stereospecific Synthesis of **8a**[a]



[a] (a) *N*-Methyl-*N*-benzylamine, sodium cyanoborohydride; (b) di-*t*-butyldicarbonate, DMAP, triethylamine; (c) a-chloroethylchloroformate, MeOH; (d) formaldehyde, sodium cyanoborohydride; (e) TFA

Scheme 4. Stereospecific Synthesis of **9a**[a]



[a] (a) (1*S*,2*S*)-1,2-diphenylethane-1,2-diol, *p*-tosic acid, 17%; (b) HCl/MeOH, 63%; (c) dimethylamine, sodium triacetoxyborohydride; (d) preparative chiral LC.

of two diastereomeric ketals. **40** was obtained by methanol recrystallization in 86.8% de and 17% yield.[14] The absolute configuration of **40** was established by X-ray crystallography as 2*S*,3*S*,7*S* (Figure 1). Acid hydrolysis then gave chiral ketone *S*-**5b**, which was subjected to reductive amination and preparative chiral HPLC. The cis isomer obtained by this method, **9a**, was established by NMR and correlated to the original material by all analytical methods. The absolute configuration of **9a** was determined as 1*R*,3*S*. By analogy, absolute configurations of the other three isomers **9b**−**d** were assigned (Table 4).

Discussion

In a series of previous communications, we have identified a number of homotryptamines with high binding affinity for hSERT.[4−10] These studies have shown that 5-indole substitution is generally optimal, with 5-CN and 5-F being the most active at inhibiting hSERT. The most potent homotrytamine SSRI's discovered thus far are the 5-CN analogues **2** and **3**, with hSERT binding affinity IC_{50} values of 0.48 and 0.13 nM, respectively.

In the current series, we maintained the C3 side chain common to the homotryptamines but arranged the indole and the tertiary amine in a 1,3 substitution pattern on a cyclopentane backbone. Several members of this series exhibited high affinity binding to hSERT, with the 5-CN and 5-F analogues again being particularly active. Resolution of all enantiomers allowed the identification of **8a** and **9a**, with hSERT binding affinity IC_{50} values of 0.22 and 0.63 nM, respectively, as the most potent of the series. These compounds shared the same cis-stereochemistry around the cyclopentane ring, ie., *S* at the indole and *R* at the dimethylamino group. They were 2−4 times more potent than the other respective cis enantiopodes and 4−9 times more potent than either of the respective trans enantiomers.

To examine the relationship of putative binding conformations of **3** and **8a** with established SSRIs such as sertraline and

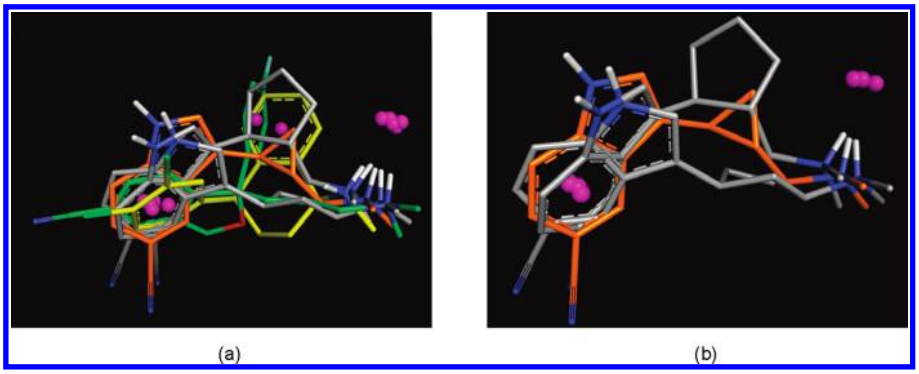


Figure 2. (a) Model shows superposition of SSRIs sertraline ((1*S*,4*S*)-stereochemistry, yellow carbon atoms), *S*-citalopram (green carbon atoms), compound **2** ((+)-**12a** from reference 6 (orange carbon atoms)), and compounds **3** and **8a** (gray carbon atoms). (b) Same model as shown in (a) with sertraline and *S*-citalopram removed to highlight similarities between possible bioactive conformations of compounds **2**, **3**, and **8a**. Magenta spheres represent centroid atoms and putative hydrogen bond acceptor site points used in the rms fitting procedure.

S-citalopram and the previously reported potent 1,2-substituted cyclopropyl homotryptamine **2**,[6] a molecular modeling study was undertaken. This revealed that low-energy conformers of compounds **3** and **8a** can be superimposed reasonably well with low-energy conformers of sertraline, *S*-citalopram, and compound **2** (Figure 2). The conformers of sertraline, *S*-citalopram, and **2** were identified and superimposed as described previously.[6] The conformers of compounds **3** and **8a** were identified via similar methods described in ref 15. The energy of the conformer of compound **3** shown in Figure 2 is 1.5 kcal/mol above that of the lowest energy conformer identified, and the conformer of compound **8a** shown is the lowest energy conformer found for that compound. The conformers of compounds **3** and **8a** were each superimposed with sertraline using three corresponding points for an rms-fitting procedure: the aromatic ring centroids, the basic nitrogen atoms and putative hydrogen-bond acceptor site points located 2.8 Å from the nitrogen atoms in the directions of the N−H bonds. As shown in Figure 2a, superposition in this manner results in reasonable overlap of the substituted aromatic rings and putative hydrogen-bond acceptor site points for all five SSRI compounds. Note, however, that the substituted aromatic rings deviate significantly from coplanarity, and the relative positions of the ring substituents differ as well. These observations suggest that although compounds **3** and **8a** fit the basic SSRI pharmacophore as represented by sertraline and *S*-citalopram, the SAR for substitution on the aromatic rings may be somewhat different for the homotryptamines and analogues of sertraline and *S*-citalopram. In Figure 2b, for clarity, only compounds **2**, **3**, and **8a** are shown. Despite the variation in the linker moieties connecting the basic amines to the indole rings, there is good correspondence between the aromatic rings and putative hydrogen-bond acceptor site points, indicating that the different homotryptamine compounds interact with the serotonin transported in a similar manner. Finally, it is interesting to note that the potency of compound **8a** is within experimental error of that determined for its enantiomer **8c**. Although not shown in Figure 2, **8c** can also adopt a conformation which fits the SSRI pharmacophore and differs from the conformer of **8a** shown primarily in the region of the cyclopentyl linker.

To confirm selectivity for the serotonin transporter, **8a** and **9a** were evaluated for binding affinity at the human dopamine (hDAT) and norepinephrine (hNET) transporters (Table 5). Neither of these compounds was a significant inhibitor of hDAT or hNET, with selectivity ratios ranging from 1000 to 10000 versus hSERT. Both compounds were also highly selective against most of the other serotonin and dopamine receptors listed in Table 5. In the single exception observed, **8a** was 200-fold less selective for 5HT6 than hSERT.

Table 5. Binding Affinities of **8a** and **9a** versus Selected Off-Target Receptors

	IC_{50} (nM ± SEM)[a]	
target	**8a**	**9a**
hSERT	0.22 ± 0.10	0.63 ± 0.21
hNET	6900	2100
hDAT	1300	1100
5HT1a	340[b]	500
5HT1b	840	28000
5HT2a	> 10000	> 10000
5HT2b	> 10000	> 10000
5HT2c	> 10000	NT[c]
5HT4	> 30000	> 30000
5HT5a	> 1000	NT
5HT6	37[b]	NT
5HT7	> 1000	NT
dopamine D1	7200	25000
dopamine D2	> 30000	> 30000

[a] All data $n = 1$, except where indicated. [b] $n = 2$. [c] Not tested.

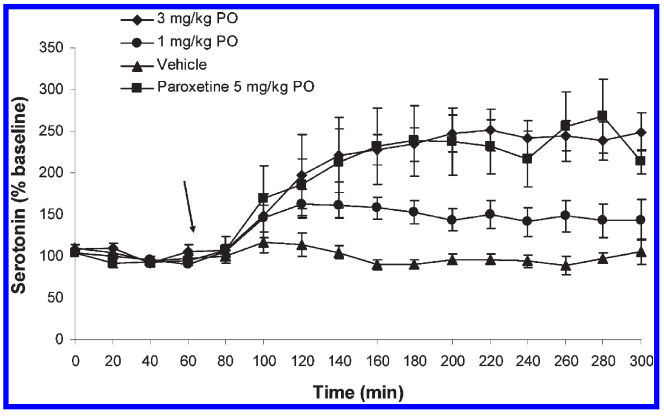


Figure 3. Effects of po administration of **8a** on extracellular serotonin levels in the frontal cortex of rats measured by microdialysis.

As a demonstration of the ability of these compounds to produce functional changes in serotonin levels in vivo, microdialysis experiments were carried out in rats.[6] Oral dosing of **8a** produced a robust, dose-dependent increase in extracellular serotonin in the frontal cortex (Figure 3). Doses of both 1 and 3

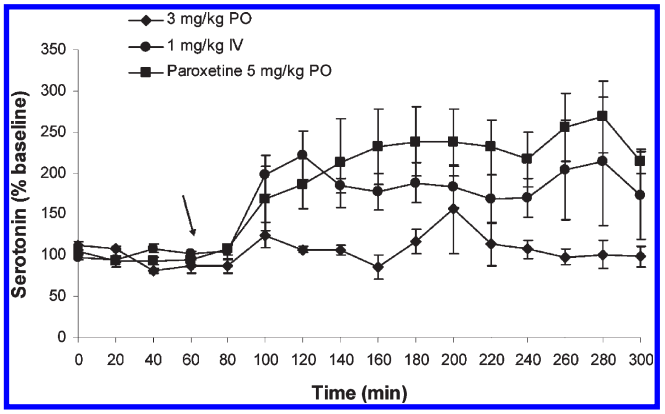


Figure 4. Effects of po and iv administration of **9a** on extracellular serotonin levels in the frontal cortex of rats measured by microdialysis.

Table 6. Pharmacokinetic Parameters Measured in Rat Microdialysis Experiments[a]

compd	brain conc, nM	plasma conc, nM	F_{po}, %	T_{max}, h	$T_{1/2}$, h
8a	1000	820	51	1.0	0.55
9a	53	37	nd	nd	nd

[a] Compounds **8a** and **9a** were administered at 3 mg/kg po. Brain and plasma concentrations were measured at 2 h.

mg/kg po produced effects which were significantly greater than vehicle control. An increase of 150% over vehicle was observed at the maximum dose tested, 3 mg/kg. This effect was similar to that seen for paroxetine dosed at 5 mg/kg po.

By contrast, **9a** did not produce a significant increase in extracellular serotonin in the frontal cortex when dosed in rats at 3 mg/kg po (Figure 4). This result, in contrast to that of **8a**, can best be understood in terms of their relative pharmacokinetic properties. Compound **9a** demonstrated low bioavailability in rats when dosed orally at 3 mg/kg; brain and plasma levels of drug measured at 2 h were, respectively, 53 and 37 nM (Table 6). By contrast, brain and plasma levels of **8a** at 2 h after 3 mg/kg oral dosing were 1000 and 820 nM, respectively Thus, brain and plasma exposures were 20-fold higher for **8a** versus **9a**. Oral bioavailability of **8a** was 51%, with a T_{max} of 1 h and a $T_{1/2}$ of 0.55 h in the rat. Additionally, when dosed at 1.0 mg/kg iv, **9a** did produce a robust increase in frontal cortex serotonin levels, similar to that observed with oral dosing of **8a**. This result further confirmed the poor oral bioavailability of **9a**.

Conclusion

In this report we presented a series of novel conformationally restricted homotryptamines and demonstrated their hSERT activity. Conformational restriction was imparted by arranging the indole and alkylamino groups in a 1,3-substitution pattern on a cyclopentane ring spacer. Nitrile and fluoro substituents at the C5-position of the indole provided compounds with highest hSERT affinities, although compounds with halogen substituents at other positions on the indole were active as well. Additionally, *N*,*N*-dimethyl substitution of the cyclopentane amino group was found to be the optimal alkylation pattern for the amine, consistent with previous findings. Resolution of the most active enantiomers in both series provided the highly potent hSERT inhibitors **8a** and **9a**, which shared the same cyclopentane cis-stereochemistry, i.e., *S* at the indole and *R* at the dimethylamino group. These compounds were found to be 2−4 times more potent than their other respective cis enantiopodes, and 4−9 times more potent than either of their respective trans enantiomers. Both compounds were highly selective relative to other neurotransporters in vitro.

While the in vitro properties of **8a** and **9a** were similar, the in vivo effects differed between the two compounds. **8a** produced a robust, dose-dependent increase in extracellular serotonin in the rat frontal cortex at 1 and 3 mg/kg po, similar to the SSRI paroxetine. In contrast, no effect was observed for **9a** at 3 mg/kg po, although an effect similar to **8a** was observed when **9a** was dosed at 1 mg/kg iv. This lack of oral activity is consistent with the relatively poor pharmacokinetic profile of **9a**, which failed to attain suitable brain concentrations under oral administration.

With the conclusion of the current series, it was informative to compare the relative binding modes of other conformationally restricted homotryptamines with SSRIs. Molecular models suggested that sertraline, *S*-citalopram, **2**, **3**, and **8a** may be able to interact with the serotonin transporter binding site in a similar manner. Furthermore, there was good correspondence between the aromatic rings and putative hydrogen-bond acceptor site points in **2**, **3**, and **8a** despite the variation in the cyclic structures connecting the basic amine to the indole ring. This proves that the homotryptamine side chain can be locked into a common favorable hSERT binding conformation, leading to higher in vitro and in vivo potency via a number of different conformationally restricted orientations.

Experimental Section

Chemistry. NMRs were recorded on Bruker Avance spectrometers. Elemental analyses were performed at Robertson Microlit Laboratories, Madison, NJ. Exact mass determinations were made using a Micromass LCT unit, and all samples were determined using a TOF ESI (+) source. ORTEP drawings of the X-ray crystal structures for **37** and **40** are given in Figure 1, with thermal ellipsoids at 30% (**37**) and 25% (**40**) probability for non-H atoms and open circles for H-atoms. Full crystallographic data have been deposited to the Cambridge Crystallographic Data Center (CCDC 793899 and 793900). Copies of the data can be obtained free of charge via the Internet at http://www.ccdc.cam.ac.uk. Purity of all compounds was determined to be >95% by either combustion analysis or analytical HPLC using at least two perpendicular methods as listed in the Supporting Information. Chiral purity was determined by chiral HPLC using one of the methods listed in the Supporting Information.

Specific details related to the synthesis of compounds **5**−**35** are included in the Supporting Information.

General Procedure for the Synthesis of 3-(1*H*-Indol-3-yl)cyclopentanones 5. 2-Cyclopenten-1-one (4.1 g, 4.2 mL, 50 mmol) was added to a stirred solution of the substituted indole (10 mmol) and ytterbium triflate hexahydrate (124 mg, 0.2 mmol) in acetonitrile (15 mL). After stirring at room temperature for 18 h to 7 days, the reaction was concentrated to an oil and diluted with ether. The red oily mixture was filtered through Celite, and the filtrate was concentrated in vacuo. The crude product was purified by flash chromatography on silica gel using a gradient of ethyl acetate in hexanes. Pure product fractions were concentrated and dried under high vacuum to give the 3-(1*H*-indol-3-yl)cyclopentanones.

General Procedure for the Synthesis of 6−17. The appropriately substituted 3-(1*H*-indol-3-yl)cyclopentanone (0.5 mmol) and dimethylamine (2.0 M solution in THF, 5.0 mmol) were dissolved in ethanol to a final volume of 5 mL. After stirring for 15 min, sodium triacetoxyborohydride (430 mg, 2.0 mmol) was added and the reaction stirred for 3 h to 3 days. The reaction was then diluted with water (10 mL) and extracted three times with

ethyl acetate (10 mL). The organic extracts were dried over sodium sulfate and concentrated in vacuo. The residue was purified by preparative reverse phase HPLC to give the product as an oily trifluoroacetic acid salt of the 4 cis/trans diastereomers. Where indicated, the free base was isolated by extraction of the TFA salt from saturated sodium carbonate solution with ethyl acetate.

General Procedure for the Synthesis of 18−35. The indicated 3-(1*H*-indol-3-yl)cyclopentanone (0.5 mmol) and amine (5.0 mmol) were dissolved in ethanol to a final volume of 5 mL. After stirring for 15 min, sodium triacetoxyborohydride (430 mg, 2.0 mmol) was added and the reaction stirred for 3 h to 3 days. The reaction was then diluted with water (10 mL) and extracted three times with ethyl acetate (10 mL). The organic extracts were dried over sodium sulfate and concentrated in vacuo. The residue was purified by preparative reverse phase HPLC to give the product as an oily trifluoroacetic acid salt of the 4 cis/trans diastereomers. Where indicated, the free base was isolated by extraction of the TFA salt from saturated sodium carbonate solution with ethyl acetate.

Synthesis of 8a−d via Chiral HPLC Resolution of Stereoisomers. The *S*- and *R*-enantiomers of 3-(3-oxocyclopentyl)-1*H*-indole-5-carbonitrile **5a** were resolved by chiral HPLC on a Chiral Technologies Chiralcel OD column (20 μ, 50 mm × 500 mm) using a mobile phase gradient of ethanol/hexanes (10−100% containing 0.01% diethylamine). Flow rate was varied over the gradient from 60 to 50 mL/min. The first isomer to elute was 3-(1*S*-3-oxocyclopentyl)-1*H*-indole-5-carbonitrile *S*-**5a** ($[\alpha]^{25}$ −24.4 (589 nm, *c* 2.62 mg/mL, MeOH); analytical chiral HPLC (method I) t_R 10.8 min. The second isomer to elute was 3-(1*R*-3-oxocyclopentyl)-1*H*-indole-5-carbonitrile *R*-**5a** ($[\alpha]^{25}$ +10.5 (589 nm, *c* 2.64 mg/mL, EtOH); analytical chiral HPLC (method I) t_R 12.5 min.

S-**5a** (112 mg, 0.5 mmol) and dimethylamine (2.0 M solution in THF, 2.5 mL, 5.0 mmol) were dissolved in ethanol (2 mL). After stirring for 15 min, sodium triacetoxyborohydride (424 mg, 2.0 mmol) was added and the reaction continued for 2 h. The reaction was then diluted with water (5 mL) and made acidic (pH 3) with 6 M HCl. The reaction was then adjusted to pH 10 with sodium carbonate. It was extracted two times with ethyl acetate (50 mL), and the extracts were dried over sodium sulfate, concentrated in vacuo, and dried under high vacuum to give 3-[(1*S*)-3-dimethylaminocyclopentyl]-1*H*-indole-5-carbonitrile (125 mg, 100%) as a cis/trans diastereomeric mixture of **8a** and **8b**. The 3*R* and 3*S* diastereomers were resolved by preparative chiral HPLC on a Chiral Technologies Chiralpak AD column (20 μ, 50 mm × 500 mm) with a mobile phase of 10% ethanol in hexanes/0.1% diethylamine at a flow rate of 75 mL/min.

3-[(1*S*,3*R*)-3-Dimethylaminocyclopentyl]-1*H*-indole-5-carbonitrile 8a. ^{1}H NMR (500 MHz, CD_3OD) δ 8.03 (1 H, d, J = 0.92), 7.46 (1 H, d, J = 8.55), 7.36 (1 H, dd, J = 8.24 1.53), 7.25 (1 H, s), 3.39 (1 H, m), 2.81 (1 H, m), 2.42 (1 H, m), 2.35 (6 H, s), 2.22 (1 H, m), 2.08 (1 H, m), 1.86 (1 H, m), 1.77 (1 H, m), 1.67 (1 H, m). $[\alpha]^{25}$ +12.95 (589 nm, *c* 1.58 mg/mL, EtOH). Analytical chiral HPLC (method J) t_R 13 min.

3-[(1*S*,3*S*)-3-Dimethylaminocyclopentyl]-1*H*-indole-5-carbonitrile 8b. ^{1}H NMR (500 MHz, CD_3OD) δ 7.99 (1 H, s), 7.45 (1 H, d, J = 8.54), 7.36 (1 H, dd, J = 8.24 1.52), 7.21 (1 H, s), 3.49 (1 H, m), 2.85 (1 H, m), 2.32 (6 H, s), 2.25 (1 H, m), 2.12 (2 H, m), 1.99 (1 H, m), 1.80 (1 H, m), 1.66 (1 H, m). $[\alpha]^{25}$ −26.50 (589 nm, *c* 1.58 mg/mL, EtOH). Analytical chiral HPLC (method J) t_R 8.4 min.

R-**5a** was reacted with dimethylamine by the same procedure to give 3-[(1*R*)-3-dimethylaminocyclopentyl]-1*H*-indole-5-carbonitrile (125 mg, 100%) as a cis/trans diastereomeric mixture of **8c** and **8d**. The 3*S* and 3*R* diastereomers were resolved by chiral HPLC on a Chiral Technologies Chiralpak AD column (20 μ, 50 mm × 500 mm) with a mobile phase of 10% ethanol in hexanes/0.1% diethylamine at a flow rate of 75 mL/min.

3-[(1*R*,3*S*)-3-Dimethylaminocyclopentyl]-1*H*-indole-5-carbonitrile 8c. ^{1}H NMR δ (500 MHz, CD_3OD) 8.03 (1 H, d, J = 0.92), 7.46 (1 H, d, J = 8.55), 7.36 (1 H, dd, J = 8.24, 1.53), 7.25 (1 H, s), 3.38 (1 H, m), 2.86 (1 H, m), 2.43 (1 H, m), 2.38 (6 H, s), 2.23 (1 H, m), 2.09 (1 H, m), 1.86 (1 H, m), 1.78 (1 H, m), 1.68 (1 H, m). $[\alpha]^{25}$ −8.12 (589 nm, *c* 1.71 mg/mL, EtOH). Analytical chiral HPLC (method J) t_R 9.7 min.

3-[(1*R*,3*R*)-3-Dimethylaminocyclopentyl]-1*H*-indole-5-carbonitrile 8d. ^{1}H NMR (500 MHz, CD_3OD) δ 8.01 (1 H, s), 7.47 (1 H, d, J = 8.24), 7.37 (1 H, dd, J = 8.24 1.52), 7.23 (1 H, s), 3.53 (1 H, m), 3.10 (1 H, m), 2.47 (6 H, s), 2.29 (1 H, m), 2.19 (2 H, m), 2.07 (1 H, m), 1.84 (1 H, m), 1.73 (1 H, m). $[\alpha]^{25}$ +13.99 (589 nm, *c* 1.5 mg/mL, EtOH). Analytical chiral HPLC (method J) t_R 8.6 min.

Synthesis of 9a−d via Chiral HPLC Resolution of Stereoisomers. The *S*- and *R*-enantiomers of 3-(5-fluoro-1*H*-indol-3-yl)-cyclopentanone **5b** were resolved by chiral HPLC on a Chiral Technologies Chiralcel OD column (20 μ, 50 mm × 500 mm) using a mobile phase of 15% isopropyl alcohol/hexanes. Flow rate was 75 mL/min. The first isomer to elute was *S*-3-(5-fluoro-1*H*-indol-3-yl)-cyclopentanone *S*-**5b**; analytical chiral HPLC (method K) t_R 21.0 min. The second isomer to elute was *R*-3-(5-fluoro-1*H*-indol-3-yl)-cyclopentanone *R*-**5b**; analytical chiral HPLC (method K) t_R 26.7 min.

A solution of *S*-**5b** (290 mg, 1.34 mmol) and dimethylamine (2.0 M solution in THF, 6.7 mL, 13.4 mmol) in ethanol (10 mL) was stirred for 15 min. Sodium triacetoxyborohydride (1.1 g, 5.4 mmol) was added and the reaction stirred for 1 h. The reaction was extracted three times with ethyl acetate/aqueous sodium bicarbonate solution. The ethyl acetate extracts were dried over magnesium sulfate and concentrated in vacuo to give [(3*S*)-3-(5-fluoro-1*H*-indol-3-yl)-cyclopentyl]-dimethylamine (400 mg, 100%) as a cis/trans diastereomeric mixture of **9a** and **9b**. The 1*R* and 1*S* diastereomers were resolved by preparative chiral HPLC on a Chiral Technologies Chiralpak AD column (20 μ, 50 mm × 500 mm) with a mobile phase of 10% ethanol in hexanes/0.1% diethylamine at a flow rate of 60 mL/min.

[(1*R*,3*S*)-3-(5-Fluoro-1*H*-indol-3-yl)-cyclopentyl]-dimethylamine 9a. ^{1}H NMR (500 MHz, CD_3OD): δ 7.27 (dd, J = 9.0, 4.5 Hz, 1H), 7.24 (dd, J = 8.7, 4.2 Hz, 1H), 7.21 (s, 1H), 6.86 (dt, J = 9.3, 2.4 Hz, 1H), 3.35 (m, 1H), 3.18 (m, 1H), 2.58 (s, 6H), 2.47 (m, 1H), 2.18 (m, 2H), 1.86 (m, 2H), and 1.75 (q, J = 10.5 Hz, 1H). FIMS: m/z 247.4 $(M + H)^+$; m/z 245.4 $(M - H)^-$. $[\alpha]^{25}$ +2.54 (589 nm, *c* 2.79 mg/mL, EtOH). Analytical HPLC (method H): t_R, 2.38 m, >99% purity; analytical chiral HPLC (method L) >98% ee, t_R 15.7 min.

[(1*S*,3*S*)-3-(5-Fluoro-1*H*-indol-3-yl)-cyclopentyl]-dimethylamine 9b. ^{1}H NMR (500 MHz, CD_3OD): δ 7.28 (dd, J = 8.7, 4.5 Hz, 1H), 7.22 (dd, J = 10.2, 2.4 Hz, 1H), 7.14 (s, 1H), 6.86 (dt, J = 2.4 Hz, 1H), 3.68 (t, 1H), 3.55 (m, 1H), 2.84 (s, 6H), 2.28 (m, 4H), and 1.88 (m, 2H). FIMS: m/z 247.4 $(M + H)^+$; m/z 245.4 $(M - H)^-$. $[\alpha]^{25}$ −13.54 (589 nm, *c* 3.07 mg/mL, EtOH). Analytical HPLC (method H): t_R, 2.32 m, >97% purity; analytical chiral HPLC (method L) >99% ee, t_R 12.1 min.

R-**5b** was reacted with dimethylamine by the same procedure on a 0.92 mmol scale to give 240 mg (100%) of [(3*R*)-3-(5-fluoro-1*H*-indol-3-yl)-cyclopentyl]-dimethylamine as a cis/trans diastereomeric mixture of **9c** and **9d**. The 1*S* and 1*R* diastereomers were resolved by preparative chiral HPLC on a Chiral Technologies Chiralpak AD column (20 μ, 50 mm × 500 mm) with a mobile phase of 10% ethanol in hexanes/0.1% diethylamine at a flow rate of 60 mL/min.

[(1*S*,3*R*)-3-(5-Fluoro-1*H*-indol-3-yl)-cyclopentyl]-dimethylamine 9c. ^{1}H NMR (500 MHz, CD_3OD): δ 7.26 (dd, J = 8.7, 4.5 Hz, 1H), 7.21 (dd, J = 9.9, 2.4 Hz, 1H), 7.11 (s, 1H), 6.83 (dt, J = 2.4 Hz, 1H), 3.31 (m, 1H), 2.90 (m, 1H), 2.41 (s, 6H), 2.39 (m, 1H), 2.20 (m, 1H), 2.10 (m, 1H), 1.80 (m, 2 H), and 1.68 (q, J = 10.5 Hz, 1H). FIMS: m/z 248.3 $(M + H)^+$; m/z 245.4 $(M - H)^-$. $[\alpha]^{25}$ −12.32 (589 nm, *c* 1.93 mg/mL, EtOH). Analytical HPLC (method H): t_R, 2.34 m, >97% purity; analytical chiral HPLC (method L) >98% ee, t_R 14.7 min.

[(1*R*,3*R*)-3-(5-Fluoro-1*H*-indol-3-yl)-cyclopentyl]-dimethylamine 9d. ^{1}H NMR (500 MHz, CD_3OD): δ 7.27 (dd, J = 8.7, 4.5 Hz, 1H), 7.22 (dd, J = 9.9, 2.4 Hz, 1H), 7.11 (s, 1H), 6.84 (dt, J = 9.0, 2.4 Hz, 1H), 3.49 (t, 1H), 3.31 (m, 1H), 2.61 (s, 6H), 2.24 (m, 2H), 2.19 (q, J = 15.3, 6.9 Hz, 2 H), and 1.80 (m, 2H). FIMS: m/z 247.4 $(M + H)^+$; m/z 245.4 $(M - H)^-$. $[\alpha]^{25}$ +14.03 (589 nm, c 1.71 mg/mL, EtOH). Analytical HPLC (method H): t_R, 2.26 m, >89% purity; analytical chiral HPLC (method L) >99% ee, t_R 13.0 min.

Enzymatic Resolution of 3-(3-Oxocyclopentyl)-1*H*-indole-5-carbonitrile *rac*-5a and 3-(1*R*,3*S*-3-hydroxycyclopentyl)-1*H*-indole-5-carbonitrile 36. (*S*)-3-(3-Oxocyclopentyl)-1*H*-indole-5-carbonitrile *S*-**5a** was obtained by enzymatic resolution of racemic 3-(3-oxocyclopentyl)-1*H*-indole-5-carbonitrile *rac*-**5a** utilizing ketoreductase KRED-1004 (Biocatalytics, Inc., Pasadena, CA) in the presence of isopropyl alcohol as cosubstrate and NADPH as cofactor. The 1 L reaction mixture consisted of 10 mM potassium phosphate buffer (pH 6.0), 15% methanol, 2% isopropyl alcohol, 50 mg NADPH, 50 mg KRED-1004, and 500 mg *rac*-**5a** in water. After incubating at 30 °C, 75 rpm for 3 days, the reaction reached completion by HPLC analysis. The reaction mixture was then extracted with 1 L of ethyl acetate to afford a mixture of *S*-**5a** and 3-(1*R*,3*S*-3-hydroxycyclopentyl)-1*H*-indole-5-carbonitrile **36** (516 mg). The ketone/alcohol mixture obtained from multiple runs (2.4 g) was purified by flash chromatography on 110 g silica gel with a step gradient of 0, 1, and 2% methanol in methylene chloride. The two components were concentrated and dried under high vacuum to yield *S*-**5a** (1.1 g, 46%) and **36** (0.94 g, 39%).

(*S*)-3-(3-Oxocyclopentyl)-1*H*-indole-5-carbonitrile *S*-5a. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (1 H, bs), 7.98 (1 H, s), 7.45 (2 H, m), 7.11 (1 H, dd, J = 2.44, 0.91 Hz), 3.71 (1 H, m), 2.77 (1 H, dd, J = 7.63, 18.31 Hz), 2.56 (1 H, m), 2.40 (3 H, m), 2.10 (1 H, m). MS m/e 223.2 $(M - H)^+$. $[\alpha]^{25}$ −22.3 (589 nm, c 1.54 mg/mL, MeOH). Analytical chiral HPLC (method I) >95% ee.

3-(1*R*,3*S*-3-Hydroxycyclopentyl)-1*H*-indole-5-carbonitrile 36. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (1 H, bs), 8.04 (1 H, s), 7.40 (2 H, m), 7.15 (1 H, dd, J = 2.44, 0.91 Hz), 4.52 (1 H, m), 3.31 (1 H, p, J = 8.24), 2.55 (1 H, m), 2.15 (1 H, m), 1.98 (2 H, m), 1.83 (1 H, m), 1.76 (1 H, m). MS m/e 225.2 $(M - H)^+$. Anal. Calcd. for $C_{14}H_{14}N_2O \cdot 0.65\ H_2O$: C, 70.66; H, 6.48; N, 11.77. Found: C, 70.87; H, 6.80; N, 11.44. $[\alpha]^{25}$ −13.8 (589 nm, c 1.54 mg/mL, MeOH). The configuration of the alcohol was established as cis by a NMR-NOE method.

(*S*)-1-(3,4-Dichlorobenzoyl)-3-(3-oxocyclopentyl)-1*H*-indole-5-carbonitrile 37. 3,4-Dichlorobenzoyl chloride (243 mg, 1.16 mmol) was added to a mixture of (*S*)-3-(3-oxocyclopentyl)-1*H*-indole-5-carbonitrile *S*-**5a** (200 mg, 0.892 mmol) and diisopropylethylamine (0.234 mL, 1.34 mmol) in DCM (1 mL) at 0 °C. Stirring was continued at room temperature overnight. The reaction was concentrated, and the residue was purified by silica gel chromatography (EtOAc/hexanes, gradient: 0−40%). Recrystallization from EtOAc/EtOH yielded (*S*)-1-(3,4-dichlorobenzoyl)-3-(3-oxocyclopentyl)-1*H*-indole-5-carbonitrile **37** (300 mg, 76%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.97−2.15 (m, 1 H) 2.27−2.46 (m, 3 H) 2.58 (m, J = 8.30, 4.20, 4.20, 2.10 Hz, 1 H) 2.78 (dd, J = 18.07, 7.53 Hz, 1 H) 3.58−3.74 (m, 1 H) 7.16 (d, J = 1.25 Hz, 1 H) 7.56 (dd, J = 8.28, 2.01 Hz, 1 H) 7.67 (d, J = 8.00 Hz, 1 H) 7.69 (dd, J = 8.70, 1.50 Hz, 1 H) 7.86 (d, J = 2.01 Hz, 1 H) 7.96 (dd, J = 1.51, 0.50 Hz, 1 H) 8.45 (dd, J = 8.53, 0.50 Hz, 1 H). LCMS: MH^+ = 397 and 399.

Synthesis of 3-[(1*S*,3*R*)-3-Dimethylaminocyclopentyl]-1*H*-indole-5-carbonitrile 8a via Procedure of Scheme 3. *tert*-Butyl 3-((1*S*,3*R*)-3-(Benzyl(methyl)amino)cyclopentyl)-5-cyano-1*H*-indole-1-carboxylate 38 and *tert*-Butyl 3-((1*S*,3*S*)-3-(benzyl(methyl)amino)cyclopentyl)-5-cyano-1*H*-indole-1-carboxylate 39. $NaBH_3CN$ (1.26 g, 20 mmol) was added to a mixture of *S*-**5a** (1.12 g, 5.0 mmol) and *N*-methylbenzylamine (6.45 mL, 50 mmol) in EtOH (75 mL). The reaction was stirred for 3 h and then diluted into EtOAc and extracted twice with aqueous $NaHCO_3$ solution and twice with brine. The organic layer was dried over sodium sulfate and concentrated to dryness. The crude product was dissolved in 50 mL DCM, and to this was added di-*t*-butyldicarbonate (5.45 g, 25 mmol), DMAP (100 mg), and triethylamine (3.5 mL, 25 mmol). The reaction was stirred at room temperature for 18 h and then washed three times with aqueous $NaHCO_3$ solution and twice with brine. The organic layer was dried over sodium sulfate, concentrated to dryness, and purified by flash chromatography on 120 g silica gel with a gradient of 0−30% EtOAc in hexanes (50 min). The faster eluting component was isolated, concentrated, and dried to *tert*-butyl 3-((1*S*,3*R*)-3-(benzyl(methyl)amino)cyclopentyl)-5-cyano-1*H*-indole-1-carboxylate **38** (1.15 g, 54%). The slower eluting trans component **39** was not characterized.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.21 (1 H, d, J = 8.31 Hz), 7.87−7.90 (1 H, m), 7.54 (1 H, dd, J = 8.56, 1.51 Hz), 7.47 (1 H, s), 7.28−7.35 (4 H, m), 7.20−7.27 (1 H, m), 3.55 (2 H, dd, J = 37.02, 13.09 Hz), 3.16−3.30 (1 H, m), 2.94−3.04 (1 H, m), 2.39 (1 H, ddd, J = 12.02, 6.30, 6.11 Hz), 2.18−2.24 (1 H, m), 2.17 (3 H, s), 2.01−2.12 (1 H, m), 1.79−1.91 (2 H, m), 1.73 (1 H, dd, J = 21.91, 11.58 Hz), 1.66 (9 H, s). 13C NMR (100 MHz, $CDCl_3$) δ ppm 28.19, 29.59, 30.96, 34.68, 37.74,40.07, 60.72, 66.06, 84.62, 105.68, 116.15, 119.95, 123.11, 124.43, 124.97, 126.95, 127.41, 128.27, 129.12, 130.49, 137.78, 139.24, 149.19. LCMS (method D) t_R 2.73 m, MH^+ 430.18. Analytical HPLC (method F) t_R 21.57 m.

3-((1*S*,3*R*)-3-(Dimethylamino)cyclopentyl)-1*H*-indole-5-carbonitrile 8a. α-Chloroethylchloroformate (2.6 mL, 23 mmol) was added to a solution of **38** (1.0 g, 2.3 mmol) in dichloroethane (100 mL) at room temperature. The reaction was heated to reflux for 2 h. After concentration of the reaction to dryness, MeOH (100 mL) was added and the reaction was heated at reflux for 30 m. The reaction was concentrated and purified by flash chromatography on 120 g silica gel with a gradient of 0 to 30% MeOH in DCM (50 min) to obtain the intermediate *tert*-butyl 5-cyano-3-((1*S*,3*R*)-3-(methylamino)cyclopentyl)-1*H*-indole-1-carboxylate (686 mg, 88%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.39 (1 H, br. s.), 8.14 (1 H, d, J = 8.31 Hz), 7.94 (1 H, s), 7.52 (1 H, s), 7.47 (1 H, d, J = 8.56 Hz), 3.58 (1 H, qd, J = 7.60, 7.43 Hz), 3.12−3.24 (1 H, m), 2.67 (3 H, s), 2.60−2.65 (1 H, m), 1.98−2.33 (5 H, m), 1.62 (9 H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 28.15, 28.61, 30.35, 31.90, 35.35, 36.43, 59.81, 84.83, 105.74, 116.15, 119.78, 122.26, 123.94, 124.33, 127.47, 129.81, 137.64, 148.97. LCMS (method E) t_R 2.82 m, MH^+ 340.21. Analytical HPLC (method G) t_R 7.71 m.

The intermediate from the previous experiment (100 mg, 0.29 mmol) was dissolved in MeOH (5 mL) and treated with 37% formaldehyde (0.5 mL) and $NaBH_3CN$ (100 mg, 1.6 mmol) at room temperature for 20 m. The reaction was concentrated and partitioned between EtOAc (20 mL) and water. The organic layer was dried over sodium sulfate and concentrated to dryness to yield *tert*-butyl 5-cyano-3-((1*S*,3*R*)-3-(dimethylamino)cyclopentyl)-1*H*-indole-1-carboxylate (86 mg, 84%). LCMS (method E) t_R 2.80 m, MH^+ 354.20.

The intermediate from the previous experiment (86 mg, 0.24 mmol) was dissolved in DCM (5 mL) and treated with TFA (2 mL) for 2 h. The reaction was concentrated and dried under high vacuum and then partitioned between EtOAc and saturated $NaHCO_3$. The organic layer was dried over sodium sulfate and concentrated to dryness to yield 3-((1*S*,3*R*)-3-(dimethylamino)cyclopentyl)-1*H*-indole-5-carbonitrile **8a** (49 mg, 81%). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.99 (1 H, d, J = 0.76 Hz), 7.43 (1 H, d, J = 8.56 Hz), 7.33 (1 H, dd, J = 8.31, 1.51 Hz), 7.21 (1 H, s), 3.25−3.37 (1 H, m), 2.68−2.79 (1 H, m), 2.32−2.40 (1 H, m), 2.30 (6 H, s), 2.11−2.22 (1 H, m), 1.94−2.07 (1 H, m), 1.67−1.86 (2 H, m), 1.63 (1 H, q, J = 11.50 Hz). LCMS (method E) t_R 1.72 m, MH^+ 254.13. Analytical HPLC (method F) t_R 8.09 m.

Synthesis of 9a via Procedure of Scheme 4. 3*S*-3-(5-Fluoro-1*H*-indol-3-yl)-cyclopentanone (*S*,*S*)-Hydro-benzoin Ketal 40. A solution of *rac*-**5b** (5 g, 23 mmol), (*S*,*S*)-(−) hydrobenzoin (5 g, 23 mmol) and *p*-toluenesulfonic acid monohydrate (0.44 g, 2.3

mmol) in benzene (150 mL) was heated to reflux under a Dean−Stark trap for 40 min. The reaction mixture was concentrated and the residue was purified by flash chromatography on silica gel using ethyl acetate/hexanes (0−20%) as the eluant. The pure fractions were concentrated to give a mixture of two diastereomers (5 g, 53%). The mixture was dissolved in ethyl acetate (5 mL) and diluted with hexanes (30 mL). The resulting solution was cooled in a refrigerator for 2 days to give the crystalline single diastereomer, 3*S*-3-(5-fluoro-1*H*-indol-3-yl)-cyclopentanone (*S*,*S*)-hydro-benzoin ketal **40** (1.6 g, 17% yield, 86.8% de by chiral HPLC method M). $[\alpha]^{25}$ −7.35 (589 nm, *c* 6.04 mg/mL, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.98 (m, 1H), 2.36 (m, 4H), 2.67 (m, 1H), 3.50 (m, 1H), 4.75 (s, 2H), 6.94 (t, 1H), 7.09 (s, 1H), 7.30 (m, 11H), 7.93 (s, 1H). M − 1 = 412.

3*S*-3-(5-Fluoro-1*H*-indol-3-yl)-cyclopentanone *S*-5b. A solution of **40** (207 mg, 0.5 mM) in methanol (35 mL) and 3N HCl (1 mL) was stirred for 18 h. The solution was concentrated, and the residue was dissolved in ethyl acetate. The solution was washed with aqueous sodium bicarbonate and brine and then dried over magnesium sulfate. The solution was concentrated to give the crude product, which was purified by flash chromatography on silica gel using ethyl acetate/hexanes (0−50%) as the eluent to give 3*S*-3-(5-fluoro-1*H*-indol-3-yl)-cyclopentanone *S*-**5b** (68 mg, 63% yield, 81% ee by chiral HPLC method K). $[\alpha]^{25}$ −10.67 (589 nm, *c* 12.36 mg/mL, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.09 (m, 1H), 2.50 (m, 4H), 2.80 (m, 1H), 3.64 (m, 1H), 6.96 (m, 1H), 7.02 (d, 1H), 7.26 (m, 2H), 8.20 (s,1H). M + 1 = 218.

[(1*R*,3*S*)-3-(5-Fluoro-1*H*-indol-3-yl)-cyclopentyl]-dimethylamine 9a. Using *S*-**5b** obtained in the previous step, conversion to **9a** was carried out according to the earlier procedure wherein chiral HPLC resolution of ketone **5b** was utilized as the source of *S*-**5b**. All analytical data were in agreement with the previous synthesis.

Supporting Information Available: Synthesis details for compounds **5**−**35**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) An analogous resolution of the CN-ketone **5a** proved unsuccessful. We were unable to crystallize either of the diastereomers formed upon condensation of **5a** with (1*S*,2*S*)-1,2-diphenylethane-1,2-diol.

(15) The conformers of compounds **3** and **8a** shown in Figure 2 were identified as follows: Initially, 7500 step Monte Carlo conformational searches with 2500 steps of PRCG[16] energy minimization per conformer using the OPLS2005 force-field[17] and GB/SA implicit water solvation model[18] were performed for compounds **3** and **8a** in their N-protonated cationic forms using *MacroModel version 9.5*; Schrödinger, LLC: New York, NY, 2007. For each compound, the set of conformations obtained was then ranked in ascending order of OPLS2005 GB/SA energy and clustered using a non-hydrogen atom RMSD cutoff of 0.25 Å. The lowest energy conformer from each cluster was then optimized using density functional theory (DFT) calculations with the B3LYP functional, 6-31+G* basis set and a self-consistent reaction field implicit water solvation model.[19,20] DFT calculations were performed with *Jaguar version 7.0*; Schrödinger, LLC: New York, NY, 2007. For compounds 3 and 8a, the lowest-energy DFT-optimized conformer that yielded a reasonable three-point overlay (see text) with the conformer of sertraline shown in Figure 5a of reference 6 was selected.

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