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Synthesis and hSERT activity of homotryptamine analogs. Part 6: [3+2] dipolar cycloaddition of 3-vinylindoles

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ABSTRACT

Substituted 1-tosyl-3-vinylindoles undergo [3+2] dipolar cycloaddition with cyclic nitrones to afford substituted isoxazoles in good yield and high diastereoselectivity. The cycloadducts were readily converted in 4 steps into ring constrained homotryptamine analogs. These analogs exhibited excellent binding affinity for the human serotonin transporter (hSERT). Indoles bearing a 5-cyano group and a pendent ethyl(tetrahydroisoquinoline) moiety at the 3-position displayed the best potency for hSERT and high selectivity versus hDAT and hNET.

Inhibition of the human serotonin reuptake transporter (hSERT) has proven utility for the treatment of depression and other related affective disorders, including anxiety, social phobia, obsessive–compulsive and panic disorders.[1] Consequently, the discovery and development of novel selective serotonin reuptake inhibitors (SSRIs) continues to be an active field of neuroscience research.[2] A series of manuscripts[3] has previously disclosed hSERT binding data for homotryptamine derivatives, including compound **1**,[3a] and has detailed our efforts to engineer conformationally restricted analogs with optimized hSERT potency and target selectivity, such as indoles **2**,[3b] **3**,[3c] and **4**,[3e] (Fig. 1). As part of an ongoing medicinal chemistry effort, we targeted 3-indolylethylamines **5,** in which the privileged homotryptamine-like scaffold is conserved and the pendant amino group is embedded or constrained within a heterocyclic ring system (Fig. 2). Early literature reports have disclosed that some 2-(3-indolylethyl)piperidines, and closely related analogs, possess useful central nervous system (CNS) activity;[4] however, characterization of their hSERT activity is absent. This communication describes a novel and expedient synthesis of several 2-(3-indolyl)ethylamines and a structure activity relationship (SAR) of their binding affinity for hSERT.

2-(3-Indolylethyl)piperidines and related molecules have been made by a few different methods including Knoevenagel condensation of indole carboxaldehydes[5] and pyridylethylation of indoles.[6] We had envisioned a more flexible retrosynthetic strategy in which the final products **5** are unmasked via hydrogenolysis/deoxygenation of bicyclic isoxazoles **6**. The isoxazoles **6** would result from [3+2] dipolar cycloaddition of cyclic nitrones **8** with 3-vinylindoles **7**. The choice of cyclic nitrone would dictate the nature of the final

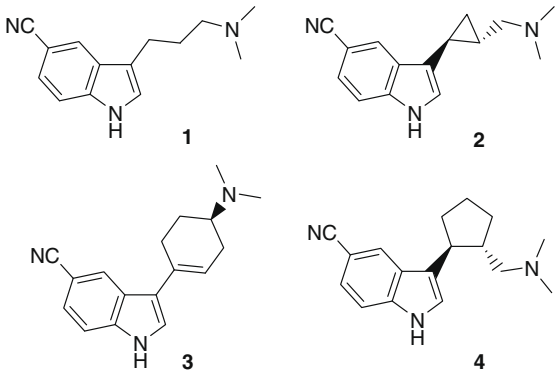

Figure 1. Known indole-based SERT ligands.

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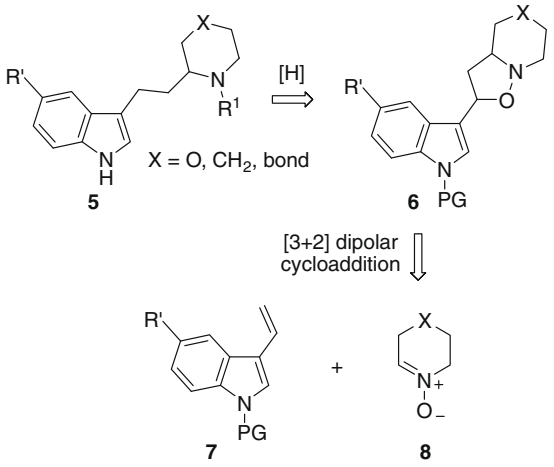
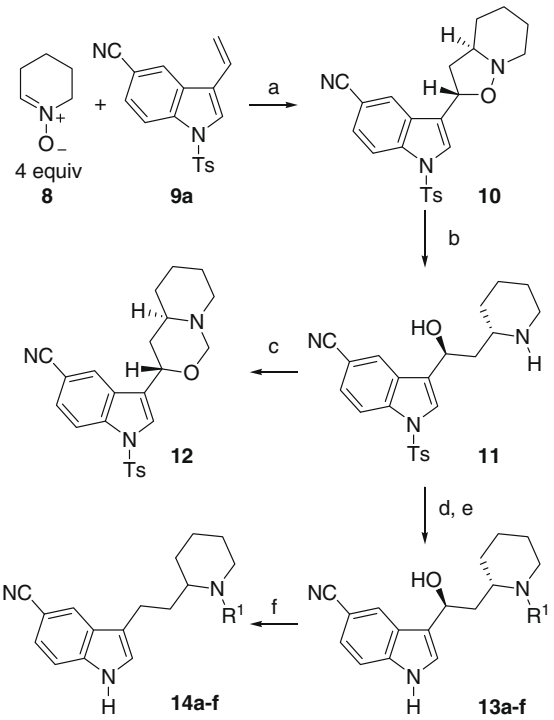


Figure 2. Retrosynthetic analysis of 3-indolylethylamines.

pendent amine. While there is no literature precedent for the [3+2] dipolar cycloaddition of 3-vinylindoles with nitrones, styrene has been reported to undergo highly regio- and diastereoselective dipolar cycloadditions with 2,3,4,5-tetrahydropyridine 1-oxide and 3,6-dihydro-2H-1,4-oxazine 4-oxide.[7] Given our previous experience with 3-vinylindoles as useful substrates in catalytic asymmetric cyclopropanation,[8] we expected that the proposed dipolar cycloaddition chemistry would proceed smoothly.

5-Cyanoindole was selected as the aromatic core for the current set of targets, because this substitution pattern provided optimal hSERT binding affinity in the related indole cyclopropane series.[3b] To our gratification, 5-cyano-1-tosyl-3-vinylindole **9a**[8] was found to undergo [3+2] dipolar cycloaddition at room temperature in the presence of 4 equiv of 2,3,4,5-tetrahydropyridine 1-oxide[7a] **8** to afford a single diastereomer of the corresponding bicyclic isoxazole **10** in 84% yield (Scheme 1). The relative stereochemistry of **10** was inferred from single crystal X-ray analysis of the corresponding aminal derivative **12** (Fig. 3).[9] The stereochemical outcome of the dipolar cycloaddition is consistent with an exo-mode approach of the dipolarophile and is in full agreement with literature reports for the dipolar cycloaddition of styrene with 2,3,4,5-tetrahydropyridine 1-oxide.[7a] Isoxazole **10** was readily converted in a routine 4-step sequence to a series of 2-(3-indolylethyl)piperidines **14a–f**. The nature of the piperidine N-substituent was dependent on the choice of aldehyde used in the reductive amination.[10] The final products **14a–f** were obtained in good overall yield (~25–40%).



Scheme 1. Reagents and conditions: (a) $ClCH_2CH_2Cl$, rt, 48 h (84%); (b) Zn, HOAc; (c) CH_2O, EtOH, H_2O (63%, 2 steps); (d) RHCO, $NaCNBH_3$, THF, EtOH; (e) NaOH, EtOH, H_2O, 65 °C; (f). TFA, $(C_2H_5)_3SiH$, CH_2Cl_2, 0 °C (38% over 4 steps for **14a**).

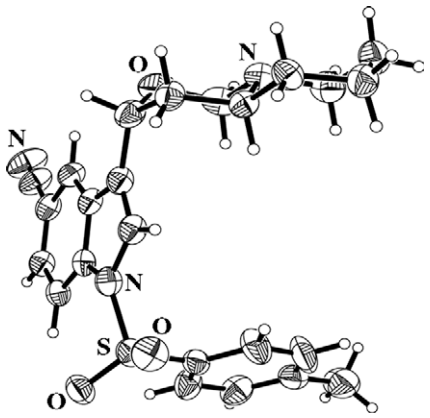


Figure 3. ORTEP drawing of 12 with thermal ellipsoids at 25% probability for non-H atoms and open circles for H-atoms.

Piperidine derivatives **15a** and **15b** and analogs **16a** and **16b** were prepared in analogous fashion from 6-methyl-2,3,4,5-tetrahydropyridine 1-oxide and 4-benzyl-2,3,4,5-tetrahydropyridine 1-oxide (Fig. 4).[11] It should be noted that the dipolar cycloaddition in the synthesis of **15a**, which forms a quaternary center, proceeded in diminished yield (32%) as compared to the related cycloaddition of **8** with **9a** (84%). Morpholine adduct **17** and pyrrolidine analogs **18a,b** were also prepared in a regio- and stereoselective fashion following the same multistep sequence and starting with the appropriate nitrones.[11]

The dipolar cycloaddition of conjugated nitrones also proceeded well. For example, 3,4-dihydroisoquinoline 2-oxide (**19**)[11] under-

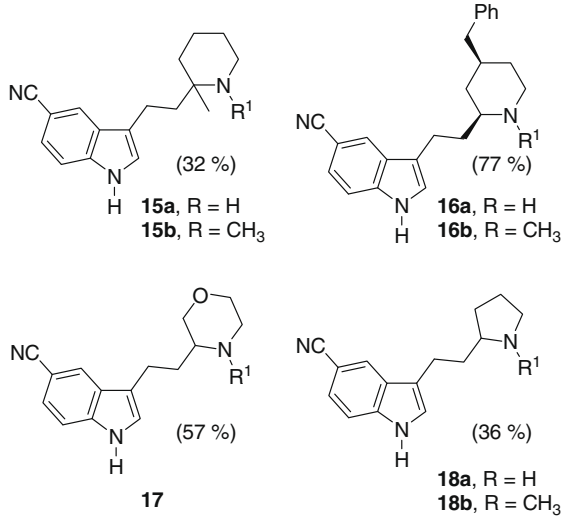
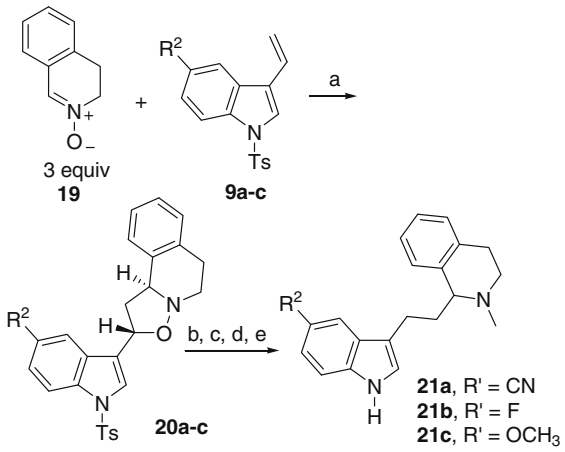


Figure 4. Various 2-(3-indolylethyl)heterocycles prepared from dipolar cycloaddition of nitrones with 5-cyano-1-tosyl-3-vinylindole. Yield of the [3+2] dipolar cycloaddition step is shown in parentheses.



Scheme 2. Reagents and conditions: (a) toluene, reflux, 24 h (61–74%); (b) Zn, HOAc; (c) H_2CO, $NaCNBH_3$, THF, EtOH; (d) NaOH, EtOH, H_2O, 65 °C; (e) TFA, $(C_2H_5)_3SiH$, CH_2Cl_2, 0 °C (17–50%, 4 steps).

went dipolar cycloaddition, in refluxing toluene, with 5-cyano, 5-fluoro, and 5-methoxy-1-tosyl-3-vinyl indoles **9a–c**[8] to afford the corresponding tricyclic isoxazoles **20a–c** in 61–74% yield (Scheme 2). The isoxazoles were subsequently transformed via the standard 4-step sequence into tetrahydroisoquinoline analogs **21a–c** (17–50% yield). The 5-cyanoindole derivative **21a** was separated into its individual enantiomers, **(+)-21a** and and **(–)-21a**, by preparative chiral HPLC.[12]

All of the final analogs **14**–**18** and **21** demonstrated potent hSERT binding with IC_{50} values $\leqslant$ 120 nM (Table 1).[13] A number of piperidine and tetrahydroisoquinoline analogs demonstrated the best potency. The most potent analog was the single enantiomer **(–)-21a** (hSERT IC_{50} = 0.42 nM), which exhibited a binding affinity for hSERT that was sixfold more potent than that observed with the marketed SSRI Fluoxetine. The 5-fluoroindole **21b** was approximately fivefold less potent than **21a**, while the 5-methoxyindole **21c** lost over 100-fold in hSERT potency. Within the piperidine series, analogs with electron-deficient *N*-alkyl substituents displayed diminished SERT affinity, as exemplified by **14d** and **14f**. The less basic morpholine derivative **17** also exhibited weaker SERT binding. These SAR trends are similar to those previously observed in the indole cyclopropane series.[3b]

Table 1
Binding affinity for hSERT of analogs **14–18** and **21**

Compound	Amine type	R^1	R^2	hSERT IC_{50}[a] (nM)
Fluoxetine	Acyclic	—	—	2.5 ± 0.5
14a	Piperidine	H		2.5 ± 0.2
14b	Piperidine	CH_3		3.9 ± 0.3
14c	Piperidine	CH_2CH_3		4.0 ± 0.7
14d	Piperidine	$CH_2CH_2CF_3$		80 ± 25
14e	Piperidine	$CH_2C_6H_5$		7.0 ± 1.8
14f	Piperidine	3,5-Bis(CF_3)Bn		46 ± 5
15a	Piperidine	H		17 ± 2
15b	Piperidine	CH_3		2.1 ± 0.4
16a	Piperidine	H		18 ± 3
16b	Piperidine	CH_3		7.6 ± 1.2
17	Morpholine	—		76 ± 5
18a	Pyrrolidine	H		17 ± 3
18b	Pyrrolidine	CH_3		8.1 ± 2.1
21a	THQ[b]	—	CN	1.1 ± 0.2
(+)-**21a**	THQ[b]	—	CN	4.2 ± 0.5
(−)-**21a**	THQ[b]	—	CN	0.42 ± 0.06
21b	THQ[b]	—	F	5.7 ± 1.3
21c	THQ[b]	—	OCH_3	120 ± 11

[a] Values are means of $\geqslant$3 experiments with ± SEM.
[b] THQ is an abbreviation for 1,2,3,4-tetrahydroisoquinoline.

Table 2
Binding affinity for selected monoaminergic transporters

Compound	SERT IC_{50}[a] (nM)	hDAT IC_{50}[b] (nM)	hNET IC_{50}[b] (nM)
1	2.0 ± 0.4	nt	nt
2	0.36 ± 0.05	4200	9200
3	0.72 ± 0.11	290	390
4	0.13 ± 0.07	690	7900
(−)-**21a**	0.42 ± 0.06	620	>10,000

[a] Values are means of $\geqslant$3 experiments with ± SEM.
[b] Values are the average of 2 experiments. (nt = not tested).

Table 2 summarizes the binding affinity of compound **(–)-21a** and previously reported analogs **1–4** for hSERT and the other aminergic transporters, hDAT (dopamine) and hNET (norepinephrine). The hSERT binding affinity of **(–)-21a** is approximately fivefold greater than that reported for the open chain analog **1** and similar in magnitude to the conformational restricted analogs **2**–**4**. A broader comparison reveals that analogs **14**–**18** displayed equal or weaker affinity for hSERT versus the flexible analog **1**. Consequently, the enhanced potency of **(–)-21a** versus **1** for hSERT is not likely the result of the pendent amine being constrained in a six-membered ring, but more likely due to favorable interactions with the second aromatic ring (1,2,3,4-tetrahydroquinoline) and the serotonin transporter. Indeed, several marketed SSRIs, including Fluoxetine, Paroxetine, Sertraline and S-citalopram contain two aromatic rings in addition to the basic amine. Compound **(–)-21a** demonstrated excellent selectivity for hSERT versus hDAT (1500-fold) and hNET (>20,000-fold). This magnitude of selectivity is similar to that observed with previous ring-constrained analogs **2** and **4**.

In conclusion, a novel and flexible route to 2-(3-indolyl)ethylamines was developed which employs a [3+2] dipolar cycloaddition of 3-vinylindoles and cyclic nitrones as the key bond-forming event. While ring constrained 2-(3-indolyl)ethylamines **14**–**18** demonstrated good hSERT binding affinity, the level of potency is not generally superior to the flexible *N*,*N*-dimethyl analog **1**. The tetrahydroisoquinoline **(–)-21a** displayed subnanomolar potency for hSERT and excellent selectivity against hDAT and hNET. Continued efforts to optimize hSERT potency of the 2-(3-indolyl)ethylamines will be focused on determining the absolute configuration of **(–)-21a** and developing additional SAR for tetrahydroisoquinoline substitution as well as the exploration of other benzylic pendent amines.

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9. Full crystallographic data have been deposited to the Cambridge Crystallographic Data Center (CCDC reference number 749351). Copies of the data can be obtained free of charge via the internet at www.ccdc.cam.ac.uk/.
10. When R = H, the reductive amination step was omitted.
11. The cyclic nitrones used in the preparation of **15**–**18** and **20** were prepared from their corresponding amines following the published method Murahashi, S.-I.; Shiota, T.; Imada, Y. *Org. Syn.* **1992**, *70*, 265.
12. Chiralcel OD column (0.05% diethylamine/4.95% ethanol/95% hexanes). The first enantiomer to elute was **(+)-21a** and the second was **(–)-21a**. Analytical data for **(–)-21a**: LC–MS $(M+H)^+$ = 316.2; ^{1}H NMR (400 MHz, d6-DMSO) δ 11.4 (s, 1H), 7.92 (s, 1H), 7.48 (d, 1H, *J* = 8.5), 7.39 (dd, 1H, *J* = 8.5,1.6), 7.32 (s, 1H), 7.16–7.10 (m, 4H), 3.49 (m, 1H), 3.16–3.10 (m, 1H), 2.85–2.60 (m, 4H), 2.56–2.52 (m, 1H), 2.42 (s, 3H), 2.12–2.05 (m, 2H). Optical rotation: $[\alpha]_D$ −1.37 (concentration = 4.23 mg/mL, CH_3OH). Anal. Calcd for $C_{21}H_{21}N_3 \cdot 1/3H_2O$: C, 78.47; H, 6.79; N, 13.07. Found: C, 78.69; H, 6.67; N, 13.01.
13. hSERT, hDAT, and hNET binding affinities were determined as previously described in Ref. 3e using membrane homogenates from stably transfected HEK-293 cell lines expressing the human form of the transporters.