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Homotryptamines as potent and selective serotonin reuptake inhibitors (SSRIs)

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Abstract—A series of *N*,*N*-dimethylhomotryptamines was prepared and their binding affinities at the serotonin transporter (SERT) were determined. Compounds possessing an electron withdrawing substituent at the C5-position of the indole nucleus were found to be potent SSRIs. Initial attempts at conformational restriction of the propylamine sidechain by incorporation of a quinuclidine bicyclic structure did not improve binding affinity at SERT.

The importance of compounds that act as selective serotonin reuptake inhibitors (SSRIs, Fig. 1) has been demonstrated by their utility in treating depression, anxiety disorders, eating disorders and sexual dysfunction.[1,2] The recent approval of Lexapro® (*S*-citalopram) for the treatment of depression and generalized anxiety disorder illustrates the continuing interest in SSRIs as promising agents for the treatment of CNS disorders.[2] The SSRIs were the first rationally designed class of compounds for the treatment of depression, and they generally possess good tolerability and reasonable safety and side-effect profiles. However, there is clearly room for improvement. For example, fluoxetine, fluvoxamine and paroxetine are all significant inhibitors of cytochrome P450 (CYP) enzymes at their pharmacologically efficacious doses.[3,4] The potential for drug–drug interactions with these compounds requires careful monitoring to avoid the risk of elevated levels of any co-administered medications. Additionally, slow onset of action is observed for SSRIs, typically resulting in a 2–6 weeks latency period before onset of antidepressant activity.[2] Thus, the need exists for improved SSRIs and SSRI platforms.

An SSRI blocks the presynaptic reuptake of serotonin (5-hydroxytryptamine, 5-HT) by the serotonin transporter protein (SERT). Reports describing SERT binding affinities of 5-hydroxytryptamine (5-HT, serotonin) and related tryptamines have been published.[5] Indolealkylamines with four carbon atom spacers in the form of 4-indolylcyclohexylamines have also been investigated.[6] More recently, indolebutylpiperazines have been reported as serotonin reuptake inhibitors.[7] Additionally, 3-(4-piperidinyl) indoles have been described as potent inhibitors of serotonin reuptake.[8] Surprisingly, little

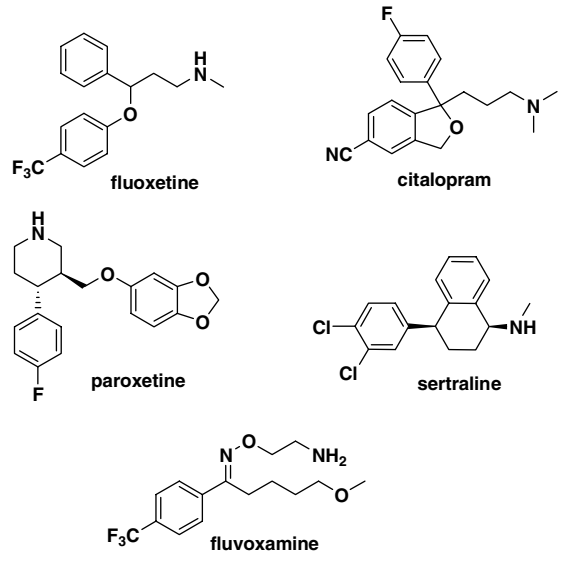

Figure 1.

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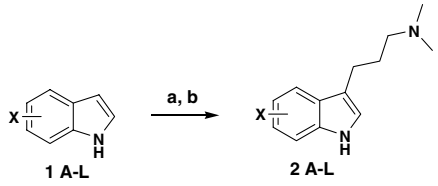
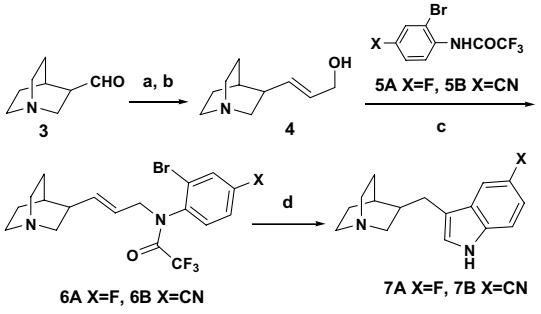
attention has been given to simple homotryptamines as potential SSRIs, despite the obvious structural similarity to serotonin and the above mentioned homologs.[5,9] Homotryptamines should generally lack the 5-HT receptor agonism of tryptamines,[10] but may retain SERT affinity.[5a] In the current work described herein, we detail the synthesis of, and in vitro SERT binding affinities for a series of substituted homotryptamines.

Homotryptamines **2A**–**L** were readily prepared utilizing recently disclosed methodology from Denhart et al.[11] In short, substituted indoles were reacted with acrolein using MacMillan catalysis, and the resulting aldehydes were immediately subjected to reductive amination using dimethylamine (Scheme 1). As an initial attempt to investigate the effect of conformational restriction on homotryptamines, compounds **7A** and **7B** were prepared using Heck methodology previously reported by Macor et al. (Scheme 2).[12] Wittig condensation of quinuclidine-3-carboxaldehyde (**3**)[13] with ethyl triphenylphosphonium acetate, followed by reduction of the resulting ester yielded the allyl alcohol (**4**). Mitsunobu coupling of the alcohol (**4**) with the trifluoroacetamidobenzene derivatives (**5A** and **5B**) afforded the key precursors (**6A** and **6B**) for intramolecular Heck cyclization. Using standard conditions,[12] **6A** and **6B** were converted to their corresponding indole derivatives (**7A** and **7B**, respectively, Scheme 2).

The SERT binding affinities of these homotryptamine analogs were determined using membrane homogenates from HEK-293 cells that stably expressed human serotonin transporters (HEK-hSERT cells). Membrane homogenates were incubated with 2 nM [^{3}H]-citalopram



Scheme 1. Reagents and conditions: (a) CH_2CHCHO, (2*S*,5*S*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one or (2*S*,5*S*)-5-benzyl-3-methyl-2-(5-methyl-furany-2-yl)-imidazolidin-4-one, TFA, *i*PrOH/CH_2Cl, −25 °C; (b) Me_2NH, $NaBH(OAc)_3$, THF, 14–37%.



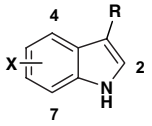
Scheme 2. Reagents and conditions: (a) Ph_3PCHCO_2Et, toluene, reflux, 40%; (b) DiBAlH, CH_2Cl_2, −78 °C, 83%; (c) diethylazodicarboxylate, Ph_3P, THF, 0 °C, 7–15%; (d) $Pd(OAc)_2$, Et_3N, DMF, 80 °C, 57–69%.

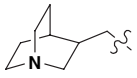
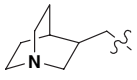
(specific activity = 85 Ci/mmol) and increasing concentrations of test compounds for 1 h at 25 °C in a total volume of 250 μL. The amount of radioligand bound in the presence and absence of competitor was analyzed by plotting (−)log drug concentration versus the amount of radioligand specifically bound. Non-specific binding was defined with 10 μM fluoxetine. The midpoint of the displacement curve (IC_{50}, nM), signified the potency.

The results of these studies are shown in Table 1. Immediately notable is the weak interaction of *N*,*N*-dimethyl serotonin (**8**, bufotenin) with SERT. Equally notable is the potent interaction of **2A**, the homotryptamine analog of **8**. This single result suggested to us that homotryptamines represented a useful, untried scaffold for potent SSRI activity. Alkylation of the 5-hydroxy group in **2A** resulted in complete loss of activity (Table 1, compounds **2A** vs **2K** and **2L**), suggesting that C5 on the indole ring of the homotryptamines was an important SAR location on the molecule.

A moderate loss in binding affinity was observed for unsubstituted homotryptamine **2B**. Substitution on the aryl portion of the indole nucleus with electron-withdrawing substituents provided compounds with a relatively narrow range of binding affinity (IC_{50}'s = 2–36 nM). The most potent SSRIs were the indoles with electron withdrawing substituents at C5 of the indole core, and of these the 5-cyano homotryptamine **2J** was the most potent compound (IC_{50} = 2 nM).

Table 1. SERT binding affinities[a] of homotryptamines



Compound	X	R	SERT IC_{50} (nM)[a]
2A	5-OH	$-(CH_2)_3NMe_2$	11 ± 2
2B	5-H	$-(CH_2)_3NMe_2$	58 ± 6
2C	5-F	$-(CH_2)_3NMe_2$	4.0 ± 0.3
2D	5-Cl	$-(CH_2)_3NMe_2$	7.0 ± 1.3
2E	5-Br	$-(CH_2)_3NMe_2$	17 ± 3
2F	5-I	$-(CH_2)_3NMe_2$	31 ± 6
2G	4-Cl	$-(CH_2)_3NMe_2$	29 ± 4
2H	6-Cl	$-(CH_2)_3NMe_2$	36 ± 6
2I	7-Cl	$-(CH_2)_3NMe_2$	32 ± 6
2J	5-CN	$-(CH_2)_3NMe_2$	2.0 ± 0.4
2K	5-OMe	$-(CH_2)_3NMe_2$	1100 ± 300[b]
2L	5-OBn	$-(CH_2)_3NMe_2$	3200[c]
7A	5-F		18 ± 3
7B	5-CN		2.0 ± 0.3
8[d]	5-OH	$-(CH_2)_2NMe_2$	1200[a]

[a] *n* = 3 for each reported IC_{50}, each *n* represents a duplicate measurement taken at five different concentrations and reported as the average ± SEM.
[b] *n* = 2, reported as previously described.
[c] *n* = 1, reported as previously described.
[d] Purchased from Cerilliant.

Compounds **2A**–**J**, **7A**,**B** were also evaluated for binding affinity at norepinephrine and dopamine transporters. They were all found to be selective for the serotonin transporter over both the norepinephrine and dopamine transporters.[14]

Because of the inherent flexible nature of the aminopropyl sidechain in our homotryptamine derivatives, conformational constraint was seen as a logical next step in understanding our new SSRI pharmacophore. While the incorporation of conformational restriction in serotonin agonists for selective binding at 5-HT receptor subtypes has been previously described,[15] fewer reports have detailed the effects of such studies on SERT ligands.[16] As an initial investigation into the effect of sidechain conformational restriction on the binding affinity of homotryptamines **2C** and **2J**, the corresponding quinuclidines **7A** and **7B** were synthesized as described above. The activities of the pairs (**2C** vs **7A** and **2J** vs **7B**) were not significantly different within each pair, suggesting that the quinuclidine conformation did not significantly alter the molecular recognition of the homotryptamines for SERT. We are continuing in our efforts to examine other conformational constraints of the aminopropyl sidechain in **2C** and **2J** and will report those results in due course.

In conclusion, simple *N*,*N*-dimethylhomotryptamines exhibited potent binding affinity at SERT. Those derivatives containing an electron withdrawing group at the C5 position of the indole nucleus were the most potent SSRIs. Introduction of a quinuclidine moiety as a conformational restriction within the propylamine side chain did not appreciably affect SERT binding affinity.

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