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Dual serotonin transporter/histamine H_3 ligands: Optimization of the H_3 pharmacophore

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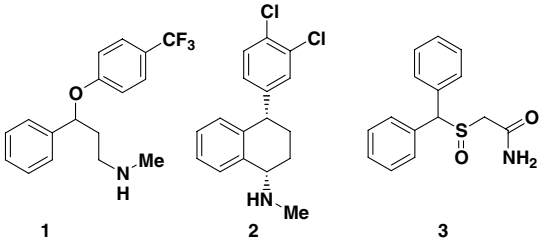
Abstract—A series of tetrahydroisoquinolines acting as dual histamine H_3/serotonin transporter ligands is described. A highly regioselective synthesis of the tetrahydroisoquinoline core involving acid mediated ring-closure of an acetophenone intermediate followed by reduction with $NaCNBH_3$ was developed. In vitro and in vivo data are discussed.

More than 340 million people suffer from depression worldwide, making it a serious global health issue.[1] One of the potentially debilitating symptoms of depression is fatigue.[2] Selective serotonin reuptake inhibitors (SSRIs), including fluoxetine **1** and sertraline **2**, are the most frequently prescribed antidepressant drugs, however, these drugs often fail to improve the symptom of fatigue even as mood improves.[3,4] Some SSRIs even induce fatigue and excessive sleepiness.[5,6]

One possible approach to mitigating the fatigue associated with depression and/or its treatment is through the use of a wake promoting agent such as modafinil (**3**), a drug which has been shown to increase wakefulness. Histamine H_3 receptor antagonists also increase wakefulness[7] without showing nonspecific stimulant effects such as increased locomotor activity.[8] Thus, the case can be made that H_3 antagonists would be useful adjuncts to antidepressant therapy. As one part of our efforts to determine the usefulness of H_3 antagonism as adjunct therapy for the treatment of depression we now describe a medicinal chemistry effort to synthesize molecules combining H_3 receptor antagonism and blockade of serotonin reuptake.[9]

Numerous H_3 pharmacophores have been reported in the literature over the past few years,[9] including several



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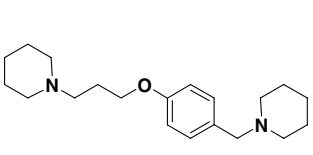

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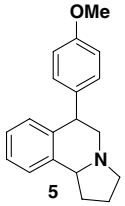

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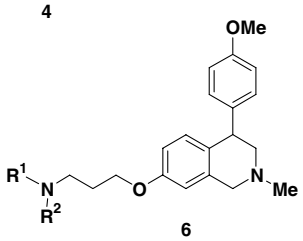

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Keywords: Serotonin transporter; Histamine H_3; Ring-closure; 5-HTP potentiation.
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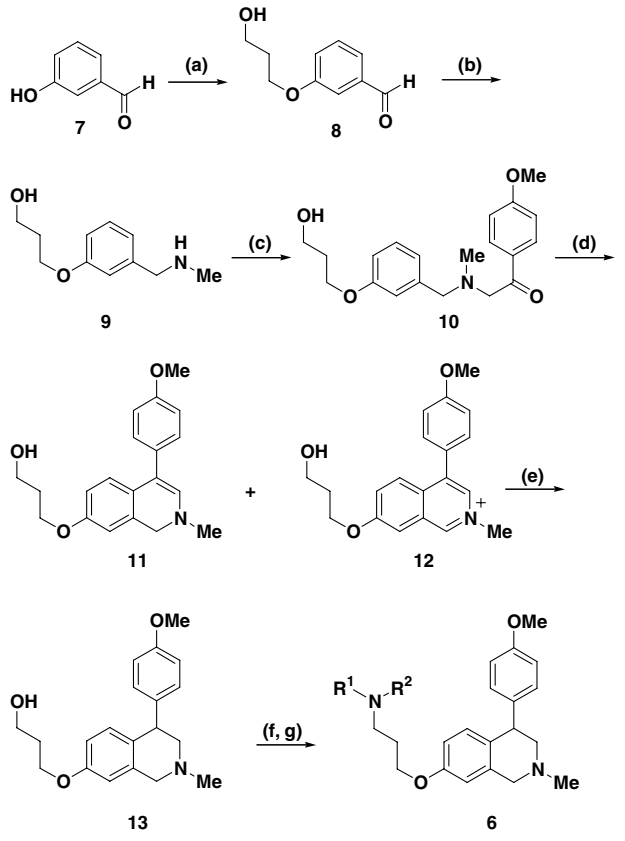
from our laboratories.[10,11] Herein we describe the combination of our potent H_3 antagonist **4**[12] with tetrahydroisoquinoline derived serotonin transporter (SERT) inhibitors such as **5**[13] to give potent dual H_3 antagonist/SERT inhibitors **6**.[14] In this paper, we describe our efforts to optimize the binding affinity at H_3 and the physical properties of molecules **6**, while retaining SERT activity, through modification of the H_3 pharmacophore.

Synthesis of tetrahydroisoquinolines **6a**–**6cc** was accomplished according to the procedure outlined in Scheme 1.[15] Thus, 3-hydroxybenzaldehyde (**7**) was treated with 3-bromo-propan-1-ol to give 3-(3-hydroxy-propoxy)-benzaldehyde **8**. Subsequent reductive amination with methylamine afforded intermediate **9** in quantitative yield. Alkylation of the resulting secondary amine gave **10**, which underwent an acid catalyzed ring-closure reaction with methanesulfonic acid (MSA). The ring-closure afforded the expected 1,2-dihydro-isoquinoline **11** along with the ring oxidized isoquinolinium salt **12**. The latter product was generally found to be the predominant component following workup and the product mixture was carried forward without further purification. The ring-closed products were treated with 1.25 M HCl in MeOH in the presence of $NaCNBH_3$, bromocresol green, and MeOH until a color change, generally from green/brown to yellow, persisted to give **13**. Conversion of the alcohol to the mesylate was accomplished under standard conditions and the mesylate used immediately in the subsequent step. Displacement of the mesylate was generally carried out in a parallel fashion using a variety of primary and secondary amines to provide the desired products **6a**–**6cc**. To improve yields, hydrochloric acid salts of the amines were neutralized with NaO*t*-Bu in *n*-BuOH prior to use. Yields ranged from 0.4% to 58%.



Scheme 1. Synthesis of tetrahydroisoquinolines. Reagents and conditions: (a) K_2CO_3, 3-bromo-propan-1-ol, acetonitrile, reflux, 48 h, 90%; (b) 40% aqueous $MeNH_2$, MeOH, 0 °C, then $NaBH_4$, 0 °C, 0.5 h, then 23 °C 18 h, 100%; (c) Hunig's base, 2-bromo-4′-methoxy-acetophenone, THF, 23 °C, 45 min; (d) MSA, 60 °C, 18 h; (e) $NaCNBH_3$, MeOH, bromocresol green, 23 °C, 5 min, then 1.25 M MeOH·HCl, 0.5 h, 28% three steps; (f) $MeSO_2Cl$, Et_3N, DCM, 0–23 °C, 20 min; (g) R^1R^2NH, Na_2CO_3, KI, *n*-BuOH, 50–80 °C, 18 h, 0.4–58%, two steps.

Rat and human SERT and human histamine H_3 binding data[16] for the tetrahydroisoquinolines **6** are shown in Tables 1 and 2.[17] Modifications to the pendant amine portion of the molecule had little effect on the SERT affinity of the compounds. All were generally potent serotonin transporter ligands with good correlation between the human and rat transporters. Affinity for the human histamine H_3 receptor varied greatly. Morpholine and substituted piperidines usually gave potent compounds with the exception of **6j**. Analogs bearing a tertiary amine were consistently more potent than the corresponding secondary amines (e.g., **6n** and **6o**).

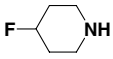
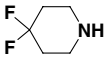
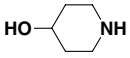
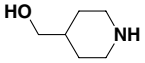
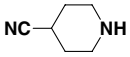
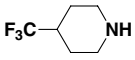
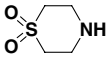
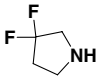
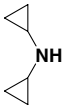
Substituted piperazines generally had high affinity for the H_3 receptor when the substituent was small (e.g., **6r** and **6s**) although a cyclopropyl group had a detrimental effect on potency (**6t**). In all but one case, aryl piperazines displayed weak affinity for the H_3 receptor. The exception was the 4-pyridyl-piperazine derivative **6x**, which had high affinity. All piperazine amides examined displayed low affinity for the H_3 receptor, regardless of the substitution (**6aa**–**6cc**).

Compounds **6b** and **6c** were examined in the 5-hydroxytryptophan (5-HTP) induced head twitch model in mice.[18] This animal model gives a qualitative measure of the blockade of the SERT, with a behavioral output. The mice were dosed at 10 mg/kg, ip ($n = 4$ for each) and observations made at 1 and 24 h. At 1 h both compounds gave a very robust response (>500% of control) and in each case, the response was diminished at 24 h, suggesting the compounds penetrate the brain quickly but are subsequently eliminated. To verify this interpretation, blood–brain barrier (BBB) experiments were performed on **6b** and **6c** to compare pharmacological responses to brain and plasma concentrations. Compounds were dosed 10 mg/kg, ip and brain concentrations determined at 1 and 24 h ($n = 3$). Compounds **6b** and **6c** showed high brain concentrations at 1 h (12.5 and 6.1 μM, respectively) and significantly lower brain concentrations at 24 h (<1 and 2.5 μM, respectively). These observed brain concentrations correlate well with the 5-HTP induced head twitch data.

Compounds **6b** and **6c** were also examined in an hH_3 functional assay and were found to be potent antagonists ($pA_2 = 8.6$ and 9.6, respectively).[19]

In conclusion, we have found a wide range of amine substituents tolerated by the H_3 receptor and the SERT.

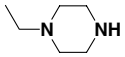
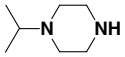
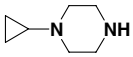
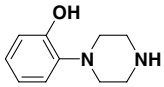
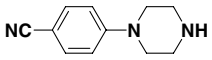
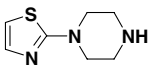
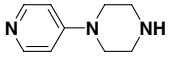
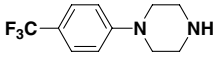
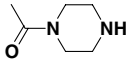
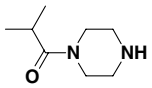
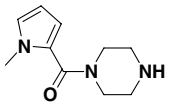
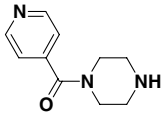
Table 1. Binding data[20] for the rat and human serotonin reuptake transporters and for the human histamine H_3 receptor for compounds **6a–q**

Compound	R^1R^2NH	Comb. yield for steps f & g	Rat SERT K_i[a] (nM)	Human SERT K_i[a] (nM)	Human H_3 K_i[a] (nM)
1	Fluoxetine	—	2.8 (±0.7)	2.0 (±0.2)	7300 (±1080)
6a		—[b]	2.0 (±0.7)	5.1 (±0.8)	2.0 (±0)
6b		22	4.8 (±0.7)	6.5 (±2)	3.8 (±0.9)
6c		25	1.6 (±0.6)	2.9 (±1)	2.0 (±0.5)
6d		30	5.7 (±0.4)	6.5 (±0.9)	8.7 (±3)
6e		11	10 (±2.6)	8.2 (±1.4)	14 (±4.6)
6f		13	1.2 (±0.5)	3.8 (±0.7)	11 (±1.4)
6g		13	2.0 (±0.7)	3.2 (±1.2)	9.5 (±4.4)
6h		14	5.3 (±2.2)	5.3 (±0.4)	7.4 (±2.7)
6i		9	19 (±7.5)	14 (±3.5)	40 (±12)
6j		12	6.3 (±2.2)	12 (±1.1)	106 (±27)
6k		0.4	1.0 (±0)	4.8 (±1)	4.0 (±0.7)
6l		13	2.0 (±0.7)	2.9 (±0.7)	69 (±7.2)
6m		14	8.0 (±1.9)	7.3 (±1.5)	9.5 (±3)
6n		4	0.73 (±0.2)	3.4 (±1.2)	47 (±3.7)
6o		30	2.2 (±0.4)	4.0 (±0)	1.7 (±0.5)
6p		58	3.0 (±0.7)	19.3 (±9.4)	38 (±9.9)
6q		9	7.6 (±1.2)	9.7 (±1.8)	7.4 (±1.5)

[a] Values are means of at least three experiments in triplicate, standard error of the mean is given in parentheses.
[b] Prepared by different route (see Ref. 17).

Two compounds, **6b** and **6c**, were examined in the 5-HTP induced head twitch PD model and in BBB experiments. These compounds demonstrated a good correlation of behavioral pharmacology with brain concentrations. Additional SAR studies describing optimization of the SERT pharmacophore, and separation and characterization of enantiomerically pure products are described in the subsequent paper.

Table 2. Binding data for the rat and human serotonin reuptake transporters and for the human histamine H_3 receptor for compounds **6r**–**6cc**

Compound	R^1R^2NH	Comb. yield for steps f & g	Rat SERT K_i[a] (nM)	Human SERT K_i[a] (nM)	Human H_3 K_i[a] (nM)
6r		28	1.5 (±0.6)	2.0 (±0)	12 (±2)
6s		17	1.3 (±0.4)	1.8 (±0.5)	9.7 (±2.7)
6t		6	10 (±1.2)	18 (±6)	30 (±8.3)
6u		31	5.7 (±1.8)	7.2 (±0.5)	1108 (±551)
6v		34	3.3 (±0.4)	8.0 (±0)	144 (±7.6)
6w		15	2.7 (±0.4)	5.3 (±1.6)	268 (±59)
6x		13	5.3 (±2.9)	4.0 (±1.4)	3.3 (±1.6)
6y		27	25 (±12)	33 (±5.3)	1440 (±347)
6z		7	15 (±1.2)	42 (±12)	267 (±225)
6aa		5	15 (±7.4)	15 (±2.9)	509 (±211)
6bb		12	8.4 (±2.6)	8.8 (±3.9)	2606 (±606)
6cc		11	21 (±7.6)	19 (±2.9)	2840 (±1408)

[a] Values are means of at least three experiments in triplicate, standard error of the mean is given in parentheses.

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16. Data obtained on the racemates.
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19. The apparent disconnect between the observed K_i's and the pA_2 values likely arises from the differences in the assays: K_i's are determined using membrane-bound protein, pA_2's from a whole cell assay.
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