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Pyrrolidino-tetrahydroisoquinolines bearing pendant heterocycles as potent dual H_3 antagonist and serotonin transporter inhibitors

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Abstract—A series of novel and potent 6-heteroaryl-pyrrolidino-tetrahydroisoquinolines with dual histamine H_3 antagonist/serotonin transporter inhibitor activity is described. In vitro and in vivo data are discussed.
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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) 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 histamine H_3 antagonist. Histamine H_3 receptor antagonists increase wakefulness[7] without showing non-specific stimulant effects such as stimulation of locomotor activity.[8] Thus, the case can be made that H_3 antagonists would be useful adjuncts to antidepressant therapy. In the current paper, we describe a medicinal chemistry effort to synthesize molecules combining H_3 receptor antagonism and blockade of serotonin reuptake.

One of our strategies for the preparation of dual activity H_3 antagonist/serotonin transporter (SERT) inhibitors was to introduce an H_3 pharmacophore to a known SERT inhibitor.[9,10] In one part of these efforts, we elected to use a pyrrolidino-tetrahydroisoquinoline scaffold, developed as part of an earlier in house antidepressant program,[11] as a template on which to add an H_3 pharmacophore (Fig. 1A). Pharmacophore models for the H_3 receptor suggest a near linear disposition (*m*- or *p*-) of two tertiary amines separated by a phenylene and a hydrophobic chain of at least four atoms would frequently lead to potent H_3 antagonists.[12] We envisioned attachment of a piperidinylpropyloxy side chain to the pyrrolidino-tetrahydroisoquinoline scaffold in such a way as to give a complete H_3 pharmacophore (Fig. 1B).

In a previous report, we disclosed the SAR of pendant phenyl ring substituents (R).[13] In this paper, we further explore the SAR of this region through the introduc-

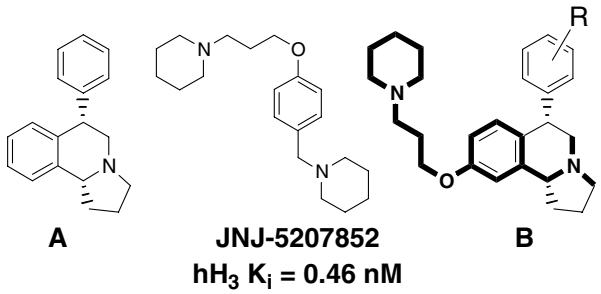

Figure 1. (A) SERT inhibitor template. (B) Dual SERT inhibitor and H_3 antagonist template with the H_3 pharmacophore in bold.

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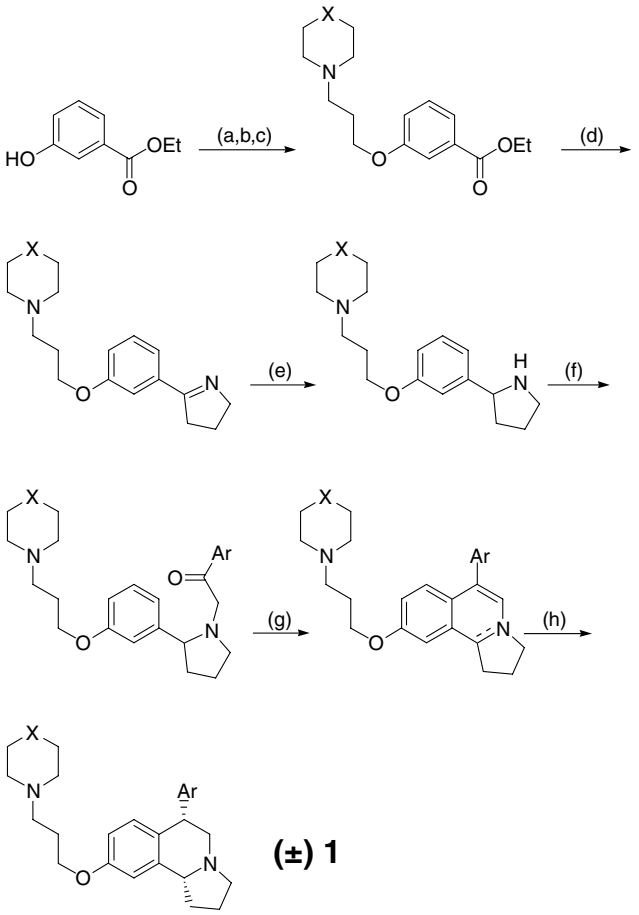
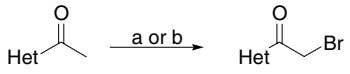
tion of aromatic heterocycles as either pendant substituents to the phenyl ring or as phenyl ring replacements. Compounds as in Figure 1B were prepared according to Scheme 1 and the bromo ketones utilized in step f were prepared by one of two methods shown in Scheme 2. Heterocyclic ketones with a protonatable nitrogen were first treated with 1 equiv of HBr in acetic acid followed by elemental bromine. Non-basic (to HBr) heterocyclic ketones were simply brominated in chloroform, methylene chloride or methanol.



Scheme 1. Reagents and conditions: (a) 1-bromo-3-chloropropane, 3 equiv K_2CO_3, acetone, reflux, 2 d, 92%; (b) 3.5 equiv NaI, acetone, reflux, 2 d, 98%; (c) 1.3 equiv piperidine or morpholine, 3 equiv K_2CO_3, EtOH, 60 °C, 2 d, 87%; (d) i—2 equiv *N*-vinylpyrrolidinone, 1.4 equiv NaH, THF rt, reflux; 2 h; ii—6 N HCl reflux, 24 h, 72%; (e) $LiAlH_4$, THF, 24 h, rt, 88%; (f) bromo-ketone, Et_3N, THF, 30 min, 80–99%; (g) MSA, rt−80 °C, 1–6 h (temperature and time depend on R); (h) $NaCNBH_3$, HCl, MeOH, bromocresol green, pH 4.5–5.5, 30 min–1 h, 15–70%.



Scheme 2. Het, aromatic heterocycle; (a) for basic heterocycles: 1 equiv HBr (48%), 0.9 M HOAc, 1.1 equiv Br_2, 0–75 °C, 1–4 h; (b) for non-basic heterocycles: 0.14 M in 5:2 $Et_2O/CHCl_3$, or 0.14 M in MeOH, 1 equiv Br_2, 0 °C-rt, 18 h, yields typically 70–80% for both methods.

In addition to varying the heteroaryl groups, the side chain was modified to contain either a piperidine or a morpholine. The piperidinyl derivatives were generally more potent, but the morpholine compounds had lower *c* log *P*'s.[14] In vitro data for the final products **1a**–**p** are found in Table 1.

Perusal of Table 1 reveals that these compounds all have a high affinity for the H_3 receptor.[15] This should not be too surprising as the H_3 pharmacophore portion of these molecules has not been modified beyond interchanging piperidine and morpholine, both of which are known to give high affinity H_3 ligands.[16] The compounds were shown to be potent antagonists in a functional assay with pA_2's in the range of 8.5–10.2. However, the nature of the pendant heteroaryl strongly influences SERT binding.[17,18] Generally, these compounds exhibited greater potency against rSERT than the hSERT. Pyrrazolo-phenyl and imidazolophenyl derivatives (**1a**–**b**) were reasonably well tolerated by the SERTs. Of the pyridyl derivatives (**1c**–**g**), the 3-pyridyl compounds were the most potent. Introduction of an additional ring nitrogen to give a pyrazine (**1h**) resulted in a significant loss of SERT potency. The most potent compounds were the thienyl derivatives (**1i**–**l**), maintaining excellent activity at both the rat and human SERTs. Thiazoles, pyrazoles, and imidazopyridines were all much less potent against the SERTs.

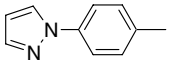
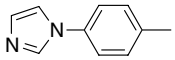
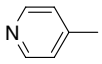
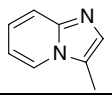
Compound **1d** was studied in a mouse brain to plasma ratio experiment.[19] After ip administration (10 mg/kg), **1d** achieved a maximal plasma concentration of 1.43 μM after 15 min, and a maximal brain concentration of 0.92 μM after 2 h. Mean residence time in the plasma was 6.57 h and 31.29 h in the brain. The blood–brain barrier (BBB) coefficient was 0.75.[20]

Compound **1d** was screened against a panel of other targets (receptors, ion channels, transporters, etc.) and those revealing significant affinity (>50% at 1 μM) were retested and K_i's determined. Other targets of interest included the dopamine transporter (DAT; K_i = 107 nM), norepinephrine transporter (NET; K_i = 460 nM), and the κ opioid receptor (K_i = 74 nM).

The BBB data as well as the DAT activity prompted us to study **1d** via in vivo microdialysis coupled with HPLC-electrochemical detection in an effort to assess the effects of **1d** on the extracellular concentration of serotonin (5-HT) and dopamine (DA) in the frontal cortex of the rat brain.[21] Within 4 h of dosing **1d** (3 mg/kg sc) the 5-HT and DA levels had increased 300% and 500% over basal levels, respectively. The increases in neurotransmitter concentrations were sustained for the duration of the experiment (21 h).

In conclusion, the described compounds are potent brain penetrating dual H_3 antagonist/SERT inhibitors with potential utility for treating depression.

Table 1. Binding data for rat and human serotonin reuptake transporters and for the human histamine H_3 receptor for compounds **1a–p**

Compound **1**	X	Ar	rSERT K_i (nM)	hSERT K_i (nM)	hH_3 K_i (nM)
a	O		6 (±1.2)	12.3 (±2.7)	5.3 (±0.4)
b	O		6.7 (±1.5)	16.7 (±2.0)	5.7 (±1.1)
c	CH_2		20 (±6.0)	66 (±32)	1 (±0.7)
d	CH_2		2 (±0.7)	8.3 (±1.8)	0.8 (±0.1)
e	O		4.3 (±0.8)	12.3 (±2.3)	1.6 (±0.4)
f	CH_2		3.3 (±0.4)	18.7 (±2.2)	0.8 (±0.1)
g	O		8.3 (±1.1)	31.3 (±0.8)	2.7 (±0.4)
h	O		22.7 (±7.6)	88 (±2.6)	4 (±0.7)
i	CH_2		1.2 (±0.5)	2.7 (±0.8)	1.0 (±0)
j	O		3 (±0.7)	6 (±0.7)	3 (±0.7)
k	CH_2		0.7 (±0.2)	1.3 (±0.4)	0.7 (±0.2)
l	O		2 (±0)	5 (±0)	3 (±0.7)
m	O		6 (±0)	19.7 (±0.4)	3.7 (±0.4)
n	O		53.3 (±20)	291 (±102)	3.3 (±0.4)
o	O		24.3 (±9.4)	121 (±27)	4 (±0.7)
p	O		39 (±7.8)	119 (±11.4)	2 (±0)

rSERT, rat serotonin transporter; hSERT, human serotonin transporter; hH_3, human histamine H_3 receptor: numbers in parentheses are the standard error of the mean (SEM) for each data set: $n \geqslant 3$ for all in vitro data.

Acknowledgments

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19. Also called a BBB experiment.
20. The BBB coefficient is defined as LOG (AUCbrain)/AUCplasma).
21. See Ref. 13 for experimental details Paxinos, G.; Watson, C. *The Rat Brain in Stereotaxic Coordinates*, Third ed.; Academic Press: San Diego, CA, 1997.