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

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Abstract—A series of novel and potent pyrrolidino-tetrahydroisoquinolines with dual histamine H_3 antagonist/serotonin transporter inhibitor activity is described. A highly regio- and diastereoselective synthesis of the pyrrolidino-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.

Depression is a major health issue, with more than 340 million people affected worldwide.[1] There is a growing awareness that patients with depressive disorders often also suffer cognitive impairment,[2] and some studies indicate that these deficits may persist even after remission.[3] Fatigue is another prominent symptom of depression.[4] Selective serotonin reuptake inhibitors (SSRIs) are the most frequently prescribed antidepressant drugs. However, these drugs often fail to improve these symptoms even as mood improves.[5,6] Some SSRIs even induce fatigue and excessive sleepiness.[7,8]

Attempts to address these therapeutic needs have largely relied on the use of modafinil in conjunction with an SSRI. This drug, a molecule of undetermined mechanism of action,[9] improves cognition and increases wakefulness.[10,11] In recent years, several small trials investigating the usefulness of modafinil as antidepressant monotherapy or as co-therapy with SSRIs have been published, bearing witness to the medical interest in the addition of a mild wakefulness promoting agent to the current antidepressant regimes.[12–15]

Histamine H_3 receptor antagonists also improve cognition in a variety of animal models[16] and increase wakefulness[17] without showing nonspecific stimulant effects such as increased locomotor activity.[18] H_3 receptor antagonists have also been shown to decrease REM sleep,[17] which has been observed to improve the mood of depressed patients in sleep deprivation studies.[20] Thus the case can be made that H_3 antagonists would be useful adjuncts to antidepressant therapy for partial responders to SSRI therapy with persistent fatigue and sleepiness.[21] In the current paper, we describe some aspects of our medicinal chemistry efforts to synthesize molecules that are both H_3 receptor antagonists and serotonin reuptake inhibitors.

One of our strategies for the preparation of a dual activity H_3 antagonist/serotonin transporter (SERT) inhibitor was to introduce an H_3 pharmacophore[22,23] to a known SERT inhibitor.[24,25] As one part of our efforts to do this, we elected to use a pyrrolidino-isoquinoline scaffold, developed as part of an earlier inhouse anti-depressant program,[26] as a template to which H_3 activity could be added (Fig. 1A). Pharmacophore models for the H_3 receptor suggest a near linear disposition (*m*- or *p*-) of two tertiary amines separated by a 3- or 4-substituted phenylene and a hydrophobic chain of at least four atoms should lead to potent antagonists.[22] We envisioned attachment of a piperidinylpropyloxy side chain to the pyrrolidino-isoquinoline scaffold in

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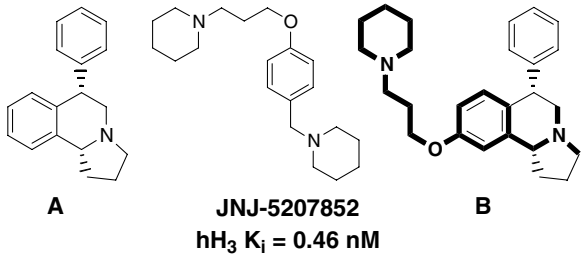


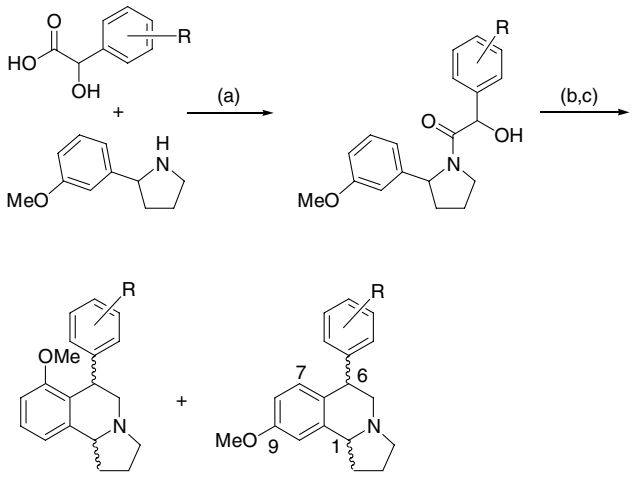
Figure 1. (A) SERT inhibitor template. (B) Dual SERT inhibitor and H_3 antagonist template with the H_3 pharmacophore in bold.

such a way as to give a complete H_3 pharmacophore (Fig. 1B).

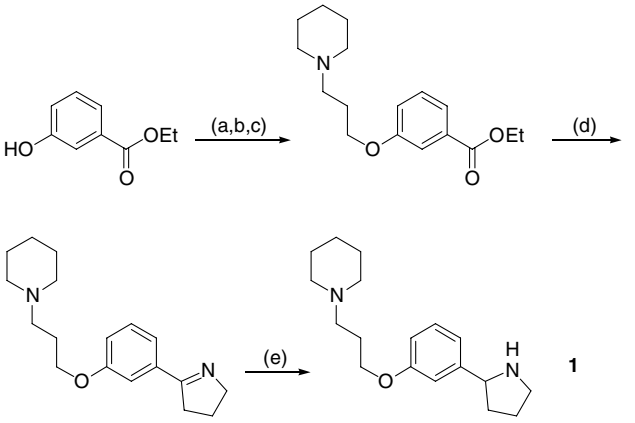
Our early synthetic approach to this class of molecules was to couple a suitably functionalized aryl pyrrolidine with a mandelic acid derivative and then perform an acid mediated ring closure on the α-hydroxyamide (Scheme 1). Reduction of the resultant lactam and installation of the basic side chain would follow.

Unfortunately, preparation of the amide (either with HATU or thermally) was low yielding and produced a number of side products. Subsequent ring closure with polyphosphoric acid (PPA) or methanesulfonic acid (MSA), then gave a mixture of regio- and diastereomeric products, of which, the desired 9-*cis* isomer was a minor component.[27] Further difficulty in installing the H_3 pharmacophore led us to examine alternate synthetic approaches to these molecules.

As it was desirable to have a common intermediate from which to develop SAR, we elected to construct an aryl pyrrolidine[28] bearing the desired basic side chain (Scheme 2). The route in Scheme 2 can be performed on a 100 g scale without the use of chromatography by subjecting the crude products to short-path or Kugelrohr distillation.



Scheme 1. Reagents and conditions: (a) refluxing in xylenes for 2 d with a Dean–Stark trap or HATU 30–50%; (b) MSA, rt, 40–85%; (c) BH_3·THF, 50–90%.



Scheme 2. 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, 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%.

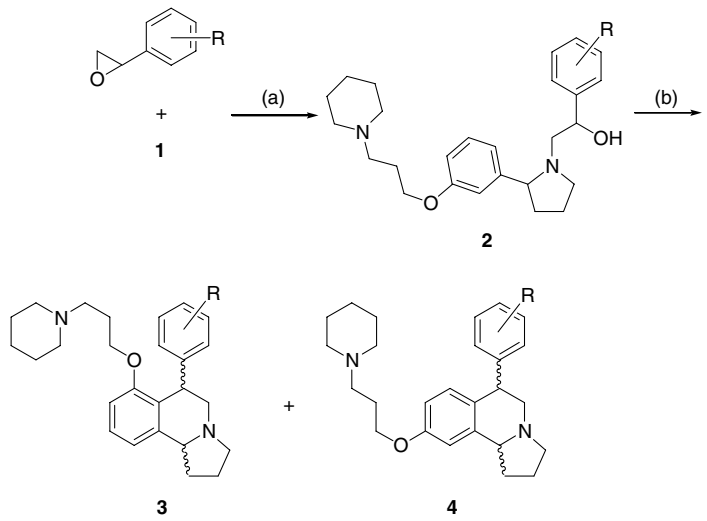
With intermediate **1** in hand we examined the use of styrene oxides and bromo-acetophenones as mandelic acid surrogates.

Alkylation of **1** with substituted styrene oxides gave suitable precursors for acid mediated ring closure (Scheme 3). The regioselectivity of epoxide opening was highly dependent on the aryl ring substituent. Strongly electron-withdrawing substituents preferentially gave products of attack at the terminal carbon. With all other substituents, significant (>50% with 4-methyl) opening occurred at the benzylic position. The regioisomeric alcohols were difficult to separate from **2** and, if carried forward, complicated isolation of products **3** and **4**.

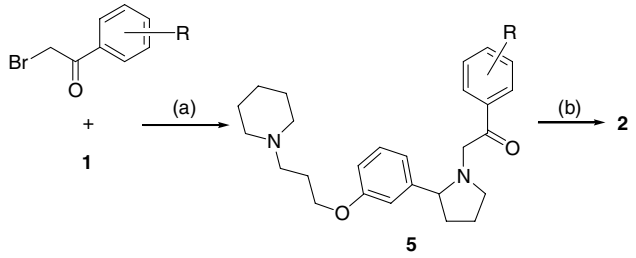
However, formation of the regioisomeric alcohol could be avoided by alkylation of **1** with suitably functionalized 2-bromo acetophenones followed by reduction of the amino ketone **5** with $NaBH_4$ to give aminoalcohol **2** (Scheme 4). This approach allowed for the introduction of strongly electron-donating substituents on the phenyl ring that were otherwise inaccessible via the epoxide route. Despite improvements to reaction cleanliness, the reaction still suffered from poor regio- and diastereoselectivity. Of four possible isomers, the desired 9-*cis* product remained a minor component.

In contrast, acid mediated ring closure of ketone **5** was regiospecific, giving only the 9-substituted product as a mixture of dihydroisoquinoline and isoquinolinium species **6** (Scheme 5). Reduction of products **6** to give **7** was then achieved using $NaCNBH_3$ and HCl.[29] Both products are reduced under these conditions and with complete diastereoselectivity for the desired 9-*cis* isomer **7**.

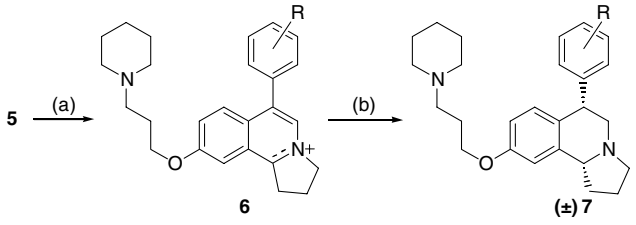
Binding affinities for compounds **7a**–**u** are shown in Table 1.[30] It is apparent from Table 1 that H_3 receptor affinity is minimally influenced by the substituents on the pendant aryl ring. All compounds in this series were shown to be potent antagonists of the H_3 receptor in our functional assay with pA_2 values ranging from 8.5 to 10.



Scheme 3. Reagents and conditions: (a) EtOH, Δ, 4 h, quantitative mix of regioisomers; (b) MSA, rt–140 °C, 1–6 h (temperature and time depend on R).



Scheme 4. Reagents and conditions:(a) Et_3N, THF, 30 min, 80–99%; (b) $NaBH_4$, quant.



Scheme 5. Reagents and conditions: (a) MSA, rt–80 °C, 1–6 h (temperature and time depend on R); (b) $NaCNBH_3$, HCl, MeOH, bromocresol green, pH 4.5–5.5, 30 min–1 h, 15–70%.

In contrast, rSERT and hSERT K_i values were strongly influenced by aryl ring substitution. Generally, substituents in the 3- or 4-positions gave more potent analogs than their 2-substituted counterparts. Both electron-donating and electron-withdrawing groups were tolerated. Exceptions include 4-CN (**7i**), 3- and 4-CF_3 (**7k** and **7l**), and 4-OH (**7r**). Compounds **7i** and **7k** are especially interesting as these moieties are found in the marketed anti-depressants citalopram (4-CN) and fluoxetine (4-CF_3). With one exception (**7m**), these compounds demonstrated somewhat weaker binding affinities for the human serotonin transporter than the rat serotonin transporter.

Racemate **7o** was resolved via chiral HPLC and the individual enantiomers examined in our in vitro binding assays. Consistent with earlier work on the pyrrolidino-isoquinoline scaffold,[31] most of the rSERT and essentially all of the hSERT affinity was due to the (-)-enantiomer.[32] Affinity for the H_3 receptor was slightly higher for the (+)-isomer.

The 4-methoxyphenyl derivative (Table 1, **7o**) was examined in the 5-hydroxytryptophan potentiated (5-HTP) head twitch model for SERT inhibition.[33] Mice dosed ip with this compound exhibited significant and dose-dependent increases in head twitches 24 h after administration. At 3 mg/kg the head twitch response (HTR) averaged 384% ($n = 3$) above vehicle treated mice ($n = 3$). At 10 mg/kg the HTR increased to 661% ($n = 3$) above vehicle. The HTR did not differ significantly from the vehicle treated animals 1 h after dosing suggesting slow uptake into the brain.

Evaluation of **7o** in a rat PK study[34] revealed the compound reached a maximal plasma concentration relatively quickly (0.67 h for the oral dose), but had a long plasma half-life (15.7 h). Bioavailability was modest at 16%. A mouse blood–brain barrier (BBB) penetration study (30 mg/kg ip) gave results consistent with the pharmacology observed in the rat 5-HTP study in that **7o** was demonstrated to slowly absorb into the brain ($C_{max} = 1.28$ μM at 24 h). The BBB coefficient was 0.96.[35]

In vivo microdialysis coupled with HPLC-electrochemical detection was used to assess the effects of **7o** on the extracellular concentration of serotonin (5-HT) and dopamine in the frontal cortex of the rat brain.[36] Compound **7o** increased extracellular levels of 5-HT 500% and dopamine (300%) over basal values 8 h after ip administration (1 mg/kg) and maintained those levels of elevation for the duration of the experiment (24 h).

The above in vivo experiments describe a compound with a delayed but prolonged pharmacological response due to slow absorption into, and subsequent very slow

Table 1. Binding data for rat and human serotonin reuptake transporters and for the human histamine H_3 receptor for compounds **7a–u**

Compound **7**	R	rSERT K_i (nM)	hSERT K_i (nM)	hH_3 K_i (nM)
a	H	2 (± 0.7)	4 (± 0)	0.9 (± 0.1)
b	4-Me	3 (± 0)	4.7 (± 0.8)	2 (± 0)
c	4-C≡CH	7 (± 1.2)	15.7 (± 4)	4 (± 1.2)
d	3-C≡CH	8.7 (± 1.8)	14.3 (± 4.1)	2 (± 0)
e	4-Cl	6.3 (± 1.5)	7.3 (± 1.6)	2.2 (± 0.5)
f	3-Cl	4.0 (± 1.9)	4.7 (± 2.8)	1.2 (± 0.5)
g	2-Cl	8.7 (± 1.8)	10.7 (± 1.8)	2.3 (± 0.4)
h	4-F	3.7 (± 1.1)	4.3 (± 1.1)	1.7 (± 0.4)
i	4-CN	24.7 (± 2.3)	59 (± 5)	1.2 (± 0.5)
j	4-NO_2	5.3 (± 2.3)	6.8 (± 0.7)	1.3 (± 0.4)
k	4-CF_3	26.7 (± 5.8)	40.3 (± 17.8)	4.7 (± 1.5)
l	3-CF_3	21.7 (± 4.0)	24 (± 7.4)	2.0 (± 0.7)
m	4-OCF_3	11 (± 0.7)	8.7 (± 1.5)	4 (±0)
n	4-SMe	3.3 (± 0.4)	5.2 (± 1.0)	2.5 (± 0.9)
o	4-MeO	2.3 (± 1.0)	3.3 (± 0.8)	0.7 (± 0.2)
(+) **o**	4-MeO	50.5 (± 2.9)	2000 (± 0)	0.8 (± 0.2)
(−) **o**	4-MeO	2.2 (±1.0)	2.3 (±1.6)	2.5 (±0.4)
p	3-MeO	4.7 (± 1.5)	7.5 (± 3.0)	1.7 (± 0.4)
q	2-MeO	14.0 (± 1.9)	33.5 (± 7.40)	1.3 (± 0.4)
r	4-OH	9.3 (± 2.3)	68.7 (± 12.5)	1.7 (± 0.4)
s	3-OH	1.3 (± 0.4)	5.3 (± 2.3)	0.7 (± 0.1)
t	2-OH	20.7 (± 4.7)	150 (± 32)	3.7 (± 1.1)
u	4-Me_2N	3.3 (± 1.1)	5.3 (± 2.0)	1.6 (± 0.5)

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.

elimination from, the brain. Despite the modest bioavailability of the compound, the relatively high brain concentrations obtained coupled with the high affinity of **7o** for the SERT, robust pharmacology was observed in both the 5-HTP and microdialysis experiments.

In conclusion, we have developed a regio- and diastereospecific synthesis of pyrrolidino-tetrahydroisoquinolines possessing potent dual H_3 antagonist/SERT inhibitor activity. A profiled member of this class gave robust responses in both 5-HTP and microdialysis experiments. Such dual activity compounds could be useful in the treatment of depression.

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