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Bioorganic & Medicinal Chemistry Letters 17 (2007) 5325–5329
Bioorganic & Medicinal Chemistry Letters

Dual serotonin transporter inhibitor/histamine H_3 antagonists: Development of rigidified H_3 pharmacophores

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Received 10 July 2007; revised 6 August 2007; accepted 8 August 2007
Available online 15 August 2007

Abstract—A series of tetrahydroisoquinolines acting as dual serotonin transporter inhibitor/histamine H_3 antagonists is described. The introduction of polar aromatic spacers as part of the histamine H_3 pharmacophore was explored. A convergent synthesis of the final products allowing late stage introduction of the aromatic side chain was developed. In vitro and in vivo data are discussed.

Fatigue is a frequent symptom experienced by the more than 340 million people worldwide who are suffering from depression.[1] While antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs), are frequently able to improve the overall sense of well being for those who use them, these drugs often fail to improve the symptom of fatigue even as mood improves.[2,3] Some SSRIs even induce fatigue and excessive sleepiness.[4,5]

One possible approach to mitigating the fatigue associated with depression and/or its treatment is through the use of a wake promoting agent. Histamine H_3 receptor antagonists are known to increase wakefulness[6] without showing nonspecific stimulant effects such as increased locomotor activity.[7] Thus the case can be made that H_3 antagonists would be useful adjuncts to antidepressant therapy.

As part of our strategy for the development of novel approaches to the treatment of depression, we have investigated the possibility of combining histamine H_3 antagonism with serotonin transporter (SERT) inhibition in a single chemical entity. We have recently described several chemical series[8–11] with high affinities for both targets (Fig. 1). The research described herein explores the effect of replacing the flexible propyloxy linker common to the earlier series with a more rigid and polar aromatic spacer in an effort to expand understanding of what is tolerated by the histamine H_3 receptor.[12] Increasing molecular rigidity has also been associated with improved oral absorption.[13] The target structure

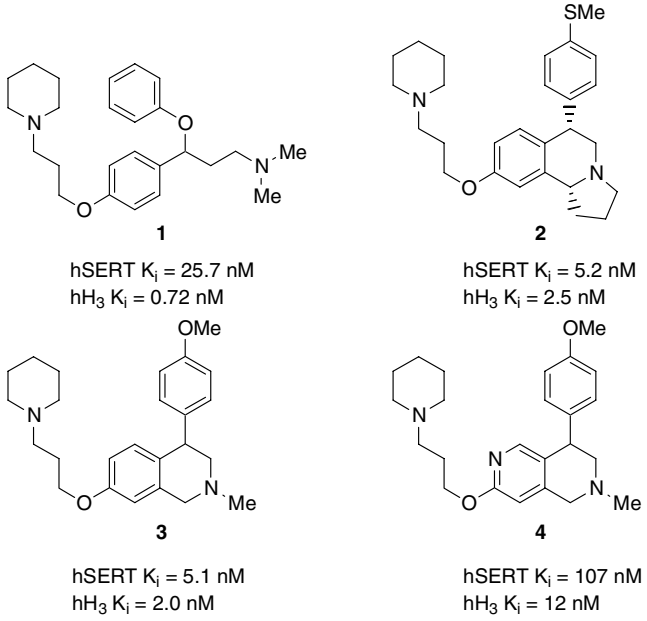

Figure 1. Dual histamine H_3/SERT inhibitors.

Keywords: Serotonin; Histamine H_3; SERT; Tetrahydroisoquinoline.
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0960-894X/$ - see front matter
doi:10.1016/j.bmcl.2007.08.017

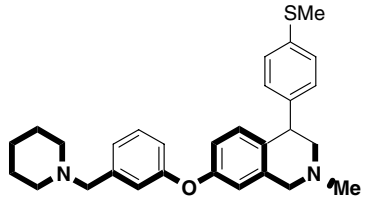
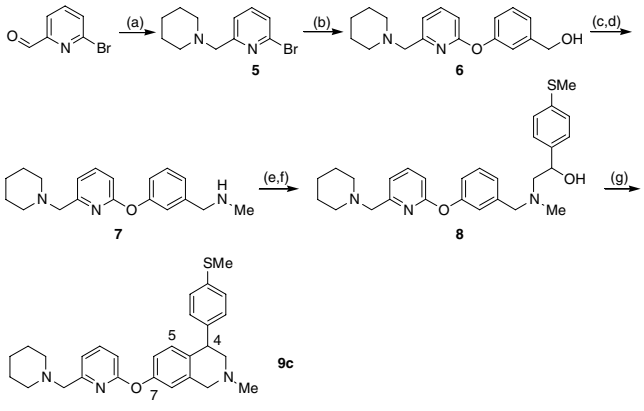


Figure 2. Target structure type with embedded H_3 pharmacophore shown in bold.

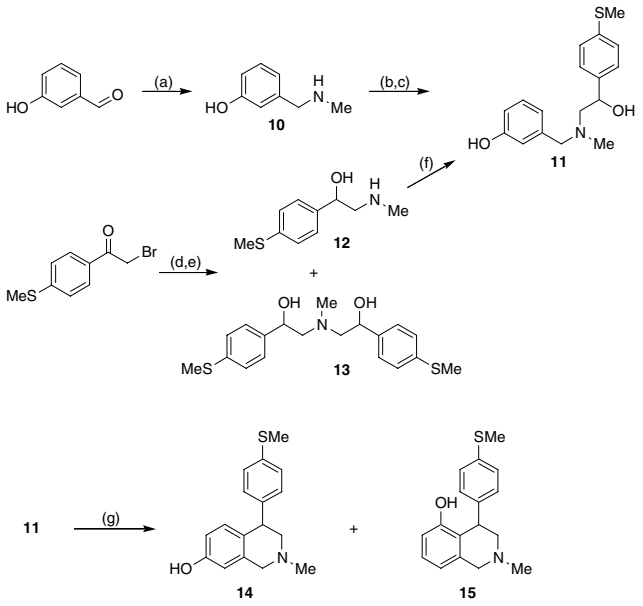
type with the embedded H_3 pharmacophore[14] is shown in Figure 2.

The initial linear synthetic route to the desired targets is shown in Scheme 1. Reductive amination of 6-bromo-2-pyridinecarboxaldehyde with piperidine gave amino bromide **5**, which was converted to biaryl ether **6** via an S_NAr reaction[15] with 3-hydroxylbenzyl alcohol. Swern oxidation of the alcohol followed by reductive amination with methylamine gave the benzylic amine **7** in good yield. Alkylation of **7** with 4-thiomethyl-2′-bromoacetophenone followed by reduction[16] of the ketone with $NaBH_4$ afforded the secondary alcohol **8**. Ring closure was affected by heating the alcohol in neat methanesulfonic acid giving the final product **9** in good yield. Other substrates similar to **8** gave a mixture of 5- and 7-substituted isomers (see Schemes 1 and 2).

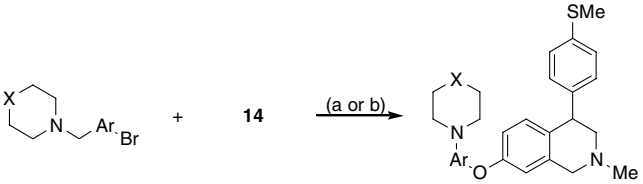
While the route shown in Scheme 1 is useful if variation of the pendant aryl ring at position four is desired, it is somewhat cumbersome if variation of the H_3 side chain is the objective. From previous work, we found tetrahydroisoquinolines with a 4-thiomethylphenyl substituent in the 4-position yielded potent SERT inhibitors.[17] Keeping the 4-thiomethylphenyl substituent constant may allow for a simplified synthetic route enabling more rapid evaluation of potential H_3 pharmacophores.



Scheme 1. (a) 1.5 equiv $NaB(OAc)_3H$, 1.0 equiv piperidine, 0.5 M 1,2-DCE, 71%; (b) 2 equiv 3-hydroxybenzyl alcohol, 2 equiv Cs_2CO_3, 0.5 M DMSO, 150 °C, 14 h, 59–63%; (c) 1.2 equiv oxalyl chloride, 2.2 equiv DMSO, 5 equiv Et_3N, 0.1 M CH_2Cl_2, −78 °C, 3 h, 86%; (d) 2.1 equiv 40%$_{(aq)}$ $MeNH_2$, 1.9 equiv $NaBH_4$, 0.5 M MeOH, 0 °C, 3.5 h, 98%; (e) 1 equiv 4-thiomethyl-2′-bromoacetophenone, 3 equiv DIPEA, 0.1 M CH_3CN, 1 h; (f) 2 equiv $NaBH_4$, 0.1 M EtOH, 80% for two steps; (g) 1.0 M MSA, 5 h, 60 °C, 64%.



Scheme 2. (a) 2.1 equiv 40%$_{(aq)}$ $MeNH_2$, 1.9 equiv $NaBH_4$, 0.5 M MeOH, 0 °C, 3.5 h, 97%; (b) 1 equiv 4-thiomethyl-2′-bromoacetophenone, 3 equiv DIPEA, 0.1 M CH_3CN, 1 h; (c) 2 equiv $NaBH_4$, 0.1 M EtOH, 16% for two steps; (d) 20 equiv 40%$_{(aq)}$ $MeNH_2$, 0.1 M EtOH, 1 h, then (e) 3 equiv $NaBH_4$, 15 h, 78% for two steps; (f) 1.3 equiv 3-hydroxybenzaldehyde, 2.5 equiv $NaB(OAc)_3H$, 1 equiv HOAc, 0.25 M, THF, 0 °C rt, 18 h, 94%; (g) 5 mL MSA/g **11**, 50 °C, 2.5 h, 67% 7-isomer, 31% 5-isomer, 98% total yield.

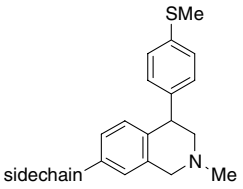


Scheme 3. (a) 1.25 equiv **14**, 2 equiv Cs_2CO_3, 0.5 M NMP, 150 °C, 2 h; (b) 1.5 equiv **14**, 2 equiv Cs_2CO_3, 0.5 equiv CuI, 0.75 M NMP, 195 °C, 2 h.

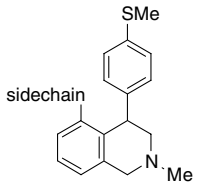
As we wished to avoid the use of protecting groups in the synthesis of the tetrahydroisoquinoline core, we envisioned **10** as a useful intermediate. Compound **10** was readily preparable via reductive amination, but was troublesome to work with due to high water solubility[18] and modest solubility in organic solvents. Nevertheless, it could be converted to **11** via alkylation with 4-thiomethyl-2′-bromoacetophenone and reduction of the corresponding ketone, albeit in modest yield.

Recognizing the high polarity of **10** as the source of difficulty with its manipulation, we desired an alternate route to **11** with more lipophilic intermediates. Alkylation of methylamine with 4-thiomethyl-2′-bromoacetophenone followed by immediate reduction of the ketone (one pot) gave **12** in reasonable yield, but also afforded significant amounts of the dialkylated product **13**. Increasing the equivalents of methylamine from five

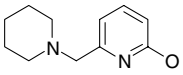
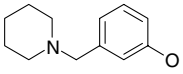
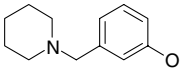
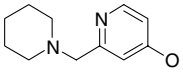
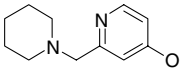
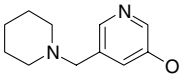
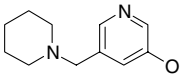
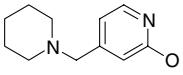
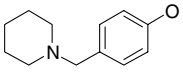
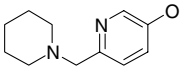
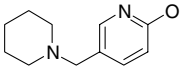
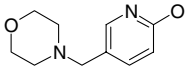
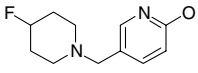
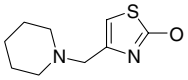
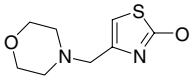
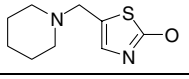
Table 1. Rat and human SERT[19] and human histamine H_3[7] in vitro binding affinities for compounds **9a**–**m** and **16a**–**c**



9a-m



16a-c

Compound	Side chain	rSERT K_i (nM)	hSERT K_i (nM)	hH_3 K_i (nM)
9a		11.7 (±3)	22.0 (±0.7)	51 (±11)
9b		11.7 (±5.8)	17.7 (±0.8)	18.0 (±0.7)
16a		403 (±38)	616 (±123)	253 (±36)
9c		25.7 (±7.3)	10.4 (±1.0)	323 (±111)
16b		182 (±40)	157 (±22)	265 (±70)
9d		9.7 (±3.5)	8.3 (±2.4)	109 (±18)
16c		174 (±19)	262 (±14)	511 (±20)
9e		8.7 (±2.7)	2.4 (±0.7)	34.3 (±5.7)
9f		4.3 (±1)	3.8 (±0.5)	22.7 (±2.5)
9g		7.5 (±1.8)	8.0 (±1.8)	24.3 (±8.6)
9h		4.5 (±1)	2.3 (±0.2)	8.2 (±0.5)
9i		11 (±1.9)	7.9 (±1.6)	260 (±36)
9j		14.3 (±2.3)	6.5 (±1.8)	110 (±10)
9k		5.2 (±0.7)	4.3 (±1.5)	20.7 (±4.7)
9l		14 (±3.9)	15.5 (±4.3)	201 (±27)
9m		4.0 (±0)	3.2 (±0.5)	20.7 (±2.3)

to 20 improved the yield of **12** from 45% to 78%. Reductive amination of 3-hydroxybenzaldehyde with **12** gave **11** in 94% yield. MSA mediated ring closure of **11** gave **14** and **15** in a 2:1 ratio with a combined yield of 98%. Compounds **14** and **15** were easily separated chromatographically.

The side chains to be attached to **14** were prepared simply by reductive amination of the precursor bromo-aldehyde with the desired amine (Scheme 3). Attachment of the side chains onto **14** was accomplished via S_NAr or by coupling in the presence of CuI. The in vitro activity for the products **9a**–**m** and **16a**–**c** is shown in Table 1.

From Table 1 it is apparent 5-substituted compounds **16a**–**c** have much lower affinity for the rat and human SERTs and for the H_3 receptor than the corresponding 7-isomers **9a**–**m**. Compounds having 1,3-disubstituted pyridyl spacers **9a**, **c**–**e** (relative spacing) were all less potent than the corresponding 1,3-disubstituted phenylene derivative **9b**. Pyridine ring nitrogen position had a large impact on H_3 affinity, but a more modest impact on hSERT binding. Greater H_3 affinity was generally found in the corresponding 1,4-disubstituted arylene derivatives, but again, the presence and location of a ring nitrogen had a significant effect on potency. Compounds possessing either 2,4 or 2,5 substituted thiazole spacers (**9k** and **9m** respectively) in the side chain retained excellent hSERT and reasonable H_3 affinity. None of the compounds prepared were as potent as **2** at the histamine H_3 receptor.

We examined two of the more promising compounds, **9h** and **9k**, in our H_3 functional assay.[7] Both compounds were antagonists with pA_2 values in the range of 7.7–7.9.

Throughout our H_3/SERT program, we have been able to qualitatively correlate slow absorption into the brain (or slow onset of pharmacological response) with brain and tissue accumulation along with concomitantly high volumes of distribution.[20] We therefore elected to use the 5-hydroxytryptophan (5-HTP) induced head twitch model of SERT blockade[21] to triage molecules on the basis of desirable physical properties. Only those molecules with a robust response in the head twitch model after 1 h and little to no response after 24 h would be profiled further. One hour post ip injection (10 mg/kg) of **9h** elicited no change in head twitch response (HTR) as compared with control animals. After 24 h, an HTR of 272% over control animals was observed. These data suggest **9h** inhibits the serotonin transporter, but gets into the brain slowly either due to slow absorption through the peritoneum or slow accumulation into the brain due to a very high volume of distribution. Compound **9k** did not show significant differences in the HTR over controls at either time point. In an effort to improve the physical properties of **9h**, the piperidine ring was replaced with morpholine and 4-fluoropiperidine.[22] When such substitutions were made in this series (**9i** and **9j**) an unacceptable decrease in H_3 affinity was observed.

In conclusion, we have prepared a series of novel dual SERT inhibitor/H_3 antagonists possessing rigidified H_3 pharmacophores. The compounds described generally were potent SERT inhibitors and some **9b**, **9f**, **9h**, **9k**, and **9m** were potent H_3 antgonists. One compound, **9h**, was modestly effective in the 5-HTP model of SERT inhibition after 24 h, but lacked the desired physical properties to warrant further development.

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15. An S_NAr reaction was not possible with some of our examples due to electronically unfavorable substitution of the aromatic ring. In those instances CuI was used as the coupling agent.
16. It is important to carry out the reduction immediately due to rapid oxidation of the amino ketone. For similar examples: (a) Babad, E.; Carruthers, N. I.; Jaret, R. S.; Steinman, M. *Synthesis* **1988**, 966; (b) Lipton, S. H.; Dutky, R. C. *Chem. Ind. (London)* **1972**, 33.

17. See Refs. 9a and 10b.
18. Compound **10** was not extracted efficiently from water with methylene chloride or ethyl acetate, but was readily extracted with *n*-butanol.
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20. While the two phenomena could not be expected to always correlate, the trend held for quite a few dibasic compounds possessing histamine H_3 and SERT activity.
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22. Previous studies by us (Ref. 9a) found replacement of the piperidine in the H_3 pharmacophore with morpholine or 4-fluoropiperidine resulted in more rapid brain penetration and subsequent elimination thus resulting in a strong physiological response after 1 h but a return to near baseline levels after 24 h.