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Benzylamine histamine H_3 antagonists and serotonin reuptake inhibitors

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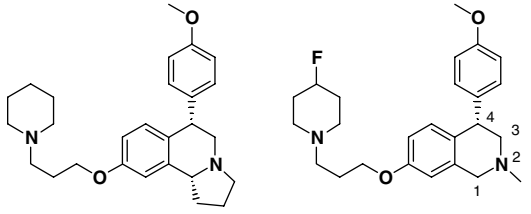
Abstract—The design, synthesis, and in vitro activity of a series of novel 5-ethynyl-2-aryloxybenzylamine-based histamine H_3 ligands that are also serotonin reuptake transporters is described.

Selective serotonin reuptake inhibitors (SSRIs), including fluoxetine and sertraline, are the most frequently prescribed drugs for depression, a major health issue that affects millions of people.[1] However, there are numerous problems with SSRI therapy. SSRIs typically have a slow onset of action (up to 4 weeks) and also often fail to improve the cognitive impairment and fatigue that is observed with many patients even as mood improves.[2,3] For these reasons, antidepressants with improved efficacy would represent an important new therapy.

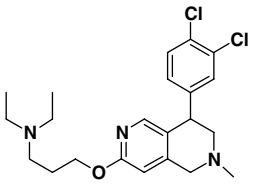
One possible approach to address some of the issues associated with SSRI therapy is to combine serotonin reuptake inhibitor activity with histamine H_3 antagonist activity in a single molecule. This appears to be a viable tactic since it is known that histamine H_3 receptor antagonists improve cognition[4] and increase wakefulness[5,6] in preclinical models. An added benefit is that histamine H_3 antagonists show these activities without undesired nonspecific stimulant effects.[7] As part of our efforts to prepare dual activity compounds we recently reported several series of serotonin reuptake inhibitors that are also high affinity histamine H_3 antagonists, including **1**,[8] **2**,[9,10] and **3**.[11] We now report data for some aryloxy benzylamine-based compounds that are also potent histamine H_3 antagonists and serotonin reuptake inhibitors.

Goals for this project included modifying the structure of our earlier compounds (i.e., **2**) in order to improve physical properties and decrease structural complexity while maintaining the high affinity for the H_3 receptor and serotonin transporter observed with **1**–**3**. Toward this end we hypothesized that it might be possible to remove C-3 of the tetrahydroisoquinoline ring of **2** to make benzyl amine compounds such as **4**. It is likely that C-4 of the tetrahydroisoquinoline could then be replaced by a variety of linkers (Y) to the aryl group; for this study we chose an oxygen linker since replacing C-4 with an oxygen would remove the chiral center and was expected to help lower the log *D* of the resulting molecules. We were also encouraged by the fact that related aryloxybenzyl amines have previously been reported to have serotonin reuptake activity.[12]

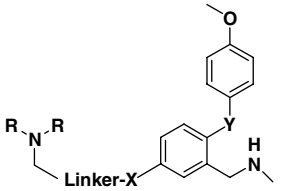


1, hH_3 K_i= 0.7 nM
hSERT K_i= 3.3 nM

2, hH_3 K_i= 4.0 nM
hSERT K_i= 2.7 nM



3, hH_3 K_i= 7 nM
hSERT K_i= 26 nM



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Keywords: Histamine H_3; Serotonin reuptake inhibitors; Benzyl amines.
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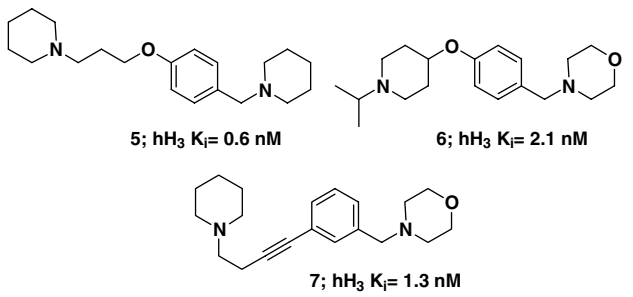
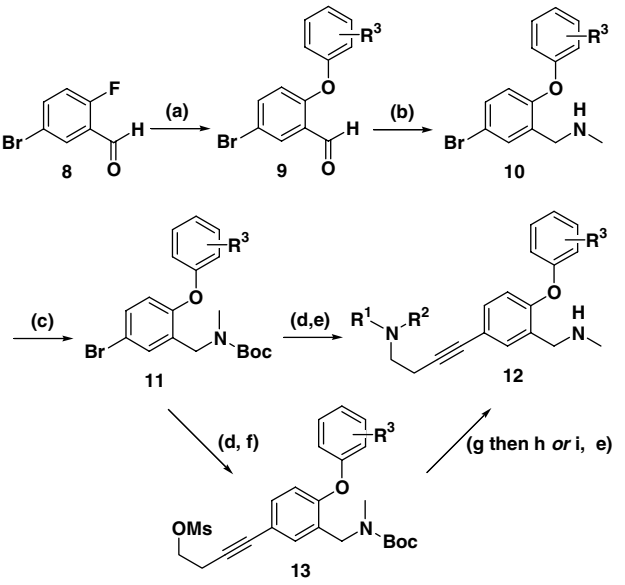
A variety of histamine H_3 pharmacophores have been reported during the past several years,[13] including compounds **5**,[14] **6**,[15] and **7**[16] from our group. For the purposes of this study we chose to focus on the piperidine alkyne H_3 pharmacophore present in **7** because we thought that this would be preferable to the masked hydroquinone compounds that would result from the installation of a piperidinepropyloxy- or piperidinealkoxy-group into the benzyl amines.



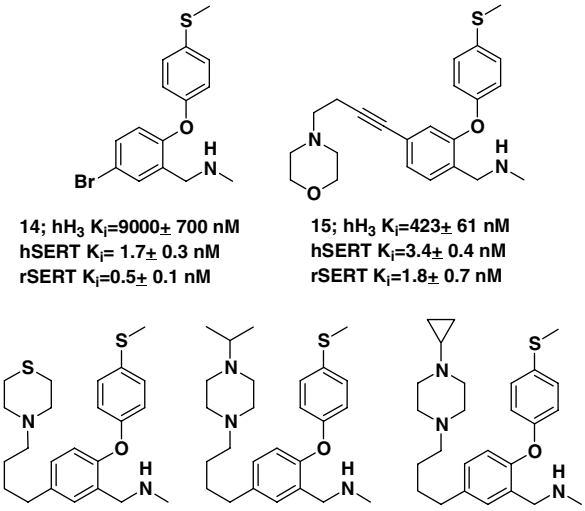
The compounds needed for this study were readily prepared in five steps from 5-bromo-2-fluorobenzaldehyde **8** by reaction with a variety of phenols, followed by reductive amination with methylamine and protection as the Boc amine (Scheme 1).

Subsequent palladium mediated coupling of the arylbromide with a fully elaborated alkyne and deprotection of the benzyl amine provided the desired compounds **12** in acceptable overall yields.



Scheme 1. Synthesis of 5-ethynyl-2-aryloxybenzylamines. Reagents and conditions: (a) K_2CO_3, ArOH, DMF, 90 °C, 20 h, 51–97%; (b) 40% aq $MeNH_2$, MeOH, 0 °C, 20 min, then $NaBH_4$, 0 °C, 0.5 h, then 23 °C, 18 h, 83–97%; (c) di-*tert*-butyl dicarbonate, DCM, 23 °C, 1 h, 96–100%; (d) various alkynes, Ph_3P, CuI, $(Ph_3P)_2PdCl_2$, DMF, Et_2NH, 100 °C, 1–3 h; (e) trifluoroacetic acid, DCM, 23 °C, 1 h, 13–71% for two steps; (f) MsCl, Et_3N, H_3CCN, 0–23 °C, 2 h, 91–100%; (g) R^1R^2NH, Et_3N, DMF/MeOH, microwave 150 °C, 25 min, 18–34%; (h) formaldehyde, $NaBH(OAc)_3$, EtOH, 23 °C, 16 h, 65%; (i) NaH, 2-bromopropane, DMF, 50 °C, 1 h, then 23 °C, 16 h, 16%.

Alternatively, **11** was coupled with but-3-yn-1-ol in a palladium mediated reaction to give the corresponding alcohol which was subsequently converted to the mesylate **13**. The mesylate was then displaced with a variety of amines (R^1R^2N) and finally deprotected to give **12**. In some instances, the amines were further functionalized via reductive amination (**12t**, **12u**) or alkylation (**12w**) prior to deprotection.

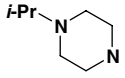
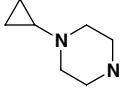


Compound **15** was prepared in a similar manner starting from 4-bromo-2-fluorobenzaldehyde, and compounds **16**–**18** were prepared as the result of catalytic hydrogenation of the corresponding compounds **12**.

Biological data for compounds **12** are shown in Table 1. All of the compounds shown have high affinity for the human and rat serotonin transporter. This was not surprising, considering that the R^3 groups utilized for this study were the better groups from our previous work.[8–11] A variety of histamine H_3 pharmacophores were used in this work and the H_3 affinity varies for these compounds. For the alkynes **12**, compounds **12v** and **12w** are poor ligands as are the piperazine **12q** and the diazepine **12x**. Compound **14**, which has no H_3 pharmacophore attached, also has no significant H_3 affinity, however it is a high affinity serotonin reuptake inhibitor. In addition, the alkyne isomer **15** has significantly lower affinity for the H_3 receptor than **12b**. The affinities of compounds **16**–**18** were comparable to the alkynes at both targets. We also verified that a number of the compounds in Table 1 are histamine H_3 antagonists at the human receptor (pA_2's 7.89–9.10).

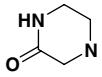
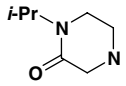
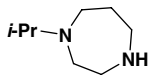
Several of the compounds were tested for affinity at the human norepinephrine (NET) and dopamine (DAT) transporters. These data are shown in Table 2. The compounds tested were $\geqslant$100-fold selective over these two important transporters as compared to the human SERT.

Table 1. Binding data for the rat and human serotonin reuptake transporters and for the human H_3 receptor for compounds **12**

Compound	R^1R^2N–	R^3	Rat SERT K_i[a] (nM)	Human SERT K_i[a] (nM)	Human H_3 K_i[a] (nM)	Human H_3 pA_2[b]
12a		4-MeS	0.7(±0.1)	0.7(±0.1)	1.7(±0.2)	8.61
12b		4-MeS	0.9(±0.1)	0.8(±0.1)	11(±2)	7.95(n = 2)
12c		3-Cl, 4-Cl	2.4(±0.7)	1.8(±0.2)	11(±3)	
12d		3-Me, 4-MeS	1.8(±0.7)	1.9(±0.3)	11(±3)	
12e		4-Cl	1.1(±0.5)	1.2(±0.1)	7.0(±0.7)	7.97
12f		H	11(±2)	30(±10)	5.7(±0.6)	8.14
12g		4-F_3C	2.0(n = 2)	2.7(±0.8)	7.3(±0.8)	7.90
12h		3-F_3C, 4-Cl	7.3(±1.5)	17(±1)	13(±2)	7.89
12i		3-F	10(±1.5)	24(±5)	3.0(±0.0)	8.45
12j		3-Cl	3.0(±1.2)	7.3(±1.6)	3.0(±0.0)	8.58
12k		2-Cl, 4-F	3.4(±1.0)	3.6(±0.4)	6.0(±1.9)	8.78
12l		4-MeS	0.9(±0.1)	2.5(±0.5)	5.4(±2.2)	
12m		3-Cl, 4-Cl	5.7(±0.2)	6.7(n = 1)	13(±5)	
12n		4-MeS	0.5(±0.1)	13(±1)	31(±4)	
12o		4-MeS	0.6(±0.1)	0.9(n = 2)	6.0(±3.1)	8.12
12p		3-Cl, 4-Cl	2.1(±0.1)	27(±9)	14(±1)	
12q		4-MeS	2.0(±0.2)	3.5(±0.4)	52(±2)	
12r		4-MeS	0.3(±0.1)	12(±2)	17(±6)	
12s		3-Cl, 4-Cl	1.8(±0.1)	1.4(±0.3)	17(±4)	
12t		4-MeS	1.3(±0.5)	1.1(±0.1)	6.1(±0.8)	9.10
12u		3-Cl, 4-Cl	6.4(±1.9)	5.9(±2.7)	9.7(±1.8)	

(*continued on next page*)

Table 1 (*continued*)

Compound	R^1R^2N–	R^3	Rat SERT K_i[a] (nM)	Human SERT K_i[a] (nM)	Human H_3 K_i[a] (nM)	Human H_3 pA_2[b]
12v		4-MeS	0.4(±0.1)	1.3(±0.1)	864(±380)	
12w		4-MeS	1.0(±0.0)	1.2(±0.2)	1867(±708)	
12x		4-MeS	0.7(±0.1)	3.6(±1.0)	93(±19)	
Fluoxetine			2.9(±0.6)	2.2(±0.6)	7300(±1100)	

[a] Values are means of at least three experiments in triplicate, SEM is in parentheses.
[b] Unless indicated, this is the result of a single experiment.

Table 2. Binding data for human NET and DAT

Compound	Human NET K_i[a] (nM)	Human DAT K_i[a] (nM)
12b	290	700
12d	240	1000
12o	96	190
12t	250	400

[a] Values are for one experiment, in triplicate.

Table 3. Plasma and brain concentrations in rat

Compound	Plasma concentration/brain concentration (μM)		
	1 h	3 h	6 h
12e	0.068/1.38	0.040/1.70	0.028/1.66
12g	0.24/1.77	0.31/4.65	0.15/5.40
12h	0.053/0.37	0.12/1.86	0.11/3.56
12i	0.11/0.82	0.091/1.42	0.048/1.87
12j	0.18/2.37	0.23/5.13	0.27/10.1
12k	0.030/0.27	0.018/0.44	0.008/0.40
12l	0.045/0.087	0.36/0.36	0.25/0.010
12o	0.023/0.044	0.008/0.063	0.010/0.13
12r	0.017/0.12	0.032/0.32	0.027/0.52
12t	0.039/0.20	0.024/0.22	0.012/0.24

As stated earlier, one of the main goals of this medicinal chemistry effort was to design molecules that have physical properties consistent with good absorption and distribution into the brain. In order to screen compounds quickly, we dosed compounds (po at 10 mg/kg) in rats and the resulting plasma and brain concentrations were measured at three time points (1, 3, and 6 h). This gave preliminary information on the extent of exposure in the brain and also gave a crude assessment of overall bioavailability. Table 3 shows plasma and brain levels in rat for compounds tested in this screen. Most of the compounds tested appear to readily penetrate the brain and several have very good brain levels (>1 μM) following oral administration. Exceptions are **12l** and **12o**, which both have rather low brain levels. Many of the compounds have a high brain to plasma ratio (>10 in some cases), indicating that the compounds are highly distributed into the tissue.

In conclusion, we have prepared a new series of benzyl amine-based histamine H_3 antagonists with serotonin reuptake activity. The compounds have suitable selectivity over human NET and DAT, and select compounds have good exposure in the brain following oral administration in rat. These characteristics should allow further pharmacological profiling of these compounds.

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