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Bioorganic & Medicinal Chemistry Letters 17 (2007) 1047–1051
Bioorganic & Medicinal Chemistry Letters

Novel tetrahydroisoquinolines are histamine H_3 antagonists and serotonin reuptake inhibitors

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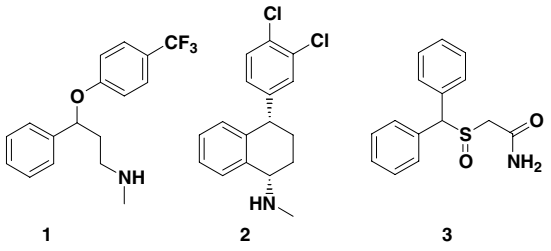
Received 6 October 2006; revised 7 November 2006; accepted 10 November 2006
Available online 16 November 2006

Abstract—A series of novel 4-aryl-1,2,3,4-tetrahydroisoquinoline-based histamine H_3 ligands that also have serotonin reuptake transporter inhibitor activity is described. The synthesis, in vitro biological data, and select pharmacokinetic data for these novel compounds are discussed.

Depression is a major health issue that affects more than 340 million people worldwide.[1] Many patients with depressive disorders suffer cognitive impairment[2] and fatigue.[3] Selective serotonin reuptake inhibitors (SSRIs) including fluoxetine **1** and sertraline **2** are frequently prescribed antidepressant drugs. However, SSRIs often fail to improve the cognitive impairment and fatigue that is often observed even as mood improves.[4,5] Some SSRIs even induce fatigue and excessive sleepiness.[6,7] Attempts to improve the efficacy of SSRIs have included co-administration of wake-promoting agents such as modafinil **3**.[8] This drug, a molecule with an undetermined mechanism of action,[9] has been shown to improve cognition and increase wakefulness.[10,11] However, modafinil has not been widely prescribed, in part because it is classified as a Schedule IV compound[12] and is a cytochrome P450 inhibitor.[13] Thus, alternative agents with wake-promoting and/or cognitive improvement activity might be useful for the treatment of depression, particularly if these agents do not exhibit stimulatory effects.



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Histamine H_3 receptor antagonists are known to improve cognition[14] and increase wakefulness[15,16] in a variety of animal models, without showing nonspecific stimulant effects.[17] This information led us to investigate the attributes of combining an H_3 antagonist with a serotonin reuptake inhibitor as an improved treatment for depression. As part of this effort, we combined known H_3 pharmacophores discovered earlier in these laboratories with a serotonin reuptake transporter (SERT) inhibitor pharmacophore to prepare a series of tetrahydroisoquinolines that are H_3 ligands with serotonin reuptake inhibitor activity.

Keywords: Histamine; Histamine H_3 antagonists; Serotonin; Serotonin reuptake inhibitors; Tetrahydroisoquinolines.
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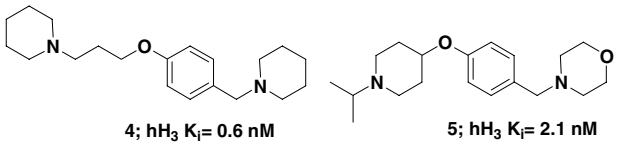
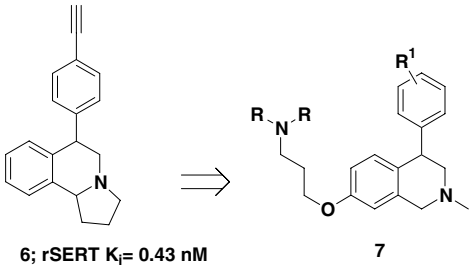
doi:10.1016/j.bmcl.2006.11.036



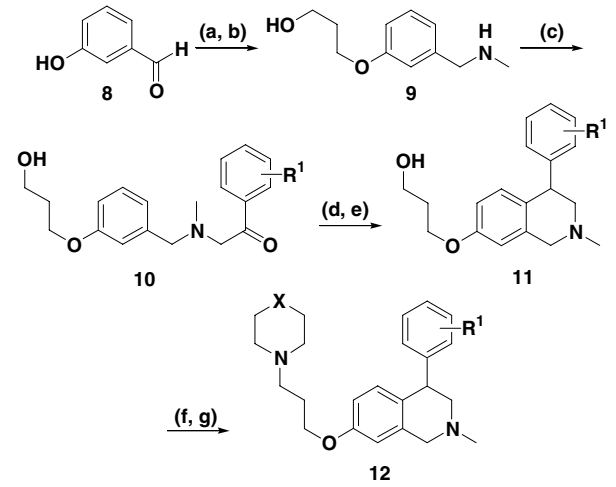
There have been numerous reports over the last few years describing a wide variety of histamine H_3 pharmacophores.[18] We previously identified numerous potent H_3 ligands, including compounds **4**[19] and **5**.[20]

High-throughput screening efforts in our laboratories recently identified the previously described hexahydropyrroloisoquinoline core **6**[21] as a template having high affinity for the serotonin transporter. This finding prompted us to combine the core structure of **6** with known histamine H_3 pharmacophores to produce tetrahydroisoquinoline-based compounds **7**. Our expectation was that these new compounds would have high affinity for the histamine H_3 receptor while maintaining the high affinity for SERT that was observed for compound **6**.



We now report the SAR of a series of 4-aryltetrahydroisoquinolines **12**. These compounds are substituted with the previously described H_3 pharmacophore **4** and analogs of **4** with related cyclic amines attached at the 7-position of the isoquinoline ring. The compounds are potent H_3 antagonists and are high affinity serotonin reuptake transporter ligands. We have recently reported on the SAR of the amino substituents on the 7-alkoxy-amino group of this class of compounds.[22] This report will focus on the biological properties of a variety of 4-aryl tetrahydroisoquinolines using the optimized amine side chains reported earlier.

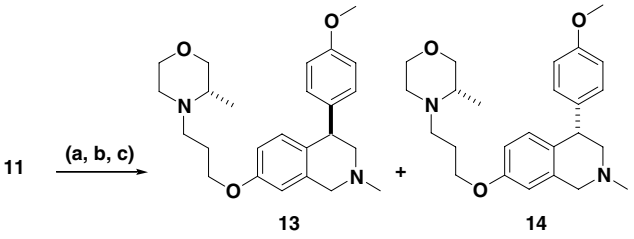
Compounds with the general structure **12** were prepared as shown in Scheme 1. Thus, 3-hydroxybenzaldehyde (**8**) was converted to **9** by reaction with 3-bromopropanol followed by reductive amination with methylamine. Due to the inherent instability of the intermediates, the next three steps to form the tetrahydroisoquinoline **11** were performed without purification. The reaction of **9** with various bromoacetophenones forms the amino ketones **10**, which were cyclized in the presence of methanesulfonic acid and reduced to form the tetrahydroisoquinolines **11** in moderate yields. Activation of the alcohol of **11** with methanesulfonyl chloride and



Scheme 1. Synthesis of 4-aryltetrahydroisoquinolines. Reagents and conditions: (a) K_2CO_3, 3-bromopropan-1-ol, MeCN, 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) $(i\text{-Pr})_2NEt$, 2-bromoacetophenones, THF, 23 °C, 45 min, (d) $MeSO_3H$, 60 °C, 18 h, (e) $NaCNBH_3$, MeOH, bromocresol green, 23 °C, 5 min, then 1.25 M MeOH · HCl, 0.5 h, typical yields 20–60% for 3 steps, (f) $MeSO_2Cl$, Et_3N, DCM, 0 °C to 23 °C, 20 min, (g) amine, Na_2CO_3, KI, *n*-BuOH, 50–80 °C, 18 h, typical yields 20–50% for two steps.

reaction with an amine then gave the desired compounds **12**. Typical yields for the final steps were 20–50%.

In several cases the racemic tetrahydroisoquinolines **12** were separated by chiral chromatography to provide single enantiomers.[23] As an example of this procedure, Scheme 2 describes the preparation of compounds **13** and **14** as single diastereomers. In this case, (*S*)-3-methylmorpholine was used to prepare compounds **13** and **14**. A single crystal X-ray structure was then obtained for compound **14**[24] (Fig. 1), confirming the tetrahydroisoquinoline stereochemistry shown for this analog. For ease of preparation on larger scale the enantiomers of intermediates **11** (with R^1 = 4-MeO–) could also be separated by chiral chromatography and used to prepare the desired tetrahydroisoquinolines as single enantiomers. Chromatographic separation of the enantiomers of **11** gave (*S*)-**11**, which was converted to both **14** and (+)-**12c**, confirming the (*S*) stereochemistry for (+)-**12c**.



Scheme 2. Synthesis of **13** and **14**. Reagents and conditions: (a) $MeSO_2Cl$, Et_3N, DCM, 0 °C to 23 °C, 20 min, (b) (*S*)-3-methylmorpholine, Na_2CO_3, KI, *n*-BuOH, 75 °C, 18 h, 37%, (c) chromatographic separation.[23]

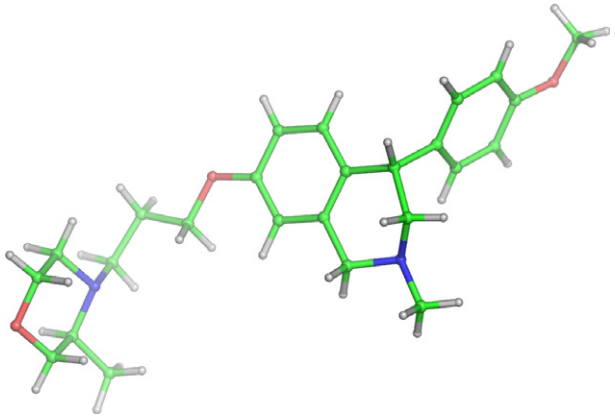


Figure 1. Crystal data for **14**. $C_{25}H_{34}N_2O_3$, M = 410.55, Monoclinic, with space group $P2_1$ and cell parameters, a = 5.9251, b = 15.3873, c = 12.3147 Å, β = 96.9246°, V = 1114.561 Å^3, T = 123 K, Z = 1, μ (Cu-Kα) = 0.63 mm-1, $F(000)$ = 444. 9046 reflections measured, 3018 unique (R_{int} = 0.0256), which were used in all calculation. R_1 = 0.0204, wR_2 = 0.0564 (all data).

Human histamine H_3[17], and rat and human SERT binding data[25] for compounds **12**–**14** are shown in Table 1. All of the compounds shown have optimized histamine H_3 pharmacophores[22] and therefore all have relatively high affinity for the histamine H_3 receptor. Many of the compounds were also tested for functional activity at the human H_3 receptor[17] and all those tested were found to be antagonists. The substituent present on the aryl ring (i.e., R^1) has little effect on the affinity for the human H_3 receptor, however more dramatic differences in affinity are seen at the rat and human SERT when changes are made to the aryl ring.

Compounds incorporating a 4-methoxy substituent (i.e., **12a-c**, **12f**, **12v**, **13**, and **14**) or a 4-thiomethyl substituent (i.e., **12o-p** and **12w-x**) are generally high affinity SERT ligands, both at the rat and the human transporter. The least potent substituents for the human transporter include 2,5-diCl (**12k**) and 4-methylsulfone (**12t**). In several cases, data were obtained for individual enantiomers (**12c**, **12p**, and **12x**). There is essentially no difference in affinity for either enantiomer at rat or human SERT or the human H_3 receptor.

Compounds (+)-**12p**, (+)-**12x**, and **14** were also screened in a panel of 50 receptor, ion channel, and transporter assays including adenosine (A_1, A_{2A}, A_3), adrenergic (α_1, α_2, β_1), angiotensin (AT1), dopamine (D_1, D_2), bradykinin (B_2), cholecystokinin (CCKA), galanin (GAL_2), melatonin (ML_1), muscarinic (M_1, M_2, M_3), neurotensin (NT_1), neurokinin (NK_2, NK_3), opiate (μ, κ, δ), serotonin (5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_3, 5-HT_{5A}, 5-HT_6, 5-HT_7), somatostatin, vasopressin (V_{1a}), norepinephrine transporter, dopamine transporter, and ion channels (sodium, calcium, potassium, and chloride). The compounds showed no affinity for the above receptors when

Table 1. Binding data for the rat and human serotonin reuptake transporters[25] and for the human H_3 receptor[17] for compounds **12**, **13** and **14**

Compound	X	R^1	Rat SERT K_i (nM)[a]	Human SERT K_i (nM)[a]	Human H_3 K_i (nM)[a]	Human H_3 pA_2[b]
12a	H_2C–	4-MeO–	2.0 (±0.7)	5.1 (±0.8)	2.0 (±0.0)	9.22
12b	HFC–	4-MeO-	1.6 (±0.6)	2.9 (±1.8)	2.0 (±0.5)	8.58
(−)-**12c**	HFC–	4-MeO–	4.5 (±1.3)	9.3 (±0.4)	3.8 (±1.1)	8.44
(+)-**12c**	HFC–	4-MeO–	1.7 (±0.3)	2.7 (±0.4)	4.0 (±1.3)	8.89
12d	HFC–	3-MeO–	4.3 (±1.1)	4.3 (±1.8)	2.0 (±0.0)	9.07
12e	HFC–	4-EtO–	2.7 (±1.5)	4.7 (±0.4)	7.3 (±2.4)	
12f	HFC–	4-MeO, 3-Cl	5.3 (±1.8)	5.7 (±2.0)	9.7 (±1.6)	8.21
12g	HFC–	4-Cl	16 (±7)	11 (±1)	8.3 (±1.1)	
12h	HFC–	3-Cl	14 (±7)	24 (±4)	3 (±0.0)	8.86
12i	HFC–	2-Cl	17 (±8)	18 (±4)	5.6 (±3.1)	
12j	HFC–	3,4-di-Cl	8.3 (±3.5)	21 (±2)	31 (±13)	7.48
12k	HFC–	2,5-di-Cl	120 (±52)	107 (±26)	9.3 (±0.8)	8.34
12l	HFC–	H	13 (±4)	46 (±7)	3.3 (±0.9)	9.14
12m	HFC–	4-F_3C–	14 (±7)	8.6 (±1.5)	18 (±3)	
12n	HFC–	3-F_3C–	30 (±9)	15 (±5)	11 (±0)	
12o	HFC–	4-MeS–	2.3 (±0.4)	8.8 (±6.0)	17 (±10)	8.21
(−)-**12p**	HFC–	4-MeS–	5.0 (±1.2)	4.2 (±0.6)	15 (±4)	8.10
(+)-**12p**	HFC–	4-MeS–	2.0 (±0.0)	2.0 (±0.7)	6.5 (±3.1)	
12q	HFC–	4-NC–	7.8 (±2.7)	16 (±2)	3.5 (±1.4)	8.85
12r	HFC–	4-Me–	4.4 (±1.4)	13 (±3)	8.3 (±2.0)	
12s	HFC–	4-F_3CS–	36 (±14)	34 (±3)	46 (±7)	
12t	HFC–	4-$MeS(O)_2$–	22 (±8)	135 (±39)	2.0 (±0.0)	9.28
12u	HFC–	4-F_2HCO–	3.0 (±1.9)	4.3 (±1.8)	10 (±2)	8.36
12v	O	4-MeO–	4.8 (±0.7)	6.5 (±2.0)	3.8 (±0.9)	8.64
12w	O	4-MeS–	4.0 (±1.2)	6.2 (±1.6)	13 (±1)	
(−)-**12x**	O	4-MeS–	3.0 (±0.7)	5.2 (±2.2)	10 (±1)	
(+)-**12x**	O	4-MeS–	2.3 (±0.9)	3.8 (±0.4)	11 (±3)	8.05
13			6.0 (±0.7)	13 (±5)	6.9 (±1.3)	8.53
14			5.0 (±1.7)	13 (±3)	5.6 (±0.3)	9.05
Fluoxetine **1**			2.9(±0.6)	2.2 (±0.6)	7300 (±1100)	

[a] Values are the means of at least three experiments in triplicate, standard error of the mean is in parentheses.
[b] The result of a single experiment.

Table 2. Binding data for human NET and DAT[26]

Compound	Human NET K_i (nM)[a]	Human DAT K_i (nM)[a]
(+)-**12p**	118 (±32)	46 (±23)
(+)-**12x**	106 (±33)	29 (±2)
14	121 (±56)	102 (±16)

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

Table 3. Rat pharmacokinetics after intravenous and oral administration

Compound	Cl_p (mL/min/kg)	V_{ss} (L/kg)	$t_{1/2}$ (h)	%F	Brain C_{max} (μM)[a]
12b	32.3	5.1	13.3	13	
(+)-**12c**	21.8	19.9	16.0	6	1.5
12e	29.9	15.5	10.3	11	
(+)-**12p**	18.5	9.6	9.9	21	2.4
(+)-**12x**	14.0	5.1	6.6	38	9.6
14	18.1	6.8	9.0	5	

[a] Brain C_{max} following oral administration of 10 mg/kg test compound.

tested at 1 μM with the exception of the norepinephrine transporter (NET) and the dopamine transporter (DAT). In-house testing confirmed these compounds do have affinity for the human NET and DAT[26], and showed that the compounds are moderately selective for the serotonin transporter over NET and DAT (Table 2).

Rat pharmacokinetic data (Table 3) were obtained for several of the more interesting compounds on Table 1. The compounds have moderate clearance and high volumes of distribution resulting in relatively long half-lives in rat. Compounds (+)-**12p** and (+)-**12x** have the highest bioavailability in rat (21% and 38%, respectively). Compounds (+)-**12p** and (+)-**12x** also show high exposure in the brain following oral administration. Ex vivo receptor occupancy data were obtained for select compounds from Table 3. As examples, compounds (+)-**12x** and **14** showed 100% receptor occupancy in the rat brain at both the SERT and H_3 receptor following subcutaneous administration of a 0.3 mg/kg dose (corresponding to brain concentrations of 0.67 and 0.88 μM, respectively). In addition, compound (+)-**12p** had an ED_{50} of 0.1 mg/kg (corresponding to a brain concentration of 0.13 μM) for the serotonin transporter and an ED_{50} of 0.05 mg/kg at the H_3 receptor as measured by receptor occupancy. Detailed pharmacological characterization of the more interesting compounds in this series will be the subject of future disclosures.

In conclusion, we have designed and prepared a new class of potent histamine H_3 antagonists with SERT inhibitor activity. The pharmacokinetic properties of these compounds should allow for thorough pre-clinical evaluation of the utility of histamine H_3 antagonists with reuptake inhibitor activity.

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23. Chromatographic conditions. Preparative; AD-H column (Chiral Technologies) (21 × 250 mm). Mobile phase; (A) 0.2% Et_3N in *i*-PrOH and (B) CO_2 eluted at 7.56 mL/min A/30 g/min B at 25 °C at a back-pressure of 100 bar. Analytical; AD-H column (4.6 × 250 mm). Mobile phase; (A) 0.2% Et_3N in *i*-PrOH and (B) CO_2 eluted at 30% A/70% B at 2 mL/min at 25 °C at a back-pressure of 100 bar. The analytical R_f's; (−)-**12p** (5.3 min), (+)-**12p** (8.4 min); (−)-**12x** (5.4 min), (+)-**12x** (8.3 min); **13** (4.1 min), **14** (7.2 min). Measured optical rotations (as the HCl salts in MeOH); (−)-**12 c** $[\alpha]_{589}$ −0.74 (c = 11.1 mg/mL), (+)-**12 c** $[\alpha]_{589}$ +0.73 (c = 9.36 mg/mL), (−)-**12p** $[\alpha]_{589}$ −13.9 (c = 9.36 mg/mL), (+)-**12p** $[\alpha]_{589}$ +12.51 (c = 9.27 mg/mL), (−)-**12x** $[\alpha]_{589}$ −9.11 (c = 10.1 mg/mL), (+)-**12x** $[\alpha]_{589}$ +9.89 (c = 10.8 mg/mL), **13** $[\alpha]_{589}$ +14.5 (c = 11.2 mg/mL), **14** $[\alpha]_{589}$ +14.0 (c = 11.1 mg/mL).

24. Crystallographic details of **14** have been deposited at the CCDC and allocated the deposition number CCDC 623130. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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26. Human NET: Membranes were prepared from MDCK (Madin-Darby Canine Kidney) expressing the human norepinephrine transporter, incubated with 5.4 nM [^{3}H]-nisoxetine plus/minus test compounds for 60 min on ice, and harvested by rapid filtration. Nonspecific binding was defined in the presence of 10 μM desipramine. Human DAT: Membranes were prepared from Chinese hamster ovary (CHO) cells expressing the human dopamine transporter, and incubated on ice with 10.9 nM [^{3}H]-WIN 35,428 for 2 h, and harvested by rapid filtration. Nonspecific binding was determined in the presence of 10 μM GBR-12909.