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Diamine derivatives containing imidazolidinylidene propanedinitrile as a new class of histamine H_3 receptor antagonists. Part I

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Abstract—Novel diamine derivatives containing imidazolidinylidene propanedinitrile were synthesized and evaluated for histamine H_3 receptor-binding affinities. High-affinity ligands **3d**, **3k**, and **3n** showed potent H_3 receptor antagonism and excellent selectivity over human H_1, H_2 and H_4 receptors.

In the central nerve system, the histamine H_3 receptor (H_3R) is thought to control the release of a various neurotransmitters such as histamine, serotonin, dopamine, and acetylcholine. H_3R antagonists induce the release of these neurotransmitters, and in animal models they have been demonstrated to enhance attention and cognition, and influence feeding. Therefore, they may be useful in the treatment of, for example, attention-deficit disorder, Alzheimer's disease, schizophrenia, and obesity.[1–7]

To obtain potent and selective H_3R antagonists, our chemical library was screened for compounds that inhibited the binding of [^{3}H]-N^α-methylhistamine ([^{3}H]-NAMH) to human H_3R. As a result, the imidazolidinylidene propanedinitrile derivative **1** was found to possess moderate affinities not only for the human H_3R (K_i = 83 nM) but also for the rat H_3R (K_i = 75 nM). Conversely, its monoamine derivative **2** showed twofold higher affinity for human H_3R (K_i = 36 nM) compared to **1**, but K_i value at rat H_3R decreased to 690 nM. Recently, researchers of Johnson & Johnson reported a new class of diamine derivatives as potent and selective H_3R antagonists. For example, JNJ-5207852 represented pK_i of 9.24 (0.57 nM) and 8.90 (1.26 nM) for the human and rat H_3Rs, respectively, and acute wake-promoting actions by H_3R antagonism.[8,9] Then, we designed a novel diamine compound **3** based upon the imidazolidinylidene propanedinitrile core with various alkyl chain length or amines (Fig. 1).

First, in order to examine the effect of the alkyl chain length on human and rat H_3R affinities, we synthesized compounds **3a–f** in which piperidine was used as amines A and B. Compound **3a**, having two piperidinoethyl side chains (m, n = 2), was prepared as follows (Scheme 1). Commercially available [bis(methylthio)methylene]malononitrile **4** and N,N'-bis(2-hydroxyethyl)ethylenediamine **5** were reacted in refluxing THF to afford imidazolidinylidene propanedinitrile **6** in 95% yield. Then, two primary hydroxyl groups of compound **6** were mesylated and the resulting dimesylate was treated with excess piperidine to give compound **3a** in good yield.

Scheme 2 shows the synthesis of dipiperidino derivatives **3b–e** with various combinations of alkyl chain length. The reaction of malononitrile **4** with N-(2-hydroxyethyl)ethylenediamine **7a** (m = 2) or N-(3-hydroxypropyl)ethylenediamine **7b** (m = 3) afforded

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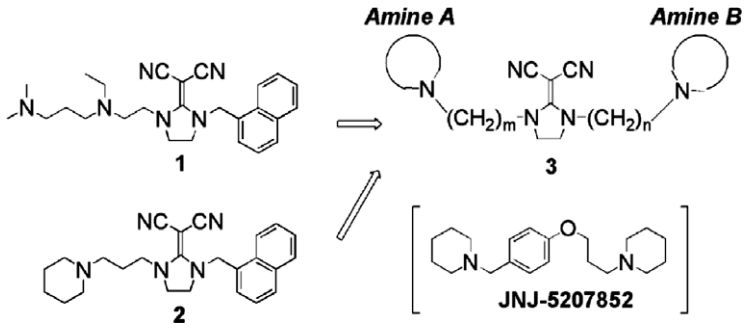
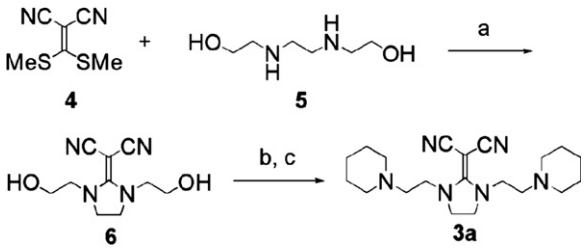


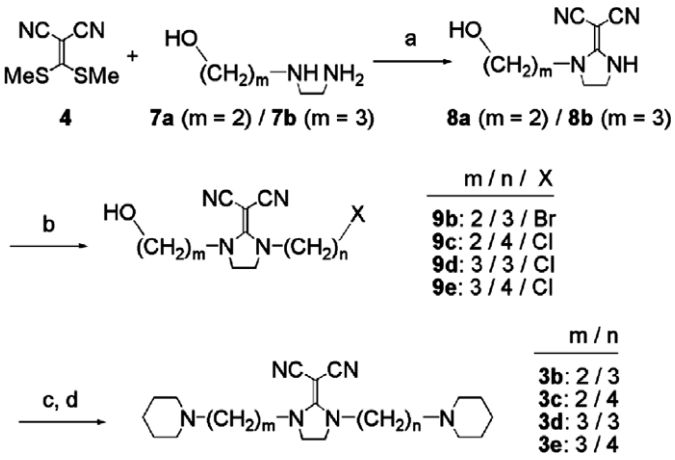
Figure 1. Design of diamine-based novel histamine H_3 receptor antagonists with imidazolidinylidene propanedinitrile moiety.



Scheme 1. Reagents and conditions: (a) THF, reflux, 1 h, 95%; (b) MsCl, TEA, CH_2Cl_2, rt, 1 h; (c) piperidine, 1,4-dioxane, reflux, 16 h, 67% (b and c two steps).

mono-substituted imidazolidinylidene propanedinitrile derivatives **8a** or **8b**. Introduction of another alkyl chain into compound **8a** or **8b** by the use of 1,3-dibromopropane ($n = 3$), 1-chloro-3-iodopropane ($n = 3$) or 1-chloro-4-iodobutane ($n = 4$) gave compounds **9b**–**e**. The hydroxyl group of each compound **9** was mesylated and the resulting intermediate treated with excess piperidine to yield compounds **3b**–**e**.

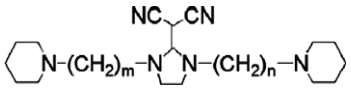
The bis(piperidinobutyl) derivative **3f** (m, $n = 4$) was prepared as shown in Scheme 3. Malononitrile **4** was reacted with ethylenediamine to give an unsubstituted imidazolidinylidene propanedinitrile **10** in 86% yield. Introduction of two (4-chlorobutyl) chains by the use of 1-chloro-4-iodobutane and K_2CO_3 in DMF afforded compound **11** in 93% yield. Subsequently, the reaction of compound **11** with excess piperidine in the presence of KI gave the target compound **3f** in 84% yield.



Scheme 3. Reagents and conditions: (a) ethylenediamine, THF, rt, 1.5 h, 86%; (b) K_2CO_3, DMF, 1-chloro-4-iodobutane, rt, 22 h, 93%; (c) piperidine, DMF, KI, 80 °C, 4 h, 84%.

Scheme 2. Reagents and conditions: (a) THF, rt, 2 h, 95% (**8a**), THF, rt, 3 h, 82% (**8b**); (b) K_2CO_3, DMF, 1,3-dibromopropane, rt, 108 h, 67% (**9b**), K_2CO_3, DMF, 1-chloro-4-iodobutane, rt, 96 h, 85% (**9c**), K_2CO_3, DMF, 1-chloro-3-iodopropane, rt, 42 h, 88% (**9d**), K_2CO_3, DMF, 1-chloro-4-iodobutane, rt, 18 h, 92% (**9e**); (c) MsCl, TEA, CH_2Cl_2, rt, 0.5–6 h; (d) piperidine, 1,4-dioxane, reflux, 15 h, 41% (**3b**: c and d two steps), piperidine, DMF, KI, 80 °C, 4 h, 62% (**3c**: c and d two steps), piperidine, DMF, K_2CO_3, 100 °C, 24 h, 53% (**3d**: c and d two steps), piperidine, DMF, NaI, 80 °C, 3 h, 77% (**3e**: c and d two steps).

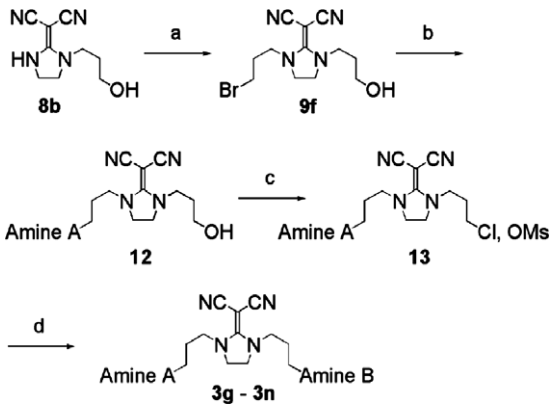
Table 1. The effect of alkyl linker length on the binding affinities to human and rat H_3 receptors



Compound	Linker	K_i (nM)	
	m, *n*	hH_3[a]	rH_3[a]
JNJ-5207852		0.57[b]	1.26[b]
1		83 ± 25[c]	75 ± 12[c]
2		36	690
3a	2, 2	24	55
3b	2, 3	6.6 ± 3.3[c]	6.3 ± 1.3[c]
3c	2, 4	16	8.6
3d	3, 3	2.4 ± 0.9[c]	2.6 ± 0.9[c]
3e	3, 4	(48/74)[d]	(65/88)[d]
3f	4, 4	(43/68)[d]	(51/85)[d]

[a] Binding potencies were assessed by the displacement of [^{3}H]-N^{α}-methylhistamine (NAMH). The human H_3 values were from cloned human H_3R expressed in COS-7 cells, while rat H_3R values were from rat striatal membranes.
[b] Data from Refs. 8 and 9.
[c] Values with standard error of the mean (SEM): $n = 3$ or 4.
[d] Percent inhibition at 0.1 μM/1 μM.

The binding assay results for compounds **3a**–**f** on human and rat H_3Rs are shown in Table 1. All compounds tested exhibited moderate to high affinities for both human and rat H_3Rs. A bell-shaped relationship between the alkyl chain length and ligand activities was observed. Among these molecules, compound **3d** (*m*, *n* = 3) was found to be the most potent ligand of human and rat H_3Rs with excellent selectivity over human H_1, H_2, and H_4 receptors (% inhibition of hH_1R, hH_2R, hH_4R at 10 μM; 21%, −4%, −1%). Interestingly, compound **3c** (*m* + *n* = 6) showed lower affinities for human and rat H_3Rs than those of compound **3d** (also, *m* + *n* = 6). These results indicate that not only the distance between two basic nitrogen atoms, but also the distance between an imidazolidinylidene propanedinitrile moiety and each nitrogen atom is important for high affinities to H_3Rs. In a functional assay,[10] compound **3d** reversed NAMH-mediated inhibition of [^{3}H]-histamine release from rat forebrain synaptosomes with an IC_{50} value of 28 nM. Therefore, compound **3d** was a potent antagonist of rat neuronal H_3R.



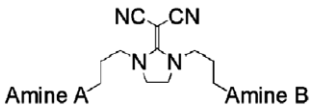
Scheme 4. Reagents and conditions: (a) K_2CO_3, DMF, 1,3-dibromopropane, rt, 25 h, 72%; (b) amine A, K_2CO_3, DMF, NaI or KI, rt, 3–10 h; (c) MsCl, TEA, CH_2Cl_2, rt, 1.5–3 h or CCl_4, Ph_3P, DMF or $CHCl_3$, rt or reflux, 1–18 h; (d) amine B, K_2CO_3, KI, 1,4-dioxane, reflux, 10–20 h.

Next, we synthesized compounds **3g**–**n** in order to investigate the effect of the piperidine modification of compound **3d** on human and rat H_3R binding affinities (Scheme 4). Common intermediate **9f** was prepared by the reaction of compound **8b** and 1,3-dibromopropane. As for compounds **3g**–**j**, 4-methylpiperazine, morpholine, (±)-3-hydroxypyrrolidine and (±)-2-methypyrrolidine were introduced to intermediate **9f** as amine A, followed by chlorination or mesylation of the primary alcohol of the resulting compound **12** to afford the corresponding chloride or mesylate **13**. Then, piperidine was reacted with compound **13** to give the desired asymmetrical derivatives **3g**–**j**. Furthermore, compounds **3k**–**n** were also prepared in the same way by the use of corresponding 2-methylpyrrolidine as amines A and B.

As shown in Table 2, the affinities for human H_3R of compounds **3g**–**i** markedly decreased as compared to the dipiperidine derivative **3d**. These cyclic amines were not tolerated for potent H_3R interaction. On the other hand, compounds **3j** possessing (±)-2-methylpyrrolidine showed 6 and 3.5 times higher affinities to human (K_i = 0.38 nM) and rat (K_i = 0.69 nM) H_3Rs than those of compound **3d**. 2-Methylpyrrolidine was reported to induce the high potency at both human and rat H_3Rs by researchers of Abbott.[11,12] Introduction of further (±)-2-methylpyrrolidine into **3j** afforded compound **3k**, it showed comparable high affinities to those of **3j** for both H_3Rs. Then, we synthesized all enantiomers of racemate **3k**, that is, **3l** (*R*,*R*), **3m** (*R*,*S*), and **3n** (*S*,*S*) by the use of the (*R*)- and (*S*)-2-methylpyrrolidine. These chiral pyrrolidines were prepared by reported procedure.[13,14] Although compound **3l** showed slightly lower affinity for human and rat H_3Rs, compounds **3m** and **3n** exhibited almost equal affinity to that of racemate **3k**. In the functional assay, compounds **3k** and **3n** were shown to be potent rat H_3R antagonists with IC_{50} values of 4.9 and 1.9 nM, respectively. These results, combined with those of compound **3d**, revealed that the potency of H_3R antagonism in rat cortical synaptosome was well correlated with the binding ability to rat forebrain H_3R for these molecules. Furthermore, compounds **3k**–**n** showed excellent selectivity over H_1, H_2 and H_4 receptors.

In conclusion, we have developed a new series of imidazolidinylidene propanedinitrile-based novel H_3R ligands. They showed potent affinities to both human and rat H_3Rs and some of which have proven to be potent antagonists at H_3Rs in rat cortical synaptosomes. Further structural modification and pharmacological evaluation of these compounds are in progress.

Table 2. The effect of piperidine modification of compound **3d** on human and rat H_3R-binding affinities and the selectivity between H_3R and other histamine receptor subtypes of compounds **3k–n**



Compound	Amine A	Amine B	K_i (nM)		% Inhibition (1 μM/10 μM)		
			hH_3[a]	rH_3[a]	hH_1[b]	hH_2[b]	hH_4[b]
JNJ-5207852			0.57[c]	1.26[c]	[d]	[d]	[d]
3d	Piperidino	Piperidino	2.4 ± 0.9[e]	2.6 ± 0.9[e]	3/21	−5/−4	11/−1
3g	4-Me-piperazinyl	Piperidino	(37/74)[f]	(43/82)[f]	[d]	[d]	[d]
3h	Morpholino	Piperidino	(37/69)[f]	(44/82)[f]	[d]	[d]	[d]
3i	(±)-3-OH-pyrrolidinyl	piperidino	(49/70)[f]	(57/86)[f]	[d]	[d]	[d]
3j	(±)-2-Me-pyrrolidinyl	Piperidino	0.38	0.69	5/9	−8/−4	2/6
3k	(±)-2-Me-pyrrolidinyl	(±)-2-Me-pyrrolidinyl	0.33 ± 0.07[e]	0.68 ± 0.08[e]	10/21	1/0	−8/−7
3l	(*R*)-2-Me-pyrrolidinyl	(*R*)-2-Me-pyrrolidinyl	1.3	1.1	0/−4	−7/−1	9/8
3m	(*R*)-2-Me-pyrrolidinyl	(*S*)-2-Me-pyrrolidinyl	0.47	0.77	−3/7	−14/−9	6/−3
3n	(*S*)-2-Me-pyrrolidinyl	(*S*)-2-Me-pyrrolidinyl	0.34	0.48	8/14	2/−2	9/0

[a] Binding potencies were assessed by the displacement of [^{3}H]-N^{α}-methylhistamine (NAMH). The human H_3 values were from cloned human H_3R expressed in COS-7 cells, while rat H_3R values were from rat striatal membranes.

[b] Affinity to H_1R, H_2R, and H_4R was assessed by the displacement of [^{3}H]-pyrilamine, [^{3}H]-tiotidine and [^{3}H]-histamine, respectively. Human H_1R, H_2R and H_4R were expressed in COS-7 cells.

[c] Data from Refs. 8 and 9.

[d] Not tested.

[e] Values with standard error of the mean (SEM): $n = 3$ or 4.

[f] Percent inhibition at 0.1 μM/1 μM.

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Supplementary data

Experimental procedures for the synthesis of compounds **3a**, **3d**, **3f**, and **3k**, and instrumental analyses data for all compounds. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2008.03.006.

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