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Histamine H_3 and H_4 receptor affinity of branched 3-(1*H*-imidazol-4-yl)propyl *N*-alkylcarbamates

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ABSTRACT

A series of imidazole-containing (non-)chiral carbamates were tested at human histamine H_3 receptor (H_3R). All compounds displayed K_i values below 100 nM. A trend for a stereoselectivity at human H_3R was observed for the chiral α-branched ligands. Selected compounds were also tested at human histamine H_4 receptor and showed moderate to weak affinities (118–1460 nM).

Imidazole moiety is present in many biologically active compounds (for review see[1]). One of the most important of them is histamine. Histamine exerts tremendous influence over a variety of physiological processes by the four known receptors subtypes: H_1, H_2, H_3 and H_4.

Histamine H_3 receptors (H_3Rs) are widely expressed in CNS and play the main role in many important processes. Nowadays, the current interest in the area of H_3R ligands (inverse agonists, antagonists) is focused on non-imidazole compounds (for review see[2–7]), whereas the first generation H_3R active structures contained the imidazole moiety (for review see[8]). These compounds were analogues of histamine with the 4-substituted imidazole ring. However, despite their high potency and clinical studies none of them have entered the market as a drug. The main drawback of these compounds was inhibition of numerous CYP450 enzymes[9,10] (although recently some studies suggested the possibilities to minimize these activities[11]), reduced oral bioavailability and poor brain penetration (e.g., thioperamide[12]). Actually, imidazole-based ligands like thioperamide, clobenpropit, and ciproxifan (Fig. 1) are mainly used as reference structures in a variety of preclinical animal models.

Despite that imidazole-containing ligands are further the subject of investigations and quite recently, Jablonowski et al. described a series of *N*-methylimidazole-containing compounds—potent H_3R ligands with improved metabolic stability. (e.g., **1**, Fig. 2)[13]

Histamine H_4 receptors (H_4Rs) are preferentially expressed on hematopoietic and immune cells (e.g., eosinophils, mast cells, macrophages) and play a role in immunological and inflammatory processes.[14]

The human H_4R is closely related to the human H_3R. These two proteins have a sequence identity of 31% and their homology in the transmembrane region is 54%.[15]

Therefore, it is not surprising, that numerous imidazole-containing H_3R ligands have also significant affinity for the human H_4R (e.g., Table 1)[16] and some of them (e.g., thioperamide, clobenpropit) have been used to characterize the H_4R. While the current medicinal chemistry efforts are concerned at finding more selective compounds, AstraZeneca continues to develop imidazole derivatives acting as dual H_3R and H_4R ligands (e.g., Fig. 3).[17] These compounds are considered as potential drugs for the treatment of histamine H_4 mediated diseases especially asthma. Also, very recently, Igel et al. described N^G-alkanoyl-imidazolylpropylguanidines as high-affinity human H_3R antagonists/partial agonists and full H_4R agonists.[18] For example, UR-PI294 with N^G-propionyl group, was tritiated, resulting the radioligand [^{3}H]UR-PI294.[19] This radioligand is considered a valuable pharmacological tool for the determination of human H_3R and human H_4R affinities.

In this Letter, we describe human H_3R affinity of branched 3-(1*H*-imidazol-4-yl)-propyl *N*-alkylcarbamates (Scheme 1). Most

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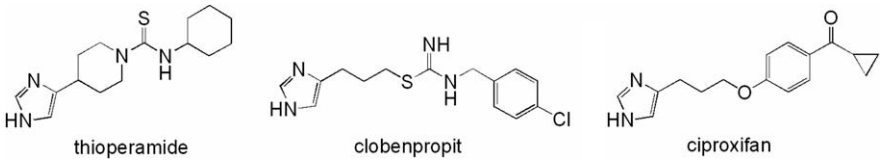
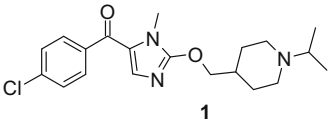


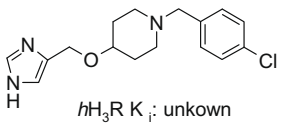
Figure 1. Some reference imidazole-containing histamine H_3 receptor ligands.



1

H_3R:
human K_i = 3 nM
rat pA_2 = 8.0
human pA_2 = 9.2
IC_{50}s > 10 mM for CYP: 1A2, 2C9, 2C19, 2D6 and 3A4

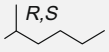
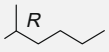
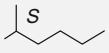
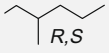
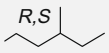
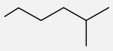
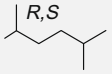
Figure 2. Structure and potency profile of **1**.[13]



hH_3R K_i: unkown
hH_4R K_i: unkown

Figure 3. Structure of one of the compounds developed by AstraZeneca.[17]

Table 1
Affinities of compounds **2**–**22** at human histamine H_3 and H_4 receptor

Compds	R	K_i[a] (nM)	hH_3R K_i[b] (nM)	hH_4R K_i[c] (nM)	Selectivity ratio hH_4R/hH_3R
2		20 ± 5	49	nt[d]	
3		19 ± 5	12	290 ± 98	24
4		23 ± 5	31	nt[d]	
5		25 ± 4	21	nt[d]	
6		12 ± 2	15	nt[d]	
7		18 ± 4	4.7 ± 0.9	118 ± 38	25
8		8.7 ± 2.9	29	695 ± 51	24
9		19 ± 4	19	426 ± 147	22
10		12 ± 5	42	nt[d]	
11		15 ± 5	8.3	162 ± 34	20
12		5.1 ± 1.9	13	123 ± 17	9
13		nt[d]	13	nt[d]	
14		nt[d]	30	nt[d]	

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