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GENERAL CONSTRUCTION PATTERN OF HISTAMINE H_3-RECEPTOR ANTAGONISTS: CHANGE OF A PARADIGM

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Abstract: Novel ω-phenyl substituted and unsubstituted alkyl and alkenyl imidazole derivatives were prepared and tested for their antagonist activity *in vitro* and *in vivo* at histamine H_3-receptors. Some compounds showed high *in vitro* and *in vivo* H_3-receptor activity despite their structure bearing no polar moiety in the centre of the molecule which is a common structural feature of all other antagonists known. Quite probably there are further *in vivo* effects for some compounds resulting from other receptor interactions. © 1998 Elsevier Science Ltd. All rights reserved.

Since the discovery of the histamine H_3-receptor[1] a large number of different antagonists have been described.[2,3] Due to their influence on H_3-auto- and H_3-heteroreceptors antagonists may prove to be potential drugs for the treatment of different diseases or conditions in the central nervous system like epilepsy,[4] stress,[5] memory and learning deficits[6] as well as cognitive and sleep disorders.[7] Although the antagonists described belong to different structural classes, they all have a general construction pattern in common[2] (Fig. 1).

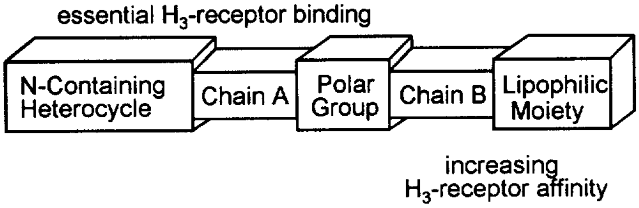

Figure 1. General construction pattern of histamine H_3-receptor antagonists

The *N*-containing heterocycle is an aromatic moiety which in most cases is an imidazole ring monosubstituted in 4-position. Almost all structural variations of this heterocycle led to a drastic loss in affinity. Chains A and B can be of different structure. The same is true for the polar group of which a large number of functionalities have been described by maintaining H_3-receptor affinity (for review see [2,3]). Many *p*-halogen phenyls have been reported to be advantageous for the lipophilic moiety, but a lot of heterocyles or

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alkyl substituents were also tolerated by the receptor. Four different antagonists are shown in Figure 2 to demonstrate their community. Whereas the first three elements seemed to be essential for H_3-receptor affinity the last two elements seemed to increase affinity. The compounds described herein possess an alkyl or alkenyl moiety instead of the polar group. Thus this element is shown not to be essential for an interaction with histamine H_3-receptors.

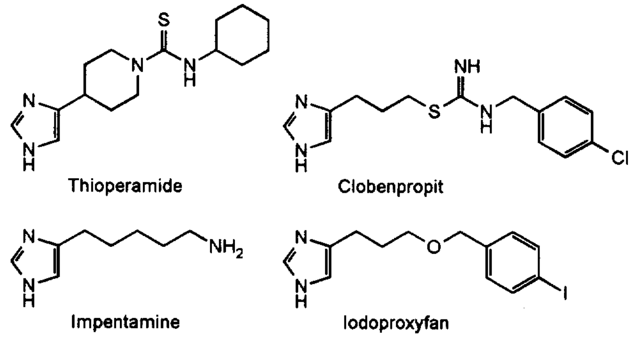
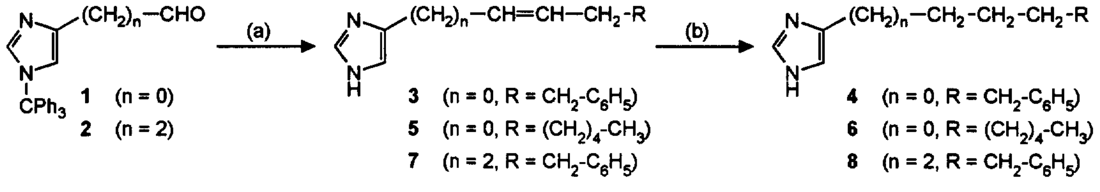


Figure 2. Structures of histamine H_3-receptor antagonists of different classes.

Chemistry.

The aldehydes as starting material are obtained by oxidation of the corresponding trityl protected alcohols. (1-Trityl-1*H*-imidazol-4-yl)methanol[8] is conveniently oxidized into **1**[8] with MnO_2, whereas Swern oxidation gave best results for the reaction with 3-(1-trityl-1*H*-imidazol-4-yl)propanol[9] for the preparation of **2**[10]. Conventional Wittig reaction with **1** predominatly resulted in the *Z*-configured alkene derivatives.[11] The configuration of **7** obtained by reaction with the propanal derivative **2** was not determined due to overlap of ^1H NMR signals of neighbouring methylene protons as well as that of alkenyl protons.[12] Acidolytic deprotection resulted in alkene derivatives in almost quantitative yields. Hydrogenation of the double bond was performed by heterogeneous catalysis under pressure (Scheme 1). All compounds were purified chromatographically, characterized in the form of their maleates (**3**,**4**) or oxalates (**5**-**8**), and gave satisfactory analytical results.

Scheme 1.



(a) i: $[Ph_3P\text{-}CH_2\text{-}CH_2\text{-}R]Br$, $KOC(CH_3)_3$, THF; 25-75%; ii: 6N HCl/acetone, reflux; 95%. (b) H_2 (10 bar), Pd/C (5%), MeOH; 95%.

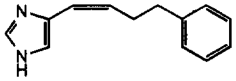
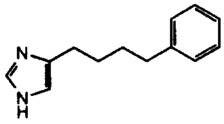
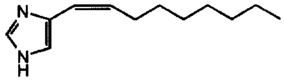
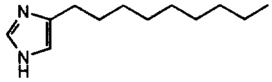
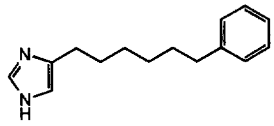
Pharmacology, Results, and Discussion.

Histamine H_3-Receptor *in Vitro* Assay on Synaptosomes of Rat Cerebral Cortex. The compounds were tested for their H_3-receptor antagonist activity in an assay with K^+-evoked depolarization-induced release of $[^3H]$histamine from synaptosomes of rat cerebral cortex according to Garbarg et al.[13] (Table 1).

Histamine H_3-Receptor Antagonist *in Vivo* Potency in Mice. Increase in N^{τ}-methylhistamine levels in Swiss mice brain 90 min after *p.o.* administration of the compounds was selected to screen histamine H_3-receptor antagonist *in vivo* activity[13] (Table 1). The ED_{50} values were calculated as mg free base • kg^{-1}.

Histamine H_1-, H_2-, and Muscarinic M_3-Receptor *in Vitro* Activity on Isolated Organs of Guinea Pig. Functional tests on guinea pig ileum for H_1- and M_3-receptors as well as on guinea pig atrium for H_2-receptor *in vitro* activity according to Ligneau et al.[14] were used to investigate selectivity.

Table 1. Histamine H_3-Receptor *in Vitro* and *in Vivo* Activity of Compounds **3**–**8**.

		Antagonist H_3-receptor activity	
Compound	Structure	*in vitro* K_i [nM] $(\bar{x} \pm s_{\bar{x}})$	*in vivo p.o.* ED_{50} [mg kg^{-1}] $(\bar{x} \pm s_{\bar{x}})$
3		> 500	> 10
4		56 ± 13	2.2 ± 0.7
5		> 500	8.6 ± 1.2
6		~ 400	3.7 ± 0.9
7		42 ± 13	0.61 ± 0.06
8		88 ± 24	1.0 ± 0.3
Thioperamide[a]		4 ± 1	1.0 ± 0.5
Clobenpropit[a]		0.6 ± 0.1	26 ± 7

(a) Ref.[9]

Histamine H_3-Receptor *in Vitro* Testing on Synaptosomes of Rat Cerebral Cortex. Compounds **3** and **5** possessing a (*Z*)-configured double bond in conjugation with the imidazole ring were devoid of any significant H_3-receptor affinity. Conjugation and electronic effects cannot be the reasons for this absence of interaction because very recently we have described a related (*E*)-configured derivative possessing moderate *in vitro* affinity.[15] More likely, the alignment of the linker and the lipophilic group with compounds **3** and **5** is sterically not favourable. An improved receptor-ligand interaction can be concluded for the phenyl derivatives **4**, **7**, and **8**. Whereas it may be possible to state for compound **7** that the double bond in the middle of the molecule mimics the polar group, it is clear that compounds **4** and **8** are devoid of such a structural element. Although compound **7** possessed slightly higher H_3-receptor potency, **4** and **8** were also H_3-receptor antagonists with remarkable affinity.

It might be speculated that the elements of the general construction pattern formerly thought to be essential were based on two essential interaction areas. By introducing another binding partner with the lipophilic moiety the resulting receptor-ligand interaction may be strong enough to omit the polar group maintaining affinity. Consequently it was shown that the polar group is not essential for antagonist H_3-receptor interaction, but by comparison of **7** and **8** this element increases affinity. By these data a three point-interaction model is suggested requiring two interaction points at least.

Histamine H_3-receptor *in Vivo* Testing in Mice Brain after *p.o.* Administration. The results for the phenyl compounds *in vivo* were in good agreement with their *in vitro* data. Although the *in vitro* potency for all compounds is more than one log-unit less than that for thioperamide, the novel highly lipophilic compounds might easily penetrate the blood-brain barrier presenting thus low ED_{50}-values. Whereas **8** was equipotent to the reference antagonist thioperamide, compound **7** was even more potent. (4-(6-Phenyl-3-hexen-1-yl)-1*H*-imidazole (**7**) is one of the compounds with the highest central *in vivo* potency reported. It serves as a novel lead for further optimization, which is currently under progress[16].

The *in vivo* results for **5** and **6** are very astonishing. Although these compounds were almost inactive *in vitro* at H_3-receptors, they enhanced *in vivo* the concentration of N^{τ}-methylhistamine in brain. It cannot be excluded that the *in vivo* screening model can also detect additional effects able to apparently enhance the turnover of histamine, as shown by an increased concentration of its main metabolite in the assay. So far, H_3-receptor blockade appears as the sole pharmacological approach to enhance brain histamine turnover[17,18], but additional studies are required to clarify the mode of action of these compounds *in vivo*.

Compounds **3** and **4** were also tested *in vitro* at H_1-, H_2, and M_3-receptors to investigate if any of these related systems may be responsible for unpredictable *in vivo* activity. The activity found was below 5.5 (pD_2'-value) showing in each case that none of these receptors had influenced the H_3-receptor *in vivo* activity measured.

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11. ^{1}H NMR data (300 MHz, DMSO-D$_6$): **$3\cdot C_4H_4O_4$** 8.91 (s, 1H, imidazole-2-H), 7.59 (s, 1H, imidazole-5-H), 7.24 (m, 5H, 5phenyl-H), 6.26 (d, J_{cis} = 12 Hz, 1H, imidazole-CH), 6.13 (s, 2H, maleic acid), 5.90 (m, 1H, imidazole-$CH=C\underline{H}$), 2.77 (t, J = 7.4 Hz, 2H, phenyl-CH_2), 2.59 (m, 2H, phenyl-CH_2-$C\underline{H}_2$); **$5\cdot C_2H_2O_4$** 8.31 (s, 1H, imidazole-2-H), 7.33 (s, 1H, imidazole-5-H), 6.24 (d, J_{cis} = 11.5 Hz, 1H, imidazole-CH), 5.68 (m, 1H, imidazole-$CH=C\underline{H}$), 2.31 (m, 2H, $=CH$-$C\underline{H}_2$), 1.41-1.25 (m, 10H, 5CH_2), 0.84 (m, 3H, CH_3).
12. ^{1}H NMR data (300 MHz, DMSO-D$_6$): **$7\cdot C_2H_2O_4$** 8.40 (s, 1H, imidazole-2-H), 7.29-7.14 (m, 6H, imidazole-5-H, 5phenyl-H), 5.36 (m, 2H, CH=CH), 2.57-2.23 (m, under solvent, 8H, 4CH_2).
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