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TWO NOVEL, POTENT AND SELECTIVE HISTAMINE H_3 RECEPTOR AGONISTS

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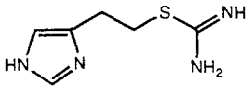
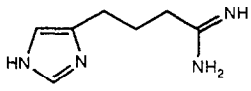
Abstract: S-[2-(4-(5)-imidazoyl)ethyl]isothiourea (**1**) and 4-(4-(5)-imidazoyl)butyramidine (**2**) were shown to be potent H_3 agonists on the guinea-pig ileum with very little activity on H_1 and H_2 receptor preparations.

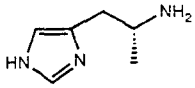
Histamine receptors have been classified into two main subtypes, H_1 and H_2, on the basis of quantitative studies in isolated tissues.[1] However, Arrang et al[2] showed that histamine inhibits its own release from depolarized slices of rat cerebral cortex, an action apparently mediated by a class of receptor (H_3) pharmacologically distinct from H_1 and H_2 receptors. Since then, studies[3] have confirmed the existence of this autoreceptor and have characterized its pharmacological properties. Ligands specific for the H_3 receptor have been synthesized, these include the agonist (R)-α-methylhistamine (**3**)[4] and antagonist thioperamide (**4**).[5] There are very few potent and selective H_3 receptor agonists. Here we report the biological activity of two such compounds.



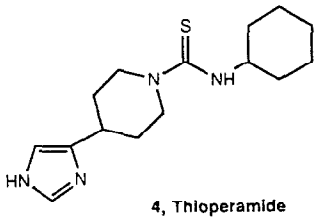
1, SK&F 91105



2, SK&F 91606



3, (R)-α-Me His



4, Thioperamide

The reported[2] higher H_3 receptor activity of Nα,Nα dimethylhistamine compared to histamine suggested that other bulkier positively charged groups might be tolerated in place of the 1° amine. Examination of a range of such compounds led to the following conclusions. That the distance between the imidazole ring and planar positively charged moiety is crucial in terms of potency and type of functional activity, with 3 atoms between the imidazole ring and Sp^2 hybridized C-atom being optimal. Also the basic moiety should

have a pKa<13 otherwise weak antagonists are obtained. This study resulted in the identification of compounds **1** and **2**.[6]

The H_3 receptor agonist activity of these compounds was assessed by their inhibition of the electrically evoked twitch response of the guinea-pig ileum. For **1** and **2**, IC_{50} values obtained were 4.6 and 1.1 nM respectively, while (R)-α-methylhistamine caused a similar effect with an IC_{50} = 6.0 nM. The maximum responses for each agonist were similar and all could be antagonized by thioperamide.
On H_1 and H_2 preparations,[8] the guinea-pig ileum and atrium respectively, **1** and **2** produced no significant effect up to a concentration of 10^{-5}M.

These data indicate that **1** and **2** are highly potent and selective histamine H_3 receptor agonists, being 10,000 times more potent at the H_3 receptor than at either the H_1 or H_2 receptor. Compound **2** is the most potent H_3 agonist known to date.

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