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Research paper

Structural modifications in the distal, regulatory region of histamine H_3 receptor antagonists leading to the identification of a potent anti-obesity agent

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ABSTRACT

A series of 4-pyridylpiperazine derivatives with varying regulatory region substituents proved to be potent histamine H_3 receptor (H_3R) ligands in the nanomolar concentration range. The most influential modification that affected the affinity toward the H_3R appeared by introducing electron-withdrawing moieties into the distal aromatic ring. In order to finally discuss the influence of the characteristic 4-pyridylpiperazine moiety on H_3R affinity, two Ciproxifan analogues **2** and **3** with a slight modification in their basic part were obtained. The replacement of piperazine in **3** with piperidine in compound **2**, led to slightly reduced affinity towards the H_3R (K_i = 3.17 and 7.70 nM, respectively). In fact, **3** showed the highest antagonistic properties among all compounds in this series, hence affirming our previous assumptions, that the 4-pyridylpiperazine moiety is the key element for suitable interaction with the human histamine H_3 receptor. While its structural replacement to piperidine is also tolerated for H_3R binding, the heteroaromatic 4-pyridyl moiety seems to be essential for proper ligand-receptor interaction. The putative protein-ligand interactions responsible for their high affinity were demonstrated using molecular modeling techniques. Furthermore, selectivity, intrinsic activity at the H_3R, as well as drug-like properties of ligands were evaluated using *in vitro* methods. Moreover, pharmacological *in vivo* test results of compound **9** (structural analogue of Abbott's A-331440) clearly indicate that it may affect the amount of calories consumed, thus act as an anorectic compound.

1. Introduction

The histamine H_3 receptor (H_3R) has been pharmacologically discovered in 1983 as presynaptic autoreceptor [1] involved in a negative feedback modulation of histamine synthesis and inhibition of its release from histaminergic neurons [1]. On the other hand, as postsynaptic H_3 heteroreceptors they also modulate the release of other neurotransmitters such as dopamine, acetylcholine, serotonin, norepinephrine, γ-aminobutyric acid, glutamate, substance P [2–4]. The H_3R is expressed predominantly in the central nervous system (CNS), especially in the regions associated with cognition, sleep, wakefulness and homeostatic regulation [5]. Regarding the distribution of the H_3R in the body combined with its regulatory impact on essential neurotransmitters, H_3R-inhibiting compounds (antagonists/inverse agonists) represent a highly attractive class of ligands in the search for new drugs.

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