

Histamine receptors in GtoPdb v.2025.3

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Abstract

Histamine receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Histamine Receptors [82, 176]**) are activated by the endogenous ligand [histamine](#). Marked species differences exist between histamine receptor orthologues [82]. The human and rat H₃ receptor genes are subject to significant splice variance [12]. The potency order of histamine at histamine receptor subtypes is H₃ = H₄ > H₂ > H₁ [176]. Some agonists at the human H₃ receptor display significant ligand bias [185]. Antagonists of all 4 histamine receptors have clinical uses: H₁ antagonists for allergies (*e.g.* [cetirizine](#)), H₂ antagonists for acid-reflux diseases (*e.g.* [ranitidine](#)), H₃ antagonists for narcolepsy (*e.g.* [pitolisant](#)/WAKIX; Registered) and H₄ antagonists for atopic dermatitis (*e.g.* [adriforant](#); Phase IIa) [176] and vestibular neuritis (AUV) (SENS-111 (Seliforant, previously UR-63325), entered and completed vestibular neuritis (AUV) Phase IIa efficacy and safety trials, respectively) [219, 8].

Histamine receptor photopharmacology has provided both agonist and antagonist tools to achieve optical control over H₃ receptor function. The best-characterized agonist is VUF15000, an azobenzene-containing compound in which the trans-isomer binds the H₃ receptor with nanomolar affinity (K_i = 4 nM) and behaves as a full agonist. Its cis-isomer is approximately 10-fold less active, thereby creating a reversible light-controlled switch for receptor activation that has been validated in binding, NanoBRET biosensor, and electrophysiology assays [78]. Also several photoswitchable antagonists have been established as tools for histamine H₃ receptor photopharmacology. The first-generation azobenzene-based antagonists included VUF14738 and VUF14862, which are part of a bidirectional toolbox [77]. VUF14738 (trans: K_i = 631 nM) shows a light-induced 10-fold increase in affinity, while VUF14862 (trans: K_i = 1.6 nM) displays the opposite, with more than a tenfold change upon illumination. Both compounds are highly fatigue-resistant, underwent rapid trans-cis isomerization, and had long thermal half-lives, allowing reversible optical control in binding and electrophysiological assays. Building on these scaffolds, recently 2nd generation ligands were developed to overcome limitations of azobenzenes [18]. The arylazopyrazole-based antagonist

VUF26063 displayed subnanomolar affinity at the H₃ receptor in its trans isomer (K_i = 0.5 nM) and a 50-fold lower affinity in the cis state. This compound showed robust switching with high photostationary state efficiency and improved aqueous solubility compared to earlier analogues. Importantly, radiolabeling yielded [³H]VUF26063, the first radiolabeled photoswitchable GPCR ligand, enabling the direct study of ligand binding kinetics and photoisomerization inside the receptor pocket in real time. These antagonists, together with the agonist VUF15000, provide a well-characterized toolkit of photosensitive ligands that can be used to dissect H₃ receptor pharmacology with spatiotemporal precision.

Contents

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Introduction to Histamine receptors

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Receptors

H₁ receptor

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H₂ receptor

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H₃ receptor

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H₄ receptor

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