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HISTAMINE SUBTYPE 3 RECEPTOR ANTAGONISTS: CURRENT STATUS WITH FUTURE PROSPECTS IN DRUG DISCOVERY AND DRUG DEVELOPMENT

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ABSTRACT: The histamine H3 receptor is an G protein-coupled receptor that regulates neurotransmission in the central nervous system and plays a major role in cognitive and homeostatic functions. The third histamine receptor was discovered in 1983 by a traditional pharmacological approach, consisting of assessing the inhibitory effect of histamine on its own release from depolarized rat brain slices. Histamine H3 receptors are found mostly in central nervous system also to some extent in peripheral tissues and involved in the regulation of release of various neurotransmitters in brain. They have been implicated in diverse potential therapeutic applications such as sleep wake disorders, attention-deficient hyperactivity disorder, epilepsy, cognitive impairment and obesity. This review is aimed to provide an overview of marketed preparations and also experimental H3 receptor antagonists under pipeline of drug discovery and development.

INTRODUCTION: Since histamine was first synthesized (1907) and isolated as a bacterial contaminant of an extract of ergot (1910), the elucidation of its role in health and disease and its molecular mechanism of action have been continuous, reflecting the application of advances in scientific knowledge, technology and therapeutics over the last 100 years. It is produced by decarboxyalation of histidine and it has wide range of physiological and pathophysiological functions in body. Its biological actions are mediated via four histamine receptors named H_1, H_2, H_3, and H_4, a classification based on their sequence, their link to differential intracellular signaling mechanisms, and their unique pharmacological.

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The H1 and H2 receptor are druggable targets as indicated by the efficacy of these antagonists in the treatment of allergy and ulcers, respectively. Furthermore, first-and second-generation therapeutics directed at the H1 histamine receptor (H1R) have long been the front-line drugs in the treatment of allergic rhinitis. [1] H_2R antagonists block H^+ secretion in parietal cells of the stomach and provided the first effective drug for the treatment of gastroduodenal ulcer and gastroesophageal reflux disease.[2] The full-length human and rat H3 receptor is made up of 445 amino acids; however, at least 20 human and nine rat H3 receptor mRNA isoforms resulting from alternative splicing of the receptor gene have been identified.

Truncations of the third intracellular loop, variations in the amino and carboxyl termini and deletions of transmembrane domains account for the number and diversity of H3 receptor isoforms. At least eight human and three rat isoforms are functionally active, showing binding and/or

signalling activity when expressed in recombinant cell sytems.[3]

Through H_3 heteroreceptors, modulates the release of a wide spectrum of vital neurotransmitters, for example, GABA, glutamate, dopamine, 5-HT, nor-adrenaline and acetylcholine, in a pathway-dependent manner. [4-5] Extensive preclinical data with histamine H_3 receptor antagonists support their potential utility for the treatment of human cognitive disorders.

The discovery of potent and selective H3 antagonists have overcome many of the liabilities of earlier antagonists, confirmed the preclinical data obtained with early agents, and significantly expanded our knowledge in this area. In several models of nociception, including acute mechanical triggering (eg, hot plate contact) or chemical-induced responses (eg, formalin induced), H_3R blockers (antagonists and inverse agonists) have been proposed to modulate pain sensitivity. [6] The present review will outline the current knowledge on the marketed preparations and the several molecules under clinical trials of H_3R antagonists. Very recently, a novel subtype was added to the histamine receptor family, namely the H_4 receptor that was cloned by several laboratories by screening the human genome databases. [7-8]

This new receptor subtype belongs to the G-protein-coupled receptors and was found to be highly expressed in the human bone marrow and, at moderate levels, also in the human colon. In bronchial asthma, H_1R antagonists are ineffective, but the results of mouse studies suggest that H_4R antagonists could be useful in the treatment of asthma. [9-10] Due to the lack of selective agonists and antagonists; however, the functional role of H4 receptors is still obscure.

TABLE 1. MAJOR HISTORICAL CHANGES DURING ONE HUNDRED YEARS OF HISTAMINE RESEARCH

S.NO	YEAR	MAJOR HISTORICAL CHANGES
1.	1907	Synthesis of histamine
2.	1910	Isolation of histamine as an extract of ergot (Barger and Dale)
3.	1936	Development of compounds shown to block the action of histamine (Bovet and Straub)
4.	1940s	Characterization of histamine antagonists through their interaction with the cell surface receptors (Well, Felkow)
5.	1960s	Differentiation of histamine receptors based on different affinity estimates for the antagonist pyrilamine in two different tissues. Two histamine receptors defined as H_1 and H_2 (Tredelenburg)
6.	1964	Initiation of development of first H_2 selective antagonist at Smith , Kline and French , work from this endeavour produced Tagamet™ for the treatment of heart burn and peptic ulcer (Black and Ganellin)
7.	1973	cAMP defined as a second messenger of H_2 receptor (Karppanen and Westermann)
8.	1983	First pharmacological description of third histamine receptor (Arrang)
9.	1996	First description of a fourth histamine receptor (Raible)
10.	1991	Cloning of the first histamine receptor, Canine H_2 (Gantz)
11.	2000	Generation of first knock-out mouse of the H_2receptor (Kobayashi)

Histamine H3 Receptor Pharmacology

The histamine H_3 receptor was first described in 1983 as an autoreceptor that regulated histamine release, and 16 years later the DNA sequence was elucidated, structurally confirming it as a member of the G protein-coupled receptor family. This receptor exhibits highest homology (~60% in the transmembrane domains) to the H4 receptor but much lower homology (~20%) to the H_1 and H_2 receptors. In the time since its cloning there has been considerable advancement in our knowledge about H_3 receptor molecular properties that have been described in detail previously[11]. Histamine H_3 receptor (H_3R) antagonists/inverse agonists have revealed potential to treat diverse disease states of the central nervous system (CNS) including Alzheimer's disease (AD), attention-deficit hyperactivity syndrome (ADHD), schizophrenia, obesity, pain, epilepsy, narcolepsy, substance abuse, etc. [12-13]

Though there is no direct pathophysiological mechanism linking any disease condition of the CNS with histamine, the distinct localization of H_3Rs in the CNS coupled with the fact that it modulates the release of other neurotransmitters in

the brain via its action on heteroreceptors on non-histaminergic neurons led to evaluation of its ligands in various brain diseases **(Table 1)**. [14] Central histaminergic fibres originating from the TMN in the posterior hypothalamus widely projects into different brain areas including the cerebral cortex, thalamus, basal ganglia, amygdala, and hippocampus, where histamine is crucially associated with a large number of basic physiological functions including sensory and motor functions, cognition, attention, learning, and memory. [5] Blockade of human H_3 autoreceptor by thioperamide evokes the increase of the neuronal histamine release.[15]

In peripheral tissues, H_3 receptors are expressed in neuro-endocrine organs and regulate their functions. For example, the activation of H_3 receptors inhibited the release of adrenocorticotropic hormone and prolactin from the pituitary gland and of histamine from enterochromaffin-like cells and histamine also release from cerebral neurones in rat cortex. The full-length human and rat H3 receptor is composed of 445 amino acids; however, at least 20 human and nine rat H_3 receptor mRNA isoforms resulting from alternative splicing of the receptor gene have been identified. At least eight human and three rat isoforms are functionally active, demonstrating binding and/or signalling activity when expressed in recombinant cell systems. [11, 16] An interesting characteristic of the H_3 receptor is its ability to transduce signalling in the absence of agonist activation, thus demonstrating inherent constitutive activity. [17]

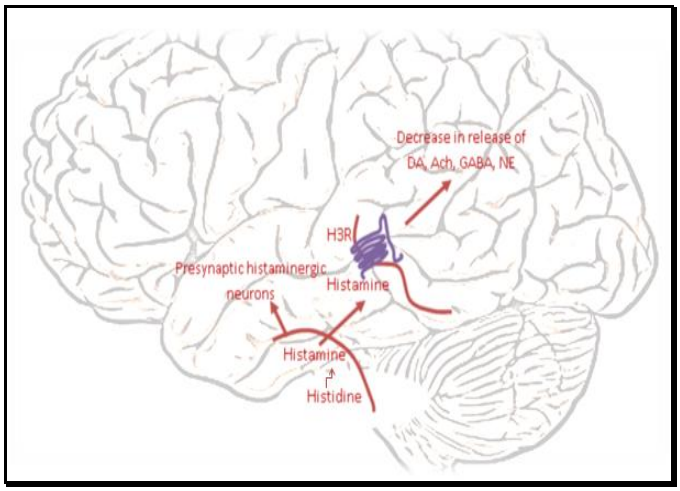


FIGURE 1: H_3R RECEPTOR FUNCTION IN CENTRAL NERVOUS SYSTEM

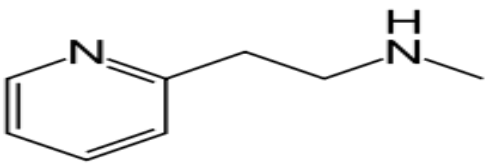
An interesting characteristic of the H_3 receptor is its ability to transduce signalling in the absence of agonist activation, thus demonstrating inherent constitutive activity. By definition, all H3 antagonists block the activity of endogenous histamine.

Downstream signalling of Histamine subtype 3 Receptors

Tremendous effort was made to identify H_3Rs, but their molecular profiles remained unknown for a decade. In the late 1990s, several groups identified the genes encoding H_3Rs and clarified their molecular profiles. Activation of the H_3 receptor, coupled to Gαi/o proteins, engages a number of intracellular signalling mechanisms, including the inhibition of adenylate cyclase, activation of mitogen-activated protein kinase (MAPK), and inhibition of the Na^+/H^+ exchange.

Further studies have shown that several splicing variants are present in humans, rats, mice, and guinea pigs. A wide range of other H_3 receptor/Gαi/o-mediated signal transduction pathways have also been identified in recombinant cell systems that include activation of mitogen-activated protein kinase, glycogen synthase kinase 3β (GSK3β), Akt, and phospholipase A2, as well as inhibition of adenylate cyclase and the Na^+/H^+ exchanger. [18]

Marketed Preparations of H_3R Antagonist Betahistine



Betahistine (N-methyl-2-pyridylethylamine), a histamine-like substance, was introduced as an active drug in the treatment of certain vascular and vasomotor disorders. Betahistine to treat severe motion intolerance. [19] Betahistine is one of the drugs currently prescribed in patients with vestibular loss for their symptomatic treatment of vertigo, and especially in Ménière's patients. After headache, vertigo is one of the most frequent presenting symptoms to physicians in many disciplines, with a life-time prevalence of almost

30%. Meniere's disease is characterized by recurrent spontaneous attacks of vertigo, fluctuating hearing loss, tinnitus, and aural fullness. Its incidence varies between 7.5 per 100,000 and 160 per 100,000 persons. Betahistine is an H_1-agonist and H_3-antagonist.

It improves the labyrinthine microcirculation by acting on the precapillary sphincters of the stria vascularis. Its activity may be explained by its direct action on histamine receptors on which, betahistine has a complex action: as a partial agonist of postsynaptic H_1 and H_2 receptor [20] and as an antagonist of presynaptic H_3 receptors. Animal studies show clearly that betahistine does not interfere with vestibular adaptation in the way that drugs with sedative effects do. Recently, betahistine were found to decrease the electrical discharge of afferents neurons in the axolotl by interfering with the postsynaptic response to excitatory amino acid agonists.

Despite reservations over the clinical efficacy of Betahistine, restricting its use to only patients with true Meniere's would save over £4000000 per annum. Betahistine comes in both a tablet form as well as an oral solution, and is taken orally. Data provided by the Prescription Pricing Authority reveal that 113 000 prescriptions for Betahistine are currently being filled each month in England. Betahistine can be used in children. [21] While claims have been made that Betahistine is associated with weight loss, these appear to be unfounded. [22]

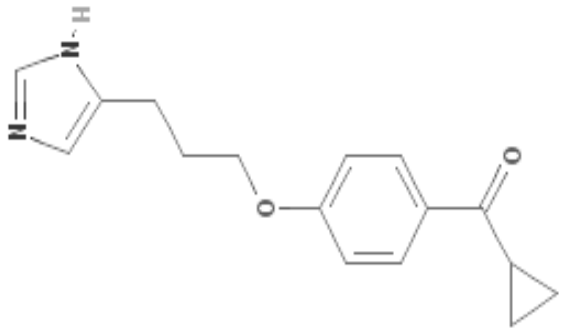
Safety and tolerability

Adverse events appear to be rare during betahistine therapy, mild skin reactions are the most common and epigastric upset is reported occasionally. Betahistine is contraindicated for people with pheochromocytoma. People with bronchial asthma and history of peptic ulcer need to be closely monitored.

Some has encountered stomach upset in several, worsening asthma, headache. [22] Although formal safety and tolerability studies have not been undertaken to modern standards the drug has been used for many decades and tens of millions of patients have been exposed without significant safety or tolerability concerns having arisen.

Molecules under investigation and pipeline of Drug Discovery and Development

Ciproxifan



Also known as: FUB-359, cyclopropyl - [4-[3-(1H-imidazol-5-yl) propoxy] phenyl] methanone, 184025-18-1, AC1O4Y0P, SureCN3335184, CHEMBL14638, FUB359;

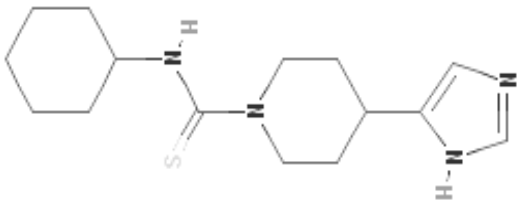
Molecular Formula: $C_{16}H_{18}N_2O_2$

Molecular Weight: 270.32632

Ciproxifan is an imidazole-containing compound that was originally described as a potent antagonist at histamine H_3 receptors, and it remains a useful tool for disseminating the role of H_3 receptors in behavior and brain function. *In -vitro,* it behaved as a competitive antagonist at the H_3 autoreceptor controlling $^{[3H]}$ histamine release from synaptosomes and displayed similar *Ki* values (0.5-1.9 nM) at the H^3 receptor controlling the electrically-induced contraction of guinea pig ileum or at the brain H3 receptor labelled with $^{[125I]}$ iodoproxyfan has been shown to act as an H3-receptor antagonist also in the mouse brain in vivo (ED50 after oral application 0.14mg/kg)[3]. Ciproxifan's efficacy is related to its ability to enhance neurotransmitter release in the frontal cortex and hippocampus, and to generate electrophysiological activity predictive of learning.

In rats, ciproxifan enhanced attention as evaluated in the five-choice task performed using a short stimulus duration. [23] Ciproxifan increasing swim speed in the swim maze, although no such effect has been seen with another H_3R Antagonist.[24] Ciproxifan appears to be an orally bioavailable whose vigilance- and attention-promoting effects are promising for therapeutic applications in aging disorders.

Thioperamide



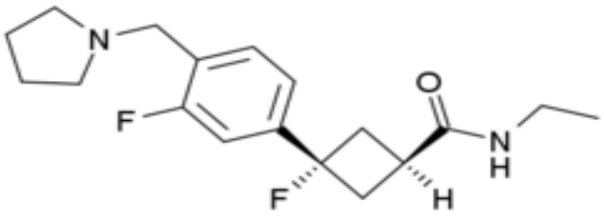
Also known as: MR 12842, N-Cyclohexy-4-(imidazol-4-yl)-1-piperidinecarbothioamide, 106243-16-7;

Molecular Formula: $C_{15}H_{24}N_4S$ **Molecular Weight:** 292.44286

H_3 antagonist, thioperamide, is a potent competitor of histamine binding to low affinity microsomal Hc; in adrenal microsomes at least some proportion of the microsomal binding sites represents P450 enzymes; and inhibition of adrenalsteroidogenesis is a prominent pharmacological response to thioperamide. Also, in adrenocortical microsomes, low affinity binding of [3H] histamine (KD 27.7 microM) was potently inhibited by TP (Ki 0.33 microM).

Thioperamide was developed as first potent selective H3R antagonist and later clobenpropit was discovered as inverse agonist. Recently, the presynaptic histamine H3 receptor has become the subject of much attention, since blockade of this receptor enhances attention and cognition across multiple animal models. thioperamide also supressed feeding and depletion of endogenous HA exerts feeding response. [25] *In -vivo*, blockage of H3-receptors with thioperamide results in an augmented pressor response to foot shocks, i.e. facilitation of sympathetic activity.

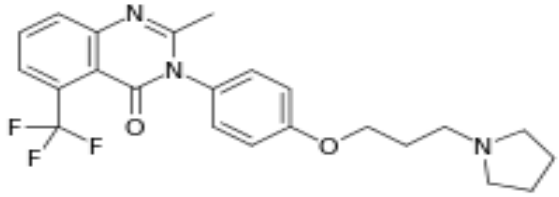
PF-03654746



IUPAC name- (1*R*, 3*R*)-*N*-ethyl-3-fluoro-3-[3-fluoro - 4 - (pyrrolidin-1-ylmethyl) phenyl] - cyclobutane-1-carboxamide)

Pfizer compound PF-03654746 showed good affinity as H3R antagonist. This compound enhanced the release of histamine in rat prefrontal cortex. It was developed from compound by optimizing the physiological properties to avoid phospolipidosis which was observed with early analogs. On the basis of favourable results when it was given in adults With Attention Deficit Hyperactivity Disorder, it entered the Phase II clinical trials but later discontinued due to insomia produced as side effect. [26]

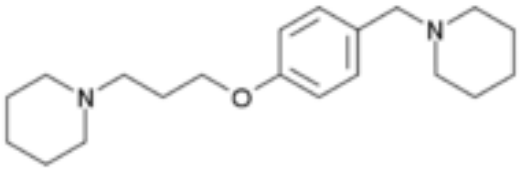
MK0249



IUPAC name- 2-Methyl-3-[4-(3-pyrrolidin-1-ylpropoxy) phenyl]-5-(trifluoromethyl) quinazolin - 4-one

The compound MK0249 was developed by Merck as a H3R antagonist.[31] It showed improved cognitive performance in patients with Alzheimer's Disease and Dementia. MK-0249 (NCT-ID NCT00475735) has completed phase II clinical trials for ADHD but the results are still awaited in public domain.[27-28]

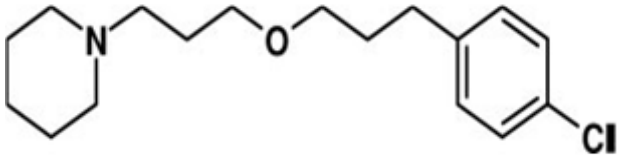
JNJ-17216498



IUPAC name- 1- {3-[4-(Piperidin – 1 -ylmethyl) phenoxy] propyl} piperidine

The compound also showed good activity at H3 receptor as antagonist. This study with a new, experimental drug was done to assess safety and tolerability, and to explore effectiveness in the treatment of narcolepsy. Later on after successfully completing Phase I and Phase II clinical trials clinical this molecule currently is in Phase III clinical trials. [29]

BF2.649

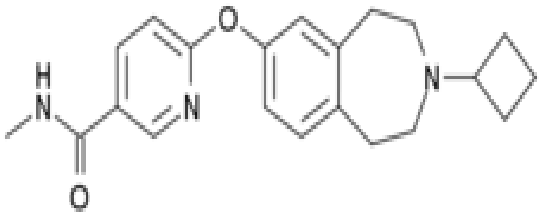


IUPAC name- 1 - {3- [3-(4-Chlorophenyl) propoxy] propyl} piperidine, hydrochloride

BF2.049 is a piperidinylpropoxyalkylphenyl H_3 antagonist that exhibits potent binding to the rat ($K_{i=}$2.7 nM) and mouse (K_i=14 nM) histamine H_3 receptors.[30-31] A study in narcoleptic patients demonstrated that the H3 antagonist BF2.649 (pitolisant, 40 mg every day for 7 days) produced a significant reduction in the number of diurnal sleep episodes, with efficacy equal in magnitude to the approved agent modafinil. [32]

BF2.649 also reduced the duration of the sleep episodes in narcoleptic patients. After 5 days of treatment BF2.649 was effective in both measures at 100 ng/ml plasma levels. BF2.649 also decreased excessive sleepiness in patients with Parkinson's disease, and phase 3 trials are ongoing (5- to 40-mg doses).

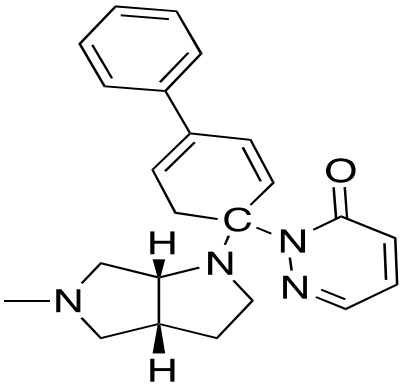
GSK189254



IUPAC name- 6- [(3-Cyclobutyl-2, 3, 4, 5-tetrahydro-1H-3-benzazepin-7-yl) oxy]-N-methyl-3-pyridinecarboxamide

GSK189254 is a potent H3 antagonist (human H3 *K*i = 0.2nM) with broad spectrum efficacy in a number of rodent models of cognition and narcolepsy. [33] GSK189254 increased ACh, NE, and DA as measured with the help of microdialysis. But later on this study was terminated at Phase II clinical trials.

ABT-288



IUPAC name 2-[4_-((3*aR*, 6*aR*)-5-methyl-hexahydro-pyrrolo [3, 4-*b*]pyrrol-1-yl)-biphenyl-4-yl]-2*H*-pyridazin-3-one

Abbott's molecule ABT-288, a potent and selective H3 antagonist that binds to rat and human H3 receptors with *K*i = 8.1 and 1.9 nM, respectively. [34-35] ABT 288 increased the release of histamine and ACh from the rat cortex and facilitates performance in attention, short-term memory, and long-term memory tests. The compound penetrated the CNS efficiently and effectively occupied rat H3 receptors with ED_{50} = 3.2ng/ml. Recently the study has been going on with this molecule in Phase III clinical trials. [36-37]

CONCLUSIONS: Brain histamine plays an important role in various CNS disorders. There has been considerable progress made in our understanding of the complex biology and properties of the H_3 receptor that has correspondingly led to an increased interest in developing H_3 antagonists to treat cognitive disorders. H3R antagonists/inverse agonists, through H3 heteroreceptors, enhance the release of various important central neurotransmitters in brain such as dopamine, gamma amino butyric acid, serotonin etc.

Therefore, their role in epilepsy, schizophrenia, ADHD, narcolepsy and other central nervous system disorders is being explored. H3 antagonists may also bring another exciting biochemical effect by increasing the phosphorylation of key intracellular proteins that play a role in the neurodegenerative process. The broad spectrum of activities of H_3R antagonists continues to expand as more and more novel therapeutic roles have been investigated including Parkinson's disease,

multiple sclerosis, cerebral ischemia, depression, etc., and hence identification of potential clinical targets. The different clinical studies presently ongoing to test the efficacy of H_3 antagonists in these human conditions may be able to provide an answer to these hypotheses and determine the place for H_3 antagonists in therapeutics.

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