Medicinal Chemical and Pharmacological Aspects of Imidazole-Containing Histamine H_3 Receptor Antagonists

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Abstract: The first antagonists known for the histamine H_3 receptor were mono-substituted imidazole-containing compounds like thioperamide. Meanwhile numerous novel leads have been developed possessing improved affinities, selectivities, specificities, and pharmacokinetic properties. Scope and limitations of this promising class are discussed concerning their structure-activity relationships as well as pharmacological and potential therapeutic aspects.

Keywords: Cipralisant; Ciproxifan; Clobenpropit; H_3 Receptor; Imidazole; SCH 79687, Radioligand; Thioperamide.

INTRODUCTION

Within the last century histamine receptor subtypes have continuously branched out. The actual current knowledge on histamine receptors is based on four cloned receptors subtypes. The third histamine receptor, described for the first time about 20 years ago [1,2], which was named H_3, is involved in the modulation of the release of various transmitters and mediators. Meanwhile numerous new findings on ligands as well on (patho)physiological functions led to several potential therapeutic applications as well as potential drugs for the market. In this review article we focus on imidazole-containing antagonists and pharmacological findings mostly based on the use of these antagonists.

Within the last years some recommendable reviews have been published, which give excellent overviews on historical as well as on recent and actual compound developments [3-16], which should not be rephrased here. This report puts emphasis on the most prominent drug developments and pharmacological findings in this field within the last two decades.

PHARMACOLOGICAL ASPECTS

Histamine H_3 receptors occur on neurons and paracrine cells. Neuronal H_3 receptors inhibit transmitter synthesis as well as exocytotic and carrier-mediated transmitter release. An inhibitory effect on *synthesis* appears to be restricted to histamine [17,18] whereas inhibition of action potential-driven, Ca^{2+}-dependent *exocytotic* transmitter release has been shown for histaminergic and non-histaminergic neurons (Fig. **1**); the receptors involved are termed presynaptic H_3 auto- and heteroreceptors, respectively. These receptors are inhibitorily coupled to high voltage-activated Ca^{2+} currents [9]. Presynaptic H_3 receptors, which inhibit histamine release and the release of other transmitters like γ-aminobutyric acid (GABA), glutamate, noradrenaline, serotonin, and dopamine have been identified in a series of brain regions [11,13,19,20]. Neuronal H_3 receptors also occur in the peripheral nervous system, in particular in the cardiovascular, gastrointestinal and bronchial system. They inhibit noradrenaline release in the cardiovascular system, thereby interfering with the positive inotropic and chronotropic effect in the heart and with the pressor effect in blood vessels [21,22]. In the gastrointestinal [23-25] and bronchial tract [26], H_3 receptors inhibit the release of acetylcholine and neuropeptides (substance P and calcitonin gene-related peptide (CGRP)). The consequence is, that at least under some circumstances, gastric acid output and gastrointestinal contractility as well as bronchoconstriction are inhibited following H_3 receptor activation. H_3 receptors also inhibit *carrier-mediated* transmitter release but this has so far been shown for one transmitter (noradrenaline) and one tissue (heart) only (Fig. **1**) [21,22]. These receptors are probably inhibitorily coupled to the Na^+/H^+ exchanger [27] and evidence for their relevance has been provided recently since lack of H_3 receptors markedly increased noradrenaline release in the hypoxic heart [28].

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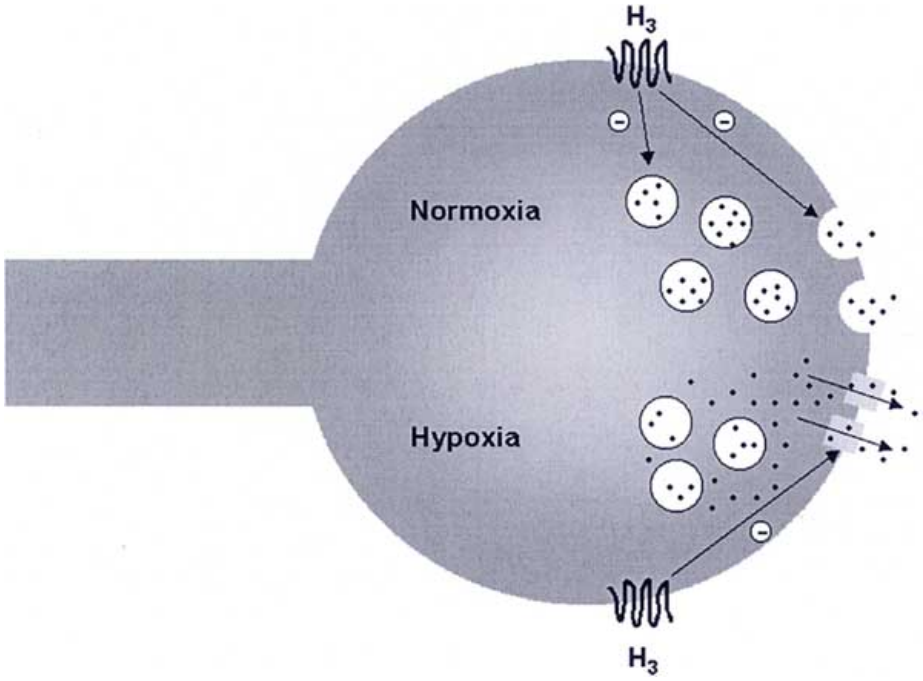

Fig. (1). Presynaptic H_3 receptors. H_3 receptors inhibit transmitter synthesis in *histaminergic* neurons (upper left arrow). Second, they inhibit the action potential-driven, exocytotic release of *various transmitters* in the brain and the peripheral nervous system (upper right arrow). Third, they inhibit carrier-mediated transmitter release in cardiac *noradrenergic* neurons (lower half of the drawing). Carrier-mediated release occurs under hypoxia when the neuronal amine transporter, usually accumulating the amine, operates in the reverse direction.

Histamine H_3 receptors are present also on *paracrine cells*, including enterochromaffin and enterochromaffin-like cells where they inhibit serotonin and histamine release, respectively [29,30]. H_3 receptors causing inhibition of the release of histamine, serotonin, and tumour necrosis factor alpha (TNFα) from mast cells have also been identified [31-34] but this is not a general phenomenon [34,35]. In some tissues, H_3 receptors are not located on mast cells themselves but on sensory nerve endings forming contacts with mast cells, thus forming a short feedback loop. In detail, histamine released from mast cells inhibits the release of neuropeptides from sensory neurons via H_3 receptors; the neuropeptides, in turn, increase histamine release from mast cells [36-38]. There is some evidence that H_3 receptors also occur on other locations [6]. In general, a postsynaptic location, as opposed to the well-established presynaptic one, seems not typical for this receptor.

Can human histamine H_3 receptors, which have been cloned recently [39], also be identified in functional models of human tissues and cells? This is indeed the case and a list of functional H_3 receptors in humans that is provided in Table **1**. One should consider, however, that with respect to H_3 receptors quantitative or even qualitative differences may exist between humans and animals, e.g., noradrenaline release in cerebral cortex slices is inhibited to a much lower extent in the human than in the mouse brain [41]. Moreover, H_3 receptors markedly inhibit gastrointestinal contractility in some animals but are essentially devoid of such effects in human gastrointestinal tissues [24]. Based on *in vitro* and *in vivo* experiments on animals and on experiments on human tissues, a series of possible indications for H_3 receptor antagonists for use in humans has been proposed (Table **2**). It is of great interest that the H_3 receptor ligand cipralisant (GT-2331, **1**, Fig. **2**), developed by Gliatech, has recently been entered into a phase II clinical trial for the treatment of attention-deficit hyperactivity disorder (ADHD) [4,49].

The ability of histamine H_3 receptor antagonists to improve learning and memory will be discussed in more detail here since a large body of evidence related to this topic has been accumulated in recent years. H_3 receptor antagonists

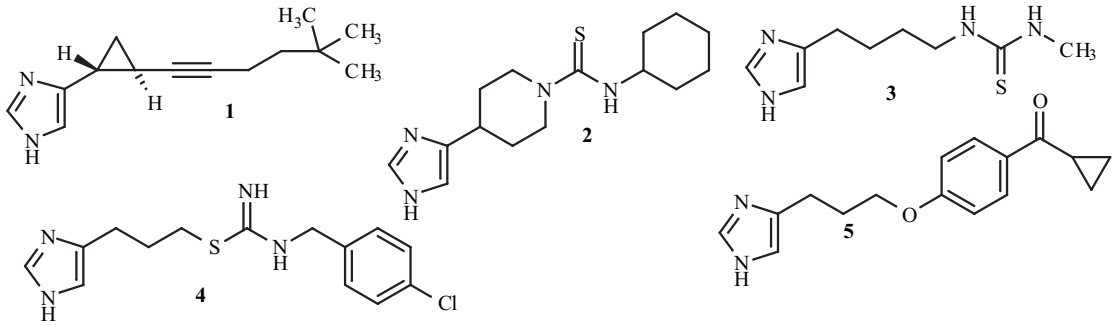

Fig. (2). First and reference histamine H_3 receptor antagonists.

have been shown to be procognitive or to have a beneficial effect in rodent models in which learning and memory: (*i*) have not yet fully developed, (*ii*) were impaired by drugs like diazepam or scopolamine; or (*iii*) were compromised on a genetic basis [11,12,50]. These data fit well to biochemical investigations in which a moderate to high concentration of H_3 receptors was found in brain regions like the hippocampus and the frontal cortex, which play a role in learning and memory [51-53]. Interesting enough, in H_3 receptor-deficient mice the amnesic effect of scopolamine was abolished [54]. But which neurotransmitters are involved in the beneficial effects of H_3 receptor antagonists on learning and memory? There are evidences from some studies that these drugs primarily act via H_3 receptors on histaminergic neurons. Blockade of the latter receptors increases histamine release and histamine, via H_1 receptors, has beneficial effects on learning and memory. This was proven by studies in which the effects of H_3 receptor antagonists were counteracted by blockade of H_1 receptors [11,50]. Since H_3 receptor blockade also increases acetylcholine release, this effect might contribute to the overall effect on learning and memory [55]. On the other hand, presynaptic H_3 receptors on serotonergic, noradrenergic, and dopaminergic neurons are probably not involved since blockade of these H_3 heteroreceptors does not affect the release of the respective neurotransmitter [19,50]. It would be an intriguing idea that H_3 receptor antagonists might become a new therapeutic tool for the treatment of diseases with cognitive decline, including Alzheimer's disease. The potential involvement of the histaminergic system in this disorder is suggested by clinical and pathological findings [56]. Thus, the histamine concentration in the cerebrospinal fluid and the post-mortem brain differs between patients suffering from Alzheimer's disease and controls. In the brain of patients with Alzheimer's disease, neurofibrillary tangles are concentrated in the tuberomammillary area and part of them also affects the histaminergic perikarya. Moreover, neurofibrillary tangles occur in high density close to cortically projecting histaminergic neurons.

When histamine H_3 receptor antagonists of different classes shall be synthesised, a series of points has to be taken into consideration. In this context, thioperamide (**2**) (Fig. **2**), the first selective H_3 receptor antagonist described [2], will be mentioned repeatedly since this drug has been thoroughly studied. First of all, H_3 receptor antagonists may have the disadvantage of offering a lower number of possible indications compared to H_3 receptor *agonists*. Note that agonists will inhibit transmitter or mediator release from all neurons and paracrine cells on which they are expressed whereas antagonists will increase release only when the corresponding H_3 receptors are (patho)physiologically "innervated". The other side of the coin will be that H_3 receptor antagonists would be expected to cause fewer H_3 receptor-related side effects than the corresponding agonists. With respect to the „innervation" of H_3 receptors, two scenarios have to be differentiated. Thus, endogenous histamine may accumulate in the biophase of H_3 receptors and the H_3 receptor antagonist will then act by competing with histamine for the H_3 receptor. Another possibility is that the H_3 receptors are constitutively active, i.e., the transduction machinery behind the receptor level is active although the receptor has not been activated by histamine. The latter scenario although typical for engineered cells expressing high quantities of a given receptor has recently been shown for transfected cells at physiological expression levels, for the native H_3 receptor in the mouse and rat brain *in vitro* and even for the mouse brain *in vivo* [57,58]. Differentiation between the two scenarios is very important since for the second scenario a compound is required "antagonising" the spontaneously active transduction machinery behind the level of the H_3 receptors, i.e., an *inverse agonist*. Thioperamide (**2**) as well as other antagonists have been identified as inverse H_3 receptor agonists [57]. For the first scenario, a drug devoid of any agonist and inverse agonist properties is required, i.e. a *neutral antagonist*. Although this differentiation is important, so far almost no information is available whether for this or that indication an inverse agonist or a neutral antagonist is more appropriate. It is much more difficult to find a neutral antagonist than an inverse agonist since neutral antagonism represents the (narrow) interface between agonism on the one and inverse agonism on the other hand. In this article, the traditional term "antagonist" will be used in most instances.

A second point to be considered is the fact that H_3 receptors show heterogeneity. Although this has been suggested many years ago on the basis of traditional

Species	*114* *119* *122*	*GenBank® accession numbers*
Rat	VVDYLLC**A**SS**V**FNI	Q9QYN8
Mouse	VVDYLLC**A**SS**V**FNI	P58406
Human	VVDYLLC**T**SS**A**FNI	AF140538
Monkey	VVDYLLC**T**SS**A**FNI	AAO63757
Guinea-pig	VVDYLLC**T**SS**V**FNI	Q9JI35
Dog	VVDYLLC**T**SS**V**FNI	AAO63755

Fig. (3). *N*-Terminal portion of the transmembrane region 3 (TM III) of the rat H_3 receptor and homologous sequences from another five mammalian species. The two amino acid residues 119 and 122 (underlined) appear to be responsible for the distinct pharmacology of the H_3 receptor in these species. Note that these amino acid residues are close to the aspartic acid residue in position 114 that is conserved in all G protein-coupled aminergic receptors. The relevance of the latter amino acid and of the amino acid in position 119 is also highlighted by the modelling study shown in Fig. (**5**).

Table 1. Native histamine H_3 receptors in Human Tissues

Location		Effect	Endogenous tone	Ref.
Brain	Cerebral cortex	Inhibition of *exocytotic* histamine release	Yes	40
	Cerebral cortex and hippocampus	Inhibition of *exocytotic* noradrenaline release	No	41
Cardiovascular system	Heart	Inhibition of *exocytotic* noradrenaline release	No	42
		Inhibition of *carrier-mediated* noradrenaline release	Yes	43
	Saphenous vein	Inhibition of *exocytotic* noradrenaline release	No	44
Bronchial system	Bronchi	Inhibition of *exocytotic* acetylcholine release[1]	ND[2]	45
Gastrointestinal system	Stomach (antrum)	Inhibition of *exocytotic* somatostatin release	Yes	46
Immune system	Alveolar macrophages	Stimulation of interleukin-10 secretion and inhibition of the release of tumor necrosis factor	ND	47
	Immature dendritic cells	Chemotaxis	ND	48
	Mature dendritic cells	Stimulation of interleukin-10 secretion and inhibition of the release of interleukin-12	ND	48

[1]Acetylcholine release has not been determined directly but via the (acetylcholine-induced) endorgan response.
[2]Not determined, i.e. the data do not allow the conclusion whether there is an endogenous tone or not.

pharmacological studies [6,15], a more precise picture was obtained when the H_3 receptors were cloned [15,39,59,60]. Thus, the H_3 receptor from humans [61-63] and other species [64-66] appears in isoforms, which are the result of an alternative splicing and show a different pattern of distribution in the brain [61,64]. It would be a fascinating idea to have histamine H_3 receptor antagonists with preference for the single isoforms. When the H_3 receptors from different species were cloned, it became apparent that two amino acid residues are of utmost importance for the pharmacological properties, namely the amino acids in position 119 and 122 of the human and rat H_3 receptor (Fig. **3**). The replacement of the amino acid in position 122 (H_3 receptor of the dog and guinea pig) and, in addition, in position 119 (H_3 receptor of the rat and mouse) strongly affects the affinities of a series of ligands, e.g., the affinity of thioperamide is 14-fold lower at the human when compared to the rat H_3 receptor [67]. The affinity of clozapine is also decreased [67] and the suggestion that the moderate affinity of this compound for H_3 receptors (based on experiments in rat and mouse tissues) might contribute to the unique clinical profile of this neuroleptic [68,69] is no longer appropriate. The marked differences in H_3 receptor pharmacology between humans and rodents question the use of rodent tissues to screen newly synthesised H_3 receptor ligands. Cultured cells expressing the human H_3 receptor should be used for *in vitro* experiments instead, whereas for *in vivo* testing the mouse model developed by the group of Schwartz [70] may be also still valuable in the future.

Third, newly synthesised ligands should not only possess high antagonist potency at, but also a high preference for, the H_3 receptor. They should be *selective*, i.e., exhibit a preference for the H_3 as opposed to other types of histamine receptors. Many H_3 receptor antagonists exhibiting high selectivity for H_3 when compared to H_1 and H_2 receptors have been prepared in the past [10,11]. The recent cloning of a fourth type of histamine receptor, termed H_4 [15], will further complicate the synthesis of selective drugs. This may be more true since the sequence homology between the H_3 and H_4 receptor (37%) is higher than that between the H_3 and the H_1 or H_2 receptor (22 and 20%, respectively) [60,71]. Newly synthesised H_3 receptor antagonists should also be *specific*, i.e., show preference for the H_3 receptor as opposed to receptors for other transmitters, to ion channels, transporter molecules, etc. Some H_3 receptor antagonists, including thioperamide, turned out to possess a remarkable specificity since an affinity for a broad panel of receptors could be excluded [72-75]. Nonetheless, there are sometimes quite unexpected unspecific effects, which could hardly be predicted, e.g., the H_3 receptor antagonist iodophenpropit (**6**) (Fig. **4**) proved to have an affinity for serotonin 5-HT_3 receptors, which is only eleven-fold lower than that for H_3 receptors [72]. This is more remarkable since 5-HT_3 receptors do not belong to the huge family of G protein-coupled receptors - to which also the histamine receptors belong - but rather to the family of ligand-gated ion channels. It has been suggested that the combined blockade of H_3 and 5-HT_3 receptors might be useful for the treatment of some disorders of the brain [76] and in this context the question arises whether compounds that combine blockade of H_3 receptors with a second property should be synthesised. So far, combined H_3 and H_1 receptor antagonists have been prepared [77-81]. Such drugs might offer advantages for the treatment of allergic rhinitis since, in an animal model, this condition was improved by combined administration of low doses of an H_1 and an H_3 receptor antagonist, which when given alone, were devoid of an effect [75,82]. On the other hand, drugs with combined blockade of H_1 and H_3 receptors should not be used for the treatment of some disorders of the brain (*cf.* Table **2**) since, as discussed above, the beneficial effect of H_3 receptor antagonists is sometimes cancelled out by simultaneous administration of an H_1 receptor antagonist. Other examples of hybrid drugs are H_3 receptor antagonists that, in addition, (*i*) inhibit histamine *N*-methyltransferase (E.C. 2.1.1.8) [83,84], (*ii*) release nitric oxide [85] (see below) or (*iii*) inhibit muscarinic M_2 receptors [86].

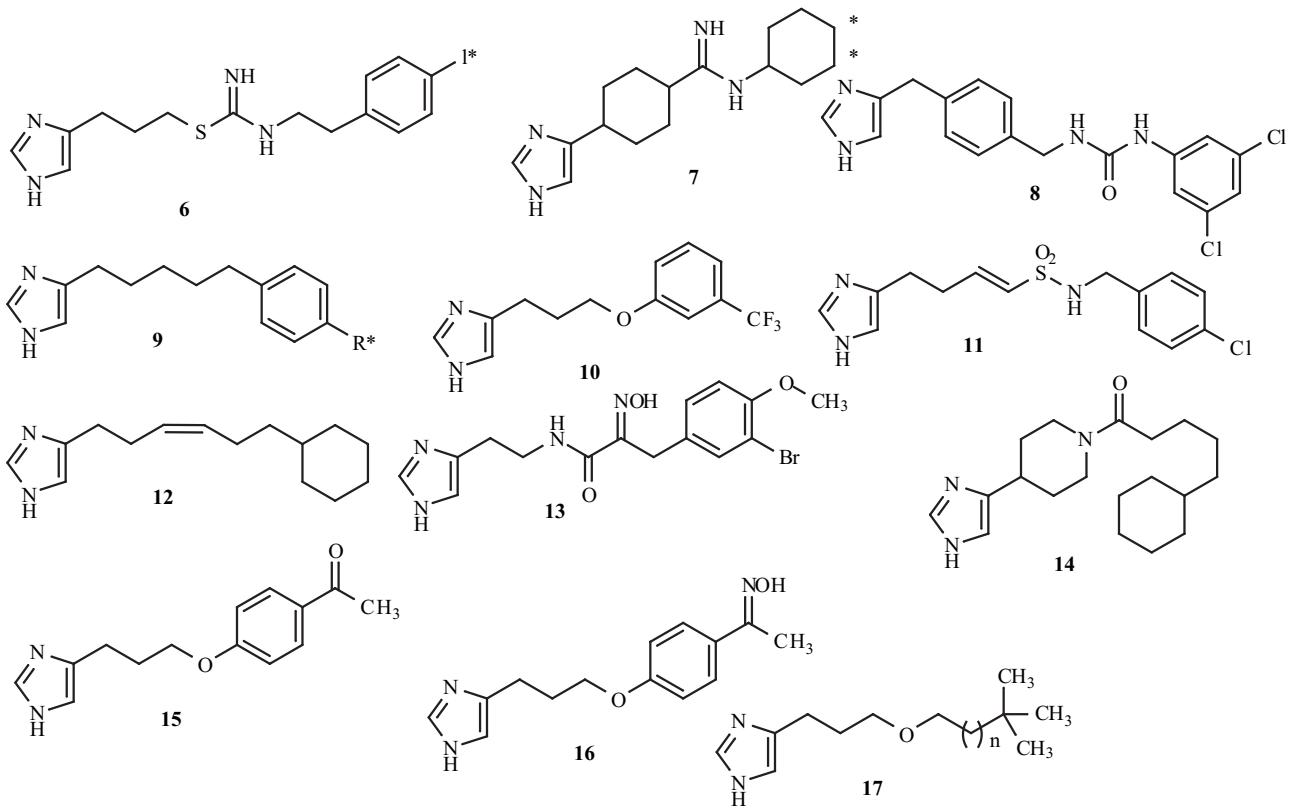

Fig. (4). Structurally different leads in imidazole-containing H_3 receptor antagonists[a].

Legend: [a]Asterisk displays positions for radiolabelling.

Table 2. Potential Indications for Histamine H_3 Receptor Antagonists[a]

Attention-Deficit Hyperactivity Disorder
Narcolepsy
Disorders with cognitive decline
Epilepsy
Schizophrenia
Drug abuse
Obesity
Antidipsogenic effect
Cardiostimulation
Allergic rhinitis[1]

[a] Compiled from [3, 11, 75]. Indications for which penetration through the blood-brain barrier is necessary are given in italics.

[1]together with an H_1 receptor antagonist [75].

Fourth, since this review focuses on *imidazole* H_3 receptor antagonists, some possible pharmacokinetic and pharmacodynamic consequences of the presence of the imidazole moiety in the structures of H_3 receptor antagonists shall be discussed. To obtain reasonably potent imidazole H_3 receptor antagonists it is usually necessary that the imidazole moiety is substituted in 4(5)-position with a side chain but is in most cases not substituted at other atoms of the imidazole moiety [5]. This might, however, have the *pharmacokinetic* consequence that such molecules, like histamine itself, are degraded by histamine *N*-methyltransferase and thus have a relatively short half-time [87]. To overcome this problem, H_3 receptor antagonists, in addition, inhibit this enzyme that may be useful [83,84]. H_3 receptor antagonists with imidazole moiety might interact with the cytochrome P450 isoenzymes in the liver. Thioperamide indeed binds to bovine and human cytochrome P450 [88,89]. The half-time of such drugs might be decreased when these enzymes are induced but increased when the enzymes are inhibited by other drugs, when hepatic function is impaired or when a polymorphism for the respective cytochrome P450 exists and the person under study belongs to the group of the poor metabolisers. The most serious consequence might be that imidazole-containing H_3 receptor antagonists inhibit cytochrome P450 3A4 (as macrolide antibiotics or antifungal agents of the azole type do), thus giving rise to life-threatening interactions with a series of drugs, including e.g., the non-sedative H_1 receptor antagonist terfenadine [90]. Another point of concern is that imidazole is a strong hydrogen bond acceptor and donor and therefore imidazole-containing H_3 receptor antagonists, which may provide additional hydrogen bond capacities, might not readily pass the blood-brain barrier [91]. Although a poor penetration into the brain may be beneficial for H_3 receptor antagonists with a peripheral site of action in order to minimize side effects, one has to consider that most of the proposed indications encompass brain disorders (Table **2**). Finally, a special *pharmacodynamic* property of imidazole H_3 receptor antagonists is that numerous structures display partial

agonism, even such compounds with a side chain that cannot be protonated, including some ethers, carbamates or compound cipralisant (GT-2331, **1**) [3,92-95]. It is premature to decide whether partial H_3 receptor agonism may be useful for one or the other of the proposed indications or should be totally avoided.

IMIDAZOLE-CONTAINING ANTAGONISTS

The first detection and characterisation of histamine H_3 receptors was based on the "selective" antagonist effects of burimamide (**3)** (Fig. **2**), which ironically was previously already used for the identification of histamine H_2 receptors as "selective" H_2 receptor antagonist. The affinity of burimamide is about two orders of magnitudes lower at rat H_3 receptors than its affinity at H_2 receptors. The first compound having no effects at histamine H_1 and H_2 receptors was the 4-piperidin-4-yl-1*H*-imidazole derivative thioperamide (**2**) [2]. Whereas burimamide and thioperamide are thiourea derivatives, the other reference compound was an isothiourea derivative, clobenpropit (**4**) [96]. The compound nowadays used in numerous experiments is the aromatic ether derivative, ciproxifan (**5**), belonging to the proxifan class [74,97]. These compounds have in common a blueprint displaying an imidazole ring (i.e. in general an *N*-containing heterocycle), which is mono-substituted in 4(5)-position [98]. Due to the possible tautomerism of the imidazole ring the position of substitution has to be related to the hydrogen-containing nitrogen in terms of nomenclature. Substitution of the imidazole nucleus is performed by a linking alkyl group, which possesses another functionality (Fig. **2**) and (**4**)), e.g. thiourea (e.g. thioperamide (**2**)), isothiourea (e.g. clobenpropit (**4**), iodophenpropit (**6**)), guanidine (e.g. GR168320 (**7**)), amidine (e.g. AQ0145), amine (e.g. impentamine (VUF 4702)), amide (e.g. GT-2016 (**14**), GT-2130), urea (e.g. SCH 79683 (**8)**), carbamate, ester, ketone, ether (e.g. FUB 181, proxyfan (**9**, R = H), ciproxifan (**5**), UCL 1470 (**10**)), thioether, sulfoxide, sulphonamide (**11**), sulphamide, unsaturated hydrocarbon atoms (e.g. GT-2331 (**1**, cipralisant), GT-2227 (**12**)), or even heterocyclic ring systems [3-6 and others]. In most cases this (polar) functionality is additionally linked directly or by a second (alkyl) spacer to a lipophilic moiety, which increases affinity, selectivity, and specificity. Even natural compounds have been shown to behave as histamine H_3 receptor antagonists like the alkaloid verongamine (**13**) from the marine sponge *Verongula gigantea* [99,100]. The different elements of the blueprint were taken on drug optimisation resulting in numerous classes of histamine H_3 receptor antagonists displaying different spacers, different polar functionalities as well as different (substituted) lipophilic moieties. Accordingly, these variations resulted in many cases in different pharmacodynamic and/or pharmacokinetic properties. In this respect, absorption and distribution into the brain are important criteria for *in vivo* evaluation of compounds. Since the sequence of human H_3 receptor has become available only recently [39], most medicinal chemistry studies have performed optimisation on rodent H_3 receptors at that time. For the sake of comparison of reference compounds pharmacological screening data on histamine receptor subtypes and different species have been listed in Table **3.** .

Variation of the alkyl spacer can be performed by change in length or by rigidisation. Exchange of a methylene group by a heteroatom, e.g. a sulphur atom as successfully shown in H_2 receptor antagonists, did not maintain potencies in H_3 receptor antagonists. Introduction of a cyclopropyl spacer with distinct stereochemistry resulted in potent antagonists, and one of the most prominent examples is GT-2331 (cipralisant, **1**) [106-108]. Cipralisant (**1**) is the first compound described as antagonist reaching human application [49]. A comparable concept was followed by the exchange of the trimethylene moiety by an α,α′-xylendiyl group (SCH 79687 (**8**)) [75,109]. With both structural changes in the linking group, additional variations of the remaining elements of the blueprint could be taken for the design of additional classes of antagonists, which are classified in most cases regarding their polar functionalities. General conclusions concerning drug optimisation should be taken carefully since the affinities and sometimes the pharmacological properties of H_3 receptor antagonists display great variability regarding different species (Table **3**).

The largest number of structural variations has been performed on the lipophilic moiety. Aliphatic as well as aromatic groups are tolerated. The aromatic groups display a greater variability concerning substitution possibilities as compared to the aliphatic ones. Optimisation of substituents and in substitution pattern was extensively followed in different compound classes. One of the most successful strategies was the improvement of the already highly active ciproxifan (**5**) [97,110-112]. The related acetylated compound, acetoproxifan (**15**), is slightly less active than ciproxifan (**5**). The transformation of the ketone functionality to an oxime led to imoproxifan (**16**) and related compounds with high affinity and extremely high antagonist potency *in*

Table 3. Affinities and Potencies of H_3 Receptor Reference Antagonists at Histamine Receptor Subtypes and on Different Species [97, 101-105]

N°	Compound	H_1	H_2	H_4	H_3						
		human pK_i	human pK_i	human pK_i	human pK_i	monkey pK_i	dog pK_i	guinea-pig pK_i	rat pK_i	mouse pA_2	in vivo ED_{50} mouse p.o. [mg/kg]
2	Thioperamide	< 5	< 5	7.32	7.14	8.04	8.17	8.34	8.44	8.67	1.0
4	Clobenpropit	5.56	5.24	7.38[1]	9.44	10.1	10.1	9.65	9.75	9.55	> 25
5	Ciproxifan	< 5	< 5	5.73	7.20	7.46	8.24	8.76	9.29	9.39	0.14

[1]Partial agonist

vivo [113]. Unfortunately, imoproxifan (**16**) is more active at the rat H_3 receptor than at the human receptor. Incorporation of the oxime moiety in different aromatic heterocycles also resulted in potent H_3 receptor antagonist but did not reach the potency of imoproxifan (**16**) [114].

Many of these known antagonist compounds have been re-characterised as inverse agonists in more detailed studies mostly on transfection systems with receptor overexpression [57,58,115]. The largest number of actual studies on drug development in this field of receptor research focuses on the recently detected non-imidazole compounds [3,4].

QSAR AND MOLECULAR MODELLING STUDIES

Historically, one of the earliest quantitative structure-activity relationships (QSAR) studies on H_3 receptor antagonists was performed on thioperamide derivatives by Bordi *et al.* [116]. While in earlier studies structural modulations of the imidazole and piperidino moiety (replacement by alkylamine chains or aromatic amines) were carried out, that all resulted in a dramatic drop in affinity. In this work a benzothiazole group replaced the cyclohexylcarbothioamide moiety of thioperamide and various substituents were introduced. Bulky substituents in 6-position on the benzene ring led to an additional drop in affinity described through a negative influence of steric and lipophilicity parameters in the QSAR equation. Electronic effects had only little influence, a fact that was interpreted as a lack of electrostatic interactions between the benzothiazole moiety and the binding cavity. Bordi *et al.* concluded that any improvement of affinity would require substitution of the benzothiazole moiety for a less bulky, more flexible structure with decreased lipophilicity and increased capacity for electronic interactions. A following QSAR study by the same group was carried out on the structural class of 4-phenyl-2-((2-(1*H*-imidazol-4-yl)ethyl)sulphanyl)-1*H*-imidazoles [117]. Based on the minimum-energy conformation of thioperamide, an alignment of eleven H_3 receptor antagonists was generated. No significant QSAR model could be derived for these ligands due to the little influence that the *para*- and *meta*-substituents had on the receptor affinity (pK_i range from 7.28 to 8.03). In summary, Bordi and co-workers drew the conclusion that all investigated ligands bind to the same receptor site and that a hydrophobic group attached to the polar heterocycle increases H_3 receptor affinity while steric hindrance beyond this hydrophobic region prevents the accommodation of bulky substituents attached to the rigid structure of piperidino-benzothiazole derivatives.

In 2001, De Esch *et al.* could deduce from a pharmacophore model that two lipophilic pockets must be available for H_3 receptor antagonist binding and that thioperamide (**2**) belongs to the smaller group of H_3 receptor ligands that addresses to the sterically more demanding ones [118]. The existence of two lipophilic pockets was tested by the synthesis of branched clobenpropit-derived compounds [119]. If one compares the data sets studied by the group of Bordi [116,117] with the ligands incorporated in the model of De Esch *et al.,* it remains questionable, if all ligands, including those lacking the sterically constraining piperidino group [117], bind to the same receptor site. Besides, the consideration of only minimum-energy structures in the pharmacophore generation of Bordi and co-workers is controversial, especially if the ligands have low binding affinities. In contrast, the procedure used by De Esch *et al.* appears to be more promising [119]. In order to identify the bioactive conformation pairs of sterically constrained H_3 receptor antagonists lacking the hydrophobic tail were allowed to flex, yielding a number of possible conformations for each pair. The conformation that was consistent within several pairs was declared the bioactive one and was subsequently used as a scaffold for the generation of a pharmacophore containing 14 imidazole derivatives of structurally diverse families. Four hydrogen-bonding sites and two lipophilic pockets were identified. Lipophilic pocket 1 was predicted to be easily accessible by antagonists with cycloalkyl- and (substituted) benzyl-groups (e.g. cipralisant (GT-2331, **1**), clobenpropit (**4**), iodoproxyan (**9**, R = I)). A high increase in affinity could be gained with the proper lipophilic tail. Lipophilic pocket 2 was supposed to be sterically more demanding and would be addressed by ligands such as thioperamide (**2**) or the pentyl-analogue of burimamide. Regarding the hydrogen bonding points only clobenpropit (**4**) was predicted to simultaneously interact with all sites explaining its high affinity.

The existence of two lipophilic pockets could as well be responsible for the ambiguity in structure-affinity relationships derived from different classes of H_3 receptor ligands [120,121]. In 2000 Windhorst and co-workers [120] studied mono-substituted benzyl analogues of thioperamide introducing chlorine, bromine, iodine and fluorine substituents in *ortho*-, *meta*- and *para*-position of the benzyl ring. Compared to the reference structure thioperamide (**2**), replacement of the cyclohexyl group by substituted benzyl groups caused a drop in affinity. A clear preference was found for a substitution in *ortho*-position compared to the *para*-substituted derivatives that were even less active than the unsubstituted compounds. An explanation for this observation can be seen in the dihedral angle between the thiourea and the benzyl moiety that was strongly correlated with the antagonist effects. In case of an *ortho*- substitution the phenyl moiety is turned out of the plane compared to the unsubstituted derivative thereby affecting the dihedral angle. In the derived QSAR study (r^2=0.93, q^2 not reported) consequently the described dihedral angle and the calculated electron density on the substituted carbon atom appeared as the main variables. These findings could be validated by an introduction of an *ortho*-*tert*-butyl and -methyl-group that were predicted consistently with this model. With respect to the pharmacophore model from De Esch *et al.*, these thioperamide-derived antagonists are predicted to address lipophilic pocket 2 [119].

In the model proposed by De Esch *et al.* also acetylene-based antagonists with a restricting *trans*-cyclopropane ring attached to the imidazole moiety were considered and predicted to address lipophilic pocket 1. If this holds true, the study of Ali *et al*. on the lipophilic and steric properties of the hydrophobic tails of H_3 receptor ligands should give some insight into the features of this binding site [107]. Starting with 4-(hex-3-ynyl)-1*H*-imidazole, hydrophobicity was subsequently increased by an introduction of hydrocarbon side chains of increasing length. Optimal hydrophobicity was reached with 4-(6-cyclopentylhex-3-ynyl)-1*H*-imidazole. Replacement of the cyclopentyl group

by a cyclohexyl or a phenyl group did not further increase affinity. To test the steric influence, the cyclopentyl group was replaced by a bulky *tert*-butyl group, which was quite well accepted. An interesting SAR-feature is, that acetylenic compounds with long carbon chains show comparable binding affinities to compounds with a cyclohexyl or a phenyl group. Substitution of the two carbon linkers between the imidazole and the acetylene group by a restricting *trans*-cyclopropane ring led to a racemic mixture of which the (1*R*,2*R*)-stereoisomer was the more active one (e.g. cipralisant (**1**), pK_i 9.92 nM). The stereospecificity is consistent with the observation of De Esch *et al.* [119] who predicted that in case of the agonists only the (1*S*,2*S*)-enantiomer of the histamine-related *trans*-2-(1*H*-imidazol-4-yl)cyclopropanamine is consistent with the pharmacophore model, while in case of antagonists only the (1*R*,2*R*) enantiomer (i.e. one of the *cis*-configured diastereomers) of cyclopropyl-containing antagonists is in good steric agreement.

Another QSAR model was described by Agrawal *et al.* [122] for 12 acetylated histamine derivatives. The model was based on the topology indices negentropy (describing molecular symmetry and structural characteristics influencing physico-chemical properties [123]), the molecular redundancy index (MRI), the valence molecular connectivity indices and two indicator parameters lp1 (describing the existence of a benzene ring in the substituent) and lp2 (related to the presence of a nitrogen atom in this benzene ring). The best model (r^2 =0.851, q^2 not reported) included the first and second order valence molecular connectivity indices (encoding structural features such as size, branching, unsaturation, heteroatom content and cyclicity), the MRI and the indicator parameter lp1. Unfortunately, topology parameters are hard to interpret in terms of possible structural improvements. The requirement for the presence of a benzene ring as predicted by the QSAR model was only partly reflected by the measured binding affinities where replacement of a benzene ring by a cyclopropyl ring even led to a slight increase in affinity (pK_i 7.10 vs. 7.30).

The first consideration of the receptor environment in modelling studies was made in 2000 by the group of Timmerman [118]. At that time only imidazole-containing antagonists were known although great effort had been made to replace the imidazole moiety. This led to the assumption that the imidazole group of agonists and antagonists would bind to the same receptor site. In the presented model only compounds with a basic moiety in the side-chain were considered, as it was not clear if ligands lacking this basic moiety binds to the same receptor site. It was speculated, that antagonists with a basic group in the imidazole side-chain are able to interact with the aspartic residue in transmembrane domain (TM) III, known from agonist binding while antagonists lacking this basic moiety are able to interact with the imidazole-binding site and a lipophilic pocket. The proposed model suggests a molecular switch mechanism in which the side chain conformation of the aspartic residue in TM III is the molecular determinant for agonism versus antagonism. Unfortunately, the model could not account well for the constitutive activity observed for the H_3 receptor, as this would require a spontaneous conformational change of the aspartate residue in absence of any interaction partner. There is also an increasing evidence that upon receptor activation large conformational changes occur involving an approach of TM III towards TM V. If this holds true, no conformational change of aspartic acid would be necessary as an optimised contact of the aspartic acid with the basic moiety of agonists and antagonists could be established by a translational movement rather than a conformational change in the side chain of aspartate.

Considering recent mutation studies it also becomes doubtful that the imidazole moiety in agonists and antagonists bind to the same receptor site. It could be shown that glutamate 206 in TM V is a key residue in agonist binding, most probably by interacting with the imidazole moiety [124]. These observations have recently been confirmed by mutation studies in which binding of histamine and the agonist immepip was strongly affected by the mutation Glu206Ala [125]. An interaction of agonists with residues of TM V has as well been reported for numerous monoaminergic G-protein coupled receptors. However, in the case of antagonists it has been reported that the binding affinity of [^{125}I]iodoproxyfan (**9**, R = [^{125}I]I) was negligibly affected by the mutation Glu206Ala, but no specific binding of [^{125}I]iodoproxyfan could be detected after mutation of the aspartate in TM III (Asp114) [125]. This suggests an interaction of the possibly protonated imidazole moiety with Asp114 rather than Glu206. Antagonists having a protonated moiety in the side chain could simultaneously interact with both receptor side points, Asp114 and Glu206. This assumption is strengthened by the drop in affinity observed for iodophenpropit (**6**) and clobenpropit (**4**) at the mutant receptors Asp114Ala/Asn and Glu206Ala/Gln [125,126]. In the case of H_3 receptor antagonists lacking a protonated moiety such as ciproxifan (**5**) or thioperamide (**2**) the mutation Glu206Gln had relatively small effects. However, given the fact that the mutant receptor Glu206Gln was reported to be constitutively active [126], these results are difficult to interpret.

Concerning our attempts to map the antagonist binding site in a homology model of the human H_3 receptor some of the authors of this article have investigated so far both possible orientations yielding however more consistent results with the model where the imidazole moiety interacts with Asp114 [127]. A possible interaction of the antagonist ciproxifan (**5**) with a model of the human H_3 receptor is shown in (Fig. **5**) [127]. In this complex it is likely to map the two lipophilic pockets between TM V and VI consistent with the orientation of retinal in bovine rhodopsin and described also for antagonists in other biogene aminergic receptors. The other lipophilic pocket is mainly composed of residues of TM V and IV. This model is as well in agreement with the preference of the (1*R*,2*R*)-enantiomers of cyclopropyl-containing antagonists. Additionally, ligands exhibiting a pronounced bending due to a sulphur atom in the side chain and branched ligands such as the ones described in [119] can be accommodated more easily. The model as well gives an explanation why antagonists lacking a protonated moiety in the imidazole side chain exhibit different binding affinities at the human versus the rat receptor while ligands such as clobenpropit (**4**) have similar affinities at both as described by [128,129]. In the human receptor Glu206 can interact with Thr119 while in the rat receptor this residue is exchanged for an alanine (Fig. **3**) where no hydrogen bonds are possible, thus resulting in a

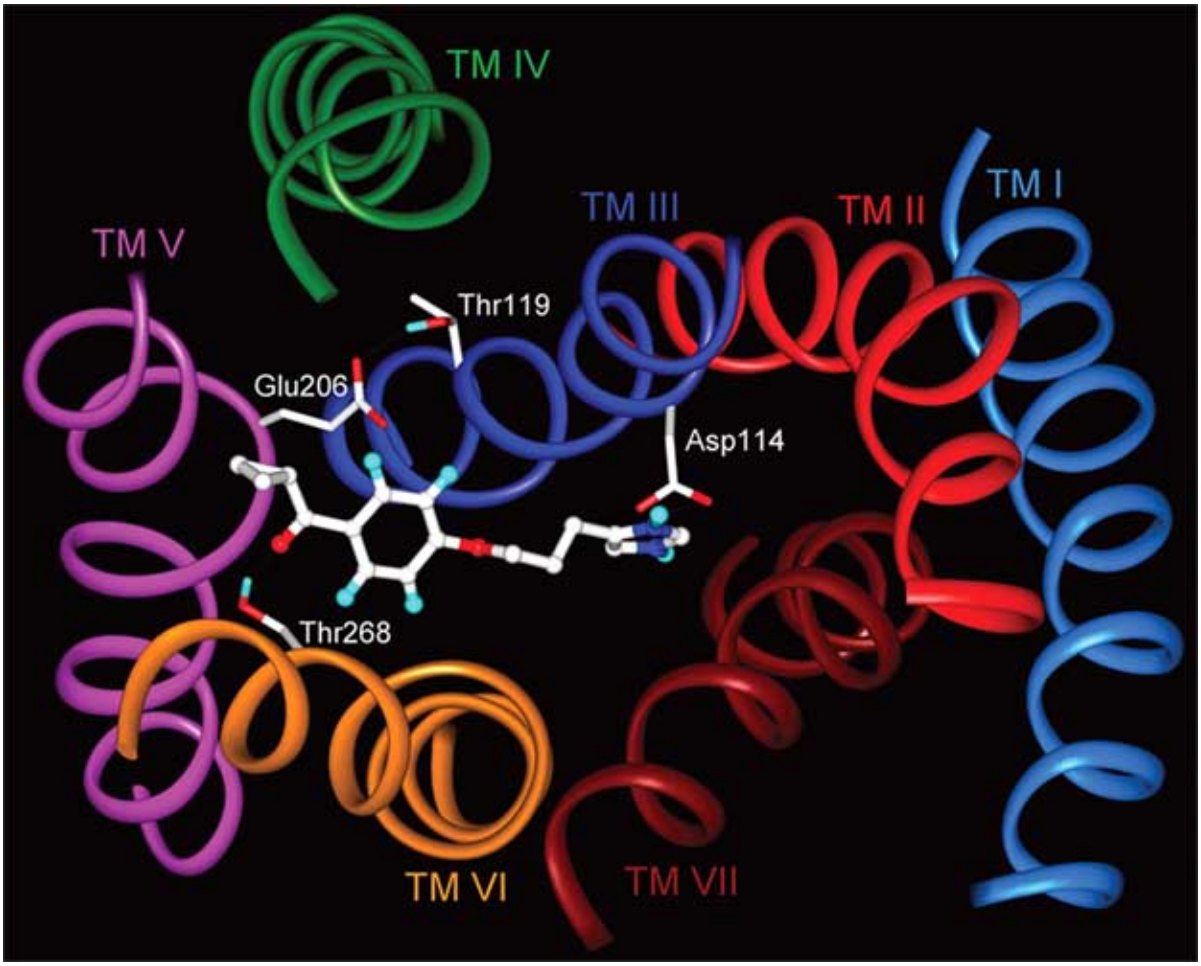

Fig. (5). Possible binding mode for the antagonist ciproxifan at the human H_3 receptor. The imidazole group interacts with Asp114 in TM III, the carbonyl group of ciproxifan with Thr268 in TM VI. Glu206 in TM V does not contribute to binding and instead interacts with Thr119 in TM III (Colour code for labelled residues: white: carbon, cyan: hydrogen, red: oxygen).

different receptor site. In the case of agonists or antagonists with a charged moiety, Glu206 can make interactions in both, the human and rat receptor, thus resulting in comparable binding affinities.

PARTIAL AGONISTS AND NEUTRAL ANTAGONISTS

Binding of ligands to the H_3 receptor can change or confirm a distinct conformation of the protein, which lead to different pharmacological behaviour. Compounds with antagonist properties, which simultaneously display agonist properties, have been described recently in the ether and the carbamate classes [92-95]. Depending on the bulkiness of the lipophilic moiety and its distance to the imidazole ring these non-aminergic compounds can be characterized as antagonists or partial agonists. Whereas the antagonist properties follow the well-known structure-activity relationships, the agonist properties of these compounds depend on relative restrictive steric demands concerning the position of the lipophilic residue. As an example *pars pro toto* the unsymmetrical aliphatic ether based on the 3-(1*H*-imidazol-4-yl)propanol scaffold is described: *in vitro* compound FUB 407 (**17**, n = 1) (Fig. **4**) possesses antagonist properties having an K_i value of 10 nM, its agonist properties in the same model showed a comparable EC_{50} value of 45 nM displaying an intrinsic activity of 55% (α = 0.55) that of histamine. When the compound was tested in an *in vivo* assay it behaved as full agonist in mice (ED_{50} = 0.29 mg/kg p.o.). Its homologue compound, FUB 665 (**17**, n = 2), displayed comparable antagonist affinity *in vitro* (K_i = 24 nM), but behaved as a partial agonist *in vivo* (ED_{50} = 0.13 mg/kg p.o., α = 0.6). The next higher homologue compound, FUB 666 (**17**, n = 3), showed slightly diminished antagonist affinity *in vitro* (K_i = 44 nM) and behaved as an antagonist without any detectable intrinsic activity *in vivo* (ED_{50} = 1.4 mg/kg p.o.). Similar observations were taken from a series of trifluoromethylated proxifan derivatives. The *meta*-substituted UCL 1470 (**10**) is a partial agonist *in vitro* (K_i = 8.4 nM, EC_{50} = 98 nM, α = 0.4) and a full agonist *in vivo* (ED_{50} = 0.6 mg/kg p.o, α = 1) [5,130]. Its corresponding *para*-substituted analogue (UCL 1409) is an antagonist (K_i = 14 nM). Due to receptor reserve, expression levels, available coupling partners etc. the intrinsic activity detected strongly depends on the test system used. The aliphatic structural features described for the ether and carbamates as partial agonists also fit to cipralisant (**1**). In fact, in functional assays on recombinant human H_3 receptors it was shown that this compound clearly acts as an agonist [131].

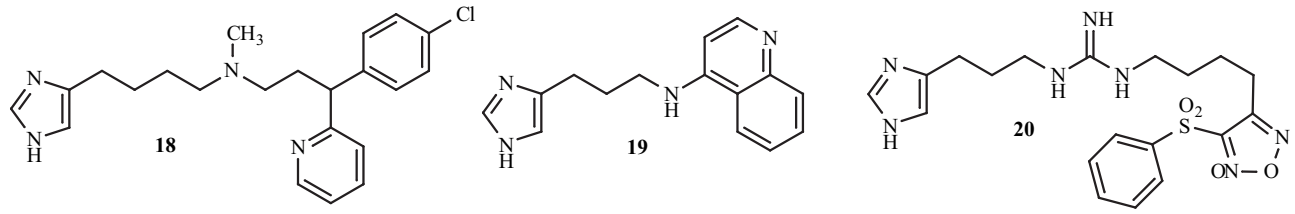

Fig. (6). Hybrid compounds.

In line with these results on variations in pharmacological behaviour one has to mention proxyfan (**9**, R = H), which belongs to a benzyl ether class. Re-characterisation of proxyfan (**9**, R = H) showed that it behaves as neutral antagonist in numerous assays [57] although depending on the test system, it is also clearly able to behave from inverse agonist to agonist behaviour. Histamine H_3 receptors show a high degree of constitutive activity at physiological expression levels. This was demonstrated for the first time *in vivo* using proxyfan (**9**, R = H), which acted as neutral antagonist counteracting the properties of inverse agonists as well as of agonists [57].

RADIOLIGANDS

Radioligands have been described in the field of histamine H_3 receptor antagonists with different kinds of radioactive labelling used for autoradiography and different binding assays. Radiolabelling has been performed on thioperamide preparing *S*-[^{11}C]- and *S*-[^{3}H]-methylated isothiourea analogues [132,133]. Tritium-labelling was also performed on the guanidine derivative [^{3}H]GR168320 (**7**) by [^{3}H]hydrogenation of a cyclohexenyl precursor, which led to a highly affine compound [134]. The most prominent limitation of these compounds is their relative high unspecific binding. The mostly used radioligands are [^{125}I]iodophenpropit (**6**) [135] and [^{125}I]iodoproxyfan (**9**, R = [^{125}I]I) [73,136]. Whereas, [^{125}I]iodoproxyfan (**9**, R = [^{125}I]I) seems to be slightly more active and showed less unspecific binding than [^{125}I]iodophenpropit (**6**), the former one is described to possess partial agonist properties (*cf.* comments above on proxyfan (**9**, R = H)) in some test models leading to a more complex binding behaviour [137]. Recent studies to use [^{125}I]iodophenpropit (**6**) also as a radioligand for the H_4 receptor did not show promising results [138]. Different attempts to radioligands, which can be used for positron emission tomography (PET) or single-photon emission computed tomography (SPECT) were of limited success only since their unspecific binding and/or *in vivo* pharmacokinetic properties have not fulfilled all criteria necessary [139-145].

HYBRID COMPOUNDS

Apart from increasing the selectivity and specificity of H_3 receptor ligands, it may be useful for some indications to have activities at two targets simultaneously. The fate of a single compound can be better overseen than a combination of two or more than two drugs. The combination of structural ligand requirements known from one target together with the H_3 receptor antagonist can be achieved by an overlap of structural features or by a connection using an appropriate linker. Whereas the first approach was used for dual H_1 and H_3 receptor antagonists some years ago by academic groups [77,78] the industry moved towards the latter one [80,81]. The connection of chlorpheniramine elements with ω-(1*H*-imidazol-4-yl)alkanamines on the amino moiety resulted in potent antagonists for both targets (**18**) (Fig. **6**) [79]. Another novel dual approach for increasing histaminergic activity is obtained by H_3 receptor antagonists (**19**), which are concurrently able to inhibit the main histamine catabolising enzyme in the brain, the histamine *N*-methyltransferase [83]. While the antagonist properties block presynaptic H_3 autoreceptors and thereby stimulate the liberation of histamine, the inactivation of this neurotransmitter is simultaneously inhibited by blockade of the catabolic enzyme. Additional or synergistic effects can be expected by this approach. Since these compounds are related to the cognition enhancing anti-Alzheimer drug tacrine, these compounds represent a new promising hybrid marked by dual influence on histamine-related transmission. The same is true for a very recently described series of novel guanidine compounds (**20**) combining H_3 receptor antagonist potency with NO-releasing properties [85]. Since nitric oxide is an important signalling molecule and supposed to have neuromodulatory effects in the periphery as well as in the central nervous system the biological effects of these compounds could become really attractive.

CONCLUSION

Numerous approaches in the medicinal chemistry field have led to several different leads for imidazole-containing histamine H_3 receptor antagonists of high affinity, high selectivity, and high specificity. In addition to their pharmacodynamic properties due to more than a few development lines also their pharmacokinetic properties have been optimised for some compounds. Extensive pharmacological *in vitro* and *in vivo* characterisation make these compounds extremely valuable pharmacological tools. The progress within the last years is clearly shown by the first introduction of an imidazole-containing antagonist in clinical trials. It may be expected that further developments on different structures will also reach this development phase in the near future. A new perspective on H_3 receptor antagonists is shown with the hybrid approaches, which combine different properties in one molecule for a potentially optimised therapy of different H_3 receptor-related diseases. Although many therapeutic H_3 receptor-related targets for antagonists focus on the central nervous system, some peripheral applications have also been taken into account. One does not have to look in a crystal ball to see that in the near future histamine H_3 receptor antagonist will most probably reach the market. At the moment it is not clear which compound or which indication will make the grade.

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