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Histamine H_3 Receptor as a Drug Discovery Target

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Introduction

Ever since its pharmacologic discovery in 1983,[1] the histamine H_3 receptor has provided a tantalizing target for drug research, 25 years later still to be validated by an approved and marketed product. The H_3 receptor is one of the four currently known histamine receptor subtypes (H_1−H_4). Successful modulation of the histamine effects in the human body was initially achieved through the development of drugs acting at H_1 receptors, which were designed to mitigate the consequences of histamine release in an allergic reaction. The Claritin−Zyrtec−Allegra trio epitomizing the new generation of nonsedating antihistamines[2] went on to gain tremendous therapeutic and commercial success. At the same time a different class of drugs was shown to mediate secretion of gastric acid through selective antagonism of the H_2 receptors, a discovery that eventually led to the development of Tagamet and Zantac.[3] The success of these drugs understandably heightened interest in the therapeutic and commercial potential of ligands of the H_3 and of the more recently discovered H_4 receptor.[4,5] With pharmaceutical industry efforts naturally delayed in the early years by the challenges of H_3 biology, including lack of molecular identification of the human H_3 receptor, medicinal chemistry programs finally shifted into high gear in the early 2000s. Importantly, the H_3 receptor position at the crossroads of neurotransmission suggests an abundance of therapeutic applications for small-molecule receptor modulators. Clearly a challenge to the tractability of in vitro and in vivo data, the complexity of H_3 biology has nevertheless set up expectations of a large payout at the end of the journey. While in mid-2009 this journey still remains to be successfully completed, a number of ongoing H_3 clinical programs, including several in phase II, an abundance of H_3 publications, and extensive H_3 patenting activity testify to the high level of interest in this area. Needless to say, the current medicinal chemistry programs are based on the monumental amount of research effort that has gone into establishing various aspects of H_3 receptor biology.

H_3 Receptor Pharmacology and Signaling Pathways

The initial role of the H_3 receptor was established by Arrang and co-workers to be that of a presynaptic autoreceptor mediating negative feedback of histamine release in rat brain.[1] Fifteen years later in 1999, Lovenberg and co-workers identified a GPCR[a] clone similar to biogenic amine receptors through a homology search of expressed sequence tag databases.[6] This clone revealed a pharmacological profile corresponding to that previously established for the H_3 receptor.[7] The availability of human H_3 cDNA facilitated further research into the structural makeup and molecular signaling mechanisms of the H_3 receptor. The H_3 receptor shows little similarity to its predecessors (20% homology to H_1 and H_2) with more similarity (60% homology) to the recently discovered H_4 receptor, though with different expression pattern in vivo.

While the H_3 receptor is a classic GPCR with seven transmembrane domains, its isoform signature is intensely complex. This aspect of H_3 pharmacology has been reviewed on more than one occasion by Leurs and co-workers.[8,9] While many human H_3 receptor isoforms have been identified, the full length 445 configuration appears to be the most functionally dominant and abundantly expressed. In addition, at least another 19 isoforms, a number of them functional as well, have been reported for the human receptor. Several additional isoforms have also been identified in rat, guinea pig, and mouse. Not surprisingly, complex isoform composition and their different expression patterns are often invoked in connection with unexpected or inconsistent in vivo H_3 biology. However, at this point there is a clear need for more data to substantiate these correlations or perhaps to provide a simpler explanation. While selective isoform targeting could in theory contribute to the selectivity of H_3 ligands, in practice

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[a] Abbreviations: $^{-/-}$, gene knockout; 6-OHDA, 6-hydroxydopamine; AD, Alzheimer's disease; ADHD, attention-deficit hyperactivity disorder; Akt, serine/threonine protein kinase; ALDH, aldehyde dehydrogenase; ATP, adenosine triphosphate; BA, bioavailability; BAT, brown adipose tissue; b.i.d., twice a day; BMI, body mass index; *B*/*P*, brain/plasma; cAMP, cyclic adenosine monophosphate; CNS, central nervous system; COX, cyclooxygenase; CSF, cerebrospinal fluid; CYP450, cytochrome P450; DIO, diet-induced obesity; DREM, direct rapid eye movement; EDS, excessive daytime sleepiness; ERK, extracellular signal-related kinase; FDA, Food and Drug Administration; GABA, γ-aminobutyric acid; GPCR, G-protein-coupled receptor; GSK-3β, glycogen synthase kinase-3β; GTPγS, guanosine 5′-*O*-(γ-thio)triphosphate; hDAT, human dopamine transporter; HDC, histidine decarboxylase; hERG, human ether-a-go-go-related gene; HNMT, histamine *N*-methyltransferase; hH_3R, human H_3 receptor; hNET, human norepinephrine transporter; hSERT, human serotonin transporter; HSV, herpes simple virus; icv, intracerebroventricular; IgE, immunoglobulin E; IL, interleukin; ip, intraperitoneal; iv, intravenous; L-dopa, 3,4-dihydroxyphenyl-L-alanine; MAO B, monoamine oxidase B; MED, minimal efficacious dose; mRNA, messenger ribonucleic acid; MS, metabolic syndrome; NHE, Na^+/H^+ exchanger; NIDCD, National Institute on Deafness and Other Communication Disorders; NK, neurokinin; NMDA, *N*-methyl-D-aspartic acid; NREM, nonrapid eye movement; PD, Parkinson's disease; PET, positron emission tomography; PGC1, proliferator-activated receptor-γ coactivator 1; PI3K, phosphatidylinositol 3-kinase; PK, pharmacokinetic; PLA_2, phospholipase A_2; po, oral; q.d., once a day; RAMH, *R*-α-methylhistamine; REM, rapid eye movement; rH_3R, rat H_3 receptor; sc, subcutaneous; SAR, structure−activity relationship; SSRI, selective serotonin reuptake inhibitor; $t_{1/2}$, half-life; TM, transmembrane domain; WT, wild-type.

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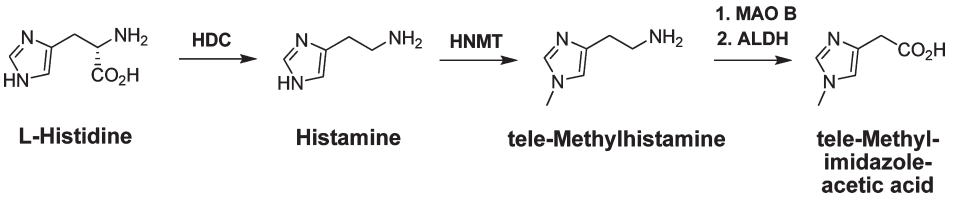

Figure 1. Biosynthesis and metabolism of histamine: HDC, histidine decarboxylase; HNMT, histamine *N*-methyltransferase; MAO B, monoamine oxidase B; ALDH, aldehyde dehydrogenase.

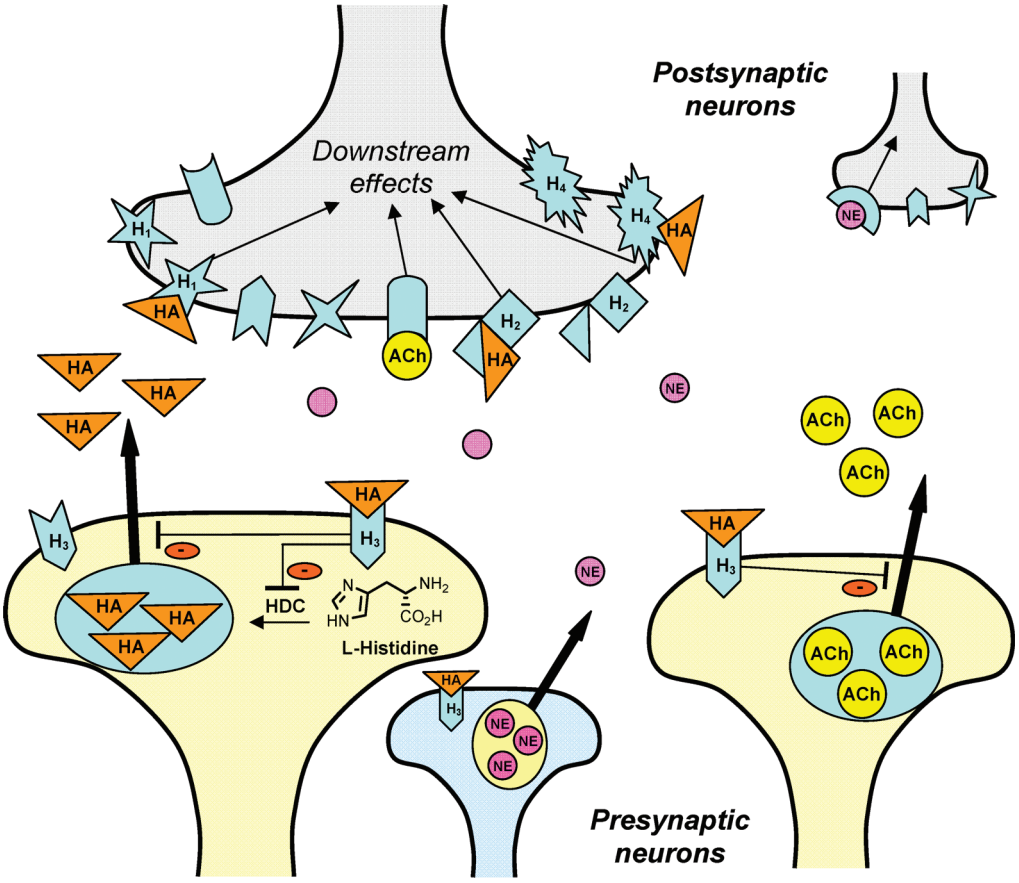

Figure 2. Biological role of H_3 receptors: HA, histamine; ACh, acetylcholine; HDC, histidine decarboxylase; NE, norepinephrine.

it remains just a vague possibility, especially in view of the questionable functional significance of many isoforms. Additionally, several instances of genetic polymorphism for the human H_3 receptor have been reported.[6,10]

Studies into H_3 receptor expression patterns have revealed its abundant presence in the CNS of rodents and humans, lower expression in the sympathetic nervous system, and yet lower expression in peripheral tissues. Detection of H_3 receptor mRNA through in situ hybridization has added to the insights into receptor distribution, earlier approached using autoradiography.[11,12] The H_3 receptor is largely expressed on, although not totally confined to, histaminergic neurons, the site of histamine synthesis in animals and humans (Figure 1). Histamine is formed in vivo from L-histidine by histidine decarboxylase (HDC) and released in the neuronal synapse, then deactivated by metabolic conversion to tele-methylhistamine by histamine *N*-methyltransferase (HNMT). Further metabolic oxidation by monoamine oxidase B (MAO B) and aldehyde dehydrogenase (ALDH) leads to tele-methylimidazoleacetic acid.[13] In the CNS of humans and rodents, the histaminergic neurons originate in the tuberomamillary nucleus of the posterior hypothalamus, from which extensive projections reach into all major areas of the brain and parts of the spinal cord.[14,15] As a result, the H_3 receptors are present in cerebral cortex, hippocampus, amygdala, striatum, and basal ganglia, in addition to hypothalamus. The H_3 receptor role appears to be mediation of functional effects of histamine in different tissues. As a neuronal presynaptic autoreceptor, H_3 provides negative feedback regulation of histamine release in the neuronal synapse, which moderates histamine inhibitory control of the firing of histamine neurons,[16] as well as its actions at the postsynaptic histamine receptors (vide infra). CNS histamine as a neurotransmitter has been implicated in diverse responses, including arousal, cognition, fluid, food and temperature homeostasis, cardiovascular control, anxiety, and pain perception, inexorably linking the central H_3 receptor system to these fundamental physiological processes.[17] In addition to a direct role in histamine signaling, the H_3 receptor is also involved in regulation of other neurotransmitter systems directly as a presynaptic heteroreceptor (Figure 2) or indirectly by affecting levels of histamine, which then acts on postsynaptic receptors. H_3 heteroreceptor modulation has the potential

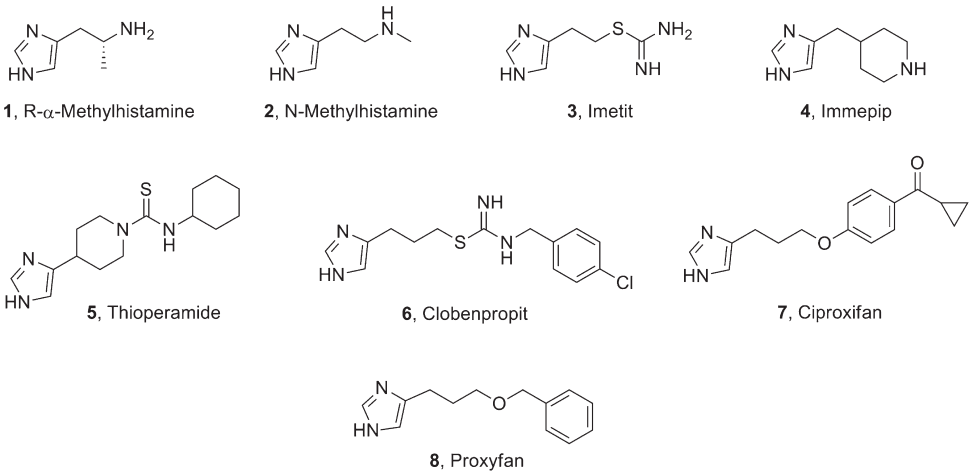

Figure 3. Early synthetic H_3 ligands.

to affect classic biogenic amine neurotransmitters such as glutamate,[18] acetylcholine,[19] norepinephrine,[20] dopamine,[21] GABA,[22] and serotonin,[23] conceivably setting up a variety of therapeutic applications for the H_3 receptor. Centrally or peripherally, the effects of H_3 activation or blockade, as evidenced by H_3 biology and discussed below, often seem to be dependent on the exact nature of the tissue, as defined by locale, cell type, and species. In addition to acting as a neurotransmitter in the sympathetic nervous system, histamine in the periphery has been linked to mediation of inflammatory, immunosuppressive, and gastrointestinal effects. Outside the neuronal system, significant sources of histamine are enterochromaffin-like cells in the gut, where its release upon gastral and vagal simulation promotes acid secretion, and mast cells and basophils, where histamine release, triggered by allergens, and accompanying downstream effects constitute inflammatory response during an allergic reaction (vide infra). However, immune and inflammatory responses to histamine in leukocytes and lymphocytes are mediated by H_1, H_2, and H_4 receptors, as H_3 receptors appear not to be expressed on these cells.[5] Histamine action on mast cells has been suggested to cause chemotaxis, but not degranulation, again mediated by H_4 rather than H_3 receptors, which appear not to be expressed on murine[24] or human mast cells,[25] although H_3 receptors have been implicated in morphological changes and histamine release from rat brain mast cells.[26] Also suspect is the role of H_3 in human gastrointestinal tissues (vide infra). Separately, the H_3 receptor may have a potentially important, even if somewhat indirect, role in the mediation of effects of allergic rhinitis through regulation of norepinephrine levels in the sympathetic nervous system and, consequently, vascular tone in nasal mucosa linked to nasal congestion.[27]

Early synthetic H_3 agonists, used for receptor characterization, included very close analogues of histamine itself, such as *R*-α-methylhistamine **1** (RAMH) and *N*-methylhistamine **2**, as well as more elaborate examples imetit **3** and immepip **4** (Figure 3).[28,29] All of these compounds have shown some activity at other histamine as well as other biogenic amine receptors, which along with low oral bioavailability and rapid metabolism, has limited their utilization in vivo (as an example, see discussion on clinical trials for migraine with **1**, vide infra). However, they have figured prominently in historic in vitro pharmacological studies. Similar to archetypal agonists, all the early H_3 antagonists were based on the 4-substituted imidazole motif. Most prominent among them are thioperamide **5**, clobenpropit **6**, and ciproxifan **7** (Figure 3).[28,30,31] Proxyfan **8**, initially identified as a neutral H_3 antagonist, has been recharacterized as a protean agonist, its functional profile dependent on the assay system used.[32] While histamine and H_3 agonists have been generally linked to the down-regulation of histamine and other neurotransmitter release in tissue preparations and in vivo and while antagonists have generally had the opposite pharmacologic response, the underlying complexity of H_3 receptor biology has often rendered exact agonist−antagonist classification challenging and dependent on the particular assay. In addition, most antagonists were reclassified as inverse agonists in view of their effect on H_3R constitutive activity in some, but not necessarily all, functional assays.[33,34] At the same time, the rate of histamine turnover appears to be another differentiating factor: concomitant to increasing histamine levels, some (e.g., **5**) but apparently not all H_3 antagonists also increase levels of tele-methylhistamine.[35,36] Although judged a poor correlate of the antagonist activity, this tele-methylhistamine-elevating effect is observed with the most recent H_3 antagonists (vide infra).

On the molecular level the H_3 receptor is associated with several major pathways of signal transduction. These pathways have been repeatedly reviewed in the literature (in particular, recently in much detail by Leurs and co-workers)[37] and are also discussed in the Supporting Information and illustrated in Figure 4 of this manuscript. Connections between the biochemical signaling mechanisms and in vivo effects of the H_3 agonists and antagonists, whether hypothetical or clearly supported by data, are contemplated throughout the review.

Regulation of neurotransmitter release is considered the main underlying cause of the observed and/or expected therapeutic effects of H_3 receptor ligands in animal models or in humans. Changes in histamine levels result in variable activation of postsynaptic histamine receptors with key therapeutically relevant effects mediated by H_1 but with some roles also reserved for H_2 and, possibly, postsynaptic H_3 receptors[38] (see Figure 2). The connection between H_3 and H_1 signaling has been demonstrated through the dependence of typical H_3-mediated effects on the presence of functional H_1 receptors in the H_1 knockout ($H_1^{-/-}$) vs wild-type mouse experiments.[39] At the same time, H_3 heteroreceptors found on nonhistaminergic neurons regulate other neurotransmitters. Increases in the levels of neurotransmitters in the presence of an H_3 antagonist are generally rationalized by the antagonist's blockade of histamine's negative feedback via H_3 (resulting in the continued neurotransmitter release, histamine itself included) and supplemented by

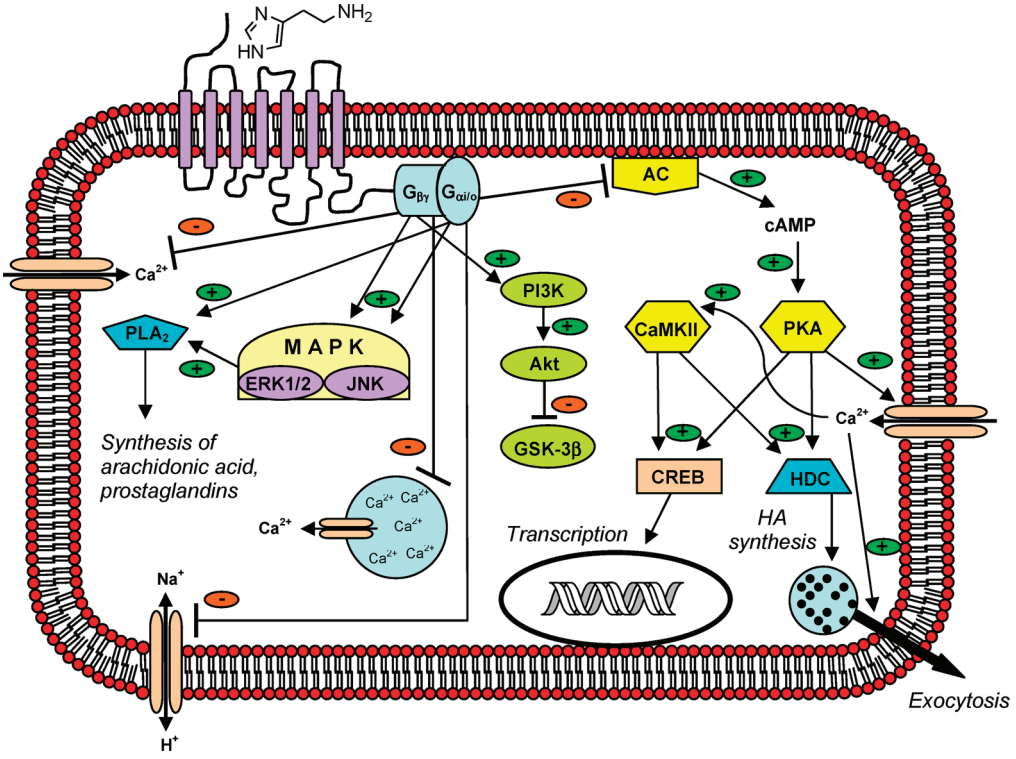

Figure 4. Molecular signaling pathways of the H3 receptor: AC, adenylyl cyclase; Akt, serine/threonine protein kinase; CaMKII, calcium/calmodulin-dependent protein kinase type II; cAMP, cyclic adenosine 3′,5′-monophosphate; CREB, cAMP responsive element-binding protein; GSK-3β, glycogen synthase kinase-3b; ERK, extracellular signal-related kinase; HDC, histidine decarboxylase; JNK, Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; PI3K, phosphoinositide 3-kinase; PKA, protein kinase A; PLA2, phospholipase A2.

histamine activation of H_1 receptors, with the latter sometimes the major factor. Thus, for example, an increase in the levels of acetylcholine was reported upon rat brain superfusion with histamine, despite the envisioned histamine's H_3 agonist action on cholinergic neurons. This acetylcholine-elevating effect was blocked by an H_1 antagonist but not affected by H_2 or H_3 antagonists, suggesting the overriding role of H_1 receptors, at least in this experiment.[19,40,41] However, the relationship between H_3 receptor activation/inhibition and the resulting neurotransmitter levels is often complex and multitiered. In addition to direct modulation by H_3 heteroreceptors on appropriate neurons, indirect pathways via other neurotransmitters have been suggested. It was shown, for example, that inhibition of acetylcholine release from rat cortex by H_3 agonists[42] may be GABAergic in nature. The effect of **4** was reversed by a GABA antagonist, suggesting positive coupling of H_3 heteroreceptors to GABA, which presumably in turn inhibits release of acetylcholine.[43] At the same time, the H_3 receptor effect does not appear to be uniform throughout the brain. Thus, several studies suggest the opposite effect in basolateral amygdala, with H_3 agonists enhancing and H_3 antagonists reducing acetylcholine release.[44,45] The complex nature of interactions between different neurotransmitter systems is well illustrated by the effects observed in H_3 knockout ($^{-/-}$) mice. Not surprisingly, histamine signaling is altered because of its reduced levels and reduced expression of H_1 receptors reported in a study of energy homeostasis effects in $H_3^{-/-}$ mice. A substantial concomitant increase in tele-methylhistamine levels (up to 135% in the hypothalamus) was also noted.[46] In a different study, which addressed behavioral changes in $H_3^{-/-}$ mice, the not easily explainable 42% reduction in brain cortex histamine content was accompanied by a reduced stimulatory effect of methamphetamine on locomotor activity, implicating decreased dopaminergic and/or serotonergic activity relative to $H_3^{+/+}$ animals. In this case, the density of H_1 receptors was reported to be unaffected by the gene knockout.[47] $H_3^{-/-}$ mice also showed resistance to the amnesic effects of the cholinergic antagonist scopolamine, suggesting perturbed cholinergic signaling as well. While these signaling interconnections appear to be extensive, more data are clearly needed to establish their exact nature. In addition to the receptor cross-talk at the functional level (concomitant response from receptors, different from the one directly activated, and arising from signaling molecules being shared across different signaling pathways), direct intramembrane interactions between different aminergic GPCRs at the molecular level, resulting in the formation of heteromeric complexes, have been reported.[48] This scenario was invoked in one particular example, where H_3 receptor displayed an antagonistic interaction with the D_2 receptor, and selective H_3 agonist **1** weakened D_2 receptor binding of the selective D_2 agonist quinpirole in sheep striatal membranes in vitro.[49] Moreover, the H_3 selective agonist **3** inhibited locomotor activation induced in reserpinized mice by the selective D_2 agonist quinpirole, while the H_3 selective antagonist **5** potentiated it. Such interactions (direct intramembrane or functional) may be of interest to drug discovery in view of the interconnecting nature and important roles of both histaminergic and dopaminergic neurotransmission in memory, attention, and psychiatric disorders (vide infra).[50]

While the abundance of cellular signaling pathways potentially influenced by H_3 receptor−ligand binding interactions would provide rationale for a variety of in vivo directions, the nature of H_3 biology often gives rise to complex in vivo profiles. This wide spectrum of in vivo effects (both already discovered and still targeted) should also be appreciated in context with the diversity of structural types developed over the 15-plus years of industrywide medicinal chemistry efforts.

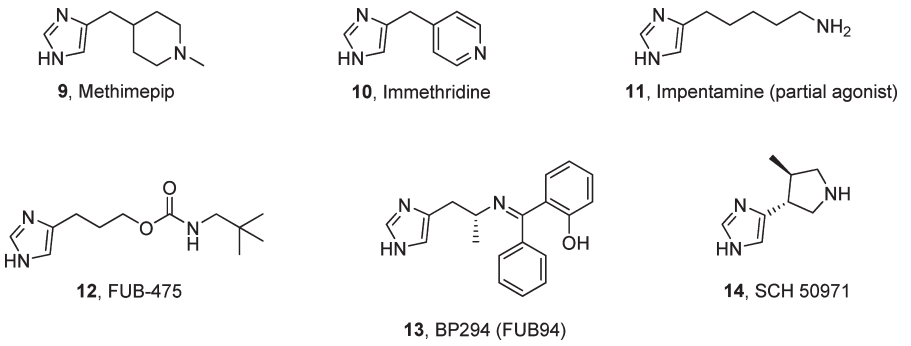

Figure 5. Historic H_3 agonists based on 4-substituted imidazole.

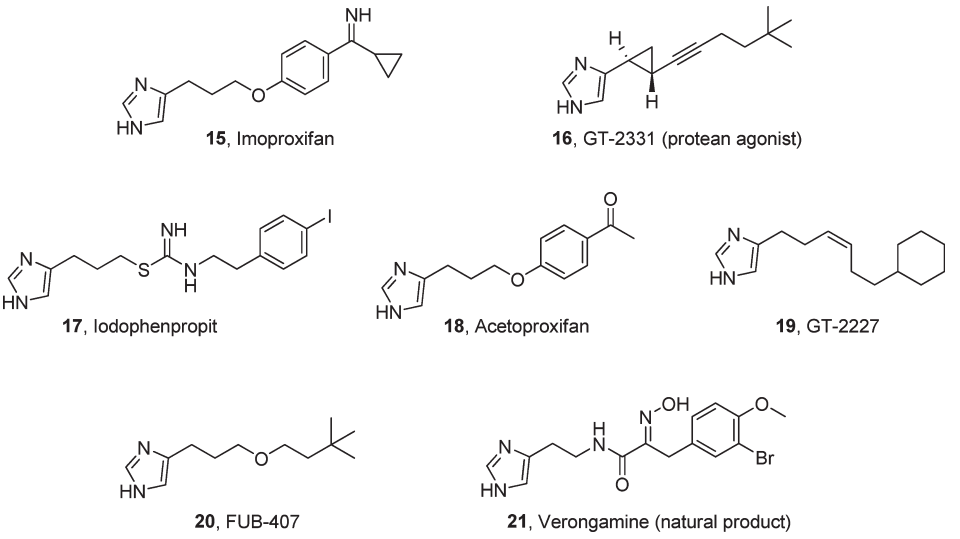

Figure 6. Historic H_3 antagonists/inverse agonists and protean ligands based on 4-substituted imidazole.

Historic H_3 Ligands

Over the past 20 years, numerous imidazole-based H_3 ligands have been described. Still in line with the archetypal 4-substituted imidazole scaffold, agonists and antagonists, in addition to those already shown in Figure 3 and used extensively in the receptor characterization, have been identified (Figures 5 and 6).[8,51] As already discussed, reclassification of many H_3 antagonists as inverse agonists, in particular the most commonly used compounds **5**−**7**, followed studies on H_3R constitutive activity. Cipralisant **16** (GT-2331, Perceptin, vide infra), designated a protean agonist similar to **8**, was one of the first H_3 compounds to advance to the clinic, reaching phase II enrollment for ADHD before progress was halted in 2002.[52] The imidazole-based natural product verongamine **21** displayed moderate H_3 binding in guinea pig membranes and was used as a template for further discoveries.[53] Numerous reviews have been published summarizing early work in the field as well as issues relating to selectivity versus H_4, differentiated receptor binding in various species (rat vs human), off-target affinities, and P450 inhibition caused by the imidazole ring.[8,51,53−57]

Therapeutic Applications of H_3 Agonists

A variety of potential therapeutic applications for H_3 agonists have been reported including inflammation, migraine, asthma, insomnia, pain, ulcer, hypertension, immunological regulation, and ischemic arrhythmias.[8,52,58] Generally associated with negative neurotransmitter modulation, H_3 agonists are expected to provide beneficial effects in cases where elevated neurotransmitter levels may be the reason for pathological conditions. In that regard, histamine's role in the maintenance of the awake state, nociceptive signaling, and inflammatory mediation sets it up as a target of therapeutic interference. For example, superfusion of rat basal forebrain with histamine produces a significant dose-dependent increase in wakefulness, presumably through excitation of cholinergic and noncholinergic neurons.[59] This arousal action, mediated by postsynaptic H_1 receptors and illustrated by the sedative effects of brain penetrating H_1 antagonists,[60,61] has been associated on its extreme end with insomnia.[64] Compounds **3**, **13** (BP294, also FUB94), and **14** (Sch 50971) have shown increased sleep time and/or sedation in preclinical animal models, effects that were neutralized by H_3 antagonists.[63−65] However, a recent sleep study with **4** showed little sleep promoting effect in rats despite a significant decrease in brain histamine concentrations.[66] At the same time, insomnia has been mentioned as the major adverse event in a clinical trial with the H_3 antagonist **59** (PF-03654746) (vide infra).

Histamine's involvement in neurogenic inflammation in various tissues, characterized by afferent nerve-mediated vasodilation, increased vascular permeability, plasma leakage, smooth muscle contraction, increased inflammatory cytokine production, and immune cell recruitment,[5] implicates it in mediation of pathological processes associated with allergic inflammation,[67] asthma,[68] and migraine.[69] As discussed above, relevance of the H_3 receptor agonists is in presynaptic regulation of histamine, the postsynaptic inflammatory effects of which appear to be

mediated via H_1 and H_4 receptors. Thus, intradermal administration of histamine induced scratching behavior in mice, reduced by H_1 and H_4, but not H_2 antagonists.[70] While the effect of H_3 antagonist−H_4 agonist **6** in this study was attributed to its H_4 agonist activity, other studies[71,72] have suggested that **6** causes pruritis and allergic rhinitis (inhibited by NK_1 receptor antagonists) through H_3 antagonist-induced release of neuropeptide substance P.[73] In general, the effects of H_3 receptor modulation may extend, directly or indirectly via histamine, to other neurotransmitters and mediators, critical or contributing to the pathology of neurogenic inflammation. Thus, in addition to histamine and substance P, other H_3-modulated neurotransmitters (e.g., acetylcholine, serotonin) also cause bronchoconstriction in allergic responses by effecting smooth muscle contraction. Alleviation of this condition by H_3 agonists (due to their moderating effect on neurotransmitter release) may be expected; however, because of multiple possibilities, the exact mechanism of action may be difficult to establish. For example, the H_3 agonist **1** acted as a smooth muscle relaxant in the perfused guinea pig bronchioles and lung strips under resting tone,[74] the effect presumably arising from the inhibition of acetylcholine and histamine background release. However, **1** also reversed bronchoconstriction induced by electrical field stimulation under the conditions of postsynaptic histamine and muscarinic receptor blockade by their respective antagonists,[75] leaving open the interpretation of the exact mechanism. In addition, **1** reversed bronchoconstriction caused by exogenously administered histamine or acetylcholine,[76] the effect hypothesized to result from increased levels of metabolites of arachidonic acid on the basis of dose-dependent bronchoconstriction increase by COX inhibitor indomethacin.[77] The bronchodilatory effect of **1** in all cases was blocked by the H_3 antagonist **5**. In another study, **1** and **3** reduced endothelial permeability in acetylcholine-induced pulmonary edema in isolated perfused rabbit lungs, a finding attributed to the H_3 agonist effect on substance P levels.[78] Compound **14** alleviated sneezing and nasal rubbing in a mouse model of allergic rhinitis[72] and was reported active in a central neurogenic vascular inflammatory model of migraine in the guinea pig.[65] As a potential drug candidate, **1** displays good in vitro potency, but its poor human oral absorption, poor brain penetration, and rapid metabolism by HNMT were discovered in early clinical trials.[54,79,80] A prodrug of **1**, benzhydrylimine **13**, displayed improved human pharmacokinetic properties over the parent compound (plasma half-life $t_{1/2} > 24$ h)[79] and reached phase II clinical trials for asthma and migraine; however, lack of information on compound progression since 1996 moderates enthusiasm for these indications.[52] Elsewhere, in a phase II trial featuring unusually low doses (1−3 ng twice weekly, subcutaneous (sc)), the nonselective H_3−H_1 agonist **2**[1] decreased the frequency, intensity, and duration of migraine attacks. However, intense headaches were reported at higher doses (4 ng in migraine patients and 10 ng, previously, in phase I healthy volunteers), possibly because of neurogenic edema caused by H_1 agonism.[81] Although phase III results, disclosed in 2006, apparently confirmed antimigraine activity of *N*-methylhistamine without evidence of adverse effects,[58,82] there seems to have been no filing for registration.

While the role of H_3 receptors in nociception has been investigated, the resulting evidence is conflicting. Sensitivity to noxious stimuli was greatly reduced in $H_1^{-/-}$ [83] and histidine decarboxylase knockout ($HDC^{-/-}$) mice,[84] while administration of exogenous histamine in the latter case significantly induced nociceptive behavior, inhibited, in turn, by the H_1 antagonist pyrilamine. Antinociceptive activity has been reported with H_3 agonists **13**[79] and **4**[85,86] in rats, although the effects were not general (model- and species-specific) and not completely understood. However, these data seem to be contradicted by the fact of analgesic effects observed with histamine itself, histidine, the HNMT inhibitor metoprine as well as H_3 antagonists.[87,88] In general the outcome may certainly be affected by the physiological differences between acute nociceptive and chronic inflammatory and neuropathic pain,[89] the latter being the ostensible clinical target of H_3 antagonists (vide infra).

Modulation of norepinephrine release in the cardiovascular system by H_3 receptors located on sympathetic nerves in heart and blood vessels suggests the use of H_3 agonists for the treatment of cardiac dysfunction and ventricular arrhythmias associated with myocardial ischemia and triggered by excessive norepinephrine levels.[90] As discussed above, activation of H_3 receptors reduces norepinephrine release by inhibiting both Ca^{2+}-mediated exocytotic[91] and carrier-mediated (Na^+/H^+ exchanger (NHE) activated) mechanisms,[92] the first being associated with acute and the second with protracted myocardial ischemic condition. On the basis of isolated guinea pig and human heart tissue experiments, the role of **3** in the reduction of norepinephrine release was established for the protracted but not the acute condition, where H_3 receptors already appear to be fully activated.[90] In addition, the role of H_3 agonists in mediating cardiovascular effects extends to the presynaptic regulation of histamine release in the heart. Positive chronotropic and inotropic effects of histamine (increase in the rate and force of heart muscle contraction) in dogs and humans have been linked to its action on postsynaptic (H_1, H_2) receptors.[93] In that regard, use of H_3 agonists under the conditions of cardiovascular distress could inhibit release of histamine and reduce its cardiac stimulatory and arrythmogenic effects. Despite all these data or perhaps precisely because of histamine's potentially fundamental role in maintaining the status quo, there have been no attempts so far to develop an H_3 agonist for cardiovascular indications.

In addition to the research directions outlined above, an apparent connection between elevated histamine levels (presumably achieved as a result of exogenous histidine administration) and increased anxiety in mice (attenuated by an H_1 antagonist) has been reported in the elevated plus-maze test.[94] Conceivably, this would suggest a role for H_3 agonists as antianxiety agents, although no relevant data have been disclosed.

Therapeutic Applications of H_3 Antagonists/Inverse Agonists

A variety of potential therapeutic applications for H_3 antagonists/inverse agonists have been proposed including CNS disorders such as Alzheimer's disease (AD), schizophrenia, dementia, anxiety, tremor (Parkinson's disease (PD)), attention deficit hyperactivity disorder (ADHD), depression, mood disorders, sleep disorders (narcolepsy), pain/itch, stroke, epilepsy, as well as metabolic syndrome (MS, including obesity and diabetes), nasal inflammation (allergic rhinitis, congestion, allergy), and cancer.[8,51,99,53,58,62,95−100]

In contrast to the early work in the field, most chemical series of current interest appear to be nonimidazole in nature, reflecting major disadvantages of the 4-substituted imidazole motif, including poor brain penetration and issues related to CYP450 inhibition, such as drug−drug interactions, extrapyramidal symptoms, liver toxicity, and inhibition of adrenal steroid synthesis.[51,57] In addition, nonimidazoles tend to be

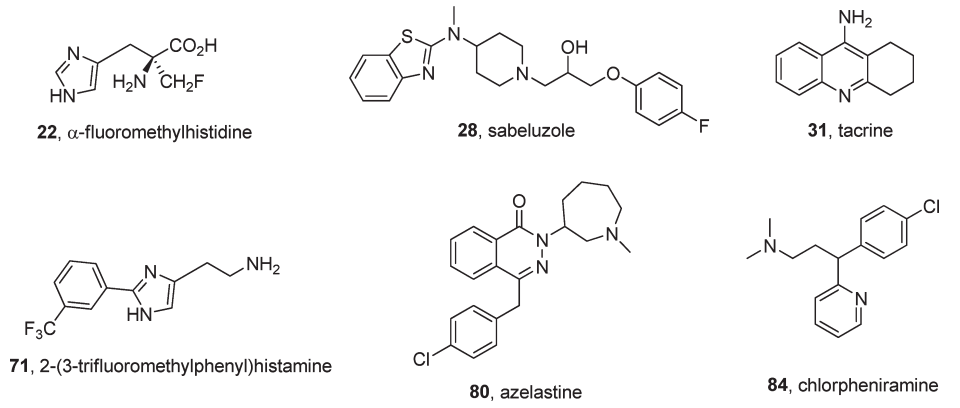

Figure 7. Miscellaneous non-H_3 compounds.

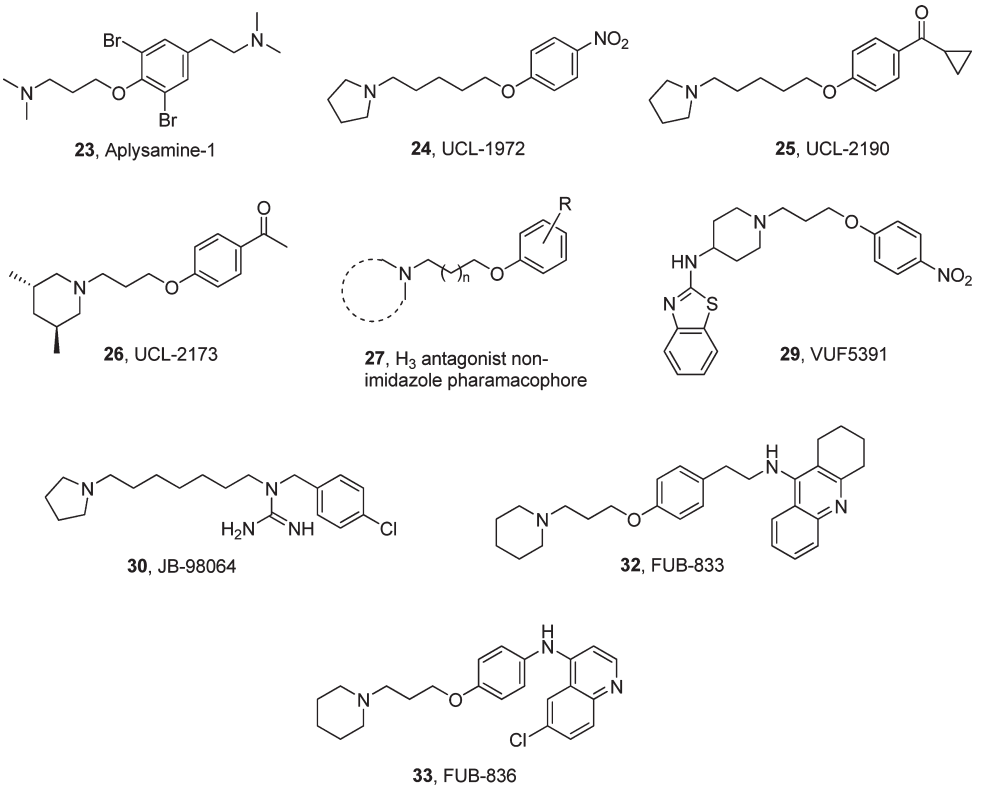

Figure 8. Early non-imidazole H_3 antagonists.

more selective for H_3 vs H_1, H_2, and H_4.[101] In 1994, a weak nonimidazole H_3 antagonist, the marine natural product aplysamine-1 (**23**, Figure 8), was patented by Harbor Branch Oceanographic Institution.[51] The compound contained a phenoxyalkyl-*N*,*N*-dialkylamine fragment that would later become an important reoccurring motif in the field. Starting in 1998, Ganellin and co-workers (University College, London) described a systematic SAR exploration that resulted in a series of compounds including **24** (UCL-1972), which showed good potency and a favorable pharmacokinetic profile.[8,51,57] The academic FUB-UCL-INSERM-Bioproject consortium has provided many additional examples of potent nonimidazole H_3 antagonists including the potent analogues of **7**, such as compounds **25** (UCL-2190) and **26** (UCL-2173), further confirming the emerging nonimidazole pharmacophore **27** as an exciting new area for H_3R research.[51] Early work by Menge and co-workers (Vrije Univerisiteit) was based on the nootropic agent sabeluzole **28** (Figure 7) and led to the potent ligand **29** (VUF5391).[8,51] The James Black Foundation also disclosed examples of early nonimidazole H_3 antagonists, including the selective and potent guanidine-based **30** (JB-98064).[51] Modeled after the acetylcholinesterase inhibitor tacrine **31** (Figure 7), compound **32** (FUB-833) demonstrated dual H_3 antagonist−acetylcholinesterase inhibitory activity,[102] whereas the truncated analogue **33** (FUB-836) was reported as the first in a new class of dual H_3 antagonist−HNMT inhibitors.[103] More details on early nonimidazole antagonists can be found in recent reviews.[8,51,57]

Evolution of the prototypic H_3 antagonist pharmacophore has been discussed elsewhere.[51] The current generally accepted model incorporates a basic amine motif separated by several atoms from the central, typically hydrophobic, core, which is joined on the other side by a structurally variable region in the form of, inter alia, another basic amine or a

polar, nonbasic arrangement (e.g., amide). The basic amine portion of the pharmacophore, historically represented by a 4-substituted imidazole, is replaced by the *N*,*N*-dialkylamino motif (most commonly, a substituted piperdine or pyrrolidine or their bicyclic variations) in more recent nonimidazole analogues. Early pharmacophore modeling based on a set of imidazole antagonists suggested two hydrophobic pockets and four hydrogen-bonding sites on the receptor, two of which engage the imidazole ring.[104] On the basis of mutational and homology modeling studies of the H_3 receptor, interaction of the imidazole ring of H_3 agonists with aspartate 114 in transmembrane domain 3 (TM3) and glutamate 206 in TM5 was proposed.[105] However, this model seems to be a long way from lending practical support to the design of new ligands. Functional consequences of the single amino acid mutations vary depending on the particular ligand, assay, and assay end point (efficacy vs potency). Occasionally virtual H_3 screening models have been considered;[106] however, the target at this point seems to be ill-suited for rational ligand design.

Despite extensive medicinal chemistry efforts waged by most major pharmaceutical companies, the overall chemical diversity of H_3 antagonists appears to be moderate, perhaps dictated by the structural requirements of the receptor. Certain structural fragments, in particular, the (*N*,*N*-dialkylamino)-propoxyphenyl motif **27** ($n = 1$), consistently repeat themselves across different series. A bicyclic fused aryl or heteroaryl linearly linked to several monocyclic fragments is perhaps the most widespread structural arrangement among nonimidazole H_3 antagonists, although a combination of three to five linearly linked monocycles is also quite common. Very few unique structural arrangements have been reported, as will be apparent from the discussion of individual series, grouped by therapeutic indication and originator company below.

Cognitive Disorders

The use of H_3 ligands to improve cognitive dysfunction associated with a number of neuropsychiatric diseases such as AD, schizophrenia, and ADHD has been investigated both preclinically and clinically. Although these conditions most likely disrupt multiple neurotransmitter pathways, treatments have traditionally focused on a single system. As discussed above, H_3 antagonists/inverse agonists may offer a unique approach in their ability to affect multiple neurotransmitters in regions of the brain associated with memory and learning.[95,97,98,107] While multiple literature reports on the cognitive effects of histamine itself as well as other histamine receptor ligands (mediated postsynaptically via H_1 receptors[108] and presynaptically via H_3 homo- and heteroreceptors (see Figure 2)) support the importance of the cholinergic system in signal transduction, other H_3-modulated neurotransmitters may be increasingly found to play a role. Functional consequences of the interaction between the histaminergic and cholinergic systems in the rat brain were discussed above.[19,40−45] While elevated histamine levels in most brain regions also led to increased levels of acetylcholine, evidence of the opposite effect in basolateral amygdala in rats has been reported and attributed to activation of postsynaptic H_2 receptors, negatively coupled to cholinergic transmission.[89] Interconnection of H_3 and cholinergic signaling is also illustrated by the insensitivity of the $H_3^{-/-}$ mice to the otherwise amnesic effects of the cholinergic receptor antagonist scopolamine.[47] In addition, as suggested by literature evidence, histamine itself may also play a direct procognitive role.[109] Inhibition of histamine synthesis deteriorates short-term memory, while administration of exogenous histamine and histidine improves short-term memory.[110] This is in good alignment with the observed increased output of acetylcholine from nucleus accumbens and cortex of freely moving rats, caused by exogenous histamine and blocked by H_1 antagonists.[19,40] Consistent with histamine signaling pathways, $H_1^{-/-}$ mice exhibit impaired memory characteristics, translating into reduced object recognition and maze performance.[111,112] At the same time, impaired cholinergic signaling is believed to play an important role in the cognitive dysfunction aspect of schizophrenia, largely untreated by the current medications. In fact, the possibility of cholinergic signaling disruption by the very antipsychotic drug therapies currently in use has been discussed.[113] Increased levels of histamine brought on by the administration of H_3 receptor antagonists may conceivably counterbalance this effect. Furthermore, both acetylcholine and histamine itself can regulate dopamine and glutamate release, abnormalities in which are also strongly associated with schizophrenia pathology.[114] In addition, dopaminergic neurotransmission and noradrenergic neurotransmission play key roles in memory and attention and are subject to histaminergic regulation, thereby linking H_3 receptor with attention-deficit hyperactivity disorder (ADHD).

An important role in the pathophysiology of ADHD is attributed to impaired catecholamine signaling, believed to be caused by dysfunction of the respective dopamine and norepinephrine transporter systems.[115] Current stimulant and nonstimulant ADHD treatments (Ritalin (methylphenidate), Adderall (a mixture of dextroamphetamine and racemic amphetamine salts), and Strattera (atomoxetine)) block reuptake of dopamine and norepinephrine and/or increase their release into the neuronal synapse.[116] In addition, however, methylphenidate and atomoxetine were also found to elevate prefrontal cortex levels of histamine in rats.[117] Similarly, the α_1 agonist modafinil (Provigil), found to be effective in the treatment of ADHD in several clinical trials,[118] although rejected for that particular indication by FDA in 2006, indirectly modulates the histaminergic system, in addition to its other CNS actions,[119] and is efficacious in the treatment of narcolepsy (vide infra). It is possible then that improvements in ADHD symptoms observed with these drugs are partly due to the increased levels of histamine itself, likely acting as an integral contributor to the overall improved signaling. In that regard, an H_3 antagonist may be a valuable addition to the existing therapies.

In addition to improving cognitive aspects, the role of H_3 antagonists may extend to provide some degree of neuronal protection in such diseases as AD and PD because of, among other possible mechanisms, their inhibitory effect on the PLA_2 signaling pathway (see Supporting Information) and the accompanying generation of cell-damaging electrophilic metabolites.[120] At the same time, in an apparent contradiction to the current prevailing view, the potential role for H_3 agonists in cognitive improvement and neuronal protection was contemplated on the basis of GSK-3β inhibition as part of the H_3-activated PI3K−Akt−GSK-3β signaling pathway (see Supporting Information).

Historic H_3 antagonists, such as **5**−**7** and **34** (GT-2016,[121] Figure 9), have been reported to improve cognitive function, memory, spatial orientation, attention, and learning in a variety of rodent models.[56,98−100,122−124] It is important to note, however, that performance in certain emotional memory

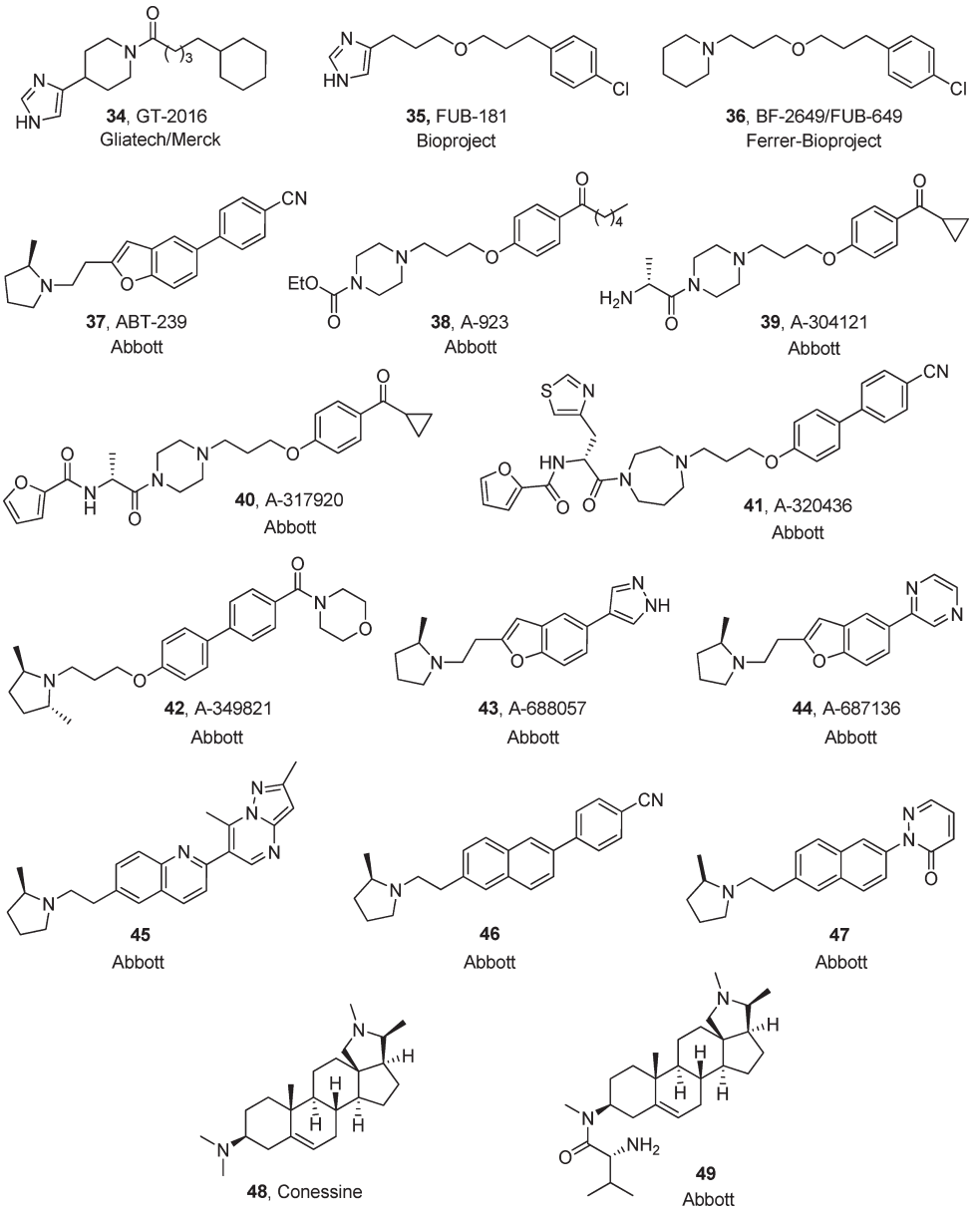

Figure 9. H_3 antagonists/inverse agonists for cognition.

tasks, such as those preceded by contextual fear conditioning and mediated by neural changes in basolateral amygdala, appears to be inhibited by histamine and H_3 antagonists.[45,125] This effect aligns with the ERK signaling pathway activated by H_3 agonists[126] (see also Supporting Information) and with the pattern of histaminergic regulation of acetylcholine in the basolateral amygdala, discussed above and seemingly different from the mechanism in the cortex. Compound **5** has also recently been shown to exhibit an antipsychotic-like profile in mice[127] and improvements in learning deficits in a childhood epilepsy model.[128] Detailed summaries of in vitro and in vivo effects of brain histaminergic modulation with historic as well as more recent H_3 ligands are available in recent reviews.[53,56,95,98,101,129]

Gliatech investigated the potential use of the imidazole-based **16**[130,131] for a variety of indications including ADHD, AD, insomnia, dementia, anxiety, sleep disorders, and eating disorders.[52] The compound has a high affinity at the rat cortical H_3R (K_i = 0.18 nM), but a 40-fold lower affinity at the human receptor. It also binds strongly to human α_{2a}, human α_{2c}, and human H_4 receptors.[52,99] Compound **16** was progressed into phase I clinical trials in 1998 and reached phase II enrollment in 2000 for the treatment of ADHD before the trials were halted. Subsequent to Gliatech's 2002 bankruptcy and transfer of intellectual rights to Merck, **16** was identified as a protean agonist[32,33] in that it displays a complex pharmacological profile ranging from full agonism to full antagonism in various in vivo or in vitro systems.[132] In contrast, recent nonimidazole H_3 ligands, displaying in vivo profiles characteristic of H_3 antagonists, have typically been reported as inverse agonists in vitro.

The FUB-UCL-INSERM-Bioproject consortium reported **35** (FUB-181) as an efficient and selective H_3 antagonist/inverse agonist that increased turnover rates of histamine, norepinephrine, and serotonin in key brain regions[54,133] and demonstrated beneficial learning and memory properties in rodents.[56] However, as previously mentioned, imidazole-based compounds such as **5**, **6**, and **35** are generally considered unsuitable for clinical development because of CYP450 liabilities. Stark and co-workers replaced the imidazole with piperidine,

leading to tiprolisant **36** (BF-2649/FUB-649),[134] which increased dopamine and acetylcholine brain levels in rats and showed memory and learning enhancing properties in mice without observable changes in locomotor activity or hepatic toxicity. The compound also showed significant activity in several mouse models of schizophrenia.[58,135] Compound **36** is being developed through a collaboration between Ferrer and Bioproject[52] and is currently in phase II clinical trials for schizophrenia (begun June 2008)[58,95,136] as well as phase II trials for narcolepsy/excessive daytime sleepiness (EDS) associated with PD (begun Oct 2007, vide infra).[52,136] However, an independent group from Abbott has recently indicated potential development concerns including CYP2D6 inhibition, high hERG activity, and other issues.[95] Another clinical trial for a cognitive indication, a phase I ADHD study with betahistine **72** by Obecure,[136] is discussed in the section Obesity and Diabetes Mellitus.

Abbott. Abbott has been very active in the H_3 receptor field, having nominated two compounds, **37** (ABT-239, Figure 9) and ABT-834 (structure not disclosed), for clinical development and having made significant contributions to the understanding of H_3R in vitro and in vivo pharmacology.[95,98,101] An initial screening hit, phenoxypropylpiperazine analogue **38** (A-923), was a potent binder of the rH_3R ($K_i = 2$ nM) and served as a useful lead despite its poor bioavailability and selectivity.[137] Lead optimization led to D-alanine type derivatives **39** (A-304121) and **40** (A-317920)[138] which showed good binding in initial screening at the rH_3R ($pK_i = 8.6$ and 9.2, respectively) but later showed significant affinity dropoff at the hH_3R when the receptor became available ($pK_i = 6.1$ and 7.0, respectively). Both compounds were selective over H_1 and H_2, showed good oral bioavailability,[139] and were active in rodent cognitive models. However, **39** caused phospholipidosis, a condition clinically linked to pulmonary dysfunction, in which high partitioning of a compound into lipid bilayers causes an impairment of phospholipid turnover. This toxicity was attributed to the compound's dibasic amine and cationic amphiphilic nature[101] and was not observed with the less basic **40**. Alternatively, a biphenyl fragment was incorporated in **41** (A-320436), which showed good binding to hH_3R ($pK_i = 8.8$) but poor brain penetration and lack of efficacy in cognitive and ADHD models.[140] The biphenyl motif has also been successfully utilized in other Abbott compounds such as **73** (A-331440) and **74** (A-417022, Figure 12), which demonstrated activity in antiobesity models (vide infra). The dimethylpyrrolidine **42** (A-349821) showed good affinity and selectivity for rH_3R and hH_3R ($pK_i = 9.4$ and 8.8, respectively) and had good bioavailability and low clearance in dog and monkey. The compound was efficacious in some cognition models, but brain penetration was modest compared to other Abbott compounds (brain/plasma (B/P) of ~1). Since the compound was not a P-glycoprotein substrate, the reduced CNS access was attributed to its amide nature. Compound **42** was not genotoxic and showed no overt toxicity in a 2-week rat study. Unfortunately, QTc prolongation-related issues in a canine safety evaluation precluded further development.[51,55,101,141]

To improve absorption and druglike properties, **37** was designed as a conformationally restricted analogue with the propyloxy spacer tied up in a benzofuran. It is potent at the rH_3R ($K_i = 0.45$ nM) and hH_3R ($K_i = 1.35$ nM) and has excellent selectivity against 80 other non-H_3 CNS receptors. Compound **37** also has good bioavailability in several species (rat 52%, dog 74%, and monkey 89% at 1 mg/kg) and no inhibition of CYP450 enzymes. Excellent activity was observed in several rat attention, cognition, and social memory models related to ADHD and schizophrenia. Increases in acetylcholine and dopamine levels in vivo have been registered at drug doses that parallel behavioral efficacy in animal models. The 4-cyanophenyl-substituted benzofuran **37** demonstrates high brain partitioning ($B/P > 34$) and potency in cognition models compared to the open-chain-spacer biphenyl analogue **42**.[95,142−144] However, high plasma protein binding and phospholipidosis have also been noted as a result of the highly lipophilic nature.[97,101] Although a process synthesis was disclosed,[145] development of **37** was halted because of QTc prolongation observed in monkeys.[52,101,146]

Additional SAR studies that explored phenyl ring substitution[147] and heterocyclic replacements resulted in the discovery of **43** (A-688057) and **44** (A-687136).[146] Pyrazole-substituted benzofuran **43** showed good affinity for the rH_3R and hH_3R ($pK_i = 8.5$ and 9.3, respectively) and an improved hERG profile and was effective in preclinical cognitive models. The lower lipophilicity, compared to **37**, also suggested a lower potential for phospholipidosis. However, less promising pharmacokinetic properties (rat oral BA 26%, $t_{1/2} = 2.9$ h; dog oral BA 30%, $t_{1/2} = 1.7$ h; monkey oral BA 8%, $t_{1/2} = 1.8$ h) suggested a short half-life in humans that may be unfavorable for conditions such as ADHD.

Replacement of the benzofuran core in **37** has led to several interesting new series exemplified by **45**, **46**, and **47**. The quinoline **45** showed good in vitro potency (rH_3R $K_i = 0.93$ nM, hH_3R $K_i = 0.24$ nM), PK in rat (90% oral BA, $t_{1/2} = 5.3$ h), brain penetration, and potency in cognitive models. However, the compound was abandoned because of photoinstability of its free base form and cardiovascular concerns such as increased heart contractility in dog.[148] The naphthalene-based **46** also showed good potency in vitro (rH_3R $K_i = 2.5$ nM, hH_3R $K_i = 0.24$ nM) and acceptable rat PK (55% oral BA, $t_{1/2} = 5.5$ h). Notably, this analogue features an even higher B/P ratio (72) than **37**.[149] The multikilogram synthesis of pyridazinone **47**, which displays favorable biological, hERG, and PK profiles (hH_3 $K_i = 0.8$ nM, rat PK (1 mg/kg, oral (po)) of 84% BA and $t_{1/2} = 4.9$ h), has been published.[150,151] ABT-834 (structure not disclosed), the backup to **37**, reportedly entered clinical trials for cognition in 2003, but no data have been released, suggesting that development may have been discontinued.[52,98]

Abbott has also disclosed the natural product conessine **48** as an H_3 antagonist discovered in a high-throughput screen.[152] The potent (hH_3R $K_i = 5.4$ nM) and novel steroid-based compound penetrates the CNS, but its profile suffers from a slow CNS clearance and adrenergic activity. Optimization efforts led to the *N*-methyl-D-valine analogue **49** which has favorable potency (hH_3R $K_i = 0.21$ nM), improved selectivity, and activity in a mouse behavioral model of cognition.[152]

GlaxoSmithKline. Researchers at GlaxoSmithKline have developed a novel H_3 active tetrahydrobenzoazepine scaffold from initial screens of the phenoxypropylamine chemotype. The observation that the propylpiperidine motif in the initial lead **50** could be replaced with various aryl or heteroaryl ethers (e.g., **51**) led to the discovery of **52** (GSK-189254).[97] The tetrahydrobenzoazepine **52** is potent and selective at rH_3R and hH_3R ($pK_i = 9.2$ and 9.9, respectively), has a good pharmacokinetic profile, and penetrates the CNS, specifically binding to key brain areas including temporal cortex

preparations derived from brain tissue from severe Alzheimer's patients. The compound promotes the release of acetylcholine, norepinephrine, and dopamine in rat cortex microdialysis studies (0.3−3 mg/kg, po) and shows activity in several rodent models of cognitive performance.[52,153] In addition, procognitive effects, receptor occupancy, and CNS exposures remained constant over multiple day twice-a-day (b.i.d.) dosing without evidence of tolerance or accumulation. Compound **52** entered phase I trials for dementia (2005, results not disclosed)[52,58] and neuropathic pain (vide infra) and phase II for narcolepsy (vide infra).[136] In addition, ^{11}C-labeled **52** has been used in a clinical study of another H_3 antagonist, GSK-239512 (structure not disclosed), to measure brain receptor occupancy with positron emission tomography (PET).[136] Glaxo is currently recruiting for a safety and tolerability study of GSK-239512 (mild to moderate AD patients),[136] but no longer lists **52** in its pipeline (Feb 2009).[52]

Two additional GSK compounds, the pyrazinetetrahydrobenzoazepine **53** (GSK-207040) and diazepane **54** (GSK-334429) have also been disclosed to possess intriguing activity in cognition and pain models.[154] Both compounds are high affinity functional inverse agonists at the hH_3R (pK_i = 9.7 and 9.5, respectively; GTPγS pIC_{50} = 9.2 and 8.6, respectively) and reverse memory impairment effects caused by scopolamine in rats in a passive avoidance model (0.3−1 mg/kg, po). In addition, the potential of **53** for the treatment of schizophrenia has been evaluated. The compound significantly enhanced object recognition memory and attenuated isolation rearing-induced deficits in prepulse inhibition but did not reverse amphetamine-induced increases in locomotor activity (3 mg/kg, po), a profile described as suggesting its therapeutic utility against cognitive and sensory-gating deficits but not positive symptoms of schizophrenia.[155]

Merck/Banyu. Merck/Banyu has disclosed a series of potent, selective, and CNS-penetrating quinazolinones including **55**, which shows reasonable pharmacokinetic profiles in multiple species without adverse cardiovascular or CNS effects in dogs (3 mg/kg, intravenous (iv)) or mice (100 mg/kg, po), and has reportedly been selected as a clinical development candidate.[156] The pyrrolidinylpropyloxy side chain in **55** was constrained as a cyclobutylpiperidinyloxy moiety in a series exemplified by **56**,[157] for which a process patent has been filed.[158] Banyu has also disclosed a regioisomeric quinazolinone **57** that was optimized to overcome initial hERG and adrenergic $h\alpha_{1A}$ activity concerns.[159] An H_3 antagonist, MK-0249 (structure not disclosed), is reported to be in several phase II trials for the treatment of AD, ADHD, cognitive impairment associated with schizophrenia, and excessive daytime sleepiness.[52,95,136]

Pfizer. Pfizer has recently disclosed the structure of **59** (PF-03654746, Figure 10), an H_3 antagonist currently in phase I clinical development for the treatment of cognitive impairment in schizophrenia and AD,[52] previously also investigated for the treatment of ADHD.[136] The compound displayed single-digit nanomolar potency at hH_3R in binding and β-lactamase reporter gene assays. Preclinically **59** enhanced histamine (drug minimal efficacious dose (MED) 1 mg/kg, sc) and acetylcholine (MED 3.2 mg/kg, sc) release in rat prefrontal cortex and demonstrated efficacy in a novel object recognition 24 h delay rat model (0.32 mg/kg, sc).[160,161] The compound was developed from the structural lead **58** and evolved into **59** as a result of optimization of, among other parameters, physicochemical properties to avoid the phospholipidosis liability seen with early analogues. Target engagement biomarkers in phase I clinical studies included histamine and tele-methylhistamine, measured in cerebrospinal fluid (CSF) of human volunteers after a multiple fixed-dose oral study (14 days, 3 mg, once a day (q.d.)). On the basis of favorable results, **59** was advanced into and completed a phase II trial study for ADHD,[136] although the program was apparently discontinued in March 2009.[52] Insomnia, presumably mechanism-based, was disclosed as the major observed adverse event.[160] Compound **59** has also completed a phase II clinical study for allergic rhinitis and is entering a phase II study for narcolepsy[136] (vide infra). Additionally, a phase I trial for AD is listed as currently active.[136]

Dual-Activity Compounds from Various Companies. Several studies have identified dual-activity compounds, with which engagement of additional targets could conceivably lead to cognitive synergy with H_3 antagonism. In addition to **32**[102] discussed above, compounds with dual H_3−acetylcholinesterase inhibitory activity have been reported by Johnson & Johnson {e.g., **60** (hH_3R K_i = 0.98 nM; AChE IC_{50} = 350 nM)}[162] and University of Parma {e.g., **61** (hH_3R pK_i = 8.70; AChE pIC_{50} = 5.96)}[163] and suggested for use in AD drug therapy. The combination of HNMT inhibition and H_3 antagonist activity in **33** was discussed above.[103] Dual H_3/M_2 (presynaptic acetylcholine) receptor antagonists {e.g., **62** (gpH_3R K_i = 18 nM; hM_2R K_i = 0.17 nM)}, optionally in further combination with an acetylcholinesterase inhibitor, were claimed for the treatment of AD and other cognitive disorders in a patent application, targeting an increase in acetylcholine levels via multiple mechanisms.[164]

Sleep−Wake

As discussed above for insomnia, histaminergic modulation has a pronounced effect on sleep and wakefulness. The wake-promoting effect of histamine stems from its activation of cortical and arousal system neurons via H_1 receptors.[165] In the sleep−wake cycle histaminergic and most other neurons release neurotransmitters and discharge at the highest rate during the waking period, decrease their activity during slow-wave or nonrapid-eye-movement (NREM) sleep, and stop firing during paradoxical or rapid-eye-movement (REM) sleep, the two forms of sleep alternating with each other on a periodic basis.[166] Reduced CSF histamine levels have been found in human hypersomnia,[167] while H_3 antagonism has been shown to have wake-promoting effect through the induction of histamine release. Several studies have been undertaken to investigate the use of H_3 antagonists to treat excessive daytime sleepiness (EDS) and narcolepsy-associated uncontrollable cataplexy (sudden loss of muscle tone), believed to result from excessive somnolence and inappropriate transitions into paradoxical sleep.[168] Current treatments of narcolepsy include classic CNS psychostimulants such as amphetamine and caffeine, whose efficacy is hampered by issues of tolerance and increased locomotor activity, and the α_1 agonist modafinil, which affects wakefulness through an indirect activation of the histaminergic system.[62,63,99,169] Classic H_3R antagonists such as **5**, **7**, **16**, and **36** have been shown to increase wakefulness and decrease sleep in rodent, feline, and canine models. Notably, the effects are absent in knockout mice lacking either the H_3 or histidine decarboxylase gene.[58,62,63,97,98,135,170] Compound **36** promoted wakefulness, decreased abnormal direct-rapid-eye-movement (DREM) sleep, and reduced EDS in orexin knockout ($Ox^{-/-}$) mouse

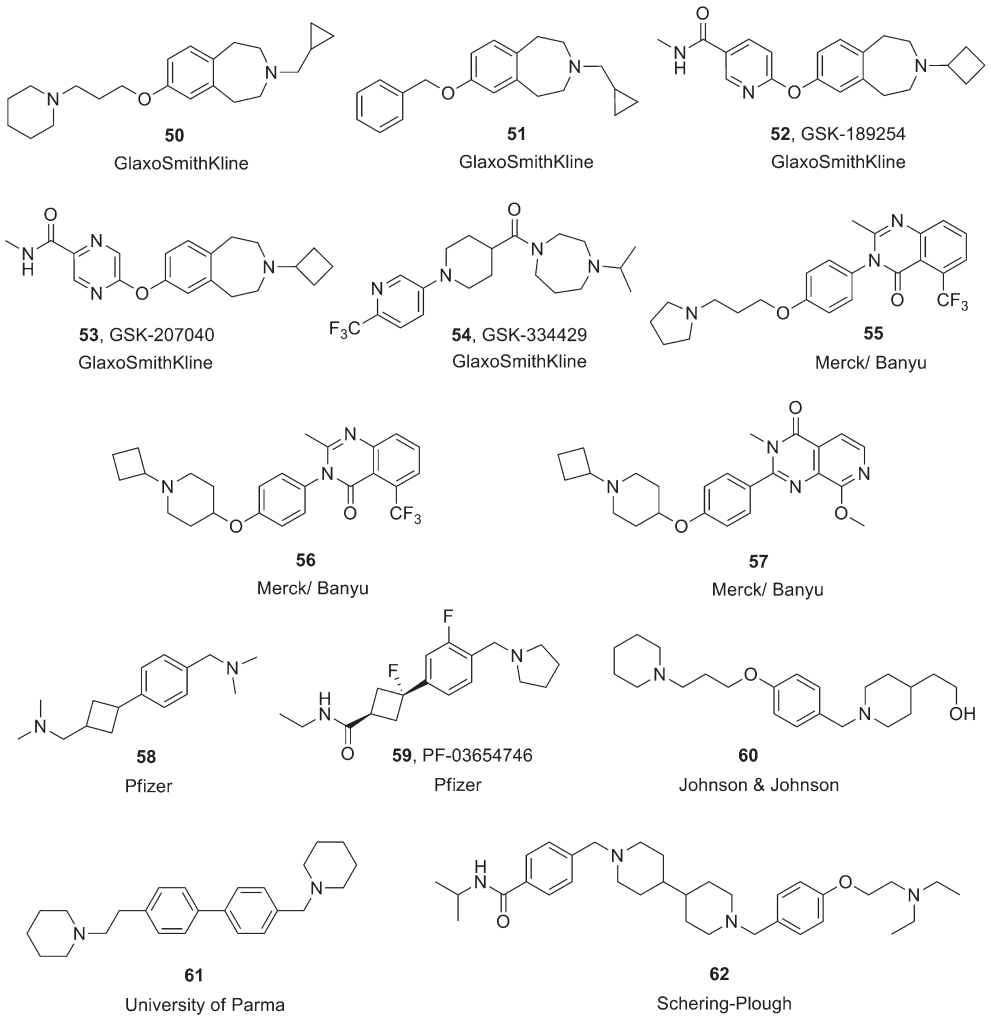

Figure 10. H_3 antagonists/inverse agonists for cognition.

model of narcolepsy as well as in two small human clinical studies.[171,172] Orexins are neuronally released excitatory peptides promoting wakefulness and closely linked to aminergic neurotransmission. Differential effects of acute and repeat dosing of the H_3 antagonist **52** on sleep−wake cycle and narcolepsy have been described. Significant reduction of the wakefulness-promoting effect and increased suppression of narcoleptic episodes in $Ox^{-/-}$ mice have been reported with subchronic dosing (8 days, 10 mg/kg, b.i.d., po).[173] Tetrahydrobenzoazepine **52** also increased wakefulness in rats and was advanced to phase II clinical study for narcolepsy, although the trial was terminated.[58,136] As discussed above, insomnia was reported as the major adverse event in a phase II clinical study for ADHD with **59**, which is currently entering a phase II study for narcolepsy.[136] The issue of higher drug dose, generally needed for robust wake effect compared to cognitive effects, was addressed in a recent wake-promoting study of **5**, **7**, **37**, and **52**, which demonstrated that relatively low levels of wake activity linearly correlated with receptor occupancy up to 80%. In contrast, a dramatic nonlinear increase in waking activity at higher receptor occupancy levels (>80%) was observed, potentially suggesting an altered mechanism due to a substantially modified overall neurotransmitter profile.[174]

Johnson & Johnson. In addition to the seminal efforts in the H_3R field, including the cloning and functional expression of the human receptor in 1999,[6] researchers from Johnson & Johnson have contributed extensively to the development of H_3R antagonists with wake-promoting and procognitive characteristics. Identified in a high-throughput screen, the calcium channel blocker **63** (RWJ-20085, also JNJ-280566, Figure 11) showed micromolar hH_3R activity.[175] Reminiscent of the natural product aplysamine, **63** exemplified the (*N*,*N*-dialkylamino)propoxyphenyl motif **27**. Early optimization efforts of this imidazopyridine provided **64** (JNJ-6379490), which displayed potent hH_3R binding (K_i = 2 nM) and excellent selectivity over other histamine receptors. Compound **64** displayed good oral bioavailability in the rat and dog as well as high brain penetration. Increased wake time was observed in rats (0.6 mg/kg, sc), although the activity appears to be limited to the first 2 h, even at high doses (10 mg/kg). Imidazopyridine **64** also demonstrated activity in a rat short-term memory model, although development was apparently halted because of idiosyncratic toxicity in the dog.[170,175]

Further work led to the 4-(aminoalkoxy)benzylamine series typified by the neutral antagonist **65** (JNJ-5207852), which showed good potency (hH_3R, pK_i = 9.24), selectivity, CNS penetration, and oral biovailability. This candidate also promoted wakefulness in rodents (10 mg/kg in the rat) and decreased NREM/REM sleep without rebound hypersomnolence.

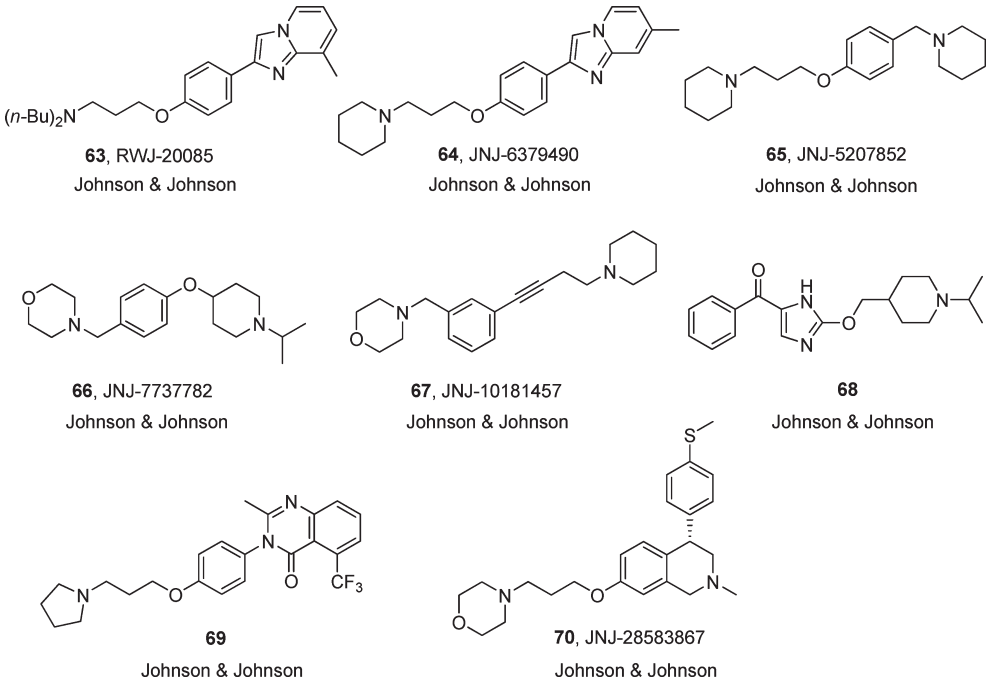

Figure 11. H_3 antagonists/inverse agonists for narcolepsy.

No effects on sleep or wakefulness were observed in $H_3^{-/-}$ mice. In addition, **65** decreased episodes of cataplexy in a genetically narcoleptic Doberman Pinscher model and showed efficacy in learning and memory tests without affecting locomotor activity. Unfortunately, **65** shared the liabilites of related diamines, including an unfavorably high volume of distribution (>100 L/kg), long plasma half-life (15−17 h), and brain residency in the rat (full receptor occupancy in the striatum observed 24 h after 30 mg/kg po dose), as well as phospholipidosis-related toxicity, precluding further development.[55,170,176,177] Conformational restriction of the aminoalkoxy chain provided compounds such as **66** (JNJ-7737782) which was active in rodent models of wakefulness (1 mg/kg, sc).[178]

Further examples of Johnson & Johnson's diamines with rigidified linkers include alkynes exemplified by **67** (JNJ-10181457) with good H_3 potency, selectivity, brain residency, and pharmacokinetic profiles.[52,170] Phenylacetylene **67** promoted wakefulness in mice and reduced cataplectic attacks in narcoleptic dogs.[179] The compound also increased noradrenaline and acetylcholine levels in rat frontal cortex without affecting dopamine and serotonin and showed activity in learning and memory models without locomotor effects (10 mg/kg, intraperitoneal (ip)).[128,170,180] Given the wake-promoting action of **67**, its differential effect on neurotransmitter levels is noteworthy and may indicate their respective critical or flexible roles in the maintenance of arousal state.

JNJ-17216498 (structure not disclosed) is an orally active and selective H_3 antagonist that has completed a phase II trial for narcolepsy.[136] The compound was reportedly active in preclinical narcoleptic models and showed a favorable pharmacokinetic profile in phase I.[52,97] The syntheses and crystal structures of the centrally substituted imidazole **68**[181] and pyrrolidinopropoxyphenylquinazoline **69**[182] have also been recently highlighted, suggesting continuing interest in these series.

Researchers from Johnson & Johnson have also investigated a series of dual H_3 antagonist−serotonin reuptake inhibitors to address fatigue, somnolence, and cognitive impairment frequently diagnosed in patients suffering from depression. Wake-promoting agents such as modafinil have been successfully used with selective serotonin reuptake inhibitors (SSRI) to treat excessive sleepiness.[183] The notable feature of serotonin in the brain is its dual role in the sleep−wake cycle. It appears that initial rapid arousal action is followed by a delayed increase in NREM sleep as a result of the stimulated synthesis and release of sleep-promoting factors.[184] This effect appears to manifest itself in the daytime sedation observed with SSRI (e.g., fluoxetine) and may be targeted for neutralization by H_3 antagonists. Fusion of H_3 and SSRI pharmacophores has been achieved in the structure of **70** (JNJ-28583867, hH_3R $K_i = 11$ nM, hSERT $K_i = 4$ nM), which increased serotonin, norepinephrine, and dopamine levels in rat brain (hNET $K_i = 121$ nM, hDAT $K_i = 102$ nM). The compound shows antidepressant activity in mice and promotes wakefulness in rats.[185,186] As could be expected from its effect on serotonin, **70** decreased NREM and suppressed REM sleep (≥ 1 mg/kg, sc).

Pain/Analgesia

The potential role of H_3R ligands in the treatment of pain remains unclear based on the conflicting data for H_3R agonists and antagonists in pain models. As discussed above for H_3 agonists, the effects of histamine itself as well as other H_3 ligands on nociception are highly dependent on the conditions of the specific pain model. In the absence of clear understanding of mechanisms involved, the practical issue of relative receptor selectivity adds an extra variable to the already complex picture, as mediation of nociception by the H_4 receptors has also been reported.[187] For example, while the moderately H_3 vs H_4 selective antagonist **5** (rH_3R $pK_i = 8.4$, hH_3R $pK_i = 7.3$, rH_4R $pK_i = 7.3$, hH_4R $pK_i = 6.9$)[8,188] demonstrated moderate activity against acute nociceptive pain in some studies,[87] in other cases it had no effect by itself and also reduced the antinociceptive effects of morphine (tail-immersion and hot-plate tests and acetic acid-induced

writhing).[189] In contrast, the H_3 agonist **1** potentiated the effects of morphine. Antinociceptive activity for the H_3R agonists **1**, **4**, and **13** has been reported in some models, while in other studies **3** caused allodynia and **1** was hyperalgesic, preventing the effects of **5**.[58,79,85,99,190] Importantly, the limitations of these compounds as in vivo H_3 tools, including poor CNS penetration and rapid metabolism of **1**[85] and H_4 agonist activity of **3** and **4** (hH_4R pEC_{50} = 7.9 and 7.8, respectively),[188] complicate the interpretation of data. There is also evidence that the effect of an H_3 antagonist in a given model may even be dependent on the delivery route. Thus, central (intracerebroventricular (icv)) administration of **5** increased while systemic (ip) administration decreased pain threshold in the rat sciatic nerve ligation model of neuropathic pain.[191] In the same study the very nature of histamine's effect was dose-dependent, with low icv dose decreasing and high icv dose increasing the nociceptive threshold, highlighting again the potential challenges of H_3-based approach to the treatment of pain.

Overall, however, it appears that H_3 antagonists are consistently more useful under the conditions of neuropathic pain, in which peripheral chronic inflammation or nerve injury and continuous CNS stimulation cause plastic changes in pain descending pathways with the dominance of facilitatory mechanism over inhibitory.[89] As a pathology of disregulated neurotransmission, neuropathic pain appears a possible if yet unproven target of H_3 modulation. This hypothesis has been given further support by the discovery of several series of selective H_3 antagonists at Glaxo, including the previously discussed tetrahydrobenzoazepines **52** and **53** and diazepane **54**, which have demonstrated a reduction of mechanical hyperalgesia and allodynia in a chronic constriction injury and varicella zoster virus rat models of neuropathic pain.[154,192] In addition, specific H_3 receptor binding sites were established in the human dorsal horn of the spinal cord and dorsal root ganglion, the key relay center for ascending and descending pain conductance. Although unknown, the mechanism of action is hypothesized to be similar to that of the neurotransmitter reuptake blockers duloxetine (Cymbalta) and venlafaxine (Effexor), which increase brain levels of monoamines such as serotonin and norepinephrine.[192,193] Compound **52** was in phase I clinical investigation in an electrical hyperalgesia translational model of neuropathic pain.[136]

Epilepsy

The involvement of histamine in seizures has long been recognized based on the proconvulsant properties of traditional H_1 antihistamines.[194] Histamine and agents that raise histamine levels, such as histidine and the HNMT inhibitor metoprine, have shown potent anticonvulsant effects most likely through H_1-mediated excitation of interneurons and inhibition of hippocampal principal neurons. Consistent with this observation, the H_3 antagonists **5** and **6** have shown protective anticonvulsant effects in various animal models based on their facilitation of brain histamine release. H_3 agonists have also been shown to prevent the protective effect of H_3 blockers.[99,100,195] No clinical data are available with the exception of a small uncontrolled trial with **36** (12 patients), in which anticonvulsant effects were observed.[172] At high doses, the H_3 antagonists **5**, **7**, **16**, **40**, and **42** have shown proconvulsant activity in animal models; however, the mechanism of this biphasic effect is unknown.[138,141]

Obesity and Diabetes Mellitus

Obesity is mainly characterized by the accumulation of an excessive amount of body fat. Globally, more than one billion adults are overweight with a body mass index (BMI) over 25 and more than 300 million are clinically obese with a BMI over 30. The medical consequences of this condition are serious and associated with a significant decrease in life expectancy. It is well established that even modest weight loss reduces the medical risk for the development of type 2 diabetes, cardiovascular disease, and cancer in the obese population. Although obesity can and has been targeted via multiple biochemical pathways, the resilience of the compensatory mechanisms against weight loss (due to multiple redundant regulatory circuits aimed at maintaining the status quo) has been a formidable problem.

The key to combating obesity and ensuing downstream pathologies appears to be in the restoration of the energy intake/expenditure balance. Appetite and food intake are centrally regulated by the hypothalamus through a number of pathways involving orexigenic and anorexigenic signaling peptides and neurotransmitters acting at the appropriate receptors.[196] The combined regulatory signals at the state of satiety were designed by nature to promote a decrease in food intake and increase in energy expenditure, supplied by increased glucose metabolism and lypolisis in adipose tissue. The efficiency of signaling, however, may be severely disrupted in states of pathology, including obesity, requiring exploitation of additional mechanisms different from those already compromised. Among the most visibly disregulated in the condition of obesity and often accompanying type 2 diabetes are the signaling pathways of insulin and leptin, the latter being the most prominent among anorexigenic signaling peptides, released by adipocytes and circulating at higher levels in the satiety state.

In addition to the regulatory action from neuropeptides, appetite and food intake effects also appear to be subject to regulation by aminergic neurotransmitters, including dopamine, norepinephrine, serotonin, and histamine. Significant work has been done demonstrating that histamine stimulates postsynaptic H_1 receptors to inhibit feeding. In 1973 it was first shown that histamine suppresses food intake when intraventricularly injected into cats.[197] Likewise, acute or continuous administration of histamine into the lateral ventricle or the suprachiasmatic nucleus of the hypothalamus in rats reduced food intake.[198,199] Intraperitoneal injection of histamine enhancing agent L-histidine, or the HNMT inhibitor metoprine, has been shown to have the same food-reducing effect,[200,201] while intracerebroventricular administration of α-fluoromethylhistidine **22** (Figure 7), an HDC inhibitor, significantly increased food intake in rats by depleting histamine.[202] Administration of the H_1 receptor agonist 2-(3-trifluoromethylphenyl)histamine **71** (Figure 7) depressed food intake in wild-type (WT) rats,[199] whereas many studies have demonstrated that H_1 antagonists induce feeding.[203] In particular, treatments with tricyclic antidepressants and atypical antipsychotics often induce body weight gain which has been proposed to be potentially mediated by H_1 antagonism.[204] The degree of increase in food intake in rodents treated with tricyclic antidepressants was related to these compounds' H_1 receptor affinities.[205] This fact is also in agreement with data in humans, where use of atypical antipsychotic drugs, such as clozapine and olanzapine (Zyprexa), results in untoward orexigenic effects arising from central H_1 antagonism

(K_d(hH$_1$R) = 3.1 nM and 0.087 nM, respectively).[206] Similarly, unwanted body weight gain in humans was observed as part of treatment of allergic conditions with H_1 antihistamines. However, this effect is significantly diminished with the second generation antihistamines because of lower brain penetration.[207]

Consistent with these findings are the data from the rodent knockout models. $H_1^{-/-}$ mice on a high-fat diet have been reported to accumulate significantly more fat than WT animals, although no statistical difference in total body weight or food intake between the two groups was observed.[208] In another study histamine-deficient HDC$^{-/-}$ mice on a high-fat diet developed significant difference in body weight relative to standard-diet group after only 2 weeks, compared with 5 weeks for WT mice. Furthermore, after 8 weeks WT mice on the high-fat diet reduced their caloric intake, whereas HDC$^{-/-}$ mice did not.[209] Paradoxically, $H_3^{-/-}$ mice demonstrated a mildly obese phenotype characterized by increased adiposity and food intake, reduced energy expenditure, and increased resistance to insulin and leptin.[46] While the orexigenic effects were not easily explainable and were tentatively attributed to the impairment of histamine synthesis as a result of unchecked histamine release, only a 15% reduction in the histamine hypothalamus levels in $H_3^{-/-}$ mice (along with 135% increase in tele-methylhistamine levels) was observed. Alternatively, reduced H_1 receptor expression was invoked, and it is conceivable that other mechanisms of H_1 receptor desensitization by higher levels of histamine, unmitigated by negative regulation via H_3, may also play a role.[210,211]

Despite the established anorexigenic role of histamine, the nature of coupling between H_3 receptors, histaminergic tone, and the overall effect on food intake and body weight has been a recurring topic of debate. The therapeutic significance of H_3 receptor stimulation vs inhibition for feeding and weight gain appears to be a subject of more controversy than in the case of cognitive indications. Significantly different results have been reported depending on experimental paradigm, administration route, and species/strain used. For example, the H_3 antagonist **5** reduced food consumption and/or appetite in normal and in Zucker obese rats that lack functional leptin receptors.[212,213] While a majority of other reports also link H_3 antagonism/inverse agonism to anorexigenic effects based on the expected increase in histamine tone (vide infra), these data are not entirely uniform. It was suggested in a 2006 study supported by $H_3^{-/-}$ mouse data that H_3 receptors may regulate food intake in rodents independently from modulation of histaminergic tone or subsequent changes in the activity of H_1 receptors.[214] Chronic dosing with the H_3 agonist **3** reduced food intake, body weight, fat mass, hyperleptinemia, and hyperinsulinemia in diet-induced obese (DIO) mice, while the opposite effects were observed with the H_3 antagonist **5**. The food- and weight-reducing effects of **3** were negligible in DIO $H_3^{-/-}$ mice and augmented upon intracerebroventricular administration in WT mice, strongly implicating central H_3 receptors in the observed anorexigenic effect. While absolute brain histamine levels increased following treatment with **3**, this was attributed to its accumulation in nerve terminals rather than neuronal synapse and was apparently supported by the fact of reduced tele-methylhistamine levels. Presumably independent of histamine tone, the effect of **3** was tentatively attributed to its postsynaptic H_3 effect (occasionally invoked in this case and others but hardly evidenced in a credible way)[38] or a presynaptic H_3 effect on release of other appetite-affecting neurotransmitters, such as dopamine and norepinephrine. These findings may offer some rationale for the obese phenotype of the $H_3^{-/-}$ mice discussed above.[46] The antiobese effects of H_3 agonists were also confirmed with **1**, while intracerebroventricular administration of **5** in rats produced orexigenic effects similar to those observed in mice.[214]

At the same time other studies by Banyu suggested strong species dependence of H_3-mediated food intake and body weight effects. Thus, the same H_3 inverse agonists (not identified) produced orexigenic effects in C57BL/6J DIO mice and anorexigenic effects in Zucker obese rats, underscoring potential differences in physiology and pharmacology in rodents and emphasizing the importance of metabolic syndrome data in nonhuman primates (vide infra).[215]

Contributions of H_3 receptors to the expenditure component of the intake/expenditure balance of energy homeostasis are less clear. For the safe increase in total energy expenditure the most promising target of pharmacological intervention in rodents and humans is believed to be adaptive thermogenesis, in mammals largely regulated in brown adipose tissue (BAT). Increase in thermogenesis has been linked to the up-regulation of the mitochondrial respiratory chain components as well as uncoupling proteins (proton transporters shifting the balance from ATP synthesis in mitochondria to heat generation) under control of a number of transcription regulators. Among these is peroxisome proliferator-activated receptor-γ coactivator 1 (PGC1), induced by cold exposure and β_3 adrenoceptor agonists in BAT and skeletal muscle.[216] Consequently, the effect of β_3 action of catecholamine neurotransmitters (linked to H_3 and histamine and released by the sympathetic nervous system) is increase in thermogenesis.[217] It is interesting to note that β_3 agonists affect PGC1 levels via cAMP-dependent activation of protein kinase A, a major signaling pathway of H_3 antagonists (see Supporting Information).

Obesity increases the risk of developing other characteristic conditions of metabolic sydrome such as type 2 diabetes, a disorder characterized by abnormally high blood glucose levels not caused by lack of insulin. It is believed to be the result of disregulated hormonal CNS signaling, with insulin and leptin being the primary compromised mediators, coupled with the loss of peripheral sensitivity to insulin.[218] Leptin and insulin signaling in hypothalamus is supplemented by the action of neurotransmitters, including H_3-mediated dopamine and serotonin, and directly influences glucose homeostasis. It is clear that reduction of body weight in rodents by histamine has favorable effects on such parameters as serum glucose and insulin;[219] however, it is less apparent whether these effects can be achieved independently of weight loss. Experiments in nonobese animal models of type 2 diabetes[220,221] may answer this question and delineate the prospects for H_3 antagonists in the treatment of type 2 diabetes not associated with excessive body weight and often found in Asian population. While molecular pathways of glucose homeostasis regulation by histaminergic system are not clear, there is substantial evidence that it acts in part as a downstream effector of leptin regulation of energy homeostasis and glucose metabolism.[222] However, one challenge in emphasizing a particular mechanism, such as H_3 antagonism, lies in the potentially opposite effects of the same signaling pathways in the CNS and in the periphery. While peripheral activation of cAMP−protein kinase A pathway (linked to H_3 antagonism and discussed in the Supporting Information attachment) is

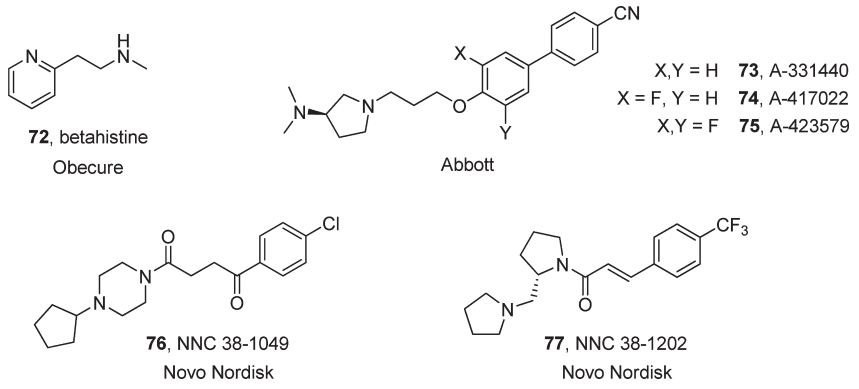

Figure 12. H_3 antagonists/inverse agonists for obesity and diabetes.

believed to increase insulin sensitivity in the skeletal muscle, its activation in the CNS increases food intake.[218] Both insulin and leptin were shown to inhibit the cAMP−protein kinase A pathway in the hypothalamus, which would seem to align them with H_3 agonist rather than H_3 antagonist or histamine-via-H_1 signaling patterns.[218,223] Clearly, additional information may be helpful in supporting the case for H_3 antagonists in diabetes. In addition, other components of metabolic syndrome, such as liver disease and hyperlipidemia (vide infra), have been considered in conjunction with H_3 antagonism.

Challenges to realizing an H_3-based approach to the treatment of obesity and diabetes are abundant. In addition to inherent species differences discussed above, the apparent dichotomy of H_3 compounds with metabolic syndrome as opposed to cognition enhancing activity has been highlighted.[101] Technical issues, likely common to all obesity programs, include difficulties in designing an animal model in which a decrease in feeding and/or body weight is exclusively due to the targeted pharmacological action of the drug rather than toxicological or any other side effects interfering with animal eating routine. In general, reliable extrapolation of such fundamental activity as feeding from animals to the evolutionally more accomplished humans remains a significant challenge. Despite these obstacles, several companies appear to be pursuing metabolic syndrome indications with H_3 antagonists. A satiety effect was observed with compound **36**, under development by Ferrer and BioProject for neurological disorders, when administered to six human volunteers also treated with olanzapine.[172] Progress of other development programs is described below.

Obecure. Obecure is developing betahistine **72** (OBE-101 or histalean, Figure 12), an H_1 agonist/H_3 antagonist for the treatment of obesity and antipsychotic medication-induced weight gain, and has considered it as a potential adjunct to statin therapy for improving blood lipid profiles.[136] Compound **72** was previously approved for human use for the treatment of Meniere's disease (vide infra) and is an orally active brain-penetrating analogue of histamine. Both molecules contain an ethylene linker between a nitrogen heteroaromatic ring and an sp^3 amine. However, **72** has a complex pharmacological profile; it exhibits a combination of weak affinity (double-digit micromolar rodent K_i) and partial agonism (relative to histamine) at the H_1 receptor with somewhat higher affinity (single-digit micromolar rat K_i) and antagonism at the H_3 receptor.[224,225] In vivo **72** reduced food intake in pygmy goats and rats.[226,227] Several standalone phase II obesity trials and several phase II trials to assess ability of **72** to prevent weight gain in patients taking olanzapine were commenced in 2007−2008.[136] Despite moderate receptor affinity, proposed human doses in efficacy trials do not seem to exceed 100 mg/day. However, in a 12-week clinical trial **72** failed to induce significant weight loss in obese patients (except in women younger than 50 years of age) at doses up to 24 mg b.i.d.[228] Separately, Obecure is recruiting for a phase I ADHD study with **72** with planned doses of up to 200 mg/day.[136]

Schering-Plough. SCH 497079 (structure not disclosed) is an H_3 receptor antagonist investigated by Schering-Plough for the treatment of obesity and diabetes mellitus. A phase II study to evaluate effect of SCH 497079 on weight in obese and overweight subjects and a phase I study to evaluate effect of SCH 497079 on metabolic parameters in subjects with type 2 diabetes mellitus began in 2008.[136]

Abbott. While neither **42** nor the conformationally restricted analogue **37**, discussed in the section Cognitive Disorders, appeared to have activity in animal models of obesity, continuation of the biphenyl motif with an added basic center in the form of a dimethylamino group at the 3-position of the pyrrolidine ring resulted in compounds that promoted food intake reduction and body weight loss. Abbott has investigated compound **73** (A-331440), which produced effects on metabolic parameters in DIO mice.[229] In a 28 day study the high dose of **73** (15 mg/kg, po, b.i.d.) reduced weight and leptin and normalized insulin tolerance to the levels observed in lean mice. Importantly, the weight loss was largely due to specific loss of abdominal and subcutaneous fat and was not generalized across tissues. Because of the genotoxic liability of **73**, Abbott developed nonclastogenic fluorinated analogues **74** (A-417022) and **75** (A-423579) with in vitro H_3 profiles similar to that of **73** and demonstrated their in vivo activity in obese rodents.[212,230] However, Abbott has not reported a clinical development program for a metabolic syndrome indication.

Novo Nordisk. TransTech Pharma, under license from Novo Nordisk, is investigating H_3 histamine antagonists for the treatment of metabolic disorders, presumed to include obesity. By screening arrays of monoacyldiamines, Novo Nordisk discovered 1-alkyl-4-acylpiperazines as a new class of nonimidazole H_3 antagonists.[231] Within this series compound **76** (NNC 38-1049, hH_3R K_i = 1.2 nM) produced significant reduction in food intake and body weight in a 2-week study in DIO rats.[232]

Exploration of other diamines led Novo Nordisk to the cinnamic amides of (*S*)-2-(aminomethyl)pyrrolidines.[233] In this novel class of compounds the two nitrogen atoms of the diamine part of the molecule are separated by a two-carbon

linker, similar to the acylpiperazine series. Selection of *S*-stereochemistry and introduction of the 4-trifluoromethyl substituent on the phenyl ring led to the discovery of **77** (NNC 38-1202), a potent and selective H_3 antagonist (hH_3R K_i = 6.7 nM). In line with the increased paraventricular histamine levels observed in normal rats (339% after single 15 mg/kg oral dose), **77** significantly reduced food intake, body weight, and plasma triglyceride levels in DIO rats.[234] In addition, **77** showed good affinity for pig and rhesus monkey H_3 receptors (pH_3R K_i = 18 nM; mH_3R K_i = 6.3 nM) and strongly reduced average caloric intake in both species (perhaps, unnervingly so, by 75% at 1 mg/kg dose in the monkeys, although no adverse effects were observed), demonstrating for the first time the anorectic effect of an H_3 antagonist in higher mammals.[235]

Allergic Rhinitis

Prior to the discovery of the H_3 receptor and consideration of H_3 agonists for minimization of histamine inflammatory effects through reduction of its extracellular levels (discussed above), postsynaptic histamine H_1 receptor antagonists had already been widely used for the symptomatic treatment of allergic inflammatory conditions, and it is the apparent promise of H_4 receptor antagonists to do so in the future.[5] Among different allergic conditions, the most pronounced response to treatment with antihistamines has been observed in the case of allergic rhinitis, characterized by nasal congestion, rhinorrea, sneezing, and pruritus and occurring in sensitized individuals upon exposure to allergens such as ragweed, grass, tree pollen, and animal dander. The allergic cascade in general is initiated by the uptake of allergens and their presentation to naive T cells, leading to their differentiation toward the T_H2-cell phenotype.[236] T_H2 cells up-regulate expression of a number of cytokines, including IL-4, IL-9, and IL-13, leading to IgE synthesis (constituting allergic sensitization) and, upon subsequent allergen exposure, to recruitment of mast cells and basophils, binding and cross-linking of IgE, degranulation of cells, and release of inflammatory mediators, including leukotrienes, prostaglandins, cytokines, and histamine. Further downstream effects arise from actions of these mediators on tissue cells, such as epithelial, endothelial, and smooth muscle cells, leading in the case of histamine to mucus production, increased vascular permeability, and bronchospasm. Additionally, mediators' signaling back to the immune cells (eosinophils, B and T cells) further prompts their stimulation, recruitment, and polarization. It is believed that release of initial mast cell mediators, including histamine, is responsible for the generation of acute symptoms, whereas further induction of cytokines and immune cell infiltration sustain the inflammatory environment. As histamine is just a small part of the overall inflammatory cascade, antihistamines are efficacious in some but not all conditions with allergic etiology. For example, they appear to lack efficacy against asthma, despite the similarity between bronchoconstrictive effects of histamine and asthma pathology. In contrast, while histamine also plays a crucial role in the development of allergic rhinitis symptoms,[237] those, with the exception of nasal congestion, appear to be well controlled by H_1 antagonists.

Lack of efficacy against nasal congestion appears to arise from a separate, H_3-mediated, inhibitory effect of histamine on norepinephrine release and the resulting disruption of normal vascular tone. Consequently, the nonsedating antihistamines, such as loratadine and cetirizine, are often combined with α-adrenergic agonists to achieve full decongestive effect. While use of α-adrenergic agonists is limited by their systemic cardiovascular and CNS stimulatory effects, a peripherally acting H_1/H_3 combination would appear to offer a viable alternative. The vasoconstrictor effect of H_3 antagonists due to the reestablished release of norepinephrine could restore the normal vascular tone in the nose. The H_3 receptor was shown to modulate sympathetic control of nasal blood flow and nasal resistance in the cat.[238] However, the action of H_3 antagonists alone is not expected to deliver a full decongestive effect in allergic rhinitis because of the need to block H_1-mediated mucus production and plasma extravasation contributing to nasal congestion. Administration of the H_1 antagonist chlorpheniramine or desloratadine in combination with the H_3 antagonist **5** or **6** was shown to block the decrease in cat nasal cavity volume caused by mast cell degranulator compound 48/80. Neither an H_3 nor H_1 antagonist was efficacious when administered alone.[239] A drug with dual H_1/H_3 antagonist properties or an H_1/H_3 antagonist combination with minimal brain penetration could prove useful for the treatment of nasal congestion and avoid the hypertensive liability of current therapies.

GlaxoSmithKline. Glaxo is developing two dual H_1/H_3 antagonists, GSK-835726 and GSK-1004723, for the treatment of allergic rhinitis. By early 2009 GSK-835726 had been advanced to a phase II environmental challenge chamber efficacy study, which it completed several months later.[136] The compound was evaluated against the H_1 antagonist cetirizine and placebo in a crossover trial at single oral doses up to 100 mg. In the absence of direct structural information, we believe that GSK-835726 may have structure **78** (Figure 13). In 2006 Glaxo disclosed **78** in a single-compound patent.[240] The human H_3 and H_1 receptor affinities (pK_i) for **78** are 9.5 and 5.6, respectively, and oral bioavailability exceeds 50% with a plasma half-life ($t_{1/2}$) of 2 h in rats and 90% with a plasma half-life of 5 h in dogs. In addition, **78** showed low CNS penetration in rats.

GSK-1004723 reached and completed a similar phase II chamber efficacy study in 2009, where it was compared against placebo at single intranasal doses up to 1000 mg.[136] Again, the structure has not been directly disclosed, but we believe GSK-1004723 may have structure **79**. In 2007 Glaxo filed a patent application covering a novel class of 4-benzylphthalazinone dual H_1/H_3 antagonists.[241] Compound **79** was reported to have H_1 receptor affinity (pK_i) of 7.8 and H_3 receptor affinity of 9.6. Compound **79** fully reversed histamine-induced nasal congestion in conscious guinea pigs for a period of 24 h following intranasal administration of 0.05 mg dose (a more robust effect compared to the H_1 antagonist azelastine) and exhibited lower CNS penetration in rats. Phtalazinone **79** is a clearly discernible combination of the common ((*N*,*N*-dialkylamino)propoxyphenyl) H_3 pharmacophore and H_1 pharmacophore mirroring the structure of azelastine **80** (Figure 7).

Glaxo is also investigating another dual H_1/H_3 antagonist, preclinical candidate **81** (GSK-541636, hH_3R pK_i = 7.3, hH_1R pK_i = 7.9).[242] Compound **81** demonstrated in vivo anti-inflammatory activity in the wheal and flare guinea pig model with ID_{50} of 0.6 mg/kg (iv) and 2.8 mg/kg (po). Oral bioavailability of 60% with a plasma half-life of 3 h in dogs and low CNS penetration in rats were disclosed. Glaxo observed that the methyl-disubstituted piperidine was the optimal amine component of the (*N*,*N*-dialkylamino)propoxyphenyl motif in this structural series. Brain penetration was reduced with the introduction of the carboxylic acid functionality,

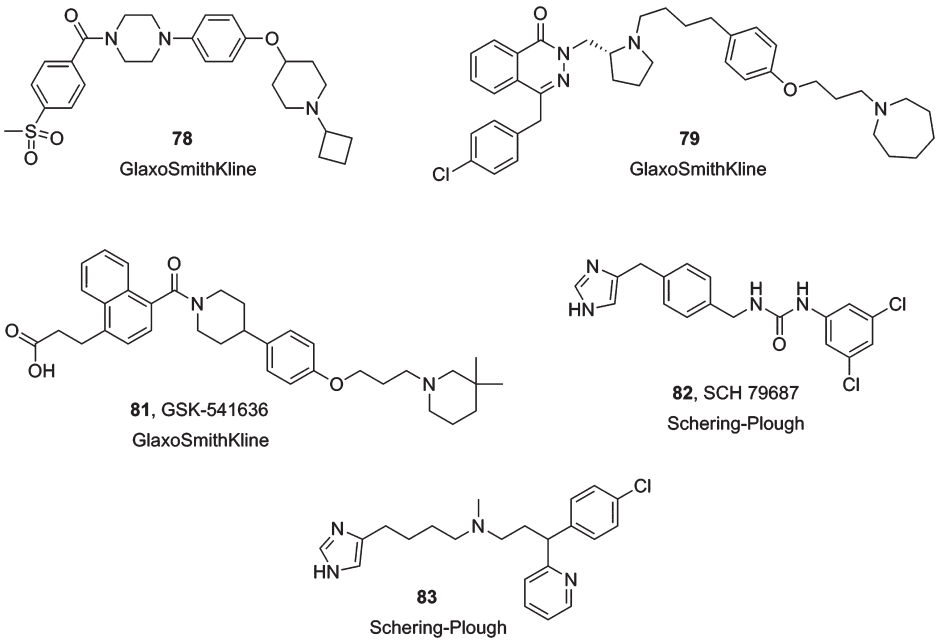

Figure 13. H_3 antagonists/inverse agonists for allergic rhinitis.

while ethylene linker improved bioavailability relative to a previous compound that contained oxymethylene linker.

Pfizer. A phase II clinical study to test the decongestive activity in allergic rhinitis of the previously discussed phenylcyclobutanecarboxamide **59** was completed in August 2008 (**59** as a stand-alone treatment against Allegra (fexofenadine), Allegra-D (fexofenadine−pseudoephedrine), and placebo).[136] No results of the study have been published, and the indication has been absent from the company's pipeline since September 2008, possibly suggesting a negative outcome.[52]

Schering-Plough. Researchers at Schering-Plough were the first to demonstrate decongestive activity of H_3 antagonists in an animal model of nasal congestion when administered in combination with an H_1 antagonist.[239]

Imidazole-based analogue **82** (SCH 79687) was reported as a potent, selective, and orally active H_3 receptor antagonist with decongestive activity and absence of blood pressure effect in the cat when coadministered with the H_1 antagonist loratadine.[243] In addition, dual H_1/H_3 receptor antagonists, exemplified by **83** (gpH_3R K_i = 15 nM, rH_1R K_i = 7 nM), a histamine homologue−H_1 antagonist chlorpheniramine **84** (Figure 7) structural hybrid, have been reported.[244]

Ménière's Disease

Ménière's disease is an abnormality of the inner ear characterized by spontaneous attacks of vertigo or severe dizziness, fluctuating hearing loss, tinnitus (ear noises), and the sensation of pressure or pain in the affected ear. This disorder usually affects only one ear and is a common cause of hearing loss. The symptoms of Ménière's disease are associated with a change in fluid (endolymph) volume within the membranous labyrinth which is necessary for hearing and balance. An increase in endolymph can cause the membranous labyrinth to balloon or dilate, a condition known as endolymphatic hydrops. On the basis of a recent study, NIDCD (National Institute on Deafness and Other Communication Disorders) estimates that there are currently 615 000 individuals with diagnosed Ménière's disease in the United States and 45 500 newly diagnosed cases each year.

The causes of Ménière's disease are not known. Some researchers believe that the symptoms are the result of a blood vessel pressing upon a nerve. Other researchers view this as a separate disease. Other investigators believe that the symptoms are the result of an autoimmune condition or an infection generated by a virus such as the herpes simple virus (HSV).

Dual H_1 agonist/H_3 antagonist **72** (Figure 12), discussed above in the section Obesity and Diabetes Mellitus, was first registered in Canada in 1968,[245] is currently approved worldwide for the treatment of Ménière's disease, and is marketed by Solvay Pharmaceuticals (now part of Abbott) in more than 90 countries (U.S. excluded) under the brand names Serc, Betaserc, and several others. While no branded form has been approved for sale in the U.S., **72** is available from compounding pharmacists. In the U.K., **72** is prescribed by 94% of otolaryngologists for this indication, and it is estimated that over 130 million people have been treated worldwide. Analysis on the efficacy of **72** suggested reduction of vertigo and some reduction of tinnitus in most trials. However, no effect on hearing loss was observed.[246]

The mechanism of action of **72** in Ménière's disease is not clear. A beneficial effect of histamine upon intravenous administration in patients with Ménière's has been described.[247] A possible explanation could be the previously mentioned histamine-mediated increase in vascular permeability possibly leading in this case to drainage and a decrease of the endolymph fluid volume in the inner ear labyrinth. This effect could be produced by **72** via up-regulation of histamine levels. In another argument, the vasodilatory effect of histamine resulting in the improved blood flow to the inner ear has been invoked. This hypothesis is supported by the fact that different vasodilators have a beneficial effect in the treatment of Ménière's and by the earlier findings of increased blood flow in monkeys and dogs upon administration of **72**.[248,249]

Cancer

Histamine and its receptors play important roles in cell proliferation in brain, colon, and breast cancers.[250−252] Elevated

expression of histamine receptors in cancer cells has been observed, suggesting that they could potentially be exploited with the goal of decreasing cellular growth and proliferation. High histamine biosynthesis and content have been reported in different human neoplasias including breast cancer, as well as in experimental tumors induced in rodents.[253]

In breast carcinomas, a higher expression of the H_3 receptor was observed in tumor cells relative to nontumoral tissue in the same patient. Histamine and other H_3 agonists (**1** and **3**) were shown to increase proliferation of human breast cancer cells at low concentrations (0.001−0.01 μM), an effect that was blocked by the H_3 antagonists **5** and **65**.[254] At the same time, no effect was observed with H_3 antagonists alone (10 μM). At higher concentrations, histamine strongly inhibited cell proliferation with similar effects exhibited by the H_1 agonist **71** (Figure 7) and the H_4 agonist−H_3 antagonist **6**, indicating involvement of H_1 and H_4 receptors. The H_4 receptor was further implicated when the significant apoptotic effect of **6** was blocked by the H_4 antagonist JNJ-7777120. The opposite outcomes of H_3 versus H_4 receptor activation were also observed in a pancreatic carcinoma cell proliferation study.[255] While it remains unclear whether selective antagonism of the H_3 receptor can consistently produce antiproliferative effect, inhibition of human melanoma and cutaneous carcinoma cell growth by the H_3 antagonist **5** has been reported.[256]

As discussed in the Supporting Information, the H_3 receptor is positively coupled via $G_{\alpha i}$ and $G_{\beta\gamma i}$ to the Ras−Raf−MEK−ERK signaling cascade. Its disregulation, often due to mutations in Ras and Raf, can contribute to aberrant cell growth and proliferation and has been linked to human cancers.[256] Research programs are currently active targeting inhibition of this pathway through small-molecule drugs.[257] In addition, H_3 receptor positive coupling to PI3K and Akt provides a connection to a signaling pathway most commonly activated in human cancers and also targeted for inhibition in drug development.[258] Whether molecular connections of these pathways with H_3 receptors prove therapeutically usable remains to be seen.

Gastrointestinal Disorders

While histamine H_2 receptor antagonists have been approved for human use as antacids and antiulcer agents,[3] the role of H_3 receptors in gastrointestinal disorders is not as clear. In line with high histamine levels in rapidly growing tissues, such as human neoplasias discussed above, and its apparent mitogenic activity, histamine also appears to play an important role in the self-renewing rapid turnover of gastric mucosa.[259] The H_3 agonists **1** and **20** were shown to promote proliferation of the mucus-secreting cells and protect the overall integrity of gastric epithelium in rats, and these effects were subject to reversal by the H_3 antagonists **6** and **7**.[260,261] There is also evidence that the H_3 receptor may control gastrointestinal motility in mice.[262] However, the potential therapeutic role of the H_3 receptor in human gastrointestinal disorders is unclear, since it has not been detected in human gastrointestinal tissues. Instead, a possibility of centrally mediated H_3 effects on acid secretion, gastrointestinal motility, and epithelial cell proliferation has been invoked.[263]

Cerebral Ischemia

Histamine has been shown to play an important role in mitigating the effects of cerebral ischemia. Strong reduction of blood flow to the brain, such as resulting from temporary occlusion of blood vessels during stroke, leads to delayed morphological damage and neuronal death, even if blood flow is resumed. The underlying reason for the rapid brain damage is the combination of high energy demand and relative lack of energy reserves in neurons, leading, upon quick ATP depletion in the absence of adequate blood supply, to compromised functioning of the Na^+/K^+-ATPase ion pumps and resulting failure to maintain neuron membrane polarization and cellular homeostasis.[264] From the outset, cerebral ischemia is characterized by the excessive release of glutamate (attributed to the loss of Na^+ gradient across the cell membrane and reversed operation of glutamate transporters) which further accelerates the process of energy depletion in cells by opening additional ligand-gated ion channels, such as NMDA receptor-linked Ca^{2+} channels, and imposing an additional burden on cellular ion pumps. Increased intracellular Ca^{2+} concentration also triggers processes leading to preprogrammed cell death, while increased Na^+ concentration causes water entry into neurons leading to cerebral edema. In a bilateral carotid artery occlusion model of ischemia in gerbil preischemic icv administration of histamine was reported to have prevented development of neuronal death.[265] This effect of exogenous histamine was blocked by H_2, but not by H_1, antagonists, thus implicating H_2 receptors in the mediation of these effects. In addition, histamine was shown to suppress ischemic release of glutamate in the rat striatum, triggered by occlusion of the middle cerebral artery, and improve the histologic outcome.[266] In line with the findings mentioned above, this effect was mirrored by the H_2 agonist dimaprit, whereas H_1 agonists showed no effect. Treatment with the histamine biosynthesis inhibitor **22** (Figure 7) aggravated neuronal death in a gerbil model of transient global ischemia.[267]

While the full potential of H_3 antagonists in cerebral ischemia still needs to be elucidated, their effect on histamine brain levels may be hoped to provide a beneficial outcome. Possibly complicating the overall picture is the fact that the inhibitory effect on glutamate release under nonischemic conditions is typically associated with H_3 agonists rather than antagonists.[18] However, the H_3 antagonist **5**, when administered in combination with L-histidine, was shown to increase brain histamine concentration and prevent development of ischemia-induced brain edema in rats, contrary to the lack of effects seen with L-histidine alone.[268] In addition, phospholipase A_2 (PLA_2), shown to be activated in cerebral ischemia and known to contribute to CNS pathologies via increased production of reactive oxygen species, is one of the downstream effectors positively coupled to H_3 receptors, as discussed in the Supporting Information. This biochemical link may provide additional stimulus to investigate H_3 antagonists for this indication. Overall, however, one needs to appreciate the significance of the challenge by considering the general lack of progress in drug development toward cerebral ischemia across different mechanistic approaches.

Tremor

Although available information is very limited, H_3 antagonists/inverse agonists have been investigated for the treatment of movement disorders, including tremor, such as essential tremor and tremor associated with PD. In a patent application directed toward use of H_3 agonists/inverse agonsits for these indications, Merck disclosed dose-dependent activity of compound **85** (Figure 14) in the harmaline-induced rat tremor

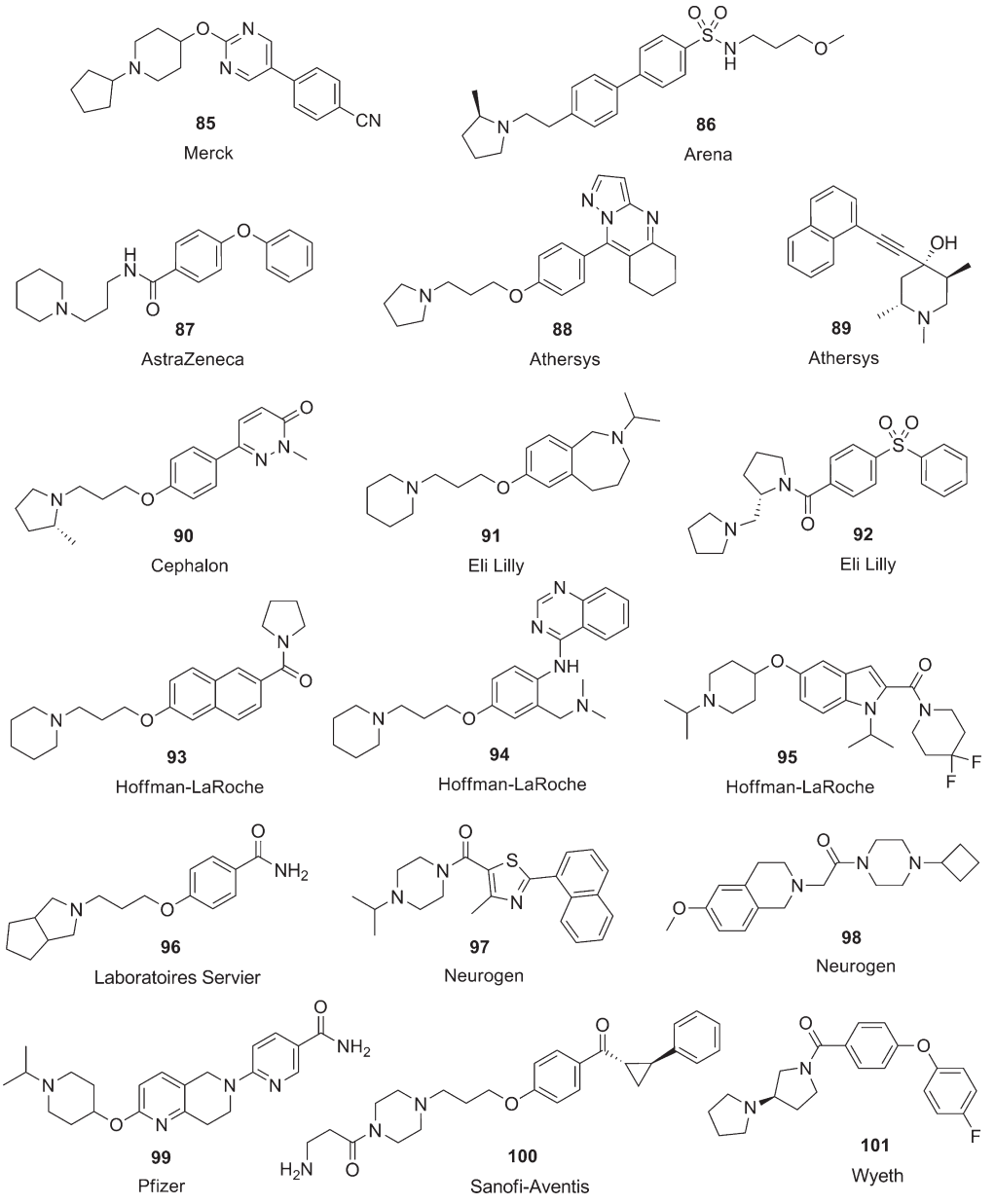

Figure 14. Miscellaneous series of H_3 antagonists/inverse agonists.

model.[269] While mechanistic explanation of such activity has not been suggested in the application, H_3 receptors are known to modulate dopaminergic signaling (vide supra), which, if compromised, has been implicated in motor dysfunctions, including those associated with PD itself or arising as side effects of the dopaminergic treatment (e.g., dyskinesia observed with L-dopa).[270] In that regard, indirect pharmacological approaches present an attractive alternative. H_3 antagonists, when administered alone, have been shown to increase the release of dopamine in the cortex,[153] although not in the movement-modulating striatum.[271] However, **6** was reported to improve motor coordination in the 6-hydroxydopamine (6-OHDA) lesioned rat model of PD, and H_3 antagonism was concluded to have potential for the improvement of motor complications in PD.[271] Separately, ether **85** was mentioned in the specifications of another patent application by Merck, claiming use of H_3 antagonists/inverse agonists for the treatment of stroke (see discussion above).[272]

Miscellaneous Series of Preclinical Compounds

In addition to those previously mentioned, companies who have also reported H_3 antagonists at earlier stages of development include Acadia,[52] Arena (e.g., **86**, patented crystalline form, Figure 14),[273] AstraZeneca (e.g., **87**),[274] Athersys (e.g., **88**, **89**),[275,276] Cephalon (**90**),[277] Eli Lilly (e.g., **91**, **92**),[278,279] Evotec AG,[52] Hoffman-La Roche (e.g., **93**, **94**, **95**),[280−282] Les Laboratoires Servier (e.g., **96**),[283] Neurogen (e.g., **97**, **98**),[284,285] Pfizer (e.g., **99**, single compound patent),[286] Sanofi-Aventis (e.g., **100**),[287] and Wyeth (e.g., **101**).[52,288] Patent applications claim cognition, obesity, diabetes, psychotic and sleep disorders, and allergic rhinitis as potential therapeutic applications of H_3 receptor antagonists/inverse agonists.

Conclusion

It seems likely, given the current activity level of research and development, that days of commercial H_3 drugs are approaching. Whether a stand-alone treatment or a valuable

add-on to an existing therapy, H_3 antagonists seem well positioned to soon share in and expand the existing drug class designation of "antihistamines". Led by the abundant preclinical data, drug companies finally seem to be in a position to probe the putative connections between the H_3 mechanism and a number of human therapeutic conditions. The pressure is clearly on clinical research to generate convincing proof-of-concept data to support or reject those connections. Further developments in H_3 biology are to be awaited with much interest and may serve to further substantiate the existing indications and suggest novel therapeutic uses. Because of the wide spectrum of the potential indications, the need to reconcile and manage as a combination the various expected H_3 therapeutic effects (most of which, adding to the level of complexity, are believed to be centrally mediated) may prove a significant challenge in itself.

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Biographies

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Supporting Information Available: Details of the H_3 receptor signaling pathways (summarized in Figure 4) and details of the clinical trials targeting H_3 receptor (as listed on www.clinicaltrials.gov). This material is available free of charge via the Internet at http://pubs.acs.org.

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