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Histamine H_3 receptor antagonists/inverse agonists: Where do they go?

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ABSTRACT

Since the discovery of the histamine H_3 receptor in 1983, tremendous advances in the pharmacological aspects of H_3 receptor antagonists/inverse agonists have been accomplished in preclinical studies. At present, there are several drug candidates that reached clinical trial studies for various indications. However, entrance of these candidates to the pharmaceutical market is not free from challenges, and a variety of difficulties is engaged with their developmental process. In this review, the potential role of H_3 receptors in the pathophysiology of various central nervous system, metabolic and allergic diseases is discussed. Thereafter, the current status for H_3 receptor antagonists/inverse agonists in ongoing clinical trial studies is reviewed and obstacles in developing these agents are emphasized.

Contents

1. Introduction

As an aminergic multifunctional neurotransmitter, histamine [2-(4-1*H*-imidazolyl)ethylamine] plays versatile roles in a wide variety of physiological processes and is therefore also implicated in several pathological conditions (Celanire, Wijtmans, Talaga, Leurs, & de Esch, 2005; Gemkow et al., 2009; Nikolic, Filipic, Agbaba, & Stark, 2014). Histamine is produced in a large number of tissues by cells such as mast cells, parietal cells of the gastric mucosa, and neurons of central/peripheral nervous system via decarboxylation of L-histidine by histidine decarboxylase (HDC). Histamine inactivation occurs via two major metabolic pathways, N-methylation and oxidation. In mammalian brain histamine

Abbreviations: ACh, Acetylcholine; AD, Alzheimer's disease; ADHD, Attention deficit hyperactivity disorder; CIAS, Cognitive impairment associated to schizophrenia; EDS, Excessive daytime sleepiness; GABA, γ-Aminobutyric acid; H_3R, Histamine H_3 receptor; HBA, H-bond acceptor; HBD, H-bond donor; MAPK, Mitogen-activated protein kinase; MLogP, Moriguchi LogP; MS, Multiple sclerosis; MW, Molecular weight; PET, Positron emission tomography; PD, Parkinson's disease.

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N-methyltransferase (HNMT) catalyzes the methylation of histamine to the H_3R inactive N^{τ}-methylhistamine, whereas monoamine oxidase and aldehyde oxidase are responsible for the formation of (N^{τ}-methyl)imidazole acetic acid by the metabolic oxidation of histamine and to some extent of N^{τ}-methylhistamine (Berlin, Boyce, & Ruiz Mde, 2011; Lemke, Williams, & Foye, 2013).

Histamine exerts its actions through the activation of four distinct receptor subtypes (H_1 to H_4), that belong to the class A family of G protein-coupled receptors (GPCRs) (Leurs, Bakker, Timmerman, & de Esch, 2005; Nikolic et al., 2014). Among the histamine receptors, the H_3 receptor (H_3R) is a pre-synaptically located autoreceptor that inhibits the synthesis and release of histamine. In addition, H_3Rs function as pre-synaptic heteroreceptors with inhibitory activity on the release of several neurotransmitters, namely acetylcholine, γ-aminobutyric acid (GABA), dopamine, serotonin, noradrenaline and glutamate (Esbenshade et al., 2008). The H_3R was discovered in 1983 by Arrang et al. by analyzing the inhibition of histamine release in depolarized slices of rat cerebral cortex (Arrang, Garbarg, & Schwartz, 1983). In 1987, the presence of the receptor was confirmed by the development of R-α-methylhistamine and thioperamide as selective H_3 receptor agonist and antagonist, respectively (Arrang et al., 1987). Later, in 1999 Lovenberg and co-workers cloned the gene of the human H_3R, which code for a 445 amino acid protein (Lovenberg et al., 1999). The H_3R is predominantly concentrated in the central nervous system (CNS); however, it is also expressed peripherally in the gastrointestinal tract, the airways, and the cardiovascular system (Celanire et al., 2005; Tiligada, Zampeli, Sander, & Stark, 2009).

The H_3R couples to $G\alpha_{i/o}$ proteins, and hence its stimulation leads to inhibition of adenylate cyclases, diminishing the level of cyclic AMP (cAMP) with the subsequent reduction in downstream signaling pathways such as protein kinase A (PKA) activation and cAMP-responsive element binding protein (CREB)-induced gene transcription. The $G\beta\gamma$ complexes of $G\alpha_{i/o}$ proteins inhibit the opening of voltage-activated calcium channels, thereby reducing neurotransmitter release (Nieto-Alamilla, Marquez-Gomez, Garcia-Galvez, Morales-Figueroa, & Arias-Montano, 2016). Like other histamine receptors, H_3R forms receptor heterodimers shown for dopamine D_1 and D_2 receptors so far (Ferrada et al., 2008; Vohora & Bhowmik, 2012). Thereby, decreased affinity of D_2 receptor ligands could be observed in presence of H_3R agonists *in vitro* as well as potentiation of D_1 and D_2 receptor mediated locomotor activity by application of the H_3R inverse agonist/antagonist thioperamide (Ferrada et al., 2008). Other effector proteins activated by H_3R stimulation include mitogen-activated protein kinases (MAPKs), phosphatidylinositol 3-kinase (PI3K) and phospholipase A2 (PLA2) producing arachidonic acid. MAPK and PI3K signaling pathways are associated with the phosphorylation of extracellular signal-regulated kinases (ERKs) and protein kinase B (PKB), respectively, and the latter inhibits glycogen synthase kinase-3β (GSK-3β). H_3R activation also inhibits the activity of the Na^+/H^+ exchanger (Bhowmik, Khanam, & Vohora, 2012; Leurs et al., 2005).

Fig. 1 illustrates the different signaling pathways elicited or modulated by H_3R activation. Collectively, the modulation of the release of histamine and other neurotransmitters through H_3R activation could be linked to several neurological disorders such as sleep disorders like narcolepsy, Alzheimer's disease, attention deficit and hyperactivity disorder (ADHD), Parkinson's disease, schizophrenia, multiple sclerosis, Tourette's syndrome, pain, obesity etc (Bhowmik et al., 2012; Brioni,

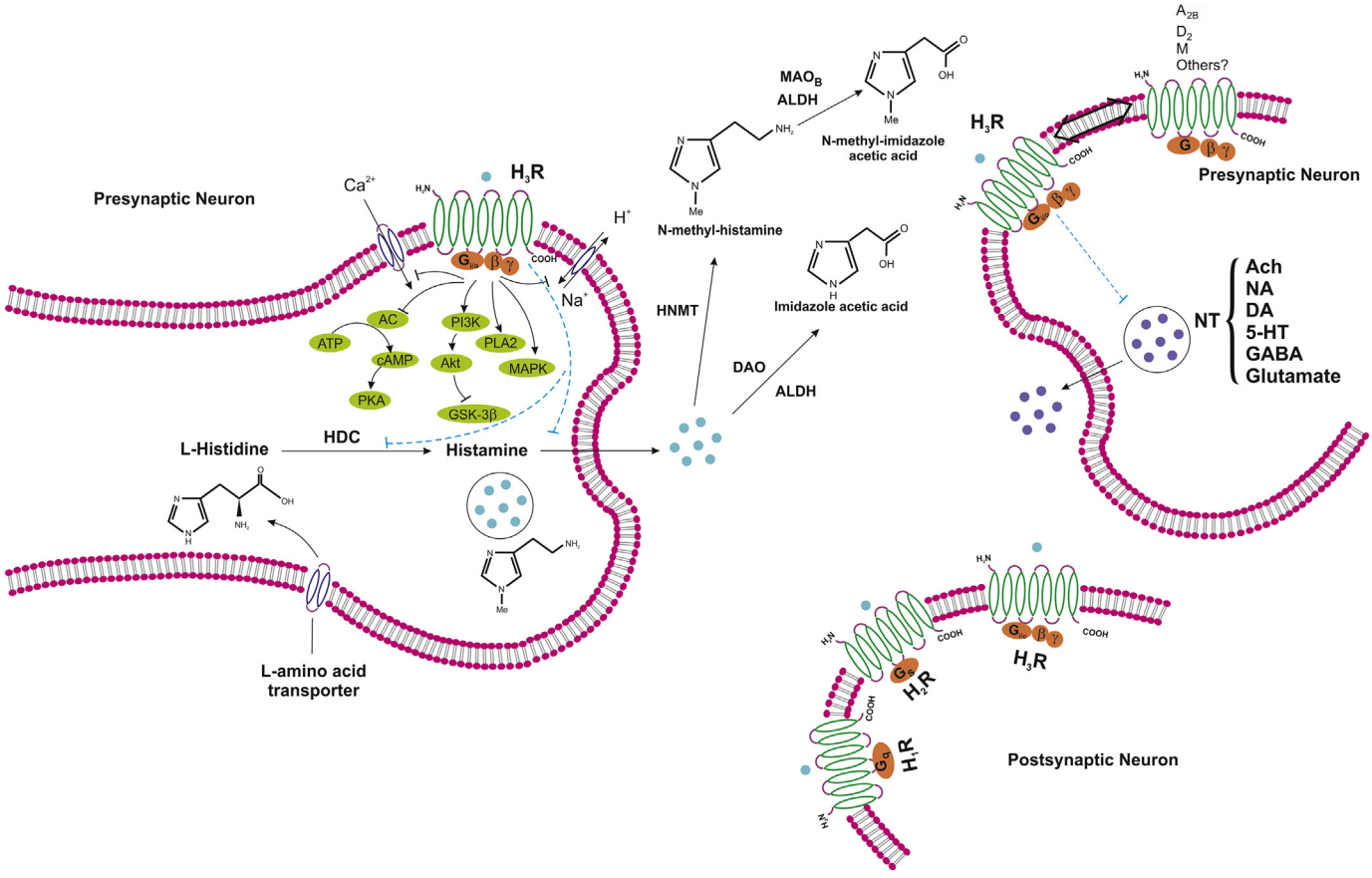

Fig. 1. Histamine H_3 receptor activation and signaling pathways. Abbreviations: 5-HT: serotonin; AC: adenylyl cyclase; ACh: acetylcholine; Akt: protein kinase B; ALDH: aldehyde dehydrogenase; ATP: adenosine triphosphate; cAMP: adenosine 3′,5′-cyclic monophosphate; DA: dopamine; DAO: Diamine oxidase; GABA: γ-aminobutyric acid; GSK-3β: glycogen synthase kinase-3β; H_1R: histamine H_1 receptor; H_2R: histamine H_2 receptor; H_3R: histamine H_3 receptor; HDC: histidine decarboxylase; HNMT: histamine *N*-methyltransferase; MAO_B: monoamine oxidase B; MAPK: mitogen-activated protein kinase, NA: noradrenaline; NT: neurotransmitter; PI3K: phosphatidylinositol 3-kinase; PKA: protein kinase A; PLA_2: phospholipase A_2.

Esbenshade, Garrison, Bitner, & Cowart, 2011; Gemkow et al., 2009; Lin, Sergeeva, & Haas, 2011; Passani et al., 2017; Passani & Blandina, 2011; Provensi, Blandina, & Passani, 2016; Shan, Bao, & Swaab, 2015). Fig. 2 shows the clinical trials reported for H_3R antagonists/inverse agonists in relation to neurological disorders and other diseases.

2. H_3Rs as a target for therapeutic discovery

Histamine has an important role in the light/dark cycle in which histamine levels increase during wakefulness to decline to the baseline level during sleep (Brioni et al., 2011; Lin et al., 2011; Meredith & Tony, 2011). Therefore, enhanced histamine neurotransmission due to H_3R blockade improves wakefulness and vigilance in individuals suffering from narcolepsy during daytime (Gondard et al., 2013). Narcolepsy is defined as uncontrollable excessive sleepiness and irregular onset of rapid eye movement (REM) sleep during the daytime that affect the quality of life. Episodes of sudden loss of muscle control (known as cataplexy) are experienced by most narcoleptic individuals (Calik, 2017). The wake promoting effect of H_3R antagonists has been well documented and several studies have shown that antagonizing H_3R receptors results in increased histamine levels, which in turn augment the activation of post-synaptic H_1 receptors leading to enhanced wakefulness (Broderick & Masri, 2011; Gondard et al., 2013; Lin et al., 2011; Parmentier et al., 2007; Thakkar, 2011). The advantage of H_3R antagonists over classical psychostimulants is the lack of locomotor activity, behavioral excitation, and sleep rebound (Berlin et al., 2011; Broderick & Masri, 2011; Lin et al., 2011).

Alzheimer's disease (AD), the most prevalent form of dementia, is a neurodegenerative disorder with cognitive deficit and memory impairment in the geriatric population. Although the cholinergic system is mainly targeted for enhancing acetylcholine levels by inhibiting its enzymatic degradation, the role of H_3Rs in modulating acetylcholine release should not be neglected. Nonetheless, the role of the histaminergic system in the pathophysiology of AD is not completely understood and some discrepancies still exist. For example, some reports indicate hyperactivity of the CNS histaminergic system, whereas other studies reveal a loss of histaminergic neurons in AD (Shan et al., 2015; Vohora & Bhowmik, 2012). However, recent reports are indicative of H_3R-mediated regulation of acetylcholine release leading to elevated levels in cortex and hippocampus (Brioni et al., 2011; Esbenshade et al., 2008; Sadek, Saad, Sadeq, Jalal, & Stark, 2016). On the other hand, H_3R antagonism increases CREB and GSK3β phosphorylation resulting in improvement of cognitive processes (Brioni et al., 2011; Leurs et al., 2005; Sadek, Saad, Sadeq, et al., 2016; Sander, Kottke, & Stark, 2008).

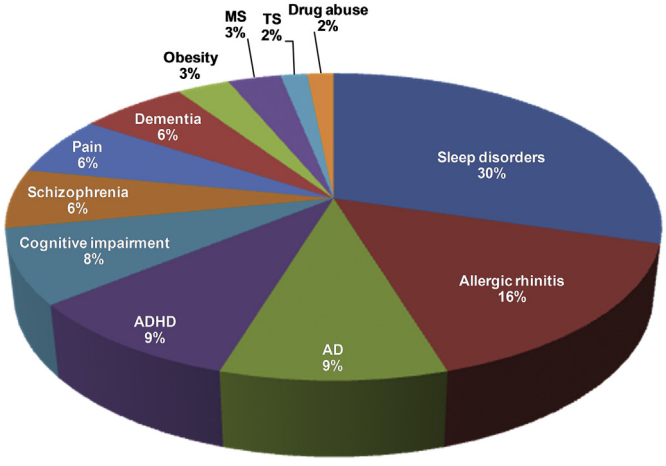

Fig. 2. Pie chart representation of ongoing clinical trial studies reported for H_3R antagonists/inverse agonists in different diseases. AD: Alzheimer's disease; ADHD: attention deficit hyperactivity disorder; MS: multiple sclerosis; TS: Tourette's syndrome.

Parkinson's disease is another neurodegenerative disorder affecting H_3Rs. The most common clinical symptoms of this disease are rigidity, bradykinesia, rest tremor, loss of postural reflexes, and gain impairment owing to progressive degeneration of the dopaminergic neurons in the nigro-striatal neuronal pathway (Ellenbroek & Ghiabi, 2014; Shan et al., 2015). As a result, the excitatory and inhibitory activity of dopamine D_1 and D_2 receptors, respectively, in the striatal GABAergic projection neurons is attenuated, leading to enhanced activity of GABAergic nigro-thalamic neurons, which in turn inhibit the activity of cortical neurons (Ellenbroek & Ghiabi, 2014; Nieto-Alamilla et al., 2016). The current pharmacotherapy of parkinsonian patients focuses is based on the strategy to replace, to prolong or to imitate the activity of endogenous dopamine. However, the main adverse effect associated with chronic administration of such therapeutics is tardive dyskinesia arising from excessive D_1 receptor-mediated signaling in the basal ganglia and enhanced cortico-striatal glutamatergic transmission (Ellenbroek & Ghiabi, 2014; Nieto-Alamilla et al., 2016). There are several reports indicating the involvement of H_3Rs in modulating striatal GABAergic, glutamatergic, and dopaminergic transmission, mainly by inhibiting the release of GABA, glutamate, and dopamine (Arias-Montaño, 2008; Garcia, Floran, Arias-Montano, Young, & Aceves, 1997; Nieto-Alamilla et al., 2016). Furthermore, studies have shown that the increased levels of histamine in substantia nigra (SN) contribute to the degeneration of dopaminergic neurons. Besides, higher expression of H_3Rs in substantia nigra pars reticulata (SNr) may contribute to the pathophysiology of Parkinson's disease (Arias-Montaño, 2008). In this respect, H_3R antagonists can be promising therapeutic agents in Parkinson's disease through the stimulation of GABA and dopamine release in the SNr and striatum, respectively. In addition, H_3R agonists can reduce dyskinesias induced by excessive dopamine D_1 receptor signaling (Ellenbroek & Ghiabi, 2014; Nieto-Alamilla et al., 2016).

The relationship between the attention deficit hyperactivity disorder (ADHD) and H_3Rs is supported by several reports (Berlin et al., 2011; Passani, Bacciottini, Mannaioni, & Blandina, 2000; Vohora & Bhowmik, 2012). ADHD is a neurobehavioral disorder with high prevalence in children, with hyperactivity, inattention, impulsivity, agitation, and disorganized behavior as the most common symptoms. The exact mechanisms of ADHD are not clearly understood; however, it may arise from the dysfunction of noradrenergic and dopaminergic signaling. The most routinely used therapeutic agents for ADHD treatment are methylphenidate and atomoxetine as stimulant and non-stimulant agents, respectively. Although it seems that these agents increase norepinephrine and dopamine concentrations in neuronal synapses, there is evidence that histamine levels in the prefrontal cortex are also augmented. Since these drugs have significant adverse effects and great potential of being abused, H_3R antagonists may represent a suitable alternative to the current therapeutics (Berlin et al., 2011; Passani et al., 2000).

In addition, the neural histaminergic system is involved in schizophrenia. This disorder is originated by hyperactivity of the dopaminergic system, with psychotic symptoms such as hallucination, delusion, emotional pauperism, and lack of motivation (Sander et al., 2008; Vohora & Bhowmik, 2012). The currently used pharmacotherapy for schizophrenia focuses on antagonizing dopamine receptors, mainly D_2 receptors, but extrapyramidal symptoms and metabolic actions (i.e. weight gain) are adverse effects associated with D_2 receptor antagonists (Sadek, Saad, Sadeq, et al., 2016). Some studies show that N^{τ}-methylhistamine is enhanced in the cerebrospinal fluid of schizophrenic patients (Rapanelli & Pittenger, 2016; Sander et al., 2008), and abnormal H_3R expression is observed in the brain of schizophrenic individuals (Rapanelli & Pittenger, 2016). In this context, compounds with inhibitory activity on H_3Rs receptors can be promising agents to replace the pharmaceuticals in use. Besides, an additional benefit of H_3R antagonists would be the induction of glutamate release, as glutamatergic hypoactivity is observed in this neuropsychiatric condition (Ellenbroek & Ghiabi, 2014).

Tourette's syndrome (TS) is a neurobehavioral disorder characterized by chronic motor and vocal tics. The histaminergic system appears to be implicated in the pathophysiology of TS because H_3R upregulation has been observed in the striatum of HDC knock-out animal models (Rapanelli et al., 2017; Rapanelli & Pittenger, 2016). Therefore, H_3Rs can be targeted by antagonists that eliminate the action of autoreceptors leading to enhanced histamine synthesis and release (Bloch, State, & Pittenger, 2011; Thenganatt & Jankovic, 2016).

With a prevalence of about 6 per 1000, Epilepsy is a frequent disease characterized by transient seizures due to abnormal synchronous or excessive activity of neurons (Fiest et al., 2017; Fisher et al., 2005; Fisher et al., 2014). Though the etiology of this disease is unknown in most cases, a disbalance between excitatory (namely glutamate) and inhibitory (GABA) neurotransmitter systems is commonly hypothesized to trigger epileptiform discharges resulting in epileptic seizures with differing onset (Fisher et al., 2017; Naylor, 2010). On a molecular level, the relationship to histamine seems to rest upon the H_3R mediated regulation of glutamate and GABA release and, inversely, their modulation of histamine release in brain (Bhowmik et al., 2012; Okakura, Yamatodani, Mochizuki, Horii, & Wada, 1992; Okakura-Mochizuki, Mochizuki, Yamamoto, Horii, & Yamatodani, 1996). From *in vivo* rodent models the involvement of brain histaminergic system is demonstrated by the anticonvulsant activity of H_3R antagonists and histidine as histamine precursor as well as the competence of histamine H_1 receptor antagonists to reverse these inhibiting effects (Lazewska et al., 2018; Sadek et al., 2016; Svob Strac et al., 2016).

Obesity is one of the worldwide concerns, with high prevalence and adverse effects on human health and life expectancy. According to the World Health Organization (WHO), obesity is defined as abnormal or excessive fat accumulation in the body with body mass index (BMI) of 30 or more. Obesity increases the risk of serious health problems such as cardiovascular disease, cancer, diabetes type 2, and obstructive sleep apnea (Berlin et al., 2011; Leurs et al., 2005; Passani, Blandina, & Torrealba, 2011; Sander et al., 2008). Metabolic homeostasis establishes a balance between food intake and energy expenditure through a large number of pathways in the body. Appetite and satiety are two critical components of eating behavior, which is regulated by a large number of orexigenic and anorexigenic signaling pathways in the central and peripheral nervous systems (Berlin et al., 2011; Lee et al., 2008; Passani et al., 2011; Sandoval, Cota, & Seeley, 2008). Several investigations reflect the paramount role of neuronal histamine in feeding behavior mediated by central H_3 and H_1 receptors. Loss of appetite and reduced body weight have been observed in response to elevated hypothalamic histamine levels in rodent models following the blockade of H_3 autoreceptors (Leurs et al., 2005; Passani et al., 2011; Plancher, 2011; Singh & Jadhav, 2013). Interestingly, the other side of the histamine action on modulating the eating behavior occurs through central H_1 receptors, whose stimulation suppresses food intake and leads to weight loss in rodents. This is the main reason behind the growing interest in developing H_3R antagonists as anti-obesity therapeutic agents. However, there is a controversy about the exact mechanism of H_3R involvement in the feeding process as few reports indicate H_3R-induced anorexia in animal models (Berlin et al., 2011; Passani et al., 2011; Schlicker & Kathmann, 2017) and conflicting observations also described reduced food-intake in mice followed by H_3R activation with imetit as agonist (Yoshimoto et al., 2006). More clarification in this area is therefore needed.

Drug addiction is a compulsive multifaceted behavior which is characterized by continuous consumption of drugs in an out of control manner. Although it is believed that mesolimbic dopaminergic system underlies in dopamine hypothesis of drug addiction, the role of histaminergic system on psychomotor and rewarding effects of addictive drugs should not be ignored (Brabant, Alleva, Quertemont, & Tirelli, 2010; Ellenbroek & Ghiabi, 2014; Vohora & Bhowmik, 2012). Studies have demonstrated that dopamine transmission can be reduced by histamine via presynaptic and postsynaptic H_3R located on dopaminergic and GABAergic neurons in striatum (C. Brabant et al., 2010; Vohora & Bhowmik, 2012). There are some lines of evidence indicating the effectiveness of H_3R antagonist/inverse agonists in alcohol abuse in animal models in preclinical studies (Galici et al., 2011; Nuutinen et al., 2016; Nuutinen, Vanhanen, Maki, & Panula, 2012; Rezvani, Lawrence, Arolfo, Levin, & Overstreet, 2012; Vanhanen et al., 2013). It has been observed that direct antagonizing of dopamine receptors is associated with some limitations including inefficacy and adverse effects, therefore, H_3R antagonist/inverse agonists can be potential alternative agents in drug abuse.

Pain, an unpleasant sensation caused by damaging stimuli, is divided into two categories consisting of nociceptive and neuropathic pains. Nociceptive pain is as a consequence of potential tissue injuries from outside or inside the body, whereas neuropathic pain is caused by damage or dysfunction of nerve fibers in nervous system.

As an inflammatory mediator, histamine plays a pivotal role in nociceptive processes in both the central and peripheral nervous systems (Gemkow et al., 2009; Hough & Rice, 2011; Tiligada et al., 2009). In this respect, the participation of H_3Rs in modulating pain, especially neuropathic pain, has attracted attention for the design of H_3R-related therapeutic agents, although the function of H_3R agonists and antagonists as pain relievers remains a debatable issue and maybe attributable to side-target effects such as sigma-1 receptor antagonism (Berlin et al., 2011; Riddy et al., 2019; Sander et al., 2008; Wijtmans, Leurs, & de Esch, 2007). The available information reveals a paradoxical effect for peripheral and central histamine. Peripheral histamine triggers the stimulation of nociceptive fibers present in the skin and spinal cord, whereas central histamine reduces the transmission of nociception in the brain. There are several reports demonstrating the antinociceptive effect of H_3R antagonists originated from augmented release of neuronal histamine (Hough & Rice, 2011). In contrast, inconsistent effects have been observed for H_3R agonists (Berlin et al., 2011; Wijtmans et al., 2007). It seems that different animal pain models and administration routes considerably affect the biological response for given H_3R agonists/antagonists. But H_3R antagonists appear more beneficial in terms of antinociceptive activity and can be promising agents for the treatment of different kinds of pain, in particular neuropathic pain (Berlin et al., 2011; Gemkow et al., 2009).

Allergic rhinitis, characterized by inflammation of the nasal membrane, results from an over-activated immune system exposed to allergens in sensitized individuals, and is associated with nasal congestion, rhinorrhea, sneezing, and pruritus. As histamine is a key mediator in triggering allergic rhinitis, preventing the histamine action is a priority in these conditions. Currently, H_1 receptor antagonists are extensively utilized for allergic rhinitis; however, in most cases for fully alleviating nasal congestion they are administered alongside α-adrenergic agonists. Since side-effects such as stimulatory CNS and cardiovascular actions have been observed following the administration of α-adrenergic agonists (Berlin et al., 2011; Leurs et al., 2005), designing compounds having fewer side-effects seems beneficial. The function of H_3Rs in controlling allergic rhinitis has been widely documented and anti-allergic features of H_3R antagonists via noradrenaline release have been reported in several studies (Berlin et al., 2011; McLeod et al., 1999; Repka-Ramirez, 2003; Varty, Gustafson, Laverty, & Hey, 2004). Based on these findings, co-administration of antagonists at H_1 and H_3 receptors may be a useful alternative to the current pharmacotherapy. On the other hand, the molecular design of hybrid compounds with dual activity on H_1 and H_3 receptors would be attractive for allergic rhinitis conditions.

An inflammatory disease resulting from demyelination and neurodegeneration in CNS is multiple sclerosis (MS), affecting especially young adults and adolescents (Jadidi-Niaragh & Mirshafiey, 2010; Tiligada, Kyriakidis, Chazot, & Passani, 2011). There is evidence indicating that histamine has a regulatory function in experimental allergic encephalomyelitis (EAE), an autoimmune model of MS. Accordingly, targeting H_3Rs can be a useful strategy for preventing MS progression (Kremer, Kury, & Dutta, 2015; Schwartzbach et al., 2017).

Apart from aforementioned clinical indications discussed above, recent preclinical studies evidenced the effectiveness of H_3 antagonists in glaucoma and traumatic brain injury in animal models (Lanzi et al., 2019; Liao et al., 2019).

A list of H_3R antagonists/inverse agonists currently being investigated in ongoing clinical studies including their clinical status, phase of development, and therapeutic indications along with the corresponding physicochemical and drug-likeness properties is provided in Fig. 3, Tables 1 and 2, and this information is briefly discussed in next section.

3. Clinical trials of current therapeutics targeting H_3Rs

ABT-288 (2-[4'-((3a*R*,6a*R*)-5-methyl-hexahydropyrrolo[3,4-b]pyrrol-1-yl)-biphenyl-4-yl]2*H*-pyridazine-3-one) is a selective H_3R antagonist/inverse agonist developed by Abbott. Structurally, it is a compound with molecular weight (MW) 372.46 g/mol, three H-bond acceptors (HBA), and Moriguchi LogP (MLogP) 3.42 (Moriguchi, Hirono, Liu, Nakagome, & Matsushita, 1992), passing all the drug-likeness properties (see Table 2). Moreover, this compound has good pharmacokinetic profile and oral bioavailability as well as a safety profile. ABT-288 induces histamine and acetylcholine release *in vitro*, and increases acetylcholine and dopamine levels in rat prefrontal cortex (Esbenshade et al., 2012). ABT-288 is currently in clinical trials and three phase studies have been completed without disclosing the results. A Phase II clinical study (ClinicalTrials.gov Identifier:NCT01018875) has been completed for determining ABT-88 efficacy and safety in adults with mild-to-moderate Alzheimer's disease, it being a randomized, double-blind, active- and placebo-controlled study. The effectiveness of ABT-288 in a randomized, double-blind, placebo-controlled, parallel-group, phase II clinical study for cognitive impairment associated with schizophrenia (CIAS) was also completed in 210 adults with schizophrenia (NCT01077700). A phase I clinical trial for ABT-288 has completed, evaluating safety, tolerability and pharmacokinetics in stable schizophrenic individuals treated with an atypical antipsychotic (NCT00888693). Although the safety and tolerability of ABT-288 have been evidenced in some trials including schizophrenic individuals, healthy young and elderly volunteers (Othman et al., 2012; Othman et al., 2014), its efficacy in Alzheimer's disease and CIAS is still debatable (Haig et al., 2014; Haig et al., 2014), and it seems that large samples are necessary for drawing any strong conclusion (Kubo, Kishi, Matsunaga, & Iwata, 2015).

Another drug candidate from Abbott is ABT-652, with no disclosed structure. ABT-652 has been investigated in three clinical trial studies. The first study has focused on the safety and efficacy of ABT-652 in combination with a non-steroidal anti-inflammatory drug (NSAID) in subjects with osteoarthritis (OA) pain in a phase II, randomized study (NCT01444365). A second phase II trial study has determined the effectiveness and safety of ABT-652 in a global multicenter, randomized, double-blind, placebo-controlled study in patients with osteoarthritis pain (NCT01207115). Furthermore, the safety, tolerability, pharmacokinetic and pharmacodynamic properties of ABT-652 have been examined in patients with excessive daytime sleepiness disorder in a phase I clinical trial study (NCT01124851). The outcomes of the above mentioned studies have not been communicated yet.

Arena Pharmaceutical introduced a biaryl sulfone derivative with antagonistic activity at H_3Rs known as APD-916, ((*R*)-1-(2-(4'-(3-methoxypropylsulfonyl)biphenyl-4-yl)ethyl)-2-methylpyrrolidine), which was rationally designed from corresponding sulfonamides in order to yield compounds with short duration of action (Semple et al., 2012). All the drug-likeness features have been observed for APD-916 with MW 401.56 g/mol, four HBA and MLogP 3.32. Good pharmacokinetic profiling as well as high selectivity over other histamine receptors have been reported for this drug candidate in preclinical studies. Orally administrated APD-916 enhanced wakefulness in different animal models (Semple et al., 2012), and there is a single ongoing clinical trial assessing APD-916 based on its tolerability and pharmacokinetics in

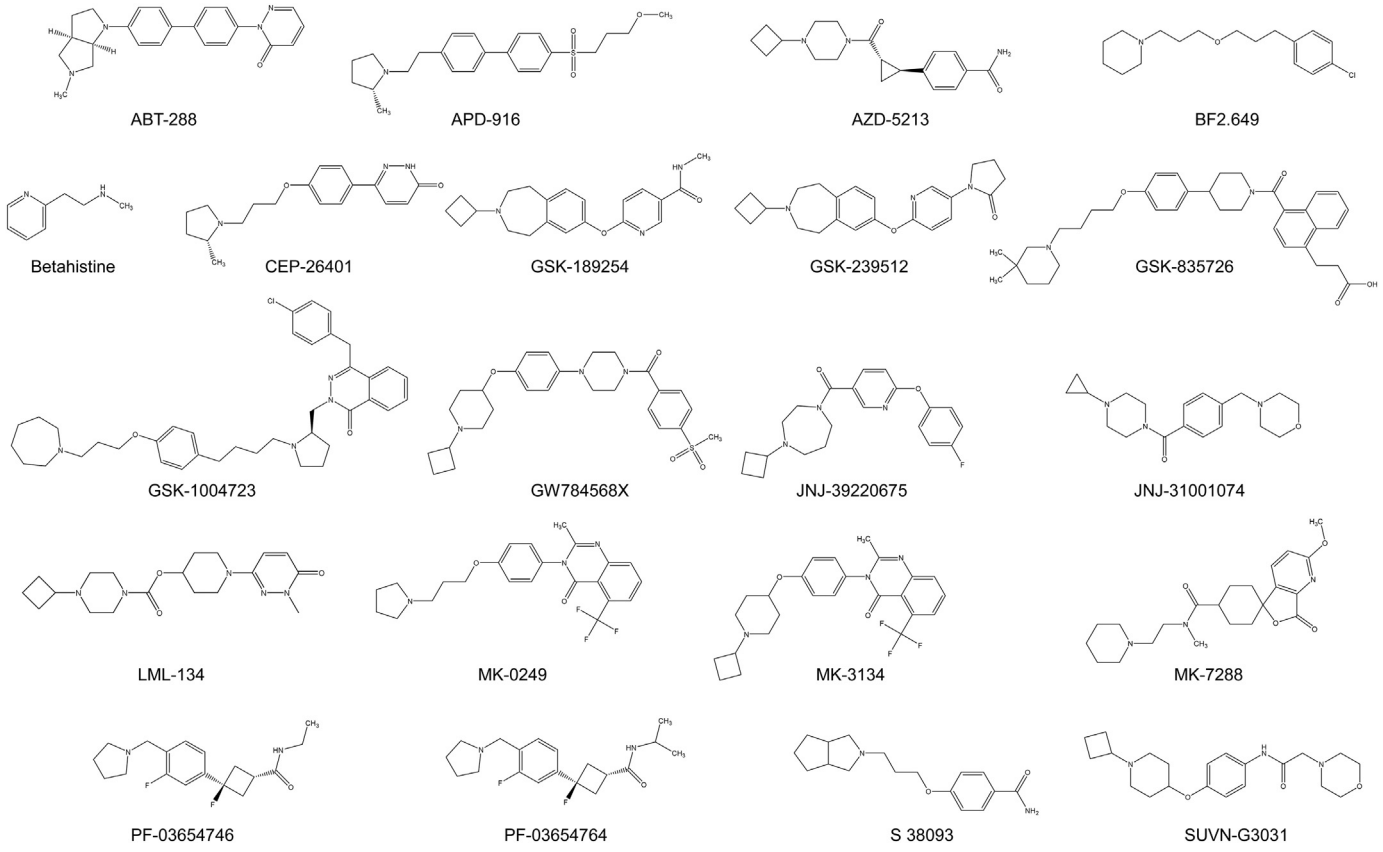

Fig. 3. Chemical structures of H_3R antagonists/inverse agonists in clinical trial studies.

Table 1
Current H_3 antagonists/inverse agonists as drug candidates in clinical trial studies.

Company	Compound	Status	Phase of development	Clinical trial identifier	Therapeutic indication/parameters under study	References
Abbott	ABT-288	C	II	NCT01018875	AD	
		C	II	NCT01077700	CIAS	(Haig, Bain, et al., 2014)
		C	I	NCT00888693	Schizophrenia	(Othman et al., 2014)
	ABT-652	C	II	NCT01444365	Osteoarthritis pain (in combination with NSAID)	
		C	II	NCT01207115	Osteoarthritis pain	
		C	I	NCT01124851	Sleep disorder	
Arena Pharmaceutical	APD-916	C	I	NCT01093508	Narcolepsy with/without cataplexy	
AstraZeneca	AZD5213	C	I	NCT01171105	Healthy (safety, tolerability, and pharmacokinetics)	
		C	I	NCT01121302	Tolerability	
		C	I	NCT01335451	Healthy (safety, tolerability, and pharmacokinetics)	
		C	I	NCT01194986	Brain distribution	(Jucaite et al., 2013)
		C	II	NCT01928381	Diabetic neuropathy	
		C	II	NCT01548287	Mild AD, mild cognition impairments	
		C	II	NCT01904773	Tourette's syndrome	
Bioprojet	BF2.649	C	III	NCT01789398	Narcolepsy	
		C	III	NCT01638403	EDS in narcolepsy	
		C	III	NCT01066442	EDS in PD	
		C	III	NCT01399606	Narcolepsy, Cataplexy	
		C	I	NCT01619033	Renal Impairment	
		C	III	NCT01036139	EDS in PD	
		C	III	NCT01067235	Narcolepsy, Cataplexy, EDS	
		C	II	NCT00690274	Schizophrenia	
		C	III	NCT01072968	Obstructive sleep apnea, EDS (refusing CPAP)	
		C	III	NCT01067222	EDS in narcolepsy	(Dauvilliers et al., 2013)
		R	III	NCT02739568	EDS in obstructive sleep apnea	
		C	II	NCT01620554	OSA, EDS	
		C	II	NCT00642928	EDS in PD	
		C	III	NCT01800045	Narcolepsy with cataplexy and EDS	(Szakacs et al., 2017)
		C	I	NCT03152123	Drug abuse	
		R	II	NCT02611687	Narcolepsy with/without cataplexy	
		C	III	NCT01071876	OSA, EDS	
		C	I	NCT02929342	Healthy Volunteers	
GlaxoSmithKline	GSK-189254	C	I	NCT00474513	Mild cognitive impairment, dementia	
		C	I	NCT00387413	Hyperalgesia	
	GSK-239512	C	I	NCT00675090	AD	(Nathan et al., 2013)
		C	II	NCT01772199	Multiple sclerosis	(Schwartzbach et al., 2017)
		C	II	NCT01009060	Schizophrenia	(Jarskog et al., 2015)
		C	I	NCT01802931	Multiple sclerosis	
		C	I	NCT00474513	Mild cognitive impairment, dementia	(Ashworth et al., 2014)
		C	II	NCT01009255	AD	(Grove et al., 2014)
	GSK-1004723	C	II	NCT00824356	Allergic rhinitis	
		C	II	NCT00972504	Allergic rhinitis (proof of concept)	(Daley-Yates et al., 2012)
		C	I	NCT00694993	Allergic rhinitis	(Daley-Yates et al., 2012)
	GSK-835726	C	II	NCT00851344	Allergic rhinitis	(Daley-Yates et al., 2012)
		C	II	NCT00972504	Allergic rhinitis (proof of concept)	(Daley-Yates et al., 2012)
		C	I	NCT00605852	Allergic rhinitis	(Daley-Yates et al., 2012)
	GW784568X	C	I	NCT00404586	Allergic rhinitis	
Johnson & Johnson	JNJ-39220675	C	II	NCT00804687	Allergic rhinitis	(Barchuk et al., 2013)
	JNJ-31001074	C	II	NCT00566449	ADHD (adults)	
		C	I	NCT00915434	Healthy (pharmacokinetic)	
		C	I	NCT00915746	Healthy (pharmacokinetic, drug interaction)	
		C	II	NCT00880217	ADHD (adults)	(Weisler et al., 2012)
		C	I	NCT00890240	ADHD (children 6-11)	
		C	I	NCT00890292	ADHD (children 12-17)	
		C	I	NCT01159821	Healthy (drug interaction)	
		R	II	NCT03194217	EDS, PD	
	JNJ-17216498	C	II	NCT00424931	Narcolepsy	
Merck	MK-0249	C	II	NCT00506077	Paranoid schizophrenia	(Egan et al., 2013)
		C	II	NCT00420420	AD	(Egan et al., 2012)
		C	II	NCT00475735	ADHD	(Herring et al., 2012)
	MK-3134	C	I	NCT01181310	Dementia	(Cho et al., 2011)
		C	I	NCT01110616	Dementia	
		C	I	NCT00887601	Dementia	
	MK-7288	C	I	NCT01092780	EDS in obstructive sleep apnea	(Sun et al., 2013)
Novartis	LML-134	C	I	NCT02334449	Healthy (safety, tolerability, and pharmacokinetics)	
Pfizer	PF-03654746	C	II	NCT00562120	Allergic rhinitis	(Stokes et al., 2012)
		C	II	NCT00531752	ADHD	
		C	I	NCT01346163	CIAS	
		C	II	NCT01006122	EDS, narcolepsy	
		C	I	NCT00730990	Healthy (PET)	
	PF-03654764	C	II	NCT01033396	Allergic rhinitis	(North et al., 2014)
		C	I	NCT00989391	Healthy (safety, tolerability, and pharmacokinetics)	
Servier	S 38093	C	II	ISRCTN89039808	mild to moderate AD	

Table 1 (*continued*)

Company	Compound	Status	Phase of development	Clinical trial identifier	Therapeutic indication/parameters under study	References
Sanofi-Aventis	SAR-110894	C	II	NCT01266525	Dementia	
Schering-Plough	SCH-497079	C	II	NCT00642993	Obesity	
		C	I	NCT00673465	Obesity (patients with diabetes mellitus)	
Suven Life Sciences	SUVN-G3031	C	I	NCT02342041	Cognitive Disorders	(Nirogi, Shinde, et al., 2019)
		C	I	NCT02881294	Cognitive Disorders	
Teva Pharmaceutical Industries	CEP-26401	C	I	NCT01903824	Cognitive impairment	(Spiegelstein et al., 2016)
	Betahistine	C	IV	NCT01468285	Gait or Balance Disorder Problems	
		C	II	NCT00748436	Obesity	
		C	I	NCT00459992	Obesity	
		C	I	NCT00852956	Healthy (safety, drug-drug interactions and pharmacokinetics)	
		C	I	NCT01168336	Healthy (safety, drug-drug interactions and pharmacokinetics)	

Abbreviations: AD: Alzheimer's disease; ADHD: Attention deficit hyperactivity disorder; CIAS: Cognitive impairment associated with schizophrenia; CPAP: Continuous Positive Airway Pressure; C: Completed; EDS: Excessive daytime sleepiness; OSA: obstructive sleep apnea; PD: Parkinson's disease; PET: Positron emission tomography; R: Recruiting.

healthy adult individuals in a randomized, double-blind, placebo-controlled, single-dose escalation phase I study (NCT01093508).

AZD5213, (4-((1*S*,2*S*)-2-(4-Cyclobutylpiperazine-1-carbonyl) cyclopropyl)benzamide) developed by AstraZeneca, is an antagonist at H_3Rs passing the Lipinski's rules of five criteria (i.e. MW 327.42 g/mol; HBA 3; HBD 1; MLogP 1.84). Additionally, this drug candidate fulfills all other drug-likeness and lead-likeness criteria listed in Table 2. Currently, seven clinical trial studies have been completed for this candidate. Three of them successfully accomplished phase I including safety, tolerability, and pharmacokinetics of AZD5213 after single and multiple oral doses in healthy volunteers in a double-blind, randomized, placebo-controlled, parallel-group assessment (NCT01171105, NCT01121302, and NCT01335451). Another study was conducted to determine H_3R occupancy (RO) of AZD5213 using a radiolabeled ligand following single-dose oral administration in healthy subjects. The results showed that AZD5213 binds to H_3Rs in a saturable, dose-, and concentration-dependent manner. Reported diurnal fluctuations of AZD5213 (i.e. high daytime and low night-time RO) make it suitable to be used during daytime with procognitive efficacy without sleep disruption in night-time (Jucaite et al., 2013) (NCT01194986). AZD5213 has also been evaluated in three phase II trials for a variety of clinical indications: a multi-center, randomized, two-part study for assessing safety, tolerability and efficacy of AZD5213 in subjects with painful diabetic neuropathy receiving pregabalin (NCT01928381); a randomized double-blind, multi-center, placebo-controlled study for testing AZD5213 on sleep duration in individuals with Alzheimer's/cognitive impairment (NCT01548287); and a two-part- randomized, multi-center, blinded study for evaluating safety, tolerability, pharmacokinetic and efficacy of AZD-5213 in patients with Tourette's syndrome (NCT01904773). A series of positron emission tomography (PET)-suitable congeners of AZD5213 have been presented recently, including [^{11}C]-carbonyl labeled AZD5213 as well as [^{11}C]-AZ13153556 and [^{11}C]-AZ13198083, being evaluated regarding brain uptake and distribution in non-human primates (Dahl et al., 2018).

The only approved H_3R antagonist/inverse agonist is BF2.649 (1-{3-[3-(4-chlorophenyl)propoxy]propyl}piperidine), developed by Bioprojet and known as pitolisant (Wakix®). It was approved by the European Medicines Agency in March 2016 and marketed in the European Union to be used in narcolepsy with or without cataplexy (Kollb-Sielecka et al., 2017; Syed, 2016). From a structural view, pitolisant is a non-imidazole based antagonist, which was rationally synthesized based on the structural modification by imidazole replacement with a piperidine group (Meier et al., 2001). As for other compounds containing imidazole moiety that interact with CYP450 enzymes, replacement with a piperidine ring reduced the hepatic toxicities (Ligneau et al., 2007). Pitolisant covers all the drug-likeness properties with MW 295.85, two HBA and MLogP 3.53 (Table 2). This compound displayed selectivity for the H_3R over the other three histamine receptors. Preliminary *in vivo* preclinical studies showed that pitolisant enhanced cerebral N^{τ}-methylhistamine levels in rodent models with good oral absorption and brain penetration (Ligneau, Perrin, et al., 2007). Additionally, the activity of rat prefrontal cortical dopaminergic and cholinergic pathways was increased by the intraperitoneal administration of pitolisant (Ligneau et al., 2007; Ligneau, Perrin, et al., 2007).

The more important effect of pitolisant is related to its wake-promoting and arousal activities as a result of enhanced histamine release in animal models (Ligneau, Perrin, et al., 2007). Moreover, its potential in the treatment of severe excessive daytime sleepiness (EDS) in narcoleptic teenagers refractory to therapeutic agents (e.g. modafinil and methylphenidate) was evaluated and the findings indicate its capability to significantly diminish sleepiness after the administration of a single dose (Inocente et al., 2012). In another study by Leu-Semenescu et al., the pitolisant efficacy in patients with symptomathic idiopathic hypersomnia refractory to current stimulants was assessed showing increased activity of the histaminergic neurons in such patients (Leu-Semenescu, Nittur, Golmard, & Arnulf, 2014). Moreover, preclinical investigations show useful effects of pitolisant on EDS in orexin$^{-/-}$ mice and narcoleptic patients (Lin et al., 2008). Pitolisant has also been shown to improve consolidation processes in mouse fear memory (C. Brabant, Charlier, & Tirelli, 2013).

Furthermore, the application of pitolisant for sleep-deficits in Prader-Willi syndrome has been demonstrated in mouse-models and described as off-label use, though this has not been investigated in interventional clinical trials yet (Balzani, Pace, Falappa, & Tucci, 2017; Falappa et al., 2018; Ghergan et al., 2017; Pace et al., 2018; Pullen, Picione, Tan, Johnston, & Stark, 2018; Pullen, Picione, Tan, Johnston, & Stark, 2019). A suppressive effect of pitolisant on epileptiform discharges in photosensitive patients with epilepsy was observed following the administration of a single dose, suggesting effectiveness in the treatment of both partial and generalized chronic seizures (Kasteleijn-Nolst Trenité et al., 2013). Further, a phase II study showed some benefit with pitolisant as adjunctive for patients suffering from epilepsy (Collart Dutilleul et al., 2016). Additional indication of pitolisant has been prompted for disorders as Guilles de la Tourette syndrome and autism that often are comorbidities with epileptic disorders (Hartmann, Martino, & Murphy, 2016). In another study, the effect of pitolisant on side-effects associated with olanzapine at the initial period of administration in mice was monitored, and the results indicated a reduction in olanzapine-induced sedation and depression-like symptoms (Dudek et al., 2016). Recently, the anti-obesity activity of pitolisant has been evaluated in terms of controlling body weight in obese mice.

Table 2
Physicochemical and drug-likeness properties antagonists/inverse agonists at histamine H_3 receptor proposed as clinical candidates.

Compound	MW g/mol	HBA	HBD	MLogP	Lipinski	Ghose	Veber	Egan	Muegge
ABT-288	372.46	3	0	3.42	Yes	Yes	Yes	Yes	Yes
APD-916	401.56	4	0	3.32	Yes	Yes	Yes	Yes	Yes
AZD-5213	327.42	3	1	1.84	Yes	Yes	Yes	Yes	Yes
BF2.649	295.85	2	0	3.53	Yes	Yes	Yes	Yes	Yes
Betahistine	136.19	2	1	0.55	Yes	No	Yes	Yes	No
CEP-26401	313.39	4	1	2.26	Yes	Yes	Yes	Yes	Yes
GSK-189254	351.44	4	1	2.67	Yes	Yes	Yes	Yes	Yes
GSK-239512	377.48	4	0	3.1	Yes	Yes	Yes	Yes	Yes
GSK-1004723	641.28	5	0	5.91	No	No	No	No	No
GSK-835726	528.68	5	1	3.32	No	No	No	Yes	No
GW784568X	497.65	5	0	2.83	Yes	Yes	Yes	Yes	Yes
JNJ-39220675	369.43	5	0	3.04	Yes	Yes	Yes	Yes	Yes
JNJ-31001074	329.44	4	0	1.52	Yes	Yes	Yes	Yes	Yes
LML-134	375.47	5	0	1.88	Yes	Yes	Yes	Yes	Yes
MK-0249	431.45	7	0	4.17	No	Yes	Yes	Yes	Yes
MK-3134	457.49	7	0	4.58	No	No	Yes	No	Yes
MK-7288	401.5	6	0	1.98	Yes	Yes	Yes	Yes	Yes
PF-03654746	322.39	4	1	3.2	Yes	Yes	Yes	Yes	Yes
PF-03654764	350.45	4	1	3.65	Yes	Yes	Yes	Yes	Yes
S 38093	288.38	3	1	2.15	Yes	Yes	Yes	Yes	Yes
SUVN-G3031	373.49	5	1	1.43	Yes	Yes	Yes	Yes	Yes

The results of this investigation supported its effectiveness in lowering plasma glucose and triglyceride levels by improving glucose tolerance and lipid profile (Kotanska, Kuder, Szczepanska, Sapa, & Kiec-Kononowicz, 2018). From a toxicity point of view, a non-clinical cardiovascular safety assessment was conducted for pitolisant and the results revealed lack of QT-liability and proarrhythmic risk according to International Conference on Harmonization (ICH) guidelines (Ligneau et al., 2017). The abuse liability of pitolisant was also tested in different *in vivo* rodent models and the outcome of the studies showed no addictive potential (Christian Brabant, Charlier, Navacerrada, Alleva, & Tirelli, 2016; Uguen et al., 2013).

At the present time, there are several clinical trial studies being conducted with a variety of indications for pitolisant. Various studies in different phases assess different aspects of pitolisant efficacy and safety in narcoleptic patients (Szakacs et al., 2017) (NCT01800045, NCT02611687, NCT03433131, NCT01399606, NCT01789398, and NCT01067235). Five phase III trials have also been completed for efficacy assessment of pitolisant in the treatment of EDS in different conditions including Parkinson's disease (NCT01066442 and NCT01036139), narcolepsy (NCT01067222 and NCT01638403) (Dauvilliers et al., 2013), and obstructive sleep apnea (OSA) (NCT02739568, NCT01072968, and NCT01071876). Moreover, two completed phase II clinical trial studies aiming at determining the minimum effective dose of pitolisant have been conducted in patients with Parkinson's disease (NCT00642928) and OSA (NCT01620554) experiencing EDS. Furthermore, a phase II study has assessed the cognitive-enhancing effect of pitolisant in subjects with schizophrenia in a randomized, double blind, and placebo-controlled study (NCT00690274). However, there is a controversy on the potential therapeutic application of pitolisant in schizophrenia according to other reports (Burban et al., 2010; Ligneau, Landais, et al., 2007). The pharmacokinetic profile of pitolisant has been studied in two phase I trials using healthy CYP2D6 genotyped individuals (NCT02929342) and subjects with renal dysfunction (NCT01619033). In addition, the addictive properties of pitolisant have also been evaluated in a randomized, double-blind, active-and placebo-controlled study in healthy, non-dependent recreational stimulant users (NCT03152123). Although several clinical trials are currently underway, no results have yet been publicized from the all above mentioned clinical trial studies.

Betahistine (*N*-methyl-2-(2-pyridyl)ethylamine) is a well-known dual H_1 receptor agonist/H_3 receptor antagonist with structural resemblance to histamine. Though it has been approved long before the discovery of H_3R to treat disorders of vestibular function as Menières-Disease, the evidence for this indication is not clear until today (Casani, Navari, Guidetti, & Lacour, 2018). Recently, a meta-analysis by the Cochrane collaboration including studies from 1967 to 2012 assessed the benefit of betahistine in treatment of patients suffering from idiopathic and secondary vertigo. Among 11 studies including 606 patients in total, the reduction of symptoms was higher in the group receiving betahistine than placebo while not showing more adverse events (Murdin, Hussain, & Schilder, 2016). Despite low evidence due to high statistical heterogeneity of the studies, betahistine remains an attractive agent still being evaluated in several studies. Among them, a phase I study (program AM-125) from Auris Medical has been completed using the drug in a formulation for intranasal application resulting in significant increase of bioavailability, presumably enhancing effectiveness (AG, 2018)

In the last years, studies investigated the employment of betahistine in further diseases, for improvement of cerebrovascular blood-flow (NCT01468285) and obesity in female patients (NCT00748436, NCT00459992) as well as obesity in patients receiving olanzapine (NCT00852956, NCT01168336).

CEP-26401, known as Irdabisant (6-{4-[3-((*R*)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-2*H*-pyridazin-3-one]), is another H_3R antagonist/inverse agonist (MW 313.39). CEP-26401 was first reported by Hudkins et al., 2011 (Hudkins et al., 2011), and is under development by Teva Pharmaceutical Industries. This candidate has excellent physicochemical properties that make it ideal from a drug-likeness (Table 2) and pharmacokinetic perspective (Hudkins, Raddatz, et al., 2011). The antagonistic effect of CEP-26401 in rat and human H_3R expressing systems was investigated with results indicative of high affinity in radioligand binding assays (Raddatz et al., 2012).The pharmacokinetic, pharmacodynamic, and safety of CEP-26401 were evaluated in two randomized, double-blind, placebo-controlled studies in healthy subjects. The findings showed that this drug candidate has dose- and time-independent pharmacokinetics, being well tolerated after single and multiple oral administrations with a major elimination pathway via renal excretion (Spiegelstein et al., 2016).

A phase I clinical trial has been completed for assessing CEP-26401 in cognitive impairment in healthy individuals without disclosing any results (NCT01903824). Although CEP-26401 is under clinical trial study, several projects are in progress for synthesizing novel irdabisant analogs in order to improve the pharmacokinetic and pharmacodynamic profile (Hudkins, Aimone, et al., 2011; Hudkins et al., 2015; Josef, Aimone, Lyons, Raddatz, & Hudkins, 2012).

GSK-189254, 6-[(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)oxy]-*N*-methyl-3-pyridinecarboxamide, is a benzazepine-based H_3R antagonist/inverse agonist under development by GlaxoSmithKline. It was introduced as one of the potential H_3R antagonists among different synthetic benzazepine derivatives (Wilson et al., 2013a; Wilson et al., 2013b). GSK-189254 has MW 351.44 g/mol, MLogP 2.67, and HBA and HBD numbers of four and one, respectively. This candidate possesses all the drug-likeness criteria listed in Table 2, and high affinity and selectivity towards the H_3R as evidenced by radioligand binding studies with recombinant and native H_3Rs of several species. GSK189254 elevated acetylcholine, noradrenaline, and dopamine levels in the anterior cingulate cortex as well as acetylcholine levels in the dorsal hippocampus, presumably by blocking H_3 heteroreceptors (Medhurst et al., 2007). In addition, the effect of GSK-189254 on histaminergic neurons was investigated in rats and the findings showed region-specific differences in the release of histamine and other neurotransmitters, attributable to distinct histaminergic pathways. This study also showed that GSK-189254 reversed the amnesic effect of scopolamine using object recognition test in rats (Giannoni et al., 2010).

GSK-189254 has also been used as PET radiotracer (in the form of [^{11}C]-GSK-189254, also used as [^{11}C]-AZ12807110 by Jucaite et al. (Jucaite et al., 2013)) to assess H_3R occupancy (Ashworth et al., 2010), and is currently used in an image-based phase I clinical trial study for investigating GSK-239512 distribution in the brain (NCT00474513). Efficacy of GSK-189254 in preclinical models of neuropathic pain has been reported (McGaraughty, Chu, Cowart, & Brioni, 2012; Medhurst et al., 2008). At present, a phase I trial has been completed for the safety and efficacy assessment of GSK-189254 in a electrical hyperalgesia model in healthy subjects in a double-blind, double-dummy, placebo-controlled, incomplete block, two period crossover study with no disclosure of the result (NCT00387413).

GSK-239512 is another drug candidate developed by GlaxoSmithKline with chemical name 1-[6-[(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)oxy]-3-pyridinyl]-2-pyrrolidinone (Wilson et al., 2013a). From structural perspectives, it is similar to GSK-189254 but with a minor structural difference in which the carboxamide group of GSK-189254 was replaced by a pyrrolidinone ring. No violation of drug-likeness criteria has been observed for GSK-239512 (MW 377.48, MLogP 3.1, and four HBA; see Table 2). Binding assays both *in vitro* and *in vivo* revealed high affinity of GSK-239512 for rat and human H_3Rs (Ashworth et al., 2014; Wilson et al., 2013a). Interestingly, the affinity was higher for human H_3Rs as shown by an *in vivo* receptor occupancy phase I clinical trial study in healthy volunteers (NCT00474513) (Ashworth et al., 2014). In a single blind, placebo-controlled, randomized phase I trial study, the efficacy, safety, and tolerability of GSK-239512 were evaluated using a titration dose regimen in patients with mild-to-moderate Alzheimer's disease. The results of this completed clinical trial study showed that this candidate has a procognitive effect with an acceptable level of tolerability (NCT00675090) (Nathan et al., 2013). Likewise, in a completed phase II clinical trial study, a modest and selective effect of GSK-239512, alongside satisfactory safety and tolerability in patients with mild-to-moderate Alzheimer's disease have been evidenced in a randomized, double-blind, placebo-controlled study (Grove et al., 2014) (NCT01009255). Moreover, GSK-239512 has completed phase II of clinical trials for stable subjects with schizophrenia in a randomized double-blind, placebo controlled, parallel group study. Although no overall beneficial effects were achieved in cognitive impairment associated to schizophrenia (CIAS), care should be taken for the interpretation of the results since the study was performed in a small sample size and for generalizing the results a larger sample size is required (Jarskog et al., 2015) (NCT01009060). The remyelination effect of GSK-239512 in subjects with relapsing-remitting multiple sclerosis was evaluated in a randomized, parallel group, placebo-controlled, and multicenter phase II study. This phase of the study has been completed and the findings show a small positive effect on remyelination (Schwartzbach et al., 2017) (NCT01772199). A drug-drug interaction phase I trial study has been also completed for GSK-239512 in order to assess the pharmacokinetics of GSK-239512 co-administered with ketoconazole in young healthy individuals (NCT01802931).

Dual H_1/H_3 receptor antagonists developed by GlaxoSmithKline have also reached clinical trials at various stages. These candidates are useful for alleviating the symptoms associated with allergic rhinitis(Daley-Yates et al., 2012). GSK-1004723, 4-[(4-chlorophenyl)methyl]-2-({(2*R*)-1-[4-(4-{[3-(hexahydro-1*H*-azepin-1-yl)propyl]oxy}phenyl) butyl]-2-pyrrolidinyl}methyl)-1(2*H*)-phthalazinone, is one of these H_1/H_3 receptor antagonists with high affinity for recombinant H_1 and H_3 receptors as shown by radioligand binding assays (Slack et al., 2011). In spite of its antagonistic effect on H_3Rs, no drug-likeness properties were observed for this compound (Table 2). Additionally, it had prolonged duration of activity at H_1 and H_3 receptors, possibly due to its lipophilic and dibasic nature as well as slow dissociation rate in the vicinity of receptors, leading to daily single dose administration of the compound (Slack et al., 2011). GSK-1004723 is formulated as suspension or solution for intranasal administration; however, single-dose intranasal administration is not significantly efficient to reduce symptoms associated with allergic rhinitis compared to cetirizine. Allergic rhinitis symptoms were reduced following intranasal administration in the form of a three-day repeated dose (Daley-Yates et al., 2012). Currently, three clinical trial studies are conducted for efficacy, safety, pharmacokinetic, and tolerability evaluation of GSK-1004723 in healthy subjects and patients with seasonal allergic rhinitis (NCT00824356; NCT00972504; NCT00694993).

GSK-835726 (3-[4-[4-[4-[4-(3,3-dimethylpiperidin-1-yl)butoxy] phenyl]piperidine-1-carbonyl]naphthalen-1-yl]propanoic acid) is a dual H_1/H_3 receptor antagonist with the potential to be used in allergic rhinitis. Likewise GSK-1004723, the drug-likeness criteria have not been passed by this drug candidate; nonetheless, it is a well-tolerated, highly bioavailable and long acting agent. The antagonistic effect of GSK-835726 at H_1 and H_3 receptors has been reported for *in vivo* animal models. Three completed clinical trial studies (i.e. phases I and II) are in progress for evaluating efficacy, safety, and tolerability of GSK-835726 in healthy individuals and subjects with seasonal allergic rhinitis (NCT00851344; NCT00605852; and NCT00972504). These studies showed that the efficacy profile of GSK-835726 in allergic rhinitis is comparable with cetirizine with once-daily oral administration (Daley-Yates et al., 2012).

Another H_3R antagonist developed by GlaxoSmithKline is GW784568X (1-{4-[(1-cyclobutyl-4-piperidinyl)oxy]phenyl]-4-{[4-(methylsulfonyl)phenyl]carbonyl piperazine). This drug candidate contains all the drug-likeness properties except Ghose parameters (Table 2). The MW, HBA, and MLogP of GW784568X are 497.65, 5, and 2.83, respectively. No comprehensive information is available in the public domain; however, some studies show that this candidate is highly selective towards H_3Rs with good CNS penetration in animal models (Norman, 2007).

Currently, a phase I trial study for GW784568X efficacy in allergic rhinitis has been completed as a randomized, placebo-controlled, 4-period, incomplete block, and crossover study (NCT00404586).

In 2010, Johnson & Johnson synthesized and identified a series of compounds with an aryloxypyridine amide scaffold as H_3R antagonists (Letavic et al., 2010). Among the synthesized compounds, JNJ-39220675 ((4-cyclobutyl-1,4-diazepan-1-yl)-[6-(4-fluorophenoxy) pyridin-3-yl]methanone) exhibited high affinity for H_3Rs receptors and enhanced histamine levels in rat frontal cortex and showed wake-promoting ability in preclinical studies (Letavic et al., 2010). Different synthesis routes for scaling up have been proposed for this compound (Pippel et al., 2011). This drug candidate with MW 369.43, five HBA, and MLogP 3.04 possesses all the drug-likeness criteria (Table 2). Preclinical PET studies using [^{11}C]-GSK-189254 in baboons showed that JNJ-39220675 has a receptor occupancy at $H_3Rs > 90\%$ following oral and intravenous administration (Logan et al., 2012).

JNJ-39220675 has completed a phase II clinical trial study in patients with allergic rhinitis in a randomized, single-dose, single-blind, double-dummy, placebo-controlled, and three-way cross-over study that compared its effectiveness with pseudoephedrine (NCT00804687), and showed that JNJ-39220675 alleviated the symptoms of allergen-induced nasal congestion (Barchuk, Salapatek, Ge, D'Angelo, & Liu, 2013). Additionally, several preclinical studies reveal that JNJ-39220675 has the potential to reduce alcohol abuse-related behaviors in rat models of alcoholism (Galici et al., 2011). Since alcoholism and drug abuse are often observed in cognitive disorders, H_3R antagonists could have beneficial effects on alcohol dependency (Galici et al., 2011; Nuutinen et al., 2012; Nuutinen et al., 2016). However, further experiments are required to verify the pharmacotherapeutic efficacy of H_3R antagonists, including JNJ-39220675, in alcohol addiction to allow their evaluation in clinical trials in the near future.

A second H_3R antagonist with benzamide-based structure from Johnson & Johnson is JNJ-31001074, known as Bavisant and under chemical IUPAC name of (4-cyclopropylpiperazin-1-yl)-[4-(morpholin-4-ylmethyl)phenyl]methanone. It is a compound with molecular weight 329.44, HBA four, and MLogP 1.52 encompassing all the properties required for drug-likeness criteria. A preclinical study of JNJ-31001074 revealed that this drug candidate has high affinity towards H_3Rs and increases acetylcholine levels in rat frontal cortex. Recent research revealed a H_3R occupancy about 90% after per oral administration decreasing to approx. 40% after 7h (Troxler et al., 2019). The pharmacokinetic profile of this candidate is satisfying in terms of plasma concentration, receptor occupancy, and safety (Letavic et al., 2015). There are eight ongoing clinical trial studies for JNJ-31001074 at different stages. JNJ-31001074 has completed phases for ADHD in pediatric and adult populations. In pediatric subjects, the pharmacokinetics, safety, and tolerability of JNJ-31001074 was evaluated in an open-label, multi-center, sequential group, ascending dose study (NCT00890240 and NCT00890292), whereas the safety and efficacy of JNJ-31001074 in adult patients was assessed using a multicenter, double-blind, placebo-controlled, randomized, and parallel-group study (NCT00566449 and NCT00880217). Although no significant effectiveness of JNJ-31001074 has been achieved in clinical trials for adults with ADHD, issues such as lack of variety in participants in terms of ethnic minorities, short-duration treatment and safety assessment make the interpretation difficult (Weisler, Pandina, Daly, Cooper, & Gassmann-Mayer, 2012). The effect of food on the pharmacokinetics of JNJ-31001074 has been evaluated in a completed phase I trial study in healthy individuals without disclosing the results (NCT00915434). Two individual open-label drug-drug interaction phase I studies are currently in progress for evaluation of the effect of ketoconazole and paroxetine on JNJ-31001074 pharmacokinetics in healthy volunteers (NCT00915746 and NCT01159821). Recently, a multicentre, multinational, randomized, double blind, parallel group and placebo controlled phase II study has been initiated to assess the safety and efficacy of JNJ-31001074 in excessive daytime sleepiness in parkinsonian patients, and is currently recruiting subjects (NCT03194217).

The H_3R antagonist JNJ-17216498, developed by Johnson & Johnson, has entered clinical trial studies, but no information regarding its structure has been publicized to date. A phase II study of JNJ-17216498 monotherapy has been completed for patients with narcolepsy, but the results are not publically available concerning the efficacy and safety of JNJ-17216498 compared to modafinil and placebo (NCT00424931).

Merck introduced in 2008 a quinazoline-based H_3R antagonist/inverse agonist known as MK-0249 (2-methyl-3-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]-5-(trifluoromethyl)quinazolin-4-one) with MW 431.45g/mol and seven HBA (Nagase et al., 2008). This compound contains all the drug-likeness properties with one violation in Lipinski rule of five (i.e. MLogP 4.17. marginally greater than the predefined value of 4.15) (Table 2). *In vitro* radioligand binding assays showed that this candidate has high affinity at human H_3Rs with antagonist activity. Moreover, an *in vivo* study showed increased brain histamine levels following oral administration of MK-0249 in rats (Nagase et al., 2008). At the moment, three clinical trial Phase II evaluations have been completed in order to assess the safety and efficacy of MK-0249 in subjects with paranoid schizophrenia (NCT00506077), Alzheimer's disease (NCT00420420), and ADHD (NCT00475735) in a randomized, double-blind, placebo-controlled study. However, for all indications no significant efficacy was observed (Egan et al., 2012; Egan et al., 2013; Herring et al., 2012). Considering the shortcomings of these studies, such as selection of appropriate dose, duration of treatment, sample size, and inclusion of patients with concomitant use of therapeutic agents (Egan et al., 2012; Egan et al., 2013; Herring et al., 2012), the interpretation of the results should be carefully handled and in some cases further evaluations seems to be essential.

MK-3134 (3-[4-(1-cyclobutylpiperidin-4-yl)oxyphenyl]-2-methyl-5-(trifluoromethyl)quinazolin-4-one) was synthesized by Merck, as the structurally constrained analogue of MK-0249 (Nagase et al., 2008). This H_3R inverse agonist has MW 457.49, seven HBA, and MLogP 4.58, with one violation in terms of drug-likeness criteria observed for Lipinski, Ghose, and Egan rules (see Table 2 for more details). MK-3134 has high binding affinity and selectivity towards H_3Rs. Moreover, this compound showed good pharmacokinetic profile in rat models (Nagase et al., 2008). Receptor occupancy using [^{11}C]-MK-8278 as radiotracer in PET scan revealed high occupation of cerebral H_3Rs by this inverse agonist (Van Laere et al., 2014). Three phase I studies involving MK-3134 are currently underway. One of the trial studies examined the effectiveness of MK-3134 in combination with donepezil in scopolamine-induced cognitive impairment using a five-period, placebo-controlled, cross-over study (NCT01181310). The outcome of this study indicates that the combination of MK-3143 and donepezil can reverse the scopolamine-induced impairment to a larger extent compared with each therapeutic agent alone (Cho et al., 2011). Additionally, a clinical trial has dealed with the electroencephalogram platform standardization of MK-3134 in healthy individuals in a double blind, randomized, crossover study (NCT01110616). Furthermore, MK-3134 has been investigated in a 4-period, placebo-controlled, cross-over study to assess the use of functional magnetic resonance imaging (fMRI) and cerebral blood flow measurements as biomarkers for measuring MK-3134-induced changes in dementia (NCT00887601). However, at this stage the findings of two latter trial studies are not publicly available.

An additional H_3R inverse agonist developed by Merck is MK-7288 (2'-methoxy-*N*-methyl-7'-oxo-*N*-[2-(1-piperidinyl)ethyl]-7'*H*-spiro[cyclohexane-1,5'-furo[3,4-b]pyridine]-4-carboxamide) with drug-likeness properties (MW 401.5, six HBA, and MLogP 1.98). A phase I clinical trial has been completed for this drug candidate to evaluate its effectiveness and pharmacodynamics in EDS in subjects with obstructive sleep apnea (Sun et al., 2013) (NCT01092780).

With LML-134 (1-(1-methyl-6-oxo-1,6-dihydropyridazin-3-yl) piperidin-4-yl 4-cyclobutylpiperazine-1-carboxylate) containing drug-likeness properties (MW 375.47, five HBA, and MLogP 1.88), Novartis presents an additional drug-candidate to treat excessive sleepiness. A phase I clinical study was performed in 2015 with pending results (NCT02334449). Despite the lacking results from clinics, first pharmacological and chemical information about this entity was published recently (Troxler et al., 2019). These results demonstrate low nanomolar H_3R binding affinity and potent abrogation of *R*-(α)-methylhistamine mediated inhibition of cAMP-formation *in vitro*. In addition, the authors present first pharmacokinetic data including promising blood-brain permeability properties that lead to high levels of receptor occupancy (about 90%) after peroral administration.

Two H_3R antagonists were introduced by Pfizer in 2011, namely PF-03654746 and PF-03654764 (Wager et al., 2011). The former, under the chemical name of *trans*-*N*-ethyl-3-fluoro-3-[3-fluoro-4-(pyrrolidinylmethyl)-phenyl]cyclobutanecarboxamide, is a drug-like molecule (Table 2) with MW 322.39, four HBA, one HBD, and MLogP

3.2. A scalable process was developed for the synthesis of this drug candidate (Hawkins et al., 2012). The result of pre-clinical binding assays showed that PF-03654746 binds to recombinant human and rat H_3Rs with high affinity (Wager et al., 2011). Recently, receptor occupancy studies using [^{11}C]-GSK-189254 PET imaging in healthy human subjects revealed that PF-03654746 fully occupies H_3R binding sites (Gallezot et al., 2017). At present, PF-03654746 is involved in five clinical trial studies. The compound has been evaluated in a randomized, double blind, double dummy, placebo controlled, four way cross-over phase II study for its nasal decongestant properties in the treatment of allergic rhinitis (NCT00562120). The results are indicative of PF-03654746 efficacy in reducing allergen-induced nasal symptoms in combination with fexofenadine (Stokes et al., 2012). The efficacy and safety of PF-03654746 has also been assessed in a randomized, double-blind, cross-over phase II study for patients with ADHD (NCT00531752). Furthermore, PF-03654746 has been evaluated in a completed phase I study for the treatment of cognitive deficits in schizophrenia, although no results have been disclosed (NCT01346163). The effect of PF-03654746 in EDS associated with narcolepsy has been determined in a randomized phase II, double blind, placebo-controlled, multi-center crossover study (NCT01006122). A trial for determining receptor occupancy of PF-03654746 in a healthy-volunteer PET study has been completed without disclosing any outcome but as well probed the qualification of a further radiolabeled ligand [^{11}C]-PF-04621053 by Pfizer with no disclosed structure (NCT00730990).

A compound structurally similar to PF-03654746 has been developed by Pfizer (PF-03654764), with a minor change in the substituent attached to the cyclobutanecarboxamide moiety (Wager et al., 2011). This compound, with the chemical name *trans*-3-fluoro-3-[3-fluoro-4-(pyrrolidin-1-ylmethyl)phenyl]-*N*-(2-ethylpropyl) cyclobutanecarboxamide possesses all the drug-likeness properties (MW 350.45, HBA 4, HBD 1, and MLogP 3.65). Binding assays showed high affinity and selectivity towards H_3Rs with excellent ADME properties (Wager et al., 2011). Likewise PF-03654746, this candidate has completed a phase II trial study for investigating its efficacy in allergic rhinitis in a randomized, double blind, placebo controlled, and four way cross-over study (NCT01033396). However, no significant reduction in allergic rhinitis-associated nasal symptoms was observed compared to the combination of fexofenadine and pseudoephedrine (North et al., 2014). In another trial study, the safety, tolerability, and pharmacokinetics of PF-03654764 in healthy individuals were assessed in a randomized, double blind, placebo controlled, and dose escalation study following oral administration (NCT00989391).

An azabicyclic compound named S 38093, (4-[3-(3,3a,4,5,6,6a-hexahydro-1*H*-cyclopenta[c]pyrrol-2-yl)propoxy]benzamide), was introduced by Servier with H_3R antagonist and inverse agonist activity (Sors et al., 2017). The compound contains all the drug-likeness criteria owing to its physicochemical properties (i.e. MW 288.38, HBA 3, HBD 1, and MLogP 2.15; Table 2). *In vitro* preclinical studies demonstrated moderate affinity of S 38093 for human and rodent H_3Rs but high selectivity relative to other histamine receptors (Sors et al., 2017). S 38093 also showed a good pharmacokinetic profiling in animal models (Panayi et al., 2017; Sors et al., 2017). In addition to the moderate affinity of S 38093 observed *in vitro*, a 30-fold higher affinity was observed at sigma-1 receptors that may therefore be involved in its potent cognition enhancing effects (Riddy et al., 2019). Furthermore, improved cholinergic neurotransmission and higher histamine turn-over were observed in animal models, suggesting a cognitive enhancement property for this agent (Panayi et al., 2017). Surprisingly, in a recent study the chronic administration of S 38093 to adult animals in a mouse model of Alzheimer's disease induced hippocampal neurogenesis, possibly due to the release of growth factors (Guilloux et al., 2017). Moreover, a synergistic effect of S 38093 in elevating memory performance was evidenced when co-administered with donepezil in middle-aged mice (Sors et al., 2016). An antinociceptive effect of S 38093 was also observed in different neuropathic pain rat models following chronic administration (Chaumette et al., 2018). The only registered clinical trial reported for S 38093 is assessing its efficacy and safety in subjects with mild to moderate Alzheimer's disease (ISRCTN89039808).

In 2012, Sanofi-Aventis developed a compound, SAR-110894, as H_3R antagonist/inverse agonist (Griebel et al., 2012). No physicochemical properties are publicly available nor has the structure been disclosed. In preclinical studies SAR-110894 displayed high potency and selectivity for recombinant and native human H_3Rs. In addition, effectiveness of SAR-110894 in different cognitive impairment animal models related to Alzheimer's disease, ADHD, and schizophrenia was evidenced (Griebel, Pichat, et al., 2012). In addition, the awakening characteristic of SAR-110894 was investigated using EEG recordings in rats during the light phase. Although this drug candidate failed to significantly modify the sleep/wakefulness profile, this can be an advantage over other similar H_3R antagonists in cognitive disorders owing to its non-wakefulness property during night-time (Griebel, Decobert, Jacquet, & Beeske, 2012). Recently, the beneficial effect of SAR-110894 in inhibiting tau pathology and cognitive deficit has been documented in transgenic mouse model of tauopathy (Delay-Goyet et al., 2016). SAR-110894 is currently under investigation in a multinational, multicenter, randomized, double-blind, parallel-group, placebo-controlled phase II clinical trial involving subjects with mild to moderate Alzheimer's disease receiving donepezil (NCT01266525).

SCH-497079 is a H_3R receptor antagonist introduced by Schering-Plough, without any publicized pharmacological and structural information. A Phase II clinical trial assessment of SCH-497079 on weight has been completed in a multicenter, randomized, parallel-group and placebo-controlled study in obese and over-weight participants (NCT00642993). A further study evaluates the effect of SCH-497079 on the metabolic profile and therapeutic response in a population with different race/ethnic origin bearing type 2 diabetes mellitus in a randomized, placebo-controlled and three-way crossover study (NCT00673465).

Recently, a novel H_3R antagonist named SUVN-G3031, (*N*-[4-(1-cyclobutylpiperidin-4-yl)oxyphenyl]-2-morpholin-4-ylacetamide), and developed by Suven Life Sciences has entered into clinical trial studies (Hung & Fu, 2017). From a structural point of view, this drug candidate possesses all the features needed for drug-likeness criteria (Table 2) with MW 373.49 g/mol, five HBA, one HBD, and MLogP 1.43. Two phase I clinical trial studies are ongoing; in the first study, safety, tolerability and pharmacokinetics of SUVN-G3031 in healthy volunteers are investigated in a single-center, double-blind, placebo-controlled, randomized study (NCT02342041), while in the second study, the pharmacokinetic profile of SUVN-G3031 is assessed with respect to food, gender, and age (NCT02881294). Recently, the results of first clinical trial study (i,e, NCT02342041) has been presented and the findings showed that SUVN-G3031 is well-tolerated in healthy subjects with favorable safety and pharmacokinetic profile (Nirogi, Shinde, et al., 2019). In addition, preclinical studies for SUVN-G3031 in treatment of narcolepsy are being conducted and the results are indicative of potential efficacy of this therapeutic agent in sleep disorders (Bhayrapuneni et al., 2019; Nirogi, Bhyrapuneni, et al., 2019).

4. Challenges in the development of H_3R antagonists/inverse agonists

The H_3 autoreceptors distributed mainly in the CNS act as a negative feedback on histamine synthesis and release from histaminergic neurons. Histamine is involved in many physiological functions such as sleep-wake regulation, circadian and feeding rhythm, thermal regulation, locomotion, learning, cognition, and memory (Berlin et al., 2011; Nikolic et al., 2014; Passani & Blandina, 2011; Sadek, Saad, Sadeq, et al., 2016; Tiligada et al., 2011). The expression of H_3Rs is not limited to histaminergic neurons but they function as also as heteroreceptors on aminergic neurons (e.g. those releasing acetylcholine, dopamine, noradrenaline, and serotonin), as well as on glutamatergic, GABAergic

and peptidergic neurons, located in different regions of the brain such as cerebral cortex, hippocampus, nucleus accumbens, nucleus basalis magnocellularis, and basal ganglia (Haas, Sergeeva, & Selbach, 2008; Nieto-Alamilla et al., 2016; Schlicker & Kathmann, 2017). The blockade of pre-synaptic H_3 autoreceptors leads to the removal of the negative feedback with the subsequent increase in the levels of histamine and other neurotransmitters. In the past decades, H_3Rs have raised widespread attention in both academia and pharmaceutical companies due to their involvement in the pathophysiology of several diseases, especially neurological disorders. There are numerous ongoing projects in which H_3Rs are considered as potential drug targets for a variety of neurodegenerative disorders (e.g. sleep disorders, Alzheimer's disease, schizophrenia, ADHD, and MS), metabolic syndrome (obesity), nasal inflammatory diseases (e.g. allergic rhinitis and congestion), and pain. In view of this, several attempts have focused on H_3R antagonists/inverse agonists for the purpose of developing novel therapeutic agents. Initially, medicinal chemistry efforts resulted in the development of imidazole-based H_3R antagonists by the structural increase of histamine in terms of bulkiness assuming that the imidazole heterocycle ring is critical for receptor binding. However, imidazole-based compounds were not successful due to drawbacks observed in several investigations. Binding discrepancies among species, low CNS penetration, rapid metabolism (HMT substrates), off-target activity, liver toxicity and, more importantly, high potential for cytochrome P450 inhibition are the reasons for excluding these agents from the therapeutic area (Berlin et al., 2011; Brioni et al., 2011; Esbenshade, Fox, & Cowart, 2006; Khanfar et al., 2016; Kuhne, Wijtmans, Lim, Leurs, & de Esch, 2011; Lazewska & Kiec-Kononowicz, 2010; Nieto-Alamilla et al., 2016; Nikolic et al., 2014; Plancher, 2011; Sadek & Stark, 2016; Sander et al., 2008; Schlicker & Kathmann, 2017; Stark, 2003; Wijtmans et al., 2007). In the continued efforts, the hurdles were relatively overcome by a new generation of H_3R antagonists/inverse agonists lacking the imidazole ring. Since this ring is capable of establishing hydrogen bonds, CNS penetration and oral bioavailability would be low for imidazole-based compounds (Sander et al., 2008). These are the driving forces for the development of non-imidazole agents through biosterically replacing imidazole with N-containing non-aromatic heterocycles such as piperidine, pyrrolidine, piperazine, and azepane. Historically, introducing non-imidazole based compounds was a milestone in the field of H_3R research as they are highly selective and potent with improved pharmacokinetic properties (Berlin et al., 2011; Esbenshade et al., 2006; Nieto-Alamilla et al., 2016; Nikolic et al., 2014; Schlicker & Kathmann, 2017). The induction of hippocampal neurogenesis by H_3R antagonists/inverse agonists evidenced by a study in mice can be regarded as an advantage of these agents for reversing age-associated cognitive deficits (Guilloux et al., 2017). In addition, the lower expression of H_3Rs in peripheral tissues compared to the CNS is a benefit for antagonists/inverse agonists having limited non-CNS side-effects (Esbenshade et al., 2008). However, it is worth mentioning that lipophilicity and polar surface area are the crucial parameters to be optimized for designing therapeutic agents targeting peripheral H_3Rs (Kuhne et al., 2011).

Although there are growing bodies of research dealing with diverse non-imidazole based compounds, they are not free from obstacles in their development pipeline and hence the design of these compounds is complicated by various factors briefly discussed below. One of the problems in designing H_3R antagonist/inverse agonists is the affinity of these agents towards the hERG K^+ channel, resulting in cardiotoxicity and originated from the similarity between the H_3R pharmacophore and hERG K^+channels (Gemkow et al., 2009; Lazewska & Kiec-Kononowicz, 2010; Łażewska & Kieć-Kononowicz, 2014; Tiligada et al., 2009). Phospholipidosis is an additional concern for non-imidazole-based compounds containing two basic sites (Gemkow et al., 2009; Lazewska & Kiec-Kononowicz, 2010; Łażewska & Kieć-Kononowicz, 2014). Prolonged duration of action as a consequence of high CNS penetration, lipophilicity, plasma protein binding and residence time, is a drawback for some non-imidazole compounds, leading to insomnia derived from a wake-promoting side-effect. This is one of the reasons for withdrawal of H_3R ligands from clinical trials (Łażewska & Kieć-Kononowicz, 2014; Singh & Jadhav, 2013). Therefore, receptor occupancy should be considered in pre-clinical studies as occupancy over 80% induces insomnia and in this context paying attention to dose schemes of drug candidates in clinical investigations is critical (Kuhne et al., 2011). Another approach to resolve this obstacle may be the characterization of ligands concerning the duration of H_3R blockade and to develop ligands with short to intermediate receptor residence times (Mocking, Verweij, Vischer, & Leurs, 2018). While screening of drug-target residence times is currently emerging to give additional information about the time-course of receptor-dissociation and the duration of target-occupancy, only some of the above-mentioned H_3R ligands have been recently characterized in this context (Mocking et al., 2018; Reiner & Stark, 2019; Riddy et al., 2019). Being substrates for P-glycoprotein is a problem reported for some non-imidazole-based compounds (Gemkow et al., 2009; Lazewska & Kiec-Kononowicz, 2010). Apart from this, it should be kept in mind that developing H_3R antagonist/inverse agonists is greatly affected by the complex pharmacology of H_3Rs. Molecular heterogeneity of different splice variants, constitutive activity, receptor oligomerization, differential signaling pathways and species-related discrepancies are determinant parameters that debilitate the design process (Bhowmik et al., 2012; Esbenshade et al., 2008; Lazewska & Kiec-Kononowicz, 2010; Łażewska & Kieć-Kononowicz, 2014; Plancher, 2011; Riddy et al., 2017; Tiligada et al., 2011; Wijtmans et al., 2007). Therefore, based on the available structural information responsible for shortcomings and failures of H_3R antagonists/inverse agonists, special notice should be paid in the rational design of such compounds. Additionally, for the appropriate assessment of new chemical entities, it has been suggested that the biological assays be performed in different functional platforms containing multiple H_3R isoforms (Lazewska & Kiec-Kononowicz, 2010).

Multi-targeting agents are of major interest in modern drug design and discovery. Design of such compounds can be applied to H_3R antagonists for the purpose of achieving optimum efficiency as performed for some preclinical candidates such as recently for contilisant (Bautista-Aguilera et al., 2017; Bautista-Aguilera et al., 2018). To this end, different pharmacophores can be combined for developing hybrid and multi-target therapeutic agents useful in the treatment of several diseases with reduced side-effects (Khanfar et al., 2016; Lazewska & Kiec-Kononowicz, 2010; Nikolic et al., 2014; Sander et al., 2008; Stark, 2003; Wijtmans et al., 2007). In context of those poly-pharmacological agents, further research is prompted by recent findings of additional potent sigma 1 receptor binding behavior of some clinically investigated H_3R ligands such as ABT-239, S 38093 and PF-3654746 as well as pitolisant (Riddy et al., 2019). Such multi-target directed ligands can be more effective in neurological diseases with multifactorial nature through different embedded pharmacophores required for interactions with multiple targets. Last, but not least, whether or not H_3R antagonists/inverse agonists can be used as monotherapy or add-on therapy is a debatable issue, which requires more intensive clinical trial studies containing larger population sizes (Berlin et al., 2011; Celanire et al., 2005; Lazewska & Kiec-Kononowicz, 2010; Tiligada et al., 2009). Overall, in spite of the difficulties faced by the development of H_3R antagonists/inverse agonists, there are several drug candidates advanced to different phases of clinical trials and it is expected to witness the marketing of H_3R ligands in the near future, in addition to pitolisant (Wakix)®, the only H_3R antagonist/inverse agonist approved by the European Medicines Agency and marketed in the European Union for the treatment of narcolepsy.

5. Conclusion

The histamine H_3 receptor has been the focus of a great deal of research over the past four decades and in this context, substantial

progress has been made in developing H_3R-related ligands. The involvement of H_3Rs in many neurological disorders has been documented by several lines of evidence in preclinical studies. In view of this, several non-imidazole based drug candidates as H_3R antagonists/inverse agonists are currently undergoing stringent assessments to be entered into the pharmaceutical market. Considering the enormous promise for therapeutic potential of these H_3R targeting clinical candidates, it is expected to witness the marketing of these agents as stand-alone or add-on therapy in the near future.

Conflict of interest

H. Stark is co-inventor of pitolisant. N. Ghamari, O. Zarei, J.-A. Arias-Montaño, D. Reiner, S. Dastmalchi, and M. Hamzeh-Mivehroud declare no conflict of interest.

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