Identification of 4-(1*H*-Imidazol-4(5)-ylmethyl)pyridine (Immethridine) as a Novel, Potent, and Highly Selective Histamine H_3 Receptor Agonist

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Abstract: In this study, the piperidine ring of immepip and its analogues was replaced by a rigid heterocyclic pyridine ring. Many compounds in the series exhibit high affinity and agonist activity at the human histamine H_3 receptor. Particularly, the 4-pyridinyl analogue of immepip (**1c**, immethridine) is identified as a novel potent and highly selective histamine H_3 receptor agonist ($pK_i = 9.07$, $pEC_{50} = 9.74$) with a 300-fold selectivity over the closely related H_4 receptor.

Histamine is a biogenic amine with multiple physiological effects. It exerts its biological activities through four histamine receptors, i.e., H_1, H_2, H_3, and H_4 receptors, which all belong to the superfamily of heptahelical (7TM) G-protein-coupled receptors.[1−4] The histamine H_1 and H_2 receptors have been identified by pharmacological means many years ago, and histamine H_1 and H_2 antagonists have been used clinically for the treatment of allergy and gastric ulcers, respectively.[5−8] The histamine H_3 receptor, however, was discovered in 1983 by Arrang et al. and was identified as a presynaptic autoreceptor in the brain controlling the release of histamine.[9,10] Subsequently, the histamine H_3 receptor was also shown to act as presynaptic heteroreceptor at nonhistaminergic neurons in the central and peripheral nervous system modulating the release of neurotransmitters such as acetylcholine,[11] dopamine,[12] serotonin,[13] and noradrenaline.[14] The therapeutic potential for histamine H_3 receptor antagonists and agonists has been suggested in a variety of disorders; antagonists have been proposed for several central nervous system disorders, e.g., epilepsy,[15] attention-deficit hyperactivity disorder,[16] Alzheimer's disease,[17] schizophrenia,[18] and obesity,[19] while agonists could be of potential use in myocardial ischemia,[20] inflammatory,[21] and gastric acid related diseases.[22]

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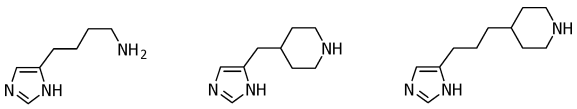
Chart 1. Binding Affinities and Functional Activities of Histamine H_3 Receptor Ligands



Imbutamine	Immepip	VUF5681
$pK_i = 8.39$	$pK_i = 9.32$	$pK_i = 8.35$
$pEC_{50} = 8.13$	$pEC_{50} = 9.88$	$pA_2 = 8.10$

A previous study on conformationally constrained analogues of histamine and its homologues demonstrated that increased rigidity by incorporation of a piperidine ring into the side chain results in increased affinity and agonist efficacy at the human histamine H_3 receptor. Immepip, a conformationally constrained analogue of imbutamine, possesses improved affinity and functional activity at the human H_3 receptor (Chart 1).[23] Although the piperidine ring is more rigid than the aliphatic alkylamine, this ring system still shows some flexibility. We hypothesized that the histamine H_3 receptor affinity could be improved further by imparting a conformational constraint of the side chain via replacement of the piperidine ring with an aromatic pyridine ring. Our previous study also showed that extension of the spacer between the imidazole and the piperidine ring resulted in a potent neutral H_3 antagonist (VUF5681, Chart 1).[23] We therefore designed a new series of compounds with variation in the spacer length between the imidazole and pyridine ring and/or alteration of nitrogen position in the pyridine ring (Figure 1).

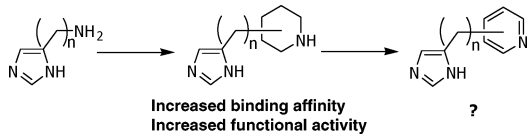


Figure 1. Design of novel histamine H_3 receptor agonists based on the hypothesis that increased rigidity leads to increased activity.

Some of the ligands have been described before[24] but were synthesized differently in this work. Compounds **1a**−**c** were synthesized from protected 4-iodoimidazole[25] (**4**) as shown in Scheme 1. The iodo compound was treated with EtMgBr, then with pyridinecarboxaldehydes to give the intermediate alcohols (**5**) in good yield (85−90%). The alcohol was acetylated by acetic anhydride using dimethylaminopyridine (DMAP) as a catalyst to obtain **6**, which was subsequently hydrogenated under 50 atm of H_2 to give **7** in moderate yield (70−75%). Deprotection of **7**, by heating in 30% HBr at reflux temperature, provided **1a**−**c**.

Compounds **2a**−**c** were synthesized according to Scheme 2. The intermediate aldehydes (**9**) were prepared from commercially available 3-pyridinepropan-1-ols via a Swern oxidation in moderate to good yield (75−85%).[26] By use of TosMIC-mediated imidazole synthesis,[27] **2a**−**c** were obtained in moderate yield (65−75%).

The synthesis of 3-(1*H*-imidazol-4(5)-yl)propylpyridines (**3a**−**c**) followed Scheme 3. The key inter-

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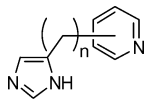
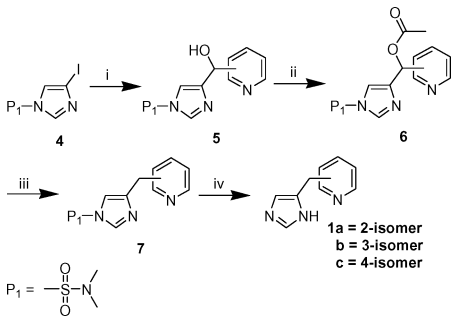
Table 1. Affinities and Functional Activities of Pyridine-Containing Ligands on the Human Histamine H_3 and H_4 Receptors



				human histamine H_3 receptor			human histamine H_4 receptor			
compd	VUF	*n*	isomer	pK_i ± SEM[a]	pEC_{50} ± SEM[b]	α[c]	pK_i ± SEM[a]	pEC_{50} ± SEM[b]	α[c]	selectivity[d]
1a	4886	1	2	6.23 ± 0.00	6.22 ± 0.05	0.9	5.34 ± 0.02	4.98 ± 0.05	1.0	8
1b	4857	1	3	7.28 ± 0.02	7.41 ± 0.12	1.0	6.16 ± 0.02	4.82 ± 0.23	0.5	5
1c	immethridine	1	4	9.07 ± 0.00	9.74 ± 0.14	0.9	6.61 ± 0.02	6.04 ± 0.07	0.8	288
2a	5912	2	2	5.93 ± 0.02	5.87 ± 0.09	0.6	4.91 ± 0.05	4.23 ± 0.19	0.6	10
2b	5913	2	3	6.85 ± 0.03	6.45 ± 0.10	1.0	5.29 ± 0.05	4.49 ± 0.07	0.3	36
2c	5889	2	4	8.16 ± 0.05	8.17 ± 0.02	0.9	5.88 ± 0.04	5.82 ± 0.34	0.4	191
3a	5914	3	2	5.98 ± 0.01	6.04 ± 0.02	0.5	5.90 ± 0.06	5.50 ± 0.10	0.6	1
3b	5915	3	3	7.48 ± 0.03	7.51 ± 0.03	1.0	6.32 ± 0.02	5.90 ± 0.13	0.4	14
3c	5916	3	4	7.81 ± 0.03	7.71 ± 0.09	1.0	6.00 ± 0.01	5.81 ± 0.11	0.4	65
	imbutamine			8.39 ± 0.03	8.13 ± 0.08	0.9	7.84 ± 0.09	7.05 ± 0.04	1.0	4
	immepip			9.32 ± 0.04	9.88 ± 0.02	1.0	7.66 ± 0.04	7.25 ± 0.16	0.7	46

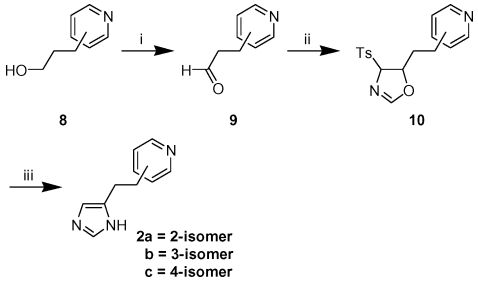
[a] The pK_i values were measured by [^{3}H]-N^{α}-methylhistamine or [^{3}H]-histamine binding to membranes of SK-N-MC cells expressing the human H_3 or H_4 receptor, respectively. [b] The pEC_{50} values were determined by the inhibition of the cAMP-stimulated β-galactosidase transcription in SK-N-MC cells expressing the human H_3 or H_4 receptor. The results were presented as the mean ± SEM of at least three independent experiments. [c] α = intrinsic activity as the ratio of the maximum response of each ligand to the maximum response of histamine. [d] Selectivity = $K_i(H_4)/K_i(H_3)$.

Scheme 1. Synthetic Pathway for **1a**−**c**[a]



[a] Reagents and conditions: (i) EtMgBr, THF, pyridinecarboxaldehyde, room temp, 16 h; (ii) DMAP, DCM, acetic anhydride, room temp, 3 h; (iii) H_2 (50 atm), 10% Pd/C, MeOH, 24 h; (iv) 30% HBr, reflux 24 h.

Scheme 2. Synthetic Pathway for **2a**−**c**[a]



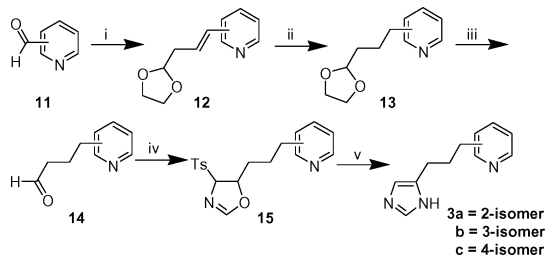
[a] Reagents and conditions: (i) oxalyl chloride, DMSO, DCM, triethylamine, −65 °C to room temp, 5 h; (ii) TosMIC, NaCN, EtOH; (iii) saturated NH_3 in EtOH, 90−110 °C, 10−12 atm, 24 h.

mediate ω-pyridinebutanals (**14**) were prepared from corresponding pyridinecarboxaldehydes (**11**) following the procedure earlier described.[23] By use of the aforementioned TosMIC chemistry, the imidazole products **3a**−**c** were obtained in moderate yield (60−70%).

Characterization and physical properties of the target compounds are shown in Table 3.

Binding affinities and functional activities of all compounds were performed using SK-N-MC cells expressing the human histamine H_3 or H_4 receptor following procedure described in ref 23.

Scheme 3. Synthetic Pathway for **3a**−**c**[a]



[a] Reagents and conditions: (i) *n*-BuLi, THF, [2-(1,3-dioxolan-2-yl)ethyl]triphenylphosphonium bromide, −30 °C, 3 h; (ii) H_2, 5% Pd/C, 1 atm, 24 h; (iii) 1 N HCl, room temp, 10 min; (iv) TosMIC, NaCN, EtOH, room temp, 2 h; (v) saturated NH_3 in EtOH, 90−110 °C, 10−12 atm, 24 h.

Table 2. Activities of H_3 Agonists on the Twitch Contraction Induced on the Paced Myenteric Plexus Isolated from Guinea Pig Ileum[a]

compd	pD_2 ± SEM	E_{max} ± SEM (%)
immethridine	7.45 ± 0.08	38.5 ± 7.56
immepip	7.97 ± 0.10	25.2 ± 4.24
imetit	7.88 ± 0.13	31.3 ± 6.00

[a] The potency (pD_2) and maximum inhibitory effect of contraction amplitude (% E_{max}) values were determined from concentration−response curves of ligands elicited on the paced isolated guinea pig ileal myenteric plexus. The results were presented as the mean ± SEM of at least five independent experiments.

Many histamine analogues have been described as selective H_3 receptor agonists.[28,29] For ligands with a basic nitrogen in the side chain, increased rigidity appears to result in an increase in binding affinity and agonist potency at the human H_3 receptor.[23] The piperidine side chain analogue, immepip, is a typical example of such a ligand that exhibits a 10-fold higher affinity for the human H_3 receptor than its flexible ligand (imbutamine) as seen in Table 1. Immepip is currently one of the most potent H_3 agonist known (pK_i = 9.32 and pEC_{50} = 9.88) but also shows reasonable potency for the recently discovered histamine H_4 receptor (pK_i = 7.66 and pEC_{50} = 7.25). In our search for potent and selective histamine H_3 and H_4 ligands, a further conformational constraint in the side chain

Table 3. Characterization and Physical Properties of Ligands

compd	salt	yield[a] (%)	mp[b] (°C)	MS[c] $[M+1]^+$	NMR (D_2O)[d]	formula
1a	HBr	55	225.1−226.3 (dec)	160.3	δ 8.6 (d, 1H, J = 7 Hz), 8.5 (s, 1H), 8.4 (t, 1H, J = 7 Hz), 7.9 (t, 1H, J = 7 Hz), 7.8 (d, 1H, J = 7 Hz), 7.4 (s, 1H), 4.6 (s, 2H)	$C_9H_{11}N_3Br_2$
1b	HBr	42	262.4−264.2	160.4	δ 8.7 (m, 2H), 8.6 (s, 1H), 8.5 (d, 1H, J = 7 Hz), 8.0 (t, 1H, J = 7 Hz), 7.3 (s, 1H), 4.4 (s, 2H)	$C_9H_{11}N_3Br_2$
immethridine	HBr	47	>300	160.4	δ 8.6 (d, 2H, J = 7 Hz), 8.5 (s, 1H), 7.9 (d, 2H, J = 7 Hz), 7.4 (s, 1H), 4.5 (s, 2H)	$C_9H_{11}N_3Br_2$
2a	HBr	63	213.5−215.4 (dec)	174.3	δ 8.5 (d, 1H, J = 7 Hz), 7.5 (m, 2H), 7.1 (m, 2H), 6.7 (s, 1H), 3.0 (m, 4H)	$C_{10}H_{13}N_3Br_2 \cdot 0.3H_2O$
2b	HBr	58	225.8−226.5	174.5	δ 8.3 (m, 2H), 7.5 (s, 1H), 7.4 (d, 1H, J = 8 Hz), 7.1 (m, 1H), 6.6 (s, 1H), 2.9 (m, 4H)	$C_{10}H_{13}N_3Br_2$
2c	HBr	68	264.8−265.6 (dec)	174.6	δ 8.4 (d, 2H, J = 7 Hz), 7.5 (s, 1H), 7.1 (d, 2H, J = 7 Hz), 2.9 (m, 4H)	$C_{10}H_{13}N_3Br_2$
3a	HCl	53	174.3−175.6	188.4	δ 8.5 (d, 1H, J = 7 Hz), 7.6 (m, 2H), 7.2 (m, 2H), 6.8 (s, 1H), 2.8 (t, 2H, J = 7 Hz), 2.6 (t, 2H, J = 7 Hz), 2.0 (quint, 2H, J = 7 Hz)	$C_{11}H_{15}N_3Cl_2 \cdot 0.3H_2O$
3b	HCl	57	190.4−191.1	188.3	δ 8.5 (m, 2H), 7.6 (s, 1H), 7.5 (d, 1H, J = 8 Hz), 7.2 (m, 1H), 6.8 (s, 1H), 2.6 (m, 4H), 2.0 (quint, 2H, J = 7 Hz)	$C_{11}H_{15}N_3Cl_2 \cdot 0.3H_2O$
3c	HBr	55	220.4−221.1 (dec)	188.6	δ 8.5 (d, 2H, J = 7 Hz), 7.6 (s, 1H), 7.1 (d, 2H, J = 7 Hz), 6.8 (s, 1H), 2.6 (m, 4H), 1.9 (m, 2H)	$C_{11}H_{15}N_3Br_2$

[a] Yields after recrystallization from EtOH/ether. [b] Melting points were determined on an Electrothermal IA9200 apparatus. [c] Mass spectrometry were performed on Finnigan LCQDECA ion-trap mass spectrometer using APCI technique. [d] ^{1}H NMR spectra were recorded on Bruker AC-200 spectrometer with the residual undeuterated solvent peak as reference.

was achieved by a replacement of the piperidine ring with a pyridine ring. Although none of the new compounds exhibits greater affinity or agonist efficacy than immepip, some do demonstrate greater selectivity for the human H_3 receptor (Table 1). At the human H_3 receptor, the 4-pyridinyl analogue of immepip, immethridine (**1c**), also acts as a full agonist with high affinity and potency (pK_i = 9.07 and pEC_{50} = 9.74). Although the affinity of immethridine at the human H_3 receptor equals the affinity of immepip, immethridine displays a 10-fold lower binding affinity at the human H_4 receptor (pK_i = 6.61 and pEC_{50} = 6.04, Table 1). This decreased binding affinity leads to a 300-fold selectivity at the human H_3 receptor over the H_4 receptor. Further evaluation of immethridine at the human H_1 and H_2 receptors indicated no binding affinity even at 10 μM (data not shown). Therefore, immethridine is one of the most potent and selective agonist for the human H_3 receptor.

Consistent with observations in the piperidine-containing series,[23] the optimal spacer length within the pyridine series is one methylene unit. Extension of the spacer length between the imidazole ring and the pyridine ring leads to reduced affinity and less agonist activity at the human histamine H_3 and H_4 receptors. Compounds **2c** and **3c** respectively exhibit pK_i values of 8.16 and 7.81 at the human H_3 receptor and 5.88 and 6.00 at the human H_4 receptor (Table 1).

We previously observed that extension of the spacer length in the 4-piperidine-containing series also resulted in a decreased agonist efficacy at the human H_3 receptor, eventually resulting in a neutral antagonist (propylene spacer).[23] In contrast, in the 4-pyridine-containing series, the longer homologues of immethridine (**2c** and **3c**) still behave as full agonists at the human H_3 receptor. At the human H_4 receptor, most of the compounds in this series behave as partial agonists (Table 1).

The 2- and 3-pyridinyl analogues exhibited decreased affinity and agonist potency at the human H_3 receptor, but this change did not significantly affect the human H_4 receptor activity. At the human histamine H_3 receptor, the full agonists **1a** and **1b** exhibit a significantly reduced affinity (pK_i = 6.23 and 7.28, respectively) compared to immethridine, whereas only a small decrease was observed at the human H_4 receptor (pK_i = 5.34 and 6.16, respectively; Table 1). This isomer preference was also observed for the longer immethridine homologues (**2c** → **b** → **a** and **3c** → **b** → **a**). On the basis of these findings, we conclude that the pyridine nitrogen plays a role in the binding to the human H_3 receptor. Moreover, the position of the pyridine nitrogen is crucial for H_3 receptor binding affinity but is less important for H_4 receptor affinity.

Histamine and other H_3 agonists inhibit the twitch contraction of the paced myenteric plexus isolated from guinea pig ileum through the activation of the histaminergic H_3 presynaptic receptor.[30−32] Immethridine was therefore evaluated in this model. Similar to the potent H_3 agonists, i.e., imetit and immepip, immethridine induces a concentration-dependent decrease of the electrically induced twitch contraction of the guinea pig ileal myenteric plexus. Immethridine again acts as a full agonist and is slightly less effective (pD_2 = 7.45) than immepip and imetit in this model (Table 2).

In this study, the replacement of the piperidine ring of immepip with a 4-pyridine ring resulted in the discovery of a potent and highly selective histamine H_3 receptor agonist (immethridine). Although immethridine possesses no improved affinity or functional activity at the human H_3 receptor (pK_i = 9.07, pEC_{50} = 9.74, α = 0.9) compared to immepip, a strongly reduced affinity at the human H_4 receptor was observed. With about 300-fold H_3 receptor selectivity over the human H_4 receptor and lack of binding affinity at the human histamine H_1 and H_2 receptors, immethridine is currently one of the most potent and selective H_3 receptor agonists. Previously, the nitrogen of histamine and other histamine H_3 receptor agonists such as imbutamine and (*R*)-α-methylhistamine has been suggested to form an ionic interaction with a conserved aspartate residue (D114) in transmembrane domain 3.[33]

Because of the weakly basic property of the pyridine nitrogen, we hypothesize that immethridine may not interact with the human H_3 receptor via an ionic interaction with the aforementioned aspartate residue. Therefore, immethridine might serve future molecular modeling studies by helping to distinguish between different models of the binding site of the human histamine H_3 receptor.

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Supporting Information Available: Experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Leurs, R.; Smit, M. J.; Timmerman, H. Molecular pharmacological aspects of histamine receptors. *Pharmacol. Ther.* **1995**, *66*, 413−463.
(2) Hill, S. J.; Ganellin, C. R.; Timmerman, H.; Schwartz, J. C.; Shankley, N. P.; Young, J. M.; Schunack, W.; Levi, R.; Haas, H. L. International union of pharmocology. XIII. classification of histamine receptors. *Pharmacol. Rev.* **1997**, *49*, 253−278.
(3) Lovenberg, T. W.; Roland, B. L.; Wilson, S. J.; Jiang, X.; Pyati, J.; Huvar, A.; Jackson, M. R.; Erlander, M. G. Cloning and functional expression of the human histamine H_3 receptor. *Mol. Pharmacol.* **1999**, *55*, 1101−1107.
(4) Oda, T.; Morikawa, N.; Saito, Y.; Masuho, Y.; Matsumoto, S. Molecular cloning and characterization of a novel type of histamine receptor preferentially expressed in leukocytes. *J. Biol. Chem.* **2000**, *275*, 36781−36786.
(5) Leid, R. W. Chemical mediators of immediate hypersensitivity reactions. *Vet. Clin. North Am. Large Anim. Pract.* **1979**, *1*, 35−42.
(6) Ciprandi, G.; Buscaglia, S.; Cerqueti, P. M.; Canonica, G. W. Drug treatment of allergic conjunctivitis. A review of the evidence. *Drugs* **1992**, *43*, 154−176.
(7) Badley, B. W. Some aspects of medical management of gastrointestinal disease. I. *Can. Med. Assoc. J.* **1975**, *112*, 200−204, 206.
(8) Ares, J. J.; Outt, P. E. Gastroprotective agents for the prevention of NSAID-induced gastropathy. *Curr. Pharm. Des.* **1998**, *4*, 17−36.
(9) Arrang, J. M.; Garbarg, M.; Schwartz, J. C. Auto-inhibition of brain histamine release mediated by a novel class (H_3) of histamine receptor. *Nature* **1983**, *302*, 832−837.
(10) Bertaccini, G.; Coruzzi, G.; Adami, M.; Pozzoli, C.; Gambarelli, E. Histamine H_3 receptors: an overview. *Ital. J. Gastroenterol.* **1991**, *23*, 378−385.
(11) Blandina, P.; Giorgetti, M.; Bartolini, L.; Cecchi, M.; Timmerman, H.; Leurs, R.; Pepeu, G.; Giovannini, M. G. Inhibition of cortical acetylcholine release and cognitive performance by histamine H_3 receptor activation in rats. *Br. J. Pharmacol.* **1996**, *119*, 1656−1664.
(12) Garcia, M.; Floran, B.; Arias-Montano, J. A.; Young, J. M.; Aceves, J. Histamine H_3 receptor activation selectively inhibits dopamine D_1 receptor-dependent [^{3}H]GABA release from depolarization-stimulated slices of rat substantia nigra pars reticulata. *Neuroscience* **1997**, *80*, 241−249.
(13) Fink, K.; Schlicker, E.; Neise, A.; Gothert, M. Involvement of presynaptic H_3 receptors in the inhibitory effect of histamine on serotonin release in the rat brain cortex. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1990**, *342*, 513−519.
(14) Celuch, S. M. Possible participation of histamine H_3 receptors in the modulation of noradrenaline release from rat spinal cord slices. *Eur. J. Pharmacol.* **1995**, *287*, 127−133.
(15) Leurs, R.; Blandina, P.; Tedford, C.; Timmerman, H. Therapeutic potential of histamine H_3 receptor agonists and antagonists. *Trends Pharmacol. Sci.* **1998**, *19*, 177−183.
(16) Chazot, P. L.; Hann, V. Overview: H_3 histamine receptor isoforms: new therapeutic targets in the CNS? *Curr. Opin. Invest. Drugs* **2001**, *2*, 1428−1431.
(17) Morisset, S.; Traiffort, E.; Schwartz, J. C. Inhibition of histamine versus acetylcholine metabolism as a mechanism of tacrine activity. *Eur. J. Pharmacol.* **1996**, *315*, R1−R2.
(18) Schwartz, J. C.; Morisset, S.; Rouleau, A.; Tardivel-Lacombe, J.; Gbahou, F.; Ligneau, X.; Heron, A.; Sasse, A.; Stark, H.; Schunack, W.; Ganellin, R. C.; Arrang, J. M. Application of genomics to drug design: the example of the histamine H_3 receptor. *Eur. Neuropsychopharmacol.* **2001**, *11*, 441−448.
(19) Takahashi, K.; Suwa, H.; Ishikawa, T.; Kotani, H. Targeted disruption of H_3 receptors results in changes in brain histamine tone leading to an obese phenotype. *J. Clin. Invest.* **2002**, *110*, 1791−1799.
(20) Levi, R.; Smith, N. C. Histamine H_3 receptors: a new frontier in myocardial ischemia. *J. Pharmacol. Exp. Ther.* **2000**, *292*, 825−830.
(21) McLeod, R. L.; Aslanian, R.; del Prado, M.; Duffy, R.; Egan, R. W.; Kreutner, W.; McQuade, R.; Hey, J. A. Sch 50971, an orally active histamine H_3 receptor agonist, inhibits central neurogenic vascular inflammation and produces sedation in the guinea pig. *J. Pharmacol. Exp. Ther.* **1998**, *287*, 43−50.
(22) Bertaccini, G.; Coruzzi, G.; Poli, E. Review article: the histamine H_3 receptor: a novel prejunctional receptor regulating gastrointestinal function. *Aliment Pharmacol. Ther.* **1991**, *5*, 585−591.
(23) Kitbunnadaj, R.; Zuiderveld, O. P.; Esch, I. J. P. D.; Vollinga, R. C.; Bakker, R.; Lutz, M.; Spek, A. L.; Cavoy, E.; Deltent, M. F.; Menge, W. M. P. B.; Timmerman, H.; Leurs, R. Synthesis and structure−activity relationships of conformationally constrained histamine H_3 receptor agonists. *J. Med. Chem.* **2003**, *46*, 5445−5457.
(24) Baxter, E. W.; Boyd, R. E.; Carson, J. R.; Jetter, M. C.; Reitz, A. B. Pyridyl/Quinolinyl Imidazoles. U.S. Patent 6,465,486 B1, 2002.
(25) De Esch, I. J.; Vollinga, R. C.; Goubitz, K.; Schenk, H.; Appelberg, U. Hacksell, U.; Lemstra, S.; Zuiderveld, O. P.; Hoffmann, M.; Leurs, R.; Menge, W. M.; Timmerman, H. Characterization of the binding site of the histamine H_3 receptor. 1. Various approaches to the synthesis of 2-(1*H*-imidazol-4-yl)cyclopropylamine and histaminergic activity of (1*R*,2*R*)- and (1*S*,2*S*)-2-(1*H*-imidazole-4-yl)cyclopropylamine. *J. Med. Chem.* **1999**, *42*, 1115−1122.
(26) Omura, K.; Swern, D. Oxidation of alcohols by "activated" dimethyl sulfoxide. A preparative, steric and mechanistic study. *Tetrahedron* **1978**, *34*, 1651−1660.
(27) Horne, D. A.; Yakushijin, K.; Buchi, G. A two-step synthesis of imidazoles from aldehydes via 4-tosyloxazolines. *Heterocycles* **1994**, *39*, 139−153.
(28) Vollinga, R. C.; de Koning, J. P.; Jansen, F. P.; Leurs, R.; Menge, W. M.; Timmerman, H. A new potent and selective histamine H_3 receptor agonist, 4-(1*H*-imidazol-4-ylmethyl)piperidine. *J. Med. Chem.* **1994**, *37*, 332−333.
(29) Vollinga, R. C.; Menge, W. M.; Leurs, R.; Timmerman, H. Homologs of histamine as histamine H_3 receptor antagonists: a new potent and selective H_3 antagonist, 4(5)-(5-aminopentyl)-1*H*-imidazole. *J. Med. Chem.* **1995**, *38*, 266−271.
(30) Trzeciakowski, J. P. Inhibition of guinea pig ileum contractions mediated by a class of histamine receptor resembling the H_3 subtype. *J. Pharmacol. Exp. Ther.* **1987**, *243*, 874−880.
(31) Hew, R. W.; Hodgkinson, C. R.; Hill, S. J. Characterization of histamine H_3 receptors in guinea-pig ileum with H_3 selective ligands. *Br. J. Pharmacol.* **1990**, *101*, 621−624.
(32) Poli, E.; Coruzzi, G.; Bertaccini, G. Histamine H_3 receptors regulate acetylcholine release from the guinea pig ileum myenteric plexus. *Life Sci.* **1991**, *48*, PL63−PL68.
(33) Uveges, A. J.; Kowal, D.; Zhang, Y.; Spangler, T. B.; Dunlop, J.; Semus, S.; Jones, P. G. The role of transmembrane helix 5 in agonist binding to the human H_3 receptor. *J. Pharmacol. Exp. Ther.* **2002**, *301*, 451−458.

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