N-Substituted Piperidinyl Alkyl Imidazoles: Discovery of Methimepip as a Potent and Selective Histamine H_3 Receptor Agonist

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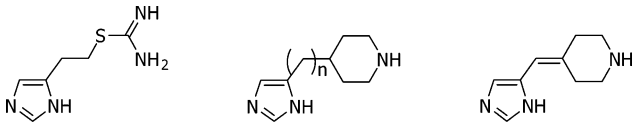
In this study, we continue our efforts toward the development of potent and highly selective histamine H_3 receptor agonists. We introduced various alkyl or aryl alkyl groups on the piperidine nitrogen of the known H_3/H_4 agonist immepip and its analogues (**1**−**3a**). We observed that *N*-methyl-substituted immepip (methimepip) exhibits high affinity and agonist activity at the human histamine H_3 receptor ($pK_i = 9.0$ and $pEC_{50} = 9.5$) with a 2000-fold selectivity at the human H_3 receptor over the human H_4 receptor and more than a 10000-fold selectivity over the human histamine H_1 and H_2 receptors. Methimepip was also very effective as an H_3 receptor agonist at the guinea pig ileum ($pD_2 = 8.26$). Moreover, in vivo microdialysis (in rat brain) showed that methimepip reduces the basal level of brain histamine to about 25% after a 5 mg/kg intraperitoneal administration.

Introduction

The histamine receptors, members of G-protein-coupled receptor (GPCR) families, were initially categorized on the basis of their pharmacological characterization, but they are currently classified as H_1, H_2, H_3, and H_4 receptors on the basis of the diversity of their amino acid sequences.[1−4] The histamine H_1 and H_2 receptors were identified decades ago,[5,6] and therapeutic substances antagonizing the activity of histamine at the histamine H_1 or H_2 receptors have been successfully used for the treatment of allergies[7,8] and gastric acid related diseases,[9,10] respectively. The histamine H_3 receptor was discovered by Arrang and colleagues in 1983 to modulate the neuronal release of histamine.[11] Many studies have shown that the histamine H_3 receptor also regulates the release of several other neurotransmitters, e.g., acetylcholine,[12,13] dopamine,[14] noradrenaline,[15] and serotonin[16] in both the central and peripheral nervous systems. In 1999, the human histamine H_3 receptor cDNA has been cloned by Lovenberg and colleagues and gene expression analysis has shown that the H_3 receptor is predominantly expressed in the brain.[3]

In 2000, a new type of histamine receptor (H_4) was discovered using the sequence information of the H_3 receptor cDNA.[4,17−20] The alignment of amino acid sequences of the human histamine H_3 and H_4 receptors indicates an overall 35% identity[21] and a 58% identity in the TM regions.[22] Characterization of several H_3 agonists at the H_4 receptor showed that many potent histamine H_3 receptor agonists also possess a high affinity at the H_4 receptor. For example, imetit and immepip (Chart 1), which have been published previously as selective potent histamine H_3 receptor agonists,[23,24] exhibit also a high affinity at the histamine H_4 receptor with pK_i values of 8.50 and 7.66, respectively.[21,25] Since the actual role of the histamine H_3 receptor in both central and peripheral nervous systems may therefore have become obscured due to the lack of H_3 receptor selective agonists, we continued our quest for compounds with high selectivity and potency at the human histamine H_3 receptor.

Chart 1



imetit immepip (n=1) VUF5510

VUF4929 (n=2)

We hypothesized that systematic modification of potent histamine H_3 ligands might result in compounds with increased selectivity and retained high affinity and agonist efficacy at the H_3 receptor. Hence, we investigated some promising potent histamine H_3 receptor ligands and eventually selected immepip, VUF4929, and VUF5510 (Chart 1) as prototypes. A series of new compounds with various alkyl or aryl alkyl groups on the piperidine nitrogen of the selected prototypes were prepared, as we reasoned that H_3 and H_4 receptor agonism might be differentially affected by substitution of the amine function. In fact, a recent study on indole piperazines as selective H_4 antagonists reported that

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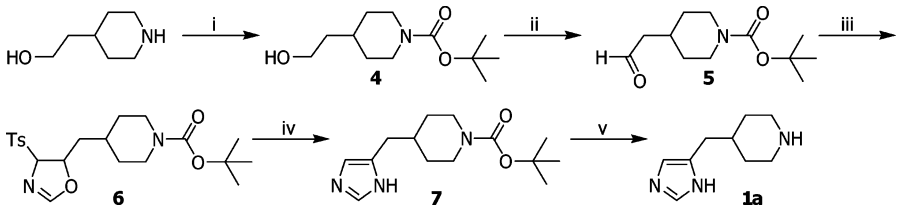
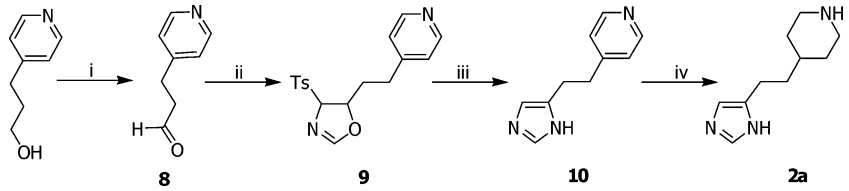
Scheme 1. Synthetic Pathway for **1a**[a]



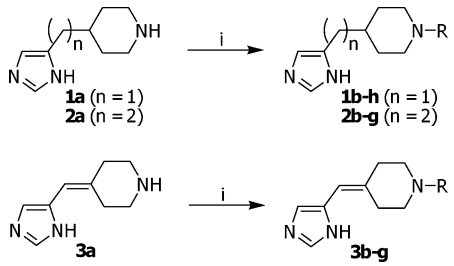
[a] Reagents and conditions: (i) di-*tert*-butyl dicarbonate, TEA, $CHCl_3$, room temperature; (ii) oxalyl chloride, DMSO, TEA, DCM, −60 °C to room temperature 5 h; (iii) TosMIC, NaCN, ethanol; (iv) saturated NH_3 in ethanol, 90−110 °C, 10−12 atm, 16 h; (v) 1 N HBr, room temperature 2 h.

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



[a] Reagents and conditions: (i) oxalyl chloride, DMSO, TEA, DCM, −60 °C to room temperature 5 h; (ii) TosMIC, NaCN, ethanol; (iii) saturated NH_3 in ethanol, 90−110 °C, 10−12 atm, 16 h; (iv) 10% Pd/C, HBr, H_2 100 atm, 48 h.

Scheme 3. Synthetic Pathway for **1b**−**g,h**, **2b**−**g**, and **3b**−**g**[a]



[a] Reagents and conditions: method A, (i) formaldehyde, formic acid, Δ, 6 h; method B, (i) alkyl iodide, K_2CO_3, ethanol, 0 °C to room temperature 16 h; method C, (i) aldehyde or ketone, acetic acid, DCE, sodium triacetoxyborohydride, room temperature 16 h.

for proper H_4 receptor affinity the piperidine ring could not be substituted with large alkyl groups.[26]

Chemistry. The synthesis of the compounds is outlined in Schemes 1−3. Although the synthesis of immepip (**1a)** using imidazole as starting chemical has been published,[24] the overall yield was less than 25%. We therefore developed a new synthetic pathway (Scheme 1) using a commercially available 2-piperidin-4-yl ethanol as starting chemical. Treatment of the piperidine compound with di-*tert*-butyl dicarbonate resulted in the protected intermediate alcohol (**4**), which was subsequently transformed into the corresponding aldehyde using a Swern oxidation to give **5** in good yield (90%). Next, the aldehyde was converted into an imidazole ring via two consecutive reactions; TosMIC chemistry gave an intermediate oxazoline (**6**), which was subsequently treated with ammonia to give **7** in 70% yield. Deprotection of **7** under acidic conditions gave **1a** in a quantitative yield.

Compound **2a** was prepared from 3-pyridin-4-yl propanol following Scheme 2. The hydroxyl group was transformed into the aldehyde and subsequently converted into an imidazole ring using the method described above to give **10** in 70% yield. After hydrogenation under acidic conditions using Pd/C as catalyst, the product (**2a**) was obtained in a moderate yield (60%).

Alkylation of the piperidine nitrogen was achieved via three different methods (A, B, and C, Scheme 3) depending on the substituent desired. The methylated amine was prepared following the Eschweiler−Clarke procedure (method A);[27,28] treatment of the amine with formaldehyde in formic acid at 100 °C gave the desired product in a good yield. In method B, treatment of the amine with an alkyl halide in the presence of base yielded the alkylated product in a moderate yield. However, this method is not the method of choice since an alkylation on the imidazole nitrogen may occur as side reaction. Fortunately, reductive amination (method C) does not lead to alkylation at the imidazole nitrogen and proved to be very useful for the synthesis of the alkylated compounds in this study. Yet, attempts to synthesize **1**−**3c** via method C failed; the ethylated product was not obtained. However, treatment of **1**−**3a** with ethyl iodide in ethanol (1.5 equiv) in the presence of potassium carbonate at room temperature (method B) gave the desired product (**1**−**3c**) in a good yield (80%) without an ethylation at the imidazole nitrogen. Compounds **1d**−**h**, **2d**−**g**, and **3d**−**g** were obtained following method C; treatment of compounds **1**−**3a** with the corresponding aldehyde or ketone in dichloroethane in the presence of a very mild reducing agent, sodium triacetoxyborohydride,[29] gave the desired products in 60−75% yield.

Pharmacology. Histamine H_1 Receptor Binding Studies. The affinity (pK_i) value was measured by displacement of [^{3}H]-mepyramine binding to membranes of COS-7 cells transiently expressing the human histamine H_1 receptor (3.2 ± 0.41 pmol/mg of protein) in the presence of ligand using the procedure described earlier.[30]

Histamine H_2 Receptor Binding Studies. The affinity (pK_i) value was measured by displacement of [^{125}I]-aminopotentidine binding to membranes of CHO cells stably expressing the human histamine H_2 receptor (1079 ± 313 fmol/mg of protein) in the presence of ligand using the procedure described earlier.[31]

Histamine H_3 and H_4 Receptor Binding Studies. The affinity (pK_i) values were measured by displace-

ment of [^{3}H]-N^{α}-methylhistamine (for H_3) or [^{3}H]-histamine (for H_4) binding to membranes of SK-N-MC cells expressing the human H_3 or H_4 receptor (131 ± 11 fmol/mg of protein for H_3 and 166 ± 26 fmol/mg of protein for H_4) in the presence of the ligand using the procedures described previously.[25]

Functional Assay for Activity at Human Histamine H_3 Receptor. Using a cAMP reporter gene assay as described previously,[25] the functional activities of all ligands were determined on SK-N-MC cells stably expressing the human histamine H_3 receptor.

Functional Studies on the Electrical Field Stimulated Guinea Pig Ileum Contraction. The inhibitory effects of histamine H_3 receptor agonists were determined on ileum obtained from 25−30 days old Dunkin−Hartley guinea pigs using the procedure described earlier.[32]

Microdialysis in Rat Brain. Characterization of histamine release from the hypothalamus of male rats of Wistar strain (8−9 weeks old, Japan SLC) were measured by in vivo microdialysis using a procedure described earlier.[33]

Results and Discussion

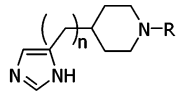
Pharmacological Evaluations and Structure−Activity Relationships. In previous studies we showed that histamine analogues containing a piperidine ring in the side chain possess improved affinities and functional activities at the human histamine H_3 receptor.[25] Immepip was identified as the most potent histamine H_3 receptor agonist with a pK_i of 9.3 and a pEC_{50} of 9.9. Characterization of immepip at the human histamine H_4 receptor, however, revealed a relative lack of selectivity at the human H_3 receptor, since immepip also possesses high H_4 receptor affinity as determined by [^{3}H]-histamine displacement studies (pK_i = 7.7).[25] Due to the high affinities of the parent compounds at the human H_3 receptor, in this study, analogues of immepip (**1a**), VUF4929 (**2a**), and VUF5510 (**3a**) were synthesized for the development of selective histamine H_3 receptor agonists. The incorporation of various lipophilic groups at the piperidine nitrogen of the selected compounds (**1b**−**h**, **2b**−**g**, and **3b**−**g**) resulted in important changes in affinity and activity at the human H_3 receptor (Table 1). Although some of these compounds were previously also reported as H_3 receptor ligands in a US patent,[34] their pharmacological evaluations at the human H_3 or H_4 receptor have not been described. In the VUF4929 (**2a**) series, the introduction of various alkyl or aryl alkyl groups at the piperidine nitrogen of **2a** leads to a decreased affinity and functional activity at the human H_3 receptor. Compounds in this series (**2b**−**g**) possess pK_i values ranging from 6.8 (**2e**) to 7.4 (**2g**) at the H_3 receptor as shown in Table 1, and none of the compounds exhibit full agonistic activity at the human H_3 receptor. The introduction of a benzyl (**2f**) or a phenethyl (**2g**) group even leads to compounds with moderate affinity but no (inverse) agonist activity. Most likely these two compounds behave as neutral antagonists at the human H_3 receptor. Interestingly, the attachment of a bulky group, i.e., isopropyl (**2d**) or cyclohexyl (**2e**), at the piperidine nitrogen results in a total loss of histamine H_3 receptor agonism, and these compounds act as partial inverse agonists. Similar results were observed in the VUF5510 (**3a**) series; an introduction of various alkyl or aryl alkyl groups on the piperidine nitrogen of VUF5510 leads to a decrease in both histamine H_3 receptor affinity and agonist activity (Table 1). However, the introduction of a small group, i.e., a methyl (**3b**), does not affect the binding and functional activity at the human H_3 receptor since this compound still displays a comparable high affinity and functional activity (pK_i of 8.3 and pEC_{50} of 8.6, Table 1). In agreement with the VUF4929 series, substitution of the piperidine nitrogen with either an isopropyl or a cyclohexyl moiety results again in compounds acting as inverse agonists; compounds **3d** and **3e** behave as partial inverse agonists at the human H_3 receptor with pK_i of 7.2 and 7.5, respectively. Surprisingly, partial agonism is observed when a benzyl (**3f**) or a phenethyl (**3g**) group is introduced at the piperidine nitrogen of VUF5510.

In the immepip (**1a**) series, an introduction at the piperidine nitrogen with various alkyl or aryl alkyl groups also results in a decreased affinity and functional activity at the human histamine H_3 receptor with pK_i values ranging from 7.2 to 9.0 and pEC_{50} values ranging from 7.5 to 9.5, respectively. The methyl derivative (methimepip, **1b**), however, possesses only a slightly decreased affinity and agonist activity (pK_i = 9.0 and pEC_{50} = 9.5) at the human histamine H_3 receptor compared to its prototype immepip (**1a**, pK_i = 9.3 and pEC_{50} = 9.9, Table 1). A further increase of the substituent size at the piperidine nitrogen (**1c**−**h**) results in a more than 25-fold decrease in affinity at the histamine H_3 receptor (Table 1). In contrast to what was observed in the VUF4929 and VUF5510 series, substitution of an isopropyl (**1d**), cyclohexyl (**1e**), benzyl (**1f**), phenethyl (**1g**), or phenylpropyl (**1h**) group at the piperidine nitrogen of immepip does not affect the agonistic activity at the human histamine H_3 receptor; compounds **1d**−**h** all display full agonism at the human H_3 receptor (Table 1), although the affinity was greatly reduced compared to immepip.

Due to the high affinity and functional activity of *N*-methyl-substituted immepip (methimepip, **1b**) at the human H_3 receptor, this compound was tested further for its affinity at the other histamine receptor types, i.e., the human histamine H_1, H_2, and H_4 receptors. Radioligand displacement studies of methimepip (**1b**) at the cloned human H_1, H_2, and H_4 receptors indicated low affinities for the other three histamine receptor subtypes (pK_i < 5 at the H_1 and H_2 receptors, and pK_i = 5.7 at the human H_4 receptor, Table 2). Thus, within the class of histamine receptors methimepip (**1b**) is identified as a novel potent and highly selective histamine H_3 receptor agonist with a pK_i of 9.0 and a pEC_{50} of 9.5 at the human H_3 receptor stably expressed on SK-N-MC cells. This new H_3 agonist (methimepip) shows a 2000-fold preference for the human H_3 receptor over the human H_4 receptor and a more than 10000-fold preference over the human H_1 and H_2 receptors.

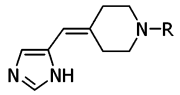
Functional Studies on the Electrical Field Stimulated Guinea Pig Ileum Contraction. In the guinea pig intestine, histamine H_3 receptor agonists inhibit the electrically evoked acetylcholine release from myenteric plexus, and thereby modulate subsequent twitch responses.[35−37] The recent discovery of the histamine H_4

Table 1. Affinities (pK_i) and Functional Activities (pEC_{50}) of Various Ligands for Human Histamine H_3 Receptor[d]

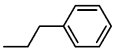
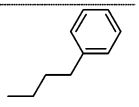


I (n = 1)

II (n = 2)



III

no	VUF	structure	R	$pK_i \pm SEM$[a]	$pEC_{50} \pm SEM$[b]	α[c]
1a	immepip	I		9.3 ± 0.0	9.9 ± 0.0	1.0
2a	4929	II	-H	7.7 ± 0.1	7.9 ± 0.1	0.6
3a	5510	III		8.2 ± 0.0	8.5 ± 0.0	0.9
1b	methimepip	I		9.0 ± 0.1	9.5 ± 0.2	0.8
2b	5858	II	$-CH_3$	7.3 ± 0.1	7.3 ± 0.1	0.8
3b	5816	III		8.2 ± 0.0	8.6 ± 0.0	1.0
1c	5813	I		7.8 ± 0.1	8.4 ± 0.0	1.0
2c	5859	II	$-C_2H_5$	7.2 ± 0.0	<5	n.d.
3c	5864	III		7.3 ± 0.0	7.6 ± 0.0	0.5
1d	5811	I		7.2 ± 0.0	8.1 ± 0.0	1.0
2d	5860	II		7.0 ± 0.0	6.7 ± 0.1	-0.5
3d	5865	III		7.2 ± 0.0	7.2 ± 0.1	-0.5
1e	5857	I		7.8 ± 0.0	8.4 ± 0.1	1.0
2e	5861	II		6.8 ± 0.0	6.5 ± 0.1	-0.5
3e	5866	III		7.5 ± 0.0	7.3 ± 0.1	-0.2
1f	5812	I		7.3 ± 0.1	7.8 ± 0.0	1.0
2f	5862	II		7.1 ± 0.0	<5	n.d.
3f	5867	III		6.4 ± 0.0	7.1 ± 0.0	0.8
1g	5814	I		8.0 ± 0.0	8.1 ± 0.0	1.0
2g	5863	II		7.4 ± 0.0	<5	n.d.
3g	5868	III		7.2 ± 0.0	7.8 ± 0.0	0.3
1h	5815	I		7.4 ± 0.0	7.5 ± 0.1	0.8

[a] The pK_i values were measured by displacement of [^{3}H]-N^{α}-methylhistamine binding to membranes of SK-N-MC cells expressing the human H_3 receptor in the presence of the ligand. [b] The pEC_{50} were determined by the inhibition of the cAMP-stimulated β-galactosidase transcription in SK-N-MC cells stably expressing the human H_3 receptor. Results are presented as 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 (for agonists) or clobenpropit (for inverse agonists). The positive and negative values represent agonism and inversed agonism, respectively. [d] n.d. = not determined.

receptor, which has high homology to the H_3 receptor, revealed the lack of selectivity of known histamine H_3 receptor agonists; e.g., histamine, imetit, and immepip also show a high affinity on the H_4 receptor.[25] Polymerase chain reaction (PCR) analysis of the histamine H_4 receptor mRNA on several tissues also indicated the expression of the H_4 receptor in the small intestine.[4] It may, therefore, be asked whether the inhibitory response observed on the ileum could (partly) be mediated by activation of the histamine H_4 receptor. In order to

Table 2. Affinities (pK_i) of Methimepip (**1b**) and Immepip (**1a**) for Human Histamine H_1, H_2, H_3, and H_4 Receptors

	$pK_i \pm SEM$[a]			
compound	*h*H_1	*h*H_2	*h*H_3	*h*H_4
methimepip	<5	<5	9.0 ± 0.1	5.7 ± 0.1
immepip		<5[b]	9.3 ± 0.0	7.7 ± 0.0

[a] n ≥ 3. [b] See ref 24.

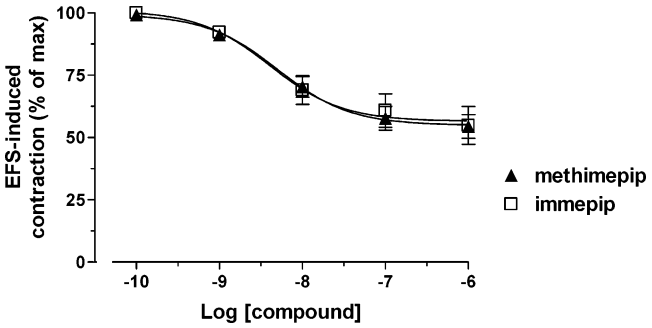


Figure 1. Effects of the histamine H_3 receptor agonists immepip and methimepip on guinea pig ileal muscle contraction evoked by electrical field stimulation (EFS). Values are mean ± SEM of 6 or 7 observations.

answer this question, methimepip (**1b**), which exhibits high selectivity at the histamine H_3 receptor, was tested for its activity on the electrically stimulated guinea pig ileum. Using the procedure described before,[32] methimepip (**1b**) was characterized in comparison with the potent but less selective H_3 receptor agonist immepip (**1a**). The results depicted in Figure 1 show that both immepip and methimepip (**1b**) inhibit the EFS-evoked contractions of the guinea pig ileum with a comparable efficacy (55% inhibition of neurogenic contraction amplitude) and potency ($pD_2 = 8.40$ and 8.26, respectively). These findings suggest that the inhibitory effect of intestinal acetylcholine release and consecutive contraction is most likely mediated through the activation of the histamine H_3 receptor.

Microdialysis Studies in Rat Brain. The histamine H_3 receptor was discovered by Arrang and colleagues and identified as an autoreceptor in the rat brain modulating the synthesis and release of histamine.[11] Activation of the histamine H_3 receptor by agonists leads to a decrease of the histamine concentration in the brain. Therefore, methimepip (**1b**) was selected for further in vivo studies in comparison with immepip. Using a previously described microdialysis technique,[33] the level of histamine was determined in the dialysate collected from rat hypothalamus at 20 min intervals after the administration of methimepip (**1b**) either by intraperitoneal (ip) injection at a dose of 5 mg/kg or by infusion via the microdialysis probe at a concentration of 1×10^{-5} M or 1×10^{-6} M. The results depicted in Figure 2A,B show that both immepip and methimepip (**1b**) significantly lowered the level of histamine in the rat hypothalamus after intraperitoneal injection or infusion via the microdialysis probe. The basal level of histamine is reduced to about 25% by the ip injection or the infusion of either immepip or methimepip (**1b**). The effect of methimepip (**1b**) was antagonized by coinfusion of clobenpropit (Figure 3). Clobenpropit is known as a potent H_3 receptor antagonists ($pK_i = 9.4$) with only limited affinity at the human

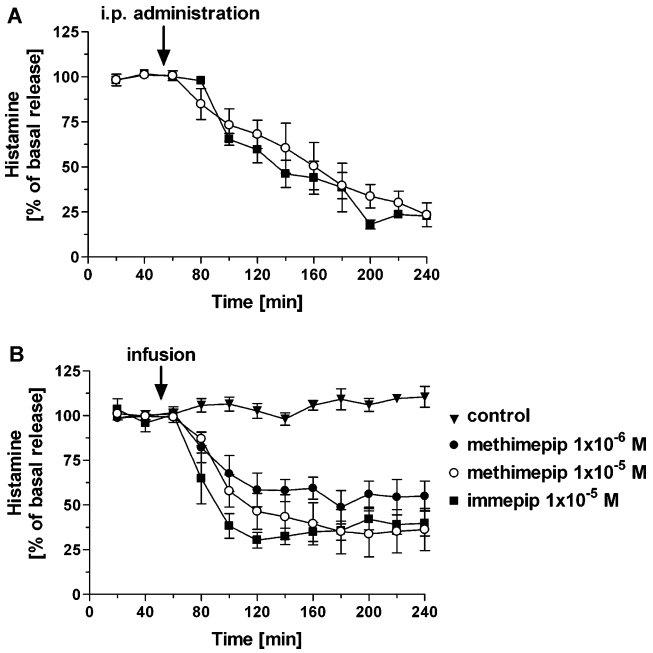


Figure 2. Effects of methimepip (circles) and immepip (squares) on the extracellular histamine concentration in rat brain determined by microdialysis (A) after an intraperitoneal (ip) injection of 5 mg/kg or (B) during infusions of 1×10^{-5} M and/or 1×10^{-6} M solutions via the microdialysis probes. Values are mean ± SEM of 4 or 5 observations.

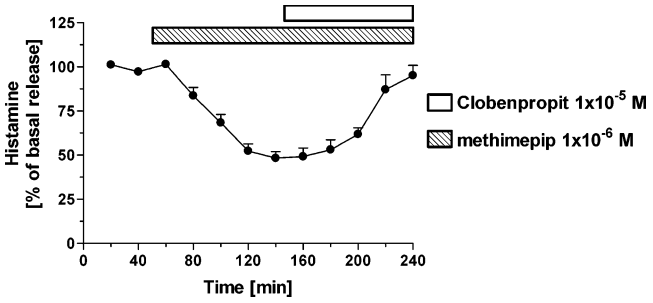


Figure 3. The extracellular histamine concentration in rat brain as determined by microdialysis during an infusion of methimepip (1×10^{-6} M) and subsequently coinfusion with clobenpropit (1×10^{-5} M). Values are mean ± SEM of 4 or 5 observations.

H_1 and H_2 receptor ($pK_i = 5.6$ and 5.2 respectively),[38] whereas it acts as a partial agonist at the human H_4 receptor.[4]

Conclusion

In this study, systematic modification, achieved by the introduction of various alkyl or aryl alkyl groups on the piperidine nitrogen of the selected potent histamine H_3 receptor agonists immepip (**1a**), VUF4929 (**2a**), and VUF5510 (**3a**), resulted in the discovery of a new, potent and selective histamine H_3 receptor agonist. The *N*-methyl-substituted immepip (methimepip, **1b**) retains high affinity and functional activity at the human H_3 receptor ($pK_i = 9.0$ and $pEC_{50} = 9.5$, Table 1). Radioligand displacement studies of methimepip (**1b**) at the other human histamine receptor types (H_1, H_2, and H_4) reveal a high selectivity of methimepip (**1b**) for the human H_3 receptor (2000-fold over the human H_4 receptor and more than 10000-fold over the human H_1 and H_2 receptors, Table 2). In contrast, immepip shows

Table 3. Synthetic Methods and Spectroscopic and Analytical Data for Compounds[a]

no	meth	yield (%)	mp (°C)	MS $[M+1]^+$	^{1}H NMR (D_2O)	elemental anal. (C, H, N)
1b	A	78	156.7−157.3	180.3	δ 8.57 (s, 1H), 7.25 (s, 1H), 3.47 (m, 2H), 2.96 (m, 2H), 2.81 (s, 3H), 2.72 (d, 2H, J = 6.7 Hz), 1.94 (m, 3H), 1.49 (m, 2H)	$C_{10}H_{19}N_3Br_2 \cdot 0.7H_2O$
2b	A	72	193.8−194.2	194.3	δ 8.54 (s, 1H), 7.18 (s, 1H), 3.60 (m, 2H), 2.93 (m, 2H), 2.80 (s, 3H), 2.75 (t, 2H, J = 7.6 Hz), 2.00 (m, 2H), 1.45−1.68 (m, 5H)	$C_{11}H_{21}N_3Br_2$
3b	A	75	217.4−219.3	178.4	δ 8.62 (s, 1H), 7.40 (s, 1H), 6.30 (s, 1H), 3.52 (m, 2H), 2.90−3.05 (m, 3H), 2.87 (s, 3H), 2.57−2.71 (m, 3H)	$C_{10}H_{17}N_3Br_2$
1c	B	80	128.0−129.8	194.3	δ 8.54 (s, 1H), 7.24 (s, 1H), 3.55 (m, 2H), 3.12 (q, 2H, J = 7.4 Hz), 2.88 (m, 2H), 2.72 (d, 2H, J = 6.8 Hz), 1.94 (m, 3H), 1.45 (m, 2H), 1.26 (t, 3H, J = 7.4 Hz)	$C_{11}H_{21}N_3Br_2 \cdot 2.3H_2O$
2c	B	74	204.5−206.1	208.4	δ 8.52 (s, 1H), 7.17 (s, 1H), 3.53 (m, 2H), 3.10 (q, 2H, J = 7.4 Hz), 2.86 (m, 2H), 2.74 (t, 2H, J = 7.5 Hz), 2.02 (m, 2H), 1.43−1.67 (m, 5H), 1.26 (t, 3H, J = 7.5 Hz)	$C_{12}H_{23}N_3Br_2$
3c	B	73	194.6−197.1	192.6	δ 8.61 (s, 1H), 7.40 (s, 1H), 6.27 (s, 1H), 3.63 (m, 2H), 3.19 (q, 2H, J = 7.4 Hz), 2.90−3.10 (m, 3H), 2.55−2.70 (m, 3H), 1.29 (t, 3H, J = 7.4 Hz)	$C_{11}H_{19}N_3Br_2$
1d	C	67	185.7−187.4	208.3	δ 8.54 (s, 1H), 7.23 (s, 1H), 3.56 (m, 3H), 3.35 (m, 2H), 2.78 (d, 2H, J = 5.6 Hz), 1.97 (m, 3H), 1.74 (m, 2H), 1.39 (d, 6H, J = 6.7 Hz)	$C_{12}H_{23}N_3Br_2 \cdot 0.4H_2O$
2d	C	63	224.3−225.9	222.3	δ 8.52 (s, 1H), 7.17 (s, 1H), 3.41 (m, 3H), 2.95 (m, 2H), 2.74 (t, 2H, J = 7.4 Hz), 2.02 (m, 2H), 1.42−1.67 (m, 5H), 1.27 (d, 6H, J = 6.7 Hz)	$C_{13}H_{25}N_3Br_2 \cdot 0.4H_2O$
3d	C	65	176.2−178.3	206.8	δ 8.57 (s, 1H), 7.37 (s, 1H), 6.26 (s, 1H), 3.47−3.53 (m, 3H), 2.95−3.02 (m, 3H), 2.58−2.72 (m, 3H), 1.26 (d, 6H, J = 6.8 Hz)	$C_{12}H_{21}N_3Br_2 \cdot 2.6H_2O$
1e	C	68	216.5−218.1	248.5	δ 8.55 (s, 1H), 7.23 (s, 1H), 3.45 (m, 2H), 3.00 (m, 3H), 2.70 (d, 2H, J = 6.6 Hz), 1.64−1.97 (m, 7H), 1.11−1.44 (m, 8H)	$C_{15}H_{27}N_3Br_2 \cdot 1.4H_2O$
2e	C	65	232.4−234.5	262.3	δ 8.50 (s, 1H), 7.15 (s, 1H), 3.47 (m, 3H), 2.98 (m, 3H), 2.72 (t, 2H, J = 7.2 Hz), 1.61−1.95 (m, 7H), 1.12−1.38 (m, 9H)	$C_{16}H_{29}N_3Br_2 \cdot 0.3H_2O$
3e	C	60	184.5−185.7	246.6	δ 8.60 (s, 1H), 7.38 (s, 1H), 6.26 (s, 1H), 3.56 (m, 2H), 3.05−3.16 (m, 4H), 2.54−2.71 (m, 3H), 1.83−1.98 (m, 4H), 1.26−1.48 (m, 6H)	$C_{15}H_{25}N_3Br_2 \cdot 2.6H_2O$
1f	C	75	241.8−242.4	256.3	δ 8.59 (s, 1H), 7.52 (m, 5H), 7.27 (s, 1H), 4.30 (s, 2H), 3.53 (m, 2H), 3.02 (m, 2H), 2.74 (d, 2H, J = 6.8 Hz), 1.95 (m, 3H), 1.44 (m, 2H)	$C_{16}H_{23}N_3Br_2 \cdot 1.3H_2O$
2f	C	68	205.5−206.4	270.6	δ 8.49 (s, 1H), 7.44 (m, 5H), 7.14 (s, 1H), 4.23 (s, 2H), 3.45 (m, 2H), 2.92 (m, 2H), 2.71 (t, 2H, J = 7.4 Hz), 1.96 (m, 2H), 1.49−1.61 (m, 5H)	$C_{17}H_{25}N_3Br_2 \cdot 1.4H_2O$
3f	C	70	223.8−224.4	254.5	δ 8.59 (s, 1H), 7.48 (m, 5H), 7.37 (s, 1H), 6.26 (s, 1H), 4.32 (s, 2H), 3.58 (m, 2H), 3.15 (m, 3H), 2.66−2.69 (m, 3H)	$C_{16}H_{21}N_3Br_2 \cdot 0.9H_2O$
1g	C	72	219.8−220.4	270.4	δ 8.56 (s, 1H), 7.25−7.38 (m, 6H), 3.62 (m, 2H), 3.38 (m, 2H), 2.92−3.09 (m, 4H), 2.72 (d, 2H, J = 6.8 Hz), 1.95 (m, 3H),1.48 (m, 2H)	$C_{17}H_{25}N_3Br_2 \cdot 1.0H_2O$
2g	C	65	214.3-215.6	284.6	δ 8.52 (s, 1H), 7.35 (m, 5H), 7.17 (s, 1H), 3.60 (m, 2H), 3.34 (m, 2H), 2.89−3.08 (m, 4H), 2.74 (t, 2H, J = 7.2 Hz), 2.00 (m, 2H), 1.37−1.64 (m, 5H)	$C_{18}H_{27}N_3Br_2$
3g	C	64	213.8−214.8	268.3	δ 8.60 (s, 1H), 7.35−7.41 (m, 6H), 6.27 (s, 1H), 3.65 (m, 2H), 3.37 (t, 2H, J = 7.2 Hz), 2.93−3.06 (m, 5H), 2.54−2.67 (m, 3H)	$C_{17}H_{23}N_3Br_2 \cdot 1.8H_2O$
1h	C	75	196.6−197.6	284.4	δ 8.53 (s, 1H), 7.21−7.34 (m, 6H), 3.50 (m, 2H), 3.05 (m, 2H), 2.99 (m, 2H), 2.67 (m, 4H), 1.86−2.01 (m, 5H),1.43 (m, 2H)	$C_{18}H_{27}N_3Br_2$

[a] All compounds are hygroscopic.

only a 45-fold preference for the human H_3 receptor over the human H_4 receptor. The microdialysis study in rat brain shows that both immepip and methimepip (**1b**) lower the basal level of histamine in rat hypothalamus to about 25% after an intraperitoneal injection (5 mg/kg). Thus, methimepip (**1b**) is identified as a novel, potent and highly selective histamine H_3 receptor agonist, which will be useful in both in vitro and in vivo studies.

Experimental Section

Material. Reagents were obtained from commercial suppliers and used without further purification. 3-Pyridin-4-yl-propanol was purified by distillation under reduced pressure. VUF5510 **(3a)** was synthesized using a procedure earlier described.[25] Solvents used were either AR or HPLC grade. Dry THF and DCM were obtained freshly from distillation over lithium aluminum hydride and calcium hydride, respectively. Thin-layer chromatography was carried out on Merck Kieselgel 60 F_{254} on aluminum sheets, and preparative flash chromatography was performed on J. T. Baker Kieselgel 60 under pressure. Melting points were determined on an Electrothermal IA9200 apparatus. Mass spectrometry was performed on a Finnigan LCQ_{DECA} ion-trap mass spectrometer using APCI technique. ^{1}H spectra were recorded on a Bruker AC-200 spectrometer with the residual undeuterated solvent peak as reference. Elemental analyses were performed at Mikroanalytisches Labor Pascher (Remagen-Bandorf, Germany). Synthetic methods and spectroscopic and analytical data for the target compounds are shown in Table 3.

Methods. 4-(2-Hydroxyethyl)piperidine-1-carboxylic Acid *tert*-Butyl Ester (4). To a cold solution of 4-piperidine ethanol (10 g, 0.08 mol) in 200 mL of $CHCl_3$ was added dropwise a solution of di-*tert*-butyl dicarbonate (19 g, 0.09 mol) and triethylamine (34 mL, 0.24 mol) in 200 mL of $CHCl_3$. The mixture was stirred in an ice bath for 1 h and subsequently at room temperature for 16 h. A saturated sodium carbonate solution (250 mL) was added, the organic layer was collected, and the aqueous layer was extracted with $CHCl_3$ (2 × 200 mL). The combined organic layers were dried over sodium sulfate and evaporated to give **4** as a light-yellow oil (18 g, 98%). ^{1}H

NMR ($CDCl_3$): δ 4.02 (m, 2H), 3.68 (t, 2H, J = 6.1 Hz), 2.66 (m, 2H), 2.00 (br, s, OH), 1.51−1.70 (m, 5H), 1.46 (s, 9H), 1.07 (m, 2H).

4-(2-Oxoethyl)piperidine-1-carboxylic Acid *tert*-Butyl Ester (5). A solution of oxalyl chloride (7.4 mL, 0.09 mol) in 100 mL of dry DCM was cooled to −60 °C under an atmosphere of dry nitrogen. A solution of dimethyl sulfoxide (13.4 mL, 0.19 mol) in 100 mL of DCM was added dropwise, and the mixture was subsequently stirred for 15 min at −60 °C. Next, a solution of **4** (18 g, 0.08 mol) in 100 mL of dry DCM was added dropwise and the mixture stirred for 45 min at −60 °C. Subsequently, triethylamine (55 mL, 0.40 mol) was added, and the mixture was warmed to room temperature. The reaction mixture was washed with water (3 × 200 mL) and dried over sodium sulfate. The solvent was evaporated under reduced pressure. After purification by flash column chromatography (EtOAc), the title compound (**5**) was obtained as a light-yellow solid (16.5 g, 90%). ^{1}H NMR ($CDCl_3$): δ 9.76 (s, 1H), 4.08 (m, 2H), 2.64 (m, 2H), 2.34 (dd, 2H, J = 6.4 and 2.2 Hz), 2.11 (m, 1H), 1.65 (m, 2H), 1.42 (s, 9H), 1.12 (m, 2H).

4-[4-(4-Methylbenzenesulfonyl)-4,5-dihydrooxazol-5-ylmethyl]piperidine-1-carboxylic Acid *tert*-Butyl Ester (6). Finely powdered sodium cyanide (0.4 g, 7 mmol) was added in one portion to a stirred suspension of tosylmethyl isocyanide (15.6 g, 0.08 mol) and **5** (16.5 g, 0.07 mol) in 500 mL of absolute ethanol. Immediately, the reaction mixture became clear, and the solution was stirred for another 2 h. The solvent was evaporated under reduced pressure, and 500 mL of $CHCl_3$ was added. The resulting mixture was filtered, and the filtrate was concentrated in vacuo to give a brown oil, which was used immediately for the next step without further purification. ^{1}H NMR ($CDCl_3$): δ 7.76 (d, 2H, J = 8.2 Hz), 7.34 (d, 2H, J = 8.2 Hz), 6.94 (s, 1H), 5.08 (m, 1H), 4.71 (d, 1H, J = 5.9 Hz), 4.08 (m, 2H), 2.66 (m, 2H), 2.41 (s, 3H), 1.44−1.61 (m, 5H), 1.41 (s, 9H), 1.20 (m, 2H).

4-(Imidazol-4-ylmethyl)piperidine-1-carboxylic Acid *tert*-Butyl Ester (7). In a stainless steel bomb, a solution of **6** in 120 mL of absolute ethanol saturated with ammonia was heated at 90−110 °C for 16 h. After cooling to room temperature, the solvent was evaporated under reduced pressure. The residue was dissolved in DCM (250 mL) and washed with 10% sodium carbonate solution (250 mL) and water (2 × 250 mL). The organic layer was dried over sodium sulfate and concentrated under reduced pressure to give a dark brown oil, which was subsequently treated with activated charcoal. Filtration and purification using flash column chromatography (MeOH: DCM, 1:9) resulted in **7** as a light-yellow oil (13.7 g, 70% based on **5**). ^{1}H NMR ($CDCl_3$): δ 7.53 (s, 1H), 6.74 (s, 1H), 4.00 (m, 2H), 2.63 (m, 2H), 2.49 (d, 2H, J = 6.8 Hz), 1.59−1.73 (m, 3H), 1.41 (s, 9H), 1.10 (m, 2H).

4-(Imidazol-4-ylmethyl)piperidine Dihydrobromide (1a). Compound **7** (13.7 g, 0.05 mol) was dissolved in 100 mL of 1 N HBr. The solution was heated at 80 °C for 2 h, and the solvent was evaporated. The residue was dissolved in 50 mL of ethanol and precipitated by slow addition of ether. The product **1a** was obtained as an off white solid (10.6 g, 65%). ^{1}H NMR (D_2O): δ 8.56 (s, 1H), 7.24 (s, 1H), 3.40 (m, 2H), 2.91 (m, 2H), 2.72 (d, 2H, J = 6.8 Hz), 1.87−1.94 (m, 3H), 1.40 (m, 2H). mp 233.6−234.8 °C (237−239 °C).[39]

3-Pyridin-4-yl-propionaldehyde (8). The compound was synthesized from 4-pyridinepropanol (15 g, 0.11 mol) using the procedure described for the synthesis of **5**. The product **8** was obtained as a yellow oil (13 g, 87%). ^{1}H NMR ($CDCl_3$): δ 9.80 (s, 1H), 8.47 (d, 2H, J = 6.0 Hz), 7.10 (d, 2H, J = 6.0 Hz), 2.75−2.97 (m, 4H).

4-{2-[4-(4-Methylbenzenesulfonyl)-4,5-dihydrooxazol-5-yl]ethyl}pyridine (9). The compound was synthesized from **8** (13 g, 0.10 mol) using the procedure described for the synthesis of **6**. The product **9** was used immediately for the next step without further purification. ^{1}H NMR ($CDCl_3$): δ 8.44 (d, 2H, J = 6.0 Hz), 7.72 (d, 2H, J = 8.2 Hz), 7.37 (d, 2H, J = 8.2 Hz), 7.12 (d, 2H, J = 6.0 Hz), 6.96 (s, 1H), 4.97 (m, 1H), 4.77 (d, 1H, J = 5.9 Hz), 2.74 (m, 2H), 2.39 (s, 3H), 1.96 (m, 2H).

4-[2-(Imidazol-4-yl)-ethyl]pyridine (10). The compound was synthesized from **9** using the procedure described for the synthesis of **7**. The product **10** was obtained as a light-yellow oil (12.1 g, 70% based on **8**). ^{1}H NMR ($CDCl_3$): δ 8.43 (d, 2H, J = 6.1 H), 7.55 (s, 1H), 7.07 (d, 2H, J = 6.1 Hz), 6.68 (s, 1H), 2.94 (m, 4H).

4-[2-(Imidazol-4-yl)-ethyl]piperidine Dihydrobromide (2a). A solution of **10** (12 g, 0.07 mol) in 10 mL of 5 N HCl was added to a suspension of 1.2 g of 10% Pd/C in 100 mL of MeOH. The mixture was hydrogenated under 100 atm of hydrogen gas for 48 h in a stainless steel bomb. The mixture was concentrated in vacuo, whereafter a saturated sodium carbonate solution was added in order to get pH ≈ 12. After extraction with $CHCl_3$ (3 × 250 mL), the organic solvent was dried over sodium sulfate and evaporated to obtain a yellow oil, which was subsequently treated with 1 N HBr (adjusted pH ≈ 3) and concentrated in vacuo. The product **2a** was recrystallized from EtOH/Et_2O as light-yellow solid (14.3 g, 60%). ^{1}H NMR (D_2O): δ 8.53 (s, 1H), 7.18 (s, 1H), 3.39 (m, 2H), 2.94 (m, 2H), 2.75 (t, 2H, J = 7.2 Hz), 1.96 (m, 2H), 1.64 (m, 3H), 1.44 (m, 2H).

General Procedures for the Synthesis of Compounds 1a−h, 2a−g, and 3a−g. Method A. The amine (**1a**, **2a**, or **3a**, 1.5 mmol) was added to cold formic acid (25 mL) followed by slow addition of 0.5 mL of formaldehyde (37% solution stabilized with methanol). The resulting mixture was refluxed for 6 h and quenched by addition of saturated sodium carbonate solution until pH ≈ 12. After concentration of the mixture in vacuo, the residue was washed with $CHCl_3$ (3 × 25 mL). The combined organic layers were dried over sodium sulfate and evaporated. The product was purified using flash column chromatography (5% TEA in MeOH). The purified compound was subsequently treated with 1 N HBr (adjusted pH ≈ 3), concentrated in vacuo, and recrystallized from EtOH/Et_2O to give a light-yellow solid.

Method B. A mixture of the amine (**1a**, **2a**, or **3a**, 1.5 mmol) and potassium carbonate (3.75 mmol) in ethanol (50 mL) was stirred at room temperature for 15 min and cooled to 0 °C in an ice bath. Ethyl iodide (1.5 mmol) was added dropwise, and the mixture was stirred at 0 °C for 1 h, followed by 16 h at room temperature. If the reaction was incomplete, additional ethyl iodide (0.75 mmol) was added and the mixture was stirred for another 16 h. After the mixture was concentrated in vacuo, the residue was washed with $CHCl_3$ (3 × 25 mL) and filtered. The filtrate was dried over sodium sulfate and the solvent was evaporated to give the product, which was purified subsequently using flash column chromatography (5% TEA in MeOH). The purified product was treated with 1 N HBr (adjusted pH ≈ 3), concentrated in vacuo, and recrystallized from EtOH/Et_2O to give a light-yellow solid.

Method C. The amine (**1a**, **2a**, or **3a**, 1.5 mmol) and sodium carbonate (1.5 mmol) were added to MeOH and warmed to 80 °C for 15 min. The solvent was evaporated under reduced pressure, and dichloroethane (20 mL) was added. The aldehyde or ketone (2.25 mmol) was dissolved in 5 mL of dichloroethane and added to the solution of amine. The resulting mixture was stirred at room temperature for 15 min, and glacial acetic acid (0.1 mL) was added. The mixture was stirred for an additional 30 min, and sodium triacetoxyborohydride (2.25 mmol) was added in a portion and stirred at room temperature for 16 h. $CHCl_3$ (25 mL) was added, and the reaction was quenched with saturated sodium carbonate solution. The organic layer was separated, and the aqueous layer was extracted with $CHCl_3$ (2 × 25 mL). The combined organic layers were dried over sodium sulfate. The solvent was evaporated, and the product was purified using flash column chromatography (5% TEA in MeOH). The purified product was treated with 1 N HBr (adjusted pH ≈ 3) and then concentrated in vacuo. The product was recrystallized from EtOH/Et_2O to give a light-yellow solid.

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Supporting Information Available: Elemental analysis data for **1b**−**g**,**h**, **2b**−**g**, and **3b**−**g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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