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Synthesis and structural and pharmacological properties of cyclopropane-based conformationally restricted analogs of 4-methylhistamine as histamine H_3/H_4 receptor ligands

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ABSTRACT

On the basis of the previous results on a histamine H_4 receptor agonist 4-methylhistamine and a cyclopropane-based conformationally restricted analog CEIC (**3**) with potent H_3/H_4 receptor antagonistic effect, 4-methylhistamine analogs **4** and **5** of CEIC were designed and synthesized. Compound **4** showed strong affinity (K_i = 38.7 nM) for the H_3 receptor, which was more potent than a well-known H_3 antagonist thioperamide. Stable tautomer and conformation of **3** and **4**, which can affect the pharmacological activity, were analyzed by ab initio calculations.

1. Introduction

Homeostatic processes related to the neurotransmitter histamine (Fig. 1) are mediated by at least four receptor subtypes termed H_1, H_2, H_3, and H_4 receptors. Recent years, much attention has been focused on histamine H_3 and H_4 receptor ligands due to their medicinal chemical interest. Antagonists to the histamine H_3 receptor are considered to be potential drugs for various diseases, such as Alzheimer's disease, attention-deficit/hyperactivity disorder (ADHD), schizophrenia, depression, dementia, and epilepsy.[1] On the other hand, the histamine H_4 receptor antagonists may be effectively used in new therapeutic modalities for the treatment of allergic diseases.[2]

G protein-coupled receptors (GPCRs), including the histamine H_3 and H_4 receptors, are major target biomolecules for drug development,[3] and accordingly, the process of identifying therapeutic agents targeting GPCRs has generated much interest. However, structural analysis of GPCRs is tremendously difficult due to the membranous nature of these proteins and to their very low natural abundance, compared with that of proteins soluble in blood or cytosol.[4] Therefore, a drawback in drug development targeting GPCRs is the structural data of the target biomolecule are lacking or poorly documented.

Thus, a method for effectively identifying compounds targeting GPCRs is required in drug development. We have devised a stereochemical diversity-oriented conformational restriction strategy to develop compounds that bind selectively to target proteins of unknown structure such as GPCRs.[5] In order to realize the strategy, we developed versatile chiral cyclopropane units with different stereochemistries, the structures of which are shown in Figure 2.[5b,6] Using these units, we designed and synthesized a series of stereochemically diverse conformationally restricted analogs of histamine.[5a,b,6] We hypothesized that some of these conformationally restricted analogs might assume a conformation superimposed on the bioactive conformations of histamine for H_3 receptor binding or H_4 receptor binding, since the imidazole moiety and the amino side-chain moiety are located in a variety of spatial arrangements due to the conformational restriction in these analogs.

Throughout these studies, we showed that several of these analogs were potent H_3 and/or H_4 receptor ligands which are, for examples, the first highly selective H_3 receptor agonist (1*S*,2*S*)-2-(2-aminoethyl)-1-(1*H*-imidazol-4-yl)cyclopropane [AEIC, **1**: K_i = 1.3 nM] with the (1*S*)-*cis*-cyclopropane structure[5a] and a potent H_3/H_4 receptor antagonist (1*R*,2*S*)-2-[2-(4-chlorobenzylamino)-ethyl]-1-(1*H*-imidazol-4-yl)cyclopropane [(*R*)-CEIC, **3**: K_i = 8.4 nM

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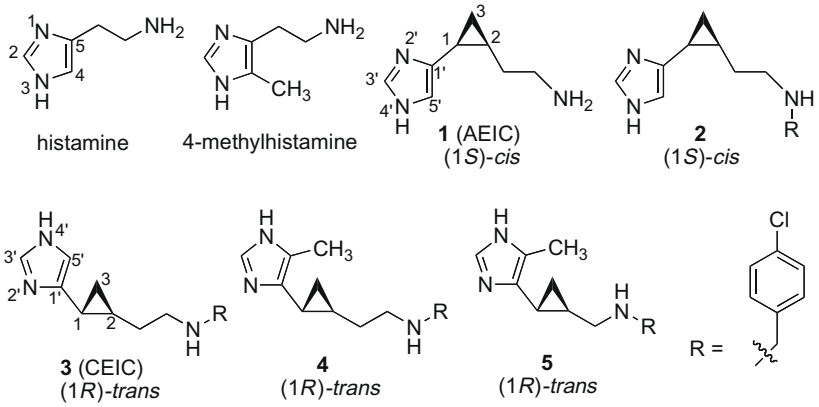


Figure 1. Histamine, 4-methylhistamine, and their cyclopropane-based conformationally restricted analogs.

for H_3 receptor, 7.6 nM for H_4 receptor] with the (1*R*)-*trans*-cyclopropane structure.[5b] In these studies, introduction of a hydrophobic group at the side-chain amino group of an cyclopropane-based H_3 and/or H_4 receptor agonists changes them into an antagonist to the receptor. For example, derivatization of AEIC (**1**) into its *N*-(4-chlorobenzyl) derivative provided a potent H_3 receptor antagonist **2** (K_i = 42 nM).[5b]

In the course of these studies, in this paper, we describe design, synthesis, structural analysis, and pharmacological effects of the cyclopropane-base conformationally restricted analogs of 4-methylhistamine, namely, **4** and **5**, structure of which are shown in Figure 1.

2. Results and discussion

2.1. Design of compounds

The H_4 receptor has significant sequence homology (about 40%) to the H_3 receptor cDNA.[7] Furthermore, the H_3 and the H_4 receptors share about 60% sequence identity in their transmembrane regions,[7] which would make it difficult to develop H_4 receptor selective ligands.[2,8,9] In fact, (*R*)-CEIC (**3**) is highly but non-selectively active to both the H_3 and the H_4 receptors.[5b]

In 2005, Leurs and co-workers identified 4-methylhistamine as a H_4 receptor agonist that has a >100-fold selectivity for the H_4 receptor over the other histamine receptor subtypes including the H_3 receptor.[8] Considering these results, we thought that H_4 receptor selective antagonists might be developed: introduction of a methyl group at the 5′-position, which corresponds the 4-position of 4-methylhistamine, of the potent H_3/H_4 antagonist (*R*)-CEIC (**3**) might change it into the H_4 receptor selective antagonist. Thus, we planned to synthesize 5′-methylimidazole analog **4** of (*R*)-CEIC (**3**) and also its one carbon-reduced analog **5**.

2.2. Synthesis

Although much effort has been devoted to developing practical methods for preparing chiral cyclopropanes, for example, enantioselective cyclopropanations, chemical or enzymatic optical resolutions, and transformations from chiral synthons, synthesis of cyclopropane derivatives of a desired stereochemistry is often troublesome.[10] We recently developed the chiral units (Fig. 2) for cyclopropane-based conformational restriction, which were composed of four stereoisomeric cyclopropane derivatives bearing two adjacent carbon substituents in a cis or a trans relationship, namely **6** and **7**, and their enantiomers ***ent*-6** and ***ent*-7**.[6] These units are generally useful for synthesizing various compounds having an asymmetric *cis*- or *trans*-cyclopropane structure, and therefore, in this study, the chiral unit **7** was employed as a synthon.

Synthesis of the target compound **4** and **5** from the unit **7**[5b,8] with the (1*R*)-*trans* cyclopropane structure is summarized in Scheme 1. The methylimidazole ring was constructed by treating **7** with 1-methyl-1-tosylmethyl isocyanide and *t*-BuOK in THF, followed by heated in saturated NH_3/EtOH in sealed tube at 125 °C.[11] The resulting 4-methylimidazole product was further treated with TrCl and Et_3N in CH_2Cl_2 to give (*N*-trityl-4-methylimidazolyl)cyclopropane derivative **8**, of which TBDPS group was subsequently removed with TBAF/THF to give cyclopropanemethanol **9** in 44%

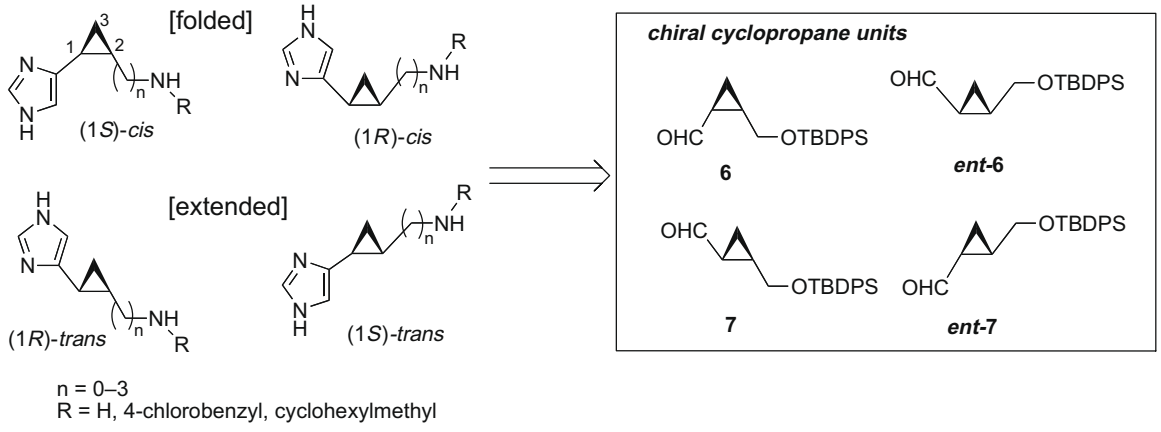
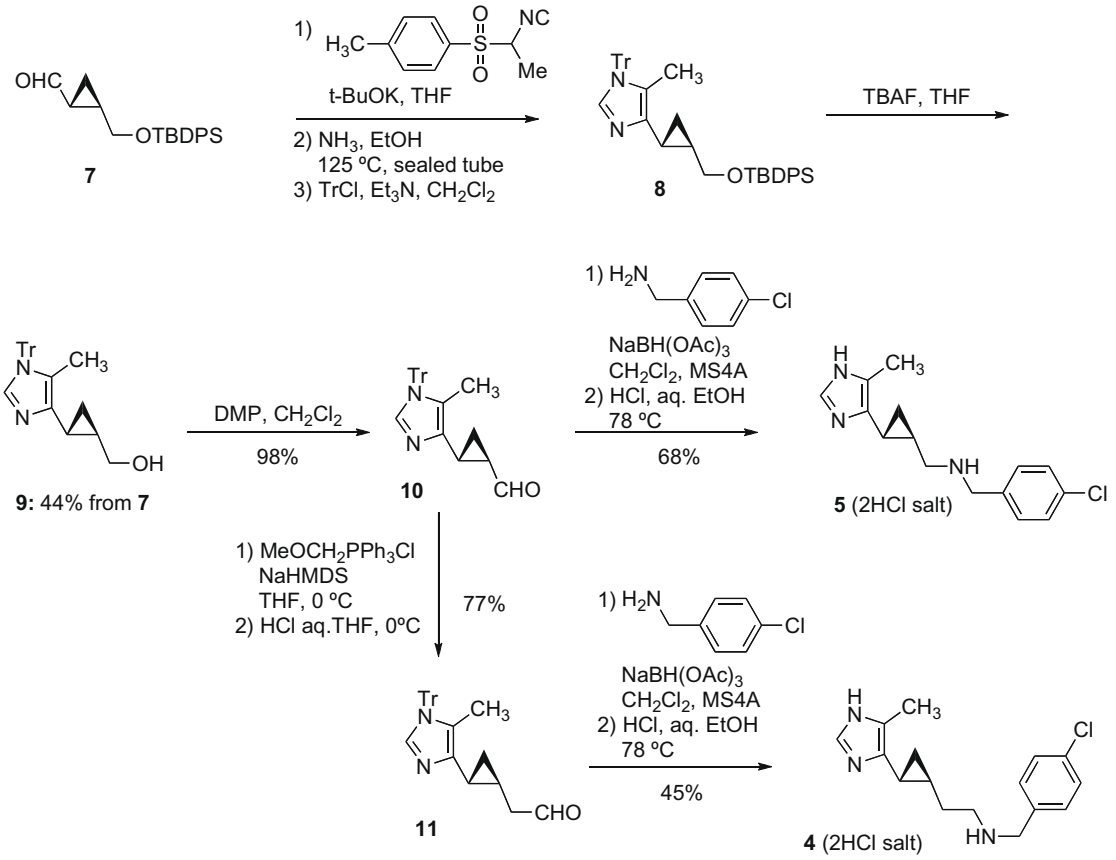


Figure 2. A series of conformationally restricted analogs of histamine with stereochemical diversity synthesized from the chiral cyclopropane units.



Scheme 1.

overall yield. Dess–Martin oxidation of **9** afforded aldehyde **10**, introduction of a 4-chlorobenzylamino function to which at the 1′-position was next investigated under reductive-amination conditions. As a result, when aldehyde **10** was treated with 4-chlorobenzylamine in the presence of $NaBH(OAc)_3$ and MS4A in CH_2Cl_2, the desired reductive-amination product was effectively obtained. Subsequent acidic treatment of the product finally gave the target compound **5** in 68% yield.

Wittig reaction of aldehyde **10** with $MeOCH_2PPh_3Cl/NaN(TMS)_2$ in THF, followed by acidic treatment gave the one-carbon elongated aldehyde **11**. As shown in Scheme 1, the other target compound **4** was synthesized from aldehyde **11**, according to the procedure same to that used for the synthesis of **5** described above.

2.3. Conformational analysis by calculations

A number of theoretical and experimental studies on the conformation of cyclopropanes attached to an unsaturated bond, such as vinylcyclopropanes, cyclopropyl ketones, or cyclopropanecarboxaldehydes, have been carried out.[12,13] We also investigated the conformation of cyclopropyl ketones, cyclopropanecarboxaldehydes, *C*-cyclopropylaldonitrones and explained the stereochemical outcomes of their hydride reductions and Grignard additions based on the bisected conformation-dependent stereoelectronic effects.[14] These studies showed that unsaturated group-attached cyclopropanes preferentially exist in the bisected *s-trans* and *s-cis* conformations, as shown in Figure 3a, due to the effective hyperconjugation between the unsaturated bond orbital and the strong electron-donating orbitals of the cyclopropane ring.[12–14] Accordingly, the imidazolylcyclopropane moiety of the cyclopropane-based conformationally restricted histamine analogs may also be stable in

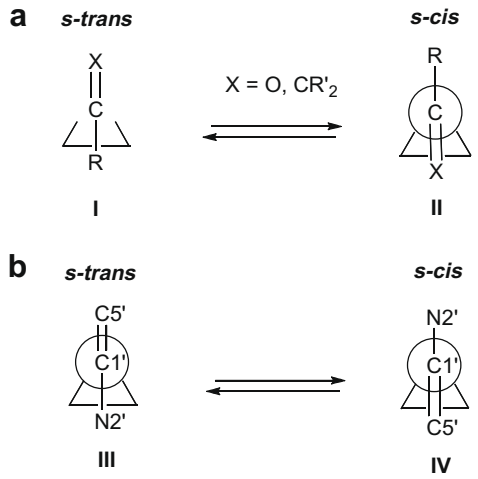


Figure 3. Bisected *s-cis* and *s-trans* conformations of α,β-unsaturated cyclopropanes (a) and imidazolylcyclopropanes (b).

their bisected *s-trans* and *s-cis* conformations, as shown in Figure 3b. This kind of conformational features is possible to affect the pharmacological activity of cyclopropane-based conformationally restricted analogs. Compared with parent compound CEIC (**3**) and its 5′-methyl derivatives **4** and **5**, their orientation around the imidazole and the cyclopropane may be different due to the steric effect of the methyl group in **4** and **5**. Since, in these imidazole-containing histamine receptor ligands, three-dimensional location of the imidazole moiety relative to the basic nitrogen can be important for their

binding to the receptors, we decided to investigate the conformational stability of **3** and **4** by theoretical calculations.

Histamine is in an equilibrium between the two differently N-protonated tautomers **A** and **B** (Fig. 4a), and relative stability of these tautomers would affect the binding affinity for the receptors. Thus, we first investigated relative stability of these tautomers by ab initio calculations at B3LYP/6-31G* with 4-methylimidazole (Fig. 4a, R = CH_3) as a model compound. As a result, it appeared that the two tautomers are almost equally stable (**A** is only 0.11 kcal/mol more stable than **B**).

Likely to histamine, imidazolylcyclopropane derivatives **3** and **4** can also equilibrate between two tautomers **A′** and **B′** (Fig. 4). However, the N4′-protonated form **A′** might be more stable than the N2′-protonated form **B′**, since the steric repulsion between the proton at the N2′-position and cyclopropane moiety might occur in **B′**.

Thus, the rotational barrier energy around the C5′–C1′–C1–H1 dihedral angle of the both tautomers **A′** and **B′** in **3** and **4** was calculated based on density functional theory (DFT). The dihedral angle was rotated from 0° to 360° at intervals of 10°, and the single point energies of the optimized conformers were calculated at B3LYP/6-31G* to obtain the energy profiles. As shown in Figure 5, in both **3** and its 5′-methyl derivative **4**, the N4′-protonated form **A′** (blue line) was relatively more stable than the N2′-protonated form **B′** (red line). It is interesting that in both **3** and **4** the tautomer **A′** is especially stable at an angle of 0°, where it just assumes the bisected *s-trans* conformations (**III**, Fig. 3b). Since the C1′–N2′ bond of **A′** has more double bonded character compared with that of **B** due to effective C5′–C1′–N2′–C3′ conjugation in **A′**, as shown in Figure 4b, hyperconjugation between the cyclopropane and the imidazole moieties significantly more effective in the bisected conformation of tautomer **A′** than that in **B′**. Therefore, the bisected *s-trans* conformation of tautomer **A′** is especially stable.

Hereafter, we mainly discuss the conformational features using relatively stable tautomer **A′** in **3** and **4**, which can be important in the binding to the receptors. For the imidazolylcyclopropane compound **3**, the minimum energy value was observed at the bisected *s-trans* conformations described above. On the other hand, the bisected *s-cis* conformation (180°) was not so stable, probably due to the steric repulsion due to the 5′-proton for the cyclopropane moiety. The energy maxims for **3** were observed in the perpendicular-like conformations around angles of 90° (Fig. 6a) and 270° (Fig. 6b), where the conjugational stabilization is minimum. The energetically minimum bisected *s-trans* conformers at 0° were about 2.5 kcal/mol more stable than the maximum energy conformers around 90° and 270°. Thus, the hyperconjugational effect can significantly affect the conformation of tautomer **A′** to stabilize the bisected *s-trans* form.

For the 5′-methyl derivative **4**, similar to **3**, minimum energy value was also observed in the bisected *s-trans* conformation of the tautomer **A′**. It is interesting that, differently from **3**, the energy of **A′** tautomer in **4** was not at a maximum in the perpendicular conformers but rather at angle of 150° (Fig. 6c) and at 210° (Fig. 6d), where C1′=C5′ bond of the imidazole eclipsed to the C1–C3 bond or the C1–C2 bond of the cyclopropane ring. In these eclipsed conformations, striking steric repulsion due to the 5′-methyl group would make it significantly unstable. The energetically maximum eclipsed conformation at 150° of the tautomer **A′** was about 4 kcal/mol more unstable than the bisected *s-trans* conformers at 0° in **4**.

These calculations showed that the conformational stability of **3** and **4** appears to be determined by the hyperconjugational stabilization by the molecular orbital interaction between the imidazole ring and the electron-donating cyclopropane ring and also by the steric effect, particularly caused by the imidazole C5′-moiety. However, the most stable conformations in **4** and the parent compound **3** is the same bisected *s-trans* form of the N4′-protonated tautomer **A′**, and therefore, conformational change by introducing the methyl group at the imidazole 5′-position is likely to be small.

2.4. Pharmacological effects and discussion

Binding affinities of the target compound **4** and **5** for the human H_3 receptor subtype using [^{3}H]N^{α}-methylhistamine[5a,b] and also for the human H_4 receptor subtype using [^{3}H]histamine[5a,b] were investigated, and were compared with those of the parent compounds CEIC (**3**). The results are summarized in Table 1. In these system, K_i values of the reference H_3 receptor antagonist thioperamide were 51.1 nM for the H_3 receptor and 124 nM for the H_4 receptor, respectively, and the parent compounds **3** showed much higher but non-selective binding affinity as shown by the K_i values of 8.4 nM for H_3 receptor and 7.6 nM for H_4 receptor, respectively.

In the two newly synthesized methylimidazole-type compounds, **5** did not show any significant binding to the H_3 receptor as well as to the H_4 receptor (K_i >1000 nM). However, compound **4** showed remarkable binding affinity for the H_3 receptor with a K_i value of 38.7 nM, which tended to be more potent than the well-known H_3 receptor antagonist thioperamide (K_i = 51.1 nM). However, the potency was somewhat decreased compared with that of the parent compound **3**. The binding affinity of **4** for the H_4 receptor was further reduced (K_i = 148 nM). Thus, compound **4** was not selective to the H_4 receptor, but rather selective to the H_3 receptor.

As described above, 5′-methylated derivative **4** is stable in the bisected *s-trans* conformation analogous to the parent compound **3**, so that the two compounds might show similar pharmacological feature, while the steric effect of the methyl group of **4** might weaken the affinity for the H_3 and H_4 receptors to some extent.

Although 4-methylhistamine is a H_4 receptor-selective agonist,[8] the cyclopropane-based conformationally restricted analog **4** is not, in spite of their having the same methylimidazole ring. These results suggested that binding modes of the two compounds to the receptors might be different, probably due to the hydrophobic 4-chlorobenzyl moiety and/or the rigid cyclopropane moiety in **4**, which are not exist in 4-methylhistamine.

The structural analysis showed that cyclopropane-based conformationally restricted histamine analogs significantly stable in the N4′-protonated form than the N2′-protonated form.

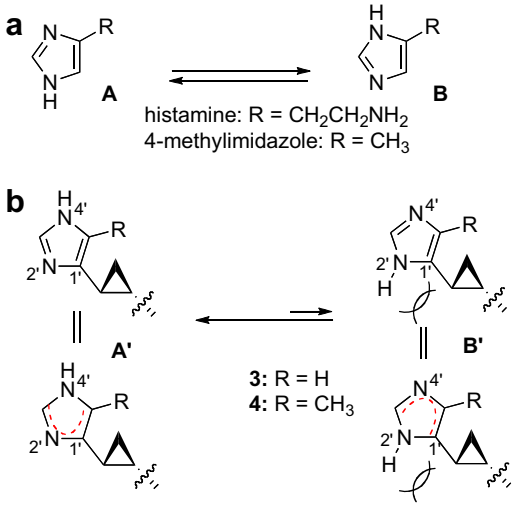


Figure 4. Equilibrium between the two tautomes **A** (**A′**) and **B** (**B′**) in histamine and 4-methylimidazole (a) and imidazolylcycropanes (b).

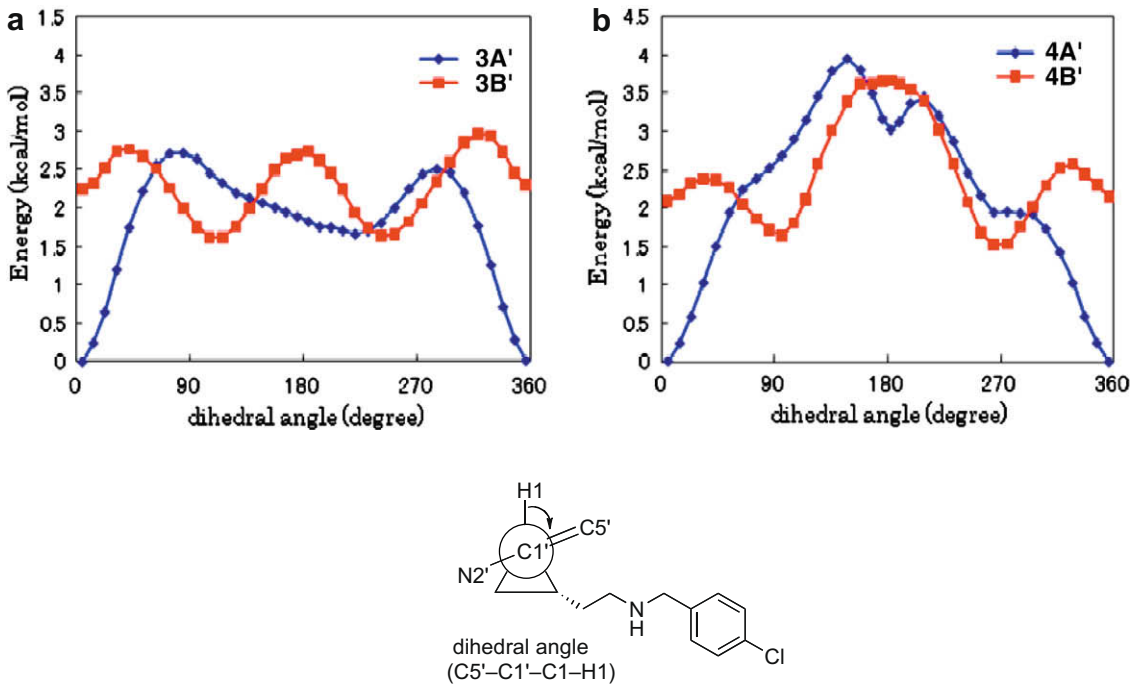


Figure 5. Rotational barrier energies around the C5′–C1′–C1–H1 dihedral angle of **3** (a) and its 5′-methyl derivative **4** (b). Calculations were carried out at B3LYP/6-31G* level, where **3A**′ and **4A**′ are protonated at 4′-N and **3B**′ and **4B**′ are protonated at 2′-N, respectively.

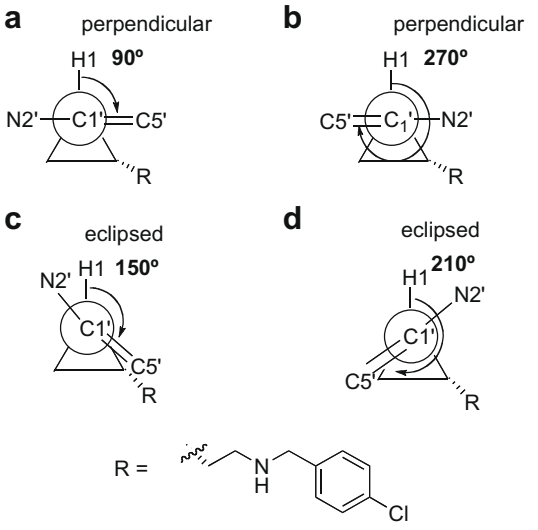


Figure 6. Newman projection of the maximum energy conformers of **3** (a and b) and its 5'-methyl derivative **4** (c and d).

Table 1
Binding affinities of compounds on the human H_3 and H_4 receptor subtypes[a]

Compound	H_3, K_i (nM)	H_4, K_i (nM)
4	38.7 ± 4.9	148 ± 51
5	>10^3	>10^3
3[b]	8.4 ± 1.5	7.6 ± 0.4
Thioperamide[b]	51.1 ± 3.8	124 ± 14

[a] Assay was carried out with cell membranes expressing human H_3, or H_4 receptor subtype (n = 3).
[b] Data were taken from Ref. 5b.

Accordingly, the highly potent cyclopropane based analogs such as **1**, **2**, **3** or **5**, would bind to the H_3 and H_4 receptors in the stable N4′-protonated tautomer **A**′. These results suggest that histamine also bind to these receptors in the analogous N4′-protonated tautomer **A**.

3. Experimental

^{1}H NMR and ^{13}C NMR spectra were obtained on JEOL JMM-ECA-500 spectrometers with tetramethylsilane as an internal standard and the resonance patterns are reported with notations as the following: br (broad), s (singlet), d (double), t (triplet) and m (multiplet). Mass spectra were obtained using a JEOL JMS-700TZ. Thin-layer chromatography was done on Merck coated plate 60F_{254}. Silica gel chromatography was done on silica gel 5715 (Merck), silica gel 60 N (Kanto Chemical Co.) or NH silica gel (Chromatorex®, Fuji Silysia Chemical). Reactions were carried out under an argon atmosphere.

3.1. (1*R*,2*R*)-2-Hydoxymethyl-1-(5(4)-methyl-1-triphenylmethyl-1*H*-imidazol-4(5)-yl)cyclopropane (9)

A solution of **7**[5b,7] (4.14 g, 12.2 mmol), 1-methyl-1-tosylmethyl isocyanide (3.15 g, 14.9 mmol), and potassium *tert*-butoxide (386 mg, 3.44 mmol) in THF (150 mL) was stirred at room temperature for 2 h. After evaporation of the solvent, the residue in ammonia-saturated absolute EtOH (200 mL) was heated at 125 °C in a stainless steal tube for 24 h. The resulting reaction mixture was evaporated, and the residue was purified by silica gel column chromatography ($CHCl_3$/MeOH, 1:0–9:1) to give the crude 4-methylimidazole derivative as a brown oil. A solution of the residual oil, Et_3N (1.78 mL 12.7 mmol) and TrCl (3.56 g, 12.7 mmol) in CH_2Cl_2 (65 mL) was stirred at room temperature for 2 h. After addition of MeOH, the mixture was partitioned between AcOEt and aqueous HCl (1 M), and the organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and evaporated. The residue was purified by silica gel column chromatography (hexane/AcOEt, 5:1) to give 1-triphenylmethyl-1*H*-4-methylimidazole derivative **8** as a pale yellow oil. A

solution of the oil and TBAF (1.0 M THF solution, 8.76 mL, 8.76 mmol) in THF (58 mL) was stirred at room temperature for 24 h. The solvent was evaporated, and the residue was purified by silica gel column chromatography (hexane/AcOEt, 1:2) to give **9** as a white solid (2.10 g, 5.37 mmol, 44% from **7**): $[\alpha]_D^{22}$ −30.6 (*c* 1.01, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.32–7.26 (m, 9H), 7.14–7.12 (m, 7H), 3.62–3.55 (m, 2H), 3.12 (br s, 1H), 1.65–1.59 (m, 2H), 1.45 (s, 3H), 1.05–1.01 (m, 1H), 0.78–0.75 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.9, 139.6, 136.8, 130.0, 127.9, 127.7, 125.2, 74.7, 66.2, 22.3, 13.9, 11.6, 11.5; LRMS (EI) *m*/*z* 394 (M^+); Anal. Calcd for $C_{26}H_{27}N_2O{\cdot}0.3H_2O$: C, 81.09; H, 6.70; N, 7.00. Found: C, 80.72; H, 6.81; N, 7.01.

3.2. (1*R*,2*R*)-2-Formyl-1-(5(4)-methyl-1-triphenylmethyl-1*H*-imidazol-4(5)-yl)cyclopropane (10)

A solution of **9** (500 mg, 1.27 mmol) and Dess–Martin periodinane (589 mg, 1.39 mmol) in CH_2Cl_2 (12 mL) was stirred at room temperature for 1 h. The resulting mixture was partitioned between saturated aqueous $NaHCO_3$/saturated aqueous $Na_2S_2O_3$ (1:1) and CH_2Cl_2, and the organic layer was washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by silica gel column chromatography (hexane/AcOEt, 1:1) to give **10** as an amorphous white solid (485 mg, 1.24 mmol, 98%): $[\alpha]_D^{24}$ −106.9 (*c* 1.02, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 9.35 (d, *J* = 4.5 Hz, 1H), 7.35–7.32 (m, 9H), 7.16–7.12 (m, 7H), 2.44–2.35 (m, 2H), 1.79–1.75 (m, 1H), 1.66–1.63 (m, 1H), 1.46 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$)δ 200.7, 141.6, 137.4, 136.8, 130.0, 128.0, 127.9, 126.2, 74.9, 32.2, 20.2, 15.5, 11.5; LR-MS (FAB) *m*/*z* 393 ($(M+H)^+$); HR-MS (FAB) calcd for $C_{27}H_{25}N_2O$ 393.1967. Found 393.1947 ($(M+H)^+$).

3.3. (1*R*,2*R*)-2-(4-Chlorobenzylamino)methyl-1-(5(4)-methyl-1*H*-imidazol-4(5)-yl)cyclopropane (5)

To a solution of **10** (13 mg, 34 mmol), 4-chlorobenzylamine (21 mL, 17 mmol), and MS4A powder (13 mg) in CH_2Cl_2 (1.0 mL) was added sodium triacetoxyborohydride (7.83 mg, 180 mmol), and the resulting mixture was stirred at room temperature for 2 h. After addition of MeOH, the mixture was filtered through Celite 545, and the filtrate was evaporated. The residue was partitioned between AcOEt and saturated aqueous $NaHCO_3$, and the organic layer was washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by NH silica gel column chromatography (hexane/AcOEt, 3:1) to give the 1-triphenylmethyl-1*H*-imidazole derivative **5** as a colorless oil. A solution of the oil in aqueous HCl (1.5 M, 0.60 mL) and EtOH (0.3 mL) was heated under reflux for 6 h, and the reaction mixture was evaporated. The residue was partitioned between CH_2Cl_2 and aqueous HCl (1 M). After addition of aqueous NaOH (1 M) to the aqueous layer, the resulting basic solution was extracted with CH_2Cl_2, and the organic layer was washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by NH silica gel column chromatography ($CHCl_3$/MeOH, 99:1) to give a free amine **5**. The free amine **5** was dissolved in aqueous HCl (4 M), and the solution was evaporated. The resulting residue was triturated with Et_2O to give a white hydroscopic amorphous solid of **5** as dihydrochloride (7.97 mg, 22.8 mmol, 68% from **11**): $[\alpha]_D^{21}$ −41.0 (*c* 0.76, CH_3OH); ^1H NMR (500 MHz, CD_3OD) δ 8.66 (s, 1H), 7.61–7.58 (m, 2H), 7.49–7.46 (m, 2H), 4.28 (s, 2H), 3.34–3.30 (m, 1H) 3.11 (dd, *J* = 13.2, 8.0 Hz, 1H), 2.36 (s, 3H), 2.16–2.11 (m, 1H), 1.70–1.63 (m, 1H), 1.27–1.20 (m, 2H); ^{13}C NMR (125 MHz, CD_3OD)δ 136.7, 132.9, 132.7, 131.3, 130.3, 129.3, 127.7, 51.8, 51.4, 17.1, 13.1, 12.5, 9.2; HR-MS (EI) calcd for $C_{15}H_{18}ClN_3$ 275.1189. Found 275.1194 ($(M-2HCl)^+$). Anal. Calcd for $C_{15}H_{20}Cl_3N_3{\cdot}0.55H_2O$: C, 50.24; H, 5.93; N, 11.72. Found: C, 50.63; H, 6.12; N, 11.33.

3.4. (1*R*,2*S*)-2-Formylmethyl-1-(5(4)-methyl-1-triphenylmethyl-1*H*-imidazol-4(5)-yl)cyclopropane (11)

To a suspension of (methoxymethyl)triphenylphosphonium chloride (312 mg, 0.910 mmol) in THF (2 mL) was added sodium hexamethyldisilazide (1.9 M THF solution, 42 mL, 0.79 mmol) at 0 °C, and the mixture was stirred at the same temperature for 1 h. To the resulting mixture was added a solution of **10** (155 mg, 0.395 mmol) in THF (2 mL) at 0 °C, and the mixture was stirred at the same temperature for 4 h. After addition of saturated aqueous NH_4Cl, the reaction mixture was evaporated, and the residue was partitioned between AcOEt and saturated aqueous NH_4Cl, and the organic layer was washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by silica gel column chromatography (hexane/AcOEt, 1:1) to give the Wittig reaction product (138 mg) as a colorless oil. A solution of the product and aqueous HCl (12 M, 1 mL) in THF (14 mL) was stirred at 0 °C for 30 min, and then saturated aqueous $NaHCO_3$ was added. The reaction mixture was concentrated and partitioned between AcOEt and saturated aqueous $NaHCO_3$, and the organic layer was washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by silica gel column chromatography (hexane/AcOEt, 1:1) to give **11** as an amorphous pale yellow solid (123 mg, 0.303 mmol, 77%): $[\alpha]_D^{20}$ −32.2 (*c* 1.01, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 9.82 (t, *J* = 2.3 Hz, 1H), 7.33–7.30 (m, 7H), 7.15–7.13 (m, 6H), 2.52 (ddd, *J* = 13.6, 5.9, 2.3 Hz, 1H), 2.35 (ddd, *J* = 13.6, 7.2, 2.3 Hz, 1H), 1.57–1.53 (m, 2H), 1.46 (s, 3H), 1.26–1.19 (m, 1H), 0.78–0.74 (m, 1H); ^{13}C NMR(125 MHz, $CDCl_3$) δ 202.2, 141.7, 139.1, 136.9, 130.0, 127.9, 127.8, 125.3, 74.8, 47.9, 15.0, 13.6, 13.2, 11.5; HR-MS (EI) calcd for $C_{28}H_{26}N_2O$ 406.2045. Found 406.2043 (M^+).

3.5. (1*R*,2*S*)-2-[2-(4-Chlorobenzylamino)ethyl]-1-(5(4)-methyl-1*H*-imidazol-4(5)-yl)cyclopropane (4)

Compound **4** was obtained as dihydrochloride (white hydroscopic amorphus solid, 16 mg, 43 mmol) from **11** (39 mg, 96 mmol) as described for the preparation of dihydrochloride of **5**: $[\alpha]_D^{21}$ −52.6 (*c* 1.04, CH_3OH, dihydrochloride); ^1H NMR (500 MHz, CD_3OD) δ 8.63 (s, 1H), 7.56 (d, J = 8.6 Hz, 1H) 7.47 (d, J = 8.6 Hz, 1H) 4.24 (s, 2H), 3.25–3.22 (m, 2H), 2.33 (s, 3H), 1.98–1.93 (m, 1H), 1.83–1.73 (m, 2H), 1.30–1.23 (m, 1H), 1.09–1.05 (m, 1H), 1.02–0.98 (m,1H); ^{13}C NMR(125 MHz, CD_3OD) δ 136.7, 132.9, 132.4, 131.4, 130.5, 130.4, 127.2, 51.6, 48.1, 30.9, 18.3, 13.4, 12.4, 9.1; LR-MS (EI) *m*/*z* 289 ($(M-2HCl)^+$); HR-MS (EI) calcd for $C_{16}H_{20}ClN_3$ 289.1346. Found 289.1350 ($(M-2HCl)^+$); Anal. Calcd for $C_{16}H_{20}ClN_3{\cdot}0.2H_2O$ (free amine): C, 65.50; H, 7.01; N, 14.32. Found: C, 65.66; H, 7.09; N, 14.32.

3.6. Calculations

All ab initio and DFT calculations were performed using the GAUSSIAN 03 W. The C5′–C1′–C1–H1dihedral angle of the compounds was rotated from 0° to 360° at the intervals of 10°, and the conformations were optimized at B3LYP/6-31G*. Finally, single point energies were calculated at RB3LYP/6-31G*.

3.7. Binding assay with human histamine receptors

The assay was performed according to the method described previously.[5b]

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