Organic &
Biomolecular
Chemistry

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 736

www.rsc.org/obc

PAPER

Cyclopropane-based stereochemical diversity-oriented conformational restriction strategy: Histamine H_3 and/or H_4 receptor ligands with the 2,3-methanobutane backbone

Mizuki Watanabe,[a] Takaaki Kobayashi,[a] Takatsugu Hirokawa,[b] Akira Yoshida,[c] Yoshihiko Ito,[c] Shizuo Yamada,[c] Naoki Orimoto,[d] Yasundo Yamasaki,[d] Mitsuhiro Arisawa[a] and Satoshi Shuto*[a]

Received 1st September 2011, Accepted 11th October 2011
DOI: 10.1039/c1ob06496g

The stereochemical diversity-oriented conformational restriction strategy can be an efficient method for developing specific ligands for drug target proteins. To develop potent histamine H_3 and/or H_4 receptor ligands, a series of conformationally restricted analogs of histamine with a chiral *trans*- or *cis*-4-amino-2,3-methano-1-(1*H*-imidazol-4-yl)butane structure was designed based on this strategy. These stereochemically diverse compounds were synthesized from previously developed versatile chiral cyclopropane units. Among these analogs, a *trans*-cyclopropane-type compound, (2*S*,3*R*)-4-(4-chlorobenzylamino)-2,3-methano-1-(1*H*-imidazol-4-yl)butane (**5b**), has remarkable antagonistic activity to both the H_3 ($K_i = 4.4$ nM) and H_4 ($K_i = 5.5$ nM) receptors, and a *cis*-cyclopropane-type compound, (2*R*,3*R*)-4-amino-2,3-methano-1-(1*H*-imidazol-4-yl)butane (**6a**), is a potent and selective H_3 receptor partial agonist ($K_i = 5.4$ nM). Although (2*S*,3*R*)-4-amino-2,3-methano-1-(1*H*-imidazol-4-yl)butane (**5a**) does not have a hydrophobic group which the usual H_3 receptor antagonists have, it was found to be a potent H_3 receptor antagonist ($K_i = 20.1$ nM). Thus, a variety of compounds with different pharmacological properties depending on the cyclopropane backbones and also on the side-chain functional groups were identified. In addition to the previously used 1,2-methanobutane backbone, the 2,3-methanobutane backbone also worked effectively as a cyclopropane-based conformational restriction structure. Therefore, the combination of these two cyclopropane backbones increases the stereochemical and three-dimensional diversity of compounds in this strategy, which can provide a variety of useful compounds with different pharmacological properties.

Introduction

The histamine H_3 receptor, a member of the G_i protein-coupled receptors (GPCRs) distributed mainly in the central nervous system, is of interest as a potential drug target.[1] Agonists and antagonists to the H_3 receptor are considered to be potential drugs for the treatment of sleep disorders, migraines, asthma, inflammation, or ulcers,[2a] and for the treatment of Alzheimer's disease, attention-deficit/hyperactivity disorder (ADHD), schizophrenia, depression, dementia, or epilepsy,[2b] respectively.

On the other hand, the histamine H_4 receptor, also one of the GPCRs, is expressed in immunocytes, such as eosinophils or mast cells, and chemotaxis of these cells *via* histamine is triggered through H_4 receptor activation.[3a] Accordingly, H_4 receptor antagonists may be effectively used in new therapeutic modalities for the treatment of allergic diseases.[3b,c]

Although GPCRs, including the H_3 and H_4 receptors, are important targets for drug development,[4] structural analysis of GPCRs is 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.[5] Therefore, structural data on the drug target GPCRs are generally poor, and a method for effectively identifying compounds that target GPCRs without any structural data is required in drug development. Thus, we previously reported a stereochemical diversity-oriented conformational restriction strategy to develop compounds that bind selectively to structure-unknown target proteins such as GPCRs.[6,7] To realize the strategy, we devised versatile chiral cyclopropane units with different stereochemistries,[6a,c] shown in Fig. 1, and, by using these units, a series of cyclopropane-based conformationally restricted analogs[8] with

---

[a] *Faculty of Pharmaceutical Sciences, Hokkaido University, Kita-ku, Sapporo, 060-0812, Japan. E-mail: shu@pharm.hokudai.ac.jp*
[b] *Computational Biology Research Center, National Institute of Advanced Industrial Science and Technology, Aomi, Koutou-ku, Tokyo, 135-0064, Japan*
[c] *Department of Pharmacokinetics and Pharmacodynamics and Global Center of Excellence (COE), School of Pharmaceutical Sciences, University of Shizuoka, 52-1 Yada, Suruga-ku, Shizuoka, 422-8526, Japan*
[d] *Hanno Research Center, Taiho Pharmaceutical Co. Lrd., Misugidai, Hanno, 357-8527, Japan*

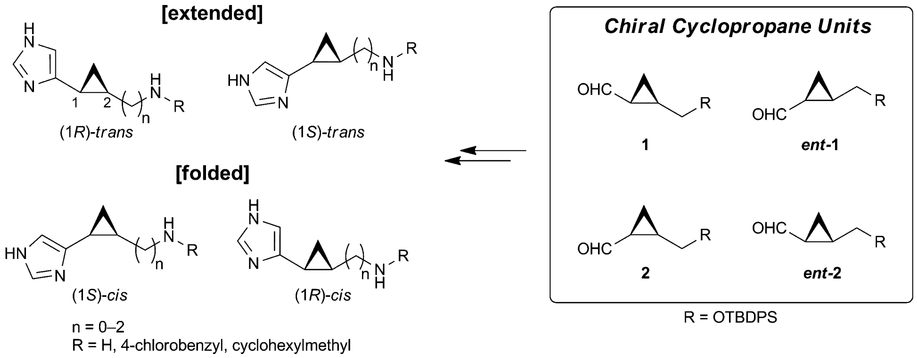


Fig. 1 Conformationally restricted analogs of histamine having the 1,2-methanoalkylimidazole backbone prepared from chiral cyclopropane units.

stereochemical diversity can be designed and synthesized effectively.

Based on the strategy, we actually designed a series of conformationally restricted analogs of histamine with different stereochemistries, which were synthesized from the chiral cyclopropane units (Fig. 1).[6] In these conformationally restricted analogs having an aminoalkyl-1,2-methanoimidazole backbone, the imidazole and the amino side-chain moieties are located in a variety of spatial arrangements due to the conformationally restricted 1,2-methanoalkyl backbone. Consequently, a series of these analogs is not only stereochemically diverse but also three-dimensionally diverse as a molecule. Some of these analogs shown in Fig. 2 were identified as potent histamine receptor ligands; *e.g.*, AEIC (**3**) with a (1*S*)-*cis*-cyclopropane structure is the first highly selective H_3 receptor agonist,[6b] and (1*R*,2*S*)-2-[2-(4-chlorobenzylamino)ethyl]-1-(1*H*-imidazol-4-yl)cyclopropane [(*R*)-CEIC (**4**)] with a (1*R*)-*trans*-cyclopropane structure and its enantiomer (*S*)-CEIC (***ent*-4**) with a (1*S*)-*trans*-cyclopropane structure were highly potent antagonists to both the H_3 receptor and the H_4 receptor.[6c]

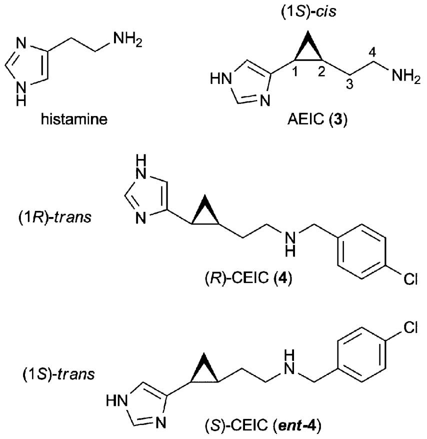


Fig. 2 Histamine and its conformationally restricted analogs having the 1,2-methanobutylimidazole backbone.

In the course of our studies to develop further potent H_3 and H_4 receptor ligands, we newly designed a series of conformationally restricted analogs of histamine based on the stereochemical diversity-oriented strategy, namely **5a**,**b** and **6a**,**b**, and their enantiomers, ***ent*-5a**,**b** and ***ent*-6a**,**b**, all having a 2,3-methanobutylimidazole structure (Fig. 3). In this report, we describe the design, synthesis, and pharmacological effects of these compounds.

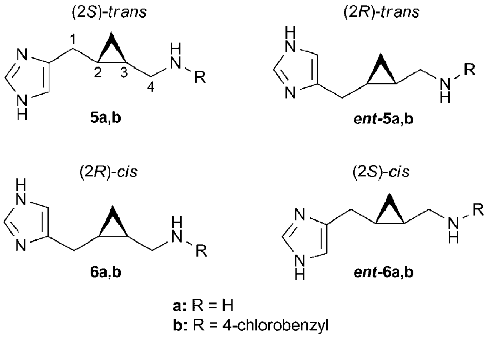
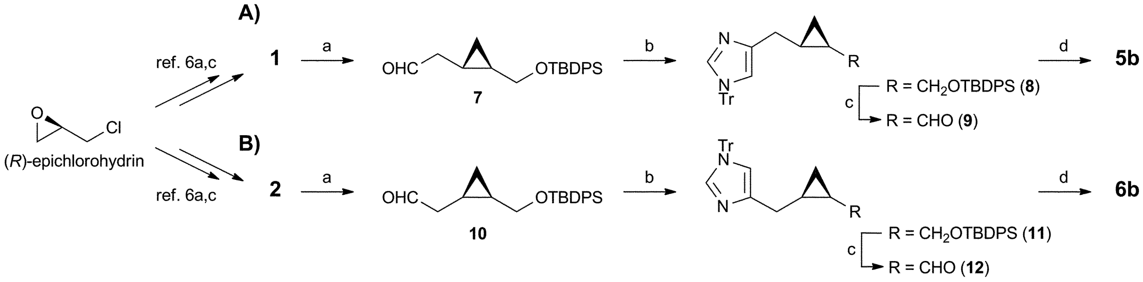


Fig. 3 Conformationally restricted analogs of histamine having the 2,3-methanobutylimidazole backbone.

Results and discussion

Design of compounds

Our previous studies demonstrated that conformational restriction of histamine by the 4-amino-1,2-methanobutane backbone was effective for the H_3 and/or H_4 receptor binding, where the folded *cis*-cyclopropane structure like AEIC (**3**) and the extended *trans*-cyclopropane structure like (*R*)- and (*S*)-CEIC (**4** and ***ent*-4**) are suitable for the binding as an agonist and an antagonist, respectively.[6b,c] They also showed that functional conversion of an agonist into an antagonist could occur by introducing a hydrophobic group, such as a chlorobenzyl group,[2b] at the terminal primary amino moiety of the 4-amino-1,2-methanobutane backbone.[6c] Considering these results, we designed the regioisomeric derivatives of AEIC (**3**) and (*R*)- and (*S*)-CEIC (**4** and ***ent*-4**), which have a 4-amino-2,3-methanobutane backbone, as shown in Fig. 3, for identifying new H_3 and/or H_4 receptor ligands. In these compounds, the folded *cis*-cyclopropane or the extended *trans*-cyclopropane structure on the four carbon (butane) backbone is preserved, and accordingly, the imidazole and the basic nitrogen moieties, which are key components in these structures for binding to the histamine receptors, might be located in space similarly to those of the previously identified potent analogs having the 4-amino-1,2-methanobutane backbone. Also, the regioisomeric 2,3-methano structure could change spatial arrangement and flexibility around the imidazole and the basic



Scheme 1 *Conditions*: a) 1) MeOCH$_2$PPh$_3$Cl, NaN(TMS)$_2$, THF, 0 °C, 2) HCl, aq. acetone, 0 °C, 85% (**7**), 92% (**10**); b) 1) TosCH$_2$NC, NaCN, EtOH, 0 °C, 2) sat. NH$_3$ in EtOH, steel tube, 120 °C, 3) TrCl, pyridine, 48% (**8**), 51% (**11**); c) 1) TBAF, THF, 2) Dess–Martin periodinane, CH$_2$Cl$_2$, 78% (**9**), 65% (**12**); d) 1) 4-chlorobenzylamine, 2-picoline borane, AcOH, MeOH, 2) TrCl, Et$_3$N, CH$_2$Cl$_2$, 3) HCl, aq. EtOH, 78 °C, 30% (**5b**), 49% (**6b**).

nitrogen moieties, compared with those in the 1,2-methano lead compounds AEIC (**3**) and (*R*)- and (*S*)-CEIC (**4** and ***ent*-4**), which would affect the biological activity. We hoped to develop both agonists and antagonists, and therefore, compounds with a free primary amino function (**a**-series, as agonists) and compounds with a 4-chlorobenzylamino function (**b**-series, as antagonists) were designed for synthesis.

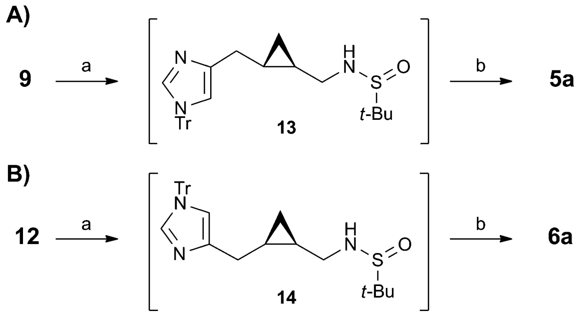
Thus, we expected that the 2,3-methanobutane backbone might be useful as an alternative conformationally restricted structure in the cyclopropane-based stereochemical diversity-oriented strategy.

Chemistry

Although much effort has been devoted to developing practical methods for preparing chiral cyclopropanes, synthesizing cyclopropane derivatives with a desired stereochemistry is often troublesome.[9] We devised the chiral units (Fig. 1), which are composed of four stereoisomeric cyclopropane derivatives bearing two adjacent carbon substituents in a *trans* or *cis* relationship, namely **1** and **2**, and their enantiomers, ***ent*-1** and ***ent*-2**, for cyclopropane-based conformational restriction.[6a] These units, which are generally useful for synthesizing various compounds having an asymmetric *trans*- or *cis*-cyclopropane structure,[6] were employed as the key intermediates in this study.

The synthesis of the *trans*-cyclopropane compound **5b** and the *cis*-cyclopropane compound **6b** with a 4-chlorobenzyl group (**b**-series) from the chiral cyclopropane unit **1** and **2**, respectively, is shown in Scheme 1. These units **1** and **2** were prepared from (*R*)-epichlorohydrin according to the method reported previously.[6a,c] The Wittig reaction of the unit **1** with MeOCH$_2$PPh$_3$Cl/NaN(TMS)$_2$, followed by acidic treatment gave the one carbon-elongated aldehyde **7**. The imidazole ring was constructed by treating **7** with tosylmethyl isocyanide and NaCN followed by heating in NH$_3$/EtOH.[10] The resulting imidazole product without purification was further treated with TrCl in pyridine to give the *N*-tritylimidazolylmethylcyclopropane derivative **8** in 48% overall yield. After removal of the silyl-protecting group of **8**, the resulting cyclopropanemethanol was oxidized to afford the aldehyde **9**. Introduction of a 4-chlorobenzylamino function at the terminal carbon was next investigated under reductive amination conditions. Thus, treatment of the aldehyde **9** with 4-chlorobenzylamine and 2-picoline borane in AcOH/MeOH, and subsequent acidic removal of the trityl group of the product gave the desired *trans*-cyclopropane-type target compound **5b** (Scheme 1A). By a similar procedure, the *cis*-cyclopropane-type target compound **6b** was synthesized from the *cis*-cyclopropane unit **2** (Scheme 1B). The enantiomers, ***ent*-5b** and ***ent*-6b**, were also synthesized from ***ent*-1** and ***ent*-2**, respectively.

The synthesis of **5a** and **6a** with a terminal primary amine (**a**-series) is shown in Scheme 2. Treatment of the aldehyde **9** with *t*-BuS(O)NH$_2$ and CuSO$_4$ in CH$_2$Cl$_2$ gave the corresponding sulfinylimine product, which was, without purification, reduced with NaBH$_4$/MeOH to afford the sulfinylamide **13**. Simultaneous removal of the trityl and sulfinyl groups by treating **13** with HCl in EtOH produced the target *trans*-cyclopropane-type compound **5a** (Scheme 2A). Similarly, the *cis*-cyclopropane-type compound **6a** was prepared from the *cis*-cyclopropane aldehyde **12** (Scheme 2B). The corresponding enantiomers, ***ent*-5a** and ***ent*-6a**, were also synthesized from the *trans*- and *cis*-cyclopropane aldehydes, ***ent*-9** and ***ent*-12**, respectively.



Scheme 2 *Conditions*: a) 1) *t*-BuS(O)NH$_2$, CuSO$_4$, CH$_2$Cl$_2$, 2) NaBH$_4$, MeOH, 0 °C; b) HCl, EtOH, 78 °C, 50% from **9** (**5a**), 59% from **12** (**6a**).

Pharmacological effects

The binding affinities of the conformationally restricted analogs with the 2,3-methanobutane backbone for the human H$_3$ receptor subtype using [^{3}H]N^{α}-methylhistamine and also for the human H$_4$ receptor subtype using [^{3}H]histamine were investigated, according to the previously reported procedure.[6c]

The binding affinities of the compounds for the H$_3$ receptor are summarized in Table 1. All of the synthesized compounds inhibited the specific binding of [^{3}H]N^{α}-methylhistamine to the H$_3$ receptor in a concentration-dependent manner. Of these compounds, all the *trans*-analogs, **5a**, ***ent*-5a**, **5b**, and ***ent*-5b**, had

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

		H_3			H_4			Selectivity
Compound	Structure	K_i (nM)	act.[b] (%)	inh.[c] (%)	K_i (nM)	act.[b] (%)	inh.[c] (%)	$K_i(H_3)/K_i(H_4)$
5a	2,3-M[d]/(2*S*)-*trans*	20.1 ± 5.1	2.5	94	119 ± 25	11	45	0.17
***ent*-5a**	2,3-M/(2*R*)-*trans*	9.3 ± 0.8	17	72	50.9 ± 11	30	40	0.18
6a	2,3-M/(2*R*)-*cis*	5.4 ± 1.1	18	57	113 ± 30	24	−1.4	0.048
***ent*-6a**	2,3-M/(2*S*)-*cis*	172 ± 39	5.0	41	222 ± 23	47	6.4	0.77
5b	2,3-M/(2*S*)-*trans*	4.4 ± 0.2	0	99	5.5 ± 0.6	0	100	0.80
***ent*-5b**	2,3-M/(2*R*)-*trans*	21.1 ± 5.1	0	99	23.2 ± 3.6	5.0	94	0.91
6b	2,3-M/(2*R*)-*cis*	110 ± 16	1.8	90	172 ± 40	3.2	72	0.64
***ent*-6b**	2,3-M/(2*S*)-*cis*	103 ± 13	6.7	86	33.5 ± 2.9	15	68	3.1
AEIC (**3**)[e]	1,2-M[d]/(1*S*)-*cis*	1.3 ± 0.2	100	—	—	—	—	—
(*R*)-CEIC (**4**)[f]	1,2-M/(1*R*)-*trans*	8.4 ± 1.5	0	100	7.6 ± 0.4	0	>100	1.1
(*S*)-CEIC (***ent*-4**)[f]	1,2-M/(1*S*)-*trans*	3.6 ±0.4	0	100	37.2 ±2.7	0	>100	0.097
Thioperamide[f]	—	51.1 ± 3.8	—	99	124 ±14	—	90	0.41

[a] Assay was carried out with cell membranes expressing human H_3 or H_4 receptor subtypes (n = 3–4). [b] Relative potency of compound (10^{-5} M) to histamine (10^{-5} M) for the receptor activation. [c] Inhibitory effect of compound (10^{-5} M) on the agonistic activity of histamine (10^{-6} M). [d] 1,2-M and 2,3-M mean 1,2-methano and 2,3-methano, respectively. [e] Data with rat H_3 receptor taken from ref. 6b. [f] Data taken from ref. 6c.

remarkably more potent activity (K_i < 30 nM) than the well-known H_3 receptor antagonist thioperamide (K_i = 51.1 nM). On the other hand, the *cis*-analogs showed relatively weaker affinity for the H_3 receptor than the *trans*-analogs, except for the (2*R*)-*cis*-analog **6a** (K_i = 5.4 nM). In order of the binding affinities, these compounds ranked as **5b**, **6a** > ***ent*-5a** > **5a**, ***ent*-5b** > ***ent*-6b**, **6b** > ***ent*-6a**, where ***ent*-5a**, **6a**, and **5b** had a significant nM level K_i.

The binding affinities of the compounds for the human H_4 receptor subtype are also summarized in Table 1. The *trans*-analogs, **5b**, ***ent*-5b**, and *cis*-analog ***ent*-6b** had significant activity ($K_i \leq 30$ nM), with **5b** being the most potent (K_i = 5.5 nM).

The relative affinity of these compounds for the H_3 and the H_4 receptors would indicate that a hydrophobic group might be required for high affinity for the H_4 receptor but not for the H_3 receptor, as shown with the non-hydrophobic analog **6a** (K_i = 5.4 nM for H_3, K_i = 113 nM for H_4) and the hydrophobic analog **5b** (K_i = 4.4 nM for H_3, K_i = 5.5 nM for H_4). Our results are consistent with the previous reports on the histamine receptor ligands.[11]

The function of the compounds on human histamine H_3 and H_4 receptor subtypes, which were expressed individually in 293-EBNA cells, was next investigated by luciferase reporter gene assay.[6b] The results are also summarized in Table 1.

All the **b**-series compounds having a hydrophobic 4-chlorobenzyl function were antagonists in accordance with the previous results of the histamine receptor ligands.[2b,6c] The (2*S*)-*trans*-analog **5b** with the 2,3-methanobutane backbone was a highly potent antagonist to both the H_3 and H_4 receptors with K_i values of 4.4 nM (for H_3) and 5.5 nM (for H_4), which was more potent than its regioisomeric parent compound (*R*)-CEIC (**4**) with the 1,2-methanobutane backbone. While (*S*)-CEIC (***ent*-4**) with the 1,2-methanobutane backbone was a H_3 receptor selective antagonist (K_i (H_3)/K_i (H_4) = 0.097), its regioisomeric *trans*-analog ***ent*-5b** with the 2,3-methanobutane backbone showed non-selective moderate antagonistic effects on both of the receptors (K_i (H_3)/K_i (H_4) = 0.91).

Based on the previous SAR studies on H_3 and H_4 receptor ligands,[2a,6b] we expected that the **a**-series compounds having the primary amino side-chain without a hydrophobic group would be full agonists. However, the activation potencies for the receptors of these compounds relative to histamine were less than 50%, as shown in Table 1. These results indicate that ***ent*-5a**, **6a**, and ***ent*-6a** work as partial agonists to both of the H_3 and H_4 receptors. Furthermore, compound **5a** with the (2*S*)-*trans*-cyclopropane structure almost completely inhibited activation of the H_3 receptor by histamine (94% inhibition). Thus, although **5a** does not have a hydrophobic group which H_3 receptor antagonists usually have, unexpectedly, it was shown to be an H_3 receptor antagonist.[12] Compound **6a** is the regioisomeric *cis*-2,3-methanobutane analog of the parent compound AEIC (**3**) with the *cis*-1,2-methanobutane backbone, and both **6a** and **3** are selectively and highly active at the H_3 receptor (K_i = 5.4 nM and 1.3 nM, respectively). However, these two regioisomers have functionally different effects on the receptor, *i.e.*, **6a** was a partial agonist (18% activation), while **3** was a full agonist (100% activation).

Docking simulation by homology modeling

We previously constructed a three-dimensional model of the H_3 receptor[6d] based on a structural template from the crystal structure of the human β_2-adrenergic GPCR recently reported by Cherezov and co-workers.[5a] Using the model, docking simulations of a series of cyclopropane-based H_3 receptor ligands were performed and a reliable correlation between binding score and pK_i was obtained.[6d]

Therefore, in order to investigate the binding modes of the conformationally restricted analogs with the 2,3-methanobutane backbone to the H_3 receptor, docking simulations of the three potent ligands (***ent*-5a**, **6a**, and **5b**) and also the three less potent ligands (***ent*-6a**, **6b**, and ***ent*-6b**) were carried out by using the H_3 receptor homology model described above, and the binding modes were compared with that of AEIC (**3**) with the 1,2-methanobutane backbone. As shown in Fig. 4a, the proposed binding modes of the three potent ligands are well-superimposed with that of the potent lead compound **3**, especially at the imidazole ring and the basic nitrogen, which are important for the binding to the receptor. On the other hand, as shown in Fig. 4b, the proposed binding modes of the three less potent ligands and that of **3** are not as well superimposed. These results suggest that this homology

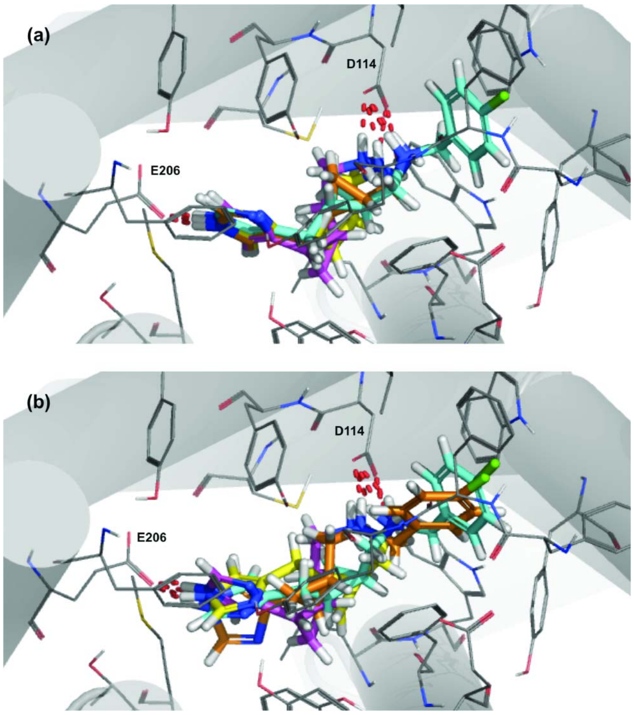


Fig. 4 Proposed models for the three potent ligands ***ent*-5a**, **6a**, **5b** and the lead compound **3** (a) and the three less potent ligands **6b**, ***ent*-6a**, ***ent*-6b** and **3** (b) binding to the homology model of the H_3 receptor[6d] from docking simulation. Carbon atoms are shown in magenta for **3**, cyan for **5b** and **6b**, yellow for **6a** and ***ent*-6a**, and orange for ***ent*-5a** and ***ent*-6b**, respectively. Hydrogen bonding and salt bridge between side-chain carboxyl group of Glu206 and an imidazole of the ligands, and between that of Asp114 and an amino group of the ligands are depicted by red dots.

model can be useful for investigation the binding modes of the H_3 receptor ligands and that the bioactive conformations of these potent ligands are analogous.

As described above, the stereochemical diversity-oriented conformational restriction strategy, employing the 2,3-methanobutane backbone, was shown to be useful for developing potent ligands of the H_3 and/or H_4 receptor in this study. It is important to note that, in addition to the previously used 1,2-methanobutane backbone, the regioisomeric 2,3-methanobutane backbone also worked effectively as an alternative cyclopropane-based conformational restriction structure. Thus, the combinational use of these two backbones not only increases the stereochemical diversity but also increases three-dimensional structural diversity of the compounds in this strategy, which can provide a variety of active compounds with different pharmacological properties.

Conclusions

We designed a series of conformationally restricted histamine analogs with a chiral *trans*- or *cis*-2,3-methanobutane backbone based on the stereochemical diversity-oriented strategy. These four stereochemical types of analogs were systematically synthesized from optically active epichlorohydrins *via* the versatile chiral cyclopropane units. Pharmacological properties of these analogs for the human H_3 and H_4 receptors were shown to be different depending on the stereochemistry of the cyclopropane backbones. Among the hydrophobic analogs (**b**-series), a *trans*-cyclopropane structure was preferred to a *cis*-cyclopropane one for both the H_3 and H_4 receptors. On the other hand, among the non-hydrophobic analogs (**a**-series), the structure of the most potent analog **6a** to both of the receptor subtypes was a *cis*-cyclopropane. In this study, a couple of potent H_3 and/or H_4 receptor ligands with a low nM K_i were identified. Analog **6a**, which has a (2*R*)-*cis*-2,3-methanobutane backbone, was the highest selective H_3 ligand, and analog **5b**, which has a (2*S*)-*trans*-2,3-methanobutane backbone, was the most potent H_3/H_4 dual ligand. Thus, the 2,3-methanobutane backbone worked effectively as the backbone of the conformationally restricted histamine analogs with stereochemical diversity as well as the 1,2-methanobutane. These differences in the stereochemistry of these backbones affected the potency and selectivity of the ligands. Therefore, the stereochemical diversity-oriented approach can be an effective strategy in medicinal chemistry studies.

Experimental

Chemical shifts (δ) are reported in ppm downfield from Me_4Si or CD_2HOD (3.31 ppm) (^1H) and $CDCl_3$ (77.0 ppm) or CD_3OD (49.0 ppm) (^{13}C). All of the ^1H-NMR assignments described were in agreement with COSY spectra. Thin-layer chromatography was done on Merck coated plate $60F_{254}$. Silica gel, Iatron beads and NH silica gel chromatographies were done on Merck silica gel 5715, Iatron 6RS-8060 (Mitsubishi Kagaku Iatron, Inc), and Chromatorex® (Fuji Silysia Chemical Ltd.), respectively. Reactions were carried out under an argon atmosphere except for hydrous reactions.

(2*S*,3*R*)-4-*tert*-Butyldiphenylsilyloxy-2,3-methanobutyraldehyde (7)

To a suspension of $MeOCH_2PPh_3Cl$ (3.63 g, 10.6 mmol) in THF (50 mL) was added $NaN(TMS)_2$ (1.0 M in THF, 9.12 mL, 9.12 mmol) at 0 °C, and the mixture was stirred at the same temperature for 20 min. To the resulting solution was added a solution of **1**[6a] (2.27 g, 7.60 mmol) in THF (10 mL) at 0 °C, and the reaction mixture was stirred at the same temperature for 5 h. After addition of saturated aqueous NH_4Cl, the solvent was evaporated, and the residue was partitioned between AcOEt and saturated aqueous NH_4Cl. The organic layer was washed with brine, dried (Na_2SO_4) and evaporated. The residue was purified by silica gel column chromatography (3% AcOEt in hexane) to give the enol ether product as an oil. To a solution of the product in acetone (40 mL) was added aqueous HCl (12 M, 20 mL), and the mixture was vigorously stirred at 0 °C for 10 s. Immediately, the mixture was poured into saturated aqueous $NaHCO_3$ (300 mL), and the resulting solution was extracted with AcOEt. The organic layer was washed with saturated aqueous $NaHCO_3$, brine, dried (Na_2SO_4) and evaporated. The residue was purified by silica gel column chromatography (5% AcOEt in hexane) to give **7** (2.27 g, 85%) as a colorless oil: $[\alpha]_D^{22}$ −12.0 (*c* 0.95, $CHCl_3$); ^1H-NMR (400 MHz, $CDCl_3$) δ 0.35 (1 H, m, cyclopropyl-CH_2), 0.52 (1 H, m, cyclopropyl-CH_2), 0.84 (1 H, m, cyclopropyl-CH), 0.91 (1 H, m, cyclopropyl-CH), 1.01 (9 H, s, *t*Bu), 2.27 (2 H, m, CH_2CHO), 3.49

(1 H, dd, J = 6.4, 10.7 Hz, CH_2OTBDPS), 3.69 (1 H, dd, J = 5.7, 10.7 Hz, CH_2OTBDPS), 7.35–7.44 (6 H, m, aromatic), 7.51–7.72 (4 H, m, aromatic), 9.75 (1 H, dd, J = 2.1, 2.3 Hz, CHO); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 9.5, 10.2, 19.4, 20.5, 27.0, 47.6, 66.6, 127.5, 129.5, 133.7, 135.4, 201.9; LRMS (FAB) m/z 353 [(M+H)$^+$]; HRMS (FAB) calcd for $C_{22}H_{29}O_2Si$ 353.1937, found 353.1928 [(M+H)$^+$]; Found: C, 75.13; H, 8.05. Calc. for $C_{22}H_{28}O_2Si$: C, 74.95; H, 8.01%.

(2*R*,3*S*)-4-*tert*-Butyldiphenylsilyloxy-2,3-methanobutyraldehyde (*ent*-7)

Compound ***ent*-7** (2.41 g, 83%, colorless oil) was prepared from ***ent*-1**[6a] (2.80 g, 8.27 mmol) as described for the preparation of **7**: $[\alpha]_D^{22}$ +11.5 (c 0.98, $CHCl_3$); LRMS (FAB) m/z 353 [(M+H)$^+$]; HRMS (FAB) calcd for $C_{22}H_{29}O_2Si$ 353.1937, found 353.1925 [(M+H)$^+$]; Found: C, 75.02; H, 7.98. Calc. for $C_{22}H_{28}O_2Si$: C, 74.95; H, 8.01%. ^{1}H- and ^{13}C-NMR spectra were consistent with those of **7**.

(2*R*,3*R*)-4-*tert*-Butyldiphenylsilyloxy-2,3-methanobutyraldehyde (10)

Compound **10** (2.27 g, 92%, colorless oil) was prepared from **2**[6c] (2.37 g, 7.00 mmol) as described for the preparation of **7**: $[\alpha]_D^{24}$ –0.8 (c 1.15, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.05 (1 H, dd, J = 5.4, 10.6 Hz, cyclopropyl-CH_2), 0.77 (1 H, m, cyclopropyl-CH_2), 1.04 (9 H, s, *t*Bu), 1.08–1.26 (2 H, m, cyclopropyl-CH ×2), 2.32 (1 H, m, CH_2CHO), 2.51 (1 H, m, CH_2CHO), 3.43 (1 H, dd, J = 8.8, 11.3 Hz, CH_2OTBDPS), 3.89 (1 H, dd, J = 5.4, 11.3 Hz, CH_2OTBDPS), 7.35–7.43 (6 H, m, aromatic), 7.64–7.69 (4 H, m, aromatic), 9.83 (1 H, t, J = 1.8 Hz, CHO); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 8.79, 9.30, 17.1, 19.2, 26.9, 42.9, 63.8, 127.6, 129.6, 133.6, 135.4, 135.5, 202.3; LRMS (FAB) m/z 353 [(M+H)$^+$]; HRMS (FAB) calcd for $C_{22}H_{29}O_2Si$ 353.1937, found 353.1938 [(M+H)$^+$]; Found: C, 74.90; H, 8.01. Calc. for $C_{22}H_{28}O_2Si$: C, 74.95; H, 8.01%.

(2*S*,3*S*)-4-*tert*-Butyldiphenylsilyloxy-2,3-methanobutyraldehyde (*ent*-10)

Compound ***ent*-10** (2.15 g, 80%, colorless oil) was prepared from ***ent*-2**[6c] (2.62 g, 7.68 mmol) as described for the preparation of **7**: $[\alpha]_D^{24}$ +0.14 (c 1.02, $CHCl_3$); LRMS (FAB) m/z 353 [(M+H)$^+$]; HRMS (FAB) calcd for $C_{22}H_{29}O_2Si$ 353.1937, found 353.1940 [(M+H)$^+$]; Found: C, 75.07; H, 8.11. Calc. for $C_{22}H_{28}O_2Si$: C, 74.95; H, 8.01%. ^{1}H- and ^{13}C-NMR spectra were consistent with those of **10**.

(2*S*,3*R*)-4-*tert*-Butyldiphenylsilyloxy-2,3-methano-1-(1-triphenylmethyl-1*H*-imidazol-4-yl)butane (8)

To a suspension of tosylmethyl isocyanide (667 mg, 3.43 mmol) and **7** (1.21 g, 3.43 mmol) in absolute EtOH (8 mL) was added sodium cyanide (17 mg, 0.34 mmol) at 0 °C, and the resulting mixture was stirred at the same temperature for 30 min. After the solvent was evaporated, the residue in a saturated solution of ammonia in absolute EtOH (60 mL) was heated at 120 °C in a steel tube for 24 h. After cooling, the solvent was evaporated, and the residue was co-evaporated with pyridine (×3). After drying the residue *in vacuo*, a solution of the residue and trityl chloride (954 mg, 3.43 mmol) in pyridine (10 mL) was stirred at room temperature for 12 h. After the solvent was evaporated, the residue was partitioned between AcOEt and aqueous HCl (1 M). The organic layer was washed with saturated aqueous $NaHCO_3$, brine, dried (Na_2SO_4), and evaporated. The residue was purified by silica gel column chromatography (20–50% AcOEt in hexane) to give **8** (1.03 g, 48%) as a colorless oil: $[\alpha]_D^{22}$ –18.7 (c 1.10, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.31–0.39 (2 H, m, cyclopropyl-CH_2), 0.81–0.90 (2 H, m, cyclopropyl-CH ×2), 1.02 (9 H, s, *t*Bu), 2.41 (1 H, dd, J = 6.8, 15.9 Hz, CH_2-imidazole), 2.59 (1 H, dd, J = 5.9, 15.9 Hz, CH_2-imidazole), 3.40 (1 H, dd, J = 6.3, 10.9 Hz, CH_2OTBDPS), 3.60 (1 H, dd, J = 5.4, 10.9 Hz, CH_2OTBDPS), 6.52 (1 H, s, imidazolyl) 7.11–7.13 (6 H, m, aromatic), 7.25–7.39 (16 H, m, aromatic & imidazolyl), 7.64–7.65 (4 H, m, aromatic); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 9.86, 15.8, 19.2, 20.4, 26.8, 32.2, 67.0, 75.0, 117.8, 127.5, 127.9, 129.4, 129.7, 134.0, 135.6, 138.2, 141.4, 142.5; LRMS (FAB) m/z 633 [(M+H)$^+$]; HRMS (FAB) calcd for $C_{43}H_{45}N_2OSi$ 633.3301; found 633.3299 [(M+H)$^+$]; Found: C, 81.55; H, 7.05; N, 4.37. Calc. for $C_{43}H_{44}N_2OSi$: C, 81.60; H, 7.01; N, 4.43%.

(2*R*,3*S*)-4-*tert*-Butyldiphenylsilyloxy-2,3-methano-1-(1-triphenylmethyl-1*H*-imidazol-4-yl)butane (*ent*-8)

Compound ***ent*-8** (755 mg, 43%, colorless oil) was prepared from ***ent*-7** (970 mg, 2.75 mmol) as described for the preparation of **8**: $[\alpha]_D^{22}$ +18.3 (c 1.35, $CHCl_3$); LRMS (FAB) m/z 633 [(M+H)$^+$]; HRMS (FAB) calcd for $C_{43}H_{45}N_2OSi$ 633.3301; found 633.3300 [(M+H)$^+$]; Found: C, 81.38; H, 6.91; N, 4.60. Calc. for $C_{43}H_{44}N_2OSi$: C, 81.60; H, 7.01; N, 4.43%. ^{1}H- and ^{13}C-NMR spectra were consistent with those of **8**.

(2*R*,3*R*)-4-*tert*-Butyldiphenylsilyloxy-2,3-methano-1-(1-triphenylmethyl-1*H*-imidazol-4-yl)butane (11)

Compound **11** (744 mg, 51%, colorless oil) was prepared from **10** (821 mg, 2.33 mmol) as described for the preparation of **8**: $[\alpha]_D^{23}$ +4.9 (c 1.01, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.04 (1 H, m, cyclopropyl-CH_2), 0.66 (1 H, m, cyclopropyl-CH_2), 1.03 (9 H, s, *t*Bu), 1.07–1.18 (2 H, m, cyclopropyl-CH ×2), 2.39 (1 H, dd, J = 7.9, 15.8 Hz, CH_2-imidazole), 2.75 (1 H, dd, J = 5.4, 15.8 Hz, CH_2-imidazole), 3.68 (2 H, d, J = 6.7 Hz, CH_2OTBDPS), 6.51 (1 H, s, imidazolyl) 7.11–7.13 (6 H, m, aromatic), 7.26–7.39 (16 H, m, aromatic & imidazolyl), 7.64–7.68 (4 H, m, aromatic); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 10.0, 15.6, 18.2, 19.5, 27.2, 28.0, 64.5, 75.3, 118.0, 127.8, 127.9, 128.2, 128.2, 129.7, 130.1, 134.4, 134.4, 135.9, 135.9, 138.6, 142.3, 142.9; LRMS (FAB) m/z 633 [(M+H)$^+$]; HRMS (FAB) calcd for $C_{43}H_{45}N_2OSi$ 633.3301; found 633.3300 [(M+H)$^+$]. Found: C, 81.84; H, 6.81; N, 4.21. Calc. for $C_{43}H_{44}N_2OSi$: C, 81.60; H, 7.01; N, 4.43%.

(2*S*,3*S*)-4-*tert*-Butyldiphenylsilyloxy-2,3-methano-1-(1-triphenylmethyl-1*H*-imidazol-4-yl)butane (*ent*-11)

Compound ***ent*-11** (922 mg, 58%, a colorless oil) was prepared from ***ent*-10** (890 mg, 2.52 mmol) as described for the preparation of **8**: $[\alpha]_D^{23}$ –4.6 (c 0.96, $CHCl_3$); LRMS (FAB) m/z 633 [(M+H)$^+$]; HRMS (FAB) calcd for $C_{43}H_{45}N_2OSi$ 633.3301; found 633.3310 [(M+H)$^+$]; Found: C, 81.77; H, 6.89; N, 4.18. Calc. for

$C_{43}H_{44}N_2OSi$: C, 81.60; H, 7.01; N, 4.43%. ^{1}H- and ^{13}C-NMR spectra were consistent with those of **11**.

(2*S*,3*R*)-4-Formyl-2,3-methano-1-(1-triphenylmethyl-1*H*-imidazol-4-yl)butane (9)

A mixture of **8** (633 mg, 1.00 mmol) and TBAF (1.0 M THF, 2.0 mL, 2.0 mmol) in THF (6 mL) was stirred at room temperature for 12 h. After the solvent was evaporated, the residue was purified by silica gel column chromatography (50% AcOEt in hexane then 3% MeOH in $CHCl_3$) to give an alcohol product. To a solution of the alcohol in CH_2Cl_2 (10 mL) was added Dess–Martin periodinane (509 mg, 1.20 mmol), and the resulting mixture was stirred at room temperature for 2 h. After addition of saturated aqueous $Na_2S_2O_3$/$NaHCO_3$ (1 : 3), the resulting mixture was stirred vigorously for 10 min. The mixture was extracted with AcOEt, and the organic layer was washed with saturated aqueous $NaHCO_3$, brine, dried (Na_2SO_4), and evaporated. The residue was purified by silica gel column chromatography (33% AcOEt in hexane) to give **9** (305 mg, 78%) as a light brown amorphous solid: $[\alpha]_D^{24}$ −26.0 (*c* 1.00, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.04 (1 H, m, cyclopropyl-CH_2), 1.32 (1 H, m, cyclopropyl-CH_2), 1.68–1.83 (2 H, m, cyclopropyl-CH ×2), 2.66 (2 H, d, J = 6.3 Hz, C*H*$_2$-imidazole), 6.57 (1 H, s, imidazolyl) 7.12–7.15 (6 H, m, aromatic), 7.32–7.36 (10 H, m, aromatic & imidazolyl), 9.01 (1 H, d, J = 5.3 Hz, C*HO*); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 12.8, 24.2, 27.2, 27.7, 75.1, 117.9, 127.9, 129.6, 138.4, 140.3, 142.5, 201.9; LRMS (EI) *m*/*z* 392 (M^+); HRMS (EI) calcd for $C_{27}H_{24}N_2O$ 392.1889; found 392.1880 (M^+); Found: C, 82.77; H, 6.39; N, 7.18. Calc. for $C_{27}H_{24}N_2O$: C, 82.62; H, 6.16; N, 7.14%.

(2*R*,3*S*)-4-Formyl-2,3-methano-1-(1-triphenylmethyl-1*H*-imidazol-4-yl)butane (*ent*-9)

Compound ***ent*-9** (305 mg, 78%, white amorphous solid) was prepared from ***ent*-8** (633 mg, 1.00 mmol) as described for the preparation of **9**: $[\alpha]_D^{24}$ +25.2 (*c* 1.00, $CHCl_3$); LRMS (EI) *m*/*z* 392 (M^+); HRMS (EI) calcd for $C_{27}H_{24}N_2O$ 392.1889; found 392.1890 (M^+); Found: C, 82.83; H, 6.23; N, 7.42. Calc. for $C_{27}H_{24}N_2O$: C, 82.62; H, 6.16; N, 7.14%. ^{1}H- and ^{13}C-NMR spectra were consistent with those of **9**.

(2*R*,3*R*)-4-Formyl-2,3-methano-1-(1-triphenylmethyl-1*H*-imidazol-4-yl)butane (12)

Compound **12** (259 mg, 65%, white amorphous solid) was prepared from **11** (637 mg, 1.01 mmol) as described for the preparation of **9**: $[\alpha]_D^{23}$ −24.5 (*c* 1.00, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.25–1.34 (2 H, m, cyclopropyl-CH_2), 1.83–1.97 (2 H, m, cyclopropyl-CH ×2), 2.67 (1 H, dd, J = 8.2, 15.5 Hz, C*H*$_2$-imidazole), 2.95 (1 H, dd, J = 6.3, 15.5 Hz, C*H*$_2$-imidazole), 6.53 (1 H, s, imidazolyl) 7.10–7.15 (6 H, m, aromatic), 7.31–7.34 (9 H, m, aromatic), 7.36 (1 H, s, imidazolyl), 9.38 (1 H, d, J = 5.0 Hz, C*HO*); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 15.0, 24.2, 27.2, 27.7, 75.1, 117.9, 127.8, 129.6, 138.4, 140.3, 142.2, 200.9; LRMS (EI) *m*/*z* 392 (M^+); HRMS (EI) calcd for $C_{27}H_{24}N_2O$ 392.1889; found 392.1890 (M^+); Found: C, 82.91; H, 6.00; N, 6.95. Calc. for $C_{27}H_{24}N_2O$: C, 82.62; H, 6.16; N, 7.14%.

(2*S*,3*S*)-4-Formyl-2,3-methano-1-(1-triphenylmethyl-1*H*-imidazol-4-yl)butane (*ent*-12)

Compound ***ent*-12** (290 mg, 65%, a white solid) was prepared from ***ent*-11** (720 mg, 1.14 mmol) as described for the preparation of **9**: $[\alpha]_D^{22}$ +25.0 (*c* 1.05, $CHCl_3$); LRMS (EI) *m*/*z* 392 (M^+); HRMS (EI) calcd for $C_{27}H_{24}N_2O$ 392.1889; found 392.1888 (M^+); Found: C, 82.78; H, 5.97; N, 6.90. Calc. for $C_{27}H_{24}N_2O$: C, 82.62; H, 6.16; N, 7.14%. ^{1}H- and ^{13}C-NMR spectra were consistent with those of **12**.

(2*S*,3*R*)-*trans*-4-(4-Chlorobenzylamino)-2,3-methano-1-(1*H*-imidazol-4-yl)butane (5b)

A mixture of **9** (48 mg, 0.12 mmol), 4-chlorobenzylamine (98%, 16 µL, 0.13 mmol) and 2-picoline borane (13 mg, 0.13 mmol) in MeOH/AcOH (10 : 1, 1.1 mL) was stirred at room temperature for 8 h. After the addition of aqueous HCl (1 M, 1 mL), the mixture was stirred at 0 °C for 10 min and then the solvent was evaporated. The residue was partitioned between Et_2O and aqueous NaOH (2 M), and the organic layer was washed with H_2O, brine, dried (Na_2SO_4), and evaporated. The residue was purified by neutral silica gel column chromatography (10–20% MeOH in $CHCl_3$) to give the crude amine product. A solution of the amine, trityl chloride (56 mg, 0.20 mmol) and Et_3N (28 µL, 0.20 mmol) in CH_2Cl_2 (1 mL) was stirred at room temperature for 12 h. After addition of MeOH (1 mL), the solvent was evaporated. The residue was partitioned between Et_2O and aqueous HCl (0.5 M), and the organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and evaporated. The residue was purified by neutral silica gel column chromatography (17–33% AcOEt in hexane) to give the amine as an amorphous solid. A solution of the amine in EtOH (2.0 mL)/aqueous HCl (4 M, 1.0 mL) was stirred at 78 °C for 2 h, and then the solvent was evaporated. The residue was partitioned between aqueous HCl (1 M) and CH_2Cl_2, and the aqueous layer was neutralized with aqueous NaOH (2 M). The resulting solution was extracted with Et_2O (×3), and the organic layer was washed with H_2O and brine, dried (Na_2SO_4), and evaporated. The residue was purified by Iatron beads column chromatography (0–100% MeOH in $CHCl_3$) to give **5b** (10 mg, 30%, colorless amorphous solid) as a free amine: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.47–0.54 (2 H, m, cyclopropyl-CH_2), 0.79–0.86 (2 H, m, cyclopropyl-CH ×2), 2.10–2.17 (2 H, m, C*H*$_2$-imidazole), 3.02–3.09 (2 H, m, C*H*$_2$NH), 3.75 (1 H, d, J = 13.2 Hz, benzyl-CH_2), 3.84 (1 H, d, J = 13.2 Hz, benzyl-CH_2), 6.77 (1 H, s, imidazolyl), 7.25–7.26 (2 H, m, aromatic), 7.30–7.32 (2 H, m, aromatic) 7.36 (1 H, s, imidazolyl); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 10.2, 17.2, 19.2, 29.3, 53.0, 53.4, 120.9, 128.7, 128.7, 129.6, 129.6, 133.1, 133.1, 134.1, 137.5; LRMS (EI) *m*/*z* 275 (M^+); HRMS (EI) calcd for $C_{15}H_{18}ClN_3$ 275.1189, found 275.1190 (M^+); Found: C, 65.03; H, 6.63; N, 15.49. Calc. for $C_{15}H_{18}ClN_3$: C, 65.33; H, 6.58; N, 15.24%; The free amine **5b** was dissolved in aqueous HCl (4 M), and the solvent was evaporated. The residue was triturated with Et_2O to give **5b dihydrochloride** (12 mg) as a white amorphous solid: $[\alpha]_D^{22}$ −25.2 (*c* 1.01, MeOH); ^{1}H-NMR (400 MHz, CD_3OD) δ 0.76 (2 H, m, cyclopropyl-CH_2), 1.18 (1 H, m, cyclopropyl-CH), 1.24 (1 H, m, cyclopropyl-CH), 2.58 (1 H, dd, J = 7.7, 14.5 Hz, C*H*$_2$-imidazole), 2.91–2.96 (2 H, m, C*H*$_2$NH), 3.14 (1 H, dd, J = 6.8, 14.5 Hz, C*H*$_2$-imidazole), 4.22 (2 H, s, benzyl-CH_2), 7.42 (1 H, s, imidazolyl), 7.47 (2 H, d, J = 8.2 Hz, aromatic), 7.55 (2 H, d, J = 8.2 Hz, aromatic), 8.83 (1 H, s, imidazolyl); LRMS (EI) m/z 275 [(M−2HCl)$^+$]; HRMS (EI) calcd for $C_{15}H_{18}ClN_3$ 275.1189, found 275.1189 [(M−2HCl)$^+$]; Found: C, 51.52; H, 5.86; N, 11.78. Calc. for $C_{15}H_{20}Cl_3N_3$: C, 51.67; H, 5.78; N, 12.05%.

(2*R*,3*S*)-*trans*-4-(4-Chlorobenzylamino)-2,3-methano-1-(1*H*-imidazol-4-yl)butane (*ent*-5b)

Compound ***ent*-5b** (18 mg, 60%, colorless amorphous solid) was prepared from ***ent*-9** (45 mg, 0.12 mmol) as described for the preparation of **5b**: LRMS (EI) m/z 275 (M$^+$); HRMS (EI) calcd for $C_{15}H_{18}ClN_3$ 275.1189, found 275.1185 (M$^+$); Found: C, 65.00; H, 6.79; N, 15.52. Calc. for $C_{15}H_{18}ClN_3$: C, 65.33; H, 6.58; N, 15.24%; ^{1}H- and ^{13}C-NMR spectra were consistent with those of **5b**; The free amine ***ent*-5b** was dissolved in aqueous HCl (4 M), and the solvent was then evaporated. The residue was triturated with Et_2O to give ***ent*-5b dihydrochloride** (20 mg) as a white amorphous solid: $[\alpha]_D^{22}$ +24.6 (c 1.10, MeOH); LRMS (EI) m/z 275 [(M−2HCl)$^+$]; HRMS (EI) calcd for $C_{15}H_{18}ClN_3$ 275.1189, found 275.1191 [(M−2HCl)$^+$]; Found: C, 51.39; H, 5.98; N, 11.81. Calc. for $C_{15}H_{20}Cl_3N_3$: C, 51.67; H, 5.78; N, 12.05%. ^{1}H-NMR spectrum was consistent with that of **5b dihydrochloride**.

(2*R*,3*R*)-*cis*-4-(4-Chlorobenzylamino)-2,3-methano-1-(1*H*-imidazol-4-yl)butane (6b)

Compound **6b** (27 mg, 49%, colorless amorphous solid) was prepared from **12** (78 mg, 0.20 mmol) as described for the preparation of **5b**: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.81 (1 H, dd, J = 5.7, 10.9 Hz, cyclopropyl-CH_2), 0.87 (1 H, m, cyclopropyl-CH_2), 1.02-1.10 (2 H, m, cyclopropyl-CH ×2), 2.08 (1 H, dd, J = 4.6, 15.5 Hz, CH_2-imidazole), 2.40 (1 H, t, J = 12.6 Hz, CH_2NH), 3.15 (1 H, dd, J = 2.3, 15.5 Hz, CH_2-imidazole), 3.34 (1 H, dd, J = 2.9, 12.6 Hz, CH_2NH), 3.78 (1 H, d, J = 12.6 Hz, benzyl-CH_2), 3.93 (1 H, d, J = 12.6 Hz, benzyl-CH_2), 6.76 (1 H, s, imidazolyl), 7.26 (1 H, s, imidazolyl), 7.30 (2 H, d, J = 8.6 Hz, aromatic), 7.35 (2 H, d, J = 8.6 Hz, aromatic); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 8.47, 15.3, 17.1, 24.4, 48.1, 53.0, 123.3, 128.9, 128.9, 129.7, 129.7, 131.3, 133.5, 134.8, 136.9; LRMS (EI) m/z 275 (M$^+$); HRMS (EI) calcd for $C_{15}H_{18}ClN_3$ 275.1189, found 275.1187 (M$^+$); Found: C, 65.10; H, 6.88; N, 14.93. Calc. for $C_{15}H_{18}ClN_3$: C, 65.33; H, 6.58; N, 15.24%; The free amine **6b** was dissolved in aqueous HCl (4 M), and the solvent was then evaporated. The residue was triturated with Et_2O to give **6b dihydrochloride** (30 mg) as a white solid: $[\alpha]_D^{22}$ −11.1 (c 0.96, MeOH); ^{1}H-NMR (400 MHz, CD_3OD) δ 0.56 (1 H, ddd, J = 5.4, 5.9, 11.3 Hz, cyclopropyl-CH_2), 1.06 (1 H, ddd, J = 8.6, 11.3, 12.6 Hz, cyclopropyl-CH_2), 1.36 (1 H, m, cyclopropyl-CH), 1.43 (1 H, m, cyclopropyl-CH), 2.74 (1 H, dd, J = 8.6, 16.3 Hz, CH_2-imidazole), 2.97 (1 H, dd, J = 6.3, 16.3 Hz, CH_2-imidazole), 3.05 (1 H, dd, J = 3.6, 12.7 Hz, CH_2NH), 3.41 (1 H, dd, J = 5.4, 12.7 Hz, CH_2NH), 4.24 (1 H, d, J = 13.1 Hz, benzyl-CH_2), 4.30 (1 H, d, J = 13.1 Hz, benzyl-CH_2), 7.44 (1 H, d, J = 1.1 Hz, imidazolyl), 7.48 (2 H, d, J = 8.6 Hz, aromatic), 7.58 (2 H, d, J = 8.6 Hz, aromatic), 8.84 (1 H, d, J = 1.1 Hz, imidazolyl); LRMS (EI) m/z 275 [(M−2HCl)$^+$]; HRMS (EI) calcd for $C_{15}H_{18}ClN_3$ 275.1189, found 275.1192 [(M−2HCl)$^+$]; Found: C, 51.42; H, 5.95; N, 11.88. Calc. for $C_{15}H_{20}Cl_3N_3$: C, 51.67; H, 5.78; N, 12.05%.

(2*S*,3*S*)-*cis*-4-(4-Chlorobenzylamino)-2,3-methano-1-(1*H*-imidazol-4-yl)butane (*ent*-6b)

Compound ***ent*-6b** (20 mg, 43%, white amorphous solid) was prepared from ***ent*-12** (69 mg, 0.17 mmol) as described for the preparation of **5b**; LRMS (EI) m/z 275 (M$^+$); HRMS (EI) calcd for $C_{15}H_{18}ClN_3$ 275.1189, found 275.1167 (M$^+$); Found: C, 65.14; H, 6.76; N, 15.00. Calc. for $C_{15}H_{18}ClN_3$: C, 65.33; H, 6.58; N, 15.24%; ^{1}H- and ^{13}C-NMR spectra were consistent with those of **6b**; The free amine ***ent*-6b** was dissolved in aqueous HCl (4 M), and the solvent was then evaporated. The residue was triturated with Et_2O to give ***ent*-6b dihydrochloride** (22 mg) as a white solid: $[\alpha]_D^{22}$ +10.8 (c 0.90, MeOH); LRMS (EI) m/z 275 [(M−2HCl)$^+$]; HRMS (EI) calcd for $C_{15}H_{18}ClN_3$ 275.1189, found 275.1188 [(M−2HCl)$^+$]; Found: C, 51.55; H, 5.96; N, 12.13. Calc. for $C_{15}H_{20}Cl_3N_3$: C, 51.67; H, 5.78; N, 12.05%. ^{1}H-NMR spectrum was consistent with that of **6b dihydrochloride**.

(2*S*,3*R*)-*trans*-4-Amino-2,3-methano-1-(1*H*-imidazol-4-yl)butane (5a)

A mixture of **9** (136 mg, 0.347 mmol), (±)-*tert*-butanesulfinamide (59 mg, 0.49 mmol) and anhydrous $CuSO_4$ (560 mg, 3.47 mmol) in CH_2Cl_2 (3 mL) was stirred at room temperature for 24 h. After filtration of the reaction mixture with Celite, the filtrate was evaporated, and the residue was partitioned between $CHCl_3$ and cold aqueous HCl (0.5 M). The organic layer was washed with H_2O and brine, dried (Na_2SO_4), and evaporated. A solution of the residue and added $NaBH_4$ (17 mg, 0.46 mmol) in MeOH (3 mL) was stirred at 0 °C for 2 h. After the solvent was evaporated, the residue was purified by silica gel column chromatography (0–2% MeOH in $CHCl_3$) to give **13** (120 mg, diastereomixture) as a colorless amorphous solid. A mixture of **13** (99 mg) and an EtOH solution of HCl (1 M, 3.0 mL) was stirred at 78 °C for 3 h. After the mixture was evaporated, the residue was washed with Et_2O. The residue was purified by NH silica gel column chromatography (0–20% MeOH in $CHCl_3$) to give **5a** (21 mg, 50% for three steps, colorless amorphous solid) as a free amine: ^{1}H-NMR (500 MHz, CD_3OD) δ 0.41 (2 H, m, cyclopropyl-CH_2), 0.80 (1 H, m, cyclopropyl-CH), 0.87 (1 H, m, cyclopropyl-CH), 2.45–2.55 (4 H, m, CH_2-imidazole & CH_2NH_2), 6.78 (1 H, s, imidazolyl), 7.52 (1 H, s, imidazolyl); ^{13}C-NMR (125 MHz, CD_3OD) δ 11.0, 18.2, 21.0, 31.2, 46.2, 117.8, 135.6, 137.4; LRMS (EI) m/z 151 (M$^+$); HRMS (EI) calcd for $C_8H_{13}N_3$ 151.1110, found 151.1100 (M$^+$); Found: C, 63.11; H, 8.89; N, 27.59. Calc. for $C_8H_{13}N_3$: C, 63.54; H, 8.67; N, 27.79%; The free amine **5a** was dissolved in aqueous HCl (4 M), and the solvent was then evaporated. The residue was triturated with Et_2O to give **5a dihydrochloride** (20 mg) as a white amorphous solid: $[\alpha]_D^{22}$ −44.1 (c 1.10, MeOH); ^{1}H-NMR (400 MHz, CD_3OD) δ 0.72 (2 H, m, cyclopropyl-CH_2), 1.12 (1 H, m, cyclopropyl-CH), 1.19 (1 H, m, cyclopropyl-CH), 2.58 (1 H, dd, J = 8.2, 15.9 Hz, CH_2-imidazole), 2.78 (1 H, dd, J = 7.7, 13.1 Hz, CH_2NH_2), 2.92 (1 H, dd, J = 6.3, 15.9 Hz, CH_2-imidazole), 2.99 (1 H, dd, J = 7.2, 13.1 Hz, CH_2NH_2), 7.42 (1 H, s, imidazolyl), 8.84 (1 H, s, imidazolyl); LRMS (EI) m/z 151 [(M−2HCl)$^+$]; HRMS (EI) calcd for $C_8H_{13}N_3$ 151.1110, found 151.1102 [(M−2HCl)$^+$]; Found: C, 41.50; H, 6.93; N, 17.99. Calc. for $C_8H_{15}Cl_2N_3\cdot 0.5H_2O$: C, 41.21; H, 6.92; N, 18.02%.

(2*R*,3*S*)-*trans*-4-Amino-2,3-methano-1-(1*H*-imidazol-4-yl)butane (*ent*-5a)

Compound ***ent*-5a** (23 mg, 61% for three steps, colorless amorphous solid) was prepared from ***ent*-9** (99 mg, 0.25 mmol) as described for the preparation of **5a**: LRMS (EI) *m*/*z* 151 (M^+); HRMS (EI) calcd for $C_8H_{13}N_3$ 151.1110, found 151.1121 (M^+); Found: C, 63.20; H, 8.98; N, 27.48. Calc. for $C_8H_{13}N_3$: C, 63.54; H, 8.67; N, 27.79%; ^{1}H- and ^{13}C-NMR spectra were consistent with those of **5a**; The free amine ***ent*-5a** was dissolved in aqueous HCl (4 M), and the solvent was then evaporated. The residue was triturated with Et_2O to give ***ent*-5a dihydrochloride** (25 mg) as a white amorphous solid: $[\alpha]_D^{22}$ +44.9 (*c* 1.12, MeOH); LRMS (EI) *m*/*z* 151 [(M−2HCl)$^+$]; HRMS (EI) calcd for $C_8H_{13}N_3$ 151.1110, found 151.1099 [(M−2HCl)$^+$]; Found: C, 42.49; H, 6.82; N, 18.35. Calc. for $C_8H_{15}Cl_2N_3\cdot0.1H_2O$: C, 42.53; H, 6.78; N, 18.60%. ^{1}H-NMR spectrum was consistent with that of **5a dihydrochloride**.

(2*R*,3*R*)-*cis*-4-Amino-2,3-methano-1-(1*H*-imidazol-4-yl)butane (6a)

Compound **6a** (18 mg, 59% for three steps, colorless amorphous solid) was prepared from **12** (79 mg, 0.20 mmol) as described for the preparation of **5a**: ^{1}H-NMR (500 MHz, CD_3OD) δ 0.18 (1 H, dd, *J* = 5.2, 10.9 Hz, cyclopropyl-CH_2), 0.84 (1 H, m, cyclopropyl-CH_2), 1.08–1.19 (2 H, m, cyclopropyl-CH ×2), 2.42 (1 H, dd, *J* = 8.6, 15.4 Hz, C*H*$_2$-imidazole), 2.75 (1 H, dd, *J* = 9.2, 13.5 Hz, C*H*$_2$NH$_2$), 2.87 (1 H, dd, *J* = 5.2, 15.4 Hz, C*H*$_2$-imidazole), 3.05 (1 H, dd, *J* = 5.7, 13.5 Hz, C*H*$_2$NH$_2$), 6.87 (1 H, s, imidazolyl), 7.61 (1 H, d, *J* = 1.1 Hz, imidazolyl); ^{13}C-NMR (125 MHz, CD_3OD) δ 10.1, 17.1, 18.3, 26.6, 41.6, 117.4, 135.8, 138.4; LRMS (EI) *m*/*z* 151 (M^+); HRMS (EI) calcd for $C_8H_{13}N_3$ 151.1110, found 151.1109 (M^+); Found: C, 63.11; H, 8.89; N, 27.59. Calc. for $C_8H_{13}N_3$: C, 63.54; H, 8.67; N, 27.79%; The free amine **6a** was dissolved in aqueous HCl (4 M), and the solvent was then evaporated. The residue was triturated with Et_2O to give **6a dihydrochloride** (20 mg) as a white amorphous solid: $[\alpha]_D^{22}$ +2.3 (*c* 0.66, MeOH); ^{1}H-NMR (500 MHz, CD_3OD) δ 0.45 (1 H, dd, *J* = 5.4, 11.3 Hz, cyclopropyl-CH_2), 1.02 (1 H, m, cyclopropyl-CH_2), 1.31 (1 H, m, cyclopropyl-CH), 1.41 (1 H, m, cyclopropyl-CH), 2.71 (1 H, dd, *J* = 8.6, 16.3 Hz, C*H*$_2$-imidazole), 2.88 (1 H, dd, *J* = 9.0, 13.1 Hz, C*H*$_2$NH$_2$), 3.00 (1 H, dd, *J* = 6.3, 16.3 Hz, C*H*$_2$-imidazole), 3.25 (1 H, dd, *J* = 5.9, 13.1 Hz, C*H*$_2$NH$_2$), 7.44 (1 H, d, *J* = 0.9 Hz, imidazolyl), 8.86 (1 H, d, *J* = 1.4 Hz, imidazolyl); LRMS (EI) *m*/*z* 151 [(M−2HCl)$^+$]; HRMS (EI) calcd for $C_8H_{13}N_3$ 151.1110, found 151.1097 [(M−2HCl)$^+$]; Found: C, 42.60; H, 6.88; N, 18.65. Calc. for $C_8H_{15}Cl_2N_3$: C, 42.87; H, 6.75; N, 18.75%.

(2*S*,3*S*)-*cis*-4-Amino-2,3-methano-1-(1*H*-imidazol-4-yl)butane (*ent*-6a)

Compound ***ent*-6a** (20 mg, 39% for three steps, colorless amorphous solid) was prepared from ***ent*-12** (131 mg, 0.334 mmol) as described for the preparation of **5a**: LRMS (EI) *m*/*z* 151 (M^+); HRMS (EI) calcd for $C_8H_{13}N_3$ 151.1110, found 151.1095 (M^+); Found: C, 63.39; H, 9.02; N, 27.36. Calc. for $C_8H_{13}N_3$: C, 63.54; H, 8.67; N, 27.79%; ^{1}H- and ^{13}C-NMR spectrum was consistent with that of **6a**; The free amine ***ent*-6a** was dissolved in aqueous HCl (4 M), and the solvent was then evaporated. The residue was triturated with Et_2O to give ***ent*-6a dihydrochloride** (22 mg) as a white solid: $[\alpha]_D^{22}$ −2.2 (*c* 0.58, MeOH); LRMS (EI) *m*/*z* 151 [(M−2HCl)$^+$]; HRMS (EI) calcd for $C_8H_{13}N_3$ 151.1110, found 151.1121 [(M−2HCl)$^+$]; Found: C, 41.31; H, 6.95; N, 17.93. Calc. for $C_8H_{15}Cl_2N_3\cdot0.5H_2O$: C, 41.21; H, 6.92; N, 18.02%. ^{1}H-NMR spectrum was consistent with that of **6a dihydrochloride**.

Binding assay with human histamine receptors

The assay was performed according to the method described previously.[6c] The dihydrochloride salts of the final compounds were used in the assay.

Luciferase reporter gene assay

The assay was performed according to the method described previously.[6b] Briefly, 3 × 10^4 cells of 293-EBNA (Invitrogen) were harvested on collagen-coated 48-well plates for 24 h. An expression plasmid for $G_{\alpha q/i}$, chimera G_α protein of $G_{\alpha q}$ and $G_{\alpha i}$, was constructed and cotransfected with an H_3- or H_4-expression plasmid and a pSRE-Luc. The following day, the cells were treated with histamine (10^{-5} or 10^{-6} M) and/or each compound (10^{-5} M) for 5 h, and laid on ice. Intracellular luciferase activity in aliquots from each lysate was measured using a model ML3000 luminometer (Dynatech Laboratories). The dihydrochloride salts of the final compounds were used in the assay.

Docking simulation

Using the homology modeling of the H_3 receptor that was constructed previously,[6d] the docking simulation was performed according to the method described previously.[6d]

Acknowledgements

This investigation was supported by a Grant-in-Aids for Scientific Research (21390028) from the Japan Society for the Promotion of Science. We are grateful to Sanyo Fine Co., Ltd. for the gift of the chiral epichlorohydrins.

References

1 (*a*) J.-M. Arrang, M. Garbarg and J.-C. Schwartz, *Nature*, 1983, **302**, 832–837; (*b*) *The Histamine H₃ Receptor: A Target for New Drugs*, ed. R. Leurs and H. Timmerman, Elsevier, Amsterdam, 1998; (*c*) R. Leurs, R. A. Bakker, H. Timmerman and I. J. P. de Esch, *Nat. Rev. Drug Discovery*, 2005, **4**, 107–120; (*d*) S. Celanire, M. Wijtmans, P. Talaga, R. Leurs and I. J. P. de Esch, *Drug Discovery Today*, 2005, **10**, 1613–1627; (*e*) T. A. Esbenshade, G. B. Fox and M. D. Cowart, *Mol. Interventions*, 2006, **6**, 77–88.

2 (*a*) M. Krause, H. Stark, and W. Schunack, Medicinal chemistry of histamine H_3 receptor agonists, pp. 175–196. In ref. 1b; (*b*) K. Onodera, and T. Watanabe, Histamine H_3 antagonists as potential therapeutics in the CNS, pp. 255–268. In ref. 1b.

3 (*a*) P. Ling, K. Ngo, S. Nguyen, R. L. Thurmond, J. P. Edwards, L. Karlsson and W. P. Fung-Leung, *Pharmacol.*, 2004, **142**, 161–171; (*b*) W. P. Fung-Leung, R. L. Thurmond, P. Ling and L. Karlsson, *Curr. Opin. Investig. Drugs*, 2004, **11**, 1174–1183; (*c*) H. D. Lim, R. M. van Rijn, P. Ling, R. L. Thurmond, R. A. Bakker and R. Leurs, *J. Pharmacol. Exp. Ther.*, 2005, **314**, 1310–1321.

4 (*a*) T. Klabunde and G. Hessler, *ChemBioChem*, 2002, **3**, 928–944; (*b*) K. Palczewski, T. Kumasaka, T. Hori, C. A. Behnke, H. Motoshima, B. A. Fox, I. Le Trong, D. C. Teller, T. Okada, R. E. Stenkamp, M. Yamamoto and M. Miyano, *Science*, 2000, **289**, 739–745; (*c*) V. Sarramegna, F. Talmont, P. Demange and A. Milon, *Cell. Mol. Life Sci.*, 2003, **60**, 1529–1546; (*d*) S. Schlyer and R. Horuk, *Drug Discovery Today*, 2006, **11**, 481–493; and references therein.

5 Recently, several X-ray crystallographic analyses of GPCR have been reported: (*a*) V. Cherezov, D. M. Rosenbaum, M. A. Hanson, S. G. Rasmussen, F. S. Thian, T. S. Kobilka, H. J. Choi, P. Kuhn, W. I. Weis, B. K. Kobilka and R. C. Stevens, *Science*, 2007, **318**, 1258–1265; (*b*) D. M. Rosenbaum, V. Cherezov, M. A. Hanson, S. G. Rasmussen, F. S. Thian, T. S. Kobilka, H. J. Choi, X. J. Yao, W. I. Weis, R. C. Stevens and B. K. Kobilka, *Science*, 2007, **318**, 1266–1273; (*c*) S. G. Rasmussen, H. J. Choi, D. M. Rosenbaum, T. S. Kobilka, F. S. Thian, P. C. Edwards, M. Burghammer, V. R. Ratnala, R. Sanishvili, R. F. Fischetti, G. F. Schertler, W. I. Weis and B. K. Kobilka, *Nature*, 2007, **450**, 383–387.

6 (*a*) Y. Kazuta, A. Matsuda and S. Shuto, *J. Org. Chem.*, 2002, **67**, 1669–1677; (*b*) Y. Kazuta, K. Hirano, K. Natsume, S. Yamada, R. Kimura, S. Matsumoto, K. Furuichi, A. Matsuda and S. Shuto, *J. Med. Chem.*, 2003, **46**, 1980–1988; (*c*) M. Watanabe, Y. Kazuta, H. Hayashi, S. Yamada, A. Matsuda and S. Shuto, *J. Med. Chem.*, 2006, **49**, 5787–5796; (*d*) M. Watanabe, T. Hirokawa, T. Kobayashi, A. Yoshida, Y. Ito, S. Yamada, N. Orimoto, Y. Yamasaki, M. Arisawa and S. Shuto, *J. Med. Chem.*, 2010, **53**, 3585–3593.

7 The cyclopropane-based stereochemical diversity-oriented strategy was also effectively used for identifying potent proteasome inhibitors: (*a*) K. Yoshida, K. Yamaguchi, T. Sone, Y. Unno, A. Asai, H. Yokosawa, A. Matsuda, M. Arisawa and S. Shuto, *Org. Lett.*, 2008, **10**, 3571–3574; (*b*) K. Yoshida, K. Yamaguchi, A. Mizuno, Y. Unno, A. Asai, T. Sone, H. Yokosawa, A. Matsuda, M. Arisawa and S. Shuto, *Org. Biomol. Chem.*, 2009, **7**, 1868–1877.

8 For examples of the cyclopropane-based conformational restriction, see the following: (*a*) P. D. Armstrong, G. J. Cannon and J. P. Long, *Nature*, 1968, **220**, 65–66; (*b*) K. Shimamoto and Y. Ofune, *J. Med. Chem.*, 1996, **39**, 407–423; (*c*) S. H. Stammer, *Tetrahedron*, 1990, **46**, 2231–2254; (*d*) S. F. Martin, M. P. Dwyer, B. Hartmann and K. S. Knight, *J. Org. Chem.*, 2000, **65**, 1305–1318; (*e*) T. Sekiyama, S. Hatsuya, Y. Tanaka, M. Uchiyama, N. Ono, S. Iwayama, M. Oikawa, K. Suzuki, M. Okunishi and T. Tsuji, *J. Med. Chem.*, 1998, **41**, 1284–1298.

9 (*a*) H. N. C. Wong, M.-Y. Hon, C.-Y. Tse and Y.-C. Yip, *Chem. Rev.*, 1989, **89**, 165–198; (*b*) V. K. Singh, A. DattaGupta and G. Sekar, *Synthesis*, 1997, 137–149; (*c*) M. P. Doyle and M. N. Protopopova, *Tetrahedron*, 1998, **54**, 7919–7946; (*d*) J. Cossy, N. Blanchard and C. Meyer, *Synthesis*, 1999, 1063–1075; (*e*) *Small Ring Compounds in Organic Synthesis VI. Topic in Current Chemistry 207*, A. de Meijere, Ed.; Springer: Berlin, 1999; (*f*) H. Lebel, J.-F. Marcoux, C. Molinaro and A. B. Charette, *Chem. Rev.*, 2003, **103**, 977–1050; (*g*) P. Garcia, D. Diez, A. B. Anton, N. M. Garrido, I. S. Marcos, P. Basabe and J. G. Urones, *Mini-Rev. Org. Chem.*, 2006, **3**, 291–314; (*h*) P. Muller, Y. ves F. Allenbach, S. Chappellet and A Ghanem, *Synthesis*, 2006, **10**, 1689–1696.

10 D. A. Horne, K. Yakushijin and G. A. Buchi, *Heterocycles*, 1994, **39**, 3957–3960.

11 (*a*) R. Kitbunnadaj, O. P. Zuiderveld, I. J. P. de Esch, R. C. Vollinga, R. Bakker, M. Lutz, A. L. Spek, E. Cavoy, M.-F. Deltent, W. M. P. B. Menge, H. Timmerman and R. Leurs, *J. Med. Chem.*, 2003, **46**, 5445–5457; (*b*) R. Kitbunnadaj, M. Hoffmann, S. A. Fratantoni, G. Bongers, R. A. Bakker, K. Wieland, A. el Jilali, I. J. P. de Esch, W. M. P. B. Menge, H. Timmerman and R. Leurs, *Bioorg. Med. Chem.*, 2005, **13**, 6309–6323.

12 An example of an H_3 receptor antagonist having a primary amino function without a hydrophobic group: R. C. Vollinga, W. M. P. B. Menge, R. Leurs and H. Timmerman, *J. Med. Chem.*, 1995, **38**, 266–271.