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SPECIAL FEATURE: ARTICLE

Optically active iodohelicene derivatives exhibit histamine *N*-methyl transferase inhibitory activity

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Abstract

Optically active helicene derivatives inhibit the activity on histamine *N*-methyl transferase (HNMT). Specifically, methyl (*P*)-1,12-dimethylbenzo[*c*]phenanthrene-8-carboxylate with 6-iodo and 5-trifluoromethanesulfonyloxy groups inhibits HNMT activity on the μM order of IC_{50}. Chirality is important, and (*M*)-isomers exhibits substantially reduced activity. The 6-iodo group is also essential, which suggests the involvement of halogen bonds in protein binding. Substituents on the sulfonate moiety also affect the inhibitory activity.

Introduction

Proteins and nucleic acids are important macromolecules in biology, and the development of small molecules to control their functions is critical for drug discovery. Biological macromolecules often contain helical partial structures [1], which implies that small molecules with helical structures may be attractive for such purposes. Studies of the effects of helical small molecules on biological activity, however, have been quite limited because of the unavailability of small molecules with helical structures in sufficient quantity; hence, the nature of the interactions between helical small molecules and biological macromolecules remains unexplored [2–8]. We previously reported that helicenedimethylamines interact with double-stranded DNA, and strong binding occurred with significant chiral recognition by right- and left-handed helical molecules [9]. As a result of this work, interactions of nucleic acids with helicene derivatives have been examined by several groups, and interesting noncovalent bond interactions and chiral recognition phenomena have been observed [10–15]. Studies, however, have been restricted to nucleic acids, and studies of proteins have not been reported. Described herein is an enzyme inhibitory activity shown by helicene derivatives, which exhibit the significant effect of chirality.

Histamine, 2-(1*H*-imidazol-4-yl)ethanamine, plays important roles as an autacoid in allergic reactions and gastric acid secretion. In the central nervous system (CNS), histamine acts as a neurotransmitter to regulate a wide range of physiological processes including the sleep–wake cycle and stress response [16, 17]. Recent studies revealed that a decrease in brain histamine concentration was associated with CNS disorders such as Alzheimer's disease [18]. Additionally, pitolisant, which induces histamine release from neurons, was approved as a therapeutic drug for narcolepsy, supporting the importance of histamine for brain functions [19]. Recently, we have investigated the roles of histamine *N*-methyl transferase (HNMT), an inactivating enzyme for histamine, and showed the predominant contribution of HNMT to brain histamine concentration [20]. Thus, HNMT inhibition may increase brain histamine and exert therapeutic effects on brain disorders. However, previously examined HNMT inhibitors did not have sufficient specificity or blood–brain barrier permeability. Therefore, HNMT inhibition by novel compounds with unique

Dedication Dedicated to Professor Samuel Danishefsky for his contribution in synthetic chemistry.

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structures is of interest as a new strategy to improve brain functions.

As part of our program to develop functional helicene derivatives with 1,12-dimethylbenzo[*c*]phenanthrene structure [6, 7], in this article, we describe the HNMT inhibitory activity of methyl (*P*)-1,12-dimethyl-6-iodo-5-(trifluoromethanesulfonyloxy)benzo[*c*]phenanthrene-8-carboxylate **1** on the μM order of IC_{50} (Fig. 1) [21]. Notably, the inhibitory activity of (*P*)-**1** was higher than (*M*)-**1**, which suggests that significant chiral recognition is involved in protein binding. This is a notable example of an optically active helicene exhibiting activity against a protein. In addition, the 6-iodo group was found to be essential for the inhibitory activity, which suggests the involvement of a halogen bond in the binding. The biological activity of organoiodine compounds has been rarely reported either for natural and synthetic compounds [22, 23].

Results and discussion

The synthesis of the helicene derivatives examined in this study started from known optically active helicenols (*P*)-**7** and (*M*)-**7** (Scheme 1) [21]. (*P*)-**7** was converted to an unstable 6-iodohelicenol (*P*)-**8**, which was immediately sulfonylated with trifluoromethane-, methane-, and ethanesulfonyl acid derivatives to provide the corresponding sulfonates (*P*)-**1**, (*P*)-**2**, and (*P*)-**3**, respectively. The enantiomers (*M*)-**1**, (*M*)-**2**, and (*M*)-**3** were synthesized from (*M*)-**7**. In addition, acetylation of (*P*)-**8** and (*M*)-**8** gave the corresponding acetates (*P*)-**4** and (*M*)-**4**, respectively. Dimethylthiophosphination of (*P*)-**8** and (*M*)-**8** gave the corresponding thiophosphinates (*P*)-**5** and (*M*)-**5**, respectively. A trifluoromethanesulfonate (*M*)-**6** lacking the 6-iodo group was also synthesized from (*M*)-**7**. The helicene derivatives were reported not to racemize up to 200 °C, as described before [6, 7].

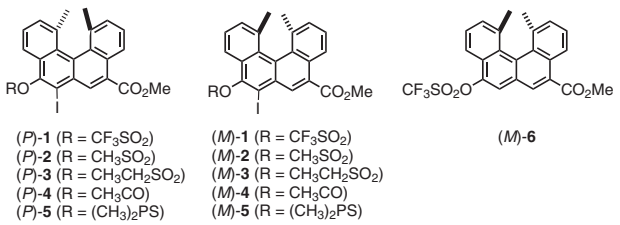
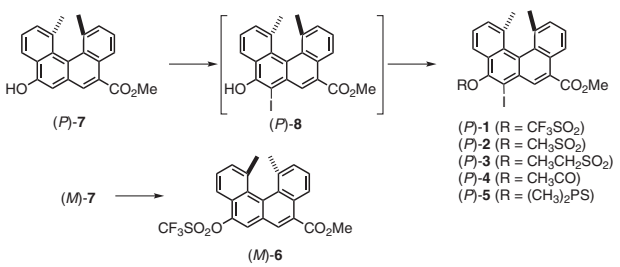


Fig. 1 Chemical structures of helicene derivatives employed in this study



Scheme 1 Synthesis of optically active helicene derivatives

The enzymatic activity of HNMT in the presence of the synthetic helicene derivative (*P*)-**1** was analyzed by a radiometric method using [^{3}H]-labeled S-adenosyl methionine (SAM), a methyl group donor, for the metabolism of histamine by HNMT. In the reaction, a [^{3}H]-labeled methyl group was transferred from SAM to histamine, and the [^{3}H]-labeled product was separated on the basis of the difference in hydrophobicity between [^{3}H]-SAM and [^{3}H]-labeled methylhistamine (MHA). The MHA formed at different concentrations of (*P*)-**1** provided a sigmoidal curve, from which an IC_{50} of 8.4 μM was obtained (Fig. 2). The same experiment using (*M*)-**1** provided an IC_{50} of 18.8 μM, which showed the significant effect of helical chirality on the enzyme inhibitory activity, indicating the specific binding of (*P*)-**1** to HNMT. Such activity of a helicene derivative with a protein enzyme has not been reported, and demonstrates that helical chirality can be an interesting structural motif to use for developing biologically active substances. The result also suggests the presence of helical space in HNMT at the binding site.

The critical role of the 6-iodo group is noteworthy, as indicated by the disappearance of inhibitory activity with (*M*)-**6**, which lacked the 6-iodo group (Table 1). It is likely that the large and polarizable iodine atom in **1** enhanced the interactions of **1** with the protein. Halogen bonds have attracted much attention in drug discovery, and the effects of chloride and bromide atoms on biological activities have been examined. The halogen atoms are considered to interact with oxygen atoms such as those in protein amide carbonyl groups. Alternatively, the effect of iodine atom can be steric. The effects of iodide atoms on biological activity have not been well examined, and the results of this study reveal an interesting effect of the iodo group [22, 23].

The effect of the ester moiety was examined (Table 1). Methanesulfonate (*P*)-**2** showed comparable activity to (*P*)-**1**, and fluorine atoms were found to be not essential for the inhibitory activity. The effect of chirality, however, was relatively small, and the activity was only slightly reduced in (*M*)-**2** compared with (*P*)-**2**. Ethanesulfonates (*P*)-**3** and (*M*)-**3** were less effective, and chirality was not required in the enzyme inhibitory activity. Dimethylthiophosphinates (*P*)-**5** and (*M*)-**5** also showed lower activity than (*P*)-**1** and (*M*)-**1**, and the effect of chirality was lost. The results suggest that bulky ester groups reduced the activity, although the effect of the trifluoromethyl group has been considered relatively complex [24, 25]. Acetate (*P*)-**4** also showed a lower inhibitory activity than (*P*)-**1** with an

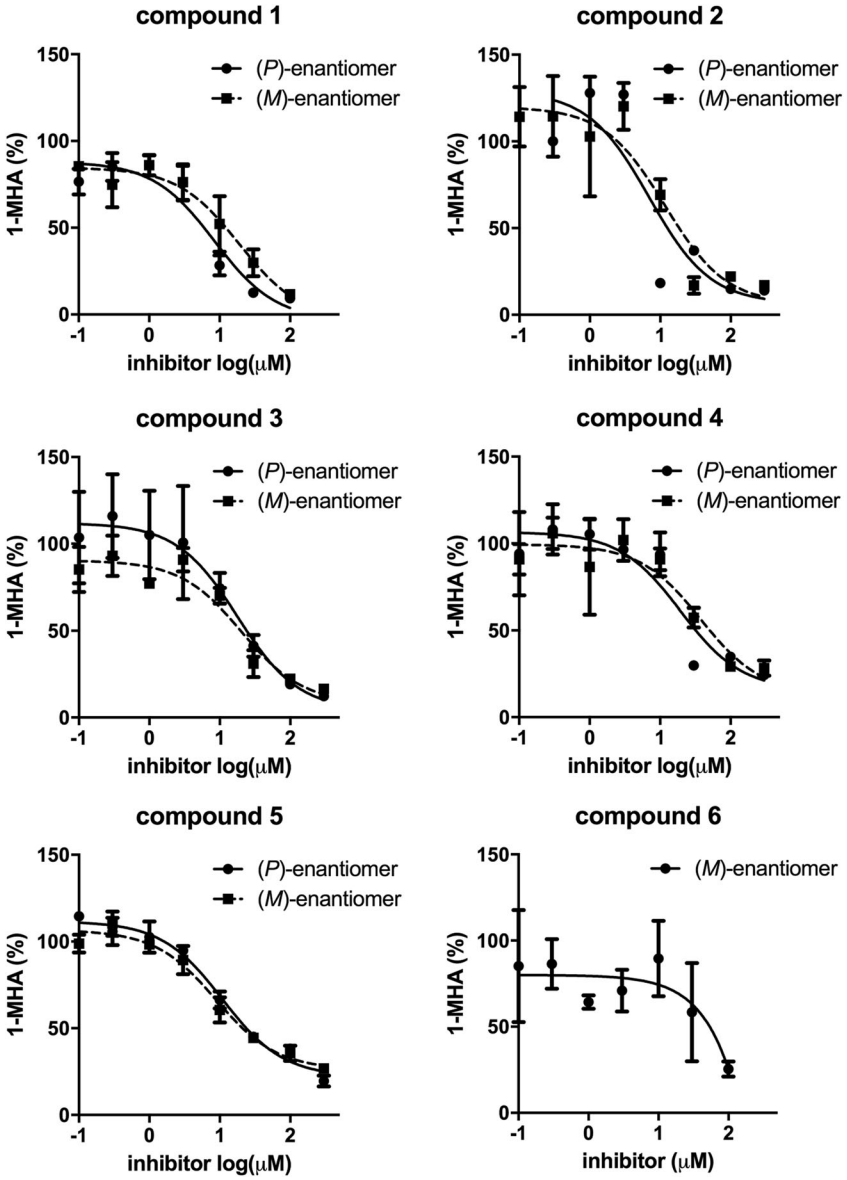


Fig. 2 Concentration dependence of HNMT inhibitory activity of (*P*)- and (*M*)-**1**, **2**, **3**, **4**, **5**, and (*M*)-**6**

Table 1 HNMT inhibitory activity of helicene derivatives shown by IC_{50} values (μM)

Compound	R	(*P*)-enantiomer	(*M*)-enantiomer
1	CF_3SO_2	8.4	18.8
2	CH_3SO_2	8.3	12.7
3	$CH_3CH_2SO_2$	18.4	20.4
4	CH_3CO	19.9	37.7
5	$(CH_3)_2PS$	10.8	8.9
6	CF3SO2	Not determined	>200

apparent effect of chirality. Modification of the ester moiety variously affects the inhibitory activity.

Inhibitors of the HNMT enzyme have been developed as drugs, some of which possess polycyclic aromatic structures, as those observed in tacrine, metroprine, and amodiaquine [26, 27]. Crystallographic analyses of the protein–drug complexes suggested an important role of the planar structure in the drugs. Three drugs are bound in the same pocket of HNMT formed by aromatic amino-acid residues such as Y15, F19, Y146, and F243, the interactions of which with the aromatic drugs appear to be critical. The structure of HNMT–amodiaquine complex shows binding of two-drug molecules, and one of the molecules binds in the above-mentioned pocket of HNMT. The involvement of chiral amino acids provides chiral structures of the pocket, and it is reasonable to consider that chiral helicene derivatives bind at the pocket exhibiting chiral recognition phenomenon.

It was also noted in this study that the (*P*)-helicene derivatives exerted HNMT inhibitory activities, which were

more potent than those of the (*M*)-enantiomers. The crystallographic analysis of the HNMT–amodiaquine complex showed the (*P*)-like configuration of the above-mentioned drug molecule [27], which is consistent with the preferential binding of the (*P*)-helicene derivatives in this study.

To summarize, the enzyme inhibitory activity of optically active helicene derivatives is described as follows. Specifically, methyl 1,12-dimethyl-6-iodo-5-(trifluoromethanesulfonyloxy)benzo[*c*]phenanthrene-8-carboxylates exhibit HNMT inhibitory activity on the μM order of IC_{50}. HNMT is an enzyme, which metabolizes histamine to inactive 1-MHA. It is the only histamine-metabolizing enzyme expressed in the CNS. Chirality plays an important role in the inhibitory activity, in which the (*P*)-enantiomer shows more potent activity than the (*M*)-enantiomer. This is a notable property of a helicene derivative interacting with a protein, which was not reported previously. The 6-iodo group is also essential for the inhibitory activity, which suggests the involvement of a halogen bond in the binding with a protein. The use of helical chiral aromatic groups and the introduction of an iodo group may be interesting approaches to develop biologically active substances.

Experimental section

^{1}H and ^{13}C NMR (nuclear magnetic resonance) spectra were recorded using a 400 MHz instrument, and tetramethylsilane was used as a standard. The following abbreviations (or combinations thereof) are used to explain multiplicities: s = singlet, d = doublet, t = triplet. IR (infrared) spectra were measured using an FT/IR (Fourier trasnfer infrared) spectrometer. Melting points were determined with a micromelting point apparatus without correction. High-resolution mass spectra (HRMS) were recorded by quadrupole or EI-TOF (electron ionization time-of-flight) MS.

Compounds (*P*)-**1**, (*M*)-**1**, (*P*)-**7**, and (*M*)-**7** were synthesized as described previously [21].

Methyl (*P*)-1,12-dimethyl-6-iodo-5-(methanesulfonyloxy) benzo[*c*]phenanthrene-8-carboxylate (*P*)-2

A mixture of (*P*)-**7** (40 mg, 0.12 mmol), iodine (31 mg, 0.13 mmol), and sodium bicarbonate (11 mg, 0.13 mmol) in 1:1 THF/water (1 mL) was prepared at 0 °C, and warmed to room temperature for 10 min. The reaction was quenched by adding 5% aqueous sodium thiosulfate, and organic materials were extracted twice with ethyl acetate. The combined organic layers were washed with brine and dried over magnesium sulfate. The solvents were removed under reduced pressure, and the resulting crude iodohelicenol (*P*)-**8** was subjected to the next reaction without further purification. The residue was dissolved in CH_2Cl_2 (1 mL) and trimethylamine (1 mL) at 0 °C, to which methanesulfonyl chloride (0.016 mL, 0.21 mmol) was added. The mixture was stirred at 0 °C for 1 h, and the reaction was quenched by adding saturated aqueous ammonium chloride. Organic materials were extracted twice with ethyl acetate. The combined organic layers were washed with brine and dried over magnesium sulfate. Silica gel chromatography (CH_2Cl_2:hexane = 1:1) gave (*P*)-**2** (20 mg, 31%). Mp 183-185 °C (CH_2Cl_2-hexane). $[\alpha]_D^{23}$–245° (c 0.50, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ1.85 (3H, s), 1.86, (3H, s), 3.66 (3H, s), 4.11 (3H, s), 7.44 (1H, d, J = 7.2 Hz), 7.49 (1H, d, J = 7.2 Hz), 7.69 (1H, t, J = 8.4 Hz), 7.70 (1H, t, J = 7.2 Hz), 8.36 (1H, d, J = 8.0 Hz), 8.81 (1H, d, J = 8.4 Hz), 8.83 (1H, s). ^{13}C NMR ($CDCl_3$) δ23.1, 23.6, 41.6, 52.6, 93.4, 121.0, 123.1, 128.0, 128.2, 128.4, 129.4, 129.5, 129.9, 130.4, 131.1, 131.3, 131.5, 133.5, 136.6, 137.1, 147.0, 167.5. One peak overlapped. IR (KBr) 1711 cm^{-1}. MS *m/z* 534 ($\mathbf{M}^+$, 31%), ($\mathbf{M}^+$–CH_3SO_2, 100%), 301 (40%). HRMS *m/z* Calcd for $C_{23}H_{19}IO_5S$: 533.9998. Found: 534.0024. (*M*)-**2**. $[\alpha]_D^{23}$ + 238° (c 0.50, $CHCl_3$).

Methyl (*P*)-1,12-dimethyl-5-(ethanesulfonyloxy)-6-iodo-benzo[*c*]phenanthrene-8-carboxylate (*P*)-3

This compound was synthesized from (*P*)-**7** and ethanesulfonyl chloride as described above in 60% yield. Mp 76–77 °C (CH_2Cl_2-hexane). $[\alpha]_D^{23}$–249° (c 0.50, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ1.77 (3 H, t, J = 7.6 Hz), 1.85 (3H, s), 1.86 (3H, s), 3.76 (1H, dt, J = 21.6, 7.2 Hz), 3.89 (1H, dt, J = 22.0, 7.6 Hz), 4.11 (3H, s), 7.44 (1H, d, J = 7.2 Hz), 7.49 (1H, d, J = 7.2 Hz), 7.68 (1H, t, J = 6.8 Hz), 7.70 (1H, t, J = 6.8 Hz), 8.37 (1H, d, J = 8.0 Hz), 8.81 (1H, d, J = 8.0 Hz), 8.84 (1H, s). ^{13}C NMR ($CDCl_3$) δ8.6, 23.1, 23.6, 49.3, 52.6, 93.3, 121.1, 123.1, 127.89, 127.92, 128.2, 128.6, 129.3, 129.5, 129.9, 130.3, 131.1, 131.3, 131.5, 133.6, 136.6., 137.0, 146.9, 167.5. IR (KBr) 1715 cm^{-1}. MS *m/z*548 ($\mathbf{M}^+$, 20%), 455 ($\mathbf{M}^+$–$C_2H_5SO_2$, 100%), 301 (40%). HRMS *m/z* Calcd for $C_{24}H_{21}IO_5S$: 548.0154. Found: 548.0187. (*M*)-**3**. $[\alpha]_D^{24}$ + 243° (c 0.50, $CHCl_3$).

Methyl (*P*)- 5-acetoxy-1,12-dimethyl-6-iodo-benzo[*c*] phenanthrene-8-carboxylate (*P*)-4

This compound was synthesized from (*P*)-**7** and acetyl chloride as described above in 31% yield. Mp 89–90 °C (CH_2Cl_2-hexane). $[\alpha]_D^{24}$–198° (c 0.50, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ1.86 (3H, s), 1.88 (3H, s), 2.61 (3H, s), 4.11 (3H, s), 7.43 (1H, d, J = 7.2 Hz), 7.47 (1H, d, J = 7.6 Hz), 7.63 (1H, t, J = 8.0 Hz), 7.67 (1H, t, J = 7.2 Hz), 7.86 (1H, d, J = 7.2 Hz), 8.81 (1H, d, J = 8.4 Hz), 8.82 (1H, s). ^{13}C NMR ($CDCl_3$) δ21.4, 23.1, 23.6, 52.6,93.0, 119.3, 123.1, 127.3 (2 peaks), 127.6, 127.8, 128.8, 129.3, 129.7, 130.0, 131.1, 131.3 (2 peaks), 133.5, 136.5, 137.6, 148,2, 167.6, 168.4. IR (KBr) 1770, 1714 cm^{-1}. MS *m/z* 498 ($\mathbf{M}^+$, 15%), 456 ($\mathbf{M}^+$–CH_2CO,

100%). HRMS *m/z* Calcd for $C_{24}H_{19}IO_4$: 498.0328. Found: 498.0334. (*M*)-**4**. $[\alpha]_D^{24} + 196°$ (c 0.50, $CHCl_3$).

Methyl (*P*)-1,12-dimethyl-5-(dimethylthiophosphinyloxy)-6-iodo-benzo[*c*]phenanthrene-8-carboxylate (*P*)-5

This compound was synthesized from (*P*)-**7** and dimethylthiophosphinyl chloride as described above in 48% yield. Mp 112–114 °C (CH_2Cl_2-hexane). $[\alpha]_D^{23}$–281° (c 0.50, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ1.86 (3H, s), 1.88 (3H, s), 2.30 (3H, d, J = 128 Hz), 2.41 (3H, d, J = 132 Hz), 4.11 (3H, s), 7.42 (1H, d, J = 7.2 Hz), 7.45 (1H, d, J = 7.6 Hz), 7.64 (1H, t, J = 8.0 Hz), 7.66 (1H, t, J = 7.2 Hz), 8.28 (1H, d, J = 8.4 Hz), 8,80 (1H, d, J = 8.4 Hz), 8.82 (1H, s). ^{13}C NMR ($CDCl_3$) δ23.2, 23.7, 25.6 (d, J = 514 Hz), 26.3 (1H, d, J = 543 Hz), 52.6, 92.8 (d, J = 67 Hz), 121.4, 123.1, 127.4, 127.6, 127.7, 128.2 (d, J = 30 Hz), 128.7 (d, J = 29 Hz), 129.3, 129.5, 130.1, 131.2, 131.4 (d, J = 23 Hz), 131.5 (d, J = 30 Hz), 133.7, 136.3, 137.0, 149.2 (d J = 4 Hz), 167.6.^{31}P NMR ($CDCl_3$) δ 99.6. IR (KBr) 1714 cm^{-1}. MS *m/z* 548 ($\mathbf{M}^+$, 3%), 421 ($\mathbf{M}^+$–I, 100%). HRMS *m/z* Calcd for $C_{24}H_{22}IO_3PS$: 548.0072. Found: 548.0061. (*M*)-**5**. $[\alpha]_D + 285°$ (c 0.50, $CHCl_3$).

Methyl (*M*)-1,12-dimethyl-5-(trifluoromethanesulfonyloxy) benzo[*c*]phenanthrene-8-carboxylate (*M*)-6

This compound was synthesized from (*M*)-**7** and trifluoromethanesulfonic anhydride as described above in 76% yield. Mp 46–48 °C (CH_2Cl_2-hexane). $[\alpha]_D^{24} + 50.8°$ (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ1.90 (3H, s), 1.95 (3H, s), 4.09 (3H, s), 7.47 (1H, d, J = 7.2 Hz), 7.55 (1H, d, J = 7.6 Hz), 7.69 (1H, t, J = 7.6 Hz), 7.75 (1H, t, J = 7.6 Hz), 7.83 (1H, s), 8.15 (1H, d, J = 8.0 Hz), 8.48 (1H, s), 8.83 (1H, t, J = 8.4 Hz). ^{13}C NMR ($CDCl_3$) δ23.2, 23.5, 52.5, 116.5, 118.5, 120.1 (J = 256 Hz), 123.2, 126.3, 127.66, 127.68, 128.08, 128.15, 129.15, 129.17, 129.3, 130.1, 130.3, 131.3, 131.9, 136.5, 137.7, 144.5, 167.6. ^{19}F NMR ($CDCl_3$) δ –73.2. IR (KBr) 1718 cm^{-1}. MS *m/z* 462 ($\mathbf{M}^+$, 39%), 329 ($\mathbf{M}^+$–CF_3SO_2, 100%), 301 (40%). HRMS *m/z* Calcd for $C_{23}H_{17}F_3O_5S$: 462.0749. Found: 462.0753.

Inhibition assay HNMT catalyzes the methylation of histamine to produce 1-MHA. To investigate the inhibitory effect of each compound on HNMT activity, we measured the amount of 1-MHA produced after the reaction of HNMT and the compound. Reactions were carried out using 10 nM human HNMT, 10 μM histamine, and 10 μM SAM in 125 mM bicine buffer (pH 8.2) with various concentrations of each compound. Reaction mixtures were incubated at 37 °C for 15 min. 1-MHA was detected by an HPLC (high performance liquid chromatography) method as described previously [28]. After reaction, samples were centrifuged at 15,000 *g* for 10 min at 4 °C, and the supernatant was applied to an HPLC system. The sample was separated into histamine and 1-MHA at 40 °C on an SC–5ODS column (3.0 i.d. × 150 mm; Eicom, Kyoto, Japan). Fluorescence from 1-MHA was excited at 335 nm and measured at 450 nm. The half maximal inhibitory concentration (IC_{50}) was calculated using Prizm 5 software (GraphPad, La Jolla, CA).

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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