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Development of novel bisubstrate-type inhibitors of histone methyltransferase SET7/9

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ABSTRACT

Histone modification, for example, by histone deacetylase (HDAC) and histone lysine methyltransferase (HMT), plays an important role in regulating gene expression. To obtain novel inhibitors as tools for investigating the physiological function of members of the HMT family, we designed and synthesized novel inhibitors, which are amine analogues of adenosylmethionine (AdoMet; the cofactor utilized in the methylation reaction) bearing various alkylamino groups coupled via an ethylene linker. The inhibitory activities of these compounds towards SET7/9, an HMT, were evaluated. It was found that introduction of an alkylamino group increased the inhibitory activity.

1. Introduction

Post-translational modification of histone protein plays an important role in the regulation of gene expression, and can be controlled by histone-modifying enzymes.[1–3] Histone lysine methylation, which is regulated by histone lysine methyltransferase (HMT) and histone demethylase, is one of those modifications, and refers to covalent methylation of histone lysine tails to produce mono-, di- or trimethylated states.[4,5] In the methylation reaction, the methyl group of the cofactor adenosylmethionine (AdoMet) is transferred to nitrogen of the substrate lysine residue, yielding methylated lysine and adenosylhomocysteine (AdoHcy) (Fig. 1). Recently, various reports have suggested that HMTs are involved in the development of various diseases, including cancer.[6,7] For example, E2H2, which targets Lys27 of histone 3 (H3K27), is overexpressed in many different types of cancer.[8] In addition, substrates of some HMTs are not limited to histone.[9] Tumor suppressor protein p53 is methylated at K372 by SET7/9 or at K370 by Smyd2.[10,11] Other substrates of SET7/9 include Tat protein of HIV-1[12] and estrogen receptor α.[13]

To elucidate the physiological function of HMTs, several HMT inhibitors have been developed (Fig. 2). Chaetocin was identified as a selective inhibitor of SUV39 from a library of natural compounds.[14] BIX-01294, a G9a inhibitor, was developed based on screening of a large chemical library.[15] In addition, derivatives of cofactors of the methylation reaction were also reported to be inhibitors; for example, AzaAdoMet, an analogue of AdoMet in which the bridging sulfur atom is replaced with nitrogen, and Sinefungin inhibit AdoMet-dependent methyltransferases, such as DNA methyltransferase.[16,17] In this paper, we report the design and synthesis of novel derivatives of these cofactors, together with the results of assay of their inhibitory activities towards histone methyltransferase SET7/9.

2. Results

2.1. Design of novel inhibitor candidates

The crystal structure of the ternary complex of human SET7/9 with histone substrate peptide and cofactor AdoHcy has been elucidated.[18] In this structure, the peptide substrate and cofactor bind on opposite surfaces of the enzyme. The target lysine residue (Lys4) of the substrate peptide is inserted into a narrow channel passing through the enzyme, affording access to the cofactor (Fig. 3a). Cofactors or their analogues conjugated with a substructure of the substrate could be utilized as bisubstrate inhibitors, which are able to interact with both substrate-binding sites, in this case the cofactor-binding site and the substrate peptide-binding site, to provide high potency and selectivity.[19] For example, ATP derivatives conjugated with substrate peptide have been reported as bisubstrate kinase inhibitors,[20] and a conjugate of substrate estradiol with adenosine, which is a substructure of cofactor NADPH, has been reported as an inhibitor of 17β-hydroxysteroid dehydrogenase.[21,22]

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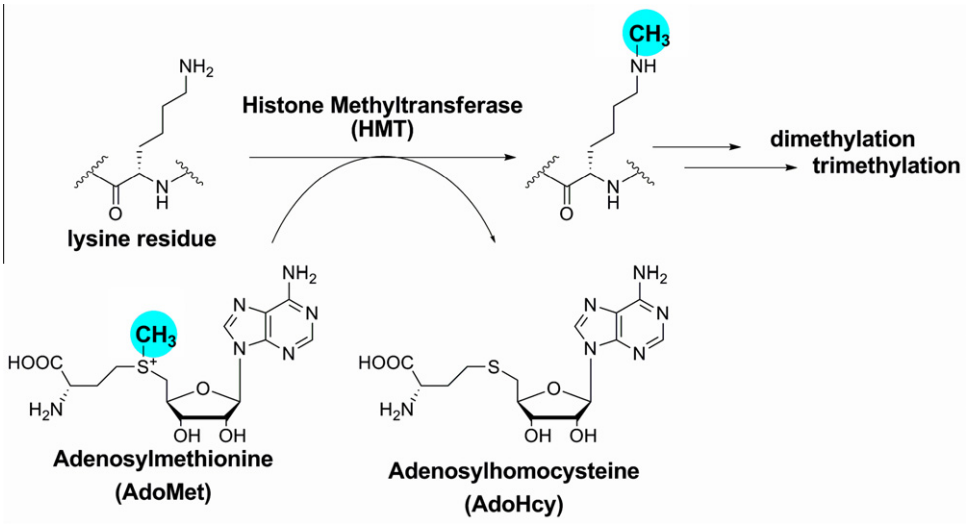


Figure 1. Methylation of lysine residue by histone methyltransferase utilizing adenosylmethionine (AdoMet) as a cofactor.

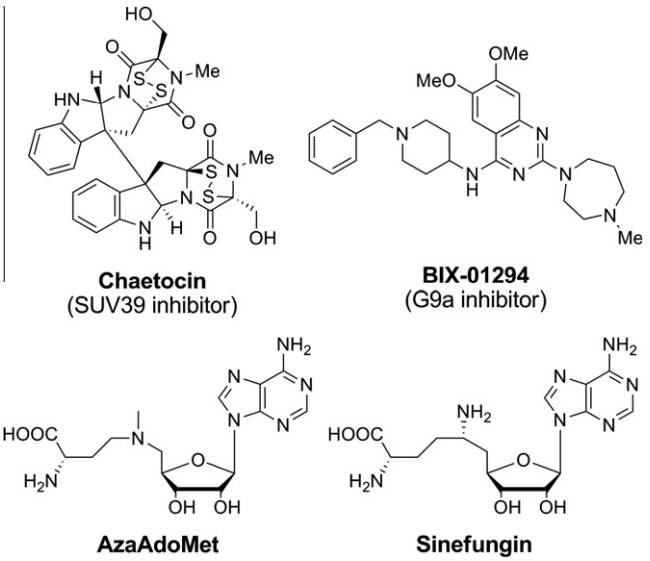


Figure 2. Structures of HMT inhibitors.

So, based on the structure of the ternary complex, we designed novel derivatives of AzaAdoMet, in which the nitrogen that replaces the sulfur atom of AdoMet is coupled to various alkylamino groups (**R** = methyl: **1a**; *n*-propyl: **1b**; *n*-hexyl: **1c**; phenethyl: **1d**) via an ethylene linker as inhibitor candidates (Fig. 3b). The introduced nitrogen is expected to form a hydrogen-bonding network similar to that of the lysine residue of substrate peptide, involving Tyr245 and a water molecule tightly bound to Tyr305. Further, the alkyl group (**R**) is expected to interact with hydrophobic side chains of amino acids that form the channel through the enzyme, such as Leu267, Tyr305, Tyr335 and Tyr337. Namely, introducing an alkylamino group is expected to result in enhanced interaction with the substrate peptide-binding site. In addition, in order to study the effect of the nitrogen atom, a derivative without such nitrogen, **1e**, was also designed (Fig. 3b).

2.2. Synthesis

The key step in the synthesis of compounds **1a**–**1e** was thought to be construction of tertiary amine structure at the 5' position of adenosine. In a reported synthetic scheme of AzaAdoMet and its derivatives, direct alkylation involving hydroxyl, halide, sulfonate ester, amino and sulfonamide at the 5' position has been utilized.[23,24] So, we first prepared the adenosine derivative with a mesyl group (**2b**) from 2',3'-isopropylidene adenosine (**2a**) using the reported method.[25] The derivative with an amino group (**2c**) at the 5' position was also prepared by means of a slight modification of the reported method.[26,27] For the synthesis of **1a**, Boc-protected *N*-methylaminoethylene with an amino (**3a**) or a nosylamido (**3b**) group was prepared,[28] for conjugation with compounds **2**. However, the reaction of **3a** or **3b** with **2b** under basic conditions did not proceed, yielding various by-products. Mitsunobu reaction between the hydroxyl group of **2a** and nosylamido compound **3b**, which has been applied for the synthesis of AzaAdoMet and other 5-aza derivatives of adenosine,[29,30] also did not proceed. These results were thought to be due to the relatively low reactivity of the 5' position of adenosine and our aminoethylene compounds **3**.

Recently, Sajiki's group reported catalytic monoalkylation of various primary amines using nitrile as an alkylating reagent.[31] In their paper, Rh/C was utilized for monoalkylation of aliphatic amines, and secondary aliphatic amines were mainly obtained by using Pd/C. So, we initially utilized Rh/C catalyst for the monoalkylation of **2c** with Boc-protected methylamino acetonitrile (**5a**). However, this reaction did not proceed, whereas the reaction using Pd/C afforded secondary amine **6a** in moderate yield (Scheme 2). These results were due to the low reactivity of our compounds, as well as failure of the alkylating reaction shown in Scheme 1. Compound **6a** was further alkylated with iodinated oxazolidinone (**4**),[24] yielding tertiary amino compound **7a**. Then, the oxazolidinone ring was opened under basic conditions to provide **8a**, and subsequent deprotection gave compound **1a**. Compound **1e**, which does not have additional nitrogen, was similarly prepared starting from compound **2c** and pentylnitrile (**5e**). Reductive alkylation and the introduction of oxazolidinone gave tertiary amino compound **7e**. After ring opening and deprotection, compound **1e** was obtained.

Next, we tried to prepare compounds **1b**, **1c** and **1d** in a similar manner. However, in the case of **1b**, reductive alkylation reaction of **2c** with the nitrile compound bearing the *n*-propyl group (**7b**) did not proceed, and rearrangement of the Boc group occurred to yield compound **10** (Scheme 3). Compound **5c** with the *n*-pentyl group behaved similarly to **5b**. So we changed the reactive group of this conjugation reaction from the nitrile group to diisobutylaluminium-imine complex with DIBAL-H, as reported by Van

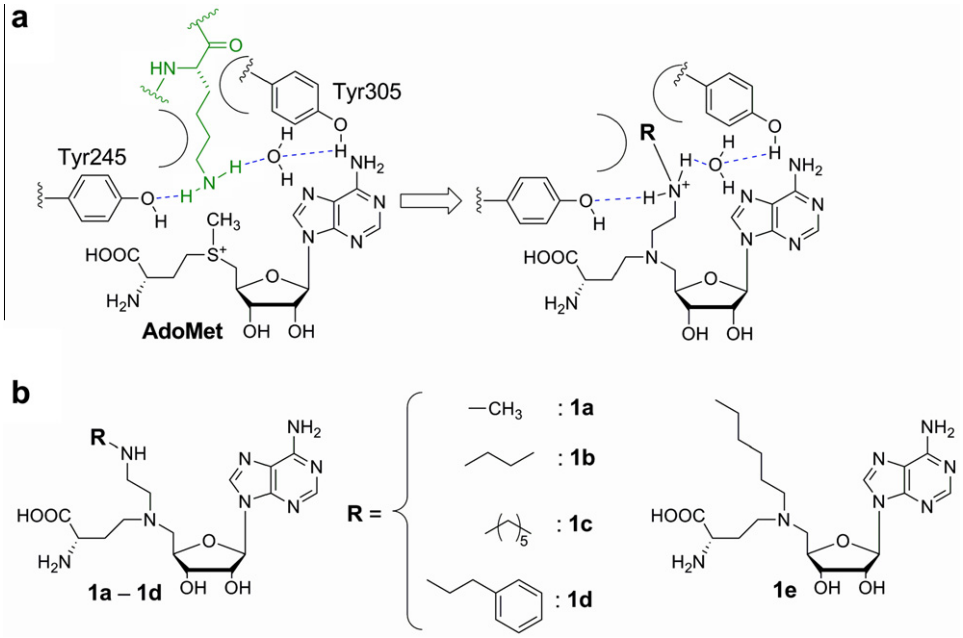
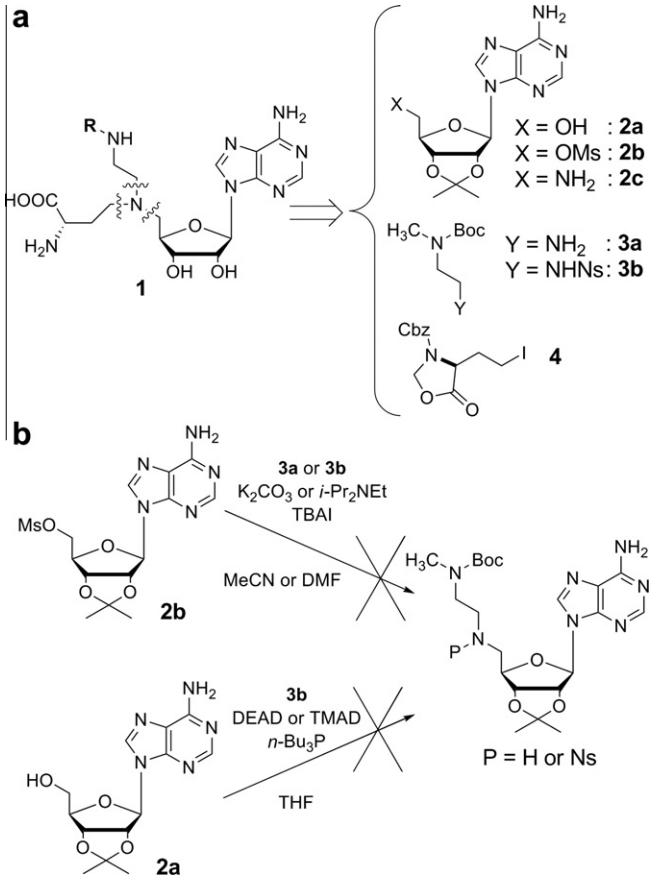


Figure 3. Design of novel inhibitor candidates. (a) On the left, a schematic representation of the structure of SET7/9 ternary complex with histone peptide (shown in green) and AdoMet is presented, and on the right, our strategy for the design of novel inhibitor candidates is shown. (b) Structure of novel SET7/9 inhibitor candidates **1a**–**1e**.



Scheme 1. (a) Retrosynthetic analysis of compounds **1** and (b) attempts to construct the secondary amino structure.

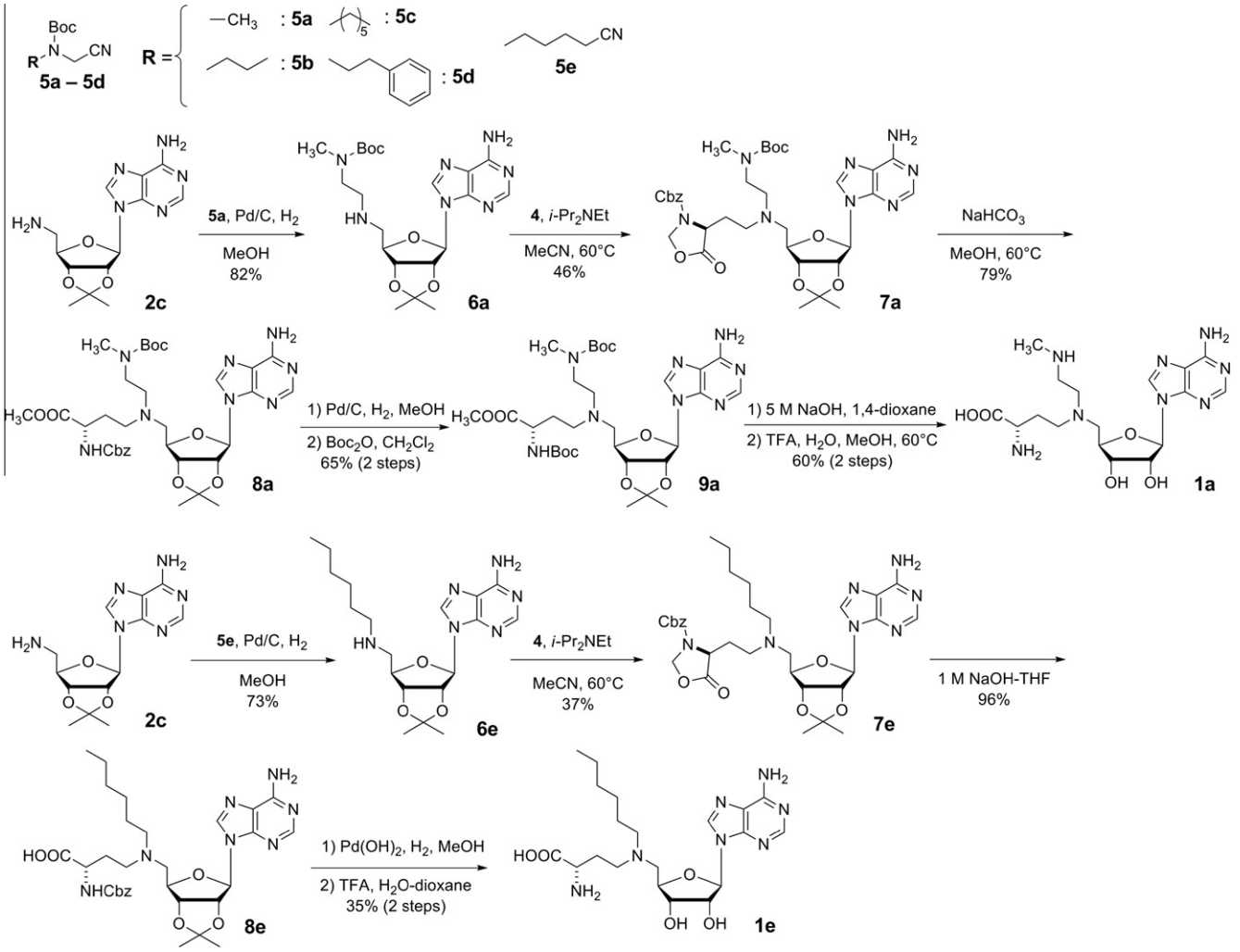
Wagene's group.[32] The conjugation of **2c** with **5b**– **5d** via the reaction with DIBAL-H proceeded in moderate yield, and secondary amine compounds **6b**–**6d** were obtained (Scheme 4). These compounds were further alkylated with oxazolidinone **4** to yield compounds **7b**–**7d**, then opening of the ozazolidinone ring gave **8b**–**8d** and deprotection afforded **1b**–**1d**.

2.3. Inhibitory activity towards SET7/9

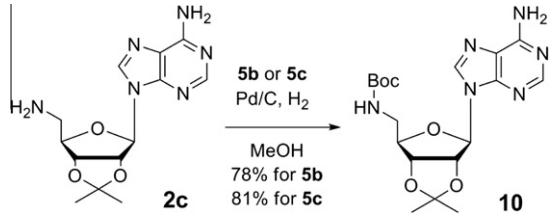
The inhibitory activity of the synthesized compounds towards histone methyltransferase SET7/9 was examined by utilizing anti-monomethyl-histone H3 (Lys4) antibody, and the results are shown in Figure 4. Compounds **1a**–**1d** showed relatively strong inhibitory activity compared with compound **1e**, which lacks the additional nitrogen. The inhibitory activities were little affected by the nature of the alkyl group attached to the nitrogen, though compound **1c** with a *n*-hexyl group was slightly more potent than the other compounds. Sinefungin, which is another derivative with a branched nitrogen substituent at the 5' position of adenosine, also showed strong inhibitory activity, so a nitrogen atom around this position seems to enhance inhibitory potency towards SET7/9.

3. Discussion

Compounds **1a**–**1d** were designed as derivatives of AzaAdoMet bearing an additional alkylamino group, which was expected to interact with the enzyme in the same manner as the lysine side chain of the substrate. Compared with **1e**, which lacks the additional nitrogen atom, **1a**–**1d** showed relatively potent inhibitory activities towards SET7/9. The nature of the alkyl group attached to this nitrogen had a small influence on the inhibitory activity. From the reported crystal structure of the ternary complex of human SET7/9 with histone peptide and cofactor, the cofactor and substrate peptide bind on opposite surfaces of the enzyme.[18] The side chain of the substrate lysine residue can access AdoMet through a narrow channel connecting the two surfaces. In the case of our compounds, it was expected that the alkylamino chain would pass thorough this channel, and interact with amino acids forming the channel. Compared with the methyl derivative (**1a**), *n*-propyl derivative (**1b**) or phenethyl (**1d**)-conjugated compound, the *n*-hexyl compound (**1c**) was slightly more potent. These results presumably reflect the better hydrophobic interaction of the



Scheme 2. Synthesis of compounds **1a** and **1e** via reductive alkylation.



Scheme 3.

n-hexyl group with side chains of amino acids forming the channel, such as Leu267, Tyr305, Tyr335 and Tyr337. Sinefungin also showed strong inhibitory activity, so in this case, the presence of the nitrogen atom around this position of adenosine appeared to enhance SET7/9 inhibition.

The in situ formation of bisubstrate inhibitors of protein arginine methyltransferase (PRMT) from a AdoMet analogue and peptide substrate has already been reported.[33] Very recently, Dowden's group developed AzaAdoMet analogues with guanidine functionality linked via various alkyl moieties as protein arginine methytransferase inhibitors.[34] Here, we have developed a versatile synthetic approach to secondary amine-containing AzaAdoMet analogues via reductive amination with various nitrile compounds in order to obtain novel histone lysine methyltransferase inhibitors. From our data in Figure 4, the position of nitrogen is an important determinant of the inhibitory activity. Our synthetic scheme via reductive amination should be useful to produce AzaAdoMet derivatives substituted with various functional groups from corresponding nitrile compounds. We are adopting this methodology in further studies aimed at obtaining more potent and selective inhibitors.

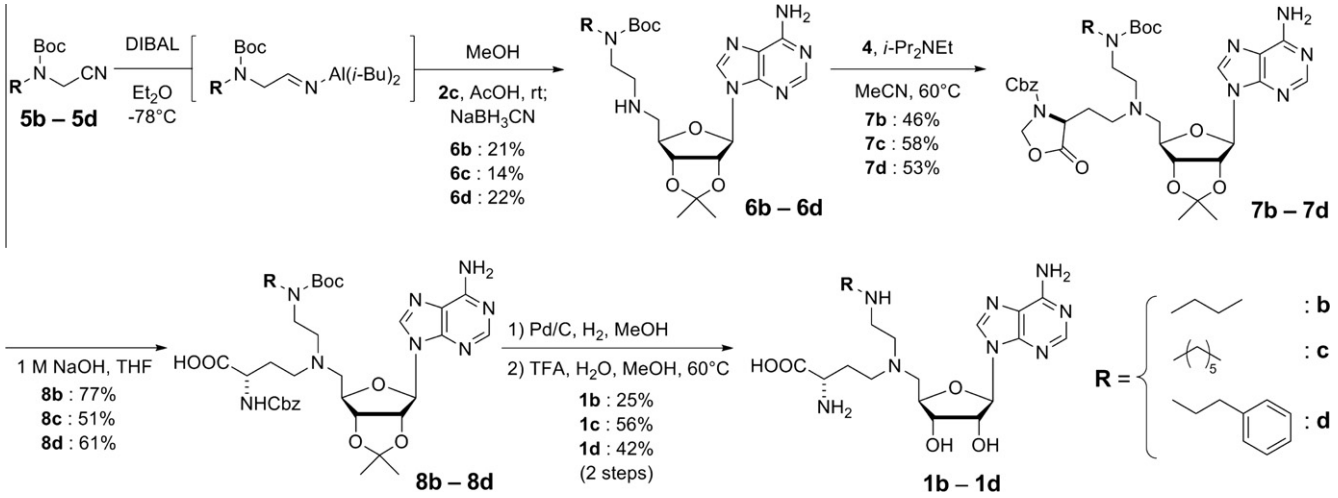
4. Conclusion

We have designed and synthesized histone lysine methytransferase (SET7/9) inhibitors, **1a**–**1d**, consisting of AzaAdoMet substituted with various alkylamino groups. These compounds showed relatively potent inhibitory activities, and are expected to be lead compounds for development of more potent and selective inhibitors.

5. Experimental

5.1. General information

All reagents were purchased from Sigma–Aldrich Chemical Co., Tokyo Kasei Kogyo Co., Wako Pure Chemical Industries, and Kanto



Scheme 4. Synthesis of compounds **1b**–**1d**.

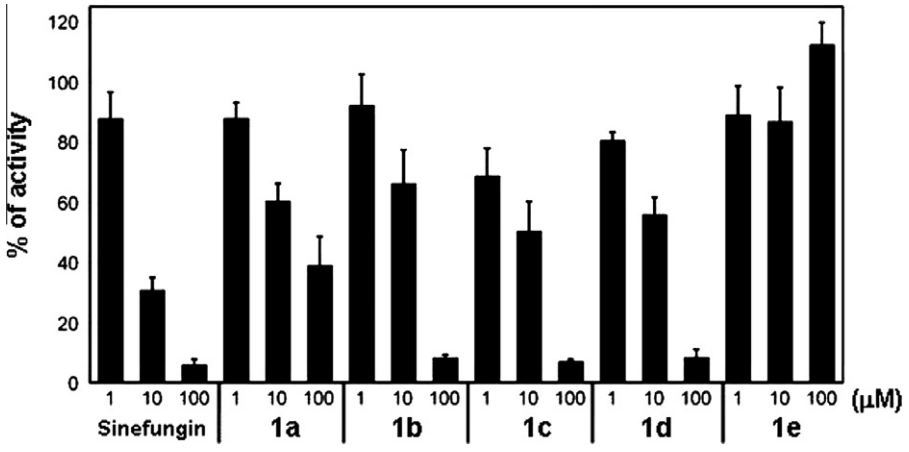


Figure 4. Inhibitory activities of compounds **1a**–**1e** and sinefungin on SET7/9. Monomethylation of H3K4 by SET7/9 and AdoMet (2 μM), and its inhibition by each inhibitor at 1–100 μM were detected with anti-monomethyl-histone H3 (Lys4), HRP-fused secondary antibody and substrate for HRP. The activity was quantified in terms of OD450, shown as a percentage of the value with no inhibitor, taken as 100%. Values are the mean ± SD for separate experiments ($n = 3$).

Kagaku Co., Inc. Silica gel for column chromatography was purchased from Kanto Kagaku Co., Inc. ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance 500 instrument. The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, dd = doublet of doublet, t = triplet, q = quartet, m = multiplet, br = broad, brs = broad singlet, br m = broad multiplet. Mass spectral data was obtained on a Bruker Daltonics microTOF-2focus in the positive and negative ion detection modes. Melting points, determined on a Yanaco Micro Melting Point Apparatus, are uncorrected. Preparative reversed-phase HPLC was performed with a reversed-phase column (Mightysil RP-18 GP 250–20 (5 μm)) on JASCO UV-2070, PU-2080, PU-2080 and MX-2080-32 components. Analytical thin layer chromatography (TLC) was performed on Merck precoated analytical plates, 0.25 mm thick, Silica Gel 60 F_{254}. Preparative TLC separations were made on Merck precoated analytical plates, 0.50 mm thick, Silica Gel 60 F_{254}. All non-aqueous reactions were carried out in oven-dried glass apparatus under a slight positive pressure of argon. All solvents were used after having been dried over molecular sieves 3A or 4A or commercially available dehydrated solvents. For the assay of methyltransferase activity, OD450 was recorded on a PerkinElmer 1420 multilabel counter, ARVO MX. All other reagents were commercial products and were used without further purification.

5.2. Synthesis

5.2.1. Synthesis of compound 6a

Compound **2c** (0.30 g, 0.98 mmol) was added to Pd/C (21 mg, 20 mol %) and **5a** (0.83 g, 5.0 equiv) in methanol (5.0 ml). The flask was purged with hydrogen. The mixture was stirred for 26 h at room temperature, then filtered through a Celite bed and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography (neat dichloromethane then 3% methanol in dichloromethane) to afford **6a** (0.37 g, 0.80 mmol, 82%) as a colorless foam.

Compound **6a**. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.32 (s, 1H), 8.14 (s, 1H), 7.30 (s, 2H), 6.07 (d, J = 2.5 Hz, 1H), 5.44 (br, 1H), 4.94 (d, J = 6.0, 3.0 Hz, 1H), 4.20–4.17 (m, 1H), 3.20 (br, 1H), 3.14–3.10 (m, 2H), 2.76–2.58 (m, 4H), 2.69 (s, 3H), 1.52 (s, 3H), 1.32 (s, 9H), 1.22 (s, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 156.25, 156.01, 148.92, 140.54, 119.29, 114.20, 90.23, 85.29, 83.40, 82.47, 79.64, 50.74, 46.75, 33.47, 27.23, 26.09, 24.17; HRMS (ESI+) calcd for $C_{21}H_{34}N_7O_5$ (M^++H) 464.2616, found 464.2612.

5.2.2. Synthesis of compound 7a

N,*N*-Diisopropylethylamine (75.2 μmol, 2.0 equiv) was added to a stirred solution of **6a** (105 mg, 1.3 equiv) and **4** (100 mg,

0.22 mmol) in acetonitrile (1.5 ml) at room temperature. The mixture was stirred at 60 °C for two days, then the solvent was removed in vacuo. The residue was purified by flash column chromatography (3% methanol in dichloromethane) to afford **7a** (70.8 mg, 0.10 mmol, 46%) as a pale brown foam.

Compound **7a**: ^{1}H NMR (500 MHz, CD_3OD) δ 8.23 (s, 2H), 7.36–7.31 (m, 5H), 6.15 (d, J = 1.6 Hz, 1H), 5.48–5.44 (m, 2H), 5.25–5.11 (m, 3H), 4.98–4.96 (m, 1H), 4.53 (br, 1H), 4.34 (m, 2H), 3.26–3.16 (br, 2H), 2.74–2.53 (m, 6H), 2.70 (s, 3H), 2.03 (br, 2H), 1.58 (s, 3H), 1.41 (s, 9H), 1.37 (s, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 172.49, 155.98, 155.87, 152.67, 148.80, 140.72, 136.51, 136.18, 128.06, 127.74, 127.36, 119.30, 114.00, 90.25, 85.42, 83.50, 83.29, 83.22, 79.56, 67.40, 67.12, 56.12, 51.48, 51.14, 34.04, 33.85, 27.37, 26.17, 24.31; HRMS (ESI+) calcd for $C_{34}H_{47}N_8O_9$ (M^++H) 711.3461, found 711.3454.

5.2.3. Synthesis of compound 8a

Sodium bicarbonate (17.0 mg, 1.2 equiv) was added to a stirred solution of **7a** (120 mg, 0.17 mmol) in methanol (1.0 ml) at room temperature. The mixture was stirred for 7 h at 60 °C, then quenched with saturated aqueous ammonium chloride and extracted with dichloromethane. The organic layer was dried over magnesium sulfate and filtered. The solvent was removed in vacuo. The residue was purified by flash column chromatography (2% methanol in dichloromethane) to afford **8a** (95.0 mg, 0.13 mmol, 79%) as a colorless foam.

Compound 8a: ^{1}H NMR (500 MHz, MeOD) δ 8.22 (s, 1H), 8.21 (s, 1H), 7.35–7.28 (m, 5H), 6.14 (d, J = 2.0 Hz, 1H), 5.49 (d, J = 5.5 Hz, 1H), 5.09–5.05 (m, 2H), 5.04–5.03 (m, 1H), 4.31–4.29 (m, 2H), 3.69 (s, 3H), 3.17–3.15 (m, 2H), 2.83–2.51 (m, 9H) 1.97 (br, 1H), 1.65 (br, 1H), 1.58 (s, 3H), 1.41 (s, 9H), 1.37 (s, 3H); ^{13}C NMR (125 MHz, MeOD) δ 173.27, 157.02, 156.00, 152.63, 152.62, 148.84, 140.64, 136.79, 128.06, 127.59, 127.38, 119.34, 114.12, 90.26, 85.50, 83.53, 83.17, 79.55, 66.21, 56.17, 52.30, 51.32, 48.08, 47.91, 33.88, 28.78, 27.42, 26.13, 24.26; HRMS (ESI+) calcd for $C_{34}H_{49}N_8O_9$ (M^++H) 713.3617, found 713.3634.

5.2.4. Synthesis of compound 9a

Compound **8a** (85.0 mg, 0.12 mmol) was added to methanol (1.0 ml) and Pd/C (25.4 mg, 20 mol %) at 0 °C under an argon atmosphere. The flask was purged with hydrogen. The mixture was stirred for one day at room temperature, then filtered through a Celite bed and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography on a short column (7% methanol in dichloromethane then 12%) to afford the amine (65.2 mg, 0.11 mmol, 95%) as colorless foam. To a stirred solution of the amine (60.0 mg, 0.10 mmol) in dichloromethane was added di-*t*-butyl bicarbonate (27.2 mg, 1.2 equiv) at room temperature. The mixture was stirred for 1 h at room temperature, then concentrated in vacuo. The residue was purified by flash column chromatography (2% methanol in dichloromethane) to afford **9a** (48.0 mg, 70 μmol, 68%) as a colorless foam.

Compound **9a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (s, 1H), 8.23 (s, 1H), 6.16 (d, J = 2.5 Hz, 1H), 5.52 (d, J = 6.0 Hz, 1H), 5.05 (br, 1H), 4.32–4.29 (m, 1H), 4.22 (br, 1H), 3.69 (s, 3H), 3.18 (br, 2H), 2.84–2.52 (m, 9H), 1.93 (br, 1H), 1.66 (br, 1H), 1.60 (s, 3H), 1.43 (s, 18H), 1.39 (s, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 173.57, 156.57, 156.02, 152.60, 148.85, 140.67, 119.30, 114.07, 90.32, 85.52, 83.52, 83.24, 79.56, 79.14, 56.14, 52.07, 51.83, 51.18, 48.08, 33.87, 28.80, 27.36, 27.26, 26.08, 24.18; HRMS (ESI+) calcd for $C_{31}H_{51}N_8O_9$ (M^++H) 679.3774, found 679.3773.

5.2.5. Synthesis of compound 1a

A solution of **9a** (12.7 mg, 19 μmol) in 1,4-dioxane (0.15 ml) and 5 M aqueous sodium hydroxide (0.15 ml) was stirred for 4.5 h at room temperature. The reaction mixture was quenched with 10% citric acid and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and filtered. The solvent was removed in vacuo, and the residue was purified by PTLC (9% methanol in dichloromethane) to afford the carboxylic acid (10.7 mg, 16 μmol, 86%) as a white solid. A solution of the carboxylic acid (10.7 mg, 16 μmol) in methanol (60 μl), water (60 μl) and trifluoroacetic acid (0.12 ml) was stirred for 1.5 h at 60 °C. The reaction mixture was concentrated in vacuo. The residue was purified by HPLC to afford **2a** (4.0 mg, 9.4 μmol, 70%) as a white solid. Mp 150 °C (acetonitrile–H_2O, decomp.).

Compound **1a**: ^{1}H NMR (500 MHz, D_2O) δ 8.43 (s, 1H), 8.42 (s, 1H), 6.16 (d, J = 3.5 Hz, 1H), 4.79 (t, J = 4.0 Hz, 1H), 4.48–4.44 (m, 2H), 3.87 (dd, J = 9.5 3.5 Hz, 1H), 3.66–3.65 (m, 2H), 3.55–3.39 (m, 6H), 2.69 (s, 3H), 2.34–2.28 (m, 1H), 2.16–2.13 (m, 1H); ^{13}C NMR (125 MHz, D_2O) δ 171.50, 150.04, 148.11, 144.52, 143.45, 119.30, 90.19, 78.09, 73.05, 71.55, 55.86, 52.33, 51.49, 48.94, 48.74, 24.61; HRMS (ESI+) calcd for $C_{17}H_{29}N_8O_5$ (M^++H) 425.2255, found 425.2255.

5.2.6. Synthesis of compound 6b

Diisobutylaluminium hydride (1.0 M solution in toluene, 1.0 ml, 2.0 equiv) was added dropwise to a stirred solution of **5b** (100 mg, 0.54 mmol) in diethyl ether (4.0 ml) over 5 min at −78 °C. The mixture was stirred for 20 min at −78 °C, then methanol (0.5 ml) was added and stirring was continued for 10 min at the same temperature. Then, **2c** (185 mg, 1.2 equiv) in methanol (3.0 ml) was added dropwise to the reaction mixture over 5 min at −78 °C and stirring was continued for 2 h at room temperature. Then, sodium borohydride (38.2 mg, 2.0 equiv) was added and the reaction mixture was stirred for 14 h at room temperature, then concentrated in vacuo. The residue was partitioned between dichloromethane and saturated aqueous sodium bicarbonate. The organic layer was dried over magnesium sulfate and filtered. The solvent was removed in vacuo, and the residue was purified by flash column chromatography (2% methanol in dichloromethane then 5%) to afford **6b** (53.0 mg, 0.11 μmol, 21%) as a colorless foam.

Compound **6b**: ^{1}H NMR (500 MHz, CD_3OD) δ 8.26 (s, 1H), 8.23 (s, 1H), 6.10 (d, J = 3.0 Hz, 1H), 5.37 (br, 1H), 4.98 (m, 1H), 4.33 (br, 1H), 3.45–3.34 (m, 4H), 3.18 (t, J = 7.5 Hz, 2H), 2.76 (t, J = 7.0 Hz, 2H), 2.94–2.92 (m, 2H), 2.73–2.71 (m, 2H), 1.60 (s, 3H), 1.52–1.47 (m, 2H), 1.42 (s, 9H), 1.40 (s, 3H), 0.85 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 156.02, 152.58, 148.92, 140.56, 119.30, 114.28, 90.23, 85.42, 83.50, 82.48, 79.66, 50.82, 48.08, 47.06, 43.08, 27.23, 26.07, 24.15, 10.01; HRMS (ESI+) calcd for $C_{23}H_{38}N_7O_5$ (M^++H) 492.2929, found 492.2917.

5.2.7. Synthesis of compound 7b

N,*N*-Diisopropylethylamine (29.8 μmol, 2.0 equiv) was added to a stirred solution of **6b** (42.0 mg, 85 μmol) and **4** (38.5 mg, 1.2 equiv) in acetonitrile (0.6 ml) at room temperature. The mixture was stirred at 60 °C for two days, then the solvent was removed in vacuo. The residue was purified by flash column chromatography (50% ethyl acetate in *n*-hexane then neat ethyl acetate) to afford **7b** (28.7 mg, 39 μmol, 46%) as a colorless foam.

Compound **7b**: ^{1}H NMR (500 MHz, CD_3OD) δ 8.23 (s, 2H), 7.36–7.31 (m, 5H), 6.15 (d, J = 2.5 Hz, 1H), 5.47 (br, 1H), 5.44 (d, J = 4.0 Hz, 1H), 5.30 (br, 1H), 5.18–5.14 (br m, 2H), 4.96–4.95 (m, 1H), 4.33–4.27 (m, 2H), 3.12 (br, 2H), 3.02–2.97 (m, 2H), 2.76–2.74 (m, 2H), 2.51 (br, 4H), 2.04 (br, 2H), 1.58 (s, 3H), 1.45–1.38 (m, 2H), 1.41 (s, 9H), 1.37 (s, 3H), 0.76 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 172.51, 167.86, 155.99, 155.80, 152.63, 148.82, 140.64, 130.91, 128.24, 128.11, 127.82, 119.27, 114.18, 90.14, 83.51, 83.49, 83.12, 79.50, 77.75, 67.37, 65.85, 56.24, 52.77, 21.29, 48.92, 27.37, 26.43, 24.20, 22.60, 10.04; HRMS (ESI+) calcd for $C_{36}H_{51}N_8O_9$ (M^++H) 739.3774, found 739.3796.

5.2.8. Synthesis of compound 8b

A solution of **7b** (27.5 mg, 37 μmol) in tetrahydrofuran (0.15 ml) and 1 M aqueous sodium hydroxide (0.15 ml) was stirred for 1.5 h at room temperature. The reaction mixture was quenched with 10% aqueous citric acid and extracted with dichloromethane. The organic layer was dried over magnesium sulfate and filtered. The solvent was removed in vacuo, and the residue was purified by PTLC (8% methanol in dichloromethane) to afford **8b** (20.7 mg, 28 μmol, 77%) as a colorless foam.

Compound **8b**: ^{1}H NMR (500 MHz, CD_3OD) δ 8.24 (s, 2H), 7.35–7.26 (m, 5H), 6.21 (br, 1H), 5.45 (d, J = 5.5 Hz, 1H), 5.10–5.07 (m, 3H), 4.50–4.40 (br m, 1H), 4.21–4.14 (br m, 1H), 3.27–2.81 (br m, 10 H), 2.06 (br, 1H), 1.80 (br, 1H), 1.59 (s, 3H), 1.48–1.32 (m, 2H), 1.40 (s, 9H), 1.37 (s, 3H), 0.78 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 175.14, 156.95, 156.24, 156.02, 152.66, 148.71, 140.74, 136.81, 128.05, 127.55, 127.36, 119.37, 114.39, 90.44, 83.75, 83.58, 83.02, 79.85, 66.17, 55.65, 53.29, 52.31, 52.04, 43.37, 27.31, 26.05, 24.14, 21.00, 10.00; HRMS (ESI+) calcd for $C_{35}H_{51}N_8O_9$ (M^++H) 727.3774, found 727.3779.

5.2.9. Synthesis of compound 1b

Compound **8b** (18.0 mg, 25 μmol) was added to methanol (0.3 ml) and Pd/C (2.6 mg, 10 mol %) at 0 °C under an argon atmosphere. The flask was purged with hydrogen, and stirred for 20 h at room temperature. The reaction mixture was filtered through a Celite bed and concentrated in vacuo. The residue was purified by PTLC (12% methanol in dichloromethane) to afford the amine (6.2 mg, 11 μmol, 42%) as a colorless foam. A solution of the amine (6.2 mg, 11 μmol) in methanol (80 μl), water (80 μl) and trifluoroacetic acid (0.16 ml) was stirred for 2 h at 60 °C. The reaction mixture was concentrated in vacuo. The residue was purified by HPLC to afford **2d** (2.8 mg, 6.2 μmol, 59%) as a white solid. Mp 168 °C (acetonitrile–H_2O, decomp.).

Compound **1b**: ^{1}H NMR (500 MHz, D_2O) δ 8.40 (s, 1H), 8.39 (s, 1H), 6.12 (d, J = 3.5 Hz, 1H), 4.77 (t, J = 4.5 Hz, 1H), 4.45–4.42 (m, 2H), 3.83–3.82 (m, 1H), 3.62 (br, 2H), 3.46–3.29 (m, 6H), 2.88 (t, J = 7.5 Hz, 2H), 2.27–2.26 (m, 1H), 2.12–2.10 (m, 1H), 1.52 (m, 2H), 0.82 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, D_2O) δ 173.08, 151.13, 148.26, 146.20, 142.95, 119.21, 89.65, 79.32, 72.87, 71.57, 55.61, 52.91, 52.71, 49.48, 48.68, 42.02, 25.39, 18.91, 9.95; HRMS (ESI+) calcd for $C_{19}H_{33}N_8O_5$ (M^++H) 453.2568, found 453.2580.

5.2.10. Synthesis of compound 6c

Compound **6c** was prepared from **5c** (150 mg, 0.62 mmol) and **2c** (382 mg, 2.0 equiv) according to the procedure described for **6b** in a yield of 14% (45.5 mg, 85 μmol, colorless foam).

Compound **6c**: ^{1}H NMR (500 MHz, CD_3OD) δ 8.27 (s, 1H), 8.22 (s, 1H), 6.15 (d, J = 2.5 Hz, 1H), 5.47 (br, 1H), 5.00 (dd, J = 6.5, 3.5 Hz, 1H), 4.34–4.31 (m, 1H), 3.26–3.18 (m, 2H), 3.12–3.08 (m, 2H), 2.90 (d, J = 6.0 Hz, 2H), 2.71–2.67 (m, 2H), 1.59 (s, 3H), 1.48–1.44 (m, 4H), 1.37 (s, 3H), 1.31 (s, 9H), 1.30–1.20 (m, 4H), 0.88 (t, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 156.02, 152.59, 148.92, 140.53, 119.31, 114.23, 90.21, 85.31, 83.45, 82.45, 79.49, 50.80, 48.11, 47.94, 47.77, 31.24, 27.29, 26.06, 24.21, 22.22, 12.93; HRMS (ESI+) calcd for $C_{26}H_{44}N_7O_5$ (M^++H) 534.3398, found 534.3385.

5.2.11. Synthesis of compound 7c

Compound **7c** was prepared from **6c** (25.2 mg, 47 μmol) and **4** (35.4 mg, 2.0 equiv) according to the procedure described for **7b** in a yield of 58% (21.5 mg, 28 μmol, colorless foam).

Compound **7c**: ^{1}H NMR (500 MHz, CD_3OD) δ 8.23 (s, 2H), 7.37–7.32 (m, 5H), 6.15 (d, J = 2.5 Hz, 1H), 5.45–5.44 (br, 2H), 5.26 (br, 1H), 5.22–5.19 (br m, 2H), 4.96–4.95 (m, 1H), 4.34–4.30 (m, 2H), 3.15–3.00 (br m, 4H), 2.76 (br, 2H), 2.58–2.53 (br m, 4H), 2.04 (br, 2H), 1.58 (s, 3H3H), 1.45–1.38 (m, 8H), 1.41 (s, 9H), 1.38 (s, 3H), 0.87 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 172.89, 155.98, 155.76, 152.67, 148.82, 140.62, 135.94, 128.25, 128.11, 128.01, 127.82, 119.28, 114.21, 90.12, 83.51, 83.46, 83.08, 77.76, 67.36, 56.26, 52.78, 52.00, 48.04, 47.87, 47.70, 31.26, 27.40, 27.34, 26.14, 26.08, 24.23,22.24, 12.95; HRMS (ESI+) calcd for $C_{39}H_{57}N_8O_9$ (M^++H) 781.4243, found 781.4266.

5.2.12. Synthesis of compound 8c

Compound **8c** was prepared from **7c** (22.0 mg, 28 μmol) according to the procedure described for **8b** in a yield of 51% (11.1 mg, 14 μmol, colorless foam.).

Compound **8c**: ^{1}H NMR (500 MHz, CD_3OD) δ 8.24 (s, 2H), 7.35–7.27 (m, 5H), 6.20 (br, 1H), 5.44 (d, J = 5.0 Hz, 1H), 5.07 (br, 3H), 4.48–4.39 (br m, 1H), 4.21–4.14 (br m, 1H), 3.20–2.81 (br m, 10H), 2.05 (br, 1H), 1.80 (br, 1H), 1.59 (s, 3H), 1.41 (s, 9H), 1.37 (s, 3H), 1.28–1.16 (br m, 8H), 0.88 (t, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 175.09, 156.90, 156.01,152.66, 148.72, 140.68, 136.82, 128.04, 127.54, 127.33, 119.35, 114.39, 90.40, 83.57, 82.82, 79.80, 66.14, 55.87, 55.63, 52.07, 48.03, 43.27, 31.24, 28.34, 27.96, 27.32, 26.06, 26.00, 24.15, 22.23, 12.93; HRMS (ESI+) calcd for $C_{38}H_{57}N_8O_9$ (M^++H) 769.4243, found 769.4256.

5.2.13. Synthesis of compound 1c

Compound **1c** was prepared from **8c** (11.0 mg, 14 μmol) according to the procedure described for **1b** in a yield of 56% (two steps, 4.0 mg, 8.2 μmol, white solid. Mp 195 °C (acetonitrile–H_2O, decomp.).

Compound **1c** ^{1}H NMR (500 MHz, D_2O) δ 8.39 (s, 1H), 8.38 (s, 1H), 6.11 (d, J = 4.0 Hz, 1H), 4.73 (t, J = 5.0 Hz, 1H), 4.42–4.37 (m, 2H), 3.83–3.81 (m, 1H), 3.54 (br, 2H), 3.40–3.29 (m, 6H), 2.86–2.82 (m, 2H), 2.26–2.23 (m, 1H), 2.11–2.07 (m, 1H), 1.43–1.39 (m, 2H), 1.18–1.10 (m, 6H), 0.76 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, D_2O) δ 172.98, 150.62, 148.20, 145.82, 142.99, 119.16, 89.72, 79.19, 72.96, 71,47, 55.51, 53.00, 52.87, 48.59, 47.91, 41.83, 30.29, 25.30, 25.15, 25.14, 21.64, 13.13; HRMS (ESI+) calcd for $C_{22}H_{39}N_8O_5$ (M^++H) 495.3038, found 495.3056.

5.2.14. Synthesis of compound 6d

Compound **6d** was prepared from **5d** (50 mg, 0.19 mmol) and **2c** (118 mg, 2.0 equiv) according to the procedure described for **6b** in a yield of 22% (23.0 mg, 42 μmol, colorless foam).

Compound **6d** ^{1}H NMR (500 MHz, CD_3OD) δ 8.29 (s, 1H), 8.24 (s, 1H), 7.28–7.23 (m, 2H), 7.17–7.11 (m, 3H), 6.17 (d, J = 3.0 Hz, 1H), 5.48 (br, 1H), 5.01 (m, 1H), 4.35–4.32 (m, 1H), 3.39–3.36 (m, 2H), 3.25–3.16 (br m, 2H), 2.91 (br, 2H), 2.77 (br, 2H), 2.68 (br, 2H), 1.61 (s, 3H), 1.39 (s, 3H), 1.37 (s, 9H); ^{13}C NMR (125 MHz, CD_3OD) δ 156.01, 152.59, 148.91, 140.53, 139.07, 128.54, 128.06, 125.88, 119.30, 114.24, 90.22, 85.23, 83.43, 82.42, 79.63, 53.36, 50.73, 49.24, 47.86, 27.19, 26.07, 24.16; HRMS (ESI+) calcd for $C_{28}H_{40}N_7O_5$ (M^++H) 554.3085, found 554.3076.

5.2.15. Synthesis of compound 7d

Compound **7d** was prepared from **6d** (37.5 mg, 68 μmol) and **4** (30.5 mg, 1.2 eq) according to the procedure described for **7b** in a yield of 53% (28.6 mg, 36 μmol, colorless foam).

Compound **7d** ^{1}H NMR (500 MHz, CD_3OD) δ 8.23 (s, 1H), 8.22 (s, 1H), 7.34–7.07 (m, 10H), 6.14 (d, J = 2.5 Hz, 1H), 5.46 (br, 1H), 5.43 (d, J = 4.0 Hz, 1H), 5.20 (br, 1H), 5.18–5.14 (br m, 2H), 4.95–4.93 (m, 1H), 4.32–4.29 (m, 2H), 3.18–2.48 (m, 12H), 2.00 (br, 2H), 1.57 (s, 3H), 1.40 (s, 9H), 1.35 (s, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 172.90, 171.55, 155.97, 155.62, 152.68, 148.82, 140.55, 139.08, 135.92, 128.59, 128.25, 128.02, 127.83, 127.61, 125.80, 119.28, 114.16, 90.16, 83.51, 83.12, 82.81, 79.33, 77.76, 67.38, 66.31, 60.10, 56.30, 53.38, 52.81, 34.51, 34.00, 27.27, 24.21; HRMS (ESI+) calcd for $C_{41}H_{53}N_8O_9$ (M^++H) 801.3930, found 801.3954.

5.2.16. Synthesis of compound 8d

Compound **8d** was prepared from **7d** (27.0 mg, 34 μmol) according to the procedure described for **8b** in a yield of 61% (16.2 mg, 21 μmol, colorless foam).

Compound **8d**: ^{1}H NMR (500 MHz, CD_3OD) δ 8.24 (s, 1H), 8.21 (s, 1H), 7.34–7.26 (m, 5 H), 7.25–7.22 (m, 2H), 7.16–7.11 (m, 3H), 6.20–6.17 (br, 1H), 5.43 (d, J = 6.0 Hz, 1H), 5.06 (br, 3H), 4.47–4.37 (br m, 1H), 4.18–4.12 (br m, 1H), 3.27–3.15 (br m, 4H), 2.93–2.68 (br m, 8H), 2.02 (br, 1H), 1.77 (br, 1H), 1.58 (s, 3H), 1.40–1.35 (m, 9H), 1.34 (s, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 176.26, 156.91, 155.99, 152.66, 148.69, 140.70, 139.03, 136.79, 128.61, 128.12, 128.05, 127.57, 127.39, 125.93, 125.85, 119.35, 114.38, 90.48, 84.67, 83.59, 83.01, 79.97, 66.18, 64.86, 56.58, 55.63, 52.19, 52.01, 49.02, 34.35, 27.18, 26.06, 24.14; HRMS (ESI+) calcd for $C_{40}H_{53}N_8O_9$ (M^++H) 789.3930, found 789.3943.

5.2.17. Synthesis of compound 1d

Compound **1d** was prepared from **8d** (15.2 mg, 19 μmol) according to the procedure described for **1b** in a yield of 42% (2 steps, 4.1 mg, 8.0 μmol, white solid). Mp 186 °C (acetonitrile–H_2O, decomp.).

Compound **1d**: ^{1}H NMR (500 MHz, D_2O) δ 8.38 (s, 1H), 8.31 (s, 1H), 7.30–7.23 (m, 3H), 7.07 (d, J = 7.5 Hz, 2H), 6.08 (d, J = 4.0 Hz, 1H), 4.65 (m, 1H), 4.41–4.35 (m, 2H), 3.85–3.83 (m, 1H), 3.58–3.34 (m, 8H), 3.11 (t, J = 7.5 Hz, 2H), 2.67 (t, J = 7.5 Hz, 2H), 2.28–2.25 (m, 1H), 2.11–2.09 (m, 1H); ^{13}C NMR (125 MHz, D_2O) δ 172.77, 149.36, 147.84, 144.97, 135.74, 129.03, 128.49, 127.46, 118.97, 89.69, 78.92, 73.01, 71.36, 55.38, 53.21, 52.67, 48.51, 48.80, 41.43, 31.10, 25.23; HRMS (ESI+) calcd for $C_{24}H_{35}N_8O_5$ (M^++H) 515.2725, found 515.2716.

5.2.18. Synthesis of compound 6e

Compound **6e** was prepared from **5e** (0.19 ml, 5.0 equiv) and **2c** (100 mg, 0.33 mmol) according to the procedure described for **6a** in a yield of 73% (93 mg, 0.24 mmol, colorless oil).

Compound **6e**: ^{1}H NMR (500 MHz, MeOD) δ 8.28 (s, 1H), 8.21 (s, 1H), 6.16 (d, J = 2.5 Hz, 1H), 5.52 (m, 1H), 5.01 (m, 1H), 4.36–4.33 (m, 1H), 2.87–2.83 (m, 2H), 2.53–2.46 (m, 2H), 1.59 (s, 3H), 1.38 (s, 3H), 1.34–1.20 (m, 8H), 0.87 (t, J = 6.0 Hz, 3H); HRMS (ESI+) calcd for $C_{19}H_{31}N_6O_3$ (M^++H) 391.2452, found 391.2458.

5.2.19. Synthesis of compound 7e

Compound **7e** was prepared from **6e** (90 mg, 0.23 mmol) and **4** (103 mg, 1.2 equiv) according to the procedure described for **7b** in a yield of 37% (55 mg, 86 μmol, pale yellow foam).

Compound **7e**: ^{1}H NMR (500 MHz, MeOD) δ 8.24 (s, 1H), 8.22 (s, 1H), 7.35–7.29 (m, 5H), 6.14 (d, J = 2.0 Hz, 1H), 5.49–5.46 (m, 1H), 5.43–5.42 (m, 1H), 5.24–5.10 (br m, 3H), 4.96 (m, 1H), 4.33–4.30 (m, 2H), 2.72–2.26 (br m, 8H), 1.57 (s, 3H), 1.36 (s, 3H), 1.22–1.10 (m, 8H), 0.84–0.82 (m, 3H); HRMS (ESI+) calcd for $C_{32}H_{44}N_7O_7$ (M^++H) 638.3297, found 638.3280.

5.2.20. Synthesis of compound 8e

Compound **8e** was prepared from **7e** (27.0 mg, 34 μmol) according to the procedure described for **8b** in a yield of 96% (52 mg, 83 μmol, colorless foam).

Compound **8e**: ^{1}H NMR (500 MHz, CD_3OD) δ 8.26 (s, 1H), 8.25 (s, 1H), 7.36–7.27 (m, 5H), 6.30 (s, 1H), 5.46 (d, J = 6.0 Hz, 1H), 5.17 (br, 1H), 5.07 (s, 2H), 4.64–4.62 (br m, 1H), 3.97 (dd, J = 7.0, 4.5 Hz, 1H), 3.69–3.63 (br m, 1H), 3.48–3.45 (br m, 1H), 3.18–3.13 (br m, 2H), 2.97–2.92 (br m, 2H), 2.09–2.06 (br m, 1H), 1.89–1.87 (br m, 1H), 1.60 (s, 3H), 1.38 (s, 3H), 1.29 (br, 2H), 1.21–1.07 (br m, 6H), 0.84 (t, J = 7.0 Hz, 3H); HRMS (ESI+) calcd for $C_{31}H_{44}N_7O_7$ (M^++H) 626.3297, found 626.3295.

5.2.21. Synthesis of compound 1e

Compound **1e** was prepared from **8e** (9.0 mg, 14 μmol) according to the procedure described for **1b** in a yield of 35% (2 steps, 2.1 mg, 4.6 μmol, white solid).

Compound **1e**: ^{1}H NMR (500 MHz, D_2O) δ 8.33 (s, 2H), 6.07 (d, J = 4.0 Hz, 1H), 4.80 (t, J = 4.5 Hz, 1H), 4.43–4.39 (m, 2H), 3.72–3.71 (m, 1H), 3.66–3.61 (m, 1H), 3.57–3.55 (m, 1H), 3.42–3.37 (m, 2H), 3.15–3.11 (m, 2H), 2.25–2.20 (m, 1H), 2.09 (br, 1H), 1.50 (br, 2H), 1.04 (br, 6H), 0.66 (br, 3H); ^{13}C NMR (125 MHz, D_2O) δ 171.76, 150.04, 148.08, 144.52, 143.58, 119.26, 90.08, 72.95, 72.89, 71.75, 54.72, 53.92, 51.62, 50.77, 30.29, 25.11, 24.62, 22.59, 21.54, 13.07; HRMS (ESI+) calcd for $C_{20}H_{34}N_7O_5$ (M+H^+) 452.2616. found 452.2628.

5.3. Assay for inhibitory activity towards SET7/9

A mixture of biotin-conjugated histone H3 peptide (residue 1–21) (Upstate), adenosylmethionine (AdoMet), human recombinant SET7/9 (Funakoshi) and a test compound in reaction buffer (50 mM Tris, 100 mM NaCl, 1 mM EDTA, 4 mM DTT, pH 8.8) was incubated in a plastic tube for 1 h. The solution was added to a streptavidin-coated microplate (BD Science), and incubated for 45 min. Each well was washed with PBST, blocked by 3% skim milk in PBST, and anti-monomethyl-histone H3 (Lys4) antibody (Upstate) was added. The plate was left for 1 h. The wells were washed again with PBST, then anti-rabbit IgG horseradish peroxidase-linked antibody (Abcam) was added and the plate was left for 30 min. The wells were washed with PBST, substrate for HRP (TMB) (BioRad) was added to each well and the plate was left for 20 min. After addition of diluted sulfuric acid to stop the reaction, the microplate was scanned to determine OD450.

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