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ORIGINAL PAPER

Three new 5,6,7,8-tetrahydroxy-5,6,7,8-tetrahydrochromone derivatives enantiomeric to agarotetrol from agarwood

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Abstract
Agarwood (*jinkoh* in Japanese) is a resinous wood from *Aquilaria* species of the family Thymelaeaceae and has been used as incense and in traditional medicines. Characteristic chromone derivatives such as agarotetrol have been isolated from agarwood. In previous study, we isolated two new 2-(2-phenylethyl)chromones together with six known compounds from MeOH extract of agarwood. Further chemical investigation of the MeOH extract led to isolation of eighteen 2-(2-phenylethyl)chromones, including three new 5,6,7,8-tetrahydroxy-5,6,7,8-tetrahydrochromones with stereochemistry enantiomeric to agarotetrol-type, viz. (5*R*,6*S*,7*S*,8*R*)-2-[2-(3′-hydroxy-4′-methoxyphenyl)ethyl]-5,6,7,8-tetrahydroxy-5,6,7,8-tetrahydrochromone (**2**), (5*R*,6*S*,7*S*,8*R*)-2-[2-(4′-methoxyphenyl)ethyl]-5,6,7,8-tetrahydroxy-5,6,7,8-tetrahydrochromone (**6**), and (5*R*,6*S*,7*S*,8*R*)-2-[2-(4′-hydroxy-3′- methoxyphenyl)ethyl]-5,6,7,8-tetrahydroxy-5,6,7,8-tetrahydrochromone (**13**). The absolute configurations of the new compounds were determined by exciton chirality method. All isolated compounds were tested for their phosphodiesterase (PDE) 3A inhibitory activity by fluorescence polarization method. Compounds **8**, **12**–**15**, **21**–**24** showed moderate PDE 3A inhibitory activity.

Keywords Agarwood · 2-(2-Phenylethyl)chromone · 5,6,7,8-Tetrahydroxy-5,6,7,8-tetrahydrochromone · Enantiomer · Phosphodiesterase inhibitor

Introduction

Agarwood (*jinkoh* in Japanese) is a resinous wood of *Aquilaria* species of the family Thymelaeaceae and has been used as incense and in traditional medicines. Characteristic sesquiterpenes and chromone derivatives have been isolated from agarwood [1–8]. In our previous study, two new 2-(2-phenylethyl)chromones (**19**, **21**) were isolated from MeOH extract of agarwood, together with six known compounds (**1**, **11**, **16**–**18**, **20**), among which **20** showed PDE 3A inhibitory activity with 50 % inhibitory concentration (IC_{50}) of 4.83 μM [9]. Further fractionation of the extract led to isolation of three new 2-(2-phenylethyl)-5,6,7,8-tetrahydroxy-5,6,7,8-tetrahydrochromones (**2**, **6**, **13**) together with eighteen known compounds, i.e., aquilarone D (**3**) [1], aquilarone A (**4**) [1], AH_{2b} (**5**) [2], isoagarotetrol (**7**) [3], aquilarone B (**8**) [1], 6,7-dihydroxy-2-(2-phenylethyl)-5,6,7,8-tetrahydrochromone (**9**) [4], 8-chloro-2-(2-phenylethyl)-5,6,7-trihydroxy-5,6,7,8-tetrahydrochromone (**10**) [4], aquilarone F (**12**) [1], AH_{2a} (**14**) [2], aquilarone C (**15**) [1], aquilarone G (**22**) [1], 6-hydroxy-7-methoxy-2-[2-(3′-hydroxy-4′-methoxyphenyl)ethyl]chromone (**23**) [5], aquilarone I (**24**) [1], flindersiachromone (**25**) [6], AH_4 (**26**) [7], AH_3 (**27**) [7], 6-methoxy-2-[2-(3′-hydroxy-4′-methoxyphenyl)ethyl]-chromone (**28**) [8], and AH_6 (**29**) [7] (Fig. 1). The new compounds (**2**, **6**, **13**) have stereochemistry enantiomeric to agarotetrol (**1**).

Results and discussion

Compound **2** was obtained as white amorphous powder. High-resolution (HR) electrospray ionization (ESI) mass spectrometry (MS) gave an $[M + Na]^+$ ion peak at *m*/*z* 387.1086 (calcd. for $C_{18}H_{20}NaO_8$, 387.1056). The nuclear magnetic resonance (NMR) spectroscopic data of **2** (Tables 1, 2) were in good agreement with

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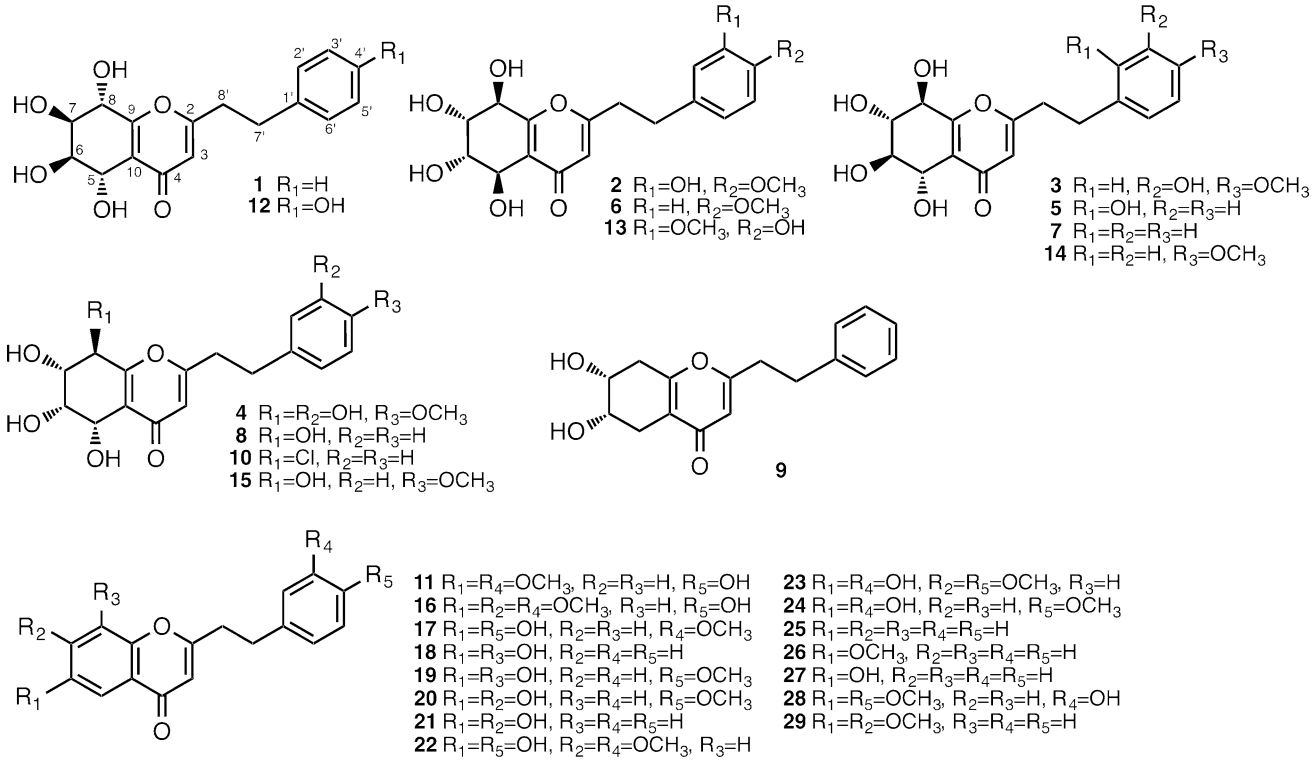


Fig. 1 Structure of compounds **1**–**29**

Table 1 ^{1}H NMR data of compounds **2**, **6**, **13** (δ in ppm, J in Hz)

No.	**2** (DMSO-d_6, 400 MHz)	**2** (CD_3OD, 600 MHz)	**6** (CD_3OD, 600 MHz)	**13** (CD_3OD, 600 MHz)
3	6.08 (1H, s)	6.11 (1H, s)	6.10 (1H, s)	6.09 (1H, s)
5	4.47 (1H, m)	4.74 (1H, d, 3.8)	4.74 (1H, d, 4.0)	4.73 (1H, d, 3.9)
5-OH	5.19 (1H, d, 4.4)			
6	3.72* (1H)	4.02 (1H, dd, 4.1, 2.5)	4.01 (1H, dd, 4.0, 2.3)	4.00 (1H, dd, 3,9, 2.3)
6-OH	4.96 (1H, d, 4.4)			
7	3.83 (1H, m)	4.04 (1H, dd, 7.4, 2.2)	4.04 (1H, dd, 7.4, 2.3)	4.03 (1H, dd, 7.3, 2.3)
7-OH	5.10 (1H, d, 4.8)			
8	4.31 (1H, dd, 7.6, 6.0)	4.57 (1H, d, 7.5)	4.56 (1H, d, 7.4)	4.57 (1H, d, 7.3)
8-OH	5.81 (1H, d, 6.0)			
2′	6.67 (1H, d, 2.4)	6.68 (1H, d, 2.2)	7.12 (1H, d, 8.5)	6.75 (1H, d, 1.7)
3′			6.82 (1H, d, 8.5)	
5′	6.81 (1H, d, 8.4)	6.81 (1H, d, 8.3)	6.82 (1H, d, 8.5)	6.68 (1H, d, 7.9)
6′	6.61 (1H, dd, 8.4, 2.4)	6.64 (1H, d, 8.3, 2.2)	7.12 (1H, d, 8.5)	6.64 (dd, 7.9, 1.7)
7′	2.80 (2H, m)	2.90 (2H, m)	2.96 (2H, m)	2.95 (2H, m)
8′	2.80 (2H, m)	2.89 (2H, m)	2.89 (2H, m)	2.89 (2H, m)
3′-OH	8.85 (1H, s)			
3′-OCH_3				3.79 (3H, s)
4′-OCH_3	3.72* (3H, s)	3.80 (3H, s)	3.73 (3H, s)	

* overlapped

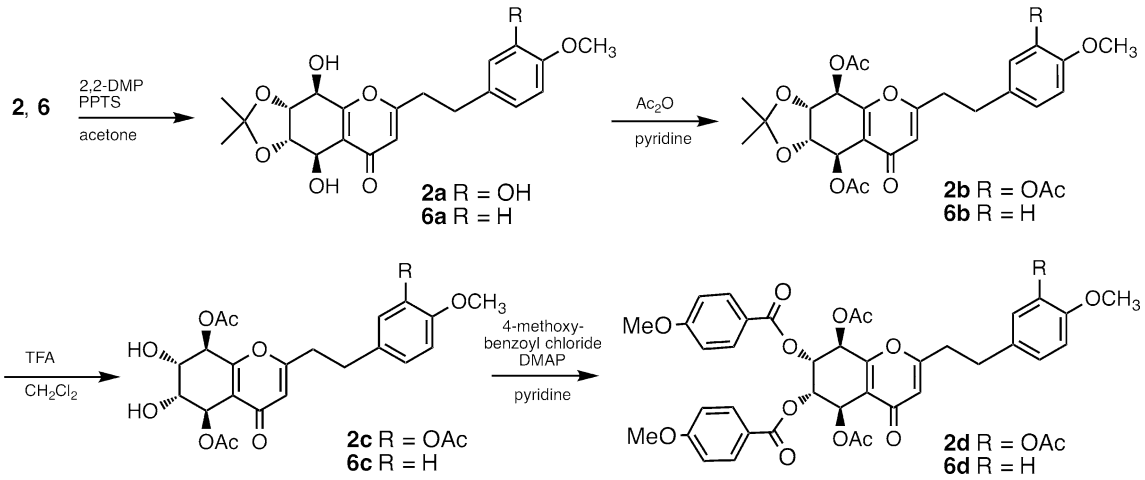
those of aquilarone E [1]. However, the optical rotation ($[\alpha]_D^{22} = +17.3$) had the opposite sign to that of aquilarone E ($[\alpha]_D^{20} = -16.0$). These data indicate that **2** was an enantiomer of aquilarone E. The absolute configuration of aquilarone E

Table 2 ^{13}C NMR data of compounds **2**, **6**, **13** (150 MHz, CD_3OD, δ in ppm)

Carbon no.	2	6	13
2	171.4	171.5	171.4
3	114.2	114.2	114.3
4	182.0	182.0	182.0
5	66.8	66.8	66.7
6	74.0	74.0	74.0
7	72.5	72.5	72.5
8	70.2	70.2	70.1
9	165.4	165.4	165.4
10	121.8	121.8	121.8
1′	134.1	133.2	132.6
2′	116.5	130.4	116.2
3′	147.7	115.0	148.9
4′	147.7	159.8	146.1
5′	113.0	115.0	113.1
6′	120.6	130.4	121.8
7	33.2	32.9	33.4
8′	36.5	36.6	36.7
3′-OCH_3			56.4
4′-OCH_3	56.5	55.7	

[1] has been determined by comparison of its optical rotation value with that of agarotetrol (**1**) [3, 10], whose absolute configuration was determined by exciton chirality method [11]. To examine the absolute configuration of **2**, its 6,7-di-*p*-methoxybenzoate derivative, together with that of **1** (**1d**) [3, 10], were prepared by a procedure similar to that of Chen et al. [1]. The derivatization method is shown in Scheme 1. In brief, treatment of **2** with 2,2-dimethoxypropane in presence of pyridinium *p*-toluenesulfonate (PPTS) afforded 6,7-acetonide derivative **2a**. The position of acetonide was confirmed by the downfield shift of C-6 and C-7 carbon chemical shifts (4.4 and 7.4 ppm, respectively) similar to those observed for the monoacetonide of **1** (**1a**) [10]. Acetylation of **2a** afforded diacetate of the acetonide (**2b**), which was hydrolyzed with trifluoroacetic acid (TFA) to yield diacetate derivative (**2c**). Finally, *p*-methoxybenzoylation of **2c** with *p*-methoxybenzoyl chloride in presence of 4-dimethylaminopyridine (DMAP) gave the target 6,7-di-*p*-methoxybenzoate derivative (**2d**). The ^{1}H NMR spectroscopic data and circular dichroism (CD) spectrum (Fig. 2) of **1d**, prepared by the same procedure from **1**, were consistent with previous report [10], and the ^{1}H NMR signals of the four methine protons of **2d** at δ_H 6.10 (1H, d, J = 4.0 Hz, H-5), 5.80 (1H, dd, J = 4.0, 2.5 Hz, H-6), 5.75 (1H, dd, J = 8.0, 2.5 Hz, H-7), and 6.32 (1H, d, J = 8.0 Hz, H-8) were in good agreement with those of **1d**. These data indicate that the C5–C10 ring of **2d** had the same half-chair conformation as that of **1d** as shown in Fig. 2. The CD spectrum of **2d** showed positive Cotton effect, opposite to that observed for **1d** (Fig. 2), indicating that the absolute configuration of **2d** was opposite to that of **1d**. Thus, the structure of **2** was determined to be (5*R*,6*S*,7*S*,8*R*)-2-[2-(3′-hydroxy-4′-methoxyphenyl)ethyl]-5,6,7,8-tetrahydroxy-5,6,7,8-tetrahydrochromone (**2**). As the absolute configuration of **2** is opposite to that of agarotetrol (**1**), the optical purity of the dibenzoates **1d** and **2d** was evaluated by high-performance liquid chromatography (HPLC) analysis with a chiral column and circular dichroism detector. Both compounds contained a small amount of the enantiomer, with (5*R*,6*S*,7*S*,8*R*):(5*S*,6*R*,7*R*,8*S*) ratio of 10.5:89.5 for **1d** and (5*R*,6*S*,7*S*,8*R*):(5*S*,6*R*,7*R*,8*S*) ratio of 94:6 for **2d**.

Compound **6** was obtained as pale-yellow amorphous powder. HR-ESI–MS gave an $[M + Na]^+$ ion peak at *m/z* 371.1141 (calcd. for $C_{18}H_{20}NaO_7$, 371.1107). The NMR of **6** (Tables 1, 2) showed very similar signals to the chromone



Scheme 1 Synthesis of 6,7-dimethoxybenzoate derivatives of compounds **2**, **6**

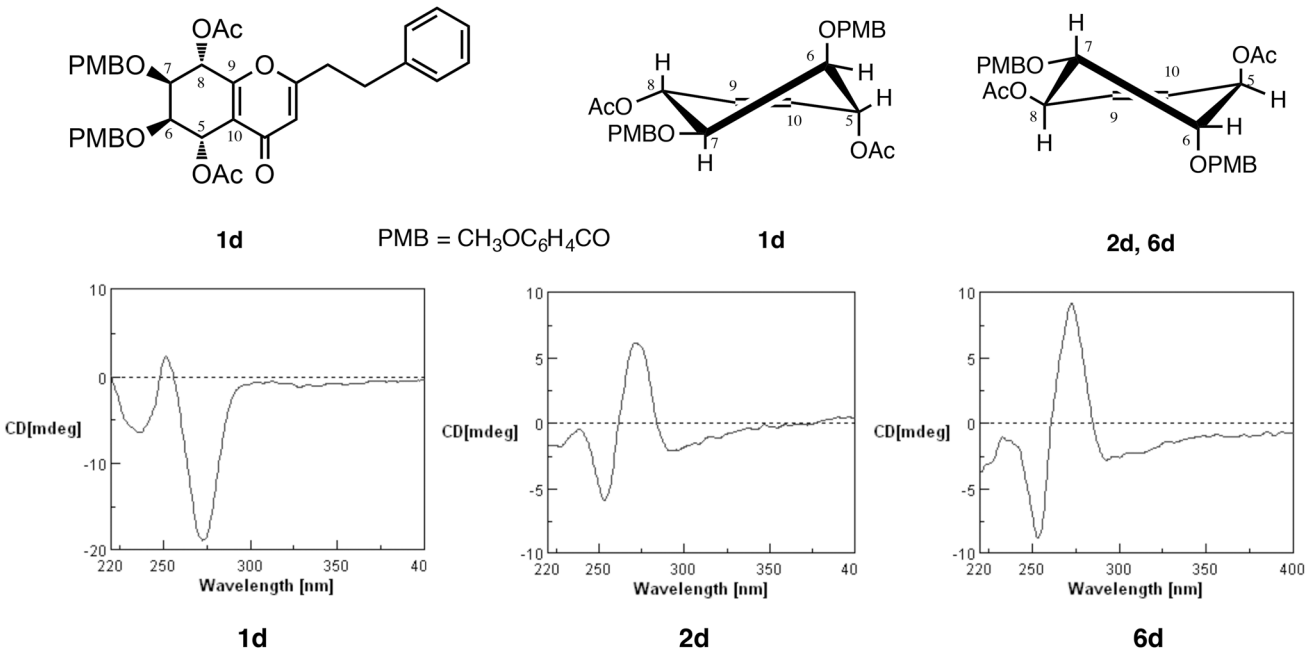


Fig. 2 Conformation and CD spectra of compounds **1d**, **2d**, **6d**

moiety of **2**, with signals of four methine protons at δ_H 4.74 (1H, d, J = 4.0 Hz), 4.01 (1H, dd, J = 4.0, 2.3 Hz), 4.04 (1H, dd, J = 7.4, 2.3 Hz), and 4.56 (1H, d, J = 7.4 Hz), which showed correlation signals to δ_C 66.8, 74.0, 72.5, and 70.2, respectively, in the C–H correlation spectroscopy (COSY) spectrum. However, **6** showed *para*-substituted phenyl signals at δ_H 7.12 (2H, d, J = 8.5 Hz) and 6.82 (2H, d, J = 8.5 Hz) instead of the signals for 3′-hydroxy-4′-methoxyphenyl group in **2**. These data indicate that **6** was a deacetyl derivative of AH_{1A} [2]. However, the sign of the optical rotation ($[\alpha]_D^{22} = +13.5$) was opposite to that of AH_{1A} ($[\alpha]_D^{14} = -14.3$). These data indicate that **6** was the enantiomer of deacetyl derivative of AH_{1A}. To confirm the absolute configuration of **6**, its 6,7-di-*p*-methoxybenzoate derivative (**6d**) was prepared using the same procedure as **2d** (Fig. 2). The ^{1}H NMR spectroscopic data of **6d** showed similar signals for four methine protons as those of **1d**, indicating that **6d** has the same conformation of C5–C10 ring as that of **1d** (Fig. 2). The CD spectrum of **6d** indicated positive chirality of 6,7-dibenzoate groups, the same as for **2d** (Fig. 2). Thus, the structure of **6** was determined to be (5*R*,6*S*,7*S*,8*R*)-2-[2-(4′-methoxyphenyl)ethyl]-5,6,7,8-tetrahydroxy-5,6,7,8-tetrahydrochromone (**6**). Chiral HPLC analysis revealed that **6d** was also a mixture of enantiomers with (5*R*,6*S*,7*S*,8*R*):(5*S*,6*R*,7*R*,8*S*) ratio of 76:24.

Compound **13** was obtained as colorless oil. ESI–MS gave an $[M + Na]^+$ ion peak at m/z = 387, and HR-fast atom bombardment (FAB)-MS gave an $[M + H]^+$ ion peak at m/z = 365.1252 (calcd. for $C_{18}H_{21}O_8$, 365.1236), showing that **13** had the same molecular formula as **2**. The ^{1}H and ^{13}C NMR spectroscopic data of **13** (Tables 1, 2) were similar to those of **2**, showing signals for four oxymethine protons at δ_H 4.73 (1H, d, J = 4.0 Hz), 4.00 (1H, dd, J = 4.0, 2.2 Hz), 4.03 (1H, dd, J = 7.4, 2.2 Hz), and 4.57 (1H, d, J = 7.4 Hz), which showed correlation signals to δ_C 66.7, 74.0, 72.5, and 70.1, respectively, in the heteronuclear multiple-quantum coherence (HMQC) spectrum. These data indicate that **13** had the same (5*R**,6*S**,7*S**,8*R**)-5,6,7,8- tetrahydroxy-5,6,7,8-tetrahydrochromone structure as **2**. The ^{1}H NMR spectrum also showed a methoxy signal at δ_H 3.79 (3H, s). However, the ^{1}H NMR pattern of the aromatic protons at δ_H 6.75 (1H, d, J = 1.9 Hz), 6.68 (1H, d, J = 8.0 Hz), and 6.64 (1H, dd, J = 8.0, 1.8 Hz) differed from that of **2**, indicating that the methoxy group was present at a different position. The locations of methoxy and hydroxy groups on the benzene ring were determined from the heteronuclear multiple-bond connectivity (HMBC) spectrum and the nuclear Overhauser effect (NOE) difference experiment, as shown in Fig. 3. The absolute configuration of **13** was assumed to be the same as that of **2**, because **13** showed the same sign of optical rotation as **2**. Consequently, the structure of **13** was determined to be (5*R*,6*S*,7*S*,8*R*)-2-[2-(4′-hydroxyl-3′-methoxyphenyl)ethyl]-5,6,7,8-tetrahydroxy-5,6,7,8-tetrahydrochromone (**13**). As compounds **2d** and **6d** were a mixture of enantiomers and **2**, **6**, and **13** showed similar optical rotation values ($[\alpha]_D^{22} = +17.3, +13.5, +7.27$, respectively), **13** may also be a mixture of enantiomers with excess of (5*R*,6*S*,7*S*,8*R*) isomer.

All isolated compounds were tested for their PDE 3A inhibitory activity. Compounds **8**, **12**–**15**, **21**–**24** showed

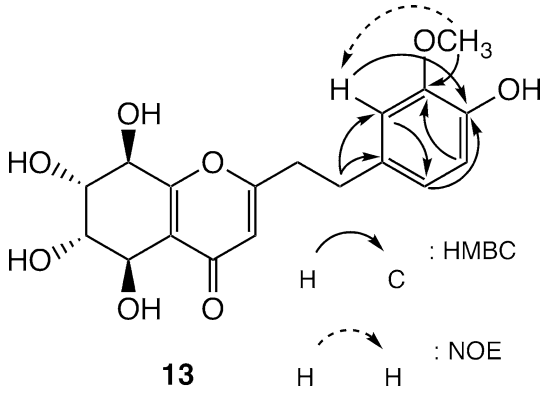


Fig. 3 Selected HMBC and NOE correlations of compound **13**

moderate PDE 3A inhibitory activity (Table 3). Interestingly, the only structural difference between compounds **8** (IC_{50}: 41.8 μM) and **15** (IC_{50}: 33.2 μM) lies in the presence or absence of methoxy group at C-4′ position. These results verify our previous structure–activity relationship hypothesis that methoxy group at C-4′ position plays an important role to increase PDE 3A inhibitory activity [9].

Experimental

General experimental procedures

Optical rotations were measured using a JASCO P-1020 (Tokyo, Japan). Circular dichroism spectra were recorded using a JASCO J-1100 spectrometer. Ultraviolet (UV) spectra were obtained on a UV–visible spectrophotometer UV-1600 (Shimadzu, Kyoto, Japan), and infrared (IR) spectra were obtained with FT-IR SPX 60 (JASCO). ESI–MS was carried out using a JMS-T100LP AccuTOF LC-plus (JEOL, Tokyo, Japan). HR-FAB-MS was measured with a JEOL JMS-7000. JEOL ECP-600 FT-NMR, VARIAN Unity Inova 500-MR (Palo Alto, CA, USA), and VARIAN 400-MR were used for measurement of NMR spectra with tetramethylsilane (TMS) as internal standard. Chiral HPLC was performed with Pu-2089plus, As-2055plus, Co-2065plus, and circular dichroism detector CD-2095plus (JASCO) using Chiralcel OD-RH 4.6 mm I.D. × 150 mm (Daicel, Osaka, Japan). Preparative HPLC was performed with LC-10AD, SPD-10A, FCV-10AL, and DGU-12A equipment (Shimadzu) using ODS columns of CAPCELL PAK C18 MG-II, 10 mm I.D. × 150 mm (Shiseido, Tokyo, Japan) and COSMOSIL 5C18-MG-II, 10 mm I.D. × 250 mm (Nacalai, Kyoto, Japan). Column chromatography was performed with silica gel (40–50, 40–100, and 100–210 μm, Kanto Chemical, Tokyo, Japan), Diaion HP-20 (Mitsubishi chemical, Tokyo, Japan), and MCI-Gel CHP20P (Mitsubishi chemical). Silica gel 60 F-254 and Silica gel 60 RP-18 F-254S (Merck, Darmstadt, Germany) were used for thin-layer chromatography (TLC), and spots were detected under UV light (254 and/or 365 nm).

Plant material

Agarwood was purchased from Uchida Wakanyaku Ltd. (lot D2R3219, from Indonesia).

Extraction and isolation

Powdered agarwood (80.0 g) was extracted twice with MeOH (2.0 L) under reflux for 2 h. The combined filtrates were concentrated under reduced pressure to give brown MeOH extract (20.2 g). MeOH extract (18.2 g) was subjected to Diaion HP-20 column chromatography (CC) (4.4φ × 24 cm) and successively eluted with H_2O, MeOH, acetone, and $CHCl_3$. The MeOH fraction (14.0 g) was applied to MCI-Gel CHP20P CC (4.0φ × 17 cm) and eluted with a gradient of H_2O/MeOH (1:0, 1:4, 2:3, 3:2, 4:1, 0:1) and acetone to yield seven fractions (M-1 to M-7). Fraction M-2 (128 mg) was then separated by semipreparative HPLC (MeCN/H_2O, 1:9–0:1) to give six fractions (M-2-1 to M-2-6). Fraction M-2-1 (4.9 mg) was purified by semipreparative HPLC (MeCN/H_2O, 8:92) to give **12** (3.4 mg). Fraction M-2-3 (3.6 mg) was purified by semipreparative HPLC (MeCN/H_2O, 8:92) to give **13** (2.3 mg). Fraction M-3 (1.1 g) was separated by semipreparative HPLC (MeCN/H_2O, 1:9–3:7) to give eight fractions (M-3-1 to M-3-8). Compounds **2** (47.9 mg), **4** (23.6 mg), **5** (24.4 mg), **6** (45.0 mg), **7** (29.2 mg), and **8** (34.9 mg) were obtained from

Table 3 PDE 3A inhibitory activity of compounds **1**–**29**

Compound	IC_{50} (μM)	Compound	IC_{50} (μM)	Compound	IC_{50} (μM)	Compound	IC_{50} (μM)	Compound	IC_{50} (μM)
Milrinone	0.92	**6**	>100	**12**	90.5	**18**	31.2	**24**	19.9
1	>100	**7**	>100	**13**	40.1	**19**	24.9	**25**	>100
2	>100	**8**	41.8	**14**	54.0	**20**	4.83	**26**	>100
3	>100	**9**	>100	**15**	33.2	**21**	32.9	**27**	>100
4	>100	**10**	>100	**16**	26.6	**22**	11.9	**28**	>100
5	>100	**11**	>100	**17**	32.8	**23**	18.9	**29**	>100

M-3-1, M-3-3, M-3-4, M-3-6, M-3-7, and M-3-8, respectively. Fraction M-3-2 (10.2 mg) was purified by silica gel CC (1.0φ × 14.5 cm) with $CHCl_3$/MeOH (9:1) to yield **3** (4.2 mg). Crystallization of fraction M-3-5 from 2-propanol gave **1** (87.4 mg). Fraction M-4 was subjected to silica gel CC (2.5φ × 22 cm) with a gradient of $CHCl_3$/MeOH (19:1–1:4) to give ten fractions (M-4-1 to M-4-10). Fraction M-4-5 was separated by semipreparative HPLC (MeCN/H_2O, 1:4–3:7) to give three fractions (M-4-5-1 to M-4-5-3). Fraction M-4-6 was separated by semipreparative HPLC (MeCN/H_2O, 1:4–3:7) to give seven fractions (M-4-6-1 to M-4-6-7). Fraction M-4-6-4 was subjected to silica gel CC (1.0φ × 13 cm) with a gradient of hexane/EtOAc (2:3–1:3) to give **9** (3.7 mg). Fractions M-4-5-3 and M-4-6-7 were combined and purified by semipreparative HPLC (MeCN/H_2O, 3:7) to give **10** (18.1 mg). Fraction M-4-8 was separated by semipreparative HPLC (MeCN/H_2O, 15:85) to give three fractions (M-4-8-1 to M-4-8-3). Fraction M-4-8-3 gave compound **15** (12.4 mg). Fraction M-4-8-2 was purified by semipreparative HPLC (MeCN/H_2O, 14:86) to give **14** (11.0 mg). Fraction M-5 (2.0 g) was subjected to silica gel CC (3.0φ × 19 cm) with a gradient of $CHCl_3$/MeOH (49:1–0:1) to give eleven fractions (M-5-1 to M-5-11). Fraction M-5-2 (241 mg) was separated by semipreparative HPLC (MeCN/H_2O, 3:7–5:5) to give nine fractions (M-5-2-1 to M-5-2-9). Fraction M-5-2-3 (19.0 mg) was subjected to silica gel CC (1.0φ × 15 cm) with a gradient of hexane/EtOAc (1:1–0:1) to give **16** (5.4 mg). Fraction M-5-2-6 (23.5 mg) was subjected to silica gel CC (1.0φ × 17 cm) with hexane/EtOAc (1:1) to obtain **11** (7.1 mg). Fraction M-5-4 (66.3 mg) was purified by semipreparative HPLC (MeCN/H_2O, 35:65) to give **17** (5.9 mg) and **21** (4.2 mg). Fraction M-5-5 (136.2 mg) was purified by semipreparative HPLC (MeCN/H_2O, 35:65) to give **18** (11.3 mg), **19** (3.7 mg), **20** (3.2 mg), and **21** (6.4 mg). Fraction M-5 (2.3 g) was subjected to silica gel CC (3.0φ × 19 cm) with a gradient of $CHCl_3$/MeOH (49:1–0:1) to give ten fractions (M-5-1 to M-5-10). Fraction M-5-3 (64.0 mg) was purified by semipreparative HPLC (MeCN/H_2O, 32:68) to give **22** (2.6 mg), **23** (4.7 mg), **17** (11.4 mg), and **24** (4.0 mg). Fraction M-6 (2.6 g) was subjected to silica gel CC (3.1φ × 18 cm) with a gradient of $CHCl_3$/MeOH (49:1–0:1) to give ten fractions (M-6-1 to M-6-10). Fractions M-6-2 (341 mg) and M-6-3 (147 mg) were combined, and a part of the mixture (428 mg) was subjected to silica gel CC (3.1φ × 18 cm) with a gradient of hexane/EtOAc (9:1–0:1) and MeOH to give thirteen fractions (M-6-2-1 to M-6-2-13). Fraction M-6-2-5 (31.6 mg) was purified by semipreparative HPLC (MeCN/H_2O, 3:2) to give **25** (6.1 mg). Fraction M-6-2-6 (15.4 mg) was purified by semipreparative HPLC (MeCN/H_2O, 1:1–1:0) to give **26** (8.1 mg). Fraction M-6-2-7 (34.4 mg) was purified by semipreparative HPLC (MeCN/H_2O, 1:1) to give **26** (2.3 mg). Fraction M-6-2-8 (19.3 mg) was purified by semipreparative HPLC (MeCN/H_2O, 2:3) to give **27** (6.1 mg). Fraction M-6-2-9 (17.6 mg) was purified by semipreparative HPLC (MeCN/H_2O, 2:3) to give **28** (3.4 mg). Fraction M-6-2-10 (84.3 mg) was separated by semipreparative HPLC (MeCN/H_2O, 2:3) to give **11** (11.3 mg), **28** (3.6 mg), and **29** (43.0 mg).

(5*R*,6*S*,7*S*,8*R*)-2-[2-(3′-Hydroxy-4′-methoxyphenyl) ethyl]-5,6,7,8-tetrahydroxy- 5,6,7,8-tetrahydrochromone (2) White amorphous powder; $[\alpha]_D^{22}$ = +17.3 (*c* = 1.0, MeOH); IR (ATR, cm^{-1}) 3291, 1653, 1575, 1514, 1446; HR-ESI–MS *m*/*z*: 387.1086 $[M + Na]^+$ (calcd. for $C_{18}H_{20}NaO_8$, 387.1056); ^1H and ^{13}C NMR (see Tables 1, 2).

(5*R*,6*S*,7*S*,8*R*)-2-[2-(4′-Methoxyphenyl)ethyl]-5,6,7,8-tetrahydroxy-5,6,7,8-tetrahydrochromone (6) Pale-yellow amorphous powder; $[\alpha]_D^{22}$ = +13.5 (*c* = 1.0, MeOH); IR (ATR, cm^{-1}) 3290, 1653, 1583, 1512, 1440, 1178; HR-ESI–MS *m*/*z*: 371.1141 $[M + Na]^+$ (calcd. for $C_{18}H_{20}NaO_7$, 371.1107); ^1H and ^{13}C NMR (see Tables 1, 2).

(5*R*,6*S*,7*S*,8*R*)-2-[2-(4′-Hydroxy-3′-methoxyphenyl) ethyl]5,6,7,8-tetrahydroxy-5,6,7,8-tetrahydrochromone (13) Colorless oil; $[\alpha]_D^{22}$ = +7.27 (c 0.22, MeOH); UV λ_{max} (MeOH) nm (log ε): 282 (3.10), 250 (3.71), 221 (3.75); HR-FAB-MS *m*/*z*: 365.1252 $[M + H]^+$ (calcd. for $C_{18}H_{21}O_8$, 365.1236); ^1H and ^{13}C NMR (see Tables 1, 2).

Compound 2a A mixture of **2** (20.0 mg), PPTS (5.8 mg), and 2,2-DMP (1.3 mL) in dry acetone (5 mL) was stirred at room temperature overnight. The solvent was removed under reduced pressure. The residue was then partitioned between EtOAc and saturated $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel CC ($CHCl_3$/MeOH = 14:1) to give **2a** (6.4 mg) as colorless oil. HR-ESI–MS *m*/*z*: 427.1273 $[M + Na]^+$ (calcd. for $C_{21}H_{24}NaO_8$, 427.1369). ^1H NMR (CD_3OD, 500 MHz) δ 1.15, 1.32 (each 3H, s, –C$\underline{H}_3$), 2.94 (4H, br s, H-7′, 8′), 3.79 (3H, s, –OC$\underline{H}_3$), 4.46 (1H, d, *J* = 2.0 Hz, H-8), 4.68 (1H, dd, *J* = 6.5, 2.0 Hz, H-6), 4.72 (1H, dd, *J* = 6.5, 2.0 Hz, H-7), 5.00 (1H, d, *J* = 2.0 Hz, H-5), 6.16 (1H, s, H-3), 6.60 (1H, dd, *J* = 8.0, 2.0 Hz, H-6′), 6.67 (1H, d, *J* = 2.0 Hz, H-2′), 6.78 (1H, d, *J* = 8.0 Hz, H-5′). ^{13}C NMR (CD_3OD, 125 MHz) δ 24.2 (–$\underline{C}H_3$), 26.7 (–$\underline{C}H_3$), 33.8 (C-7′), 36.3 (C-8′), 56.4 (4′-OCH_3), 63.3 (C-5), 69.5 (C-8), 78.8 (C-6), 79.9 (C-7), 109.7 [–$(O)_2$–$\underline{C}$–$(CH_3)_2$], 112.8 (C-5′), 115.1 (C-3), 116.4 (C-2′), 120.6 (C-6′), 123.7 (C-10), 133.9 (C-1′), 147.6 (C-4′), 147.7 (C-3′), 167.9 (C-9), 171.1 (C-2), 180.2 (C-4).

Compound 2b A mixture of **2a** (6.4 mg), pyridine (1 mL), and acetic anhydride (1 mL) was stirred at room temperature until **2a** disappeared according to TLC. The mixture was

concentrated under reduced pressure to give **2b** (9.3 mg) as colorless oil that was used without purification for the next step. HR-ESI–MS *m/z*: 553.1655 $[M + Na]^+$ (calcd. for $C_{27}H_{30}NaO_{11}$, 553.1686). ^{1}H NMR (CD_3OD, 400 MHz) δ 1.23, 1.33 (each 3H, s, –C$\underline{H}_3$), 2.03, 2.11, 2.23 (each 3H, s, –OCOC$\underline{H}_3$), 2.93 (4H, m, H-7′, 8′), 3.77 (3H, s, –OC$\underline{H}_3$), 4.62 (1H, dd, J = 6.4, 1.6 Hz, H-6), 4.69 (1H, dd, J = 6.4, 2.0 Hz, H-7), 5.64 (1H, d, J = 2.0 Hz, H-8), 6.07 (1H, d, J = 1.6 Hz, H-5), 6.21 (1H, s, H-3), 6.90 (1H, d, J = 2.4 Hz, H-2′), 6.96 (1H, d, J = 8.4 Hz, H-5′), 7.05 (1H, dd, J = 8.4, 2.4 Hz, H-6′). ^{13}C NMR (CD_3OD, 100 MHz) δ 20.5 (–OCO$\underline{C}H_3$), 20.6 (–OCO$\underline{C}H_3$), 20.8 (–OCO$\underline{C}H_3$), 24.2 (–$\underline{C}H_3$), 26.7 (–$\underline{C}H_3$), 32.7 (C-7′), 36.1 (C-8′), 56.4 (4′-OCH_3), 65.2 (C-5), 69.6 (C-8), 75.9 (C-6), 77.1 (C-7), 110.2 [–$(O)_2$–$\underline{C}$–$(CH_3)_2$], 113.6 (C-5′), 115.3 (C-3), 121.6 (C-10′), 123.8 (C-2′), 127.8 (C-6′), 133.5 (C-1′), 141.1 (C-3′), 151.4 (C-4′), 164.2 (C-9), 170.7 (–O$\underline{C}OCH_3$), 171.0 (–O$\underline{C}OCH_3$), 171.3 (–O$\underline{C}OCH_3$), 171.5 (C-2), 179.2 (C-4).

Compound 2c A mixture of **2b** (9.3 mg), dry CH_2Cl_2 (1 mL), and TFA (0.2 mL) was stirred at room temperature until **2b** disappeared according to TLC. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel CC ($CHCl_3$/MeOH = 14:1) to give **2c** (6.9 mg) as colorless oil. HR-ESI–MS *m/z*: 513.1380 $[M + Na]^+$ (calcd. for $C_{24}H_{26}NaO_{11}$, 513.1373). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.07, 2.22, 2.31 (each 3H, s, OCOC$\underline{H}_3$), 2.77 (2H, m, H-8′), 2.86 (2H, m, H-7′), 3.82 (3H, s, 4′-OCH_3), 4.13 (1H, br d, J = 7.0 Hz, H-7), 4.22 (1H, dd, J = 3.5, 2.5 Hz, H-6), 5.97 (1H, d, J = 3.5 Hz, H-5), 5.97 (1H, d, J = 7.0 Hz, H-8), 6.12 (1H, s, H-3), 6.86 (1H, d, J = 2.0 Hz, H-2′), 6.90 (1H, d, J = 8.5 Hz, H-5′), 6.99 (1H, dd, J = 8.5, 2.0 Hz, H-6′).

Compound 2d To a mixture of **2c** (6.9 mg) and DMAP (8.9 mg) in pyridine (1 mL), *p*-methoxybenzoyl chloride (0.5 mL) was added dropwise at 0 °C, and the mixture was stirred at room temperature overnight. The resulting solution was diluted with EtOAc and saturated NH_4Cl. The organic layer was washed with saturated $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel CC ($CHCl_3$/MeOH = 39:1) and HPLC (MeCN/H_2O = 3:7–1:0) to give **2d** (1.5 mg) as colorless oil, $[\alpha]_D^{24}$ = +28.4 (c = 0.15, MeOH), UV λ_{max} (MeOH) nm (log ε): 257 (4.21), CD λ_{ext} (MeOH) nm ($\Delta\varepsilon$): 254 (–4.53), 271 (4.81), HR-ESI–MS *m/z*: 781.2182 $[M + Na]^+$ (calcd. for $C_{40}H_{38}NaO_{15}$, 781.2108). ^{1}H NMR (CD_3OD, 600 MHz) δ 2.13, 2.18, 2.21 (each 3H, s, –OCOC$\underline{H}_3$), 2.98 (4H, d, J = 4.4 Hz, –C$\underline{H}_2$–C$\underline{H}_2$–), 3.77, 3.84, 3.87 (each 3H, s, –OC$\underline{H}_3$), 5.75 (1H, dd, J = 8.0, 2.5 Hz, H-7), 5.80 (1H, dd, J = 4.0, 2.5 Hz, H-6), 6.10 (1H, d, J = 4.0 Hz, H-5), 6.24 (1H, s, H-3), 6.32 (1H, d, J = 8.0 Hz, H-8), 6.93 (1H, d, J = 2.2 Hz, H-2′), 6.95 (2H, d, J = 9.1 Hz), 6.98 (1H, d, J = 8.5 Hz, H-5′), 7.01 (2H, d, J = 9.1 Hz), 7.08 (1H, dd, J = 8.5, 2.2 Hz, H-6′), 7.84 (2H, d, J = 9.1 Hz), 7.89 (2H, d, J = 9.1 Hz).

Compounds **1d** and **6a**–**d** were prepared by same procedure as compounds **2a**–**d**.

Compound 1d Colorless oil, $[\alpha]_D^{24}$ = −76.9 (c = 0.82, MeOH), UV λ_{max} (MeOH) nm (log ε): 259 (4.15), CD λ_{ext} (MeOH) nm ($\Delta\varepsilon$): 251 (1.71), 272 (–11.7), HR-ESI–MS (positive) *m/z*: 693.1967 $[M + Na]^+$ (calcd. for $C_{37}H_{34}NaO_{12}$, 693.1948). ^{1}H NMR (CD_3OD, 600 MHz) δ 2.12, 2.18 (each 3H, s, –OCOC$\underline{H}_3$), 2.98 (4H, m, H-7′, 8′), 3.85, 3.86 (each 3H, s, –OC$\underline{H}_3$), 5.74 (1H, dd, J = 8.3, 2.5 Hz, H-7), 5.81 (1H, dd, J = 4.0, 2.5 Hz, H-6), 6.10 (1H, d, J = 4.0 Hz, H-5), 6.21 (1H, s, H-3), 6.31 (1H, d, J = 8.3 Hz, H-8), 6.95 (2H, d, J = 9.1 Hz), 7.00 (2H, d, J = 9.0 Hz), 7.20 (3H, m, J = 7.5 Hz, H-2′, 4′, 6′), 7.27 (2H, t, J = 7.4 Hz, H-3′, 5′), 7.84 (2H, d, J = 9.1 Hz), 7.89 (2H, d, J = 9.0 Hz). ^{13}C NMR (CD_3OD, 150 MHz) δ 20.5 (–OCO$\underline{C}H_3$), 20.6 (–OCO$\underline{C}H_3$), 33.6 (C-7′), 36.0 (C-8′), 56.1 (–O$\underline{C}H_3$), 56.1 (–O$\underline{C}H_3$), 65.3 (C-5), 67.9 (C-8), 69.9 (C-6), 70.9 (C-7), 114.9 (C-3), 115.0, 115.1, 120.0 (C-10), 122.1, 122.2, 127.6 (C-4′), 129.4 (C-2′, 6′), 129.7 (C-3′, 5′), 132.9, 133.0, 140.9 (C-1′), 161.5 (C-9), 165.7, 165.8, 166.0, 166.4, 171.0 (C-2), 171.3 (–O$\underline{C}OCH_3$), 171.5 (–O$\underline{C}OCH_3$), 179.2 (C-4).

Compound 6a Colorless oil, $[\alpha]_D^{23}$ = −8.6 (c = 1.0, MeOH), HR-ESI–MS *m/z*: 411.1471 $[M + Na]^+$ (calcd. for $C_{21}H_{24}NaO_7$, 411.1420). ^{1}H NMR (CD_3OD, 500 MHz) δ 1.15, 1.32 (each 3H, s, –C$\underline{H}_3$), 2.90 (2H, m, H-8′), 2.95 (2H, m, H-7′), 3.73 (3H, s, 4′-OCH_3), 4.46 (1H, d, J = 2.0 Hz, H-8), 4.68 (1H, dd, J = 7.0, 2.0 Hz, H-6), 4.72 (1H, dd, J = 7.0, 2.0 Hz, H-7), 5.01 (1H, d, J = 2.0 Hz, H-5), 6.14 (1H, s, H-3), 6.80 (2H, d, J = 8.5 Hz, H-3′, 5′), 7.09 (2H, d, J = 8.5 Hz, H-2′, 6′). ^{13}C NMR (CD_3OD, 125 MHz) δ 22.8 (–$\underline{C}H_3$), 25.3 (–$\underline{C}H_3$), 31.6 (C-7′), 35.1 (C-8′), 54.2 (4′–O$\underline{C}H_3$), 61.9 (C-5), 68.1 (C-8), 77.4 (C-6), 78.4 (C-7), 108.2 [–$(O)_2$–$\underline{C}$–$(CH_3)_2$], 113.6 (C-3′, 5′), 113.8 (C-3), 122.4 (C-10), 129.0 (C-2′, 6′), 131.5 (C-1′), 158.4 (C-4′), 166.5 (C-9), 169.5 (C-2), 178.7 (C-4).

Compound 6b Colorless oil, $[\alpha]_D^{23}$ = +5.4 (c = 1.0, MeOH), HR-ESI–MS *m/z*: 495.1675 $[M + Na]^+$ (calcd. for $C_{25}H_{28}NaO_9$, 495.1631). ^{1}H NMR (CD_3OD, 500 MHz) δ 1.22, 1.33 (each 3H, s, –C$\underline{H}_3$), 2.03 (3H, s, 5-OCOC$\underline{H}_3$), 2.11 (3H, s, 8-OCOC$\underline{H}_3$), 2.91 (2H, m, H-8′), 2.94 (2H, m, H-7′), 3.73 (3H, s, 4′-OCH_3), 4.62 (1H, dd, J = 6.5, 1.5 Hz, H-6), 4.69 (1H, dd, J = 6.5, 2.0 Hz, H-7), 5.64 (1H, d, J = 2.0 Hz, H-8), 6.07 (1H, d, J = 1.5 Hz, H-5), 6.17 (1H, s, H-3), 6.80 (2H, d, J = 8.5 Hz, H-3′, 5′), 7.08 (2H, d, J = 8.5 Hz, H-2′, 6′). ^{13}C NMR (CD_3OD, 125 MHz) δ 20.6 (8-OCO$\underline{C}H_3$), 20.8 (5-OCO$\underline{C}H_3$), 24.2 (–$\underline{C}H_3$), 26.7

(–$\underline{C}H_3$), 32.9 (C-7′), 36.4 (C-8′), 55.6 (4′-O$\underline{C}H_3$), 65.2 (C-5), 69.6 (C-8), 75.8 (C-6), 77.1 (C-7), 110.1 [–$(O)_2$–$\underline{C}$–$(CH_3)_2$], 115.0 (C-3′, 5′), 115.3 (C-3), 121.6 (C-10), 130.4 (C-2′, 6′), 132.8 (C-1′), 159.8 (C-4′), 164.1 (C-9), 171.0 (8-O$\underline{C}OCH_3$), 171.4 (5-O$\underline{C}OCH_3$), 171.5 (C-2), 179.2 (C-4).

Compound 6c Colorless oil, $[\alpha]_D^{23}$ = +12.8 (*c* = 1.0, MeOH), HR-ESI–MS *m/z*: 455.1377 $[M + Na]^+$ (calcd. for $C_{22}H_{24}NaO_9$, 495.1318). ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* 2.06 (3H, s, OCOC$\underline{H}_3$), 2.22 (3H, s, OCOC$\underline{H}_3$), 2.77 (2H, m, H-8′), 2.86 (2H, t, *J* = 7.4 Hz, H-7′), 3.71 (3H, s, 4′-OCH_3), 4.13 (1H, dd, *J* = 7.8, 2.4 Hz, H-7), 4.22 (1H, dd, *J* = 3.2, 2.4 Hz, H-6), 5.97 (1H, d, *J* = 3.2 Hz, H-5), 6.02 (1H, d, *J* = 7.8 Hz, H-8), 6.13 (1H, s, H-3), 6.83 (2H, d, *J* = 8.6 Hz, H-3′, 5′), 7.07 (2H, d, *J* = 8.6 Hz, H-2′, 6′). ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* 20.8 (OCO$\underline{C}H_3$), 20.9 (OCO$\underline{C}H_3$), 31.7 (C-7′), 35.5 (C-8′), 55.2 (4′-O$\underline{C}H_3$), 66.7 (C-5), 69.7 (C-8), 69.9 (C-7), 70.0 (C-6), 113.7 (C-3), 114.1 (C-3′, 5′), 118.6 (C-10), 129.1 (C-2′, 6′), 131.3 (C-1′), 158.3 (C-4′), 160.3 (C-9), 168.7 (C-2), 170.6 (O$\underline{C}OCH_3$), 170.6 (O$\underline{C}OCH_3$), 178.0 (C-4).

Compound 6d Colorless oil, $[\alpha]_D^{24}$ = +64.7 (*c* = 1.0, MeOH), UV λ_{max} (MeOH) nm (log *ε*): 258 (4.54), CD λ_{ext} (MeOH) nm (Δ*ε*): 254 (–6.90), 273 (6.63), HR-ESI–MS *m/z*: 723.2106 $[M + Na]^+$ (calcd. for $C_{38}H_{36}NaO_{13}$, 723.2054). ^{1}H NMR (CD_3OD, 600 MHz) *δ* 2.12, 2.18 (each 3H, s, –OCOC$\underline{H}_3$), 2.98 (4H, m, –C$\underline{H}_2$–C$\underline{H}_2$–), 3.85, 3.86 (each 3H, s, -OC$\underline{H}_3$), 5.74 (1H, dd, *J* = 8.3, 2.5 Hz, H-7), 5.81 (1H, dd, *J* = 4.0, 2.5 Hz, H-6), 6.10 (1H, d, *J* = 4.0 Hz, H-5), 6.21 (1H, s, H-3), 6.31 (1H, d, *J* = 8.3 Hz, H-8), 6.95 (2H, d, *J* = 9.1 Hz), 7.00 (2H, d, *J* = 9.0 Hz), 7.20 (3H, m, *J* = 7.5 Hz, H-2′, 6′, H-4′), 7.27 (2H, t, *J* = 7.4 Hz, H-3′, 5′), 7.84 (2H, d, *J* = 9.1 Hz), 7.89 (2H, d, *J* = 9.0 Hz). ^{13}C NMR (CD_3OD, 150 MHz) *δ* 20.5 (–OCO$\underline{C}H_3$), 20.6 (–OCO$\underline{C}H_3$), 33.6 (C-7′), 36.0 (C-8′), 55.6 (–O$\underline{C}H_3$), 56.1 (–O$\underline{C}H_3$), 56.1 (–O$\underline{C}H_3$), 65.3 (C-5), 67.9 (C-8), 69.9 (C-6), 70.9 (C-7), 114.9 (C-3), 115.0, 115.1, 120.0, 122.1, 122.2, 127.6 (C-4′), 129.4 (C-2′, 6′), 129.7 (C-3′, 5′), 132.9, 133.0, 140.9 (C-1′), 161.5 (C-9), 165.7, 165.8, 166.0, 166.4, 171.0 (C-2), 171.3 (–O$\underline{C}OCH_3$), 171.5 (–O$\underline{C}OCH_3$), 179.2 (C-4).

PDE 3A inhibitory activity

PDE 3A inhibitory activity was measured with PDE 3A assay kit provided by BPS Bioscience (San Diego, USA). In brief, reaction mixture containing PDE assay buffer, 200 nM FAM-cAMP, 400 pg human recombinant PDE 3A, and a test compound was incubated at room temperature for 60 min. Then, binding agent (1:100 dilution by binding agent diluent) was added and incubated for 60 min. Fluorescence was measured by M-1000 (Tecan, Männedorf, Swiss) at 475 nm (excitation) and 518 nm (emission). The data were processed using i-control software (Tecan). Percentage inhibition was calculated by taking the polarization of without-enzyme group and control group as 0 and 100 % of PDE activity, respectively. All compounds were screened at 100 μM, and active compounds were further tested at 10 μM. Compounds **20** and **21** were tested at 3, 10, 30, and 100 μM. Milrinone, a representative PDE 3 inhibitor, was used as positive control, and the inhibitory activity was measured at 0.5, 5, and 50 μM. The assay was triplicated. Fifty percent inhibitory concentration (IC_{50}) values were calculated by a line segment through 50 %, i.e., using the following equation: $IC_{50} = 10^{[\log(A/B) \times (50 - C)/(D - C) + \log(B)]}$, where *A* = high concentration through 50 %, *B* = low concentration through 50 %, *C* = inhibitory activity (%) at *B*, and *D* = inhibitory activity (%) at *A*.

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