SYNTHETIC STUDIES OF FISETIN, MYRICETIN AND NOBILETIN ANALOGS AND RELATED PROBE MOLECULES

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Abstract – We synthesized a series of analogs of fisetin, myricetin and nobiletin, as well as related fluorescein- and biotin-based flavone-probe molecules, on a suitable scale for biological and structure-activity relationship studies.

INTRODUCTION
Flavones, as represented by fisetin (1),1 myricetin (2)2 and nobiletin (3),3 are widely distributed in the plant kingdom, and have been reported to show beneficial effects on health.4 In particular, fisetin (1) and nobiletin (3) enhance PKA/ERK/CREB signaling in cell culture systems and prevent fibril formation of amyloid β protein (Aβ), so they are considered to be promising lead compounds for developing drugs to treat Alzheimer’s disease.5 However, it is often difficult to obtain sufficient amounts of natural products for clinical and epidemiological studies, or for investigating structure-activity relationships (SAR). Further, for imaging studies and/or analysis of the dynamics of flavones we require tools such as fluorescence probes and biotin-labeled probes. We have recently developed an efficient synthetic route to the flavone skeleton through a β-diketone intermediate.6 Herein, we described the application of this method to synthesize a series of fisetin, myricetin and nobiletin analogs for SAR studies, as well as several fluorescein- and biotin-based flavone probes.

Figure 1. Natural flavonoids: Attracting seeds of the drug
RESULTS AND DISCUSSION

Natural flavones have oxygen-containing functional groups at the 5- and/or 7-positions as a consequence of their biosynthesis via the polyketide pathway7 (Scheme 1). Although flavonoids have been investigated for decades, no detailed SAR studies of deoxy derivatives have been reported, to our knowledge. During the course of our investigation of epigallocatechin gallate (EGCg), we found that synthetic deoxyepigallocatechin gallate (DOEGCg) possessed more potent anti-influenza infection activity than natural EGCg.8 Inspired this finding, we aimed to synthesize a series of flavones and flavonols lacking hydroxyl groups at the 5- and/or 7-positions on the A-ring as candidate bioactive agents.

Scheme 1. Biosynthetic pathway to flavonoids

Our synthetic plan is illustrated in Scheme 2. The flavone ring of 4 is constructed by condensation of acetophenone (6) and acyl benzotriazoles9 7, followed by cyclization of the β-diketone intermediate 5.

Scheme 2. Strategy for flavonoid synthesis via β-diketone

For this synthesis, benzotriazoles 10a-c were considered to be suitable acyl donors that could be readily obtained from the corresponding benzoic acid derivatives 8a-c. The Bn-protected benzoic acids 9a-c were obtained by esterification, incorporation of benzyl ether and hydrolysis of methyl ester. After treatment with SOCl₂, condensation with benzotriazole afforded the C-acylation donors 10a-c. Although 10a-c are activated acylating reagents, they are very stable crystalline solids that can be stored in refrigerator for several years without decomposition.

Scheme 3. Synthesis of acyl benzotriazoles 10a-c as C-acylation reagents
Upon treatment of acetophenone and 10a-c with LHMDS at -78 °C, the C-acylation reaction proceeded smoothly to give the desired β-diketones. Subsequent acidic cyclization afforded the corresponding protected flavones. Deprotection of the Bn groups gave the desired flavones 12a-c. Flavonols 14a-c were obtained by oxidation of 11a-c with DMDO followed by deprotection. However, 11b and 11c were poorly soluble in the reaction solvents, and the reproducibility of the oxidation steps was poor. Furthermore, polyphenol derivatives 14b and 14c readily formed complexes with Pd derivatives under hydrogenolysis conditions, and it was difficult to remove palladium metal from the complexes.

Therefore, we decided to change the protecting groups of 12b,c from Bn ether to TBS. The flavone derivatives 15b,c were prepared by replacing Bn with TBS. The DMDO-mediated oxidation of 15b,c proceeded smoothly to give the corresponding flavonols 16b,c in moderate yields with good reproducibility, since the TBS flavones 15b,c were readily soluble in CH2Cl2, as expected. Deprotection of TBS with TBAF in the presence of AcOH proceeded smoothly to give the desired flavonols 14b,c in good yield.

Scheme 4. Synthesis of flavone and flavonol analogs
On the other hand, 7-deoxymyricetin (20) was synthesized from acetophenone 17 and acyl benzotriazole 18 in the same manner as described for the preparation of 14c.

Nobiletin (3) is considered an attractive candidate for treatment of Alzheimer’s disease. Recently we accomplished a practical total synthesis of 3,6b and applied it to obtain 11C-labeled nobiletin, which is suitable for positron emission tomography (PET) analysis. However, for detailed biodistribution and metabolism studies of 3, authentic samples of candidate metabolites of nobiletin are required.11 As shown in Scheme 7, nobiletin (3), 3'-demethylnobiletin (23b) and 4'-demethylnobiletin (23c) were synthesized by our reported method. The two metabolites were obtained by using Bn-protected 22b,c instead of 22a, followed by deprotection. Upon treatment of 21 and 22b,c with LHMDS at 0 °C, the C-acylation reaction proceeded smoothly to give the desired β-diketone intermediates. Subsequent acidic cyclization and deprotection afforded 23b,c. Compounds 23b,c have been used in a detailed investigation of the metabolism of 3 in a collaborative study involving our group12 (Onoue et al.).
Next, we turned our attention to the preparation of probe molecules for chemical-biological studies of flavone 20 and nobiletin (3). For this purpose, compounds labeled with fluorescein and biotin moieties are expected to be particularly useful. During the course of our work on tea catechins, we found that a precursor having a side chain on A-ring and a reactive amine unit was readily convertible into probe molecules. We envisioned that a similar approach would be also applicable for the preparing flavonoid probes. Furthermore, a terminal alkyne group is useful for incorporation of a probe moiety via Huisgen reaction. Thus, introduction of two different types of alkyne linker moiety was performed by alkylation of the phenolic hydroxyl group at the 5-position of each flavone. Since regioselective removal of the 5-methyl group of nobiletin (3) proceeded smoothly, a terminal alkyne group was introduced by alkylation reaction of Boc-5-aminopentyl-1-iodide with 5-demethylnobiletin 24. After removal of the Boc group, incorporation of a propiolic acid derivative provided the desired nobiletin probe precursor 25. For the preparation of the flavone probe precursor, we first examined alkylation of flavone 19. However, incorporation reaction did not proceeded and decomposition of the TBS ether of 19 was observed. Thus, alkylation reaction was performed using Bn ether derivative 26 to afford 27. After deprotection of Bn ether by treatment with BCl3 at -78 °C, protection with TBS groups afforded the flavone-probe precursor 28. Since the Huisgen reaction proceeded smoothly under extra-mild conditions and is compatible with many functional groups, terminal alkyne probe precursors are convenient for easy incorporation of several lengths of side chain and hydrophobic as well as hydrophilic linkers. This flexible synthetic strategy should be useful for optimization of probe molecules.
Using this approach, we prepared the fluorescein- and biotin-based probes 31, 32 and 33. Fluorescein is well-known to be suitable for in vivo imaging under physiological conditions. Among several fluorescein variants, we selected TokyoGreen\(^\text{15}\) (TG) as a reliable photophore. As shown in Scheme 9, TG-conjugated alkyl azide 29 was prepared by condensation of a TG derivative with 3-aminopropyl-1-azide. Hüisgen reaction of nobiletin probe precursor 25 and TG derivative 29 proceeded smoothly to provide the fluorescent probe 31. Incorporation of biotin moiety 30 instead of 29 into nobiletin precursor 25 was also carried out. The biotin-alkyl azide 30 was prepared by condensation of a biotin derivative with 3-aminopropyl-1-azide, and condensation reaction of probe precursor 25 and biotin-alkyl azide 30 provided the nobiletin-biotin probe 32. Flavonol probe 33 was also synthesized by TBAF-mediated deprotection of TBS after click coupling of 28 with 30. Our group is currently undertaking fluorescence imaging studies with 31 and target-protein detection with 32 and 33. The results will be reported in due course.

In summary, we have synthesized a series of flavonoid analogs for SAR studies, including 7-deoxymyricetin (20), which is a more potent inhibitor of Aβ fibril aggregation than myricetin. We found that a terminal alkyne group was useful for development of various fluorescein- and biotin-based flavonoid probe molecules that are expected to be useful for imaging studies of flavones at the cellular and organ level, respectively, as well as for investigations into the localization and target sites of flavones.
EXPERIMENTAL

General. Nuclear magnetic resonance \([^{13}\text{C} \text{NMR} (68 \text{ MHz})]\) spectra were determined on a JEOL EX-270 instrument, \([^{1}\text{H} \text{NMR} (400 \text{ MHz}) \text{ and } ^{13}\text{C} \text{NMR} (100 \text{ MHz})]\) spectra were determined on a JEOL-LA400 instrument, and \([^{1}\text{H} \text{NMR} (500 \text{ MHz}) \text{ and } ^{13}\text{C} \text{NMR} (125 \text{ MHz})]\) spectra were determined on a JEOL ECA 500 instrument and JEOL α-500 instrument. Chemical shifts for \(^1\text{H} \text{NMR}\) are reported in parts per million (ppm) downfield from tetramethylsilane (δ) in deuterochloroform (CDCl₃) or deuteromethanol (CD₃OD) as an internal standard or relative to the signal at 7.26 (3.31) ppm for deuterochloroform (deuteromethanol), while coupling constants are in hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad. Chemical shifts for \(^{13}\text{C} \text{NMR}\) are reported in ppm relative to the centerline of the triplet at 77.0 ppm for deuterochloroform or the centerline of a septet at 118.2 (49.0) ppm for deuteriacetonitrile (CD₃CN) [deuteromethanol (CD₃OD)]. Melting points (mp) were determined on a Yanaco Micro Melting Point Apparatus. Infrared spectra (IR), which are reported in wavenumbers (cm⁻¹), were recorded on a JASCO FT/IR-410 Fourier Transform Infrared Spectrometer. Mass spectra (MS) were obtained on a JEOL JMS-GCmate MS-DIP20 with polyethylene glycol as the internal standard or a JEOL MStation 700 using the Fast Atom Bombardment (FAB) method and 3-nitrobenzylalcohol as the matrix. Analytical thin layer chromatography (TLC) was performed on 0.25-mm thick Merck precoated analytical plates of silica gel 60 F254. Preparative TLC separations were conducted on 0.50-mm thick Merck precoated of silica gel 60 F254. Compounds were eluted from the adsorbent with 10% methanol (MeOH) in chloroform (CHCl₃). Flash column chromatography separations were performed on KANTO CHEMICAL Silica Gel 60 (40-100 mesh). All non-aqueous reactions were carried out in oven-dried glass apparatuses under a slight positive pressure of argon. Prior to use, all solvents were dried over molecular sieves 3A or 4A. All other reagents were commercially available, and unless otherwise specified, were used without further purification.

4-Benzylxybenzoic acid (9a)

To a solution of \(8a\) (15.0 g, 0.109 mol) in MeOH (360 mL) was added SOCl₂ (7.90 mL, 0.109 mol) for dropwise at 60 °C. After stirring at 60 °C for 5 h, the reaction mixture was evaporated under reduced pressure. The crude mixture was applied to following reaction without further purification.

To a mixture of crude residue and K₂CO₃ (45.2 g, 0.329 mol) in DMF (182 mL) was added benzyl bromide (19.4 mL, 0.163 mol) at 100 °C. The reaction mixture was stirred at 100 °C for 16 h. Then, the reaction mixture was filtered through a pad of Celite, diluted with H₂O, and extracted with CH₂Cl₂. The organic layer was washed with water followed by brine, dried over anhydrous MgSO₄, and evaporated under reduced pressure. The crude residue was applied to following reaction without further purification.
To a stirred solution of crude residue in MeOH/THF (1/1, 360 mL) was added 4 M NaOH aq. (90 mL, 0.36 mol) at 80 °C. The reaction mixture was stirred at 80 °C for 1 h. Then, the reaction mixture was quenched with 6 M HCl aq., and filtered. The filtrate was washed with H₂O to give 9a (23.9 g, 0.104 mol, 96%) as a white solid.

Spectral data for 9a were in good agreement with those reported in reference.16

3,4-Dibenzyloxybenzoic acid (9b)

To a solution of 8b (15.0 g, 97.4 mmol) in MeOH (360 mL) was added SOCl₂ (7.9 mL, 48.7 mmol) for dropwise at 60 °C. The reaction mixture was stirred at 60 °C for 10 h. Then, the reaction mixture was evaporated under reduced pressure. The crude mixture was applied to following reaction without further purification.

To a mixture of crude residue and K₂CO₃ (40.4 g, 0.292 mol) in DMF (162 mL) was added benzyl bromide (29.0 mL, 0.244 mol) at 100 °C. The reaction mixture was stirred at 100 °C for 16 h. Then, the reaction mixture was filtered through a pad of Celite, diluted with H₂O, and extracted with EtOAc. The organic layer was washed with water and brine, dried over anhydrous MgSO₄, and evaporated under reduced pressure. The crude mixture was applied to following reaction without further purification.

To a stirred solution of crude residue in MeOH/THF (1/1, 324 mL) were added 4 M NaOH aq. (85 mL, 0.34 mol) at 80 °C. The reaction mixture was stirred at same temperature for 1 h. Then, the reaction mixture was quenched with 6 M HCl aq., filtered and washed with H₂O to give 9b (32.2 g, 96.3 mmol, 99%) as a white solid.

Spectral data for 9b were in good agreement with those reported in reference.16

3,4,5-Tribenzyloxybenzoic acid (9c)

To a solution of 8c (60.0 g, 0.318 mol) in MeOH (638 mL) was added SOCl₂ (23.2 mL, 0.319 mol) for dropwise at 60 °C. The reaction mixture was stirred at 60 °C for 8 h. Then, the reaction mixture was evaporated under reduced pressure. The crude mixture was applied to following reaction without further purification.

To a mixture of crude material (2.00 g, 10.9 mmol) and K₂CO₃ (6.78 g, 49.0 mmol) in DMF (36.0 mL) were added benzyl bromide (4.10 mL, 35.9 mmol) and TBAI (1.60 g, 4.33 mmol) at room temperature. The reaction mixture was stirred at room temperature for 11 h. Then, the reaction mixture was filtered through a pad of Celite, diluted with H₂O, and extracted with CH₂Cl₂. The organic layer was washed with water and brine, dried over anhydrous MgSO₄, and evaporated under reduced pressure. The crude mixture was applied to following reaction without further purification.

To a stirred solution of crude residue in MeOH/THF (1/1, 36.3 mL) was added 4 M NaOH aq. (9.50 mL, 38.0 mmol) at 80 °C. The reaction mixture was stirred at 80 °C for 1 h. Then, the reaction mixture was quenched with 6 M HCl aq., and filtered. The filtrate was washed with H₂O to give 9c (3.30 g, 7.49 mmol,
68%) as a white solid.

Spectral data for 9c were in good agreement with those reported in reference.\textsuperscript{16}

\textbf{(1H-Benzo[d][1,2,3]triazol-1-yl)[4-(benzyloxy)phenyl]methanone (10a)}

To a solution of 9a (10.0 g, 43.8 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (100 mL) were added SOCl\textsubscript{2} (4.8 mL, 66.0 mmol) and DMF (1.4 mL, 18.0 mmol) at 0 °C under an Ar atmosphere, and the reaction mixture was stirred at 0 °C for 2 h. Then, the reaction mixture was evaporated under reduced pressure. The crude mixture was applied to following reaction without further purification.

To a solution of crude material in CH\textsubscript{2}Cl\textsubscript{2} (150 mL) were added Et\textsubscript{3}N (6.1 mL, 43.8 mmol) and benzotriazole (5.2 g, 43.8 mmol) at 0 °C under an Ar atmosphere, and the reaction mixture was stirred at room temperature for 1 h. Then, the reaction mixture was quenched with sat. NH\textsubscript{4}Cl solution and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous MgSO\textsubscript{4} and concentrated under reduced pressure to give a residue including 10a. The residue was recrystallized from n-hexane/CH\textsubscript{2}Cl\textsubscript{2} to afford 10a (9.1 g, 62%) as a white powder.

IR (film) 3072, 3034, 2916, 2857, 1694, 1605, 1361, 1267, 1177, 1047, 939 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): \textsuperscript{6}8.38 (d, J = 8.0 Hz, 1H), 8.30 (d, J = 9.2 Hz, 2H), 8.16 (d, J = 8.0 Hz, 1H), 7.69 (t, J = 8.0 Hz, 1H), 7.54 (t, J = 8.0 Hz, 1H), 7.50-7.30 (m, 5H), 7.14 (d, J = 9.2 Hz, 2H), 5.21 (s, 2H); \textsuperscript{13}C NMR (67.8 MHz, CDCl\textsubscript{3}): \textsuperscript{6}165.5, 163.3, 145.6, 135.9, 134.4, 132.5, 130.1, 128.7, 128.3, 127.4, 126.1, 123.6, 120.0, 114.8, 114.7, 70.2; MS (FAB): m/z 330 (M+H\textsuperscript{+}); HRMS (FAB) calcd for C\textsubscript{20}H\textsubscript{16}N\textsubscript{3}O\textsubscript{2}\textsuperscript{+}, (M+H\textsuperscript{+}) 330.1243, found 330.1231.

\textbf{(1H-Benzo[d][1,2,3]triazol-1-yl)[3,4-bis(benzyloxy)phenyl]methanone (10b)}

To a solution of 9b (11.0 g, 33.0 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (100 mL) were added SOCl\textsubscript{2} (7.2 mL, 99.0 mmol) and DMF (1.0 mL, 13.2 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 4 h. Then, the reaction mixture was concentrated under reduced pressure. The crude mixture was applied to following reaction without further purification.

To a solution of crude material in CH\textsubscript{2}Cl\textsubscript{2} (110 mL) were added Et\textsubscript{3}N (4.6 mL, 33.0 mmol) and benzotriazole (3.9 g, 33.0 mmol) at 0 °C under an Ar atmosphere, and the reaction mixture was stirred at room temperature for 12 h. Then, the reaction mixture was quenched with sat. NH\textsubscript{4}Cl solution and extracted with CH\textsubscript{2}Cl\textsubscript{2}. The organic layer was washed with 3 M NaOH aq., dried over anhydrous MgSO\textsubscript{4} and concentrated under reduced pressure. The residue was recrystallized from n-hexane/CH\textsubscript{2}Cl\textsubscript{2} to afford 10b (11.4 g, 77%) as a white powder.

IR (film) 3062, 3032, 2916, 2870, 1692, 1597, 1514, 1360, 1271, 1144 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): \textsuperscript{6}8.35 (d, J = 8.6 Hz, 1H), 8.17 (d, J = 8.6 Hz, 1H), 7.97 (dd, J\textsubscript{1} = 8.6, J\textsubscript{2} = 1.8 Hz, 1H), 7.94 (d, J = 2.5 Hz, 1H), 7.69 (td, J\textsubscript{1} = 8.6, J\textsubscript{2} = 0.95 Hz, 1H), 7.54 (td, J\textsubscript{1} = 8.6, J\textsubscript{2} = 0.95 Hz, 1H), 7.53-7.45 (m, 4H), 7.43-7.30 (m, 6H), 7.07 (d, J = 8.6 Hz, 1H), 5.22 (s, 2H), 5.19 (s, 2H); \textsuperscript{13}C NMR (67.8 MHz, CDCl\textsubscript{3}): \textsuperscript{6}
165.5, 153.9, 148.3, 145.7, 136.5, 136.2, 132.6, 130.2, 128.6, 128.5, 128.1, 128.0, 127.4, 127.1, 126.1, 123.6, 120.0, 117.5, 114.8, 112.9, 71.3, 70.8; MS (FAB): m/z 435 (M+H)+; HRMS (FAB) calcd for C$_{27}$H$_{21}$N$_3$O$_3$+, (M+H)+ 435.1583, found 435.1555.

(1H-Benzoz[d][1,2,3]triazol-1-yl][3,4,5-tris(benzyloxy)phenyl]methanone (10c)

To a solution of 9c (10.0 g, 23.0 mmol) in CH$_2$Cl$_2$ (52 mL) were added SOCl$_2$ (2.5 mL, 35.0 mmol) and DMF (0.70 mL, 9.0 mmol) at 0 °C, and the mixture was stirred at 0 °C for 2 h. Then, the reaction mixture was concentrated under reduced pressure. The crude mixture was applied to following reaction without further purification.

To a solution of crude material in CH$_2$Cl$_2$ (80 mL) were added Et$_3$N (3.2 mL, 23.0 mmol) and benzotriazole (2.7 g, 23.0 mmol) at 0 °C under an Ar atmosphere. After stirring at 0 °C for 24 h, the reaction mixture was quenched with sat. NH$_4$Cl solution and extracted with EtOAc. The organic layer was washed with 3 M NaOH aq., dried over anhydrous MgSO$_4$ and concentrated under reduced pressure. The residue was recrystallized from n-hexane/EtOAc to afford 10c (11 g, 88%) as a white powder.

IR (film) 3090, 3028, 2981, 2851, 1686, 1582, 1423, 1361, 1130 cm$^{-1}$; 1H NMR (500 MHz, CDCl$_3$): $\delta$ 8.36 (d, $J = 8.3$ Hz, 1H), 8.18 (d, $J = 8.3$ Hz, 1H), 7.71 (td, $J_1 = 7.3$, $J_2 = 1.0$ Hz, 1H), 7.68 (s, 2H), 7.50-7.20 (m, 15H), 5.20 (s, 2H), 5.19 (s, 4H); 13C NMR (67.8 MHz, CDCl$_3$): δ 165.6, 152.5, 145.6, 143.5, 137.3, 136.6, 132.6, 130.4, 128.6, 128.5, 128.2, 128.1, 128.0, 127.6, 126.3, 125.9, 120.2, 114.9, 111.8, 75.3, 71.4; MS (FAB): m/z 542 (M+H)+; HRMS (FAB) calcd for C$_{34}$H$_{28}$N$_3$O$_4$+, (M+H)+ 542.2080, found 542.2032.

2-[4-(Benzyloxy)phenyl]-4H-chromen-4-one (11a)

To a mixture of 2'-hydroxyacetophenone (1.0 g, 7.48 mmol) and 10a (2.6 g, 7.85 mmol) in THF (24.9 mL) was added LHMDS (29.9 mL, 29.9 mmol, 1 M sol. in THF) at -78 °C under an Ar atmosphere. The reaction mixture was stirred at -78 °C for 2 h. Then, the reaction mixture was quenched with sat. NH$_4$Cl solution, and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous MgSO$_4$, and concentrated under reduced pressure to give a residue as a yellow solid. The crude mixture was applied to following reaction without further purification.

To a solution of crude residue in toluene (25 mL) was added TFA (5.56 mL, 74.8 mmol) at 60 °C. The reaction mixture was stirred at 60 °C for 3 h. Then, the resulting solution was evaporated under reduced pressure to give a residue including 11a. The residue was washed with Et$_2$O to afford 11a (1.30 g, 5.5 mmol, 74%) as a white solid.

Spectral data for 11a were in good agreement with those reported in reference.$^{17}$

2-[3,4-(Dibenzyloxy)phenyl]-4H-chromen-4-one (11b)

To a mixture of 2'-hydroxyacetophenone (1.0 g, 7.37 mmol) and 10b (3.4 g, 7.74 mmol) in THF (24.6 mL) was added LHMDS (29.5 mL, 29.5 mmol, 1 M sol. in THF) at -78 °C under an Ar atmosphere. The
reaction mixture was stirred at -78 °C for 3 h. Then, the reaction mixture was quenched with sat. NH₄Cl solution, and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous MgSO₄, and concentrated under reduced pressure to give a residue as a yellow solid. The crude mixture was applied to following reaction without further purification.

To a solution of crude residue in toluene (25 mL) was added TFA (5.48 mL, 7.37 mmol) at 60 °C. The reaction mixture was stirred at 60 °C for 1 h. Then, the resulting solution was evaporated under reduced pressure to give a residue including 11b. The residue was washed with Et₂O to afford 11b (2.64 g, 6.1 mmol, 82%) as a white solid.

IR (film) 3051, 3034, 2864, 1645, 1599, 1518, 1433, 1329, 1271, 1142, 1018 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 8.22 (dd, J₁ = 7.9, J₂ = 1.6 Hz, 1H), 7.68 (td, J₁ = 7.9, J₂ = 1.6 Hz, 1H), 7.55-7.30 (m, 14H), 7.03 (d, J = 8.5 Hz, 1H), 6.68 (s, 1H), 5.27 (s, 4H); ¹³C NMR (67.8 MHz, CDCl₃): δ 178.3, 163.1, 156.1, 152.0, 148.9, 136.7, 136.4, 133.5, 128.6, 128.1, 127.3, 127.1, 125.6, 124.6, 123.9, 120.5, 117.9, 114.1, 112.8, 106.4, 71.5, 70.9; MS (FAB): m/z 434 (M+H)+; HRMS (FAB) calcd for C₂₉H₂₂O₄⁺, (M+H)⁺ 434.1518, found 434.1548.

2-[3,4,5-(Triphenyloxy)phenyl]4H-chromen-4-one (11c)

To a mixture of 2'-hydroxyacetophenone (0.5 g, 3.63 mmol) and 10c (2.06 g, 3.81 mmol) in THF (12.7 mL) was added LHMDS (14.5 mL, 14.5 mmol, 1 M sol. in THF) at -78 °C under an Ar atmosphere. The reaction mixture was stirred at -78 °C for 2.5 h. Then, the reaction mixture was quenched with H₂O and sat. NH₄Cl solution, and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous MgSO₄, and concentrated under reduced pressure to give a residue as a yellow solid. The crude mixture was applied to following reaction without further purification.

To a solution of crude residue (3.0 g) in toluene (17.8 mL) was added TFA (3.96 mL, 53.3 mmol) at 60 °C. The reaction mixture was stirred at 60 °C for 0.5 h. Then, the resulting solution was evaporated under reduced pressure to give a residue including 11c. The residue was washed with Et₂O to afford 11c (2.9 g, 5.36 mmol, 99%) as a white solid.

IR (film) 3048, 2834, 1632, 1585, 1025 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 8.22 (dd, J₁ = 7.9, J₂ = 1.6 Hz, 1H), 7.70 (td, J₁ = 7.9, J₂ = 1.6 Hz, 1H), 7.53 (d, J = 7.9 Hz, 1H), 7.50-7.30 (m, 14H), 7.21 (s, 2H), 6.68 (s, 1H), 5.20 (s, 4H), 5.16 (s, 2H); ¹³C NMR (67.8 MHz, CDCl₃): δ 180.8, 163.0, 153.2, 136.5, 133.7, 130.6, 128.7, 128.6, 128.3, 128.2, 128.1, 127.5, 127.0, 125.7, 125.3, 118.0, 116.1, 111.3, 107.3, 106.3, 75.3, 71.5; MS (FAB): m/z 541 (M+H)+; HRMS (FAB) calcd for C₃₆H₂₉O₅⁺, (M+H)⁺ 541.2015, found 541.2020.

3-Hydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-one (12a)

To a solution of 11a (100 mg, 0.30 mmol) in EtOH (12 mL) was added 10% Pd(OH)₂ on charcoal (5 mg) at room temperature, and the reaction mixture was stirred at 60 °C for 1 h under H₂ atmosphere. Then, the
reaction mixture was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure to give a residue including **12a**. The residue was washed with Et₂O to afford **12a** (71 mg, 99%) as a white powder.

IR (film) 2918, 1636, 1601, 1564, 1481, 1389, 1267 cm⁻¹; ¹H NMR (270 MHz, DMSO-d₆): δ 8.02 (dd, J₁ = 8.6, J₂ = 1.4 Hz, 1H), 7.95 (d, J = 8.6 Hz, 2H), 7.83-7.70 (m, 2H), 7.47 (td, J = 8.6, J = 1.4 Hz, 1H), 6.93 (d, J = 8.6 Hz, 2H), 6.85 (s, 1H); ¹³C NMR (67.8 MHz, DMSO-d₆): δ 177.1, 163.3, 161.1, 155.7, 134.2, 125.5, 124.8, 123.4, 121.7, 118.5, 104.9; MS (FAB): m/z 239 (M+H)⁺; HRMS (FAB) calcd for C₁₅H₁₁O₃⁺, (M+H)⁺ 239.0708, found 239.0734.

3-Hydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-one (12b)

To a solution of **11b** (100 mg, 0.30 mmol) in EtOH (14 mL) was added 10% Pd(OH)₂ in charcoal (5 mg) at room temperature, and the reaction mixture was stirred at 60 °C for 1 h under H₂ atmosphere. Then, the reaction mixture was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure to give a residue including **12b**. The residue was washed with Et₂O to give **12b** (36 mg, 62%) as a white powder.

IR (film) 3107, 2747, 1607, 1557, 1385, 1281, 1134, 1121 cm⁻¹; ¹H NMR (270 MHz, DMSO-d₆): δ 8.08 (d, J = 7.9 Hz, 1H), 8.85-7.65 (m, 4H), 7.59 (d, J = 7.3 Hz, 1H), 7.44 (t, J = 7.9 Hz, 1H), 6.89 (d, J = 7.9 Hz, 1H); ¹³C NMR (67.8 MHz, DMSO-d₆): δ 176.9, 163.4, 155.6, 149.6, 145.8, 134.2, 125.4, 124.8, 121.9, 118.9, 118.4, 116.1, 113.4, 104.9; MS (FAB): m/z 255 (M+H)⁺; HRMS (FAB) calcd for C₁₅H₁₁O₄⁺, (M+H)⁺ 255.0657, found 255.0629.

2-(3,4,5-Trihydroxyphenyl)-4H-chromen-4-one (12c)

To a solution of **11c** (100 mg, 0.18 mmol) in EtOH (4 mL) was added 10% Pd(OH)₂ on charcoal (9 mg) at room temperature, and the mixture was stirred at 60 °C for 2.5 h under a H₂ atmosphere. Then, the reaction mixture was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure to give a residue including **12c**. The residue was washed with Et₂O to give **12c** (26 mg, 54%) as a green solid.

IR (film) 3087, 2849, 1605, 1553, 1211 cm⁻¹; ¹H NMR (270 MHz, DMSO-d₆): δ 8.08 (d, J = 7.9 Hz, 1H), 7.77 (td, J₁ = 7.9, J₂ = 1.3 Hz, 1H), 7.66 (d, J = 7.9 Hz, 1H), 7.44 (t, J = 7.9 Hz, 1H), 7.29 (s, 2H), 6.89 (s, 1H); ¹³C NMR (67.8 MHz, CDCl₃): δ 177.0, 163.6, 155.7, 146.4, 137.7, 134.2, 125.5, 124.9, 123.4, 120.9, 118.3, 105.7, 104.9; MS (FAB): m/z 271 (M+H)⁺; HRMS (FAB) calcd for C₁₅H₁₁O₅⁺, (M+H)⁺ 271.0606, found 271.0611.

3-Hydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-one (14a)

To a solution of **11a** (100 mg, 0.30 mmol) in CH₂Cl₂ (5 mL) was added DMDO (9.00 mL, 0.09-0.11 M in acetone) at room temperature under an Ar atmosphere, and the reaction mixture was stirred at 30 °C for 1.8 h. Then, the reaction mixture was concentrated under reduced pressure to give a residue including **13a**.
The residue was purified by silica gel column chromatography (CH₂Cl₂) to afford 13a (93.6 mg, 89%) as a light brown powder.

Spectral data for 13a were in good agreement with those reported in reference.18

To a solution of 13a (100 mg, 0.29 mmol) in EtOH (16 mL) was added 10% Pd(OH)₂ on charcoal (5 mg) at room temperature, and the reaction mixture was stirred at 60 °C for 1 h under H₂ atmosphere. Then, the reaction mixture was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure to give a residue including 14a. The residue was washed with Et₂O to give 14a (44 mg, 67%) as a white powder.

1H NMR (270 MHz, DMSO-d₆): δ 10.13 (brs, 1H), 9.32 (brs, 1H), 8.10 (d, J = 9.2 Hz, 2H), 8.09 (d, J = 7.9 Hz, 1H), 7.65-7.85 (m, 2H), 7.44 (t, J = 7.9 Hz, 1H), 6.93 (d, J = 9.2 Hz, 2H); ¹³C NMR (67.8 MHz, DMSO-d₆): δ 172.6, 159.2, 154.4, 146.2, 137.8, 133.5, 124.7, 124.5, 122.0, 121.4, 118.3; IR (film, cm⁻¹) 2980, 2868, 1604, 1557, 1420, 1207, 1107, 1015; MS (FAB): m/z 255 (M+H)+; HRMS (FAB) calcd for C₁₅H₁₁O₄⁺, (M+H)+ 255.0657, found 255.0671.

3-Hydroxy-2-(3,4-dihydroxyphenyl)-4H-chromen-4-one (14b)

To a solution of 11b (100 mg, 0.231 mmol) in CH₂Cl₂ (10.0 mL) was added DMDO (6.90 mL, 0.1 M in acetone) at 0 °C under an Ar atmosphere. The reaction mixture was stirred at room temperature for 3 h. Then, the reaction mixture was concentrated under reduced pressure to give a residue including 13b. The crude material was applied to following reaction without further purification.

To a solution of crude residue including 13b in EtOH (25.0 mL) was added 20% Pd(OH)₂/C (3.41 mg) at 0 °C under an Ar atmosphere, and the reaction mixture was stirred at 60 °C under H₂ atmosphere for 3 h. Then, the reaction mixture was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure to give a residue including 14b. The residue was washed with CH₂Cl₂/MeOH (30 / 1) to give 14b (38.4 mg, 59%) as a green solid.

¹H NMR (270 MHz, DMSO-d₆): δ 8.07 (d, J = 7.9 Hz, 1H), 8.85-7.65 (m, 3H), 7.59 (dd, J₁ = 7.9, J₂ = 2.0 Hz, 1H), 7.44 (t, J = 7.9 Hz, 1H), 6.89 (d, J = 8.6 Hz, 1H); ¹³C NMR (67.8 MHz, DMSO-d₆): δ 172.5, 154.4, 147.7, 146.2, 145.2, 137.9, 133.5, 124.8, 124.5, 122.3, 121.3, 120.1, 118.2, 115.6, 115.3; MS (FAB): m/z 271 (M+H)+; HRMS (FAB) calcd for C₁₅H₁₁O₅⁺, (M+H)+ 271.0606, found 271.0566.

2-(3,4,5-Tris(( tert-butyl(dimethyl)silyl)oxy)phenyl)-4H-chromen-4-one (15c)

To a solution of 12c (300 mg, 1.11 mmol) in DMF (1.5 mL) were added TBSCl (1.00 g, 6.67 mmol, 6.0 equiv) and imidazole (0.53 g, 7.78 mmol, 7.0 equiv) and DMAP (68 mg, 0.556 mmol, 0.5 equiv) under an Ar atmosphere. The reaction mixture was stirred at 100 °C for 24 h. The reaction mixture were added TBSCl (0.50 g, 3.34 mmol, 3.0 equiv) and imidazole (0.26 g, 3.89 mmol, 3.5 equiv) at 100 °C. The reaction mixture was stirred at 100 °C for 30 h. The resulting mixture was quenched with H₂O, and extracted with CH₂Cl₂. The organic layer was washed with water followed by brine, dried over anhydrous...
MgSO₄, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (n-hexane/EtOAc = 20/1) to afford 15c (607 mg, 0.989 mmol, 89%) as a white solid.

IR (film): 2953, 2959, 2856, 1645, 1564, 1492, 1097 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 8.22 (dd, J₁ = 7.7 Hz, J₂ = 1.2 Hz, 1H, Ar), 7.67 (dt, J₁ = 7.5 Hz, J₂ = 1.2 Hz, 1H, Ar), 7.48 (d, J = 8.0 Hz, 1H, Ar), 7.40 (t, J = 7.4 Hz, 1H, Ar), 7.11 (s, 2H, Ar), 6.65 (s, 1H), 1.00 (s, 9H), 0.98 (s, 18H), 0.27 (s, 12H), 0.16 (s, 6H); ¹³C NMR (125 MHz, CDCl₃): δ 178.5, 163.3, 156.2, 149.3, 142.2, 133.7, 125.8, 125.2, 124.0, 123.6, 118.0, 112.4, 106.4, 26.3, 26.2, 19.0, 18.6, -3.5, -3.8; MS (ESI): m/z 652 (M+Na)+; HRMS (ESI): calcd for C₃₃H₅₃NaO₆Si, (M+Na)+ 652.3042, found 652.3038.

3-Hydroxy-2-(3,4,5-trihydroxyphenyl)-4H-chromen-4-one (14c)

To a solution of 15c (115 mg, 0.155 mmol) in CH₂Cl₂ (0.52 mL) was added DMDO (3.1 mL, 0.1 M in acetone) at 0 °C under an Ar atmosphere. The reaction mixture was stirred at room temperature for 2 h. The resulting solution was diluted with acetone and concentrated under reduced pressure to give a residue including 16c. The crude residue was applied to following reaction without further purification.

To a solution of crude residue including 16c in THF (2.3 mL) were added TBAF (0.69 mL, 0.69 mmol, 5.0 equiv) and AcOH (40 µL) at 0 °C under an Ar atmosphere. The reaction mixture was stirred at room temperature for 0.5 h. The resulting mixture was quenched with H₂O, and extracted with CH₂Cl₂. The organic layer was washed with water, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was washed with Et₂O and hexane to afford 14c (29 mg, 0.096 mmol, 69%) as a yellow solid.

IR (film): 3265, 1585, 1537, 1506, 1489, 1346, 1398, 1209, 1035 cm⁻¹; ¹H NMR (270 MHz, DMSO-d₆): δ 9.27 (s, 1H, OH), 9.25 (s, 2H, OH), 8.81 (s, 1H, OH), 8.50 (dd, J₁ = 7.4, J₂ = 1.7 Hz, 1H, Ar), 7.74 (td, J₁ = 8.5, J₂ = 1.7 Hz, 1H, Ar), 7.64 (d, J = 8.5 Hz, 1H, Ar), 7.42 (t, J = 7.4 Hz, 1H, Ar), 7.27 (s, 2H, Ar); ¹³C NMR (125 MHz, DMSO-d₆): δ 172.9, 154.8, 146.7, 146.3, 138.5, 136.3, 133.9, 125.3, 124.9, 121.8, 121.7, 118.6, 107.8; MS (FAB): m/z 287 (M+H)+; HRMS (FAB) calcd for C₁₅H₁₁O₆, (M+H)+ 287.1556, found 287.1574.

1-(2-((tert-Butyldimethylsilyl)oxy)-6-hydroxyphenyl)ethanone (17)

To a solution of 2',6'-dihydroxyacetophenone (500 mg, 3.30 mmol) in DMF (11 mL) were added TBSCl (497 mg, 3.30 mmol, 1.0 equiv) and imidazole (247 mg, 3.63 mmol, 1.2 equiv) at 0 °C under an Ar atmosphere. The reaction mixture was stirred at room temperature for 13 h. The resulting mixture was quenched with sat. NH₄Cl solution and extracted with EtOAc. The organic layer was washed with H₂O followed by brine, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (n-hexane/EtOAc = 30/1) to afford 17 (806 mg, 92%) as a yellow solid.
IR (film): 2956, 2927, 2856, 1614, 1591, 1452, 1255, 1222, 831, 786 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 12.91 (s, 1H, OH), 7.23 (dd, J₁ = 8.6 Hz, J₂ = 8.0 Hz, 1H), 6.54 (dd, J₁ = 8.6 Hz, J₂ = 1.2 Hz, 1H), 6.34 (dd, J₁ = 8.6 Hz, J₂ = 1.2 Hz, 1H), 2.68 (s, 3H), 1.00 (s, 9H), 0.34 (s, 6H); ¹³C NMR (125 MHz, CDCl₃): δ 205.2, 164.2, 157.9, 135.5, 113.8, 110.6, 109.6, 33.3, 26.1, 18.8, -3.6; MS (ESI): m/z 289 (M+Na)⁺; HRMS (ESI) calcd for C₁₄H₂₂NaO₃Si⁺, (M+Na)⁺ 289.1230, found 289.1240.

5-Hydroxy-2-(3,4,5-tris((tert-butyldimethylsilyl)oxy)phenyl)-4H-chromen-4-one (19)

To a mixture of 17 (553 mg, 2.08 mmol) and crude material 18 (1.66 g, 2.70 mmol, 1.3 equiv) in THF (7 mL) was added LHMDS (8.3 mL, 8.31 mmol, 1M sol. in THF) at -78 °C under an Ar atmosphere. The reaction mixture was stirred at -78 °C for 3.5 h. Then, the reaction mixture was quenched with sat. NH₄Cl solution, and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous MgSO₄, and concentrated under reduced pressure to give a residue as a yellow solid. The crude mixture was applied to following reaction without further purification.

To a solution of crude residue in toluene (10 mL) was added TFA (1 mL) at 60 °C. The reaction mixture was stirred at 60 °C for 5 min. Then, the resulting solution was evaporated under reduced pressure to give a residue including 19. The residue was purified by silica gel column chromatography (n-hexane/EtOAc = 50/1) to give 19 (955 mg, 1.52 mmol, 73%) as a yellow powder.

IR (film): 2929, 2856, 1658, 1616, 1359, 1095 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 12.65 (s, 1H, OH), 7.53 (t, J = 8.3 Hz, 1H), 7.09 (s, 2H), 6.92 (d, J = 8.3 Hz, 1H), 7.05 (d, J = 8.5 Hz, 1H), 6.55 (s, 1H), 1.01 (s, 9H), 0.98 (s, 18H), 0.28 (s, 12H), 0.17 (s, 6H); ¹³C NMR (125 MHz, CDCl₃): δ 183.6, 164.6, 160.9, 156.4, 149.4, 142.7, 135.3, 123.0, 112.5, 111.4, 110.8, 106.9, 104.8, 26.3, 26.2, 19.0, 18.6, -3.5, -3.8; MS (ESI): m/z 651 (M+Na)⁺; HRMS (ESI): calcd for C₃₃H₅₂NaO₆Si₃⁺, (M+Na)⁺ 651.2949, found. 651.2963.

3,5-Dihydroxy-2-(3,4,5-trihydroxyphenyl)-4H-chromen-4-one (20)

To a solution of 19 (364 mg, 0.579 mmol) in DMF (0.58 mL) were added imidazole (394 mg, 5.79 mmol) and TBSCl (872 mg, 5.79 mmol) and DMAP (2.0 mg) at room temperature and the mixture was stirred at 100 °C for 9 h and allowed to cool to room temperature. Then, the reaction mixture was quenched with sat. NH₄Cl solution and extracted with CH₂Cl₂. The organic layer was washed with H₂O and brine. The extract was dried over anhydrous MgSO₄ and concentrated under reduced pressure to give a residue including 19’. The residue was purified by silica gel column chromatography (n-hexane/EtOAc = 30/1) to afford 19’ (397 mg, 92%) as a yellow solid.

IR (film): 2954, 2858, 1710, 1654, 1490, 1355, 1253, 1089 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 7.45 (dd, J₁ = 8.5 Hz, J₂ = 7.9 Hz, 1H), 7.07 (s, 2H), 7.05 (d, J = 8.5 Hz, 1H), 6.77 (d, J = 7.9 Hz, 1H), 6.48 (s, 1H), 1.07 (s, 9H, t-Bu), 1.00 (s, 9H, t-Bu), 0.97 (s, 18H, t-Bu), 0.27 (s, 6H, Me), 0.27 (s, 12H, Me), 0.16 (s, 6H, Me); ¹³C NMR (125 MHz, CDCl₃): δ 178.1, 161.0, 157.9, 155.6, 149.1, 141.7, 132.9, 116.9, 112.0, 111.9, 110.5, 107.3, 26.2, 26.1, 25.9, 18.8, 18.7, 18.5, -3.6, -3.9, -4.4; MS (ESI): m/z 743 (M+H)⁺; HRMS (ESI):
calcd for C\textsubscript{39}H\textsubscript{67}O\textsubscript{6} Si\textsubscript{4}\textsuperscript{+}, (M+H)\textsuperscript{+} 743.4009, found 743.4015.  

To a solution of 19' (105 mg, 0.155 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (0.52 mL) was added DMDO (3.1 mL, 0.09 - 0.11 M in acetone) at 0 °C under an Ar atmosphere, and the reaction mixture was stirred at room temperature for 2 h. Then, the reaction mixture was concentrated under reduced pressure to give a pale yellow amorphous.  

To a solution of the crude material in THF (2.3 mL) were added AcOH (100 µL) and TBAF (0.69 mL, 5.0 equiv) at 0 °C under an Ar atmosphere, and the mixture was stirred at room temperature for 0.5 h. Then, the reaction mixture was diluted with CH\textsubscript{2}Cl\textsubscript{2}. The resulting solution was washed with H\textsubscript{2}O. The organic layer was dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated under reduced pressure to give a residue including 20. The residue was washed with Et\textsubscript{2}O to give 20 (28.8 mg, 69%) as an orange solid.  

IR (film): 3338, 1597, 1525, 1463, 1192, 1012, 800 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (500 MHz, DMSO-\textit{d}\textsubscript{6}): \textit{\delta} 12.43 (s, 1H, OH), 9.56 (brs, 1H, OH), 9.23 (brs, 2H, OH), 7.61 (dd, \textit{J\textsubscript{1}} = 8.6 Hz, \textit{J\textsubscript{2}} = 8.0 Hz, 1H), 7.32 (s, 2H), 7.08 (d, \textit{J\textsubscript{1}} = 8.6 Hz, 1H), 6.75 (d, \textit{J\textsubscript{1}} = 8.0 Hz, 1H); \textsuperscript{13}C NMR (125 MHz, DMSO-\textit{d}\textsubscript{6}): \textit{\delta} 177.2, 159.8, 155.0, 148.7, 146.3, 137.2, 136.9, 135.6, 121.1, 109.7, 109.4, 108.1, 107.8, 103.3; MS (ESI): \textit{m/z} 325 (M+Na)\textsuperscript{+}; HRMS (ESI): calcd for C\textsubscript{15}H\textsubscript{10}NaO\textsubscript{7}, (M+Na)\textsuperscript{+} 325.0318, found 325.0306.  

(1\textit{H}-Benzo[\textit{d}][1,2,3]triazol-1-yl)(3-(benzyloxy)-4-methoxyphenyl)methanone (22b)  

To a solution of 3-(benzyloxy)-4-methoxybenzoic acid (1.27 g, 4.91 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (16.4 mL) were added SOCl\textsubscript{2} (3.08 mL, 44.2 mmol, 9.0 equiv) and DMF (0.15 mL, 1.97 mmol, 0.4 equiv) at 0 °C under an Ar atmosphere. The reaction mixture was stirred at room temperature for 1.5 h. The reaction mixture was concentrated under reduced pressure. The crude mixture was applied to following reaction without further purification.  

To a solution of crude material in CH\textsubscript{2}Cl\textsubscript{2} (16.4 mL) were added Et\textsubscript{3}N (1.03 mL, 7.37 mmol, 2.5 equiv) and benzotriazole (1.17 g, 9.83 mmol, 2.0 equiv) at 0 °C under an Ar atmosphere. The reaction mixture was stirred at room temperature for 30 min. After stirring, the reaction mixture was quenched with sat. NH\textsubscript{4}Cl solution at 0 °C and extracted with CH\textsubscript{2}Cl\textsubscript{2}. The organic layer was dried over anhydrous MgSO\textsubscript{4}, and concentrated under reduced pressure to give a residue including 22b. The crude residue was purified by recrystallization from \textit{n}-hexane/CH\textsubscript{2}Cl\textsubscript{2} to afford 22b (1.10 g, 3.06 mmol, 82%) as a white solid.  

IR (film): 3086, 3012, 2937, 2837, 1699, 1595, 1516, 1357, 1267, 1145 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): \textit{\delta} 8.37 (d, \textit{J\textsubscript{1}} = 8.3 Hz, 1H, Ar), 8.17 (d, \textit{J\textsubscript{1}} = 8.3 Hz, 1H, Ar), 8.03 (t, \textit{J\textsubscript{1}} = 8.3 Hz, 1H, Ar), 7.90 (t, \textit{J\textsubscript{1}} = 8.3 Hz, 1H, Ar), 7.89 (t, \textit{J\textsubscript{1}} = 8.3 Hz, 1H, Ar), 7.56-7.26 (m, 6H, Ar), 7.01 (d, \textit{J\textsubscript{1}} = 8.3 Hz, 1H, Ar), 5.26 (s, 2H, CH\textsubscript{2}), 4.00 (s, 3H, OCH\textsubscript{3}); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}): \textit{\delta} 165.4, 154.7, 147.9, 145.6, 136.4, 132.0, 130.2, 128.7, 128.2, 127.0, 126.2, 123.3, 120.1, 116.6, 114.9, 110.7, 77.4, 76.9, 71.2, 56.2; MS (ESI): \textit{m/z} 382 (M+Na)\textsuperscript{+}; HRMS (ESI): calcd for C\textsubscript{21}H\textsubscript{16}NaO\textsubscript{3} , (M+Na)\textsuperscript{+} 382.1162, found 382.1174.  

(1\textit{H}-Benzo[\textit{d}][1,2,3]triazol-1-yl)(4-(benzyloxy)-3-methoxyphenyl)methanone (22c)
To a solution of 4-(benzyloxy)-3-methoxybenzoic acid (1.0 g, 3.87 mmol) in CH₂Cl₂ (13.0 mL) were added SOCl₂ (0.84 mL, 11.6 mmol, 3.0 equiv) and DMF (0.12 mL, 1.55 mmol, 0.4 equiv) at 0 °C under an Ar atmosphere. The reaction mixture was stirred at room temperature for 1.5 h. The reaction mixture was concentrated under reduced pressure. The crude mixture was applied to following reaction without further purification.

To a solution of crude material in CH₂Cl₂ (13.0 mL) were added Et₃N (0.81 mL, 5.81 mmol, 1.5 equiv) and benzotriazole (0.51 g, 5.81 mmol, 1.1 equiv) at 0 °C under an Ar atmosphere. The reaction mixture was stirred at room temperature for 30 min. After stirring, the reaction mixture was quenched with sat. NH₄Cl solution at 0 °C, and extracted with CH₂Cl₂. The organic layer was dried over anhydrous MgSO₄, and concentrated under reduced pressure to give a residue including 22c. The crude residue was purified by recrystallization from n-hexane/CH₂Cl₂ to afford 22c (1.10 g, 3.06 mmol, 79%) as a white solid. IR (film): 3111, 3030, 2958, 2875, 1701, 1597, 1512, 1359, 1215, 1145 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 8.37 (d, J = 8.3 Hz, 1H, Ar), 8.15 (d, J = 8.3 Hz, 1H, Ar), 7.95 (dd, J₁ =8.3 Hz, J₂ = 2.6 Hz 1H, Ar), 7.82 (s, 1H, Ar), 7.65 (d, J = 8.3 Hz, 1H, Ar), 7.56-7.26 (m, 6H, Ar), 7.04 (d, J = 8.3 Hz, 1H, Ar), 5.28 (s, 2H, CH₂), 4.00 (s, 3H, OCH₃); ¹³C NMR (125 MHz, CDCl₃): δ 165.6, 153.2, 149.3, 147.8, 136.1, 130.2, 128.8, 128.3, 127.3, 127.0, 126.2, 123.6, 120.1, 114.9, 112.3, 77.4, 77.2, 76.9, 70.9, 56.2; MS (ESI): m/z 382 (M+Na)+; HRMS (ESI): calcld for C₂₁H₁₇N₃NaO₃, (M+Na)+ 382.1162, found 382.1100.

3'-Demethylnobiletin (23b)

To a mixture of 21 (110 mg, 0.43 mmol) and 22b (169.1 mg, 0.470 mmol, 1.1 equiv) in THF (1.43 mL) was added LHMDS (1.72 mL, 1.72 mmol, 4.0 equiv, 1 M sol. in THF) under an Ar atmosphere at -78 °C. The reaction mixture was stirred at -78 °C for 2 h. The resulting mixture was quenched with sat. NH₄Cl solution at 0 °C, and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous MgSO₄, and concentrated under reduced pressure to give a residue including 22b as a yellow solid. The crude solid was applied to following reaction without further purification.

To a solution of crude solid including 22b (283.1 mg) in toluene (1.96 mL) was added TFA (0.44 mL) at room temperature. The reaction mixture was stirred at 60 °C for 30 min. After stirring, the reaction mixture was concentrated under reduced pressure to give a residue including 22b as a pale yellow solid. The crude solid was applied to following reaction without further purification.

To a mixture of 22b (50.0 mg) in EtOH (10 mL) added Pd(OH)₂ (1.46 mg, 2.09 μmol) under an Ar atmosphere, then purged with H₂ gas. The reaction mixture was stirred at 60 °C for 2 h. The resulting mixture was filtered with a pad of Celite. The filtrate was concentrated under reduced pressure to give a residue including 23b. The crude residue was purified by recrystallization from n-hexane/CH₂Cl₂ to afford 23b (23.6 mg, 23%, 3 steps from 21) as a yellow solid.
IR (film): 2939, 2841, 1629, 1509, 1438, 1359, 1280, 1016, 842, 808 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 7.49 (dd, J₁ = 8.4 Hz, J₂ = 2.4 Hz, 1H, Ar), 7.46 (d, J = 8.4 Hz, 1H, Ar), 6.97 (d, J = 8.4 Hz, 1H, Ar), 6.58 (s, 1H, CH), 4.09 (s, 3H, OCH₃), 4.01-3.95 (m, 12H, OCH₃). ¹³C NMR (125 MHz, CDCl₃): δ 179.6, 163.9, 153.3, 152.6, 149.3, 149.1, 148.3, 145.6, 139.6, 124.9, 119.8, 115.3, 113.8, 112.7, 106.8, 110.7, 62.6, 62.6, 62.2, 62.1; MS (ESI): m/z 411 (M+Na)+; HRMS (ESI): calcd for C₂₀H₂₀NaO₈⁺, (M+Na)+ 411.1050, found 411.1067.

**4′-Demethylnobiletin (23c)**

To a mixture of 21 (100 mg, 0.39 mmol) and 22c (154 mg, 0.429 mmol, 1.1 equiv) in THF (1.3 mL) was added LHMDS (1.56 mL, 1.56 mmol, 4.0 equiv, 1 M sol. in THF) under an Ar atmosphere at -78 °C. The reaction mixture was stirred at -78 °C for 2 h. The resulting mixture was quenched with sat. NH₄Cl solution at 0 °C, and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous MgSO₄, and concentrated under reduced pressure to give a residue including 22c⁺ as a yellow solid. The crude solid was applied to following reaction without further purification.

To a solution of crude solid including 22c⁺ (280.4 mg) in toluene (1.95 mL) was added TFA (0.43 mL) at room temperature. The reaction mixture was stirred at 60 °C for 30 min. After stirring, the reaction mixture was concentrated under reduced pressure to give a residue including 22c'' as a pale yellow solid. The crude solid was applied to following reaction without further purification.

To a mixture of 22c'' (51.0 mg, 0.107 mmol) in EtOH (10 mL) was added Pd(OH)₂ (1.5 mg, 2.14 µmol) under an Ar atmosphere, then purged with H₂ gas. The reaction mixture was stirred at 60 °C for 2 h. The resulting mixture was filtered with a pad of Cellite. The filtrate was concentrated under reduced pressure to give a residue including 23c. The crude residue was purified by silica gel column chromatography with (n-hexane/AcOEt = 2 : 3) to afford 23c (39.7 mg, 39%, 3 steps from 21) as a white solid.

**5-Demethylnobiletin (24)**

To a solution of 3 (50 mg, 0.13 mmol) in CH₂Cl₂ (40 mL) was added AlCl₃ (33 mg, 0.26 mmol, 2.0 equiv) in EtSH (0.66 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1 h. The resulting mixture was quenched with 6 M HCl aq. at 0 °C, and extracted with CH₂Cl₂. The organic layer was washed with brine, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (n-hexane/EtOAc = 2/1, 1/1) to afford 24 (36 mg, 76%) as a yellow powder.
Spectral data for 24 were in good agreement with those reported in reference.19

\[ N-(5-((2-(3,4-Dimethoxyphenyl)-6,7,8-trimethoxy-4-oxo-4H-chromen-5-yl)oxy)pentyl)propionylamide \] (25)

To a mixture of 24 (0.28 g, 0.73 mmol) and tert-butyl (5-iodopentyl)carbamate (0.68 g, 2.2 mmol, 3.0 equiv) in acetone (2.4 mL) was added K$_2$CO$_3$ (0.30 g, 2.2 mmol, 3.0 equiv) at 50 °C. The reaction mixture was stirred at 50 °C for 48 h, and allowed to cool to room temperature. The resulting mixture was poured into Et$_2$O, and filtered through a pad of Celite. The filtrate was concentrated under reduced pressure to give a residue including 24a. The residue was purified by silica gel column chromatography (n-hexane/EtOAc = 2/1, 1/1) to give a crude material including 24a. The crude material including 24a was applied to following reaction without further purification.

To a solution of crude 24a in CH$_2$Cl$_2$ (2.0 mL) and MeOH (10 mL) was added 2 M HCl aq. (5.0 mL). The reaction mixture was stirred at room temperature for 12 h. The resulting mixture was quenched with 2 M NaOH aq. at 0 °C, concentrated under reduced pressure to remove MeOH, extracted with CH$_2$Cl$_2$. The organic layer was washed with brine, dried over anhydrous MgSO$_4$, and concentrated under reduced pressure to give a residue including 24b. The residue was purified by silica gel column chromatography (CH$_2$Cl$_2$/MeOH/i-PrNH$_2$ = 10/10/0.1) to afford 24b (0.25 g, 71%) as a yellow oil.

IR (film): 3404, 2939, 1629, 1517, 1429, 1367, 1273, 1024 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.55 (dd, $J_1$ = 8.5 Hz, $J_2$ = 2.7 Hz, 1H, Ar), 7.41 (s, 1H, Ar), 6.98 (d, $J$ = 8.5 Hz, 1H, Ar), 6.60 (s, 1H, CH), 4.10 (s, 3H, OCH$_3$), 4.03 (s, 3H, OCH$_3$), 4.02 (t, $J$ = 6.8 Hz, 2H, CH$_2$), 3.98 (s, 3H, OCH$_3$), 3.96 (s, 3H, OCH$_3$), 3.92 (s, 3H, OCH$_3$), 2.80 (t, $J$ = 6.8 Hz, 2H, CH$_2$), 1.91 (m, 2H, CH$_2$), 1.60 (m, 4H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 177.9, 161.5, 152.0, 151.7, 149.3, 147.8, 147.4, 144.3, 137.9, 123.8, 119.9, 114.7, 111.2, 108.6, 106.7, 74.7, 62.0, 61.9, 61.7, 56.1, 39.7, 29.3, 27.2, 22.7; MS (ESI): $m/z$ 474 (M+H)$^+$; HRMS (ESI): calcd for C$_{25}$H$_{32}$N$_1$O$_8$, (M+H)$^+$ 474.2121, found 474.2122.

To a mixture of 24b (66 mg, 0.14 mmol) and 3-(trimethylsilyl)propionic acid (40 mg, 0.28 mmol, 2.0 equiv) in CH$_2$Cl$_2$ (0.50 mL) were added EDCI (0.16 g, 0.83 mmol, 4.0 equiv) and HOBt (2.0 mg) at room temperature. The reaction mixture was stirred at room temperature for 24 h. The resulting mixture was poured into H$_2$O. The organic layer was separated, and aqueous phase was extracted with CH$_2$Cl$_2$. The organic layer was separated, and aqueous phase was extracted with CH$_2$Cl$_2$. The organic layer was...
combined, washed with H$_2$O followed by brine, dried over anhydrous MgSO$_4$, and concentrated under reduced pressure to give a residue including 25. The residue was purified by silica gel column chromatography (n-hexane/EtOAc = 2/1) to afford 25 (50 mg, 68%) as a colorless oil.

IR (film): 3232, 2939, 2104, 1637, 1629, 1518, 1365, 1273 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.56 (dd, $J_1 = 8.5$ Hz, $J_2 = 2.3$ Hz, 1H, Ar), 7.42 (s, 1H, Ar), 7.00 (d, $J = 8.5$ Hz, 1H, Ar), 6.61 (s, 1H, CH), 4.11 (s, 3H, OCH$_3$), 4.07 (t, $J = 5.9$ Hz, 2H, CH$_2$), 3.98 (s, 3H, OCH$_3$), 3.97 (s, 3H, OCH$_3$), 3.93 (s, 3H, OCH$_3$), 3.39 (q, $J = 5.9$ Hz, 2H, CH$_2$), 2.74 (s, 1H, CH) 1.89 (m, 2H, CH$_2$), 1.70 (m, 4H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 177.6, 161.2, 152.4, 152.0, 151.6, 149.3, 147.9, 147.6, 144.3, 137.9, 123.9, 119.7, 114.9, 111.3, 108.5, 106.9, 74.4, 72.5, 62.0, 61.9, 61.7, 56.1, 56.0, 39.9, 29.6, 28.2, 23.0, 22.9; MS (ESI): m/z 548 (M+H)$^+$; HRMS (ESI): calcd for C$_{28}$H$_{31}$N$_1$O$_9$, (M+H)$^+$ 548.1891, found 548.1893.

5-Hydroxy-2-(3,4,5-tris(benzyloxy)phenyl)-4H-chromen-4-one (26)

To a mixture of 17 (1.0 g, 3.75 mmol) and 10c (2.04 g, 4.96 mmol, 1.3 equiv) in THF (12.7 mL) was added LHMDS (15.0 mL, 15.0 mmol, 4.0 equiv, 1 M sol. in THF) at -78 °C under an Ar atmosphere. The reaction mixture was stirred at -78 °C for 2.5 h. Then, the reaction mixture was quenched with sat. NH$_4$Cl solution and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous MgSO$_4$, and concentrated under reduced pressure to give a residue including 10c' as a yellow solid. The crude mixture was applied to the following reaction without further purification.

To a solution of the crude residue including 10c' (3.14 g) in toluene (12.5 mL) was added TsOH (1.43 g, 7.5 mmol) at 60 °C. The reaction mixture was stirred at 60 °C for 3 h. The crude mixture was diluted with EtOAc and washed with water. The organic layer was washed with brine, dried over anhydrous MgSO$_4$, and concentrated under reduced pressure to give a residue including 26. The residue was purified by silica gel column chromatography (CH$_2$Cl$_2$/n-hexane = 15/1) to afford 26 (2.00 g, 95%, 2 steps) as a white solid.

IR (film): 3032, 1649, 1633, 1159, 1433, 1340, 1120 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 12.57 (s, OH), 7.54 (dd, $J = 8.6$ Hz, $J_2 = 8.0$ Hz 1H, Ar), 7.46-7.34 (m, 15H, Ar), 7.17 (s, 2H, Ar), 6.95 (d, $J = 8.6$ Hz, 1H, Ar), 6.81 (d, $J = 8.6$ Hz, 1H, Ar), 6.57 (s, 1H, Ar), 5.19 (s, 4H), 5.17 (s, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 183.5, 164.3, 160.9, 156.4, 153.3, 142.0, 137.4, 136.6, 135.4, 128.8, 128.7, 128.4, 128.3, 128.2, 127.6, 126.4, 111.6, 110.9, 107.1, 106.5, 105.8, 75.4, 71.6; MS (ESI): m/z 579 (M+Na)$^+$; HRMS (ESI): calcd for C$_{36}$H$_{28}$NaO$_6$, (M+Na)$^+$ 579.1778, found 579.1769.

5-(Pent-4-yn-1-yl oxy)-2-(3,4,5-tris(benzyloxy)phenyl)-4H-chromen-4-one (27)

To a mixture of 6 (300 mg, 0.54 mmol) and 1-iodo-4-pentyn (420 mg, 2.2 mmol, 4.0 equiv) in DMF (4.0 mL) was added K$_2$CO$_3$ (300 mg, 2.2 mmol, 4.0 equiv) at room temperature. The reaction mixture was stirred at 100 °C for 8 h, and allowed to cool to room temperature. The resulting mixture was diluted with Et$_2$O, and filtered through a pad of Celite. The filtrate was concentrated under reduced pressure and
extracted with CH₂Cl₂. The organic layer was washed with H₂O and brine, dried over anhydrous MgSO₄ and evaporated under reduced pressure to give a residue including 27. The residue was recrystallized from CH₂Cl₂/Et₂O to afford 27 (297 mg, 92%) as a white solid.

IR (film): 3213, 2332, 1637, 1126, 837 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 7.59 (dd, J₁ = 8.6 Hz, J₂ = 8.0 Hz, 1H, Ar), 7.47-7.34 (m, 15H, Ar), 7.17 (s, 2H, Ar), 7.06 (d, J = 8.6 Hz, 1H, Ar), 6.82 (d, J = 8.0 Hz, 1H, Ar), 6.53 (s, 1H, Ar), 5.18 (s, 4H), 5.15 (s, 2H), 4.21 (dd, J₁ = 6.3 Hz, J₂ = 5.7 Hz, 2H), 2.60 (dt, J₁ = 6.9 Hz, J₂ = 2.9 Hz, 2H), 2.14 (quint, J = 6.3 Hz, 2H), 1.97 (t, J = 2.6 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃): δ 178.0, 160.7, 159.2, 158.2, 153.2, 141.3, 137.5, 136.7, 133.7, 128.7, 128.4, 128.2, 128.1, 127.6, 126.8, 114.9, 110.1, 108.9, 107.8, 106.2, 83.9, 75.4, 69.0, 67.7, 28.1, 15.2; MS (ESI): m/z 645 (M+Na)+; HRMS (ESI): calcd for C₄₁H₃₄NaO₆, (M+Na)+ 645.2247, found 645.2245.

5-(Pent-4-yn-1-yloxy)-2-(3,4,5-tris(tert-butyldimethylsilyloxy)phenyl)-4H-chromen-4-one (28)

To a mixture of 27 (200 mg, 0.32 mmol) in CH₂Cl₂ (6.40 mL) was added BCl₃ (1.0 mL, 1.0 mmol, 3.1 equiv, 1 M sol. in THF) at -78 °C under an Ar atmosphere. The reaction mixture was stirred at -78 °C for 1.5 h. Then, the reaction mixture was quenched with MeOH at -78 °C and concentrated under reduced pressure to give a residue the reaction mixture as an orange solid. The crude mixture was applied to the following reaction without further purification.

To a solution of the reaction mixture (190 mg) in DMF (0.65 mL) were added imidazole (220 mg, 3.21 mmol, 10 equiv) and TBSCl (480 mg, 3.21 mmol, 10 equiv) at room temperature under an Ar atmosphere. The reaction mixture was stirred at 100 °C for 5 h. Then, the reaction mixture was quenched with H₂O and sat. NH₄Cl solution, and extracted with Et₂O. The organic layer was washed with brine, dried over anhydrous MgSO₄, and concentrated under reduced pressure to give a residue including 28 as a brown oil. The residue was purified by silica gel column chromatography (n-hexane/EtOAc = 6/1) to afford 28 (154 mg, 70%, 2 steps) as a white solid.

IR (film): 3236, 2928, 2856, 2324, 1645, 1602, 1481, 1084 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 7.51 (dd, J₁ = 8.6 Hz, J₂ = 8.0 Hz, 1H, Ar), 7.06 (s, 2H, Ar), 7.03 (d, J = 8.6 Hz, 1H, Ar), 6.80 (d, J = 8.0 Hz, 1H, Ar), 6.49 (s, 1H, Ar), 4.21 (dd, J₁ = 6.3 Hz, J₂ = 5.7 Hz, 2H), 2.59 (dt, J₁ = 6.9 Hz, J₂ = 2.3 Hz, 2H), 2.13 (quint, J = 6.9 Hz, 2H), 1.93 (t, J = 2.3 Hz, 1H), 1.00 (s, 9H), 0.97 (s, 18H), 0.26 (s, 12H), 0.16 (s, 6H); ¹³C NMR (125 MHz, CDCl₃): δ 178.2, 161.0, 159.2, 158.2, 154.2, 141.9, 133.5, 123.3, 114.9, 112.1, 110.1, 108.0, 107.8, 83.9, 68.8, 67.7, 28.1, 26.3, 26.2, 19.0, 18.6, 15.1, -3.5, -3.8; MS (ESI): m/z 717 (M+Na)+; HRMS (ESI): calcd for C₃₈H₅₈NaO₆Si₃, (M+Na)+ 717.3433, found 717.3432.

N-(3-Azidopropyl)-4-(6-hydroxy-3-oxo-3H-xanthen-9-yl)-3-methylbenzamide (29)

To a mixture of TokyoGreen (0.10 g, 0.30 mmol) and 3-azidopropan-1-amine (60 mg, 0.60 mmol, 2.0 equiv) in DMF (1.0 mL) was added EDCI (0.23 g, 1.2 mmol, 4.0 equiv) at room temperature. The reaction mixture was stirred at room temperature for 12 h. After stirring, the reaction mixture was...
concentrated under reduced pressure to give a residue including 29. The residue was purified by silica gel column chromatography (CH$_2$Cl$_2$/MeOH = 10/1) to afford 29 (97 mg, 76%) as an orange solid.

IR (film): 3251, 2094, 1633, 1600, 1099, 913, 836 cm$^{-1}$; $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 8.63 (t, $J = 5.4$ Hz, 1H, NH), 7.91 (s, 1H), 7.83 (d, $J = 8.0$ Hz, 1H), 7.35 (d, $J = 7.5$ Hz, 1H), 6.80 (d, $J = 9.2$ Hz, 2H), 6.55 (d, $J = 8.0$ Hz, 4H) 3.47-3.39 (m, 4H), 2.04 (s, 3H), 1.78 (quint, $J = 5.4$ Hz, 2H); $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 166.4, 149.1, 136.5, 136.0, 135.6, 125.5, 104.1, 79.8, 79.5, 79.2, 49.1, 28.9, 19.6; MS (ESI): m/z 429 (M+H)$^+$; HRMS (ESI): calcd for C$_{24}$H$_{21}$N$_4$O$_4^+$, (M+H)$^+$ 429.1559, found 429.1557.

N-((3-Azidopropyl)-5-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanamide (30)

To a mixture of biotin (0.30 g, 1.2 mmol) and 3-azidopropan-1-amine (0.25 g, 2.5 mmol, 2.0 equiv) in DMF (4.0 mL) was added EDCI (0.47 g, 2.5 mmol, 2.0 equiv) at room temperature. The reaction mixture was stirred at room temperature for 10 h. After stirring, the reaction mixture was concentrated under reduced pressure to give a residue including 30. The residue was purified by silica gel column chromatography (CH$_2$Cl$_2$/MeOH = 10/1) to afford 30 (0.30 g, 74%) as a white solid.

IR (film): 3278, 2098, 1690, 1672, 1642, 1544, 1262 cm$^{-1}$; $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 7.83 (t, $J = 5.7$ Hz, 1H, NH), 6.43 (s, 1H, NH), 6.36 (s, 1H, NH), 4.29 (t, $J = 5.7$ Hz, 1H, CH), 4.12 (t, $J = 5.7$ Hz, 1H, CH), 3.33 (t, $J = 7.1$ Hz, 2H, CH$_2$), 3.10-3.05 (m, 3H), 2.81 (dd, $J_1 = 17.6$ Hz, $J_2 = 7.1$ Hz, 1H, CH), 2.56 (d, $J = 17.6$ Hz, 1H, CH), 2.49 (s, 1H, CH), 2.04 (t, $J = 7.1$ Hz, 2H, CH$_2$) 1.65-1.41 (m, 6H, CH$_2$), 1.35-1.23 (m, 2H, CH$_2$); $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 172.6, 163.2, 61.5, 59.7, 55.9, 48.9, 36.2, 35.7, 28.9, 28.7, 28.5, 25.8; MS (ESI): m/z 349 (M+Na)$^+$; HRMS (ESI): calcd for C$_{13}$H$_{22}$N$_6$NaO$_2$S$^+$, (M+Na)$^+$ 349.1417, found 349.1419.

N-(5-((2-(3,4-Dimethoxyphenyl)-6,7,8-trimethoxy-4-oxo-4H-chromen-5-yl)oxy)pentyl)-1-(3-(4-(6-hydroxy-3-oxo-3H-xanthen-9-yl)-3-methylbenzamido)propyl)-1H-1,2,3-triazole-4-carboxamide (31)

To a mixture of 25 (25 mg, 48 µmol, 1.2 equiv) and 29 (17 mg, 40 µmol, 1.0 equiv) in CH$_2$Cl$_2$ (0.10 mL) and MeOH (0.10 mL) were added CuSO$_4$ (0.63 mg, 4.0 µmol, 0.10 equiv) and sodium L-ascorbate (1.2 mg, 5.9 µmol, 0.15 equiv) at room temperature. The reaction mixture was stirred at room temperature for 24 h. The resulting mixture was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure to give a residue including 31. The residue was purified by silica gel column chromatography (CH$_2$Cl$_2$/MeOH = 30/1, 20/1, 10/1) to afford 31 (27 mg, 2.8 µmol, 71%) as an orange solid.

IR (film): 1636, 1588, 1262, 1202, 849 cm$^{-1}$; $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 8.68 (t, $J = 5.7$ Hz, 1H), 8.61 (s, 1H), 8.54 (t, $J = 5.7$ Hz, 1H), 7.91 (s, 1H), 7.83 (d, $J = 7.4$ Hz, 1H), 7.63 (d, $J = 8.5$ Hz, 1H), 7.52 (s, 1H), 7.37 (d, $J = 7.4$ Hz, 1H), 7.14 (d, $J = 8.5$ Hz, 1H), 6.82 (d, $J = 4.0$ Hz, 2H), 6.80 (s, 1H), 6.58 (brs, 2H) 4.49 (t, $J = 6.2$ Hz, 2H), 4.00 (s, 3H, OCH$_3$), 3.95 (s, 3H, OCH$_3$), 3.89 (t, $J = 6.2$ Hz, 2H, CH$_2$), 3.86
N-((5-((2-(3,4-Dimethoxyphenyl)-6,7,8-trimethoxy-4-oxo-4H-chromen-5-yl)oxy)pentyl)-1-(3-(5-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanamido)propyl)-1H-1,2,3-triazole-4-arboxamide (32)

To a mixture of 25 (7.0 mg, 13 µmol) and 30 (4.4 mg, 13 µmol) in CH$_2$Cl$_2$ (0.10 mL) and MeOH (0.10 mL) were added CuSO$_4$ (0.42 mg, 2.7 µmol, 0.2 equiv) and sodium L-ascorbate (0.80 mg, 4.0 µmol, 0.30 equiv) at room temperature. The reaction mixture was stirred at room temperature for 4 h. The resulting mixture was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure to give a residue including 32. The residue was purified by preparative TLC (CH$_2$Cl$_2$/MeOH = 20/1, 15/1) to afford 32 (5.5 mg, 48%) as a white solid.

IR (film): 2937, 1701, 1647, 1637, 1629, 1273 cm$^{-1}$; $^1$H NMR (500 MHz, DMSO-d$_6$): $\delta$ 8.55 (s, 1H), 8.52 (dd, $J_1 = 6.3$ Hz, 1H, Ar), 7.89 (t, $J = 5.7$ Hz, 1H, Ar), 7.64 (dd, $J_1 = 8.6$ Hz, $J_2 = 2.3$ Hz, 1H, Ar), 7.53 (d, $J = 2.3$ Hz, 1H, Ar), 7.16 (d, $J = 8.6$ Hz, 1H, Ar), 6.83 (s, 1H), 6.42 (s, 1H), 6.36 (s, 1H), 4.39 (t, $J = 6.9$ Hz, 2H), 4.29 (t, $J = 6.3$ Hz, 1H), 4.12 (t, $J = 5.2$ Hz, 1H), 4.01 (s, 3H, OCH$_3$), 3.97 (s, 3H, OCH$_3$), 3.91 (t, $J = 6.3$ Hz, 2H, CH$_2$), 3.88 (s, 3H, OCH$_3$), 3.85 (s, 3H, OCH$_3$), 3.81 (s, 3H, OCH$_3$), 3.29 (q, $J = 6.3$ Hz, 2H), 3.09 (q, $J = 5.7$ Hz, 2H), 3.03 (q, $J = 6.3$ Hz, 2H), 2.81 (dd, $J_1 = 12.3$ Hz, $J_2 = 5.2$ Hz, 1H), 2.57 (d, $J = 12.6$ Hz, 1H), 2.06 (t, $J = 7.5$ Hz, 2H) 1.96 (quint, $J = 6.9$ Hz, 2H), 1.78 (quint, $J = 6.87$ Hz, 1H), 1.65-1.56 (m, 4H), 1.56-1.42 (m, 8H), 1.36-1.23 (m, 2H); $^{13}$C NMR (125 MHz, DMSO-d$_6$): $\delta$ 176.4, 172.7, 172.6, 163.2, 160.7, 160.2, 151.5, 149.5, 147.7, 147.3, 144.2, 143.5, 138.0, 126.9, 123.7, 119.9, 115.0, 112.4, 109.4, 106.9, 75.0, 62.3, 62.0, 61.6, 59.7, 56.3, 56.2, 55.9, 48.9, 48.1, 39.0, 36.3, 36.0, 35.7, 30.3, 29.9, 29.5, 28.7, 28.6, 25.8, 23.4; MS (ESI): m/z 875 (M+Na)$^+$; HRMS (ESI): calcd for C$_{41}$H$_{54}$N$_7$NaO$_{11}$S$^+$, (M+Na)$^+$ 875.3492, found 875.3494.

N-(3-(4-(3-((4-Oxo-2-(3,4,5-trihydroxyphenyl)-4H-chromen-5-yl)oxy)propyl)-1H-1,2,3-triazol-1-yl)propyl)-5-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanamide (33)

To a mixture of 28 (100 mg, 0.14 mmol, 1.1 equiv) and 30 (43 mg, 0.13 mmol, 1.0 equiv) in CH$_2$Cl$_2$ (1.00 mL) and MeOH (1.00 mL) were added CuSO$_4$•5H$_2$O (10 mg, 0.065 mmol, 0.5 equiv) and sodium L-ascorbate (13 mg, 0.065 mmol, 0.5 eq) at room temperature. The reaction mixture was stirred at room temperature for 5 h. The resulting mixture was filtered through a pad of Celite. The filtrate was
concentrated under reduced pressure to give a residue including 28'. The residue was purified by silica gel column chromatography (CH$_2$Cl$_2$/MeOH = 20/1) to afford 28' (124 mg, 0.12 mmol, 91%) as a white solid.

IR (film): 3284, 2958, 2858, 1701, 1647, 1460, 1427, 1357, 1261, 1095, 1051, 896, 839 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.62 (s, 1H), 7.51 (t, $J = 5.8$ Hz, 1H), 7.05 (s, 2H), 7.03 (d, $J = 8.5$ Hz, 1H), 6.79 (d, $J = 8.5$ Hz, 1H), 6.68 (dd, $J_1 = 6.2$ Hz, $J_2 = 5.7$ Hz, 1H), 6.50 (s, 1H), 4.49 (dd, $J_1 = 6.8$ Hz, $J_2 = 5.7$ Hz, 2H), 4.37 (t, $J = 6.8$ Hz, 1H), 4.30 (dd, $J_1 = 6.2$ Hz, $J_2 = 5.7$ Hz, 1H), 4.13 (dd, $J_1 = 6.2$ Hz, $J_2 = 5.8$ Hz, 1H), 3.27-3.11 (m, 2H), 3.04, (dd, $J_1 = 7.4$ Hz, $J_2 = 6.8$ Hz, 2H), 2.89 (dd, $J_1 = 13.0$ Hz, $J_2 = 5.1$ Hz, 1H), 2.73 (d, $J = 13.0$ Hz, 1H), 2.29 (quint, $J = 6.8$ Hz, 2H), 2.18 (quint, $J = 6.8$ Hz, 2H), 2.08 (quint, $J = 6.8$ Hz, 2H), 1.76-1.60 (m, 1H), 1.41 (quint, $J = 6.8$ Hz, 2H), 1.33 (t, $J = 6.8$ Hz 1H), 0.99 (s, 9H), 0.96 (s, 18H), 0.25 (s, 12H), 0.15 (s, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 178.6, 178.5, 174.0, 164.4, 164.4, 161.3, 158.9, 158.3, 158.2, 149.3, 149.2, 147.3, 142.0, 133.8, 123.1, 114.6, 112.5, 112.1, 110.0, 107.8, 107.7, 77.3, 76.8, 70.5, 68.2, 61.8, 60.3, 55.9, 47.9, 40.8, 40.7, 36.3, 35.8, 30.1, 28.5, 28.2, 27.9, 26.3, 26.2, 26.1, 22.0, 19.0, 18.9, 18.5, -3.41, -3.50, -3.80; MS (ESI): m/z 1043 (M+Na)$^+$; HRMS (ESI): calcd for C$_{51}$H$_{80}$N$_6$NaO$_8$S$_3$, (M+Na)$^+$ 1043.4958, found 1043.4951.

To a mixture of 28' (25 mg, 48 µmol, 1.0 equiv) in THF (0.10 mL) were added AcOH (6.3 µL, 4.0 µmol, 3.5 equiv) and TBAF (1.2 µL, 5.9 µmol, 3.0 equiv, 1 M sol. in THF) at room temperature. The reaction mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure to give a residue including 33. The residue was washed with EtOAc and 2 M HCl aq. to give 33 (13.3 mg, 44%) as an orange solid.

IR (film): 3246, 2962, 2875, 1629, 1438, 1269, 1095, 1054, 881, 848 cm$^{-1}$; $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 7.97 (s, 1H, NH), 7.92 (s, 1H), 7.60 (t, $J = 8.0$ Hz, 1H), 7.13 (d, $J = 8.0$ Hz, 1H), 6.94 (t, $J = 8.0$ Hz, 1H), 6.93 (s, 2H), 6.37 (s, 1H), 4.29 (m, 3H), 4.07 (dd, $J_1 = 13.2$ Hz, $J_2 = 6.8$ Hz, 2H), 3.98 (q, $J_1 = 13.2$ Hz, $J_2 = 6.8$ Hz, 1H), 3.08-3.01 (m, 1H), 2.98, (dd, $J_1 = 12.0$ Hz, $J_2 = 6.3$ Hz, 2H), 2.89 (t, $J = 7.45$ Hz, 2H), 2.77 (dd, $J_1 = 12.0$ Hz, $J_2 = 6.3$ Hz, 1H), 2.53 (d, $J = 8.0$ Hz, 1H), 2.08 (t, $J = 6.8$ Hz, 1H), 2.03 (t, $J = 7.5$ Hz, 1H), 1.88 (t, $J = 6.8$ Hz, 2H), 1.49 (m, 4H), 1.25 (m, 4H); $^{13}$C NMR (125 MHz, CD$_3$OD): $\delta$ 178.6, 178.5, 174.0, 164.4, 164.4, 161.3, 158.9, 158.3, 158.2, 149.3, 149.2, 147.3, 142.0, 133.8, 123.1, 114.6, 112.5, 112.1, 110.0, 107.8, 107.7, 77.3, 76.8, 70.5, 68.2, 61.8, 60.3, 55.9, 47.9, 40.8, 40.7, 36.3, 35.8, 30.1, 28.5, 28.2, 27.9, 26.3, 26.2, 26.1, 22.0, 19.0, 18.9, 18.5, -3.41, -3.50, -3.80; MS (ESI): m/z 701 (M+Na)$^+$; HRMS (ESI): calcd for C$_{33}$H$_{38}$N$_6$NaO$_8$S$^+$, (M+Na)$^+$ 701.2588, found 701.2579.

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