Supporting Information

Enhanced Anti-influenza Agents Conjugated with Anti-inflammatory Activity

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Figure s1. Incubation of zanamivir conjugates in rat plasma and the mass spectrometric analyses. (A) MALDI-TOF MS analyses of ZA-1-HNAP conjugate (12): (a) standard MS signal of ZA-1-HNAP (m/z 561, [M + H]⁺); (b) after 24 h incubation in plasma showing ZA (m/z 333, [M + H]⁺) and HNAP (m/z 189, [M + H]⁺). (B) LC–QTOF MS analyses of ZA-1-HNAP conjugate (12): (a) After incubation of ZA-1-HNAP conjugate in plasma for 24 h, the LC–QTOF mass spectrum indicates no signal at m/z 561 [M + H]⁺ for the parental ZA-1-HNAP in the product mixture. (b) The degradative product of ZA at m/z 333 [M + H]⁺ is recorded. (c) The degradative product of HNAP at m/z 189 [M + H]⁺ is recorded. (C) MALDI-TOF MS analyses of ZA-1-CA conjugate (9): (a) after 24 h incubation in plasma showing ZA (m/z 333, [M + H]⁺) and CA (m/z 181, [M + H]⁺); (b) standard MS signal of ZA-1-CA conjugate at m/z 553 [M + H]⁺. (D) MALDI-TOF MS analyses of ZA-7-CA conjugate (1): (a) ZA-7-CA conjugate at m/z 596 [M + H]⁺ and the degradative product ZA-7-HP at m/z 434 [M + H]⁺ after incubation in plasma for 24 h, (b) standard MS signal of ZA-7-CA conjugate (1), and (c) standard MS signal of ZA-7-HP (6). (E) MALDI-TOF MS analyses of ZA-7-CA-amide conjugate (7): (a) No degradative product ZA-7-HP (m/z 434 [M + H]⁺) is observed in the mixture after incubation in plasma for 24 h; (b) standard MS signal of ZA-7-CA-amide conjugate at m/z 617 [M + Na]⁺.
Materials and Methods

All the reagents and solvents were reagent grade and were used without further purification unless otherwise specified. All solvents were anhydrous grade unless indicated otherwise. CH$_2$Cl$_2$ was distilled from CaH$_2$. All non-aqueous reactions were carried out in oven-dried glassware under a slight positive pressure of argon unless otherwise noted. Reactions were magnetically stirred and monitored by thin-layer chromatography on silica gel using aqueous $p$-anisaldehyde as visualizing agent. Silica gel (0.040–0.063 mm particle sizes) and LiChroprep® RP-18 (0.040–0.063 mm particle sizes) were used for column chromatography. Flash chromatography was performed on silica gel of 60–200 μm particle size. Molecular sieves were activated under high vacuum at 220 °C over 6 h.

Melting points were recorded on a Yanaco or Electrothermal MEL-TEMP 1101D apparatus in open capillaries and are not corrected. Optical rotations were measured on digital polarimeter of Japan JASCO Co. DIP-1000; $[\alpha]_D$ values are given in units of 10$^{-1}$ deg cm$^2$ g$^{-1}$. Infrared (IR) spectra were recorded on Nicolet Magna 550-II or Thermo Nicolet 380 FT-IR spectrometers. UV-visible spectra were measured on a Perkin Elmer Lambda 35 spectrophotometer; extinction coefficients ($\varepsilon$) are given in units of M$^{-1}$ cm$^{-1}$. Nuclear magnetic resonance (NMR) spectra were obtained on Bruker Advance-400 (400 MHz) spectrometer. Chemical shifts (δ) are given in parts per million (ppm) relative to δ$_H$ 7.24 / δ$_C$ 77.0 (central line of t) for CHCl$_3$/CDCl$_3$, δ$_H$ 4.80 for H$_2$O/D$_2$O, δ$_H$ 3.31 / δ$_C$ 48.2 for CD$_3$OD, or δ$_H$ 2.49 / δ$_C$ 39.5 for DMSO-$d_6$. The splitting patterns are reported as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (double of doublets) and br (broad). Coupling constants (J) are given in Hz. Distortionless enhancement polarization transfer (DEPT) spectra were taken to determine the types of carbon signals. The ESI–MS experiments were conducted on a Bruker Daltonics BioTOF III high-resolution mass spectrometer. The MALDI–TOFMS measurements were performed on a Bruker Daltonics Ultraflez II MALDI–
TOF/TOF 2000 mass spectrometer. The MALDI matrix 2,5-dihydroxybenzoic acid (DHB) was photoionized at different irradiances of a UV laser with $\lambda_{\text{max}}$ at 337 or 355 nm. The LC–QTOF MS analyses were performed using a nanoACQUITY UltraPerformance LC system coupled to a Q-TOF Premier (both from Waters Corp., Milford, MA). Element analysis data were acquired using HERAEUS VarioEL-III.

Influenza virus A/VietNam/1194/2004 RG14 (H5N1) and A/Cal/7/2009 (H1N1) were from the Center for Disease Control and Prevention in Taiwan and influenza A/WSN/1933 (H1N1) was from Dr. Shin-Ru Shih in Chang Gung University in Taiwan. All viruses were cultured in the allantoic cavities of 10-day-old embryonated chicken eggs for 72 h, and purified by sucrose gradient centrifugation. Madin-Darby canine kidney (MDCK) cells were obtained from American Type Culture Collection, and were grown in DMEM (Dulbecco's modified Eagle medium, Invitrogen) containing 10% fetal bovine serum (Invitrogen) and penicillin-streptomycin (Invitrogen) at 37 °C under 5% CO$_2$. Sprague Dawley® rat plasma was obtained from the Development Center for Biotechnology in Taiwan.

**Synthetic Procedures and Compound Characterization**

ZA was prepared from sialic acid by a procedure similar to the previous report through the ethyl ester 13 instead of the corresponding methyl ester.$^{37}$

5-Acetylamino-4-[2,3-bis(tert-butoxycarbonyl)guanidino]-6-[(2,2-dimethyl-[1,3]dioxolan-4-yl)-hydroxy-methyl]-5,6-dihydro-4H-pyran-2-carboxylic acid ethyl ester (14). To a solution of 13 (1100 mg, 1.60 mmol) in anhydrous ethanol (10 mL) was added NaOEt (54.4 mg, 0.80 mmol). The mixture was stirred at room temperature for 1 h, neutralized by Dowex 50W×8 (H$^+$), filtered, and concentrated under reduced pressure to afford yellow solids. The residue was dissolved in anhydrous acetone (10 mL), and p-toluenesulfonic acid and 2,2-dimethoxypropane were added. The mixture was stirred at room temperature for 12 h.
After concentration, the residue was purified by silica gel column chromatography (EtOAc/hexane = 2:3) to afford compound 14 (635 mg, 66%). C_{27}H_{44}N_{4}O_{11}; white solid, mp 118–120 °C; TLC (EtOAc/hexane = 2:3) \( R_f = 0.22 \); \([\alpha]^{20}_{D} = -33.4 \) (c = 1.0, CHCl); IR \( \nu_{\text{max}} \) (neat) 3309, 2981, 1725, 1647, 1609, 1559, 1369, 1251, 1151 cm\(^{-1}\); \( ^{1}H \) NMR (400 MHz, CDCl) \( \delta \) 11.30 (1 H, s), 8.54 (1 H, d, \( J = 7.2 \) Hz), 7.91 (1 H, d, \( J = 4.4 \) Hz), 5.71 (1 H, d, \( J = 2.4 \) Hz), 5.21 (1 H, br s), 5.08–5.05 (1 H, m), 4.33–4.30 (1 H, m), 4.19–4.13 (2 H, m), 4.11–4.00 (2 H, m), 3.98–3.88 (1 H, m), 3.45 (1 H, d, \( J = 3.6 \) Hz), 1.93 (3 H, s), 1.44 (9 H, s), 1.41 (9 H, s), 1.34 (3 H, s), 1.28–1.22 (6 H, m); \( ^{13}C \) NMR (100 MHz, CDCl) \( \delta \) 173.8, 162.2, 161.3, 157.5, 155.7, 152.5, 147.0, 108.9, 106.3, 84.2, 79.9, 78.5, 74.1, 69.6, 67.3, 61.4, 51.9, 48.3, 28.1 (3 ×), 27.9 (3 ×), 26.9, 25.1, 22.8, 13.9; ESI-HRMS (negative mode) calcd for C_{27}H_{43}N_{4}O_{11}: 599.2928, found: \( m/z \) 599.2926 [M – H].

5-Acetylamino-4-[2,3-bis(tert-butoxycarbonyl)guanidino]-6-[(2,2-dimethyl-[1,3]dioxolan-4-yl)-(4-nitrophenoxy)carbonyloxy)methyl]-5,6-dihydro-4H-pyran-2-carboxylic acid ethyl ester (15). A solution of compound 14 (540 mg, 0.8 mmol), 4-nitrophenyl chloroformate (1131 mg, 5.6 mmol) and 4-dimethylaminopyridine (4-DMAP, 327 mg, 5.6 mmol) in anhydrous pyridine (12 mL) was stirred at room temperature for 16 h. After concentration, the mixture was added EtOAc, and then filtered. The filtrate was concentrated under reduced pressure, and purified by silica gel column chromatography (EtOAc/hexane = 1:2) to give carbonate 15 (360 mg, 60%). C_{34}H_{47}N_{5}O_{15}; white solid, mp 127–128 °C; TLC (EtOAc/hexane = 2:3) \( R_f = 0.35 \); \([\alpha]^{20}_{D} = -45.7 \) (c = 1.0, CHCl); IR \( \nu_{\text{max}} \) (neat) 2981, 1777, 1729, 1645, 1612, 1527, 1369, 1253, 1221, 1149 cm\(^{-1}\); \( ^{1}H \) NMR (400 MHz, CDCl) \( \delta \) 11.29 (1 H, s), 8.44 (1 H, d, \( J = 8.8 \) Hz), 8.16 (2 H, d, \( J = 9.2 \) Hz), 7.44 (2 H, d, \( J = 9.2 \) Hz), 6.54 (1 H, d, \( J = 8.8 \) Hz), 5.81 (1 H, d, \( J = 2.0 \) Hz), 5.25 (1 H, dd, \( J = 5.6, 1.6 \) Hz), 5.13–5.08 (1 H, m), 4.38–4.31 (2 H, m), 4.19–4.14 (4 H, m), 4.09–3.99 (1 H, m), 1.82 (3 H, s), 1.39 (18 H, s), 1.31 (3 H, s), 1.28–1.22(6 H, m); \( ^{13}C \) NMR (100 MHz, CDCl) \( \delta \) 171.2, 162.5, 160.9, 157.0, 155.7, 152.4, 152.3, 145.3, 125.0 (2 ×), 122.2 (2 ×), 108.9, 108.5, 83.8, 79.6, 77.3, 75.2, 73.9.
5-Acetylamino-6-[(2,2-dimethyl-[1,3]dioxolan-4-yl)-3-[(hydroxypropyl)carbamoyloxy]methyl-4-[2,3-bis(tert-butoxycarbonyl)guanidino]-5,6-dihydro-4H-pyran-2-carboxylic acid ethyl ester (16). To a solution of carbonate 15 (400 mg, 0.52 mmol) in CH₃CN (7 mL) was added 3-amino-1-propanol (0.084 mL, 1.1 mmol) and Et₃N (0.153 mL, 1.1 mmol). The mixture was stirred at room temperature for 2 h, and then concentrated under reduced pressure. The residue was partitioned between EtOAc and 1 M HCl. The organic layer was washed with saturated NaHCO₃ and brine, dried over MgSO₄, filtered, and concentrated by rotary evaporation under reduced pressure. The crude material was purified by silica gel column chromatography (EtOAc/hexane = 3:1) to yield carbamate 16 (320 mg, 88%). C₃₁H₅₁N₅O₁₃; white solid, mp 135–137 °C; TLC (EtOAc/hexane = 4:1) Rf = 0.38; [α]²⁰D = −24.2 (c = 1.0, CHCl₃); IR ν max (neat) 3315, 2981, 1731, 1643, 1613, 1250, 1144, 1057 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 11.28 (1 H, s), 8.34 (1 H, d, J = 8.8 Hz), 6.55 (1 H, d, J = 9.6 Hz), 5.79 (1 H, d, J = 1.2 Hz), 5.22–5.14 (2 H, m), 5.04–5.00 (1 H, m), 4.29–4.20 (2 H, m), 4.17–4.06 (4 H, m), 4.04–3.89 (2 H, m), 3.60 (2 H, s), 3.39–3.30 (1 H, m), 3.10–3.03 (1 H, m), 1.82 (3 H, s), 1.72–1.60 (1 H, m), 1.59–1.50 (1 H, m), 1.39 (9 H, s), 1.37 (9 H, s), 1.27 (3 H, s), 1.25–1.20 (6 H, m); ¹³C NMR (100 MHz, CDCl₃) δ 171.1, 162.9, 161.4, 157.0, 156.0, 152.7, 145.4, 109.5, 108.7, 83.7, 79.6, 77.7, 74.9, 69.7, 65.8, 61.5, 59.5, 49.2, 47.9, 38.3, 31.7, 28.2 (3 ×), 28.0 (3 ×), 26.4, 25.3, 23.0, 14.1; ESI-HRMS calcd for C₃₁H₅₁N₅O₁₃: 702.3562, found: m/z 702.3560 [M + H]^⁺.

5-Acetylamino-4-[2,3-bis(tert-butoxycarbonyl)guanidino]-6-[2,2-dimethyl-[1,3]dioxolan-4-yl)-hydroxy-methyl]-5,6-dihydro-4H-pyran-2-carboxylic acid 3-hydroxypropyl ester (17). To a solution of ester 14 (500 mg, 0.83 mmol) in THF (10 mL) was added 1 M KOH (5 mL). The solution was stirred at room temperature for 1.5 h, neutralized by Dowex 50W×8 (H⁺), filtered and concentrated under reduced pressure. The residue was dissolved in CH₂Cl₂
(20 mL) and extracted with 1 M HCl and brine, dried over MgSO$_4$, concentrated under reduced pressure, and purified by flash silica gel column chromatography (MeOH/CH$_2$Cl$_2$ = 1:9) to afford the corresponding acid (428 mg, 90%). C$_{25}$H$_{40}$N$_4$O$_{11}$; white solid, mp 118–120°C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 11.28 (1 H, s), 8.57 (1 H, d, $J$ = 7.6 Hz), 8.00 (1 H, d, $J$ = 4.4 Hz), 5.74 (1 H, d, $J$ = 2.4 Hz), 5.08–5.03 (1 H, m), 4.32 (1 H, d, $J$ = 5.6 Hz), 4.09–3.89 (4 H, m), 3.41 (1 H, d, $J$ = 8.8 Hz), 1.95 (3 H, s), 1.41 (9 H, s), 1.39 (9 H, s), 1.33 (3 H, s), 1.26 (3 H, s); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 174.1, 171.2, 162.0, 157.3, 152.3, 146.7, 109.2, 106.9, 84.1, 79.9, 77.9, 73.6, 69.6, 67.2, 51.6, 48.3, 28.0 (3 ×), 27.8 (3 ×), 26.9, 24.9, 22.7; ESI-HRMS (negative mode) calcd for C$_{25}$H$_{39}$N$_4$O$_{11}$: 571.2615, found: m/z 571.2615 [M – H]$^-$.

To a solution of the above-prepared acid (402 mg, 0.80 mmol) in MeOH (5 mL) was added KOH (45 mg, 0.80 mmol). The mixture was stirred at room temperature for 30 min, and then concentrated under reduced pressure to give the corresponding potassium salt. The salt was dissolved in DMF (5 mL), and then added 3-iodo-1-propanol (93 μL, 1.00 mmol). After stirring at 50 °C for 4 h, the mixture was evaporated under reduced pressure. The residue was dissolved in CH$_2$Cl$_2$ (20 mL) and extracted with 1 M HCl and brine, dried over MgSO$_4$, concentrated under reduced pressure, and purified by flash silica gel column chromatography (EtOAc/hexane = 1:1 to EtOAc/hexane = 4:1) to afford ester 17 (285 mg, 57%). C$_{28}$H$_{46}$N$_4$O$_{12}$; colorless solid, mp 86–88 °C; TLC (EtOAc/hexane = 4:1) $R_f$ = 0.48; [$\alpha$]$^21_D$ = –23.1 (c = 1.0, CHCl$_3$); IR ν$_{max}$ (neat) 3275, 2931, 1727, 1646, 1611, 1558, 1150 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 11.32 (1 H, s), 8.58 (1 H, d, $J$ = 7.6 Hz), 7.96 (1 H, d, $J$ = 0.8 Hz), 5.76 (1 H, d, $J$ = 2.0 Hz), 5.26 (1 H, d, $J$ = 4.4 Hz), 5.12–5.08 (1 H, m), 4.34–4.28 (2 H, m), 4.14–4.10 (1 H, m), 4.07–3.91 (3 H, m), 3.68 (2 H, t, $J$ = 6.0 Hz), 3.47–3.44 (1 H, m), 1.96 (3 H, s), 1.90–1.87 (2 H, m), 1.46 (9 H, s), 1.44 (9 H, s), 1.37 (3 H, s), 1.31 (3 H, s); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 173.9, 162.2, 161.6, 157.5, 152.6, 146.7, 109.1, 107.0, 84.3, 80.0, 78.5, 74.0, 69.7, 67.4, 62.7, 59.1, 51.7, 48.3, 31.4, 28.1 (3 ×), 27.9 (3 ×), 26.9, 25.1, 22.9;
3-(3,4-Bis-allyloxyphenyl)acrylic acid (18). To a solution of caffeic acid (1000 mg, 5.56 mmol) and ally bromide (2 mL, 22.2 mmol) in anhydrous acetone (15 ml) was added finely powdered K$_2$CO$_3$ (3069 mg, 22.2 mmol). The mixture was stirred for 4 h at 60 °C, and then concentrated under reduced pressure. The residue was partitioned between EtOAc and 1 M HCl. The organic layer was washed with saturated NaHCO$_3$ and brine, dried over MgSO$_4$, filtered, and concentrated by rotary evaporation under reduced pressure. The crude material was purified by silica gel column chromatography (EtOAc/hexane = 1:9) to yield a fully allylation product, 3-(3,4-bis-allyloxyphenyl)acrylic acid allyl ester (1320 mg, 79%).

C$_{18}$H$_{20}$O$_4$; TLC (EtOAc/hexane = 1:9) $R_f = 0.80$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.60 (1 H, d, $J = 16.0$ Hz), 7.05 (2 H, m), 6.84 (1 H, d, $J = 8.8$ Hz), 6.27 (1 H, d, $J = 16.0$ Hz), 6.12–5.90 (3 H, m), 5.42–5.25 (6 H, m), 4.65 (2 H, dd, $J = 5.6$, 1.0 Hz), 4.60 (4 H, dd, $J = 3.6$, 1.8 Hz).

To a solution of the fully allylation derivative of caffeic acid (845 mg, 2.82 mmol) in MeOH (20 mL) was added 1M NaOH (2 mL). The mixture was stirred for 4 h at 60 °C, and then concentrated under reduced pressure. H$_2$O (20 mL) was added and washed with ether, acidified with 1M HCl, then extracted with CH$_2$Cl$_2$. The organic layer was dried over MgSO$_4$, filtered, and concentrated by rotary evaporation under reduced pressure. The crude material was purified by silica gel column chromatography (EtOAc/hexane = 3:7) to yield the bis-allyl ether 18 (695 mg, 95%). C$_{15}$H$_{16}$O$_4$; TLC (EtOAc/hexane = 3:7); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.68 (1 H, d, $J = 16.0$ Hz), 7.08 (2 H, m), 6.86 (1 H, d, $J = 8.0$ Hz), 6.26 (1 H, d, $J = 16.0$ Hz), 6.09–6.03 (2 H, m), 5.44–5.27 (4 H, m), 4.63 (4 H, dd, $J = 3.2$, 1.6 Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 172.5, 151.0, 148.5, 146.9, 133.0, 132.8, 127.2, 123.1, 118.0, 117.9, 114.9, 113.3, 112.8, 69.9, 69.7; ESI-HRMS (negative mode) calcd for C$_{15}$H$_{15}$O$_4$: 259.0970, found: m/z 259.0957 [M – H]$^-$. 

**Compound 19.** To a solution of alcohol 16 (210 mg, 0.30 mmol) in CH$_2$Cl$_2$ (10 mL) was added the allyl ether of caffeic acid 18 (86 mg, 0.33 mmol),
1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI, 63 mg, 0.33 mmol) and 4-DMAP (37 mg, 0.33 mmol). The mixture was stirred at room temperature for 1.5 h. The resulting solution was extracted with 1 M HCl, saturated NaHCO₃ and brine, dried over MgSO₄, concentrated under reduced pressure, and purified by flash silica gel column chromatography (EtOAc/hexane = 2:3 to EtOAc/hexane = 3:2) to afford ester 19 (240 mg, 85%). C₄₆H₆₅N₅O₁₆; colorless solid, mp 98–100 °C; TLC (EtOAc/hexane = 3:2) Rₓ = 0.30; [α]²⁴D −20.3 (c = 1.0, CHCl₃); IR νmax (neat) 3316, 2980, 1728, 1638, 1609, 1510, 1306, 1253, 1142 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 11.36 (1 H, s), 8.37 (1 H, d, J = 8.4 Hz), 7.54 (1 H, d, J = 16.0 Hz), 7.03 (2 H, m), 6.82 (1 H, d, J = 8.8 Hz), 6.21 (1 H, d, J = 16.0 Hz), 6.16 (1 H, d, J = 9.6 Hz), 6.08–5.96 (2 H, m), 5.83 (1 H, d, J = 2.0 Hz), 5.40–5.38 (1 H, m), 5.36–5.34 (1 H, m), 5.26–5.16 (4 H, m), 5.10–5.06 (1 H, m), 4.59 (4 H, dd, J = 2.8, 2.4 Hz), 4.36–4.28 (2 H, m), 4.24–4.16 (3 H, m), 4.09–3.95 (4 H, m), 3.28–3.19 (2 H, m), 1.84 (5 H, s), 1.42 (9 H, s), 1.41 (9 H, s), 1.34 (3 H, s), 1.30–1.18 (6 H, m); ¹³C NMR (100 MHz, CDCl₃) δ 170.8, 167.3, 163.0, 161.4, 157.0, 155.6, 152.7, 150.6, 148.5, 145.4, 144.8, 133.0, 132.8, 127.5, 122.7, 117.9, 117.8, 115.6, 113.4, 112.6, 109.5, 108.7, 83.6, 79.6, 77.5, 74.9, 69.9, 69.7, 65.9, 61.6, 61.5, 48.7, 48.4, 37.9, 36.6, 29.6, 29.0, 28.2 (3 ×), 28.0 (3 ×), 25.3, 23.0, 14.1; ESI-HRMS calcd for C₄₆H₆₅N₅O₁₆: 944.4505, found: m/z 944.4518 [M + H]⁺.

2-Allyloxy-5-tert-butoxycarbonylamino-benzoic acid (21). To a stirred solution of mesalazine (500 mg, 3.27 mmol) in CH₂Cl₂ (10 ml) was added Et₃N (0.9 mL, 6.54 mmol), followed by Boc₂O (784 mg, 3.60 mmol). The mixture was stirred at room temperature for 2 h, and then quenched by adding saturated NaHCO₃. The mixture was poured into water and extracted with EtOAc (3 ×). The combined organic layer was dried over MgSO₄, filtered, and concentrated under reduced pressure to give the N-Boc protected derivative, 5-tert-butoxycarbonylamino-2-hydroxybenzoic acid (803 mg, 97%). The crude product was used in the next reaction without further purification. Pale yellow solid; C₁₂H₁₅NO₅; ¹H NMR (400 MHz, CD₃OD) δ 7.92 (1 H, d, J = 2.0 Hz), 7.44 (1 H, d, J = 8.8 Hz), 6.84 (1 H, d, J =
8.8 Hz), 1.51 (9 H, s); $^{13}$C NMR (100 MHz, CD$_3$OD) δ 172.6, 158.3, 155.0, 131.3, 128.0, 121.2, 117.5, 112.8, 80.2, 28.0 (3 ×); ESI-HRMS (negative mode) calcd for C$_{12}$H$_{14}$NO$_5$: 252.0872, found: m/z 252.0862 [M − H]$^−$.

To a solution of the above-prepared N-Boc protected derivative (605 mg, 2.39 mmol) in anhydrous acetone (10 mL) were added allyl bromide (0.6 mL, 7.17 mmol) and finely powdered K$_2$CO$_3$ (990 mg, 7.17 mmol). The mixture was stirred for 4 h at 60 °C, and then concentrated under reduced pressure. The residue was partitioned between EtOAc and 1 M HCl. The organic layer was washed with saturated NaHCO$_3$ and brine, dried over MgSO$_4$, filtered, and concentrated by rotary evaporation under reduced pressure. The crude material was purified by silica gel column chromatography (EtOAc/hexane = 2:8) to yield the allylation product, 2-allyloxy-5-tert-butoxycarbonylamino-benzoic acid allyl ester (620 mg, 78%). C$_{18}$H$_{23}$NO$_5$; white solid, mp 77–78 °C; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.72 (1 H, d, $J = 2.8$ Hz), 7.50 (1 H, br), 7.18 (1 H, s), 6.76 (1 H, d, $J = 9.2$ Hz), 5.94–5.85 (2 H, m), 5.37–5.27 (2 H, m), 5.18–5.11 (2 H, m), 4.68 (2 H, m), 4.34 (2 H, m), 1.38 (9 H, s); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 165.4, 153.6, 153.0, 132.6, 131.9, 131.5, 124.1, 122.1, 120.2, 117.8, 117.0, 114.3, 79.8, 69.7, 65.2, 28.0 (3 ×); ESI-HRMS (negative mode) calcd for C$_{18}$H$_{22}$NO$_5$: 332.1498 found: m/z 332.1499 [M − H]$^−$.

To a solution of the allylation compound (500 mg, 1.50 mmol) in MeOH (20 mL) was added 1 M NaOH (2 mL). The mixture was stirred for 4 h at 60 °C, and then concentrated under reduced pressure. H$_2$O (20 mL) was added and washed with ether, acidified with 1 M HCl, then extracted with CH$_2$Cl$_2$. The organic layer was dried over MgSO$_4$, filtered, and concentrated by rotary evaporation under reduced pressure. The crude material was purified by silica gel column chromatography (EtOAc/hexane = 2:3) to yield 2-allyloxy-5-tert-butoxycarbonylamino-benzoic acid (21, 405 mg, 92%). C$_{15}$H$_{19}$NO$_5$; [α]$_D^{22}$ +2.1 (c = 0.5, CHCl$_3$); IR $\nu_{max}$ (neat) 3347, 1694, 1589, 1523, 1416, 1260, 1239, 1163 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.71 (1 H, d, $J = 2.8$ Hz), 7.50 (1 H, s), 7.18 (1 H, s), 6.86 (1 H,
d, $J = 8.8$ Hz), 6.05–5.96 (2 H, m), 6.76 (1 H, d, $J = 9.2$ Hz), 5.43 (1 H, dt, $J = 17.2$, 1.6 Hz), 5.23 (1 H, dt, $J = 10.4$, 1.6 Hz), 4.54 (2 H, m), 1.47 (9 H, s); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 165.9, 152.8, 133.0, 131.1, 125.5, 123.2, 119.6, 117.8, 113.7, 80.2, 77.2, 70.7, 28.0 (3 ×);
ESI-HRMS (negative mode) calculated for C$_{15}$H$_{18}$NO$_5$: 292.1185 found: m/z 292.1179 [M – H]$^-$.

1-Allyloxy-2-naphthoic acid (22). To a solution of 1-hydroxy-2-napthoic acid (HNAP, 1.04 g, 5.51 mmol) in anhydrous acetone (12 mL) were added ally bromide (1.4 mL, 16.53 mmol) and finely powdered K$_2$CO$_3$ (2.28 g, 16.53 mmol). The mixture was stirred for 4 h at 60 °C, and then concentrated under reduced pressure. The residue was partitioned between EtOAc and 1 M HCl. The organic layer was washed with saturated NaHCO$_3$ and brine, dried over MgSO$_4$, filtered, and concentrated by rotary evaporation under reduced pressure. The crude material was purified by silica gel column chromatography (EtOAc/hexane = 1:9) to yield the bis-allylation product (1180 mg, 80%). C$_{17}$H$_{16}$O$_3$; TLC (EtOAc/hexane = 1:9) $R_f$ = 0.65; IR $\nu_{\text{max}}$ (neat) 1722, 1334, 1274, 1233, 1131 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.27–8.24 (1 H, m), 7.87 (1 H, d, $J = 8.4$ Hz), 7.77–7.27 (1 H, m), 7.53 (1 H, d, $J = 8.4$ Hz), 7.51–7.47 (2 H, m), 6.24–6.17 (1 H, m), 6.09–6.02 (1 H, m), 5.50–5.40 (2 H, m), 5.30–5.25 (2 H, m), 4.87–4.84 (2 H, m), 4.61–4.62 (2 H, m); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 165.4, 156.7, 136.4, 133.5, 131.9, 128.5, 128.0, 127.5, 126.3, 126.2, 123.4, 123.3, 119.3, 118.2, 117.4, 76.3, 65.4; ESI-HRMS calcd for C$_{17}$H$_{17}$O$_3$: 269.1178, found: m/z 269.1184 [M + H]$^+$.

To a solution of the above-prepared bis-allylation compound (350 mg, 1.31 mmol) in MeOH (10 mL) was added 1 M NaOH (1 mL). The mixture was stirred for 4 h at 60 °C, and then concentrated under reduced pressure. H$_2$O (20 mL) was added and washed with ether, acidified with 1 M HCl, then extracted with CH$_2$Cl$_2$. The organic layer was dried over MgSO$_4$, filtered, and concentrated by rotary evaporation under reduced pressure. The crude material was purified by silica gel column chromatography (EtOAc/hexane = 3:7) to yield the allyl ether 22 of HNAP (289 mg, 97%). C$_{14}$H$_{12}$O$_3$; yellow solid, mp 99–101 °C; TLC
(EtOAc/hexane = 3:7) $R_f = 0.18$; IR $\nu_{\text{max}}$ (neat) 3455, 1738, 1365, 1232, 1228 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.21 (1 H, d, $J = 9.6$ Hz), 8.03 (1 H, d, $J = 8.4$ Hz), 7.83 (1 H, dd, $J = 8.4$, 1.2 Hz), 7.63 (1 H, d, $J = 8.8$ Hz), 7.60–7.52 (2 H, m), 6.28–6.17 (1 H, m), 5.50 (1 H, dd, $J = 17.2$, 1.2 Hz), 5.37 (1 H, dd, $J = 10.4$, 0.8 Hz), 4.71 (1 H, d, $J = 6.0$ Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 169.2, 157.1, 137.2, 132.5, 128.8, 128.0, 127.8, 126.7, 126.6, 124.3, 119.2, 118.2, 77.4; ESI-HRMS (negative mode) calcd for C$_{14}$H$_{11}$O$_3$: 227.0708, found: m/z 227.0715 [M − H]$^+$.  

### 3,4-(Bis-allyloxy)benzoic acid allyl ester (23). To a solution of 3,4-dihydroxybenzoic acid (DHBA, 676 mg, 4.39 mmol) in anhydrous acetone (10 ml) were added ally bromide (1.5 mL, 17.56 mmol) and finely powdered K$_2$CO$_3$ (2426 mg, 17.56 mmol). The mixture was stirred for 4 h at 60 °C, and then concentrated under reduced pressure. The residue was partitioned between EtOAc and 1 M HCl. The organic layer was washed with saturated NaHCO$_3$ and brine, dried over MgSO$_4$, filtered, and concentrated by rotary evaporation under reduced pressure. The crude material was purified by silica gel column chromatography (EtOAc/hexane = 1:9) to yield a fully allylation product (852 mg, 71%). C$_{16}$H$_{18}$O$_4$; yellow oil; TLC (EtOAc/hexane = 1:9) $R_f = 0.52$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.63 (1 H, dd, $J = 8.4$, 1.6 Hz), 7.55 (1 H, d, $J = 1.6$ Hz), 6.84 (1 H, d, $J = 8.4$ Hz), 6.01–5.92 (3 H, m), 5.43–5.33 (3 H, m), 5.27–5.21 (3 H, m), 4.75 (2 H, d, $J = 5.6$ Hz), 4.62–4.60 (4 H, m); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 165.2, 152.5, 147.9, 133.0, 132.7, 132.4, 123.8, 122.7, 118.0 (2 ×), 117.9, 114.6, 112.4, 69.8, 69.6, 65.3; ESI-HRMS calcd for C$_{16}$H$_{19}$O$_4$: 275.1283, found: m/z 275.1293 [M + H]$^+$.  

To a solution of the above-prepared allyl ester (300 mg, 1.09 mmol) in MeOH (5 mL) was added 1 M NaOH (0.5 mL). The mixture was stirred for 4 h at 60 °C, and then concentrated under reduced pressure. H$_2$O (15 mL) was added and washed with ether, acidified with 1 M HCl, then extracted with CH$_2$Cl$_2$. The organic layer was dried over MgSO$_4$, filtered, and concentrated by rotary evaporation under reduced pressure. The crude material was purified
by silica gel column chromatography (EtOAc/hexane = 3:7) to yield 3,4-(bis-allyloxy)benzoic acid (23, 235 mg, 92%). C_{13}H_{14}O_4; TLC (EtOAc/hexane = 3:7) R_f = 0.35; \^1H NMR (400 MHz, CDCl_3) δ 7.71 (1 H, dd, J = 8.8, 1.0 Hz), 7.59 (1 H, d, J = 2.0 Hz), 6.89 (1 H, d, J = 8.8 Hz), 6.12–6.01 (2 H, m), 5.45–5.39 (2 H, m), 5.31–5.27 (2 H, m), 4.66–4.63 (4 H, m); \^13C NMR (100 MHz, CDCl_3) δ 172.0, 153.1, 147.8, 132.8, 132.5, 124.6, 121.8, 118.1, 118.0, 114.8, 112.3, 69.8, 69.6; ESI-HRMS (negative mode) calcd for C_{13}H_{13}O_4: 233.0814, found: m/z 233.0812 [M – H].

**Compound 25.** A solution of bis-Boc carbonate (Boc_2O, 500 mg, 2.29 mmol) in 1,4-dioxane (10 mL) was added over 3 h to a stirring solution of 1,3-diaminopropane (2.5 mL, 11.45 mmol) in 1,4-dioxane (10 mL) at room temperature. After stirring for 16 h, the solvent was removed under reduced pressure. Water (20 mL) was added to the residue, and the insoluble side product was collected by filtration. The filtrate was extracted with CH_2Cl_2. The organic extract was dried over MgSO_4, filtered and concentrated under reduced pressure to afford tert-butyl 3-aminopropyl carbamate (358 mg, 90%). C_8H_{18}N_2O_2; colorless oil; \^1H NMR (400 MHz, CDCl_3) δ 5.32 (1 H, br), 2.95 (2 H, m), 2.51 (2 H, t, J = 6.4 Hz), 1.48 (1 H, br), 1.38 (2 H, t, J = 6.4 Hz), 1.20 (9 H, s); \^13C NMR (100 MHz, CDCl_3) δ 175.1445 [M + H]^+.

To a solution of bis-allyl ether of caffeic acid 18 (134 mg, 0.51 mmol) in CH_2Cl_2 (5 mL) was added the above-prepared tert-butyl 3-aminopropyl carbamate (98 mg, 0.56 mmol), EDCI (108 mg, 0.56 mmol) and 4-DMAP (68 mg, 0.56 mmol). The mixture was stirred at room temperature for 1.5 h. The resulting solution was extracted successively with 1 M HCl, saturated NaHCO_3 and brine, dried over MgSO_4, concentrated under reduced pressure, and purified by flash silica gel column chromatography (EtOAc/hexane = 1:3 to EtOAc/hexane = 2:3) to afford a coupling product (154 mg, 73%). C_{23}H_{32}N_2O_5; colorless solid, mp 115–117 °C; [α]_{D}^{24} = 3.7 (c = 0.25, CHCl_3); IR ν_max (neat) 3306, 2925, 1694, 1658, 1510, 1257 cm^{-1}; \^1H NMR (400 MHz, CDCl_3) δ 7.46 (1 H, d, J = 15.6 Hz), 6.97 (2 H, m), 6.82 (1 H, br), 6.76 (1 H, S15
d, $J = 8.0$ Hz), 6.28 (1 H, d, $J = 15.6$ Hz), 6.03–5.95 (2 H, m), 5.35 (2 H, d, $J = 17.2$ Hz), 5.23–5.20 (3 H, m), 4.53 (4 H, s), 3.35 (2 H, t, $J = 5.6$ Hz), 3.12 (2 H, t, $J = 5.2$ Hz), 1.61 (2 H, s), 1.38 (9 H, s); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 166.5, 156.6, 149.8, 148.3, 140.3, 133.0, 132.8, 128.0, 121.8, 118.8, 117.7, 117.6, 113.4, 112.7, 79.1, 69.8, 69.6, 36.9, 35.9, 30.1, 28.2 (3 ×); ESI-HRMS calcd for C$_{23}$H$_{33}$N$_2$O$_5$: 417.2389, found: m/z 417.2388 [M + H]$^+$.  

To a solution of the above-prepared coupling compound (150 mg, 0.36 mmol) in CH$_2$Cl$_2$ (2 mL) was added TFA (2 mL). After stirring at room temperature for 1 h, the mixture was evaporated under reduced pressure to give the corresponding amine 24. The crude amine product was dissolved in CH$_3$CN (7 mL), and added carbonate 15 (260 mL, 0.34 mmol) and Et$_3$N (0.075 mL, 0.50 mmol). The mixture was stirred at room temperature for 2 h, and then concentrated under reduced pressure. The residue was partitioned between CH$_2$Cl$_2$ and saturated NaHCO$_3$. The organic layer was dried over MgSO$_4$, filtered, and concentrated by rotary evaporation under reduced pressure. The crude material was purified by silica gel column chromatography (EtOAc/hexane = 4:1) to yield carbamate 25 (224 mg, 70%). C$_{46}$H$_{66}$N$_6$O$_{15}$; TLC (EtOAc/hexane = 4:1) $R_f$ = 0.15; white solid, mp 113–115 °C; [$\alpha$]$^{24}_{D}$ +13.5 (c = 1.0, CHCl$_3$); IR $\nu_{\text{max}}$ (neat) 3308, 2979, 2930, 1728, 1641, 1611, 1511, 1253, 1140 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 11.36 (1 H, s), 8.45 (1 H, d, $J = 8.4$ Hz), 7.44 (1 H, d, $J = 15.6$ Hz), 7.32 (1 H, t, $J = 2.0$ Hz), 6.98 (2 H, d, $J = 6.8$ Hz), 6.79 (1 H, d, $J = 8.8$ Hz), 6.50 (1 H, d, $J = 9.2$ Hz), 6.31 (1 H, d, $J = 15.6$ Hz), 6.05–5.95 (2 H, m), 5.84 (1 H, d, $J = 1.2$ Hz), 5.34 (1 H, d, $J = 17.2$ Hz), 5.26–5.18 (3 H, m), 5.12–5.05 (2 H, m), 4.56–4.52 (4 H, m), 4.30–4.25 (2 H, m), 4.22–4.12 (3 H, m), 4.08–4.01 (3 H, m), 3.98–3.94 (1 H, m), 3.50–3.45 (1 H, m), 3.38–3.32 (3 H, m), 3.05–3.00 (1 H, m), 1.97 (3 H, s), 1.41 (9 H, s), 1.33 (9 H, s), 1.30–1.18 (9 H, m); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 171.0, 166.5, 163.0, 161.2, 156.9, 155.6, 152.6, 149.7, 148.3, 145.1, 139.9, 133.0, 133.0, 128.2, 121.4, 119.2, 117.6, 113.5, 113.1, 109.4, 108.6, 83.5, 79.4, 75.0, 69.6, 69.5, 65.6, 61.4, 60.2, 49.2, 47.8, 38.1, 36.1, 29.5, 28.5, 28.1 (3 ×), 27.8 (3 ×), 26.3, 25.2, 23.0, 14.0; ESI-HRMS calcd for C$_{46}$H$_{67}$N$_6$O$_{15}$: 943.4664, found: m/z 943.4664 [M + H]$^+$.  

S16
Compound 27. To a solution of HNAP (300 mg, 1.60 mmol) in CH₂Cl₂ (5 mL) was added tert-butyl 3-aminopropyl carbamate (306 mg, 1.76 mmol), EDCI (334 mg, 1.76 mmol) and 4-DMAP (215 mg, 1.76 mmol). The mixture was stirred at room temperature for 12 h. The resulting solution was washed with 1 M HCl, dried over MgSO₄, concentrated under reduced pressure, and purified by flash silica gel column chromatography (hexane to EtOAc/hexane = 1:4) to afford a coupling product (378 mg, 69%).

C₁₉H₂₄N₂O₄; TLC (EtOAc/hexane = 3:7) Rᵢ = 0.31; red foam; IR νmax (neat) 3356, 2976, 1692, 1619, 1609, 1538, 1392, 1365, 1282 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 14.16 (1 H, s), 8.43 (1 H, d, J = 8.4 Hz), 7.94 (1 H, s), 7.73 (1 H, d, J = 8.0 Hz), 7.53 (3 H, m), 7.25 (1 H, d, J = 8.8 Hz), 5.22 (1 H, s), 3.51 (2 H, m), 3.23 (2 H, t, J = 6.0 Hz), 1.71 (2 H, t, J = 5.2 Hz), 1.49 (9 H, s); ¹³C NMR (100 MHz, CDCl₃) δ 170.7, 160.2, 157.1, 136.0, 128.5, 127.1, 125.4, 123.5, 121.3, 118.0, 106.8, 79.5, 77.0, 36.9, 35.5, 29.8, 28.2 (3 ×); ESI-HRMS (negative mode) calcd for C₁₉H₂₃N₂O₄: 343.1658, found: m/z 343.1648 [M – H]⁻.

To a solution of the above-prepared coupling compound (189 mg, 0.55 mmol) in CH₂Cl₂ (2 mL) was added TFA (2 mL). After stirring at room temperature for 1 h, the mixture was evaporated under reduced pressure to give the corresponding amine 26. The crude amine product was dissolved in CH₃CN (7 mL), and added carbonate 15 (236 mL, 0.31 mmol) and Et₃N (0.05 mL, 0.34 mmol). The mixture was stirred at room temperature for 2 h, and then concentrated under reduced pressure. The residue was partitioned between CH₂Cl₂ and saturated NaHCO₃. The organic layer was dried over MgSO₄, filtered, and concentrated by rotary evaporation under reduced pressure. The crude material was purified by silica gel column chromatography (EtOAc/hexane = 1:4 to EtOAc/hexane = 2:3) to yield carbamate 27 (165 mg, 61%). C₄₂H₅₈N₆O₁₄; TLC (EtOAc/hexane = 1:1) Rᵢ = 0.55; white solid, mp 157–160 °C; [α]²⁴D +14.6 (c = 0.5, CHCl₃); IR νmax (neat) 3413, 1641, 1634, 1252, 1142 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 14.08 (1 H, s), 11.36 (1 H, s), 8.56 (1 H, d, J = 8.4 Hz), 8.46 (1 H, s), 7.65 (1 H, d, J = 8.0 Hz), 7.43 (1 H, d, J = 8.4 Hz), 7.25 (1 H, d, J = 8.0 Hz), 5.22 (1 H, s), 3.51 (2 H, m), 3.23 (2 H, t, J = 5.2 Hz), 1.71 (2 H, t, J = 5.2 Hz), 1.49 (9 H, s).
8.35 (1 H, d, J = 8.0 Hz), 7.66 (1 H, t, J = 8.0 Hz), 7.60 (1 H, t, J = 8.8 Hz), 7.50–7.41 (2 H, m), 7.16 (1 H, d, J = 8.8 Hz), 6.62 (1 H, d, J = 8.4 Hz), 5.88 (1 H, d, J = 2.0 Hz), 5.30 (1 H, d, J = 5.2 Hz), 5.13–5.08 (2 H, m), 4.35–4.15 (6 H, m), 4.11–3.95 (3 H, m), 3.71–3.66 (1 H, m), 3.41 (2 H, br), 3.04 (1 H, br), 1.92 (3 H, s), 1.46 (9 H, s), 1.43 (9 H, s), 1.34–1.25 (9 H, m); 

13C NMR (100 MHz, CDCl3) δ 171.4, 171.0, 162.5, 161.2, 160.3, 156.9, 155.6, 152.6, 145.3, 136.1, 128.3, 127.1, 125.5, 125.3, 123.6, 122.0, 117.7, 109.2, 108.8, 107.2, 83.8, 79.9, 77.3, 74.9, 69.6, 65.7, 61.5, 49.4, 47.5, 38.0, 35.9, 28.3, 28.1 (3 ×), 26.3, 25.2, 23.0, 14.0; 

ESI-HRMS (negative mode) calcd for C_{42}H_{57}N_{6}O_{14}: 869.3933, found: m/z 869.3932 [M – H]⁻.

ZA-7-CA conjugate (1). See main text.

ZA-7-MCA conjugate (2). To a solution of ZA-7-HP derivative 16 (90 mg, 0.13 mmol) in CH2Cl2 (5 mL) were added 3,4-(methylenedioxy)cinnamic acid (20, MCA, 27 mg, 0.14 mmol), EDCI (27 mg, 0.14 mmol) and 4-DMAP (17 mg, 0.14 mmol). The mixture was stirred at room temperature for 1.5 h, and then was extracted with 1 M HCl, saturated NaHCO₃ and brine. The organic phase was dried over MgSO₄, concentrated under reduced pressure, and purified by flash silica gel column chromatography (EtOAc/hexane = 3:7 to EtOAc/hexane = 1:1) to afford an ester product (98 mg, 86%). C_{41}H_{57}N_{5}O_{16}; colorless solid, mp 112–114 °C; TLC (EtOAc/hexane = 3:2) Rf = 0.18; [α]_{25}^{D} = −19.2 (c = 1.0, CH₃Cl); IR ν_{max} (neat) 3316, 2980, 2931, 1729, 1639, 1609, 1250, 1152 cm⁻¹; ¹H NMR (400 MHz, CDCl3) δ 11.34 (1 H, s), 8.34 (1 H, d, J = 8.4 Hz), 7.51 (1 H, d, J = 16.0 Hz), 6.97 (1 H, s), 6.94 (1 H, d, J = 8.0 Hz), 6.73 (1 H, d, J = 8.0 Hz), 6.30 (1 H, d, J = 9.2 Hz), 6.19 (1 H, d, J = 16.0 Hz), 5.94 (2 H, s), 5.82 (1 H, d, J = 2.4 Hz), 5.24–5.11 (3 H, m), 4.33–4.72 (2 H, m), 4.22–4.16 (4 H, m), 4.14–4.04 (2 H, m), 4.02–3.95 (1 H, m), 3.22–3.19 (2 H, m), 1.84 (5 H, s), 1.41 (9 H, s), 1.40 (9 H, s), 1.31 (3 H, s), 1.28–1.23 (6 H, m); ¹³C NMR (100 MHz, CDCl3) δ 170.6, 167.1, 162.9, 161.3, 156.8, 155.5, 152.4, 149.5, 148.2, 145.3, 144.5, 128.6, 124.4, 115.7, 109.6, 108.6, 108.4, 106.4, 101.4, 83.4, 79.4, 77.5, 74.9, 69.6, 65.7, 61.6, 61.4, 48.7, 48.1, 37.8, 28.9, 28.1 (3 ×), 27.9 (3 ×), 26.3, 25.2, 22.9, 14.0; ESI-HRMS calcd for C_{41}H_{58}N_{6}O_{16}: 876.3879, found: S18
m/z 876.3876 [M + H]^+.

To a solution of the above-prepared compound (98 mg, 0.11 mmol) in THF (2 mL) was added 1 M KOH (2 mL). The solution was stirred at room temperature for 1.5 h, neutralized by Dowex 50W×8 (H⁺), filtered and concentrated under reduced pressure. The residue was dissolved in CH₂Cl₂ (2 mL) and TFA (2 mL). After stirring at room temperature for 3 h, the mixture was evaporated under reduced pressure. The residue was triturated with Et₂O, and centrifuged to give the ZA-7-MCA conjugate 2 (48 mg, 71%). C₂₆H₃₃N₅O₁₂; white solid, mp 218–220 °C; [α]²⁰⁺ +11.4 (c = 0.33, H₂O); IR v max (neat) 3369, 2920, 1686, 1629, 1449, 1252, 1038 cm⁻¹; ¹H NMR (400 MHz, CD₃OD) δ 7.60 (1 H, d, J = 16.0 Hz), 7.14 (1 H, s), 7.10 (1 H, d, J = 8.0 Hz), 6.87 (1 H, d, J = 8.0 Hz), 6.35 (1 H, d, J = 16.0 Hz), 6.01 (2 H, s), 5.59 (1 H, d, J = 2.0 Hz), 4.93 (1 H, dd, J = 7.6, 1.6 Hz), 4.48 (1 H, dd, J = 10.4, 1.6 Hz), 4.36 (1 H, dd, J = 9.2, 2.0 Hz), 4.26–4.14 (3 H, m), 4.08–4.03 (1 H, m), 3.63 (1 H, dd, J = 12.0, 2.8 Hz), 3.51–3.46 (1 H, m), 3.21 (2 H, t, J = 6.4 Hz), 1.95 (3 H, s), 1.90 (2 H, t, J = 6.8 Hz); ¹³C NMR (100 MHz, CD₃OD) δ 174.0, 169.7, 158.7, 158.1, 151.4, 151.3, 149.8, 146.6, 146.4, 130.0, 126.1, 126.0, 116.5, 109.7, 107.5, 103.2, 103.1, 76.9, 71.2, 70.2, 64.4, 63.5, 53.4, 38.8, 29.8, 23.1; ESI-HRMS (negative mode) calcd for C₂₆H₃₂N₅O₁₂: 606.2047, found: m/z 606.2044 [M – H].

ZA-7-ME conjugate (3). To a solution of ZA-7-HP derivative 16 (70 mg, 0.10 mmol) in CH₂Cl₂ (5 mL) was added the N-Boc-O-allyl mesalazine derivative 21 (33 mg, 0.11 mmol), EDCI (21 mg, 0.11 mmol) and 4-DMAP (13 mg, 0.11 mmol). The mixture was stirred at room temperature for 1.5 h. The resulting solution was extracted with 1 M HCl, saturated NaHCO₃ and brine, dried over MgSO₄, concentrated under reduced pressure, and purified by flash silica gel column chromatography (EtOAc/hexane = 3:7 to EtOAc/hexane = 1:1) to afford an ester product (75 mg, 77%). C₄₆H₆₈N₆O₁₇; light yellow solid, mp 114–116 °C; TLC (EtOAc/hexane = 7:3) Rf = 0.33; [α]²⁰D −11.5 (c = 1.0, CH₃Cl); IR v max (neat) 3319, 2979, 1728, 1610, 1248, 1154 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 11.32 (1 H, s), 8.29 (1 H, d, J =
8.8 Hz), 7.70 (1 H, br), 7.57 (1 H, d, \( J = 2.4 \) Hz), 7.00 (1 H, br), 6.87 (1 H, d, \( J = 9.2 \) Hz), 6.15 (1 H, d, \( J = 9.2 \) Hz), 6.07–5.97 (1 H, m), 5.79 (1 H, d, \( J = 2.0 \) Hz), 5.42 (1 H, s), 5.38 (1 H, s), 5.26–5.16 (2 H, m), 4.56 (1 H, d, \( J = 4.8 \) Hz), 4.42–4.19 (7 H, m), 4.09–3.89 (4 H, m), 3.35–3.24 (2 H, m), 1.98–1.92 (2 H, m), 1.85 (3 H, s), 1.46 (9 H, s), 1.43 (9 H, s), 1.42 (9 H, s), 1.32 (3 H, s), 1.31–1.25 (6 H, m); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 170.8, 166.2, 163.1, 161.5, 156.9, 155.6, 153.8, 153.1, 152.8, 145.4, 132.9, 131.8, 124.4, 122.3, 120.4, 117.9, 114.6, 109.6, 108.8, 83.7, 80.3, 79.6, 74.9, 70.1, 69.6, 65.8, 63.1, 61.5, 48.7, 48.4, 38.7, 29.7, 28.5, 28.3 (3 ×), 28.2 (3 ×), 28.0 (3 ×), 26.5, 25.4, 23.0, 14.1; ESI-HRMS calcd for C\(_{46}\)H\(_{69}\)N\(_6\)O\(_{17}\): 977.4719, found: \( m/z \) 977.4716 [M + H]\(^{+}\).

To a solution of the above-prepared ester compound (70 mg, 0.07 mmol) in THF (4 mL) was added 1 M KOH (4 mL). The solution was stirred at room temperature for 1.5 h, neutralized by Dowex 50W\(\times\)8 (H\(^{+}\)), filtered and concentrated under reduced pressure. The residue was dissolved in anhydrous THF (5 mL), then added Pd(PPh\(_3\))\(_4\) (12 mg, 0.01 mmol) and morpholine (0.1 mL, 1.4 mmol). The mixture was stirred at room temperature for 4 h. The resulting solution was extracted with 1 M HCl and brine, dried over MgSO\(_4\), concentrated under reduced pressure, and purified by flash silica gel column chromatography (MeOH/CH\(_2\)Cl\(_2\) = 1:20 to MeOH/CH\(_2\)Cl\(_2\) = 1:9). The residue was dissolved in CH\(_2\)Cl\(_2\) (2 mL) and TFA (2 mL). After stirring at room temperature for 3 h, the mixture was evaporated under reduced pressure. The residue was triturated with Et\(_2\)O, and centrifuged to give ZA-7-ME conjugate 3 (28 mg, 69%). C\(_{23}\)H\(_{32}\)N\(_6\)O\(_{11}\); orange solid, mp 210–212 °C; \([\alpha]_{D}^{22}\) = 53.0 (c = 0.5, MeOH); IR \( \nu_{\text{max}} \) (neat) 3351, 1673, 1622, 1493, 1403, 1228 cm\(^{-1}\); \(^1\)H NMR (400 MHz, D\(_2\)O) \( \delta \) 7.38 (1 H, d, \( J = 2.8 \) Hz), 7.10 (1 H, dd, \( J = 8.8, 2.8 \) Hz), 6.88 (1 H, d, \( J = 8.8 \) Hz), 5.67 (1 H, d, \( J = 2.0 \) Hz), 4.93 (1 H, dd, \( J = 9.2, 1.6 \) Hz), 4.50 (1 H, dd, \( J = 10.4, 1.6 \) Hz), 4.47–4.38 (3 H, m), 4.09–4.01 (2 H, m), 3.64 (1 H, dd, \( J = 12.0, 2.8 \) Hz), 3.48–3.43 (1 H, m), 3.32–3.28 (2 H, m), 2.00–1.96 (5 H, m); \(^{13}\)C NMR (100 MHz, D\(_2\)O) \( \delta \) 173.6, 169.8, 168.6, 157.0, 156.6, 153.6, 149.4, 136.9, 125.8, 117.8, 117.3, 112.9, 104.5, 75.2, 69.8, 68.5, 63.6, 62.5, 51.9, 47.3, 37.8, 26.5.
ZA-7-HNAP conjugate (4). To a solution of ZA-7-HP derivative 16 (96 mg, 0.14 mmol) in CH₂Cl₂ (5 mL) was added HNAP allyl ether 22 (34 mg, 0.15 mmol), EDCI (29 mg, 0.15 mmol) and 4-DMAP (18 mg, 0.15 mmol). The mixture was stirred at room temperature for 1.5 h. The resulting solution was extracted successively with 1 M HCl, saturated NaHCO₃ and brine, dried over MgSO₄, concentrated under reduced pressure, and purified by flash silica gel column chromatography (EtOAc/hexane = 1:4 to EtOAc/hexane = 1:1) to afford a coupling product (101 mg, 82%). C₄₅H₆₁N₅O₁₅; white solid, mp 95–97 °C; TLC (EtOAc/hexane = 1:1) Rₜ = 0.62; [α]₂⁰D −17.0 (c = 1.0, CHCl₃); IR νₚₘₐₓ (neat) 3316, 2979, 2930, 1724, 1641, 1610, 1369, 1249, 1141 cm⁻¹; ESI-HRMS calcd for C₄₅H₆₂N₅O₁₅: 912.4242, found: m/z 912.4249 [M + H]⁺.

To a solution of the above-prepared coupling product (84 mg, 0.09 mmol) in THF (3 mL) was added 1 M KOH (3 mL). The solution was stirred at room temperature for 1.5 h, neutralized by Dowex 50W×8 (H⁺), filtered and concentrated under reduced pressure. The residue was dissolved in anhydrous THF (5 mL), then added Pd(PPh₃)₄ (12 mg, 0.01 mmol) and morpholine (0.24 mL, 2.3 mmol). The mixture was stirred at room temperature for 4 h. The resulting solution was extracted with 1 M HCl and brine, dried over MgSO₄, concentrated under reduced pressure, and purified by flash silica gel column chromatography (MeOH/CH₂Cl₂ = 1:9 to MeOH/CH₂Cl₂ = 1:4). The residue was dissolved in CH₂Cl₂ (2 mL) and TFA (2 mL). After stirring at room temperature for 3 h, the mixture was evaporated under reduced pressure. The residue was triturated with Et₂O, and centrifuged to give ZA-7-HNAP conjugate 4 (30 mg, 55%). C₂₇H₃₃N₅O₁₁; colorless solid, mp 230–232 °C; [α]₂⁴D −5.0 (c = 0.5, CH₃OH); IR νₚₘₐₓ (neat) 3402, 1740, 1655, 1596, 1406, 1369, 1256, 1163 cm⁻¹; ¹H NMR (400 MHz, CD₃OD) δ 8.34 (1 H, d, J = 8.4 Hz), 7.80 (2 H, d, J = 8.8 Hz), 7.61 (1 H, m), 7.51 (1 H, t, J = 7.6 Hz), 7.31 (1 H, d, J = 8.8 Hz), 5.58 (1 H, d, J = 2.0 Hz), 4.97 (1 H, m), 4.49–4.44 (3 H, m), 4.34 (1 H, d, J = 8.8 Hz), 4.23–4.18 (1 H, m), 4.07–4.02 (1 H, m), 3.64 (1 H, dd, J =
12.0, 2.4 Hz), 3.51–3.46 (1 H, m), 3.30–3.27 (2 H, m), 2.04–1.97 (2 H, m), 1.93 (3 H, s); \(^{13}\)C NMR (100 MHz, CD\(_3\)OD) δ 172.1, 170.9, 160.4, 157.5, 156.8, 137.3, 129.1, 127.3, 125.5, 124.5, 124.0, 123.1, 118.4, 105.5, 103.3, 75.7, 69.8, 68.8, 63.1, 62.8, 52.0, 47.8, 37.3, 29.3, 28.5, 21.5; ESI-HRMS (negative mode) calcd for C\(_{27}\)H\(_{32}\)N\(_5\)O\(_{11}\): 602.2098, found: m/z 602.2087 [M − H]\(^{-}\).

**ZA-7-DHBA conjugate (5).** To a solution of ZA-7-HP derivative 16 (100 mg, 0.14 mmol) in CH\(_2\)Cl\(_2\) (5 mL) was added 3,4-(bis-allyloxy)benzoic acid (23, 37 mg, 0.16 mmol), EDCI (30 mg, 0.16 mmol) and 4-DMAP (20 mg, 0.16 mmol). The mixture was stirred at room temperature for 1.5 h. The resulting solution was extracted with 1 M HCl, saturated NaHCO\(_3\) and brine, dried over MgSO\(_4\), concentrated under reduced pressure, and purified by flash silica gel column chromatography (EtOAc/hexane = 3:7 to EtOAc/hexane = 3:2) to afford a coupling product (90 mg, 70 %). C\(_{44}\)H\(_{63}\)N\(_5\)O\(_{16}\); white solid, mp 102–104 °C; [\(\alpha\)]\(^{20}\)\(_D\) −26.5 (c = 0.5, CHCl\(_3\)); IR \(\nu\)\(_{\text{max}}\) (neat) 3315, 2980, 2931, 1729, 1641, 1608, 1267, 1141 cm\(^{-1}\); \(^{1}\)H NMR (400 MHz, CDCl\(_3\)) δ 11.36 (1 H, s), 8.40 (1 H, d, \(J = 8.8\) Hz), 7.59 (1 H, d, \(J = 8.4\) Hz), 7.52 (1 H, s), 6.85 (1 H, d, \(J = 8.8\) Hz), 6.11 (1 H, d, \(J = 5.2\) Hz), 6.08–5.98 (2 H, m), 5.84 (1 H, d, \(J = 2.0\) Hz), 5.40 (2 H, dd, \(J = 17.2, 4.8\) Hz), 5.27–5.16 (5 H, m), 5.10–5.07 (1 H, m), 4.61 (1 H, t, \(J = 5.6\) Hz), 4.33–4.31 (5 H, m), 4.23–3.97 (6 H, m), 3.28–3.25 (2 H, m), 1.95–1.92 (2 H, m), 1.86 (3 H, s), 1.44 (9 H, s), 1.42 (9 H, s), 1.34 (3 H, s), 1.30–1.26 (6 H, m); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) δ 170.7, 166.3, 163.0, 161.4, 157.0, 155.6, 152.7, 152.5, 147.9, 145.5, 133.0, 132.7, 123.7, 122.7, 118.0, 117.9, 114.6, 112.5, 109.5, 108.7, 83.6, 79.5, 77.6, 74.9, 69.8, 69.6, 65.9, 62.0, 61.5, 48.9, 48.4, 38.0, 29.6, 29.1, 28.2 (3 ×), 28.0 (3 ×), 26.4, 25.3, 23.0, 14.1; ESI-HRMS (negative mode) calcd for C\(_{44}\)H\(_{62}\)N\(_5\)O\(_{16}\): 916.4192, found: m/z 916.4194 [M – H]\(^{-}\).

To a solution of the above-prepared coupling compound (80 mg, 0.09 mmol) in THF (3 mL) was added 1 M KOH (3 mL). The solution was stirred at room temperature for 1.5 h, neutralized by Dowex 50W×8 (H\(^{+}\)), filtered and concentrated under reduced pressure. The
residue was dissolved in anhydrous THF (5 mL), then added Pd(PPh$_3$)$_4$ (23 mg, 0.02 mmol) and morpholine (0.4 mL, 4.5 mmol). The mixture was stirred at room temperature for 4 h. The resulting solution was extracted with 1 M HCl and brine, dried over MgSO$_4$, concentrated under reduced pressure, and purified by flash silica gel column chromatography (MeOH/CH$_2$Cl$_2$ = 1:9 to MeOH/CH$_2$Cl$_2$ = 1:4). The residue was dissolved in CH$_2$Cl$_2$ (2 mL) and TFA (2 mL). After stirring at room temperature for 3 h, the mixture was evaporated under reduced pressure. The residue was triturated with Et$_2$O, and centrifuged to give ZA-7-DHBA conjugate (5, 26 mg, 52%). C$_{23}$H$_{31}$N$_5$O$_{12}$; yellow solid, mp 223–225 °C; [$\alpha$]$^\text{D}_{25}$−6.5 ($c = 0.33$, H$_2$O); IR $\nu_{\text{max}}$ (neat) 3376, 1674, 1618, 1405, 1296, 1234, 1119 cm$^{-1}$; $^1$H NMR (400 MHz, CD$_3$OD) $\delta$ 7.44 (1 H, s), 7.42 (1 H, d, $J = 8.0$ Hz), 6.80 (1 H, dd, $J = 8.0$ Hz), 5.58 (1 H, d, $J = 2.0$ Hz), 4.95 (1 H, m), 4.46 (1 H, dd, $J = 10.4$, 2.0 Hz), 4.36–4.29 (3 H, m), 4.20–4.15 (1 H, m), 4.06–4.01 (1 H, m), 3.62 (1 H, dd, $J = 12.0$, 2.8 Hz), 3.49–3.45 (1 H, m), 3.30–3.22 (2 H, m), 1.94 (3 H, s), 1.93–1.91 (2 H, m); $^{13}$C NMR (100 MHz, CD$_3$OD) $\delta$ 173.7, 169.3, 168.5, 159.0, 158.3, 151.8, 151.7, 146.3, 123.8, 122.9, 117.6, 116.1, 104.6, 77.1, 71.3, 70.4, 64.6, 63.5, 39.0, 30.2, 23.0; ESI-HRMS (negative mode) calcd for C$_{23}$H$_{30}$N$_5$O$_{12}$: 568.1891, found: m/z 568.1893 [M − H]$^\text{−}$.

**ZA-7-HP conjugate (6).** To a solution of carbamate 16 (100 mg, 0.14 mmol) in THF (2 mL) was added 1 M KOH (2 mL). The solution was stirred at room temperature for 1.5 h, neutralized by Dowex 50W×8 (H$^+$), filtered and concentrated under reduced pressure. The residue was dissolved in CH$_2$Cl$_2$ (2 mL) and TFA (2 mL). After stirring at room temperature for 3 h, the mixture was evaporated under reduced pressure. The residue was triturated with Et$_2$O, and centrifuged to give the ZA-7-HP conjugate 6 (51 mg, 84 %). C$_{16}$H$_{27}$N$_5$O$_5$; colorless solid, mp 265–267 °C; [$\alpha$]$^\text{D}_{20}$−218.7 ($c = 1.0$, H$_2$O); IR $\nu_{\text{max}}$ (neat) 3410, 1674, 1544, 1263, 1140 cm$^{-1}$; $^1$H NMR (400 MHz, D$_2$O) $\delta$ 6.05 (1 H, d, $J = 2.4$ Hz), 4.99 (1 H, dd, $J = 8.8$, 2.0 Hz), 4.60 (1 H, dd, $J = 10.0$, 2.0 Hz), 4.48 (1 H, dd, $J = 10.0$, 2.0 Hz), 4.18 (1 H, dd, $J = 9.6$, 9.2 Hz), 4.08–4.03 (1 H, m), 3.72–3.63 (3 H, m), 3.56–3.51(1 H, m), 3.17 (1 H, dd, $J = 6.8$, 9.2 Hz), 3.58–3.51 (3 H, m), 3.07–3.01 (1 H, m), 2.84–2.78 (3 H, m), 2.40–2.32 (2 H, m), 1.93 (1 H, s), 1.89–1.81 (2 H, m); $^{13}$C NMR (100 MHz, D$_2$O) $\delta$ 176.1, 167.3, 159.0, 158.3, 151.8, 151.7, 146.3, 123.8, 122.9, 117.6, 116.1, 104.6, 77.1, 71.3, 70.4, 64.6, 63.5, 39.0, 30.2, 23.0; ESI-HRMS (negative mode) calcd for C$_{16}$H$_{27}$N$_5$O$_5$: 568.1891, found: m/z 568.1893 [M − H]$^\text{−}$. 

S23
6.8 Hz), 2.00 (3 H, s), 1.78–1.71 (3 H, m); \textsuperscript{13}C NMR (100 MHz, D\textsubscript{2}O) δ 173.9, 164.8, 157.0, 156.6, 145.0, 109.1, 75.8, 69.5, 68.8, 62.3, 59.1, 51.1, 47.1, 37.5, 31.2, 21.8; ESI-HRMS (negative mode) calcd for C\textsubscript{16}H\textsubscript{26}N\textsubscript{5}O\textsubscript{9}: 432.1731, found: m/z 432.1727 [M – H]–.

**ZA-7-CA-amide conjugate (7).** To a solution of compound 25 (100 mg, 0.11 mmol) in THF (4 mL) was added 1 M KOH (2 mL). The solution was stirred at room temperature for 1.5 h, neutralized by Dowex 50W\times8 (H\textsuperscript{+}), filtered and concentrated under reduced pressure. The residue was dissolved in anhydrous THF (5 mL), then added Pd(PPh\textsubscript{3})\textsubscript{4} (23 mg, 0.02 mmol) and morpholine (0.4 mL, 4.5 mmol). The mixture was stirred at room temperature for 4 h. The resulting solution was extracted with 1 M HCl and brine, dried over MgSO\textsubscript{4}, concentrated under reduced pressure, and purified by flash silica gel column chromatography (MeOH/CH\textsubscript{2}Cl\textsubscript{2} = 1:9 to MeOH/CH\textsubscript{2}Cl\textsubscript{2} = 1:4). The residue was dissolved in CH\textsubscript{2}Cl\textsubscript{2} (2 mL) and TFA (2 mL). After stirring at room temperature for 3 h, the mixture was evaporated under reduced pressure. The residue was triturated with Et\textsubscript{2}O, and centrifuged to give ZA-7-CA-amide conjugate 7 (35 mg, 56%). C\textsubscript{25}H\textsubscript{34}N\textsubscript{6}O\textsubscript{11}; yellow solid, mp 288–290 °C; [α]\textsuperscript{19}_D +220.1 (c = 0.50, H\textsubscript{2}O); IR v\textsubscript{max} (neat) 3422, 1702, 1655, 1545, 1259, 1202, 1131, 1064 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (400 MHz, D\textsubscript{2}O) δ 7.36 (1 H, d, J = 15.6 Hz), 7.13 (1 H, s), 7.06 (1 H, d, J = 7.6 Hz), 6.94 (1 H, d, J = 8.0 Hz), 6.40 (1 H, dd, J = 16.0 Hz), 5.74 (1 H, d, J = 2.0 Hz), 4.99 (1 H, dd, J = 9.2, 2.0 Hz), 4.46 (1 H, dd, J = 8.4, 3.2 Hz), 4.45 (1 H, d, J = 7.2 Hz), 4.18–4.11 (2 H, m), 3.72 (1 H, dd, J = 12.0, 2.0 Hz), 3.57–3.52 (1 H, m), 3.35 (2 H, t, J = 6.0 Hz), 3.18 (2 H, t, J = 6.4 Hz), 2.02 (3 H, s), 1.78 (2 H, m); \textsuperscript{13}C NMR (100 MHz, D\textsubscript{2}O) δ 173.8, 169.0, 168.5, 157.0, 156.7, 149.2, 146.3, 144.2, 140.7, 127.4, 121.9, 117.8, 116.2, 114.8, 104.8, 75.3, 69.8, 68.6, 62.5, 51.8, 47.4, 38.2, 37.0, 28.4, 21.9; ESI-HRMS (negative mode) calcd for C\textsubscript{25}H\textsubscript{33}N\textsubscript{6}O\textsubscript{11}: 593.2207, found: m/z 593.2222 [M – H]–.

**ZA-7-HNAP-amide conjugate (8).** To a solution of compound 27 (95 mg, 0.11 mmol) in THF (3 mL) was added 1 M KOH (1 mL). The solution was stirred at room temperature for 1.5 h, neutralized by Dowex 50W\times8 (H\textsuperscript{+}), filtered and concentrated under reduced pressure.
The residue was dissolved in CH₂Cl₂ (2 mL) and treated with TFA (2 mL). After stirring at room temperature for 3 h, the mixture was evaporated under reduced pressure. The residue was triturated with Et₂O, and centrifuged to give ZA-7-HNAP-amide conjugate 8 (41 mg, 62%). C₂₇H₃₄N₆O₁₀; light yellow solid, mp 230–232 °C; [α]D²⁴ +17.1 (c = 1.0, CH₃OH); IR νmax (neat) 3423, 1637, 1405, 1145 cm⁻¹; ¹H NMR (400 MHz, CD₃OD) δ 8.33 (1 H, d, J = 8.0 Hz), 7.78 (1 H, d, J = 8.0 Hz), 7.72 (1 H, d, J = 8.8 Hz), 7.57 (1 H, t, J = 9.2 Hz), 7.49 (1 H, t, J = 8.0 Hz), 7.30 (1 H, d, J = 8.8 Hz), 5.55 (1 H, d, J = 2.4 Hz), 4.93 (1 H, dd, J = 9.2, 6.4 Hz), 4.46 (1 H, dd, J = 10.4, 6.0 Hz), 4.32 (1 H, dd, J = 9.2, 2.0 Hz), 4.22 (1 H, d, J = 10.0 Hz), 4.07–4.02 (1 H, m), 3.66–3.61 (1 H, m), 3.60–3.43 (3 H, m), 3.27–3.20 (1 H, m), 3.17–3.10 (1 H, m), 1.97 (3 H, s), 1.89–1.75 (2 H, m); ¹³C NMR (100 MHz, CD₃OD) δ 172.6, 171.5, 169.2, 160.2, 157.9, 157.2, 150.9, 136.7, 128.7, 127.4, 125.7, 125.6, 123.4, 122.2, 118.1 (2×), 107.5, 103.0, 76.0, 70.2, 69.2, 63.6, 52.6, 38.2, 36.6, 29.3, 21.9; ESI-HRMS calcd for C₂₇H₃₅N₆O₁₀: 603.2415, found: m/z 603.2405 [M + H]⁺.

ZA-1-CA conjugate (9). To a solution of 17 (86 mg, 0.14 mmol) in CH₂Cl₂ (5 mL) was added the allyl ether of caffeic acid 18 (39 mg, 0.15 mmol), EDCI (29 mg, 0.15 mmol) and 4-DMAP (18 mg, 0.15 mmol). The mixture was stirred at room temperature for 1.5 h. The resulting solution was extracted with 1 M HCl, saturated NaHCO₃ and brine, dried over MgSO₄, concentrated under reduced pressure, and purified by flash silica gel column chromatography (EtOAc/hexane = 1:4 to EtOAc/hexane = 2:3) to afford a coupling product (101 mg, 85%). C₄₃H₆₀N₄O₁₅; light yellow solid, mp 70–72 °C; TLC (EtOAc/hexane = 2:3) Rf = 0.24; [α]D²⁰ −18.7 (c = 1.0, CHCl₃); IR νmax (neat) 3311, 2979, 2930, 1724, 1646, 1607, 1253, 1153 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 11.34 (1 H, s), 8.60 (1 H, d, J = 8.0 Hz), 7.96 (1 H, d, J = 5.2 Hz), 7.56 (1 H, d, J = 16.0 Hz), 7.03 (2 H, s), 6.83 (1 H, d, J = 8.8 Hz), 6.22 (1 H, d, J = 16.0 Hz), 6.21–5.98 (2 H, m), 5.77 (1 H, d, J = 2.0 Hz), 5.39 (2 H, dd, J = 17.2, 5.2 Hz), 5.28–5.44 (2 H, m), 5.14–5.10 (1 H, m), 4.61–4.55 (4 H, m), 4.37–4.33 (1 H, m), 4.30–4.24 (4 H, m), 4.16–4.12 (2 H, m), 4.06–3.93 (3 H, m), 2.09–2.05 (2 H, m), 1.98 (3 H, s).
1.47 (9 H, s), 1.45 (9 H, s), 1.38 (3 H, s), 1.32 (3 H, s); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 173.9, 166.9, 162.2, 157.5, 152.6, 148.5, 146.7, 144.8, 133.0, 132.8, 127.4, 122.7, 117.8, 117.7, 115.4, 113.3, 112.6, 109.0, 106.9, 84.2, 80.0, 78.5, 77.2, 73.9, 69.8, 69.7, 67.4, 62.1, 60.6, 51.8, 48.3, 29.6, 28.1 (3 ×), 27.9 (3 ×), 26.9, 25.0, 22.8; ESI-HRMS (negative mode) calcd for C$_{43}$H$_{59}$N$_4$O$_{15}$: 803.3351, found: m/z 803.3351 [M – H]$^-$.

To a solution of the above-prepared coupling compound (60 mg, 0.07 mmol) in anhydrous THF (4 mL) was added Pd(PPh$_3$)$_4$ (12 mg, 0.01 mmol) and morpholine (0.1 mL, 1.4 mmol). The mixture was stirred at room temperature for 4 h. The resulting solution was extracted with 1 M HCl and brine, dried over MgSO$_4$, concentrated under reduced pressure, and purified by flash silica gel column chromatography (MeOH/CH$_2$Cl$_2$ = 1:20 to MeOH/CH$_2$Cl$_2$ = 1:9). The residue was dissolved in CH$_2$Cl$_2$ (2 mL) and TFA (2 mL). After stirring at room temperature for 3 h, the mixture was evaporated under reduced pressure. The residue was triturated with Et$_2$O, and centrifuged to give ZA-1-CA conjugate 9 (23 mg, 61%). C$_{24}$H$_{32}$N$_4$O$_{11}$; orange solid, mp 135–137 °C; [α]$^2$$_D$ +6.6 (c = 1.0, H$_2$O); IR $\nu_{\text{max}}$ (neat) 3414, 1675, 1636, 1276, 1203, 1185, 1141 cm$^{-1}$; $^1$H NMR (400 MHz, CD$_3$OD) δ 7.55 (1 H, d, $J$ = 16.0 Hz), 7.04 (1 H, d, $J$ = 2.0 Hz), 6.95 (1 H, dd, $J$ = 8.0, 2.0 Hz), 6.79 (1 H, d, $J$ = 8.0 Hz), 6.25 (1 H, d, $J$ = 15.6 Hz), 5.90 (1 H, d, $J$ = 2.4 Hz), 4.35–4.19 (6 H, m), 3.88–3.81 (2 H, m), 3.71–3.67 (3 H, m), 2.11–2.07 (2 H, m), 1.99 (3 H, s); $^{13}$C NMR (100 MHz, CD$_3$OD) δ 174.6, 169.3, 163.4, 159.0, 149.8, 147.3, 147.0, 146.6, 127.8, 123.2, 116.7, 115.3, 115.0, 109.0, 78.1, 71.5, 70.3, 64.8, 63.5, 62.1, 51.5, 50.0, 29.2, 22.8; ESI-HRMS calcd for C$_{24}$H$_{33}$N$_4$O$_{11}$: 553.2146, found: m/z 553.2150 [M + H]$^+$.

ZA-1-MCA conjugate (10). To a solution of alcohol 17 (40 mg, 0.06 mmol) in CH$_2$Cl$_2$ (3 mL) was added (3,4-methylenedioxy)cinnamic acid (13 mg, 0.07 mmol), EDCI (13 mg, 0.07 mmol) and 4-DMAP (9 mg, 0.07 mmol). The mixture was stirred at room temperature for 1.5 h. The resulting solution was extracted with 1 M HCl, saturated NaHCO$_3$ and brine, dried over MgSO$_4$, concentrated under reduced pressure, and purified by flash silica gel column
chromatography (EtOAc/hexane = 1:4 to EtOAc/hexane = 2:3) to afford a coupling product (43 mg, 84%). C_{38}H_{52}N_{15}O_{15}; pale yellow solid, mp 73–75 °C; TLC (EtOAc/hexane = 1:1) \( R_f = 0.20; [\alpha]^{20}_{D} = -17.3 \) (c = 1.0, CHCl₃); IR \( \nu_{\text{max}} \) (neat) 2924, 1723, 1646, 1607, 1250, 1154, 1127 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl₃) \( \delta \) 11.34 (1 H, s), 8.59 (1 H, d, \( J = 7.9 \) Hz), 7.95 (1 H, d, J = 5.2 Hz), 7.55 (1 H, d, J = 16.0 Hz), 7.00 (1 H, s), 6.98 (1 H, d, J = 8.0 Hz), 6.78 (1 H, d, J = 8.0 Hz), 6.22 (1 H, d, J = 15.6 Hz), 5.97 (2 H, s), 5.77 (1 H, d, J = 1.6 Hz), 5.27 (1 H, br), 5.13–5.09 (1 H, m), 4.38–4.32 (1 H, m), 4.29–4.25 (3 H, m), 4.21–4.13 (2 H, m), 4.18–4.06 (3 H, m), 2.09–2.05 (2 H, m), 1.98 (3 H, s), 1.48 (9 H, s), 1.46 (9 H, s), 1.39 (3 H, s), 1.33 (3 H, s); \(^{13}\)C NMR (100 MHz, CDCl₃) \( \delta \) 146.8, 144.7, 128.7, 124.4, 115.7, 109.1, 108.5, 106.9, 106.5, 101.5, 84.3, 80.1, 78.6, 74.0, 69.8, 67.5, 62.2, 60.8, 51.9, 48.4, 29.7, 28.2 (3 \( \times \)), 28.0 (3 \( \times \)), 27.0, 25.1, 22.9; ESI-HRMS (negative mode) calcd for C_{38}H_{51}N_{14}O_{15}: 803.3351, found: \( m/z \) 803.3351 [M – H]⁻.

To a solution of the above-prepared compound (48 mg, 0.06 mmol) in CH₂Cl₂ (2 mL) was added TFA (2 mL). After stirring at room temperature for 3 h, the mixture was evaporated under reduced pressure. The residue was triturated with Et₂O, and centrifuged to give ZA-1-MCA conjugate 10 (21 mg, 62 %). C_{25}H_{32}N_{4}O_{11}; white solid, mp 130–132 °C; [\alpha]^{19}_{D} +17.2 (c = 0.5, CH₃OH); IR \( \nu_{\text{max}} \) (neat) 3395, 1682, 1634, 1253, 1203, 1040 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CD₃OD) \( \delta \) 7.61 (1 H, d, \( J = 16.0 \) Hz), 7.17 (1 H, d, \( J = 1.2 \) Hz), 7.09 (1 H, dd, J = 8.0, 2.0 Hz), 6.85 (1 H, d, \( J = 8.0 \) Hz), 6.37 (1 H, d, \( J = 16.0 \) Hz), 6.00 (2 H, s), 5.89 (1 H, d, J = 2.8 Hz), 4.47–4.19 (7 H, m), 3.90–3.81 (2 H, m), 3.71–3.67 (2 H, m), 2.11 (2 H, t, J = 6.4 Hz), 2.01 (3 H, s); \(^{13}\)C NMR (100 MHz, CD₃OD) \( \delta \) 173.6, 168.1, 162.5, 158.1, 150.6, 149.2, 145.7, 145.6, 131.5, 129.3, 125.1, 115.6, 108.7, 107.9, 106.7, 102.3, 77.2, 70.5, 69.5, 63.9, 62.5, 61.2, 50.6, 28.3, 21.8; ESI-HRMS calcd for C_{25}H_{33}N_{4}O_{11}: 565.2146, found: \( m/z \) 565.2144 [M + H]⁺.

**ZA-1-ME conjugate (11).** To a solution of 17 (100 mg, 0.16 mmol) in CH₂Cl₂ (5 mL) was added the N-Boc-\(O\)-allyl mesalazine derivative 21 (47 mg, 0.16 mmol), EDCI (31 mg, S27
0.16 mmol) and 4-DMAP (18 mg, 0.16 mmol). The mixture was stirred at room temperature for 1.5 h. The resulting solution was extracted with 1 M HCl, saturated NaHCO₃ and brine, dried over MgSO₄, concentrated under reduced pressure, and purified by flash silica gel column chromatography (EtOAc/hexane = 1:4 to EtOAc/hexane = 2:3) to afford a coupling product (98 mg, 70%). C₄₃H₆₃N₅O₁₆; light yellow solid, mp 82–84 °C; TLC (EtOAc/hexane = 1:1) Rf = 0.18; [α]20D −21.0 (c = 1.0, CHCl₃); IR νmax (neat) 3312, 2978, 2927, 1725, 1646, 1248, 1231, 1155 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 11.32 (1 H, s), 8.55 (1 H, d, J = 8.0 Hz), 7.90 (1 H, d, J = 3.6 Hz), 7.61 (1 H, s), 7.58 (1 H, d, J = 2.8 Hz), 6.87 (1 H, d, J = 9.2 Hz), 6.69 (1 H, s), 6.07–5.95 (1 H, m), 5.73 (1 H, d, J = 2.4 Hz), 5.41 (2 H, dd, J = 16.8, 1.0 Hz), 5.25–5.21 (2 H, m), 5.10–5.01 (1 H, m), 4.54 (2 H, d, J = 5.2 Hz), 4.38–4.29 (4 H, m), 4.16–3.91 (2 H, m), 3.48–3.44 (2 H, m), 2.14–2.07 (2 H, m), 1.98 (3 H, s), 1.47 (9 H, s), 1.46 (18 H, s), 1.39 (3 H, s), 1.32 (3 H, s); ¹³C NMR (100 MHz, CDCl₃) δ 173.9, 165.7, 162.3, 161.3, 157.5, 154.1, 153.2, 152.6, 146.5, 132.9, 131.4, 131.0, 120.6, 117.7, 114.6, 114.0, 109.1, 107.1, 84.3, 80.1, 78.5, 77.2, 74.0, 71.2, 70.1, 69.8, 67.4, 62.4, 61.5, 51.5, 48.3, 36.6, 29.6, 28.3 (3 ×), 28.2 (3 ×), 28.0 (3 ×), 27.0, 25.1, 22.9; ESI-HRMS (negative mode) calcd for C₄₃H₆₂N₅O₁₆: 904.4192, found: m/z 904.4214 [M − H]⁻.

To a solution of the above-prepared coupling compound (34 mg, 0.04 mmol) in anhydrous THF (3 mL) was added Pd(PPh₃)₄ (12 mg, 0.01 mmol) and morpholine (0.1 mL, 1.4 mmol). The mixture was stirred at room temperature for 4 h. The resulting solution was extracted with 1 M HCl and brine, dried over MgSO₄, concentrated under reduced pressure, and purified by flash silica gel column chromatography (MeOH/CH₂Cl₂ = 1:20 to MeOH/CH₂Cl₂ = 1:9). The residue was dissolved in CH₂Cl₂ (2 mL) and TFA (2 mL). After stirring at room temperature for 3 h, the mixture was evaporated under reduced pressure. The residue was triturated with Et₂O, and centrifuged to give ZA-1-ME conjugate 11 (23 mg, 62 %). C₂₂H₃₁N₅O₁₀; yellow solid, mp 126–128 °C; [α]¹⁸D +18.6 (c = 0.25, CH₃OH); IR νmax (neat) 3422, 1677, 1493, 1204, 1137 cm⁻¹; ¹H NMR (400 MHz, CD₃OD) δ 7.73 (1 H, d, J = 2.8 Hz),
7.38 (1 H, dd, $J = 9.2$, 2.8 Hz), 5.86 (1 H, d, $J = 2.8$ Hz), 4.53–4.38 (6 H, m), 4.20–4.16 (1 H, m), 3.89–3.80 (2 H, m), 3.71–3.66 (3 H, m), 2.21 (2 H, t, $J = 6.4$ Hz), 2.00 (3 H, s); $^{13}$C NMR (100 MHz, CD$_3$OD) $\delta$ 173.7, 172.1, 169.5, 162.4, 160.0, 158.1, 145.7, 129.1, 122.2, 119.3, 113.4, 108.1, 77.3, 70.6, 69.4, 64.1, 63.9, 62.8, 62.5, 50.6, 28.1, 21.8; ESI-HRMS calcd for C$_{22}$H$_{32}$N$_{5}$O$_{10}$: 526.2149, found: m/z 526.2146 [M + H]$^+$.

**ZA-1-HNAP conjugate (12).** To a solution of alcohol 17 (117 mg, 0.19 mmol) in CH$_2$Cl$_2$ (3 mL) was added 1-allyloxy-2-naphthoic acid (22, 43 mg, 0.19 mmol), EDCI (36 mg, 0.19 mmol) and 4-DMAP (21 mg, 0.19 mmol). The mixture was stirred at room temperature for 1.5 h. The resulting solution was extracted with 1 M HCl, saturated NaHCO$_3$ and brine, dried over MgSO$_4$, concentrated under reduced pressure, and purified by flash silica gel column chromatography (EtOAc/hexane = 1:4 to EtOAc/hexane = 2:3) to afford a coupling product (105 mg, 68%). C$_{42}$H$_{56}$N$_4$O$_{14}$; light yellow foam; TLC (EtOAc/hexane = 2:3) $R_f$ = 0.22; [$\alpha$]$^\text{D}$ = −25.5 (c = 1.0, CHCl$_3$); IR $\nu_{\text{max}}$ (neat) 2980, 2930, 1726, 1647, 1607, 1565, 1369, 1250, 1152, 1129 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 11.32 (1 H, s), 8.57 (1 H, d, $J = 7.6$ Hz), 8.22 (1 H, d, $J = 8.0$ Hz), 7.94 (1 H, d, $J = 4.8$ Hz), 7.81 (1 H, d, $J = 8.8$ Hz), 7.58–7.47 (3 H, m), 6.21–6.11 (1 H, m), 5.75 (1 H, d, $J = 2.0$ Hz), 5.45 (1 H, d, $J = 17.2$, 1.2 Hz), 5.27 (2 H, d, $J = 11.6$ Hz), 5.09–5.04 (1 H, m), 4.61 (1 H, d, $J = 5.6$ Hz), 4.45–4.42 (2 H, m), 4.38–4.33 (3 H, m), 4.16–4.01 (3 H, m), 3.97–3.91 (2 H, m), 3.47–3.44 (1 H, m), 2.18–2.14 (2 H, m), 1.97 (3 H, s), 1.46 (9 H, s), 1.45 (9 H, s), 1.37 (3 H, s), 1.31 (3 H, s); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 173.9, 165.9, 162.2, 161.2, 157.5, 156.9, 152.6, 146.7, 136.6, 133.6, 128.7, 128.3, 127.8, 126.5, 126.4, 123.6, 119.5, 117.6, 109.0, 106.8, 84.2, 80.0, 78.5, 76.5, 73.9, 69.7, 67.4, 62.3, 61.5, 60.3, 51.9, 48.3, 28.1 (3 $\times$), 27.9 (3 $\times$), 26.9, 25.0, 22.9, 14.1; ESI-HRMS calcd for C$_{42}$H$_{57}$N$_4$O$_{14}$: 841.3871, found: m/z 841.3907 [M + H]$^+$.

To a solution of the above-prepared coupling compound (65 mg, 0.08 mmol) in anhydrous THF (4 mL) was added Pd(PPh$_3$)$_4$ (12 mg, 0.01 mmol) and morpholine (0.1 mL, 1.4 mmol). The mixture was stirred at room temperature for 4 h. The resulting solution was extracted...
with 1 M HCl and brine, dried over MgSO₄, concentrated under reduced pressure, and purified by flash silica gel column chromatography (EtOAc/hexane = 1:4 to EtOAc/hexane = 1:1). The residue was dissolved in CH₂Cl₂ (2 mL) and TFA (2 mL). After stirring at room temperature for 3 h, the mixture was evaporated under reduced pressure. The residue was triturated with Et₂O, and centrifuged to give ZA-1-HNAP conjugate 12 (33 mg, 75 %). C₂₆H₃₂N₄O₁₀; pale yellow solid, mp 120–122 °C; [α]²¹_D +19.3 (c = 1.0, MeOH); UV-vis (MeOH) λ_max 316 nm (ε = 5340), 260 nm (ε = 28990); UV-vis (PBS) λ_max 316 nm (ε = 4180), 260 nm (ε = 4420); IR ν_max (neat) 3422, 1719, 1663, 1638, 1253, 1203, 1139, 1090 cm⁻¹; ¹H NMR (400 MHz, CD₃OD) δ 8.35 (1 H, d, J = 8.4 Hz), 7.81 (1 H, d, J = 8.4 Hz), 7.77 (1 H, d, J = 8.8 Hz), 7.63 (1 H, m), 7.53 (1 H, m), 7.33 (1 H, d, J = 8.8 Hz), 5.89 (1 H, d, J = 2.8 Hz), 4.54–4.51 (2 H, m), 4.46–4.41 (4 H, m), 4.23–4.18 (1 H, m), 3.89–3.81 (2 H, m), 3.72–3.67 (2 H, m), 2.26–2.20 (2 H, m), 2.00 (3 H, s); ¹³C NMR (100 MHz, CD₃OD) δ 173.5, 171.3, 162.4, 161.0, 158.0, 145.6, 137.8, 129.8, 127.8, 126.1, 125.0, 124.3, 123.6, 119.0, 108.0, 105.7, 77.1, 70.5, 69.3, 63.8, 62.5, 62.3, 50.4, 47.9, 28.1, 21.7; ESI-HRMS calcd for C₂₆H₃₃N₄O₁₀: 561.2197, found: m/z 561.2194 [M + H]⁺.
$^1$H NMR spectrum of compound 1 (400 MHz, in CD$_3$OD)

$^{13}$C NMR spectrum of compound 1 (100 MHz, in CD$_3$OD)
$^1$H NMR spectrum of compound 2 (400 MHz, in CD$_3$OD)

$^{13}$C NMR spectrum of compound 2 (100 MHz, in CD$_3$OD)
$^1$H NMR spectrum of compound 3 (400 MHz, in D$_2$O)

$^{13}$C NMR spectrum of compound 3 (100 MHz, in D$_2$O)
$^1$H NMR spectrum of compound 4 (400 MHz, in CD$_3$OD)

$^{13}$C NMR spectrum of compound 4 (100 MHz, in CD$_3$OD)
\(^1\)H NMR spectrum of compound 5 (400 MHz, in CD\(_3\)OD)

\(^{13}\)C NMR spectrum of compound 5 (100 MHz, in CD\(_3\)OD)
$^1$H NMR spectrum of compound 6 (400 MHz, in D$_2$O)

$^{13}$C NMR spectrum of compound 6 (100 MHz, in D$_2$O)
$^1$H NMR spectrum of compound 7 (400 MHz, in D$_2$O)

$^{13}$C NMR spectrum of compound 7 (100 MHz, in D$_2$O)
$^1$H NMR spectrum of compound 8 (400 MHz, in CD$_3$OD)

$^{13}$C NMR spectrum of compound 8 (100 MHz, in CD$_3$OD)
$^1$H NMR spectrum of compound 9 (400 MHz, in CD$_3$OD)

$^{13}$C NMR spectrum of compound 9 (100 MHz, in CD$_3$OD)
$^1$H NMR spectrum of compound 10 (400 MHz, in CDCl$_3$)

$^{13}$C NMR spectrum of compound 10 (100 MHz, in CD$_3$OD)
$^1$H NMR spectrum of compound 11 (400 MHz, in CD$_3$OD)

$^{13}$C NMR spectrum of compound 11 (100 MHz, in CD$_3$OD)
$^1$H NMR spectrum of compound 12 (400 MHz, in D$_2$O)

$^13$C NMR spectrum of compound 12 (100 MHz, in D$_2$O)
$^1$H NMR spectrum of compound 13 (400 MHz, in CDCl$_3$)

$^{13}$C NMR spectrum of compound 13 (100 MHz, in CDCl$_3$)
$^1$H NMR spectrum of compound 14 (400 MHz, in CDCl$_3$)

$^{13}$C NMR spectrum of compound 14 (100 MHz, in CDCl$_3$)
$\text{H NMR spectrum of compound 15 (400 MHz, in CDCl}_3\text{)}$

$\text{13C NMR spectrum of compound 15 (100 MHz, in CDCl}_3\text{)}$
$^1$H NMR spectrum of compound 16 (400 MHz, in CDCl$_3$)

$^{13}$C NMR spectrum of compound 16 (100 MHz, in CDCl$_3$)
$^1$H NMR spectrum of compound 17 (400 MHz, in CDCl$_3$)

$^{13}$C NMR spectrum of compound 17 (100 MHz, in CDCl$_3$)
$^{1}$H NMR spectrum of compound 18 (400 MHz, in CDCl$_3$)

$^{13}$C NMR spectrum of compound 18 (100 MHz, in CDCl$_3$)
$\text{H NMR spectrum of compound 19 (400 MHz, in CDCl}_3\text{)}$

$\text{C NMR spectrum of compound 19 (100 MHz, in CDCl}_3\text{)}$
$^1$H NMR spectrum of compound 21 (400 MHz, in CDCl$_3$)

$^{13}$C NMR spectrum of compound 21 (100 MHz, in CDCl$_3$)
$^{1}H$ NMR spectrum of compound 22 (400 MHz, in CDCl$_3$)

$^{13}C$ NMR spectrum of compound 22 (100 MHz, in CDCl$_3$)
\( ^1 \text{H NMR spectrum of compound 23 (400 MHz, in CDCl}_3 \)\)

\( ^{13} \text{C NMR spectrum of compound 23 (100 MHz, in CDCl}_3 \)\)
$^1$H NMR spectrum of compound 25 (400 MHz, in CDCl$_3$)

$^{13}$C NMR spectrum of compound 25 (100 MHz, in CDCl$_3$)
$^1$H NMR spectrum of compound 27 (400 MHz, in CDCl$_3$)

$^{13}$C NMR spectrum of compound 27 (100 MHz, in CDCl$_3$)