

Simplified platensimycin analogues as antibacterial agents

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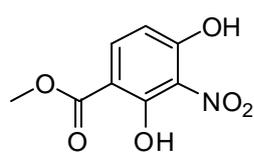
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Electronic Supplementary Information

General

All reagents were purchased from Aldrich and used without further purification. LR grade methanol, hexanes, ethyl acetate, diethyl ether and dichloromethane were purchased from Merck and were used without further purification. All ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance III 400 Ultrashield Plus spectrometer at 400.13 and 100.62 MHz respectively. Unless stated otherwise, samples were dissolved in CDCl_3 or $\text{DMSO}-d_6$. Thin-layer chromatography was conducted on 0.2 mm plates using Merck silica gel 60 F_{254} . Flash Chromatography was performed using Merck Silica Gel 60, 230-400 mesh ASTM. High resolution mass spectra (HR-ESI) were obtained on a Waters LCT Premier XE (TOF) using electrospray ionization. LCMS data was obtained on a Agilent 1200 series LC coupled directly to a photodiode array detector and an Agilent 6100 Quadrupole MS, using a Phenomenex column (Luna 5 μm C8, 50 mm \times 4.60 mm ID). Analytical reverse-phase HPLC was performed on a Waters HPLC system fitted with a Phenomenex® Luna C8 (2) 100Å column (150 mm \times 4.6 mm, 5 μm) using a binary solvent system; solvent A: 0.1% TFA/ H_2O ; solvent B: 0.1% TFA/80% ACN/ H_2O . Isocratic elution was carried out using appropriate percentages of solvent B over 20 min at a flow rate of 1.0 mL/min. Gradient elution was achieved using 100% solvent A to 100% solvent B over 20 min at a flow rate of 1 mL/min.

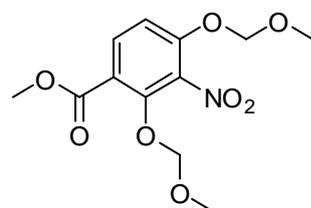
Methyl 2,4-dihydroxy-3-nitrobenzoate (6; scheme 1, R₁ = OH)



Methyl 2,4-dihydroxybenzoate (5.00 g, 29.7 mmol) was dissolved in a mixture of glacial acetic acid (33 mL) and acetic anhydride (17 mL) using sonication. After cooling to 0 °C (ice bath) a mixture of fuming nitric acid (100%) (2.06 g, 32.7 mmol, 1.1 equiv.) in glacial acetic acid (15 mL) was added over 15 min. After the addition was completed, the mixture was allowed to rise to room temperature and stirring continued for a further 1 hour. Water (70 mL) was added, the mixture was then rested for 30 min without stirring. The precipitate was filtered and rinsed with small amounts of water. The brown filtrate was extracted with diethyl ether (3 × 50 mL), the combined extracts were washed with water (3 × 50 mL), brine (3 × 50 mL), dried over anhydrous sodium sulfate and then evaporated to dryness to give the crude product as a dark orange solid (1.9 g, 30%). The crude sample was purified using flash column chromatography (dichloromethane/hexane, 1:1) giving rise to the title compound as a yellow solid (1.41 g, 22%).

¹H NMR (400 MHz, CDCl₃) δ 12.86 (s, 1H), 11.17 (s, 1H), 7.99 (d, *J* = 9 Hz, 1H), 6.03 (d, *J* = 9 Hz, 1H), 3.98 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 169.9, 160.7, 160.1, 136.8, 125.3, 109.2, 105.7, 52.9.

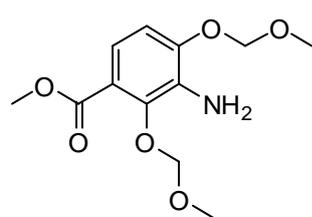
Methyl 2,4-bis(methoxymethoxy)-3-nitrobenzoate (7; scheme 1, R₃ = OMOM)



To a stirred suspension of NaH (60%) (1.73 g, 43.2 mmol) in anhydrous dimethoxyethane (70 mL) was added chloromethyl methyl ether (3.77 mL, 49.6 mmol), a solution of the phenol (2.30 g, 10.8 mmol) in anhydrous *N,N*-dimethylformamide (35 mL) and *N,N*-diisopropylethylamine (9.18 mL, 54.0 mmol) consecutively. The yellow suspension was heated to 55 °C for 1 h. After this time the reaction mixture was diluted with water (50 mL)

and saturated aqueous NaHCO₃ (30 mL) and extracted with diethyl ether (4 × 25 mL). The organic phase was washed with aqueous hydrochloric acid (1 M, 2 × 15 mL), brine and then dried over magnesium sulfate. The solvent was removed under reduced pressure to give a yellow oil. This material was further purified using flash column chromatography (hexanes/ethyl acetate, 3:1) to afford the title compound (3.10 g, 95%) as a pale yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 7.98 (d, *J* = 9.0 Hz, 1H), 7.08 (d, *J* = 9.0 Hz, 1H), 5.28 (s, 2H), 5.15 (s, 2H), 3.90 (s, 3H), 3.49 (s, 3H), 3.48 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 164.5, 152.4, 150.9, 138.7, 134.2, 118.2, 110.8, 102.4, 95.1, 58.0, 57.0, 52.6.

Methyl 3-amino-2,4-bis(methoxymethoxy)benzoate (8; scheme 1, R₃ = OMOM)

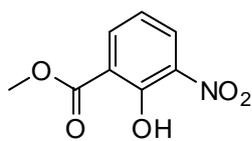


Methyl 2,4-bis(methoxymethoxy)-3-nitrobenzoate (170 mg, 0.56 mmol) was hydrogenated with ambient pressure of H₂ using PtO₂ (17 mg, 10% w/w) in methanol (15 mL) overnight. The resulting suspension was filtered through a pad of CeliteTM and washed with

methanol. The solvent was removed under reduced pressure to afford the desired product as an oil (145 mg) 97% yield.

¹H NMR (400 MHz, CDCl₃) δ 7.24 (d, *J* = 8.7 Hz, 1H), 6.85 (d, *J* = 8.7 Hz, 1H), 5.24 (s, 2H), 5.10 (s, 2H), 4.22 (s, 2H), 3.85 (s, 3H), 3.60 (s, 3H), 3.48 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 166.2, 148.6, 145.4, 131.7, 120.1, 118.0, 109.5, 101.1, 94.8, 57.6, 56.3, 51.8.

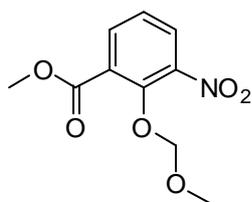
Methyl 2-hydroxy-3-nitrobenzoate (**6**; scheme 1, R₁ = H)



Salicylic acid (5.00 g, 36.3 mmol) was dissolved in 200 mL of dichloromethane, to which concentrated nitric acid (69%, 2.51 g, 39.8 mmol) was added with stirring at 0 °C. Concentrated sulfuric acid (95%, 5 mL, 70 mmol) was then added dropwise to the reaction mixture. After 20 min, the reaction was quenched with 250 mL of distilled water and the mixture was filtered. The yellow residue was then dried under vacuum overnight and the crude product was directly used in the next step without further purification. The crude compound (6.18 g) was dissolved in methanol (120 mL), to which concentrated sulfuric acid (10 mL, 140 mmol) was added. The mixture was heated at reflux for 2 days. The solvent was then removed in vacuo and the residue dissolved in dichloromethane (100 mL), washed with water (3 × 50 mL), washed with saturated NaHCO₃ (3 × 50 mL) and dried over sodium sulfate. The solvent was removed under reduced pressure to give a yellow solid. This material was further purified using gradient flash column chromatography (hexanes → dichloromethane/hexanes, 1:6) to afford the title compound (900 mg, 13%) as a bright yellow solid.

¹H NMR (400 MHz, CDCl₃) δ 11.99 (s, 1H), 8.19 – 8.12 (m, 2H), 7.01 (dd, *J* = 8.0, 8.0 Hz, 1H), 4.02 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 169.2, 155.7, 135.8, 131.4, 118.4, 115.8, 53.2; LCMS calcd for C₈H₆NO₅⁻ (M-H) 196.0, found 196.0, *t*_R 5.58 min.

Methyl 2-(methoxymethoxy)-3-nitrobenzoate (**7**; scheme 1, R₃ = H)

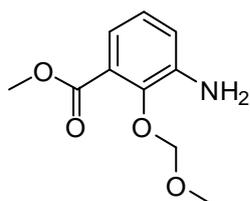


To a stirred suspension of Sodium hydride (60% dispersion) (160 mg, 4.16 mmol, 2 equiv) in anhydrous dimethoxyethane (4 mL) was added choromethyl methyl ether (316 μL, 4.16 mmol, 2 equiv), a solution of methyl 2-hydroxy-3-nitrobenzoate (410 mg, 1.27 mmol) in anhydrous *N,N*-dimethylformamide (2 mL) and *N,N*-diisopropylethylamine (905 μL, 5.20 mmol, 2.5

equiv) consecutively. The yellow suspension was heated to 55 °C for 1 h. After this time the reaction mixture was diluted with water (20 mL) and saturated NaHCO₃ (30 mL) and extracted with diethyl ether (4 × 20 mL). The organic phase was washed with brine and then dried over magnesium sulfate. The solvent was removed under reduced pressure to give a yellow oil. This material was further purified using flash chromatography (100% hexanes → diethyl ether/hexanes, 2:1) to afford the title compound (425 mg, 85%) as a yellow oil.

¹H NMR (400 MHz, CDCl₃) δ 8.02 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.89 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.30 (app t, *J* = 8.0 Hz, 1H), 5.15 (s, 2H), 3.94 (s, 3H), 3.51 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 164.8, 150.1, 146.5, 135.1, 128.0, 127.8, 124.2, 102.4, 58.0, 52.8.

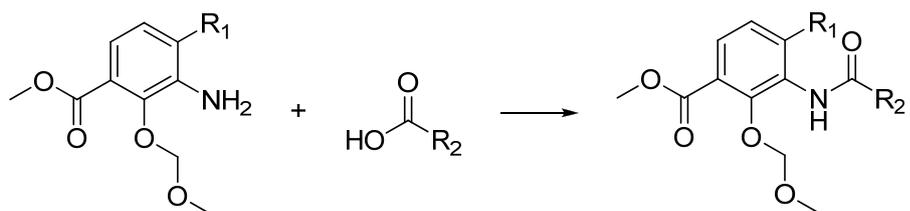
Methyl 3-amino-2-(methoxymethoxy)benzoate (**8**; scheme 1, R₃ = H)



Methyl 2-(methoxymethoxy)-3-nitrobenzoate (200 mg, 0.56 mmol) was hydrogenated with ambient pressure of H₂ using PtO₂ (20 mg, 10% w/w) in methanol (15 mL) overnight. The resulting suspension was filtered through a pad of CeliteTM and washed with methanol. The solvent was removed under reduced pressure to afford the desired product as a light yellow oil (171 mg) 97% yield.

¹H NMR (400 MHz, CDCl₃) δ 7.17 (dd, *J* = 7.7, 1.7 Hz, 1H), 6.96 (app t, *J* = 7.8 Hz, 1H), 6.90 (dd, *J* = 7.9, 1.7 Hz, 1H), 5.08 (s, 2H), 4.12 (br s, 2H), 3.88 (s, 3H), 3.59 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 166.7, 141.4, 125.0, 124.6, 120.2, 119.6, 101.1, 90.9, 57.6, 52.1.

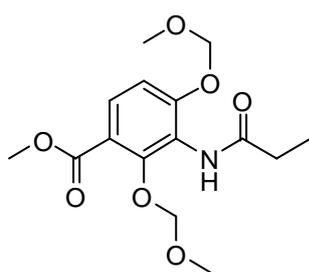
General amide coupling procedure



Where R₁ = H, OMOM, R₂ = see Table 1

To a cooled solution (0–5 °C, ice bath) of the appropriate carboxylic acid (0.70 mmol, 1.05 equiv.) in dichloromethane (15 mL) and a catalytic amount of *N,N*-dimethylformamide is added oxalyl chloride (63 μL, 0.73 mmol, 1.1 equiv.). The reaction was gradually allowed to reach room temperature over 1 hour, at which time it was transferred using cannula addition into a cooled suspension (0–5 °C, ice bath) of the appropriate protected aniline (180 mg, 0.66 mmol, 1 equiv.) and potassium carbonate (920 mg, 10 equiv.) in dichloromethane (50 mL). The reaction mixture was gradually allowed to reach room temperature over 2 hours, at which point it was filtered through Celite™ and purified using flash column chromatography (ethyl acetate/petroleum spirits, gradient elution 1:6 → 1:3).

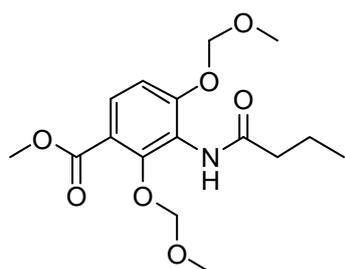
Methyl 2,4-bis(methoxymethoxy)-3-propionamidobenzoate (9a)



92 mg as an off-white solid, yield 38%. ¹H NMR (400 MHz, CDCl₃) δ 7.78 (d, *J* = 8.8 Hz, 1H), 7.39 (s, 1H), 7.02 (d, *J* = 9.0 Hz, 1H), 5.23 (s, 2H), 5.07 (s, 2H), 3.86 (s, 3H), 3.56 (s, 3H), 3.49 (s, 3H), 2.41 (br s, 2H), 1.24 (br s, 3H); ¹³C NMR (101 MHz, CDCl₃)

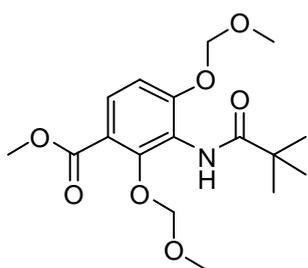
δ 172.2, 165.4, 156.9, 154.4, 130.5, 121.9, 117.9, 110.8, 101.6, 94.8, 57.3, 56.5, 52.0, 29.7, 9.7; HRMS calcd for C₁₅H₂₁NNaO₇⁺ (M+Na)⁺ 350.1210, found 350.1222; LCMS calcd for C₁₅H₂₁NNaO₇⁺ (M+Na)⁺ 350.1, *t*_R 5.26 min, found 350.1; HPLC purity: 98.8%, *t*_R 5.82 min (isocratic); >99%, *t*_R 7.10 min (gradient).

Methyl 3-butylamido-2,4-bis(methoxymethoxy)benzoate (9b)



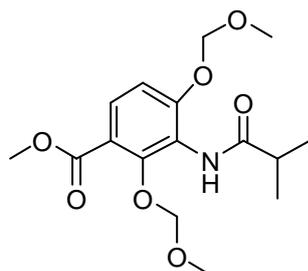
110 mg as a colourless oil, yield 46%. ^1H NMR (400 MHz, CDCl_3) δ 7.79 (d, $J = 8.8$ Hz, 1H), 7.35 (s, 1H), 7.02 (d, $J = 9.0$ Hz, 1H), 5.23 (s, 2H), 5.08 (s, 2H), 3.87 (s, 3H), 3.57 (s, 3H), 3.50 (s, 3H), 2.37 (br s, 2H), 1.76 (br s, 2H), 1.02 (br s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 171.2, 165.4, 156.8, 154.4, 130.4, 121.9, 117.9, 110.8, 101.6, 94.8, 57.4, 56.5, 52.0, 38.7, 19.2, 13.7; HRMS calcd for $\text{C}_{16}\text{H}_{24}\text{NO}_7^+$ ($\text{M}+\text{H}$) $^+$ 342.1547, found 342.1559; LCMS calcd for $\text{C}_{16}\text{H}_{23}\text{NNaO}_7^+$ ($\text{M}+\text{Na}$) $^+$ 364.1, t_{R} 5.32 min, found 364.1; HPLC purity: 98.0%, t_{R} 4.09 min (isocratic); >99%, t_{R} 8.51 min (gradient).

Methyl 2,4-bis(methoxymethoxy)-3-pivalamidobenzoate (9c)



122 mg as a colourless oil, yield 22%. ^1H NMR (400 MHz, CDCl_3) δ 7.76 (d, $J = 8.9$ Hz, 1H), 7.54 (s, 1H), 6.99 (d, $J = 9.0$ Hz, 1H), 5.21 (s, 2H), 5.06 (s, 2H), 3.86 (s, 3H), 3.51 (s, 3H), 3.50 (s, 3H), 1.34 (s, 9H); ^{13}C NMR (101 MHz, CDCl_3) δ 176.8, 165.5, 156.7, 154.0, 130.2, 122.2, 117.8, 110.9, 101.5, 94.9, 57.5, 56.5, 52.0, 39.3, 27.7; HRMS calcd for $\text{C}_{34}\text{H}_{50}\text{N}_2\text{NaO}_{14}^+$ ($2\text{M}-2\text{CH}_2\text{OCH}_3+2\text{H}+\text{Na}$) $^+$ 645.2630, found 645.2609; LCMS calcd for $\text{C}_{15}\text{H}_{22}\text{NO}_6^+$ ($\text{M}-\text{CH}_2\text{OCH}_3+2\text{H}$) $^+$ 312.1, t_{R} 5.45 min, found 312.1; HPLC purity: 95.2%, t_{R} 4.85 min (isocratic); 96.0%, t_{R} 9.05 min (gradient).

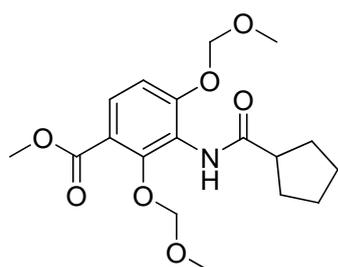
Methyl 3-isobutyramido-2,4-bis(methoxymethoxy)benzoate (9d)



130 mg as a yellow oil, yield 57%. ^1H NMR (400 MHz, CDCl_3) δ 7.77 (d, $J = 8.9$ Hz, 1H), 7.35 (s, 1H), 7.00 (d, $J = 9.0$ Hz, 1H), 5.21 (s, 2H), 5.07 (s, 2H), 3.86 (s, 3H), 3.55 (s, 3H), 3.49 (s, 3H), 2.59 (sept, $J = 6.7$ Hz, 1H), 1.26 (d, $J = 6.1$ Hz, 6H); ^{13}C NMR (101

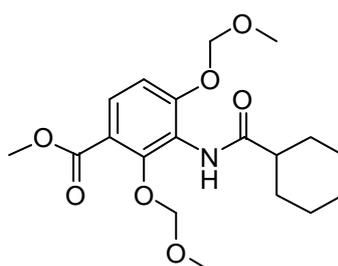
MHz, CDCl₃) δ 175.3, 165.5, 156.8, 154.3, 130.4, 121.9, 117.9, 110.8, 101.5, 94.9, 57.4, 56.5, 52.0, 35.9, 19.6; HRMS calcd for C₁₆H₂₃NNaO₇⁺ (M+Na)⁺ 364.1367, found 364.1377; LCMS calcd for C₁₆H₂₃NNaO₇⁺ (M+Na)⁺ 364.1, *t*_R 5.09 min, found 364.3; HPLC purity: 96.0%, *t*_R 5.69 min (isocratic); 95.1%, *t*_R 8.35 min (gradient).

Methyl 3-(cyclopentanecarboxamido)-2,4-bis(methoxymethoxy)benzoate (9e)



153 mg as a yellow oil, 57%. ¹H NMR (400 MHz, CDCl₃) δ 7.77 (d, *J* = 8.9 Hz, 1H), 7.33 (s, 1H), 7.00 (d, *J* = 9.0 Hz, 1H), 5.22 (s, 2H), 5.07 (s, 2H), 3.86 (s, 3H), 3.56 (s, 3H), 3.50 (s, 3H), 2.84 – 2.70 (m, 1H), 2.05 – 1.84 (m, 4H), 1.84 – 1.72 (m, 2H), 1.61 (br s, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 174.6, 165.5, 156.8, 154.3, 130.4, 122.1, 117.9, 110.8, 101.5, 94.9, 57.4, 56.5, 52.0, 46.0, 30.5, 26.0; HRMS calcd for C₁₈H₂₆NO₇⁺ (M+H)⁺ 368.1704, found 368.1716; LCMS calcd for C₁₈H₂₆NO₇⁺ (M+H)⁺ 368.2, *t*_R 5.46 min, found 368.3; HPLC purity: 96.9%, *t*_R 5.74 min (isocratic); 96.5%, *t*_R 9.56 min (gradient).

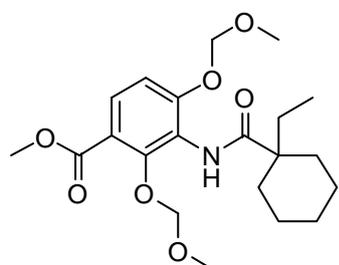
Methyl 3-(cyclohexanecarboxamido)-2,4-bis(methoxymethoxy)benzoate (9f)



47 mg as an off-white solid, yield 19%. ¹H NMR (400 MHz, CDCl₃) δ 7.77 (d, *J* = 8.9 Hz, 1H), 7.31 (s, 1H), 7.00 (d, *J* = 9.0 Hz, 1H), 5.21 (s, 2H), 5.07 (s, 2H), 3.86 (s, 3H), 3.55 (s, 3H), 3.49 (s, 3H), 2.31 (t, *J* = 11.4 Hz, 1H), 2.00 (d, *J* = 10.7 Hz, 2H), 1.83 (d, *J* = 10.9 Hz, 2H), 1.69 (d, *J* = 9.5 Hz, 2H), 1.63 – 1.49 (m, 2H), 1.41 – 1.21 (m, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 174.3, 165.5, 156.6, 154.2, 130.4, 121.9, 117.9, 110.9, 101.5, 94.9, 57.5, 56.5, 52.0, 45.8, 29.7, 25.8, 25.7; HRMS calcd for C₁₉H₂₈NO₇⁺ (M+H)⁺ 382.1860, found 382.1870; LCMS calcd for C₁₇H₂₄NO₆⁺ (M-CH₂OCH₃+2H)⁺, 338.2, *t*_R 7.00

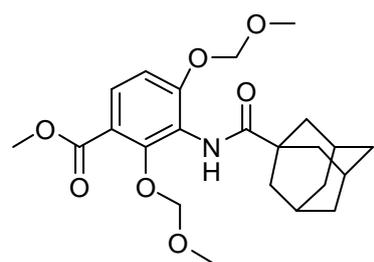
min, found 338.2; HPLC purity: 98.0%, t_R 7.18 min (isocratic); 95.5%, t_R 9.80 min (gradient).

Methyl 3-(1-ethylcyclohexancarboxamido)-2,4-bis(methoxymethoxy)benzoate (9g)



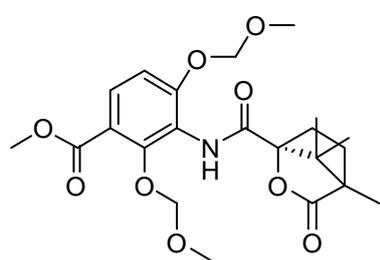
95 mg as a yellow oil, yield 31%. ^1H NMR (400 MHz, CDCl_3) δ 7.76 (d, $J = 8.9$ Hz, 1H), 7.69 (s, 1H), 7.02 (d, $J = 9.0$ Hz, 1H), 5.21 (s, 2H), 5.08 (s, 2H), 3.86 (s, 3H), 3.50 (s, 3H), 3.48 (s, 3H), 2.10 (d, $J = 13.5$ Hz, 2H), 1.67 – 1.55 (m, 7H), 1.41 – 1.28 (m, 3H), 0.96 (t, $J = 7.5$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 174.5, 165.6, 156.6, 153.6, 129.9, 122.5, 117.7, 110.8, 101.6, 94.7, 57.4, 56.4, 52.0, 47.4, 34.3, 33.8, 26.3, 23.0, 8.3; HRMS calcd for $\text{C}_{21}\text{H}_{32}\text{NO}_7^+$ ($\text{M}+\text{H}$) $^+$ 410.2173, found 410.2188; LCMS calcd for $\text{C}_{21}\text{H}_{31}\text{NNaO}_7^+$ ($\text{M}+\text{Na}$) $^+$ 432.2, t_R 6.074 min, found 432.3; HPLC purity: 98.2%, t_R 7.25 min (isocratic); 98.7%, t_R 11.1 min (gradient).

Methyl 3-((3r,5r,7r)-adamantane-1-carboxamido)-2,4-bis(methoxymethoxy)benzoate (9h)



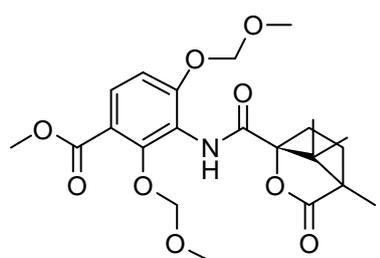
58 mg as a colourless oil, yield 19%. ^1H NMR (400 MHz, CDCl_3) δ 7.75 (d, $J = 8.9$ Hz, 1H), 7.44 (s, 1H), 6.99 (d, $J = 8.9$ Hz, 1H), 5.20 (s, 2H), 5.06 (s, 2H), 3.86 (s, 3H), 3.53 (s, 3H), 3.50 (s, 3H), 2.10 (s, 3H), 2.01 (d, $J = 2.3$ Hz, 6H), 1.83 – 1.72 (m, 6H); ^{13}C NMR (101 MHz, CDCl_3) δ 176.2, 165.6, 156.7, 154.0, 130.1, 122.2, 117.9, 110.9, 101.4, 94.9, 57.6, 56.5, 52.0, 41.3, 39.3, 36.6, 28.2; HRMS calcd for $\text{C}_{23}\text{H}_{32}\text{NO}_7^+$ ($\text{M}+\text{H}$) $^+$ 434.2173, found 434.2184; LCMS calcd for $\text{C}_{23}\text{H}_{31}\text{NNaO}_7^+$ ($\text{M}+\text{Na}$) $^+$ 456.2, t_R 6.19 min, found 456.1; HPLC purity: 96.8%, 9.30 min (isocratic); 97.6%, 11.1 min (gradient).

Methyl 2,4-bis(methoxymethoxy)-3-((1S)-4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxamido)benzoate (9i)



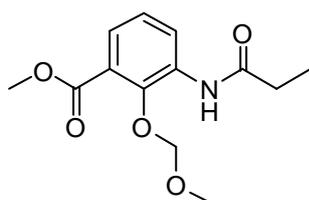
200 mg as a yellow oil, yield 67%. ^1H NMR (400 MHz, CDCl_3) δ 8.28 (s, 1H), 7.82 (d, $J = 9.0$ Hz, 1H), 7.02 (d, $J = 9.0$ Hz, 1H), 5.23 (q, $J = 6.8$ Hz, 2H), 5.08 (s, 2H), 3.86 (s, 3H), 3.62 (s, 3H), 3.49 (s, 3H), 2.60 (ddd, $J = 14.2, 10.9, 4.2$ Hz, 1H), 2.06 – 1.94 (m, 2H), 1.79 – 1.69 (m, 1H), 1.15 (s, 3H), 1.14 (s, 3H), 1.09 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 178.2, 165.3, 165.4, 156.5, 154.8, 131.1, 120.5, 117.9, 110.5, 102.0, 94.7, 92.8, 57.9, 56.5, 55.4, 54.2, 52.1, 30.5, 29.2, 16.8, 16.7, 9.8; HRMS calcd for $\text{C}_{22}\text{H}_{30}\text{NO}_9^+$ ($\text{M}+\text{H}$) $^+$ 452.1915, found 452.1902; LCMS calcd for $\text{C}_{22}\text{H}_{29}\text{NNaO}_9^+$ ($\text{M}+\text{Na}$) $^+$ 474.2, t_{R} 5.68 min, found 474.2; HPLC purity: 97.3%, t_{R} 7.13 min (isocratic); 100%, t_{R} 9.95 min (gradient).

Methyl 2,4-bis(methoxymethoxy)-3-((1R)-4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxamido)benzoate (9j)



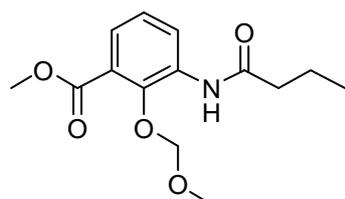
83 mg as a yellow oil, yield 29%. ^1H NMR (400 MHz, CDCl_3) δ 8.27 (s, 1H), 7.82 (d, $J = 9.0$ Hz, 1H), 7.02 (d, $J = 9.0$ Hz, 1H), 5.22 (q, $J = 6.8$ Hz, 2H), 5.08 (s, 2H), 3.87 (s, 3H), 3.62 (s, 3H), 3.49 (s, 3H), 2.60 (ddd, $J = 14.2, 11.0, 4.3$ Hz, 1H), 2.04 – 1.94 (m, 2H), 1.78 – 1.69 (m, 1H), 1.15 (s, 3H), 1.14 (s, 3H), 1.09 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 178.3, 165.5, 165.4, 156.6, 154.9, 131.2, 120.6, 118.0, 110.7, 102.2, 94.8, 92.9, 58.1, 56.7, 55.5, 54.3, 52.2, 30.6, 29.3, 16.9, 16.8, 9.9; HRMS calcd for $\text{C}_{22}\text{H}_{30}\text{NO}_9^+$ ($\text{M}+\text{H}$) $^+$ 452.1915, found 452.1906; LCMS calcd for $\text{C}_{22}\text{H}_{29}\text{NNaO}_9^+$ ($\text{M}+\text{Na}$) $^+$ 474.2, t_{R} 5.82 min, found 474.1; HPLC purity: 96.4%, t_{R} 6.00 min (isocratic); >99%, t_{R} 9.60 min (gradient).

Methyl 2-(methoxymethoxy)-3-propionamidobenzoate (9k)



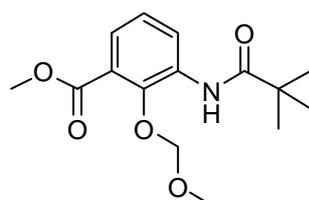
155 mg as a yellow oil, yield 67%. ^1H NMR (400 MHz, CDCl_3) δ 8.60 (dd, $J = 8.2, 1.1$ Hz, 1H), 8.51 (s, 1H), 7.54 (dd, $J = 7.9, 1.7$ Hz, 1H), 7.18 (app t, $J = 8.0$ Hz, 1H), 5.13 (s, 2H), 3.89 (s, 3H), 3.60 (s, 3H), 2.44 (q, $J = 7.6$ Hz, 2H), 1.27 (t, $J = 7.6$ Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 172.2, 165.8, 147.2, 133.3, 125.4, 124.8, 124.6, 124.0, 102.3, 57.7, 52.2, 31.1, 9.5; HRMS calcd for $\text{C}_{13}\text{H}_{18}\text{NO}_5^+$ ($\text{M}+\text{H}$) $^+$ 268.1179, found 268.1183; LCMS calcd for $\text{C}_{13}\text{H}_{17}\text{NNaO}_5^+$ ($\text{M}+\text{Na}$) $^+$ 290.1, found 290.0, t_{R} 5.47 min; HPLC purity: 98.9%, t_{R} 5.69 min (isocratic); 96.9%, t_{R} 8.26 min (gradient).

Methyl 3-butyrarnido-2-(methoxymethoxy)benzoate (9l)



157 mg as a colourless oil, yield 65%. ^1H NMR (400 MHz, CDCl_3) δ 8.60 (dd, $J = 8.2, 1.1$ Hz, 1H), 8.51 (s, 1H), 7.54 (dd, $J = 7.9, 1.7$ Hz, 1H), 7.18 (app t, $J = 8.0$ Hz, 1H), 5.13 (s, 2H), 3.89 (s, 3H), 3.60 (s, 3H), 2.38 (t, $J = 7.4$ Hz, 2H), 1.78 (sext, $J = 7.4$ Hz, 2H), 1.02 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 171.5, 165.8, 147.2, 133.3, 125.4, 124.8, 124.6, 124.0, 102.3, 57.7, 52.2, 40.0, 18.9, 13.8; HRMS calcd for $\text{C}_{14}\text{H}_{20}\text{NO}_5^+$ ($\text{M}+\text{H}$) $^+$ 282.1336, found 282.1325; LCMS calcd for $\text{C}_{14}\text{H}_{19}\text{NNaO}_5^+$ ($\text{M}+\text{Na}$) $^+$ 304.1, t_{R} 5.65 min, found 304.0; HPLC purity: 99.1%, t_{R} 4.91 min (isocratic); 100%, t_{R} 9.08 min, (gradient).

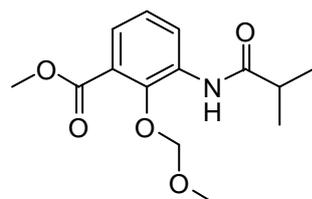
Methyl 2-(methoxymethoxy)-3-pivalamidobenzoate (9m)



172 mg as an off-white solid, yield 66%. ^1H NMR (400 MHz, CDCl_3) δ 8.71 (s, 1H), 8.64 (dd, $J = 8.2, 1.6$ Hz, 1H), 7.55 (dd, $J = 7.9, 1.7$ Hz, 1H), 7.18 (app t, $J = 8.1$ Hz, 1H), 5.14 (s, 2H), 3.90 (s, 3H), 3.53 (s, 3H), 1.34 (s, 9H); ^{13}C NMR (101 MHz, CDCl_3) δ 177.1, 165.8, 147.3, 133.5,

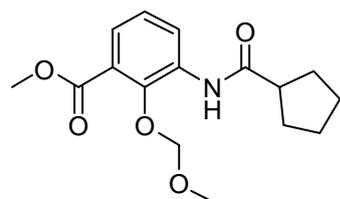
125.4, 124.7, 124.6, 123.6, 102.4, 57.8, 52.2; 40.1, 27.5. HRMS calcd for $C_{15}H_{22}NO_5^+$ ($M+H$)⁺ 296.1492, found 296.1487; LCMS calcd for $C_{15}H_{22}NO_5^+$ ($M+H$)⁺ 296.1, t_R 5.90 min, found 296.2; HPLC purity: >99%, t_R 4.76 min (isocratic); >99%, t_R 10.1 min (gradient).

Methyl 3-isobutyramido-2-(methoxymethoxy)benzoate (9n)



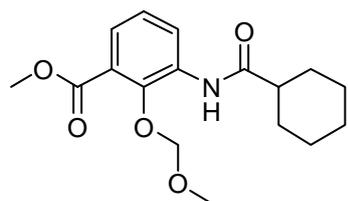
135 mg as a yellow oil, yield 56%. ¹H NMR (400 MHz, CDCl₃) δ 8.62 (dd, J = 8.2, 1.5 Hz, 1H), 8.54 (s, 1H), 7.54 (dd, J = 7.9, 1.7 Hz, 1H), 7.18 (app t, J = 8.0 Hz, 1H), 5.14 (s, 2H), 3.90 (s, 3H), 3.59 (s, 3H), 2.55 (sept, J = 6.9 Hz, 1H), 1.29 (s, 3H), 1.27 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 175.5, 165.8, 147.3, 133.4, 125.3, 124.8, 124.6, 123.9, 102.3, 57.7, 52.2, 37.1, 19.5. HRMS calcd for $C_{14}H_{20}NO_5^+$ ($M+H$)⁺ 282.1336, found 282.1340, LCMS calcd for $C_{12}H_{16}NO_4^+$ ($M-CH_2OCH_3 + 2H$)⁺, t_R 5.58 min, found 238.1; HPLC purity: >99%, t_R 4.84 min (isocratic); >99%, t_R 9.31 min, (gradient).

Methyl 3-(cyclopentanecarboxamido)-2-(methoxymethoxy)benzoate (9o)



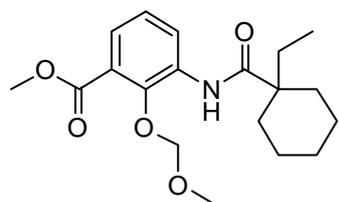
142 mg as a colourless oil, yield 57%. ¹H NMR (400 MHz, CDCl₃) δ 8.62 (dd, J = 8.2, 1.5 Hz, 1H), 8.53 (s, 1H), 7.53 (dd, J = 7.9, 1.7 Hz, 1H), 7.17 (t, J = 8.0 Hz, 1H), 5.13 (s, 2H), 3.89 (s, 3H), 3.59 (s, 3H), 2.75 (app p, J = 8.1 Hz, 1H), 2.02 – 1.87 (m, 4H), 1.85 – 1.74 (m, 2H), 1.69 – 1.60 (m, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 174.7, 165.8, 147.2, 133.5, 125.2, 124.8, 124.5, 123.9, 102.3, 57.7, 52.2, 47.2, 30.3, 26.0; HRMS calcd for $C_{16}H_{22}NO_5^+$ ($M+H$)⁺ 308.1492, found 308.1500; LCMS calcd for $C_{16}H_{22}NO_5^+$ ($M+H$)⁺ 308.1, t_R 6.03 min, found 308.1; HPLC purity: >99%, t_R 7.78 min (isocratic); 95.4%, t_R 10.1 min (gradient).

Methyl 3-(cyclohexanecarboxamido)-2-(methoxymethoxy)benzoate (9p)



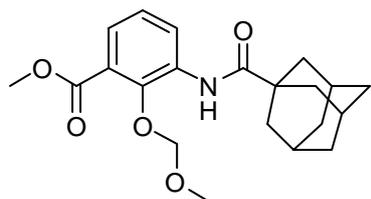
48 mg as a colourless oil, yield 18%. ^1H NMR (400 MHz, CDCl_3) δ 8.62 (dd, $J = 8.2, 1.4$ Hz, 1H), 8.54 (s, 1H), 7.53 (dd, $J = 7.9, 1.7$ Hz, 1H), 7.17 (app t, $J = 8.0$ Hz, 1H), 5.14 (s, $J = 7.7$ Hz, 2H), 3.89 (s, $J = 5.2$ Hz, 3H), 3.58 (s, $J = 7.4$ Hz, 3H), 2.28 (tt, $J = 11.7, 3.5$ Hz, 1H), 1.99 (d, $J = 13.1$ Hz, 2H), 1.88 – 1.82 (m, 2H), 1.75 – 1.68 (m, 1H), 1.61 – 1.49 (m, 2H), 1.40 – 1.20 (m, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 174.7, 165.9, 147.4, 133.5, 125.4, 124.8, 124.7, 124.0, 102.4, 57.8, 52.3, 47.0, 29.6, 25.8; HRMS calcd for $\text{C}_{17}\text{H}_{24}\text{NO}_5^+$ ($\text{M}+\text{H}$) $^+$ 322.1649, found 322.1652; LCMS calcd for $\text{C}_{17}\text{H}_{24}\text{NO}_5^+$ ($\text{M}+\text{H}$) $^+$ 322.2, t_{R} 6.08 min, found 322.1; HPLC purity 96.7%, t_{R} 10.7 min (isocratic); 96.2%, t_{R} 10.7 min (gradient).

Methyl 3-(1-ethylcyclohexanecarboxamido)-2-(methoxymethoxy)benzoate (9q)



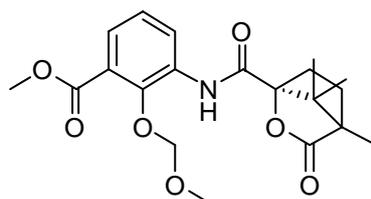
80 mg as an off-white solid, yield 25%. ^1H NMR (400 MHz, CDCl_3) δ 8.73 – 8.66 (m, 2H), 7.55 (dd, $J = 7.9, 1.7$ Hz, 1H), 7.18 (app t, $J = 8.1$ Hz, 1H), 5.13 (s, 2H), 3.90 (s, 3H), 3.52 (s, 3H), 2.18 – 2.07 (m, 2H), 1.69 – 1.27 (m, 10H), 0.87 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 175.2, 165.9, 147.1, 133.5, 125.3, 124.7, 124.6, 123.6, 102.3, 57.8, 52.2, 48.1, 33.9, 33.5, 26.1, 23.1, 8.5; HRMS calcd for $\text{C}_{19}\text{H}_{28}\text{NO}_5^+$ ($\text{M}+\text{H}$) $^+$ 350.1962, found 350.1967; LCMS calcd for $\text{C}_{19}\text{H}_{27}\text{NNaO}_5^+$ ($\text{M}+\text{Na}$) $^+$ 372.2, t_{R} 6.73 min, found 372.1; HPLC purity: 98.7%, t_{R} 5.50 min (isocratic); 98.6%, t_{R} 11.7 min (gradient).

Methyl 3-((3r,5r,7r)-adamantane-1-carboxamido)-2-(methoxymethoxy)benzoate (9r)



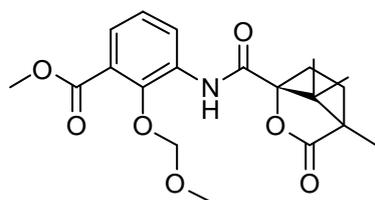
56 mg as a colourless oil, yield 18%. ^1H NMR (400 MHz, CDCl_3) δ 8.73 – 8.59 (m, 2H), 7.54 (dd, $J = 7.9, 1.7$ Hz, 1H), 7.17 (app t, $J = 8.1$ Hz, 1H), 5.15 (s, 2H), 3.90 (s, 3H), 3.55 (s, 3H), 2.11 (s, 3H), 2.00 (d, $J = 2.7$ Hz, 6H), 1.84 – 1.73 (m, 6H); ^{13}C NMR (101 MHz, CDCl_3) δ 176.6, 165.9, 147.3, 133.5, 125.3, 124.7, 124.7, 123.6, 102.4, 58.0, 52.2, 42.0, 39.1, 36.5, 28.2; HRMS calcd for $\text{C}_{21}\text{H}_{28}\text{NO}_5^+$ ($\text{M}+\text{H}$) $^+$ 374.1962, found 374.1952; LCMS calcd for $\text{C}_{21}\text{H}_{28}\text{NO}_5^+$ ($\text{M}+\text{H}$) $^+$ 374.2, t_{R} 6.61 min, found 374.1; HPLC purity: 97.2%, t_{R} 8.63 (isocratic); >99%, t_{R} 12.8 min (gradient).

Methyl 2-(methoxymethoxy)-3-((1S)-4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxamido)benzoate (9s)



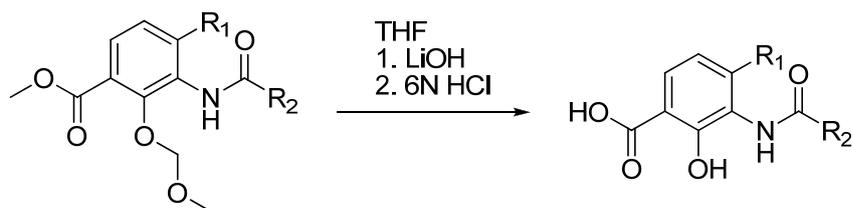
310 mg as an off-white solid, yield 67%. ^1H NMR (400 MHz, CDCl_3) δ 9.41 (s, 1H), 8.63 (dd, $J = 8.2, 1.6$ Hz, 1H), 7.61 (dd, $J = 7.9, 1.7$ Hz, 1H), 7.20 (app t, $J = 8.1$ Hz, 1H), 5.14 (q, $J = 6.5$ Hz, 2H), 3.90 (s, 3H), 3.73 (s, 3H), 2.62 (ddd, $J = 14.2, 11.0, 4.3$ Hz, 1H), 2.08 – 1.93 (m, 2H), 1.80 – 1.69 (m, 1H), 1.16 (s, 3H), 1.15 (s, 3H), 1.00 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 177.8, 165.9, 165.8, 148.3, 132.3, 126.6, 124.85, 124.7, 124.4, 103.1, 92.4, 58.6, 55.5, 54.4, 52.4, 30.6, 29.2, 16.9, 16.7, 9.9; HRMS calcd for $\text{C}_{20}\text{H}_{25}\text{NNaO}_7^+$ ($\text{M}+\text{Na}$) $^+$ 414.1523, found 414.1517; LCMS calcd for $\text{C}_{18}\text{H}_{22}\text{NO}_6^+$ ($\text{M}-\text{CH}_2\text{OCH}_3+2\text{H}$) $^+$ 348.1, t_{R} 6.06 min, found 348.1; HPLC purity: 98.8%, t_{R} 7.28 min (isocratic); >99%, t_{R} 11.1 min (gradient).

Methyl 2-(methoxymethoxy)-3-((1R)-4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxamido)benzoate (9t)



200 mg as a yellow oil, yield 66%. ^1H NMR (400 MHz, CDCl_3) δ 9.40 (s, 1H), 8.63 (dd, $J = 8.2, 1.6$ Hz, 1H), 7.61 (dd, $J = 7.9, 1.7$ Hz, 1H), 7.19 (app t, $J = 8.1$ Hz, 1H), 5.13 (q, $J = 6.5$ Hz, 2H), 3.90 (s, 3H), 3.73 (s, 3H), 2.62 (ddd, $J = 14.2, 11.0, 4.3$ Hz, 1H), 2.10 – 1.90 (m, 2H), 1.79 – 1.70 (m, 1H), 1.16 (s, $J = 3.0$ Hz, 3H), 1.15 (s, 3H), 0.99 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 177.7, 165.8, 165.8, 148.2, 132.3, 126.5, 124.8, 124.6, 124.3, 103.0, 92.3, 58.5, 55.4, 54.3, 52.3, 30.5, 29.1, 16.8, 16.6, 9.8; HRMS calcd for $\text{C}_{18}\text{H}_{22}\text{NO}_6^+$ ($\text{M}-\text{CH}_2\text{OCH}_3+2\text{H}$) $^+$ 348.1442, found 348.1451; LCMS calcd for $\text{C}_{18}\text{H}_{22}\text{NO}_6^+$ ($\text{M}-\text{CH}_2\text{OCH}_3+2\text{H}$) $^+$ 348.1, t_{R} 6.26 min, found 348.1; HPLC purity: 98.5%, t_{R} 12.1 min (isocratic); 99.0%, t_{R} 10.8 min (gradient).

General deprotection procedure



Where $R_1 = \text{H, OMOM}$, $R_2 = \text{see Table 1}$

To a solution of the appropriate MOM-protected methyl benzoate (0.04 mmol – 0.46 mmol) in tetrahydrofuran (1 mL) was added lithium hydroxide (0.40 mmol – 4.60 mmol, 10 equiv.) dissolved in water (0.5 mL). The reaction mixture was then stirred at 80 °C for 3 hours and reaction progress monitored by TLC. Upon full conversion of the starting material, the reaction mixture was cooled in an ice bath, and 6 N HCl (20 equiv.) was added cautiously. The reaction mixture was then allowed to warm to room temperature, and stirred for 2 hours. The reaction mixture was concentrated *in vacuo*, partitioned between 1 N HCl/ethyl acetate and the aqueous layer extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with 1N HCl, water, brine, dried over anhydrous sodium sulfate and evaporated to dryness to afford the target compound as an off-white solid, unless otherwise stated.

2,4-Dihydroxy-3-propionamidobenzoic acid (10a)

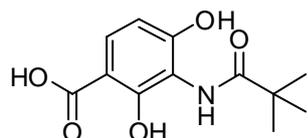
17 mg as a brown solid, yield 81%. $^1\text{H NMR}$ (400 MHz, DMSO) δ 13.49 (br s, 1H), 11.81 (s, 1H), 10.29 (s, 1H), 8.95 (s, 1H), 7.55 (d, $J = 8.8$ Hz, 1H), 6.48 (d, $J = 8.8$ Hz, 1H), 2.33 (q, $J = 7.5$ Hz, 2H), 1.07 (t, $J = 7.5$ Hz, 3H); $^{13}\text{C NMR}$ (101 MHz, DMSO) δ 172.7, 172.1, 159.2, 158.9, 128.7, 112.8, 107.8, 104.3, 28.3, 9.7; HRMS calcd for $\text{C}_{10}\text{H}_{12}\text{NO}_5^+$ ($\text{M}+\text{H}$) $^+$ 226.0710, found 226.0716; LCMS calcd for $\text{C}_{10}\text{H}_{10}\text{NO}_5^-$ ($\text{M}-\text{H}$) $^-$ 224.1, t_{R} 4.26 min, found 224.2; HPLC purity: 98.3%, t_{R} 6.48 min (isocratic); 98.4%, t_{R} 5.97 min (gradient).

3-Butyramido-2,4-dihydroxybenzoic acid (10b)



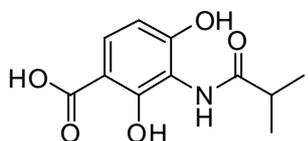
46 mg as a dark red solid, yield 85%. ^1H NMR (400 MHz, DMSO) δ 13.51 (br s, 1H), 11.81 (s, 1H), 10.28 (s, 1H), 8.97 (s, 1H), 7.55 (d, $J = 8.8$ Hz, 1H), 6.47 (d, $J = 8.8$ Hz, 1H), 2.30 (t, $J = 7.2$ Hz, 2H), 1.65 – 1.54 (m, 2H), 0.94 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (101 MHz, DMSO) δ 172.2, 172.0, 159.2, 159.0, 128.8, 112.9, 107.8, 104.4, 37.1, 18.7, 13.5; HRMS calcd for $\text{C}_{11}\text{H}_{14}\text{NO}_5^+$ (M+H) $^+$ 240.0866, found 240.0868; LCMS calcd for $\text{C}_{11}\text{H}_{14}\text{NO}_5^+$ (M+H) $^+$ 240.1, t_{R} 4.87 min, found 240.1; HPLC purity: >99%, t_{R} 4.41 min (isocratic); >99%, t_{R} 6.93 min (gradient).

2,4-Dihydroxy-3-pivalamidobenzoic acid (10c)



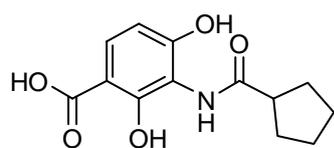
36 mg, yield 84%. ^1H NMR (400 MHz, d_6 -acetone) δ 12.11 (br s, 1H), 11.07 (s, 1H), 11.03 (s, 1H), 8.44 (s, 1H), 7.65 (d, $J = 8.9$ Hz, 1H), 6.50 (d, $J = 8.9$ Hz, 1H), 1.39 (s, 9H); ^{13}C NMR (101 MHz, DMSO) δ 177.2, 172.2, 159.6, 159.4, 128.9, 113.2, 107.7, 104.3, 27.4, 27.3; HRMS calcd for $\text{C}_{12}\text{H}_{16}\text{NO}_5^+$ (M+H) $^+$ 254.1023, found 254.1020; LCMS calcd for $\text{C}_{12}\text{H}_{16}\text{NO}_5^+$ (M+H) $^+$ 254.1, t_{R} 5.36 min, found 254.2; HPLC purity: 97.1%, t_{R} 4.46 min (isocratic); 95.5%, t_{R} 8.23 min (gradient).

2,4-Dihydroxy-3-isobutyramidobenzoic acid (10d)



74 mg, yield 88%. ^1H NMR (400 MHz, DMSO) δ 13.45 (br s, 1H), 11.80 (s, 1H), 10.22 (s, 1H), 8.92 (s, 1H), 7.56 (d, $J = 8.8$ Hz, 1H), 6.45 (d, $J = 8.8$ Hz, 1H), 2.69 (sept, $J = 6.7$ Hz, 1H), 1.10 (d, $J = 6.8$ Hz, 6H); ^{13}C NMR (101 MHz, DMSO) δ 176.1, 172.2, 159.1, 158.8, 128.7, 112.9, 107.8, 104.3, 33.8, 19.5; HRMS calcd for $\text{C}_{11}\text{H}_{12}\text{NO}_5^-$ (M-H) $^-$ 238.0721, found 238.0719; LCMS calcd for $\text{C}_{11}\text{H}_{12}\text{NO}_5^-$ (M-H) $^-$ 238.1, t_{R} 6.13 min, found 238.1; HPLC purity: >99%, t_{R} 5.86 min (isocratic); 95.2%, t_{R} 7.24 min (gradient).

3-(Cyclopentanecarboxamido)-2,4-dihydroxybenzoic acid (10e)



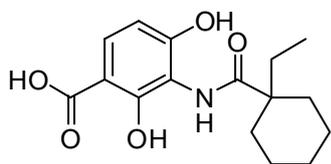
83 mg, yield 94%. ^1H NMR (400 MHz, DMSO) δ 13.49 (br s, 1H), 11.74 (s, 1H), 10.21 (s, 1H), 8.93 (s, 1H), 7.56 (d, $J = 8.8$ Hz, 1H), 6.44 (d, $J = 8.8$ Hz, 1H), 2.89 (app p, $J = 7.9$ Hz, 1H), 1.89 – 1.49 (m, 8H); ^{13}C NMR (101 MHz, DMSO) δ 175.4, 172.2, 159.1, 158.9, 128.8, 113.1, 107.9, 104.4, 44.0, 30.0, 25.7; HRMS calcd for $\text{C}_{13}\text{H}_{16}\text{NO}_5^+$ ($\text{M}+\text{H}$) $^+$ 266.1023, found 266.1036; LCMS calcd for $\text{C}_{13}\text{H}_{16}\text{NO}_5^+$ ($\text{M}+\text{H}$) $^+$ 266.1, t_{R} 5.39 min, found 266.2; HPLC purity; 97.7%, t_{R} 4.91 min (isocratic); 95.2%, t_{R} 8.48 min (gradient).

3-(Cyclohexanecarboxamido)-2,4-dihydroxybenzoic acid (10f)



22 mg, yield 76%. ^1H NMR (400 MHz, DMSO) δ 13.51 (br s, 1H), 11.75 (s, 1H), 10.22 (s, 1H), 8.89 (s, 1H), 7.55 (d, $J = 8.8$ Hz, 1H), 6.44 (d, $J = 8.8$ Hz, 1H), 2.47 – 2.39 (m, 1H), 1.86 – 1.60 (m, 6H), 1.45 – 1.14 (m, 4H); ^{13}C NMR (101 MHz, DMSO) δ 175.2, 172.2, 159.1, 158.8, 128.7, 113.0, 107.9, 104.4, 43.7, 29.3, 25.5, 25.2; HRMS calcd for $\text{C}_{14}\text{H}_{18}\text{NO}_5^+$ ($\text{M}+\text{H}$) $^+$ 280.1179, found 280.1190; LCMS calcd for $\text{C}_{14}\text{H}_{18}\text{NO}_5^+$ ($\text{M}+\text{H}$) $^+$ 280.1, t_{R} 5.73 min, found 280.1; HPLC purity: >99%, t_{R} 7.03 min (isocratic); 96.9%, t_{R} 9.27 min (gradient).

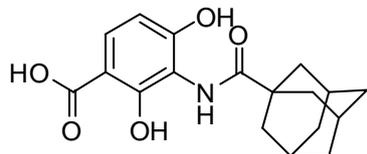
3-(1-Ethylcyclohexanecarboxamido)-2,4-dihydroxybenzoic acid (10g)



63 mg, yield 93%. ^1H NMR (400 MHz, DMSO) δ 13.45 (br s, 1H), 11.68 (s, 1H), 10.24 (s, 1H), 8.38 (s, 1H), 7.56 (d, $J = 8.8$ Hz, 1H), 6.44 (d, $J = 8.8$ Hz, 1H), 2.20 – 2.07 (m, 2H), 1.59 – 1.44 (m, 7H), 1.23 – 1.08 (m, 3H), 0.87 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (101 MHz, DMSO) δ 174.5, 172.3, 159.7, 159.5, 128.8, 113.2, 107.5, 104.2, 46.4, 33.7, 33.3, 25.8, 22.6, 8.1; HRMS calcd for $\text{C}_{16}\text{H}_{22}\text{NO}_5^+$ ($\text{M}+\text{H}$) $^+$ 308.1492, found 308.1505; LCMS calcd for

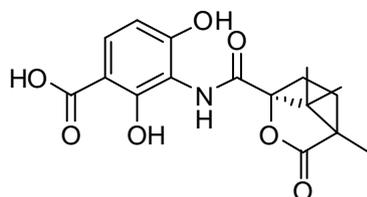
$C_{16}H_{22}NO_5^+$ (M+H)⁺ 308.1, t_R 6.20 min, 308.2; HPLC purity: >99%, t_R 11.2 min (isocratic); 97.8%, t_R 10.4 min (gradient).

3-((3r,5r,7r)-Adamantane-1-carboxamido)-2,4-dihydroxybenzoic acid (10h)



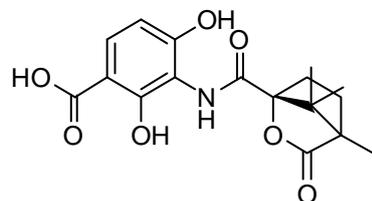
13 mg, yield 76%. ¹H NMR (400 MHz, DMSO) δ 13.49 (br s, 1H), 11.82 (s, 1H), 10.20 (s, 1H), 8.33 (s, 1H), 7.55 (d, J = 8.8 Hz, 1H), 6.43 (d, J = 8.8 Hz, 1H), 2.00 (s, 3H), 1.91 (d, J = 2.7 Hz, 6H), 1.69 (s, 6H); ¹³C NMR (101 MHz, DMSO) δ 176.6, 172.1, 159.2, 159.1, 128.7, 113.1, 107.6, 104.3, 40.3, 38.6, 36.0, 27.6; HRMS calcd for $C_{18}H_{22}NO_5^+$ (M+H)⁺ 332.1492, found 332.1496; LCMS calcd for $C_{18}H_{22}NO_5^+$ (M+H)⁺ 332.1, t_R 6.29 min, found 332; HPLC purity: 95.4%, t_R 8.38 min (isocratic); 96.3%, t_R 11.4 min (gradient).

2,4-Dihydroxy-3-((1S)-4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxamido)benzoic acid (10i)



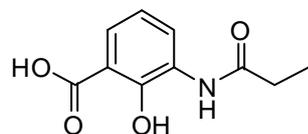
83 mg, yield 89%. ¹H NMR (400 MHz, DMSO) δ 13.55 (br s, 1H), 11.72 (s, 1H), 10.41 (s, 1H), 8.84 (s, 1H), 7.59 (d, J = 8.8 Hz, 1H), 6.46 (d, J = 8.8 Hz, 1H), 2.49 – 2.43 (m, 1H), 1.97 (tt, J = 17.0, 5.5 Hz, 1H), 1.89 (ddd, J = 13.4, 9.2, 4.4 Hz, 1H), 1.57 (ddd, J = 16.0, 10.1, 5.4 Hz, 1H), 1.03 (s, 3H), 1.01 (s, 3H), 1.00 (s, 3H); ¹³C NMR (101 MHz, DMSO) δ 178.2, 172.2, 165.3, 159.9, 159.6, 129.5, 111.6, 107.4, 104.3, 92.4, 54.5, 53.4, 29.7, 28.4, 16.4, 16.3, 9.6; HRMS calcd for $C_{17}H_{20}NO_7^+$ (M+H)⁺ 350.1234, found 350.1237; LCMS calcd for $C_{17}H_{18}NO_7^-$ (M-H)⁻ 348.1, t_R 5.58 min, found 348.1; HPLC purity: >99%, t_R 4.77 min (isocratic); >99%, t_R 7.87 min (gradient).

2,4-Dihydroxy-3-((1R)-4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxamido)benzoic acid (10j)



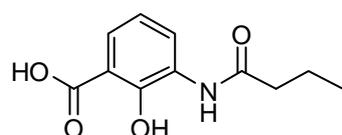
36 mg, yield 71%. $^1\text{H NMR}$ (400 MHz, DMSO) δ 13.52 (br s, 1H), 11.74 (s, 1H), 10.41 (s, 1H), 8.84 (s, 1H), 7.59 (d, $J = 8.8$ Hz, 1H), 6.45 (d, $J = 8.8$ Hz, 1H), 2.49 – 2.41 (m, 1H), 1.96 (tt, $J = 17.1, 5.5$ Hz, 1H), 1.88 (ddd, $J = 13.4, 9.1, 4.4$ Hz, 1H), 1.57 (ddd, $J = 12.8, 9.1, 4.1$ Hz, 1H), 1.03 (s, 3H), 1.01 (s, 3H), 1.00 (s, 3H); $^{13}\text{C NMR}$ (101 MHz, DMSO) δ 178.2, 172.2, 165.3, 159.9, 159.6, 129.5, 111.6, 107.4, 104.3, 92.4, 54.5, 53.4, 29.7, 28.4, 16.4, 16.3, 9.6; HRMS calcd for $\text{C}_{17}\text{H}_{18}\text{NO}_7^-$ (M-H) $^-$ 348.1089, found 348.1089; LCMS calcd for $\text{C}_{17}\text{H}_{18}\text{NO}_7^-$ (M-H) $^-$ 348.1, t_{R} 5.27 min, found 348.1; HPLC purity: 98.6%, t_{R} 5.07 min (isocratic); 96.2%, t_{R} 8.02 min (gradient).

2-Hydroxy-3-propionamidobenzoic acid (10k)



93 mg as a brown solid, yield 93%. $^1\text{H NMR}$ (400 MHz, DMSO) δ 11.98 (br s, 1H), 9.20 (s, 1H), 8.11 (dd, $J = 7.8, 1.6$ Hz, 1H), 7.53 (dd, $J = 8.0, 1.4$ Hz, 1H), 6.88 (app t, $J = 8.0$ Hz, 1H), 2.40 (q, $J = 7.5$ Hz, 2H), 1.06 (t, $J = 7.5$ Hz, 3H); $^{13}\text{C NMR}$ (101 MHz, DMSO) δ 172.5, 172.3, 152.3, 127.7, 127.0, 124.8, 118.4, 112.6, 29.1, 9.6; HRMS calcd for $\text{C}_{10}\text{H}_{12}\text{NO}_4^+$ (M+H) $^+$ 210.0761, found 210.0759; LCMS calcd for $\text{C}_{10}\text{H}_{12}\text{NO}_4^+$ (M+H) $^+$ 210.1, t_{R} 4.87 min, found 210.1; HPLC purity: >99%, t_{R} 5.11 min (isocratic); 97.7%, t_{R} 6.81 min (gradient).

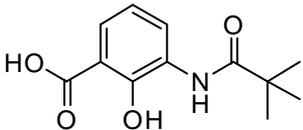
3-Butyramido-2-hydroxybenzoic acid (10l)



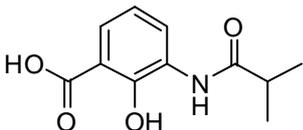
91 mg, yield 96%. $^1\text{H NMR}$ (400 MHz, DMSO) δ 11.92 (br s, 1H), 9.21 (s, 1H), 8.13 (dd, $J = 7.7, 1.6$ Hz, 1H), 7.54 (dd, $J = 7.9, 1.3$ Hz, 1H), 6.89 (app t, $J = 8.0$ Hz, 1H), 2.39 (t, $J = 7.3$ Hz, 2H), 1.66 – 1.55 (m, 2H),

0.92 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (101 MHz, DMSO) δ 172.3, 171.5, 152.4, 127.8, 127.0, 124.8, 118.3, 112.6, 37.8, 18.6, 13.6; HRMS calcd for $\text{C}_{11}\text{H}_{14}\text{NO}_4^+$ (M+H) $^+$ 224.0917, found 224.0911; LCMS calcd for $\text{C}_{11}\text{H}_{12}\text{NO}_4^-$ (M-H) $^-$ 222.1, t_{R} 5.18 min, found 222.1; HPLC purity: 98.8%, t_{R} 4.37 min (isocratic); 98.8%, t_{R} 7.64 min (gradient).

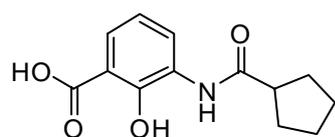
2-Hydroxy-3-pivalamidobenzoic acid (10m)

 101 mg as a dark red solid, yield 94%. ^1H NMR (400 MHz, DMSO) δ 12.01 (br s, 1H), 8.52 (s, 1H), 8.03 (dd, $J = 7.9, 1.6$ Hz, 1H), 7.58 (dd, $J = 8.0, 1.6$ Hz, 1H), 6.91 (app t, $J = 8.0$ Hz, 1H), 1.25 (s, 9H); ^{13}C NMR (101 MHz, DMSO) δ 176.2, 172.1, 152.8, 128.1, 126.9, 125.1, 118.4, 112.6, 39.1, 27.1; HRMS calcd for $\text{C}_{12}\text{H}_{16}\text{NO}_4^+$ (M+H) $^+$ 238.1074, found 238.1075; LCMS calcd for $\text{C}_{12}\text{H}_{14}\text{NO}_4^-$ (M-H) $^-$ 236.1, t_{R} 5.56 min, found 236.1; HPLC purity: >99%, t_{R} 7.21 min (isocratic); >99%, t_{R} 8.71 min (gradient).

2-Hydroxy-3-isobutyramidobenzoic acid (10n)

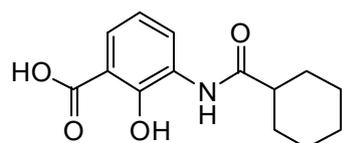
 96 mg, yield 93%. ^1H NMR (400 MHz, DMSO) δ 11.84 (br s, 1H), 9.14 (s, 1H), 8.12 (dd, $J = 7.8, 1.0$ Hz, 1H), 7.55 (dd, $J = 8.0, 1.6$ Hz, 1H), 6.89 (app t, $J = 8.0$ Hz, 1H), 2.82 (sept, $J = 6.8$ Hz, 1H), 1.10 (d, $J = 6.8$ Hz, 6H); ^{13}C NMR (101 MHz, DMSO) δ 175.6, 172.3, 152.5, 127.9, 127.0, 124.8, 118.3, 112.6, 34.3, 19.5; HRMS calcd for $\text{C}_{11}\text{H}_{14}\text{NO}_4^+$ (M+H) $^+$ 224.0917, found 224.0915; LCMS calcd for $\text{C}_{11}\text{H}_{12}\text{NO}_4^-$ (M-H) $^-$ 222.1, t_{R} 5.22 min, found 222.1; HPLC purity: >99%, t_{R} 4.47 min (isocratic); >99%, t_{R} 7.64 min (gradient).

3-(Cyclopentanecarboxamido)-2-hydroxybenzoic acid (10o)



84 mg, yield 87%. ^1H NMR (400 MHz, DMSO) δ 12.08 (br s, 1H), 9.13 (s, 1H), 8.13 (dd, $J = 7.9, 1.0$ Hz, 1H), 7.54 (dd, $J = 8.0, 1.6$ Hz, 1H), 6.88 (app t, $J = 8.0$ Hz, 1H), 3.05 – 2.94 (m, 1H), 1.90 – 1.78 (m, 2H), 1.77 – 1.61 (m, 4H), 1.61 – 1.48 (m, 2H). ^{13}C NMR (101 MHz, DMSO) δ 174.8, 172.3, 152.4, 127.7, 127.1, 124.7, 118.3, 112.5, 44.6, 30.1, 25.7; HRMS calcd for $\text{C}_{13}\text{H}_{16}\text{NO}_4^+$ (M+H) $^+$ 250.1074, found 250.1069; LCMS calcd for $\text{C}_{13}\text{H}_{16}\text{NO}_4^+$ (M+H) $^+$ 250.1, t_{R} 5.55 min, found 250.1; HPLC purity: >99%, t_{R} 7.58 min (isocratic); >99%, t_{R} 8.77 min (gradient).

3-(Cyclohexanecarboxamido)-2-hydroxybenzoic acid (10p)



44 mg, yield 77%. ^1H NMR (400 MHz, DMSO) δ 12.03 (br s, 1H), 9.10 (s, 1H), 8.10 (dd, $J = 7.8, 1.0$ Hz, 1H), 7.54 (dd, $J = 8.0, 1.5$ Hz, 1H), 6.89 (app t, $J = 8.0$ Hz, 1H), 2.59 – 2.50 (m, 1H), 1.85 – 1.60 (m, 6H), 1.46 – 1.14 (m, 4H); ^{13}C NMR (101 MHz, DMSO) δ 174.7, 172.3, 152.4, 127.8, 127.0, 124.8, 118.3, 112.6, 44.2, 29.2, 25.4, 25.1; HRMS calcd for $\text{C}_{14}\text{H}_{18}\text{NO}_4^+$ (M+H) $^+$ 264.1230, found 264.1229; LCMS calcd for $\text{C}_{14}\text{H}_{18}\text{NO}_4^+$ (M+H) $^+$ 264.1, t_{R} 6.02 min, 264.1; HPLC purity: 99.0%, t_{R} 12.1 min (isocratic); 95.6%, t_{R} 9.43 min (gradient).

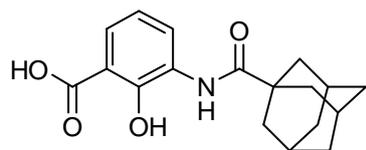
3-(1-Ethylcyclohexanecarboxamido)-2-hydroxybenzoic acid (10q)



51 mg, yield 94%. ^1H NMR (400 MHz, DMSO) δ 11.76 (br s, 1H), 8.53 (s, 1H), 7.92 (dd, $J = 7.9, 1.6$ Hz, 1H), 7.59 (dd, $J = 8.0, 1.6$ Hz, 1H), 6.91 (app t, $J = 7.9$ Hz, 1H), 2.13 – 2.03 (m, 2H), 1.56 (dd, $J = 15.0, 7.5$ Hz, 5H), 1.40 (ddd, $J = 13.9, 9.2, 3.3$ Hz, 2H), 1.31 – 1.20 (m, 3H), 0.81 (t, $J = 7.5$ Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 174.1, 172.2, 153.3, 129.2, 126.8, 125.5, 118.4, 112.7, 46.9,

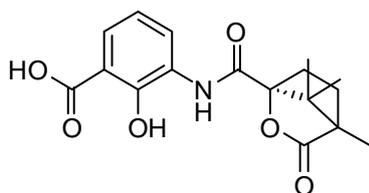
33.3, 32.8, 25.6, 22.6, 8.2; HRMS calcd for $C_{16}H_{20}NO_4^-$ (M-H) $^-$ 290.1398, found 290.1400; LCMS calcd for $C_{16}H_{22}NO_4^+$ (M+H) $^+$ 292.2, t_R 6.22 min, found 292.1; HPLC purity: 99.0%, t_R 12.4 min (isocratic); 95.9%, t_R 10.8 min (gradient).

3-((3r,5r,7r)-Adamantane-1-carboxamido)-2-hydroxybenzoic acid (10r)



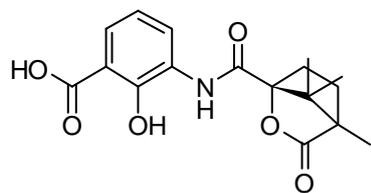
9 mg, yield 90%. 1H NMR (400 MHz, DMSO) δ 12.03 (br s, 1H), 9.10 (s, 1H), 8.10 (dd, $J = 7.8, 1.0$ Hz, 1H), 7.54 (dd, $J = 8.0, 1.5$ Hz, 1H), 6.89 (app t, $J = 8.0$ Hz, 1H), 2.03 (s, 3H), 1.94 – 1.88 (m, 6H), 1.73 – 1.69 (m, 6H). ^{13}C NMR (101 MHz, DMSO) δ 174.2, 172.1, 153.1, 129.1, 127.0, 125.4, 118.1, 112.3, 40.9, 38.4, 35.8, 27.4; HRMS calcd for $C_{18}H_{22}NO_4^+$ (M+H) $^+$ 316.1543, found 316.1535; LCMS calcd for $C_{18}H_{20}NO_4^-$ (M-H) $^-$ 314.1, t_R 6.06 min, found 314.1; HPLC purity: 97.8%, t_R 7.38 min (isocratic); 98.4%, t_R 9.74 min (gradient).

2-Hydroxy-3-((1S)-4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxamido)benzoic acid (10s)



102 mg, yield 86%. 1H NMR (400 MHz, DMSO) δ 11.99 (br s, 1H), 9.19 (s, 1H), 8.96 (s, 1H), 8.14 (dd, $J = 7.9, 1.5$ Hz, 1H), 7.63 (dd, $J = 8.0, 1.5$ Hz, 1H), 6.96 (app t, $J = 8.0$ Hz, 1H), 2.52 – 2.45 (m, 1H), 2.08 – 1.91 (m, 2H), 1.67 – 1.58 (m, 1H), 1.07 (s, 3H), 1.05 (s, 3H), 0.92 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 177.5, 171.9, 165.0, 152.3, 127.3, 126.0, 125.5, 118.7, 113.0, 92.0, 54.7, 53.7, 29.8, 28.3, 16.3, 16.2, 9.5; HRMS calcd for $C_{17}H_{20}NO_6^+$ (M+H) $^+$ 334.1285, found 334.1290; LCMS calcd for $C_{17}H_{20}NO_6^+$ (M+H) $^+$ 334.1, t_R 6.10 min, found 334.1; HPLC purity: 99.0%, t_R 14.5 min (isocratic); >99%, t_R 10.8 min (gradient).

2-Hydroxy-3-((1*R*)-4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxamido)benzoic acid (10t)



129 mg, yield 84%. ^1H NMR (400 MHz, DMSO) δ 12.01 (br s, 1H), 9.22 (s, 1H), 8.98 (s, 1H), 8.18 (dd, $J = 8.0, 1.5$ Hz, 1H), 7.60 (dd, $J = 8.0, 1.5$ Hz, 1H), 6.96 (app t, $J = 8.0$ Hz, 1H), 2.50 – 2.43 (m, 1H), 2.06 – 1.90 (m, 2H), 1.65 – 1.53 (m, 1H), 1.05 (s, 3H), 1.03 (s, 3H), 0.90 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 177.4, 171.9, 165.0, 152.2, 127.3, 126.0, 125.5, 118.7, 113.0, 92.1, 54.7, 53.7, 29.8, 28.3, 16.3, 16.2, 9.5; HRMS calcd for $\text{C}_{17}\text{H}_{20}\text{NO}_6^+$ ($\text{M}+\text{H}$) $^+$ 334.1285, found 334.1280; LCMS calcd for $\text{C}_{17}\text{H}_{18}\text{NO}_6^-$ ($\text{M}-\text{H}$) $^-$ 332.1, t_{R} 5.83 min, found 332.1; HPLC purity: >99%, t_{R} 15.4 min (isocratic); >99%, t_{R} 9.60 min (gradient).