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SUPPORTING INFORMATION

Uncharged nucleoside inhibitors of β-1,4-galactosyltransferase with activity in cells

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CONTENT

(1) .... Experimental section

(2) .... Additional tables

(3) .... ^{1}H, ^{13}C and ^{31}P NMR spectra

(4) .... GalT inhibition experiments

(5) .... Control experiments

(6) .... PSGL-1 expression assay

(7) .... Cell viability assay

(8) .... References

(1) Experimental section.

General. All chemical reagents were obtained commercially and used as received, unless stated otherwise. Microwave-assisted reactions were carried out on a Monowave 300 microwave synthesis reactor from Anton Paar. Thin layer chromatography (TLC) was performed on pre-coated plates of Silica Gel 60 F_{254} (Merck), with IPA:H_2O:NH_3 = 6:3:1 as the mobile phase, unless otherwise stated. Spots were visualised under UV light (254/365nm). NMR spectra were recorded at 300 K on a Bruker BioSpin machine at, respectively, 400.13 MHz (^{1}H-NMR), 100.62 MHz (^{13}C-NMR) and 161 MHz (^{31}P-NMR). Prior to the recording of ^{31}P-NMR spectra, a drop of triethylamine was added to each sample to suppress line broadening and enhance resolution. Chemicals shifts (δ) are reported in ppm (parts per million) and coupling constants (J) in Hz. Mass spectra were recorded at the EPSRC National Mass Spectrometry Facility in Swansea. All yields (%) are isolated yields.

Column chromatography. Preparative reverse-phase chromatography was performed on a Biologic LP chromatography system equipped with a peristaltic pump and a 254 nm UV Optics Module under the following conditions: Ion-pair chromatography was performed using Lichroprep RP-18 resin equilibrated with 0.05 M TEAB (triethylammonium bicarbonate, pH 7.3). Gradient: 0-30 % MeOH against 0.05 M TEAB over a total volume of 400 mL. Flow rate: 2 mL/min. Product-containing fractions were combined and repeatedly co-evaporated with methanol to remove residual TEAB.

Suzuki cross-coupling reactions: compounds 2a-j.

General method A: 5-Iodouridine [1] (1 equiv.), boronic acid (1.5 equiv.) and Cs_2CO_3 (2 equiv.) in degassed water were combined in a sealable microwave tube under nitrogen atmosphere. Na_2PdCl_4 (0.025 equiv.) and TPPTs (0.0625 equiv.) were added. The vessel was sealed and the mixture was heated in the microwave reactor at 120°C for 30min. After cooling to room temperature, the solvent was evaporated and the reaction purified by column chromatography.

General method B. 5-Iodouridine [1] (1 equiv.) and boronic acid (1.5 equiv.) in degassed DME/water (3:1) were combined in a sealable microwave tube under nitrogen atmosphere. $PdCl_2$(dppf)DCM (0.05 equiv.) and $NaHCO_3$ (3 equiv.) were added. The vessel was sealed and the mixture was heated in the microwave reactor at 130°C for 30min. After cooling to room temperature, the solvent was evaporated and the reaction purified by column chromatography.

General method C. 5-Iodouridine [1] (1 equiv.) and boronic acid (1.5 equiv.) in degassed dioxane/water (3:1) were combined in a sealable microwave tube under nitrogen atmosphere. $PdCl_2$(dppf)DCM (0.05 equiv.) and $NaHCO_3$ (3 equiv.) were added. The vessel was sealed and the mixture was heated in the microwave reactor at 130°C for 30min. After cooling to room temperature, the solvent was evaporated and the reaction purified by column chromatography.

General method D: 5-Iodouridine [1] (1 equiv.) and boronic acid (1.5 equiv.) were combined in degassed DME in a sealable microwave tube under nitrogen atmosphere. $PdCl_2$(dppf)DCM (0.05 equiv.) and K_2CO_3 (2 equiv.) were added. The vessel was sealed and the mixture was heated in the microwave reactor at 130°C for 30min. After cooling to room temperature, the solvent was evaporated and the reaction purified by column chromatography.

5-(1,2,3,4-tetrahydro-1-((2*R*,3*S*,4*R*,5*R*)-tetrahydro-3,4-dihydroxy-5-(hydroxymethyl)furan-2-yl)-2,4-dioxopyrimidin-5-yl)thiophene-2-carbaldehyde (2a). Compound **2a** was synthesised from 5-iodouridine (50 mg, 0.135 mmol) and 5-formyl-2-thiopheneboronic acid via general method A, and obtained as a white powder in a yield of 54 % (25.5 mg). ^{1}H-NMR (400 MHz, MeOD) 3.85 (1H, dd, J = 2, 12 Hz), 4.03 (1H, dd, J = 2.4, 12 Hz), 4.11 (1H, m), 4.28 (2H, m), 5.99 (1H, d, J = 3.2 Hz), 7.63 (1H, d, J = 4 Hz), 7.84 (1H, d, J = 4 Hz), 9.12 (1H, s), 9.86 (1H, s). ^{13}C-NMR (100 MHz, DMSO-d_6) 59.5, 68.6,

74.4, 84.3, 89.4, 106.7, 122.7, 137.1, 138.5, 141.4, 144.2, 149.2, 161.2, 184.1. m/z (ESI) 355.0627 $[M+H]^+$, $C_{14}H_{15}N_2O_7S$ requires 355.0600.

1-((2*R*,3*S*,4*R*,5*R*)-tetrahydro-3,4-dihydroxy-5-(hydroxymethyl)furan-2-yl)-5-(pyridin-3-yl) pyrimidine-2,4(1*H*,3*H*)-dione (2b). Compound **2b** was synthesised from 5-iodouridine (20 mg, 0.054 mmol) and 3-pyridineboronic acid via general method B, and obtained as a white powder in a yield of 20 % (4.1 mg). ^{1}H-NMR (400 MHz, MeOD) 3.80 (1H, dd, *J* = 2.4, 12 Hz), 3.93 (1H, dd, *J* = 2.8, 12 Hz), 4.07 (1H, m), 4.27 (2H, m), 5.99 (1H, d, *J* = 3.2 Hz), 7.47 (1H, m), 8.08 (1H, dt, *J* = 2.0, 8.0 Hz), 8.48 (1H, dd, *J* = 1.6, 5.2 Hz), 8.59 (1H, s), 8.78 (1H, d, *J* = 1.2, 2.4 Hz). ^{13}C-NMR (100 MHz, MeOD) 61.6, 70.8, 76.3, 86.2, 91.2, 112.2, 124.9, 131.4, 137.8, 140.8, 140.9, 148.7, 149.3, 152.0. m/z (ESI) 322.2961 $[M+H]^+$, $C_{14}H_{16}N_3O_6$ requires 322.1039.

1-((2*R*,3*S*,4*R*,5*R*)-tetrahydro-3,4-dihydroxy-5-(hydroxymethyl)furan-2-yl)-5-(pyridin-4-yl) pyrimidine-2,4(1*H*,3*H*)-dione (2c). Compound **2c** was synthesised from 5-iodouridine (20 mg, 0.054 mmol) and 4-pyridineboronic acid via general method B, and obtained as a light yellow powder in a yield of 27 % (5 mg). ^{1}H-NMR (400 MHz, D_2O) 3.66 (1H, dd, *J* = 5.6, 12.8 Hz), 3.78 (1H, dd, *J* = 3.2, 12.4 Hz), 3.99 (1H, m), 4.28 (1H, t, *J* = 6 Hz), 4.38 (1H, m), 5.75 (1H, d, *J* = 3.2 Hz), 6.49 (2H, d, *J* = 7.6 Hz), 7.80 (1H, d, *J* = 6.8 Hz), 7.94 (1H, s). ^{13}C-NMR (100 MHz, DMSO-d_6) 60.1, 69.3, 73.9, 84.7, 88.2, 127.9, 128.0, 128.6, 145.1, 146.0, 148.1, 150.1, 150.3, 160.5. m/z (ESI) 322.2951 $[M+H]^+$, $C_{14}H_{16}N_3O_6$ requires 322.1039.

1-((2*R*,3*S*,4*R*,5*R*)-tetrahydro-3,4-dihydroxy-5-(hydroxymethyl)furan-2-yl)-5-(isoquinolin-4-yl) pyrimidine-2,4(1*H*,3*H*)-dione (2d). Compound **2d** was synthesised from 5-iodouridine (20 mg, 0.054 mmol) and 4-isoquinolineboronic acid via general method A, and obtained as a light yellow powder in a yield of 25 % (4.7 mg). ^{1}H-NMR (400 MHz, MeOD), 3.67 (1H, dd, *J* = 2.8, 12 Hz), 3.79 (1H, dd, *J* = 2.8, 12 Hz), 4.05 (1H, m), 4.22 (1H, t, *J* = 5.2 Hz), 4.32 (1H, t, *J* = 4.8 Hz), 6.04 (1H, d, *J* = 4.4 Hz), 7.73 (1H, dt, *J* = 1.2, 6.8 Hz), 7.81 (1H, dt, *J* = 1.2, 7.6 Hz), 7.87 (1H, m), 8.17 (1H, dd, *J* = 1.2, 8.4 Hz), 8.37 (1H, s), 8.39 (1H, s), 9.26 (1H, s). ^{13}C-NMR (100 MHz, MeOD) 61.8, 71.1, 76.1, 86.4, 91.0, 111.9, 126.1, 127.0, 127.1, 129.1, 129.3, 129.9, 132.4, 136.8, 142.5, 143.8, 152.7, 153.8. m/z (ESI) 372.1290 $[M+H]^+$, $C_{18}H_{18}N_3O_6$ requires 372.1196.

1-((2*R*,3*S*,4*R*,5*R*)-tetrahydro-3,4-dihydroxy-5-(hydroxymethyl)furan-2-yl)-5-(1*H*-indol-4-yl) pyrimidine-2,4(1*H*,3*H*)-dione (2e). Compound **2e** was synthesised from 5-iodouridine (60 mg, 0.162 mmol) and indole-4-boronic acid via general method A, and obtained as a white powder in a yield of 43 % (18 mg). ^{1}H-NMR (400 MHz, MeOD) 3.67 (1H, dd, *J* = 3.2, 12 Hz), 3.77 (1H, dd, *J* = 2.8, 12 Hz), 4.04 (1H, m), 4.18 (1H, t, *J* = 5.6 Hz), 4.32 (1H, t, *J* = 5.2 Hz), 6.06 (1H, d, *J* = 5.2 Hz), 6.42 (1H, d, *J* = 3.2 Hz), 7.08 (1H, d, *J* = 1.2, 7.2 Hz), 7.17 (1H, t, *J* = 7.6 Hz), 7.27 (1H, d , *J* = 3.2 Hz), 7.40 (1H, d, *J* = 8 Hz), 8.23 (1H, s). ^{13}C-NMR (100 MHz, MeOD) 62.4, 71.2, 75.8, 86.5 90.6, 101.8, 112.2, 116.5, 121.4, 122.1, 125.7, 125.9, 128.5, 137.9, 140.6, 152.5, 164.9. m/z (ESI) 360.1193 $[M+H]^+$, $C_{17}H_{18}N_3O_6$ requires 360.1196.

1-((2*R*,3*S*,4*R*,5*R*)-tetrahydro-3,4-dihydroxy-5-(hydroxymethyl)furan-2-yl)-5-(2-(4-methylpiperazin-1-yl)pyridin-4-yl) pyrimidine-2,4(1*H*,3*H*)-dione (2f). Compound **2f** was synthesised from 5-iodouridine (20 mg, 0.054 mmol) and 2-(4-methylpiperazin-1-yl)pyridine-4-boronic acid via general method B, and obtained as a white powder in a yield of 35 % (8 mg). ^{1}H-NMR (400 MHz, MeOD) 2.36 (3H, s), 2.60 (4H, m), 3.57 (4H, m), 3.80 (1H, dd, *J* = 2.4, 12.4 Hz), 3.93 (1H, dd, *J* = 2.4, 12.4 Hz), 4.08 (1H, m), 4.7 (1H, m), 5.99 (1H, d, *J* = 3.6 Hz), 6.97 (1H, dd, *J* = 1.2, 5.6 Hz), 7.19 (1H, s), 8.07 (1H, d, *J* = 1.2, 5.6 Hz), 8.64 (1H, s). ^{13}C-NMR (100 MHz, MeOD) 46.1, 46.3, 55.7, 61.6, 70.9, 76.4, 86.3, 91.2, 107.9, 113.3, 113.8, 141.5, 144.4, 148.3, 151.8, 161.2, 164.0. m/z (ESI) 420.1911 $[M+H]^+$, $C_{19}H_{26}N_5O_6$ requires 420.1883.

1-((2*R*,3*S*,4*R*,5*R*)-tetrahydro-3,4-dihydroxy-5-(hydroxymethyl)furan-2-yl)-5-(1*H*-indazol-4-yl) pyrimidine-2,4(1*H*,3*H*)-dione (2g). Compound **2g** was synthesized from 5-iodouridine (60 mg, 0.152

mmol) and 1H-indazole-4-boronic acid via general method D, and obtained as a light grey powder in a yield of 10 % (6 mg). ^{1}H-NMR (400 MHz, MeOD) 3.70 (1H, dd, *J* = 2.4, 12 Hz), 3.82 (1H, dd, *J* = 2.8, 12 Hz), 4.06 (1H, m), 4.22 (1H, t, *J* = 4.8 Hz), 4.33 (1H, t, *J* = 4.4 Hz), 6.06 (1H, d, *J* = 4.8 Hz), 7.22 (1H, d, *J* = 8 Hz), 7.43 (1H, dd, *J* = 8.8, 7.2 Hz), 7.54 (1H, d, *J* = 8.4 Hz), 8.01 (1H, s), 8.44 (1H, s). ^{13}C-NMR (100 MHz, MeOD) 62.1, 71.5, 76.1, 86.5, 90.7, 110.9, 115.0, 122.6, 123.3, 127.5, 127.8, 127.9, 135.0, 141.2, 152.3, 164.5. m/z (ESI) 361.1146 $[M+H]^+$, $C_{16}H_{17}N_4O_6$ requires 361.1148.

1-((2*R*,3*S*,4*R*,5*R*)-tetrahydro-3,4-dihydroxy-5-(hydroxymethyl)furan-2-yl)-5-(1-methyl-1*H*-indol-4-yl) pyrimidine-2,4(1*H*,3*H*)-dione (2h). Compound **2h** was synthesized from 5-iodouridine (60 mg, 0.152 mmol) and 1-methyl-1H-indole-4-boronic acid pinacol ester via general method C, and obtained as a white powder in a yield of 58 % (35 mg). ^{1}H-NMR (400 MHz, MeOD) dd, *J* = 3.6, 12.8 Hz), 3.69 (3H, s), 3.70 (1H, dd, *J* = 3.2, 12.4 Hz), 3.98 (1H, m), 4.08 (1H, t, *J* = 5.6 Hz), 4.23 (1H, t, *J* = 4 Hz), 5.85 (1H, d, *J* = 4 Hz), 6.23 (1H, d, *J* = 4 Hz), 6.96 (1H, d, *J* = 7.2 Hz), 7.16 (1H, d, *J* = 3.2 Hz), 7.18 (1H, d, *J* = 7.2 Hz), 7.38 (1H, d, *J* = 8.4 Hz), 7.92 (1H, s). ^{13}C-NMR (100 MHz, MeOD) 47.8, 62.4, 71.8, 75.9, 86.5, 90.5, 101.1, 110.2, 116.2, 121.5, 122.2, 126.0, 129.0, 130.3, 138.5, 140.8, 152.4, 164.9. m/z (ESI) 374.1350 $[M+H]^+$, $C_{18}H_{20}N_3O_6$ requires 374.1352.

1-((2*R*,3*S*,4*R*,5*R*)-tetrahydro-3,4-dihydroxy-5-(hydroxymethyl)furan-2-yl)-5-(1*H*-indol-5-yl) pyrimidine-2,4(1*H*,3*H*)-dione (2i). Compound **2i** was synthesized from 5-iodouridine (60 mg, 0.152 mmol) and indole-5-boronic acid via general method A, and obtained as a light grey powder in a yield of 70 % (45 mg). ^{1}H-NMR (400 MHz, MeOD) 3.75 (1H, dd, *J* = 2.8, 12 Hz), 3.86 (1H, dd, *J* = 2.8, 12 Hz), 4.06 (1H, m), 4.24 (1H, t, *J* = 4.8 Hz), 4.32 (1H, t, *J* = 4.8 Hz), 6.04 (1H, d, *J* = 4.8 Hz), 6.47 (1H, s), 7.25 (1H, d, *J* = 2.8 Hz), 7.27 (1H, dd, *J* = 1.2, 4.4 Hz), 7.40 (1H, d, *J* = 8.4 Hz), 7.75 (1H, s), 8.22 (1H, s). ^{13}C-NMR (100 MHz, MeOD) 62.2, 71.4, 75.9, 86.2, 91.2, 102.7, 111.9, 118.3, 121.5, 123.4, 125.7, 126.1, 129.5, 137.2, 138.8, 154.7, 168.5. m/z (ESI) 360.1194 $[M+H]^+$, $C_{17}H_{18}N_3O_6$ requires 360.1196.

1-((2*R*,3*S*,4*R*,5*R*)-tetrahydro-3,4-dihydroxy-5-(hydroxymethyl)furan-2-yl)-5-(1*H*-indol-6-yl) pyrimidine-2,4(1*H*,3*H*)-dione (2j). Compound **2j** was synthesized from 5-iodouridine (60 mg, 0.152 mmol) and indole-6-boronic acid via general method A, and obtained as a white powder in a yield of 64 % (40 mg). ^{1}H-NMR (400 MHz, MeOD) 3.76 (1H, dd, *J* = 2.8, 12 Hz), 3.87 (1H, dd, *J* = 2.8, 12 Hz), 4.07 (1H, m), 4.24 (1H, t, *J* = 4.8 Hz), 4.31 (1H, t, *J* = 4.8 Hz), 6.03 (1H, d, *J* = 4.4 Hz), 6.44 (1H, d, *J* = 4 Hz), 7.17 (1H, dd, *J* = 1.6, 8.4 Hz), 7.25 (1H, d, *J* = 3.2 Hz), 7.55 (1H, dd, *J* = 8.4 Hz), 7.66 (1H, s), 7.28 (1H, s). ^{13}C-NMR (100 MHz, MeOD) 62.1, 71.4, 76.0, 86.3, 90.9, 102.3, 112.5, 117.5, 120.7, 121.0, 126.5, 126.9, 129.1, 137.6, 139.3, 152.3, 165.2. m/z (ESI) 360.1194 $[M+H]^+$, $C_{17}H_{18}N_3O_6$ requires 360.1196.

Reductive amination reactions: compounds 3a-e.

General protocol. Under nitrogen, the respective amino acid (3 equiv.) was added to a stirred solution of **2a** (1 equiv.) in degassed methanol. After stirring for 1h, $NaBH_3CN$ (0.1 equiv) in methanol was added through a syringe. After stirring for 24h, the solvent was removed under reduced pressure and the residue was purified by reverse phase column chromatography (0.05M TEAB against methanol, gradient: 0-20%).

2-((5-(1,2,3,4-tetrahydro-1-((2*R*,3*S*,4*R*,5*R*)-tetrahydro-3,4-dihydroxy-5-(hydroxymethyl)furan-2-yl)-2,4-dioxopyrimidin-5-yl)thiophen-2-yl)methylamino)-6-aminohexanoic acid (3a). Compound **3a** was synthesized from **2a** (10 mg, 0.028 mmol) and L-lysine, and obtained as a light yellow powder in a yield of 68 % (9.2 mg). ^{1}H-NMR (400 MHz, D_2O) 1.30 (2H, m), 1.54 (2H, m), 1.68 (2H, m), 2.77 (2H, m), 3.75 (1H, dd, *J* = 3.2, 12.8 Hz), 3.90 (1H, dd, J = 2.8, 12.8 Hz), 4.03 (1H, m), 4.08 (1H, m), 4.18 (1H, t, J = 5.6 Hz), 4.25 (1H, dd, J = 3.2, 5.2 Hz), 5.34 (1H, s), 5.85 (1H, 3.2 Hz), 6.98 (1H, d, J = 3.6 Hz), 8.21 (1H, s). ^{13}C-NMR (100 MHz, D_2O) 22.1, 23.2, 30.2, 42.2, 46.2, 60.0, 67.7, 68.7, 74.2, 80.7, 81.5, 102.4, 118.6, 124.0, 130.35, 130.7, 131.9, 136.6, 145.3, 160.8. m/z (ESI) 483.1697 $[M-H]^-$, $C_{20}H_{27}N_4O_8S$ requires 483.1550.

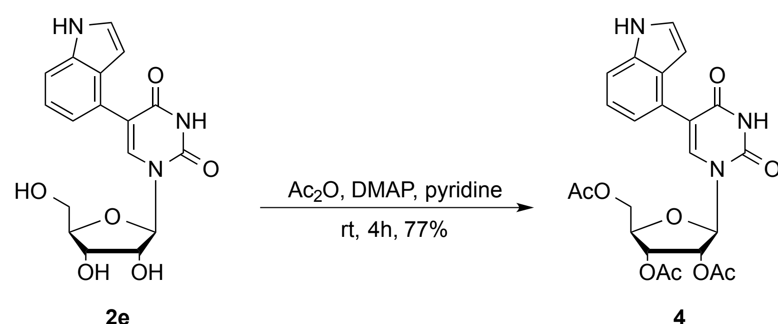
2-((5-(1,2,3,4-tetrahydro-1-((2*R*,3*S*,4*R*,5*R*)-tetrahydro-3,4-dihydroxy-5-(hydroxymethyl)furan-2-yl)-2,4-dioxopyrimidin-5-yl)thiophen-2-yl)methylamino) acetic acid (3b). Compound **3b** was synthesised from **2a** (11 mg, 0.031 mmol) and glycine, and obtained as a light yellow powder in a yield of 27 % (3.5 mg). ^{1}H-NMR (400 MHz, D_2O) 3.26 (2H, s), 3.78 (1H, dd, *J* = 3.2, 12.8 Hz), 3.90 (1H, dd, *J* = 4.4, 12 Hz), 4.07 (1H, m), 4.21 (1H, m), 4.27 (1H, m), 4.40 (2H, s), 5.85 (1H, d, *J* = 2.8 Hz), 7.14 (1H, d, *J* = 4 Hz), 7.20 (1H, d, *J* = 3.6 Hz), 8.40 (1H, s). ^{13}C-NMR (100 MHz, D_2O) 57.8, 61.7, 70.0, 71.0, 76.4, 86.3, 91.1, 110.1, 124.2, 127.6, 136.0, 137.4, 141.7, 151.7, 161.5, 163.4. m/z (ESI) 412.1789 [M-H]$^-$, $C_{16}H_{18}N_3O_8S$ requires 412.0815.

2-((5-(1,2,3,4-tetrahydro-1-((2*R*,3*S*,4*R*,5*R*)-tetrahydro-3,4-dihydroxy-5-(hydroxymethyl)furan-2-yl)-2,4-dioxopyrimidin-5-yl)thiophen-2-yl)methylamino)-4-methylpentanoic acid (3c). Compound **3c** was synthesised from **2a** (10 mg, 0.028 mmol) and L-leucine, and obtained as a white powder in 22 % yield (3 mg). ^{1}H-NMR (400 MHz, MeOD) 0.90 (3H, d, *J* = 6.4 Hz), 0.96 (3H, d, *J* = 6.4 Hz), 1.45 (1H, m), 1.56 (1H, m), 1.80 (1H, m), 3.82 (1H, dd, *J* = 2, 8 Hz), 3.90 (1H, m), 3.96 (1H, dd, *J* = 2, 8 Hz), 4.28 (2H, m), 6.00 (1H, d, *J* = 3.6 Hz), 6.97 (1H, d, *J* = 3.6 Hz), 7.34 (1H, d, *J* = 3.6 Hz), 8.59 (1H, s). ^{13}C-NMR (100 MHz, DMSO-d_6) 21.1, 22.2, 22.7, 24.3, 56.0, 58.4, 60.1, 69.3, 74.2, 84.6, 88.6, 108.4, 113.6, 121.8, 128.4, 133.2, 135.3, 149.5, 150.3, 161.3. m/z (ESI) 468.1444 [M-H]$^-$, $C_{20}H_{26}N_3O_8S$ requires 468.1441.

2-((5-(1,2,3,4-tetrahydro-1-((2*R*,3*S*,4*R*,5*R*)-tetrahydro-3,4-dihydroxy-5-(hydroxymethyl)furan-2-yl)-2,4-dioxopyrimidin-5-yl)thiophen-2-yl)methylamino)-3-(1*H*-indol-3-yl) propanoic acid (3d). Compound **3d** was synthesised from **2a** (10 mg, 0.028 mmol) and L-glutamic acid, and obtained as a light yellow powder in 18 % yield (2.5 mg). ^{1}H-NMR (400 MHz, D_2O) 1.21 (2H, m), 2.10 (1H, m), 2.45 (1H, m), 3.70 (1H, dd, *J* = 2, 12 Hz), 3.84 (1H, dd, *J* = 2, 12 Hz), 3.97 (1H, m), 4.15 (3H, m), 4.49 (2H, m), 5.88 (1H, d, *J* = 3.6 Hz), 6.85 (1H, d, *J* = 3.6 Hz), 7.22 (1H, d, *J* = 4 Hz), 8.61 (1H, s). ^{13}C-NMR (100 MHz, MeOD) 27.3, 30.6, 57.8, 61.7, 69.9, 71.0, 76.4, 86.3, 91.1, 110.7, 124.2, 126.1, 127.6, 136.0, 137.4, 141.7, 151.6, 163.5, 176.0. m/z (ESI) 484.0966 [M-H]$^-$, $C_{19}H_{22}N_3O_{10}S$ requires 484.1026.

2-((5-(1,2,3,4-tetrahydro-1-((2*R*,3*S*,4*R*,5*R*)-tetrahydro-3,4-dihydroxy-5-(hydroxymethyl)furan-2-yl)-2,4-dioxopyrimidin-5-yl)thiophen-2-yl)methylamino)-3-(1*H*-indol-3-yl) propanoic acid (3e). Compound **3e** was synthesised from **2a** (8 mg, 0.023 mol) and L-tryptophan, and obtained as a light yellow powder in 30 % yield (3.7 mg). ^{1}H-NMR (400 MHz, D_2O) 2.92 (1H, m), 3.42 (1H, t, *J* = 6.8 Hz), 3.74 (2H, m), 3.88 (2H, m), 4.06 (1H, m), 4.19 (1H, t, *J* = 6.4 Hz), 4.27 (1H, t, *J* = 4.8 Hz), 5.87 (1H, d, *J* = 3.6 Hz), 6.71 (1H, d, *J* = 3.6 Hz), 6.88 (1H, t, *J* = 8 Hz), 6.93 (1H, d, *J* = 8.4 Hz), 6.98 (1H, t, *J* = 8.4 Hz), 7.07 (1H, s), 7.28 (1H, d, *J* = 8 Hz), 7.39 (1H, d, *J* = 8 Hz), 8.08 (1H, s). ^{13}C-NMR (100 MHz, D_2O) 28.0, 61.4, 64.0, 66.8, 70.0, 73.8, 83.6, 88.9, 108.9, 109.4, 110.3, 111.5, 118.5, 119.0, 121.5, 124.2, 124.3, 126.6, 127.6, 133.9, 135.7, 136.2, 153.4, 166.4, 178.7. m/z (ESI) 541.1383 [M-H]$^-$, $C_{25}H_{26}N_4O_8S$ requires 541.1393.

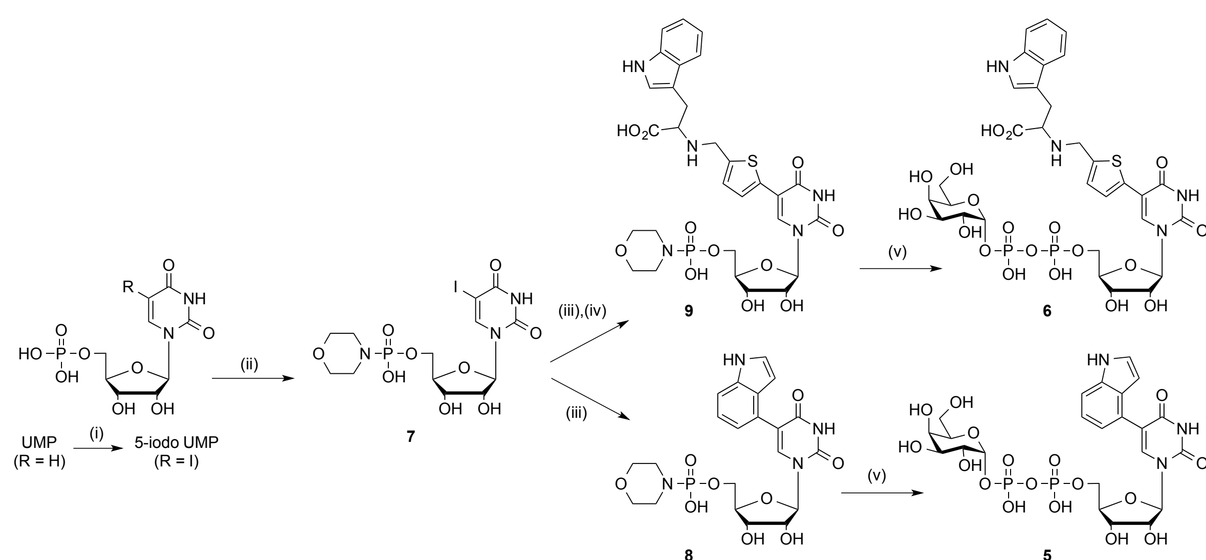
Acetylation of 2e: compound 4.



Scheme S1 Synthesis of peracetylated pro-drug **4**.

(2*R*,3*R*,4*R*,5*R*)-2-(5-(1*H*-indol-4-yl)-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-5-(acetoxymethyl) tetrahydrofuran-3,4-diyl diacetate. To a solution of **2e** (54 mg, 0.15 mmol) and DMAP (0.9 mg, 0.075 mmol) in pyridine (0.5 mL) was added acetic anhydride (54 mg, 0.52 mmol). The reaction was stirred for 4 h at rt and quenched with water. The solvent was removed by evaporation and the residue co-evaporated with toluene (3x). The light yellow crude was purified by flash chromatography (hexane/EA, gradient: 2:1 to 1:1) to yield target compound **4** as a grey solid in 77 % yield (58 mg). ^{1}H-NMR (400 Hz, $CDCl_3$) 1.79 (3H, s), 2.04 (3H, s), 2.07 (3H, s), 4.30 (3H, m), 5.30 (1H, dd, *J* = 4, 6 Hz), 5.39 (1H, t, *J* = 6 Hz), 6.14 (1H, d, *J* = 6 Hz), 6.43 (1 H, m), 7.03 (1H, dt, *J* = 1.2, 8 Hz), 7.09 (1H, m), 7.52 (1H, m), 7.58 (1H, s), 8.51 (1H, s). ^{13}C-NMR (100 MHz, $CDCl_3$) 20.5, 20.6, 63.3, 70.4, 72.7, 80.1, 86.9, 102.3, 111.6, 117.3, 119.6, 120.7, 120.7, 125.2, 125.5, 127.9, 135.8, 135.9, 150.0, 162.3, 169.8, 170.4. m/z (ESI) 486.1501 $[M+H]^+$, $C_{23}H_{24}N_3O_9$ requires 486.1513.

Synthesis of sugar-nucleotides: compounds 5 & 6.



Scheme S2 Synthesis of UDP-sugars **5** and **6**. *Reagents & conditions*: (i) I_2, 2M HNO_3, $CHCl_3$, 18h, 90 ^{o}C, 75 %; (ii) morpholine, dipyridyldisulfide, PPh_3, DMSO, rt, 1.5 h, 78 %; (iii) indole-4-boronic acid (for **8**) or 5-formylthien-2-yl-boronic acid (for **9**), Cs_2CO_3, TPPTs, Na_2PdCl_4, H_2O, MW 120 ^{o}C, 30 min, 44 % (**8**) or 47 % (**9**); (iv) tryptophan, $NaBH_3CN$, methanol, rt, overnight, 40 %; (v) α-D-galactose-1-phosphate, NMICl, dry DMF, rt, 9 h / 38 % (**5**) or 15 h / 35 % (**6**).

General protocol. 5-Iodo UMP and its phosphoromorpholidate **7** were synthesised as previously reported [2]. The 5-substituted derivatives **8** and **9** were obtained by Suzuki cross-coupling (General Method A) of 5-iodo UMP phosphoromorpholidate **7** with, respectively, 5-formyl-2-thiopheneboronic acid or indole-4-boronic acid, followed in the case of **9** by reductive amination. Phosphoromorpholidates **8** and **9** were freeze-dried overnight and added separately to α-D-galactose-1-phosphate and tetrazole in dry DMF. The reactions were stirred at room temperature. All solvents were removed under reduced pressure, and the crude products were purified by anion-exchange and reverse phase chromatography. Product-containing fractions were combined and reduced to dryness. Residues were repeatedly co-evaporated with methanol to remove excess TEAB.

5-(Indol-4-yl) UDP-α-D-galactose (5). Compound **5** (triethylammonium salt) was obtained from phosphoromorpholidate **8** and α-D-galactose-1-phosphate (triethylammonium salt) in a yield of 38 % after purification and lyophilisation. ^{1}H-NMR (400 MHz, D_2O) 1.12 (9H, t, *J* = 7.8 Hz), 3.04 (6H, q, *J* = 7.2 Hz), 3.46 (1H, dd, *J* = 4.8, 12 Hz), 3.54 (1H, dd, *J* = 7.6, 12 Hz), 3.56 (1H, m), 3.68 (1H, m), 3.77 (1H, d, *J* = 4.8 Hz), 3.92 (1H, dd, *J* = 4.8, 7.6 Hz), 4.00 (2H, m), 4.14 (1H, m), 4.20 (1H, m), 4.31 (1H, m), 5.40

(1H, m), 5.91 (1H, d, *J* = 6 Hz), 6.27 (1H, d, *J* = 2.8 Hz), 7.01 (1H, d, *J* =7.2 Hz), 7.15 (1H, t, *J* = 7.6 Hz), 7.28 (1H, d, *J* = 2.8 Hz), 7.43 (1H, d, *J* = 8.4 Hz), 7.73 (1H, s). ^{13}C-NMR (100 MHz, D_2O) 8.1, 46.5, 60.9, 69.0, 69.2, 69.8, 71.8, 73.0, 83.1, 83.2, 88.6, 95.6, 95.7, 100.1, 112.1, 115.8, 120.6, 121.8, 123.5, 126.1, 126.4, 135.7, 139.1, 151.6, 164.5. ^{31}P-NMR (161 MHz, D_2O) -11.2 (d, *J* = 21.2Hz), -13.6 (d, *J* = 21.2 Hz). m/z (ESI) 680.0885 [M-H]$^-$, $C_{23}H_{28}N_3O_{17}P_2$ requires 680.0894.

((5-(1-((2R,3R,4S,5R)-3,4-dihydroxy-5-(((hydroxy((hydroxy(((2R,3R,4S,5R,6R)-3,4,5-trihydroxy-6-(hydroxylmethyl)tetrahydro-2H-pyran-2-yl)oxy)phosphoryl)oxy)phosphoryl)oxy)methyl) tetrahydrouran-2-yl)-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)thiophen-2-yl)methyl) tryptophan. Compound **6** (triethylammonium salt) was obtained from phosphoromorpholidate **9** and α-D-galactose-1-phosphate (triethylammonium salt) in a yield of 35 % after purification and lyophilisation. ^{1}H-NMR (400 MHz, D_2O) 1.10 (9H, t, *J* = 7.2 Hz), 3.00 (6H, q, *J* = 7.2 Hz), 3.48 (2H, m), 3.55 (1H, dd, *J* = 3.2, 8 Hz), 3.6 (1H, m), 3.72 (3H, m), 3.94 (1H, m), 3.96 (1H, m), 4.13 (2H, m), 4.17 (1H, m), 4.26 (1H, t, *J* = 4 Hz), 4.32 (1H, t, *J* = 4 Hz), 5.49 (1H, dd, J = 4, 8 Hz), 5.93 (1H, d, *J* = 5.2 Hz), 6.72 (1H, d, *J* = 4 Hz), 6.84 (1H, t, *J* = 8 Hz), 6.94 (1H, t, *J* = 8 Hz), 7.10 (1H, s), 7.25 (1H, d, *J* = 7.6 Hz), 7.37 (1H, d, *J* = 8 Hz), 7.76 (1H, s). ^{13}C-NMR (100 MHz, D_2O) 27.2, 58.9, 60.4, 61.0, 68.3, 69.1, 69.3, 69.9, 71.9, 73.7, 83.7, 95.7, 95.8, 107.7, 109.9, 111.8, 118.3, 118.3, 119.2, 121.6, 124.4, 124.9, 126.1, 130.0, 130.0, 134.6, 135.8, 135.9, 136.5, 163.8. ^{31}P-NMR (161 MHz, D_2O) -11.3 (d, *J* = 19.3Hz), -12.8 (d, *J* = 19.3 Hz). m/z (ESI) 863.1251 [M-H]$^-$, $C_{31}H_{37}N_4O_{19}P_2S$ requires 863.1248.

(2) Additional tables.

Table S1 Suzuki-Miyaura coupling of 5-iodo uridine with various arylboronic acids R-$B(OH)_2$

Entry	R	Products[a]	Reagents	Conditions	Yield (%)[b]
1	5-formylthien-2-yl-	**2a**	Na_2PdCl_4, TPPTs, Cs_2CO_3, H_2O	rt, 2d[c]	26
2	5-formylthien-2-yl-	**2a**	Na_2PdCl_4, TPPTs, Cs_2CO_3, H_2O	MW 120 °C, 0.5h	54
3	5-pyridinyl-3-yl-	**2b**	$PdCl_2$(dppf)DCM, $NaHCO_3$, DME/H_2O (3:1)	MW 130 °C, 0.5h	20
4	5-pyridinyl-4-yl-	**2c**	$PdCl_2$(dppf)DCM, $NaHCO_3$, DME/H_2O (3:1)	MW 130 °C, 0.5h	27
5	5-isoquinolinyl-4-yl-	**2d**	Na_2PdCl_4, TPPTs, Cs_2CO_3, H_2O	MW 120 °C, 0.5h	25
6	5-indole-4-yl-	**2e**	Na_2PdCl_4, TPPTs, Cs_2CO_3, H_2O	MW 120 °C, 0.5h	43
7	5-(2-(4-methylpiperazin-1-yl)-pyridine-4-yl-	**2f**	$PdCl_2$(dppf)DCM, $NaHCO_3$, DME/H_2O (3:1)	MW 130 °C, 0.5h	35
8	5-(1H-indazole)-4-yl	**2g**	$PdCl_2$(dppf)DCM, aqueous K_2CO_3, DME	MW 130 °C, 0.5h	10
9	5-(1-methyl-indole)-4-yl	**2h**	$PdCl_2$(dppf)DCM, $NaHCO_3$, Dioxane/H_2O (3:1)	MW 130 °C, 0.5h	58
10	5-indole-5-yl	**2i**	Na_2PdCl_4, TPPTs, Cs_2CO_3, H_2O	MW 120 °C, 0.5h	70
11	5-indole-6-yl	**2j**	Na_2PdCl_4, TPPTs, Cs_2CO_3, H_2O	MW 120 °C, 0.5h	64

[a]See Scheme 1 for structures; [b]isolated yields; [c]reaction carried out under conventional conditions.

Table S2 Reductive amination of **2a** with various amino acids

Entry	Amino acids	Products[a]	Reagents	Yield (%)[b]
1	L-Lysine	**3a**	$NaBH_3CN$, methanol	68
2	Glycine	**3b**	$NaBH_3CN$, methanol	27
3	L-Leucine	**3c**	$NaBH_3CN$, methanol	22
4	L-Glutamic acid	**3d**	$NaBH_3CN$, methanol	30
5	L-Tryptophan	**3e**	$NaBH_3CN$, methanol	18

[a]See Scheme 1 for structures; [b]isolated yields.

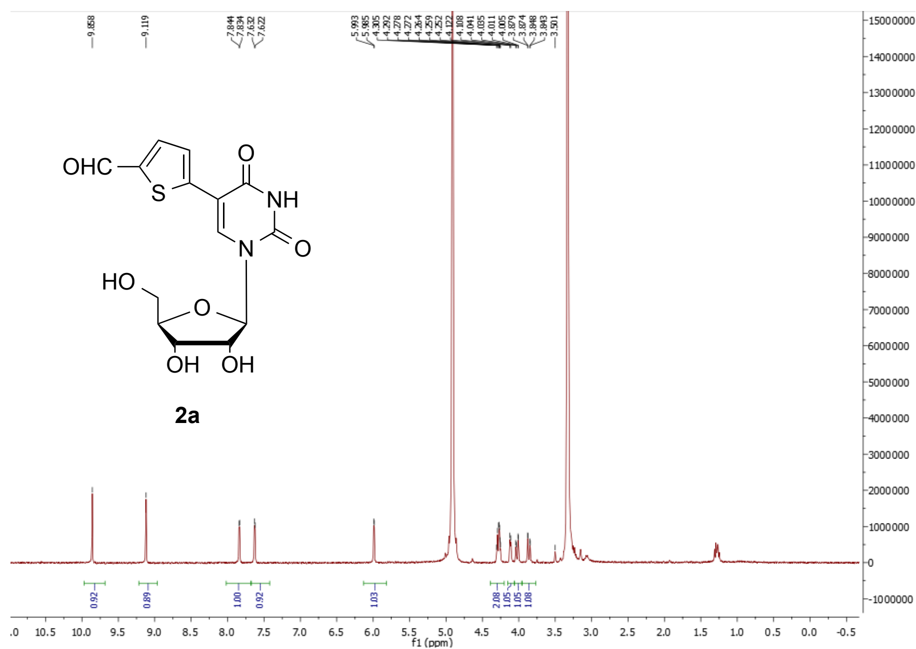
Table S3 Inhibitory activity of uridine derivatives **2** and **3** towards β-1, 4-GalT.

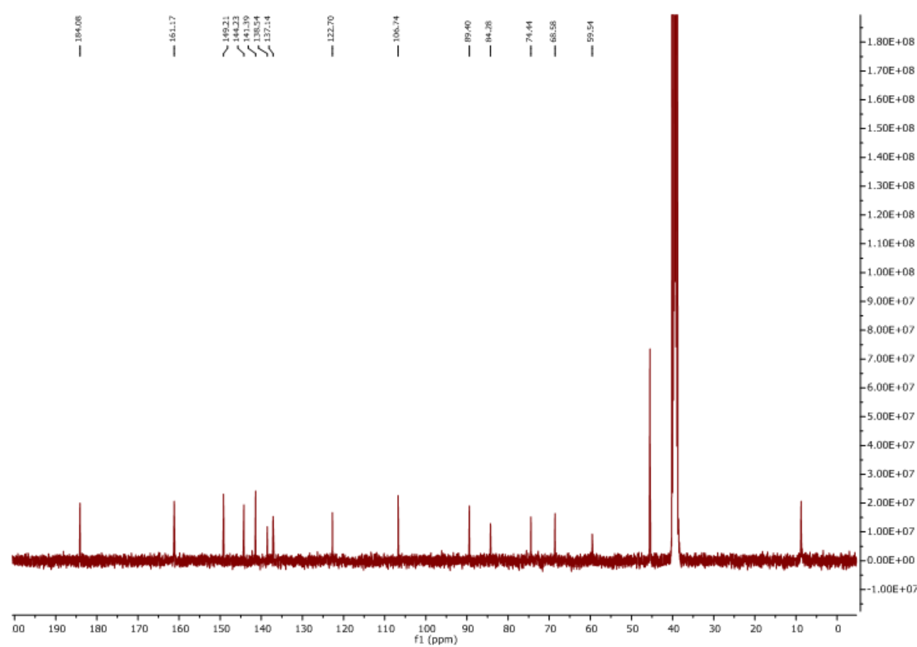
Entry	Cmpd[a]	Substituent R^1 or R^2	IC_{50} (μM)[b]	Turnover (%)[c]
1	**2a**	5-formylthien-2-yl-	>1000	25 %
2	**2b**	pyridin-3-yl-	>1000	20 %
3	**2c**	pyridin-4-yl-	>1000	28 %
4	**2d**	isoquinolin-4-yl-	>1000	23 %
5	**2e**	1*H*-indol-4-yl-	207 ± 37	21 %
6	**2f**	2-(4-methylpiperazin-1-yl)-pyridin-4-yl-	>1000	29 %
7	**2g**	1*H*-indazol-4-yl-	>1000	42 %
8	**2h**	1-methyl-1*H*-indol-4-yl-	163 ± 30	32 %
9	**2i**	1*H*-indol-5-yl-	>1000	47 %
10	**2j**	1*H*-indol-6-yl-	250 ± 24	34 %
11	**3a**	1-aminobut-4-yl-	>1000	20 %
12	**3b**	H-	>1000	23 %
13	**3c**	isobutyl-	>1000	26 %
14	**3d**	1-carboxeth-2-yl-	>1000	22 %
15	**3e**	(1*H*-indol-3-yl)-methyl-	284 ± 26	33 %

[a]See Scheme 1 for structures; [b]each experiment was carried out in triplicate; [c]100 % = complete conversion of UDP-Gal donor

(3) ^{1}H, ^{13}C and ^{31}P NMR spectra.

Compound 2a (^{1}H, ^{13}C)



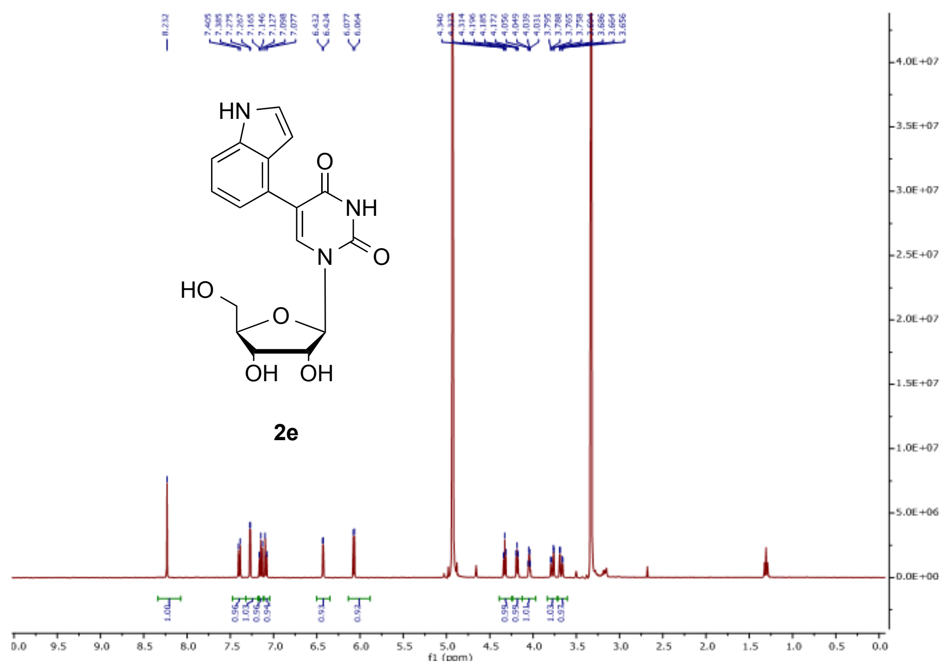


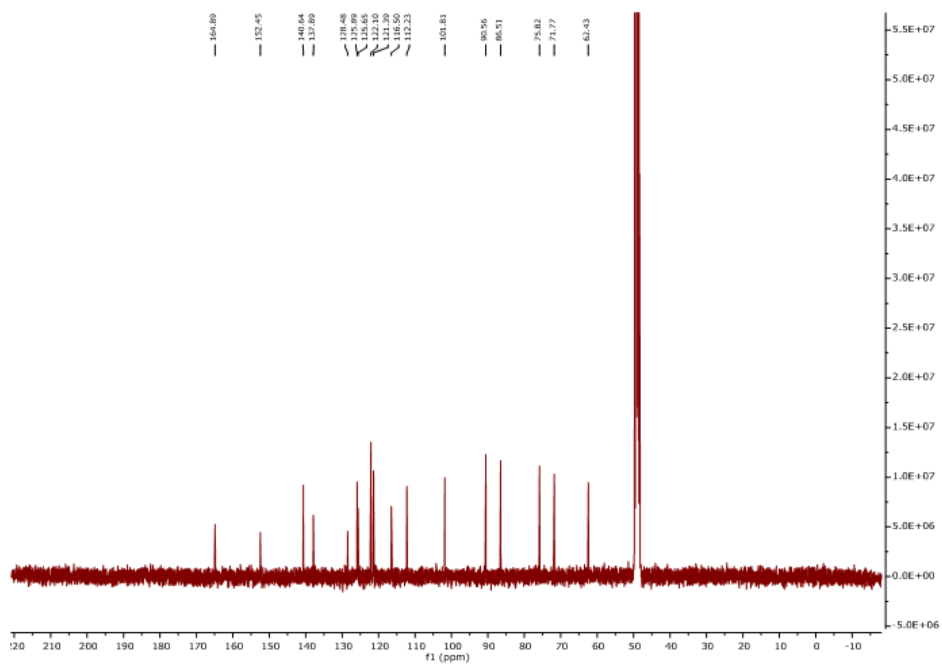
Compound 2b (^{1}H, ^{13}C)

Compound 2c (^{1}H, ^{13}C)

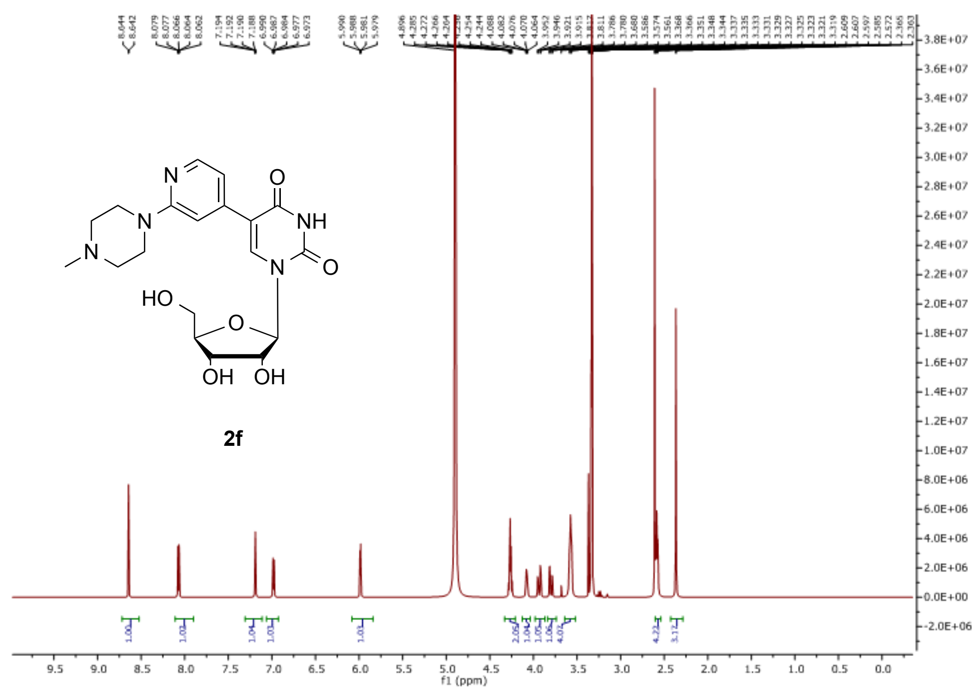
Compound 2d (^{1}H, ^{13}C)

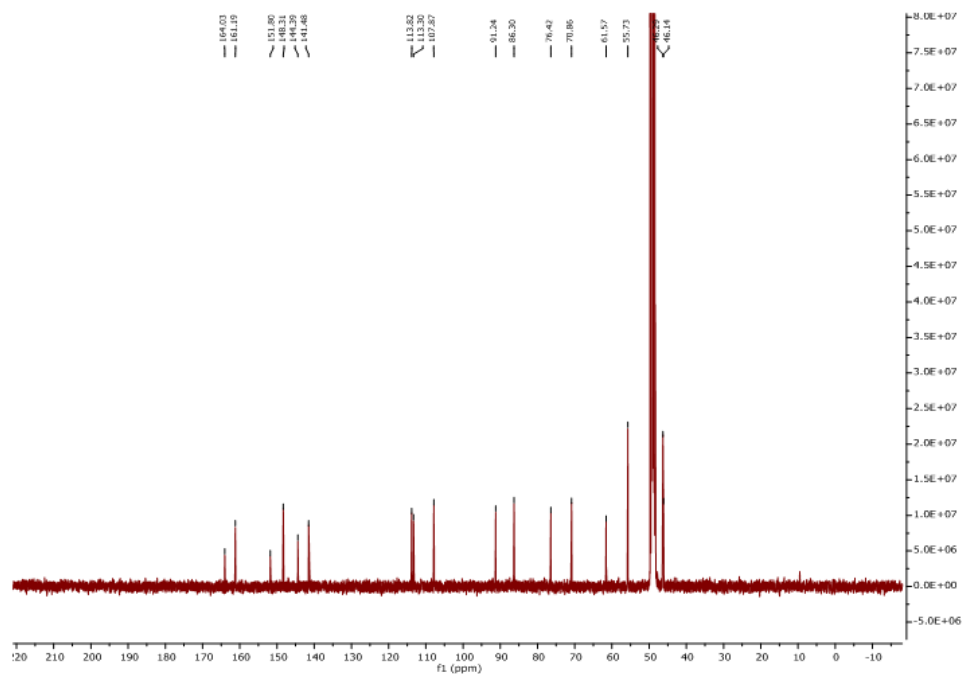
Compound 2e (^{1}H, ^{13}C)



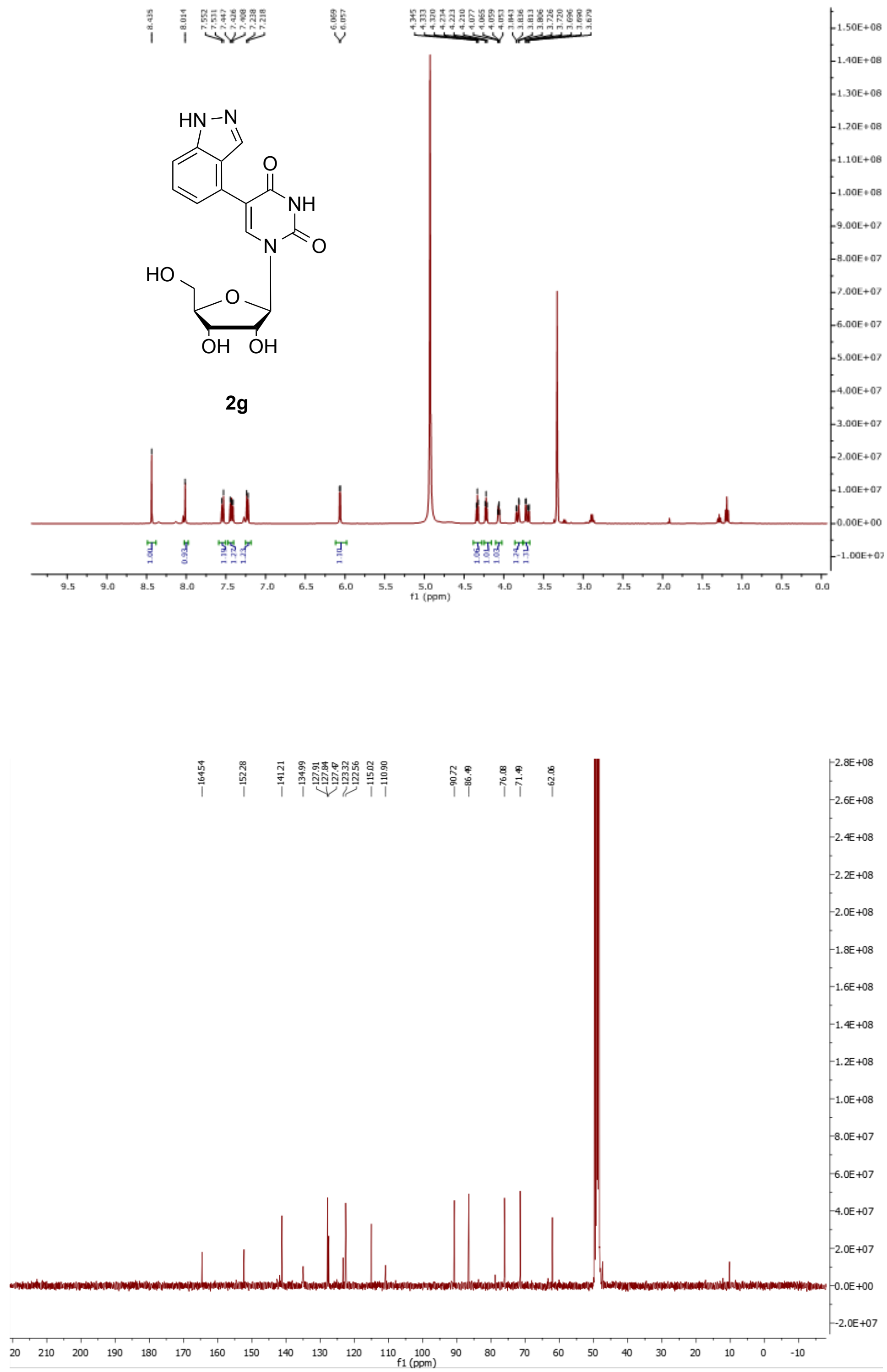


Compound 2f (^{1}H, ^{13}C)

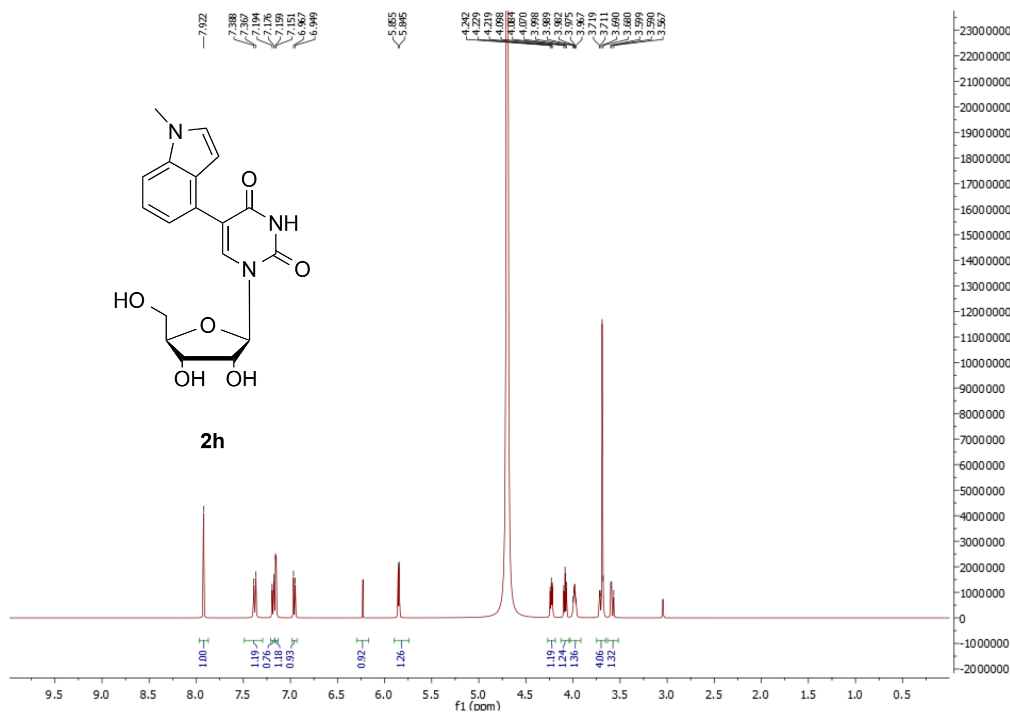


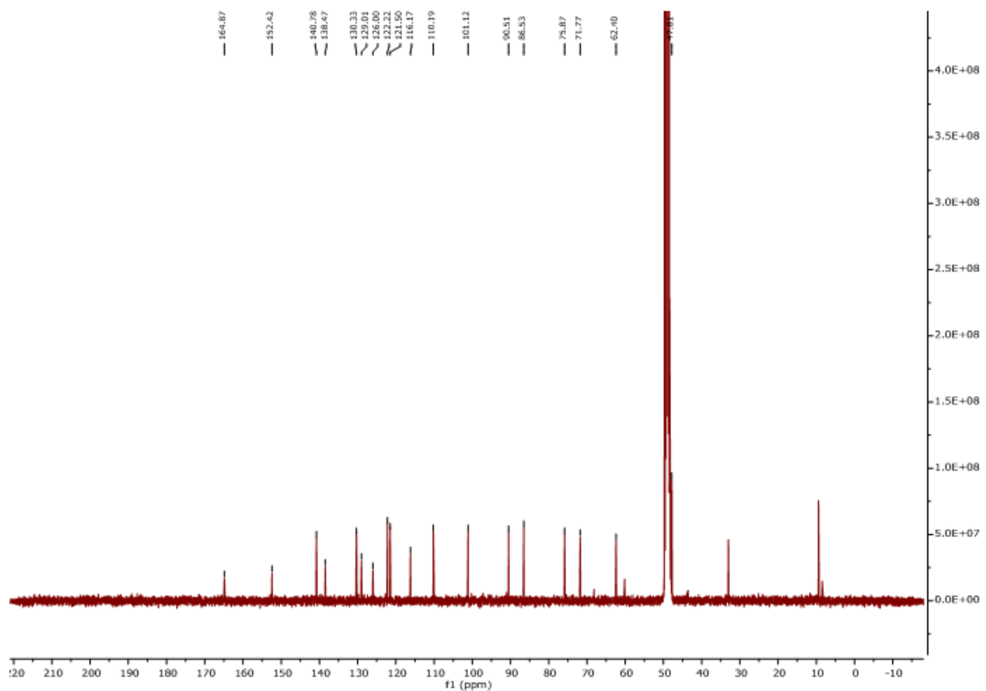


Compound 2g (^{1}H, ^{13}C)

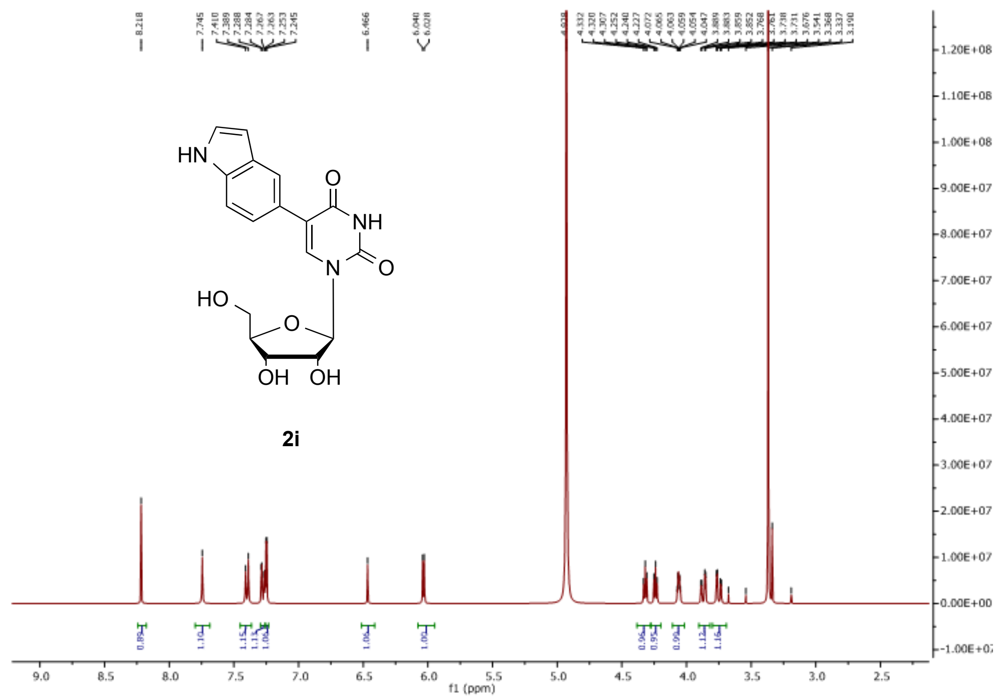


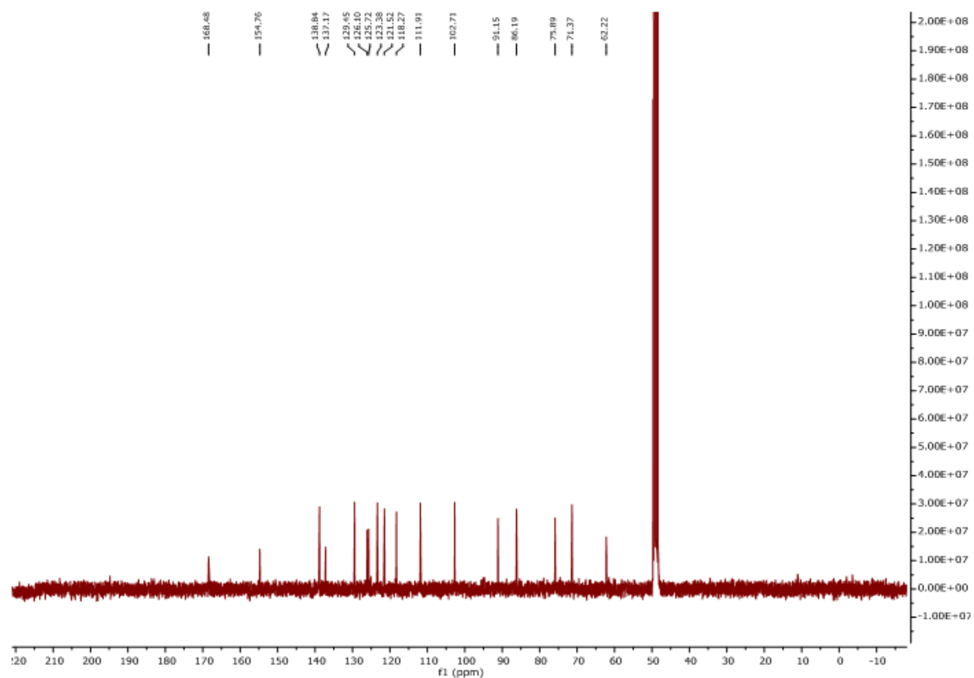
Compound 2h (^{1}H, ^{13}C)



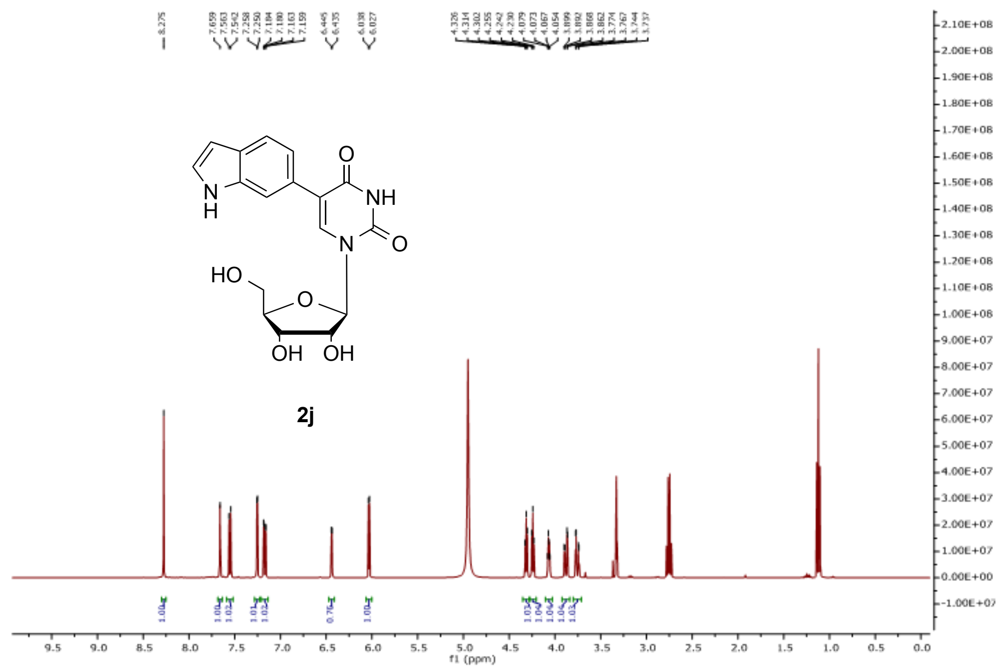


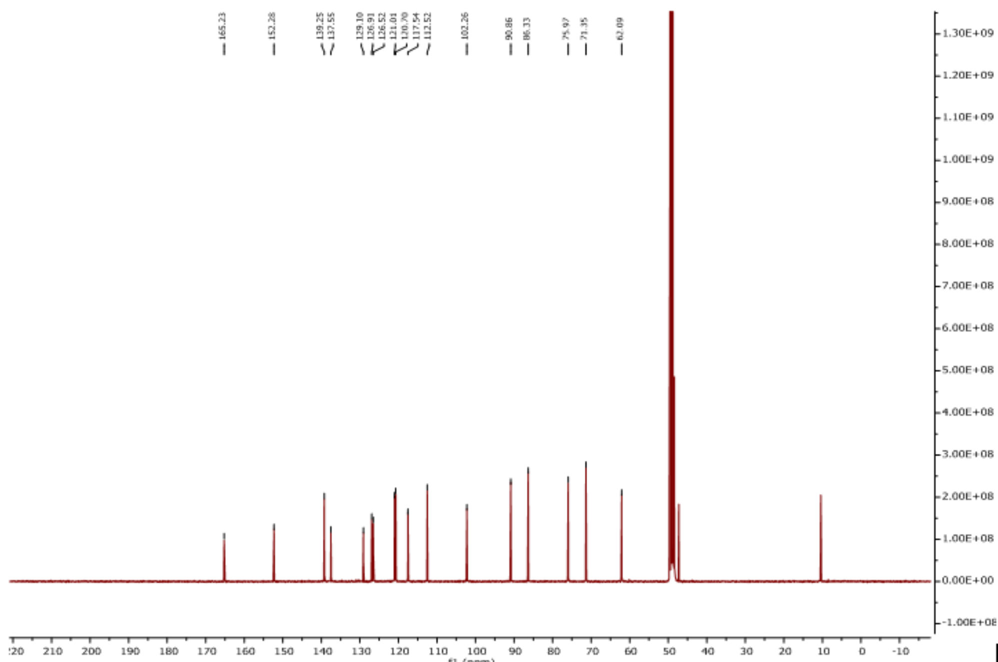
Compound 2i (^{1}H, ^{13}C)



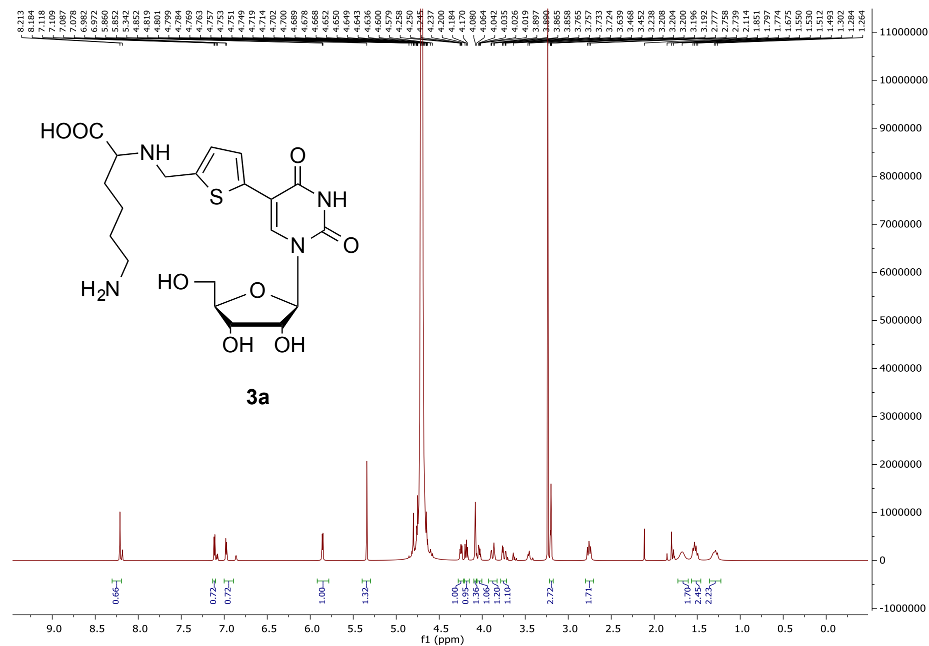


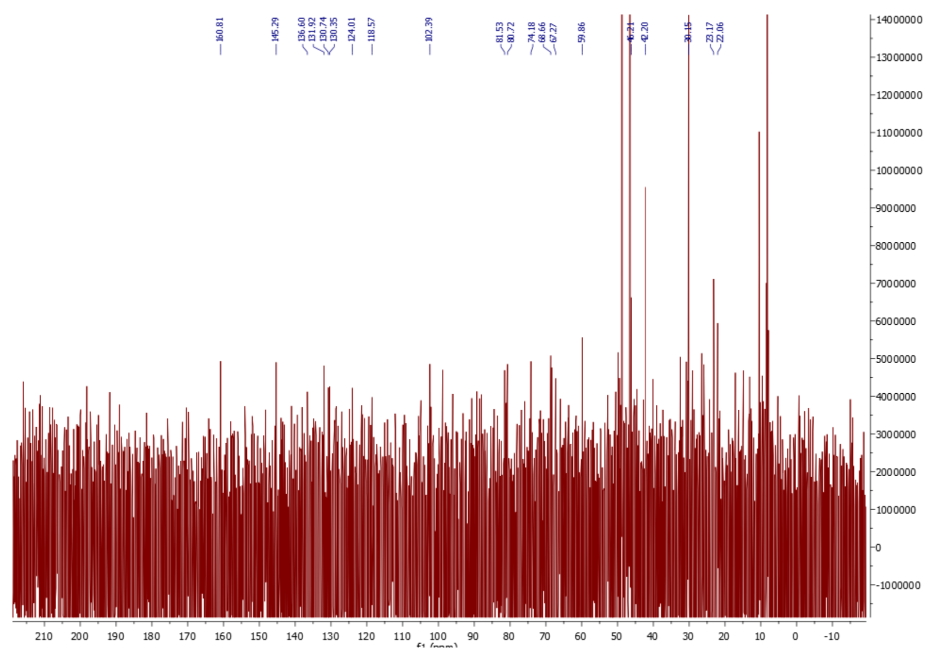
Compound 2j (^{1}H, ^{13}C)



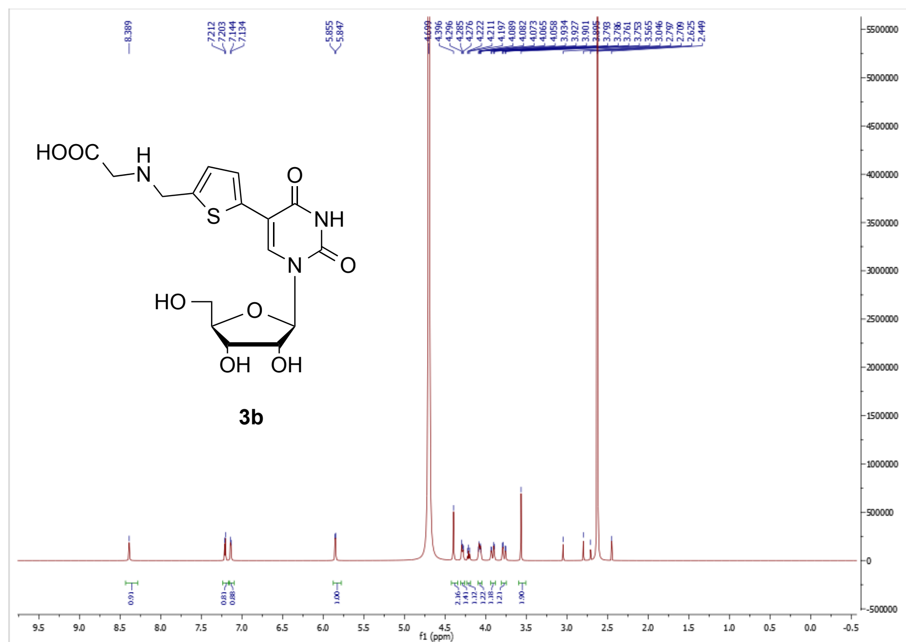


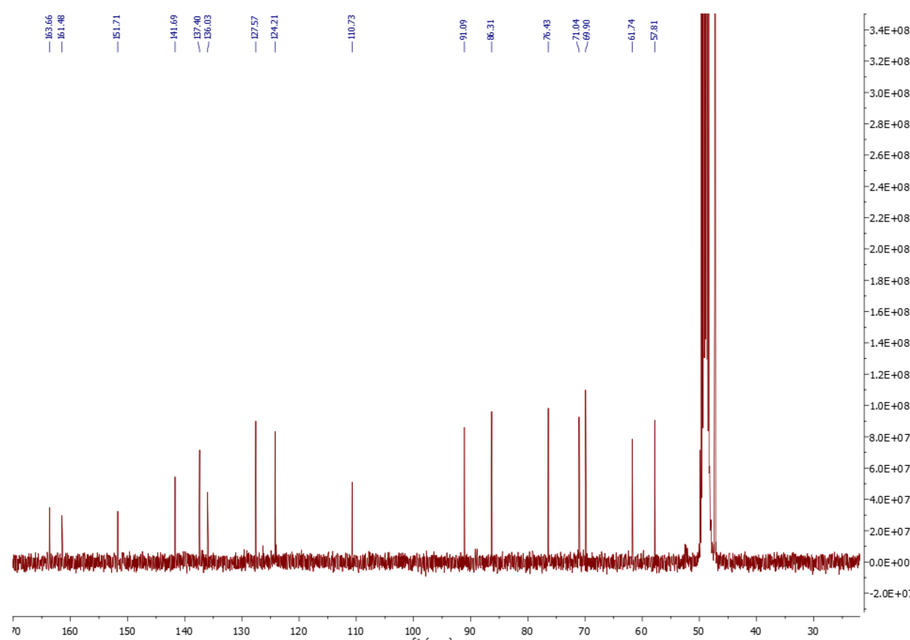
Compound 3a (^{1}H, ^{13}C)



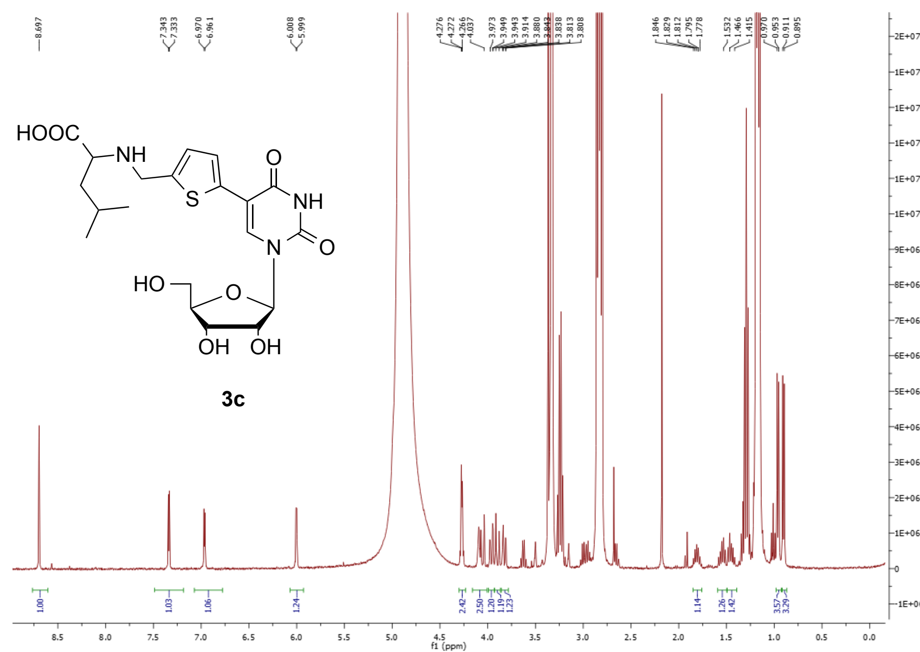


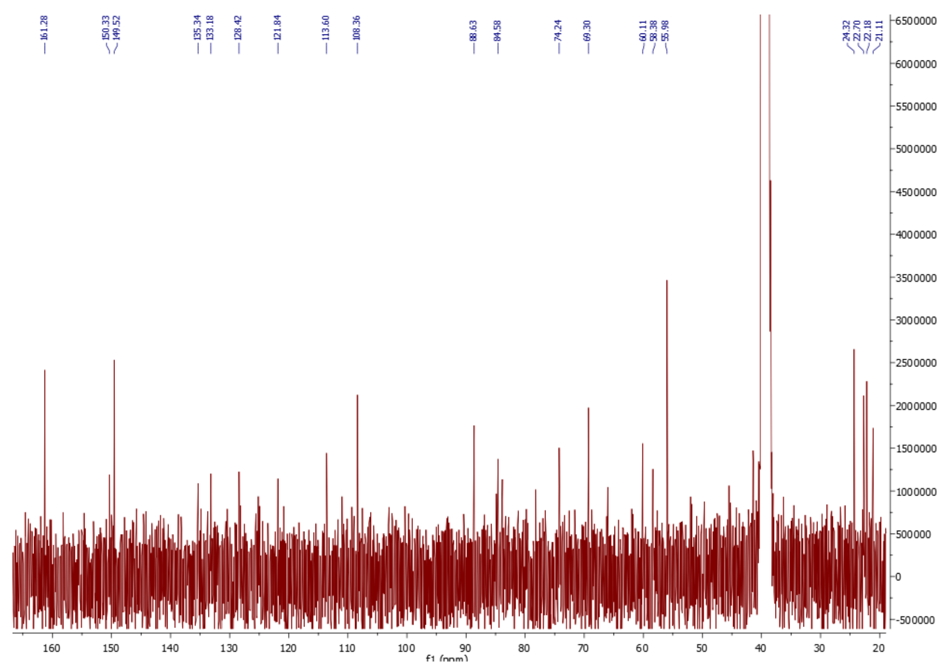
Compound 3b (^{1}H, ^{13}C)



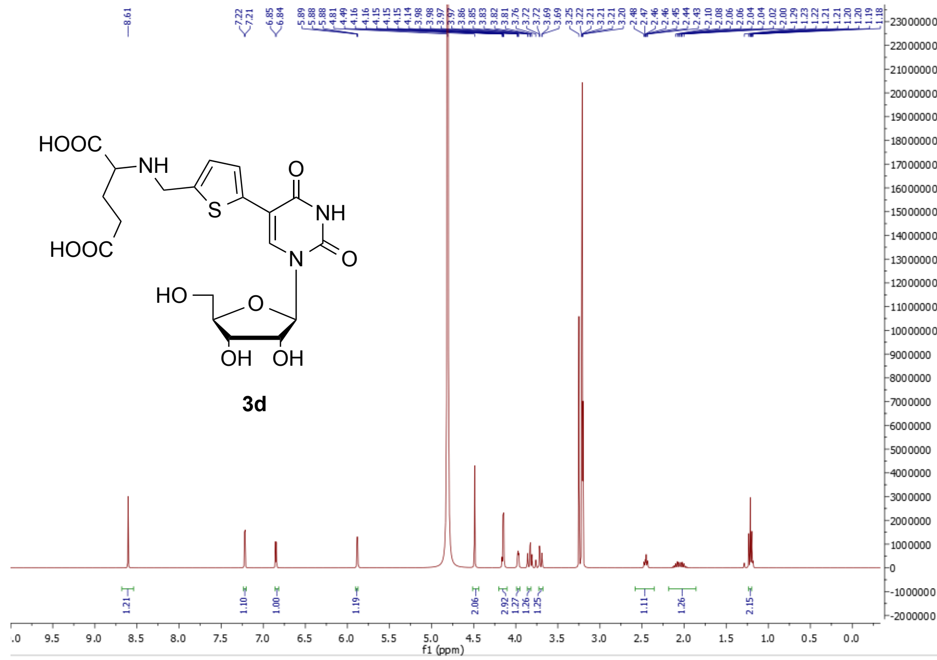


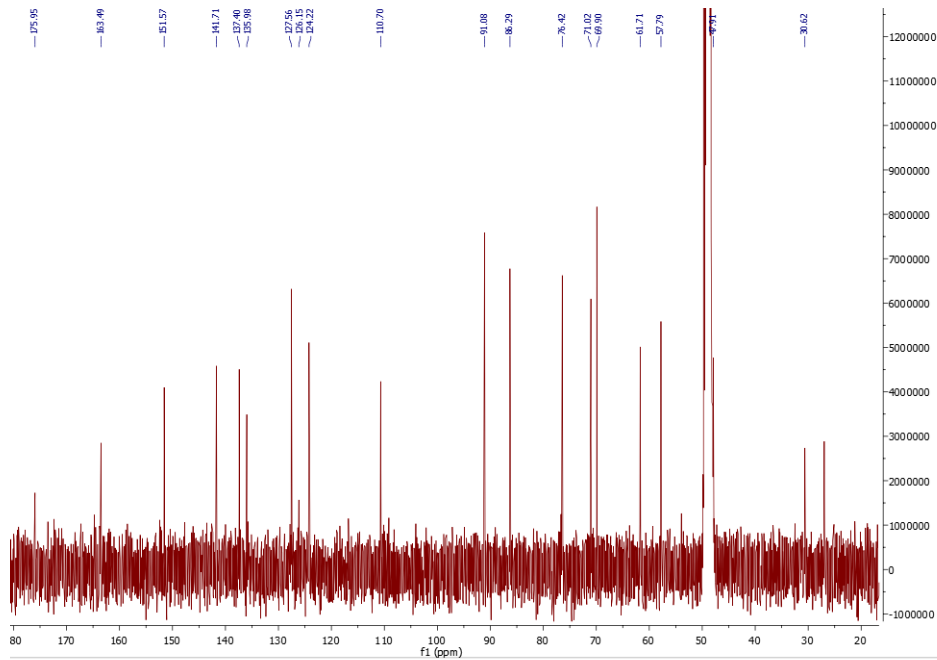
Compound 3c (^{1}H, ^{13}C)





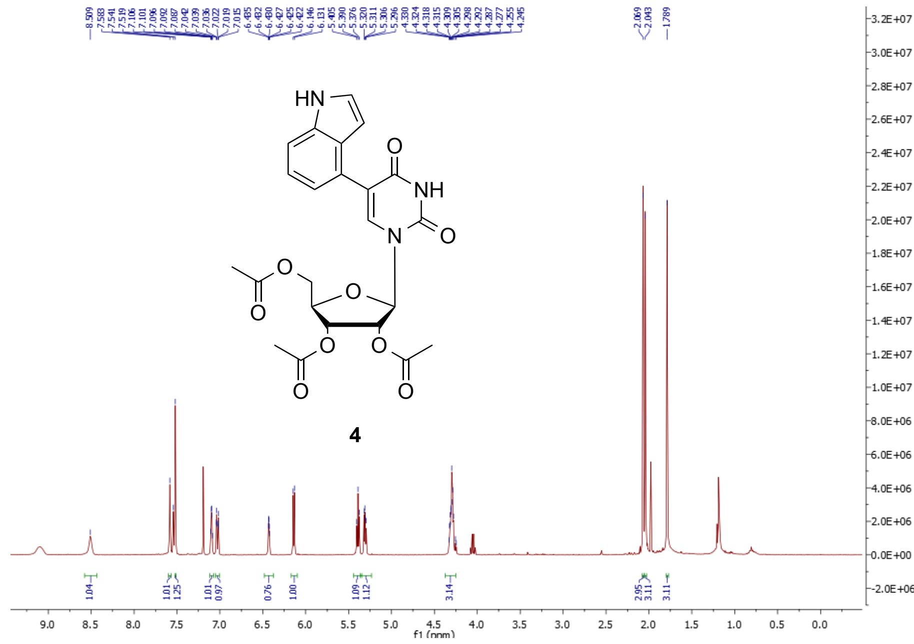
Compound 3d (^{1}H, ^{13}C)

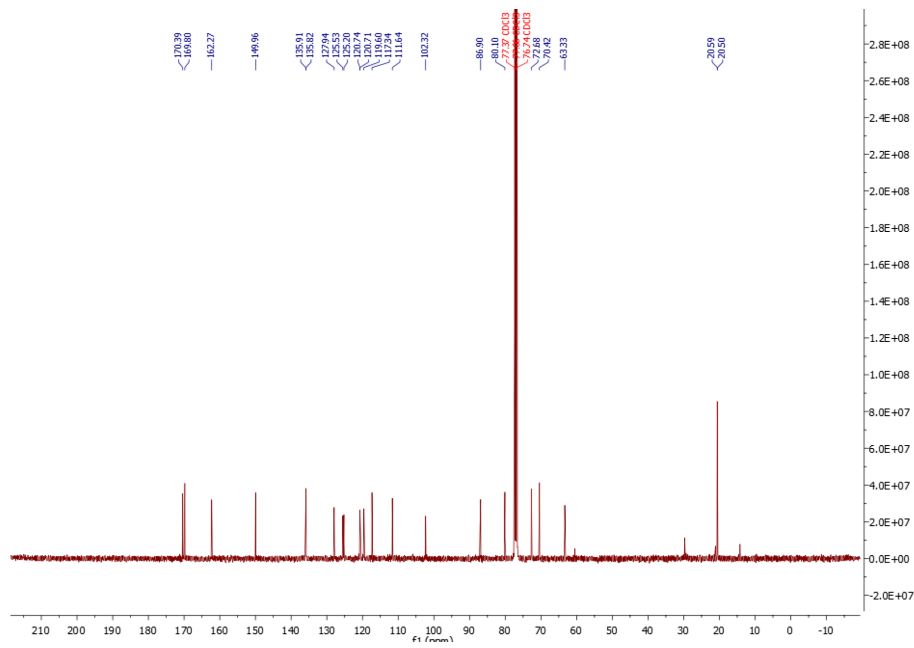




Compound 3e (^{1}H, ^{13}C)

Compound 4 (^{1}H, ^{13}C)





Compound 5 (^1H, ^{13}C, ^{31}P)

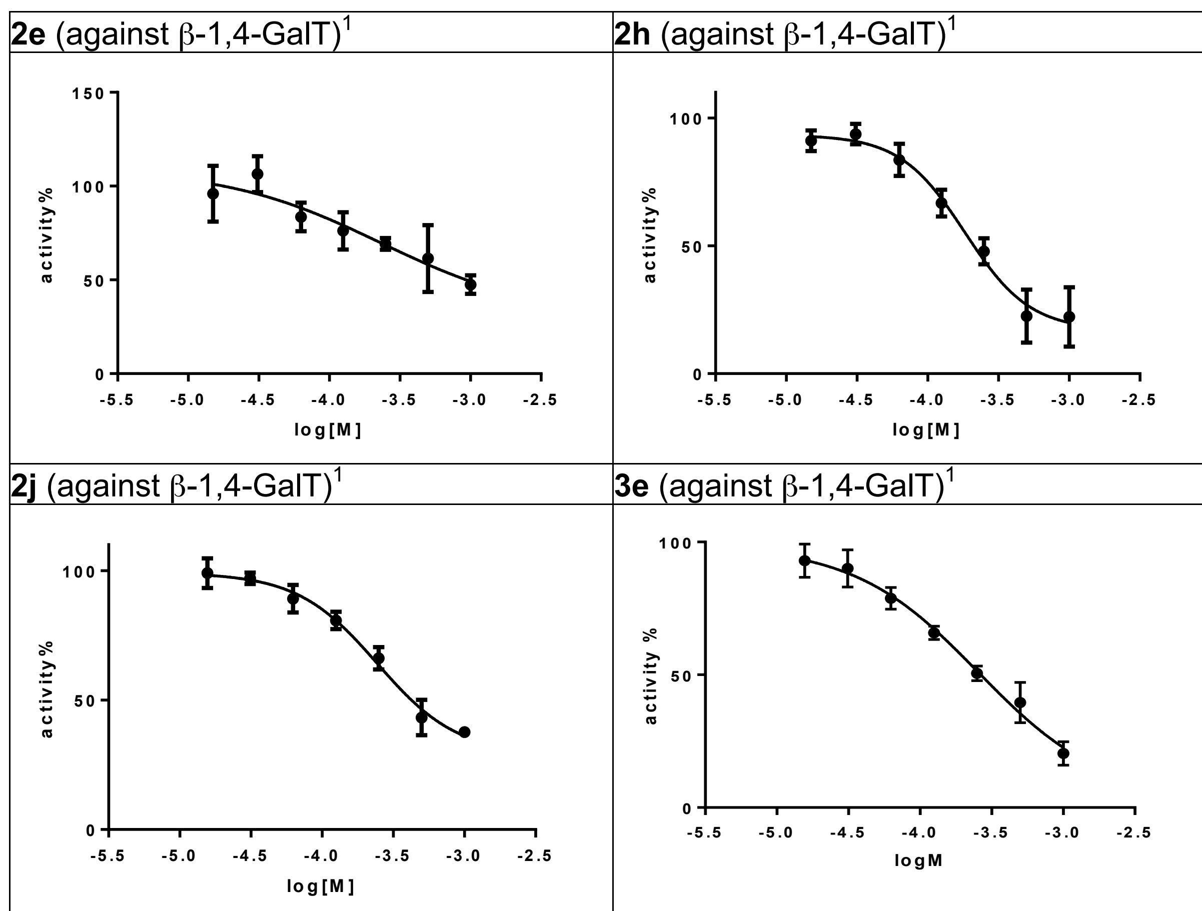
Compound 6 (^{1}H, ^{13}C, ^{31}P)

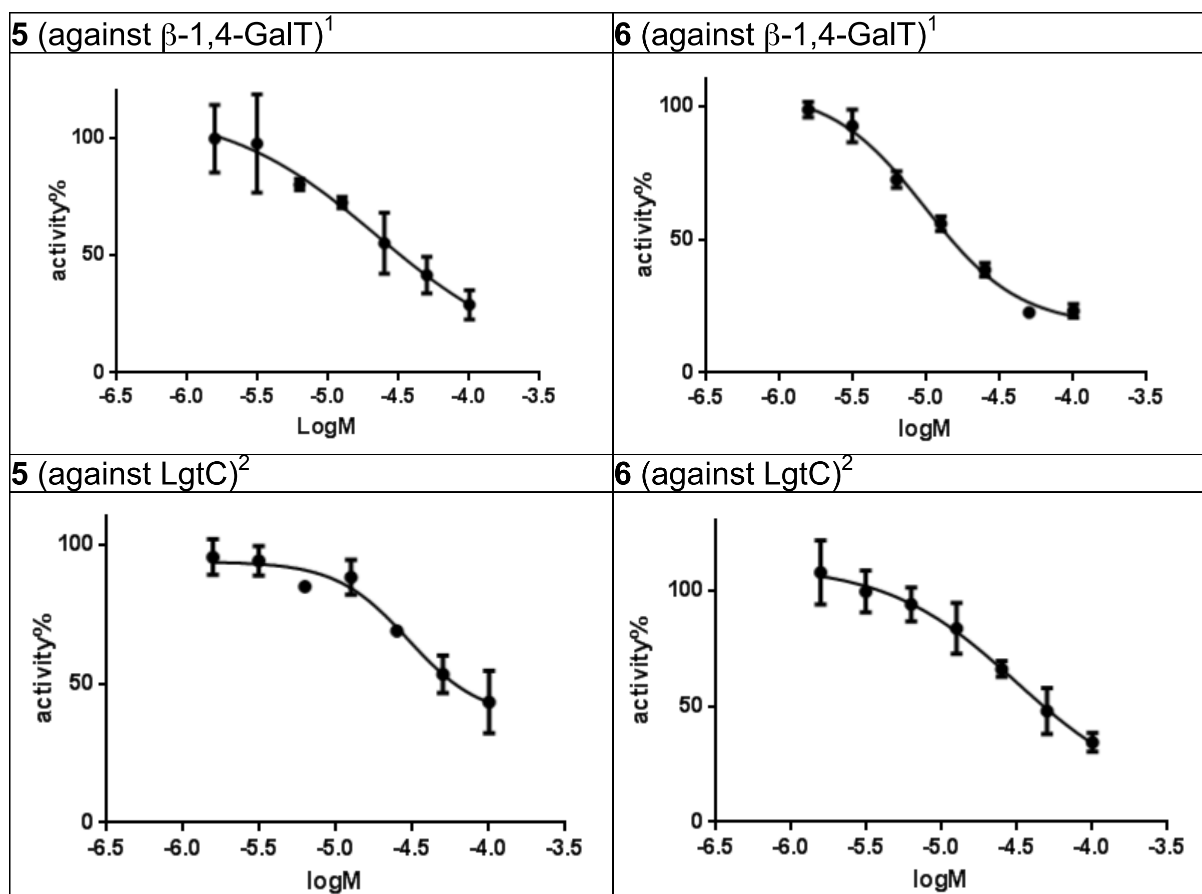
(4) GalT Inhibition experiments.

General. All reagents for the biochemical assays were obtained commercially and used as received, unless otherwise stated. 5-FT UDP-Gal was prepared as previously reported [3] and used as a positive control. Bovine β-1, 4-GalT was expressed, purified and refolded using an adaptation of a previously reported protocol [4]. LgtC was expressed and purified as previously reported [5]. Inhibition assays were carried out as previously reported [6] and briefly described below. Absorbance measurements were carried out on a BMG Labtech POLARstar Optima multiplate reader.

Data collection and analysis protocol. Assays were carried out on 96-well plates. On each microplate, sample, control and background wells were included in triplicate. A calibration curve (0-12.5 μM UDP, corresponding to 0-25 μM P_i) was constructed for each microplate by linear regression. The calibration curve was used to convert absorbance measurements at 620 nm in sample and control wells to [UDP] (μM). For each sample and control well, a corresponding background well (containing identical components but no acceptor) was included, to account for non-specific hydrolysis of donor. Corrected absorbance values for each well were obtained by subtracting the corresponding background reading from the absorbance of the respective sample or control well. Inhibition (%) was calculated by dividing absorbance in the presence of inhibitor by maximum absorbance (negative control, no inhibitor). Percentage inhibition was plotted over log[inhibitor] and analysed with GraphPad Prism 6 software to obtain relative IC_{50} values. Averages and standard deviations were calculated in Microsoft Excel.

Concentration-response curves





[1]**Conditions:** β-1,4-GalT, GlcNAc acceptor (10 mM), UDP-Gal donor (28 μM), $MnCl_2$ (5 mM), chicken egg-white lysozyme (1 mg/mL), calf-intestinal phosphatase (10 U/mL), inhibitor (0-1000 μM for uridine derivatives, 0-100 μM for UDP-Gal derivatives), DMSO (10 %) and buffer (13 mM HEPES, pH 7.0, 50 mM KCl) were incubated on a 96-well plate at 30 ^{o}C with shaking for 20 min. The reaction was stopped by the addition of malachite reagents, and the absorbance was recorded at 620 nm after 30 min. All concentrations are final concentrations. Bars indicate mean values ± S.D. of triplicate experiments.

[2]**Conditions:** LgtC (activated by DTT at 30 ^{o}C for 30min), lactose acceptor (2 mM), UDP-Gal donor (28 μM), $MnCl_2$ (5 mM), chicken egg-white lysozyme (1 mg/mL), calf-intestinal phosphatase (10 U/mL), inhibitor (0-1000 μM for uridine derivatives, 0-100 μM for UDP-Gal derivatives), DMSO (10 %) and buffer (13 mM HEPES, pH 7.0) were incubated on a 96-well plate at 30 ^{o}C with shaking for 20 min. The reaction was stopped by the addition of malachite reagents, and the absorbance was recorded at 620 nm after 30 min. All concentrations are final concentrations. Bars indicate mean values ± S.D. of triplicate experiments.

(5) Control experiments.

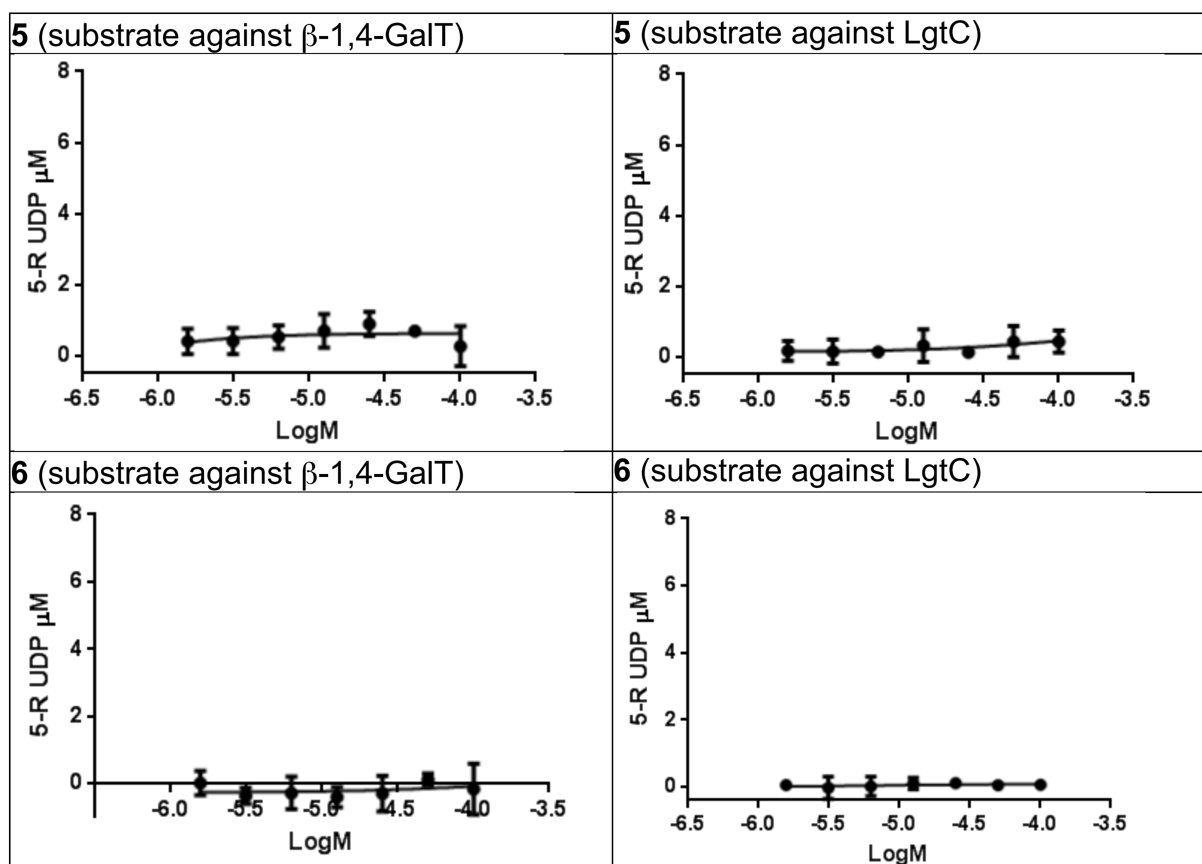
(a) Potential substrate activity of UDP-Gal derivatives **5** and **6** towards β-1,4-GalT and LgtC.

To assess the potential activity of UDP-Gal derivatives **5** and **6** as donor analogues, the biochemical assays were carried out with each of these derivatives, instead of the natural donor UDP-Gal, under the following conditions:

β-1,4-GalT substrate assay. β-1,4-GalT, donor analogue **5** or **6** (0-100 μM), GlcNAc acceptor (10 mM), $MnCl_2$ (5 mM), chicken egg-white lysozyme (1 mg/mL), calf-intestinal phosphatase (10 U/mL), DMSO (10 %) and buffer (13 mM HEPES, pH 7.0, 50 mM KCl) were incubated on a 96-well plate at 30 ^{o}C with shaking for 20 min. The reaction was stopped by the addition of malachite reagents, and the absorbance was recorded at 620 nm after 30 min. All concentrations are final concentrations. Bars indicate mean values ± S.D. of triplicate experiments.

LgtC substrate assay. LgtC (activated by DTT at 30 ^{o}C for 30 min), donor analogue **5** or **6** (0-100 μM), lactose acceptor (2 mM), $MnCl_2$ (5 mM), chicken egg-white lysozyme (1mg/mL), calf-intestinal phosphatase (10 U/mL), DMSO (10 %) and buffer (13 mM HEPES, pH 7.0) were incubated on a 96-well plate at 30 ^{o}C with shaking for 20 min. The reaction was stopped by the addition of malachite reagents, and the absorbance was recorded at 620 nm after 30 min. All concentrations are final concentrations. Bars indicate mean values ± S.D. of triplicate experiments.

No substrate activity was observed for compound 5 or 6 in any of these experiments:

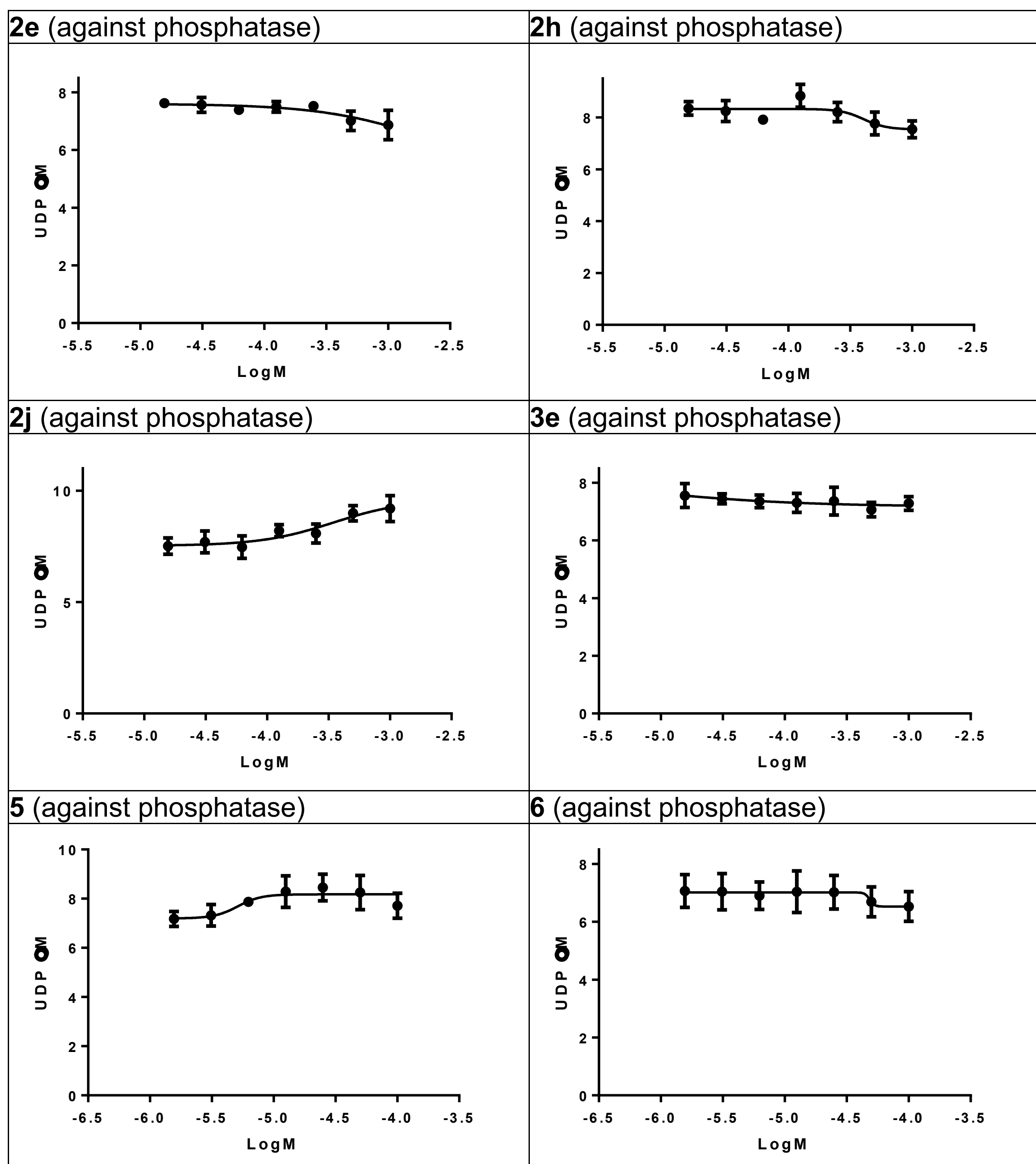


(b) Potential inhibition of CIP by active compounds (**2e**, **2h**, **2j**, **3e**, **5** and **6**).

To establish that the activity of compounds **2e**, **2h**, **2j**, **3e**, **5** and **6** in the biochemical assay is not due to inhibition of the phosphatase, the inhibitory activity of these compounds towards CIP was tested under the following conditions:

CIP assay. Calf-intestinal phosphatase (10 U/mL), UDP (28 μM), $MnCl_2$ (5 mM), chicken egg-white lysozyme (1 mg/mL), inhibitor (0-1000 μM for uridine derivatives and 0-100 μM for UDP-Gal derivatives), DMSO and buffer (13 mM HEPES, pH 7.0, 50 mM KCl) were incubated on a 96-well plate at 30 ^{o}C with shaking for 20 min. The reaction was stopped by the addition of malachite reagents, and the absorbance was recorded at 620 nm after 30 min. All concentrations are final concentrations. Bars indicate mean values ± S.D. of triplicate experiments.

No CIP inhibitory activity was observed in any of these experiments:



(6) PSGL-1 expression assay.

Full details of the PSGL-1 expression assay will be published elsewhere [7]. In brief, the following protocol was used:

Isolation of hPBMCs and treatments. The study was approved by the national research ethics committee at Guy's and St Thomas' Hospitals (10/H0807/99). Peripheral venous blood was collected from healthy donors (n=5) into syringes containing 10 % v/v acid citrate dextrose. Then transferred to leucosep tubes pre-spun with Histopaque-1077. The samples were centrifuged at 1000 g for 10 min. Following centrifugation, mononuclear cells were separated by density from platelets, plasma, granulocytes and red blood cells. Monocyte layers were gently aspirated off and washed twice with media (RPMI-1640 medium with GlutaMAX™ supplemented with 2 % FBS, 100 units/mL penicillin and 100 µg/mL streptomycin). 0.4×10^6 cells were seeded into each well of a 96-well plate, and compounds **2e** or **4** at 1, 10 or 100 µM were added for 1 h, followed by either media alone or 10 ng/mL IL-1β in the continued presence of compounds for 72 h at 37 °C and 5 % CO_2. Cells were harvested and analysed by flow cytometry.

Flow cytometry. The cell surface expression of PSGL-1 (CD162) was measured by flow cytometry on a Cytomics FC500 instrument (Beckman Coulter, High Wycombe, UK). Treated cells were harvested and fixed with 4 % paraformaldehyde for 20 min. Cells were then centrifuged (1200 rpm, 5 min, 4 °C) and resuspended in FACS buffer (PBS supplemented with 1 % BSA and 5 mM sodium azide). Cells were immunostained with mouse anti-human CD162 PE- and mouse anti-human CD14 FITC-conjugated antibodies (1:25) or isotype controls for 20 min at 4 °C. Stained cells were washed twice with FACS buffer, and the mean fluorescence intensity (MFI) was measured to quantify the responses.

(7) Cell viability assay.

Cell viability was examined using the MTT reduction assay in living cells. hPBMCs were isolated as described above. Cells were seeded at a density of 200,000 cells per well and treated with inhibitor (**2e** or **4**, 0.1-10 µM) or vehicle (40 % DMSO) for 1 h followed by either media alone or 10 ng/mL IL-1β. Cell viability after 72 h was examined by conversion of MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) into formazan in living cells by mitochondrial dehydrogenases. All treatment media was gently removed and cells were treated with media containing 0.8 mg/mL MTT for 4 h. Formazan crystals were dissolved in 10 % sodium dodecyl sulphate in 0.01M HCl for 16 h and read on a spectrophotometer at 550 nm. A reagent blank excluding cells was included as a background control. Using this protocol, 4 independent experiments using 4 human donors (n=4) were carried out.

No significant effect on cell viability was observed for either inhibitor, compared to respective controls, at any of the concentrations tested (Figure 1).

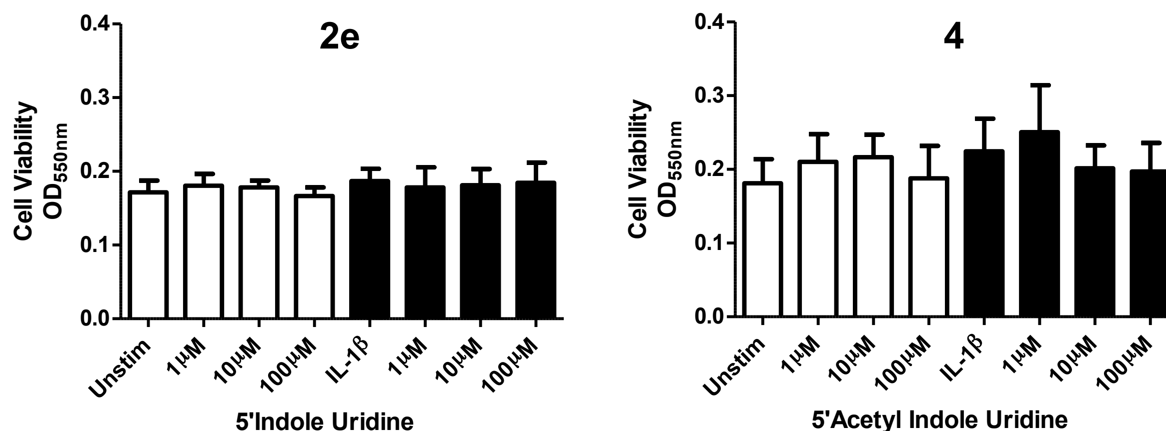


Figure 1. *Viability of hPBMCs in the presence of inhibitors **2e** and **4***. Cell viability was examined using the MTT reduction assay. Neither compound significantly affected cell viability at any concentration examined (0.1-100 μM) compared to either unstimulated or 10 ng/mL IL-1β treated controls. White bars represent basal responses, and black bars represent responses in the presence of 10 ng/mL IL-1β. Controls are labelled "unstim" and "IL-1β" respectively. No significant differences between inhibitor samples and controls were found with 1 way ANOVA. Data are from 4 independent experiments using 4 human donors (n=4).

(8) References

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