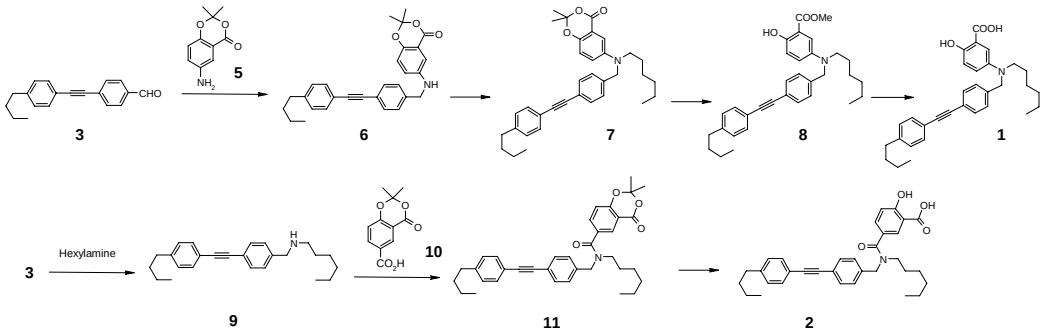
Synthesis of compounds 1 and 2

The synthesis of compounds 1 and 2 use a common intermediate 3, as depicted in Scheme1. Then a series of reductive alkylation, hydrolysis or amidification were used successfully to prepare these novel compounds as shown in the following detailed protocol. Compound 1 and 2 are prepared in eight and six steps respectively, from commercially available reagents.



Scheme 1. Synthesis of Compounds **1** and **2**.

Compound **3.** A solution of 4-bromobenzyldehyde (90 g; 486 mmol), $Pd(OAc)_2$, (2.18 g; 9.73 mmol), triphenylphosphine (10.2 g; 39 mmol) and cuprous iodide (1.85 g; 9.7 mmol) in THF (1.8 L) in presence of triethylamine (203 mL; 1.46 mol) was degassed for 30 min by nitrogen bubbling at 50 °C. A THF solution of 1-butyl-4-ethynylbenzene (100 g; 632 mmol.) in 600 mL of THF was then added dropwise and the resulting reaction mixture was stirred 10 minutes under nitrogen at 50°C. The reaction mixture was filtered and the cake was washed with 150 mL of THF. The filtrate was concentrated to about 800mL and an aqueous solution of HCl 1 N (1 L) was added. The resulting mixture was extracted with MTBE (2 x 800mL) and combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated to give a brown cream solid. Purification by flash chromatography on silica (cHex:DCM; 9:1) afforded 109 g (86%) of **3** as an off-white solid. HPLC (max plot) 99.19%; Rt 5.18 min. LC/MS:

^{1}H NMR ($CDCl_3$) δ 10.02 (s, 1H), 7.86 (d, J = 7.47 Hz, 2H), 7.66 (d, J = 7.98 Hz, 2H), 7.47 (d, J = 7.2 Hz, 2H), 7.19 (d, J = 7.68 Hz, 2H), 2.64 (t, J = 7.5Hz, 2H), 1.63 (quint, J = 7.2Hz, 2H), 1.36 (m, 2H), 0.94 (t, J = 7.2 Hz, 3H). Melting point: 76-78 ^{o}C.

Compound **5.** A mixture of 2-hydroxy-5-nitrobenzoic acid (Aldrich, 50.0 g, 0.27 mol), acetone (40 mL, 0.54 mol) and trifluoroacetic anhydride (TFAA) (Aldrich, 100 mL, 0.71 mol) in trifluoroacetic acid (TFA) (Aldrich, 300 mL) was heated at reflux. After 1 hour, an additional amount of acetone (60 mL, 0.82 mol) was added and the resulting reaction mixture was heated under reflux for an additional 48 hrs. The reaction mixture was concentrated under reduced pressure. The residual brown solid was dissolved in DCM (800 mL) and washed with a mixture of an aqueous saturated solution of $NaHCO_3$ (400 mL) and water (400 mL). The aqueous layer was extracted with DCM (2 x 400 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residual brown oil was taken up in cold pentane (300 mL) at 0°C and a yellow solid precipitated off. Filtration and washing with pentane gave 53.8 g (88%) of 6-nitro-2,2-dimethyl-4H-1,3-benzodioxin-4-one **4** as a yellow solid. HPLC, Rt: 2.9 min (purity: 99.8%). ^{1}H NMR ($CDCl_3$) δ 8.88 (d, *J* =2.8 Hz, 1H), 8.44 (dd, *J* = 9.0, 2.8 Hz, 1H), 7.14 (d, *J* = 9.0 Hz, 1H), 1.80 (s, 6H).

To a solution of **4** (4.1 g) in EtOH (30 mL) was added Pd/C (1.947 g) under nitrogen atmosphere. Hydrogenation was performed for 12 hrs at rt using 10 bars of H_2 gas. The reaction mixture was filtered through a bed of celite, washed with EtOH and THF. The filtrates were concentrated under vacuum to give **5** (3.5 g, 98%). Pale yellow solid. ^{1}H NMR ($CDCl_3$) δ 7.71 (d, J = 8.7 Hz, 1H), 7.15 (d, J = 2.6 Hz, 1H), 6.83 (dd, J = 8.7 Hz, 2.6 Hz, 1H), 3.44 (brs, 2H), 2.63 (s, 6H).

Compound **6**. A solution of **3** (5.43 g, 20.7 mmol) and **5** (4.00 g, 20.7 mmol) in toluene (60 mL) was heated at reflux for 3.5 hours with azeotropic removal of water. Then the mixture was cooled down to 0 °C and anhydrous THF (60 mL) and MeOH (60 mL) were added. $NaBH_4$ (1.65 g, 43.6 mmol) was added portionwise and the reaction mixture was stirred for 30 min at 0 °C and 45 min at rt. The reaction mixture was poured into a saturated solution of NaCl and extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and the solvents were removed under reduced pressure to give the crude product **6**. Precipitation from a mixture of EtOAc/MeOH gave 7.1 g (75%) of **6** as a yellow powder. HPLC, Rt: 5.4 min (purity: 97.5%). ^{1}H NMR ($CDCl_3$) δ 7.45 (d, *J* = 8.3 Hz, 2H), 7.39 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.3 Hz, 2H), 7.15-7.06 (m, 3H), 6.80-6.70 (m, 2H), 4.20 (s, 2H), 4.04 (brs, 1H), 2.57 (t, *J* = 7.7 Hz, 2H), 1.65 (s, 6H), 1.61-1.49 (m, 2H), 1.37-1.23 (m, 2H), 0.88 (t, *J* = 7.3 Hz, 3H).

Compound **7**. To a solution of **6** (4.00 g, 9.1 mmol) in anhydrous DCE (60 mL) were added hexanal (Aldrich, 1.80 mL, 14.6 mmol) and sodium triacetoxyborohydride (6.17 g, 29.1 mmol). The resulting mixture was stirred at 70 °C overnight. Then the reaction mixture was poured into water (60 mL) and extracted with DCM (2x60 mL). The combined organic layers were dried over $MgSO_4$ and the solvents were removed under reduced pressure to give a yellow oil. Purification by flash chromatography on silica gel (c-Hex/EtOAc (9/1)) gave **7** (4.41 g, (92%) as a yellow oil. HPLC, Rt: 6.2 min (purity: 100%). LC/MS, M^+(ESI): 524.1. ^{1}H NMR ($CDCl_3$) δ 7.48 (d, *J* = 8.3 Hz, 2H), 7.44 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* =3.0 Hz, 1H), 7.20 (d, *J* = 8.3 Hz, 2H), 7.16 (d, *J* = 8.3 Hz, 2H), 6.86 (dd, *J* = 9.0, 3.0 Hz, 1H), 6.79 (d, *J* = 9.0 Hz, 1H), 4.51 (s, 2H), 3.37 (t, *J* = 7.7 Hz, 2H), 2.63 (t, *J* = 7.7 Hz, 2H), 1.71 (s, 6H), 1.61 (m, 4H), 1.40-1.25 (m, 8H), 0.94 (t, *J* = 7.3 Hz, 3H), 0.90 (t, *J* = 6.7 Hz, 3H).

Compound **1.** To a solution of **7** (4.41 g, 8.4 mmol) in MeOH (500 mL) and water (30 mL) was added an aqueous solution of NaOH (7.0 mL, 5N). The reaction mixture was stirred at rt for 2 hrs and a yellow powder precipitated out progressively. Filtration and washing with water (2x) gave **8** as a yellow powder. HPLC, Rt: 5.3 min (purity: 98.7%). LC/MS, M^+(ESI): 498.3. ^{1}H NMR ($CDCl_3$) δ 10.16 (s, 1H), 7.45 (m, 4H), 7.19 (m, 5H), 6.94 (dd, *J* = 9.0, 3.0 Hz, 1H), 6.86 (d, *J* = 9.0 Hz, 1H), 4.43 (s, 2H), 3.92 (s, 3H), 3.28 (t, *J* = 7.5 Hz, 2H), 2.63 (t, *J* = 7.5 Hz, 2H), 1.60 (m, 4H), 1.30 (m, 8H), 0.92 (m, 6H). To a solution of **8** in MeOH (400 mL) and water (40 mL) was added an aqueous solution of NaOH (6.0 mL, 5N). The reaction mixture was stirred at 60 °C overnight. Then an aqueous solution of HCl (10 mL, 5N) was added and the solvents were removed under reduced pressure. The residue was taken up in water and extracted with Et_2O (3x). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure to give a yellow solid. Precipitation from a DCM/MeOH mixture gave 2.17 g of **1** as a beige powder (53% yield for the last two steps). HPLC, Rt: 4.8 min (purity: 99.7%). LC/MS, M^+(ESI): 484.4, M^-(ESI): 482.2. ^{1}H NMR (DMSO-d_6 with 12 % vol CD_3OD, 300 MHz): δ 7.50-7.33 (m, 4H), 7.30 –7.15 (m, 5H), 6.69 (dd, *J* = 8.7 Hz, *J* = 3.4 Hz, 1H), 6.54 (d, *J* = 8.7 Hz, 1H), 4.35 (s, 2H), 4.15 (s, broad, 3H), 3.90 (m, 1H), 3.69 (m, 1H), 3.61 (m, 1H), 3.56-3.36 (m, 3H), 3.17 (m, 2H), 3.01 (m, 2H), 2.57 (m, 2H), 2.55 (s, 3H), 1.60-1.40 (m, 4H), 1.37-1.13 (m, 8H), 0.95-0.75 (m, 6H). ^{13}C {^{1}H} NMR (DMSO-d_6 with 12 % vol CD_3OD, 75.5 MHz): δ 173.21, 154.16, 143.67, 141.19, 140.67, 131.61, 131.58, 128.99, 127.86, 121.15, 120.27, 120.21, 120.10, 116.73, 116.22, 89.39, 89.14, 71.63, 70.76, 70.66, 68.72, 63.62, 55.71, 52.41,

51.26, 35.18, 33.36, 33.18, 31.64, 27.23, 26.71, 22.59, 22.16, 14.07, 13.92. Compound **1** was obtained as a meglumine salt by treating a solution of **1** (1.650 g, 3.41 mmol) in freshly distilled THF (20 mL) with a solution of N-methyl-D-glucamine (666 mg) in water (4 mL). Water (200 mL) was added and the resulting solution was lyophilized to give 1.93 g (81%) of **1** as a pale yellow powder. HPLC, Rt: 4.8 min (purity: 98.8%). LC/MS, M^+(ESI): 484.0, M^-(ESI): 482.0.

Compound **9**. To a solution of **3** (334 mg, 1.27 mmol) and hexylamine (Aldrich, 98 µL, 1.53 mmol) in DCE (15.00 mL) was added acetic acid (110 µL) and sodium triacetoxyborohydride (405 mg, 1.91 mmol) and the resulting mixture was stirred at rt for 3 hrs. The reaction mixture was then diluted with DCM and washed with a saturated aqueous solution of $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$ and the solvents were removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (DCM, DCM/MeOH/NH_4OH 98:2:1 then 95:5:1) to give **9** (144 mg, 32%). HPLC, Rt: 4.59 min (purity: 98.7%). ^{1}H NMR (CD_3Cl_3, 300 MHz) δ 0.87 (t, *J* = 6.9 Hz, 3H), 0.91 (t, *J* = 7.3 Hz, 3H), 1.28-1.64 (m, 13H), 2.6 (t, *J* = 7.3 Hz, 4H), 3.78 (s, 2H), 7.14 (d, *J* = 8.1 Hz, 2H), 7.28 (d, *J* = 8.3 Hz, 2H), 7.42 (d, *J* = 8.3 Hz, 2H), 7.47 (d, *J* = 8.1 Hz, 2H).

Compound **10**. A suspension of 4-hydroxyisophtalic acid (Aldrich, 5.0 g, 27.5 mmol) in acetone (10 mL), TFA (30 mL) and TFAA (10 mL) was heated at 100°C for 24 hrs. The reaction mixture was concentrated under reduced pressure. The residue was taken up with an aqueous solution of HCl (100 mL, 1N) and extracted with EtOAc (3 x 200 mL). The combined organic layers were dried over $MgSO_4$ and the solvents were removed under reduced pressure. The crude compound was recrystallized from Et_2O (50 mL) to give 4.67 g (77%) of **10** as a beige powder. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.37 (d, *J* =1.9 Hz, 1H), 8.19 (dd, *J* =2.2, 8.7 Hz, 1H), 7.23 (d, *J* =8.3 Hz, 1H), 1.72 (s, 6H). HPLC, Rt: 2.40 min (purity: 95.7%).

Compound **11**. A solution of **10** (144 mg, 0.41 mmol), **9** (92 mg. 0.41 mmol), EDC.HCl (87 mg, 0.46 mmol), HOBT (61 mg, 0.46 mmol) and DIEA (105 µL, 0.62 mmol) in DCM (10 mL) was stirred at rt overnight. Then the reaction mixture was diluted with DCM and washed with a saturated aqueous solution of $NaHCO_3$, a saturated aqueous solution of NH_4Cl and brine. The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silicagel (EtOAc/c-Hex (20/80)) to give **11** (108 mg, 47%) as a colorless oil. HPLC, Rt: 6.14 min (purity: 99.9%). ^{1}H NMR (CD_3Cl_3, 300

MHz) δ 0.82 (m, 3H), 0.91 (t, *J* =7.3 Hz, 3H), 1.32-1.40 (m, 10H), 1.57 (m, 2H), 1.72 (s, 6H), 2.59 (t, *J* =7.6 Hz, 2H), 3.16-3.41 (m, 2H), 4.40-4.72 (m, 2H), 7.00 (m, 2H), 7.14 (d, *J* =8.3 Hz, 2H), 7.25 (m, 1H), 7.42 (d, *J* =8.1 Hz, 2H), 7.48 (d, *J* = 8.1 Hz, 2H), 7.61 (m, 1H), 8.03 (s, 1H).

Compound **2**. A solution of **11** (108 mg, 0.20 mmol) and lithium hydroxide (120 mg, 2.9 mmol) in THF (1 mL) and water (1 mL) was heated at 70 °C overnight. The solvents were removed under reduced pressure. The residue was taken up in EtOAc and washed with an aqueous solution of HCl (1N) and brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure to give 91 mg (91%) of **2**. HPLC, Rt: 5.72 min (purity: 98.9%).

Compound **2** was transformed into a meglumine salt by treating a solution of **11** (91 mg, 98 mmol) in MeOH (2 mL) was added a solution of N-methyl-D-glucamine (35 mg, 0.18 mmol) in water (2 mL). Water (20 mL) was added and the resulting solution was lyophilized to give 103 mg of **2** as a white powder. HPLC, Rt: 5.73 min (purity: 99.6%). LC/MS, M^+(ESI): 512.2, M^- (ESI): 510.2. ^{1}H NMR (CD_3OD, 300 MHz): δ 8.01 (d, *J* = 2.5 Hz, 1H), 7.50 (br d, *J* = 8.0 Hz, 2H), 7.45–7.30 (m, 5H), 7.19 (d, *J* = 8.0 Hz, 2H), 6.80 (br d, *J* = 8.0 Hz, 1H), 4.87 (s, 3H, CD3O*H*), 4.73 (br m, 2H), 3.98 (m, 2H), 3.46 (m, 2H), 3.36 (br m, 2H), 3.31 (m, C*H*D2OD), 3.19 (s, 9H), 2.63 (app t, *J* = 7.5 Hz, 2H), 1.70-1.46 (m, 4H), 1.46-1.00 (m, 8H), 0.94 (t, *J* = 7.5 Hz, 3H), 0.85 (br m, 3H). ^{13}C {1H} NMR (CD_3OD, 75.5 MHz): δ 174.84, 174.57, 164.44, 144.80, 132.79, 132.57, 132.49, 130.70, 129.64, 128.88 (br), 126.62, 123.90 (br), 121.73, 120.02, 117.64, 90.58, 89.26, 69.03 (t, 1J(14N-C) = 3 Hz), 57.04, 54.64 (t, 1J(14N-C) = 4 Hz), 49.00 (sep, *C*D3OD), 36.53, 34.71, 32.37 (br), 29.16 (br), 27.28 (br), 23.53, 23.33, 14.33, 14.26. M^+(ESI): 512.2, M^-(ESI): 510.2.