Supplementary Material

Experimental procedures

*2-(2-hydroxyethoxy)ethyl 4-methylbenzenesulfonate (**1a**) & oxybis(ethane-2,1-diyl) bis(4-methylbenzenesulfonate) (**1b**).* In a 100 mL 2-neck round bottom flask, diethylene glycol (0.50 ml, 4.2 mmol) was dissolved in DCM (42 mL) and cooled to 0 °C in an ice bath. Ag_2O (1.47 g, 6.32 mmol), TsCl (0.88 g, 4.6 mmol), and catalytic amount of KI (0.14 g, 0.84 mmol) was added and the mixture was stirred for 6 hours. The reaction mixture was filtered through a pad of silica and washed with EtOAc. Solvents were removed under vacuum and the crude was purified using silica gel column chromatography using a gradient of EtOAc:hexane (30-60%) to afford mono-substituted product **1a** as a clear oil (848 mg, 77%), and di-substituted product (**1b**) as a solid (80 mg, 8%). **1a**: ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.79 (d, *J*=8.0 Hz, 2H), 7.34 (d, *J*=8.0 Hz, 2H), 4.18 (t, *J*=4.8 Hz, 2H), 3.68 (t, *J*=4.8 Hz, 2H), 3.66 (t, *J*=4.5 Hz, 2H), 3.52 (t, *J*=4.5 Hz, 2H), 2.44 (s, 3H), 2.12 (s, br, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ=145.27, 133.28, 130.16, 128.25, 72.79, 69.49, 68.88, 61.93, 21.94 ppm. HRMS-ESI *m/z* $[M+H]^+$ calcd for $C_{11}H_{16}O_5S$: 261.0791, found: 261.0992. **1b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.78 (d, *J*=8.1 Hz, 4H), 7.35 (d, *J*=8.4 Hz, 4H), 4.09 (t, *J*=4.6 Hz, 4H), 3.60 (t, *J*=4.7 Hz, 4H), 2.45 (s, 6H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 145.30, 133.20, 130.24, 128.29, 69.33, 39.09, 21.99 ppm. HRMS-ESI *m/z* $[M+Na]^+$ calcd for $C_{18}H_{22}O_7S_2Na$: 437.0699, found: 437.1125.

*1-azido-2-(2-azidoethoxy)ethane (**2**).* In a 100 mL 2-neck round bottom flask, **1b** (2.00 g, 4.83 mmol) and NaN3 (689 mg, 10.6 mmol) were dissolved in DMF (26 mL) and the mixture was refluxed at 50 °C overnight. Reaction mixture was cooled to ambient temperature and 5% LiCl(aq) (30 mL) was added and product was extracted with EtOAc (2 × 30 mL). Combined

organics were washed with 5% LiCl(aq) (30 mL), then brine (30 mL). Organic phase was then dried on MgSO4, and concentrated to afford **2** as pale yellow oil (680 mg, 90%). 1H NMR (300 MHz, CDCl3): δ=3.66 (t, J=5.1 Hz, 4H), 3.39 (t, J=4.9 Hz, 4H). 13C NMR (75.5 MHz, CDCl3): δ=70.35, 51.03 ppm. HRMS-ESI m/z $[M+H]^+$ calcd for C4H7N6O: 155.0687, found: 155.1585.*2-(2-azidoethoxy)ethan-1-amine (**3**).* In a 50 mL 2-neck round bottom flask equipped with a purge needle attached to a bubbler, **2** (680 mg, 4.35 mmol) was dissolved in 1:1 mixture of Et_2O:EtOAc (10 mL) and 5% $HCl_{(aq)}$ (10 mL), cooled to 0 °C, and stirred at 300 rpm. PPh_3 (1.14 g, 4.35 mmol) was dissolved in 1:1 mixture of Et_2O:EtOAc (12 mL) and added at a rate of 0.2 mL/min. The solution was allowed to reach ambient temperature while stirring overnight. 2 M $HCl_{(aq)}$ (10 mL) was added and the mixture was transferred to a separating funnel. Organic layer was extracted and the aqueous phase was re-extracted using DCM (3 × 20mL). Using 10 M NaOH, pH of the aqueous phase was adjusted to 12 and the product was extracted with DCM (3 × 20mL). Combined extracts were combined, dried on $MgSO_4$, and concentrated to afford **3** as faint yellow oil (373 mg, 66%). ^{1}H NMR (500 MHz, $CDCl_3$): δ=3.64 (t, *J*=5.0 Hz, 2H), 3.50 (t, *J*=5.2 Hz, 2H), 3.36 (t, *J*=5.0 Hz, 2H), 2.87 (t, *J*=4.7 Hz, 2H), 1.58 (s, br, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ=73.66, 70.26, 51.03, 42.06 ppm. HRMS-ESI *m/z* $[M+H]^+$ calcd for $C_4H_{11}N_4O$: 131.0927, found: 131.0971.

*1-(methyl(4-nitrophenyl carbonate))-7-(4'-(Trans-3''-(3'''-pyridyl)acrylamido)butyl)-1,7-dicarbadodecaborane (**4**).* In a 10 mL round bottom flask under nitrogen, hm-MC4-PPEA (12 mg, 30 μmol) was dissolved in THF (1 mL) and pyridine (3.9 μL, 50 μmol) was added. Solution was cooled to 0 °C in an ice bath while stirring. 4-nitrophenyl chloroformate (10 mg, 50 μmol) was dissolved in THF (0.5 mL) and added to the reaction mixture drop wise. The reaction was allowed to stir overnight while reach ambient temperature. Reaction was quenched using 1 M

$NH_4Cl_{(aq)}$ (5 mL) and Et_2O (5 mL) was added. It was then transferred to a separatory funnel and the organic layer was separated. Et_2O (5 mL) was used to extract again and combined organics were wash with saturated $NaHCO_3$ (3 x 10 mL), brine (10 mL), dried on $MgSO_4$, filtered, and concentrated, and purified using silica gel column chromatography using a gradient of MeOH:$CHCl_3$ (2-10%) to afford **4** as peach colored solid (15 mg, 88%). ^{1}H NMR (500 MHz, $CDCl_3$): δ=8.76 (s, 1H), 8.57 (d, *J*=3.5 Hz, 1H), 8.31-8.27 (m, 2H), 7.79 (d, *J*=8.0 Hz, 1H), 7.61 (d, *J*=16.0 Hz, 1H), 7.40-7.27 (m, 2H), 7.33 (dd, *J*=7.8, *J*=5.0 Hz, 1H), 6.47 (d, *J*=15.5 Hz, 1H), 5.83 (s, br, 1H), 4.44 (s, 2H), 3.36 (q, *J*=6.7 Hz, 2H), 2.00 (t, *J*=8.5 Hz, 2H), 1.52 (p, *J*=7.2 Hz, 2H), 1.46-1.40 (m, 2H), 3.30-1.60 (m, 10H, B-H). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ=165.44, 155.47, 151.93, 150.43, 149.16, 146.02, 137.80, 135.07, 131.11, 125.76, 124.16, 123.12, 122.07, 76.56, 71.47, 69.08, 39.64, 36.83, 29.54, 27.63 ppm. HRMS-ESI *m/z* $[M+H]^+$ calcd for $C_{22}H_{32}B_{10}N_3O_6$: 542.3300, found: 542.3369.

*1-(methyl(2-(2-azidoethoxy)ethyl)carbamate))-7-(4'-(Trans-3''-(3'''-pyridyl)acrylamido)butyl)-1,7-dicarbadodecaborane (**5**).* In a 50 mL pear-shaped flask under nitrogen, **4** (109 mg, 200 μmol) was dissolved in DCM (2.0 mL) and Hünig's base (105 μL, 600 μmol), and (**3**) (32 mg, 0.24 mmol) was added and the reaction was allowed to stir overnight. Solvent was removed under vacuum, and the crude was purified using silica gel column chromatography using a gradient of MeOH:$CHCl_3$ (1-10%) to afford **5** as yellow oil (105 mg, 98%). ^{1}H NMR (500 MHz, $CDCl_3$): δ=8.75 (s, 1H), 8.57 (d, *J*=4.5 Hz, 1H), 7.84 (d, *J*=8.0 Hz, 1H), 7.62 (d, *J*=16.0 Hz, 1H), 7.38 (dd, *J*=8.0, *J*=5.0 Hz, 1H), 6.52 (d, *J*=15.5 Hz, 1H), 6.06 (s, br, 1H), 5.29 (s, br, 1H), 4.25 (s, 2H), 3.66 (t, *J*=4.8 Hz, 2H), 3.56 (t, *J*=5.0 Hz, 2H), 3.40-3.34 (m, 6H), 1.94 (t, *J*=8.2 Hz, 2H), 1.50 (p, *J*=7.2 Hz, 2H), 1.43-1.37 (m, 2H), 3.10-1.60 (m, 10H, B-H). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ=165.69, 155.42, 150.03, 148.73, 137.70, 135.52, 131.38, 124.47, 123.33, 76.06,

73.45, 70.42, 70.16, 65.29, 50.97, 41.29, 39.84, 36.80, 29.41, 27.58 ppm. HRMS-ESI *m/z* $[M+Cl]^-$ calcd for $C_{20}H_{36}B_{10}N_6O_4Cl$: 568.3470, found: 568.3664.

*1-(methyl(2-chloroethyl)carbonate)-7-(4'-(Trans-3''-(3'''-pyridyl)acrylamido)butyl)-1,7-dicarbadodecaborane (**6**)*. In a 10 mL round bottom flask under nitrogen, hm-MC4-PPEA (50 mg, 0.13 mmol) was dissolved in THF (0.5 mL) and Hünig's base (46.3 µL, 0.27 mmol) was added. Solution was cooled to 0 °C in an ice bath while stirring and 2-chloroethyl chloroformate (27.5 µL, 0.27 mmol) was added drop wise. The reaction was allowed to stir overnight while reach ambient temperature. Reaction was quenched using 1 M $NH_4Cl_{(aq)}$ (2 mL) and Et_2O (2 mL) was added. It was then transferred to a separatory funnel and the organic layer was separated. Et_2O (2 × 2 mL) was used to extract again and combined organics were wash with saturated $NaHCO_3$ (3 mL), brine (4 mL), dried on $MgSO_4$, filtered, and concentrated, to afford **6** as light orange oil (52 mg, 81%). The product was used without further purification and immediately used in the next step of the synthesis. HRMS-ESI *m/z* $[M-H]^-$ calcd for $C_{18}H_{30}B_{10}ClN_2O_4$: 482.2888, found: 482.2832.

*1-(methyl(2-azidoethyl)carbonate)-7-(4'-(Trans-3''-(3'''-pyridyl)acrylamido)butyl)-1,7-dicarbadodecaborane (**7**)*. In a 10 mL round bottom flask, **6** (20 mg, 0.04 mmol) was dissolved in DMF (1.5 mL). NaN_3 (77 mg, 1.18 mmol), and catalytic amount of NaI (2 mg, 0.01 mmol) was added and the mixture was refluxed at 60 °C while stirring overnight. The solution was cooled to room temperature, Et_2O (3 mL) was added and washed with 5% $LiCl_{(aq)}$ (3 × 3 mL). Combined aq phase were re-extracted with Et_2O (9 mL), and all organic phase were combined and washed with brine (5 mL). Organic phase was then dried on $MgSO_4$, concentrated, and purified using silica gel column chromatography using a gradient of MeOH:$CHCl_3$ (2-10%) to afford **7** as yellow oil (20 mg, 99%). ^1H NMR (500 MHz, CD_2Cl_2): δ=8.75 (s, 1H), 8.55 (s, 1H),

7.84 (d, *J*=7.5 Hz, 1H), 7.56 (d, *J*=15.5 Hz, 1H), 7.35-7.32 (m, 1H), 6.51 (d, *J*=16.0 Hz, 1H), 5.95 (s, br, 1H), 4.34 (s, 2H), 4.29 (t, *J*=5.0 Hz, 2H), 3.54 (t, *J*=5.0 Hz, 2H), 3.31 (q, *J*=6.5 Hz, 2H), 1.99 (t, *J*=8.5 Hz, 2H), 1.51-1.39 (m, 4H), 2.9-1.55 (m, 10H, B-H). ^{13}C NMR (125.8 MHz, CD_2Cl_2): δ=165.18, 154.15, 150.28, 149.26, 137.15, 134.84, 131.35, 124.20, 123.57, 76.77, 72.31, 68.32, 67.23, 50.05, 39.56, 36.91, 29.55, 27.73 pm. ^{11}B (dc) NMR (96.3 MHz, CD_2Cl_2): δ = -5.97 (1B), -7.69 (1B), -11.07 (6B), -14.05 (2B). HRMS-ESI *m/z* $[M+H]^+$ calcd for $C_{18}H_{32}B_{10}N_5O_4$: 490.3461, found: 490.3444.

*2-(2-azidoethoxy)ethan-1-ol (**8**).* In a 25 mL 3-neck round bottom flask, 2-(2-chloroethoxy)ethan-1-ol (5.00 g, 4.24 ml, 40.1 mmol) was dissolved in H_2O (50 mL). NaN_3 (5.22 g, 80.3 mmol) was added and the mixture was refluxed at 70 °C overnight. Solvents were removed under vacuum and the crude was redissolved in H_2O (8 mL) and extracted with EtOAc (5 × 8 mL). Combined organics were washed with brine (10 mL) and the brine solution was re-extracted using EtOAc (4 × 10 mL). Organic phase was then dried on $MgSO_4$, and concentrated to afford **8** as clear oil (4.56 g, 89%). ^{1}H NMR (500 MHz, $CDCl_3$): δ=3.71 (t, *J*=4.7 Hz, 2H), 3.66 (t, *J*=5.0 Hz, 2H), 3.57 (t, *J*=4.5 Hz, 2H), 3.38 (t, *J*=4.8 Hz, 2H), 2.49-2.46 (m, br, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ=72.69, 70.24, 61.95, 50.94 ppm. HRMS-ESI *m/z* $[M+Na]^+$ calcd for $C_4H_9N_3O_2Na$: 154.0587, found: 154.0674.

Reagent **8** was also synthesized using **1a** (824 mg, 3.17 mmol) and NaN_3 (412 mg, 6.33 mmol) in 1:1 solution of EtOH/H_2O (8 mL), using the same conditions described above to afford **8** as clear oil (347 mg, 84%).

*2-(2-azidoethoxy)acetic acid (**9**).* In a 50 mL 2-neck round bottom flask, **8** (500 mg, 3.81 mmol) was dissolved in acetone (5 mL) and cooled to 0 °C in an ice bath. CrO_3 (762 mg, 7.62 mmol)

was dissolved in 1.5 M $H_2SO_{4(aq)}$ (7.62 mL) and added to the reaction mixture drop wise. Ice bath was removed and the solution was stirred for 3 hours. Mixture was filtered and solvents were removed under reduced pressure. Crude was dissolved in 2M $HCl_{(aq)}$ (10 mL) and extracted using EtOAc (3 × 15mL). Combined organics were dried on $MgSO_4$, filtered, and concentrated. Crude product was further purified using a short neutral alumina plug using EtOAc to afford **9** as dark blue oil (406 mg, 73%). ^{1}H NMR (500 MHz, $CDCl_3$): δ=10.17 (s, br, 1H), 4.21 (s, 2H), 3.76 (t, *J*=4.8 Hz, 2H), 3.47 (t, *J*=4.8 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ=175.57, 70.79, 68.35, 51.02 ppm. HRMS-ESI *m/z* $[M]^+$ calcd for $C_4H_7N_3O_3$: 145.0493, found: 144.9862.

*2-(2-azidoethoxy)acetyl chloride (**10**).* In a 50 mL 2-neck round bottom flask attached to a vacuum line equipped with a secondary trap, **9** (78 mg, 60 µL, 0.54 mmol) was dissolved in DCM (0.6 mL) and DMF (2 µL, 0.03 mmol) was added as a catalyst. While stirring, thionyl chloride (78 µL, 1.07 mmol) was added and the reaction mixture was allowed to stir for 2 hours at room temperature. The vessel was evacuated under reduced pressure to remove solvent and any gaseous byproducts. This afforded quantitative amount of **10**, which was used without further purification.

*1-(methyl(2-(2-azidoethoxy)acetate))-7-(4'-(Trans-3''-(3'''-pyridyl)acrylamido)butyl)-1,7-dicarbadodecaborane (**11**).* In a 10 mL round bottom flask under nitrogen, hm-MC4-PPEA (85 mg, 0.23 mmol) was dissolved in THF (1.0 mL) and added to (**10**) (88 mg, 0.54 mmol). Pyridine (43.3 µL, 0.54 mmol) was dissolved in THF (1.0 mL) and added to the reaction mixture drop wise. The reaction was allowed to stir overnight. $CHCl_3$ (2.0 ml) was added to the reaction mixture and filtered over celite. Crude was concentrated, Hünig's base (5 drops) was added and purified using silica gel column chromatography using a gradient of MeOH:$CHCl_3$ (0-10%) to afford **11** as yellow oil (83 mg, 73%). ^{1}H NMR (500 MHz, $CDCl_3$): δ=8.76 (s, br, 1H), 8.57 (s,

br, 1H), 7.80 (d, *J*=7.5 Hz, 1H), 7.61 (d, *J*=16.0 Hz, 1H), 7.33 (dd, 7.5, *J*=5.0 Hz, 1H), 6.47 (d, *J*=15.5 Hz, 1H), 5.86 (s, br, 1H), 4.35 (s, 2H), 4.19 (s, 2H), 3.75 (t, *J*=5.0 Hz, 2H), 3.45 (t, *J*=5.0 Hz, 2H), 3.35 (q, *J*=6.7 Hz, 2H), 1.96 (t, *J*=8.3 Hz, 2H), 1.50 (p, *J*=7.1 Hz, 2H), 1.44-1.38 (m, 2H), 3.20-1.60 (m, 10H, B-H). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ=169.12, 165.44, 150.50, 149.24, 137.80, 134.96, 131.07, 124.14, 123.07, 76.30, 72.21, 70.90, 68.46, 64.90, 51.07, 39.66, 36.81, 29.50, 27.61 pm. HRMS-ESI *m/z* $[M+Cl]^-$ calcd for $C_{19}H_{33}B_{10}N_5O_4Cl$: 539.3204, found: 539.3143.

*3-(2-(2-azidoethoxy)ethoxy)prop-1-yne (**12**).* In a 100 mL 2-neck round bottom flask, THF (20 mL) was added to 60% dispersion of NaH in mineral oil (0.85 g, 21 mmol). The suspension was cooled to 0 °C, while stirring, and **8** (1.39 g, 1.25 mL, 10.6 mmol) was added gradually. The reaction was allowed to reach ambient temperature and once hydrogen gas stopped bubbling out of the reaction mixture, the solution was cooled to 0 °C again and 80 wt. % propargyl bromide in toluene (1.89 g, 1.42 mL, 12.7 mmol) was added drop wise. The resulting solution was allowed to stir for 3 hours while slowly reaching ambient temperature. Reaction mixture was then cooled to 0 °C and quenched with H_2O (3 mL). 1 M $NH_4Cl_{(aq)}$ (20 mL) and Et_2O (3 mL) was added and the organic layer was extracted. Et_2O (2 × 23 mL) was used to extract again and combined organics were dried on $MgSO_4$, filtered, and concentrated under reduced pressure and purified by silica gel column chromatography using a EtOAc:Hexane gradient, to afford **12** as orange oil (1.15 g, 64%). ^{1}H NMR (500 MHz, $CDCl_3$): δ=4.21 (d, *J*=2.5 Hz, 2H), 3.73-3.66 (m, 6H), 3.40 (t, *J*=5.0 Hz, 2H), 2.43 (t, *J*=2.2 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ=79.87, 74.92, 70.83, 70.39, 69.50, 58.82, 51.00 ppm.

*2-(2-(prop-2-yn-1-yloxy)ethoxy)ethan-1-amine (**13**).* In a 50 mL 2-neck round bottom flask equipped with a purge needle attached to a bubbler, **12** (1.12 g, 6.60 mmol) was dissolved in

THF (11 mL). PPh_3 (2.60 g, 9.90 mmol) and DI water (0.20 mL) was added all at once and the solution was stirred overnight. All solvents were removed under reduced pressure and crude was redissolved in 2 M $HCl_{(aq)}$ (11 mL) and Et_2O (11 mL) while stirring vigorously. The ppt was filtered using a medium grade frit funnel and the filtrate was transferred to a separating funnel. The organic layer was extracted and Et_2O (2 × 20 mL) was used to extract again. 10 M $NaOH_{(aq)}$ was added to the aqueous layer to adjust the pH to 12 and DCM (3 × 20 mL) was used to extract the product. Combined organics were dried on $MgSO_4$, filtered, and concentrated under reduced pressure to afford **13** as dark orange oil (0.76 g, 80%). ^{1}H NMR (500 MHz, $CDCl_3$): δ=4.20 (d, *J*=2.0 Hz, 2H), 3.70-3.67 (m, 2H), 3.65-3.61 (m, 2H), 3.51 (t, *J*=5.3 Hz, 2H), 2.87 (t, *J*=4.8 Hz, 2H), 2.43 (t, *J*=2.5 Hz, 1H), 1.79 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ=79.90, 74.91, 73.57, 70.42, 69.41, 58.74, 42.00 ppm. HRMS-ESI *m/z* $[M+H]^+$ calcd for $C_7H_{14}NO_2$: 144.1019, found: 144.0943.

*5-(dimethylamino)-N-(2-(2-(prop-2-yn-1-yloxy)ethoxy)ethyl)naphthalene-1-sulfonamide (**14**)*. In a 10 mL round bottom flask under nitrogen, dansyl chloride (100 mg, 0.370 mmol) was dissolved in THF (1 mL) and cooled to 0 °C in an ice bath. Hünig's base (71 µL, 0.41 mmol), and **13** (58 mg, 0.41 mmol) were dissolved in THF (1 mL) and added to the reaction mixture drop wise. Ice bath was removed and the reaction vessel was cover with foil and allowed to stir overnight. Following day, Et_2O was added to the reaction mixture to promote precipitation and the mixture was filtered using a fine grade frit funnel. The filtrate was concentrated under vacuum, and the crude was purified using silica gel column chromatography using a gradient of EtOAc:Hexane (5-100%) to afford **14** as yellow/green thick oil that hardened overtime in the fridge (134 mg, 96%). ^{1}H NMR (300 MHz, CD_2Cl_2): δ=8.60 (d, J=8.7 Hz, 1H), 8.31-8.25 (m, 2H), 7.67-7.56 (m, 2H), 7.26 (d, *J*=7.2 Hz, 1H), 5.32 (t, *J*=5.5 Hz, 1H), 4.14 (d, *J*=2.4 Hz, 2H),

3.53-3.5 (m, 2H), 3.39-3.35 (m, 4H), 3.10 (q, *J*=5.3 Hz, 2H), 2.93 (s, 6H), 2.53 (t, *J*=2.4 Hz, 1H). ^{13}C NMR (75.5 MHz, CD_2Cl_2): δ=152.57, 135.41, 130.80, 130.31, 129.96, 129.78, 128.73, 123.60, 118.95, 115.57, 80.03, 74.69, 70.41, 69.35, 69.31, 58.60, 45.59, 43.52 ppm. HRMS-ESI *m/z* $[M+H]^+$ calcd for $C_{19}H_{25}N_2O_4S$: 377.1530, found: 377.1586.

*Carbamate prodrug (**15**).* In a 10 mL round bottom flask, **5** (35 mg, 66 μmol) was dissolved in degassed DMSO (1 mL). Hünig's base (17.3 μL, 99 μmol) and PMDETA (20.7 μL, 99 μmol) were added to the reaction mixture. **14** (30 mg, 79 μmol) was dissolved in degassed DMSO (1 mL) and transferred to the reaction mixture. CuI (19 mg, 99 μmol) was added and the mixture was sonicated for an hour in a sonication bath. EtOAc (18 mL), and EtO_2 (3 mL) were added to the reaction mixture and the mixture was washed using DI H_2O (2 × 20 mL). Combined aqueous phase were further extracted with EtO_2 (20 mL). The organic extracts were combined and washed with 5% $Na_2S_2O_{3(aq)}$ (20 mL), then with brine (2 × 25 mL), dried on $MgSO_4$, concentrated, and purified using silica gel column chromatography using a gradient of MeOH:$CHCl_3$ (1-5%) to afford **15** as green/orange oil (45 mg, 75%). ^{1}H NMR (500 MHz, $CDCl_3$): δ=8.76 (s, br, 1H), 8.56 (s, br, 1H), 8.52 (d, *J*=8.5 Hz, 1H), 8.23 (d, *J*=8.5 Hz, 1H), 8.20 (d, *J*=7.5 Hz, 1H), 7.84 (s, 1H), 7.76 (d, *J*=7.5 Hz, 1H), 7.58 (d, *J*=16.0 Hz, 1H), 7.517.47 (m, 2H), 7.29 (s, br, 1H), 7.16 (d, *J*=7.5 Hz, 1H), 6.55 (d, *J*=15.5 Hz, 1H), 6.42 (s, br, 1H), 5.93 (s, br, 1H), 5.34 (t, *J*=4.8 Hz, 2H), 3.56 (s, br, 1H), 4.70 (s, br, 2H), 4.53 (t, *J*=5.0 Hz, 2H), 4.21 (s, 2H), 3.82 (t, *J*=5.0 Hz, 2H), 3.59 (t, *J*=4.2 Hz, 2H), 3.47 (t, *J*=5.0 Hz, 4H), 3.41 (t, *J*=4.5 Hz, 2H), 3.35-3.29 (m, 4H), 3.08-3.07 (m, 2H), 2.87 (s, 6H), 1.92 (t, *J*=8.5 Hz, 2H), 1.48 (p, *J*=7.0 Hz, 2H), 1.44-1.38 (m, 2H), 2.70-1.65 (m, 10H, B-H). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ=165.63, 155.35, 152.29, 150.23, 149.15, 145.18, 137.27, 135.21, 135.06, 130.79, 130.24, 129.95, 129.65, 128.66, 128.66, 124.39, 123.60, 123.52, 119.15, 115.60, 76.26, 73.50, 70.52,

70.21, 69.88, 69.55, 69.36, 65.20, 64.96, 50.55, 45.74, 43.38, 41.12, 39.64, 36.89, 29.33, 27.67 ppm. HRMS-ESI *m/z* $[M+H]^+$ calcd for $C_{39}H_{61}B_{10}N_8O_8S$: 910.5325, found: 910.5494. 1H and 13C NMR spectra are depicted in Figure S8 and Figure S9 respectively.

*Carbonate prodrug (**16**).* In a 10 mL round bottom flask, (**7**) (31 mg, 62 μmol) was dissolved in degassed DMSO (0.5 mL). Hünig's base (12 μL, 66 μmol) and PMDETA (14 μL, 66 μmol) were added to the reaction mixture. **14** (23 mg, 61 μmol) was dissolved in degassed DMSO (1.0 mL) and transferred to the reaction mixture. CuI (13 mg, 66 μmol) was added and the mixture was sonicated for an hour in a sonication bath. EtOAc (10 mL), and EtO_2 (1 mL) were added to the reaction mixture and the mixture was washed using DI H_2O (3 × 10 mL). Combined aqueous phase were further extracted with EtOAc (5 × 10 mL). The organic extracts were combined and washed with brine (2 × 25 mL), dried on $MgSO_4$, concentrated, and purified using silica gel column chromatography using a gradient of MeOH:$CHCl_3$ (1-5%) to afford **16** as green/orange oil (53 mg, 99%). ^{1}H NMR (500 MHz, $CDCl_3$): δ=8.74 (s, br, 1H), 8.54 (s, br, 1H), 8.52 (s, br, 1H), 8.23, (d, *J*=9.0 Hz, 1H), 8.21 (d, *J*=7.0 Hz, 1H), 7.84 (s, 1H), 7.77 (d, *J*=8.0 Hz, 1H), 7.58 (d, *J*=16.0 Hz, 1H), 7.50 (t, *J*=8.2 Hz, 2H), 7.31-7.29 (m, br, 1H), 7.17 (d, *J*=7.5 Hz, 1H), 6.61 (t, br, *J*=5.2 Hz, 1H), 6.56 (d, *J*=15.5 Hz, 1H), 5.89 (t, br, *J*=6.0 Hz, 1H), 4.70-4.68 (m, 4H), 4.59 (t, *J*=4.8 Hz, 2H), 4.26 (s, 2H), 3.59-3.57 (m, 2H), 3.45-3.43 (m, 2H), 3.41 (t, *J*=5.0 Hz, 2H), 3.37 (q, *J*=6.2 Hz, 2H), 3.08 (q, *J*=5.2 Hz, 2H), 2.88 (s, 6H), 1.95-1.92 (m, 2H), 1.53-1.48 (m, 2H), 1.47-1.40 (m, 2H), 2.70-1.40 (m, br, 10H, B-H). ^{13}C NMR (126 MHz, $CDCl_3$): δ=165.61, 153.97, 152.24, 149.72, 148.68, 145.61, 136.99, 135.53, 135.27, 130.77, 130.24, 129.97, 129.68, 128.69, 128.13, 124.20, 123.92, 123.55, 119.21, 115.63, 114.29, 76.54, 72.04, 70.51, 69.93, 69.59, 68.32, 66.50, 64.88, 49.33, 45.77, 43.40, 39.58, 36.97, 29.32, 27.70 ppm. HRMS-ESI *m/z* $[M+H]^+$ calcd for $C_{37}H_{56}B_{10}N_7O_8S$: 867.4902, found: 867.5270. 1H and 13C NMR spectra are

depicted in Figure S10 and Figure S11 respectively.

*Ester prodrug (**17**).* In a 10 mL round bottom flask, **11** (25 mg, 67.4 μmol) was dissolved in degassed DMSO (0.5 mL). Hünig's base (11.7 μL, 67.4 μmol) and PMDETA (14.1 μL, 67.4 μmol) were added to the reaction mixture. **14** (25 mg, 67.4 μmol) was dissolved in degassed DMSO (1.0 mL) and transferred to the reaction mixture. CuI (13 mg, 67.4 μmol) was added and the mixture was sonicated for an hour in a sonication bath. EtOAc (12 mL), and EtO_2 (8 mL) were added to the reaction mixture and the mixture was washed using DI H_2O (3 × 10 mL). The organic phase was washed with brine (10 mL), dried on $MgSO_4$, concentrated, and purified using silica gel column chromatography using a gradient of MeOH:$CHCl_3$ (2-10%) to afford **17** as green/orange oil (35 mg, 60%). ^{1}H NMR (500 MHz, $CDCl_3$): δ=8.78 (s, br, 1H), 8.51 (d, *J*=8.5 Hz, 1H), 8.23 (d, *J*=8.5 Hz, 1H), 8.20 (dd, *J*=7.5, *J* 1.0 Hz, 1H), 7.86 (s, 1H), 7.75 (d, *J*=8.0 Hz, 1H), 7.58 (d, *J*=15.5 Hz, 1H), 7.49 (t, *J*=7.7 Hz, 2H), 7.30 (s, br, 1H), 7.16 (d, *J*=7.5 Hz, 1H), 6.54 (d, *J*=16.0 Hz, 1H), 6.47 (t, br, *J*=5.2 Hz, 1H), 5.88 (t, br, *J*=5.7 Hz, 1H), 4.66 (s, 2H), 4.58 (t, *J*=5.0 Hz, 2H), 4.29 (s, 2H), 4.09 (s, 2H), 3.95 (t, *J*=5.0 Hz, 2H), 3.56-3.54 (m, 2H), 3.41-3.39 (m, 2H), 3.37 (t, *J*=5.0 Hz, 2H), 3.33 (q, *J*=6.7 Hz, 2H), 3.07 (q, *J*=5.2 Hz, 2H), 2.86 (s, 6H), 1.92 (t, *J*=8.5 Hz, 2H), 1.51-1.45 (m, 2H), 1.42-1.36 (m, 2H), 2.80-1.63 (m, 10H, BH). ^{13}C NMR (126 MHz, $CDCl_3$): δ=168.91, 165.62, 152.24, 150.16, 149.08, 145.09, 137.27, 135.31, 134.99, 130.71, 130.19, 129.92, 129.59, 128.66, 128.09, 124.55, 123.56, 123.50, 119.16, 115.56, 114.23, 76.42, 72.09, 70.52, 70.15, 69.76, 69.51, 68.40, 64.93, 64.82, 50.52, 45.73, 43.37, 39.55, 36.83, 29.32, 27.65 ppm. HRMS-ESI *m/z* $[M+H]^+$ calcd for $C_{38}H_{58}B_{10}N_7O_8S$: 881.5059, found: 881.5225. 1H and 13C NMR spectra are depicted in Figure S12 and Figure S13 respectively.

Relevant figures

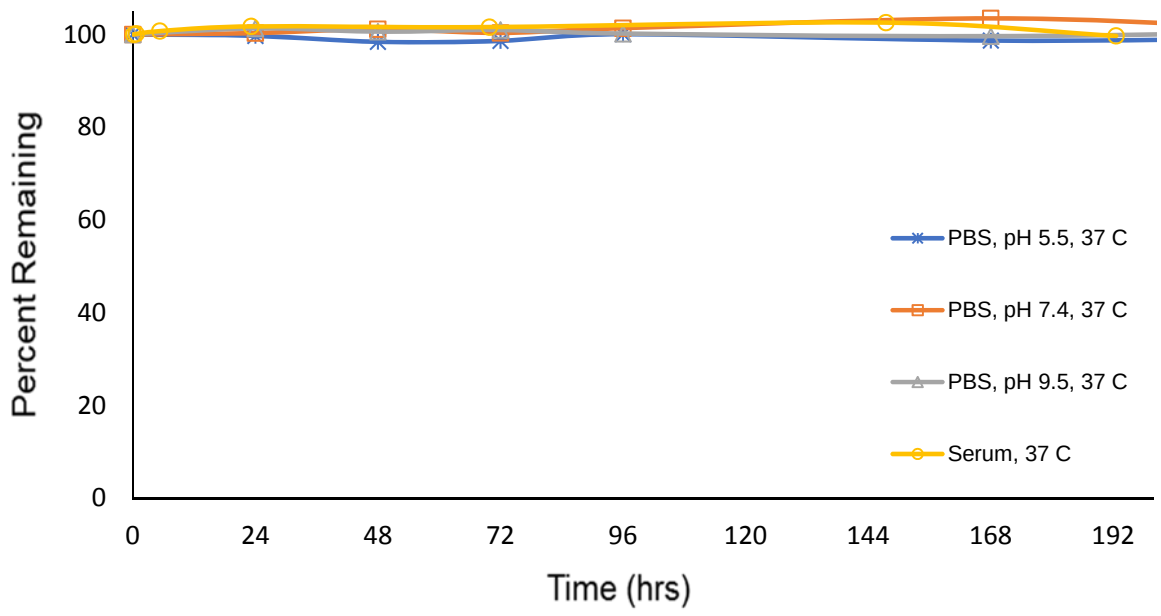

Figure S1. Depicts the stability of **15** over several days for each test condition.

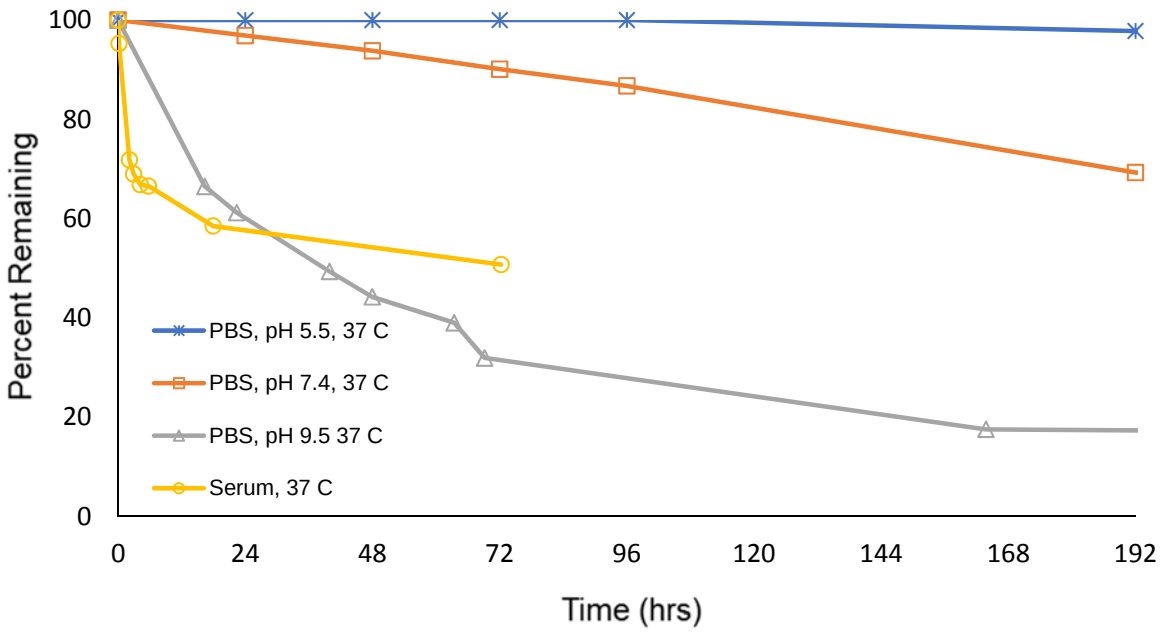

Figure S2. Depicts the stability of **16** over several days for each test condition.

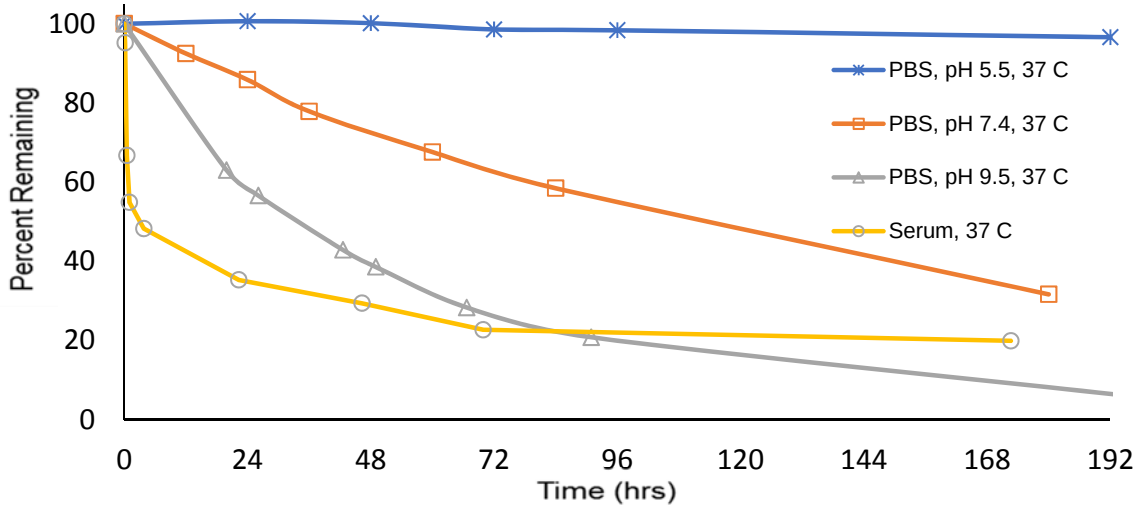

Figure S3. Depicts the stability of **17** over several days for each test condition.

Cell Lines and Reagents

MCF7 and 184A1 cells were purchased from ATCC (Manassas, VA). An MTT assay kit was purchased from Promega (Madison, WI). FK866 was purchased from Enzo Life Sciences (Farmingdale, NY).

MTT assay

The MTT assay was performed according to the manufacturer's protocol.[1] Briefly, 184A1 or MCF7 cells were plated in 96 well plates at a density of 10,000 cells per well. The cells were maintained at 37° C overnight under an atmosphere containing 5% CO_2 and saturated water vapor. These cells were then treated with varying doses of each test agent and incubated for a period of 72 h. The MTT reagent was then added to the cells for a period of 3 h to allow for the development of formazan crystals. Solubilization buffer was added to the wells and the optical density was measured at 570 nm.

Recombinant Nampt Inhibition Assay

The NAMPT assay was performed according to the manufacturers protocol (CycLex NAMPT Colorimetric Assay Kit, MBL International Corp., Woburn, MA. Briefly, we used the "1-Step Assay Method" for which following reagents were mixed to produce the assay buffer: 10 µl each of 10X Nampt assay buffer, nicotinamide, PRPP, ATP and EtOH; 2 µl each of recombinant NMNAT1, WST-1, ADH, diaphorase and dH2O. These solutions were stored in an ice bath before starting each assay.

The Nampt inhibition assay was performed by mixing 2 µl of various concentrations (to make 1 pM-100 nM) of each test agent (or 2 µl DMSO as vehicle control) with the following: 2 µl recombinant Nampt and 36 µl dH2O. The reaction was initiated by adding 60 µL of 1- Step Assay Buffer to each well and mixed thoroughly, followed by incubation at 30° C for 20 mins. After this period, the absorbance at 450 nm was measured and compared with the positive control.

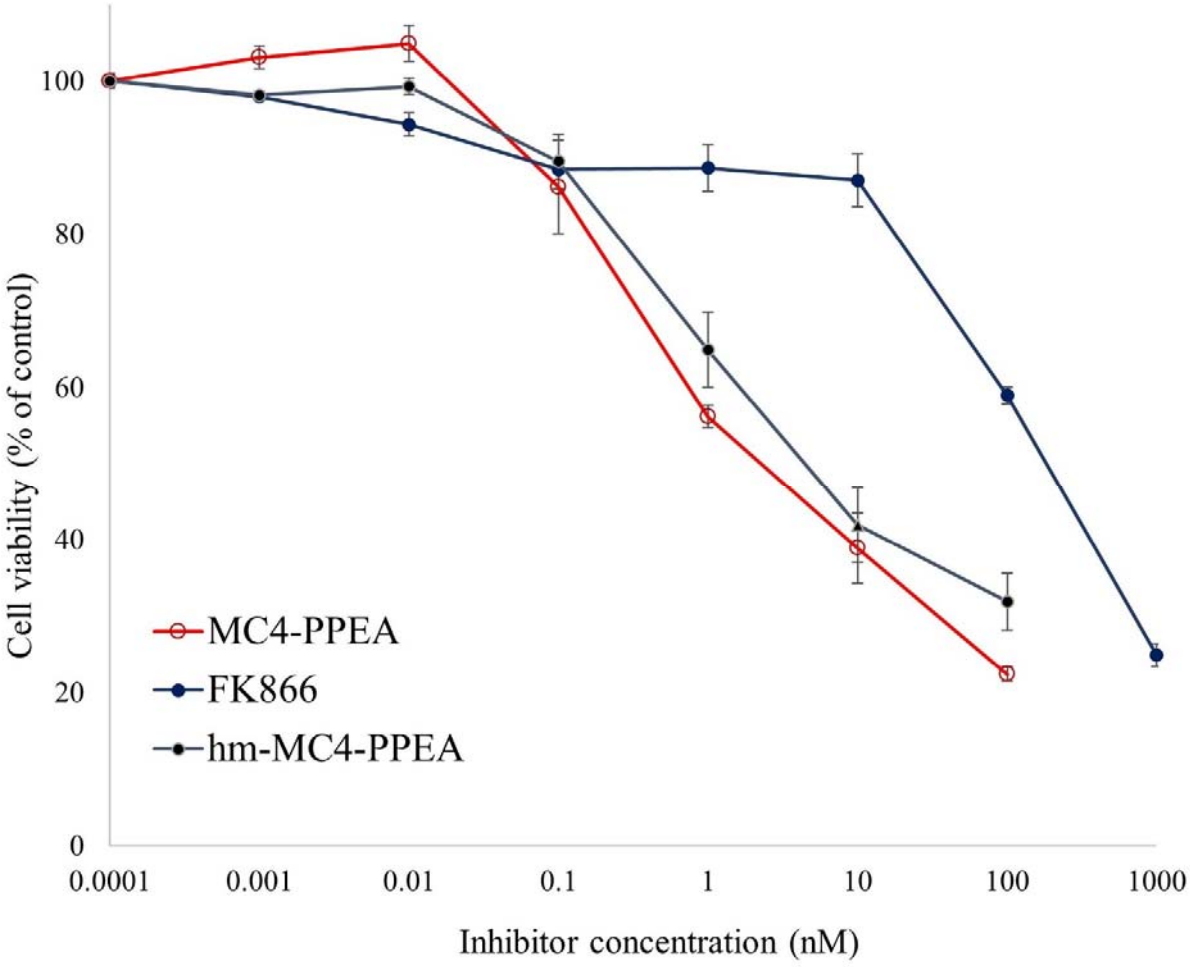

Figure S4. Concentration dependent cell viability exhibited by MC4-PPEA, hm-MC4-PPEA, and FK866 against the A549 human lung cancer cell line. Error bars represent the mean ± SD, n=4.

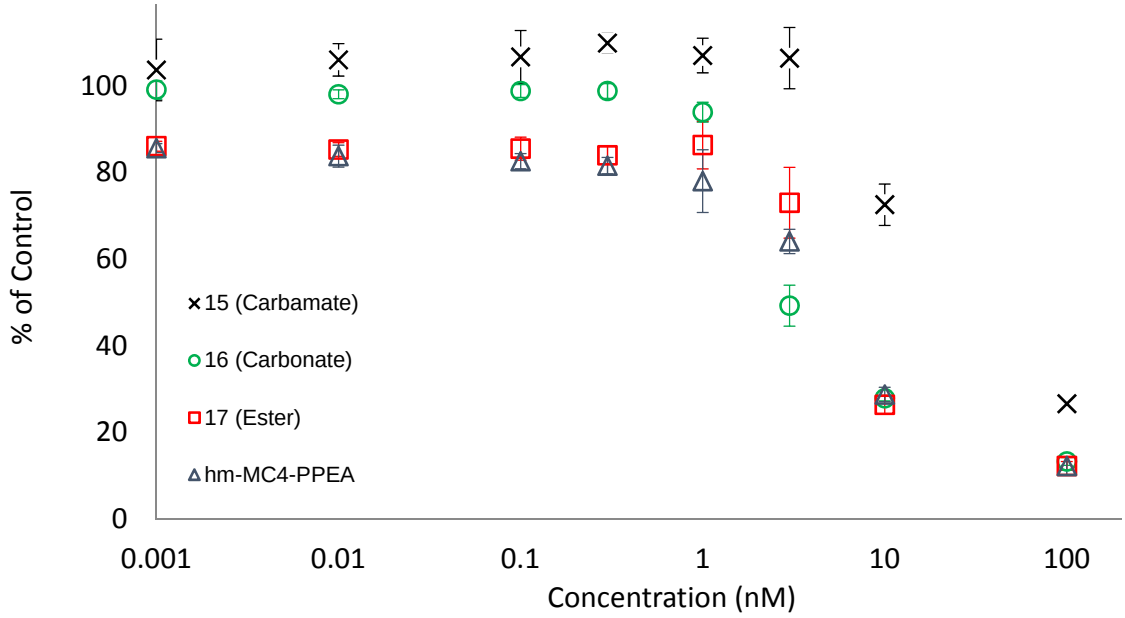

Figure S5. Concentration dependent cell viability of **15**, **16**, **17**, and **hm-MC4-PPEA** against the T47D human breast cancer cell line. Error bars represent the mean ± SD, n=4.

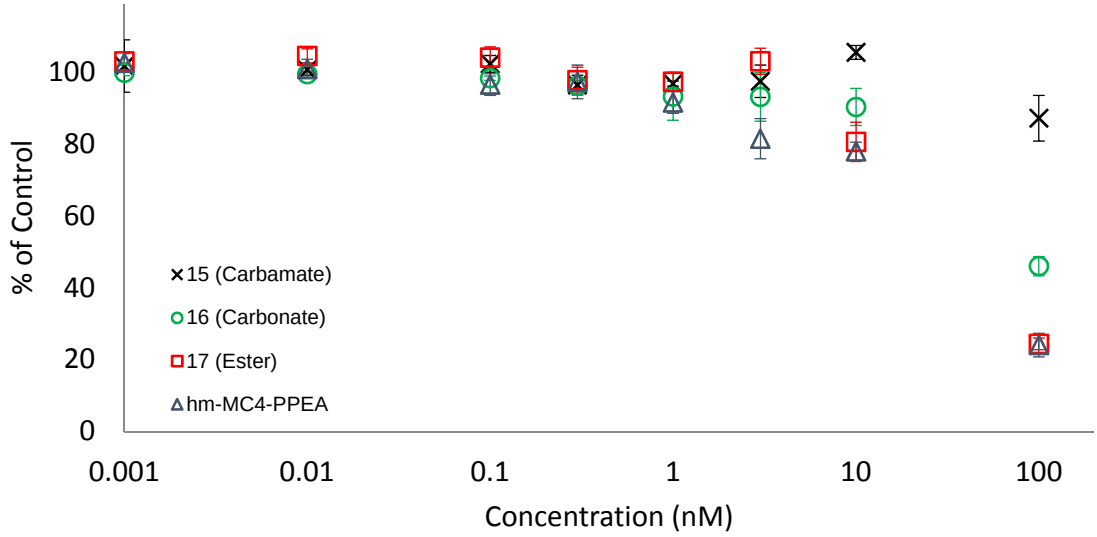

Figure S6. Concentration dependent cell viability of **15**, **16**, **17**, and **hm-MC4-PPEA** against the MCF7 human breast cancer cell line. Error bars represent the mean ± SD, n=4.

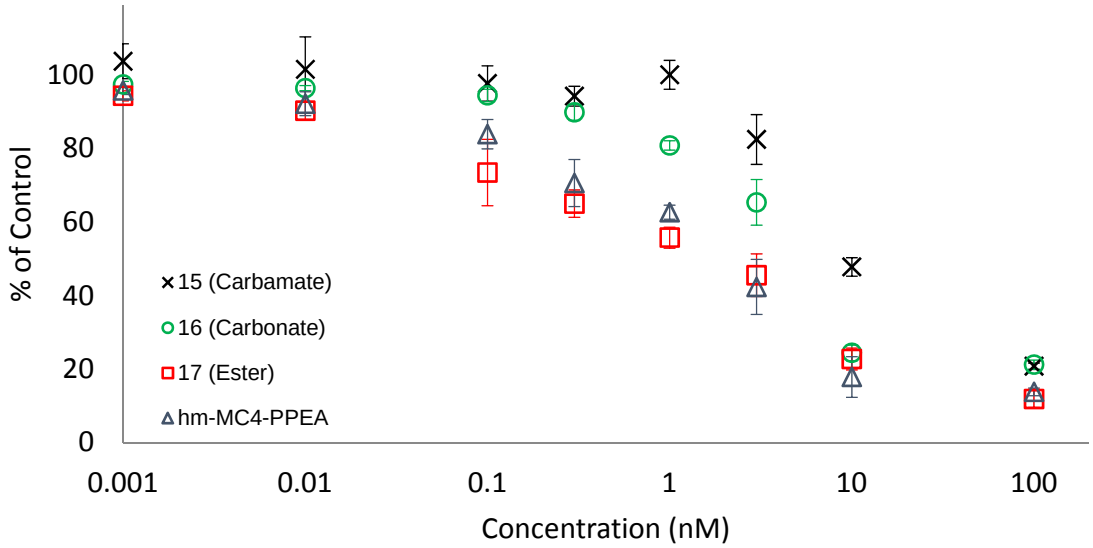

Figure S7. Concentration dependent cell viability of **15**, **16**, **17**, and **hm-MC4-PPEA** against the 184A1 human breast cancer cell line. Error bars represent the mean ± SD, n=4.

[1]H and [13]C NMR spectra of compounds 15-17

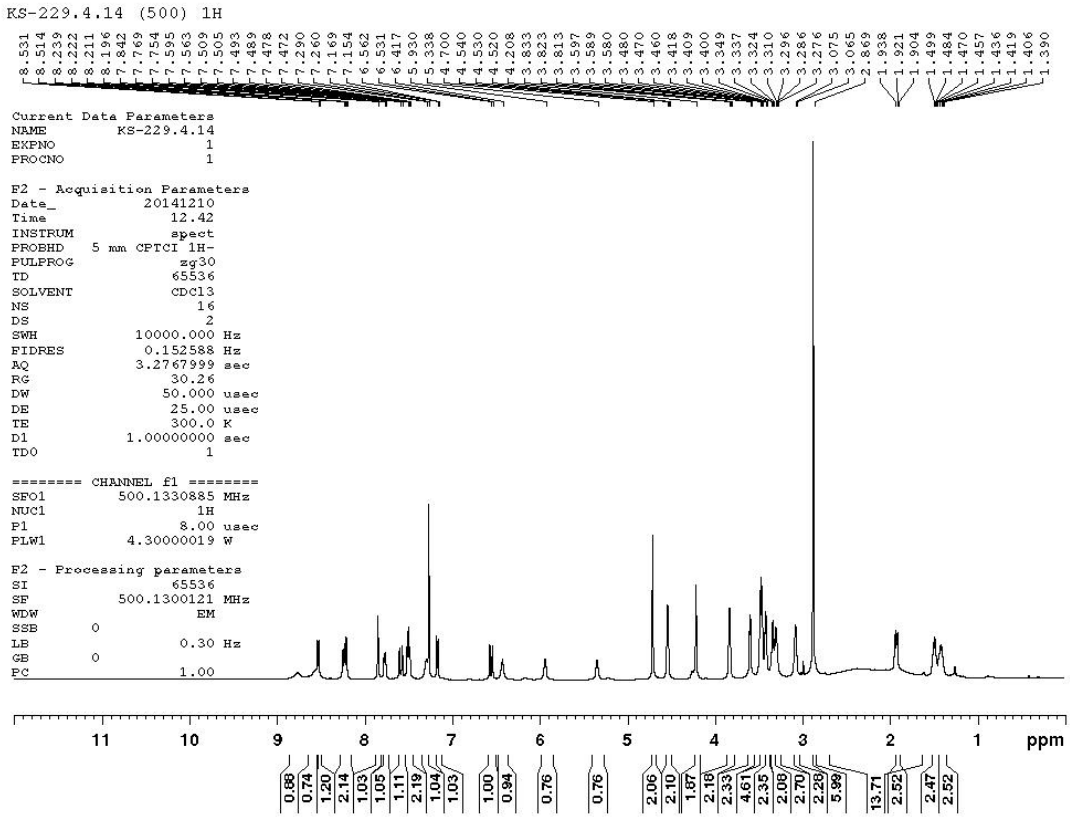

Figure S8. 1H NMR spectrum (CDCl3, 500 MHz) of carbamate prodrug (**15**)

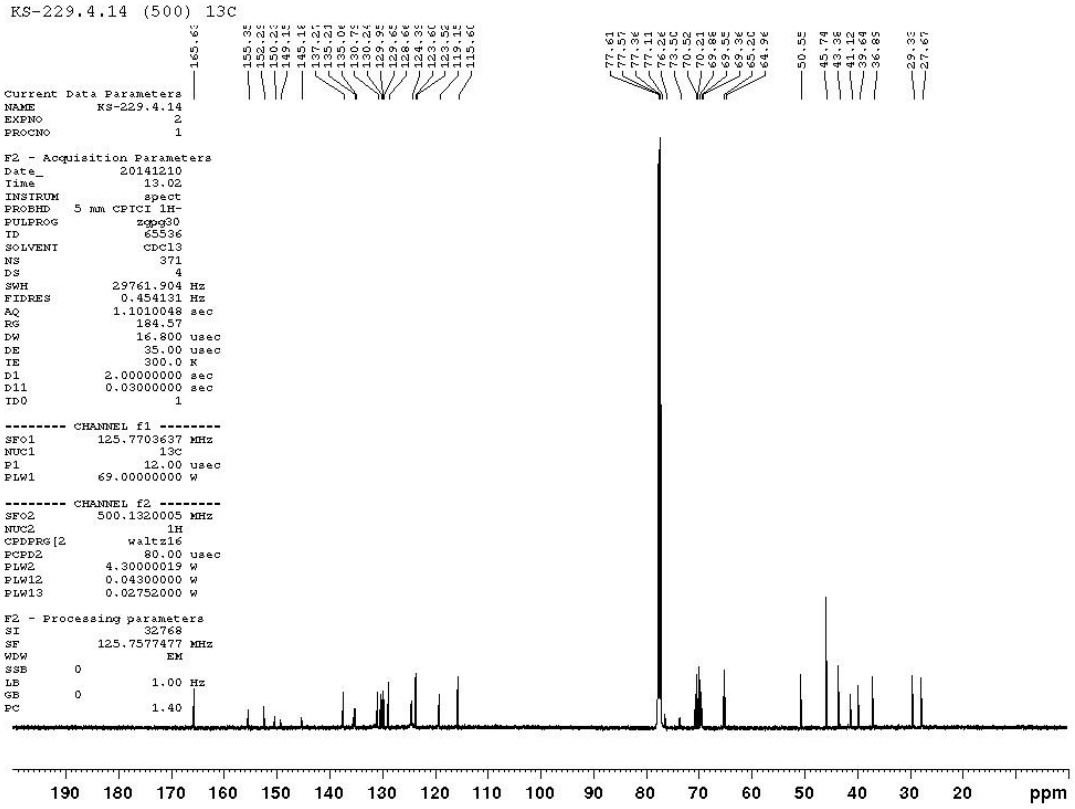

Figure S9. 13C NMR spectrum (CDCl3, 125.8 MHz) of carbamate prodrug (**15**)

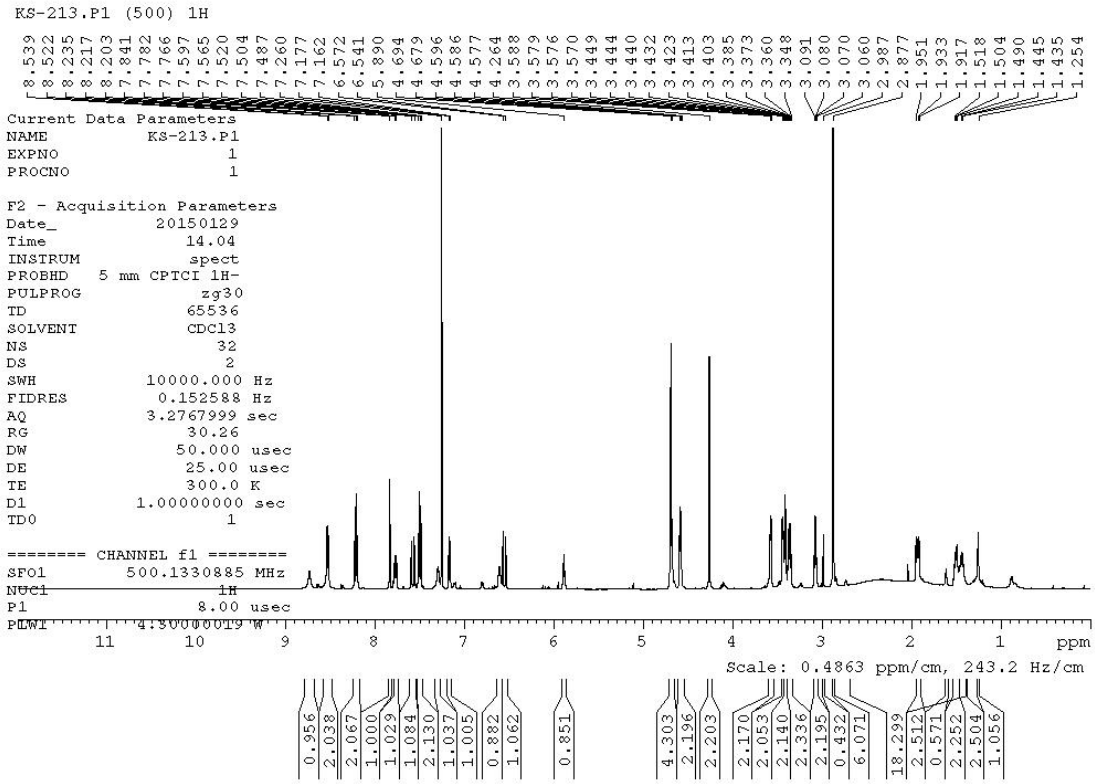

Figure S10. 1H NMR spectrum (CDCl3, 500 MHz) of carbonate prodrug (**16**)

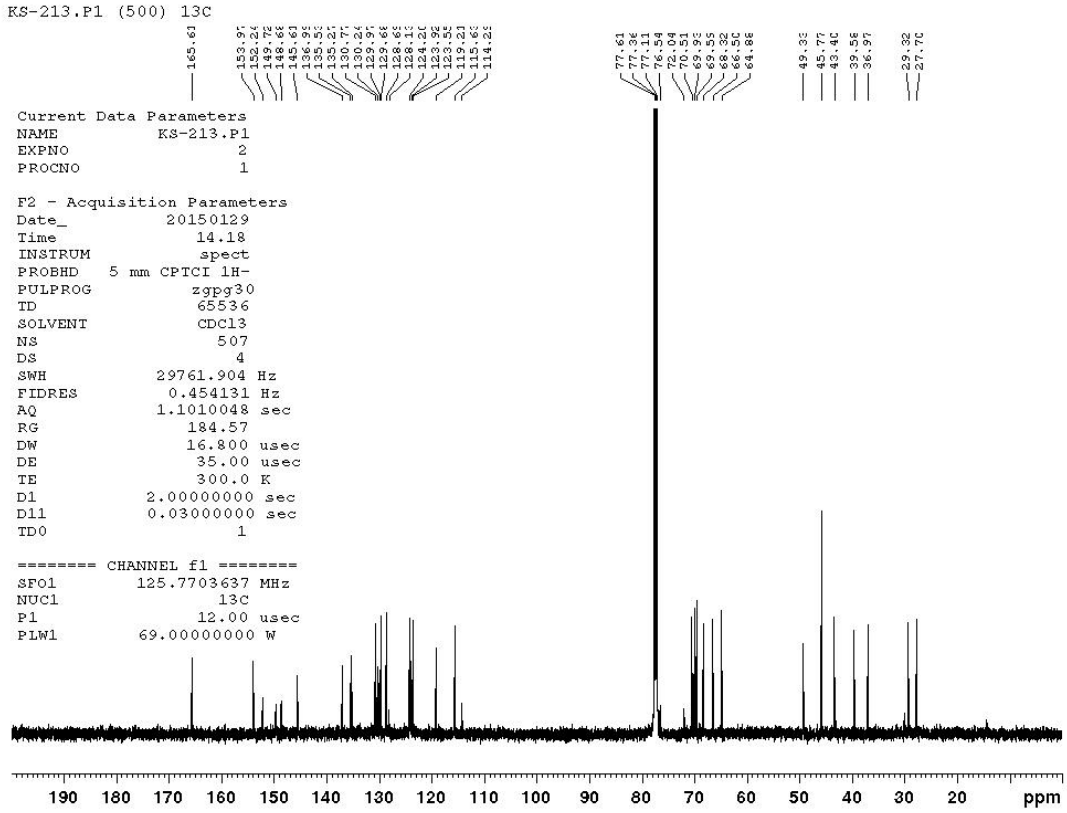

Figure S11. 13C NMR spectrum (CDCl3, 125.8 MHz) of carbonate prodrug (**16**)

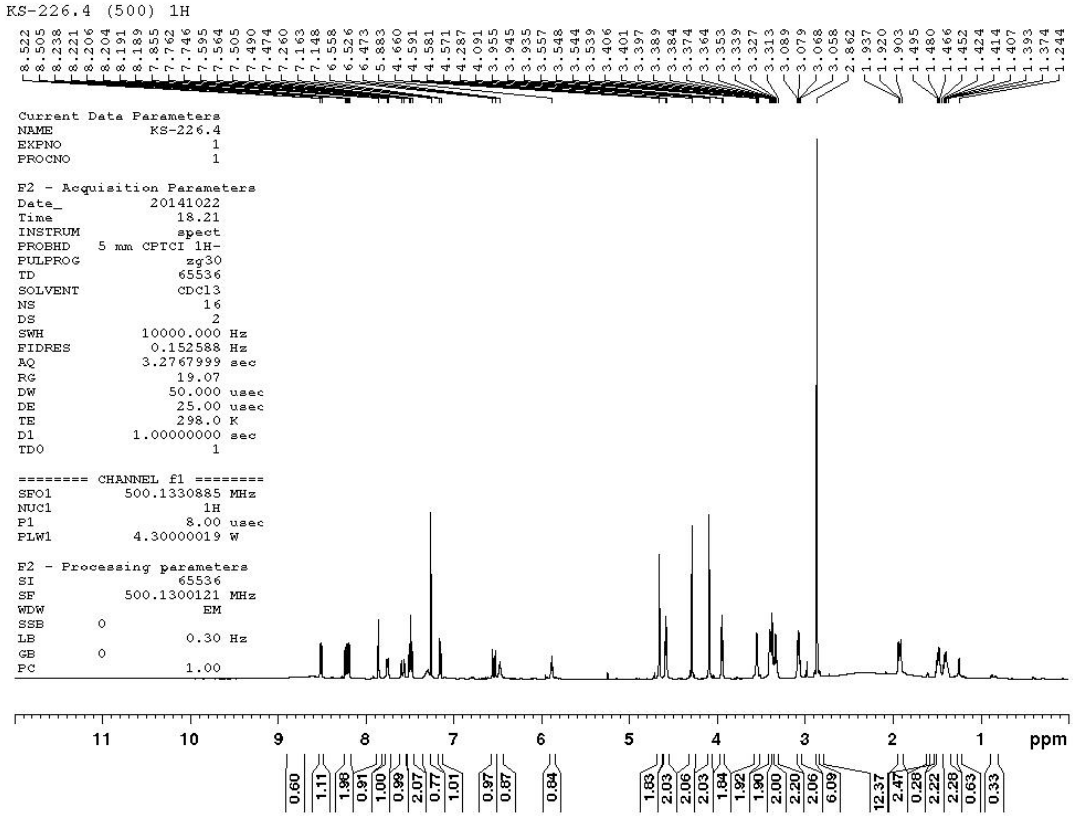

Figure S12. 1H NMR spectrum (CDCl3, 500 MHz) of ester prodrug (**17**)

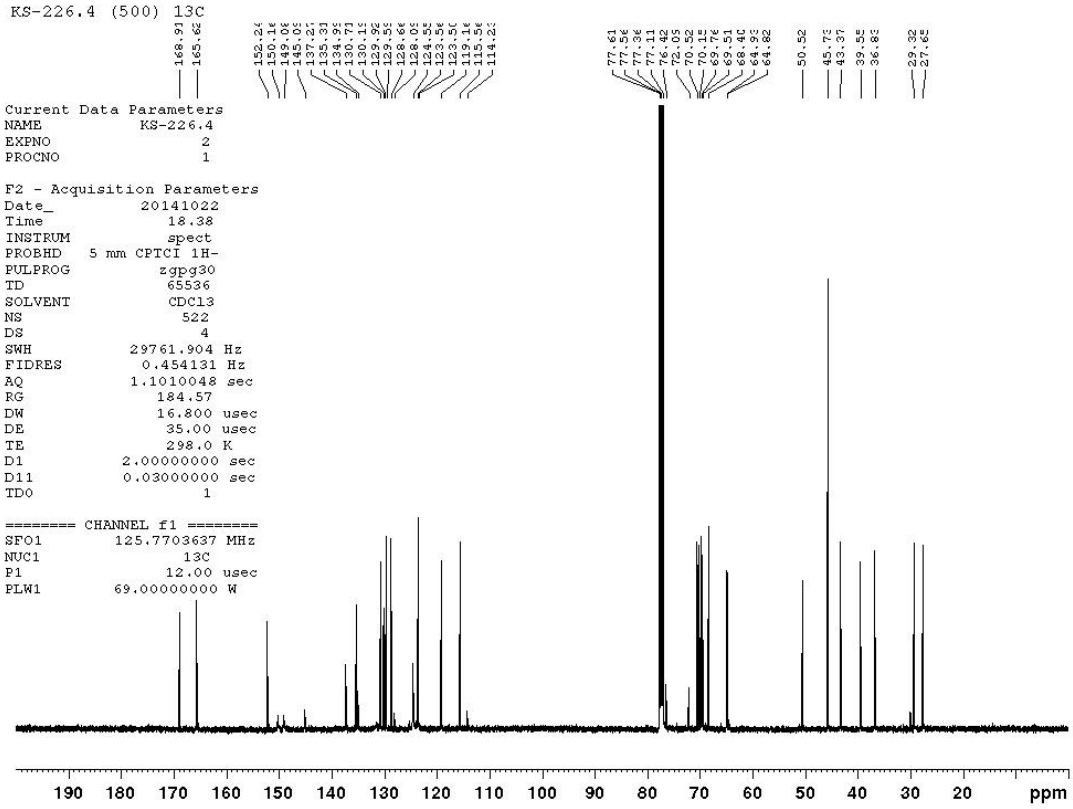

Figure S13. 13C NMR spectrum (CDCl3, 125.8 MHz) of ester prodrug (**17**)

REFERENCES

1. Campling BG, Pym J, Galbraith PR, Cole SP. Use of the MTT assay for rapid determination of chemosensitivity of human leukemic blast cells. *Leuk. Res.* 1988;12(10):823-831.