Supporting Information:

Incorporation and Controlled Release of Silyl Ether Prodrugs from PRINT Nanoparticles

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Methods and Materials. All chemicals were purchased from Sigma-Aldrich or Fisher Scientific and used without any purification, unless otherwise noted. Camptothecin was purchase from Sigma-Aldrich, dasatinib was purchase from LC Laboratories, and gemcitabine was purchase from Ava Chem and each chemotherapeutic was used without purification. The solution buffered at pH 7.4 (Fisher SB110) was comprise of potassium phospahte monobasic and sodium hydroxide at a concentration of 50 mM. The solution buffered at pH 5.0 (Fisher SB102) was comprise of potassium acid phthalate and sodium hydroxide at a concentration of 50 mM. NMR spectra were collected on Bruker AVANCE III 400 MHz Nanobay and Bruker Avance III 600 MHz. ^{1}H spectra were recorded at 400 or 600 MHz and ^{13}C NMR spectra were recorded at 100 or 150 MHz. Exact masses of the ABS prodrugs were determined by Bruker BioTOF II with a standard electrospray source using internal and external calibration for accuracy < 5 ppm.

High Performance Liquid Chromatography (HPLC). HPLC was run on an Agilent 1200 series HPLC system. The mobile phase consisted of mixtures of H_2O with 0.1% TFA (solvent A) and acetonitrile with 0.1% TFA (solvent B). The elution protocol for gemcitabine consisted of a gradient starting at 100:0 (A to B) and finishing at 97.5:2.5 (A to B) over 15 minutes. The product was eluted at a flow rate of 1 mL/min and monitored at a wavelength of 267 nm. The elution protocol for Et-GEM prodrug consisted of a gradient starting at 100:0 (A to B) to 97.5:2.5 (A to B) over 15 minutes and then to 0:100 (A to B) for an additional 10 minutes. The product was eluted at a flow rate of 1 mL/min and monitored at a wavelength of 267 nm. The elution protocol for camptothecin consisted of a gradient starting at 100:0 (A to B) and finishing at 0:100 (A to B) over 20

minutes followed by 0:100 (A to B) for an additional 5 minutes. The product was eluted at a flow rate of 1 mL/min and monitored at a wavelength of 254 nm.

PRINT Nanoparticle Preparation. For these experiments, **ABS prodrug loaded PRINT particles** were fabricated from a mixture of 20 wt % ABS prodrug, 58 wt % poly(ethylene glycol) dimethacrylate (MW ~1000 g/mol), 20 wt % of 2-aminoethyl methacrylate hydrochloride (AEM-HCl), 1 wt % of fluorescein o-acrylate (FOA) and 1 wt % of 1-hydroxycyclohexyl phenyl ketone (HCPK). **Blank particles** were fabricated from a mixture 78 wt % poly(ethylene glycol) dimethacrylate (MW ~1000 g/mol), 20 wt % of 2-aminoethyl methacrylate hydrochloride (AEM-HCl), 1 wt % of fluorescein o-acrylate (FOA) and 1 wt % of 1-hydroxycyclohexyl phenyl ketone (HCPK). A 4.5 % (wt/vol) solution of this mixture in DMF was prepared and then casted into a thin film onto a poly(ethylene terephthalate) (PET) sheet. The DMF was removed by gently heating with a heat gun to give a homogeneous transparent thin film. The pre-particle film was laminated onto a piece of fluorocur patterned mold (4.5 × 9 inch, cylindrical, d = 200 nm, h = 200 nm), provided by Liquidia Technologies. To remove the excess pre-particle mixture the mold was delaminated and relaminated onto a virgin sheet of PET. The laminated mold/PET was placed in a UV curing chamber where UV irradiation was applied (λ = 365 nm, power 90 mW/cm2) for 4 min. The mold and the PET were separated, with all of the PRINT NPs being transferred from the mold to the PET sheet. The particles were harvested by placing a 300 µL of PBS (pH 7.4) on the PET sheet bearing the PRINT NPs. The PBS was gradually moved along the surface of the PET using a cell scraper, which enabled the release of the particles from the PET sheet. The

harvested nanoparticles were washed separately with ethanol (to remove residual monomers or oligomers) and PBS. Centrifugation was used to isolate the particles from the washing liquid. The particles were finally dispersed in PBS and the particle concentration was determined by Thermal Gravimetric Analysis (TGA).

Physical Characterization of the PRINT Nanoparticles. The PRINT particles were visualized using a Hitachi modelS-4700 scanning electron microscopy. The hydrodynamic diameters and zeta potential of the PRINT NPs was measured by a Malvern Nano-ZS Zeta-Sizer. PRINT particles were dispersed in 1mM KCl solution at 0.02 mg / mL concentration.

Drug Release. Approximately 2-4 mgs of the 200x200 nm particles were made from each ABS prodrug. Identical particles (same batch) were separated and dispersed in pH 5.0 and 7.4 buffered solutions at a concentration of 1 mg / mL. Each sample was place in a controlled environment held at 37°C. Aliquots (~60 µL) of the solution were taken at different time point and underwent centrifugation to separate the particles from the supernatant. The supernatant (10 µL) was injected onto an HPLC to determine drug concentration. Actual drug concentration was determined using a calibration curve of the parent drug within the concentration range of 1mM to 1µM.

Data Fitting. The data obtained for release half-lives ($t_{1/2}$) or IC_{50} values were determined by fitting to an exponential growth, an exponential decay or linear fit where appropriate. The fitting data was compiled using OriginPRO 8, with all fits having R^2 values > 0.99.

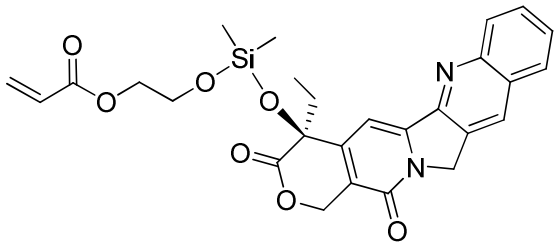
In Vitro Cytotoxicity by ATP-Luciferase Assay. Cells were seeded in 200 µL of media [RMPI 1640 Medium and supplemented with 10% fetal bovine serum] at a density of 5000 cells per cm^2 into a 96-well microtiter plate. Cells were allowed to adhere for 24 h and subsequently incubated with PRINT particles at concentrations ranging from 100 µg/mL to 1.28 ng/mL for 72 h at 37 °C in a humidified 5% CO_2 atmosphere. After the incubation period, all medium/particles were aspirated off cells. 100 µL fresh medium was added back to cells followed by the addition of 100 µL CellTiter-Glo®Luminescent S8 Cell Viability Assay reagent. Plates were placed on a microplate shaker for 2 min, then incubated at room temperature for 10 minutes to stabilize luminescent signal. The luminescent signal was recorded on a Molecular Dynamics SpectraMax M5 plate reader. The viability of the cells exposed to PRINT particles was expressed as a percentage of the viability of cells grown in the absence of particles.

PathScan Apoptosis and Proliferation Multiplex Assay. LNCaP cells grown on coverslips were incubated with 4ug/ml of either Et-GEM, tBu-GEM, blank particles, or 40nM free Gemcitabine for 72hours. Subsequently, cells were fixed in 4% paraformaldehyde (pre-warmed to 37°C) for 15 minutes at room temperature. Aspirate

fixative, rinse three times in 1X DPBS for 5 minutes each. Each sample was incubated in Blocking Buffer (1X PBS / 5% normal goat serum / 0.3% Triton X-100) for 60 minutes. Aspirate blocking solution, apply diluted (1:100 in Antibody Dilution Buffer- 1X PBS / 1% BSA / 0.3% Triton X-100) primary cocktail. Samples were incubated overnight at 4°C. Following the overnight incubation, rinse samples three times in PBS for 5 minutes each. Detection cocktail (diluted 1:100 in Antibody Dilution Buffer) was added to samples and incubated 1.5 hours at room temperature in the dark. Following incubation, rinse samples three times in PBS for 5 minutes each. The coverslips were mounted in glass slides with Prolong® Gold Antifade solution(Molecular Probes), and the cells were examined under an Olympus confocal microscope (laser scanning microscope FV500, Olympus America).

SYNTHESIS

Dimethyl ABS of Camptothecin (Me-CPT)

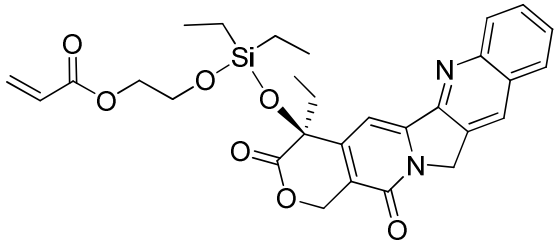


Chemical Formula: $C_{27}H_{28}N_2O_7Si$
Exact Mass: 520.1666

In a dry 20 mL scintillation vial equipped with a magnetic stir bar (purged with N_2), camptothecin (0.500 g, 1.43 mmol), 4 - dimethylaminopyridine (4 - DMAP) (0.175 g, 1.43 mmol) and imidazole (0.681 g, 10.01 mmol) were dissolved in anhydrous DMF (12 mL) to form a heterogeneous mixture. A clear reaction mixture was achieved after dichlorodimethylsilane (0.553 g, 4.29 mmol) was added and allowed to react for 30 mins. After 3.5 h, hydroxyethyl acrylate (0.830 g, 7.15 mmol) was added and stirred for an

additional 2 h. The reaction mixture was diluted with ethyl acetate (150 mL) and washed with saturated NaCl (150 mL) to remove the DMF. The organic layer was removed by rotary evaporation, and the product was isolated by column chromatography. The product was eluted using a mixture of hexanes, ethyl acetate and methanol (7:2:1), and dried *in vacuo*. Yield: 0.107 g (14 %), yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.06 (s, 3H), 0.27 (s, 3H), 0.90 (t, 3H, *J* = 7.0 Hz), 1.93 (m, 2H), 3.99 (s, 2H), 4.28 (s, 2H), 5.29 (s, 2H), 5.49 (s, 2H), 5.85 (d, 1H, *J* = 10.2 Hz), 6.16 (dd, 1H, *J* = 10.28 Hz, 17.24 Hz), 6.28 (d, 1H, *J* = 17.32 Hz), 7.37 (s, 1H), 7.71 (t, 1H, *J* = 7.4 Hz), 7.86 (t, 1H, *J* = 8.0 Hz), 8.14 (t, 2H, *J* = 9.48 Hz), 8.69 (s, 1H). ^{13}C NMR (150 MHz $CDCl_3$): δ = -0.68, -0.57, 8.06, 32.68, 50.18, 61.16, 65.89, 66.24, 76.29, 98.30, 118.98, 128.14, 128.21, 128.26, 128.53, 128.62, 130.01, 130.73, 130.91, 131.22, 146.22, 149.01, 151.14, 152.51, 157.72, 166.35, 172.05. HR MS (m/z) calcd for $C_{27}H_{28}N_2O_7Si$, $[M]^+$ = 520.1666, $[M + Na]^+$ = 543.1566, $[M + Cs]^+$ = 653.0766; found $[M + Cs]^+$ = 653.0720.

Diethyl ABS of Camptothecin (Et-CPT)



Chemical Formula: $C_{29}H_{32}N_2O_7Si$
Exact Mass: 548.1979

In a dry 20 mL scintillation vial equipped with a magnetic stir bar (purged with argon), camptothecin (0.501 g, 1.44 mmol), imidazole (0.684 g, 10.05 mmol) and 4 -DMAP (0.182 g, 1.49 mmol) were dissolved in anhydrous DMF (13 mL) to form a heterogeneous mixture. A clear reaction mixture was achieved after dichlorodiethylsilane (0.6 mL, 4.05 mmol) was added and allowed to react for 30 mins. After 92 h, hydroxyethyl acrylate (1 mL, 9.56 mmol) was added and stirred for an additional 90 mins. The reaction mixture was diluted with ethyl acetate (150 mL) and washed with saturated NaCl (150 mL) to remove the DMF. The organic layer was removed by rotary evaporation, and the product was isolated by column chromatography. The product was

eluted using a mixture of dichloromethane and ethyl acetate (8:2) and dried *in vacuo*. Yield: 0.165 g (21 %), off-white liquid. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.71 (m, 2H, *J* = 7.8 Hz), 0.84 (m, 2H, *J* = 7.8 Hz), 0.94 – 1.07 (m, 6H, *J* = 7.8 Hz), 4.10 (m, 2H), 4.31 (m, 2H), 5.33 (s, 2H), 5.40 (d, 1H, *J* = 16.2 Hz), 5.56 (d, 1H, *J* = 16.2 Hz), 5.80 (dd, 1H, *J* = 1.8 Hz, *J* = 10.2 Hz), 6.14 (dd, 1H, *J* = 10.2 Hz, *J* = 17.4 Hz), 6.32 (dd, 1H, *J* = 1.8 Hz, *J* = 17.4 Hz), 7.52 (s, 1H), 7.72 (t, 1H, *J* = 7.2 Hz), 7.88 (t, 1H, *J* = 7.2 Hz), 7.96 (s, 2H), 8.11 (d, 1H, *J* = 7.8 Hz), 8.22 (d, 1H, *J* = 8.4 Hz), 8.68 (s, 1H). HR MS (m/z) calcd for $C_{29}H_{32}N_2O_7Si$, $[M]^+$ = 548.1979, $[M + Na]^+$ = 571.1877, $[M + Cs]^+$ = 681.1033; found $[M + Na]^+$ m/z = 571.1862, $[M + Cs]^+$ = 783.1003.

A model degradation of the Et-CPT monomer was conducted to confirmed acid sensitivity and to demonstrate that the prodrug reverts back to its original starting material. The HPLC chromatograms of this experiment clearly prove that the starting material HEA and CPT were successfully converted to the Et-CPT ABS prodrug in high purity. Upon exposure to acid, the silyl ether linkage degraded to yield both the unmodified CPT and HEA.

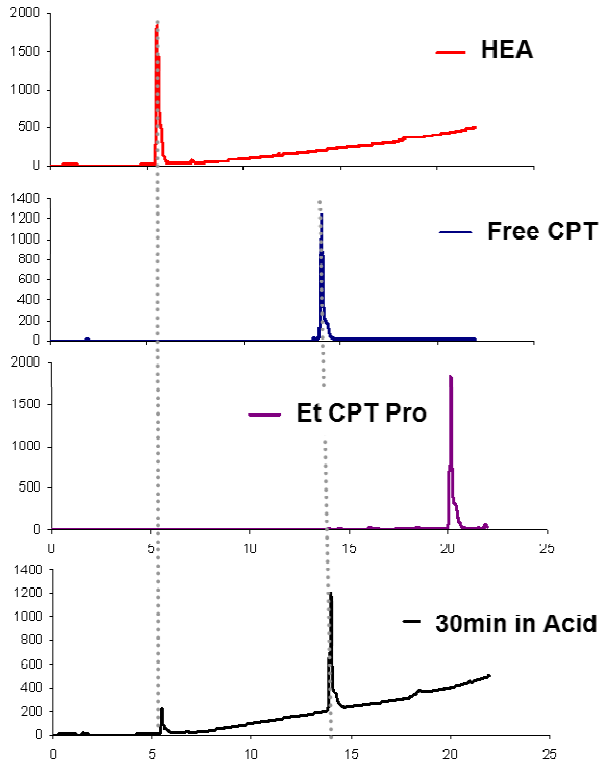
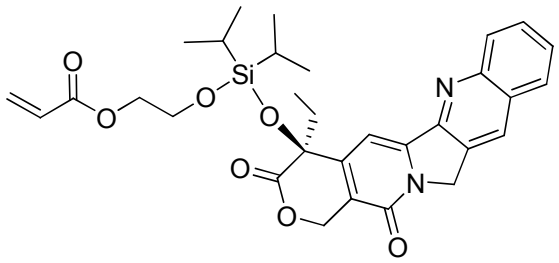


Figure S1. The Isolation of the Et-CPT prodrug in high purity and its ability to revert back to starting materials under acidic conditions (pH 3.0).

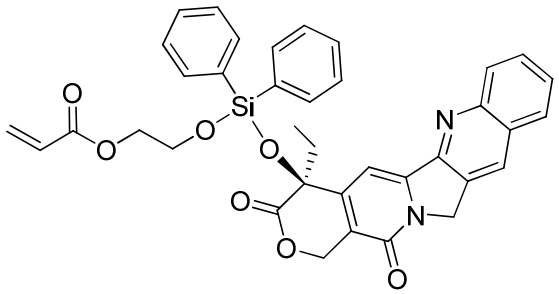
Diisopropyl ABS of Camptothecin (iPr-CPT)



Chemical Formula: $C_{31}H_{36}N_2O_7Si$
Exact Mass: 576.2292

In a dry 20 mL scintillation vial equipped with a magnetic stir bar (purged with argon), camptothecin (0.250 g, 0.718 mmol), imidazole (0.342 g, 5.02 mmol) and 4 - DMAP (0.090 g, 0.737 mmol) were dissolved in anhydrous DMF (8 mL) to form a heterogeneous mixture. A clear reaction mixture was achieved after dichlorodiisopropylsilane (0.4 mL, 2.22 mmol) was added and allowed to react for 30 mins. After 92 h, hydroxyethyl acrylate (1 mL, 9.56 mmol) was added and stirred for an additional 90 mins. The reaction mixture was diluted with ethyl acetate (150 mL) and washed with saturated NaCl (150 mL) to remove the DMF. The organic layer was removed by rotary evaporation, and the product was isolated by column chromatography. The product was eluted using a mixture of dichloromethane and ethyl acetate (1:1) and dried *in vacuo*. Yield 0.118 g (29 %), off-white liquid. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.90 – 1.40 (m, 14H), 1.95 – 2.15 (m, 2H), 4.13 (m, 2H), 4.33 (m, 2H), 5.32 (s, 2H), 5.70 (d, 1H, J = 25.2 Hz), 5.77 (dd, 1H, J = 1.8 Hz, J = 15.6 Hz), 6.11 (dd, 1H, J = 15.6 Hz, J = 26.4 Hz), 6.38 (dd, 1H, J = 1.8 Hz, J = 26.4 Hz), 7.67 (m, 2H), 7.83 (t, 1H, J = 10.8 Hz), 7.94 (d, 1H, J = 12 Hz), 8.26 (d, 1H, J = 13.2 Hz), 8.40 (s, 1H). HR MS (m/z) calcd for $C_{31}H_{36}N_2O_7Si$, $[M]^+$ = 576.2292, $[M + H]^+$ = 577.2370, $[M + Na]^+$ = 599.2189, $[M + Cs]^+$ = 709.1346; found $[M + H]^+$ = 577.2362, $[M + Na]^+$ = 599.2207, $[M + Cs]^+$ = 709.1329.

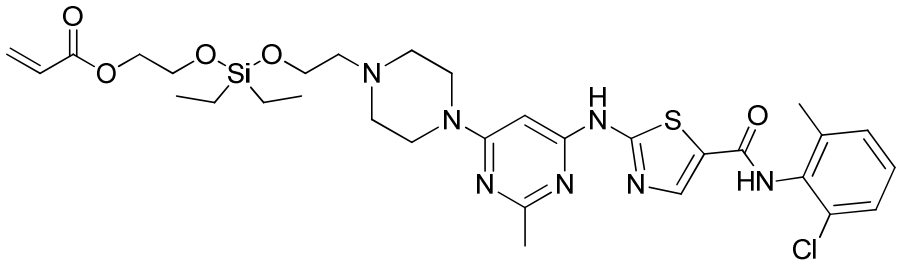
Diphenyl ABS of Camptothecin (Ph-CPT)



Chemical Formula: $C_{37}H_{32}N_2O_7Si$
Exact Mass: 644.1979

In a dry 20 mL scintillation vial equipped with a magnetic stir bar (purged with argon), camptothecin (0.500 g, 1.44 mmol), imidazole (0.684 g, 10.05 mmol) and 4 - DMAP (0.180 g, 1.47 mmol) were dissolved in anhydrous DMF (15 mL) to form a heterogeneous mixture. A clear reaction mixture was achieved after dichlorodiphenylsilane (1.0 mL, 4.74 mmol) was added and allowed to react for 45 mins. After 92 h, hydroxyethyl acrylate (1 mL, 9.56 mmol) was added and stirred for an additional 60 mins. The reaction mixture was diluted with ethyl acetate (150 mL) and washed with saturated NaCl (150 mL) to remove the DMF. The organic layer was removed by rotary evaporation, and the product was isolated by column chromatography. The product was eluted using a mixture of dichloromethane and ethyl acetate (8:2) and dried *in vacuo*. Yield: 0.178 g (19 %). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.01 (t, 3H), 2.08 – 2.30 (m, 2H), 4.12 (br, 2H), 4.37 (br, 2H), 5.26 (m, 3H), 5.47 (d, 1H, J = 16.8 Hz), 5.77 (d, 1H, J = 10.2 Hz), 6.07 (m, 1H), 6.35 (d, 1H, J = 17.4 Hz), 7.30 – 7.50 (m, 4H), 7.57 (s, 1H), 7.70 (br, 5H), 7.87 (t, 1H, J = 7.2 Hz), 7.97 (d, 1H, J = 7.8 Hz), 8.24 (d, 1H, J = 8.4 Hz), 8.40 (s, 1H). HR MS (m/z) calcd for $C_{37}H_{32}N_2O_7Si$, $[M]^+$ = 644.1979, $[M + Na]^+$ = 667.1876, $[M + Cs]^+$ = 777.1033; found $[M + Cs]^+$ = 777.1141.

Diethyl ABS of Dasatinib (Et-DAS)



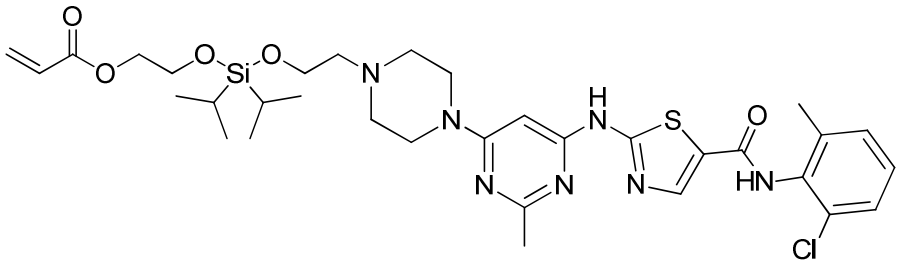
Chemical Formula: $C_{31}H_{42}ClN_7O_5SSi$
Exact Mass: 687.2426
Molecular Weight: 688.3126

In a dry 20 mL scintillation vial equipped with a magnetic stir bar (purged with N_2), dasatinib (0.500 g, 1.02 mmol), imidazole (0.486 g, 7.13 mmol) and 4 - DMAP (0.124 g, 1.01 mmol) were dissolved in anhydrous DMF (12 mL). After 30 mins dichlorodiethylsilane (0.480 g, 3.05 mmol) was added to the mixture. After 2.5 h, hydroxyethyl acrylate (0.592 g, 5.09 mmol) was added and allowed to react for an additional 1 h. The reaction mixture was diluted with ethyl acetate (150 mL) and washed with saturated NaCl (150 mL) to remove the DMF. The organic layer was removed by rotary evaporation, and the product was isolated by column chromatography. The product was eluted using a mixture of hexanes, ethyl acetate and methanol (7:2:1) and dried *in vacuo*. Yield: 0.122 g (17 %), white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.58 (q, 4H, *J* = 8.04 Hz), 0.91 (t, 6H, *J* = 7.88 Hz), 2.23 (s, 3H), 2.40 (s, 3H), 2.62* (m, 6H), 3.44 (s, 1H), 3.49 (s, 4H), 3.78 (t, 2H, *J* = 6.0 Hz), 3.90 (m, 2H), 4.20 (m, 2H), 5.96 (dd, 1H, *J* = 1.56 Hz, 10.28 Hz), 6.04 (s, 1H), 6.19 (dd, 1H, *J* = 10.32 Hz, 17.26 Hz), 6.34 (dd, 1H, *J* = 1.56 Hz, 17.26 Hz), 7.28 (m, 2H), 7.39 (m, 1H), 8.21 (s, 1H), 9.87 (s, 1H), 11.46 (s, 1H). ^{13}C NMR (150 MHz DMSO-d_6): δ = 3.04, 3.31, 6.38, 6.44, 18.37, 25.64, 43.63, 49.84, 52.81, 59.77, 59.81, 59.99, 60.31, 65.44, 82.70, 125.70, 127.06, 128.21, 128.24,

* Determined using MeOD-d_4

129.07, 131.76, 132.47, 133.56, 138.86, 140.88, 157.01, 159.97, 162.41, 162.65, 165.19, 165.52. HR MS (m/z) calcd for $C_{31}H_{42}ClN_7O_5SSi$, $[M]^+$ = 687.2426, $[M + H]^+$ = 688.2426, $[M + Cs]^+$ = 820.1480; found $[M + H]^+$ m/z = 688.2504, $[M + Cs]^+$ = 820.1480.

Diisopropyl ABS of Dasatinib (iPr-DAS)



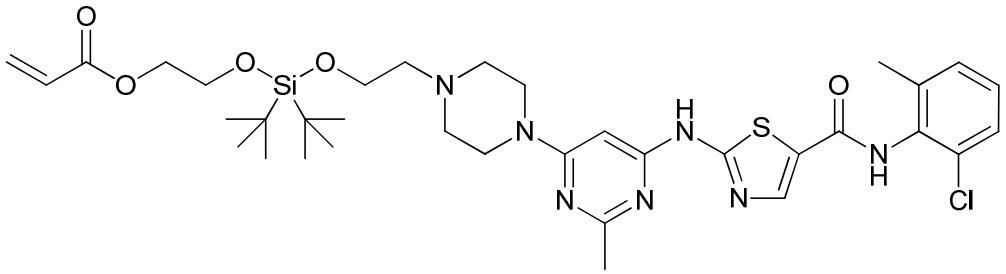
Chemical Formula: $C_{33}H_{46}ClN_7O_5SSi$
Exact Mass: 715.2739
Molecular Weight: 716.3657

In a dry 20 mL scintillation vial equipped with a magnetic stir bar (purged with N_2), dasatinib (0.500 g, 1.02 mmol), imidazole (0.486 g, 7.13 mmol) and 4 - DMAP (0.124 g, 1.01 mmol) were dissolved in anhydrous DMF (15 mL). After 15 mins, dichlorodiisopropylsilane (0.568 g, 3.06 mmol) was added to the mixture. After 45 mins, hydroxyethyl acrylate (0.594 g, 5.11 mmol) was added and allowed to react for an additional 45 mins. The reaction mixture was diluted with ethyl acetate (150 mL) and washed with saturated NaCl (150 mL) to remove the DMF. The organic layer was removed by rotary evaporation, and the product was isolated by column chromatography. The product was eluted using a mixture of hexanes, ethyl acetate and methanol (7:2:1) and dried *in vacuo*. Yield: 0.161 g (22 %), white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.99 (s, 14H), 2.23 (s, 3H), 2.40 (s, 3H), 2.65* (m, 6H), 3.49 (s, 4H), 3.84 (t, 2H, *J* = 6.04 Hz), 3.96 (m, 2H), 4.23 (m, 2H), 5.96 (dd, 1H, *J* = 1.6 Hz, 10.28 Hz), 6.04 (s, 1H), 6.18 (dd, 1H, *J* = 10.28 Hz, 17.34 Hz), 6.34 (dd, 1H, *J* = 1.6 Hz, 17.28 Hz), 7.27 (m, 2H), 7.39 (m, 1H), 8.21 (s, 1H), 9.87 (s, 1H), 11.46 (s, 1H). ^{13}C NMR (150 MHz DMSO-d_6): δ = 11.39, 17.13, 17.14, 18.31, 25.59, 43.64, 52.83, 59.75, 60.64, 60.70, 65.34, 82.64, 125.70, 127.02, 128.13, 128.24, 129.04, 131.66, 132.44, 133.52, 138.83, 140.83, 156.95,

* Determined using MeOD – d_4

159.92, 162.38, 162.56, 165.17, 165.47. HR MS (m/z) calcd for $C_{33}H_{46}ClN_7O_5SSi$, $[M]^+$ = 715.2739, $[M + Na]^+$ = 738.2636; found $[M + Na]^+$ m/z = 738.2637, $[M + Cs]^+$ = 848.1793.

Di-tertbutyl ABS of Dasatinib (^{t}Bu-DAS)



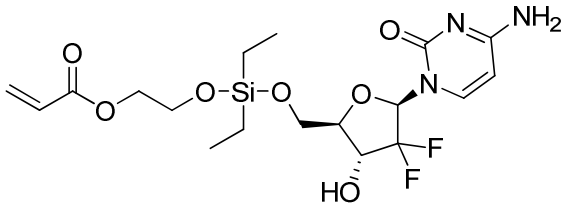
Chemical Formula: $C_{35}H_{50}ClN_7O_5SSi$
Exact Mass: 743.3052
Molecular Weight: 744.4189

In a dry 20 mL scintillation vial equipped with a magnetic stir bar (purged with N_2), dasatinib (0.500 g, 1.02 mmol), imidazole (0.486 g, 7.13 mmol) and 4 - DMAP (0.124 g, 1.01 mmol) were dissolved in anhydrous DMF (12 mL). After 10 mins, di-tert-butylsilyl bis(trifluoromethanesulfonate) (1.340 g, 3.04 mmol) was added to the mixture. After 45 mins, hydroxyethyl acrylate (HEA) (0.592 g, 5.09 mmol) was added and allowed to react for an additional 45 mins. The reaction mixture was diluted with ethyl acetate (150 mL) and washed with saturated NaCl (150 mL) to remove the DMF. The organic layer was removed by rotary evaporation, and the product was isolated by column chromatography. The product was eluted using a mixture of hexanes, ethyl acetate and methanol (7:2:1) and dried *in vacuo*. Yield: 0.167 g (22 %), white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.97 (s, 18H), 2.23 (s, 3H), 2.40 (s, 3H), 2.66* (m, 6H), 3.49 (s, 4H), 3.94 (t, 2H, *J* = 5.96 Hz), 4.05 (m, 2H), 4.24 (m, 2H), 5.96 (dd, 1H, *J* = 1.56 Hz, 10.28 Hz), 6.04 (s, 1H), 6.17 (dd, 1H, *J* = 10.32 Hz, 17.26 Hz), 6.34 (dd, 1H, *J* = 1.56 Hz, 17.24 Hz), 7.27 (m, 2H), 7.39 (m, 1H), 8.21 (s, 1H), 9.88 (s, 1H), 11.46 (s, 1H). ^{13}C NMR (150 MHz DMSO-d_6): δ = 18.37, 20.78, 25.64, 27.58, 43.68, 52.91, 59.92, 61.68, 65.39, 82.69, 125.73, 127.05, 128.20, 128.27, 129.06, 131.65, 132.48, 133.57, 138.86,

* in MeOD – d_4

140.88, 157.00, 159.98, 162.40, 162.63, 165.18, 165.46. HR MS (m/z) calcd for $C_{35}H_{50}ClN_7O_5SSi$, $[M]^+$ = 743.3052, $[M + Na]^+$ = 766.2949, $[M + Cs]^+$ = 876.2106; found $[M + Na]^+$ m/z = 766.2950, $[M + Cs]^+$ = 876.2106.

Diethyl ABS of Gemcitabine (Et-GEM)



Chemical Formula: $C_{18}H_{27}F_2N_3O_7Si$
Exact Mass: 463.1586

In a dry 20 mL scintillation vial equipped with a magnetic stir bar (purged with argon), gemcitabine hydrochloride (0.500 g, 1.67 mmol), imidazole (0.264 g, 3.88 mmol) and 4 - DMAP (0.204 g, 1.67 mmol) were dissolved in anhydrous DMF (15 mL). After 15 mins, dichlorodiethylsilane (0.2 mL, 1.35 mmol) was added and allowed to react. After 60 mins, hydroxyethyl acrylate (1 mL, 9.56 mmol) was added and stirred for an additional 30 mins. The reaction mixture was diluted with ethyl acetate (150 mL) and washed with saturated NaCl (150 mL) to remove the DMF. The organic layer was removed by rotary evaporation, and the product was isolated by column chromatography. The product was eluted using a mixture of dichloromethane and methanol (9:1) and dried *in vacuo*. 1° Alcohol isomer, Yield: 0.282 g (38 %), clear colorless liquid. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.66 (m, 4H, *J* = 7.8 Hz), 0.96 (t, 6H, *J* = 7.8 Hz), 1.50 – 2.30 (br, 1H), 3.90 - 4.18 (m, 5H), 4.20 – 4.40 (m, 3H), 5.80 – 5.90 (m, 2H), 6.10 – 6.20 (dd, 1H, *J* = 10.2 Hz, *J* = 17.4 Hz), 6.31 (t, 1H, *J* = 7.2 Hz), 6.42 (dd, 1H, *J* = 1.2 Hz, *J* = 17.4Hz), 7.70 (d, 1H, *J* = 7.8 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 3.67, 6.35, 6.36, 50.98, 60.35, 60.93, 61.37, 65.70, 66.36, 69.31 (t, J_{C-F} = 22.5 Hz), 80.75, 84.31 (m), 95.55, 122.52 (t, J_{C-F} = 258 Hz), 128.18, 131.57, 131.66, 140.93, 156.01, 165.92, 166.68. HR MS (m/z) calcd for $C_{18}H_{27}F_2N_3O_7Si$, $[M]^+$ = 463.1586, $[M + Na]^+$ = 486.1484, $[M + Cs]^+$ = 596.0641; found $[M + Na]^+$ m/z = 486.1483, $[M + Cs]^+$ = 596.0662. 2° Alcohol isomer, Yield: 0.195 g (27 %), foam. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.69 (q, 4H, *J* = 7.8 Hz), 0.98 (t, 6H, *J* = 7.8 Hz), 1.50 – 2.20 (br, 3H), 3.80 (dd, 1H, *J* = 2.4 Hz, 12.6 Hz),

3.91 (d, 1H, J = 8.4 Hz), 3.95 (t, 2H, J = 4.8 Hz), 4.04 (d, 1H, J = 12 Hz), 4.22 – 4.30 (m, 2H, J = 6.6 Hz, 4.8 Hz), 4.43 – 4.63 (br, 1H), 5.85 (dd, 2H, J = 1.2 Hz, 10.8 Hz), 6.05 – 6.35 (br and dd, 2H, J = 10.2 Hz, J = 17.4 Hz), 6.42 (dd, 1H, J = 1.2 Hz, 17.4 Hz), 7.10 – 7.50 (br, 1H), 7.58 (d, 1H, J = 7.2 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 3.82, 3.89, 6.11, 6.14, 59.38, 61.01, 65.55, 69.76 (t, $J_{C\text{-}F}$ = 22.5 Hz), 81.06, 84.90 (m), 96.34, 122.31 (t, $J_{C\text{-}F}$ = 258 Hz), 128.24, 131.40, 141.13, 156.18, 166.22, 166.46. HR MS (m/z) calcd for $C_{18}H_{27}F_2N_3O_7Si$, $[M]^+$ = 463.1586, $[M + Na]^+$ = 486.1484, $[M + Cs]^+$ = 596.0641; found $[M + Na]^+$ m/z = 486.1467, $[M + Cs]^+$ = 596.0649.

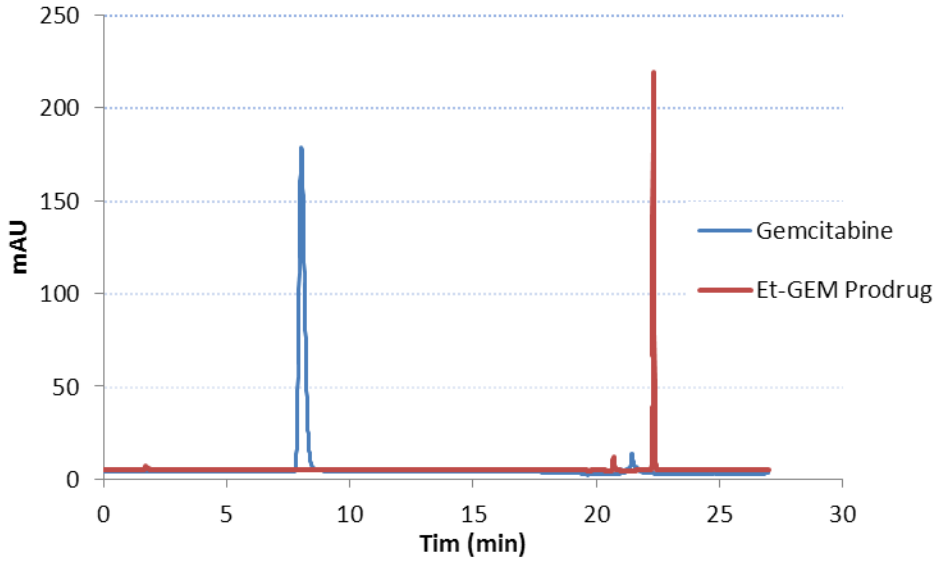
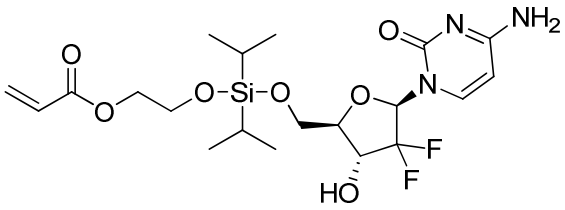


Figure S2. The HPLC trace of Et-GEM and free Gemcitabine.

Diisopropyl ABS of Gemcitabine (iPr-GEM)

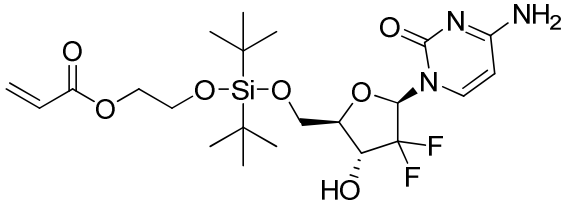


Chemical Formula: $C_{20}H_{31}F_2N_3O_7Si$
Exact Mass: 491.1899

In a dry 20 mL scintillation vial equipped with a magnetic stir bar (purged with argon), gemcitabine hydrochloride (0.507 g, 1.69 mmol), imidazole (0.271 g, 3.98 mmol)

and 4 - DMAP (0.209 mg, 1.71 mmol) were dissolved in anhydrous DMF (13 mL). After 15 mins dichlorodiisopropylsilane (0.25 mL, 1.39 mmol) was added and allowed to react. After 135 mins hydroxyethyl acrylate (1 mL, 9.56 mmol) was added and stirred for an additional 60 mins. The reaction mixture was diluted with ethyl acetate (150 mL) and washed with saturated NaCl (150 mL) to remove the DMF. The organic layer was removed by rotary evaporation *in vacuo*, and the product was isolated by column chromatography. The product was eluted using a mixture of dichloromethane and methanol (9:1) and dried *in vacuo*. 1° Alcohol isomer, Yield: 0.260 g (33 %), white solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.05 (d, 14H, *J* = 2.4 Hz), 3.99 (t, 2H, *J* = 4.8 Hz), 4.01 – 4.45 (m, 6H), 4.70 - 5.60 (br, 1H), 5.85 (m, 2H), 6.15 (dd, 1H, *J* = 10.8 Hz, *J* = 17.4 Hz), 6.26 (br, 1H), 6.35 (t, 1H, *J* = 7.8 Hz), 6.42 (dd, 1H, *J* = 1.2 Hz, *J* = 17.4 Hz), 7.64 (d, 1H, *J* = 7.2 Hz), 7.86 (br, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 11.85, 11.92, 17.11, 17.13, 17.17, 60.61, 61.10, 61.14, 65.53, 65.57, 66.49, 69.41 (t, J_{C-F} = 22.5 Hz), 72.89, 80.84, 84.02 (q, J_{C-F} = 24 Hz, 36 Hz), 95.50 (d, *J* = 6 Hz), 96.26, 122.37 (t, J_{C-F} = 258 Hz), 128.10, 131.47, 139.92 (m), 140.80, 155.51, 155.86, 165.82, 166.55. HR MS (m/z) calcd for $C_{20}H_{31}F_2N_3O_7Si$, $[M]^+$ = 491.1899, $[M + Na]^+$ = 514.1797, $[M + Cs]^+$ = 624.0954; found $[M + Na]^+$ m/z = 514.1765, $[M + Cs]^+$ = 624.0959. 2° Alcohol isomer, Yield: 0.193 g (24%), clear oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.03 (s, 14H), 3.79 (d, 1H, *J* = 10.8 Hz), 3.88 (d, 1H, *J* = 7.8 Hz), 4.00 (t, 2H, *J* = 4.8 Hz), 4.05 (d, 1H, *J* = 12.6 Hz), 4.27 (m, 2H, *J* = 5.4 Hz, *J* = 6.6 Hz), 4.51 (br, 2H), 5.85 (t, 2H, J = 9.6 Hz, 7.2 Hz), 6.12 (dd, 1H, *J* = 10.5 Hz, *J* = 17.4 Hz), 6.22 (br, 1H), 6.41 (d, 1H, *J* = 17.4 Hz), 6.80 (br, 1H), 7.53 (d, 1H, *J* = 7.8 Hz), 7.90 (br, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 11.87, 11.99, 16.70, 16.80, 16.85, 16.88, 50.67 (p, *J* = 7.5 Hz, *J* = 3 Hz), 59.37, 61.27, 65.39, 69.79 (t, J_{C-F} = 22.5 Hz), 81.21, 84.90 (m), 96.12, 122.15 (t, J_{C-F} = 258 Hz), 128.04, 131.34, 141.01, 155.97, 165.97, 166.37. HR MS (m/z) calcd for $C_{20}H_{31}F_2N_3O_7Si$, $[M]^+$ = 491.1899, $[M + Na]^+$ = 514.1797, $[M + Cs]^+$ = 624.0954; found $[M + Na]^+$ m/z = 514.1780, $[M + Cs]^+$ = 624.0894.

Di-tert-butyl ABS of Gemcitabine (tBu-GEM)



Chemical Formula: $C_{22}H_{35}F_2N_3O_7Si$
Exact Mass: 519.2212

To a 50 mL round bottom flask equipped with a magnetic stir bar (purged with argon) di-*tert*-butylsilyl bis(trifluoromethanesulfonate) (0.84 g, 1.90 mmol) was dissolved in anhydrous DMF (12 mL) and anhydrous pyridine (1 mL) and cooled in an ice bath. Hydroxyethyl acrylate (0.22 g, 1.90 mmol) was diluted in 6 mL of anhydrous DMF and added to the reaction in a drop wise fashion over 2 hours. The reaction was allowed to stir and warm to room temperature for 2 h after which gemcitabine (0.50 g, 1.90 mmol) was added and allowed to react overnight. The reaction mixture was diluted with ethyl acetate (150 mL) and washed with saturated NaCl (150 mL) to remove the DMF. The organic layer was removed by rotary evaporation, and the product was isolated by column chromatography. The product was eluted using a mixture of dichloromethane and methanol (92:8) and dried *in vacuo*. 1^o Alcohol isomer, Yield: 0.192 g (20 %), colorless foam. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.00 (d, 18H, *J* = 2.0 Hz), 4.00 – 4.23 (m, 5H), 4.23 - 4.37 (m, 3H), 5.84 (d, 1H, *J* = 10.4 Hz), 5.89 (d, 1H, *J* = 7.6 Hz), 6.10 (dd, 1H, *J* = 10.4 Hz, 17.4 Hz), 6.27 (t, 1H, *J* = 8.0 Hz), 6.39 (dd, 1H, *J* = 1.6 Hz, 17.4 Hz), 7.54 (d, 1H, *J* = 7.2Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 21.27, 21.33, 27.81, 27.87, 61.85, 62.22, 65.87, 69.90 (dd, J_{CF} = 18.0 Hz, 27.0 Hz), 81.51, 83.99 (m), 96.20, 119.35, 120.67, 122.40, 124.12, 128.28, 131.69, 141.04, 155.90, 165.36, 166.78. MS (m/z) calcd for $C_{22}H_{35}F_2N_3O_7Si$, $[M]^+$ = 519.2212, $[M + Na]^+$ = 542.2110, $[M + Cs]^+$ = 652.1267; found $[M + Na]^+$ m/z = 542.17, $[M + Cs]^+$ = 652.08.