Supplementary information

Antibody-mediated co-delivery of programmable drug combinations

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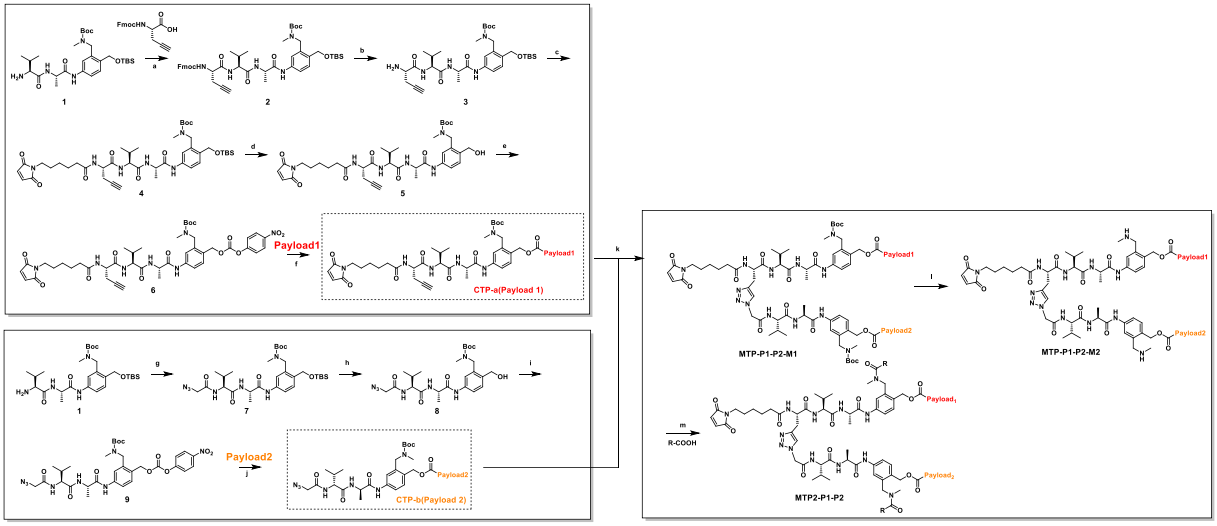
General Experimental

Solvents were obtained from Sinopharm Chemical Reagent Co., Ltd, and used directly without further purification. All substrates that were purchased from the cheapest supplier and used without further purification. Reactions were monitored by thin layer chromatography (TLC) carried out on precoated, glass-backed silica plates (250μ) using short-wave UV light as the visualizing agent, and by Liquid chromatograph-mass spectrometer (LCMS) performing on an Agilent 6152 MSD Series spectrometer. ^{1}H NMR spectra were recorded on Bruker AMX-400. The spectra were calibrated by using residual undeuterated solvents (for ^{1}H NMR) as internal references: undeuterated chloroform (δ_H = 7.26 ppm) and $CDCl_3$ (δ_C = 77.16 ppm); undeuterated methanol (δ_H = 3.31 ppm) and methanol-d_4 (δ_C = 49.00 ppm); undeuterated DMSO (δ_H = 2.50 ppm) and DMSO-d_6 (δ_C = 39.50 ppm). The following abbreviations (or combinations thereof) were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Coupling constants, *J*, were reported in Hertz unit (Hz). Flash column chromatography was performed on Biotage losera One (prepacked columns, Santai Technologies, Inc.). High-resolution mass spectra (HRMS) were recorded on an Thermo Scientific Q Exactive™ Plus Hybrid Quadrupole-Orbitrap™ Mass Spectrometer using ESI-TOF (electrospray ionization time-of-flight). Preparative high performance liquid chromatography (pre-HPLC) was carried out on Waters MS-triggered Pre-HPLC (Column: WELCH Xtimate 21.2*250mm 10um C18, Mobile phase: A = 0.1% Formic acid in Water, B = ACN).

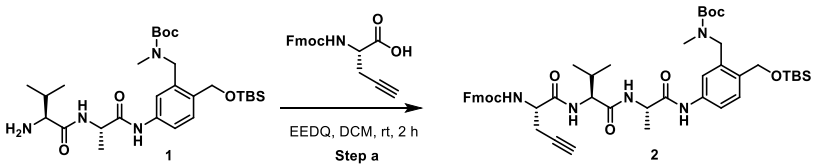
Synthetic scheme of MTP2 series



Scheme 1. Synthesis of MTP2 series: a) EEDQ, DCM, rt, 2 h; b) piperidine, DMF, rt, 1 h; c) N-succinimidyl 6-maleimidohexanoate, DMF, rt, 8 h; d) 65% HF/Pyridine, THF, rt, 6 h; e) bis(4-nitrophenyl) carbonate, DIEA, DMF, rt, 3 h; f) Method A: Pyridine, DIEA, HOBt, DMF, rt, 8 h, or Method B: DIEA, HOBt, DMF, rt, 8 h; g) EEDQ, DCM, rt, 6 h; h) 65% HF/Pyridine, THF, 0 ^{o}C to rt, 2 h; i) bis(4-nitrophenyl) carbonate, DIEA, DMF, rt, 3 h; j) DIEA, HOBt, DMF, rt, 2 h; k) sodium ascorbate, $CuSO_4$, DCM/MeOH/H_2O, rt, 2-10 h; l) TFA, DCM, rt, 5 minutes; m) HATU, DMF, DIPEA, rt, 0.1-1 h

Synthetic procedure of CTP-a series

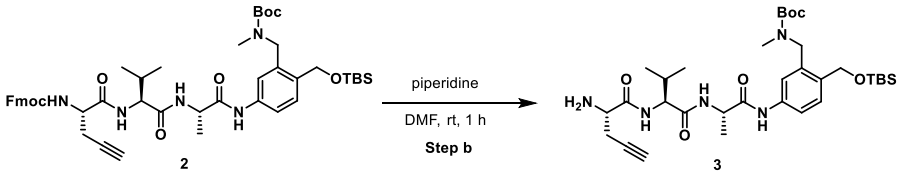
Synthesis of Compound 2



To a solution of compound **1** (1.0 g, 1.8 mmol) in DCM (30 mL) was added (S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)pent-4-ynoic acid (600 mg, 1.8 mmol) and EEDQ (890 mg, 3.6 mmol) and the reaction was stirred at room temperature for 2 h. The reaction was monitored by LC-MS. Upon completion, the solvent was removed under reduced pressure. The residue was subjected to flash column chromatography for purification using petroleum ether/ ethyl acetate (1:1) as eluent to give the compound **2** (1.3 g, 89%) as light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (s, 1H), 8.14 (d, J = 6.8 Hz, 1H), 7.84 (d, J = 7.6 Hz, 2H), 7.79 – 7.59 (m, 4H), 7.49 (dd, J = 8.4, 4.4 Hz, 1H), 7.36 (t, J = 7.2 Hz, 2H), 7.32 – 7.20 (m, 4H), 4.59 (s, 2H), 4.44 –

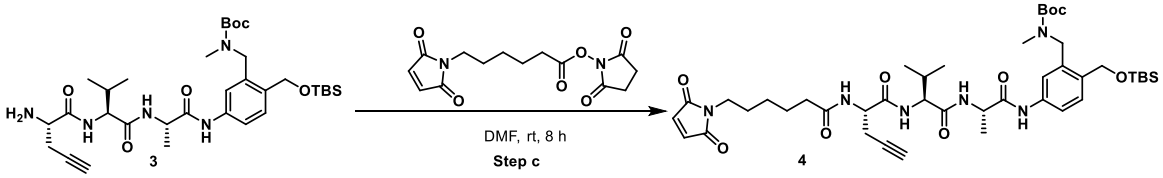
4.32 (m, 3H), 4.30 – 4.11 (m, 5H), 3.03 (s, 1H), 2.69 (s, 3H), 2.59 – 2.49 (m, 1H), 2.43 – 2.33 (m, 1H), 1.97 – 1.90 (m, 1H), 1.45 – 1.21 (m, 12H), 0.88 – 0.73 (m, 15H), 0.05 (s, 6H); MS (ESI): m/z calcd for $C_{48}H_{65}N5NaO_8Si$ $[M+Na]^+$: 890.4; found 890.3.

Synthesis of Compound 3



To a solution of compound **2** (1.2 g, 3.6 mmol) in DMF (5 mL) was added piperidine (1 mL) and the reaction was stirred at room temperature for 1 h. The reaction was monitored by LC-MS. Upon completion, ethyl acetate (50 mL) was added to dilute the reaction, and it was washed with water (3 × 40 mL). The separated organic phase was washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The residue was subjected to flash column chromatography for purification using CH_2Cl_2/MeOH (10:1) as eluent to give the compound **3** (0.7 g, 78%) as light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.96 (s, 1H), 8.31 (d, J = 7.8 Hz, 1H), 8.00 (d, J = 9.2 Hz, 1H), 7.54 (s, 1H), 7.33 – 7.30 (m, 2H), 4.64 (s, 2H), 4.50 – 4.34 (m, 3H), 4.25 (dd, J = 8.8, 6.4 Hz, 1H), 3.35 (t, J = 5.6 Hz, 1H), 3.17 (d, J = 5.2 Hz, 1H), 2.82 (t, J = 2.8 Hz, 1H), 2.75 (s, 3H), 2.49 – 2.43 (m, 2H), 2.12 – 1.91 (m, 3H), 1.44 – 1.29 (m, 12H), 0.89 – 0.86 (m, 12H), 0.05 (s, 6H); MS (ESI): m/z calcd for $C_{33}H_{55}N_5O_6Si$ $[M+Na]^+$: 646.4; found 646.4.

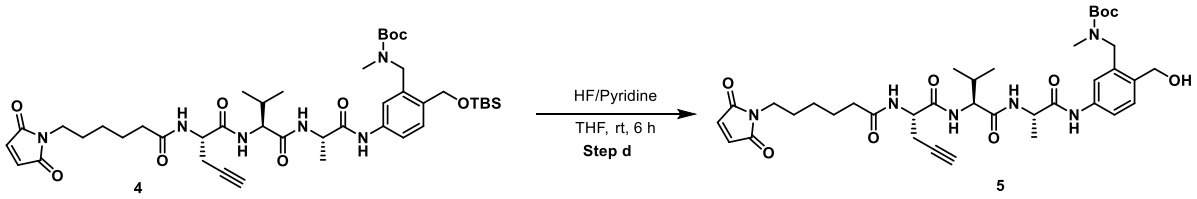
Synthesis of Compound 4



To a solution of compound **3** (660 mg, 1.02 mmol) in DMF (4 mL) was added 2,5-dioxopyrrolidin-1-yl 6-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)hexanoate (314 mg, 1.02 mmol). The reaction mixture was stirred at room temperature for 8 h. The reaction was monitored by LC-MS. Upon completion, ethyl acetate (50 mL) was added to dilute the reaction, and it was washed with water (3 × 40 mL). The separated organic phase was washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The residue was subjected to flash column

chromatography for purification using CH_2Cl_2/MeOH (15:1) as eluent to give the compound **4** (850 mg, 99%) as light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.94 (s, 1H), 8.24 – 8.11 (m, 2H), 7.95 (s, 1H), 7.72 (d, J = 8.8 Hz, 1H), 7.54 (s, 1H), 7.30 (s, 2H), 7.01 – 6.69 (m, 2H), 4.64 (s, 2H), 4.53 – 4.33 (m, 4H), 4.20 (dd, J = 8.8, 6.4 Hz, 1H), 3.36 (t, J = 7.2 Hz, 2H), 2.81 – 2.75 (m, 3H), 2.59 – 2.52 (m, 1H), 2.46 – 2.39 (m, 1H), 2.19 – 2.08 (m, 2H), 2.03 – 1.95 (m, 1H), 1.53 – 1.36 (m, 14H), 1.29 (d, J = 7.2 Hz, 3H), 1.25 – 1.13 (m, 3H), 0.92 – 0.83 (m, 12H), 0.81 (d, J = 6.8 Hz, 3H), 0.05 (s, 6H); MS (ESI): m/z calcd for $C_{43}H_{66}N_6NaO_9Si$ $[M+Na]^+$: 861.5; found 861.3.

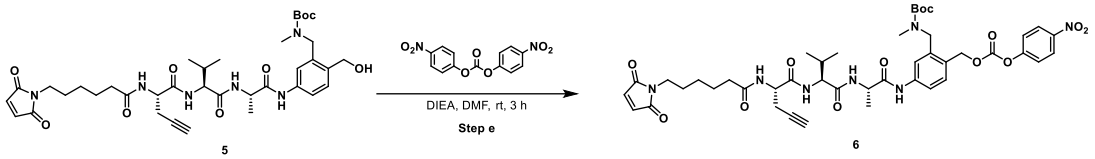
Synthesis of Compound 5



4 5

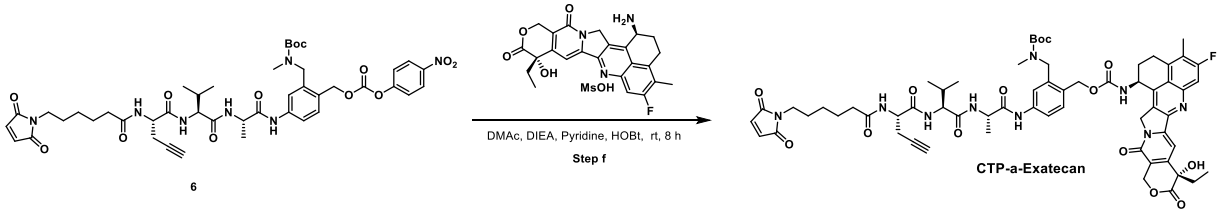
To a solution of compound **4** (800 mg, 0.95 mmol) in THF (10 mL) at 0 °C under N_2 atmosphere was added 65wt.% pyridine hydrofluoride (1160 mg, 7.62 mmol). The reaction mixture was stirred at room temperature for 6 h. The reaction was monitored by LC-MS. Upon completion, ethyl acetate (100 mL) was added to dilute the reaction, then it was poured into water (100 mL). The separated organic phase was washed with water (2 × 50 mL) and saturated aq. $NaHCO_3$ (3 × 60 mL). The organic phase was washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum to give the crude compound **5** (650 mg, 94%) as light yellow solid, which was directly used in the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.25 – 8.09 (m, 2H), 7.72 (d, J = 8.8 Hz, 1H), 7.51 (s, 1H), 7.33 – 7.28 (m, 2H), 7.01 – 7.00 (m, 2H), 5.03 (s, 1H), 4.63 – 4.30 (m, 6H), 4.20 (dd, J = 8.8, 6.4 Hz, 1H), 3.36 (t, J = 7.2 Hz, 2H), 2.83 – 2.70 (m, 4H), 2.57 – 2.52 (m, 1H), 2.46 – 2.39 (m 1H), 2.14 – 2.01 (m, 2H), 2.01 – 1.96 (m, 1H), 1.52 – 1.34 (m, 12H), 1.29 (d, J = 7.2 Hz, 3H), 1.25 – 1.17 (m, 3H), 0.86 – 0.80 (m, 6H); MS (ESI): m/z calcd for $C_{37}H_{52}N_6NaO_9$ $[M+Na]^+$: 747.4; found 747.3.

Synthesis of Compound 6



To a solution of compound **5** (600 mg, 0.83 mmol) in DMF (5 mL) was added bis(4-nitrophenyl) carbonate (503 mg, 1.65 mmol) and N, N-Diisopropylethylamine (890 mg, 3.6 mmol) and the reaction was stirred at room temperature for 3 h. The reaction was monitored by LC-MS. Upon completion, water (50 mL) was added, and the resultant mixture was extracted with ethyl acetate (3 × 50 mL). The combined organic phases were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The residue was subjected to flash column chromatography for purification using CH_2Cl_2/ MeOH (16:1) as eluent to give the compound **6** (650 mg, 88%) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.08 (s, 1H), 8.39 – 8.27 (m, 2H), 8.21 – 8.16 (m, 2H), 7.96 (s, 1H), 7.72 (d, J = 8.8 Hz, 1H), 7.59 – 7.55 (m, 3H), 7.47 (s, 1H), 7.40 (d, J = 8.4 Hz, 1H), 7.01 – 7.00 (m, 2H), 5.30 (s, 2H), 4.56 – 4.44 (m, 3H), 4.43 – 4.36 (m, 1H), 4.21 (dd, J = 8.4, 6.4 Hz, 1H), 3.37 (t, J = 7.2 Hz, 2H), 2.79 (s, 3H), 2.61 – 2.52 (m, 1H), 2.46 – 2.39 (m, 1H), 2.18 – 2.08 (m, 2H), 2.03 – 1.95 (m, 1H), 1.54 – 1.37 (m, 12H), 1.31 (d, J = 7.2 Hz, 3H), 1.28 – 1.12 (m, 3H), 0.86 (d, J = 6.8 Hz, 3H), 0.82 (d, J = 6.8 Hz, 3H); MS (ESI): m/z calcd for $C_{44}H_{55}N_7NaO_{13}$ $[M+Na]^+$: 912.4; found 912.3.

Synthesis of compound CTP-a-Exatecan

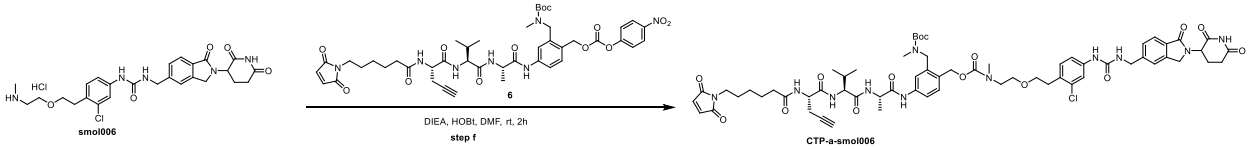


Method A

To a solution of exatecan mesylate (376 mg, 0.71 mmol) in DMAc (8 mL) was added N, N-Diisopropylethylamine (92 mg, 0.71 mmol) at 0 °C in ice-water bath. After stirring for 0.5 h, compound **6** (600 mg, 0.67 mmol), HOBt (9 mg, 0.067 mmol) and pyridine (168 mg, 2.13 mmol) were added to reaction mixture. The resulting solution was kept stirring at the same temperature for 10 minutes, then, the mixture was warmed to room temperature and allowed to stir at that temperature for 8 h. The reaction was monitored by LC-MS. Upon completion, 2-MeTHF (100

mL) and water (80 mL) was added, the organic layer was separated, and the resultant aqueous solution was extracted with 2-MeTHF (3 × 50 mL). The combined organic phases were washed with 0.5 M aq. HCl (50 mL), brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The residue was subjected to flash column chromatography for purification using CH_2Cl_2/ MeOH (11:1) as eluent to give the CTP-a-Exatecan (437 mg, 55%) as yellow solid.^{1}H NMR (400 MHz, DMSO-d_6) δ 9.99 (s, 1H), 8.20 – 8.13 (m, 2H), 8.03 (d, J = 8.4 Hz, 1H), 7.78 (d, J = 10.8 Hz, 1H), 7.70 (d, J = 8.8 Hz, 1H), 7.55 (s, 1H), 7.44 – 7.34 (m, 2H), 7.31 (s, 1H), 6.99 (s, 2H), 6.51 (s, 1H), 5.43 (s, 2H), 5.29 (s, 3H), 5.11 (s, 2H), 4.53 – 4.41 (m, 3H), 4.41 – 4.33 (m, 1H), 4.19 (dd, J = 8.4, 6.4 Hz, 1H), 3.36 (t, J = 7.2 Hz, 2H), 3.27 – 3.19 (m, 1H), 3.17 – 3.07 (m, 1H), 2.59 – 2.52 (m, 1H), 2.45 – 2.39 (m, 1H), 2.38 (s, 3H), 2.21 – 2.08 (m, 4H), 1.99 – 1.93 (m, 1H), 1.91 – 1.81 (m, 2H), 1.53 – 1.26 (m, 18H), 1.23 – 1.58 (m, 3H), 0.91 – 0.78 (m, 10H); MS (ESI): m/z calcd for $C_{62}H_{73}FN_9O_{14}$ $[M+H]^+$: 1186.5; found 1186.4.

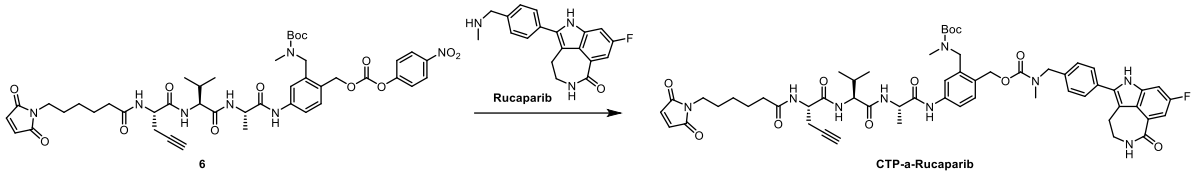
Synthesis of compound CTP-a-Smol006



Method B

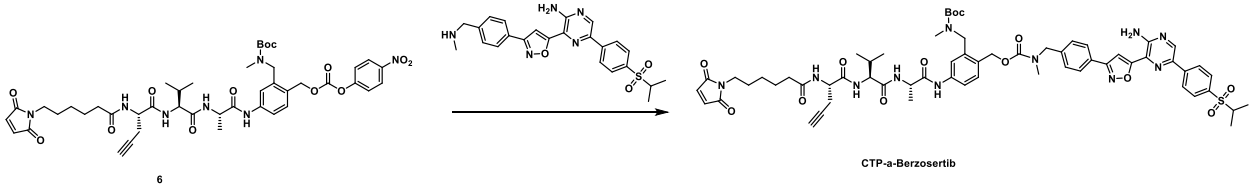
To a solution of smol006 (360 mg, 0.64 mmol) in DMF (5 mL) was added N, N-Diisopropylethylamine (248 mg, 1.91 mmol) at 0 ºC in ice-water bath. After stirring for 10 minutes, Compound **6** (568 mg, 0.64 mmol) and HOBt (43 mg, 0.32 mmol) were added to reaction mixture. The resulting solution was warmed to room temperature and allowed to stir at that temperature for 2 h. and the reaction was stirred at room temperature for 2 h. The reaction was monitored by LC-MS. Upon completion, ethyl acetate (60 mL) and water (50 mL) were added, the organic layer was separated, and the resultant aqueous solution was extracted with ethyl acetate (3 × 50 mL). The combined organic phases were washed with 0.5 M aq. HCl (50 mL), brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The residue was subjected to flash column chromatography for purification using CH_2Cl_2/MeOH (93:7) as eluent to give the compound CTP-a-Smol006 (470 mg, 58%) as yellow solid. MS (ESI): m/z calcd for $C_{64}H_{80}ClN_{11}O_{15}$ $[M+Na]^+$: 1300.5; found 1300.3.

Synthesis of compound CTP-a-Rucaparib



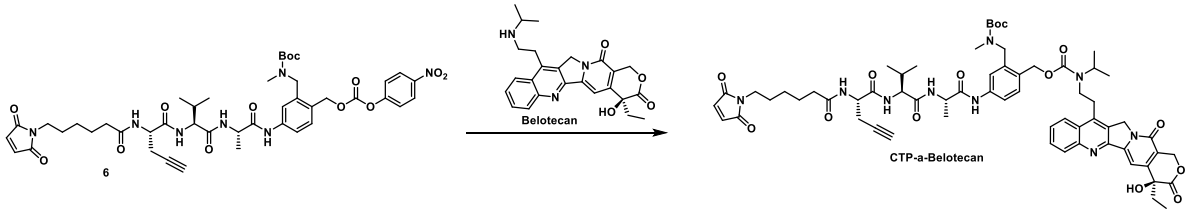
Compound CTP-a-Rucaparib was prepared from Rucaparib (CAS: 283173-50-2) following the previously established Method B. Purification by flash column chromatography (using CH_2Cl_2/MeOH = 94/6) afforded compound CTP-a-Rucaparib (2.73 g, 82%, 3.10 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{57}H_{69}FN_9O_{11}$ $[M+H]^+$: 1074.5; found 1074.4.

Synthesis of compound CTP-a-Berzosertib



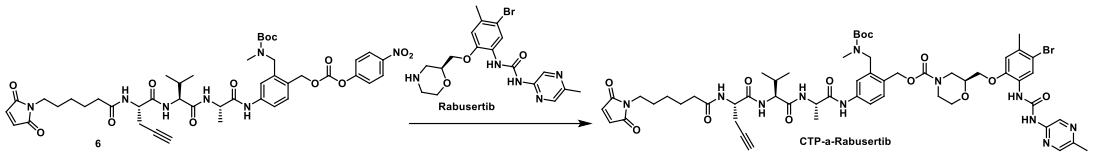
Compound CTP-a-Berzosertib was prepared from Berzosertib (CAS: 1232416-25-9) following the previously established Method B. Purification by flash column chromatography (using CH_2Cl_2/MeOH = 94/6) afforded compound CTP-a-Berzosertib (720 mg, 62%, 0.95 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{62}H_{77}N_{11}O_{13}S$ $[M+2H]^{+2}$: 607.3; found 607.3.

Synthesis of compound CTP-a-Belotecan



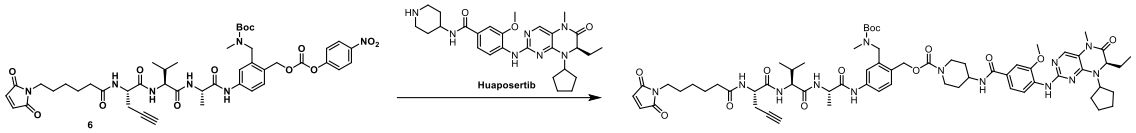
Compound CTP-a-Belotecan was prepared from belotecan (CAS: 213819-48-8) following the previously established Method A. Purification by flash column chromatography (using CH_2Cl_2/MeOH = 93/7) afforded CTP-a-Belotecan (360 mg, 71%, 0.43 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{63}H_{78}N_9O_{14}$ $[M+H]^+$: 1184.6; found 1184.5.

Synthesis of compound CTP-a-Rabusertib



Compound CTP-a-Rabusertib was prepared from belotecan (CAS: 213819-48-8) following the previously established Method B. Purification by flash column chromatography (using CH_2Cl_2/MeOH = 92/8) afforded CTP-a-Rabusertib (1.0 g, 42%, 2.01 mmol scale) as a white solid. **MS** (ESI): m/z calcd for $C_{56}H_{73}BrN_{11}O_{13}$ $[M+H]^+$: 1186.5; found 1186.3.

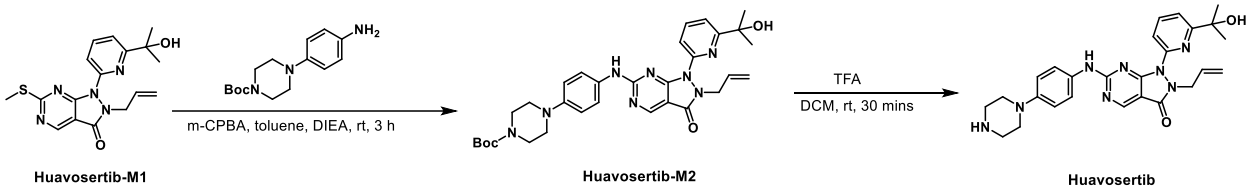
Synthesis of compound CTP-a-Huaposertib



Huaposertib, the starting material, was prepared as described in the patent literature (WO2009141575 A1). Compound CTP-a-huaposertib was synthesized following the previously established Method B. Purification by flash column chromatography (using CH_2Cl_2/MeOH = 93/7) afforded CTP-a-huaposertib (600 mg, 68%, 0.70 mmol scale) as a white solid. MS (ESI): m/z calcd for $C_{56}H_{73}BrN_{11}O_{13}$ $[M+H]^+$: 1258.7; found 1259.5.

Synthesis of compound CTP-a-Huavosertib

1) Synthesis of Huavosertib

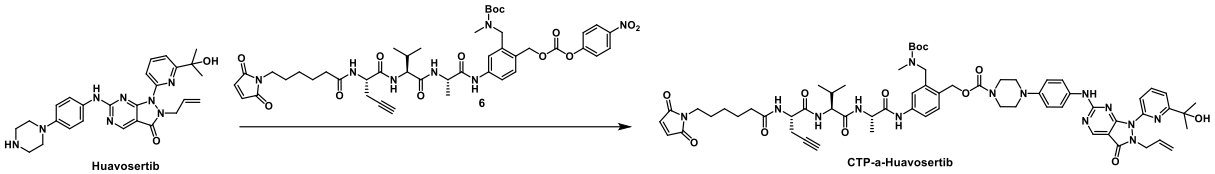


To a solution of Huavosertib-M1 (BioDuro-Sundia, 2.0 g, 5.596 mmol) in toluene (30 mL) was added m-CPBA (1.36 g, 6.715 mmol, 85%wt) and the reaction was stirred at room temperature for 1 h. Then N, N-Diisopropylethylamine (3.25 g, 25.180 mmol) and tert-butyl 4-(4-aminophenyl)piperazine-1-carboxylate (1.55 g, 6.715 mmol) was added and the resultant mixture was stirred at room temperature for 2 h. The reaction was monitored by LC-MS. Upon completion, water (100 mL) was added, and the resultant mixture was extracted with ethyl acetate (3 × 100

mL). The combined organic phases were washed with brine (150 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The residue was subjected to flash column chromatography for purification using CH_2Cl_2/ EtOAc (3:7) as eluent to give the compound Huavosertib-M2 (2.2 g, 67%) as dark-green solid. MS (ESI): m/z calcd for $C_{31}H_{39}N_8O_4$ $[M+H]^+$: 587.3; found 587.3.

To a solution of Huavosertib-M2 (2.1 g, 3.573 mmol) in DCM (15 mL) was added trifluoroacetic acid (5 mL) and the reaction was stirred at room temperature for 0.5 h. The reaction was monitored by LC-MS. Upon completion, the solvent was removed under reduced pressure to give the compound Huavosertib (2.1 g, 100%) as a tan solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.19 (s, 1H), 8.84 (s, 1H), 8.04 (t, J = 8.0 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.61 (d, J = 7.6 Hz, 3H), 6.97 (d, J = 92 Hz, 2H), 5.71 – 5.61 (m, 1H), 5.33 (s, 1H), 4.99 (dd, J = 10.4, 1.2 Hz, 1H), 4.82 (dd, J = 17.2, 1.2 Hz, 1H), 4.68 (d, J = 5.6 Hz, 2H), 3.23 – 3.17 (m, 4H), 3.14 – 3.12 (m, 4H), 1.46 (s, 6H); MS (ESI): m/z calcd for $C_{26}H_{32}N_8O_2$ $[M+H]^+$: 487.3; found 487.2.

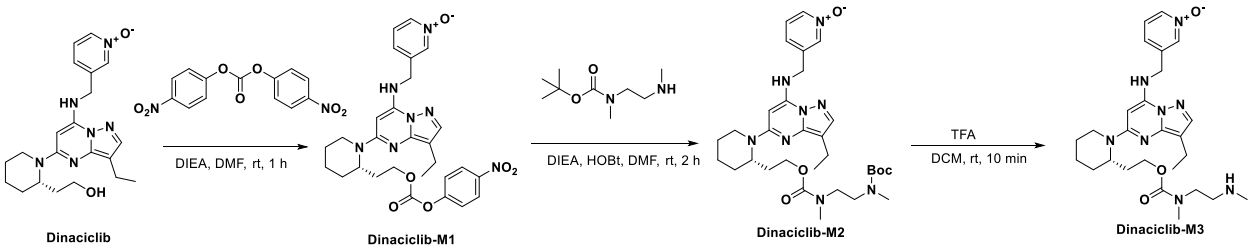
2) CTP-a-Huavosertib



Compound CTP-a-Huavosertib was synthesized following the previously established Method B. Purification by flash column chromatography (using CH_2Cl_2/MeOH = 93/7) afforded CTP-a-Huavosertib (2.1 g, 47%, 3.57 mmol scale) as a white solid. MS (ESI): m/z calcd for $C_{64}H_{81}N_{14}O_{12}$ $[M+H]^+$: 1237.6; found 1237.5.

Synthesis of compound CTP-a-Dinaciclib

1) Synthesis of Intermediate Dinaciclib-M3

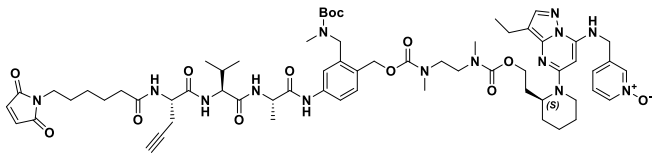


Compound Dinaciclib-M1: To a solution of Dinaciclib (BioDuro-Sundia, 2.11 g, 5.3 mmol) in DMF (50 mL) was added bis(4-nitrophenyl) carbonate (503 mg, 1.65 mmol) and N, N-Diisopropylethylamine (3.22 g, 10.6 mmol) and the reaction was stirred at room temperature for 5 h. The reaction was monitored by LC-MS. Upon completion, ethyl acetate (100 mL) was added, and the resultant mixture was washed with water (3 × 50 mL). The organic phase was then washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The residue was subjected to flash column chromatography for purification using CH_2Cl_2/ MeOH (94:6) as eluent to give the compound Dinaciclib-M1 (2.63 g, 88%) as yellow solid. MS (ESI): m/z calcd for $C_{28}H_{32}N_7O_6$ $[M+H]^+$: 562.2; found 562.2.

Compound Dinaciclib-M3: To a solution of Dinaciclib-M1 (2.83 g, 4.68 mmol) in DMF (35 mL) was added N, N-Diisopropylethylamine (1.8 g, 14.03 mmol). After stirring for 10 minutes, tert-butyl methyl(2-(methylamino)ethyl)carbamate (1.76 g, 9.36 mmol) and HOBt (0.32 g, 2.34 mmol) were added to reaction mixture. The resulting solution was stirred at room temperature for 2 h. The reaction was monitored by LC-MS. Upon completion, ethyl acetate (60 mL) and water (50 mL) were added, the organic layer was separated, and the resultant aqueous solution was extracted with ethyl acetate (3 × 50 mL). The combined organic phases were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The residue was subjected to flash column chromatography for purification using CH_2Cl_2/MeOH (94:6) as eluent to give the compound Dinaciclib-M2 (2.26 g, 79%) as yellow solid. MS (ESI): m/z calcd for $C_{31}H_{47}N_8O_5$ $[M+H]^+$: 611.4; found 611.8.

To a solution of Dinaciclib-M2 (1.9 g, 3.1 mmol) in Methylene chloride (21 mL) was added trifluoroacetic acid (7 mL) and the reaction was stirred at room temperature for 0.5 h. The reaction was monitored by LC-MS. Upon completion, the solvent was removed under reduced pressure to give the compound Dinaciclib-M3 (1.9 g, 100%) as a tan solid.MS (ESI): m/z calcd for $C_{26}H_{39}N_8O_3$ $[M+H]^+$: 511.3; found 511.3.

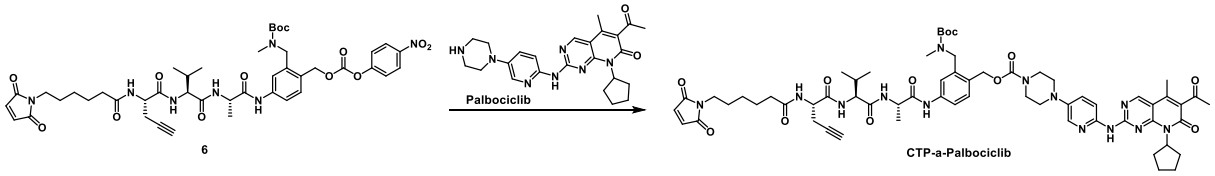
2) CTP-a-Dinaciclib



Compound CTP-a-Dinaciclib was synthesized following the previously established Method B. Purification by flash column chromatography (using CH_2Cl_2/MeOH = 93/7) afforded CTP-a-Dinaciclib (2.6 g, 66%, 3.1 mmol scale) as a yellow solid.

MS (ESI): m/z calcd for $C_{56}H_{73}BrN_{11}O_{13}$ $[M+H]^+$: 1261.7; found 1261.8.

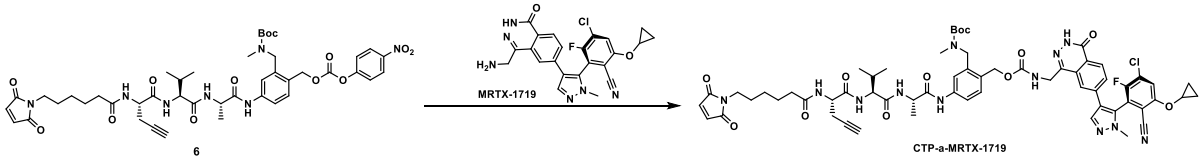
Synthesis of compound CTP-a-Palbociclib



Compound CTP-a-Palbociclib was synthesized following the previously established Method B. Purification by flash column chromatography (using CH_2Cl_2/MeOH = 90/10) afforded CTP-a-Palbociclib (350 mg, 44%, 0.67 mmol scale) as a yellow solid.

MS (ESI): m/z calcd for $C_{62}H_{80}N_{13}O_{12}$ $[M+H]^+$: 1198.6; found 1198.5.

Synthesis of compound CTP-a-MRTX-1719

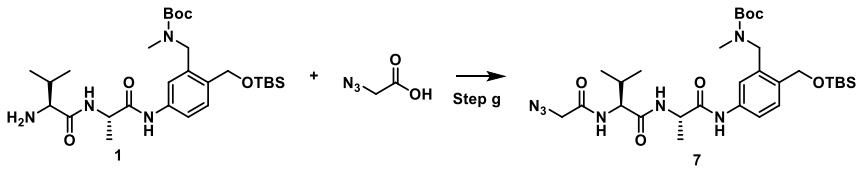


Compound CTP-a-MRTX-1719 was prepared from MRTX-1719 (CAS: 2630904-44-6) following the previously established Method B. Purification by flash column chromatography (using CH_2Cl_2/MeOH = 90/10) afforded CTP-a-MRTX-1719 (380 mg, 60%, 0.54 mmol scale) as a yellow solid.

MS (ESI): m/z calcd for $C_{62}H_{80}N_{13}O_{12}$ $[M+H]^+$: 1198.6; found 1198.5.

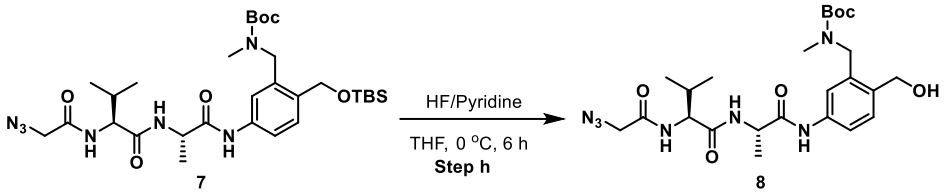
Synthetic procedure of CTP-b series

Compound **7**



To a solution of compound **1** (1.0 g, 1.8 mmol) in DCM (30 mL) was added 2-azidoacetic acid (182 mg, 1.8 mmol) and EEDQ (890 mg, 3.6 mmol) and the reaction was stirred at room temperature for 2 h. The reaction was monitored by LC-MS. Upon completion, the solvent was removed under reduced pressure. The residue was subjected to flash column chromatography for purification using CH_2Cl_2/MeOH (95:5) as eluent to give the compound **7** (1.1 g, 94%) as light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 – 8.54 (m, 1H), 7.67 – 7.46 (m, 1H), 7.38 – 7.28 (m, 2H), 7.26 – 7.01 (m, 2H), 4.86 – 4.71 (m, 1H), 4.66 – 4.63 (m, 2H), 4.56 – 4.40 (m, 3H), 4.04 (s, 2H), 2.81 – 2.74 (m, 3H), 2.19 – 2.06 (m, 1H), 1.46 – 1.45 (m, 12H), 0.97 – 0.87 (m, 15H), 0.07 (s, 6H); MS (ESI): m/z calcd for $C_{30}H_{51}N_7NaO_6Si$ $[M+Na]^+$: 656.4; found 656.3.

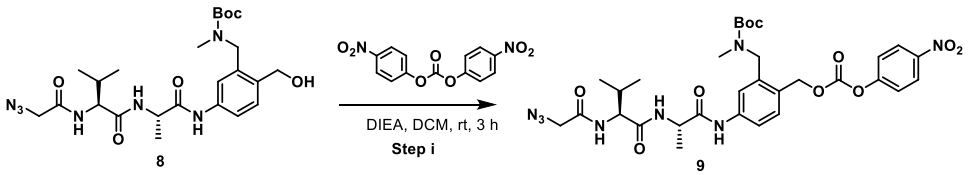
Compound **8**



7 8

To a solution of compound **4** (1.1 g, 1.7 mmol) in THF (20 mL) at 0 °C under N_2 atmosphere was added 65wt.% Pyridine hydrofluoride (2193 mg, 14.4 mmol). The reaction mixture was stirred at room temperature for 6 h. The reaction was monitored by LC-MS. Upon completion, ethyl acetate (100 mL) was added to dilute the reaction, then it was poured into water (100 mL). The separated organic phase was washed with water (2 × 50 mL) and saturated aq. $NaHCO_3$ (3 × 60 mL). The organic phase was washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum to give the crude compound **8** (700 mg, 77%) as light yellow solid, which was directly used in the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.34 (d, J = 7.2 Hz, 1H), 8.13 (d, J = 8.8 Hz, 1H), 7.51 (d, J = 6.8 Hz, 1H), 7.34 (d, J = 1.6 Hz, 1H), 7.29 (d, J = 8.4 Hz, 1H), 4.49 – 4.35 (m, 5H), 4.26 (dd, J = 8.8, 6.8 Hz, 1H), 3.89 (d, J = 3.2 Hz, 2H), 2.76 (s, 3H), 2.05 – 1.91 (m, 2H), 1.44 – 1.35 (m, 9H), 1.30 (t, J = 6.8 Hz, 3H), 0.89 (d, J = 6.8 Hz, 3H), 0.84 (d, J = 6.8 Hz, 3H); MS (ESI): m/z calcd for $C_{24}H_{37}N_7NaO_6$ $[M+Na]^+$: 542.3; found 542.3.

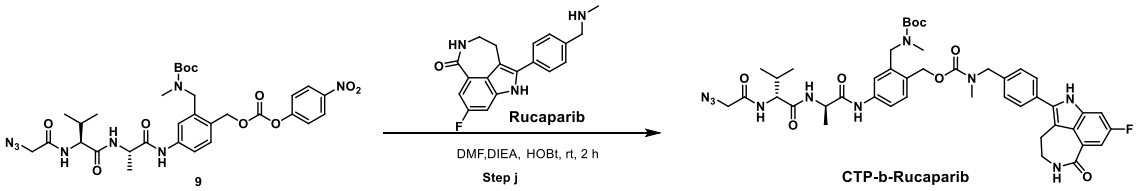
Compound **9**



8 9

To a solution of compound **5** (400 mg, 0.77 mmol) in DMF (5 mL) was added bis(4-nitrophenyl) carbonate (468 mg, 1.54 mmol) and N, N-Diisopropylethylamine (298 mg, 2.31 mmol) and the reaction was stirred at room temperature for 3 h. The reaction was monitored by LC-MS. Upon completion, water (50 mL) was added, and the resultant mixture was extracted with ethyl acetate (3 × 50 mL). The combined organic phases were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The residue was subjected to flash column chromatography for purification using CH_2Cl_2/MeOH (95:5) as eluent to give the compound **6** (410 mg, 78%) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.08 (s, 1H), 8.38 (t, J = 6.4 Hz, 1H), 8.31 (d, J = 9.2 Hz, 2H), 8.13 (t, J = 9.2 Hz, 1H), 7.57 – 7.55 (m, 3H), 7.48 (s, 1H), 7.40 (d, J = 8.4 Hz, 1H), 5.29 (s, 2H), 4.52 (s, 2H), 4.46 – 4.35 (m, 1H), 4.27 (dd, J = 8.8, 6.8 Hz, 1H), 3.89 (d, J = 3.2 Hz, 2H), 2.78 (s, 3H), 2.02 – 1.94 (m, 1H), 1.43 – 1.31 (m, 12H), 0.89 (d, J = 6.8 Hz, 3H), 0.84 (d, J = 6.8 Hz, 3H); MS (ESI): m/z calcd for $C_{31}H_{40}N_8NaO_{10}$ $[M+Na]^+$: 707.3; found 707.3.

Synthesis of compound CTP-b-Rucaparib

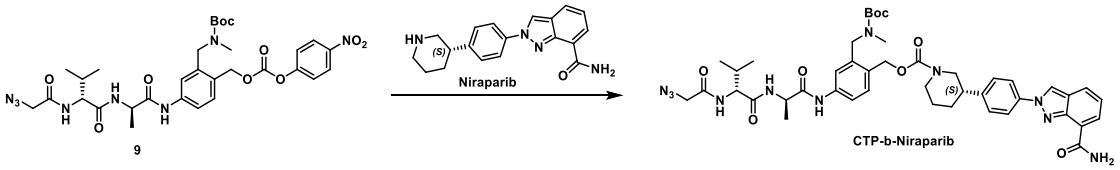


9

To a solution of Rucaparib (600 mg, 0.87 mmol) in DMF (8 mL) was added N, N-Diisopropylethylamine (337 mg, 2.61 mmol). After stirring for 10 minutes , Compound **9** (596 mg, 0.87 mmol) and HOBt (58 mg, 0.44 mmol) were added to reaction mixture. The resulting solution was stirred at room temperature for 2 h. The reaction was monitored by LC-MS. Upon completion, ethyl acetate (60 mL) and water (50 mL) were added, the organic layer was separated, and the resultant aqueous solution was extracted with ethyl acetate (3 × 50 mL). The combined organic phases were washed with 0.5 M aq. HCl (50 mL), brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The residue was subjected to flash column chromatography for purification using CH_2Cl_2/MeOH (10:1) as eluent to give the compound CTP-

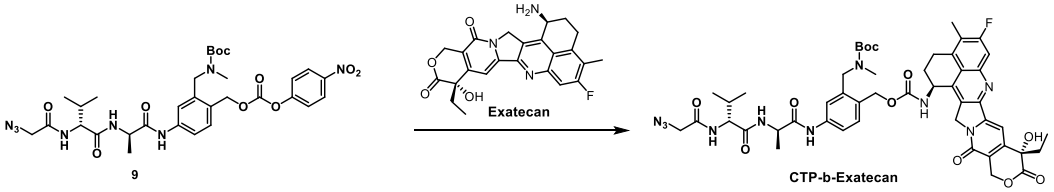
b-Rucaparib (500 mg, 66%) as light-yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.66 (s, 1H), 10.02 (s, 1H), 8.36 (d, J = 6.8 Hz, 1H), 8.25 (t, J = 5.6 Hz, 1H), 8.13 (d, J = 8.8 Hz, 1H), 7.59 (s, 3H), 7.45 – 7.17 (m, 6H), 5.10 (s, 2H), 4.49 (s, 3H), 4.41 (d, J = 8.0 Hz, 2H), 4.26 (t, J = 7.6 Hz, 1H), 3.88 (d, J = 3.2 Hz, 2H), 3.39 (s, 2H), 3.03 (s, 2H), 2.85 (s, 3H), 2.77 (s, 1H), 2.69 (s, 1H), 2.54 (s, 1H), 1.98 – 1.92 (m, 1H), 1.41 – 1.29 (m, 12H), 0.88 (d, J = 6.0 Hz, 3H), 0.83 (d, J = 6.0 Hz, 3H). MS (ESI): m/z calcd for $C_{44}H_{53}FN_{10}O_8$ $[M+H]^+$: 869.4; found 869.3.

Synthesis of compound CTP-b-Niraparib



Compound CTP-b-Niraparib was prepared from Niraparib (CAS: 1038915-60-4) following the previously established synthetic procedure of CTP-b series step j. Purification by flash column chromatography (using CH_2Cl_2/MeOH = 90/10) afforded CTP-b-Niraparib (300 mg, 79%, 0.46 mmol scale) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.02 (s, 1H), 9.28 (s, 1H), 8.56 (s, 1H), 8.36 (d, J = 6.8 Hz, 1H), 8.14 – 8.08 (m, 5H), 7.89 (s, 1H), 7.60 – 7.47 (m, 3H), 7.42 (t, J = 7.2 Hz, 1H), 7.35 – 7.24 (m, 2H), 5.06 (s, 2H), 4.56 – 4.34 (m, 3H), 4.30 – 4.20 (m, 1H), 4.06 – 4.00 (m, 2H), 3.88 (d, J = 2.8 Hz, 2H), 2.76 – 2.73 (m, 4H), 1.99 – 1.88 (m, 2H), 1.77 – 1.68 (m, 2H), 1.58 – 1.22 (m, 15H), 0.88 (d, J = 6.4 Hz, 3H), 0.83 (d, J = 6.4 Hz, 3H); MS (ESI): m/z calcd for $C_{44}H_{56}N_{11}O_8$ $[M+H]^+$: 866.4; found 866.4.

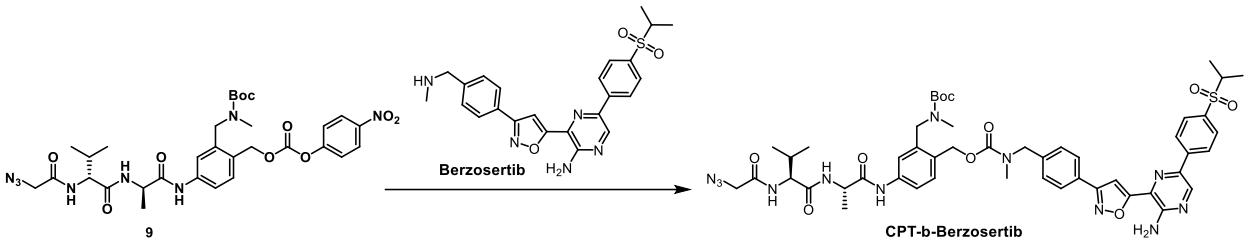
Synthesis of compound CTP-b-Exatecan



Compound CTP-b-Exatecan was prepared from Exatecan mesylate (CAS: 169869-90-3) following the previously established synthetic procedure of CTP-b series, step j. Purification by flash column chromatography (using CH_2Cl_2/MeOH = 93/7) afforded compound CTP-b-Exatecan (1.47 g, 80%, 1.88 mmol scale) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.99 (s, 1H), 8.34 (d, J =

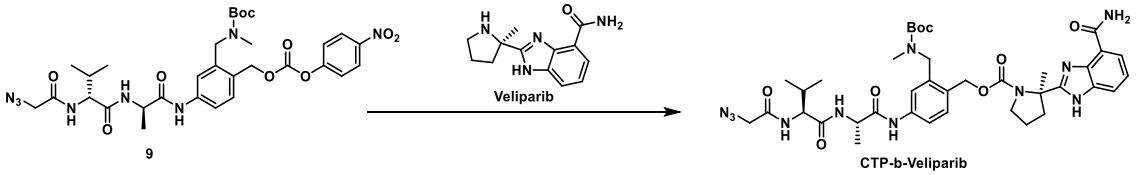
6.8 Hz, 1H), 8.12 (d, *J* = 8.8 Hz, 1H), 8.02 (d, *J* = 9.2 Hz, 1H), 7.77 (d, *J* = 10.8 Hz, 1H), 7.55 (s, 1H), 7.43 – 7.28 (m, 3H), 6.51 (s, 1H), 5.43 (s, 2H), 5.28 (s, 3H), 5.11 (s, 2H), 4.47 – 4.36 (m, 3H), 4.28 – 4.21 (m, 1H), 3.88 (d, *J* = 3.6 Hz, 2H), 3.26 – 3.10 (m, 3H), 2.77 (s, 3H), 2.37 (s, 3H), 2.18 (s, 2H), 2.04 – 1.82 (m, 3H), 1.40 – 1.29 (m, 12H), 0.89 – 0.78 (m, 9H); MS (ESI): m/z calcd for $C_{49}H_{58}FN_{10}NaO_{11}$ $[M+H]^+$: 981.4; found 981.3.

Synthesis of compound CPT-b-Berzosertib



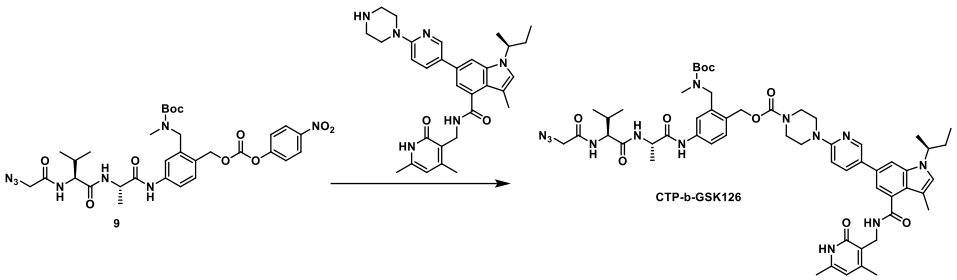
Compound CPT-b-Berzosertib was prepared from Berzosertib (CAS: 1232416-25-9) following the previously established synthetic procedure of CTP-b series, step j. Purification by flash column chromatography (using CH_2Cl_2/MeOH = 93/7) afforded compound CPT-b-Berzosertib (1.70 g, 78%, 2.16 mmol scale) as a yellow solid. MS (m/z): $[M+Na]^+$ calcd for $C_{49}H_{60}N_{12}NaO_{10}S$ 1031.4; found 1031.3.

Synthesis of compound CTP-b-Veliparib



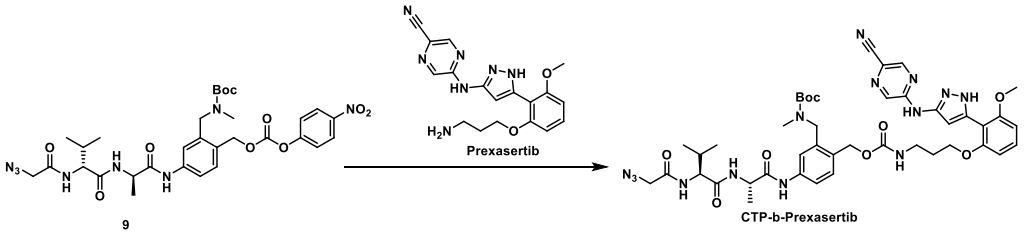
Compound CTP-b-Veliparib was prepared from Veliparib (CAS: 912444-00-9) following the previously established synthetic procedure of CTP-b series, step j. Purification by flash column chromatography (using CH_2Cl_2/MeOH = 93/7) afforded CTP-b-Veliparib (140 mg, 81%, 0.22 mmol scale) as a white solid. MS (ESI): m/z calcd for $C_{38}H_{51}N_{11}O_8$ $[M+H]^+$: 790.4; found 790.3.

Synthesis of compound CTP-b-GSK126



Compound CTP-b-GSK126 was prepared from GSK126 (CAS: 1346574-57-9) following the previously established synthetic procedure of CTP-b series, step j. Purification by flash column chromatography (using CH_2Cl_2/MeOH = 93/7) afforded CTP-b-GSK126 (180 mg, 88%, 0.19 mmol scale) as a white solid. MS (ESI): m/z calcd for $C_{56}H_{74}N_{13}O_9$ $[M+H]^+$: 1072.6; found 1072.5.

Synthesis of compound CTP-b-Prexasertib

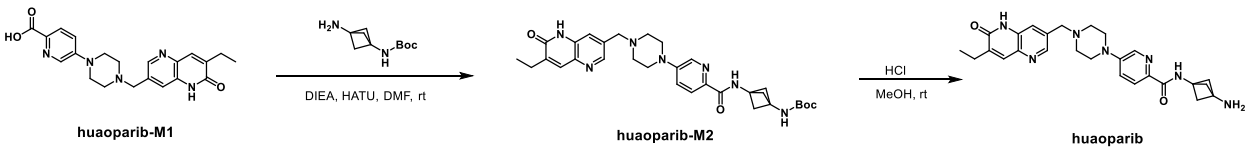


Compound CTP-b-Prexasertib was prepared from Prexasertib (CAS: 1234015-52-1) following the previously established synthetic procedure of CTP-b series, step j. Purification by flash column chromatography (using CH_2Cl_2/MeOH = 93/7) afforded CTP-b-Prexasertib (200 mg, 81%, 0.27 mmol scale) as a white solid. MS (ESI): m/z calcd for $C_{43}H_{55}N_{14}O_9$ $[M+H]^+$: 911.4; found 911.4.

Synthesis of compound CTP-b-Huaoparib

Huaoparib-M1, the starting material, was prepared as described in the patent literature (WO2023066363 A1).

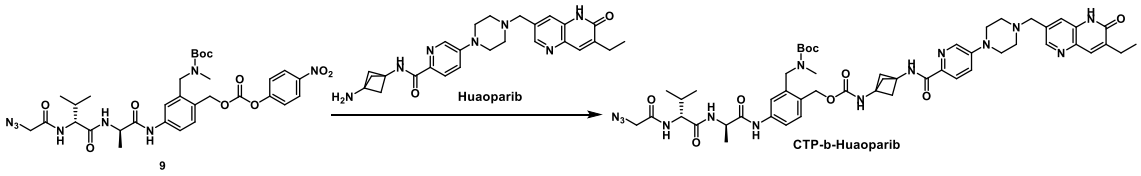
1) Synthsis of Huaoparib



To a solution of huaoparib-M1 (500 mg, 1.27 mmol) in DMF (5 mL) was added tert-butyl (3-aminobicyclo[1.1.1]pentan-1-yl)carbamate (503 mg, 2.54 mmol) and N, N-Diisopropylethylamine (491 mg, 3.81 mmol), followed by the addition of HATU (965 mg, 2.54 mmol). The reaction was stirred at room temperature for 1 h. The reaction was monitored by LC-MS. Upon completion, water (100 mL) was added, and the resultant mixture was extracted with ethyl acetate (3 × 100 mL). The combined organic phases were washed with brine (80 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The residue was subjected to flash column chromatography for purification using CH_2Cl_2/ MeOH (10:1) as eluent to give the compound huaoparib-2 (538 mg, 74%) as white solid. MS (ESI): m/z calcd for $C_{31}H_{40}N_7O_4$ $[M+H]^+$: 574.3; found 574.3.

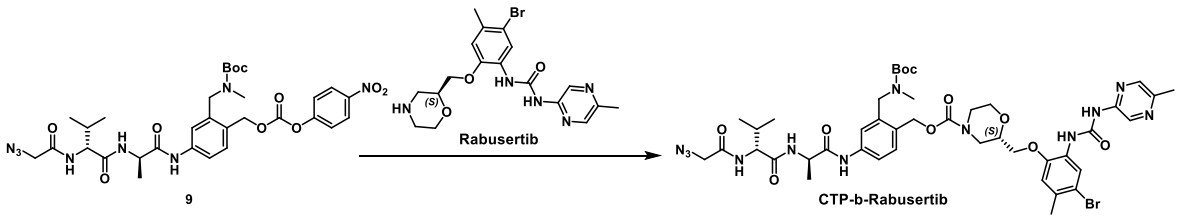
To a solution of huaoparib-M2 (538 mg, 0.94 mmol) in MeOH (10 mL) was added 5.0 M aq. HCl (5 mL) and the reaction was stirred at room temperature for 2 h. The reaction was monitored by LC-MS. Upon completion, the solvent was removed under reduced pressure to give the compound huaoparib (478 mg, 100%) as white solid. MS (ESI): m/z calcd for $C_{26}H_{32}N_7O_2$ $[M+H]^+$: 474.3; found 474.3.

2) CTP-b-Huaoparib



Compound CTP-b-Huaoparib was prepared from Huaoparib following the previously established synthetic procedure of CTP-b series, step j. Purification by flash column chromatography (using CH_2Cl_2/MeOH = 10/1) afforded CTP-b-Huaoparib (351 mg, 44%, 0.78 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{51}H_{67}N_{14}O_9$ $[M+H]^+$: 1019.5; found 1019.5.

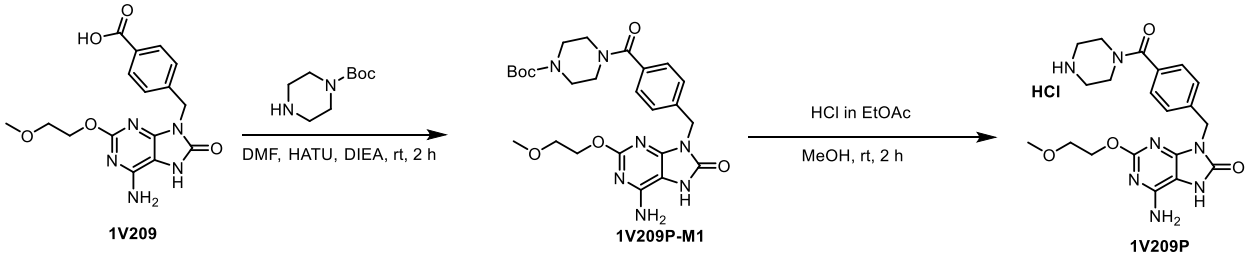
Synthesis of compound CTP-b-Rabusertib



Compound CTP-b-Rabusertib was prepared from Rabusertib (CAS: 911222-45-2) following the previously established synthetic procedure of CTP-b series, step j. Purification by flash column chromatography (using CH_2Cl_2/MeOH = 12/1) afforded CTP-b-Rabusertib (200 mg, 89%, 0.23 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{43}H_{58}BrN_{12}O_{10}$ $[M+H]^+$: 981.4; found 981.2.

Synthesis of compound CTP-b-1V209P

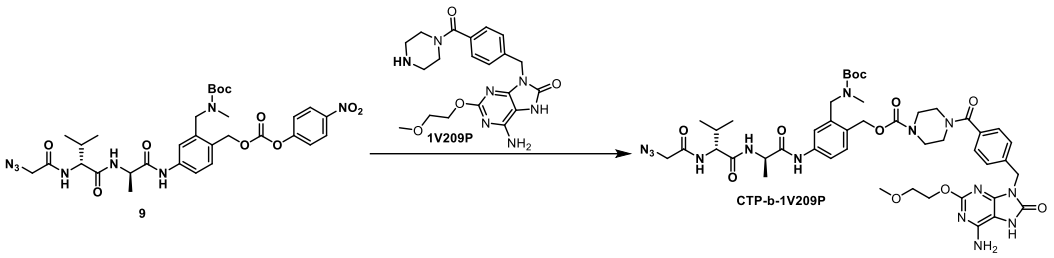
1) Synthsis of 1V209P



To a solution of 1V209 (100 mg, 0.28 mmol) in DMF (3 mL) was added tert-butyl piperazine-1-carboxylate (156 mg, 0.84 mmol) and N, N-Diisopropylethylamine (108 mg, 0.84 mmol), followed by the addition of HATU (159 mg, 0.42 mmol). The reaction was stirred at room temperature for 2 h. The reaction was monitored by LC-MS. Upon completion, water (60 mL) was added, and the resultant mixture was extracted with ethyl acetate (3 × 60 mL). The combined organic phases were washed with brine (80 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The residue was subjected to flash column chromatography for purification using CH_2Cl_2/ MeOH (10:1) as eluent to give the compound 1V209P-M1 (140 mg, 95%) as white solid. MS (ESI): m/z calcd for $C_{25}H_{34}N_7O_6$ $[M+H]^+$: 528.3; found 528.3.

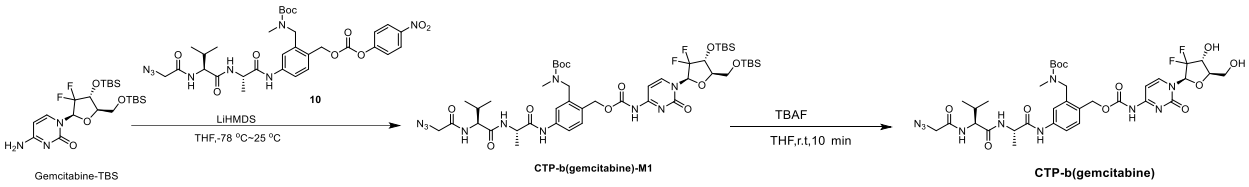
To a solution of 1V209-M1 (140 mg, 0.27 mmol) in MeOH (2 mL) was added 4.0 M HCl in ethyl acetate (2 mL) and the reaction was stirred at room temperature for 2 h. The reaction was monitored by LC-MS. Upon completion, the solvent was removed under reduced pressure to give the compound 1V209P (123 mg, 100%) as white solid. MS (ESI): m/z calcd for $C_{20}H_{26}N_7O_4$ $[M+H]^+$: 428.2; found 428.1.

2) CTP-b-1V209P



Compound CTP-b-1V209P was synthesized following the previously established synthetic procedure of CTP-b series, step j. Purification by flash column chromatography (using CH_2Cl_2/MeOH = 92/8) afforded CTP-b-1V209P (140 mg, 56%, 0.26 mmol scale) as a white solid. MS (ESI): m/z calcd for $C_{45}H_{61}N_{14}O_{11}$ $[M+H]^+$: 973.5; found 973.3.

Synthesis of compound CTP-b-Gemcitabine

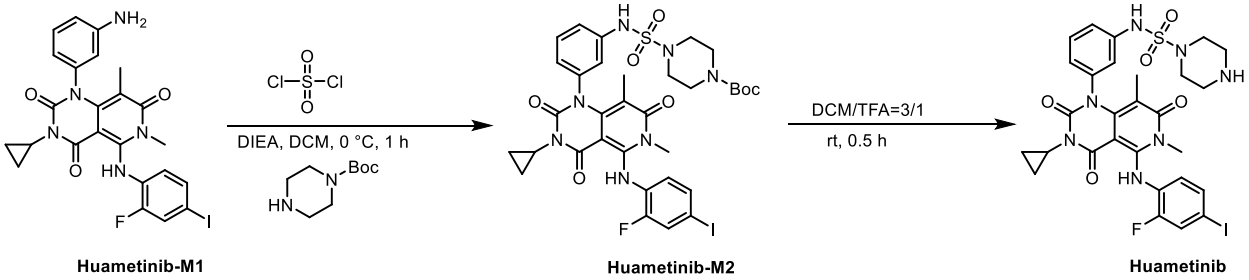


To an inert atmosphere solution of Gemcitabine-TBS (550 mg, 1.02 mmol, synthesized according to literature (Angewandte Chemie, International Edition 2018, 57(21), 6141-6145) in anhydrous THF (40 mL) was added 1.0 M LiHMDS (1.0 mL, 1.0 mmol) in THF slowly at -78 °C (dry ice/acetone bath) and the mixture was gradually allowed to warm to ambient temperature then stirred for 30 min. At this point, compound 10 (500 mg, 0.73 mmol) was added as a solution in anhydrous THF (30 mL), and the reaction mixture was stirred at ambient temperature for 1 h. At this point, the reaction mixture was concentrated under vacuum. The residue was subjected to flash column chromatography for purification using CH_2Cl_2/ MeOH (97:3) as eluent to give the CTP-b-Gemcitabine-1 (500 mg, 66%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.01 (s, 1H), 10.04 (s, 1H), 8.36 (d, J = 6.8 Hz, 1H), 8.14 (d, J = 8.8 Hz, 1H), 8.02 (d, J = 7.6 Hz, 1H), 7.56 (s, 1H), 7.43 (s, 1H), 7.35 (d, J = 8.4 Hz, 1H), 7.12 (d, J = 7.2 Hz, 1H), 6.21 (t, J = 7.2 Hz, 1H), 5.16 (s, 2H), 4.49 (s, 2H), 4.44 – 4.31 (m, 2H), 4.30 – 4.22 (m, 1H), 4.04 – 3.94 (m, 2H), 3.92 – 3.75 (m, 3H), 2.77 (s, 3H), 2.04 – 1.93 (m, 1H), 1.41 – 1.26 (m, 12H), 0.90 – 0.83 (m, 24H), 0.11 – 0.10 (m, 12H); MS (ESI): m/z calcd for $C_{46}H_{74}F_2N_{10}NaO_{11}Si_2$ $[M+Na]^+$: 1059.5; found 1059.3.

To a solution of CTP-b-Gemcitabine-M1 (500 mg, 0.48 mmol) in THF (25 mL) was added 1.0 M TBAF (0.96mL, 0.96 mmol) in THF and the reaction was stirred at room temperature for 10 minutes. The reaction was monitored by LC-MS. Upon completion, the solvent was removed under reduced pressure. The residue was subjected to flash reverse-phase column chromatography for purification using H_2O/ CH_3CN (60:40) as eluent to give the CTP-b-Gemcitabine (360 mg, 90%) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.96 (s, 1H), 10.04 (s, 1H), 8.37 (d, J = 6.8 Hz, 1H), 8.22 (d, J = 7.6 Hz, 1H), 8.14 (d, J = 8.8 Hz, 1H), 7.54 (s, 1H), 7.43 (s, 1H), 7.35 (d, J = 8.4 Hz, 1H), 7.09 (d, J = 7.6 Hz, 1H), 6.33 (d, J = 4.8 Hz, 1H), 6.16 (t, J = 7.6 Hz, 1H), 5.31 (t, J = 5.2 Hz, 1H), 5.15 (s, 2H), 4.49 (s, 2H), 4.43 – 4.36 (m, 1H), 4.26 (dd, J = 8.8, 6.8 Hz, 1H), 4.21 – 4.14 (m, 1H), 3.89 (d, J = 3.2 Hz, 2H), 3.82 – 3.78 (m, 1H), 3.70 – 3.61 (m, 1H), 3.17 (d, J = 5.2 Hz, 1H), 2.78 (s, 3H), 2.00 – 1.95 (m, 1H), 1.42 – 1.35 (m, 9H), 1.31 (d, J = 7.2 Hz, 3H), 0.89 (d, J = 6.8 Hz, 3H), 0.83 (d, J = 6.8 Hz, 3H). MS (ESI): m/z calcd for $C_{34}H_{46}F_2N_{10}NaO_{11}$ $[M+Na]^+$: 831.3; found 831.2.

Synthesis of compound CTP-b- Huametinib

1) Synthsis of Huametinib

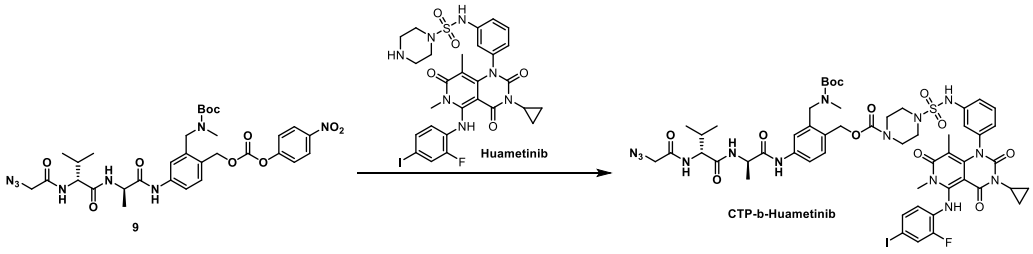


To an inert atmosphere solution of sulfuryl dichloride (257 mg, 1.919 mmol) in anhydrous methylene chloride (40 mL) was added tert-butyl piperazine-1-carboxylate (357 mg, 1.919 mmol) in one portion at -0 °C (ice-water bath) and the mixture was stirred at that temperature for 30 min. Then, Huametinib-M1 (Bidepharm, 110 mg, 0.192 mmol) and N, N-Diisopropylethylamine (248 mg, 1.919 mmol) were added as a solution in anhydrous methylene chloride (2 mL). The reaction mixture was stirred at -0 °C for 0.5 h. The reaction was monitored by LC-MS. Upon completion, the solvent was removed under reduced pressure. The residue was subjected to flash reverse-phase column chromatography for purification using 0.1% Formic acid in H_2O/ CH_3CN (60:40) as eluent

to give Huametinib-M2 (130 mg, 82%) as a white solid. MS (ESI): m/z calcd for $C_{33}H_{37}FIN_7O_7S$ $[M+H]^+$: 822.2; found 822.0.

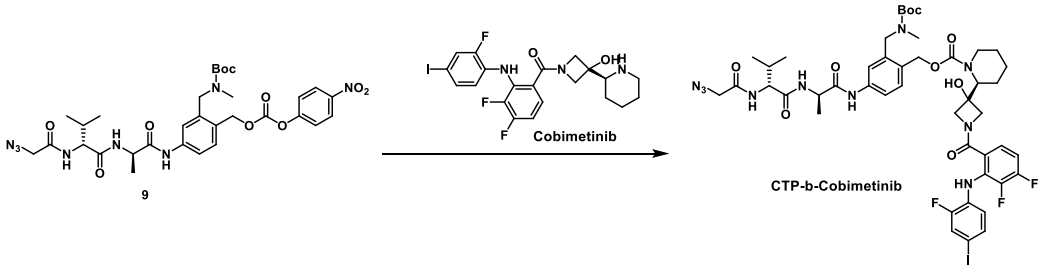
To a solution of Huametinib-M2 (130 mg, 0.158 mmol) in methylene chloride (3 mL) was added trifluoroacetic acid (1 mL) and the reaction was stirred at room temperature for 0.5 h. The reaction was monitored by LC-MS. Upon completion, the solvent was removed under reduced pressure to give the compound Huametinib (130 mg, 100%) as a tan solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.06 (s, 1H), 8.18 (s, 1H), 7.79 (dd, J = 10.4, 1.6 Hz, 1H), 7.55 (dd, J = 8.4, 1.2 Hz, 1H), 7.37 (t, J = 8.0 Hz, 1H), 7.22 (t, J = 2.0 Hz, 1H), 7.20 – 7.14 (m, 1H), 7.05 (dd, J = 8.0, 1.2 Hz, 1H), 6.92 (t, J = 8.8 Hz, 1H), 3.08 (s, 3H), 3.05 – 2.98 (m, 4H), 2.66 – 2.62 (m, 5H), 1.26 (s, 3H), 0.98 – 0.93 (m, 2H), 0.69 – 0.65 (m, 2H); MS (ESI): m/z calcd for $C_{28}H_{30}FIN_7O_5S$ $[M+H]^+$: 722.1; found 722.0.

2) CTP-b-Huametinib



Compound CTP-b-Huametinib was synthesized following the previously established synthetic procedure of CTP-b series, step j. Purification by flash column chromatography (using CH_2Cl_2/MeOH = 93/7) afforded CTP-b- Huametinib (140 mg, 70%, 0.16 mmol scale) as a white solid. MS (ESI): m/z calcd for $C_{53}H_{65}FIN_{14}O_{12}S$ $[M+H]^+$: 1267.4; found 1267.2.

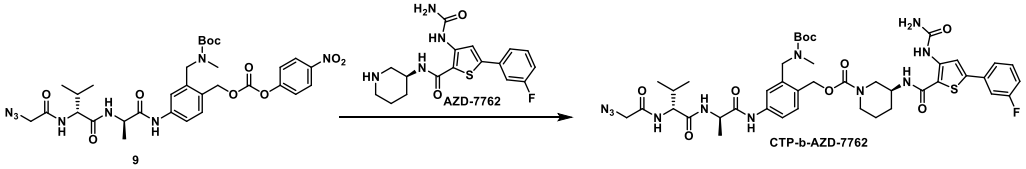
Synthesis of compound CTP-b-Cobimetinib



Compound CTP-b-Cobimetinib was prepared from Cobimetinib (CAS: 934660-93-2) following the previously established synthetic procedure of CTP-b series, step j. Purification by flash column

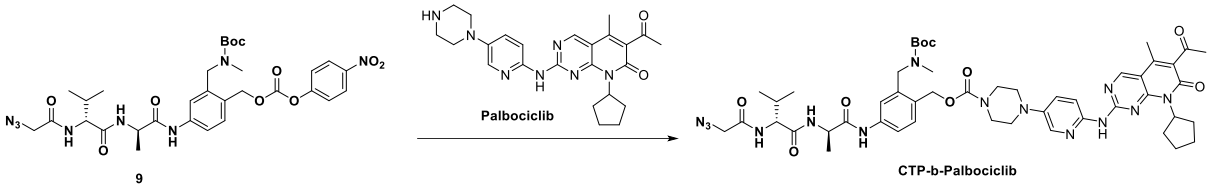
chromatography (using CH_2Cl_2/MeOH = 92/8) afforded CTP-b-Cobimetinib (100 mg, 48%, 0.19 mmol scale) as a white solid. MS (ESI): m/z calcd for $C_{46}H_{56}F_3IN_{10}NaO_9$ $[M+Na]^+$: 1099.3; found 1099.3.

Synthesis of compound CTP-b-AZD-7762



Compound CTP-b-AZD-7762 was prepared from AZD-7762 (CAS: 860352-01-8) following the previously established synthetic procedure of CTP-b series, step j. Purification by flash column chromatography (using CH_2Cl_2/MeOH = 93/7) afforded CTP-b-AZD-7762 (1.3 g, 58%, 2.49 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{42}H_{54}FN_{11}NaO_9S$ $[M+Na]^+$: 930.4; found 930.7.

Synthesis of compound CTP-b-Palbociclib

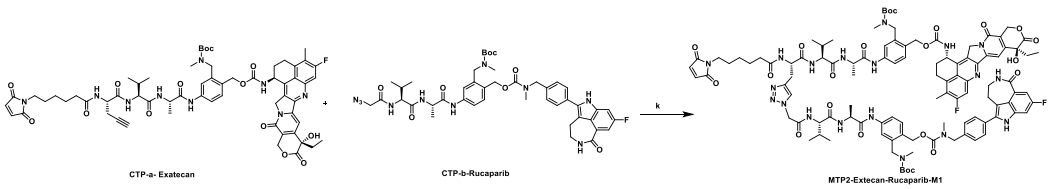


Compound CTP-b-Palbociclib was prepared from Palbociclib (CAS: 571190-30-2) following the previously established synthetic procedure of CTP-b series, step j. Purification by flash column chromatography (using CH_2Cl_2/MeOH = 96/4) afforded CTP-b-Palbociclib (260 mg, 82%, 0.32 mmol scale) as a white solid. MS (ESI): m/z calcd for $C_{49}H_{65}N_{14}O_9$ $[M+H]^+$: 993.5; found 993.4.

Synthetic procedure of MTP2 series

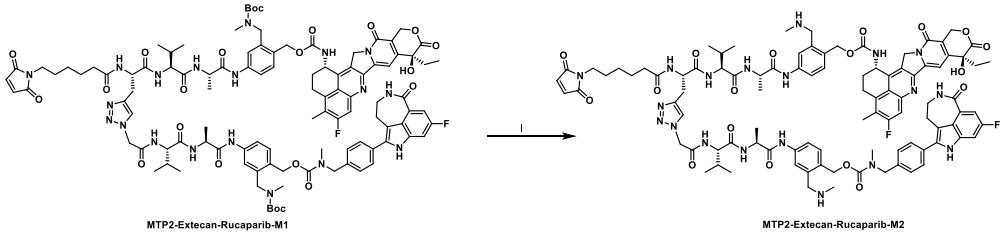
Synthesis of MTP2-Exatecan-Rucaparib

1) Compound MTP2-Exatecan-Rucaparib-M1



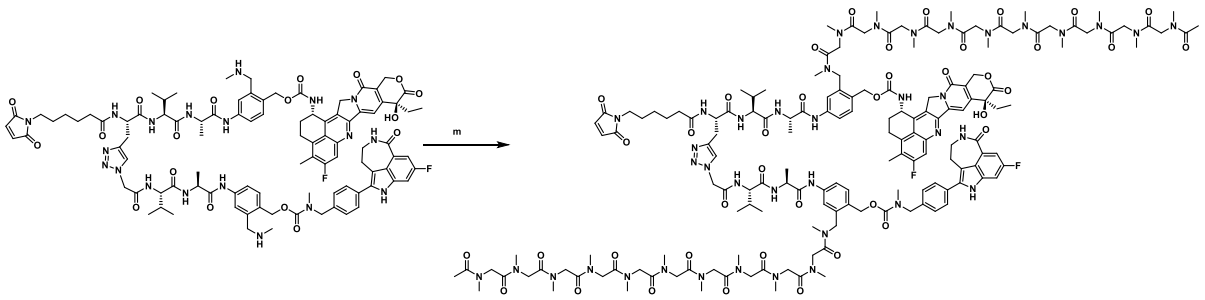
To a solution of CTP-a-Exatecan (150 mg, 0.13 mmol) and CTP-b-Rucaparib (115 mg, 0.13 mmol) in a mixture of MeOH (3 mL) and CH_2Cl_2 (3 mL) was added a solution of $CuSO_4$ (6.5 mg, 0.026 mmol) in deionized water (100 uL) and a solution of sodium ascorbate solution (10.3 mg, 0.052 mmol) in deionized water (100 uL) via syringe. The reaction mixture was degassed with vacuum and then purged with N_2 (2 cycles). The resulting solution was then allowed to stir at room temperature for 4 h. The reaction was monitored by LC-MS. Upon completion, the solvent was removed under reduced pressure to give the crude MTP2-Exatecan-Rucaparib-M1 (265 mg, 100%) as gray solid, which was directly used in the next step without further purification. MS (ESI): m/z calcd for $C_{106}H_{127}F_2N_{19}O_{22}$ $[M+2H]^{+2}$: 1028.0; found 1028.1.

2) Compound MTP2-Extecan-Rucaparib-M2



The crude MTP2-Extecan-Rucaparib-M1 obtained from above was suspended in CH_2Cl_2 (3 mL). To this suspension, TFA (1 mL) was added and the solution was stirred at room temperature for 5 minutes before the solvent was removed under vacuum. The crude MTP2-Exatecan-Rucaparib-M2 (265 mg, 100%) was directly used in next step. MS (ESI): m/z calcd for $C_{96}H_{111}F_2N_{19}O_{18}$ $[M+2H]^{+2}$: 927.9; found 928.1.

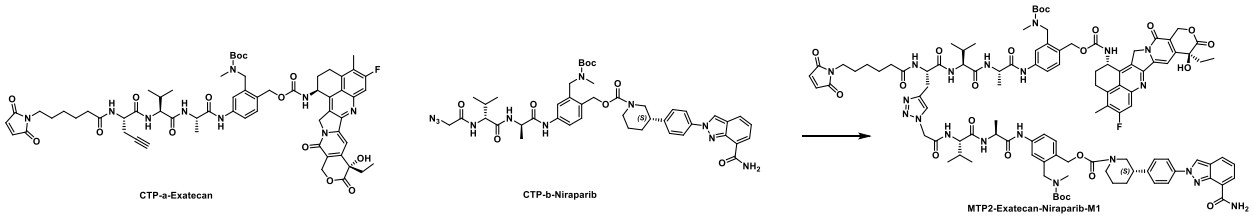
3) Compound MTP2-Exatecan-Rucaparib



To a solution of MTP2-Exatecan-Rucaparib-M2 (265 mg, 0.13 mmol) in DMF (5 mL) was added Ac-Sar10-COOH (Wuxi Apptec, 210 mg, 0.27 mmol) and N, N-Diisopropylethylamine (419 mg, 3.25 mmol), followed by the addition of HATU (114 mg ,0.30 mmol). The reaction was stirred at room temperature for 0.5 h. The reaction was monitored by LC-MS. Upon completion, ethyl acetate was added and the mixture was filtered to give the crude product, which was purified by prep-HPLC (Column: WELCH Xtimate 21.2*250mm 10um C18, Mobile phase: A = 0.1% Formic acid in Water, B = ACN) to give MTP2-Exatecan-Rucaparib (69.9mg, 16%) as a yellow powder. HRMS (ESI-TOF): m/z calcd for $C_{160}H_{215}F_2N_{39}O_{40}$ $[M+2H]^{+2}$: 1680.2973 Found 1680.2957. Also observed 1120.5337 $[M+3H]^{+3}$ and 840.6516 $[M+4H]^{+4}$.

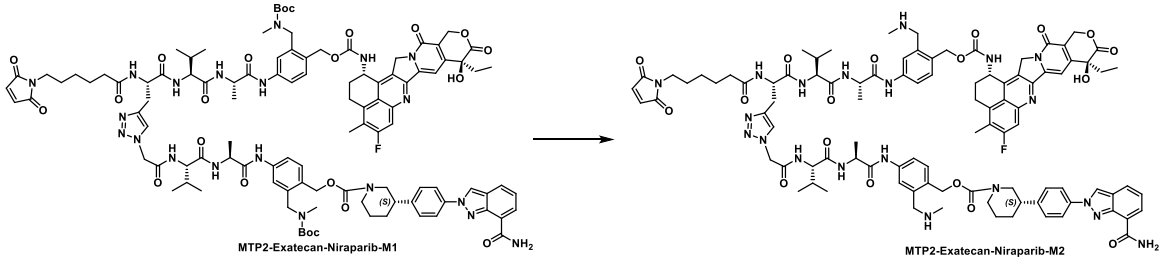
Synthesis of MTP2-Exatecan-Niraparib

1) Compound MTP2-Exatecan-Niraparib-M1



Compound MTP2-Exatecan-Niraparib-M1 was synthesized following the previously established synthetic procedure of MTP2 series (step k). Purification was same as described above to afforded MTP2-Exatecan-Niraparib-M1 (95 mg, 100%, 0.046 mmol scale) as a gray solid. MS (ESI): m/z calcd for $C_{106}H_{127}FN_{20}O_{22}$ $[M+2H]^{+2}$: 1026.5; found 1026.7.

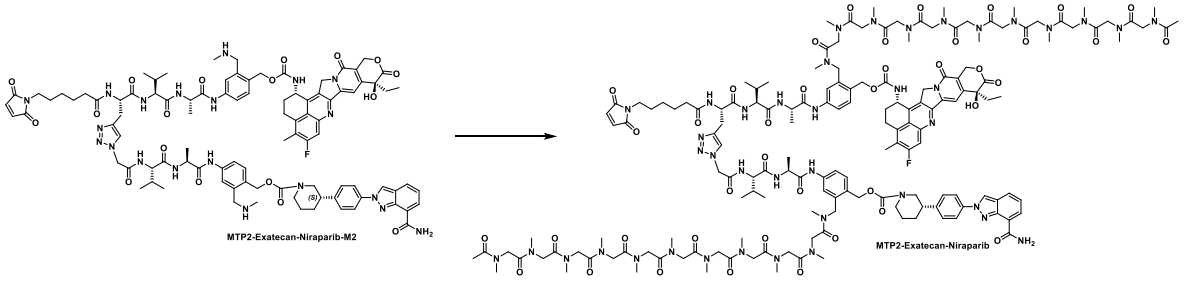
2) Compound MTP2-Exatecan-Niraparib-M2



Compound MTP2-Exatecan-Niraparib-M2 was synthesized following the previously established synthetic procedure of MTP2 series (step l). Purification was same as described above to afforded

MTP2-Exatecan-Niraparib-M2 (95 mg, 100%, 0.046 mmol scale) as a tan solid. MS (ESI): m/z calcd for $C_{96}H_{111}FN_{20}O_{18}$ $[M+2H]^{+2}$: 926.4; found 926.4.

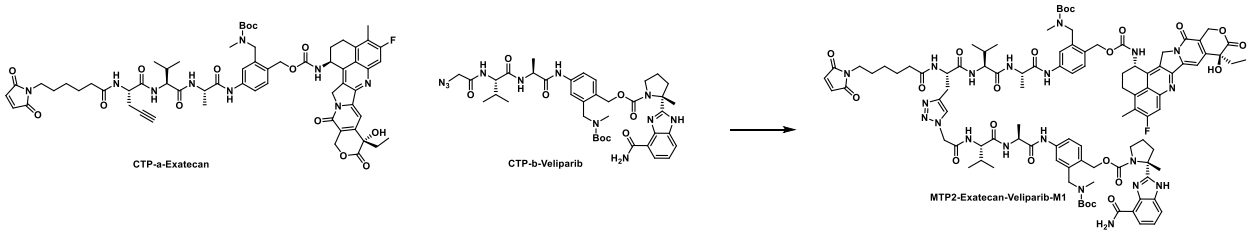
3) Compound MTP2-Exatecan-Niraparib



Compound MTP2-Exatecan-Niraparib was synthesized following the previously established synthetic procedure of MTP2 series (step m). Purification was same as described above to afforded MTP2-Exatecan-Niraparib (11.08 mg, 12%, 0.046 mmol scale) as a yellow power. HRMS (ESI-TOF): m/z calcd for $C_{160}H_{217}FN_{40}O_{40}$ $[M+2H]^{+2}$: 1678.8075 Found 1678.8044. Also observed 1119.5400 $[M+3H]^{+3}$ and 839.9064 $[M+4H]^{+4}$.

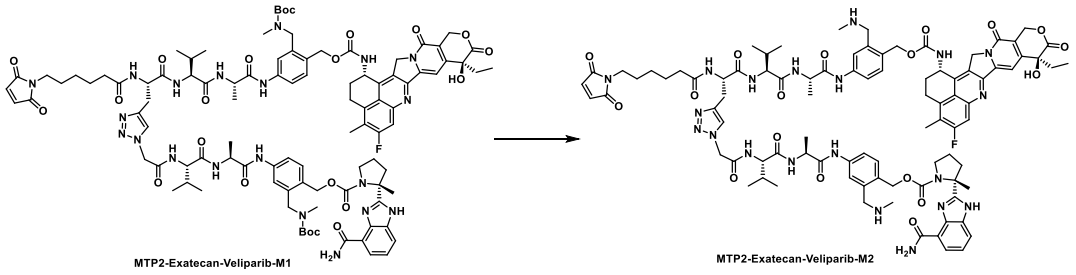
Synthesis of MTP2-Exatecan-Veliparib

1) Compound MTP2-Exatecan-Veliparib-M1



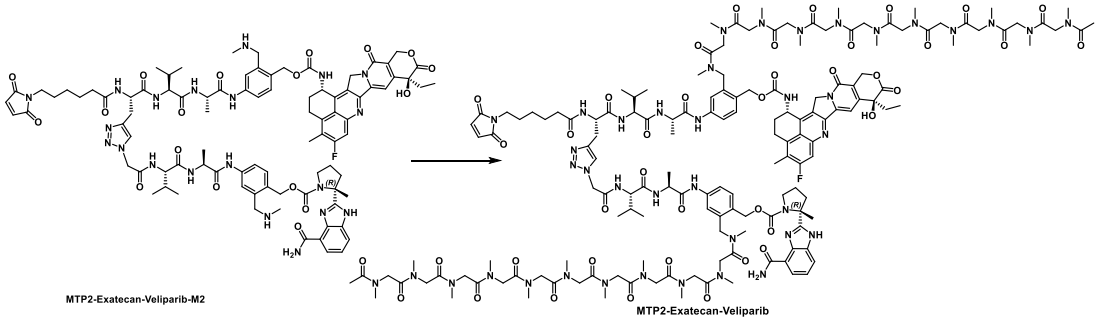
Compound MTP2-Exatecan-Veliparib-M1 was synthesized following the previously established synthetic procedure of MTP2 series (step k). Purification was same as described above to afforded afforded MTP2-Exatecan-Veliparib-M1 (166 mg, 100%, 0.08 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{100}H_{125}FN_{20}O_{22}$ $[M+2H]^{+2}$: 988.5; found 988.5.

2) Compound MTP2-Exatecan-Veliparib-M2



Compound MTP2-Exatecan-Veliparib-M2 was synthesized following the previously established synthetic procedure of MTP2 series (step l). Purification was same as described above to afforded crude MTP2-Exatecan-Veliparib-M2 (40 mg, 100%, 0.019 mmol scale) as a tan solid. MS (ESI): m/z calcd for $C_{90}H_{109}FN_{20}O_{18}$ $[M+2H]^{+2}$: 888.4; found 888.8.

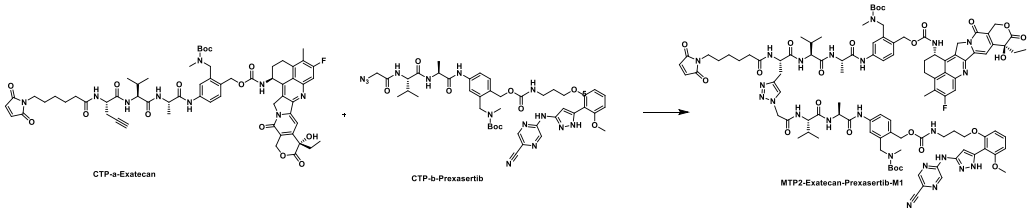
3) Compound MTP2-Exatecan-Veliparib



Compound MTP2-Exatecan-Veliparib was synthesized following the previously established synthetic procedure of MTP2 series (step m). Purification was same as described above to afforded compound MTP2-Exatecan-Veliparib (5.11 mg, 1.8%, 0.08 mmol scale) as a white powder. HRMS (ESI-TOF): m/z calcd for $C_{154}H_{213}FN_{40}O_{40}$ $[M+2H]^{+2}$: 1640.7918 Found 1640.7915. Also observed 1094.1969 $[M+3H]^{+3}$ and 820.8989 $[M+4H]^{+4}$.

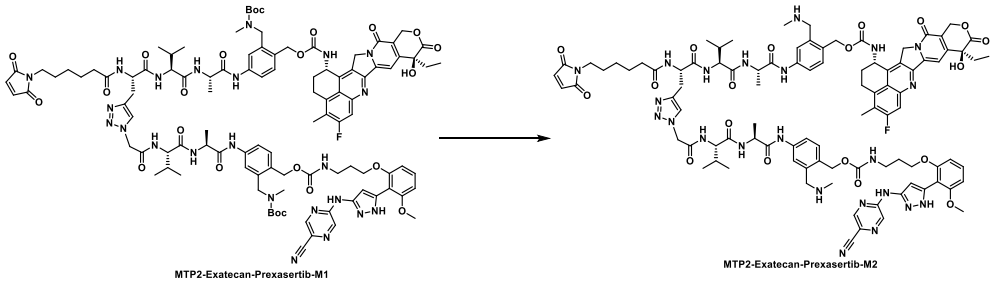
Synthesis of MTP2-Exatecan-Prexasertib

1) Compound MTP2-Exatecan-Prexasertib-M1



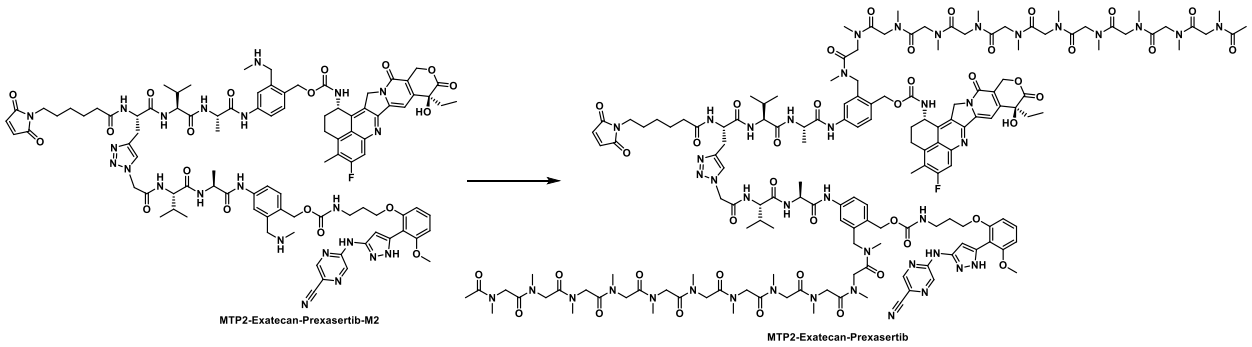
Compound MTP2-Exatecan-Prexasertib-M1 was synthesized following the previously established synthetic procedure of MTP2 series (step k). Purification by pre-HPLC (Column: WELCH Xtimate 21.2*250mm 10um C18, Mobile phase: A = 0.1% Formic acid in Water, B = ACN) afforded MTP2-Exatecan-Prexasertib-M1 (40 mg, 23%, 0.08 mmol scale) as a white solid. MS (ESI): m/z calcd for $C_{105}H_{128}FN_{23}O_{23}$ $[M+2H]^{+2}$: 1049.0; found 1049.5.

2) Compound MTP2-Exatecan-Prexasertib-M2



Compound MTP2-Exatecan-Prexasertib-M2 was synthesized following the previously established synthetic procedure of MTP2 series (step l). Purification was same as described above to afforded crude MTP2-Exatecan-Prexasertib-M2 (40 mg, 100%, 0.019 mmol scale) as a tan solid. MS (ESI): m/z calcd for $C_{95}H_{112}FN_{23}O_{19}$ $[M+2H]^{+2}$: 948.9; found 949.0.

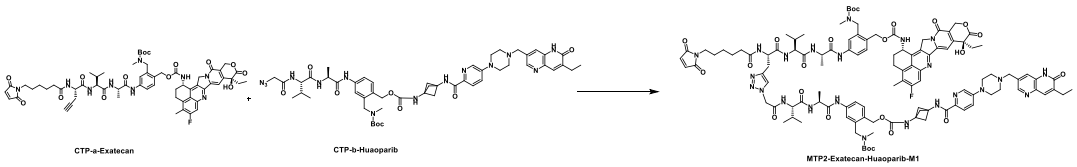
3) Compound MTP2-Exatecan-Prexasertib



Compound MTP2-Exatecan-Prexasertib was synthesized following the previously established synthetic procedure of MTP2 series (step m). Purification was same as described above to afforded compound MTP2-Exatecan-Prexasertib (6.5 mg, 10%, 0.019 mmol scale) as a white powder. HRMS (ESI-TOF): m/z calcd for $C_{159}H_{216}FN_{43}O_{41}$ $[M+2H]^{+2}$: 1701.3056 Found 1701.3027. Also observed 1134.5394 $[M+3H]^{+3}$ and 851.1558 $[M+4H]^{+4}$.

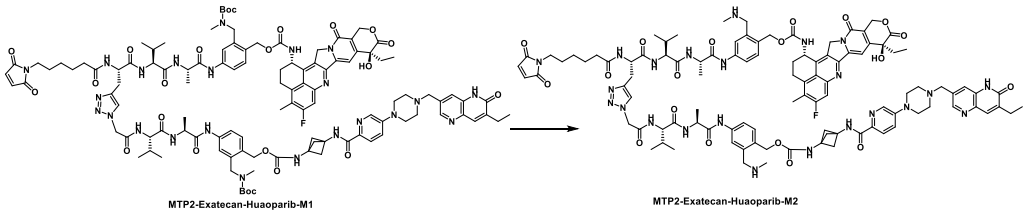
Synthesis of MTP2-Exatecan-Huaoparib

1) Compound MTP2-Exatecan-Huaoparib-M1



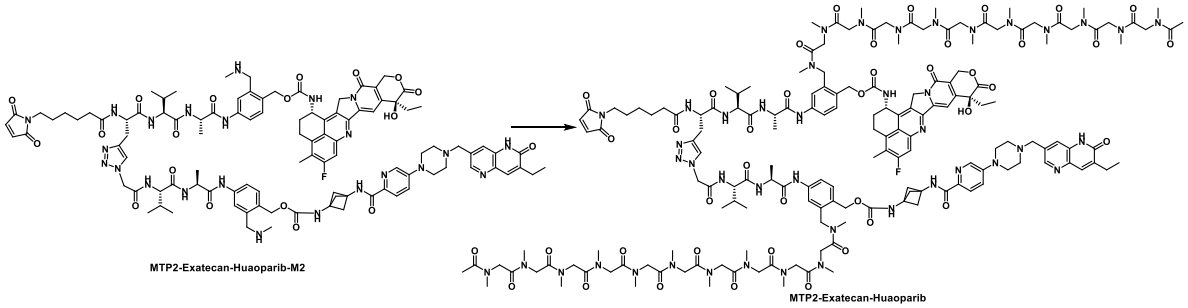
Compound MTP2-Exatecan-Huaoparib-M1 was synthesized following the previously established synthetic procedure of MTP2 series (step k). Purification was same as described above to afforded MTP2-Exatecan-Huaoparib-M1 (430 mg, 100%, 0.20 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{110}H_{130}F_2N_{20}O_{23}$ $[M+2H]^{+2}$: 1103.0; found 1103.6.

2) Compound MTP2-Exatecan-Huaoparib-M2



Compound MTP2-Exatecan-Huaoparib-M2 was synthesized following the previously established synthetic procedure of MTP2 series (step l). Purification was same as described above to afforded crude MTP2-Exatecan-Huaoparib-M2 (430 mg, 100%, 0.20 mmol scale) as a tan solid. MS (ESI): m/z calcd for $C_{103}H_{124}FN_{23}O_{19}$ $[M+2H]^{+2}$: 1003.0; found 1003.4.

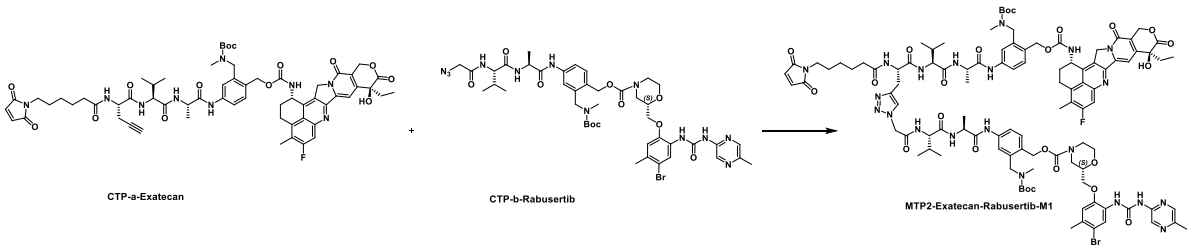
3) Compound MTP2-Exatecan-Huaoparib



Compound MTP2-Exatecan-Huaoparib was synthesized following the previously established synthetic procedure of MTP2 series (step m). Purification was same as described above to afforded compound MTP2-Exatecan-Huaoparib (95 mg, 27%, 0.1 mmol scale) as a white solid. HRMS (ESI-TOF): m/z calcd for $C_{167}H_{228}FN_{43}O_{41}$ $[M+2H]^{+2}$: 1755.3526 Found 1755.3503. Also observed 1170.5708 $[M+3H]^{+3}$ and 878.1796 $[M+4H]^{+4}$.

Synthesis of MTP2-Exatecan-Rabusertib

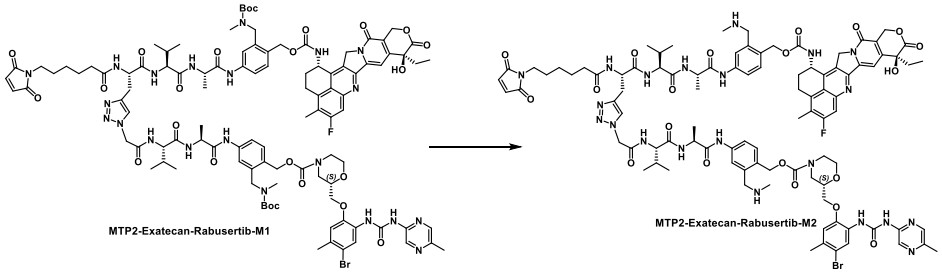
1) Compound MTP2-Exatecan-Rabusertib-M1



Compound MTP2-Exatecan-Rabusertib-M1 was synthesized following the previously established synthetic procedure of MTP2 series (step k). Purification was same as described above to afforded MTP2-Exatecan-Rabusertib-M1 (183 mg, 100%, 0.084 mmol scale) as a yellow solid.

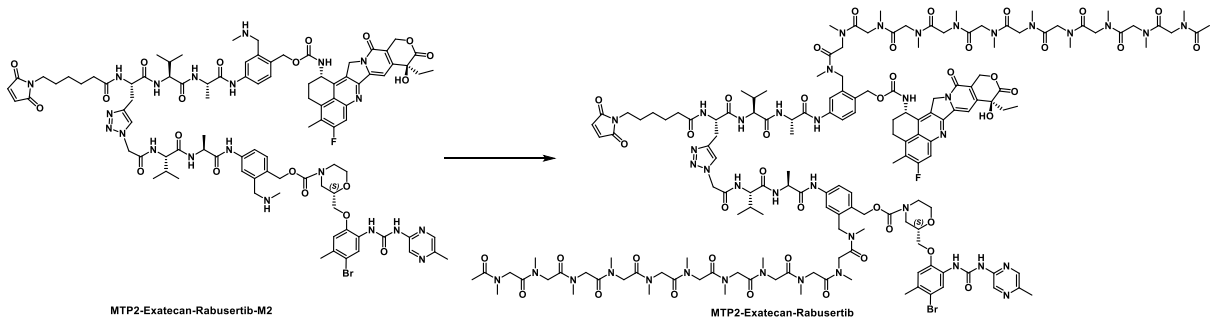
MS (ESI): m/z calcd for $C_{105}H_{131}BrFN_{21}O_{24}$ $[M+2H]^{+2}$: 1083.9; found 1083.7.

2) Compound MTP2-Exatecan-Rabusertib-M2



Compound MTP2-Exatecan-Rabusertib-M2 was synthesized following the previously established synthetic procedure of MTP2 series (step l). Purification was same as described above to afforded crude MTP2-Exatecan-Rabusertib-M2 (183 mg, 100%, 0.084 mmol scale) as a tan solid. MS (ESI): m/z calcd for $C_{95}H_{115}BrFN_{21}O_{20}$ $[M+2H]^{+2}$: 983.9; found 984.0.

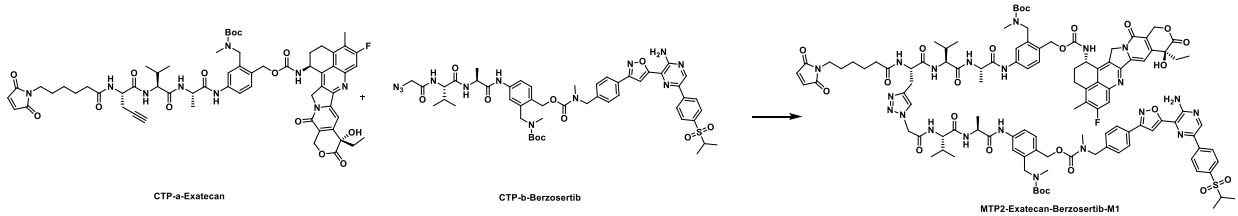
3) Compound MTP2-Exatecan-Rabusertib



Compound MTP2-Exatecan-Rabusertib was synthesized following the previously established synthetic procedure of MTP2 series (step m). Purification was same as described above to afforded compound MTP2-Exatecan-Rabusertib (74 mg, 25%, 0.084 mmol scale) as a white solid. HRMS (ESI-TOF): m/z calcd for $C_{159}H_{219}BrFN_{41}O_{42}$ $[M+2H]^{+2}$: 1736.2709 Found 1736.2689. Also observed 1157.8490 $[M+3H]^{+3}$ and 868.6384 $[M+4H]^{+4}$.

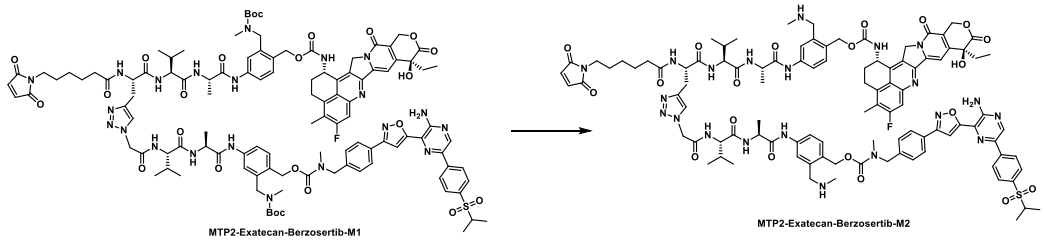
Synthesis of MTP2-Exatecan-Berzosertib

1) Compound MTP2-Exatecan-Berzosertib-M1



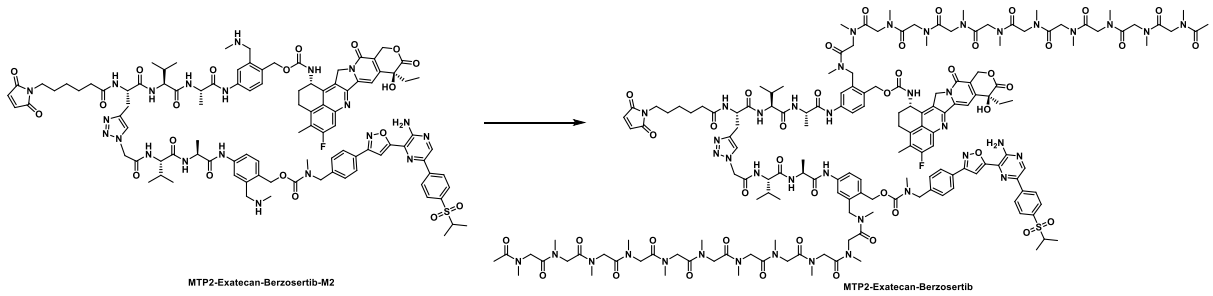
Compound MTP2-Exatecan-Berzosertib-M1 was synthesized following the previously established synthetic procedure of MTP2 series (step k). Purification was same as described above to afforded MTP2-Exatecan-Berzosertib-M1 (185 mg, 100%, 0.084 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{111}H_{134}FN_{21}O_{24}S$ $[M+2H]^{+2}$: 1098.0; found 1098.3.

2) Compound MTP2-Exatecan-Berzosertib-M2



Compound MTP2-Exatecan-Berzosertib-M2 was synthesized following the previously established synthetic procedure of MTP2 series (step l). Purification was same as described above to afforded crude MTP2-Exatecan-Berzosertib-M2 (185 mg, 100%, 0.084 mmol scale) as a tan solid. MS (ESI): m/z calcd for $C_{95}H_{115}BrFN_{21}O_{20}$ $[M+2H]^{+2}$: 997.9; found 998.1.

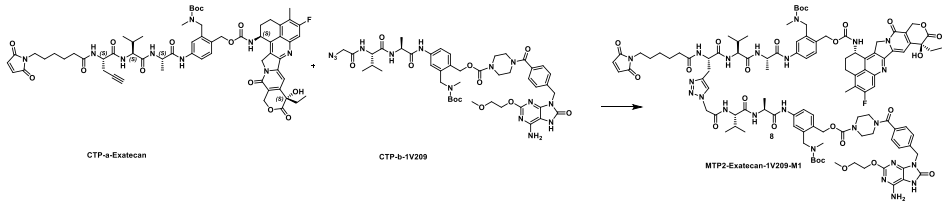
3) Compound MTP2-Exatecan-Berzosertib



Compound MTP2-Exatecan-Berzosertib was synthesized following the previously established synthetic procedure of MTP2 series (step m). Purification was same as described above to afforded compound MTP2-Exatecan-Berzosertib (79 mg, 27%, 0.084 mmol scale) as a yellow solid. HRMS (ESI-TOF): m/z calcd for $C_{165}H_{222}FN_{41}O_{42}S$ $[M+2H]^{+2}$: 1750.3095 Found 1750.3071. Also observed 1167.2092 $[M+3H]^{+3}$ and 875.6580 $[M+4H]^{+4}$.

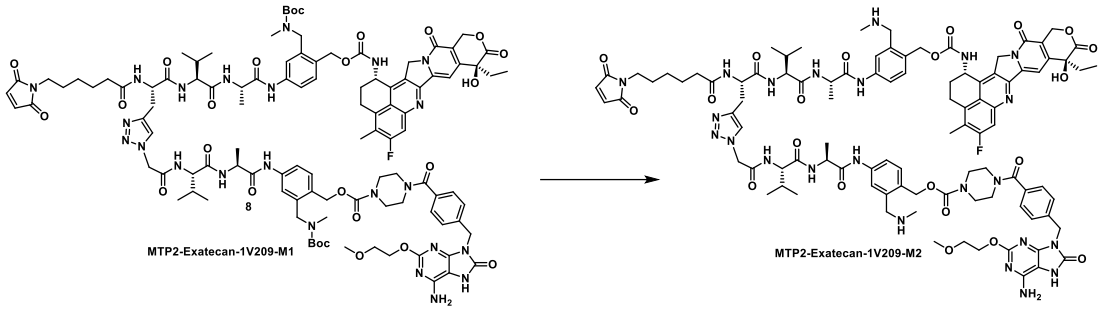
Synthesis of MTP2-Exatecan-1V209

1) Compound MTP2-Exatecan-1V209-M1



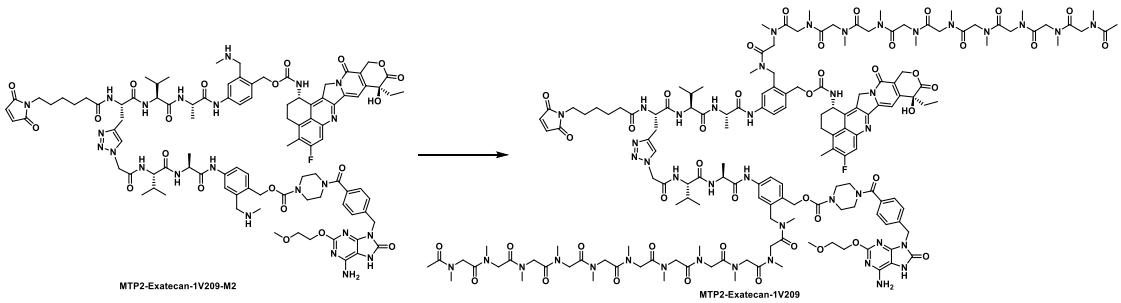
Compound MTP2-Exatecan-1V209-M1 was synthesized following the previously established synthetic procedure of MTP2 series (step k). Purification was same as described above to afforded MTP2-Exatecan-1V209-M1 (182 mg, 100%, 0.084 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{107}H_{134}FN_{23}O_{25}$ $[M+2H]^{+2}$: 1080.0; found 1080.5.

2) Compound MTP2-Exatecan-1V209 M2



Compound MTP2-Exatecan-1V209-M2 was synthesized following the previously established synthetic procedure of MTP2 series (step l). Purification was same as described above to afforded crude MTP2-Exatecan-1V209-M2 (185 mg, 100%, 0.084 mmol scale) as a tan solid. MS (ESI): m/z calcd for $C_{97}H_{118}FN_{23}O_{21}$ $[M+2H]^{+2}$: 980.0; found 979.9.

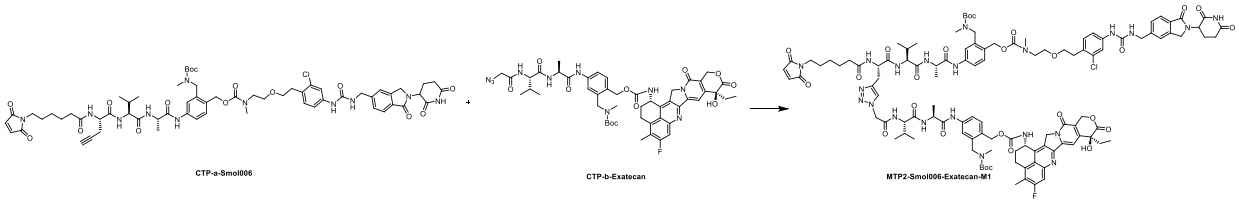
3) Compound MTP2-Exatecan-1V209



Compound MTP2-Exatecan-1V209 was synthesized following the previously established synthetic procedure of MTP2 series (step m). Purification was same as described above to afforded compound MTP2-Exatecan-1V209 (40 mg, 14%, 0.084 mmol scale) as a white solid. HRMS (ESI-TOF): m/z calcd for $C_{161}H_{222}FN_{43}O_{43}$ $[M+2H]^{+2}$: 1732.3240 Found 1732.3214. Also observed 1155.2180 $[M+3H]^{+3}$ and 866.6650 $[M+4H]^{+4}$.

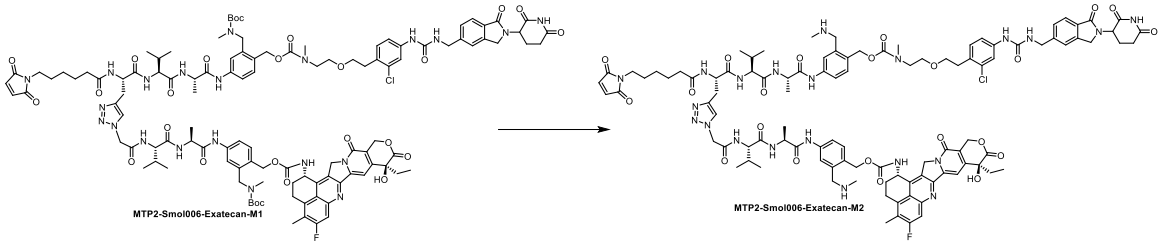
Synthesis of MTP2-Smol006-Exatecan

1) Compound MTP2-Smol006-Exatecan-M1



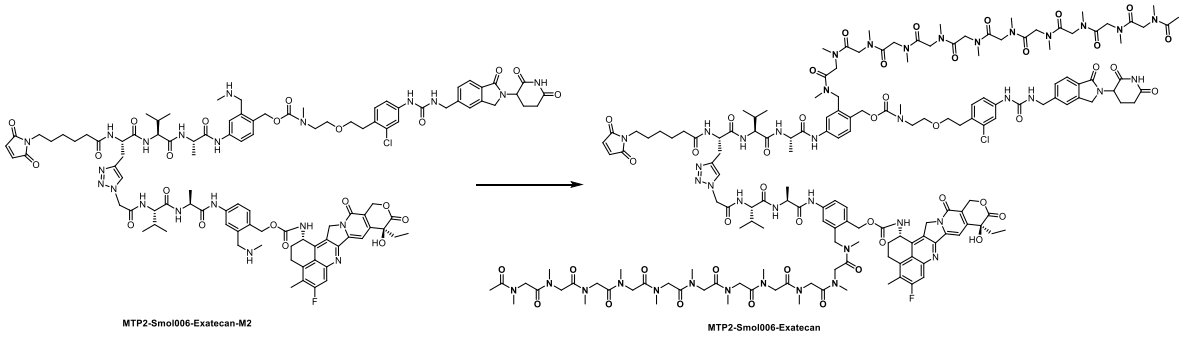
Compound MTP2-Smol006-Exatecan-M1 was synthesized following the previously established synthetic procedure of MTP2 series (step k). Purification was same as described above to afforded MTP2-Smol006-Exatecan-M1 (247 mg, 100%, 0.11 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{113}H_{139}ClFN_{21}O_{26}$ $[M+2H]^{+2}$: 1130.0; found 1130.6.

2) Compound MTP2-Smol006-Exatecan-M2



Compound MTP2-Smol006-Exatecan-M2 was synthesized following the previously established synthetic procedure of MTP2 series (step l). Purification was same as described above to afforded crude MTP2-Smol006-Exatecan-M2 (247 mg, 100%, 0.11 mmol scale) as a tan solid. MS (ESI): m/z calcd for $C_{103}H_{123}ClFN_{21}O_{22}$ $[M+2H]^{+2}$: 1029.9; found 1030.1.

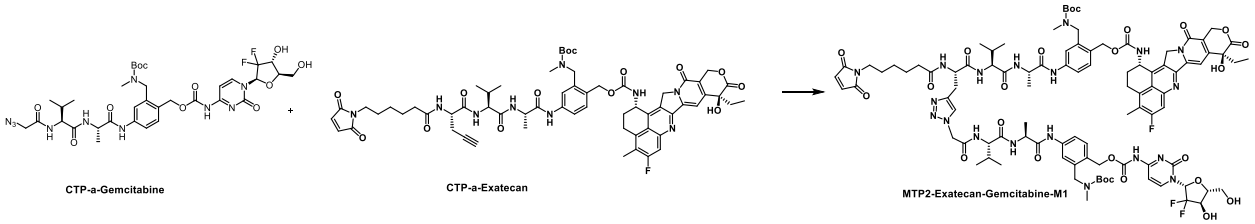
3) Compound MTP2-Smol006-Exatecan



Compound MTP2-Smol006-Exatecan was synthesized following the previously established synthetic procedure of MTP2 series (step m). Purification was same as described above to afforded compound MTP2-Smol006-Exatecan (59 mg, 15%, 0.11 mmol scale) as a white solid. HRMS (ESI-TOF): m/z calcd for $C_{167}H_{227}ClFN_{41}O_{44}$ $[M+2H]^{+2}$: 1782.3224 Found 1782.3201. Also observed 1188.5502 $[M+3H]^{+3}$ and 891.6639 $[M+4H]^{+4}$.

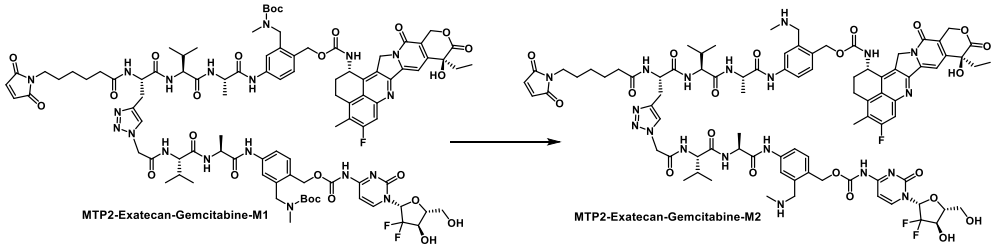
Synthesis of MTP2-Exatecan-Gemcitabine

1) Compound MTP2-Exatecan-Gemcitabine-M1



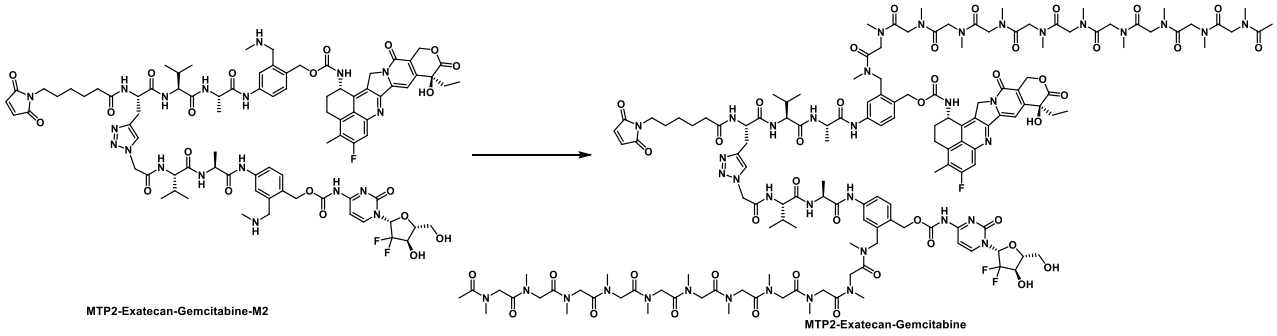
Compound MTP2-Exatecan-Gemcitabine-M1 was synthesized following the previously established synthetic procedure of MTP2 series (step k). Purification was same as described above to afforded MTP2-Exatecan-Gemcitabine-M1 (222 mg, 100%, 0.11 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{96}H_{118}F_3N_{19}O_{25}$ $[M+H]^+$: 1994.9; found 1995.8.

2) Compound MTP2-Exatecan-Gemcitabine-M2



Compound MTP2-Exatecan-Gemcitabine-M2 was synthesized following the previously established synthetic procedure of MTP2 series (step l). Purification was same as described above to afforded crude MTP2-Exatecan-Gemcitabine-M2 (222 mg, 100%, 0.11 mmol scale) as a tan solid. MS (ESI): m/z calcd for $C_{86}H_{102}F_3N_{19}O_{21}$ $[M+H]^+$: 1794.8; found 1794.5.

3) Compound MTP2-Exatecan-Gemcitabine

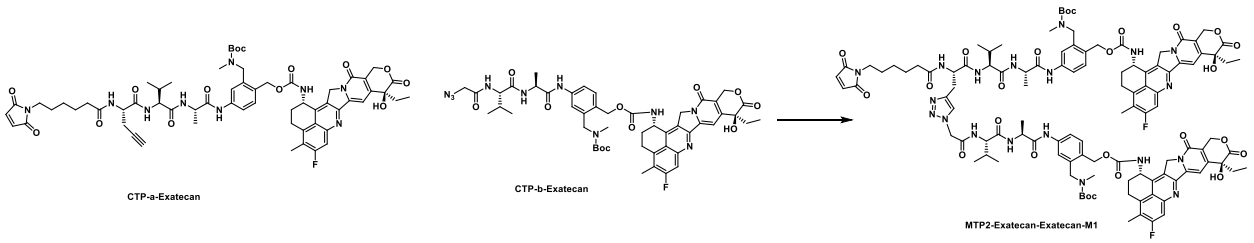


Compound MTP2-Exatecan-Gemcitabine was synthesized following the previously established synthetic procedure of MTP2 series (step m). Purification was same as described above to afforded compound MTP2-Exatecan-Gemcitabine (65.3 mg, 18%, 0.11 mmol scale) as a white solid.

HRMS (ESI-TOF): m/z calcd for $C_{150}H_{208}F_3N_{39}O_{43}$ $[M+2H]^{+2}$: 1650.2615 Found 1650.2599. Also observed 1100.5103 $[M+3H]^{+3}$ and 825.6339 $[M+4H]^{+4}$.

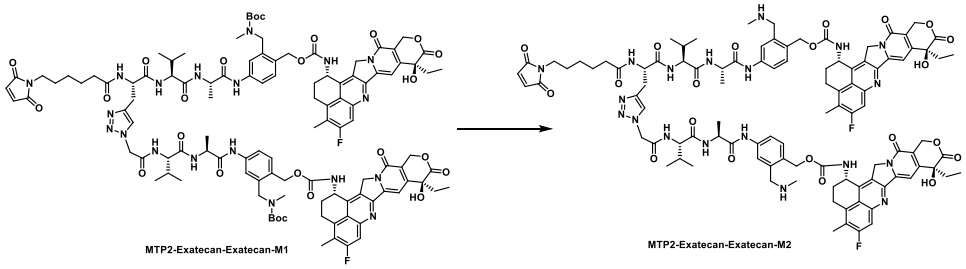
Synthesis of MTP2-Exatecan-Exatecan

1) Compound MTP2-Exatecan-Exatecan-M1



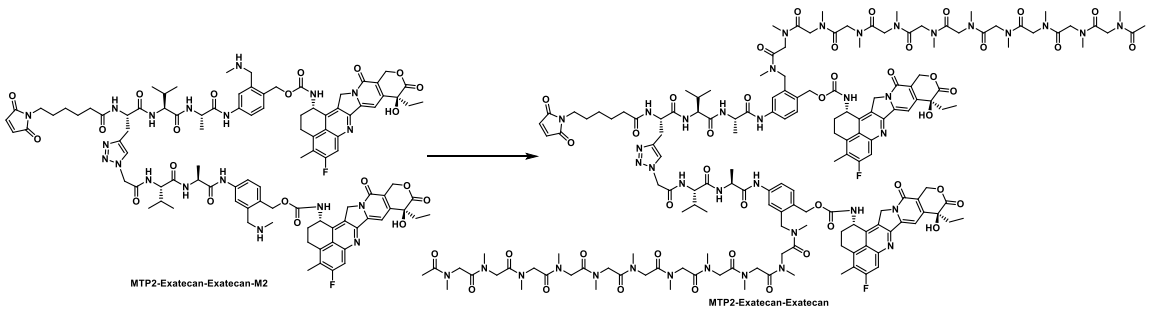
Compound MTP2-Exatecan-Exatecan-M1 was synthesized following the previously established synthetic procedure of MTP2 series (step k). Purification was same as described above to afforded MTP2-Exatecan-Exatecan-M1 (282 mg, 100%, 0.13 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{111}H_{129}F_2N_{19}O_{25}$ $[M+2H]^{+2}$: 1084.0; found 1084.3.

2) Compound MTP2-Exatecan- Exatecan-M2



Compound MTP2-Exatecan-Exatecan-M2 was synthesized following the previously established synthetic procedure of MTP2 series (step l). Purification was same as described above to afforded MTP2-Exatecan-Exatecan-M2 (282 mg, 100%, 0.13 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{101}H_{113}F_2N_{19}O_{21}$ $[M+2H]^{+2}$: 983.9; found 984.0.

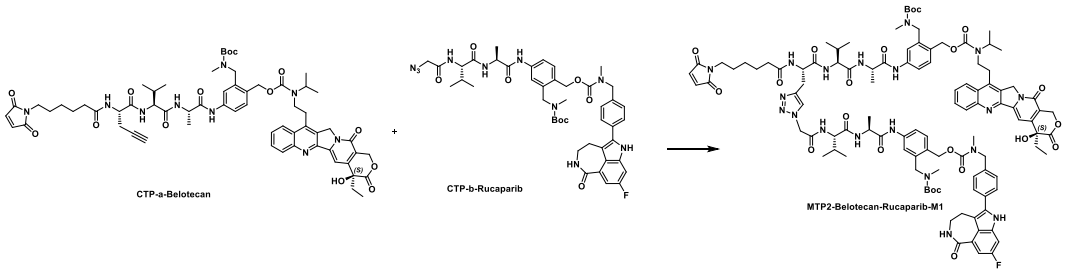
3) Compound MTP2-Exatecan-Exatecan



Compound MTP2-Exatecan-Exatecan was synthesized following the previously established synthetic procedure of MTP2 series (step m). Purification was same as described above to afforded compound MTP2-Exatecan- Exatecan (38 mg, 8%, 0.13 mmol scale) as a white solid. HRMS (ESI-TOF): m/z calcd for $C_{165}H_{219}F_2N_{39}O_{43}$ $[M+2H]^{+2}$: 1736.3053 Found 1736.3033. Also observed 1157.8727 $[M+3H]^{+3}$ and 868.6559 $[M+4H]^{+4}$.

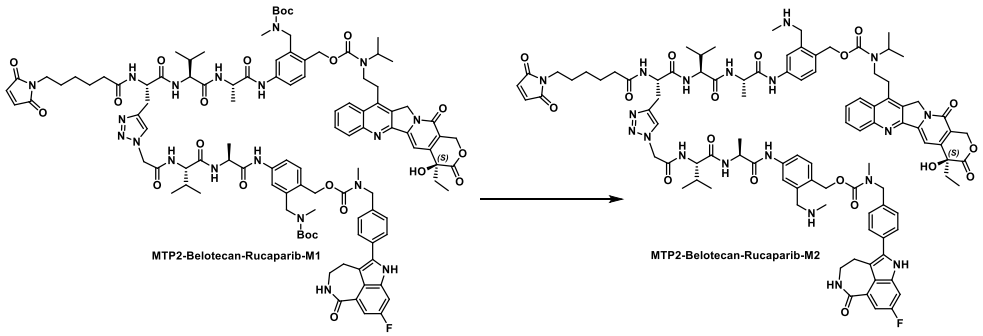
Synthesis of MTP2-Belotecan-Rucaparib

1) Compound MTP2-Belotecan-Rucaparib-M1



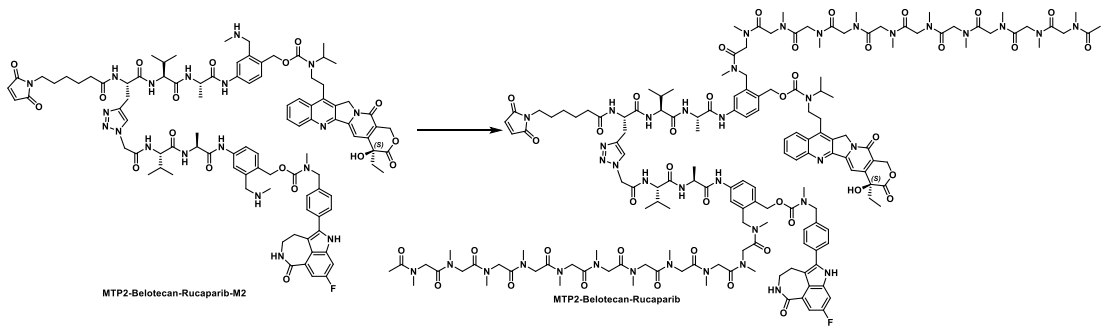
Compound MTP2-Belotecan-Rucaparib-M1 was synthesized following the previously established synthetic procedure of MTP2 series (step k). Purification was same as described above to afforded MTP2-Belotecan-Rucaparib-M1 (434 mg, 100%, 0.21 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{107}H_{130}FN_{19}O_{22}$ $[M+2H]^{+2}$: 1027.0; found 1027.4.

2) Compound MTP2-Belotecan-Rucaparib-M2



Compound MTP2-Belotecan-Rucaparib-M2 was synthesized following the previously established synthetic procedure of MTP2 series (step l). Purification was same as described above to afforded MTP2-Belotecan-Rucaparib-M2 (434 mg, 100%, 0.21 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{97}H_{114}FN_{19}O_{18}$ $[M+2H]^{+2}$: 926.9; found 927.0.

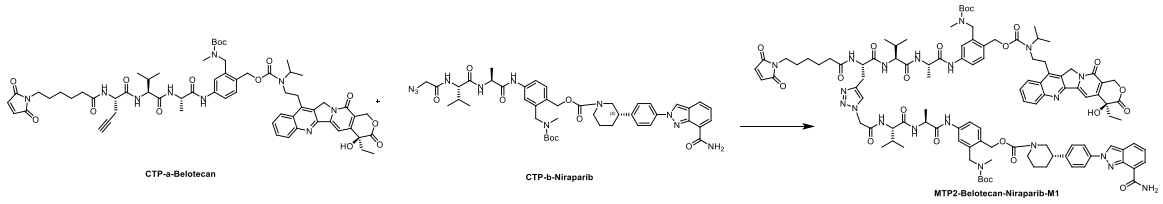
3) Compound MTP2-Belotecan-Rucaparib



Compound MTP2-Belotecan-Rucaparib was synthesized following the previously established synthetic procedure of MTP2 series (step m). Purification was same as described above to afforded compound MTP2-Belotecan-Rucaparib (135 mg, 19%, 0.21 mmol scale) as a white solid. HRMS (ESI-TOF): m/z calcd for $C_{161}H_{220}FN_{39}O_{40}$ $[M+2H]^{+2}$: 1679.3177 Found 1679.3163. Also observed 1119.8810 $[M+3H]^{+3}$ and 840.1625 $[M+4H]^{+4}$.

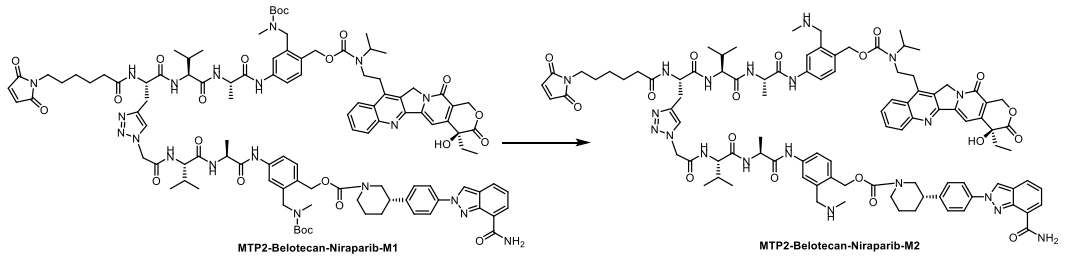
Synthesis of MTP2-Belotecan-Niraparib

1) Compound MTP2-Belotecan-Niraparib-M1



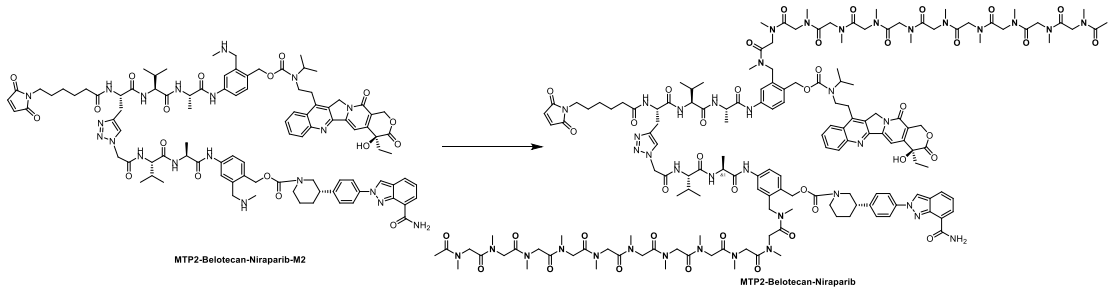
Compound MTP2-Belotecan-Niraparib-M1 was synthesized following the previously established synthetic procedure of MTP2 series (step k). Purification was same as described above to afforded MTP2-Belotecan-Niraparib-M1 (260 mg, 100%, 0.13 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{107}H_{132}N_{20}Na_2O_{22}$ $[M+2Na]^{+2}$: 1047.5; found 1047.9.

2) Compound MTP2-Belotecan-Niraparib M2



Compound MTP2-Belotecan-Niraparib-M2 was synthesized following the previously established synthetic procedure of MTP2 series (step l). Purification was same as described above to afforded MTP2-Belotecan-Niraparib-M2 (260 mg, 100%, 0.13 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{97}H_{118}N_{20}O_{18}$ $[M+2H]^{+2}$: 925.4; found 925.9.

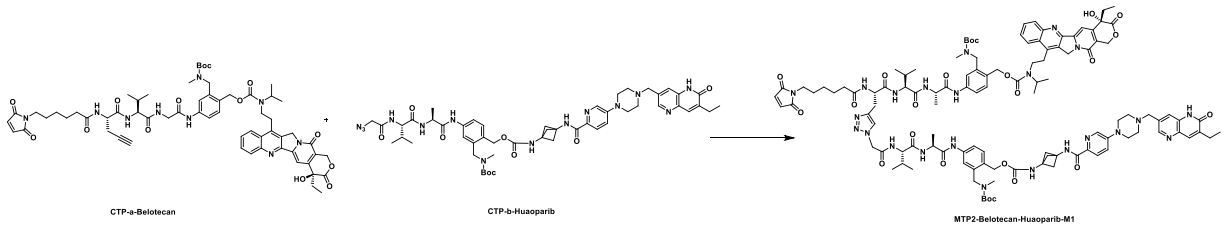
3) Compound MTP2-Belotecan-Niraparib



Compound MTP2-Belotecan-Niraparib was synthesized following the previously established synthetic procedure of MTP2 series (step m). Purification was same as described above to afforded compound MTP2-Belotecan-Niraparib (55.4 mg, 13%, 0.13 mmol scale) as a white solid. HRMS (ESI-TOF): m/z calcd for $C_{161}H_{222}N_{40}O_{40}$ $[M+2H]^{+2}$: 1677.8278 Found 1677.8267. Also observed 1118.8877 $[M+3H]^{+3}$ and 839.4172 $[M+4H]^{+4}$.

Synthesis of MTP2-Belotecan-Huaoparib

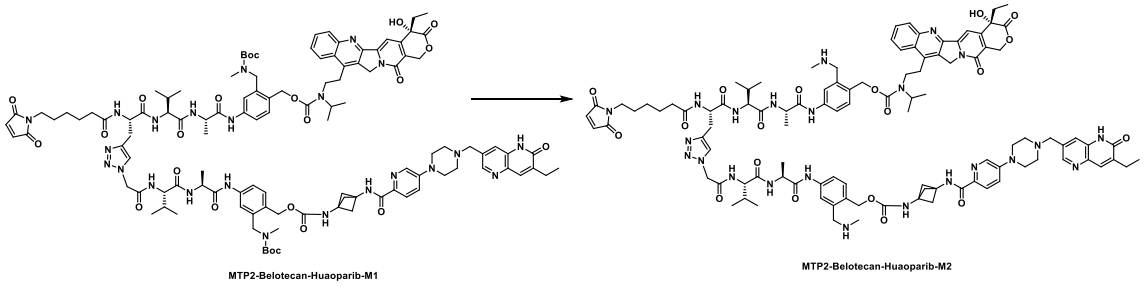
1) Compound MTP2-Belotecan-Huaoparib-M1



Compound MTP2-Belotecan-Huaoparib-M1 was synthesized following the previously established synthetic procedure of MTP2 series (step k). Purification was same as described above to afforded

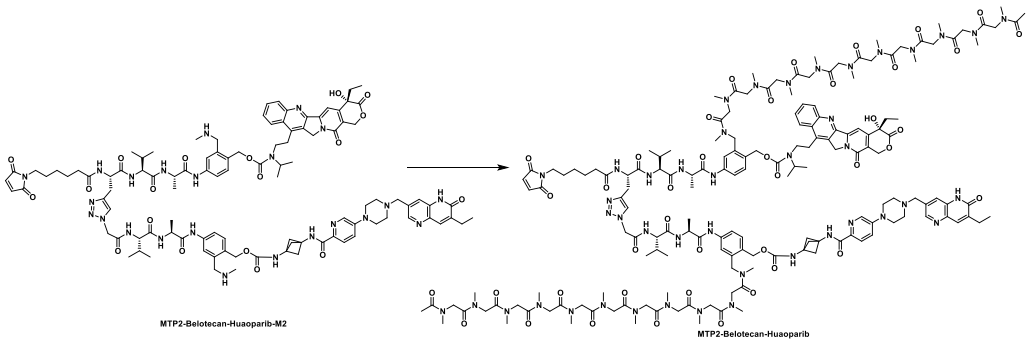
MTP2-Belotecan-Huaoparib-M1 (149 mg, 100%, 0.068 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{114}H_{143}N_{23}O_{23}$ $[M+2H]^{+2}$: 1102.0; found 1102.4.

2) Compound MTP2-Belotecan-Huaoparib-M2



Compound MTP2-Belotecan-Huaoparib-M2 was synthesized following the previously established synthetic procedure of MTP2 series (step l). Purification was same as described above to afforded MTP2-Belotecan-Huaoparib-M2 (149 mg, 100%, 0.068 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{114}H_{143}N_{23}O_{23}$ $[M+2H]^{+2}$: 1002.0; found 1001.9.

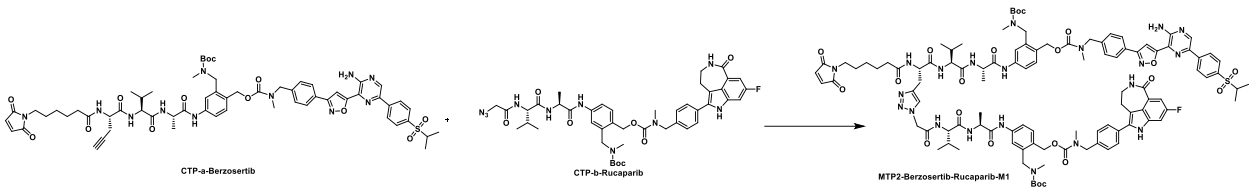
3) Compound MTP2-Belotecan-Huaoparib



Compound MTP2-Belotecan-Huaoparib was synthesized following the previously established synthetic procedure of MTP2 series (step m). Purification was same as described above to afforded compound MTP2-Belotecan-Huaoparib (13.7 mg, 6%, 0.13 mmol scale) as a white solid. MS (ESI): m/z calcd for $C_{168}H_{233}N_{43}O_{41}$ $[M+2H]^{+}$: 1754.4; found 1755.2.

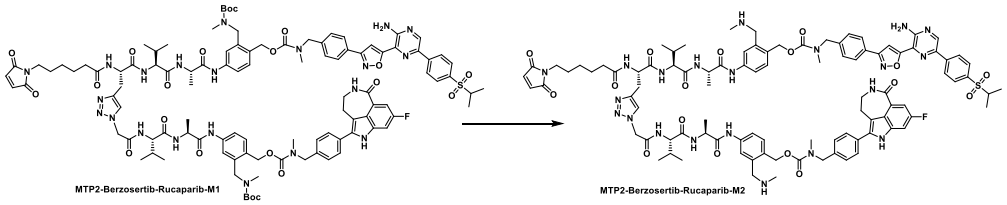
Synthesis of MTP2-Berzosertib-Rucaparib

1) Compound MTP2-Berzosertib-Rucaparib-M1



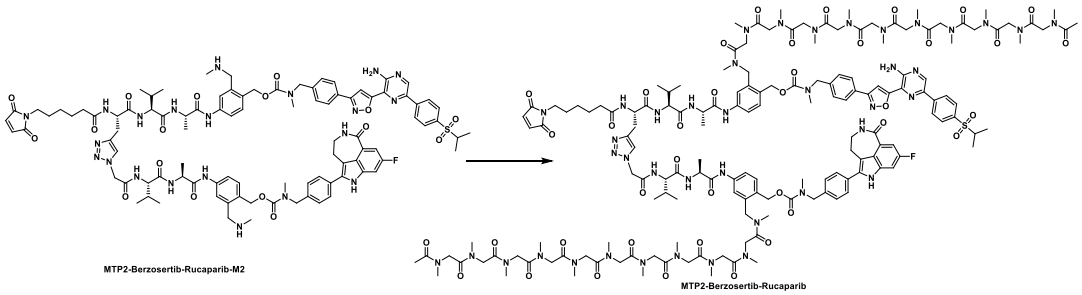
Compound MTP2-Berzosertib-Rucaparib-M1 was synthesized following the previously established synthetic procedure of MTP2 series (step k). Purification was same as described above to afforded MTP2-Berzosertib-Rucaparib-M1 (437 mg, 100%, 0.21 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{106}H_{130}FN_{21}O_{21}S$ $[M+2H]^{+2}$: 1042.0; found 1041.9.

2) Compound MTP2-Berzosertib-Rucaparib M2



Compound MTP2-Berzosertib-Rucaparib-M2 was synthesized following the previously established synthetic procedure of MTP2 series (step l). Purification was same as described above to afforded MTP2-Berzosertib-Rucaparib-M2 (437 mg, 100%, 0.21 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{106}H_{130}FN_{21}O_{21}S$ $[M+2H]^{+2}$: 941.9; found 942.0.

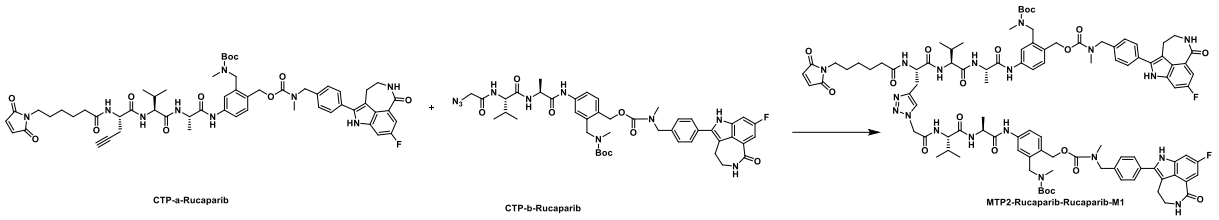
3) Compound MTP2-Berzosertib-Rucaparib



Compound MTP2-Berzosertib-Rucaparib was synthesized following the previously established synthetic procedure of MTP2 series (step m). Purification was same as described above to afforded compound MTP2-Berzosertib-Rucaparib (239 mg, 33%, 0.21 mmol scale) as a yellow solid. HRMS (ESI-TOF): m/z calcd for $C_{160}H_{218}FN_{41}O_{39}S$ $[M+2H]^{+2}$: 1694.3015 Found 1694.2988. Also observed 1129.8699 $[M+3H]^{+3}$ and 847.6535 $[M+4H]^{+4}$.

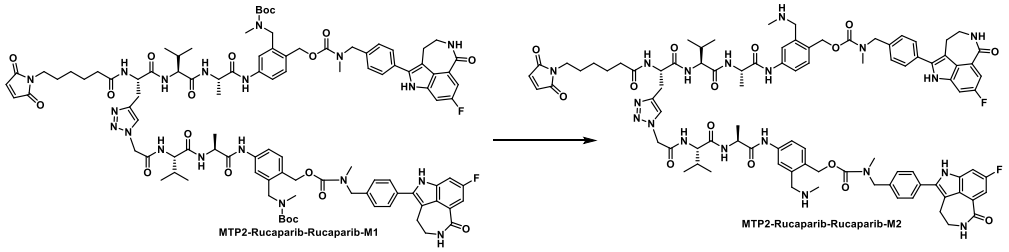
Synthesis of MTP2-Rucaparib-Rucaparib

1) Compound MTP2-Rucaparib-Rucaparib-M1



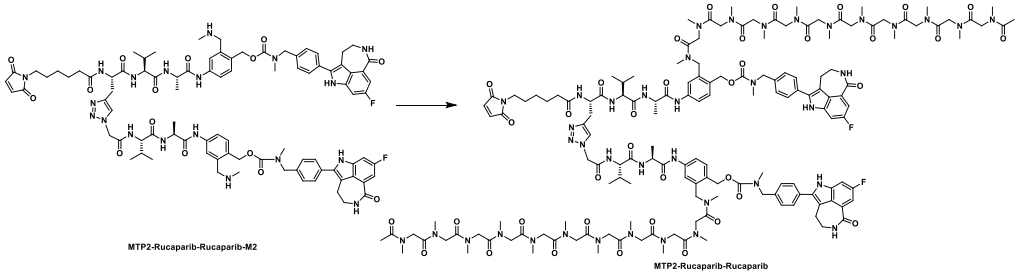
Compound MTP2-Rucaparib-Rucaparib-M1 was synthesized following the previously established synthetic procedure of MTP2 series (step k). Purification was same as described above to afforded MTP2-Rucaparib-Rucaparib-M1 (362 mg, 100%, 0.19 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{101}H_{123}F_2N_{19}O_{19}$ $[M+2H]^{+2}$: 972.0; found 972.0.

2) Compound MTP2-Rucaparib-Rucaparib-M2



Compound MTP2-Rucaparib-Rucaparib-M2 was synthesized following the previously established synthetic procedure of MTP2 series (step l). Purification was same as described above to afforded MTP2-Rucaparib-Rucaparib-M2 (362 mg, 100%, 0.19 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{91}H_{107}F_2N_{19}O_{15}$ $[M+2H]^{+2}$: 871.9; found 872.0.

3) Compound MTP2-Rucaparib-Rucaparib

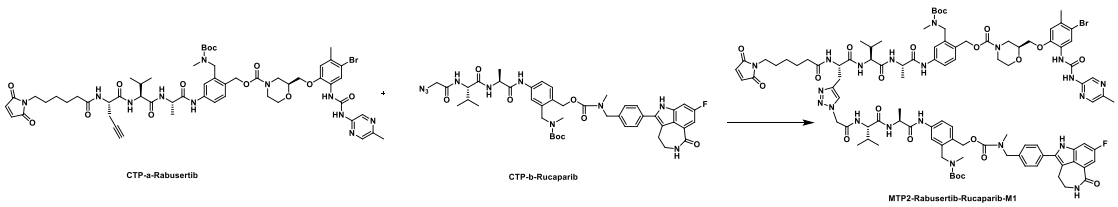


Compound MTP2-Rucaparib-Rucaparib was synthesized following the previously established synthetic procedure of MTP2 series (step m). Purification was same as described above to afforded MTP2-Rucaparib-Rucaparib (57 mg, 9%, 0.19 mmol scale) as a white powder. HRMS (ESI-TOF):

m/z calcd for $C_{155}H_{211}F_2N_{39}O_{37}$ $[M+2H]^{+2}$: 1624.2893 Found 1624.2875. Also observed 1083.1953 $[M+3H]^{+3}$ and 812.6476 $[M+4H]^{+4}$.

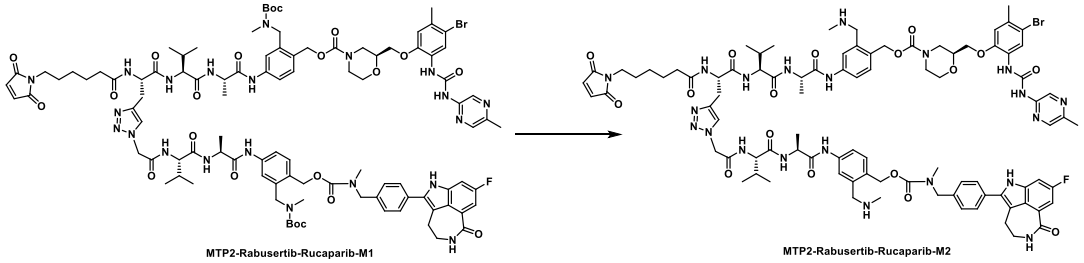
Synthesis of MTP2-Rabusertib-Rucaparib

1) Compound MTP2-Rabusertib-Rucaparib-M1



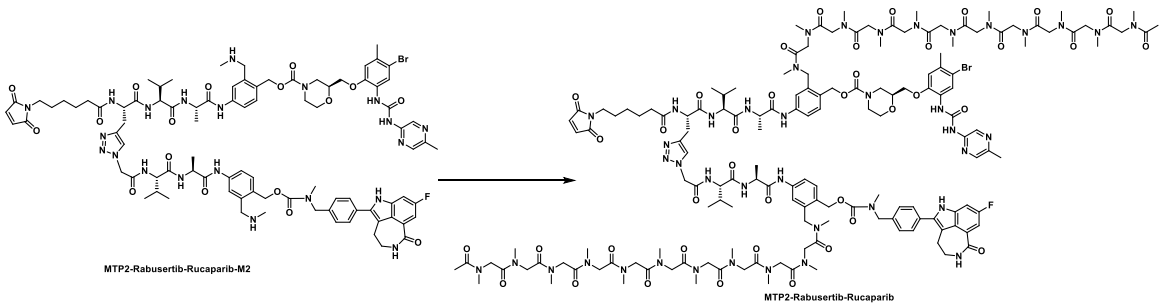
Compound MTP2-Rabusertib-Rucaparib-M1 was synthesized following the previously established synthetic procedure of MTP2 series (step k). Purification was same as described above to afforded MTP2-Rabusertib-Rucaparib-M1 (347 mg, 100%, 0.17 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{100}H_{127}BrFN_{21}O_{21}$ $[M+2H]^{+2}$: 1027.9; found 1027.9.

2) Compound MTP2-Rabusertib-Rucaparib-M2



Compound MTP2-Rabusertib-Rucaparib-M2 was synthesized following the previously established synthetic procedure of MTP2 series (step l). Purification was same as described above to afforded MTP2-Rabusertib-Rucaparib-M2 (347 mg, 100%, 0.17 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{90}H_{111}BrFN_{21}O_{17}$ $[M+2H]^{+2}$: 927.9; found 928.2.

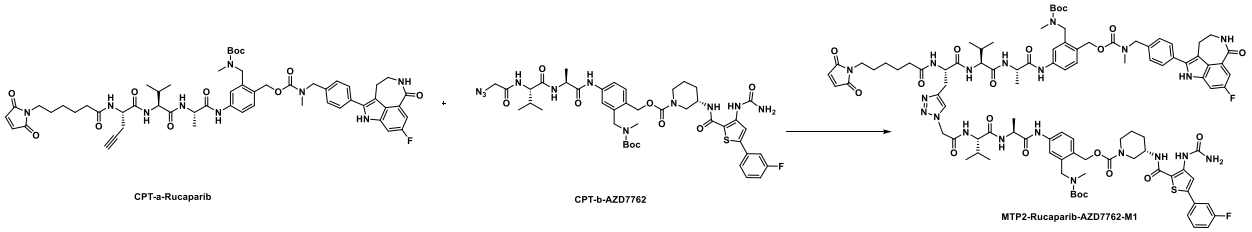
3) Compound MTP2-Rabusertib-Rucaparib



Compound MTP2-Rabusertib-Rucaparib was synthesized following the previously established synthetic procedure of MTP2 series (step m). Purification was same as described above to afforded compound MTP2-Rabusertib-Rucaparib (120 mg, 21%, 0.17 mmol scale) as a yellow solid. HRMS (ESI-TOF): m/z calcd for $C_{154}H_{215}BrFN_{41}O_{39}$ $[M+2H]^{+2}$: 1680.2629 Found 1680.2620. Also observed 1120.5111 $[M+3H]^{+3}$ and 840.6347 $[M+4H]^{+4}$.

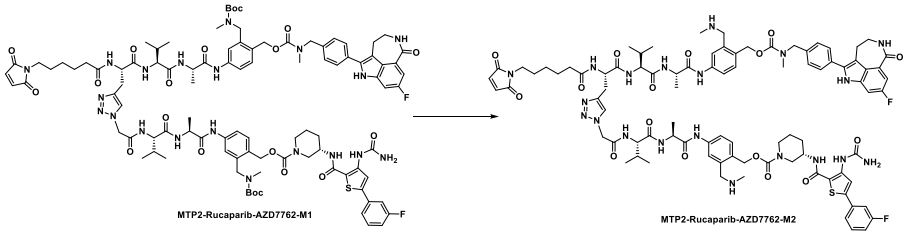
Synthesis of MTP2-Rucaparib-AZD7762

1) Compound MTP2-Rucaparib-AZD7762-M1



Compound MTP2-Rucaparib-AZD7762-M1 was synthesized following the previously established synthetic procedure of MTP2 series (step k). Purification was same as described above to afforded MTP2-Rucaparib-AZD7762-M1 (369 mg, 100%, 0.19 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{99}H_{124}F_2N_{20}O_{20}S$ $[M+2H]^{+2}$: 991.4; found 991.1.

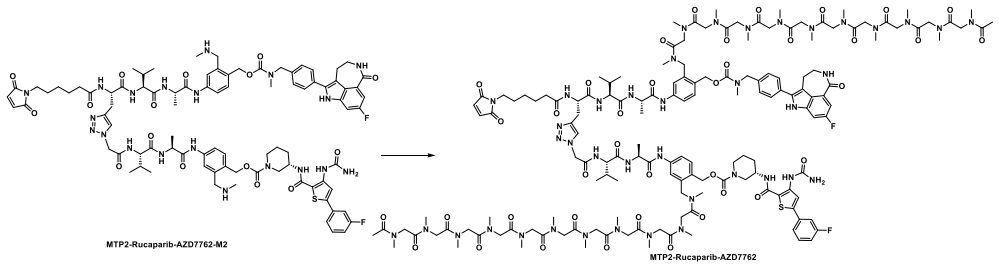
2) Compound MTP2-Rucaparib-AZD7762-M2



Compound MTP2-Rucaparib-AZD7762-M2 was synthesized following the previously established synthetic procedure of MTP2 series (step l). Purification was same as described above to afforded

MTP2-Rucaparib-AZD7762-M2 (347 mg, 100%, 0.17 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{89}H_{108}F_2N_{20}O_{16}S$ $[M+2H]^{+2}$: 891.4; found 891.5.

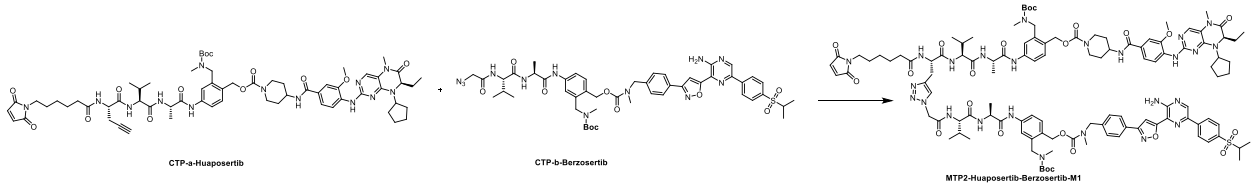
3) Compound MTP2-Rucaparib-AZD7762



Compound MTP2-Rucaparib-AZD7762 was synthesized following the previously established synthetic procedure of MTP2 series (step m). Purification was same as described above to afforded compound MTP2-Rucaparib-AZD7762 (209.6 mg, 38%, 0.17 mmol scale) as a yellow solid. HRMS (ESI-TOF): m/z calcd for $C_{153}H_{212}F_2N_{40}O_{38}S$ $[M+2H]^{+2}$: 1643.7782 Found 1643.7771. Also observed 1096.1880 $[M+3H]^{+3}$ and 822.3925 $[M+4H]^{+4}$.

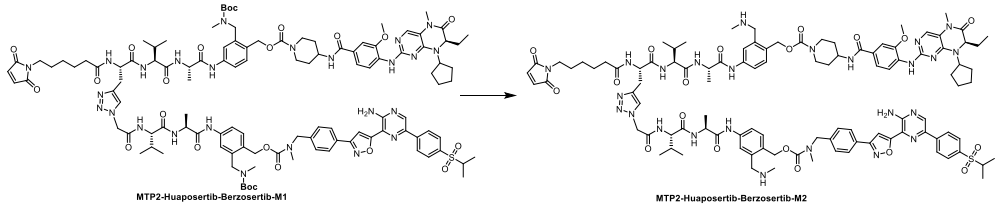
Synthesis of MTP2-Huaposertib-Berzosertib

1) Compound MTP2-Huaposertib-Berzosertib-M1



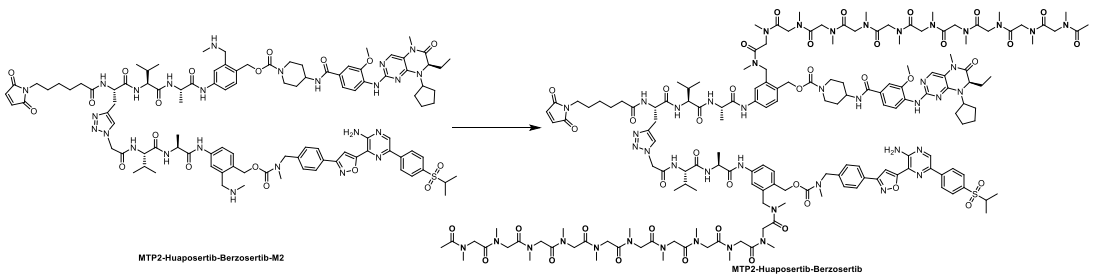
Compound MTP2-Huaposertib-Berzosertib-M1 was synthesized following the previously established synthetic procedure of MTP2 series (step k). Purification was same as described above to afforded MTP2-Huaposertib-Berzosertib-M1 (337 mg, 100%, 0.15 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{114}H_{149}N_{25}O_{23}S$ $[M+2H]^{+2}$: 1134.0; found 1134.1.

2) Compound MTP2-Huaposertib-Berzosertib-M2



Compound MTP2-Huaposertib-Berzosertib-M2 was synthesized following the previously established synthetic procedure of MTP2 series (step l). Purification was same as described above to afforded MTP2-Huaposertib-Berzosertib-M2 (337 mg, 100%, 0.15 mmol scale) as a tan solid. MS (ESI): m/z calcd for $C_{104}H_{133}N_{25}O_{19}S$ $[M+2H]^{+2}$: 1034.0; found 1034.1.

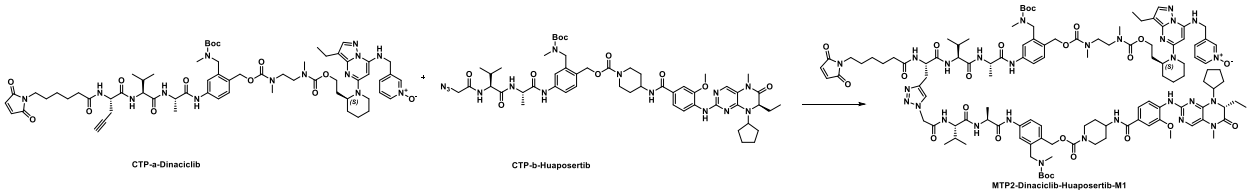
3) Compound MTP2-Huaposertib-Berzosertib



Compound MTP2-Huaposertib-Berzosertib was synthesized following the previously established synthetic procedure of MTP2 series (step m). Purification was same as described above to afforded compound MTP2-Huaposertib-Berzosertib (45.9 mg, 9%, 0.15 mmol scale) as a yellow powder. HRMS (ESI-TOF): m/z calcd for $C_{168}H_{237}N_{45}O_{41}S$ $[M+2H]^{+2}$: 1786.3777 Found 1786.3751. Also observed 1191.2544 $[M+3H]^{+3}$ and 893.6922 $[M+4H]^{+4}$.

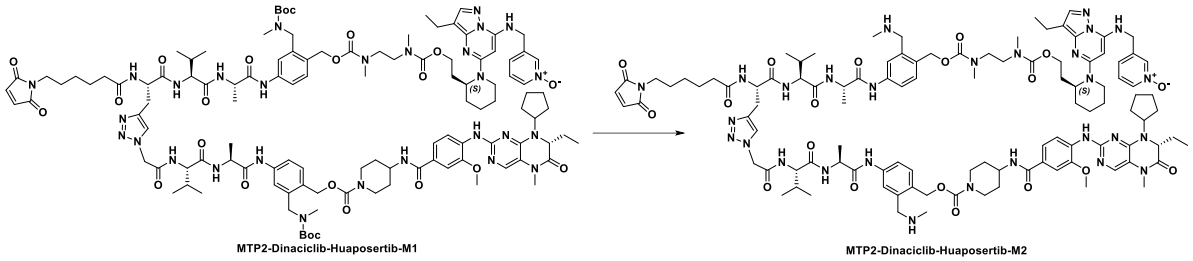
Synthesis of MTP2-Dinaciclib-Huaposertib

1) Compound MTP2-Dinaciclib-Huaposertib-M1



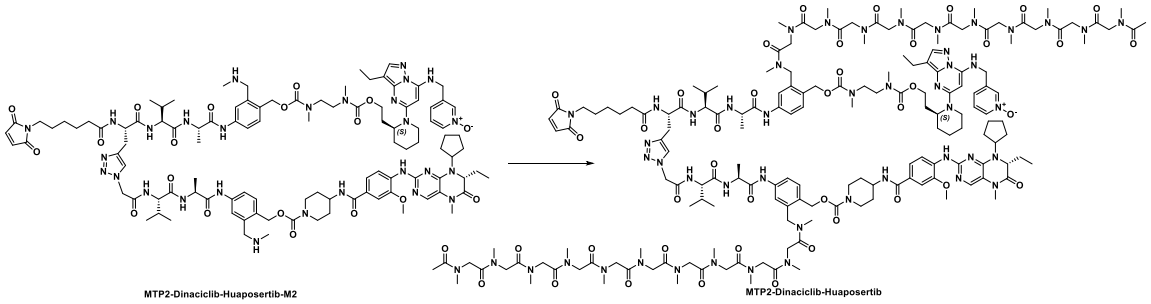
Compound MTP2-Dinaciclib-Huaposertib-M1 was synthesized following the previously established synthetic procedure of MTP2 series (step k). Purification was same as described above to afforded MTP2-Dinaciclib-Huaposertib-M1 (215 mg, 100%, 0.093 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{116}H_{162}N_{28}O_{23}$ $[M+2H]^{+2}$: 1157.6; found 1158.1.

2) Compound MTP2-Dinaciclib-Huaposertib-M2



Compound MTP2-Dinaciclib-Huaposertib-M2 was synthesized following the previously established synthetic procedure of MTP2 series (step l). Purification was same as described above to afforded MTP2-Dinaciclib-Huaposertib-M2 (215 mg, 100%, 0.093 mmol scale) as a tan solid. MS (ESI): m/z calcd for $C_{106}H_{146}N_{28}O_{19}$ $[M+2H]^{+2}$: 1057.6; found 1057.7.

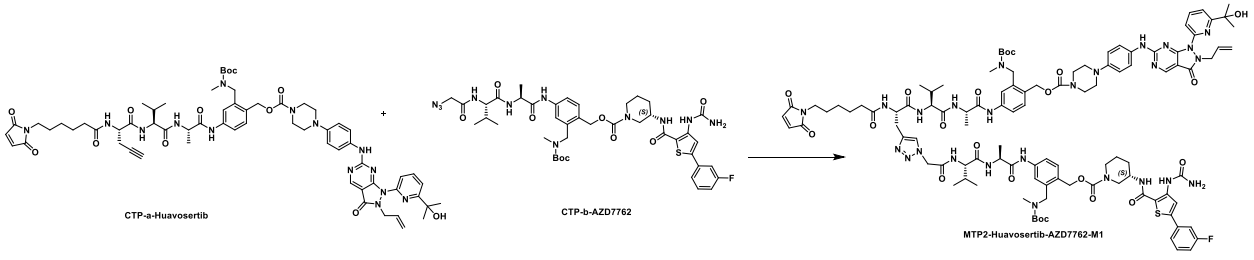
3) Compound MTP2-Dinaciclib-Huaposertib



Compound MTP2-Dinaciclib-Huaposertib was synthesized following the previously established synthetic procedure of MTP2 series (step m). Purification was same as described above to afforded compound MTP2-Dinaciclib-Huaposertib (63.5 mg, 19%, 0.093 mmol scale) as a white powder. HRMS (ESI-TOF): m/z calcd for $C_{170}H_{250}N_{48}O_{41}$ $[M+2H]^{+2}$: 1809.9471 Found 1809.9436. Also observed 1206.9664 $[M+3H]^{+3}$ and 905.4772 $[M+4H]^{+4}$.

Synthesis of MTP2-Huavosertib-AZD7762

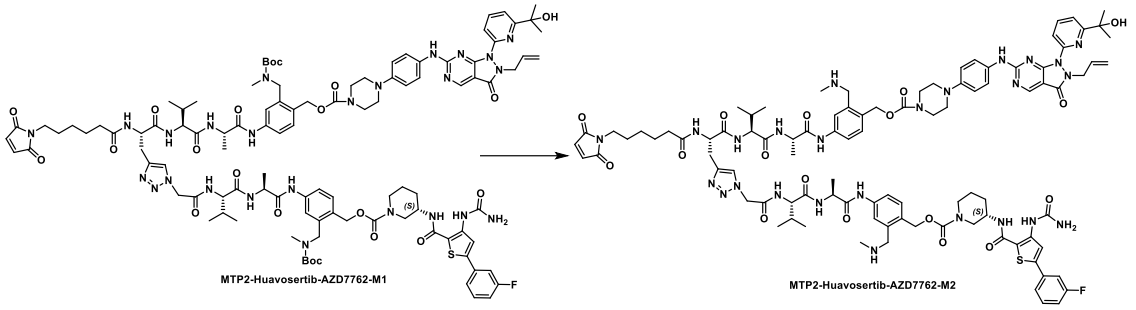
1) Compound MTP2-Huavosertib-AZD7762-M1



Compound MTP2-Huavosertib-AZD7762-M1 was synthesized following the previously established synthetic procedure of MTP2 series (step k). Purification was same as described above

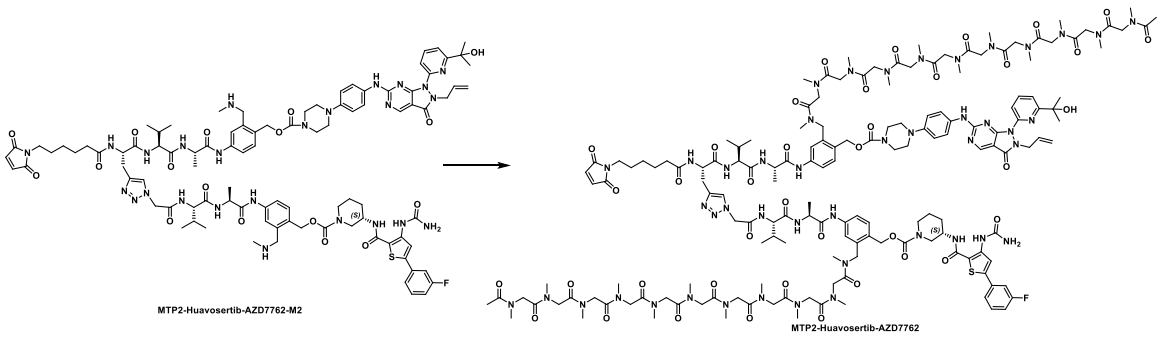
to afforded MTP2-Huavosertib-AZD7762-M1 (347 mg, 100%, 0.16 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{106}H_{136}FN_{25}O_{21}S$ $[M+2H]^{+2}$: 1073.0; found 1073.3.

2) Compound MTP2-Huavosertib-AZD7762-M2



Compound MTP2-Huavosertib-AZD7762-M2 was synthesized following the previously established synthetic procedure of MTP2 series (step l). Purification was same as described above to afforded MTP2-Huavosertib-AZD7762-M2 (347 mg, 100%, 0.16 mmol scale) as a tan solid. MS (ESI): m/z calcd for $C_{96}H_{120}FN_{25}O_{17}S$ $[M+2H]^{+2}$: 972.9; found 973.3.

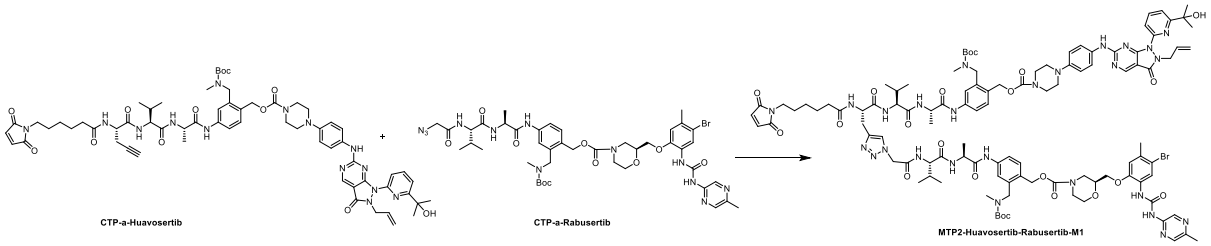
3) Compound MTP2-Huavosertib-AZD7762



Compound MTP2-Huavosertib-AZD7762 was synthesized following the previously established synthetic procedure of MTP2 series (step m). Purification was same as described above to afforded compound MTP2-Huavosertib-AZD7762 (212.7 mg, 38%, 0.16 mmol scale) as a yellow powder. HRMS (ESI-TOF): m/z calcd for $C_{160}H_{224}FN_{45}O_{39}S$ $[M+2H]^{+2}$: 1725.3311 Found 1725.3296. Also observed 1150.5568 $[M+3H]^{+3}$ and 863.1691 $[M+4H]^{+4}$.

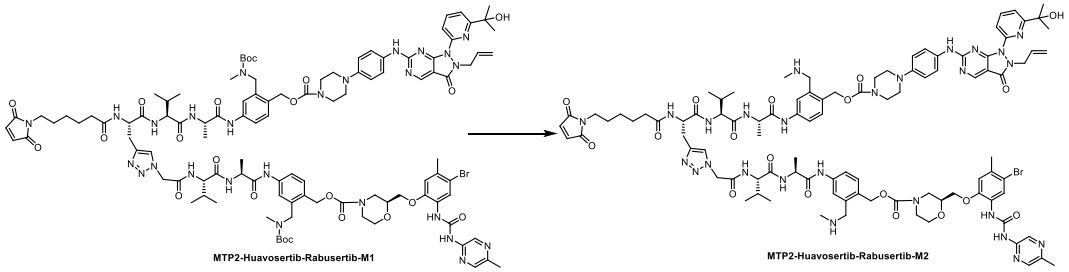
Synthesis of MTP2-Huavosertib-Rabusertib

1) Compound MTP2-Huavosertib-Rabusertib-M1



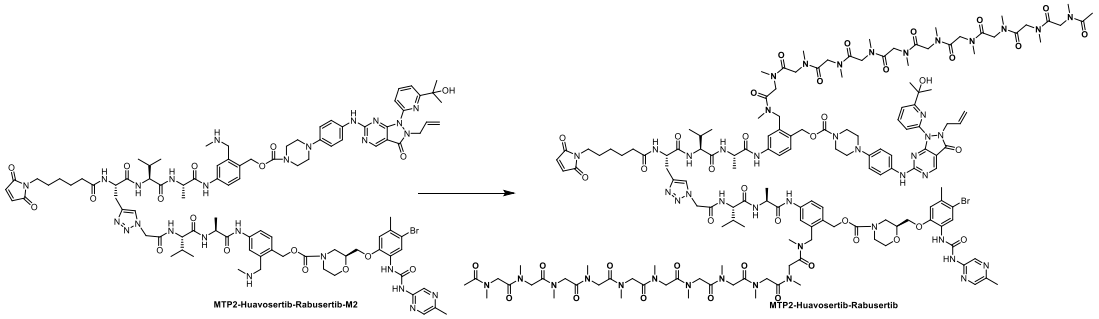
Compound MTP2-Huavosertib-Rabusertib-M1 was synthesized following the previously established synthetic procedure of MTP2 series (step k). Purification was same as described above to afforded MTP2-Huavosertib-Rabusertib-M1 (359 mg, 100%, 0.16 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{107}H_{139}BrN_{26}O_{22}$ $[M+2H]^{+2}$: 1109.5; found 1110.4.

2) Compound MTP2-Huavosertib-Rabusertib-M2



Compound MTP2-Huavosertib-Rabusertib-M2 was synthesized following the previously established synthetic procedure of MTP2 series (step l). Purification was same as described above to afforded MTP2-Huavosertib-Rabusertib-M2 (359 mg, 100%, 0.16 mmol scale) as a tan solid. MS (ESI): m/z calcd for $C_{97}H_{123}BrN_{26}O_{18}$ $[M+2H]^{+2}$: 1009.4; found 1009.5.

3) Compound MTP2-Huavosertib-Rabusertib

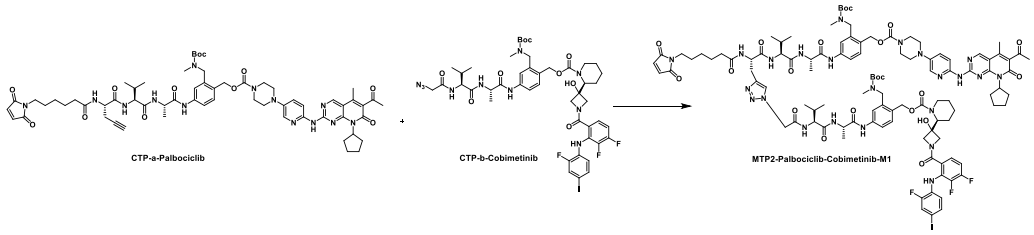


Compound MTP2-Huavosertib-Rabusertib was synthesized following the previously established synthetic procedure of MTP2 series (step m). Purification was same as described above to afforded compound MTP2-Huavosertib-Rabusertib (167.2 mg, 29%, 0.16 mmol scale) as a white powder.

HRMS (ESI-TOF): m/z calcd for $C_{161}H_{227}BrN_{46}O_{40}$ $[M+2H]^{+2}$: 1761.8158 Found 1761.8149. Also observed 1174.8796 $[M+3H]^{+3}$ and 881.4114 $[M+4H]^{+4}$.

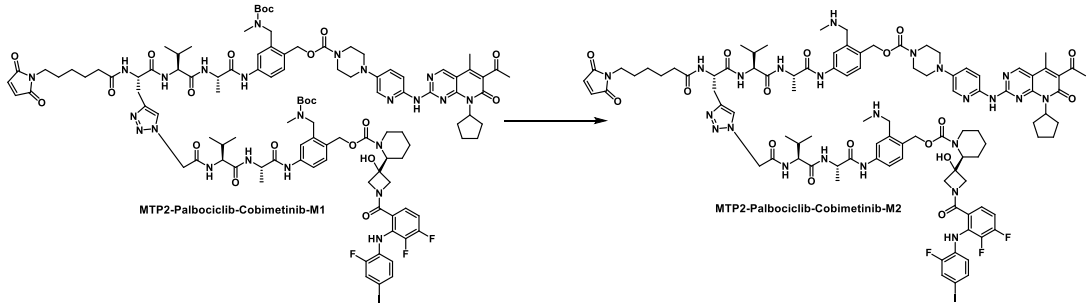
Synthesis of MTP2-Palbociclib-Cobimetinib

1) Compound MTP2-Palbociclib-Cobimetinib-M1



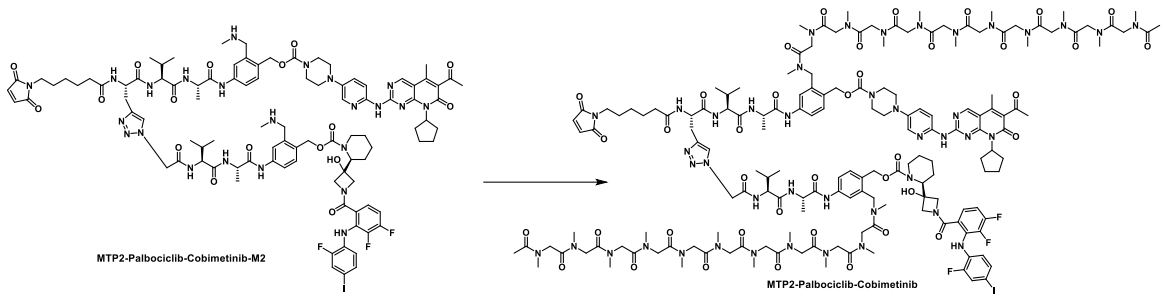
Compound MTP2-Palbociclib-Cobimetinib-M1 was synthesized following the previously established synthetic procedure of MTP2 series (step k). Purification was same as described above to afforded MTP2-Palbociclib-Cobimetinib-M1 (190 mg, 100%, 0.083 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{108}H_{137}F_3IN_{23}O_{21}$ $[M+2H]^{+2}$: 1138.0; found 1137.9.

2) Compound MTP2-Palbociclib-Cobimetinib-M2



Compound MTP2-Palbociclib-Cobimetinib-M2 was synthesized following the previously established synthetic procedure of MTP2 series (step l). Purification was same as described above to afforded MTP2-Dinaciclib-Huametinib-M2 (190 mg, 100%, 0.083 mmol scale) as a tan solid. MS (ESI): m/z calcd for $C_{98}H_{121}F_3IN_{23}O_{17}$ $[M+2H]^{+2}$: 1037.9; found 1038.3.

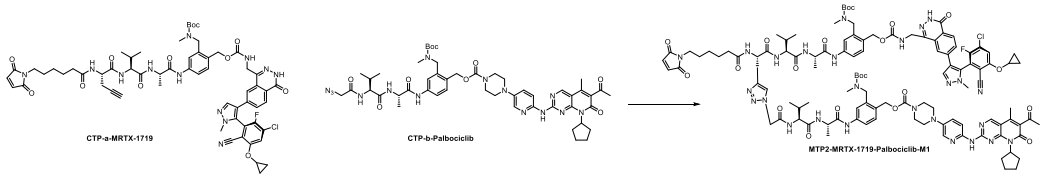
3) Compound MTP2-Palbociclib-Cobimetinib



Compound MTP2-Palbociclib-Cobimetinib was synthesized following the previously established synthetic procedure of MTP2 series (step m). Purification was same as described above to afforded compound MTP2-Palbociclib-Cobimetinib (24 mg, 8%, 0.083 mmol scale) as a white powder. HRMS (ESI-TOF): m/z calcd for $C_{162}H_{225}F_3IN_{43}O_{39}$ $[M+2H]^{+2}$: 1790.2966 Found 1790.2954. Also observed 1193.8672 $[M+3H]^{+3}$ and 895.6516 $[M+4H]^{+4}$.

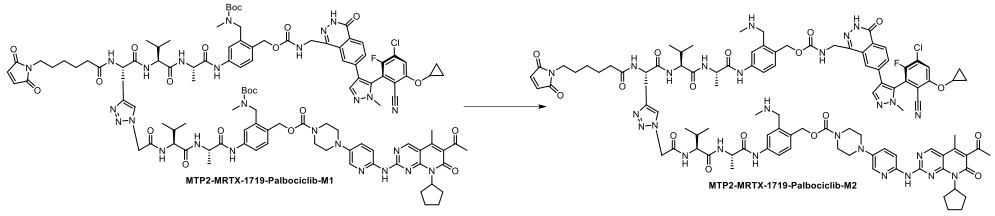
Synthesis of MTP2-MRTX1719-Palbociclib

1) Compound MTP2-MRTX1719-Palbociclib-M1



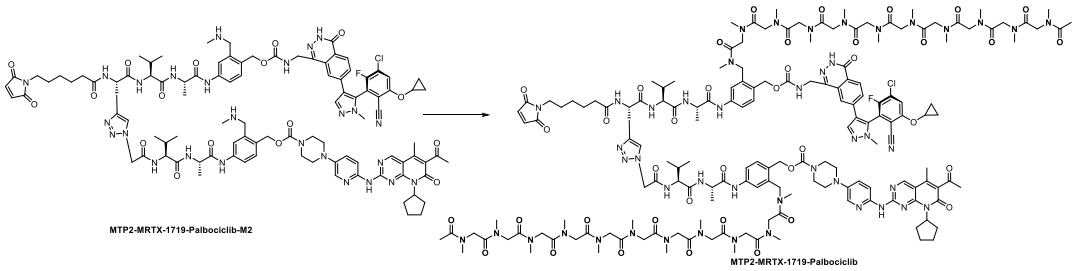
Compound MTP2-MRTX1719-Palbociclib-M1 was synthesized following the previously established synthetic procedure of MTP2 series (step k). Purification was same as described above to afforded MTP2-MRTX1719-Palbociclib-M1 (182 mg, 100%, 0.082 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{110}H_{134}ClFN_{26}O_{21}$ $[M+2H]^{+2}$: 1104.5; found 1104.4.

2) Compound MTP2-MRTX-1719-Palbociclib-M2



Compound MTP2-MRTX1719-Palbociclib-M2 was synthesized following the previously established synthetic procedure of MTP2 series (step l). Purification was same as described above to afforded MTP2-MRTX1719-Palbociclib-M2 (182 mg, 100%, 0.082 mmol scale) as a tan solid. MS (ESI): m/z calcd for $C_{100}H_{118}ClFN_{26}O_{17}$ $[M+2H]^{+2}$: 1004.4; found 1004.5.

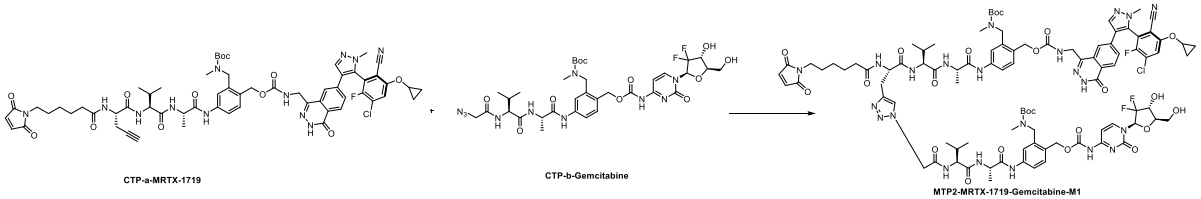
3) Compound MTP2-MRTX1719-Palbociclib



Compound MTP2-MRTX1719-Palbociclib was synthesized following the previously established synthetic procedure of MTP2 series (step m). Purification was same as described above to afforded compound MTP2-MRTX1719-Palbociclib (76.7 mg, 27%, 0.082 mmol scale) as a yellow powder. HRMS (ESI-TOF): m/z calcd for $C_{164}H_{222}ClFN_{46}O_{39}$ $[M+2H]^{+2}$: 1756.8232 Found 1756.8214. Also observed 1171.5513 $[M+3H]^{+3}$ and 879.9144 $[M+4H]^{+4}$.

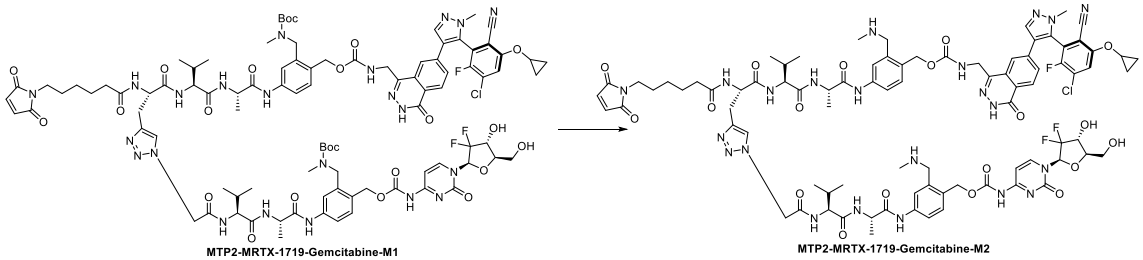
Synthesis of MTP2-MRTX-1719-Gemcitabine

1) Compound MTP2-MRTX-1719-Gemcitabine-M1



Compound MTP2-MRTX-1719-Gemcitabine-M1 was synthesized following the previously established synthetic procedure of MTP2 series (step k). Purification was same as described above to afforded MTP2-MRTX-1719-Gemcitabine-M1 (175 mg, 100%, 0.086 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{95}H_{114}ClF_3N_{22}Na_2O_{23}$ $[M+2Na]^{+2}$: 1034.4; found 1034.8.

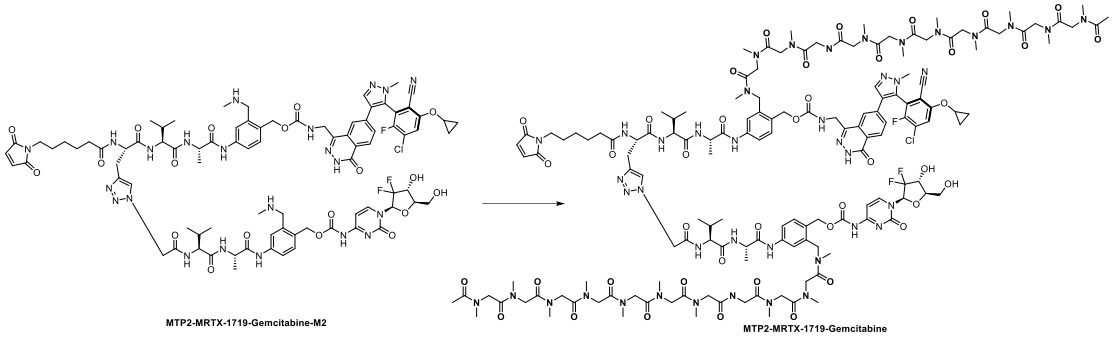
2) Compound MTP2-MRTX-1719-Gemcitabine-M2



Compound MTP2-MRTX-1719-Gemcitabine-M2 was synthesized following the previously established synthetic procedure of MTP2 series (step l). Purification was same as described above

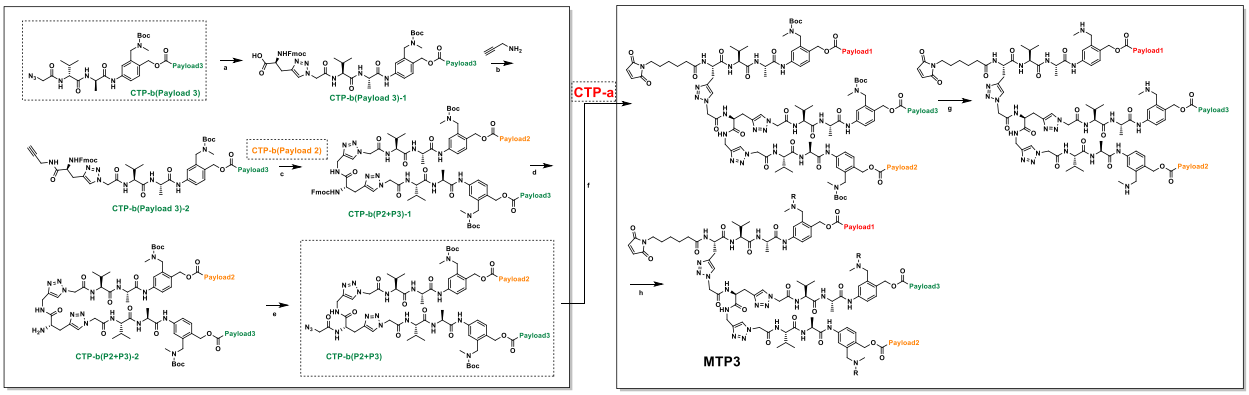
to afforded MTP2-MRTX-1719-Gemcitabine-M2 (175 mg, 100%, 0.086 mmol scale) as a tan solid. MS (ESI): m/z calcd for $C_{85}H_{100}ClF_3N_{22}O_{19}$ $[M+2H]^{+2}$: 912.4; found 912.8.

3) Compound MTP2-MRTX-1719-Gemcitabine



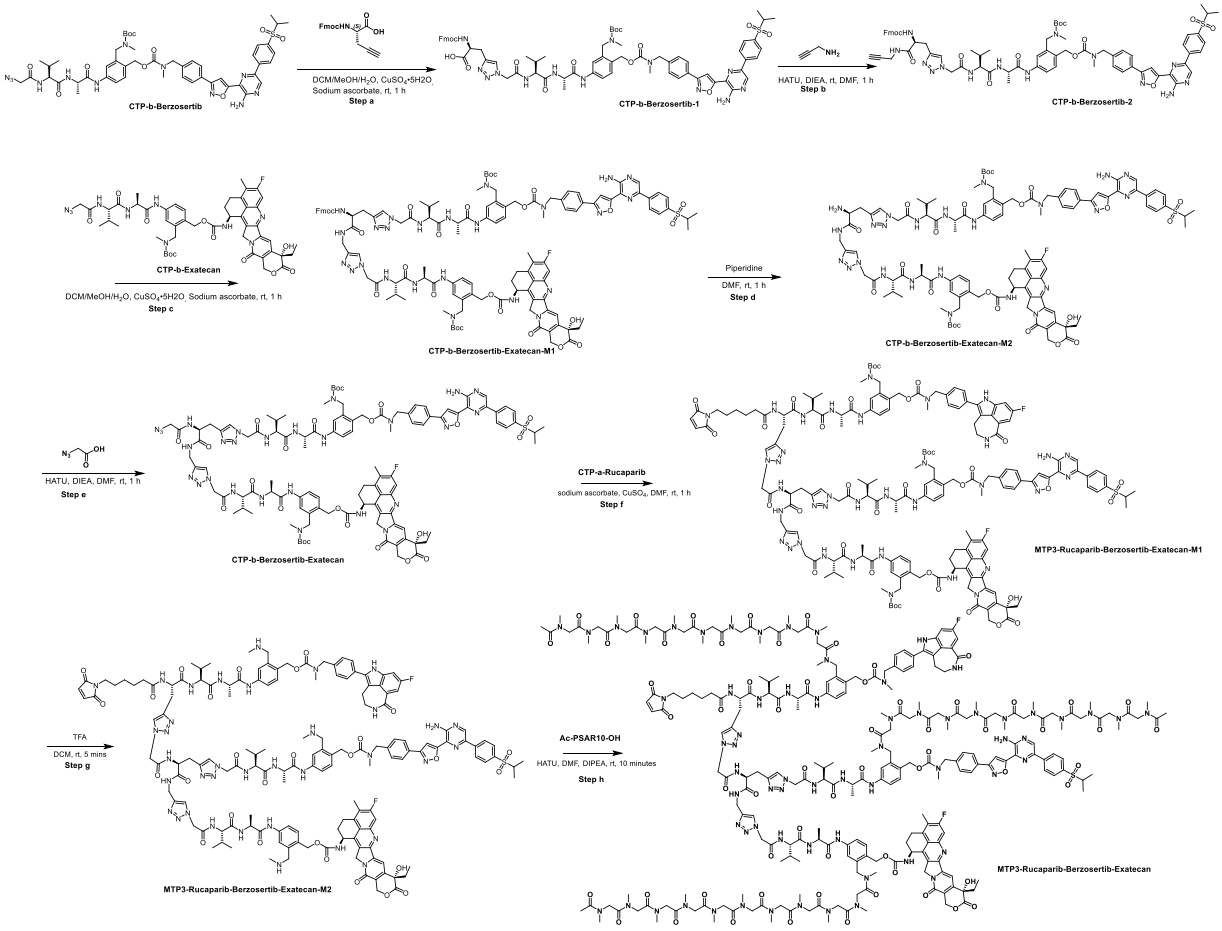
Compound MTP2-MRTX-1719-Gemcitabine was synthesized following the previously established synthetic procedure of MTP2 series (step m). Purification was same as described above to afforded compound MTP2-MRTX-1719-Gemcitabine (34.3 mg, 12%, 0.086 mmol scale) as a white powder. HRMS (ESI-TOF): m/z calcd for $C_{149}H_{204}ClF_3N_{42}O_{41}$ $[M+2H]^{+2}$: 1664.7400 Found 1664.7384. Also observed 1110.1625 $[M+3H]^{+3}$ and 832.8734 $[M+4H]^{+4}$.

Synthetic scheme of MTP3 series

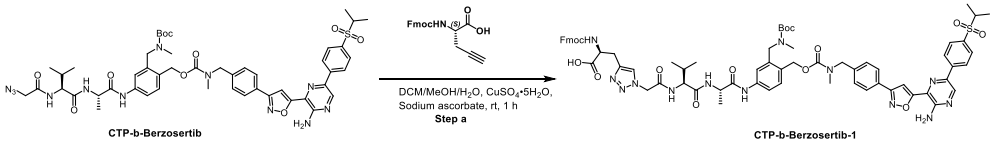


Scheme 2. Synthesis of MTP3 series: : a) sodium ascorbate, CuSO4, DCM/MeOH/H_2O, rt, 2-10 h; b) HATU, DIEA, DMF, rt, 1 h; c) sodium ascorbate, CuSO4, DCM/MeOH/H_2O, rt, 2-10 h; d) piperidine , DMF, rt, 1 h; e) 2-azidoacetic acid, DIEA, HATU, DMF, rt, 1 h; f) sodium ascorbate, CuSO4, DMF/H_2O, rt, 2-16 h; g) TFA, DCM, rt, 0.08-0.5 h; h) Ac-Sar10-COOH, DIEA, HATU, 0 ºC to rt, 1 h;

Synthesis of MTP3-Rucaparib-Berzosertib-Exatecan



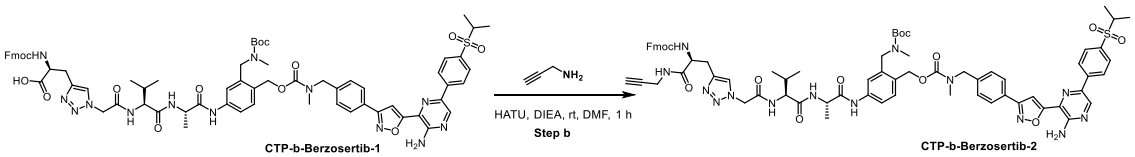
1) Compound CTP-b-Berzosertib-1



To a solution of compound CTP-b-Berzosertib (3.0 g, 2.970 mmol) and compound (S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)pent-4-ynoic acid (1.01 g, 2.970 mmol) in a mixture of MeOH (30 mL) and CH_2Cl_2 (30 mL) was added a solution of $CuSO_4$ (149 mg, 0.594 mmol) in deionized water (2 mL) and a solution of sodium ascorbate solution (235 mg, 1.188 mmol) in deionized water (2 mL) via syringe. The reaction mixture was degassed with vacuum and then purged with N_2 (2 cycles). The resulting solution was then allowed to stir at room temperature for 1 h. The reaction was monitored by LC-MS. Upon completion, the solvent was removed under reduced pressure. The crude was triturated in ethyl acetate for 0.5 h and the suspension was filtered.

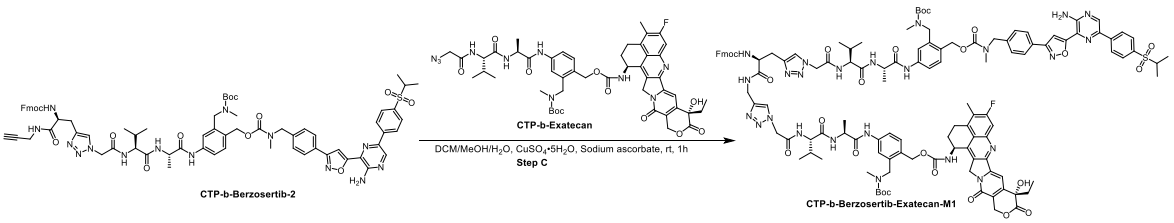
The solid was collected and dried to give the compound CTP-b-Berzosertib-1 (3.4 g, 85%) as yellow solid. MS (ESI): m/z calcd for $C_{69}H_{77}N_{13}NaO_{14}S$ $[M+Na]^+$: 1366.5; found 1366.4.

2) Compound CTP-b-Berzosertib-2



To a solution of CTP-b-Berzosertib-1 (450 mg, 0.334 mmol) in DMF (5 mL) was added HATU (166 mg, 0.435 mmol) and N, N-Diisopropylethylamine (131 mg, 1.003 mmol), followed by the addition of prop-2-yn-1-amine (28 mg, 0.502 mmol). The reaction was stirred at room temperature for 1 h and monitored by LC-MS. Upon completion, 2-MeTHF (100 mL) and water (50 mL) was added, the organic layer was separated, and the resultant aqueous solution was extracted with 2-MeTHF (3 × 50 mL). The combined organic phases were washed with water (50 mL), brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The resultant residue was triturated in ethyl acetate (20 mL) for 1 h, then isolated by filtration, washed with ethyl acetate (10 mL), and dried under vacuum to give compound CTP-b-Berzosertib-2 (420 mg, 91%) as a yellow solid. MS (ESI): m/z calcd for $C_{72}H_{80}N_{14}NaO_{13}S$ $[M+Na]^+$: 1403.6; found 1403.4.

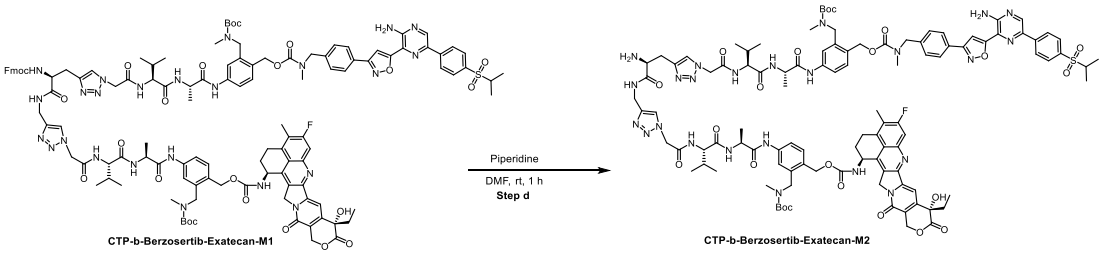
3) Compound CTP-b-Berzosertib-Exatecan-M1



To a solution of CTP-b-Berzosertib-2 (400 mg, 0.289 mmol) and compound CTP-b-Exatecan (285 mg, 0.289 mmol) in a mixture of MeOH (5 mL) and CH_2Cl_2 (5 mL) was added a solution of $CuSO_4$ (14.5 mg, 0.0579 mmol) in deionized water (200 uL) and a solution of sodium ascorbate solution (22.9 mg, 0.116 mmol) in deionized water (200 uL) via syringe. The reaction mixture was degassed with vacuum and then purged with N_2 (2 cycles). The resulting solution was then allowed to stir at room temperature for 1 h. The reaction was monitored by LC-MS. Upon completion, the solvent was removed under reduced pressure to afford a gray solid which was slurried in MeOH (20 mL) for 30 min and collected by vacuum filtration. The solid was dried to give compound Berzosertib-

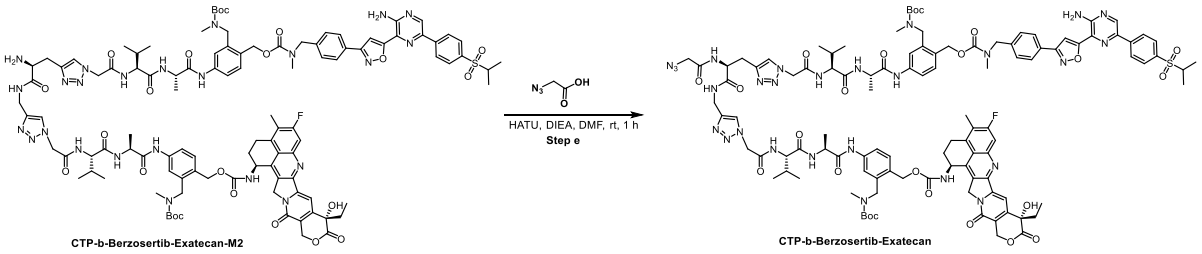
Exatecan-M1 (500 mg, 73%) as a yellow solid. MS (ESI): m/z calcd for $C_{121}H_{137}FN_{24}Na_2O_{24}S$ $[M+2Na]^{+2}$: 1203.5; found 1203.8.

4) Compound CTP-b-Berzosertib-Exatecan-M2



To a solution of compound CTP-b-Berzosertib-Exatecan-M1 (500 mg, 0.212 mmol) in DMF (5 mL) was added piperidine (1 mL). The reaction was stirred at room temperature for 1 h and monitored by LC-MS. Upon completion, the reaction mixture was poured into tert-Butyl methyl ether (100 mL), the resulting suspension was isolated by filtration and washed with tert-Butyl methyl ether (30 mL). The solid was triturated in ethyl acetate (20 mL) for 1 h and collected by vacuum filtration. The solid was dried to give compound CTP-b-Berzosertib-Exatecan-M2 (430 mg, 95%) as a yellow solid. MS (ESI): m/z calcd for $C_{106}H_{129}FN_{24}O_{22}S$ $[M+2H]^{+2}$: 1070.9; found 1070.9.

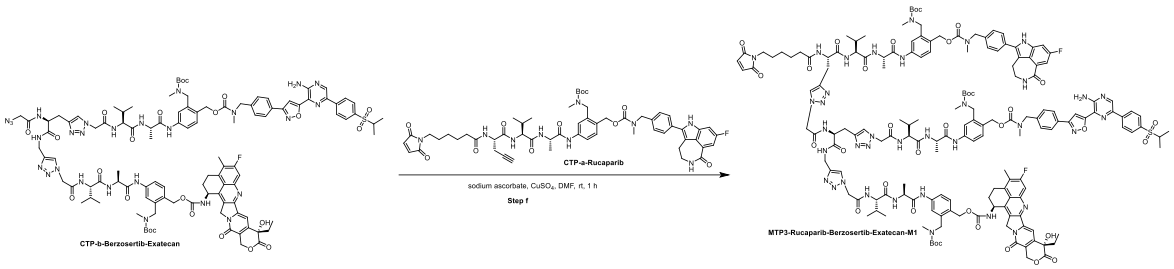
5) Compound CTP-b-Berzosertib-Exatecan



To a solution of compound CTP-b-Berzosertib-Exatecan (420 mg, 0.196 mmol) in DMF (5 mL) was added N, N-Diisopropylethylamine (76 mg, 0.588 mmol) and compound 2-azidoacetic acid (32 mg, 0.314 mmol), followed by HATU (127 mg, 0.333 mmol). The reaction was stirred at room temperature for 1 h and monitored by LC-MS. Upon completion, the reaction mixture was poured into tert-Butyl methyl ether (100 mL), the resulting suspension was isolated by filtration and washed with tert-Butyl methyl ether (30 mL). The solid was triturated in MeOH (20 mL) for 1 h, then isolated by filtration, washed with MeOH (10 mL), and dried under vacuum to give compound

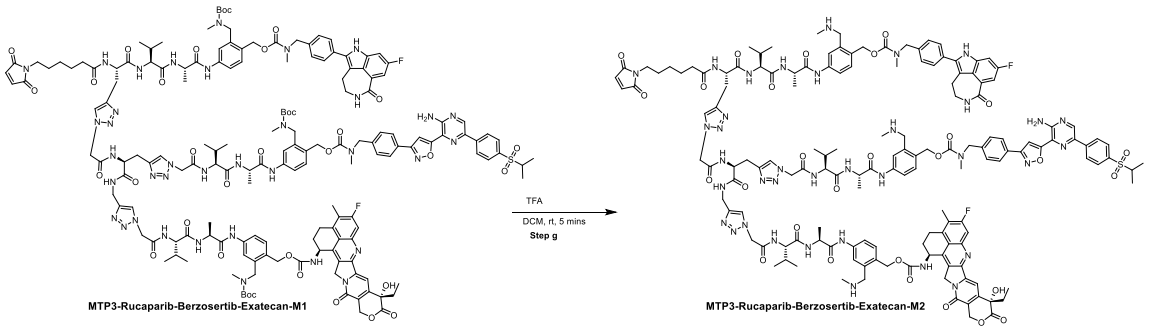
CTP-b-Berzosertib-Exatecan (420 mg, 96%) as a yellow solid. MS (ESI): m/z calcd for $C_{108}H_{130}FN_{27}O_{23}S$ $[M+2H]^{+2}$: 1112.0; found 1112.3.

6) Compound MTP3-Rucaparib-Berzosertib-Exatecan-M1



To a solution of compound CTP-b-Berzosertib-Exatecan (207 mg, 0.093 mmol) and compound CTP-a-Rucaparib (100 mg, 0.093 mmol) in DMF (4 mL) was added a solution of $CuSO_4$ (2.3 mg, 0.0093 mmol) in deionized water (100 uL) and a solution of sodium ascorbate solution (7.4 mg, 0.0372 mmol) in deionized water (100 uL) via syringe. The reaction mixture was degassed with vacuum and then purged with N_2 (2 cycles). The resulting solution was then allowed to stir at room temperature for 1 h. The reaction was monitored by LC-MS. Upon completion, the mixture was poured into ethyl acetate (80 mL), the resulting suspension was isolated by filtration and washed with ethyl acetate (30 mL). The solid was triturated in MeOH (30 mL) for 1 h, then isolated by filtration, washed with MeOH (10 mL), and dried under vacuum to give compound MTP3-Rucaparib-Berzosertib-Exatecan-M1 (280 mg, 91%) as a yellow solid. MS (ESI): m/z calcd for $C_{165}H_{198}F_2N_{36}O_{34}S$ $[M+2H]^{+2}$: 1648.7; found 1649.4.

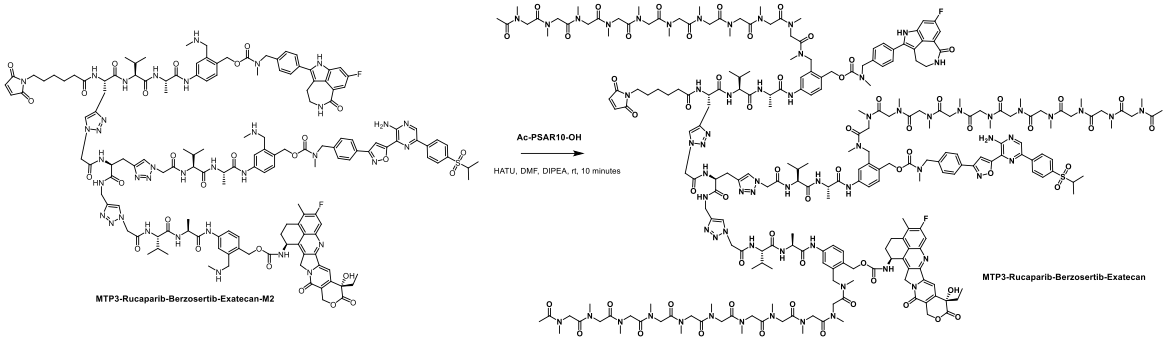
7) Compound MTP3-Rucaparib-Berzosertib-Exatecan-M2



The compound MTP3-Rucaparib-Berzosertib-Exatecan-M1 (260 mg, 0.079 mmol) obtained from above was suspended in CH_2Cl_2 (3 mL). To this suspension, TFA (1 mL) was added and the solution was stirred at room temperature for 5 minutes before the solvent was removed under vacuum. The crude compound MTP3-Rucaparib-Berzosertib-Exatecan-M2 (260 mg, 100%) was

directly used for next step. MS (ESI): m/z calcd for $C_{150}H_{174}F_2N_{36}O_{28}S$ $[M+2H]^{+2}$: 1498.6; found 1499.1.

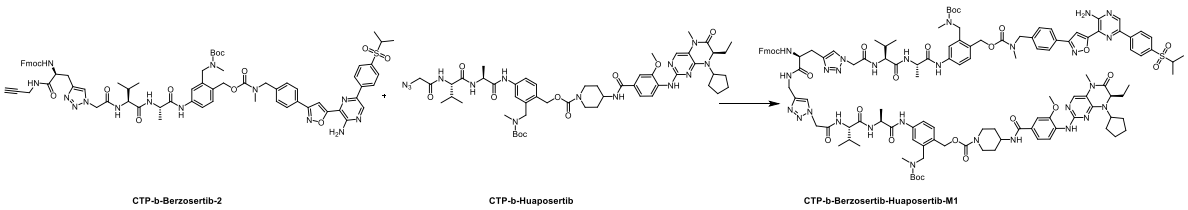
8) Compound MTP3-Rucaparib-Berzosertib-Exatecan



To a solution of compound MTP3-Rucaparib-Berzosertib-Exatecan-M2 (260 mg, 0.079 mmol) in DMF (3 mL) was added compound Ac-PSAR10-OH (Wuxi apptec, 189 mg, 0.24 mmol) and N, N-Diisopropylethylamine (306 mg, 2.37 mmol), followed by the addition of HATU (96 mg ,0.25 mmol). The reaction was stirred at room temperature for 1 h. The reaction was monitored by LC-MS. Upon completion, ethyl acetate was added and the mixture was filtered to give the crude product. The crude was purified by prep-HPLC (Column: WELCH Xtimate 21.2*250mm 10um C18, Mobile phase: A = 0.1% Formic acid in Water, B = ACN) to give MTP3-Rucaparib-Berzosertib-Exatecan (42.5 mg, 10%) as a yellow powder. HRMS (ESI-TOF): m/z calcd for $C_{246}H_{330}F_2N_{66}O_{61}S$ $[M+2H]^{+2}$: 2628.2247 Found 2628.2280. Also observed 1752.4812 $[M+3H]^{+3}$, 1314.6139 $[M+H]^{+4}$ and 1051.8929 $[M+5H]^{+5}$.

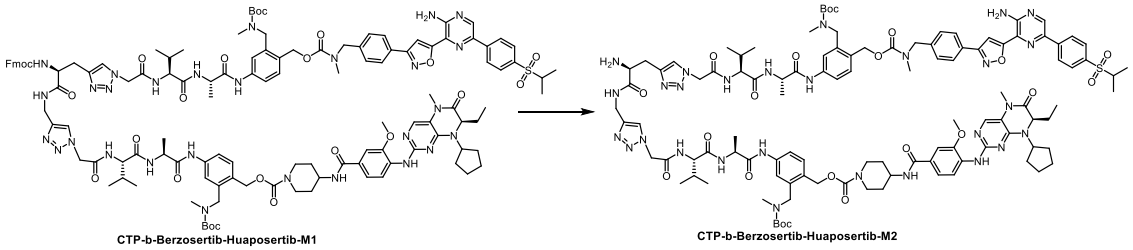
Synthesis of MTP3-Dinaciclib-Berzosertib-Huaposertib

1) Compound CTP-b-Berzosertib-Huaposertib-M1



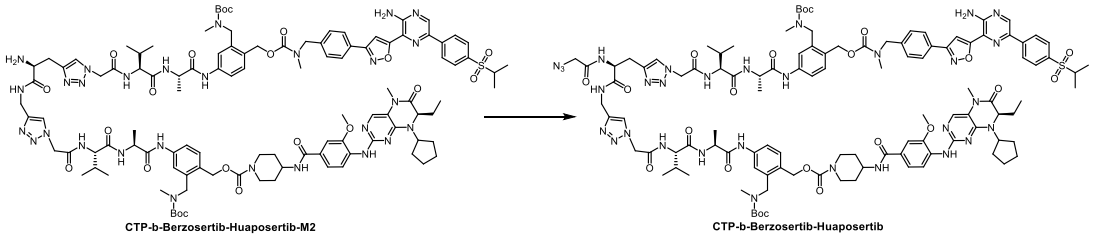
Compound CTP-b-Berzosertib-Huaposertib-M1 was synthesized following the previously established synthetic procedure of MTP3 series (step c). Purification was same as described above to afforded CTP-b-Berzosertib-Huaposertib-M1 (400 mg, 91%, 0.18 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{124}H_{154}N_{28}O_{23}S$ $[M+2H]^{+2}$: 1217.6; found 1218.0.

2) Compound CTP-b-Berzosertib-Huaposertib-M2



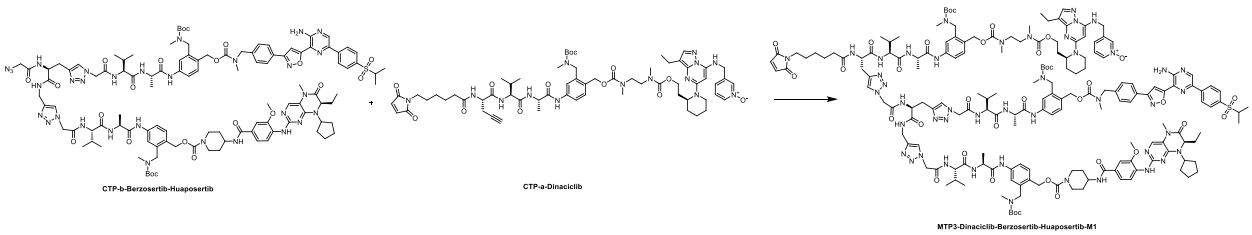
Compound CTP-b-Berzosertib-Huaposertib-M2 was synthesized following the previously established synthetic procedure of MTP3 series (step d). Purification was same as described above to afforded CTP-b-Berzosertib-Huaposertib-M2 (273 mg, 75%, 0.16 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{109}H_{144}N_{28}O_{21}S$ $[M+2H]^{+2}$: 1106.5; found 1106.9.

3) Compound CTP-b-Berzosertib-Huaposertib



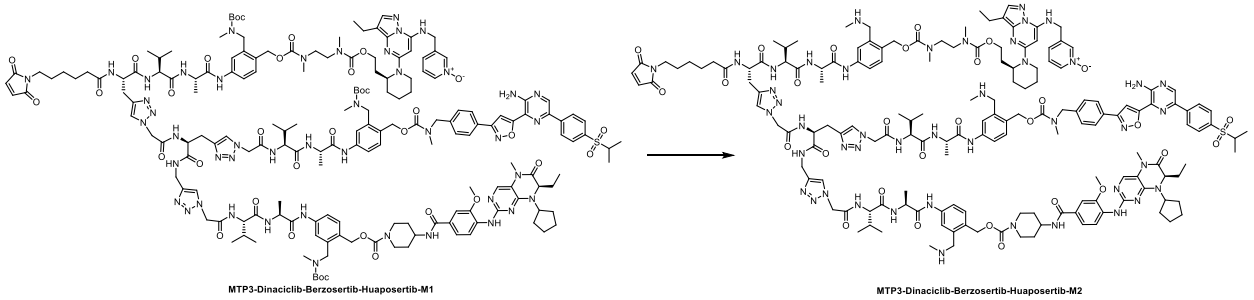
Compound CTP-b-Berzosertib-Huaposertib was synthesized following the previously established synthetic procedure of MTP3 series (step e). Purification was same as described above to afforded CTP-b-Berzosertib-Huaposertib (260 mg, 92%, 0.12 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{111}H_{145}N_{31}O_{22}S$ $[M+2H]^{+2}$: 1148.0; found 1148.5.

4) Compound MTP3-Dinaciclib-Berzosertib-Huaposertib-M1



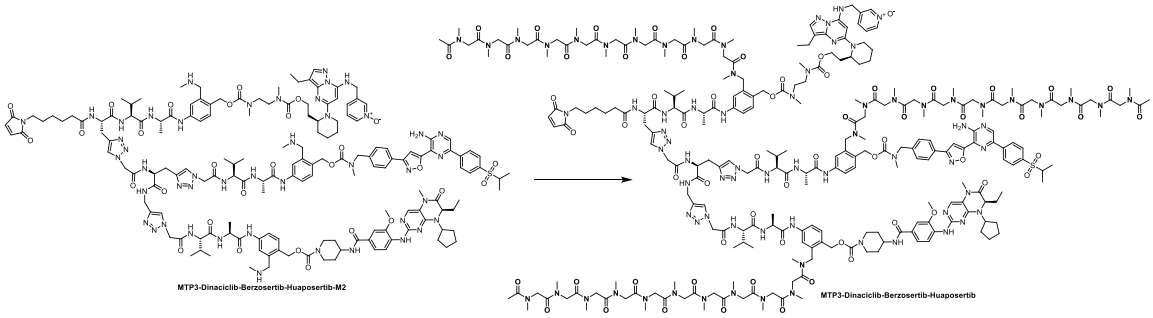
Compound MTP3-Dinaciclib-Berzosertib-Huaposertib-M1 was synthesized following the previously established synthetic procedure of MTP3 series (step f). Purification was same as described above to afforded MTP3-Dinaciclib-Berzosertib-Huaposertib-M1 (346 mg, 86%, 0.11 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{175}H_{233}N_{45}O_{35}S$ $[M+2H]^{+2}$: 1778.4; found 1778.8.

5) Compound MTP3-Dinaciclib-Berzosertib-Huaposertib-M2



Compound MTP3-Dinaciclib-Berzosertib-Huaposertib-M2 was synthesized following the previously established synthetic procedure of MTP3 series (step g). Purification was same as described above to afforded MTP3-Dinaciclib-Berzosertib-Huaposertib-M2 (200 mg, 100%, 0.056 mmol scale). MS (ESI): m/z calcd for $C_{160}H_{209}N_{45}O_{29}S$ $[M+2H]^{+2}$: 1628.3; found 1629.1.

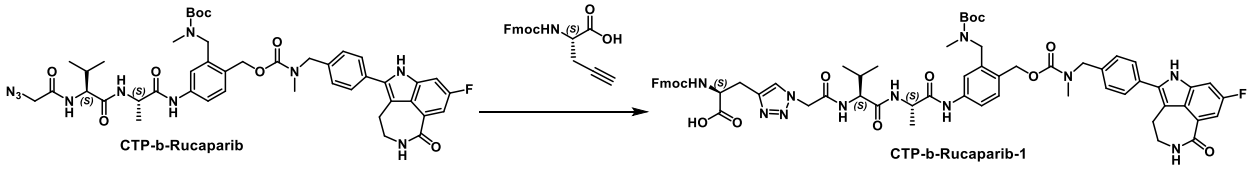
6) Compound MTP3-Dinaciclib-Berzosertib-Huaposertib



Compound MTP3-Belotecan-Rucaparib-Rabusertib was synthesized following the previously established synthetic procedure of MTP3 series (step h). Purification was same as described above to afforded MTP3-Belotecan-Rucaparib-Rabusertib (96.6 mg, 31%, 0.046 mmol scale) as a white solid. MS (ESI): m/z calcd for $C_{256}H_{366}N_{75}O_{62}S$ $[M+3H]^{+}$: 1838.2; found 1839.1.

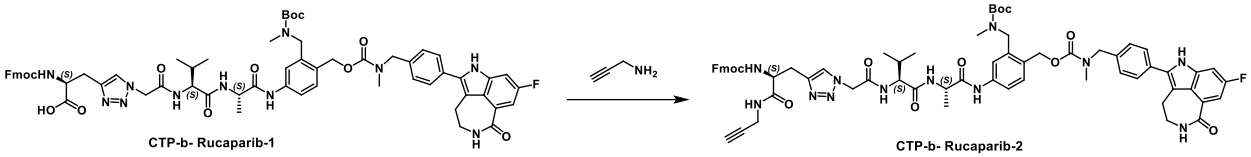
Synthesis of MTP3-Belotecan-Rucaparib-Rabusertib

1) Compound CTP-b-Rucaparib-1



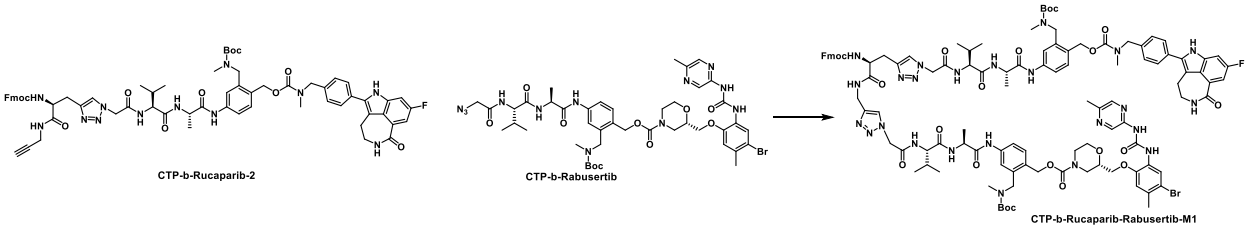
Compound CTP-b-Rucaparib-1 was synthesized following the previously established synthetic procedure of MTP3 series (step a). Purification was same as described above to afforded CTP-b-Rucaparib-1 (345 mg, 83%, 0.345 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{64}H_{70}FN_{11}NaO_{12}$ $[M+Na]^{+}$: 1226.5; found 1226.4.

2) Compound CTP-b-Rucaparib-2



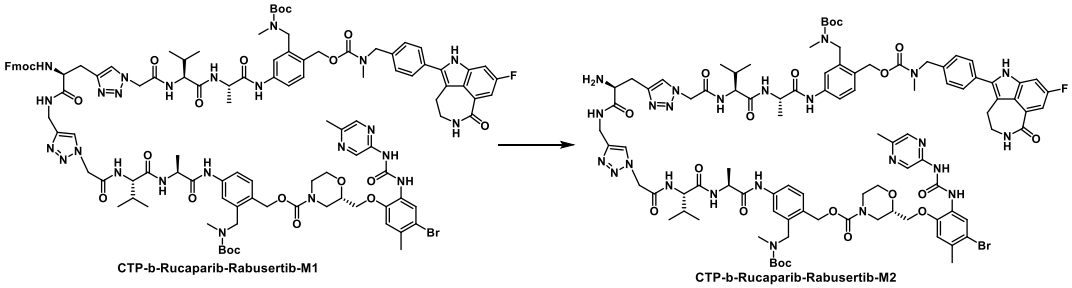
Compound CTP-b-Rucaparib-2 was synthesized following the previously established synthetic procedure of MTP3 series (step b). Purification was same as described above to afforded CTP-b-Rucaparib-2 (274 mg, 77%, 0.29 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{67}H_{73}FN_{12}O_{11}$ $[M+Na]^{+}$: 1263.5; found 1263.4.

3) Compound CTP-b-Rucaparib-Rabusertib-M1



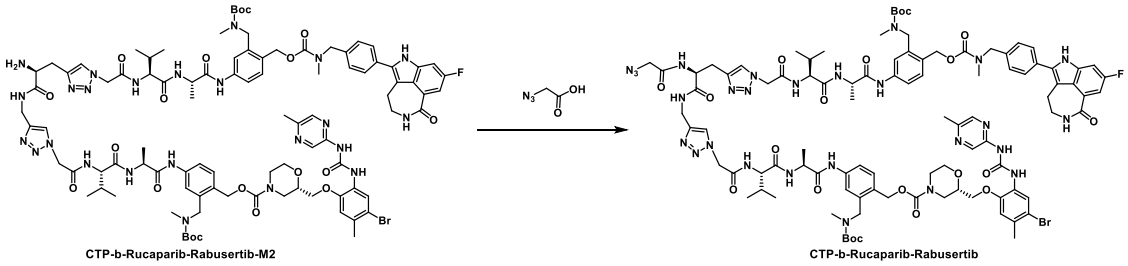
Compound CTP-b-Rucaparib-Rabusertib-M1 was synthesized following the previously established synthetic procedure of MTP3 series (step c). Purification was same as described above to afforded CTP-b-Rucaparib-Rabusertib-M1 (371 mg, 76%, 0.22 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{110}H_{130}BrFN_{24}Na_2O_{21}$ $[M+2Na]^{+2}$: 1133.4; found 1133.4.

4) Compound CTP-b-Rucaparib-Rabusertib-M2



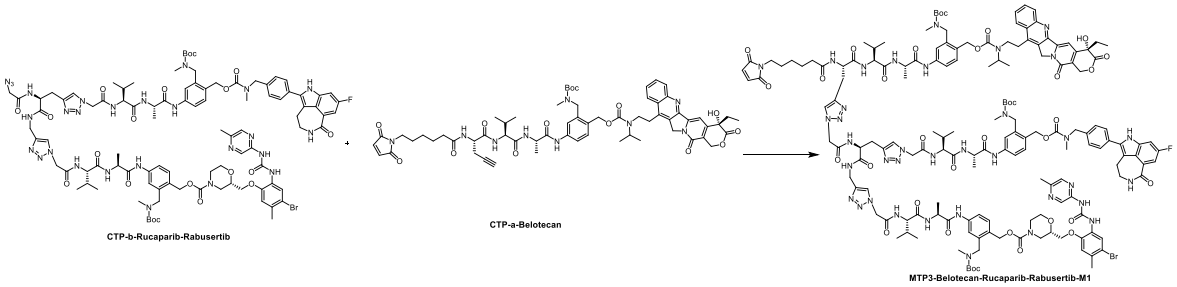
Compound CTP-b-Rucaparib-Rabusertib-M2 was synthesized following the previously established synthetic procedure of MTP3 series (step d). Purification was same as described above to afforded CTP-b-Rucaparib-Rabusertib-M2 (280 mg, 78%, 0.18 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{95}H_{122}BrFN_{24}O_{19}$ $[M+2H]^{+2}$: 1000.4; found 1000.3.

5) Compound CTP-b-Rucaparib-Rabusertib



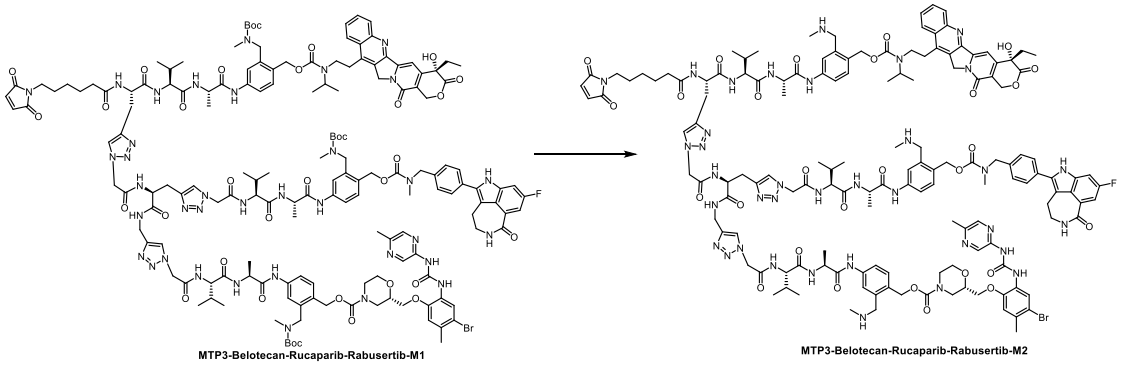
Compound CTP-b-Rucaparib-Rabusertib was synthesized following the previously established synthetic procedure of MTP3 series (step e). Purification was same as described above to afforded CTP-b-Rucaparib-Rabusertib (228 mg, 73%, 0.15 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{97}H_{123}BrFN_{27}O_{20}$ $[M+2H]^{+2}$: 1041.9; found 1041.8.

6) Compound MTP3-Belotecan-Rucaparib-Rabusertib**-**M1



Compound MTP3-Belotecan-Rucaparib-Rabusertib**-**M1 was synthesized following the previously established synthetic procedure of MTP3 series (step f). Purification was same as described above to afforded MTP3-Belotecan-Rucaparib-Rabusertib**-**M1 (291 mg, 81%, 0.11 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{160}H_{200}BrFN_{36}O_{34}$ $[M+2H]^{+2}$: 1633.7; found 1634.1.

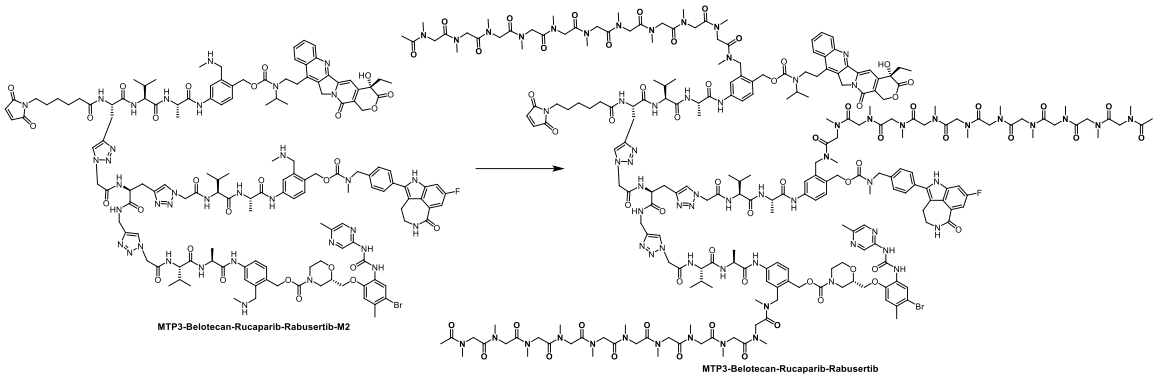
7) Compound MTP3-Belotecan-Rucaparib-Rabusertib**-**M2



Compound MTP3-Belotecan-Rucaparib-Rabusertib**-**M2 was synthesized following the previously established synthetic procedure of MTP3 series (step g). Purification was same as described above

to afforded MTP3-Belotecan-Rucaparib-Rabusertib-M2 (136 mg, 100%, 0.046 mmol scale). MS (ESI): m/z calcd for $C_{145}H_{177}BrFN_{36}O_{28}$ $[M+3H]^{+3}$: 989.4; found 990.3.

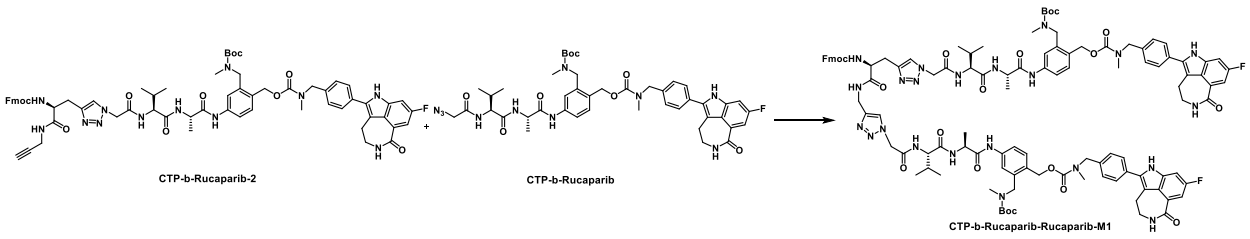
8) Compound MTP3-Belotecan-Rucaparib-Rabusertib



Compound MTP3-Belotecan-Rucaparib-Rabusertib was synthesized following the previously established synthetic procedure of MTP3 series (step h). Purification was same as described above to afforded MTP3-Belotecan-Rucaparib-Rabusertib (34.9 mg, 15%, 0.046 mmol scale). HRMS (ESI-TOF): m/z calcd for $C_{241}H_{333}BrFN_{66}O_{61}$ $[M+3H]^{+3}$: 1741.8045 Found 1741.8064. Also observed 1306.6047 $[M+4H]^{+4}$ and 1045.4868 $[M+5H]^{+5}$.

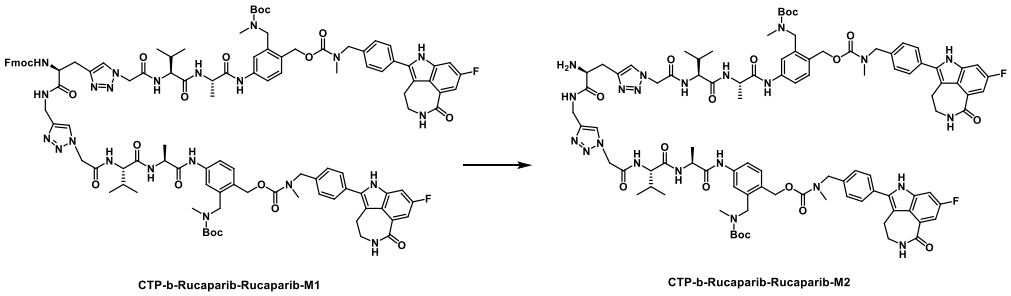
Synthesis of MTP3-Exatecan-Rucaparib-Rucaparib

1) Compound CTP-b-Rucaparib-Rucaparib-M1



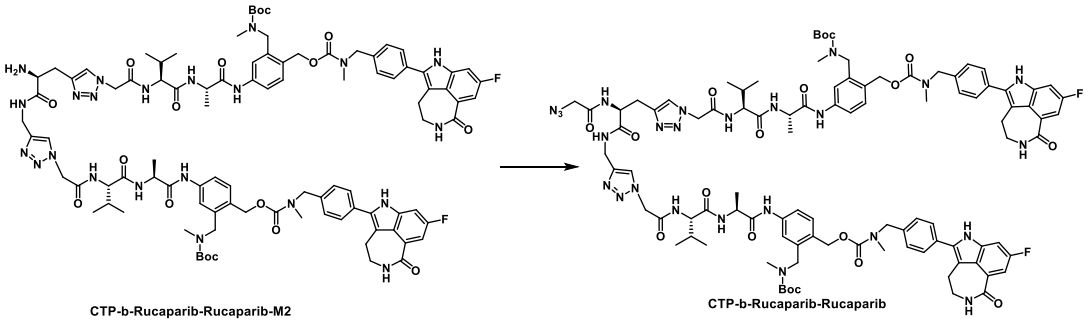
Compound CTP-b-Rucaparib-Rucaparib-M1 was synthesized following the previously established synthetic procedure of MTP3 series (step c). Purification was same as described above to afforded CTP-b-Rucaparib-Rucaparib-M1 (960 mg, 91%, 0.50 mmol scale) as a gray solid. MS (ESI): m/z calcd for $C_{111}H_{128}F_2N_{22}O_{19}$ $[M+2H]^{+2}$: 1055.5; found 1055.7.

2) Compound CTP-b-Rucaparib-Rucaparib-M2



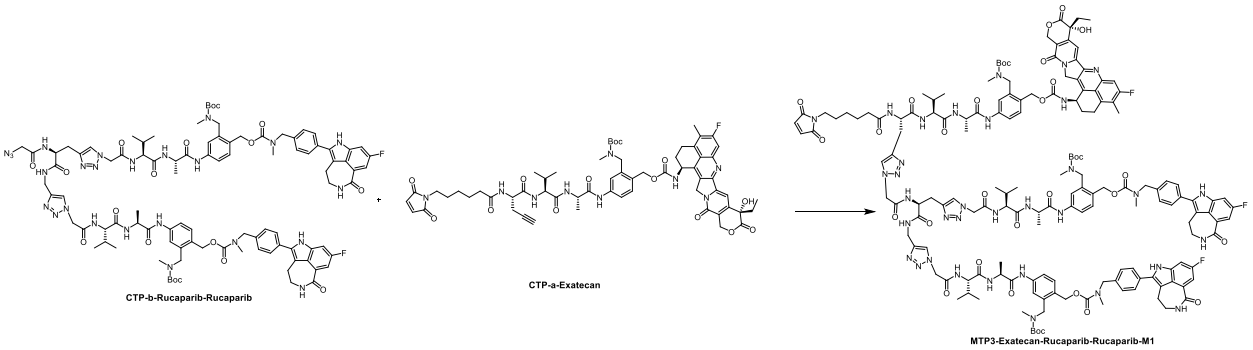
Compound CTP-b-Rucaparib-Rucaparib-M2 was synthesized following the previously established synthetic procedure of MTP3 series (step d). Purification was same as described above to afforded CTP-b-Rucaparib-Rucaparib-M2 (602 mg, 71%, 0.45 mmol scale) as a gray solid. MS (ESI): m/z calcd for $C_{96}H_{118}F_2N_{22}O_{17}$ $[M+2H]^{+2}$: 944.5; found 944.7.

3) Compound CTP-b-Rucaparib-Rucaparib



Compound CTP-b-Rucaparib-Rucaparib was synthesized following the previously established synthetic procedure of MTP3 series (step e). Purification was same as described above to afforded CTP-b-Rucaparib-Rucaparib (408 mg, 83%, 0.25 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{98}H_{119}F_2N_{25}O_{18}$ $[M+2H]^{+2}$: 986.0; found 986.3.

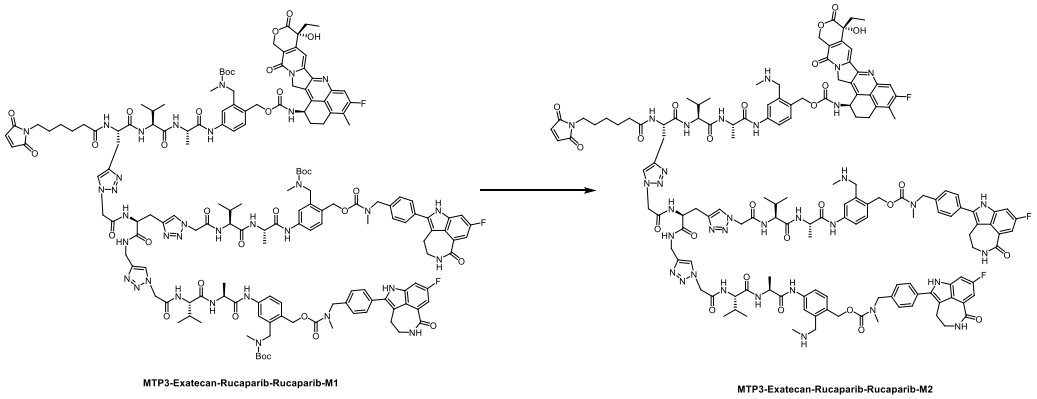
4) Compound MTP3-Exatecan-Rucaparib-Rucaparib-M1



Compound MTP3-Exatecan-Rucaparib-Rucaparib-M1 was synthesized following the previously established synthetic procedure of MTP3 series (step f). Purification was same as described above

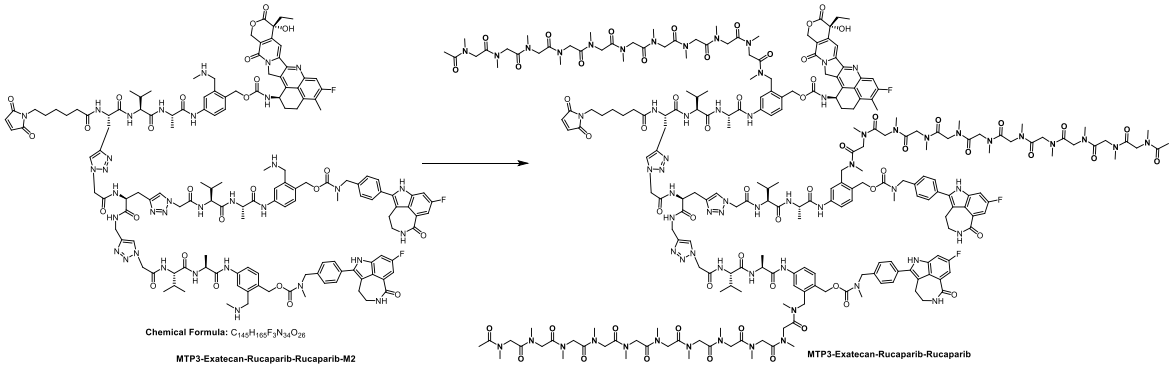
to afforded MTP3-Exatecan-Rucaparib-Rucaparib-M1 (418 mg, 87%, 0.15 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{160}H_{191}F_3N_{34}O_{32}$ $[M+2H]^{+2}$:1578.7; found 1579.1.

5) Compound MTP3-Exatecan-Rucaparib-Rucaparib-M2



Compound MTP3-Exatecan-Rucaparib-Rucaparib-M2 was synthesized following the previously established synthetic procedure of MTP3 series (step g). Purification was same as described above to afforded MTP3-Exatecan-Rucaparib-Rucaparib-M2 (200 mg, 100%, 0.063 mmol scale). MS (ESI): m/z calcd for $C_{145}H_{167}F_3N_{34}O_{26}$ $[M+2H]^{+2}$: 1428.6; found 1428.9.

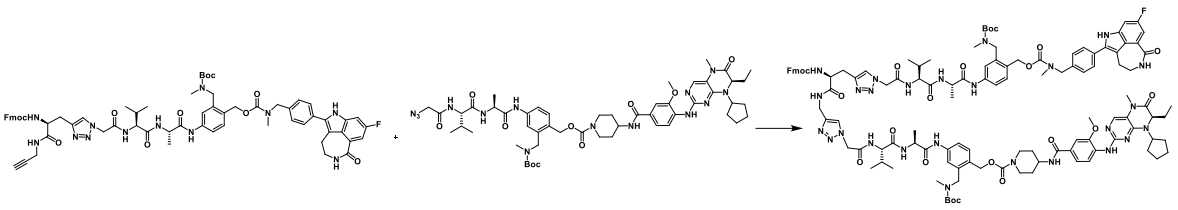
6) Compound MTP3-Exatecan-Rucaparib-Rucaparib



Compound MTP3-Exatecan-Rucaparib-Rucaparib was synthesized following the previously established synthetic procedure of MTP3 series (step h). Purification was same as described above to afforded MTP3-Exatecan-Rucaparib-Rucaparib (54.8 mg, 17%, 0.063 mmol scale). MS (ESI): m/z calcd for $C_{241}H_{324}F_3N_{64}O_{59}$ $[M+3H]^{+}$: 1705.1; found 1705.6.

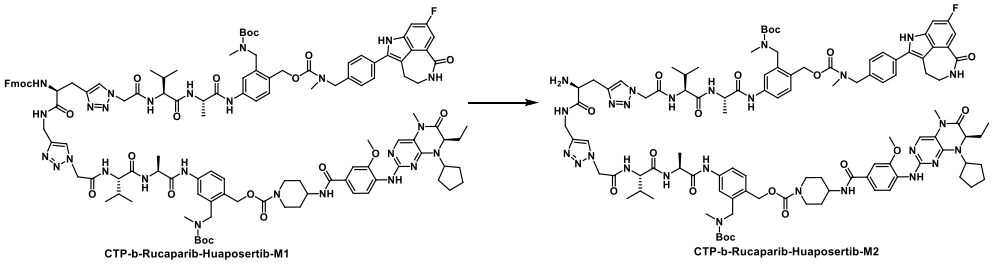
Synthesis of MTP3-Dinaciclib-Rucaparib-Huaposertib

1) Compound CTP-b-Rucaparib-Huaposertib-M1



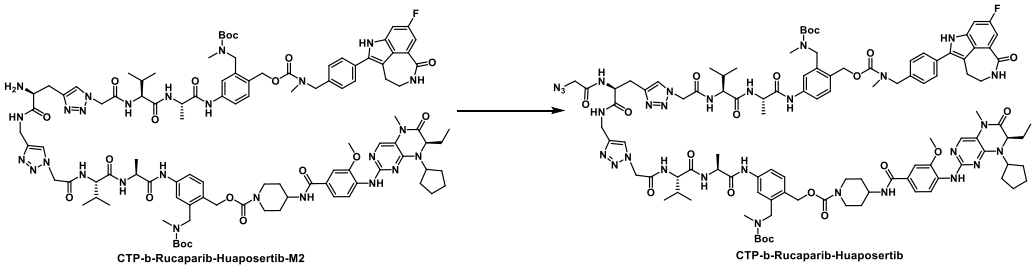
Compound CTP-b-Rucaparib-Huaposertib-M1 was synthesized following the previously established synthetic procedure of MTP3 series (step c). Purification was same as described above to afforded CTP-b-Rucaparib-Huaposertib-M1 (2.2 g, 70%, 1.368 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{119}H_{147}FN_{26}O_{21}$ $[M+2H]^{+2}$: 1147.6; found 1147.9.

2) Compound CTP-b-Rucaparib-Huaposertib-M2



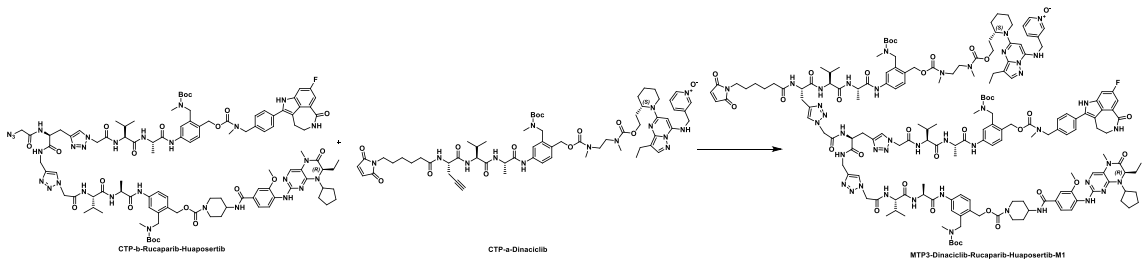
Compound CTP-b-Rucaparib-Huaposertib-M2 was synthesized following the previously established synthetic procedure of MTP3 series (step d). Purification was same as described above to afforded CTP-b-Rucaparib-Huaposertib-M2 (1.7 g, 85%, 0.96 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{104}H_{137}FN_{26}O_{19}$ $[M+2H]^{+2}$: 1036.5; found 1036.7.

3) Compound CTP-b-Rucaparib-Huaposertib



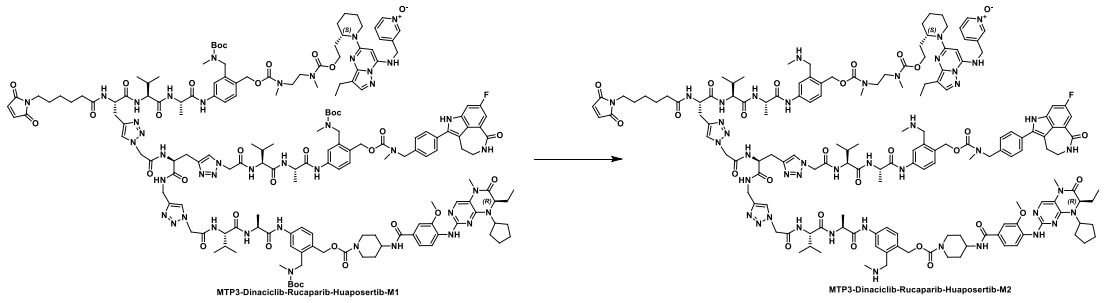
Compound CTP-b-Rucaparib-Huaposertib was synthesized following the previously established synthetic procedure of MTP3 series (step e). Purification was same as described above to afforded CTP-b-Rucaparib-Huaposertib (1.5 g, 90%, 0.77 mmol scale) as a gray solid. MS (ESI): m/z calcd for $C_{106}H_{138}FN_{29}O_{20}$ $[M+2H]^{+2}$: 1078.0; found 1078.2.

4) Compound MTP3-Dinaciclib-Rucaparib-Huaposertib-M1



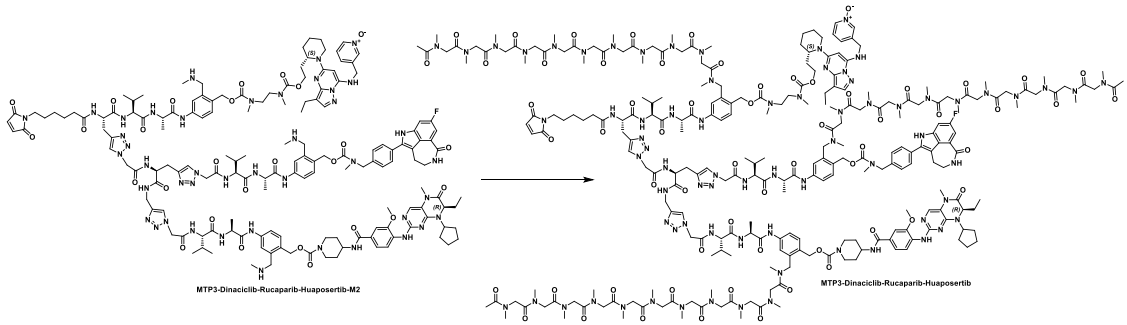
Compound MTP3-Dinaciclib-Rucaparib-Huaposertib-M1 was synthesized following the previously established synthetic procedure of MTP3 series (step f). Purification was same as described above to afforded MTP3-Dinaciclib-Rucaparib-Huaposertib-M1 (2.6g, 91%, 0.83 mmol scale) as a gray solid. MS (ESI): m/z calcd for $C_{170}H_{226}FN_{43}O_{33}$ $[M+2H]^{+2}$: 1708.3; found 1709.0.

5) Compound MTP3-Dinaciclib-Rucaparib-Huaposertib**-**M2



Compound MTP3-Dinaciclib-Rucaparib-Huaposertib-M2 was synthesized following the previously established synthetic procedure of MTP3 series (step g). Purification was same as described above to afforded MTP3-Dinaciclib-Rucaparib-Huaposertib-M2 (1.5 g, 100%, 0.44 mmol scale). MS (ESI): m/z calcd for $C_{155}H_{200}FN_{43}O_{27}$ $[M+2H]^{+2}$: 1558.3; found 1558.6.

6) Compound MTP3-Dinaciclib-Rucaparib-Huaposertib

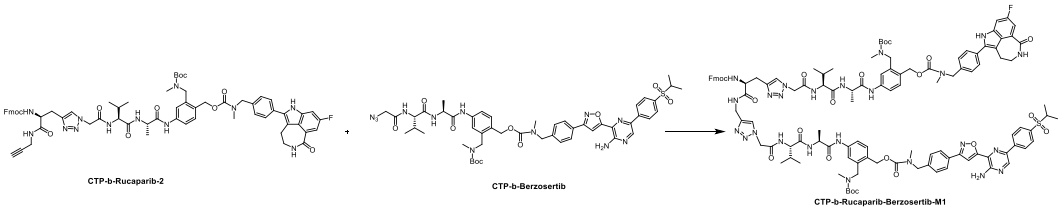


Compound MTP3-Dinaciclib-Rucaparib-Huaposertib was synthesized following the previously established synthetic procedure of MTP3 series (step h). Purification was same as described above to afforded MTP3-Dinaciclib-Rucaparib-Huaposertib (500 mg, 21%, 0.44 mmol scale) as a white

powder. HRMS (ESI-TOF): m/z calcd for $C_{251}H_{359}FN_{73}O_{60}$ $[M+3H]^{+3}$: 1791.5751 Found 1791.5771. Also observed 1343.9326 $[M+4H]^{+4}$ and 1075.3484 $[M+5H]^{+5}$.

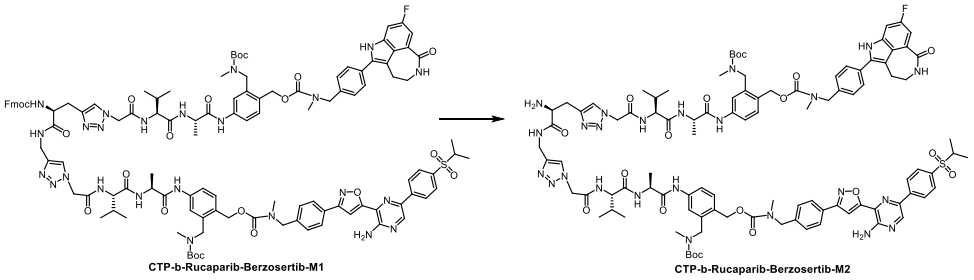
Synthesis of MTP3-Huaposertib-Rucaparib-Berzosertib

1) Compound CTP-b-Rucaparib-Berzosertib-M1



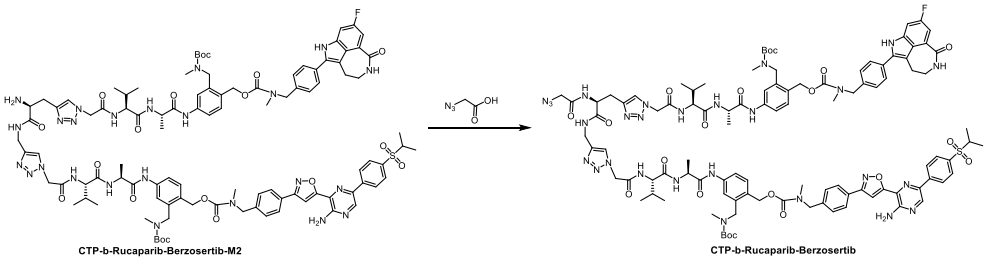
Compound CTP-b-Rucaparib-Berzosertib-M1 was synthesized following the previously established synthetic procedure of MTP3 series (step c). Purification was same as described above to afforded CTP-b-Rucaparib-Berzosertib-M1 (380 mg, 85%, 0.198 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{116}H_{133}FN_{24}Na_2O_{21}S$ $[M+2Na]^{+2}$: 1147.5; found 1147.4.

2) Compound CTP-b-Rucaparib-Berzosertib-M2



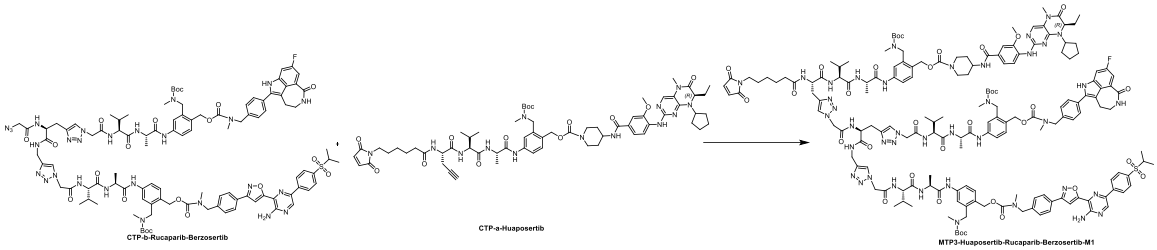
Compound CTP-b-Rucaparib-Berzosertib-M2 was synthesized following the previously established synthetic procedure of MTP3 series (step d). Purification was same as described above to afforded CTP-b-Rucaparib-Berzosertib-M2 (300 mg, 88%, 0.168 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{101}H_{125}FN_{24}O_{19}S$ $[M+2H]^{+2}$: 1014.5; found 1014.5.

3) Compound CTP-b-Rucaparib-Berzosertib



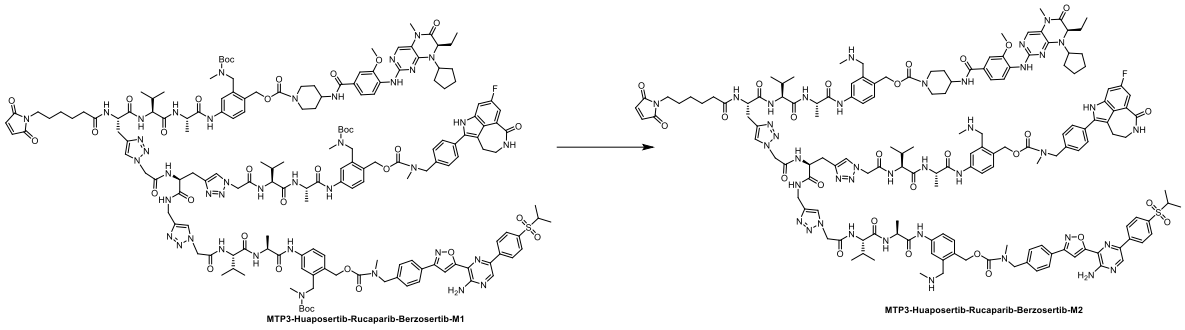
Compound CTP-b-Rucaparib-Berzosertib was synthesized following the previously established synthetic procedure of MTP3 series (step e). Purification was same as described above to afforded CTP-b-Rucaparib-Berzosertib (360 mg, 98%, 0.172 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{103}H_{124}FN_{27}Na_2O_{20}S$ $[M+2Na]^{+2}$: 1078.0; found 1078.4.

4) Compound MTP3-Huaposertib-Rucaparib-Berzosertib-M1



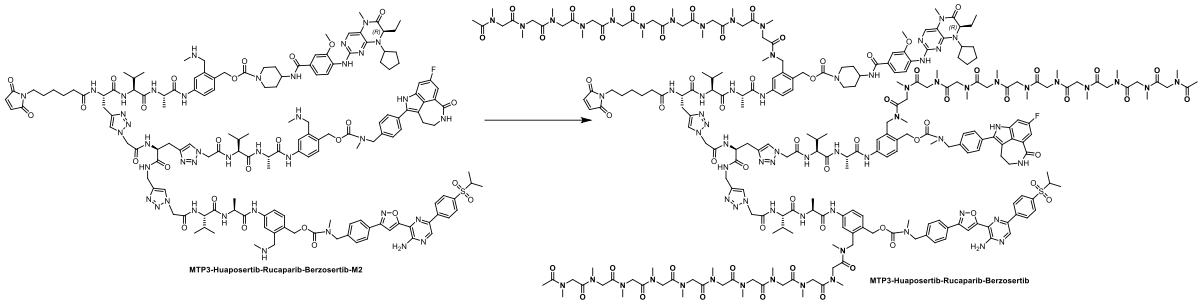
Compound MTP3-Huaposertib-Rucaparib-Berzosertib-M1 was synthesized following the previously established synthetic procedure of MTP3 series (step f). Purification was same as described above to afforded MTP3-Huaposertib-Rucaparib-Berzosertib-M1 (200 mg, 69%, 0.085 mmol scale) as a gray solid. MS (ESI): m/z calcd for $C_{168}H_{213}FN_{40}O_{33}S$ $[M+2H]^{+2}$: 1684.8; found 1685.6.

5) Compound MTP3-Huaposertib-Rucaparib-Berzosertib-M2



Compound MTP3-Huaposertib-Rucaparib-Berzosertib-M2was synthesized following the previously established synthetic procedure of MTP3 series (step g). Purification was same as described above to afforded MTP3-Huaposertib-Rucaparib-Berzosertib-M2 (200 mg, 100%, 0.059 mmol scale). MS (ESI): m/z calcd for $C_{153}H_{189}FN_{40}O_{27}S$ $[M+2H]^{+2}$: 1534.7; found 1535.1.

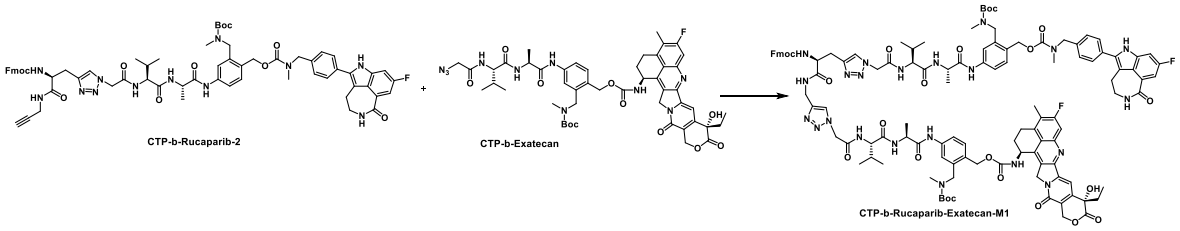
6) Compound MTP3-Huaposertib-Rucaparib-Berzosertib



Compound MTP3-Huaposertib-Rucaparib-Berzosertib was synthesized following the previously established synthetic procedure of MTP3 series (step h). Purification was same as described above to afforded MTP3-Huaposertib-Rucaparib-Berzosertib (500 mg, 21%, 0.44 mmol scale) as a yellow powder. HRMS (ESI-TOF): m/z calcd for $C_{249}H_{346}FN_{70}O_{60}S$ $[M+3H]^{+3}$: 1775.8621 Found 1775.8608. Also observed 1332.1456 $[M+4H]^{+4}$ and 1065.9199 $[M+5H]^{+5}$.

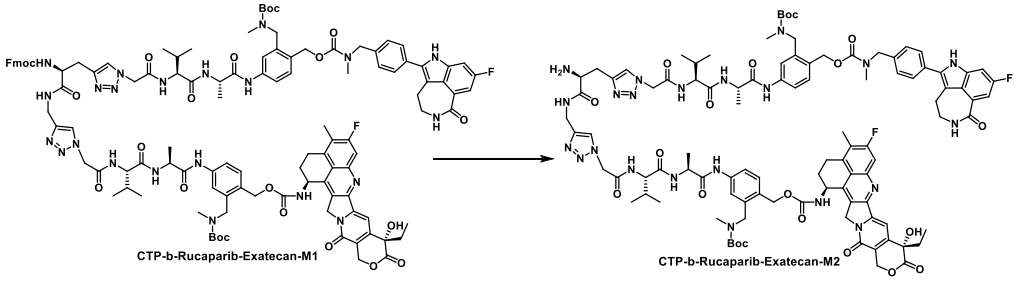
Synthesis of MTP3-Smol006-Rucaparib-Exatecan

1) Compound CTP-b-Rucaparib-Exatecan-M1



Compound CTP-b-Rucaparib-Exatecan-M1 was synthesized following the previously established synthetic procedure of MTP3 series (step c). Purification was same as described above to afforded CTP-b-Rucaparib-Exatecan-M1 (1.3 g, 81%, 0.73 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{116}H_{132}F_2N_{22}O_{22}$ $[M+2H]^{+2}$: 1111.5; found 1111.8.

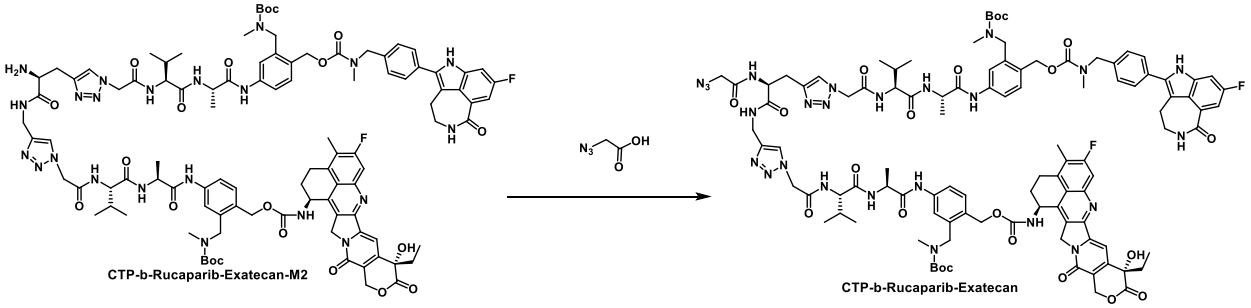
2) Compound CTP-b-Rucaparib-Exatecan-M2



Compound CTP-b-Rucaparib-Exatecan-M2 was synthesized following the previously established synthetic procedure of MTP3 series (step d). Purification was same as described above to afforded

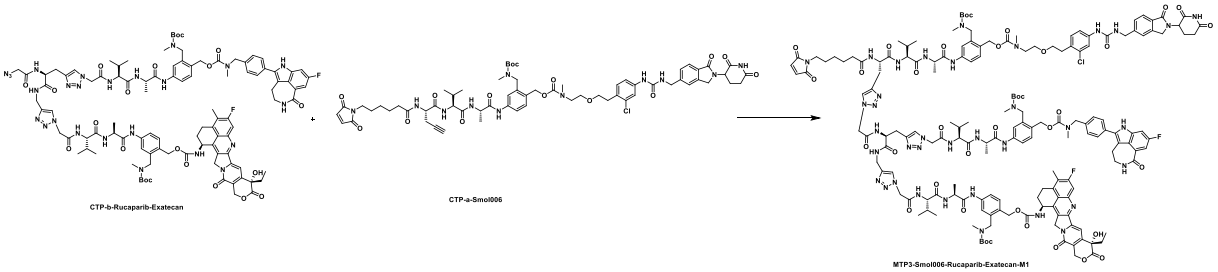
CTP-b-Rucaparib-Exatecan-M2 (700 mg, 60%, 0.59 mmol scale) as a gray solid. MS (ESI): m/z calcd for $C_{101}H_{122}F_2N_{22}O_{20}$ $[M+2H]^{+2}$: 1000.5; found 1000.8.

3) Compound CTP-b-Rucaparib-Exatecan



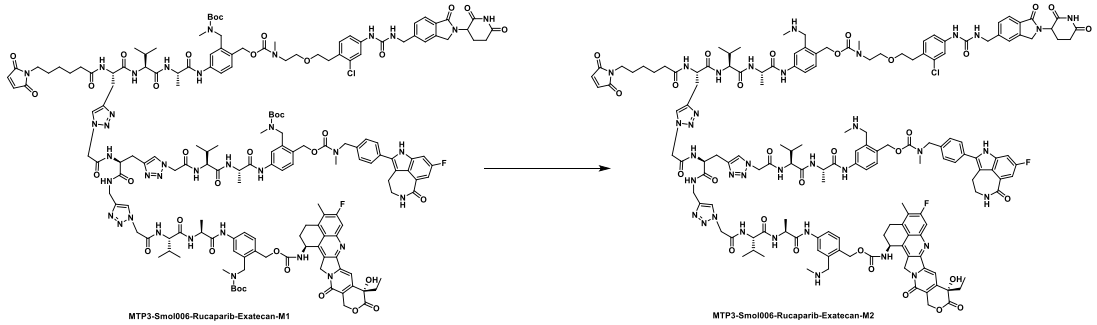
Compound CTP-b-Rucaparib-Exatecan was synthesized following the previously established synthetic procedure of MTP3 series (step e). Purification was same as described above to afforded CTP-b-Rucaparib-Exatecan (600 mg, 82%, 0.35 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{103}H_{123}F_2N_{25}O_{21}$ $[M+2H]^{+2}$: 1042.0; found 1042.3.

4) Compound MTP3-Smol006-Rucaparib-Exatecan-M1



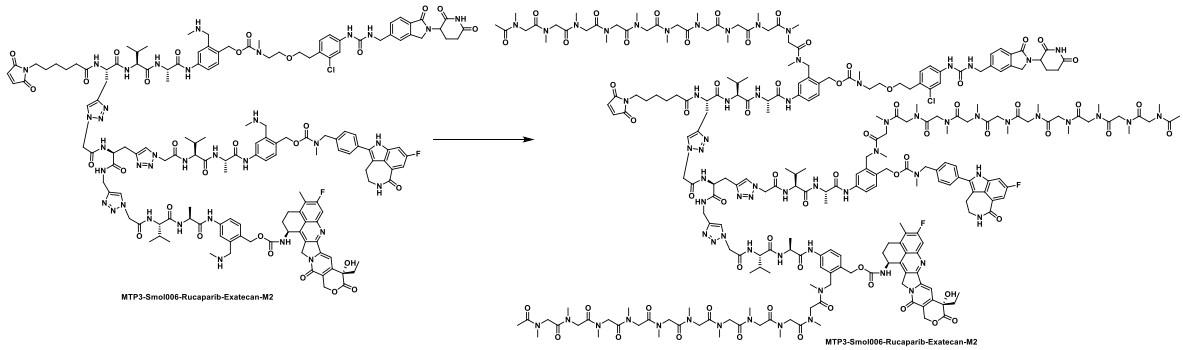
Compound MTP3-Smol006-Rucaparib-Exatecan-M1 was synthesized following the previously established synthetic procedure of MTP3 series (step f). Purification was same as described above to afforded MTP3-Smol006-Rucaparib-Exatecan-M1 (230 mg, 89%, 0.077 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{167}H_{203}ClF_2N_{36}O_{36}$ $[M+2H]^{+2}$: 1680.7; found 1681.7.

5) Compound MTP3-Smol006-Rucaparib-Exatecan-M2



Compound MTP3-Smol006-Rucaparib-Exatecan-M2 was synthesized following the previously established synthetic procedure of MTP3 series (step g). Purification was same as described above to afforded MTP3-Smol006-Rucaparib-Exatecan-M2 (230 mg, 100%, 0.068 mmol scale). MS (ESI): m/z calcd for $C_{152}H_{179}ClF_2N_{36}O_{30}$ $[M+2H]^{+2}$: 1530.7; found 1531.1.

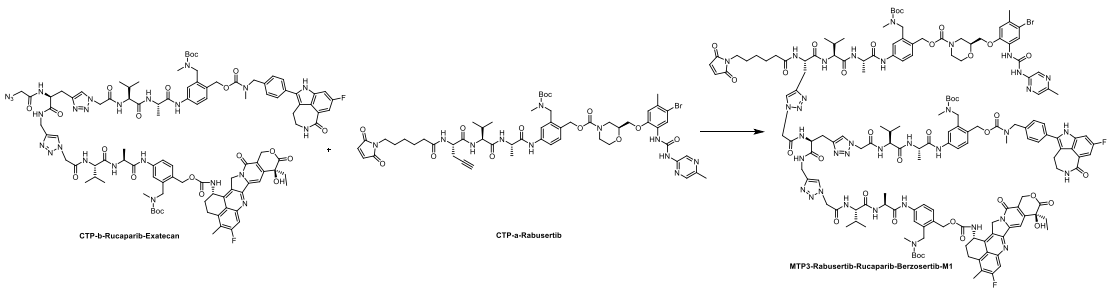
6) Compound MTP3-Smol006-Rucaparib-Exatecan



Compound MTP3-Smol006-Rucaparib-Exatecan was synthesized following the previously established synthetic procedure of MTP3 series (step h). Purification was same as described above to afforded MTP3-Smol006-Rucaparib-Exatecan (80 mg, 22%, 0.068 mmol scale) as a yellow powder. HRMS (ESI-TOF): m/z calcd for $C_{248}H_{336}ClF_2N_{66}O_{63}$ $[M+3H]^{+3}$: 1773.1586 Found 1773.1549. Also observed 1330.1198 $[M+4H]^{+4}$ and 1064.2948 $[M+5H]^{+5}$.

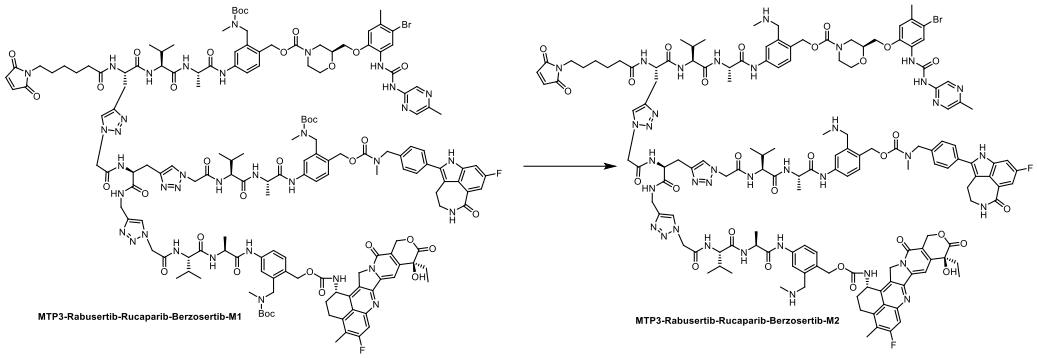
Synthesis of MTP3-Rabusertib-Rucaparib-Exatecan

1) Compound MTP3-Rabusertib-Rucaparib-Exatecan-M1



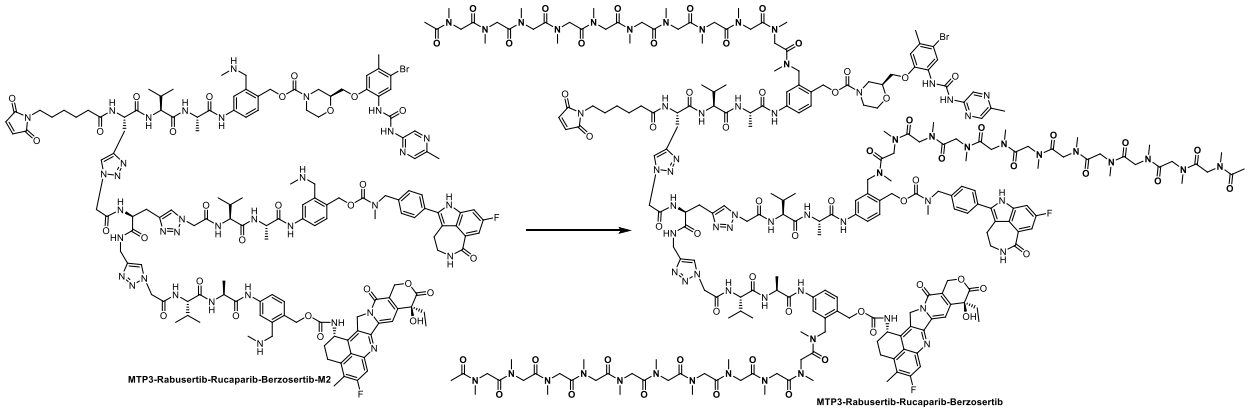
Compound MTP3-Rabusertib-Rucaparib-Exatecan-M1 was synthesized following the previously established synthetic procedure of MTP3 series (step f). Purification was same as described above to afforded MTP3-Rabusertib-Rucaparib-Exatecan-M1 (700 mg, 94%, 0.227 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{159}H_{195}BrF_2N_{36}O_{34}$ $[M+2H]^{+2}$: 1634.7; found 1634.9.

2) Compound MTP3- MTP3-Rabusertib-Rucaparib-Exatecan-M2



Compound MTP3-Rabusertib-Rucaparib-Exatecan-M2 was synthesized following the previously established synthetic procedure of MTP3 series (step g). Purification was same as described above to afforded MTP3-Rabusertib-Rucaparib-Exatecan-M2 (600 mg, 100%, 0.183 mmol scale). MS (ESI): m/z calcd for $C_{144}H_{171}BrF_2N_{36}O_{28}$ $[M+2H]^{+2}$: 1484.6; found 1485.4.

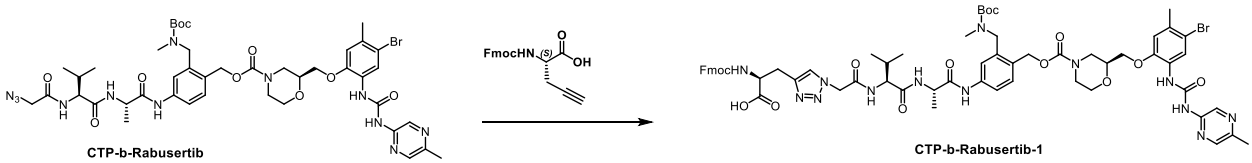
3) Compound MTP3-Rabusertib-Rucaparib-Exatecan



Compound MTP3-Rabusertib-Rucaparib-Exatecan was synthesized following the previously established synthetic procedure of MTP3 series (step h). Purification was same as described above to afforded MTP3-Rabusertib-Rucaparib-Exatecan (180 mg, 19%, 0.183 mmol scale) as a white powder. HRMS (ESI-TOF): m/z calcd for $C_{240}H_{328}BrF_2N_{66}O_{61}$ $[M+3H]^{+3}$: 1742.4576 Found 1742.4598. Also observed 1307.0953 $[M+4H]^{+4}$ and 1045.8774 $[M+5H]^{+5}$.

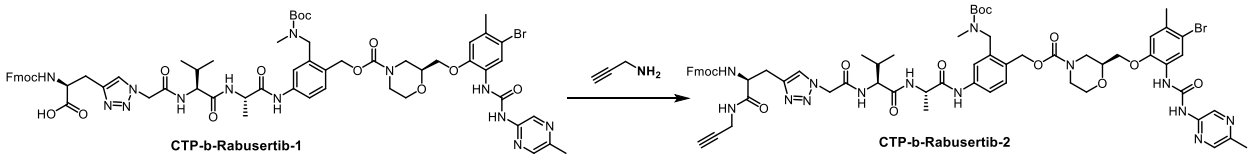
Synthesis of MTP3-Huavosertib-Rabusertib-Belotecan

1) Compound CTP-b-Rabusertib-1



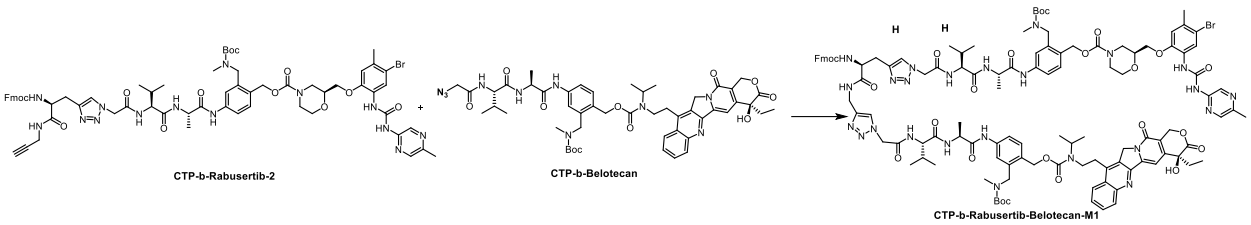
Compound CTP-b-Rabusertib-1 was synthesized following the previously established synthetic procedure of MTP3 series (step a). Purification was same as described above to afforded CTP-b-Rabusertib-1 (609 mg, 89%, 0.519 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{63}H_{75}BrN_{13}O_{14}$ $[M+H]^+$: 1316.5; found 1316.4.

2) Compound CTP-b-Rabusertib-2



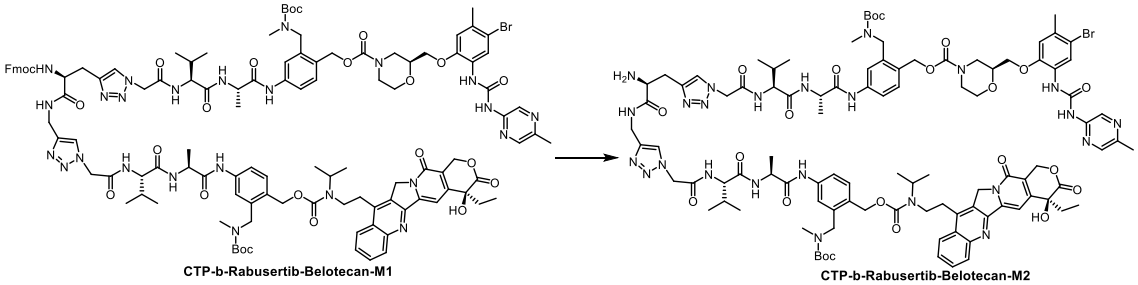
Compound CTP-b-Rabusertib-2 was synthesized following the previously established synthetic procedure of MTP3 series (step b). Purification was same as described above to afforded CTP-b-Rabusertib-2 (480 mg, 70%, 0.51 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{66}H_{78}BrN_{14}O_{13}$ $[M+H]^+$: 1353.5; found 1354.3.

3) Compound CTP-b-Rabusertib-Belotecan-M1



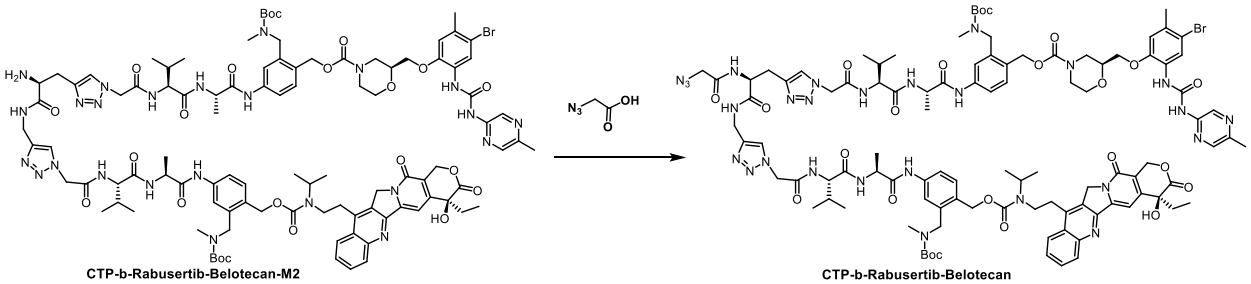
Compound CTP-b-Rabusertib-Belotecan-M1 was synthesized following the previously established synthetic procedure of MTP3 series (step c). Purification was same as described above to afforded CTP-b-Rabusertib-Belotecan-M1 (666 mg, 86%, 0.33 mmol scale) as a brown solid. MS (ESI): m/z calcd for $C_{116}H_{141}BrN_{24}O_{24}$ $[M+2H]^{+2}$: 1166.5; found 1167.4.

4) Compound CTP-b-Rabusertib-Belotecan-M2



Compound CTP-b-Rabusertib-Belotecan-M2 was synthesized following the previously established synthetic procedure of MTP3 series (step d). Purification was same as described above to afforded CTP-b-Rabusertib-Belotecan-M2 (430 mg, 72%, 0.28 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{101}H_{131}BrN_{24}O_{22}$ $[M+2H]^{+2}$: 1055.5; found 1056.3.

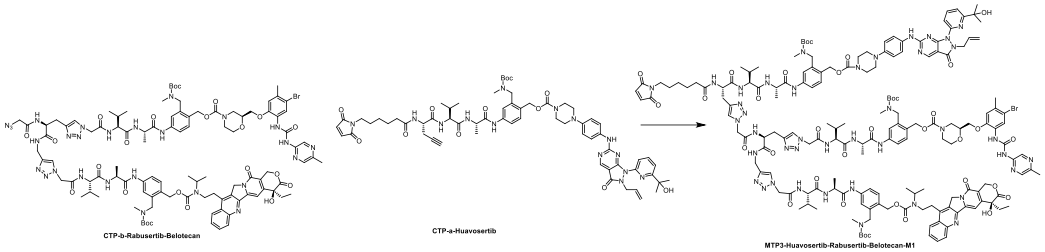
5) Compound CTP-b-Rabusertib-Belotecan



Compound CTP-b-Rabusertib-Belotecan was synthesized following the previously established synthetic procedure of MTP3 series (step e). Purification was same as described above to afforded

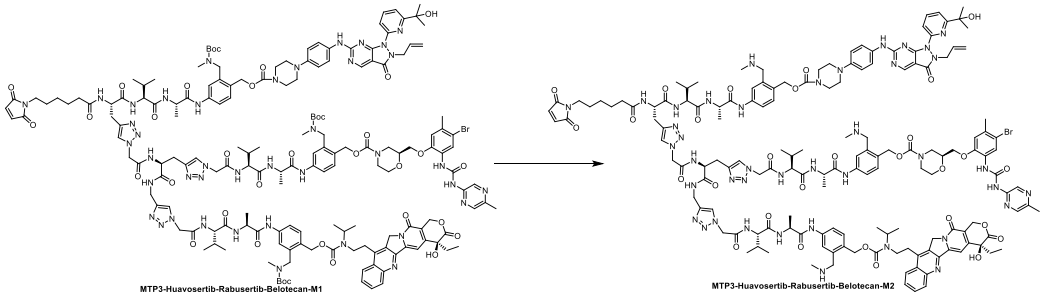
CTP-b-Rabusertib-Belotecan (290 mg, 66%, 0.20 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{103}H_{132}BrN_{27}O_{23}$ $[M+2H]^{+2}$: 1097.0; found 1097.6.

6) Compound MTP3-Huavosertib-Rabusertib-Belotecan-M1



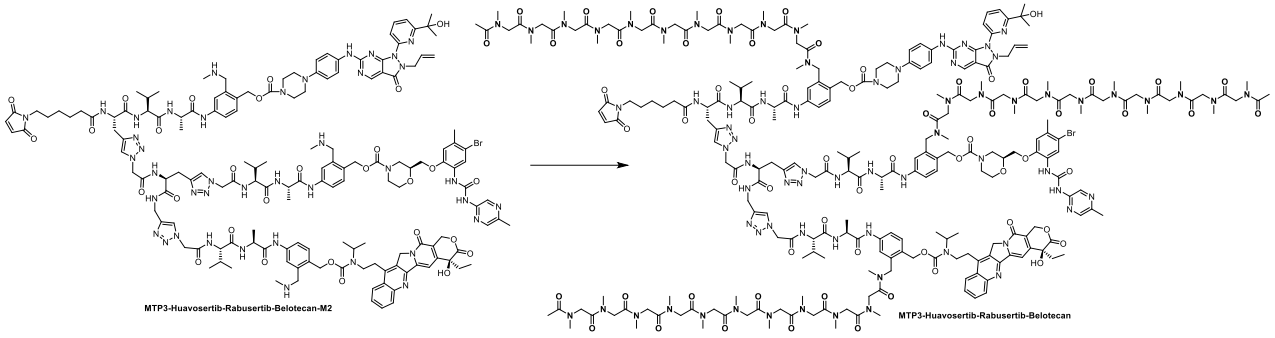
Compound MTP3-Huavosertib-Rabusertib-Belotecan-M1 was synthesized following the previously established synthetic procedure of MTP3 series (step f). Purification was same as described above to afforded MTP3-Huavosertib-Rabusertib-Belotecan-M1 (125 mg, 81%, 0.045 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{167}H_{210}BrN_{41}Na_2O_{35}$ $[M+2Na]^{+2}$: 1737.2; found 1737.0.

7) Compound MTP3-Huavosertib-Rabusertib-Belotecan-M2



Compound MTP3-Huavosertib-Rabusertib-Belotecan-M2 was synthesized following the previously established synthetic procedure of MTP3 series (step g). Purification was same as described above to afforded MTP3-Huavosertib-Rabusertib-Belotecan-M2 (125 mg, 100%, 0.036 mmol scale) as a tan solid. MS (ESI): m/z calcd for $C_{152}H_{188}BrN_{41}O_{29}$ $[M+2H]^{+2}$: 1565.2; found 1565.6.

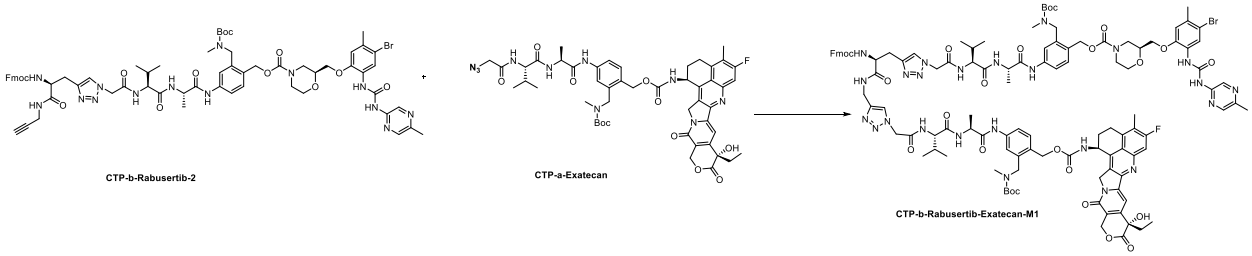
8) Compound MTP3-Huavosertib-Rabusertib-Belotecan



Compound MTP3-Huavosertib-Rabusertib-Belotecan was synthesized following the previously established synthetic procedure of MTP3 series (step h). Purification was same as described above to afforded MTP3-Huavosertib-Rabusertib-Belotecan (44.3 mg, 23%, 0.036 mmol scale) as a tan solid. HRMS (ESI-TOF): m/z calcd for $C_{248}H_{345}BrN_{71}O_{62}$ $[M+3H]^{+3}$: 1796.1731 Found 1796.1718. Also observed 1347.3813 $[M+4H]^{+4}$ and 1078.1066 $[M+5H]^{+5}$.

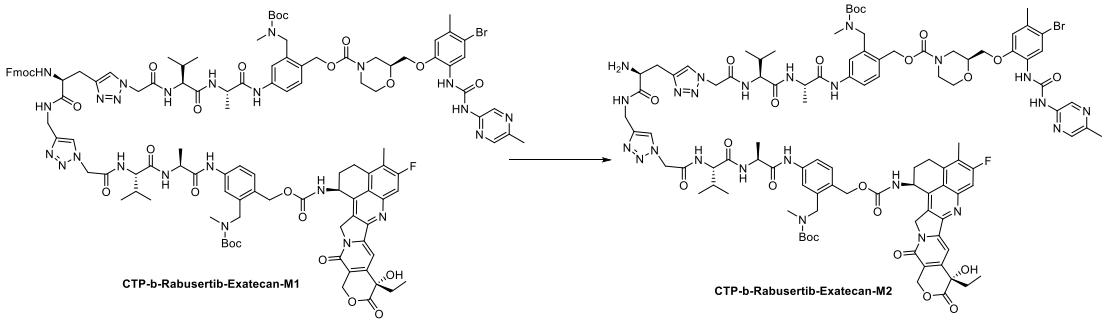
Synthesis of MTP3-Huavosertib-Rabusertib-Exatecan

1) Compound CTP-b-Rabusertib-Exatecan-M1



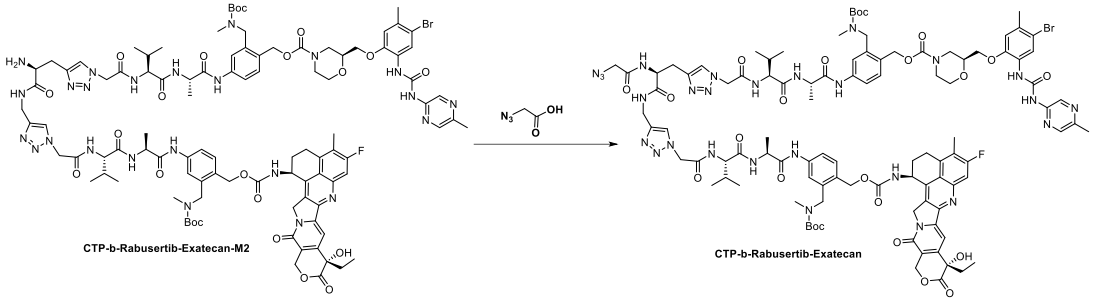
Compound CTP-b-Rabusertib-Exatecan-M1 was synthesized following the previously established synthetic procedure of MTP3 series (step c). Purification was same as described above to afforded CTP-b-Rabusertib-Exatecan-M1 (280 mg, 80%, 0.15 mmol scale) as a brown solid. MS (ESI): m/z calcd for $C_{115}H_{136}BrFN_{24}O_{24}$ $[M+2H]^{+2}$: 1167.5; found 1168.0.

2) Compound CTP-b-Rabusertib-Exatecan-M2



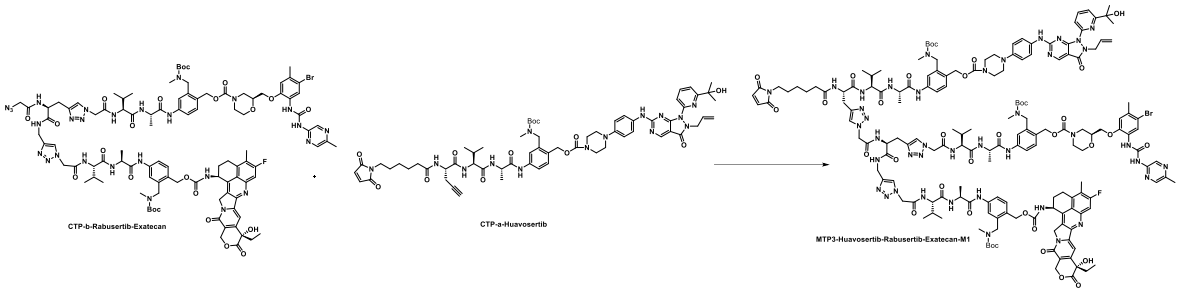
Compound CTP-b-Rabusertib-Exatecan-M2 was synthesized following the previously established synthetic procedure of MTP3 series (step d). Purification was same as described above to afforded CTP-b-Rabusertib-Exatecan-M2 (180 mg, 71%, 0.12 mmol scale) as a gray solid. MS (ESI): m/z calcd for $C_{100}H_{126}BrFN_{24}O_{22}$ $[M+2H]^{+2}$: 1056.4; found 1057.3.

3) Compound CTP-b-Rabusertib-Exatecan



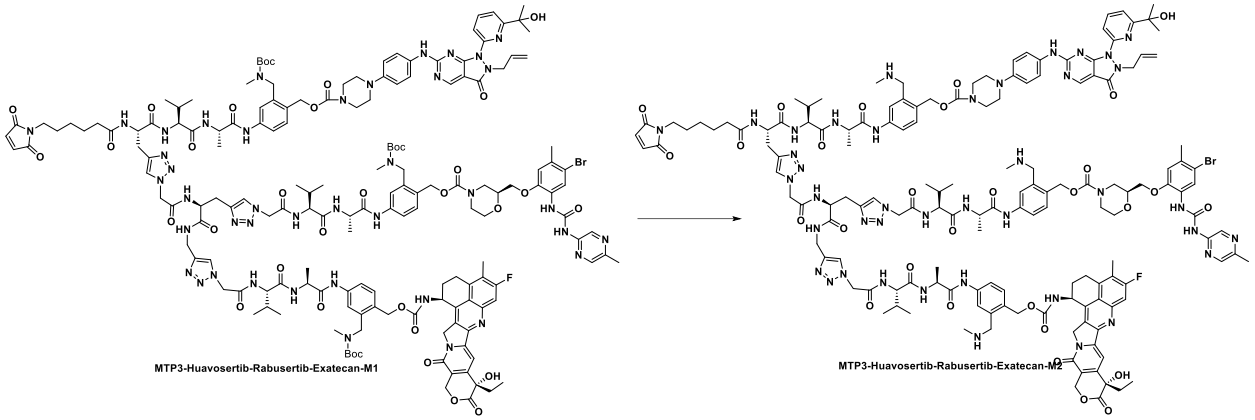
Compound CTP-b-Rabusertib-Exatecan was synthesized following the previously established synthetic procedure of MTP3 series (step e). Purification was same as described above to afforded CTP-b-Rabusertib-Exatecan (170 mg, 66%, 0.085 mmol scale) as a green solid. MS (ESI): m/z calcd for $C_{102}H_{127}BrFN_{27}O_{23}$ $[M+2H]^{+2}$: 1097.9; found 1098.6.

4) Compound MTP3-Huavosertib-Rabusertib-Exatecan-M1



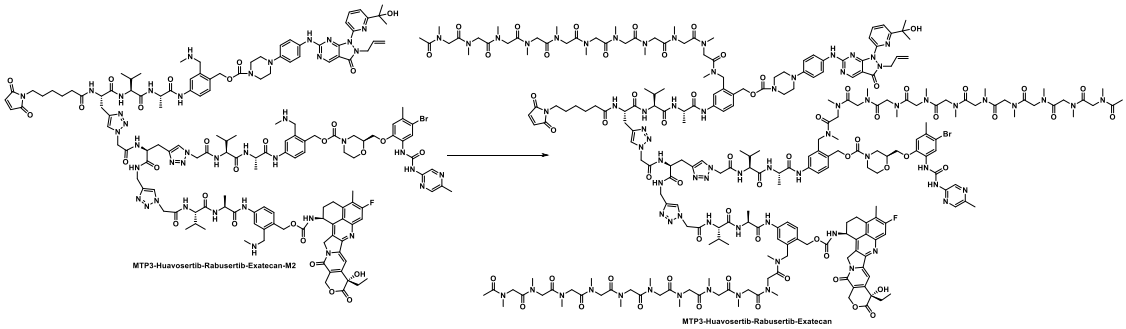
Compound MTP3-Huavosertib-Rabusertib-Exatecan-M1 was synthesized following the previously established synthetic procedure of MTP3 series (step f). Purification was same as described above to afforded MTP3-Huavosertib-Rabusertib-Exatecan-M1 (220 mg, 83%, 0.077 mmol scale) as a green solid. MS (ESI): m/z calcd for $C_{166}H_{208}BrFN_{41}O_{35}$ $[M+3H]^{+3}$: 1144.5; found 1145.3.

5) Compound MTP3-Huavosertib-Rabusertib-Exatecan-M2



Compound MTP3-Huavosertib-Rabusertib-Exatecan-M2 was synthesized following the previously established synthetic procedure of MTP3 series (step g). Purification was same as described above to afforded MTP3-Huavosertib-Rabusertib-Exatecan-M2 (220 mg, 100%, 0.064 mmol scale) as a tan solid. MS (ESI): m/z calcd for $C_{151}H_{184}BrFN_{41}O_{29}$ $[M+3H]^{+3}$: 1044.4; found 1045.1.

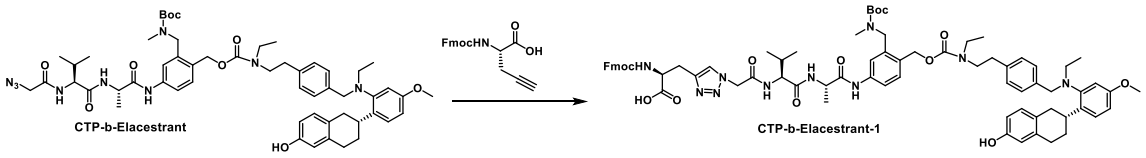
6) Compound MTP3-Huavosertib-Rabusertib-Exatecan



Compound MTP3-Huavosertib-Rabusertib-Exatecan was synthesized following the previously established synthetic procedure of MTP3 series (step h). Purification was same as described above to afforded MTP3-Huavosertib-Rabusertib-Exatecan (74.2 mg, 22%, 0.064 mmol scale) as a yellow powder. HRMS (ESI-TOF): m/z calcd for $C_{248}H_{348}BrN_{71}O_{59}$ $[M+3H]^{+3}$: HRMS (ESI-TOF): m/z calcd for $C_{247}H_{340}BrFN_{71}O_{62}$ $[M+3H]^{+3}$: 1796.8262 Found 1796.8228. Also observed 1347.8698 $[M+4H]^{+4}$ and 1078.4960 $[M+5H]^{+5}$.

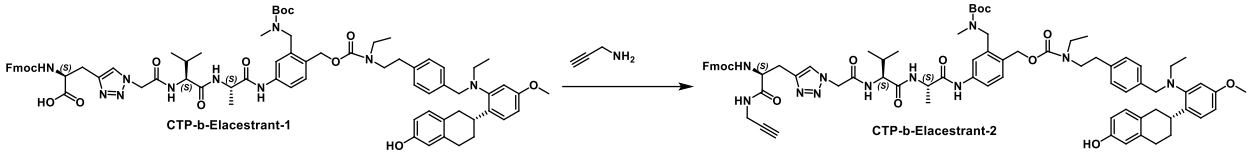
Synthesis of MTP3-Palbociclib-Elacestrant-Hualisib

1) Compound CTP-b-Elacestrant-1



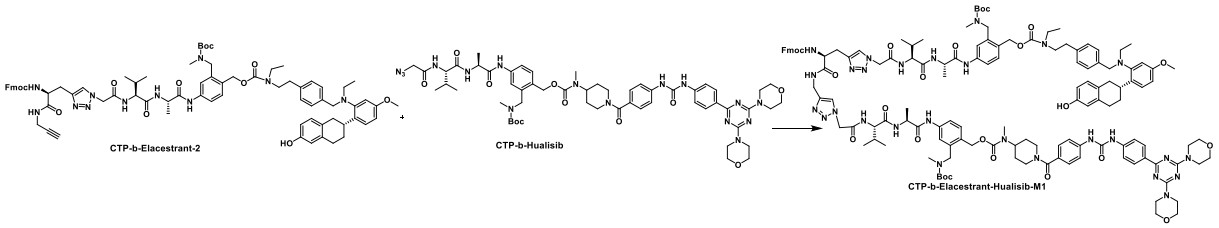
Compound CTP-b-Elacestrant-1 was synthesized following the previously established synthetic procedure of MTP3 series (step a). Purification was same as described above to afforded CTP-b-Elacestrant-1 (375 mg, 80%, 0.35 mmol scale) as a gray solid. MS (ESI): m/z calcd for $C_{75}H_{91}N_{10}O_{13}$ $[M+H]^+$: 1339.7; found 1339.6.

2) Compound CTP-b-Elacestrant-2



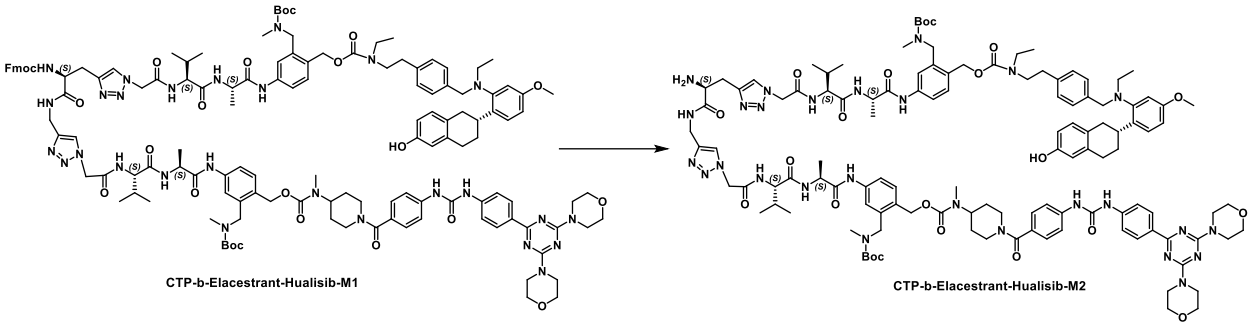
Compound CTP-b-Elacestrant-2 was synthesized following the previously established synthetic procedure of MTP3 series (step b). Purification was same as described above to afforded CTP-b-Elacestrant-2 (289 mg, 80%, 0.28 mmol scale) as a gray solid. MS (ESI): m/z calcd for $C_{78}H_{94}N_{11}O_{12}$ $[M+H]^+$: 1376.7; found 1377.6.

3) Compound CTP-b-Elacestrant-Hualisib-M1



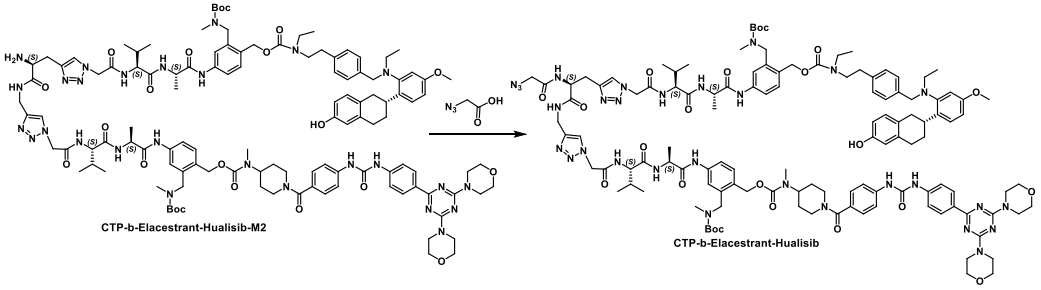
Compound CTP-b-Elacestrant-Hualisib-M1 was synthesized following the previously established synthetic procedure of MTP3 series (step c). Purification was same as described above to afforded CTP-b-Elacestrant-Hualisib-M1 (366 mg, 73%, 0.20 mmol scale) as a brown solid. MS (ESI): m/z calcd for $C_{134}H_{169}N_{27}O_{23}$ $[M+2H]^{+2}$: 1262.1; found 1262.6.

4) Compound CTP-b-Elacestrant-Hualisib-M2



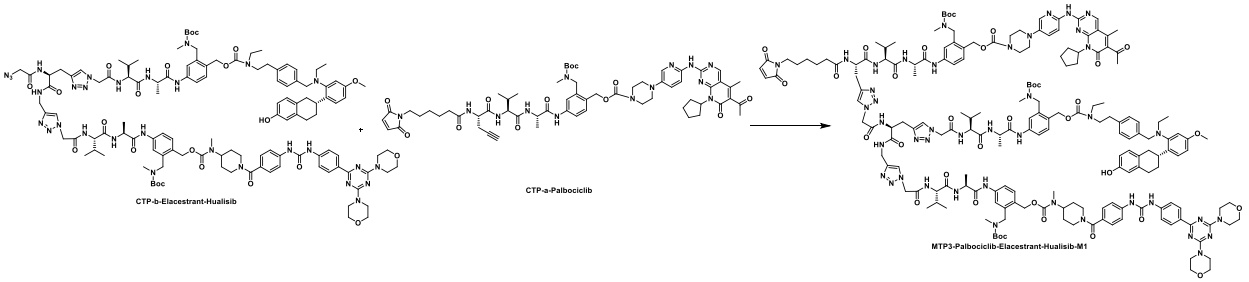
Compound CTP-b-Elacestrant-Hualisib-M2 was synthesized following the previously established synthetic procedure of MTP3 series (step d). Purification was same as described above to afforded CTP-b-Elacestrant-Hualisib-M2 (250 mg, 75%, 0.15 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{119}H_{159}N_{27}O_{21}$ $[M+2H]^{+2}$: 1151.1; found 1500.9.

5) Compound CTP-b-Elacestrant-Hualisib



Compound CTP-b-Elacestrant-Hualisib was synthesized following the previously established synthetic procedure of MTP3 series (step e). Purification was same as described above to afforded CTP-b-Elacestrant-Hualisib (142 mg, 55%, 0.11 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{121}H_{160}N_{30}O_{22}$ $[M+2H]^{+2}$: 1192.6; found 1193.1.

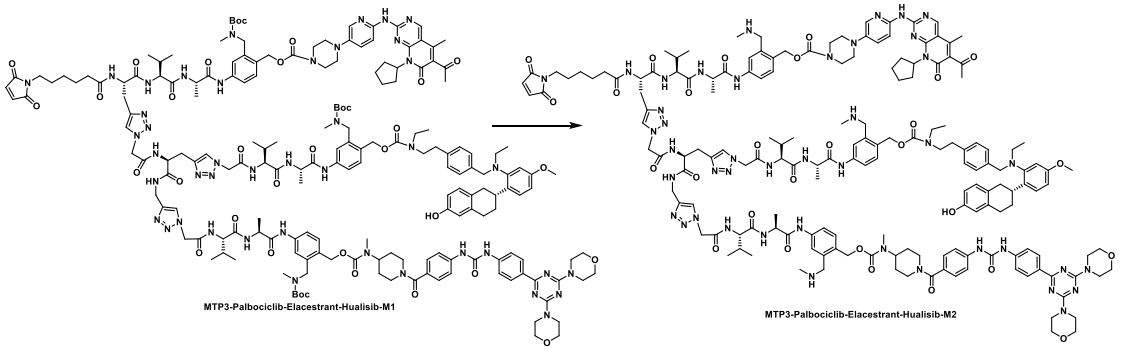
6) Compound MTP3-Palbociclib-Elacestrant-Hualisib-M1



Compound MTP3-Palbociclib-Elacestrant-Hualisib-M1 was synthesized following the previously established synthetic procedure of MTP3 series (step f). Purification was same as described above

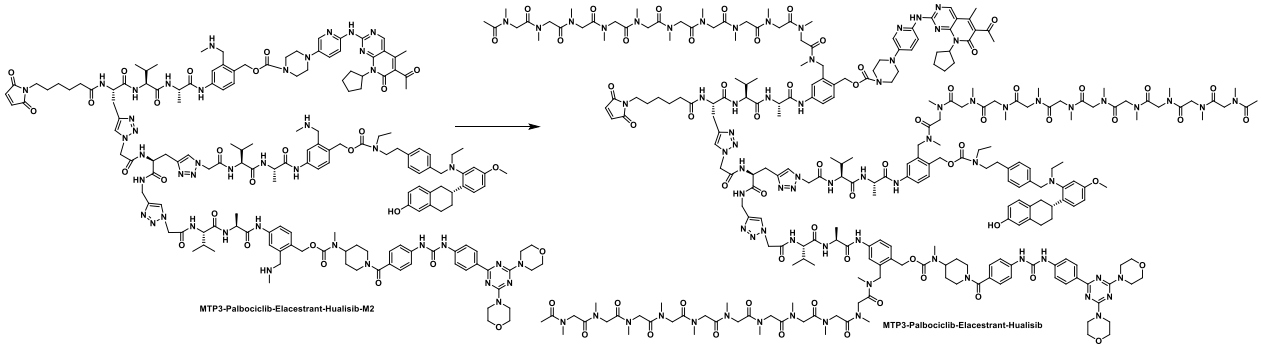
to afforded MTP3-Palbociclib-Elacestrant-Hualisib-M1 (170 mg, 80%, 0.06 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{183}H_{240}N_{43}O_{34}$ $[M+3H]^{+3}$: 1194.6; found 1195.1.

7) Compound MTP3-Palbociclib-Elacestrant-Hualisib-M2



Compound MTP3-Palbociclib-Elacestrant-Hualisib-M2 was synthesized following the previously established synthetic procedure of MTP3 series (step g). Purification was same as described above to afforded MTP3-Palbociclib-Elacestrant-Hualisib-M2 (170 mg, 100%, 0.047 mmol scale). MS (ESI): m/z calcd for $C_{168}H_{215}N_{43}O_{28}$ $[M+2H]^{+2}$: 1641.3; found 1641.3.

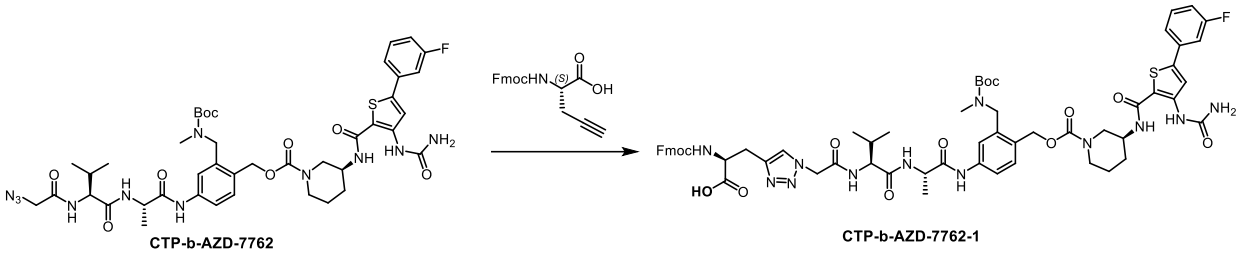
8) Compound MTP3-Palbociclib-Elacestrant-Hualisib



Compound MTP3-Palbociclib-Elacestrant-Hualisib was synthesized following the previously established synthetic procedure of MTP3 series (step g). Purification was same as described above to afforded MTP3-Palbociclib-Elacestrant-Hualisib (51 mg, 20%, 0.047 mmol scale) as a yellow powder. HRMS (ESI-TOF): m/z calcd for C265H371N73O61 $[M+3H]^{+3}$: HRMS (ESI-TOF): m/z calcd for $C_{264}H_{372}N_{73}O_{61}$ $[M+3H]^{+3}$: 1846.9412 Found 1846.9447. Also observed 1385.4579 $[M+4H]^{+4}$, 1108.5681 $[M+5H]^{+5}$ and 923.9724 $[M+6H]^{+6}$.

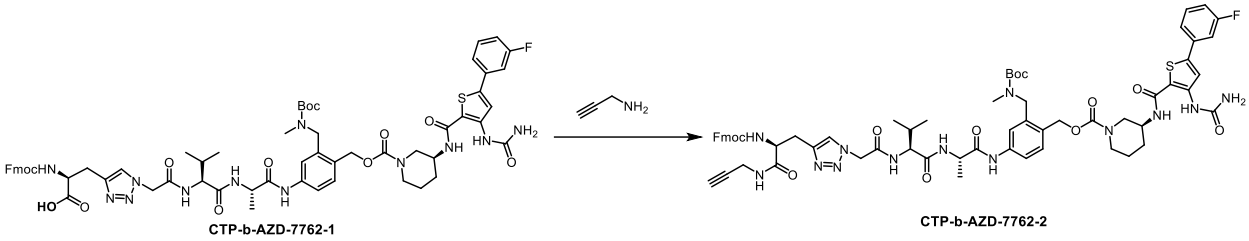
Synthesis of MTP3-Huaosertib-AZD-7762-Belotecan

1) Compound CTP-b-AZD-7762-1



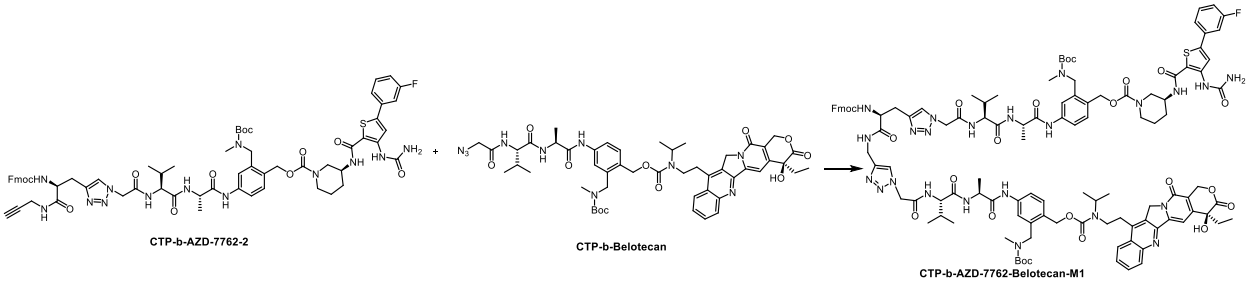
Compound CTP-b-AZD-7762-1 was synthesized following the previously established synthetic procedure of MTP3 series (step a). Purification was same as described above to afforded CTP-b-AZD-7762-1 (594 mg, 87%, 0.55 mmol scale) as a gray solid. MS (ESI): m/z calcd for $C_{62}H_{71}FN_{12}NaO_{13}S$ $[M+H]^+$: 1265.5; found 1266.3.

2) Compound CTP-b-AZD-7762-2



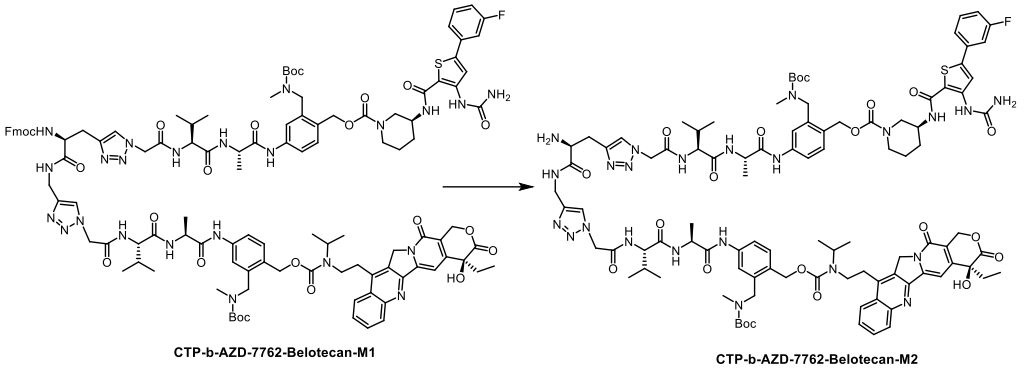
Compound CTP-b-AZD-7762-2 was synthesized following the previously established synthetic procedure of MTP3 series (step b). Purification was same as described above to afforded CTP-b-AZD-7762-2 (495 mg, 81%, 0.48 mmol scale) as a gray solid. MS (ESI): m/z calcd for $C_{65}H_{74}FN_{13}NaO_{12}S$ $[M+H]^+$: 1302.5; found 1302.3.

3) Compound CTP-b-AZD-7762-Belotecan-M1



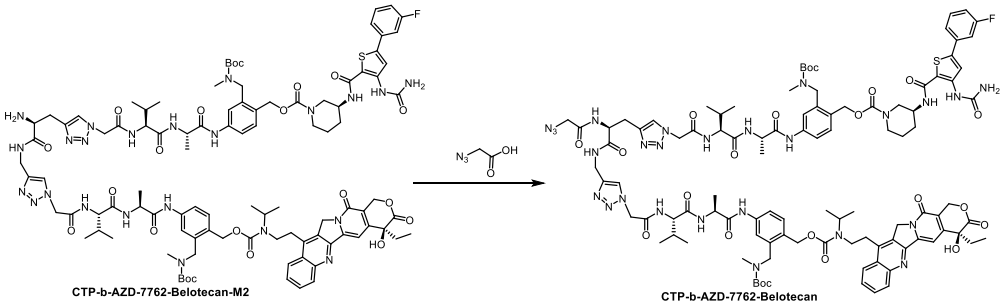
Compound CTP-b-AZD-7762-Belotecan-M1 was synthesized following the previously established synthetic procedure of MTP3 series (step c). Purification was same as described above to afforded CTP-b-AZD-7762-Belotecan-M1 (810mg, 91%, 0.39 mmol scale) as a brown solid. MS (ESI): m/z calcd for $C_{115}H_{138}FN_{23}O_{23}S$ $[M+2H]^{+2}$: 1130.0; found 1130.1.

4) Compound CTP-b-AZD-7762-Belotecan-M2



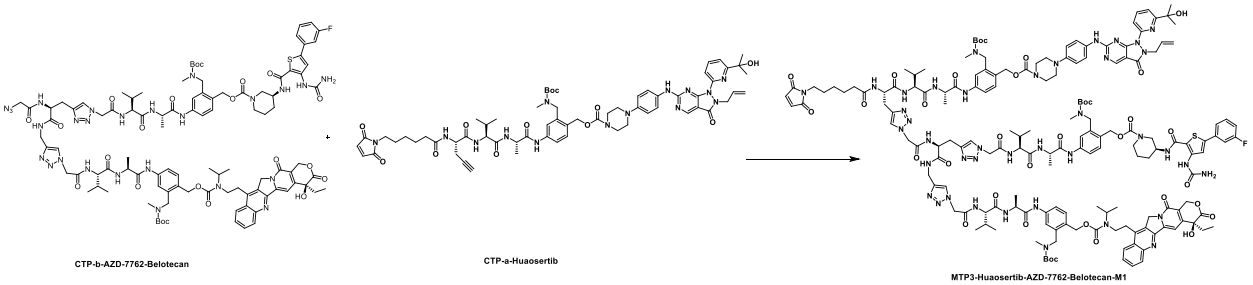
Compound CTP-b-AZD-7762-Belotecan-M2 was synthesized following the previously established synthetic procedure of MTP3 series (step d). Purification was same as described above to afforded CTP-b-AZD-7762-Belotecan-M2 (548 mg, 75%, 0.36 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{100}H_{128}FN_{23}O_{21}S$ $[M+2H]^{+2}$: 1019.0; found 1019.3.

5) Compound CTP-b-AZD-7762-Belotecan



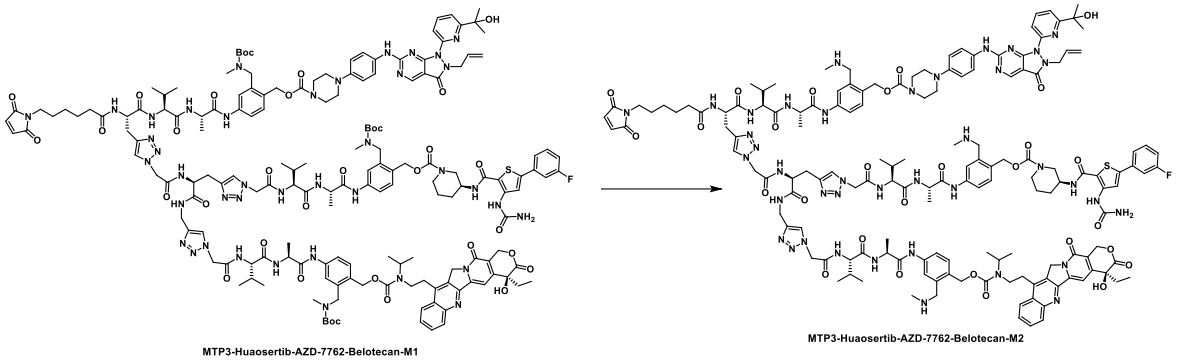
Compound CTP-b-AZD-7762-Belotecan was synthesized following the previously established synthetic procedure of MTP3 series (step e). Purification was same as described above to afforded CTP-b-AZD-7762-Belotecan (508 mg, 89%, 0.27 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{102}H_{129}FN_{26}O_{22}S$ $[M+2H]^{+2}$: 1060.5; found 1060.8.

6) Compound MTP3-Huaosertib-AZD-7762-Belotecan-M1



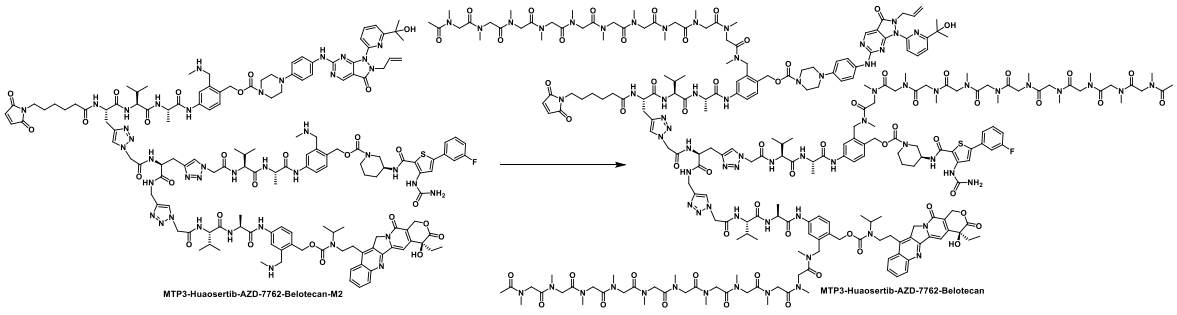
Compound MTP3-Huaosertib-AZD-7762-Belotecan-M1 was synthesized following the previously established synthetic procedure of MTP3 series (step f). Purification was same as described above to afforded MTP3-Huaosertib-AZD-7762-Belotecan-M1 (700 mg, 87%, 0.24 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{166}H_{209}FN_{40}O_{34}S$ $[M+2H]^{+2}$: 1678.8; found 1679.0.

7) Compound MTP3-Huaosertib-AZD-7762-Belotecan-M2



Compound MTP3-Huaosertib-AZD-7762-Belotecan-M2 was synthesized following the previously established synthetic procedure of MTP3 series (step g). Purification was same as described above to afforded MTP3-Huaosertib-AZD-7762-Belotecan-M2 (220 mg, 100%, 0.066 mmol scale). MS (ESI): m/z calcd for $C_{151}H_{185}FN_{40}O_{28}S$ $[M+2H]^{+2}$: 1528.7; found 1529.4.

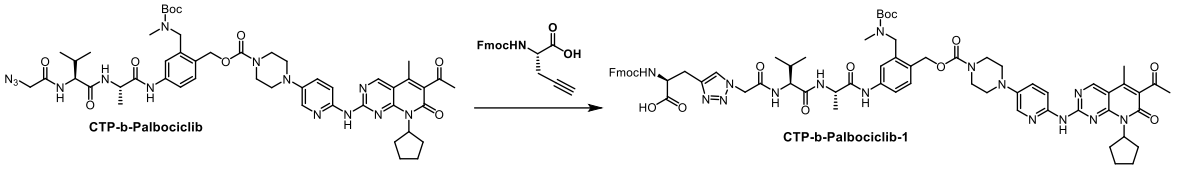
8) Compound MTP3-Huaosertib-AZD-7762-Belotecan



Compound MTP3-Huaosertib-AZD-7762-Belotecan was synthesized following the previously established synthetic procedure of MTP3 series (step g). Purification was same as described above to afforded MTP3-Huaosertib-AZD-7762-Belotecan (50.3 mg, 14%, 0.066 mmol scale) as a yellow powder. HRMS (ESI-TOF): m/z calcd for $C_{247}H_{342}FN_{70}O_{61}S$ $[M+3H]^{+3}$: 1771.8500 Found 1771.8439. Also observed 1329.1381 $[M+4H]^{+4}$ and 1063.5137 $[M+5H]^{+5}$.

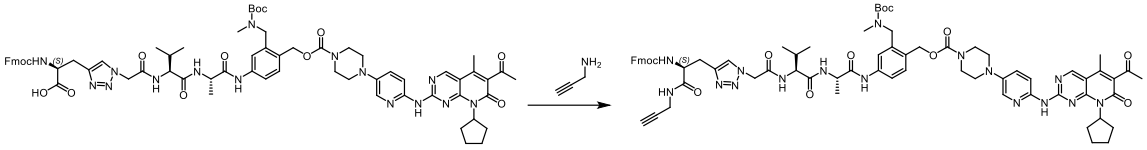
Synthesis of MTP3-Cobimetinib-Palbociclib-GSK126

1) Compound CTP-b-Palbociclib-1



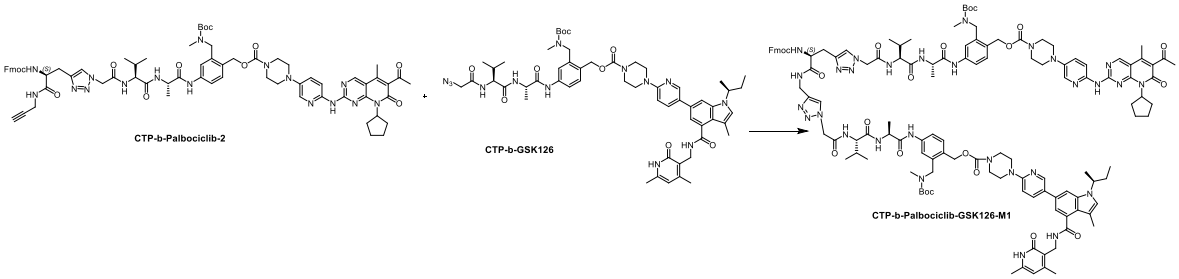
Compound CTP-b-Palbociclib-1 was synthesized following the previously established synthetic procedure of MTP3 series (step a). Purification was same as described above to afforded CTP-b-Palbociclib-1 (320 mg, 89%, 0.27 mmol scale) as a gray solid. MS (ESI): m/z calcd for $C_{69}H_{82}N_{15}O_{13}$ $[M+H]^+$: 1328.6; found 1329.5.

2) Compound CTP-b-Palbociclib-2



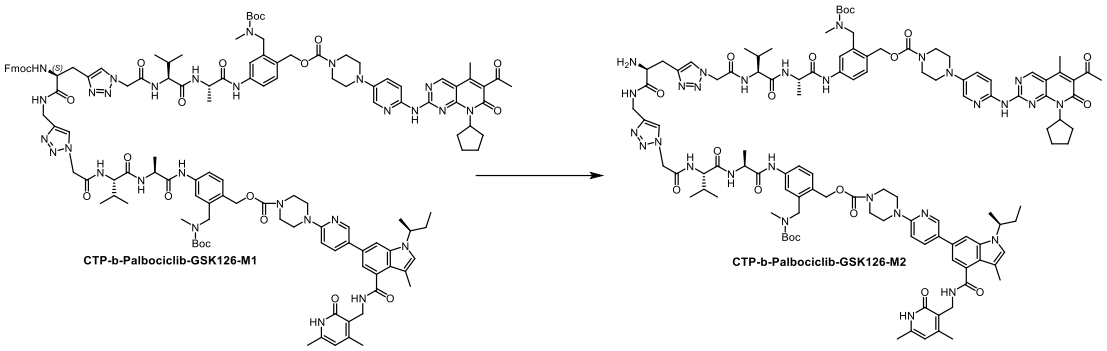
Compound CTP-b-Palbociclib-2 was synthesized following the previously established synthetic procedure of MTP3 series (step b). Purification was same as described above to afforded CTP-b-Palbociclib-2 (200 mg, 70%, 0.21 mmol scale) as a yellow solid. MS (ESI): m/z calcd for C72H84N16O12 $[M+Na]^+$: 1387.6; found 1387.4.

3) Compound CTP-b-Palbociclib-GSK126-M1



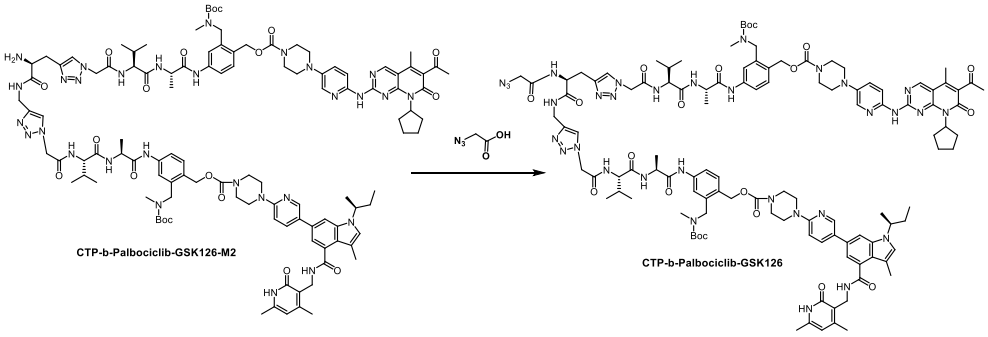
Compound CTP-b-Palbociclib-GSK126-M1 was synthesized following the previously established synthetic procedure of MTP3 series (step c). Purification was same as described above to afforded CTP-b-Palbociclib-GSK126-M1 (207 mg, 86%, 0.099 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{128}H_{159}N_{29}O_{21}$ $[M+2H]^{+2}$: 1219.1; found 1219.6.

4) Compound CTP-b-Palbociclib-GSK126-M2



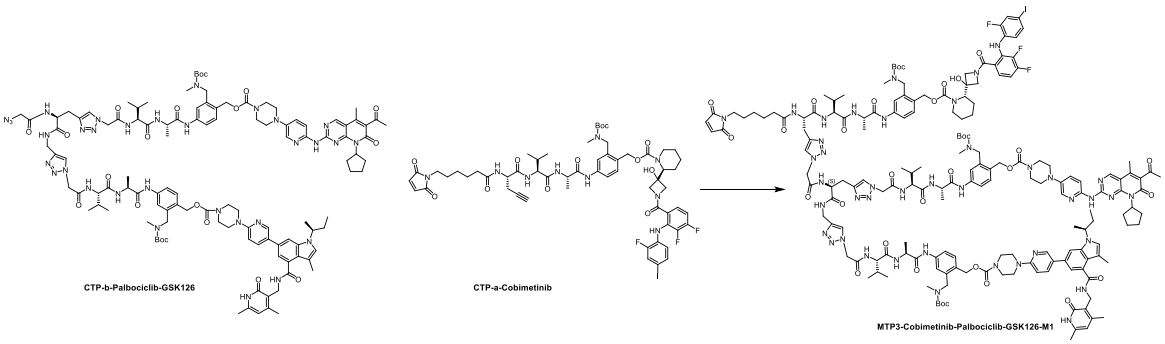
Compound CTP-b-Palbociclib-GSK126-M2 was synthesized following the previously established synthetic procedure of MTP3 series (step d). Purification was same as described above to afforded Compound CTP-b-Palbociclib-GSK126-M2 (147 mg, 82%, 0.081 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{113}H_{149}N_{29}O_{19}$ $[M+2H]^{+2}$: 1108.1; found 1108.5.

5) Compound CTP-b-Palbociclib-GSK126



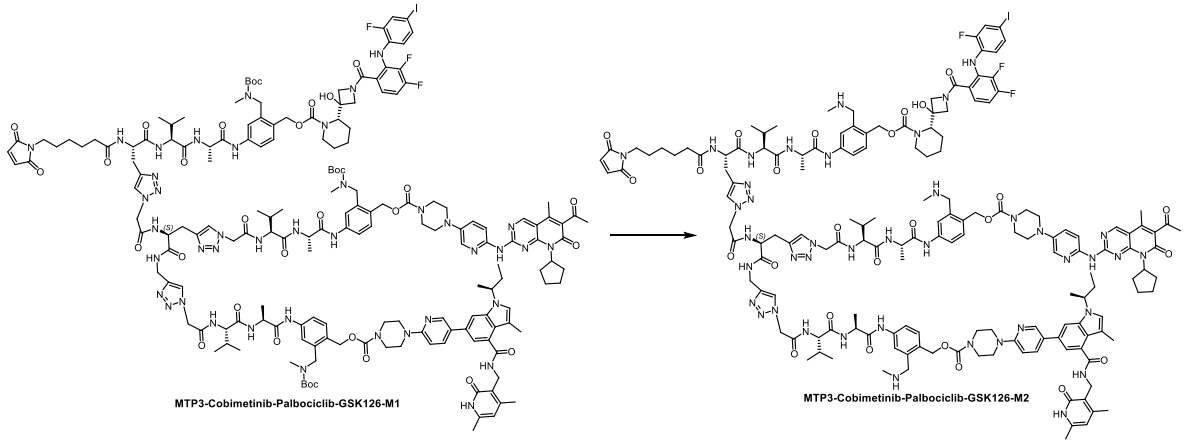
Compound CTP-b-Palbociclib-GSK126 was synthesized following the previously established synthetic procedure of MTP3 series (step e). Purification was same as described above to afforded CTP-b-Palbociclib-GSK126 (132 mg, 83%, 0.069 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{115}H_{150}N_{32}O_{20}$ $[M+2H]^{+2}$: 1149.6; found 1150.1.

6) Compound MTP3-Cobimetinib-Palbociclib-GSK126-M1



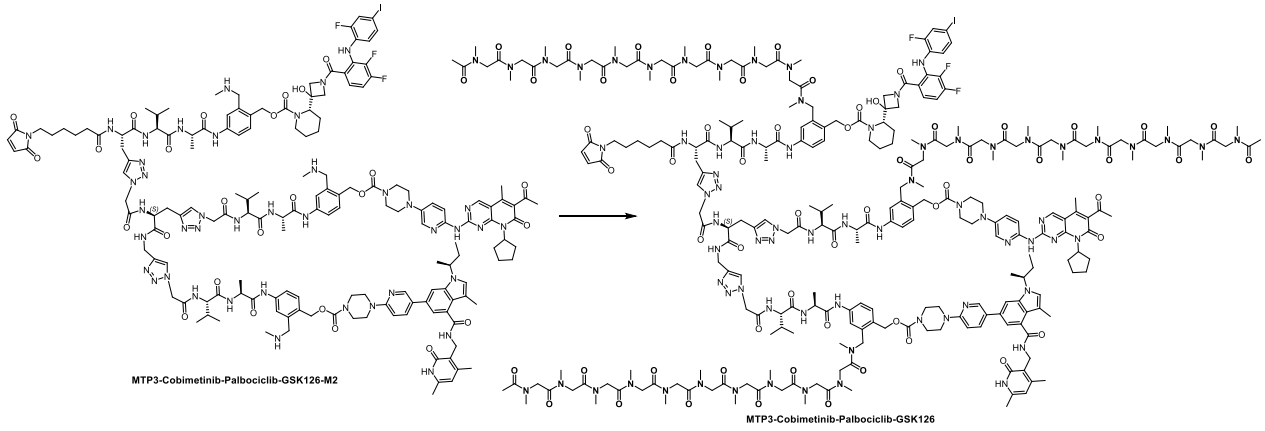
Compound MTP3-Cobimetinib-Palbociclib-GSK126-M1 was synthesized following the previously established synthetic procedure of MTP3 series (step f). Purification was same as described above to afforded MTP3-Cobimetinib-Palbociclib-GSK126-M1 (146 mg, 74%, 0.055 mmol scale) as a yellow solid. MS (ESI): m/z calcd for $C_{174}H_{222}F_3IN_{41}O_{32}$ $[M+3H]^{+3}$: 1193.9; found 1194.4.

7) Compound MTP3-Cobimetinib-Palbociclib-GSK126-M2



Compound MTP3-Cobimetinib-Palbociclib-GSK126-M2 was synthesized following the previously established synthetic procedure of MTP3 series (step g). Purification was same as described above to afforded MTP3-Cobimetinib-Palbociclib-GSK126-M2 (146 mg, 100%, 0.041 mmol scale). MS (ESI): m/z calcd for $C_{159}H_{197}F_3IN_{41}O_{26}$ $[M+2H]^{+2}$: 1640.2; found 1641.1.

8) Compound MTP3-Cobimetinib-Palbociclib-GSK126

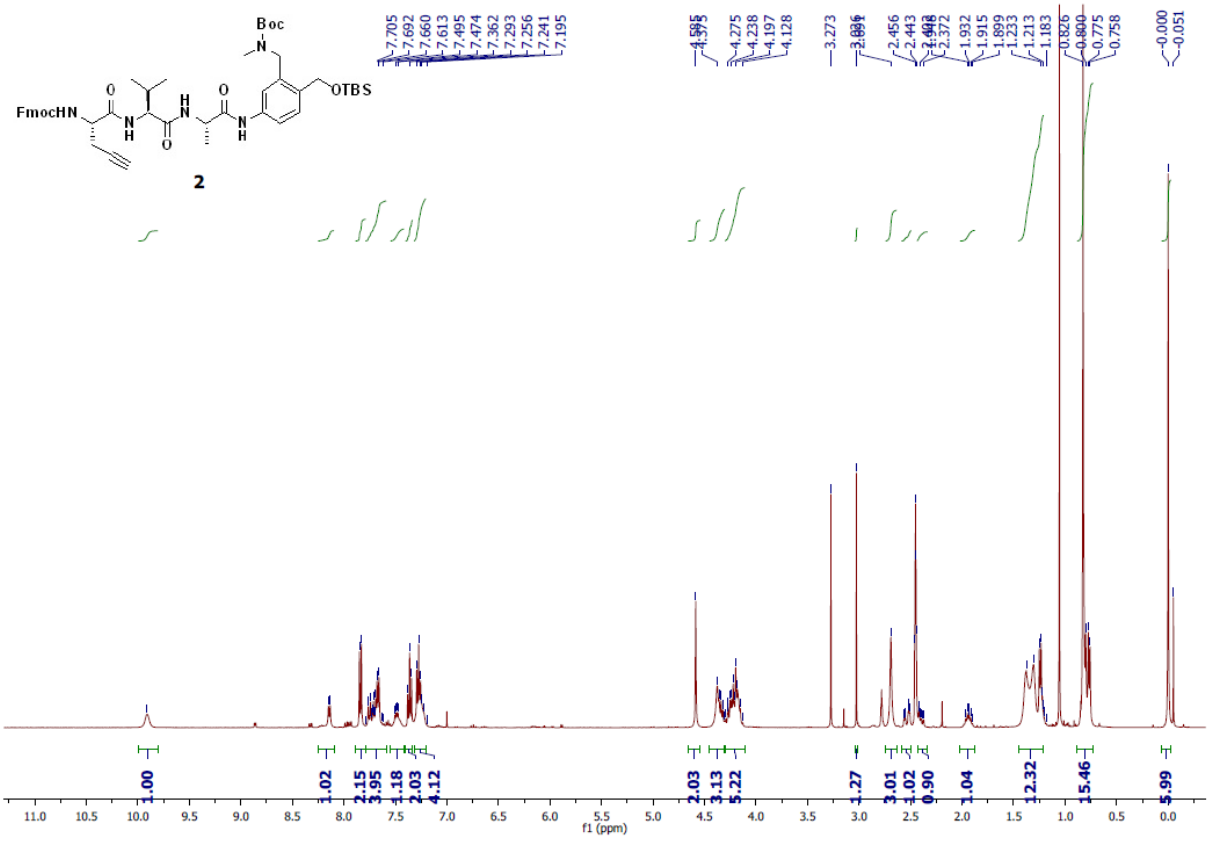


Compound MTP3-Cobimetinib-Palbociclib-GSK126 was synthesized following the previously established synthetic procedure of MTP3 series (step g). Purification was same as described above

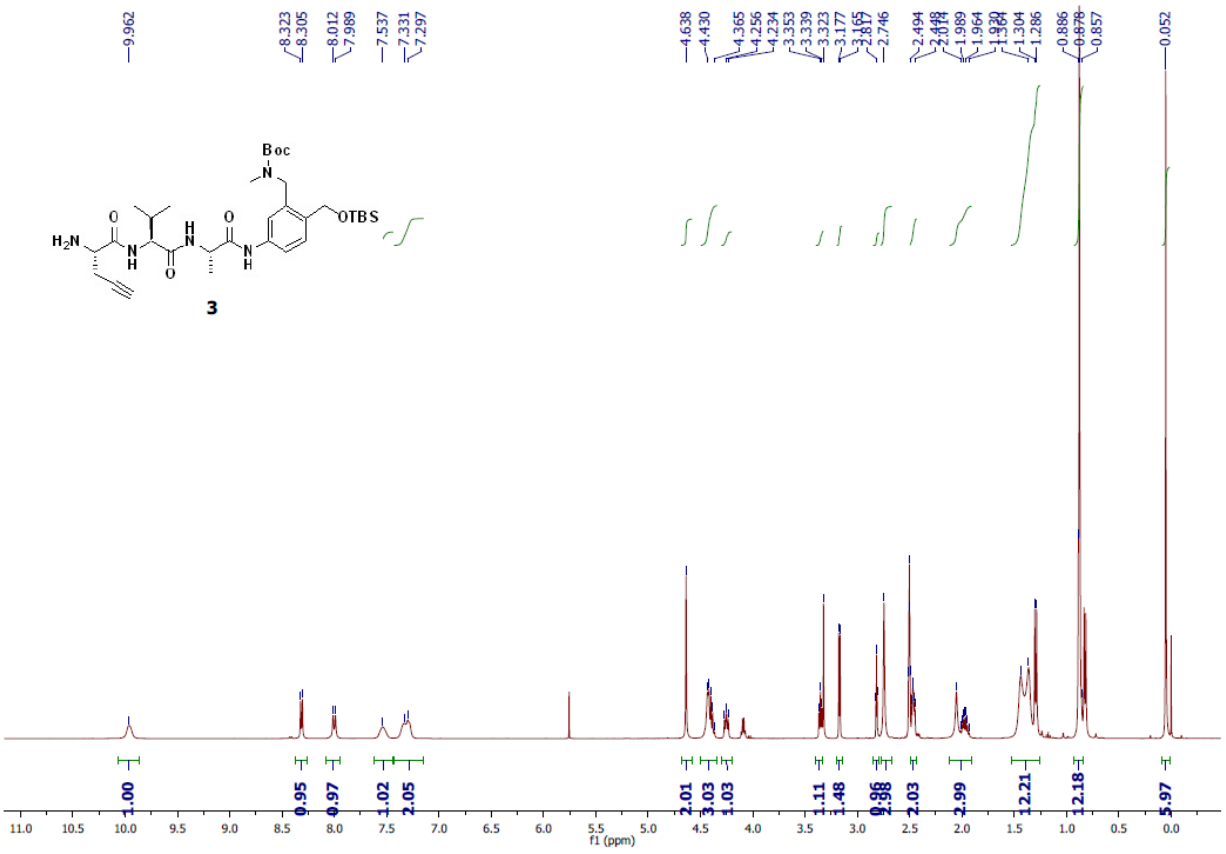
to afforded MTP3-Cobimetinib-Palbociclib-GSK126 (34 mg, 15%, 0.041 mmol scale) as a yellow powder. MS (ESI): m/z calcd for $C_{255}H_{354}F_3IN_{71}O_{59}$ $[M+3H]^+$: 1846.2; found 1846.8.

^{1}H NMR Spectra of Compounds

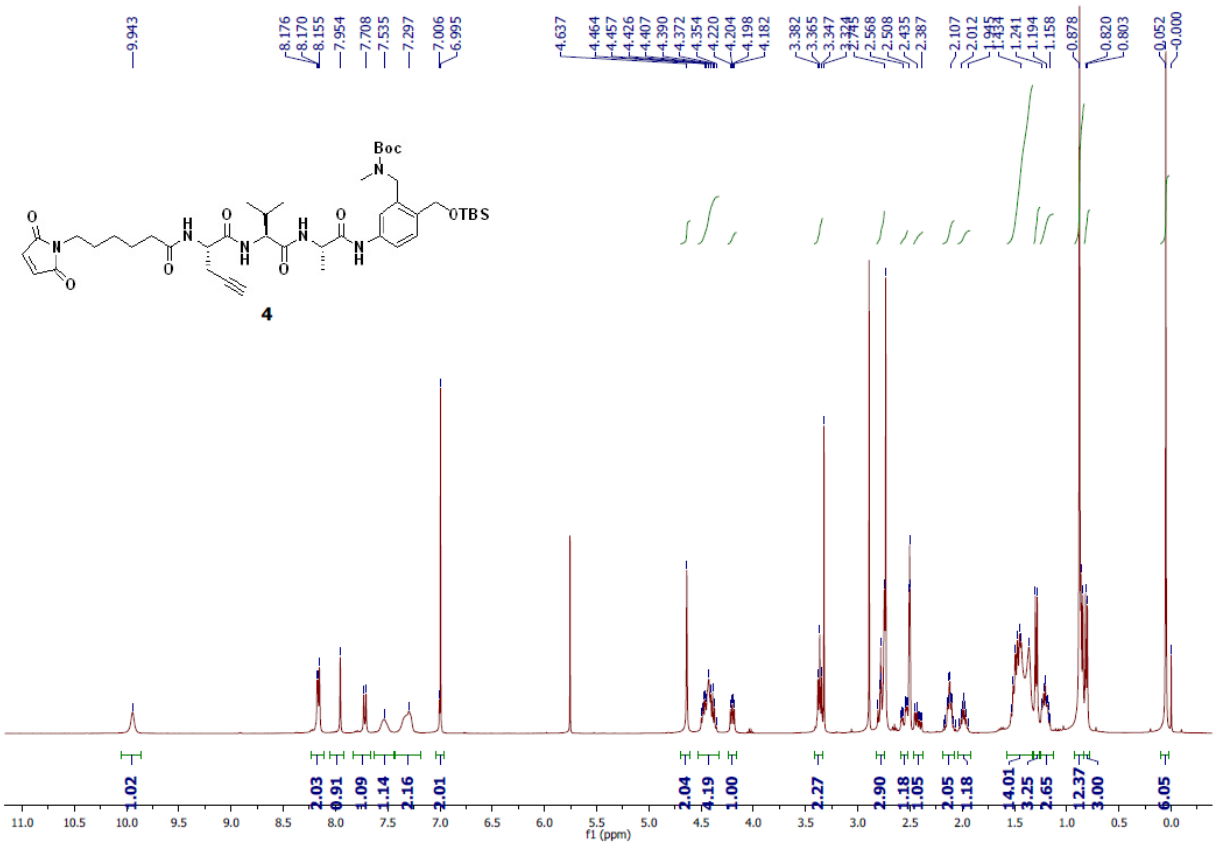
^{1}H NMR Spectrum of Compound 2 (400 MHz, DMSO-d_6)



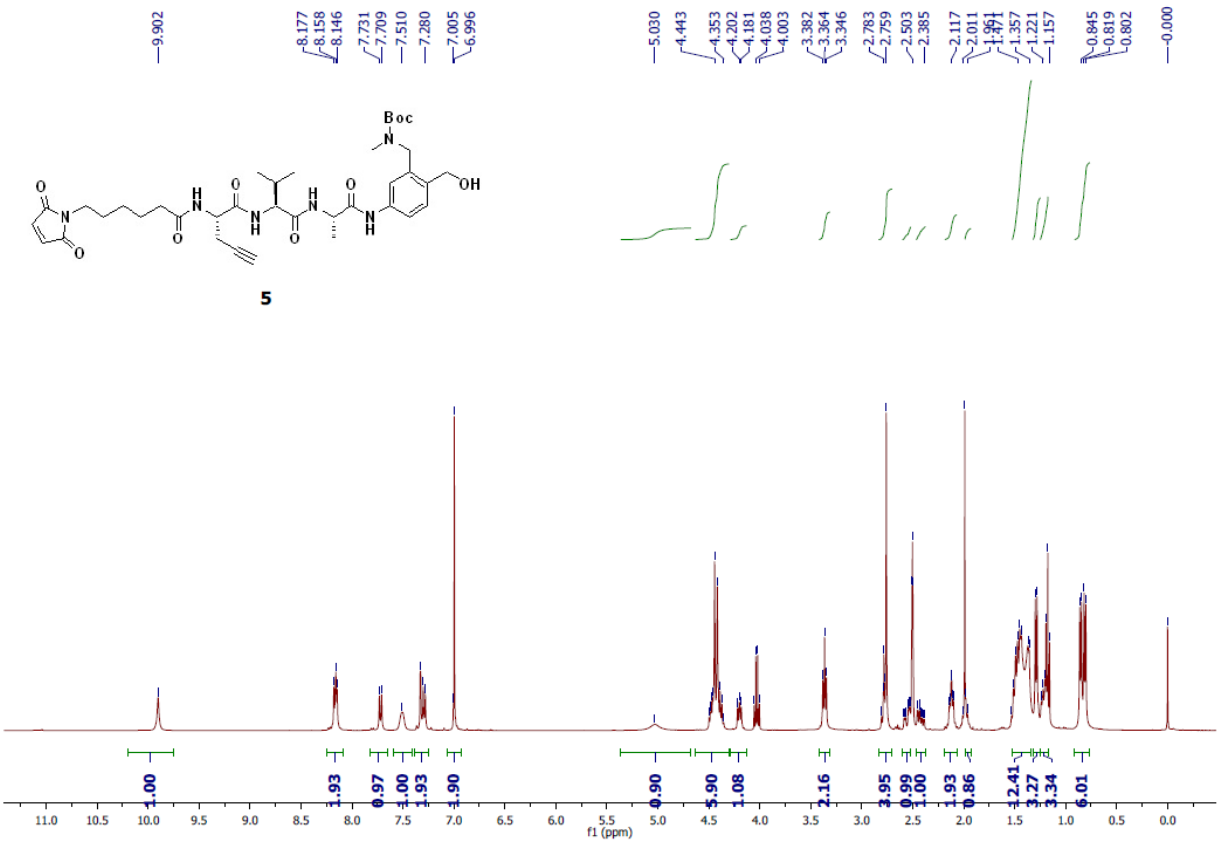
^{1}H NMR Spectrum of Compound 3 (400 MHz, DMSO-d_6)



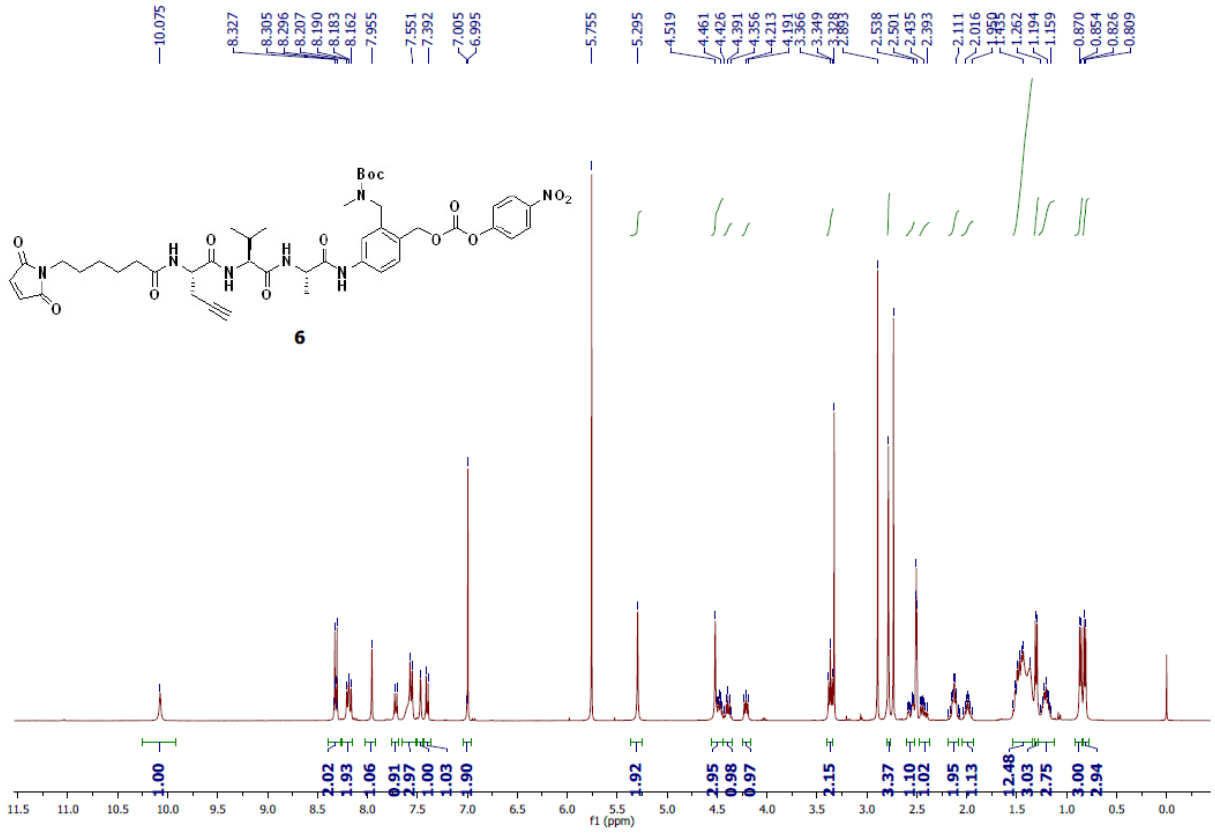
^{1}H NMR Spectrum of Compound 4 (400 MHz, DMSO-d_6)



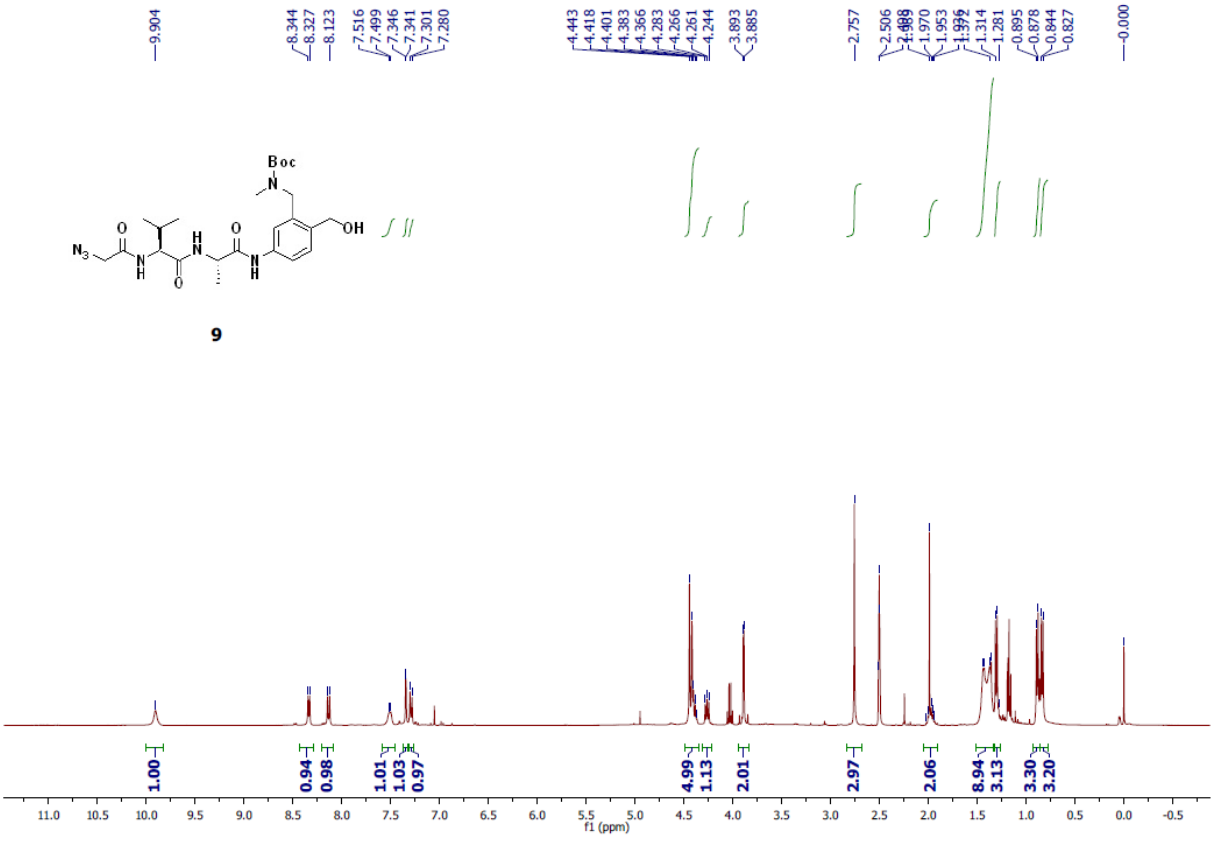
^{1}H NMR Spectrum of Compound 5 (400 MHz, DMSO-d_6)



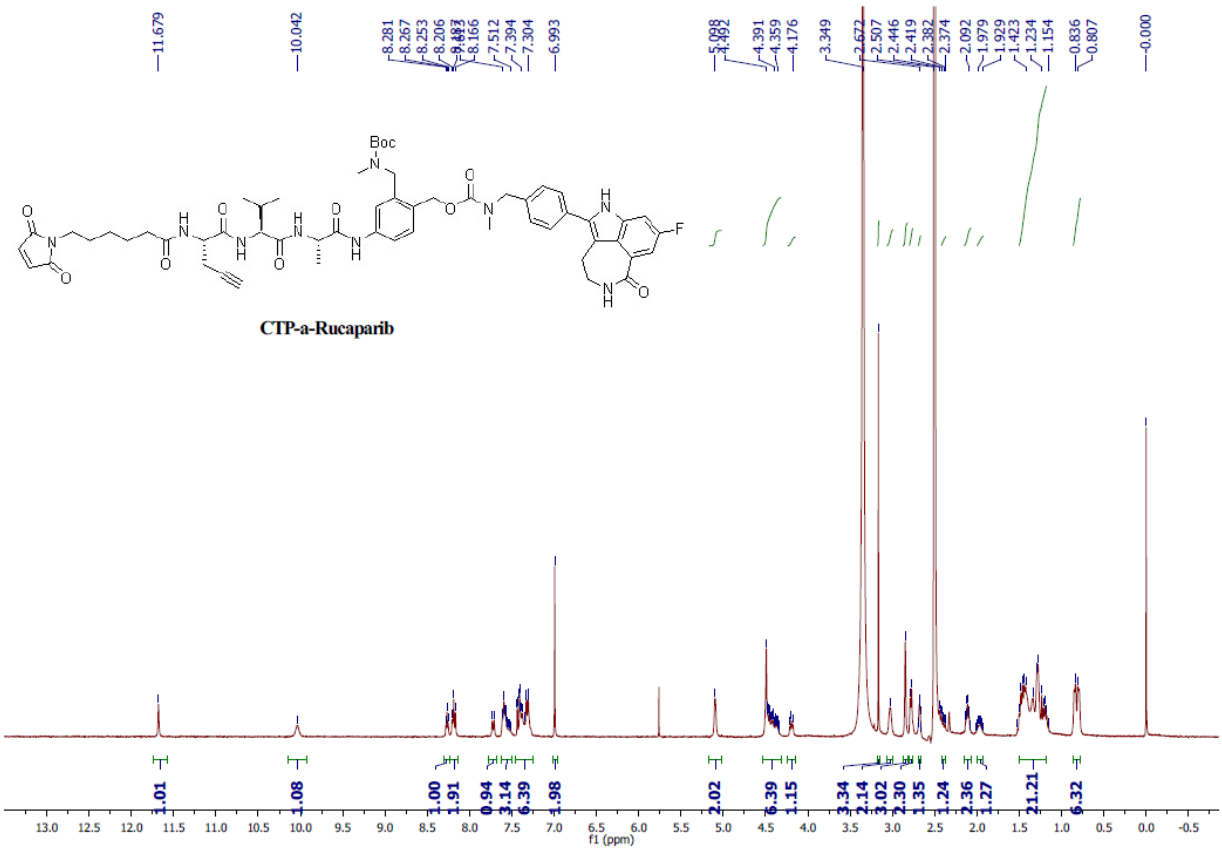
^{1}H NMR Spectrum of Compound 6 (400 MHz, DMSO-d_6)



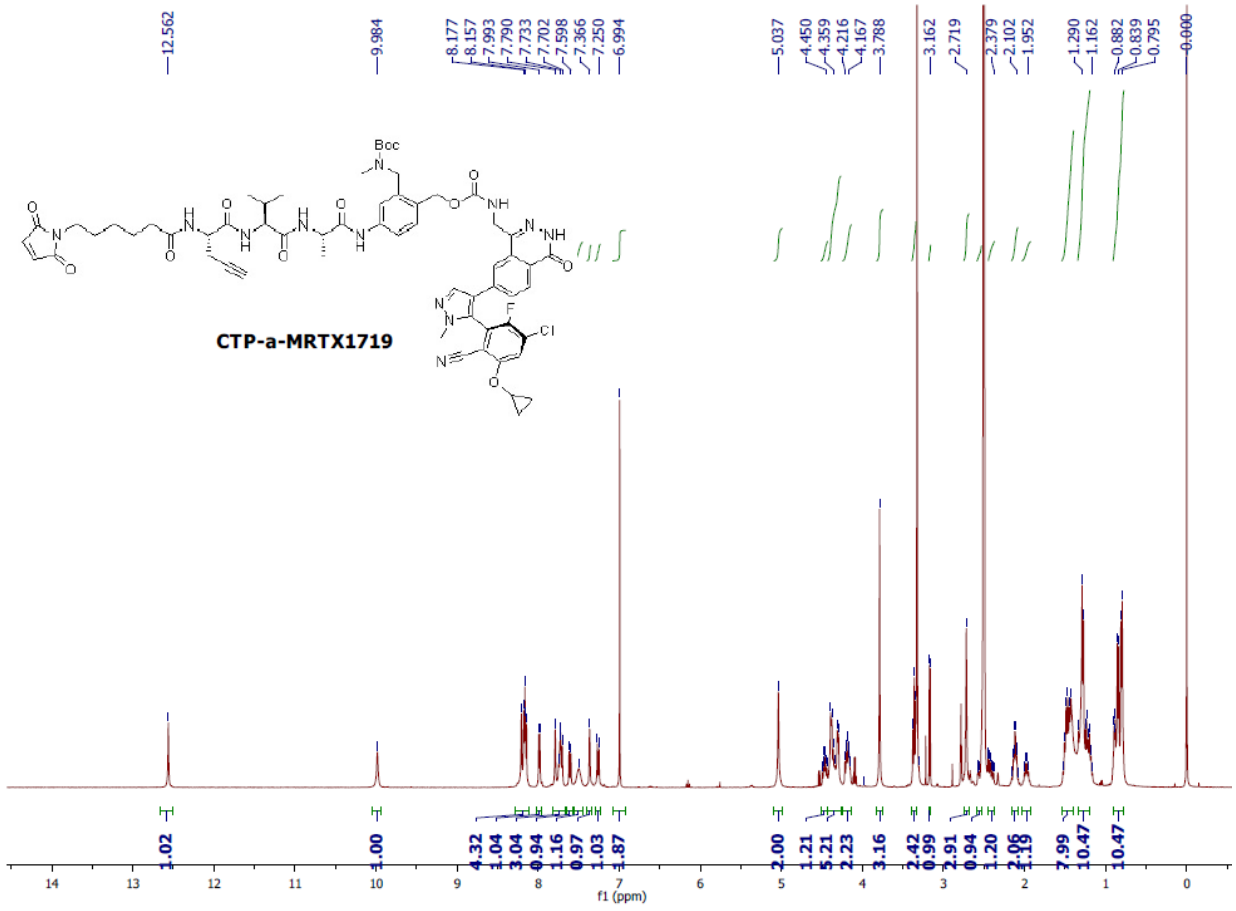
^{1}H NMR Spectrum of Compound 9 (400 MHz, DMSO-d_6)



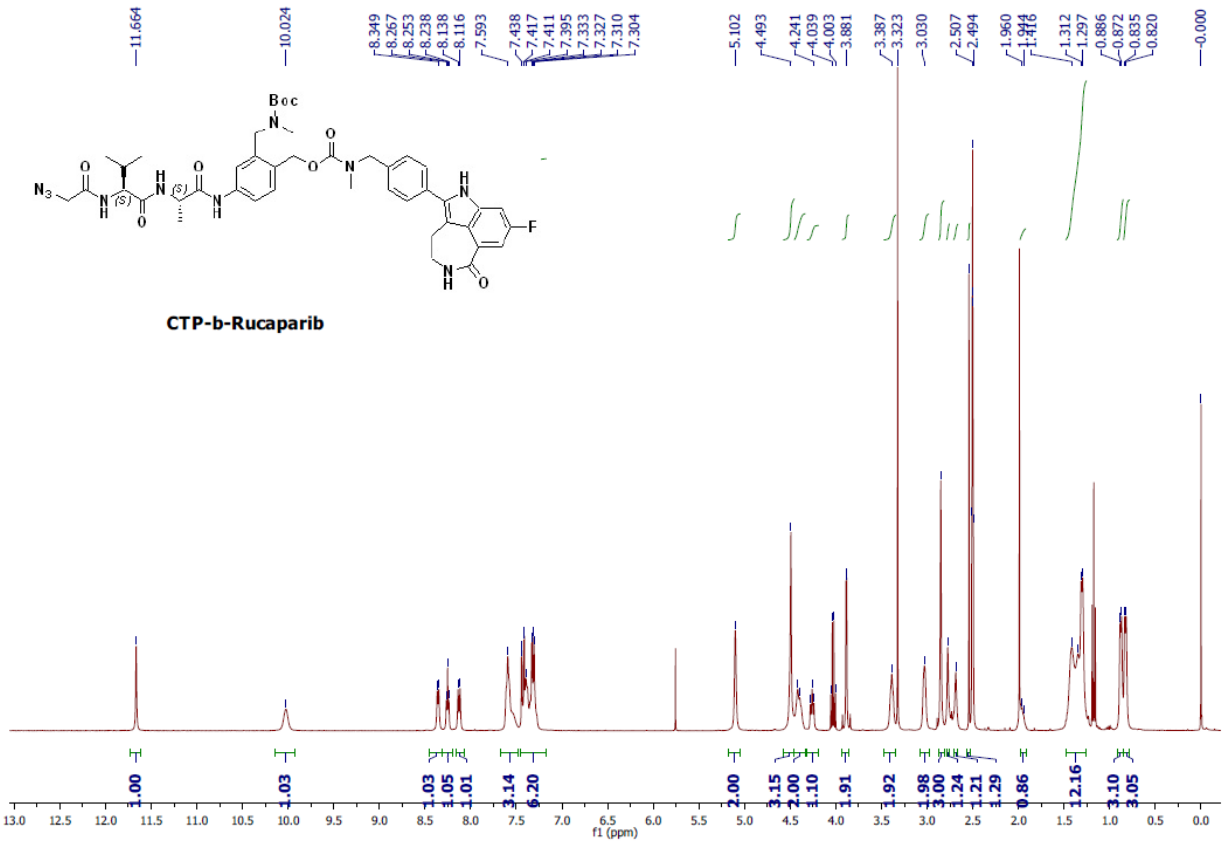
^{1}H NMR Spectrum of Compound CTP-a-Rucaparib (400 MHz, DMSO-d_6)



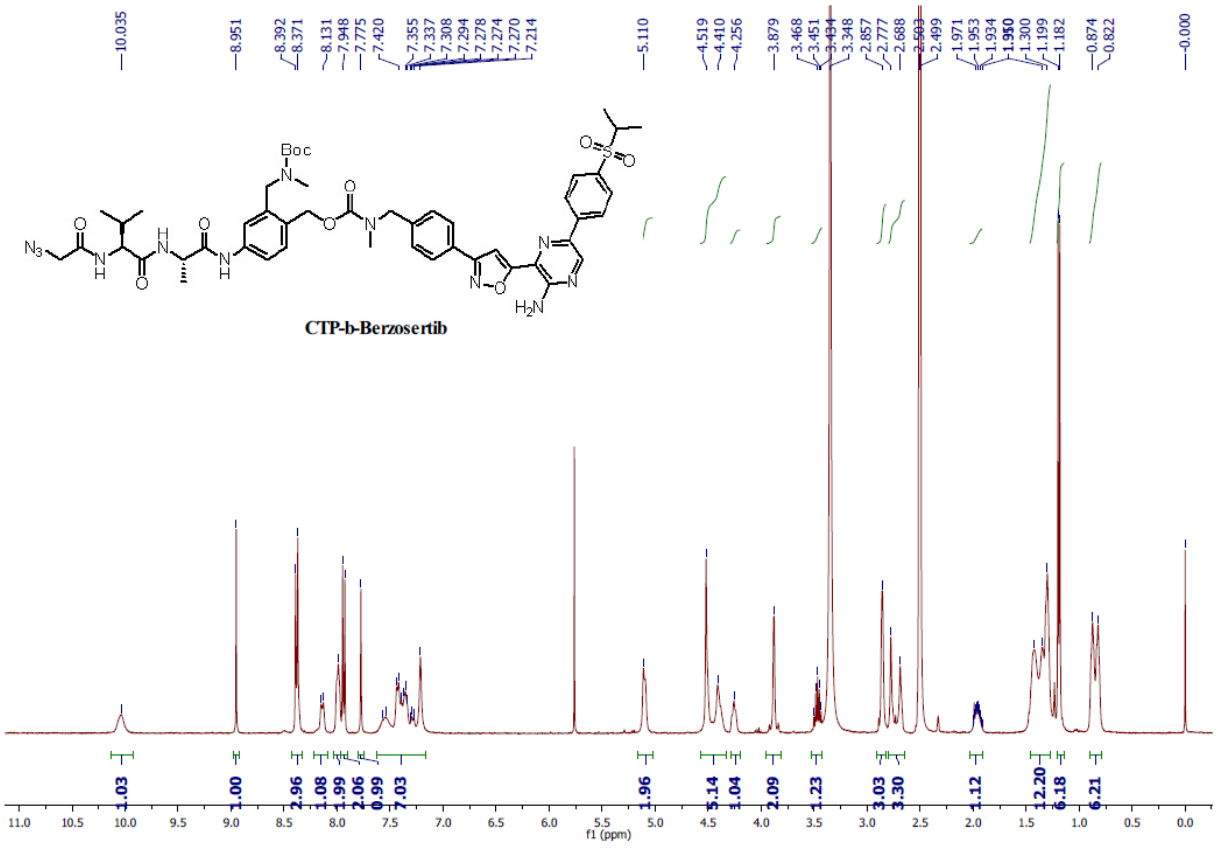
^{1}H NMR Spectrum of Compound CTP-a-MRTX1719 (400 MHz, DMSO-d_6)



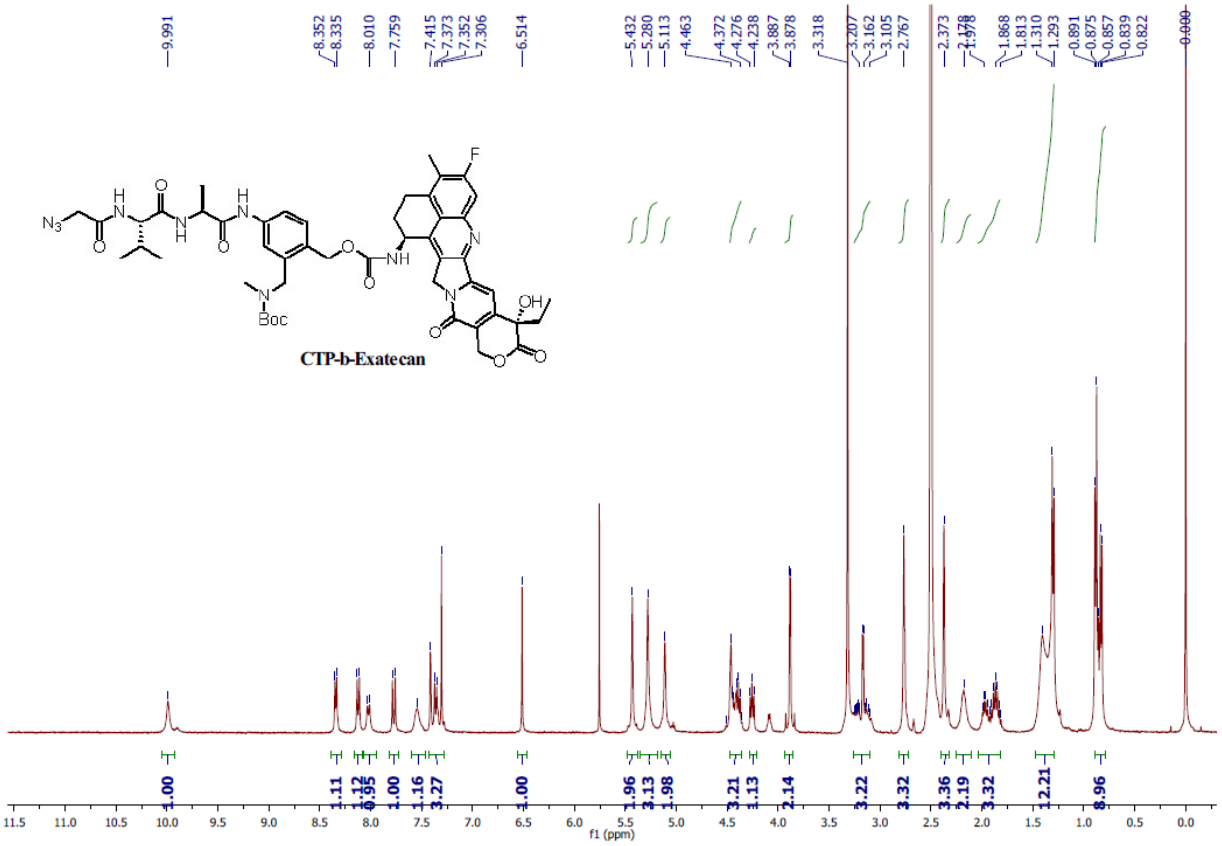
^{1}H NMR Spectrum of Compound CTP-b-Rucaparib (400 MHz, DMSO-d_6)



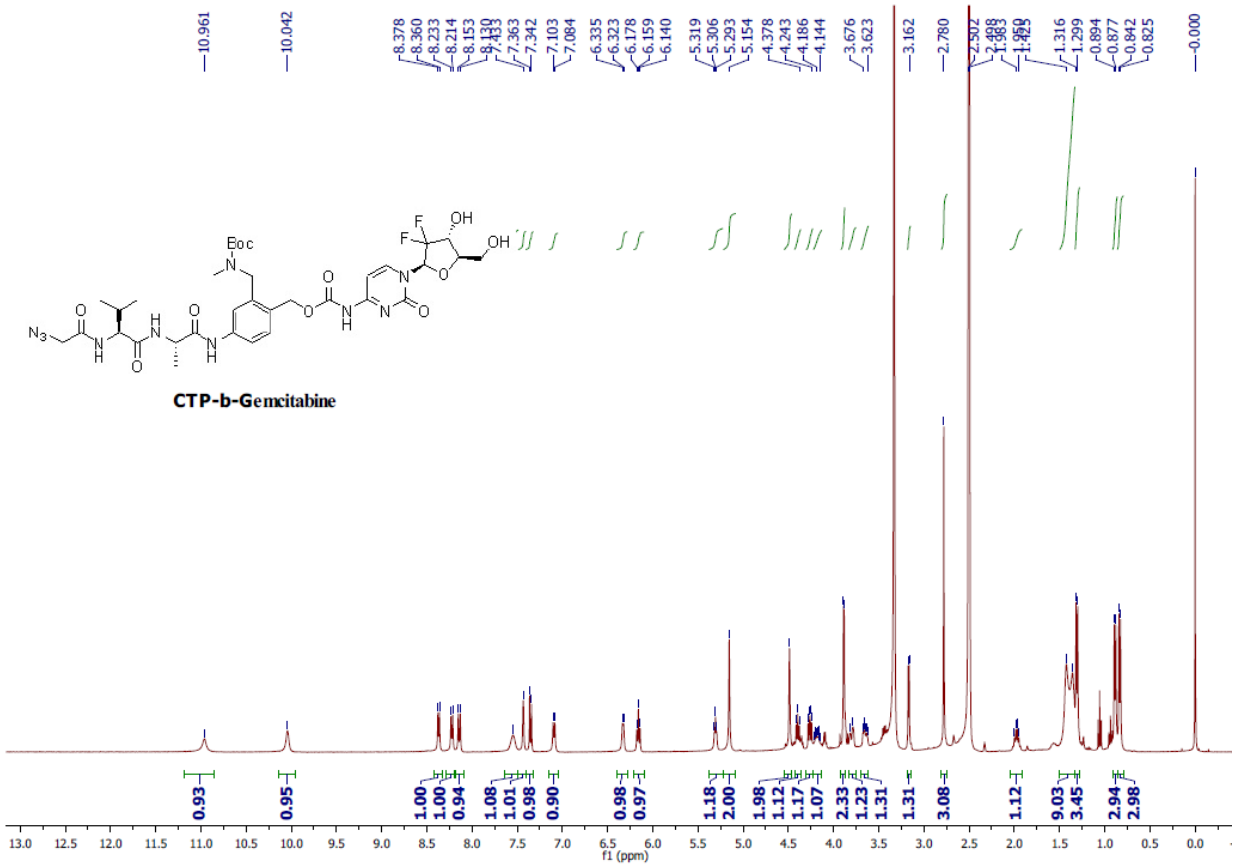
^{1}H NMR Spectrum of Compound CTP-b-Berzosertib (400 MHz, DMSO-d_6)



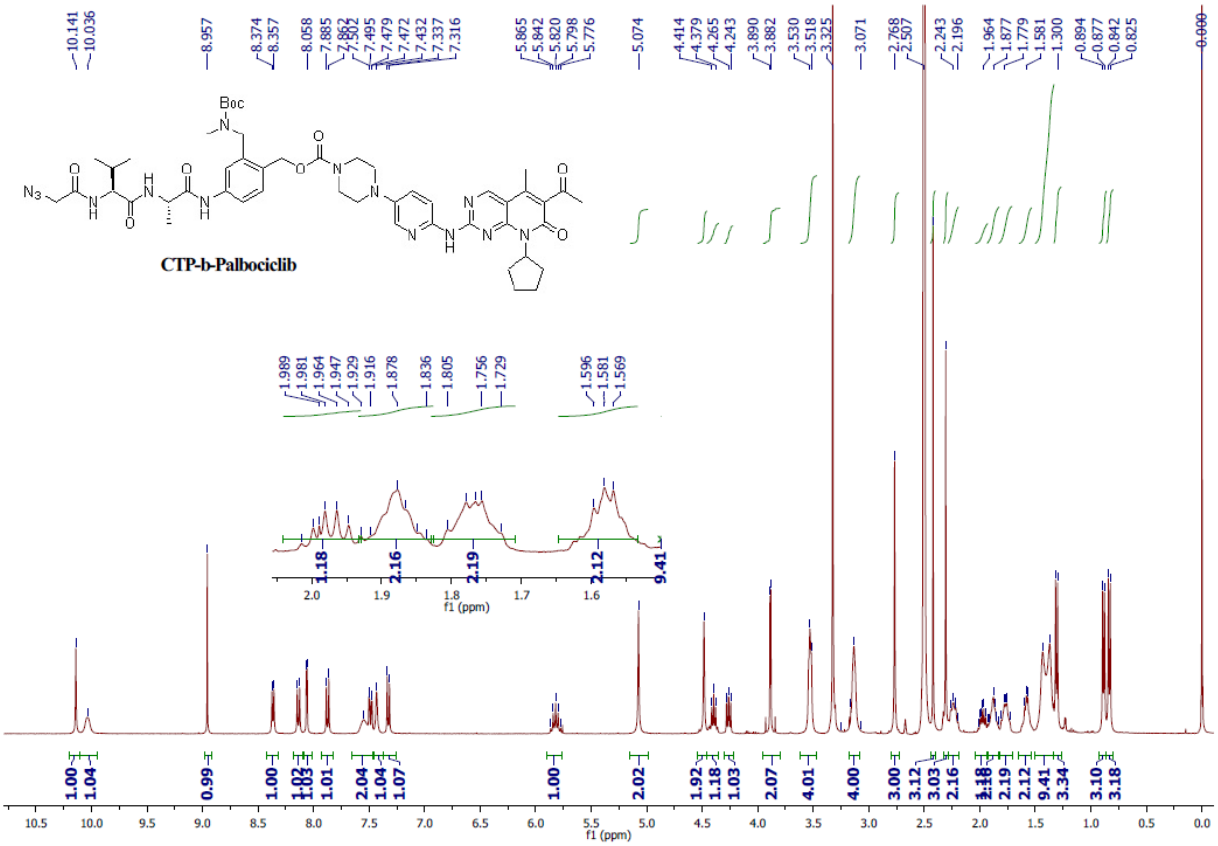
^{1}H NMR Spectrum of Compound CTP-b-Exatecan (400 MHz, DMSO-d_6)



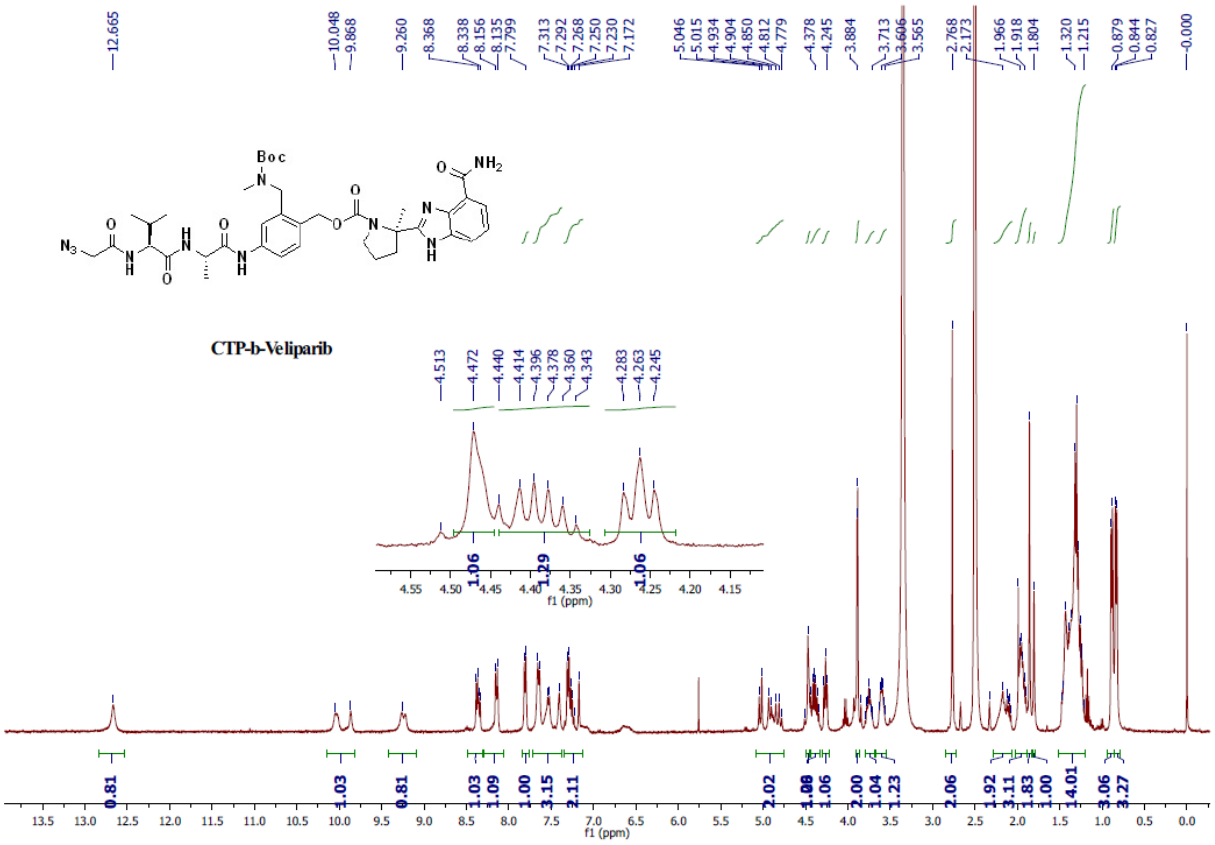
^{1}H NMR Spectrum of Compound CTP-b-Gemcitabine (400 MHz, DMSO-d_6)



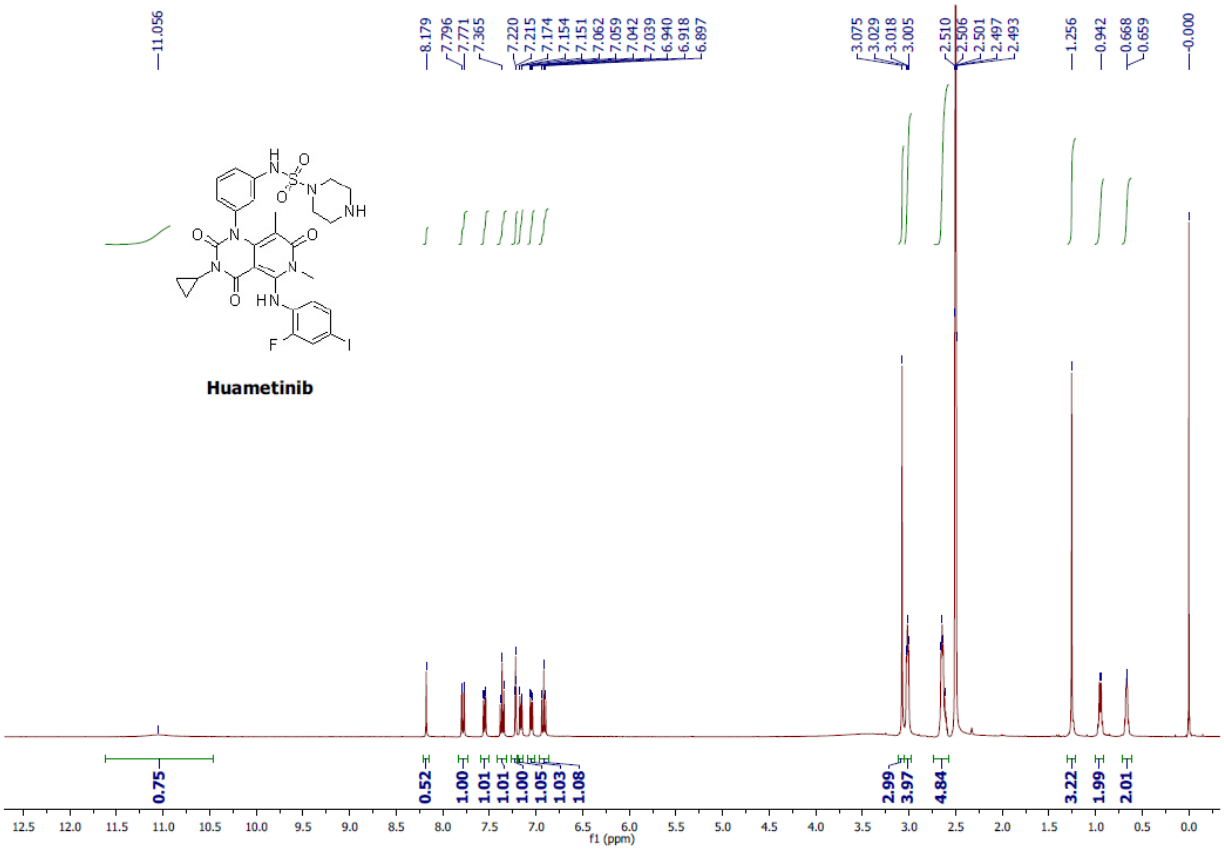
^{1}H NMR Spectrum of Compound CTP-b-Palbociclib (400 MHz, DMSO-d_6)



^{1}H NMR Spectrum of Compound CTP-b-Veliparib (400 MHz, DMSO-d_6)



^{1}H NMR Spectrum of Compound Huametinib (400 MHz, DMSO-d_6)



^{1}H NMR Spectrum of Compound Huavosertib (400 MHz, DMSO-d_6)