Supplementary Information (SI) for RSC Medicinal Chemistry.
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Novel hydrophobic tag leads to the efficient degradation of Programmed death-ligand 1

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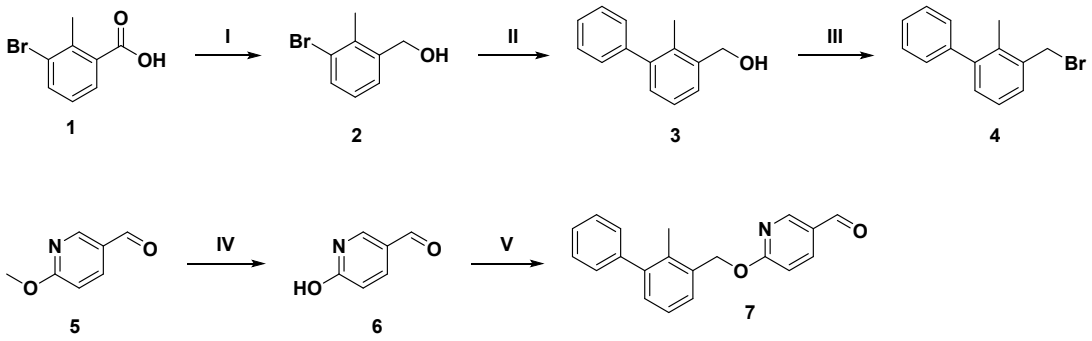
A. The detailed synthesis procedure of designed HyTTDs



Reagent and conditions: (I)BH_3-THF, THF, r.t.; (II) $[(C_6H_5)_3P]_2PdCl_2$, Phenylboronic Acid, $NaHCO_3$, toluene, EtOH, H_2O,80°C (III)PBr_3, DCM, r.t.; (IV) C_3H_9ISi, DCM, r.t.; (V) Compound 4, K_2CO_3, DMF, r.t.

Scheme 1. The synthesis of PD-L1 binder motif derived from BMS-220

I: To a solution of 3-bromo-2-methylbenzoic acid (5.0 g, 23.2 mmol) in anhydrous THF (25 mL) was cautiously added dropwise BH_3-THF complex (1 M solution in THF, 35 mL) at 0°C under nitrogen atmosphere. The ice–salt bath is maintained in position throughout the 30 minutes of

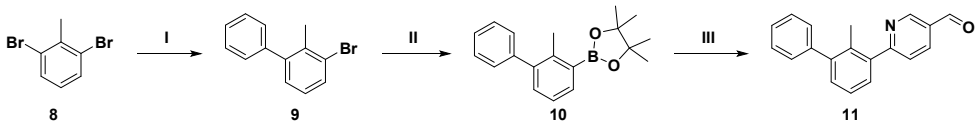
addition. The stirred reaction mixture was then gradually warmed to room temperature over the next 8–10 hours. The reaction was carefully quenched at room temperature by dropwise addition of 1 M hydrochloric acid. The solution was extracted with EtOAc (EA, 3 x 50 mL), and the organic phase was concentrated to afford **compound 2** (4.6 g; 99%) as a colorless solid without further purification.

II: Bis(triphenylphosphine)palladium dichloride (10 mol%) was added to a solution of **compound 2** (1.0 mmol, 1.0 eq) and phenylboronic acid (1.2 eq, 1.2 mmol) in 3:1:3 (volume) mixture of toluene (1.55 mL), ethanol (0.52 mL) and 2M sodium bicarbonate (1.55 mL) at room temperature under nitrogen atmosphere. The mixture was warmed to 80°C and stirred overnight. The solution was extracted by EA, and the organic layer was dried by Na_2SO_4 and concentrated to give crude, which was purified by silica gel column chromatography (0-40% EA/petroleum) to afford **compound 3** as a white solid.

III: PBr_3 (3.0 eq) was added dropwise to a solution of **compound 3** (2 mmol, 1.0 eq) in DCM (10 ml) at 0°C. The mixture reaction was warmed to room temperature and stirred for another 3 hours. Then the reaction was quenched by $NaHCO_3$, the solution was extract by EA, and the organic layer was dried by Na_2SO_4 and concentrated to give **compound 4** as a pale-yellow solid (y=85%).

IV: Iodotrimethylsilane (1.3 eq) was added dropwise to a solution of 6-Methoxy-3-pyridinecarboxaldehyde in DCM at 0°C under a nitrogen atmosphere. The mixture reaction was stirred for 2 hours and quenched with methanol. The residue was concentrated and recrystallized to give **compound 6** as a pale-yellow solid.

V: **Compound 4** (1.0 eq) was added to a solution of **Compound 6** (1.0 eq) and K_2CO_3 (2.0 eq) in DMF at room temperature. The reaction was stirred for 2 hours and monitored by TLC. The solution was extracted by EA, and the organic layer was dried by Na_2SO_4 and concentrated to give crude. The residue was purified by column chromatography to afford **compound 7** as a white solid. (HyTs with **compound 7** as the PD-L1 targeted motif was denoted as L series).



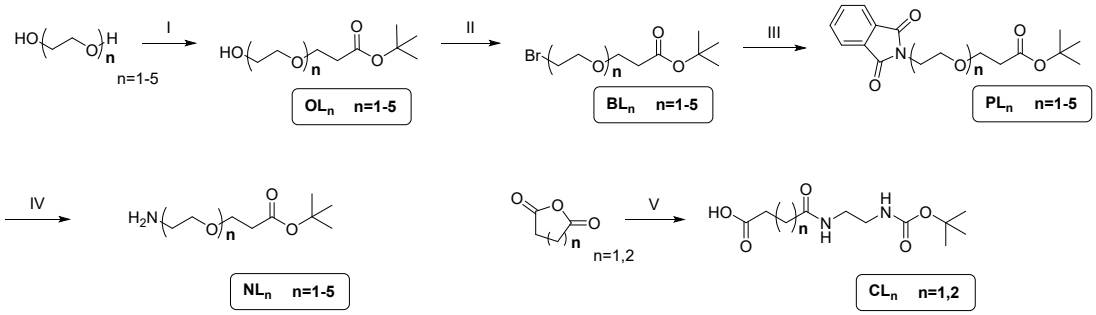
Reagent and conditions: (I) $[(C_6H_5)_3P]_2PdCl_2$, Phenylboronic Acid, $NaHCO_3$, toluene, EtOH, H_2O,80°C; (II) bis(pinacolato)diboron, $PdCl_2$(dppf), KOAc, 1,4-Dioxane, 100°C; (III)2-Bromo-5-formylpyridine, $Pd[P(C_6H_5)_3]_4$, KOAc, 1,4-Dioxane, H_2O, 90°C

Scheme 2. The synthesis of PD-L1 binder motif derived from R3

I: Bis(triphenylphosphine)palladium dichloride (0.01 eq) and sodium bicarbonate (3.0 eq) were added to a solution of 2,6-dibromotoluene and phenylboronic acid (1.0 eq) in toluene/ethanol/water (3/1/1) under nitrogen atmosphere. The mixture reaction was warmed to 80°C and stirred for 3 hours. The mixture was filtered through diatomaceous earth. The filtrate was dried by Na_2SO_4 and concentrated to give crude. The residue was purified by column chromatography to give **compound 9** as a colorless oily liquid.

II: 1,1'-bis-diphenylphosphoryl ferrocene palladium dichloride (0.06 eq) was added to a solution of **compound 9**, biboronic acid pinacol ester (2.0 eq), and KOAc (2.0 eq) in dioxane under nitrogen atmosphere. The mixture reaction was warmed to 100°C and stirred for 3 hours. The mixture was filtered through diatomaceous earth. The filtrate was dried by Na_2SO_4 and concentrated to give crude. The residue was purified by column chromatography to give **compound 10** as a colorless oily liquid.

III: Tetrakis(triphenylphosphine)palladium (0.05 eq) was added to a solution of **compound 10**, 2-bromo-5-formylpyridine (1.0 eq), KOAc (2.0 eq) in dionxane/H_2O (9/1) under nitrogen atmosphere. The mixture reaction was warmed to 100°C and stirred for 3 h. The mixture was filtered through diatomaceous earth. The filtrate was dried by Na_2SO_4 and concentrated to give crude. The residue was purified by column chromatography to give **compound 11** as a white solid.



Reagent and conditions:(I) Triton B, MeCN, RT; (II) CBr_4, DCM; (III) Phthalimide, K_2CO_3, DMF, RT; (IV) $N_2H_4 \cdot H_2O$, EtOH, 90 Celsius degree; (V) N-boc-ethylenediamine, Et_3N, THF, RT.

Scheme 3. The synthesis of linkers of HyTTDs

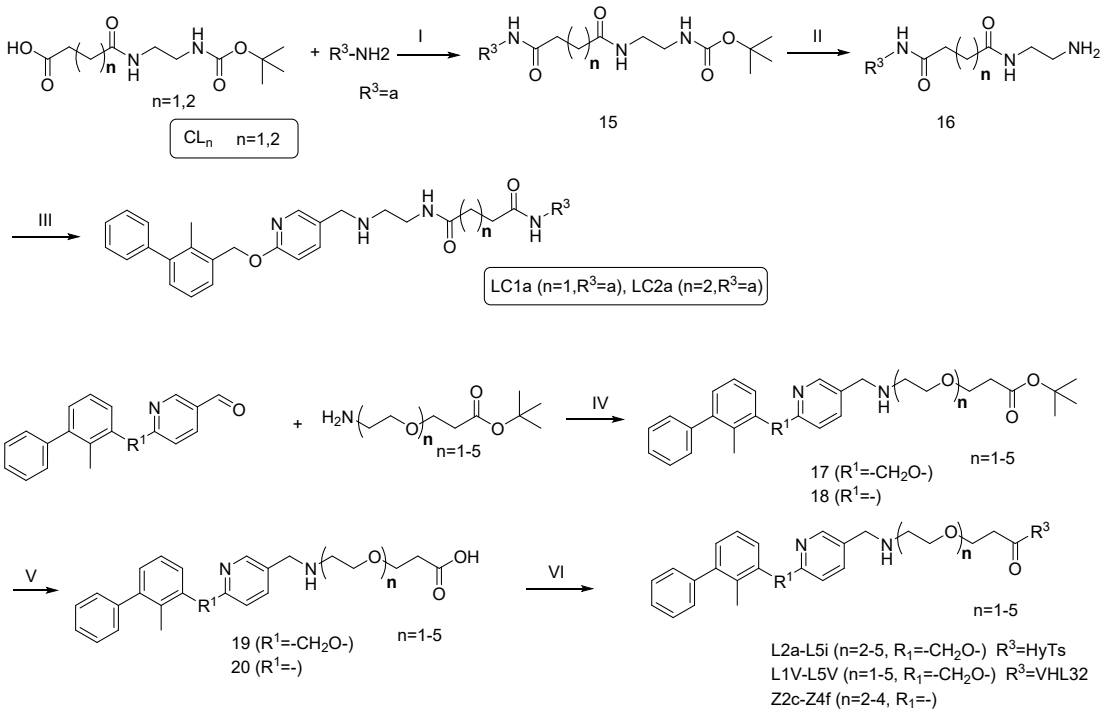
I: Triton B (0.037 eq) was added to a solution of Polyethylene glycols and tert-butyl acrylate (1.0 eq) in MeCN. The reaction was stirred for 72 h. The mixture was concentrated in vacuum. The residue was purified by column chromatography to give **OL_1-OL_5** as a colorless oil.

II: Carbon tetrabromide (CBr_4, 2.0 eq) was added dropwise to the solution of **OL_1-OL_5** and triphenyl phosphorus (PPh_3, 2.0 eq) in DCM over 5 mins. The mixture reaction was stirred for 10 h. The mixture was concentrated in vacuum and purified by column chromatography to give **BL_1-BL_5** as a colorless oil.

III: **BL_1-BL_5** was added to the solution of phthalimide (1.3 eq) and K_2CO_3 (2.0 eq) in DMF. The mixture reaction was stirred for 10 hours at room temperature. TLC monitored the reaction. The mixture was concentrated in vacuum and purified by column chromatography to give **PL_1-PL_5** as a colorless oil.

IV: Hydrazine hydrate (3.0 eq) was added dropwise to the solution of **PL_1-PL_5** in ethanol. The reaction was warm to reflux and stirred for 2 hours. The mixture reaction was filtered, and the filtrate was slowly added 1M HCl to make the pH value equal to 3.0. The solution was extracted with EA (6 x 50 mL). Then 4M sodium hydroxide aqueous solution was added to aqueous phases to adjust the pH value equal to 9.0. The solution was extracted with **EA**. The organic phase was concentrated to get **NL_1-NL_5** as a yellow oil.

V: **Succinic anhydride** (or Glutaric anhydride, 1.0 eq) was added dropwise to a solution of N-Boc-1,2-ethylenediamine (3.0 eq) and triethylamine (1.0 eq) in THF over 10 mins at 0°C under nitrogen atmosphere. The resulting mixture was extracted with EA/H_2O. Then the aqueous phase was adjusted with the pH value equal to 1.0 using 1M HCl. The aqueous phase was extracted with EA. The organic phase was concentrated in vacuum to give CL4-CL5 as a white solid.



Reagent and conditions: (I) HATU, DIPEA, DCM; (II) TFA, DCM, RT; (III) Compound 7, $NaBH_4$, MeOH, 40 Celsius degree; (IV) $NaBH_4$, MeOH, 40 Celsius degree; (V) TFA, DCM, RT; (VI) 20a-20i, HATU, DIPEA, DCM, RT; (VII) TFA, DCM; (VIII)R^3, HATU,DIPEA,DCM; (IX) Compound 1/2, $NaBH_4$, MeOH, RT.

Scheme 4. The synthesis of HyTTDs

I: **R^3-NH2** (R^3=a) was added dropwise to the solution of **$CL_{1,2}$** (1.0 eq), HATU (1.5 eq) and DIPEA (3.0 eq) in DMF. The reaction was stirred for 3 hours. The solution was extracted with EA (3 x 50 mL), and the organic phase was dried by Na_2SO_4 and concentrated to give crude. Which was purified by silica gel column chromatography to give **Compound 15**.

II: TFA was added to the solution of **Compound 15** in DCM was added TFA. The mixture reaction was stirred for 2 hours at room temperature. The resulting mixture was concentrated in vacuum to give **Compound 16** (crude) without further purification.

III: **Compound 7** was added to the solution of **Compound 16** (1.0 eq) in methanol at room temperature. The reaction was warmed to 40 °C and stirred overnight, and further monitored by the TLC. Then the $NaBH_4$ (3.0 eq) was added. The mixture reaction was stirred for another 2 hours. The resulting mixture was concentrated to afford the crude product, which was purified by column chromatography to give LC1a and LC2a as a white solid.

IV: **NL_2-NL_5** was added to the solution of **Compound 7 (or compound 11)** in methanol. The mixture reaction was warmed to 40 °C and stirred overnight. Then the $NaBH_4$ (3.0 eq) was added. The mixture reaction was stirred for another 2 hours. The mixture resulting was concentrated in

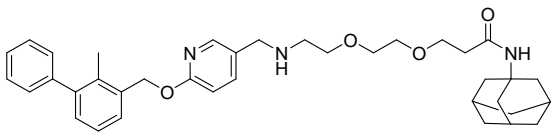
vacuum to give crude. Which was purified by column chromatography to give **compound 17 (or compound 18)**.

V: TFA was added to the solution of **Compound 17 (or compound 18)** in DCM. The mixture reaction was stirred for 2 hours at room temperature. The resulting mixture was concentrated in vacuum to give **compound 19 (or compound 20,** crude**)** without further purification.

VI: **R^3-NH_2** (1.0 eq) was added to a solution of **Compound 19**, HATU (1.5 eq) and DIPEA (5.0 eq) in DCM. The reaction was stirred for 3 hours at room temperature. The solution was extracted with EA/H_2O, and the organic phase was dried with anhydrous sodium sulfate and concentrated in vacuum to afford crude. The residue was purified by column chromatography (DCM: MeOH 100-10%, with 0.5% EtN_3) to give compounds **L2a-L5i**

VII: **VHL032** (1.0 eq) was added to the solution of **Compound 19**, HATU (1.5 eq) and DIPEA (5.0 eq) in DCM. The reaction was stirred for 3 hours at room temperature. The solution was extracted with EA/H_2O, and the organic phase was dried with anhydrous sodium sulfate and concentrated in vacuum to afford crude. The residue was purified by column chromatography (DCM: MeOH 100-10%, with 0.5% EtN_3) to give compounds **L1V-L5V**.

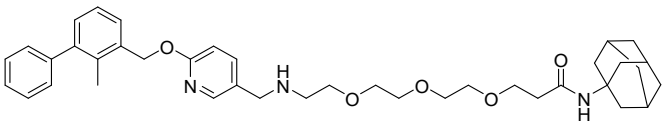
VIII: **R^3-NH_2** (R^3 =HyT c-f, 1.0 eq) was added to the solution of **Compound 20**, HATU (1.5 eq) and DIPEA (5.0 eq) in DCM. The reaction was stirred for 3 hours at room temperature. The solution was extracted with EA/H_2O, and the organic phase was dried with anhydrous sodium sulfate and concentrated in vacuum to afford crude. The residue was purified by column chromatography (DCM: MeOH 100-10%, with 0.5% EtN_3) to give compounds **Z2c-Z4f**.



N-**((3s,5s,7s)-adamantan-1-yl)-3-(2-(2-((((6-((2-methyl-[1,1'-biphenyl]-3-yl)methoxy)pyridin-3-yl)methyl)amino)ethoxy)ethoxy)propenamide** (**L2a**, yellow solid, 40% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (m, 1H), 7.43 – 7.30 (m, 5H), 7.24 (s, 1H), 7.19 (d, *J* = 2.28 Hz, 1H), 7.18 (s, 1H), 6.97 – 6.92 (m, 1H), 6.62 (d, *J* = 9.32 Hz, 1H), 5.95 (s, 1H), 5.18 (s, 2H), 3.68 (m, 6H), 3.58 (s, 4H), 2.90 – 2.85 (m, 2H), 2.33 (t, *J* = 5.88 Hz, 2H), 2.16 (s, 3H), 2.03 (s, 3H), 1.95 (s, 6H), 1.63 (s, 6H).

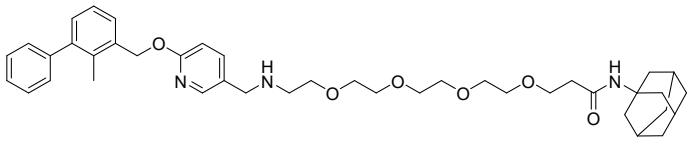
MS-ESI (m/z): calcd for [M + H]+ 598.3567；found 598.3627.



N-**((3s,5s,7s)-adamantan-1-yl)-1-(6-((2-methyl-[1,1'-biphenyl]-3-yl)methoxy)pyridin-3-yl)-5,8,11-trioxa-2-azatetradecan-14-amide** (**L3a**, yellow oil, 38% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (m, 1H), 7.38 (t, *J* = 7.2 Hz, 2H), 7.34 – 7.29 (m, 1H), 7.25 (d, *J* = 1.5 Hz, 1H), 7.24 – 7.20 (m, 2H), 7.19 – 7.15 (m, 2H), 6.91 (m, 1H), 6.62 (d, *J* = 9.32 Hz, 1H), 6.01 (s, 1H), 5.17 (s, 2H), 3.65 (t, *J* = 5.88 Hz, 2H), 3.57 (d, *J* = 3.6 Hz, 13H), 2.78 (t, *J* = 5.0 Hz, 2H), 2.33 (t, *J* = 5.88 Hz, 2H), 2.14 (s, 3H), 2.01 (s, 3H), 1.95 (d, *J* = 2.6 Hz, 6H), 1.63 (s, 6H).

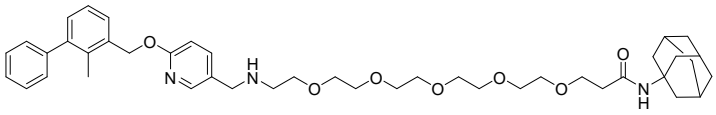
MS-ESI (m/z): calcd for [M + H]+ 642.3829；found (m/z) 642.3892.



N-**(adamantan-1-yl)-1-(6-((2-methyl-[1,1'-biphenyl]-3-yl)methoxy)pyridin-3-yl)-5,8,11,14-tetraoxa-2-azaheptadecan-17-amide** (**L4a**, oil, 35% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51-7.48 (m, 1H), 7.43 (t, *J* = 7.64 Hz, 2H), 7.36 (t, *J* = 7.12 Hz, 1H), 7.30 (s, 1H), 7.27 (s, 2H), 7.24 – 7.20 (m, 2H), 6.99 – 6.94 (m, 1H), 6.67 (d, *J* = 9.32 Hz, 1H), 6.13 (s, 1H), 5.21 (s, 2H), 3.70 (t, *J* = 5.88 Hz, 2H), 3.66 – 3.60 (m, 16H), 2.83 (t, *J* = 4.92 Hz, 2H), 2.39 (t, *J* = 5.96 Hz, 2H), 2.19 (s, 3H), 2.06 (s, 3H), 1.99-2.00 (m, 6H), 1.67 (s, 6H).

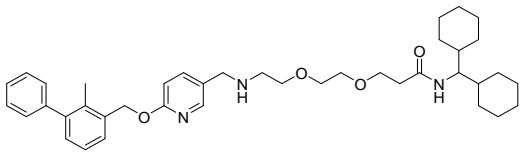
MS-ESI (m/z): calcd for [M + H]+ 686.4124；found 686.4156.



N-(adamantan-1-yl)-1-(6-((2-methyl-[1,1'-biphenyl]-3-yl)methoxy)pyridin-3-yl)-5,8,11,14,17-pentaoxa-2-azaicosan-20-amide (**L5a**, yellow oil, 20% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ7.52-7.49 (m, 1H), 7.45 – 7.40 (m, 2H), 7.38-7.34 (m , 1H), 7.29-7.27 (d, *J* = 1.6 Hz, 3H), 7.23 – 7.20 (m, 2H), 6.97-6.95 (m, 1H), 6.66 (d, *J* = 9.28 Hz, 1H), 6.11 (s, 1H), 5.21 (s, 2H), 3.70 (t, *J* = 5.88 Hz, 2H), 3.66 – 3.59 (m, 20H), 2.84 (t, *J* = 4.9 Hz, 2H), 2.39 (t, *J* = 5.8 Hz, 2H), 2.18 (s, 3H), 2.06 (s, 3H), 2.00 (s, 6H), 1.67 (s, 6H).

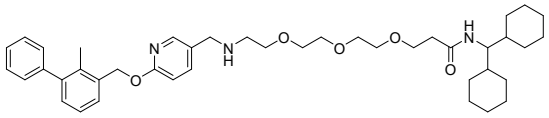
MS-ESI (m/z): calcd for [M + H]+ 730.4387；found 730.4421.



N-(dicyclohexylmethyl)-3-(2-(2-(((6-((2-methyl-[1,1'-biphenyl]-3-yl)methoxy)pyridin-3-yl)methyl)amino)ethoxy)ethoxy)propenamide (**L2b**, oil, 35% yield).

1H NMR (400 MHz, CDCl3) δ 7.44-7.48 (m, 1H), 7.30-7.34 (m, 3H), 7.29 – 7.26 (m, 1H), 7.20-7.16 (m, 2H), 7.13-7.10 (m, 2H), 6.57-6.53 (m, 1H), 6.58 – 6.50 (m, 1H), 5.97 – 5.80 (m, 1H), 5.12 (s, 2H), 4.08-4.01 (m, 4H), 3.65 (d, J = 9.7 Hz, 4H), 3.10-3.06 (m, 2H), 2.85 (d, J = 4.9 Hz, 2H), 2.73 – 2.71 (m, 1H), 2.4-2.36 (m, 2H), 2.09 (s, 3H), 1.65-1.51 (m, 10H), 1.37 – 1.32 (m, 2H), 1.12 – 1.02 (m, 6H), 0.96 – 0.90 (m, 2H), 0.82-0.78 (m, 2H).

MS-ESI (m/z): calcd for [M + H]+ 642.4226；found 642.4282.

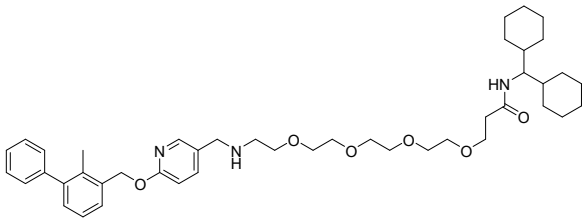


N-(dicyclohexylmethyl)-1-(6-((2-methyl-[1,1'-biphenyl]-3-yl)methoxy)pyridin-3-yl)-5,8,11-trioxa-2-azatetradecan-14-amide (**L3b**, oil, 30% yield).

1H NMR (400 MHz, CDCl3) δ 7.57-7.54 (m, 1H), 7.50 (d, J = 2.5 Hz, 1H), 7.43-7.39 (m, 2H), 7.37 – 7.33 (m, 1H), 7.28 – 7.25 (m, 2H), 7.21-7.19 (m, 2H), 6.97-6.95 (m, 1H), 6.63 (d, J = 9.3 Hz, 1H), 6.00 (d, J = 10.3 Hz, 1H), 5.19 (s, 2H), 3.87 (s, 2H), 3.74-3.68 (m, 4H), 3.60-3.59 (d, J = 5.2 Hz, 9H), 3.06 (t, J = 4.9 Hz, 2H), 2.46 (t, J = 5.8 Hz, 2H), 2.17 (s, 3H), 1.75 – 1.58 (m, 10H),

1.49 – 1.38 (m, 2H), 1.22 – 0.86 (m, 10H).

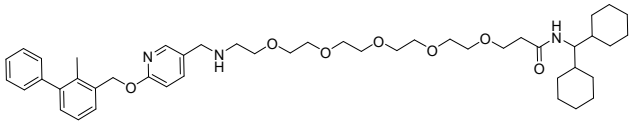
MS-ESI (m/z): calcd for [M + H]+ 686.4488；found 686.4496.



N-(dicyclohexylmethyl)-1-(6-((2-methyl-[1,1'-biphenyl]-3-yl)methoxy)pyridin-3-yl)-5,8,11,14-tetraoxa-2-azaheptadecan-17-amide (**L4b,** oil, 15% yield).

1H NMR (400 MHz, CDCl3) δ 7.70-7.67 (m, 1H), 7.58 (d, J = 2.5 Hz, 1H), 7.43 (t, J = 7.2 Hz, 2H), 7.37 (t, J = 7.2 Hz, 1H), 7.30 (d, J = 1.7 Hz, 1H), 7.28 (s, 1H), 7.26 – 7.19 (m, 2H), 7.02-7.00 (m, 1H), 6.72-6.66 (m, 2H), 5.22 (s, 2H), 3.92 (s, 2H), 3.78-3.75 (m, 4H), 3.67 – 3.58 (m, 13H), 3.08 (t, J = 4.6 Hz, 2H), 2.52 (t, J = 6.5 Hz, 2H), 2.20 (s, 3H), 1.76 – 1.58 (m, 10H), 1.54-1.47 (m, 2H), 1.22 – 0.91 (m, 10H).

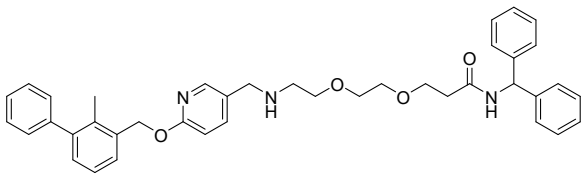
MS-ESI (m/z): calcd for [M + H]+ 730.4750；found 730.4723.



N-(dicyclohexylmethyl)-1-(6-((2-methyl-[1,1'-biphenyl]-3-yl)methoxy)pyridin-3-yl)-5,8,11,14,17-pentaoxa-2-azaicosan-20-amide (**L5b**, yellow oil, 20% yield).

1H NMR (400 MHz, CDCl3) δ 7.68 – 7.61 (m, 2H), 7.45-7.41 (m, 3H), 7.39 – 7.36 (m, 1H), 7.30 (d, J = 1.7 Hz, 1H), 7.25 – 7.22 (m, 2H), 7.02-6.99 (m, 1H), 6.69 (d, J = 9.2 Hz, 1H), 6.49 (d, J = 10.3 Hz, 1H), 5.23 (s, 2H), 3.93 (s, 2H), 3.81 (t, J = 4.7 Hz, 2H), 3.76 (t, J = 6.3 Hz, 2H), 3.65 – 3.61 (m, 17H), 3.09 (t, J = 4.6 Hz, 2H), 2.56 (t, J = 6.3 Hz, 2H), 2.20 (s, 3H), 1.68 (m, 10H), 1.43 – 1.39 (m, 2H), 1.12 – 0.84 (m, 10H).

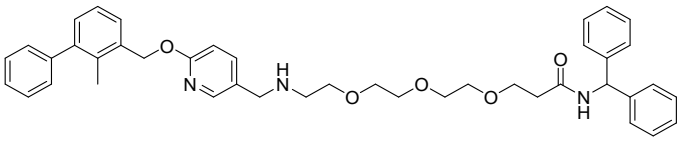
MS-ESI (m/z): calcd for [M + H]+ 774.5019；found 774.5024.



N-benzhydryl-3-(2-(2-(((6-((2-methyl-[1,1'-biphenyl]-3-yl)methoxy)pyridin-3-yl)methyl) amino) ethoxy)ethoxy) propanamide (**L2c**, oil, 25% yield).

1H NMR (400 MHz, CDCl3) δ 7.46 – 7.38 (m, 3H), 7.38 – 7.32 (m, 2H), 7.29 (t, J = 7.2 Hz, 8H), 7.24 – 7.18 (m, 7H), 6.91 (t, J = 4.6 Hz, 1H), 6.56 (d, J = 9.3 Hz, 1H), 6.20 (d, J = 7.9 Hz, 1H), 5.13 (s, 2H), 3.73 (t, J = 5.7 Hz, 2H), 3.60 – 3.56 (m, 2H), 3.52 (dd, J = 10.0, 5.0 Hz, 6H), 2.71 (t, J = 5.0 Hz, 2H), 2.50 (t, J = 5.7 Hz, 2H), 2.16 (s, 3H).

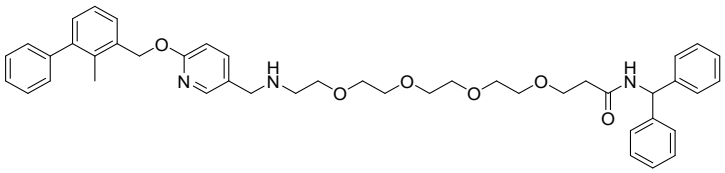
MS-ESI (m/z): calcd for [M + H]+ 630.3287; found :630.3325.



N-benzhydryl-1-(6-((2-methyl-[1,1'-biphenyl]-3-yl)methoxy)pyridin-3-yl)-5,8,11-trioxa-2-azatetradecan-14-amide (**L3c**, oil, 35% yield).

1H NMR (400 MHz, CDCl3) δ 7.45 – 7.39 (m, 4H), 7.38 – 7.35 (m, 1H), 7.29 (d, J = 6.8 Hz, 7H), 7.24-7.20 (m, 8H), 6.93 (t, J = 4.5 Hz, 1H), 6.60 (d, J = 9.2 Hz, 1H), 6.23 (d, J = 8.1 Hz, 1H), 5.16 (s, 2H), 3.73 (t, J = 5.6 Hz, 2H), 3.59 – 3.49 (m, 12H), 2.75 (t, J = 5.0 Hz, 2H), 2.54 (t, J = 5.7 Hz, 2H), 2.17 (s, 3H).

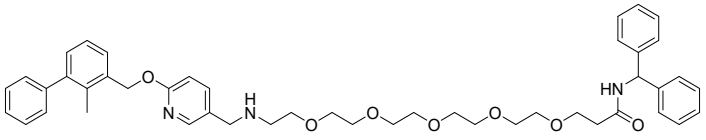
MS-ESI (m/z): calcd for [M + H]+ 674.3594；found 674.3592.



N-benzhydryl-1-(6-((2-methyl-[1,1'-biphenyl]-3-yl)methoxy)pyridin-3-yl)-5,8,11,14-tetraoxa-2-azaheptadecan-17-amide (**L4c**, yellow oil, 38% yield).

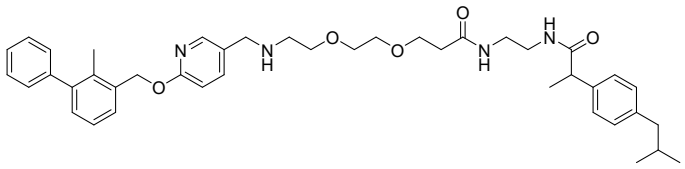
1H NMR (400 MHz, CDCl3) δ 7.51 (d, J = 8.4 Hz, 1H), 7.46 – 7.40 (m, 3H), 7.39 – 7.34 (m, 1H), 7.33 – 7.29 (m, 7H), 7.28 – 7.19 (m, 8H), 6.95 (t, J = 4.5 Hz, 1H), 6.63 (d, J = 9.3 Hz, 1H), 6.28 (d, J = 8.3 Hz, 1H), 5.18 (s, 2H), 3.77 (t, J = 5.8 Hz, 2H), 3.64-3.61 (m, 2H), 3.60 – 3.50 (m, 14H), 2.77 (t, J = 5.0 Hz, 2H), 2.57 (t, J = 5.8 Hz, 2H), 2.17 (s, 3H).

MS-ESI (m/z): calcd for [M + H]+ 718.3811; found 718.3856.



N-benzhydryl-1-(6-((2-methyl-[1,1'-biphenyl]-3-yl)methoxy)pyridin-3-yl)-5,8,11,14,17-pentaoxa-2-azaicosan-20-amide (**L5c**, yellow oil, 30% yield).

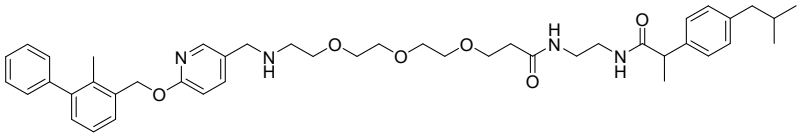
1H NMR (400 MHz, CDCl3) δ 8.01 (d, J = 8.4 Hz, 1H), 7.55-7.52 (m, 1H), 7.48 (d, J = 2.6 Hz, 1H), 7.45 – 7.40 (m, 2H), 7.40 – 7.34 (m, 1H), 7.31 – 7.28 (m, 2H), 7.28 – 7.20 (m, 8H), 6.98 (t, J = 8.7 Hz, 5H), 6.62 (d, J = 9.4 Hz, 1H), 6.25 (d, J = 8.3 Hz, 1H), 5.17 (s, 2H), 3.83 (s, 2H), 3.76 (t, J = 6.0 Hz, 2H), 3.73 – 3.68 (m, 2H), 3.61 – 3.52 (m, 16H), 3.02 (t, J = 4.8 Hz, 2H), 2.60 (t, J = 6.0 Hz, 2H), 2.17 (s, 3H).



2-(4-isobutylphenyl)-N-(1-(6-((2-methyl-[1,1'-biphenyl]-3-yl)methoxy)pyridin-3-yl)-11-oxo-5,8-dioxa-2,12-diazatetradecan-14-yl)propanamide (**L2h**, yellow oil, 35% yield).

1H NMR (600 MHz, CDCl3) δ 7.51-7.49 (m, J = 9.3, 2.5 Hz, 1H), 7.41 (t, J = 7.5 Hz, 2H), 7.37 – 7.32 (m, 2H), 7.28-7.26 (m, 2H), 7.22 – 7.18 (m, 4H), 7.08 (d, J = 7.8 Hz, 3H), 6.97 – 6.91 (m, 1H), 6.70 (d, J = 7.3 Hz, 1H), 6.64 (d, J = 9.3 Hz, 1H), 5.20 (s, 2H), 3.68 – 3.61 (m, 6H), 3.55 (s, 4H), 3.29-3.26 (m, 4H), 3.05 (q, J = 7.3 Hz, 1H), 2.85 (t, J = 5.0 Hz, 2H), 2.43 (d, J = 7.2 Hz, 2H), 2.36 (t, J = 5.8 Hz, 2H), 2.17 (s, 3H), 1.99 – 1.94 (m, 2H), 1.86-1.80 (m, 1H), 1.46 (d, J = 7.1 Hz, 3H), 0.89 (d, J = 6.6 Hz, 6H).

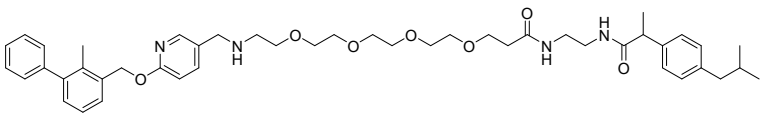
MS-ESI (m/z): calcd for [M + H]+ 695.4128；found 695.4108.



N-(2-(2-(4-isobutylphenyl)propanamido)ethyl)-1-(6-((2-methyl-[1,1'-biphenyl]-3-yl)methoxy)pyridin-3-yl)-5,8,11-trioxa-2-azatetradecan-14-amide (**L3h**, yellow oil, 25% yield).

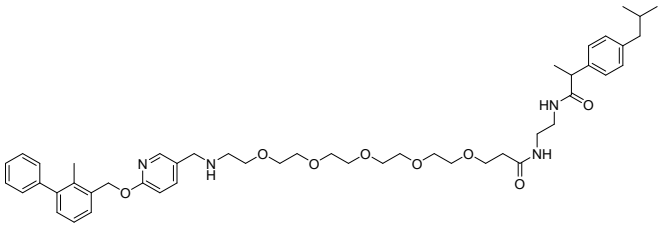
1H NMR (400 MHz, CDCl3) δ 7.52-7.51 (m, 1H), 7.44-7.40 (m, 2H), 7.38 – 7.32 (m, 1H), 7.30 – 7.25 (m, 3H), 7.22-7.20 (m, 4H), 7.08 (d, J = 7.9 Hz, 3H), 6.97-6.94 (m, 1H), 6.77 (d, J = 5.1 Hz, 1H), 6.64 (d, J = 9.3 Hz, 1H), 5.20 (s, 2H), 3.63 – 3.55 (m, 11H), 3.46 (d, J = 8.4 Hz, 4H), 3.47-3.45 (m, 4H), 2.82 (t, J = 4.9 Hz, 2H), 2.43 (d, J = 7.1 Hz, 2H), 2.36 (t, J = 5.7 Hz, 2H), 2.17 (s, 3H), 1.83 (d, J = 6.7 Hz, 1H), 1.46 (d, J = 7.1 Hz, 3H), 0.89 (d, J = 6.6 Hz, 6H).

MS-ESI (m/z): calcd for [M + H]+ 739.4390；found 739.4366.



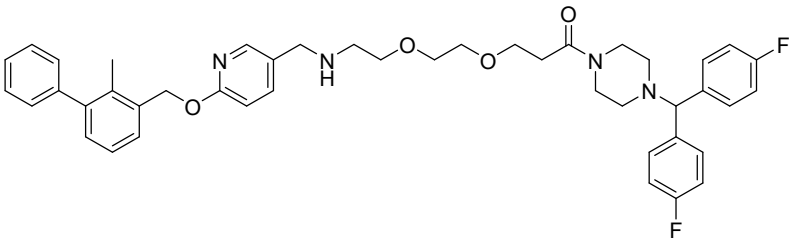
N-(2-(2-(4-isobutylphenyl)propanamido)ethyl)-1-(6-((2-methyl-[1,1'-biphenyl]-3-yl)methoxy)pyridin-3-yl)-5,8,11,14-tetraoxa-2-azaheptadecan-17-amide (**L4h**, yellow oil, 35% yield). 1H NMR (600 MHz, CDCl3) δ 7.52-7.50 (m, 1H), 7.41 (t, J = 7.6 Hz, 2H), 7.38 – 7.33 (m, 2H), 7.32 (d, J = 2.5 Hz, 1H), 7.30 – 7.27 (m, 2H), 7.24 – 7.19 (m, 4H), 7.07 (d, J = 8.1 Hz, 2H), 6.96-6.94 (m, 1H), 6.80 (t, J = 5.1 Hz, 1H), 6.65 (d, J = 9.3 Hz, 1H), 5.20 (s, 2H), 3.68 – 3.57 (m, 18H), 3.54 (d, J = 7.1 Hz, 1H), 3.36-3.31 (m, 2H), 3.31 – 3.27 (m, 2H), 2.85 (t, J = 4.9 Hz, 2H), 2.42 (d, J = 7.1 Hz, 2H), 2.37 (t, J = 6.0 Hz, 2H), 2.17 (s, 3H), 1.87-1.78 (m, 1H), 1.46 (d, J = 7.0 Hz, 3H), 0.89 (d, J = 6.6 Hz, 6H).

MS-ESI (m/z): calcd for [M + H]+ 783.4652；found 783.4666.



N-(2-(2-(4-isobutylphenyl)propanamido)ethyl)-1-(6-((2-methyl-[1,1'-biphenyl]-3-yl)methoxy) pyridin-3-yl)-5,8,11,14,17-pentaoxa-2-azaicosan-20-amide (**L5h**, yellow oil, 15% yield). 1H NMR (600 MHz, CDCl3) δ 7.56-7.54(m, 1H), 7.47 (t, J = 5.6 Hz, 1H), 7.43 – 7.39 (m, 3H), 7.37 – 7.34 (m, 1H), 7.28 – 7.26 (m, 2H), 7.23 – 7.19 (m, 4H), 7.07 (d, J = 7.8 Hz, 2H), 6.95-6.4(m, 1H), 6.86 (s, 1H), 6.66 (d, J = 9.4 Hz, 1H), 5.20 (s, 2H), 3.77 (s, 2H), 3.68-3.52 (m, 4H), 3.62 – 3.51 (m, 17H), 3.37 – 3.31 (m, 2H), 3.30 – 3.24 (m, 2H), 2.97 – 2.89 (m, 2H), 2.44 – 2.39 (m, 4H), 2.18 (s, 3H), 1.86-1.79 (m, 1H), 1.46 (d, J = 7.1 Hz, 3H), 0.89 (d, J = 6.6 Hz, 6H).

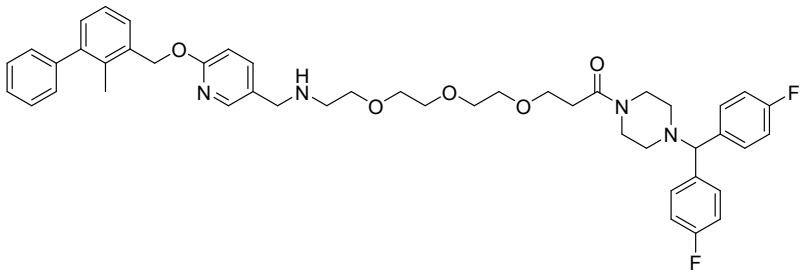
MS-ESI (m/z): calcd for [M + H]+ 827.4914；found 827.4930[M + H]+.



1-(4-(bis(4-fluorophenyl)methyl)piperazin-1-yl)-3-(2-(2-(((6-((2-methyl-[1,1'-biphenyl]-3-yl)methoxy)pyridin-3-yl)methyl)amino)ethoxy)ethoxy)propan-1-one (**L2d**, yellow oil, 40% yield).

1H NMR (400 MHz, CDCl3) δ 7.53-7.50 (m, 1H), 7.43 (t, J = 7.3 Hz, 2H), 7.38-7.35 (m, 6H), 7.31 – 7.27 (m, 3H), 7.22 (d, J = 4.5 Hz, 2H), 7.00 (t, J = 8.5 Hz, 5H), 6.65 (d, J = 9.3 Hz, 1H), 5.20 (s, 2H), 4.24 (s, 1H), 3.76 (t, J = 6.3 Hz, 2H), 3.70 (s, 2H), 3.66 (d, J = 4.9 Hz, 2H), 3.60 (d, J = 6.9 Hz, 6H), 3.46 (t, J = 5.0 Hz, 2H), 2.87 (t, J = 5.0 Hz, 2H), 2.57 (t, J = 6.3 Hz, 2H), 2.34 (q, J = 4.2 Hz, 4H), 2.18 (s, 3H).

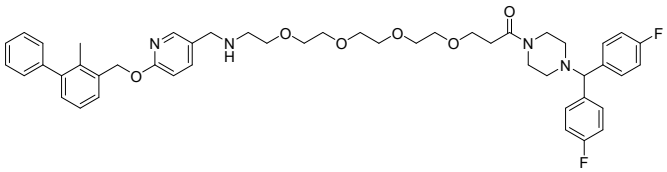
MS-ESI (m/z): calcd for [M + H]+ 735.3677；found 735.3624.



14-(4-(bis(4-fluorophenyl)methyl)piperazin-1-yl)-1-(6-((2-methyl-[1,1'-biphenyl]-3-yl)methoxy)pyridin-3-yl)-5,8,11-trioxa-2-azatetradecan-14-one

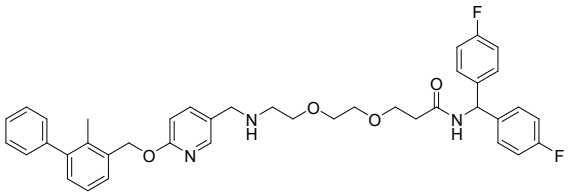
(**L3d**, yellow oil, 25% yield). 1H NMR (400 MHz, CDCl3) δ 7.53-7.50 (m, 1H), 7.43-7.39 (m, 3H), 7.36-7.32 (m, 6H), 7.29 – 7.26 (m, 2H), 7.20 (d, J = 3.7 Hz, 2H), 7.01-6.94 (m, 5H), 6.62 (d, J = 9.3 Hz, 1H), 5.18 (s, 2H), 4.22 (s, 1H), 3.73 (t, J = 6.3 Hz, 2H), 3.65 – 3.56 (m, 14H), 3.45 (t, J = 5.0 Hz, 2H), 2.85 (t, J = 4.9 Hz, 2H), 2.57 (t, J = 6.3 Hz, 2H), 2.37 – 2.30 (m, 4H), 2.16 (s, 3H).

MS-ESI (m/z): calcd for [M + H]+ 779.3939；found 779.3847.



17-(4-(bis(4-fluorophenyl)methyl)piperazin-1-yl)-1-(6-((2-methyl-[1,1'-biphenyl]-3-yl)methoxy)pyridin-3-yl)-5,8,11,14-tetraoxa-2-azaheptadecan-17-one (**L4d**, yellow oil, 30% yield). 1H NMR (400 MHz, CDCl3) δ 7.57-7.54 (m, 1H), 7.49 – 7.39 (m, 4H), 7.37-7.32 (m, 5H), 7.28 (t, J = 4.3 Hz, 2H), 7.21 (d, J = 5.8 Hz, 2H), 6.98 (t, J = 8.7 Hz, 5H), 6.64 (d, J = 9.3 Hz, 1H), 5.20 (s, 2H), 4.23 (s, 1H), 3.75 (t, J = 6.6 Hz, 2H), 3.72 (s, 2H), 3.69 (t, J = 4.9 Hz, 2H), 3.65 – 3.55 (m, 14H), 3.46 (t, J = 5.0 Hz, 2H), 2.90 (t, J = 4.8 Hz, 2H), 2.58 (t, J = 6.6 Hz, 2H), 2.38 – 2.27 (m, 4H), 2.18 (s, 3H).

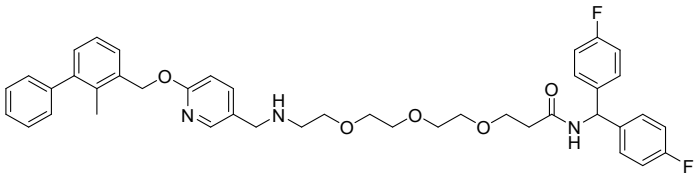
MS-ESI (m/z): calcd for [M + H]+ 823.4201; found 823.4126.



N-(bis(4-fluorophenyl)methyl)-3-(2-(2-(((6-((2-methyl-[1,1'-biphenyl]-3-yl)methoxy)pyridin-3-yl)methyl)amino)ethoxy)ethoxy)propenamide (**L2e**, yellow oil, 35% yield).

1H NMR (400 MHz, CDCl3) δ 7.68 (d, J = 8.0 Hz, 1H), 7.50-7.32 (m, 6H), 7.25 – 7.22 (m, 2H), 7.22 – 7.16 (m, 6H), 6.97 – 6.92 (m, 4H), 6.91-6.89 (m, 1H), 6.50 (d, J = 9.3 Hz, 1H), 6.14 (d, J = 7.9 Hz, 1H), 5.12 (s, 2H), 3.82 (s, 2H), 3.69 (t, J = 5.8 Hz, 2H), 3.63 (d, J = 5.0 Hz, 2H), 3.55 – 3.47 (m, 4H), 2.97 (t, J = 4.9 Hz, 2H), 2.48 (t, J = 5.8 Hz, 2H), 2.13 (s, 3H).

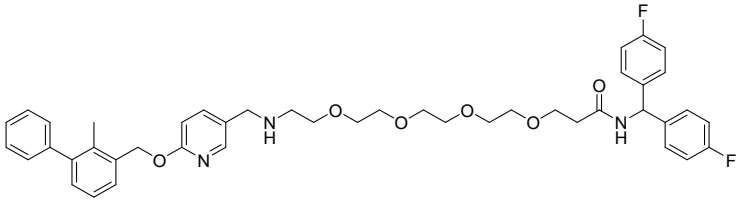
MS-ESI (m/z): calcd for [M + H]+ 666.3099；found 666.3110.



N-(bis(4-fluorophenyl)methyl)-1-(6-((2-methyl-[1,1'-biphenyl]-3-yl)methoxy)pyridin-3-yl)-5,8,11-trioxa-2-azatetradecan-14-amide (**L3e**, yellow oil, 35% yield).

1H NMR (400 MHz, CDCl3) δ 7.47-7.42 (m, 5H), 7.39 – 7.33 (m, 1H), 7.28 – 7.25 (m, 2H), 7.24 – 7.18 (m, 5H), 7.04 – 6.96 (m, 4H), 6.94 (t, J = 4.6 Hz, 1H), 6.57 (d, J = 9.2 Hz, 1H), 6.16 (d, J = 7.9 Hz, 1H), 5.17 (s, 2H), 3.74 (s, 2H), 3.70 (t, J = 5.7 Hz, 2H), 3.64 – 3.59 (m, 2H), 3.54 (d, J = 5.4 Hz, 8H), 2.93 (t, J = 5.0 Hz, 2H), 2.55 (t, J = 5.7 Hz, 2H), 2.17 (s, 3H).

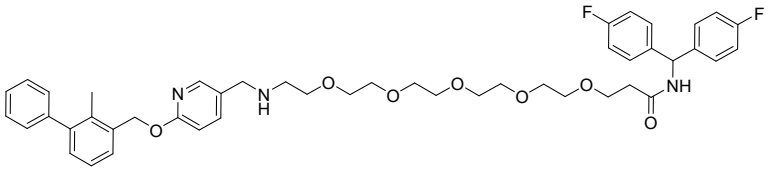
MS-ESI (m/z): calcd for [M + H]+ 710.3361；found 710.3371.



N-(bis(4-fluorophenyl)methyl)-1-(6-((2-methyl-[1,1'-biphenyl]-3-yl)methoxy)pyridin-3-yl)-5,8,11,14-tetraoxa-2-azaheptadecan-17-amide (**L4e**, yellow oil, 35% yield). 1H NMR (400 MHz, CDCl3) δ 8.15 (d, J = 8.4 Hz, 1H), 7.51-7.48 (m, 1H), 7.44-7.42 (m, 3H), 7.39 – 7.34 (m, 1H), 7.29 – 7.21 (m, 8H), 7.04 – 6.91 (m, 5H), 6.59 (d, J = 9.4 Hz, 1H), 6.24 (d, J = 8.4 Hz, 1H), 5.16 (s, 2H), 3.80 – 3.71 (m, 4H), 3.68-3.65 (m, 2H), 3.64 – 3.60 (m, 2H), 3.60 – 3.50 (m, 10H),

2.99 (t, J = 4.7 Hz, 2H), 2.52 (t, J = 6.2 Hz, 2H), 2.16 (s, 3H).

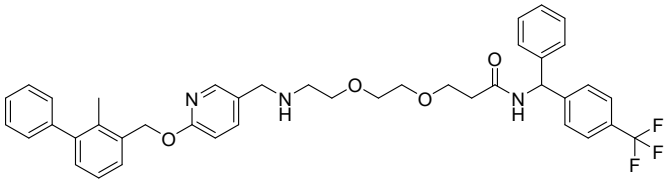
MS-ESI (m/z): calcd for [M + H]+ 754.3632；found 754.3634.



N-(bis(4-fluorophenyl)methyl)-1-(6-((2-methyl-[1,1'-biphenyl]-3-yl)methoxy)pyridin-3-yl)-5,8,11,14,17-pentaoxa-2-azaicosan-20-amide (**L5e**, yellow oil, 25% yield).

1H NMR (400 MHz, CDCl3) δ 8.03-8.01 (m 1H), 7.55-7.52 (m, 1H), 7.48 (d, J = 2.6 Hz, 1H), 7.45 – 7.40 (m, 2H), 7.40 – 7.34 (m, 1H), 7.30 – 7.28 (m, 2H), 7.28 – 7.25 (m, 3H), 7.25 (d, J = 2.1 Hz, 1H), 7.23 – 7.20 (m, 2H), 7.02 – 6.93 (m, 5H), 6.62 (d, J = 9.4 Hz, 1H), 6.25 (d, J = 8.3 Hz, 1H), 5.17 (s, 2H), 3.83 (s, 2H), 3.76 (t, J = 6.0 Hz, 2H), 3.73 – 3.68 (m, 2H), 3.61 – 3.52 (m, 16H), 3.02 (t, J = 4.8 Hz, 2H), 2.60 (t, J = 6.0 Hz, 2H), 2.17 (s, 3H).

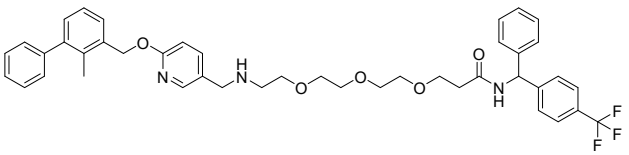
MS-ESI (m/z): calcd for [M + H]+ 798.3385；found 798.3856.



3-(2-(2-(((6-((2-methyl-[1,1'-biphenyl]-3-yl)methoxy)pyridin-3-yl)methyl)amino) ethoxy) ethoxy) -N-(phenyl(4-(trifluoromethyl)phenyl)methyl)propenamide (**L2f**, yellow oil, 20% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.2 Hz, 2H), 7.46 – 7.35 (m, 7H), 7.35 – 7.21 (m, 9H), 7.20 (s, 1H), 6.97 – 6.87 (m, 1H), 6.59 (d, *J* = 9.3 Hz, 1H), 6.27 (d, *J* = 7.9 Hz, 1H), 5.16 (s, 2H), 3.76-3.74 (m, 2H), 3.61-3.59 (m, 2H), 3.55 – 3.44 (m, 6H), 2.70 (t, *J* = 5.0 Hz, 2H), 2.54 (t, *J* = 5.6 Hz, 2H), 2.17 (s, 3H).

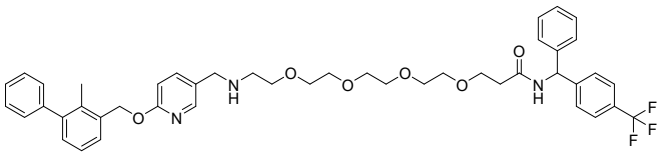
MS-ESI (m/z): calcd for [M + H]+ 698.3168；found 698.3161.



1-(6-((2-methyl-[1,1'-biphenyl]-3-yl)methoxy)pyridin-3-yl)-N-(phenyl(4-(trifluoromethyl) phenyl) methyl)-5,8,11-trioxa-2-azatetradecan-14-amide (**L3f**, yellow oil, 28% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.54 (d, *J* = 8.0 Hz, 2H), 7.46 – 7.38 (m, 5H), 7.38 – 7.33 (m, 2H), 7.30 (s, 2H), 7.28 – 7.22 (m, 5H), 7.20 (d, *J* = 4.5 Hz, 2H), 6.94 (t, *J* = 4.6 Hz, 1H), 6.58 (d, *J* = 9.3 Hz, 1H), 6.26 (d, *J* = 8.0 Hz, 1H), 5.16 (s, 2H), 3.72-3.75 (m, 2H), 3.68 – 3.50 (m, 12H), 2.87 (s, 2H), 2.59 (s, 2H), 2.16 (s, 3H).

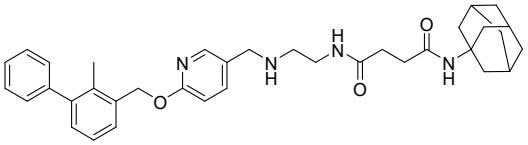
MS-ESI (m/z): calcd for [M + H]+ 742.3423；found 742.3438.



1-(6-((2-methyl-[1,1'-biphenyl]-3-yl)methoxy)pyridin-3-yl)-N-(phenyl(4-(trifluoromethyl) phenyl)methyl)-5,8,11,14-tetraoxa-2-azaheptadecan-17-amide (**L4f**, yellow oil, 30% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 7.8 Hz, 1H), 7.60 – 7.47 (m, 5H), 7.46 – 7.29 (m, 8H), 7.28 – 7.17 (m, 5H), 7.06 – 6.87 (m, 1H), 6.60 (d, *J* = 9.4 Hz, 1H), 6.34 (d, *J* = 8.5 Hz, 1H), 5.17 (s, 2H), 3.76 (d, *J* = 6.2 Hz, 2H), 3.70 (s, 2H), 3.68 – 3.61 (m, 4H), 3.60 – 3.52 (m, 10H), 2.94 (d, *J* = 2.4 Hz, 2H), 2.59-2.61 (m, 2H), 2.16 (s, 3H).

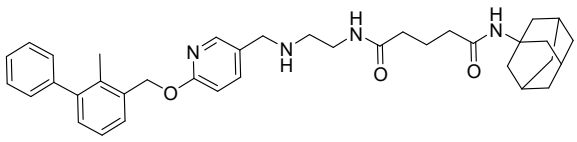
MS-ESI (m/z): calcd for [M + H]+ 786.3685；found 786.3676.



N1-(adamantan-1-yl)-N4-(2-(((6-((2-methyl-[1,1'-biphenyl]-3-yl)methoxy)pyridin-3-yl)methyl)amino)ethyl)succinimide (**LC1a**, yellow oil, 30% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.41 (m, 3H), 7.40-7.34 (m, 1H), 7.30 (d, *J* = 1.4 Hz, 1H), 7.28 – 7.28 (m, 1H), 7.25 – 7.21 (m, 2H), 7.18 (d, *J* = 2.1 Hz, 1H), 6.96-6.95 (m, 1H), 6.67 (d, *J* = 9.3 Hz, 1H), 6.55 (s, 1H), 5.47 (s, 1H), 5.21 (s, 2H), 3.54 (s, 2H), 3.35 (dd, *J* = 11.5, 5.7 Hz, 2H), 2.74 (t, *J* = 5.8 Hz, 2H), 2.45 (s, 4H), 2.19 (s, 3H), 2.07 (s, 3H), 1.97 (d, *J* = 2.4 Hz, 6H), 1.66 (s, 6H).

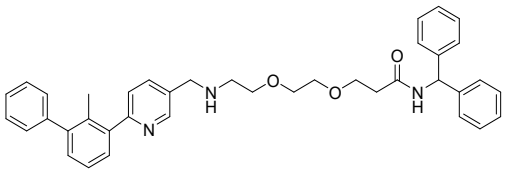
MS-ESI (m/z): calcd for [M + H]+ 581.3472；found 581.3447.



N1-(adamantan-1-yl)-N5-(2-(((6-((2-methyl-[1,1'-biphenyl]-3-yl)methoxy)pyridin-3-yl)methyl)amino)ethyl)glutaramide (**LC2a**, yellow oil, 35% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.41 (m, 3H), 7.39 – 7.33 (m, 1H), 7.30 (d, *J* = 1.5 Hz, 1H), 7.26 (s, 1H), 7.26 – 7.19 (m, 2H), 7.16 (d, *J* = 2.1 Hz, 1H), 6.97-6.96 (m, 1H), 6.67 (d, *J* = 9.3 Hz, 1H), 6.41 (s, 1H), 5.44 (s, 1H), 5.21 (s, 2H), 3.53 (s, 2H), 3.36 (q, *J* = 5.7 Hz, 2H), 2.74 (t, *J* = 5.8 Hz, 2H), 2.25 (t, *J* = 7.1 Hz, 2H), 2.19 (s, 3H), 2.15 (t, *J* = 7.0 Hz, 2H), 2.07 (d, *J* = 5.3 Hz, 3H), 1.99 (d, *J* = 2.6 Hz, 6H), 1.99-1.91 (m, 2H), 1.68 (s, 6H).

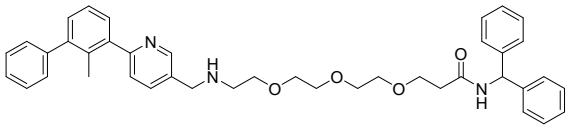
MS-ESI (m/z): calcd for [M + H]+ 595.3603；found 595.3628.



N-benzhydryl-3-(2-(2-(((6-(2-methyl-[1,1'-biphenyl]-3-yl) pyridin-3-yl)methyl) amino) ethoxy) ethoxy) propanamide (**Z2c**, yellow oil, 25% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (d, *J* = 1.7 Hz, 1H), 7.83-7.81 (m, 1H), 7.62 (d, *J* = 8.3 Hz, 1H), 7.45 – 7.28 (m, 12H), 7.26 – 7.23 (m, 5H), 6.28 (d, *J* = 8.3 Hz, 1H), 6.02 (s, 1H), 3.92 (s, 2H), 3.78 (t, *J* = 5.7 Hz, 2H), 3.65 – 3.55 (m, 6H), 2.93 – 2.82 (m, 2H), 2.54 (t, *J* = 5.7 Hz, 2H), 2.16 (s, 3H).

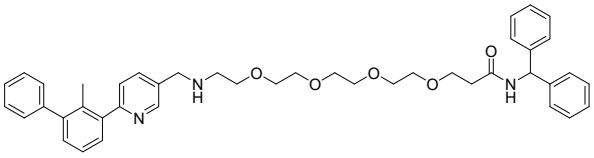
MS-ESI (m/z): calcd for [M + H]+ 600.3199；found 600.3181.



N-benzhydryl-1-(6-(2-methyl-[1,1'-biphenyl]-3-yl)pyridin-3-yl)-5,8,11-trioxa-2-azatetradecan-14-amide (Z3c, yellow oil, 25% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, *J* = 1.7 Hz, 1H), 7.77-7.74 (m, 1H), 7.44 – 7.27 (m, 14H), 7.24 (d, *J* = 7.4 Hz, 5H), 6.27 (d, *J* = 8.3 Hz, 1H), 3.83 (s, 2H), 3.75 (t, *J* = 5.6 Hz, 2H), 3.560-3.58 (m, 6H), 3.52 (d, *J* = 3.4 Hz, 4H), 2.82 (t, *J* = 5.0 Hz, 2H), 2.54 (t, *J* = 5.6 Hz, 2H), 2.15 (s, 3H).

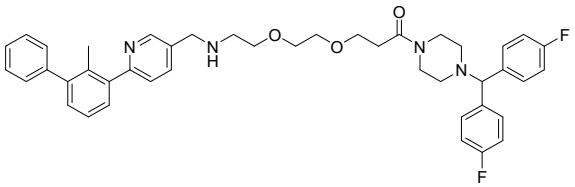
MS-ESI (m/z): calcd for [M + H]+ 644.3460；found 644.3444.



N-benzhydryl-1-(6-(2-methyl-[1,1'-biphenyl]-3-yl)pyridin-3-yl)-5,8,11,14-tetraoxa-2-azaheptadecan-17-amide (**Z4c**, yellow oil, 30% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, *J* = 1.6 Hz, 1H), 7.92 (dd, *J* = 13.0, 5.1 Hz, 2H), 7.46 – 7.27 (m, 12H), 7.25 – 7.17 (m, 5H), 6.25 (d, *J* = 8.3 Hz, 1H), 4.06 (s, 2H), 3.74 (t, *J* = 6.0 Hz, 2H), 3.71 – 3.66 (m, 2H), 3.57 (d, *J* = 12.5 Hz, 10H), 3.07 – 3.01 (m, 2H), 2.52 (t, *J* = 6.0 Hz, 2H), 2.14 (s, 2H).

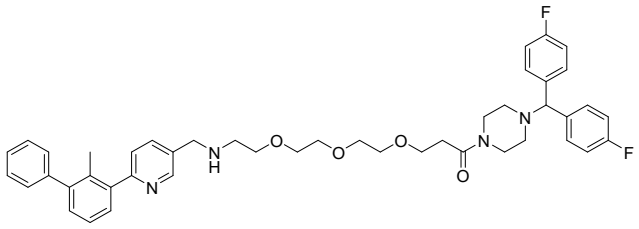
MS-ESI (m/z): calcd for [M + H]+ 688.3723；found 688.3706.



1-(4-(bis(4-fluorophenyl)methyl)piperazin-1-yl)-3-(2-(2-(((6-(2-methyl-[1,1'-biphenyl]-3-yl)pyridin-3-yl)methyl)amino)ethoxy)ethoxy)propan-1-one (**Z2d**, yellow oil, 30% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (s, 1H), 7.95 (d, *J* = 6.5 Hz, 1H), 7.49 – 7.41 (m, 3H), 7.46-7.31 (m, 10H), 6.98 (t, *J* = 8.6 Hz, 4H), 4.23 (s, 1H), 4.04 (s, 2H), 3.79 (t, *J* = 6.3 Hz, 2H), 3.75 – 3.70 (m, 2H), 3.64 (s, 4H), 3.61 – 3.57 (m, 2H), 3.50 – 3.44 (m, 2H), 3.02 – 2.93 (m, 2H), 2.60 (t, *J* = 6.3 Hz, 2H), 2.36-2.32 (m, 4H), 2.17 (s, 3H).

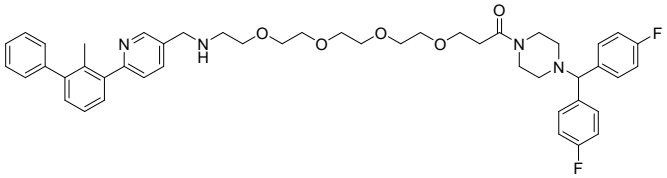
MS-ESI (m/z): calcd for [M + H]+ 705.3564；found 705.3572.



14-(4-(bis(4-fluorophenyl)methyl)piperazin-1-yl)-1-(6-(2-methyl-[1,1'-biphenyl]-3-yl)pyridin-3-yl)-5,8,11-trioxa-2-azatetradecan-14-one (**Z3d**, yellow oil, 30% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (s, 1H), 8.12 (d, *J* = 8.0 Hz, 1H), 7.49-7.43 (m, 3H), 7.37 (t, *J* = 7.4 Hz, 4H), 7.35 – 7.30 (m, 7H), 6.97 (t, *J* = 8.6 Hz, 4H), 4.28 (s, 2H), 4.21 (s, 1H), 3.83 (d, *J* = 4.2 Hz, 2H), 3.71 (t, *J* = 5.6 Hz, 2H), 3.65 (d, *J* = 2.3 Hz, 4H), 3.61 (d, *J* = 3.4 Hz, 4H), 3.58 (d, *J* = 5.0 Hz, 2H), 3.47 – 3.43 (m, 2H), 3.22 (s, 2H), 2.56 (t, *J* = 5.6 Hz, 2H), 2.36 – 2.30 (m, 4H), 2.15 (s, 3H).

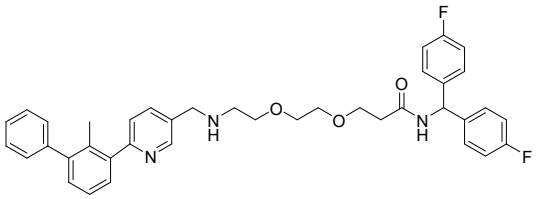
MS-ESI (m/z): calcd for [M + H]+ 749.3834；found 749.3835.



17-(4-(bis(4-fluorophenyl)methyl)piperazin-1-yl)-1-(6-(2-methyl-[1,1'-biphenyl]-3-yl)pyridin-3-yl)-5,8,11,14-tetraoxa-2-azaheptadecan-17-one (**Z4d**, yellow oil, 30% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (d, *J* = 1.6 Hz, 1H), 7.96 (d, *J* = 7.2 Hz, 1H), 7.47 – 7.41 (m, 3H), 7.41 – 7.29 (m, 10H), 6.99 (t, *J* = 8.6 Hz, 4H), 4.23 (s, 1H), 4.00 (s, 2H), 3.79-.3.72 (m, 4H), 3.63 (dd, *J* = 18.2, 8.9 Hz, 14H), 3.50 – 3.43 (m, 2H), 2.97 (s, 2H), 2.60 (s, 2H), 2.34 (d, *J* = 4.4 Hz, 4H), 2.18 (s, 3H).

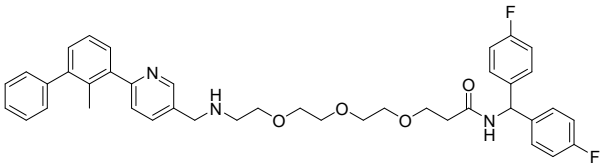
MS-ESI (m/z): calcd for [M + H]+ 793.4096；found 793.4094.



N-(bis(4-fluorophenyl)methyl)-3-(2-(2-(((6-(2-methyl-[1,1'-biphenyl]-3-yl)pyridin-3-yl)methyl)amino)ethoxy)ethoxy)propenamide (**Z2e**, yellow oil, 25% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, *J* = 1.9 Hz, 1H), 7.75-7.72 (m, 1H), 7.54 (d, *J* = 8.1 Hz, 1H), 7.47 – 7.29 (m, 10H), 7.21 – 7.16 (m, 4H), 7.20-7.16 (m, 4H), 6.23 (d, *J* = 8.1 Hz, 1H), 3.83 (s, 2H), 3.77 (t, *J* = 5.6 Hz, 2H), 3.59-3.56 (m, 2H), 3.60 – 3.55 (m, 4H), 2.82 – 2.78 (m, 2H), 2.53 (t, *J* = 5.6 Hz, 2H), 2.16 (s, 3H).

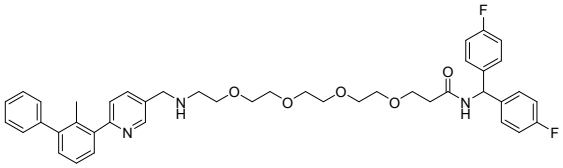
MS-ESI (m/z): calcd for [M + H]+ 636.3002；found 636.2993.



N-(bis(4-fluorophenyl)methyl)-1-(6-(2-methyl-[1,1'-biphenyl]-3-yl)pyridin-3-yl)-5,8,11-trioxa-2-azatetradecan-14-amide (**Z3e**, yellow oil, 25% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, *J* = 1.8 Hz, 1H), 7.78-7.76 (m, 1H), 7.55 – 7.29 (m, 11H), 7.24 – 7.19 (m, 4H), 7.04 – 6.97 (m, 4H), 6.25 (d, *J* = 8.2 Hz, 1H), 3.86 (s, 2H), 3.76 (t, *J* = 5.6 Hz, 2H), 3.63-3.53 (m, 10H), 2.85 (t, *J* = 5.1 Hz, 2H), 2.55 (t, *J* = 5.6 Hz, 2H), 2.17 (s, 3H).

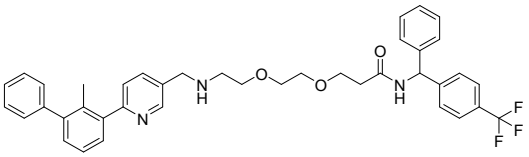
MS-ESI (m/z): calcd for [M + H]+ 680.3261；found 680.3225.



N-(bis(4-fluorophenyl)methyl)-1-(6-(2-methyl-[1,1'-biphenyl]-3-yl)pyridin-3-yl)-5,8,11,14-tetraoxa-2-azaheptadecan-17-amide (**Z4e**, yellow oil, 30% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (d, *J* = 1.9 Hz, 1H), 7.85-7.82 (m, 1H), 7.67 (s, 1H), 7.46-7.22 (m, 9H), 7.29-7.22 (m, 4H), 7.00 (t, *J* = 8.7 Hz, 4H), 6.25 (d, *J* = 8.3 Hz, 1H), 3.93 (s, 2H), 3.76 (t, *J* = 5.8 Hz, 2H), 3.68 – 3.64 (m, 2H), 3.64 – 3.55 (m, 12H), 2.95 – 2.90 (m, 2H), 2.54 (t, *J* = 5.8 Hz, 2H), 2.17 (s, 3H).

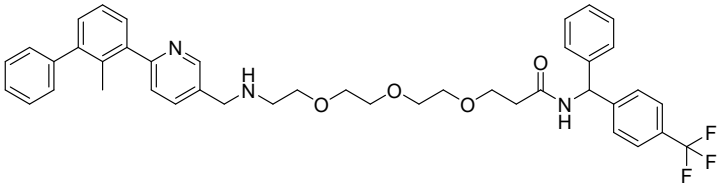
MS-ESI (m/z): calcd for [M + H]+ 724.3523；found 742.3517.



3-(2-(2-(((6-(2-methyl-[1,1'-biphenyl]-3-yl)pyridin-3-yl)methyl)amino)ethoxy)ethoxy)-N-(phenyl(4-(trifluoromethyl)phenyl)methyl)propenamide (**Z2f,** yellow oil, 25% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, *J* = 1.5 Hz, 1H), 7.74-7.71 (m, 1H), 7.57 (d, *J* = 8.2 Hz, 2H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.47 – 7.42 (m, 2H), 7.42 – 7.35 (m, 6H), 7.35 – 7.28 (m, 6H), 7.21 (d, *J* = 6.8 Hz, 2H), 6.32 (d, *J* = 8.0 Hz, 1H), 3.80 (d, *J* = 7.2 Hz, 4H), 3.69 – 3.63 (m, 2H), 3.62 – 3.54 (m, 4H), 2.78 (t, *J* = 5.0 Hz, 2H), 2.57 (t, *J* = 5.5 Hz, 2H), 2.17 (s, 3H).

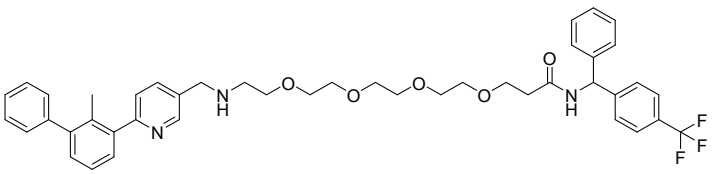
MS-ESI (m/z): calcd for [M + H]+ 668.3007；found 668.3055.



1-(6-(2-methyl-[1,1'-biphenyl]-3-yl)pyridin-3-yl)-N-(phenyl(4-(trifluoromethyl)phenyl) methyl) -5,8,11-trioxa-2-azatetradecan-14-amide (**Z3f,** yellow oil, 25% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, *J* = 1.7 Hz, 1H), 7.79-7.77 (m, 1H), 7.61 – 7.54 (m, 3H), 7.46 – 7.29 (m, 13H), 7.26 – 7.21 (m, 2H), 6.30 (d, *J* = 8.0 Hz, 1H), 3.90 (s, 2H), 3.74 (m, 2H), 3.65 – 3.50 (m, 10H), 2.86 (t, *J* = 5.0 Hz, 2H), 2.60 – 2.49 (m, 2H), 2.16 (s, 3H).

MS-ESI (m/z): calcd for [M + H]+ 712.3281；found 712.3317.

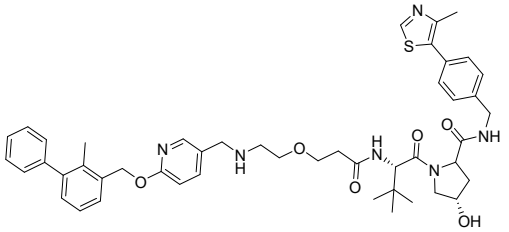


1-(6-(2-methyl-[1,1'-biphenyl]-3-yl)pyridin-3-yl)-N-(phenyl(4-(trifluoromethyl)phenyl)methyl)-5,8,11,14-tetraoxa-2-azaheptadecan-17-amide (**Z4f,** yellow

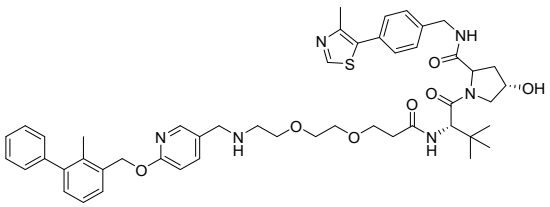
oil, 25% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1H), 7.81 (m, 1H), 7.56 (t, *J* = 9.2 Hz, 3H), 7.44 (t, *J* = 7.1 Hz, 5H), 7.39 – 7.30 (m, 8H), 7.26 (d, *J* = 7.9 Hz, 3H), 6.26 (d, *J* = 7.8 Hz, 1H), 3.99 (s, 2H), 3.75 (t, *J* = 5.3 Hz, 2H), 3.67 – 3.62 (m, 3H), 3.59 (d, *J* = 3.5 Hz, 6H), 3.56 – 3.49 (m, 6H), 3.00 – 2.92 (m, 2H), 2.59 (d, *J* = 3.7 Hz, 2H), 2.16 (s, 3H).

MS-ESI (m/z): calcd for [M + H]+ 756.3553；found 756.3580.

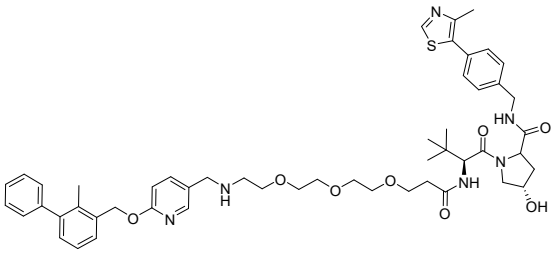


(4S)-1-((S)-3,3-dimethyl-2-(3-(2-(((6-((2-methyl-[1,1'-biphenyl]-3-yl)methoxy)pyridin-3-yl)methyl)amino)ethoxy)propanamido)butanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (**LV1**, yellow solid, 33% yield). 1H NMR (400 MHz, CDCl3) δ 8.68 (s, 1H), 8.57 (s, 1H), 8.49 (d, J = 4.3 Hz, 1H), 8.20 (d, J = 8.4 Hz, 1H), 7.65 (dd, J = 9.4, 2.5 Hz, 1H), 7.59 (dd, J = 7.4, 5.1 Hz, 1H), 7.48 (d, J = 2.5 Hz, 1H), 7.38 (dd, J = 18.9, 6.4 Hz, 7H), 7.26 (s, 1H), 7.20 – 7.13 (m, 2H), 6.91 (d, J = 7.1 Hz, 1H), 6.70 (d, J = 9.4 Hz, 1H), 5.17 (s, 2H), 4.66 (d, J = 6.8 Hz, 2H), 4.27 (d, J = 5.7 Hz, 1H), 4.20 (dd, J = 10.8, 5.5 Hz, 1H), 4.12 – 4.03 (m, 2H), 3.94 (t, J = 11.2 Hz, 2H), 3.73 (dd, J = 10.8, 4.5 Hz, 1H), 3.53 – 3.48 (m, 1H), 3.40 (d, J = 11.4 Hz, 1H), 3.12 (d, J = 13.2 Hz, 1H), 3.02 (d, J = 12.4 Hz, 1H), 2.87 (t, J = 11.2 Hz, 2H), 2.53 (s, 3H), 2.35 (t, J = 5.9 Hz, 2H), 2.16 (s, 3H), 1.07 (s, 9H). MS-ESI (m/z): calcd for [M + H]+ 833.4016；found 833.3999.

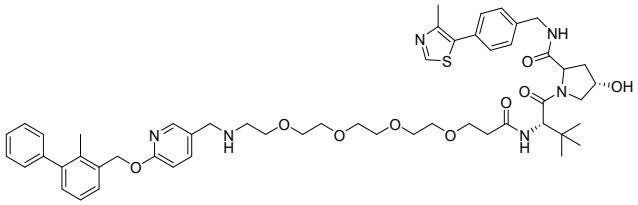


(4S)-1-((S)-13-(tert-butyl)-1-(6-((2-methyl-[1,1'-biphenyl]-3-yl)methoxy)pyridin-3-yl)-11-oxo-5,8-dioxa-2,12-diazatetradecan-14-oyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (**L2V**, yellow solid, 25% yield). 1H NMR (600 MHz, CDCl3) δ 8.64 (s, 1H), 7.73 (t, J = 6.1 Hz, 1H), 7.67 (dd, J = 2.5 Hz, 1H), 7.56 (s, 1H), 7.41 (d, J = 8.3 Hz, 1H), 7.37 (t, J = 7.5 Hz, 2H), 7.35 – 7.29 (m, 5H), 7.24 (d, J = 6.7 Hz, 2H), 7.18 – 7.15 (m,

2H), 6.94 (dd, J = 6.7, 2.4 Hz, 1H), 6.61 (d, J = 9.4 Hz, 1H), 5.18 (s, 2H), 4.65 (t, J = 6.9 Hz, 1H), 4.60 – 4.54 (m, 1H), 4.37 (dd, J = 15.2, 6.0 Hz, 2H), 4.27 (d, J = 6.6 Hz, 1H), 4.05 (dd, J = 10.6, 5.5 Hz, 1H), 3.82 (s, 1H), 3.76 – 3.65 (m, 4H), 3.60 – 3.47 (m, 6H), 3.42 (s, 2H), 2.94 (d, J = 5.3 Hz, 2H), 2.48 (s, 3H), 2.27 – 2.24 (m, 2H), 2.15 (s, 3H), 1.04 (s, 9H). MS-ESI (m/z): calcd for [M + H]+ 877.4278；found 877.4323.

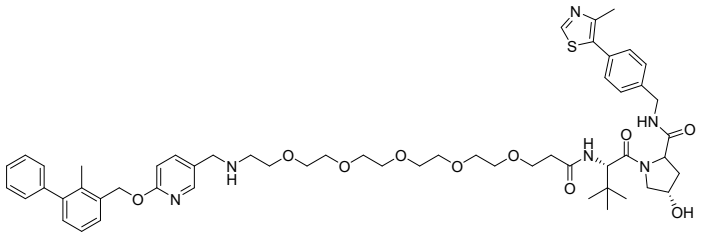


(4S)-1-((S)-16-(tert-butyl)-1-(6-((2-methyl-[1,1'-biphenyl]-3-yl)methoxy)pyridin-3-yl)-14-oxo-5,8,11-trioxa-2,15-diazaheptadecan-17-oyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (**L3V**, yellow solid, 30% yield). 1H NMR (600 MHz, CDCl3) δ 8.67 (s, 1H), 7.59 (dd, J = 7.1, 5.0 Hz, 1H), 7.49 – 7.40 (m, 4H), 7.37 (t, J = 7.6 Hz, 3H), 7.31 (d, J = 8.1 Hz, 2H), 7.28 (s, 1H), 7.21 (s, 2H), 7.16 (d, J = 2.5 Hz, 1H), 7.11 (d, J = 6.4 Hz, 1H), 6.95 (dd, J = 6.0, 3.1 Hz, 1H), 6.66 (d, J = 9.3 Hz, 1H), 5.20 (s, 2H), 4.73 (dd, J = 8.7, 4.1 Hz, 1H), 4.63 – 4.53 (m, 2H), 4.29 – 4.24 (m, 1H), 4.13 (dd, J = 10.4, 6.1 Hz, 1H), 3.58 (s, 6H), 3.57 – 3.54 (m, 4H), 3.52 (s, 2H), 3.40 (t, J = 7.1 Hz, 2H), 2.86 (s, 2H), 2.79 (d, J = 7.3 Hz, 2H), 2.74 (t, J = 5.1 Hz, 2H), 2.52 (s, 3H), 2.39 (t, J = 8.1 Hz, 2H), 2.17 (s, 3H), 1.07 (s, 9H). MS-ESI (m/z): calcd for [M + Na]+ 943.4540；found 943.4402.



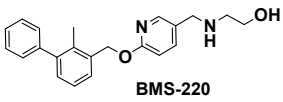
(4S)-1-((S)-19-(tert-butyl)-1-(6-((2-methyl-[1,1'-biphenyl]-3-yl)methoxy)pyridin-3-yl)-17-oxo-5,8,11,14-tetraoxa-2,18-diazaicosan-20-oyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (**L4V**, yellow solid, 11% yield). 1H NMR (600 MHz, CDCl3) δ 8.66 (s, 1H), 7.78 (t, J = 6.1 Hz, 1H), 7.75 – 7.67 (m, 3H), 7.38 (dt, J = 20.8, 7.4 Hz, 5H), 7.33 (t, J = 8.2 Hz, 3H), 7.27 – 7.24 (m, 2H), 7.21 – 7.18 (m, 2H), 7.00 (dd, J = 6.3, 2.9 Hz, 1H), 6.64 (d, J = 9.4 Hz, 1H), 5.22 (s, 2H), 4.71 (t, J = 6.9 Hz, 1H), 4.58 – 4.53 (m, 1H), 4.40 (dq, J = 15.7, 6.2 Hz, 2H), 4.28 (d, J = 6.3 Hz, 1H), 4.07 (dd, J = 10.7, 5.5 Hz, 1H), 4.01 (s, 1H), 3.81 (dt, J

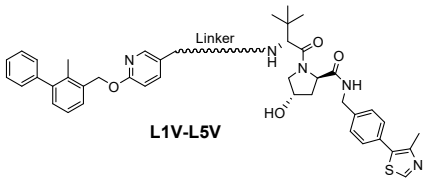
= 9.6, 5.3 Hz, 2H), 3.72 – 3.68 (m, 2H), 3.66 (d, J = 6.7 Hz, 2H), 3.63 – 3.60 (m, 2H), 3.58 – 3.55 (m, 4H), 3.53 – 3.42 (m, 8H), 3.06 (t, J = 5.0 Hz, 2H), 2.51 (s, 3H), 2.29 (dd, J = 8.3, 5.7 Hz, 2H), 2.18 (s, 3H), 1.10 (s, 9H). MS-ESI (m/z): calcd for [M + H]+ 965.4802；found 965.4860.

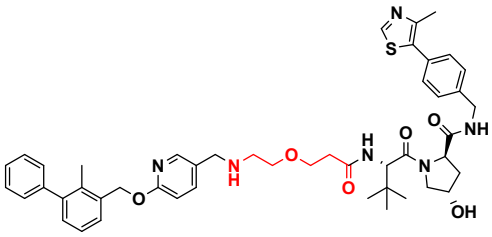
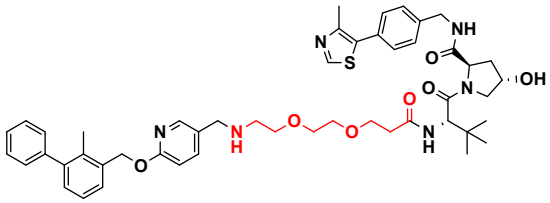
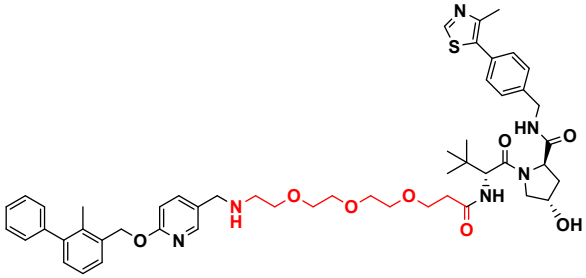
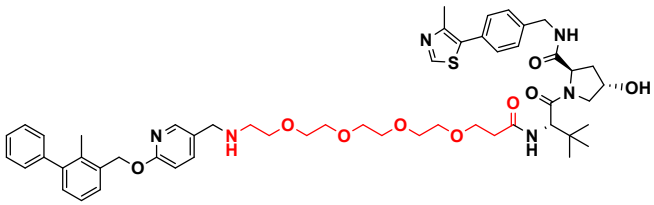
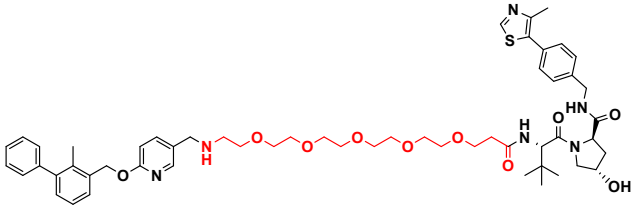


(4S)-1-((S)-22-(tert-butyl)-1-(6-((2-methyl-[1,1'-biphenyl]-3-yl)methoxy)pyridin-3-yl)-20-oxo-5,8,11,14,17-pentaoxa-2,21-diazatricosan-23-oyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (**L5V**, yellow solid, 19% yield). 1H NMR (400 MHz, CDCl3) δ 8.65 (s, 1H), 7.74 – 7.71 (m, 2H), 7.41 – 7.30 (m, 9H), 7.24 (dd, J = 6.8, 1.6 Hz, 2H), 7.16 (d, J = 5.9 Hz, 3H), 6.97 (dd, J = 5.9, 3.2 Hz, 1H), 6.64 (d, J = 9.3 Hz, 1H), 5.29 (s, 2H), 4.69 (t, J = 6.8 Hz, 1H), 4.55 (t, J = 5.4 Hz, 1H), 4.37 (dq, J = 15.5, 6.1 Hz, 3H), 4.19 (d, J = 5.8 Hz, 1H), 3.98 (d, J = 7.5 Hz, 2H), 3.80 (t, J = 4.8 Hz, 2H), 3.63 (dd, J = 13.3, 6.6 Hz, 4H), 3.54 (dd, J = 5.0, 2.6 Hz, 8H), 3.48 – 3.44 (m, 4H), 3.43 – 3.36 (m, 6H), 3.03 (d, J = 4.8 Hz, 2H), 2.49 (s, 3H), 2.29 (t, J = 6.3 Hz, 2H), 2.18 (s, 3H), 1.09 (s, 9H). MS-ESI (m/z): calcd for [M + H]+ 1009.5064；found 1009.5105.

Table S1. The PROTACs from BMS-220 linked with the von Hippel-Lindau (VHL) ligand,





Compounds	Structure
L1V	
L2V	
L3V	
L4V	
L5V	

B. Purity and Peak Attributions by HPLC analysis

Compound	Method*	Compound	Method*
L2a	t_R:4.336min, 100%	**L2f**	t_R: 4.396min, 100%
L3a	t_R: 4.572min, 96.87%	**L3f**	t_R: 4.237min, 88.14%
L4a	t_R=4.488min,88.93%	**L4f**	NT
L5a	t_R: 4.462min, 94.38%	**L2h**	t_R: 4.157min, 91.78%
L2b	t_R: 5.819min, 95.26%	**L3h**	t_R: 4.436min, 94.99%
L3b	t_R: 3.978min, 93.68%	**L4h**	NT
L4b	t_R: 4.374min,82.50%	**L5h**	t_R: 4.314min, 88.24%
L5b	NT	**Z2c**	t_R:5.009min, 100%
L2c	t_R:4.038min,99.38%	**Z3c**	t_R: 4.458min, 98.91%
L3c	t_R: 3.824min, 95.75%	**Z4c**	NT
L4c	t_R: 4.343min, 69.10%	**Z2d**	t_R: 5.398min, 96.65%
L5c	t_R: 4.035min, 96.92%	**Z3d*** **	t_R: 3.789min, 95.20%
L2d	t_R: 4.403min,98.15%	**Z4d*** **	t_R: 3.925min, 93.14%
L3d	t_R: 4.212min, 98.528%	**Z2e**	t_R: 5.225min, 97.20%
L4d**	t_R: 4.550min，93.96%	**Z4e**	t_R: 4.392min, 97.77%
L2e	t_R: 3.927min, 97.82%	**Z2f**	t_R: 5.174min, 96.58%
L3e	t_R: 4.024min, 100%	**Z4f**	t_R: 7.018min, 99.355%
L4e	NT		

Note: Agilent 5 TC-C18(2) 250*4.6mm; *For most compounds, the solvent system: 90% Methanol and 10% H_2O at a flow of 1 mL/min. ** Solvent system: 70% Methanol and 30% H_2O at a flow of 1 mL/min.*** Solvent system: Methanol at a flow of 1 mL/min.

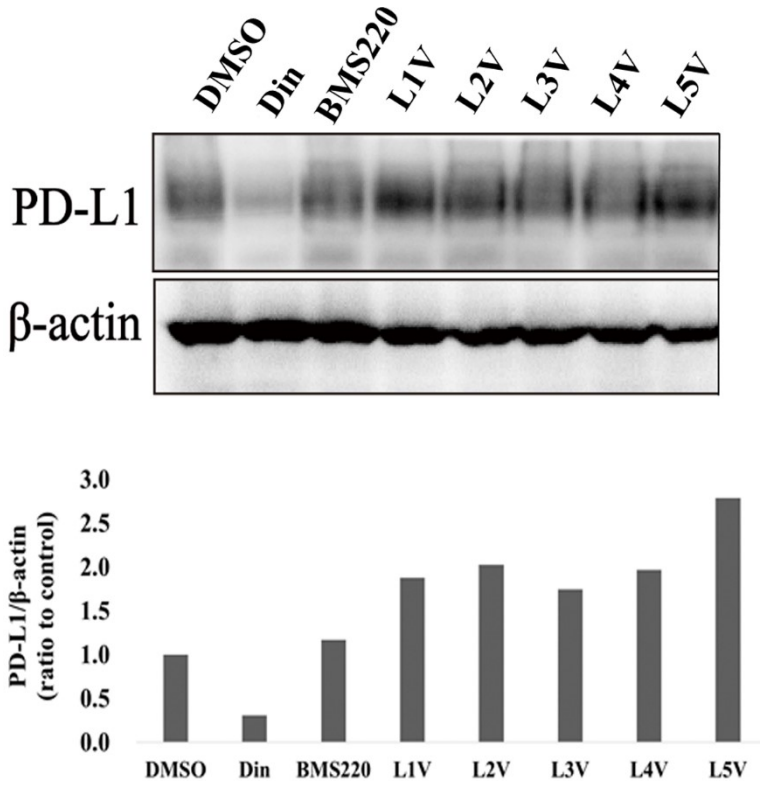


Figure S1. Effect of PROTACs inked with the von Hippel-Lindau (VHL) ligand, such as L1V-L5V on protein levels of PD-L1 in NCI-H460 cells.

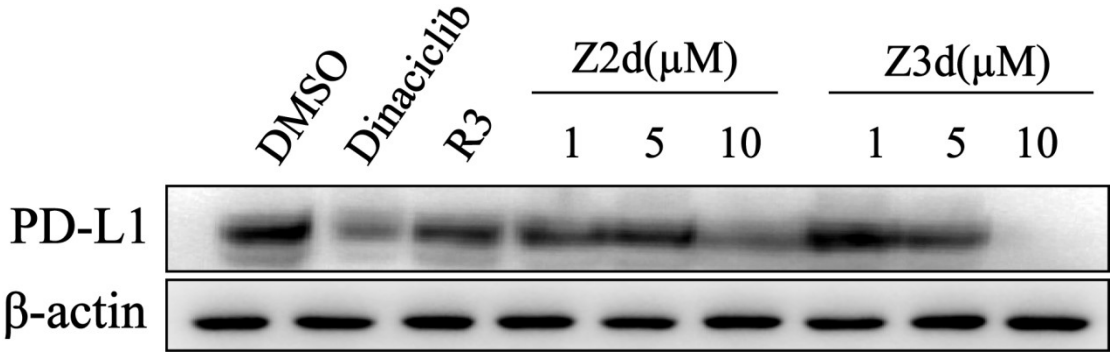


Figure S2. Effect of Z2d and Z3d on protein levels of PD-L1 in H-1080 cells.