Supporting Information

Identification of New Small-Molecule Inducers of Estrogen-Related Receptor α (ERRα) Degradation

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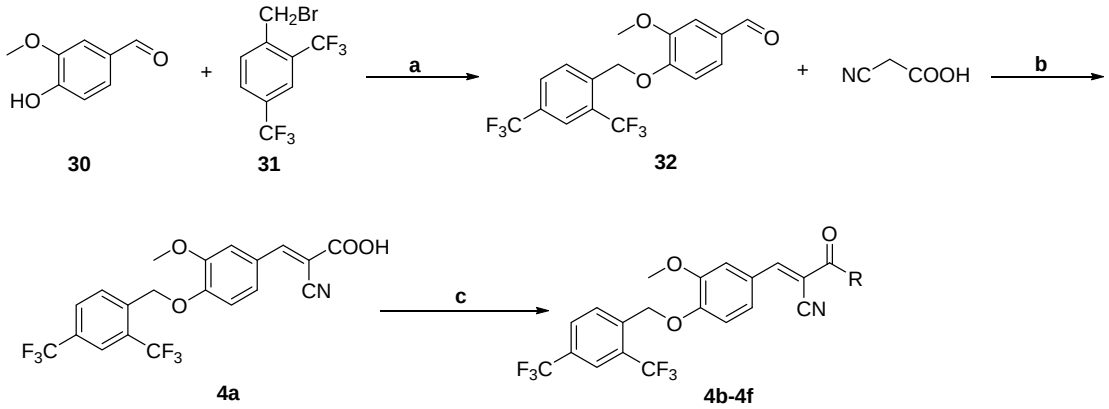
1. General information

All reagents and solvents were obtained from commercial sources and were used without further treatment unless otherwise noted. Flash chromatography was performed using silica gel (200-300 mesh). All reactions were monitored by TLC, using silica gel plates with fluorescence F254 and UV light visualization. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV-400 spectrometer at 400 MHz and 100MHz, respectively. Coupling constants (*J*) are expressed in hertz (Hz). Chemical shifts (δ) of NMR are reported in parts per million (ppm) units relative to internal control (TMS). High resolution ESI-MS were recorded on an AB SCIEX X500r QTOF mass spectrometer. Purity of compounds was determined by reverse-phase high performance liquid chromatography (HPLC) analysis to be >95%. HPLC instrument: Dionex Summit HPLC (Column: Diamonsil C18, 5.0μm, 4.6×250 mm (Dikma Technologies); detector: PDA-100 photodiode array; inJector: ASI-100 autoinJector; pump: p-680A). A flow rate of 1.0 mL/min was used with mobile phase of MeOH in H_2O.

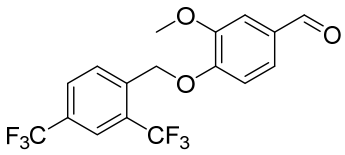
2 Synthetic procedures and compound characterization

2.1 Procedure for preparing compound 4a-4f.



30 31 32 4a 4b-4f

Reagents and conditions: (a) K_2CO_3, DMF, 80 ℃, 5 h, 85%; (b) Piperidine, CH_3CN, 80℃, 5 h, 75%; (c) for **4b**: CH_3I, K_2CO_3, DMF, rt, 1 h, 93%; for **4c**: oxalyl chloride, DMF, DCM, $NH_3.H_20$, 3 h, 54.5%; for **4d:** 2-methoxyethan-1-amine, HATU, DIPEA, DMF, rt, 1 h, 81%; for **4e** : (1) tert-butyl 5-aminopentanoate, HATU, DIPEA, DMF, rt, 1 h, 68% ; (2) TFA, DCM, rt, 1 h, 93%; for **4f**: (1) tert-butyl 3-(2-aminoethoxy)propanoate, HATU, DIPEA, DMF, rt, 1 h, 66% ; (2) TFA, DCM, rt, 1 h, 86%.

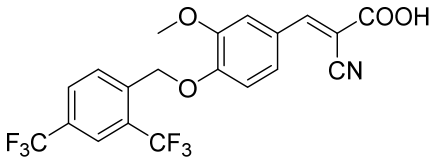


32

4-((2, 4-bis(trifluoromethyl)benzyl)oxy)-3-methoxybenzaldehyde (32).

To a solution of 1-(bromomethyl)-2,4-bis(trifluoromethyl)benzene (3.07 g, 10 mmol, 1eq) in DMF (10 mL), Vanillin (1.52 g, 10 mmol, 1 eq) and K_2CO_3 (1.9 g, 14 mmol, 1.4 eq) were added and stirred at 80 ℃ for 3 h. After cooling to room temperature, the resulting mixture was extracted with ethyl acetate and H_2O. The organic layer was separated, washed with brine, dried with Na_2SO_4. After filtration and evaporation, the residue was purified by silica gel column chromatography (PE / EA = 7 : 1) to afford **32** as a white solid (3.21 g, 8.50 mmol, 85%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.87 (s,

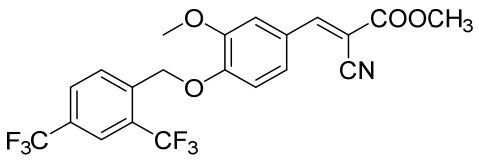
1H), 7.97 (d, *J* = 8.4 Hz, 2H), 7.85 (d, *J* = 8.5 Hz, 1H), 7.48 (d, *J* = 1.7 Hz, 1H), 7.42 (dd, *J* = 8.2, 1.8 Hz, 1H), 6.93 (d, *J* = 8.2 Hz, 1H), 5.47 (s, 2H), 3.99 (s, 3H).



4a

(*E*)-3-(4-((2, 4-bis(trifluoromethyl)benzyl)oxy)-3-methoxyphenyl)-2-cyanoacrylic acid (4a).

To a solution of compound **32** (2.9 g, 7.7 mmol, 1 eq) and 2-cyanoacetic acid (977.9 mg, 11.4 mmol, 1.5 eq) in acetonitrile (20 mL), piperidine (1.5 mL) was added and stirred at 80 ℃ for 3 h. After cooling to room temperature, the resulting mixture was treated with water. Then hydrochloric acid (2 N) was added to precipitate solid. The mixture was extracted with ethyl acetate and H_2O. The organic layer was separated, washed with brine, dried with Na_2SO_4. After filtration and evaporation, the residue was purified by silica gel column chromatography (PE / EA = 1 : 1) to afford **4a** as a slightly yellow solid (2.6 g, 5.8 mmol, 75%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.79 (s, 1H), 8.27 (s, 1H), 8.18 (d, *J* = 8.1 Hz, 1H), 8.11 (s, 1H), 8.02 (d, *J* = 8.1 Hz, 1H), 7.81 (d, *J* = 2.0 Hz, 1H), 7.70 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.26 (d, *J* = 8.6 Hz, 1H), 5.46 (s, 2H), 3.83 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.13, 154.48, 151.73, 149.42, 139.74, 131.67, 130.45, 129.79(q, *J* = 33.33Hz), 128.16(q, *J* = 31.31 Hz), 126.40, 125.59, 125.17, 123.66, 122.44, 117.18, 113.85, 101.12, 66.68, 56.14. HRMS (ESI$^+$): calculated for $C_{20}H_{13}F_6N_2NaO_3$ $[M + Na]^+$: 468.0636, found 468.0641. HPLC analysis: MeOH : H_2O : TFA (90 : 10 : 0.01), 5.70 min, 98.94% purity.

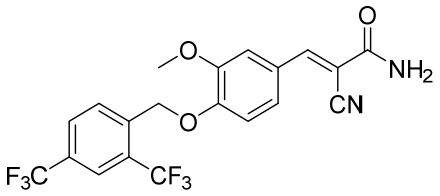


4b

Methyl (*E*)-3-(4-((2, 4-bis(trifluoromethyl)benzyl)oxy)-3-methoxyphenyl)-2-cyanoacrylate (4b).

4a (200 mg, 0.44 mmol, 1 eq) was dissolved in 3 mL anhydrous DMF. K_2CO_3 (121.6 mg, 0.88 mmol, 2 eq) and CH_3I (41 μL, 0.66 mmol, 1.5 eq) were added into reaction.

After being stirred for 1 h, the resulting mixture was extracted with ethyl acetate and saturated $NaHCO_3$. The organic layer was separated, washed with brine, dried with Na_2SO_4. After filtration and evaporation, the residue was purified by silica gel column chromatography (PE : EA =2 : 1) to give **4b** as a white solid (188 mg, 0.41 mmol, 93% yield): ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.35 (s, 1H), 8.18 (d, J = 7.7 Hz, 1H), 8.12 (s, 1H), 8.02 (d, J = 7.8 Hz, 1H), 7.84 (s, 1H), 7.75 (d, J = 8.2 Hz, 1H), 7.28 (d, J = 8.4 Hz, 1H), 5.47 (s, 2H), 3.84 (d, J = 6.5 Hz, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 163.26, 155.26, 152.09, 149.43, 139.67, 131.72, 130.47, 129.32, 128.03, 126.81, 125.40, 123.70, 122.41, 116.73, 114.02, 113.88, 99.46, 66.69, 56.17, 53.68. HRMS (ESI$^+$): calculated for $C_{21}H_{15}F_6NNaO_4$ $[M + Na]^+$: 482.0797, found 482.0782. HPLC analysis: MeOH : H_2O (80 : 20), 23.45 min, 100% purity.

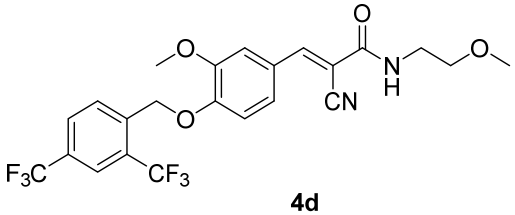


4c

(*E*)-3-(4-((2,4-bis(trifluoromethyl)benzyl)oxy)-3-methoxyphenyl)-2-cyanoacrylamide (4c).

Oxalyl chloride (0.5 mL) and and a drop of DMF was added to a solution of **4a** (100 mg, 0.22 mmol, 1 eq) in DCM (2 mL). The solution was concentrated in vacuo and the crude product is used without further purification after being stirred for 5 h at room temperature. The crude product obtained above was dissolved in CH_2Cl_2 (2 mL) and 28% ammonia solution (1 mL) was added at 0 ℃. After being stirred at room temperature for 2 hours, the mixture was extracted with DCM and H_2O. The organic layer was separated, washed with brine, dried with Na_2SO_4. After filtration and evaporation, the residue was purified by silica gel column chromatography (PE / EA = 3 : 1) to afford the product (**4c**) (55 mg, 0.12 mmol, 55% yield) as white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.18 (d, J = 8.2 Hz, 1H), 8.12 (d, J = 7.4 Hz, 2H), 8.03 (d, J = 8.1 Hz, 1H), 7.88 − 7.64 (m, 3H), 7.57 (dd, J = 8.5, 1.9 Hz, 1H), 7.24 (d, J = 8.5 Hz, 1H), 5.44 (s, 2H), 3.84 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 163.41, 151.05, 150.87, 149.43, 139.86, 131.63, 130.42, 129.76 (q, J = 32.32Hz), 128.12 (q, J

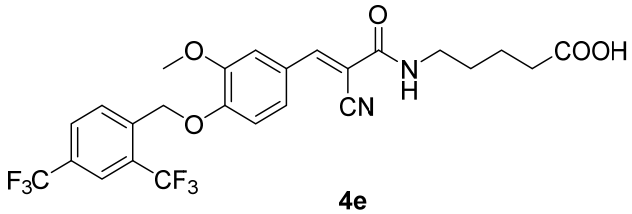
= 31.31Hz), 125.95, 125.53, 125.13, 123.65, 122.46, 117.54, 113.92, 113.28, 104.11, 66.62, 56.11. HRMS (ESI^+): calculated for $C_{20}H_{15}F_6N_2O_3$ $[M + H]^+$: 445.0981, found 445.0973. HPLC analysis: MeOH : H_2O (80 : 20), 11.20 min, 96.20% purity.



4d

(*E*)-3-(4-((2, 4-bis(trifluoromethyl)benzyl)oxy)-3-methoxyphenyl)-2-cyano-*N*-(2-methoxyethyl) acrylamide (4d).

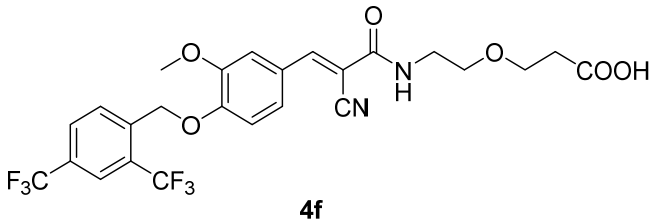
2-methoxyethan-1-amine (39.8 mg, 0.53 mmol, 1.2 eq), HATU (216.7 mg, 0.57 mmol, 1.3 eq) and DIPEA (0.22 ml, 1.3 mmol, 3 eq) was added to a solution of Carboxylic acid **4a** (200 mg, 0.44 mmol, 1 eq) in dry DMF (3 mL). After being stirred for 1 h at RT, the resulting mixture was extracted with ethyl acetate and saturated $NaHCO_3$. The organic layer was separated, washed with brine, dried with Na_2SO_4. After filtration and evaporation, the residue was purified by silica gel column chromatography (PE / EA = 3 : 1) to give **4d** (183 mg, 0.36 mmol, 82% yield) as white solid: ^1H NMR (400 MHz, DMSO-d_6) δ 8.36 (s, 1H), 8.18 (d, J = 7.9 Hz, 1H), 8.12 (d, J = 6.2 Hz, 2H), 8.03 (d, J = 8.1 Hz, 1H), 7.72 (s, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.24 (d, J = 8.4 Hz, 1H), 5.44 (s, 2H), 3.84 (s, 3H), 3.43 (d, J = 4.6 Hz, 2H), 3.38 (d, J = 5.2 Hz, 2H), 3.27 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.73, 151.06, 150.83, 149.42, 139.86, 131.62, 130.41, 129.74 (q, J = 36.36 Hz), 128.11 (q, J = 32.32 Hz), 125.94, 125.44, 125.18, 123.63, 122.45, 117.42, 113.91, 113.40, 103.73, 70.59, 66.61, 58.37, 56.12. HRMS (ESI^+): calculated for $C_{23}H_{21}F_6N_2O_4$ $[M + H]^+$: 503.1400, found 503.1383. HPLC analysis: MeOH : H_2O (80 : 20), 15.19 min, 100% purity.



4e

(*E*)-5-(3-(4-((2, 4-bis(trifluoromethyl)benzyl)oxy)-3-methoxyphenyl)-2-cyano acrylamido) pentanoic acid (4e).

Tert-butyl 5-aminopentanoate (91.8 mg, 0.53 mmol, 1.2 eq), HATU (216.7 mg, 0.57 mmol, 1.3 eq) and DIPEA (0.22 ml, 1.3 mmol, 3 eq) was added to a solution of Carboxylic acid **4a** (200 mg, 0.44 mmol, 1 eq) in dry DMF (3 mL). After being stirred for 1 h at RT, the resulting mixture was extracted with ethyl acetate and saturated $NaHCO_3$. The organic layer was separated, washed with brine, dried with Na_2SO_4. After filtration and evaporation, the residue was purified by silica gel column chromatography (PE / EA = 2 : 1) to give tert-butyl ester intermediate (178 mg, 0.30 mmol, 68% yield) as yellow solid. TFA (1 mL) was added to a solution of tert-butyl ester intermediate above in DCM (2 mL). After being stirred for 1 h, the solvents were removed in vacuo, and residual TFA was removed by the addition and evaporation of toluene (3 x 3mL) to give **4e** (155 mg, 0.28 mmol, 93%) as yellow solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.01 (s, 1H), 8.38 (t, J = 5.7 Hz, 1H), 8.19 (d, J = 8.2 Hz, 1H), 8.12 (d, J = 3.9 Hz, 2H), 8.04 (d, J = 8.1 Hz, 1H), 7.72 (d, J = 2.0 Hz, 1H), 7.59 (dd, J = 8.6, 2.0 Hz, 1H), 7.25 (d, J = 8.6 Hz, 1H), 5.45 (s, 2H), 3.84 (s, 3H), 3.22 (d, J = 5.7 Hz, 2H), 2.25 (t, J = 6.8 Hz, 2H), 1.56–1.50 (m, 4H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.85, 161.54, 150.99, 150.62, 149.42, 139.87, 130.41, 129.76 (q, J= 33.33 Hz), 128.11 (q, J= 32.32 Hz), 126.00, 125.35, 125.18, 125.13, 123.62, 122.44, 117.45, 113.91, 113.39, 103.97, 79.44(t, J = 33.33Hz), 66.63, 56.13, 33.74, 28.88, 22.35. HRMS (ESI$^+$): calculated for $C_{25}H_{23}F_6N_2O_5$ $[M + H]^+$: 545.1506, found 545.1495. HPLC analysis: MeOH : H_2O : TFA (80 : 20 : 0.02), 7.67 min, 96.85% purity.



4f

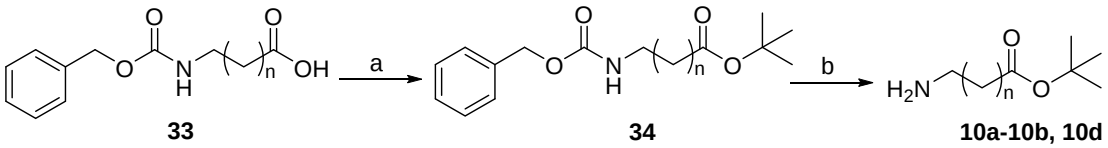
(*E*)-3-(2-(3-(4-((2, 4-bis(trifluoromethyl)benzyl)oxy)-3-methoxyphenyl)-2-cyano acrylamido)ethoxy)propanoic acid (4f).

Tert-butyl 3-(2-aminoethoxy)propanoate (100.3 mg, 0.53 mmol, 1.2 eq), HATU (216.7 mg, 0.57 mmol, 1.3 eq) and DIPEA (0.22 mL, 1.3mmol, 3eq) was added to a solution of Carboxylic acid **4a** (200 mg, 0.44 mmol, 1 eq) in dry DMF (3 mL). After

being stirred for 1 h at RT, the resulting mixture was extracted with ethyl acetate and saturated $NaHCO_3$. The organic layer was separated, washed with brine, dried with Na_2SO_4. After filtration and evaporation, the residue was purified by silica gel column chromatography (PE / EA = 2 : 1) to give tert-butyl ester intermediate (178 mg, 0.29 mmol, 66% yield) as yellow solid. TFA (1 mL) was added to a solution of tert-butyl ester intermediate above in DCM (2 mL). After being stirred for 1 h, the solvents were removed in vacuo, and residual TFA was removed by the addition and evaporation of toluene (3 x 3mL) to give **4f** (140 mg, 0.25 mmol, 86%) as yellow solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.18 (s, 1H), 8.35 (s, 1H), 8.19 (s, 1H), 8.13 (s, 2H), 8.04 (s, 1H), 7.73 (s, 1H), 7.59 (s, 1H), 7.25 (s, 1H), 5.46 (s, 2H), 3.85 (s, 3H), 3.63 (d, J = 6.0 Hz, 2H), 3.49 (s, 2H), 3.37 (s, 4H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.09, 161.76, 151.07, 150.84, 149.42, 139.87, 131.64, 130.47, 129.96, 128.28, 125.95, 125.47, 123.66, 117.40, 113.92, 113.40, 103.72, 68.76, 67.01, 66.42, 56.13, 35.13. HRMS (ESI^+): calculated for Chemical Formula: $C_{25}H_{23}F_6N_2O_6$ $[M + H]^+$: 561.1455, found 561.1444. HPLC analysis: MeOH : H_2O : TFA (80 : 20 : 0.02), 11.91 min, 97.96% purity.

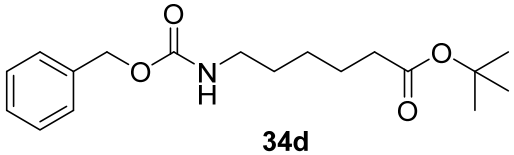
2.2 General Procedure for Preparing Linker

A) Synthesis of Linker (10a-10b, 10d):



33 **34** **10a-10b, 10d**

Reaction conditions: (a) tert-Butanol, DCC, DMAP, DCM, rt; (b) Pd/C, H_2, EtOH, 40 ℃.

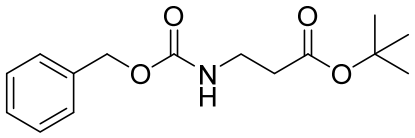


34d

Tert-butyl 6-(((benzyloxy)carbonyl)amino)hexanoate(34d). General procedure for syntheses of 34a-34b.

6-(((benzyloxy)carbonyl)amino)hexanoic acid (1.0 g , 3.8 mmol, 1 eq), DMAP (92.8

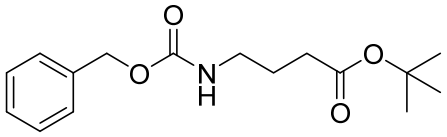
mg, 0.76 mmol, 0.2 eq) and DCC (862.5 mg, 4.2 mmol, 1.1 eq were added to a solution of tert-butanol (0.73 ml, 7.6 mmol, 2.0 eq) in DCM (5 mL) and stirred at room temperaturethe for 3 h. The mixture was evaporated to obtain the residue. The residue was purified by flash chromatography (PE / EA = 6 : 1) to afford **34d** (1.1 g, 3.4 mmol, 89% yield) as colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (dd, J = 15.1, 11.0 Hz, 5H), 5.09 (s, 2H), 4.77 (s, 1H), 3.19 (dd, J = 13.1, 6.6 Hz, 2H), 2.20 (t, J = 7.4 Hz, 2H), 1.58 (dd, J = 15.4, 7.6 Hz, 2H), 1.50 (dd, J = 14.7, 7.3 Hz, 2H), 1.43 (d, J = 3.8 Hz, 9H), 1.34 (dd, J = 15.2, 8.2 Hz, 2H).



34a

Tert-butyl 3-(((benzyloxy)carbonyl)amino)propanoate (34a).

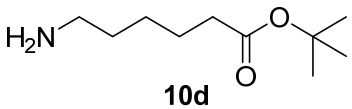
Yield: 76%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.28 (m, 5H), 5.29 (s, 1H), 5.09 (s, 2H), 3.42 (dd, J = 12.1, 6.1 Hz, 2H), 2.45 (t, J = 6.0 Hz, 2H), 1.44 (s, 9H).



34b

Tert-butyl 4-(((benzyloxy)carbonyl)amino)butanoate (34b).

Yield: 83%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.27 (m, 5H), 5.09 (s, 2H), 4.90 (s, 1H), 3.23 (dd, J = 13.0, 6.6 Hz, 2H), 2.26 (t, J = 7.2 Hz, 2H), 1.84−1.73 (m, 2H), 1.43 (s, 9H).

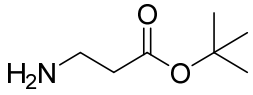


10d

Tert-butyl 6-aminohexanoate (10d). General procedure for syntheses of 10a, 10b.

10% palladium on carbon catalyst (90 mg) was added to a solution of the ester **34d** (730 mg, 2.3 mmol, 1 eq) in ethanol (6 mL). The mixture were stirred under an atmosphere of hydrogen for 24 h at 45 ℃. The reaction mixture was filtered through a pad of Celite, washed with ethyl acetate and the filtrate was evaporated to obtain **10d** (201 mg, 1.1 mmol, 48% yield) as colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.68 (t,

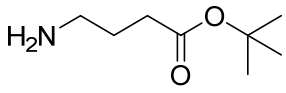
J = 7.0 Hz, 2H), 2.20 (t, *J* = 7.5 Hz, 2H), 1.59 (dd, *J* = 15.1, 7.5 Hz, 2H), 1.47−1.42 (m, 11H), 1.37 − 1.30 (m, 2H).



10a

Tert-butyl 3-aminopropanoate (10a).

Yield: 55%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.92(t, *J* = 6.2 Hz, 2H), 2.36 (t, *J* = 6.2 Hz, 2H), 1.44 (s, 9H).

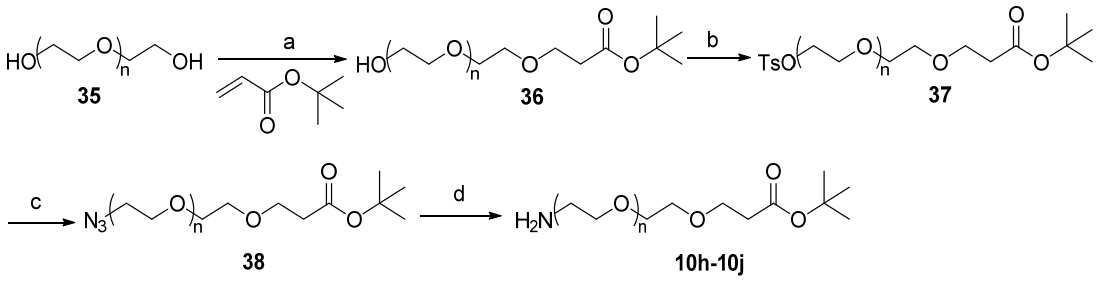


10b

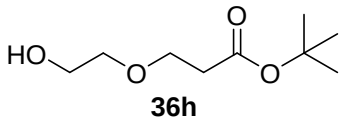
Tert-butyl 4-aminobutanoate (10b).

Yield: 47%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.70 (t, *J* = 7.1 Hz, 2H), 2.25 (t, *J* = 7.4 Hz, 2H), 1.76−1.67 (m, 2H), 1.43 (s, 9H).

B) Synthesis of Linker (10h-10j):



Reaction conditions: (a)Na, THF, rt; (b) TsCl, DMAP, TEA, DCM, rt; (c) NaN_3, DMF, 100℃, 2h; (d)PPh_3, H_2O, THF, rt.

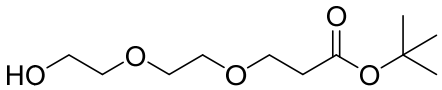


36h

Tert-butyl 3-(2-hydroxyethoxy)propanoate (36h). General procedure for syntheses of 36i, 36j.

To a solution of anhydrous ethylene glycol (10 g, 161.1 mmol, 3 eq) in dry THF (40 mL), Sodium metal (62.0 mg, 2.70 mmol, 0.05 eq) was added and stirred at RT for 2 h. Tert-butyl acrylate (6.90 g, 53.7 mmol, 1 eq) was added and allowed to stir for 10 h.

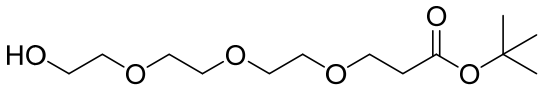
The resulting mixture was concentrated in vacuo, and extracted with ethyl acetate and H_2O. The organic layer was separated, washed with brine, dried with Na_2SO_4. After filtration and evaporation, the residue was purified by silica gel column chromatography (PE / EA = 2 : 1) to obtain **36h** (5.0 g, 26.3 mmol, 49% yield) as colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77 − 3.67 (m, 4H), 3.61-3.53 (m, 2H), 2.54-2.43 (m, 3H), 1.45 (s, 9H).



36i

Tert-butyl 3-(2-(2-hydroxyethoxy)ethoxy)propanoate (36i).

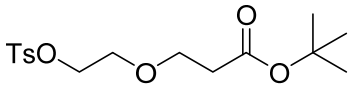
Yield: 51%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (dd, J = 8.4, 4.4 Hz, 4H), 3.67 − 3.57 (m, 6H), 2.58 (s, 1H), 2.50 (t, J = 6.4 Hz, 2H), 1.44 (s, 9H).



36j

Tert-butyl 3-(2-(2-(2-hydroxyethoxy)ethoxy)ethoxy)propanoate (36j).

Yield: 46%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.70 (t, J = 6.5 Hz, 4H), 3.67−3.57 (m, 10H), 2.82 (s, 1H), 2.50 (t, J = 6.5 Hz, 2H), 1.43 (s, 9H).

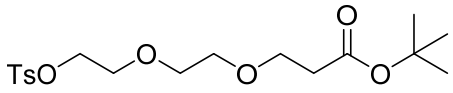


37h

Tert-butyl 3-(2-(tosyloxy)ethoxy)propanoate (37h). General procedure for syntheses of 37i, 37j.

A solution of tosyl chloride (3.23 g, 17 mmol, 1.3 eq) in dry CH_2Cl_2 (5 mL) was added dropwise to a solution of **36h** (2.5 g, 13.1 mmol, 1 eq), NEt_3 (2.4 mL, 17 mmol, 1.3 eq) and DMAP (402.8 mg, 3.3 mmol, 0.25 eq) in dry CH_2Cl_2 (5 mL) at -10 ℃. The reaction mixture was stirred for 8 hours at room temperature. The resulting mixture was treated with saturated $NaHCO_3$ and the aqueous phase was extracted with CH_2Cl_2. The organic layer was separated, washed with brine, dried with Na_2SO_4. After filtration and evaporation, the residue was purified by silica gel column chromatography (PE / EA = 7 : 1) to obtain **37h** (3.9 g, 11.3 mmol, 86%) as colorless

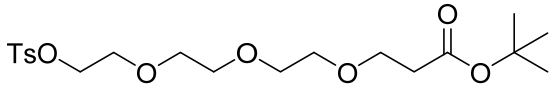
oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ7.81 (d, J = 8.3 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 4.15 (dd, J = 5.4, 4.2 Hz, 2H), 3.65 (dd, J = 8.1, 4.3 Hz, 4H), 2.46 (s, 3H), 2.43 (t, J = 6.4 Hz, 2H), 1.45 (s, 9H).



37i

Tert-butyl 3-(2-(2-(tosyloxy)ethoxy)ethoxy)propanoate (37i).

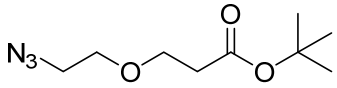
Yield: 74%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 8.3 Hz, 2H), 7.33 (d, J = 8.1 Hz, 2H), 4.16 − 4.12 (m, 2H), 3.69-3.63 (m, 4H), 3.57 − 3.50 (m, 4H), 2.46 (t, J = 6.5 Hz, 2H), 2.43 (s, 3H), 1.43 (s, 9H).



37j

Tert-butyl 3-(2-(2-(2-(tosyloxy)ethoxy)ethoxy)ethoxy)propanoate (37j).

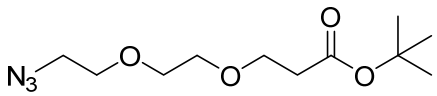
Yield: 77%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 4.18 − 4.14 (m, 2H), 3.69 (dd, J = 11.6, 5.3 Hz, 4H), 3.58 (d, J = 5.5 Hz, 8H), 2.49 (t, J = 6.6 Hz, 2H), 2.45 (s, 3H), 1.44 (s, 9H).



38h

Tert-butyl 3-(2-azidoethoxy)propanoate (38h), General procedure for syntheses of 38i, 38j.

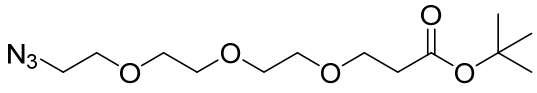
37h (3.0 g, 8.6 mmol, 1 eq) and NaN_3 (2.8 g, 43 mmol, 5 eq) were dissolved in DMF(8 ml). The reaction mixture was heated to reflux for 3 h at 100 ℃. After cooling to room temperature, the mixture was extracted with ethyl acetate and H_2O. The organic layer was separated, washed with brine, dried with Na_2SO_4. After filtration and evaporation, the residue was purified by silica gel column chromatography (PE / EA = 8 : 1) to obtain **38h** (1.7g, 7.9mmol, 92%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (t, J = 6.4 Hz, 2H), 3.65 − 3.58 (m, 2H), 3.35 (t, J = 5.0 Hz, 2H), 2.51 (t, J = 6.4 Hz, 2H), 1.45 (s, 9H).



38i

Tert-butyl 3-(2-(2-azidoethoxy)ethoxy)propanoate.(38i).

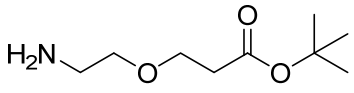
Yield: 88%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (t, J = 6.5 Hz, 2H), 3.69 − 3.60 (m, 6H), 3.38 (t, J = 5.1 Hz, 2H), 2.50 (t, J = 6.5 Hz, 2H), 1.44 (s, 9H).



38j

Tert-butyl 3-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)propanoate(38j).

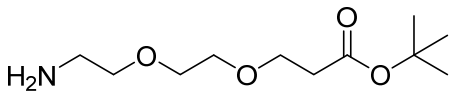
Yield: 79%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74 − 3.59 (m, 12H), 3.39 (t, J = 5.1 Hz, 2H), 2.50 (t, J = 6.6 Hz, 2H), 1.44 (s, 9H).



10h

Tert-butyl 3-(2-aminoethoxy)propanoate (10h), General procedure for syntheses of 10i, 10j.

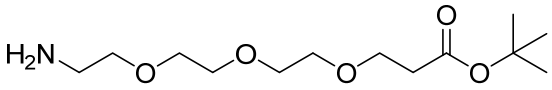
PPh_3 (1.84 g, 7.0 mmol, 1.5 eq) and water (3 mL) were added to a solution of **38h** (1.0 g, 4.7 mmol, 1eq) in THF (18 mL) and stirred at room temperature overnight. After evaporation of the solvent, the residue was purified by silica gel column chromatography (2% MeOH / CH_2Cl_2 to 10% MeOH / CH_2Cl_2) to obtain **10h** (525 mg, 2.8 mmol, 60%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.68 (t, J = 6.4 Hz, 2H), 3.46 (t, J = 5.2 Hz, 2H), 2.83 (t, J = 5.2 Hz, 2H), 2.48 (t, J = 6.4 Hz, 2H), 1.44 (s, 9H).



10i

Tert-butyl 3-(2-(2-aminoethoxy)ethoxy)propanoate (10i).

Yield: 59%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.71 (t, J = 6.5 Hz, 2H), 3.60 (d, J = 3.7 Hz, 4H), 3.49 (t, J = 5.2 Hz, 2H), 2.85 (t, J = 5.2 Hz, 2H), 2.50 (t, J = 6.5 Hz, 2H), 1.43 (s, 9H).

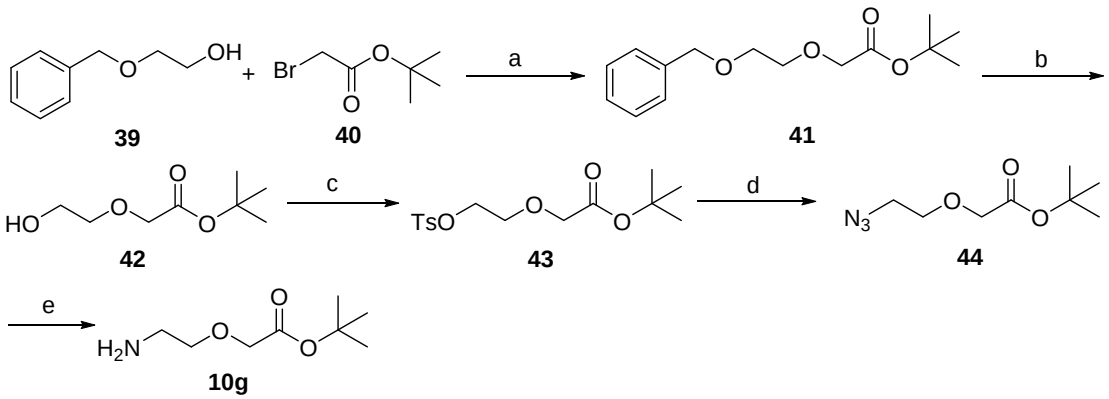


10j

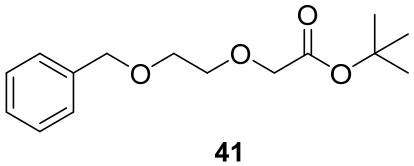
Tert-butyl 3-(2-(2-(2-aminoethoxy)ethoxy)ethoxy)propanoate(10j).

Yield: 65%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.70 (t, J = 6.5 Hz, 2H), 3.66 − 3.57 (m, 8H), 3.50 (t, J = 5.2 Hz, 2H), 2.86 (t, J = 5.2 Hz, 2H), 2.49 (t, J = 6.5 Hz, 2H), 1.43 (s, 9H).

C) Synthesis of linker 10g:



Reaction conditions: (a) Potassium tertbutoxide, tertbutanol, rt; (b) Pd / C, H_2, EtOH, 40 ℃; (c) TsCl, DMAP, TEA, DCM, rt; (d) NaN_3, DMF, 100 ℃, 2 h; (e) PPh_3, H_2O, THF, rt.

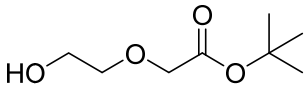


41

Tert-butyl 2-(2-(benzyloxy)ethoxy)acetate (41).

To a solution of Potassium tertbutoxide (2.24 g, 20 mmol, 1 eq) in anhydrous tertbutanol (24 mL), compound **39** (3.00 g, 20 mmol, 1 eq) was added and stirred at RT for 30 min. Then the flask was cooled to 10 ℃ and tert-butyl bromoacetate (3.90 g, 20 mmol, 1 eq) was added and stirred at RT for 16 h. The mixture was extracted with ethyl acetate and H_2O. The organic layer was separated, washed with brine, dried with Na_2SO_4. After filtration and evaporation, the residue was purified by silica gel column chromatography (PE / EA = 6 : 1) to obtain **41** (2.60 g, 9.76 mmol, 49 %) as a

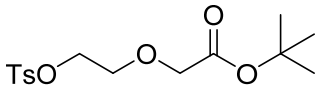
colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.22 (m, 5H), 4.58 (s, 2H), 4.04 (s, 2H), 3.74 (dd, J = 5.7, 3.4 Hz, 2H), 3.67 (dd, J = 5.9, 3.4 Hz, 2H), 1.47 (s, 9H).



42

Tert-butyl 2-(2-hydroxyethoxy)acetate (42).

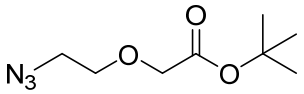
Ester **41** (2.40 g, 9.01 mmol, 1 eq) and 10% palladium on carbon catalyst (200 mg) were mixed in ethanol (15 mL), stirred for 24 h at 45 ℃ under an atmosphere of hydrogen. The reaction mixture was filtered through a pad of Celite, washed with ethyl acetate. The filtrate was extracted with ethyl acetate and H_2O. The combined organic layer were washed with brine and dried with Na_2SO_4. After filtration and evaporation, the residue was purified by silica gel column chromatography(PE / EA = 1 : 1) to obtain **42** (680 mg, 3.86 mmol, 43 %) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.01 (s, 2H), 3.73 (t, J = 4.4 Hz, 2H), 3.66 (dd, J = 5.2, 3.4 Hz, 2H), 2.97 (s, 1H), 1.48 (s, 9H).



43

Following the procedure used in the synthesis of linker 10h, linker 10g was obtained with 42 instead of 36h. Tert-butyl 2-(2-(tosyloxy)ethoxy)acetate (43).

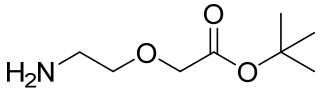
Yield: 78%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 8.2 Hz, 2H), 4.22 – 4.16 (m, 2H), 3.94 (s, 2H), 3.78 – 3.74 (m, 2H), 2.44 (s, 3H), 1.45 (s, 9H).



44

Tert-butyl 2-(2-azidoethoxy)acetate (44).

Yield: 85%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.02 (s, 2H), 3.73 (dd, J = 6.9, 3.3 Hz, 2H), 3.44 (t, J = 5.1 Hz, 2H), 1.48 (s, 9H).



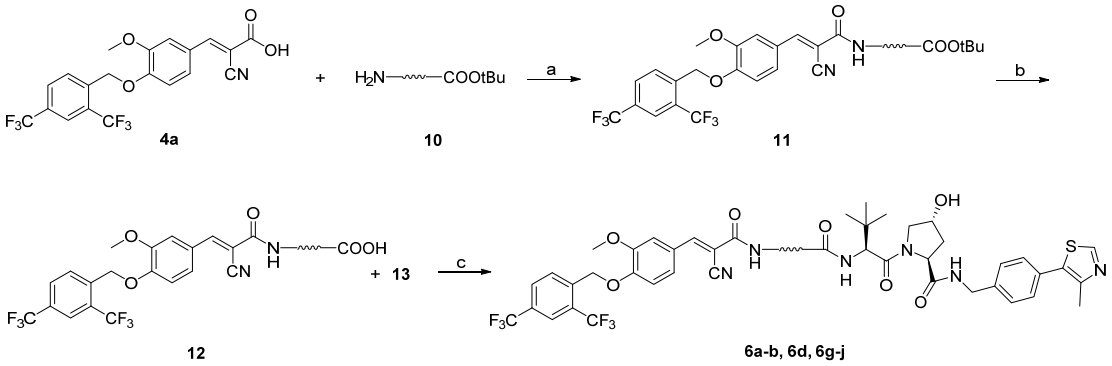
10g

Tert-butyl 2-(2-aminoethoxy)acetate(10g).

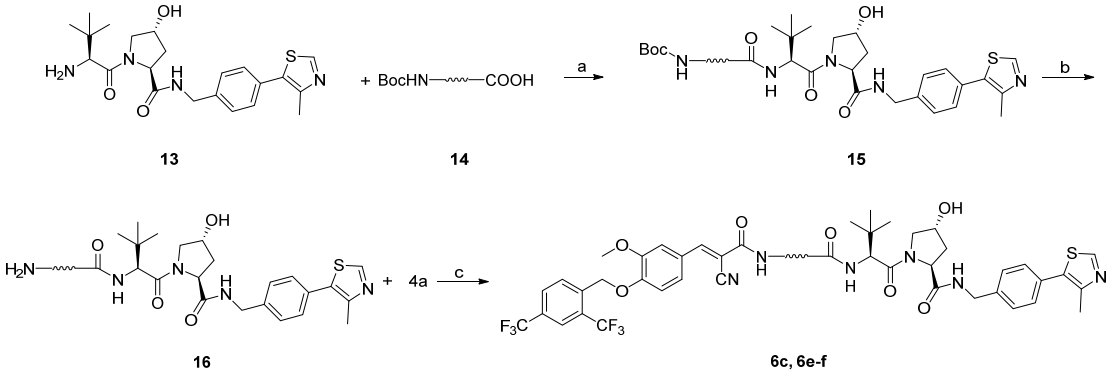
Yield: 55%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.94 (s, 2H), 3.79 (t, J = 5.0 Hz, 2H), 3.52 (t, J = 5.0 Hz, 2H), 1.43 (s, 9H).

2.3 General procedure for preparing ERRα-PROTACS

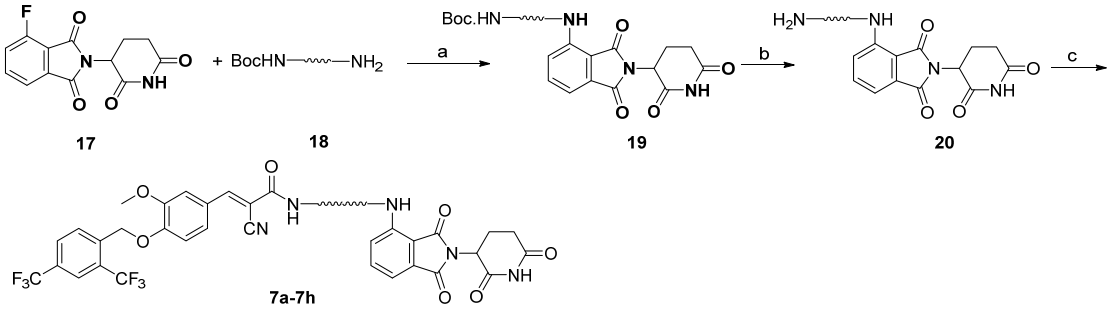
A) Synthesis of PROTAC 6a-b, 6d, 6g-j:



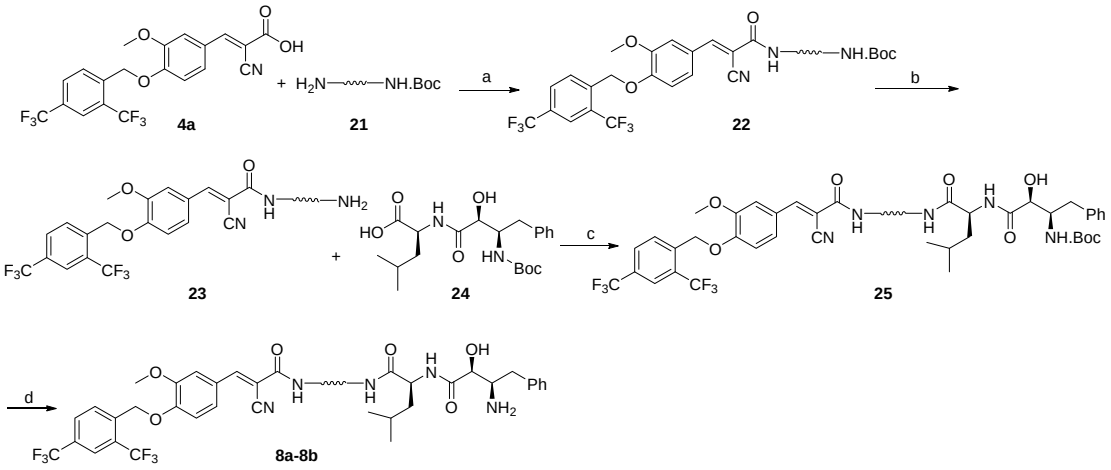
B) Synthesis of PROTAC 6c, 6e-f:



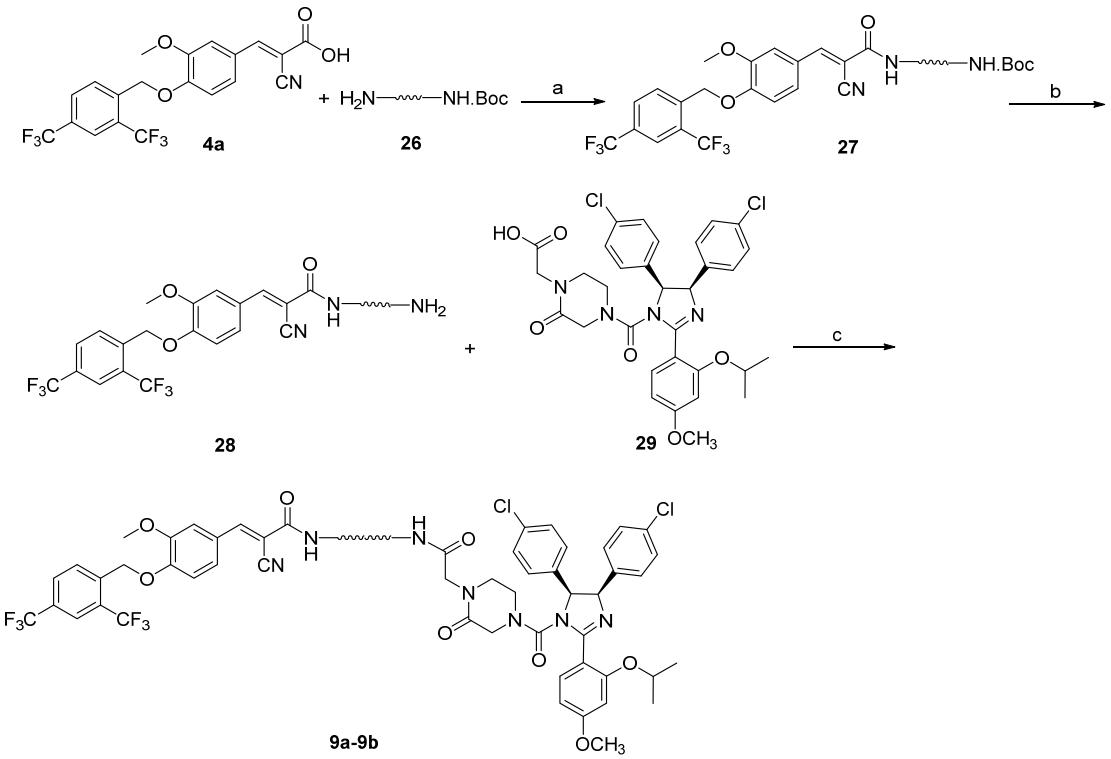
C) Synthesis of PROTAC 7a-h:



D) Synthesis of PROTAC 8a-b:

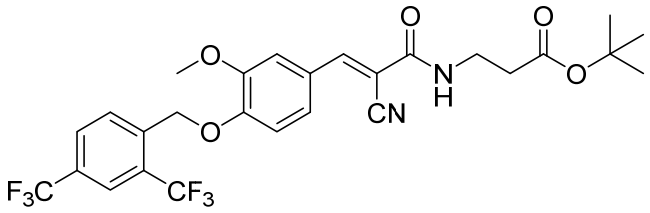


E) Synthesis of PROTAC 9a-b:



Reagents and conditions: (a) HATU, DIPEA, DMF, rt; (b) TFA, DCM, rt; (c) HATU, DIPEA, DMF, rt; B. (a) HATU, DIPEA, DMF, rt; (b) TFA, DCM, rt; (c) HATU, DIPEA, DMF, rt; C. (a) DIPEA, DMF, 90℃; (b) TFA, DCM, rt; (c) HATU, DIPEA, DMF, rt; D. (a) HATU, DIPEA, DMF, rt; (b) TFA, DCM, rt; (c) HATU, DIPEA, DMF, rt; (d) 4 N HCl in 1,4-dioxane, DCM, rt; E. (a) HATU, DIPEA, DMF, rt; (b) TFA,

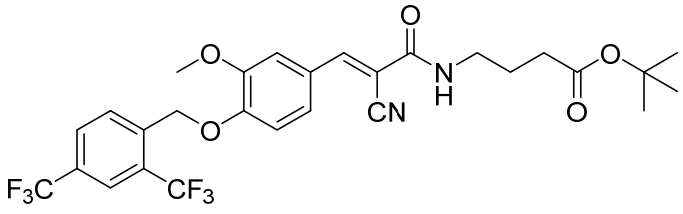
DCM, rt; (c) HATU, DIPEA, DMF, rt.



11a

Tert-butyl (*E*)-3-(3-(4-((2,4-bis(trifluoromethyl)benzyl)oxy)-3-methoxyphenyl)-2-cyanoacrylamido)propanoate (11a). General procedure for syntheses of 11b, 11d, 11g-11j.

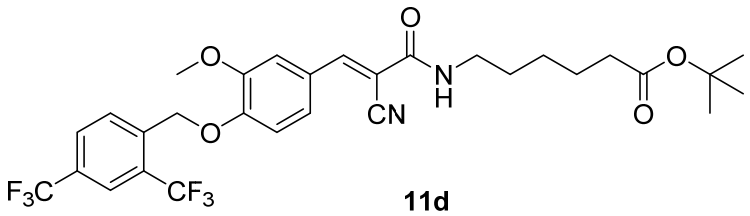
10a (77 mg, 0.53 mmol, 1.2 eq), HATU (216.7 mg, 0.57 mmol, 1.3 eq) and DIPEA (0.22 mL, 1.3 mmol, 3 eq) was added to a solution of carboxylic acid **4a** (200 mg, 0.44 mmol, 1 eq) in dry DMF (3 mL). After being stirred for 1 h at RT, the resulting mixture was extracted with ethyl acetate and saturated $NaHCO_3$. The organic layer was separated, washed with brine, dried with Na_2SO_4. After filtration and evaporation, the residue was purified by silica gel column chromatography (PE / EA = 2 : 1) to give **11a** (170 mg, 0.30 mmol, 68% yield) as yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.95 (d, J = 5.7 Hz, 2H), 7.85 (d, J = 8.3 Hz, 1H), 7.74 (d, J = 2.0 Hz, 1H), 7.39 (dd, J = 8.5, 2.1 Hz, 1H), 6.94 (t, J = 5.8 Hz, 1H), 6.87 (d, J = 8.4 Hz, 1H), 5.46 (s, 2H), 3.98 (s, 3H), 3.66 (dd, J = 12.1, 6.0 Hz, 2H), 2.55 (t, J = 6.1 Hz, 2H), 1.49 (s, 9H).



11b

Tert-butyl (*E*)-4-(3-(4-((2,4-bis(trifluoromethyl)benzyl)oxy)-3-methoxyphenyl)-2-cyanoacrylamido)butanoate (11b).

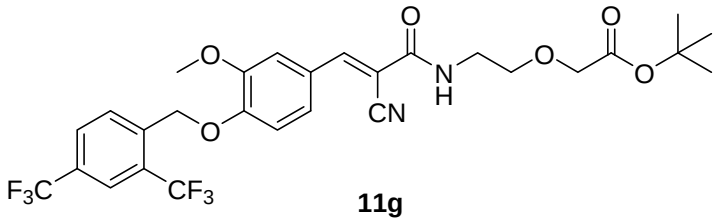
Yield: 61%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.95 (d, J = 5.3 Hz, 2H), 7.85 (d, J = 8.2 Hz, 1H), 7.73 (d, J = 2.0 Hz, 1H), 7.40 (dd, J = 8.5, 2.0 Hz, 1H), 6.87 (d, J = 8.4 Hz, 1H), 6.59 (t, J = 5.4 Hz, 1H), 5.46 (s, 2H), 3.98 (s, 3H), 3.47 (dd, J = 12.8, 6.8 Hz, 2H), 2.33 (t, J = 7.1 Hz, 2H), 1.90 (t, J = 7.0 Hz, 2H), 1.46 (s, 9H).



11d

Tert-butyl (*E*)-6-(3-(4-((2,4-bis(trifluoromethyl)benzyl)oxy)-3-methoxyphenyl)-2-cyanoacrylamido)hexanoate (11d).

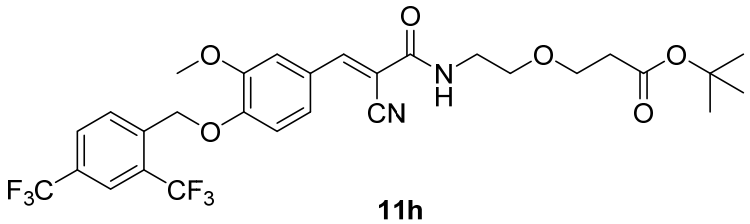
Yield: 54%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.95 (d, J = 3.8 Hz, 2H), 7.85 (d, J = 8.2 Hz, 1H), 7.71 (d, J = 2.0 Hz, 1H), 7.40 (dd, J = 8.5, 2.0 Hz, 1H), 6.87 (d, J = 8.5 Hz, 1H), 6.34 (t, J = 5.6 Hz, 1H), 5.46 (s, 2H), 3.98 (s, 3H), 3.42 (dd, J = 13.2, 7.0 Hz, 2H), 2.23 (t, J = 7.4 Hz, 2H), 1.67 – 1.58 (m, 4H), 1.44 (s, 9H), 1.42–1.35 (m, 2H).



11g

Tert-butyl (*E*)-2-(2-(3-(4-((2,4-bis(trifluoromethyl)benzyl)oxy)-3-methoxyphenyl)-2-cyanoacrylamido)ethoxy)acetate (11g).

Yield: 69%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.95 (d, J = 4.6 Hz, 2H), 7.85 (d, J = 8.0 Hz, 1H), 7.74 (d, J = 2.1 Hz, 1H), 7.41 (dd, J = 8.6, 2.0 Hz, 1H), 7.21 (t, J = 4.8 Hz, 1H), 6.87 (d, J = 8.5 Hz, 1H), 5.46 (s, 2H), 4.01 (s, 2H), 3.99 (s, 3H), 3.72 (t, J = 4.9 Hz, 2H), 3.67 – 3.62 (m, 2H), 1.49 (s, 9H).

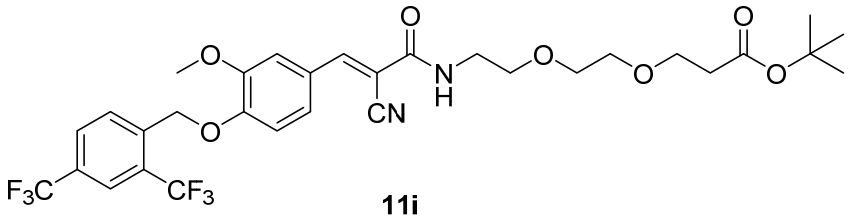


11h

Tert-butyl (*E*)-3-(2-(3-(4-((2,4-bis(trifluoromethyl)benzyl)oxy)-3-methoxyphenyl)-2-cyanoacrylamido)ethoxy)propanoate (11h).

Yield: 66%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.95 (d, J = 5.0 Hz, 2H), 7.85 (d, J = 8.2 Hz, 1H), 7.73 (d, J = 2.0 Hz, 1H), 7.40 (dd, J = 8.5, 2.0 Hz, 1H), 6.87 (d, J = 8.4 Hz, 1H), 6.76 (s, 1H), 5.46 (s, 2H), 3.98 (s, 3H), 3.72 (t, J = 6.3 Hz, 2H), 3.61 (d,

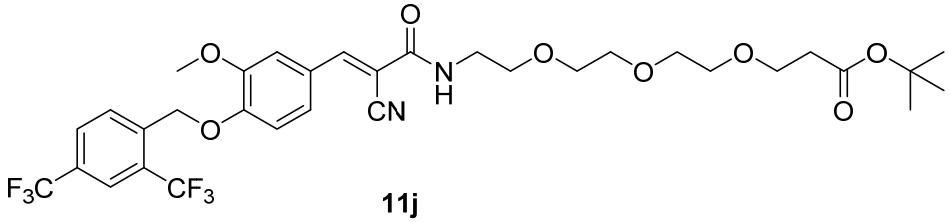
J = 2.5 Hz, 4H), 2.52 (t, *J* = 6.3 Hz, 2H), 1.46 (s, 9H).



11i

Tert-butyl (*E*)-3-(2-(2-(3-(4-((2,4-bis(trifluoromethyl)benzyl)oxy)-3-methoxyphenyl)-2-cyanoacrylamido)ethoxy)ethoxy)propanoate (11i).

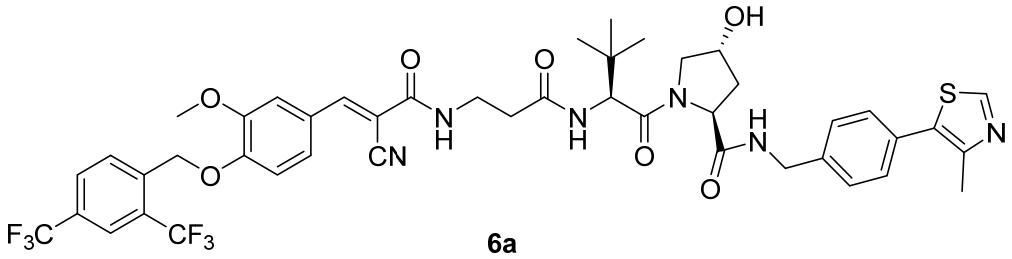
Yield: 54%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.95 (d, *J* = 4.1 Hz, 2H), 7.85 (d, *J* = 8.2 Hz, 1H), 7.73 (s, 1H), 7.40 (d, *J* = 8.4 Hz, 1H), 6.85 (dd, *J* = 14.3, 6.7 Hz, 2H), 5.46 (s, 2H), 3.98 (s, 3H), 3.74 (t, *J* = 6.5 Hz, 2H), 3.69 – 3.58 (m, 8H), 2.52 (t, *J* = 6.5 Hz, 2H), 1.44 (s, 9H).



11j

Tert-butyl (*E*)-1-(4-((2,4-bis(trifluoromethyl)benzyl)oxy)-3-methoxyphenyl)-2-cyano-3-oxo-7,10,13-trioxa-4-azahexadec-1-en-16-oate (11j).

Yield: 56%. ^{1}H N;;MR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.95 (s, 2H), 7.85 (d, *J* = 8.2 Hz, 1H), 7.73 (s, 1H), 7.40 (d, *J* = 8.4 Hz, 1H), 6.91 − 6.80 (m, 2H), 5.46 (s, 2H), 3.98 (s, 3H), 3.74-3.59 (m, 14H), 2.49 (t, *J* = 6.6 Hz, 2H), 1.43 (s, 9H).

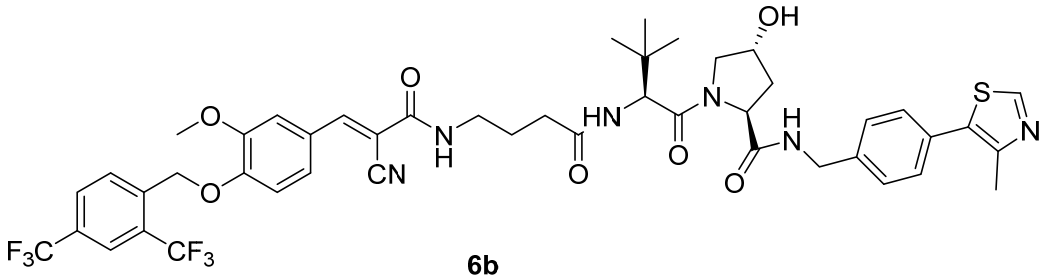


6a

(2*S*,4*R*)-1-((*S*)-2-(3-((*E*)-3-(4-((2,4-bis(trifluoromethyl)benzyl)oxy)-3-methoxyphenyl)-2-cyanoacrylamido)propanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (6a). General procedure for syntheses of 6b, 6d, 6g-6j.

TFA (1 mL) was added to a solution of Compound **11a** (100 mg, 0.17 mmol, 1 eq) in

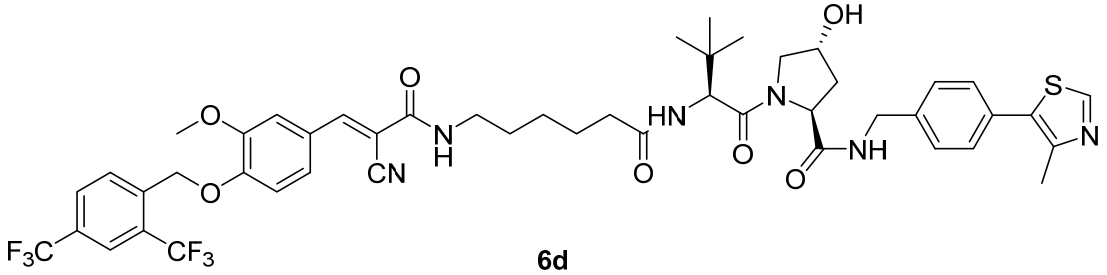
DCM (2 mL). After being stirred for 1 h, the solvent was removed in vacuo, and residual TFA was removed by the addition and evaporation of toluene (3 x 3mL). The crude product was used to next step without further purification. HATU (83.6 mg, 0.22 mmol, 1.3 eq), DIPEA (85 μL, 0.51 mmol, 3 eq) and **13** (86.1 mg, 0.2 mmol, 1.2 eq) was added to a solution of the crude product obtained above (1.0 eq.) in DMF (2 ml) at 25 ℃. After being stirred for 1 h, the resulting mixture was extracted with ethyl acetate and saturated $NaHCO_3$. The organic layer was separated, washed with brine, dried with Na_2SO_4. After filtration and evaporation, the residue was purified by silica gel column chromatography (MeOH : CH_2Cl_2 = 4 : 96) to give **6a** (62 mg, 0.067 mmol, 39%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (s, 1H), 8.17 (s, 1H), 7.94 (d, J = 8.7 Hz, 2H), 7.84 (d, J = 8.1 Hz, 1H), 7.66 (d, J = 1.9 Hz, 1H), 7.40 – 7.28 (m, 6H), 7.23 (s, 1H), 6.84 (d, J = 8.5 Hz, 1H), 6.53 (t, J = 9.9 Hz, 1H), 5.42 (s, 2H), 4.72 (t, J = 8.1 Hz, 1H), 4.58 (dd, J = 16.4, 7.9 Hz, 3H), 4.29 (dd, J = 15.1, 5.2 Hz, 1H), 4.08 (d, J = 11.0 Hz, 1H), 3.94 (s, 3H), 3.75 (dd, J = 12.8, 6.4 Hz, 1H), 3.67-3.51 (m, 2H), 3.38 (s, 1H), 2.58 – 2.45 (m, 6H), 2.16 (dd, J = 13.5, 8.0 Hz, 1H), 0.93 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.98, 171.70, 170.79, 160.89, 152.45, 151.14, 150.29, 149.69, 148.46, 139.04, 138.07, 131.53, 130.94, 130.55 (q, J = 34.34 Hz), 129.47, 129.24, 128.69, 128.02, 127.79 (q, J = 33.33 Hz), 126.46, 125.85, 124.70 (d, J = 25.25 Hz), 123.20, 122.00 (q, J = 23.23 Hz), 117.41, 113.01, 112.26, 101.46, 77.24, 70.26, 66.25, 58.59, 57.91, 57.07, 56.07, 43.19, 36.67, 36.07, 35.17, 34.99, 26.41, 16.06. HRMS (ESI$^+$): calculated for $C_{45}H_{47}F_6N_6O_7S$ [M + H]$^+$: 929.3126, found 929.3132. HPLC analysis: MeOH : H_2O (85 : 15), 10.13 min, 95.17% purity.



6b

(2*S*,4*R*)-1-((*S*)-2-(4-((*E*)-3-(4-((2,4-bis(trifluoromethyl)benzyl)oxy)-3-methoxyphenyl)-2-cyanoacrylamido)butanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (6b).

Yield: 59%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.21 (s, 1H), 7.95 (d, J = 6.7 Hz, 2H), 7.85 (d, J = 8.5 Hz, 1H), 7.68 (d, J = 1.9 Hz, 1H), 7.42 − 7.31 (m, 6H), 7.28 (s, 1H), 6.87 (d, J = 8.5 Hz, 1H), 6.57 (d, J = 8.5 Hz, 1H), 5.45 (s, 2H), 4.74 (t, J = 8.0 Hz, 1H), 4.62−.48 (m, 3H), 4.32 (dd, J = 14.9, 5.2 Hz, 1H), 4.17 (d, J = 11.4 Hz, 1H), 3.97 (s, 3H), 3.61 (dd, J = 11.3, 3.4 Hz, 1H), 3.54 − 3.35 (m, 3H), 2.59 − 2.48 (m, 4H), 2.35 (dd, J = 11.7, 6.0 Hz, 2H), 2.15 (dd, J = 13.4, 8.1 Hz, 1H), 1.97 − 1.85 (m, 2H), 0.95 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.48, 171.89, 170.73, 161.15, 152.68, 151.11, 150.30, 149.71, 148.47, 139.08, 138.06, 131.56, 130.98, 130.55 (q, J = 33.33 Hz), 129.52 129.25, 128.71, 128.11, 127.80 (q, J = 32.32 Hz), 126.44, 125.90, 124.71 (d, J = 25.25 Hz), 123.24, 122.00 (d, J = 23.23 Hz), 117.47, 113.05, 112.27, 101.44, 77.24, 70.18, 66.24, 58.56, 58.02, 56.93, 56.08, 43.25, 40.28, 35.83, 34.71, 33.66, 26.45, 24.76, 16.07. HRMS (ESI$^+$): calculated for $C_{46}H_{49}F_6N_6O_7S$ $[M + H]^+$: 943.3282, found 943.3287. HPLC analysis: MeOH : H_2O (85 : 15), 10.80 min, 98.13% purity.

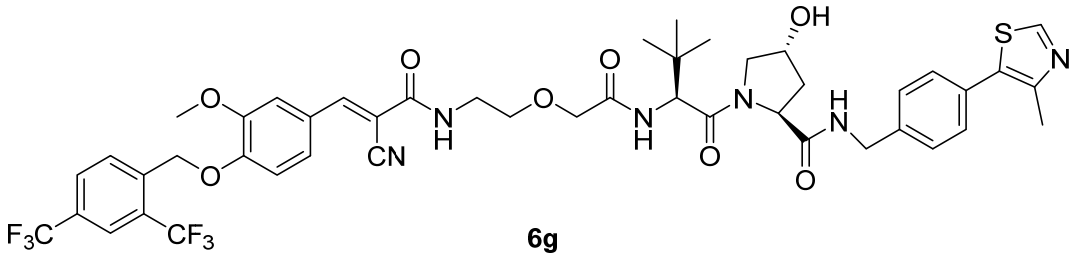


6d

(2*S*,4*R*)-1-((*S*)-2-(6-((*E*)-3-(4-((2,4-bis(trifluoromethyl)benzyl)oxy)-3-methoxyphenyl)-2-cyanoacrylamido)hexanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (6d).

Yield: 44%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.19 (s, 1H), 7.96 (s, 2H), 7.85 (d, J = 7.7 Hz, 1H), 7.69 (s, 1H), 7.35 (s, 6H), 6.86 (d, J = 8.3 Hz, 1H), 6.48 (s, 1H), 6.17 (d, J = 7.6 Hz, 1H), 5.45 (s, 2H), 4.73 (t, J = 7.7 Hz, 1H), 4.56 (dd, J = 21.1, 7.0 Hz, 3H), 4.33 (dd, J = 14.9, 4.6 Hz, 1H), 4.11 (d, J = 9.9 Hz, 1H), 3.97 (s, 3H), 3.59 (d, J = 9.5 Hz, 1H), 3.39 (d, J = 5.8 Hz, 3H), 2.50 (s, 3H), 2.19 (dd, J = 22.4, 6.1 Hz, 3H), 1.70 –1.54 (m, 4H), 1.40 (dd, J = 26.9, 12.1 Hz, 3H), 0.93 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.51, 171.89, 170.79, 160.67, 152.38, 151.10, 150.30, 149.72, 148.47, 139.09, 138.08, 131.56, 130.96, 130.54 (q, J = 34.34Hz), 129.51, 129.25,

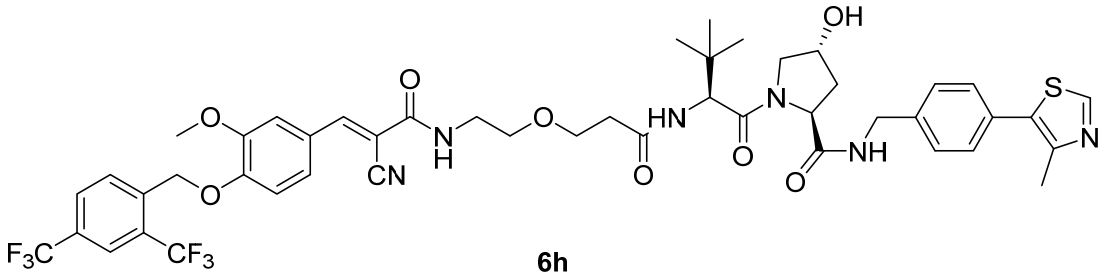
128.71, 128.07, 127.80 (q, J = 32.32Hz), 126.49, 125.91, 124.71 (d, J = 25.25Hz), 123.22, 122.00 (d, J = 23.23Hz), 117.64, 113.05, 112.15, 101.43, 77.24, 70.06, 66.24, 58.51, 57.48, 56.82, 56.08, 43.23, 40.32, 36.05, 35.96, 34.94, 29.00, 26.41, 26.17, 24.92, 16.07. HRMS (ESI^+): calculated for $C_{48}H_{53}F_6N_6O_7S$ $[M + H]^+$: 971.3595, found 971.3595. HPLC analysis: MeOH : H_2O (85 : 15), 10.73 min, 96.53% purity.



6g

(2*S*,4*R*)-1-((*S*)-2-(((2-((*E*)-3-(4-((2,4-bis(trifluoromethyl)benzyl)oxy)-3-methoxyphenyl)-2-cyanoacrylamido)ethoxy)methyl)amino)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (6g).

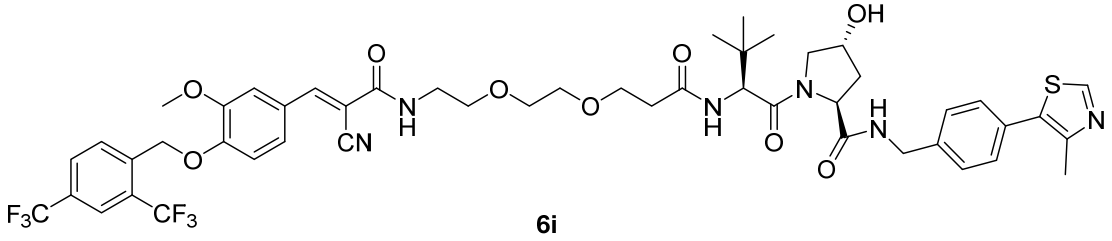
Yield: 35%. ^1H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.22 (s, 1H), 7.94 (d, J = 6.8 Hz, 2H), 7.84 (d, J = 8.2 Hz, 1H), 7.68 (s, 1H), 7.46 − 7.29 (m, 6H), 7.15 (d, J = 8.6 Hz, 1H), 7.07 (s, 1H), 6.86 (d, J = 8.4 Hz, 1H), 5.44 (s, 2H), 4.72 (t, J = 7.8 Hz, 1H), 4.53 (dd, J = 16.0, 7.9 Hz, 3H), 4.31 (dd, J = 15.0, 5.4 Hz, 1H), 4.04 (t, J = 12.9 Hz, 2H), 3.94 (s, 3H), 3.77 − 3.69 (m, 1H), 3.62 (dd, J = 15.8, 4.0 Hz, 4H), 2.49 (s, 4H), 2.11 (dd, J = 13.5, 8.1 Hz, 1H), 1.99 (s, 2H), 0.94 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.36, 170.73, 169.87, 161.15, 152.83, 151.20, 150.30, 149.72, 148.44, 139.04, 138.13, 131.56, 130.92, 130.56 (q, J = 33.33 Hz), 129.46, 129.25, 128.72, 128.09, 127.80 (q, J = 32.32 Hz), 126.52, 125.86, 124.7 (d, J = 24.24 Hz), 123.24, 122.00 (d, J = 23.23 Hz), 117.44, 113.06, 112.27, 101.28, 77.24, 70.18, 66.25, 60.42, 58.58, 57.02, 56.84, 56.07, 43.18, 40.33, 35.91, 35.28, 26.41, 16.05. HRMS (ESI^+): calculated for $C_{46}H_{49}F_6N_6O_8S$ $[M + H]^+$: 959.3231, found 959.3239. HPLC analysis: MeOH : H_2O (85 : 15), 9.62 min, 99.10% purity.



6h

(2*S*,4*R*)-1-((*S*)-2-(3-(2-((*E*)-3-(4-((2,4-bis(trifluoromethyl)benzyl)oxy)-3-methoxyphenyl)-2-cyanoacrylamido)ethoxy)propanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (6h).

Yield: 56%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (s, 1H), 8.20 (s, 1H), 7.95 (d, J = 7.0 Hz, 2H), 7.85 (d, J = 8.2 Hz, 1H), 7.67 (d, J = 2.0 Hz, 1H), 7.40 − 7.32 (m, 6H), 7.20 (t, J = 5.1 Hz, 1H), 7.04 (d, J = 8.7 Hz, 1H), 6.87 (d, J = 8.5 Hz, 1H), 5.44 (s, 2H), 4.77 (t, J = 8.0 Hz, 1H), 4.59 (q, J = 6.6 Hz, 2H), 4.51 (s, 1H), 4.30 (dd, J = 15.0, 5.1 Hz, 1H), 4.10 (d, J = 11.3 Hz, 1H), 3.95 (s, 3H), 3.74 (td, J = 9.9, 4.0 Hz, 2H), 3.67 − 3.54 (m, 5H), 3.13 (s, 1H), 2.56 − 2.45 (m, 6H), 2.13 (dd, J = 13.5, 8.1 Hz, 1H), 0.94 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.79, 171.66, 170.92, 161.10, 152.71, 151.14, 150.28, 149.70, 148.43, 139.06, 138.15, 131.57, 130.88, 130.55 (q, J= 33.33 Hz), 129.41, 129.25, 128.71, 128.03, 127.80 (q, J= 32.32 Hz), 126.44, 125.88, 124.71 (d, J = 25.25 Hz), 123.24, 122.00 (d, J = 23.23 Hz), 117.49, 113.05, 112.28, 101.46, 77.24, 70.19, 69.22, 66.56(d, J = 57.57 Hz) , 66.24, 58.48, 57.44, 56.92, 56.07, 43.16, 40.79, 36.58, 36.04, 35.38, 26.41, 16.06. HRMS (ESI^+): calculated for $C_{47}H_{50}F_6N_6NaO_8S$ $[M + Na]^+$: 995.3207, found 995.3209**.** HPLC analysis: MeOH: H_2O (85 : 15),10.18 min, 96.36% purity.

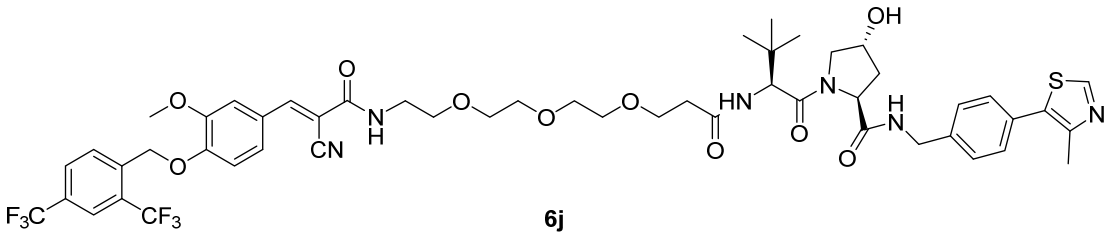


6i

(2*S*,4*R*)-1-((*S*,*E*)-16-(4-((2,4-bis(trifluoromethyl)benzyl)oxy)-3-methoxyphenyl)-2-(tert-butyl)-15-cyano-4,14-dioxo-7,10-dioxa-3,13-diazahexadec-15-enoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (6i).

Yield: 61%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (s, 1H), 8.19 (s, 1H), 7.95 (d, J = 7.1

Hz, 2H), 7.84 (d, *J* = 8.2 Hz, 1H), 7.69 (d, *J* = 1.8 Hz, 1H), 7.46 − 7.29 (m, 6H), 7.06 (d, *J* = 7.6 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 1H), 5.44 (s, 2H), 4.72 (t, *J* = 8.0 Hz, 1H), 4.63 − 4.46 (m, 3H), 4.31 (dd, *J* = 15.0, 5.2 Hz, 1H), 4.11 (d, *J* = 10.8 Hz, 1H), 3.96 (s, 3H), 3.72 (d, *J* = 6.8 Hz, 2H), 3.67 − 3.27 (m, 10H), 2.58 − 2.38 (m, 6H), 2.12 (dd, *J* = 13.5, 8.1 Hz, 1H), 0.94 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.06, 171.91, 170.80, 160.93, 152.52, 151.11, 150.27, 149.73, 148.45, 139.09, 138.14, 131.57, 130.92, 130.54 (q, *J*=33.33 Hz), 129.4, 129.25, 128.70, 128.08, 127.79 (q, *J*= 32.32 Hz), 126.54, 125.88, 124.71 (d, *J* = 25.25 Hz), 123.23, 122.00(d, *J* = 23.23 Hz), 117.42, 113.04, 112.17, 101.50, 77.23, 70.31, 70.19, 70.13, 69.19, 67.15, 66.23, 58.37, 57.59, 56.76, 56.12, 43.22, 40.23, 36.70, 35.93, 34.99, 26.41, 16.07. HRMS (ESI$^+$): calculated for $C_{49}H_{55}F_6N_6O_9S$ $[M + H]^+$: 1017.3650, found 1017.3635. HPLC analysis: MeOH : H_2O (85 : 15),10.31 min, 98.32% purity.

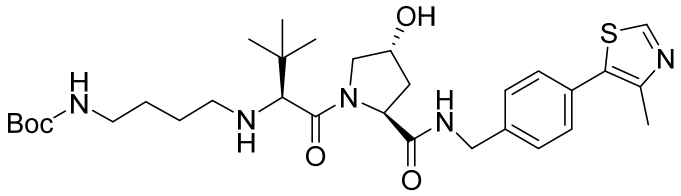


6j

(2*S*,4*R*)-1-((*S*,*E*)-19-(4-((2,4-bis(trifluoromethyl)benzyl)oxy)-3-methoxyphenyl)-2-(tert-butyl)-18-cyano-4,17-dioxo-7,10,13-trioxa-3,16-diazanonadec-18-enoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (6j).

Yield: 40%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (s, 1H), 8.21 (s, 1H), 7.95 (d, *J* = 4.6 Hz, 2H), 7.85 (d, *J* = 8.1 Hz, 1H), 7.70 (d, *J* = 1.8 Hz, 1H), 7.44 − 7.30 (m, 6H), 7.05 − 6.94 (m, 2H), 6.87 (d, *J* = 8.5 Hz, 1H), 5.45 (s, 2H), 4.73 (t, *J* = 8.0 Hz, 1H), 4.61 − 4.44 (m, 3H), 4.33 (dd, *J* = 15.0, 5.2 Hz, 1H), 4.13 (d, *J* = 11.5 Hz, 1H), 3.97 (s, 3H), 3.71 (t, *J* = 6.9 Hz, 2H), 3.68 − 3.52 (m, 13H), 3.47 (s, 1H), 2.57 − 2.42 (m, 6H), 2.13 (dd, *J* = 13.4, 8.2 Hz, 1H), 0.93 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.15, 171.88, 170.81, 160.83, 152.38, 151.07, 150.29, 149.71, 148.47, 139.11, 138.15, 131.58, 130.91, 130.53 (q, *J*= 34.34 Hz), 129.49, 129.24, 128.71, 128.10, 127.80 (q, *J* = 32.32 Hz), 126.45, 125.95, 124.71 (d, *J* = 24.24 Hz), 123.21, 122.00 (d, *J* = 22.22 Hz), 117.42, 113.07, 112.26, 101.59, 77.23, 70.52, 70.38, 70.11, 69.43, 67.12, 66.25, 58.28, 57.72, 56.68, 56.100, 43.22, 40.32, 36.62, 35.89, 34.71, 26.40, 16.07. HRMS

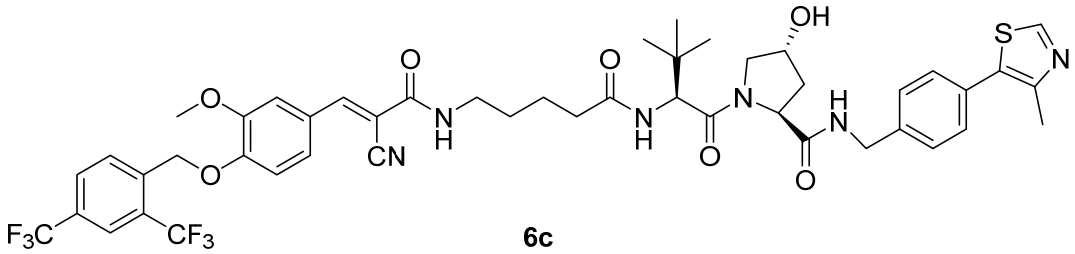
(ESI) calculated for $C_{51}H_{59}F_6N_6O_{10}S$ $[M + H]^+$: 1061.3912, found 1061.3887. HPLC analysis: MeOH : H_2O (85 : 15), 10.36 min, 95.08% purity.



15

Tert-butyl(5-(((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-5-oxopentyl)carbamate (15).

HATU (133 mg, 0.35 mmol, 1.5 eq), DIPEA (0.20 mL, 1.2 mmol, 5 eq) and **13** (100 mg, 0.23 mmol, 1 eq) was added to a solution of 5-((tert-butoxycarbonyl)amino)pentanoic acid (61 mg, 0.28 mmol, 1.2 eq) in dry DMF (2 mL). After being stirred for 1 h at RT, the resulting mixture was extracted with ethyl acetate and saturated $NaHCO_3$. The organic layer was separated, washed with brine, dried with Na_2SO_4. After filtration and evaporation, the residue was purified by silica gel column chromatography (DCM / MeOH=20 : 1) to give **15** (89 mg, 0.15 mmol, 65% yield) as white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (s, 1H), 7.40 − 7.32 (m, 5H), 6.33 (d, J = 8.3 Hz, 1H), 4.72 (t, J = 7.9 Hz, 2H), 4.62 − 4.49 (m, 3H), 4.33 (dd, J = 15.0, 5.2 Hz, 1H), 4.10 (d, J = 9.9 Hz, 1H), 3.60 (d, J = 8.5 Hz, 1H), 3.08 (d, J = 6.0 Hz, 2H), 2.51 (s, 4H), 2.26 − 2.11 (m, 3H), 1.59 (d, J = 15.0 Hz, 2H), 1.48 −1.39 (m, 12H), 0.93 (s, 9H).

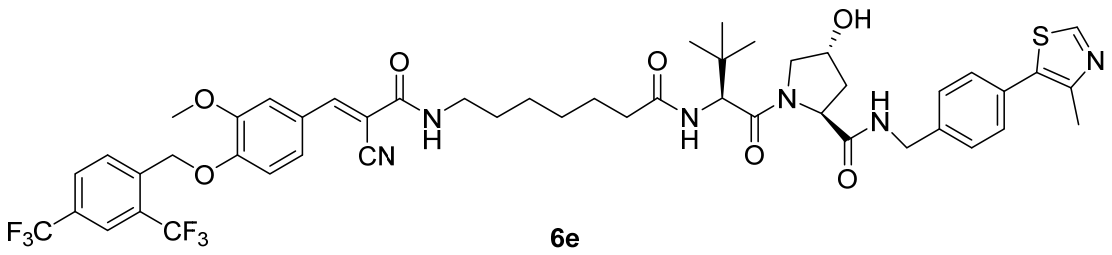


6c

(2*S*,4*R*)-1-((*S*)-2-((4-((*E*)-3-(4-((2,4-bis(trifluoromethyl)benzyl)oxy)-3-methoxyphenyl)-2-cyanoacrylamido)butyl)amino)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (6c).

TFA (1 mL) was added to a solution of Compound **15** (80 mg, 0.13 mmol, 1 eq) in

DCM (2 mL). After being stirred for 1 h, the solvents were removed in vacuo, and residual TFA was removed by the addition and evaporation of toluene (3 x 3mL). The crude product was used to next step without further purification. HATU (76 mg, 0.20 mmol, 1.5 eq), DIPEA (110 μL, 0.65 mmol, 5 eq) and **4a** (73 mg, 0.16 mmol, 1.2 eq) was added to a solution of the crude product obtained above (1.0 eq) in DMF (2 ml) at 25 ℃. After being stirred for 1 h, the resulting mixture was extracted with ethyl acetate and saturated $NaHCO_3$. The organic layer was separated, washed with brine, dried with Na_2SO_4. After filtration and evaporation, the residue was purified by silica gel column chromatography (MeOH : CH_2Cl_2 =4 : 96) to give **6c** (81 mg, 0.085 mmol, 65%) as white solid: [α]25 D -22.39° (*c* 0.134, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.22 (s, 1H), 7.97 (d, *J* = 6.8 Hz, 2H), 7.87 (d, *J* = 8.2 Hz, 1H), 7.71 (d, *J* = 2.0 Hz, 1H), 7.41 − 7.31 (m, 6H), 6.91 − 6.80 (m, 2H), 6.31 (d, *J* = 5.8 Hz, 1H), 5.45 (d, *J* = 14.3 Hz, 2H), 4.74 (t, *J* = 8.0 Hz, 1H), 4.62 − 4.53 (m, 3H), 4.35 (dd, *J* = 15.0, 5.3 Hz, 1H), 4.15 (d, *J* = 11.2 Hz, 1H), 3.98 (s, 3H), 3.64 (dd, *J* = 11.3, 3.3 Hz, 1H), 3.57 − 3.30 (m, 3H), 2.52 (s, 4H), 2.29 (dt, *J* = 15.0, 7.5 Hz, 2H), 2.17 (dd, *J* = 13.4, 8.0 Hz, 1H), 1.70 (dd, *J* = 13.4, 6.7 Hz, 2H), 1.66 − 1.56 (m, 2H), 0.94 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.79, 171.66, 170.92, 161.10, 152.71, 151.14, 150.28, 149.70, 148.43, 139.06, 138.15, 131.57, 130.88, 130.55 (q, *J* = 33.00 Hz), 129.41, 129.25, 128.71, 128.03, 127.80 (q, *J* = 32.32 Hz), 126.44, 125.88, 124.71 (d, *J* = 25.25 Hz), 123.24, 122.00 (d, *J* = 23.23 Hz), 117.49, 113.05, 112.28, 101.46, 77.24, 70.19, 69.22, 66.84, 66.26 (q, *J* = 23.23 Hz), 58.48, 57.44, 56.92, 56.07, 43.16, 40.79, 36.58, 36.04, 35.38, 26.41, 16.06. HRMS (ESI^+): calculated for $C_{47}H_{51}F_6N_6O_7S$ [M + H]$^+$: 957.3439, found 957.3435. HPLC analysis: MeOH: H_2O (85 : 15), 10.69 min, 96.40 % purity.

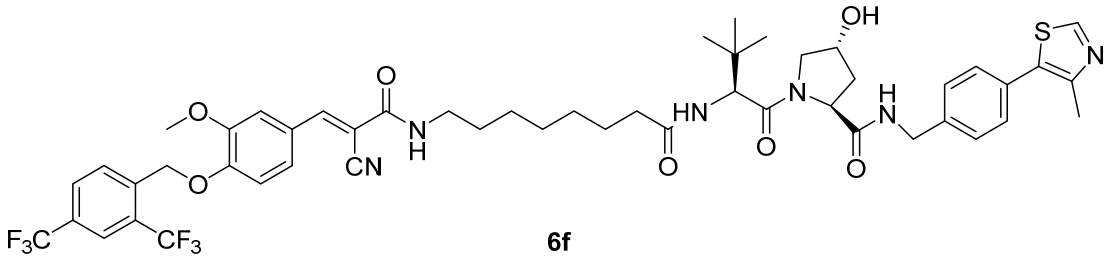


6e

(2*S*,4*R*)-1-((*S*)-2-(7-((*E*)-3-(4-((2,4-bis(trifluoromethyl)benzyl)oxy)-3-methoxyphe

nyl)-2-cyanoacrylamido)heptanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamid (6e). Compound 6e was synthesized from 7-((tert-butoxycarbonyl)amino)heptanoic acid with similar procedure to that of 6c.

Yield: 71%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.17 (s, 1H), 7.95 (d, J = 5.9 Hz, 2H), 7.85 (d, J = 8.2 Hz, 1H), 7.69 (d, J = 1.5 Hz, 1H), 7.41 − 7.31 (m, 6H), 6.86 (d, J = 8.4 Hz, 1H), 6.44 (t, J = 5.4 Hz, 1H), 6.18 (d, J = 8.7 Hz, 1H), 5.45 (s, 2H), 4.73 (t, J = 8.0 Hz, 1H), 4.60-4.50 (m, 3H), 4.34 (dd, J = 15.0, 5.2 Hz, 1H), 4.12 (d, J = 11.4 Hz, 1H), 3.97 (s, 3H), 3.60 (dd, J = 11.3, 3.1 Hz, 1H), 3.49 − 3.34 (m, 3H), 2.50 (s, 4H), 2.27 − 2.11 (m, 3H), 1.60 (dd, J = 13.9, 7.0 Hz, 4H), 1.33 (d, J = 4.6 Hz, 4H), 0.93 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.74, 171.92, 170.76, 160.66, 152.30, 151.09, 150.30, 149.72, 148.47, 139.10, 138.09, 131.56, 130.96, 130.54 (q, J = 33.33Hz), 129.51, 129.25, 128.71, 128.08, 127.80 (q, J = 33.33 Hz), 126.51, 125.91, 124.71 (d, J = 24.24 Hz), 123.22, 122.00 (q, J = 22.22 Hz), 117.64, 113.04, 112.12, 101.45, 77.23, 70.05, 66.24, 58.45, 57.48, 56.80, 56.09, 43.24, 40.34, 36.18, 35.90, 34.83, 29.71, 29.05, 28.35, 26.42, 26.23, 25.26, 16.07. HRMS (ESI^+): calculated for $C_{49}H_{55}F_6N_6O_7S$ $[M + H]^+$: 985.3752, found 985.3723. HPLC analysis: MeOH : H_2O (85 : 15), 12.65 min, 95.80 % purity.

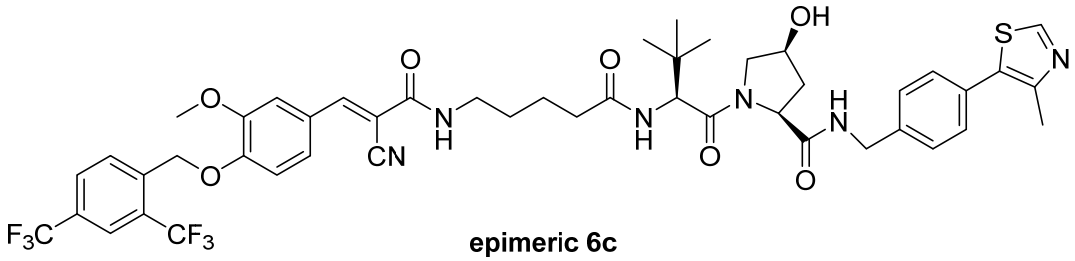


6f

(2*S*,4*R*)-1-((*S*)-2-(8-((*E*)-3-(4-((2,4-bis(trifluoromethyl)benzyl)oxy)-3-methoxyphenyl)-2-cyanoacrylamido)octanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (6f). Compound 6f was synthesized from 8-((tert-butoxycarbonyl)amino)octanoic acid with similar procedure to that of 6c.

Yield: 50%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.20 (s, 1H), 7.95 (d, J = 6.8 Hz, 2H), 7.85 (d, J = 8.2 Hz, 1H), 7.70 (d, J = 2.0 Hz, 1H), 7.40 − 7.31 (m, 6H), 6.86

(d, *J* = 8.5 Hz, 1H), 6.41 (t, *J* = 5.7 Hz, 1H), 6.17 (d, *J* = 8.8 Hz, 1H), 5.45 (s, 2H), 4.72 (t, *J* = 8.0 Hz, 1H), 4.60 − 4.50 (m, 3H), 4.33 (dd, *J* = 15.0, 5.2 Hz, 1H), 4.11 (d, *J* = 10.9 Hz, 1H), 3.97 (s, 3H), 3.60 (dd, *J* = 11.4, 3.5 Hz, 1H), 3.39 (dd, *J* = 13.4, 6.7 Hz, 3H), 2.57 − 2.46 (m, 4H), 2.24 − 2.09 (m, 3H), 1.58 (dd, *J* = 14.1, 7.2 Hz, 4H), 1.32 (d, *J* = 3.4 Hz, 6H), 0.93 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.83, 171.92, 170.69, 160.57, 152.32, 151.07, 150.32, 149.72, 148.47, 139.10, 138.07, 131.57, 130.98, 130.54 (q, *J* = 33.33 Hz), 129.53, 129.22, 128.70, 128.11, 127.80 (q, *J* = 32.32 Hz), 126.48, 125.94, 124.71 (q, *J* = 24.24 Hz), 123.22, 122.00 (q, *J* = 22.22 Hz), 117.67, 113.06, 112.16, 101.47, 77.23, 70.06, 58.44, 57.44, 56.76, 56.10, 43.26, 40.56, 36.30, 35.81, 34.83, 29.71, 29.21, 28.77, 28.71, 26.55, 26.41, 25.32, 16.06. HRMS (ESI^+): calculated for $C_{50}H_{57}F_6N_6O_7S$ $[M + H]^+$: 999.3908, found 999.3888. HPLC analysis: MeOH : H_2O (85 : 15), 14.56 min, 95.60 % purity.

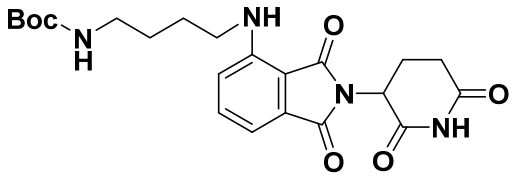


epimeric 6c

(2*S*,4*S*)-1-((*S*)-2-(5-((*E*)-3-(4-((2,4-bis(trifluoromethyl)benzyl)oxy)-3-methoxyphenyl)-2-cyanoacrylamido)pentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (epimeric 6c). Compound epimeric 6c was synthesized from epimeric 10 with similar procedure to that of 6c.

Yield: 64%. [α]25 D -17.39° (*c* 0.115, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.20 (s, 1H), 7.95 (d, *J* = 5.9 Hz, 2H), 7.84 (d, *J* = 8.2 Hz, 1H), 7.70 (d, *J* = 1.6 Hz, 1H), 7.50 (s, 1H), 7.35 (q, *J* = 8.6 Hz, 5H), 6.86 (d, *J* = 8.5 Hz, 1H), 6.59 (s, 1H), 6.08 (d, *J* = 8.4 Hz, 1H), 5.54 (d, *J* = 9.9 Hz, 1H), 5.44 (s, 2H), 4.72 (d, *J* = 8.9 Hz, 1H), 4.63 (dd, *J* = 14.9, 7.0 Hz, 1H), 4.53–4.44 (m, 2H), 4.29 (dd, *J* = 14.9, 5.0 Hz, 1H), 3.96 (s, 4H), 3.80 (d, *J* = 10.9 Hz, 1H), 3.41 (dd, *J* = 6.1, 2.8 Hz, 2H), 2.50 (s, 3H), 2.34 (d, *J* = 14.1 Hz, 1H), 2.27 (dd, *J* = 13.3, 7.0 Hz, 2H), 2.23–2.15 (m, 1H), 1.69 (dd, *J* = 14.4, 7.2 Hz, 2H), 1.62 (dd, *J* = 13.8, 6.8 Hz, 2H), 0.92 (s, 9H). ^{13}C

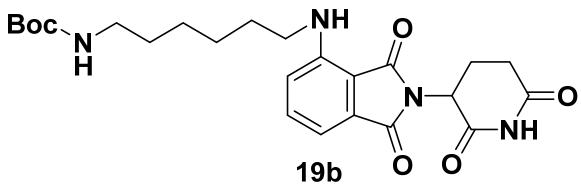
NMR (101 MHz, $CDCl_3$) δ 172.75, 172.57, 172.23, 160.72, 152.39, 151.12, 150.36, 149.73, 148.55, 139.07, 137.32, 131.45, 131.25, 130.55 (q, *J* = 33.33 Hz), 129.62, 129.25, 128.71, 128.14, 127.80 (q, *J* = 32.32 Hz), 126.51, 125.90, 124.70 (d, *J* = 24.24 Hz), 123.24, 122.00 (d, *J* = 23.23 Hz), 117.61, 113.06, 112.12, 101.41, 77.24, 71.13, 66.25, 59.90, 58.64, 57.16, 56.08, 43.49, 39.75, 35.47, 35.11, 34.79, 28.83, 26.36, 22.32, 16.08. HRMS (ESI^+): calculated for $C_{47}H_{51}F_6N_6O_7S$ $[M + H]^+$: 957.3439, found 957.3423. HPLC analysis: MeOH : H_2O (85 : 15), 8.97 min, 98.90 % purity.



19a

Tert-butyl(4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)butyl)carbamate (19a). General procedure for syntheses of 19b-19h.

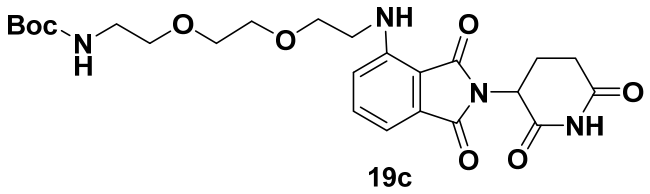
To a solution of **17** (276.2 mg, 1 mmol, 1eq) in DMF (3 mL), **18a** (188.3 mg, 1 mmol, 1 eq) and DIPEA (258.5 mg, 2 mmol, 2 eq) were added and stirred at 90 ℃ for 8 h. After cooling to room temperature, the resulting mixture was extracted with ethyl acetate and H_2O. The organic layer was separated, washed with brine, dried with Na_2SO_4. After filtration and evaporation, the residue was purified by silica gel column chromatography (PE / EA = 1 : 1 to MeOH / DCM = 2.5 %) to afford **19a** as yellow oil (201 mg, 0.45 mmol, 45%): ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.48 (dd, *J* = 8.3, 7.3 Hz, 1H), 7.08 (d, *J* = 7.0 Hz, 1H), 6.88 (d, *J* = 8.5 Hz, 1H), 6.23 (t, *J* = 5.6 Hz, 1H), 4.91 (dd, *J* = 12.1, 5.4 Hz, 1H), 4.60 (s, 1H), 3.29 (dd, *J* = 12.8, 6.6 Hz, 2H), 3.21 – 3.13 (m, 2H), 2.91 – 2.83 (m, 1H), 2.76 (ddd, *J* = 19.3, 14.3, 4.3 Hz, 2H), 2.17 – 2.09 (m, 1H), 1.73 – 1.65 (m, 2 H), 1.60 (tt, *J* = 12.7, 6.3 Hz, 2 H), 1.43 (s, 9H).



19b

Tert-butyl(6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)hexyl)carbamate (19b).

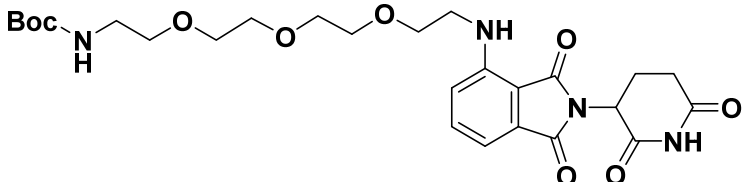
Yield: 34%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1H), 7.53 – 7.42 (m, 1H), 7.06 (d, *J* = 7.1 Hz, 1H), 6.85 (d, *J* = 8.5 Hz, 1H), 6.21 (t, *J* = 5.5 Hz, 1H), 4.93 – 4.87 (m, 1H), 4.58 (s, 1H), 3.24 (dd, *J* = 12.8, 6.9 Hz, 2H), 3.09 (d, *J* = 6.0 Hz, 4H), 2.88 – 2.81 (m, 1H), 2.78 – 2.68 (m, 2H), 2.10 (dt, *J* = 8.9, 3.8 Hz, 1H), 1.69 – 1.59 (m, 2H), 1.52 – 1.45 (m, 2H), 1.42 (s, 9H), 1.38 – 1.31 (m, 2H).



19c

Tert-butyl(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)ethyl)carbamate (19c).

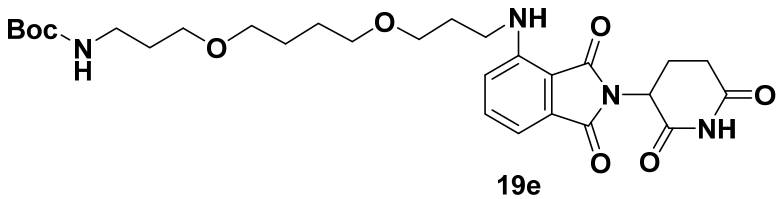
Yield: 49%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (s, 1H), 7.49 (dd, *J* = 8.3, 7.4 Hz, 1H), 7.10 (d, *J* = 7.1 Hz, 1H), 6.90 (d, *J* = 8.5 Hz, 1H), 6.51 (s, 1H), 5.08 (s, 1H), 4.91 (dd, *J* = 11.7, 5.1 Hz, 1H), 3.72 (t, *J* = 5.3 Hz, 2H), 3.65 (s, 4H), 3.56 (t, *J* = 5.1 Hz, 2H), 3.47 (dd, *J* = 10.5, 5.3 Hz, 2H), 3.32 (dd, *J* = 10.3, 5.2 Hz, 2H), 2.90 – 2.83 (m, 1H), 2.81 – 2.69 (m, 2H), 2.16 – 2.09 (m, 1H), 1.42 (s, 9 H).



19d

Tert-butyl(2-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)ethoxy)ethyl)carbamate (19d).

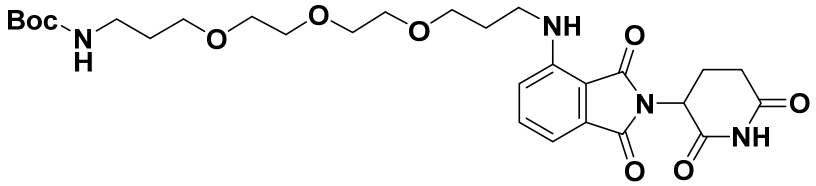
Yield: 46%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.49 (dd, *J* = 8.3, 7.3 Hz, 1H), 7.10 (d, *J* = 7.0 Hz, 1H), 6.92 (d, *J* = 8.5 Hz, 1H), 6.49 (t, *J* = 5.3 Hz, 1H), 5.07 (d, *J* = 3.1 Hz, 1H), 4.92 (dd, *J* = 12.1, 5.4 Hz, 1H), 3.72 (t, *J* = 5.4 Hz, 2H), 3.69 – 3.59 (m, 8H), 3.53 (t, *J* = 5.0 Hz, 2H), 3.47 (dd, *J* = 10.9, 5.5 Hz, 2H), 3.35 – 3.28 (m, 2H), 2.91 – 2.84 (m, 1H), 2.77 (ddd, *J* = 19.3, 14.3, 4.3 Hz, 2H), 2.18 – 2.08 (m, 1H), 1.43 (s, 9H), 0.86 (ddd, *J* = 11.1, 7.6, 4.7 Hz, 1H).



19e

Tert-butyl(3-(4-(3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)propoxy)butoxy)propyl)carbamate (19e).

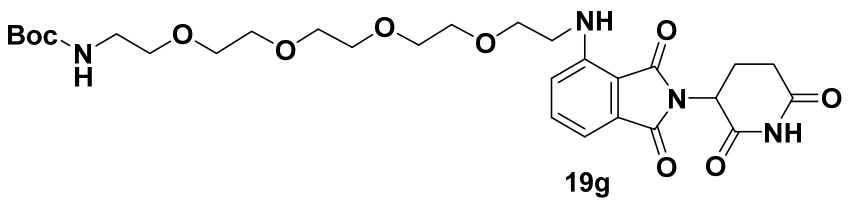
Yield: 50%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.48 (dd, *J* = 8.4, 7.3 Hz, 1H), 7.11 – 7.03 (m, 1H), 6.91 (d, *J* = 8.6 Hz, 1H), 6.45 (s, 1H), 4.98 – 4.86 (m, 2H), 3.53 (t, *J* = 5.8 Hz, 2H), 3.43 (tt, *J* = 18.9, 6.4 Hz, 8H), 3.26 – 3.18 (m, 2H), 3.10 (s, 1H), 2.96 – 2.85 (m, 1H), 2.82 – 2.65 (m, 2H), 2.13 (ddd, *J* = 9.4, 7.3, 4.3 Hz, 1H), 1.96 – 1.86 (m, 2H), 1.73 (dd, *J* = 12.2, 6.0 Hz, 2H), 1.70 – 1.66 (m, 2H), 1.43 (s, 9H), 0.86 (ddd, *J* = 11.0, 7.7, 4.7 Hz, 1H).



19f

Tert-butyl(3-(2-(2-(3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)propoxy)ethoxy)ethoxy)propyl)carbamate (19f).

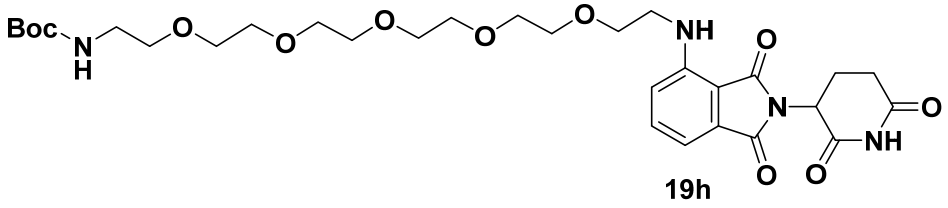
Yield: 40%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.49 (dd, *J* = 8.3, 7.3 Hz, 1H), 7.10 (d, *J* = 7.1 Hz, 1H), 6.92 (d, *J* = 8.5 Hz, 1H), 6.50 (t, *J* = 5.4 Hz, 1H), 5.14 (s, 1H), 4.91 (dd, *J* = 12.1, 5.4 Hz, 1H), 3.72 (t, *J* = 5.4 Hz, 2H), 3.69 – 3.64 (m, 8H), 3.63 – 3.59 (m, 4H), 3.53 (t, *J* = 5.0 Hz, 2H), 3.47 (q, *J* = 5.5 Hz, 2H), 3.30 (d, *J* = 4.9 Hz, 2H), 2.87 (ddd, *J* = 11.3, 8.9, 4.2 Hz, 1H), 2.75 (tdd, *J* = 17.4, 12.9, 4.2 Hz, 2H), 2.12 (ddd, *J* = 9.4, 5.7, 3.0 Hz, 1H), 1.43 (s, 9H).



19g

Tert-butyl(14-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-3,6,9, 12-tetraoxatetradecyl)carbamate (19g).

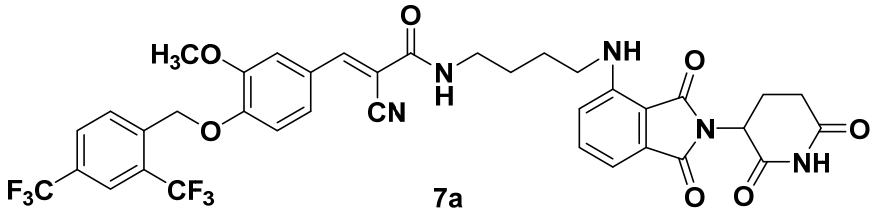
Yield: 33%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.48 (dd, *J* = 8.4, 7.3 Hz, 1H), 7.08 (d, *J* = 7.0 Hz, 1H), 6.93 (d, *J* = 8.6 Hz, 1H), 6.44 (t, *J* = 5.4 Hz, 1H), 4.97 (s, 1H), 4.90 (dd, *J* = 12.1, 5.4 Hz, 1H), 3.70 – 3.67 (m, 2H), 3.65 – 3.56 (m, 9H), 3.53 (t, *J* = 6.0 Hz, 2H), 3.40 (q, *J* = 6.4 Hz, 2H), 3.21 (d, *J* = 6.0 Hz, 2H), 2.91 – 2.82 (m, 1H), 2.76 (ddd, *J* = 19.6, 14.2, 4.4 Hz, 2H), 2.12 (ddd, *J* = 9.4, 5.6, 3.0 Hz, 1H), 1.97 – 1.89 (m, 2H), 1.75 (dd, *J* = 12.4, 6.2 Hz, 2H), 1.43 (s, 9H).



19h

Tert-butyl(17-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-3,6,9, 12,15-pentaoxaheptadecyl)carbamate (19h).

Yield: 32%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (s, 1H), 7.49 (t, *J* = 7.8 Hz, 1H), 7.10 (d, *J* = 7.1 Hz, 1H), 6.91 (d, *J* = 8.5 Hz, 1H), 6.49 (t, *J* = 5.2 Hz, 1H), 5.17 (s, 1H), 4.91 (dd, *J* = 12.0, 5.3 Hz, 1H), 3.71 (t, *J* = 5.3 Hz, 2H), 3.69 – 3.59 (m, 16H), 3.52 (t, *J* = 4.8 Hz, 2H), 3.46 (dd, *J* = 10.8, 5.4 Hz, 2H), 3.30 (d, *J* = 5.0 Hz, 2H), 2.86 (dd, *J* = 13.9, 10.6 Hz, 1H), 2.76 (td, *J* = 14.8, 3.8 Hz, 2H), 2.18 – 2.07 (m, 1H), 1.43 (s, 9H).



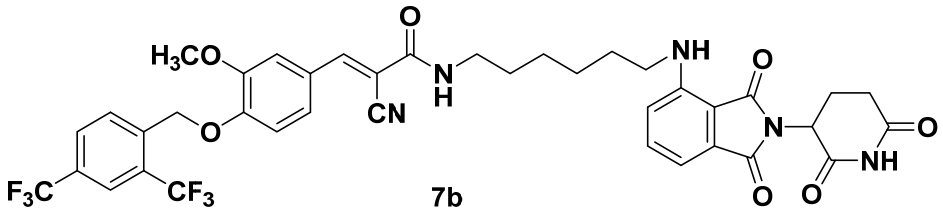
7a

(*E*)-3-(4-((2,4-bis(trifluoromethyl)benzyl)oxy)-3-methoxyphenyl)-2-cyano-N-(4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)butyl)acrylamide(7a).

General procedure for syntheses of 7b-7h.

TFA (2 mL) was added to a solution of Compound **19a** (150 mg, 0.34 mmol, 1 eq) in DCM (4 mL). After being stirred for 1 h, the solvents were removed in vacuo, and residual TFA was removed by the addition and evaporation of toluene (3 x 3mL). The

crude product was used to next step without further purification. HATU (194 mg, 0.51 mmol, 1.5 eq), DIPEA (220 mg, 1.7 mmol, 5 eq) and **4a** (151.4 mg, 0.34 mmol, 1 eq) was added to a solution of the crude product obtained above in DMF (3 ml) at 25 ℃. After being stirred for 1 h, the resulting mixture was extracted with ethyl acetate and saturated $NaHCO_3$. The organic layer was separated, washed with brine, dried with Na_2SO_4. After filtration and evaporation, the residue was purified by silica gel column chromatography (MeOH : CH_2Cl_2 =2.5 : 100) to give **7a** (115 mg, 0.15 mmol, 44%) as yellow solid: ^{1}H NMR (400 MHz, DMSO) δ 11.09 (s, 1H), 8.39 (t, *J* = 5.6 Hz, 1H), 8.18 (d, *J* = 8.1 Hz, 1H), 8.10 (s, 2H), 8.03 (d, *J* = 8.1 Hz, 1H), 7.71 (d, *J* = 1.9 Hz, 1H), 7.57 (ddd, *J* = 8.3, 4.5, 2.5 Hz, 2H), 7.23 (d, *J* = 8.6 Hz, 1H), 7.12 (d, *J* = 8.6 Hz, 1H), 7.01 (d, *J* = 7.0 Hz, 1H), 6.58 (t, *J* = 5.9 Hz, 1H), 5.44 (s, 2H), 5.05 (dd, *J* = 12.9, 5.3 Hz, 1H), 3.83 (s, 3H), 3.33 (s, 2H), 3.26 (d, *J* = 5.4 Hz, 2H), 2.93 – 2.83 (m, 2H), 2.73 (s, 1H), 2.69 (s, 2H), 2.63 – 2.51 (m, 2H), 2.08 – 1.96 (m, 1H). ^{13}C NMR (101 MHz, DMSO) δ 173.27, 170.56, 169.38, 167.75, 162.75, 161.58, 151.00, 150.67, 149.42, 146.85, 139.86, 136.72, 132.68, 131.61, 130.44, 129.77 (q, *J* = 33.33 Hz), 128.11 (q, *J* = 32.32 Hz), 126.00, 125.39, 125.13, 123.63, 122.45, 117.57 (d, *J* = 23.23 Hz), 113.90, 113.37, 110.86, 109.50, 103.91, 66.63, 56.12, 49.00, 41.97, 38.71, 36.25, 31.45, 26.70 (d, *J* = 17.17 Hz), 22.63. HRMS (ESI) calculated for $C_{37}H_{32}F_6N_5O_7$ $[M + H]^+$: 772.2200, found 772.2200. HPLC analysis: MeOH : H2O (85 : 15), 9.35 min, 100% purity.

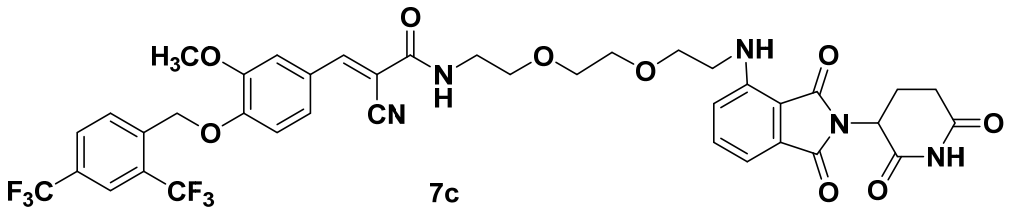


7b

(E) -3-(4-((2,4-bis(trifluoromethyl)benzyl)oxy)-3-methoxyphenyl)-2-cyano-N-(6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)hexyl)acrylamide(7b)

Yield: 48%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (s, 2H), 7.94 (d, *J* = 8.1 Hz, 2H), 7.84 (d, *J* = 8.2 Hz, 1H), 7.70 (s, 1H), 7.48 (t, *J* = 7.8 Hz, 1H), 7.40 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.08 (d, *J* = 7.0 Hz, 1H), 6.87 (dd, *J* = 8.4, 3.9 Hz, 2H), 6.41 (s, 1H), 6.23 (t, *J* = 5.4 Hz, 1H), 5.46 (s, 2H), 4.92 (dd, *J* = 12.0, 5.3 Hz, 1H), 3.98 (s, 3H), 3.41 (dd, *J* =

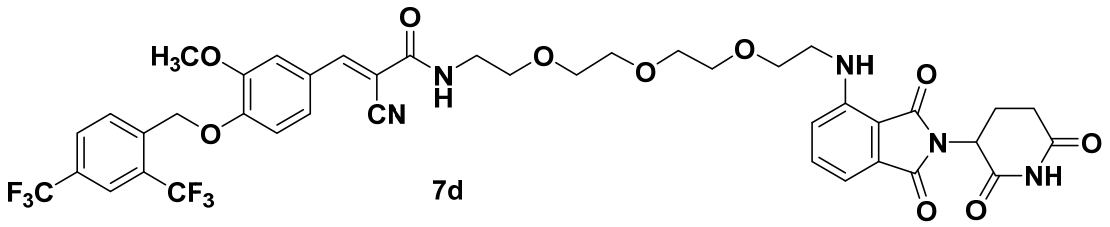
13.2, 6.6 Hz, 2H), 3.27 (dd, *J* = 12.3, 6.1 Hz, 2H), 2.92 (dt, *J* = 12.7, 4.7 Hz, 1H), 2.82 – 2.66 (m, 2H), 2.17 – 2.08 (m, 1H), 1.69 (d, *J* = 6.0 Hz, 2H), 1.65 – 1.57 (m, 2H), 1.44 (s, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.32, 169.29, 168.60, 167.61, 160.82, 152.35, 150.95, 149.57, 146.73, 136.00, 132.47, 130.50 (q, *J* = 33.33), 129.24, 128.68, 127.77 (q, *J* = 32.32), 126.42, 125.90, 124.71 (d, *J* = 23.23 Hz), 121.99 (d, *J* = 22.22 Hz), 117.54, 116.75, 112.92, 112.24, 111.61, 110.26, 101.41, 77.26, 70.77, 70.43, 69.40, 69.29, 66.19, 56.09, 48.85, 42.27, 40.32, 31.41, 22.88. HRMS (ESI) calculated for $C_{39}H_{36}F_6N_5O_7$ $[M + H]^+$: 800.2513, found 800.2502. HPLC analysis: MeOH : H_2O (85 : 15), 11.66 min, 97.92% purity.



7c

(*E*)-3-(4-((2,4-bis(trifluoromethyl)benzyl)oxy)-3-methoxyphenyl)-2-cyano-N-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)ethyl)acrylamide (7c).

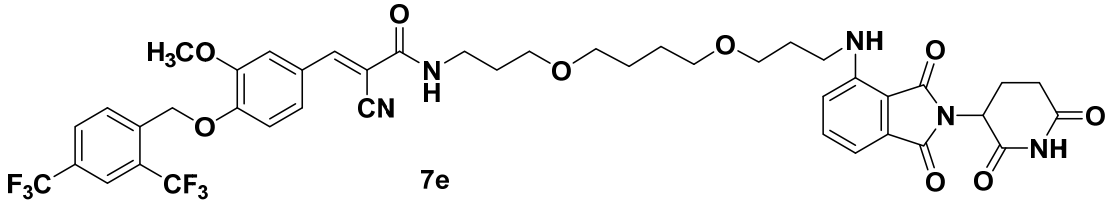
Yield: 54%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (s, 1H), 8.20 (s, 1H), 7.95 (d, *J* = 8.0 Hz, 2H), 7.85 (d, *J* = 8.4 Hz, 1H), 7.67 (d, *J* = 2.0 Hz, 1H), 7.44 (dd, *J* = 8.3, 7.3 Hz, 1H), 7.39 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.03 (d, *J* = 7.0 Hz, 1H), 6.93 – 6.83 (m, 3H), 6.54 (t, *J* = 5.4 Hz, 1H), 5.46 (s, 2H), 4.94 – 4.87 (m, 1H), 3.96 (s, 3H), 3.76 (t, *J* = 5.2 Hz, 2H), 3.71 – 3.67 (m, 5H), 3.66 – 3.58 (m, 3H), 3.48 (dd, *J* = 10.5, 5.3 Hz, 2H), 2.92 – 2.79 (m, 1H), 2.72 (qd, *J* = 13.0, 3.9 Hz, 2H), 2.17 – 2.09 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.32, 169.29, 168.60, 167.61, 160.82, 152.35, 150.95, 149.57, 146.73, 136.00, 132.47 (s), 130.5 (q, *J* = 33.33), 129.24 (s), 128.68 (s), 127.77 (q, *J* = 32.32), 126.42, 125.90, 124.71 (d, *J* = 23.23 Hz), 123.21 (s), 122.00 (d, *J* = 22.22 Hz), 117.54, 116.75, 112.92, 112.24, 111.61, 110.26, 101.41, 77.26, 70.77, 70.43, 69.40, 69.29, 66.19, 56.09, 48.85, 42.27, 40.32, 31.41, 22.88. HRMS (ESI) calculated for $C_{39}H_{36}F_6N_5O_9$ $[M + H]^+$: 832.2412, found 832.2402. HPLC analysis: MeOH : H_2O (85 : 15), 8.30 min, 99.34% purity.



7d

(*E*)-3-(4-((2,4-bis(trifluoromethyl)benzyl)oxy)-3-methoxyphenyl)-2-cyano-N-(2-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)ethoxy)ethyl)acrylamide (7d).

Yield: 35%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 8.21 (s, 1H), 7.95 (d, *J* = 4.9 Hz, 2H), 7.85 (d, *J* = 8.2 Hz, 1H), 7.71 (d, *J* = 2.1 Hz, 1H), 7.46 (dd, *J* = 8.3, 7.3 Hz, 1H), 7.40 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.08 (d, *J* = 6.9 Hz, 1H), 6.93 – 6.84 (m, 3H), 6.49 (t, *J* = 5.5 Hz, 1H), 5.45 (s, 2H), 4.91 (dd, *J* = 12.2, 5.5 Hz, 1H), 3.97 (s, 3H), 3.74 – 3.59 (m, 14H), 3.46 (q, *J* = 5.5 Hz, 2H), 2.86 (ddd, *J* = 11.2, 7.2, 4.6 Hz, 1H), 2.81 – 2.69 (m, 2H), 2.18 – 2.07 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.18, 169.25, 168.46, 167.61, 160.82, 152.37, 151.02, 149.68, 146.81, 139.13, 136.01, 132.51, 130.52 (q, *J* = 33.33 Hz), 129.22, 128.71, 127.80 (q, *J* = 32.32 Hz), 126.45, 125.98, 124.71 (d, *J* = 24.24 Hz), 123.21, 120.00 (d, *J* = 23.23 Hz), 117.45, 116.76, 113.06, 112.28, 111.63, 110.28, 101.55, 77.24, 70.83, 70.67, 70.45, 69.44, 69.35, 66.26 (d, *J* = 4.04 Hz), 56.10, 48.87, 42.40, 40.29, 31.43, 22.81. HRMS (ESI) calculated for $C_{41}H_{40}F_6N_5O_{10}$ $[M + H]^+$: 876.2674, found 876.2645. HPLC analysis: MeOH : H_2O (85 : 15), 8.53 min, 95.89% purity.

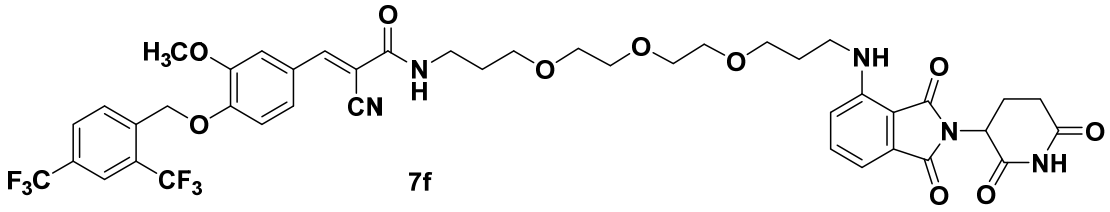


7e

(*E*)-3-(4-((2,4-bis(trifluoromethyl)benzyl)oxy)-3-methoxyphenyl)-2-cyano-N-(3-(4-(3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)propoxy)butoxy)propyl)acrylamide (7e).

Yield: 41%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 1H), 8.24 (s, 1H), 7.97 (d, *J* = 8.6 Hz, 2H), 7.87 (d, *J* = 8.1 Hz, 1H), 7.72 (d, *J* = 1.7 Hz, 1H), 7.53 – 7.46 (m, 1H), 7.42 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.17 (t, *J* = 4.9 Hz, 1H), 7.09 (d, *J* = 7.1 Hz, 1H), 6.92 (d, *J*

= 8.6 Hz, 1H), 6.87 (d, *J* = 8.5 Hz, 1H), 6.47 (t, *J* = 5.3 Hz, 1H), 5.47 (s, 2H), 4.92 (dd, *J* = 12.0, 5.4 Hz, 1H), 3.99 (s, 3H), 3.61 – 3.46 (m, 10H), 3.40 (dd, *J* = 12.4, 6.2 Hz, 2H), 2.96 – 2.70 (m, 3H), 2.22 – 2.08 (m, 1H), 1.99 – 1.86 (m, 4H), 1.72 (s, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.13, 169.32, 168.46, 167.67, 160.58, 152.00, 150.82, 149.58, 146.96, 139.13, 136.08, 132.48, 130.48 (q, *J* = 34.34 Hz), 129.27, 128.67, 127.75 (q, *J* = 32.32 Hz), 126.32, 126.03, 124.71 (d, *J* = 24.24 Hz), 123.24, 121.99 (d, *J* = 22.22 Hz), 117.45, 116.62, 112.94, 112.19, 111.33, 109.81, 101.80, 77.26, 71.29, 71.02, 70.05, 68.36, 66.21, 56.09, 48.82, 40.35, 39.73, 31.43, 29.36, 28.79, 26.30 (d, *J* = 15.15 Hz), 22.83. HRMS (ESI) calculated for $C_{43}H_{44}F_6N_5O_9$ $[M + H]^+$: 888.3038, found 888.3043. HPLC analysis: MeOH : H_2O (85 : 15), 13.82 min, 96.03% purity.

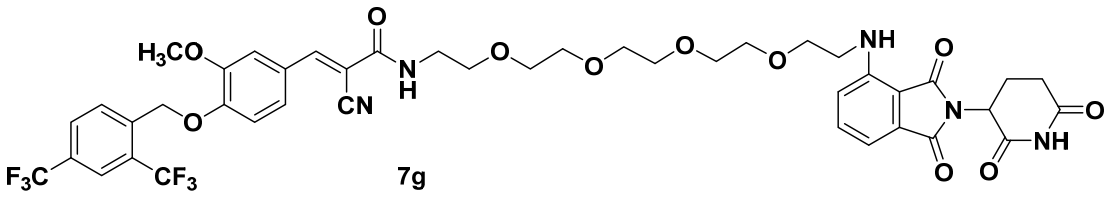


7f

(*E*)-3-(4-((2,4-bis(trifluoromethyl)benzyl)oxy)-3-methoxyphenyl)-2-cyano-N-(3-(2-(2-(3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)propoxy)ethoxy)ethoxy)propyl)acrylamide (7f).

Yield: 42%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 1H), 8.21 (s, 1H), 7.94 (d, *J* = 8.2 Hz, 2H), 7.84 (d, *J* = 8.2 Hz, 1H), 7.70 (d, *J* = 1.9 Hz, 1H), 7.51 – 7.43 (m, 1H), 7.39 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.17 (t, *J* = 5.1 Hz, 1H), 7.06 (d, *J* = 7.1 Hz, 1H), 6.91 (d, *J* = 8.6 Hz, 1H), 6.85 (d, *J* = 8.5 Hz, 1H), 6.44 (t, *J* = 5.6 Hz, 1H), 5.45 (s, 2H), 4.90 (dd, *J* = 12.0, 5.4 Hz, 1H), 3.97 (s, 3H), 3.76 – 3.68 (m, 4H), 3.67 – 3.51 (m, 10H), 3.39 (q, *J* = 6.3 Hz, 2H), 2.92 – 2.82 (m, 1H), 2.81 – 2.66 (m, 2H), 2.16 – 2.09 (m, 1H), 1.95 – 1.81 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.16, 169.34, 168.47, 167.67, 160.62, 151.98, 150.84, 149.60, 146.97, 139.14, 136.12, 132.47, 130.48 (q, *J* = 34.34 Hz), 129.28, 128.67, 127.76 (q, *J* = 32.32 Hz), 126.34, 126.02, 124.71 (d, *J* = 24.24 Hz), 123.24, 122.00 (d, *J* = 21.21 Hz), 117.49, 116.67, 112.96, 112.17, 111.35, 109.81, 101.83, 77.26, 70.58, 70.53, 70.47, 70.45, 68.83, 66.19, 56.09, 48.83, 40.20, 39.50, 31.43, 29.27, 28.69, 22.83. HRMS (ESI) calculated for $C_{43}H_{44}F_6N_5O_{10}$ $[M + H]^+$:

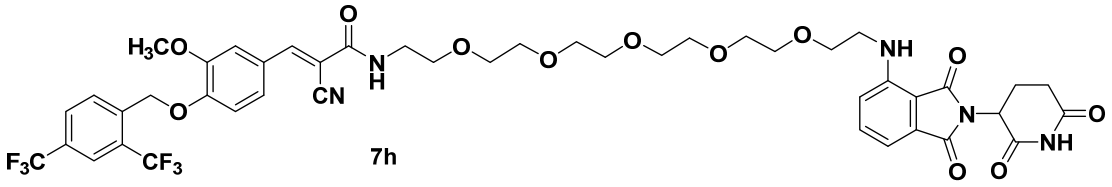
904.2987, found 904.2960. HPLC analysis: MeOH : H_2O (85 : 15), 10.46 min, 97.39% purity.



7g

(*E*)-3-(4-((2,4-bis(trifluoromethyl)benzyl)oxy)-3-methoxyphenyl)-2-cyano-N-(14-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-3,6,9,12-tetraoxatetradecyl)acrylamide (7g).

Yield: 50%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H), 8.21 (s, 1H), 7.94 (d, *J* = 8.2 Hz, 2H), 7.85 (d, *J* = 8.3 Hz, 1H), 7.71 (d, *J* = 1.8 Hz, 1H), 7.47 (t, *J* = 7.8 Hz, 1H), 7.39 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.09 (d, *J* = 7.1 Hz, 1H), 6.96 (s, 1H), 6.90 (d, *J* = 8.5 Hz, 1H), 6.85 (d, *J* = 8.5 Hz, 1H), 6.49 (t, *J* = 5.3 Hz, 1H), 5.45 (s, 2H), 4.91 (dd, *J* = 12.2, 5.4 Hz, 1H), 3.97 (s, 3H), 3.72 – 3.60 (m, 18H), 3.45 (q, *J* = 5.4 Hz, 2H), 2.93 – 2.81 (m, 1H), 2.80 – 2.68 (m, 2H), 2.20 – 2.05 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.23, 168.60, 167.63, 160.86, 152.30, 150.93, 149.61, 146.78, 139.12, 136.05, 132.50, 130.48 (q, *J* = 34.34 Hz), 129.28, 128.67, 127.75 (q, *J* = 32.32 Hz), 126.49, 125.95, 124.71 (d, *J* = 24.24 Hz), 123.22, 121.99 (d, *J* = 22.22 Hz), 117.41, 116.77, 112.93, 112.14, 111.65, 110.25, 101.61, 77.26, 70.83, 70.67, 70.65, 70.54, 70.50, 70.41, 69.45, 69.37, 66.18, 56.10, 48.84, 42.34, 40.28, 31.43, 22.84. HRMS (ESI) calculated for $C_{43}H_{44}F_6N_5O_{11}$ $[M + H]^+$: 920.2936, found 920.2913. HPLC analysis: MeOH : H2O (85 : 15), 8.43 min, 95.97% purity.

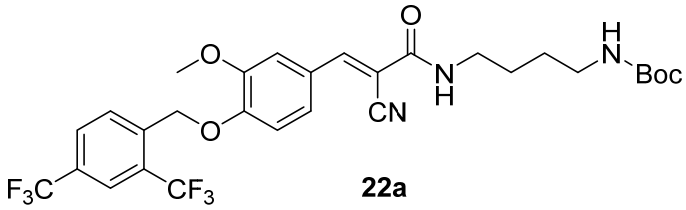


7h

(*E*)-3-(4-((2,4-bis(trifluoromethyl)benzyl)oxy)-3-methoxyphenyl)-2-cyano-N-(17-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-3,6,9,12,15-pentaoxaheptadecyl)acrylamide (7h).

Yield: 49%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (s, 1H), 8.22 (s, 1H), 7.94 (d, *J* = 7.9 Hz, 2H), 7.84 (d, *J* = 8.3 Hz, 1H), 7.72 (s, 1H), 7.47 (t, *J* = 7.8 Hz, 1H), 7.40 (dd, *J* =

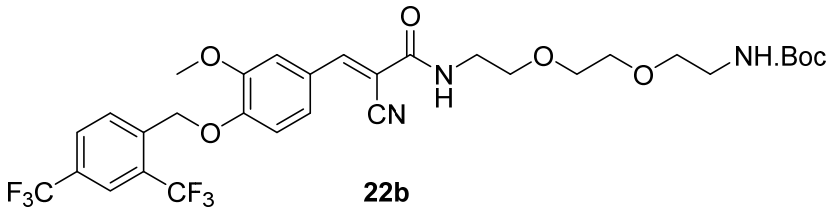
8.4, 1.9 Hz, 1H), 7.08 (d, *J* = 7.0 Hz, 1H), 6.92 (dd, *J* = 15.0, 6.4 Hz, 2H), 6.85 (d, *J* = 8.5 Hz, 1H), 6.49 (t, *J* = 5.3 Hz, 1H), 5.45 (s, 2H), 4.92 (dd, *J* = 11.9, 5.3 Hz, 1H), 3.97 (s, 3H), 3.70 (t, *J* = 5.3 Hz, 2H), 3.68 – 3.59 (m, 20H), 3.45 (q, *J* = 5.3 Hz, 2H), 2.95 – 2.67 (m, 3H), 2.17 – 2.07 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.41, 169.24, 168.57, 167.65, 160.83, 152.27, 150.92, 149.61, 146.78, 139.12, 136.04, 132.50, 130.48 (q, *J* = 33.33 Hz), 129.24, 128.67, 127.75 (q, *J* = 32.32 Hz), 126.49, 125.97, 124.71 (d, *J* = 23.23 Hz), 123.22, 122.99 (d, *J* = 22.22 Hz), 117.41, 116.77, 112.94, 112.14, 111.64, 110.26, 101.63, 77.27, 70.79, 70.67, 70.58, 70.55, 70.51, 70.46, 70.40, 69.40, 66.18, 56.10, 53.50, 52.76, 48.86, 42.35, 40.28, 31.47, 22.81. HRMS (ESI) calculated for $C_{45}H_{48}F_6N_5O_{12}$ $[M + H]^+$: 964.3198, found 964.3158. HPLC analysis: MeOH : H_2O (85 : 15), 8.46 min, 96.24% purity.



22a

Tert-butyl(*E*)-(4-(3-(4-((2,4-bis(trifluoromethyl)benzyl)oxy)-3-methoxyphenyl)-2-cyanoacrylamido)butyl)carbamate (22a). General procedure for syntheses of 22b, 27a-27b.

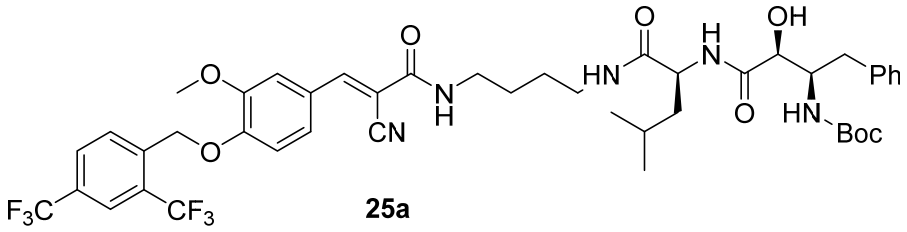
HATU (194 mg, 0.51 mmol, 1.5 eq), DIPEA (220 mg, 1.7 mmol, 5 eq) and **4a** (150 mg, 0.34 mmol, 1 eq) was added to a solution of **21a** (77.2 mg, 0.41 mmol, 1.2 eq) in dry DMF (2 mL). After being stirred for 1 h at RT, the resulting mixture was extracted with ethyl acetate and saturated $NaHCO_3$. The organic layer was separated, washed with brine, dried with Na_2SO_4. After filtration and evaporation, the residue was purified by silica gel column chromatography (DCM / MeOH=100 : 2.5) to give **22a** (123 mg, 0.20 mmol, 60% yield) as yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.94 (d, *J* = 7.6 Hz, 2H), 7.84 (d, *J* = 7.6 Hz, 1H), 7.71 (d, *J* = 1.9 Hz, 1H), 7.39 (dd, *J* = 8.5, 1.9 Hz, 1H), 6.86 (d, *J* = 8.4 Hz, 1H), 6.44 (s, 1H), 5.45 (s, 2H), 4.63 (s, 1H), 3.98 (s, 3H), 3.43 (dd, *J* = 13.0, 6.7 Hz, 2H), 3.13 (ddd, *J* = 15.8, 11.2, 4.6 Hz, 2H), 1.68 – 1.50 (m, 4H), 1.42 (d, *J* = 6.7 Hz, 9H).



22b

Tert-butyl(*E*)-(2-(2-(2-(3-(4-((2,4-bis(trifluoromethyl)benzyl)oxy)-3-methoxyphenyl)-2-cyanoacrylamido)ethoxy)ethoxy)ethyl)carbamate (22b).

Yield: 70%. ^{1}H NMR (400 MHz, DMSO) δ 8.36 (t, *J* = 5.6 Hz, 1H), 8.18 (d, *J* = 8.1 Hz, 1H), 8.12 (d, *J* = 5.8 Hz, 2H), 8.02 (d, *J* = 8.2 Hz, 1H), 7.72 (d, *J* = 2.0 Hz, 1H), 7.58 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.24 (d, *J* = 8.6 Hz, 1H), 6.78 (t, *J* = 5.6 Hz, 1H), 5.44 (s, 2H), 3.83 (s, 3H), 3.51 (dd, *J* = 7.4, 3.2 Hz, 6H), 3.41 – 3.36 (m, 4H), 3.06 (q, *J* = 6.0 Hz, 2H), 1.36 (s, 9H).

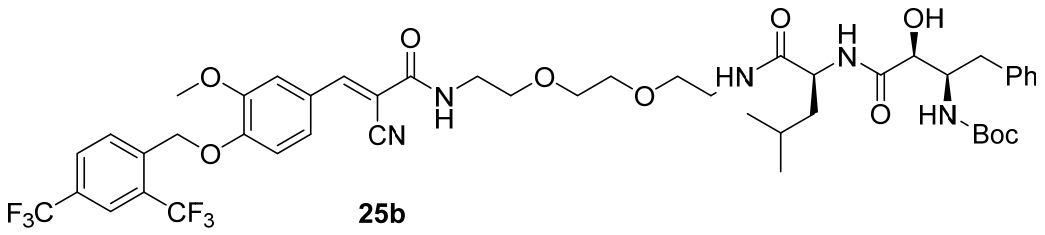


25a

Tert-butyl((2*R*,3*S*)-4-(((S)-1-((4-((*E*)-3-(4-((2,4-bis(trifluoromethyl)benzyl)oxy)-3-methoxyphenyl)-2-cyanoacrylamido)butyl)amino)-4-methyl-1-oxopentan-2-yl)amino)-3-hydroxy-4-oxo-1-phenylbutan-2-yl)carbamate (25a). General procedure for syntheses of 25b.

TFA (2 mL) was added to a solution of Compound **22a** (115 mg, 0.19 mmol, 1 eq) in DCM (4 mL). After being stirred for 1 h, the solvents were removed in vacuo, and residual TFA was removed by the addition and evaporation of toluene (3 x 3mL). The crude product was used to next step without further purification. HATU (110.3 mg, 0.29 mmol, 1.5 eq), DIPEA (123 mg, 0.95 mmol, 5 eq) and **24** (77.6 mg, 0.19 mmol, 1 eq) was added to a solution of the crude product obtained above in DMF (3 ml) at 25 ℃. After being stirred for 1 h, the resulting mixture was extracted with ethyl acetate and saturated $NaHCO_3$. The organic layer was separated, washed with brine, dried with Na_2SO_4. After filtration and evaporation, the residue was purified by silica gel column chromatography (MeOH : CH_2Cl_2 =2.5 : 100) to give **25a** (118 mg, 0.13 mmol, 68%) as colorless solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.95 (d, *J*

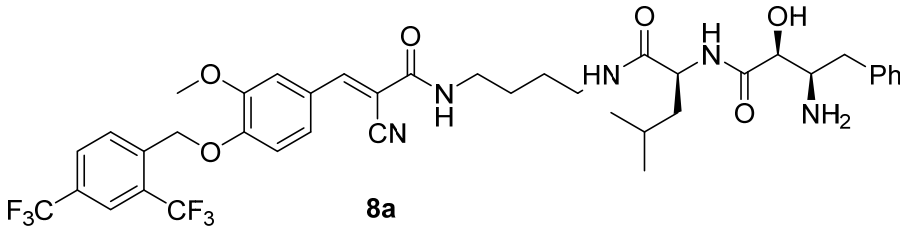
= 8.6 Hz, 2H), 7.85 (d, *J* = 8.2 Hz, 1H), 7.71 (d, *J* = 1.8 Hz, 1H), 7.39 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.26 – 7.16 (m, 5H), 6.87 (d, *J* = 8.5 Hz, 1H), 6.78 (s, 1H), 6.57 (s, 1H), 5.50 (s, 1H), 5.46 (s, 2H), 5.03 (d, *J* = 8.2 Hz, 1H), 4.53 – 4.41 (m, 1H), 4.11 (dd, *J* = 19.4, 6.3 Hz, 2H), 3.98 (s, 3H), 3.54 – 3.28 (m, 3H), 3.19 – 3.03 (m, 2H), 4.4 Hz, 1H), 2.80 (s, 2H), 1.68 (s, 2H), 1.65 – 1.46 (m, 6H), 1.36 (s, 9H), 0.90 (dd, *J* = 12.1, 6.3 Hz, 6H).



25b

Tert-butyl((15*S*,18*S*,19*R*,*E*)-1-(4-((2,4-bis(trifluoromethyl)benzyl)oxy)-3-methoxyphenyl)-2-cyano-18-hydroxy-15-isobutyl-3,14,17-trioxo-20-phenyl-7,10-dioxa-4,13,16-triazaicos-1-en-19-yl)carbamate (25b).

Yield: 27%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.92 (d, *J* = 6.1 Hz, 2H), 7.82 (d, *J* = 8.7 Hz, 1H), 7.67 (d, *J* = 1.7 Hz, 1H), 7.40 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.23 – 7.09 (m, 5H), 6.85 (d, *J* = 8.5 Hz, 1H), 6.75 (d, *J* = 8.5 Hz, 1H), 5.90 (d, *J* = 28.0 Hz, 1H), 5.41 (d, *J* = 16.0 Hz, 3H), 5.21 (dd, *J* = 8.1, 4.9 Hz, 1H), 4.57 – 4.41 (m, 1H), 4.14 – 4.03 (m, 1H), 3.96 – 3.88 (m, 4H), 3.64 – 3.30 (m, 16H), 3.00 – 2.91 (m, 2H), 1.33 (s, 9H), 0.88 (dd, *J* = 12.7, 4.8 Hz, 6H).

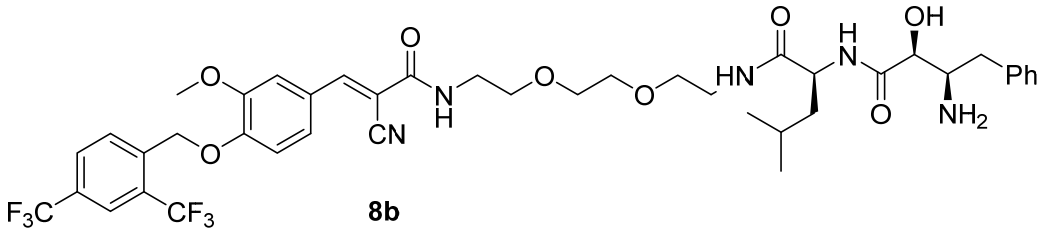


8a

(*S*)-2-((2*S*,3*R*)-3-amino-2-hydroxy-4-phenylbutanamido)-N-(4-((*E*)-3-(4-((2,4-bis(trifluoromethyl)benzyl)oxy)-3-methoxyphenyl)-2-cyanoacrylamido)butyl)-4-methylpentanamide (8a). General procedure for syntheses of 8b.

4 N HCl in 1,4-dioxane (6 mL) was added to a solution of Compound **25a** (118 mg, 0.13 mmol, 1 eq) in DCM (3 mL) at 0℃. After being stirred for 8 h at rt, the solvents were removed in vacuo, and the resulting mixture was extracted with ethyl acetate and saturated $NaHCO_3$. The organic layer was separated, washed with brine, dried with

Na_2SO_4. After filtration and evaporation, the residue was purified by silica gel column chromatography (MeOH : CH_2Cl_2 =1 : 15) to give **8a** (62 mg, 0.077 mmol, 59%) as colorless solid: ^{1}H NMR (400 MHz, DMSO) δ 8.38 (t, *J* = 5.4 Hz, 1H), 8.18 (d, *J* = 6.9 Hz, 2H), 8.11 (d, *J* = 6.5 Hz, 2H), 8.02 (d, *J* = 8.1 Hz, 1H), 7.72 (d, *J* = 8.7 Hz, 2H), 7.58 (d, *J* = 8.5 Hz, 1H), 7.31 – 7.15 (m, 6H), 5.49 (d, *J* = 36.9 Hz, 3H), 4.27 (dd, *J* = 14.0, 8.9 Hz, 1H), 3.83 (s, 3H), 3.75 (d, *J* = 2.0 Hz, 1H), 3.19 (d, *J* = 5.8 Hz, 2H), 3.12 (dd, *J* = 6.6, 4.7 Hz, 1H), 3.04 (d, *J* = 4.7 Hz, 2H), 2.77 (dd, *J* = 13.1, 6.5 Hz, 1H), 1.62 – 1.33 (m, 9H), 1.22 (s, 1H), 0.84 (dd, *J* = 9.2, 6.6 Hz, 6H). ^{13}C NMR (101 MHz, DMSO) δ 173.08, 172.07, 161.54, 150.98, 150.63, 149.37, 140.27, 139.85, 131.63, 130.44, 129.75 (q, *J* = 33.33 Hz), 129.68, 128.65, 128.11 (q, *J* = 32.32 Hz), 126.34, 125.95, 125.37, 125.17, 123.67, 122.45, 117.47, 113.84, 113.31, 103.90, 72.98, 66.59, 56.09, 51.19, 41.65, 40.94, 38.67, 26.92, 26.82, 24.69, 23.54, 22.05. HRMS (ESI) calculated for $C_{40}H_{46}F_6N_5O_6$ $[M + H]^+$: 806.3347, found 806.3317. HPLC analysis: MeOH : H_2O : TEA (90 : 10 : 0.01), 13.76 min, 99.48% purity.

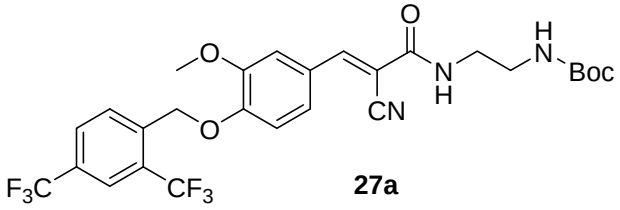


8b

(*S*)-2-((2*S*,3*R*)-3-amino-2-hydroxy-4-phenylbutanamido)-N-(2-(2-(2-((E)-3-(4-((2, 4-bis(trifluoromethyl)benzyl)oxy)-3-methoxyphenyl)-2-cyanoacrylamido)ethoxy) ethoxy)ethyl)-4-methylpentanamide (8b).

Yield: 58%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.94 (d, *J* = 8.1 Hz, 2H), 7.85 (d, *J* = 8.3 Hz, 1H), 7.69 (d, *J* = 2.0 Hz, 1H), 7.59 (d, *J* = 8.7 Hz, 1H), 7.42 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.33 – 7.26 (m, 2H), 7.25 – 7.17 (m, 3H), 7.14 (s, 1H), 7.00 (t, *J* = 4.8 Hz, 1H), 6.87 (d, *J* = 8.5 Hz, 1H), 5.45 (s, 2H), 4.54 – 4.43 (m, 1H), 3.99 (d, *J* = 2.6 Hz, 1H), 3.97 (s, 3H), 3.66 – 3.52 (m, 10H), 3.42 (tdd, *J* = 14.0, 9.3, 4.7 Hz, 2H), 2.96 (dd, *J* = 13.5, 5.1 Hz, 1H), 2.56 (dd, *J* = 13.4, 9.6 Hz, 1H), 1.76 – 1.71 (m, 1H), 1.64 – 1.55 (m, 2H), 0.90 (dt, *J* = 12.4, 6.2 Hz, 8H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.35, 171.97, 160.92, 152.54, 151.05, 149.65, 139.08, 138.18, 130.51(q, *J* = 33.33 Hz), 129.31, 129.24, 128.82, 128.74, 128.66, 127.76 (q, *J* = 32.32 Hz), 126.73, 126.42,

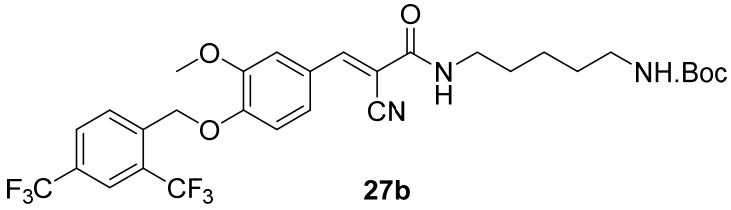
125.89, 124.71 (d, J = 23.23 Hz), 123.22, 122.00 (d, J = 22.22 Hz), 117.52, 112.98, 112.28, 101.45, 77.26, 72.53, 70.52, 70.34, 70.20, 69.82, 69.37, 66.23, 56.10, 54.44, 51.71, 40.75, 40.27, 39.35, 39.03, 31.95, 29.73, 29.69, 29.56, 29.40, 24.88, 22.99, 22.73, 21.83, 14.18. HRMS (ESI) calculated for $C_{42}H_{50}F_6N_5O_8$ $[M + Na]^+$: 888.3378, found 888.3370. HPLC analysis: MeOH : H_2O : TEA (90 : 10 : 0.01), 13.17 min, 98.32% purity.



27a

Tert-butyl(*E*)-(2-(3-(4-((2,4-bis(trifluoromethyl)benzyl)oxy)-3-methoxyphenyl)-2-cyanoacrylamido)ethyl)carbamate (27a).

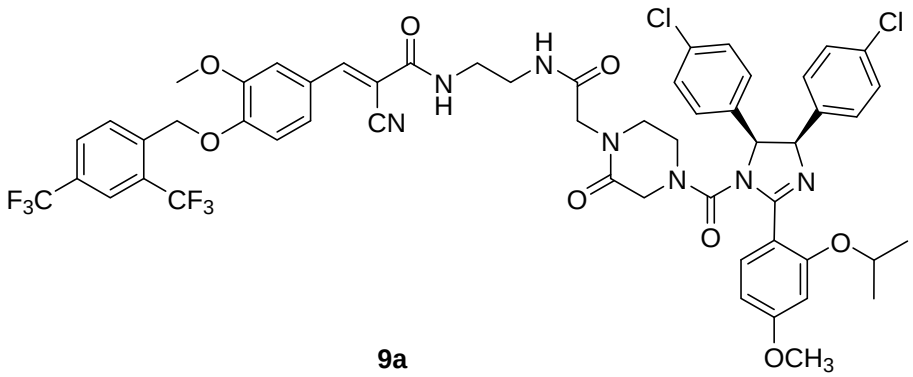
Yield: 62%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.95 (d, J = 8.8 Hz, 2H), 7.85 (d, J = 8.0 Hz, 1H), 7.74 (d, J = 1.7 Hz, 1H), 7.39 (dd, J = 8.5, 2.0 Hz, 1H), 7.05 (s, 1H), 6.86 (d, J = 8.4 Hz, 1H), 5.46 (s, 2H), 3.99 (s, 3H), 3.54 (dd, J = 11.1, 5.4 Hz, 2H), 3.42 – 3.33 (m, 2H), 2.80 (s, 1H), 1.45 (s, 9H).



27b

Tert-butyl(*E*)-(5-(3-(4-((2,4-bis(trifluoromethyl)benzyl)oxy)-3-methoxyphenyl)-2-cyanoacrylamido)pentyl)carbamate (27b).

Yield: 55%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.95 (d, J = 8.5 Hz, 2H), 7.85 (d, J = 8.2 Hz, 1H), 7.71 (d, J = 2.0 Hz, 1H), 7.39 (dd, J = 8.5, 2.0 Hz, 1H), 6.86 (d, J = 8.5 Hz, 1H), 6.34 (s, 1H), 5.46 (s, 2H), 4.56 (s, 1H), 3.99 (s, 3H), 3.42 (dd, J = 13.3, 6.9 Hz, 2H), 3.13 (dd, J = 13.0, 6.5 Hz, 2H), 1.64 – 1.58 (m, 2H), 1.52 (dd, J = 14.7, 7.3 Hz, 2H), 1.43 (s, 10H), 1.41 – 1.34 (m, 2H).

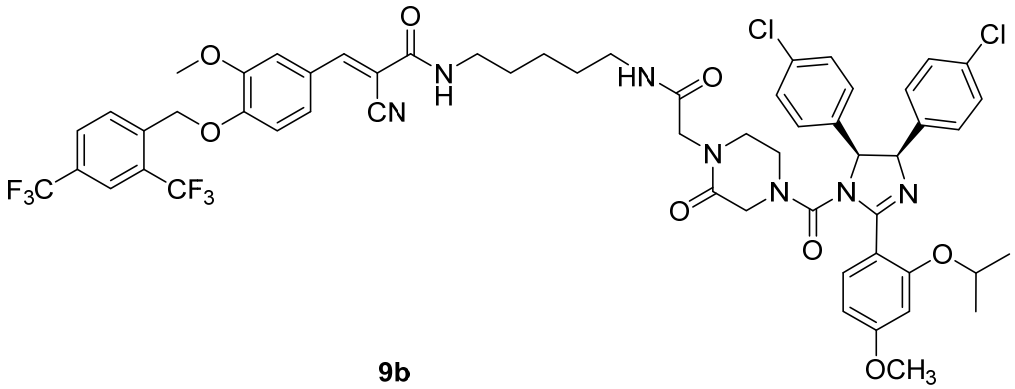


9a

(*E*)-N-(2-(2-(4-((4*R*,5*S*)-4,5-bis(4-chlorophenyl)-2-(2-isopropoxy-4-methoxypheny l)-4,5-dihydro-1H-imidazole-1-carbonyl)-2-oxopiperazin-1-yl)acetamido)ethyl)-3-(4-((2,4-bis(trifluoromethyl)benzyl)oxy)-3-methoxyphenyl)-2-cyanoacrylamide (9a).

TFA (2 mL) was added to a solution of Compound **27a** (124 mg, 0.21 mmol, 1 eq) in DCM (4 mL). After being stirred for 1 h, the solvents were removed in vacuo, and residual TFA was removed by the addition and evaporation of toluene (3 x 3mL). The crude product was used to next step without further purification. HATU (121.7 mg, 0.32 mmol, 1.5 eq), DIPEA (156.4 mg, 1.1 mmol, 5 eq) and **29** (134.3 mg, 0.21 mmol, 1 eq) was added to a solution of the crude product obtained above in DMF (3 ml) at 25 ℃. After being stirred for 1 h, the resulting mixture was extracted with ethyl acetate and saturated $NaHCO_3$. The organic layer was separated, washed with brine, dried with Na_2SO_4. After filtration and evaporation, the residue was purified by silica gel column chromatography (MeOH : CH_2Cl_2 =2.5 : 100) to give **9a** (107 mg, 0.096 mmol, 46%) as colorless solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.97 (d, *J* = 9.0 Hz, 2H), 7.87 (d, *J* = 8.1 Hz, 1H), 7.70 (s, 1H), 7.60 (d, *J* = 8.5 Hz, 1H), 7.37 (d, *J* = 8.6 Hz, 1H), 7.11 (dd, *J* = 18.4, 5.5 Hz, 2H), 7.05 – 6.79 (m, 9H), 6.55 (dd, *J* = 8.5, 2.2 Hz, 1H), 6.49 (d, *J* = 2.1 Hz, 1H), 5.58 (d, *J* = 9.6 Hz, 1H), 5.49 (d, *J* = 12.8 Hz, 3H), 4.64 (dt, *J* = 12.0, 6.0 Hz, 1H), 4.03 – 3.90 (m, 4H), 3.86 (s, 4H), 3.67 (dd, *J* = 28.0, 16.1 Hz, 2H), 3.58 – 3.50 (m, 2H), 3.43 (dd, *J* = 13.9, 5.2 Hz, 2H), 3.30 – 3.04 (m, 3H), 1.43 – 1.32 (m, 7H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.37, 165.82, 163.04, 162.24, 160.22, 157.00, 154.73, 152.87, 151.23, 149.61, 139.03, 135.91, 135.05, 133.10, 132.90, 132.26, 130.53 (q, *J* = 33.33 Hz), 129.27, 128.70, 128.49, 128.03,

127.99, 127.78 (q, *J* = 32.32 Hz), 126.71, 125.72, 124.70 (d, *J* = 24.24 Hz), 123.24, 122.00 (d, *J* = 22.22 Hz), 117.38, 113.19, 112.87, 112.33, 104.48, 100.60, 100.06, 77.26, 71.82, 70.88, 69.19, 66.18, 56.08, 55.59, 50.91, 49.62, 47.37, 42.16, 40.62, 31.45, 30.18, 29.73, 22.16, 22.04. HRMS (ESI) calculated for $C_{54}H_{50}Cl_2F_6N_7O_8$ [M + H]$^+$: 1108.2997, found 1108.3023. HPLC analysis: MeOH : H_2O (90 : 10), 8.52 min, 95.09% purity.



9b

(*E*)-N-(5-(2-(4-((4*R*,5*S*)-4,5-bis(4-chlorophenyl)-2-(2-isopropoxy-4-methoxypheny l)-4,5-dihydro-1H-imidazole-1-carbonyl)-2-oxopiperazin-1-yl)acetamido)pentyl)-3-(4-((2,4-bis(trifluoromethyl)benzyl)oxy)-3-methoxyphenyl)-2-cyanoacrylamide (9b).

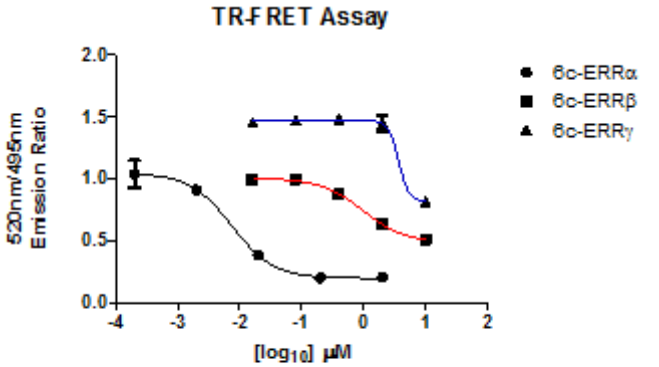
Yield: 70%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.95 (d, *J* = 8.1 Hz, 2H), 7.85 (d, *J* = 8.1 Hz, 1H), 7.70 (d, *J* = 2.0 Hz, 1H), 7.58 (d, *J* = 8.5 Hz, 1H), 7.40 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.08 (d, *J* = 8.4 Hz, 2H), 7.02 (d, *J* = 8.5 Hz, 2H), 6.93 (d, *J* = 8.4 Hz, 2H), 6.87 (dd, *J* = 8.4, 1.7 Hz, 3H), 6.54 (dd, *J* = 8.5, 2.2 Hz, 1H), 6.47 (d, *J* = 2.2 Hz, 2H), 6.19 (t, *J* = 5.7 Hz, 1H), 5.52 (dd, *J* = 31.1, 9.8 Hz, 2H), 5.46 (s, 2H), 4.61 (dt, *J* = 12.1, 6.0 Hz, 1H), 3.97 (s, 3H), 3.91 (d, *J* = 3.3 Hz, 1H), 3.86 (d, *J* = 10.3 Hz, 4H), 3.67 (dd, *J* = 12.4, 5.6 Hz, 2H), 3.52 (dd, *J* = 8.9, 4.6 Hz, 1H), 3.39 (dd, *J* = 13.2, 6.8 Hz, 2H), 3.26 – 3.17 (m, 3H), 3.13 (t, *J* = 5.0 Hz, 2H), 1.58 (dd, *J* = 14.7, 7.3 Hz, 2H), 1.50 (dd, *J* = 14.6, 7.1 Hz, 2H), 1.35 (dd, *J* = 15.8, 6.0 Hz, 8H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.26, 167.66, 165.68, 163.00, 160.72, 160.15, 156.99, 154.63, 152.45, 151.06, 149.66, 139.07, 135.97, 135.03, 133.18, 132.90, 132.25, 130.51(q, *J* = 33.33 Hz), 129.27, 128.67, 128.45, 128.12, 128.00, 127.77 (q, *J* = 32.32 Hz), 126.52, 125.86, 124.71 (d, *J* = 23.23 Hz), 123.26, 122.99 (d, *J* = 22.22 Hz), 117.69, 113.27, 112.96,

112.13, 104.46, 101.29, 100.05, 77.26, 71.79, 70.93, 69.14, 66.23, 60.46, 56.11, 55.59, 50.83, 49.71, 47.27, 42.14, 40.26, 39.27, 29.01, 28.89, 23.97, 22.17, 22.04, 21.12, 14.23. HRMS (ESI) calculated for $C_{57}H_{56}Cl_2F_6N_7O_8$ $[M + H]^+$: 1150.3466, found 1150.3453. HPLC analysis: MeOH : H_2O (90 : 10), 12.56 min, 98.74% purity.

3. *In Vitro* TR-FRET Assay

LanthaScreen™ Estrogen Related Receptor alpha TR-FRET Coactivator Assay (Invitrogen, PV4663) were performed to examine the functional response of ERRα ligands. Compounds were successively diluted in complete assay buffer (2×) with 5 different concentrations. 10 μl of 10 nM this solution was transferred to 384-well black assay plates (Thermo, #267461), 5 μl of 20 nM ERR alpha-LBD (4×) in complete assay buffer was added. Next, 5 μl of 2 μM fluorescein-PGC1α and 20 nM Tb anti-GST antibody solution in complete assay buffer (4×) was added to each well to give a final 20 μl of reagent solution volumes. All determinations were performed in triplicate and DMSO as a control. The samples were incubated in the dark for 1h at room temperature on a plate shaker. Fluorescence intensity at 495 nm and 520 nm were measured using microplate reader (Bio-Tek, Synergy H1). The TR-FRET ratio was calculated by dividing the emission signal at 520 nm by the emission signal at 495 nm, and a binding curve by plotting the emission ratio vs. the log [ligand] was generated. Finally, the IC_{50} value was provided by GraphPad Prism.

Likewise, the commercial TR-FRET assay was used to evaluate the functional response of PROATC 6c against the ERRβ (Invitrogen, PV4800) and ERRγ (Invitrogen, PV4408) receptor, respectively.



	6c-ERRα	6c-ERRβ	6c-ERRγ
IC50	0.007439	0.9767	~3.688

Figure **S1**. PROTAC **6c** showed no significant effects on inhibiting PGC-1α binding with ERRβ and ERRγ.

4. Computational Study

All the procedure was performed in Maestro (version 9.9, Schrödinger, LLC, New York, NY, 2014) implemented in the Schrödinger program (http://www.schrödinger.com). The crystal structure of ERRα protein with compound 1 (XCT790) (PDB code: 3K6P) were taken from the Protein Data Bank (http://www.pdb.org). The protein was prepared using the Protein Preparation Wizard workflow in Maestro to add bond orders and to add hydrogens. All heteroatom (het) residues and crystal water molecules were removed. The ligand XCT790 was prepared using LigPrep (version 3.1, Schrödinger, LLC, New York, NY, 2014) with the OPLS-2005 force field. In this study, molecular docking study was performed with the Glide program (version 6.4, Schrödinger, LLC, New York, NY, 2014) using the SP (Standard precision) score mode. The grid-enclosing box was placed on the centroid of the binding ligand in the optimized crystal structure as described above, and bounding box was set to 18 Å. For all of the methods, Glide docks flexible ligands were fit into a rigid receptor structure. The Figure 2a was generated using PyMol.

5. Western Blot Analysis

MDA-MB-231 cell line was purchased from the ATCC and cultured in RPMI 1640 media supplemented with 10% (v/v) fetal bovine serum (FBS) and 1% (v/v) penicillin-streptomycin at 37℃ in a humidified incubator with 5% CO_2.

The cells were treated with compound of indicated concentrations for various times in 12-well plates. Next, cells washed with phosphate buffered saline (PBS) and lysed in 150ul of 1x sodium dodecyl sulfate (SDS) lysis buffer (CST recommended) with protease and phosphatase inhibitors. Immunoblotting was performed using standard protocols, here, glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was used as loading control. The antibodies used were ERRα (1:1000, Cell Signaling Technology, #2101), ERRβ (1:1200, Sigma-Aldrich, E0156), ERRγ (1:100, Santa Cruz, sc-393969), ERα (1:1000, CST, 13258s), MCAD (1:10000, abcam, ab92461), PDK4 (1:100, Santa Cruz, sc-130841), ATP5B (1:300, Santa Cruz, sc-33618) and GAPDH (1:4000, Beyotime, AG019-1). Peroxidase reaction were detected using ECL western blotting Detection Kit (Thermo Scientific, Waltham, MA) by Amersham Imager 600 system (GE, America). D (%) values were generated by ImageJ software analysis. The data are means from at least three independent experiments and the variations are less than 20%.

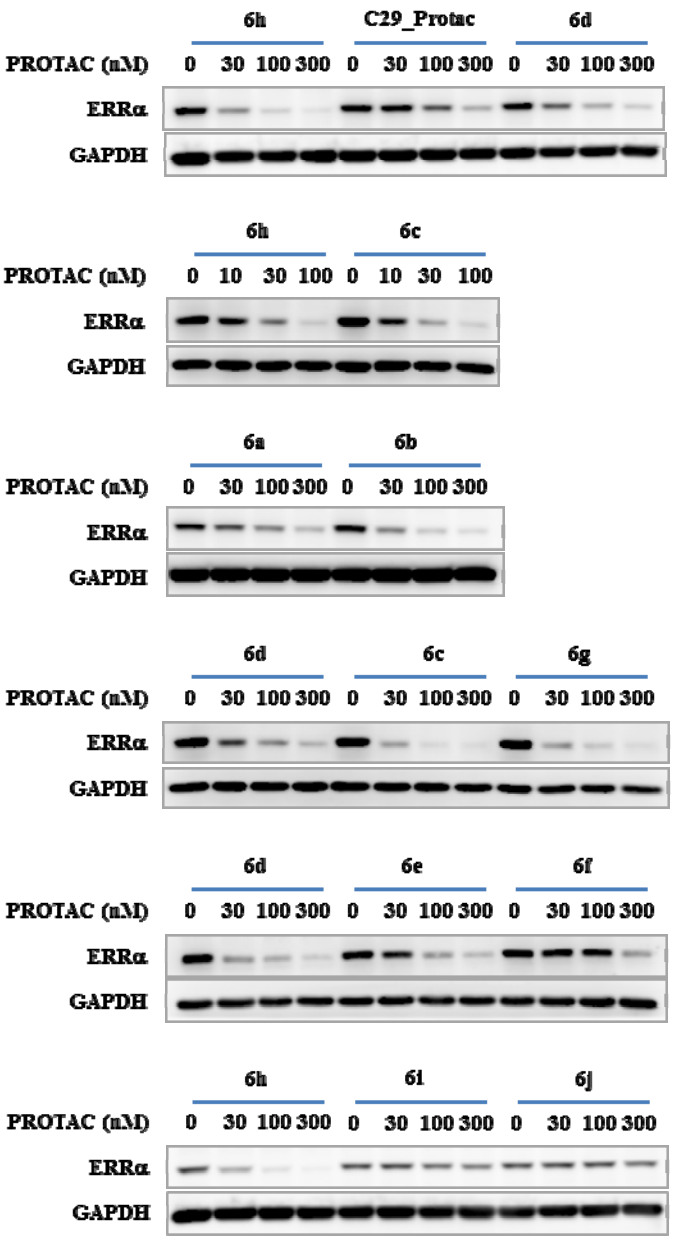


Figure **S2**. Degradation effects of PROTACs **6a-6j** on ERRα proteins in MDA-MB-231 cells at indiated concentrations for 4 h.

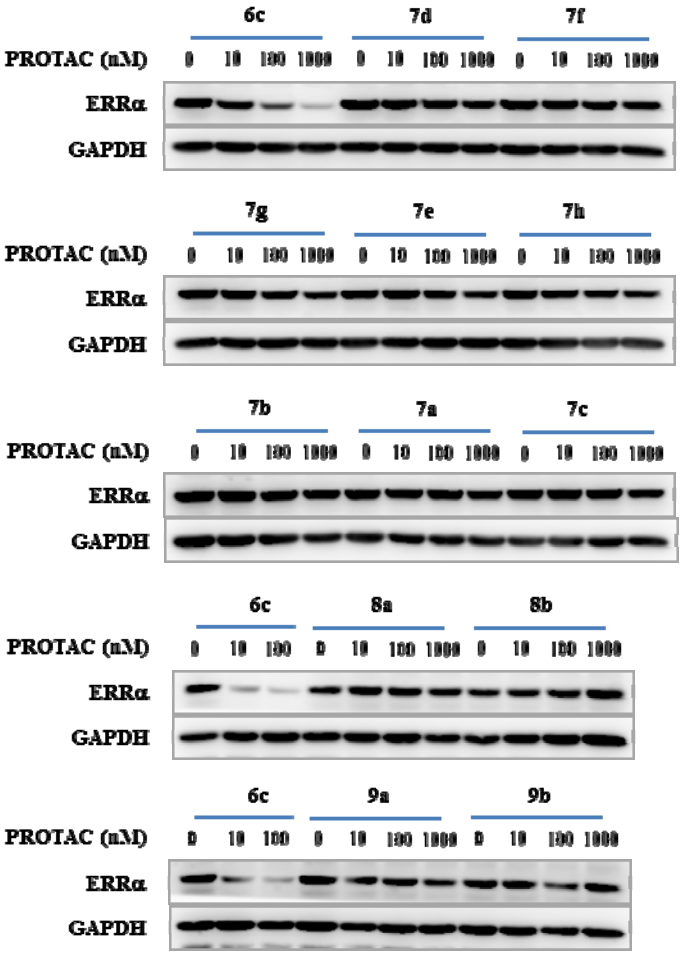
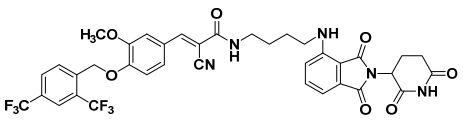
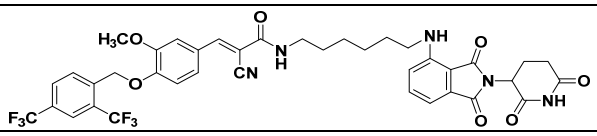
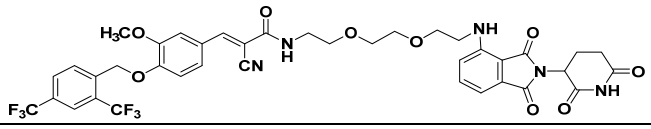
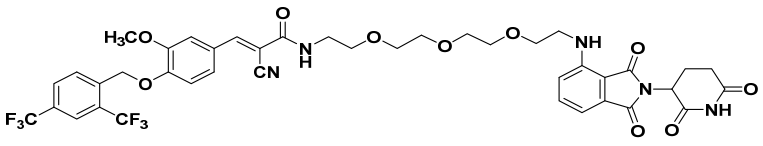
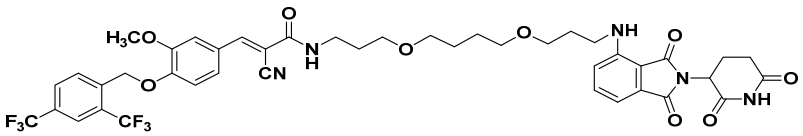
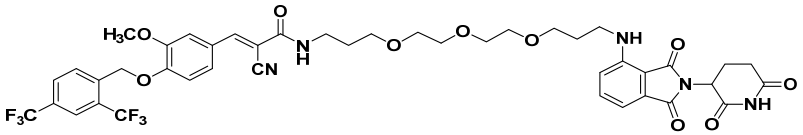
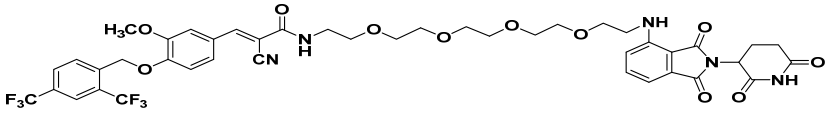
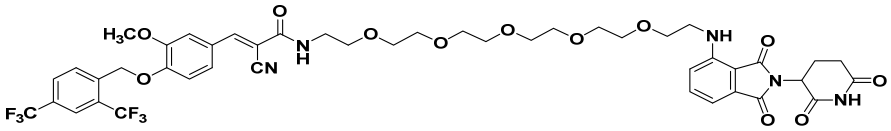
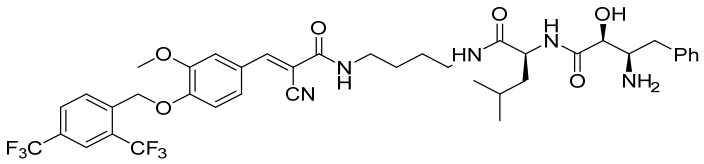
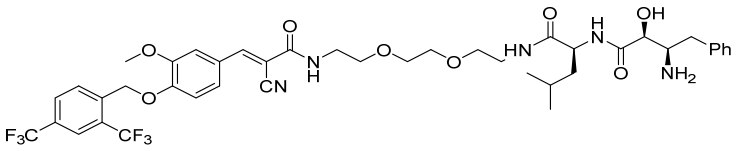
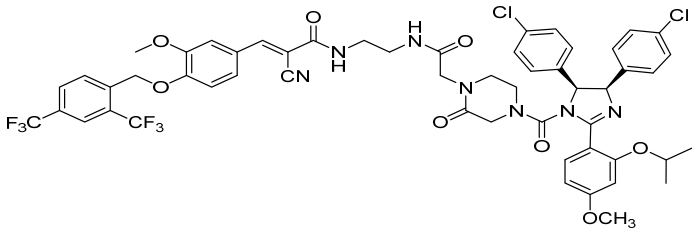
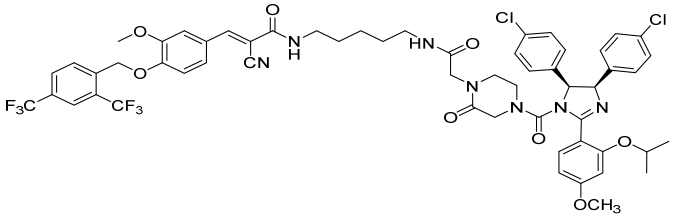


Figure **S3**. Degradation effects of PROTACs **7a-7h, 8a-8b, 9a-9b** on ERRα proteins in MDA-MB-231 cells at indiated concentrations for 4 h.

Cpd. No.	Structure
7a	
7b	
7c	
7d	

7e	
7f	
7g	
7h	
8a	
8b	
9a	
9b	

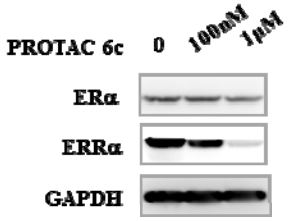


Figure **S4**. Western blotting analysis of ERα and ERRα in MCF-7 cells treated with PROTAC **6c** at the indicated concentrations at 4.0 hrs.

Western blotting analysis showed that PROTAC **6c** dose-dependently induced ERRα degradation, did not show obvious effect on ERα in MCF-7 breast cancer cell lines.

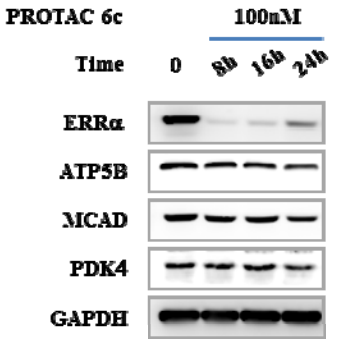
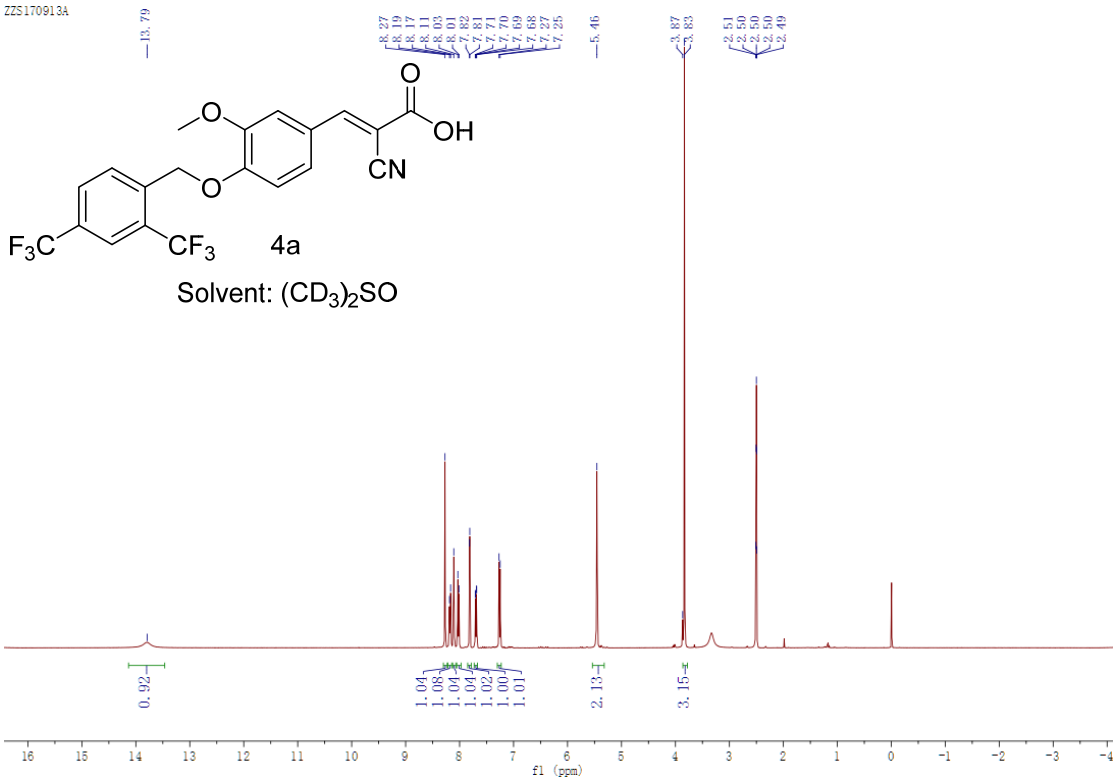
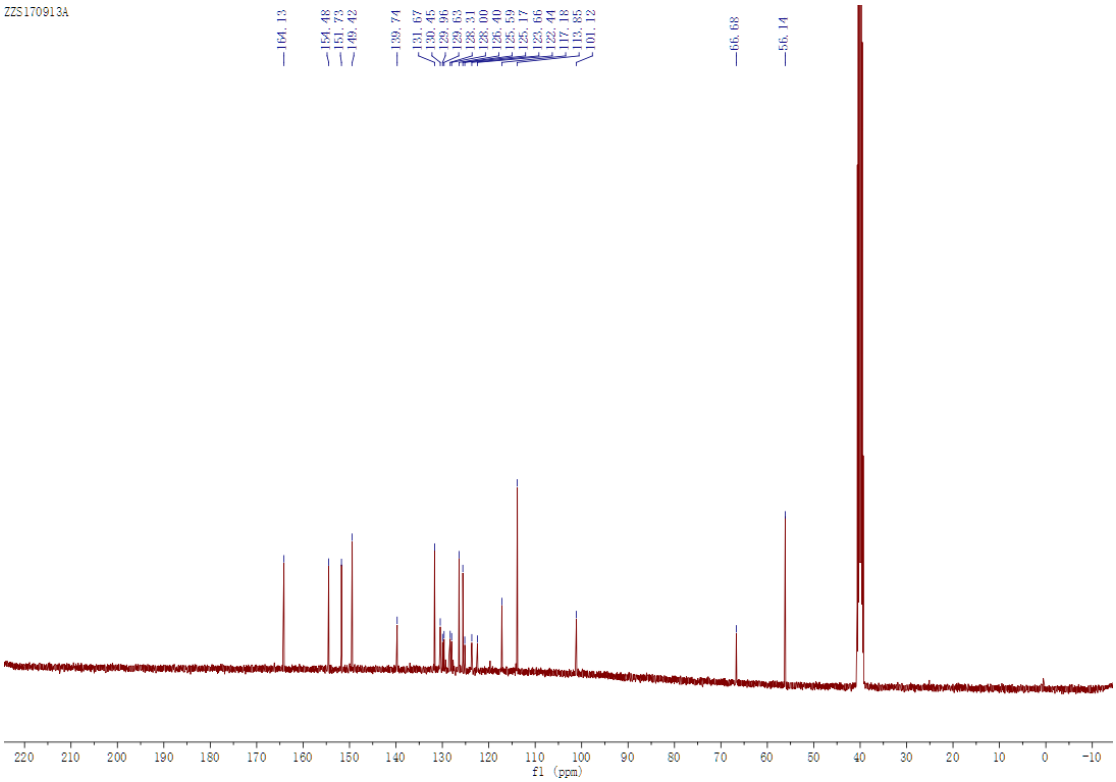


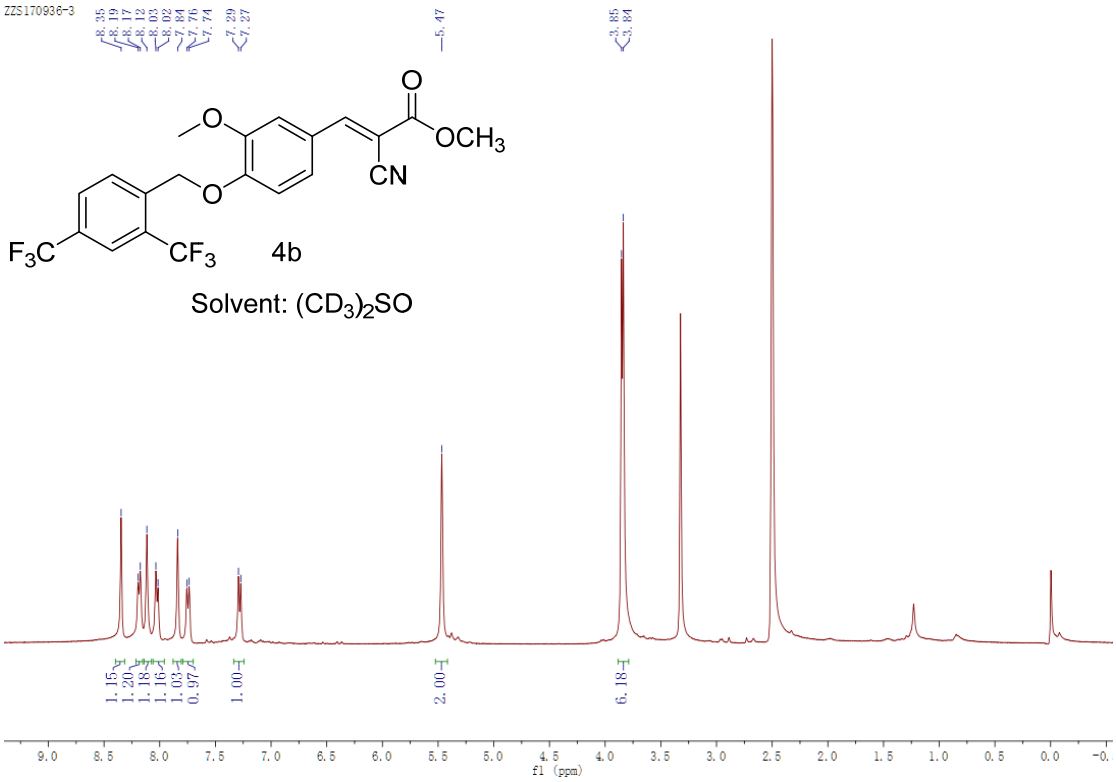
Figure **S5**. Western blotting analysis of the target gene of ERRα in MDA-MB-231 cells treated with PROTAC **6c** at the indicated concentration and time points.

Western blotting analysis showed that PROTAC **6c** potently decreased the protein levels of ATP5B, MCAD and PDK4 at the concentration of 100nM in the MDA-MB-231 cell line after a 24-hr treatment.

6. ^{1}H and ^{13}C NMR Spectra



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8.17
8.12
8.03
8.02
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7.76
7.74
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7.27
5.47
3.85
3.84
O
OCH3
CN
O
O
F3C
CF3
4b
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1.16
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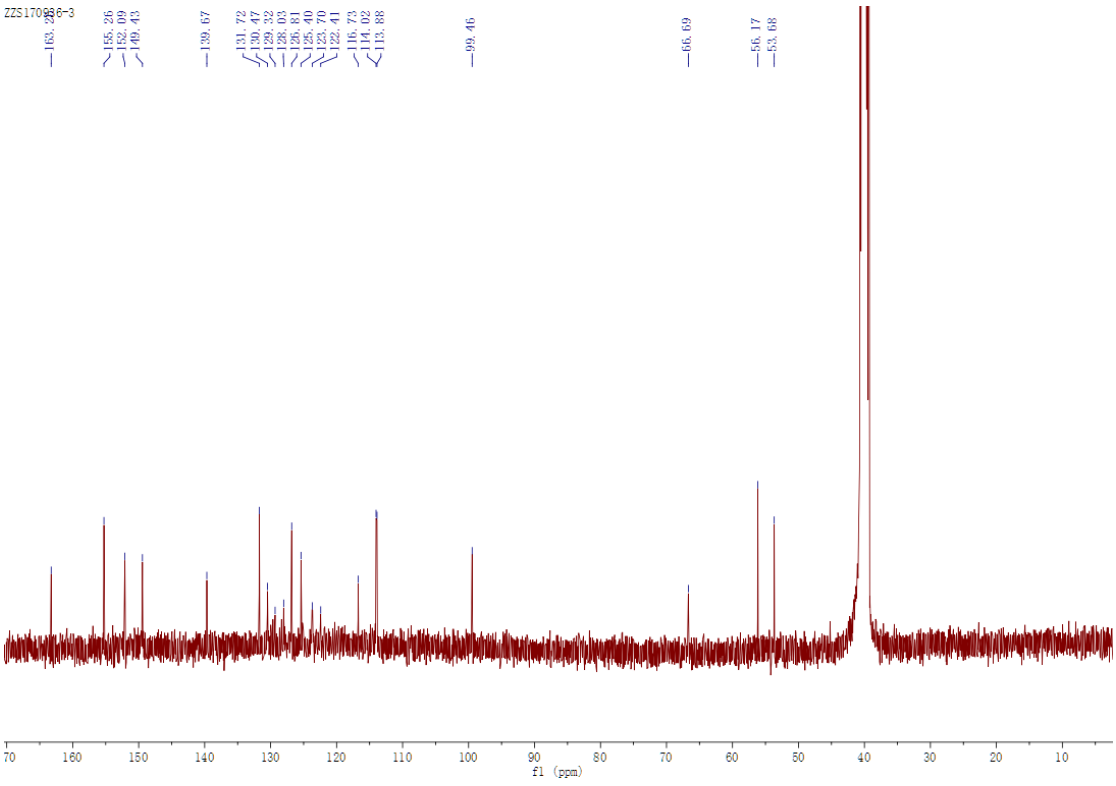
2.00
6.18
f1 (ppm)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114.02
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66.69
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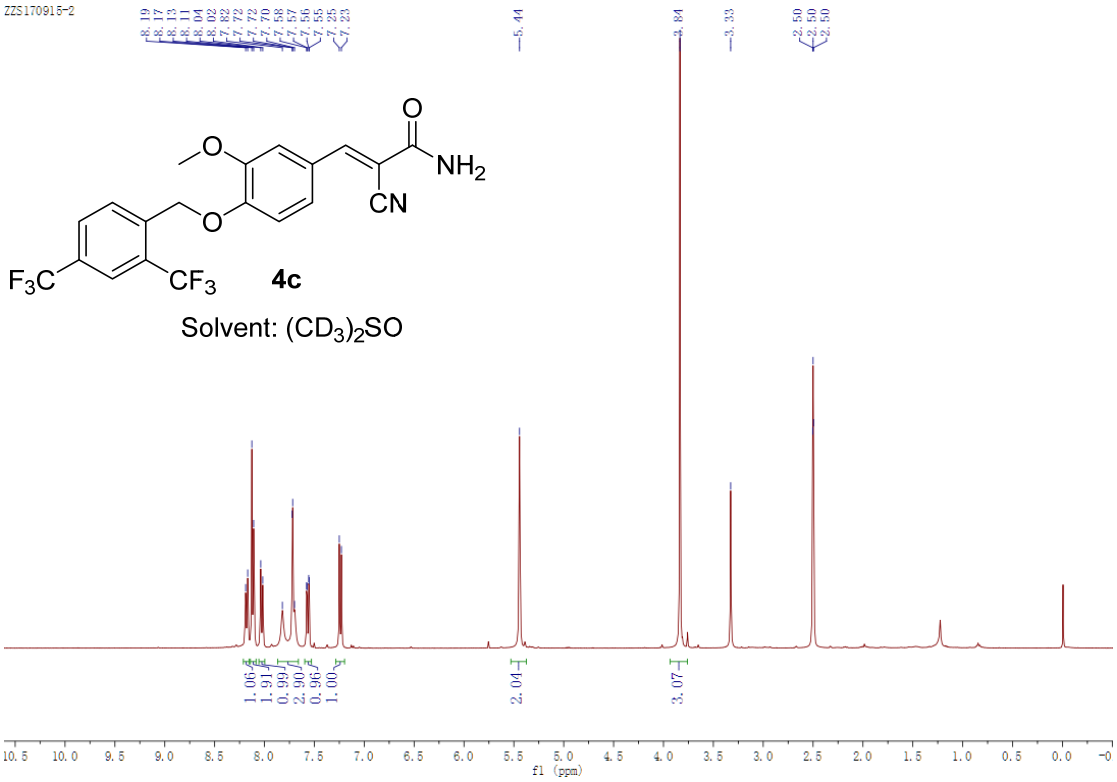
53.68
f1 (ppm)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8.04
8.02
7.82
7.72
7.72
7.70
7.58
7.57
7.56
7.55
7.25
7.23
5.44
3.84
3.33
2.50
2.50
2.50
O
NH2
CN
O
O
F3C
CF3
4c
Solvent: (CD3)2SO
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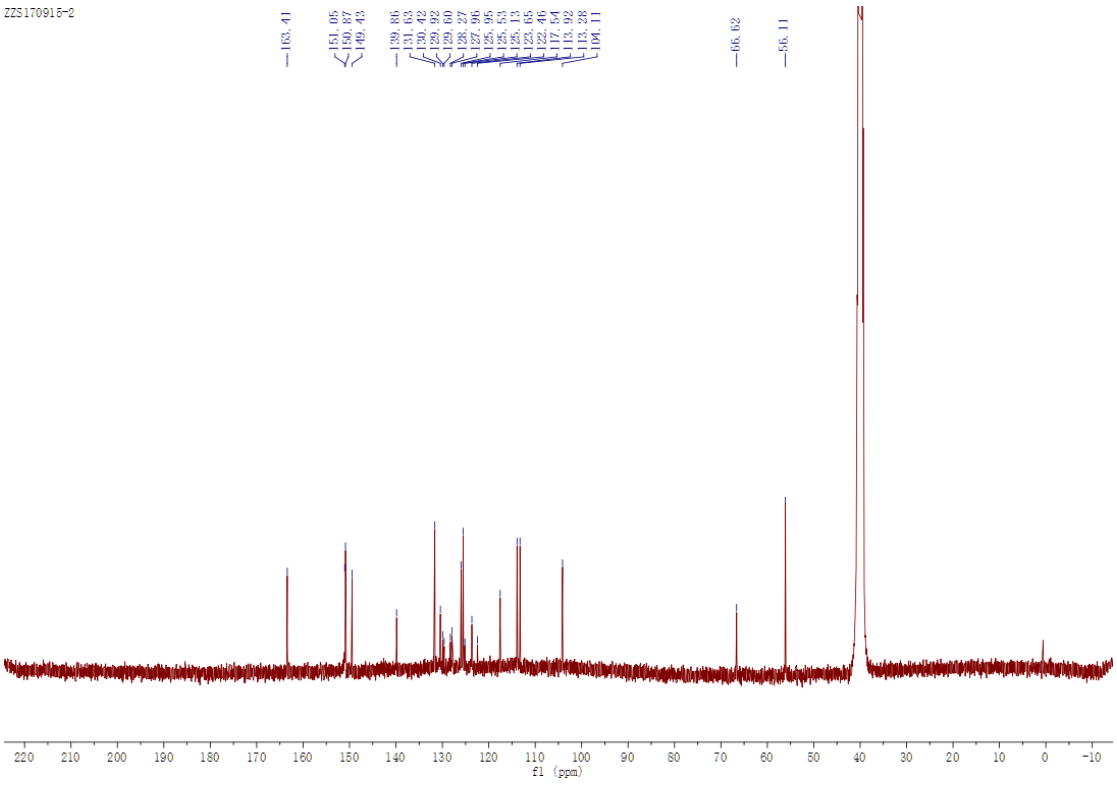
0.99
2.90
0.96
1.00
2.04
3.07
f1 (ppm)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125.13
123.65
122.46
117.54
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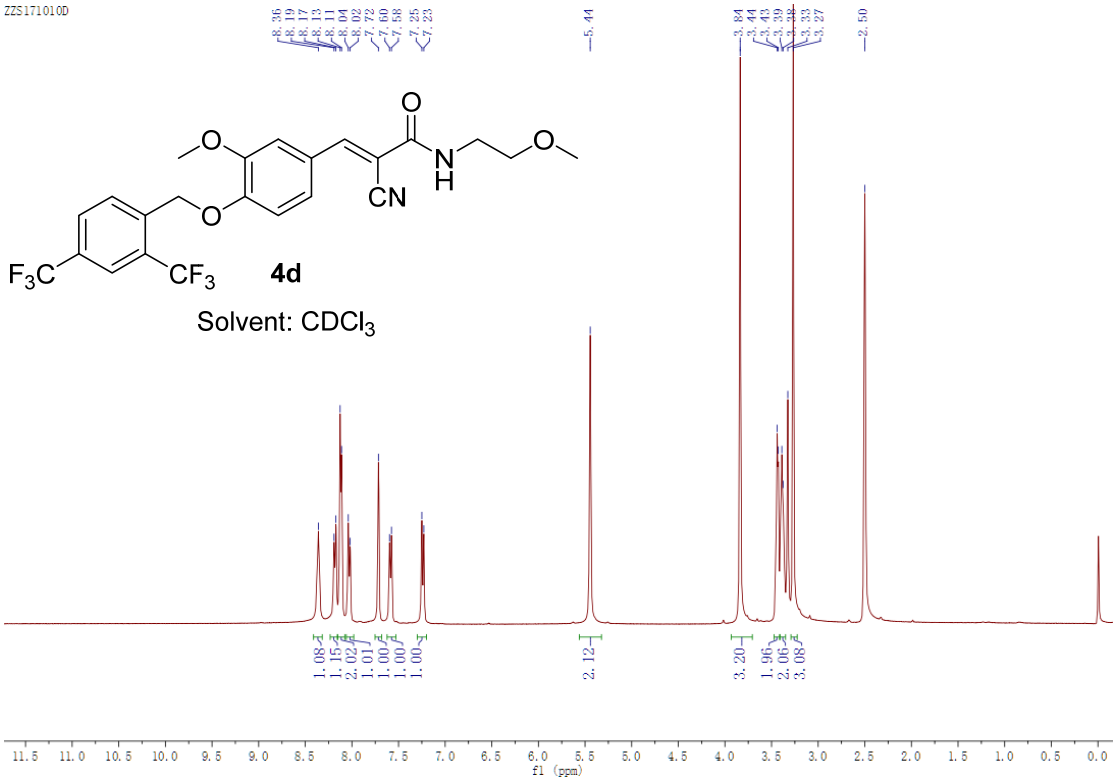
113.28
104.11
66.62
56.11
f1 (ppm)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8.11
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7.60
7.58
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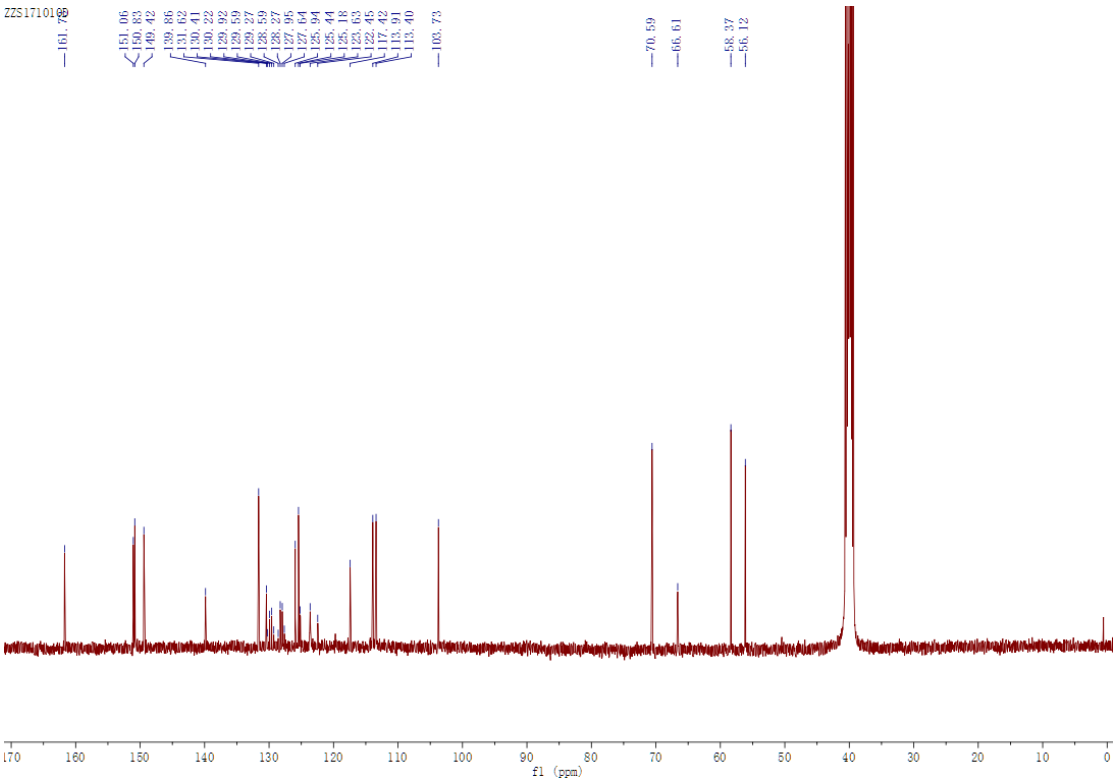
7.23
5.44
3.84
3.44
3.43
3.39
3.38
3.33
3.27
2.50
O
O
N
H
O
CN
O
F3C
CF3
4d
Solvent: CDCl3
1.08
1.15
2.02
1.01
1.00
1.00
1.00
2.12
3.20
1.96
2.06
3.08
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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129.27
128.59
128.27
127.95
127.64
125.94
125.44
125.18
123.63
122.45
117.42
113.91
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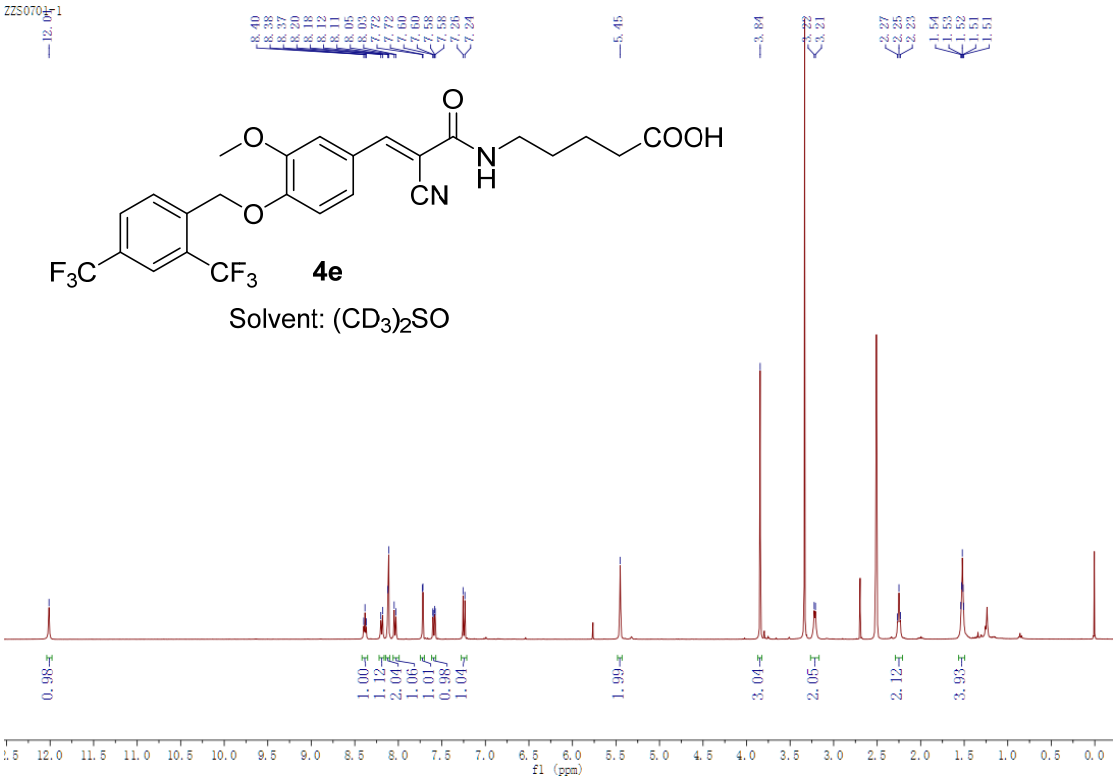
70.59
66.61
58.37
56.12
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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8.03
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7.58
7.58
7.26
7.24
5.45
3.84
3.22
3.21
2.27
2.25
2.23
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1.52
1.51
1.51
O
O
N
H
COOH
CN
O
F3C
CF3
4e
Solvent: (CD3)2SO
0.98
1.00
1.12
2.04
1.06
1.01
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1.04
1.99
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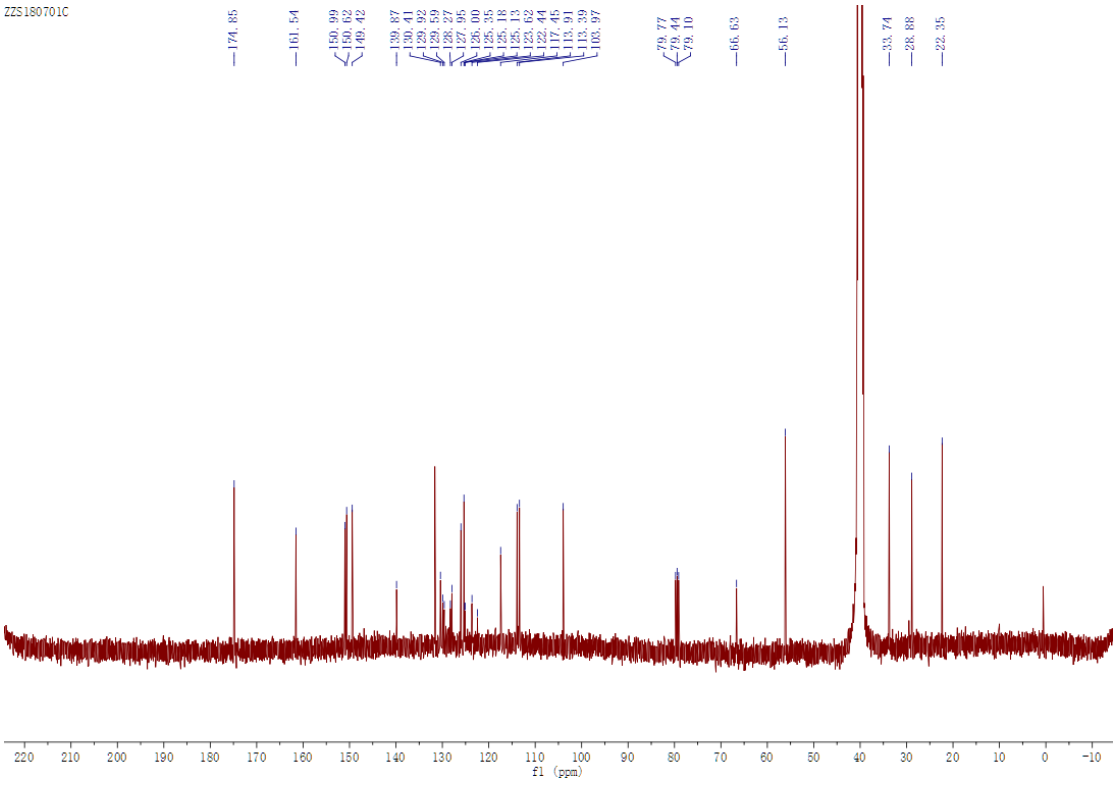
2.05
2.12
3.93
f1 (ppm)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125.18
125.13
123.62
122.44
117.45
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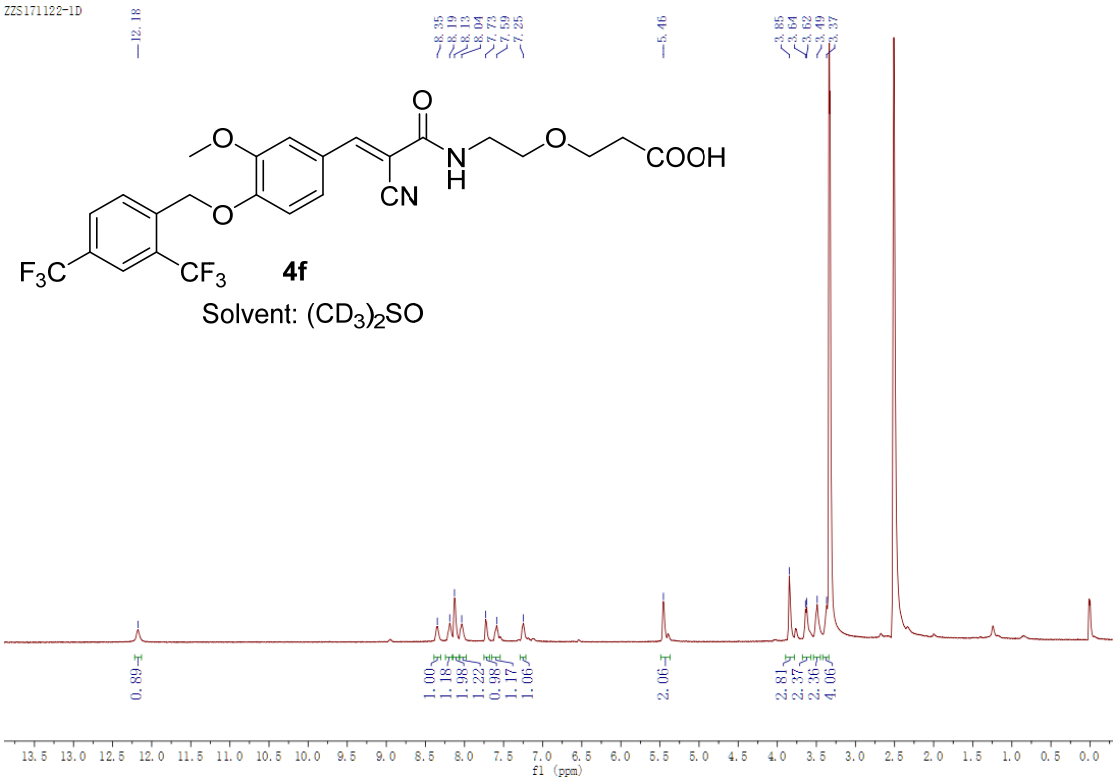
22.35
f1 (ppm)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3.49
3.37
O
O
N
H
O
COOH
CN
O
F3C
CF3
4f
Solvent: (CD3)2SO
0.89
1.00
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1.22
0.98
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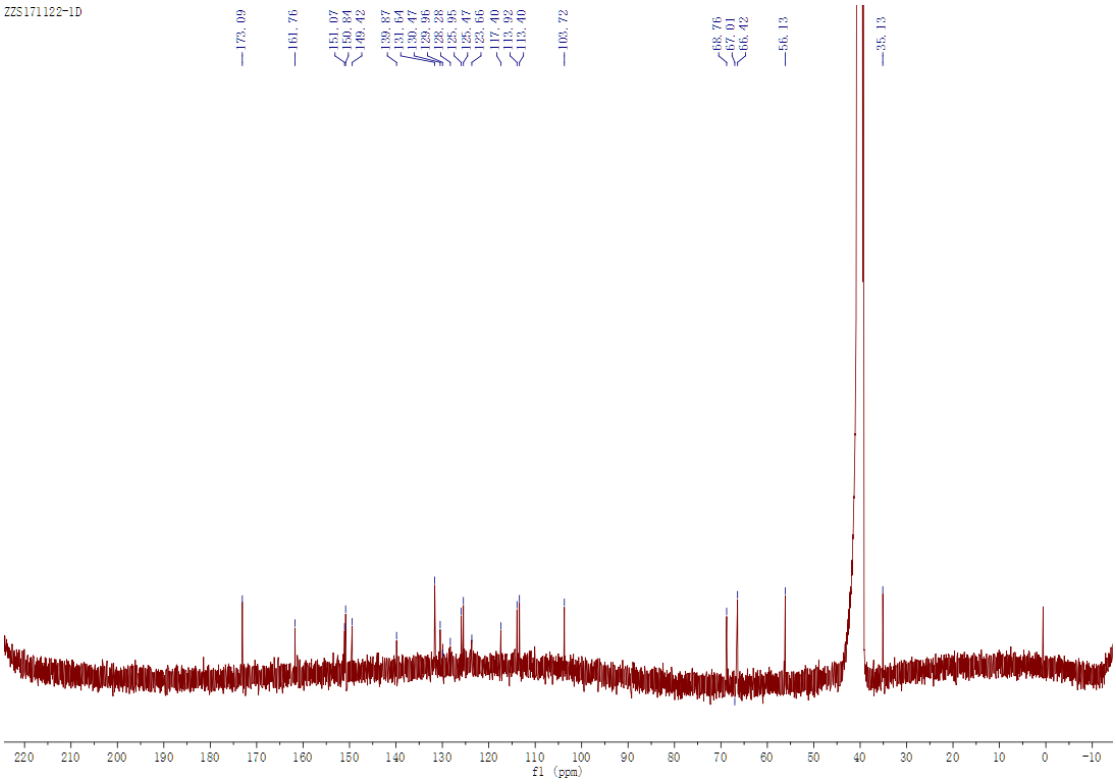
1.06
2.06
2.81
2.37
2.36
4.06
f1 (ppm)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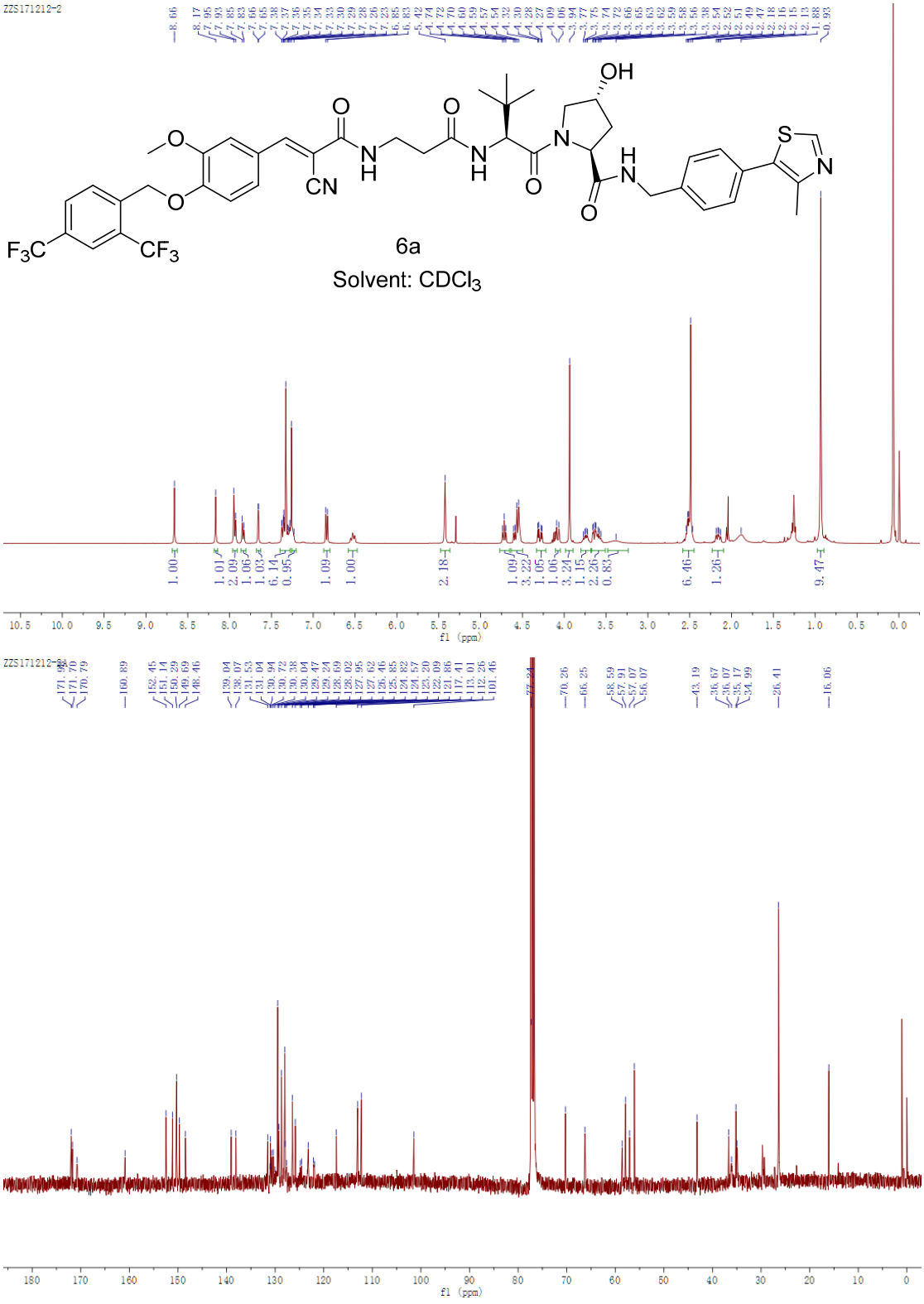
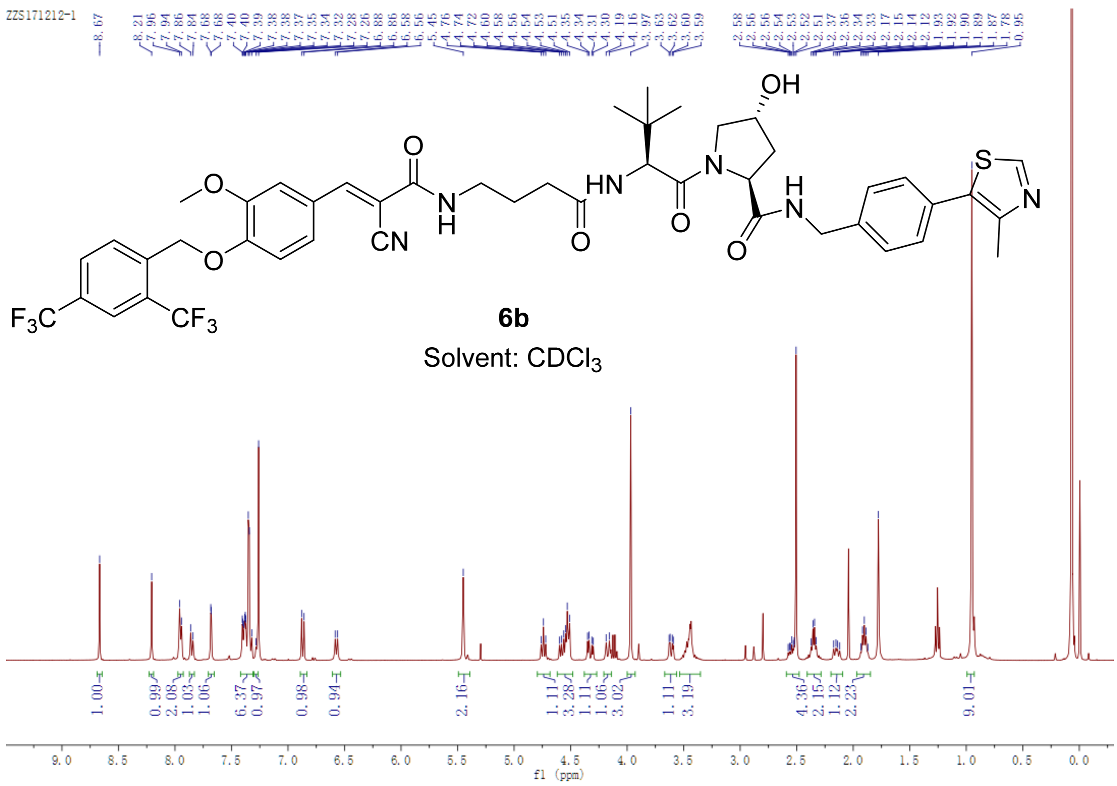
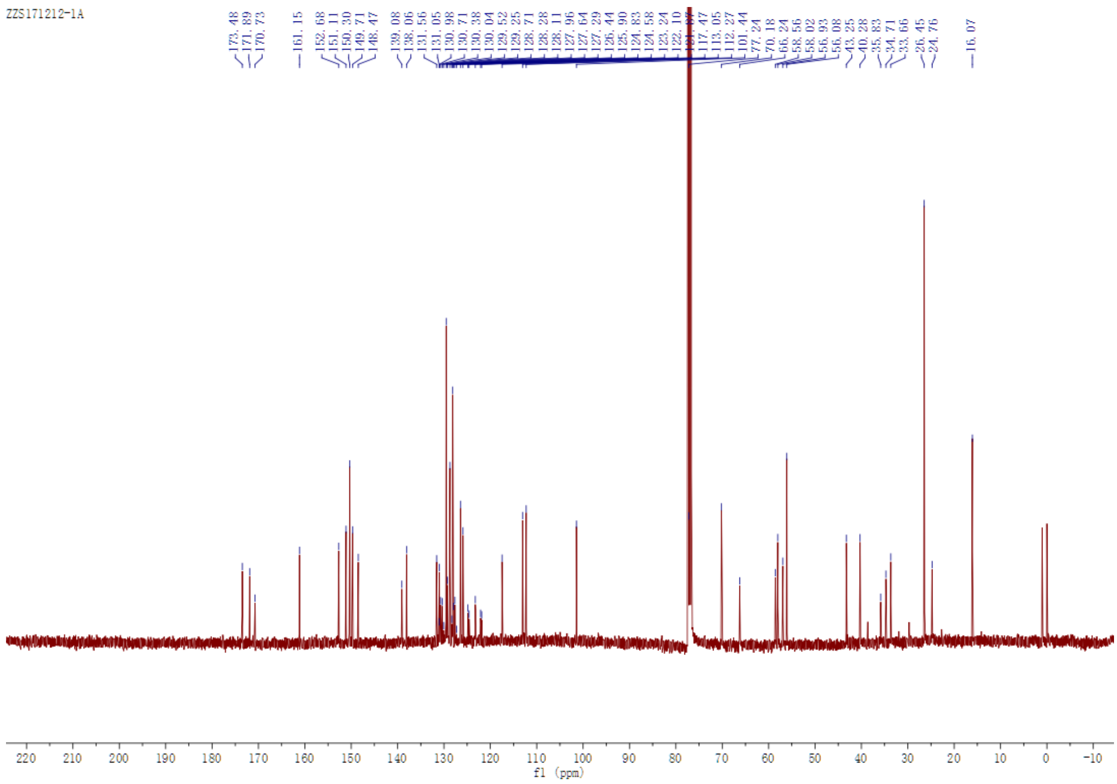
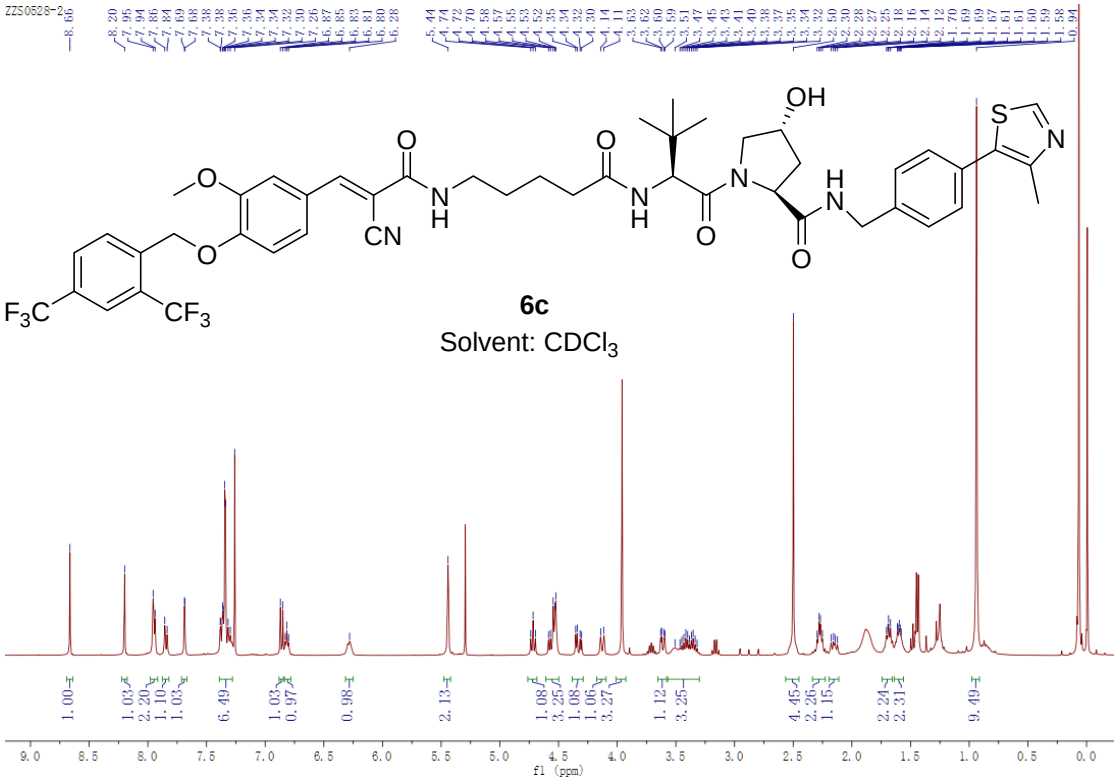
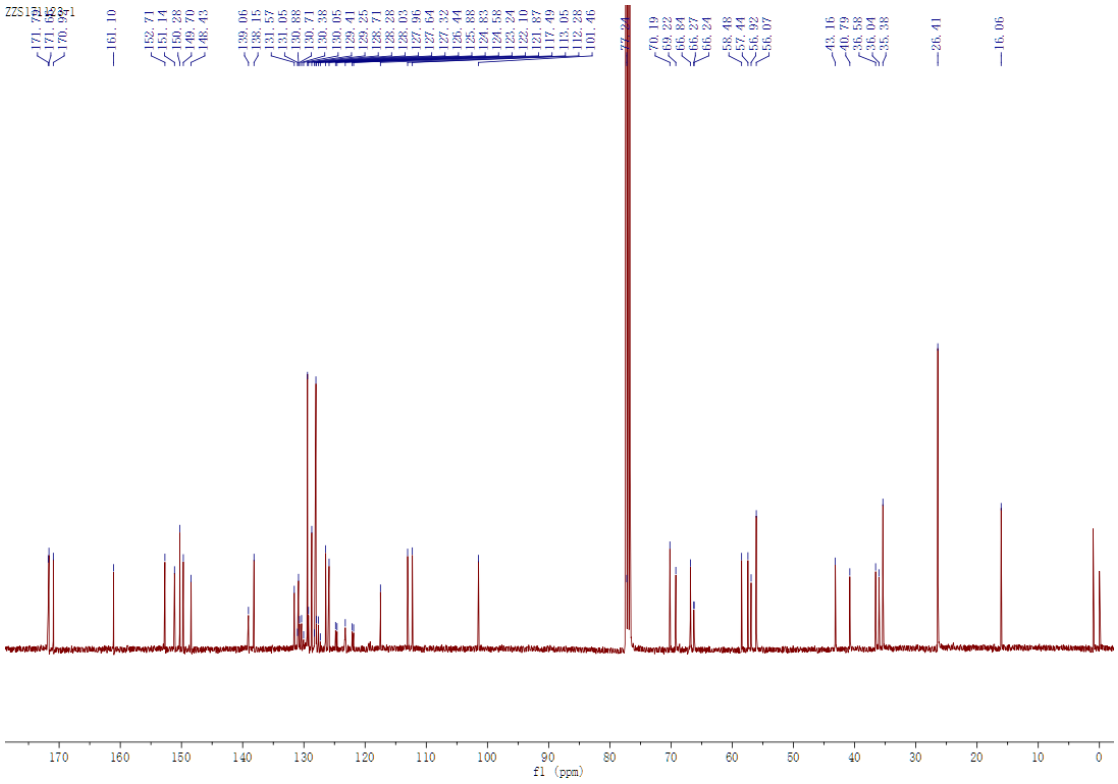
125.47
123.66
117.40
113.92
113.40
103.72
68.76
67.01
66.42
56.13
35.13
f1 (ppm)

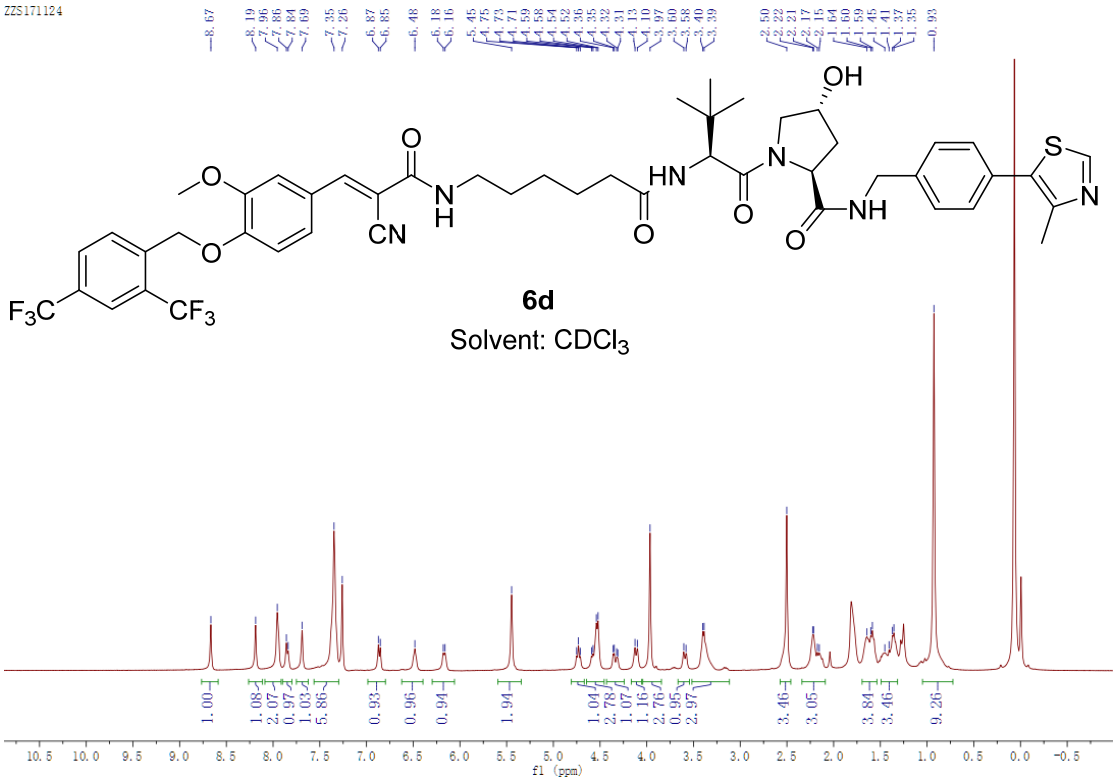

ZZS171212-2
6a
Solvent: CDCl3
f1 (ppm)
ZZS171212-C1
f1 (ppm)

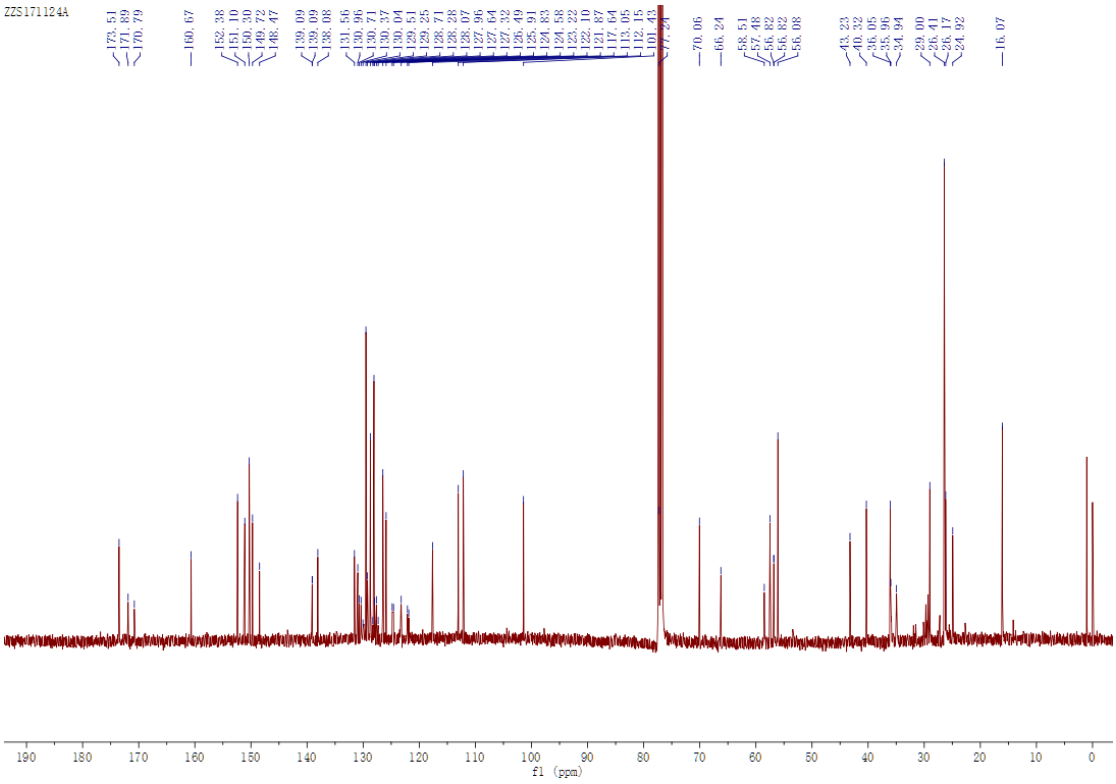

ZZS171212-1
6b
Solvent: $CDCl_3$
f1 (ppm)

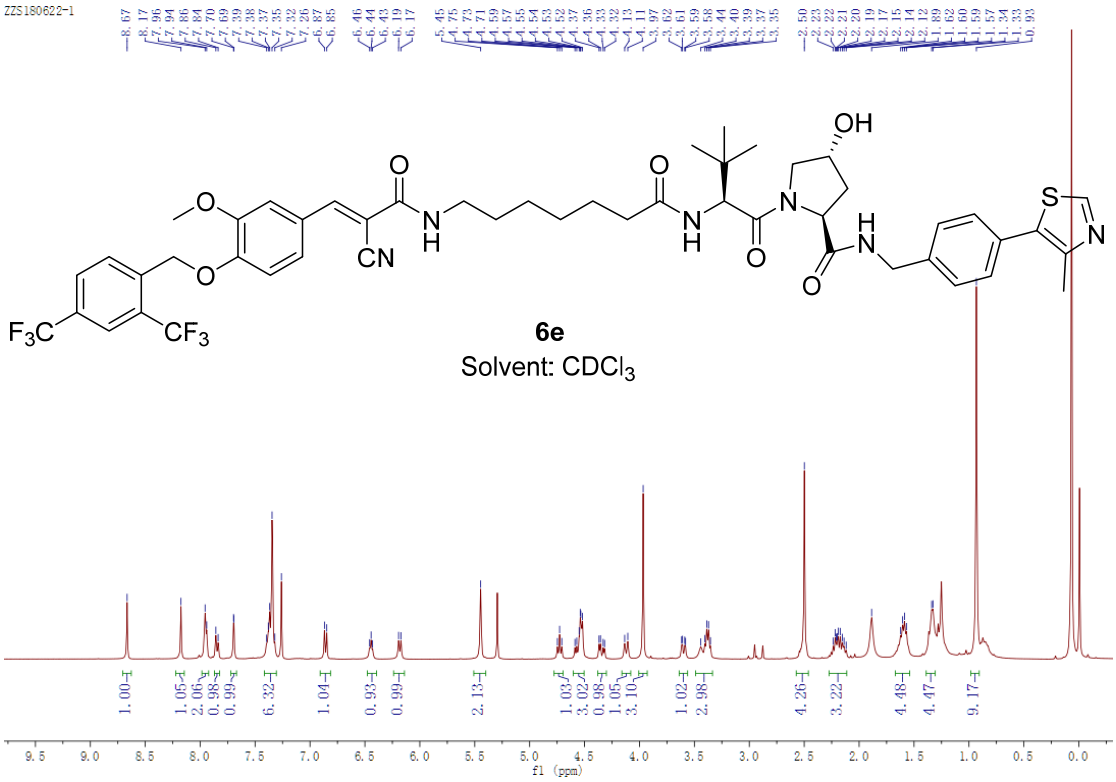

ZZS171212-1A
f1 (ppm)

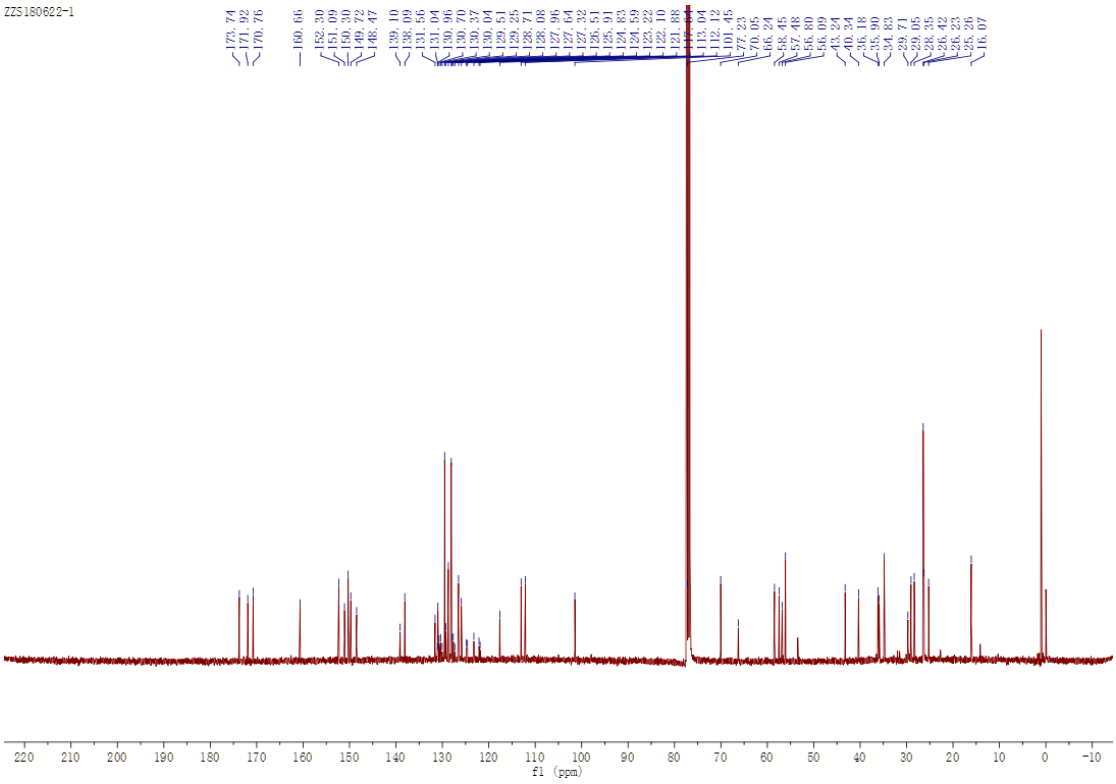

OH
S
N
O
N
H
CN
F3C
CF3
6c
Solvent: CDCl3
f1 (ppm)

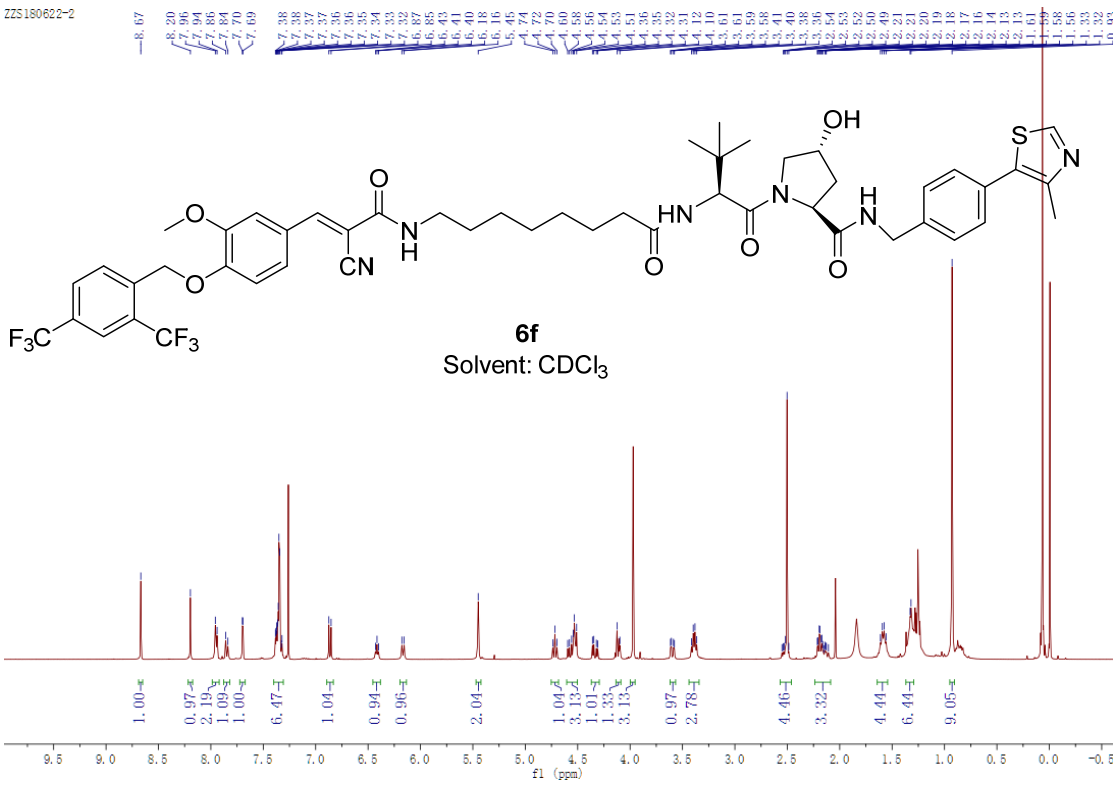

f1 (ppm)

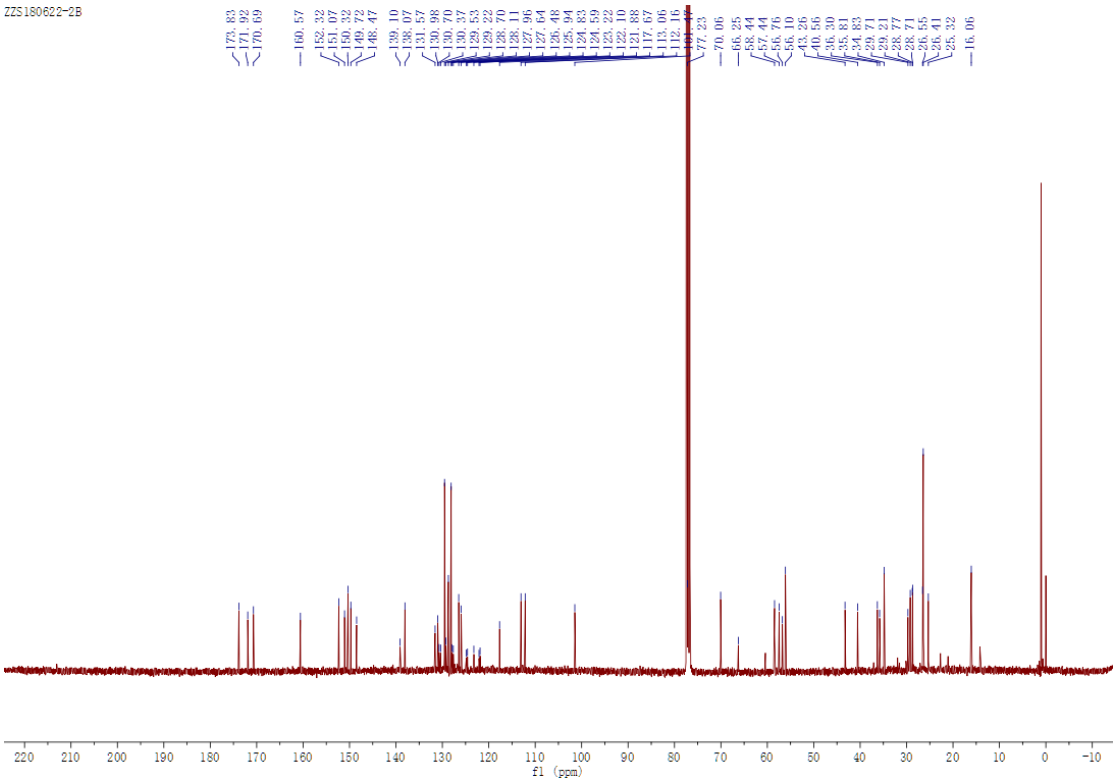

ZZS171124
6d
Solvent: CDCl3
f1 (ppm)

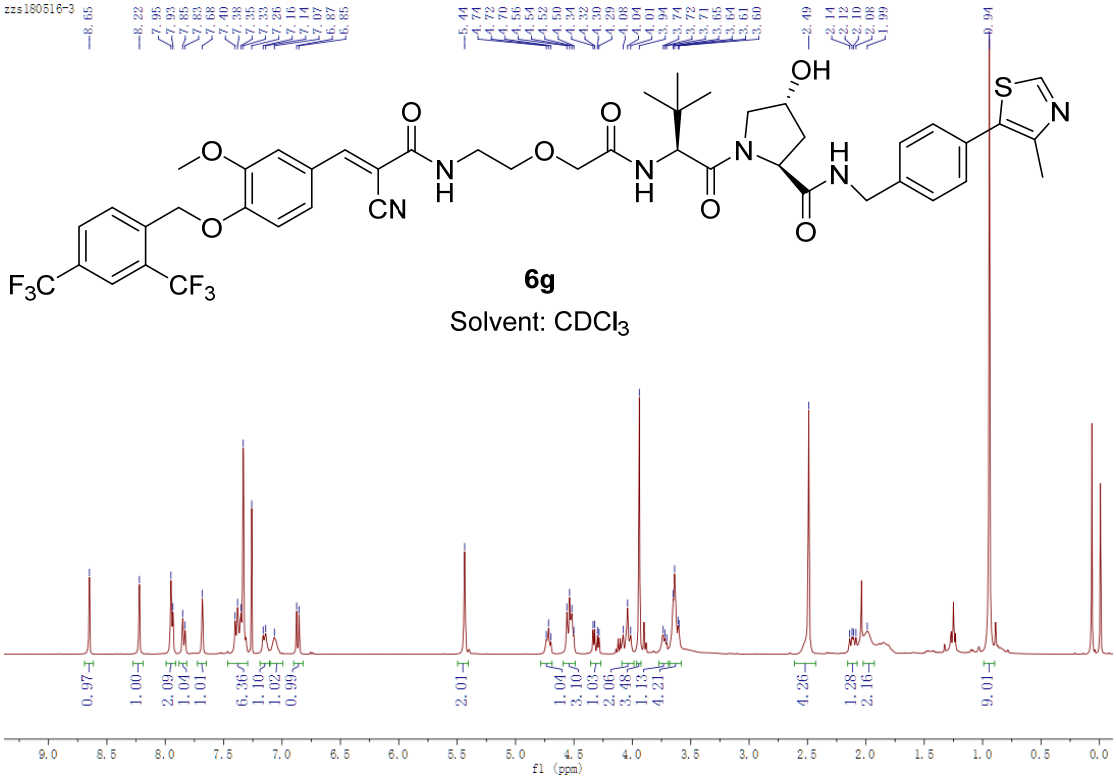

ZZS171124A
f1 (ppm)

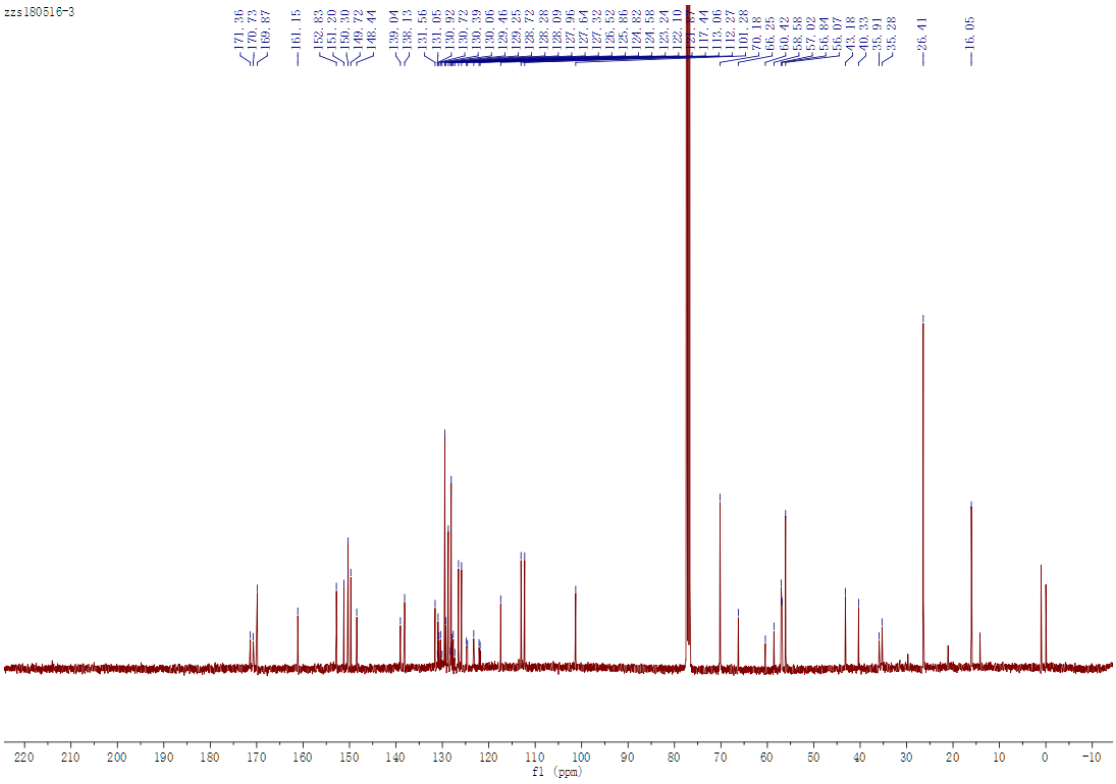

ZZS180622-1
6e
Solvent: CDCl3

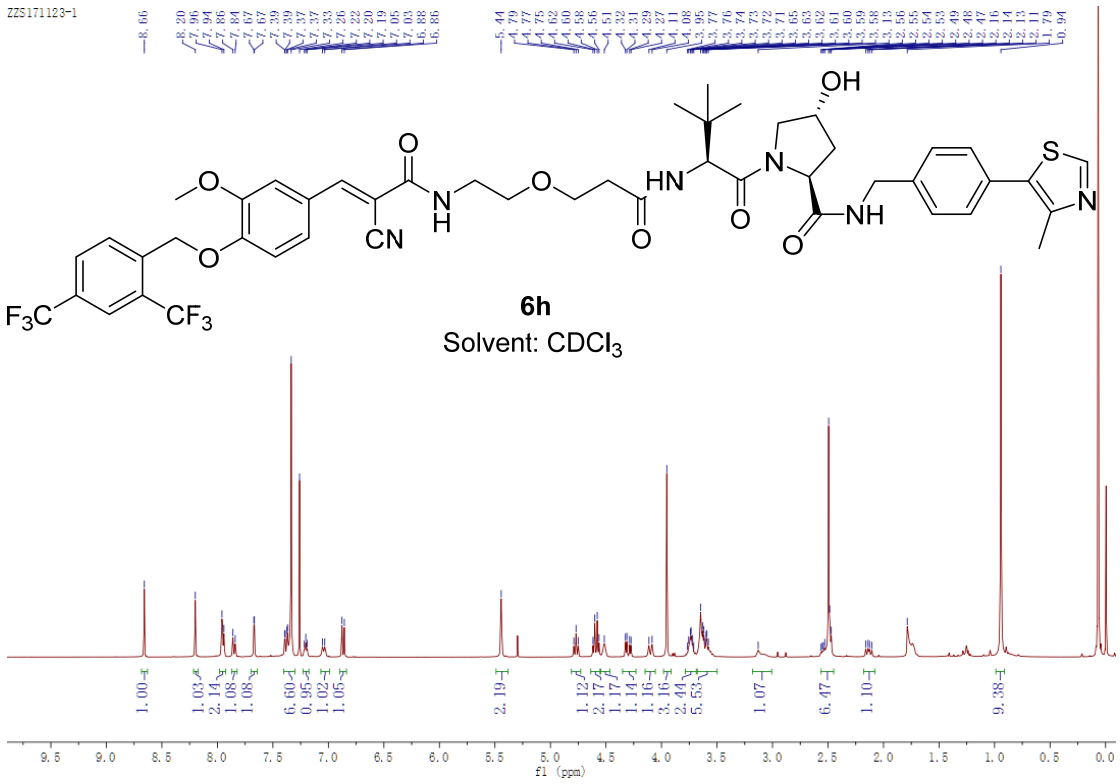

ZZS180622-1
f1 (ppm)

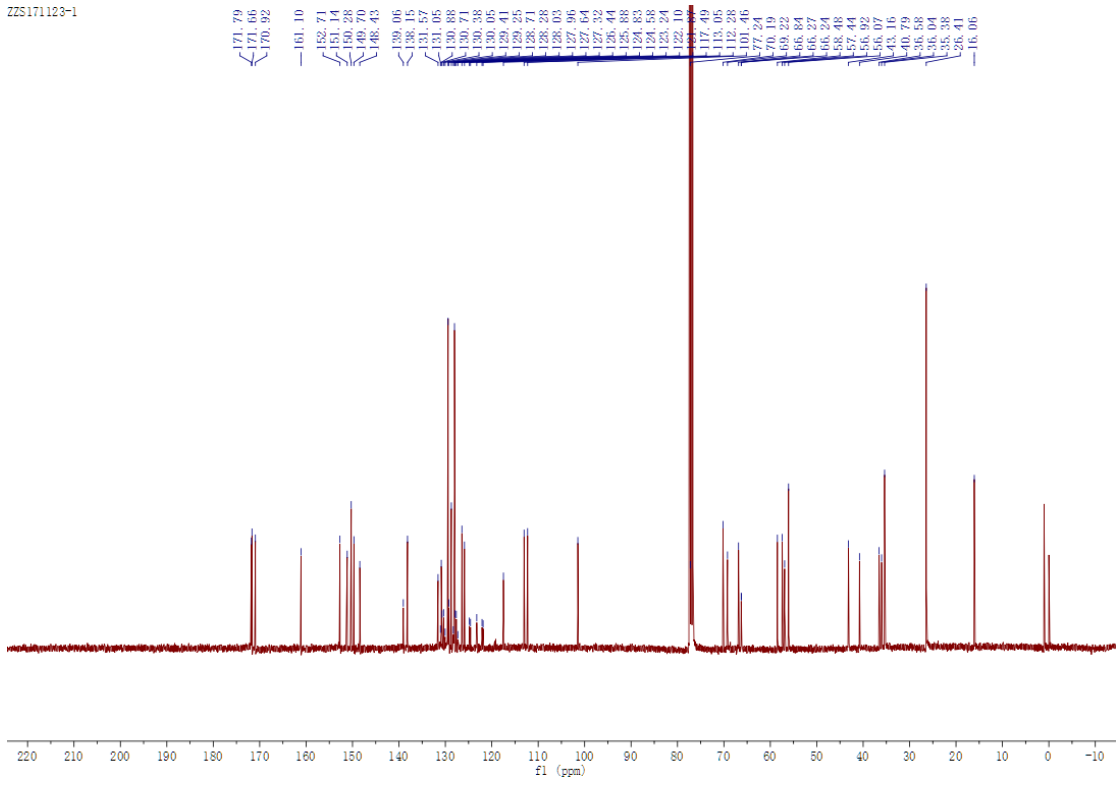

ZZS180622-2
6f
Solvent: CDCl3
f1 (ppm)

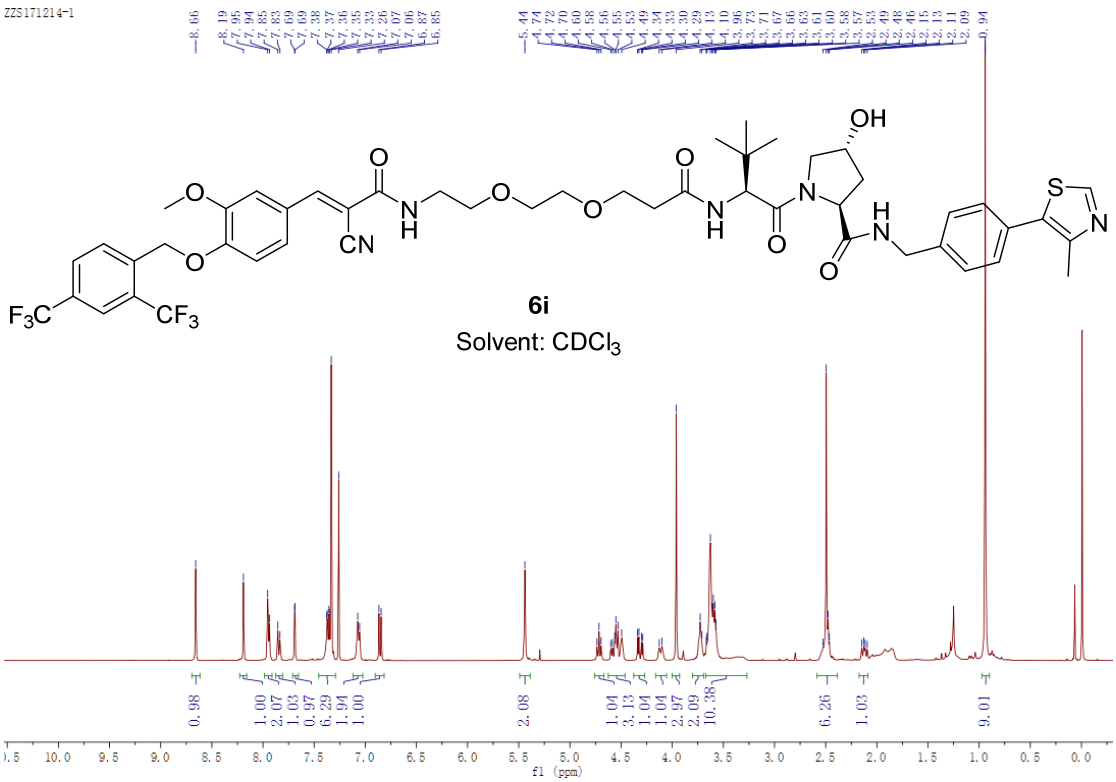

ZZS180622-2B
f1 (ppm)

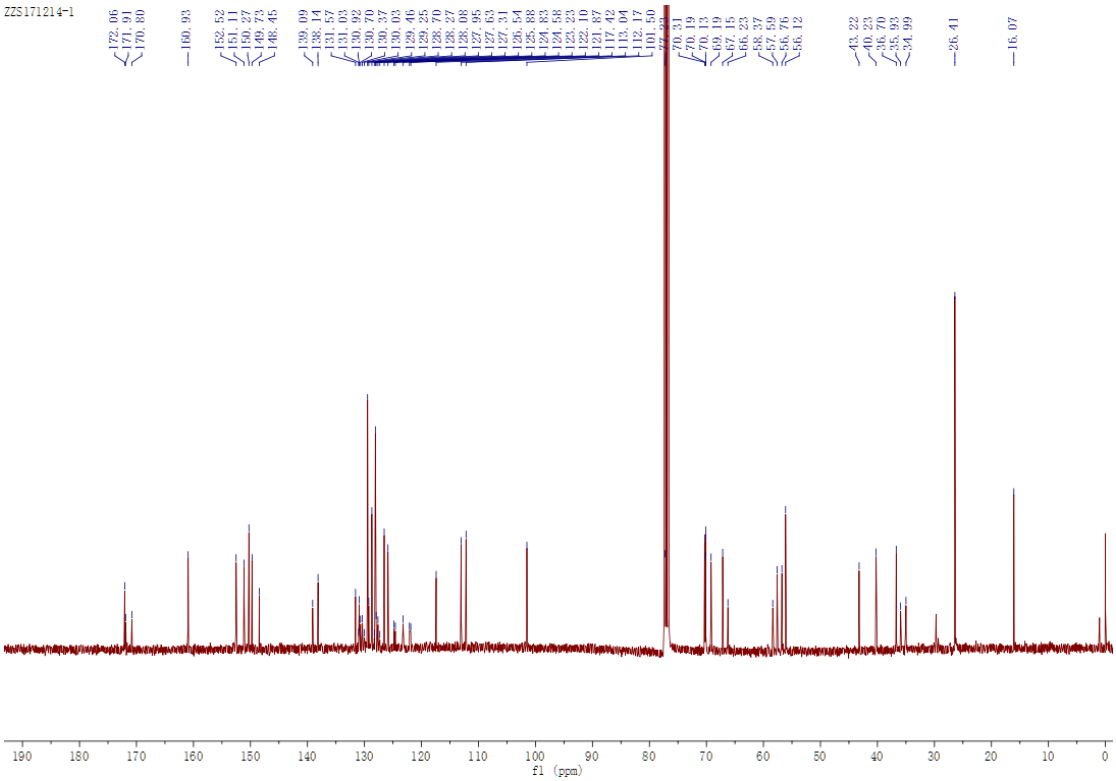

zzs180516-3
OH
S
N
O
N
H
CN
F3C
CF3
6g
Solvent: CDCl3
f1 (ppm)

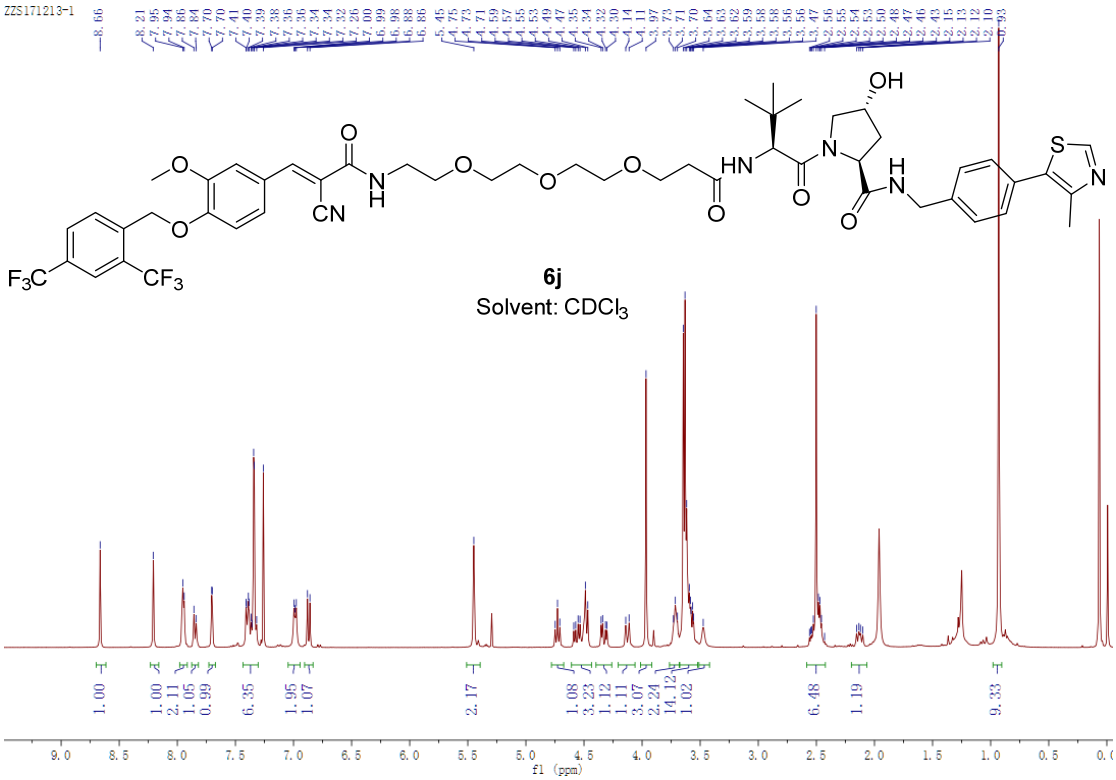

zzs180516-3
f1 (ppm)

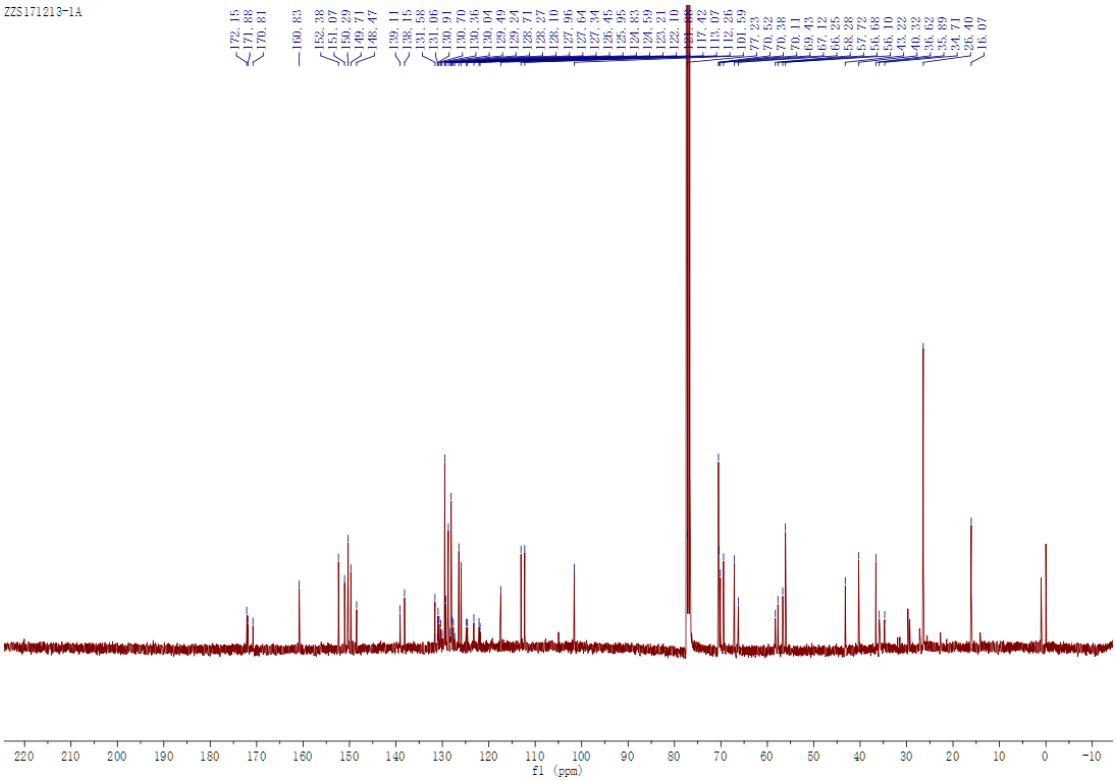

ZZS171123-1
6h
Solvent: CDCl3
f1 (ppm)

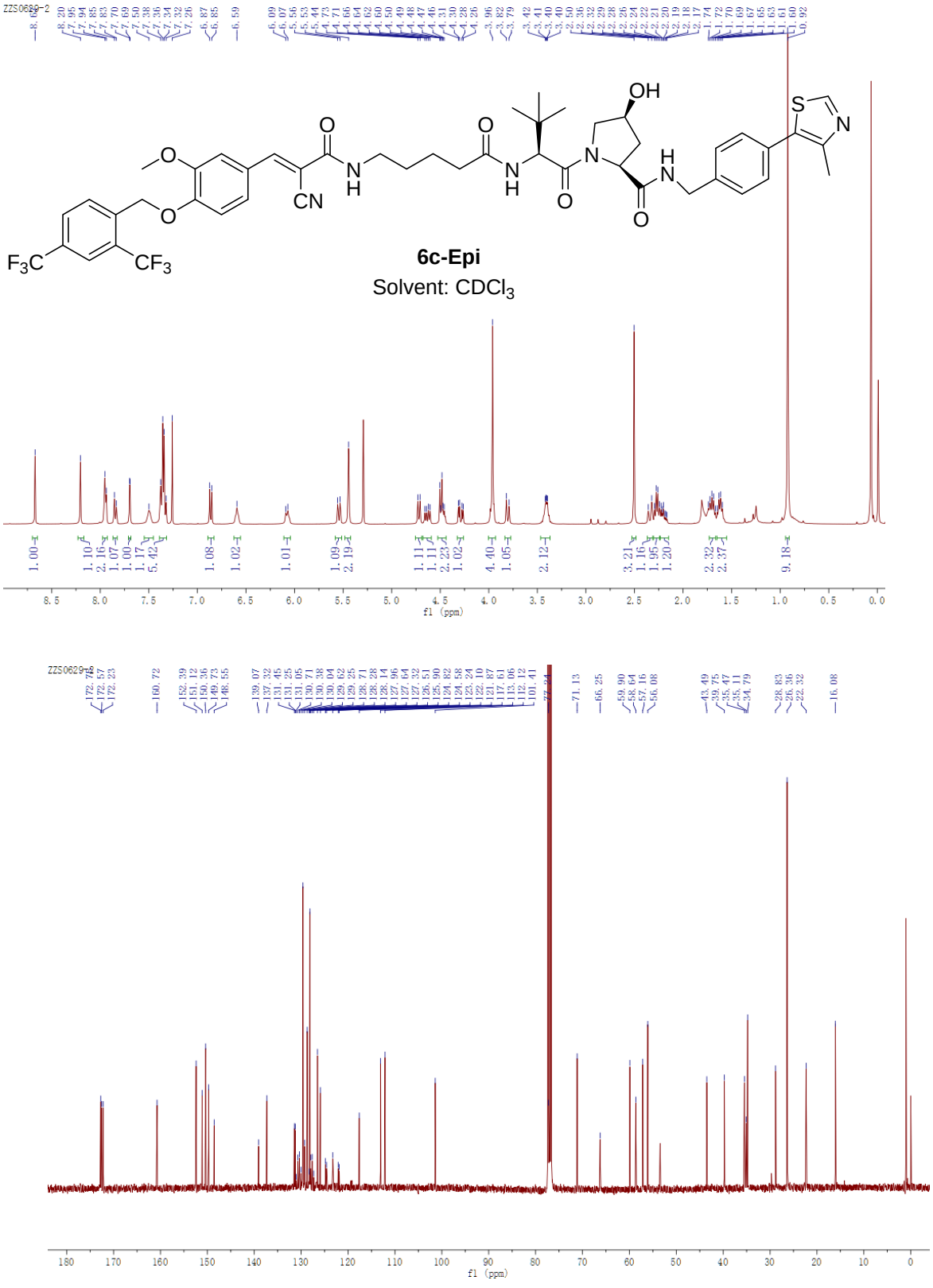

ZZS171123-1
f1 (ppm)

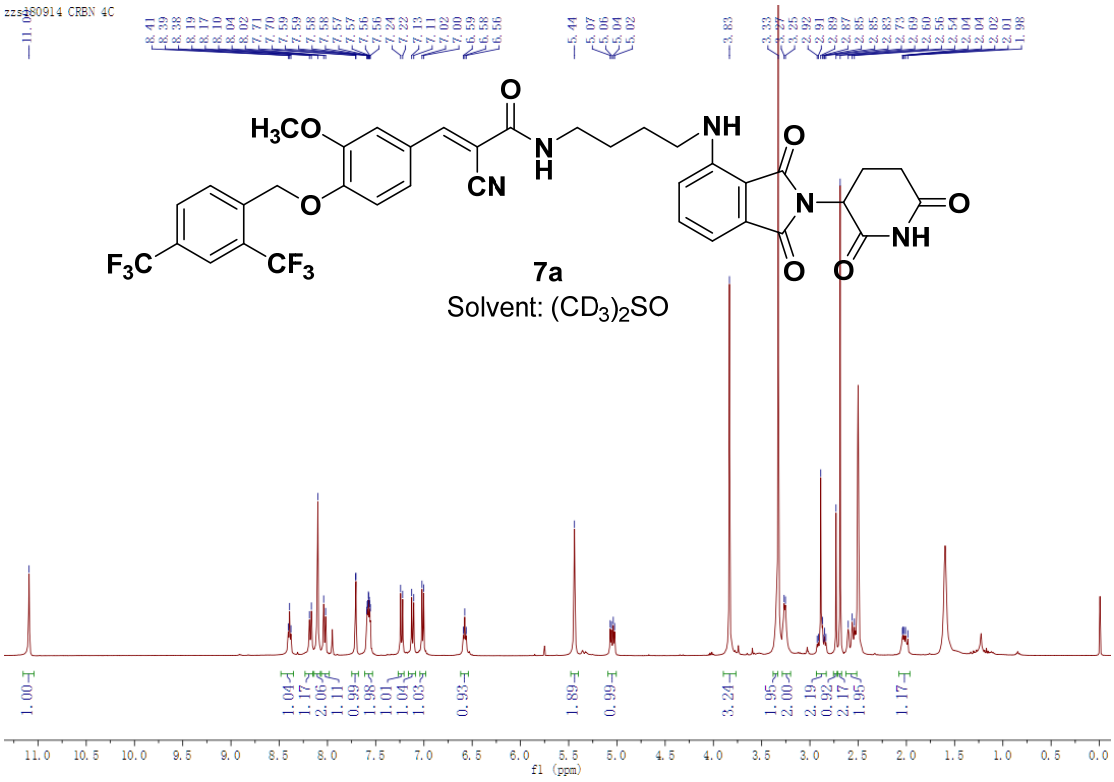

ZZS171214-1
6i
Solvent: CDCl3
f1 (ppm)

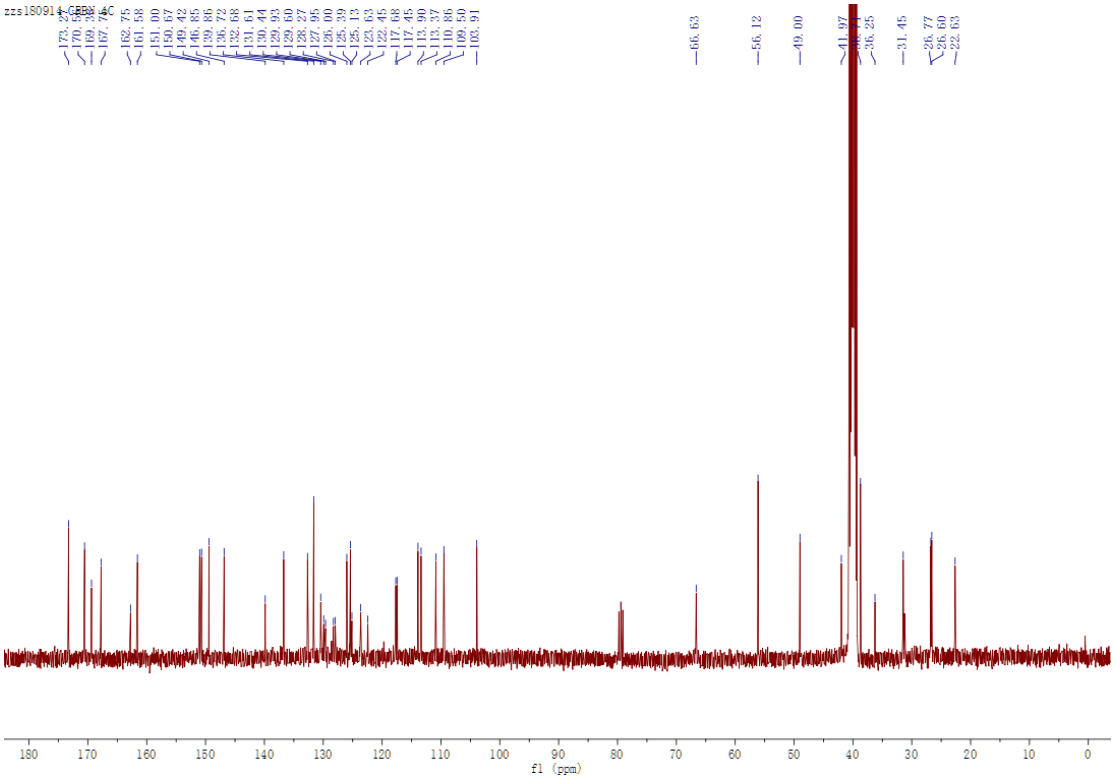

ZZS171214-1
f1 (ppm)

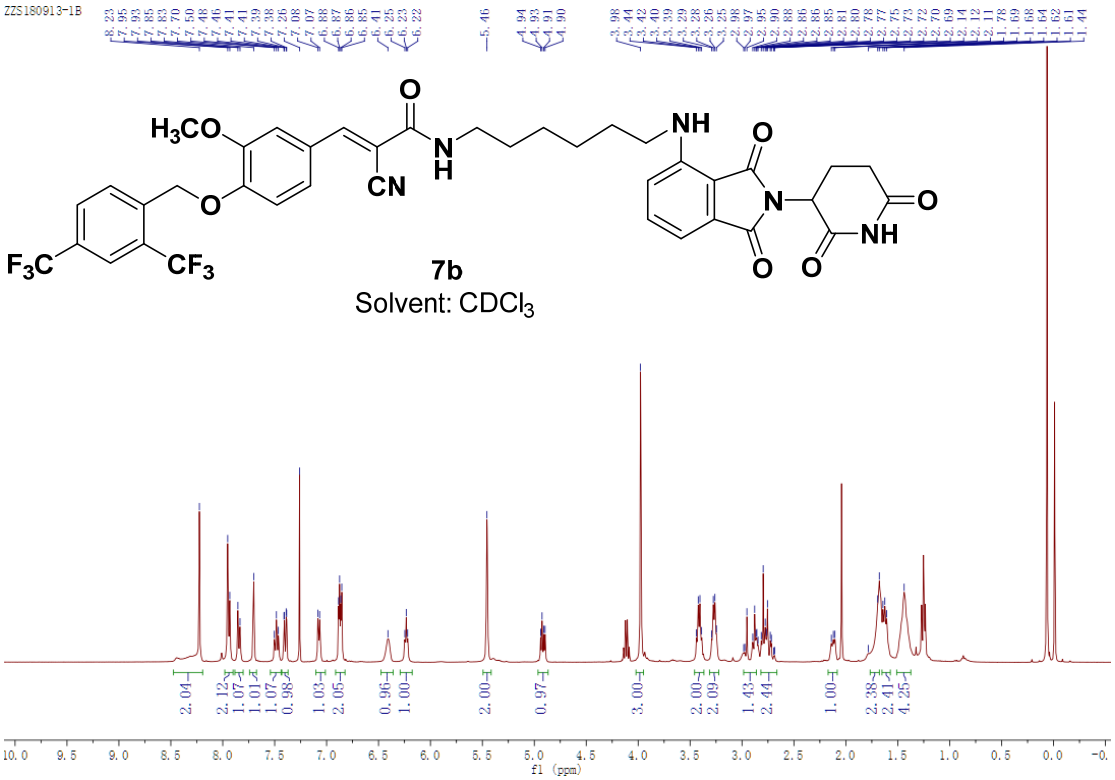

ZZS171213-1
6j
Solvent: CDCl3

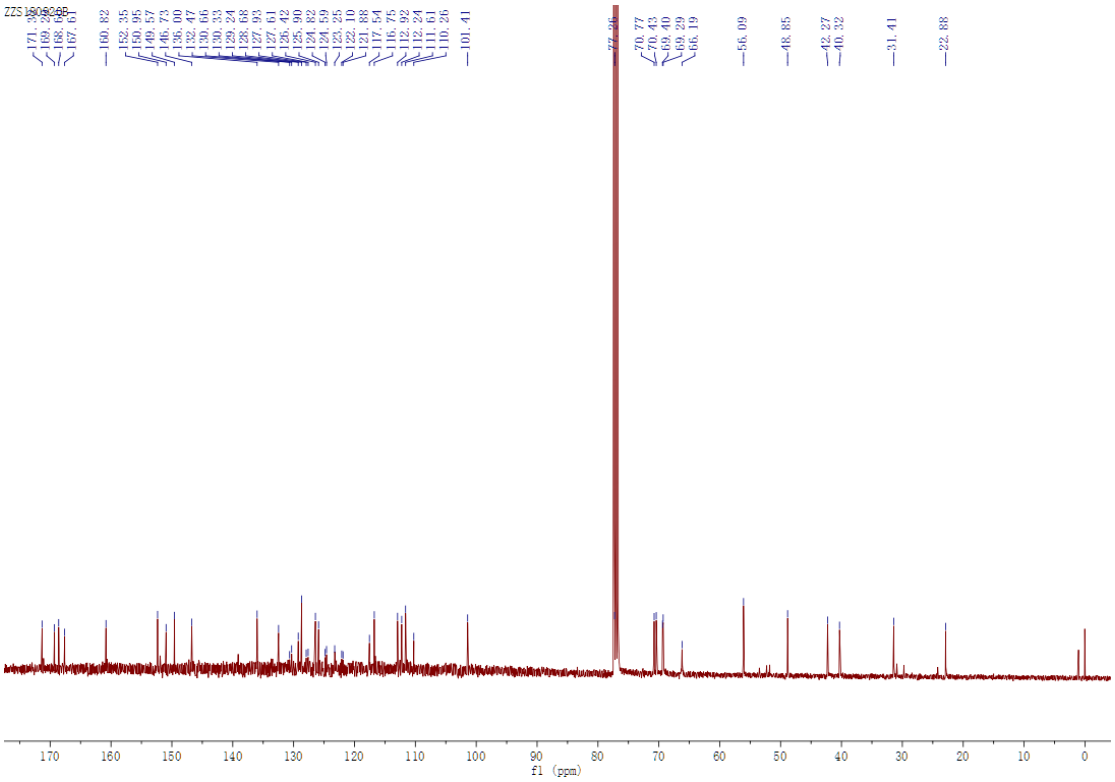

ZZS171213-1A

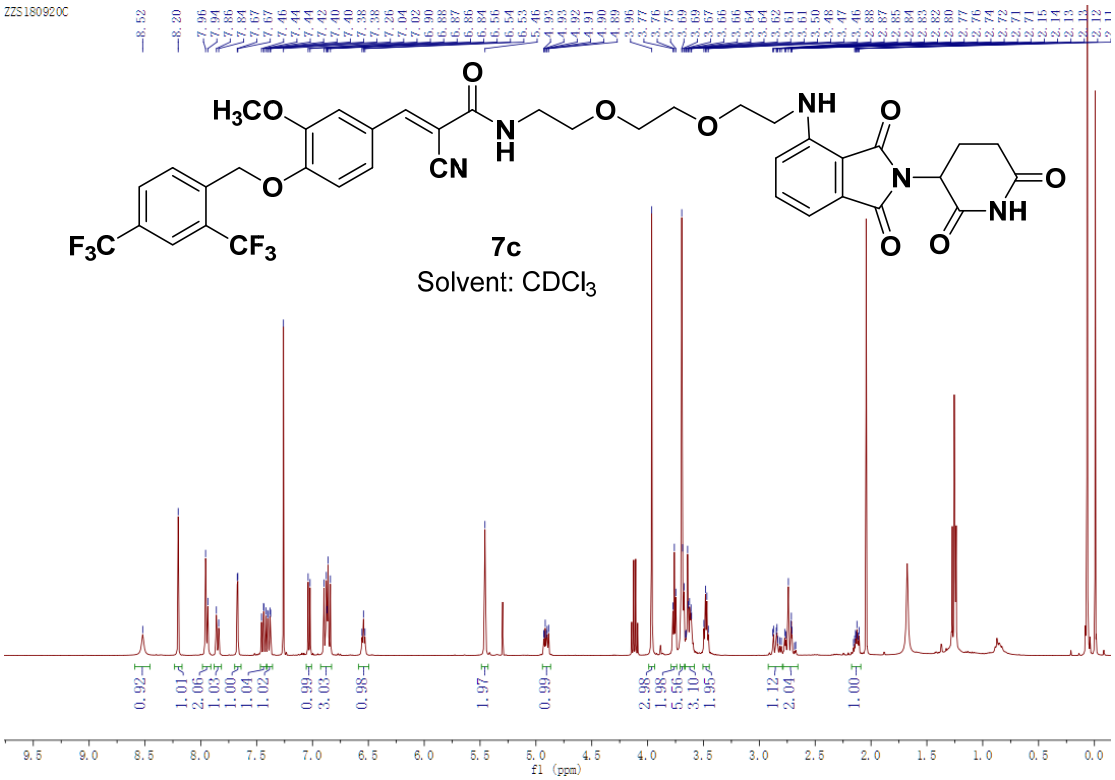

ZZS0629-2
OH
S
N
O
N
H
CN
F3C
CF3
6c-Epi
Solvent: CDCl3
f1 (ppm)
ZZS0629-13C
f1 (ppm)

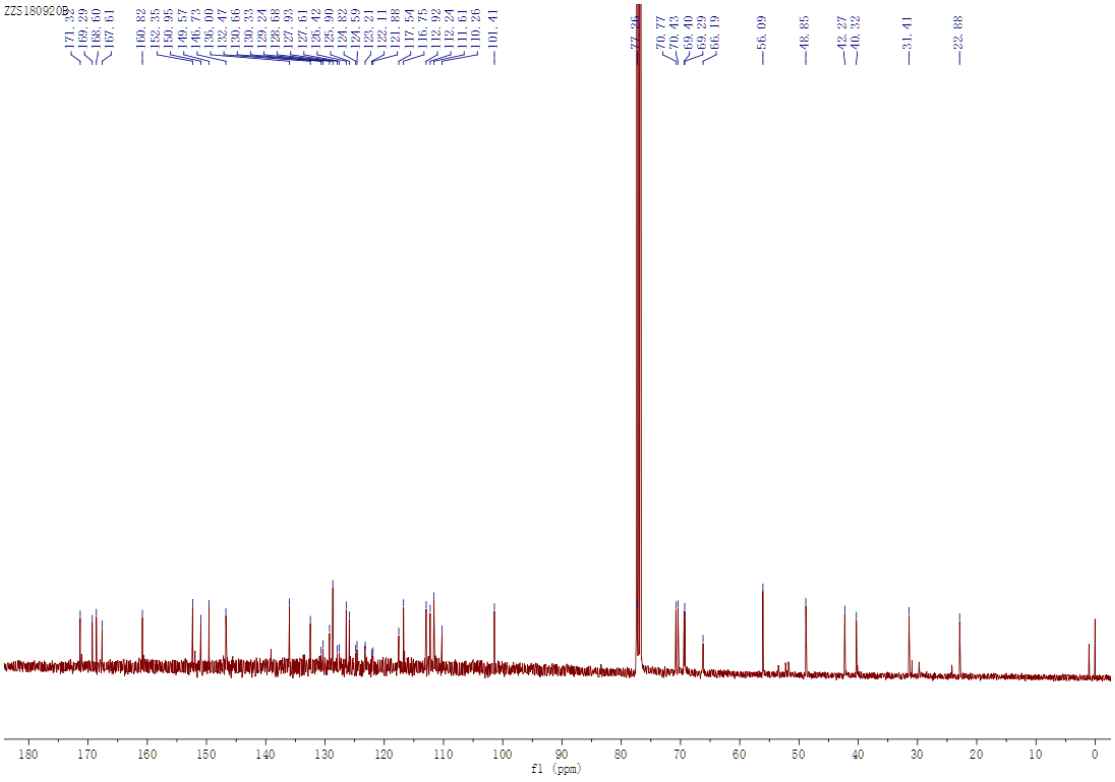

zzs180914 CRBN 4C
7a
Solvent: (CD3)2SO
f1 (ppm)

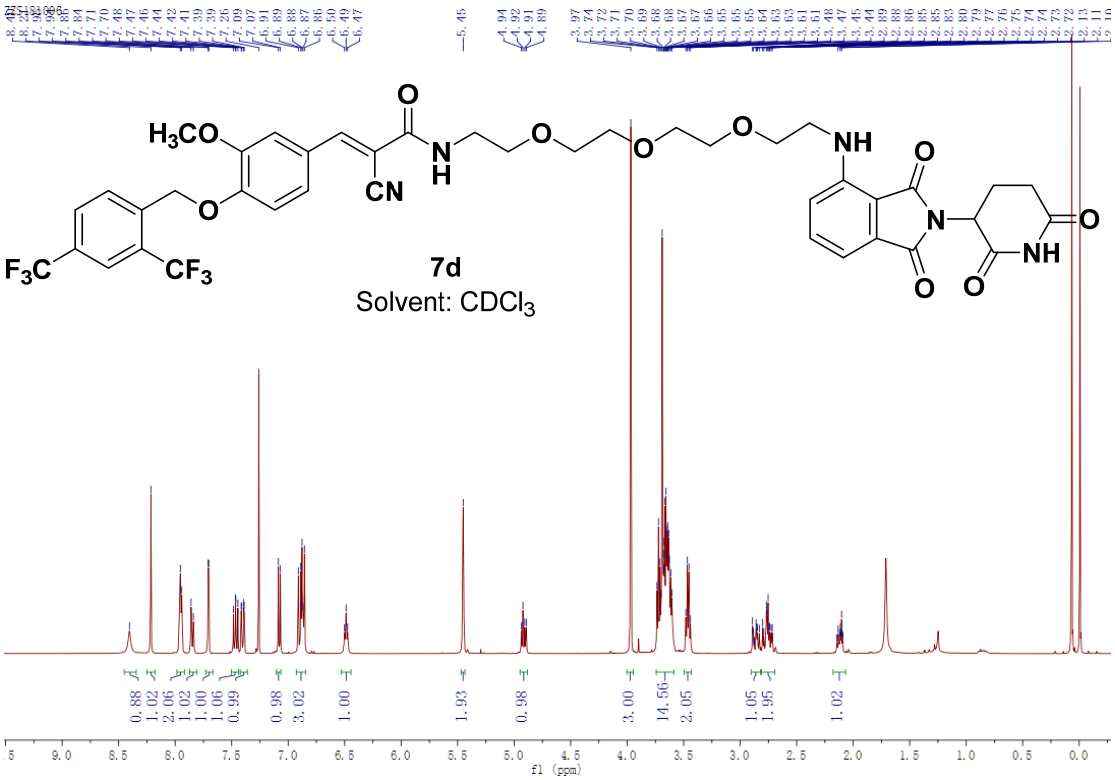

zzs180914 CRBN 4C
f1 (ppm)

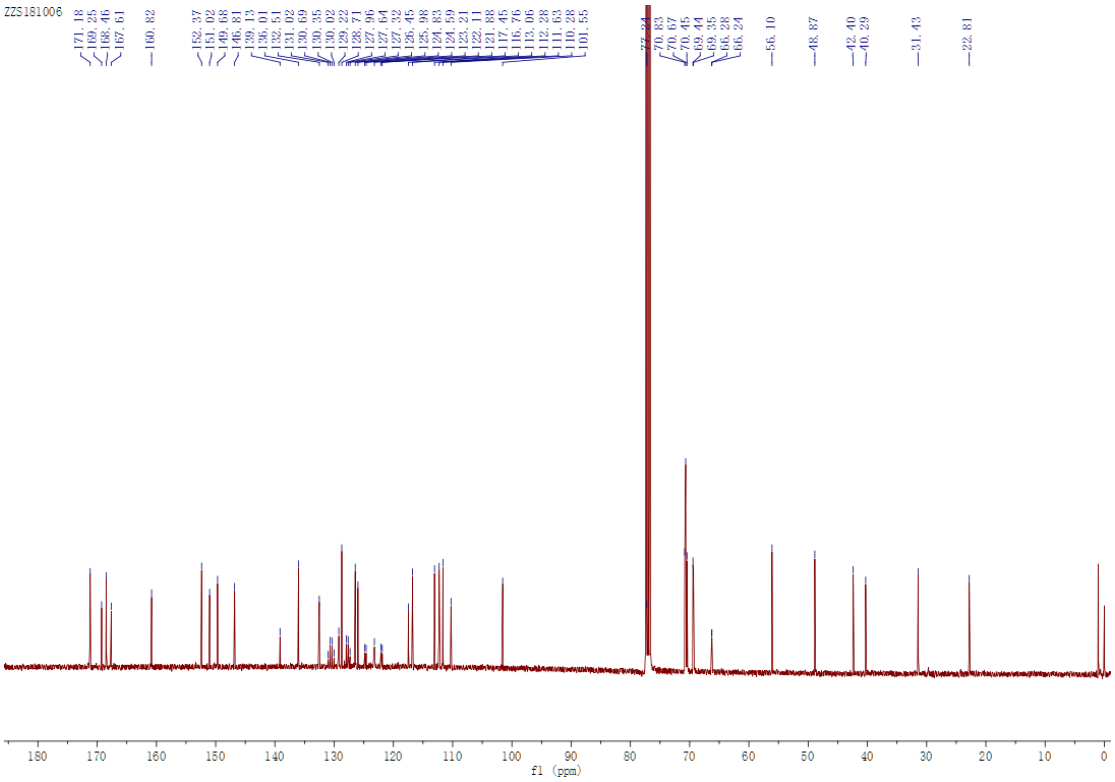

ZZS180913-1B
7b
Solvent: CDCl3

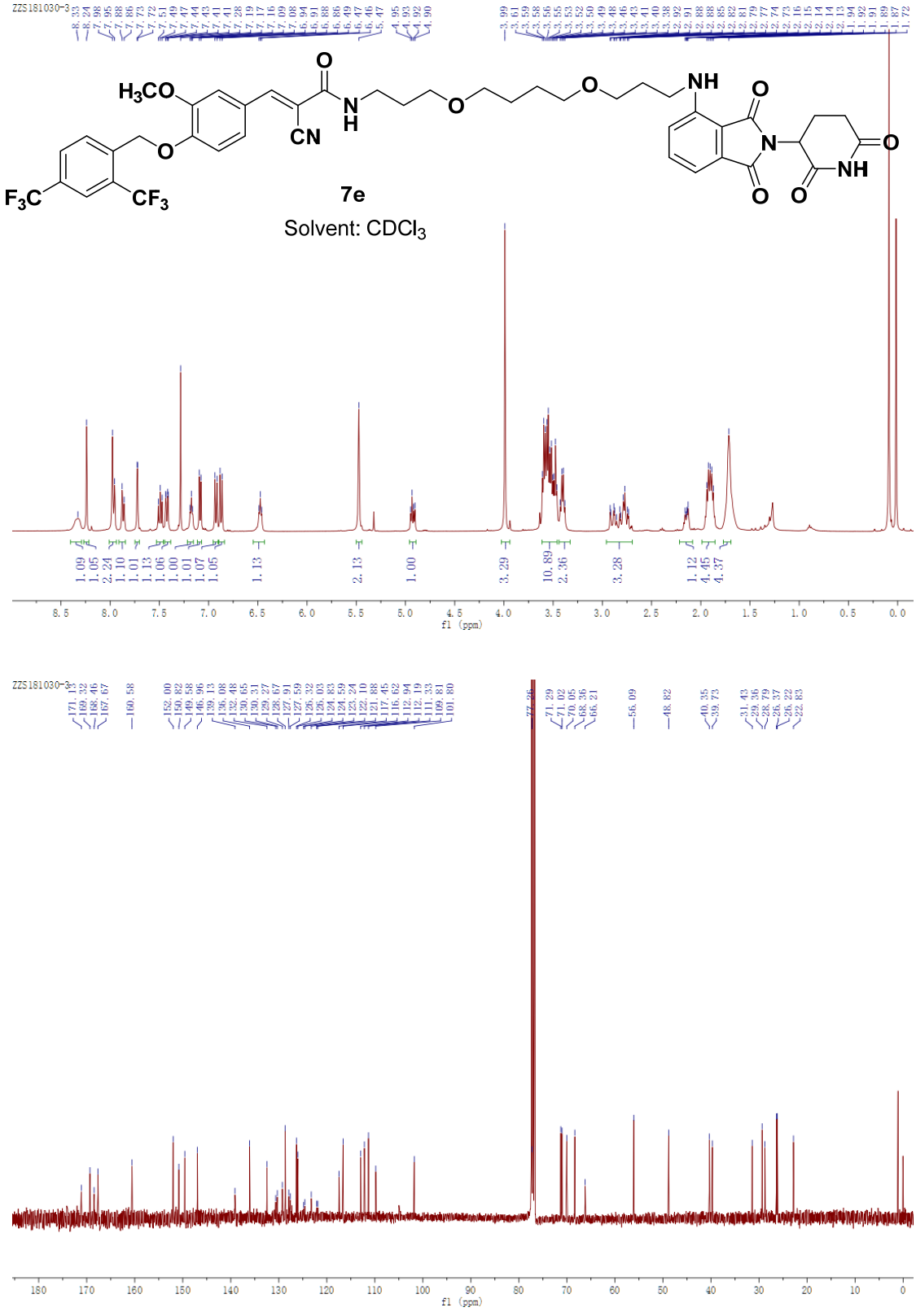

ZZS180908B

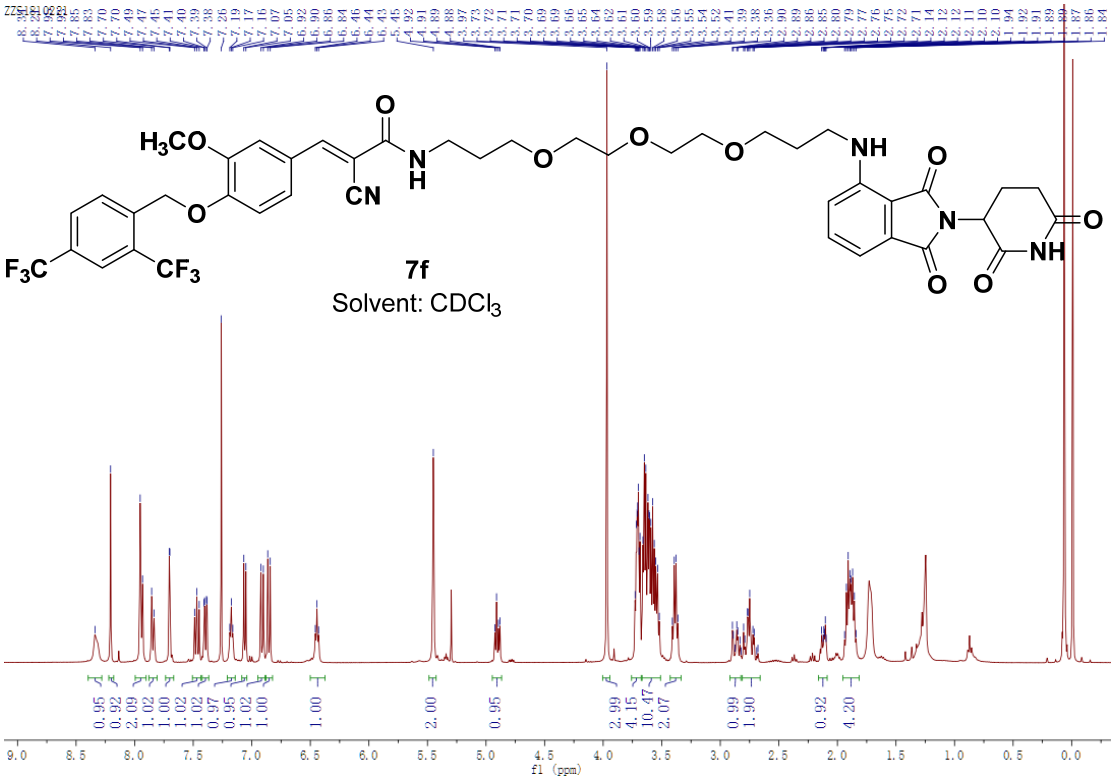

ZZS180920C
7c
Solvent: CDCl3
f1 (ppm)

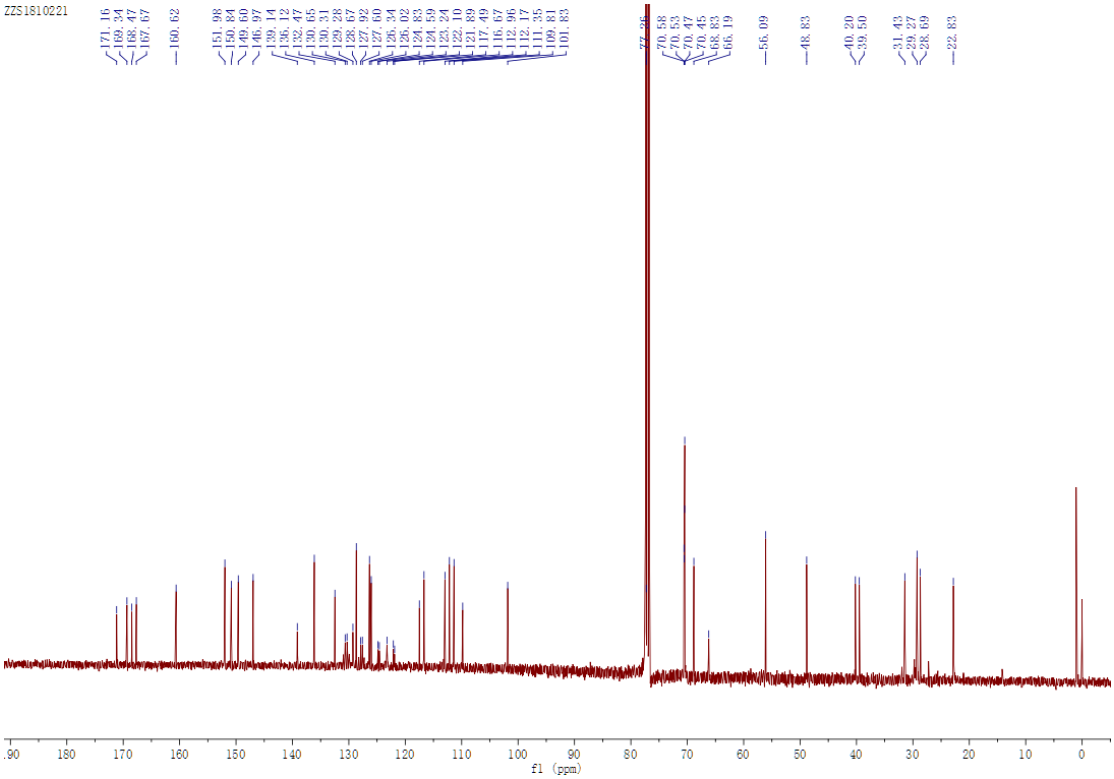

ZZS180920B
f1 (ppm)

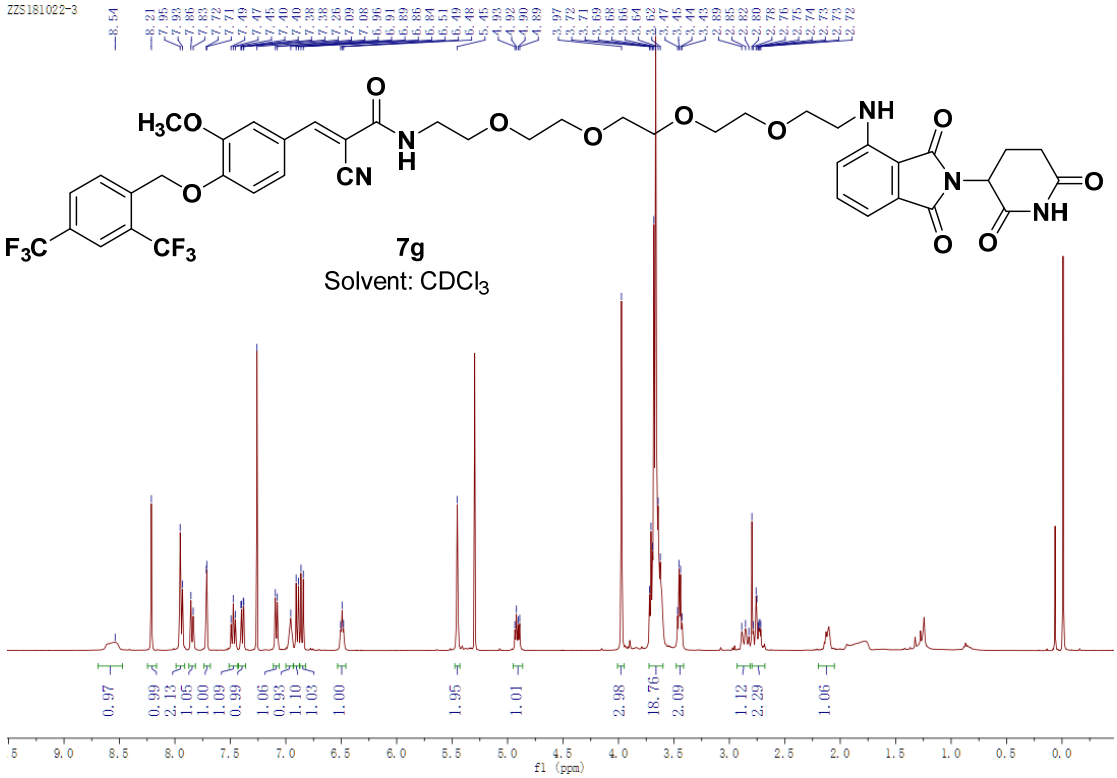

7d
Solvent: CDCl3
f1 (ppm)

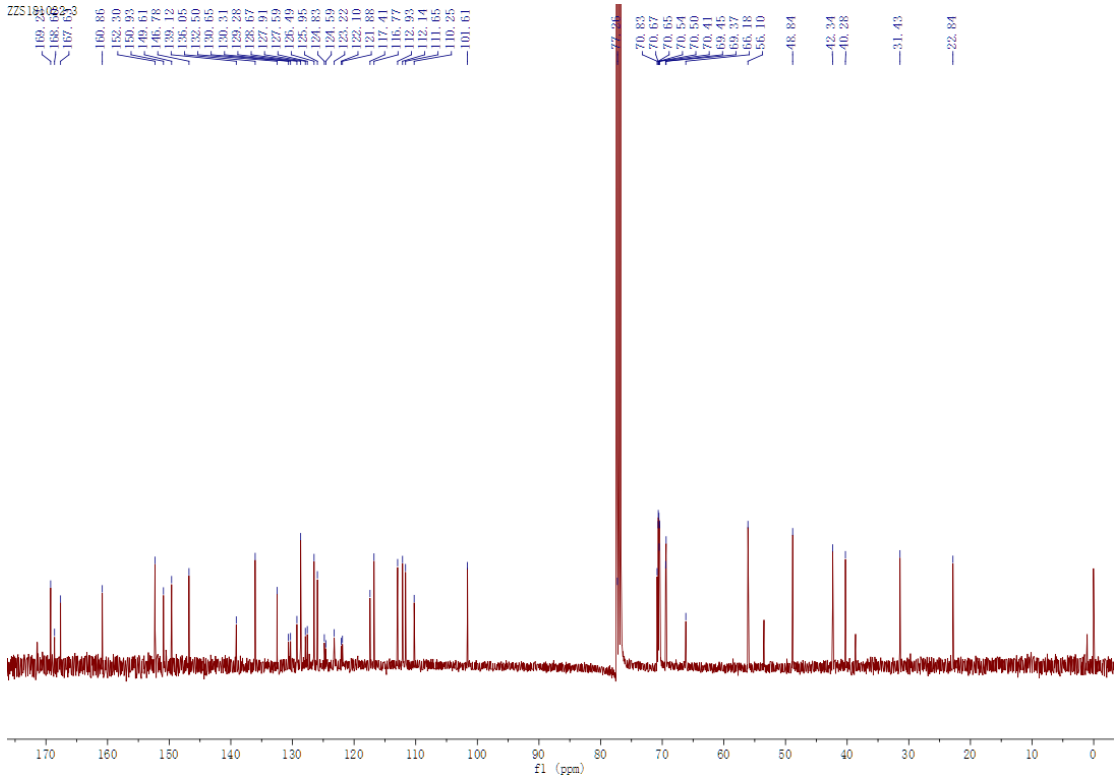

f1 (ppm)

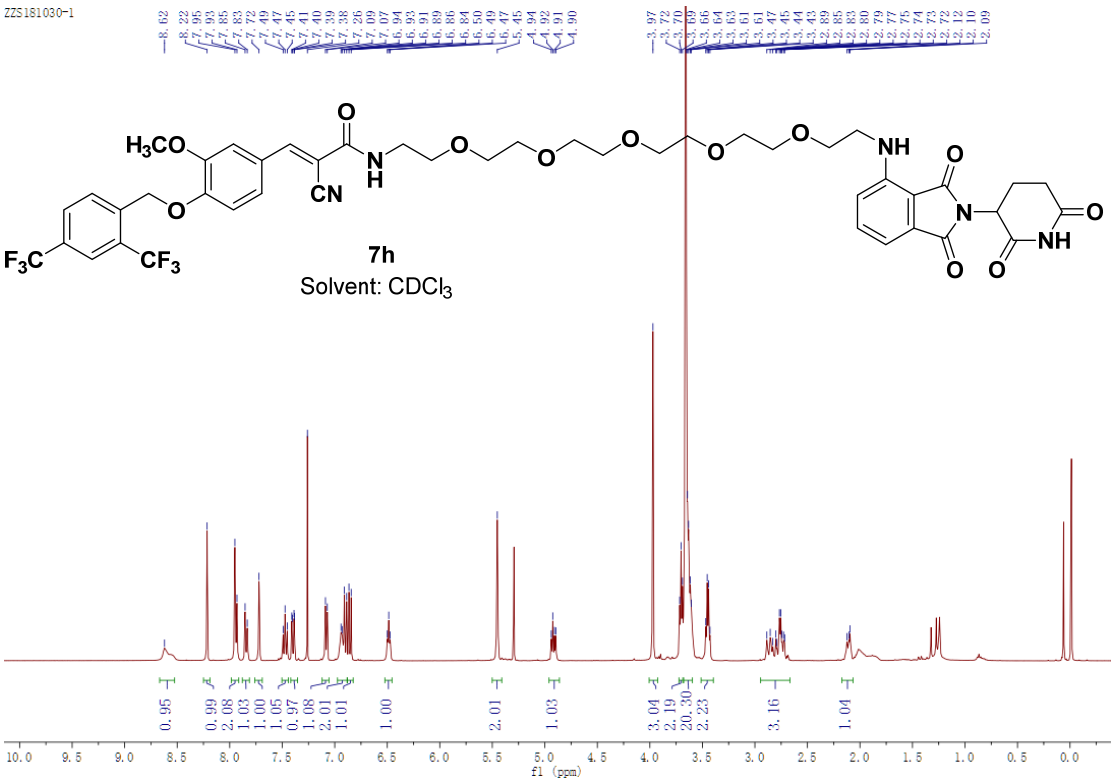

ZZS181030-3
7e
Solvent: CDCl3
f1 (ppm)
f1 (ppm)

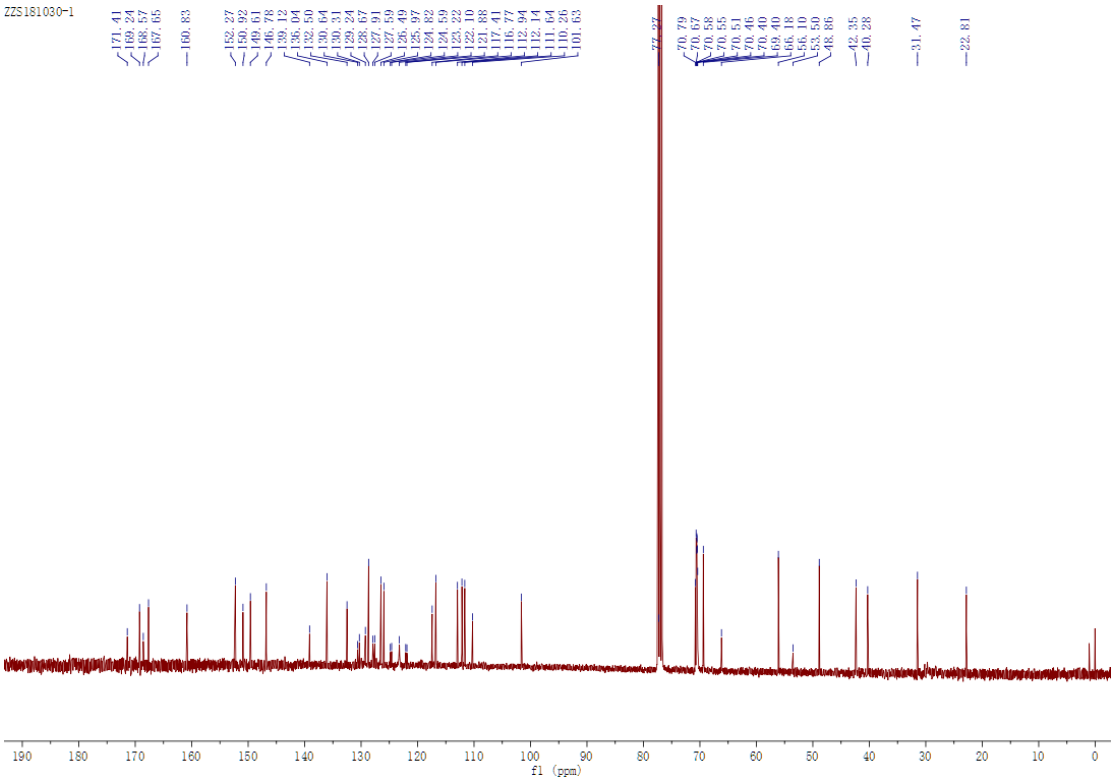

7f
Solvent: CDCl3

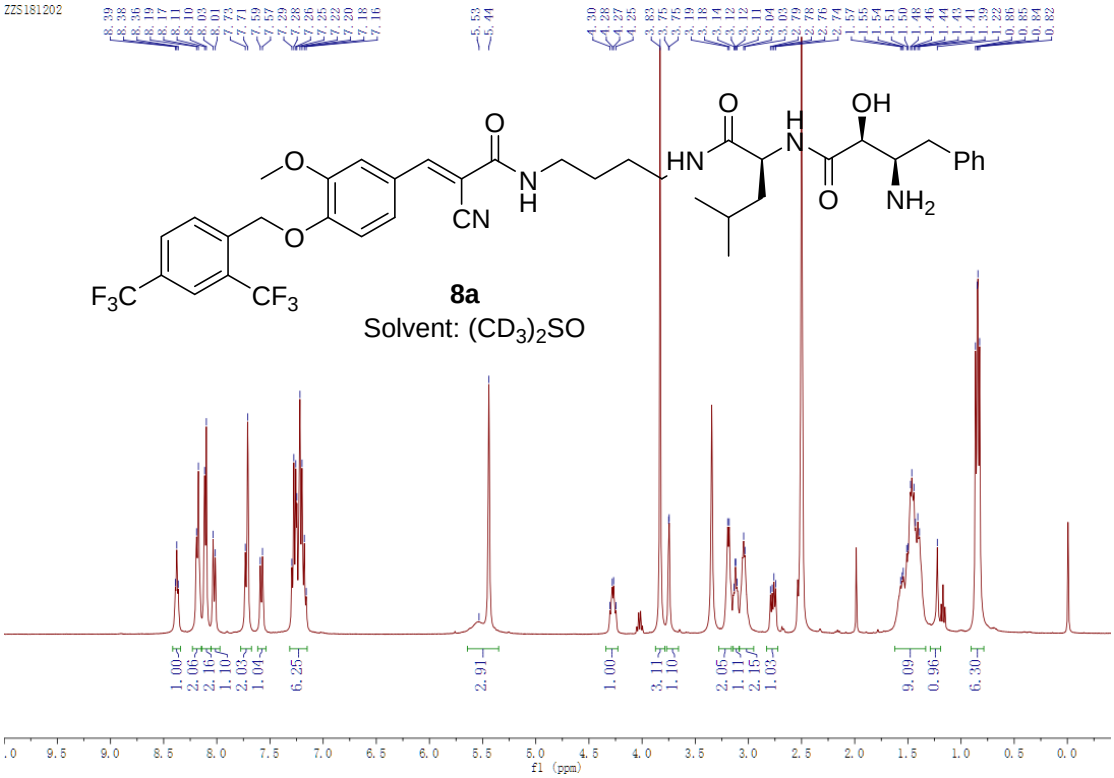


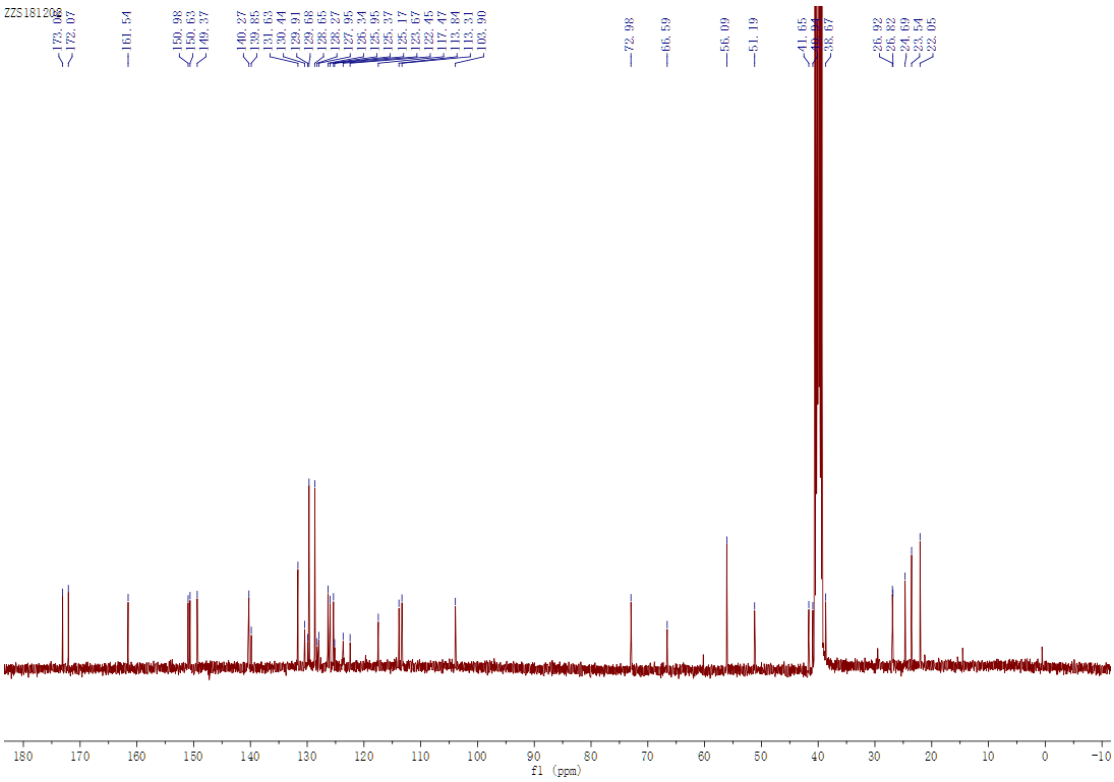

ZZS181022-3
7g
Solvent: CDCl3
f1 (ppm)

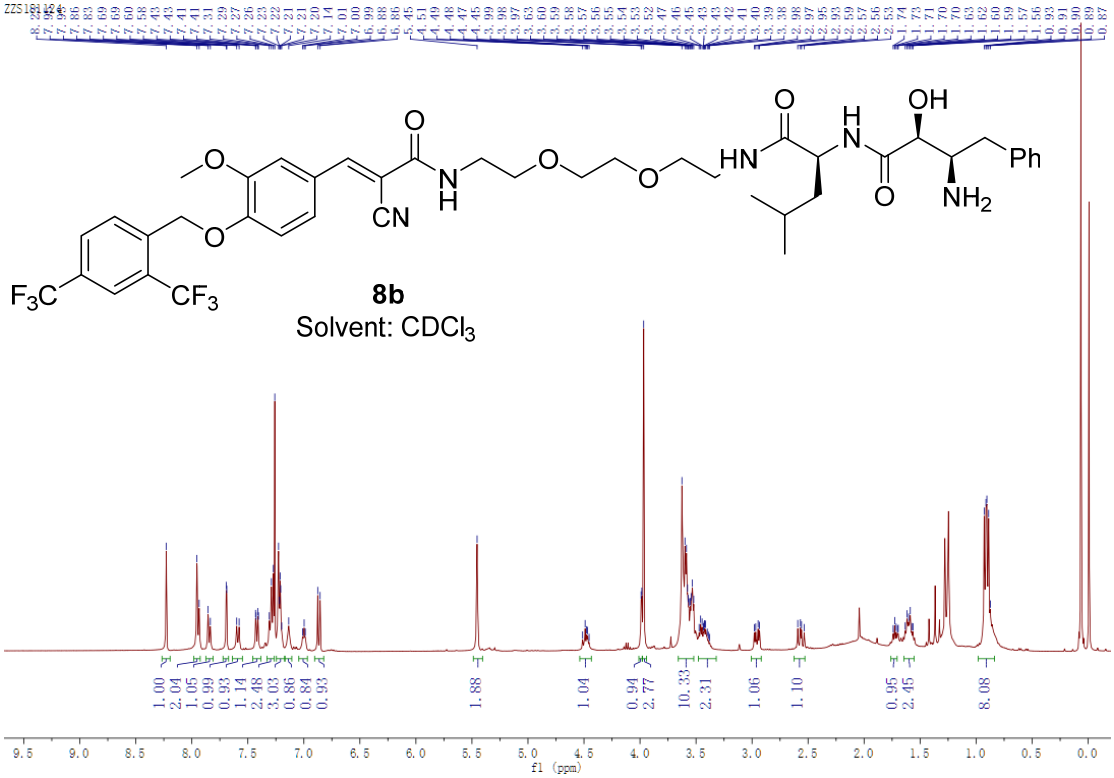

f1 (ppm)

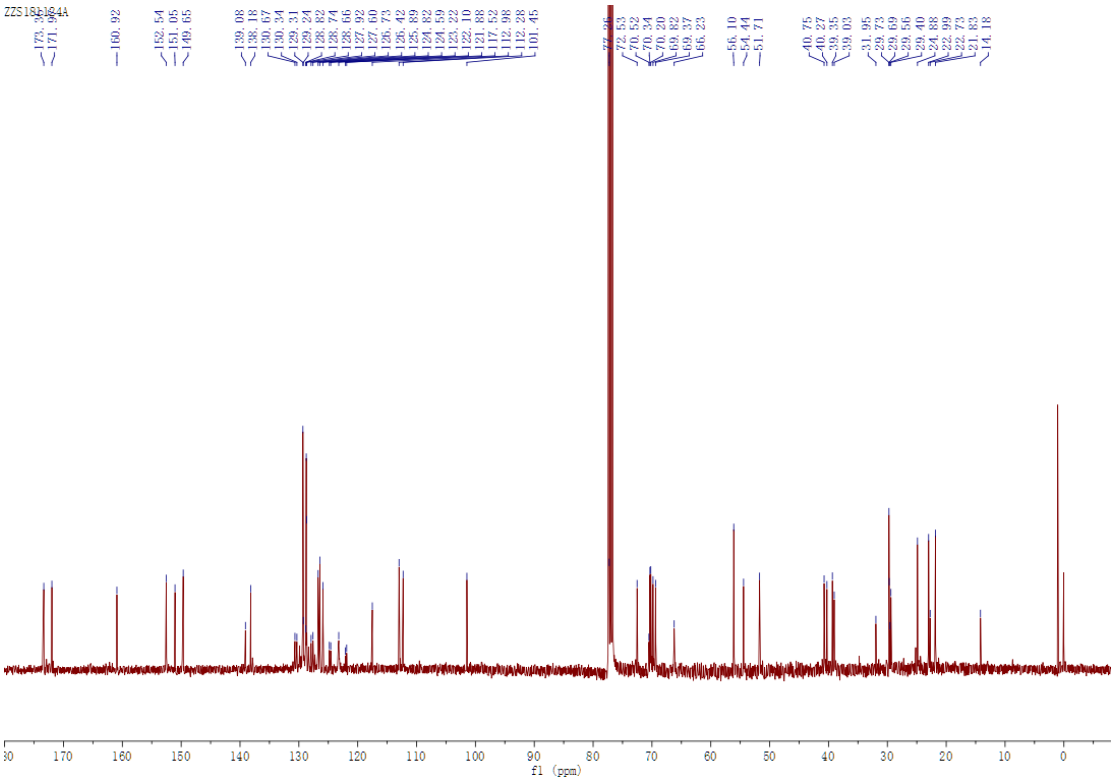

ZZS181030-1
7h
Solvent: CDCl3
f1 (ppm)

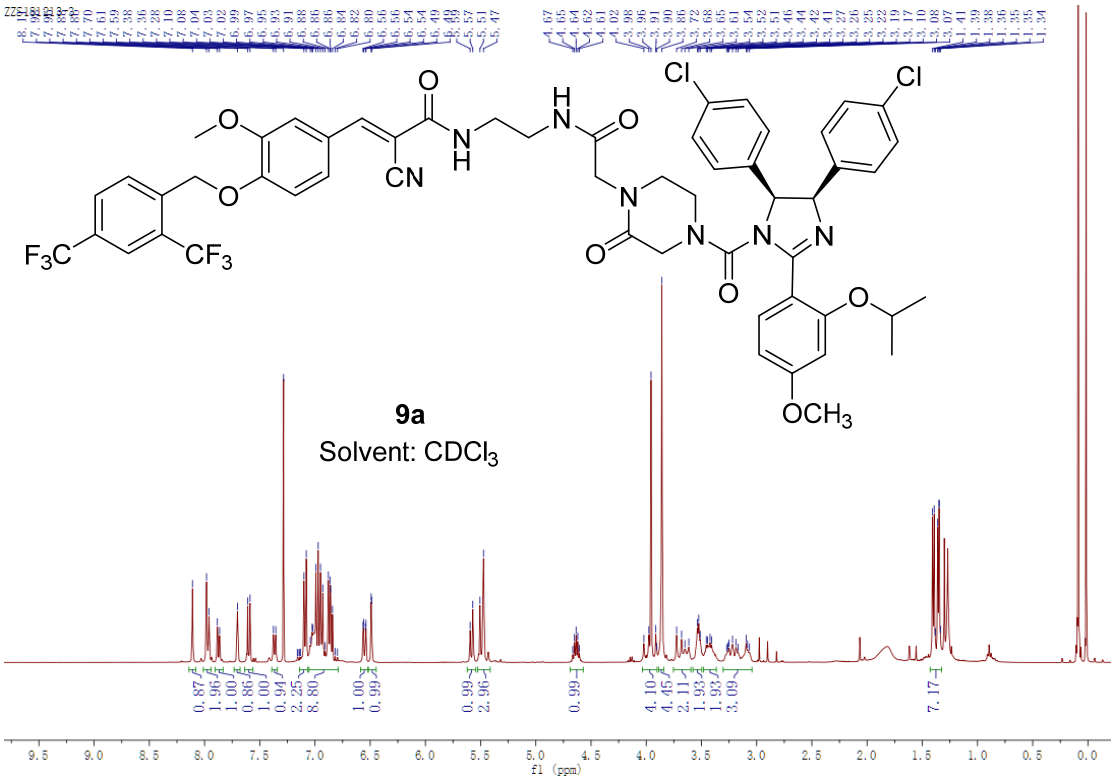

ZZS181030-1
f1 (ppm)

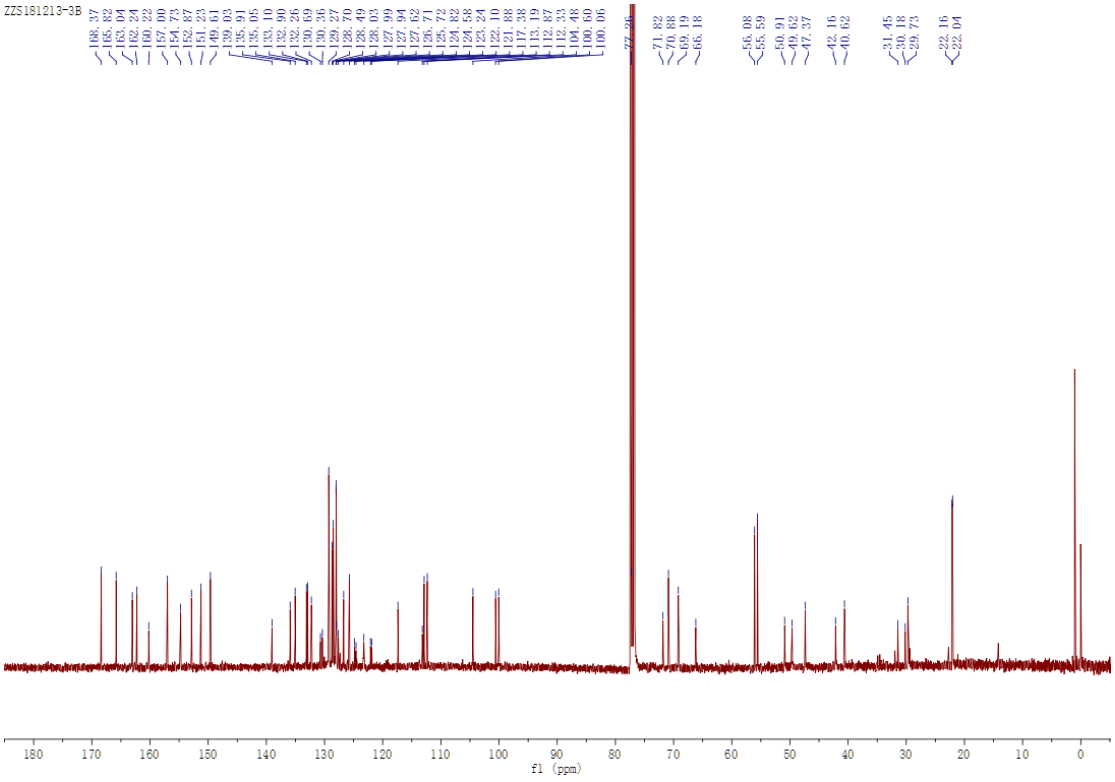

ZZS181202
8a
Solvent: (CD3)2SO
f1 (ppm)

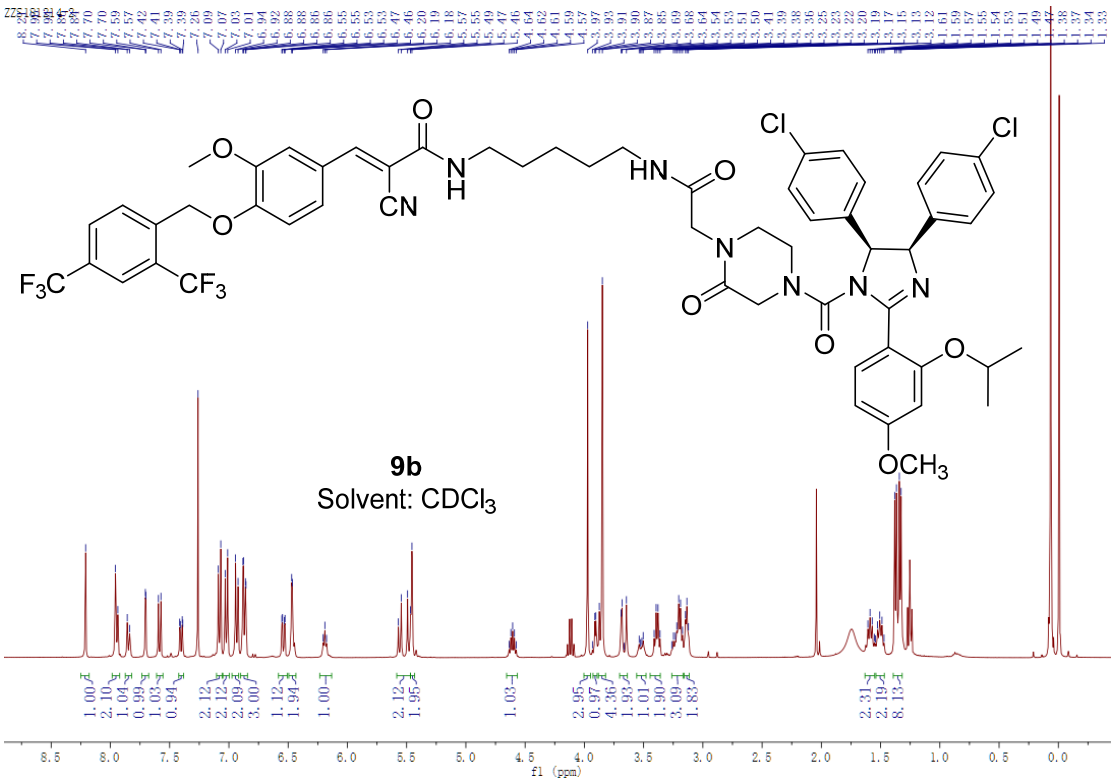

ZZS181203
f1 (ppm)

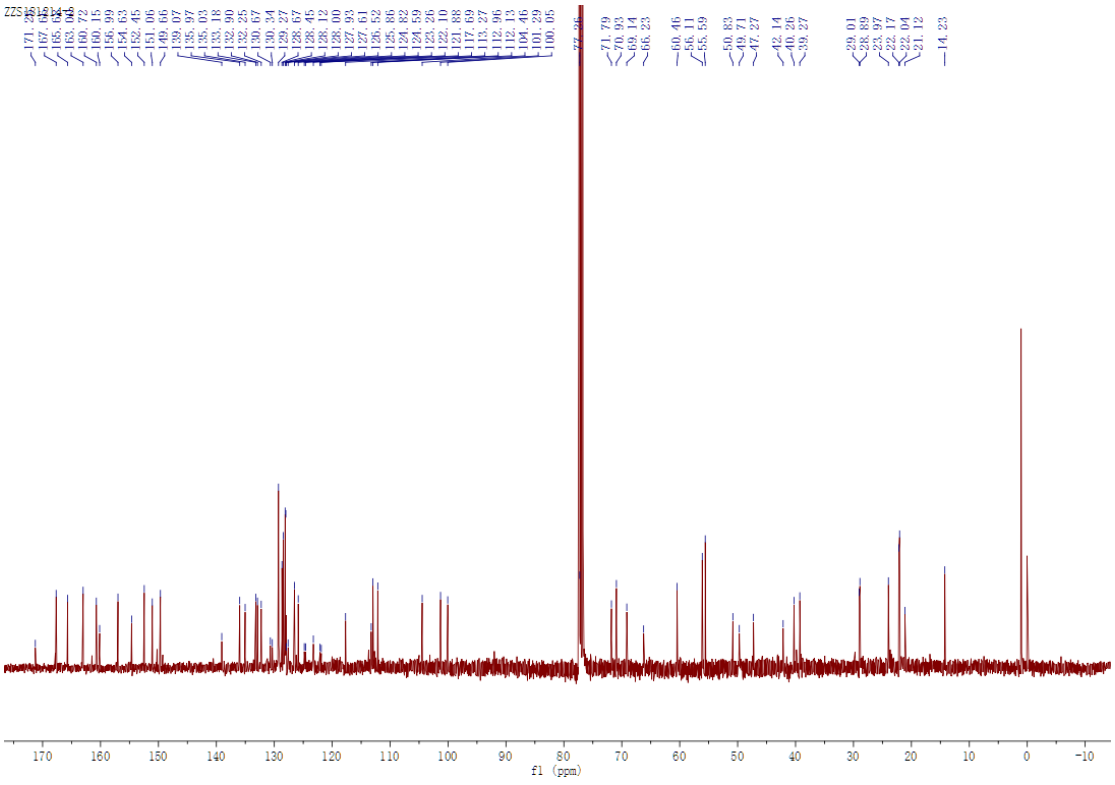

8b
Solvent: CDCl3




9a
Solvent: CDCl3

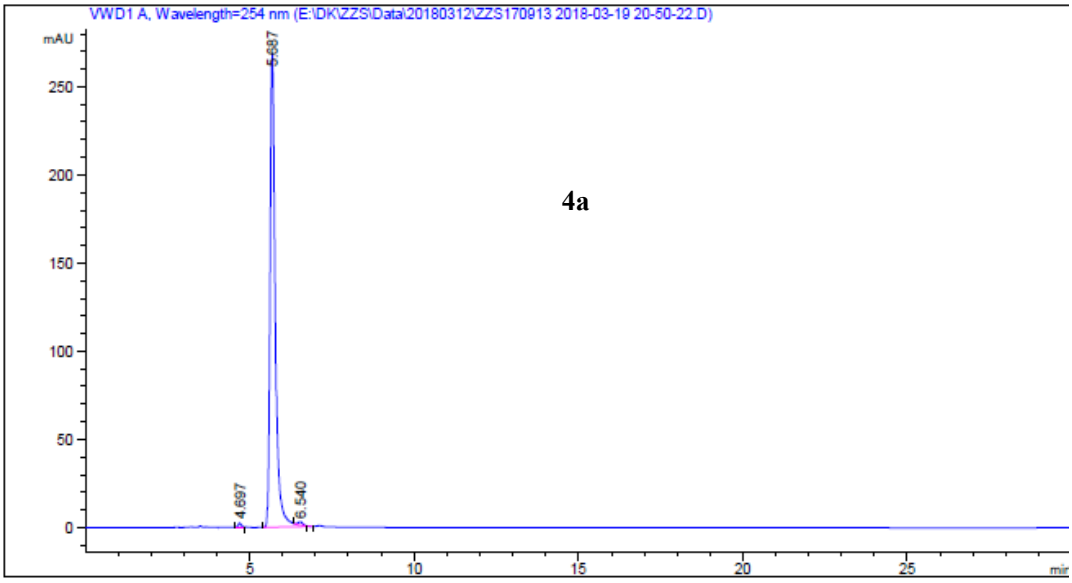



9b
Solvent: CDCl3



7. HPLC Purity Analysis

```
Acq. Operator   : 系统
Sample Operator : 系统
Acq. Instrument : 1260LC                          Location :   1
Injection Date  : 19/03/2018 20:51:01
                                                  Inj Volume : 5.000 µl
Acq. Method     : E:\DK\TL\方法90C-10A-30min-1u.M
Last changed    : 04/07/2017 19:18:29 by 系统
Analysis Method : E:\DK\ZHANGXIN\METHOD\80C-20A-30min-10uL.M
Last changed    : 08/02/2018 16:13:05 by 系统
```



4a

```
=====================================================================
                      Area Percent Report
=====================================================================

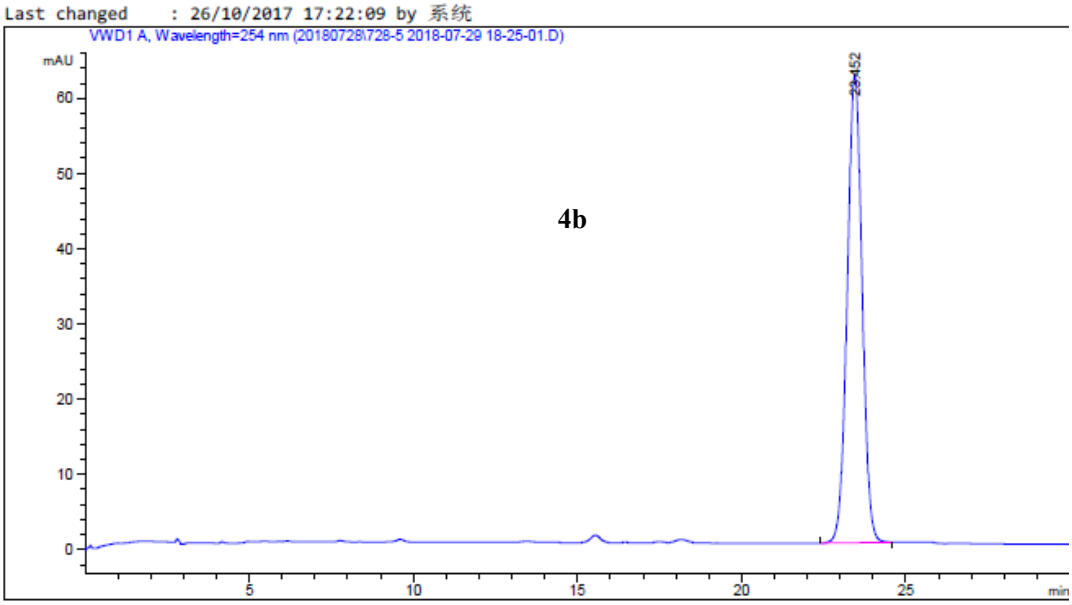
Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Sample Amount:                :     20.00000  [ng/ul]    (not used in calc.)
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=254 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   4.697 BB    0.1081   14.75901    2.14892   0.4868
   2   5.687 BV R  0.1663 2999.98804  268.59540  98.9425
   3   6.540 VB E  0.1392   17.30550    1.91996   0.5708

Totals :                  3032.05255  272.66428
```

Acq. Operator : 系统
Sample Operator : 系统
Acq. Instrument : 1260LC Location : 1
Injection Date : 29/07/2018 18:25:41
Inj Volume : 5.000 µl
Method : E:\DK\TL\方法\80C-20A-30min-1u.M
Last changed : 26/10/2017 17:22:09 by 系统



4b

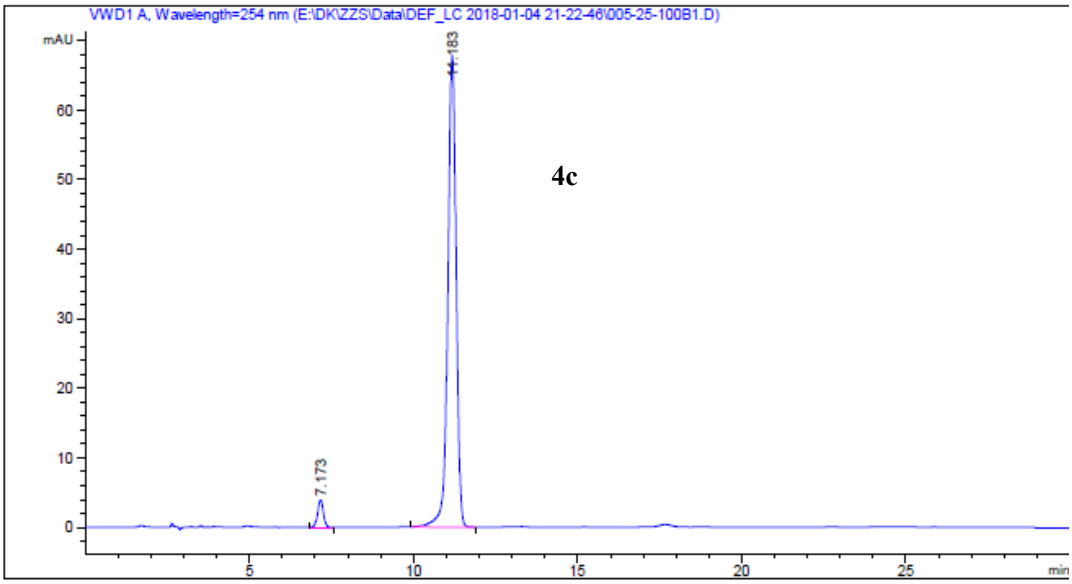
Area Percent Report

Sorted By : Signal
Multiplier : 2.0000
Dilution : 1.0000
Sample Amount: : 10.00000 [ng/ul] (not used in calc.)
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	23.452	BB	0.4904	1959.64551	62.05481	100.0000
Totals :				1959.64551	62.05481	

```
Acq. Operator   : 系统                          Seq. Line :   5
Acq. Instrument : 1260LC                        Location :   25
Injection Date  : 04/01/2018 23:46:39               Inj :   1
                                              Inj Volume : 5.000 µl
Different Inj Volume from Sample Entry!  Actual Inj Volume : 10.000 µl
Method          : E:\DK\ZZS\Data\DEF_LC 2018-01-04 21-22-46\80C-20D-30min-1u.M (Sequence
                  Method)
Last changed    : 04/01/2018 21:22:46 by 系统
```




```
=====================================================================
                        Area Percent Report
=====================================================================

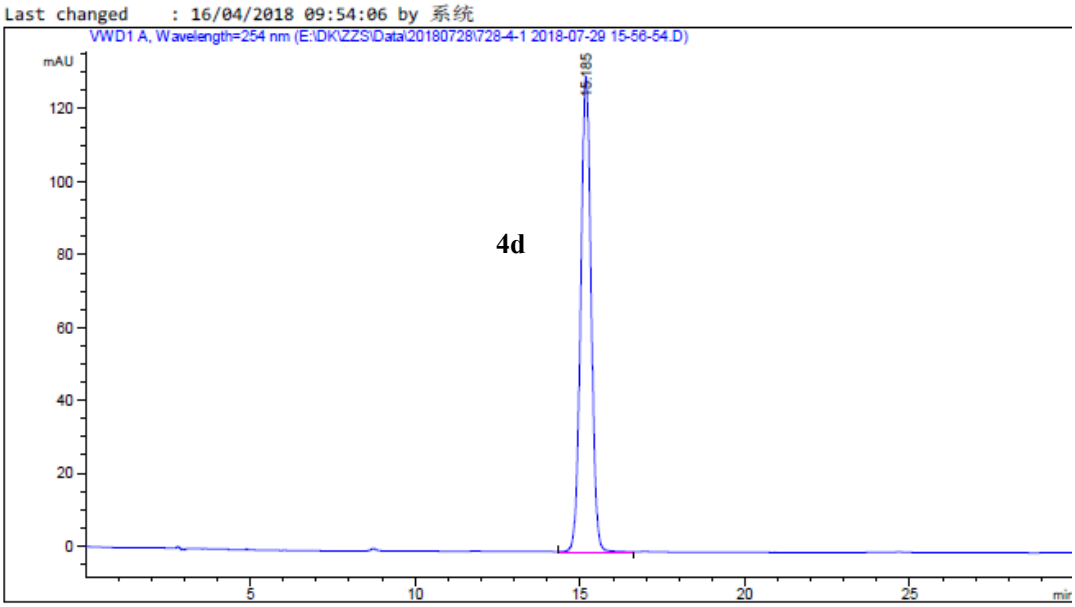
Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=254 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   7.173 BB    0.1876   47.33358   3.89890   3.7951
   2  11.183 BB    0.2715 1199.90393   67.78896  96.2049

Totals :                  1247.23751   71.68786
```

Acq. Operator : 系统
Sample Operator : 系统
Acq. Instrument : 1260LC Location : 1
Injection Date : 29/07/2018 15:57:34
Inj Volume : 5.000 µl
Acq. Method : E:\DK\TL\方法\80C-20A-30min-1u.M
Last changed : 26/10/2017 17:22:09 by 系统
Analysis Method : E:\DK\ZHANGXIN\METHOD\100C-60min-5uL.M
Last changed : 16/04/2018 09:54:06 by 系统



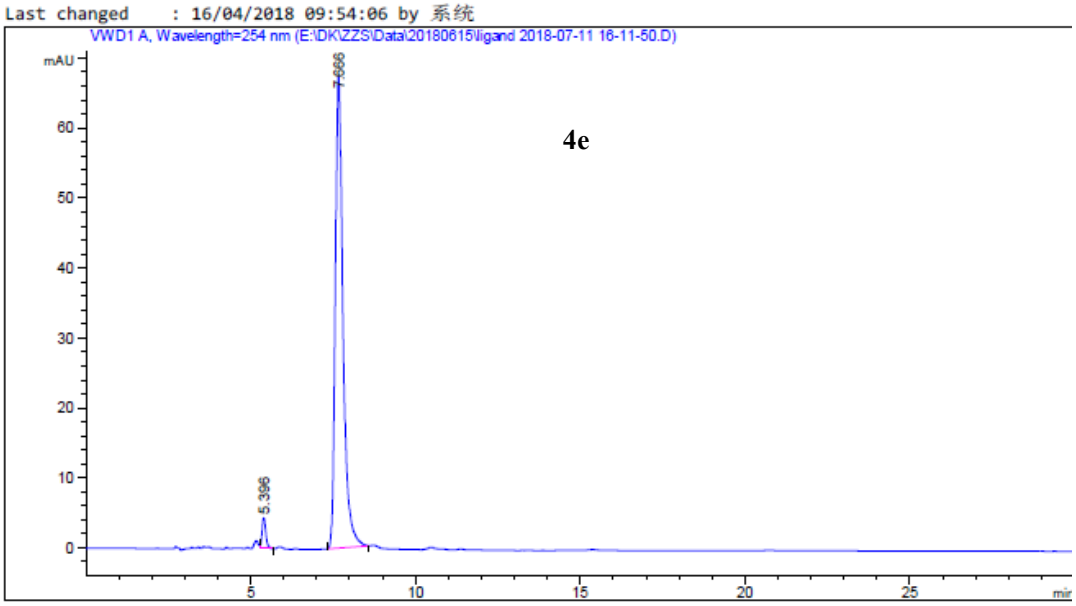
Area Percent Report

Sorted By : Signal
Multiplier : 2.0000
Dilution : 1.0000
Sample Amount: : 10.00000 [ng/ul] (not used in calc.)
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.185	BB	0.3407	2871.36914	130.50970	100.0000
Totals :				2871.36914	130.50970	

Acq. Operator : 系统
Sample Operator : 系统
Acq. Instrument : 1260LC Location : 2
Injection Date : 11/07/2018 16:12:32
Inj Volume : 5.000 µl
Acq. Method : E:\DK\TL\方法\85C-15A-30min-1u.M
Last changed : 09/12/2017 11:38:08 by 系统
Analysis Method : E:\DK\ZHANGXIN\METHOD\100C-60min-5uL.M
Last changed : 16/04/2018 09:54:06 by 系统



4e

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Area Percent Report

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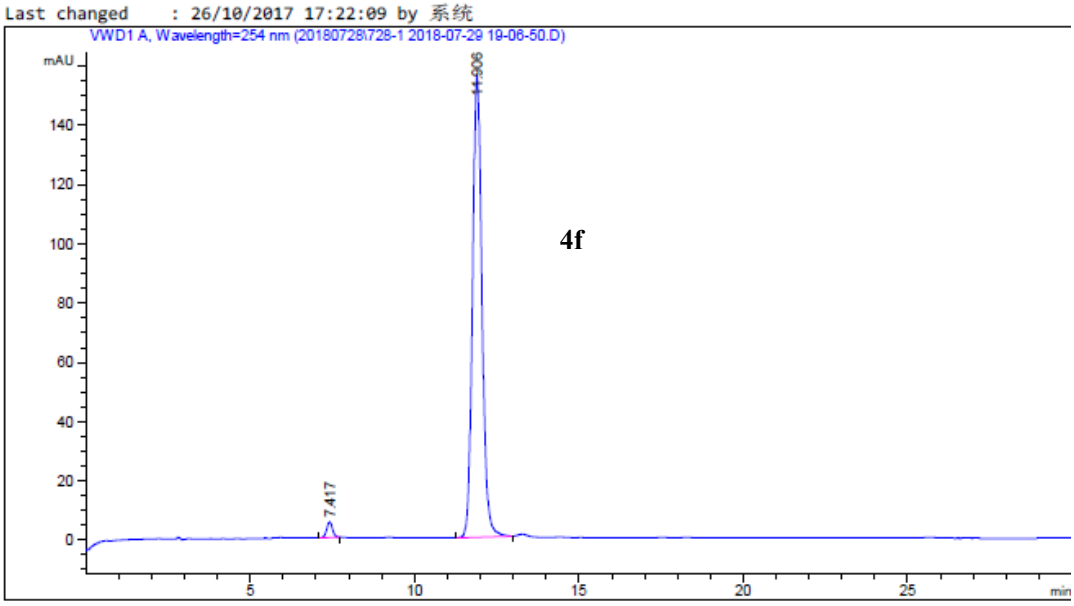
Sorted By : Signal
Multiplier : 2.0000
Dilution : 1.0000
Sample Amount: : 10.00000 [ng/ul] (not used in calc.)
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.396	VB	0.1240	35.84205	4.40191	3.1504
2	7.666	BB	0.2443	1101.84070	67.53761	96.8496
Totals :				1137.68275	71.93952	

Acq. Operator : 系统
Sample Operator : 系统
Acq. Instrument : 1260LC Location : 1
Injection Date : 29/07/2018 19:07:33
Inj Volume : 5.000 µl
Method : E:\DK\TL\方法\80C-20A-30min-1u.M
Last changed : 26/10/2017 17:22:09 by 系统



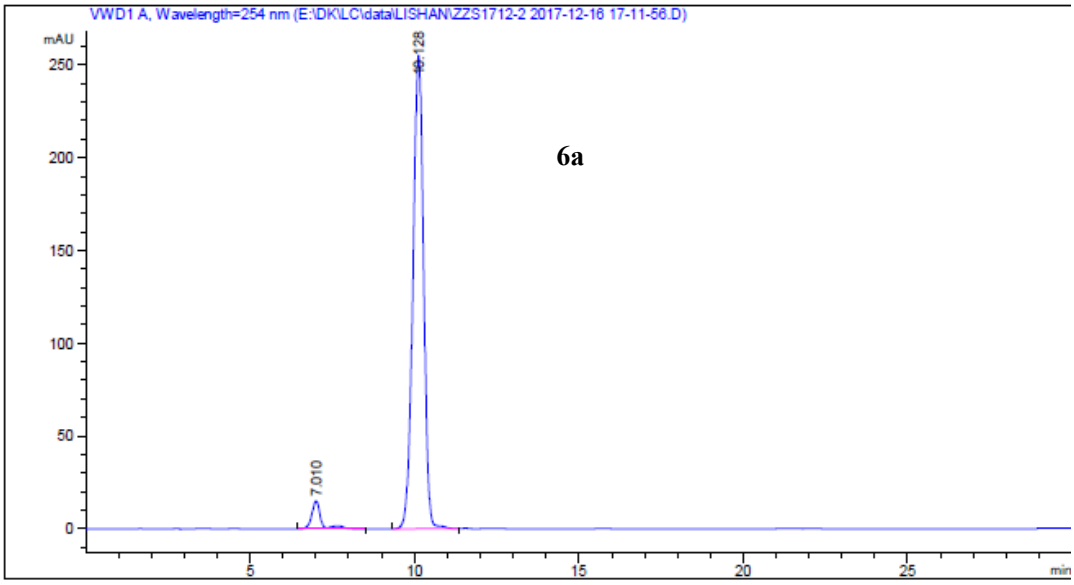
Area Percent Report

Sorted By : Signal
Multiplier : 2.0000
Dilution : 1.0000
Sample Amount: : 10.00000 [ng/ul] (not used in calc.)
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.417	BB	0.1917	64.96856	5.27423	2.0405
2	11.906	BB	0.3076	3119.06226	155.77315	97.9595
Totals :				3184.03082	161.04737	

```
Acq. Operator   : 系统
Sample Operator : 系统
Acq. Instrument : 1260LC                          Location :   2
Injection Date  : 16/12/2017 17:12:35
                                                  Inj Volume : 5.000 µl
Acq. Method     : E:\DK\TL\方法85C-15A-30min-1u.M
Last changed    : 16/12/2017 16:37:44 by 系统
                  (modified after loading)
Analysis Method : E:\DK\TL\方法80C-20D-30min-1u.M
Last changed    : 04/07/2017 21:08:28 by 系统
```



6a

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==================================================================
                      Area Percent Report
==================================================================

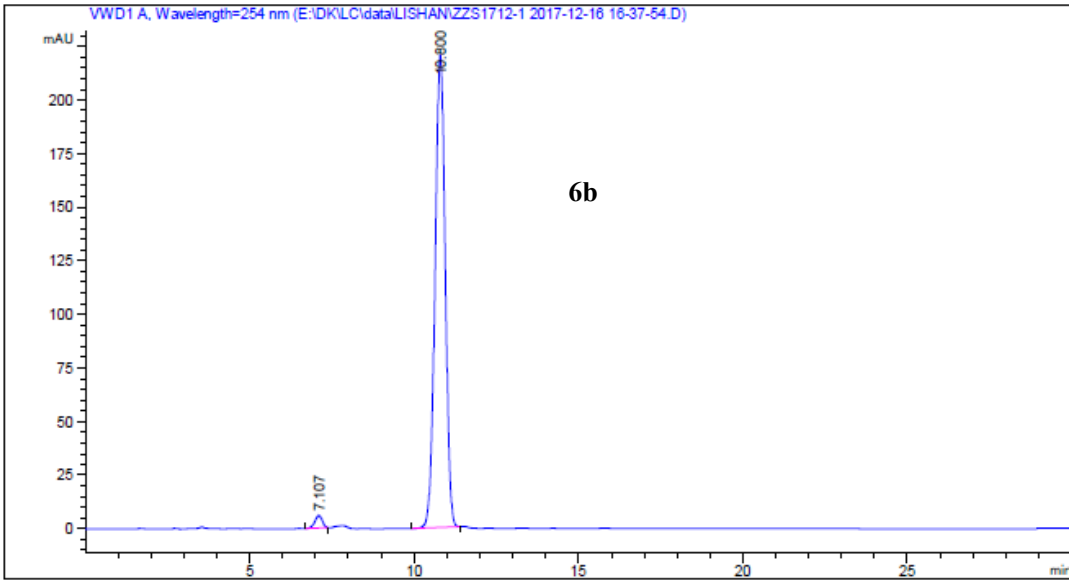
Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Sample Amount:        :     20.00000  [ng/ul]    (not used in calc.)
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=254 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   7.010 BV R  0.2868  291.56857   15.06461   4.8314
   2  10.128 BB    0.3495 5743.27344  255.25952  95.1686

Totals :                  6034.84201  270.32413
```

Acq. Operator : 系统
Sample Operator : 系统
Acq. Instrument : 1260LC Location : 1
Injection Date : 16/12/2017 16:38:38
Inj Volume : 5.000 µl
Acq. Method : E:\DK\TL\方法85C-15A-30min-1u.M
Last changed : 16/12/2017 16:37:44 by 系统
(modified after loading)
Analysis Method : E:\DK\TL\方法80C-20D-30min-1u.M
Last changed : 04/07/2017 21:08:28 by 系统



6b

==========
Area Percent Report
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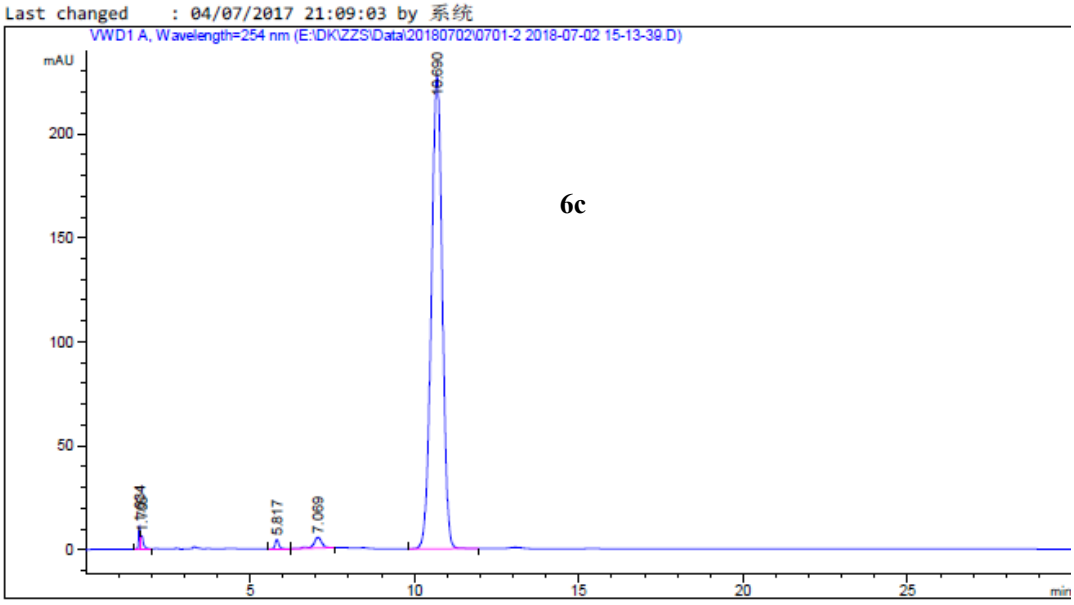
Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Sample Amount: : 20.00000 [ng/ul] (not used in calc.)
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.107	BB	0.2432	90.29964	5.78235	1.8698
2	10.800	BB	0.3346	4739.15674	220.60747	98.1302
Totals :				4829.45638	226.38982	

Acq. Operator : 系统
Sample Operator : 系统
Acq. Instrument : 1260LC Location : 1
Injection Date : 02/07/2018 15:14:23
Inj Volume : 5.000 µl
Acq. Method : E:\DK\TL\方法\85C-15A-30min-1u.M
Last changed : 09/12/2017 11:38:08 by 系统
Analysis Method : E:\DK\TL\方法\85C-15D-30min-1u.M
Last changed : 04/07/2017 21:09:03 by 系统



6c

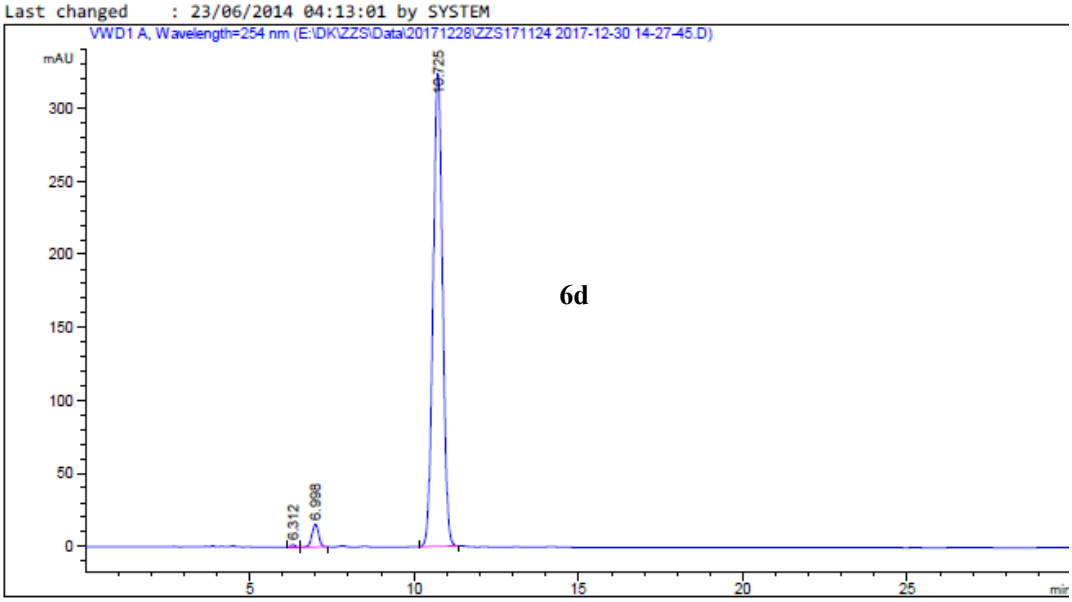
Area Percent Report

Sorted By : Signal
Multiplier : 2.0000
Dilution : 1.0000
Sample Amount: : 10.00000 [ng/ul] (not used in calc.)
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.634	BV	0.0565	42.81990	11.22754	0.7857
2	1.705	VB	0.0735	32.30190	6.33572	0.5927
3	5.817	BB	0.1177	33.12532	4.30737	0.6078
4	7.069	VB R	0.2545	87.76083	5.18298	1.6103
5	10.690	BB	0.3584	5253.95557	227.56870	96.4035
Totals :				5449.96352	254.62230	

Acq. Operator : 系统
Sample Operator : 系统
Acq. Instrument : 1260LC Location : 1
Injection Date : 30/12/2017 14:28:28
Inj Volume : 5.000 µl
Acq. Method : E:\DK\TL\方法\85C-15A-30min-1u.M
Last changed : 09/12/2017 11:38:08 by 系统
Analysis Method : C:\Chem32\1\Methods\DEF_LC.M
Last changed : 23/06/2014 04:13:01 by SYSTEM



6d

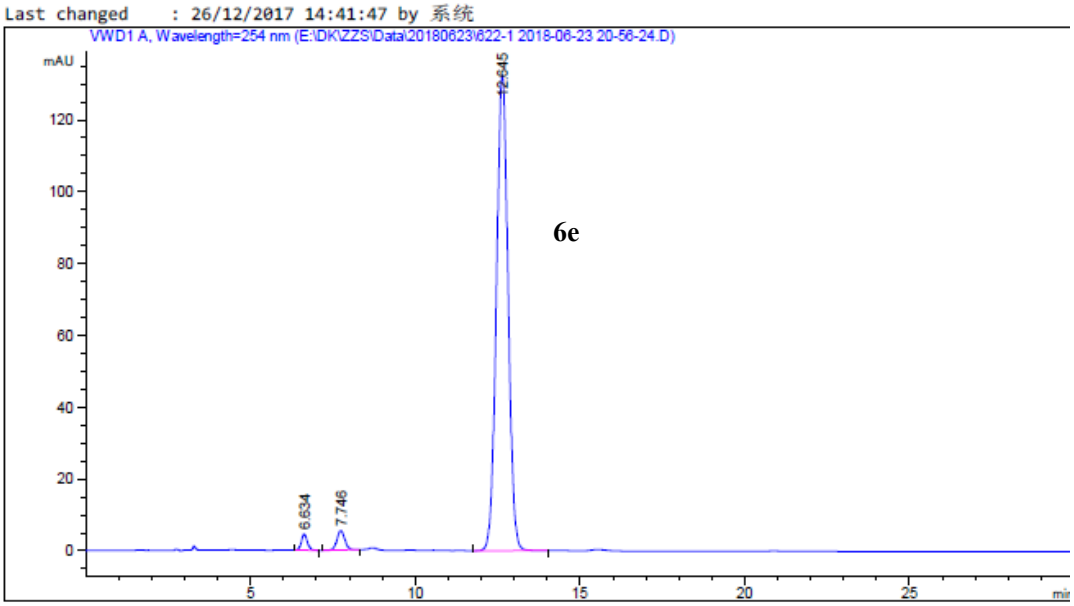
Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Sample Amount: : 20.00000 [ng/ul] (not used in calc.)
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.312	BB	0.1175	13.81890	1.82117	0.2051
2	6.998	BB	0.2183	219.65315	15.69065	3.2606
3	10.725	BB	0.3122	6503.16846	323.95517	96.5343
Totals :				6736.64051	341.46699	

Acq. Operator : 系统
Sample Operator : 系统
Acq. Instrument : 1260LC Location : 1
Injection Date : 23/06/2018 20:57:08
Inj Volume : 5.000 µl
Acq. Method : E:\DK\TL\方法\85C-15A-30min-1u.M
Last changed : 09/12/2017 11:38:08 by 系统
Analysis Method : E:\DK\ZHANGXIN\METHOD\90C-10D-30min-10uL.M
Last changed : 26/12/2017 14:41:47 by 系统



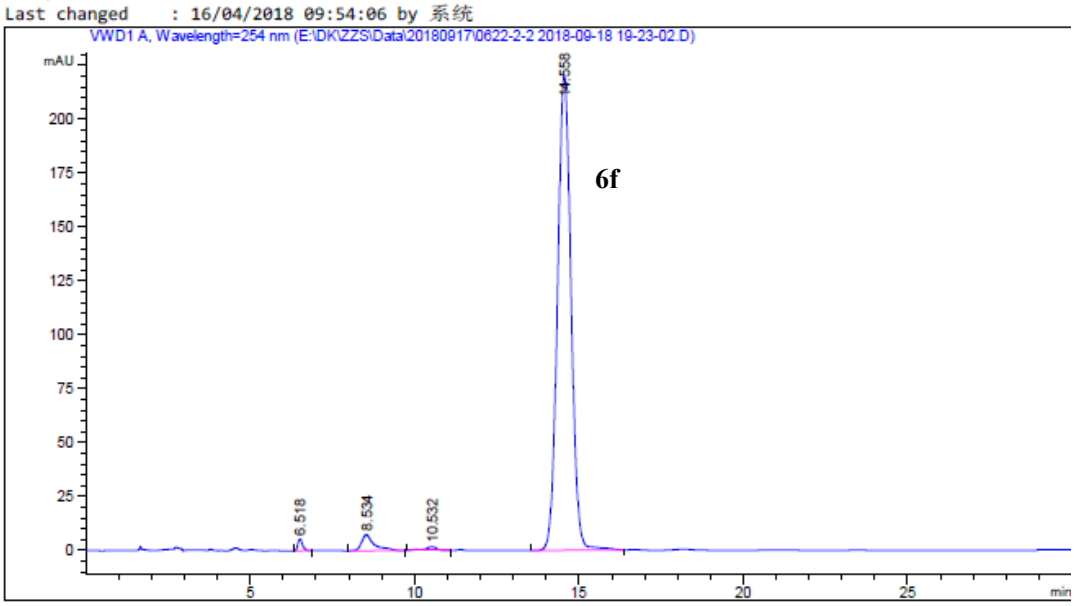
Area Percent Report

Sorted By : Signal
Multiplier : 2.0000
Dilution : 1.0000
Sample Amount: : 10.00000 [ng/ul] (not used in calc.)
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.634	BB	0.1931	55.10929	4.40067	1.6181
2	7.746	BB	0.2527	87.93238	5.38062	2.5819
3	12.645	BB	0.3829	3262.68750	132.23456	95.8000
Totals :				3405.72917	142.01585	

Acq. Operator : 系统
Sample Operator : 系统
Acq. Instrument : 1260LC Location : 1
Injection Date : 18/09/2018 19:23:55
Inj Volume : 50.000 µl
Acq. Method : E:\DK\TL\方法\85C-15A-30min-1u.M
Last changed : 18/09/2018 19:22:59 by 系统
(modified after loading)
Analysis Method : E:\DK\ZHANGXIN\METHOD\100C-60min-5uL.M
Last changed : 16/04/2018 09:54:06 by 系统



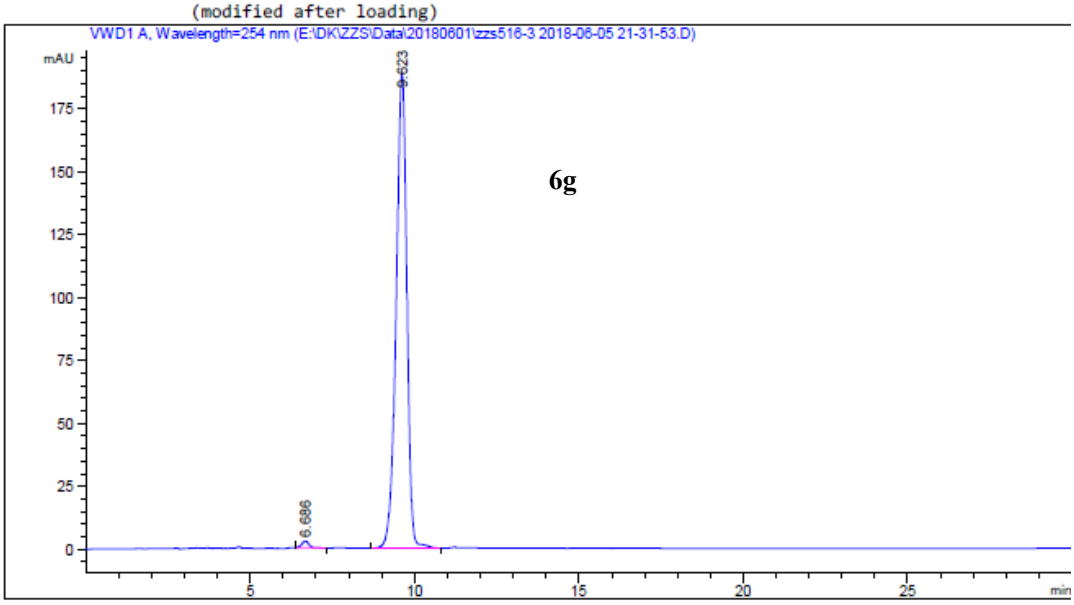
Area Percent Report

Sorted By : Signal
Multiplier : 2.0000
Dilution : 1.0000
Sample Amount: : 10.00000 [ng/ul] (not used in calc.)
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.518	BB	0.1516	52.30556	5.32589	0.7942
2	8.534	BB	0.3748	192.24989	7.35789	2.9192
3	10.532	BB	0.3736	44.99976	1.71258	0.6833
4	14.558	BB	0.4452	6296.18457	219.80826	95.6033
Totals :				6585.73978	234.20462	

Acq. Operator : 系统
Sample Operator : 系统
Acq. Instrument : 1260LC Location : 1
Injection Date : 05/06/2018 21:32:32
Inj Volume : 5.000 µl
Acq. Method : E:\DK\TL\方法\85C-15A-30min-1u.M
Last changed : 09/12/2017 11:38:08 by 系统
Analysis Method : E:\DK\TL\方法\90C-10A-30min-1u.M
Last changed : 28/07/2018 18:29:28 by 系统
(modified after loading)



6g

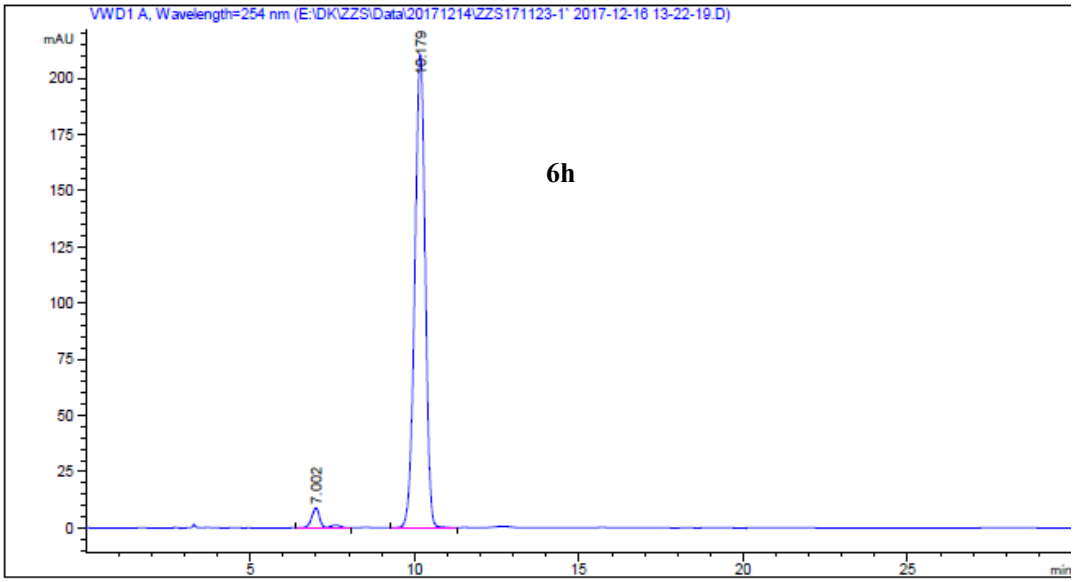
Area Percent Report

Sorted By : Signal
Multiplier : 2.0000
Dilution : 1.0000
Sample Amount: : 5.00000 [ng/ul] (not used in calc.)
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.686	BB	0.2267	38.90159	2.62779	0.9077
2	9.623	BB	0.3455	4246.87061	188.03697	99.0923
Totals :				4285.77220	190.66476	

Acq. Operator : 系统
Sample Operator : 系统
Acq. Instrument : 1260LC Location : 1
Injection Date : 16/12/2017 13:23:00
Inj Volume : 5.000 µl
Acq. Method : E:\DK\TL\方法85C-15A-30min-1u.M
Last changed : 09/12/2017 11:38:08 by 系统
Analysis Method : E:\DK\TL\方法80C-20D-30min-1u.M
Last changed : 04/07/2017 21:08:28 by 系统



6h

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Area Percent Report
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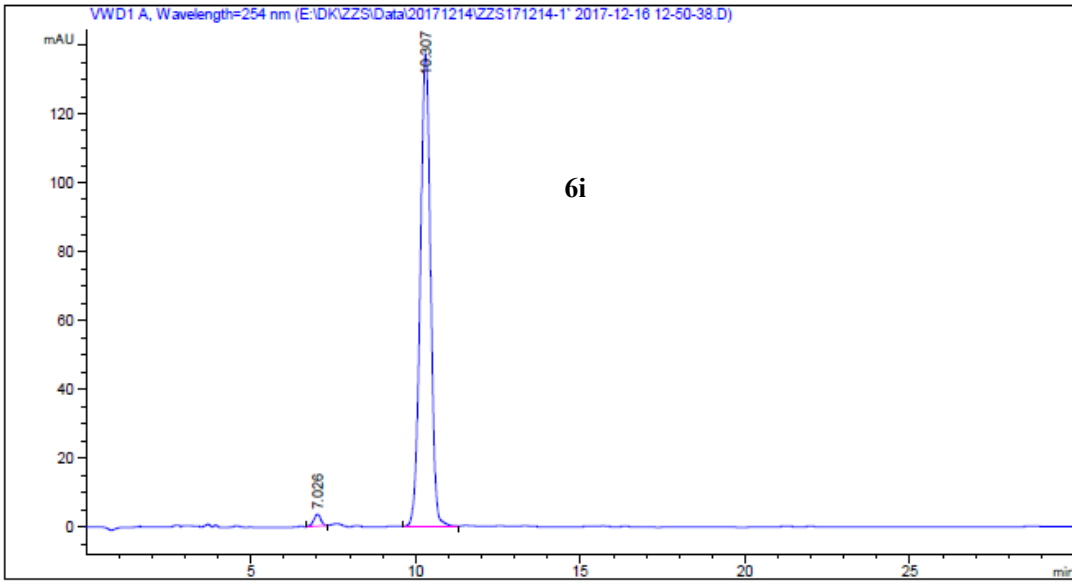
Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Sample Amount: : 5.00000 [ng/ul] (not used in calc.)
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.002	BV R	0.2873	174.79730	8.97302	3.6404
2	10.179	BB	0.3402	4626.79053	210.65396	96.3596
Totals :				4801.58783	219.62699	

Acq. Operator : 系统
Sample Operator : 系统
Acq. Instrument : 1260LC Location : 1
Injection Date : 16/12/2017 12:51:20
Inj Volume : 5.000 µl
Acq. Method : E:\DK\TL\方法85C-15A-30min-1u.M
Last changed : 09/12/2017 11:38:08 by 系统
Analysis Method : E:\DK\TL\方法80C-20D-30min-1u.M
Last changed : 04/07/2017 21:08:28 by 系统



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Area Percent Report

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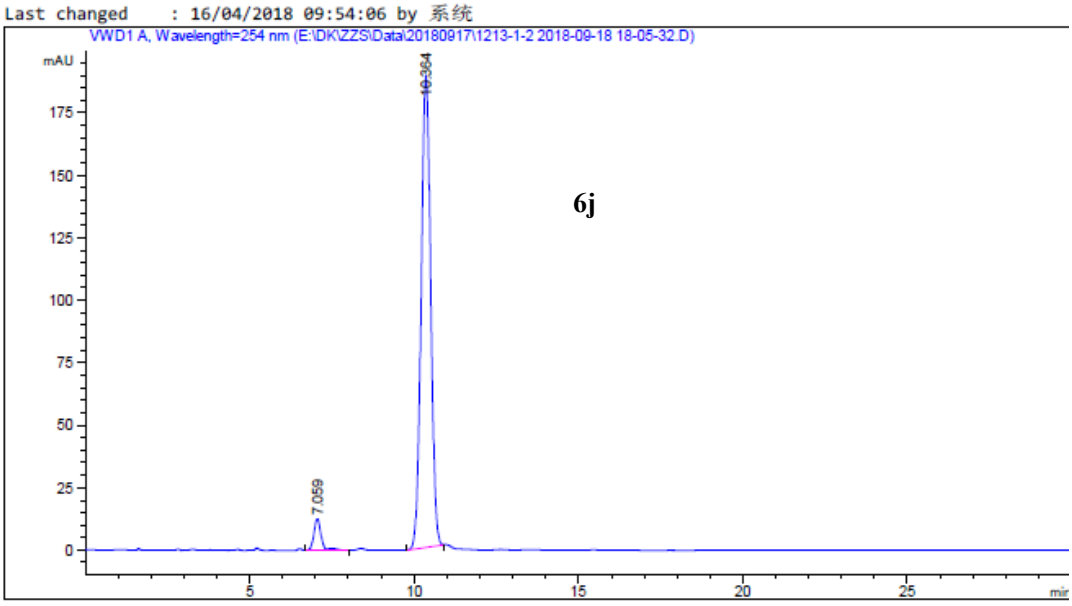
Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Sample Amount: : 5.00000 [ng/ul] (not used in calc.)
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.026	BB	0.2293	50.70133	3.43298	1.6766
2	10.307	BB	0.3361	2973.29468	137.07841	98.3234
Totals :				3023.99601	140.51139	

Acq. Operator : 系统
Sample Operator : 系统
Acq. Instrument : 1260LC Location : 1
Injection Date : 18/09/2018 18:06:12
Inj Volume : 5.000 µl
Acq. Method : E:\DK\TL\方法\85C-15A-30min-1u.M
Last changed : 09/12/2017 11:38:08 by 系统
Analysis Method : E:\DK\ZHANGXIN\METHOD\100C-60min-5uL.M
Last changed : 16/04/2018 09:54:06 by 系统



6j

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Area Percent Report

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Sorted By : Signal
Multiplier : 2.0000
Dilution : 1.0000
Sample Amount: : 10.00000 [ng/ul] (not used in calc.)
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.059	BV R	0.2372	195.99672	12.54745	4.9228
2	10.364	BB	0.3120	3785.39819	188.75014	95.0772
Totals :				3981.39491	201.29758	

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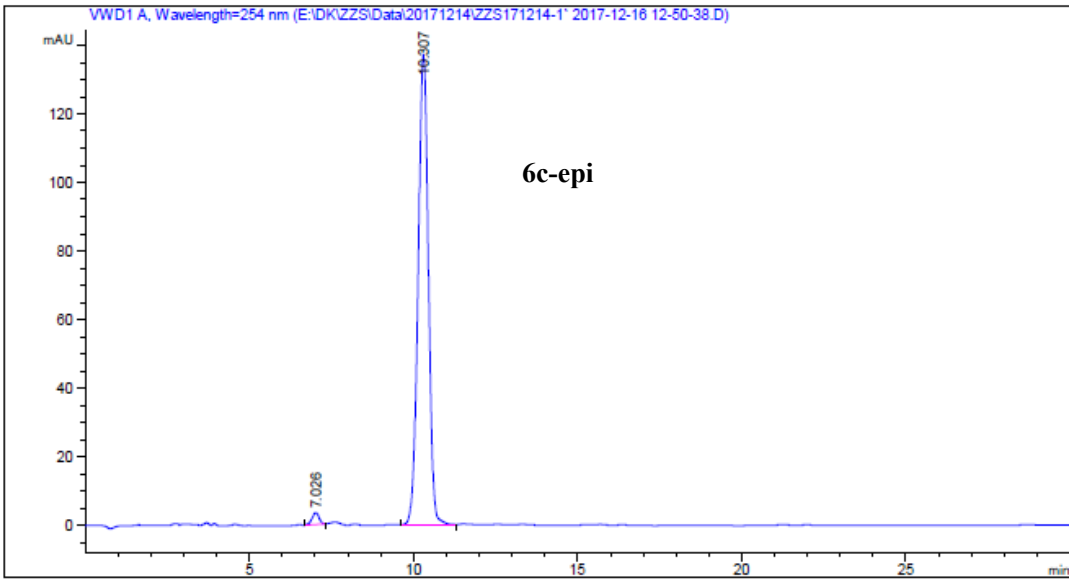
```
Acq. Operator   : 系统
Sample Operator : 系统
Acq. Instrument : 1260LC                          Location :   1
Injection Date  : 16/12/2017 12:51:20
                                                  Inj Volume : 5.000 µl
Acq. Method     : E:\DK\TL\方法85C-15A-30min-1u.M
Last changed    : 09/12/2017 11:38:08 by 系统
Analysis Method : E:\DK\TL\方法80C-20D-30min-1u.M
Last changed    : 04/07/2017 21:08:28 by 系统
```

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=====================================================================
                      Area Percent Report
=====================================================================

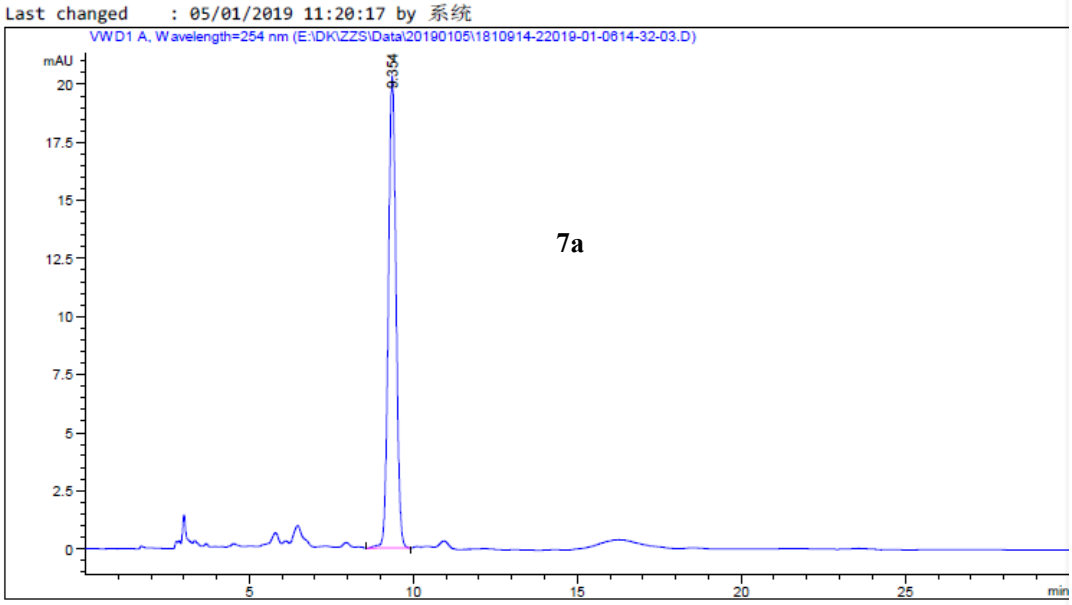
Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Sample Amount:                :      5.00000  [ng/ul]    (not used in calc.)
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=254 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   7.026 BB    0.2293   50.70133    3.43298   1.6766
   2  10.307 BB    0.3361 2973.29468  137.07841  98.3234

Totals :                  3023.99601  140.51139
```

Acq. Operator : 系统
Sample Operator : 系统
Acq. Instrument : 1260LC Location : 1
Injection Date : 06/01/2019 14:32:42
Inj Volume : 5.000 µl
Acq. Method : E:\DK\TL\方法\85C-15A-30min-1u.M
Last changed : 06/01/2019 14:31:40 by 系统
(modified after loading)
Analysis Method : E:\DK\SJY\METHOD\shuijiada.M
Last changed : 05/01/2019 11:20:17 by 系统



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Area Percent Report

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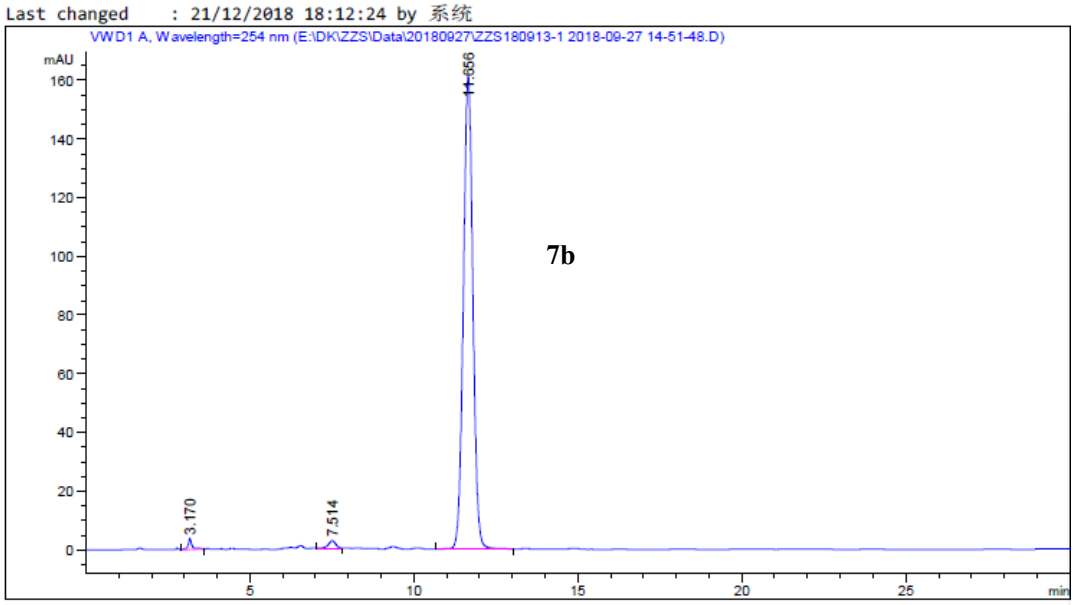
Sorted By : Signal
Multiplier : 2.0000
Dilution : 1.0000
Sample Amount: : 30.00000 [ng/ul] (not used in calc.)
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.354	BB	0.2526	329.94098	20.29972	100.0000
Totals :				329.94098	20.29972	

Acq. Operator : 系统
Sample Operator : 系统
Acq. Instrument : 1260LC Location : 1
Injection Date : 27/09/2018 14:52:31
Inj Volume : 5.000 µl
Acq. Method : E:\DK\TL\方法\85C-15A-30min-1u.M
Last changed : 09/12/2017 11:38:08 by 系统
Analysis Method : E:\DK\SJY\METHOD\XSXZ.M
Last changed : 21/12/2018 18:12:24 by 系统



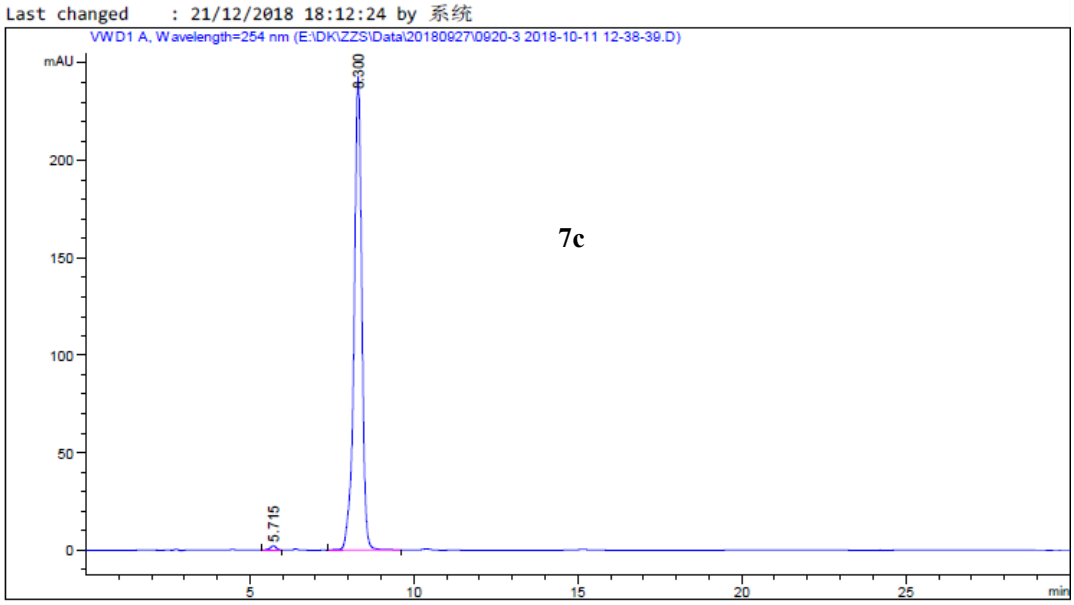
Area Percent Report

Sorted By : Signal
Multiplier : 2.0000
Dilution : 1.0000
Sample Amount: : 10.00000 [ng/ul] (not used in calc.)
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.170	BV R	0.1210	30.50074	3.59347	0.9150
2	7.514	BB	0.2307	38.92440	2.55482	1.1677
3	11.656	BB	0.3132	3263.93237	161.24055	97.9173
Totals :				3333.35751	167.38884	

Acq. Operator : 系统
Sample Operator : 系统
Acq. Instrument : 1260LC Location : 1
Injection Date : 11/10/2018 12:39:23
Inj Volume : 10.000 µl
Acq. Method : E:\DK\TL\方法\85C-15A-30min-1u.M
Last changed : 11/10/2018 12:38:34 by 系统
(modified after loading)
Analysis Method : E:\DK\SJY\METHOD\XSXZ.M
Last changed : 21/12/2018 18:12:24 by 系统



7c

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Area Percent Report

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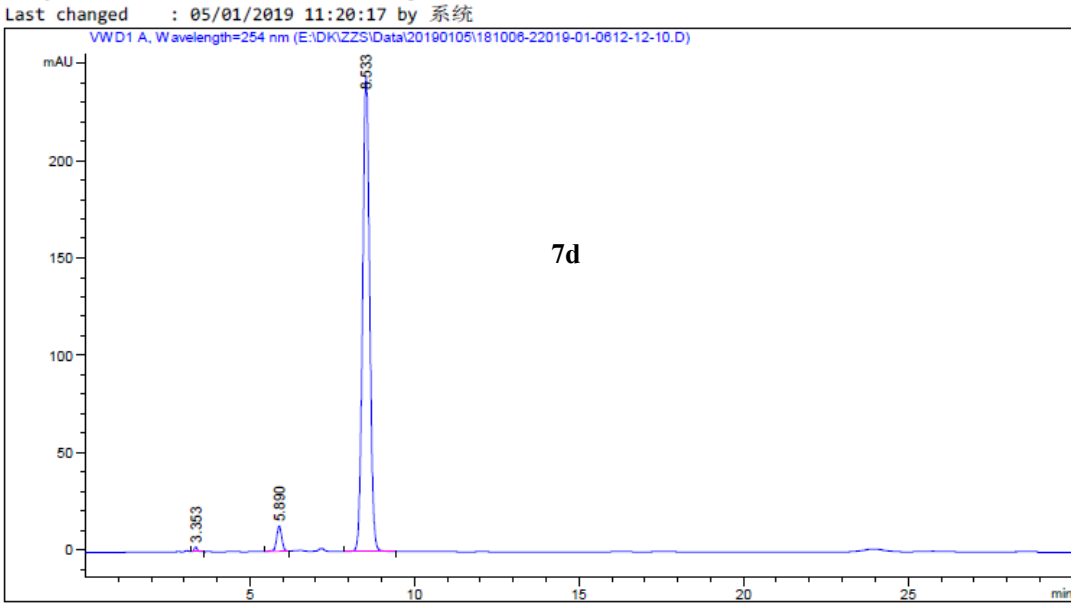
Sorted By : Signal
Multiplier : 2.0000
Dilution : 1.0000
Sample Amount: : 20.00000 [ng/ul] (not used in calc.)
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.715	BB	0.1929	26.39357	2.10992	0.6572
2	8.300	BB	0.2486	3989.97437	242.92328	99.3428
Totals :				4016.36794	245.03320	

Acq. Operator : 系统
Sample Operator : 系统
Acq. Instrument : 1260LC Location : 1
Injection Date : 06/01/2019 12:12:48
Inj Volume : 3.000 µl
Acq. Method : E:\DK\TL\方法\85C-15A-30min-1u.M
Last changed : 06/01/2019 12:08:53 by 系统
(modified after loading)
Analysis Method : E:\DK\SJY\METHOD\shuijiada.M
Last changed : 05/01/2019 11:20:17 by 系统



7d

```
=====================================================================
                    Area Percent Report
=====================================================================

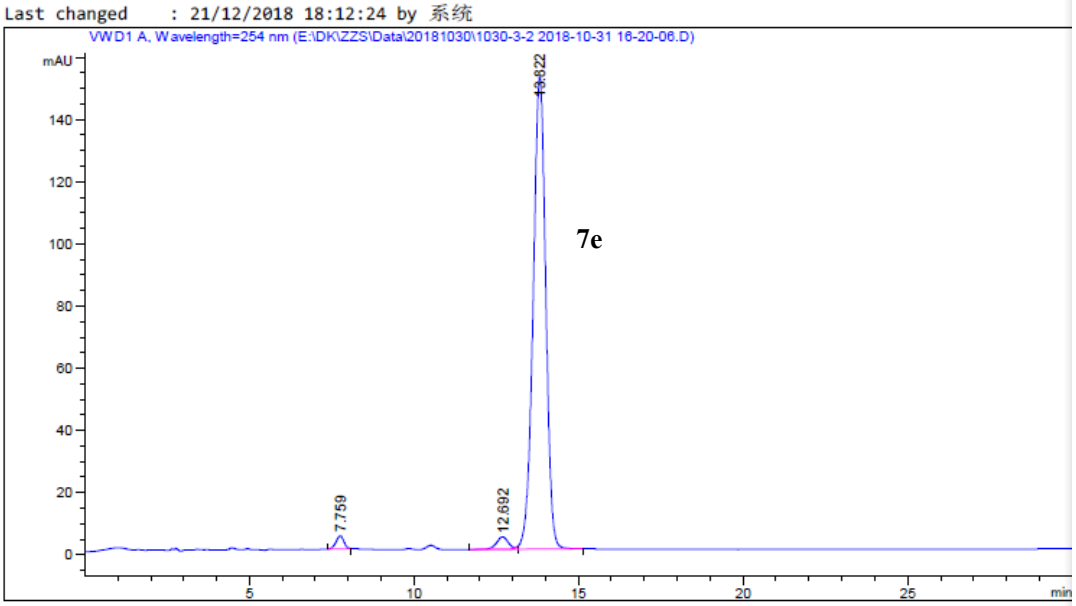
Sorted By             :      Signal
Multiplier            :      2.0000
Dilution              :      1.0000
Sample Amount:              :     30.00000  [ng/ul]   (not used in calc.)
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=254 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   3.353 BB    0.0974   15.67063    2.45591   0.4104
   2   5.890 BB    0.1679  141.10254   12.97621   3.6956
   3   8.533 BB    0.2333 3661.34229  243.70903  95.8940

Totals :                   3818.11546  259.14115
```

Acq. Operator : 系统
Sample Operator : 系统
Acq. Instrument : 1260LC Location : 1
Injection Date : 31/10/2018 16:20:50
Inj Volume : 20.000 µl
Acq. Method : E:\DK\TL\方法\85C-15A-30min-1u.M
Last changed : 31/10/2018 16:20:00 by 系统
(modified after loading)
Analysis Method : E:\DK\SJY\METHOD\XSXZ.M
Last changed : 21/12/2018 18:12:24 by 系统



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Area Percent Report

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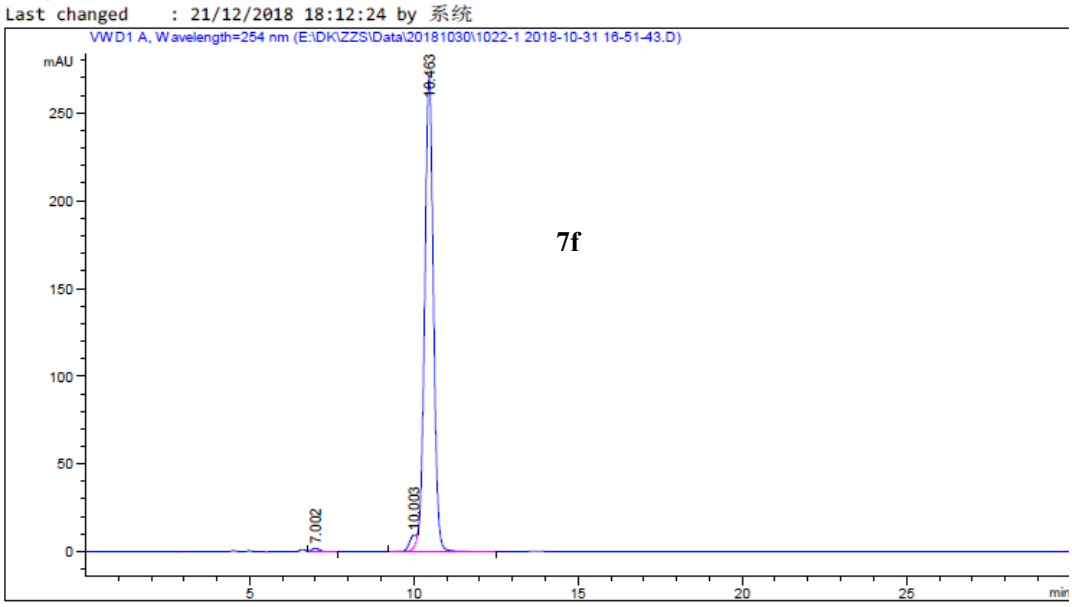
Sorted By : Signal
Multiplier : 2.0000
Dilution : 1.0000
Sample Amount: : 50.00000 [ng/ul] (not used in calc.)
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.759	BB	0.2551	68.98974	4.16894	1.6405
2	12.692	BV E	0.3812	98.16505	3.96063	2.3343
3	13.822	VB R	0.4098	4038.17725	152.06833	96.0252

Totals : 4205.33204 160.19790

```
------------------------------------------------------------------------
Acq. Operator   : 系统
Sample Operator : 系统
Acq. Instrument : 1260LC                        Location :   1
Injection Date  : 31/10/2018 16:52:33
                                                Inj Volume : 30.000 µl
Acq. Method     : E:\DK\TL\方法\85C-15A-30min-1u.M
Last changed    : 31/10/2018 16:51:38 by 系统
                  (modified after loading)
Analysis Method : E:\DK\SJY\METHOD\XSXZ.M
Last changed    : 21/12/2018 18:12:24 by 系统
```



7f

```
========================================================================
                      Area Percent Report
========================================================================

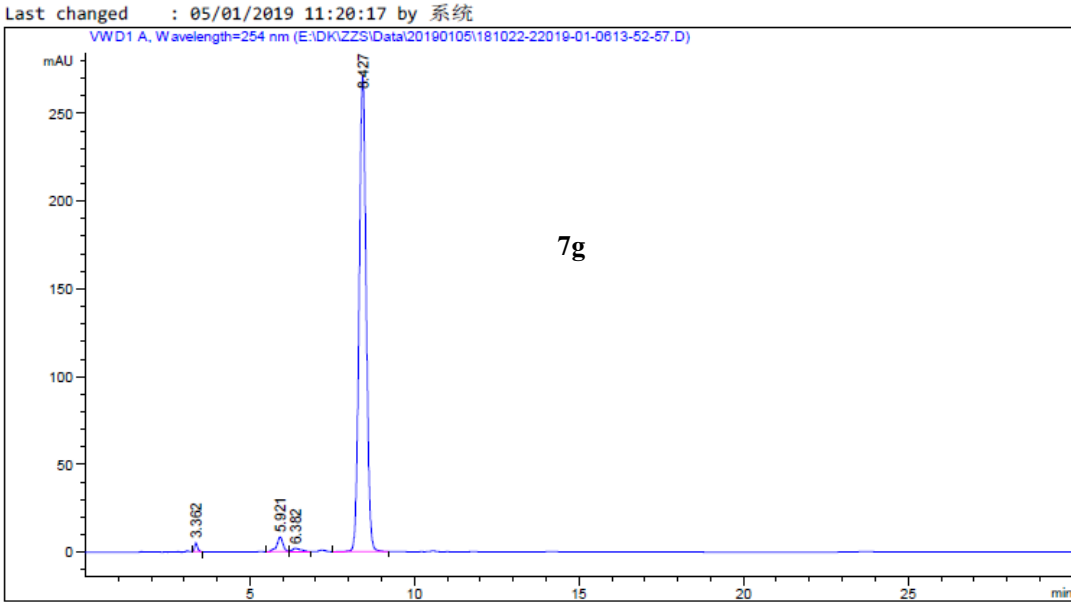
Sorted By             :      Signal
Multiplier            :      2.0000
Dilution              :      1.0000
Sample Amount:        :     50.00000  [ng/ul]   (not used in calc.)
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=254 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   7.002 VB    0.2582   30.51808    1.84316   0.5839
   2  10.003 BV E  0.2309  106.14196    6.80778   2.0309
   3  10.463 VB R  0.2905 5089.73877  270.50864  97.3852

Totals :                  5226.39881  279.15957
```

Acq. Operator : 系统
Sample Operator : 系统
Acq. Instrument : 1260LC Location : 1
Injection Date : 06/01/2019 13:53:35
Inj Volume : 3.000 µl
Acq. Method : E:\DK\TL\方法\85C-15A-30min-1u.M
Last changed : 06/01/2019 13:52:49 by 系统
(modified after loading)
Analysis Method : E:\DK\SJY\METHOD\shuijiada.M
Last changed : 05/01/2019 11:20:17 by 系统



7g

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Area Percent Report
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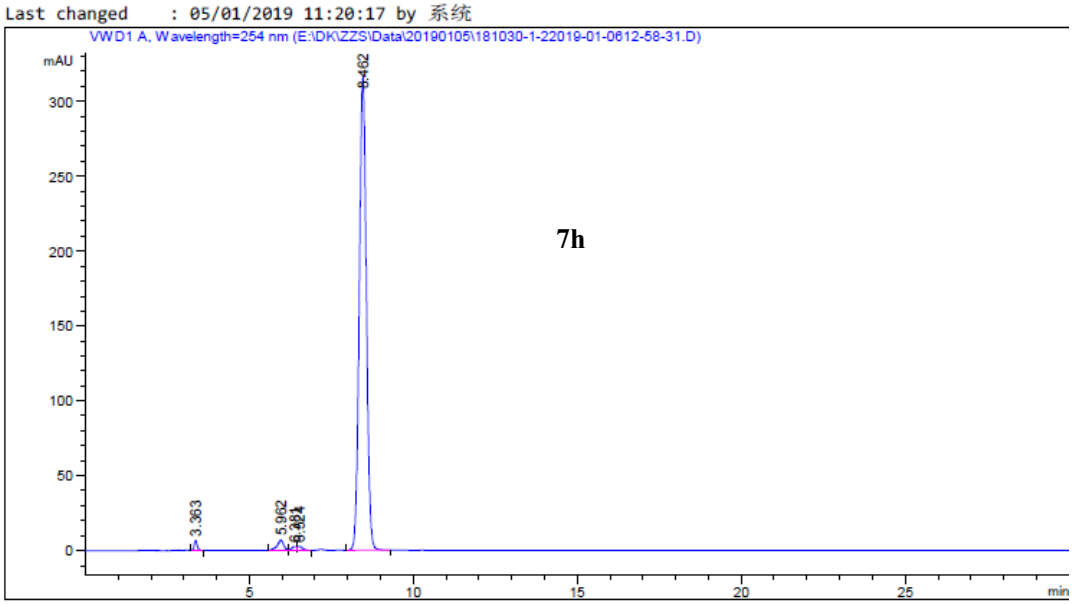
Sorted By : Signal
Multiplier : 2.0000
Dilution : 1.0000
Sample Amount: : 30.00000 [ng/ul] (not used in calc.)
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.362	BB	0.0952	30.00751	4.84892	0.7082
2	5.921	BV	0.1922	108.53032	8.37350	2.5615
3	6.382	VB	0.2525	32.05448	1.76847	0.7565
4	8.427	BB	0.2332	4066.38916	270.70895	95.9737
Totals :				4236.98147	285.69985	

Acq. Operator : 系统
Sample Operator : 系统
Acq. Instrument : 1260LC Location : 1
Injection Date : 06/01/2019 12:59:09
Inj Volume : 2.000 µl
Acq. Method : E:\DK\TL\方法\85C-15A-30min-1u.M
Last changed : 06/01/2019 12:58:21 by 系统
(modified after loading)
Analysis Method : E:\DK\SJY\METHOD\shuijiada.M
Last changed : 05/01/2019 11:20:17 by 系统



7h

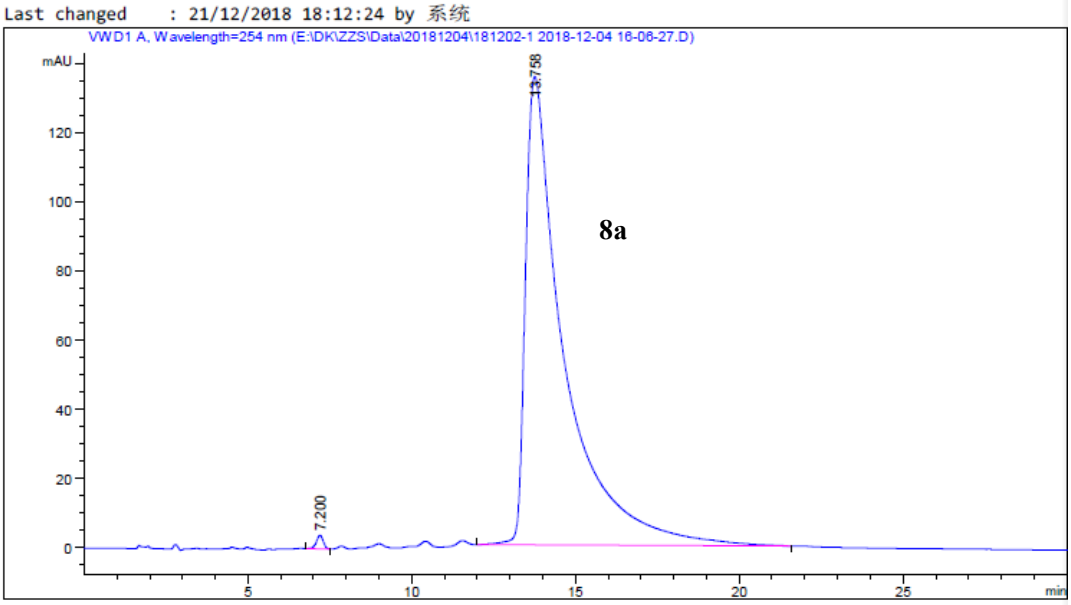
Area Percent Report

Sorted By : Signal
Multiplier : 2.0000
Dilution : 1.0000
Sample Amount: : 30.00000 [ng/ul] (not used in calc.)
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.363	BB	0.0960	41.48325	6.63238	0.8385
2	5.962	BV	0.1992	92.26182	6.80352	1.8650
3	6.381	VV	0.1477	22.24336	2.28322	0.4496
4	6.524	VB	0.1785	29.92163	2.50253	0.6048
5	8.462	BB	0.2336	4761.16748	316.34982	96.2420

```
Acq. Operator   : 系统
Sample Operator : 系统
Acq. Instrument : 1260LC                        Location :   1
Injection Date  : 04/12/2018 16:07:15
                                                Inj Volume : 20.000 µl
Acq. Method     : E:\DK\TL\方法\90C-10D-30min-1u.M
Last changed    : 04/12/2018 16:06:02 by 系统
                  (modified after loading)
Analysis Method : E:\DK\SJY\METHOD\XSXZ.M
Last changed    : 21/12/2018 18:12:24 by 系统
```

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=====================================================================
                        Area Percent Report
=====================================================================

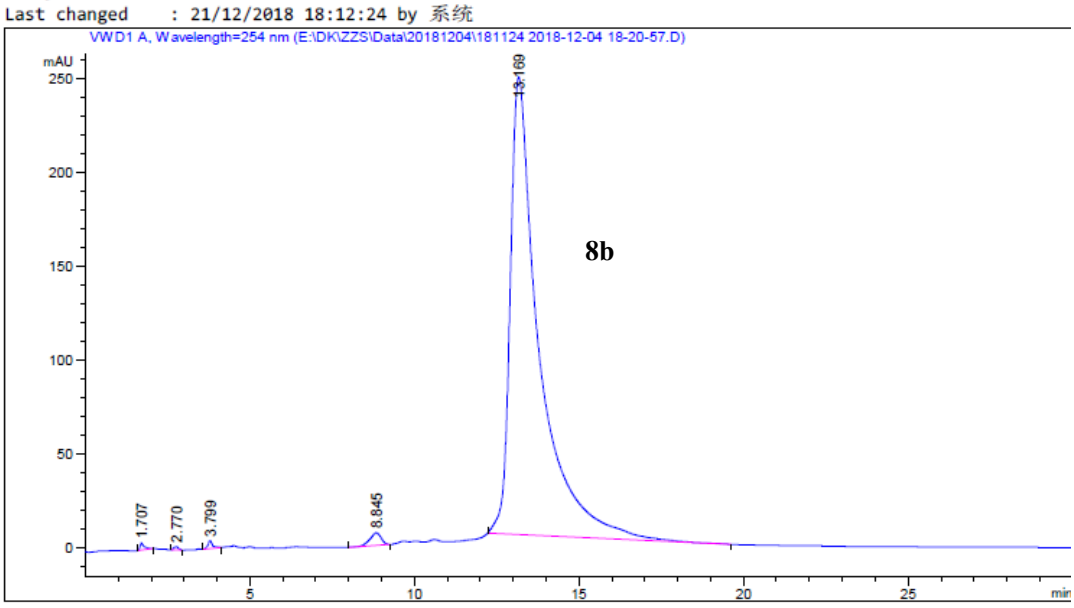
Sorted By             :      Signal
Multiplier            :      2.0000
Dilution              :      1.0000
Sample Amount:                :    100.00000  [ng/ul]   (not used in calc.)
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=254 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   7.200 BB    0.2251   58.05653    3.95913   0.5191
   2  13.758 BB    1.1390 1.11262e4   135.50314  99.4809

Totals :                  1.11843e4   139.46228
```

Acq. Operator : 系统
Sample Operator : 系统
Acq. Instrument : 1260LC Location : 1
Injection Date : 04/12/2018 18:21:58
Inj Volume : 30.000 µl
Acq. Method : E:\DK\TL\方法\90C-10D-30min-1u.M
Last changed : 04/12/2018 18:20:52 by 系统
(modified after loading)
Analysis Method : E:\DK\SJY\METHOD\XSXZ.M
Last changed : 21/12/2018 18:12:24 by 系统



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Area Percent Report

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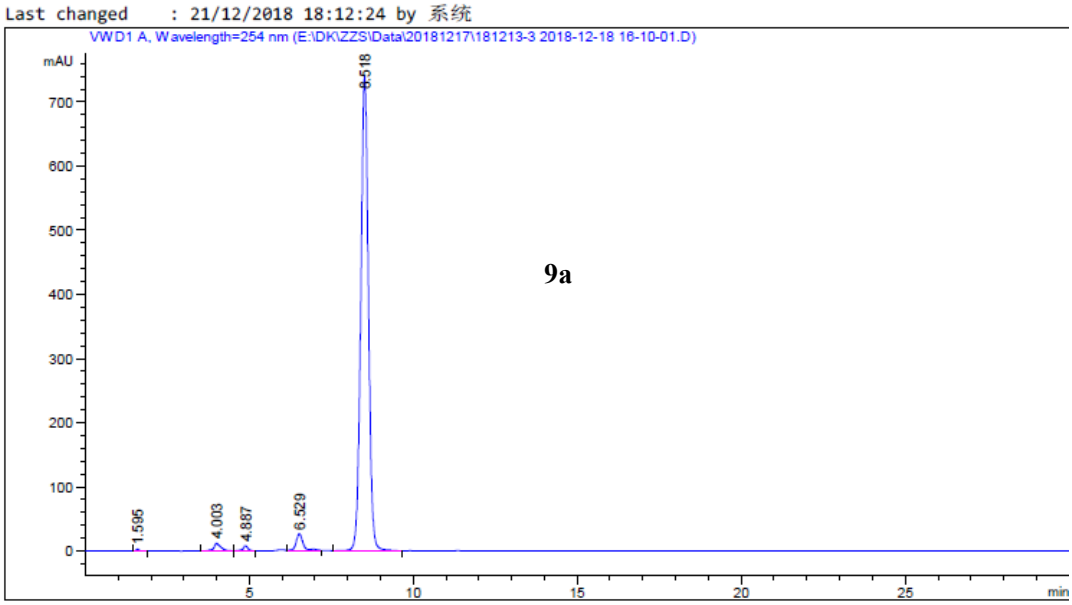
Sorted By : Signal
Multiplier : 2.0000
Dilution : 1.0000
Sample Amount: : 100.00000 [ng/ul] (not used in calc.)
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.707	BB	0.1331	36.19023	3.76690	0.2401
2	2.770	BB	0.1362	18.62228	1.80722	0.1235
3	3.799	BB	0.1455	42.28354	4.23525	0.2805
4	8.845	BB	0.3492	156.73187	6.66848	1.0398
5	13.169	BB	0.8325	1.48189e4	243.66263	98.3160

Acq. Operator : 系统
Sample Operator : 系统
Acq. Instrument : 1260LC Location : 1
Injection Date : 18/12/2018 16:10:42
Inj Volume : 10.000 µl
Acq. Method : E:\DK\TL\方法\90C-10A-30min-1u.M
Last changed : 18/12/2018 16:09:57 by 系统
(modified after loading)
Analysis Method : E:\DK\SJY\METHOD\XSXZ.M
Last changed : 21/12/2018 18:12:24 by 系统



9a

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Area Percent Report

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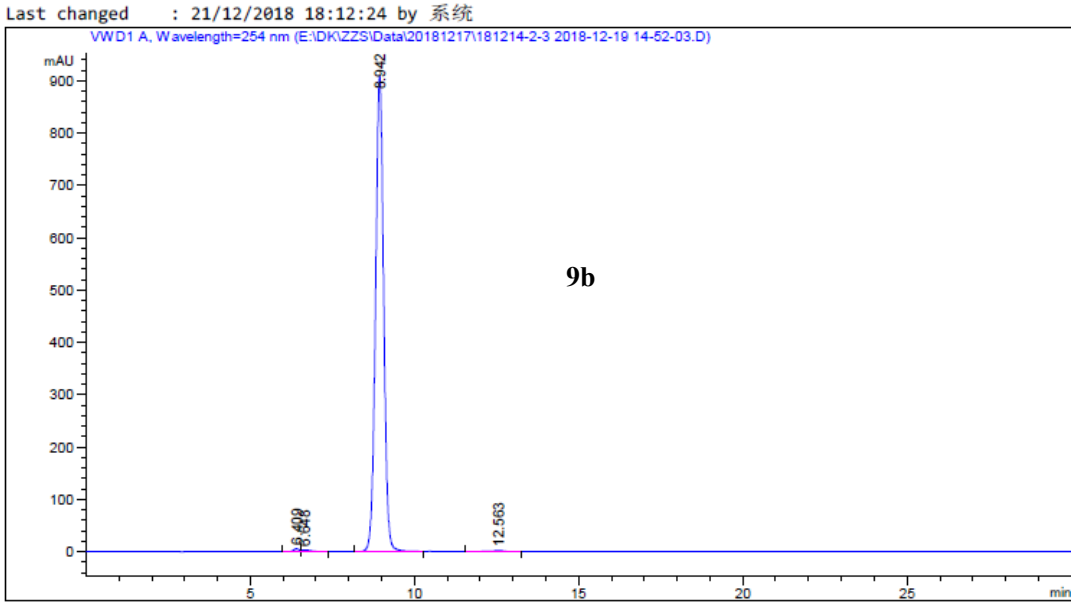
Sorted By : Signal
Multiplier : 2.0000
Dilution : 1.0000
Sample Amount: : 100.00000 [ng/ul] (not used in calc.)
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.595	BB	0.0743	17.24165	3.38976	0.1361
2	4.003	BB	0.1917	170.35944	12.06598	1.3448
3	4.887	BB	0.1498	80.00353	7.92377	0.6315
4	6.529	BV R	0.2118	354.70419	25.41198	2.7999
5	8.518	BB	0.2523	1.20461e4	738.51459	95.0877

Acq. Operator : 系统
Sample Operator : 系统
Acq. Instrument : 1260LC Location : 1
Injection Date : 19/12/2018 14:52:43
Inj Volume : 10.000 µl
Acq. Method : E:\DK\TL\方法\90C-10A-30min-1u.M
Last changed : 19/12/2018 14:51:53 by 系统
(modified after loading)
Analysis Method : E:\DK\SJY\METHOD\XSXZ.M
Last changed : 21/12/2018 18:12:24 by 系统



9b

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Area Percent Report
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Sorted By : Signal
Multiplier : 2.0000
Dilution : 1.0000
Sample Amount: : 100.00000 [ng/ul] (not used in calc.)
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.409	BV	0.2005	71.30328	5.31602	0.4513
2	6.648	VB	0.2890	62.24963	3.09055	0.3940
3	8.942	BB	0.2644	1.55988e4	908.14166	98.7362
4	12.563	BB	0.4755	66.10728	1.95019	0.4184
Totals :				1.57985e4	918.49843	