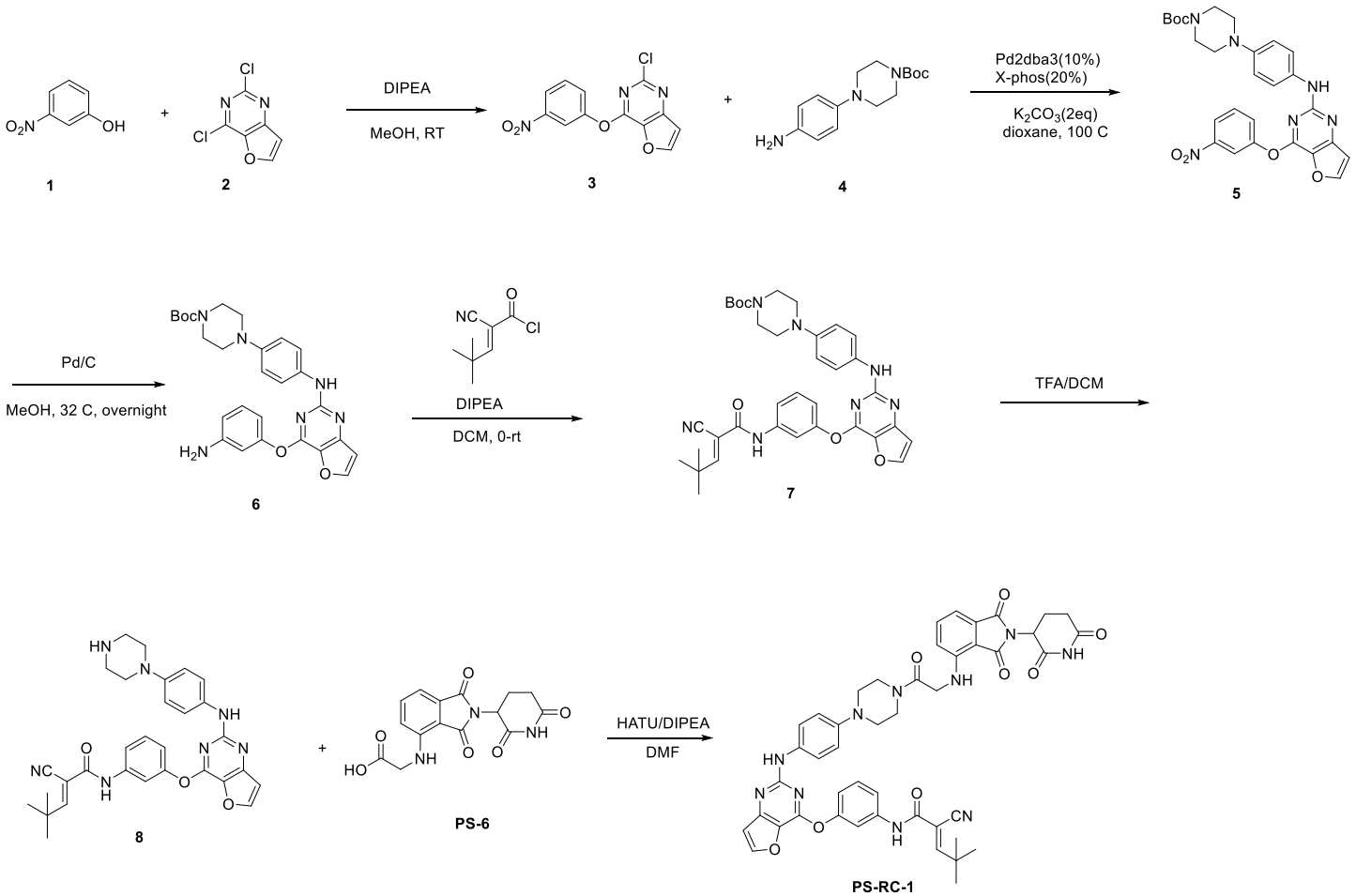
Compound Synthesis and Characterization

Materials: All chemicals were purchased from Sigma-Aldrich, Combi-blocks or Alfa Aesar, unless otherwise specified. All solvents and reagents were used as obtained without further purification.

Instrumentation: ^{1}H NMR and ^{13}C NMR spectra were on a Varian (Palo Alto, CA) 400-MR spectrometer. Chemical shifts (δ) are reported in ppm, and coupling constants (J) are in Hertz (Hz). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Flash chromatography was performed on a Teledyne ISCO CombiFlash Rf 200. ESI mass spectrometry was measured on an Agilent Mass Spectrometer.

General Procedure of RC PROTACs Synthesis (PS-RC-1).



2-Chloro-4-(3-nitrophenoxy)furo[3,2-d]pyrimidine(3).

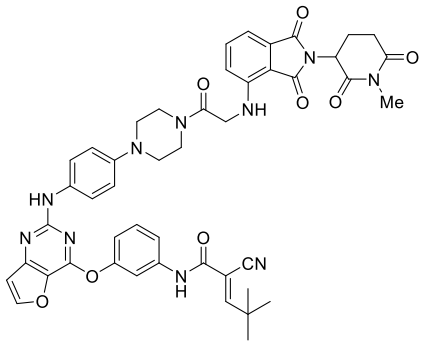
To a 250 mL of Schlenk tube equipped with a magnetic stir bar were added compound **1** (3 g, 21.6 mmol), **4** (4 g, 21.6 mmol) and DIPEA (6.5 g, 50 mmol) in MeOH (300 mL). The mixture was stirred under air at room temperature overnight. Upon the completion of the reaction, the resulting solid was filtered and dried over under a reduced pressure to obtain the title compound **3** (3.7 g, 60 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.63 (d, J = 2.3 Hz, 1H), 8.34 (t, J = 2.3 Hz, 1H), 8.23 (dd, J = 8.0, 2.0 Hz, 1H), 7.96 – 7.87 (m, 1H), 7.82 (t, J = 8.2 Hz, 1H), 7.29 (d, J = 2.2 Hz, 1H).

***tert*-Butyl 4-(4-((4-(3-nitrophenoxy)furo[3,2-*d*]pyrimidin-2-yl)amino)phenyl)piperazine-1-carboxylate (5).** To a 25 mL of Schlenk tube equipped with a magnetic stir bar were added compound **3** (1.5 g, 5 mmol), **4** (1.4 g, 5 mmol), K_2CO_3 (1.4 g, 10 mmol), $Pd_2(dba)_3$ (456 mg, 10 mol%) and X-phos (457 mg, 20 mol%). Then dioxane (20 mL) was added under N_2. The Schlenk tube was screw capped and heated to 100 ˚C for 12 hours. Then the reaction mixture was cooled to room temperature, and sat. NH_4Cl aq. was poured into the reaction mixture and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography to afford **5** (1.9 g, 73%) as a yellow solid. MS(EI): m/z 533.2 $[M+H]^+$.

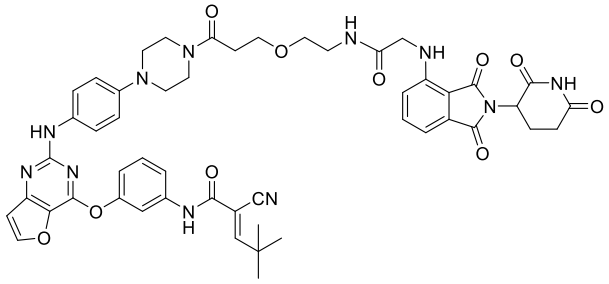
***tert*-Butyl 4-(4-((4-(3-aminophenoxy)furo[3,2-d]pyrimidin-2-yl)amino)phenyl)piperazine-1-carboxylate (6).** To a flask was added compound **5** (1.06 g, 2 mmol) and Pd/C (110 mg, 10%) in MeOH (50 mL). The mixture was stirred under 1atm H_2 at room temperature overnight. LC-MS showed compound **5** converted into compound **6** completely. Then the reaction mixture was filtered, and the filtrate was concentrated *in vacuo.* And the mixtrue was extracted with EtOAc and washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography to afford **6** (1.9 g, 90%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.12 (s, 1H), 8.26 (d, *J* = 2.2 Hz, 1H), 7.48 (d, *J* = 8.7 Hz, 2H), 7.10 (t, *J* = 8.0 Hz, 1H), 6.92 (d, *J* = 2.2 Hz, 1H), 6.78 (d, *J* = 9.1 Hz, 2H), 6.51 (dd, *J* = 7.9, 2.1 Hz, 1H), 6.45 (t, *J* = 2.2 Hz, 1H), 6.41 (dd, *J* = 7.9, 2.3 Hz, 1H), 5.32 (s, 2H), 3.49 – 3.39 (m, 4H), 2.95 (t, *J* = 5.1 Hz, 4H), 1.42 (s, 9H).
MS(EI): m/z 503.2 $[M+H]^+$.

***tert*-Butyl (*E*)-4-(4-((4-(3-(2-cyano-4,4-dimethylpent-2-enamido)phenoxy)furo[3,2-d]pyrimidin-2-yl)amino) phenyl)piperazine-1-carboxylate (7).** To compound **6** (500 mg, 1 mmol) was added compound (*E*)-2-cyano-4,4-dimethylpent-2-enoyl chloride (257 mg, 1.5 mol) and DIPEA (387 mg, 3 mmol) in DCM (20 mL). The mixture was stirred at room temperature for 30 min. LC-MS showed compound **6** converted into compound **7** completely.Then the reaction mixture was concentrated *in vacuo* to give compound **7**. MS(EI): m/z 638.2 $[M+H]^+$.

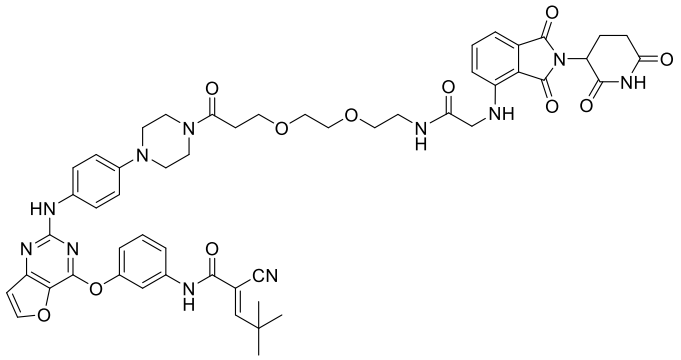
(*E*)-2-cyano-N-(3-((2-((4-(4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)glycyl)piperazin-1-yl) phenyl)amino)furo[3,2-d]pyrimidin-4-yl)oxy)phenyl)-4,4-dimethylpent-2-enamide (PS-RC-1). In a 25 mL flask was added **7** (32 mg, 0.05 mmol) in TFA/DCM (5 mL, 1/1). The mixture was stirred for 30 min at room temperature. Then remove the solvent *in vacuo* to give the deprotected intermediate, which was used for next step without further purification. To above intermediate was added compound **PS-6** (33 mg, 0.1 mol), HATU (38 mg, 0.1 mmol) and DIPEA (32 mg, 0.25 mmol) in DMF (2 mL). The mixture was stirred at room temperature for 30 min. Then the reaction mixture was concentrated *in vacuo* and the residue was purified by PrepHPLC with a reverse phase C18 column to afford the product as a yellow solid **PS-RC-1** (13 mg, 30%).^{1}H NMR (400 MHz, DMSO-d_6) δ 11.09 (s, 1H), 10.44 (s, 1H), 9.18 (s, 1H), 8.30 (d, *J* = 2.2 Hz, 1H), 7.71 – 7.55 (m, 3H), 7.53 – 7.45 (m, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.16 – 7.03 (m, 4H), 6.95 (d, *J* = 2.2 Hz, 1H), 6.76 (d, *J* = 8.5 Hz, 2H), 5.08 (dd, *J* = 12.9, 5.5 Hz, 1H), 4.24 (d, *J* = 4.5 Hz, 2H), 3.71 – 3.54 (m, 4H), 3.12 – 2.97 (m, 4H), 2.89 (td, *J* = 17.6, 15.6, 5.4 Hz, 1H), 2.67 – 2.52 (m, 2H), 2.04 (d, *J* = 12.1 Hz, 1H), 1.27 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.3, 170.5, 169.3, 167.8, 167.1, 166.8, 161.2, 156.7, 156.6, 153.4, 153.1, 152.6, 145.9, 145.8, 139.9, 136.6, 134.1, 132.5, 130.4, 129.0, 120.0, 1187, 118.2, 116.9, 115.5, 114.4, 111.3, 110.0, 109.6, 107.4, 50.0, 49.7, 49.0, 44.2, 44.1, 41.9, 34.9, 31.4, 29.0, 22.6. HRMS (m/z): [M+H]+ calcd. for $C_{45}H_{43}N_{10}O_8$, 851.3265; found: 851.3267.



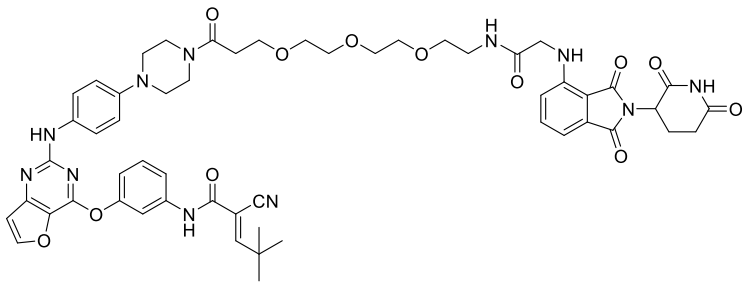
(*E*)-2-cyano-4,4-dimethyl-N-(3-((2-((4-(4-((2-(1-methyl-2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl) glycyl)piperazin-1-yl)phenyl)amino)furo[3,2-d]pyrimidin-4-yl)oxy)phenyl)pent-2-enamide (PS-RC-1-Me). Follow the ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.43 (s, 1H), 9.18 (s, 1H), 8.30 (d, *J* = 2.2 Hz, 1H), 7.67 – 7.53 (m, 3H), 7.52 – 7.45 (m, 2H), 7.42 (d, *J* = 8.6 Hz, 2H), 7.17 – 7.01 (m, 4H), 6.95 (d, *J* = 2.2 Hz, 1H), 6.77 (d, *J* = 8.3 Hz, 2H), 5.14 (dd, *J* = 13.0, 5.4 Hz, 1H), 4.25 (d, *J* = 4.5 Hz, 2H), 3.65 (d, *J* = 10.2 Hz, 4H), 3.07 (s, 2H), 3.03 (s, 3H), 3.00 – 2.90 (m, 2H), 2.82 – 2.72 (m, 1H), 2.62 – 2.50 (m, 2H), 2.06 (d, *J* = 10.3 Hz, 1H), 1.27 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.3, 170.3, 169.2, 167.8, 167.0, 166.8, 164.9, 161.2, 156.7, 156.6, 153.4, 153.1, 152.8, 152.6, 145.9, 145.7, 139.9, 136.7, 134.1, 132.4, 130.4, 129.0, 120.0, 118.7, 118.2, 116.9, 115.5, 114.4, 111.3, 110.0, 107.4, 50.0, 49.7, 49.6, 44.1, 41.9, 34.9, 31.6, 29.3, 29.0, 27.01, 23.6. HRMS (m/z): [M+H]+ calcd. for $C_{46}H_{45}N_{10}O_8$, 865.3422; found: 865.3412.



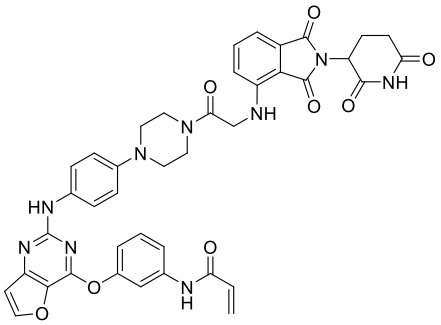
(*E*)-2-cyano-N-(3-((2-((4-(4-(3-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)acetamido) ethoxy)propanoyl)piperazin-1-yl)phenyl)amino)furo[3,2-d]pyrimidin-4-yl)oxy)phenyl)-4,4-dimethylpent-2-enamide.(PS-RC-2).^{1}H NMR (400 MHz, DMSO-d_6) δ 9.13 (d, *J* = 3.9 Hz, 1H), 8.27 (d, *J* = 2.2 Hz, 1H), 8.14 (t, *J* = 5.6 Hz, 1H), 7.64 – 7.51 (m, 3H), 7.50 – 7.39 (m, 2H), 7.37 (d, *J* = 8.3 Hz, 2H), 7.06 (dd, *J* = 11.9, 7.1 Hz, 2H), 6.92 (t, *J* = 4.1 Hz, 2H), 6.83 (d, *J* = 8.5 Hz, 1H), 6.70 (d, *J* = 8.5 Hz, 2H), 5.04 (dd, *J* = 12.8, 5.4 Hz, 1H), 3.91 (d, *J* = 5.6 Hz, 2H), 3.60 (t, *J* = 6.4 Hz, 2H), 3.54 (s, 4H), 3.39 (t, *J* = 5.8 Hz, 2H), 3.23 (d, *J* = 5.7 Hz, 2H), 2.99 – 2.88 (m, 4H), 2.88 – 2.79 (m, 1H), 2.62 – 2.50 (m, 4H), 1.99 (d, *J* = 11.9 Hz, 1H), 1.24 (s, 5H), 1.01 – 0.89 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.3, 170.5, 169.2, 169.1, 169.0, 167.8, 161.3, 156.7, 156.6, 153.4, 153.1, 152.8, 146.3, 145.9, 139.9, 136.7, 134.0, 132.5, 130.6, 129.0, 120.0, 117.9, 116.8, 111.4, 110.3, 107.4, 69.1, 66.9, 50.3, 49.8, 49.0, 45.6, 45.3, 43.2, 33.2, 31.4, 29.3, 29.1, 23.6, 22.6. MS(EI): m/z 966.3 $[M+H]^+$.



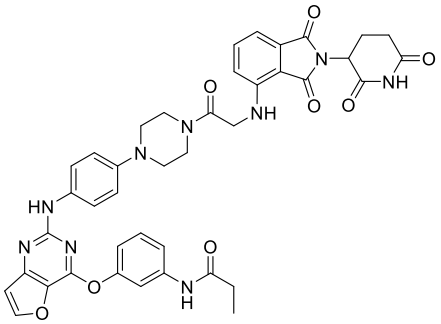
(*E*)-2-cyano-N-(3-((2-((4-(4-(3-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)acetamido)ethoxy)ethoxy)propanoyl)piperazin-1-yl)phenyl)amino)furo[3,2-d]pyrimidin-4-yl)oxy)phenyl)-4,4-dimethylpent-2-enamide(PS-RC-3). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.15 (d, *J* = 3.8 Hz, 1H), 8.30 (t, *J* = 1.8 Hz, 1H), 8.17 (t, *J* = 5.7 Hz, 1H), 7.59 (td, *J* = 14.6, 13.7, 8.3 Hz, 3H), 7.53 – 7.42 (m, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.08 (dd, *J* = 14.4, 7.5 Hz, 2H), 6.94 (d, *J* = 1.9 Hz, 2H), 6.85 (d, *J* = 8.4 Hz, 1H), 6.72 (d, *J* = 8.5 Hz, 2H), 5.06 (dd, *J* = 12.9, 5.4 Hz, 1H), 3.93 (d, *J* = 5.5 Hz, 2H), 3.63 (t, *J* = 6.7 Hz, 2H), 3.56 (d, *J* = 5.2 Hz, 4H), 3.48 (d, *J* = 3.5 Hz, 4H), 3.40 (d, *J* = 5.8 Hz, 2H), 3.25 (d, *J* = 6.0 Hz, 2H), 3.02 – 2.90 (m, 4H), 2.88 – 2.81 (m, 1H), 2.65 – 2.51 (m, 4H), 2.01 (d, *J* = 11.8 Hz, 1H), 1.26 (d, *J* = 1.3 Hz, 5H), 1.04 – 0.90 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.3, 170.5, 169.2, 169.1, 169.0, 167.8, 164.9, 156.7, 156.6, 153.4, 153.1, 152.8, 152.7, 152.6, 146.2, 145.9, 139.9, 136.6, 134.0, 132.5, 130.6, 130.2, 129.0, 120.0, 119.9, 117.9, 116.8, 111.4, 110.3, 107.4, 70.0, 69.4, 67.2, 50.3, 49.7, 49.0, 45.6, 45.4, 43.2, 39.1, 33.2, 31.4, 29.3, 29.1, 23.6, 22.6. MS(EI): m/z 1010.4 $[M+H]^+$.



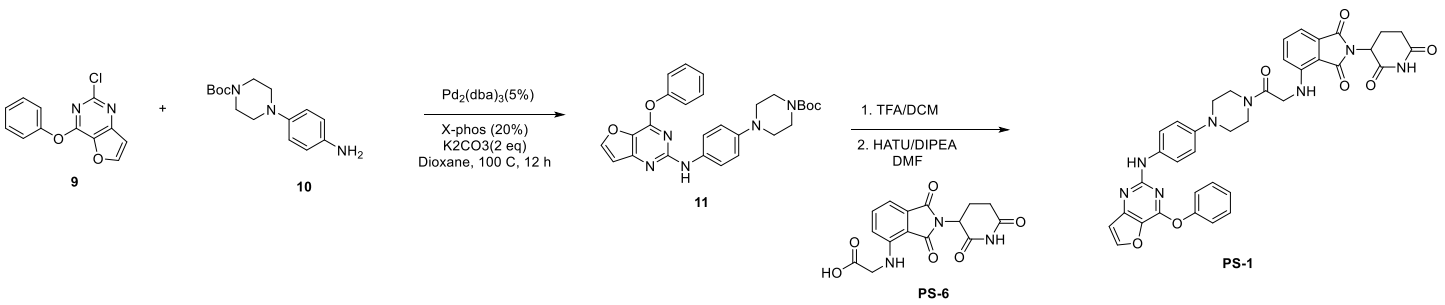
(*E*)-2-cyano-N-(3-((2-((4-(4-(1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-2-oxo-6,9,12-trioxa-3-azapentadecan-15-oyl)piperazin-1-yl)phenyl)amino)furo[3,2-d]pyrimidin-4-yl)oxy)phenyl)-4,4-dimethylpent-2-enamide (PS-RC-4). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.16 (s, 1H), 8.30 (d, *J* = 2.2 Hz, 1H), 8.16 (t, *J* = 5.7 Hz, 1H), 7.65 – 7.52 (m, 3H), 7.47 (d, *J* = 7.3 Hz, 2H), 7.40 (d, *J* = 8.7 Hz, 2H), 7.13 – 7.03 (m, 2H), 6.94 (t, *J* = 3.5 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 1H), 6.73 (d, *J* = 8.4 Hz, 2H), 5.07 (dd, *J* = 12.9, 5.4 Hz, 1H), 3.93 (d, *J* = 5.6 Hz, 2H), 3.63 (t, *J* = 6.6 Hz, 2H), 3.56 (d, *J* = 5.5 Hz, 4H), 3.48 (d, *J* = 6.1 Hz, 8H), 3.41 (t, *J* = 5.7 Hz, 2H), 3.24 (t, *J* = 5.9 Hz, 2H), 2.96 (d, *J* = 23.0 Hz, 4H), 2.90 – 2.81 (m, 1H), 2.64 – 2.52 (m, 4H), 2.02 (d, *J* = 11.5 Hz, 1H), 1.27 (s, 5H), 0.98 (d, *J* = 27.6 Hz, 4H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.3, 170.5, 169.2, 169.1, 169.0, 167.8, 153.4, 153.1, 152.8, 152.6, 146.3, 145.9, 136.6, 134.0, 132.5, 120.0, 119.9, 117.9, 116.9, 116.8, 111.4, 110.3, 107.4, 70.21, 70.16, 70.1, 70.0, 69.4, 67.2, 50.3, 49.7, 49.0, 45.6, 45.4, 43.2, 39.1, 33.2, 31.4, 29.3, 23.6, 22.6. MS(EI): m/z 1054.4 $[M+H]^+$.



N-(3-((2-((4-(4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)glycyl)piperazin-1-yl)phenyl)amino) furo[3,2-d]pyrimidin-4-yl)oxy)phenyl)acrylamide (PS-IRC-1). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.11 (s, 1H), 10.37 (s, 1H), 9.17 (s, 1H), 8.30 (d, *J* = 2.2 Hz, 1H), 7.73 – 7.59 (m, 3H), 7.51 – 7.34 (m, 3H), 7.17 – 7.03 (m, 4H), 6.95 (d, *J* = 2.2 Hz, 1H), 6.75 (d, *J* = 8.7 Hz, 2H), 6.44 (dd, *J* = 17.0, 10.1 Hz, 1H), 6.27 (dd, *J* = 17.0, 2.1 Hz, 1H), 5.78 (dd, *J* = 10.0, 2.1 Hz, 1H), 5.08 (dd, *J* = 12.9, 5.4 Hz, 1H), 4.25 (d, *J* = 4.5 Hz, 2H), 3.65 (dd, *J* = 11.4, 5.9 Hz, 4H), 3.11 – 2.96 (m, 4H), 2.89 (td, *J* = 17.0, 15.3, 5.4 Hz, 1H), 2.65 – 2.51 (m, 2H), 2.12 – 2.00 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.3, 170.5, 169.2, 167.8, 166.8, 163.8, 156.7, 156.6, 153.4, 153.1, 152.7, 145.9, 145.8, 140.8, 136.6, 134.1, 132.5, 132.1, 130.4, 129.0, 127.8, 120.0, 118.7, 117.2, 117.0, 116.9, 113.3, 111.3, 110.0, 107.4, 50.0, 49.7, 49.0, 44.1, 41.9, 31.4, 22.6.HRMS (m/z): [M+H]+ calcd. for $C_{40}H_{36}N_9O_8$, 770.2687; found: 770.2690.

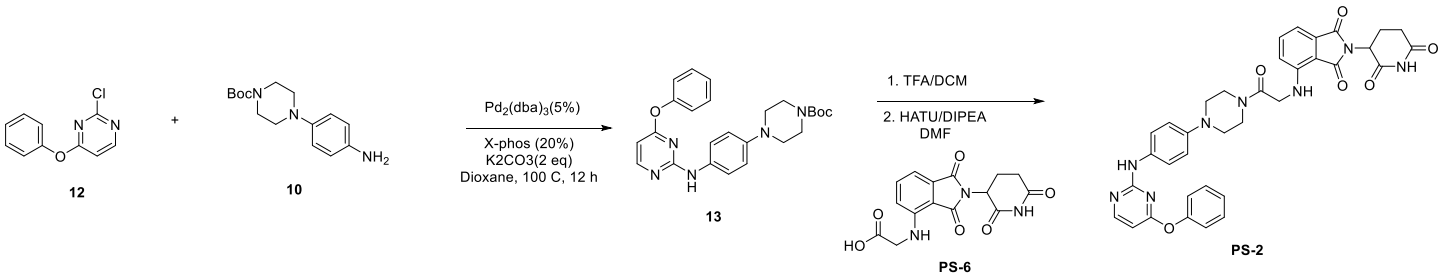


N-(3-((2-((4-(4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)glycyl)piperazin-1-yl)phenyl)amino) furo[3,2-d]pyrimidin-4-yl)oxy)phenyl)propionamide(PS-RNC-1). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.11 (s, 1H), 10.08 (s, 1H), 9.15 (s, 1H), 8.30 (d, *J* = 2.2 Hz, 1H), 7.69 – 7.57 (m, 2H), 7.55 (d, *J* = 8.2 Hz, 1H), 7.41 (t, *J* = 8.2 Hz, 3H), 7.19 – 7.06 (m, 3H), 7.04 – 6.99 (m, 1H), 6.95 (d, *J* = 2.1 Hz, 1H), 6.77 (d, *J* = 8.7 Hz, 2H), 5.08 (dd, *J* = 12.9, 5.4 Hz, 1H), 4.25 (d, *J* = 4.5 Hz, 2H), 3.65 (d, *J* = 10.9 Hz, 4H), 3.05 (dd, *J* = 25.9, 6.1 Hz, 4H), 2.89 (ddd, *J* = 17.3, 13.9, 5.5 Hz, 1H), 2.66 – 2.52 (m, 2H), 2.33 (q, *J* = 7.5 Hz, 2H), 2.12 – 1.96 (m, 1H), 1.07 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.3, 172.7, 170.5, 169.2, 167.8, 166.8, 156.7, 156.5, 153.4, 153.0, 152.8, 145.9, 145.8, 141.2, 136.6, 134.2, 132.5, 130.3, 129.0, 120.0, 118.7, 116.9, 116.7, 116.6, 112.8, 111.3, 110.0, 107.4, 50.03, 49.7, 49.0, 44.2, 44.1, 41.9, 31.4, 30.0, 22.6, 10.0. HRMS (m/z): [M+H]+ calcd. for $C_{40}H_{38}N_9O_8$, 772.2843; found: 772.2831.



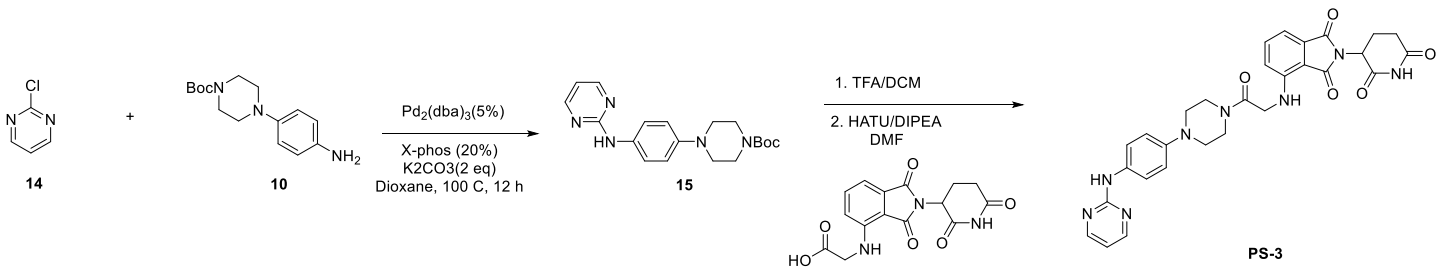
***tert*-Butyl 4-(4-((4-phenoxyfuro[3,2-d]pyrimidin-2-yl)amino)phenyl)piperazine-1-carboxylate (11).** To a 25 mL of Schlenk tube equipped with a magnetic stir bar were added compound **9** (49 mg, 0.2 mmol), **10** (55 mg, 0.2 mmol), K_2CO_3 (55 mg, 0.4 mmol), $Pd_2(dba)_3$ (18 mg, 10 mol%) and X-phos (19 mg, 20 mol%). Then dioxane (5 mL) was added under N_2. The Schlenk tube was screw capped and heated to 100 ˚C for 12 hours. Then the reaction mixture was cooled to room temperature, and sat. NH_4Cl aq. was poured into the reaction mixture and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography to afford **11** (63 mg, 65%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.38 – 9.28 (m, 1H), 8.29 (dd, *J* = 5.5, 1.9 Hz, 1H), 7.54 – 7.45 (m, 2H), 7.40 – 7.27 (m, 3H), 7.27 – 7.19 (m, 2H), 6.72 (d, *J* = 8.5 Hz, 2H), 6.33 (dd, *J* = 5.6, 1.9 Hz, 1H), 3.43 (d, *J* = 5.4 Hz, 4H), 2.94 (t, *J* = 5.2 Hz, 4H), 1.41 (d, *J* = 2.0 Hz, 9H). MS(EI): m/z 488.2 $[M+H]^+$.

2-(2,6-Dioxopiperidin-3-yl)-4-((2-oxo-2-(4-(4-((4-phenoxyfuro[3,2-d]pyrimidin-2-yl)amino)phenyl)piperazin-1-yl)ethyl)amino)isoindoline-1,3-dione(PS-1). In a 25 mL flask was added **11** (27 mg, 0.05 mmol) in TFA/DCM (5 mL, 1/1). The mixture was stirred for 30 min at room temperature. Then remove the solvent *in vacuo* to give the deprotected intermediate, which was used for next step without further purification. To above intermediate was added compound **PS-6** (33 mg, 0.1 mol), HATU (38 mg, 0.1 mmol) and DIPEA (32 mg, 0.25 mmol) in DMF (2 mL). The mixture was stirred at room temperature for 30 min. Then the reaction mixture was concentrated *in vacuo* and the residue was purified by PrepHPLC with a reverse phase C18 column to afford the product as a yellow solid **PS-1** (14 mg, 40%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.12 (s, 1H), 9.12 (s, 1H), 8.28 (d, *J* = 2.2 Hz, 1H), 7.61 (t, *J* = 7.8 Hz, 1H), 7.55 – 7.47 (m, 2H), 7.42 (d, *J* = 8.5 Hz, 2H), 7.36 (d, *J* = 7.6 Hz, 3H), 7.15 – 7.05 (m, 3H), 6.94 (d, *J* = 2.2 Hz, 1H), 6.76 (d, *J* = 8.8 Hz, 2H), 5.08 (dd, *J* = 12.9, 5.4 Hz, 1H), 4.24 (d, *J* = 4.6 Hz, 2H), 3.65 (dt, *J* = 12.2, 4.9 Hz, 4H), 3.04 (dt, *J* = 25.5, 5.1 Hz, 4H), 2.89 (ddd, *J* = 17.2, 14.0, 5.5 Hz, 1H), 2.65 – 2.52 (m, 2H), 2.10 – 1.98 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.3, 170.5, 169.3, 167.8f, 166.8, 156.7, 156.4, 153.5, 152.9, 152.5, 145.9, 145.8, 136.6, 134.2, 132.5, 130.2, 129.1, 126.1, 122.4, 120.0, 118.7, 117.0, 111.3, 110.0, 107.4, 50.0, 49.8, 49.0, 44.2, 44.1, 42.0, 31.4, 22.6. HRMS (m/z): [M+H]+ calcd. for $C_{37}H_{33}N_8O_7$, 701.2472; found: 701.2459.



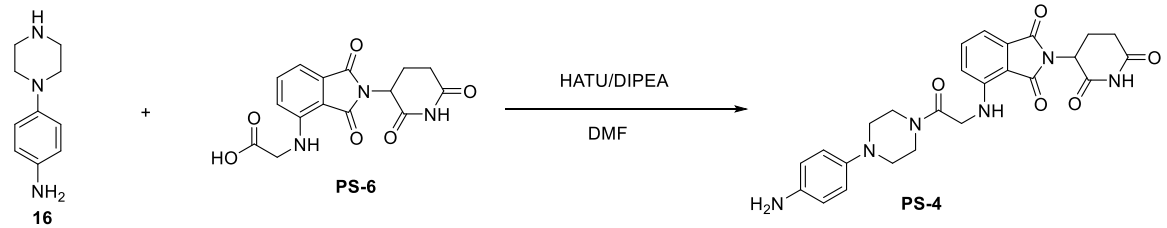
***tert*-Butyl 4-(4-((4-phenoxypyrimidin-2-yl)amino)phenyl)piperazine-1-carboxylate(13).** To a 25 mL of Schlenk tube equipped with a magnetic stir bar were added compound **12** (41 mg, 0.2 mmol), **10** (55 mg, 0.2 mmol), K_2CO_3 (55 mg, 0.4 mmol), $Pd_2(dba)_3$ (18 mg, 10 mol%) and X-phos (19 mg, 20 mol%). Then dioxane (5 mL) was added under N_2. The Schlenk tube was screw capped and heated to 100 ˚C for 12 hours. Then the reaction mixture was cooled to room temperature, and sat. NH_4Cl aq. was poured into the reaction mixture and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography to afford **13** (67 mg, 75%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.11 (s, 1H), 8.28 (t, *J* = 1.5 Hz, 1H), 7.54 – 7.48 (m, 2H), 7.44 – 7.31 (m, 5H), 6.94 (t, *J* = 1.5 Hz, 1H), 6.72 (d, *J* = 8.7 Hz, 2H), 3.44 (t, *J* = 5.1 Hz, 4H), 2.94 (t, *J* = 5.1 Hz, 4H), 1.42 (s, 9H). MS(EI): m/z 448.2 $[M+H]^+$.

2-(2,6-Dioxopiperidin-3-yl)-4-((2-oxo-2-(4-(4-((4-phenoxypyrimidin-2-yl)amino)phenyl)piperazin-1-yl)ethyl) amino)isoindoline-1,3-dione (PS-2). In a 25 mL flask was added **13** (22 mg, 0.05 mmol) in TFA/DCM (5 mL, 1/1). The mixture was stirred for 30 min at room temperature. Then remove the solvent *in vacuo* to give the deprotected intermediate, which was used for next step without further purification. To above intermediate was added compound **PS-6** (33 mg, 0.1 mol), HATU (38 mg, 0.1 mmol) and DIPEA (32 mg, 0.25 mmol) in DMF (2 mL). The mixture was stirred at room temperature for 30 min. Then the reaction mixture was concentrated *in vacuo* and the residue was purified by PrepHPLC with a reverse phase C18 column to afford the product as a yellow solid **PS-2** (11 mg, 34%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.11 (s, 1H), 9.37 (s, 1H), 8.29 (dd, *J* = 5.6, 1.6 Hz, 1H), 7.62 (dd, *J* = 8.5, 7.0 Hz, 1H), 7.52 – 7.44 (m, 2H), 7.34 (dt, *J* = 14.8, 7.9 Hz, 3H), 7.26 – 7.20 (m, 2H), 7.16 – 7.03 (m, 3H), 6.76 (d, *J* = 8.5 Hz, 2H), 6.34 (dd, *J* = 5.6, 1.6 Hz, 1H), 5.08 (dd, *J* = 12.7, 5.2 Hz, 1H), 4.25 (d, *J* = 4.2 Hz, 2H), 3.63 (d, *J* = 9.7 Hz, 4H), 3.12 – 2.99 (m, 4H), 2.93 – 2.79 (m, 1H), 2.65 – 2.52 (m, 2H), 2.09 – 1.96 (m, 1H). 13C NMR (100 MHz, DMSO-d6) δ 173.3, 170.5, 169.8, 169.2, 167.8, 166.8, 160.3, 160.2, 152.9, 145.9, 136.6, 133.4, 132.5, 130.2, 125.9, 122.4, 120.5, 118.7, 116.9, 111.3, 110.0, 49.9, 49.7, 49.0, 44.1, 41.9, 31.4, 22.6. HRMS (m/z): [M+H]+ calcd. for $C_{35}H_{33}N_8O_6$, 661.2523; found: 661.2514.



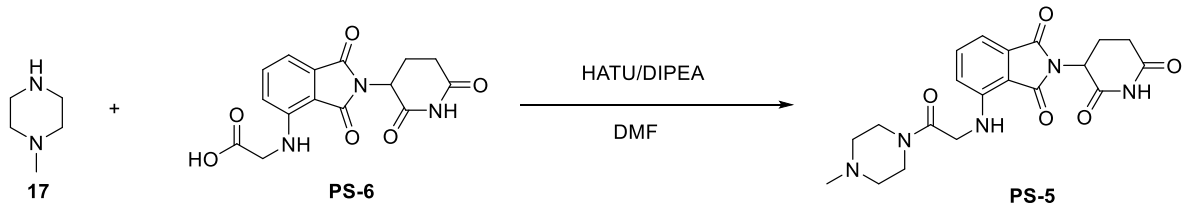
***tert*-Butyl 4-(4-(pyrimidin-2-ylamino)phenyl)piperazine-1-carboxylate (15).** To a 25 mL of Schlenk tube equipped with a magnetic stir bar were added compound **14** (23 mg, 0.2 mmol), **10** (55 mg, 0.2 mmol), K_2CO_3 (55 mg, 0.4 mmol), $Pd_2(dba)_3$ (18 mg, 10 mol%) and X-phos (19 mg, 20 mol%). Then dioxane (5 mL) was added under N_2. The Schlenk tube was screw capped and heated to 100 ˚C for 12 hours. Then the reaction mixture was cooled to room temperature, and sat. NH_4Cl aq. was poured into the reaction mixture and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography to afford **15** (50 mg, 70%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.35 (s, 1H), 8.40 (d, *J* = 4.7 Hz, 2H), 7.57 (d, *J* = 8.9 Hz, 2H), 6.90 (d, *J* = 8.9 Hz, 2H), 6.74 (t, *J* = 4.8 Hz, 1H), 3.45 (t, *J* = 5.0 Hz, 4H), 3.00 (t, *J* = 5.1 Hz, 4H), 1.42 (s, 9H). MS(EI): m/z 356.2 $[M+H]^+$.

2-(2,6-Dioxopiperidin-3-yl)-4-((2-oxo-2-(4-(4-(pyrimidin-2-ylamino)phenyl)piperazin-1-yl)ethyl)amino) isoindoline-1,3-dione(PS-3). In a 25 mL flask was added **15** (18 mg, 0.05 mmol) in TFA/DCM (5 mL, 1/1). The mixture was stirred for 30 min at room temperature. Then remove the solvent *in vacuo* to give the deprotected intermediate, which was used for next step without further purification. To above intermediate was added compound **PS-6** (33 mg, 0.1 mol), HATU (38 mg, 0.1 mmol) and DIPEA (32 mg, 0.25 mmol) in DMF (2 mL). The mixture was stirred at room temperature for 30 min. Then the reaction mixture was concentrated *in vacuo* and the residue was purified by PrepHPLC with a reverse phase C18 column to afford the product as a yellow solid **PS-3** (13 mg, 45%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.11 (s, 1H), 9.37 (s, 1H), 8.41 (d, *J* = 4.8 Hz, 2H), 7.65 – 7.52 (m, 3H), 7.15 – 7.03 (m, 3H), 6.94 (d, *J* = 9.0 Hz, 2H), 6.75 (t, *J* = 4.8 Hz, 1H), 5.07 (dd, *J* = 12.9, 5.4 Hz, 1H), 4.26 (d, *J* = 4.5 Hz, 2H), 3.67 (d, *J* = 10.6 Hz, 4H), 3.10 (d, *J* = 26.3 Hz, 4H), 2.95 – 2.80 (m, 1H), 2.67 – 2.55 (m, 2H), 2.09 – 1.97 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.3, 170.5, 169.3, 167.8, 166.9, 160.6, 158.4, 146.3, 145.9, 136.6, 133.7, 132.5, 120.7, 118.7, 117.1, 112.1, 111.3, 110.0, 49.9, 49.6, 49.0, 44.1, 41.9, 31.4, 22.6. HRMS (m/z): [M+H]+ calcd. for $C_{29}H_{29}N_8O_5$, 569.2261; found: 569.2249.



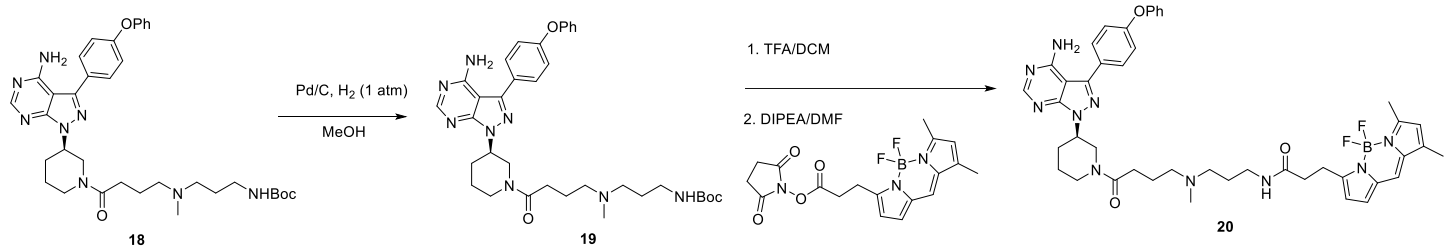
4-((2-(4-(4-Aminophenyl)piperazin-1-yl)-2-oxoethyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (PS-4). To a 100 mL flask was added compound **16** (18 mg, 0.1 mmol), **PS-6** (50 mg, 0.15 mmol), HATU (57 mg, 0.15 mmol) and DIPEA (65 mg, 0.5 mmol) in DMF (2 mL). The mixture was stirred at room temperature for 30 min. Then the reaction mixture was concentrated *in vacuo* and the residue was purified by PrepHPLC with a reverse phase C18 column to afford the product as a yellow solid **PS-4** (24 mg, 50%).^{1}H NMR (400 MHz,

DMSO-d_6) δ 11.11 (s, 1H), 7.95 (s, 2H), 7.61 (t, J = 7.8 Hz, 1H), 7.19 – 7.00 (m, 3H), 6.79 – 6.67 (m, 1.5H), 6.57 – 6.40 (m, 1.5H), 5.07 (dd, J = 12.8, 5.4 Hz, 1H), 4.23 (d, J = 4.6 Hz, 2H), 3.62 (dt, J = 12.2, 4.9 Hz, 4H), 2.99 – 2.89 (m, 4H), 2.85 (d, J = 5.7 Hz, 1H), 2.64 – 2.52 (m, 2H), 2.04 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.3, 170.5, 167.9, 166.8, 162.8, 145.9, 143.3, 142.4, 136.6, 132.5, 119.2, 118.7, 115.1, 111.3, 110.0, 51.3, 51.0, 49.0, 44.4, 44.1, 42.2, 31.2, 22.6. HRMS (m/z): [M+H]+ calcd. for $C_{25}H_{27}N_6O_5$, 491.2043; found: 491.2042.



17 PS-6 PS-5

2-(2,6-Dioxopiperidin-3-yl)-4-((2-(4-methylpiperazin-1-yl)-2-oxoethyl)amino)isoindoline-1,3-dione(PS-5). To a 100 mL flask was added compound **17** (10 mg, 0.1 mmol), **PS-6** (50 mg, 0.15 mmol), HATU (57 mg, 0.15 mmol) and DIPEA (65 mg, 0.5 mmol) in DMF (2 mL). The mixture was stirred at room temperature for 30 min. Then the reaction mixture was concentrated *in vacuo* and the residue was purified by PrepHPLC with a reverse phase C18 column to afford the product as a yellow solid **PS-5** (27 mg, 65%).^{1}H NMR (400 MHz, DMSO-d_6) δ 11.11 (s, 1H), 7.60 (dd, J = 8.5, 7.1 Hz, 1H), 7.12 – 7.04 (m, 3H), 5.07 (dd, J = 12.9, 5.3 Hz, 1H), 4.18 (d, J = 4.5 Hz, 2H), 3.49 (dt, J = 10.2, 4.9 Hz, 4H), 2.89 (ddd, J = 17.6, 13.9, 5.5 Hz, 1H), 2.64 – 2.51 (m, 2H), 2.33 (dt, J = 25.4, 5.0 Hz, 4H), 2.21 (s, 3H), 2.07 – 1.99 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.3, 170.5, 169.2, 167.8, 166.8, 145.9, 136.6, 132.5, 118.7, 111.2, 110.0, 54.9, 54.6, 49.0, 46.0, 44.1, 44.0, 41.9, 31.4, 22.6 HRMS (m/z): [M+H]+ calcd. for $C_{20}H_{24}N_5O_5$, 414.1777; found: 414.1768.

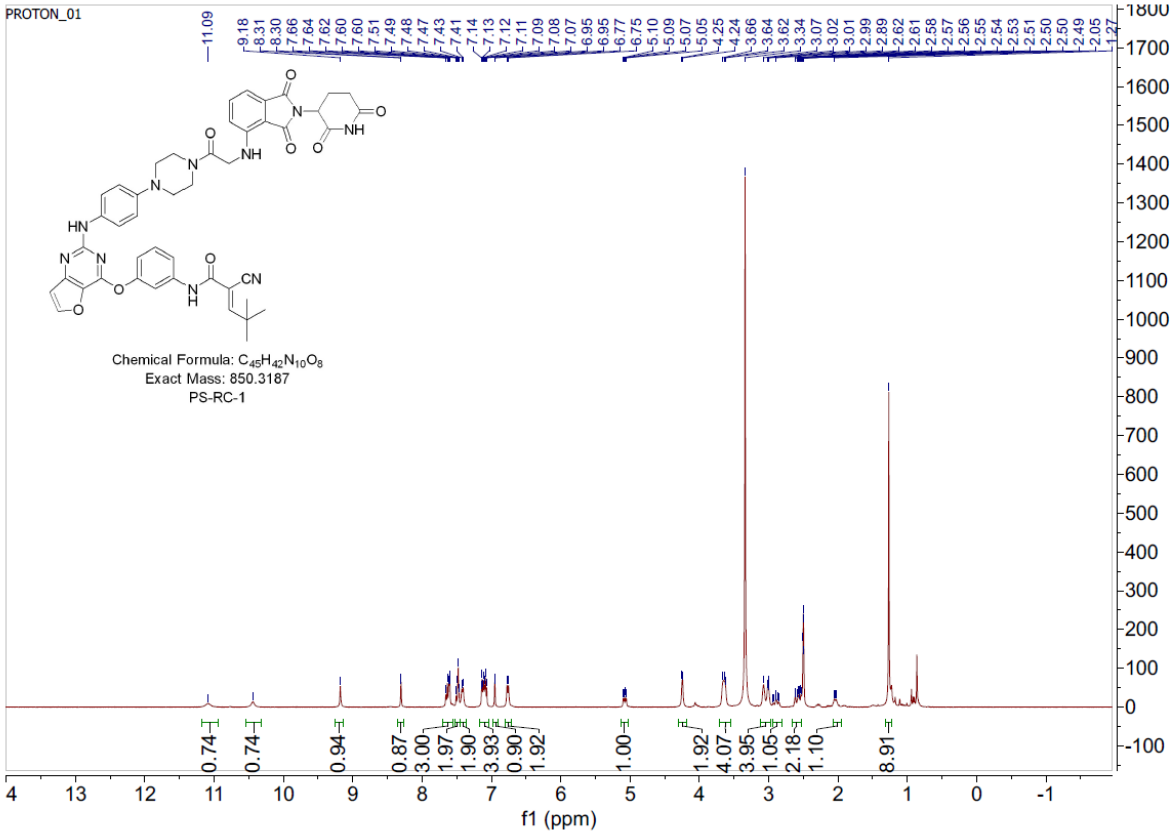


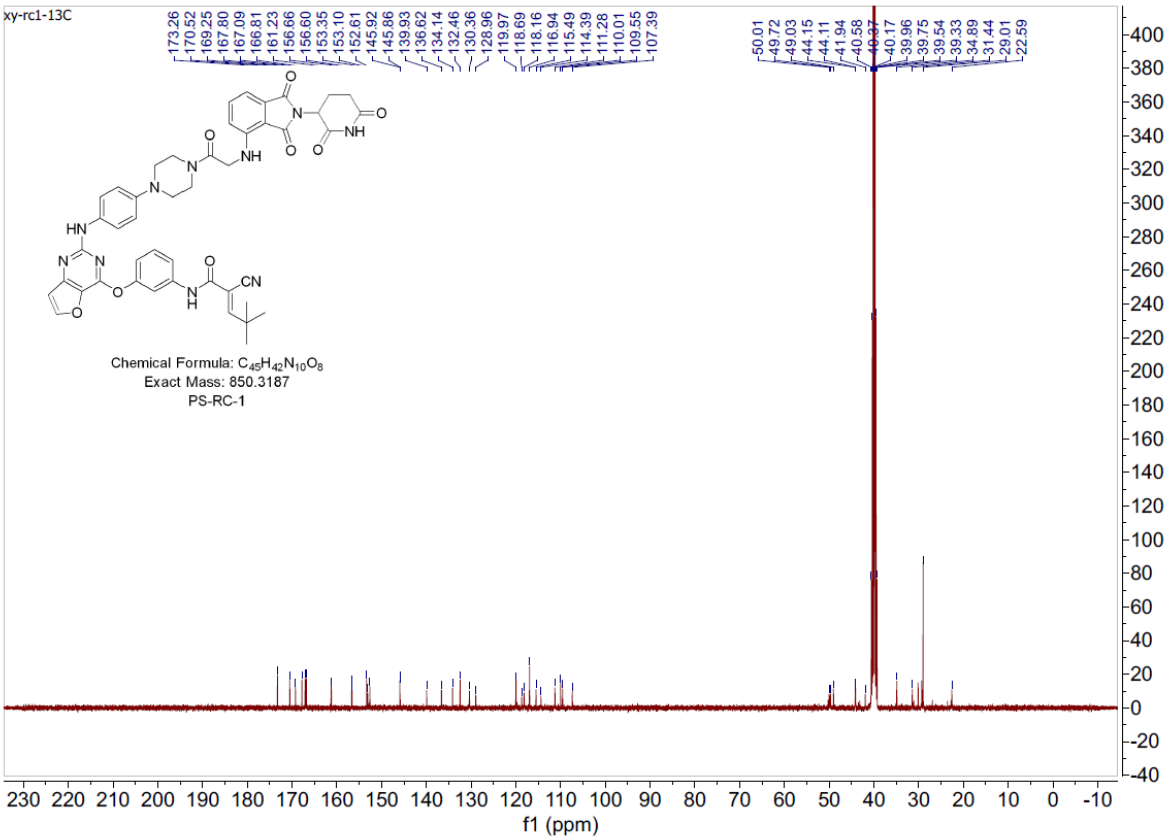
18 19 20

***tert*-Butyl (*R*)-(3-((4-(3-(4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)piperidin-1-yl)-4-oxobutyl)(methyl)amino)propyl)carbamate(19).** To a flask was added compound **18** (6.5 mg, 0.01 mmol) and Pd/C (1 mg) in MeOH (2 mL). The mixture was stirred under 1atm H_2 at room temperature overnight. LC-MS showed compound **18** converted into compound **19** completely. Then the reaction mixture was filtered, and the filtrate was concentrated *in vacuo* to provide compound **19** (5.5 mg, 90%) without further purification. In a 25 mL flask was added **18** (5 mg, 0.05 mmol) in TFA/DCM (5 mL, 1/1). The mixture was stirred for 30 min at room temperature. Then remove the solvent *in vacuo* to give the deprotected intermediate, which was used for next step without further purification. To above intermediate was added BODIPY-FL (2 mg, 0.005 mol), and DIPEA (3.2 mg, 0.025 mmol) in DMF (2 mL). The mixture was stirred at room temperature for 30 min. Then the reaction

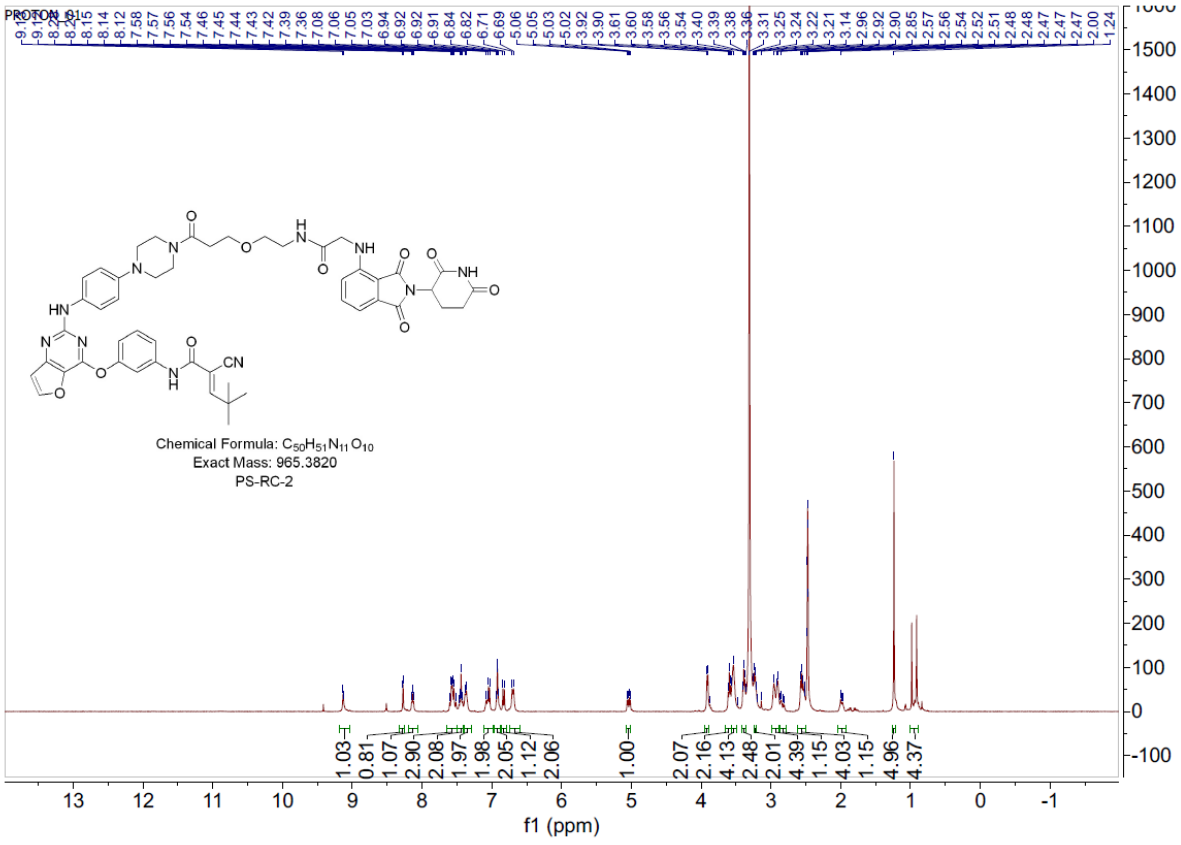
mixture was concentrated *in vacuo* and the residue was purified by PrepHPLC with a reverse phase C18 column to afford the product as a dark blue solid **20** (2 mg, 50%). MS(EI): m/z 816.4.

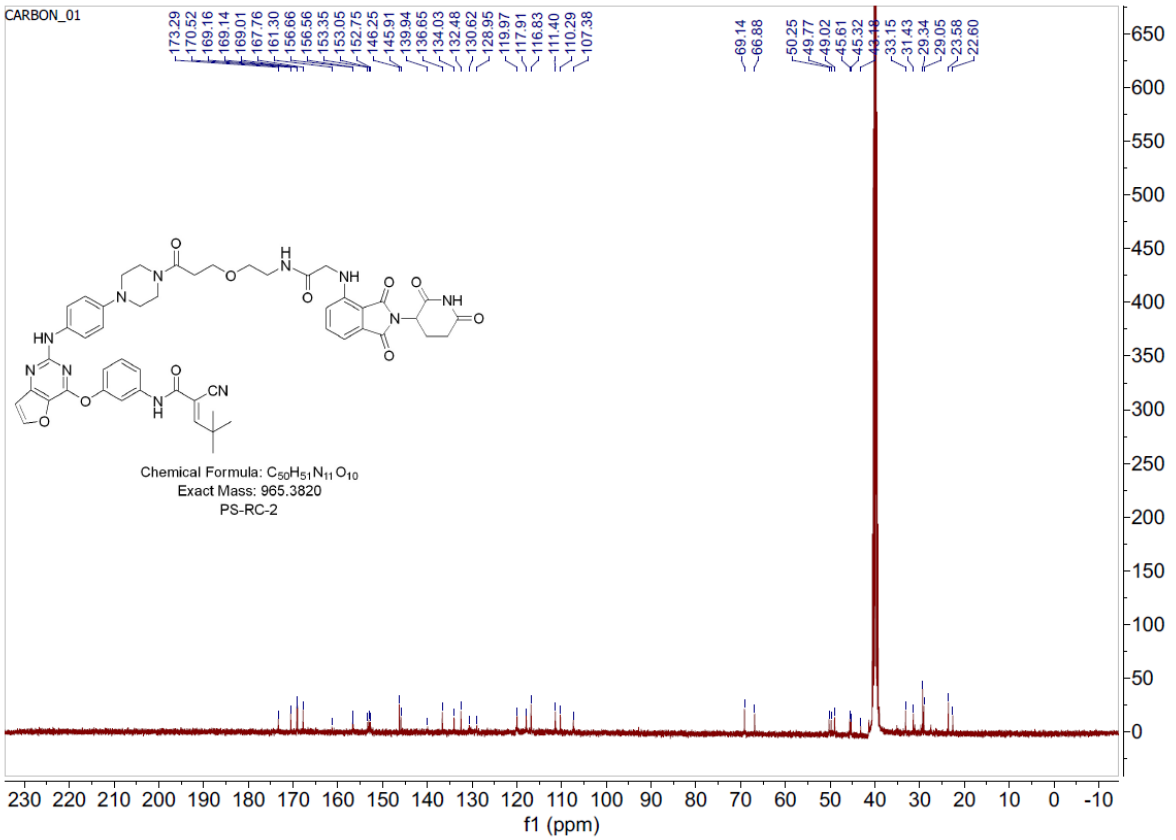
^{1}HNMR and ^{13}CNMR (PS-RC-1)



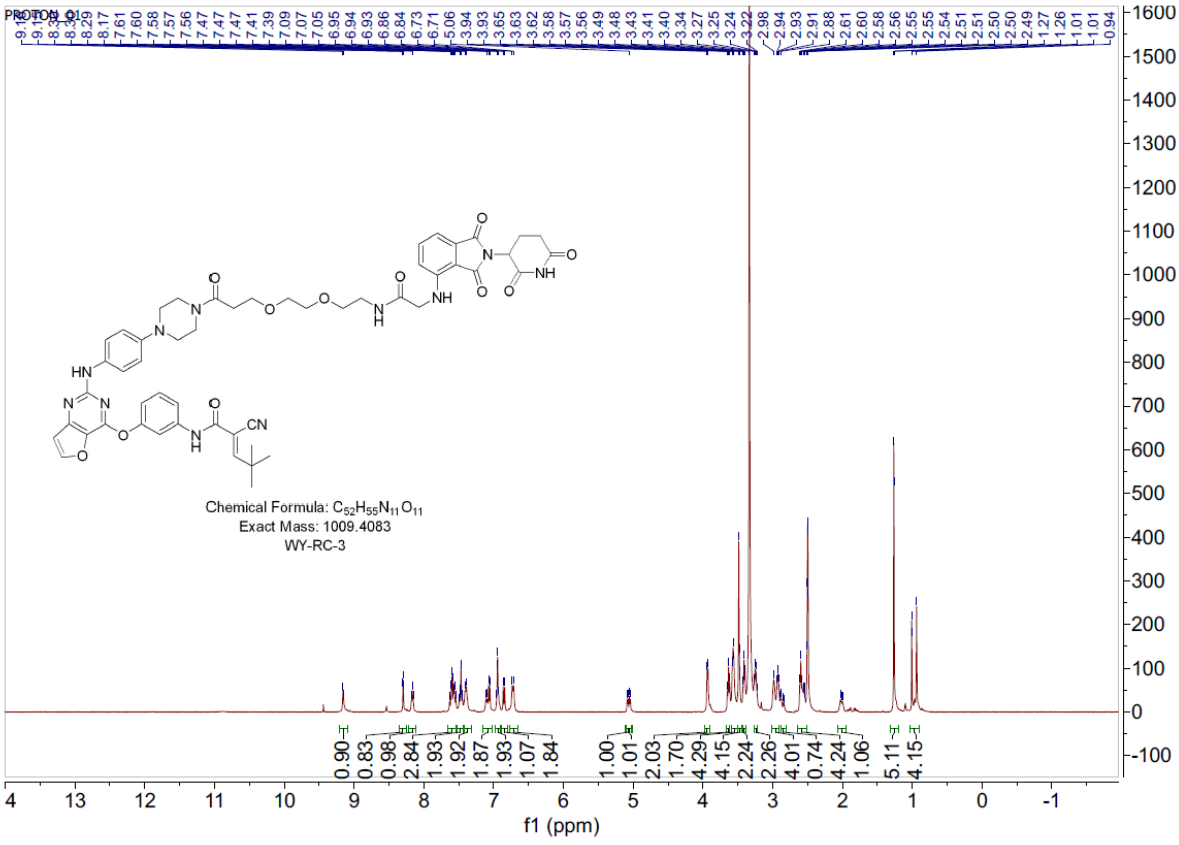


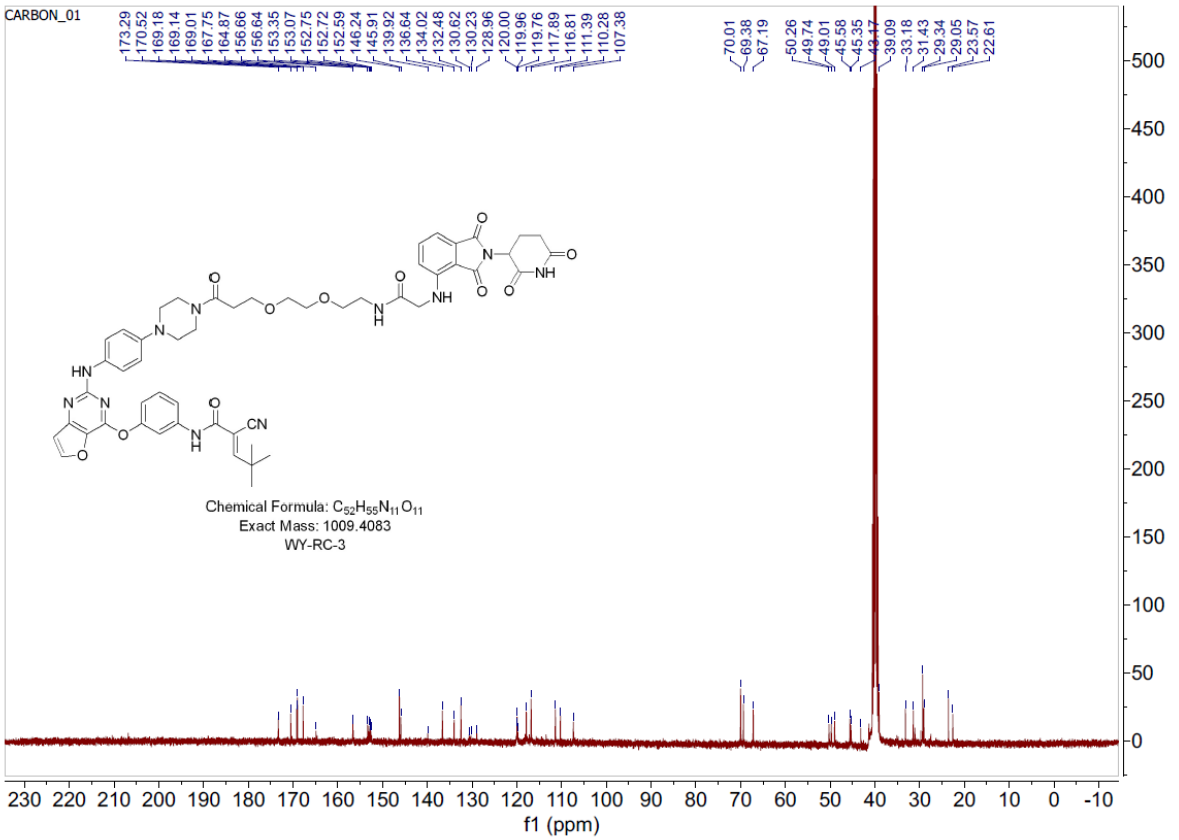
^{1}HNMR and ^{13}CNMR (PS-RC-2)



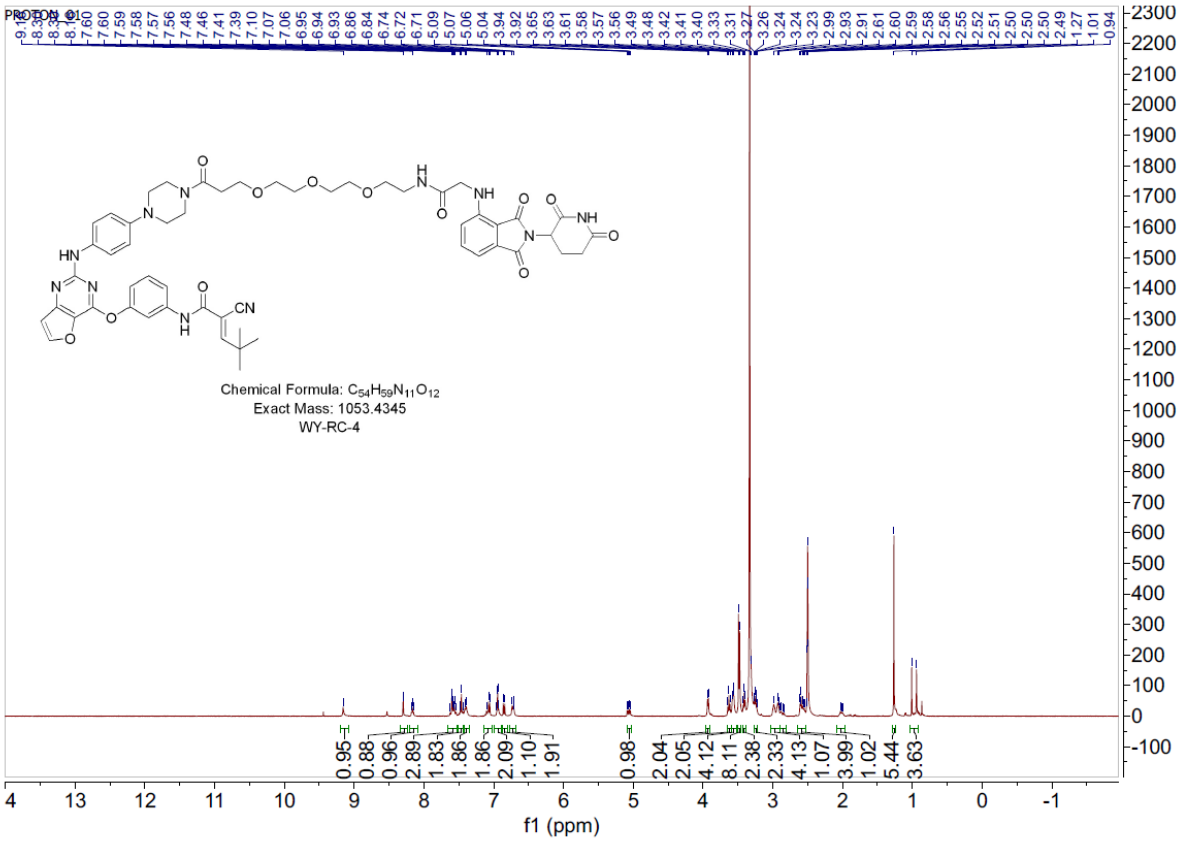


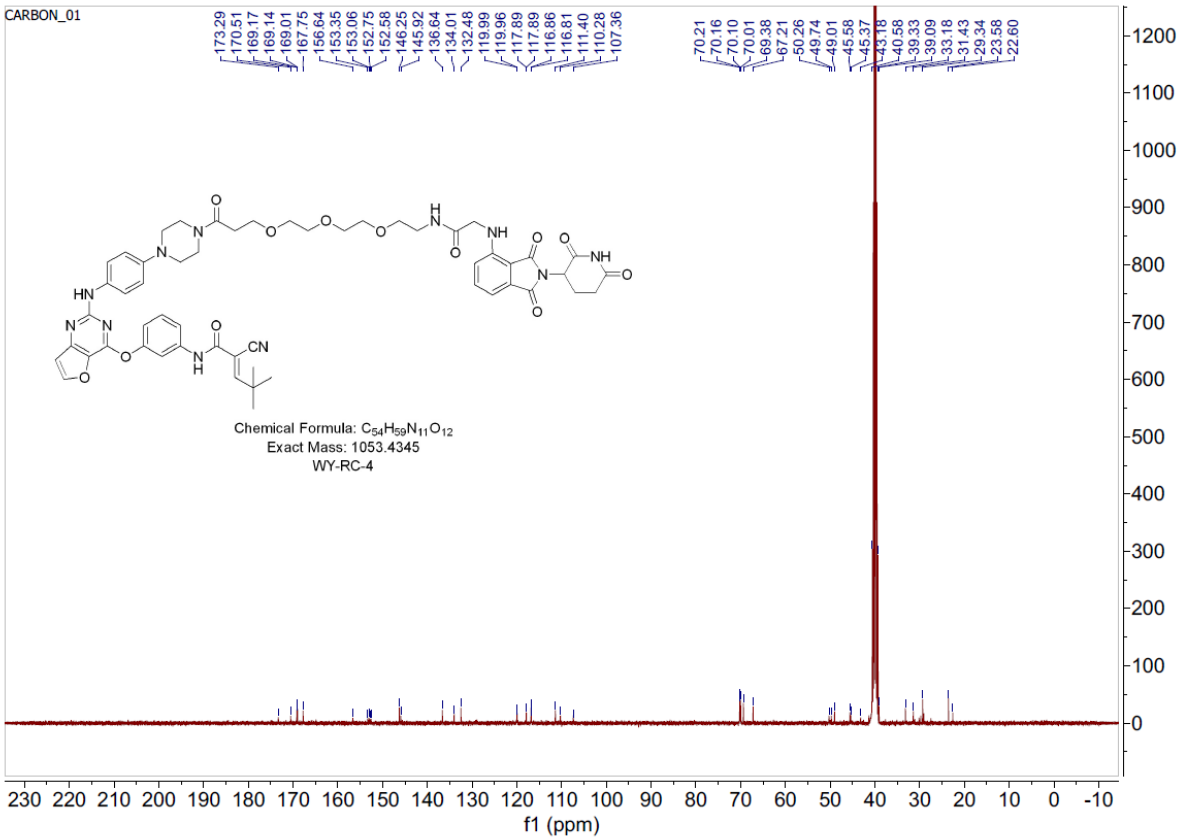
^{1}HNMR and ^{13}CNMR (PS-RC-3)



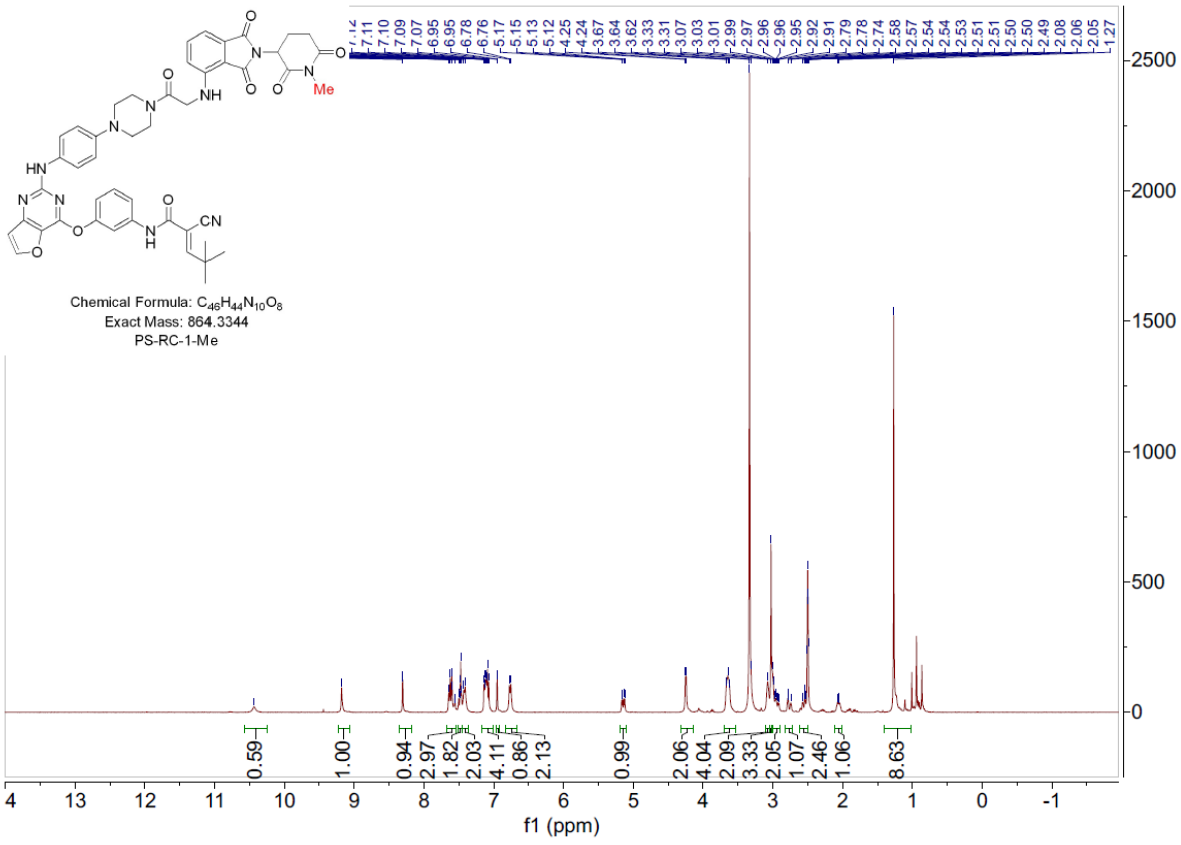


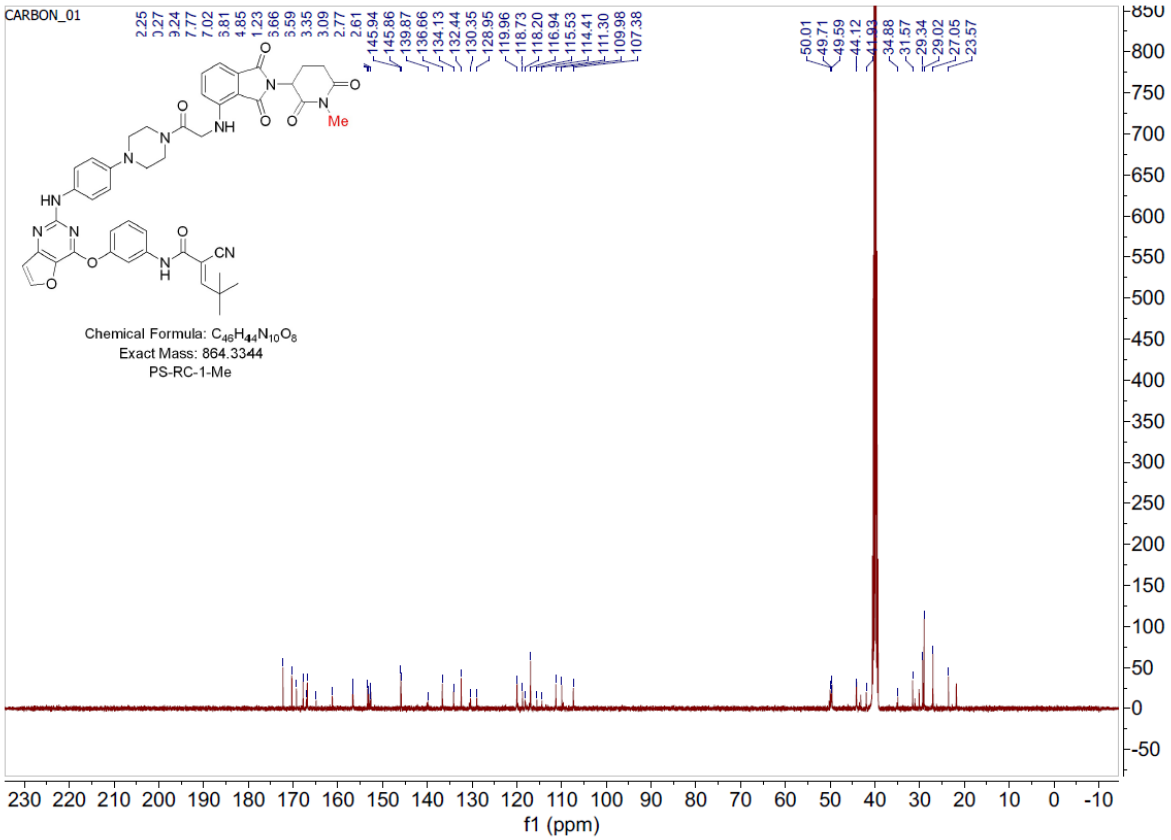
^{1}HNMR and ^{13}CNMR (PS-RC-4)



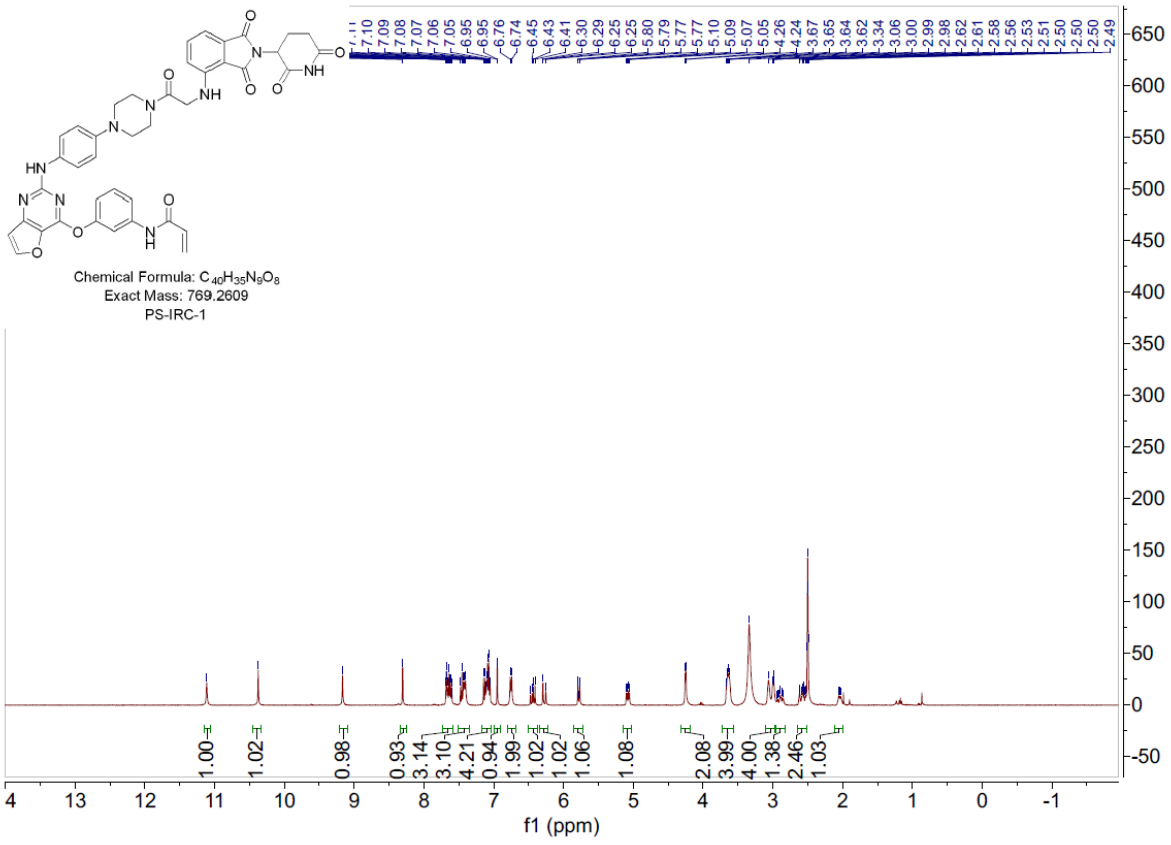


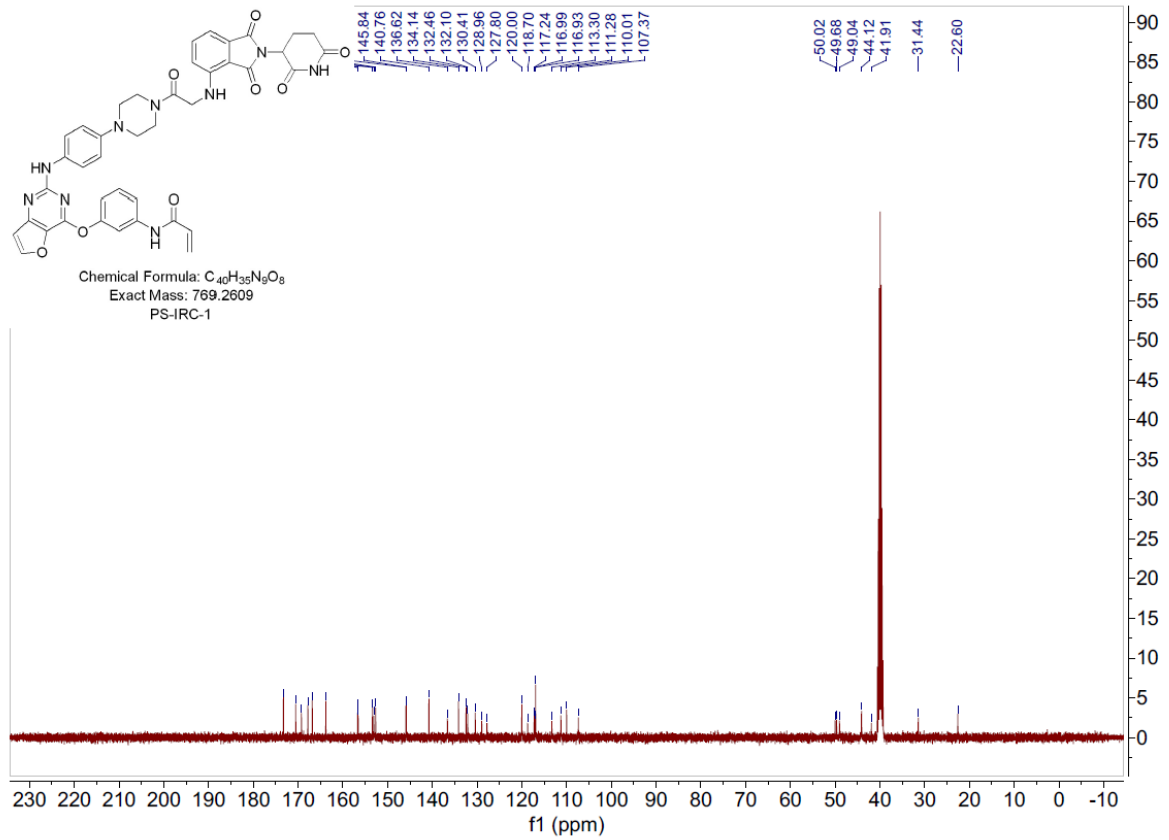
^{1}HNMR and ^{13}CNMR (PS-RC-1-Me)



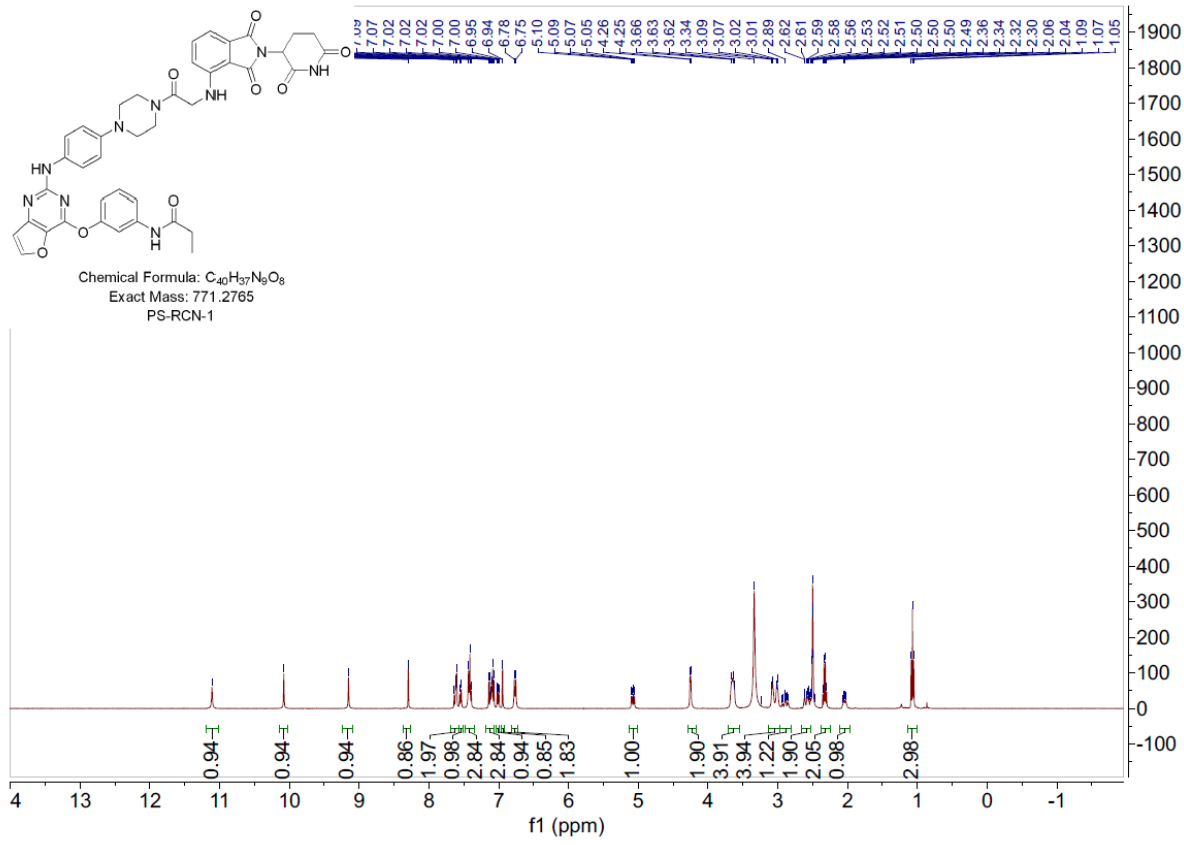


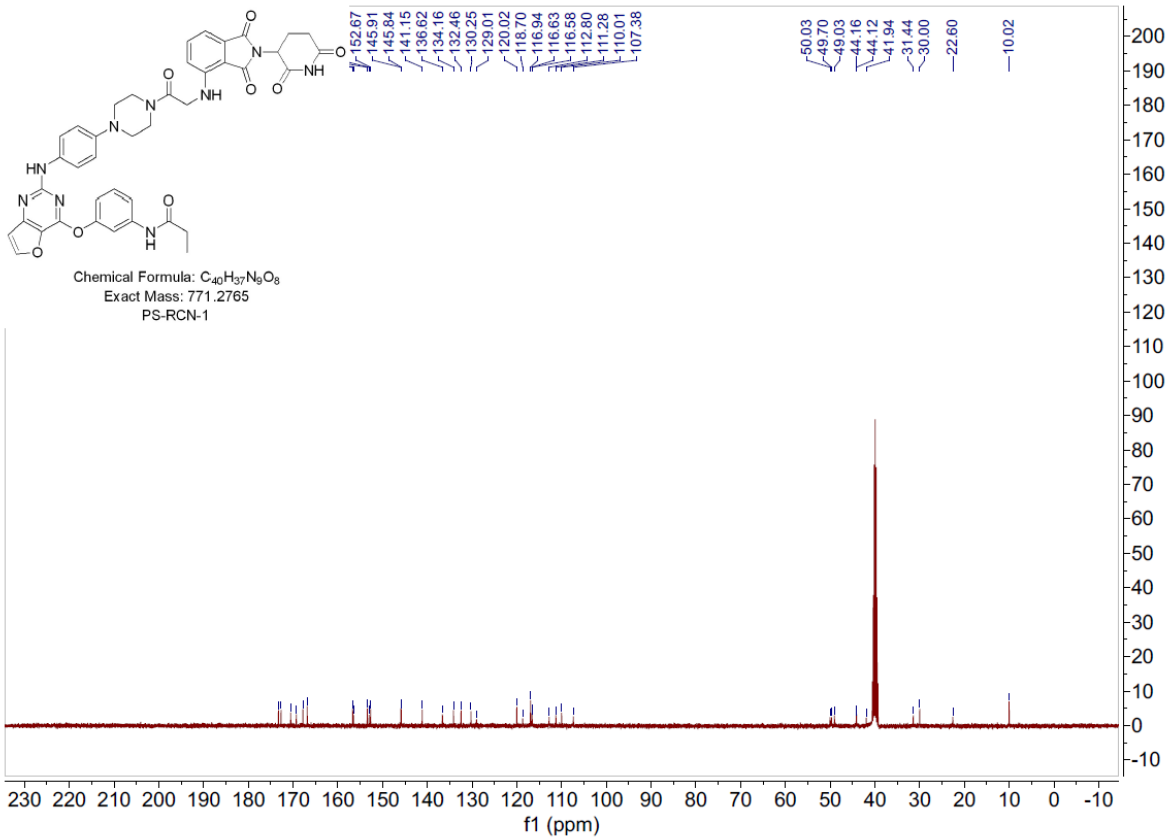
^{1}HNMR and ^{13}CNMR (PS-IRC-1)



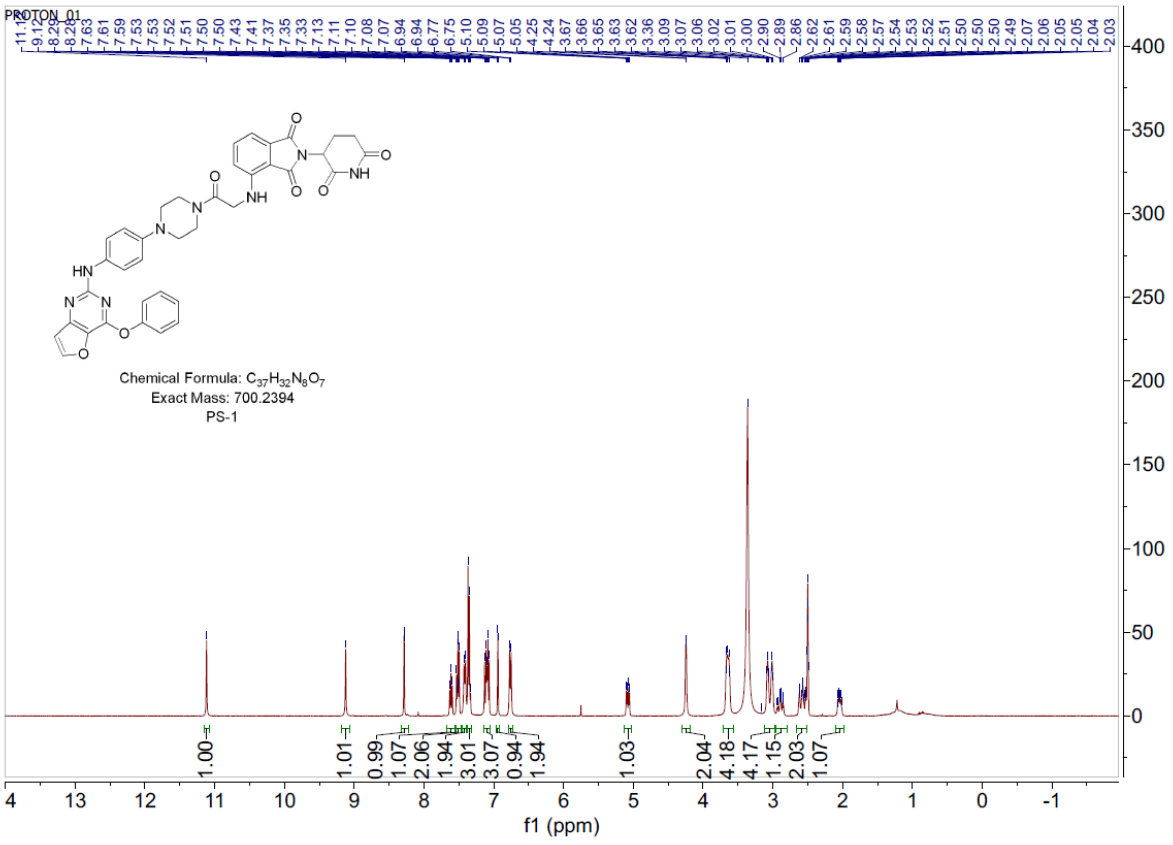


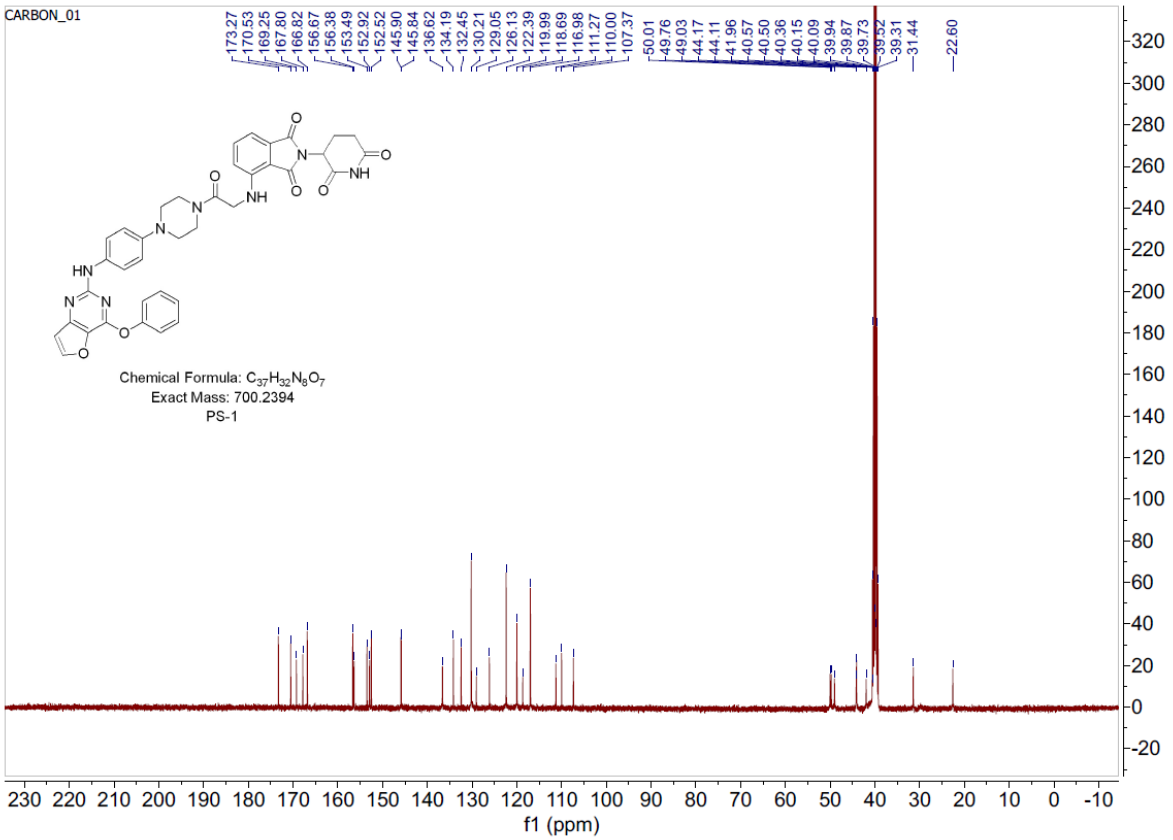
^{1}HNMR and ^{13}CNMR (PS-RNC-1)



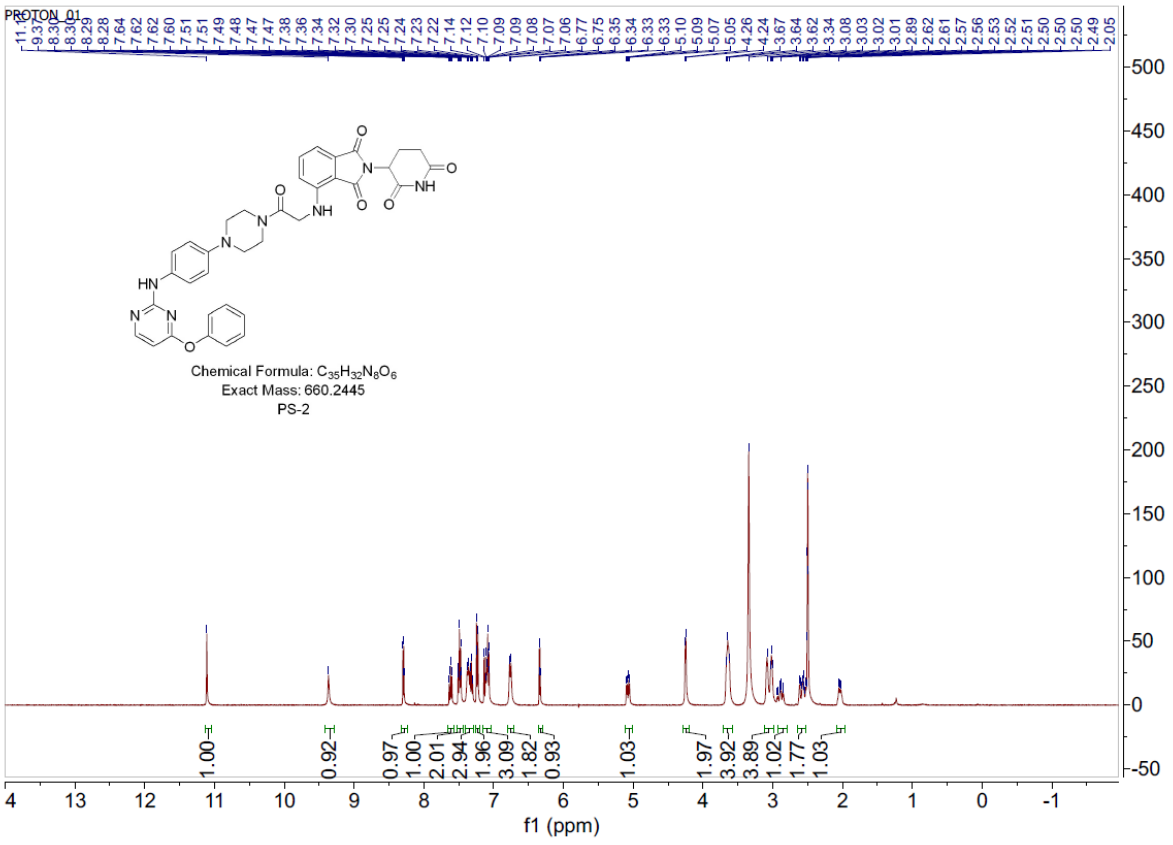


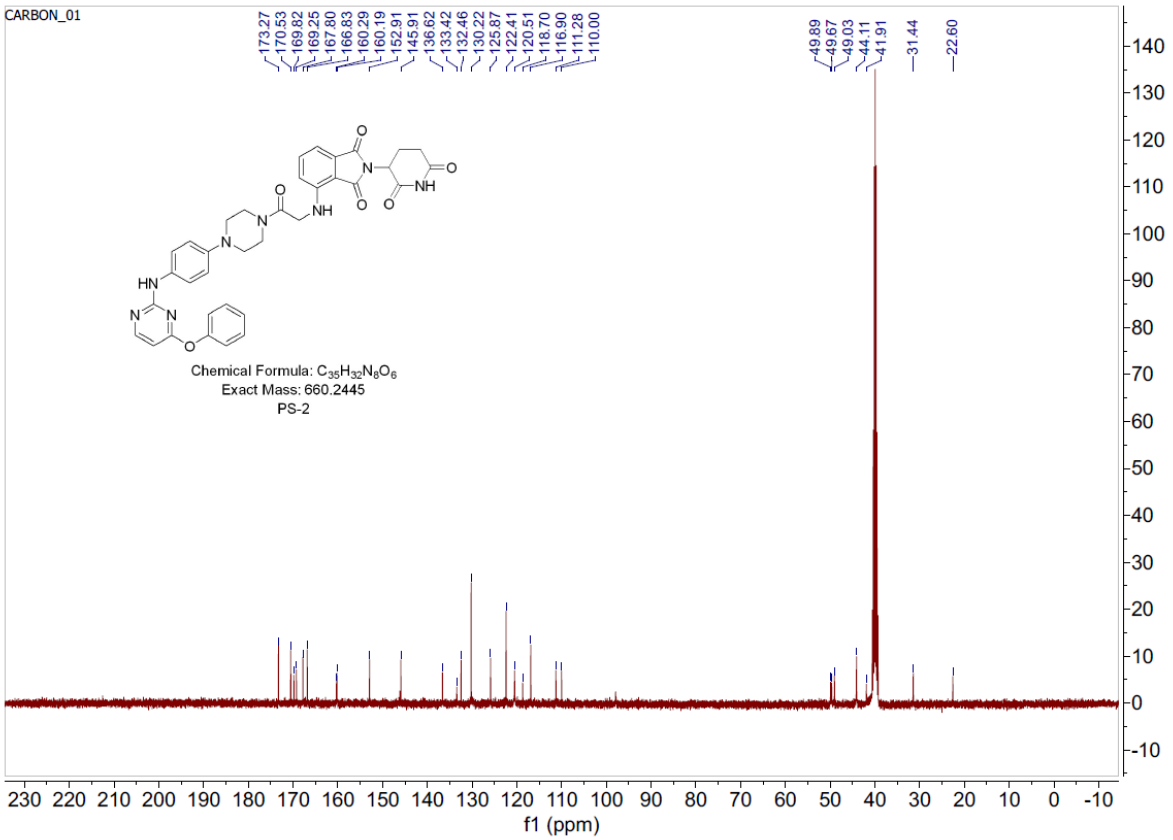
^{1}HNMR and ^{13}CNMR (PS-1)



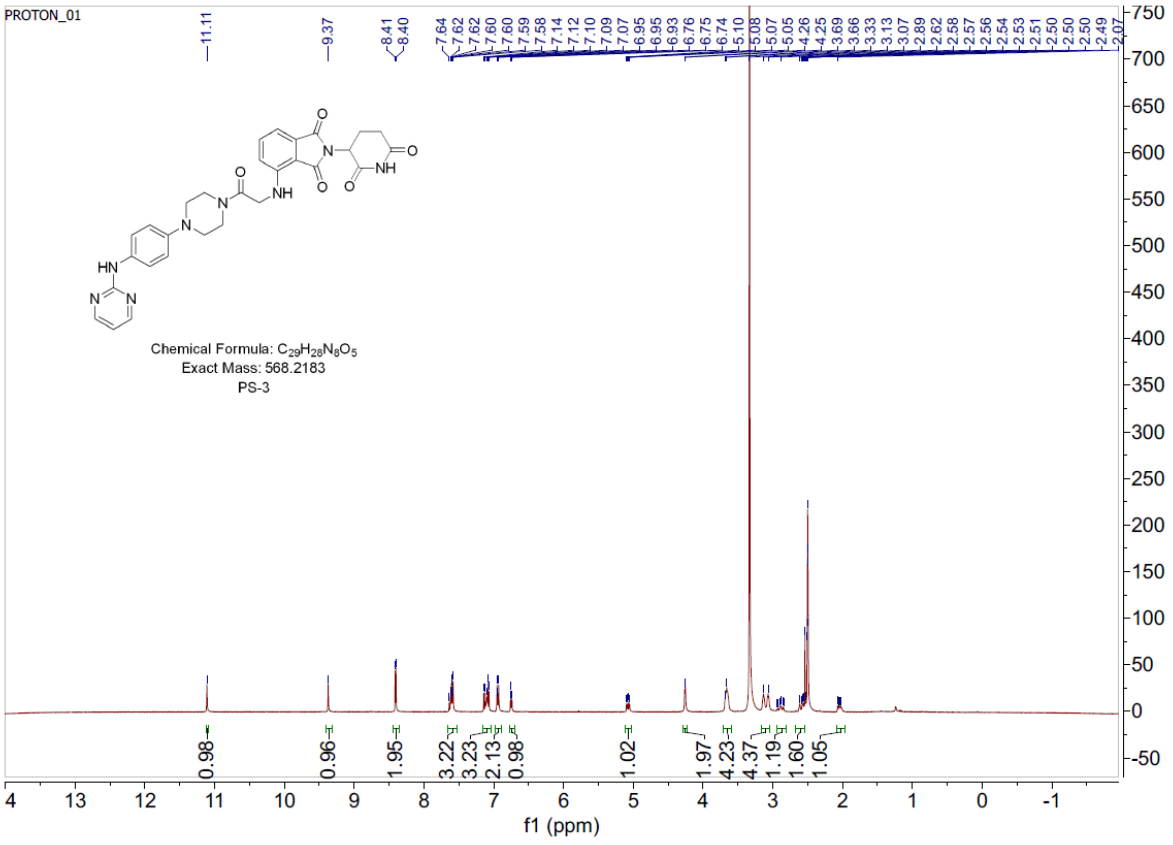


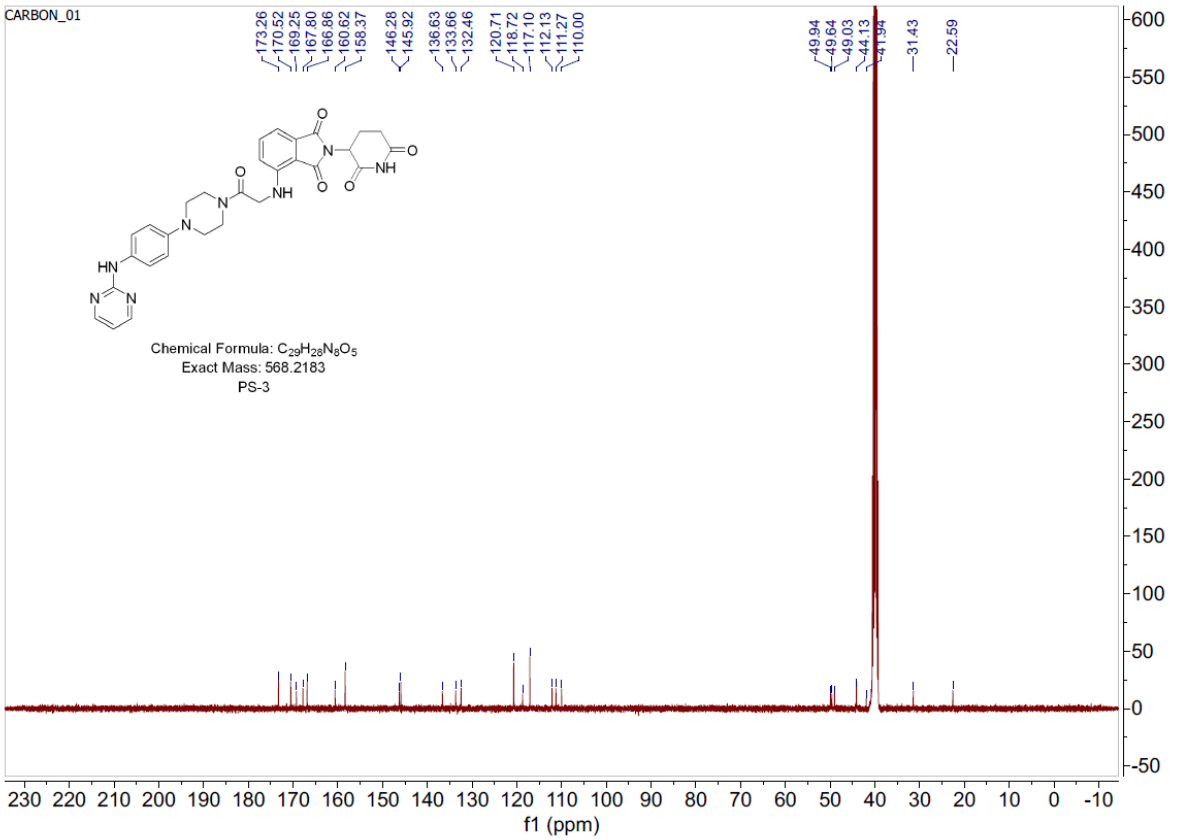
^{1}HNMR and ^{13}CNMR (PS-2)



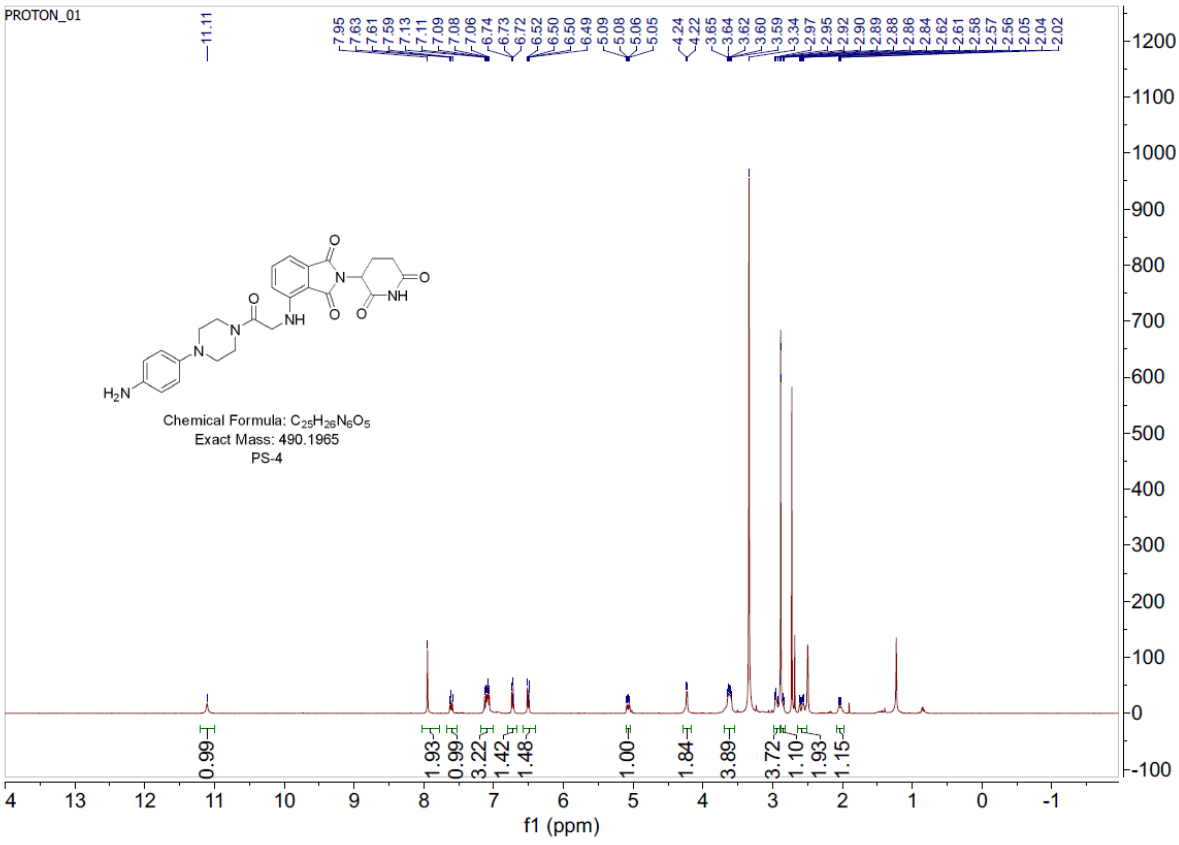


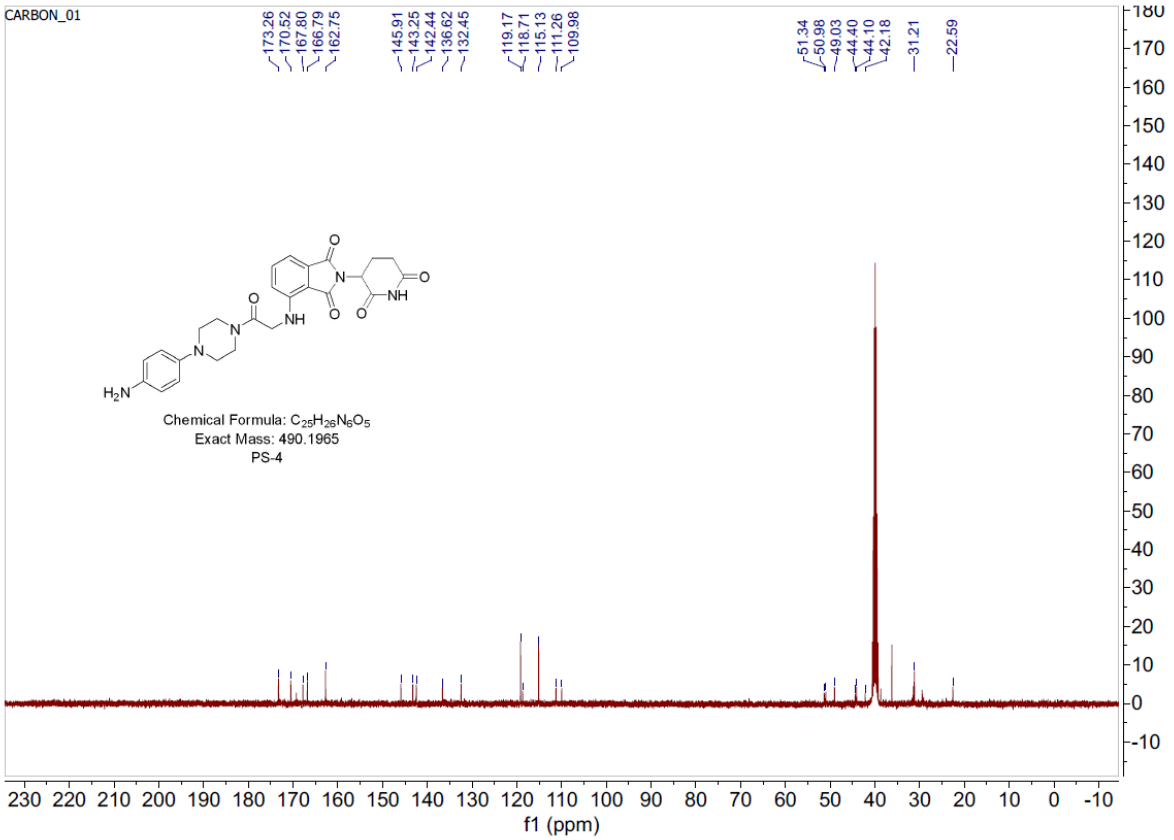
^{1}HNMR and ^{13}CNMR (PS-3)



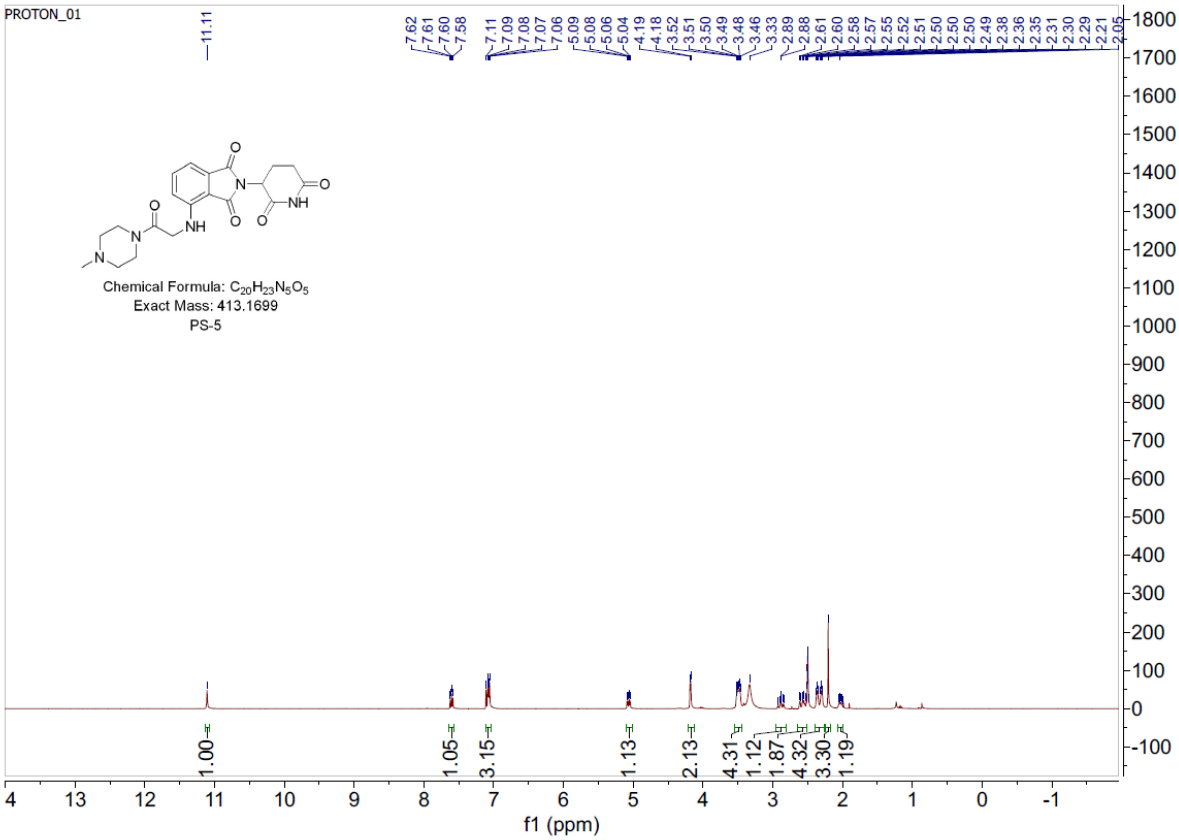


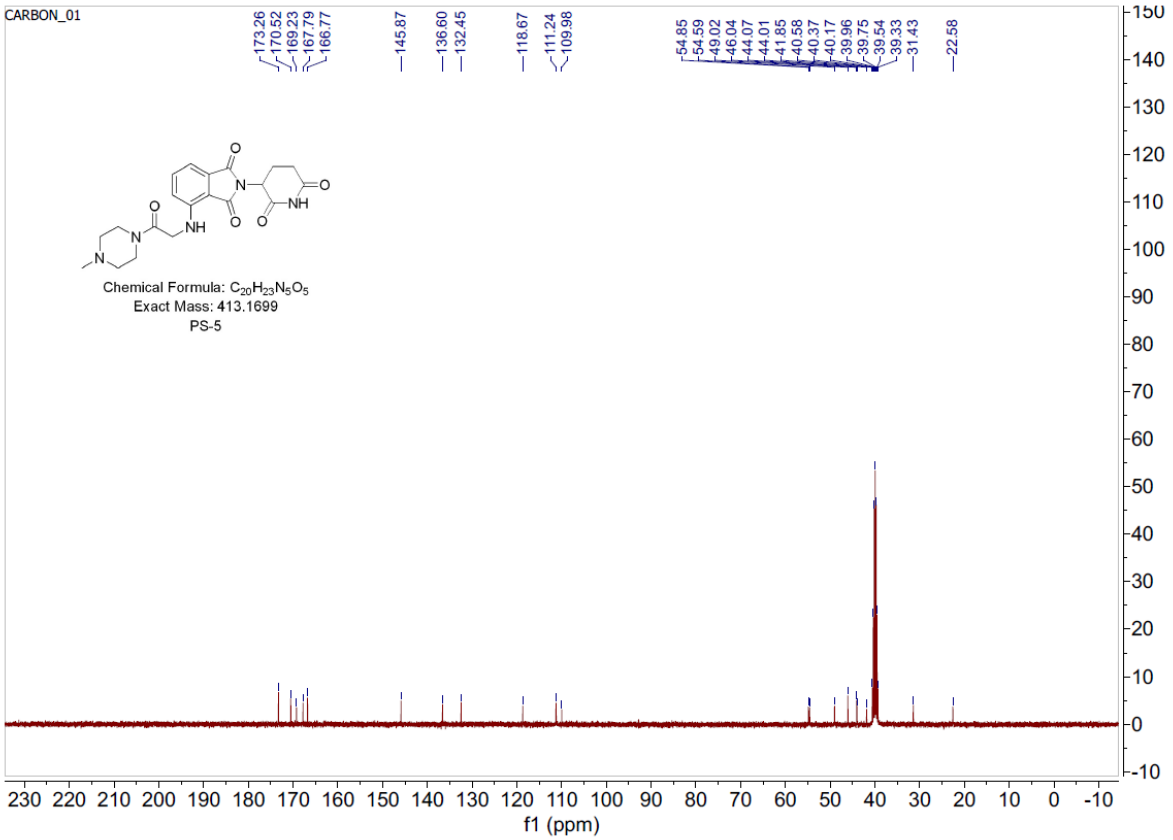
^{1}HNMR and ^{13}CNMR (PS-4)





^{1}HNMR and ^{13}CNMR (PS-5)




CARBON_01
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170.52
169.23
167.79
166.77
145.87
136.60
132.45
118.67
111.24
109.98
54.85
54.59
49.02
46.04
44.07
44.01
41.85
40.58
40.37
40.17
39.96
39.75
39.54
39.33
31.43
22.58
Chemical Formula: C20H23N5O5
Exact Mass: 413.1699
PS-5
f1 (ppm)