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Supporting Information

The tale of proteolysis targeting chimeras (PROTACs) for Leucine-Rich Repeat Kinase 2 (LRRK2)

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General remarks

Nuclear magnetic resonance spectra were recorded on a Bruker Avance 500 spectrometer (^{1}H-NMR at 500 MHz and ^{13}C-NMR at 126 MHz with tetramethylsilane (TMS) as internal standard). Chemical shifts for ^{1}H-NMR were reported as δ values and coupling constants were in hertz (Hz). The following abbreviations were used for spin multiplicity: s = singlet, b = broad singlet, d = doublet, t = triplet, q = quartet, dd = double of doublets, ddd = double of doublet of doublets, dt = doublet of triplets, td = triplet of doublets, m = multiplet. Chemical shifts for ^{13}C-NMR were reported in ppm relative to the solvent peak. Thin layer chromatography was performed on Fluka precoated silica gel plates (0.20 mm thick, particle size 25 µm). Flash chromatography was performed on a Teledyne ISCO Combiflash Rf, using RediSep Rf Normal-phase Silica Flash Columns (Silica Gel 60 Å, 230 - 400 mesh) and on a Reveleris® X2 Flash Chromatography, using Grace® Reveleris Silica flash cartridges (12 grams). Reagents were purchased from commercial suppliers (Sigma Aldrich, ABCR, Acros, AK Scientific, Combiblocks, Fluorochem) and used without any purification unless otherwise noted. Electrospray ionization mass spectra (ESI-MS) were recorded on a Waters Investigator Semi-prep 15 SFC-MS instrument. High resolution mass spectra were recorded using Orbitrap-Velos (Thermo) at a resolution of 60000@m/z400. Microwave reactions were carried out in a Biotage Initiator™ Microwave Synthesizer. The hydrogenation reaction was performed with a Parr Apparatus.

General experimental procedures

Procedure A1 (Protecting step with SEM-Cl): in a 500ml round bottom flash 4-chloro-5-iodo-7H-pyrrolo[2,3-d]pyrimidine (17.9 mmol, 1 equiv) was dissolved in dry THF (120ml). Cooling in an ice-bath and addition of NaH (19.69 mmol, 1.1 equiv) in portions as solid. The reaction mixture was stirred at 0^{o}C for 1h and then (2-chloromethoxyethyl)trimethylsilane (SEM-Cl) (19.3 mmol, 1.08 equiv) was added dropwise. After the addition, the reaction mixture was allowed to reach rt. Stirring at rt for 4h. The reaction was quenched with saturated $NaHCO_3$ (120 ml). THF was removed under reduced pressure and the residue was extracted with EtOAc (100 ml x 3). The combined organic phases were dried over $MgSO_4$, filtered and the crude product was purified by column chromatography (PE – EtOAc, 0 – 20% EtOAc in PE).

Procedure A2 (Protecting step with trityl-Cl): in a round bottom flash 4-chloro-5-iodo-7H-pyrrolo[2,3-d]pyrimidine (17.9 mmol, 1 equiv) was suspended in dry $CHCl_3$ (45ml). Triethylamine was added (27 mmol, 1.5 equiv) and the suspension was cooled at 0^{o}C. Trityl chloride (21.48 mmol, 1.2 equiv) was added in portions as solid. The reaction mixture was stirred at 0^{o}C for 15 min under $CaCl_2$ tube and then at rt for 1h. Solvent was removed under reduced pressure. 100ml MeOH were added in the residue and the formed solid was filtered under reduced pressure and dried under vacuum.

Procedure B1 (Suzuki coupling on intermediate 1): in a 3-neck 500ml round bottom flask 4-chloro-5-iodo-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine **(1)** (7.1 mmol, 1equiv), (3-cyanophenyl)boronic acid (7.81 mmol, 1.1 equiv) and K_2CO_3 (21.3 mmol, 3 equiv) were dissolved in a mixture of DME – H_2O (4:1, 100ml). The reaction mixture was degassed for 15min and then Pd(dppf)Cl_2 (0.355mmol, 0.05 equiv) was added in one portion. The reaction mixture was heated at reflux for 3h, under N_2 flow. Then, it was allowed to reach rt and was diluted with saturated NaCl (100ml) and it was extracted with EtOAc (100ml x3). The combined organic phases were dried over $MgSO_4$, filtered and the crude product was purified by column chromatography (PE – EtOAc, 0 – 20% EtOAc in PE).

Procedure B2 (Suzuki coupling on intermediate 4): In a 3-neck round bottom flask 4-chloro-5-iodo-7-trityl-7H-pyrrolo[2,3-d]pyrimidine **(4)** (9.6 mmol, 1 equiv) and (3-cyanophenyl) boronic acid (19.2 mmol, 2 equiv) were suspended in a 5:1 mixture toluene : EtOH (15 ml : 3 ml), followed by the addition of a saturated solution of $NaHCO_3$ (18ml). The reaction mixture was degassed for 15min and then $Pd(dppf)Cl_2$ (0.0384 mmol, 0.004 equiv) was added in one portion. The reaction mixture was heated overnight at 85°C under N_2 flow. The next day, the reaction mixture was allowed to reach rt, H_2O was added and the reaction mixture was extracted with EtOAc (x3). The combined organic phases were washed with 1N NaOH (x2), Brine (x3), dried over $MgS0_4$, filtered and the solvents were removed under reduced pressure. The crude product was purified by column chromatography (PE – EtOAc, 0 – 20% EtOAc in PE).

Procedure C1 (Deprotection of SEM-group): 3-(4-chloro-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)benzonitrile **(2)** (2 mmol, 1 equiv) was dissolved in 5ml TFA. Stirring rt overnight under $CaCl_2$ tube. DCM was added (10 ml) and the solvents were removed under reduced pressure to get a yellow oil. 15ml of methanol were added to get a yellow suspension. Under stirring at 0°C, solid K_2CO_3 was added in small portions until pH>12. Methanol was removed under reduced pressure and water was added (5ml). The suspension was filtered under vacuum and the obtained solid was washed with water and dried under vacuum.

Procedure C2 (Deprotection of trityl-group): 4-chloro-5-iodo-7-trityl-7H-pyrrolo[2,3-d]pyrimidine **(5)** (5.1mmol, 1 equiv) was dissolved in DCM (20ml). The solution was cooled in an ice-bath and TFA (10ml) was added. Stirring at 0°C for 10 min and then rt overnight under $CaCl_2$ tube. Solvents were removed under reduced pressure. The oily residue was dissolved in 20ml MeOH. Under stirring at 0°C, solid K_2CO_3 was added in small portions until pH>12. Methanol was removed under reduced pressure and water was added (5ml). The suspension was filtered under vacuum and the obtained solid was washed with water and dried under vacuum. The obtained solid was triturated with diethylether to remove impurities.

Procedure D1 (Nucleophilic aromatic substitution with morpholine): 3-(4-chloro-7H-pyrrolo[2,3-d]pyrimidin-5-yl)benzonitrile **(3)** (0.39 mmol, 1 equiv) was suspended in *tert*-butanol (5 ml). DIPEA (0.78 mmol, 2 equiv) and morpholine (0.43 mmol, 1.1 equiv) were added and the reaction mixture was heated at reflux for 3h. Solvent was removed and the crude was purified by column chromatography (DCM – MeOH, 0 – 6% MeOH in DCM).

Procedure D2 (Nucleophilic aromatic substitution with 3-substituted morpholines or Boc-piperazine): in a microwave vial 3-(4-chloro-7H-pyrrolo[2,3-d]pyrimidin-5-yl)benzonitrile **(3)** (0.39 mmol, 1 equiv) was suspended in ethanol (2 ml). DIPEA (0.78 mmol, 2 equiv) and the appropriate secondary amine (0.43 mmol, 1.1 equiv) were added and the reaction mixture was subjected to microwave irradiation (1h, 150°C). Solvent was removed and the crude was purified by column chromatography (DCM – MeOH, 0 – 6% MeOH in DCM).

Procedure E (Ester hydrolysis): the ethyl ester (1equiv) was suspended in a mixture of THF – H_2O (2:1, 0.2M) and LiOH (2 equiv) was added. The reaction mixture was stirred rt overnight. Solvents were removed under reduced pressure and the residue was dissolved in 5ml H_2O. Cooling at 0°C and acidification with 2N HCl until pH = 1. Extraction with EtOAc (50 ml x3), drying over $MgSO_4$, filtration and evaporation under reduced pressure.

Procedure F (Substitution of fluorine with methoxy group): In a round bottom flask, 2,5-difluoro-4-nitrobenzoic acid (24.6 mmol, 1 equiv) was dissolved in methanol (80 ml) at room temperature. A solution of freshly prepared KOH (73.8 mmol, 3 equiv) in 30 ml MeOH was added dropwise over 20 min. The formed suspension was stirred at room temperature for 2 h and eventually the reaction mixture became a yellow solution. Methanol was removed under reduced pressure and the residue was suspended in 50 ml of EtOAc. While cooling in an ice-bath acidification with 2N aqueous HCl, until pH =1 and extraction with EtOAc (80 ml x3), drying over $MgSO_4$, filtration and evaporation under reduced pressure.

Procedure G (Esterification): 2-fluoro-5-methoxy-4-nitrobenzoic acid **(12)** (9.3 mmol, 1 equiv) was dissolved in ethanol under stirring. N-Ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ, 11.2 mmol, 1.2 equiv) was added in portions. The reaction mixture was heated at reflux for 5 h. Solvent was removed under reduced pressure and the residue was dissolved in EtOAc (100 ml) and washed with 1N HCl (x2), H_2O (x2) and Brine (x2). The organic phase was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure.

Procedure H (Reduction with stannous chloride): ethyl 2-fluoro-5-methoxy-4-nitrobenzoate **(13)** (9.1 mmol, 1 equiv) was suspended in a mixture of ethanol – water (65 ml : 6.5 ml). Stannous chloride (36.4 mmol, 4 equiv) was added in portions at room temperature. The reaction mixture was heated at reflux for 4h. Solvent was removed under reduced pressure and the residue was diluted with 50 ml EtOAc. Under stirring, saturated $NaHC0_3$ was added until pH=8. Extraction with EtOAc (80 ml x3). The combined organic phases were dried over $MgSO_4$, then passed through a pad of celite and the solvent was removed under reduced pressure.

Procedure I (Selective nucleophilic aromatic substitution of chlorine): ethyl 4-amino-2-fluoro-5-methoxybenzoate **(14)** (9.0 mmol, 1 equiv) was dissolved in a mixture of diethylether (6.0 ml), *tert*-butanol (4.0 ml) and DCM (15 ml) and was then cooled in an ice-bath. At 0^{o}C under stirring, zinc chloride (18.0 mmol, 2 equiv) was added in portions as solid, followed by the addition of 2,4-dichloro-5-(trifluoromethyl)pyrimidine (9.0 mmol, 1.0 equiv) and triethylamine (9.9 mmol, 1.1 equiv). The reaction mixture was stirred at 0^{o}C for 1h under $CaCl_2$ tube and then at room temperature for 48h. The reaction was monitored by TLC (PE: EtOAc 8:2). The reaction mixture was diluted with 40 ml DCM and slowly 40 ml of water were added (bubbling was observed). Stirring rt for 15 min and then extraction with DCM (50 ml x3). The combined organic phases were washed with Brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude residue was purified by column chromatography PE: EtOAc (0-50% EtOAc in PE).

Procedure J (Nucleophilic aromatic substitution of chlorine): ethyl 4-((4-chloro-5-(trifluoromethyl)pyrimidin-2-yl)amino)-2-fluoro-5-methoxybenzoate **(15)** (3.3 mmol, 1 equiv) was dissolved in 15 ml dry THF. Cooling at 0^{o}C and then dropwise addition of a 2N solution of ethanamine (6.6 mmol, 2.2 equiv) under N_2 flow. The reaction mixture was stirred at 0^{o}C for 30 min and then rt for 2 h. Solvent was removed under reduced pressure. The residue was diluted with EtOAc (50ml) and washed with H_2O (x2) and Brine (x2). The organic phase was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure.

Procedure K (Synthesis of substituted 2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-diones): In a round-bottom flask, the appropriate 4-substituted-isobenzofuran-1,3-dione (1 equiv), 3-aminopiperidine-2,6-dione hydrochloride (1 equiv) and sodium acetate (1.2 equiv) were mixed in AcOH (20 ml for

5mmol scale). The resulting mixture was heated at 120°C overnight. After cooling to room temperature, most of the AcOH was removed under reduced pressure and the residue was dissolved in the water, filtered and washed with water and dried with vacuum to obtain the crude compound.

Procedure L (Reduction): To a solution of 2-(2,6-dioxopiperidin-3-yl)-4-nitroisoindoline-1,3-dione (8 mmol, 1.0 equiv) in dry DMF (50 ml) was added the Pd/C (1.6mmol, 0.2 equiv) under N_2. The reaction mixture was hydrogenated with 3.0 atm H_2 pressure at room temperature for 4 h (Parr Apparatus). The progress of the reaction was monitored by TLC. The reaction mixture was filtered over a pad of celite. The filtrate was diluted with EtOAc and the organic phase was washed with H_2O and Brine (x3), dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure, to obtain a solid, which was used directly in the next step.

Procedure M (Anhydride opening): A mixture of 4-amino-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (7.3 mmol, 1.0 equiv), potassium acetate (29.3 mmol, 4.0 equiv) and glutaric anhydride (29.23 mmol, 4.0 equiv) in glacial AcOH (60 ml) was heated at reflux under nitrogen for 3h. After cooling at room temperature, acetic acid was removed under reduced pressure and the residue was extracted with (EtOAc – H_2O). The organic phases were dried with $MgSO_4$, filtered and solvents were removed under reduced pressure. The crude product was purified by column chromatography (DCM – MeOH, 0 – 10% MeOH in DCM).

Procedure N (Amidation): To a stirred suspension of 4-amino-2-(2,6-dioxo(3-piperidyl))isoindoline-1,3-dione (5.00 mmol, 1 equiv) in THF (30 ml), chloroacetyl chloride (5.5 mmol, 1.1 equiv) was added. The mixture was heated to reflux for 30 minutes. The solvent was evaporated under reduced pressure and the obtained solid was treated with diethyl ether (20 ml) and filtered to give the product, which was used directly in the next step.

Procedure O (Aliphatic substitution): A mixture of 2-chloro-*N*-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)acetamide (3.44 mmol, 1.0 equiv), *tert*-butyl (piperidin-4-ylmethyl) carbamate (3.8 mmol, 1.1 equiv), NaI (3.44 mmol, 1.0 equiv) and K_2CO_3 (6.88 mmol, 2 equiv) in THF (30 ml) was stirred at room temperature overnight. The solvent was removed under reduced pressure, water (50 ml) was added, and the reaction mixture was extracted with EtOAc (3 × 100 ml). The combined organic phases were washed with brine (50 ml), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (DCM: MeOH = 20:1).

Procedure P (Nucleophilic aromatic substitution of fluorine): The appropriate mono-Boc protected diamine (1.13 mmol, 1.1 equiv) was added to a stirred solution of 2-(2,6-dioxopiperidin-3-yl)-4-fluoroisoindoline-1,3-dione (1.03 mmol, 1.0 equiv) in DMF (1 M) and DIPEA (2.06 mmol, 2.0 equiv). The reaction mixture was stirred at 90 °C for 12 h. Then the mixture was cooled to room temperature, poured into H_2O, and extracted twice with EtOAc (3 x 50 ml). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and filtered. Solvents were removed under reduced pressure and the crude product was purified by column chromatography (PE – EtOAc, 0 - 50% EtOAc in PE).

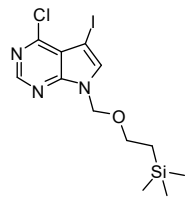
Procedure Q1 (Amide coupling with boc-protected amines): The appropriate boc-protected amine (1 equiv) was deprotected with 4N HCl in dioxane with stirring rt overnight. The reaction mixture was dried under vacuum. Diethylether was added (x2) and was removed under reduced pressure. The obtained HCl salt was used directly in the amide coupling. The HCl salt (1 equiv) was suspended in $CHCl_3$ (0.1M). Under stirring DIPEA (2 equiv) was added, followed by the addition of the carboxylic

acid (1 equiv) and EEDQ (2 equiv). The reaction mixture was heated at reflux for 2h. Then it was allowed to reach rt and was purified directly by column chromatography (DCM – MeOH, 0 – 10% MeOH in DCM).

Procedure Q2 (Amide coupling with secondary amines): the carboxylic acid (1 equiv) and EEDQ (2 equiv) were stirred at rt in $CHCl_3$ (0.1M), followed by the addition of the secondary amine (1 equiv). The reaction mixture was heated at reflux for 2h. Then it was allowed to reach rt and was purified directly by column chromatography (DCM – MeOH, 0 – 10% MeOH in DCM).

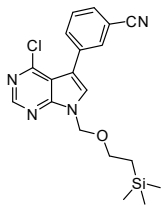
Characterization data

4-chloro-5-iodo-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine (1)



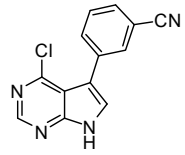
Obtained using procedure A1 on 17.9 mmol scale; 2.9 g, 7.1 mmol, yield 40%, white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.69 (s, 1H), 8.14 (s, 1H), 5.60 (s, 2H), 3.51 (t, *J* = 8.0 Hz, 2H), 0.82 (t, *J* = 8.0 Hz, 2H), -0.10 (s, 9H). ^{1}H NMR is in good agreement with published data. [s1]

3-(4-chloro-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl) benzonitrile (2)



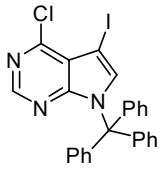
Obtained using procedure B1 on 7.1 mmol scale; 800 mg, 2.1 mmol, yield 30%, off-white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.75 (s, 1H), 8.13 (s, 1H), 8.01 (b, 1H), 7.90 – 7.86 (m, 2H), 7.72 – 7.66 (m, 1H), 5.70 (s, 2H), 3.59 (t, *J* = 8.0 Hz, 2H), 0.86 (t, *J* = 8.0 Hz, 2H), -0.08 (s, 9H). ^{1}H NMR is in good agreement with published data.[s1]

3-(4-chloro-7H-pyrrolo[2,3-d]pyrimidin-5-yl)benzonitrile (3)



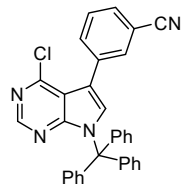
Obtained using procedure C1 on 2.0 mmol scale; 305 mg, 1.2 mmol, yield 60%, white solid. Obtained also using procedure C2 on 5.1 mmol scale; 1.2 g, 4.6 mmol, yield 90%, white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.48 (s, 1H), 7.94 (s, 1H), 7.87 – 7.85 (m, 2H), 7.71 (d, *J* = 7.9 Hz, 1H), 7.60 (t, *J* = 7.8 Hz, 1H).^{1}H NMR is in good agreement with published data.[s1] HRMS (ESI): m/z calcd for $C_{13}H_8N_4Cl$ $[M+H]^+$: 255.0432; found 255.0432.

4-chloro-5-iodo-7-trityl-7H-pyrrolo[2,3-d]pyrimidine (4)



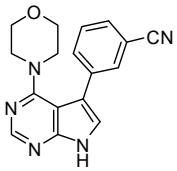
Obtained using procedure A2 on 17.9 mmol scale; 9.3 g, 17.85 mmol, yield 99%, white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.38 (s, 1H), 7.31– 7.28 (m, 10H), 7.13 – 7.11 (m, 5H).^{1}H NMR is in good agreement with published data.[s2]HRMS (ESI): m/z calcd for $C_{25}H_{18}N_3Cl$ $[M+H]^+$: 522.0228; found 522.0227.

4-chloro-5-iodo-7-trityl-7H-pyrrolo[2,3-d]pyrimidine (5)



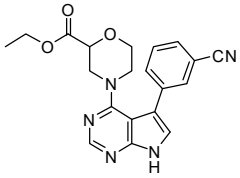
Obtained using procedure B2 on 9.6 mmol scale; 2.8 g, 5.7 mmol, yield 60%, white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.77 – 7.74 (m, 2H), 7.66 – 7.63 (m, 1H), 7.51 (t, *J* = 7.8 Hz, 1H), 7.34 – 7.30 (m, 10H), 7.20 – 7.18 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.7, 152.0, 150.0, 141.6, 134.9, 134.2, 133.5, 131.8, 131.4, 130.8, 130.6, 130.0, 129.8, 129.7, 128.7, 128.0, 127.8, 118.6, 116.1, 113.8, 112.2, 76.8.HRMS (ESI): m/z calcd for $C_{32}H_{22}N_4Cl$ $[M+H]^+$:497.1528; found 497.1525.

3-(4-morpholino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)benzonitrile (6) [PF-06447475]



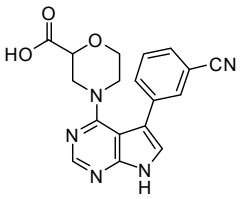
Obtained using procedure D1 on 0.39 mmol scale; 32 mg, 0.10 mmol, yield 26%, white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.54 (s, 1H), 8.54 (s, 1H), 7.86 (s, 1H), 7.78 (d, *J* = 7.7 Hz, 1H), 7.62 (d, *J* = 7.7 Hz, 1H), 7.57 (t, *J* = 7.7 Hz, 1H), 7.28 (b, 1H), 3.56 – 3.54 (m, 4H), 3.32 – 3.30 (m, 4H).HRMS (ESI): m/z calcd for $C_{17}H_{16}ON_5$ $[M+H]^+$: 306.1349; found 306.1344.

ethyl 4-(5-(3-cyanophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)morpholine-2-carboxylate (7)



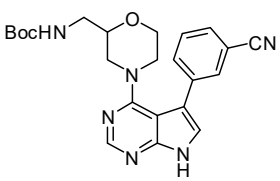
Obtained using procedure D2 on 0.39 mmol scale; 45 mg, 0.12 mmol, yield 30%, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.79 (s, 1H), 8.56 (s, 1H), 7.85 - 7.84 (m, 1H), 7.79 – 7.77 (m, 1H), 7.63 – 7.62 (m, 1H), 7.58 (d, *J* = 7.7 Hz, 1H), 7.36 (b, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 4.04 (dd, *J* = 9.9, 2.8 Hz, 1H), 3.97 – 3.95 (m, 1H), 3.89 (dd, *J* = 8.9, 2.7 Hz, 1H), 3.59 – 3.56 (m, 1H), 3.50 (td, *J* = 11.3, 2.4 Hz, 1H), 3.08 – 3.02 (m, 2H), 1.24 (t, *J* = 7.1 Hz, 3H). HRMS (ESI): m/z calcd for $C_{20}H_{20}O_3N_5$ $[M+H]^+$:378.1561; found 378.1555.

4-(5-(3-cyanophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)morpholine-2-carboxylic acid (8)



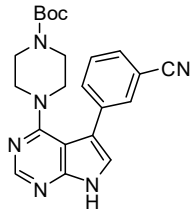
Obtained using procedure E on 0.12 mmol scale; 30 mg, 0.08 mmol, yield 65%, yellow solid.^{1}H NMR (500 MHz, DMSO-d_6) δ 12.37 (s, 1H), 8.42 (s, 1H), 8.01 (b, 1H), 7.83 (d, *J* = 7.8 Hz, 1H), 7.76 (d, *J* = 7.7 Hz, 1H), 7.72 - 7.71 (m, 1H), 7.66 (t, *J* = 7.8 Hz, 1H), 4.02 – 4.00 (m, 1H), 3.73 – 3.71 (m, 2H), 3.04 – 2.99 (m, 2H), 2.87 – 2.84 (m, 2H). HRMS (ESI): m/z calcd for $C_{18}H_{16}O_3N_5$ $[M+H]^+$:350.1248; found 350.1244.

***tert*-butyl((4-(5-(3-cyanophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)morpholin-2-yl)methyl) carbamate (9)**



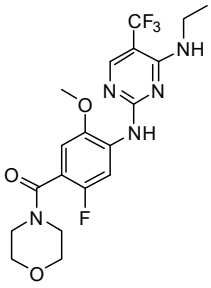
Obtained using procedure D2 on 0.39 mmol scale; 52 mg, 0.12 mmol, yield 30%, yellow solid.^{1}H NMR (500 MHz, $CDCl_3$) δ 12.24 (s, 1H), 8.52 (s, 1H), 7.82 (s, 1H), 7.77 (d, *J* = 7.6 Hz, 1H), 7.60 (d, *J* = 7.7 Hz, 1H), 7.56 (t, *J* = 7.7 Hz, 1H), 7.34 (b, 1H), 4.81 (b, 1H), 3.72 – 3.69 (m, 2H), 3.61 – 3.59 (m, 1H), 3.47 – 3.42 (m, 2H), 3.17 – 3.15 (m, 1H), 2.94 – 2.90 (m, 2H), 2.71 – 2.68 (m, 1H), 1.43 (s, 9H).^{13}C NMR (126 MHz, MeOD-d_4) δ 161.7, 158.2, 154.2, 151.6, 138.0, 134.0, 132.9, 130.9, 124.4, 119.8, 116.2, 113.7, 104.4, 80.2, 75.6, 67.0, 53.4, 50.4, 43.6, 28.8. HRMS (ESI): m/z calcd for $C_{23}H_{27}O_3N_6$ $[M+H]^+$:435.2139; found 435.2135.

***tert*-butyl 4-(5-(3-cyanophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperazine-1-carboxylate (10)**



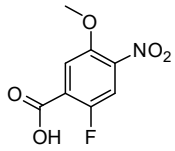
Obtained using procedure D2 on 2 mmol scale; 240 mg, 0.6 mmol, yield 30%, white solid.^{1}H NMR (500 MHz, $CDCl_3$) δ 11.04 (s, 1H), 8.52 (s, 1H), 7.84 (s, 1H), 7.77 (d, *J* = 7.7 Hz, 1H), 7.62 (d, *J* = 7.6 Hz, 1H), 7.56 (t, *J* = 7.7 Hz, 1H), 7.30 (s, 1H), 3.27 (b, 8H), 1.43 (s, 9H).^{13}C NMR (126 MHz, $CDCl_3$) δ 160.3, 154.5, 153.5, 150.9, 136.5, 132.5, 131.7, 130.1, 129.5, 121.8, 118.7, 115.3, 112.8, 103.2, 80.1, 49.5, 43.3, 28.4.

(4-((4-(ethylamino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-2-fluoro-5-methoxyphenyl) (morpholino)methanone (11) [GNE-7915]



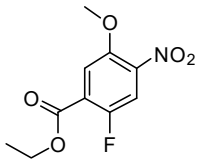
Obtained using procedure Q2 on 0.26 mmol scale; 46 mg, 0.103 mmol, yield 40%, white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 (d, *J* = 12.3 Hz, 1H), 8.19 (s, 1H), 7.85 (s, 1H), 6.91 (d, *J* = 5.9 Hz, 1H), 5.22 (b, 1H), 3.91 (s, 3H), 3.80 – 3.77 (m, 4H), 3.68 – 3.66 (m, 2H), 3.62 – 3.59 (m, 2H), 3.45 – 3.43 (m, 2H), 1.32 (t, *J* = 7.2 Hz, 3H). ^{1}H NMR is in good agreement with published data.[s3] ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.5, 160.3, 158.8, 154.4 (d, *J*=5.0 Hz), 152.3 (d, *J* =238.5 Hz), 144.1, 131.8 (d, *J* =12.3 Hz), 124.7 (q, *J* =270.3 Hz), 114.4 (d, *J* =19.2 Hz), 109.7 (d, *J* =5.0 Hz), 105.6 (d, *J* =31.8 Hz), 99.7, 66.8, 56.2, 47.7, 42.7, 36.4, 14.4. HRMS (ESI): m/z calcd for $C_{19}H_{22}O_3N_5F_4$ $[M+H]^+$:444.1653; found 444.165.

2-fluoro-5-methoxy-4-nitrobenzoic acid (12)



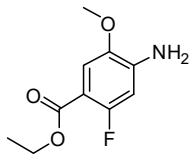
Obtained using procedure F on 24.6 mmol scale; 4.87 g, 22.6 mmol, yield 92%, light yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J* = 5.5 Hz, 1H), 7.66 (d, *J* = 9.2 Hz, 1H), 4.02 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.2 (d, *J* = 3.8 Hz), 155.0 (d, *J* = 260.3 Hz), 148.4 (d, *J* = 3.2 Hz), 142.5 (d, *J* = 7.3 Hz), 121.6 (d, *J* = 11.1 Hz), 116.9, 114.6 (d, *J* = 28.7 Hz), 57.2.

ethyl 2-fluoro-5-methoxy-4-nitrobenzoate (13)



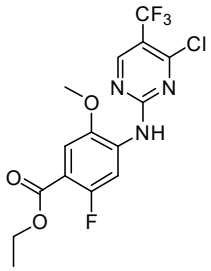
Obtained using procedure G on 9.3 mmol scale; 2.2 g, 9.1 mmol, yield 98%, off-white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 – 7.62 (m, 2H), 4.44 (q, *J* = 7.1 Hz, 2H), 3.99 (s, 3H), 1.42 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.9 (d, *J* = 4.3 Hz), 154.2 (d, *J* = 257.5 Hz), 148.4 (d, *J* = 3.0 Hz), 141.5 (d, *J* = 8.1 Hz), 123.51 (d, *J* = 12.0 Hz), 116.5, 114.4 (d, *J* = 29.0 Hz), 62.3, 57.1, 14.1.

ethyl 4-amino-2-fluoro-5-methoxybenzoate (14)



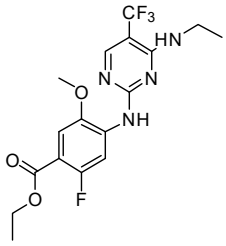
Obtained using procedure H on 9.1 mmol scale; 1.92 g, 9.0 mmol, yield 98%, light orange solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, *J* = 6.4 Hz, 1H), 6.37 (d, *J* = 11.9 Hz, 1H), 4.34 (q, *J* = 7.1 Hz, 4H), 3.86 (s, 3H), 1.37 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.90 (d, *J* = 4.3 Hz), 158.4, (d, *J* = 252.8 Hz), 142.4 (d, *J* = 12.1 Hz), 142.25 (d, *J* = 1.4 Hz), 111.92 (d, *J* = 2.8 Hz), 106.0 (d, *J* = 10.8 Hz), 101.4 (d, *J* = 28.4 Hz), 60.65, 55.95, 14.38.

ethyl 4-amino-2-fluoro-5-methoxybenzoate (15)



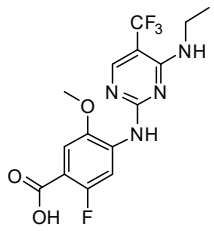
Obtained using procedure I on 9.0 mmol scale; 1.4 g, 3.6 mmol, yield 40%, off-white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.66 (s, 1H), 8.40 (d, *J* = 12.9 Hz, 1H), 8.29 (s, 1H), 7.40 (d, *J* = 6.3 Hz, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 3.95 (s, 3H), 1.40 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.3 (d, *J* =4.3 Hz), 159.6, 159.4, 157.3 (q, *J* = 4.9 Hz)**,** 157.0 (d, *J* = 252.8 Hz), 143.4, 132.5 (d, *J* = 12.2 Hz), 122.3 (q, *J* = 272.2 Hz),111.7, 115.1 (d, *J* = 34.2 Hz), 111.6 (d, *J* = 1.6 Hz), 107.3 (d, *J* = 32.1 Hz), 99.8, 61.3, 56.4, 14.3. HRMS (ESI): m/z calcd for $C_{15}H_{13}O_3N_3ClF_4$ $[M+H]^+$:394.0576; found 394.0572.

ethyl 4-amino-2-fluoro-5-methoxybenzoate (16)



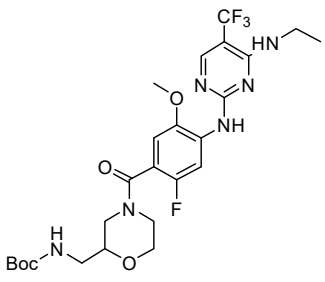
Obtained using procedure J on 3.3 mmol scale; 1.2 g, 2.9 mmol, yield 88%, off-white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.48 (d, *J* = 13.7 Hz, 1H), 8.19 (s, 1H), 7.93 (s, 1H), 7.37 (d, *J* = 6.4 Hz, 1H), 5.24 (s, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 3.94 (s, 3H), 3.63 - 3.59 (m, 2H), 1.40 (t, *J* = 7.1 Hz, 3H), 1.33 (t, *J* = 7.2 Hz, 3H).^{13}C NMR (126 MHz, $CDCl_3$) δ 164.6 (d, *J* = 4.3 Hz), 160.2, 158.9, 157.3 (d, *J* = 251.5 Hz), 154.6 (q, *J* = 5.3 Hz), 143.1, 134.4 (d, *J* = 12.9 Hz), 124.7 (q, *J* = 270.4 Hz), 111.2, 109.7 (d, *J* = 11.6 Hz), 106.4 (d, *J* = 32.6 Hz), 99.8, 61.1, 56.3, 36.5, 14.4, 14.3. HRMS (ESI): m/z calcd for $C_{17}H_{19}O_3N_4F_4$ $[M+H]^+$:403.1388; found 403.1385.

4-((4-(ethylamino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-2-fluoro-5-methoxybenzoic acid (17)



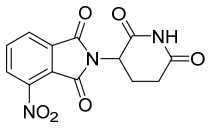
Obtained using procedure E on 1.85 mmol scale; 670 mg, 1.8 mmol, yield 97%, yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.93 (s, 1H), 8.35 (d, *J* = 13.7 Hz, 1H), 8.26 (s, 1H), 8.16 (s, 1H), 7.46 (t, *J* = 5.3 Hz, 1H), 7.36 (d, *J* = 6.7 Hz, 1H), 3.91 (s, 3H), 3.50 – 3.47 (m, 2H), 1.17 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 164.8 (d, *J* = 3.5 Hz), 160.0, 157.8, 156.2 (d, *J* = 250.0 Hz), 154.6, 143.5, 133.8 (d, *J* = 12.5 Hz), 124.6 (q, *J* = 270.3 Hz), 111.8, 110.3 (d, *J* = 11.5 Hz), 106.4 (d, *J* = 23.2 Hz), 99.5 (d, *J* = 32.0 Hz), 56.4, 35.7, 14.2. HRMS (ESI): m/z calcd for $C_{15}H_{15}O_3N_4F_4$ $[M+H]^+$:375.1075; found 375.1071.

***tert*-butyl((4-(4-((4-(ethylamino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-2-fluoro-5-methoxybenzoyl)morpholin-2-yl)methyl)carbamate (18)**



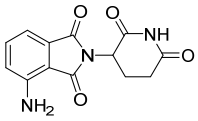
Obtained using procedure Q2 on 0.26 mmol scale; 55 mg, 0.11 mmol, yield 40%, yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (t, *J* = 11.1 Hz, 1H), 8.18 (s, 1H), 7.90 (s, 1H), 6.88 (s, 1H), 5.24 (s, 1H), 4.91 (s, 1H), 4.56 (t, *J* = 14.4 Hz, 1H), 3.91 (s, 3H), 3.60 – 3.49 (m, 6H), 3.37 – 3.21 (m, 2H), 3.03 – 2.94 (m, 2H), 1.38 (s, 9H), 1.31 (b, 3H).^{13}C NMR (126 MHz, $CDCl_3$) δ 165.6 (d, *J* = 12.7 Hz), 160.2, 158.8, 155.8, 154.4 (q, *J* = 4.9 Hz), 152.2 (d, *J* = 239.0 Hz), 144.2, 132.0 (d, *J* = 12.9 Hz), 124.7 (q, *J* = 269.7 Hz), 114.0, 109.7, 105.6 (d, *J* = 30.4 Hz), 99.8, 79.5, 74.9, 66.6, 56.2, 47.1, 42.4, 42.1, 36.429.6, 28.3, 28.2, 14.4. HRMS (ESI): m/z calcd for $C_{25}H_{33}O_5N_6F_4$ $[M+H]^+$: 573.2443; found 573.244.

2-(2,6-dioxopiperidin-3-yl)-4-nitroisoindoline-1,3-dione (19)



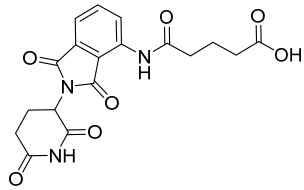
Obtained using procedure K on 10 mmol scale; 2.7 g, 8.9 mmol, yield 90%, purple solid. The crude product was used directly in the next step. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.20 (s, 1H), 8.36 (dd, *J* = 8.1, 0.7 Hz, 1H), 8.25 (dd, *J* = 7.5, 0.5 Hz, 1H), 8.14 – 8.11 (m, 1H), 5.21 (dd, *J* = 12.9, 5.4 Hz, 1H), 2.90 (ddd, *J* = 17.3, 14.0, 5.4 Hz, 1H), 2.64 – 2.61 (m, 1H), 2.56– 2.52 (m, 1H), 2.11 -2.06 (m, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 172.8, 169.6, 165.3, 162.6, 144.5, 136.9, 133.1, 129.0, 127.4, 122.6, 49.5, 30.9, 21.8.

4-amino-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (20)



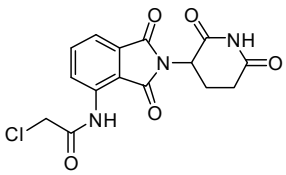
Obtained using procedure L on 8 mmol scale; 2.0 g, 7.3 mmol, yield 92%, yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.09 (s, 1H), 7.46 (dd, *J* = 8.4, 7.0 Hz, 1H), 7.02 – 6.99 (m, 2H), 6.52 (b, 2H), 5.04 (dd, *J* = 12.7, 5.4 Hz, 1H), 2.88 (ddd, *J* = 17.0, 13.9, 5.5 Hz, 1H), 2.54 – 2.50 (m, 1H), 2.04 – 2.00 (m, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 172.9, 170.2, 168.6, 167.4, 146.8, 135.5, 132.0, 121.7, 111.0, 108.5, 48.5, 31.01, 22.2.

5-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-5-oxopentanoic acid (21)



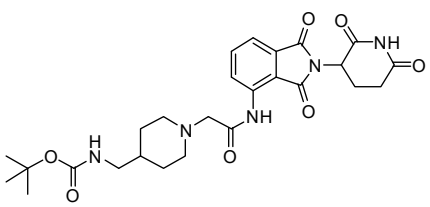
Obtained using procedure M on 7.3mmol scale; 904 mg, 2.4 mmol, yield 32%, white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.14 (s, 1H), 9.73 (s, 1H), 8.43 (d, *J* = 8.3 Hz, 1H), 7.84 – 7.81 (m, 1H), 7.61 (d, *J* = 7.3 Hz, 1H), 5.14 (dd, *J* = 12.9, 5.4 Hz, 1H), 2.92 – 2.85 (m, 1H), 2.62 – 2.50 (m, 4H), 2.30 (t, *J* = 7.3 Hz, 2H), 2.08 – 2.05 (m, 1H), 1.86 – 1.80 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 174.0, 172.7, 171.5, 169.7, 167.5, 166.6, 136.3, 136.0, 131.4, 126.5, 118.3, 117.2, 48.8, 35.5, 32.7, 30.7, 21.9, 20.1. HRMS (ESI): m/z calcd for $C_{18}H_{18}O_7N_3$ $[M+H]^+$:388.1139; found 388.114.

2-chloro-N-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)acetamide (22)



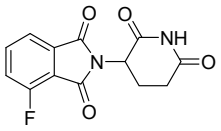
Obtained using procedure N on 5 mmol scale; 1.61 g, 4.6 mmol, yield 92%, yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.03 (s, 1H), 10.20 (s, 1H), 7.81 (d, *J* = 7.6 Hz, 1H), 7.57 – 7.51 (m, 2H), 5.16 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.32 (s, 2H), 2.95 – 2.88 (m, 1H), 2.62 – 2.59 (m, 1H), 2.34 (dd, *J* = 13.1, 4.4 Hz, 1H), 2.04 – 2.00 (m, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 172.8, 171.1, 167.7, 165.0, 134.1, 132.9, 132.8, 128.8, 125.6, 125.4, 119.8, 51.5, 43.1, 31.2, 22.6.

***tert*-butyl((1-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-2-oxoethyl) piperidin-4-yl)methyl)carbamate (23)**



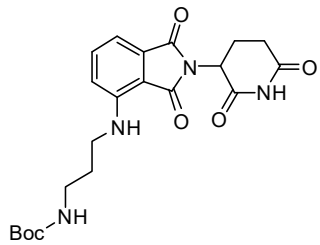
Obtained using procedure O on 3.44 mmol scale; 1.47 g, 2.8 mmol, yield 81%, light yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.14 (s, 1H), 11.02 (s, 1H), 8.79 (d, *J* = 8.5 Hz, 1H), 7.84 (t, *J* = 7.9 Hz, 1H), 7.58 (d, *J* = 7.3 Hz, 1H), 6.88 (t, *J* = 5.7 Hz, 1H), 5.16 (dd, *J* = 12.9, 5.3 Hz, 1H), 4.10 (q, *J* = 5.2 Hz, 2H), 3.17 (d, *J* = 5.2 Hz, 6H), 2.87 – 2.82 (m, 3H), 2.63 – 2.54 (m, 2H), 2.21 – 2.07 (m, 2H), 1.65 – 1.63 (m, 2H), 1.37 (s, 9H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 172.8, 170.5, 169.9, 168.0, 166.8, 163.2, 159.8, 155.7, 136.4, 131.4, 124.1, 117.9, 115.7, 77.4, 61.8, 53.3, 48.9, 45.5, 35.5, 30.9, 29.6, 28.3, 21.9. HRMS (ESI): m/z calcd for $C_{26}H_{34}O_7N_5$ $[M+H]^+$:528.2453; found 528.2448.

2-(2,6-dioxopiperidin-3-yl)-4-fluoroisoindoline-1,3-dione (24)



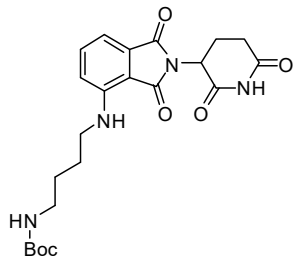
Obtained using procedure K on 5 mmol scale; 1.2 g, 4.3 mmol, yield 85%, white solid. The crude product was purified by column chromatography (DCM – MeOH, 0 – 5% MeOH in DCM). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.16 (s, 1H), 7.96 – 7.92 (m, 1H), 7.79 (d, *J* = 7.3 Hz, 1H), 7.75 – 7.7.2 (m, 1H), 5.16 (dd, *J* = 13.0, 5.4 Hz, 1H), 2.91 – 2.85 (m, 1H), 2.63 – 2.58 (m, 1H), 2.53 – 2.51 (m, 1H), 2.07 – 2.04 (m, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 172.8, 169.7, 166.1, 164.0, 156.8 (d, *J* = 262.3 Hz), 138.0 (d, *J* = 7.9 Hz), 133.5, 123.0 (d, *J* = 19.6 Hz), 120.1 (d, *J* = 3.2 Hz), 117.0 (d, *J* = 12.6 Hz), 49.1, 30.9, 21.9.

***tert*-butyl (3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)propyl)carbamate (25)**



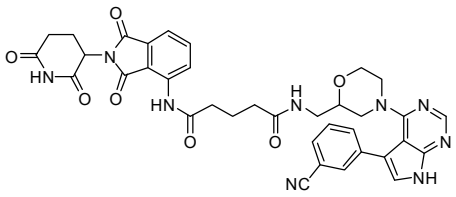
Obtained using procedure P on 1.03 mmol scale; 266 mg, 0.6 mmol, yield 60%, yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.51 – 7.48 (m, 1H), 7.10 (d, *J* = 7.1 Hz, 1H), 6.88 (d, *J* = 8.5 Hz, 1H), 6.31 (s, 1H), 4.91 (dd, *J* = 12.4, 5.3 Hz, 1H), 4.65 (s, 1H), 3.35 – 3.31 (m, 2H), 3.26 – 3.25 (m, 2H), 2.82 – 2.72 (m, 3H), 2.14 – 2.10 (m, 1H), 1.87 – 1.83 (m, 2H), 1.44 (s, 9H).^{13}C NMR (126 MHz, $CDCl_3$) δ 171.0, 169.4, 168.3, 167.6, 156.1, 146.7, 136.2, 132.5, 116.5, 111.6, 110.1, 79.5, 48.9, 43.4, 40.0, 31.4, 29.9, 28.4, 22.8.

***tert*-butyl (4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)butyl)carbamate (26)**



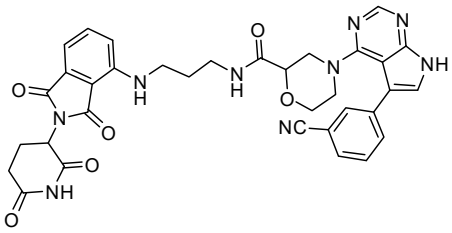
Obtained using procedure P on 1.03 mmol scale; 270 mg, 0.6 mmol, yield 60%, yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.47 (dd, *J* = 8.3, 7.3 Hz, 1H), 7.08 (d, *J* = 7.1 Hz, 1H), 6.87 (d, *J* = 8.5 Hz, 1H), 6.23 (d, *J* = 5.6 Hz, 1H), 4.91 (dd, *J* = 12.3, 5.4 Hz, 1H), 4.62 (s, 1H), 3.31 – 3.27 (m, 2H), 3.18 – 3.16 (m, 2H), 2.86 – 2.72 (m, 3H), 2.13 – 2.10 (m, 1H), 1.70 – 1.67 (m, 2H), 1.65 – 1.57 (m, 2H), 1.43 (s, 9H).^{13}C NMR (126 MHz, $CDCl_3$) δ 171.2, 169.5, 168.4, 167.6, 156.0, 146.8, 136.1, 132.4, 116.6, 111.5, 109.9, 79.3, 48.8, 42.2, 31.4, 28.4, 27.5, 26.4, 22.8.

***N*1-((4-(5-(3-cyanophenyl)-7*H*-pyrrolo[2,3-d]pyrimidin-4-yl)morpholin-2-yl)methyl)-N5-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)glutaramide (27)**



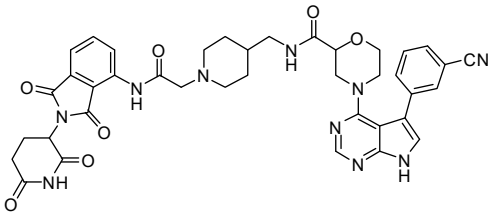
Obtained using procedure Q1 on 0.27 mmol scale; 75 mg, 0.11 mmol, yield 40%, yellow solid.^{1}H NMR (500 MHz, $CDCl_3$) δ 11.10 (s, 1H), 9.40 (s, 1H), 8.75 (d, *J* = 8.5 Hz, 1H), 8.46 (s, 1H), 7.77 – 7.75 (m, 1H), 7.71 (d, *J* = 7.8 Hz, 1H), 7.69 – 7.65 (m, 1H), 7.60 – 7.58 (m, 1H), 7.52 (dd, *J* = 9.9, 7.6 Hz, 2H), 6.07 – 6.05 (m, 1H), 4.97 (dd, *J* = 12.2, 5.4 Hz, 1H), 3.69 – 3.64 (m, 2H), 3.57 – 3.52 (m, 1H), 3.46 – 3.39 (m, 2H), 3.33 (dd, *J* = 8.9, 4.9 Hz, 1H), 3.00 – 2.97 (m, 1H), 2.90 – 2.85 (m, 2H), 2.80 – 2.76 (m, 2H), 2.65 – 2.63 (m, 1H), 2.52 (t, *J* = 7.2 Hz, 2H), 2.29 (t, *J* = 7.1 Hz, 2H), 2.15 – 2.13 (m, 1H), 2.07 – 2.03 (m, 2H), 1.87 – 1.85 (m, 2H).^{13}C NMR (126 MHz, $CDCl_3$) δ 172.1, 171.8, 169.0, 168.8, 166.7, 160.1, 153.3, 150.7, 137.6, 136.5, 136.3, 132.3, 131.6, 131.1, 130.1, 129.5, 125.3, 122.2, 118.7, 118.5, 115.4, 115.0, 112.6, 103.0, 76.8, 74.0, 66.0, 51.6, 49.3, 41.3, 36.6, 35.0, 31.4, 22.7, 21.0, 20.9. HRMS (ESI): m/z calcd for $C_{36}H_{34}O_7N_9$ $[M+H]^+$:704.2576; found 704.2571.

4-(5-(3-cyanophenyl)-7*H*-pyrrolo[2,3-d]pyrimidin-4-yl)-N-(3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)propyl)morpholine-2-carboxamide (28)



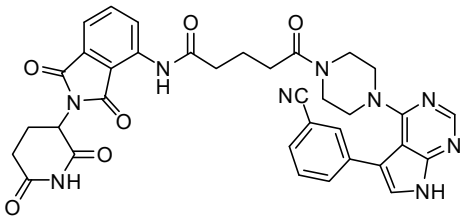
Obtained using procedure Q1 on 0.10 mmol scale; 35 mg, 0.05 mmol, yield 50%, white solid.^{1}H NMR (500 MHz, $CDCl_3$) δ 10.46 (s, 1H), 9.00 (s, 1H), 8.52 (s, 1H), 7.83 (s, 1H), 7.78 (d, *J* = 7.5 Hz, 1H), 7.60 – 7.54 (m, 2H), 7.51 – 7.48 (m, 1H), 7.10 (d, *J* = 7.1 Hz, 1H), 6.87 (d, *J* = 8.6 Hz, 1H), 6.62 (t, *J* = 5.3 Hz, 1H), 6.41 (t, *J* = 5.8 Hz, 1H), 4.96 – 4.93 (m, 1H), 4.06 (d, *J* = 11.5 Hz, 1H), 3.83 (d, *J* = 10.8 Hz, 2H), 3.70 (d, *J* = 12.7 Hz, 1H), 3.57 (t, *J* = 11.4 Hz, 1H), 3.35 (q, *J* = 6.5 Hz, 2H), 3.31 – 3.28 (m, 2H), 2.97 (t, *J* = 12.1 Hz, 1H), 2.90 – 2.86 (m, 1H), 2.83 – 2.74 (m, 2H), 2.71 – 2.66 (m, 2H), 2.14 – 2.11 (m, 1H), 1.84 – 1 .79 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.5, 169.3, 169.1, 167.6, 160.0, 153.4, 146.6, 136.4, 136.1, 132.6, 132.4, 131.9, 130.1, 129.6, 127.5, 122.1, 118.8, 116.4, 115.3, 112.6, 111.6, 110.2, 88.8, 74.7, 66.0, 52.0, 48.9, 39.9, 36.2, 31.5, 30.9, 29.2, 22.8. HRMS (ESI): m/z calcd for $C_{34}H_{32}O_6N_9$ $[M+H]^+$:662.247; found 662.2467.

4-(5-(3-cyanophenyl)-7*H*-pyrrolo[2,3-d]pyrimidin-4-yl)-N-((1-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-2-oxoethyl)piperidin-4-yl)methyl)morpholine-2-carboxamide (29)



Obtained using procedure Q1 on 0.10 mmol scale; 30 mg, 0.04 mmol, yield 40%, yellow solid.^{1}H NMR (500 MHz, $CDCl_3$) δ 11.39 (s, 1H), 10.95 (s, 1H), 8.85 – 8.81 (m, 1H), 8.50 (d, *J* = 10.7 Hz, 1H), 7.81 (d, *J* = 6.0 Hz, 1H), 7.73 – 7.68 (m, 2H), 7.59 – 7.53 (m, 3H), 6.48 – 6.47 (m, 1H), 5.04 – 4.99 (m, 1H), 3.99 (d, *J* = 12.7 Hz, 1H), 3.87 (d, *J* = 11.0 Hz, 1H), 3.80 – 3.74 (m, 2H), 3.62 – 3.59 (m, 1H), 3.31 – 3.21 (m, 2H), 3.18 – 3.02 (m, 3H), 2.95 – 2.86 (m, 4H), 2.81 – 2.77 (m, 1H), 2.64 – 2.61 (m, 1H), 2.34 – 2.30 (m, 1H), 2.23 – 2.20 (m, 2H), 2.01 – 2.00 (b, 1H), 1.80 – 1.78 (m, 1H), 1.71 – 1.62 (m, 3H), 1.47 – 1.42 (m, 2H).^{13}C NMR (126 MHz, $CDCl_3$) δ 172.0, 170.9, 168.6, 168.2, 166.9, 160.1, 153.4, 150.7, 137.0, 136.1, 132.8, 131.5, 130.1, 129.5, 124.7, 122.3, 119.0, 118.3, 116.0, 115.2, 112.6, 103.3, 74.8, 66.0, 62.1, 53.8, 52.4, 49.2, 48.2, 44.2, 35.2, 31.2, 30.0, 23.1. HRMS (ESI): m/z calcd for $C_{39}H_{39}O_7N_{10}$ $[M+H]^+$:759.2998; found 759.3002.

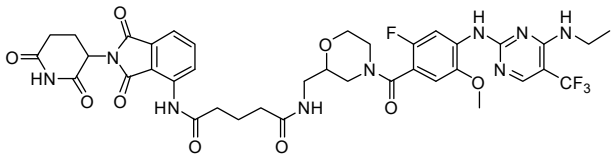
5-(4-(5-(3-cyanophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperazin-1-yl)-N-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)-5-oxopentanamide (30)



Obtained using procedure Q1 on 0.12 mmol scale; 40 mg, 0.06 mmol, yield 50%, off-white solid.^{1}H NMR (500 MHz, $CDCl_3$) δ 11.29 (s, 1H), 10.05 (s, 1H), 9.39 (s, 1H), 8.77 (d, *J* = 8.5 Hz, 1H), 7.80 (s, 1H), 7.75 – 7.68 (m, 2H), 7.59 (d, *J* = 7.7 Hz, 1H), 7.54 – 7.52 (m, 2H), 7.28 (s, 1H), 4.96 (dd, *J* = 12.3, 5.3 Hz, 1H), 3.41 – 3.37 (m, 6H), 3.18 (b, 2H), 2.93 – 2.90 (m, 1H), 2.82 – 2.77 (m, 2H), 2.55 (dd, *J* = 6.8, 5.3 Hz, 2H), 2.42 (t, *J* = 7.1 Hz, 2H), 2.16 – 2.10 (m, 1H), 2.08 – 2.00 (m, 3H).^{13}C NMR (126 MHz, $CDCl_3$) δ 171.8, 171.7, 170.4, 169.0, 168.7, 166.7, 160.0, 153.3, 150.5, 137.6, 136.5, 136.4, 132.4, 131.7, 131.1, 130.1, 129.5, 125.3, 122.3, 118.6, 118.5, 115.4,

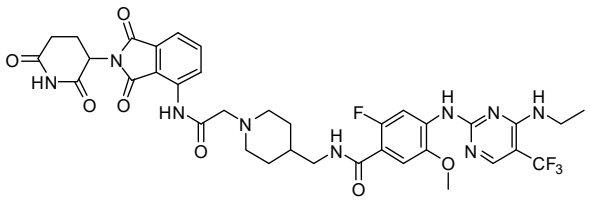
115.1, 112.7, 49.3, 48.7, 44.7, 40.8, 36.8, 31.9, 31.4, 29.7, 22.7, 20.4. HRMS (ESI): m/z calcd for $C_{35}H_{32}O_6N_9$ $[M+H]^+$:674.247; found 674.2466.

N^1-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)-N^5-((4-(4-((4-(ethylamino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-2-fluoro-5-methoxybenzoyl)morpholin-2-yl)methyl)glutaramide (31)



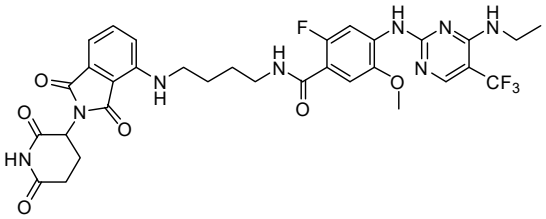
Obtained using procedure Q1 on 0.11 mmol scale; 32 mg, 0.04 mmol, yield 35%, white solid.^{1}H NMR (500 MHz, $CDCl_3$) δ 9.42 (b, 1H), 8.78 (t, *J* = 7.3 Hz, 1H), 8.43 (dd, *J* = 12.1, 8.6 Hz, 1H), 8.19 (s, 1H), 7.89 – 7.85 (m, 1H), 7.70 (t, *J* = 7.9 Hz, 1H), 7.55 (d, *J* = 7.3 Hz, 1H), 6.90 (d, *J* = 5.7 Hz, 1H), 6.03 (s, 1H), 5.21 (s, 1H), 4.96 – 4.94 (m, 1H), 4.59 – 4.56 (m, 1H), 3.90 (s, 3H), 3.62 – 3.57 (m, 4H), 3.56 – 3.50 (m, 3H), 3.32 – 3.30 (m, 1H), 3.01 – 2.99 (m, 1H), 2.90 (dd, *J* = 12.9, 2.4 Hz, 1H), 2.76 (d, *J* = 11.3 Hz, 3H), 2.58 – 2.48 (m, 2H), 2.34 – 2.28 (m, 2H), 2.17 – 2.03 (m, 4H), 1.32 (t, *J* = 7.2 Hz, 3H).^{13}C NMR (126 MHz, $CDCl_3$) δ 172.1, 171.6, 170.9, 169.0, 168.0, 166.6, 165.7, 160.2, 158.8, 154.5, 152.2 (d, *J* = 238.5 Hz), 151.9, 144.3, 137.6, 136.4, 132.01, 131.1, 124.4 (d, *J* = 270 Hz) 118.6, 115.4, 109.8 (d, *J* = 4.6 Hz), 105.6, 99.9, 74.6, 66.6, 56.3, 49.3, 44.8, 42.2, 41.1, 36.4, 35.1, 31.3, 22.7, 21.0, 14.4. HRMS (ESI): m/z calcd for $C_{38}H_{40}O_9N_9F_4$ $[M+H]^+$:842.288; found 842.2875.

N-((1-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-2-oxoethyl) piperidin-4-yl)methyl)-4-((4-(ethylamino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-2-fluoro-5-methoxybenzamide (32)



Obtained using procedure Q1 on 0.2 mmol scale; 80 mg, 0.11 mmol, yield 52%, off-wwhite solid.^{1}H NMR (500 MHz, $CDCl_3$) δ 11.31 (s, 1H), 8.85 (d, *J* = 8.4 Hz, 1H), 8.43 (d, *J* = 15.2 Hz, 1H), 8.19 (s, 1H), 7.98 (b, 1H), 7.70 – 7.66 (m, 1H), 7.54 (dd, *J* = 20.0, 7.2 Hz, 2H), 6.86 (dt, *J* = 11.7, 5.6 Hz, 1H), 5.27 (b, 1H), 4.94 (dd, *J* = 11.9, 5.6 Hz, 1H), 3.93 (s, 3H), 3.61 – 3.58 (m, 2H), 3.50 – 3.46 (m, 1H), 3.40 – 3.47 (m, 1H), 3.21 – 3.12 (m, 2H), 2.95 – 2.92 (m, 2H), 2.89 – 2.86 (m, 2H), 2.78 – 2.74 (m, 2H), 2.33 (t, *J* = 10.1 Hz, 1H), 2.26 (t, *J* = 10.5 Hz, 1H), 2.18 – 2.15 (m, 1H), 1.78 – 1.76 (m, 2H), 1.65 – 1.63 (m, 3H), 1.30 (t, *J* = 7.2 Hz, 3H).^{13}C NMR (126 MHz, $CDCl_3$) δ 171.4, 170.9, 168.3, 168.0, 166.9, 163.5 (d, *J* = 3.8 Hz), 160.1, 158.7, 155.4 (d, *J* = 237.5 Hz), 144.0, 137.0, 136.1, 133.1 (d, *J* = 13.7 Hz), 131.4, 124.9, 124.6 (q, *J* = 267.9 Hz), 118.3, 116.0, 112.2 (d, *J* = 13.1 Hz), 111.2 (d, *J* = 3.3 Hz), 105.5 (d, *J* = 35.8 Hz), 99.8 (q, *J* = 32.3 Hz), 62.2, 56.3, 53.9, 49.2, 45.5, 36.4, 35.42, 31.3, 30.0, 29.75, 22.9, 14.4. HRMS (ESI): m/z calcd for $C_{36}H_{38}O_7N_9F_4$ $[M+H]^+$: 784.2825; found 784.282.

***N*-(4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)butyl)-4-((4-(ethylamino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-2-fluoro-5-methoxybenzamide (33)**



Obtained using procedure Q1 on 0.16 mmol scale; 58 mg, 0.08 mmol, yield 52%, yellow solid.[1]H NMR (500 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.45 (d, *J* = 15.2 Hz, 1H), 8.20 (s, 1H), 7.97 (s, 1H), 7.55 (d, *J* = 7.1 Hz, 1H), 7.47 – 7.44 (m, 1H), 7.06 (d, *J* = 7.1 Hz, 1H), 6.88 (d, *J* = 8.5 Hz, 2H), 6.25 (t, *J* = 5.7 Hz, 1H), 5.26 (b, 1H), 4.91 (dd, *J* = 12.3, 5.3 Hz, 1H), 3.93 (s, 3H), 3.62 – 3.57 (m, 2H), 3.54 – 3.52 (m, 2H), 3.32 (d, *J* = 5.8 Hz, 2H), 2.88 – 2.80 (m, 1H), 2.77 – 2.69 (m, 2H), 2.13 – 2.09 (m, 1H), 1.76 – 1.74 (m, 4H), 1.32 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.3, 169.5, 168.6, 167.6, 163.5 (d, *J* = 3.8 Hz), 160.2, 158.8, 155.5 (d, *J* = 237.4 Hz), 146.8, 144.0, 136.1, 133.2 (d, *J* = 13.9 Hz), 132.5, 124.7 (q, *J* = 270.4 Hz), 116.7, 112.2 (d, *J* = 13.1 Hz), 111.5, 111.1 (d, *J* = 3.5 Hz), 110.0, 105.6 (d, *J* = 35.3 Hz), 99.9 (q, *J* = 33.2 Hz), 56.3, 48.9, 42.2, 39.5, 36.4, 31.4, 27.1, 26.7, 22.8, 14.4. HRMS (ESI): m/z calcd for $C_{32}H_{33}O_6N_8F_4$ $[M+H]^+$:701.2454; found 701.2451.

Biological screening

- **Kinase assays**

a. **In vitro radioactive kinase assay**

LRRK2 kinase activity was measured using the previously described radiometric based LRRKtide assay.[s4, s5] Shortly, the reaction mixture consist of 0.1µM of purified full-length Strep flag LRRK2, 75µM LRRKtide (SignalChem, Cat No. L10-58), 25µM ATP (2 Ci/mmol, hot ATP from Perkin Elmer, Cat No.: BLU502Z250UC), kinase buffer (25mM Tris (pH 7.5), 15mM MgCl2, 20mM β-Glycerol phosphate, 1mM NaF, 1mM EGTA, 1mM Na3VO4, 2mM DTT) and the indicated concentrations of PROTACs or DMSO as control. The reaction was started by adding 75 µM (2 Ci/mmol) ATP-γ-32P and the mixture was incubated at 30°C. Samples were taken after 30 seconds and 30 minutes and spotted on nitrocellulose filters, washed with 75 mM phosphoric acid and dried before scintillation counting (Perkin Elmer).

b. **In-vitro kinase assay (Western Blot)**

The assay was performed for four different concentrations (1nM, 10nM, 0.1µM and 1µM) of PROTACs and their parent kinase inhibitor. The reaction mixture for every concentration included the solvent (DMSO) and consists of 100µM GDP, 25µM ATP, kinase buffer (containing 25mM Tris (pH 7.5), 15mM MgCl2, 20mM β-Glycerol phosphate, 1mM NaF, 1mM EGTA, 1mM Na_3VO_4, and 2mM DTT), and the indicated concentration of PROTACs (DMSO as control). The reaction was started by the addition of 0.1µM of purified full-length Strep flag LRRK2 and the mixture was incubated at 30°C. Samples were taken after 30 seconds and 30 minutes and immediately mixed with 4X Laemmli buffer and denatured at 95^{o}C for 10 minutes. Auto-phosphorylation of LRRK2 was determined by western blotting using anti-phospho LRRK2 (phospho S1292) [MJFR-19-7-8] rabbit monoclonal antibody; 1:1000 dilution (Abcam, ab203181) and secondary goat anti-rabbit (HRP), 1:5000 dilution (Cell Signaling Technology®, #7074). Total LRRK2 was detected using anti-LRRK2 mouse monoclonal antibody; 1:1000 dilution (Biolegend®, AB_2750047 (BioLegend Cat. No. 844402)) and the secondary antibody anti-mouse m-IgGκ BP 1:5000 dilution (Santa Cruz Biotechnology®, sc-516142). Blots were visualized using LI-COR® WesternSure® PREMIUM Chemiluminescent Substrate with LI-COR C-DiGit® Blot Scanner (Model: 3600).

- **Cell culture**

LRRK2 parental RAW 264.7 cells (ATCC® SC-6003™, passage number 3-13) were cultured in Dulbecco's Modified Eagle's medium (DMEM, ATCC® 30-2002™) supplemented with 10% FBS and 1% penicillin-streptomycin (Gibco™, 15070063). HEK293 cells were grown in Dulbecco's Modified Eagle's medium (DMEM, Gibco™, 11960044) supplemented with 10% FBS and 1% penicillin-streptomycin-Glutamine (Gibco™, 10378016). The cells used for the experiments were mycoplasma free (tested with MycoAlert™ Plus Mycoplasma Detection Kit, Lonza # LT07-703)

- **Microscopy**

HEK293 cells were seeded in 8-well ibidi slide (# 80824) coated with poly L-lysine (30,000 cells/well). The next day cells were transfected with GFP-tagged LRRK2 using jetPEI® (101-10N) (Polyplus) according to the manufacturer's protocol. After 24hours of transfection, 10µM of different PROTACs, original kinase inhibitors and DMSO as controls were incubated for 3h, and followed by live imaging. Data acquisition was done using a 63x/1.40 oil-immersion plan apochromat objective of a LSM800 Airyscan confocal laser scanning microscope (Carl Zeiss) and image analysis was done using ZEN 2.3 lite (Carl Zeiss).

- **Western blotting for endogenous LRRK2 expression**

RAW 264.7 cells were seeded in 6-well plate (600,000 cells/well) overnight before treatment with PROTACs (10μM) along with the original kinase inhibitors (10μM) and DMSO as controls. 24 hours after incubation, cells were washed with 50 mM Tris; pH 7.5, 100 mM NaCl, 5 mM MgCl2, 5% Glycerol and lysed for 1hr at 4°C using lysis buffer (50 mM Tris; pH 7.5, 100 mM NaCl, 5 mM MgCl2, 5% Glycerol, 1% Triton X-100) containing protease inhibitor cocktail powder, P2714 (Sigma (P2714-1BTL)), β-glycerophosphate (20 mM), NaF (5 mM) and Na_3VO_4 (1 mM). The cell lysates were centrifuged at 13,000 g for 10 minutes and the total protein content of the supernatant was determined using Pierce™ BCA Protein Assay kit. Samples were mixed with 4X Laemmli buffer and denatured at 95^{o}C for 10 minutes. 40 μg of total protein per sample was loaded on 8% polyacrylamide gels. Following SDS-PAGE, the proteins were transferred to nitrocellulose membrane, incubated overnight at 4°C with anti-LRRK2 24D8 rat monoclonal antibody; 1:1000 dilution (Provided by Dr. Gloeckner, DZNE Tübingen, Germany) or anti-GAPDH rabbit monoclonal antibody; 1:5000 dilution (Cell Signaling Technology®, 14C10 #2118). The secondary antibodies used were goat anti-rat (HRP) 1:5000 dilution (ab97057) or goat anti-rabbit (HRP) 1:5000 dilution (Cell Signaling Technology®, #7074). The proteins were detected using the LI-COR® WesternSure® PREMIUM Chemiluminescent Substrate with LI-COR C-DiGit® Blot Scanner (Model: 3600).

- **Ubiquitin assay**

HEK293 cells were transfected with GFP-tagged LRRK2 using jetPEI® for 48 hours and then treated with 10 μM of compound **11** (original kinase inhibitor) and PROTAC **33** (PROTAC compound derived from compound **11**) and DMSO control for 24 hours with or without the addition of 5 μM MG132 (proteasome inhibitor). After treatment, cells were collected, washed with washing buffer and lysed with lysis buffer (10 mM Tris/Cl pH 7.5; 150 mM NaCl; 0.5 mM EDTA; 0.5% NP-40) containing P2714, β-glycerophosphate (10 mM), NaF (50 mM) and Na_3VO_4 (1 mM), sodium pyrophosphate (1mM), 0.1 μg/ml mycocystin-LR (Enzo Life Sciences, Switzerland) and 10 mM of NEM (ubiquitinase inhibitor, to preserve the ubiquitin signal) for 1 hour at 4^{o}C. The cell lysates were centrifuged at 20,000 rcf for 10 minutes at 4^{o}C and the total protein content of the clear supernatant was determined using Pierce™ BCA Protein Assay kit. Immunoprecipitation was performed using GFP-Trap®_Dynabeads (ChromoTek, gtd-20) to pull down LRRK2 overnight at 4^{o}C. Western blot was performed for both the input sample and the immunoprecipitated GFP-tagged LRRK2 using anti-ubiquitin P4D1 mouse monoclonal antibody 1: 500 dilution (Cell Signaling Technology®, #3936) and anti-GFP (Invitrogen, A-1122) 1:2000 dilution.

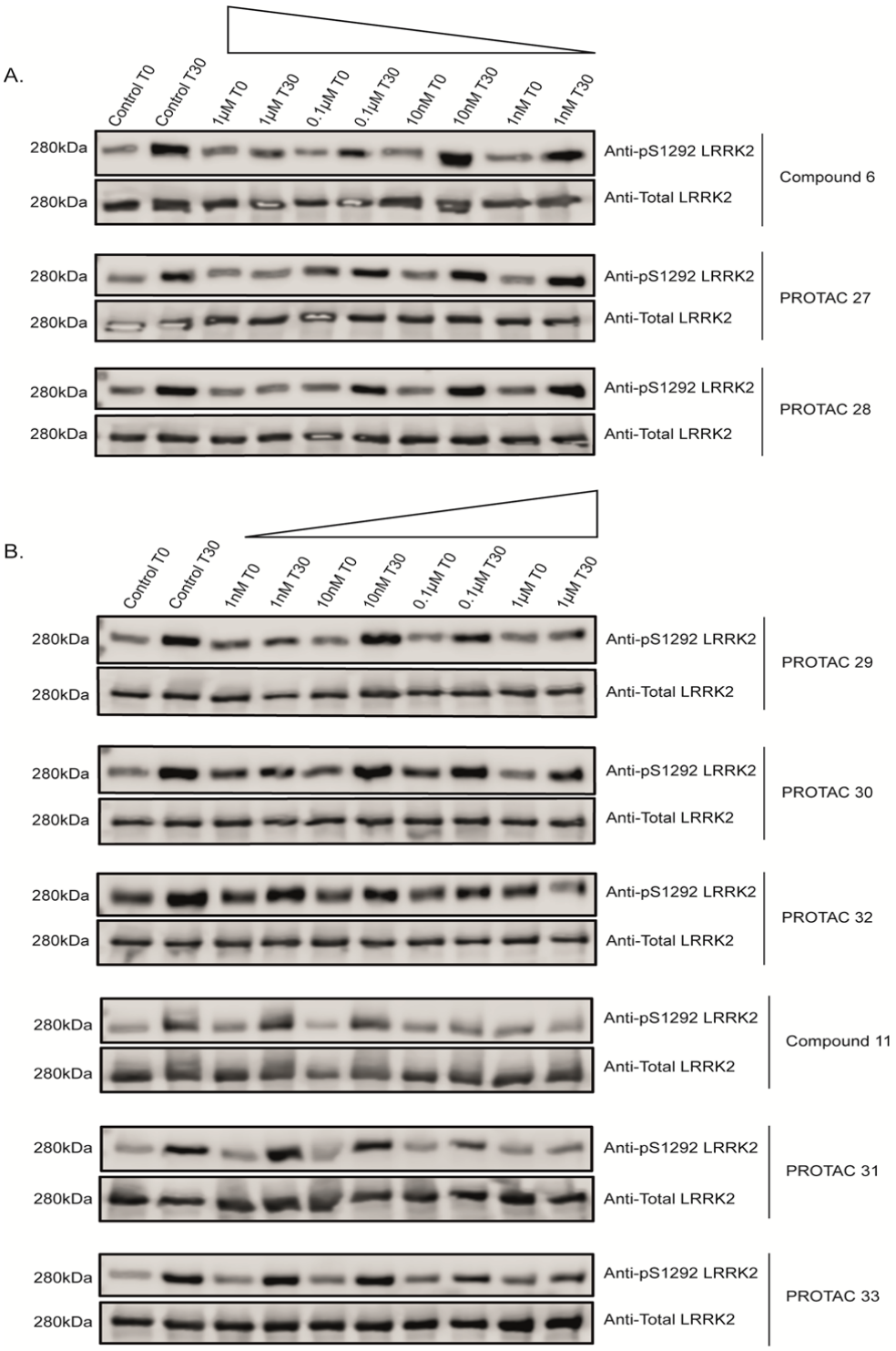


Figure S1. Western blot. PROTACs and their original kinase inhibitors inhibit LRRK2 kinase activity in a concentration-dependent manner. A and B represents the pS1292 autophosphorylation of LRRK2 signal and total LRRK2 signal at T0 (0 minutes) and at T30 (30 minutes) for 1nM, 10nM, 0.1µM and 1µM concentrations of all PROTACs and their original kinase inhibitors.

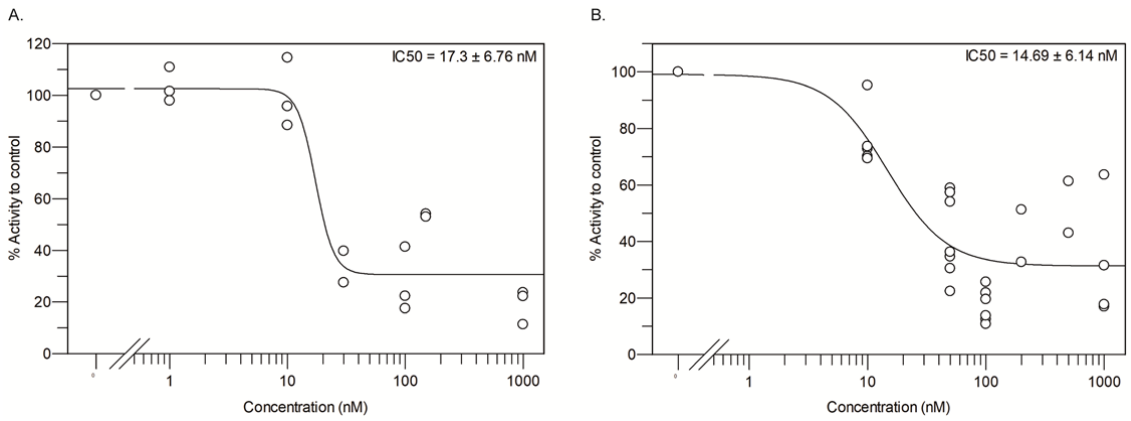


Figure S2. A and B represent the measurement of the kinase activity of LRRK2 (IC_{50}) at different concentrations of Compound (**11**) and PROTAC (**33**) respectively. The results are presented as percentage of kinase activity relative to the control.

Copies of ^{1}H and ^{13}C-NMR

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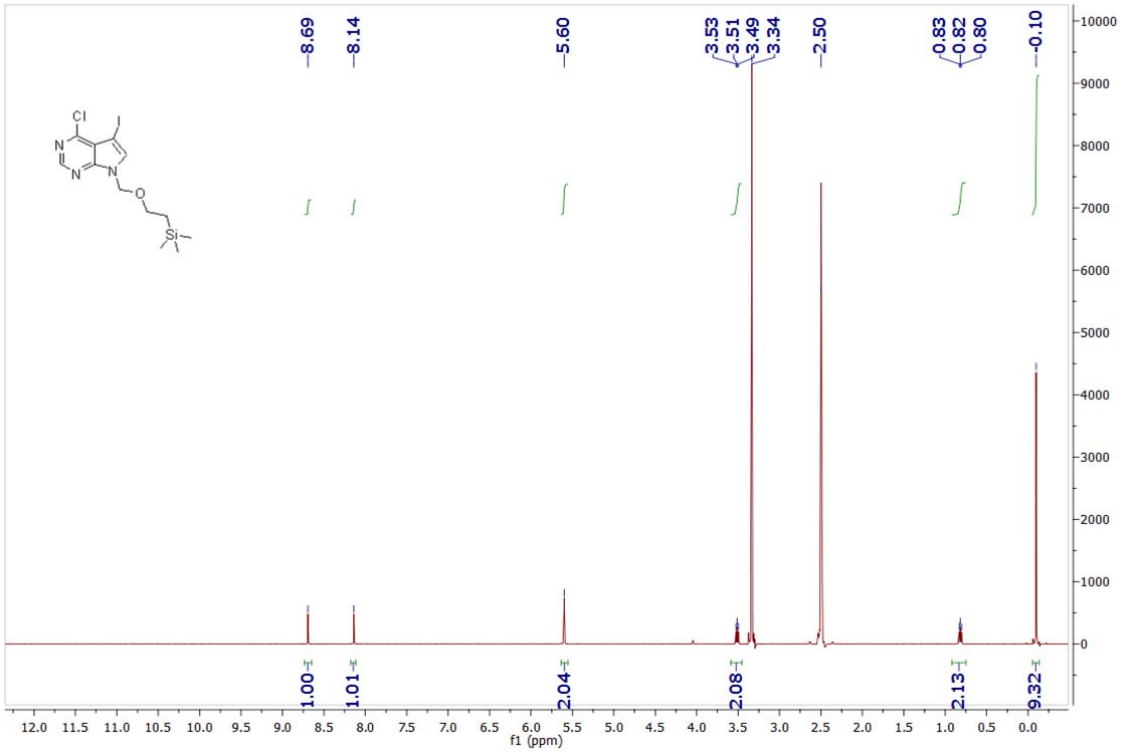
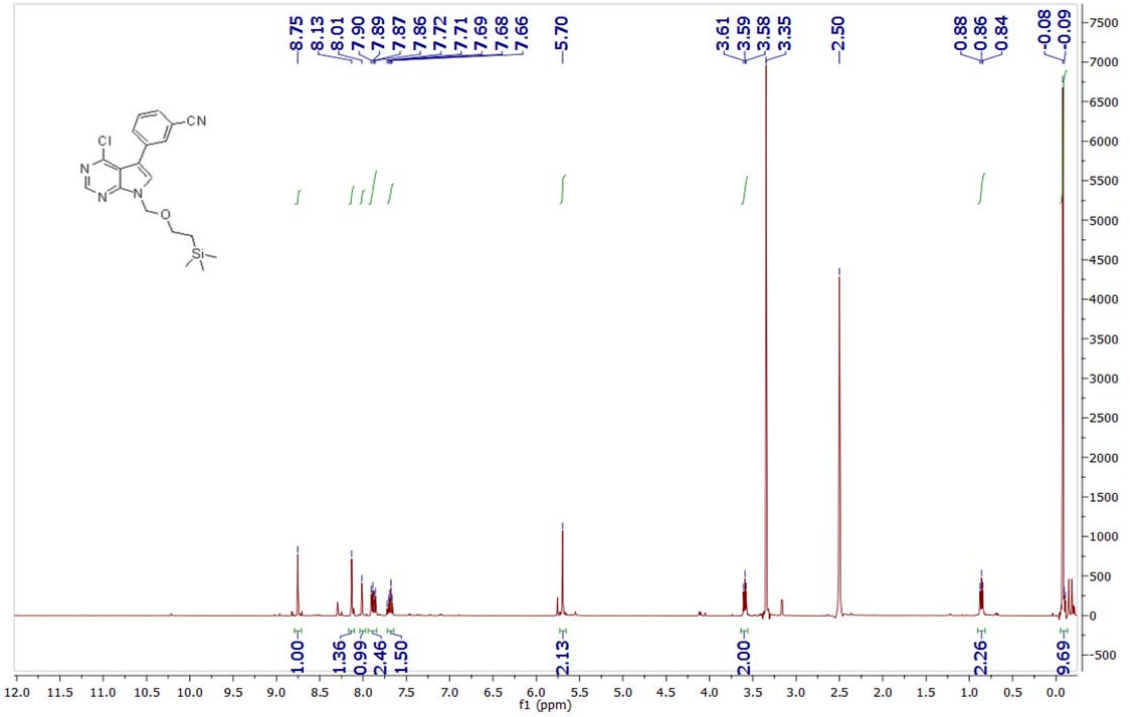
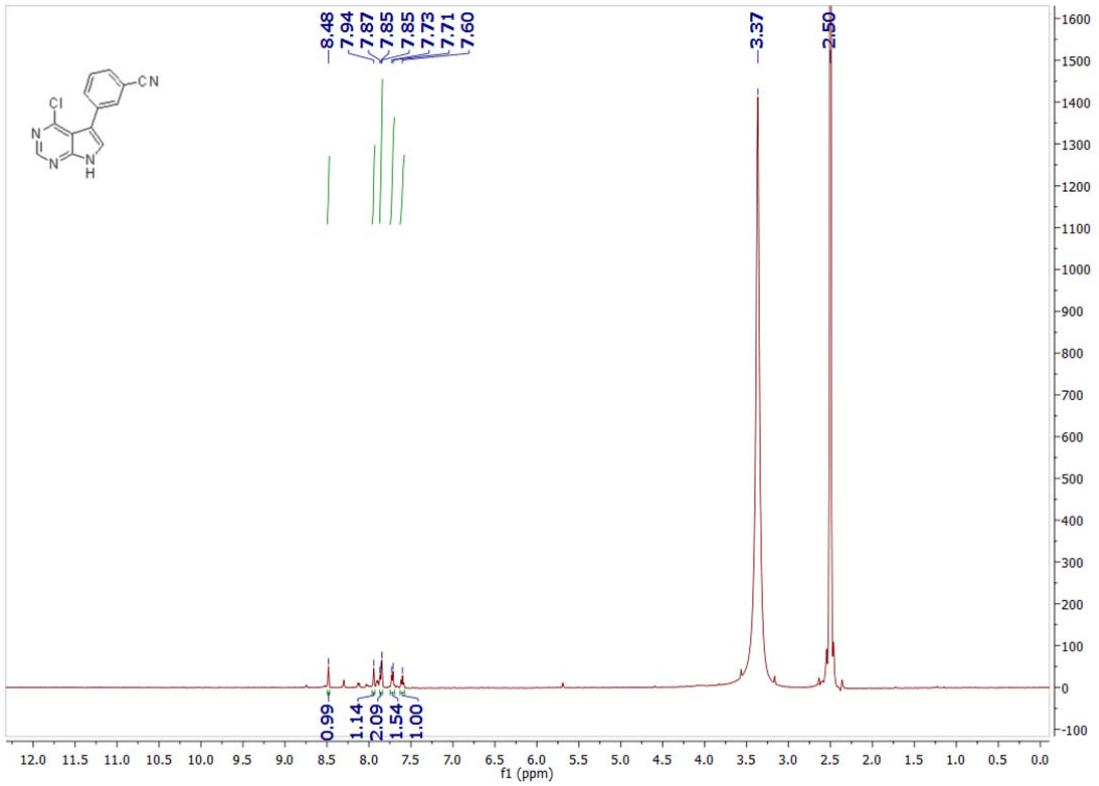


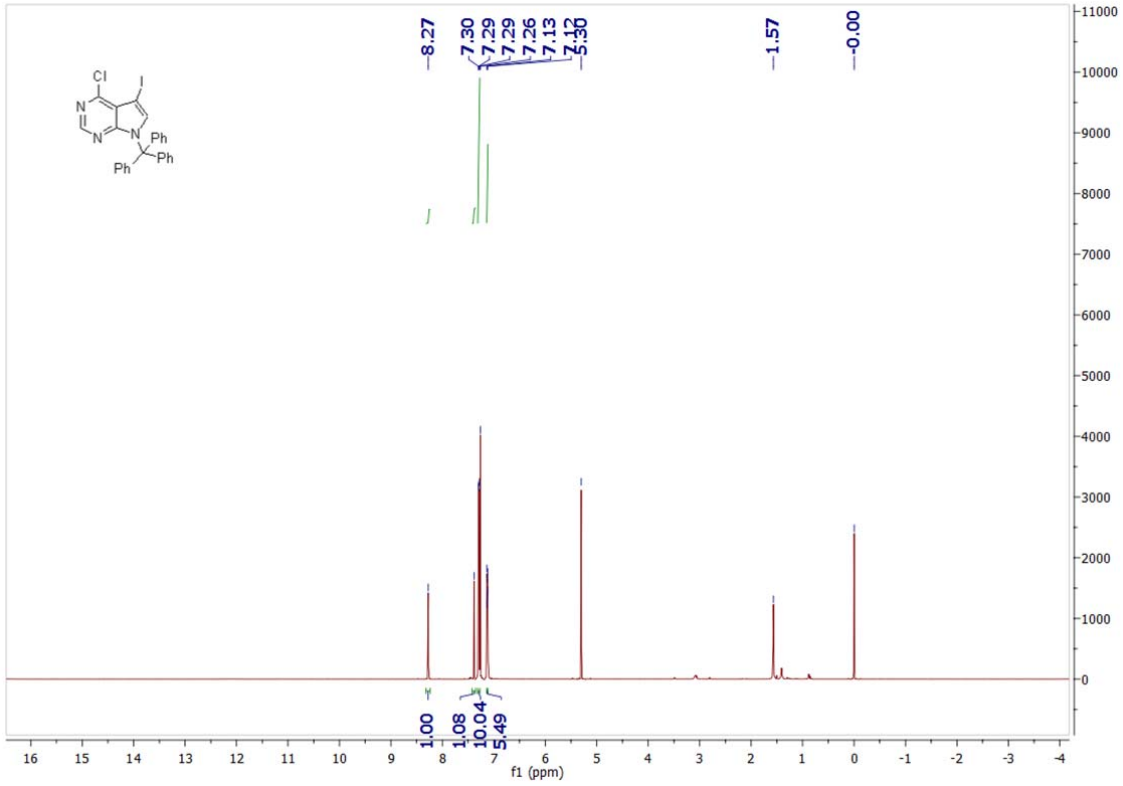
3-(4-chloro-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl) benzonitrile (2)



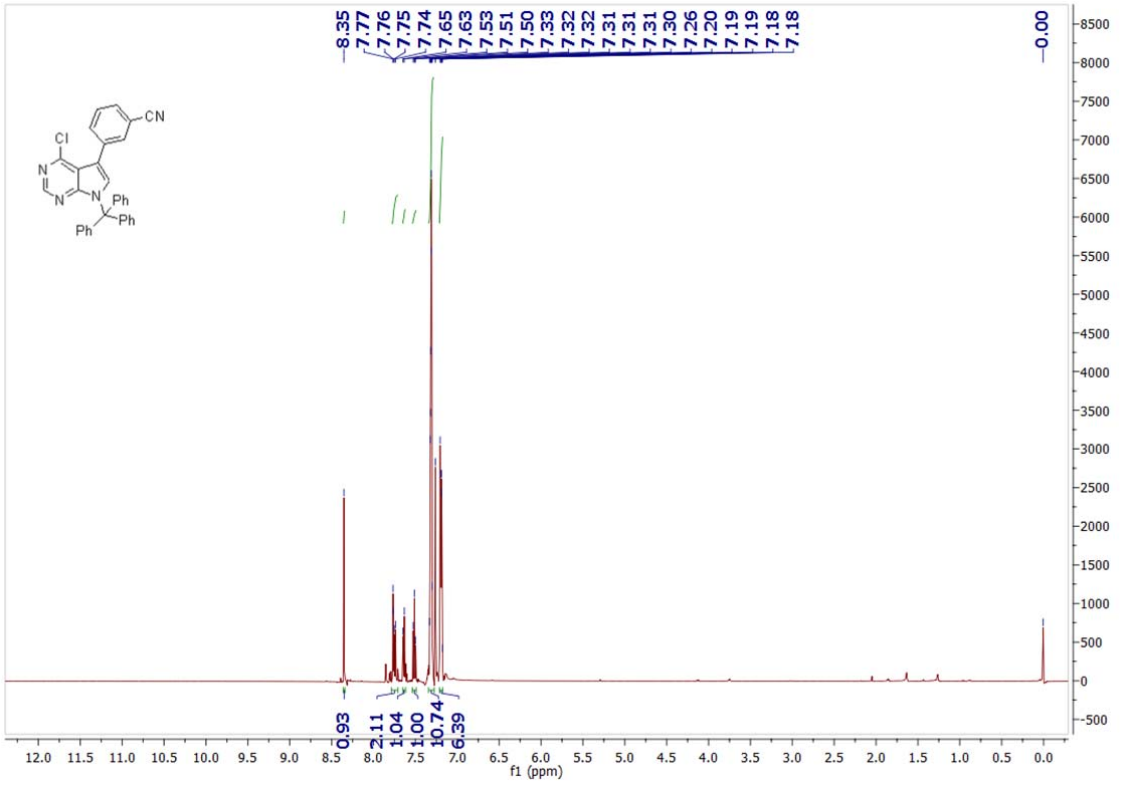
3-(4-chloro-7H-pyrrolo[2,3-d]pyrimidin-5-yl)benzonitrile (3)

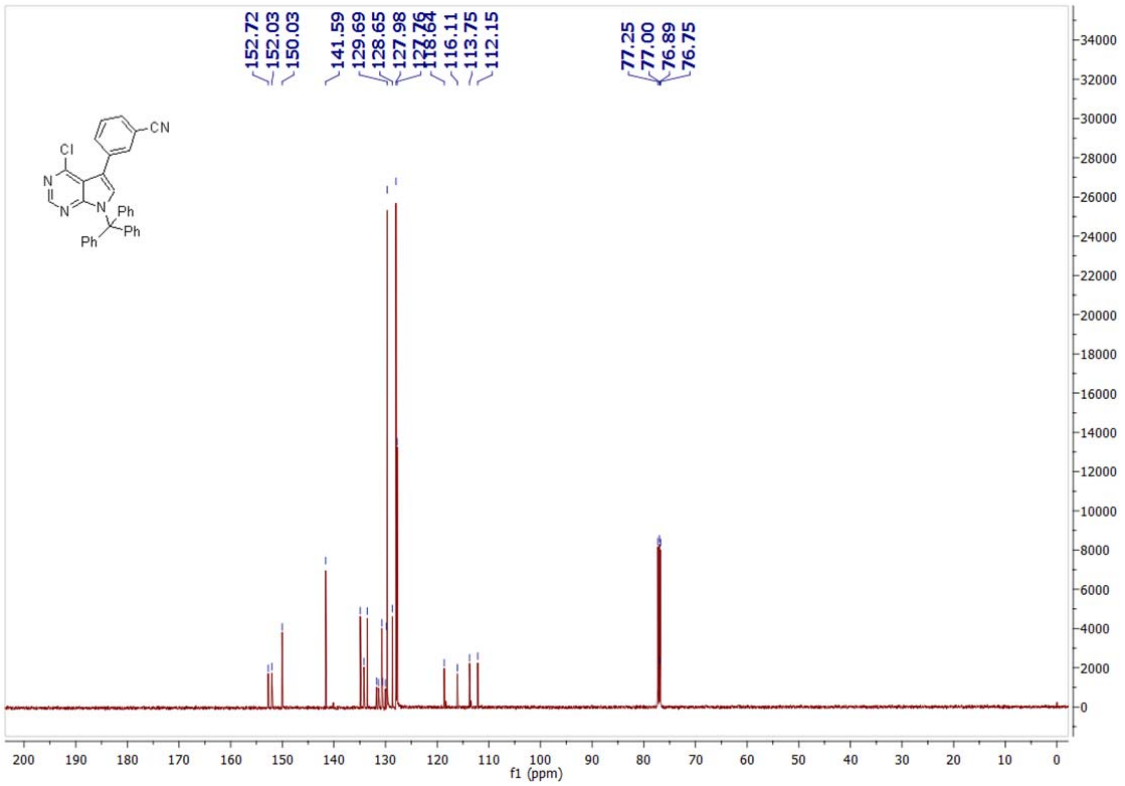


4-chloro-5-iodo-7-trityl-7H-pyrrolo[2,3-d]pyrimidine (4)

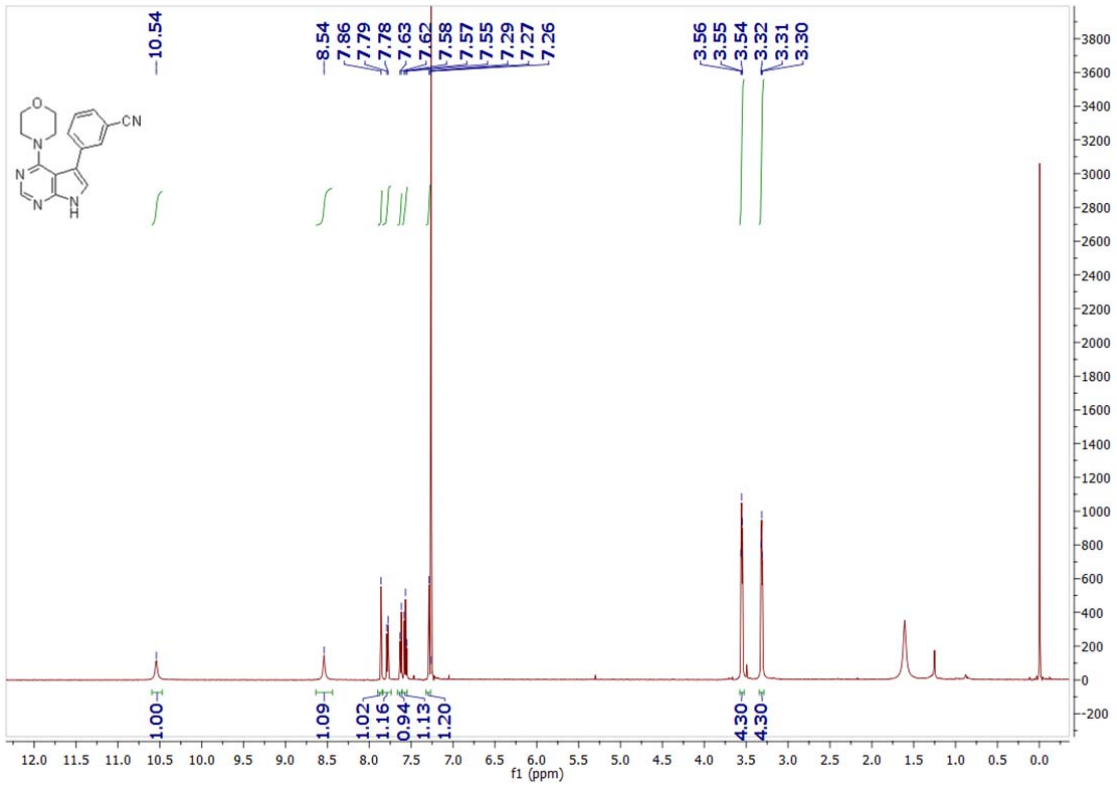


4-chloro-5-iodo-7-trityl-7H-pyrrolo[2,3-d]pyrimidine (5)

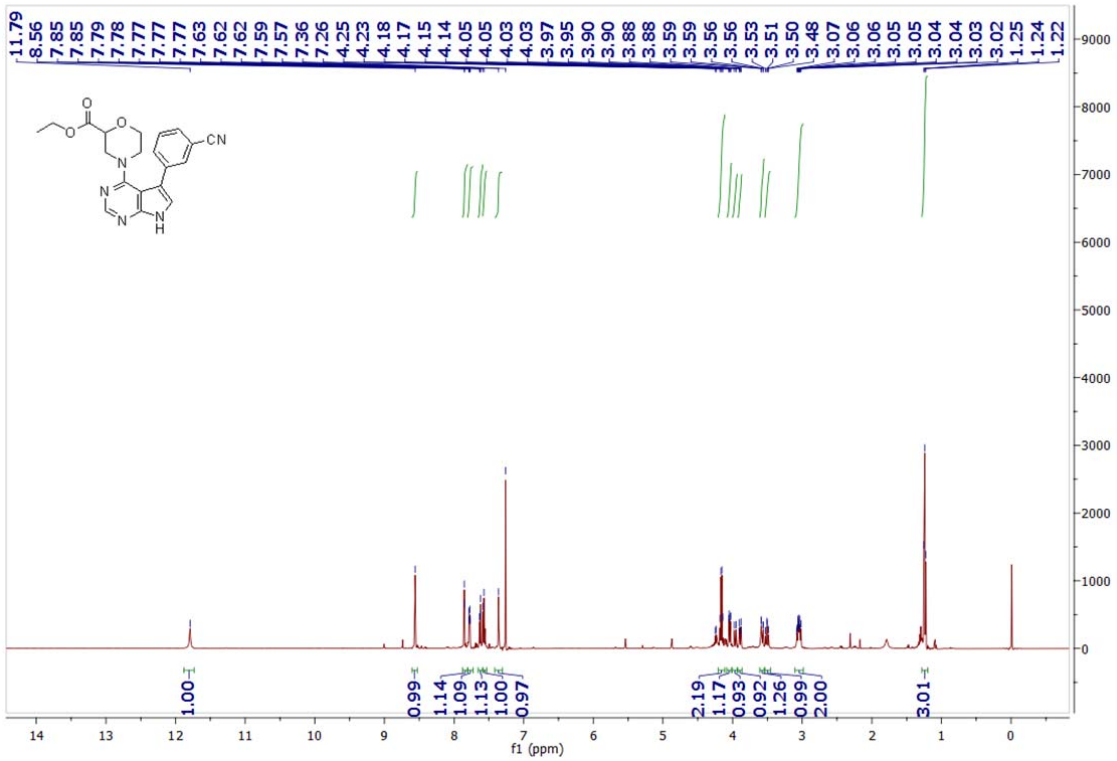




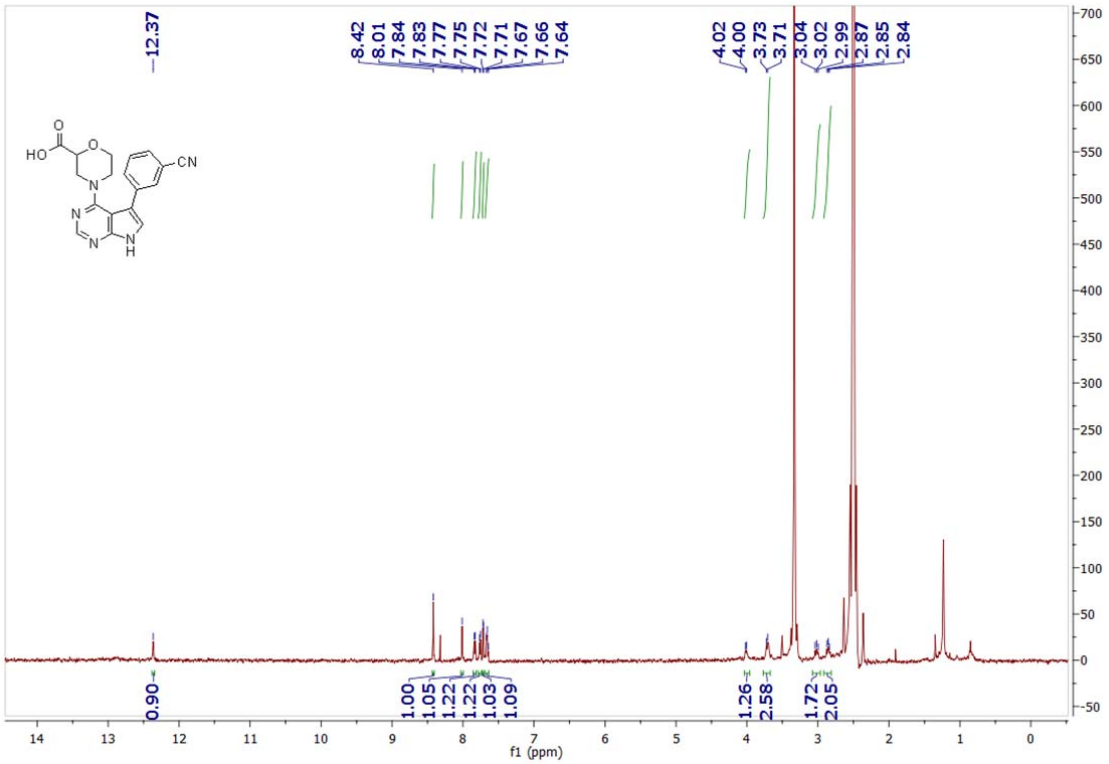
3-(4-morpholino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)benzonitrile (6) [PF-06447475]



ethyl 4-(5-(3-cyanophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)morpholine-2-carboxylate (7)



4-(5-(3-cyanophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)morpholine-2-carboxylic acid (8)



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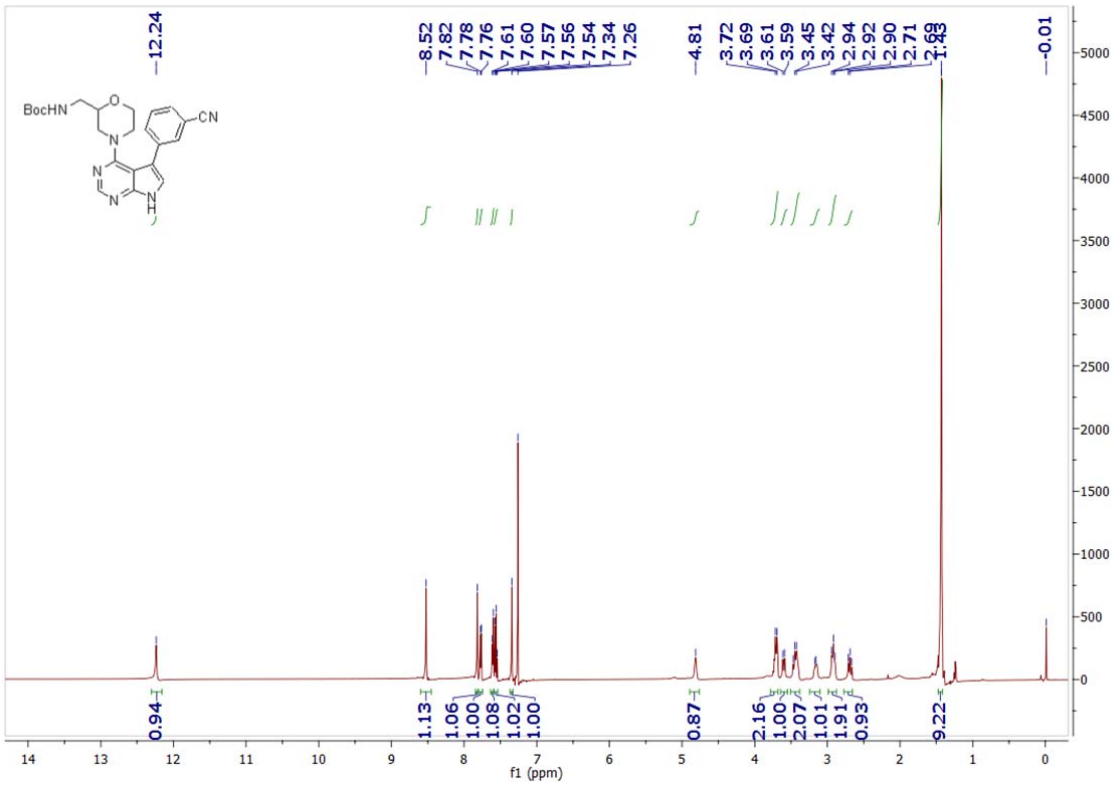
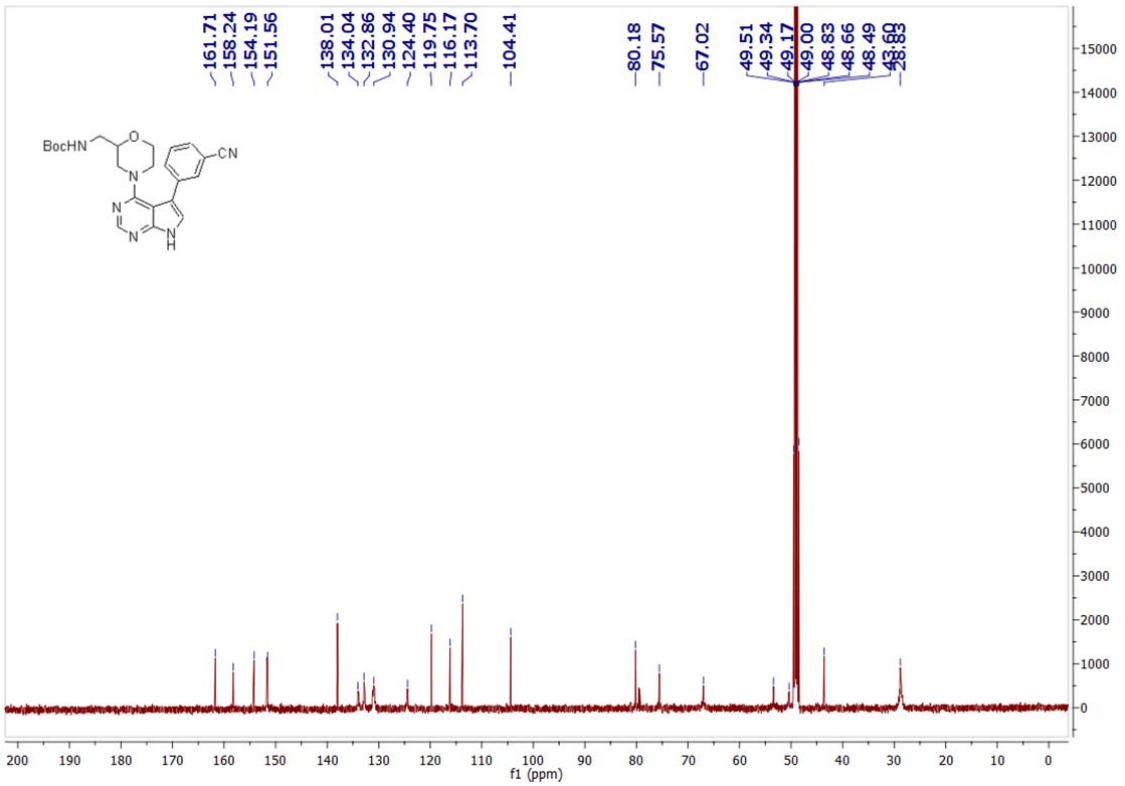
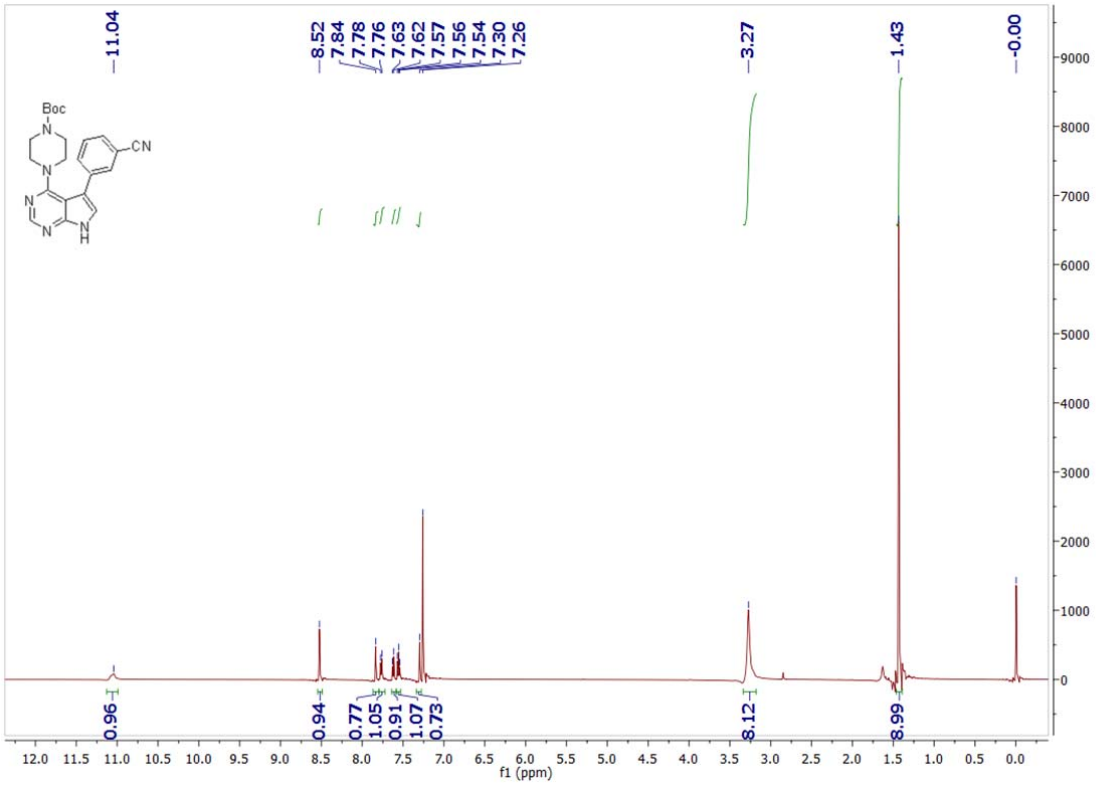
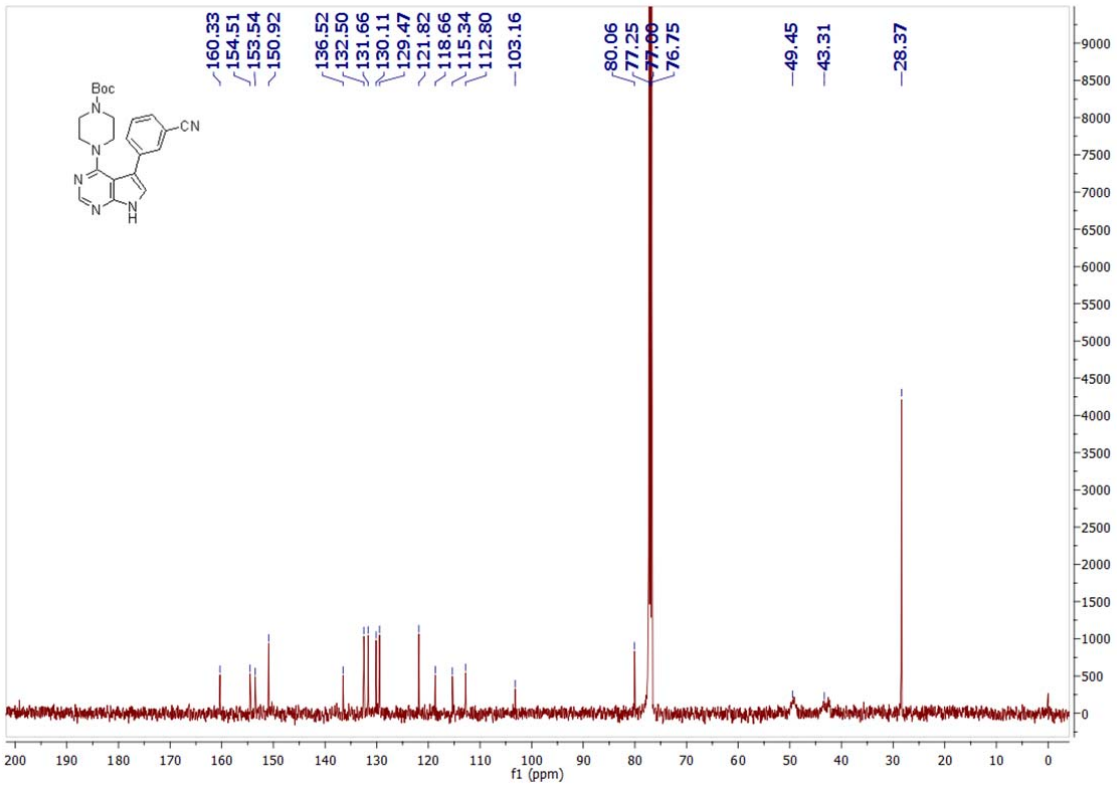


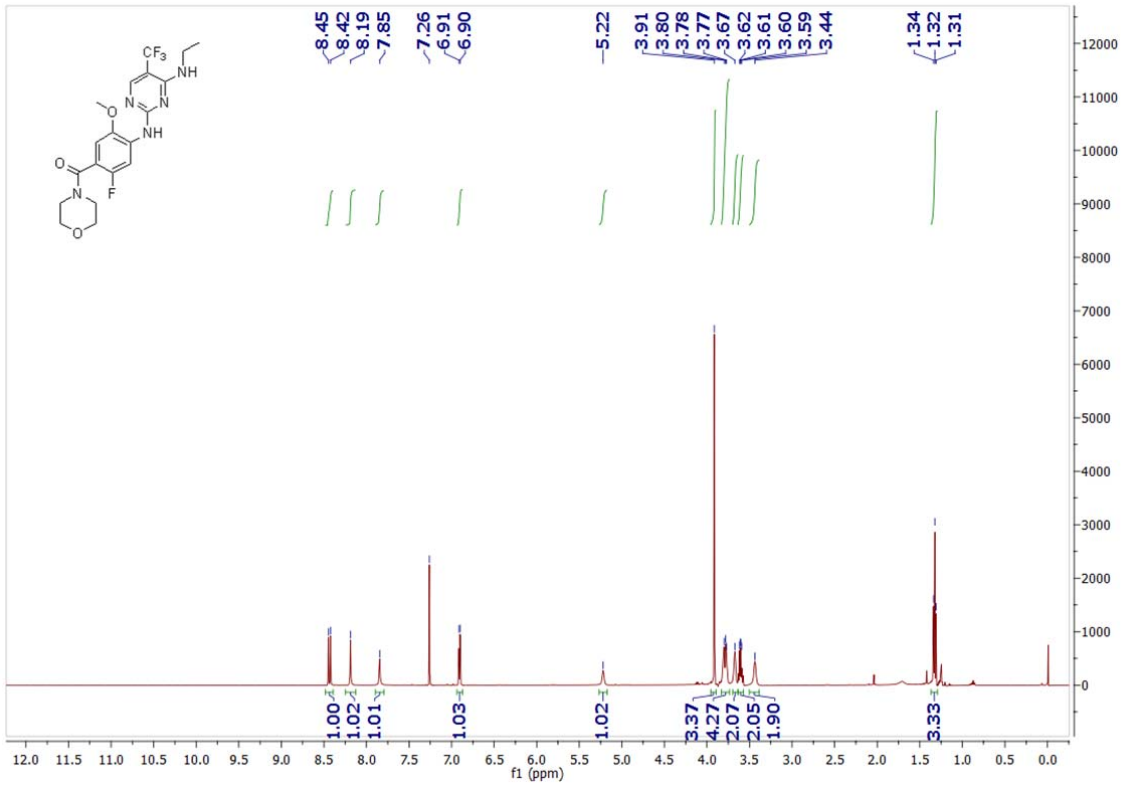


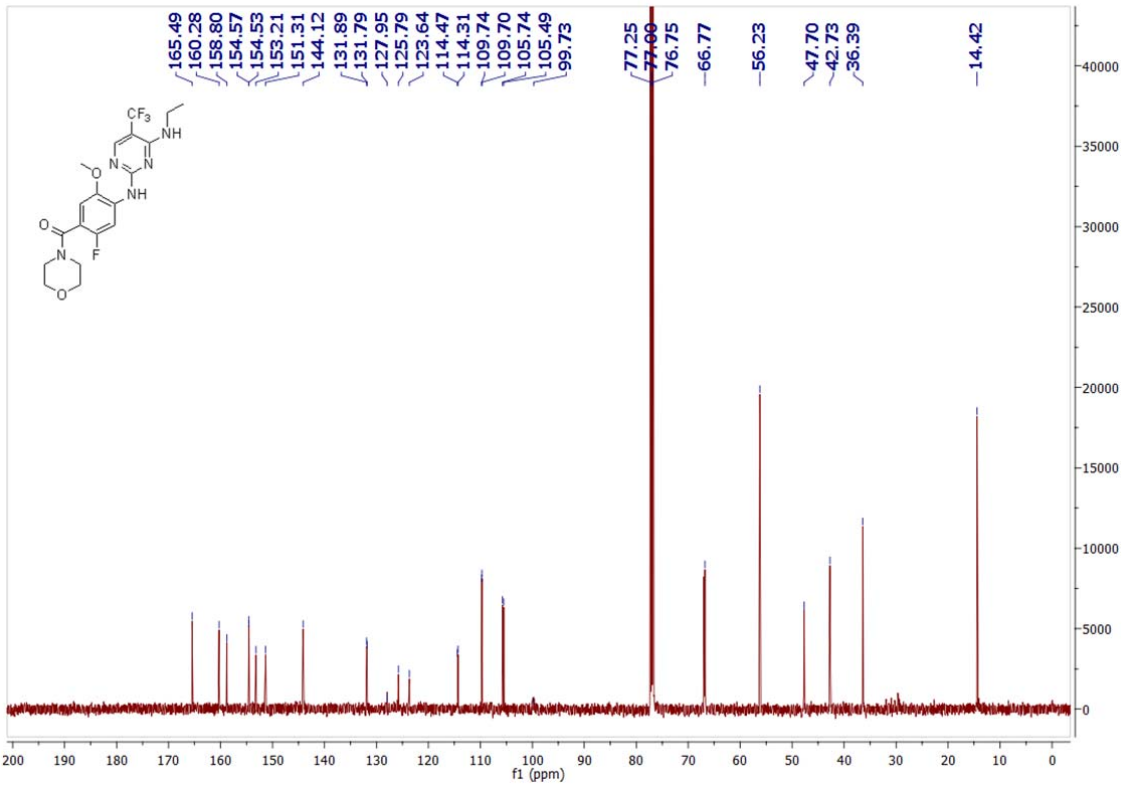
***tert*-butyl 4-(5-(3-cyanophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperazine-1-carboxylate (10)**



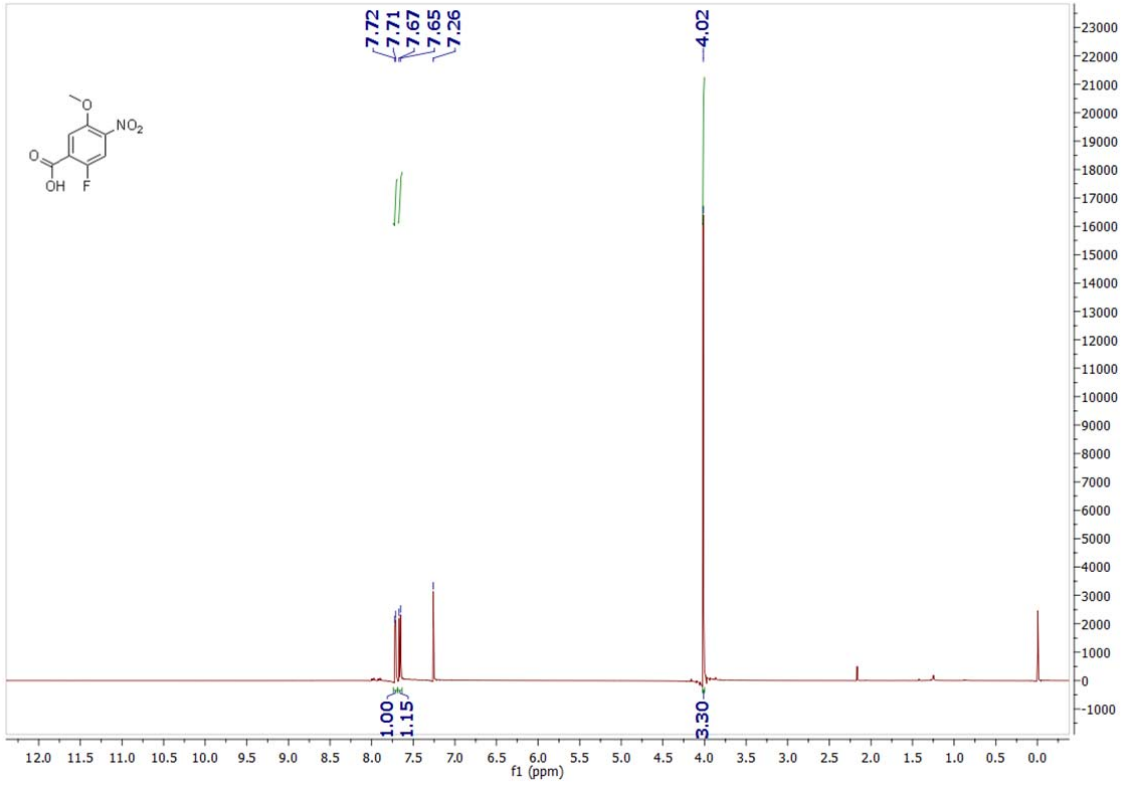


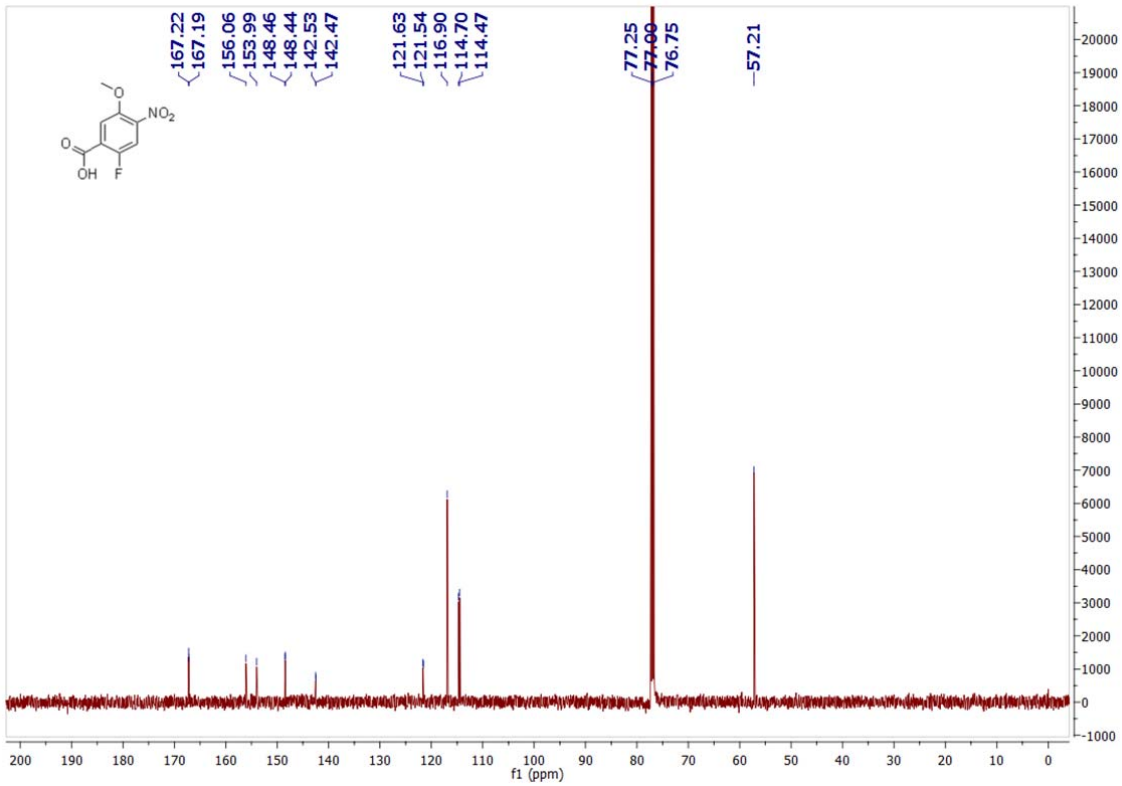
(4-((4-(ethylamino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-2-fluoro-5-methoxyphenyl) (morpholino)methanone (11) [GNE-7915]



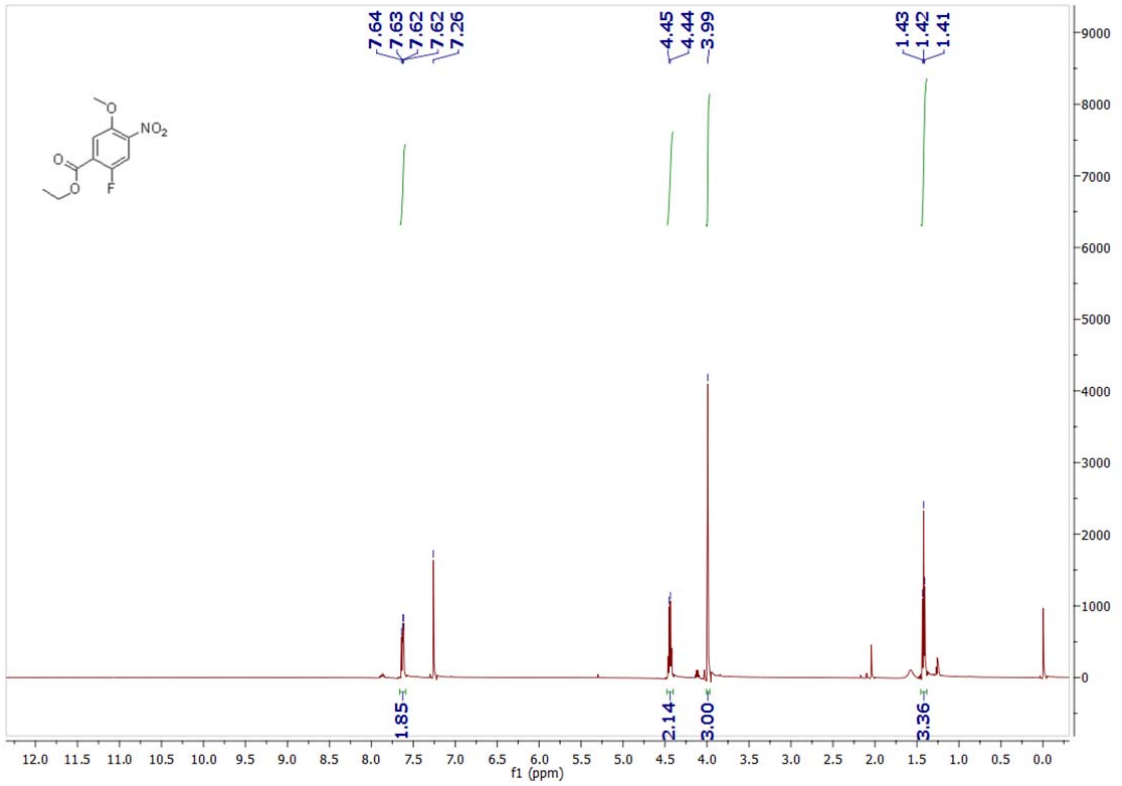


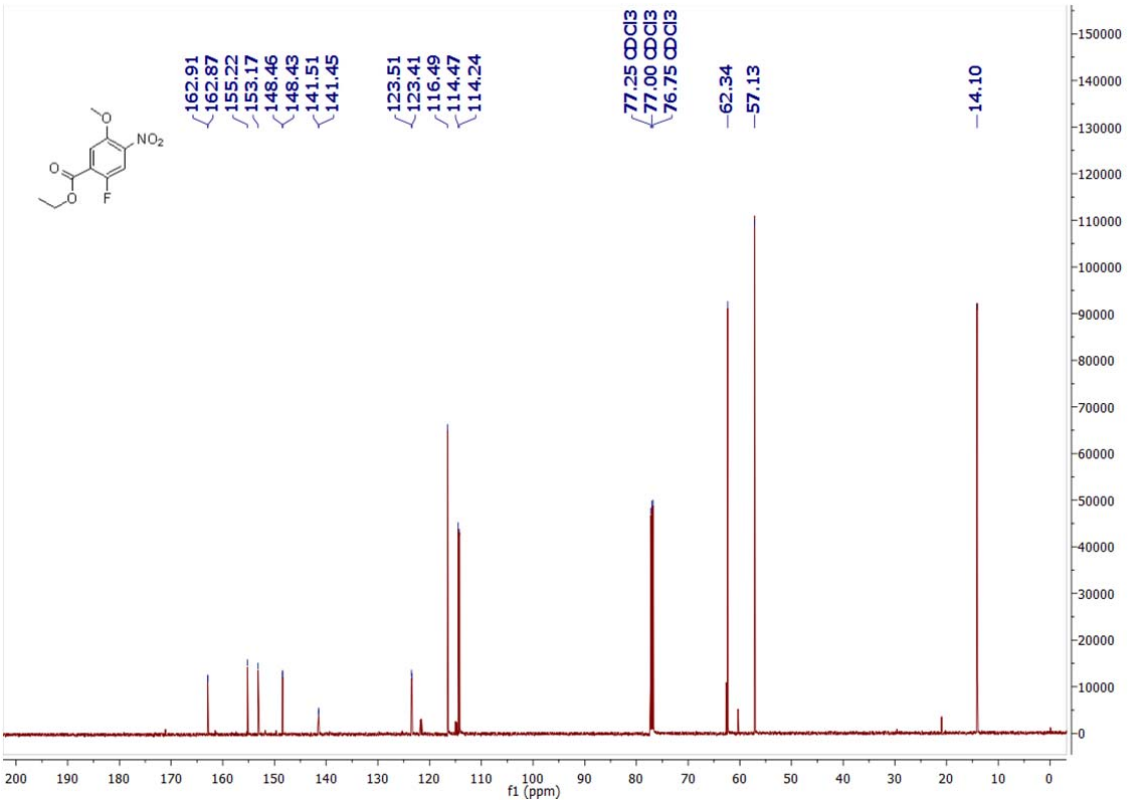
2-fluoro-5-methoxy-4-nitrobenzoic acid (12)



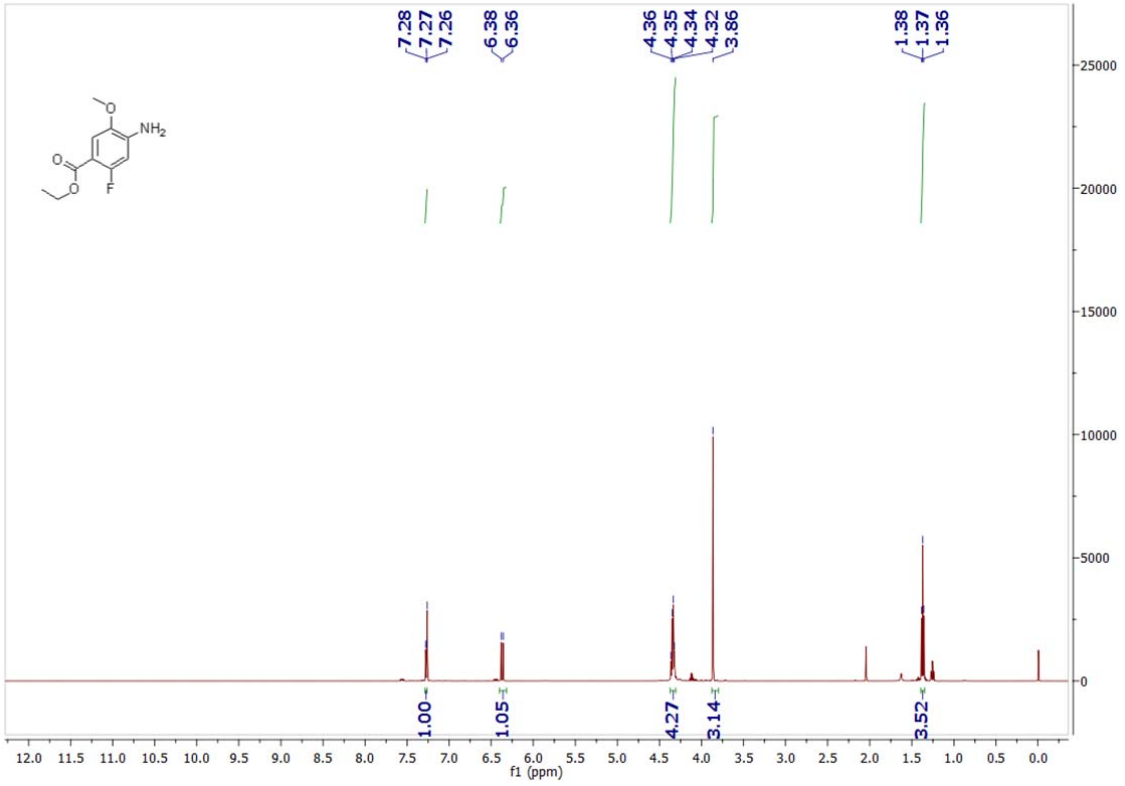


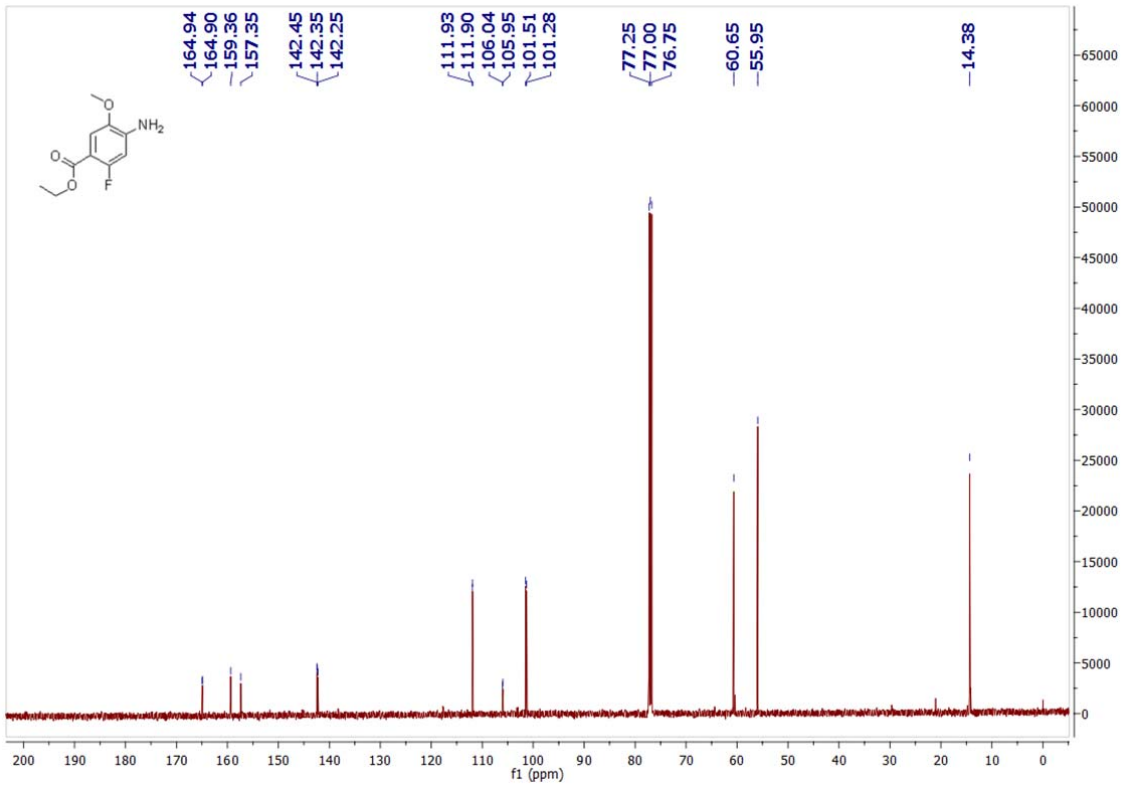
ethyl 2-fluoro-5-methoxy-4-nitrobenzoate (13)



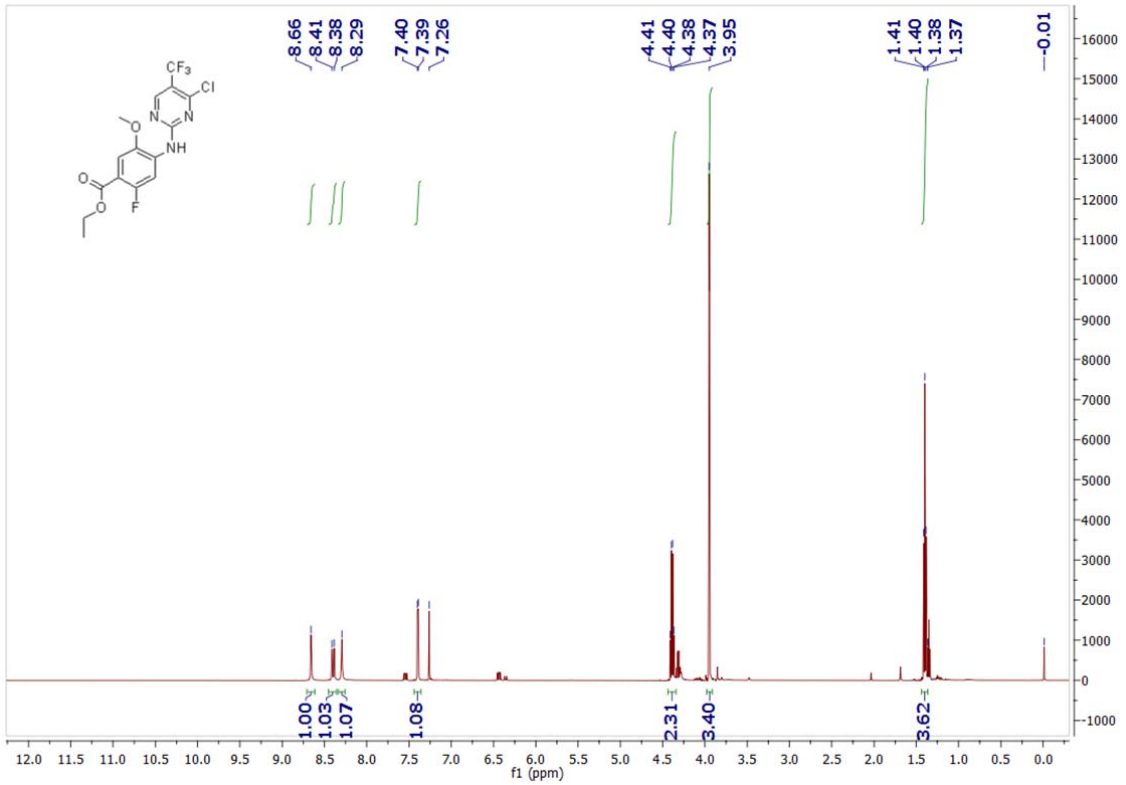


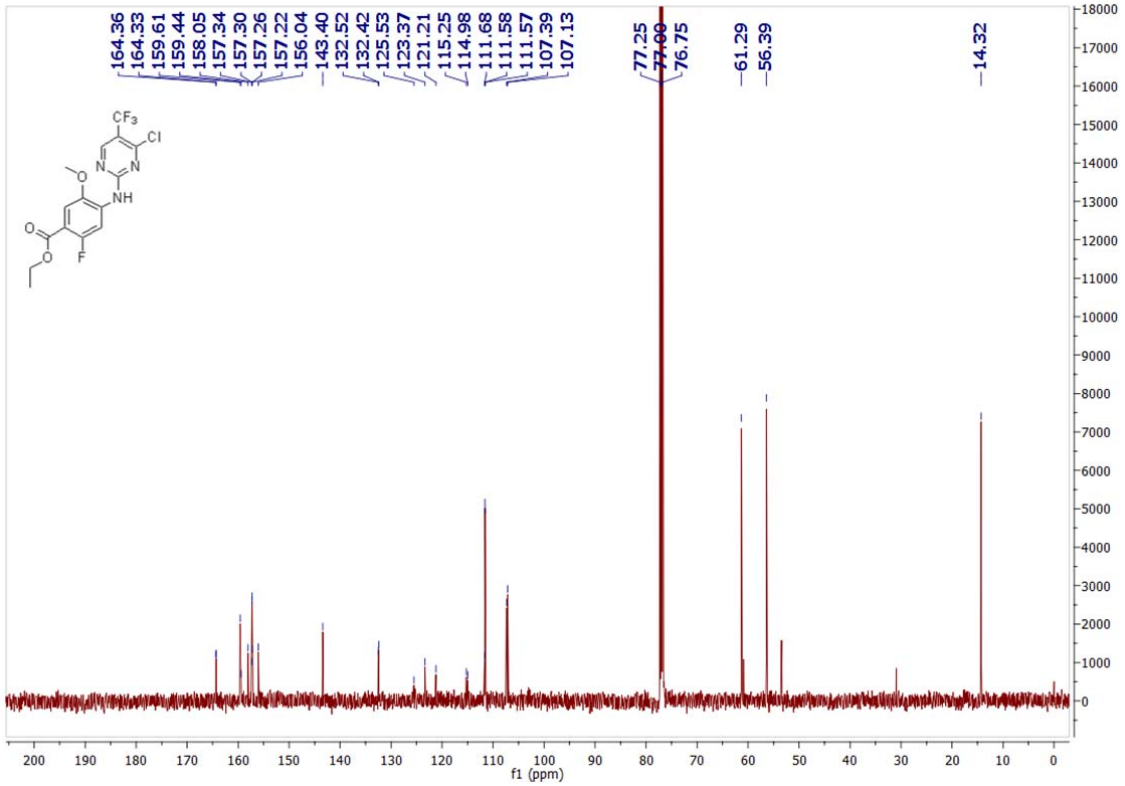
ethyl 4-amino-2-fluoro-5-methoxybenzoate (14)



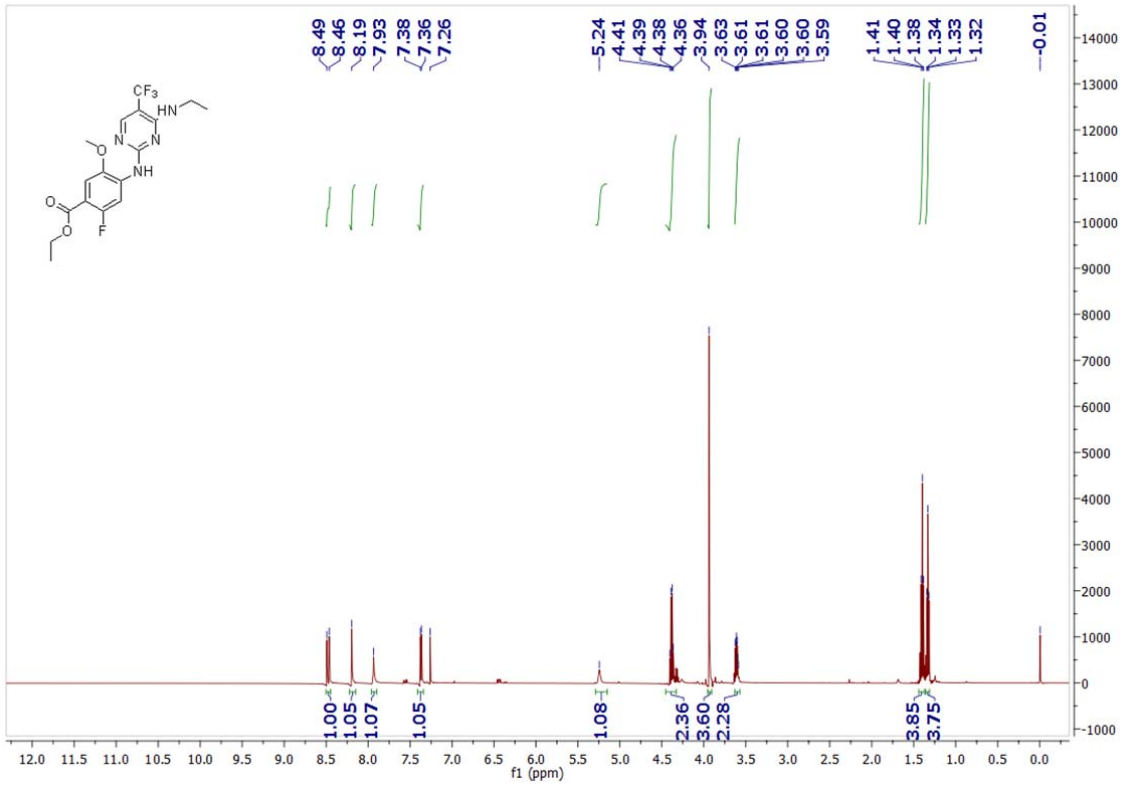


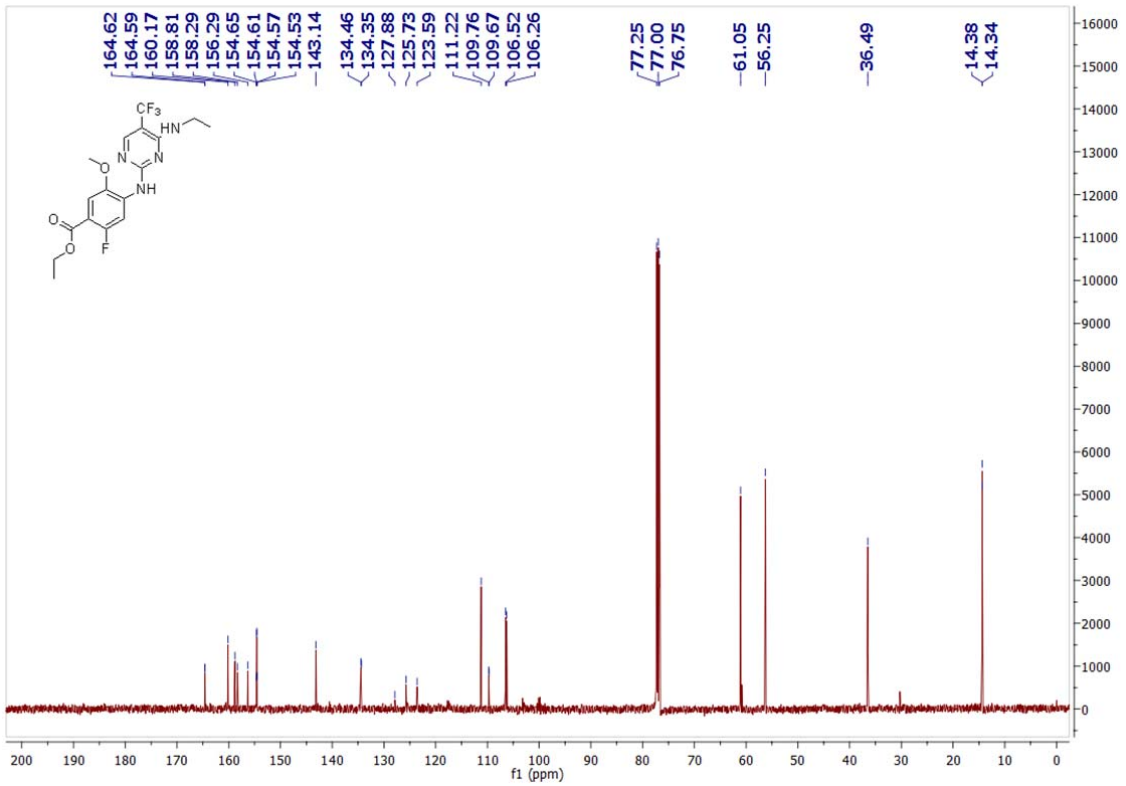
ethyl 4-amino-2-fluoro-5-methoxybenzoate (15)



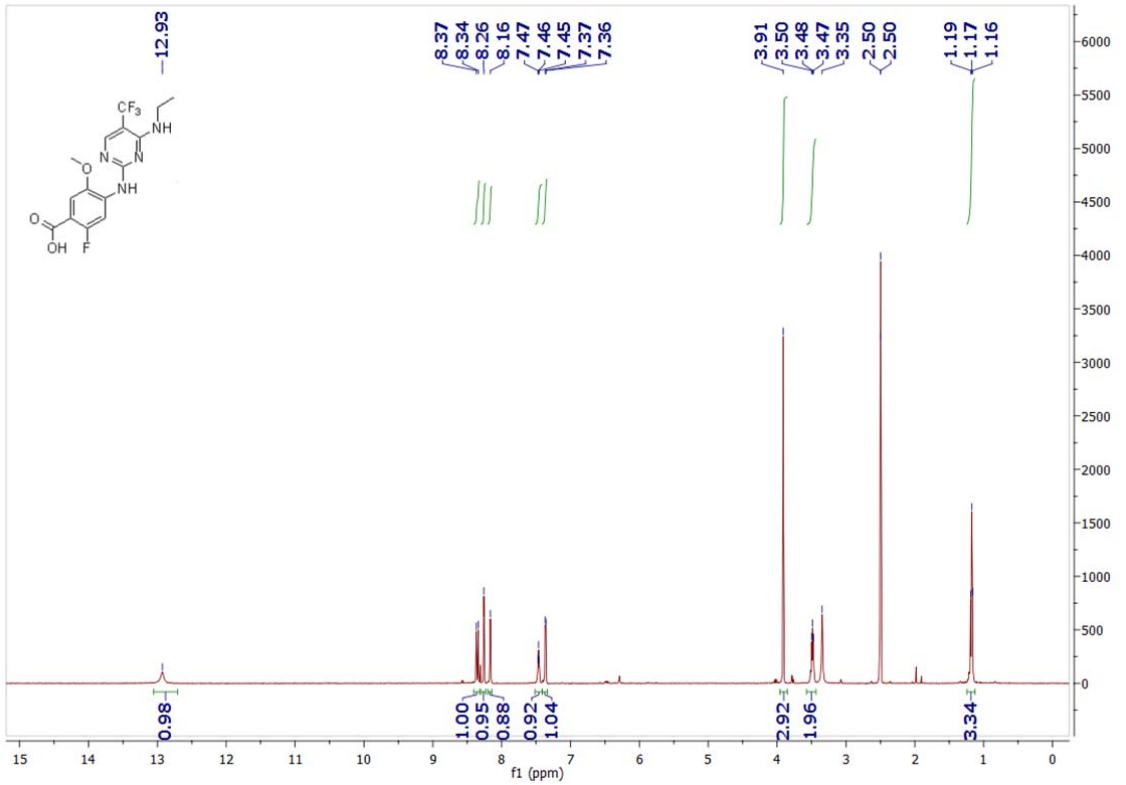


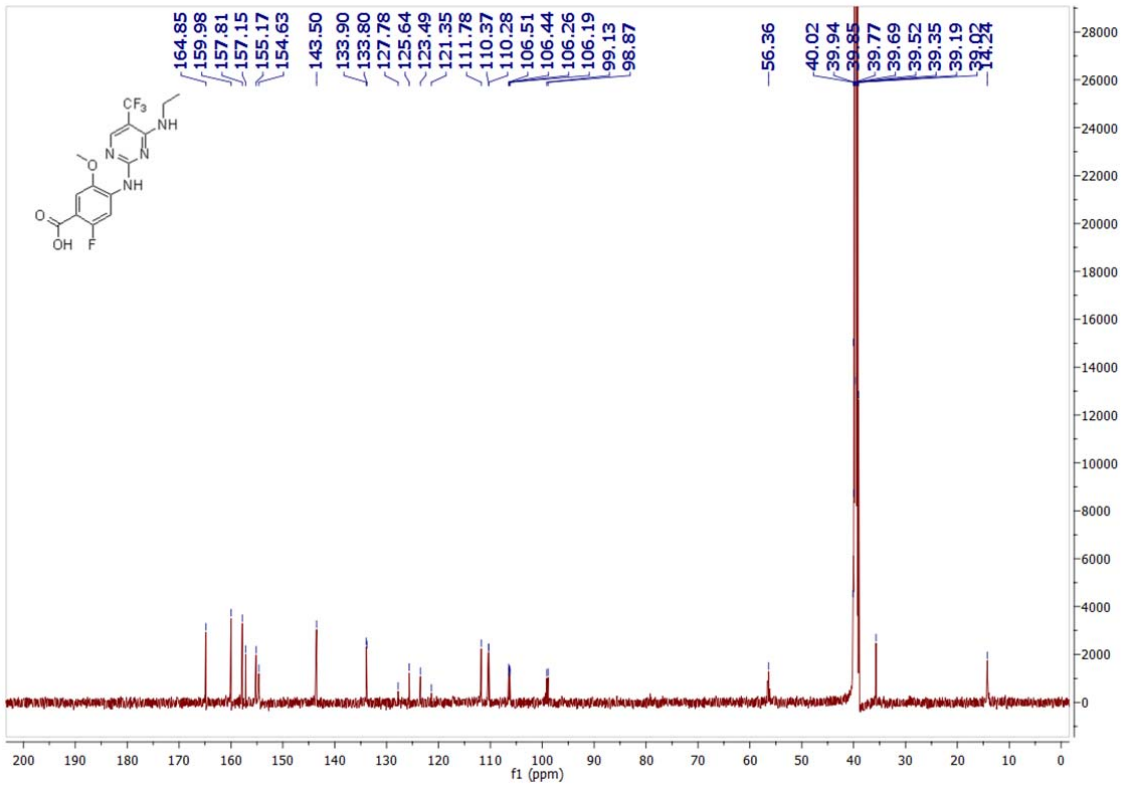
ethyl 4-amino-2-fluoro-5-methoxybenzoate (16)



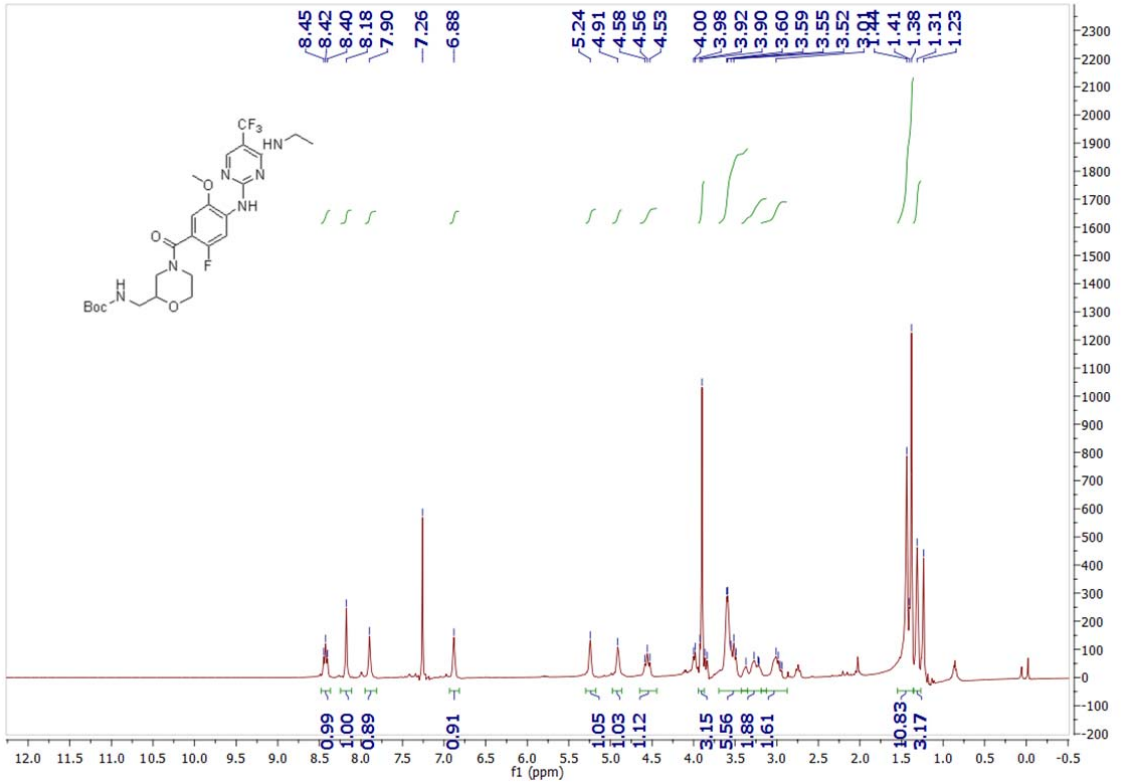


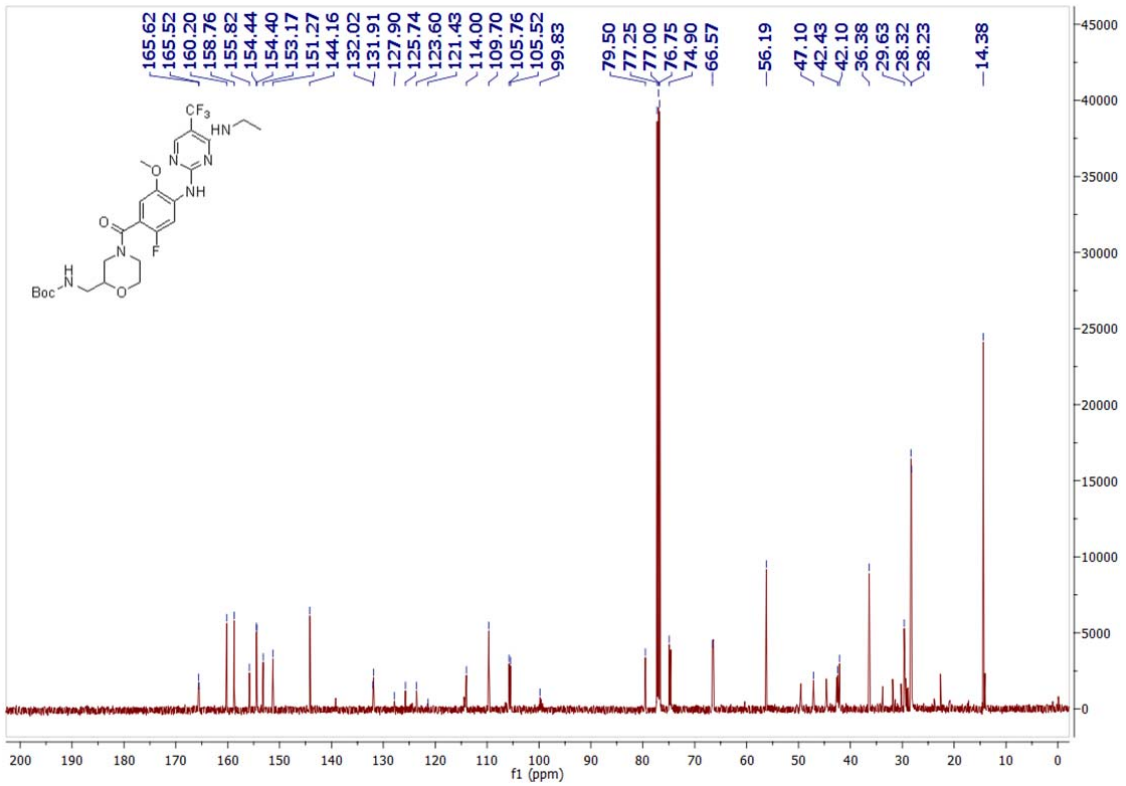
4-((4-(ethylamino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-2-fluoro-5-methoxybenzoic acid (17)



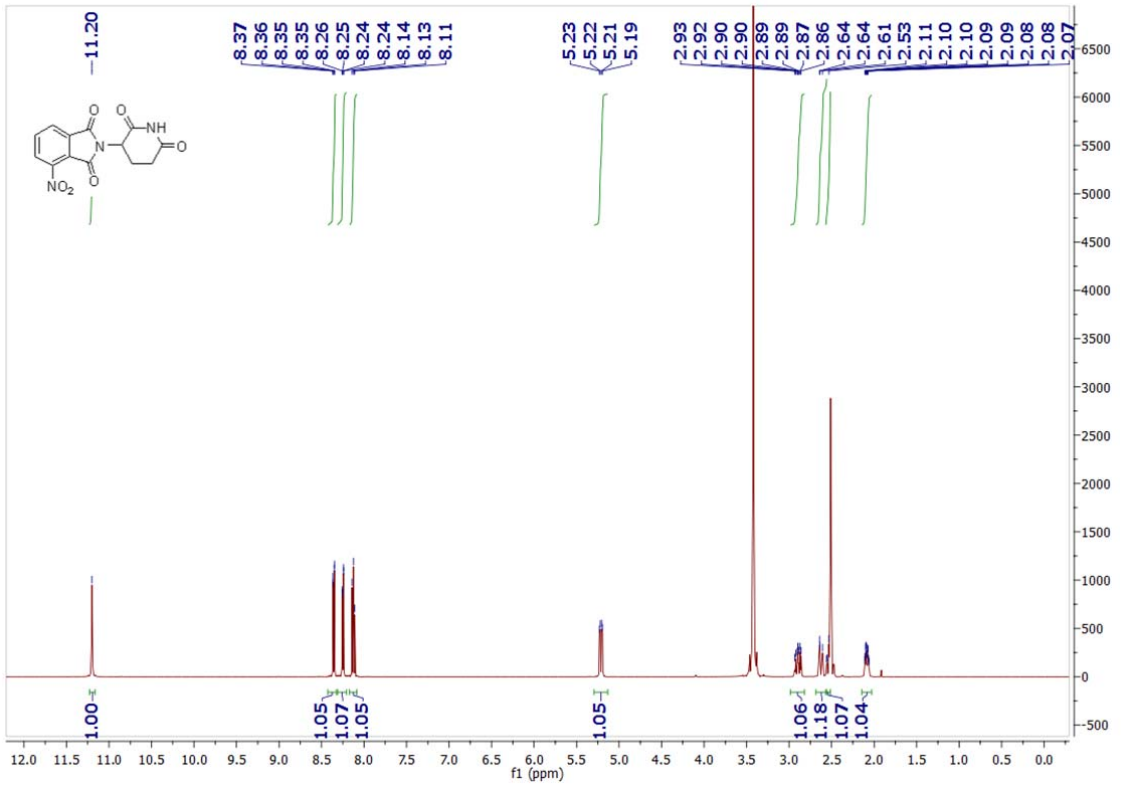


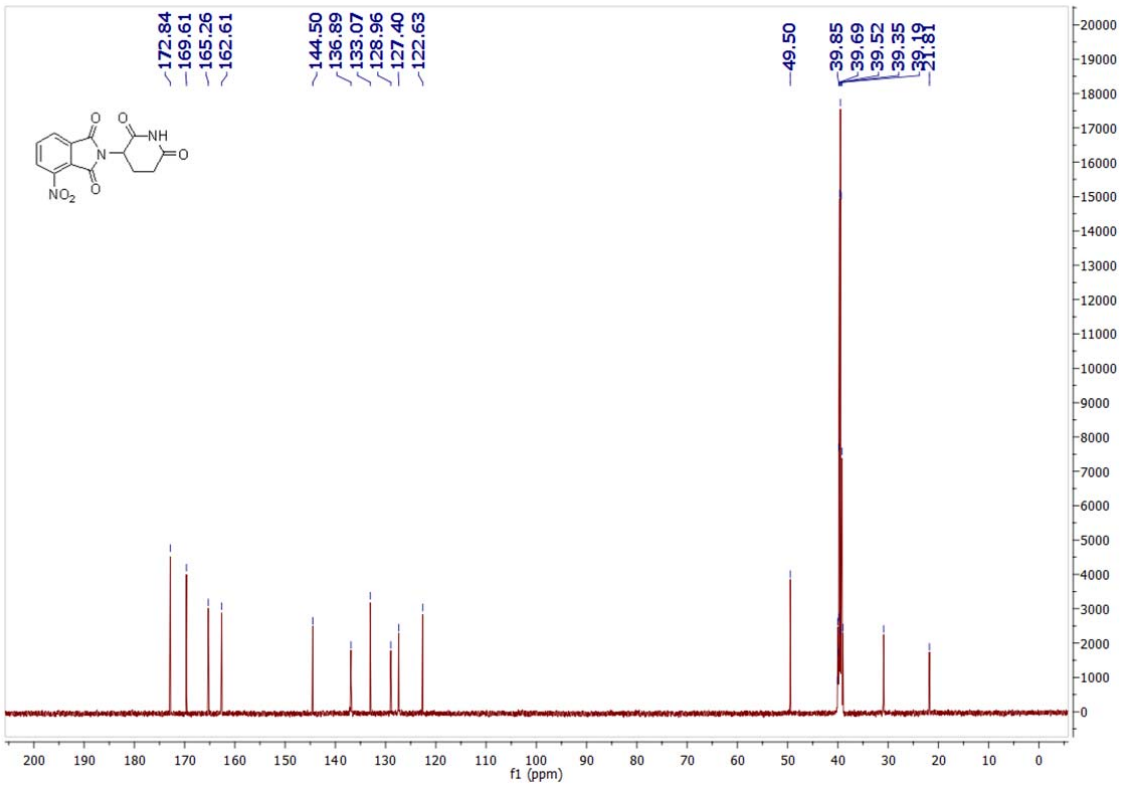
***tert*-butyl((4-(4-((4-(ethylamino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-2-fluoro-5-methoxybenzoyl)morpholin-2-yl)methyl)carbamate (18)**



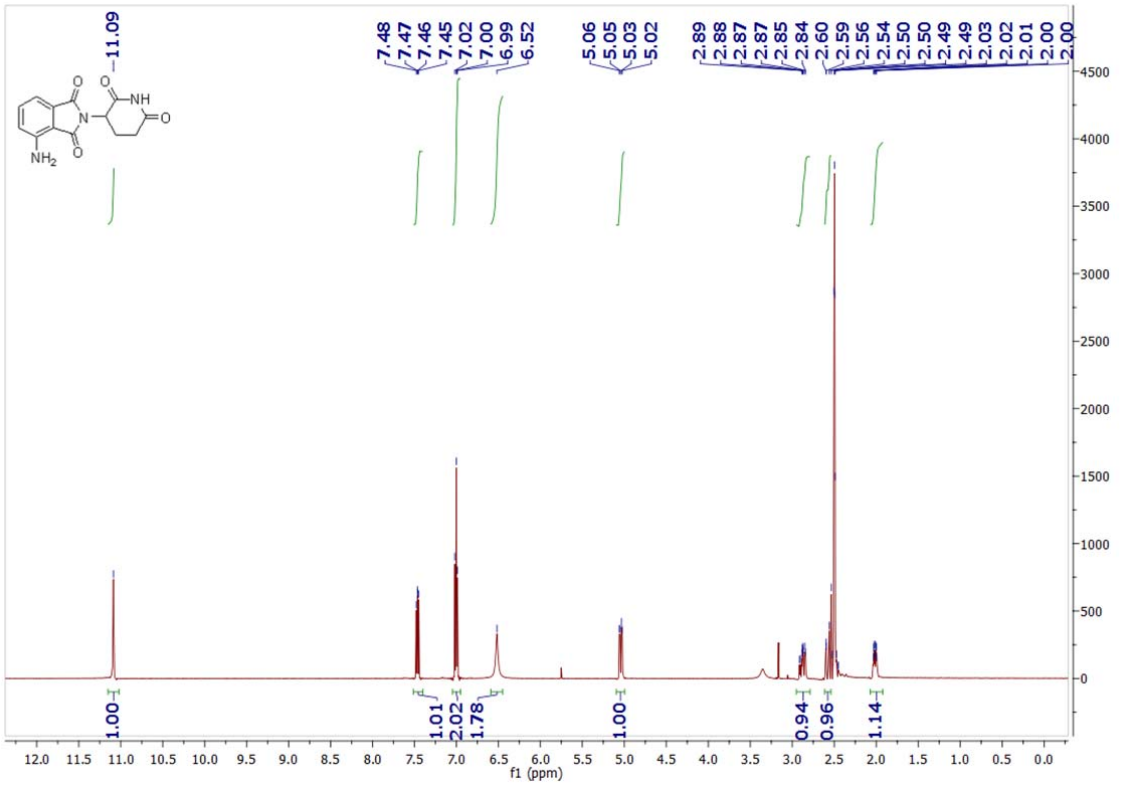


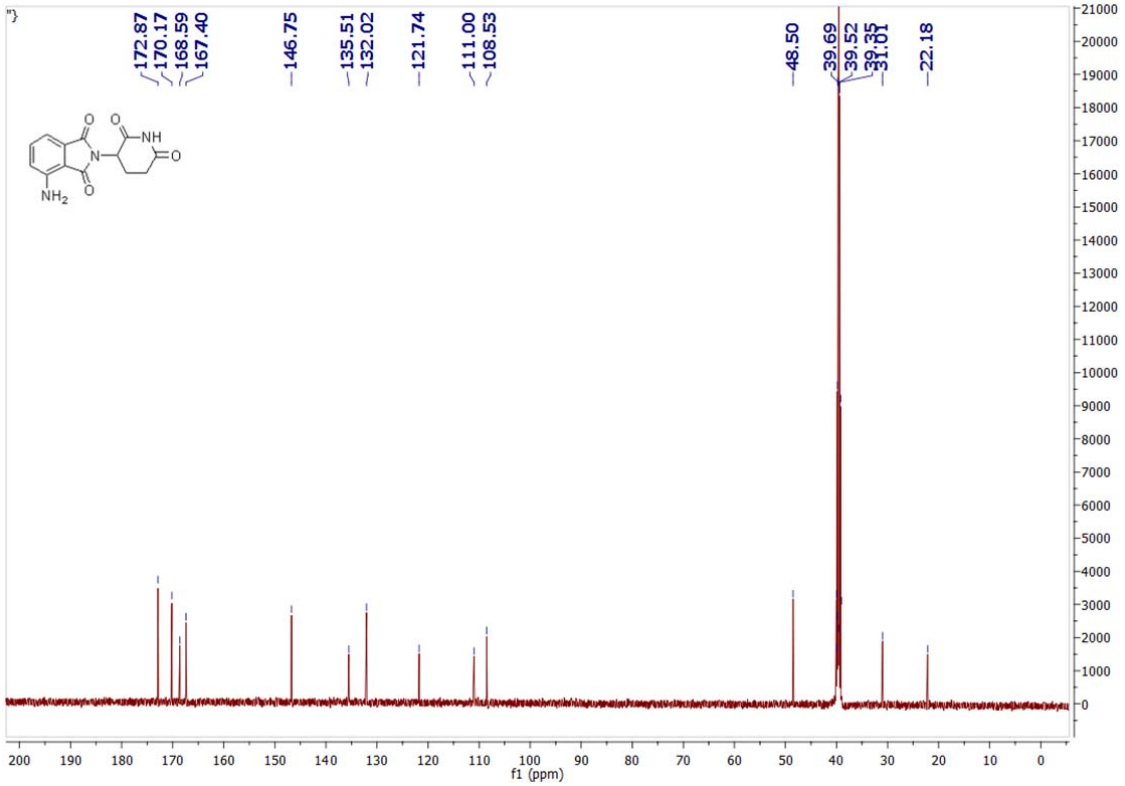
2-(2,6-dioxopiperidin-3-yl)-4-nitroisoindoline-1,3-dione (19)



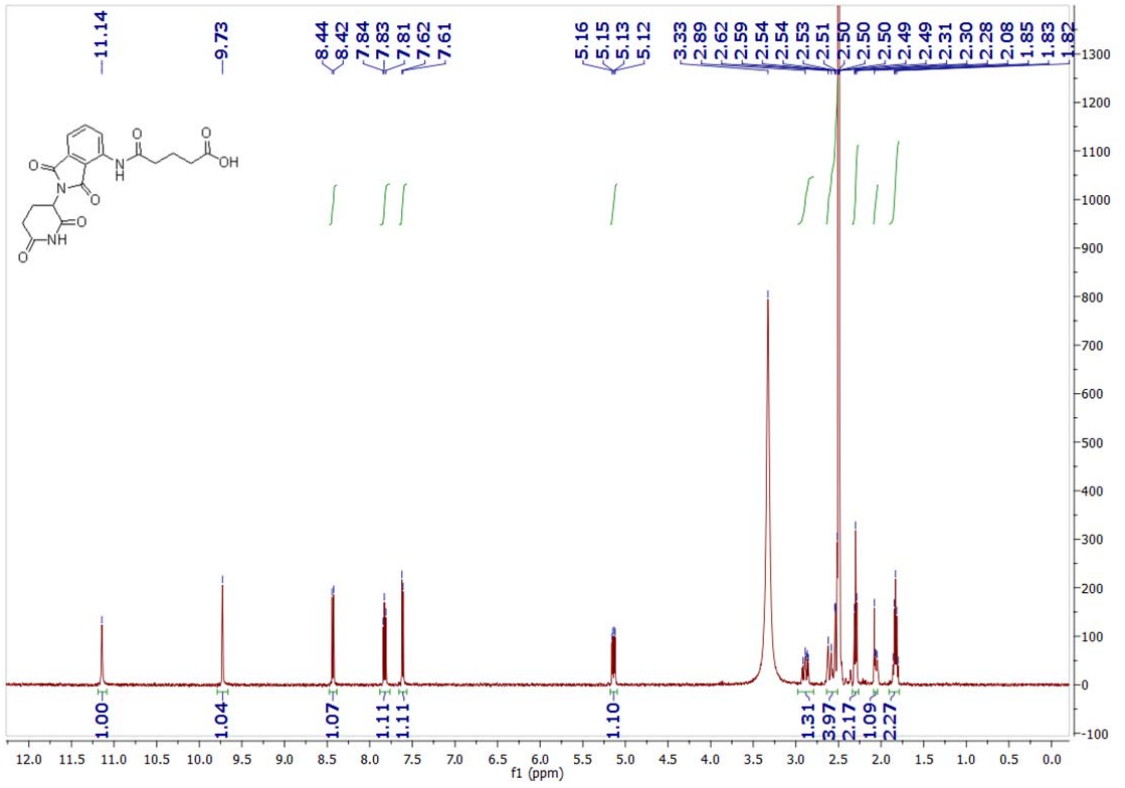


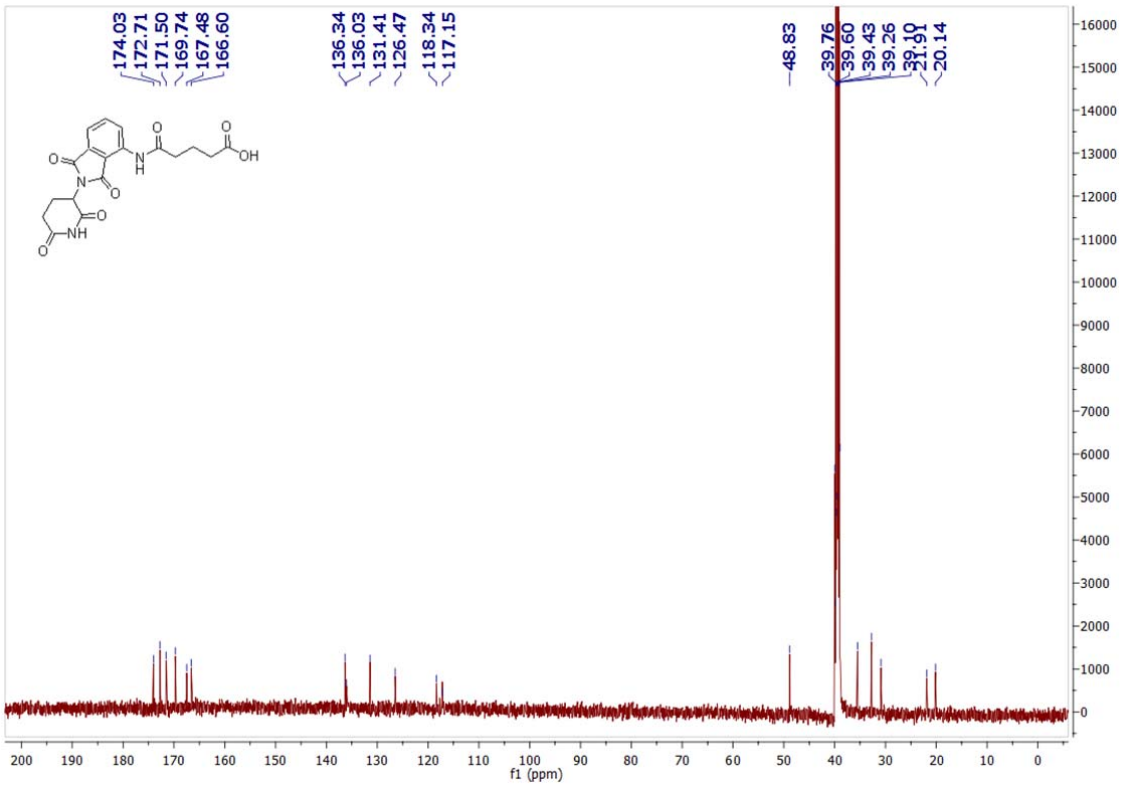
4-amino-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (20)



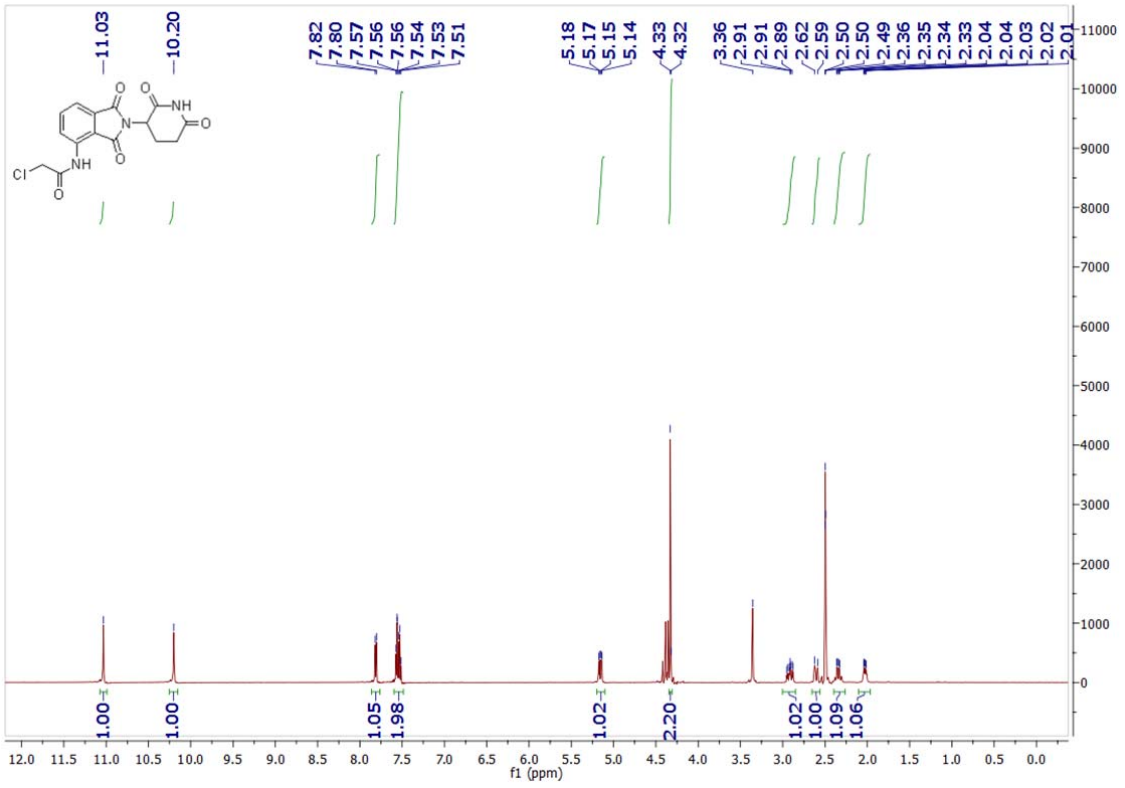


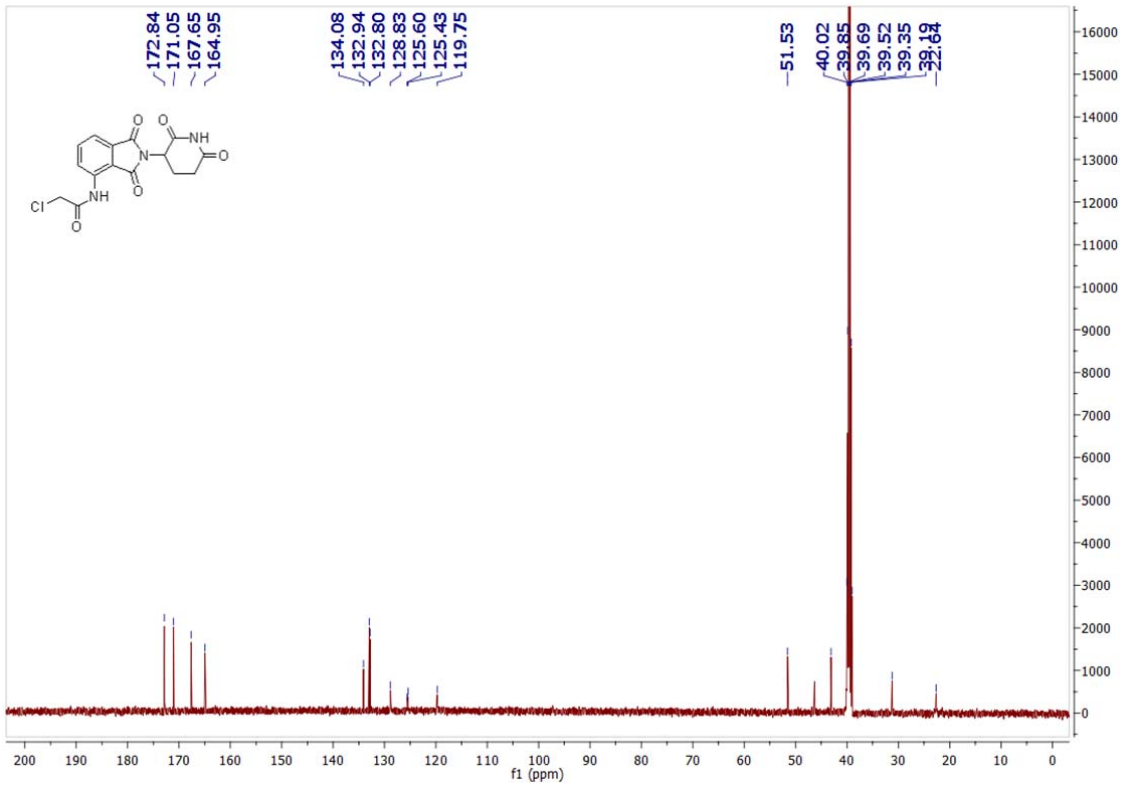
5-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-5-oxopentanoic acid (21)



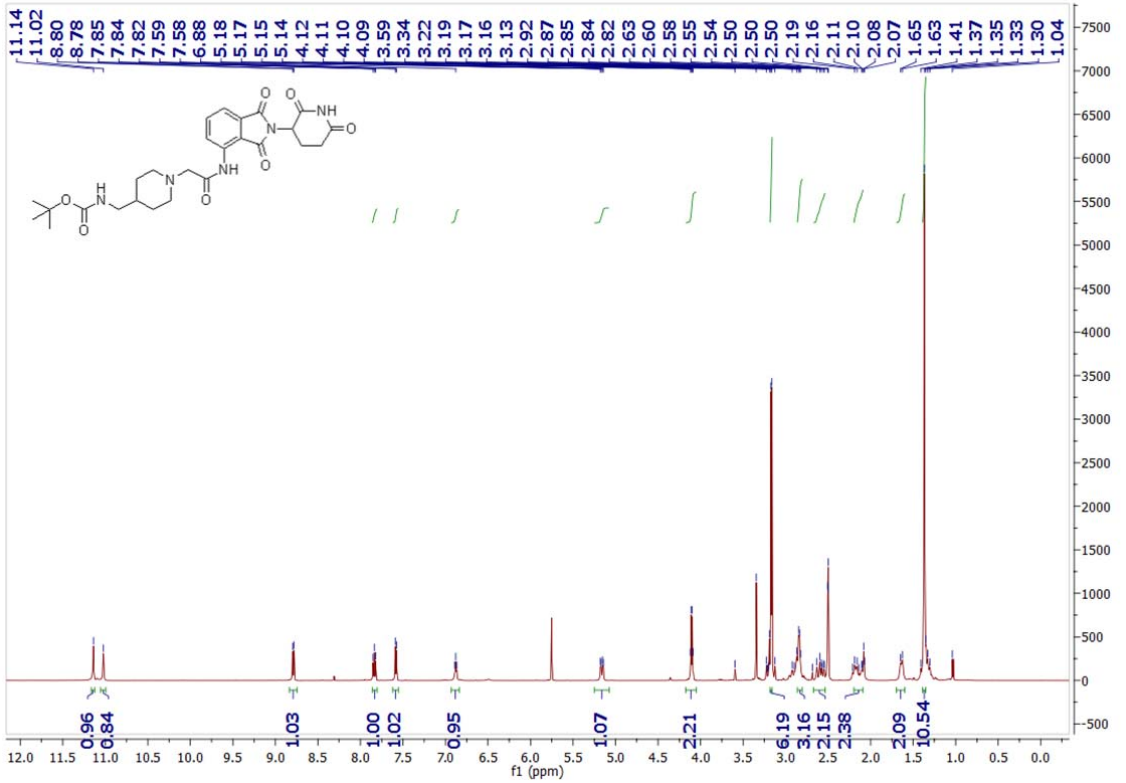


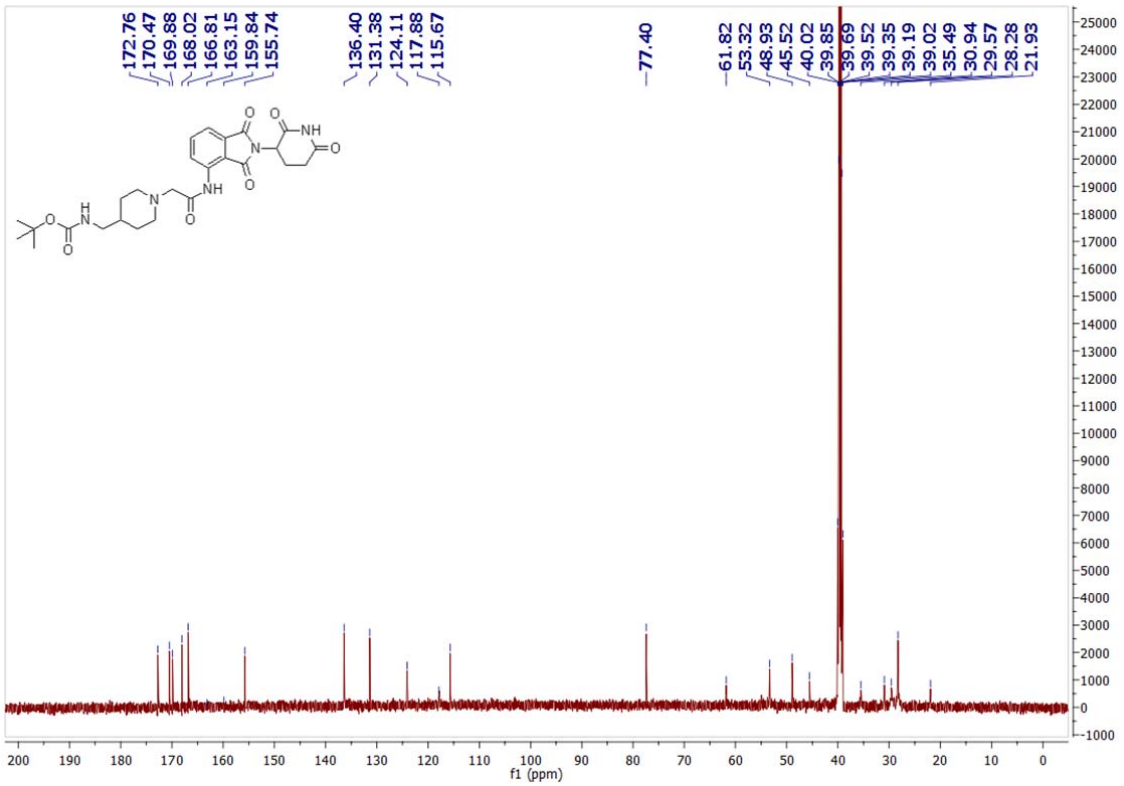
2-chloro-N-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)acetamide (22)



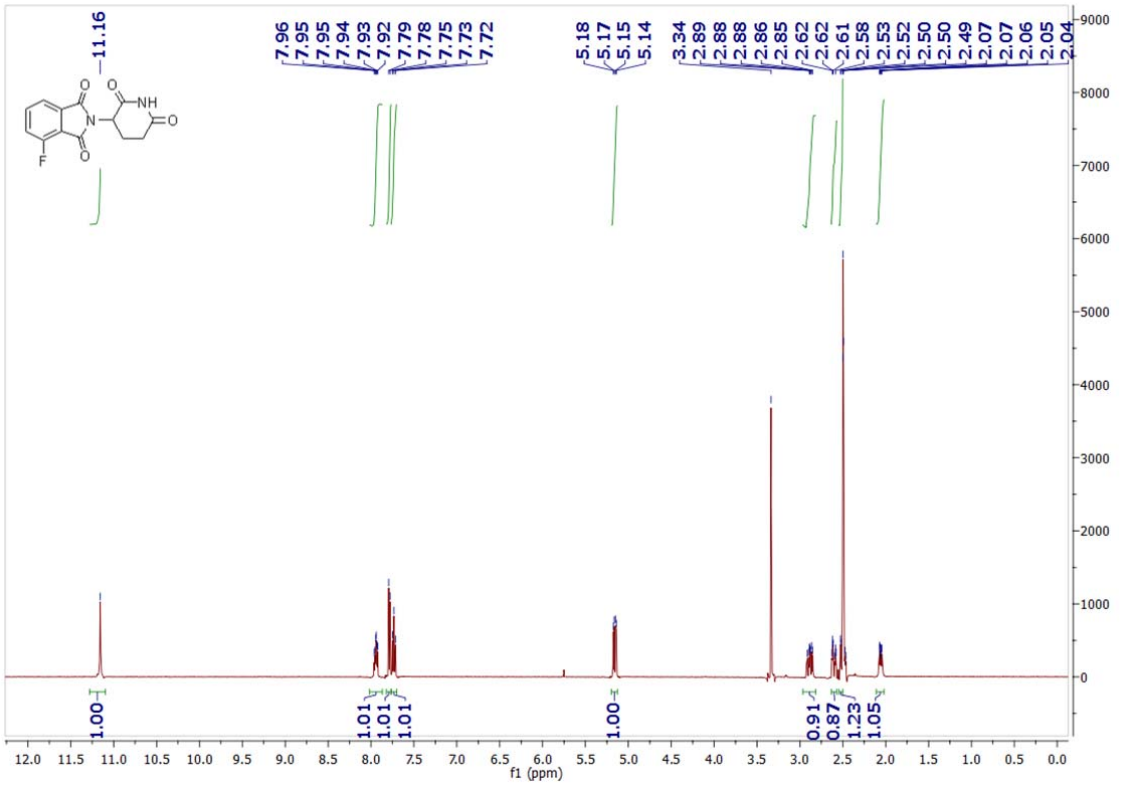


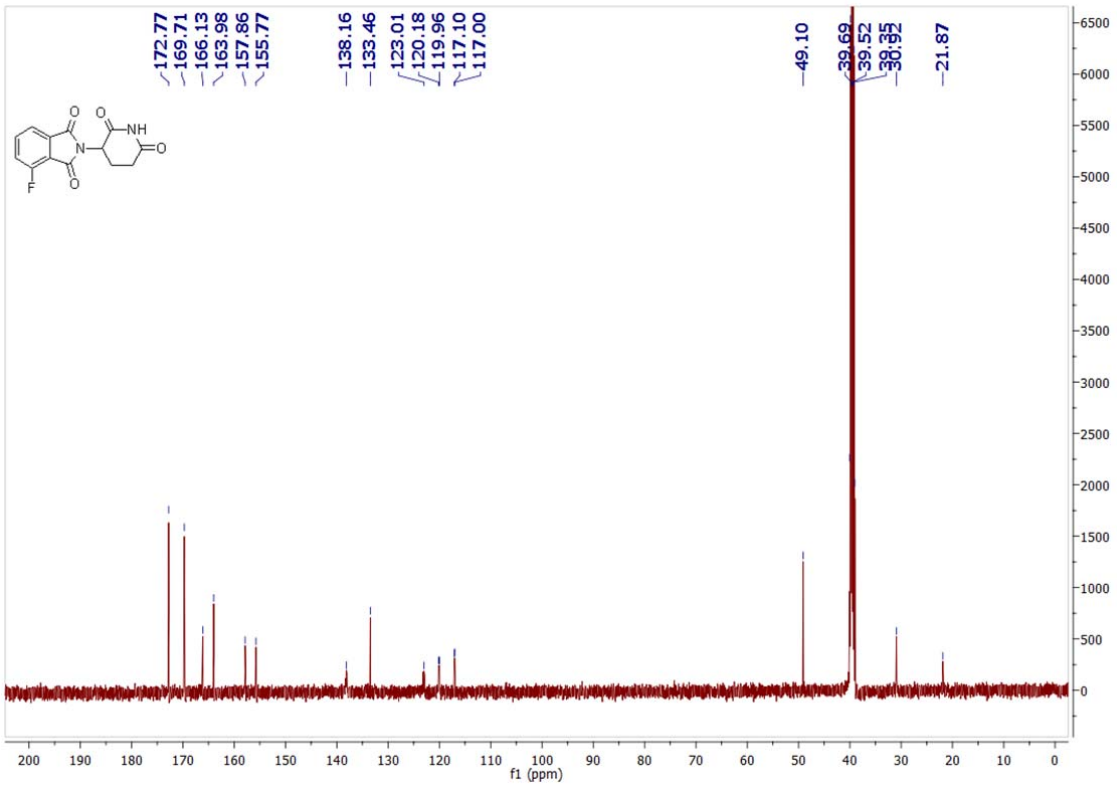
***tert*-butyl((1-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-2-oxoethyl) piperidin-4-yl)methyl)carbamate (23)**



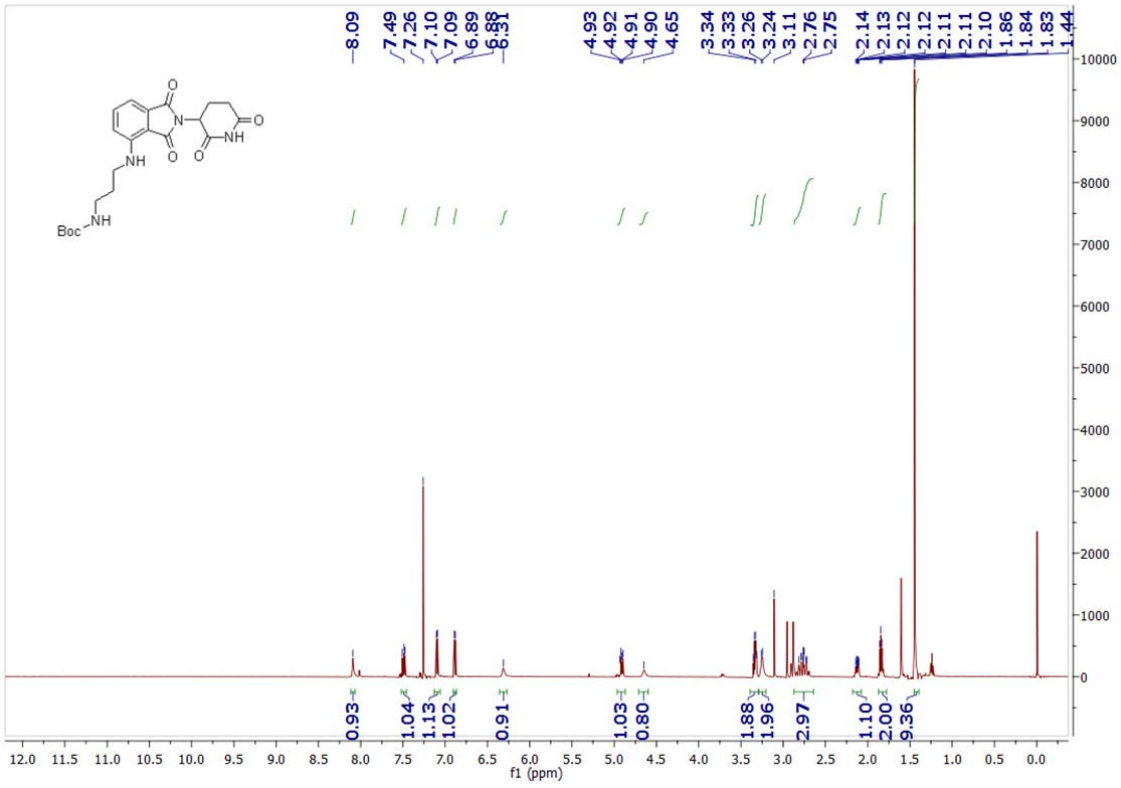


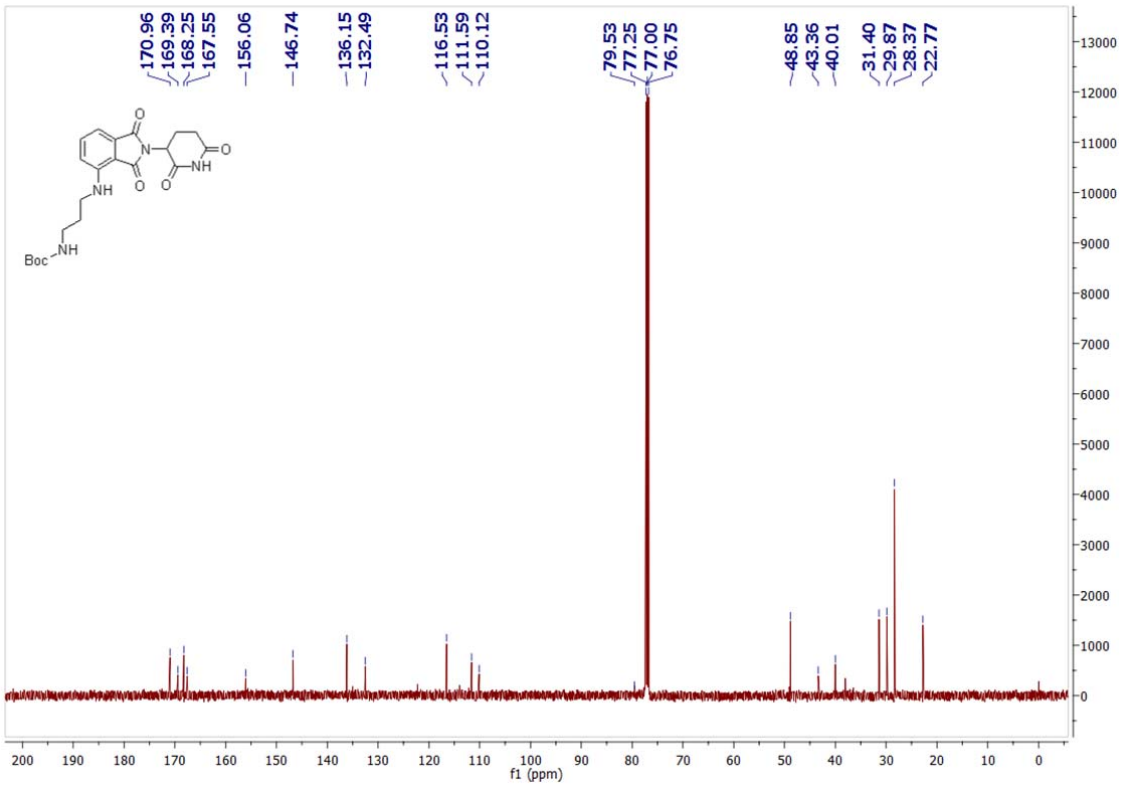
2-(2,6-dioxopiperidin-3-yl)-4-fluoroisoindoline-1,3-dione (24)



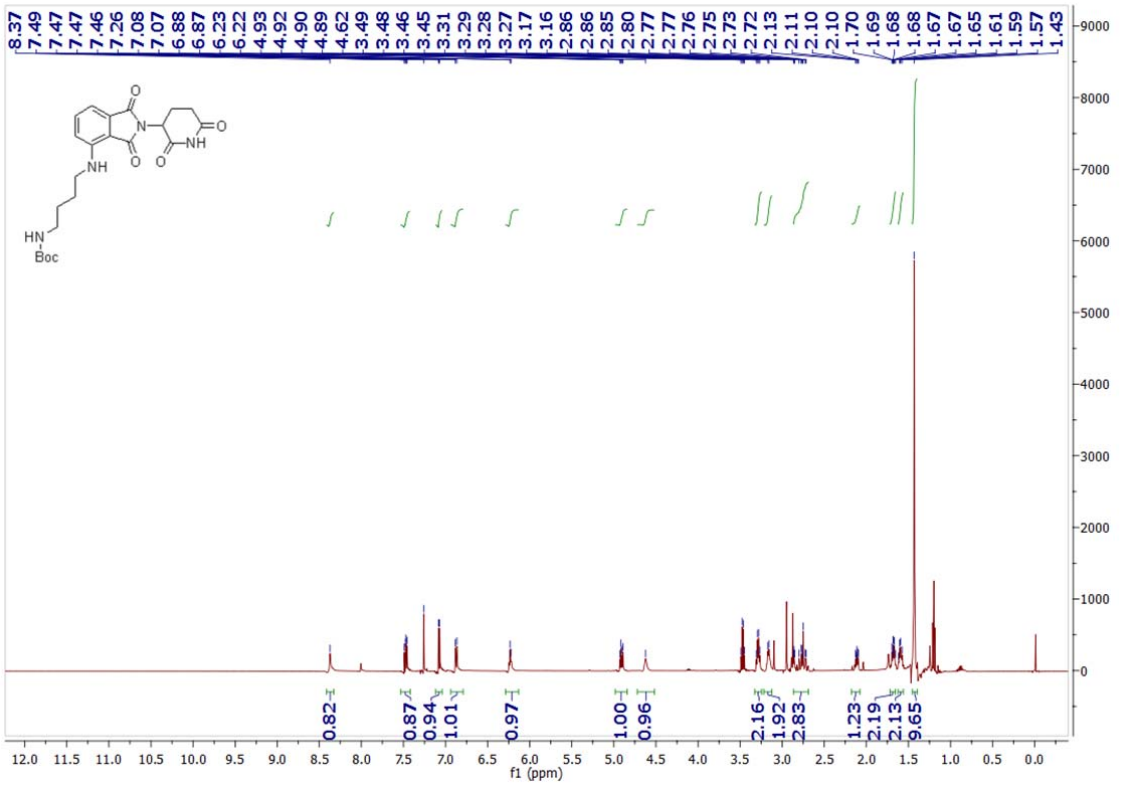


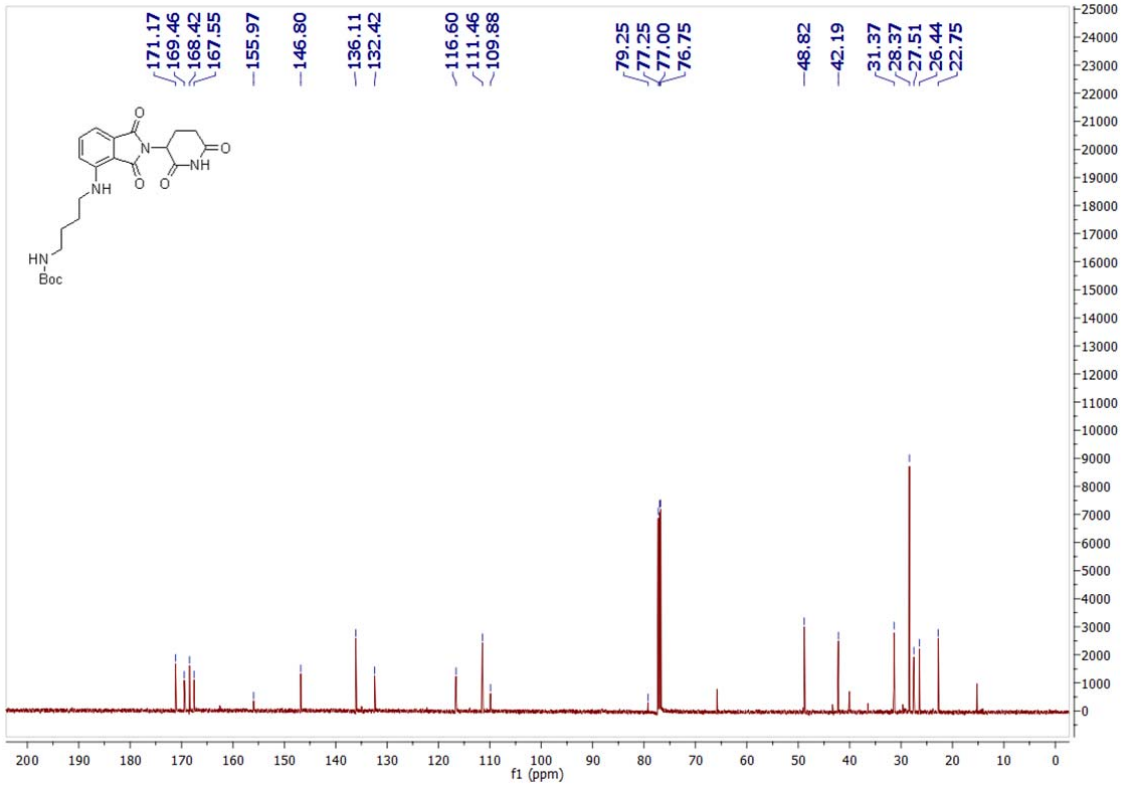
***tert*-butyl (3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)propyl)carbamate (25)**



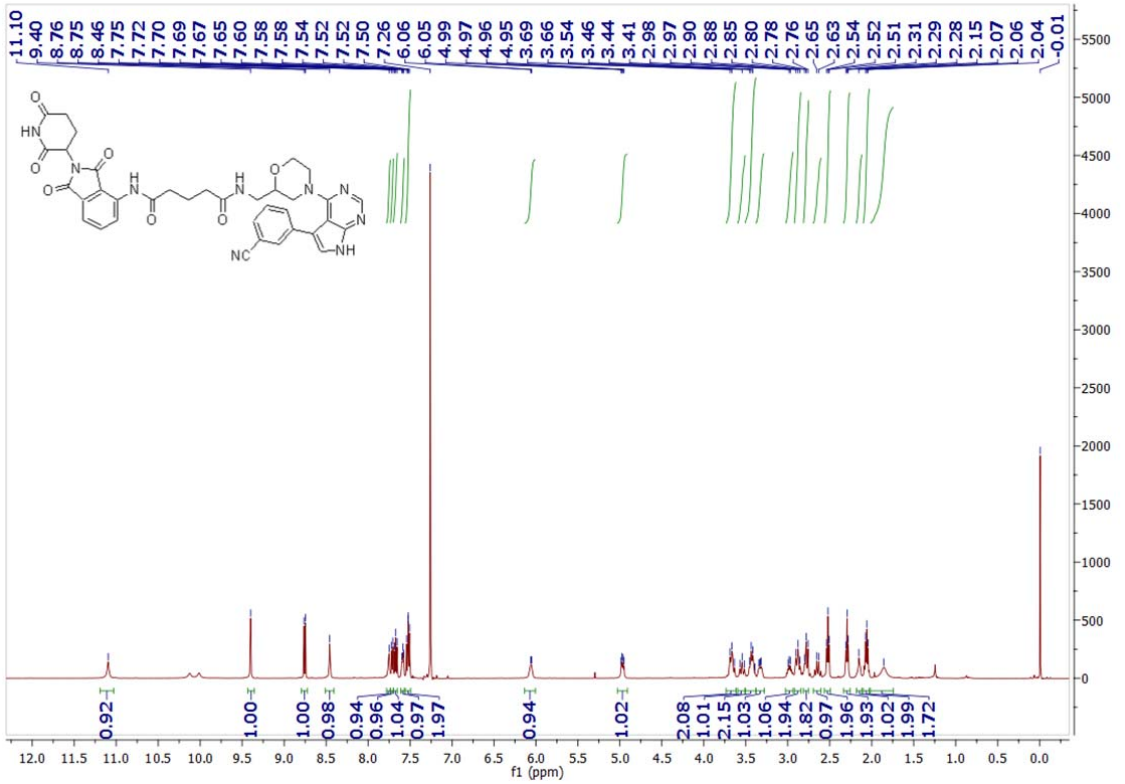


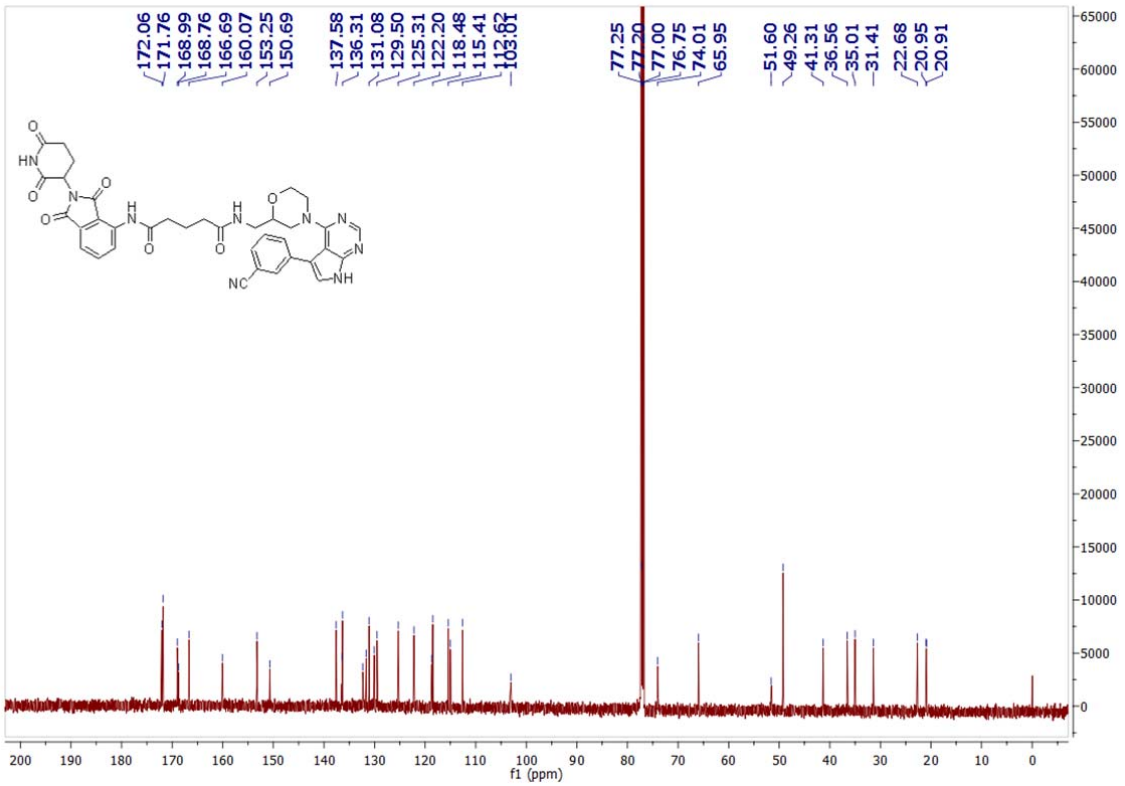
***tert*-butyl (4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)butyl)carbamate (26)**



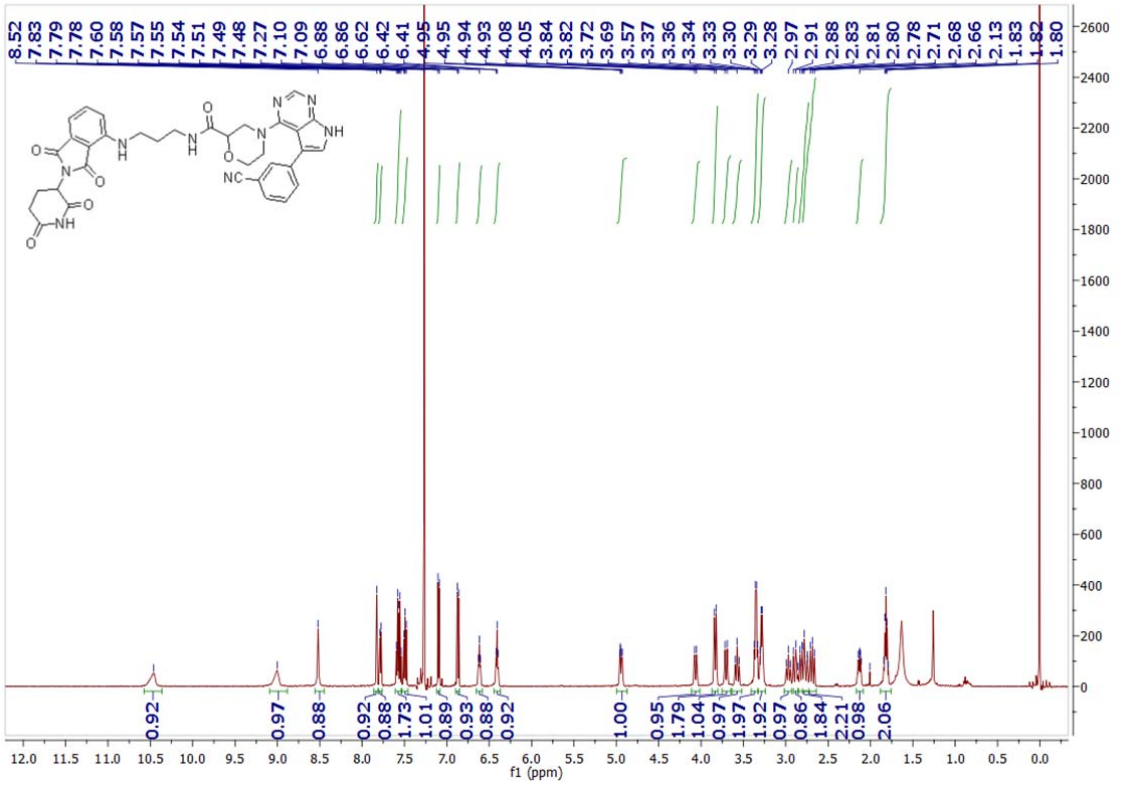


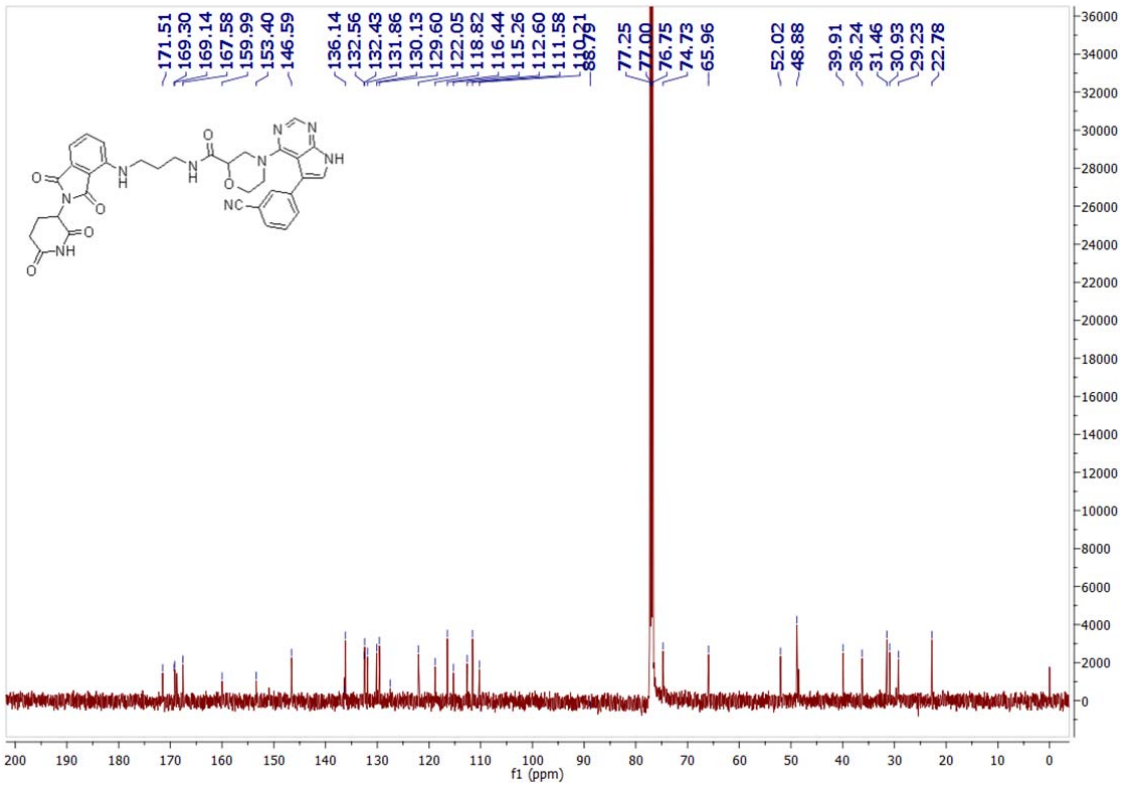
***N*1-((4-(5-(3-cyanophenyl)-7*H*-pyrrolo[2,3-d]pyrimidin-4-yl)morpholin-2-yl)methyl)-N5-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)glutaramide (27)**



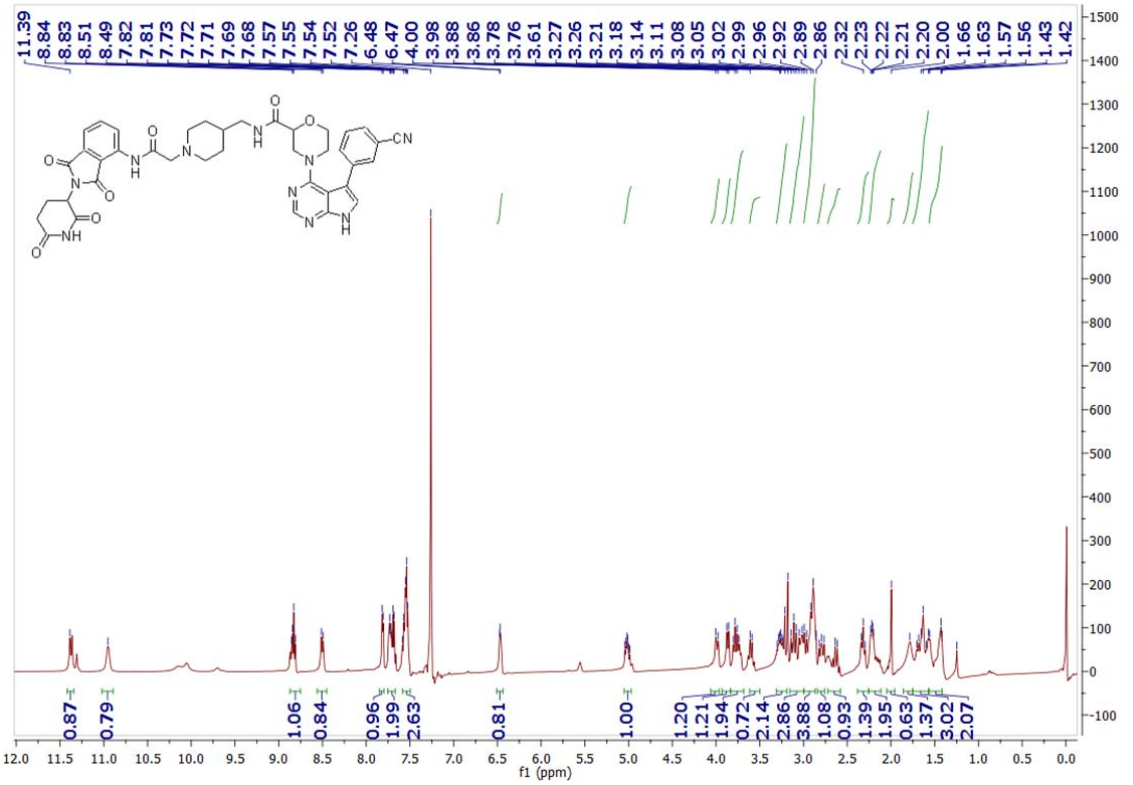


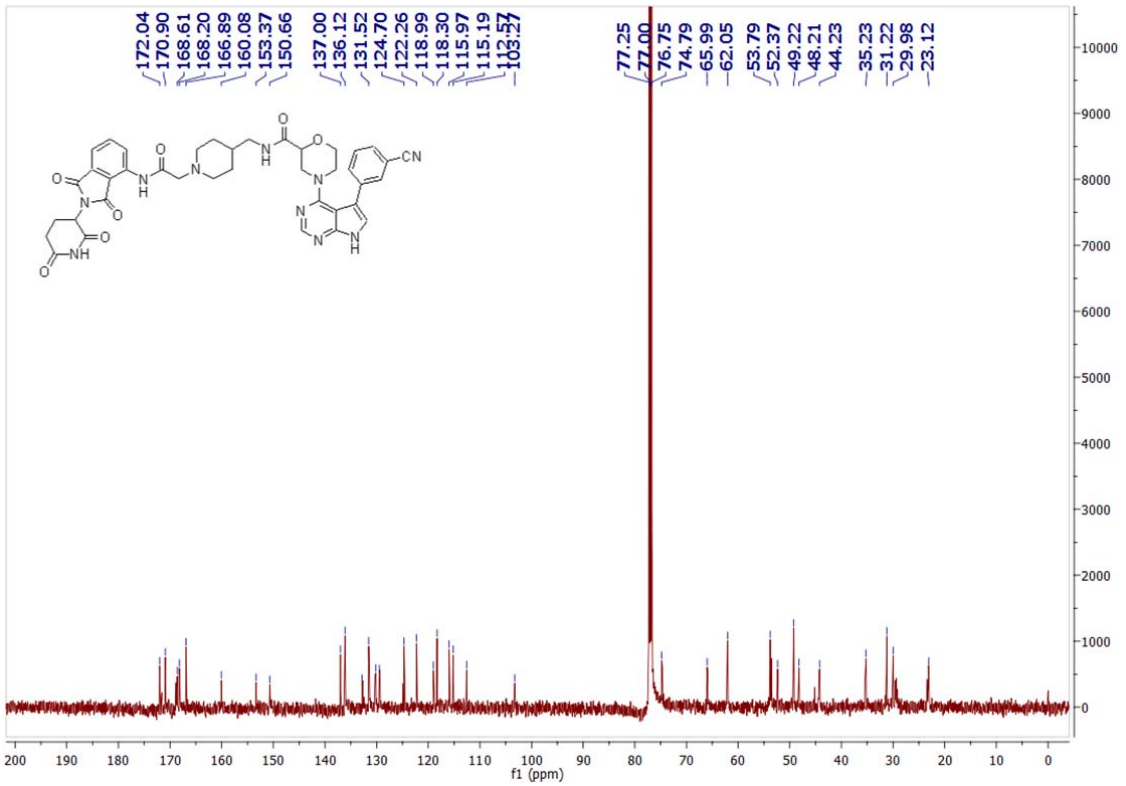
4-(5-(3-cyanophenyl)-7*H*-pyrrolo[2,3-d]pyrimidin-4-yl)-N-(3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)propyl)morpholine-2-carboxamide (28)



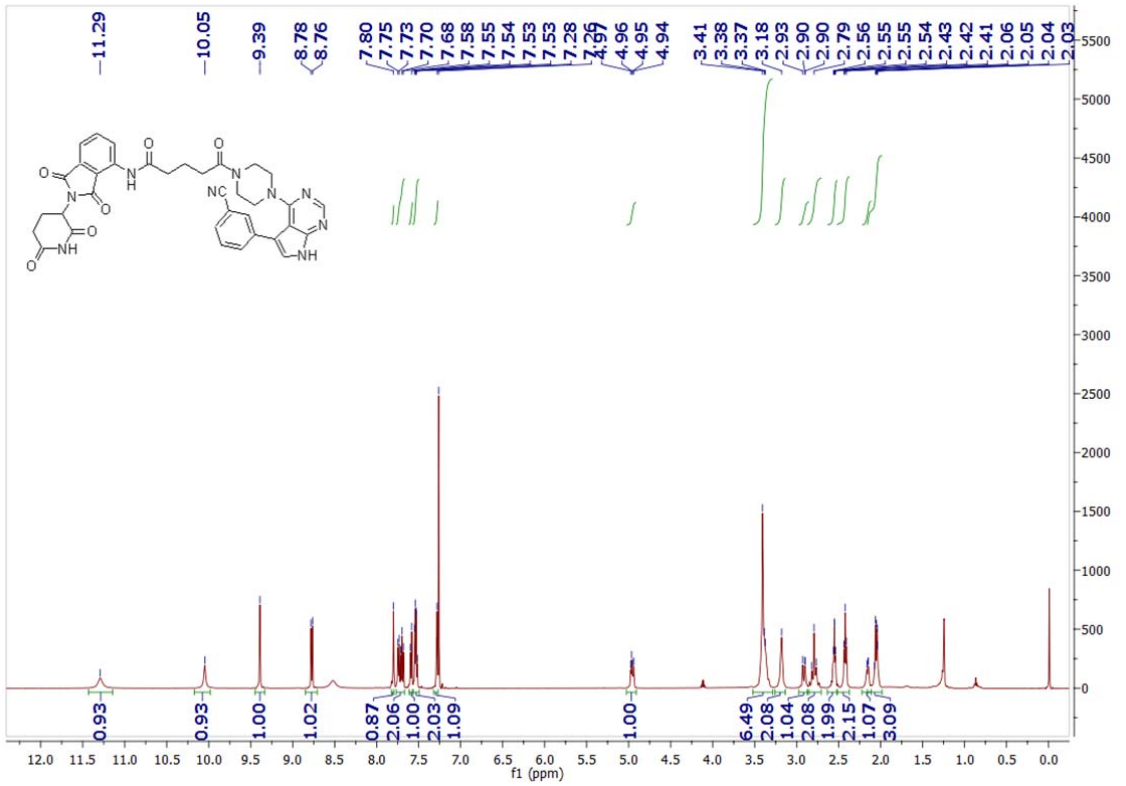


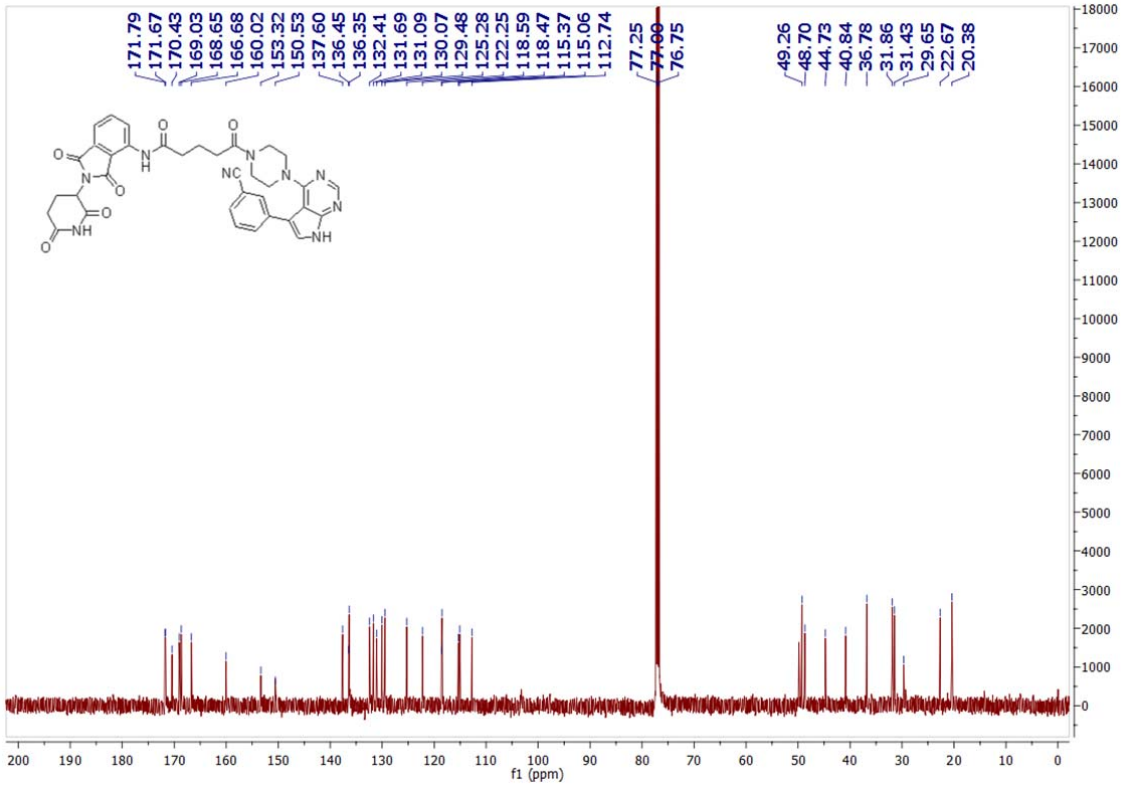
4-(5-(3-cyanophenyl)-7*H*-pyrrolo[2,3-d]pyrimidin-4-yl)-N-((1-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-2-oxoethyl)piperidin-4-yl)methyl)morpholine-2-carboxamide (29)



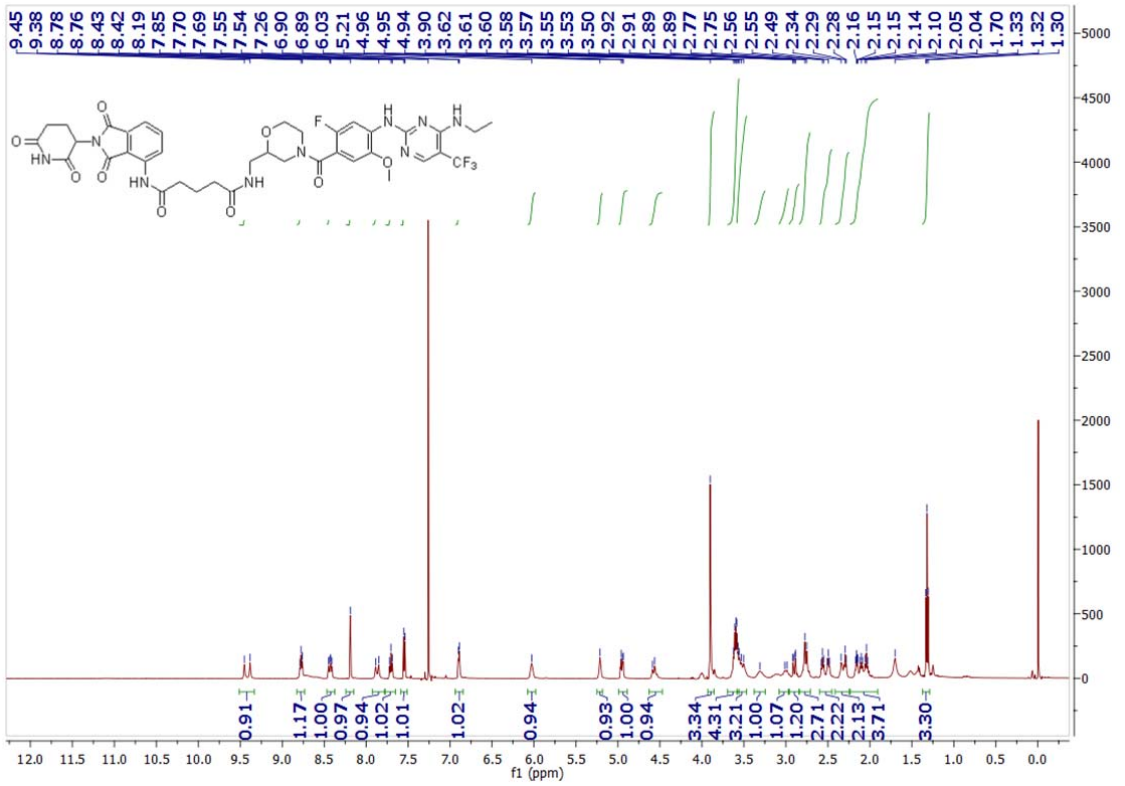


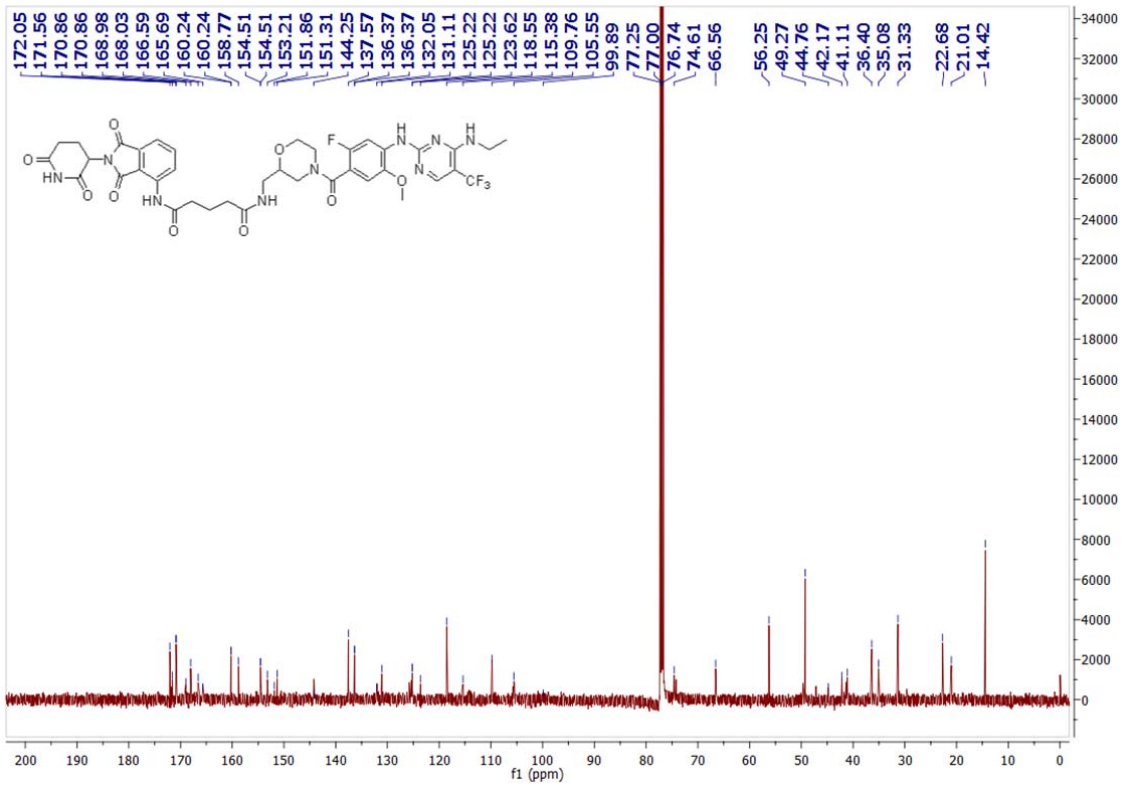
5-(4-(5-(3-cyanophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperazin-1-yl)-N-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)-5-oxopentanamide (30)



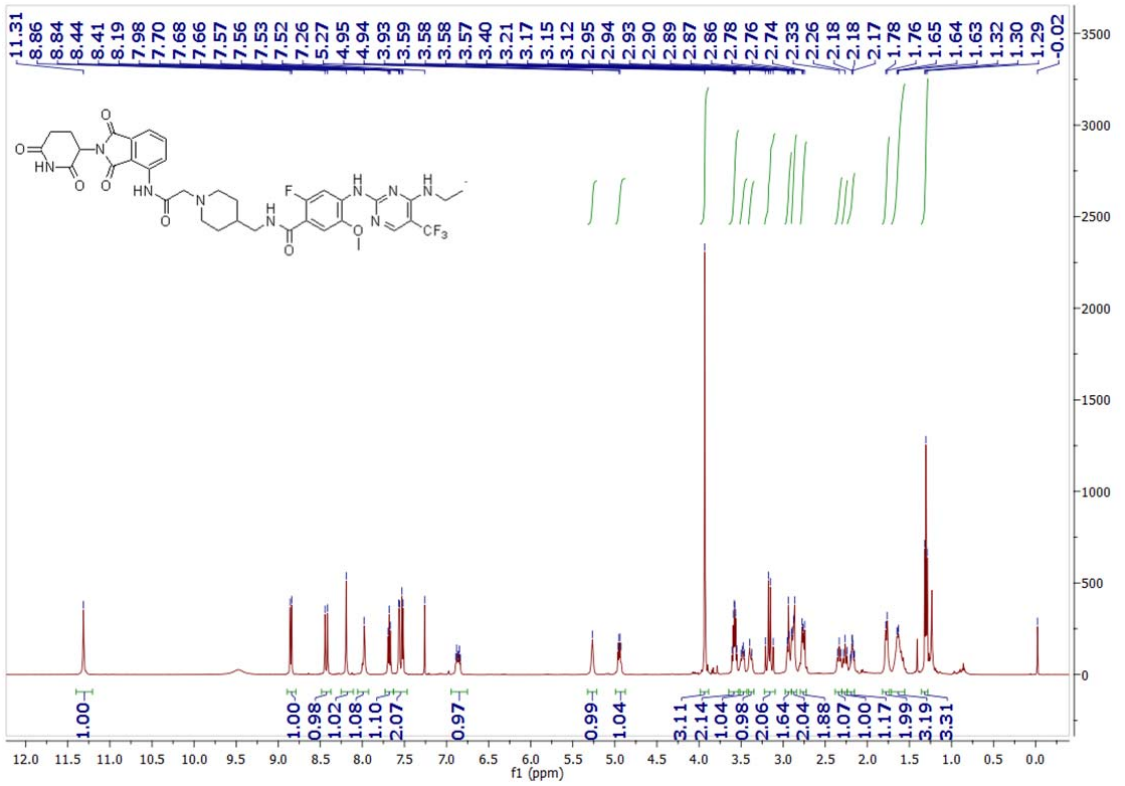


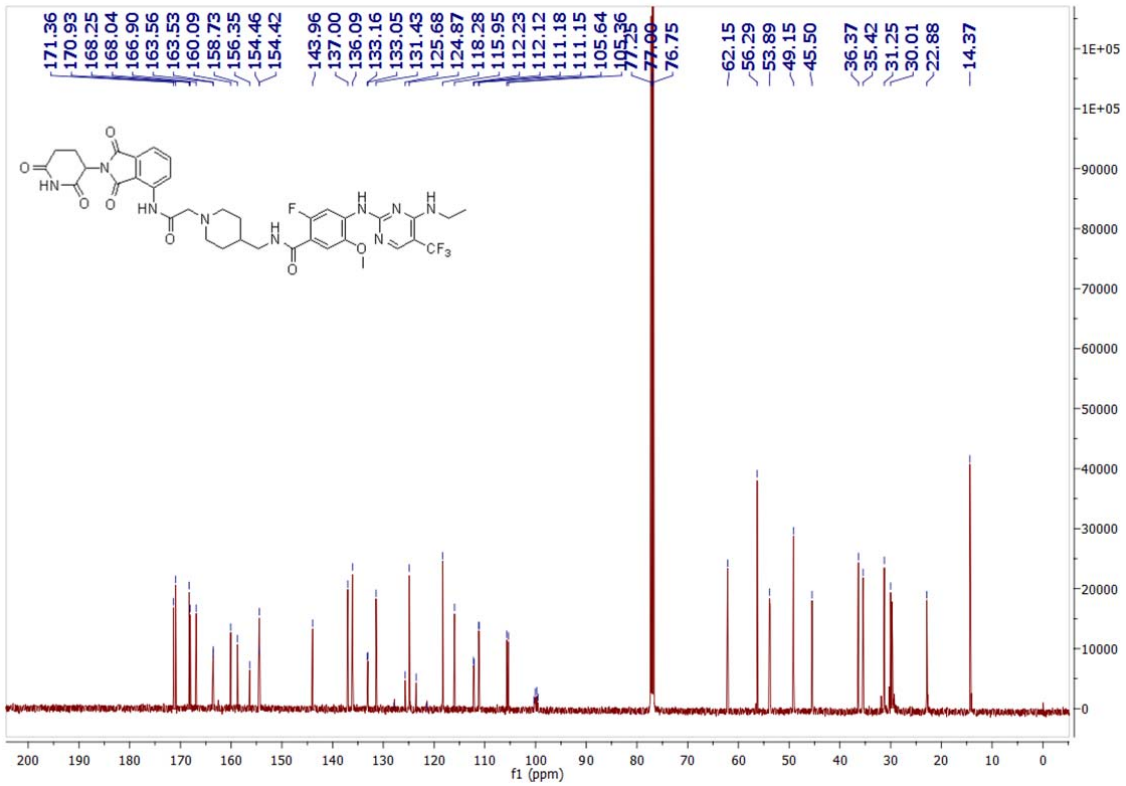
N^1-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)-N^5-((4-(4-((4-(ethylamino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-2-fluoro-5-methoxybenzoyl)morpholin-2-yl)methyl)glutaramide (31)



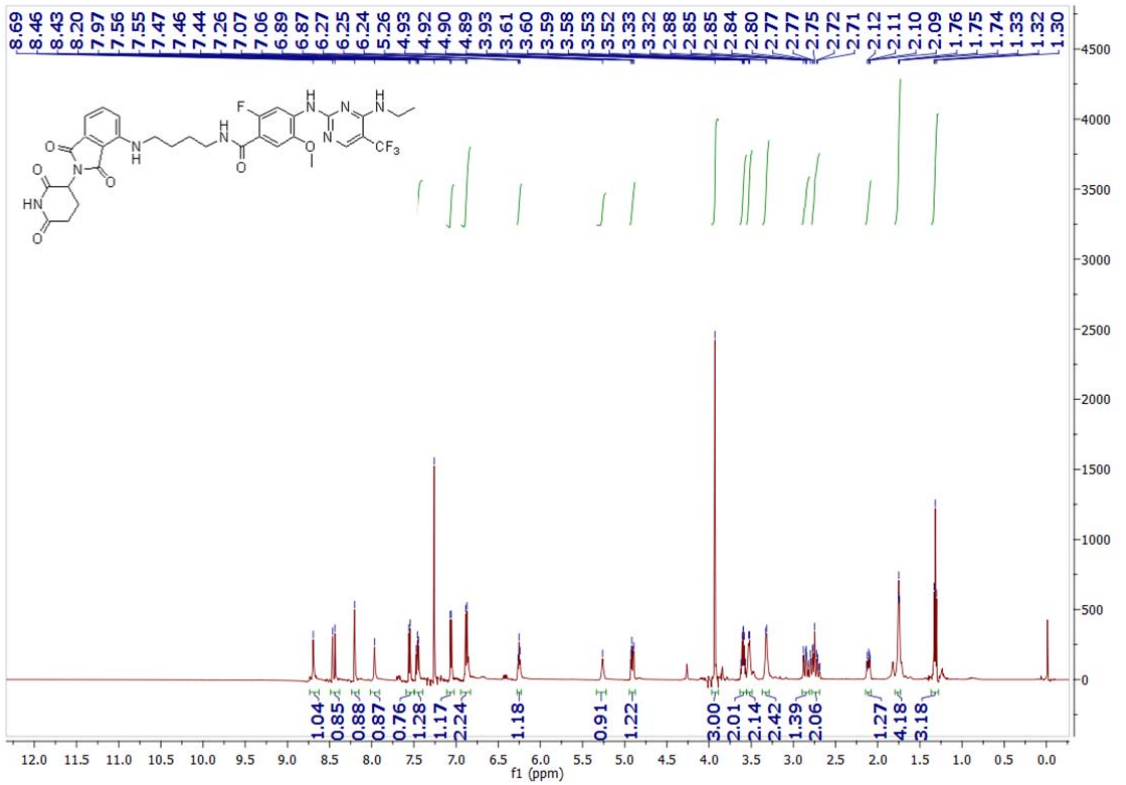


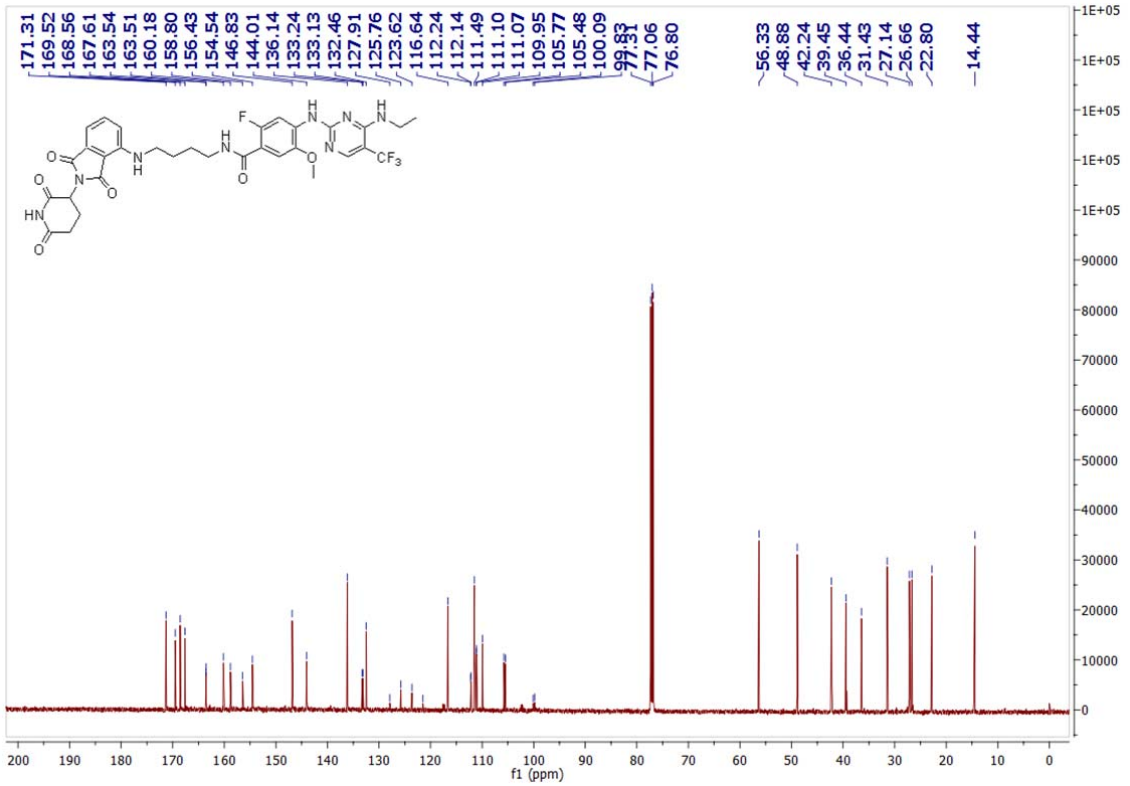
N-((1-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-2-oxoethyl) piperidin-4-yl)methyl)-4-((4-(ethylamino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-2-fluoro-5-methoxybenzamide (32)





***N*-(4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)butyl)-4-((4-(ethylamino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-2-fluoro-5-methoxybenzamide (33)**




171.31
169.52
168.56
167.61
163.54
163.51
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156.43
154.54
146.83
144.01
136.14
133.24
133.13
132.46
127.91
125.76
123.62
116.64
112.24
112.14
111.49
111.10
111.07
109.95
105.77
105.48
100.09
99.83
77.31
77.06
76.80
56.33
48.88
42.24
39.45
36.44
31.43
27.14
26.66
22.80
14.44
f1 (ppm)

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