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Efficient green synthesis of the targeted proteolysis system component

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1. Synthesis of target compounds.

1.1. General experimental information.

All reactions were carried out in glassware with magnetic stirring. Solvents and commercial reagents were used without additional purification. Visualization on TLC (analytical thin layer chromatography) was achieved by the use of UV light (254 nm) and treatment with phosphomolybdic acid ethanol solution followed by heating. TLC was performed on Imid Ltd Sorbfil plates. Unless otherwise noted, yields refer to chromatographically and spectroscopically pure compounds. Mass spectra were recorded using Shimadzu LCMS 2020 system with ESI. Proton and carbon magnetic resonance spectra (^{1}H NMR at 300 MHz and ^{13}C NMR at 75 MHz) were recorded on a Bruker DPX-300 spectrometer with solvent resonance as the internal standard (^{1}H NMR: $CDCl_3$ at 7.25 ppm, DMSO-d6 at 2.49 ppm; ^{13}C NMR: $CDCl_3$ at 77.00 ppm, DMSO-d6 at 39.50 ppm). NMR data are represented as follows: chemical shift (δ ppm), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant in Hertz (Hz). Melting points were measured with a Buchi B-520 melting point apparatus and were not corrected.

*2-(2,6-Dioxopiperidin-3-yl)-4-nitro-1H-isoindole-1,3(2H)-dione (**3a**)*

A mixture of the 3-nitrophthalic anhydride **2a** (1.74 g, 7.62 mmol) and *tert*-butyl *N*-(2,6-dioxo-3-piperidyl)carbamate **1** (1.77 g, 9.15 mmol), and sodium acetate (0.81 g, 9.9 mmol) in glacial acetic acid (20 mL) was refluxed for 12 hours, then was cooled. The reaction mixture was poured on to water (100 mL). The solid formed was filtered and washed with distilled water (3x5 mL) and petroleum ether (3x5 mL), then was dried *in vacuo* to obtain 4-nitropthalidomide **3a**.Yield 2.20 g (95%), white solid, m.p. 175-176°C (lit.[S1] 176-176.5°C). ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.14 (s, 1H), 8.35 (dd, *J* = 8.0, 0.7 Hz, 1H), 8.24 (dd, J_1 = 7.5 , 0.7 Hz, 1H), 8.12 (t, *J* = 7.8 Hz, 1H), 5.21 (d, *J*=5.5Hz, 0.5H), 5.19 (d, *J*=5.3Hz, 0.5H), 2.98-2.82 (m, 1H), 2.68-2.43 (m, 2H), 2.15-2.02 (m, 1H);^{13}C NMR (75 MHz, DMSO-d6) δ 172.61, 169.41, 165.12, 162.47, 144.41, 136.76, 132.98, 128.81, 127.24, 122.52, 49.43, 30.83, 21.70. LCMS (ESI): m/z (M+ H^+) calcd, 304.1; found, 304.1.

*2-(2,6-Dioxopiperidin-3-yl)-5-nitro-1H-isoindole-1,3(2H)-dione (**3b**)*

Synthesized similarly **3a** from 4-nitrophthalic anhydride **2b** (0.65 g, 2.85 mmol) and *tert*-butyl N-(2,6-dioxo-3-piperidyl)carbamate **1** (0.66 g, 3.42 mmol), and sodium acetate (0.31 g, 3.7 mmol). Yield 0.73 g (85%), light-yellow solid, m.p. 229°C (lit.[S2] 230-231°C). ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.15 (s, 1H), 8.64 (dd, *J* = 8.2, 2.0 Hz, 1H), 8.53 (d, *J* = 2.0 Hz, 1H), 8.16 (d, *J* = 8.1 Hz, 1H), 5.22-5.19 (m, 1H), 2.87 (m, 1H), 2.66 – 2.49 (m, 2H), 2.06 (m, 1H);^{13}C NMR (75 MHz, DMSO-d6) δ 173.11, 169.92, 165.97, 165.70, 152.14, 136.15, 132.95, 130.50, 125.41, 118.79, 49.91, 31.31, 22.25. LCMS (ESI): m/z (M+ H^+) calcd, 304.1; found, 304.0.

*4-Amino-2-(2,6-dioxopiperidin-3-yl)-1H-isoindole-1,3(2H)-dione (pomalidomide, **4a**)*

Ammonium formate (0.71 g, 11.2 mmol) and 10% Pd/C (70 mg, 10% mass) were added to a suspension of **3a** (0.68 g, 2.24 mmol) in 10 mL of DMF. The reaction mixture was vigorously stirred at 80°C for 4 hrs. After the reaction was complete (TLC monitoring, $CHCl_3$-MeOH=5:1), the mixture was filtered through a Celite layer, the filter cake was washed with DMF (2x2 ml), then EtOAc (3x10 mL), and the volatiles from the filtrate were removed *in vacuo*. The residue was dispersed in cold water, and the precipitated orange solid was dried *in vacuo*. Yield 0.60 g (98%), orange solid, m.p. >250°C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.05 (s, 1H), 7.49-7.43 (m, 1H), 7.05-6.97 (m, 2H), 6.50 (br.s, 2H), 5.06 (d, *J* = 5,3 Hz, 0.5H), 5.02 (d, *J* = 5,6 Hz, 0.5H), 2.96-2.80 (m, 1H), 2.65 – 2.44 (m, 2H), 2.08-1.96 (m, 1H);^{13}C NMR (75 MHz, DMSO-d6) δ 172.83, 170.14, 168.57, 167.38, 146.73, 135.48, 132.01,121.71, 110.98, 108.52, 48.49, 30.99, 22.17. LCMS (ESI): m/z (M+ H^+) calcd, 274.1; found, 274.2.

*5-Amino-2-(2,6-dioxopiperidin-3-yl)-1H-isoindole-1,3(2H)-dione (**4b**)*

Synthesized similarly **4a** from **3b** (0.42g, 1.39mmol) with 0.20 g ammonium formate and 40 mg of Pd/C in 2 mL of DMF. Yield 0.29 g (77%), yellow-orange solid, m.p. >250°C (lit.[S2] 320-322°C). ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.07 (s, 1H), 7.52 (d, *J* = 8.2 Hz, 1H), 6.94 (br.s, 1H), 6.82 (dd, *J* = 7.5, 1.2 Hz, 1H), 6.55 (br.s, 2H), 5.06-4.99 (m, 1H), 2.89-2.85 (m, 1H), 2.5 – 2.44 (m, 2H), 2.14-1.95 (m, 1H); LCMS (ESI): m/z (M+ H^+) calcd, 274.1; found, 274.0.

*Ethyl 3-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]acrylate (**8**)*

Pomalidomide **4a** (0.24g, 0.88 mmol) was dissolved in a 1:1 mixture of 48% tetrafluoroboric and acetic acids (5 mL) at 70°C. The reaction mixture was then cooled to 0°C and sodium nitrite solution (73 mg, 1.05 mmol in 1 mL of distilled water) was added dropwise with vigorous stirring. The color of the mixture changed from orange to bright yellow and the precipitate completely dissolved within 15 min. Ethyl acrylate (0.26 g, 0.29 mL, 0.26 mmol) and palladium diacetate (10 mg, 0.04 mmol) were added to the mixture, then carefully heated in a water bath. At a temperature of 52-54°C, an intense reaction occurs with the release of nitrogen and the precipitation of a gray solid. The precipitate was filtered, washed on the filter with distilled water (3x1 mL) and dried in a vacuum. Yield 0.29 g (93%), gray solid, m.p. 242-245°C with decomposition. ^{1}H NMR (300 MHz, DMSO-d6) δ 11.12 (s, 1H), 8.52 (d, *J* = 16.2 Hz, 1H, *trans* ArC<u>H</u>=CHCOOH), 8.37 (d, *J* = 7.7 Hz, 1H), 7.95-7.85 (m, 2H), 6.96 (d, *J* = 16.2 Hz, 1H, *trans* ArCH=C<u>H</u>COOH), 5.21-5.11 (m, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 2.98–2.82 (m, 1H), 2.74–2.48 (m, 2H), 2.13–2.01 (m, 1H), 1.28 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d6) δ 172.87,

170.03, 166.72, 165.76, 164.30, 137.11, 134.70, 132.11, 131.87, 127.76, 124.94, 123.73, 122.56, 60.95, 49.26, 30.87, 22.07, 14.40. LCMS (ESI): m/z (M+ H^+) calcd, 357.1; found, 357.1.

*(2E)-3-[2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]acrylic acid (**6**)*

Pomalidomide **4a** (0.59g, 2.16 mmol) was dissolved in a 1:1 mixture of 48% tetrafluoroboric and acetic acids (10 ml) at 70°C. The reaction mixture was then cooled to 0°C and sodium nitrite solution (0.18 g, 2.59 mmol in 2 ml of distilled water) was added dropwise with vigorous stirring. The color of the mixture changed from orange to bright yellow and the precipitate completely dissolved within 15 min. *tert*-Butyl acrylate (0.63 ml, 4.32 mmol) and palladium diacetate (24 mg, 0.11 mmol) were added to the mixture, then carefully heated in a water bath. At a temperature of 50-52°C, an intense reaction occurs with the release of nitrogen and the precipitation of a light gray solid. The precipitate was filtered, washed on the filter with distilled water (3x5 ml) and dried in a vacuum. Yield of **6** 0.66 g (94%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.16 (s, 1H), 8.47 (d, *J* = 16.3 Hz, 1H, *trans* ArC<u>H</u>=CHCOOH), 8.34 (br.d, *J* = 7.7 Hz, 1H), 7.98 – 7.83 (m, 2H), 6.86 (d, *J* = 16.3 Hz, 1H, *trans* ArCH=C<u>H</u>COOH), 5.22-5.11 (m, 1H), 2.99–2.81 (m, 1H), 2.67–2.49 (m, 2H), 2.13–2.01 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.85, 169.86, 167.40, 167.12, 166.62, 136.26, 134.93, 132.69, 132.01, 127.64, 124.81, 122.40, 49.03, 30.97, 21.95. LCMS (ESI): m/z (M+ H^+) calcd, 329.1; found, 329.0.

*Alternative synthesis of (2E)-3-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]acrylic acid (**6**)*

Ethyl ester **8** (0.17g, 0.48 mmol) was added to a solution of KOH (54 mg, 0.95 mmol) in an ethanol-water mixture (3:1, 5 mL) at room temperature with stirring. Within approximately 10 minutes the solid was completely dissolved. The mixture was stirred for 2 hours and then carefully neutralized with 1 M hydrochloric acid. The precipitate was filtered, washed on the filter with distilled water (2x1 mL) and dried in a vacuum. Yield of **6** 85 mg (54%), gray solid, characterisation matches to compound synthesized from **4a**.

*Ethyl 3-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]propanoate (**9**)*

Ammonium formate (0.18 g, 3.9 mmol) and 10% Pd/C (35 mg, 10% mass) were added to a suspension of **8** (0.35 g, 0.98 mmol) in 2 mL of DMF. The reaction mixture was vigorously stirred at 80°C for 6 hrs. After the reaction was complete (TLC monitoring, $CHCl_3$-MeOH=5:1), the mixture was filtered through a Celite layer, the filter cake was washed with EtOH (2x10 mL), and the volatiles from the filtrate were removed in vacuo. The residue was dissolved in cold water (5 mL), and extracted with EtOAc (3x5 mL). The organic phases were combined and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo*. Yield 0.26 g (74%), a

colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.82 (s, 1H), 7.77-7.70 (m, 1H), 7.67-7.55 (m, 2H), 5.02-4.93 (m, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.36 (t, *J* = 7.1 Hz, 2H), 2.95–2.72 (m, 3H), 2.71 (t, *J* = 7.1 Hz, 2H), 2.19–2.09 (m, 1H), 1.21 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.53, 171.53, 168.50, 167.77, 167.29, 141.17, 136.27, 134.37, 132.39, 128.34, 122.22, 60.71, 49.21, 34.57, 31.43, 26.73, 22.69, 14.25. LCMS (ESI): m/z (M+ H^+) calcd, 359.1; found, 359.1.

*3-[2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]propanoic acid (**7**)*

Method A. From (2*E*)-3-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]acrylic acid (**6**).

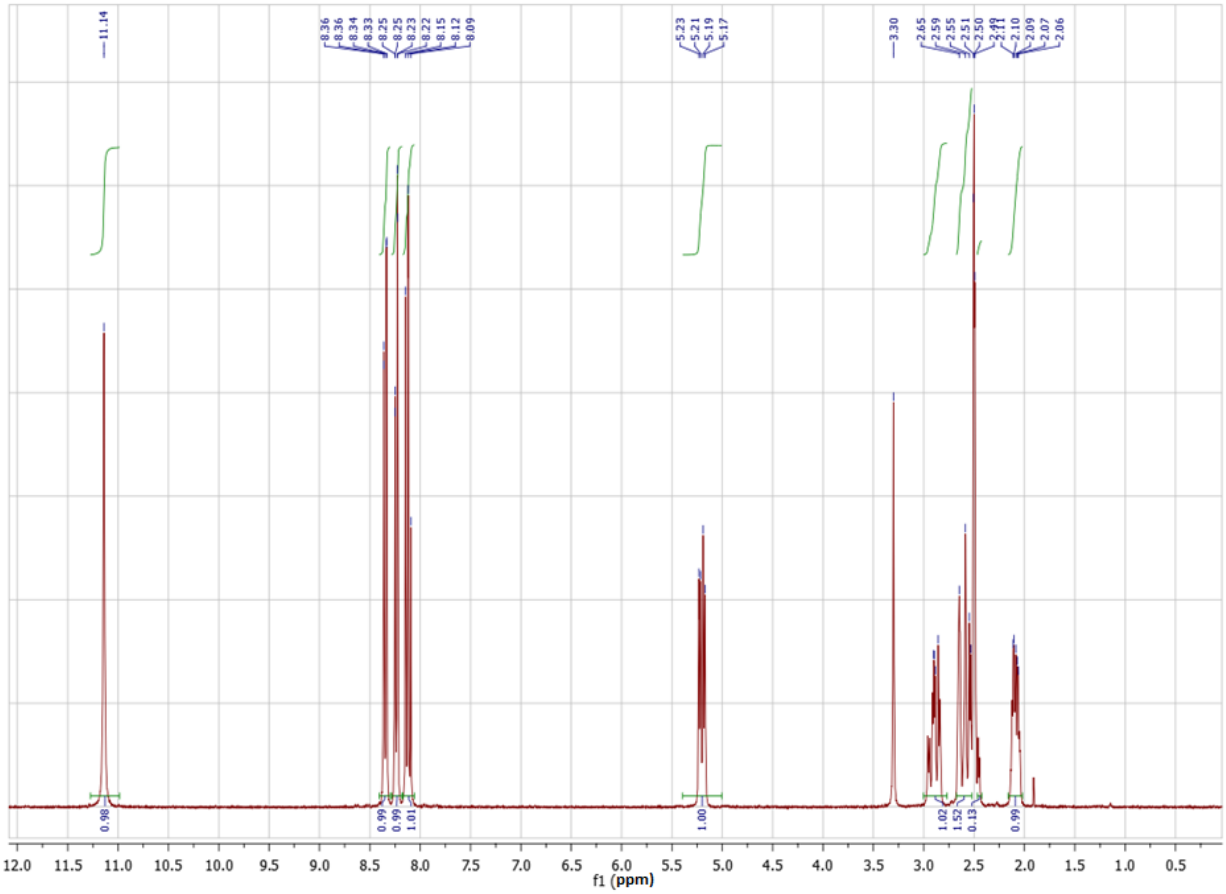
Ammonium formate (0.15 g, 3.1 mmol) and 10% Pd/C (34 mg, 10% mass) were added to a suspension of **6** (0.34 g, 1.03 mmol) in 10 mL of EtOH. The reaction mixture was vigorously stirred at reflux for 4 hrs. After the reaction was complete (TLC monitoring, $CHCl_3$-MeOH=5:1), the mixture was filtered through a Celite layer, the filter cake was washed with EtOH (2x2 mL), and the volatiles from the filtrate were removed *in vacuo*. The residue was dissolved in cold water (5 mL), and extracted with EtOAc (3x5 mL). The organic phases were combined and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo*. Yield 0.20 g (59%), a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.14 (s, 1H), 7.81-7.67 (m, 3H), 5.15 (d, *J* = 5.3 Hz, 1H), 5.11 (d, *J* = 5.4 Hz, 1H), 3.25 (t, *J* = 7.6 Hz, 2H), 2.96–2.82 (m, 1H), 2.66–2.49 (m, 3H), 2.11–2.01 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d6) δ 173.45, 172.84, 169.94, 167.62, 167.03, 140.82, 135.97, 134.59, 131.83, 127.79, 121.54, 48.85, 33.94, 30.97, 25.97, 22.02. LCMS (ESI): m/z (M+ H^+) calcd, 331.1; found, 331.1.

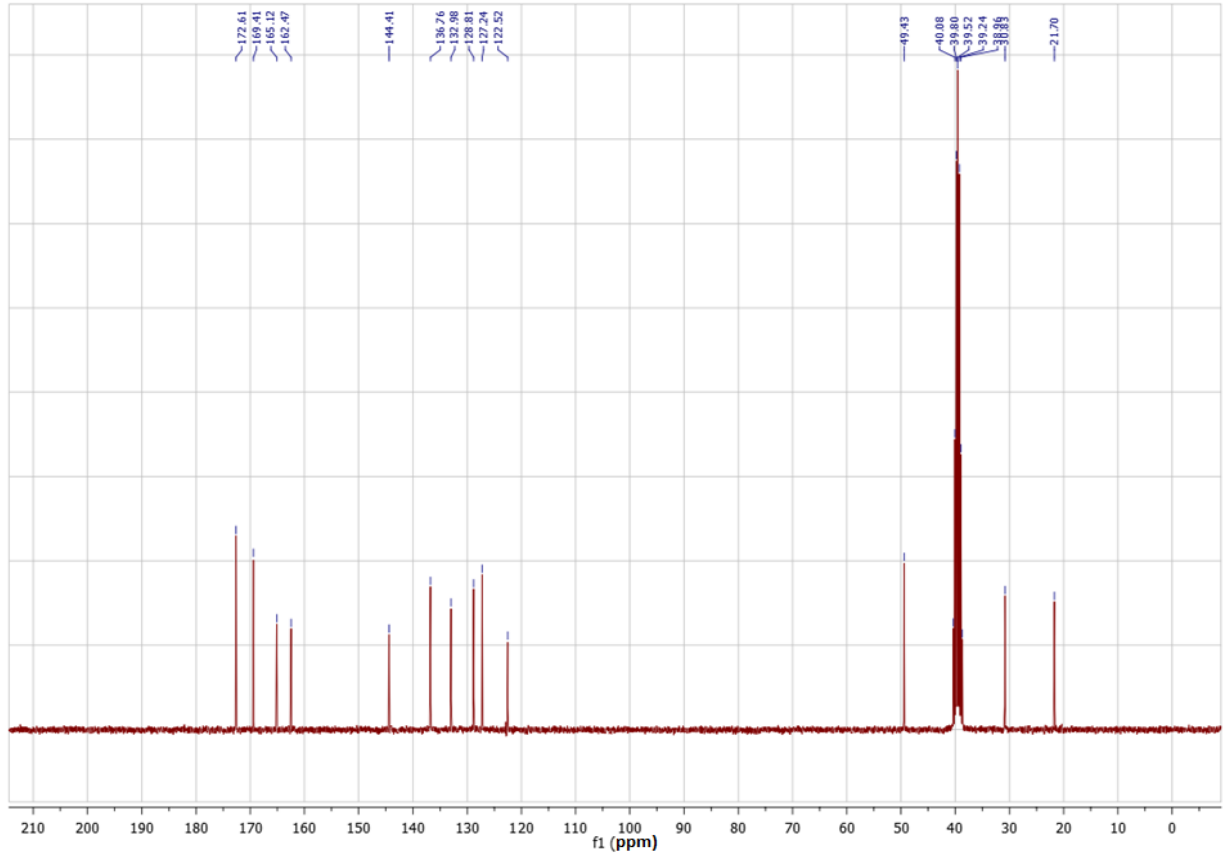
Method B. From ethyl 3-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]propanoate (**9**).

Compound **9** (0.22 g, 0.61 mmol) was added to a solution of KOH (69 mg, 1.23 mmol) in an ethanol-water mixture (3:1, 5 mL) at room temperature with stirring. Within approximately 10 minutes the solid was completely dissolved. The mixture was stirred for 2 hours and then carefully neutralized with 1 M hydrochloric acid. The precipitate was filtered, washed on the filter with distilled water (2x1 mL) and dried in a vacuum. Yield 0.12 g (59%), white solid, characterisation matches to compound synthesized from **6**.

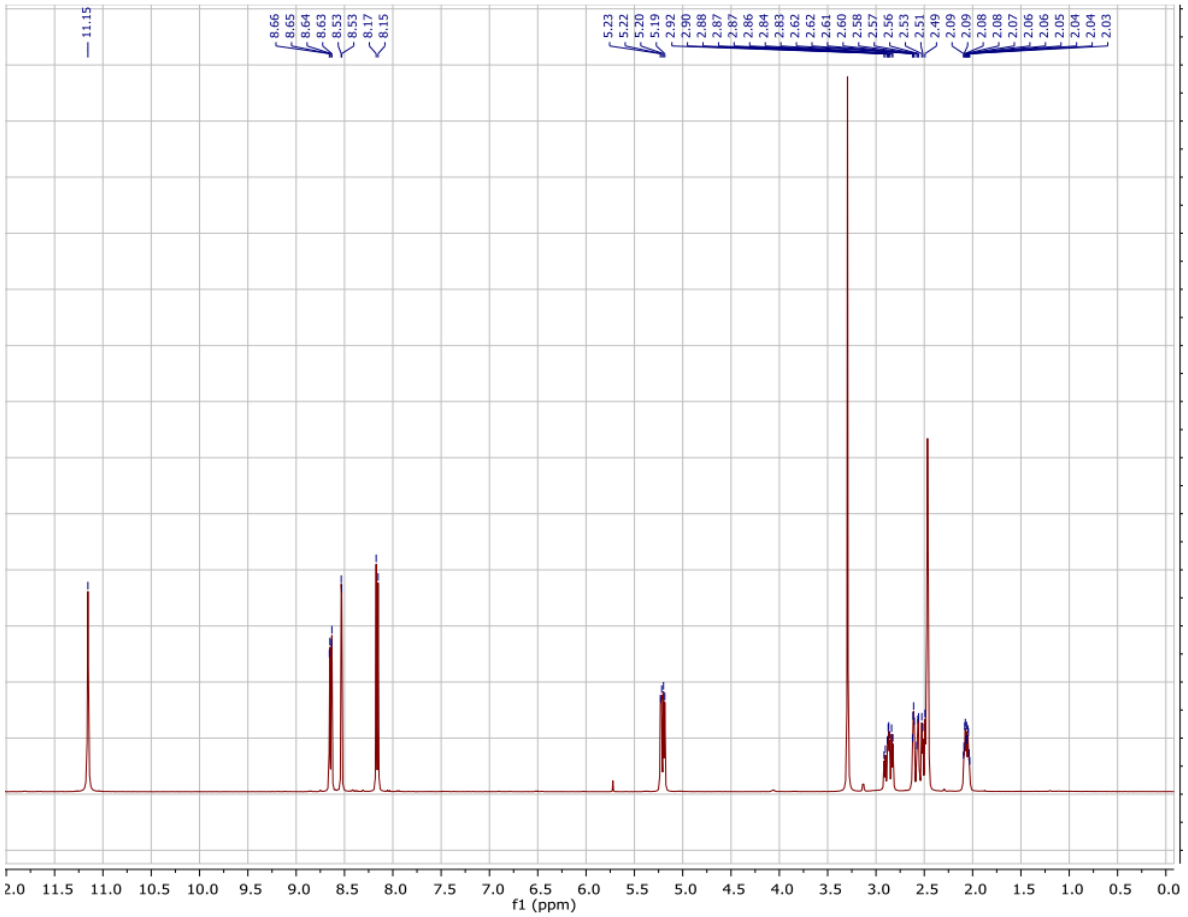
2. Spectra of target compounds.

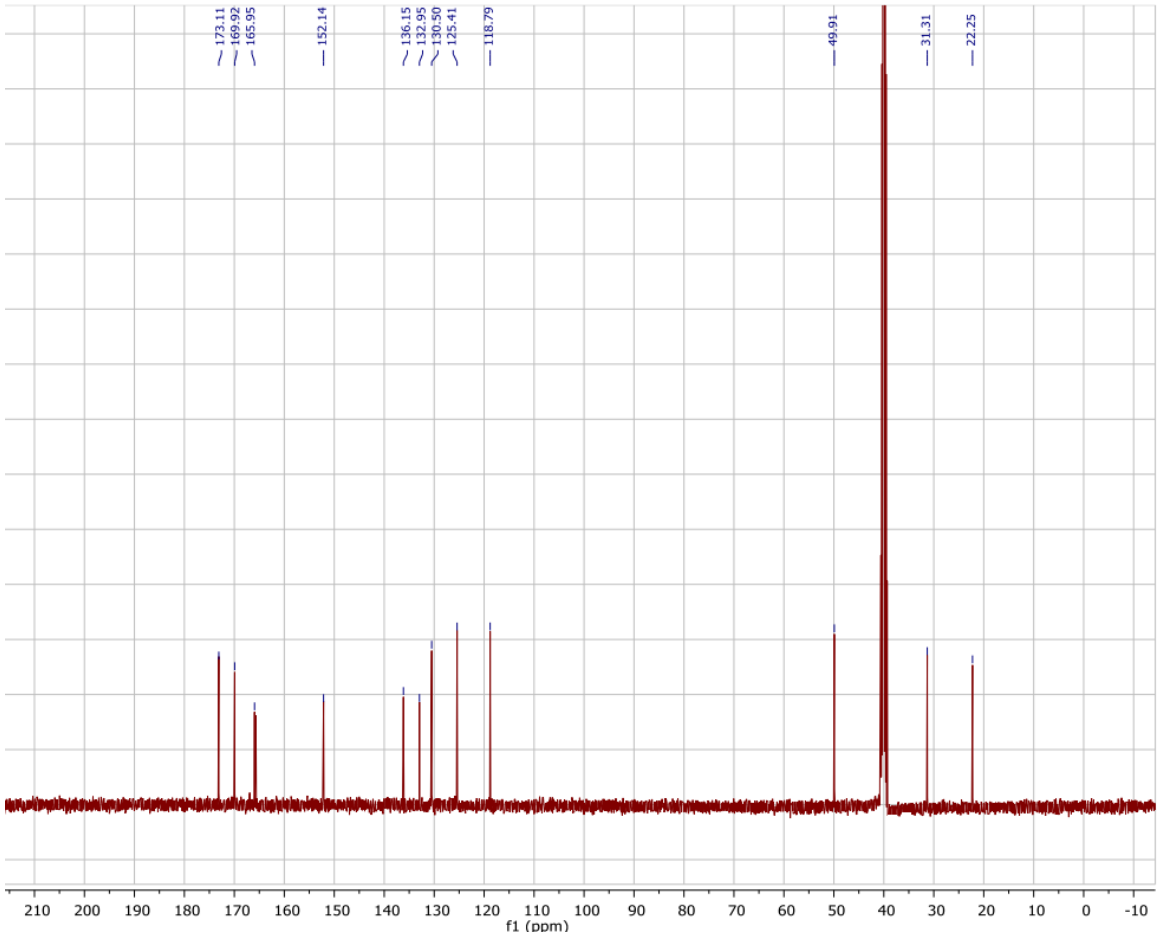
*2-(2,6-dioxopiperidin-3-yl)-4-nitro-1H-isoindole-1,3(2H)-dione (**3a**)*



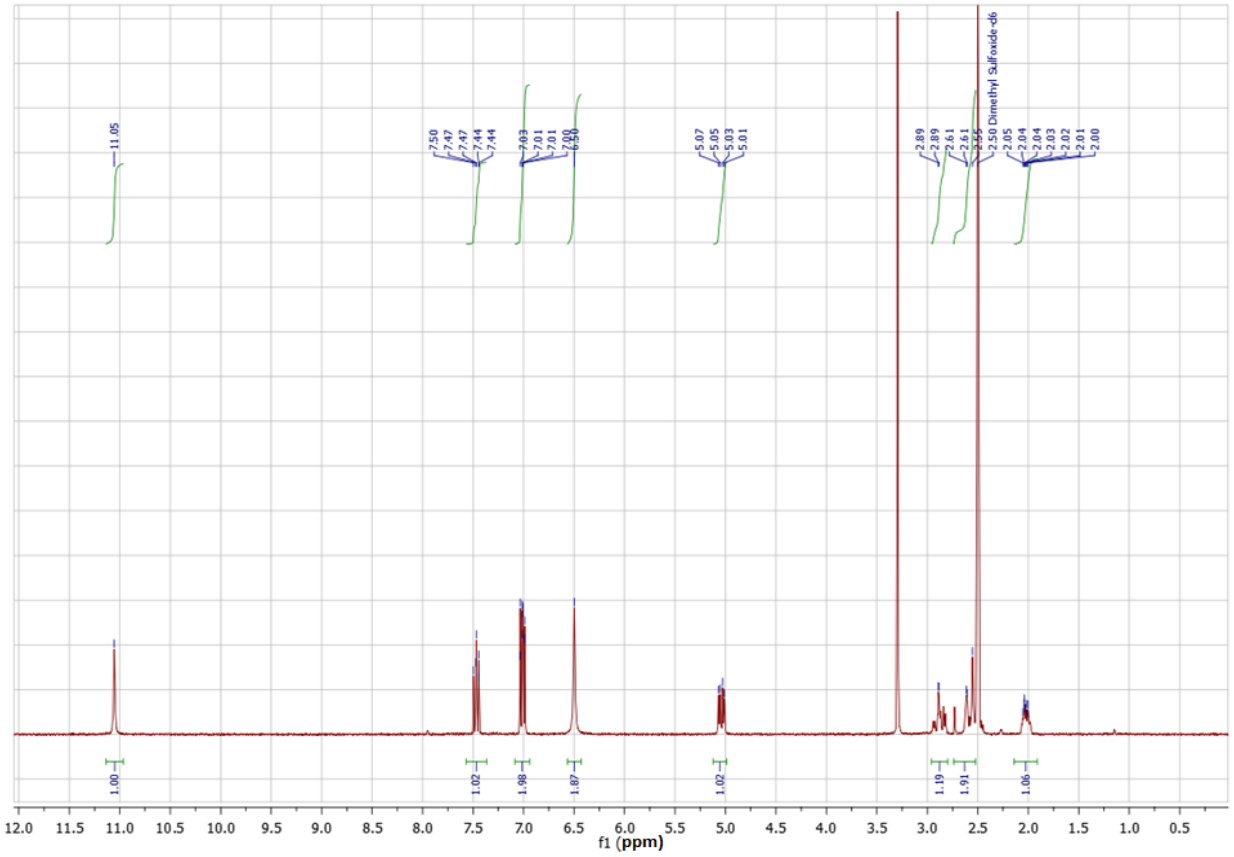


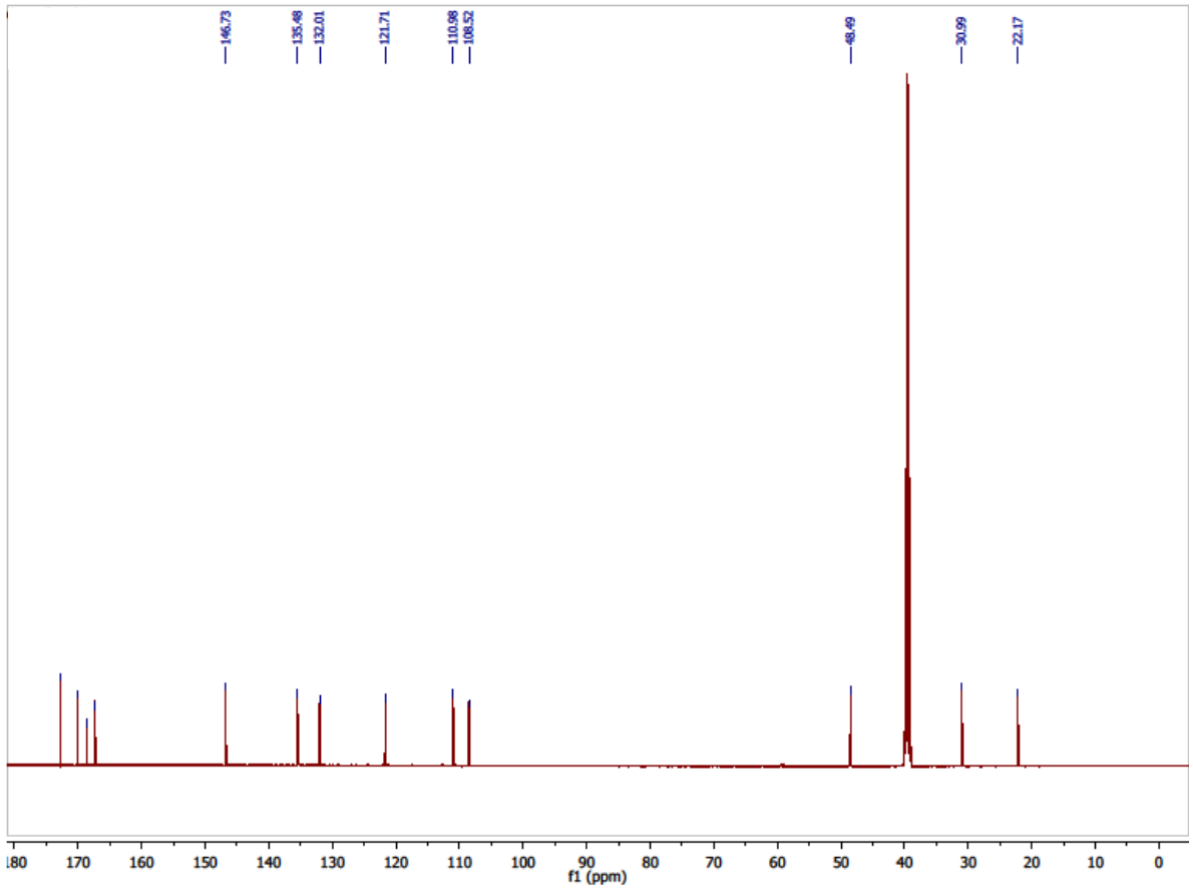
*2-(2,6-dioxopiperidin-3-yl)-5-nitro-1H-isoindole-1,3(2H)-dione (**3b**)*



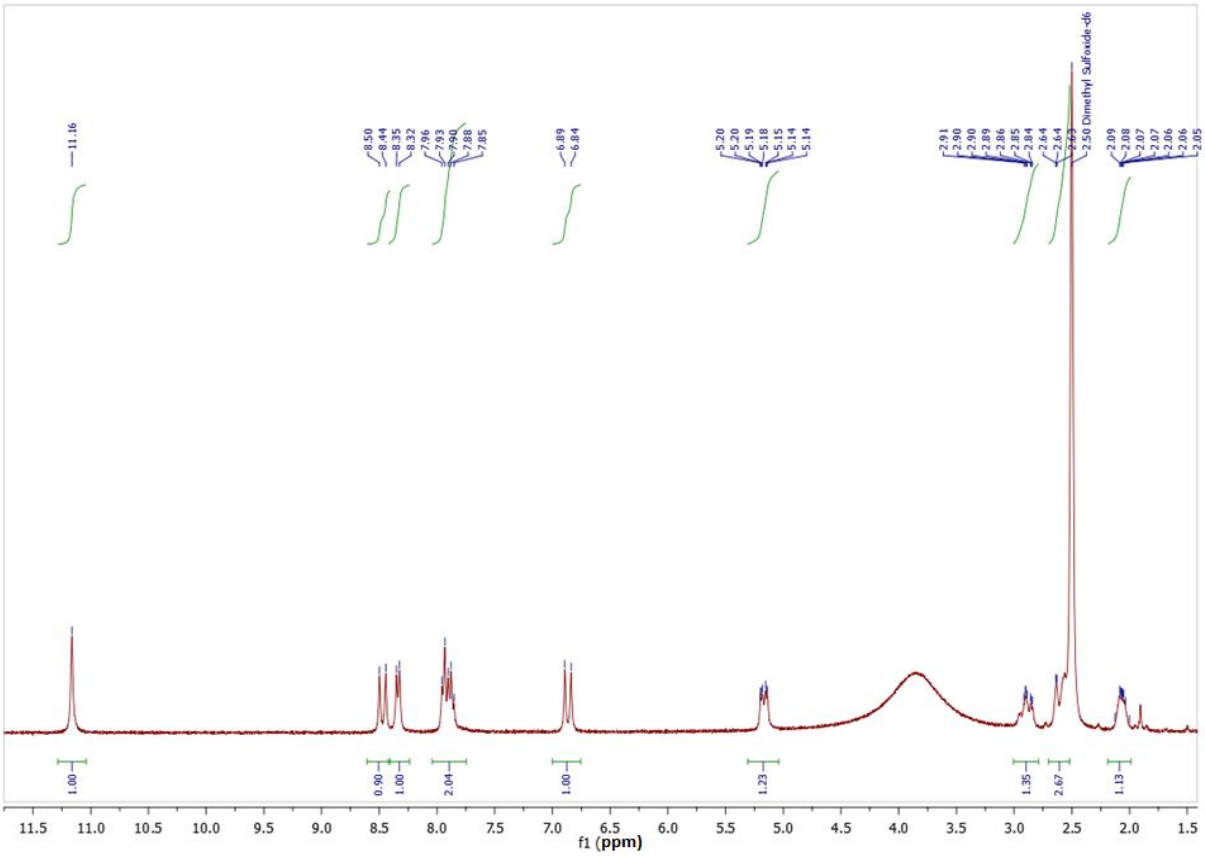


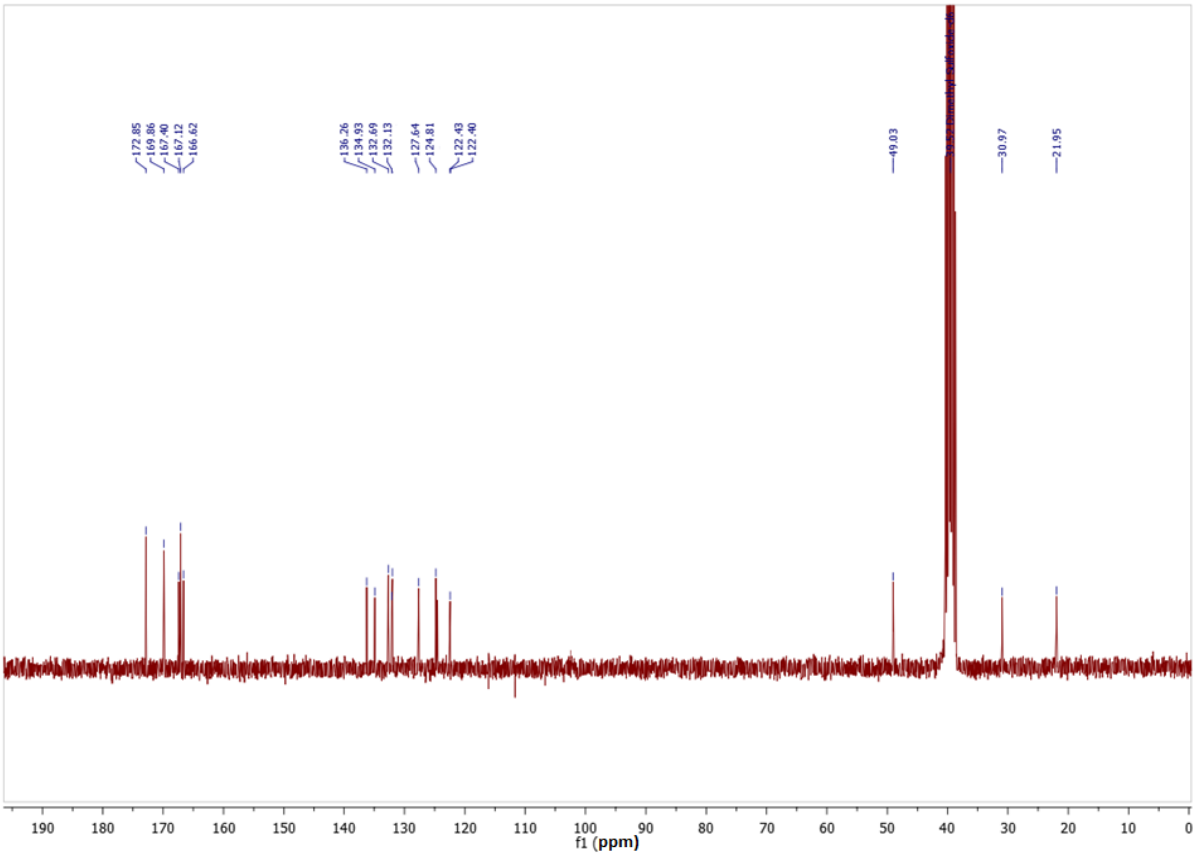
*4-amino-2-(2,6-dioxopiperidin-3-yl)-1H-isoindole-1,3(2H)-dione (pomalidomide, **4a**)*



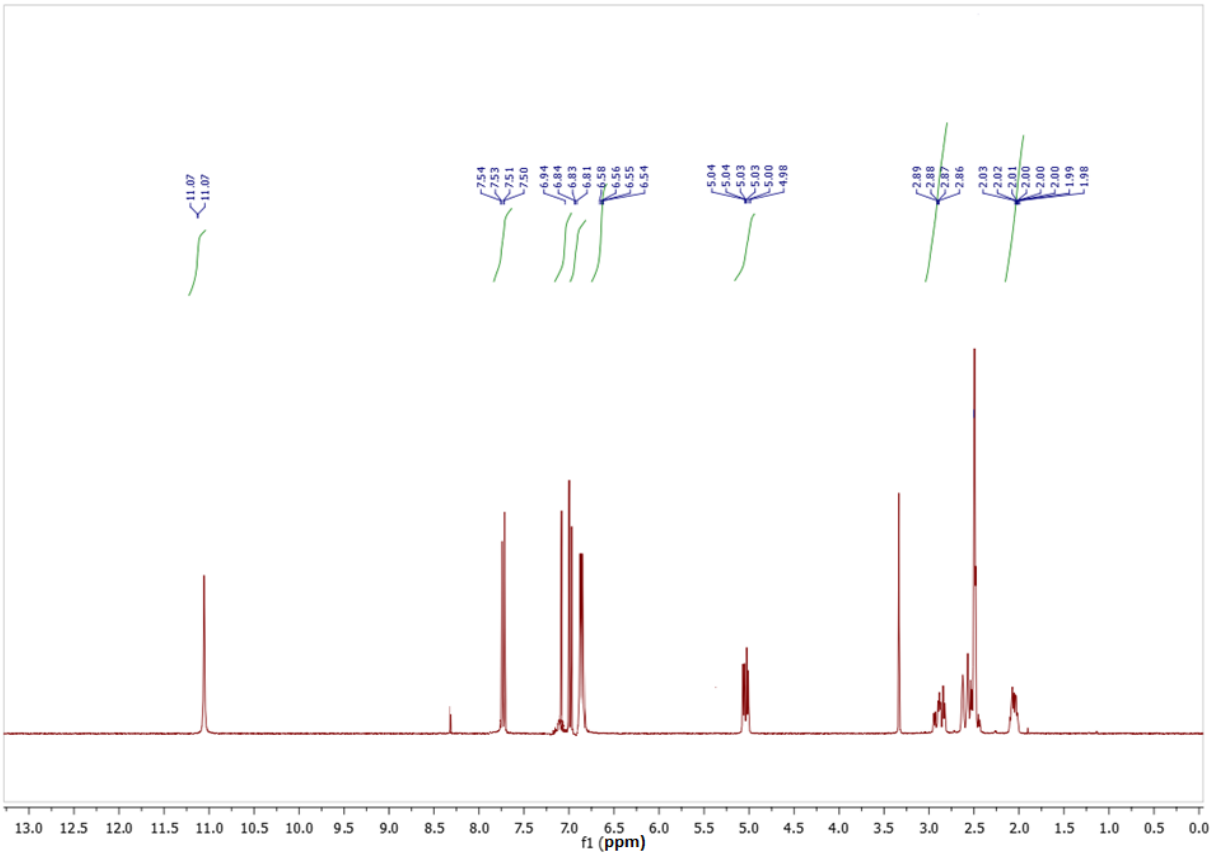


*(2E)-3-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]acrylic acid (**6**)*

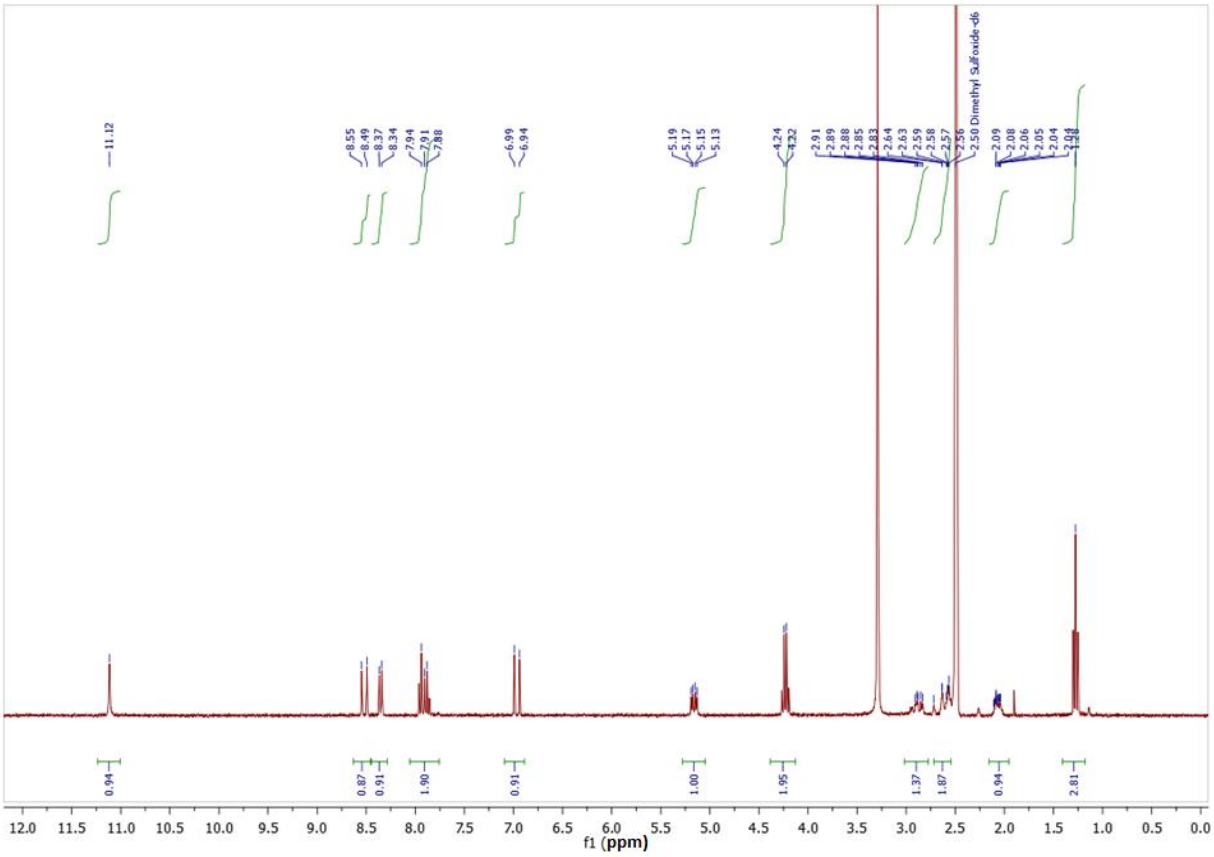


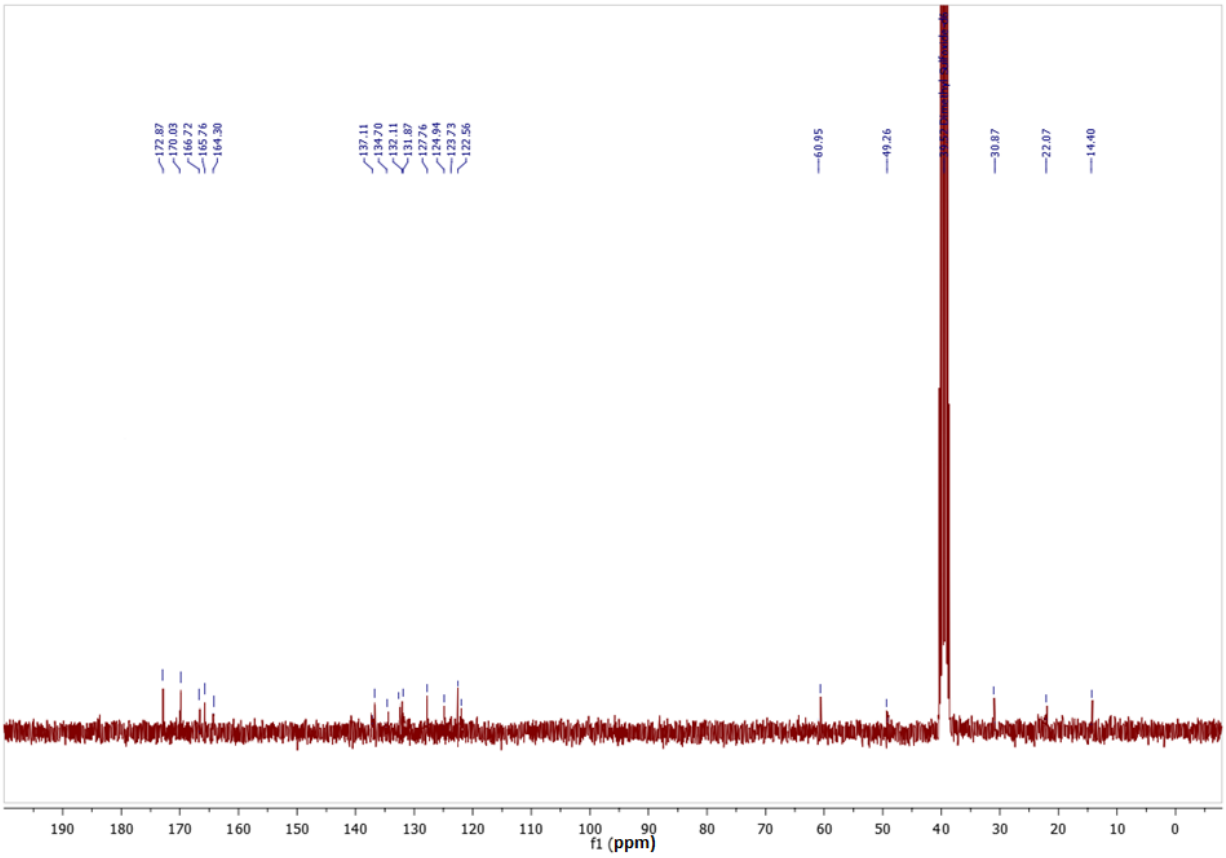


*5-amino-2-(2,6-dioxopiperidin-3-yl)-1H-isoindole-1,3(2H)-dione (**4b**)*

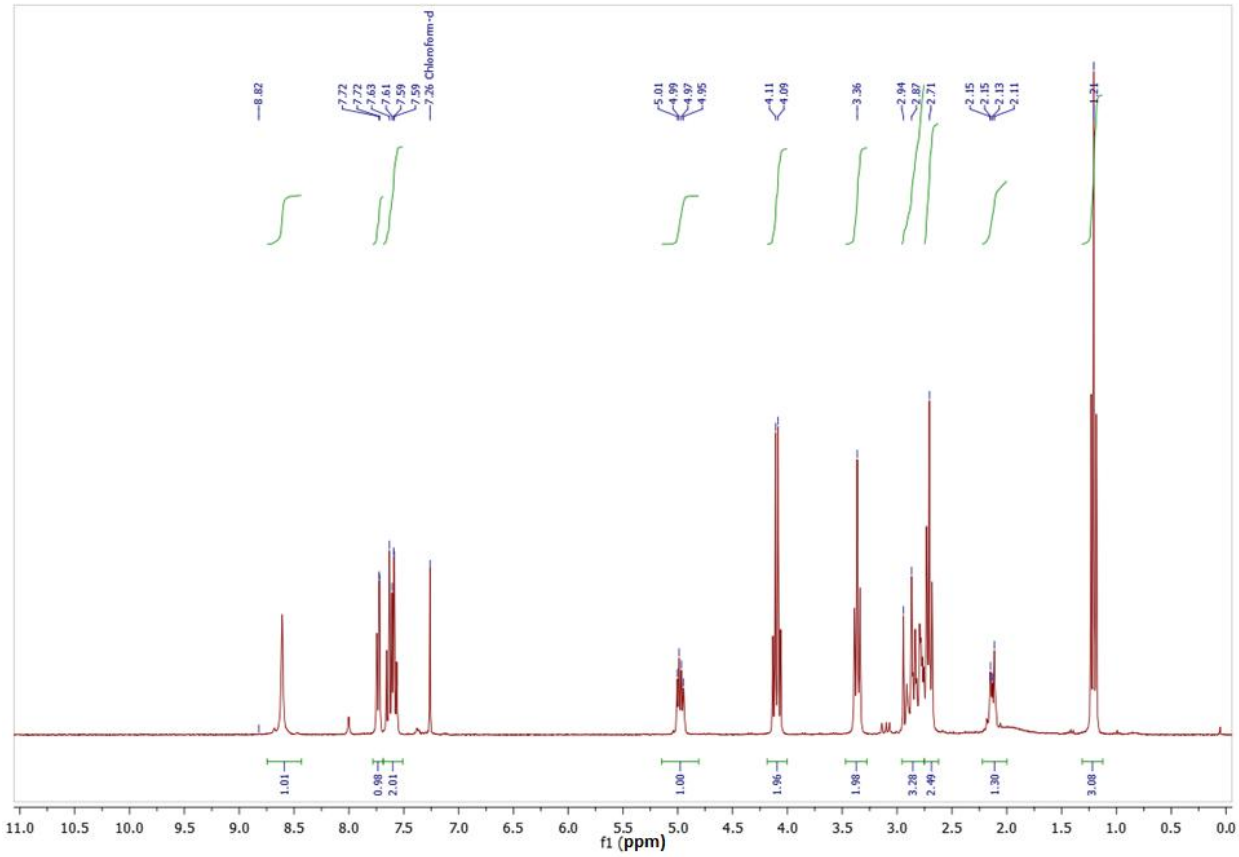


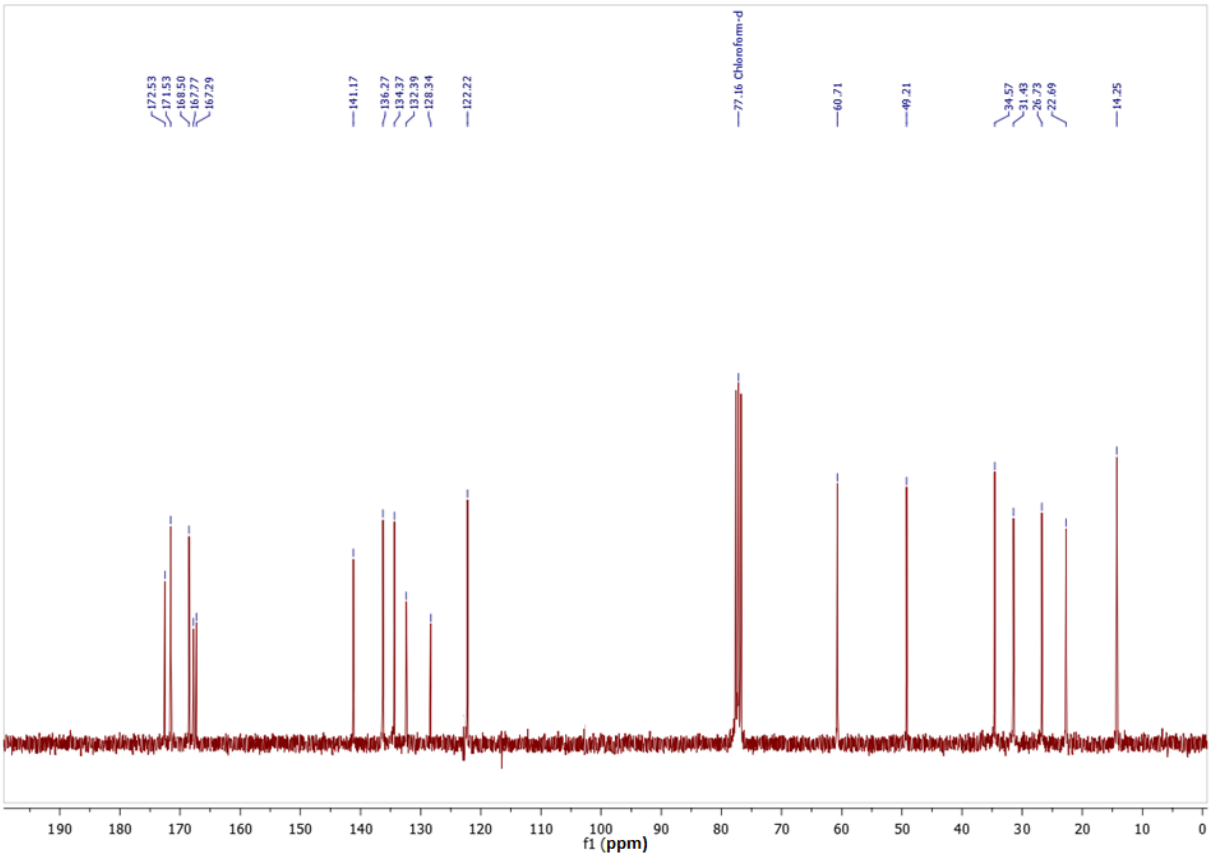
*ethyl 3-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]acrylate (**8**)*



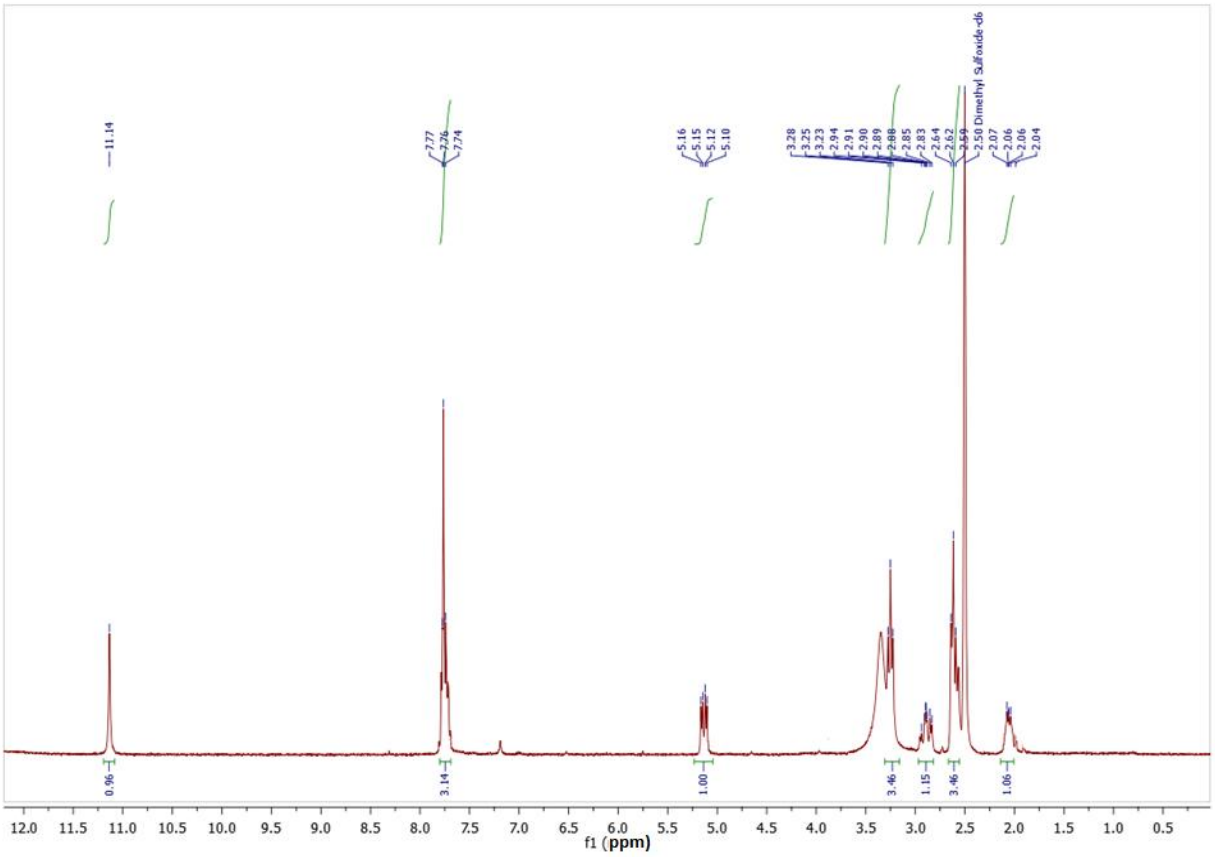


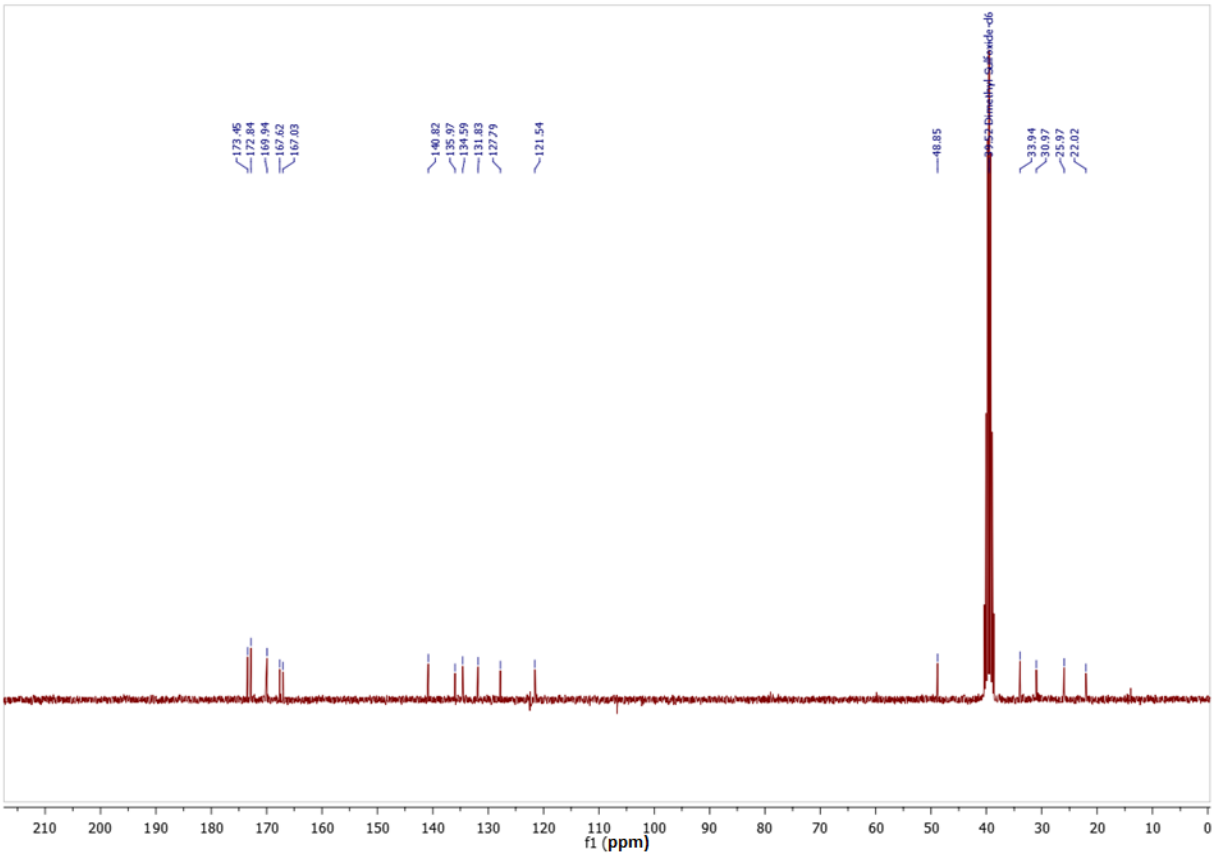
*ethyl 3-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]propanoate (**9**)*





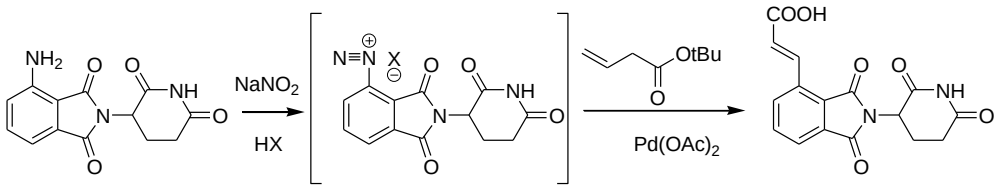
*3-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]propanoic acid (**7**)*





3. Synthesis optimization.

Table S1. Optimization of the Heck–Matsuda reaction conditions.



Entry	HX	Equiv Bu^tOAcr	Equiv $Pd(OAc)_2$	Yield (%)
1	HBF_4 (48%)	2	0.1	38
2	HBF_4 (48%)-AcOH 1:2	2	0.1	56
3	HBF_4 (48%)-AcOH 1:1	2	0.1	92
4	AcOH	2	0.1	-
5	H_2SO_4	2	0.1	20
6	HCl	2	0.1	-
7	HBF_4 (48%)-AcOH 1:1	1	0.1	61
8	HBF_4 (48%)-AcOH 1:1	2	0.05	94
9	HBF_4 (48%)-AcOH 1:1	2	0.01	76
10	HBF_4 (48%)-AcOH 1:1	2	0.01	-
11	HBF_4 (48%)-AcOH 1:1	2	0.01	22

References

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