Supporting Information for

Chemoselective Electrosynthesis Using Rapid Alternating Polarity

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General experimental

Tetrahydrofuran (THF), *N*,*N*-dimethylformamide (DMF), toluene, acetonitrile (CH_3CN), and dichloromethane (CH_2Cl_2) were obtained by passing the previously degassed solvents through an activated alumina column. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous material, unless otherwise stated. Reactions were monitored by LC/MS, and thin layer chromatography (TLC). TLC was performed using 0.25 mm E. Merck silica plates (60F-254), using short-wave UV light for visualization, and phosphomolybdic acid and $Ce(SO_4)_2$, acidic ethanolic anisaldehyde, or $KMnO_4$ and heat as developing agents. NMR spectra were recorded on Bruker DRX-600, DRX-500, and AMX-400 instruments and are calibrated using residual undeuterated solvent ($CHCl_3$ at 7.26 ppm ^{1}H NMR, 77.16 ppm ^{13}C NMR; CH_3OH at 3.31 ppm ^{1}H NMR, 49.0 ppm ^{13}C NMR; DMSO at 2.5 ppm ^{1}H NMR, 39.5 ppm ^{13}C NMR). The following abbreviations were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Column chromatography was performed using E. Merck silica (60, particle size 0.043–0.063 mm), and pTLC was performed on Merck silica plates (60F-254). High-resolution mass spectra (HRMS) were recorded on an Agilent LC/MSD TOF mass spectrometer by electrospray ionization time of flight reflectron experiments, a Waters LC-TOF (I-Class and G2-XS) mass spectrometer using ESI or APCI ion sources, and a Thermo Fisher Scientific LTQ Orbitrap XL mass spectrometer using ESI ion source. Optical rotations were recorded on a Rudolph Research Analytical Autopol III Automatic Polarimeter. Alternating current electrolysis with sinusoidal waveform (Figure 2, entry 13) was performed by using LABQUEST® 2 with Vernier Power Amplifier.

Classification of alternating current

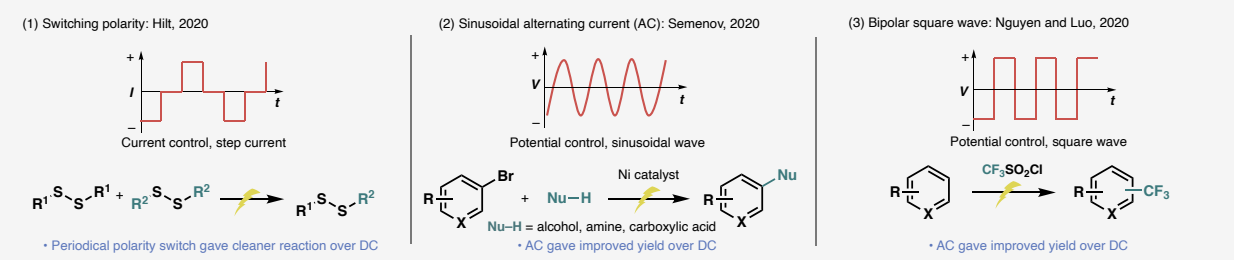


Figure S1. Classification of alternating current in organic synthesis.

Alternative current electrolysis could be further classified into several subclasses based on the waveform applied. The major waveforms found useful for organic synthesis are three types based on the recently published review,(*1*) and these are categorized into (1) switching polarity (Figure S1, left), (2) canonical alternating current with sinusoidal potential waveform (middle), and (3) bipolar square wave (right). Following this classification, rAP can be classified as bipolar square waves with either current or potential being controlled. In addition, rAP pulse duration is on the millisecond timescale, which distinguishes it from conventional "alternating polarity" technique that is sometimes applied during direct current electrolysis for avoiding electrode fouling (typically the polarity switch frequency timescale is several seconds to minutes).

A survey of alternating current electrolysis in organic synthesis

Additional literature precedents that are not covered in the main text are summarized below. This survey primarily includes literatures discussing AC electrolysis of organic compounds, and mostly limited to preparative scale electrolysis due to the relevance to our work. Applications of alternating current to some other areas are not included (e.g., application to metal plating and CO_2 reduction as well as electroanalytical application) in this survey. In addition, slow alternating polarity intended for electrode cleaning or alleviation of electrode fouling is also outside the scope of this survey.

1. Wilson, C. L. & W. T. Lippincott, Anodic Reactions. II. The Mechanism of the Kolbe Electrosynthesis. *J. Am. Chem. Soc.* **78**, 4290 (1956).
2. Fleischmann, M., Mansfield, H. R. & Wynne-Jones, L. The anodic oxidation of aqueous solutions of acetate ions at smooth platinum electrodes: part II. The non-steady state of the Kolbe synthesis of ethane. *J. Electroanal. Chem.* **10**, 522 (1965).
3. Fleischmann, M., Mansfield, H. R., Thirsk, H. G. E. & Wynne-Jones, L. R The investigation of the kinetics of electrode reactions by the application of repetitive square pulses of potential. *Electrochim. Acta*, **12**, 967 (1967).
4. Atherton, G., Fleischmann, M. & Goodridge, F. Kinetic Study of the Hofer-Moest Reaction. *Trans. Faraday Soc.,* **63**, 1468 (1967).
5. Vijh, A. K. & Conway, B. E. Electrode kinetic aspects of the Kolbe reaction. *Chem. Rev.* **67**, 623 (1967).
6. Fleischmann, M. & Goodridge, F. Anodic oxidation under pulse conditions. *Discuss. Faraday Soc.* **45**, 254–260 (1968)
7. Fleischmann, M. & Pletcher, D. Physical Parameters For the Control of Organic Electrode Processes. *Adv. Phys. Org. Chem*, **10**, 155, (1973).
8. Fahidy, T. Z. The chemical engineering approach to some electrochemical processes. *The Can. J. Chem. Eng.* **51**, 521–535 (1973).
9. Mayeda, E. A. & Bard, A. J. Production of singlet oxygen in electrogenerated radical ion electron transfer reactions. *J. Am. Chem. Soc.* **95**, 6223 (1973).

10. Ogumi, Z., Takehara, Z. & Yoshizawa, S. An Application of Current-pulse Electrolysis to an Electro-initiated Polymerization of Acrylamide. *Bull. Chem. Soc. Jpn.* **49**, 2883 (1976).
11. Kunkely, H., Merz, A. & Vogler, A. Alternating current electrolysis of transition-metal carbonyl complexes: electrochemically induced photochemistry. *J. Am. Chem. Soc.* **105**, 7241 (1983).

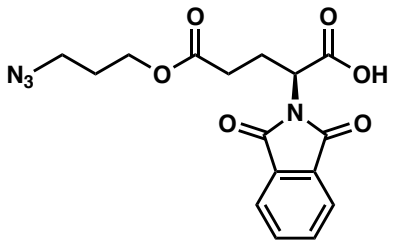
In addition, the following articles contain an excellent historical overview of AC applications into organic electrochemistry (these two articles are cited in the main text).

1. Schotten, C. *et al*. Alternating polarity for enhanced electrochemical synthesis. *React. Chem. Eng.* **6**, 147–151 (2021).
2. Rodrigo, S., Gunasekera, D., Mahajan, J. P. & Luo, L. Alternating current electrolysis for organic synthesis. *Current Opinion in Electrochemistry* **28**, 100712 (2021).

Synthesis of starting materials

Imide starting materials for **5**, **6**, **7**, **10**, **14**, **16**, **17**, **21**, and **56** and compounds **25**, **29**, and **57** were purchased and used without further purification. Imide starting materials for **2**(*2*), **4**(*3*), **8**(*4*), **11**(*5*), **13**(*6*), **19**(*7*), **22**(*8*), 27(*9*), **33**(*10*), and **35**(*11*) were prepared by following the literature procedures. Thalidomide analogs for **42-52** were provided by BMS. The following imides were either synthesized by modified procedures or are newly characterized.

(*S*)-5-(3-azidopropoxy)-2-(1,3-dioxoisoindolin-2-yl)-5-oxopentanoic acid (s1)



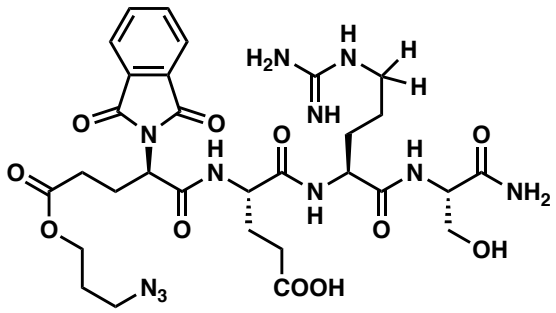
To a round-bottom flask equipped with a stir bar were added *N*-phthaloyl-L-glutalic anhydride (3.8 g, 15 mmol), 3-azido-1-propanol (1.6 g, 16 mmol), and pyridine (3.6 mL, 45 mmol). The resulting solution was heated gently at 50 ºC. After 1 h, the solution was poured into 1 N HCl aq., followed by extraction with AcOEt. The combined organic layer was dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography (hexane/CH_2Cl_2/AcOEt = 1:1:0.5 with 1% AcOH v/v) to afford the desired amino acid in 53% yield (2.9 g).

^{1}H NMR (600 MHz, DMSO-d_6): δ 7.89 – 7.85 (m, 4H), 4.66 – 4.64 (m, 1H), 4.00 – 3.92 (m, 2H), 3.35 (t, *J* = 6.8 Hz, 2H), 2.5 (t, *J* = 1.9 Hz, 2H), 2.42 – 2.34 (m, 3H), 2.27 – 2.32 (m, 1H), 1.75 (p, *J* = 6.5 Hz, 2H).

^{13}C NMR (151 MHz, DMSO-d_6): δ 172.3, 170.2, 167.6, 134.7, 131.4, 123.2, 61.2, 51.8, 47.6, 30.7, 27.6, 23.9.

HRMS (ESI-TOF, m/z): HRMS (ESI) Calcd for $[M+H]^+$ 361.1148; Found 361.1140.

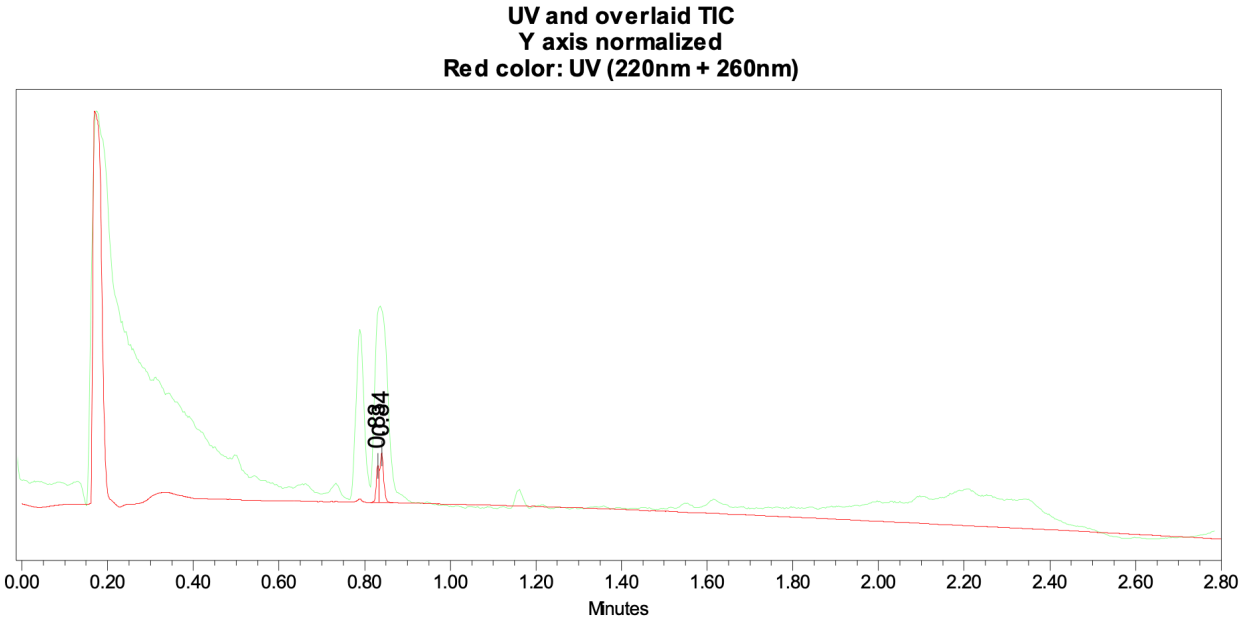
Tetrapeptide 1



Tetrapeptides were chain assembled by hand at 0.2 mmole scale on Rink Amide AM Polystyrene resin 200-400 mesh (Novabiochem 8.55004.0025). The initial three amino acids were coupled using an equivalent ratio of [5]:[5]:[5] of [Fmoc-protected amino acid]/[Oxyma Pure (0.4 M in coupling

DMF)]/[DIC] for 30 min with standard SPPS protocols for N-terminal Fmoc-protection, including deprotection with 20 % 4-methylpiperidine in DMF. *N*-Phthaloyl-Glu(3-azidopropylester)-OH (**s1**) was coupled with a [2.5]:[2.5]:[2.5] equivalent ratio for a period of 2 hours. Peptides were cleaved in 10 mL each of a [95]:[2.5]:[2.5] mixture of [TFA]/[TIPS]/[H_2O] for 1 hour. TFA was evaporated by gentle bubbling of nitrogen followed by precipitation of crude peptide in diethyl ether. The peptide was purified by mass-directed reverse-phase HPLC on a Waters 2545 Quaternary Gradient Module equipped with an Acquity QDa Detector and a Waters 2767 Sample Manager. The column was a Waters XBridge Prep C18 with a H_2O/CH_3CN gradient mobile phase containing 0.1% formic acid. The tetrapeptide **1** was obtained in 33% yield.

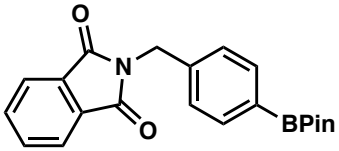
HRMS (ESI-TOF, m/z): HRMS (ESI) Calcd for $[M+Na]^+$ 732.3065; Found 732.3055.



Major UV Peaks

	RT	Area	Base Peak (m/z)
1	0.83	55794	732.5
2	0.84	103626	732.3

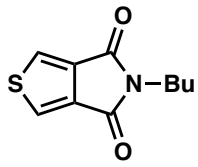
Compound 9s



To a mixture of *N*-(4-iodobenzyl) phthalimide (200 mg, 0.55 mmol), potassium acetate (108 mg, 1.1 mmol), and bis(pinacolato)diboron (182 mg, 0.72 mmol) in dioxane (5 mL) was added $PdCl_2(PPh_3)_2$ (19 mg, 0.027 mmol) under inert atmosphere and the reaction mixture was stirred at 100 °C for 18 h. The reaction mixture was diluted with AcOEt. The organic layer was washed with water and brine,

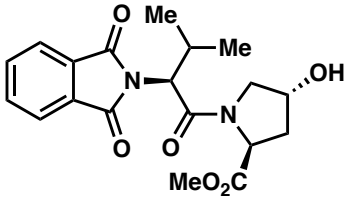
then dried over Na_2SO_4, and filtered. After concentration, the resulting residue was purified by flash column chromatography (hexane → hexane/AcOEt = 10:1) to furnish **9s** (147 mg, 74%) as a white solid. The ^{1}H NMR was consistent with the reported spectral data.(*12*)

Compound 12s



A solution of thiophene-3,4-dicarboxylic acid (500 mg, 2.9 mmol) in acetic anhydride (5 mL) was stirred under inert atmosphere at 120 °C for 21 h. The reaction mixture was concentrated under reduced pressure, and the resulting solid was washed with hexanes to afford thiophene-3,4-dicarboxylic acid anhydride (368 mg, 82%). To a suspension of thiophene-3,4-dicarboxylic acid anhydride (326 mg, 2.1 mmol) in dioxane (4 mL) was added DMAP (385 mg, 3.2 mmol) and butan-1-amine (230 mg, 3.2 mmol) under inert atmosphere at r.t. and the reaction mixture was stirred at 60 °C. After stirring overnight, acetic anhydride (1 mL) was added, then stirred at 90 °C for 27 h. The reaction mixture was diluted with AcOEt. The organic layer was washed with sat. $NaHCO_3$ aq. and brine, then dried over Na_2SO_4, and filtered. After concentration, the resulting residue was purified by flash column chromatography (hexane → hexane/AcOEt = 10:1 → 5:1) to furnish **12s** (322 mg, 73%) as a white solid. The ^{1}H NMR was consistent with the reported spectral data.(*13*)

Compound 53



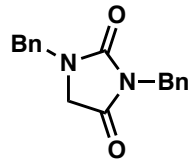
To a stirred solution of *N*-phthaloyl-$_L$-valine (741 mg, 3 mmol) in DMF (15 mL) was added HATU (1.25 g, 3.3 mmol) under inert atmosphere at r.t. After 5 min, $_L$-4-hydroxyproline methyl ester hydrochloride (724 mg, 4 mmol) and *i*Pr_2NEt (1.3 mL, 9 mmol) were added. The resulting solution was stirred overnight and then poured into brine. Organic compounds were extracted with the solvent mixture (hexane/AcOEt = 3:1), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography (hexane/AcOEt = 2:1) to afford **53** in 80% yield.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.79 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.69 (dd, *J* = 5.5, 3.0 Hz, 2H), 4.58 – 4.56 (m, 2H), 4.54 (d, *J* = 10.9 Hz, 1H), 3.95 (d, *J* = 11.0 Hz, 1H), 3.83 (dd, *J* = 11.0, 4.3 Hz, 1H), 3.71 (s, 3H), 3.24 – 3.17 (m, 1H), 2.26 (ddd, *J* = 11.7, 8.1, 1.9 Hz, 1H), 2.05 (ddd, *J* = 13.2, 8.0, 4.8 Hz, 1H), 1.10 (d, *J* = 6.7 Hz, 3H), 0.91 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 172.6, 168.4, 168.4, 134.4, 131.6, 123.7, 70.4, 59.2, 58.2, 55.6, 52.4, 37.5, 27.6, 19.8, 19.7.

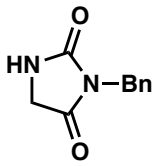
HRMS (ESI-TOF, m/z): HRMS (ESI) Calcd for $[M+H]^+$ 375.1556; Found 375.1555.

Compound 23



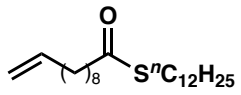
To a 50 mL round-bottom flask charged with 2,4-imidazolidinedione (1.0 g, 10 mmol), potassium carbonate (2.9 g, 21 mmol), and benzyl bromide (2.5 mL, 21 mmol) was added 15.0 mL of DMF. The mixture was heated to 90 °C with an oil bath under argon atmosphere. After stirring for 12 hours at 90 °C, water was added and extracted with CH_2Cl_2. The organic layer was washed with sat. $NaHCO_3$ aq. and brine, then dried over Na_2SO_4, and filtered. After concentration, the resulting residue was purified by silica gel column chromatography (CH_2Cl_2/hexane = 1:1 → CH_2Cl_2/hexane/AcOEt = 5:5:1) to furnish **23** (662 mg, 24%). The spectral data matched with the reported values.(*14*)

Compound 24



To a 50 mL round-bottom flask charged with 2,4-imidazolidinedione (1.0 g, 10 mmol), potassium carbonate (1.38 g, 10 mmol), and benzyl bromide (1.18 mL, 10 mmol) was added 10.0 mL of DMF. The mixture was heated to 90 °C with an oil bath under argon atmosphere. After stirring for 12 hours at 90 °C, the solution was concentrated under reduced pressure to reduce the volume to 2.5 mL, then deionized water was added, and the resulting precipitate was filtered off. After filtration, the precipitate was recrystallized in EtOH to furnish **24** (520 mg, 24%). The spectral data matched with the reported values.(*15*)

Compound 31



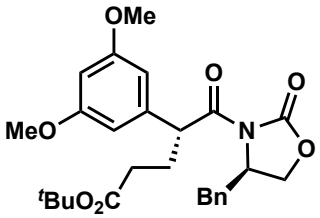
To a 50 mL round-bottom flask charged with 9-decenoic acid (553 mg, 3 mmol) and 1-methylimidazole (739 mg, 9 mmol) was added 3.0 mL of CH_3CN. The mixture was cooled to 0 °C with an ice bath and a solution of tosyl chloride (TsCl) (686 mg, 3.6 mmol) in 3.0 mL of CH_3CN was added dropwise. After stirring for 40 min at 0 °C, a solution of 1-dodecanethiol (729 mg, 3.6 mmol) in 3.0 mL of CH_2Cl_2 was added dropwise. The reaction mixture was quenched with 0.5 M HCl aq. after stirring for 1 hour at 0 °C and extracted

with AcOEt. The organic layer was washed with sat. $NaHCO_3$ aq. and brine, then dried over Na_2SO_4, and filtered. After concentration, the resulting residue was purified by flash column chromatography (hexane → hexane/AcOEt = 20:1) to furnish **31** (583 mg, 53%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.81 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 4.99 (dq, *J* = 17.1, 1.7 Hz, 1H), 4.93 (ddt, *J* = 10.2, 2.3, 1.2 Hz, 1H), 2.88 – 2.83 (m, 2H), 2.55 – 2.50 (m, 2H), 2.07 – 2.00 (m, 2H), 1.65 (p, *J* = 7.5 Hz, 2H), 1.59 – 1.51 (m, 2H), 1.40 – 1.21 (m, 28H), 0.88 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 200.0, 139.3, 114.3, 44.3, 33.9, 32.1, 29.79, 29.78, 29.74, 29.73, 29.6, 29.5, 29.4, 29.34, 29.28, 29.2, 29.1, 29.03, 28.99, 28.97, 25.9, 22.8, 14.3.

Compound 36



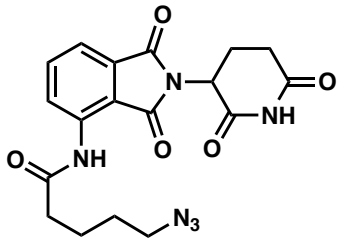
The procedure was adapted from diastereoselective alkylation described by Evans et al.(*16*) To 3 mL of CH_2Cl_2 were added $TiCl_4$ (2 M in CH_2Cl_2, 0.6 mL, 0.9 mmol) and Ti(O*i*Pr)$_4$ (78 μL, 0.3 mmol) at 0 ºC under argon atmosphere, and the solution was stirred for 15 min at the same temperature. Then *i*Pr_2NEt (0.28 mL, 2.0 mmol) was added, followed by the addition of **35**(*11*) (315 mg, 0.9 mmol). The reaction temperature was maintained at 0 ºC for another 1 h, then *t*-butyl acrylate (0.2 mL, 1.4 mmol) was added. The solution was slowly warmed up to r.t., then the reaction mixture was stirred overnight. After completion of the reaction, the brown solution was poured into sat. NH_4Cl aq., and organic compounds were extracted with CH_2Cl_2. After removal of solvents, the crude product was purified by column chromatography (hexane/AcOEt = 3:1) to furnish the alkylation product **36** in 48% yield as a single diastereomer.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.34 (t, *J* = 7.4 Hz, 2H), 7.28 (d, *J* = 7.4 Hz, 1H), 7.23 (d, *J* = 6.7 Hz, 2H), 6.53 (d, *J* = 2.3 Hz, 2H), 6.36 (s, 1H), 5.01 (d, *J* = 7.7 Hz, 1H), 4.71 – 4.47 (m, 1H), 4.10 (dd, *J* = 9.1, 2.4 Hz, 1H), 4.08 – 4.02 (m, 1H), 3.77 (s, 6H), 3.36 (dd, *J* = 13.4, 3.4 Hz, 1H), 2.79 (dd, *J* = 13.4, 9.8 Hz, 1H), 2.45 – 2.28 (m, 1H), 2.26 – 2.06 (m, 3H), 1.46 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 173.3, 172.3, 161.0, 152.9, 140.2, 129.6, 129.1, 127.5, 106.8, 99.8, 80.6, 66.0, 56.0, 55.5, 48.0, 38.2, 33.4, 29.2, 28.3.

HRMS (ESI-TOF, m/z): HRMS (ESI) Calcd for $[M+Na]^+$ 506.2155; Found 506.2151.

Compound 38



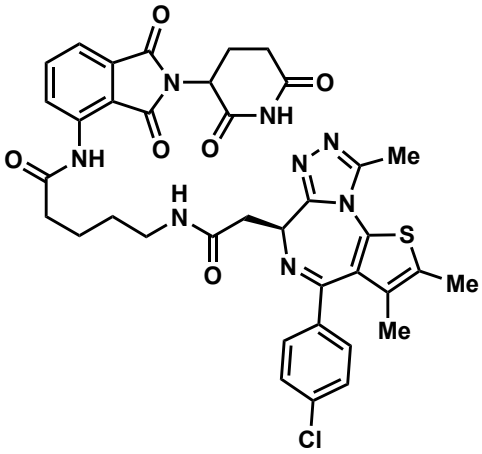
To a stirred solution of 5-azidovaleric acid (1.0 mmol, 140 mg) in CH_2Cl_2 (5 mL, with one drop of DMF) was added oxalyl chloride (1.0 mmol, 86 μL) at 0 ºC. After stirring the solution for 1 h at r.t., pomalidomide (240 mg, 0.9 mmol) and pyridine (0.33 mL, 4 mmol) were added in one portion. The resulting suspension was stirred overnight. During this period, the yellow solid was gradually consumed, and the progress of the reaction was monitored by TLC. After completion of the reaction, the solution was poured into brine, and organic compounds were extracted with CH_2Cl_2. After removal of solvents, the crude product was purified by column chromatography (CH_2Cl_2/AcOEt = 5:1) to furnish **38** in 85% yield.

^{1}H NMR (600 MHz, $CDCl_3$): δ 9.41 (s, 1H), 8.81 (d, *J* = 7.9 Hz, 1H), 8.43 (s, 1H), 7.71 (dd, *J* = 8.5, 7.3 Hz, 1H), 7.55 (dd, *J* = 7.3, 0.8 Hz, 1H), 4.96 (dd, *J* = 12.4, 5.4 Hz, 1H), 3.34 (t, *J* = 6.7 Hz, 2H), 2.92 – 2.89 (m, 1H), 2.81 – 2.75 (m, 2H), 2.51 (t, *J* = 7.3 Hz, 2H), 2.18 – 2.14 (m, 1H), 1.86 – 1.81 (m, 2H), 1.72 – 1.67 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 171.7, 171.0, 169.3, 168.1, 166.8, 137.9, 136.6, 131.2, 125.4, 118.7, 115.5, 51.2, 49.4, 37.2, 31.5, 28.4, 22.8, 22.4.

HRMS (ESI-TOF, m/z): HRMS (ESI) Calcd for $[M+Na]^+$ 421.1236; Found 421.1230.

Compound 40



To a stirred solution of **38** (0.2 mmol, 80 mg) in CH_3OH (2 mL) and CH_2Cl_2 (2 mL) was added Pd/C (5 wt%, 20 mg). The atmosphere was exchanged to H_2 (atmospheric pressure), and the suspension was stirred for 2 h. After completion of the reaction, the mixture was filtered and concentrated under reduced pressure. The crude product was redissolved into DMF (1.0 mL), and (+)-JQ1 carboxylic acid (84 mg, 0.21 mmol), HATU (80 mg, 0.21 mmol) and *i*Pr$_2$NEt (0.6 mmol) were added at r.t. The resulting solution was stirred for 30 min before quenching with aqueous citric acid solution (100 g/mL). The crude product was extracted with CH_2Cl_2 and concentrated. At this point, DMF was

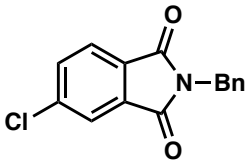
thoroughly removed before column chromatography. The residue was purified by column chromatography (CH_2Cl_2/AcOEt/CH_3OH = 1:0.2:0.2) to furnish **40** in 90% yield.

^{1}H NMR (600 MHz, $CDCl_3$, mixture of rotamers): δ 9.49 (s, 0.5H), 9.46 (s, 0.5H), 9.27 (br, 0.5H), 8.97 (br, 0.5H), 8.78 (s, 0.5H), 8.76 (s, 0.5H), 7.71 – 7.68 (m, 1H), 7.53 (t, *J* = 7.1 Hz, 1H), 7.40 – 7.38 (m, 2H), 7.31 – 7.30 (m, 2H), 6.83 (s, 0.5H), 6.77 (s, 0.5H), 4.98 – 4.91 (m, 1H), 4.63 (q, *J* = 6.6 Hz, 1H), 3.55 (ddd, *J* = 20.4, 14.2, 7.2 Hz, 1H), 3.44 – 3.29 (m, 3H), 2.82 – 2.70 (m, 3H), 2.65 (s, 3H), 2.53 – 2.50 (m, 1H), 2.38 (s, 3H), 2.12 – 2.10 (m, 1H), 1.84 – 1.80 (m, 2H), 1.65 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 172.01, 171.95, 171.2, 171.1, 170.82, 170.79, 169.40, 169.35, 168.3, 168.2, 166.8, 164.3, 164.2, 155.73, 155.69, 150.14, 150.13, 137.80, 137.78, 136.94, 136.90, 136.74, 136.71, 136.5, 132.3, 132.2, 131.26, 131.25, 131.07, 131.06, 130.99, 130.98, 130.62, 130.60, 130.0, 128.9, 128.8, 125.58, 125.56, 118.7, 118.6, 115.8, 115.7, 54.57, 54.55, 49.5, 49.4, 39.30, 39.28, 39.1, 39.0, 37.47, 37.47, 31.5, 31.4, 28.8, 28.7, 23.0, 22.9, 22.7, 22.6, 14.51, 14.49, 13.2, 11.94, 11.92.

HRMS (ESI-TOF, m/z): HRMS (ESI) Calcd for $[M+H]^+$ 755.2167; Found 755.2165.

Compound 54



To a stirred solution of 4-chlorophthalic anhydride (546 mg, 3 mmol) in AcOH (5 mL) was added benzylamine (0.34 mL, 3.1 mmol). The mixture was heated to 100 ºC for 15 h, then water was added to precipitate the product. Filtration of white solid afforded **54** in 65% yield (528 mg).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81 (d, *J* = 1.8 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.67 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.42 (d, *J* = 6.8 Hz, 2H), 7.33 – 7.27 (m, 3H), 4.84 (s, 2H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 167.2, 166.9, 140.9, 136.2, 134.2, 133.9, 130.3, 128.9, 128.8, 128.1, 124.7, 124.0, 42.0.

General procedures for rAP reduction

To an ElectraSyn reaction vial charged with imide substrate (0.1 mmol), pivalic acid (30.6 mg, 0.3 mmol), tetramethylammonium tetrafluoroborate (32 mg, 0.2 mmol) was added 2.5 mL of CH_3OH. Using an RVC anode and cathode the reaction mixture was electrolyzed under a constant current of 20 mA with rapid alternating polarity (50-100 ms, 5-10 Hz) for 12-48 F/mol. The reaction mixture was then concentrated under the reduced pressure. The crude reaction mixture was purified by preparative thin-layer chromatography (pTLC) or silica gel chromatography column. See the individual entries below for detailed conditions.

Graphical guide for rAP reduction (reduction of 2)

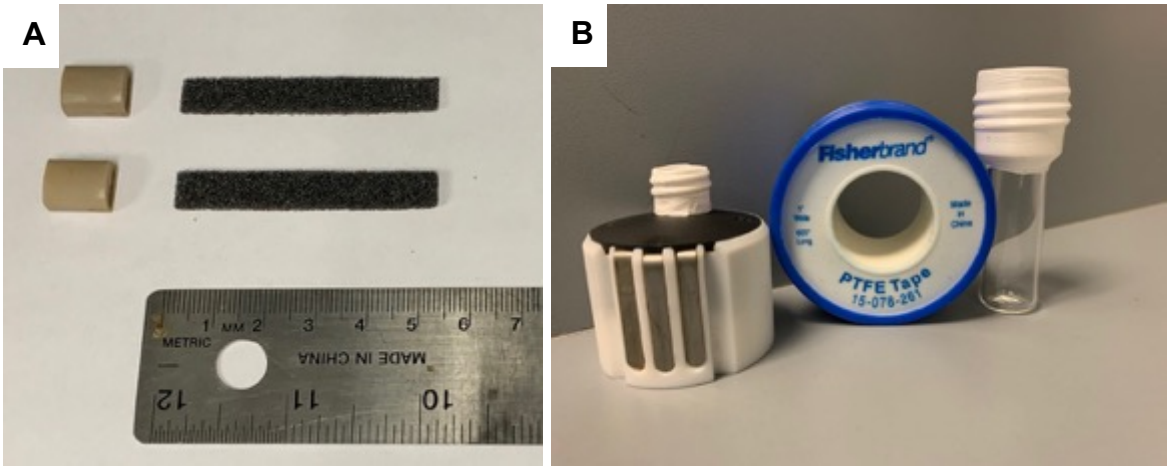


Figure S2. Equipment and setup for electrolysis: **(A)** RVC electrodes are cut into small blocks (approximate size: 1 mm x 5.5 cm x 0.75 cm). **(B)** IKA ElectraSyn cap and IKA ElectraSyn 5 mL vial are wrapped with PTFE tape to improve sealing. (Pro-Seal can be used without this treatment.)

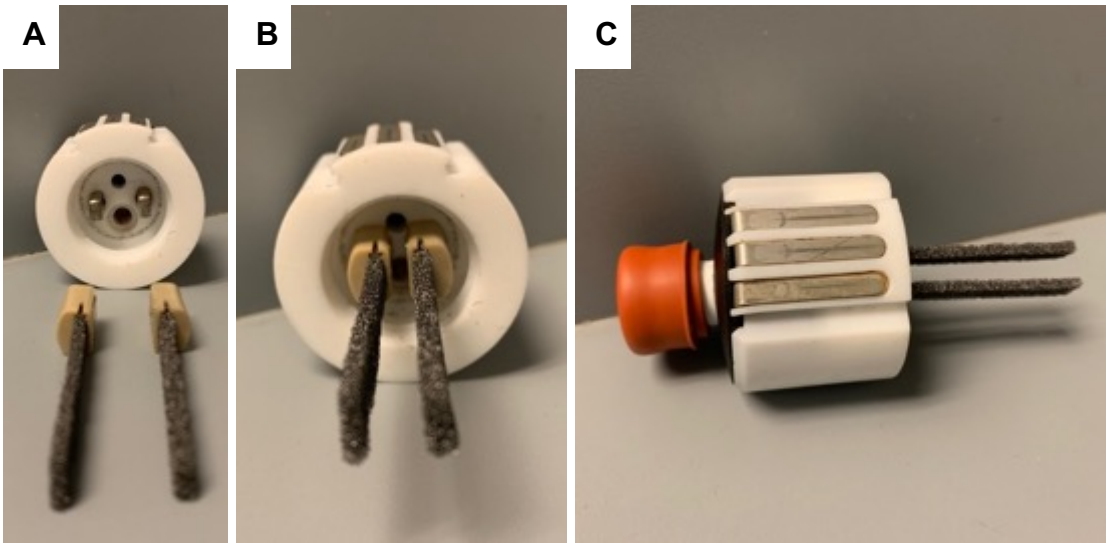


Figure S3. (A, B) RVC electrodes are fitted tightly into the plastic adaptors and then placed onto the IKA ElectraSyn cap over the contacts. **(C)** A septum is placed tightly over the top of the cap and folded over itself.

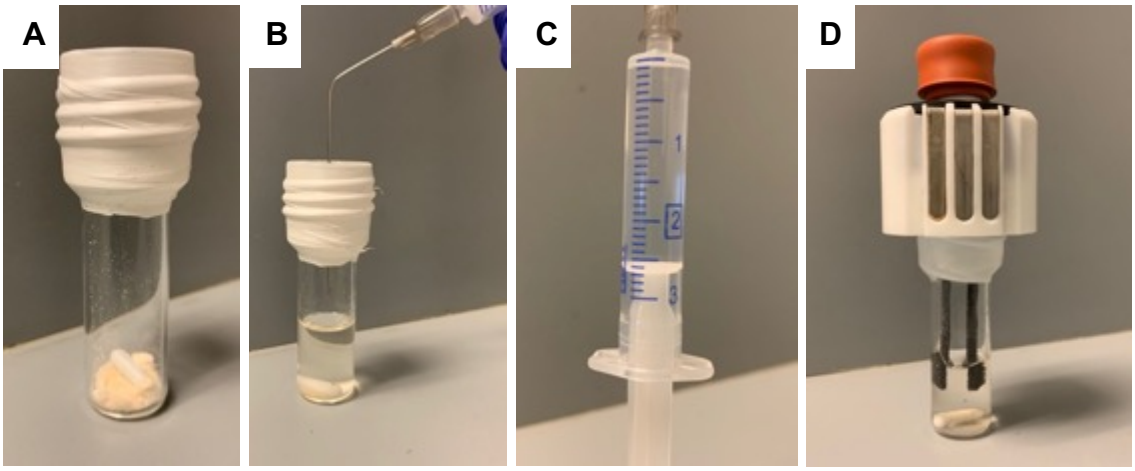


Figure S4. (A) A 5 mL ElectraSyn vial with a Teflon-coated stir bar is charged with $Me_4N•BF_4$ (32 mg, 0.2 mmol), substrate (33.0 mg, 0.1 mmol), and pivalic acid (30.6 mg, 0.3 mmol). **(B, C)** To the charged vial, CH_3OH (2.5 mL) is added. **(D)** IKA ElectraSyn cap fitted with electrodes and septum is assembled together with the ElectraSyn vial. (Ensure that electrodes are immersed in solvent.)

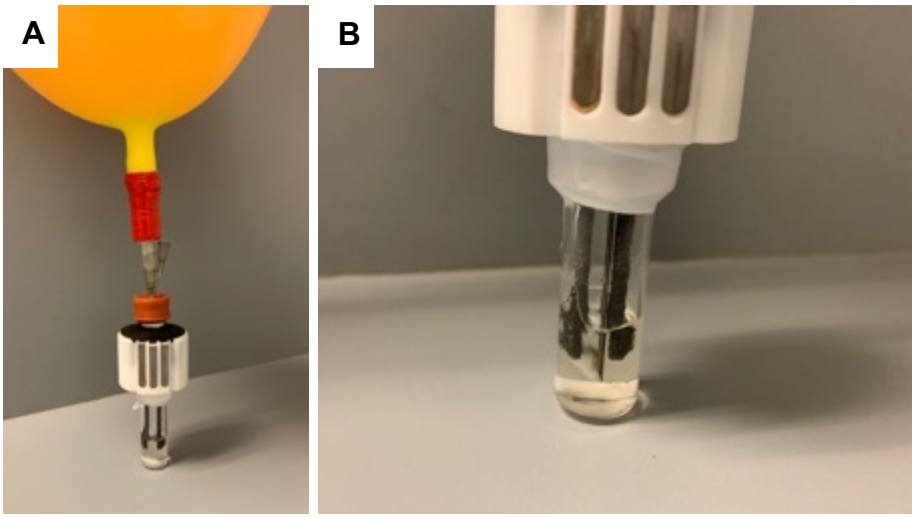
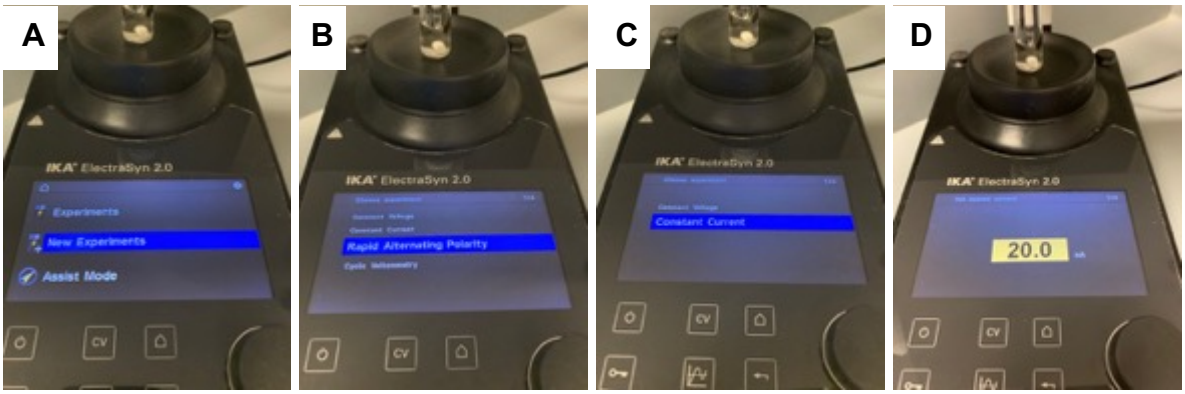


Figure S5. (A) To the assembled IKA ElectraSyn vial, an argon balloon is attached (a second needle on the septum serves as a vent). **(B)** Be sure to bubble Ar through solvent as depicted above for roughly 30-60 seconds. After Ar purge, the vent needle is removed and the tip of the needle connected to the balloon should be checked to make sure that no gas is escaping. (This serves as a convenient check for air tightness.) Then this needle is raised above the reaction solution before performing electrolysis.

IKA ElectraSyn 2.0 settings



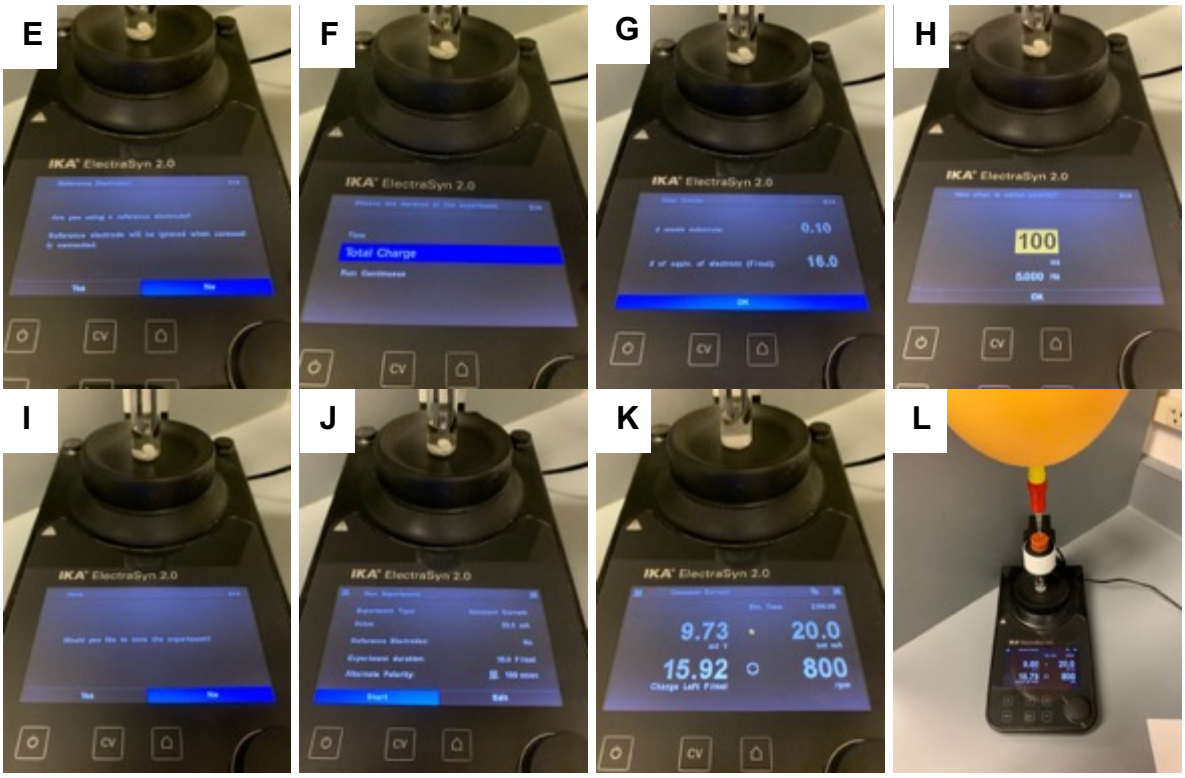


Figure S6. (A) Select "*New Experiment*". **(B)** Select "*Rapid Alternating Polarity*". To use this program, please ensure that the software version is up-to-date. For the latest software update, please visit https://www.ika.com/en/Services/Firmware-update-csrvf-8.html, and follow the instructions. **(C)** Select "*Constant Current*". **(D)** Set desired current. **(E)** Reference electrode is not necessary. **(F)** Select "*Total Charge*". **(G)** Using the dial, set the amount of substrate present (mmol), and the electron amount (F/mol). **(H)** Set frequency of alternating polarity. **(I)** Choose to save the experiment settings (optional). **(J)** Check that all parameters match desired settings and select "*Start*" or edit parameters. **(K)** The home screen will display actual reaction voltage, rate of stirring, charge remaining, time of reaction, and the set current. **(L)** Entire reaction setup.

Reaction workup

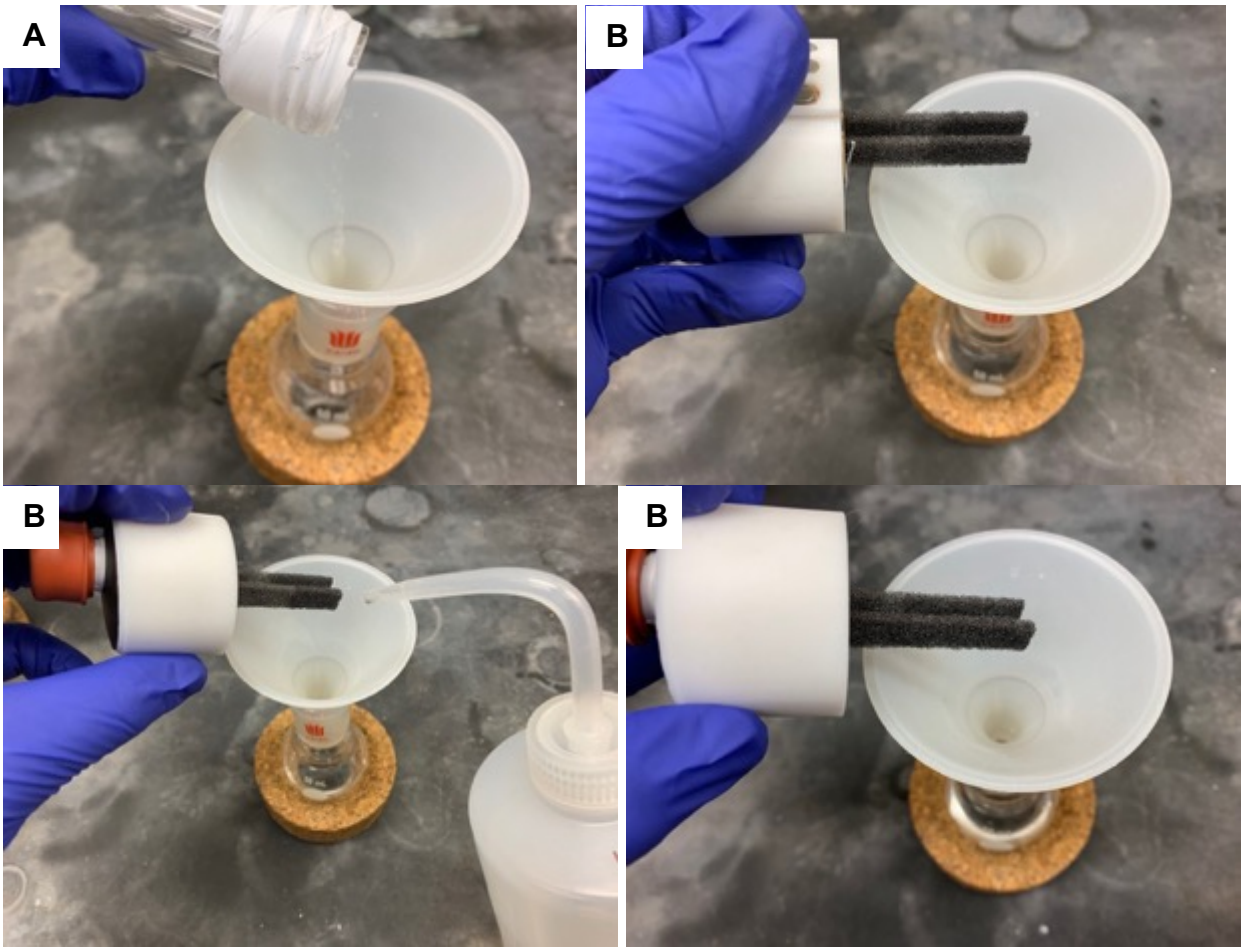


Figure S7. (A) The cap is unscrewed and contents of reaction vial are poured into a round bottom flask. **(B)** The porous RVC electrodes are washed thoroughly as they can hold considerable amounts of solvent containing desired product. Ethyl acetate (AcOEt) or dichloromethane (CH_2Cl_2) can be used for washing.

Electrode cleaning

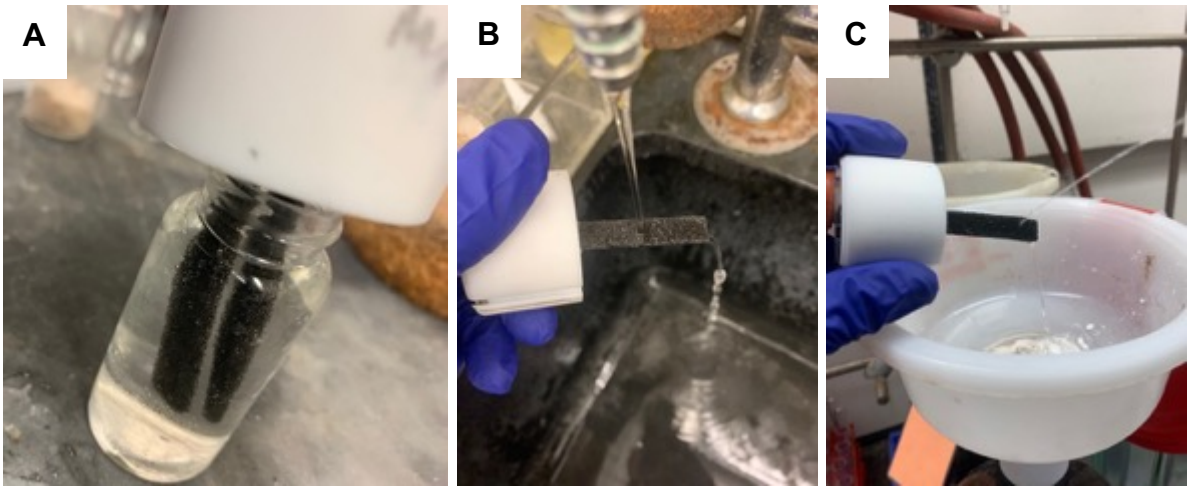


Figure S8. (A) Electrodes are immersed in 1 M aq. HCl for 15 seconds. **(B)** Electrodes are then rinsed with deionized water. **(C)** After washing with DI water, electrodes are washed with CH_3OH, CH_2Cl_2, or AcOEt, then finally washed with acetone and dried.

Scale-up reaction (1 gram scale thalidomide reduction)

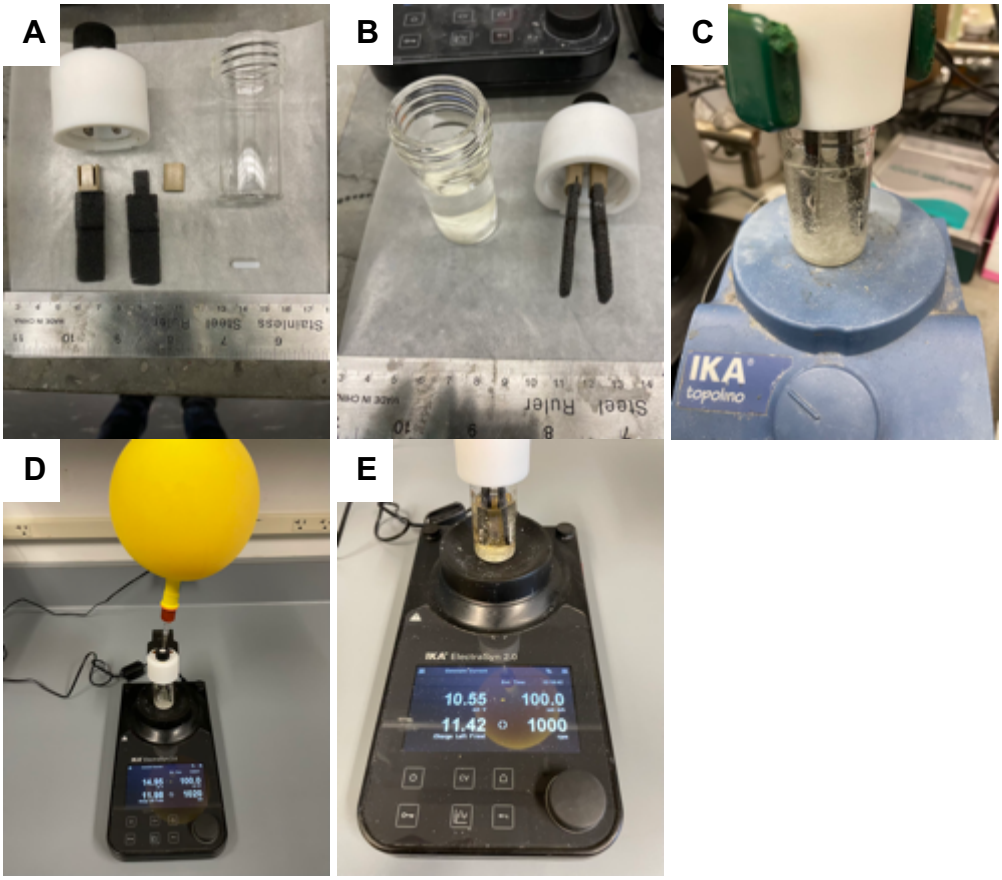
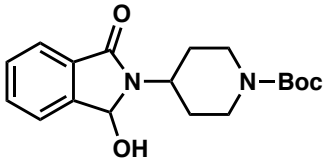


Figure S9. Reaction setup for 1 gram scale reaction. **(A)** Picture of RVC electrode (approximate size: 44 mm x 15 mm x 3 mm without the upper connecting area for a plastic adaptor) and 20 mL vial used for the reaction. **(B)** Thalidomide (4 mmol, 1.02 g), $Me_4N•BF_4$ (1.3 mmol, 208 mg), pivalic acid (12 mmol, 1.2 g), CH_3CN (7 mL) and *t*BuOH (7 mL) were added to the vial. **(C)** Sparging Ar to the reaction solution. Note: thalidomide does not dissolve completely. **(D)** Entire reaction setup. The solution was electrolyzed under a constant current of 100 mA with rapid alternating polarity (100 ms, 5 Hz) for 12 F/mol. **(E)** The initial reaction voltage could sometimes be as high as 15 V, but usually slowly decreases over 20 min and stabilizes around 11 V.

rAP Reduction of carbonyl compounds

Compound 3a



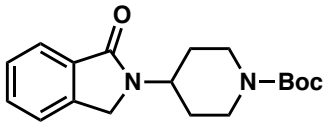
Following the general procedure, the reaction was performed with **2** (33.0 mg, 0.1 mmol), pivalic acid (30.6 mg, 0.3 mmol), tetramethylammonium tetrafluoroborate (32 mg, 0.2 mmol), and 2.5 mL of CH_3OH. The resulting reaction mixture was electrolyzed under a constant current of 20 mA with rapid alternating polarity (25 ms, 20 Hz) for 20 F/mol. The reaction mixture was concentrated, and the residue was passed through a short silica gel plug with AcOEt as eluent. ^{1}H NMR spectroscopic analysis of the crude reaction mixture found **3a** in 82%. The crude reaction mixture was purified by preparative thin-layer chromatography (hexane/AcOEt = 1:2) to furnish product **3a** (27 mg, 81%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.65 (d, *J* = 7.5 Hz, 1H), 7.55 (d, *J* = 7.5 Hz, 1H), 7.52 (t, *J* = 7.3 Hz, 1H), 7.43 (t, *J* = 7.3 Hz, 1H), 5.87 (s, 1H), 4.19 – 4.16 (m, 1H), 4.12 – 4.07 (m, 2H), 2.75 (br, 2H), 2.07 – 1.85 (m, 4H), 1.75 – 1.72 (m, 1H), 1.39 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 167.2, 154.8, 144.2, 132.3, 131.7, 129.8, 123.24, 123.22, 81.4, 80.0, 50.2, 31.4, 29.5, 28.5.

HRMS (ESI-TOF, m/z): HRMS (ESI) Calcd for $[M\text{-}OH]^+$ 315.1709; Found 315.1712.

Compound 3b



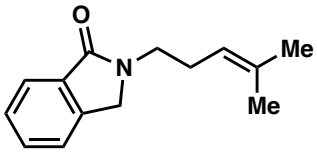
Following the general procedure, the reaction was performed with **1** (33.0 mg, 0.1 mmol), pivalic acid (30.6 mg, 0.3 mmol), tetramethylammonium tetrafluoroborate (32 mg, 0.2 mmol), and 2.5 mL of CH_3OH. The resulting reaction mixture was electrolyzed under a constant current of 20 mA with rapid alternating polarity (50 ms, 10 Hz) for 16 F/mol. The reaction mixture was concentrated, and the residue was passed through a short silica gel plug with AcOEt as eluent. ^{1}H NMR spectroscopic analysis of the crude reaction mixture found **3b** in 79%. The crude reaction mixture was purified by pTLC (hexane/AcOEt = 1:1.2) to furnish product **3b** (24 mg, 76%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.83 (d, *J* = 7.5 Hz, 1H), 7.52 (t, *J* = 6.9 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 2H), 4.40 (tt, *J* = 12.1, 4.1 Hz, 1H), 4.32 (s, 2H), 4.24 (br, 2H), 2.85 (br, 2H), 1.82 – 1.80 (m, 2H), 1.66 – 1.65 (m, 2H), 1.46 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 168.17, 154.76, 141.22, 133.00, 131.39, 131.39, 128.20, 123.77, 122.88, 79.89, 49.02, 46.10, 30.38, 28.54.

HRMS (ESI-TOF, m/z): HRMS (ESI) Calcd for $[M+Na]^+$ 339.1685; Found 339.1679.

Compound 4



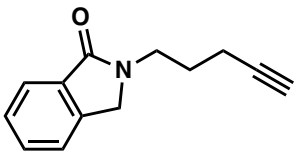
Following the general procedure, the reaction was performed with *N*-(4-methyl-3-pentenyl)phthalimide (22.9 mg, 0.1 mmol), pivalic acid (30.6 mg, 0.3 mmol), tetramethylammonium tetrafluoroborate (32 mg, 0.2 mmol), and 2.5 mL of CH_3OH. The resulting reaction mixture was electrolyzed under a constant current of 20 mA with rapid alternating polarity (50 ms, 10 Hz) for 16 F/mol. The reaction mixture was concentrated, and the residue was passed through a short silica gel plug with AcOEt as eluent. The crude reaction mixture was purified by pTLC (CH_2Cl_2/Et_2O = 4:1) to furnish product **4** (12.9 mg, 60%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.84 (d, *J* = 7.5 Hz, 1H), 7.51 (d, *J* = 7.4 Hz, 1H), 7.46 – 7.42 (m, 2H), 5.15 (t, *J* = 7.2 Hz, 1H), 4.38 (s, 2H), 3.61 (t, *J* = 7.3 Hz, 2H), 2.37 (q, *J* = 7.3 Hz, 2H), 1.68 (s, 3H), 1.60 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 168.6, 141.3, 134.5, 133.2, 131.2, 128.1, 123.8, 122.7, 120.7, 50.4, 42.5, 27.5, 25.9, 17.9.

HRMS (ESI-TOF, m/z): HRMS (ESI) Calcd for $[M+H]^+$ 216.1388; Found 216.1388.

Compound 5



Following the general procedure, the reaction was performed with *N*-(4-pentynyl)phthalimide (21.3 mg, 0.1 mmol), pivalic acid (30.6 mg, 0.3 mmol), tetramethylammonium tetrafluoroborate (32 mg, 0.2 mmol), and 2.5 mL of CH_3OH. The resulting reaction mixture was electrolyzed under a constant current of 20 mA with rapid alternating polarity (100 ms, 5 Hz) for 12 F/mol. The reaction mixture was concentrated, and the residue was passed through a short silica gel plug with

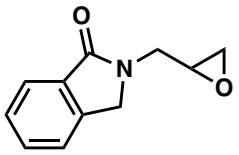
AcOEt as eluent. The crude reaction mixture was purified by pTLC (hexane/AcOEt = 1.5:1) to furnish product **5** (15 mg, 75%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.83 (d, *J* = 7.5 Hz, 1H), 7.52 (td, *J* = 7.4, 1.3 Hz, 1H), 7.46 – 7.43 (m, 2H), 4.41 (s, 2H), 3.71 (t, *J* = 7.1 Hz, 2H), 2.27 (td, *J* = 7.1, 2.7 Hz, 2H), 1.96 (t, *J* = 2.7 Hz, 1H), 1.91 (p, *J* = 7.1 Hz, 2H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 168.8, 141.2, 133.0, 131.1, 128.2, 123.8, 122.8, 83.3, 69.2, 50.4, 41.7, 27.3, 16.2.

HRMS (ESI-TOF, m/z): HRMS (ESI) Calcd for $[M+H]^+$ 200.1075; Found 200.1072.

Compound 6



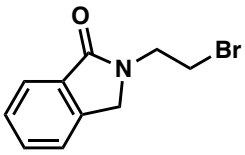
Following the general procedure, the reaction was performed with *N*-(2,3-epoxypropyl)phthalimide (20.3 mg, 0.1 mmol), pivalic acid (30.6 mg, 0.3 mmol), tetramethylammonium tetrafluoroborate (32 mg, 0.2 mmol), and 2.5 mL of CH_3OH. The resulting reaction mixture was electrolyzed under a constant current of 20 mA with rapid alternating polarity (50 ms, 10 Hz) for 16 F/mol. The reaction mixture was concentrated, and the residue was passed through a short silica gel plug with AcOEt as eluent. The crude reaction mixture was purified by pTLC (hexane/AcOEt = 1:5) to furnish product **6** (11.3 mg, 60%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.86 (d, *J* = 7.5 Hz, 1H), 7.55 (td, *J* = 7.4, 1.2 Hz, 1H), 7.52 – 7.39 (m, 2H), 4.58 (d, *J* = 17.0 Hz, 1H), 4.47 (d, *J* = 17.0 Hz, 1H), 4.21 (dd, *J* = 14.9, 2.7 Hz, 1H), 3.44 (dd, *J* = 14.8, 6.2 Hz, 1H), 3.20 (td, *J* = 6.4, 2.7 Hz, 1H), 2.83 (t, *J* = 4.4 Hz, 1H), 2.61 (dd, *J* = 4.7, 2.6 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 168.8, 141.7, 132.3, 131.7, 128.2, 123.9, 122.9, 51.5, 51.0, 44.8, 44.4.

HRMS (ESI-TOF, m/z): HRMS (ESI) Calcd for $[M+H]^+$ 190.8068; Found 190.0867.

Compound 7



Following the general procedure, the reaction was performed with *N*-(2-bromoethyl)phthalimide (25.4 mg, 0.1 mmol), pivalic acid (30.6 mg, 0.3 mmol), tetramethylammonium tetrafluoroborate (32 mg, 0.2 mmol), and 2.5 mL of CH_3OH. The resulting reaction mixture was electrolyzed under a constant current of 20 mA with rapid alternating polarity (50 ms, 10 Hz) for 16 F/mol. The reaction mixture was concentrated,

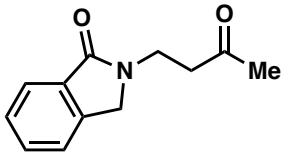
and the residue was passed through a short silica gel plug with AcOEt as eluent. The crude reaction mixture was purified by pTLC (hexane/AcOEt = 1.5:1) to furnish product **7** (12.7 mg, 53%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.86 (d, *J* = 7.6 Hz, 1H), 7.55 (t, *J* = 6.9 Hz, 1H), 7.48 – 7.45 (m, 2H), 4.57 (s, 2H), 4.03 (t, *J* = 6.3 Hz, 2H), 3.64 (t, *J* = 6.3 Hz, 2H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 168.9, 141.4, 132.4, 131.8, 128.3, 124.0, 122.9, 51.3, 44.8, 30.2.

HRMS (ESI-TOF, m/z): HRMS (ESI) Calcd for $[M+H]^+$ 240.0024; Found 240.0020.

Compound 8



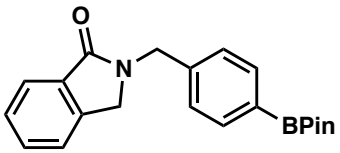
Following the general procedure, the reaction was performed with *N*-(3-oxobutyl)phthalimide (21.7 mg, 0.1 mmol), pivalic acid (30.6 mg, 0.3 mmol), tetramethylammonium tetrafluoroborate (32 mg, 0.2 mmol), and 2.5 mL of *t*BuOH/CH_3CN (1:1 v/v). The resulting reaction mixture was electrolyzed under a constant current of 20 mA with rapid alternating polarity (100 ms, 5 Hz) for 14 F/mol. The reaction mixture was concentrated, and the residue was passed through a short silica gel plug with AcOEt as eluent. The crude reaction mixture was purified by pTLC (AcOEt/CH_3OH = 20:1) to furnish product **8** (13.5 mg, 67%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.81 (d, *J* = 7.6 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 1H), 7.45 – 7.41 (m, 2H), 4.45 (s, 2H), 3.85 (t, *J* = 6.3 Hz, 2H), 2.90 (t, *J* = 6.3 Hz, 2H), 2.18 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 207.4, 168.9, 141.7, 132.8, 131.4, 128.1, 123.6, 122.8, 51.4, 42.5, 37.7, 30.2.

HRMS (ESI-TOF, m/z): HRMS (ESI) Calcd for $[M+H]^+$ 204.1025; Found 204.1025.

Compound 9



Following the general procedure, the reaction was performed with **9s** (23.6 mg, 0.1 mmol), pivalic acid (30.6 mg, 0.3 mmol), tetramethylammonium tetrafluoroborate (32 mg, 0.2 mmol), and 2.5 mL of CH_3OH. The resulting reaction mixture was electrolyzed under a constant current of 20 mA with rapid alternating polarity (100 ms, 5 Hz) for 16 F/mol. The reaction mixture was diluted with AcOEt and washed with sat. $NaHCO_3$ aq., then brine. The organic layer was then dried over Na_2SO_4, filtered, and concentrated under reduced pressure. ^{1}H NMR spectroscopic analysis of the

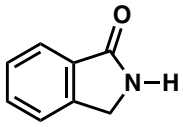
crude reaction mixture found **9** in 53%. The crude reaction mixture was purified by preparative thin-layer chromatography (hexanes/AcOEt = 1:1) to furnish product **9** (7.4 mg, 42%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.92 (dt, *J* = 7.5, 1.0 Hz, 1H), 7.82 – 7.77 (m, 2H), 7.54 (td, *J* = 7.4, 1.3 Hz, 1H), 7.49 (td, *J* = 7.5, 1.1 Hz, 1H), 7.39 (dt, *J* = 7.5, 1.0 Hz, 1H), 7.36 – 7.31 (m, 2H), 4.85 (s, 2H), 4.26 (s, 2H), 1.36 (s, 12H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 168.7, 141.4, 140.3, 135.4, 132.7, 131.5, 128.2, 127.7, 124.1, 122.9, 84.0, 49.6, 46.6, 25.0.

HRMS (ESI-TOF, m/z): HRMS (ESI) Calcd for $[M+H]^+$ 350.1927; Found 350.1928.

Compound 10



Following the general procedure, the reaction was performed with phthalimide (14.7 mg, 0.1 mmol), pivalic acid (30.6 mg, 0.3 mmol), tetramethylammonium tetrafluoroborate (32 mg, 0.2 mmol), and 2.5 mL of *t*BuOH/CH_3CN (1:1 v/v). The resulting reaction mixture was electrolyzed under a constant current of 20 mA with rapid alternating polarity (100 ms, 5 Hz) for 12 F/mol. The reaction mixture was concentrated, and the residue was passed through a short silica gel plug with AcOEt as eluent. The crude reaction mixture was purified by pTLC (hexane/AcOEt = 1:5) to furnish product **10** (13.6 mg, 67%).

^{1}H NMR (600 MHz, Acetone-d_6): δ 7.73 (d, *J* = 7.6 Hz, 1H), 7.61 – 7.57 (m, 2H), 7.49 (t, *J* = 7.6 Hz, 1H), 4.46 (s, 2H), 2.92 (br, 1H).

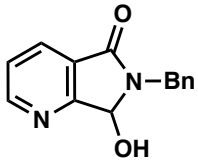
^{13}C NMR (151 MHz, Acetone): δ 171.12, 145.22, 133.77, 132.13, 128.48, 124.42, 123.88, 45.86.

HRMS (ESI-TOF, m/z): HRMS (ESI) Calcd for $[M+H]^+$ 134.0606; Found 134.0609.

[5 mmol scale]

Phthalimide (710 mg, 5 mmol), pivalic acid (1.53 g, 15 mmol), and tetramethylammonium tetrafluoroborate (160 mg, 1.0 mmol) in 14 mL of *t*BuOH/CH_3CN (1:1 v/v) were electrolyzed using the reaction setup described in Figure S9. A constant current of 100 mA with rapid alternating polarity (150 ms, 3.3 Hz) for 12 F/mol was applied to the reaction. After the reaction, the solution was poured into $NaHCO_3$ aq. and organic compounds were extracted with CH_2Cl_2. Removal of the solvent and column chromatography (AcOEt/CH_3OH = 10:1) of the crude products furnished **10** in 52% yield as white solid.

Compound 11



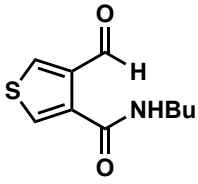
Following the general procedure, the reaction was performed with *N*-benzyl-4-azaphthalimide (23.8 mg, 0.1 mmol), pivalic acid (30.6 mg, 0.3 mmol), tetramethylammonium tetrafluoroborate (32 mg, 0.2 mmol), and 2.5 mL of CH_3OH. Using an RVC anode and cathode, the resulting reaction mixture was electrolyzed under a constant current of 20 mA with rapid alternating polarity (50 ms, 10 Hz) for 12 F/mol. The reaction mixture was concentrated, and the residue was passed through a short silica gel plug with AcOEt as eluent. Recrystallization from CH_2Cl_2/hexane afforded **11** as white needles (17.2 mg, 72%).

^{1}H NMR (600 MHz, DMSO-d_6): δ 8.78 (dd, *J* = 5.0, 1.6 Hz, 1H), 8.11 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.57 (dd, *J* = 7.6, 5.0 Hz, 1H), 7.34 – 7.33 (m, 4H), 7.28 – 7.25 (m, 1H), 6.97 (d, *J* = 8.8 Hz, 1H, O–**H** with partial H-D exchange), 5.64 (d, *J* = 6.5 Hz, 1H), 4.93 (d, *J* = 15.4 Hz, 1H), 4.42 (d, *J* = 15.4 Hz, 1H).

^{13}C NMR (151 MHz, DMSO-d_6): δ 164.7, 163.8, 152.8, 137.4, 131.1, 128.5, 127.7, 127.2, 125.1, 124.6, 80.6, 42.1.

HRMS (ESI-TOF, m/z): HRMS (ESI) Calcd for $[M+H]^+$ 241.0977; Found 241.0972.

Compound 12



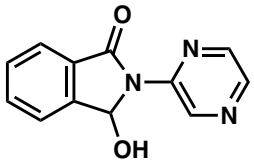
To an ElectraSyn reaction vial charged with substrate **12s** (21 mg, 0.1 mmol), pivalic acid (204 mg, 2.0 mmol), and tetramethylammonium tetrafluoroborate (32 mg, 0.2 mmol) was added 3.00 mL of CH_3CN. The resulting reaction mixture was electrolyzed under a constant current of 20 mA with rapid alternating polarity (50 ms, 10 Hz) for 32 F/mol. The reaction mixture was diluted with AcOEt and washed with sat. $NaHCO_3$ aq., then brine. The organic layer was then dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude reaction mixture was purified by flash column chromatography (hexane → hexanes/AcOEt = 5:1 → 2:1) to furnish product **12** (11 mg, 52%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 9.89 (d, *J* = 1.0 Hz, 1H), 9.43 (s, 1H), 8.37 (dd, *J* = 3.6, 1.0 Hz, 1H), 8.28 (d, *J* = 3.6 Hz, 1H), 3.44 (td, *J* = 7.1, 5.3 Hz, 2H), 1.63 (tt, *J* = 7.7, 6.5 Hz, 2H), 1.48 – 1.40 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 187.1, 161.0, 146.2, 138.5, 136.6, 136.3, 39.7, 31.5, 20.4, 13.9.

HRMS (ESI-TOF, m/z): HRMS (ESI) Calcd for $[M+H]^+$ 212.0745; Found 212.0741.

Compound 13



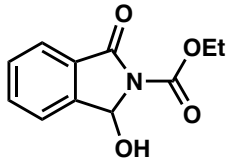
Following the general procedure, the reaction was performed with *N*-(2-pyrazyl)phthalimide (22.6 mg, 0.1 mmol), pivalic acid (30.6 mg, 0.3 mmol), tetramethylammonium tetrafluoroborate (32 mg, 0.2 mmol), 2.5 mL of *t*BuOH/MeCN (1/1 v/v). The resulting reaction mixture was electrolyzed under a constant current of 20 mA with rapid alternating polarity (100 ms, 5 Hz) for 20 F/mol. The reaction mixture was concentrated, and the residue was passed through short silica-gel plug with AcOEt as eluent. Recrystallization of crude product from hexane/CH_2Cl_2 furnished the product **13** (10.8 mg, 48%)

^{1}H NMR (600 MHz, Chloroform-*d*) δ 9.92 (d, *J* = 1.5 Hz, 1H), 8.41 (d, *J* = 2.6 Hz, 1H), 8.33 (dd, *J* = 2.7, 1.6 Hz, 1H), 7.93 (d, *J* = 7.6 Hz, 1H), 7.73 – 7.70 (m, 2H), 7.61 (ddd, *J* = 8.3, 6.3, 2.2 Hz, 1H), 6.76 (d, *J* = 2.7 Hz, 1H), 5.22 (d, *J* = 3.6 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 166.34, 148.62, 142.51, 141.25, 139.92, 137.70, 137.69, 133.94, 131.23, 130.52, 124.51, 123.94, 81.81.

HRMS (ESI-TOF, m/z): HRMS (ESI) Calcd for $[M+H]^+$ 228.0773; Found 228.0774.

Compound 14



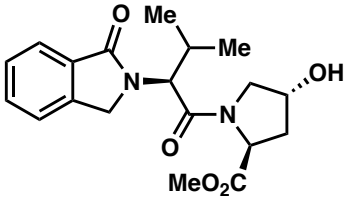
Following the general procedure, the reaction was performed using substrate *N*-ethoxycarbonylphthalimide (22 mg, 0.1 mmol), pivalic acid (153 mg, 1.5 mmol), tetramethylammonium tetrafluoroborate (32 mg, 0.2 mmol), and 3.00 mL of CH_3CN. The resulting reaction mixture was electrolyzed under a constant current of 20 mA with rapid alternating polarity (50 ms, 10 Hz) for 48 F/mol. The reaction mixture was diluted with AcOEt and washed with sat. $NaHCO_3$ aq., then brine. The organic layer was then dried over Na_2SO_4, filtered, and concentrated under reduced pressure. ^{1}H NMR spectroscopic analysis of the crude reaction mixture found **14** in 74%. The crude reaction mixture was purified by flash column chromatography (hexane → hexanes/AcOEt = 2:1) to furnish product **14** (15 mg, 68%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.89 (dt, *J* = 7.7, 0.9 Hz, 1H), 7.71 (td, *J* = 7.5, 1.1 Hz, 1H), 7.66 (dq, *J* = 7.6, 0.9 Hz, 1H), 7.58 (td, *J* = 7.5, 1.1 Hz, 1H), 6.47 (s, 1H), 4.46 (q, *J* = 7.1 Hz, 2H), 4.29 (s, 1H), 1.45 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 164.5, 152.9, 142.0, 134.5, 130.7, 130.5, 125.0, 124.2, 81.3, 63.5, 14.5.

HRMS (ESI-TOF, m/z): HRMS (ESI) Calcd for $[M+Na]^+$ 244.0586; Found 244.0580.

Compound 15



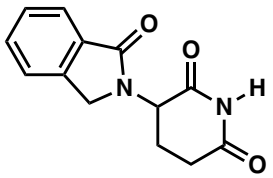
Following the general procedure, the reaction was performed with **15s** (36.0 mg, 0.1 mmol), pivalic acid (30.6 mg, 0.3 mmol), tetramethylammonium tetrafluoroborate (32 mg, 0.2 mmol), and 2.5 mL of CH_3OH. The resulting reaction mixture was electrolyzed under a constant current of 20 mA with rapid alternating polarity (100 ms, 5 Hz) for 20 F/mol. The reaction mixture was concentrated, and the residue was passed through a short silica gel plug with AcOEt as eluent. The crude reaction mixture was purified by pTLC (AcOEt/CH_3OH = 10:1) to furnish product **15** (30.2 mg, 87%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.62 (d, *J* = 7.5 Hz, 1H), 7.35 (t, *J* = 7.4 Hz, 1H), 7.30 (t, *J* = 7.4 Hz, 1H), 7.18 (d, *J* = 7.5 Hz, 1H), 4.76 (d, *J* = 11.0 Hz, 1H), 4.64 – 4.55 (m, 3H), 4.46 (br, 1H), 4.35 (d, *J* = 11.4 Hz, 1H), 4.26 (d, *J* = 17.7 Hz, 1H), 3.84 (dd, *J* = 11.3, 3.6 Hz, 1H), 3.75 (s, 3H), 2.41 – 2.37 (m, 1H), 2.35 – 2.31 (m, 1H), 2.00 – 1.96 (m, 1H), 1.08 (d, *J* = 6.6 Hz, 3H), 0.80 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 172.8, 169.4, 169.3, 142.0, 131.6, 131.3, 127.8, 123.6, 122.7, 70.3, 58.4, 58.1, 56.2, 52.3, 47.5, 37.8, 29.2, 19.0, 18.9.

HRMS (ESI-TOF, m/z): HRMS (ESI) Calcd for $[M+Na]^+$ 383.1583; Found 383.1583.

Compound 16



Following the general procedure, the reaction was performed with thalidomide (25.8 mg, 0.1 mmol), pivalic acid (30.6 mg, 0.3 mmol), tetramethylammonium tetrafluoroborate (32 mg, 0.2 mmol), and 2.5 mL of *t*BuOH/CH_3CN (1:1 v/v). The resulting reaction mixture was electrolyzed under a constant current of 20 mA with rapid alternating polarity (100 ms, 5 Hz) for 12 F/mol. The

reaction mixture was then poured into $NaHCO_3$ aq., followed by extraction with CH_2Cl_2. Recrystallization from CH_2Cl_2/hexane afforded **16** in 90% yield (21.8 mg) as an off-white solid.

[1 gram scale]

Thalidomide (1.04 mg, 4 mmol), pivalic acid (1.22 g, 12 mmol), and tetramethylammonium tetrafluoroborate (200 mg, 1.3 mmol) in 14 mL of *t*BuOH/CH_3OH (1:1 v/v) were electrolyzed using the reaction setup described in **Figure S9**. A constant current of 100 mA with rapid alternating polarity (100 ms, 5 Hz) for 13 F/mol was applied to the reaction. After the reaction, the solution was poured into $NaHCO_3$ aq., and organic compounds were extracted with CH_2Cl_2. Removal of the solvent and recrystallization from CH_2Cl_2/hexane afforded **16** in 70% yield.

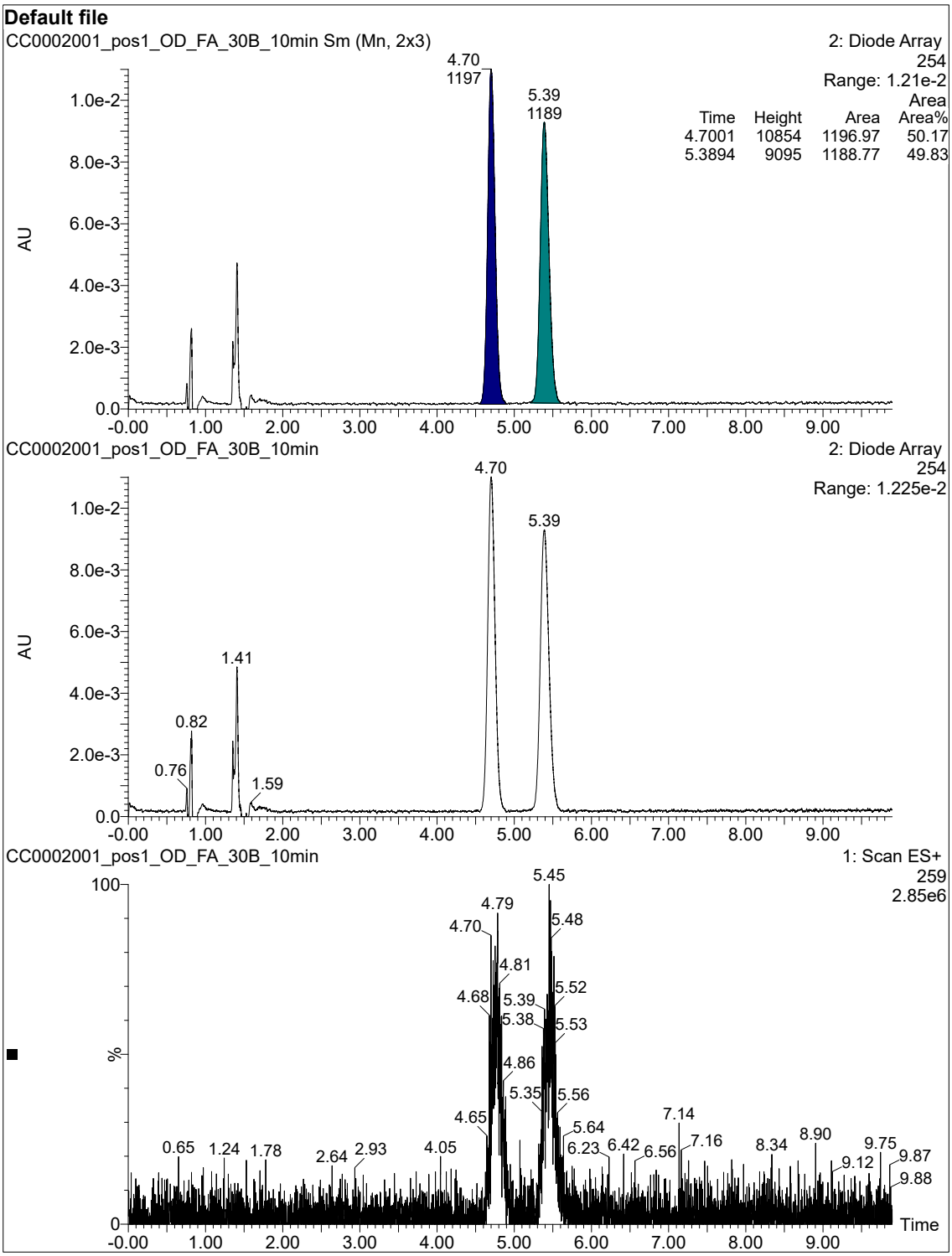
^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ 11.07 – 10.63 (m, 1H), 7.72 (d, *J* = 7.6 Hz, 1H), 7.64 – 7.59 (m, 2H), 7.50 (t, *J* = 7.6 Hz, 1H), 5.10 (dd, *J* = 13.3, 5.2 Hz, 1H), 4.45 (d, *J* = 17.2 Hz, 1H), 4.32 (d, *J* = 17.2 Hz, 1H), 2.90 (ddd, *J* = 17.3, 13.6, 5.4 Hz, 1H), 2.58 (ddd, *J* = 17.4, 4.5, 2.3 Hz, 1H), 2.38 (qd, *J* = 13.3, 4.5 Hz, 1H), 1.99 (dtd, *J* = 12.4, 5.2, 2.2 Hz, 1H).

^{13}C NMR (151 MHz, CD_3OD): δ 174.7, 172.2, 171.6, 143.7, 133.4, 133.1, 132.7, 129.3, 129.0, 124.4, 53.7, 32.4, 24.1.

HRMS (ESI-TOF, m/z): HRMS (ESI) Calcd for $[M+H]^+$ 245.0926; Found 245.0923.

[Reduction of enantioenriched thalidomide]

The enantioenriched starting material (93:7 er, 0.05 mmol) was treated under the same reaction conditions. The enantiomeric ratio of the product was determined as 89:11 by chiral HPLC analysis.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1189
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4.81
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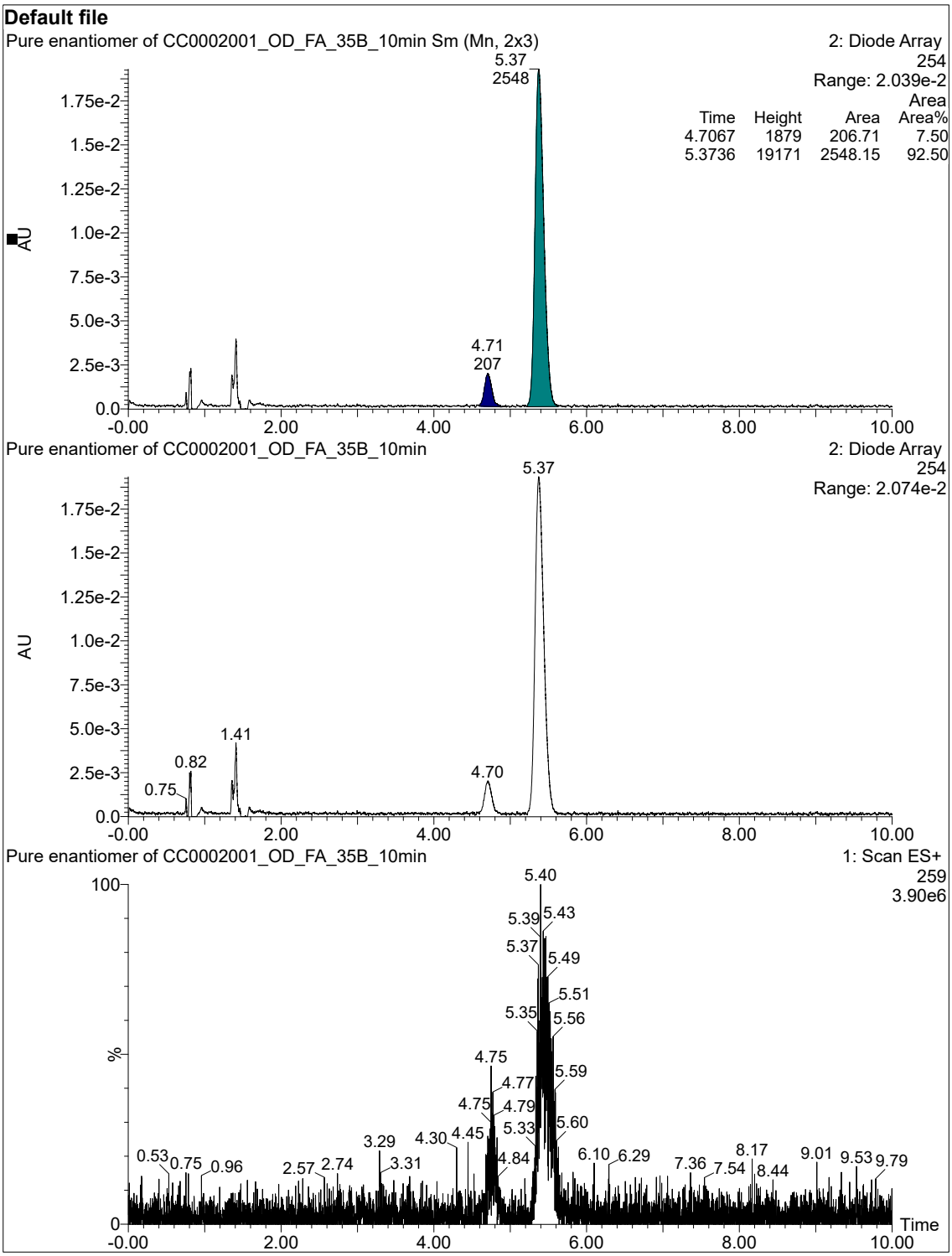
5.39
5.38
5.53
4.86
5.35
5.56
4.65
7.14
5.64
0.65
1.24
1.78
2.64
2.93
4.05
6.23
6.42
6.56
7.16
8.34
8.90
9.75
9.87
9.12
9.88
%
Time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Time Height Area Area%
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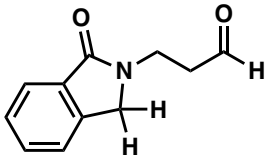
%
Time

Compound 18a



Following the general procedure, the reaction was performed with **17** (20.3 mg, 0.1 mmol), pivalic acid (30.6 mg, 0.3 mmol), tetramethylammonium tetrafluoroborate (32 mg, 0.2 mmol), and 2.5 mL of CH_3OH. The resulting reaction mixture was electrolyzed under a constant current of 20 mA with rapid alternating polarity (50 ms, 10 Hz) for 12 F/mol. The reaction mixture was concentrated, and the residue was passed through a short silica gel plug with AcOEt as eluent. The crude reaction mixture was purified by pTLC (hexane/AcOEt = 1:5) to furnish product **18a** (8.6 mg, 45%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 9.86 (t, *J* = 1.1 Hz, 1H), 7.83 (dt, *J* = 7.6, 1.0 Hz, 1H), 7.53 (td, *J* = 7.5, 1.2 Hz, 1H), 7.47 – 7.43 (m, 2H), 4.45 (s, 2H), 3.93 (t, *J* = 6.2 Hz, 2H), 2.93 (td, *J* = 6.3, 1.1 Hz, 2H).

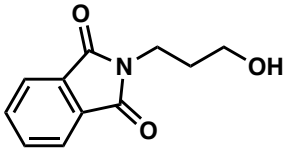
^{13}C NMR (151 MHz, $CDCl_3$): δ 200.7, 169.0, 141.5, 132.5, 131.6, 128.2, 123.7, 122.8, 51.1, 43.1, 36.3.

HRMS (ESI-TOF, m/z): HRMS (ESI) Calcd for $[M+H]^+$ 190.0868; Found 190.0870.

[Direct current electrolysis**]**

The identical reaction setup and conditions to rAP reduction were employed. Direct current electrolysis was performed by applying constant current (20 mA, 12 F/mol). Complex mixture was confirmed by the crude ^{1}H NMR analysis after removal of the solvent.

[DIBAL reduction]



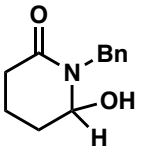
18b

To a stirred solution of **17** (0.1 mmol) in THF (1.0 mL) in a screw-capped tube was added DIBAL solution (1 M in hexane, 0.11 mmol) at −78 ºC under Ar atmosphere. The solution was kept at −78 ºC for an additional 5 min and was quenched with 1 M HCl. Extraction with AcOEt, followed by PTLC (hexane/AcOEt = 1:1) afforded **18b** in 73% yield. The ^{1}H NMR spectrum of **18b** matched with that of commercially available *N*-(3-hydroxypropyl)phthalimide. No formation of **18a** was confirmed by ^{1}H NMR.

[$LiBH_4$ reduction]

To a stirred solution of **17** (0.1 mmol) in THF in a screw-capped tube was added $LiBH_4$ solution (0.1 M in THF, 0.04 mmol) at −78 ºC under Ar atmosphere. The solution was kept at −78 ºC for an additional 5 min and was quenched with 1 M HCl. Extraction with AcOEt, followed by PTLC (hexane/AcOEt = 1:1) afforded **18b** in 33% yield. No formation of **18a** was confirmed by ^{1}H NMR.

Compound 19



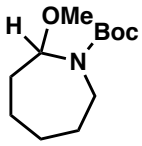
Following the general procedure, the reaction was performed with *N*-benzylglutalimide (20.3 mg, 0.1 mmol), pivalic acid (30.6 mg, 0.3 mmol), tetramethylammonium tetrafluoroborate (32 mg, 0.2 mmol), and 2.5 mL of CH_3OH. The resulting reaction mixture was electrolyzed under a constant current of 20 mA with rapid alternating polarity (100 ms, 5 Hz) for 12 F/mol. The reaction mixture was concentrated, and the residue was passed through a short silica gel plug with AcOEt as eluent. The crude reaction mixture was purified by pTLC (AcOEt/CH_3OH = 10:1) to furnish product **19** (16.2 mg, 80%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.33 – 7.31 (m, 2H), 7.29 – 7.28 (m, 2H), 7.27 – 7.26 (m, 1H), 5.16 (d, *J* = 14.9 Hz, 1H), 4.92 (s, 1H), 4.31 (d, *J* = 14.9 Hz, 1H), 3.85 (br, 1H), 2.53 (dt, *J* = 17.9, 4.1 Hz, 1H), 2.41 (ddd, *J* = 16.6, 11.0, 5.8, 1H), 2.15 – 2.07 (m, 1H), 1.93 – 1.90 (m, 1H), 1.83 (ddt, *J* = 13.7, 12.2, 3.7 Hz, 1H), 1.75 – 1.69 (m, 1H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 170.9, 137.7, 128.7, 128.2, 127.5, 78.9, 47.0, 32.5, 31.0, 15.9.

HRMS (ESI-TOF, m/z): HRMS (ESI) Calcd for $[M+H]^+$ 206.1181; Found 205.1179.

Compound 20



Following the general procedure, the reaction was performed with *N*-butoxycarbonylcaprolactam (42.6 mg, 0.2 mmol), pivalic acid (61.2 mg, 0.3 mmol), tetramethylammonium tetrafluoroborate (32 mg, 0.2 mmol), and 2.5 mL of CH_3OH. The resulting reaction mixture was electrolyzed under a constant current of 20 mA with rapid alternating polarity (100 ms, 5 Hz) for 12 F/mol. A considerable quantity of hemiaminal was visible by TLC immediately after the electrolysis, and this hemiaminal was slowly converted to **20** by leaving the reaction mixture at r.t. for 1.5 days without workup. Then, the reaction mixture was concentrated, and the residue was passed through a short silica gel plug with AcOEt as eluent.

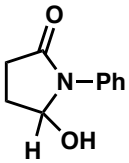
The crude reaction mixture was purified by pTLC (hexane/CH_2Cl_2/Et_2O = 1:1:0.15) to furnish product **20** (37.8 mg, 83%).

^{1}H NMR (600 MHz, DMSO-d_6, mixture of rotamers): δ 5.21 (t, *J* = 8.1 Hz, 0.5H), 5.11 (t, 0.5H), 3.53 (d, *J* = 14.3 Hz, 0.5H), 3.46 (d, *J* = 14.6 Hz, 0.5H), 3.13 (s, 1.5H), 3.10 (s, 1.5H), 2.81 (q, 1H), 2.18 – 2.12 (m, 1H), 1.72 – 1.70 (m, 1H), 1.59 – 1.37 (m, 13H), 1.29 – 1.23 (m, 1H), 1.00 (p, *J* = 12.3 Hz, 1H).

^{13}C NMR (151 MHz, DMSO-d_6): δ 155.5, 154.4, 85.74, 85.72, 84.71, 84.70, 79.1, 78.8, 54.19, 54.16, 34.1, 33.9, 29.30, 29.25, 28.02, 27.98, 27.7, 27.3, 22.3, 22.2.

HRMS (ESI-TOF, m/z): HRMS (ESI): N.D. due to fragmentation.

Compound 21



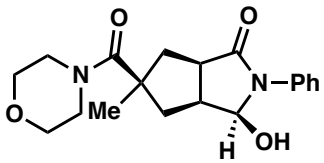
Following the general procedure, the reaction was performed with *N*-phenylsuccinimide (17.5 mg, 0.1 mmol), pivalic acid (30.6 mg, 0.3 mmol), tetramethylammonium tetrafluoroborate (32 mg, 0.2 mmol), and 2.5 mL of CH_3OH. The resulting reaction mixture was electrolyzed under a constant current of 20 mA with rapid alternating polarity (50 ms, 10 Hz) for 15 F/mol. The reaction mixture was concentrated, and the residue was passed through a short silica gel plug with AcOEt as eluent. The crude reaction mixture was purified by pTLC (hexane/AcOEt = 1:5) to furnish product **21** (11.1 mg, 70%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.50 (d, *J* = 7.9 Hz, 2H), 7.39 (t, *J* = 7.9 Hz, 2H), 7.24 (t, *J* = 7.5 Hz, 1H), 5.65 (s, 1H), 3.24 (d, *J* = 6.3 Hz, 1H), 2.77 (dd, *J* = 17.4, 8.5 Hz, 1H), 2.49 – 2.39 (m, 2H), 2.05 – 2.01 (m, 1H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 174.4, 137.2, 129.3, 126.5, 123.8, 85.3, 29.8, 28.3.

HRMS (ESI-TOF, m/z): HRMS (ESI) Calcd for $[M+H]^+$ 178.0868; Found 178.0864.

Compound 22



Following the general procedure, the reaction was performed with imide starting material (34 mg, 0.1 mmol), pivalic acid (102 mg, 1.0 mmol), tetramethylammonium tetrafluoroborate (32 mg, 0.2 mmol), and 3.0 mL of CH_3OH. The resulting reaction mixture was electrolyzed under a constant current of 20 mA with rapid alternating polarity (100 ms, 5 Hz) for 24 F/mol. The reaction mixture was diluted with AcOEt and washed with sat. $NaHCO_3$ aq., then brine. The

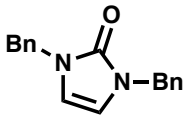
organic layer was then dried over Na_2SO_4, filtered, and concentrated under reduced pressure. ^1H NMR spectroscopic analysis of the crude reaction mixture found **22** in 33% (brsm 46%). The crude reaction mixture was purified by flash column chromatography (CH_2Cl_2 → CH_2Cl_2/CH_3OH = 10:1) to furnish product **22** (11.0 mg, 32%).

^1H NMR (600 MHz, $CDCl_3$): δ 7.46 – 7.41 (m, 2H), 7.40 – 7.34 (m, 2H), 7.25 – 7.19 (m, 1H), 6.59 (d, *J* = 12.8 Hz, 1H), 5.69 (dd, *J* = 12.6, 7.5 Hz, 1H), 3.78 (s, 7H), 3.68 (ddt, *J* = 9.5, 6.6, 2.9 Hz, 2H), 3.60 (s, 2H), 3.24 – 3.14 (m, 2H), 3.13 (dd, *J* = 15.4, 2.3 Hz, 1H), 2.92 (dd, *J* = 13.5, 2.4 Hz, 1H), 1.88 (dd, *J* = 13.6, 8.4 Hz, 1H), 1.66 – 1.59 (m, 1H), 1.40 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 175.6, 174.0, 137.4, 129.0, 126.4, 124.4, 85.2, 66.4 (br, 4C), 49.9, 48.9, 40.9, 40.5, 39.1, 25.4.

HRMS (ESI-TOF, m/z): HRMS (ESI) Calcd for $[M\text{-}H_2O+H]^+$ 327.1709; Found 327.1705.

Compound 23



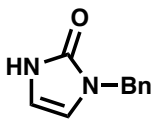
Following the general procedure, the reaction was performed with 1,3-dibenzylimidazolidine-2,4-dione (28.0 mg, 0.1 mmol), pivalic acid (32 mg, 0.3 mmol), tetramethylammonium tetrafluoroborate (32 mg, 0.2 mmol), and 3.0 mL of CH_3OH. The resulting reaction mixture was electrolyzed under a constant current of 20 mA with rapid alternating polarity (100 ms, 5 Hz) for 16 F/mol. The reaction mixture was diluted with AcOEt and washed with sat. $NaHCO_3$ aq., then brine. The organic layer was then dried over Na_2SO_4, filtered, and concentrated under reduced pressure. ^1H NMR spectroscopic analysis of the crude reaction mixture found **23** in 50%. The crude reaction mixture was purified by pTLC (hexane/AcOEt = 1:1) to furnish product **23** (12.2 mg, 46%).

^1H NMR (500 MHz, $CDCl_3$): δ 7.34 (dd, *J* = 7.9, 6.5 Hz, 4H), 7.31 – 7.26 (m, 6H), 6.10 (s, 2H), 4.82 (s, 4H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 137.1, 128.9, 128.0, 127.9, 110.5, 47.4.

HRMS (ESI-TOF, m/z): HRMS (ESI) Calcd for $[M+H]^+$ 281.1290; Found 281.1294.

Compound 24



Following the general procedure, the reaction was performed with 3-benzylimidazolidine-2,4-dione (19.0 mg, 0.1 mmol), pivalic acid (32 mg, 0.3 mmol), tetramethylammonium tetrafluoroborate (32 mg, 0.2 mmol), and 3.0 mL of

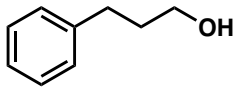
CH_3OH. The resulting reaction mixture was electrolyzed under a constant current of 20 mA with rapid alternating polarity (100 ms, 5 Hz) for 16 F/mol. The reaction mixture was diluted with AcOEt and washed with sat. $NaHCO_3$ aq., then brine. The organic layer was then dried over Na_2SO_4, filtered, and concentrated under reduced pressure. ^{1}H NMR spectroscopic analysis of the crude reaction mixture found **24** in 51%. The crude reaction mixture was purified by pTLC (Cl_2CH_2/CH_3OH = 50:1) to furnish product **24** (8.6 mg, 49%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 10.14 (br, 1H), 7.35 (t, *J* = 7.2 Hz, 1H), 7.32 – 7.25 (m, 2H), 7.25 (s, 1H), 6.30 (s, 1H), 6.13 (s, 1H), 4.81 (s, 2H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 136.9, 129.0, 128.0, 127.9, 111.7, 108.7, 46.9, 29.84, 29.80.

HRMS (ESI-TOF, m/z): HRMS (ESI) Calcd for $[M+H]^+$175.0871; Found 175.0869.

Compound 26



Following the general procedure, the reaction was performed with substrate **25** (13 mg, 0.1 mmol), pivalic acid (102 mg, 1.0 mmol), tetramethylammonium tetrafluoroborate (32 mg, 0.2 mmol), and 3.0 mL of CH_3OH. The resulting reaction mixture was electrolyzed under a constant current of 20 mA with rapid alternating polarity (100 ms, 5 Hz) for 16 F/mol. The reaction mixture was diluted with AcOEt and washed with sat. $NaHCO_3$ aq., then brine. The organic layer was then dried over Na_2SO_4, filtered, and concentrated under reduced pressure. ^{1}H NMR spectroscopic analysis of the crude reaction mixture found **25** in 77%. The crude reaction mixture was purified by flash column chromatography (hexane → hexane/AcOEt = 5:1) to furnish product **26** (8.7 mg, 64%).

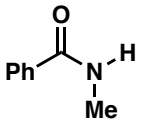
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.32 – 7.27 (m, 2H), 7.21 (dt, *J* = 8.2, 2.0 Hz, 2H), 3.68 (t, *J* = 6.4 Hz, 2H), 2.72 (dd, *J* = 8.6, 6.8 Hz, 2H), 1.94 – 1.87 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 128.6, 128.5, 126.0, 62.4, 34.4, 32.2.

Compounds 28a and 28b

Following the general procedure, the reaction was performed with substrate **27** (29 mg, 0.1 mmol), pivalic acid (32 mg, 0.3 mmol), tetramethylammonium tetrafluoroborate (32 mg, 0.2 mmol), and 3.0 mL of CH_3OH. The resulting reaction mixture was electrolyzed under a constant current of 20 mA with rapid alternating polarity (50 ms, 10 Hz) for 16 F/mol. The reaction mixture was concentrated under reduced pressure. The crude reaction mixture was purified by flash column

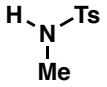
chromatography (hexane → hexanes/AcOEt = 10:1 → 5:1 → 1:1 → AcOEt) to furnish products **28a** (8.3 mg, 61%) and **28b** (7.7 mg, 38%) with benzyl alcohol (2.3 mg, 21%) and methyl 4-methylbenzenesulfinate (3.0 mg, 18%).



28a:

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.79 – 7.73 (m, 2H), 7.52 – 7.45 (m, 1H), 7.42 (ddt, *J* = 8.2, 6.5, 1.2 Hz, 2H), 6.20 (s, 1H), 3.01 (d, *J* = 4.9 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 168.4, 134.8, 131.5, 128.7, 127.0, 27.0.

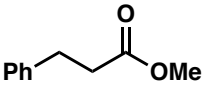


28b:

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.77 – 7.72 (m, 2H), 7.34 – 7.29 (m, 2H), 4.49 (s, 1H), 2.64 (s, 3H), 2.43 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 143.7, 135.9, 129.9, 127.4, 29.5, 21.7.

Compound 30

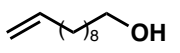


Following the general procedure, the reaction was performed with substrate **29** (16 mg, 0.1 mmol), pivalic acid (102 mg, 1.0 mmol), tetramethylammonium tetrafluoroborate (32 mg, 0.2 mmol), and 3.0 mL of CH_3OH. The resulting reaction mixture was electrolyzed under a constant current of 20 mA with rapid alternating polarity (50 ms, 10 Hz) for 24 F/mol. The reaction mixture was diluted with AcOEt and washed with sat. $NaHCO_3$ aq., then brine. The organic layer was then dried over Na_2SO_4, filtered, and concentrated under reduced pressure. ^{1}H NMR spectroscopic analysis of the crude reaction mixture found **30** in 62%. The crude reaction mixture was purified by flash column chromatography (hexane → hexanes/AcOEt = 10:1) to furnish product **30** (8.2 mg, 50%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.33 – 7.26 (m, 2H), 7.25 – 7.16 (m, 3H), 3.68 (s, 3H), 2.96 (t, *J* = 6.0 Hz, 2H), 2.64 (t, *J* = 6.0, 2H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 173.5, 140.7, 128.7, 128.4, 126.4, 51.8, 35.9, 31.1.

Compound 32



Following the general procedure, the reaction was performed with substrate **30** (37mg, 0.1 mmol), pivalic acid (102 mg, 1.0 mmol), tetramethylammonium

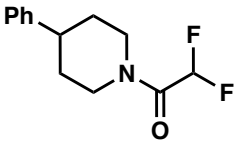
tetrafluoroborate (32 mg, 0.2 mmol), and 3.0 mL of CH_3OH. The resulting reaction mixture was electrolyzed under a constant current of 20 mA with rapid alternating polarity (150 ms, 3.3 Hz) for 32 F/mol. The reaction mixture was diluted with AcOEt and washed with sat. $NaHCO_3$ aq., then brine. The organic layer was then dried over Na_2SO_4, filtered, and concentrated under reduced pressure. ^{1}H NMR spectroscopic analysis of the crude reaction mixture found **32** in 60%. The crude reaction mixture was purified by preparative thin-layer chromatography (CH_2Cl_2/AcOEt = 20:1) to furnish product **32** (9.0 mg, 53%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.81 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 4.99 (dq, *J* = 17.1, 1.7 Hz, 1H), 4.93 (ddt, *J* = 10.2, 2.3, 1.3 Hz, 1H), 3.64 (t, *J* = 6.6 Hz, 2H), 2.10 – 1.99 (m, 2H), 1.57 (dq, *J* = 8.0, 6.6 Hz, 2H), 1.41 – 1.26 (m, 12H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 139.4, 114.3, 63.3, 34.0, 33.0, 29.7, 29.57, 29.55, 29.3, 29.1, 25.9.

Compounds 34a, 34b

Following the general procedure, the reaction was performed with substrate **33** (26 mg, 0.1 mmol), pivalic acid (32 mg, 0.3 mmol), tetramethylammonium tetrafluoroborate (32 mg, 0.2 mmol), and 3.00 mL of CH_3OH. The resulting reaction mixture was electrolyzed under a constant current of 20 mA with rapid alternating polarity (100 ms, 5 Hz) for 16 F/mol. The reaction mixture was diluted with AcOEt and washed with sat. $NaHCO_3$ aq., then brine. The organic layer was then dried over Na_2SO_4, filtered, and concentrated under reduced pressure. ^{1}H NMR spectroscopic analysis of the crude reaction mixture found **34a** in 34% and **34b** in 39%. The crude reaction mixture was purified by flash column chromatography (hexane → hexanes/AcOEt = 5:1 → 1:1) to furnish products **34a** (7.0 mg, 29%) and **34b** (7.1 mg, 32%).

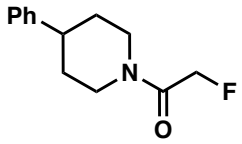


34a:

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.35 – 7.29 (m, 2H), 7.26 – 7.21 (m, 1H), 7.23 – 7.18 (m, 2H), 6.15 (t, J_{H-F} = 64.0 Hz, 1H), 4.68 (ddt, *J* = 13.3, 4.3, 2.3 Hz, 1H), 4.23 (ddt, *J* = 13.8, 4.2, 2.2 Hz, 1H), 3.21 (ddd, *J* = 13.7, 12.6, 2.6 Hz, 1H), 2.85 – 2.76 (m, 2H), 1.96 (dtt, *J* = 13.1, 4.5, 2.2 Hz, 2H), 1.78 – 1.61 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 160.8 (t, J_{C-F} = 24.2 Hz), 144.7, 128.8, 126.9, 126.8, 111.1 (t, J_{C-F} = 255.2 Hz), 45.6 (t, J_{C-F} = 4.5 Hz), 43.6, 42.7, 33.8, 32.9.

HRMS (ESI-TOF, m/z): HRMS (ESI) Calcd for $[M+H]^+$ 240.1200; Found 240.1196.



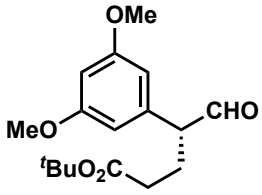
34b:

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.35 – 7.30 (m, 2H), 7.25 – 7.21 (m, 1H), 7.21 – 7.17 (m, 2H), 5.04 (dd, $J_{H\text{-}F}$ = 48 Hz, J = 18 Hz, 1H), 5.01 (dd, $J_{H\text{-}F}$ = 48 Hz, J = 18 Hz, 1H), 4.79 – 4.69 (m, 1H), 3.91 – 3.79 (m, 1H), 3.17 (t, J = 13.0 Hz, 1H), 2.82 – 2.66 (m, 2H), 1.95 (s, 2H), 1.68 (dtd, J = 13.5, 12.4, 4.3 Hz, 2H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 165.3 (d, $J_{C\text{-}F}$ = 18.1 Hz), 145.0, 128.8, 126.83, 126.79, 80.2 (d, $J_{C\text{-}F}$ = 179.7 Hz), 45.5 (d, $J_{C\text{-}F}$ = 4.5 Hz), 43.0, 42.8, 33.9, 32.9.

HRMS (ESI-TOF, m/z): HRMS (ESI) Calcd for $[M+H]^+$ 222.1294; Found 222.1290

Compound 37

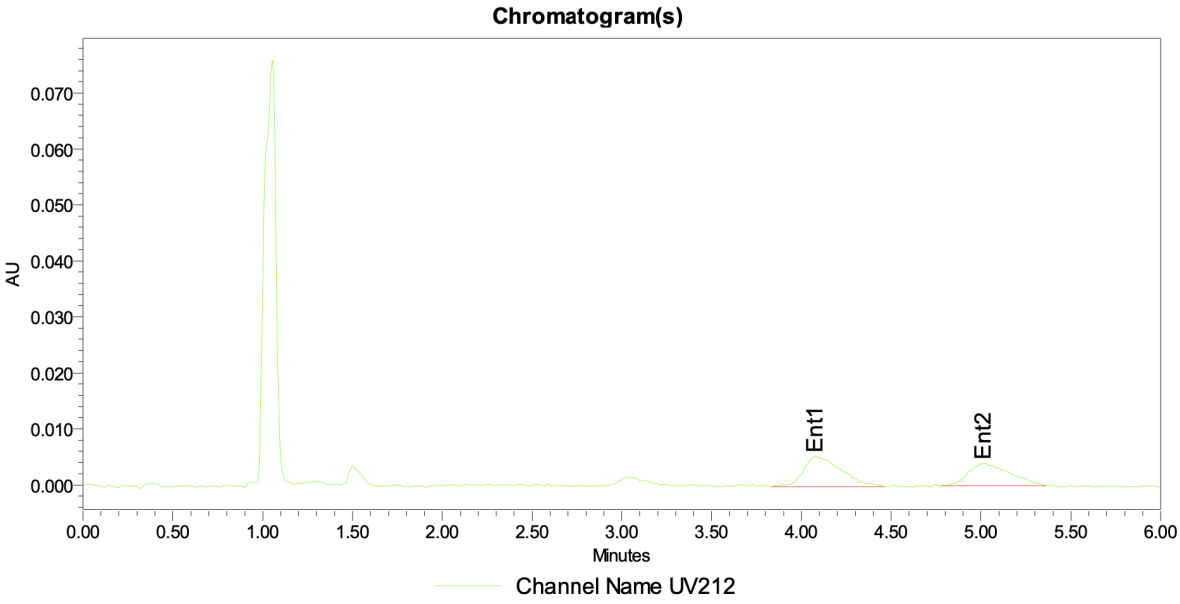


Following the general procedure, the reaction was performed with **36** (48.3 mg, 0.1 mmol), pivalic acid (61.2 mg, 6 equiv.), tetramethylammonium tetrafluoroborate (32 mg, 0.2 mmol), and 2.5 mL of CH_3OH. The resulting reaction mixture was electrolyzed under a constant current of 20 mA with rapid alternating polarity (100 ms, 5 Hz) for 12 F/mol. After electrolysis, 0.2 mL of sat. $NaHCO_3$ aq. was added to the reaction mixture and the resulting solution was stirred for 5 h to hydrolyze the hemiaminal to give the aldehyde **37**. Then the mixture was poured into brine, followed by CH_2Cl_2 extraction. The crude reaction mixture was purified by pTLC (hexane/AcOEt = 10:1) to furnish aldehyde **37** (18.0 mg, 59%). The stereocenter is prone to epimerize, and ee analysis showed variable ee (60 and 40% ee) under the same reaction conditions.

^{1}H NMR (600 MHz, $CDCl_3$): δ 9.65 (d, J = 1.5 Hz, 1H), 6.39 (t, J = 2.3 Hz, 1H), 6.31 (d, J = 2.3 Hz, 2H), 3.78 (s, 6H), 3.51 (t, J =7.9 Hz, 1H), 2.35 – 2.29 (m, 1H), 2.24 – 2.15 (m, 2H), 1.98 – 1.91 (m, 1H), 1.42 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 200.0, 172.4, 161.5, 137.9, 107.1, 99.7, 80.6, 58.4, 55.5, 32.7, 28.2, 24.8.

HRMS (ESI-TOF, m/z): HRMS (ESI) Calcd for $[M+H]^+$ 309.1702; Found 309.1700.



Peak Info

	Channel Name	Name	RT	Area	Height (µV)	ent1	ent2	ee
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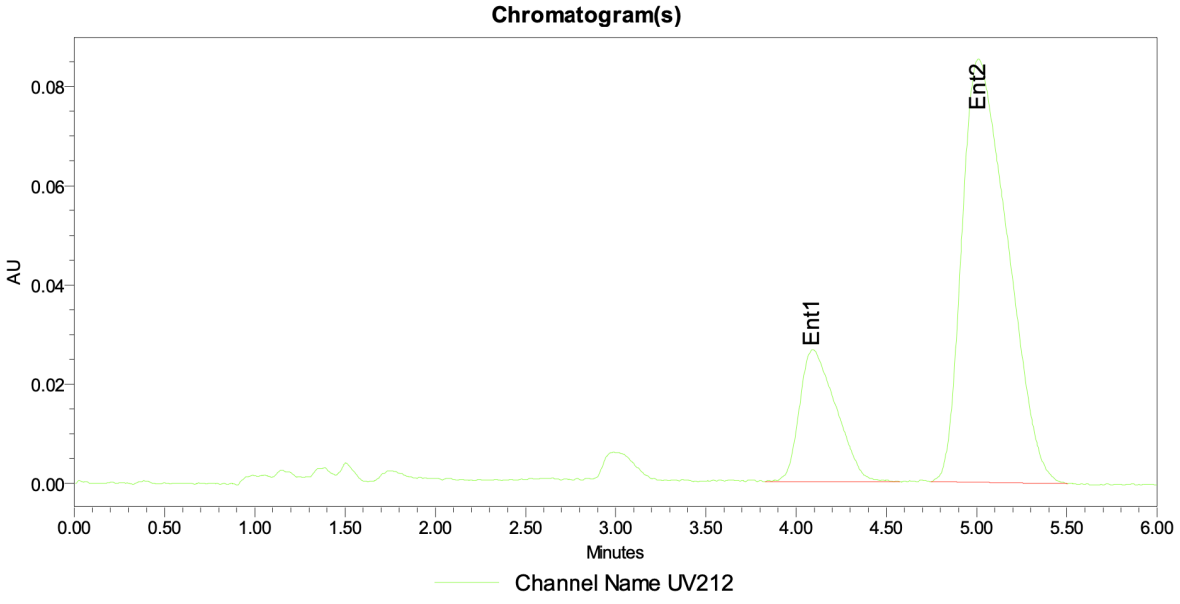
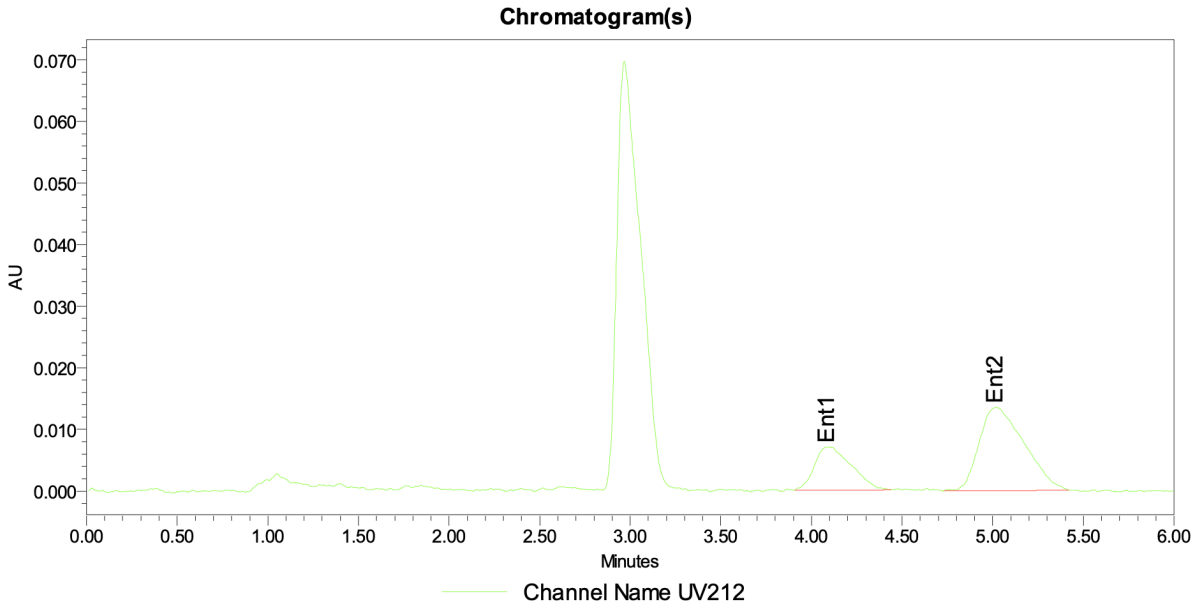
2	UV212	Ent2	5.02	64619	4038	55.03	44.97	10.06



Peak Info

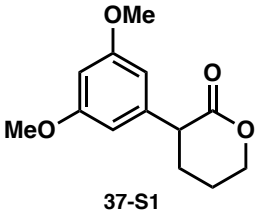
	Channel Name	Name	RT	Area	Height (µV)	ent1	ent2	ee
1	UV212	Ent1	4.09	374137	26562	20.03	79.97	-59.94
2	UV212	Ent2	5.01	1493737	85369	20.03	79.97	-59.94



Peak Info

	Channel Name	Name	RT	Area	Height (μV)	ent1	ent2	ee
1	UV212	Ent1	4.09	99321	7018	29.89	70.11	-40.22
2	UV212	Ent2	5.02	232959	13553	29.89	70.11	-40.22

[DIBAL reduction]



37-S1

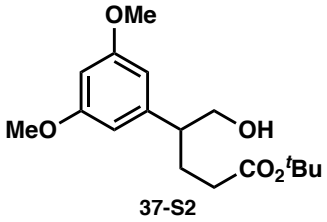
To a stirred solution of **36** (48.3 mg, 0.1 mmol) in THF in a screw-capped tube was added DIBAL solution (2 M in hexane, 0.11 mmol) at −78 ºC under Ar atmosphere. The solution was kept at −78 ºC for an additional 5 min and then slowly warmed up to r.t. The reaction was continued overnight, and then the reaction mixture was quenched with 1 M HCl. Extraction with AcOEt, followed by PTLC (hexane/AcOEt = 1:1) afforded **37-S1** in 10 % yield.

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.39 (s, 3H), 4.47 – 4.42 (m, 2H), 3.78 (s, 6H), 3.72 (dd, *J* = 10.0, 7.1 Hz, 1H), 2.30 – 2.26 (m, 1H), 2.12 – 2.07 (m, 1H), 2.06 – 1.97 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 172.2, 161.1, 141.2, 106.7, 99.3, 69.4, 55.5, 47.5, 28.2, 22.1.

HRMS (ESI-TOF, m/z): HRMS (ESI) Calcd for $[M+H]^+$ 237.1127; Found 237.1127.

[$LIBH_4$ reduction]

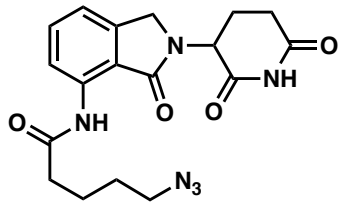


37-S2

To a stirred solution of **36** (48.3 mg, 0.1 mmol) in THF in a screw-capped tube was added $LiBH_4$ solution (0.1 M in THF, 0.04 mmol) at −78 ºC under Ar atmosphere. The solution was kept at −78 ºC for an additional 5 min and then slowly warmed up to r.t. The reaction was continued overnight, and then the reaction mixture was quenched with 1 M HCl. Extraction with AcOEt, followed by PTLC (hexane/AcOEt = 1:1) afforded **37-S2** in 36% yield.

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.35 (s, 3H), 3.78 (s, 6H), 3.73 (t, *J* = 6.4 Hz, 2H), 2.75 – 2.71 (m, 1H), 2.17 – 2.11 (m, 2H), 2.03 – 1.97 (m, 1H), 1.82 – 1.75 (m, 1H), 1.42 (s, 9H).
^{13}C NMR (151 MHz, $CDCl_3$): δ 172.7, 171.7, 160.4, 152.3, 139.6, 134.9, 128.5, 126.9, 106.2, 99.2, 65.4, 54.9, 47.4, 37.6, 32.8, 28.7, 27.7.
HRMS (ESI-TOF, m/z): HRMS (ESI) Calcd for $[M+H]^+$ 311.1858; Found 311.1854.

Compound 39

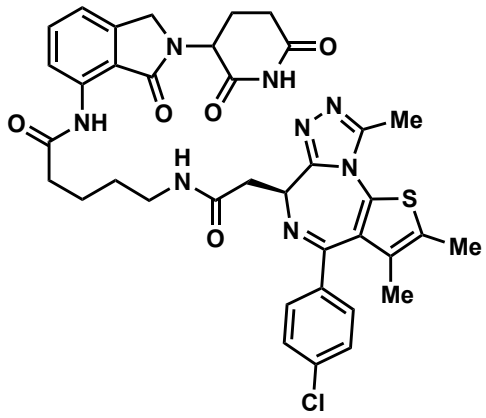


Following the general procedure, the reaction was performed with **38** (39.8 mg, 0.1 mmol), pivalic acid (102 mg, 1.0 mmol), tetramethylammonium tetrafluoroborate (32 mg, 0.2 mmol), and 2.5 mL of *t*BuOH/CH_3CN (1:1 v/v). The resulting reaction mixture was electrolyzed under a constant current of 20 mA with rapid alternating polarity (50 ms, 10 Hz) for 22 F/mol. The reaction mixture was concentrated, and the residue was passed through a short silica gel plug with CH_2Cl_2/CH_3OH (5:1) as eluent. The crude reaction mixture was purified by pTLC (CH_2Cl_2/AcOEt/CH_3OH = 1:1:0.1) to furnish the product **39** (30.0 mg, 75%). The position of the carbonyl group was determined by comparing ^{1}H NMR spectrum of **39** with that of *N*-(5-azidopentanoyl)lenalidomide (regioisomer of **39**) that was prepared separately. The ^{1}H NMR of **39** did not match with that of the regioisomer, leading to the above structural assignment.
^{1}H NMR (600 MHz, $CDCl_3$): δ 10.19 (s, 1H), 8.51 (d, *J* = 8.3 Hz, 1H), 8.09 (s, 1H), 7.54 (t, *J* = 8.0 Hz, 1H), 7.12 (d, *J* = 7.5 Hz, 1H), 5.08 (dd, *J* = 13.4, 5.1 Hz, 1H), 4.47 (d, *J* = 16.1 Hz, 1H), 4.35 (d, *J* = 16.1 Hz, 1H), 3.33 (t, *J* = 6.9 Hz, 2H), 2.94 (d, *J* = 16.8 Hz, 1H), 2.83 (ddd, *J* = 18.6, 13.6, 5.3 Hz, 1H), 2.49 (t, *J* = 7.4 Hz, 2H), 2.39 (ddd, *J* = 17.9, 13.3, 4.6 Hz, 1H), 2.26 – 2.22 (m, 1H), 1.84 (p, *J* = 7.4 Hz, 2H), 1.70 (p, *J* = 7.0 Hz, 2H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 171.6, 170.8, 170.6, 169.2, 141.7, 138.1, 134.1, 118.2, 117.3, 116.9, 52.0, 51.3, 47.5, 37.3, 31.7, 28.5, 23.5, 22.6.

HRMS (ESI-TOF, m/z): HRMS (ESI) Calcd for $[M+H]^+$ 385.1624; Found 385.1624.

Compound 41



Following the general procedure, the reaction was performed with **40** (34 mg, 0.045 mmol), pivalic acid (51 mg, 0.5 mmol), tetramethylammonium tetrafluoroborate (32 mg, 0.2 mmol), and 2.5 mL of CH_3OH. The resulting reaction mixture was electrolyzed under a constant current of 20 mA with rapid alternating polarity (50 ms, 10 Hz) for 12 F/mol. The reaction mixture was concentrated, and the residue was redissolved in CH_2Cl_2. An insoluble solid was filtered off, and the solution was concentrated again. To this crude mixture were added CH_2Cl_2 (1 mL), Et_3SiH (0.1 mL), and TFA (0.1 mL) at r.t. After 30 min, solvents were removed under reduced pressure, and the residue was treated with DDQ (0.03 mmol, 6.8 mg) in CH_2Cl_2 (1 mL) for 2 min to remove impurities that could contaminate the product during purification. The CH_2Cl_2 solution was then poured into sat. $NaHCO_3$ aq. and the crude product was extracted with CH_2Cl_2. pTLC purification (CH_2Cl_2/AcOEt/CH_3OH = 1:0.2:0.12) afforded **41** in 28% yield (9 mg). The regiochemistry was assigned by analogy to **39**.

^{1}H NMR (600 MHz, DMSO-d_6): δ 11.03 (s, 1H), 10.26 (s, 1H), 8.31 (d, J = 8.2 Hz, 1H), 8.21 (br, 1H), 7.56 (t, J = 7.9 Hz, 1H), 7.45 (d, J = 8.3 Hz, 2H), 7.40 (d, J = 8.2 Hz, 2H), 7.25 (d, J = 7.6 Hz, 1H), 5.06 (dd, J = 13.3, 5.2 Hz, 1H), 4.51 – 4.46 (m, 2H), 4.35 (d, J = 17.6 Hz, 1H), 3.25 (dd, J = 15.1, 8.7 Hz, 1H), 3.15 – 3.21 (m, 2H), 3.12 – 3.08 (m, 1H), 2.92 – 2.86 (m, 1H), 2.62 – 2.58 (m, 4H), 2.47 – 2.40 (m, 6H), 2.04 – 2.00 (m, 1H), 1.68 (p, J = 8.6 Hz, 2H), 1.60 (s, 3H), 1.52 (p, J = 7.2 Hz, 2H).

^{13}C NMR (151 MHz, DMSO-d_6): δ 172.8, 171.2, 170.8, 169.4, 169.2, 163.0, 155.1, 149.8, 142.6, 137.1, 136.7, 135.2, 133.2, 132.3, 130.7, 130.1, 129.8, 129.6, 128.5, 117.7, 117.0, 116.8, 53.9, 51.6, 48.6, 47.5, 38.13, 38.10, 37.7, 36.6, 31.2, 28.7, 22.4, 22.2, 14.0, 12.7, 11.3.

HRMS (ESI-TOF, m/z): HRMS (ESI) Calcd for $[M+H]^+$ 741.2374; Found 741.2371.

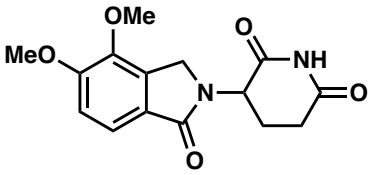
[DIBAL reduction]

To a stirred solution of **40** (0.01 mmol, 7.5 mg) in THF in a screw-capped tube was added DIBAL solution (2 M in hexane, 0.02 mmol) at −78 ºC under Ar atmosphere. The solution was kept at −78 ºC for an additional 5 min and then slowly warmed up to r.t. The reaction was continued overnight, and then the reaction mixture was quenched with aqueous citric acid solution (100 mg/mL). Extraction with CH_2Cl_2 resulted in mostly recovery of the starting material **40**.

[$LiBH_4$ reduction]

To a stirred solution of **40** (0.01 mmol, 7.5 mg) in THF in a screw-capped tube was added solution $LiBH_4$ (0.1 M in THF, 0.02 mmol) at −78 ºC under Ar atmosphere. The solution was kept at −78 ºC for an additional 5 min and then slowly warmed up to r.t. The reaction was continued overnight, and then the reaction mixture was quenched with aqueous citric acid solution (100 mg/mL). Extraction with CH_2Cl_2 afforded a complex mixture of products, which was confirmed by ^{1}H NMR analysis.

Compound 42



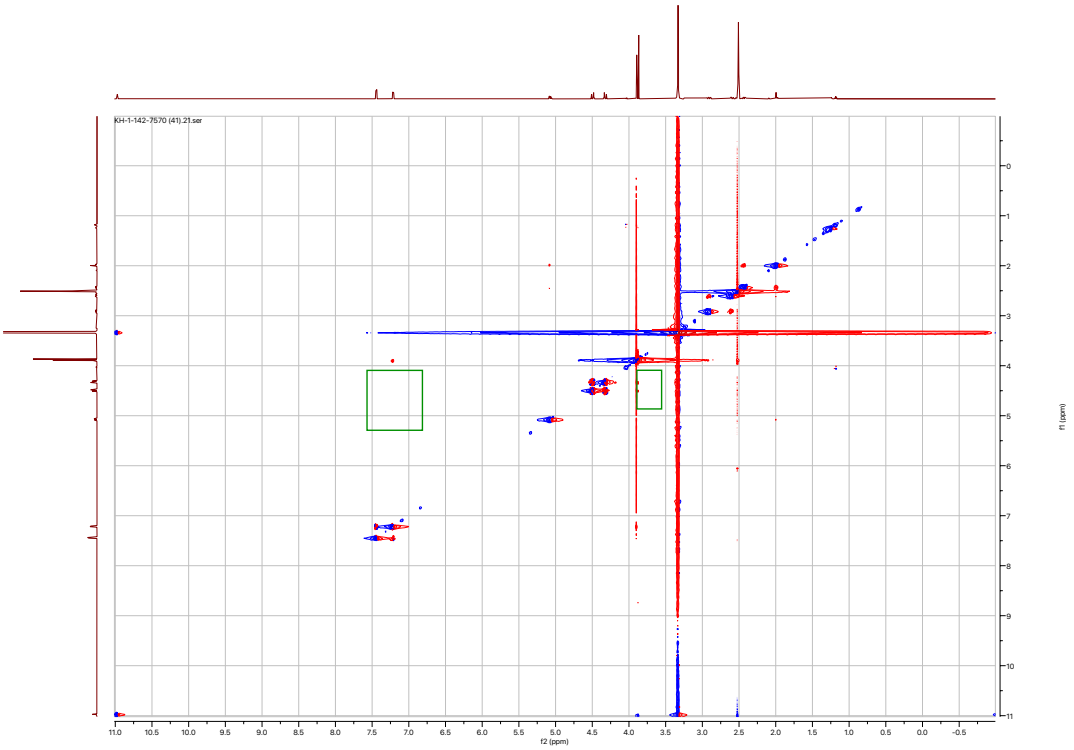
Following the general procedure, the reaction was performed with imide starting material (10 mg, 0.031 mmol), pivalic acid (30.6 mg, 0.3 mmol), tetramethylammonium tetrafluoroborate (40 mg, 0.25 mmol), and 2.5 mL of *t*BuOH/CH_3CN (1:1 v/v). The resulting reaction mixture was electrolyzed under a constant current of 20 mA with rapid alternating polarity (100 ms, 5 Hz) for 12 F/mol. The reaction mixture was then concentrated, and the crude mixture was subjected to pTLC purification (AcOEt) to afford **42** in 42% yield (4.0 mg). The regiochemistry was established by NOESY and HMBC.

^{1}H NMR (600 MHz, DMSO-*d*$_6$): δ 11.00 (s, 1H), 7.47 (d, *J* = 8.2 Hz, 1H), 7.24 (d, *J* = 8.3 Hz, 1H), 5.11 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.53 (d, *J* = 16.8 Hz, 1H), 4.35 (d, *J* = 16.8 Hz, 1H), 3.93 (s, 3H), 3.90 (s, 3H), 2.94 (ddd, *J* = 17.2, 13.7, 5.4 Hz, 1H), 2.66 – 2.55 (m, 1H), 2.47 (td, *J* = 13.1, 4.5 Hz, 1H), 2.06 – 1.98 (m, 1H).

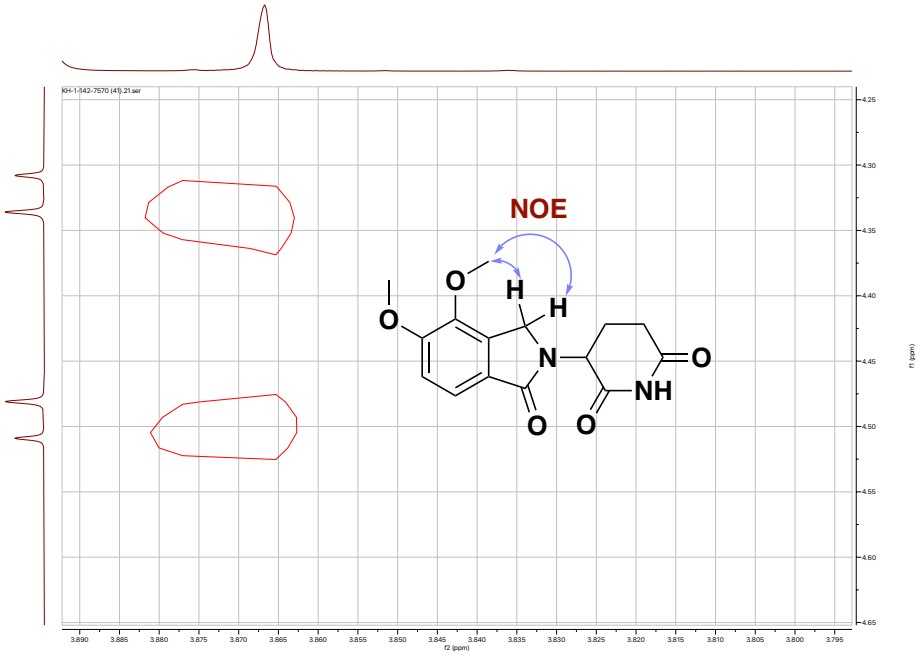
^{13}C NMR (151 MHz, DMSO-*d*$_6$): δ 171.1, 167.7, 154.5, 143.3, 133.2, 125.1, 118.8, 113.3, 59.7, 56.3, 51.6, 45.0, 31.2, 22.4.

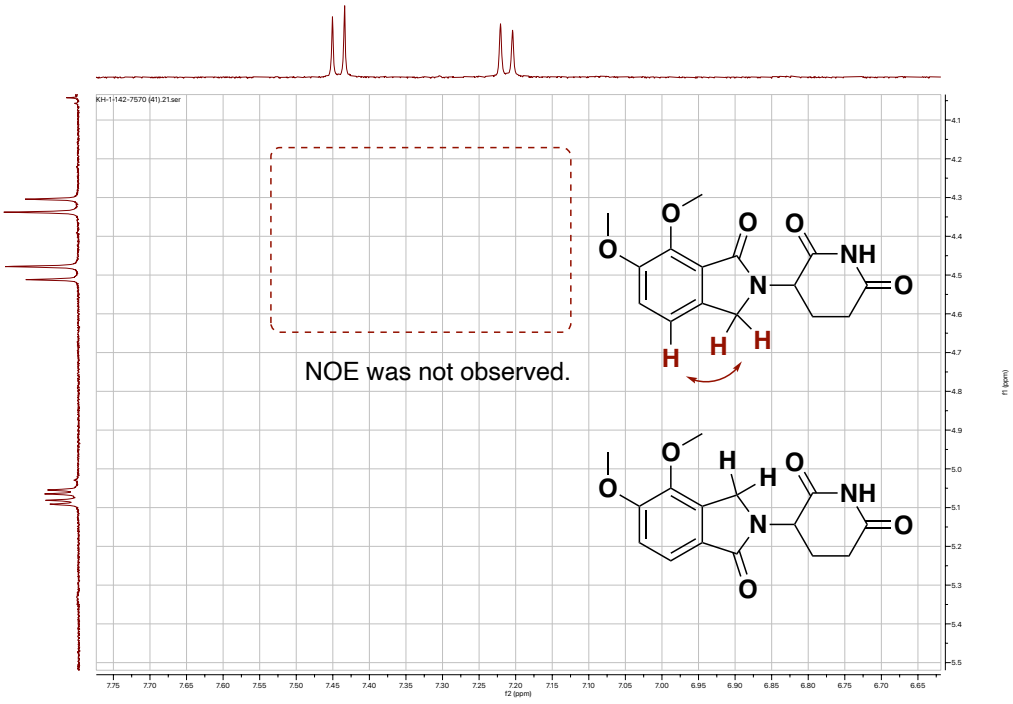
HRMS (ESI-TOF, m/z): HRMS (ESI) Calcd for $[M+H]^+$ 305.1137; Found 305.1136.

NOESY of compound **42**:



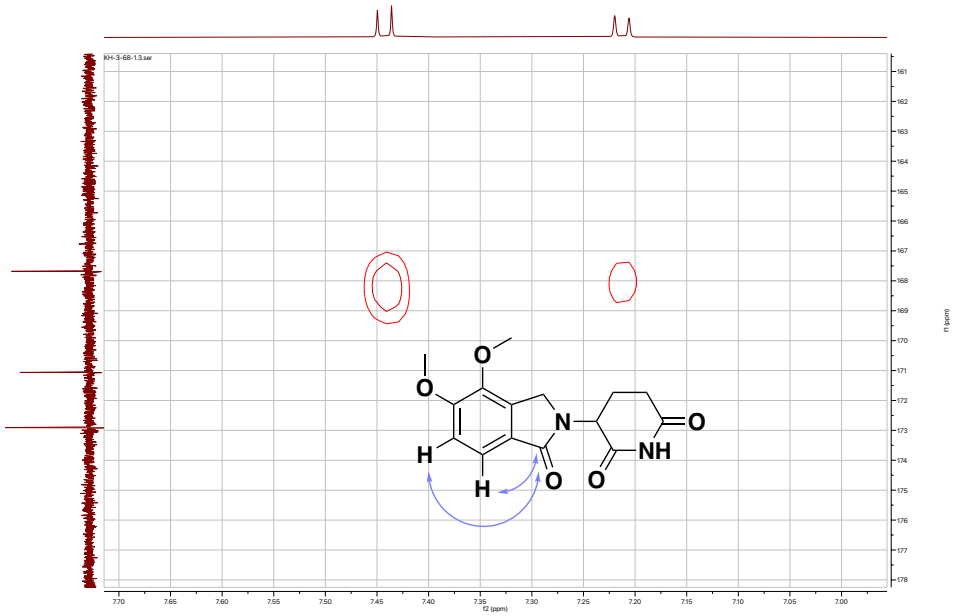
The areas highlighted with a green frame are magnified below.


NOE
O
H
H
O
N
O
NH
O
O

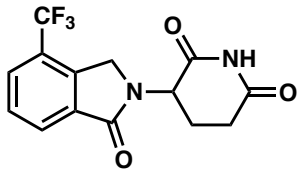

NOE was not observed.
O
O
O
NH
O
N
H
H
H
O
H
H
O
NH
O
N
O

HMBC of compound **42**:

The area highlighted with a green frame is magnified below.



Compound 43



Following the general procedure, the reaction was performed with imide starting material (10 mg, 0.031 mmol), pivalic acid (30.6 mg, 0.3 mmol), tetramethylammonium tetrafluoroborate (40 mg, 0.25 mmol), and 2.5 mL of CH_3OH. The resulting reaction mixture was electrolyzed under a constant current of 20 mA with rapid alternating polarity (50 ms, 10 Hz) for 12 F/mol. The reaction mixture was then concentrated, and the crude mixture was subjected to pTLC purification (CH_2Cl_2/ CH_3OH = 1:0.1) to afford **43** in 50% yield (4.8 mg). The regiochemistry was established by NOESY and HMBC.

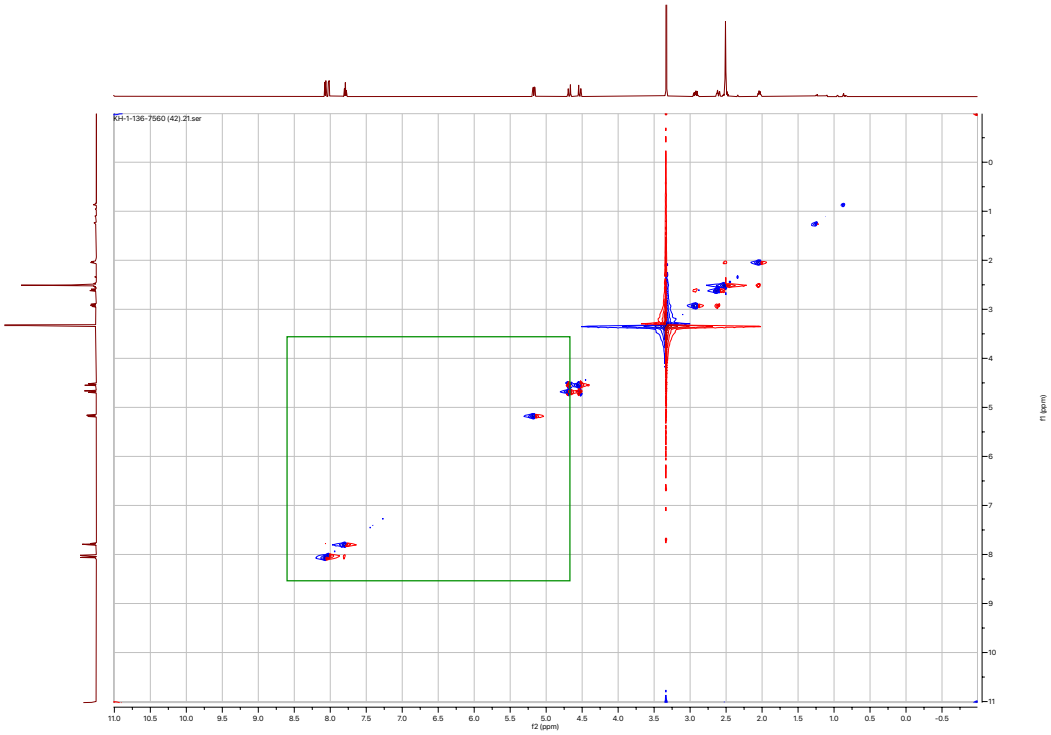
^{1}H NMR (600 MHz, DMSO-*d*$_6$): δ 11.05 (s, 1H), 8.10 (d, *J* = 7.6 Hz, 1H), 8.05 (dt, *J* = 7.7, 0.9 Hz, 1H), 7.82 (td, *J* = 7.7, 1.1 Hz, 1H), 5.20 (dd, *J* = 13.4, 5.1 Hz, 1H), 4.71 (d, *J* = 17.9 Hz, 1H), 4.56 (d, *J* = 17.9 Hz, 1H), 2.95 (ddd, *J* = 17.3, 13.6, 5.4 Hz, 1H), 2.68 – 2.60 (m, 1H), 2.55 – 2.45 (m, 1H), 2.07 (dtd, *J* = 12.7, 5.3, 2.2 Hz, 1H).

^{13}C NMR (151 MHz, DMSO-*d*$_6$): δ 172.8, 170.8, 166.5, 139.0 (q, $J_{C\text{-}F}$ = 3.0 Hz), 133.4, 129.4, 128.8 (q, $J_{C\text{-}F}$ = 3.0 Hz), 124.3 (q, $J_{C\text{-}F}$ = 34.7 Hz), 123.8 (q, $J_{C\text{-}F}$ = 273 Hz), 51.8, 46.6, 31.2, 22.2.

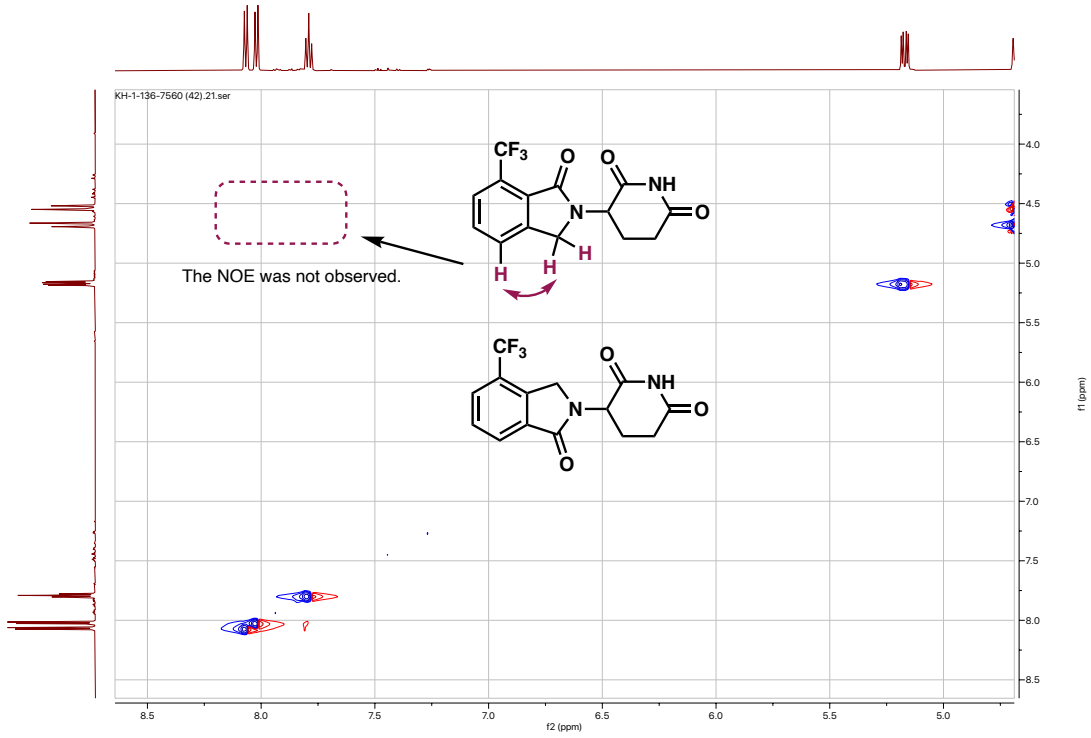
^{19}F NMR (376 MHz, DMSO): δ -63.01.

HRMS (ESI-TOF, m/z): HRMS (ESI) Calcd for $[M+H]^+$ 313.0800; Found 313.0796.

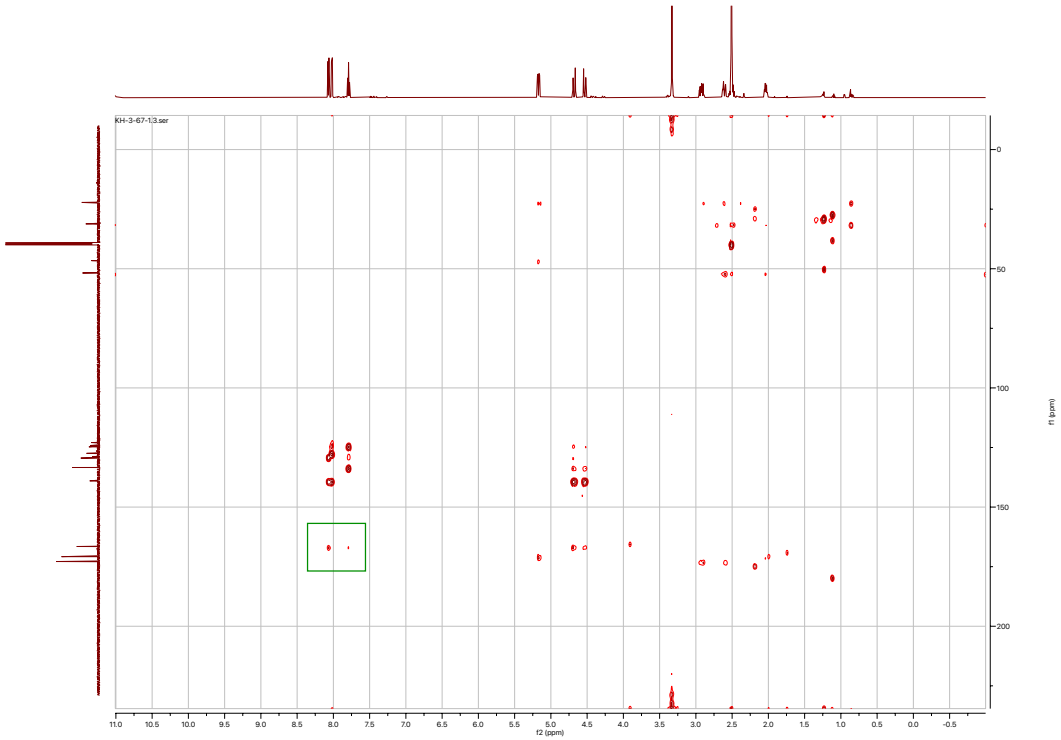
NOESY of compound **43**:



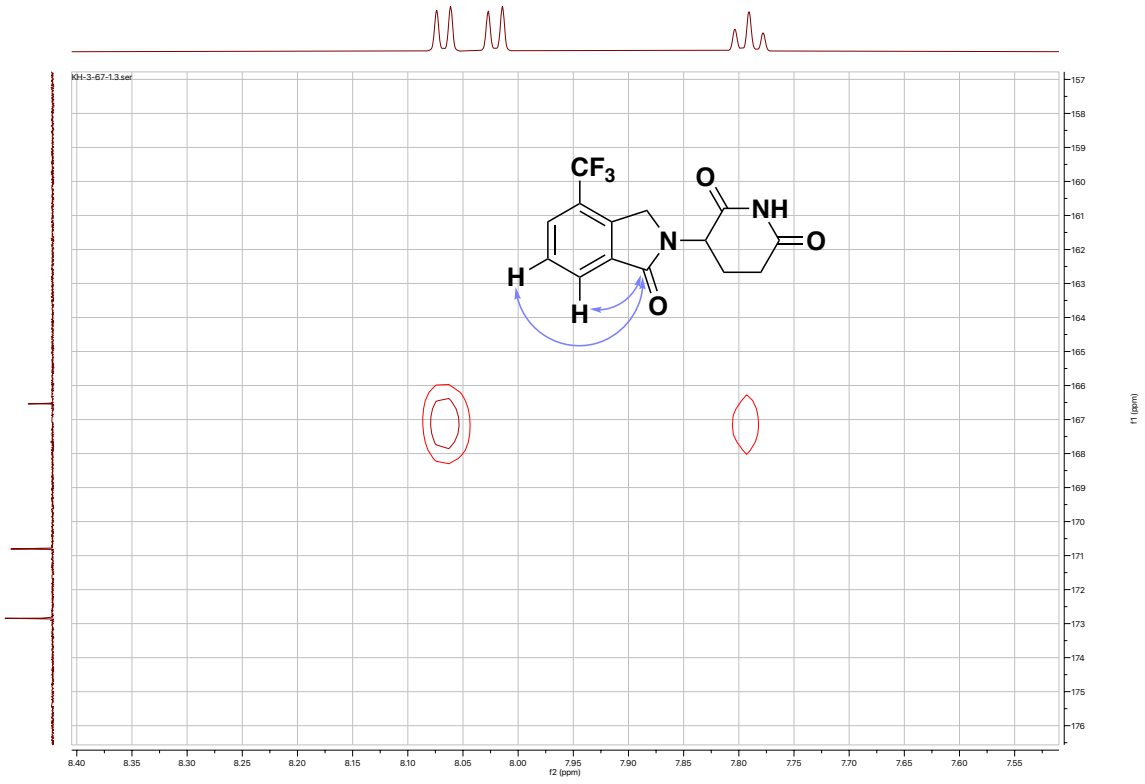
The area highlighted with a green frame is magnified below.



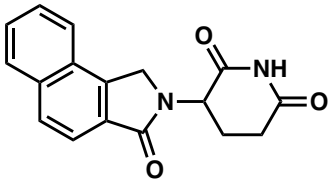
HMBC of compound **43**:



The area highlighted with a green frame is magnified below.



Compound 44



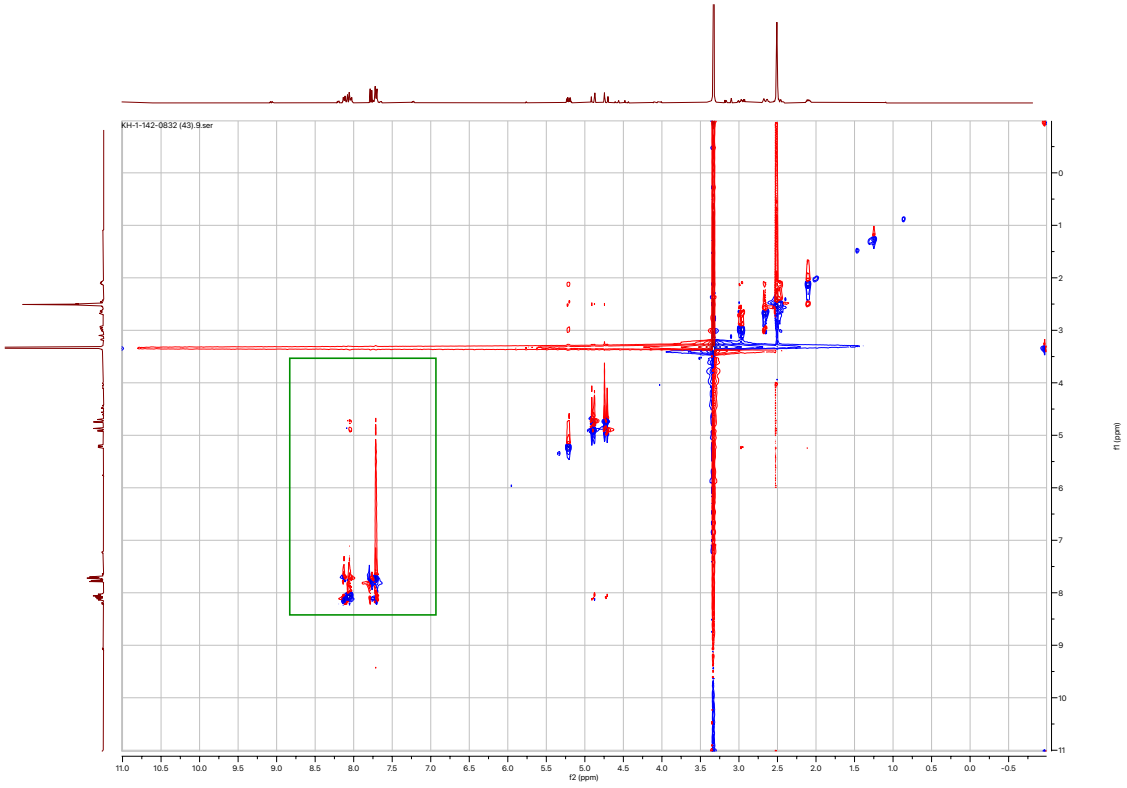
Following the general procedure, the reaction was performed with imide starting material (6 mg, 0.019 mmol), pivalic acid (30.6 mg, 0.3 mmol), tetramethylammonium tetrafluoroborate (40 mg, 0.25 mmol), and 2.5 mL of CH_3OH. The resulting reaction mixture was electrolyzed under a constant current of 20 mA with rapid alternating polarity (50 ms, 10 Hz) for 12 F/mol. The reaction mixture was then concentrated, and the crude mixture was subjected to pTLC purification (CH_2Cl_2/CH_3OH = 1:0.1) to afford **44** in 46% yield (2.6 mg). The regiochemistry was established by the NOESY.

^{1}H NMR (600 MHz, DMSO-*d*$_6$): δ 11.07 (s, 1H), 8.19 – 8.13 (m, 1H), 8.12 – 8.04 (m, 2H), 7.81 (d, *J* = 8.3 Hz, 1H), 7.77 – 7.71 (m, 2H), 5.24 (dd, *J* = 13.3, 5.2 Hz, 1H), 4.98 – 4.86 (d, *J* = 18.0 Hz, 1H), 4.79 – 4.71 (d, *J* = 18.0 Hz, 1H), 3.00 (ddd, *J* = 17.4, 13.7, 5.4 Hz, 1H), 2.69 (ddd, *J* = 17.4, 4.4, 2.3 Hz, 1H), 2.49 (td, *J* = 13.2, 4.5 Hz, 1H), 2.13 (dtd, *J* = 12.8, 5.4, 2.3 Hz, 1H).

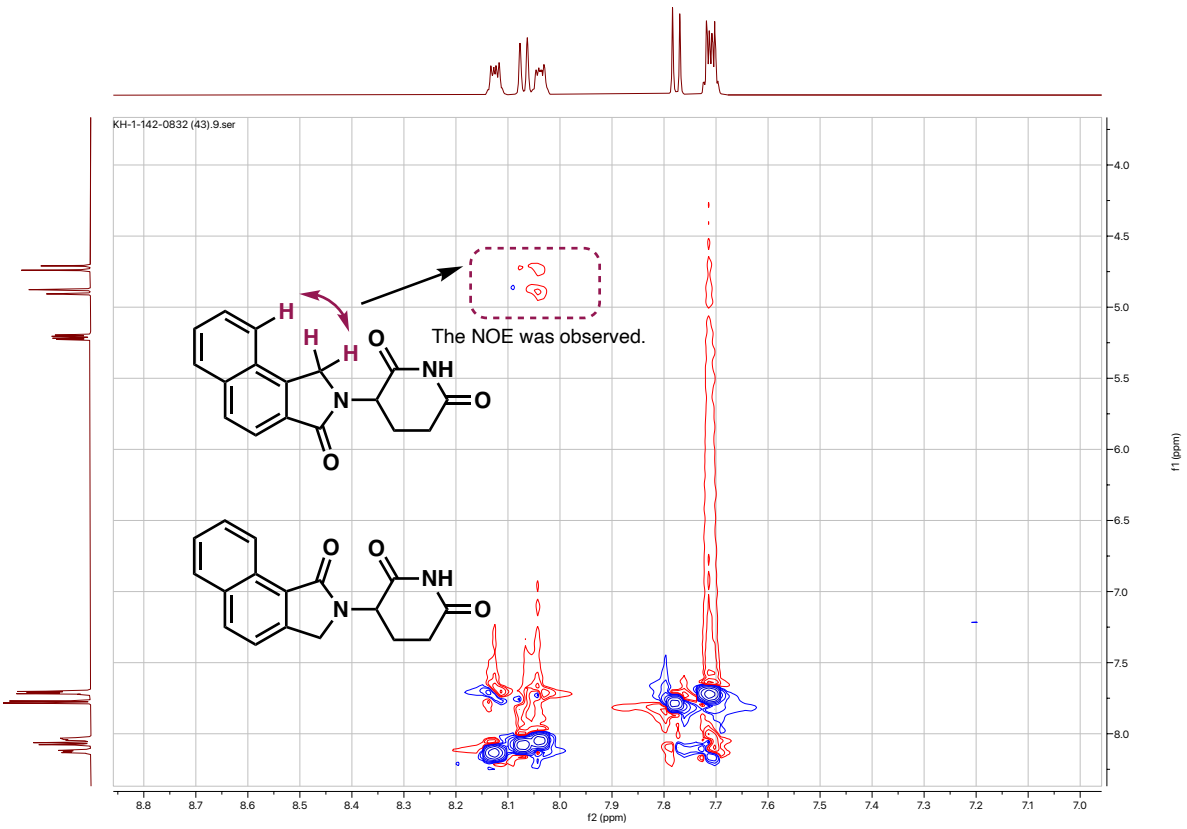
^{13}C NMR (151 MHz, DMSO-d_6): δ 172.9, 171.2, 168.8, 141.5, 134.5, 128.94, 128.93, 128.86, 128.1, 127.6, 127.5, 123.8, 119.4, 51.7, 46.7, 31.3, 22.8.

HRMS (ESI-TOF, m/z): HRMS (ESI) Calcd for $[M+H]^+$ 295.1083; Found 295.1082.

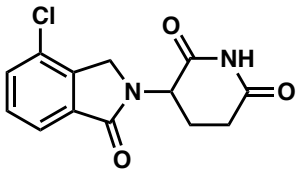
NOESY of compound **44**:



The area highlighted with a green frame is magnified below.



Compound 45



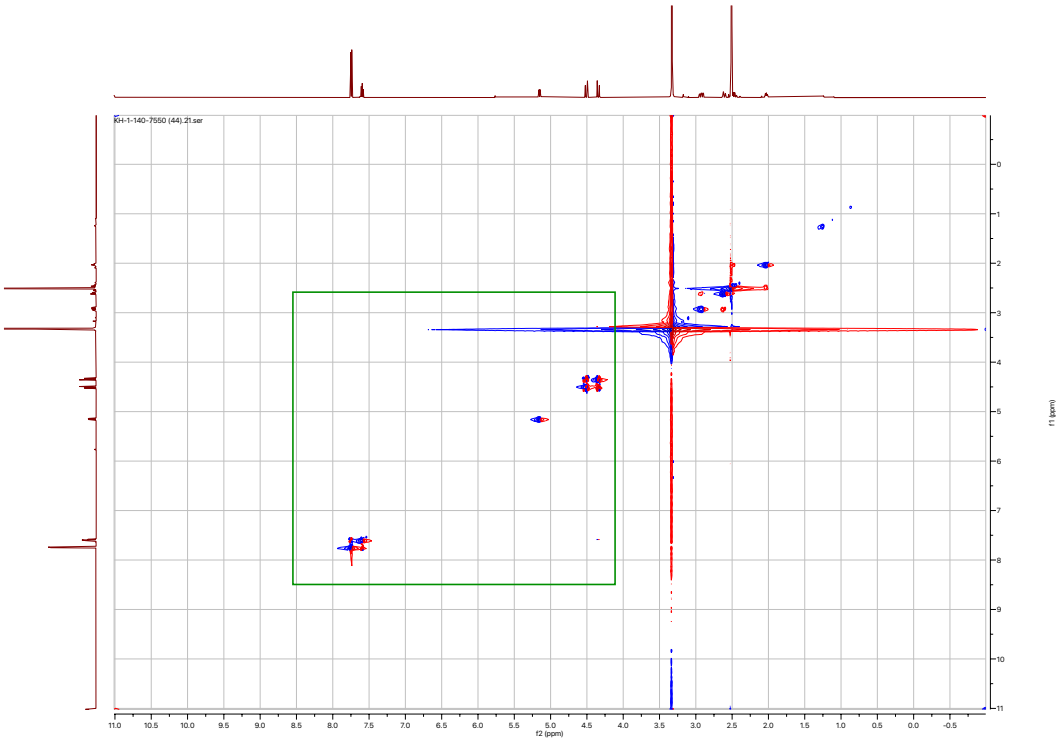
Following the general procedure, the reaction was performed with imide starting material (10 mg, 0.034 mmol), pivalic acid (30.6 mg, 0.3 mmol), tetramethylammonium tetrafluoroborate (40 mg, 0.25 mmol), trifluoroacetic acid (57 mg, 0.5 mmol), and 2.5 mL of *t*BuOH/CH_3CN (1:1 v/v). The resulting reaction mixture was electrolyzed under a constant current of 20 mA with rapid alternating polarity (100 ms, 5 Hz) for 12 F/mol. The reaction mixture was then concentrated, and the crude mixture was subjected to pTLC purification (CH_2Cl_2/CH_3OH = 1:0.1) to afford **45** in 17% yield (1.6 mg). The regiochemistry was established by NOESY, HMBC and ^{1}H NMR similarity to compound **51**.

^{1}H NMR (600 MHz, DMSO-d_6): δ 11.05 (s, 1H), 7.78 (m, 2H), 7.63 (dd, *J* = 8.1, 7.3 Hz, 1H), 5.18 (dd, *J* = 13.3, 5.2 Hz, 1H), 4.54 (d, *J* = 17.6 Hz, 1H), 4.37 (d, *J* = 17.6 Hz, 1H), 2.96 (ddd, *J* = 17.4, 13.7, 5.5 Hz, 1H), 2.68 – 2.60 (m, 1H), 2.53 – 2.45 (m, 1H), 2.06 (dtd, *J* = 12.7, 5.3, 2.3 Hz, 1H).

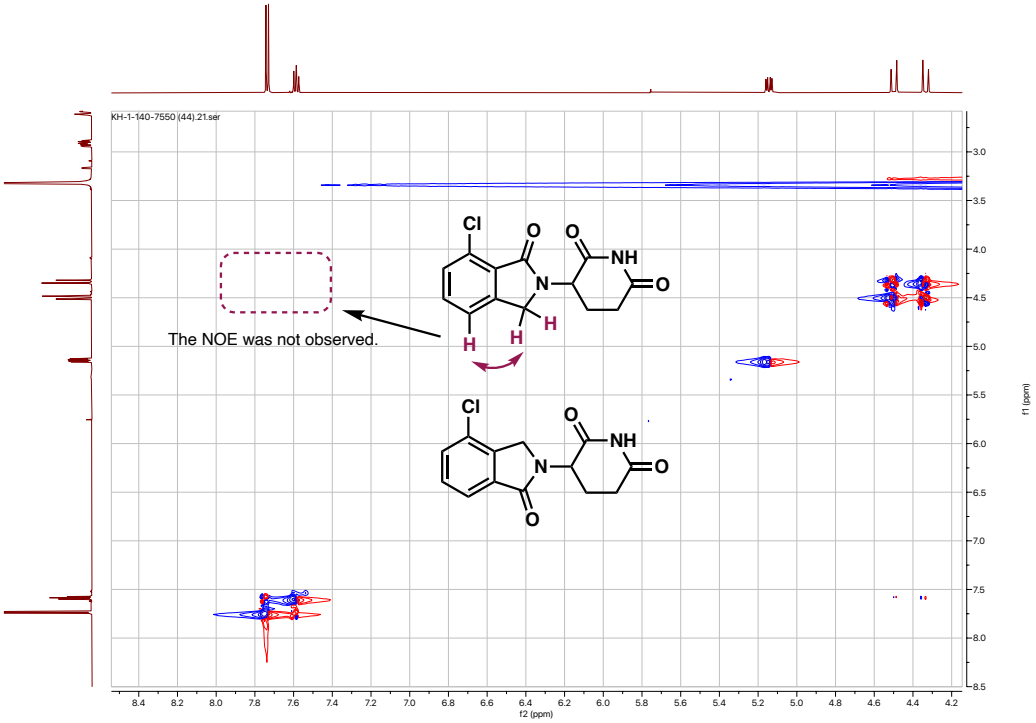
^{13}C NMR (151 MHz, DMSO-d_6): δ 172.8, 170.8, 167.1, 139.9, 133.9, 131.7, 130.4, 128.4, 122.1, 51.7, 46.4, 31.2, 22.3.

HRMS (ESI-TOF, m/z): HRMS (ESI) Calcd for $[M+H]^+$ 279.0536; Found 279.0532.

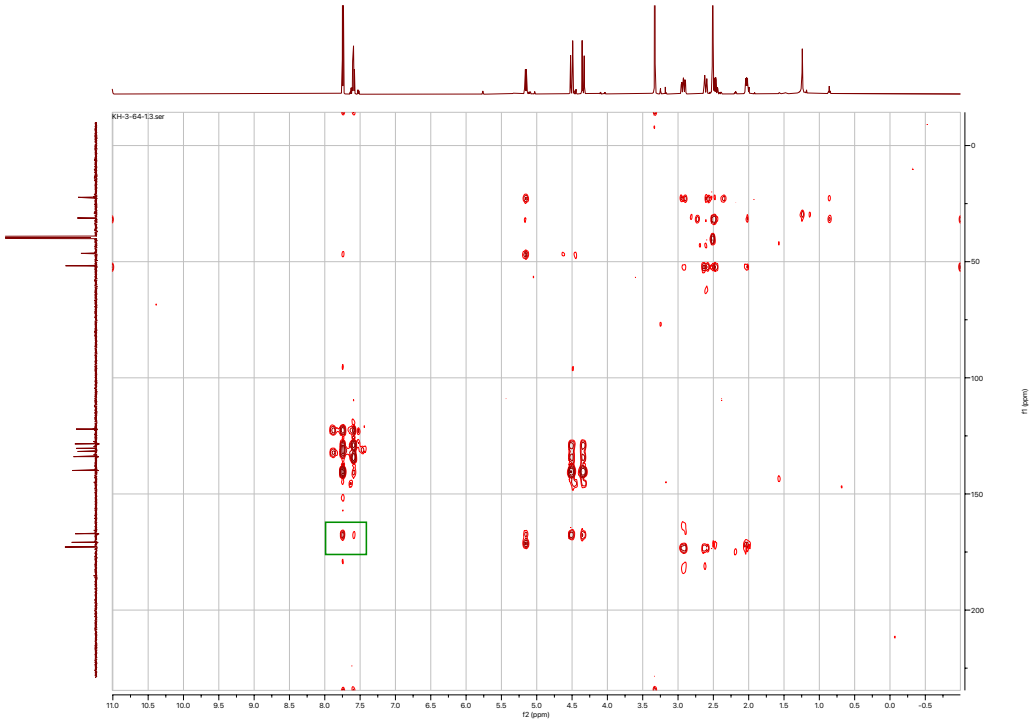
NOESY of compound **45**:



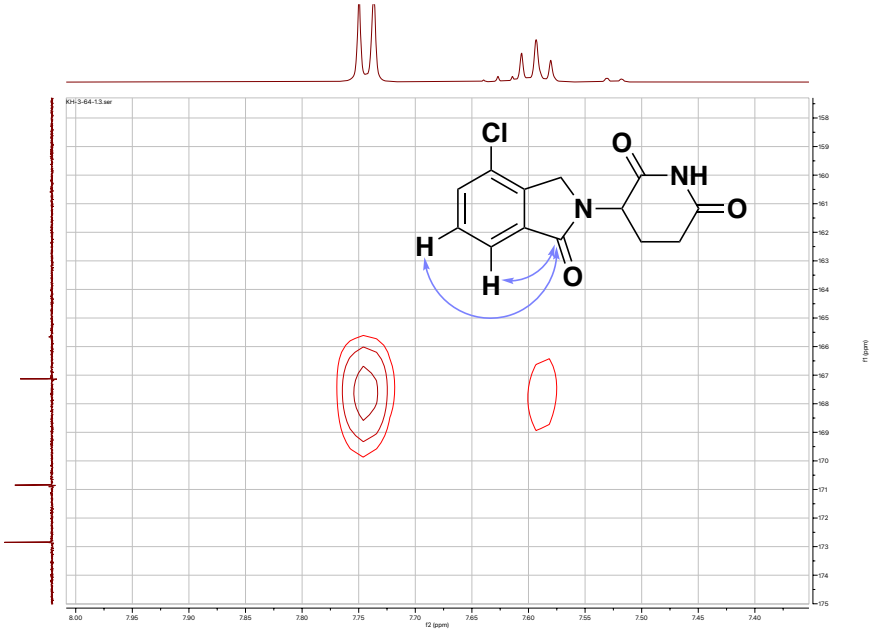
The area highlighted with a green frame is magnified below.



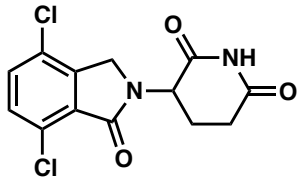
HMBC of compound **45**:



The area highlighted with a green frame is magnified below.



Compound 46



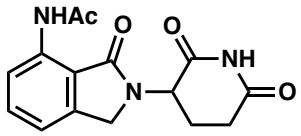
Following the general procedure, the reaction was performed with imide starting material (10 mg, 0.030 mmol), pivalic acid (30.6 mg, 0.3 mmol), tetramethylammonium tetrafluoroborate (40 mg, 0.25 mmol), trifluoroacetic acid (57 mg, 0.5 mmol), and 2.5 mL of *t*BuOH/CH_3CN (1:1 v/v). The resulting reaction mixture was electrolyzed under a constant current of 20 mA with rapid alternating polarity (100 ms, 5 Hz) for 32 F/mol. The reaction mixture was then concentrated, and the crude mixture was subjected to pTLC purification (CH_2Cl_2/CH_3OH = 1:0.1) to afford **46** in 46% yield (4.3 mg).

^{1}H NMR (600 MHz, DMSO-*d*$_6$): δ 11.06 (s, 1H), 7.77 (d, *J* = 8.4 Hz, 1H), 7.63 (d, *J* = 8.5 Hz, 1H), 5.16 (dd, *J* = 13.3, 5.2 Hz, 1H), 4.51 (d, *J* = 18.0 Hz, 1H), 4.35 (d, *J* = 17.9 Hz, 1H), 2.95 (ddd, *J* = 17.2, 13.7, 5.4 Hz, 1H), 2.64 (ddd, *J* = 17.4, 4.5, 2.3 Hz, 1H), 2.54 – 2.45 (m, 1H), 2.06 (dtd, *J* = 12.8, 5.4, 2.3 Hz, 1H).

^{13}C NMR (151 MHz, DMSO-*d*$_6$): δ 172.82, 170.71, 164.94, 142.52, 132.86, 131.37, 129.21, 128.60, 127.21, 51.77, 45.79, 31.14, 22.09.

HRMS (ESI-TOF, m/z): HRMS (ESI) Calcd for $[M+Na]^+$ 313.0147; Found 313.0149.

Compound 47



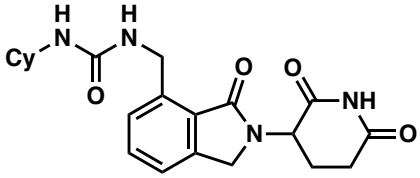
Following the general procedure, the reaction was performed with imide starting material (10 mg, 0.032 mmol), pivalic acid (30.6 mg, 0.3 mmol), tetramethylammonium tetrafluoroborate (32 mg, 0.2 mmol), and 2.5 mL of *t*BuOH/CH_3CN (1:1 v/v). The resulting reaction mixture was electrolyzed under a constant current of 20 mA with rapid alternating polarity (100 ms, 5 Hz) for 12 F/mol. The reaction mixture was then concentrated, and the crude mixture was subjected to pTLC purification (CH_2Cl_2/AcOEt/CH_3OH = 1:1:0.1) to afford **47** in 23% yield (2.3 mg). The regiochemistry was assigned by analogy to **39**.

^{1}H NMR (600 MHz, CD_3OD): δ 8.35 (d, *J* = 8.2 Hz, 1H), 7.56 (dd, *J* = 8.3, 7.6 Hz, 1H), 7.25 (dd, *J* = 7.6, 0.9 Hz, 1H), 5.11 (dd, *J* = 13.4, 5.2 Hz, 1H), 4.50 (d, *J* = 17.1 Hz, 1H), 4.44 (d, *J* = 17.1 Hz, 1H), 2.91 (ddd, *J* = 17.7, 13.6, 5.4 Hz, 1H), 2.79 (ddd, *J* = 17.7, 4.7, 2.5 Hz, 1H), 2.50 (qd, *J* = 13.4, 4.6 Hz, 1H), 2.22 – 2.16 (m, 4H).

^{13}C NMR (151 MHz, DMSO-d_6): δ 172.9, 170.8, 169.1, 168.6, 142.7, 137.1, 133.2, 117.7, 117.0, 116.8, 51.7, 47.6, 31.2, 24.5, 22.4.

HRMS (ESI-TOF, m/z): HRMS (ESI) Calcd for $[M+H]^+$ 302.1141; Found 302.1141.

Compound 48



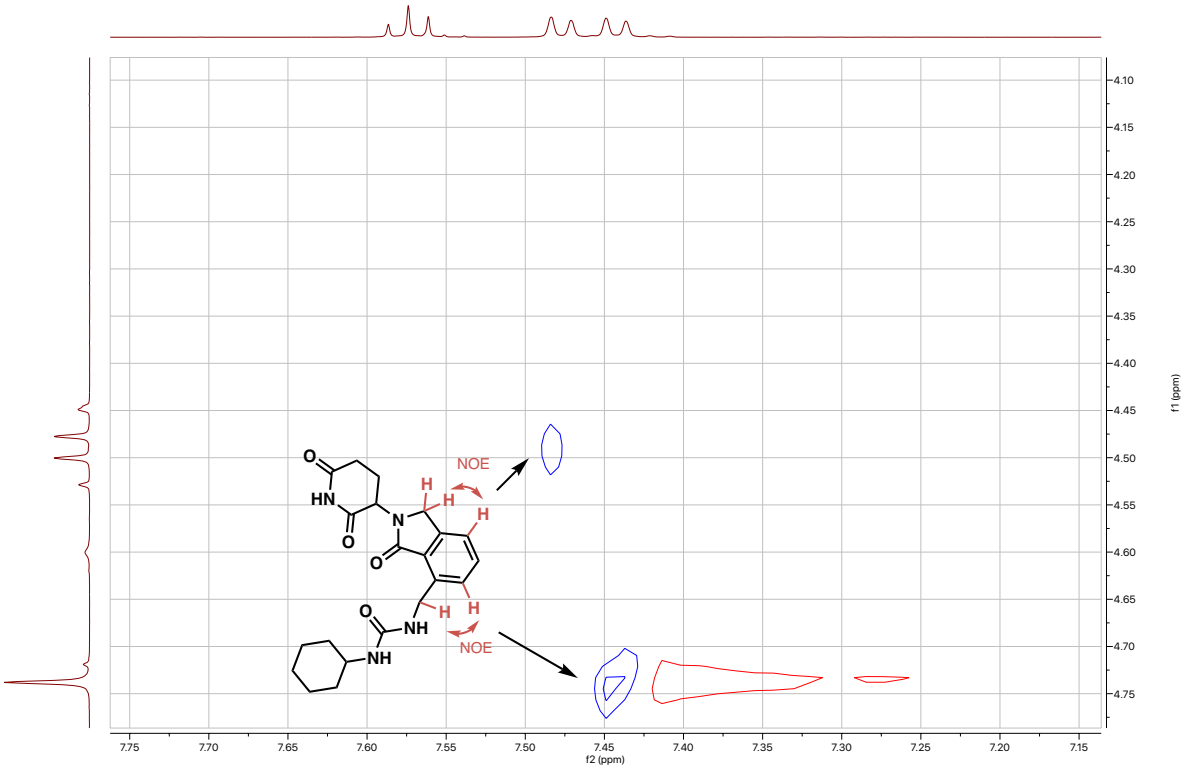
Following the general procedure, the reaction was performed with imide starting material (10 mg, 0.024 mmol), pivalic acid (30.6 mg, 0.3 mmol), tetramethylammonium tetrafluoroborate (32 mg, 0.2 mmol), and 2.5 mL of *t*BuOH/CH_3CN (1:1 v/v). The resulting reaction mixture was electrolyzed under a constant current of 20 mA with rapid alternating polarity (100 ms, 5 Hz) for 12 F/mol. The reaction mixture was then concentrated, and the crude mixture was subjected to pTLC purification (CH_2Cl_2/AcOEt/CH_3OH = 1:0.2:0.05) to afford **48** in 48% yield (4.3 mg). Regiochemistry was assigned by NOE.

^{1}H NMR (600 MHz, CD_3OD): δ 7.55 (t, *J* = 7.6 Hz, 1H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.42 (d, *J* = 7.6 Hz, 1H), 5.13 (dd, *J* = 13.3, 5.2 Hz, 1H), 4.72 (s, 2H), 4.49 (d, *J* = 17.0 Hz, 1H), 4.44 (d, *J* = 17.0 Hz, 1H), 3.45 – 3.41 (m, 1H), 2.91 (ddd, *J* = 17.6, 13.6, 5.4 Hz, 1H), 2.79 (ddd, *J* = 17.7, 4.6, 2.4 Hz, 1H), 2.50 (qd, *J* = 13.3, 4.6 Hz, 1H), 2.19 – 2.15 (m, 1H), 1.85 – 1.82 (m, 2H), 1.72 – 1.69 (m, 2H), 1.60 – 1.58 (m, 1H), 1.36 – 1.29 (m, 3H), 1.19 – 1.11 (m, 2H).

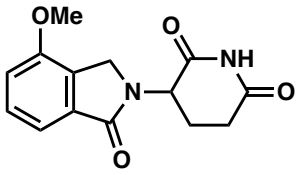
^{13}C NMR (151 MHz, CD_3OD): δ 174.7, 172.4, 171.6, 160.3, 144.5, 140.2, 133.1, 128.9, 123.1, 53.5, 40.8, 34.7, 32.4, 26.7, 26.1, 24.1.

HRMS (ESI-TOF, m/z): HRMS (ESI) Calcd for $[M+H]^+$ 399.2032; Found 399.2028.

NOESY of compound **48** for regiochemical assignment. The area highlighted with a green circle is magnified below.



Compound 49



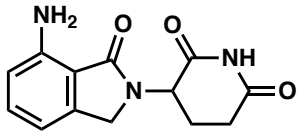
Following the general procedure, the reaction was performed with imide starting material (10 mg, 0.037 mmol), pivalic acid (30.6 mg, 0.3 mmol), tetramethylammonium tetrafluoroborate (32 mg, 0.2 mmol), and 2.5 mL of *t*BuOH/CH_3CN (1:1 v/v). The resulting reaction mixture was electrolyzed under a constant current of 20 mA with rapid alternating polarity (100 ms, 5 Hz) for 12 F/mol. The reaction mixture was then concentrated, and the crude mixture was subjected to pTLC purification (CH_2Cl_2/AcOEt/CH_3OH = 5:1:0.5) to afford **49** in 55% yield (5.1 mg). The regiochemistry was assigned based on a similar appearance of aromatic protons in ^{1}H NMR to a known compound.(*17*)

^{1}H NMR (600 MHz, CD_3OD): δ 7.50 (t, *J* = 7.8 Hz, 1H), 7.39 (d, *J* = 7.5 Hz, 1H), 7.22 (d, *J* = 8.1 Hz, 1H), 5.14 (dd, *J* = 13.4, 5.2 Hz, 1H), 4.45 (d, *J* = 17.2 Hz, 1H), 4.39 (d, *J* = 17.3 Hz, 1H), 3.94 (s, 3H), 2.90 (ddd, *J* = 17.6, 13.6, 5.4 Hz, 1H), 2.78 (ddd, *J* = 17.7, 4.6, 2.4 Hz, 1H), 2.51 (qd, *J* = 13.3, 4.6 Hz, 1H), 2.17 (ddd, *J* = 10.5, 5.4, 2.7 Hz, 1H).

^{13}C NMR (151 MHz, CD_3OD): δ 174.7, 172.2, 171.6, 156.3, 134.2, 131.4, 131.2, 116.3, 114.8, 56.2, 53.7, 46.9, 32.4, 24.1.

HRMS (ESI-TOF, m/z): HRMS (ESI) Calcd for $[M+H]^+$ 275.1032; Found 275.1031.

Compound 50



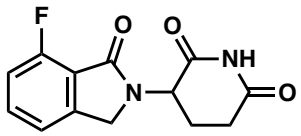
Following the general procedure, the reaction was performed with imide starting material (10 mg, 0.037 mmol), pivalic acid (30.6 mg, 0.3 mmol), tetramethylammonium tetrafluoroborate (32 mg, 0.2 mmol), *i*Pr$_2$NEt (25.8 mg, 0.2 mmol), and 2.5 mL of *t*BuOH/CH_3CN (1:1 v/v). The resulting reaction mixture was electrolyzed under a constant current of 20 mA with rapid alternating polarity (100 ms, 5 Hz) for 28 F/mol. The reaction mixture was then concentrated, and the crude mixture was subjected to pTLC purification (CH_2Cl_2/AcOEt/CH_3OH = 1:1:0.1) to afford **50** in 32% yield (3.0 mg). The regiochemistry was assigned based on the mismatch to ^{1}H NMR of lenalidomide (regioisomer of **50,** commercially available).

^{1}H NMR (600 MHz, CD_3OD): δ 7.27 (t, *J* = 7.8 Hz, 1H), 6.70 (d, *J* = 7.3 Hz, 1H), 6.64 (d, *J* = 8.2 Hz, 1H), 5.04 (dd, *J* = 13.4, 5.2 Hz, 1H), 4.37 (d, *J* = 16.7 Hz, 1H), 4.32 (d, *J* = 16.7 Hz, 1H), 2.89 (ddd, *J* = 17.6, 13.6, 5.4 Hz, 1H), 2.77 (ddd, *J* = 17.6, 4.6, 2.4 Hz, 1H), 2.45 (qd, *J* = 13.3, 4.6 Hz, 1H), 2.14 (ddd, *J* = 12.9, 5.4, 2.3 Hz, 1H).

^{13}C NMR (151 MHz, CD_3OD): δ 173.4, 171.6, 171.1, 146.9, 143.2, 133.1, 113.5, 113.0, 110.2, 51.7, 31.0, 22.8.

HRMS (ESI-TOF, m/z): HRMS (ESI) Calcd for $[M+H]^+$ 260.1035; Found 260.1031.

Compound 51



Following the general procedure, the reaction was performed with imide starting material (10 mg, 0.036 mmol), pivalic acid (30.6 mg, 0.3 mmol), tetramethylammonium tetrafluoroborate (32 mg, 0.2 mmol), and 2.5 mL of *t*BuOH/CH_3CN (1:1 v/v). The resulting reaction mixture was electrolyzed under a constant current of 20 mA with rapid alternating polarity (100 ms, 5 Hz) for 12 F/mol. The reaction mixture was then concentrated, and the crude mixture was subjected to pTLC purification (CH_2Cl_2/AcOEt/CH_3OH = 1:1:0.1, 1% TFA) to afford **51** in 28% yield (2.7 mg). The

regiochemistry was assigned based on ^{13}C NMR. The signal at 167.0 ppm (the lactam carbonyl carbon) appears as a doublet due to ^{13}C–F coupling.

^{1}H NMR (600 MHz, DMSO-d_6): δ 11.01 (s, 1H), 7.62 – 7.57 (m, 2H), 7.51 – 7.48 (m, 1H), 5.12 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.57 (d, *J* = 17.4 Hz, 1H), 4.40 (d, *J* = 17.3 Hz, 1H), 2.91 (ddd, *J* = 18.2, 13.6, 5.4 Hz, 1H), 2.62 – 2.59 (m, 1H), 2.44 (dd, *J* = 12.9, 4.9 Hz, 1H), 2.03 – 2.00 (m, 1H).

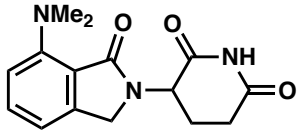
^{13}C NMR (151 MHz, DMSO-d_6): δ 172.9, 170.8, 167.0 (d, *J* = 1.9 Hz), 157.1 (d, *J* = 248.5 Hz), 134.9 (d, *J* = 4.8 Hz), 130.8 (d, *J* = 6.4 Hz), 127.9 (d, *J* = 18.3 Hz), 119.5 (d, *J* = 3.2 Hz), 118.5 (d, *J* = 19.3 Hz), 51.8, 44.3, 31.2, 22.3.

^{19}F NMR (376 MHz, DMSO): δ -122.46.

HRMS (ESI-TOF, m/z): HRMS (ESI) Calcd for $[M+H]^+$ 263.0832; Found 263.0828.

Compound 52

Following the general procedure, the reaction was performed with imide starting material (10 mg, 0.035 mmol), pivalic acid (30.6 mg, 0.3 mmol), tetramethylammonium tetrafluoroborate (32 mg, 0.2 mmol), *i*Pr$_2$NEt (25.8 mg, 0.2 mmol), and 2.5 mL of *t*BuOH/CH$_3$CN (1:1 v/v). The resulting reaction mixture was electrolyzed under a constant current of 20 mA with rapid alternating polarity (100 ms, 5 Hz) for 30 F/mol. The reaction mixture was then concentrated, and the crude mixture was subjected to pTLC purification (CH_2Cl_2/AcOEt/EtOH = 1:0.3:0.05) to afford **52a** in 7% yield (0.7 mg) and **52b** in 10% yield (1.0 mg). The regiochemistry was assigned based on the appearance of aromatic protons in the ^{1}H NMR. Namely, the aromatic protons of **52a** are analogous to those of **50**, whereas the aromatic protons of **52b** are analogous to those of lenalidomide.

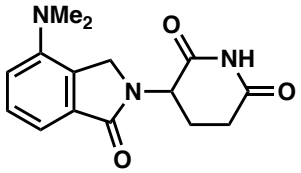


Compound 52a

^{1}H NMR (600 MHz, CD$_3$OD): δ 7.46 (dd, *J* = 8.2, 7.4 Hz, 1H), 7.02 (dd, *J* = 7.5, 0.9 Hz, 1H), 6.96 (dd, *J* = 8.2, 0.8 Hz, 1H), 5.08 (dd, *J* = 13.3, 5.2 Hz, 1H), 4.41 (d, *J* = 16.9 Hz, 1H), 4.36 (d, *J* = 16.9 Hz, 1H), 2.93 (s, 6H), 2.90 – 2.86 (m, 1H), 2.78 (ddd, *J* = 17.7, 4.6, 2.4 Hz, 1H), 2.47 (qd, *J* = 13.3, 4.6 Hz, 1H), 2.15 (ddd, *J* = 12.9, 5.3, 2.4 Hz, 1H).

^{13}C NMR (151 MHz, CD$_3$OD): δ 174.8, 172.5, 170.8, 153.0, 146.7, 134.1, 121.5, 116.7, 115.9, 53.6, 44.5, 32.4, 24.1.

HRMS (ESI-TOF, m/z): HRMS (ESI) Calcd for $[M+H]^+$ 288.1348; Found 288.1345.



Compound 52b

^{1}H NMR (600 MHz, CD_3OD): δ 7.41 (t, *J* = 7.7 Hz, 1H), 7.31 (d, *J* = 7.4 Hz, 1H), 7.09 (d, *J* = 8.1 Hz, 1H), 5.14 (dd, *J* = 13.4, 5.1 Hz, 1H), 4.60 (d, *J* = 17.1 Hz, 1H), 4.55 (d, *J* = 16.8 Hz, 1H), 2.93 (s, 6H), 2.92 – 2.8\8 (m, 1H), 2.81 – 2.77 (m, 1H), 2.55 (qd, *J* = 13.2, 4.6 Hz, 1H), 2.18 (ddd, *J* = 10.8, 5.6, 3.2 Hz, 1H).

^{13}C NMR (151 MHz, CD_3OD): δ 174.7, 172.3, 171.8, 149.7, 134.1, 132.5, 130.5, 120.1, 115.8, 53.7, 42.9, 32.4, 24.1.

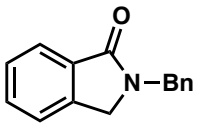
HRMS (ESI-TOF, m/z): HRMS (ESI) Calcd for $[M+H]^+$ 288.1348; Found 288.1347.

Compound 55

Following the general procedure, the reaction was performed with *N*-benzyl-4-chlorophthalimide (27.1 mg, 0.1 mmol), pivalic acid (30.6 mg, 0.3 mmol), tetramethylammonium tetrafluoroborate (32 mg, 0.2 mmol), and 2.5 mL of CH_3OH. The resulting reaction mixture was electrolyzed under a constant current of 20 mA with rapid alternating polarity (100 ms, 5 Hz) for 16 F/mol. The reaction mixture was concentrated, and the residue was passed through a short silica gel plug with AcOEt as eluent. The crude reaction mixture was purified by pTLC (hexane/AcOEt = 2:1) to furnish products **55a** (8.2 mg, 37%) and **55b** (9.7 mg, 39%).

Reduction of N-benzyl-4-chlorophthalimide in the presence of TFA

Following the general procedure, the reaction was performed with imide starting material (27.1 mg, 0.1 mmol), pivalic acid (30.6 mg, 0.3 mmol), tetramethylammonium tetrafluoroborate (32 mg, 0.2 mmol), trifluoroacetic acid (23 mg, 0.2 mmol), and 2.5 mL of CH_3OH. The resulting reaction mixture was electrolyzed under a constant current of 20 mA with rapid alternating polarity (100 ms, 5 Hz) for 36 F/mol. The reaction mixture was then concentrated, and the crude mixture was purified by flash column chromatography (hexane → hexanes/AcOEt = 5:1 → 4:1), then subjected to pTLC purification (CH_2Cl_2/CH_3OH = 1:0.1) to furnish **55b** in 50% yield as a mixture of regioisomers (**55b major**: 8.4 mg, **55b minor**: 4.6 mg). The regiochemistry was determined by the NOE.

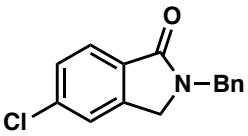


Compound 55a:

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.90 (d, *J* = 7.5 Hz, 1H), 7.51 (td, *J* = 7.4, 1.3 Hz, 1H), 7.46 (t, *J* = 7.4 Hz, 1H), 7.38 (d, *J* = 7.4 Hz, 1H), 7.37 – 7.26 (m, 5H), 4.81 (s, 2H), 4.26 (s, 2H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 143.8, 134.4, 131.9, 128.2, 123.9, 123.6, 123.3, 45.9.

HRMS (ESI-TOF, m/z): HRMS (ESI) Calcd for $[M+H]^+$ 224.1075; Found 224.1074.

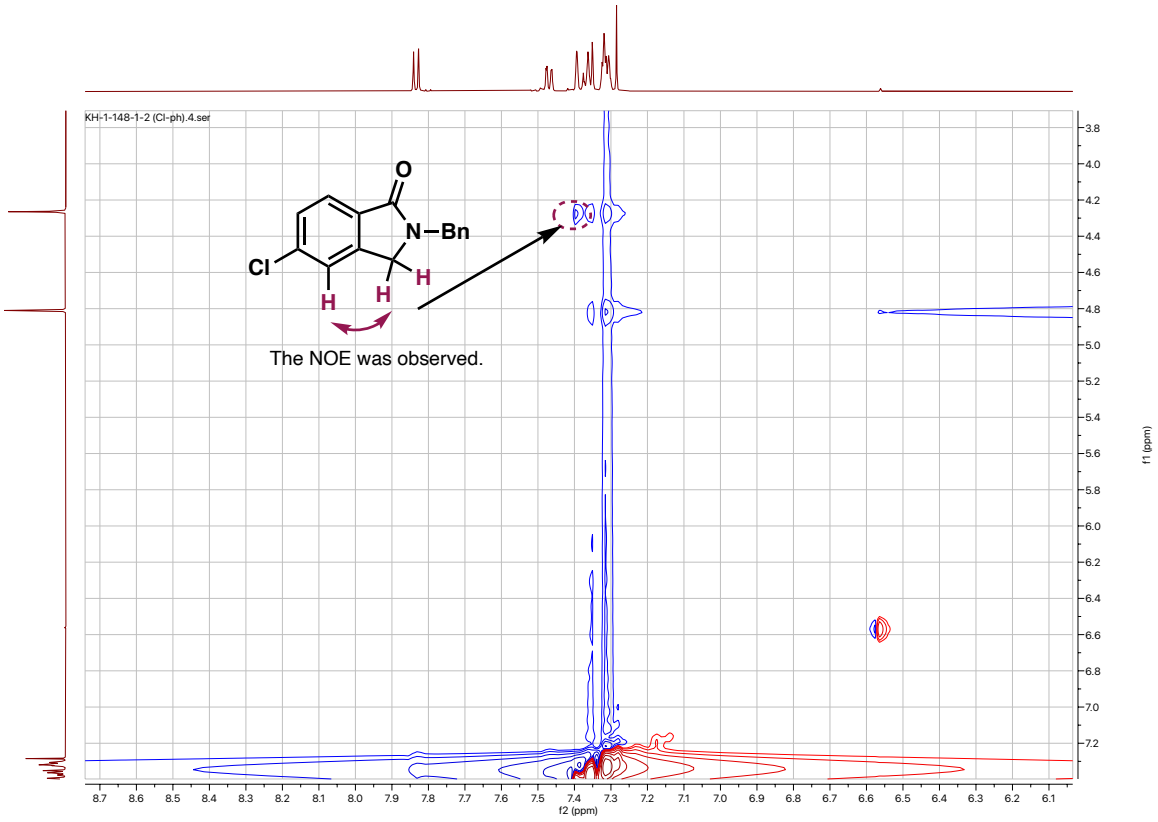


Compound 55b major:

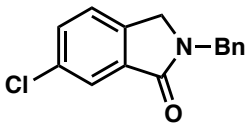
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.81 (d, *J* = 8.1 Hz, 1H), 7.46 – 7.44 (m, 1H), 7.38 – 7.36 (m, 1H), 7.36 – 7.32 (m, 2H), 7.31 – 7.27 (m, 3H), 4.79 (s, 2H), 4.24 (s, 2H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 167.6, 142.9, 137.9, 136.9, 131.3, 129.0, 128.9, 128.3, 128.0, 125.2, 123.4, 49.1, 46.6.

HRMS (ESI-TOF, m/z): HRMS (ESI) Calcd for $[M+H]^+$ 258.0686; Found 258.0684.



NOESY of compound **55b** for regiochemical assignment.



55b minor:

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, *J* = 2.0 Hz, 1H), 7.48 (dd, *J* = 8.1, 2.0 Hz, 1H), 7.37 – 7.27 (m, 6H), 4.79 (s, 2H), 4.24 (s, 2H).

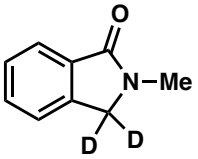
^{13}C NMR (151 MHz, $CDCl_3$): δ 167.3, 139.5, 136.8, 134.6, 134.6, 131.7, 129.0, 128.3, 128.0, 124.3, 124.1, 49.3, 46.7.

HRMS (ESI-TOF, m/z): HRMS (ESI) Calcd for $[M+H]^+$ 258.0686; Found 258.0679.

Reduction in CD_3OD

Following the general procedure, the reaction was performed with *N*-methylphthalimide (16.1 mg, 0.1 mmol), 1-phenyl-1-cyclopentylcarboxylic acid (38.4 mg, 0.2 mmol), tetramethylammonium tetrafluoroborate (32 mg, 0.2 mmol), and 2.5 mL of CH_3OH. The resulting reaction mixture was electrolyzed under a constant current of 20 mA with rapid alternating polarity (100 ms, 5 Hz) for 12 F/mol. The reaction mixture was concentrated, and the residue was passed through a short silica gel plug with AcOEt as eluent. At this point, the yield of **59-*d*** was determined to be 70% based on ^{1}H NMR. The crude reaction mixture was purified by pTLC (hexane/CH_2Cl_2 = 1:1) to isolate **59-*d*** (6.0 mg, 40%, a considerable amount of the product was lost due to the volatile nature of this compound), then the same plate was developed again with hexane/AcOEt = 1:3 to furnish **58-*d*** (6.0 mg, 40%).

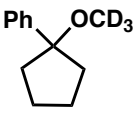
Compound 58-*d*:



^{1}H NMR (600 MHz, $CDCl_3$): δ 7.83 (d, *J* = 7.3 Hz, 1H), 7.51 (td, *J* = 7.5, 1.2 Hz, 1H), 7.46 – 7.42 (m, 2H), 3.19 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 168.8, 141.0, 133.1, 131.2, 128.1, 123.7, 122.7, 52.0 – 51.8 (m), 29.6.

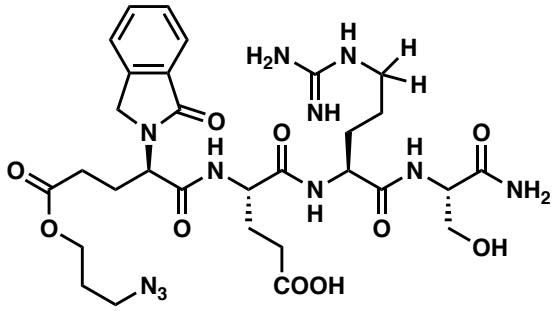
HRMS (ESI-TOF, m/z): HRMS (ESI) Calcd for $[M+H]^+$ 150.0888; Found 150.0881.



Compound 59-*d*:

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42 (d, *J* = 7.0 Hz, 2H), 7.34 (t, *J* = 7.6 Hz, 2H), 7.26 (t, *J* = 7.6 Hz, 1H), 2.97 (s, 3H), 2.19 – 2.15 (m, 2H), 1.89 – 1.85 (m, 4H), 1.77 – 1.72 (m, 2H).
^{13}C NMR (151 MHz, $CDCl_3$): δ 143.6, 128.2, 127.1, 126.8, 88.4, 49.9 (p, 21 Hz), 36.7, 23.2.

Compound 62

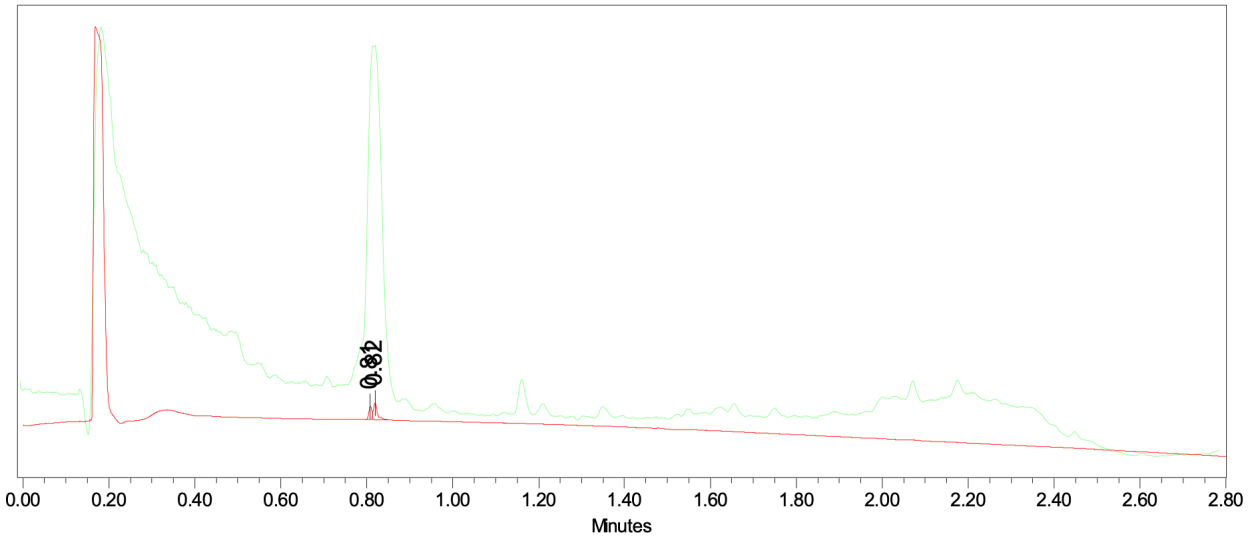


Following the general procedure, the reaction was performed with peptide starting material (15 mg, 0.018 mmol), pivalic acid (30.6 mg, 0.3 mmol), tetramethylammonium tetrafluoroborate (32 mg, 0.2 mmol), and 2.5 mL of CH_3OH. The resulting reaction mixture was electrolyzed under a constant current of 40 mA with rapid alternating polarity (25 ms, 20 Hz) for 30 F/mol. The reaction mixture was evaporated, then the crude reaction mixture was was purified on a Waters Autopurification LC with a Waters BEH C18 column (5 μm, 19x160 mm) using a 0.1% aqueous formic acid/CH_3CN gradient (30 mL/min, main segment of gradient at 15-35% acetonitrile over 8 minutes) at ambient temperature to furnish product **62** (2.1 mg, 14%). Fractionation was triggered by a Waters QDa single quadrupole mass spec (ESI+).

To determine the yield without HPLC purification, the reaction was performed with peptide starting material (7 mg, 0.0082 mmol), pivalic acid (30.6 mg, 0.3 mmol), tetramethylammonium tetrafluoroborate (32 mg, 0.2 mmol), and 2.5 mL of CH_3OH. The resulting reaction mixture was electrolyzed under a constant current of 40 mA with rapid alternating polarity (25 ms, 20 Hz) for 40 F/mol, and the reaction mixture was evaporated. ^{1}H NMR spectroscopic analysis of the crude reaction mixture found **62** in 52%.

HRMS (ESI-TOF, m/z): HRMS (ESI) Calcd for $[M+Na]^+$ 718.3273; Found 718.3277.

UV and overlaid TIC
Y axis normalized
Red color: UV (220nm + 260nm)



Major UV Peaks

	RT	Area	Base Peak (m/z)
1	0.81	22867	718.5
2	0.82	39289	718.4

Determination of solution resistance and electrical double layer capacitance

Electrochemical cell was prepared by following the general procedure. The sample solution contains *N*-methylphthalimide (0.1 mmol), pivalic acid (30.6 mg, 0.3 mmol), tetramethylammonium tetrafluoroborate (32 mg, 0.2 mmol) in 2.5 mL of CH_3OH. RVC anode and RVC cathode were used, and Ag wire was used for pseudo-reference electrode. Before collecting electrochemical data, 20 mA-rAP(100ms) was applied to electrochemical cell for 2 min to stabilize the electrode surface.

Determination of solution resistance ($R_{solution}$)

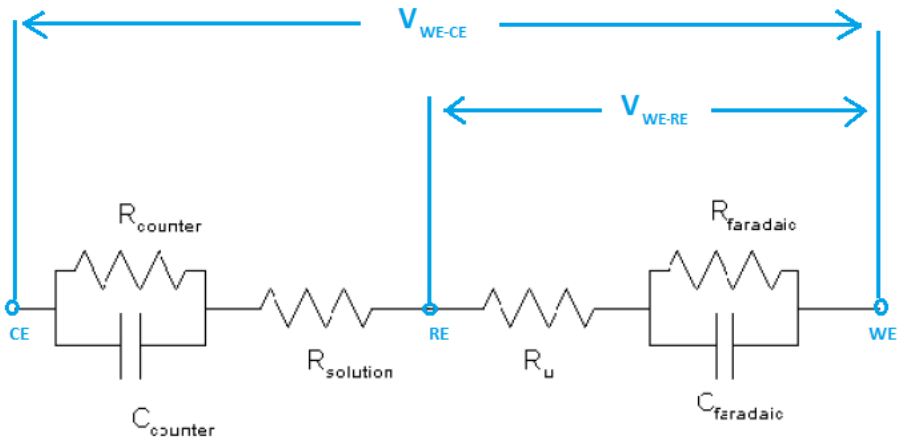


Figure S10. Equivalent circuit

In this equivalent circuit, we have made two assumption: a) $R_{counter}$ is negligible compared to $R_{solution}$, b) The uncompensated resistance (R_u) is not considered as it's a constant current experiment. Based on these assumptions, the solution resistance ($R_{solution}$) was determined by measuring the voltage between working electrode (WE) and reference electrode (RE) as well as between WE and counter electrode (CE) during the reaction. During this measurement, 20 mA was applied to the cell and the voltage was measured by a multimeter. The voltage across WE-RE was 4.56 V, that of WE-CE was 6.88 V. Accordingly, based on Ohm's law, $R_{solution}$ was determined by following calculation:

$(6.88-4.56)/0.02 = 116\ (\Omega)$

Determination of electric double layer capacitance (C) of RVC electrode

The double layer capacitance of RVC electrode was determined by following the method described in Org. Lett. 2020, 22, 6719–6723. Since the electrochemical setup used in our work is considerably different from that described in this reference, we initially validated the method by measuring the capacitance of glassy carbon with our setup, and compare the value with the reported value (4 mF).

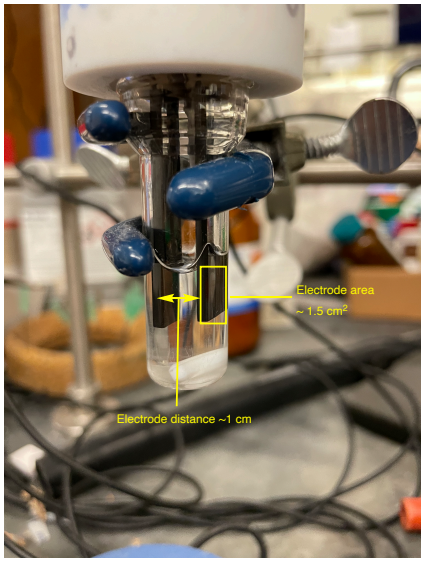


Figure S11. Reaction setup used for the determination of double layer capacitance

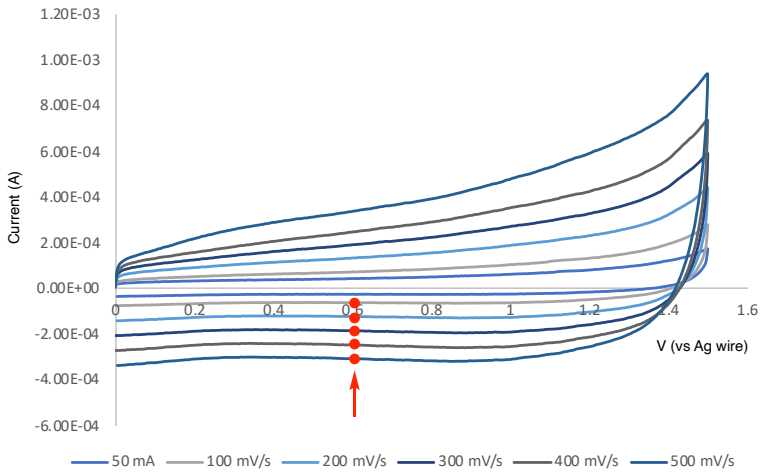


Figure S12. Cyclic voltammogram of the sample solution at various scan rate. The most flat region (0.6V) were used for the determination of double layer capacitance.

The plot of current vs scan rate was generated based on the CV data (current value at 0.6 V was used). Based on Figure S13, the capacitance was determined as 0.62 mF with our experimental setup. This capacitance is very similar to the reported value if we consider the difference of electrode surface area and electrode distance. Since the capacitance is a function of surface area and electrode distance ($C = \varepsilon A/d$) and our setup has 1.5 times larger surface area and 10 times larger electrode distance than reported conditions, the reported value (4 mF) would be corrected to:

4*1.5/10 = 0.6 (mF)

Thus, our measurement matches well with the reported value.

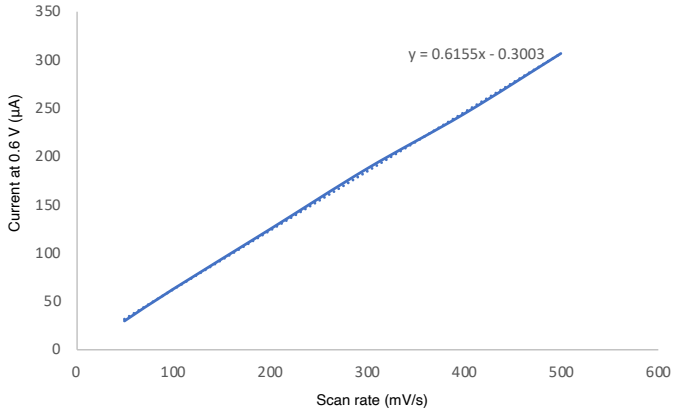


Figure S13. Plot of current vs scan rate.

Based on this procedure, the same set of experiments and analysis were performed by using RVC electrode as working electrode, yielding 0.28 mF (average of the values at three different voltage) as a double layer capacitance under our reaction conditions.

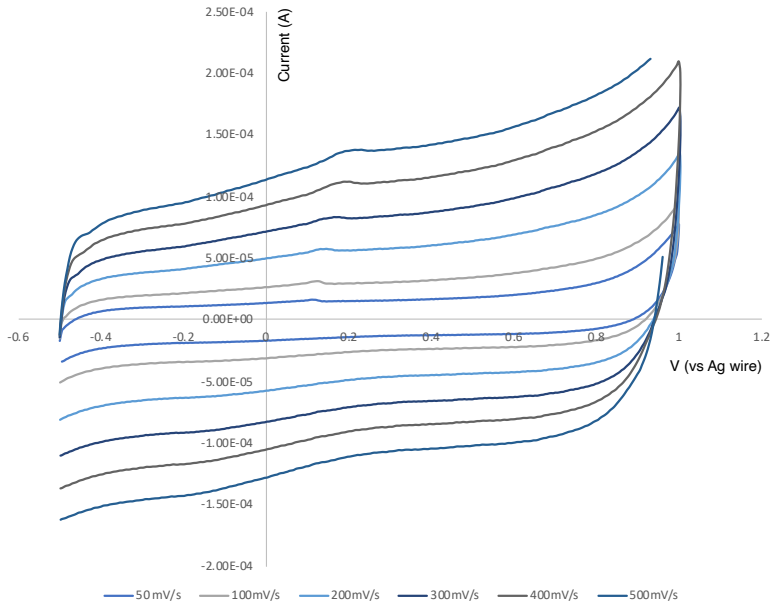


Figure S14. Cyclic voltammogram of the sample solution with RVC working electrode at various scan rate.

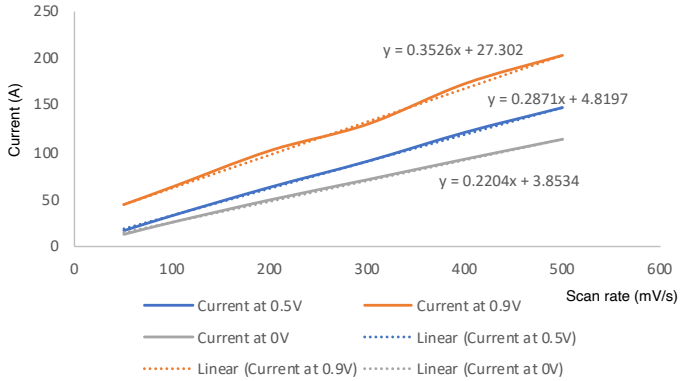


Figure S15. Current vs scan rate plot. The current values at 0V, 0.5V, 0.9V were used for the determination of the double layer capacitance.

Evaluation of the contribution of solution resistance and electric double layer capacitance to the overall current

The total energy (J) used for one rAP cycle (20 mA, 50 ms pulse) is:

J = (current)*(time)*(reaction voltage) = 0.020*0.1*6.88 = 0.0138 (J)

The energy used for Joule heating is:

J_{heat} = (current)*(current)*(solution resistance)*(time) = 0.02*0.02*116*0.1 = 0.0046 (J)

The energy used for charging double layer is:

J_{DL} = ½*(capacitance)*(voltage)*(voltage)= 0.5*0.00028*4.56*4.56 = 0.0029 (J)

Accordingly, 55% of the total energy was used for non-faradaic processes. The contribution from the double layer capacitance account for roughly 20% of the energy loss. Considering an experimental result that 16 F/mol led to 72% of the lactam + 11% of the hemiaminal (Figure 2A entry 11), the current efficiency is :

Current efficiency = (0.72*4+0.11*2)*100/16 = 19 (%)

Based on above considerations, the current efficiency without non-faradaic processes is

19/0.45 = 42 (%)

This falls into typical current efficiency for various bulk electrochemical reactions without particular optimization for improving current efficiency.

Comparisons with direct current

The procedure is adapted from Y. Bai et al.(*18*) To an ElectraSyn reaction vial charged with substrate (0.1 mmol, 1.0 mmol), diisopropylamine (61 mg, 6.0 mmol), and tetrabutylammonium tetrafluoroborate (82 mg, 0.25 mmol) was added 2.5 mL of EtOH. Using a graphite anode and an RVC cathode, the reaction mixture was electrolyzed under a constant direct current of 25 mA or 30 mA for 6-12 F/mol. The reaction mixture was then concentrated under reduced pressure. The product yield was determined by NMR analysis of the crude reaction mixture after passing through a short silica gel pad. See the individual entries below for detailed conditions.

Compound 3b

Following the general procedure, the reaction was performed with imide starting material **2** (33 mg, 0.1 mmol), diisopropylamine (61 mg, 0.6 mmol), and tetrabutylammonium tetrafluoroborate (82 mg, 0.25 mmol) in 2.5 mL of EtOH. The resulting reaction mixture was electrolyzed under a constant direct current of 30 mA for 12 F/mol. The reaction mixture was then concentrated under reduced pressure. The product yield was determined by NMR analysis of the crude reaction mixture after passing through a short silica gel pad (**3a** in 17% yield, **3b** in 33%).

electrolysis conditions	products
DC, 25 mA, 6 F/mol	**3a**: 23%, **3b**: 38%
DC, 25 mA, 12 F/mol	**3a**: 22%, **3b**: 44%
DC, 30 mA, 12 F/mol	**3a**: 33%, **3b**: 17%

Compound 4

Following the general procedure, the reaction was performed with imide starting material (23 mg, 0.1 mmol), diisopropylamine (61 mg, 0.6 mmol), and tetrabutylammonium tetrafluoroborate (82 mg, 0.25 mmol) in 2.5 mL of EtOH. The resulting reaction mixture was electrolyzed under a constant direct current of 25 mA for 6 F/mol. The reaction mixture was then concentrated under reduced pressure. The product yield was determined by NMR analysis of the crude reaction mixture after passing through a short silica gel pad (**4** in 75% yield).

Compound 5

Following the general procedure, the reaction was performed with imide starting material (21 mg, 0.1 mmol), diisopropylamine (61 mg, 0.6 mmol), and tetrabutylammonium tetrafluoroborate (82 mg, 0.25 mmol) in 2.5 mL of EtOH. The resulting reaction mixture was electrolyzed under a constant direct current of 25 mA for 6 F/mol. The reaction mixture was then concentrated under reduced pressure. The product yield was determined by NMR analysis of the crude reaction mixture after passing through a short silica gel pad (**5** in 83% yield).

Compound 6

Following the general procedure, the reaction was performed with imide starting material (20 mg, 0.1 mmol), diisopropylamine (61 mg, 0.6 mmol), and tetrabutylammonium tetrafluoroborate (82 mg, 0.25 mmol) in 2.5 mL of EtOH. The resulting reaction mixture was electrolyzed under a constant direct current of 25 mA for 6 F/mol. The reaction mixture was then concentrated under reduced pressure. The product yield was determined by NMR analysis of the crude reaction mixture after passing through a short silica gel pad (**6** in 36% yield).

Compound 7

Following the general procedure, the reaction was performed with imide starting material (25 mg, 0.1 mmol), diisopropylamine (61 mg, 0.6 mmol), and tetrabutylammonium tetrafluoroborate (82 mg, 0.25 mmol) in 2.5 mL of EtOH. The resulting reaction mixture was electrolyzed under a constant direct current of 25 mA for 6 F/mol. The reaction mixture was then concentrated under reduced pressure. The desired product was not identified in ^{1}H NMR analysis.

electrolysis conditions	yield of **7**
DC, 25 mA, 12 F/mol	0%
DC, 30 mA, 6 F/mol	0%

Compound 8

Following the general procedure, the reaction was performed with imide starting material (22 mg, 0.1 mmol), diisopropylamine (61 mg, 0.6 mmol), and tetrabutylammonium tetrafluoroborate (82 mg, 0.25 mmol) in 2.5 mL of EtOH. The resulting reaction mixture was electrolyzed under a constant direct current of 25 mA for 6 F/mol. The reaction mixture was then concentrated under

reduced pressure. The product yield was determined by NMR analysis of the crude reaction mixture after passing through a short silica gel pad (**8** in 17% yield).

electrolysis conditions	yield of **8**
DC, 25 mA, 6 F/mol	17%
DC, 25 mA, 12 F/mol	13%
DC, 30 mA, 12 F/mol	0%

Compound 9

Following the general procedure, the reaction was performed with imide starting material (18 mg, 0.05 mmol), diisopropylamine (31 mg, 0.6 mmol), and tetrabutylammonium tetrafluoroborate (82 mg, 0.25 mmol) in 2.5 mL of EtOH. The resulting reaction mixture was electrolyzed under a constant direct current of 25 mA for 6 F/mol. The reaction mixture was then concentrated under reduced pressure. The product yield was determined by NMR analysis of the crude reaction mixture after passing through a short silica gel pad (**9** in 24% yield).

Compound 10

Following the general procedure, the reaction was performed with imide starting material (15 mg, 0.1 mmol), diisopropylamine (61 mg, 0.6 mmol), and tetrabutylammonium tetrafluoroborate (82 mg, 0.25 mmol) in 2.5 mL of EtOH. The resulting reaction mixture was electrolyzed under a constant direct current of 25 mA for 6 F/mol. The reaction mixture was then concentrated under reduced pressure. The product yield was determined by NMR analysis of the crude reaction mixture after passing through a short silica gel pad (**10** in 37% yield).

Compound 12

Following the general procedure, the reaction was performed with imide starting material (21 mg, 0.1 mmol), diisopropylamine (61 mg, 0.6 mmol), and tetrabutylammonium tetrafluoroborate (82 mg, 0.25 mmol) in 2.5 mL of EtOH. The resulting reaction mixture was electrolyzed under a constant direct current of 25 mA for 6 F/mol. The reaction mixture was then concentrated under reduced pressure. Compound **12** was not observed by NMR analysis of the crude reaction mixture.

Compound 13

Following the general procedure, the reaction was performed with imide starting material (22 mg, 0.1 mmol), diisopropylamine (61 mg, 0.6 mmol), and tetrabutylammonium tetrafluoroborate (82 mg, 0.25 mmol) in 2.5 mL of EtOH. The resulting reaction mixture was electrolyzed under a constant direct current of 25 mA for 6 F/mol. The reaction mixture was then concentrated under reduced pressure. Only trace amount of Compound **13** was observed by LCMS analysis of the crude reaction mixture.

Compound 14

Following the general procedure, the reaction was performed with imide starting material (22 mg, 0.1 mmol), diisopropylamine (61 mg, 0.6 mmol), and tetrabutylammonium tetrafluoroborate (82 mg, 0.25 mmol) in 2.5 mL of EtOH. The resulting reaction mixture was electrolyzed under a constant direct current of 25 mA for 12 F/mol. The reaction mixture was then concentrated under reduced pressure. Compound **14** was not observed by NMR analysis of the crude reaction mixture.

Compound 15

Following the general procedure, the reaction was performed with imide starting material (37 mg, 0.1 mmol), diisopropylamine (61 mg, 0.6 mmol), and tetrabutylammonium tetrafluoroborate (82 mg, 0.25 mmol) in 2.5 mL of EtOH. The resulting reaction mixture was electrolyzed under a constant direct current of 25 mA for 6 F/mol. The reaction mixture was then concentrated under reduced pressure. The product yield was determined by NMR analysis of the crude reaction mixture after passing through a short silica gel pad (**15** in 51% yield).

Compound 16

Following the general procedure, the reaction was performed with imide starting material (26 mg, 0.1 mmol), diisopropylamine (61 mg, 0.6 mmol), and tetrabutylammonium tetrafluoroborate (82 mg, 0.25 mmol) in 2.5 mL of EtOH. The resulting reaction mixture was electrolyzed under a constant direct current of 25 mA for 6 F/mol. The reaction mixture was then concentrated under reduced pressure. Compound **16** was not observed by NMR analysis of the crude reaction mixture.

Compound 19

Following the general procedure, the reaction was performed with imide starting material (20 mg, 0.1 mmol), diisopropylamine (61 mg, 0.6 mmol), and tetrabutylammonium tetrafluoroborate (82 mg, 0.25 mmol) in 2.5 mL of EtOH. The resulting reaction mixture was electrolyzed under a constant direct current of 25 mA for 6 F/mol, then 30 mA for 6 F/mol. The reaction mixture was then concentrated under reduced pressure. The product yield was determined by NMR analysis of the crude reaction mixture after passing through a short silica gel pad (**19** in 14% yield).

Compound 20

Following the general procedure, the reaction was performed with imide starting material (21 mg, 0.1 mmol), diisopropylamine (61 mg, 0.6 mmol), and tetrabutylammonium tetrafluoroborate (82 mg, 0.25 mmol) in 2.5 mL of EtOH. The resulting reaction mixture was electrolyzed under a constant direct current of 25 mA for 6 F/mol, then 30 mA for 6 F/mol. The reaction mixture was then concentrated under reduced pressure. The product yield was determined by NMR analysis of the crude reaction mixture after passing through a short silica gel pad (hemiaminal analogue of **20**, with OH instead of OMe, in 13% yield).

Compound 22

Following the general procedure, the reaction was performed with imide starting material (34 mg, 0.1 mmol), diisopropylamine (61 mg, 0.6 mmol), and tetrabutylammonium tetrafluoroborate (82 mg, 0.25 mmol) in 2.5 mL of EtOH. The resulting reaction mixture was electrolyzed under a constant direct current of 25 mA for 9 F/mol. The reaction mixture was then concentrated under reduced pressure. The product yield was determined by NMR analysis of the crude reaction mixture after passing through a short silica gel pad (**22** in 29% yield).

Compound 23

Following the general procedure, the reaction was performed with hydantoin starting material (28 mg, 0.1 mmol), diisopropylamine (61 mg, 0.6 mmol), and tetrabutylammonium tetrafluoroborate (82 mg, 0.25 mmol) in 2.5 mL of EtOH. The resulting reaction mixture was electrolyzed under a constant direct current of 25 mA for 12 F/mol. The reaction mixture was then concentrated under reduced pressure. The product yield was determined by NMR analysis of the crude reaction mixture after passing through a short silica gel pad (**23** in 13% yield).

Compound 24

Following the general procedure, the reaction was performed with hydantoin starting material (19 mg, 0.1 mmol), diisopropylamine (61 mg, 0.6 mmol), and tetrabutylammonium tetrafluoroborate (82 mg, 0.25 mmol) in 2.5 mL of EtOH. The resulting reaction mixture was electrolyzed under a constant direct current of 25 mA for 12 F/mol. The reaction mixture was then concentrated under reduced pressure. The product yield was determined by NMR analysis of the crude reaction mixture after passing through a short silica gel pad (**24** in <5% yield).

Compound 26

Following the general procedure, the reaction was performed with starting material **25** (13 mg, 0.1 mmol), diisopropylamine (61 mg, 0.6 mmol), and tetrabutylammonium tetrafluoroborate (82 mg, 0.25 mmol) in 2.5 mL of EtOH. The resulting reaction mixture was electrolyzed under a constant direct current of 25 mA for 6 F/mol. The reaction mixture was then concentrated under reduced pressure. The product yield was determined by NMR analysis of the crude reaction mixture after passing through a short silica gel pad (**26** in 19% yield).

reaction conditions		products
iPr$_2$NH, TBABF$_4$ EtOH	DC, 25 mA, 12 F/mol (+)C/(–)RVC	**26**: 19%, **25**: 0%
Pivalic acid, TMABF$_4$ MeOH	DC, 20 mA, 12 F/mol (+)RVC/(–)RVC	**26**: 0%, **25**: 14%

Compounds 28a, 28b

Following the general procedure, the reaction was performed with starting material **27** (29 mg, 0.1 mmol), diisopropylamine (61 mg, 0.6 mmol), and tetrabutylammonium tetrafluoroborate (82 mg, 0.25 mmol) in 2.5 mL of EtOH. The resulting reaction mixture was electrolyzed under a constant direct current of 25 mA for 12 F/mol. The reaction mixture was then concentrated under reduced pressure. The product yield was determined by NMR analysis of the crude reaction mixture after passing through a short silica gel pad (**28a** in 66% yield, **28b** in 0% yield).

reaction conditions		products
iPr$_2$NH, TBABF$_4$ EtOH	DC, 25 mA, 12 F/mol (+)C/(–)RVC	**28a**: 66%, **28b**: 0%, **27**: 0%
Pivalic acid, TMABF$_4$ MeOH	DC, 20 mA, 12 F/mol (+)RVC/(–)RVC	**28a**: 53%, **28b**: 0%, **27**: 0%

Compound 30

Following the general procedure, the reaction was performed with starting material **29** (16 mg, 0.1 mmol), diisopropylamine (61 mg, 0.6 mmol), and tetrabutylammonium tetrafluoroborate (82 mg, 0.25 mmol) in 2.5 mL of EtOH. The resulting reaction mixture was electrolyzed under a constant direct current of 25 mA for 6 F/mol. The reaction mixture was then concentrated under reduced pressure. The product yield was determined by NMR analysis of the crude reaction mixture after passing through a short silica gel pad (**30** in 24% yield).

reaction conditions		products
iPr$_2$NH, TBABF$_4$ EtOH	DC, 25 mA, 6 F/mol (+)C/(–)RVC	**30**: 24%, **29**: 29%
iPr$_2$NH, TBABF$_4$ EtOH	DC, 25 mA, 14 F/mol (+)C/(–)RVC	**30**: 0%, **29**: 19%
Pivalic acid, TMABF$_4$ MeOH	DC, 20 mA, 6 F/mol (+)RVC/(–)RVC	**30**: 28%, **29**: 5%

Compound 32

Following the general procedure, the reaction was performed with starting material **31** (37 mg, 0.1 mmol), diisopropylamine (61 mg, 0.6 mmol), and tetrabutylammonium tetrafluoroborate (82 mg, 0.25 mmol) in 2.5 mL of EtOH. The resulting reaction mixture was electrolyzed under a constant direct current of 25 mA for 16 F/mol. The reaction mixture was then concentrated under reduced pressure. Compound **32** was not observed by NMR analysis of the crude reaction mixture.

reaction conditions		products
iPr$_2$NH, TBABF$_4$ EtOH	DC, 25 mA, 16 F/mol (+)C/(–)RVC	**32**: 0%, **31**: 65%
Pivalic acid, TMABF$_4$ MeOH	DC, 20 mA, 16 F/mol (+)RVC/(–)RVC	**32**: 0%, **31**: 90%

Compounds 34a, 34b

Following the general procedure, the reaction was performed with starting material **33** (26 mg, 0.1 mmol), diisopropylamine (61 mg, 0.6 mmol), and tetrabutylammonium tetrafluoroborate (82 mg, 0.25 mmol) in 2.5 mL of EtOH. The resulting reaction mixture was electrolyzed under a constant direct current of 25 mA for 16 F/mol. The reaction mixture was then concentrated under reduced pressure. The product yield was determined by NMR analysis of the crude reaction mixture after passing through a short silica gel pad (**34a** in 18% yield, **34b** in 8% yield).

reaction conditions		products
iPr$_2$NH, TBABF$_4$ EtOH	DC, 25 mA, 16 F/mol (+)C/(–)RVC	**34a**: 18%, **34b**: 8%, **33**: 10%
Pivalic acid, TMABF$_4$ MeOH	DC, 20 mA, 16 F/mol (+)RVC/(–)RVC	**34a**: 16%, **34b**: 10%, **33**:16%

Compound 39

Following the general procedure, the reaction was performed with starting material **38** (20 mg, 0.05 mmol), diisopropylamine (61 mg, 0.6 mmol), and tetrabutylammonium tetrafluoroborate (82 mg, 0.25 mmol) in 2.5 mL of EtOH. The resulting reaction mixture was electrolyzed under a constant direct current of 25 mA for 24 F/mol. The reaction mixture was then concentrated under reduced pressure. Compound **39** was not observed by NMR analysis of the crude reaction mixture.

Compound 62

Following the general procedure, the reaction was performed with starting peptide substrate (3 mg, 0.0035 mmol), diisopropylamine (61 mg, 0.6 mmol), and tetrabutylammonium tetrafluoroborate (82 mg, 0.25 mmol) in 2.5 mL of EtOH. The resulting reaction mixture was electrolyzed under a constant direct current of 25 mA for 51 F/mol. The reaction mixture was then concentrated under reduced pressure. Compound **62** was not observed by LCMS and NMR analysis of the crude reaction mixture.

Miscellaneous

Experimental procedures for the experiment with sinusoidal waveform (Figure 2, entry 14)

The reaction solution was prepared by following the general procedure described above. Potential-controlled sinusoidal waveform was generated by LABQUEST® 2 with Vernier Power Amplifier. Additional experimental details are included in Figure S16.

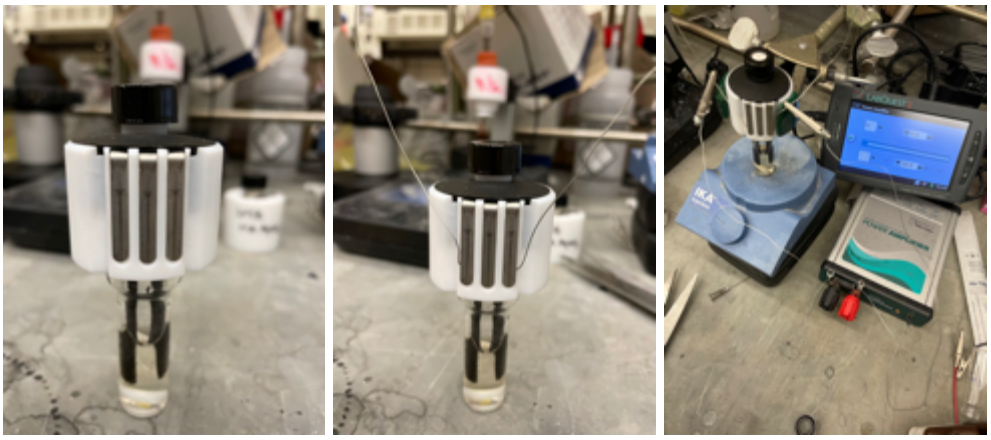
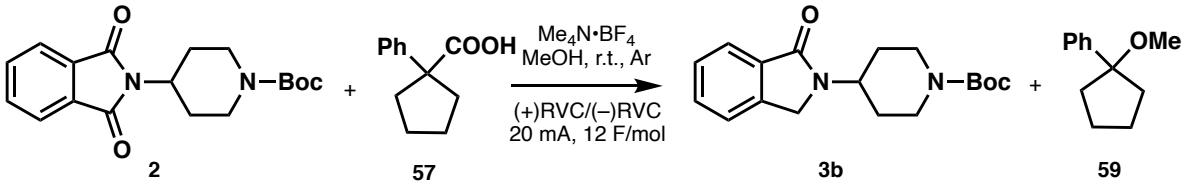


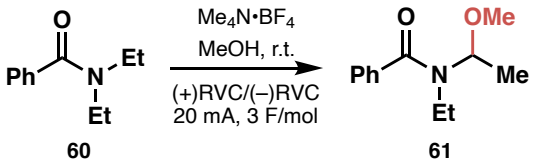
Figure S16. Graphical procedure for electrolysis with sinusoidal waveform. (A) The reaction solution was prepared by following general procedure. (B) Wires were attached to the left and right sides of ElectraSyn cap. (C) Power Amplifier was connected to the cell with alligator clips. AC sinusoidal waveform and reaction voltage (8 V cell potential) were specified on LABQUEST® 2. The reaction was performed for 2 hours 40 min (cf. rAP reaction time for the same reaction was 2 hours 8 min to deliver 16 F/mol of electricity.)

Study on reaction efficiency at various frequencies (Figure 4D)



Scheme S1. Model reaction to study the effect of frequency.

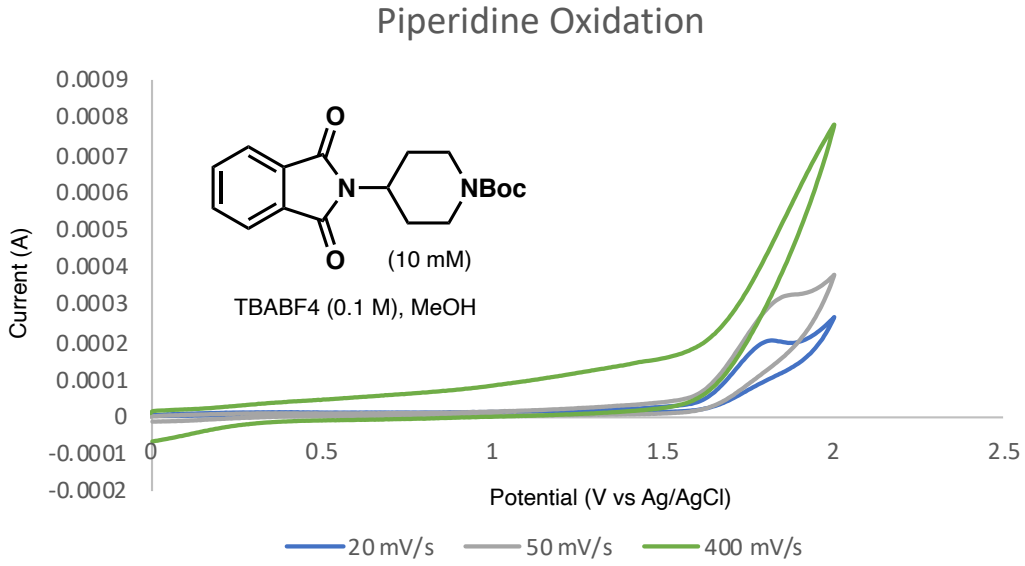
The reaction was set up following the general procedure described above, with the frequency (0, 1, 2, 5, 10 Hz) being the only variable. After passing 12 F/mol of electricity, each reaction was transferred to a round-bottom flask, and solvents were removed by a rotary evaporator. The remaining mixture was redissolved in CH_2Cl_2, and then the solution was passed through a short silica gel plug with AcOEt as eluent to remove electrolyte. The resulting solution was concentrated, and yields of **3b** and **59** were determined by ^1H NMR analysis with nitromethane as an internal standard. Yield of **3b**: 17% (DC), 16% (1 Hz), 53% (2 Hz), 69% (5 Hz), 75% (10 Hz). Yield of **59**: 45% (DC), 77% (1 Hz), 74% (2 Hz), 69% (5 Hz), 63% (10 Hz).

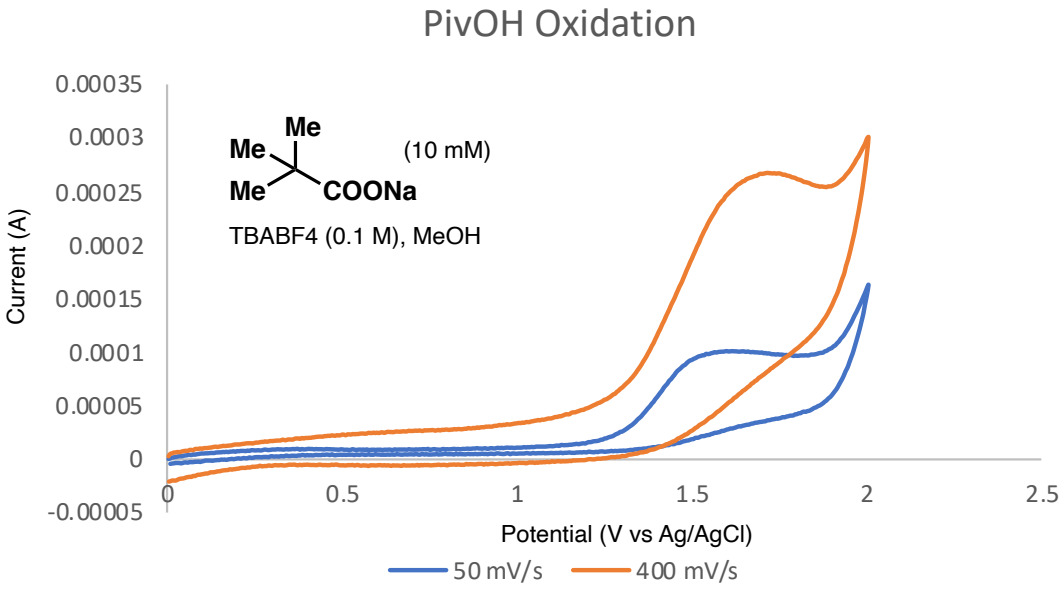


Scheme S2. Model Shono oxidation for the study on the effect of frequency.

ElectraSyn2.0 was used to perform the reaction. To a 5 mL ElectraSyn vial equipped with a stir bar were charged with **60** (0.1 mmol), tetramethylammonium tetrafluoroborate (0.2 mmol), and CH_3OH (2.5 mL). 3 F/mol of electricity were passed through the solution at variable frequency. Then, the solution was transferred to a round-bottom flask, and the solvents were removed by a rotary evaporator. The crude mixture was redissolved in CH_2Cl_2, and the insoluble material was filtered off. After the concentration of the resulting solution, the yield of **61** was determined by ^1H NMR analysis. Yield of **61**: 72% (DC), 6% (1 Hz), 7% (2 Hz), 3% (5 Hz), 1% (10 Hz).

Additionally, CV studies were conducted to gain further insight on the kinetics of Shono oxidation and oxidative decarboxylation, which are competing anodic processes under rAP conditions. Anodic oxidation of piperidine-derivative is irreversible at any scan rate (the peak became indistinguishable at 400 mV/s), indicating that Shono oxidation is irreversible. Although we could not find literature evidence to clearly stating that oxidative decarboxylation (Hofer-Moest) is faster than Shono oxidation, it is clear from the study with various frequency that efficiency of Shono oxidation becomes considerably less than that of oxidative decarboxylation above 1 Hz. In addition, we found that Shono oxidation peak (CV below) is observable at slow scan rate (20-50 mV/s), but not observable at 400 mV/s. In contrast, oxidation of pivalic acid is still observable at 400 mV/s. These observations also support our assumption that Shono oxidation is slower than decarboxylation.



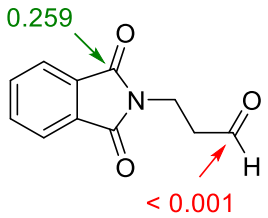
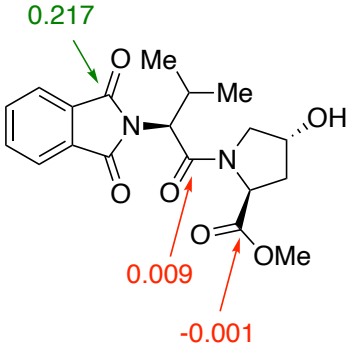

PivOH Oxidation
0.00035
0.0003
0.00025
0.0002
0.00015
0.0001
0.00005
0
-0.00005
Current (A)
Me
Me
Me
COONa
(10 mM)
TBABF4 (0.1 M), MeOH
0
0.5
1
1.5
2
2.5
Potential (V vs Ag/AgCl)
50 mV/s
400 mV/s

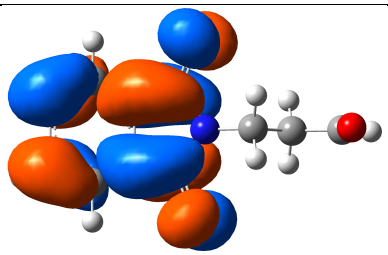
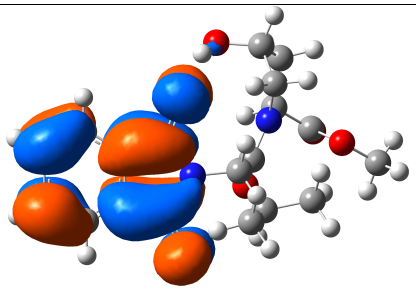
LUMO calculation

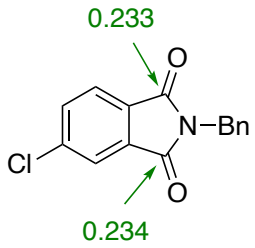
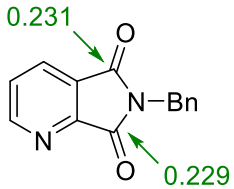
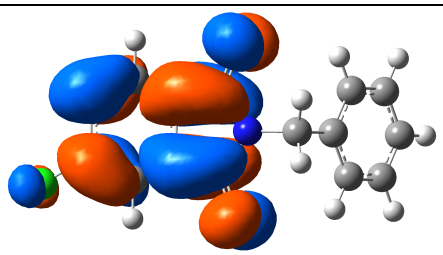
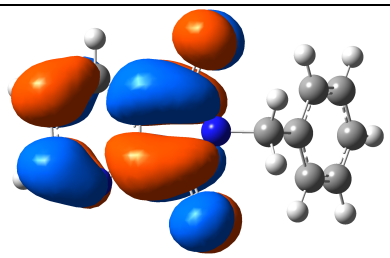
The Gaussian 09 software program was used to carry out all the density functional theory calculations reported herein.(*19*) The hybrid B3LYP functional was used to perform the geometry optimizations in the gas phase without symmetry constraints.(*20,21*) The 6-31+G(d,p) basis set was used to describe all the elements.(*22,23*) The self-consistent field (SCF) calculations were carried out using an ultrafine grid and a convergence criterion of 10^{-8} Ha. All structures were optimized until the maximum force, root-mean-square force, maximum displacement, and root-mean-square displacement reached values of 4.5×10^{-4} Ha/a_0, 3.0×10^{-4} Ha/a_0, 1.8×10^{-3} a_0, and 1.2×10^{-3} a_0, respectively where a_0 is the Bohr radius. E(RB3LYP) energies are given in Hartrees. Molecular orbital coefficients were obtained using the population analysis pop=full keyword. Visualization of the spin density maps (SPM)(*24*) for the radical anions was carried out with Spartan'14.(*25*)

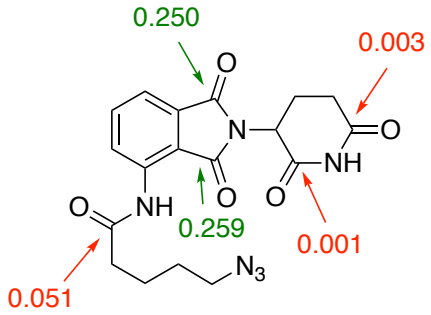
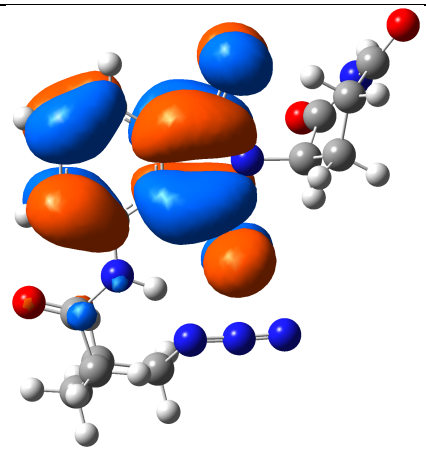
Cartesian coordinates and LUMO coefficients for optimized structures

Selected LUMO coefficients for the carbonyl carbon atoms ($2p_z$ eigenvalues at the B3LYP/6-31+G(d,p) level) and calculated LUMO surfaces. The green numbers correspond to the reactive C=O functions, and the red numbers correspond to the unreactive C=O functions.

 **17**	 **53**
E(RB3LYP) = -705.0803184	E(RB3LYP) = -1298.24905368

	
LUMO surface of **17** (-0.09830 au)	LUMO surface of **53** (-0.10154 au)
C -0.221151 -3.955169 0.700893 C -0.221151 -3.955169 -0.700893 C -0.086493 -2.761419 -1.425270 C 0.046593 -1.586091 -0.698864 C 0.046593 -1.586091 0.698864 C -0.086493 -2.761419 1.425270 C 0.207967 -0.176151 -1.164740 N 0.302521 0.603418 0.000000 C 0.207967 -0.176151 1.164740 O 0.252349 0.256351 2.301536 O 0.252349 0.256351 -2.301536 C 0.502246 2.047982 0.000000 C -0.823537 2.814755 0.000000 C -0.648035 4.313687 0.000000 H -1.593354 4.898625 0.000000 O 0.424906 4.881482 0.000000 H -0.326826 -4.895622 1.233233 H -0.326826 -4.895622 -1.233233 H -0.084235 -2.750986 -2.510420 H -0.084235 -2.750986 2.510420 H 1.087973 2.301741 0.885573 H 1.087973 2.301741 -0.885573 H -1.430989 2.550561 -0.877691 H -1.430989 2.550561 0.877691	C 5.527756 -0.682462 -1.456030 C 5.307089 -1.773859 -0.603665 C 4.163664 -1.840983 0.204972 C 3.264958 -0.785327 0.123302 C 3.484095 0.300456 -0.724528 C 4.613455 0.378745 -1.527435 C 1.975116 -0.559872 0.826445 N 1.489992 0.683661 0.402674 C 2.347941 1.259082 -0.573751 O 2.199282 2.324613 -1.130466 O 1.408591 -1.297286 1.624415 C 0.140075 1.127643 0.803798 C -0.049343 2.661462 0.859138 C -0.861709 0.460280 -0.168094 C -1.482023 2.976625 1.322993 C 0.974974 3.317430 1.796010 N -1.740357 -0.459152 0.319060 C -2.543478 -1.232727 -0.641467 C -3.069328 -2.437821 0.187858 C -2.106424 -2.516406 1.377587 C -1.830723 -1.038203 1.666522 C -3.685495 -0.465880 -1.295986 O -4.194529 -0.810816 -2.341668 O -0.835020 0.749905 -1.364173 O -0.935003 -3.209575 0.955438 O -4.112026 0.580137 -0.560218 C -5.206359 1.331766 -1.124095 H 6.421539 -0.661275 -2.072233 H 6.033481 -2.580215 -0.572385 H 3.983394 -2.681726 0.866882 H 4.773500 1.226957 -2.185003 H 0.015324 0.744441 1.817894 H 0.086141 3.052130 -0.152002 H -1.632703 4.060407 1.353355 H -2.235929 2.554472 0.652073 H -1.668493 2.589872 2.333707

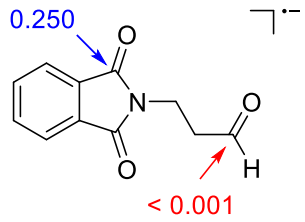
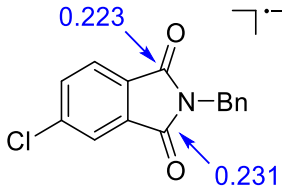
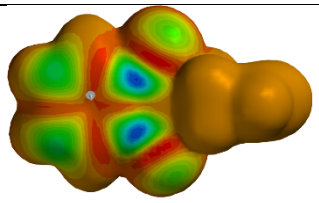
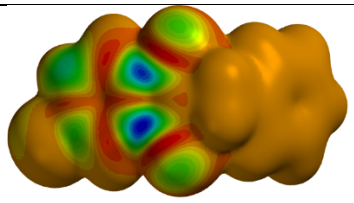
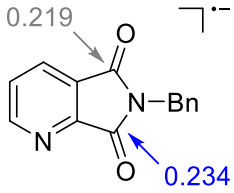
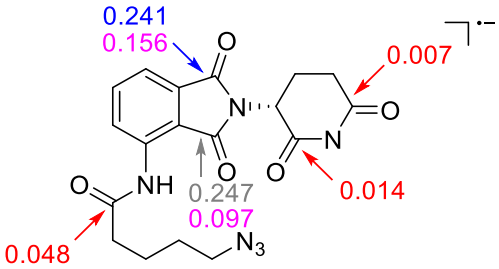
	H 0.805592 4.398506 1.836199 H 2.002825 3.161014 1.459624 H 0.883786 2.928836 2.818678 H -1.900210 -1.564791 -1.459553 H -3.072182 -3.359277 -0.396204 H -4.087152 -2.251856 0.547932 H -2.555059 -3.020725 2.244171 H -2.667807 -0.596216 2.223968 H -0.911480 -0.897086 2.232766 H -0.147570 -2.816468 1.363037 H -6.080323 0.690081 -1.258898 H -5.415205 2.123556 -0.405226 H -4.914727 1.752297 -2.088992
 **54**	 **11**
E(RB3LYP) = -1243.0984322	E(RB3LYP) = -799.5338525
	
LUMO surface of **54** (-0.10300 au)	LUMO surface of **11** (-0.10347 au)
C -3.589501 1.149968 -0.685107 C -3.719884 -0.213635 -0.390417 C -2.673271 -0.960514 0.167098 C -1.491090 -0.279347 0.413563 C -1.344390 1.079131 0.125921 C -2.384808 1.815251 -0.424260 C -0.204507 -0.774538 0.995823 N 0.652917 0.333761 1.018853 C 0.036316 1.491092 0.515396 O 0.556717 2.588474 0.440695 O 0.074394 -1.892364 1.386924 C 2.035749 0.289230 1.507040	C -4.269943 0.631597 -1.001305 C -4.185581 -0.767752 -0.940335 N -3.134994 -1.443500 -0.440740 C -2.145453 -0.679399 0.005201 C -2.127361 0.715739 -0.008821 C -3.212711 1.412668 -0.521247 C -0.852424 -1.158781 0.617780 N -0.138007 0.013192 0.928123 C -0.839859 1.177061 0.588469 O -0.451040 2.316066 0.769942 O -0.468624 -2.288999 0.828649 C 1.195988 0.013467 1.540641

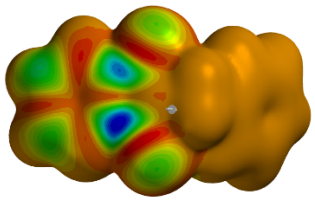
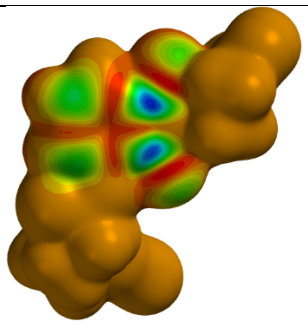
C 3.045357 -0.051311 0.425780 C 3.373285 -1.387677 0.156821 C 4.297190 -1.701853 -0.842816 C 4.904171 -0.682794 -1.582392 C 4.583073 0.651668 -1.318373 C 3.658667 0.965716 -0.318931 Cl -5.242911 -1.012078 -0.730509 H -4.429573 1.683054 -1.116229 H -2.783552 -2.015108 0.392788 H -2.269601 2.871104 -0.646380 H 2.246535 1.272187 1.934619 H 2.060701 -0.456778 2.304820 H 2.898868 -2.180425 0.728766 H 4.544672 -2.740847 -1.040923 H 5.624864 -0.926999 -2.357576 H 5.053318 1.448504 -1.887502 H 3.405807 2.003115 -0.117534	C 2.324103 0.000261 0.525123 C 2.818036 -1.214711 0.029224 C 3.850364 -1.226806 -0.911855 C 4.400779 -0.024470 -1.365041 C 3.914524 1.190112 -0.873399 C 2.881497 1.202230 0.067292 H -5.157233 1.094702 -1.420658 H -5.005935 -1.376587 -1.312108 H -3.234441 2.497631 -0.545800 H 1.252080 0.906800 2.166804 H 1.242799 -0.871276 2.179894 H 2.387494 -2.149491 0.377647 H 4.225664 -2.174239 -1.287967 H 5.205674 -0.034221 -2.094436 H 4.340025 2.127874 -1.219184 H 2.500437 2.147137 0.445032
 **38**	
E(RB3LYP) = -1401.4971509	
	
LUMO surface of **38** (-0.10605 au)	
C -0.782162 3.946099 -0.717519	

C -1.826090 3.121258 -0.292940 C -1.572910 1.792523 0.125935 C -0.235959 1.372562 0.091030 C 0.793536 2.214656 -0.340393 C 0.554458 3.514008 -0.753370 C 0.354783 0.072738 0.469501 N 1.741040 0.189504 0.259000 C 2.074603 1.457281 -0.252877 O 3.201994 1.813332 -0.542907 O -0.204209 -0.927867 0.895791 C 2.649312 -0.945255 0.404781 N -2.546785 0.894603 0.564207 C -3.908432 1.107079 0.691212 C -4.693779 -0.080158 1.233035 C -5.687659 -0.641185 0.193058 C -5.068233 -1.237073 -1.083714 O -4.457224 2.163649 0.397110 C -4.285249 -2.538522 -0.912512 C 3.421841 -1.161362 -0.911364 N 4.805044 -1.148184 -0.830199 C 5.609770 -0.657954 0.207083 C 4.866505 -0.143249 1.419336 C 3.551640 -0.896474 1.651891 O 2.848222 -1.393321 -1.959784 O 6.820618 -0.648074 0.082436 N -3.010545 -2.280414 -0.188054 N -2.237367 -3.241799 -0.113199 N -1.452133 -4.059997 0.014802 H -1.023154 4.957051 -1.032286 H -2.843458 3.485629 -0.280908 H 1.359010 4.159429 -1.088096 H 1.982050 -1.809093 0.487032 H -2.210353 -0.047647 0.751792 H -4.026912 -0.865785 1.594372 H -5.264195 0.299787 2.087863 H -6.303171 -1.404884 0.686010 H -6.365213 0.169210 -0.096909 H -5.883625 -1.451824 -1.785666 H -4.426035 -0.498744 -1.579879 H -4.882462 -3.273575 -0.353581 H -4.060740 -2.966562 -1.898190 H 5.295341 -1.383136 -1.689052 H 5.538425 -0.226038 2.276565 H 4.679224 0.921996 1.240140 H 2.992659 -0.454835 2.481711 H 3.776793 -1.930547 1.938990	

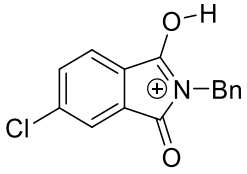
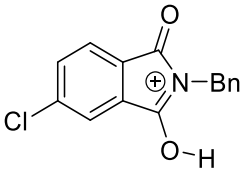
Spin density maps (SDM) for the radical anions of compounds leading to regioisomers

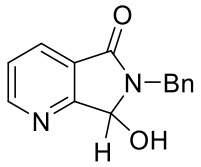
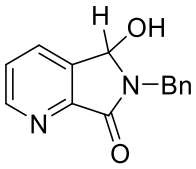
SDM visualizations show reactive sites with high spin density in blue. The numbers represent the alpha spin $2p_z$ coefficients for the carbon atoms in the SOMO. Blue numbers correspond to the major reactive C=O functions, grey numbers correspond to the minor reactive C=O functions, red numbers correspond to the unreactive C=O functions, and purple numbers correspond to Mulliken charges.

	
	
SDM of the radical anion of **17** (symmetric reference)	SDM of the radical anion of **54**
	

	
SDM of the radical anion of **11**	SDM of the radical anion of **38**

Cartesian coordinates and stabilities of isomeric species in chemoselective reductions

	
E(RB3LYP) = -1243.438322 Most stable **54**-H^+ leads to major product	E(RB3LYP) = -1243.4302276 Least stable **54**-H^+ (+5.1 kcal mol)
C -3.341055 1.630176 0.016270 C -3.873867 0.344657 -0.168400 C -3.063286 -0.809742 -0.130338 C -1.716832 -0.611800 0.103121 C -1.174424 0.670613 0.288574 C -1.972543 1.810073 0.247187 C -0.608694 -1.595957 0.197335 N 0.595137 -0.790349 0.449931 C 0.253492 0.501398 0.500453 O 1.055859 1.498258 0.707634 O -0.577801 -2.790245 0.101351 C 1.921982 -1.413254 0.690129 C 3.067426 -0.583180 0.147391 C 3.311814 -0.518985 -1.234256 C 4.365042 0.252850 -1.725402 C 5.184747 0.969220 -0.845104 C 4.955721 0.905713 0.530332 C 3.900435 0.130351 1.028016 Cl -5.570552 0.162694 -0.451720 H -4.003273 2.487743 -0.022068 H -3.484131 -1.798390 -0.276611	C -3.621342 1.102824 -0.676349 C -3.696102 -0.269498 -0.399354 C -2.606994 -0.970162 0.153170 C -1.457055 -0.236077 0.407014 C -1.374921 1.138819 0.132456 C -2.449324 1.826247 -0.408907 C -0.159370 -0.624655 0.970303 N 0.659321 0.407462 1.045113 C -0.028604 1.608374 0.527739 O 0.494161 2.685262 0.495351 O 0.231328 -1.801039 1.379657 C 2.080518 0.416623 1.497517 C 3.037502 0.007436 0.397782 C 3.528180 -1.304434 0.340443 C 4.414669 -1.679324 -0.671869 C 4.814072 -0.746254 -1.632211 C 4.333474 0.565448 -1.574706 C 3.450690 0.943775 -0.561744 Cl -5.157840 -1.133635 -0.740362 H -4.484173 1.603317 -1.101840 H -2.700428 -2.032450 0.355634

H -1.560636 2.803565 0.388349 H 2.027244 -1.575564 1.767704 H 1.863779 -2.393783 0.211793 H 2.688815 -1.083891 -1.923111 H 4.553256 0.289261 -2.793727 H 6.005900 1.564254 -1.231746 H 5.600180 1.443166 1.218572 H 3.752086 0.050048 2.103081 H 2.005992 1.223343 0.743750	H -2.389941 2.888688 -0.620830 H 2.258823 1.441134 1.829412 H 2.143293 -0.249135 2.360511 H 3.234655 -2.028893 1.095754 H 4.800333 -2.693558 -0.703278 H 5.507163 -1.036478 -2.415626 H 4.655423 1.296707 -2.309448 H 3.095662 1.969582 -0.509252 H -0.449035 -2.487997 1.281557
 **11**	
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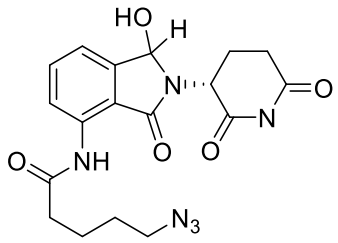
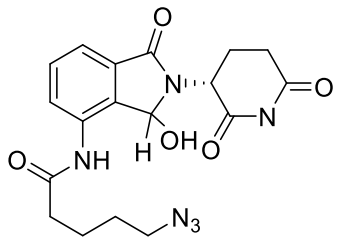
H 1.878910 2.009068 -0.537332 O -0.784251 2.376252 1.098075 H 0.061270 -1.425527 -0.512996 H -1.090301 -2.849541 0.947164	H -5.175415 -1.518709 0.523426 H -3.272906 -0.769262 1.924439 H -0.156217 -1.299156 -0.412891 H -0.478113 -2.126121 1.575430
 **39**	
E(RB3LYP) = -1402. 6865588 Most stable **39**	E(RB3LYP) = - 1402.6857154 Least stable isomer (+0.5 kcal mol)
C 0.673758 3.926447 0.796886 C 1.689053 3.133093 0.252622 C 1.425799 1.793845 -0.099028 C 0.119447 1.325873 0.119965 C -0.878791 2.126336 0.667935 C -0.625069 3.444342 1.020146 C -0.446526 -0.005555 -0.168815 N -1.783250 0.046102 0.176373 C -2.158275 1.315028 0.784475 O -3.269056 1.854366 0.067545 O 0.130181 -0.995975 -0.623137 C -2.613864 -1.159605 0.096385 N 2.351895 0.903032 -0.647534 C 3.679543 1.126024 -0.944397 C 4.398806 -0.062109 -1.573729 C 5.687398 -0.428718 -0.811819 C 5.501089 -0.905492 0.639489 O 4.251129 2.192950 -0.738402 C 4.835072 -2.268283 0.826157 C -3.815677 -1.041188 1.043049 N -5.071089 -1.026143 0.457120 C -5.398774 -0.815133 -0.892658 C -4.219924 -0.691649 -1.828264 C -3.025740 -1.518002 -1.343182 O -3.688358 -0.993705 2.256424 O -6.567873 -0.727516 -1.220095 N 3.389146 -2.186969 0.483411 N 2.724643 -3.198341 0.726836 N 2.015265 -4.074601 0.911490 H 0.909407 4.954481 1.056638	C 0.925167 4.050396 0.412728 C 1.976248 3.161839 0.152730 C 1.717394 1.813541 -0.169371 C 0.373551 1.415959 -0.217247 C -0.655592 2.318598 0.038828 C -0.412877 3.649407 0.363064 C -0.209893 0.051319 -0.505062 N -1.651184 0.313448 -0.500685 C -1.952782 1.599738 -0.071697 O 0.236638 -0.545828 -1.716047 C -2.595501 -0.803957 -0.483716 N 2.715296 0.862838 -0.447006 C 4.081001 0.983857 -0.288052 C 4.875743 -0.268286 -0.643586 C 5.356631 -1.029992 0.612709 C 4.260830 -1.613319 1.522906 O 4.632386 2.000701 0.121252 C 3.459991 -2.784879 0.954666 C -3.051301 -1.089835 0.961080 N -4.411700 -1.140543 1.200677 C -5.460668 -0.708635 0.373518 C -5.043456 -0.100657 -0.943130 C -3.754252 -0.717126 -1.500517 O -2.241475 -1.316802 1.846354 O -6.610482 -0.808638 0.760946 N 2.533889 -2.313941 -0.116536 N 1.835128 -3.191913 -0.636355 N 1.145337 -3.919534 -1.181476 H 1.170010 5.078627 0.661831 H 3.002320 3.497283 0.207962

H 2.680692 3.533853 0.097694 H -1.390074 4.086591 1.445846 H -2.009993 -1.980330 0.500633 H 1.991833 -0.039342 -0.787594 H 3.734284 -0.924897 -1.659012 H 4.672145 0.248994 -2.589601 H 6.217466 -1.203113 -1.381825 H 6.334281 0.454843 -0.801549 H 6.493759 -0.976248 1.101654 H 4.947317 -0.156366 1.218629 H 5.320093 -3.022517 0.189490 H 4.941355 -2.591094 1.870321 H -5.856813 -1.030927 1.101983 H -4.554397 -0.991953 -2.823787 H -3.956660 0.372740 -1.870501 H -2.162985 -1.388149 -1.999673 H -3.282119 -2.584414 -1.364961 H -2.445183 1.162747 1.833330 H -3.782807 2.421041 0.658447	H -1.230014 4.331799 0.570503 H -1.990004 -1.674598 -0.752772 H 2.384162 -0.055700 -0.726751 H 4.301444 -0.929393 -1.297917 H 5.754813 0.076817 -1.196532 H 6.021720 -1.840456 0.286726 H 5.970080 -0.344404 1.207943 H 4.742875 -1.982349 2.436580 H 3.566037 -0.827550 1.843257 H 4.135592 -3.547845 0.542902 H 2.868832 -3.250963 1.753310 H -4.684176 -1.427771 2.137087 H -5.877558 -0.218714 -1.638616 H -4.897790 0.968835 -0.754991 H -3.415313 -0.157130 -2.376250 H -3.968883 -1.737033 -1.841505 O -3.077233 2.021242 0.170022 H 0.039401 -0.682653 0.269240 H 0.079019 0.077534 -2.441665

Frequently asked questions

Question 1: The reaction described here does not work. What should I do?

Answer: There are two possible scenarios.

(1) Electrochemical issue (connection problem)

(2) Non-electrochemical issue (insufficient Ar purge, electrode surface area)

For **(1)**, make sure the contacts of the cap are in full contact with the contacts of the ElectraSyn. If contacts make a good connection, remove the cap and adjust the electrodes making sure there is a solid connection between the reaction electrodes and metal pins in the cap. If the pins are dirty, a cotton ball soaked in 1.0 M HCl can be used to quickly clean them, followed by a water rinse and drying completely. Ensure that the electrodes are submerged in solvent (0.5-1 cm) and do not touch one another.

Figure S17. Example of rusty metal contacts. Connection problems frequently occur with such contacts.

For **(2)**, wrap the top of the vial with Teflon tape or use ProSeal to ensure a strong seal between the vial and the cap (as demonstrated in the graphical guide). Plunge a needle attached to an Ar balloon into the fully assemble vial; little to no bubbles will appear if a good seal is formed. Vent the vial to degas solvent once good seal is achieved. When a reaction still does not work or remains irreproducible, modulate applied current (mA) to double or half with the same F/mol. This treatment may solve inappropriate current density issue that originates from porous nature of RVC electrode.

Question 2: How can I tune the current and frequency?

Answer: You can start from constant current at 20 mA with 100 ms (5 Hz) rAP. If a reaction is messy, try faster rAP (increase frequency to 10 Hz or higher) to improve the precision of redox reactions. You might see much lower conversion with increased frequency since current efficiency typically decreases as frequency increases. In this case, you can increase the current (while

maintaining the same frequency) so that the reactivity is restored. Electron amounts (F/mol) can be optimized simply by monitoring the reaction by TLC or NMR.

Question 3: What kind of solvents can be use for rAP?

Answer: Within the scope of this study, we confirmed that we could use common solvents for electrosynthesis such as CH_3CN, acetone, CH_3OH, THF, H_2O, CH_2Cl_2 and DMF under rAP conditions.

Question 4: Is rAP safe? Are there any concerns regarding heating effects?

Answer: rAP was found to generate a small amount of heat during a reaction. However, this exothermicity was found to be similar to heat generated from using direct current electrolysis. Please see the following section titled "Exothermicity of rAP" for the detailed investigation on this point.

Question 5: What is the limit for large scale rAP chemistry using IKA ElectraSyn?

Answer: In this study, a 5 mmol-scale reaction was carried out using a 20 mL ElectraSyn vial. On this scale, the reaction was completed in one day. This was the largest scale that could be conveniently run. Otherwise, reaction times on even larger scales might be very long, and a 20 mL vial might not be able to accommodate the entire amount of substrate. To overcome this limit, employing a flow apparatus for rAP chemistry is currently under investigation.

Question 6: Is there any appropriate reaction voltage?

Answer: Typically, the reaction voltage under the conditions described above is between 8-11 V (no reference). When the reaction voltage is more than 30.0 V, this may indicate (1) electrolyte concentration is too low, (2) solvent is not suitable for electrolysis (dielectric constant is too high), or (3) there is a connection issue (please see Q1 for troubleshooting).

Exothermicity of rAP

As alternating current is known to be useful for Joule heating, the exothermic effect during electrolysis was studied to address safety concerns. Two identical reactions of the reduction of *N*-(*N*-Boc-piperidin-4-yl)phthalimide **2**, were performed by applying direct current **(A)** (20 mA, 12 F/mol) and rAP **(B)** (20 mA, 12 F/mol, 0.1 mmol, 100ms). FLIR ONE Gen 3 – iOS -Thermal Imaging Camera was used to monitor the temperature during these experiments. The accuracy of the measurement is claimed to be ± 0.1°C, and our calibration result also confirmed that the error is within ± 1 ºC (Figure S22). In both reactions, a marginal increase of reaction temperature was observed during electrolysis, and the temperature under rAP conditions was slightly higher than that under direct current conditions. Therefore, it was concluded that the heating effect by rAP is similar to that of DC.

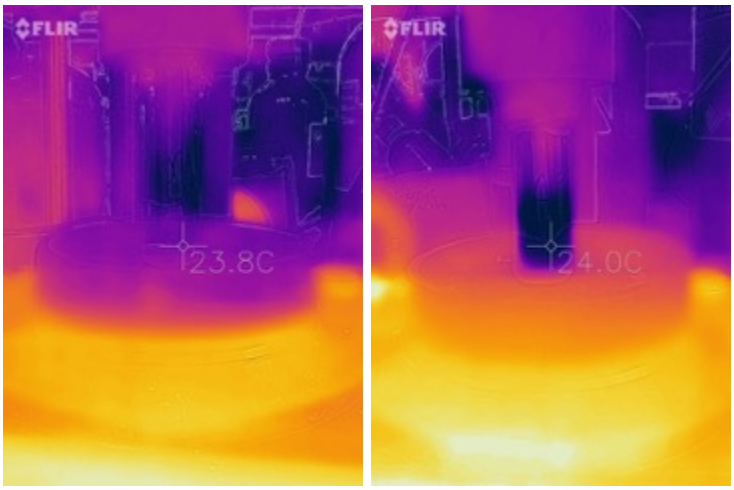


Figure S18. Time: 0 (DC = left, rAP = right).

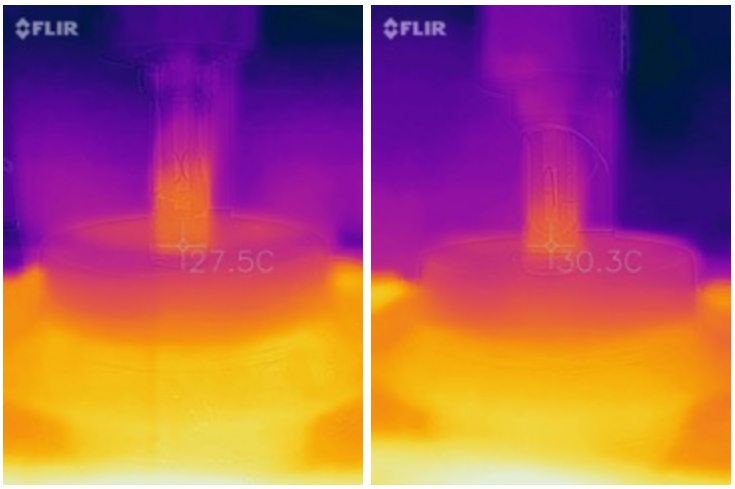


Figure S19. Time: 30 min (DC = left, rAP = right).

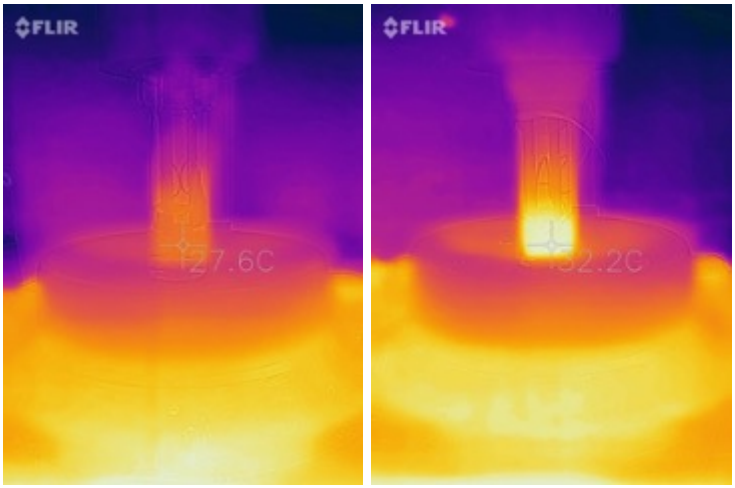


Figure S20. Time: 60 min (DC = left, rAP = right).

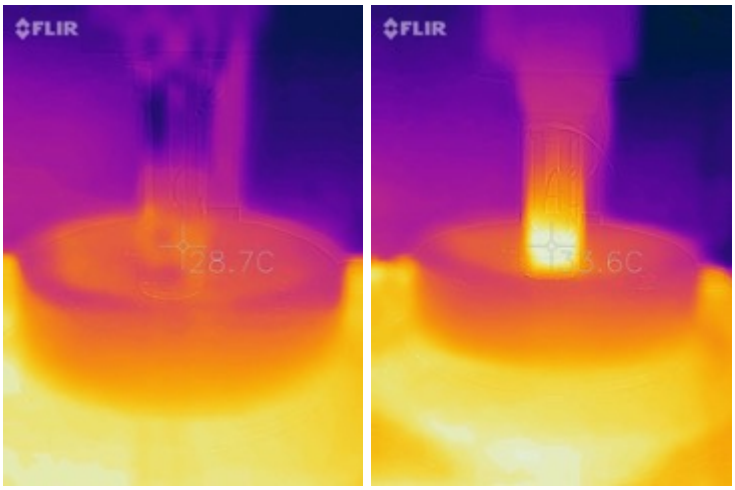


Figure S21. Time: 90 min (DC = left, rAP = right).

Figure S22. Oil bath heated to 60.0 °C (to confirm that device is calibrated).

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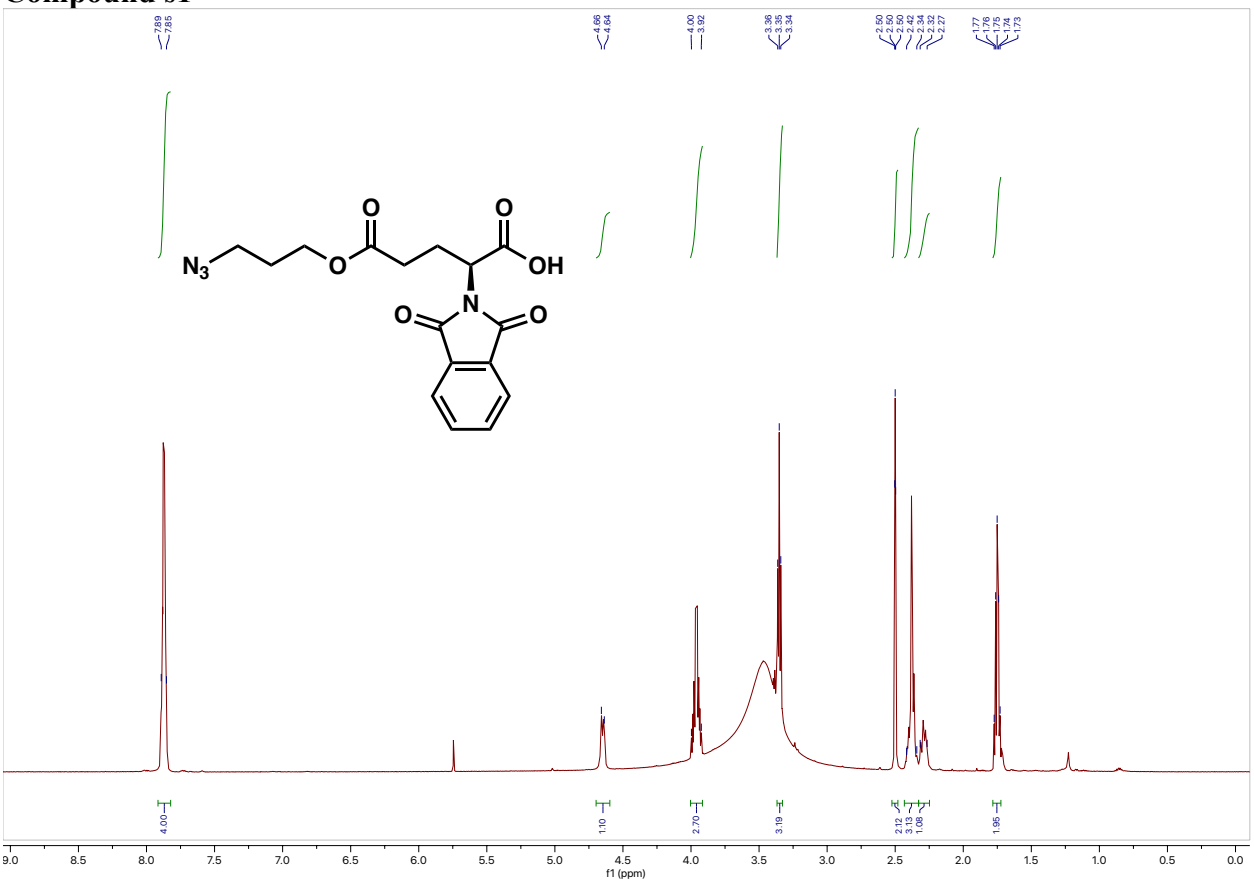
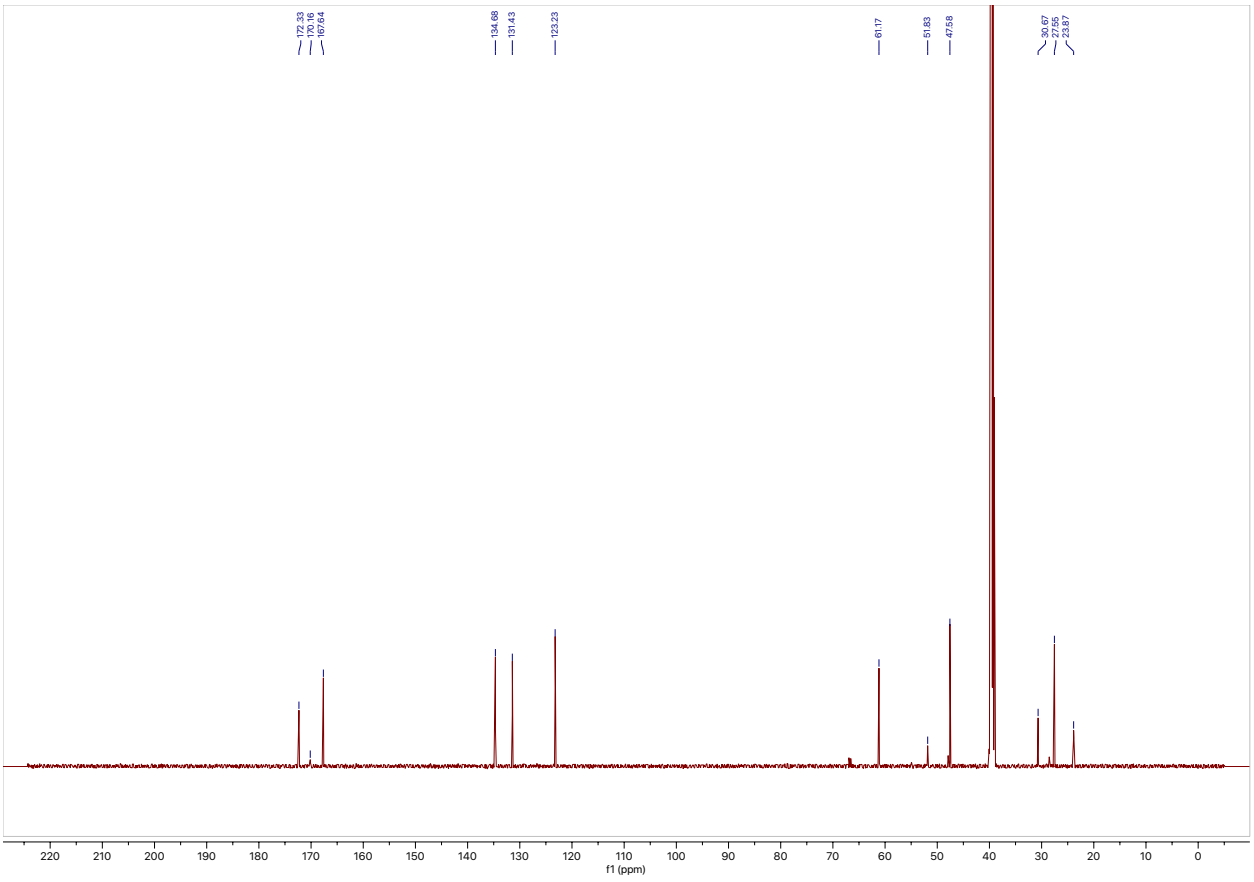
NMR Spectra

Compound s1

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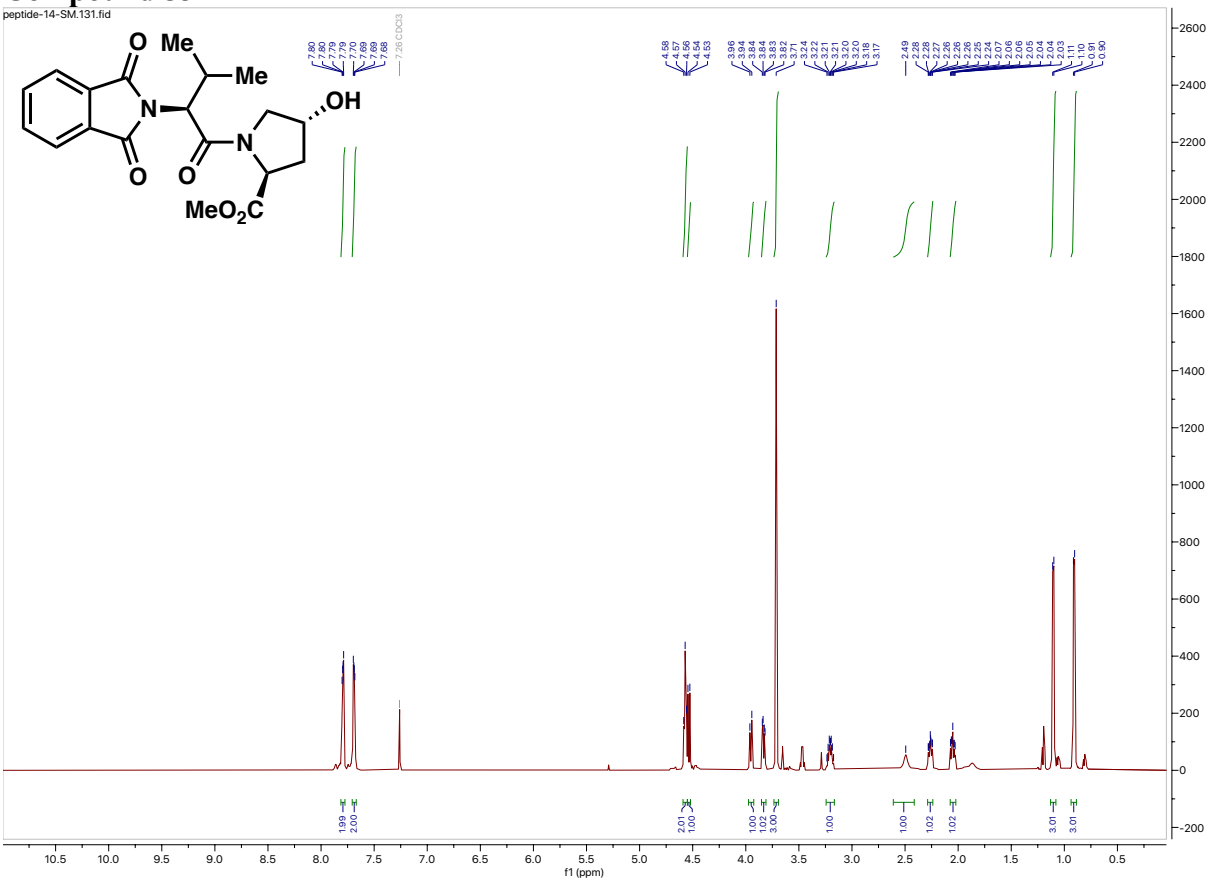
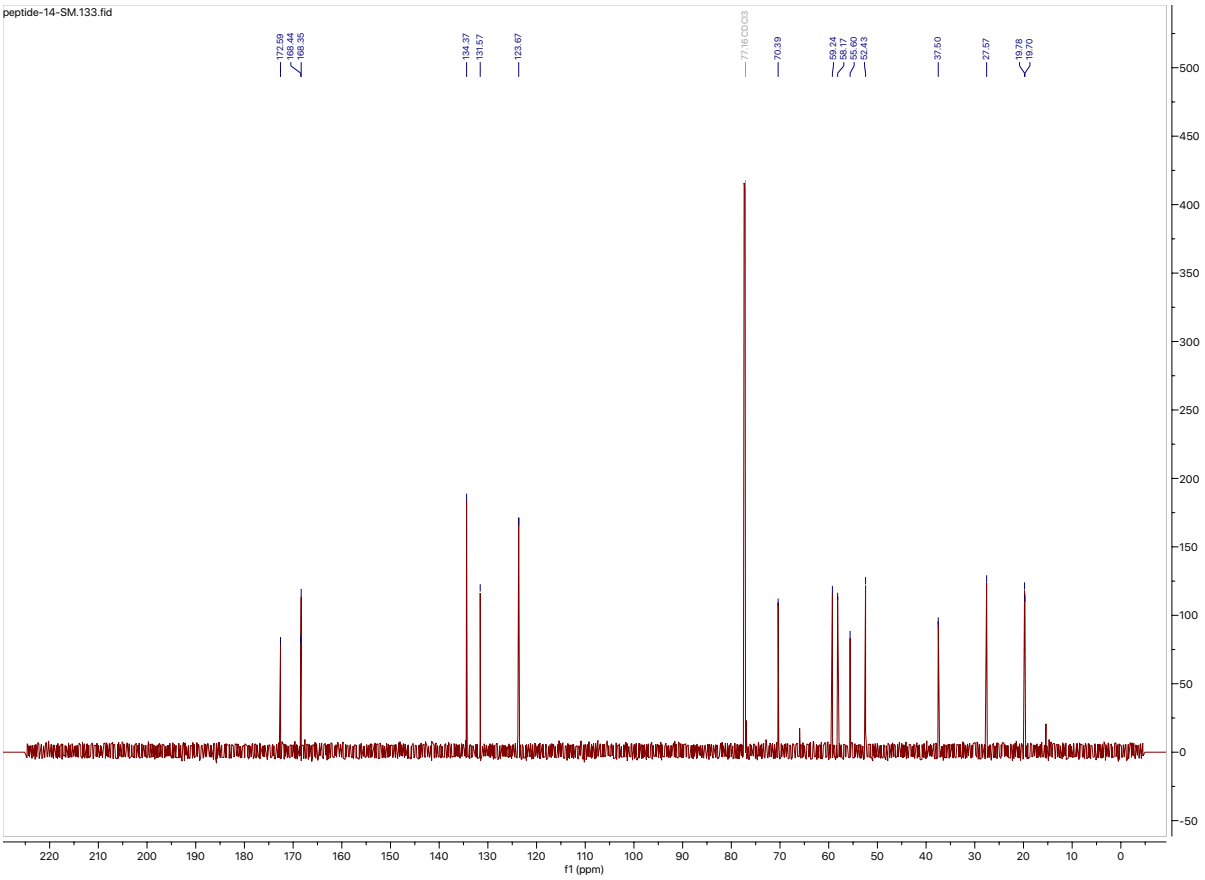
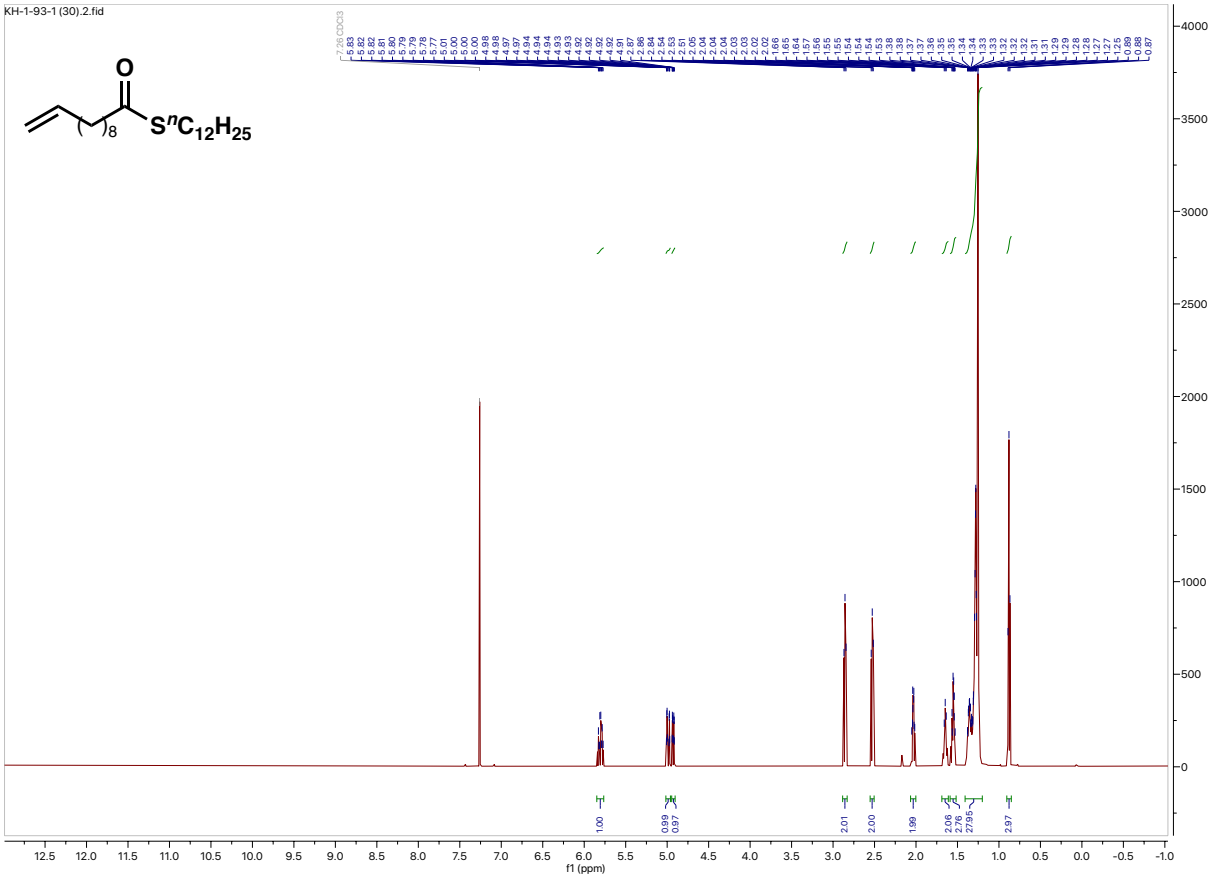
10
0
f1 (ppm)

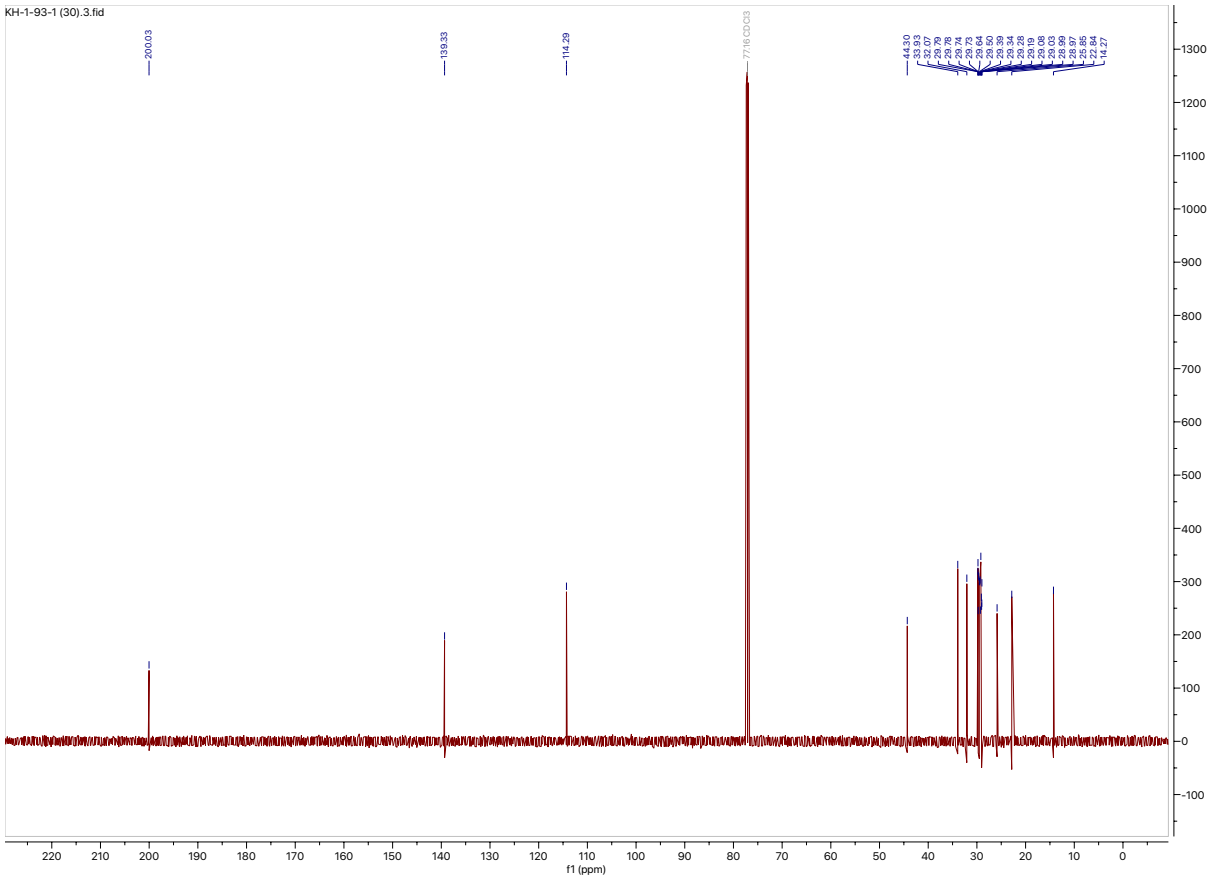
Compound 53



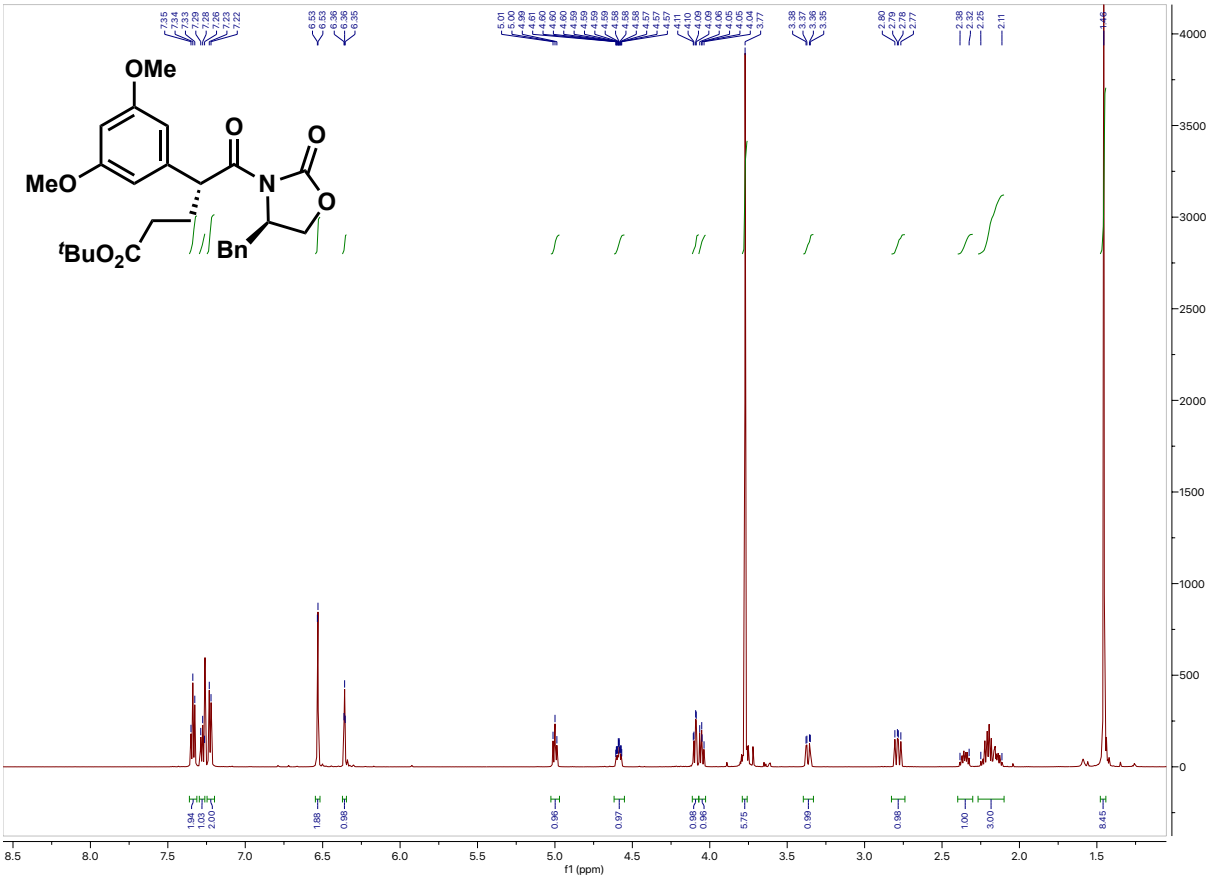

peptide-14-SM.133.fid
172.59
168.44
168.35
134.37
131.57
123.67
77.16 CDCl3
70.39
59.24
58.17
55.60
52.43
37.50
27.57
19.78
19.70
f1 (ppm)

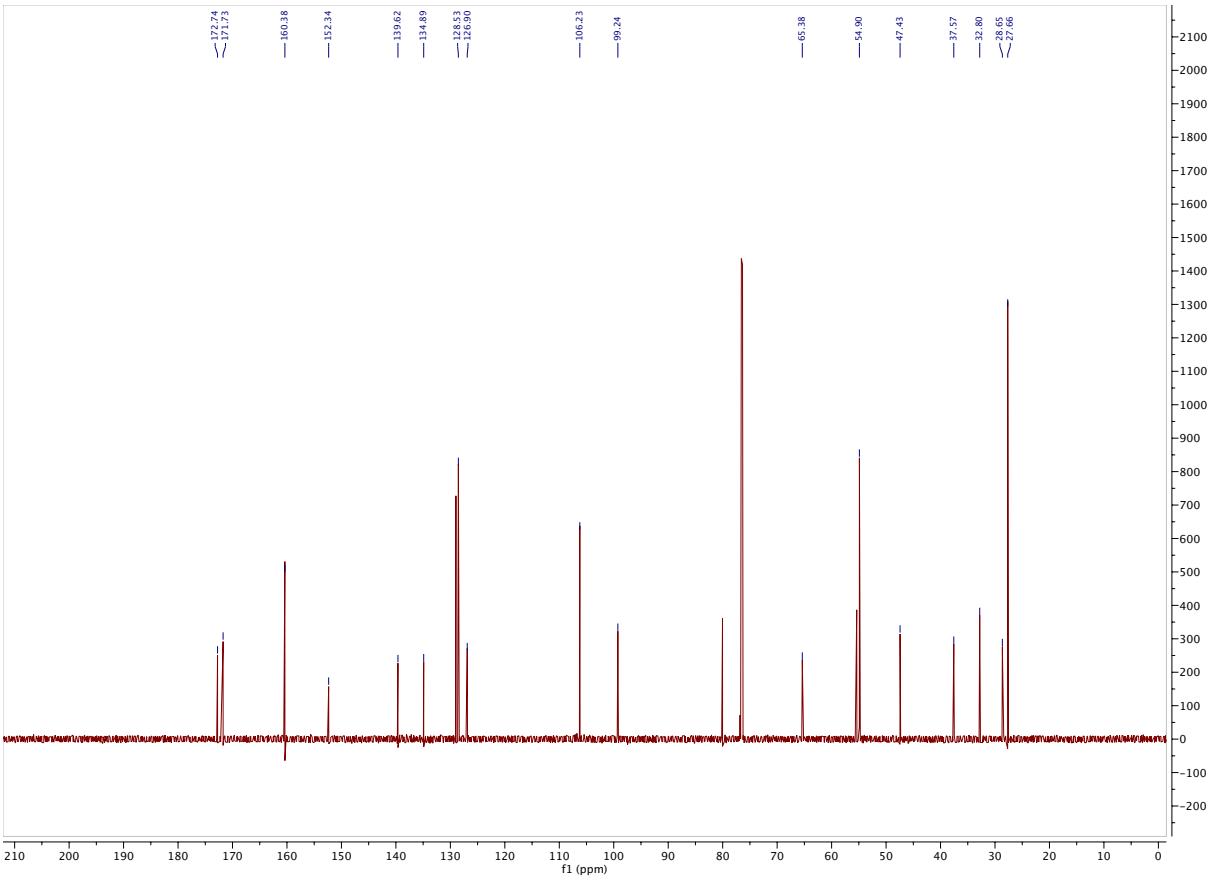
Compound 31



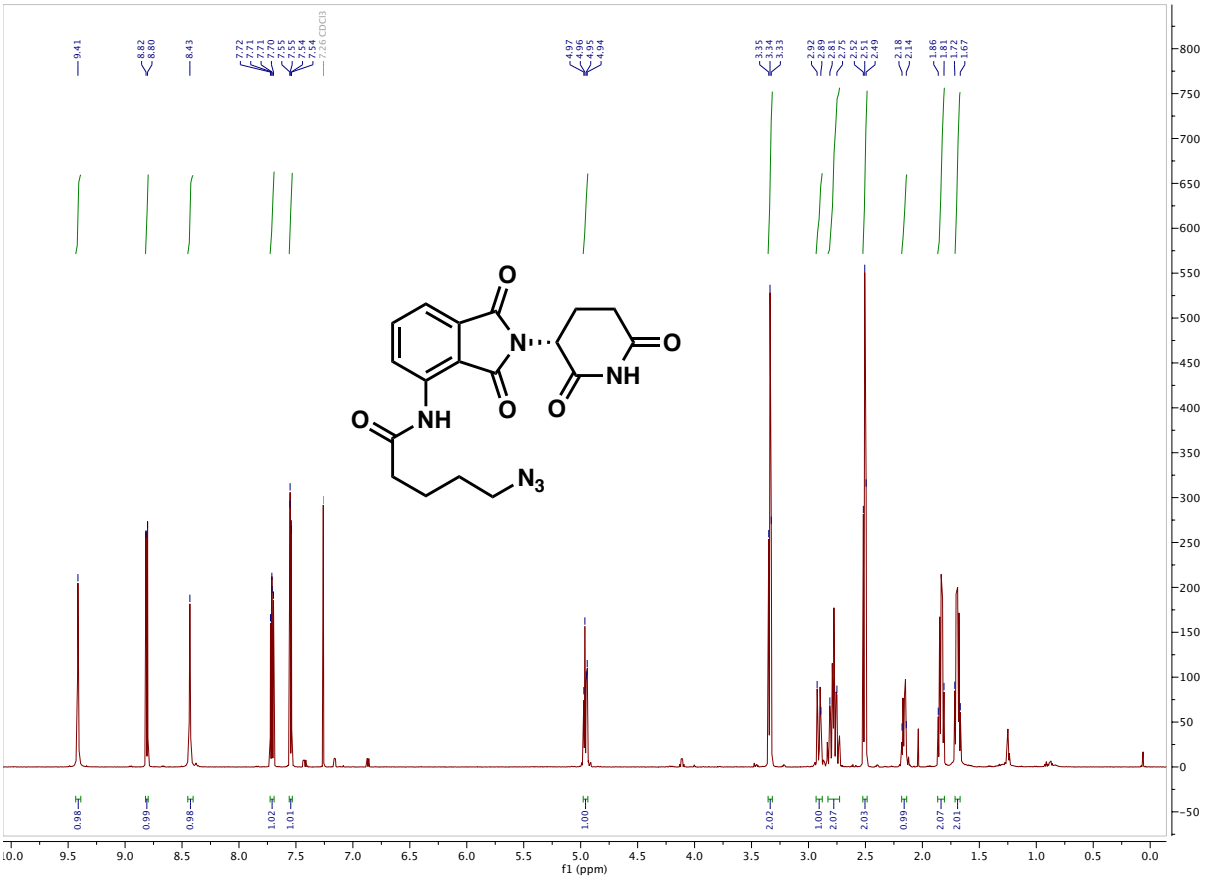

KH-1-93-1 (30).3.fid
200.03
139.33
114.29
77.16 CDCl3
44.30
43.93
32.07
29.79
29.78
29.74
29.73
29.64
29.60
29.39
29.34
29.28
29.19
29.08
29.03
28.99
28.97
25.85
22.84
14.27
f1 (ppm)

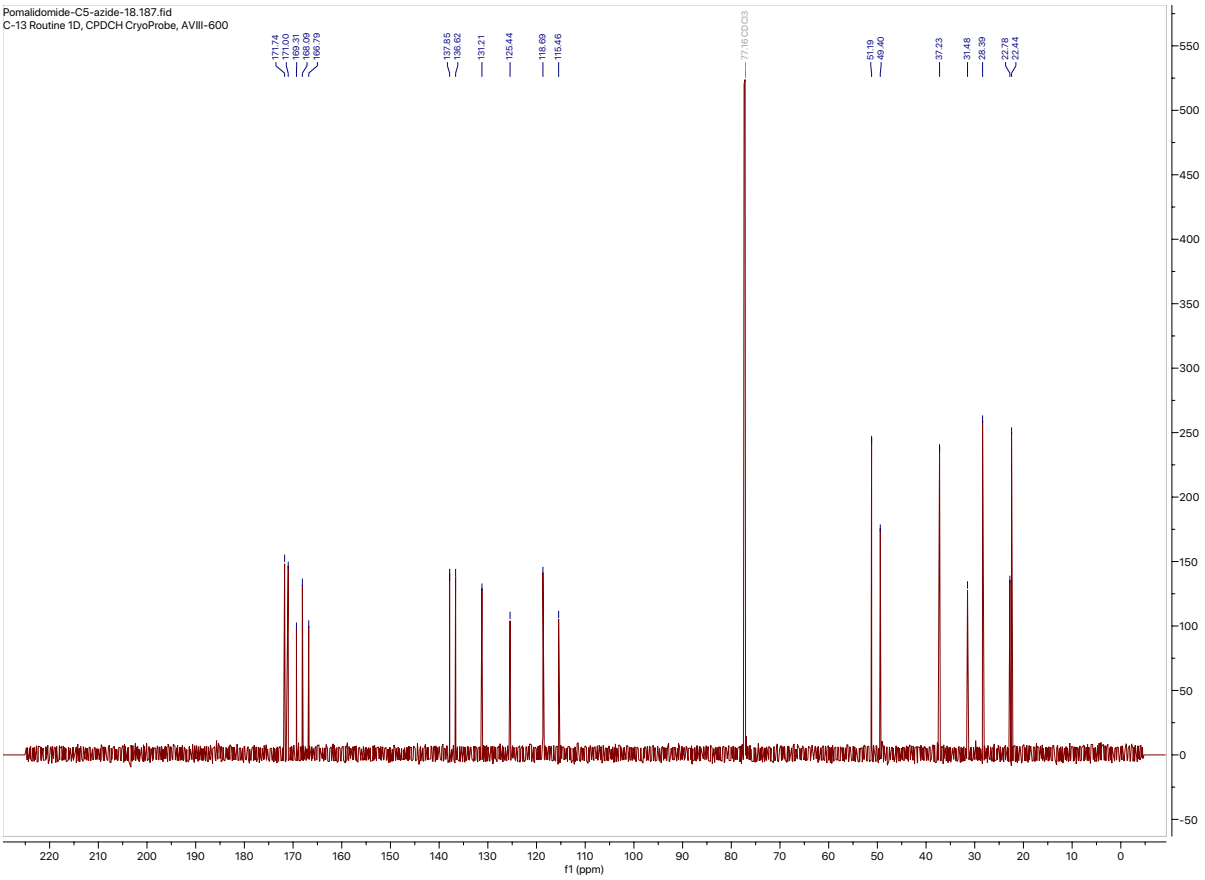
Compound 36



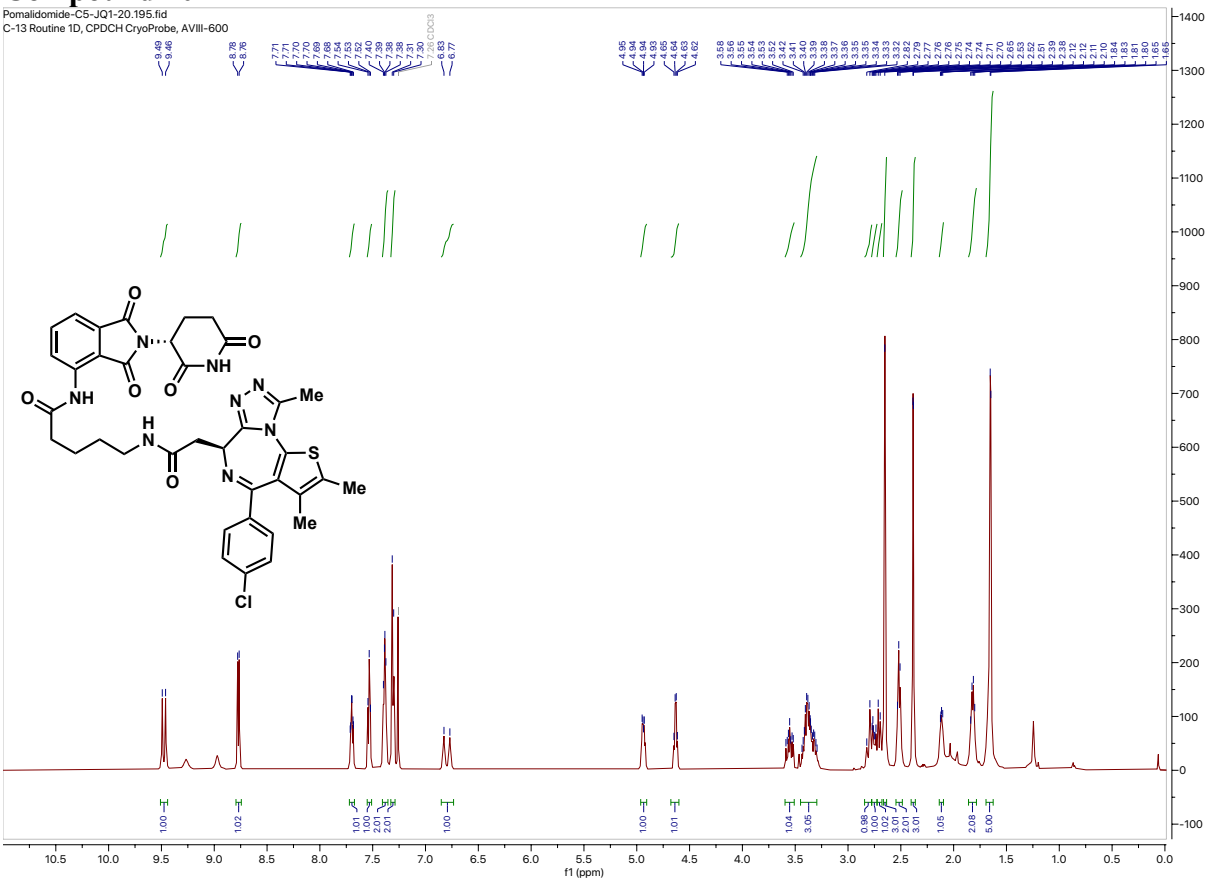

172.74
171.73
160.38
152.34
139.62
134.89
128.53
128.00
106.23
99.24
65.38
54.90
47.43
37.57
32.80
28.65
27.66
f1 (ppm)

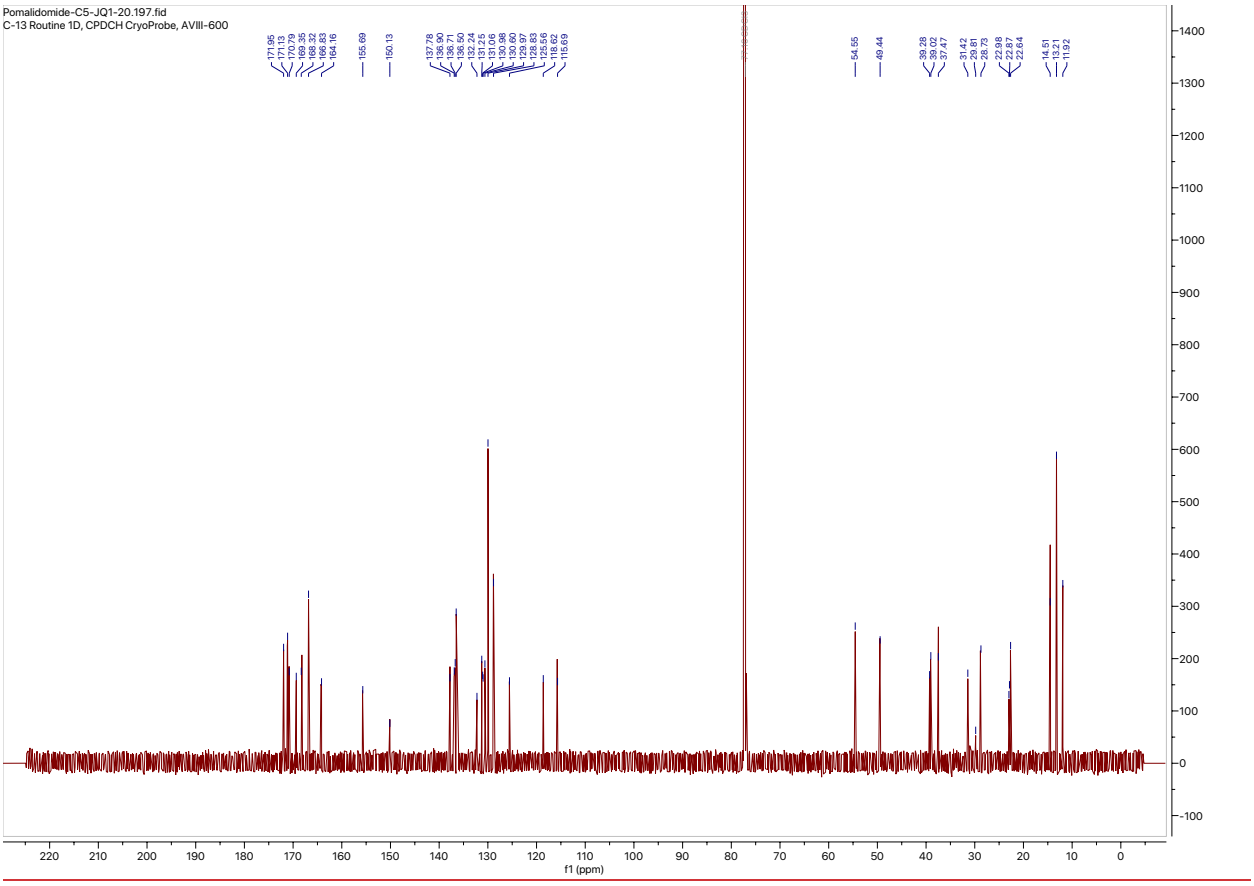
Compound 38


9.41
8.82
8.80
8.43
7.72
7.71
7.71
7.70
7.55
7.55
7.54
7.54
7.26 CDCl3
4.97
4.96
4.95
4.94
3.35
3.34
3.33
2.92
2.89
2.81
2.75
2.52
2.51
2.49
2.18
2.14
1.86
1.81
1.72
1.67
O
N
O
NH
O
O
O
NH
N3
0.98
0.99
0.98
1.02
1.01
1.00
2.02
1.00
2.07
2.03
0.99
2.07
2.01
f1 (ppm)

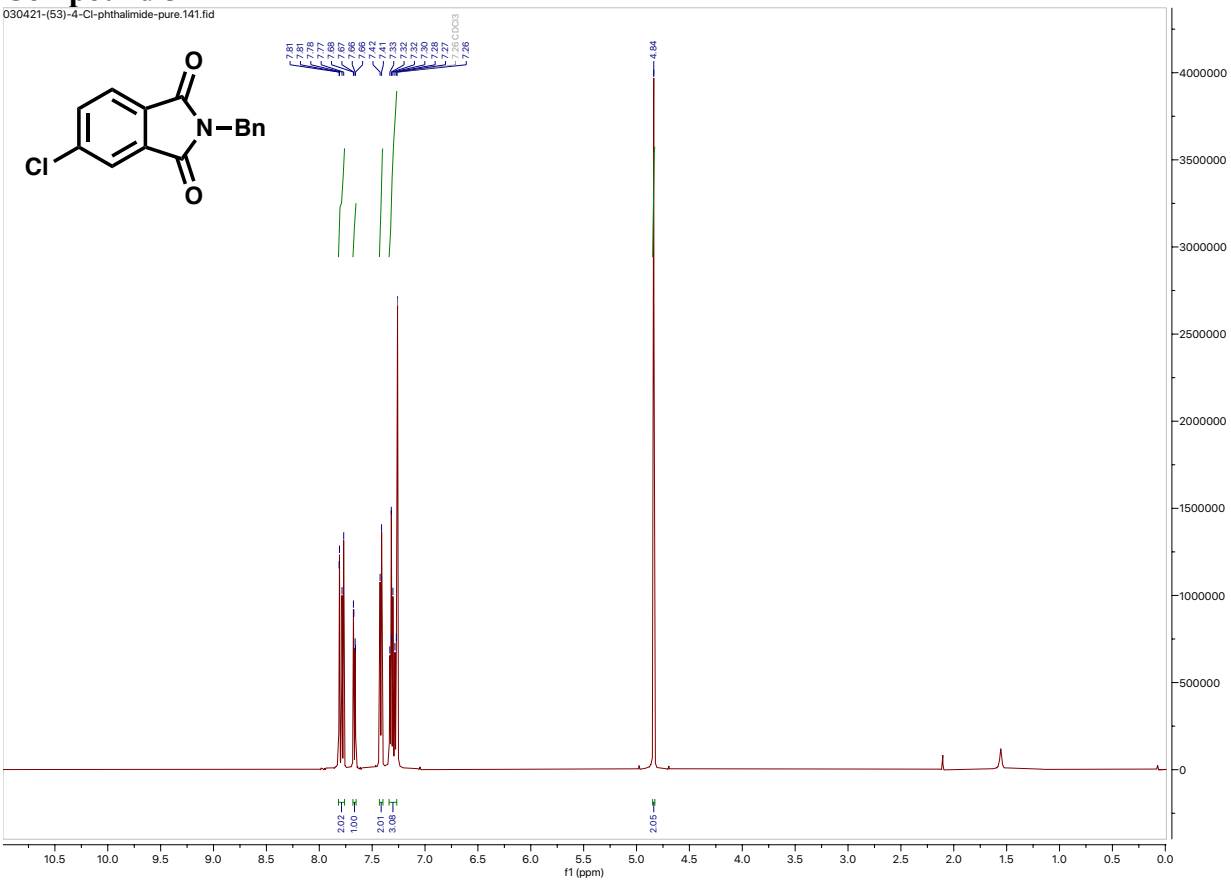

Pomalidomide-C5-azide-18.187.fid
C-13 Routine 1D, CPDCH CryoProbe, AVIII-600
171.74
171.00
169.31
168.09
166.79
137.85
136.62
131.21
125.44
118.69
115.46
77.16 CDCl3
51.19
49.40
37.23
31.48
28.39
22.78
22.44
f1 (ppm)

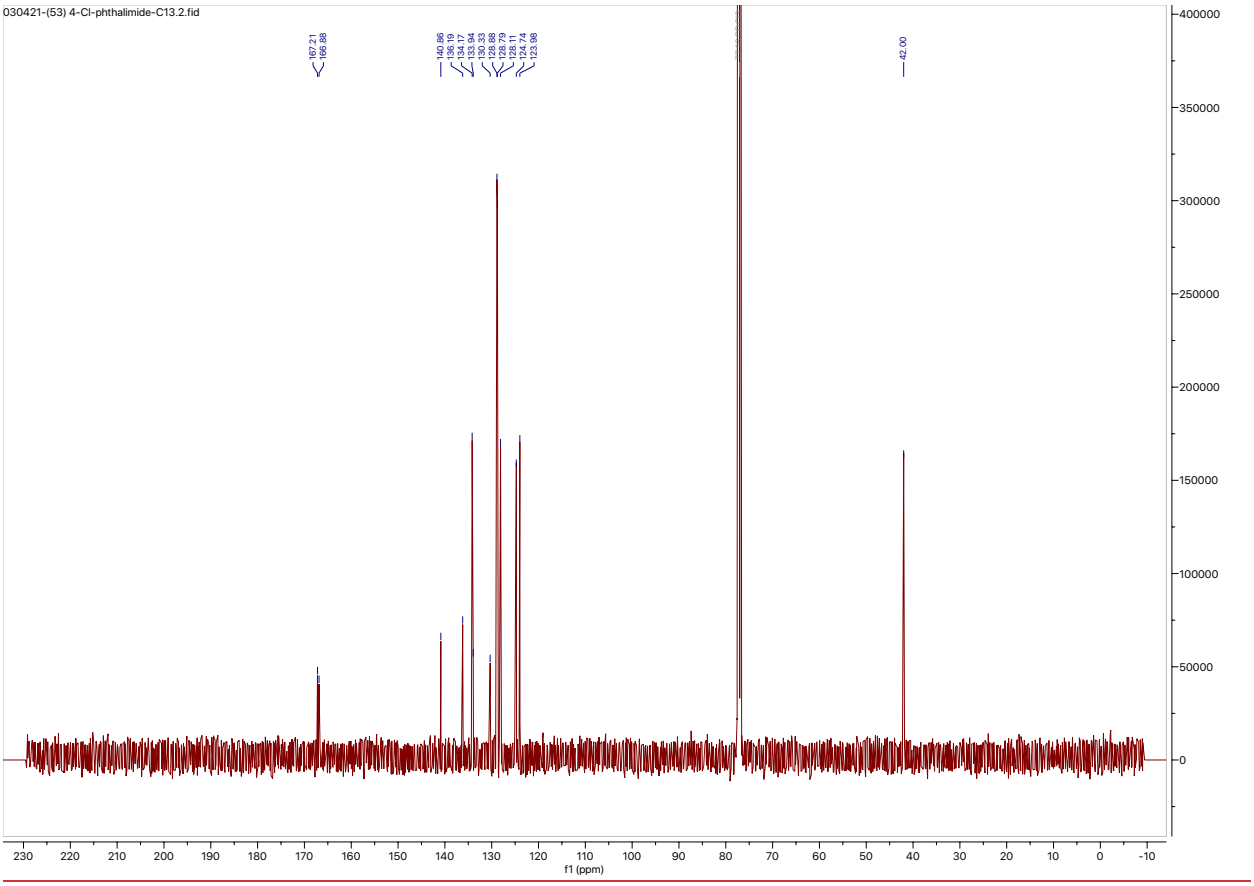
Compound 40


Pomalidomide-C5-JQ1-20.195.fid
C-13 Routine 1D, CPDCH CryoProbe, AVIII-600
f1 (ppm)

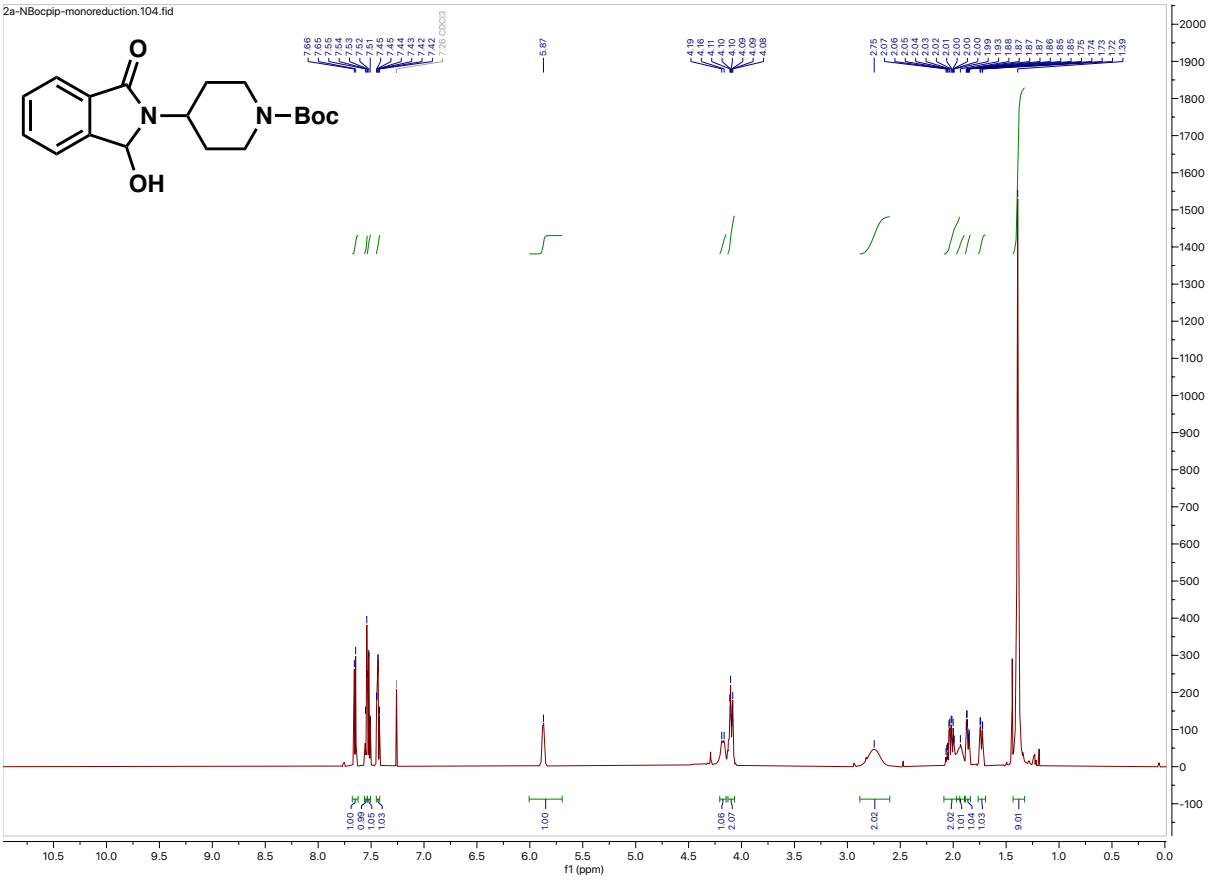

Pomalidomide-C5-JQ1-20.197.fid
C-13 Routine 1D, CPDCH CryoProbe, AVIII-600
171.95
171.13
170.79
169.35
168.32
166.83
164.16
155.69
150.13
137.78
136.90
136.71
136.50
132.24
131.45
131.06
130.98
130.60
129.97
128.83
125.56
116.62
116.69
77.16 76.73 76.31
54.55
49.44
39.28
39.02
37.47
31.42
28.81
28.73
22.98
22.87
22.64
14.51
13.21
11.92
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

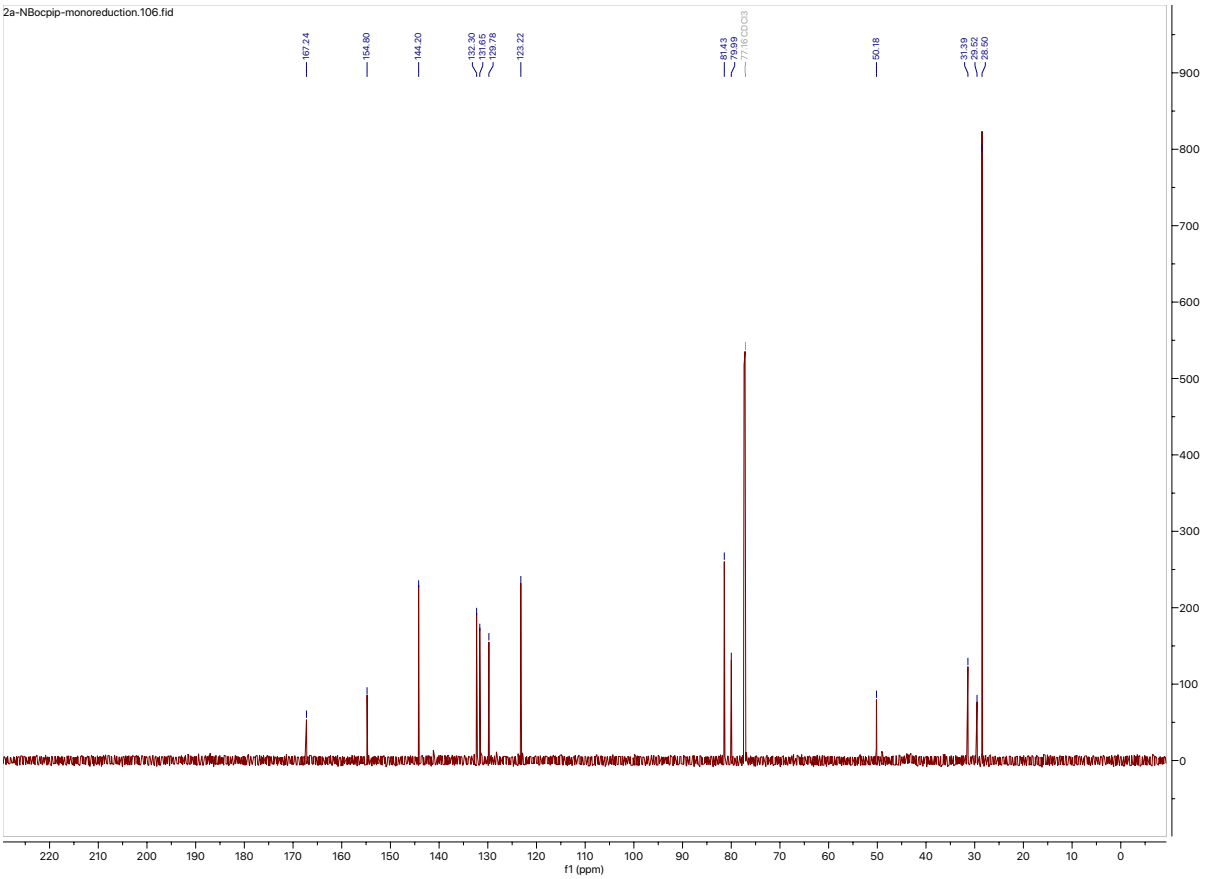
Compound 54


030421-(53)-4-Cl-phthalimide-pure.141.fid
O
N–Bn
Cl
O
7.81
7.80
7.78
7.77
7.68
7.67
7.66
7.66
7.42
7.41
7.33
7.32
7.32
7.30
7.28
7.27
7.26
4.84
2.02
1.00
2.01
3.08
2.05
4000000
3500000
3000000
2500000
2000000
1500000
1000000
500000
0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

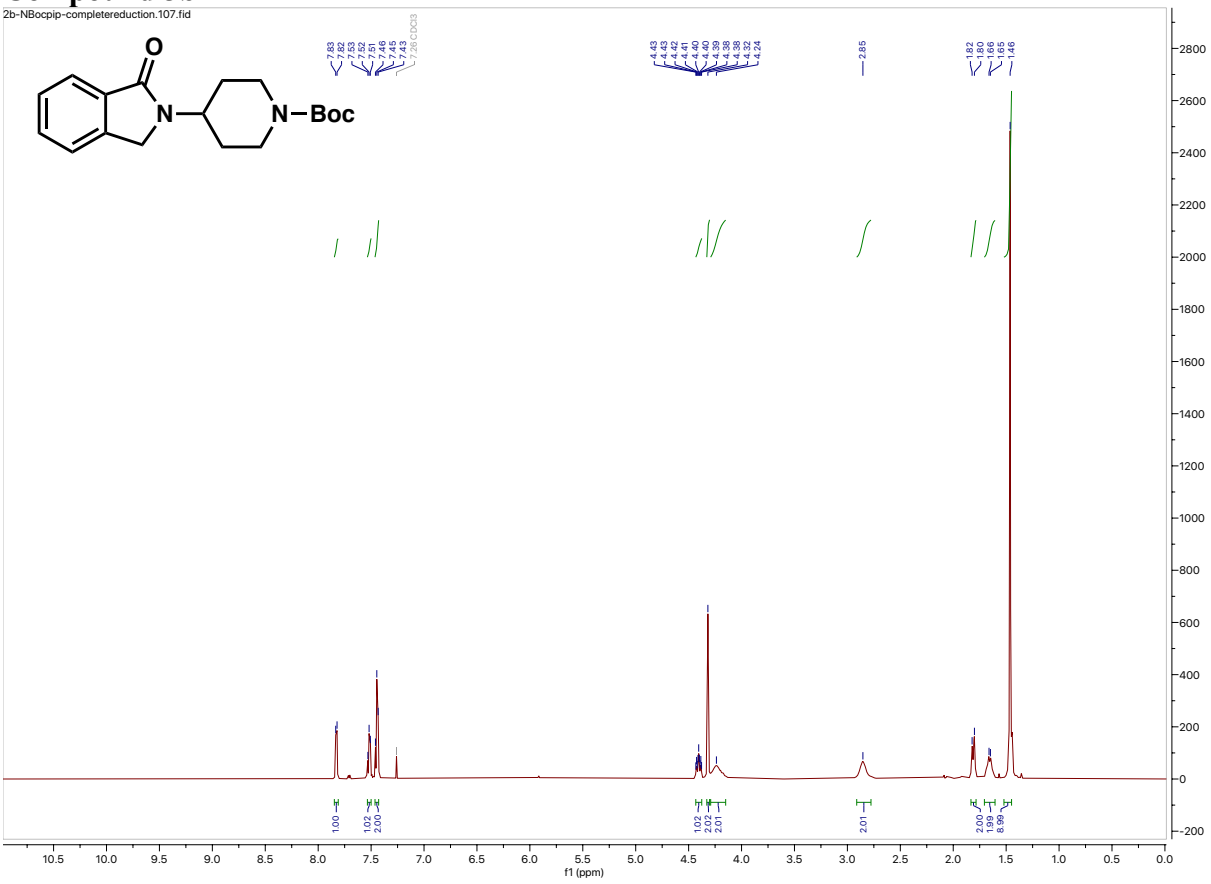

030421-(53) 4-Cl-phthalimide-C13.2.fid
167.21
166.88
140.86
136.19
134.17
133.94
133.53
128.88
128.79
125.11
124.74
123.98
42.00
400000
350000
300000
250000
200000
150000
100000
50000
0
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

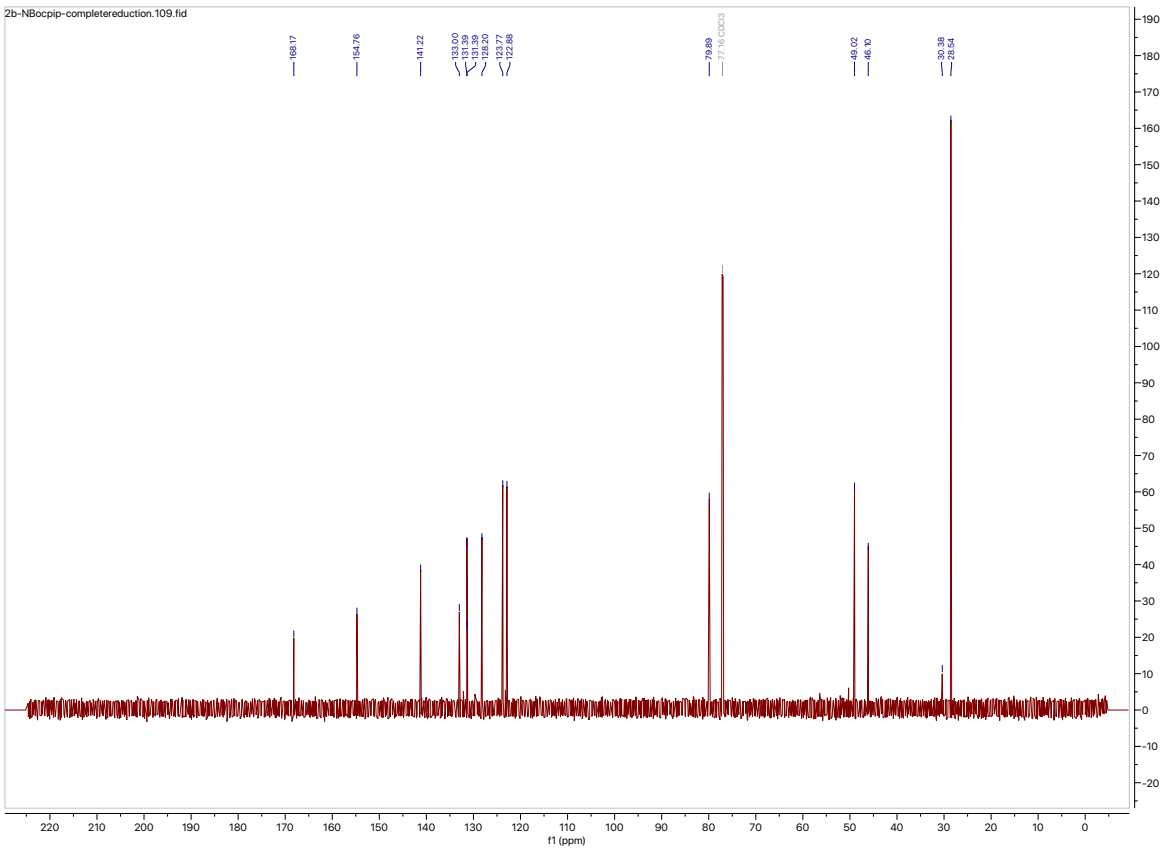
Compound 3a



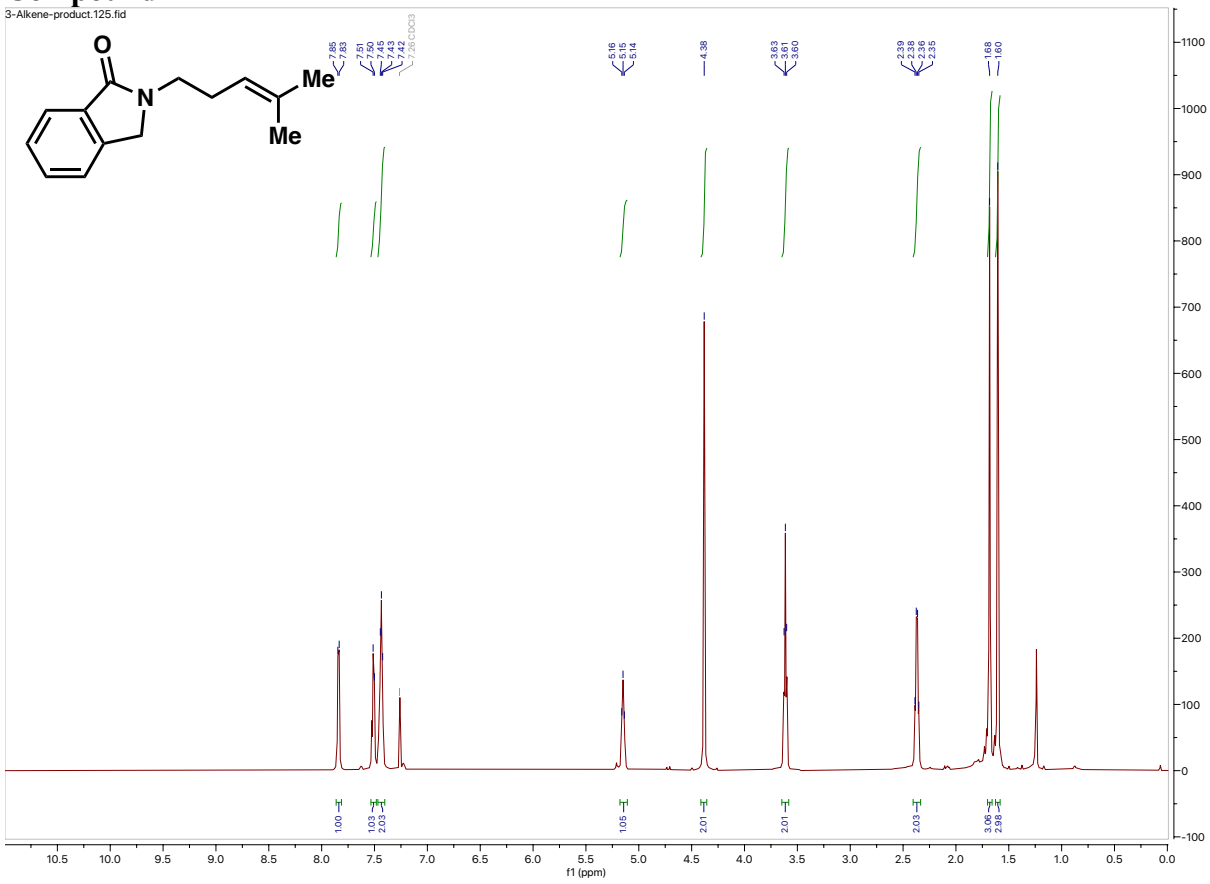

2a-NBocpip-monoreduction.106.fid
167.24
154.80
144.20
132.30
130.65
129.78
123.22
81.43
79.89
77.16 CDCl3
50.18
31.39
28.52
28.00
f1 (ppm)

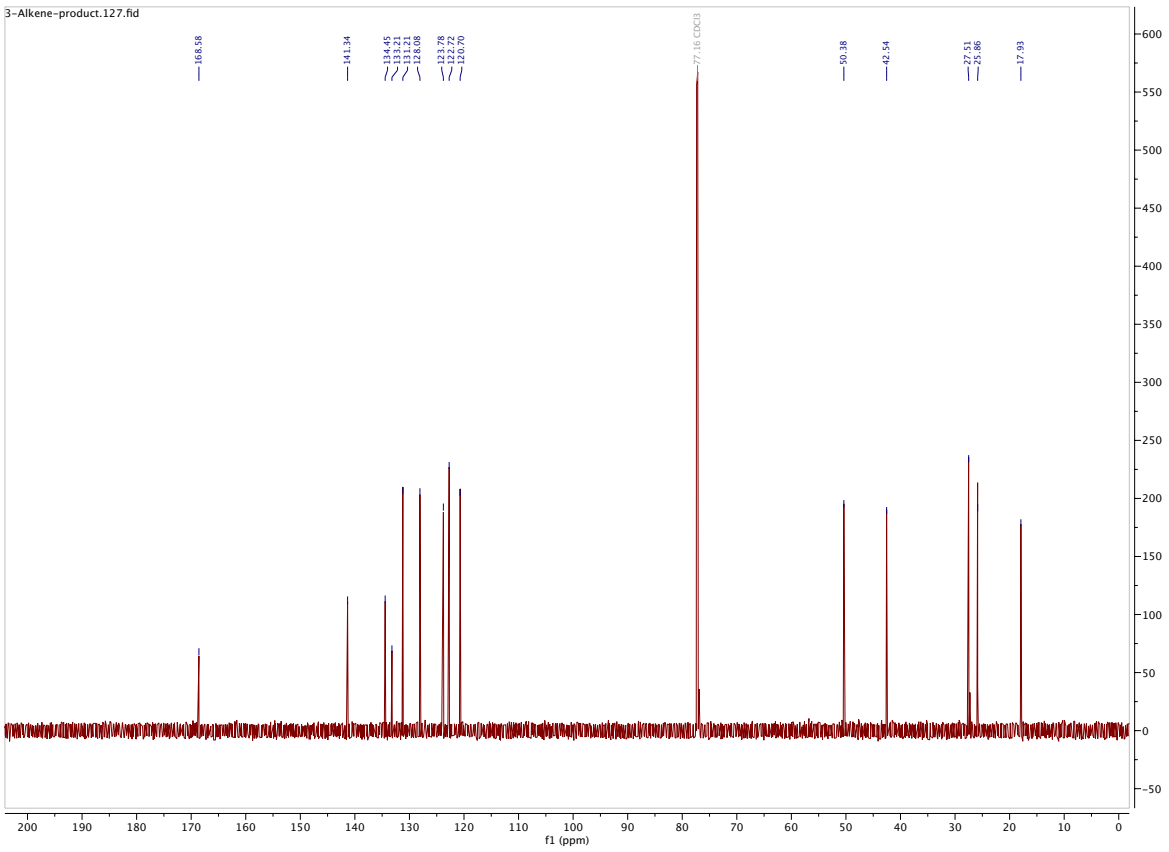
Compound 3b


2b-NBocpip-completereduction.107.fid
O
N
N–Boc
7.83
7.82
7.53
7.52
7.51
7.46
7.45
7.43
7.26 CDCl3
4.43
4.43
4.42
4.41
4.40
4.40
4.39
4.38
4.38
4.32
4.24
2.85
1.82
1.80
1.66
1.65
1.46
1.00
1.02
2.00
1.02
2.02
2.01
2.01
2.00
1.99
8.99
f1 (ppm)

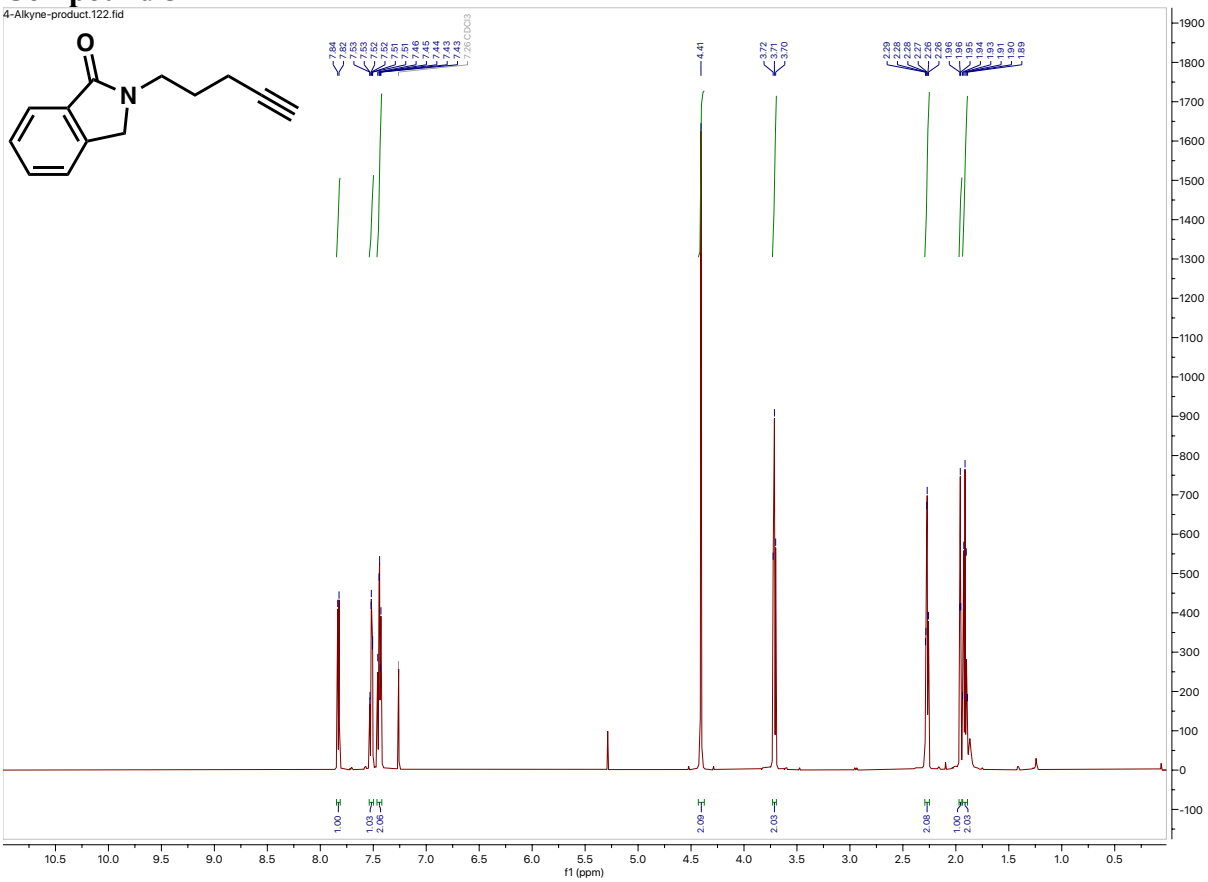

2b-NBocpip-completereduction.109.fid
168.17
154.76
141.22
133.00
131.39
131.30
128.20
123.77
122.88
79.89
77.16 CDCl3
49.02
46.10
30.38
28.54
f1 (ppm)

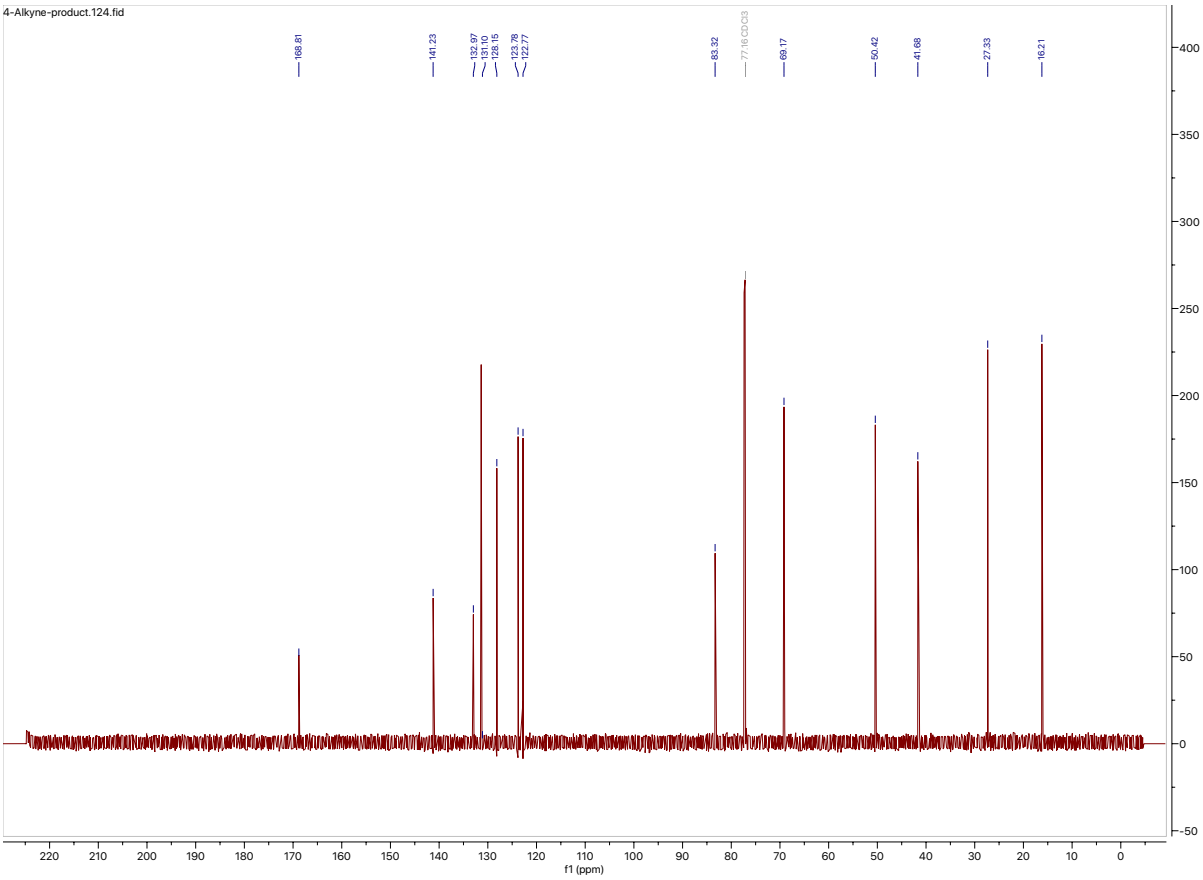
Compound 4


3-Alkene-product.125.fid
O
N
Me
Me
7.85
7.83
7.51
7.50
7.45
7.43
7.42
5.16
5.15
5.14
4.38
3.63
3.61
3.60
2.39
2.38
2.36
2.35
1.68
1.60
1.00
1.03
2.03
1.05
2.01
2.01
2.03
3.06
2.98
f1 (ppm)

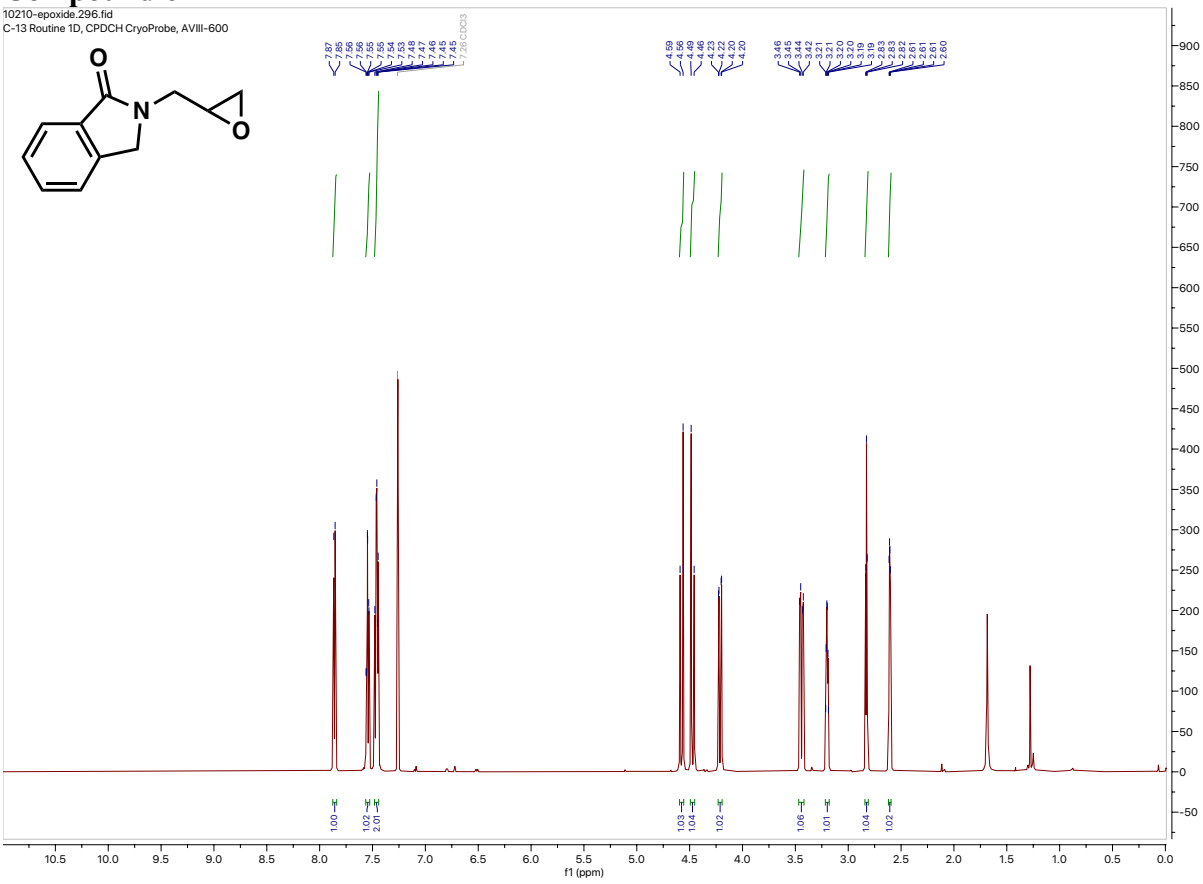

3-Alkene-product.127.fid
168.58
141.34
134.45
133.21
131.21
128.08
123.78
122.72
120.70
77.16 CDCl3
50.38
42.54
27.51
25.86
17.93
f1 (ppm)

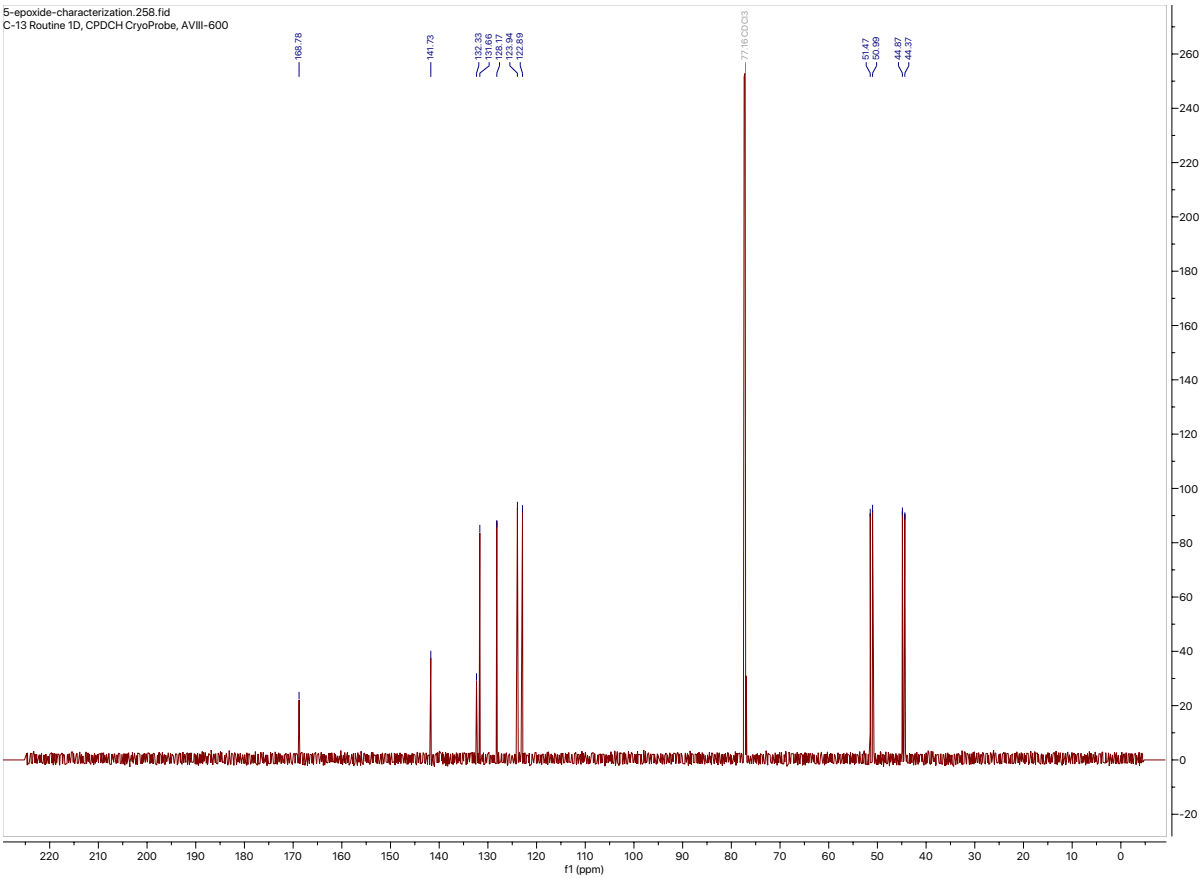
Compound 5


4-Alkyne-product.122.fid
O
N
7.84
7.82
7.53
7.53
7.52
7.52
7.52
7.51
7.51
7.46
7.45
7.44
7.43
7.43
4.41
3.72
3.71
3.70
2.29
2.28
2.28
2.27
2.27
2.26
2.26
1.96
1.96
1.95
1.94
1.93
1.91
1.90
1.89
1.00
1.03
2.06
2.09
2.03
2.08
1.00
2.03
f1 (ppm)

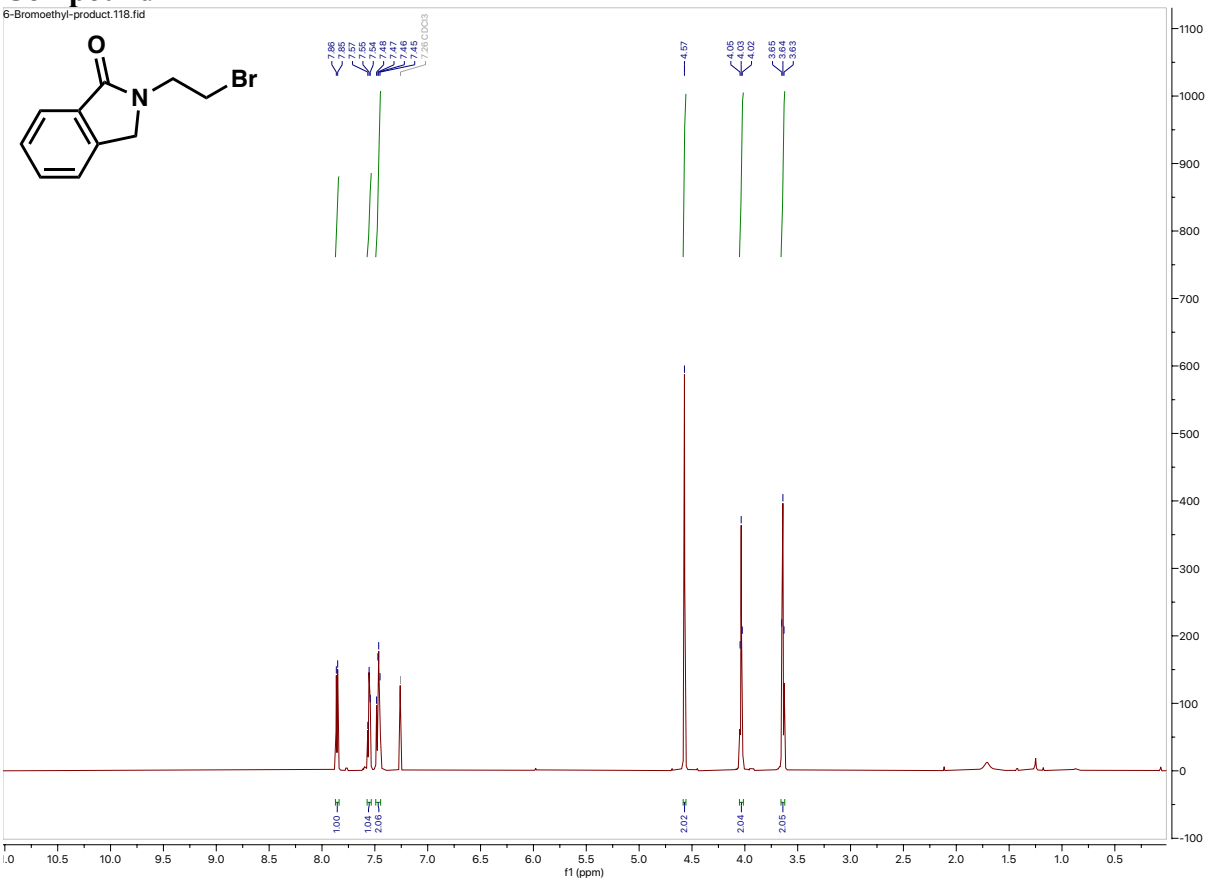

4-Alkyne-product.124.fid
168.81
141.23
132.97
131.10
128.15
123.78
122.77
83.32
77.16 CDCl3
69.17
50.42
41.68
27.33
16.21
f1 (ppm)

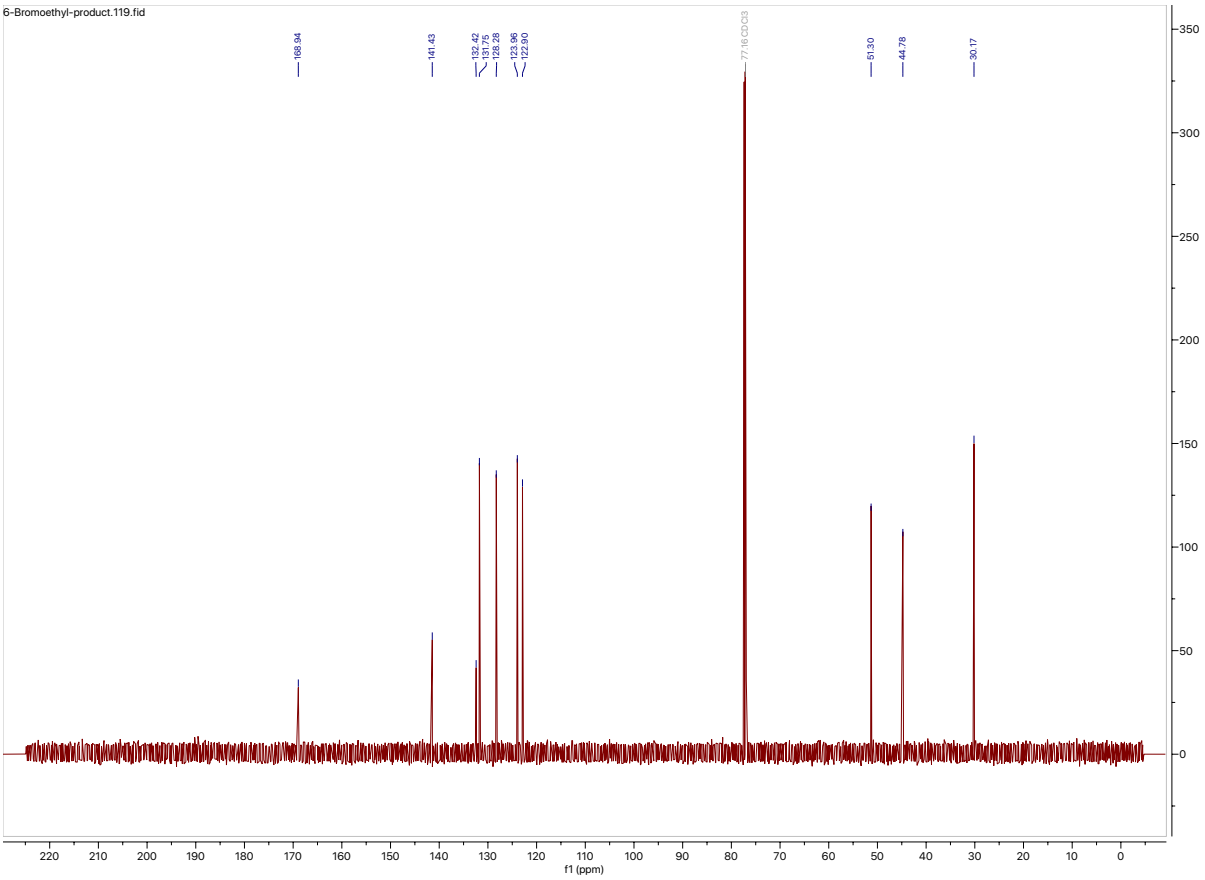
Compound 6


10210-epoxide.296.fid
C-13 Routine 1D, CPDCH CryoProbe, AVIII-600
f1 (ppm)

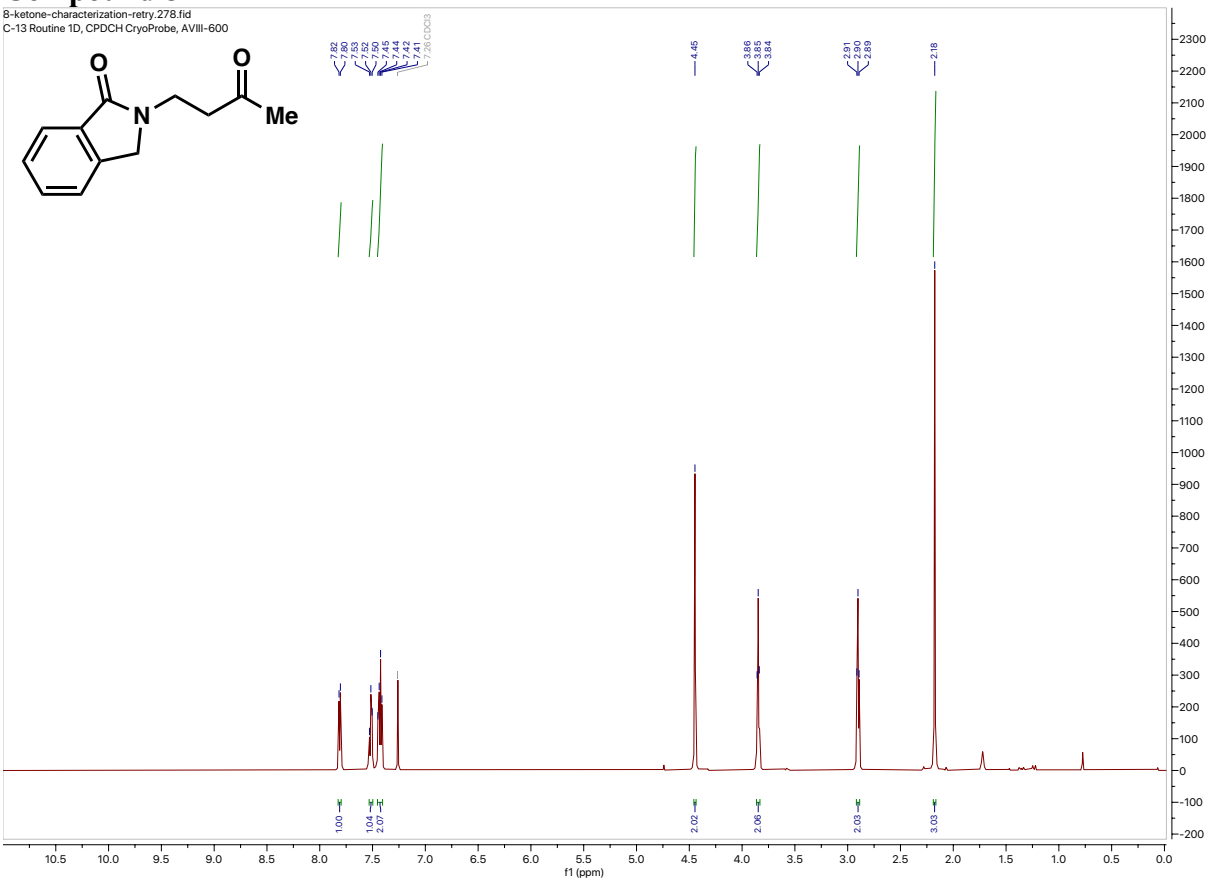

5-epoxide-characterization.258.fid
C-13 Routine 1D, CPDCH CryoProbe, AVIII-600
168.78
141.73
132.33
131.66
128.17
123.94
122.89
77.16 CDCl3
51.47
50.99
44.87
44.37
f1 (ppm)

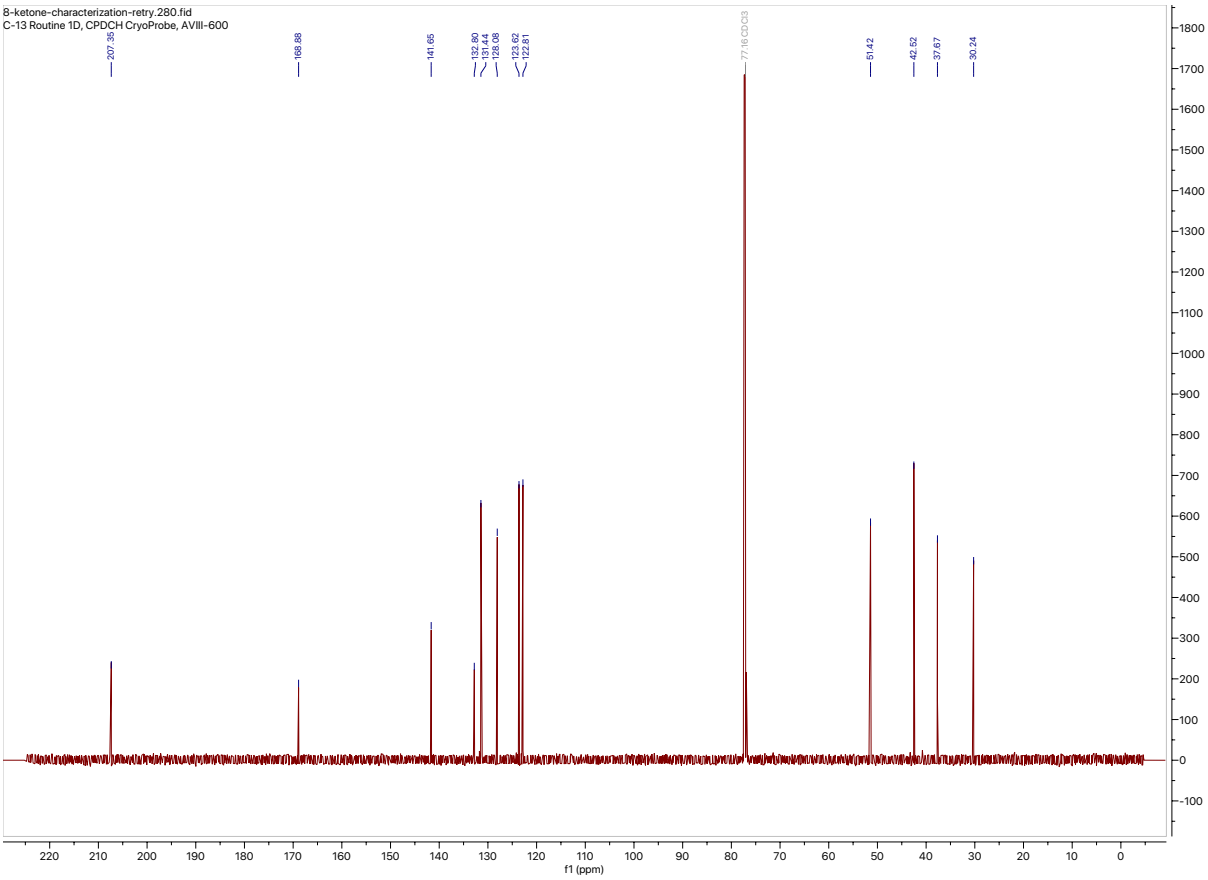
Compound 7


6-Bromoethyl-product.118.fid
O
N
Br
7.86
7.85
7.57
7.55
7.54
7.48
7.47
7.46
7.45
4.57
4.05
4.03
4.02
3.65
3.64
3.63
1.00
1.04
2.06
2.02
2.04
2.05
f1 (ppm)

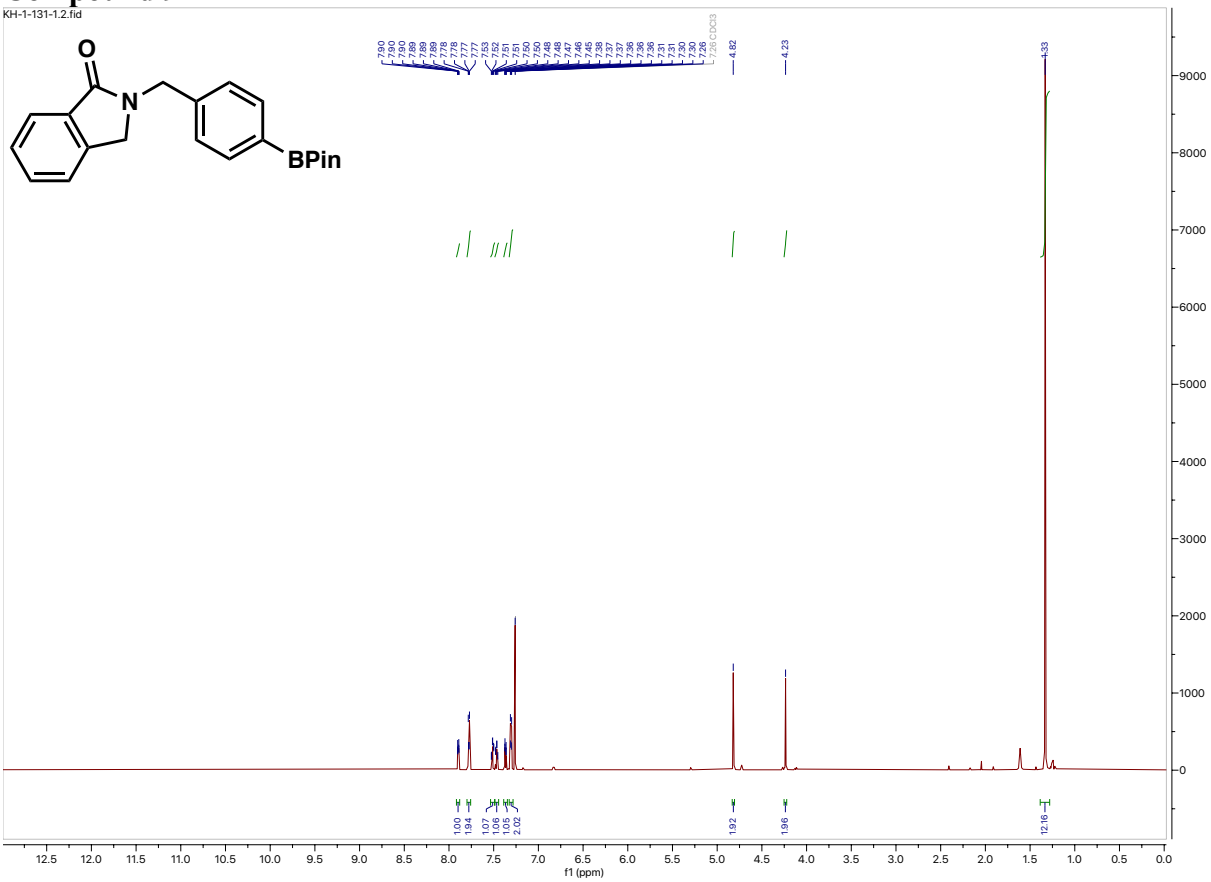

6-Bromoethyl-product.119.fid
168.94
141.43
132.42
131.75
128.28
123.96
122.90
77.16 CDCl3
51.30
44.78
30.17
350
300
250
200
150
100
50
0
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

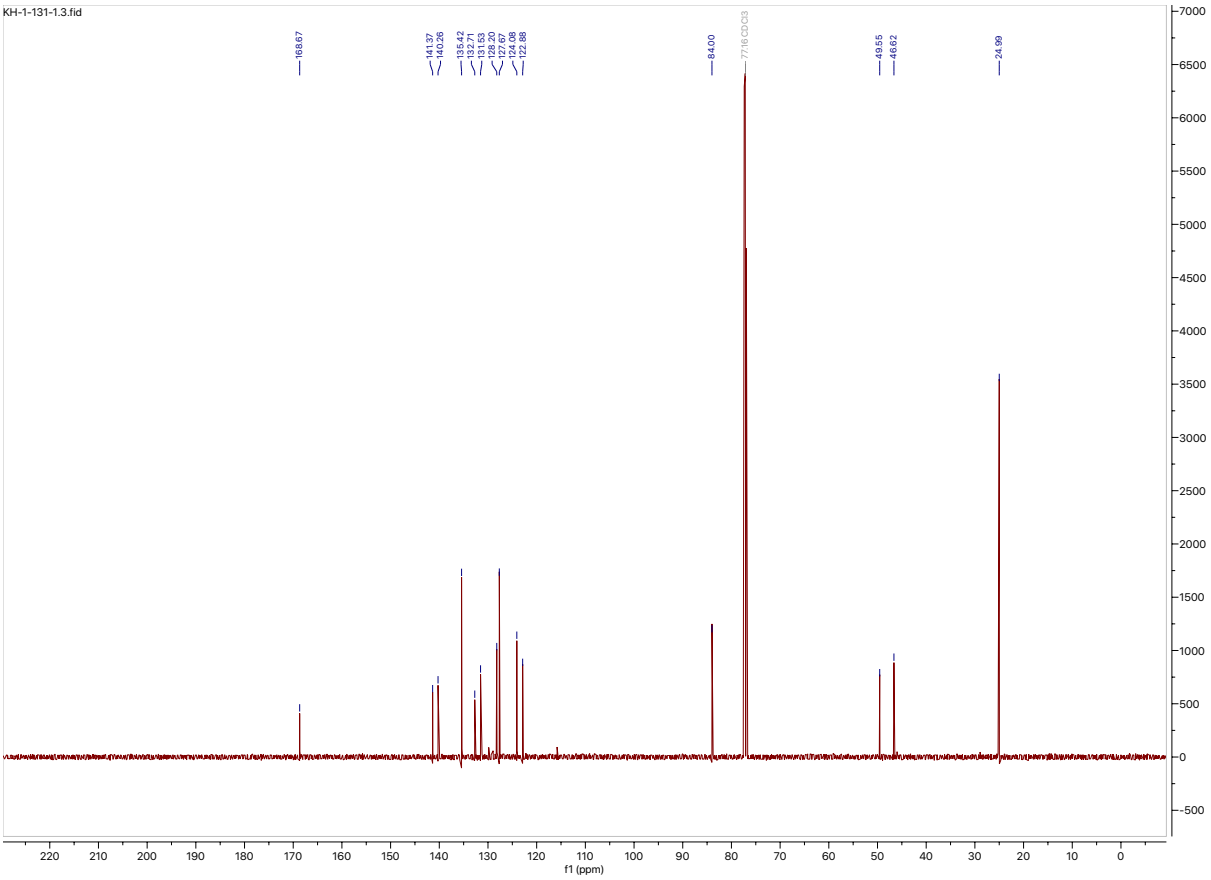
Compound 8


8-ketone-characterization-retry.278.fid
C-13 Routine 1D, CPDCH CryoProbe, AVIII-600
O
O
N
Me
7.82
7.80
7.53
7.52
7.50
7.45
7.44
7.42
7.41
4.45
3.86
3.85
3.84
2.91
2.90
2.89
2.18
1.00
1.04
2.07
2.02
2.06
2.03
3.03
f1 (ppm)

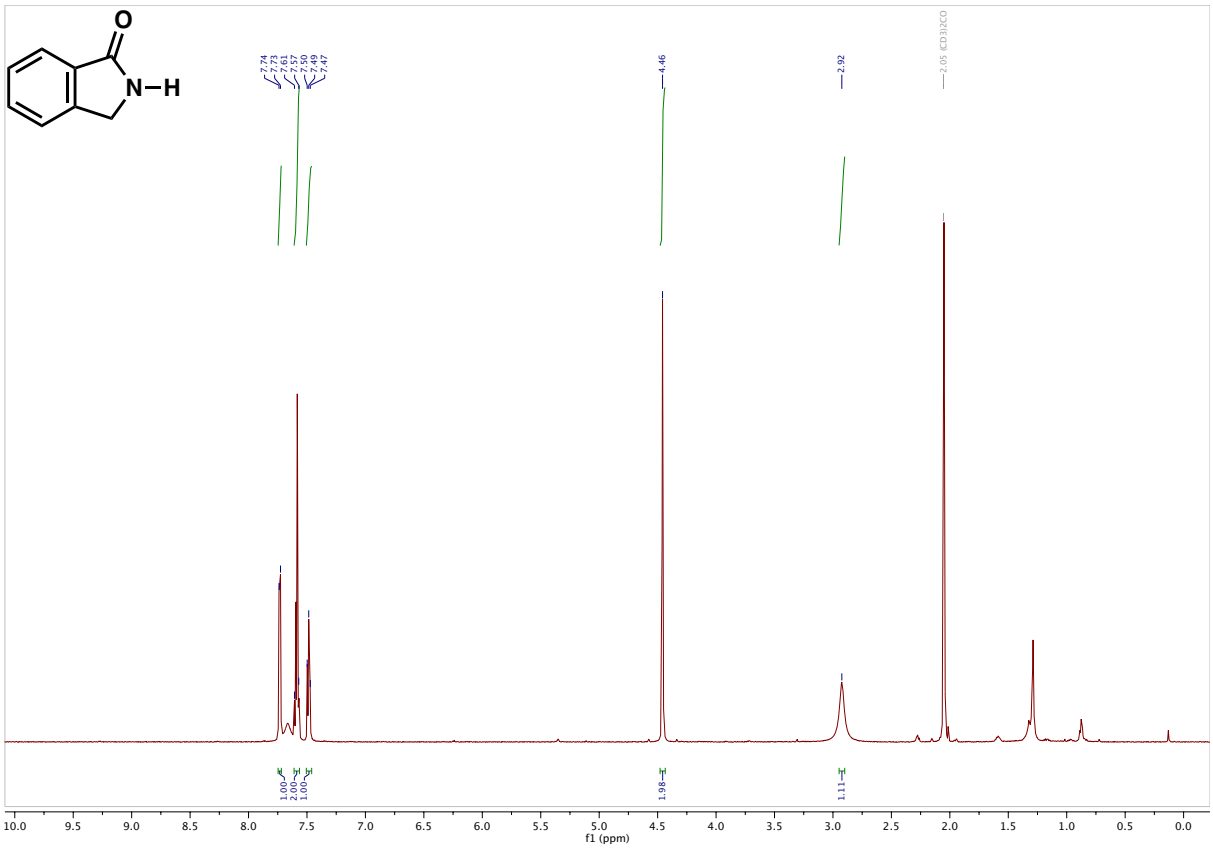

8-ketone-characterization-retry.280.fid
C-13 Routine 1D, CPDCH CryoProbe, AVIII-600
207.35
168.88
141.65
132.80
131.44
128.98
123.62
122.81
77.16 CDCl3
51.42
42.52
37.67
30.24
f1 (ppm)

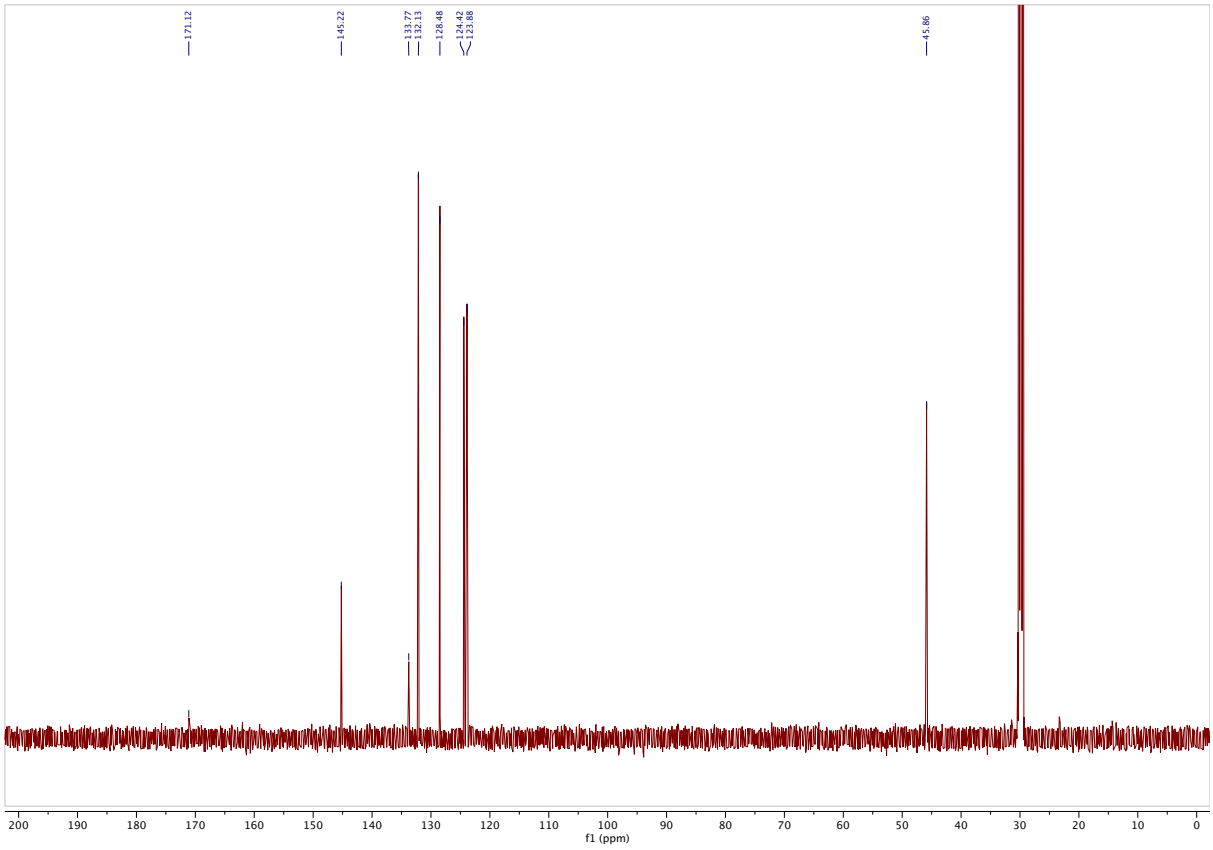
Compound 9


KH-1-131-1.2.fid
O
N
BPin
7.90
7.90
7.90
7.89
7.89
7.78
7.78
7.77
7.77
7.53
7.52
7.51
7.51
7.50
7.50
7.48
7.48
7.47
7.46
7.45
7.38
7.37
7.37
7.36
7.36
7.31
7.31
7.30
7.30
7.26
7.26 CDCl3
4.82
4.23
1.33
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
1.00
1.04
1.07
1.05
1.05
2.02
1.92
1.96
12.16
12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

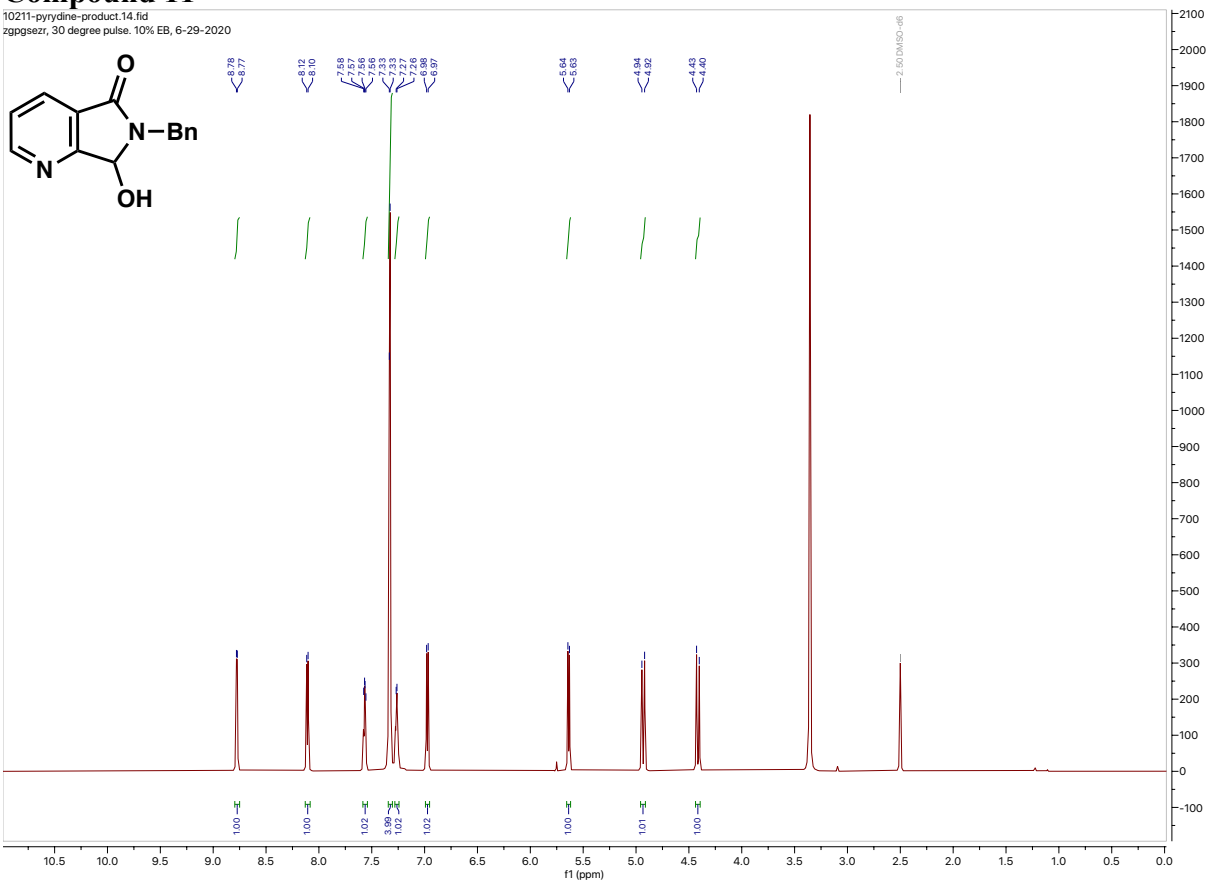

KH-1-131-1.3.fid
168.67
141.37
140.26
135.42
134.71
131.53
128.20
127.67
123.98
122.88
84.00
77.16 CDCl3
49.55
46.62
24.99
f1 (ppm)

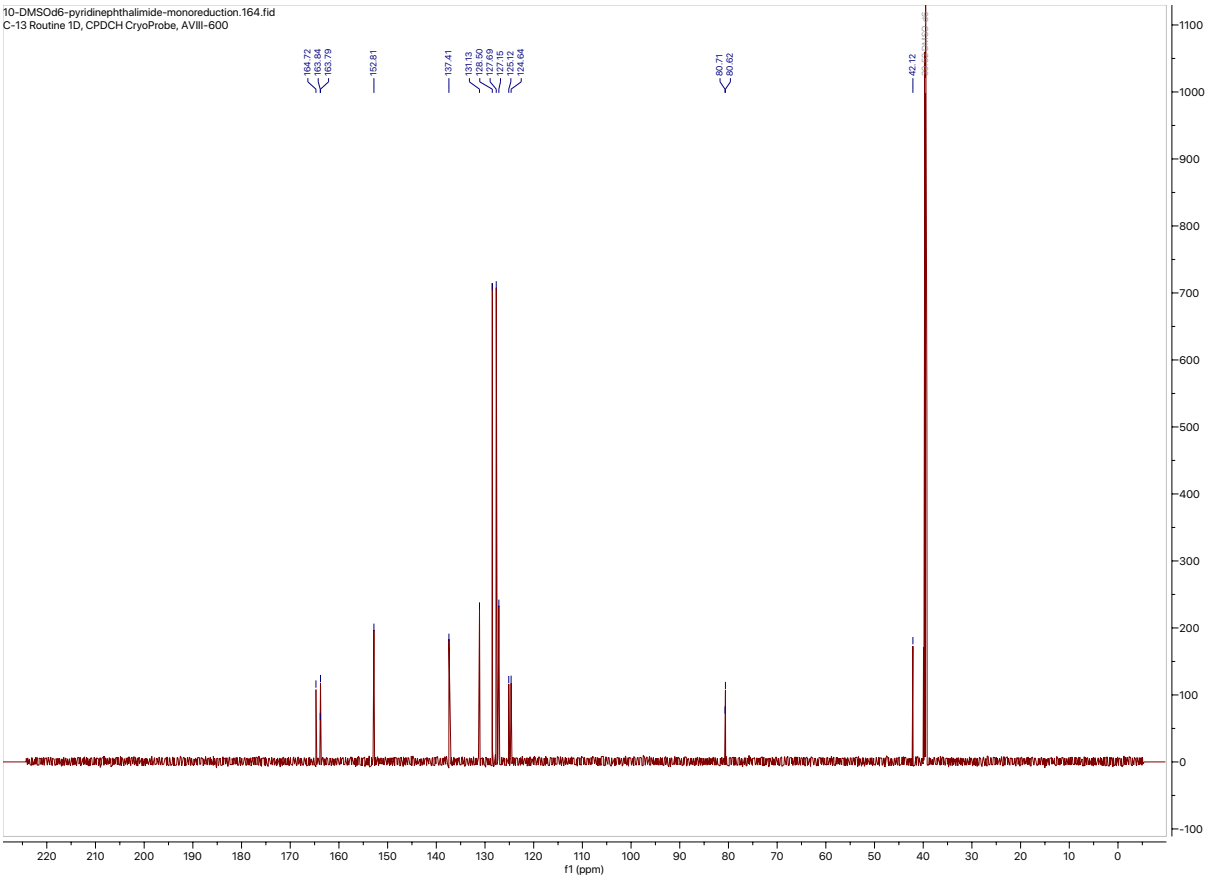
Compound 10


O
N–H
7.74
7.73
7.61
7.57
7.50
7.49
7.47
4.46
2.92
2.05
(CD3)2CO
1.00
2.00
1.00
1.98
1.11
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

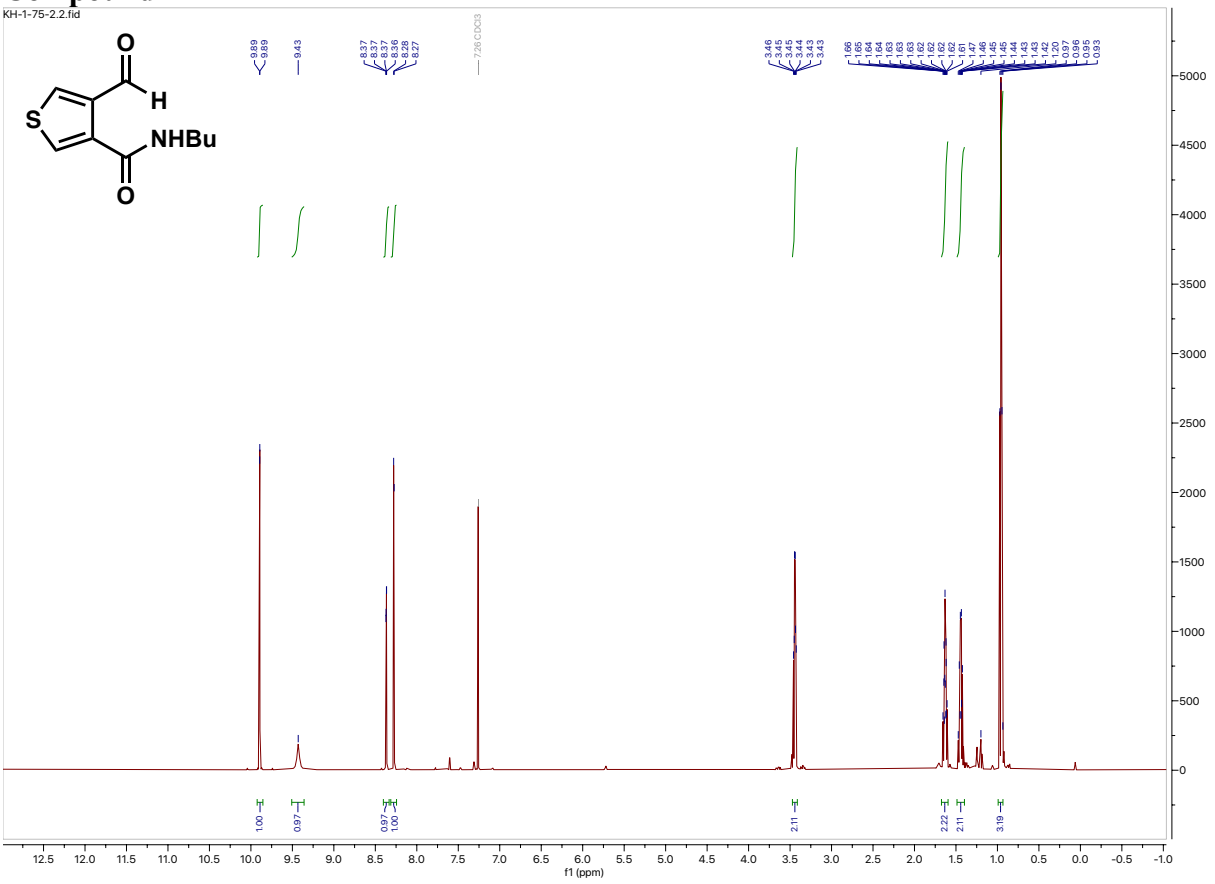

171.12
145.22
133.77
132.13
128.48
124.42
123.88
45.86
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

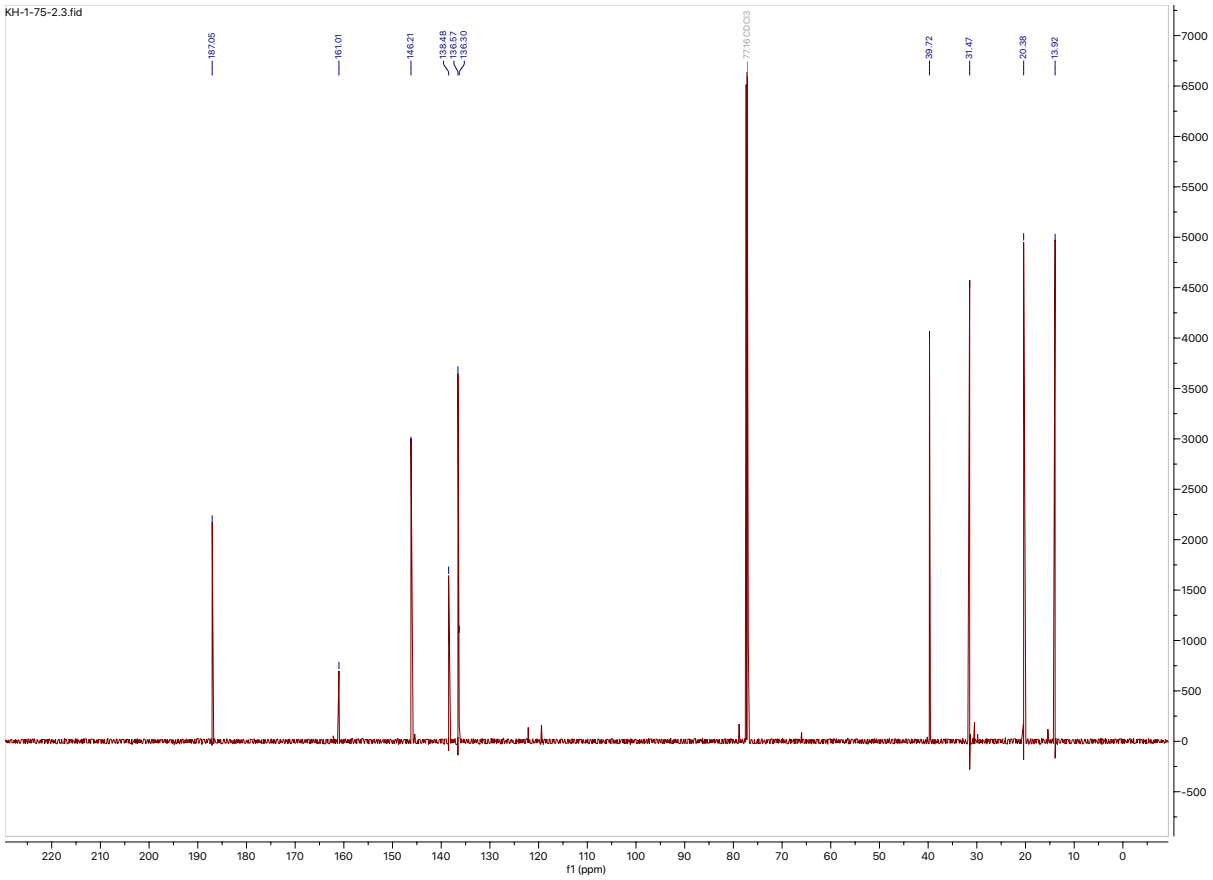
Compound 11


10211-pyrydine-product.14.fid
zgpgsezr, 30 degree pulse. 10% EB, 6-29-2020
O
N–Bn
N
OH
8.78
8.77
8.12
8.10
7.58
7.57
7.56
7.56
7.33
7.33
7.27
7.26
6.98
6.97
5.64
5.63
4.94
4.92
4.43
4.40
2.50 DMSO-d6
1.00
1.00
1.02
3.99
1.02
1.02
1.00
1.01
1.00
f1 (ppm)

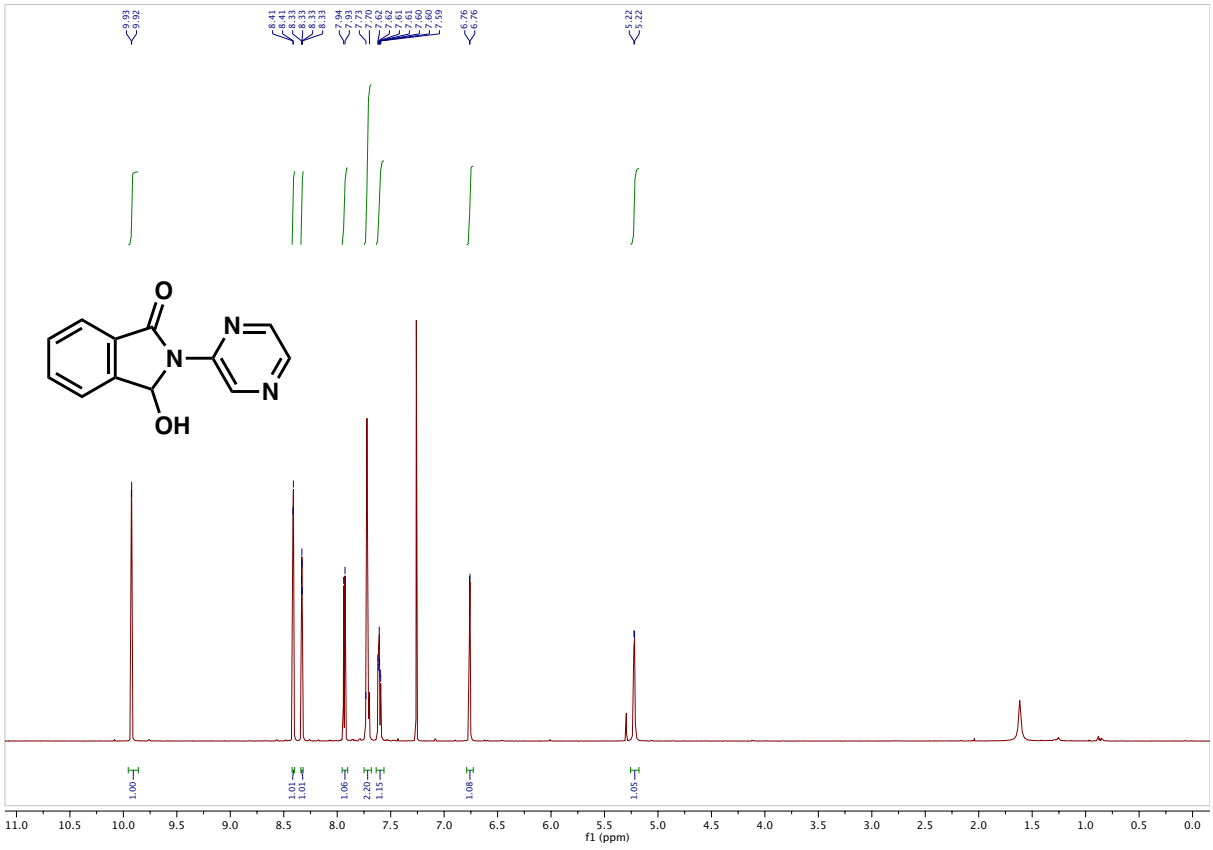

10-DMSOd6-pyridinephthalimide-monoreduction.164.fid
C-13 Routine 1D, CPDCH CryoProbe, AVIII-600
164.72
163.84
163.79
152.81
137.41
131.13
128.50
127.69
127.15
125.23
124.64
80.71
80.62
42.12
f1 (ppm)

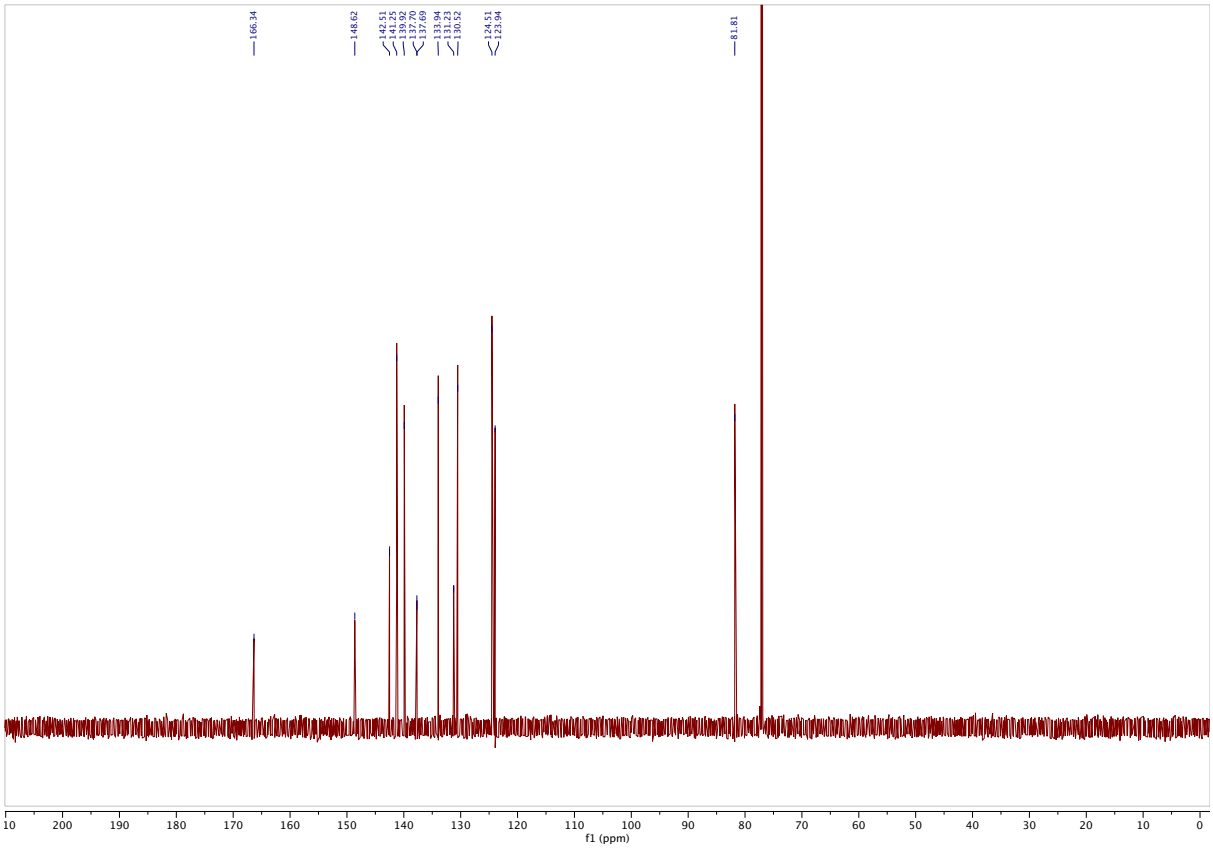
Compound 12


KH-1-75-2.2.fid
O
H
S
NHBu
O
9.89
9.89
9.43
8.37
8.37
8.37
8.37
8.36
8.28
8.27
7.26 CDCl3
3.46
3.45
3.45
3.44
3.43
3.43
1.66
1.65
1.64
1.64
1.63
1.63
1.63
1.62
1.62
1.62
1.62
1.61
1.47
1.46
1.45
1.45
1.44
1.43
1.43
1.42
1.40
0.97
0.96
0.95
0.93
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
1.00
0.97
0.97
1.00
2.11
2.22
2.11
3.19
12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

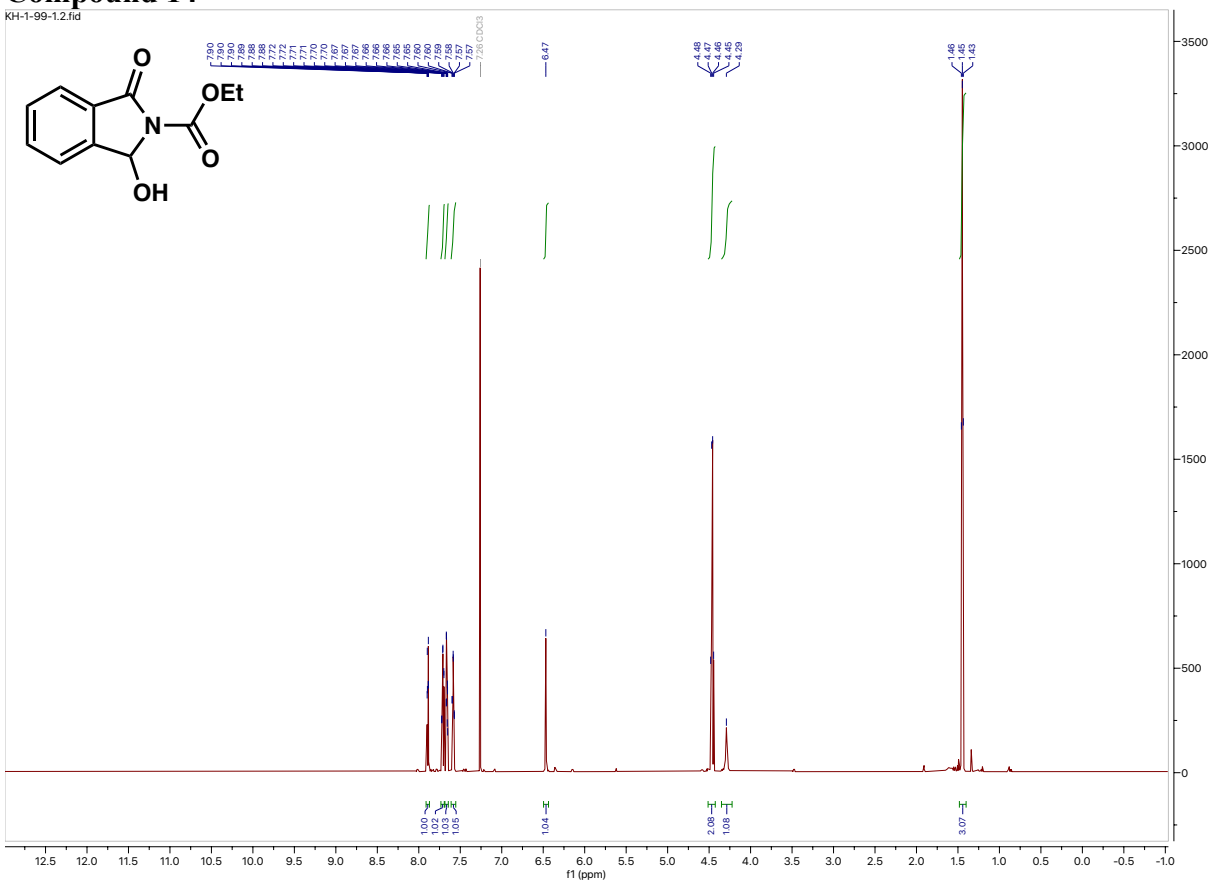

KH-1-75-2.3.fid
187.05
161.01
146.21
138.48
135.57
136.30
77.16 CDCl3
39.72
31.47
20.38
13.92
f1 (ppm)

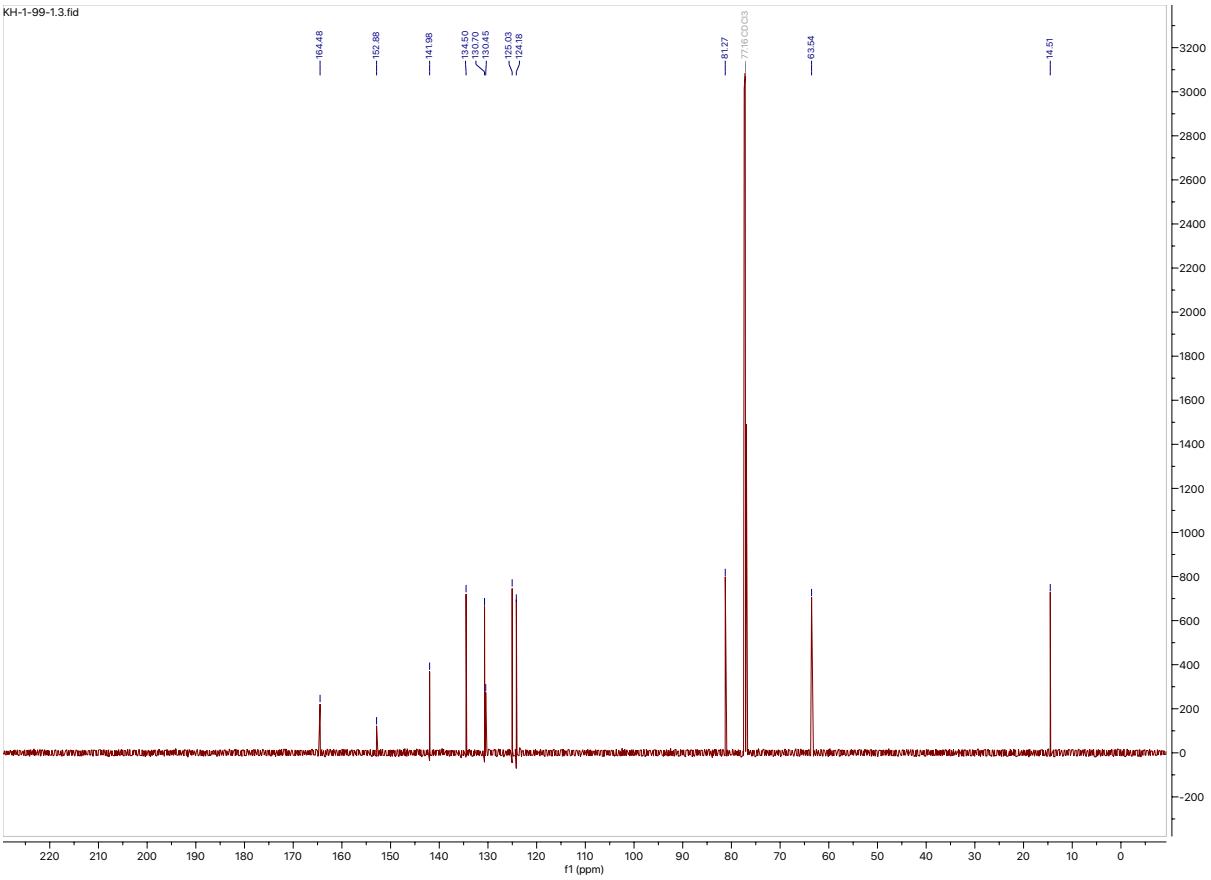
Compound 13


9.93
9.92
8.41
8.41
8.33
8.33
8.33
8.33
7.94
7.93
7.73
7.70
7.62
7.62
7.61
7.61
7.60
7.60
7.59
6.76
6.76
5.22
5.22
O
N
N
N
OH
1.00
1.01
1.01
1.06
2.20
1.15
1.08
1.05
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

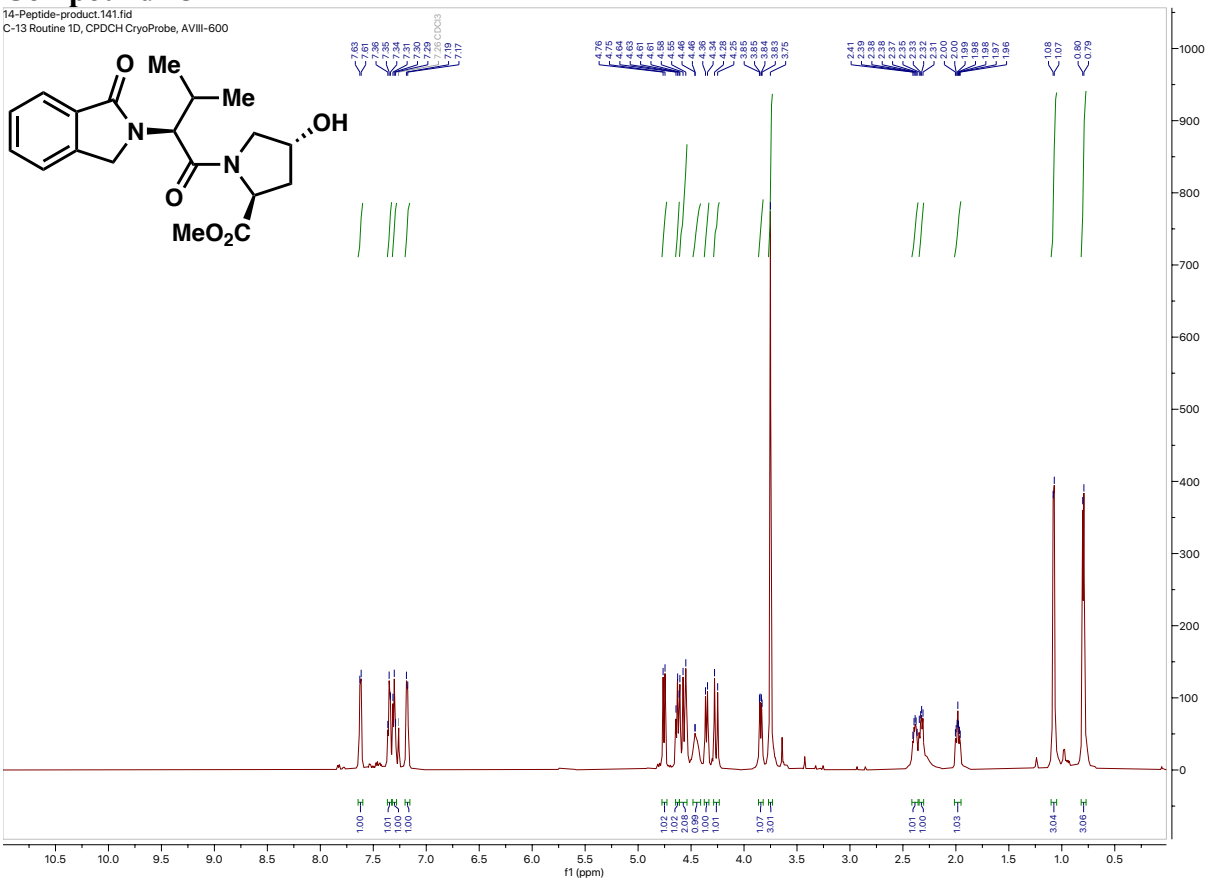

166.34
148.62
142.51
141.25
139.92
137.70
137.69
133.94
133.25
130.52
124.51
123.94
81.81
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

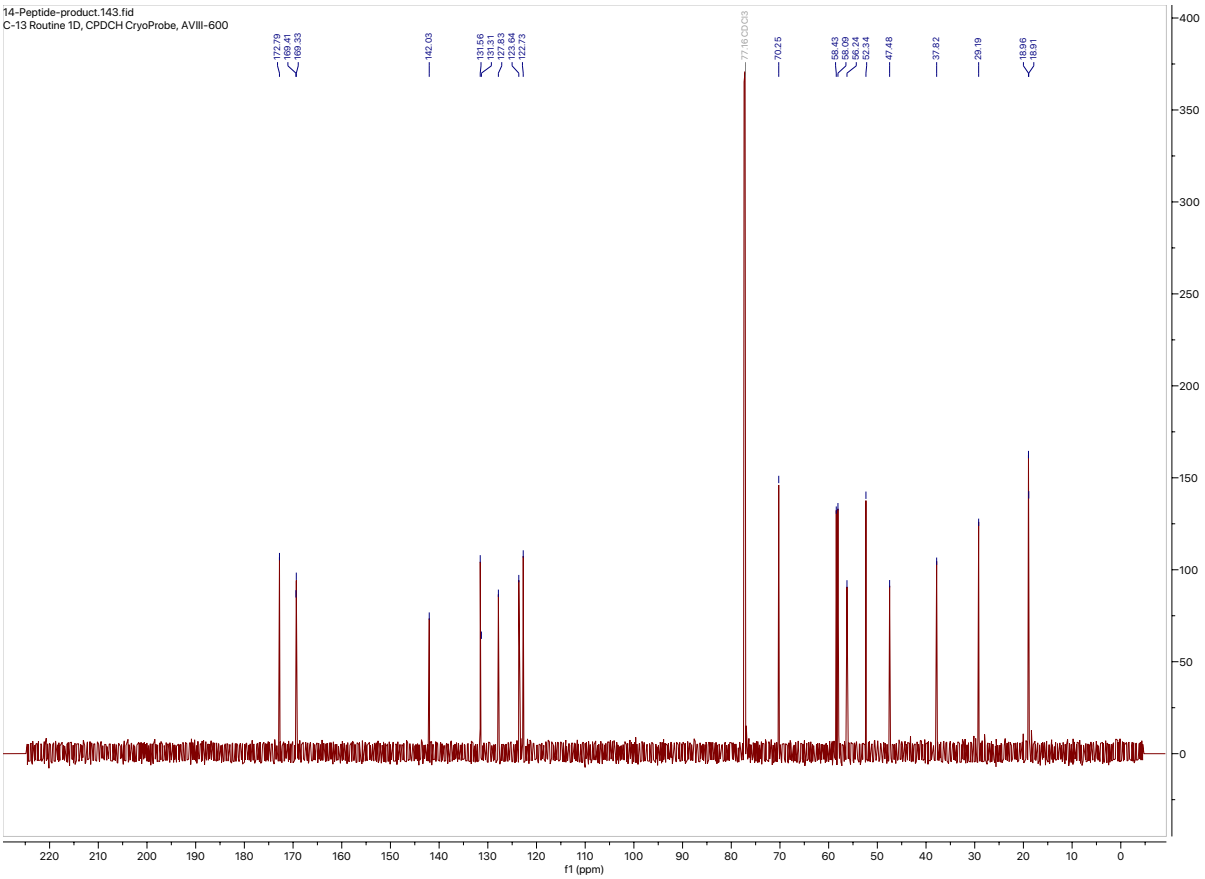
Compound 14


KH-1-99-1.2.fid
O
OEt
N
O
OH
7.90
7.90
7.90
7.90
7.89
7.88
7.88
7.73
7.72
7.71
7.71
7.70
7.70
7.67
7.67
7.67
7.67
7.66
7.66
7.66
7.65
7.65
7.60
7.60
7.60
7.59
7.58
7.57
7.57
7.26 CDCl3
6.47
4.48
4.47
4.46
4.45
4.45
4.29
1.46
1.45
1.45
1.43
1.00
1.02
1.03
1.05
1.04
2.08
1.08
3.07
f1 (ppm)

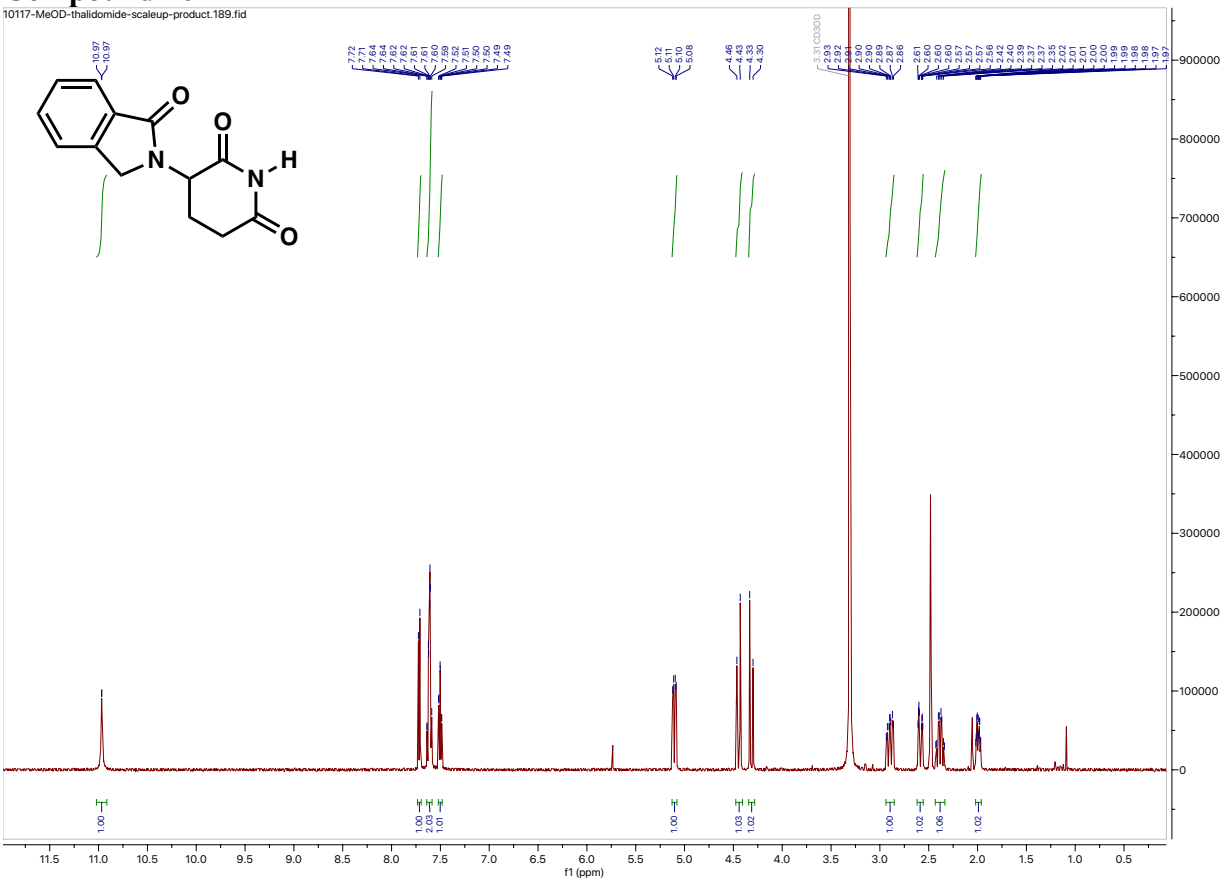

KH-1-99-1.3.fid
164.48
152.88
141.98
134.50
130.70
130.45
125.03
124.18
81.27
77.16 CDCl3
63.54
14.51
f1 (ppm)

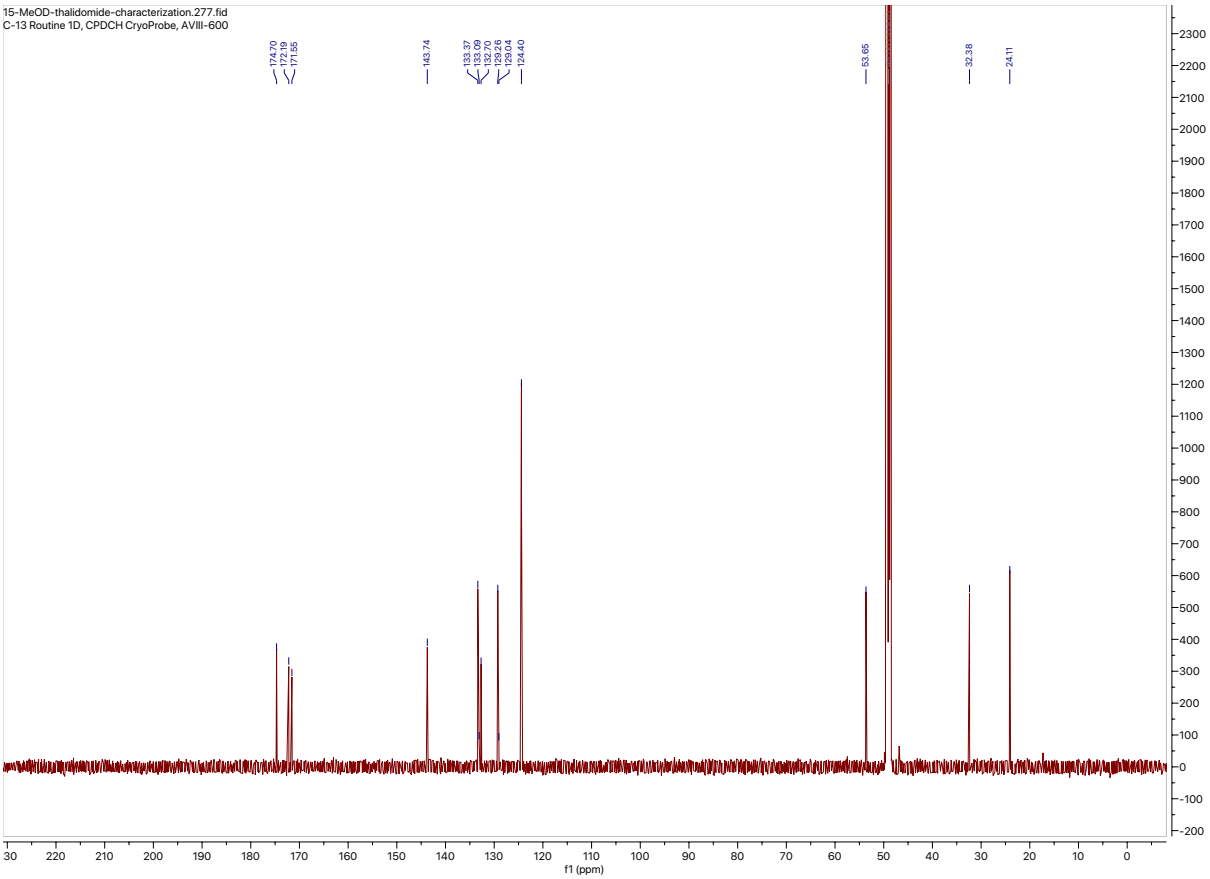
Compound 15


14-Peptide-product.141.fid
C-13 Routine 1D, CPDCH CryoProbe, AVIII-600
O
Me
Me
N
OH
N
O
MeO2C
f1 (ppm)

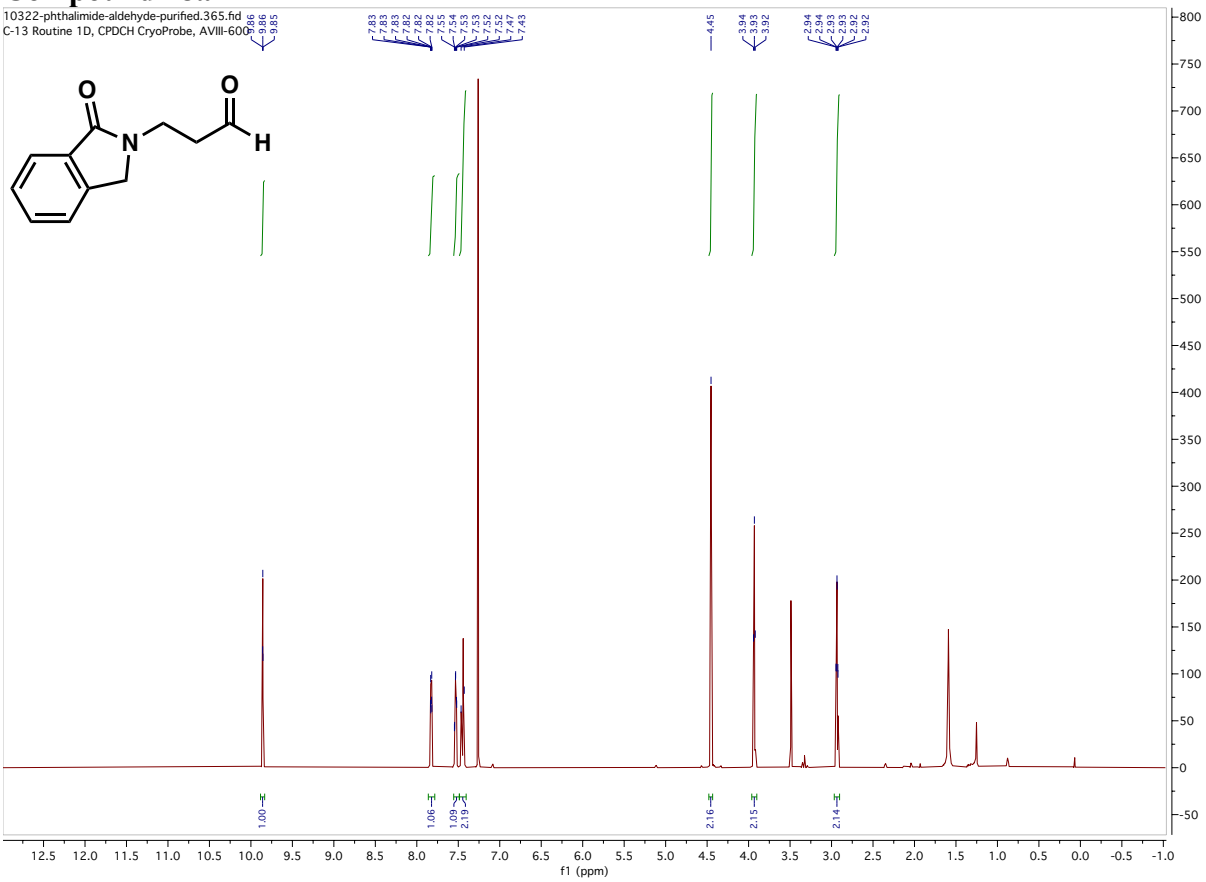

14-Peptide-product.143.fid
C-13 Routine 1D, CPDCH CryoProbe, AVIII-600
172.79
169.41
169.33
142.03
131.56
131.31
127.83
123.64
122.73
77.16 CDCl3
70.25
58.43
58.09
56.24
52.34
47.48
37.82
29.19
18.96
18.91
f1 (ppm)

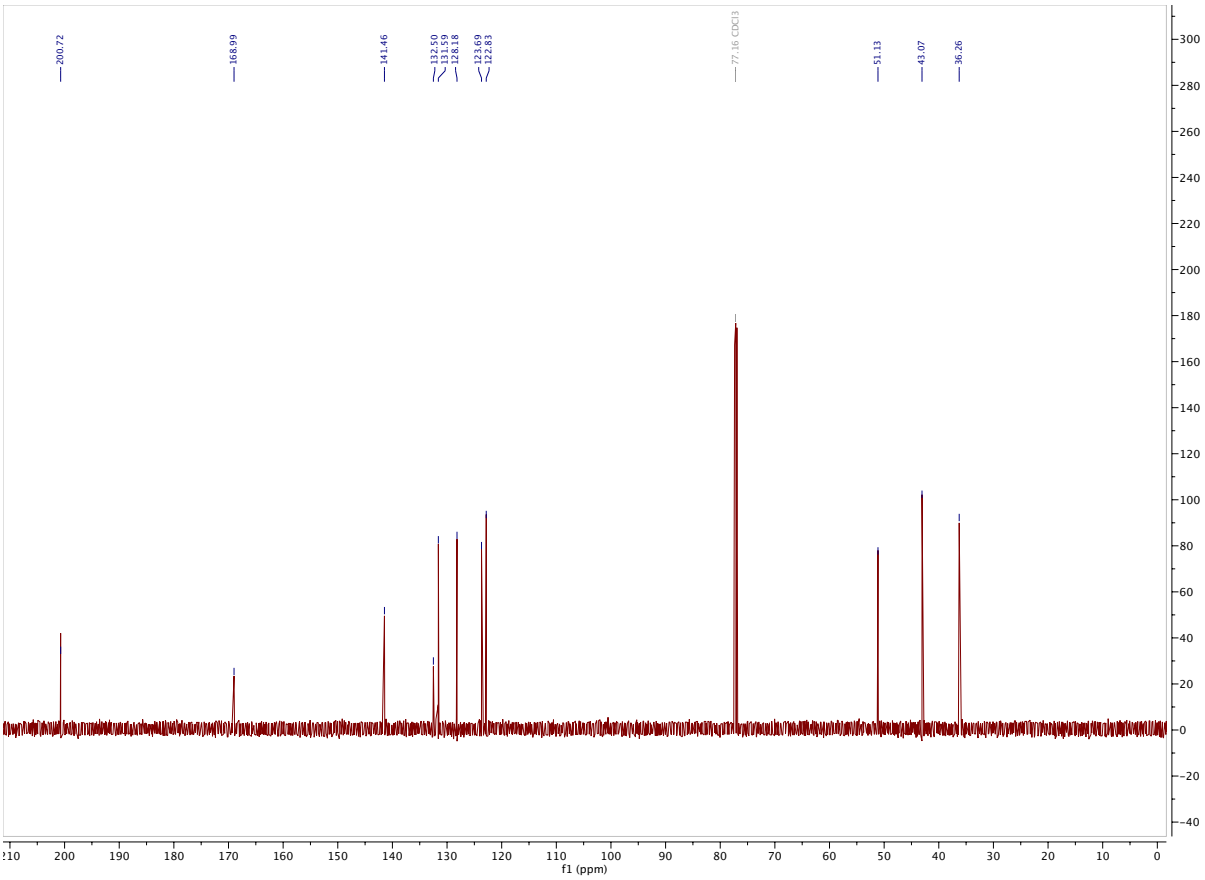
Compound 16



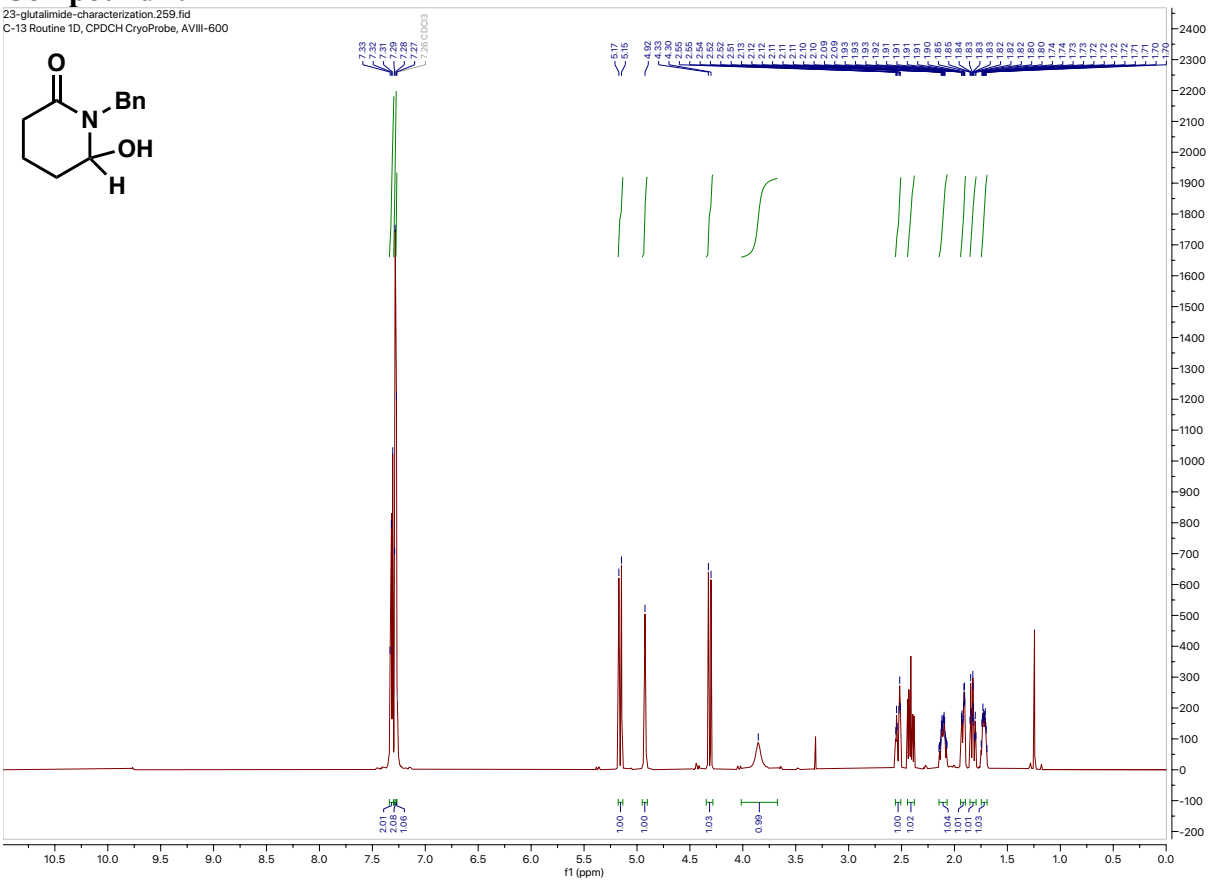

15-MeOD-thalidomide-characterization.277.fid
C-13 Routine 1D, CPDCH CryoProbe, AVIII-600
174.70
172.19
171.55
143.74
133.37
133.09
132.70
129.56
129.04
124.40
53.65
32.38
24.11
f1 (ppm)

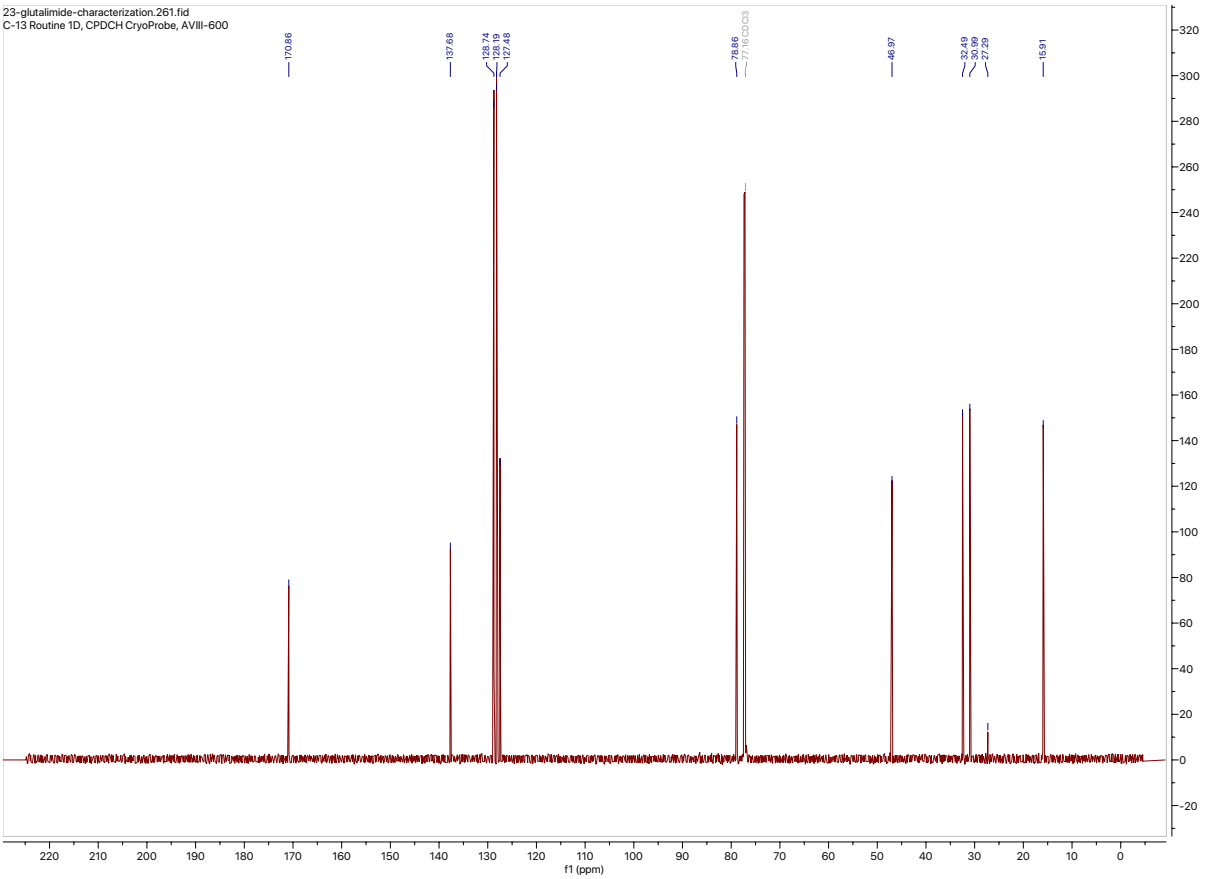
Compound 18a



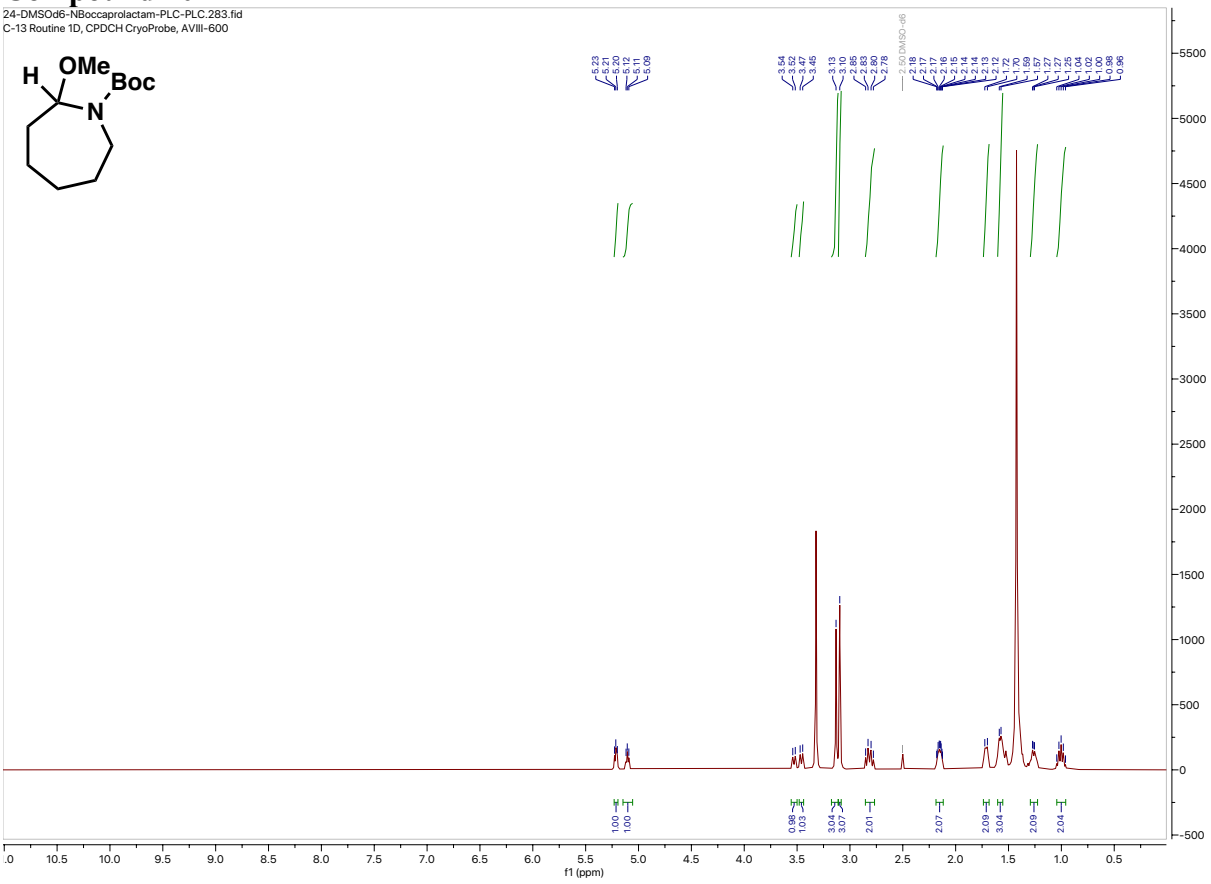

200.72
168.99
141.46
132.50
131.59
126.18
123.69
122.83
77.16 CDCl3
51.13
43.07
36.26
f1 (ppm)

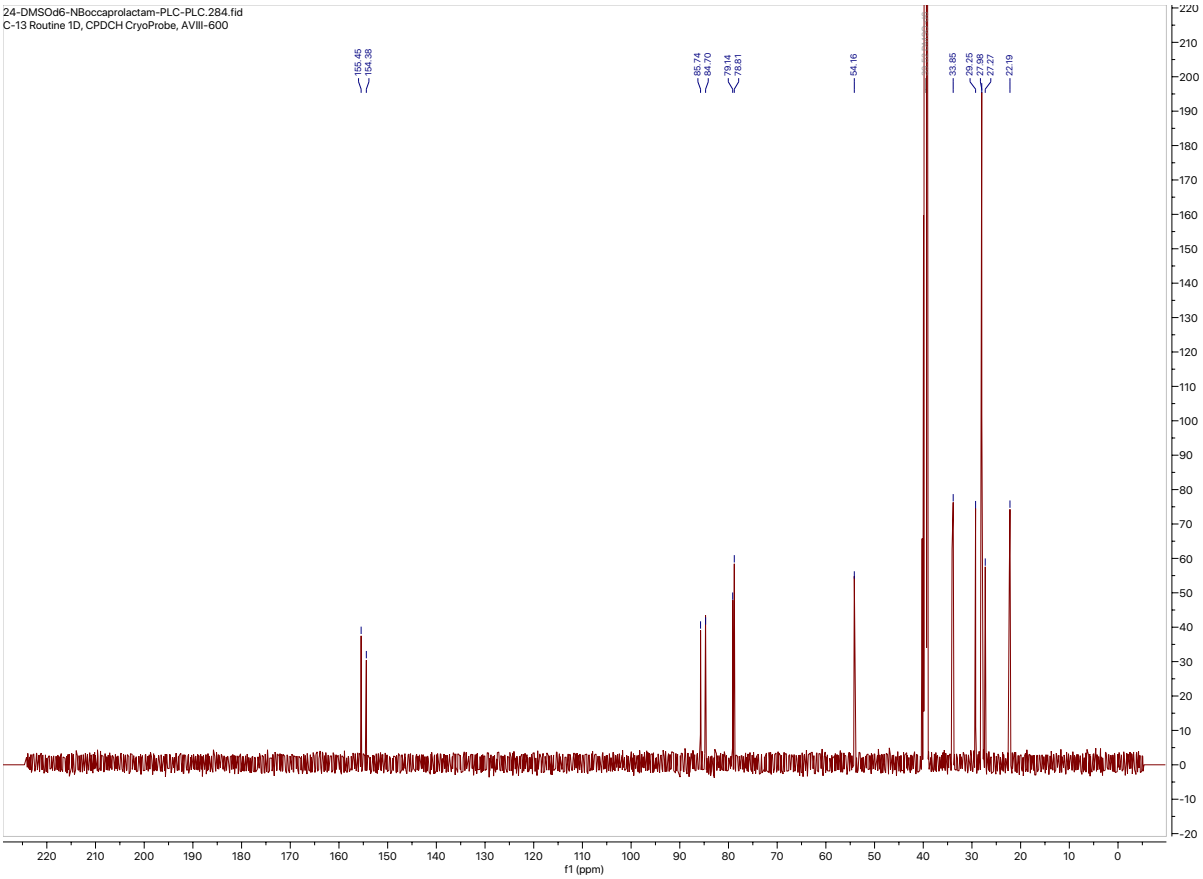
Compound 19


23-glutalimide-characterization.259.fid
C-13 Routine 1D, CPDCH CryoProbe, AVIII-600
O
N
Bn
OH
H
f1 (ppm)

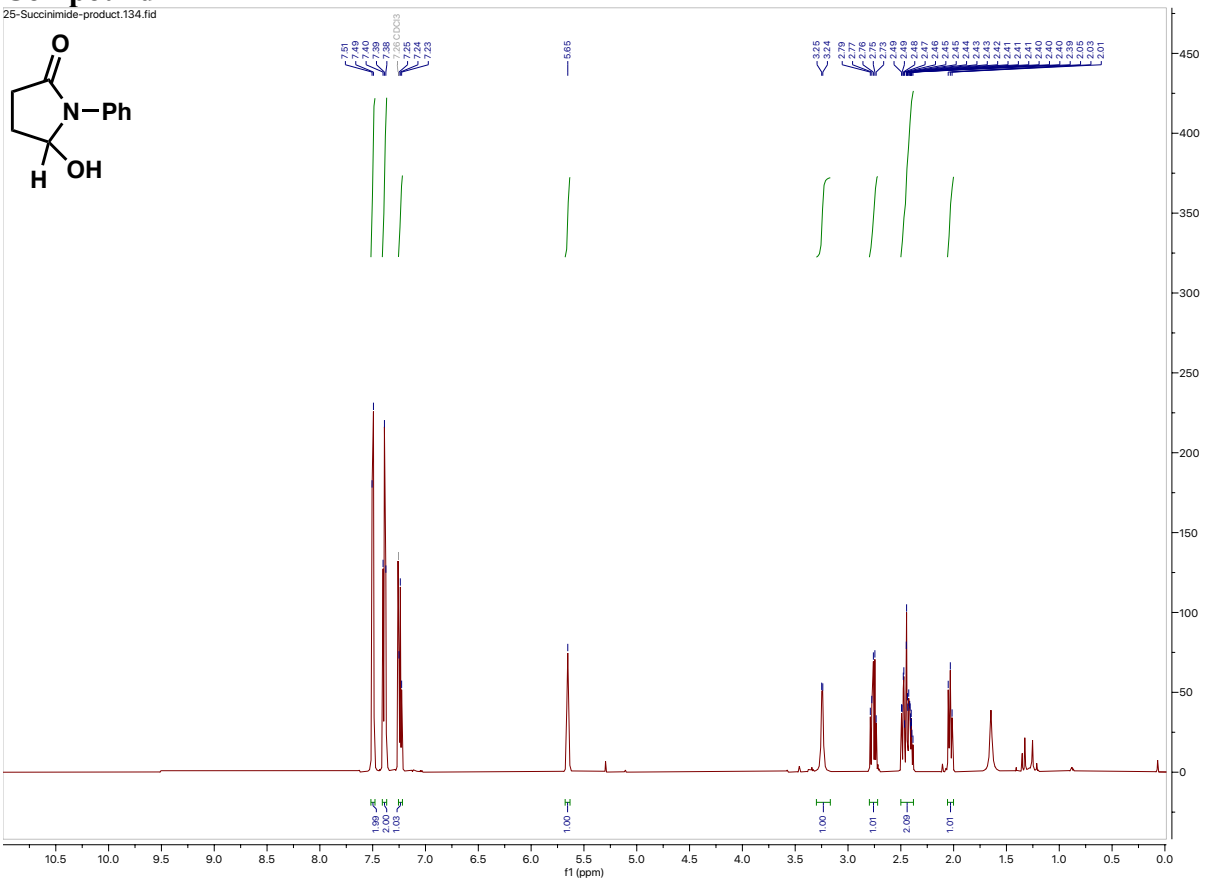

23-glutalimide-characterization.261.fid
C-13 Routine 1D, CPDCH CryoProbe, AVIII-600
170.86
137.68
128.74
128.59
127.48
78.86
77.16 CDCl3
46.97
32.49
30.99
27.29
15.91
f1 (ppm)

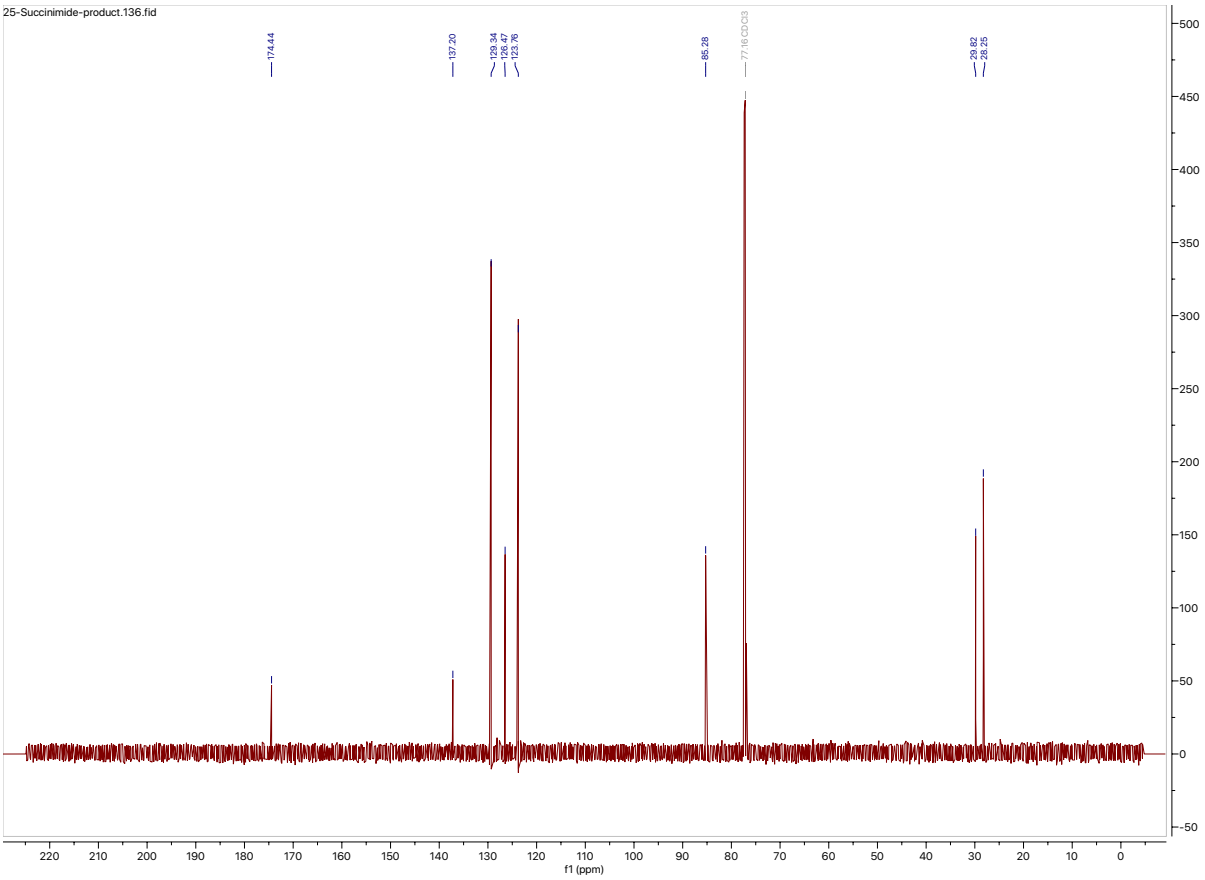
Compound 20


24-DMSOd6-NBoccaprolactam-PLC-PLC.283.fid
C-13 Routine 1D, CPDCH CryoProbe, AVIII-600
H
OMe
Boc
N
f1 (ppm)

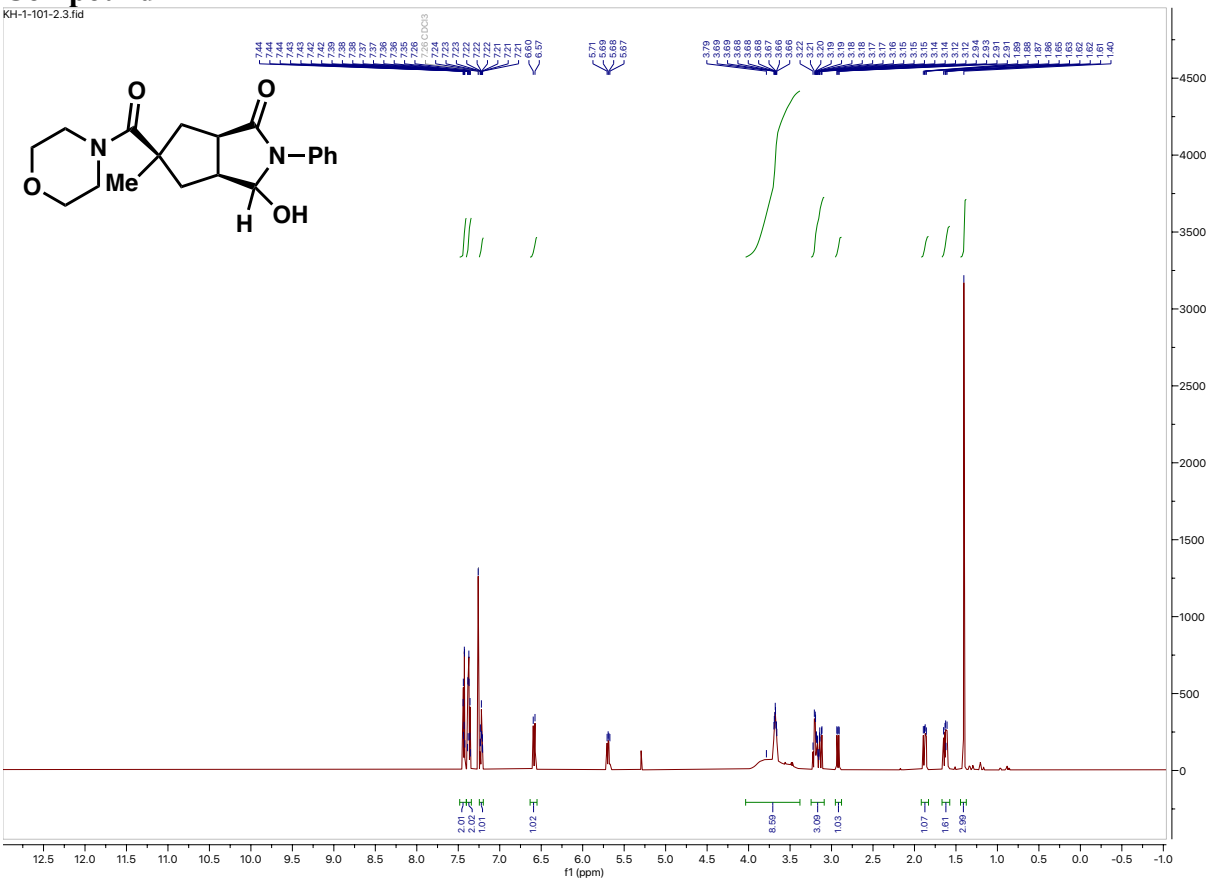

24-DMSOd6-NBoccaprolactam-PLC-PLC.284.fid
C-13 Routine 1D, CPDCH CryoProbe, AVIII-600
156.46
154.39
85.74
84.70
79.14
78.81
54.16
33.86
29.25
27.98
27.27
22.19
f1 (ppm)

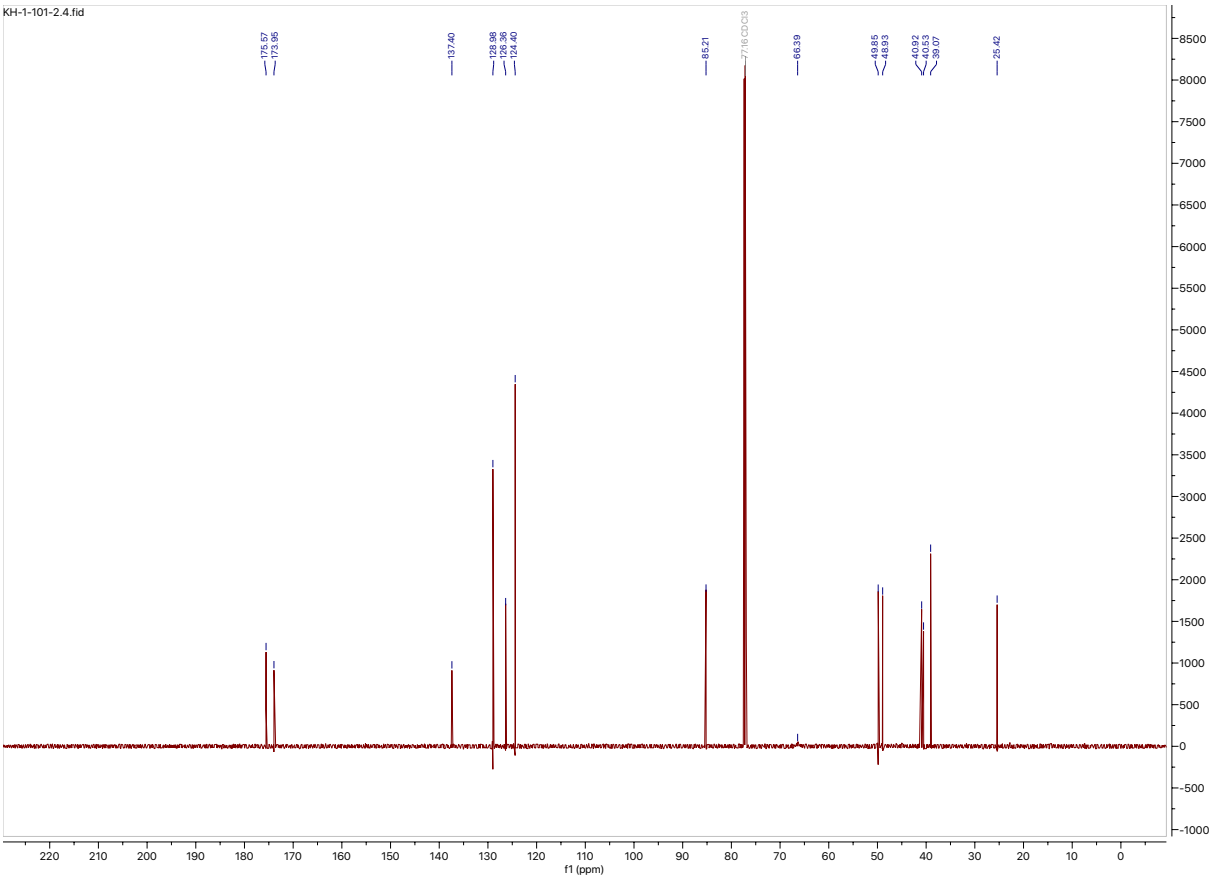
Compound 21



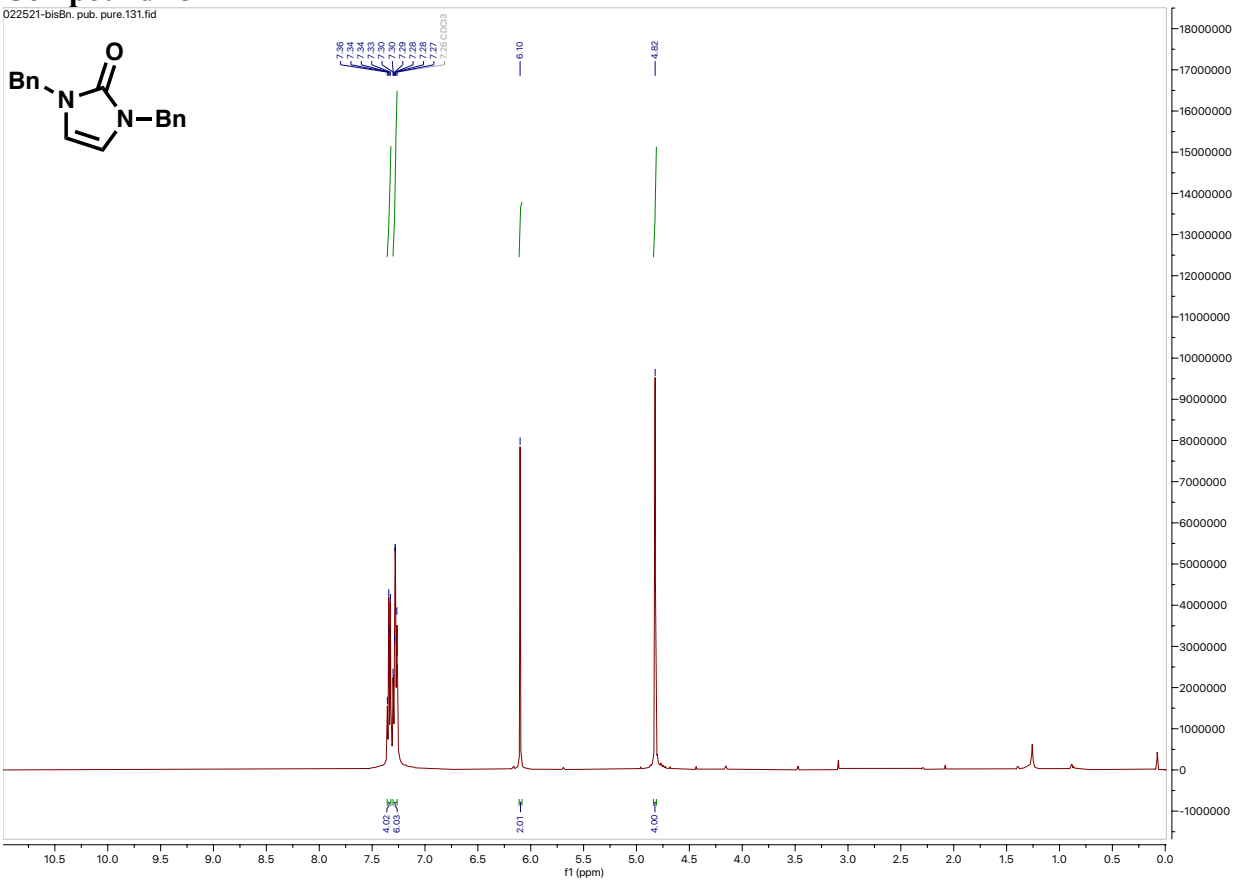

25-Succinimide-product.136.fid
174.44
137.20
129.34
126.47
123.76
85.28
77.16 CDCl3
29.82
28.25
f1 (ppm)

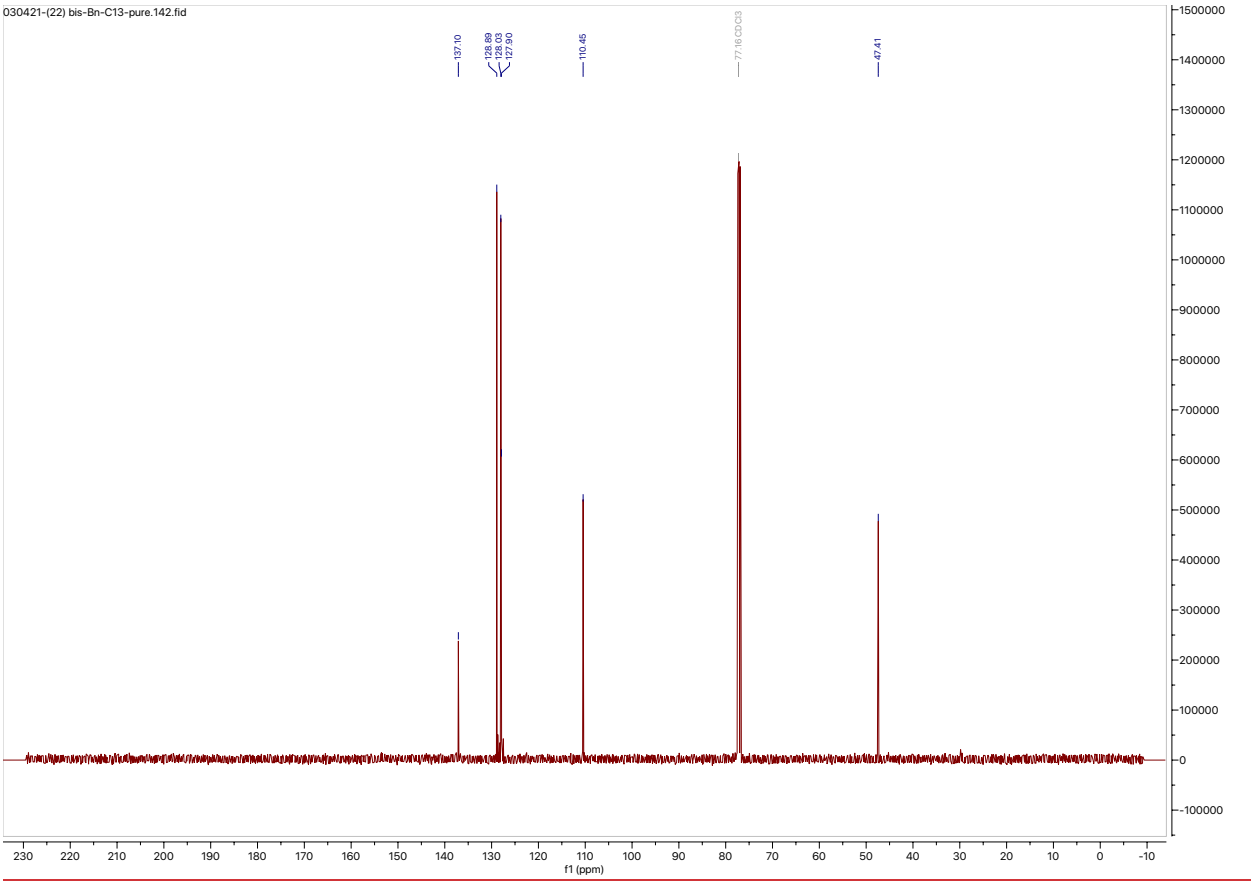
Compound 22



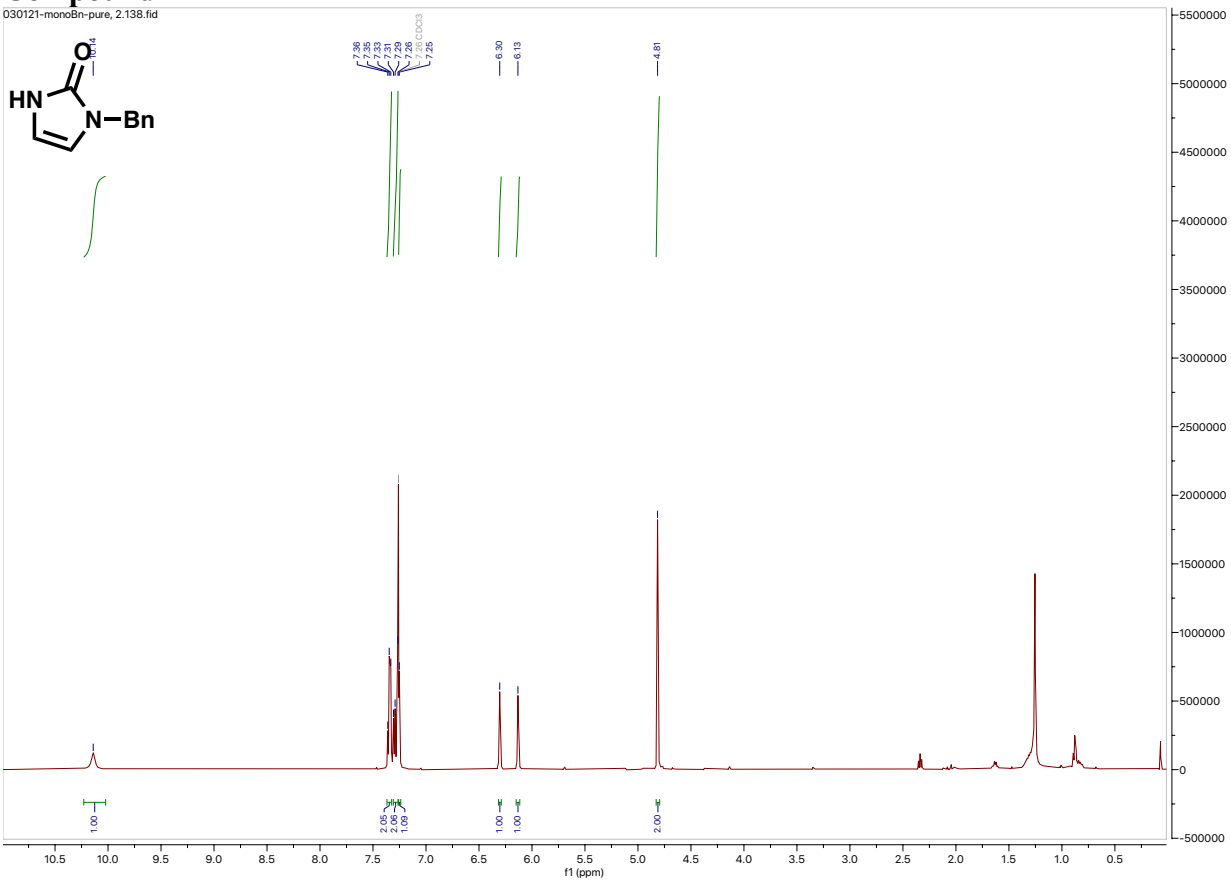

KH-1-101-2.4.fid
175.57
173.95
137.40
128.98
126.36
124.40
85.21
77.16 CDCl3
66.39
49.85
49.93
40.92
40.53
39.07
25.42
f1 (ppm)

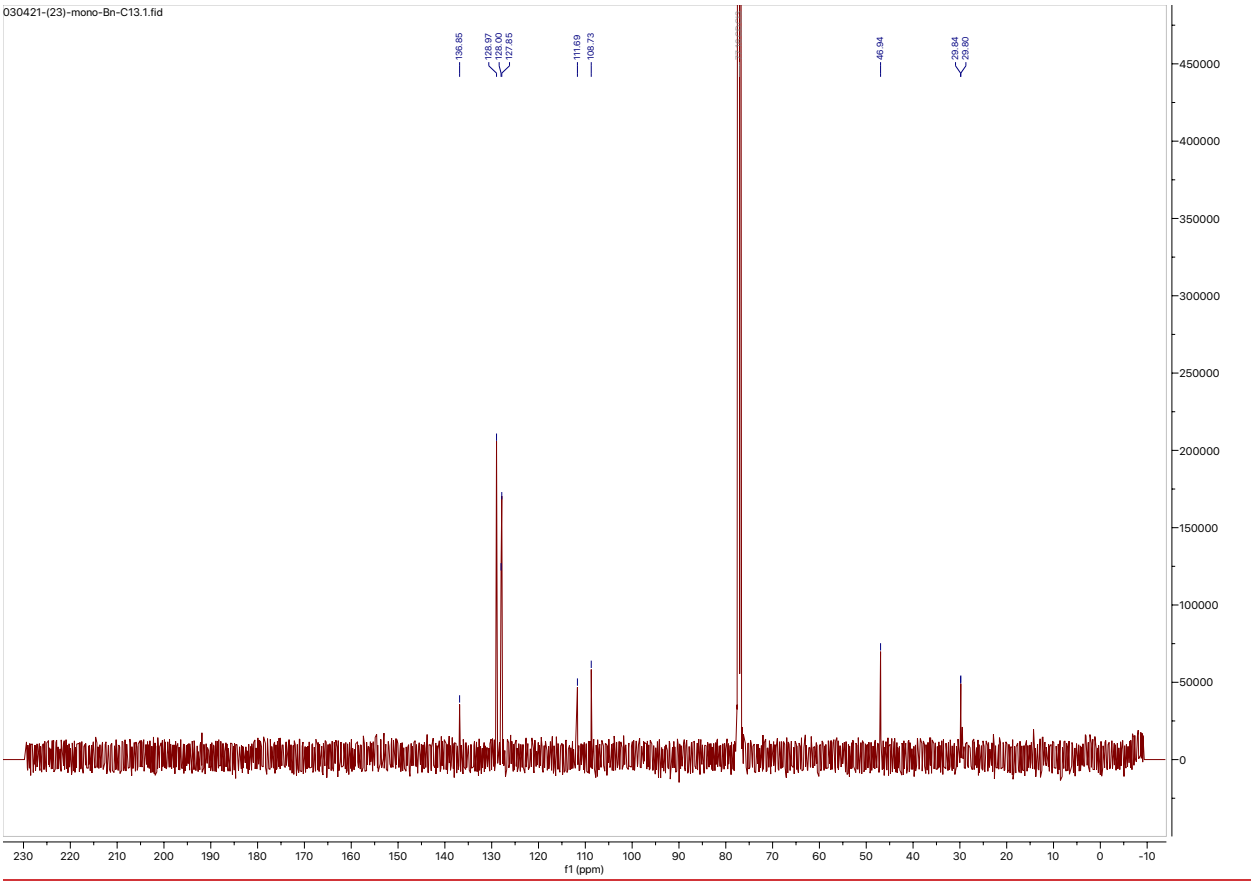
Compound 23


022521-bisBn. pub. pure.131.fid
Bn
N
O
N–Bn
7.36
7.34
7.33
7.33
7.30
7.29
7.28
7.28
7.27
7.26 CDCl3
6.10
4.82
4.02
6.03
2.01
4.00
f1 (ppm)

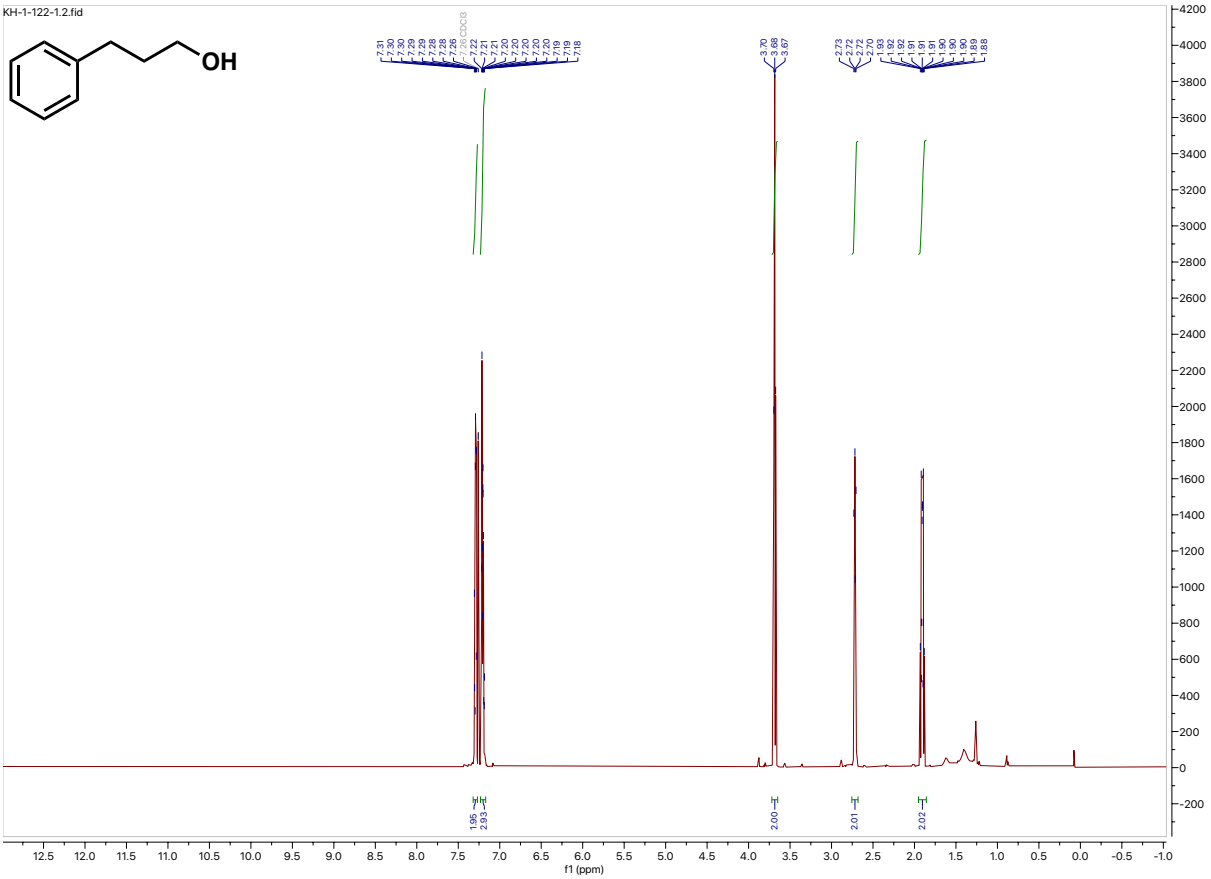

030421-(22) bis-Bn-C13-pure.142.fid
137.10
128.89
128.03
127.90
110.45
77.16 CDCl3
47.41
f1 (ppm)

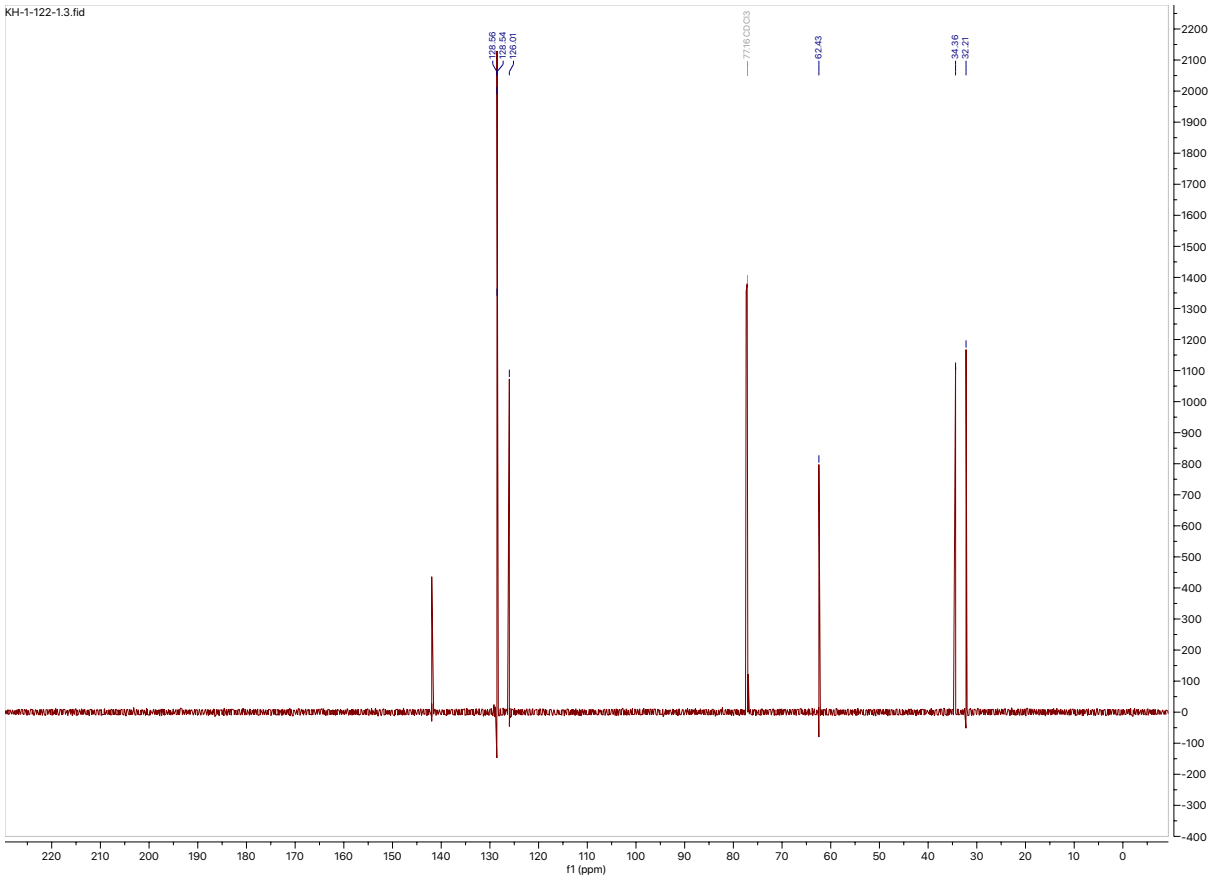
Compound 24


030121-monoBn-pure, 2.138.fid
HN
N–Bn
O
10.14
7.36
7.35
7.33
7.31
7.29
7.26
7.25
6.30
6.13
4.81
1.00
2.05
2.08
1.09
1.00
1.00
2.00
f1 (ppm)

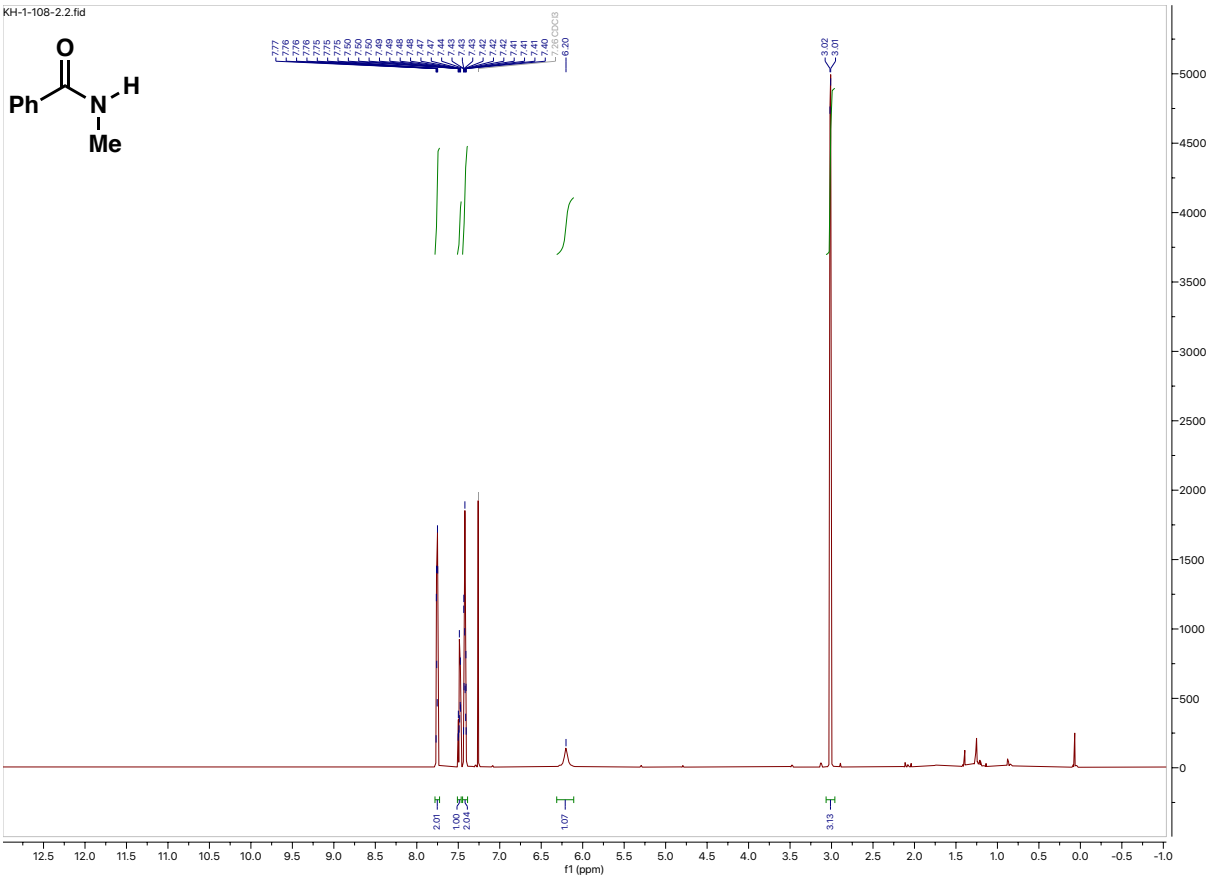

030421-(23)-mono-Bn-C13.1.fid
136.85
128.97
128.60
127.85
111.69
108.73
46.94
29.84
29.80
450000
400000
350000
300000
250000
200000
150000
100000
50000
0
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

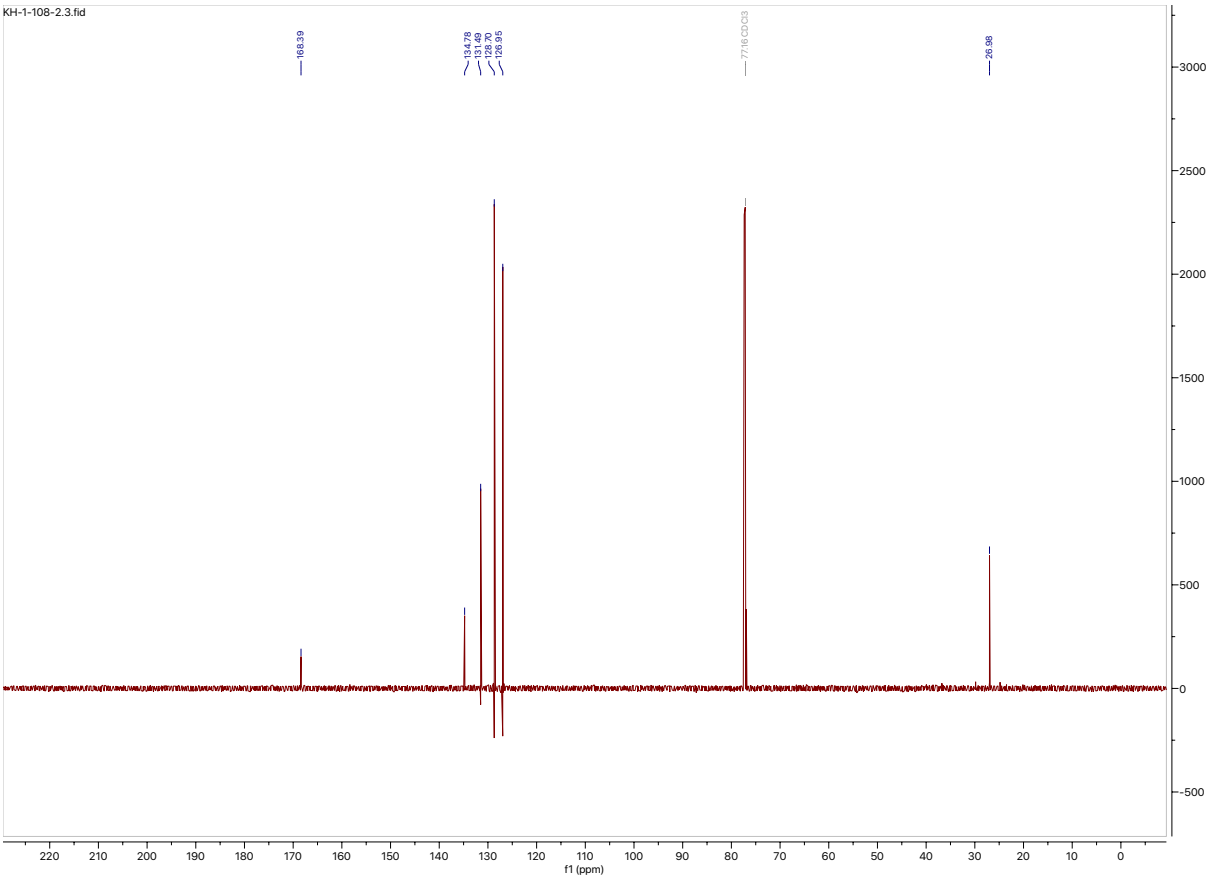
Compound 26



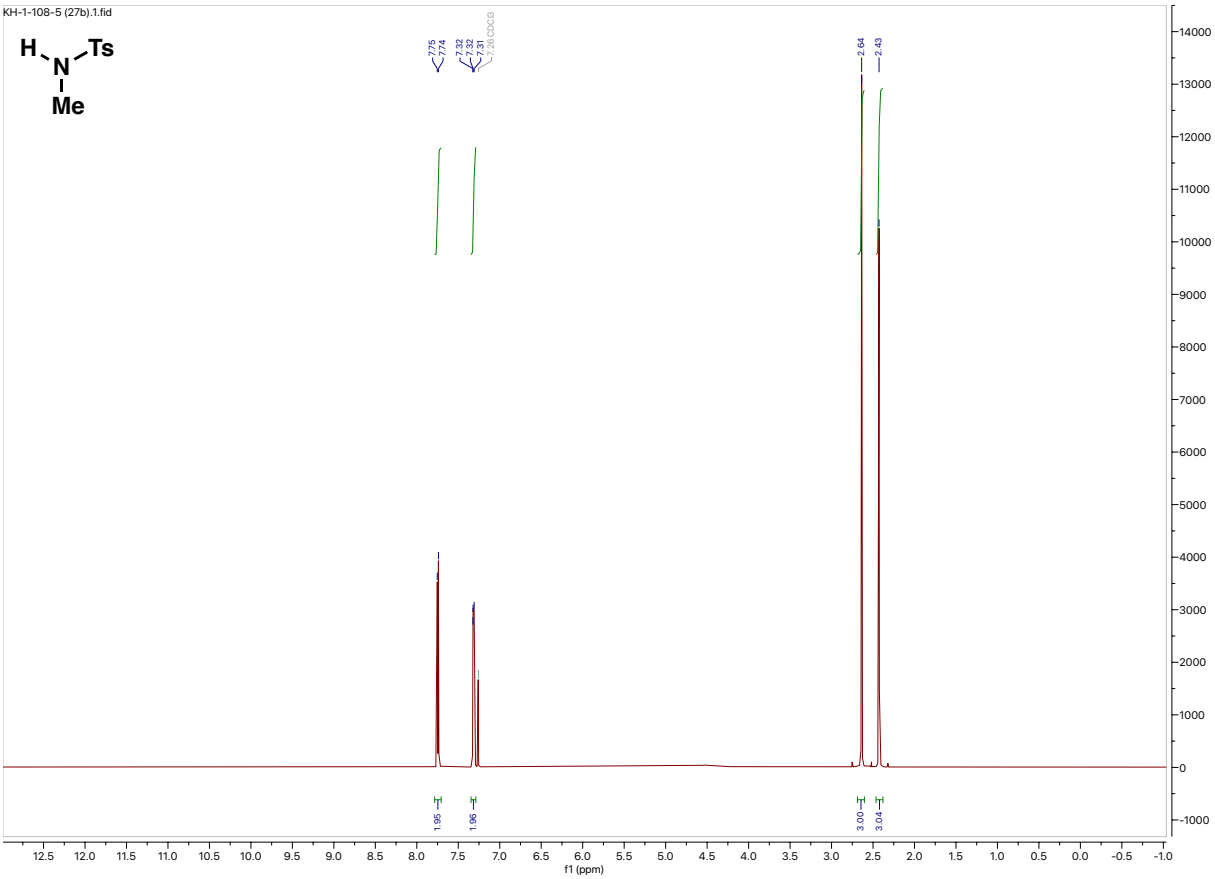

KH-1-122-1.3.fid
128.56
128.54
128.01
77.16 CDCl3
62.43
34.36
32.21
f1 (ppm)

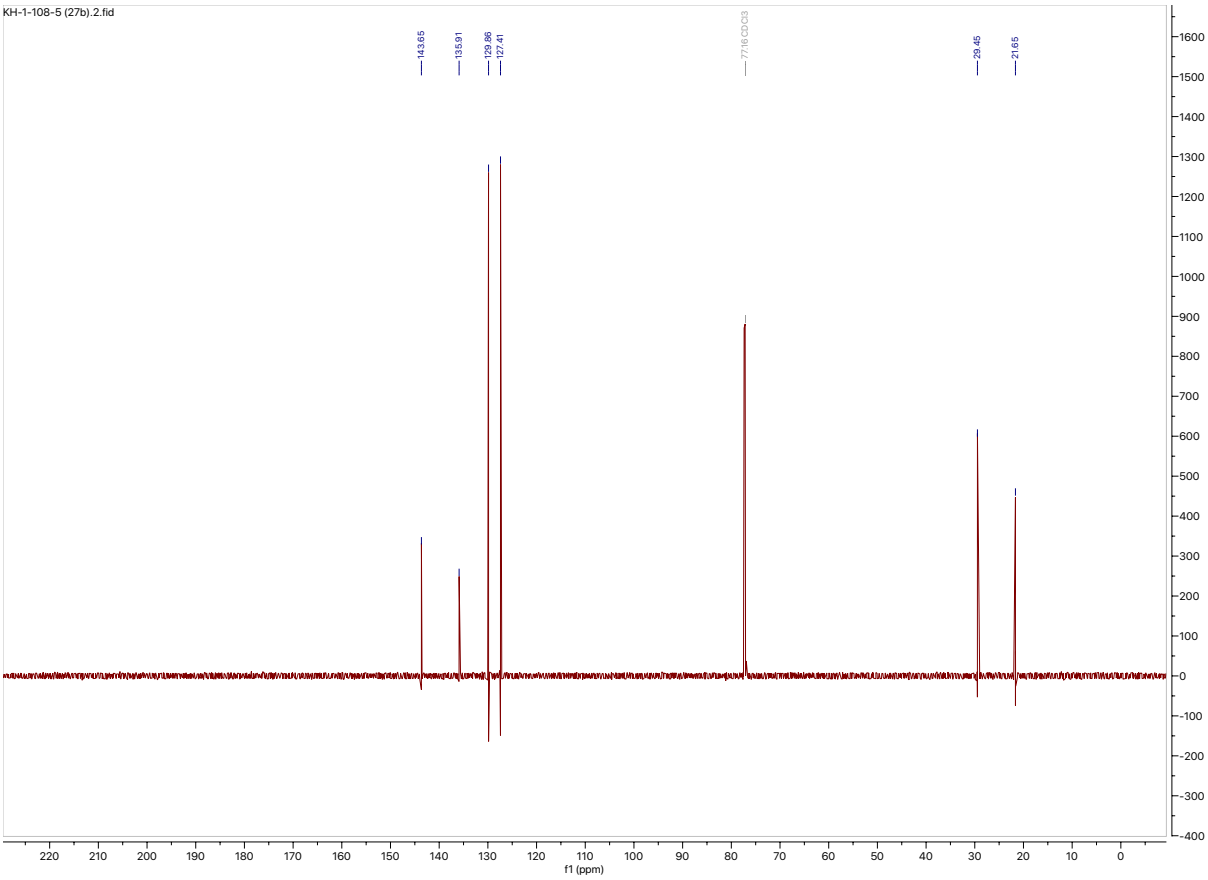
Compound 28a



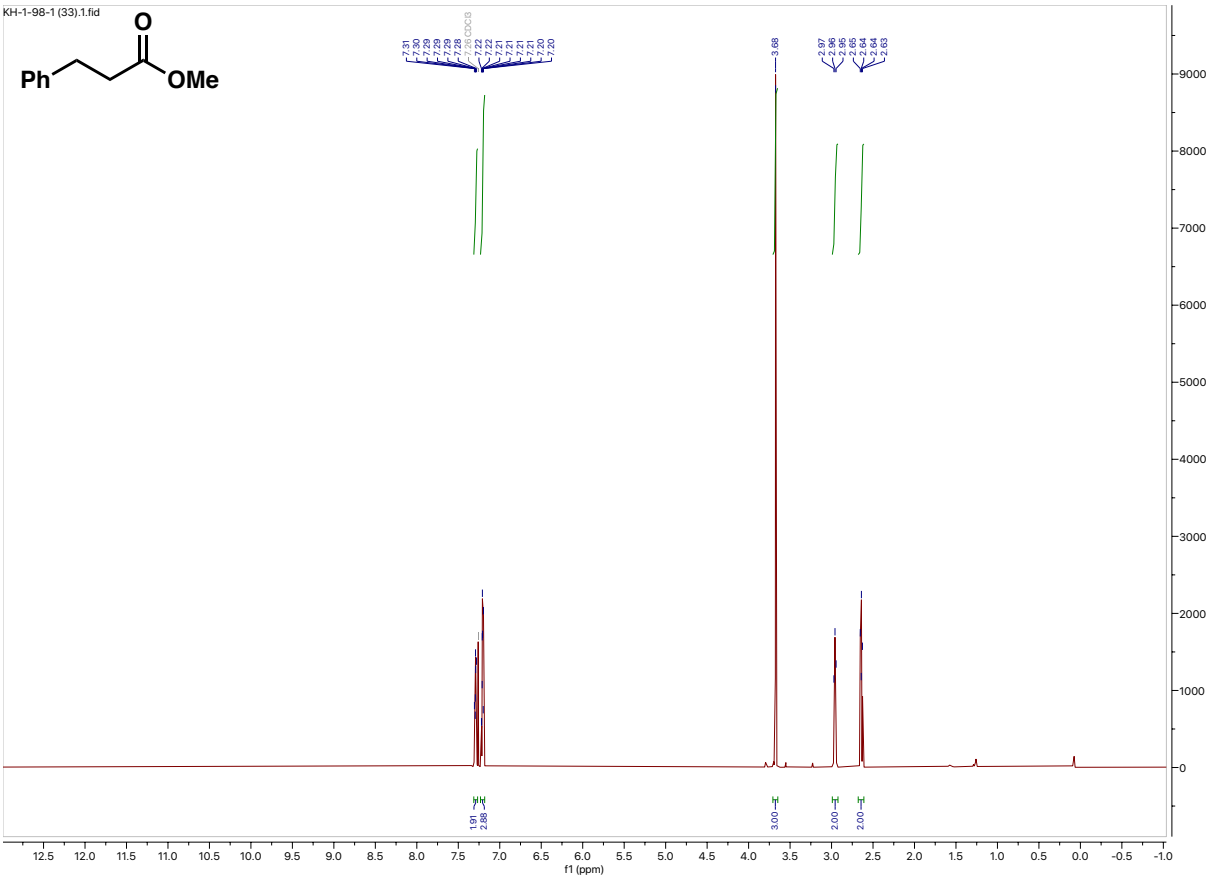

KH-1-108-2.3.fid
168.39
134.78
131.49
128.70
126.95
77.16 CDCl3
26.98
3000
2500
2000
1500
1000
500
0
-500
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

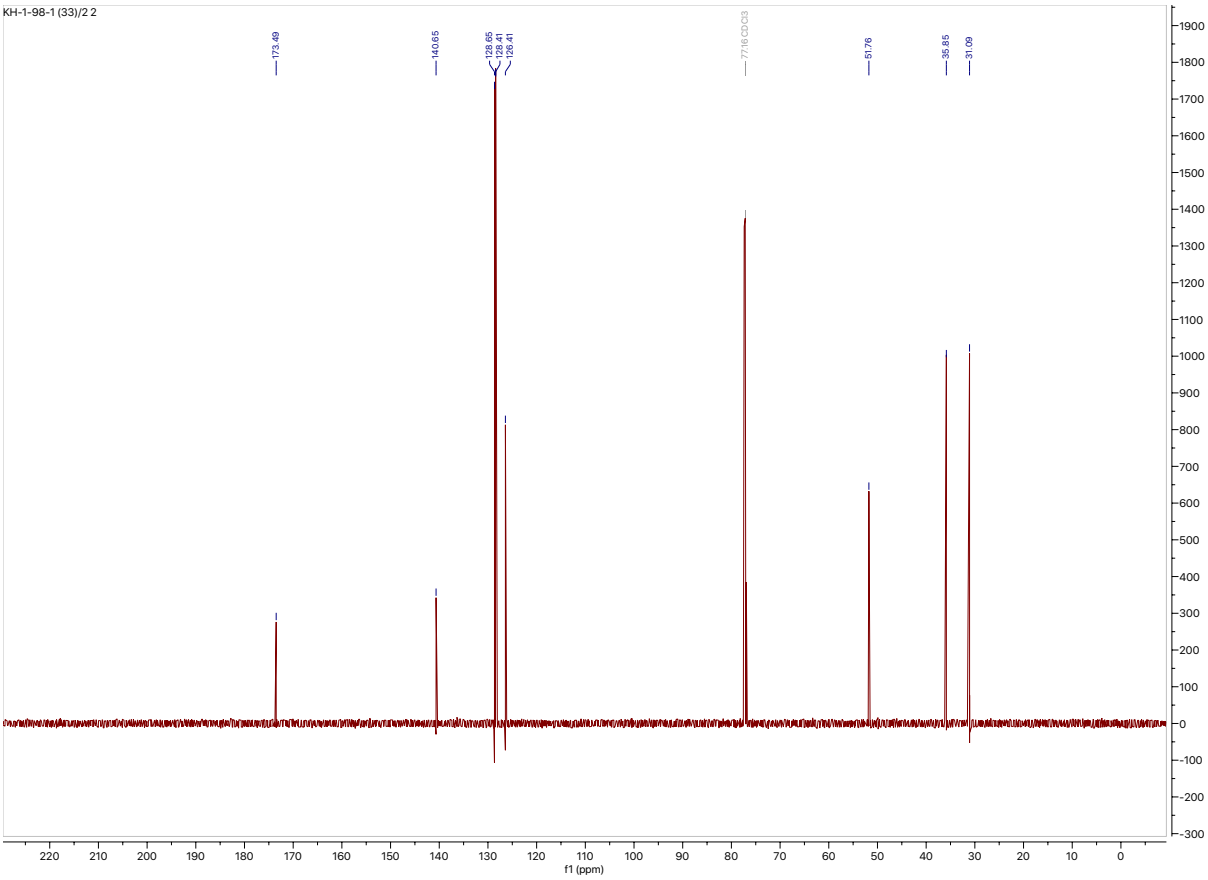
Compound 28b



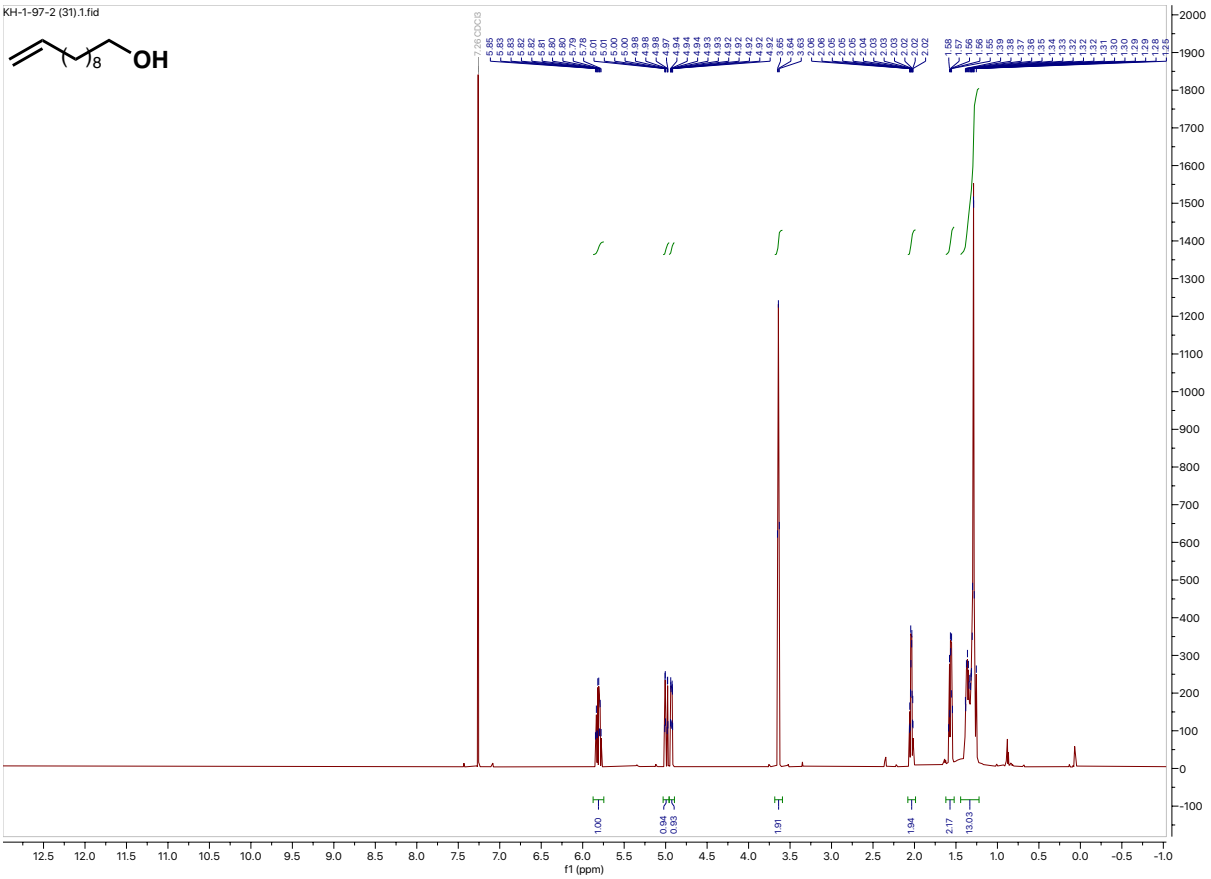

KH-1-108-5 (27b).2.fid
143.65
135.91
129.86
127.41
77.16 CDCl3
29.45
21.65
f1 (ppm)

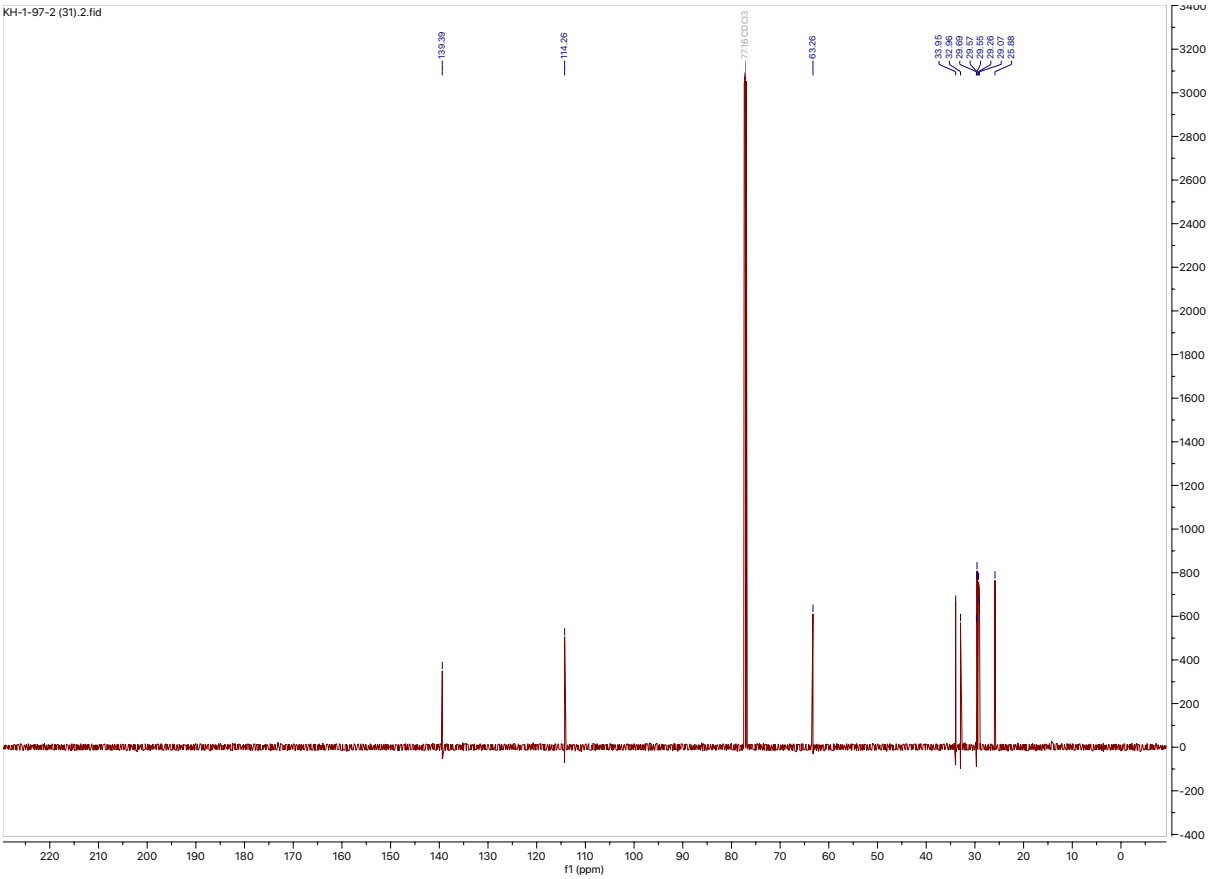
Compound 30


KH-1-98-1 (33).1.fid
O
Ph
OMe
7.31
7.30
7.29
7.29
7.28
7.28
CDCl3
7.22
7.22
7.21
7.21
7.21
7.21
7.20
7.20
3.68
2.97
2.96
2.95
2.65
2.64
2.64
2.63
1.91
2.88
3.00
2.00
2.00
f1 (ppm)

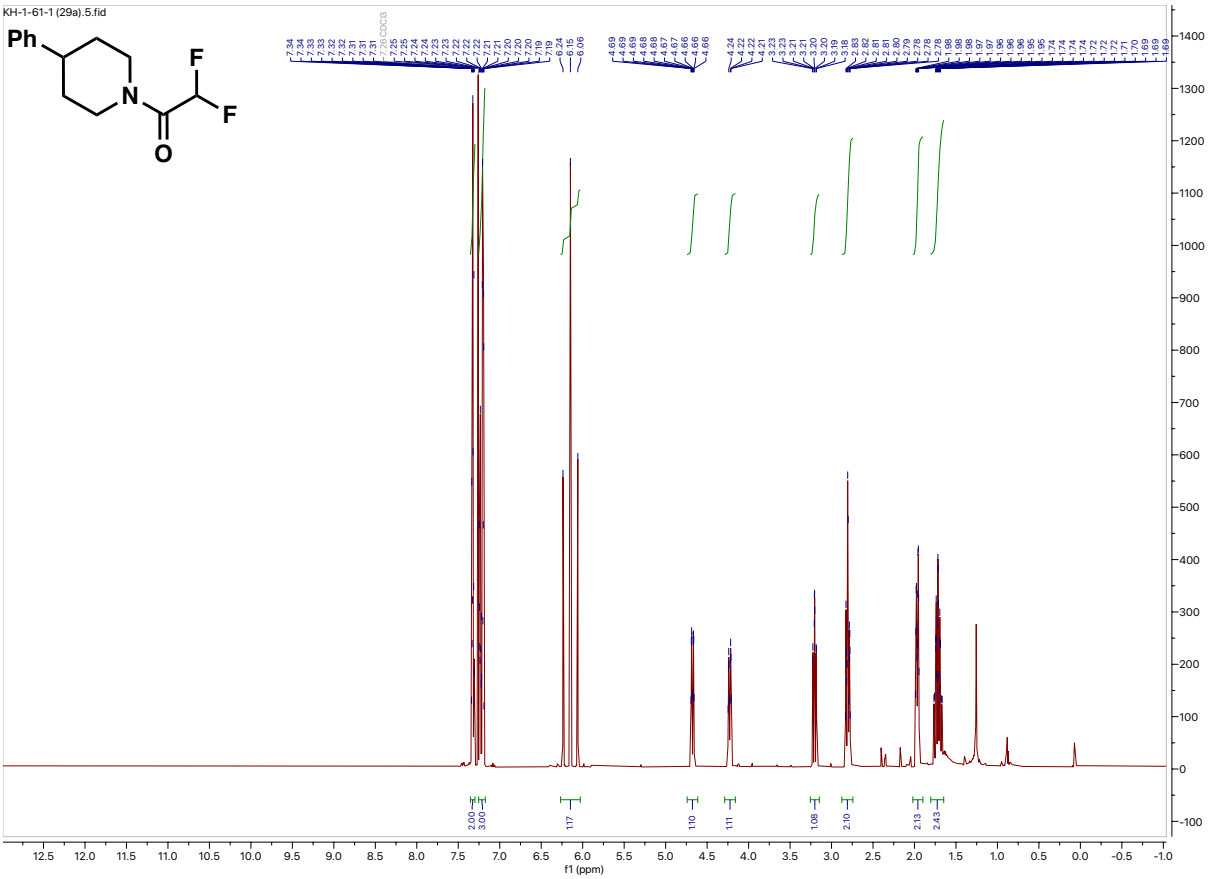

KH-1-98-1 (33)/2 2
173.49
140.65
128.65
128.41
126.41
77.16 CDCl3
51.76
35.85
31.09
f1 (ppm)

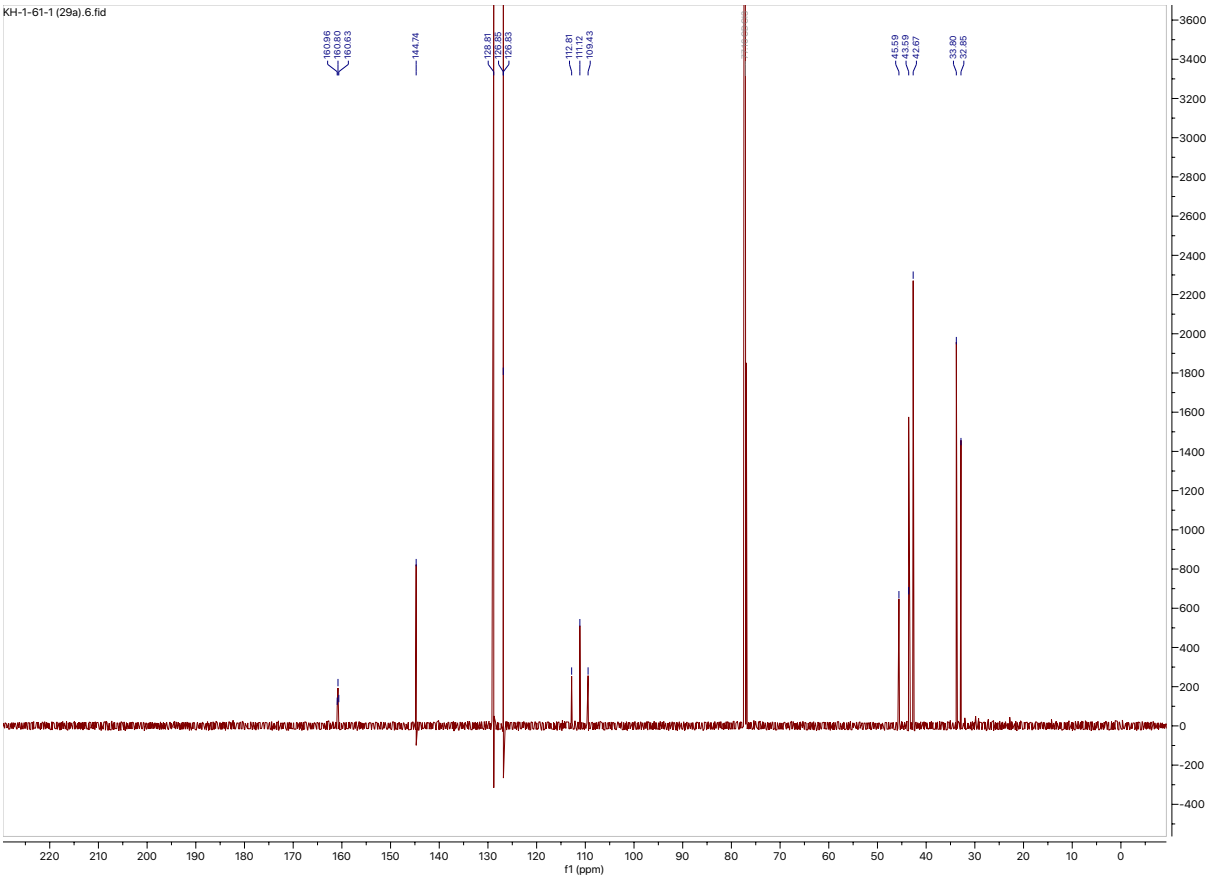
Compound 32



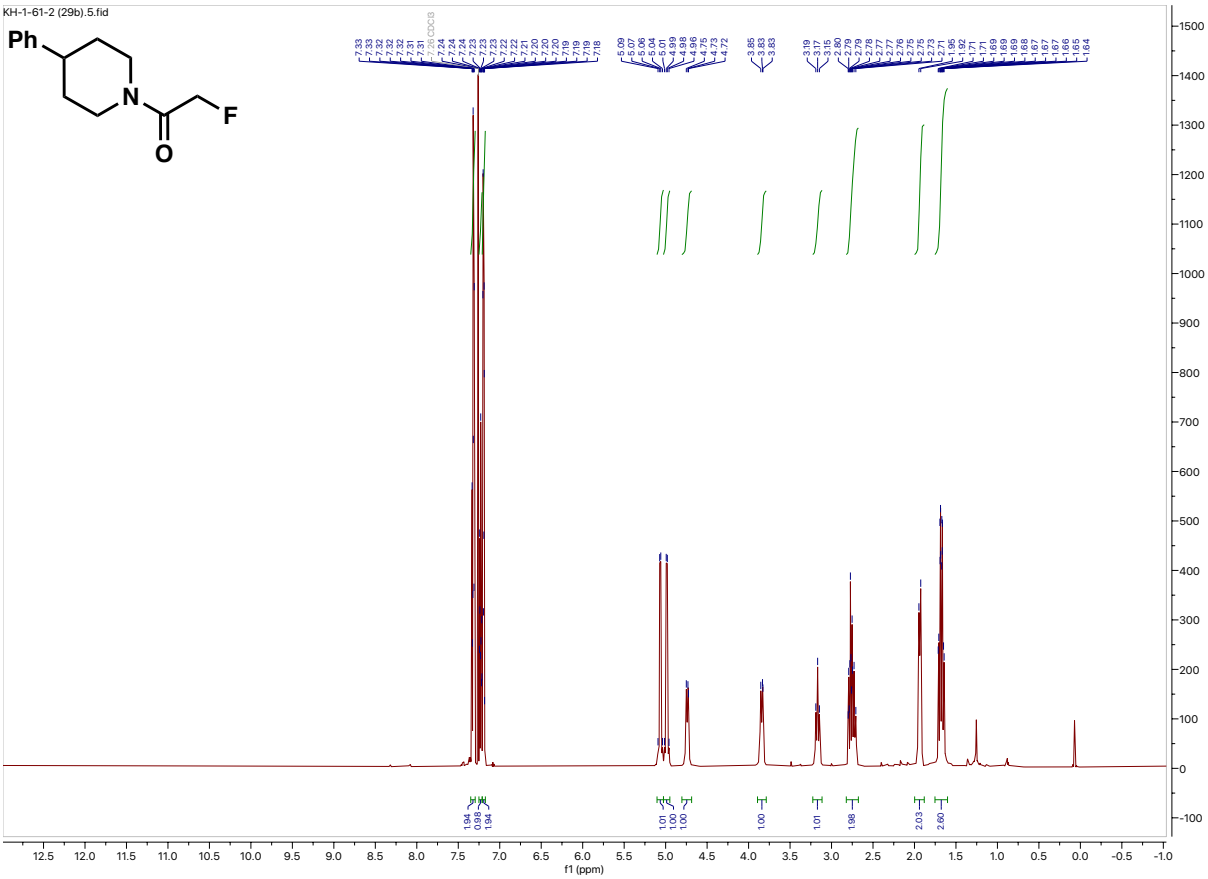

KH-1-97-2 (31).2.fid
139.39
114.26
77.16 CDCl3
63.26
33.95
32.96
29.69
29.57
29.55
29.26
29.07
25.88
f1 (ppm)

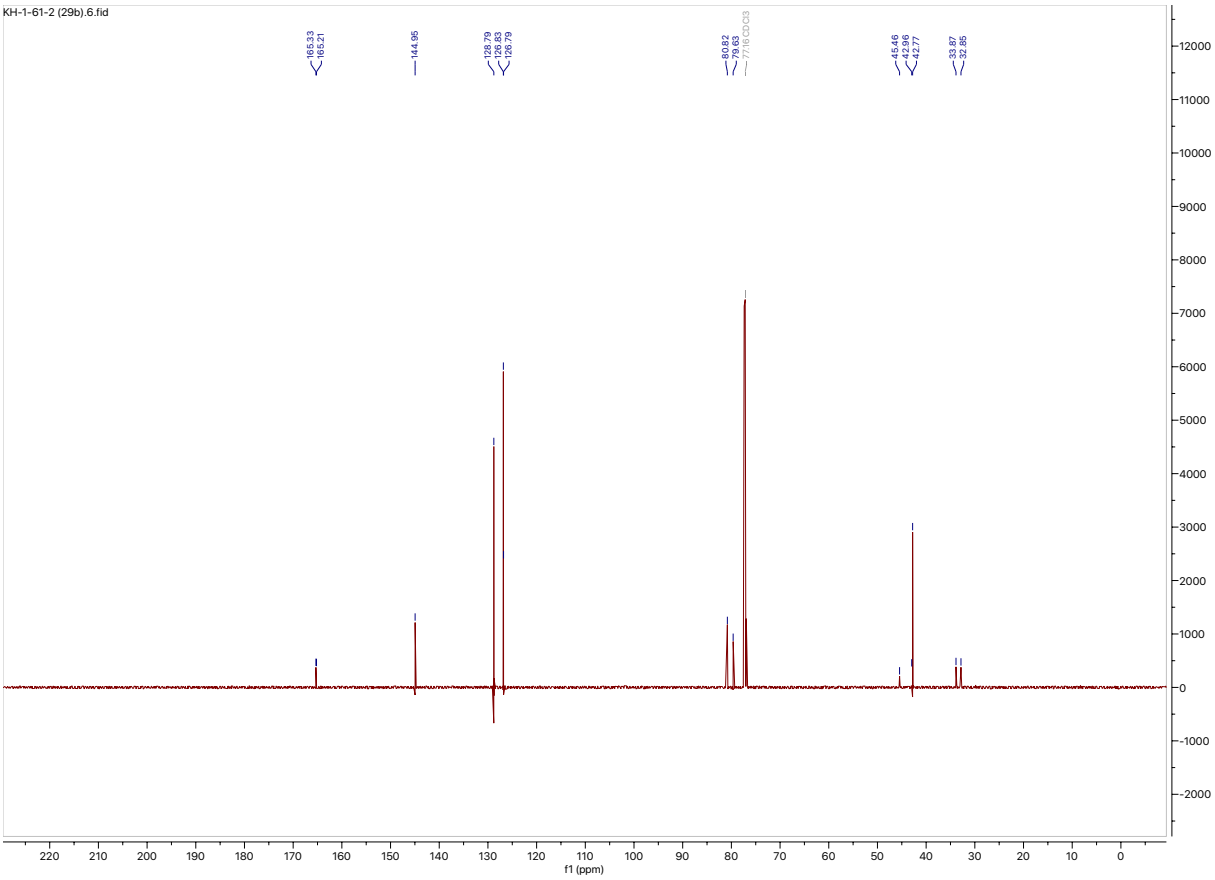
Compound 34a



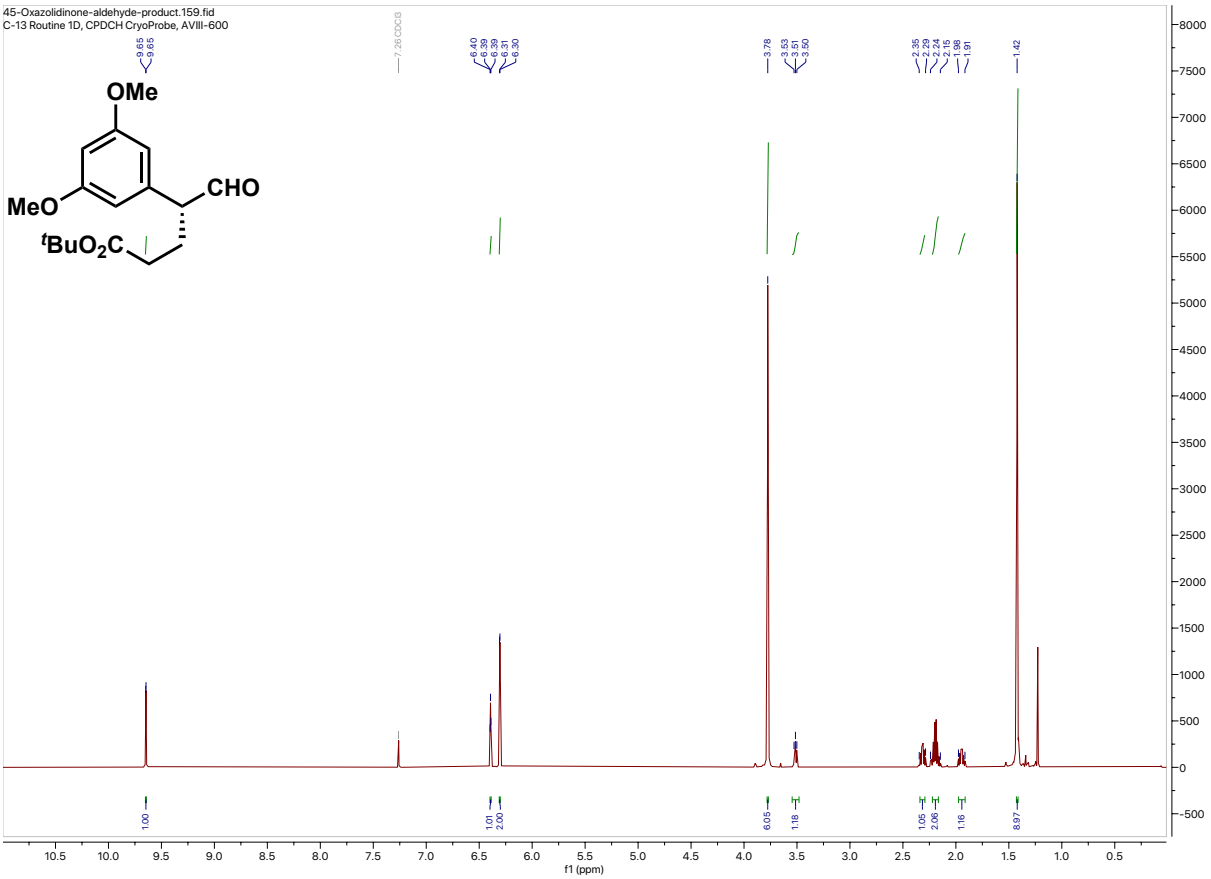

KH-1-61-1 (29a).6.fid
160.96
160.80
160.63
144.74
128.81
128.65
128.53
128.83
112.81
111.72
109.43
45.59
43.59
42.67
33.80
32.85
f1 (ppm)

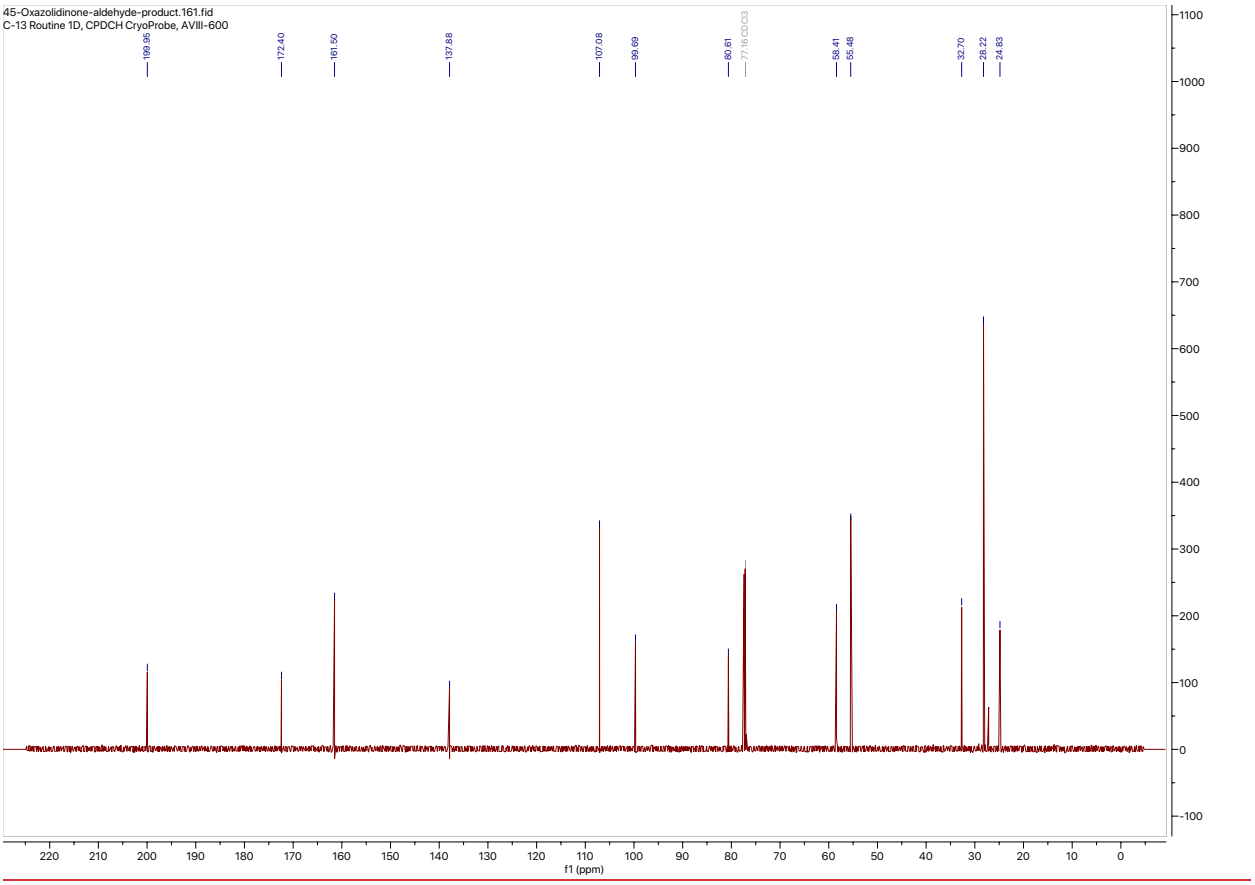
Compound 34b



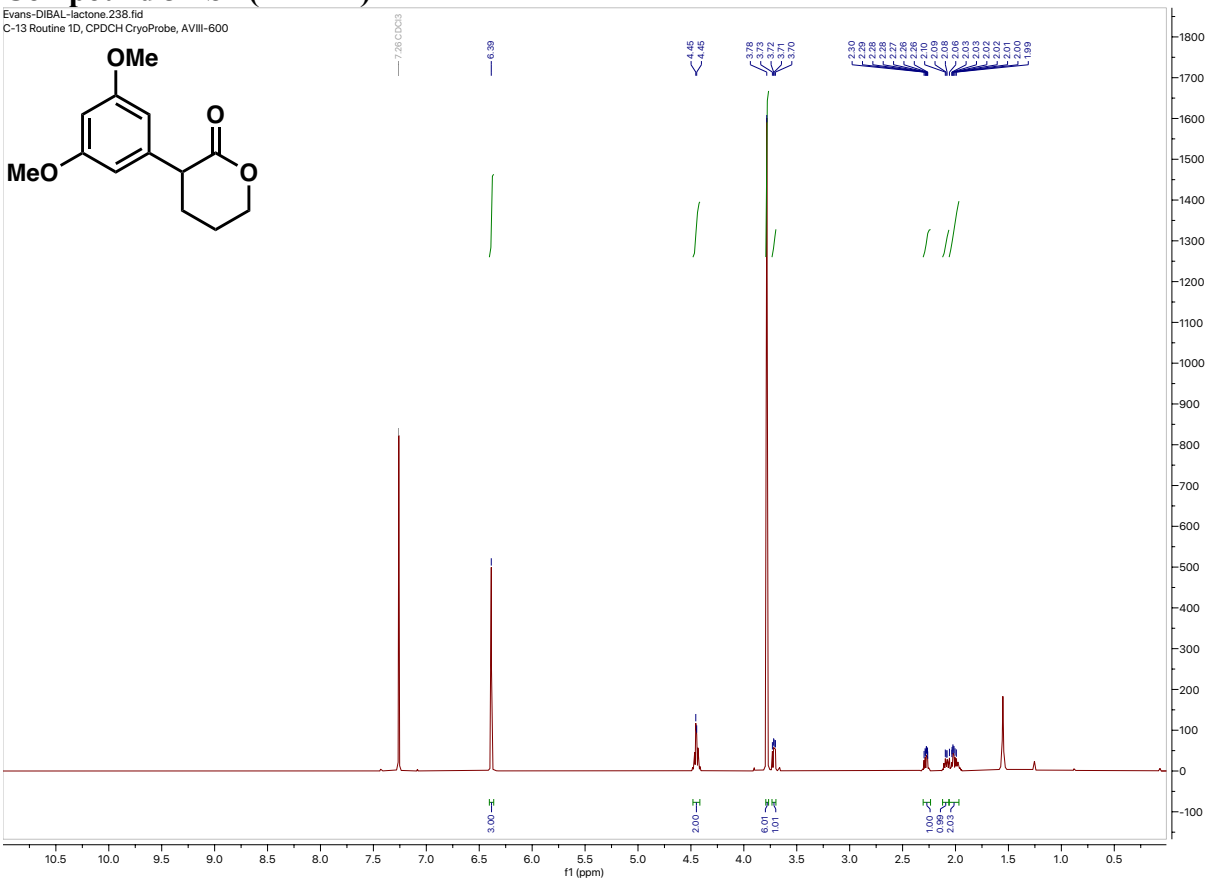

KH-1-61-2 (29b).6.fid
165.33
165.21
144.95
128.79
128.63
128.59
80.82
79.65
77.16 CDCl3
45.46
43.96
42.77
33.87
32.85
f1 (ppm)

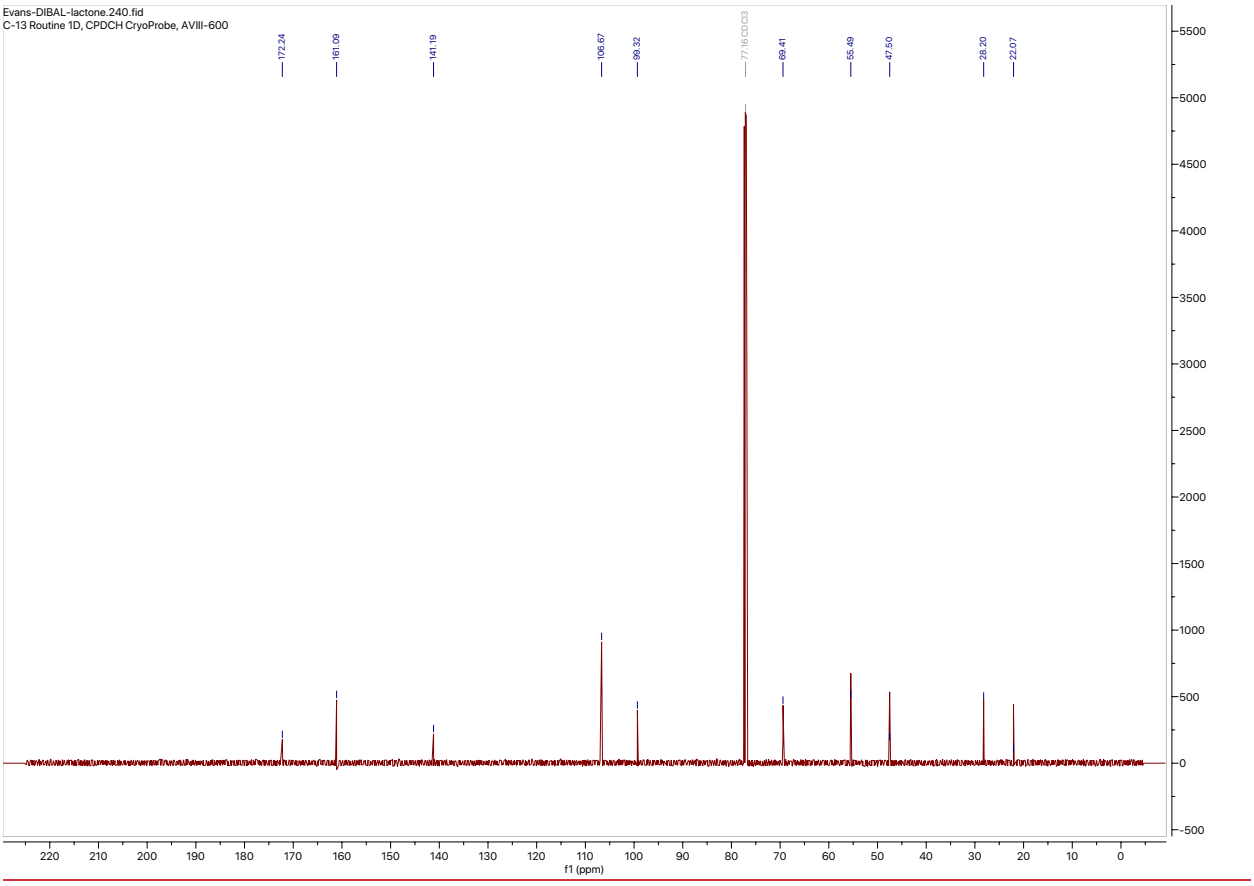
Compound 37


45-Oxazolidinone-aldehyde-product.159.fid
C-13 Routine 1D, CPDCH CryoProbe, AVIII-600
OMe
MeO
CHO
tBuO2C
f1 (ppm)

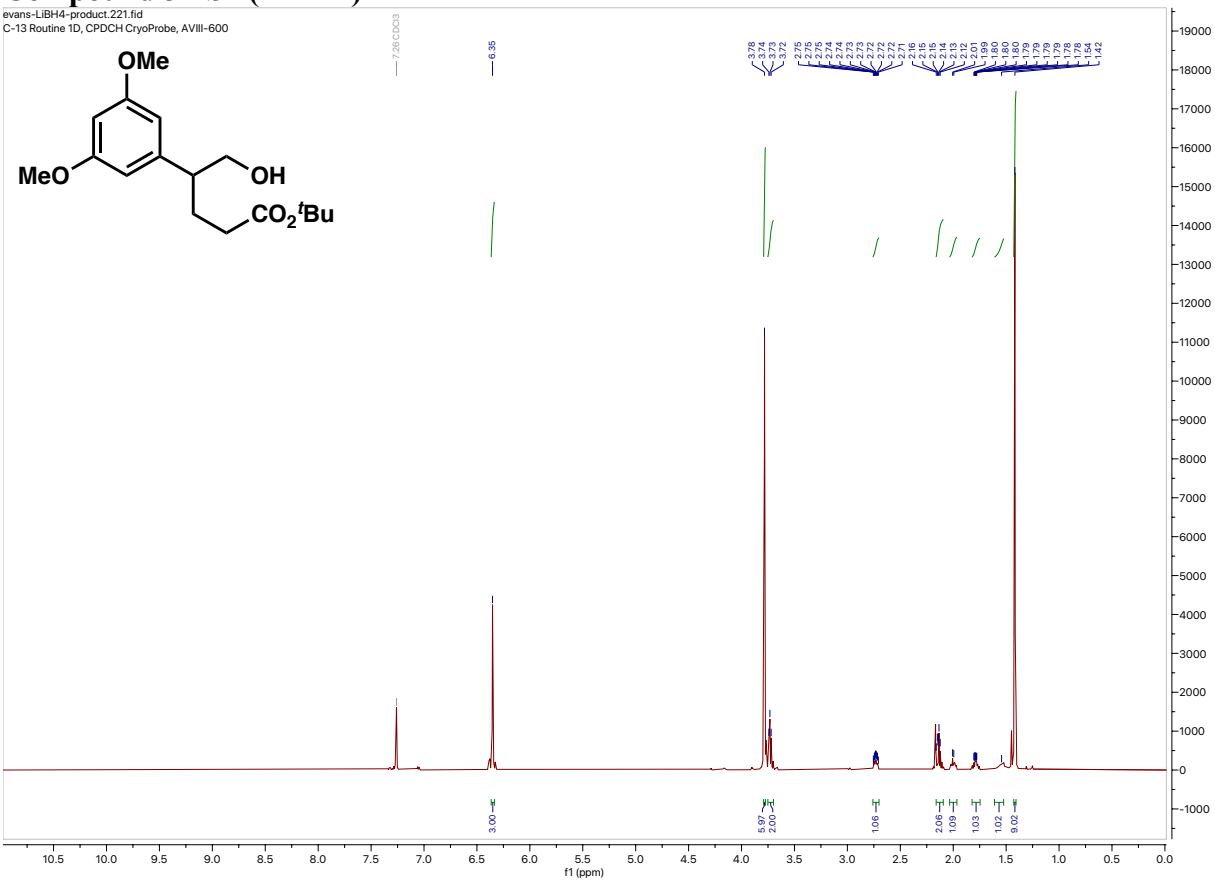

45-Oxazolidinone-aldehyde-product.161.fid
C-13 Routine 1D, CPDCH CryoProbe, AVIII-600
199.99
172.40
161.50
137.88
107.08
99.69
80.61
77.16 CDCl3
58.41
55.48
32.70
28.22
24.83
f1 (ppm)

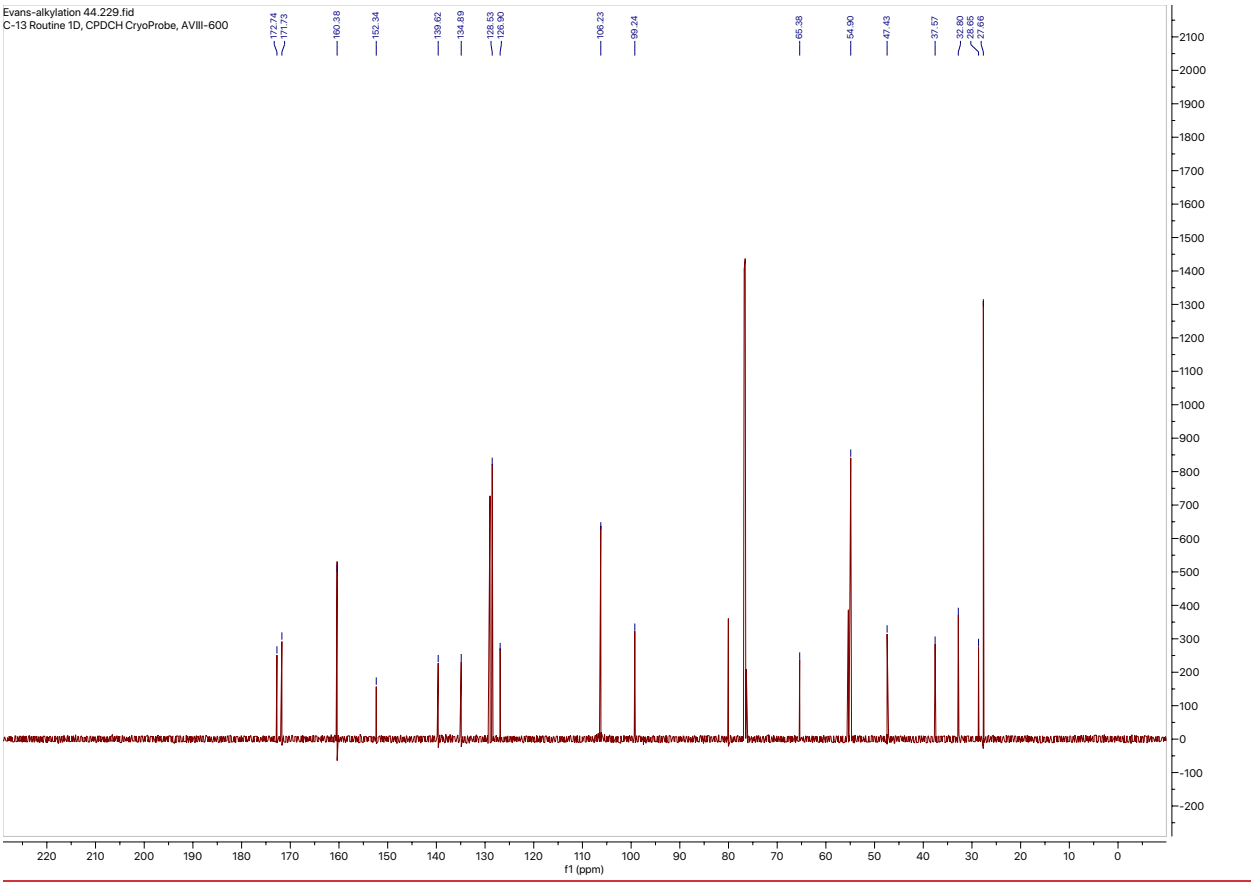
Compound 37-S1 (DIBAL)



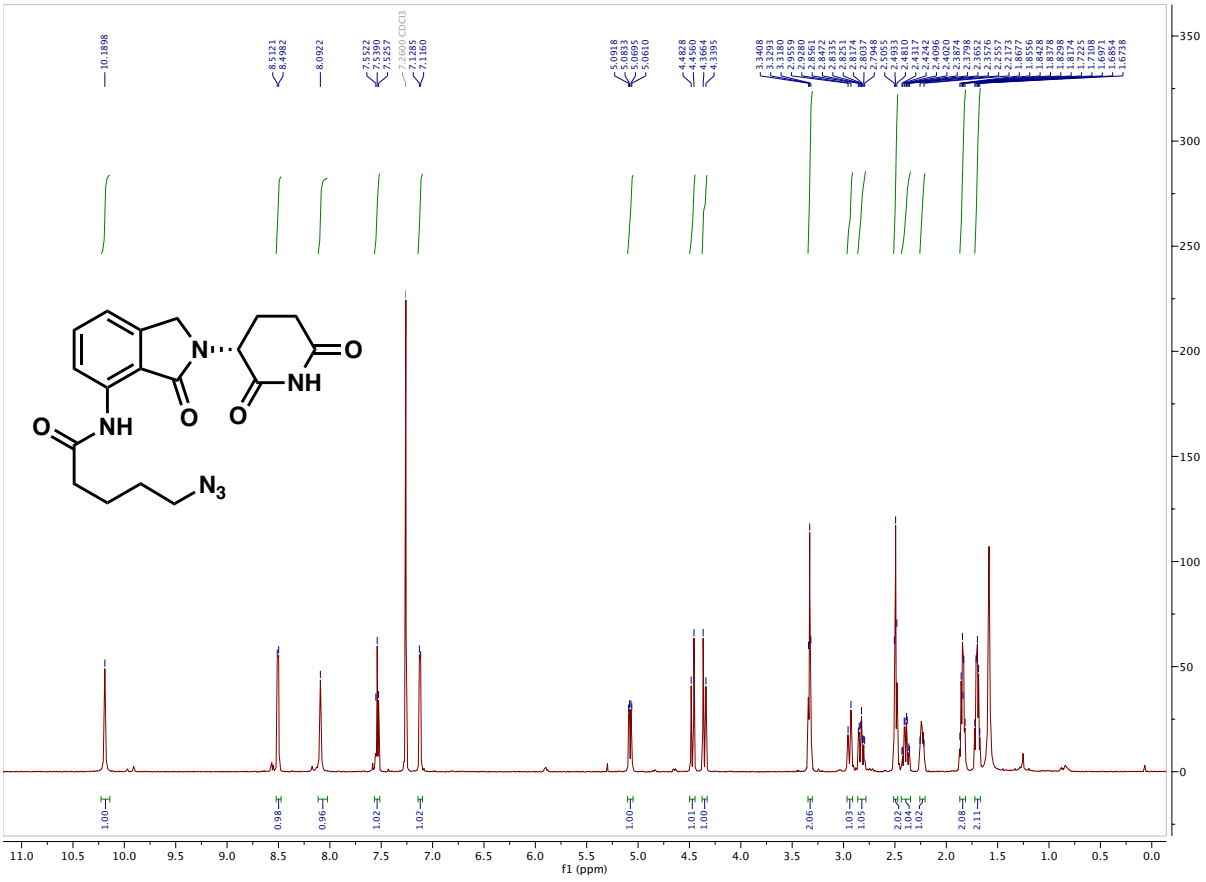

Evans-DIBAL-lactone.240.fid
C-13 Routine 1D, CPDCH CryoProbe, AVIII-600
172.24
161.09
141.19
106.67
99.32
77.16 CDCl3
69.41
55.49
47.50
28.20
22.07
f1 (ppm)

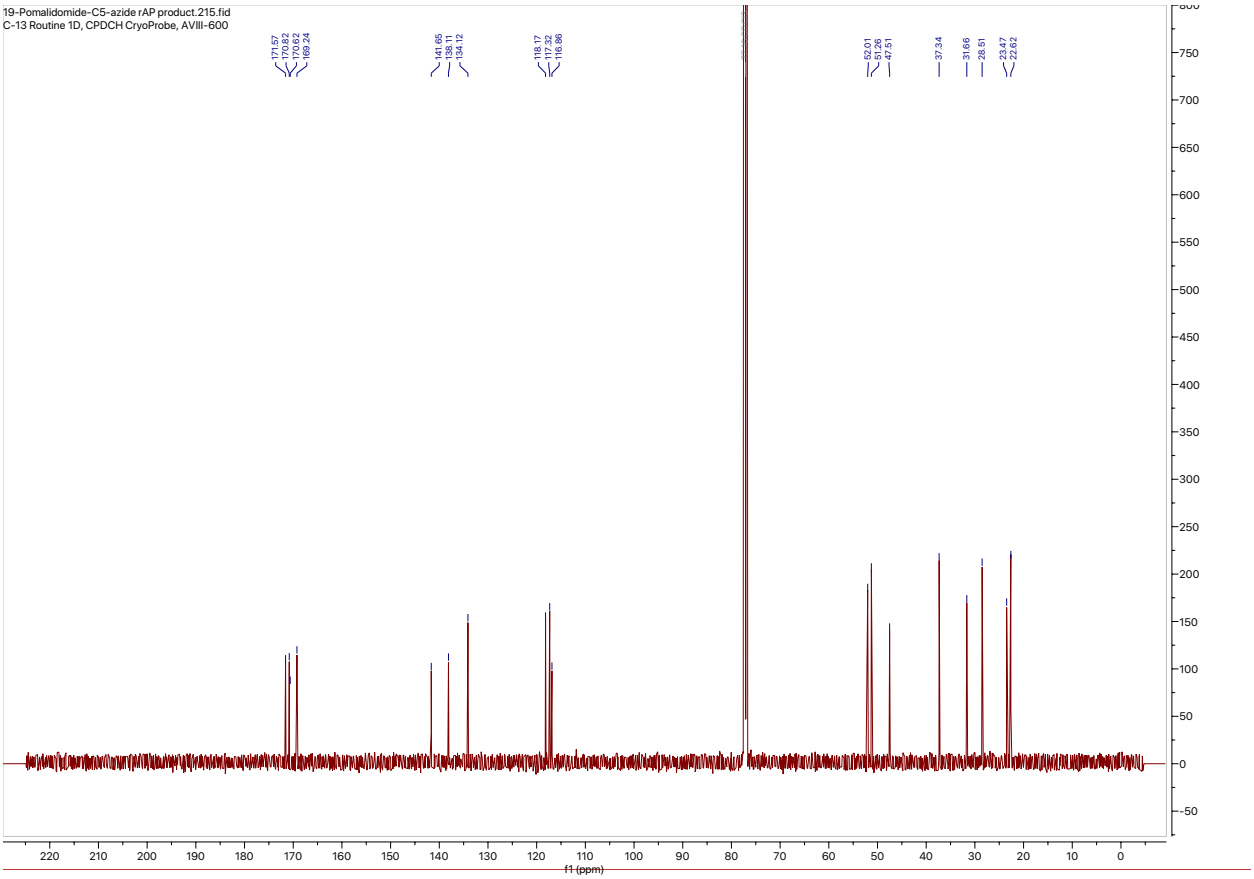
Compound 37-S2 (LiBH4)



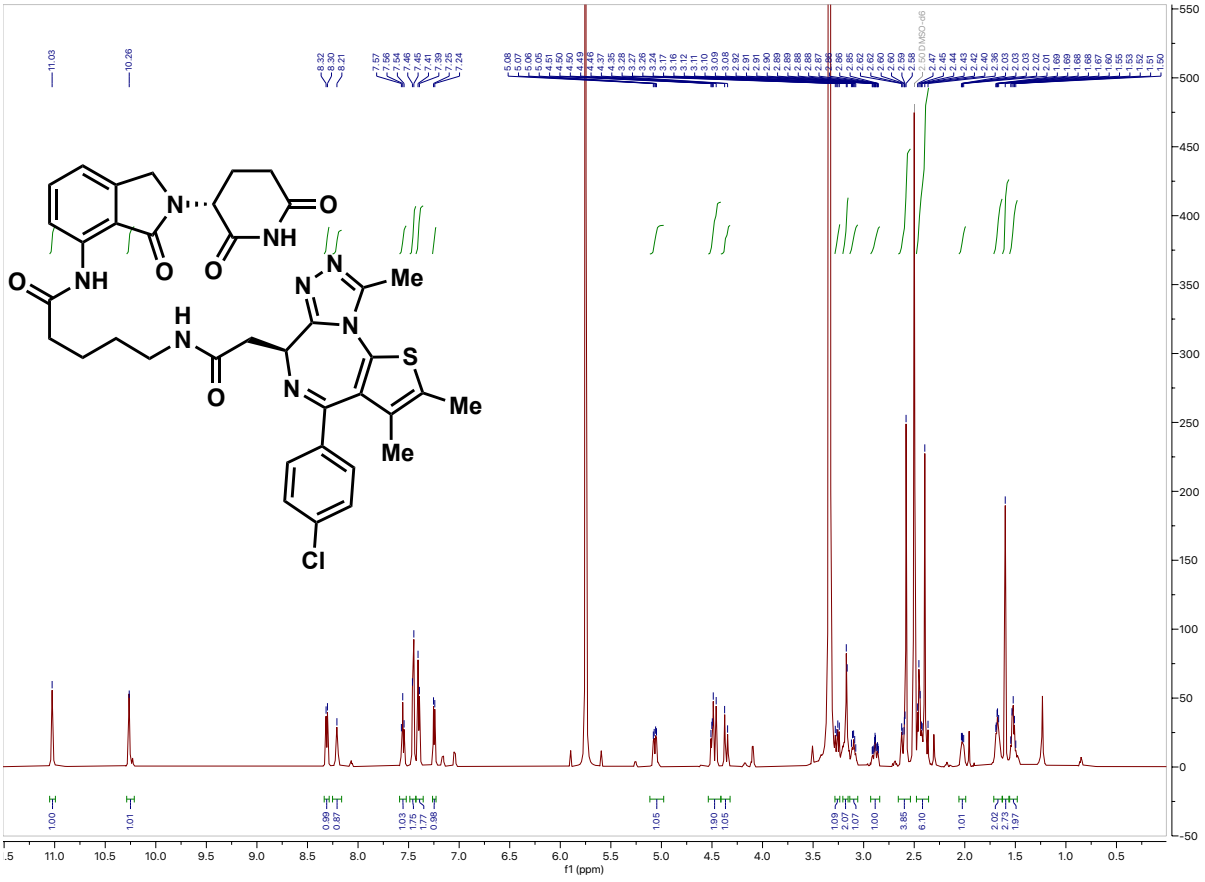

Evans-alkylation 44.229.fid
C-13 Routine 1D, CPDCH CryoProbe, AVIII-600
172.74
171.73
160.38
152.34
139.62
134.89
128.53
126.90
106.23
99.24
65.38
54.90
47.43
37.57
32.90
28.65
27.66
f1 (ppm)

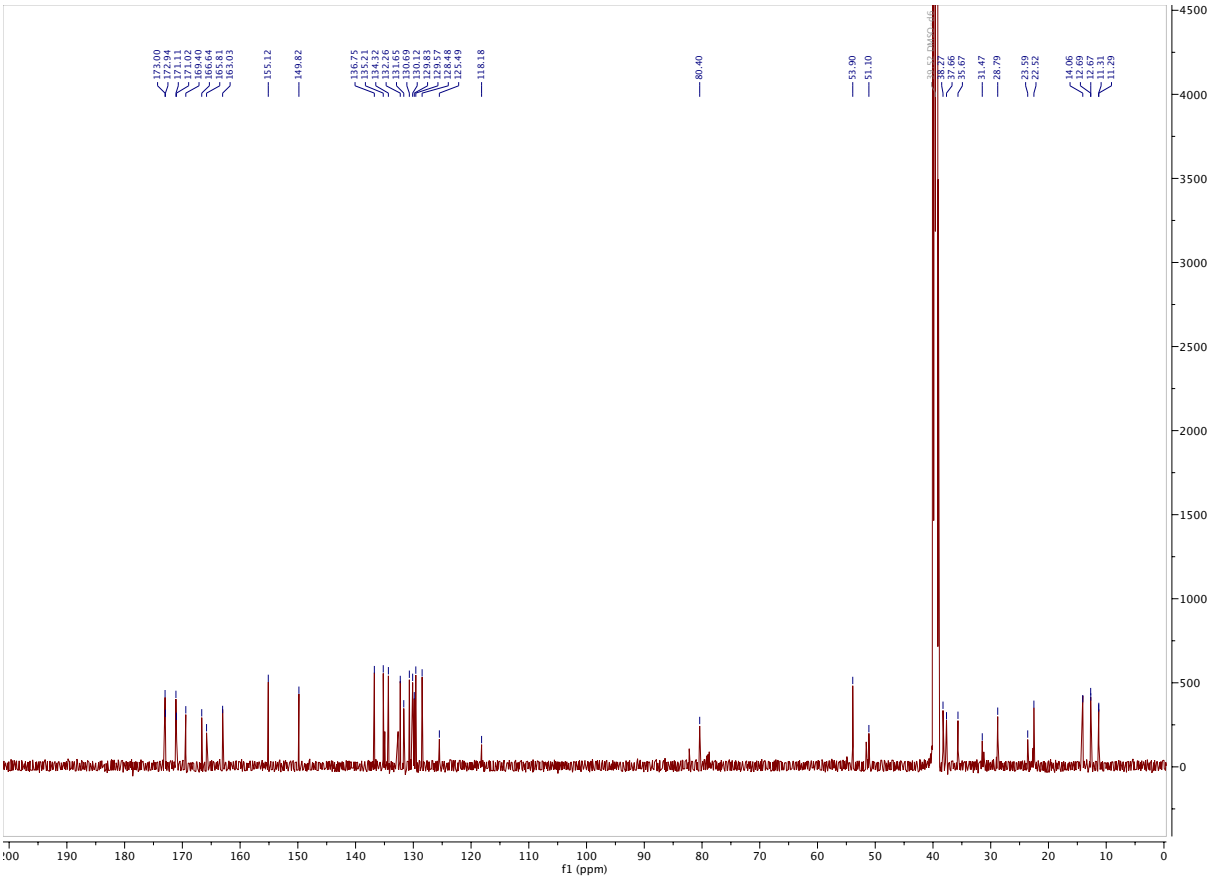
Compound 39


10.1898
8.5121
8.4982
8.0922
7.5522
7.5390
7.5257
7.2600
7.2485
7.1160
5.0918
5.0783
5.0695
5.0610
4.4828
4.4660
4.3664
4.3395
3.3408
3.3293
3.3180
3.2959
3.2850
2.9280
2.8961
2.8472
2.8355
2.8251
2.8174
2.8037
2.7948
2.5505
2.4933
2.4810
2.4417
2.4242
2.4096
2.4020
2.3854
2.3798
2.3652
2.3576
2.3357
2.2173
1.8677
1.8556
1.8428
1.8378
1.8298
1.8134
1.7225
1.7108
1.6971
1.6864
1.6738
O
NH
O
O
N
O
NH
O
N3
1.00
0.98
0.96
1.02
1.02
1.00
1.01
1.00
2.06
1.03
1.05
2.02
1.04
1.02
2.08
2.11
f1 (ppm)

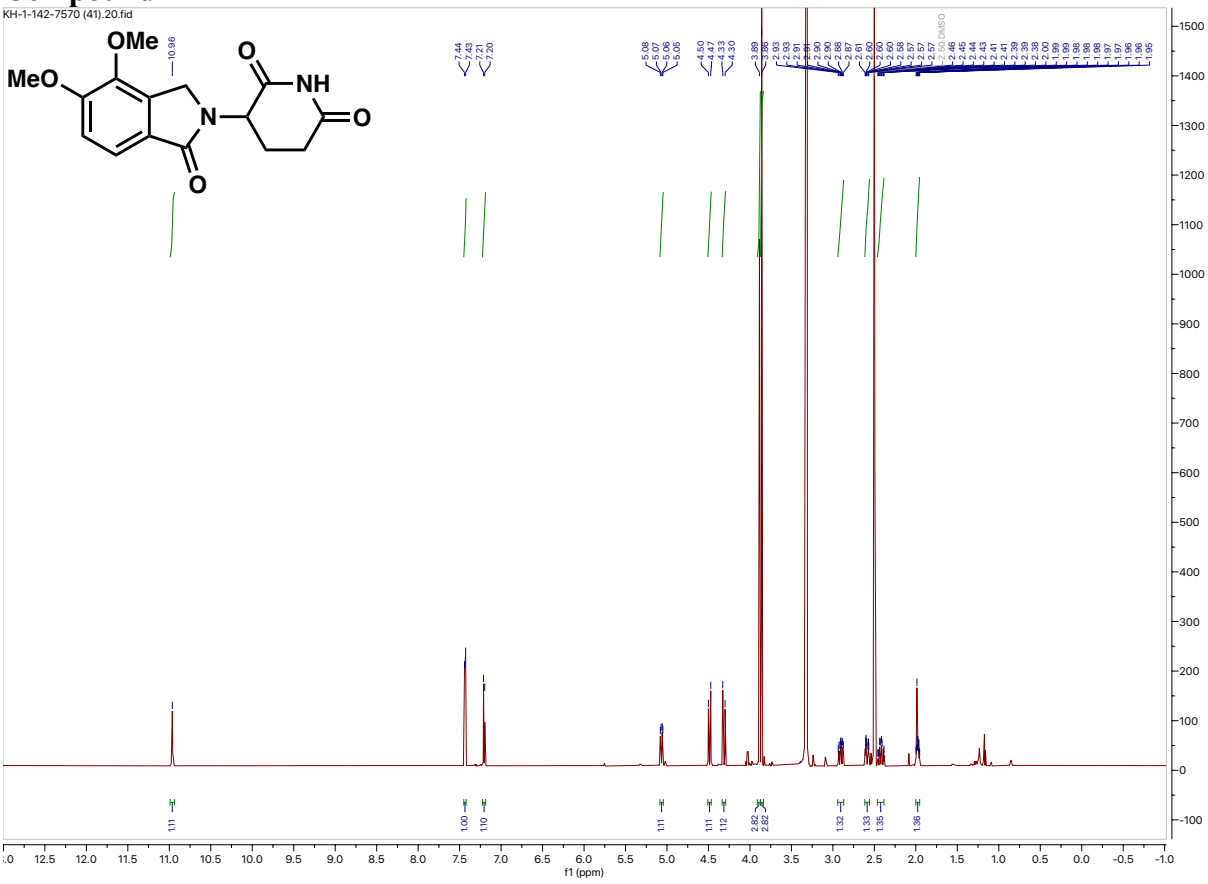

19-Pomalidomide-C5-azide rAP product.215.fid
C-13 Routine 1D, CPDCH CryoProbe, AVIII-600
171.57
170.93
170.62
169.24
141.65
138.11
134.12
118.17
117.32
116.86
52.01
51.26
47.51
37.34
31.66
28.51
23.47
22.62
f1 (ppm)

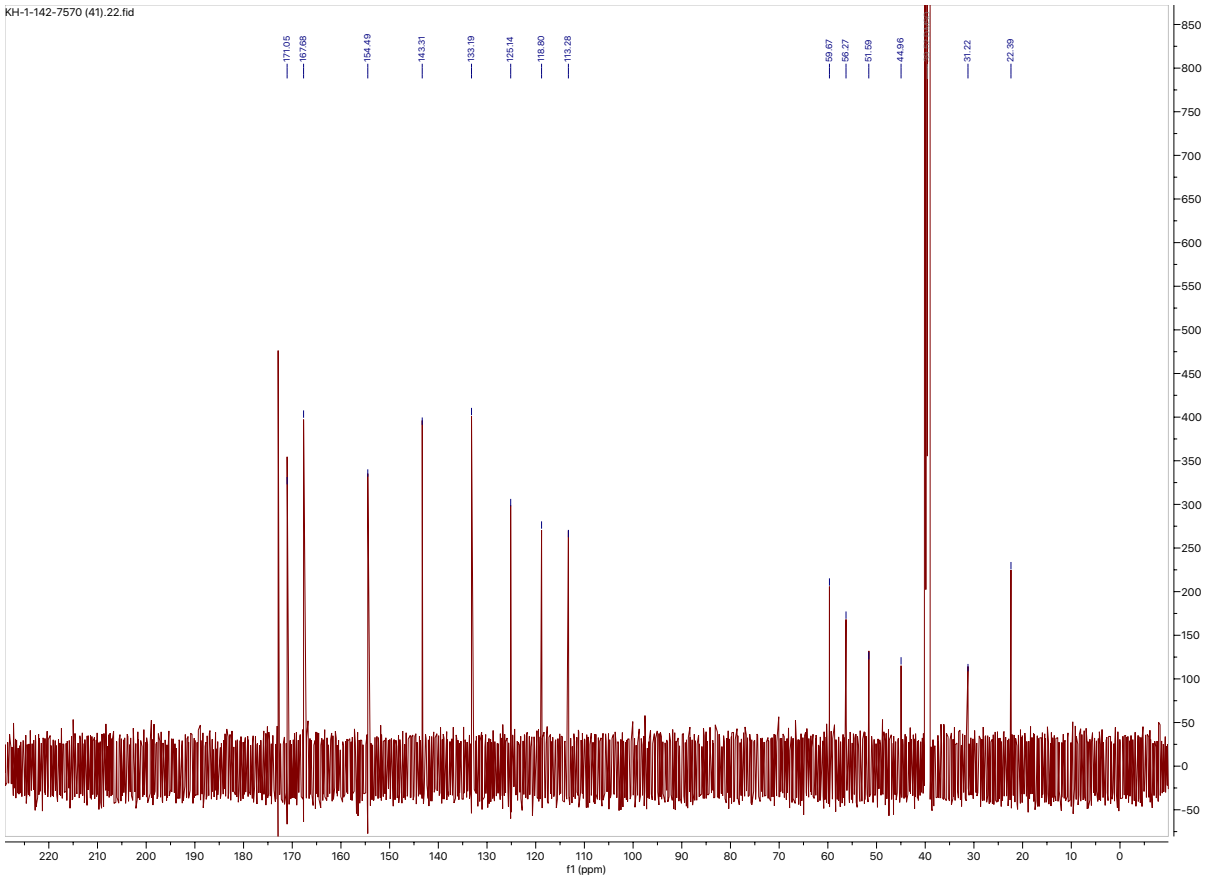
Compound 41


11.03
10.26
8.32
8.30
8.21
7.57
7.56
7.54
7.46
7.45
7.41
7.39
7.25
7.24
5.08
5.07
5.06
5.05
4.61
4.50
4.50
4.49
4.46
4.37
4.35
4.28
3.27
3.26
3.24
3.17
3.16
3.12
3.10
3.10
3.09
3.08
2.92
2.91
2.91
2.90
2.89
2.89
2.88
2.88
2.87
2.86
2.86
2.85
2.62
2.62
2.60
2.60
2.59
2.59
2.58
2.50
DMSO-d6
2.47
2.46
2.44
2.43
2.42
2.40
2.36
2.03
2.03
2.03
2.02
2.01
1.69
1.69
1.68
1.68
1.67
1.60
1.55
1.53
1.52
1.51
1.50
1.00
1.01
0.99
0.87
1.03
1.75
1.77
0.98
1.05
1.90
1.05
1.08
2.07
1.07
1.00
3.85
6.10
1.01
2.02
2.73
1.97
f1 (ppm)
O
NH
N
O
O
NH
O
N
N
Me
N
H
N
S
O
N
Me
Me
Cl

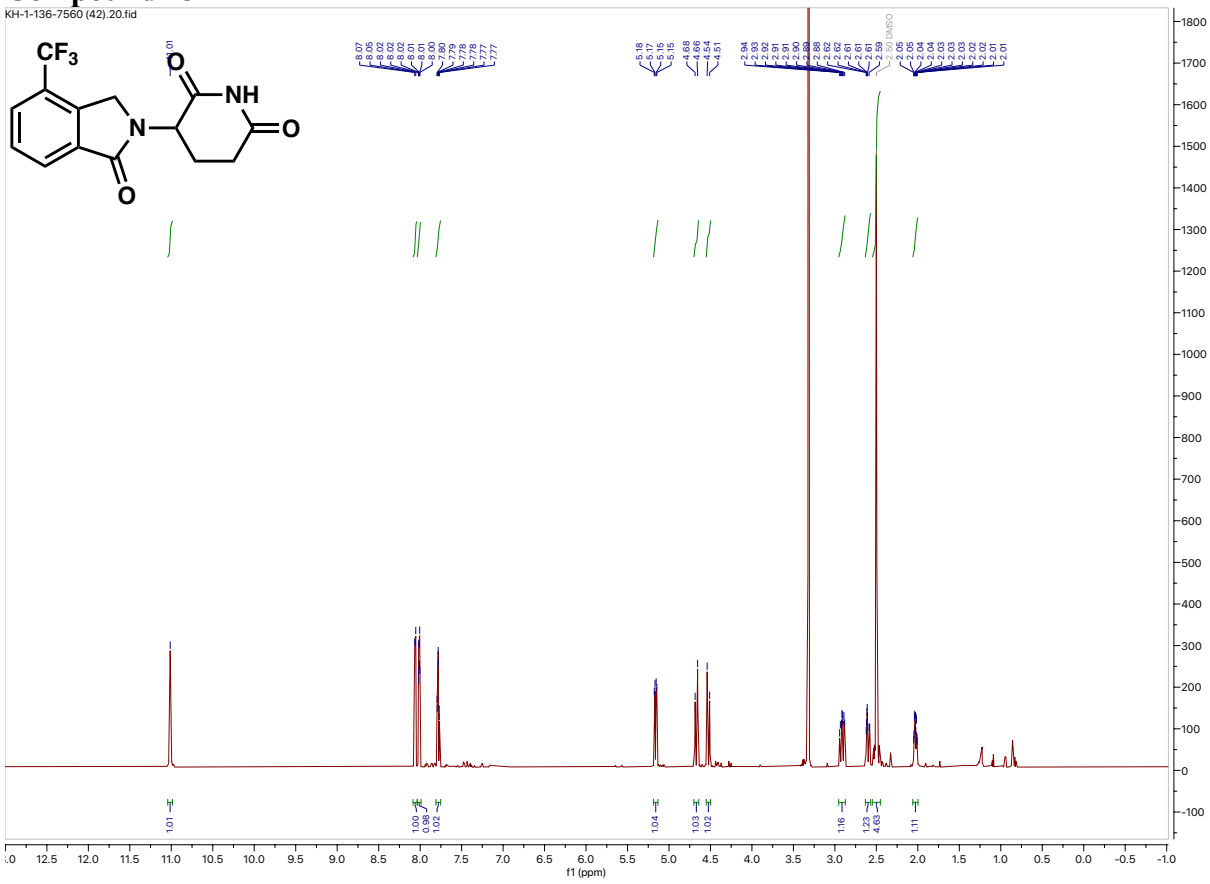

173.00
172.94
171.11
171.00
169.40
166.64
165.81
163.03
155.12
149.82
136.75
135.21
134.32
132.26
131.65
130.69
130.12
129.83
129.57
128.48
125.49
118.18
80.40
53.90
51.10
39.52 DMSO-d6
38.27
37.66
35.67
31.47
28.79
23.59
22.52
14.06
12.69
12.67
11.31
11.29
4500
4000
3500
3000
2500
2000
1500
1000
500
0
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

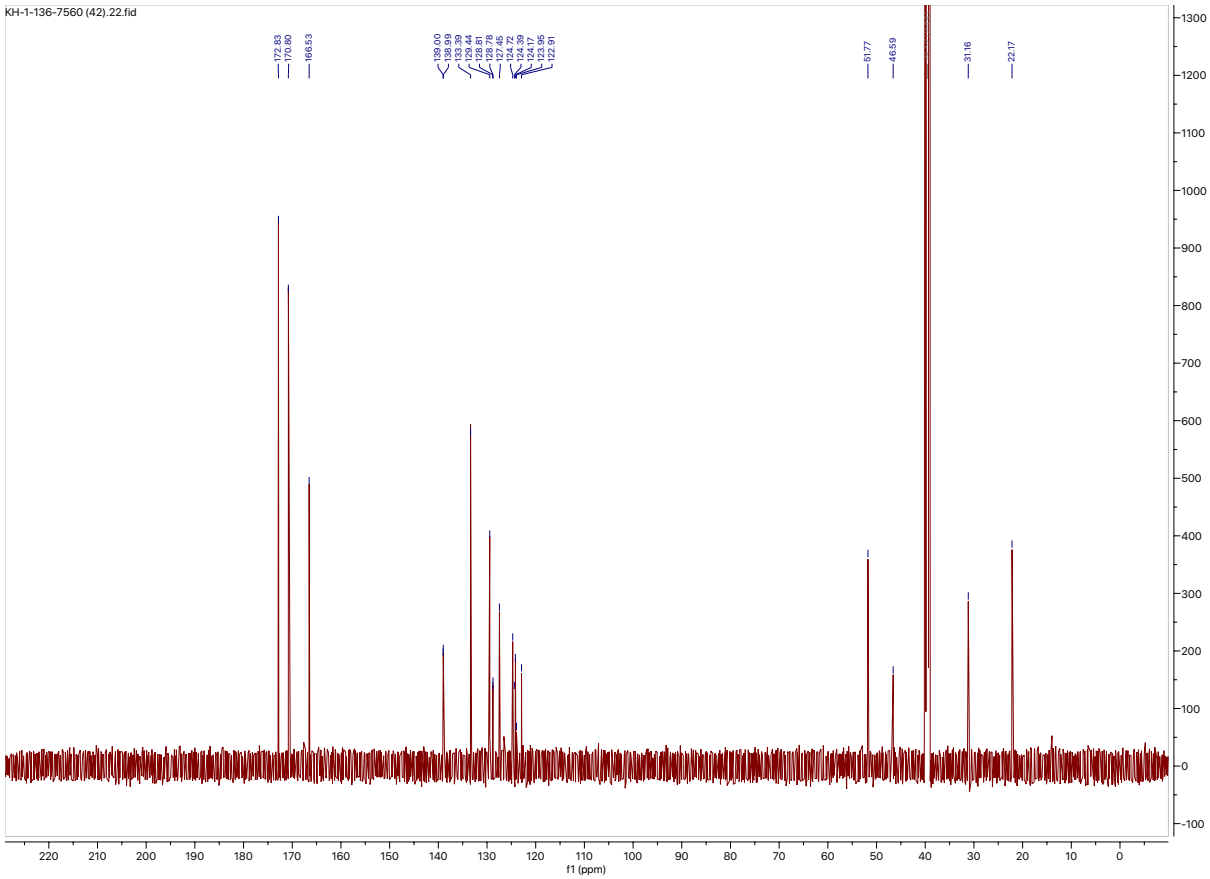
Compound 42

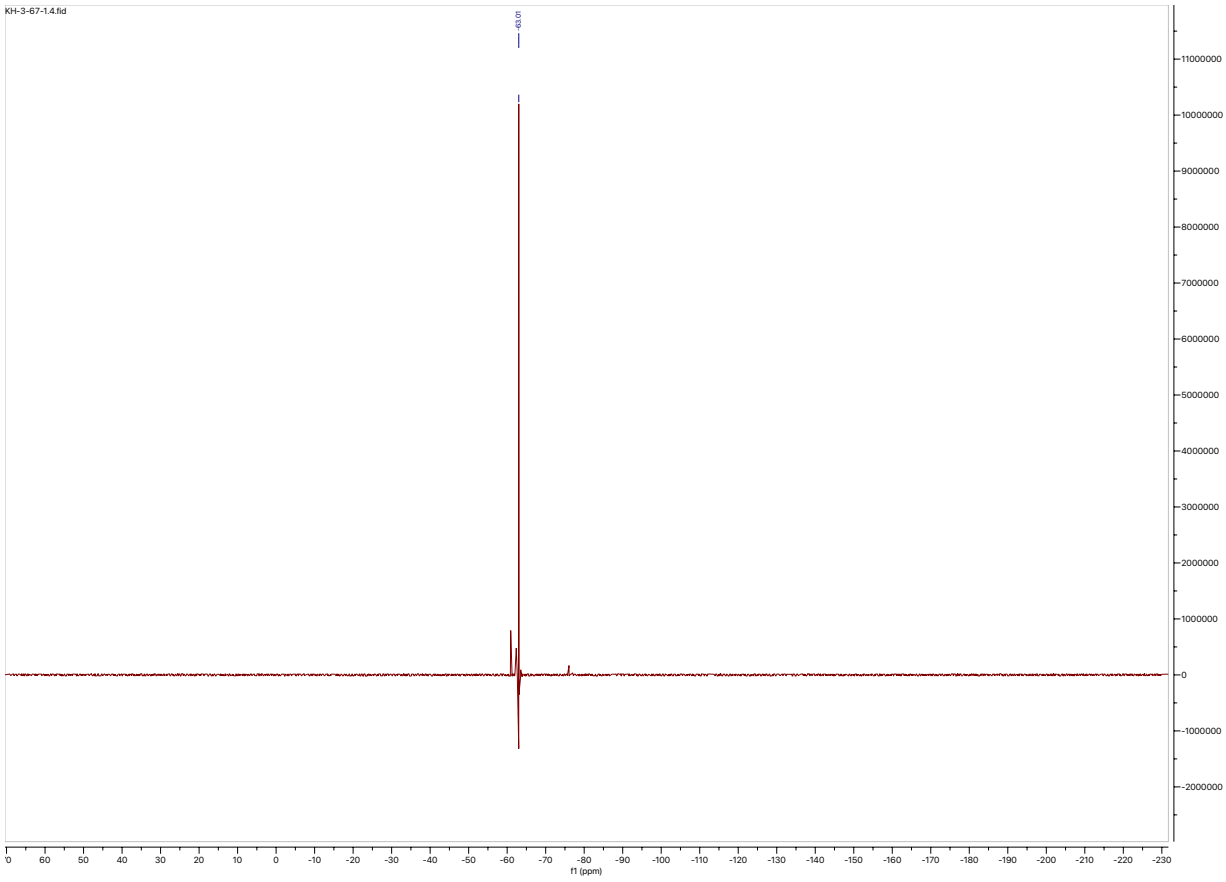



KH-1-142-7570 (41).22.fid
171.05
167.68
154.49
143.31
133.19
125.14
118.80
113.28
59.67
56.27
51.59
44.96
31.22
22.39
f1 (ppm)

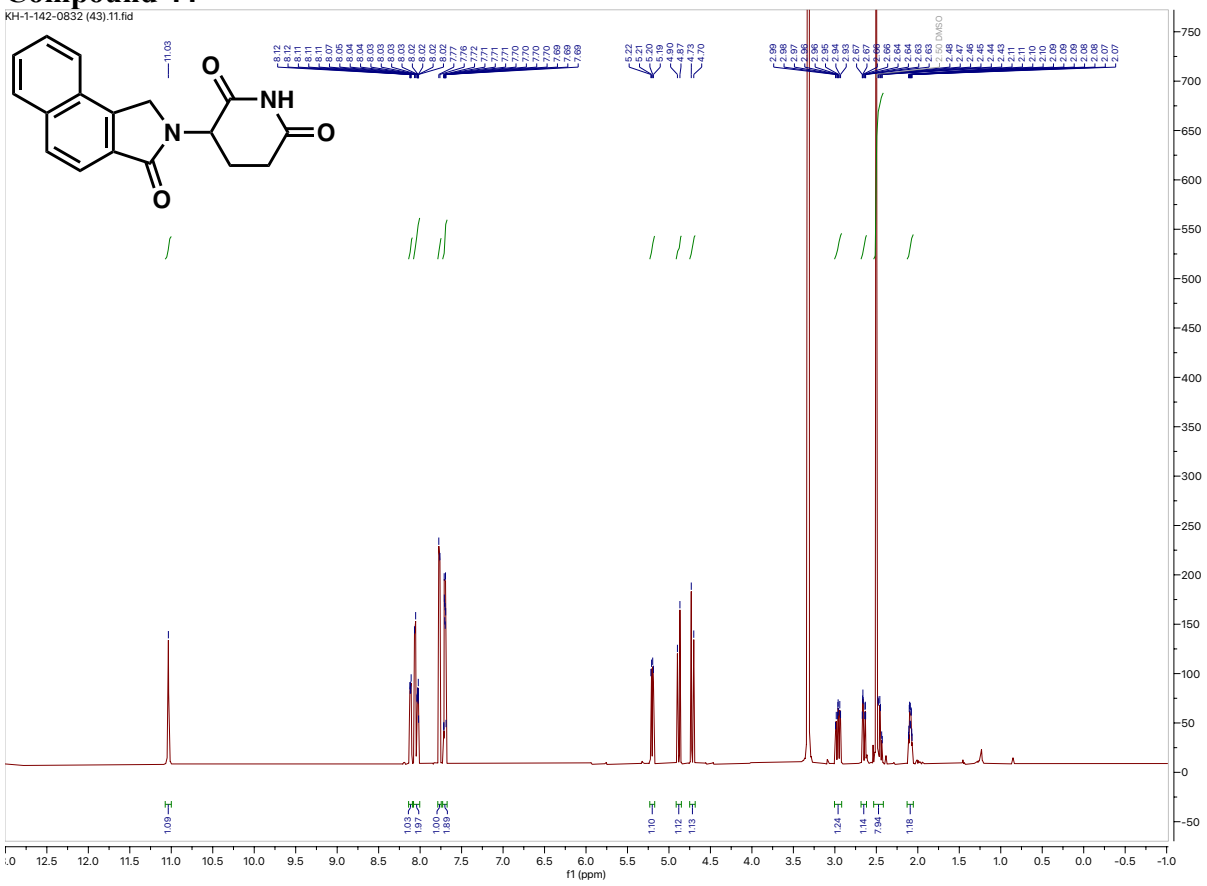
Compound 43

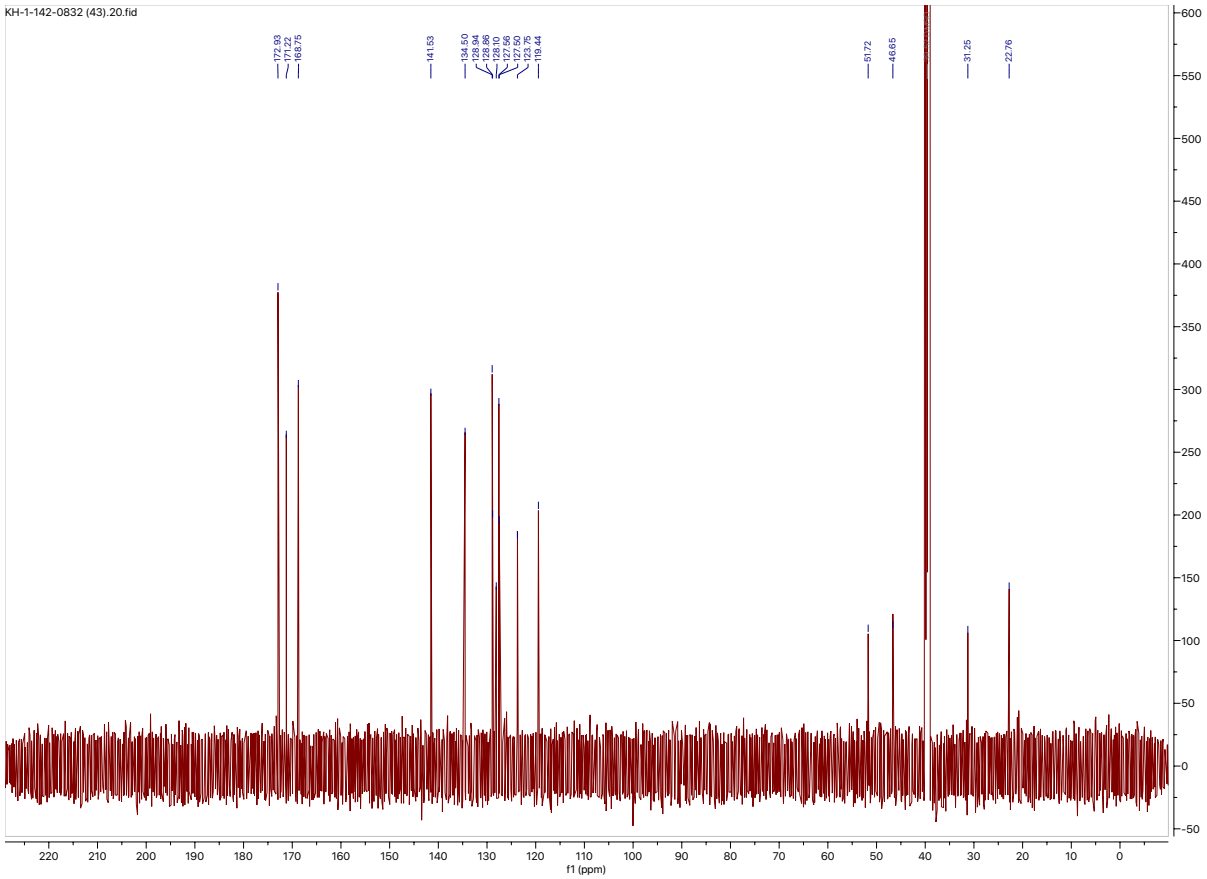



KH-1-136-7560 (42).22.fid
172.83
170.80
166.53
139.00
138.99
133.39
129.44
128.81
129.78
127.46
124.42
124.39
124.17
123.95
122.91
51.77
46.59
31.16
22.17
f1 (ppm)

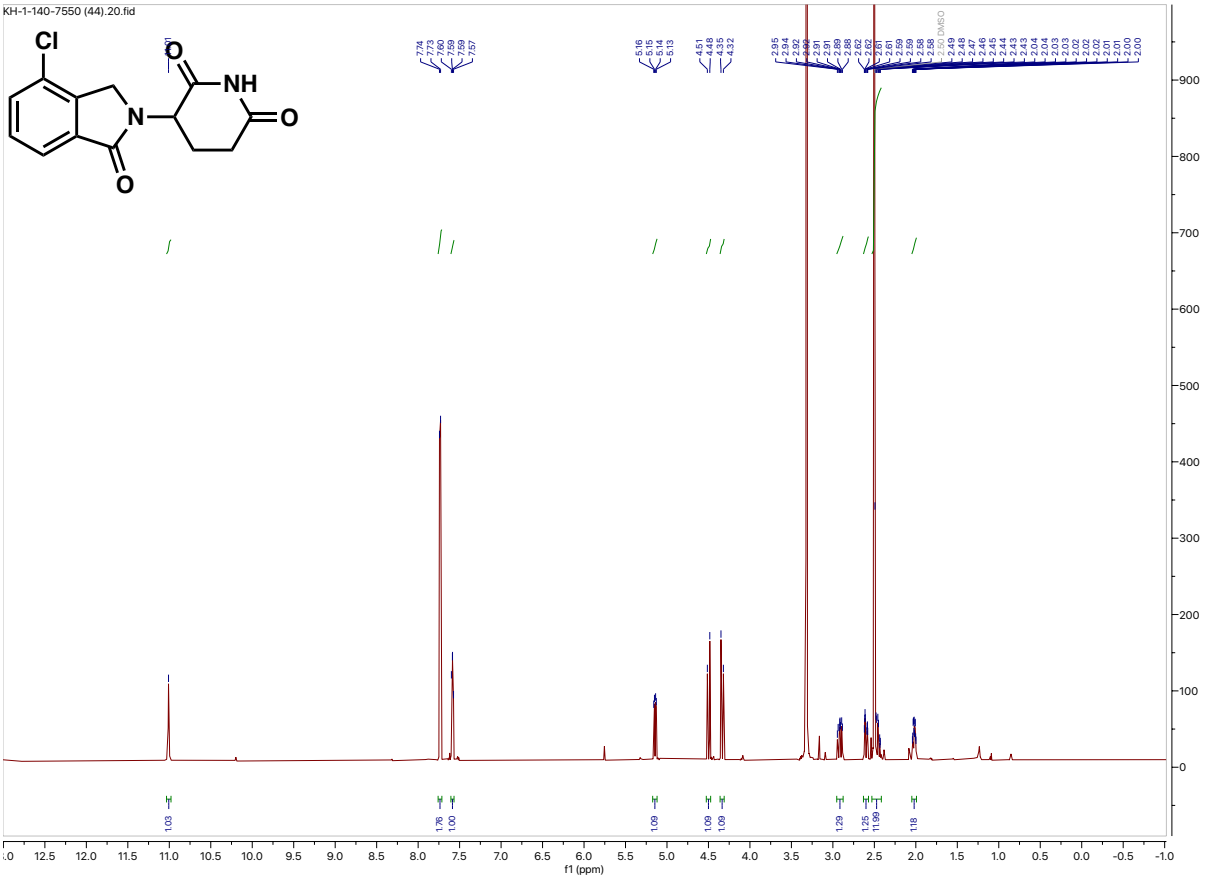

KH-3-67-1.4.fid
-63.01
11000000
10000000
9000000
8000000
7000000
6000000
5000000
4000000
3000000
2000000
1000000
0
-1000000
-2000000
60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230
f1 (ppm)

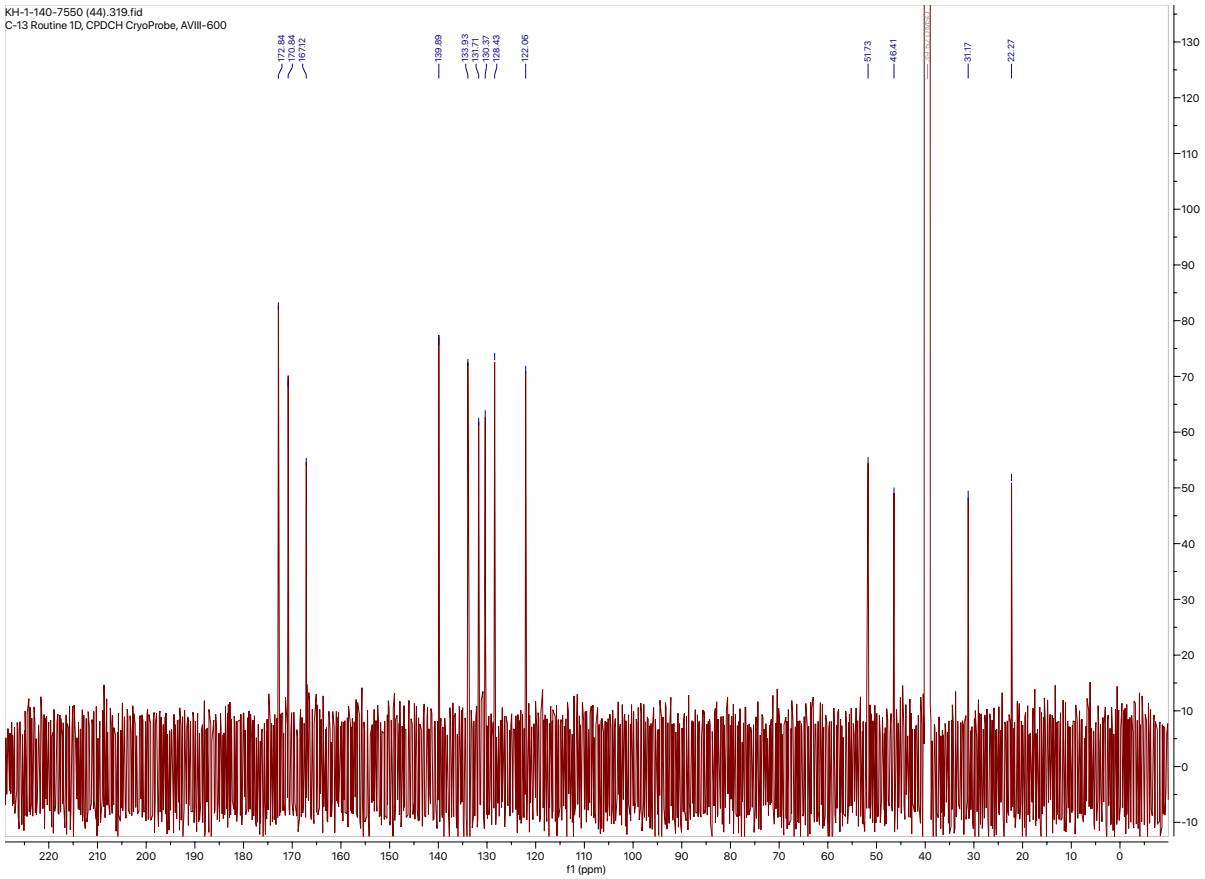
Compound 44



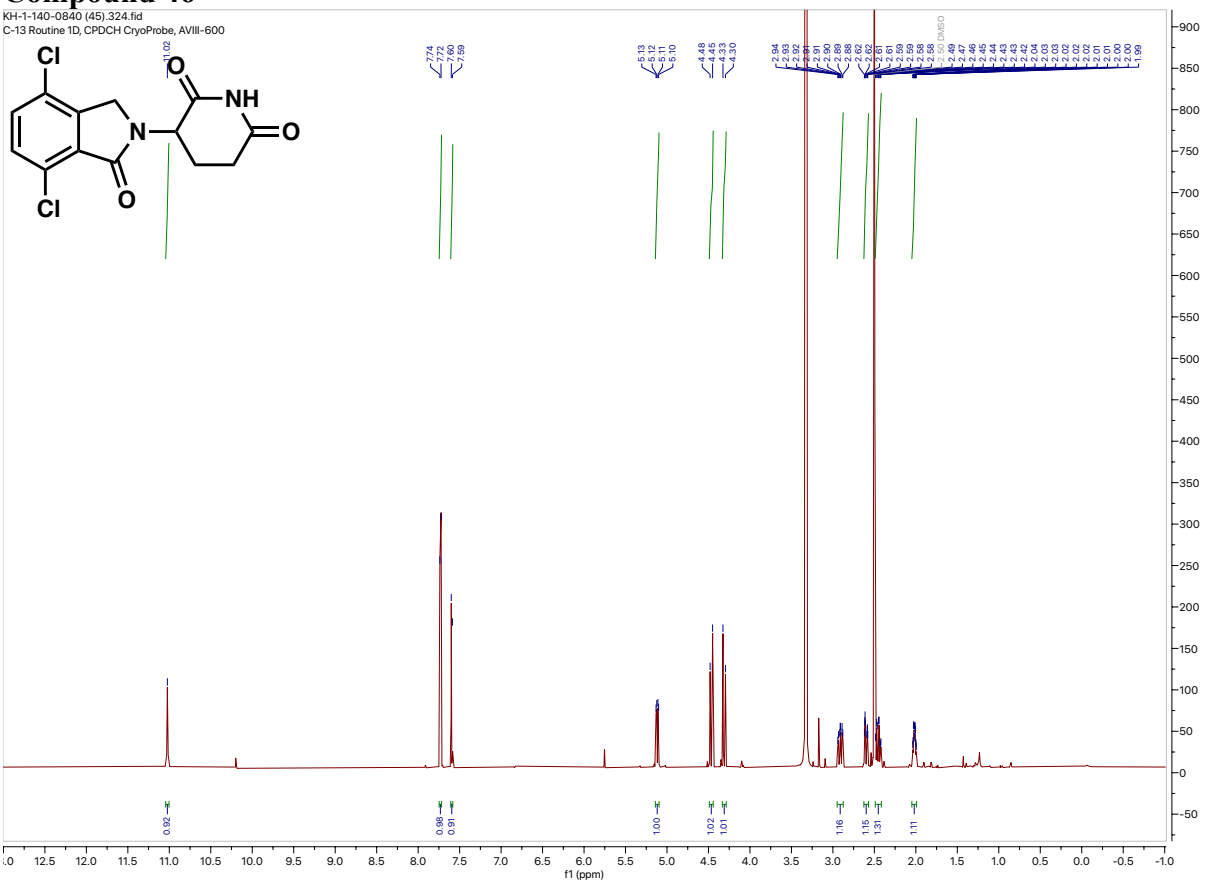

KH-1-142-0832 (43).20.fid
172.93
172.22
168.75
141.53
134.50
129.94
128.86
128.80
128.70
127.56
127.50
123.75
119.44
51.72
46.65
31.25
22.76
f1 (ppm)

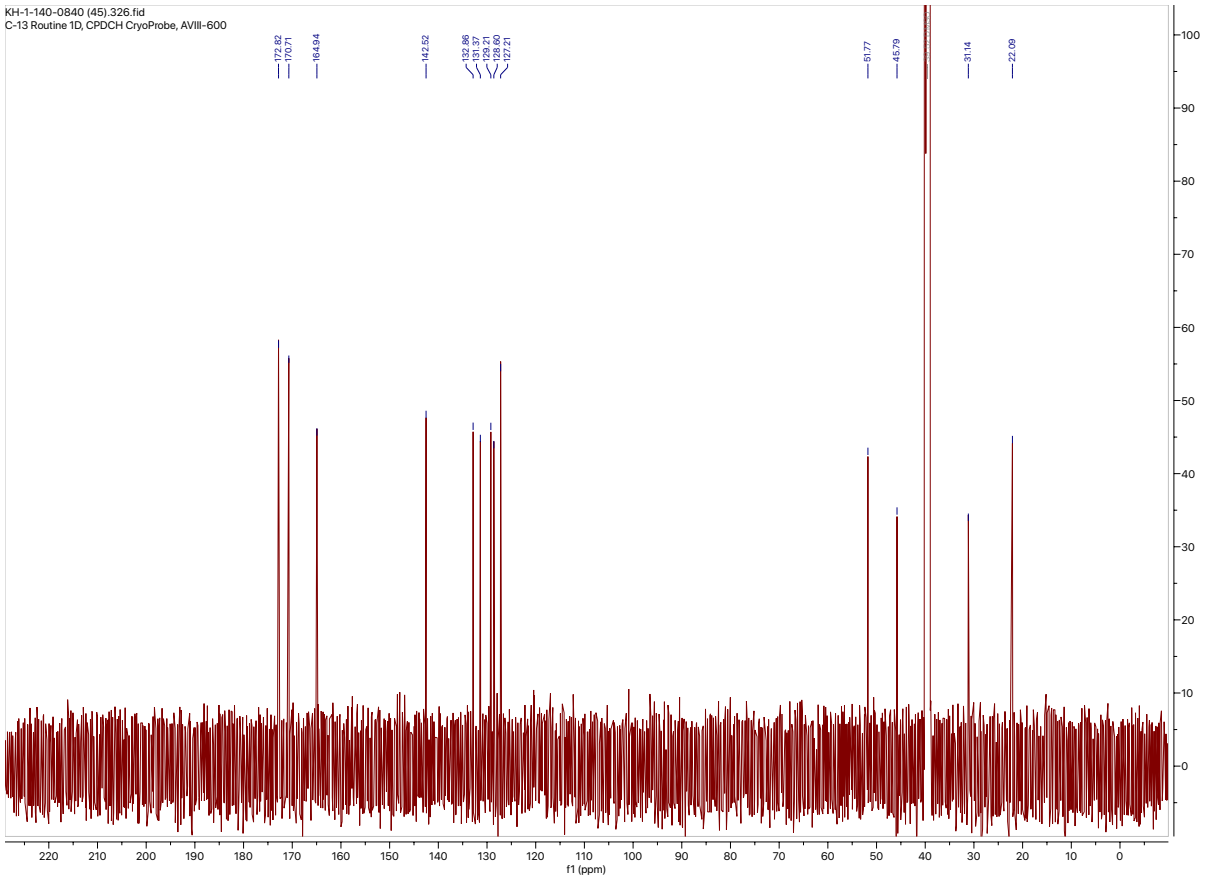
Compound 45



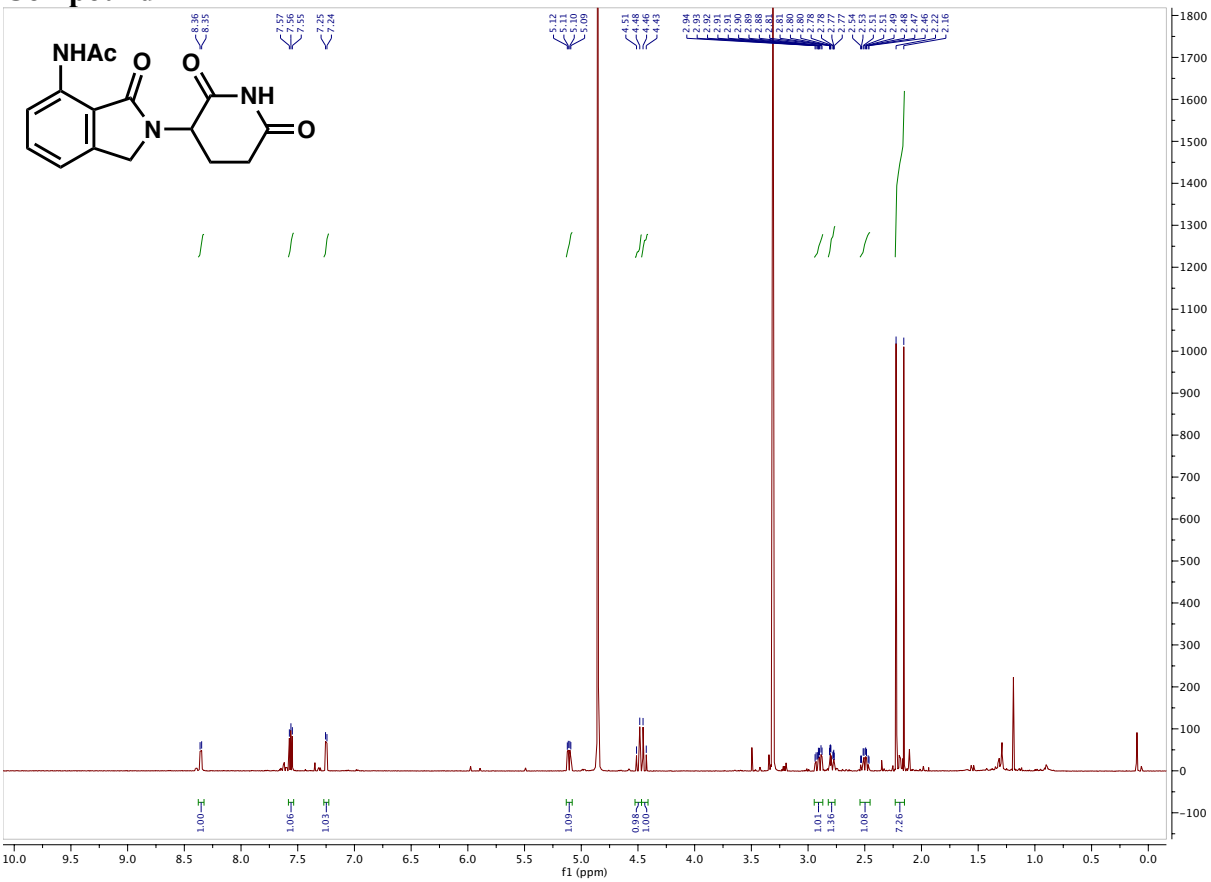

KH-1-140-7550 (44).319.fid
C-13 Routine 1D, CPDCH CryoProbe, AVIII-600
172.84
170.84
167.12
139.89
133.93
131.71
130.37
129.43
122.06
51.73
46.41
31.17
22.27
f1 (ppm)

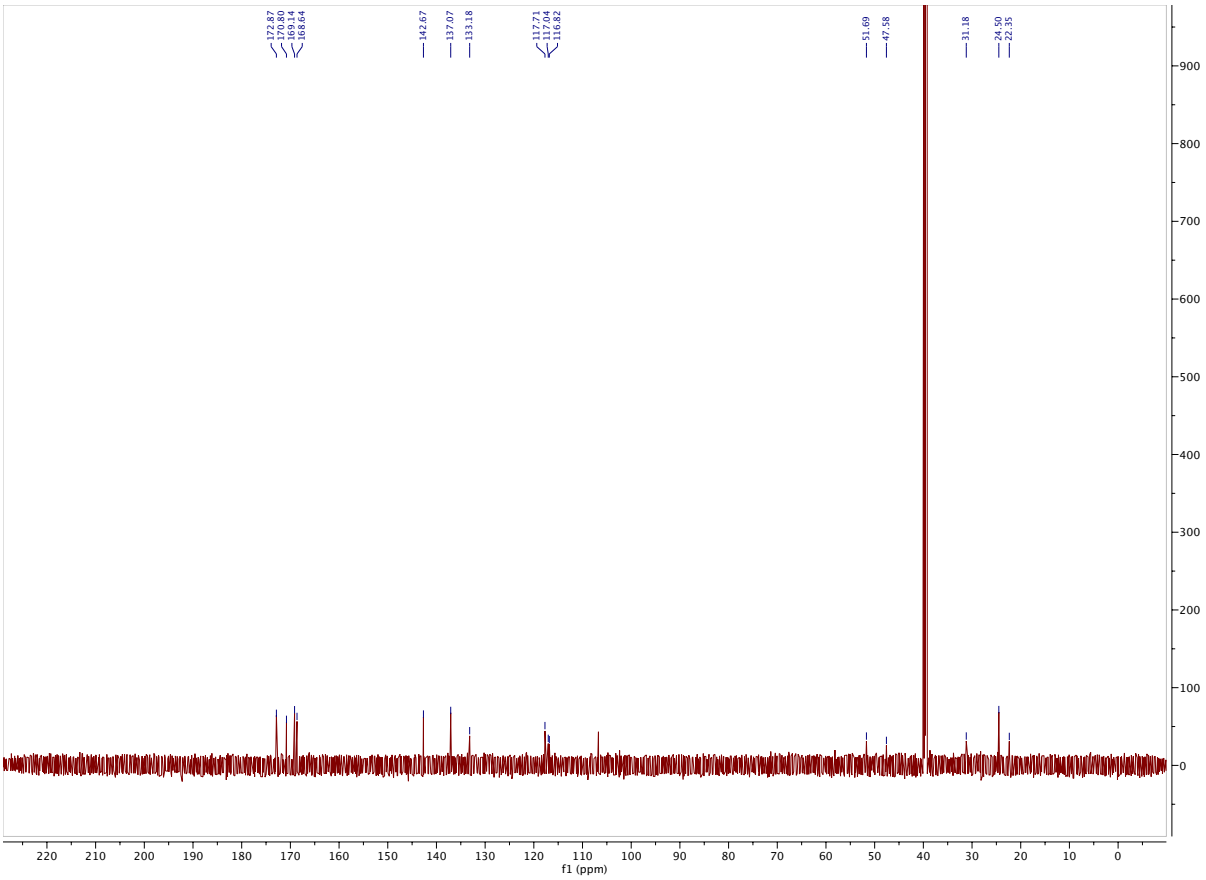
Compound 46


KH-1-140-0840 (45).324.fid
C-13 Routine 1D, CPDCH CryoProbe, AVIII-600
Cl
O
NH
N
O
O
Cl
11.02
7.74
7.72
7.60
7.59
5.13
5.12
5.11
5.10
4.48
4.45
4.33
4.30
2.94
2.93
2.92
2.91
2.90
2.89
2.88
2.63
2.62
2.61
2.60
2.59
2.58
2.58
2.50 DMSO
2.49
2.47
2.46
2.45
2.44
2.43
2.42
2.42
2.04
2.03
2.03
2.02
2.02
2.02
2.01
2.01
2.00
2.00
2.00
1.99
0.92
0.98
0.91
1.00
1.02
1.01
1.16
1.15
1.31
1.11
f1 (ppm)

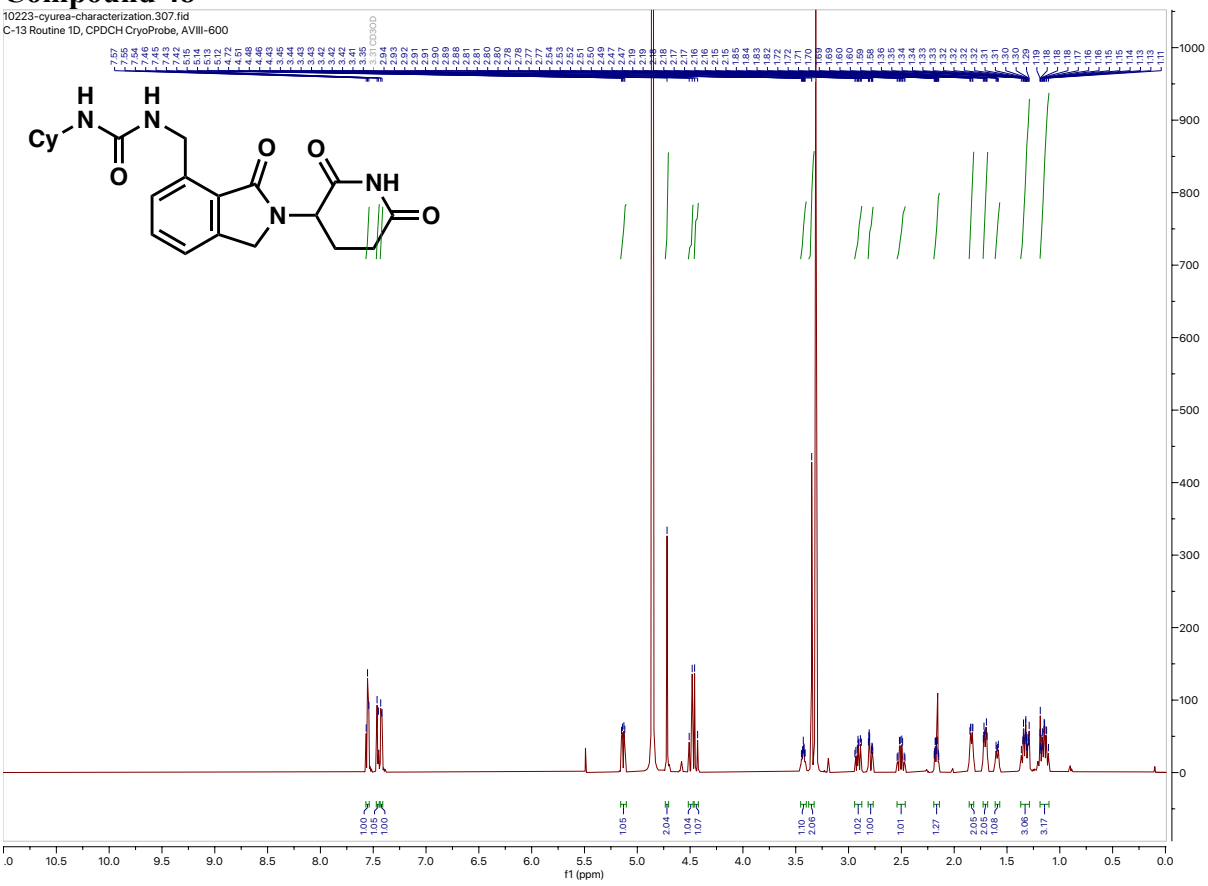

KH-1-140-0840 (45).326.fid
C-13 Routine 1D, CPDCH CryoProbe, AVIII-600
172.82
170.71
164.94
142.52
132.86
131.37
129.21
128.60
127.21
51.77
45.79
31.14
22.09
f1 (ppm)

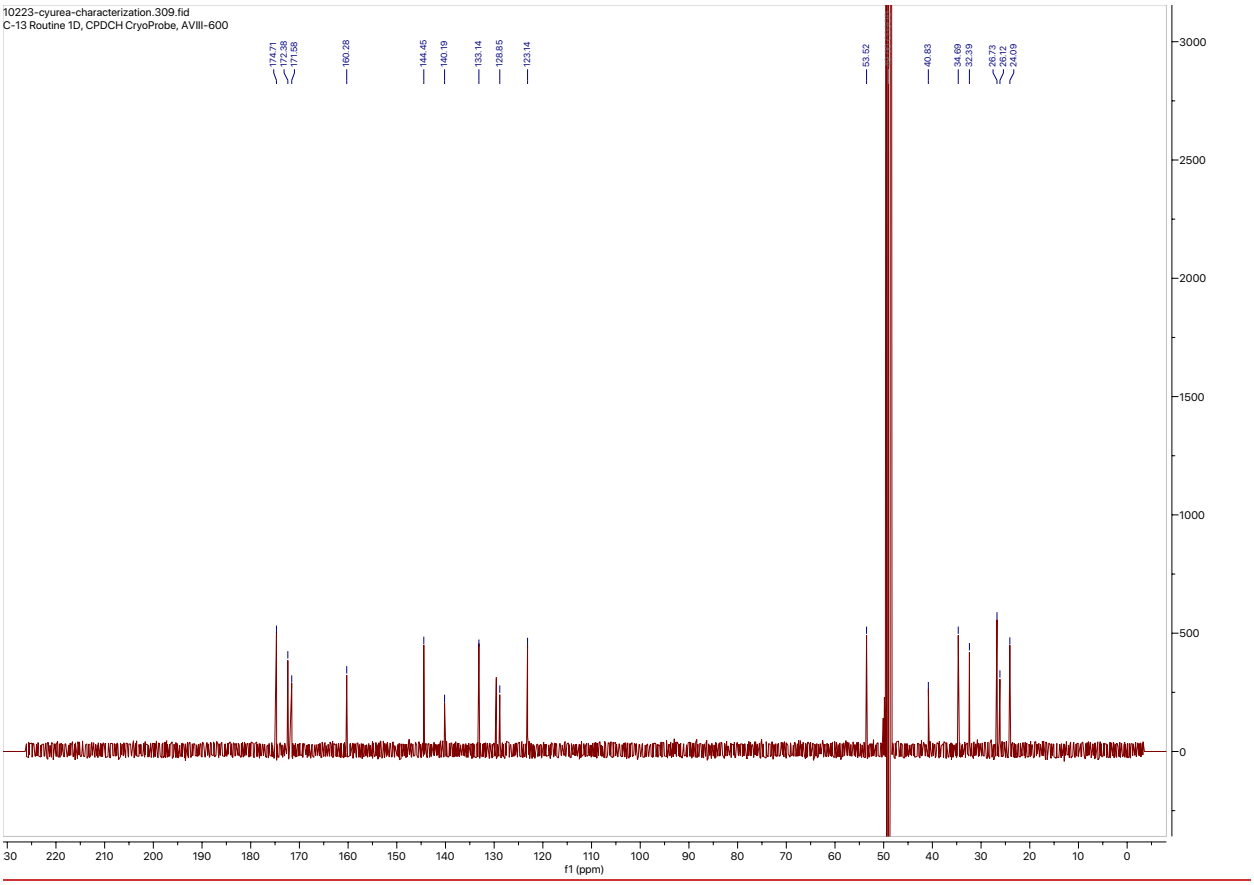
Compound 47



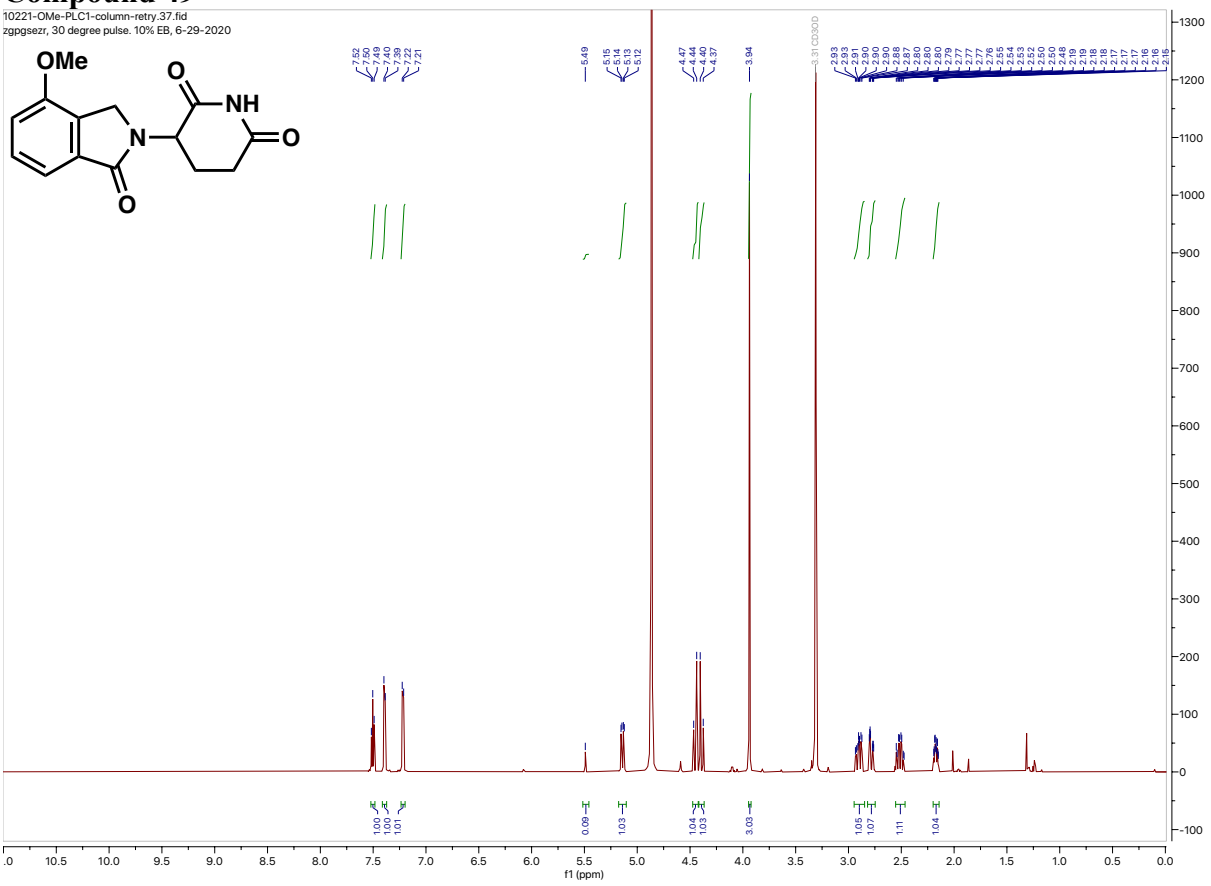

172.87
170.80
169.14
168.64
142.67
137.07
133.18
117.71
117.04
116.82
51.69
47.58
31.18
24.50
22.35
900
800
700
600
500
400
300
200
100
0
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

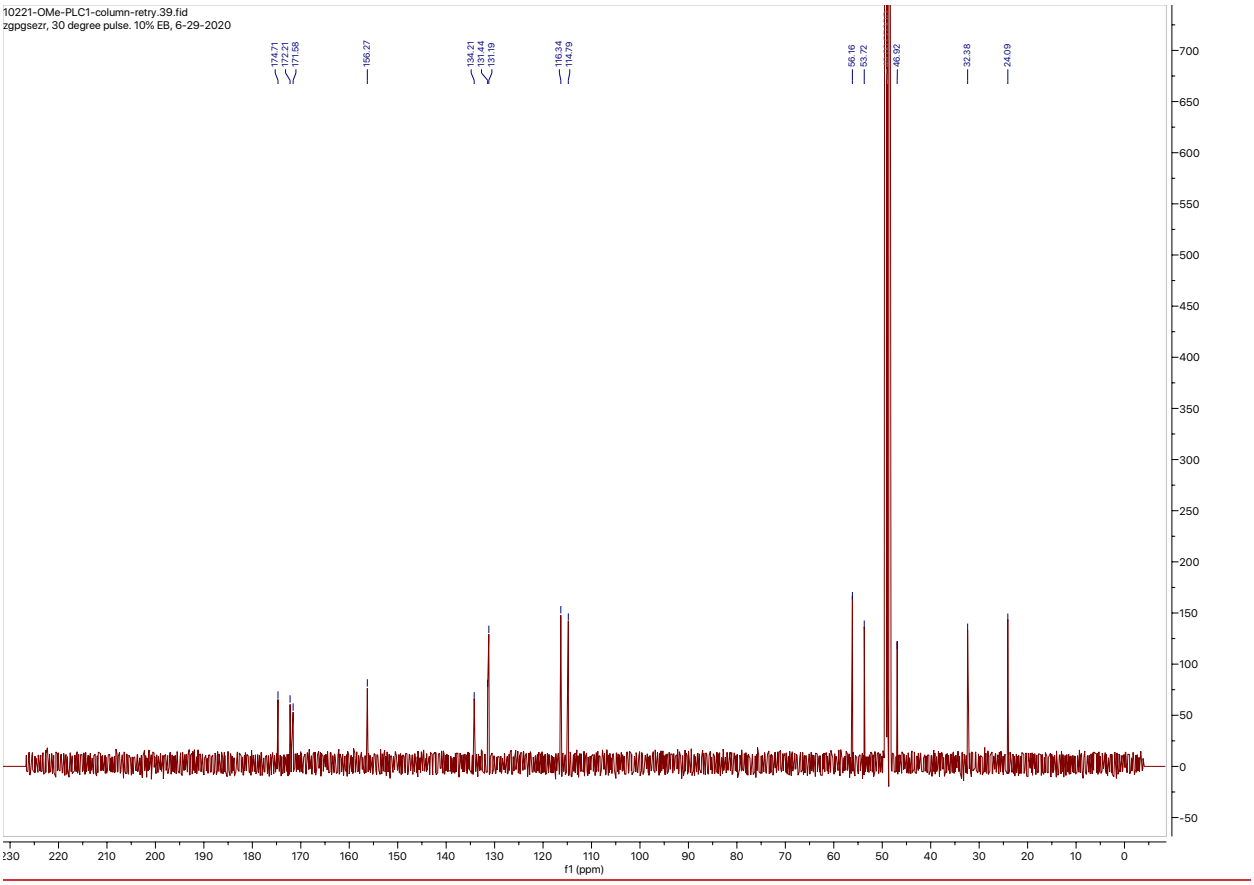
Compound 48


10223-cyurea-characterization.307.fid
C-13 Routine 1D, CPDCH CryoProbe, AVIII-600
Cy
H
N
O
NH
f1 (ppm)

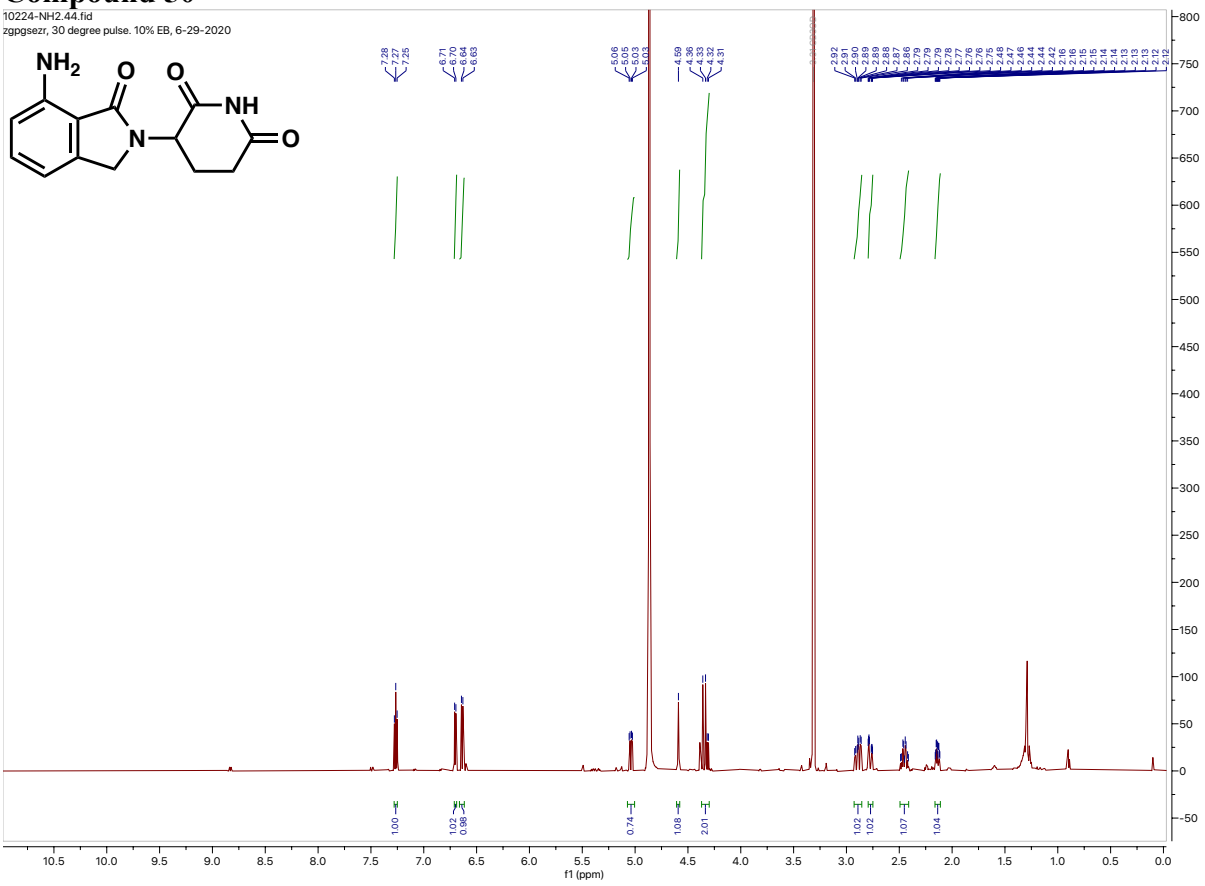

10223-cyurea-characterization.309.fid
C-13 Routine 1D, CPDCH CryoProbe, AVIII-600
174.71
172.38
171.58
160.28
144.45
140.19
133.14
128.85
123.14
53.52
40.83
34.69
32.39
26.73
26.12
24.49
3000
2500
2000
1500
1000
500
0
30 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

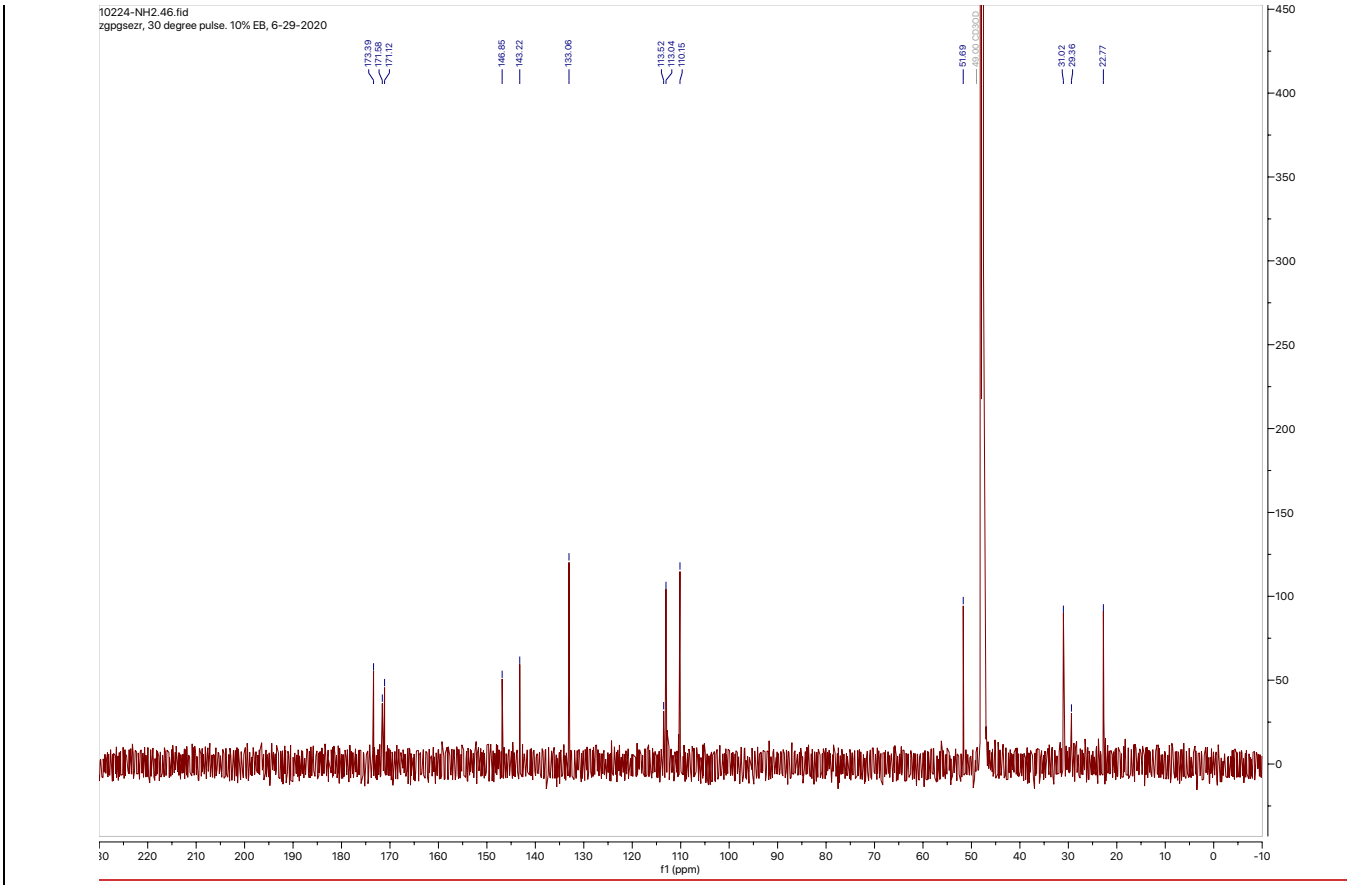
Compound 49


10221-OMe-PLC1-column-retry.37.fid
zgpgsezr, 30 degree pulse. 10% EB, 6-29-2020
OMe
O
NH
N
O
O
f1 (ppm)

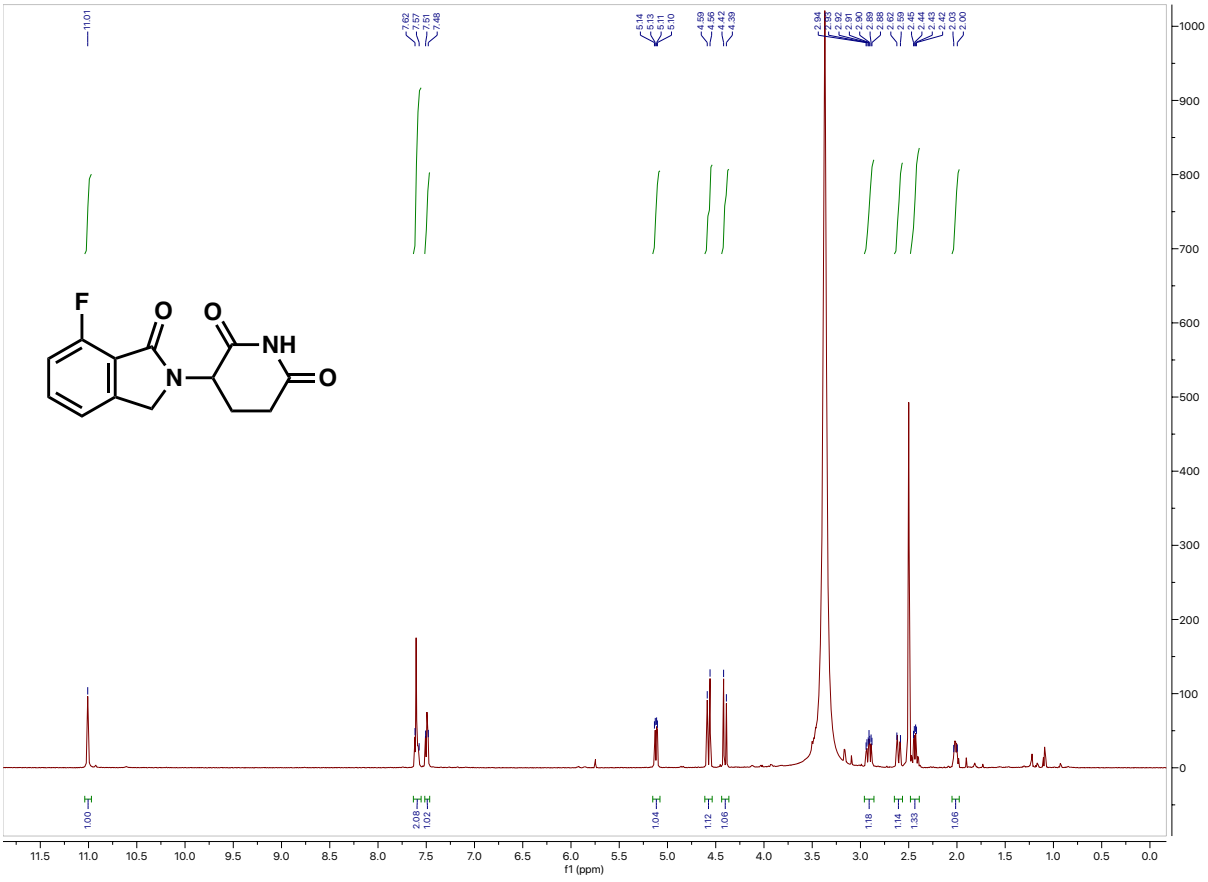

10221-OMe-PLC1-column-retry.39.fid
zgpgsezr, 30 degree pulse. 10% EB, 6-29-2020
174.71
172.21
171.58
156.27
134.21
131.44
131.19
116.34
114.79
66.16
53.72
46.92
32.38
24.09
f1 (ppm)

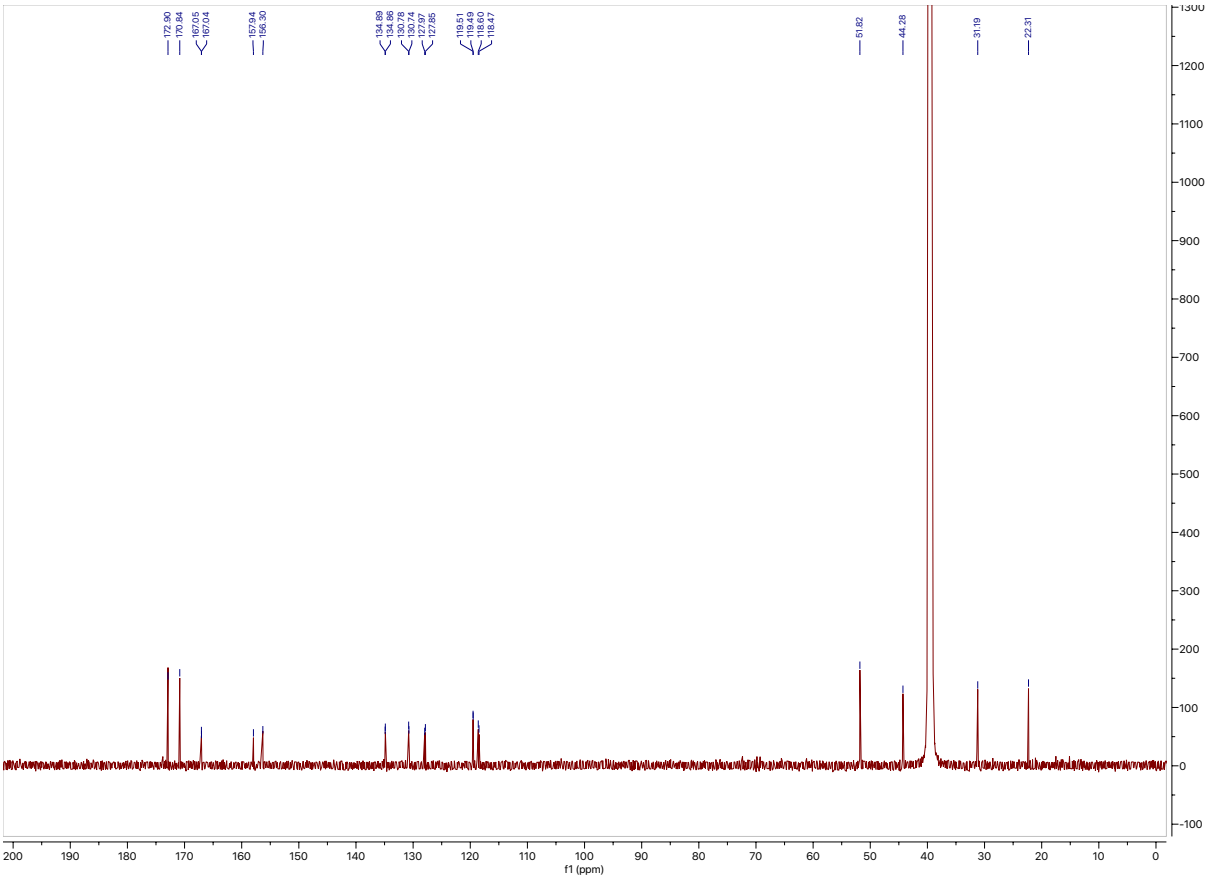
Compound 50

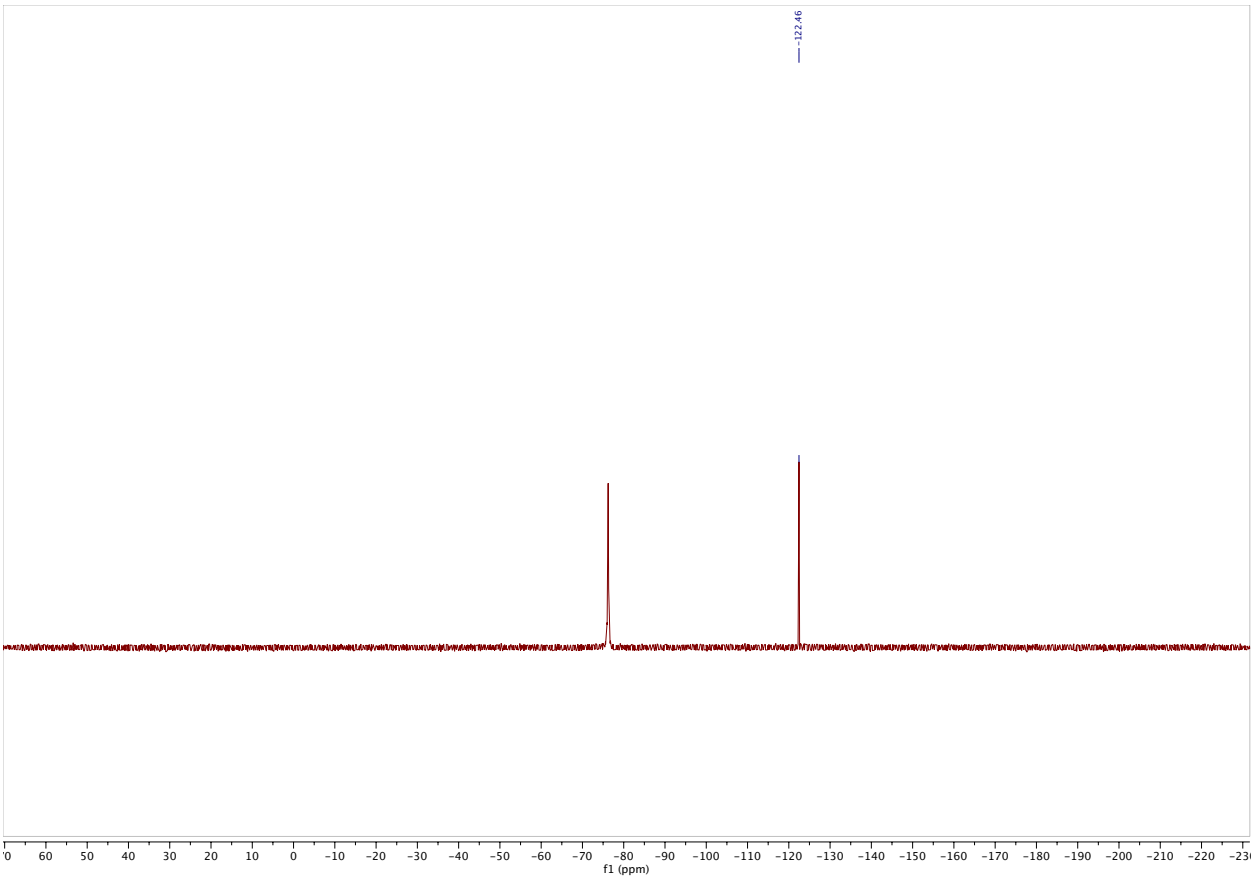

10224-NH2.44.fid
zgpgsezr, 30 degree pulse. 10% EB, 6-29-2020
NH2
O
O
NH
N
O
f1 (ppm)


10224-NH2.46.fid
zgpgsezr, 30 degree pulse. 10% EB, 6-29-2020
173.39
171.58
171.12
146.85
143.22
133.06
113.52
113.04
110.15
51.69
49.00
31.02
29.36
22.77
f1 (ppm)

Compound 51

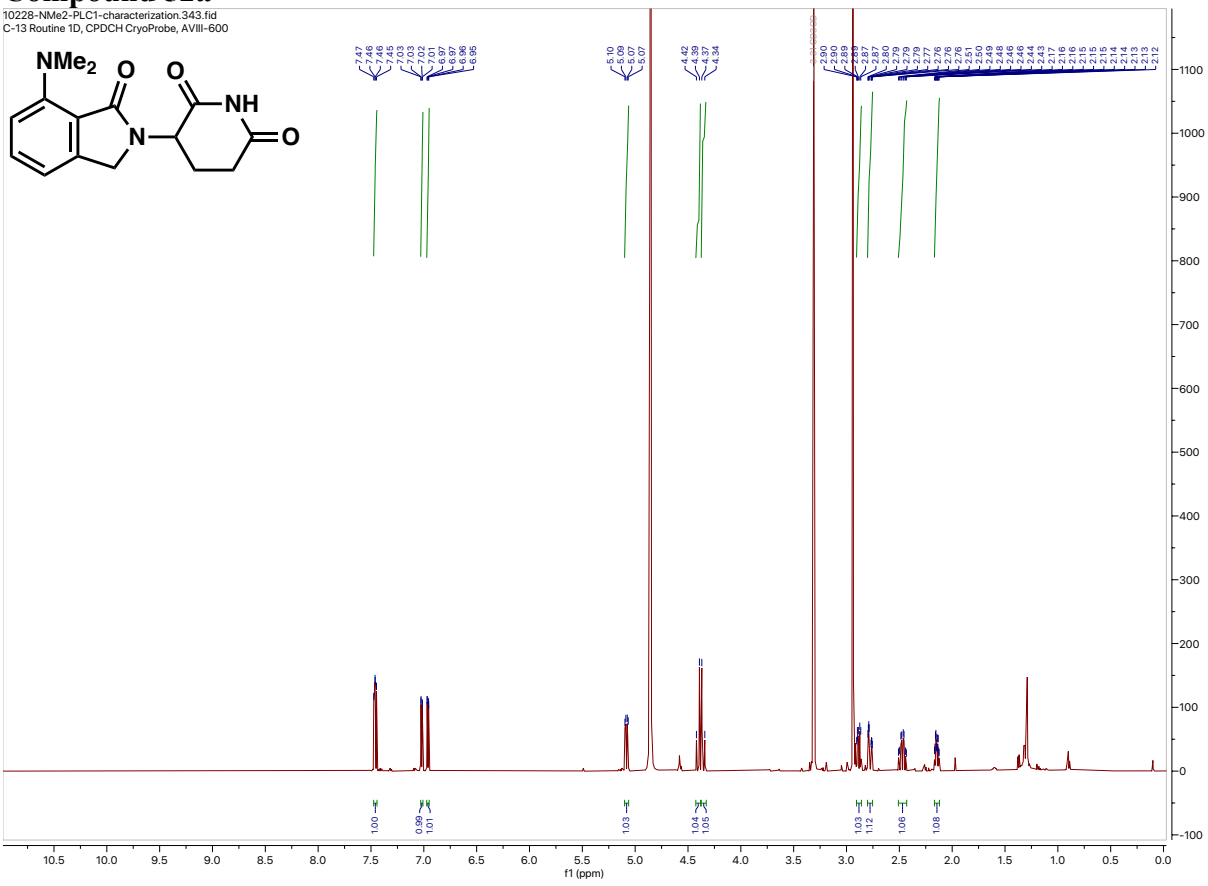

F
O
O
NH
N
O
11.01
7.62
7.57
7.51
7.48
5.14
5.13
5.11
5.10
4.69
4.66
4.47
4.42
4.39
2.94
2.93
2.92
2.91
2.90
2.89
2.88
2.62
2.59
2.45
2.44
2.43
2.42
2.03
2.00
1.00
2.08
1.02
1.04
1.12
1.06
1.18
1.14
1.33
1.06
f1 (ppm)

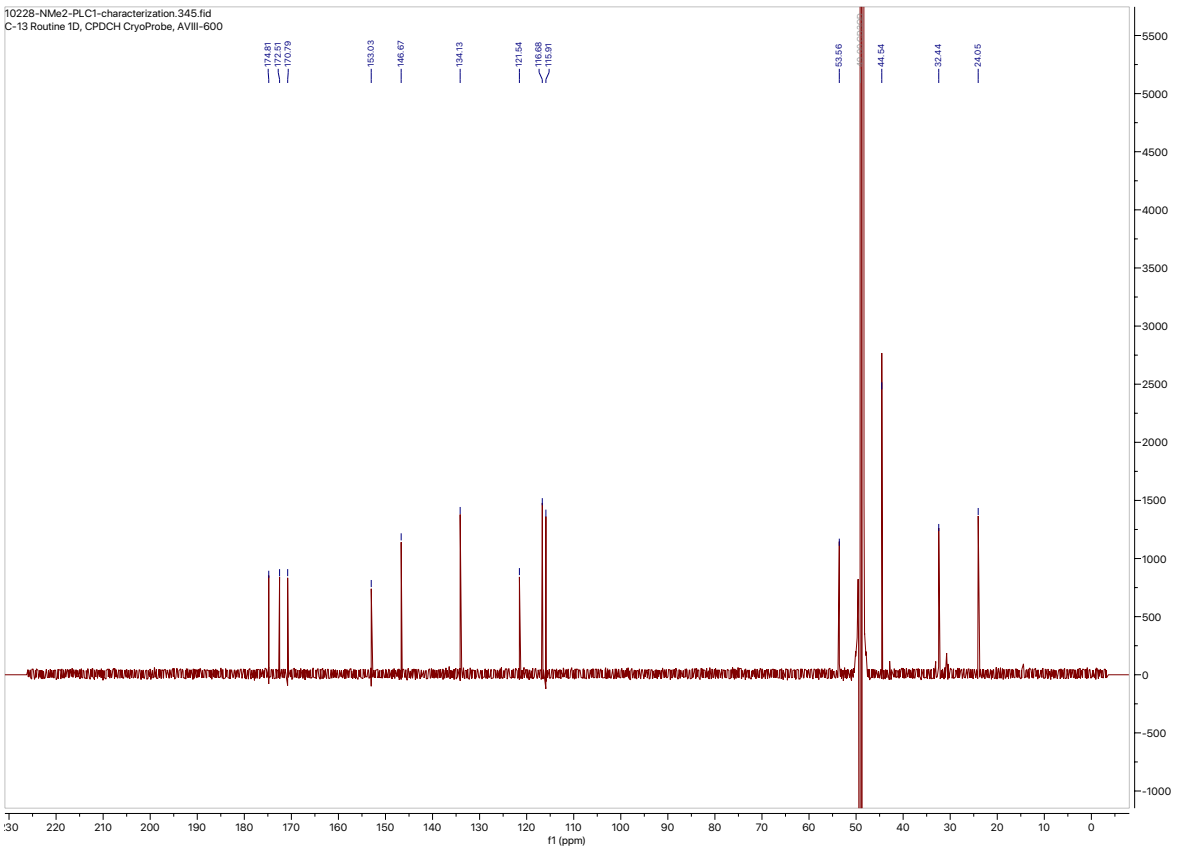

172.90
170.84
167.05
167.04
157.94
156.30
134.89
134.86
130.78
130.74
127.97
127.85
119.51
119.49
118.60
118.47
51.82
44.28
31.19
22.31
f1 (ppm)



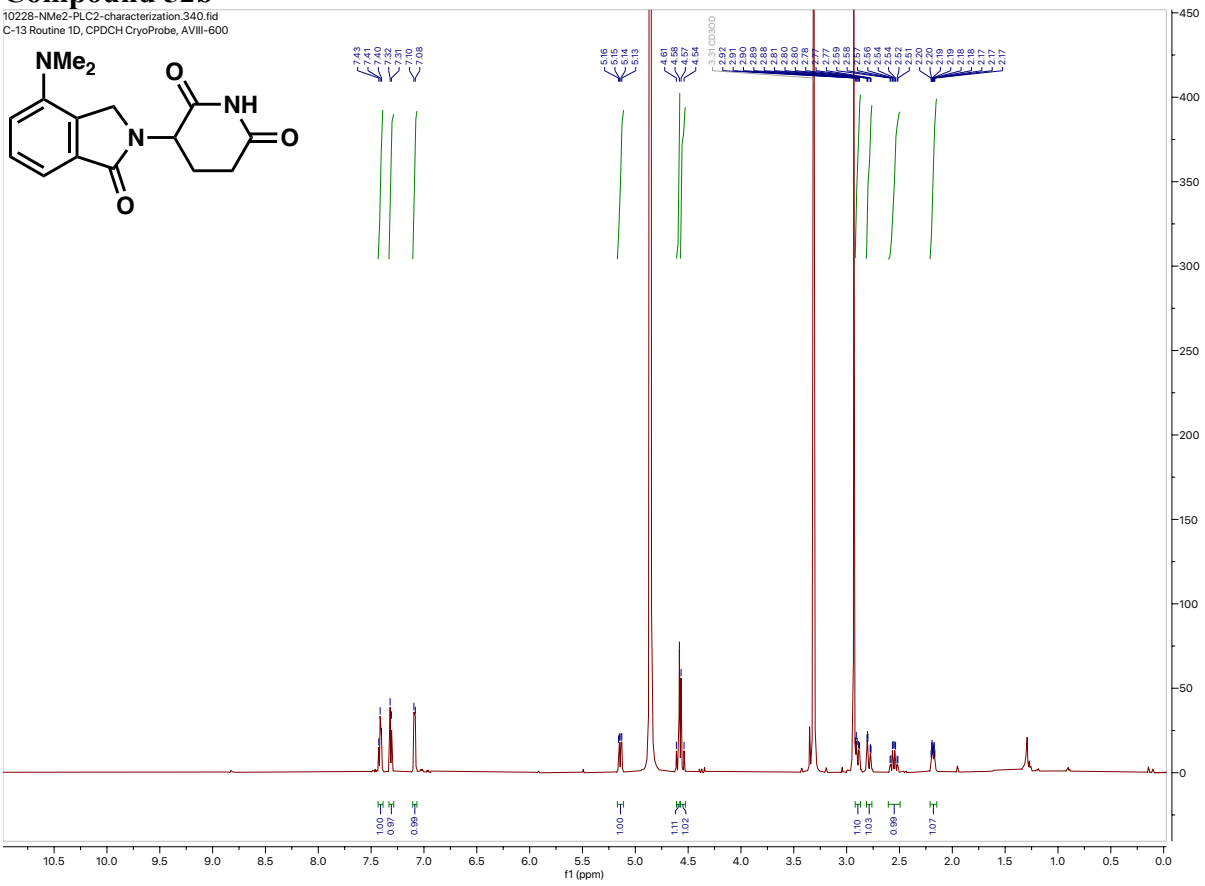
*The signal at -76 ppm is TFA added to improve the solubility of the compound.

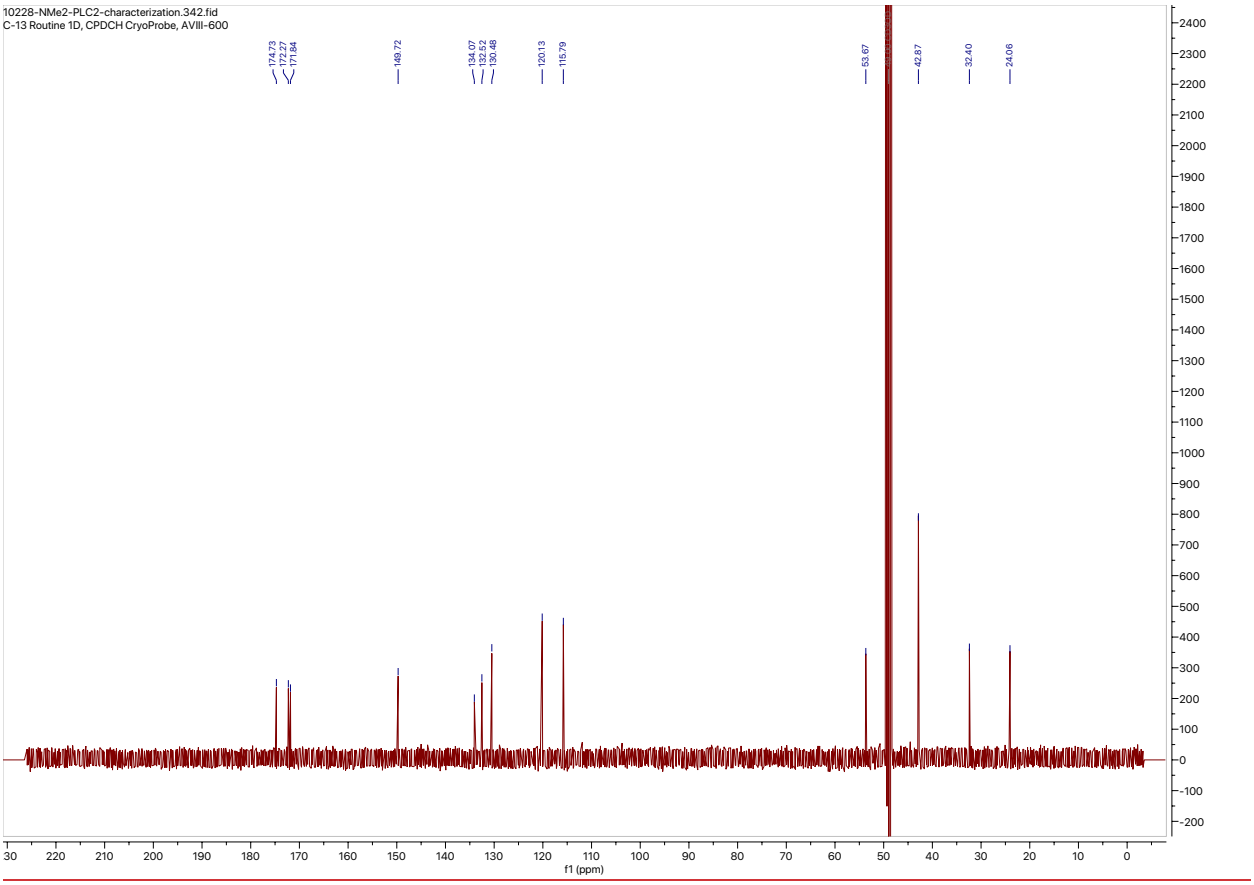
Compound 52a



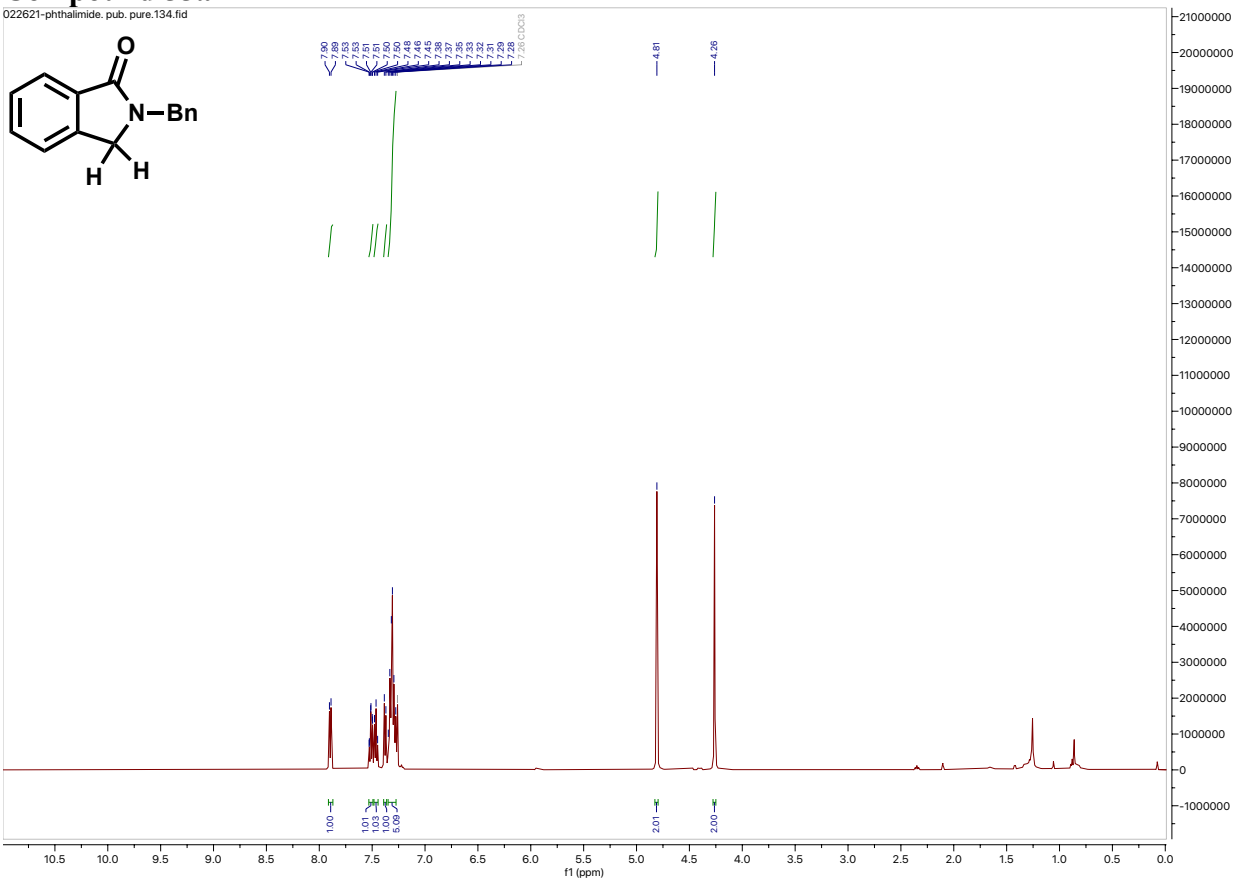

10228-NMe2-PLC1-characterization.345.fid
C-13 Routine 1D, CPDCH CryoProbe, AVIII-600
174.81
172.51
170.79
153.03
146.67
134.13
121.54
116.68
115.91
53.56
44.54
32.44
24.05
f1 (ppm)

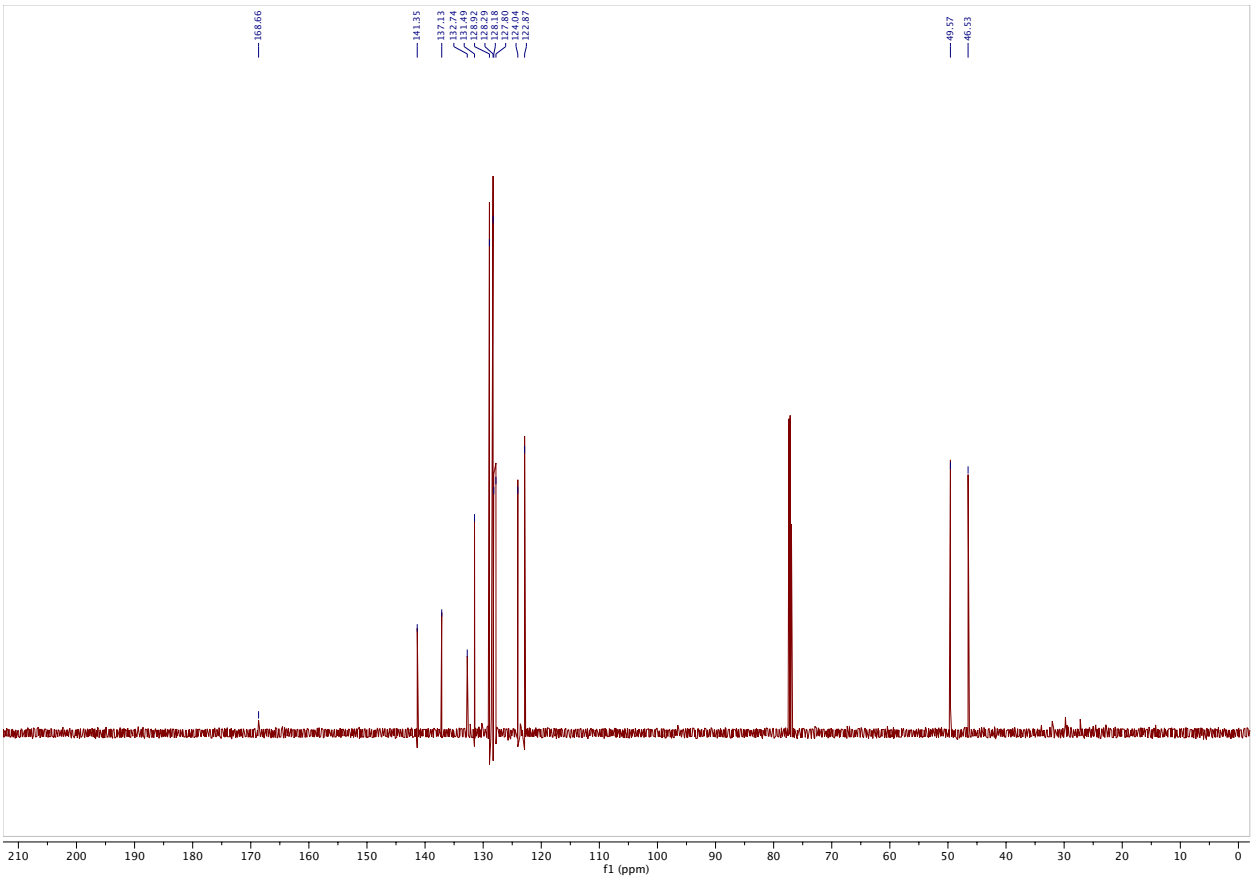
Compound 52b



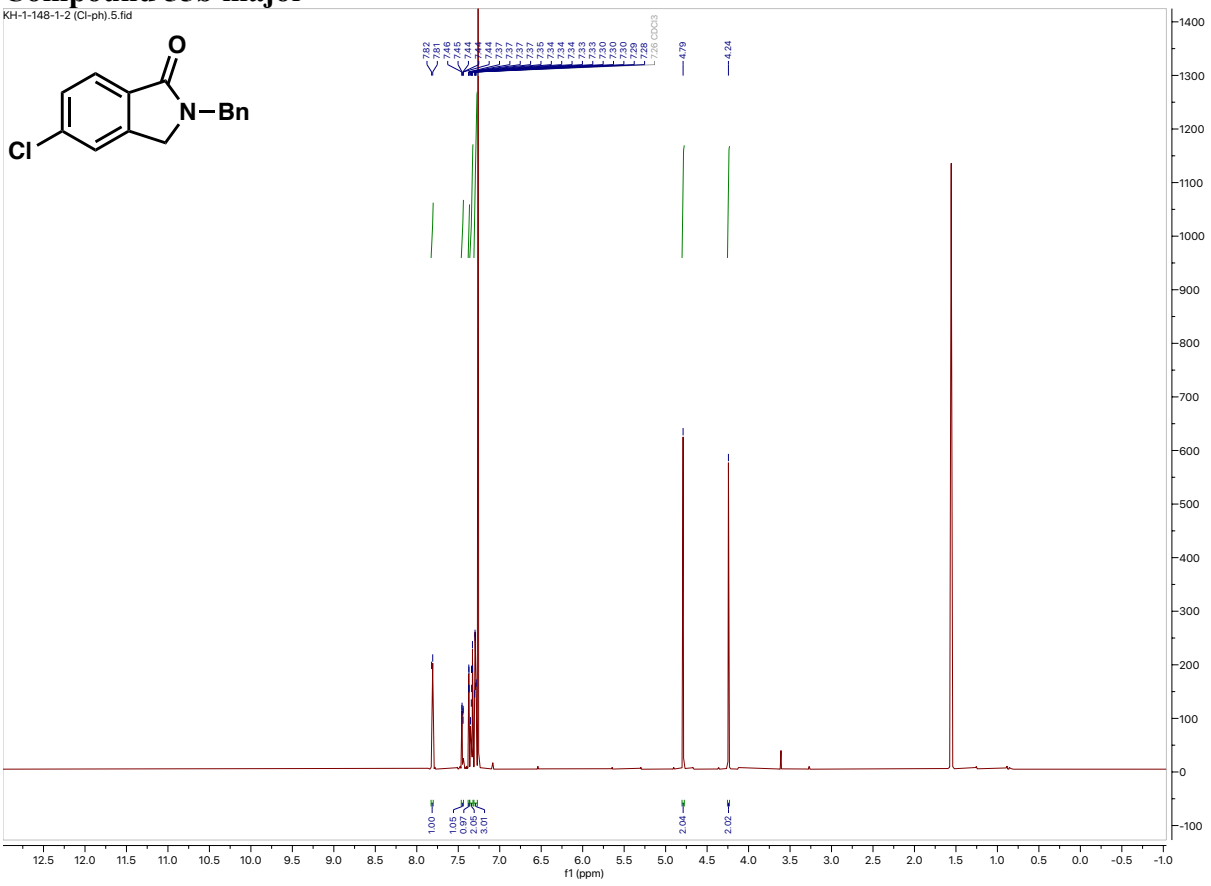

10228-NMe2-PLC2-characterization.342.fid
C-13 Routine 1D, CPDCH CryoProbe, AVIII-600
174.73
172.27
171.84
149.72
134.07
133.52
130.48
120.13
115.79
53.67
42.87
32.40
24.06
f1 (ppm)

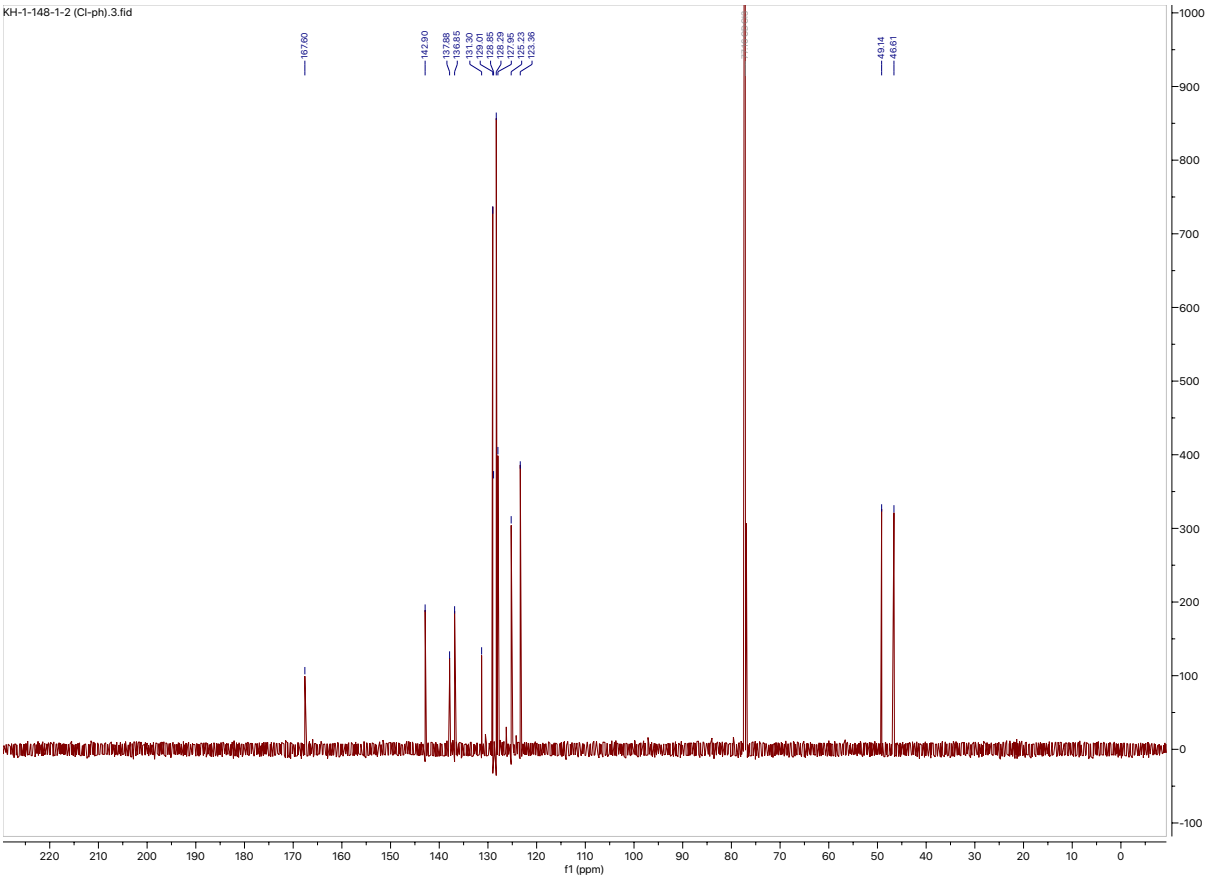
Compound 55a



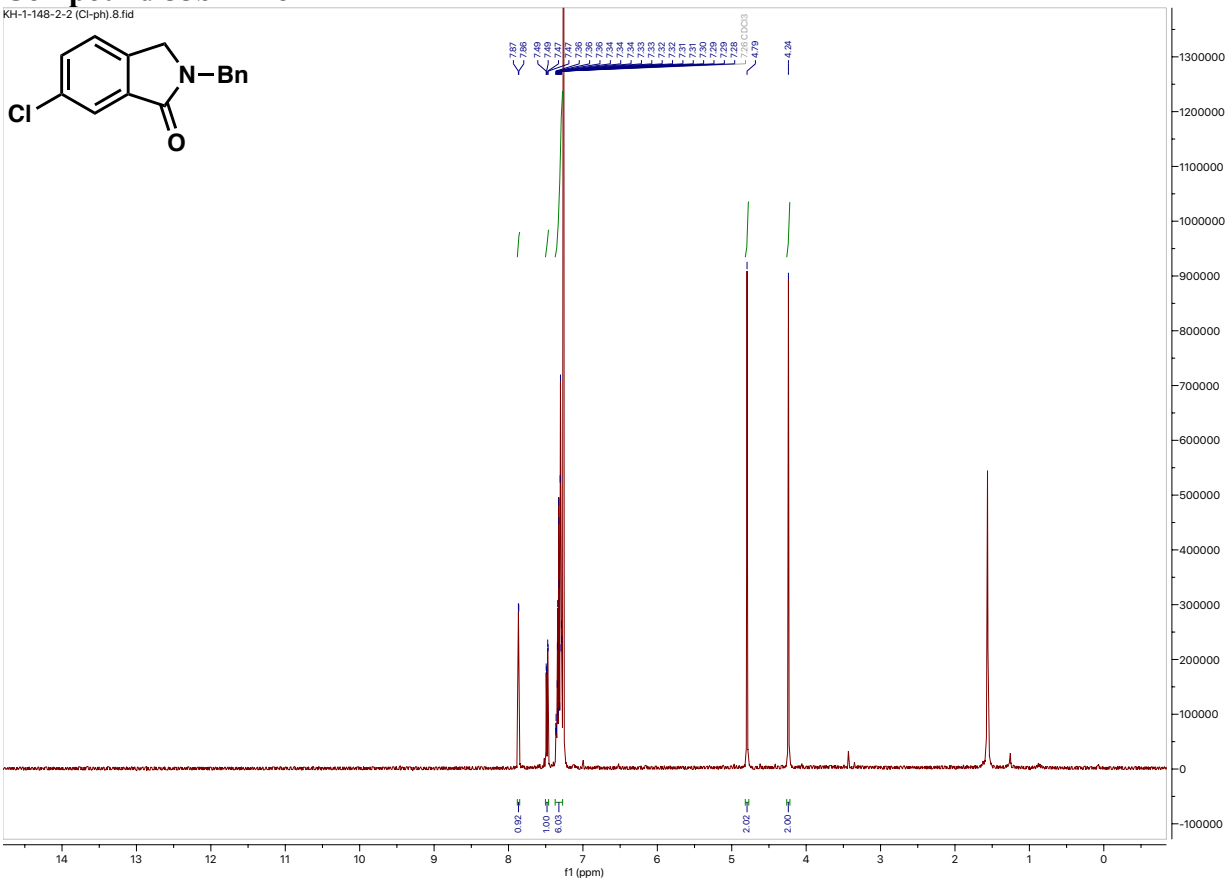

168.66
141.35
137.13
132.74
131.49
128.92
128.89
128.38
127.80
124.04
122.87
49.57
46.53
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

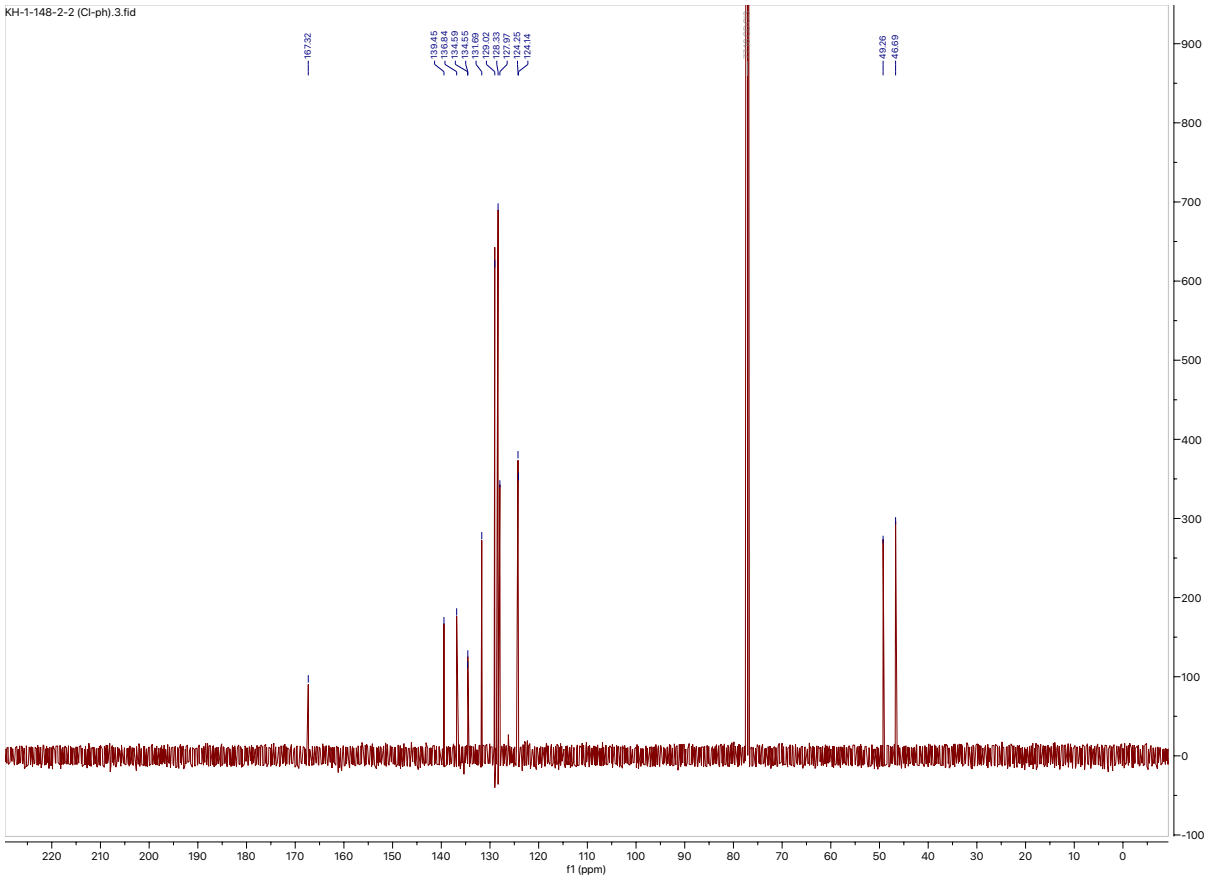
Compound 55b major



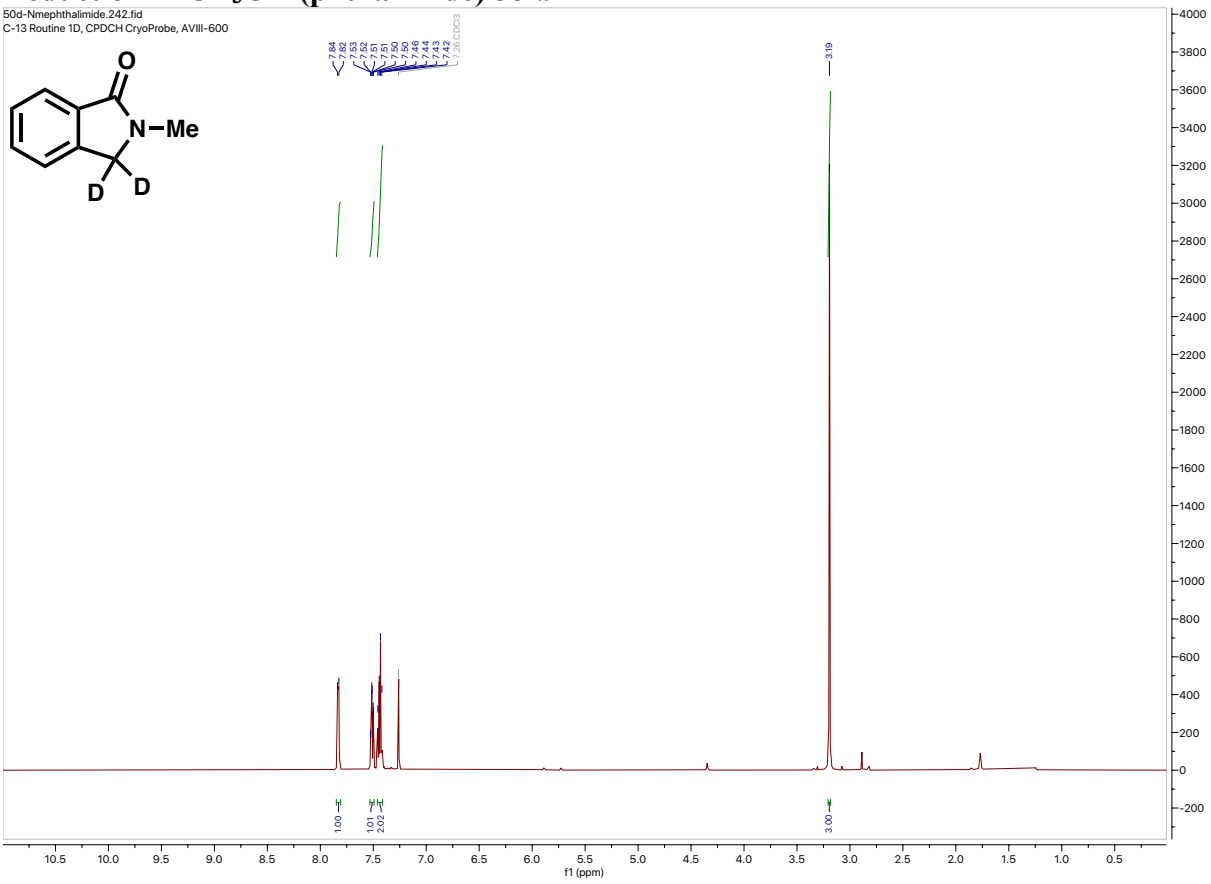

KH-1-148-1-2 (Cl-ph).3.fid
167.60
142.90
137.88
136.85
131.30
129.01
128.85
128.29
127.95
125.23
123.36
49.14
46.61
f1 (ppm)

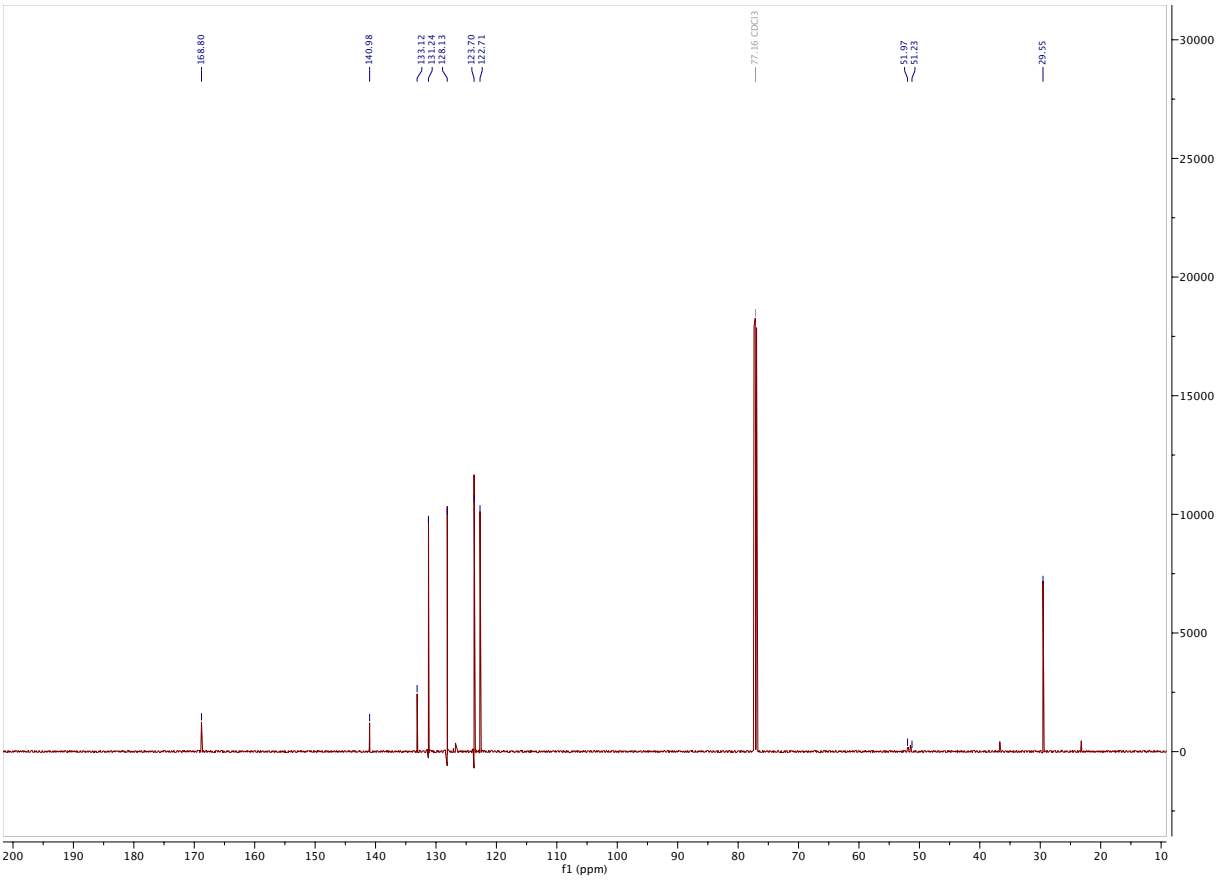
Compound 55b minor



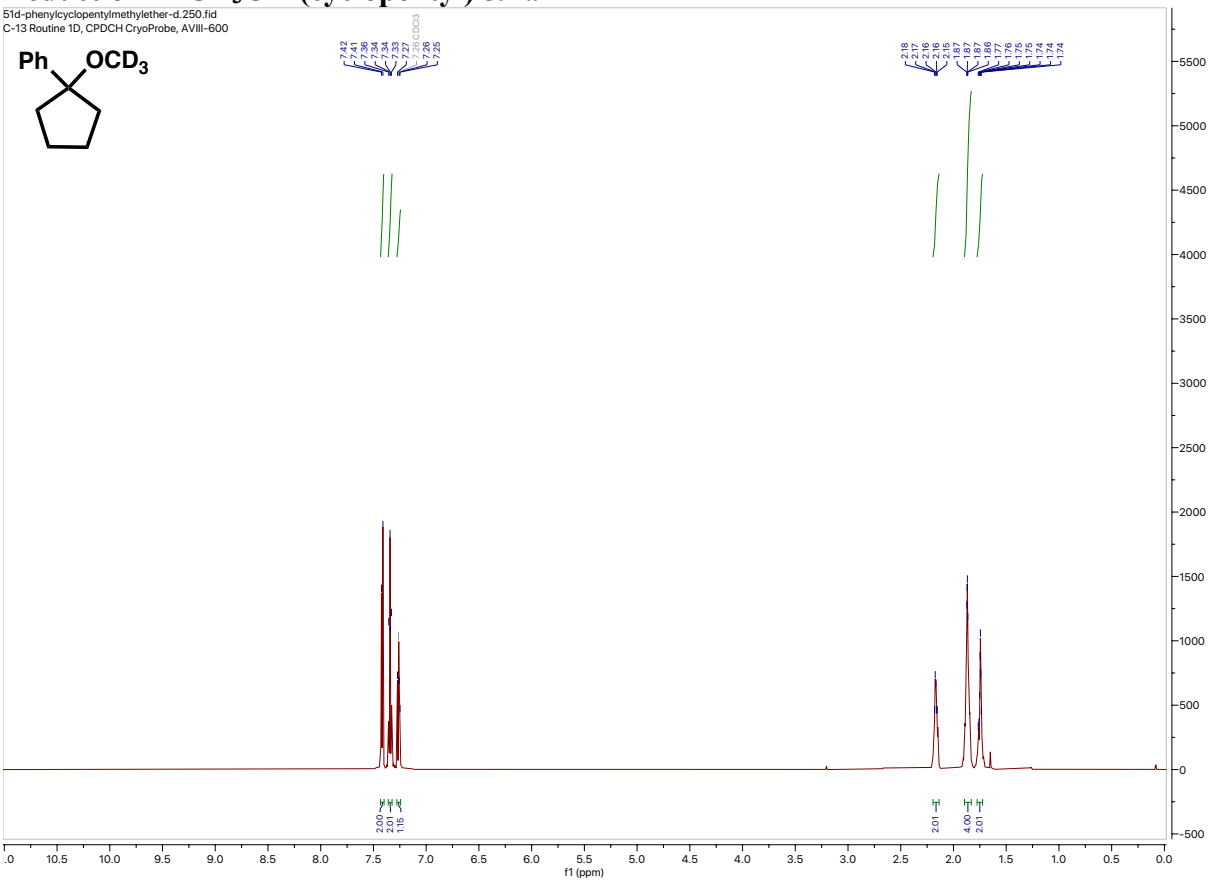

KH-1-148-2-2 (Cl-ph).3.fid
167.32
139.45
137.84
134.89
134.55
131.69
129.02
128.33
127.97
124.25
124.14
49.26
46.69
f1 (ppm)

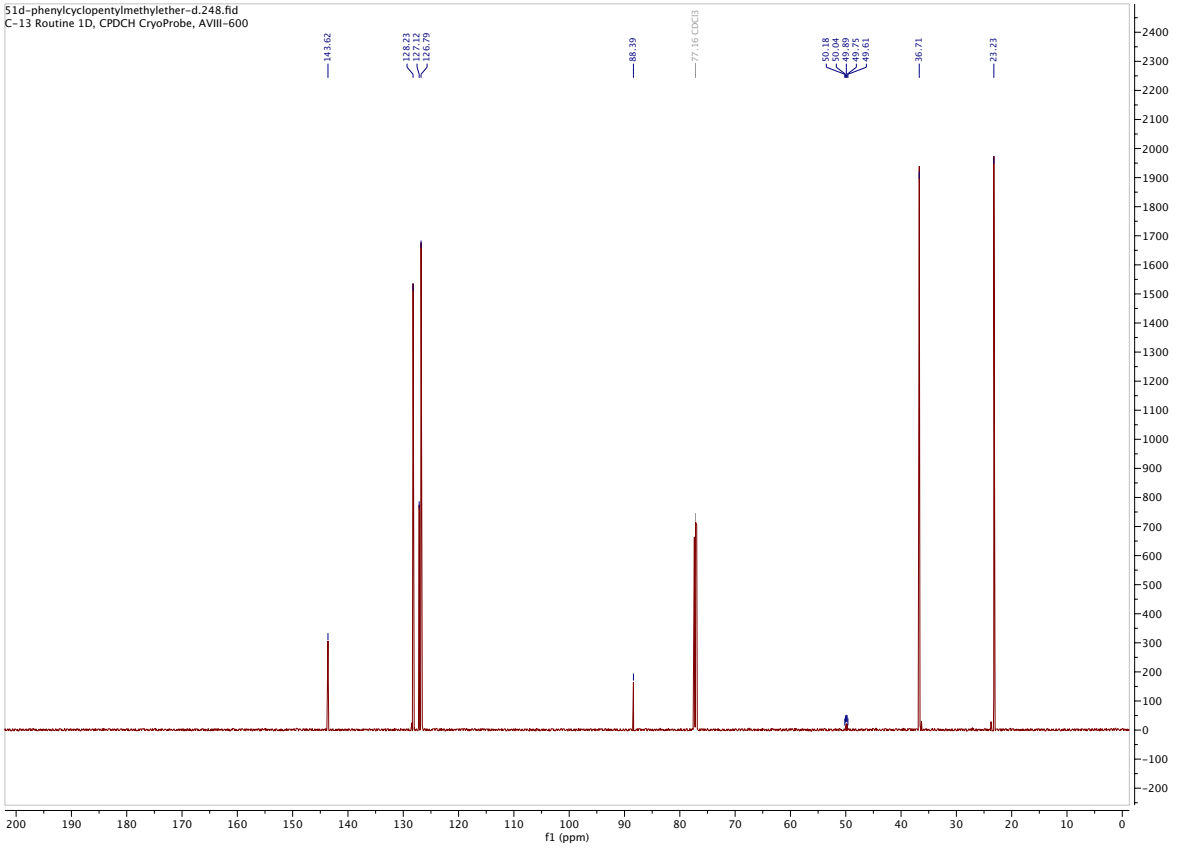
Reduction in CD_3OD (phthalimide) 58-*d*




168.80
140.98
133.12
131.24
126.13
123.70
122.71
77.16 CDCl3
51.97
51.22
29.55
30000
25000
20000
15000
10000
5000
0
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

Reduction in CD_3OD (cyclopentyl) 59-*d*




51d-phenylcyclopentylmethylether-d.248.fid
C-13 Routine 1D, CPDCH CryoProbe, AVIII-600
143.62
128.23
127.12
126.79
88.39
77.16 CDCl3
50.18
50.04
49.89
49.75
49.61
36.71
23.23
f1 (ppm)