Electronic Supplementary Material (ESI) for RSC Medicinal Chemistry.

Photochemical Synthesis of an Epigenetic Focused Tetrahydroquinoline Library

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General Experimental

Solvents were removed under reduced pressure using an IKA rotary evaporator equipped with an IKA MVP10 basic vacuum pump. Dry solvents and reagents were purchased from commercial suppliers and used without further purification. Thin-layer chromatography was conducted with Macherey-Nagel Polygram SIL G/UV254 0.2mm silica gel 60 with fluorescent indicator plates. Flash column chromatography was conducted using a Teledyne ISCO CombiFlash NextGen 300+ purification system using 4g, 12g, or 24g RediSep Rf silica cartridges. Reactions were irradiated using a Kessil A160WE (Tuna Blue) LED lamp at 5cm. The synthesis of compounds **4**, **6**, **8** and **9** have been previously reported using a different UV light source.[1]

Analytical LC-MS was performed using a system comprising an Agilent 1260 Infinity II HPLC instrument equipped with an Agilent InfinityLab LS/MSD XT MS detector with electrospray ionisation. The system ran with a positive and negative switching mode and UV diode array detector using an Agilent ZORBAX SB-C18 RRHT (50 mm × 4.6 mm × 1.8 μm) column and gradient elution with two binary solvent systems: MeCN/H_2O or MeCN/H_2O plus 0.1% formic acid. Preparative HPLC was performed using a system comprising an Agilent 1260 Infinity II HPLC system equipped with an Agilent 1290 Prep Bin Pump, an Agilent Prep-C18 column (250 mm × 21.2 mm × 10 μm), and an Agilent prep autosampler and fraction collector. The system ran using a UV diode array detector and purification was performed using a gradient elution using a MeCN/H_2O binary solvent system.

NMR analysis was conducted using a Bruker NEO400 spectrometer equipped with a 5mm BBFO IProbe (^1H = 400 MHz and ^{13}C = 100 MHz) or a Bruker NEO600 spectrometer equipped with a Prodigy BBO cryoprobe (^1H = 600 MHz and ^{13}C = 150 MHz). Chemical shifts are quoted in parts per million (ppm) and coupling constants are given in Hz. Splitting patterns have been abbreviated as follows: s (singlet), d (doublet), dd (doublet of doublets), ddd (doublet of doublets of doublets), td (triplet of doublets), t (triplet), q (quartet) and m (multiplet). NMR data is reported in the format: ppm (number of protons, splitting pattern, coupling constant).

General procedures

General Procedure A[2]

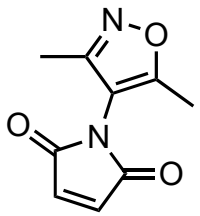
To a 100 mL round bottom flask, *cis*-5-norbornene-*endo*-2,3-dicarboxylic anhydride (1 g, 6 mmol) and a primary amine (6 mmol) were suspended in Toluene (35 mL) and stirred at room temperature for 1 hour, then heated to reflux for a further 20 hours. The reaction was then cooled to room temperature and the solvent removed under reduced pressure to give the crude product which was purified by flash column chromatography.

General Procedure B

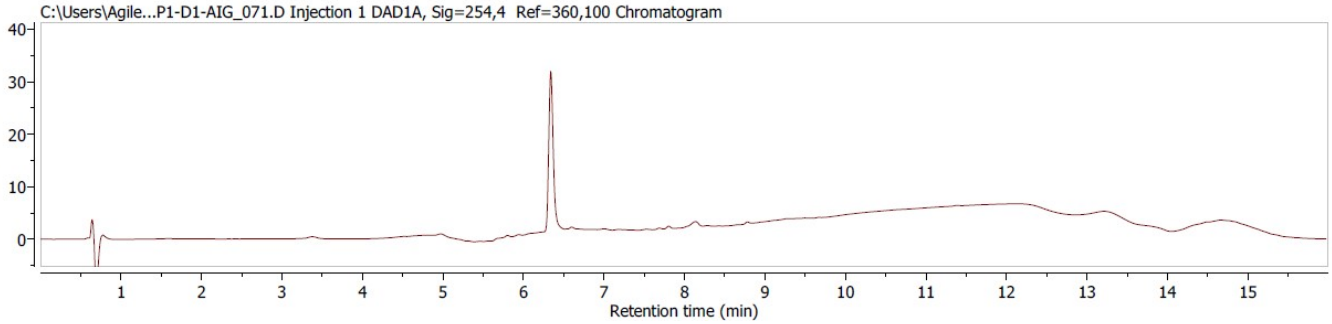
A maleimide (0.25 mmol) and an *N*-methylaniline (1.75 mmol) were added to a 10 mL vial and dissolved in 1,4-dioxane (3 mL) and stirred. The reaction was then irradiated with a blue LED light (Kessil A160WE lamp). After 18 hours at room temperature, the solvent was evaporated under reduced pressure to give the crude product and purified by flash column chromatography.

Synthesis of compounds

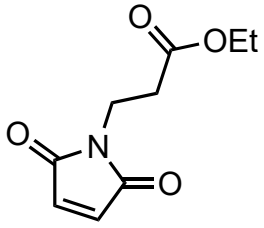
1-(3,5-Dimethylisoxazol-4-yl)-1*H*-pyrrole-2,5-dione, **1**



4-Amino-3,5-dimethylisoxazole (1 g, 8.9 mmol) was dissolved in acetic acid (9 mL), and portions of sodium acetate (2.2 g, 26.7 mmol) and furan-2,5-dione (873 mg, 8.9 mmol) were added. The reaction was heated to 120°C for 4 hours. The solvent was subsequently evaporated and the black solid dissolved in a 1:1:1 mixture of CH_2Cl_2/methanol/acetone and dry loaded onto silica (8 g) and purified by column chromatography eluting 6:4 hexane/ethyl acetate. Compound **1** was obtained as a white solid (220 mg, 13%), R_f 0.6 (6:4 hexane/ethyl acetate). δ_H (400 MHz, chloroform-d) 6.90 (2H, s), 2.30 (3H, s) and 2.14 (3H, s). δ_C (100 MHz, chloroform-d) 168.4, 166.2, 157.8, 135.0, 108.5, 11.5 and 10.0. LCMS (ESI): $C_9H_8N_2O_3$ requires [M+H], calculated 193.1, found 193.1.

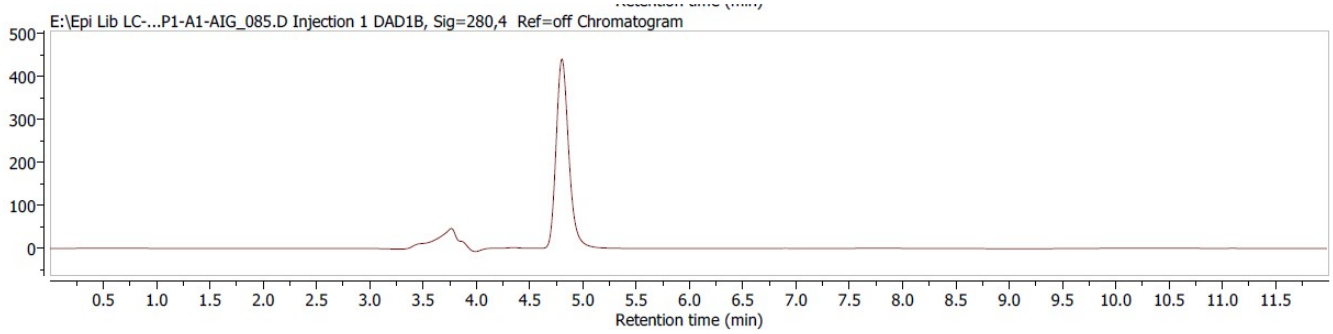


Ethyl 3-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)propanoate, **2**

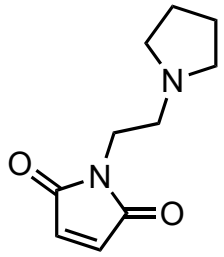


According to general procedure **A**, *cis*-5-norbornene-*endo*-2,3-dicarboxylic anhydride (1 g, 6 mmol) and β-alanine ethyl ester hydrochloride (925 mg, 6 mmol) were reacted to give a crude product which was purified by flash column chromatography eluting 7:3 hexane/ethyl acetate to afford product **2** as a

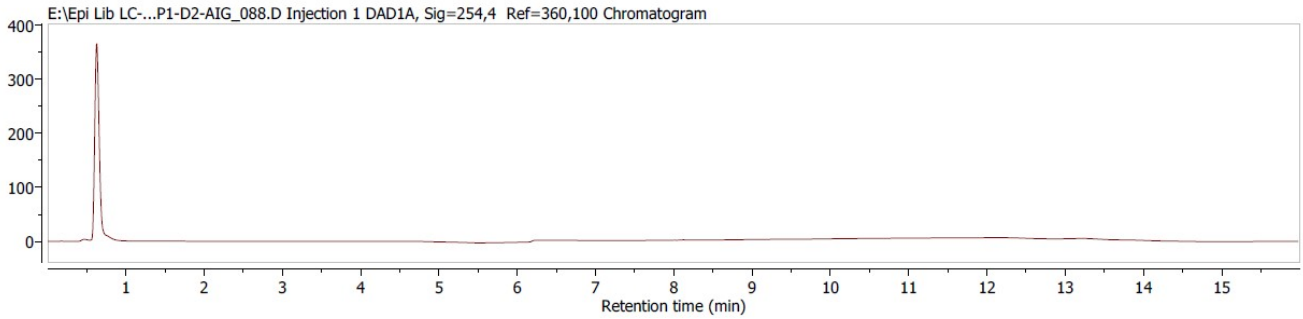
colourless oil (300 mg, 25%). δ_H (400 MHz, chloroform-d) 6.70 (2H, s), 4.11 (2H, q, *J* 7.2), 3.83 (2H, t, *J* 7.1), 2.61 (2H, t, *J* 7.1) and 1.22 (3H, t, *J* 7.2). δ_C (100 MHz, chloroform-d) 171.0, 170.5, 60.9, 33.8, 33.0 and 14.2. LCMS (ESI): $C_9H_{11}NO_4$ requires [M+H], calculated 198.1, found 198.1.



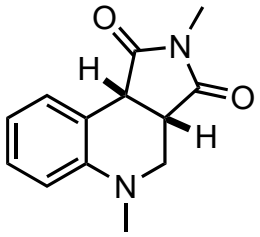
1-(2-(Pyrrolidin-1-yl)ethyl)-1*H*-pyrrole-2,5-dione, **3**



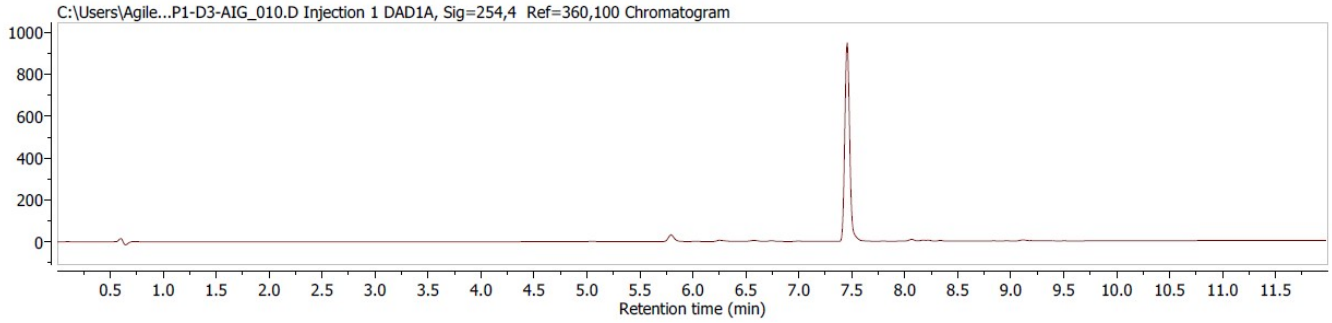
According to general procedure **A**, *cis*-5-norbornene-*endo*-2,3-dicarboxylic anhydride (717 mg, 4.4 mmol) and 1-(2-aminoethyl)pyrrolidine (500 mg, 4.4 mmol) were reacted to give a crude product which was purified by flash column chromatography eluting 2:8 hexane/ethyl acetate to afford product **3** as a yellow oil (200 mg, 24%).%). δ_H (400 MHz, chloroform-d) 6.67 (2H, s), 3.36 (2H, t, *J* 6.8), 2.63 (2H, t, *J* 6.8), 2.52 (4H, broad s) and 1.72 (4H, broad s). δ_C (100 MHz, chloroform-d) 170.9, 134.2, 54.2, 53.9, 37.1 and 23.6. LCMS (ESI): $C_{10}H_{14}N_2O_2$ requires [M+H+], calculated 195.1, found 195.1.



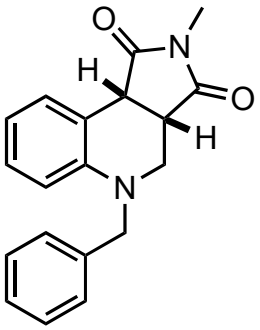
2,5-Dimethyl-3a,4,5,9b-tetrahydro-1H-pyrrolo[3,4-*c*]quinoline-1,3(2H)-dione, **4**



N-methylmaleimide (28 mg, 0.25 mmol) and *N*-benzyl-*N*-methylaniline (330 µL, 1.75 mmol) dissolved in 1,4-dioxane (3 mL) were reacted according to general procedure **B** and the crude material was purified by flash column chromatography eluting 8:2 hexane/ethyl acetate to afford the product **4** as a white solid (50 mg, 87%). δ_H (400 MHz, chloroform-d) 7.48 (1H, d, *J* 7.5), 7.21 (1H, m), 6.89 (1H, td, *J* 7.5 and 1.1), 6.69 (1H, d, *J* 8.2), 4.00 (1H, d, *J* 9.5), 3.53 (1H, dd, *J* 11.5 and 2.4), 3.36 (1H, ddd, *J* 9.5, 4.5 and 2.4), 3.03 (1H, dd, *J* 11.5 and 4.5), 2.98 (3H, s) and 2.79 (3H, s). δ_C (100 MHz, chloroform-d) 178.9, 177.0, 148.5, 130.3, 128.7, 119.7, 118.8, 112.6, 50.6, 43.7, 42.2, 39.5 and 25.5. LCMS (ESI): $C_{13}H_{14}N_2O_2$ requires [M+H], calculated 231.1, found 231.1.

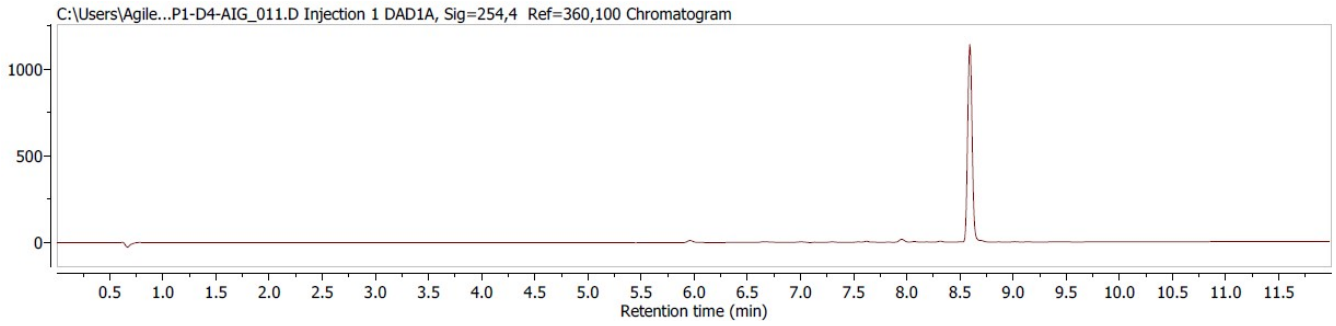


5-Benzyl-2-methyl-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione, **5**

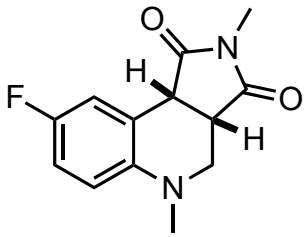


N-Methylmaleimide (28 mg, 0.25 mmol) and *N*-benzyl-*N*-methylaniline (330 µL, 1.75 mmol) dissolved in 1,4-dioxane (3 mL) were reacted according to general procedure **B** and the crude material was purified

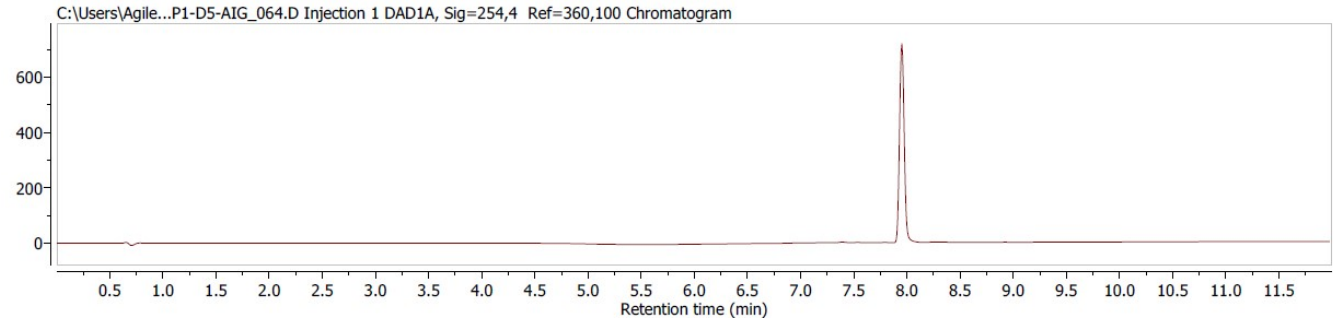
by flash column chromatography eluting 8:2 hexane/ethyl acetate to afford the product **5** as a white solid (52 mg, 68%). δ_H (400 MHz, chloroform-d) 7.51 (1H, broad d, *J* 8.0), 7.33 – 7.25 (3H, m), 7.21 – 7.19 (2H, m), 7.15 – 7.10 (1H, m), 6.87 (1H, td, *J* 7.5 and 1.0), 6.71 (1H, broad d, *J* 8.3), 4.43 (1H, d, *J* 15.2), 4.25 (1H, d, *J* 15.3), 4.03 (1H, d, *J* 9.3), 3.58 (1H, dd, *J* 11.8 and 2.8), 3.37 (1H, ddd, *J* 9.3, 4.4 and 2.8), 3.18 (1H, dd, *J* 11.7 and 4.4) and 3.02 (3H, s). δ_C (100 MHz, chloroform-d) 178.6, 177.0, 147.6, 137.8, 130.5, 128.7, 128.6, 127.6, 127.5, 119.7, 119.0, 113.5, 53.4, 48.5, 44.2, 42.4 and 25.5. LCMS (ESI): $C_{19}H_{18}N_2O_2$ requires [M+H], calculated 307.1, found 307.2.



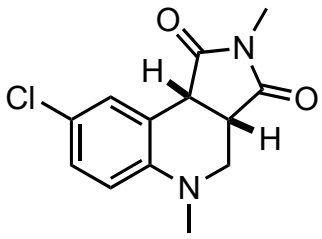
8-Fluoro-2,5-dimethyl-3a,4,5,9b-tetrahydro-1H-pyrrolo[3,4-*c*]quinoline-1,3(2H)-dione, **6**



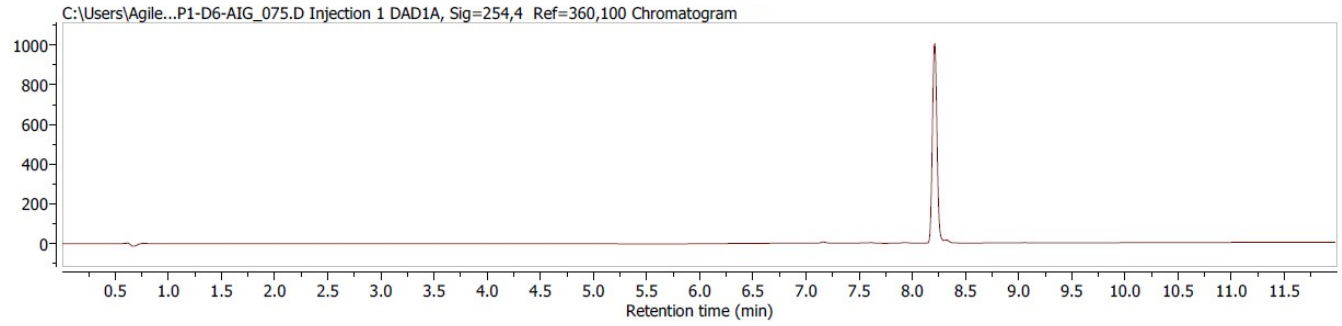
N-Methylmaleimide (28 mg, 0.25 mmol) and 4-fluoro-*N,N*-dimethylaniline (244 mg, 1.75 mmol) dissolved in 1,4-dioxane (3 mL) were reacted according to general procedure **B** and the crude material was purified by flash column chromatography eluting 7:3 hexane/ethyl acetate to afford the product **6** as a light-yellow solid (44 mg, 70%). δ_H (400 MHz, chloroform-d) 7.22 (1H, dd, *J* 8.6 and 2.2), 6.90 (1H, td, *J* 8.8 and 2.3), 6.62 (1H, dd, *J* 9.0 and 4.6), 3.95 (1H, d, *J* 9.4), 3.50 (1H, d, *J* 11.5), 3.37 – 3.32 (1H, m), 3.02 – 2.96 (4H, m) and 2.76 (3H, s). δ_C (100 MHz, chloroform-d) 178.5, 176.2, 156.6 (d, $J_{C\text{-}F}$ 237.1), 144.9 (d, $J_{C\text{-}F}$ 2.0), 120.2 (d, $J_{C\text{-}F}$ 7.6), 116.8 (d, $J_{C\text{-}F}$ 23.1), 114.9 (d, $J_{C\text{-}F}$ 21.7), 113.3 (d, $J_{C\text{-}F}$ 7.6), 50.9, 43.5, 42.1 (d, $J_{C\text{-}F}$ 1.4), 39.7 and 25.4. LCMS (ESI): $C_{13}H_{13}FN_2O_2$ requires [M+H], calculated 249.1, found 249.1.



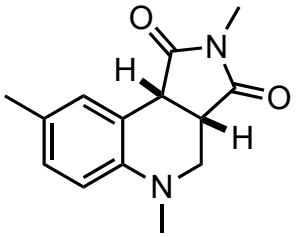
8-Chloro-2,5-dimethyl-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione, **7**



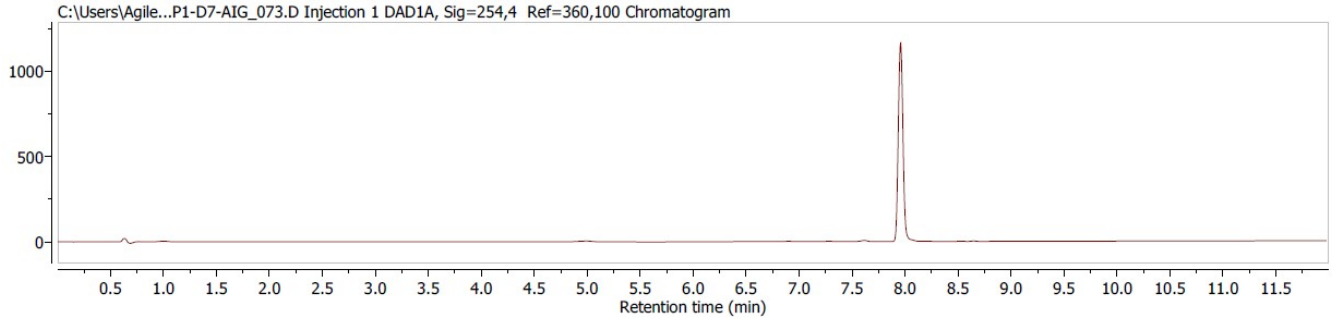
N-Methylmaleimide (28 mg, 0.25 mmol) and 4-chloro-*N,N*-dimethylaniline (272 mg, 1.75 mmol) dissolved in 1,4-dioxane (3 mL) were reacted according to general procedure **B** and the crude material was purified by flash column chromatography eluting 7:3 hexane/ethyl acetate to afford the product **7** as a white solid (29 mg, 44%). δ_H (400 MHz, chloroform-d) 7.44 (1H, s), 7.13 (1H, d, *J* 8.7), 6.60 (1H, d, *J* 8.8), 3.93 (1H, d, *J* 9.4), 3.51 (1H, d, *J* 11.6), 3.36 – 3.34 (1H, m), 3.01 (1H, dd, *J* 11.6 and 4.4), 2.98 (3H, s) and 2.77 (3H, s). δ_C (100 MHz, chloroform-d) 178.4, 176.2, 147.1, 129.9, 128.5, 124.5, 120.3, 113.8, 50.5, 43.4, 41.9, 39.6 and 25.5. LCMS (ESI): $C_{13}H_{13}{}^{35}ClN_2O_2$ requires [M+H], calculated 265.1, found 265.1.



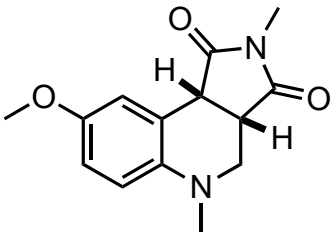
2,5,8-Trimethyl-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione, **8**



N-Methylmaleimide (28 mg, 0.25 mmol) and 4,*N*,*N*-trimethylaniline (253 µL, 1.75 mmol) dissolved in 1,4-dioxane (3 mL) were reacted according to general procedure **B** and the crude material was purified by flash column chromatography eluting 7:3 hexane/ethyl acetate to afford the product **8** as an off-white solid (53 mg, 86%). δ_H (400 MHz, chloroform-d) 7.29 (1H, broad s), 7.00 (1H, d, *J* 7.6), 6.60 (1H, d, *J* 8.3), 3.95 (1H, d, *J* 9.4), 3.51 (1H, dd, *J* 11.4 and 2.2), 3.35 – 3.31 (1H, m), 2.98 (3H, s), 2.96 (1H, dd, *J* 11.4 and 4.4), 2.76 (3H, s) and 2.30 (3H, s). δ_C (100 MHz, chloroform-d) 179.0, 177.0, 146.4, 130.8, 129.2, 129.1, 118.8, 112.6, 50.9, 43.7, 42.2, 39.6, 25.4 and 20.5. LCMS (ESI): $C_{14}H_{16}N_2O_2$ requires [M+H], calculated 245.1, found 245.1.

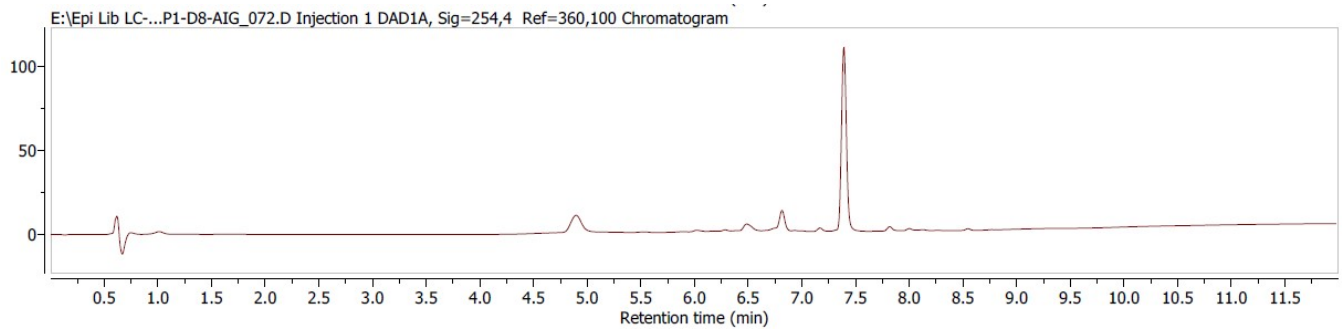


8-Methoxy-2,5-dimethyl-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione, **9**

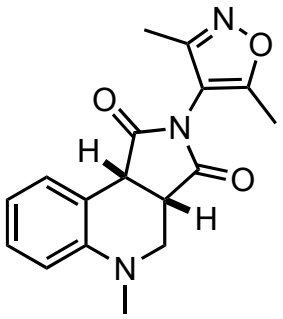


N-Methylmaleimide (28 mg, 0.25 mmol) and 4-methoxy-*N,N*-dimethylaniline (265 mg, 1.75 mmol) dissolved in 1,4-dioxane (3 mL) were reacted according to general procedure **B** and the crude material was purified by flash column chromatography eluting 7:3 hexane/ethyl acetate to afford the product **9** as a light yellow solid (30 mg, 46%). δ_H (400 MHz, chloroform-d) 7.08 (1H, d, *J* 2.9), 6.79 (1H, dd, *J* 8.8

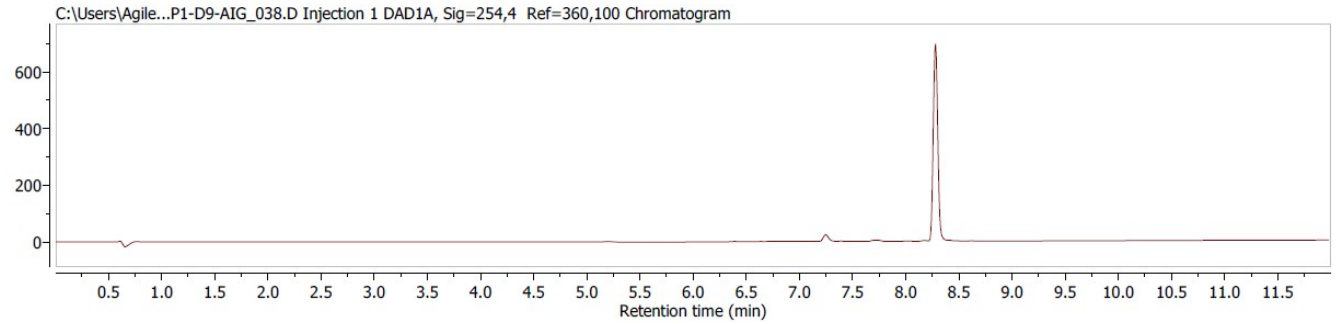
and 2.9), 6.64 (1H, d, *J* 8.9), 3.96 (1H, d, *J* 9.4), 3.79 (3H, s), 3.49 (1H, dd, *J* 11.4 and 2.4), 3.36 – 3.32 (1H, m), 3.00 (3H, s), 2.94 (1H, dd, *J* 11.2 and 4.2) and 2.75 (3H, s). δ_C (100 MHz, chloroform-d) 179.0, 176.8, 153.4, 142.8, 120.1, 115.8, 114.4, 113.5, 55.9, 51.3, 43.7, 42.5, 39.9 and 25.5. LCMS (ESI): $C_{14}H_{16}N_2O_3$ requires [M+H], calculated 261.1, found 261.1.



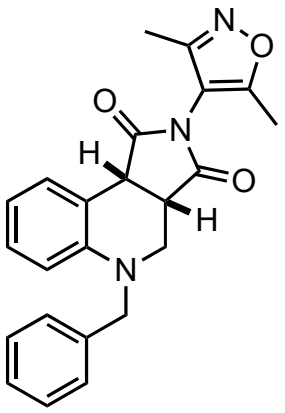
2-(3,5-Dimethylisoxazol-4-yl)-5-methyl-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione, **10**



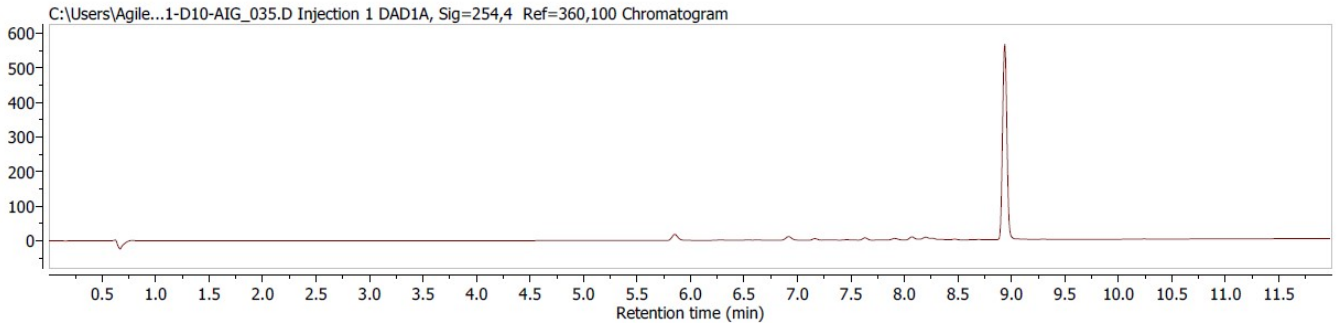
1-(3,5-dimethylisoxazol-4-yl)-1*H*-Pyrrole-2,5-dione (48 mg, 0.25 mmol) and *N,N*-dimethylaniline (222 µL, 1.75 mmol) dissolved in 1,4-dioxane (3 mL) were reacted according to general procedure **B** and the crude material was purified by flash column chromatography eluting 7:3 hexane/ethyl acetate to afford the product **10** as an orange oil (59 mg, 76%). δ_H (400 MHz, chloroform-d) 7.46 (1H, broad d, *J* 7.3), 7.24 (1H, td, *J* 7.9 and 1.4), 6.94 – 6.90 (1H, m), 6.75 (1H, d, *J* 8.2), 4.19 (1H, d, *J* 9.1), 3.60 – 3.55 (2H, m), 3.11 – 3.07 (1H, m) and 2.84 (3H, s). δ_C (100 MHz, chloroform-d) 177.0 (rot A+B), 175.0 (rot A+B), 168.4 (rot A), 166.2 (rot B), 157.7 (rot A+B), 148.7 (rot A+B), 135.0 (rot A+B), 130.3 (rot A), 129.1 (rot B), 120.2 (rot A+B), 118.6 (rot A+B), 112.7 (rot A+B), 109.7 (rot A+B), 51.3 (rot A+B), 44.2 (rot A+B), 42.7 (rot A+B), 39.4 (rot A+B), 11.4 (rot A+B) and 10.0 (rot A+B). LCMS (ESI): $C_{17}H_{17}N_3O_3$ requires [M+H], calculated 312.1, found 312.1.



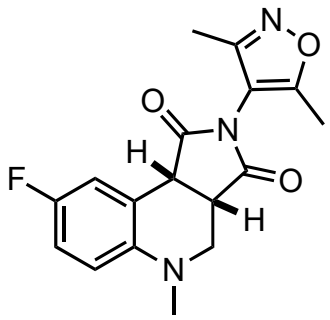
5-Benzyl-2-(3,5-dimethylisoxazol-4-yl)-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione, **11**



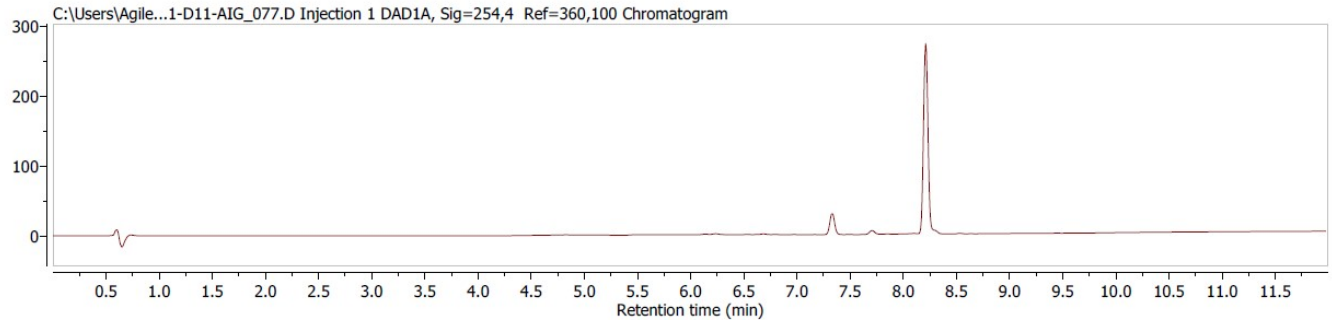
1-(3,5-dimethylisoxazol-4-yl)-1*H*-Pyrrole-2,5-dione (48 mg, 0.25 mmol) and *N*-benzyl-*N*-methylaniline (330 µL, 1.75 mmol) dissolved in 1,4-dioxane (3 mL) were reacted according to general procedure **B** and the crude material was purified by flash column chromatography eluting 8:2 hexane/ethyl acetate to afford the product **11** as an orange oil (60 mg, 62%). δ_H (400 MHz, chloroform-d) 7.54 (1H, d, *J* 7.0), 7.34 – 7.28 (3H, m), 7.26 – 7.24 (2H, m), 7.20 – 7.15 (1H, m), 6.91 (1H, td, *J* 7.5 and 1.1), 6.78 (1H, d, *J* 8.3), 4.48 (1H, d, *J* 15.4), 4.34 (1H, d, *J* 15.4), 4.26 (1H, d, *J* 9.4), 3.72 (1H, dd, *J* 11.8 and 2.8), 3.62 (1H, ddd, *J* 9.4, 4.1 and 2.8), 3.30 (1H, dd, *J* 11.8 and 4.1) and 2.37 – 1.90 (6H, m). δ_C (100 MHz, chloroform-d) 176.5, 175.1, 165.9, 157.4, 147.4, 137.6, 130.6, 129.2, 129.0, 128.8, 127.6, 127.5, 120.0, 113.8, 109.6, 55.8, 48.8, 44.2, 42.6, 12.3 and 11.5. LCMS (ESI): $C_{23}H_{21}N_3O_3$ requires [M+H], calculated 388.2, found 388.1.



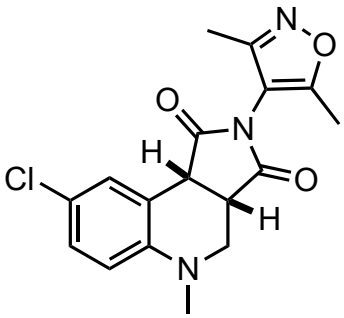
2-(3,5-Dimethylisoxazol-4-yl)-8-fluoro-5-methyl-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione, **12**



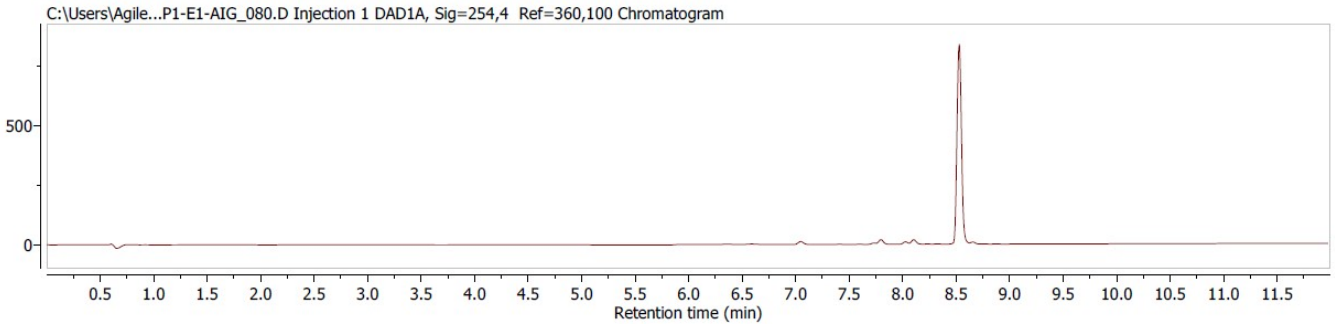
1-(3,5-dimethylisoxazol-4-yl)-1*H*-Pyrrole-2,5-dione (48 mg, 0.25 mmol) and 4-fluoro-*N,N*-dimethylaniline (244 mg, 1.75 mmol) dissolved in 1,4-dioxane (3 mL) were reacted according to general procedure **B** and the crude material was purified by flash column chromatography eluting 7:3 hexane/ethyl acetate to afford the product **12** as a yellow oil (51 mg, 62%). δ_H (400 MHz, chloroform-d) 7.20 (1H, dd, *J* 8.6 and 2.8), 6.94 (1H, td, *J* 8.6 and 3.0), 6.68 (1H, dd, *J* 9.0 and 4.6), 4.14 (1H, d, *J* 9.2), 3.57 – 3.53 (2H, m), 3.04 (1H, dd, *J* 12.0 and 4.8), 2.81 (3H, s), 2.29 (3H, s) and 2.14 (3H, s). δ_C (100 MHz, chloroform-d) 176.7 (rot A+B), 174.4 (rot A+B), 168.4 (rot A), 166.2 (rot B), 157.8 (rot A), 157.4 (rot B), 156.9 (d, $J_{C\text{-}F}$ 237.8) (rot A+B), 145.2 (d, $J_{C\text{-}F}$ 2.1) (rot A+B), 135.0 (rot A+B), 120.1 (d, $J_{C\text{-}F}$ 7.6) (rot A+B), 117.0 (d, $J_{C\text{-}F}$ 23.2) (rot A+B), 115.4 (d, $J_{C\text{-}F}$ 21.9) (rot A+B), 113.6 (d, $J_{C\text{-}F}$ 7.6) (rot A+B), 51.7 (rot A+B), 44.1 (rot A+B), 42.8 (rot A+B), 39.7 (rot A+B), 11.4 (rot A+B) and 10.0 (rot A+B). LCMS (ESI): $C_{17}H_{16}FN_3O_3$ requires [M+H], calculated 330.1, found 330.1.



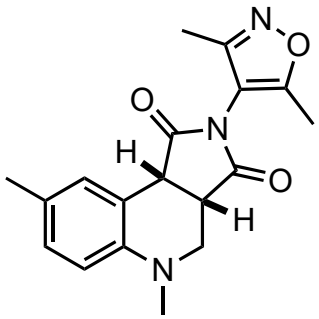
8-Chloro-2-(3,5-dimethylisoxazol-4-yl)-5-methyl-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione, **13**



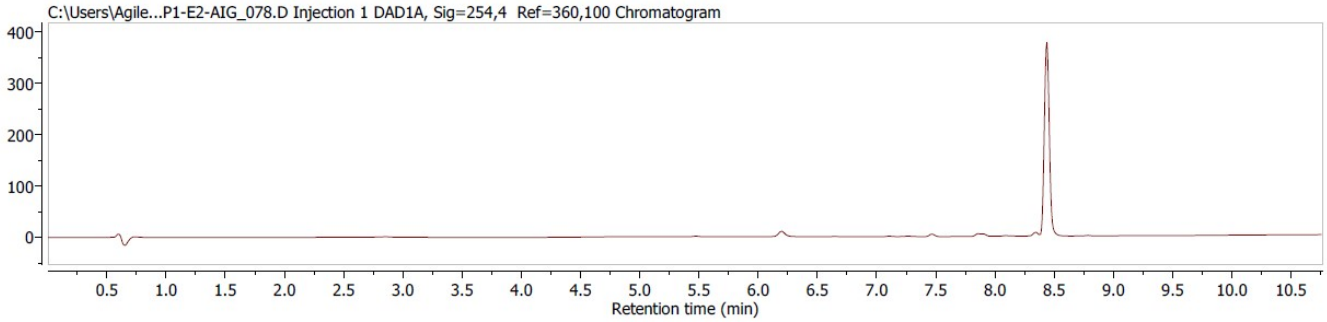
1-(3,5-dimethylisoxazol-4-yl)-1*H*-Pyrrole-2,5-dione (24 mg, 0.125 mmol) and 4-chloro-*N,N*-dimethylaniline (136 mg, 0.875 mmol) dissolved in 1,4-dioxane (1.5 mL) were reacted according to general procedure **B** and the crude material was purified by flash column chromatography eluting 7:3 hexane/ethyl acetate to afford the product **13** as an orange oil (28 mg, 65%). δ_H (400 MHz, chloroform-d) 7.45 (1H, d, *J* 2.1), 7.19 (1H, dd, *J* 8.7 and 2.4), 6.67 (1H, d, *J* 8.7), 4.13 (1H, d, *J* 9.2), 3.59 – 3.54 (2H, m), 3.08 (1H, m), 2.83 (3H, s) and 2.34 – 1.91 (6H, m). δ_C (100 MHz, chloroform-d) 176.5, 174.3, 157.3, 147.3, 135.0, 130.0, 129.0, 125.1, 120.1, 114.0, 109.5, 51.2, 43.9, 42.4, 39.5, 11.5 and 10.0. LCMS (ESI): $C_{17}H_{16}{}^{35}ClN_3O_3$ requires [M+H], calculated 346.1, found 346.1.



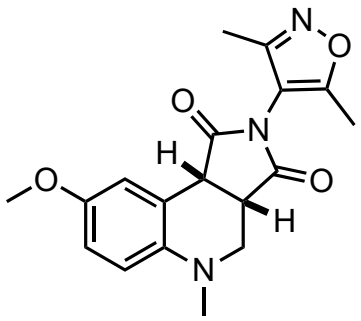
2-(3,5-Dimethylisoxazol-4-yl)-5,8-dimethyl-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione, **14**



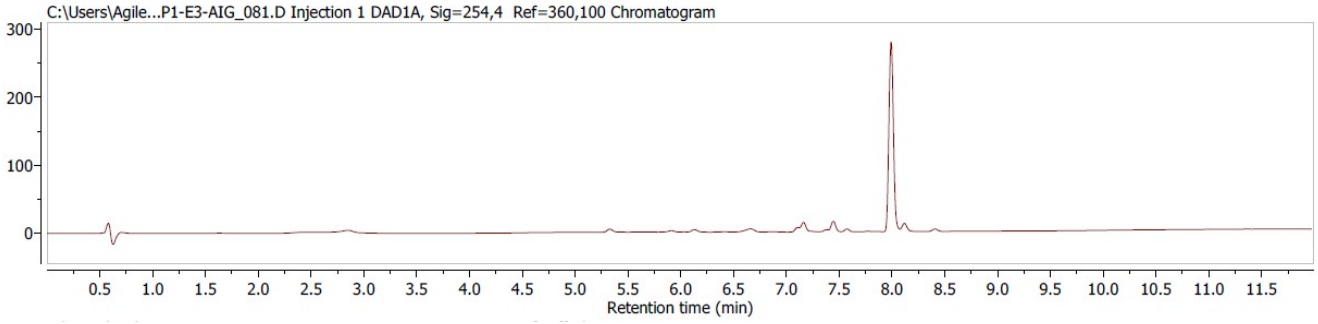
1-(3,5-dimethylisoxazol-4-yl)-1*H*-Pyrrole-2,5-dione (24 mg, 0.125 mmol) and 4,*N*,*N*-trimethylaniline (126 µL, 0.875 mmol) dissolved in 1,4-dioxane (1.5 mL) were reacted according to general procedure **B** and the crude material was purified by flash column chromatography eluting 7:3 hexane/ethyl acetate to afford the product **14** as a yellow solid (35 mg, 86%). δ_H (400 MHz, chloroform-d) 7.26 (1H, broad s), 7.03 (1H, dd, *J* 8.3 and 2.0), 6.65 (1H, d, *J* 8.3), 4.13 (1H, d, *J* 9.1), 3.56 – 3.52 (2H, m), 3.01 (1H, dd, *J* 12 and 4.8), 2.80 (3H, s), 2.29 (3H, s), 2.29 (3H, s) and 2.14 (3H, s). δ_C (100 MHz, chloroform-d) 177.1 (rot A+B), 175.1 (rot A+B), 168.4 (rot A), 166.2 (rot B), 157.7 (rot A+B), 146.6 (rot A+B), 135.0 (rot A+B), 130.8 (rot A+B), 129.6 (rot A), 129.5 (rot B), 118.7 (rot A+B), 112.7 (rot A+B), 109.7 (rot A), 108.5 (rot B), 51.7 (rot A+B), 44.2 (rot A+B), 42.8 (rot A+B), 39.5 (rot A+B), 20.5 (rot A+B), 11.4 (rot A+B), and 10.0 (rot A+B). LCMS (ESI): $C_{18}H_{19}N_3O_3$ requires [M+H], calculated 326.1, found 326.1.



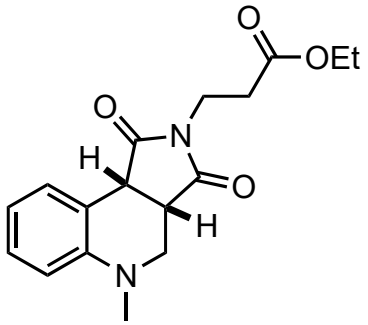
2-(3,5-Dimethylisoxazol-4-yl)-8-methoxy-5-methyl-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione, **15**



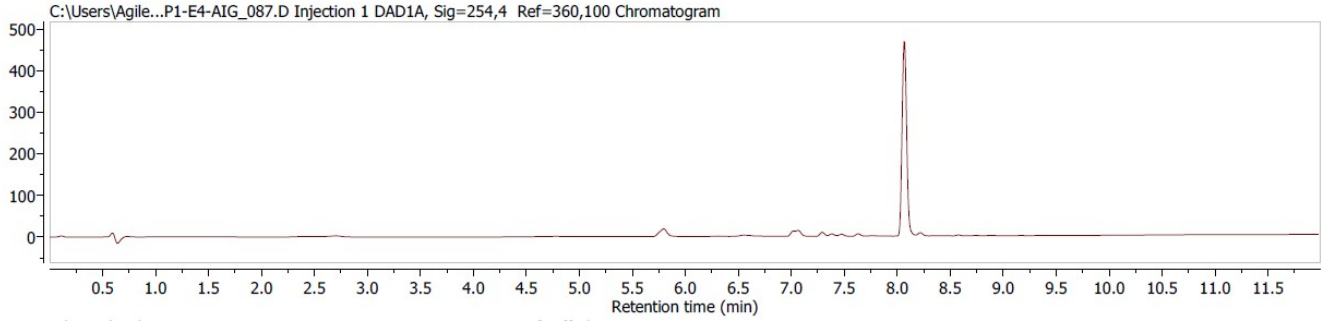
1-(3,5-dimethylisoxazol-4-yl)-1*H*-Pyrrole-2,5-dione (24 mg, 0.125 mmol) and 4-methoxy-*N,N*-dimethylaniline (132 mg, 0.875 mmol) dissolved in 1,4-dioxane (1.5 mL) were reacted according to general procedure **B** and the crude material was purified by flash column chromatography eluting 7:3 hexane/ethyl acetate to afford the product **15** as an orange oil (22 mg, 52%). δ_H (400 MHz, chloroform-d) 7.05 (1H, d, *J* 2.9), 6.81 (1H, dd, *J* 8.9 and 2.9), 6.69 (1H, d, *J* 8.9), 4.15 (1H, d, *J* 9.2), 3.79 (3H, s), 3.56 – 3.51 (2H, m), 2.99 (1H, dd, *J* 11.9 and 4.8), 2.79 (3H, s), 2.30 (3H, s) and 2.15 (3H, s). δ_C (100 MHz, chloroform-d) 177.1 (rot A+B), 174.8 (rot A+B), 168.4 (rot A), 166.2 (rot B), 157.8 (rot A), 153.6 (rot B), 143.0 (rot A+B), 135.0 (rot A+B), 119.9 (rot A+B), 115.9 (rot A+B), 114.6 (rot A+B), 113.6 (rot A+B), 109.7 (rot A+B), 55.9 (rot A+B), 52.1 (rot A+B), 44.2 (rot A+B), 43.1 (rot A+B), 39.8 (rot A+B), 11.5 (rot A+B) and 10.0 (rot A+B). LCMS (ESI): $C_{18}H_{19}N_3O_4$ requires [M+H], calculated 342.1, found 342.1.



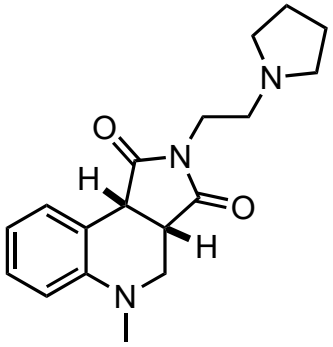
Ethyl 3-(5-methyl-1,3-dioxo-1,3,3a,4,5,9b-hexahydro-2*H*-pyrrolo[3,4-*c*]quinolin-2-yl)propanoate, **16**



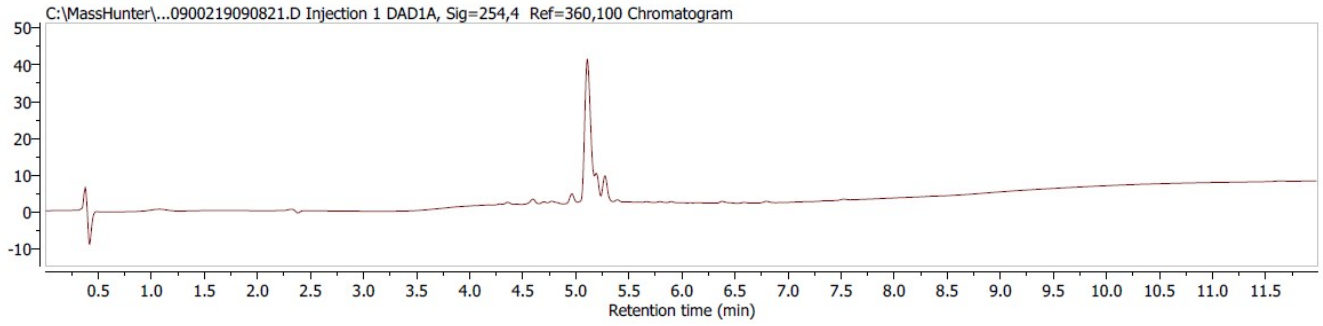
Ethyl 3-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)propanoate (50 mg , 0.25 mmol) and *N,N*-dimethylaniline (222 µL, 1.75 mmol) dissolved in 1,4-dioxane (3 mL) were reacted according to general procedure **B** and the crude material was purified by flash column chromatography eluting 7:3 hexane/ethyl acetate to afford the product **16** as an orange oil (45 mg, 57%). δ_H (400 MHz, chloroform-d) 7.46 (1H, d, *J* 7.5), 7.20 (1H, app. t, *J* 7.8), 6.88 (1H, app. t, *J* 7.4), 6.69 (1H, d, *J* 8.2), 4.05 (2H, q, *J* 7.2), 3.98 (1H, d, *J* 9.4), 3.83 – 3.73 (2H, m), 3.49 (1H, dd, *J* 11.5 and 2.4), 3.38 – 3.34 (1H, m), 3.03 (1H, dd, *J* 11.5 and 4.5), 2.79 (3H, s), 2.58 (2H, t, *J* 7.2) and 1.19 (3H, t, *J* 7.2). δ_C (100 MHz, chloroform-d) 178.4, 176.5, 170.7, 148.5, 130.3, 128.7, 119.7, 118.7, 112.6, 60.9, 50.7, 43.6, 42.1, 39.5, 35.1, 32.2 and 14.2. LCMS (ESI): $C_{17}H_{20}N_2O_4$ requires [M+H], calculated 317.2, found 317.2.



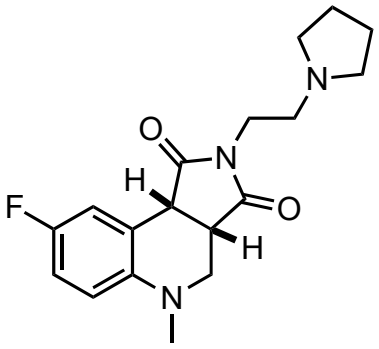
5-Methyl-2-(2-(pyrrolidin-1-yl)ethyl)-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione, **17**



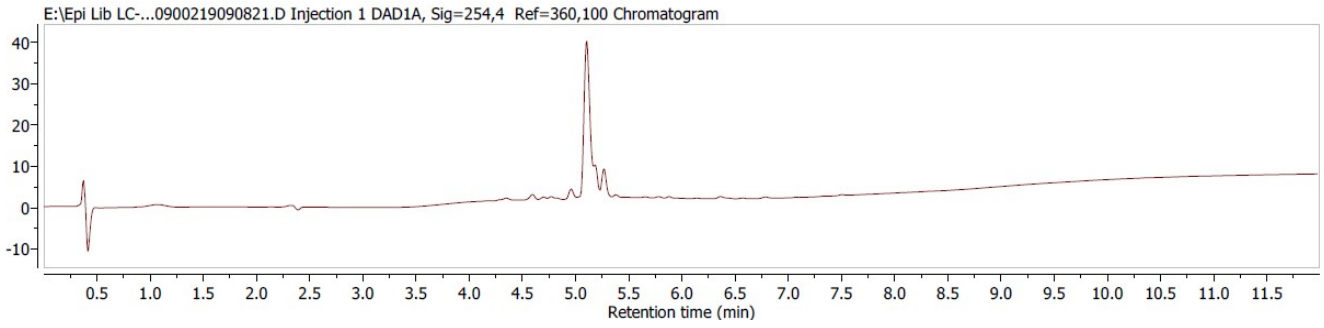
1-(2-(pyrrolidin-1-yl)ethyl)-1*H*-Pyrrole-2,5-dione (49 mg , 0.25 mmol) and *N,N*-dimethylaniline (222 µL, 1.75 mmol) dissolved in 1,4-dioxane (3 mL) were reacted according to general procedure **B** and the crude material was purified by flash column chromatography eluting 7:3 hexane/ethyl acetate to afford the product **17** as a light yellow oil (23 mg, 30%). δ_H (400 MHz, chloroform-d) 7.50 (1H, d, *J* 7.3), 7.20 (1H, td, *J* 7.2 and 1.5), 6.88 (1H, td, *J* 7.4 and 1.0), 6.69 (1H, d, *J* 7.3), 4.00 (1H, d, *J* 9.4), 3.68 – 3.60 (2H, m), 3.50 (1H, dd, *J* 11.5 and 2.7), 3.38 (1H, ddd, *J* 9.4, 4.5 and 2.6), 3.03 (1H, dd, *J* 11.5 and 4.5), 2.79 (3H, s), 2.65 – 2.61 (2H, m), 2.54 – 2.50 (4H, m) and 1.76 – 1.67 (4H, m). δ_C (100 MHz, chloroform-d) 178.8 (rot A+B), 176.9 (rot A+B), 148.5 (rot A+B), 134.3 (rot A), 130.3 (rot A+B), 129.6 (rot B), 128.6 (rot A+B), 119.6 (rot A), 119.0 (rot B), 112.5 (rot A+B), 54.1 (rot A+B), 52.9 (rot A+B), 50.7 (rot A+B), 43.6 (rot A+B), 42.1 (rot A+B), 39.5 (rot A+B), 38.4 (rot A+B) and 23.7 (rot A+B). LCMS (ESI): $C_{18}H_{23}N_3O_2$ requires [M+H], calculated 314.2, found 314.2.



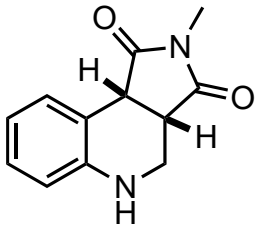
8-Fluoro-5-methyl-2-(2-(pyrrolidin-1-yl)ethyl)-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione, **18**



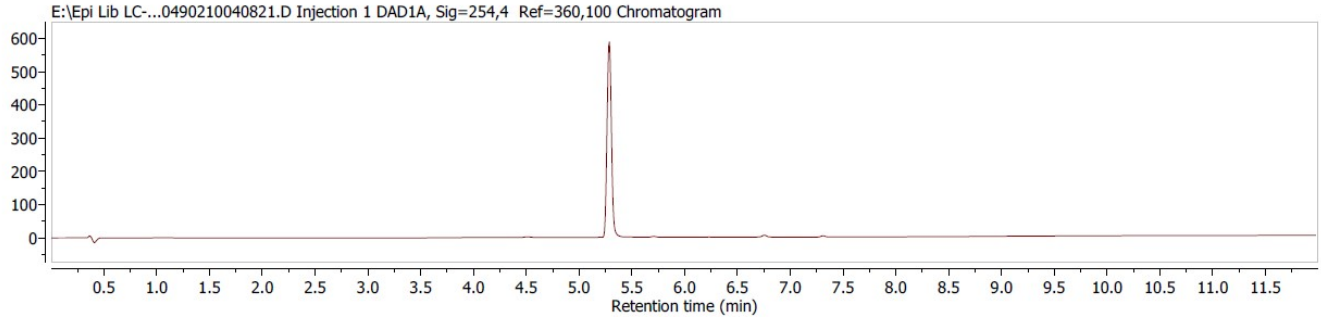
1-(2-(pyrrolidin-1-yl)ethyl)-1*H*-Pyrrole-2,5-dione (25 mg , 0.125 mmol) and 4-fluoro-*N,N*-dimethylaniline (122 mg, 0.875 mmol) dissolved in 1,4-dioxane (1.5 mL) were reacted according to general procedure **B** and the crude material was purified by flash column chromatography eluting 7:3 hexane/ethyl acetate to afford the product **18** as a light yellow oil (20 mg, 48%). δ_H (400 MHz, chloroform-d) 7.22 (1H, dd, *J* 8.8 and 3.0), 6.90 (1H, td, *J* 8.6 and 2.9), 6.60 (1H, dd, *J* 9.0 and 4.6), 3.96 (1H, d, *J* 9.4), 3.64 (2H, q, *J* 13.4 and 6.8), 3.47 (1H, dd, *J* 11.4 and 2.7), 3.39 – 3.35 (1H, m), 2.98 (1H, dd, *J* 11.4 and 4.5), 2.76 (3H, s), 2.64 (2H, t, *J* 6.6), 2.51 (4H, broad s) and 1.69 (4H, broad s). δ_C (100 MHz, chloroform-d) 178.5, 176.3, 156.7 (d, $J_{C\text{-}F}$ 236.9), 145.0 (d, $J_{C\text{-}F}$ 2.0), 120.5 (d, $J_{C\text{-}F}$ 7.6), 117.0 (d, $J_{C\text{-}F}$ 23.1), 115.0 (d, $J_{C\text{-}F}$ 18.8), 113.3 (d, $J_{C\text{-}F}$ 7.6), 54.1, 52.8, 51.0, 43.4, 42.2, 42.2, 39.8, 38.4 and 23.7. LCMS (ESI): $C_{18}H_{22}FN_3O_2$ requires [M+H], calculated 332.2, found 332.2.



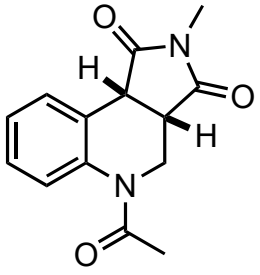
2-Methyl-3a,4,5,9b-tetrahydro-1H-pyrrolo[3,4-*c*]quinoline-1,3(*2H*)-dione, **19**



Portions of 10% Pd/C (112 mg) were added to a stirred solution of compound **5** (170 mg, 0.56 mmol) and ammonium formate (710 mg, 11.2 mmol) in methanol (5 mL) and THF (5 mL). The reaction was heated to reflux for 6 hours, then cooled to room temperature and filtered through celite (150 mL methanol). The crude material was subsequently dry loaded onto silica (5g) and purified by column chromatography eluting 6:4 hexane/ethyl acetate to afford compound **19** as a white solid (100 mg, 83%). δ_H (400 MHz, DMSO-d^6) 7.29 (1H, d, *J* 7.4), 6.98 (1H, td, *J* 7.7 and 1.4), 6.68 (1H, td, *J* 7.4 and 1.2), 6.61 (1H, dd, *J* 8.0 and 1.0), 5.60 (1H, s), 4.00 (1H, d, *J* 8.9), 3.45 – 3.37 (2H, m), 2.99 (1H, dd, *J* 10.9 and 4.3) and 2.81 (3H, s). δ_C (100 MHz, DMSO-d^6) 178.8, 177.1, 147.1, 130.1, 127.5, 118.1, 117.0, 115.1, 42.8, 40.9, 40.6 and 24.7. LCMS (ESI): $C_{12}H_{12}N_2O_2$ requires [M+H], calculated 217.1, found 217.1.

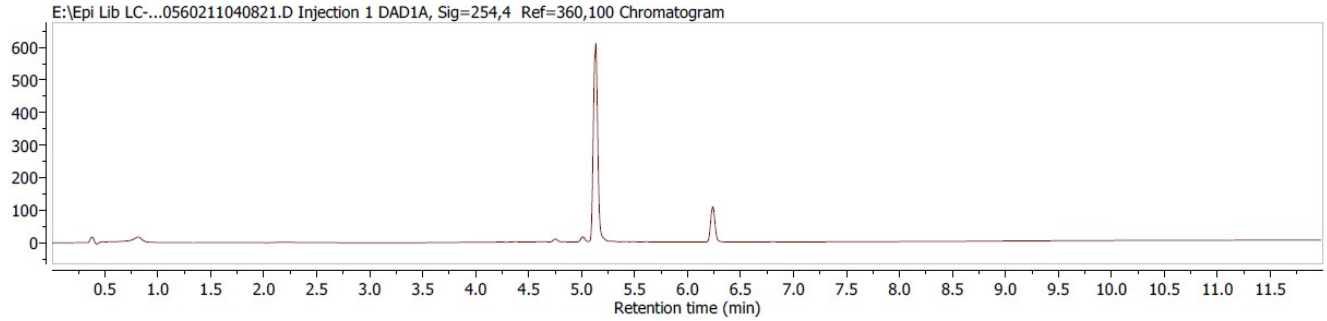


5-Acetyl-2-methyl-3a,4,5,9b-tetrahydro-1H-pyrrolo[3,4-*c*]quinoline-1,3(*2H*)-dione, **20**

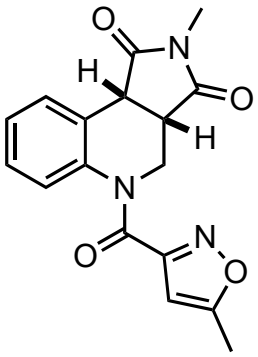


Acetyl chloride (4 uL, 0.48 mmol) was added to a stirred solution of compound **19** (10 mg, 0.046 mmol) in CH_2Cl_2 (0.5 mL) and stirred for 1 hour. The solvent was then removed under reduced pressure and the

crude residue was purified by column chromatography eluting 7:3 hexane/ethyl acetate to afford **20** as a yellow solid (10 mg, 84%). δ_H (400 MHz, chloroform-d) 7.62 (1H, d, *J* 6.9), 7.37 – 7.28 (3H, m), 4.85 (1H, m), 4.09 (1H, d, *J* 8.9), 3.52 – 3.38 (2H, m), 3.02 (3H, m) and 2.22 (3H, m). δ_C (100 MHz, chloroform-d) 177.3 (rot A+B), 175.5 (rot A+B), 169.2 (rot A+B), 147.5 (rot A+B), 130.5 (rot A), 130.4 (rot B), 128.3 (rot A), 128.2 (rot B), 126.9 (rot A), 126.8 (rot B), 120.1 (rot A+B), 115.7 (rot A+B), 43.8 (rot A), 43.3 (rot B), 42.7 (rot A+B), 41.5 (rot A), 41.4 (rot B), 29.7 (rot A+B) and 25.6 (rot A+B). LCMS (ESI): $C_{14}H_{14}N_2O_3$ requires [M+H], calculated 259.1, found 259.1.

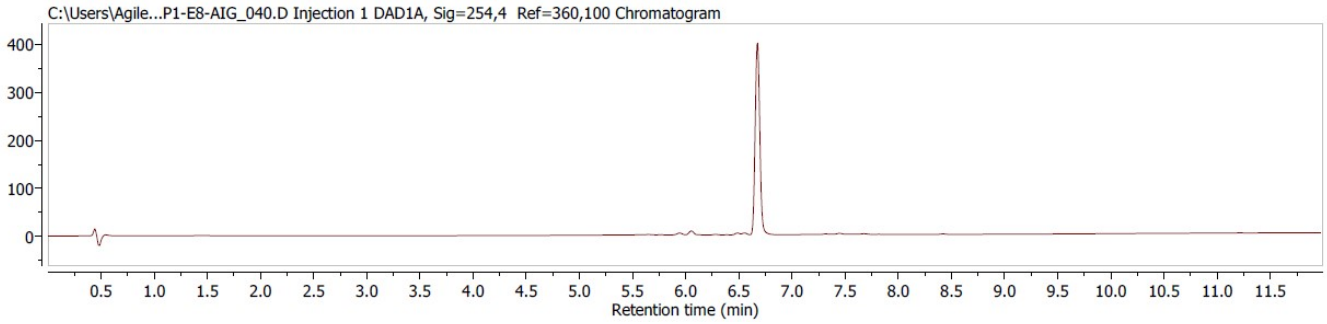


2-Methyl-5-(5-methylisoxazole-3-carbonyl)-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione, **21**

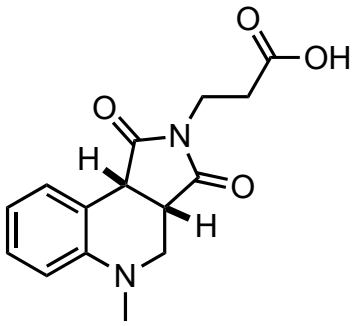


5-Methylisoxazole-3-carboxylic acid (5.8 mg, 0.046 mmol) and *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (11.5 mg, 0.06 mmol) were added sequentially to a stirred solution of compound **19** (10 mg, 0.046 mmol) and DMAP (1 mg, 0.01 mmol) in CH2Cl2 (1 mL). After 18 hours, the solvent was removed under reduced pressure and the crude residue was purified by column chromatography eluting 6:4 hexane/ethyl acetate to afford the product **21** as a yellow solid (11 mg, 74%). δ_H (400 MHz, chloroform-d) 7.66 – 7.63 (1H, m), 7.28 – 7.25 (3H, m), 6.26 (1H, broad s), 5.02 (1H, d, *J* 8.4), 4.14 – 4.11 (1H, m), 3.70 – 3.50 (2H, m), 2.98 (3H, s), and 2.46 (3H, broad s). δ_C (100 MHz,

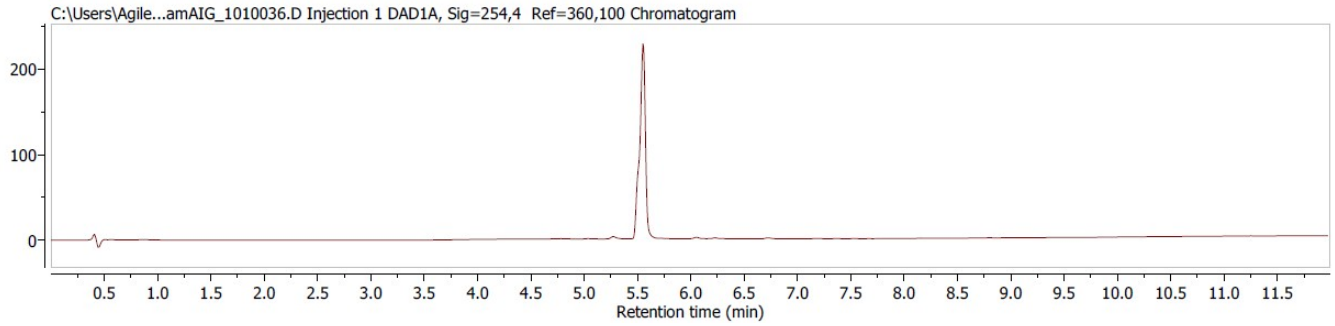
chloroform-d) 176.7 (rot A+B), 175.7 (rot A+B), 170.5 (rot A+B), 166.3 (rot A+B), 155.5 (rot A+B), 144.3 (rot A+B), 135.0 (rot A+B), 130.4 (rot A+B), 128.2 (rot A+B), 126.9(rot A+B), 124.9 (rot A+B), 116.0 (rot A+B), 60.5 (rot A+B), 43.6 (rot A), 36.7 (rot B), 25.7 (rot A+B), 24.8 (rot A), 21.2 (rot B), 14.3 (rot A) and 12.4 (rot B). LCMS (ESI): $C_{17}H_{15}N_3O_4$ requires [M+H], calculated 326.1, found 326.1.



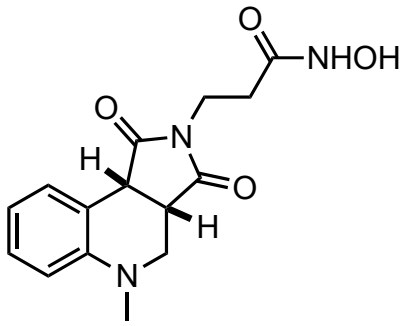
3-(5-Methyl-1,3-dioxo-1,3,3a,4,5,9b-hexahydro-2*H*-pyrrolo[3,4-*c*]quinolin-2-yl)propanoic acid, **22**



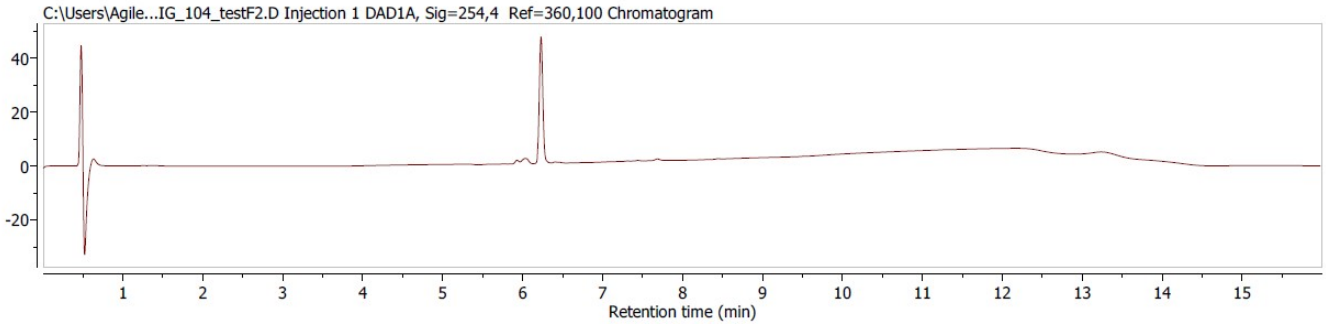
LiOH (15 mg, 0.64 mmol) was added to a solution of compound **16** (100 mg, 0.32 mmol) in 1:1 tetrahydrofuran/water (4 mL) and stirred for 2 hours. The reaction mixture was then acidified to pH 3 with 1 N HCl, extracted with ethyl acetate (3 x 30 mL), the organics dried with $MgSO_4$, and the solvent removed under vacuum to give compound **22** as a yellow waxy solid (57 mg, 62%). δ_H (400 MHz, 4:1 chloroform-d/methanol-d^4) 7.38 – 7.24 (1H, m), 7.10 – 6.97 (1H, m), 6.59 – 6.55 (2H, m), 3.94 (1H, broad s), 3.72 – 3.57 (2H, m), 3.35 – 3.24 3H, m), 2.87 (3H, s), and 2.49 – 2.36 (2H, m). δ_C (100 MHz, 4:1 chloroform-d/methanol-d^4) 174.4, 174.0, 173.0, 145.3, 129.0, 128.9, 118.4, 116.1, 111.3, 46.2, 40.3, 38.2, 34.9, 33.5 and 29.4. LCMS (ESI): $C_{15}H_{16}N_2O_4$ requires [M-H], calculated 287.1, found 287.1.



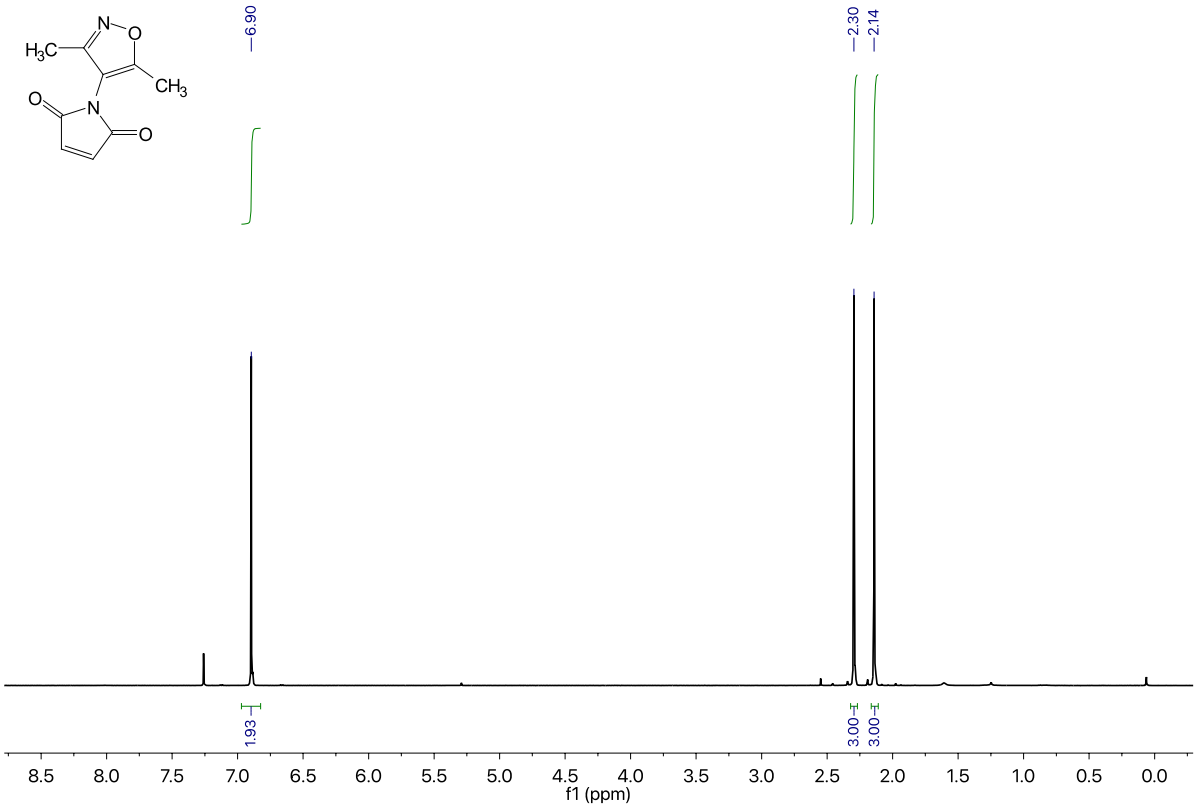
N-Hydroxy-3-(5-methyl-1,3-dioxo-1,3,3a,4,5,9b-hexahydro-2H-pyrrolo[3,4-*c*]quinolin-2-yl)propanamide, **23**



Portions of 1-hydroxybenzotriazole hydrate (14 mg, 0.09) and 1-(3-dimethylamino-propyl)-3-ethyl-carboiimide hydrochloride (21 mg, 0.11 mmol) were added to a stirred solution of compound **22** (20 mg, 0.07 mmol) in anhydrous DMF (1 mL). After 1 hour, hydroxylamine hydrochloride (5.5 mg, 0.08 mmol) and triethylamine (11 μL, 0.08 mmol) were added and the reaction left overnight. The reaction was then diluted with EtOAc (5 mL), neutralized to pH 7 using 1N HCl, diluted with brine (10 mL) and the aqueous layer was extracted with EtOAc (3 x 30 mL). The organics were collected, dried with $MgSO_4$, and the solvent removed under vacuum. The crude residue was purified by reverse-phase HPLC eluting a 95:5 to 5:95 gradient of water/acetonitrile to afford **23** as a a colourless oil (3.9 mg, 18%). δ_H (600 MHz, DMSO-d^6) 7.35 (1H, d, *J* 7.2), 7.15 (1H, app. t, *J* 7.5), 6.82 (1H, app. t, *J* 7.5), 6.71 (1H, d, *J* 8.2), 4.45 (1H, broad s), 4.06 (1H, d, *J* 9.3), 3.50 – 3.46 (3H, m), 2.94 – 2.90 (1H, m), 2.71 (3H, m) and 2.26 – 2.13 (2H, m). δ_C (150 MHz, DMSO-d^6) 178.4 (rot A+B), 148.5 (rot A+B), 130.1 (rot A+B), 128.0 (rot A+B), 119.4 (rot A+B), 118.8 (rot A+B), 112.4 (rot A+B), 62.9 (rot A), 62.8 (rot B), 50.4 (rot A), 50.4 (rot B) 42.6 (rot A), 41.3 (rot B), 40.4 (rot A), 40.1 (rot B), 35.6 (rot A), 35.6 (rot B), 25.7 (rot A) and 25.4 (rot B). Pyrrolidine-dione carbonyls not observed. LCMS (ESI): $C_{15}H_{17}N_3O_4$ requires [M+H], calculated 304.1, found 304.1.


C:\Users\Agile...IG_104_testF2.D Injection 1 DAD1A, Sig=254,4 Ref=360,100 Chromatogram
40
20
0
-20
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
Retention time (min)

Spectra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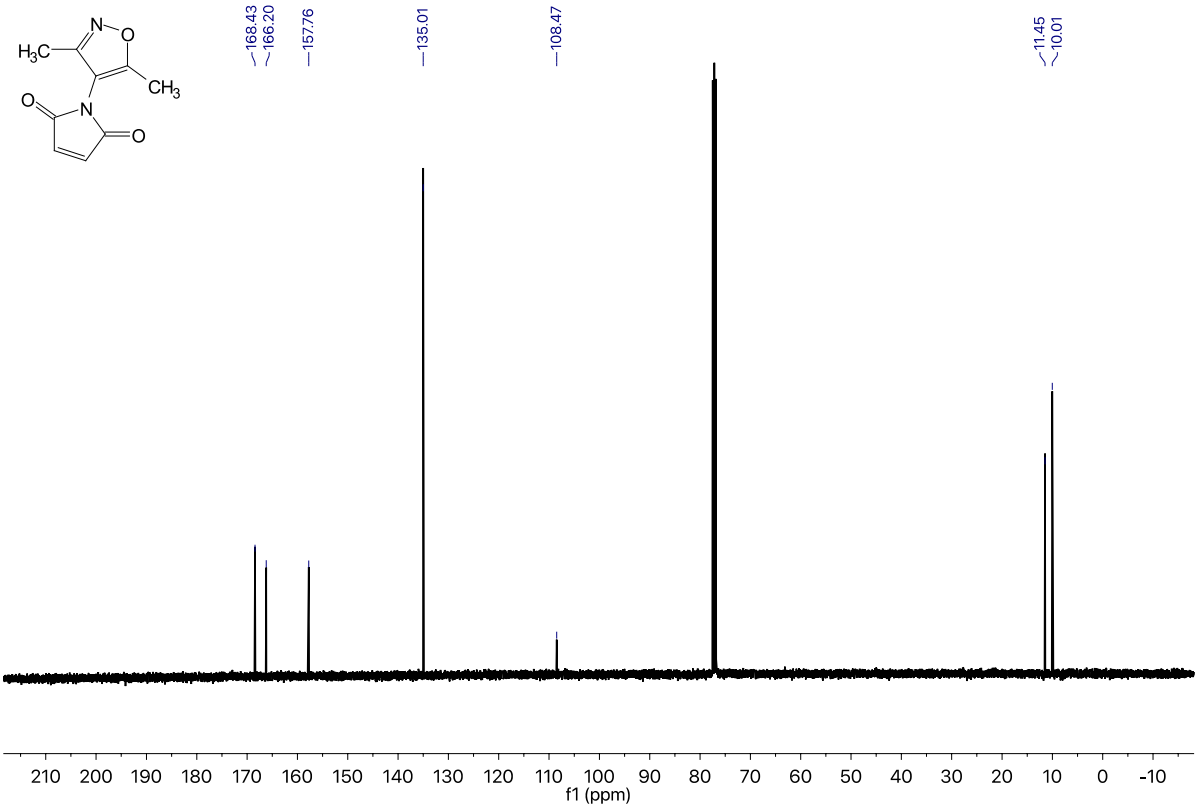
2.30
2.14
1.93
3.00
3.00
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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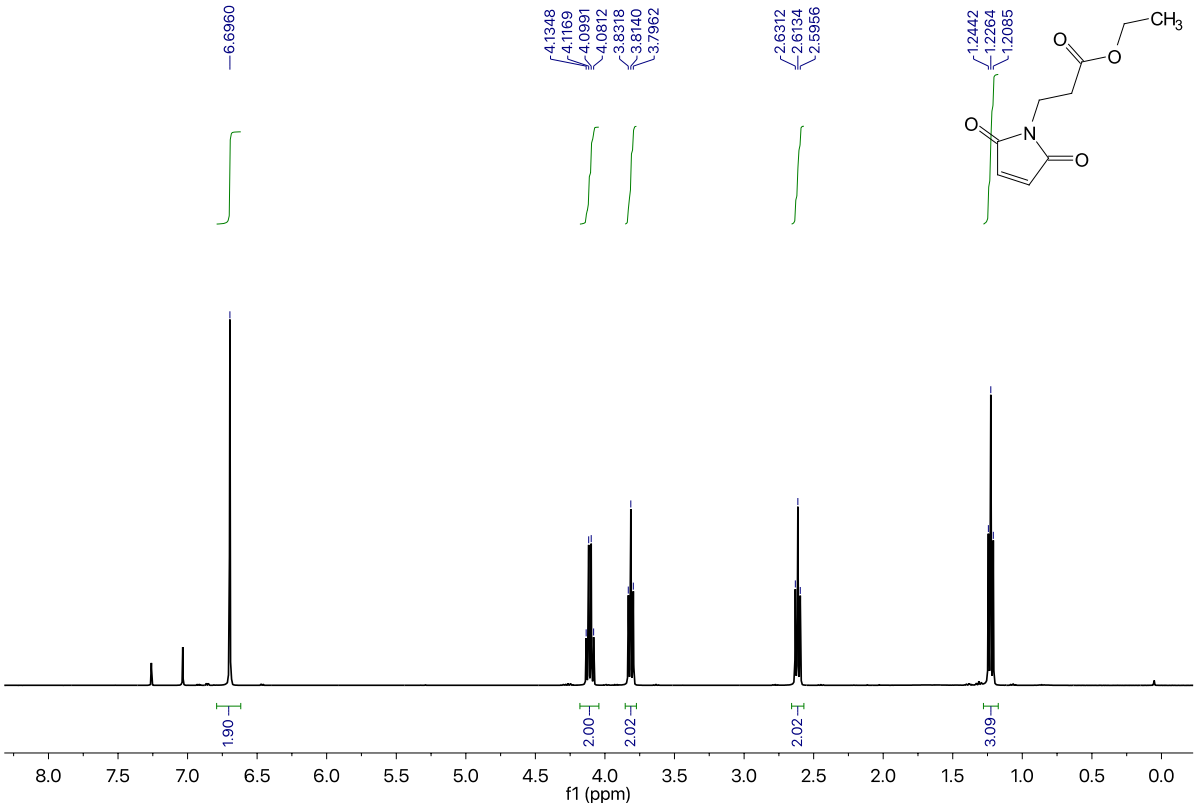
166.20
157.76
135.01
108.47
11.45
10.01
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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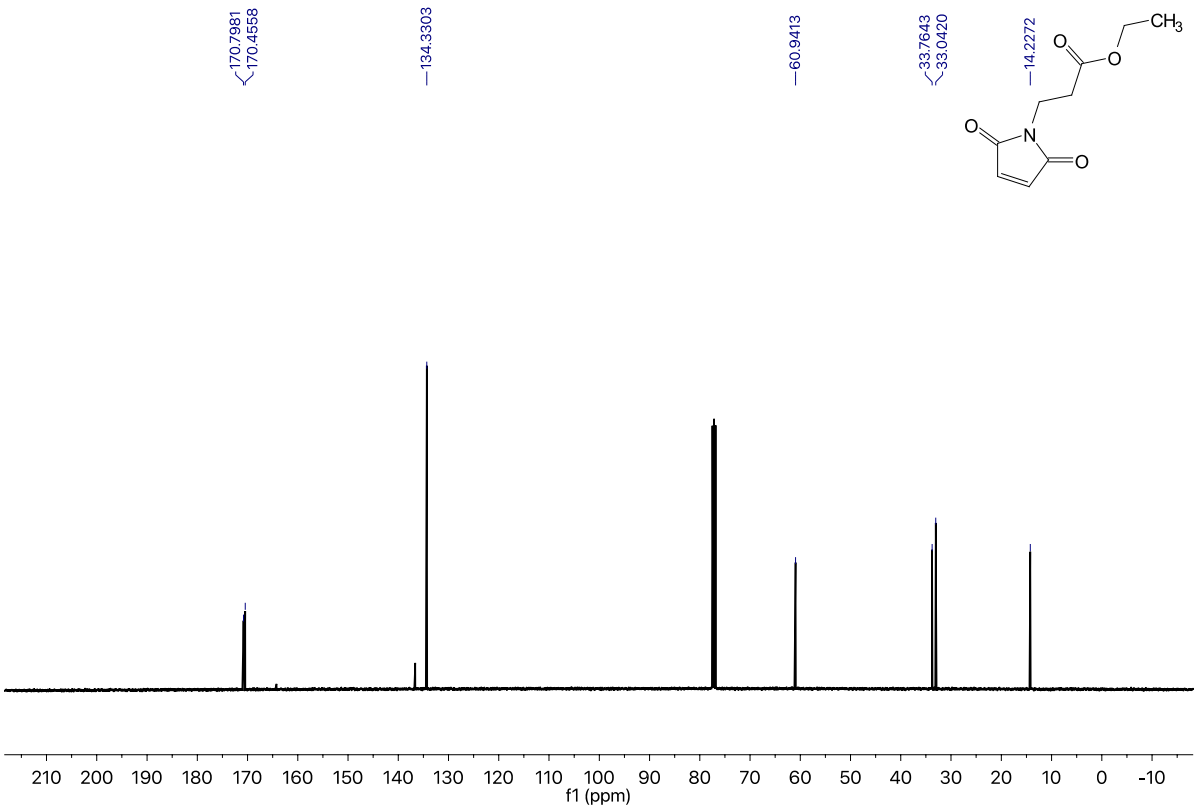
4.1169
4.0991
4.0812
3.8318
3.8140
3.7962
2.6312
2.6134
2.5956
1.2442
1.2264
1.2085
CH3
O
O
N
O
O
1.90
2.00
2.02
2.02
3.09
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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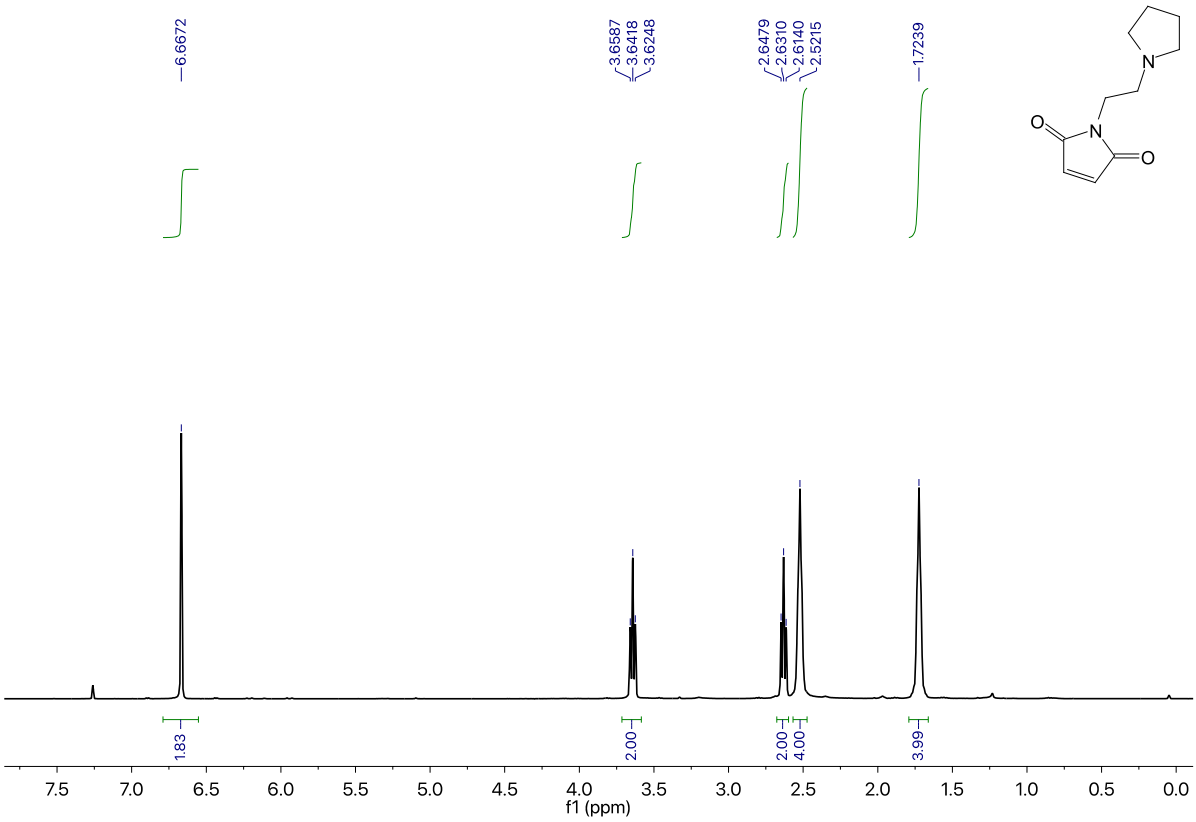
170.4558
134.3303
60.9413
33.7643
33.0420
14.2272
CH3
O
O
N
O
O
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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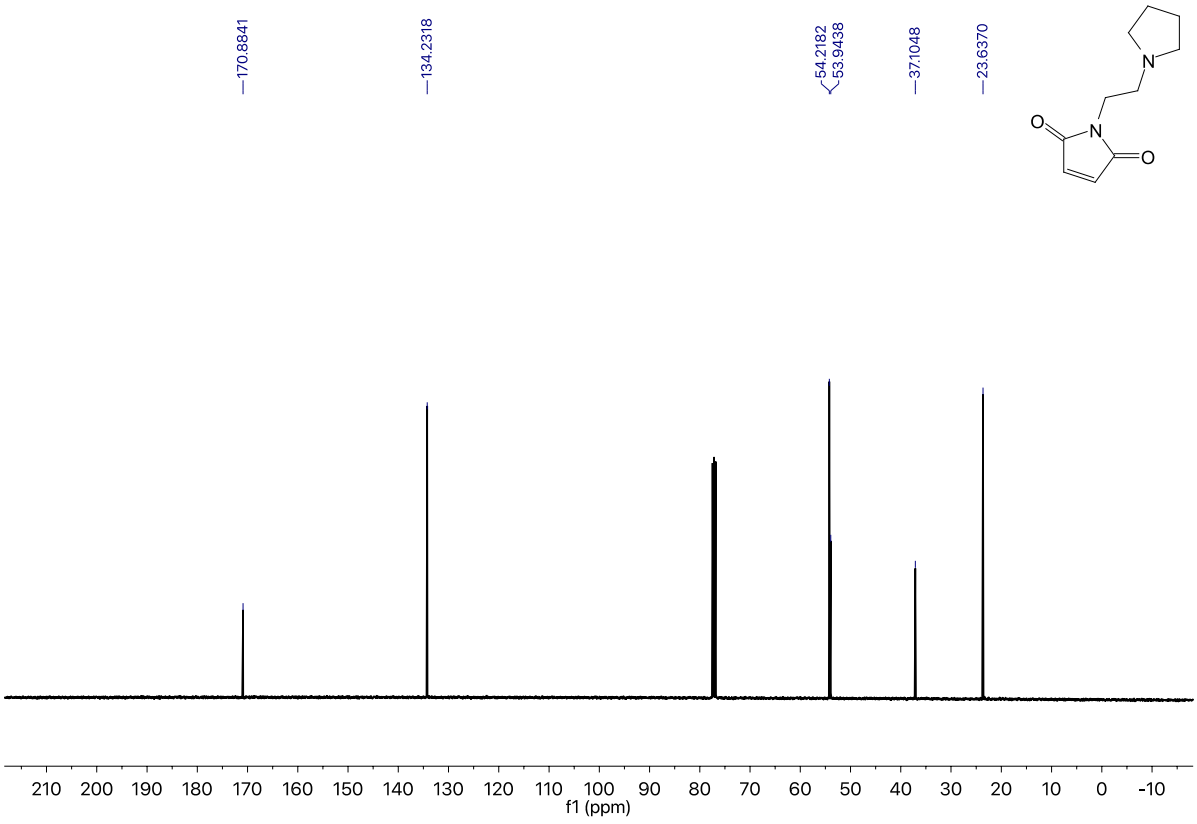
3.6248
2.6479
2.6310
2.6140
2.5215
1.7239
1.83
2.00
2.00
4.00
3.99
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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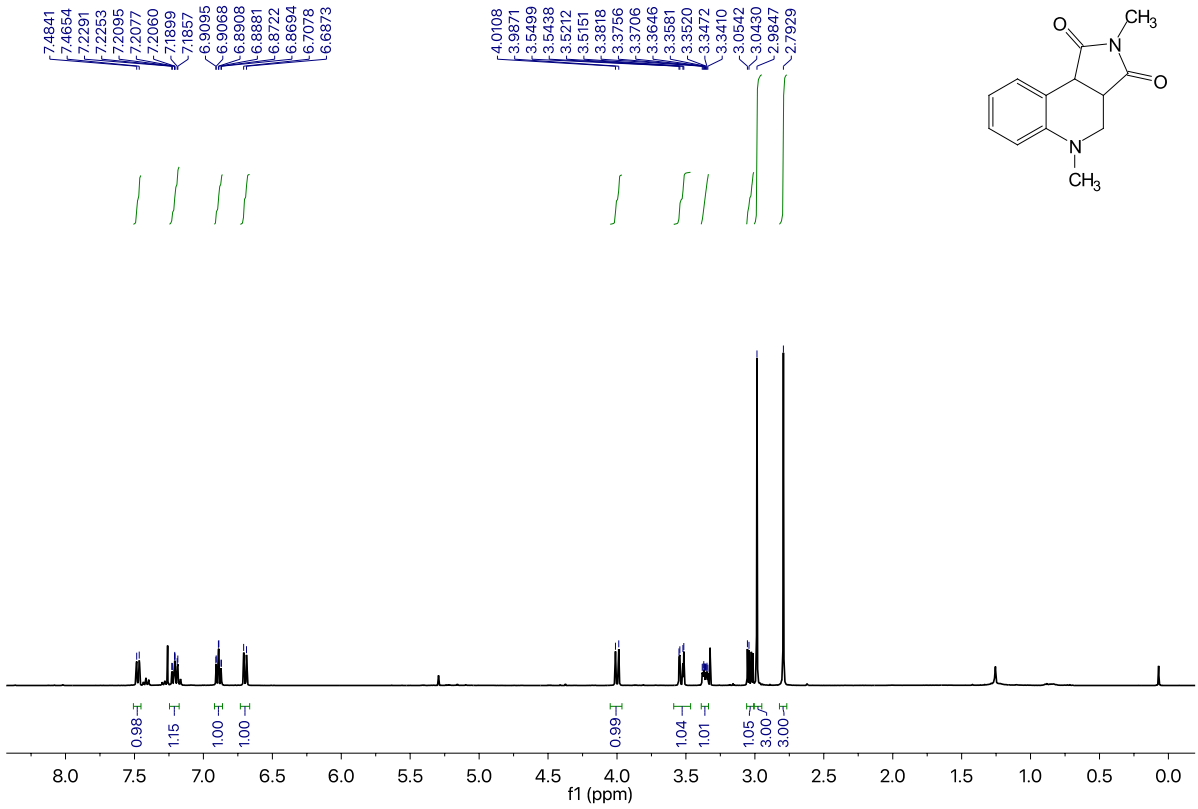
37.1048
23.6370
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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7.2077
7.2060
7.1899
7.1857
6.9095
6.9068
6.8908
6.8881
6.8722
6.8694
6.7078
6.6873
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3.9871
3.5499
3.5438
3.5212
3.5151
3.3818
3.3756
3.3706
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3.3520
3.3472
3.3410
3.0542
3.0430
2.9847
2.7929
O
N
CH3
O
N
CH3
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1.15
1.00
1.00
0.99
1.04
1.01
1.05
3.00
3.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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3.5
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2.5
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1.5
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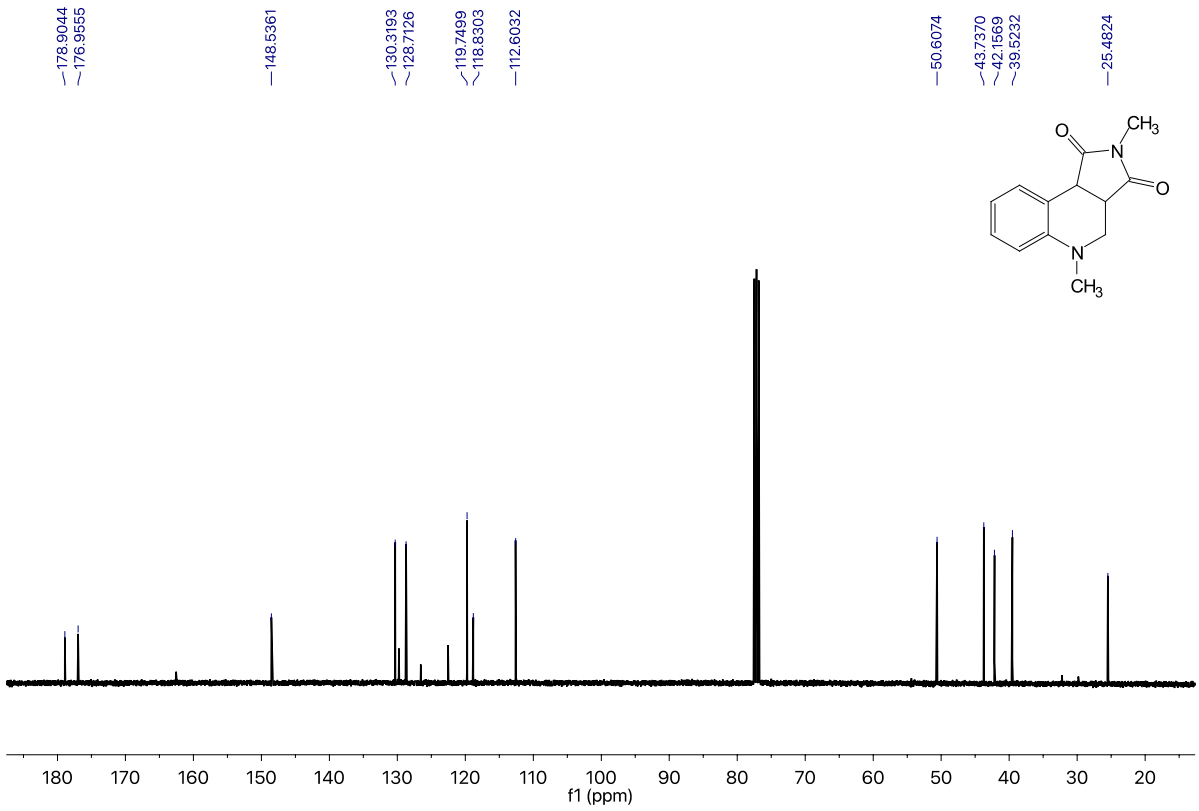
0.5
0.0
f1 (ppm)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43.7370
42.1569
39.5232
25.4824
O
N
CH3
O
N
CH3
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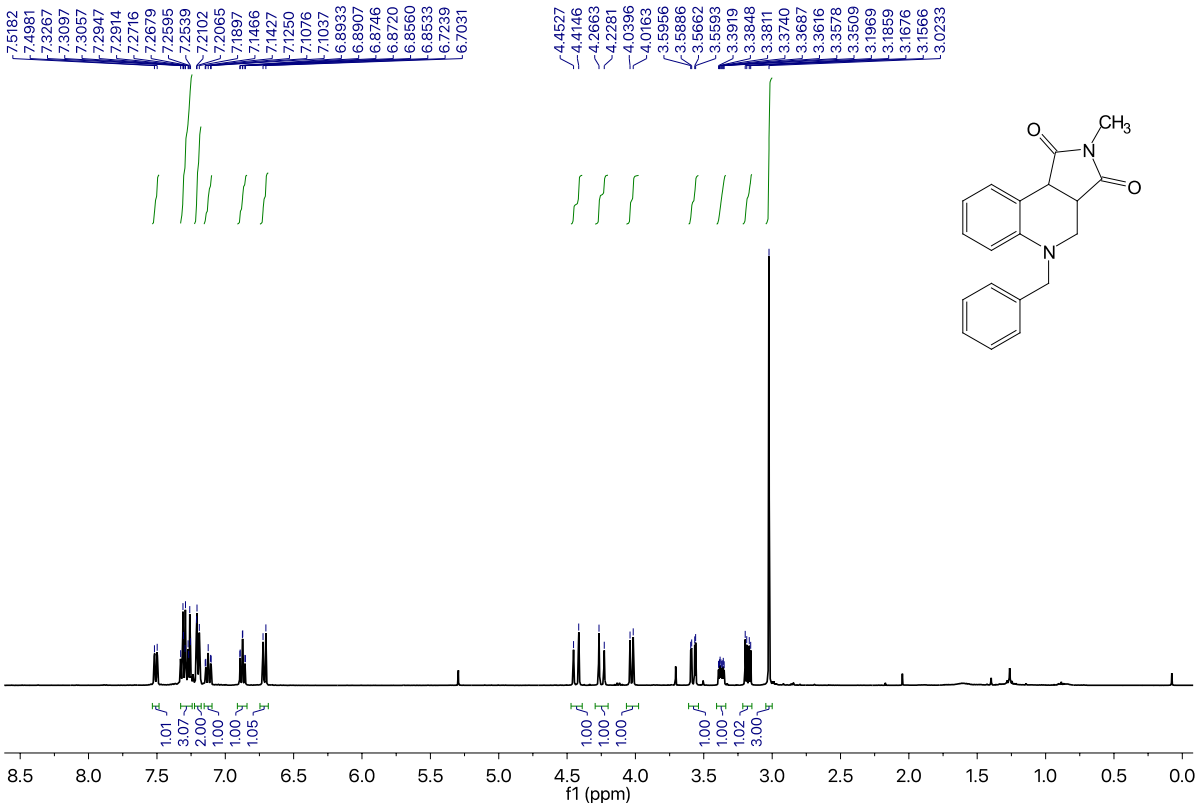
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)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7.1897
7.1466
7.1427
7.1250
7.1076
7.1037
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6.8720
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3.5886
3.5662
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3.3811
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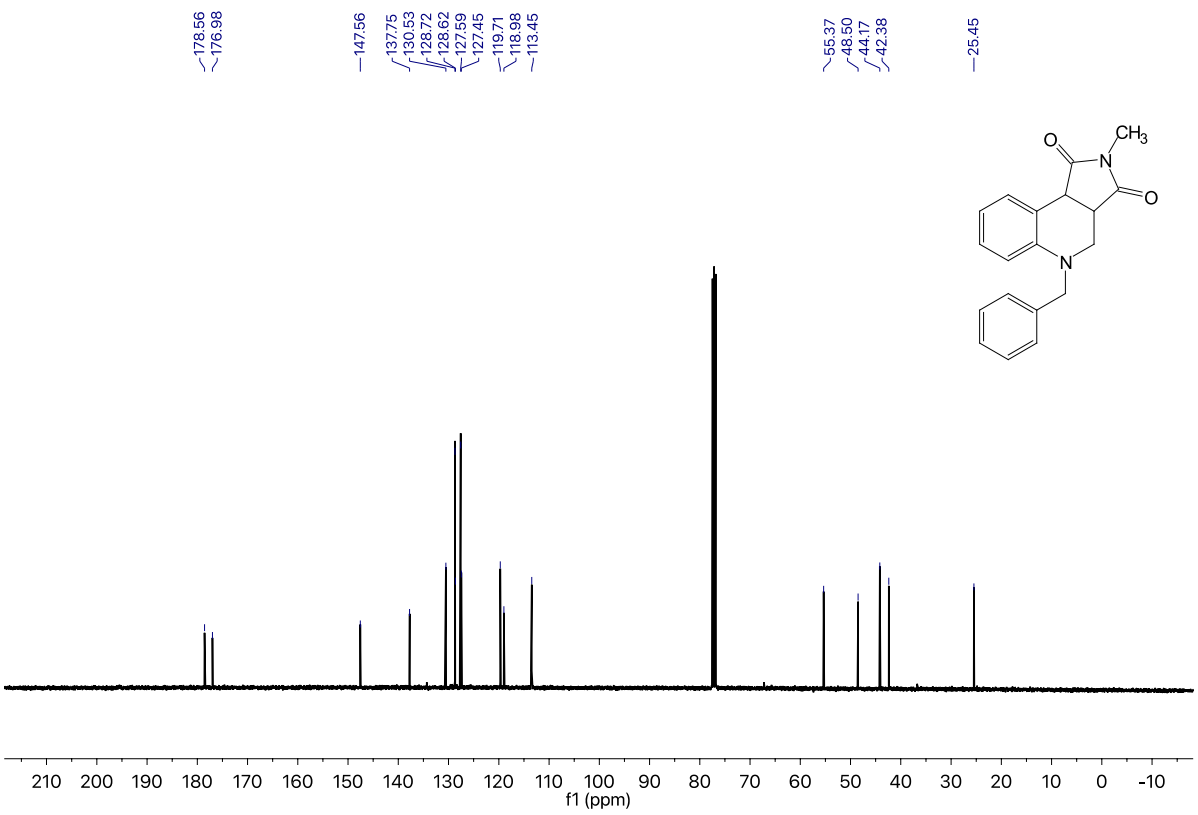
f1 (ppm)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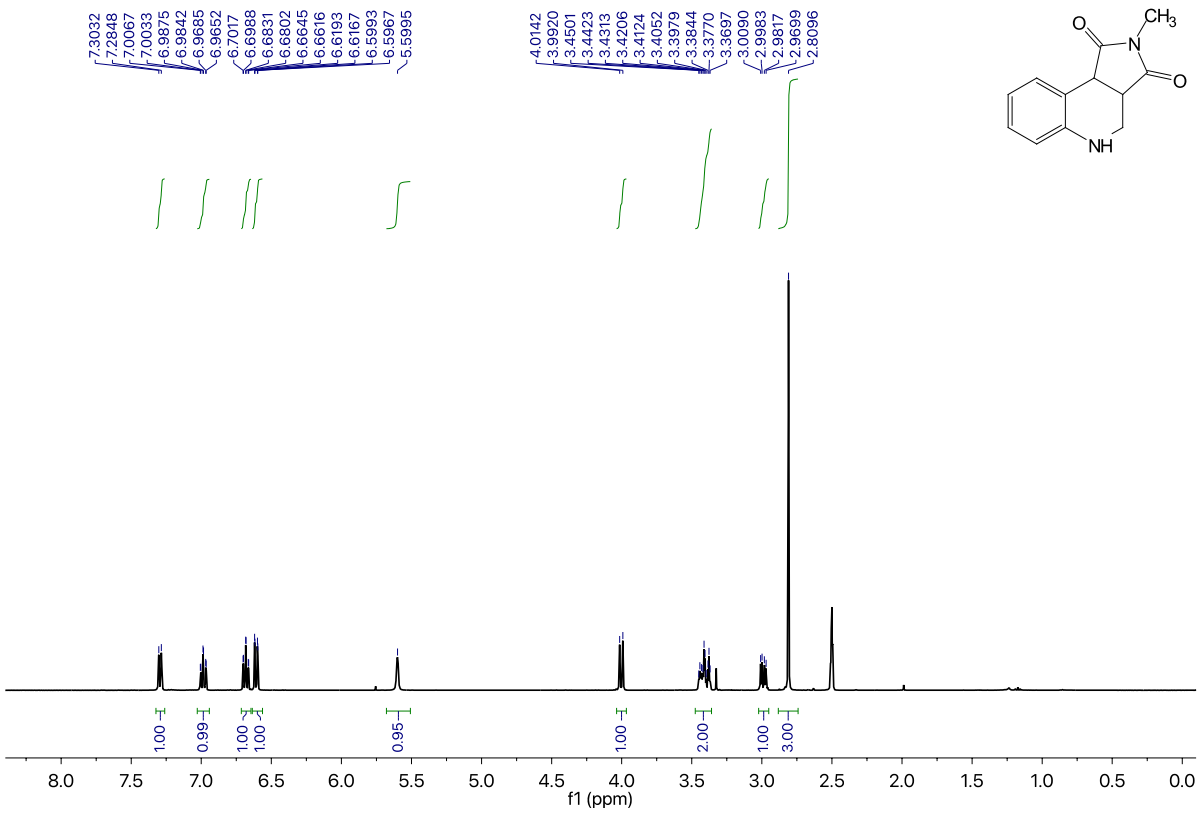
44.17
42.38
25.45
f1 (ppm)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6.6831
6.6802
6.6645
6.6616
6.6193
6.6167
6.5993
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3.3979
3.3844
3.3770
3.3697
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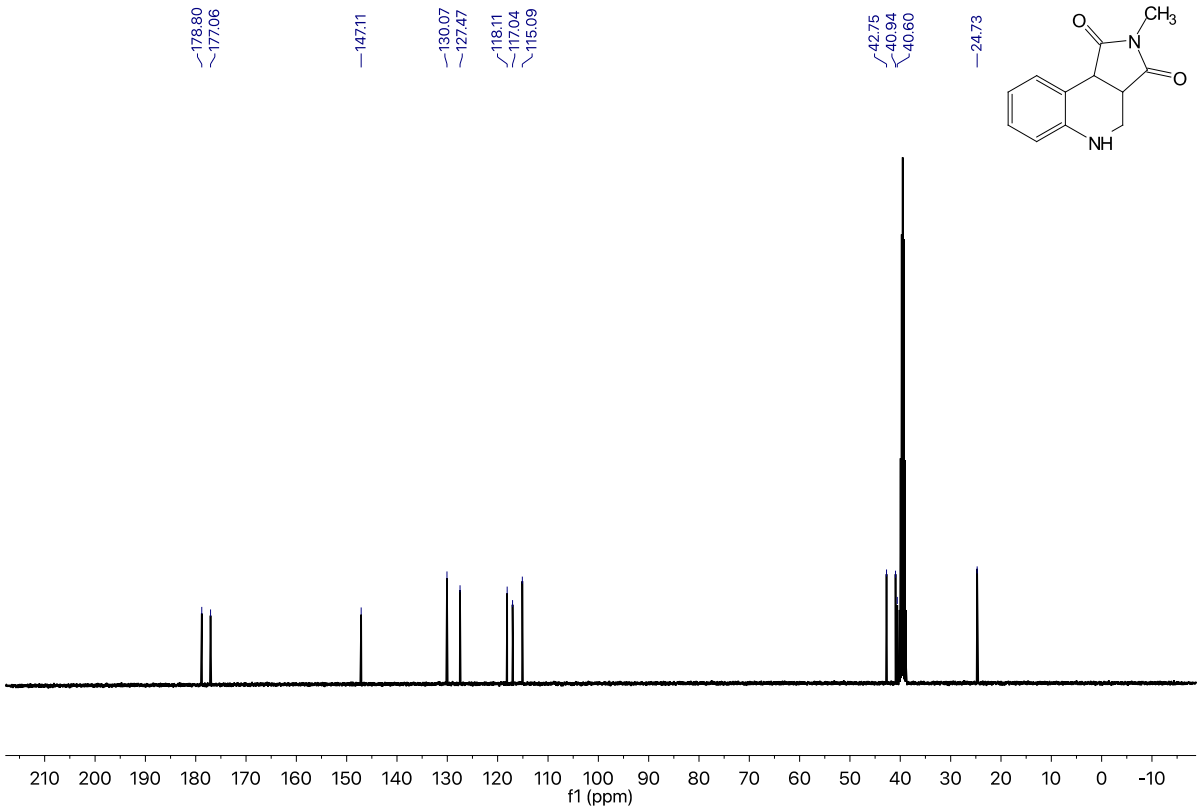
f1 (ppm)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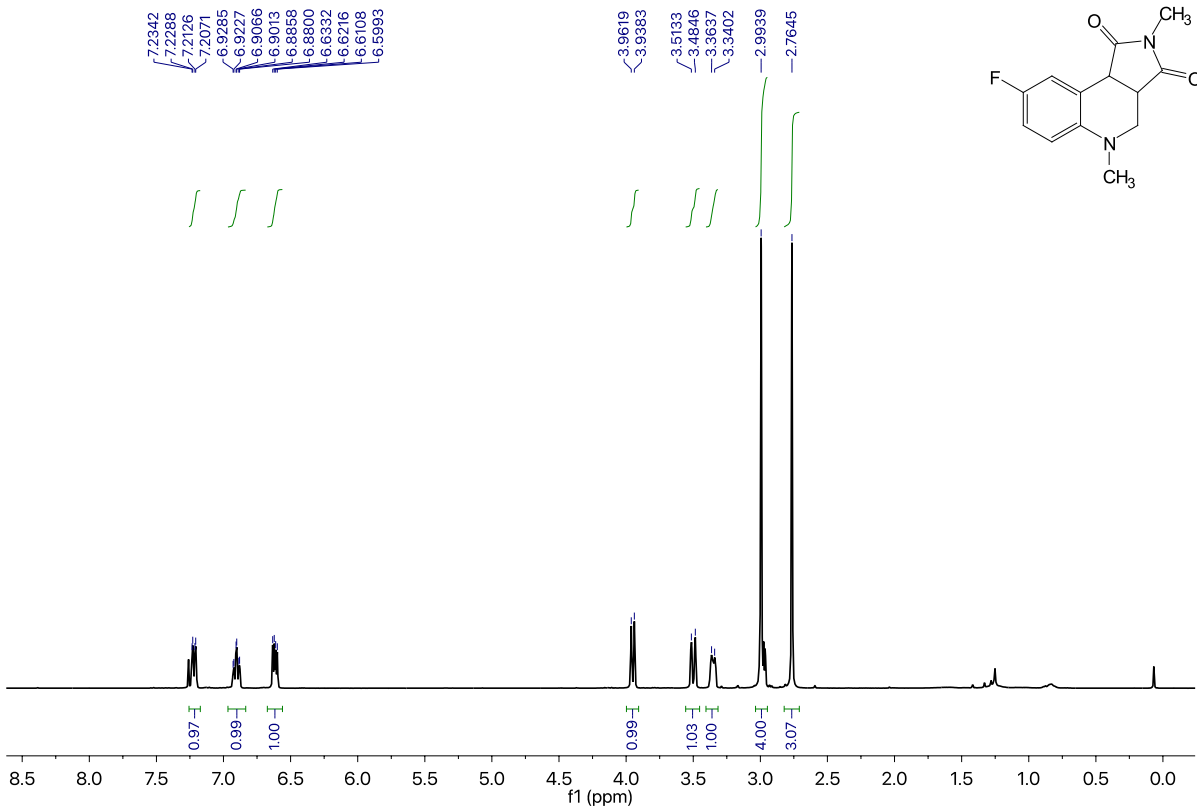
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6.5993
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3.9383
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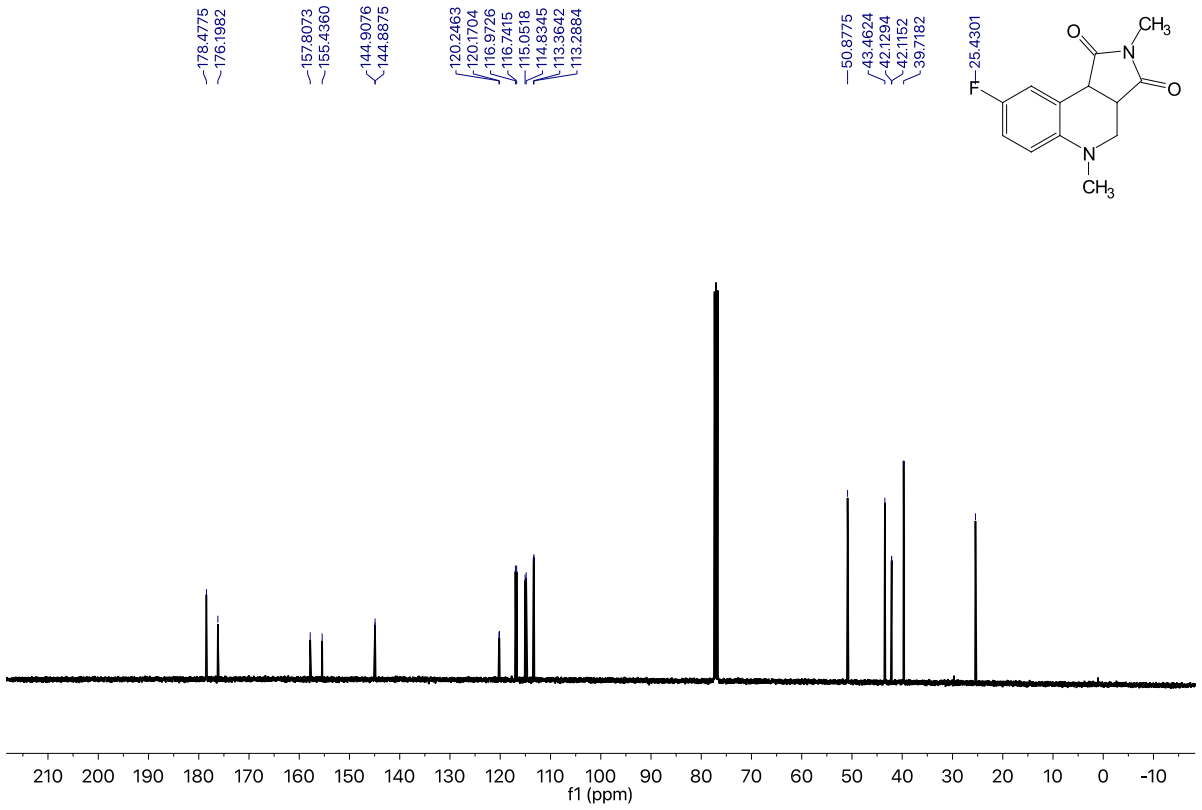
f1 (ppm)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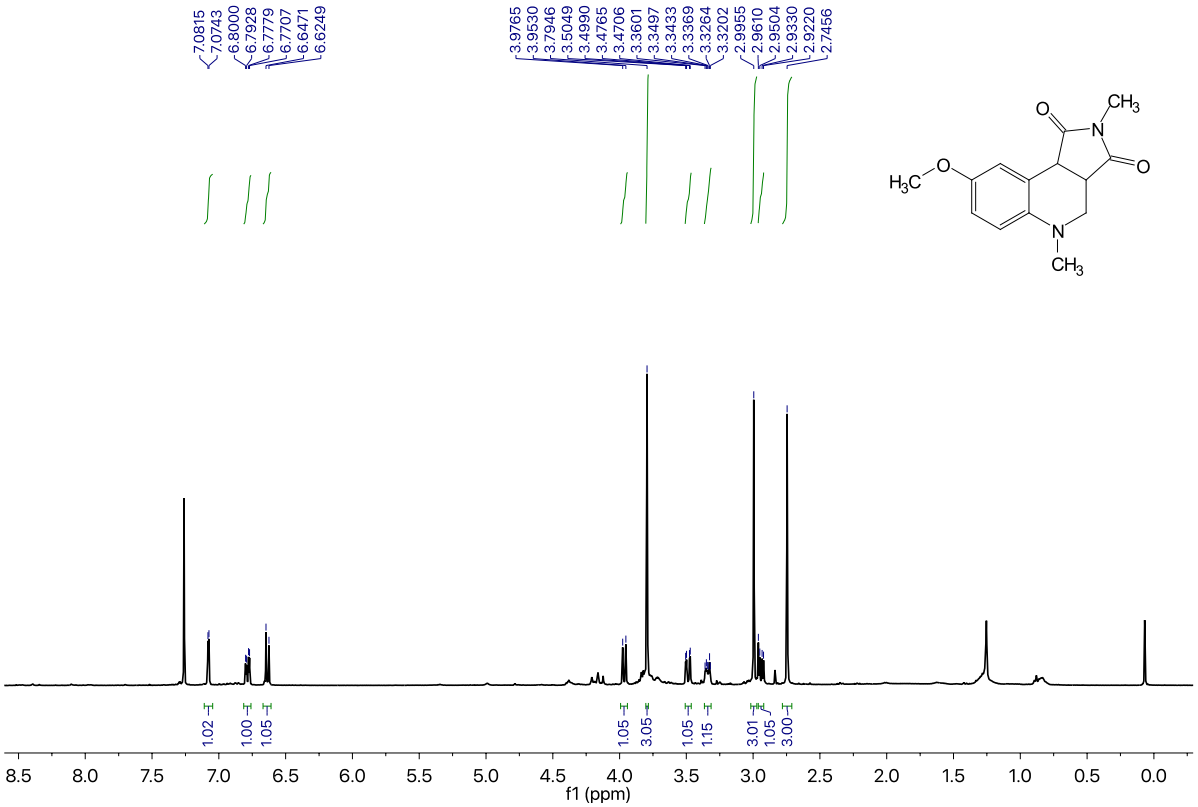
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2.9610
2.9504
2.9330
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3.00
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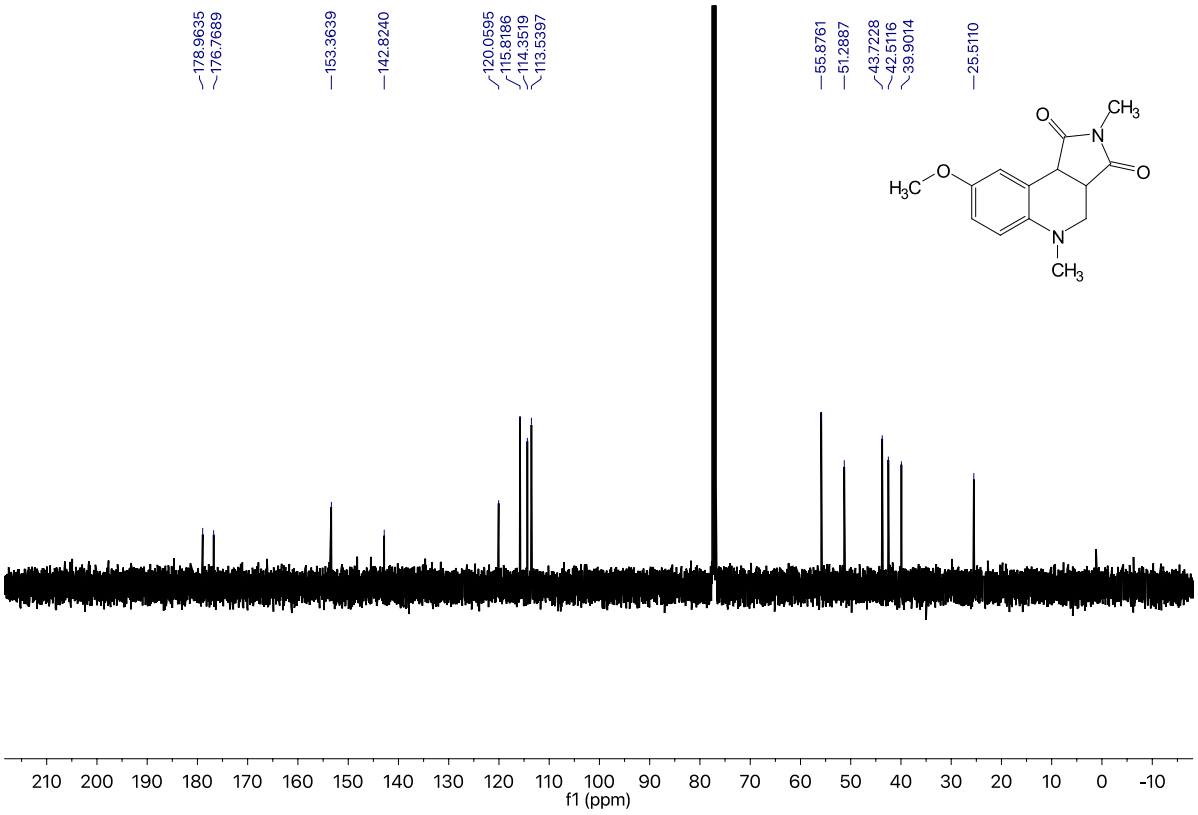
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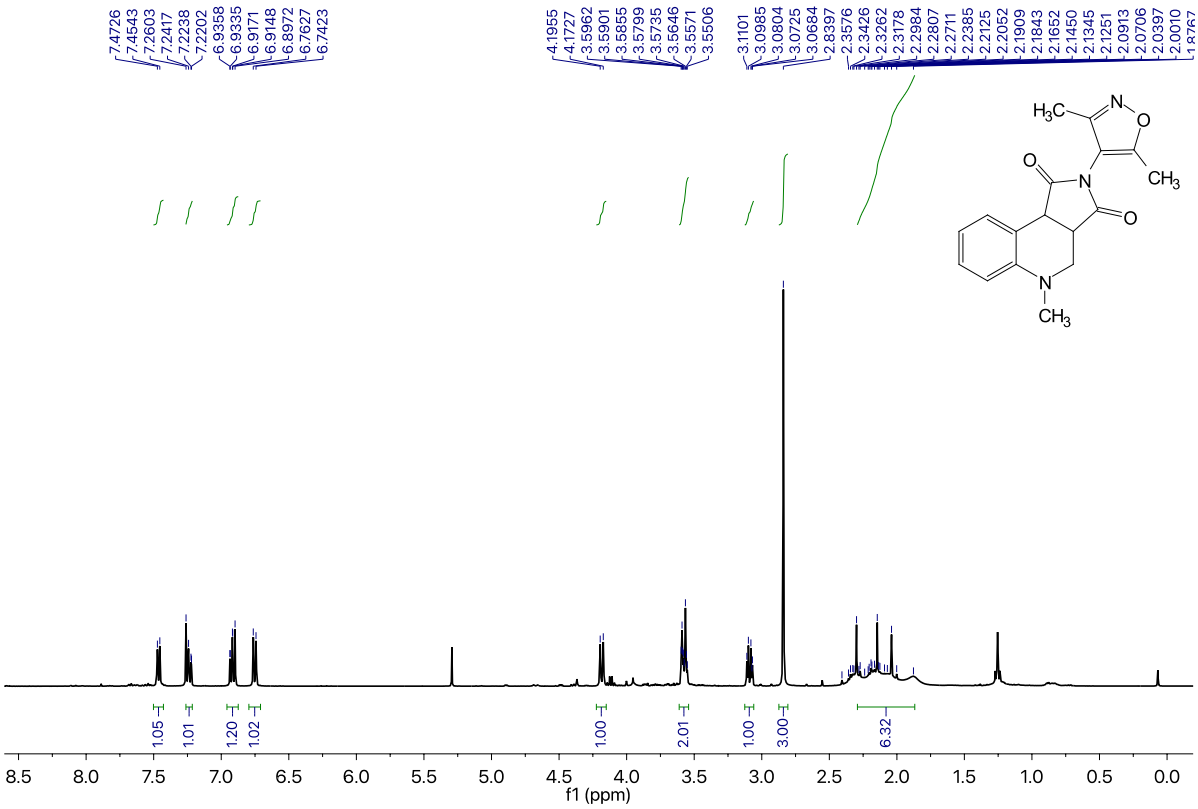
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1.01
1.20
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1.00
2.01
1.00
3.00
6.32
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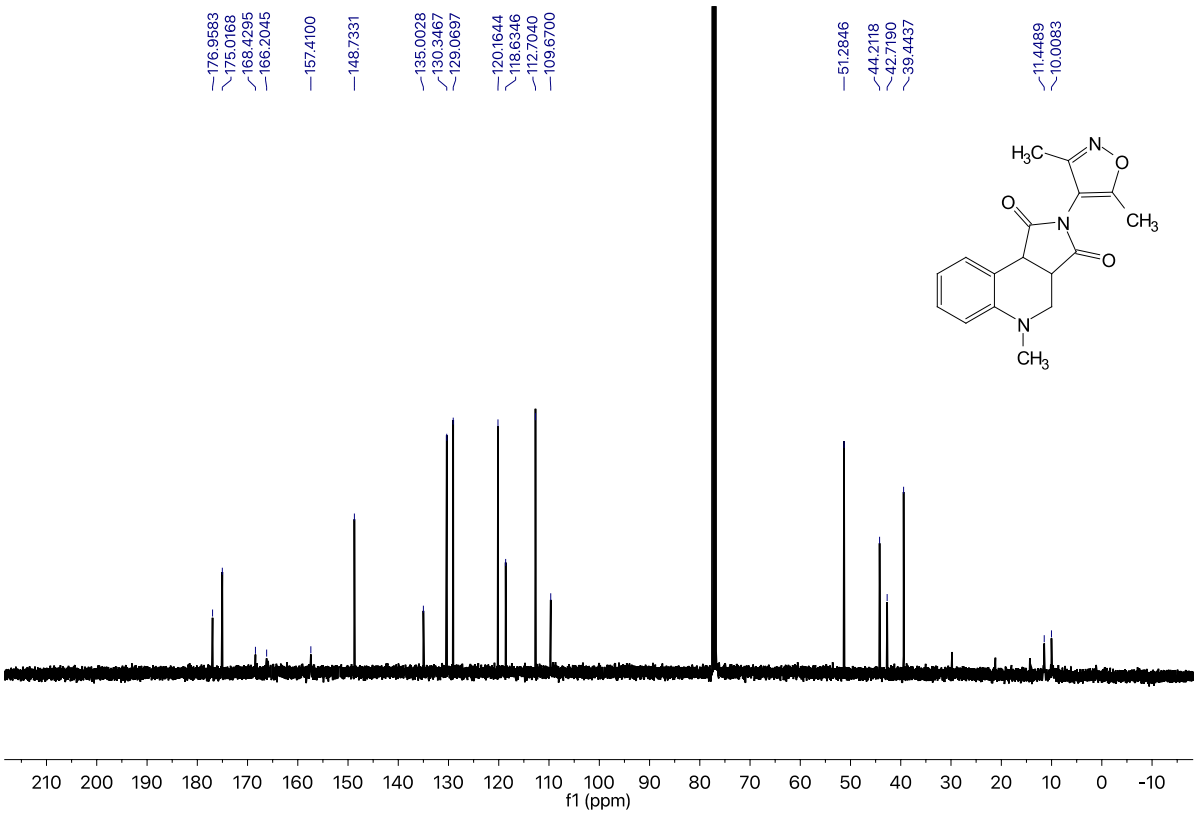
f1 (ppm)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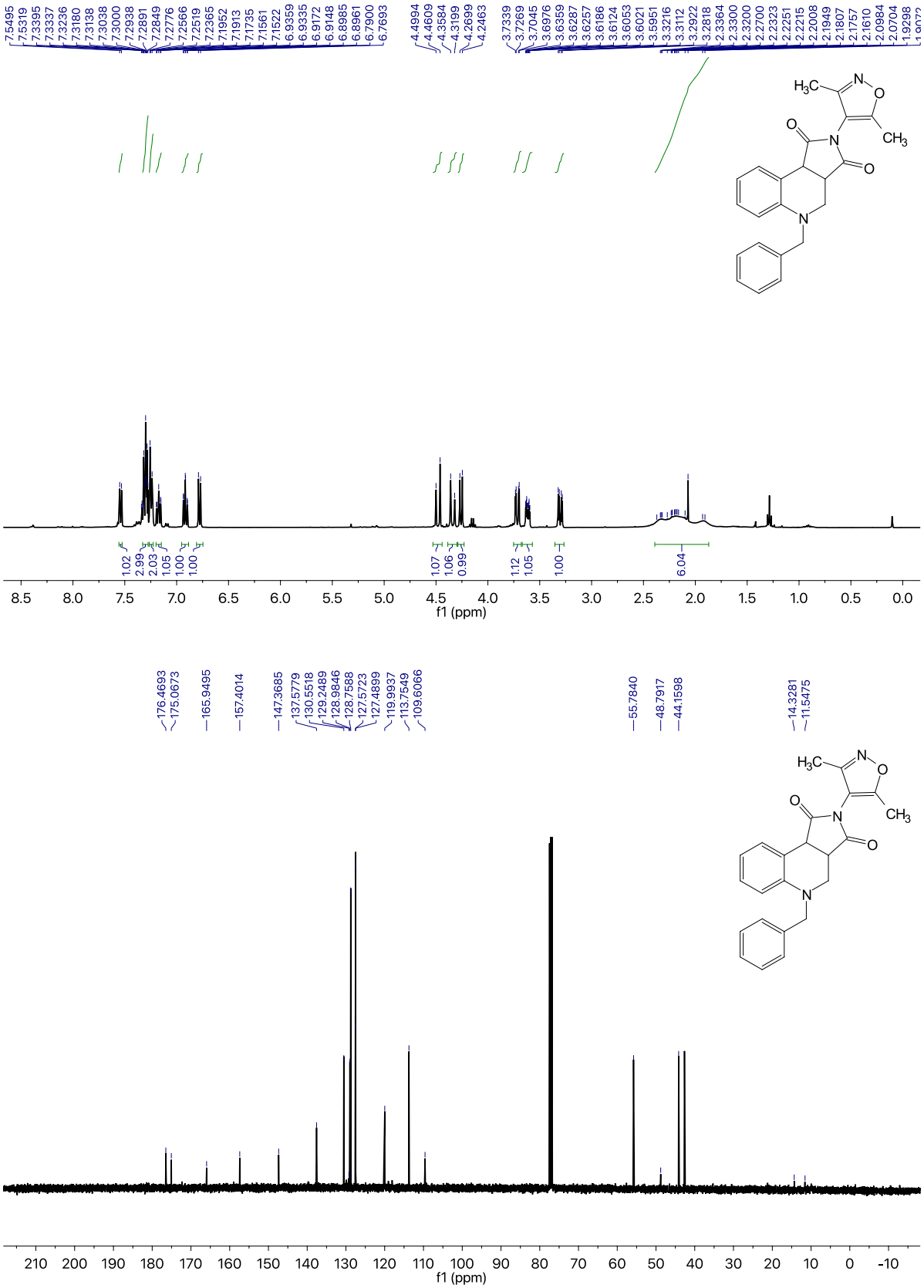
f1 (ppm)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7.3000
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7.2849
7.2776
7.2566
7.2519
7.2365
7.1952
7.1913
7.1735
7.1561
7.1522
6.9359
6.9335
6.9172
6.9148
6.8985
6.8961
6.7900
6.7693
4.4994
4.4609
4.3584
4.3199
4.2699
4.2463
3.7339
3.7269
3.7045
3.6976
3.6359
3.6287
3.6257
3.6186
3.6124
3.6053
3.6021
3.5951
3.3216
3.3112
3.2922
3.2818
2.3364
2.3300
2.3200
2.2700
2.2323
2.2251
2.2215
2.2008
2.1949
2.1807
2.1757
2.1610
2.0984
2.0704
1.9298
H3C
N
O
CH3
O
N
O
N
1.02
2.99
2.03
1.05
1.00
1.00
1.07
1.06
0.99
1.12
1.05
1.00
6.04
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)
176.4693
175.0673
165.9495
157.4014
147.3685
137.5779
130.5518
129.2489
128.9846
128.7588
127.5723
127.4899
119.9937
113.7549
109.6066
55.7840
48.7917
44.1598
14.3281
11.5475
H3C
N
O
CH3
O
N
O
N
210
200
190
180
170
160
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140
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120
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100
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80
70
60
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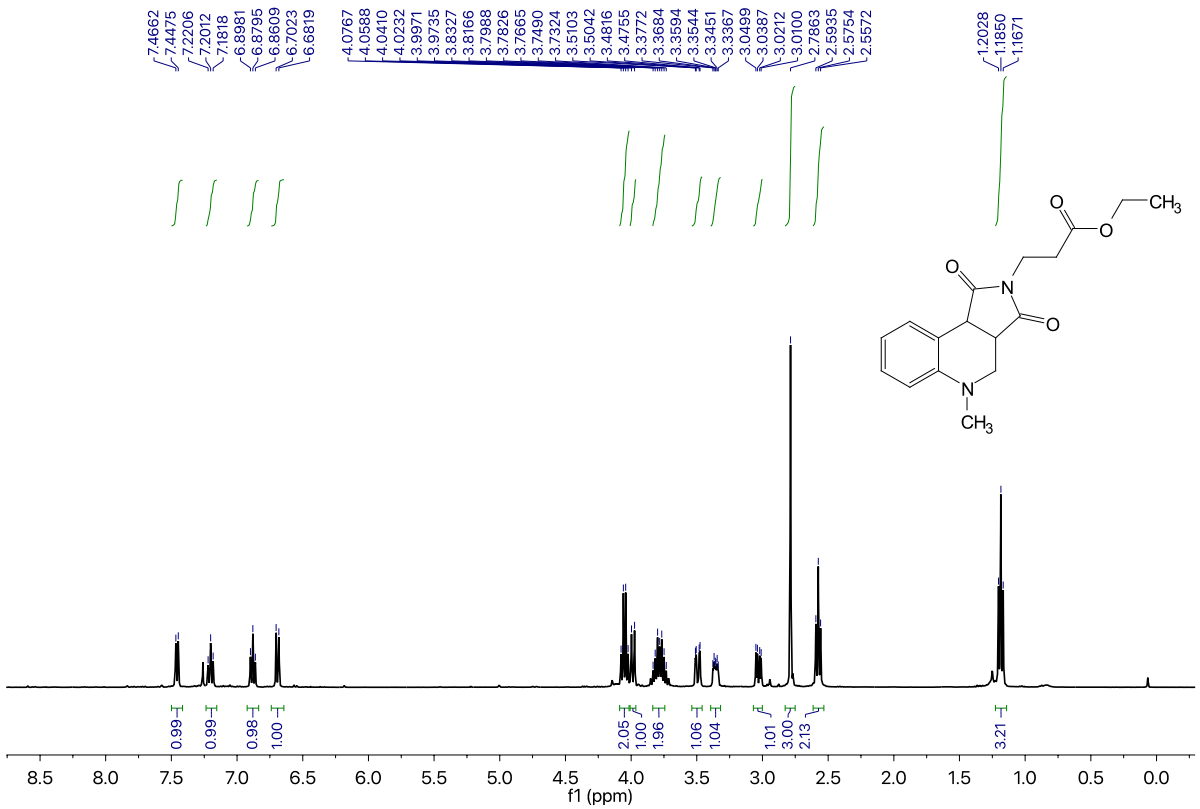
40
30
20
10
0
-10
f1 (ppm)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4.0410
4.0232
3.9971
3.9735
3.8327
3.8166
3.7988
3.7826
3.7665
3.7490
3.7324
3.5103
3.5042
3.4816
3.4755
3.3772
3.3684
3.3594
3.3544
3.3451
3.3367
3.0499
3.0387
3.0212
3.0100
2.7863
2.5935
2.5754
2.5572
1.2028
1.1850
1.1671
0.99
0.99
0.98
1.00
2.05
1.00
1.96
1.06
1.04
1.01
3.00
2.13
3.21
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)
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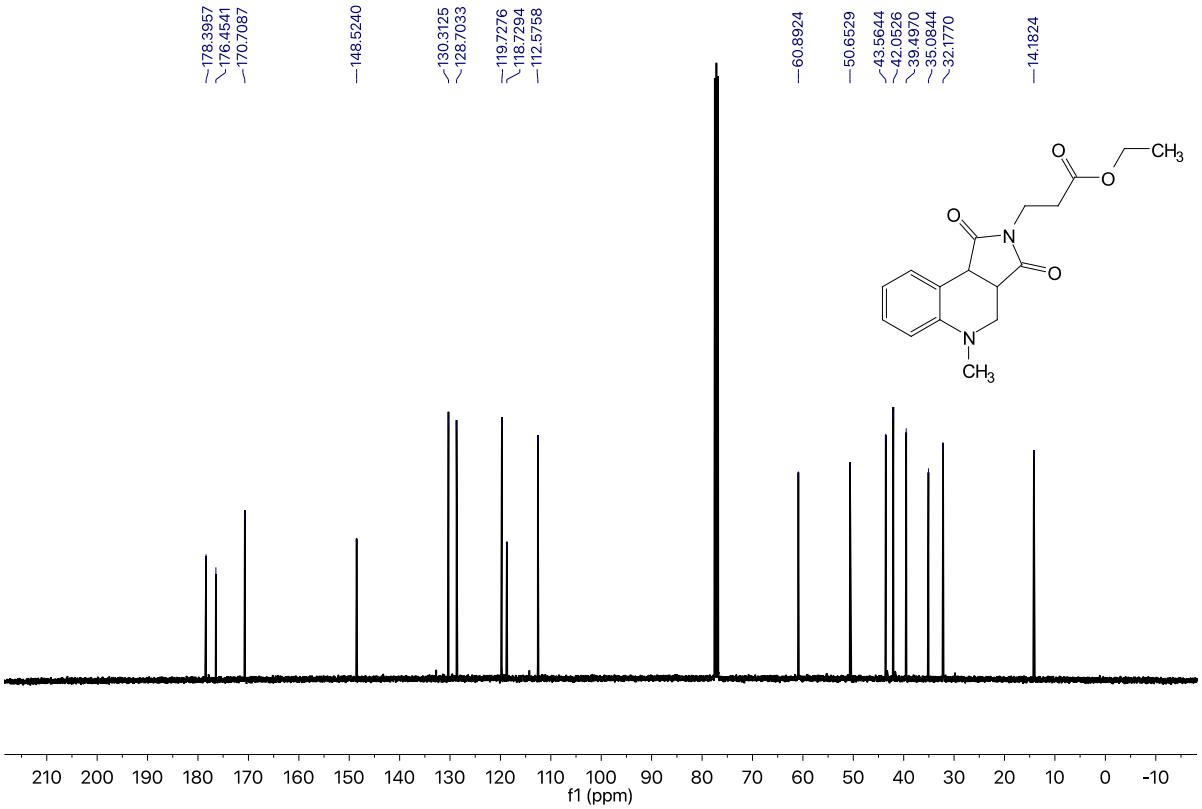
O
CH3
O
N
O
N
CH3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119.7276
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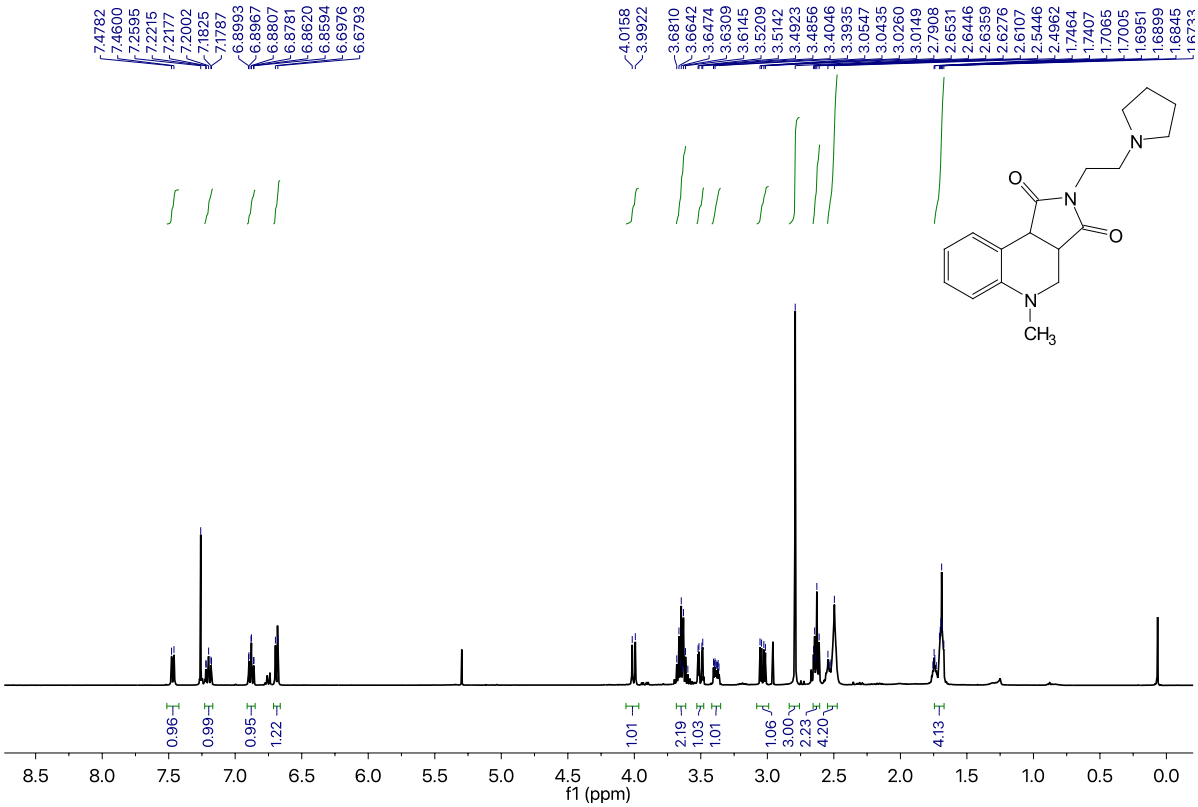
112.5758
60.8924
50.6529
43.5644
42.0526
39.4970
35.0844
32.1770
14.1824
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)
O
O
CH3
O
N
O
N
CH3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7.1825
7.1787
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6.8967
6.8807
6.8781
6.8620
6.8594
6.6976
6.6793
4.0158
3.9922
3.6810
3.6642
3.6474
3.6309
3.6145
3.5209
3.5142
3.4923
3.4856
3.4046
3.3935
3.0547
3.0435
3.0260
3.0149
2.7908
2.6531
2.6446
2.6359
2.6276
2.6107
2.5446
2.4962
1.7464
1.7407
1.7065
1.7005
1.6951
1.6899
1.6845
0.96
0.99
0.95
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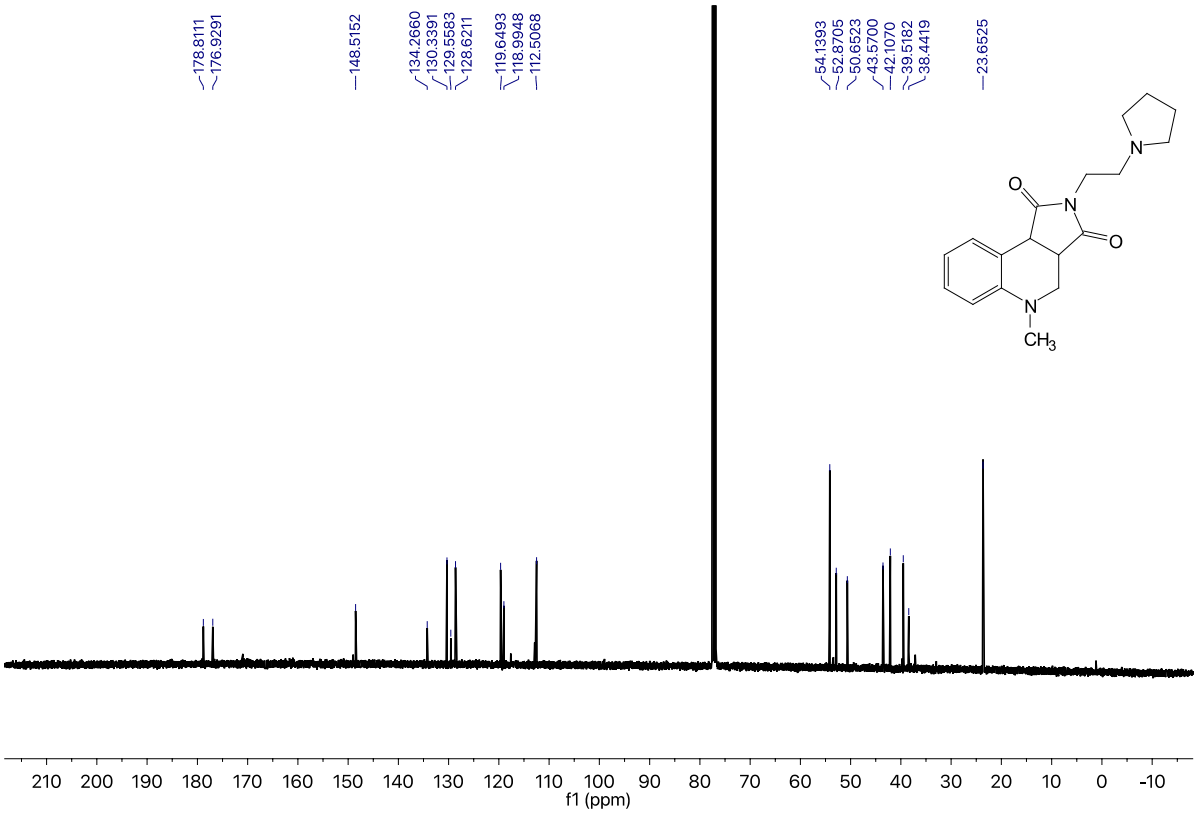
1.01
2.19
1.03
1.01
1.06
3.00
2.23
4.20
4.13
f1 (ppm)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118.9948
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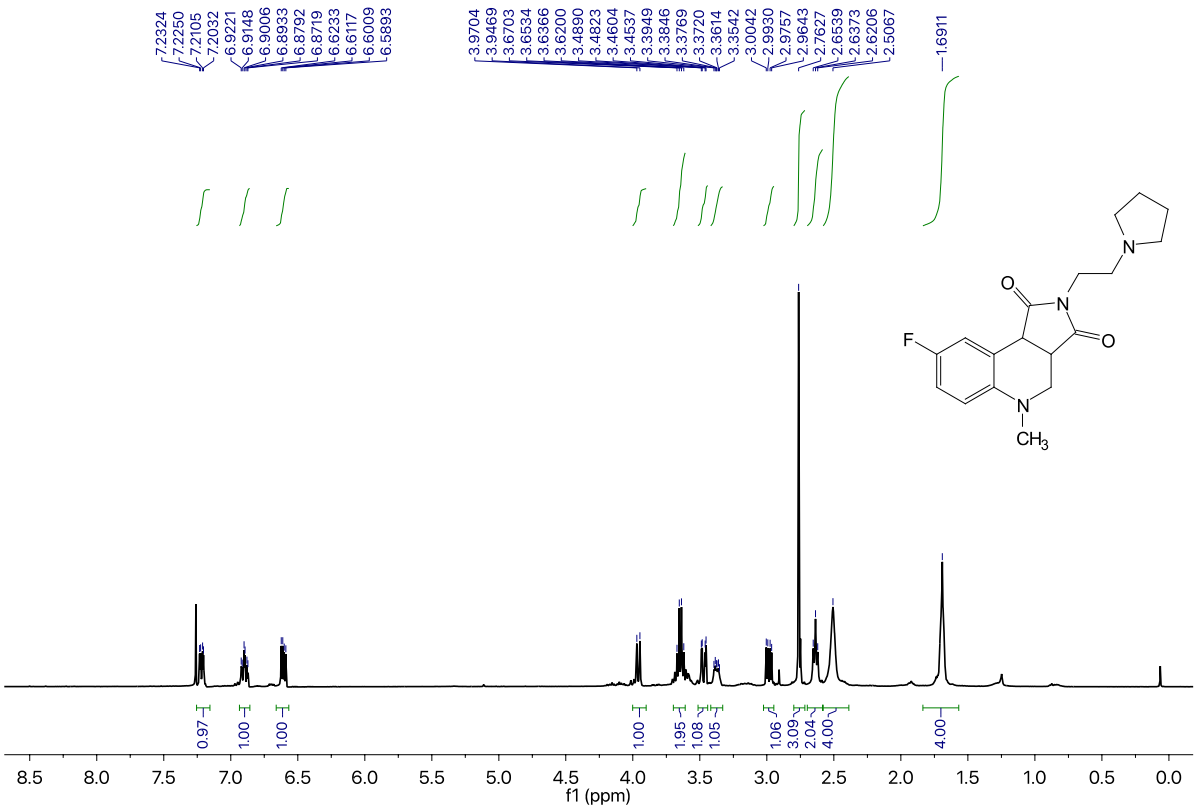
54.1393
52.8705
50.6523
43.5700
42.1070
39.5182
38.4419
23.6525
f1 (ppm)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6.9148
6.9006
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6.8792
6.8719
6.6233
6.6117
6.6009
6.5893
3.9704
3.9469
3.6703
3.6534
3.6366
3.6200
3.4890
3.4823
3.4604
3.4537
3.3949
3.3846
3.3769
3.3720
3.3614
3.3542
3.0042
2.9930
2.9757
2.9643
2.7627
2.6539
2.6373
2.6206
2.5067
1.6911
0.97
1.00
1.00
1.00
1.95
1.08
1.05
1.06
3.09
2.04
4.00
4.00
F
O
O
N
N
CH3
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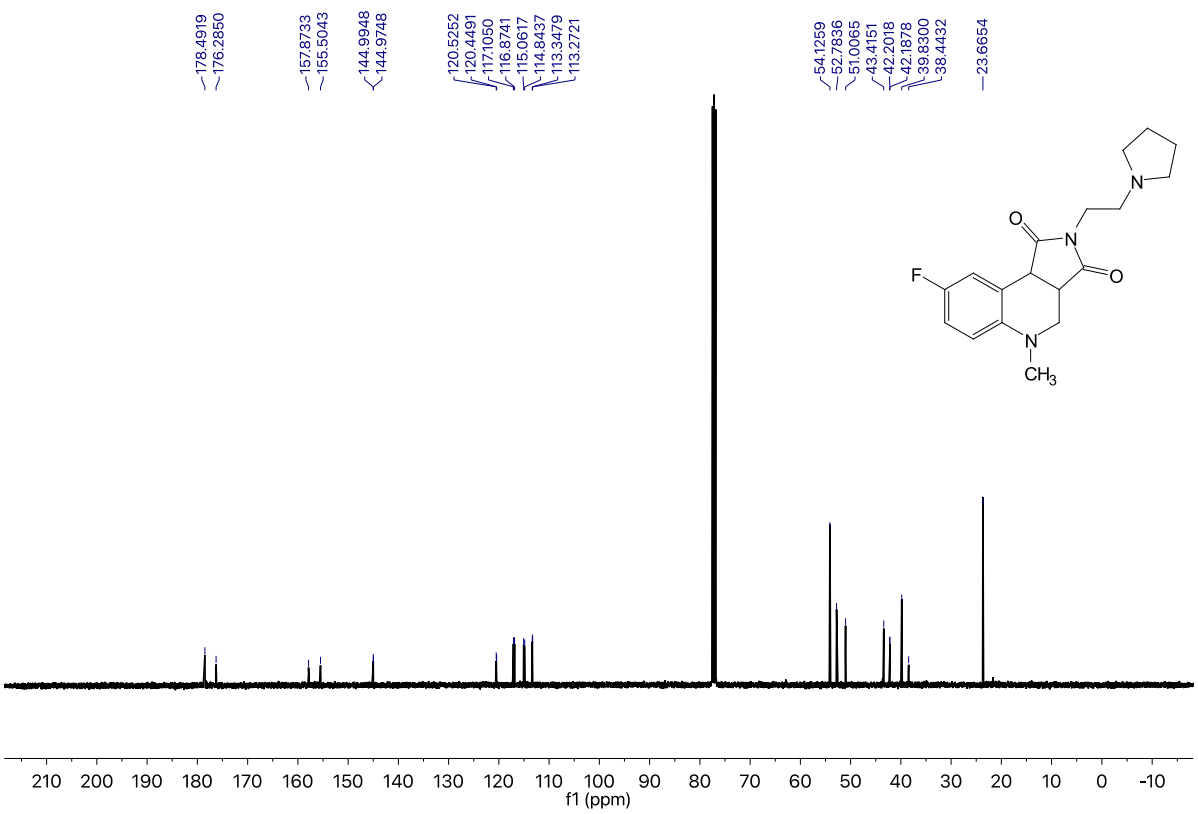
f1 (ppm)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144.9748
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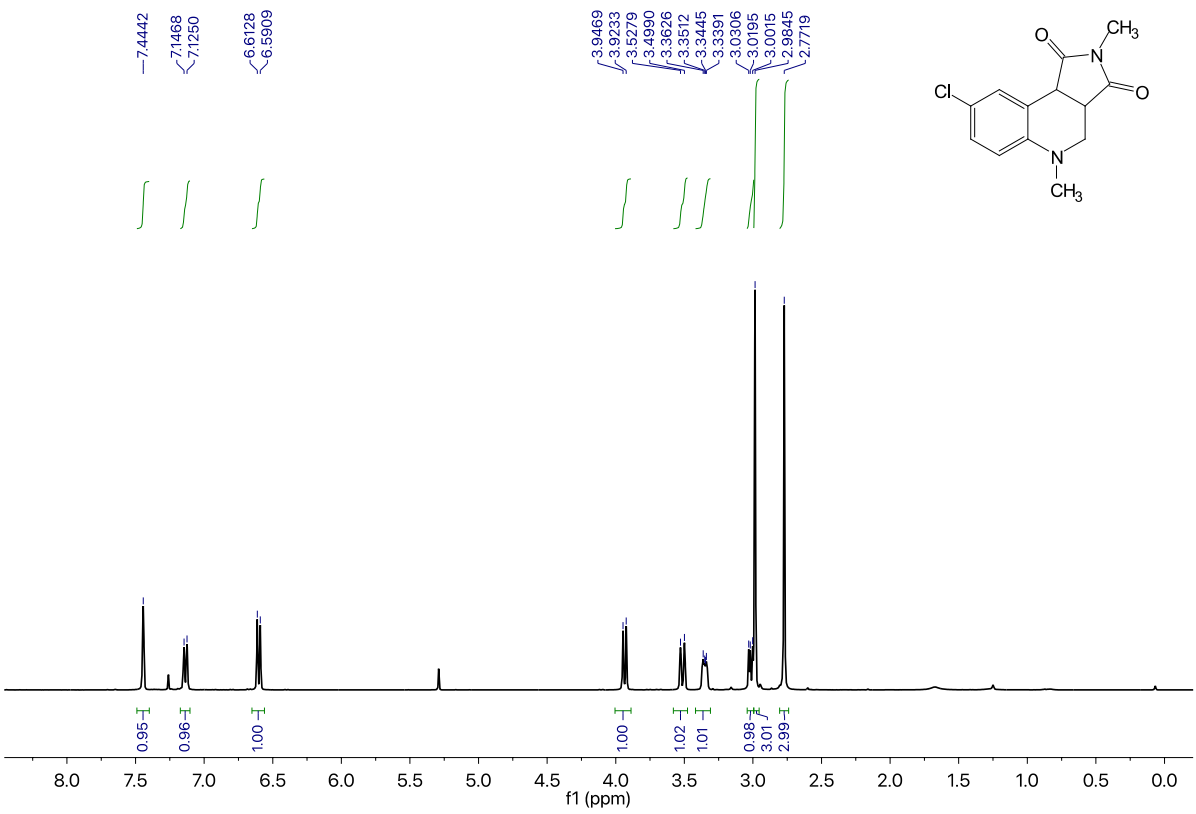
116.8741
115.0617
114.8437
113.3479
113.2721
54.1259
52.7836
51.0065
43.4151
42.2018
42.1878
39.8300
38.4432
23.6654
F
O
O
N
N
CH3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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7.1250
6.6128
6.5909
3.9469
3.9233
3.5279
3.4990
3.3626
3.3512
3.3445
3.3391
3.0306
3.0195
3.0015
2.9845
2.7719
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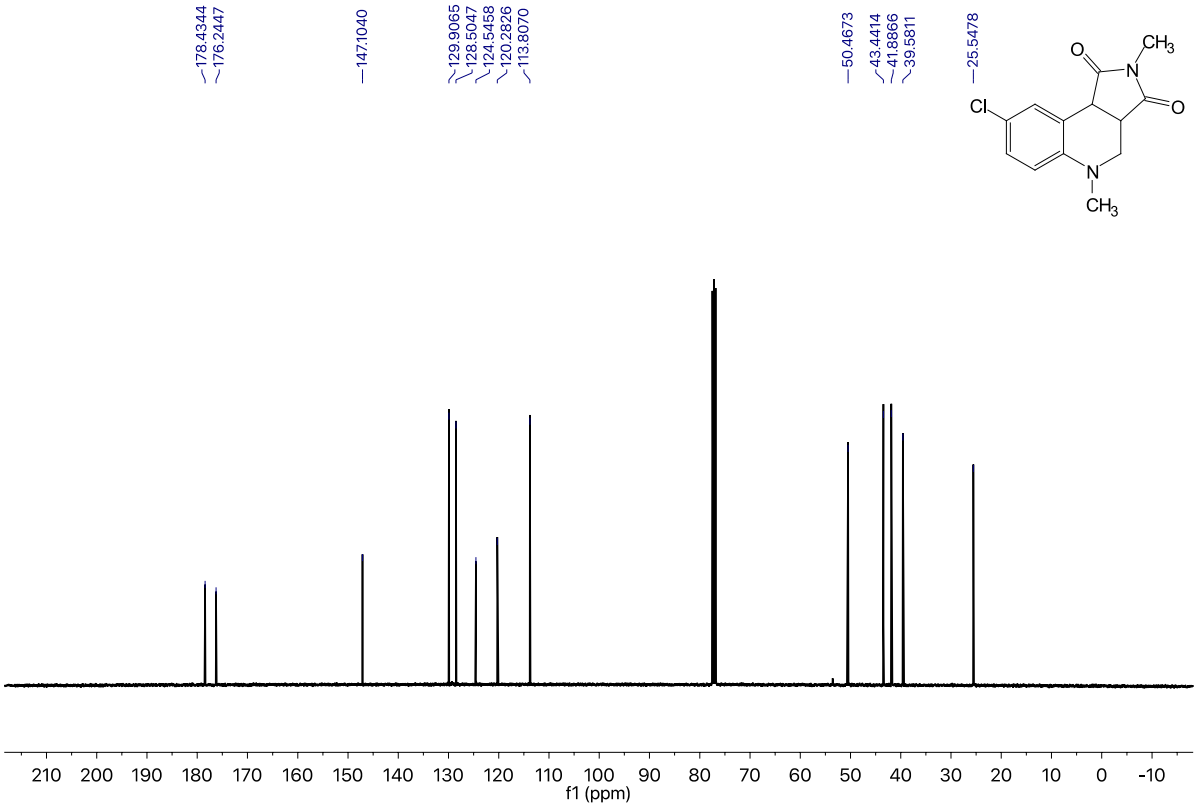
0.96
1.00
1.00
1.02
1.01
0.98
3.01
2.99
f1 (ppm)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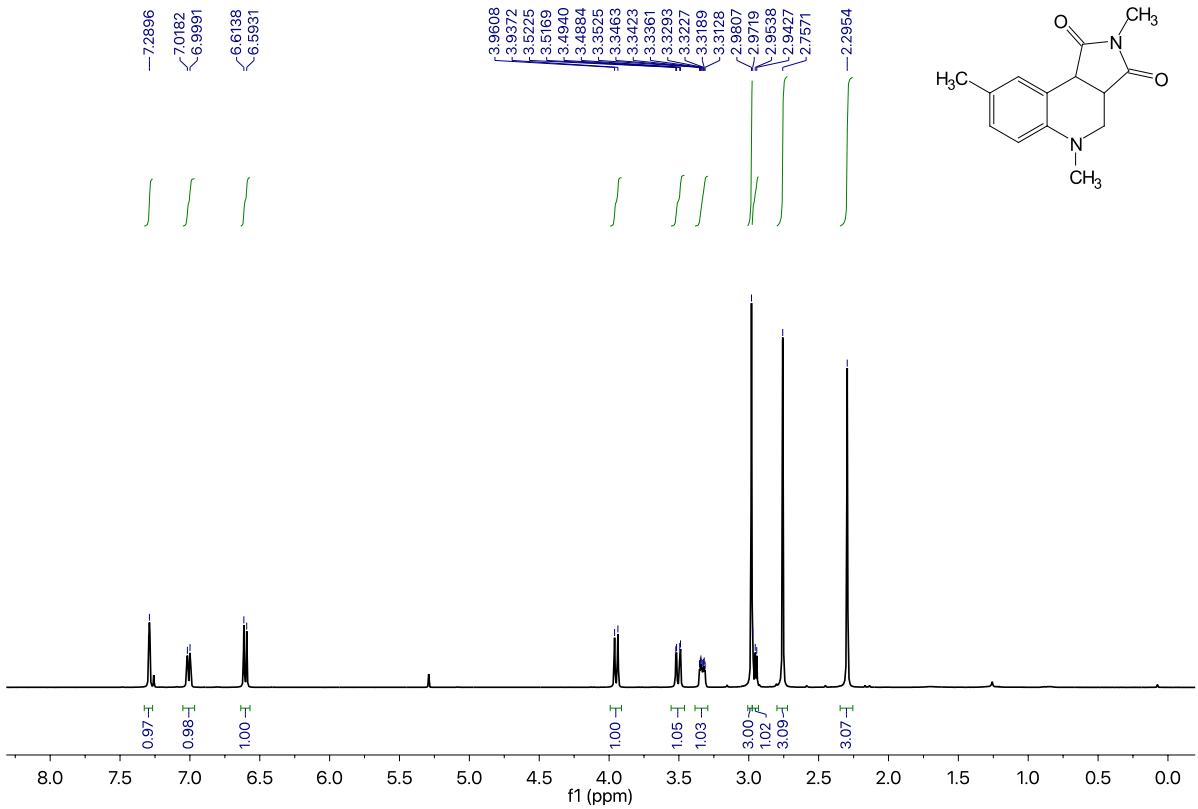
43.4414
41.8866
39.5811
25.5478
f1 (ppm)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6.5931
3.9608
3.9372
3.5225
3.5169
3.4940
3.4884
3.3525
3.3463
3.3423
3.3361
3.3293
3.3227
3.3189
3.3128
2.9807
2.9719
2.9538
2.9427
2.7571
2.2954
0.97
0.98
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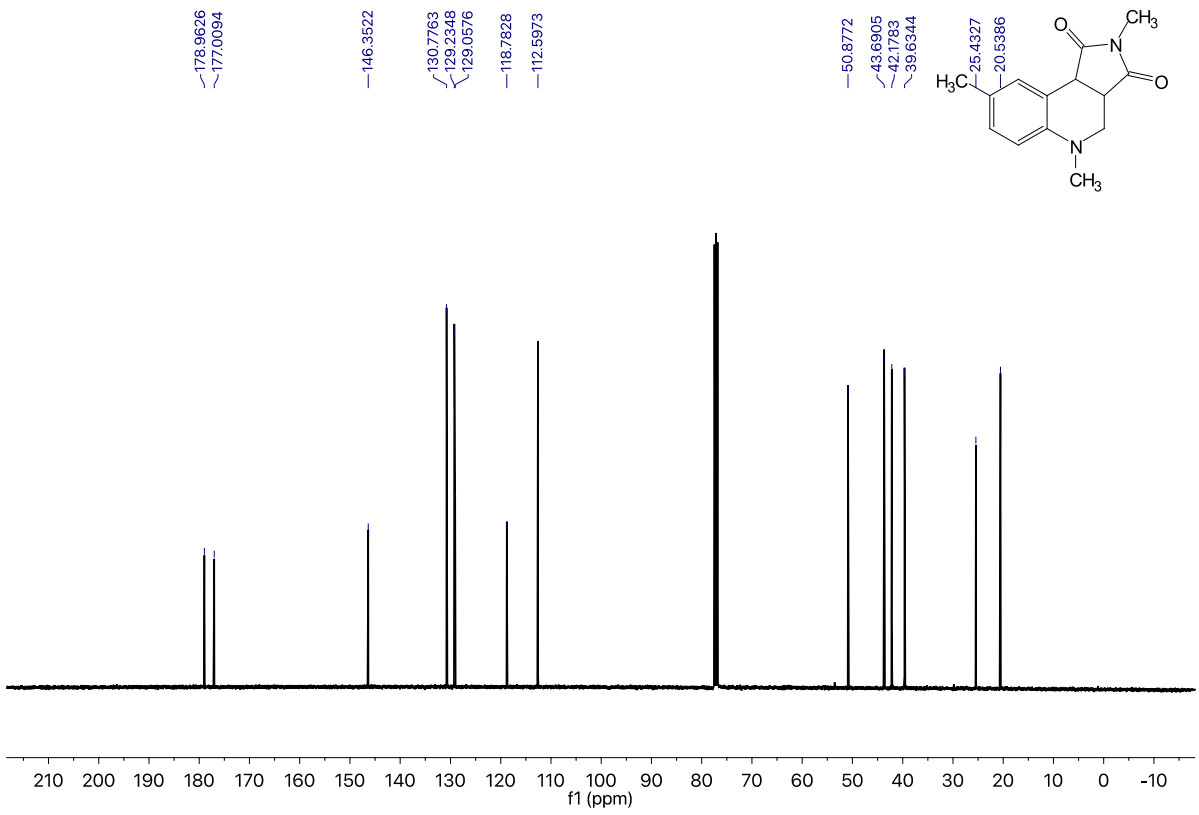
1.00
1.05
1.03
3.00
1.02
3.09
3.07
f1 (ppm)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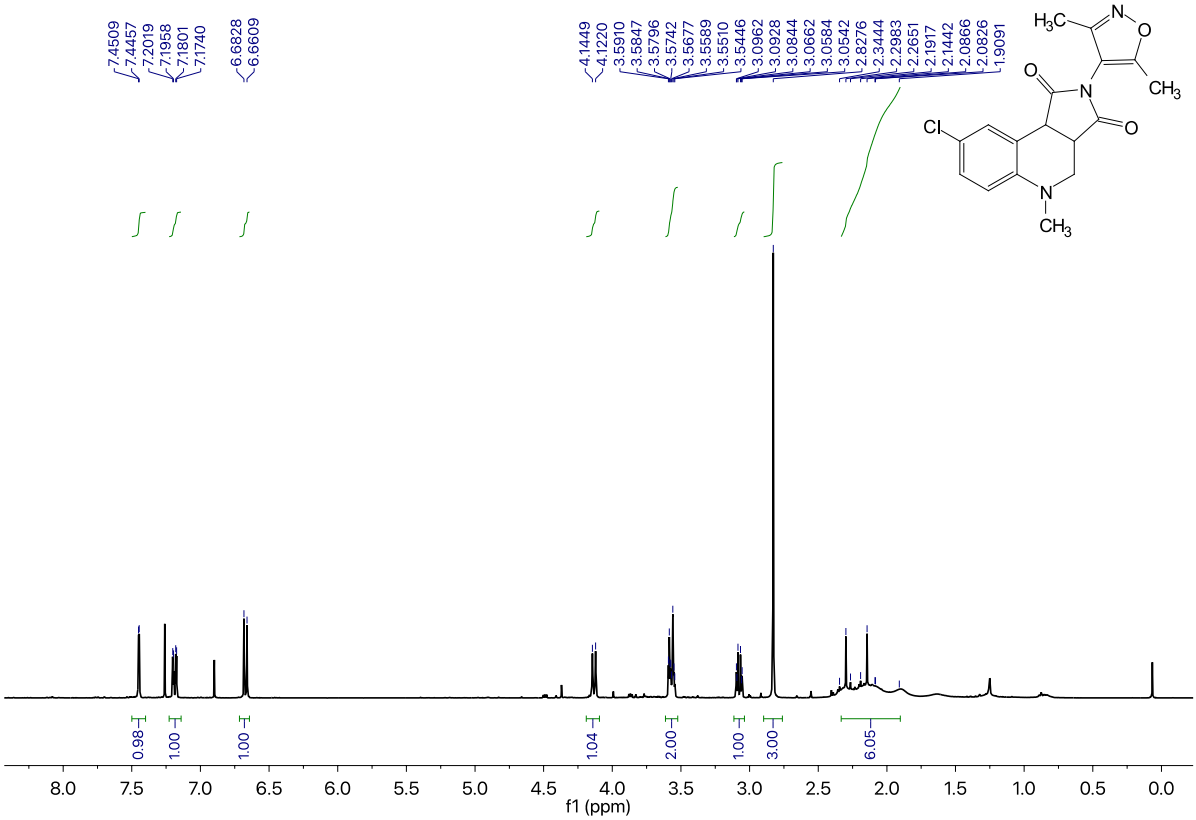
f1 (ppm)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4.1220
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3.5847
3.5796
3.5742
3.5677
3.5589
3.5510
3.5446
3.0962
3.0928
3.0844
3.0662
3.0584
3.0542
2.8276
2.3444
2.2983
2.2651
2.1917
2.1442
2.0866
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1.00
1.00
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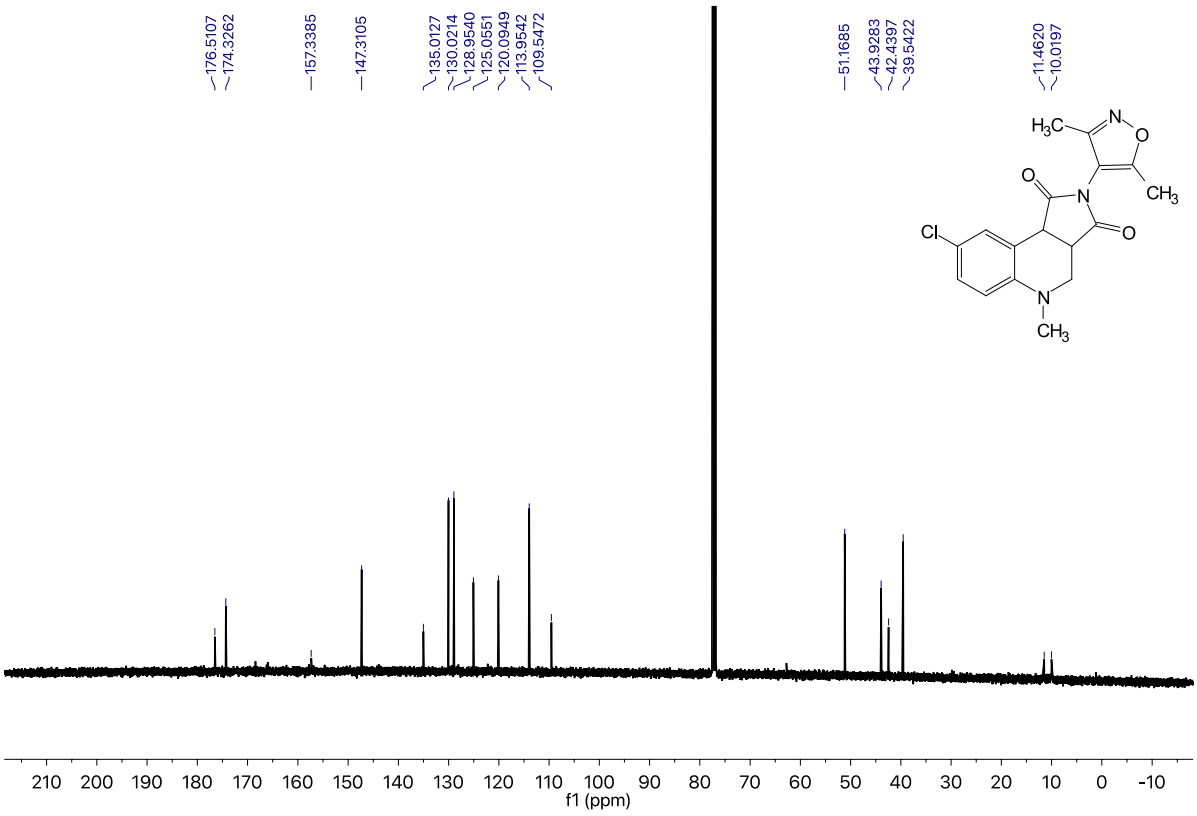
2.00
1.00
3.00
6.05
f1 (ppm)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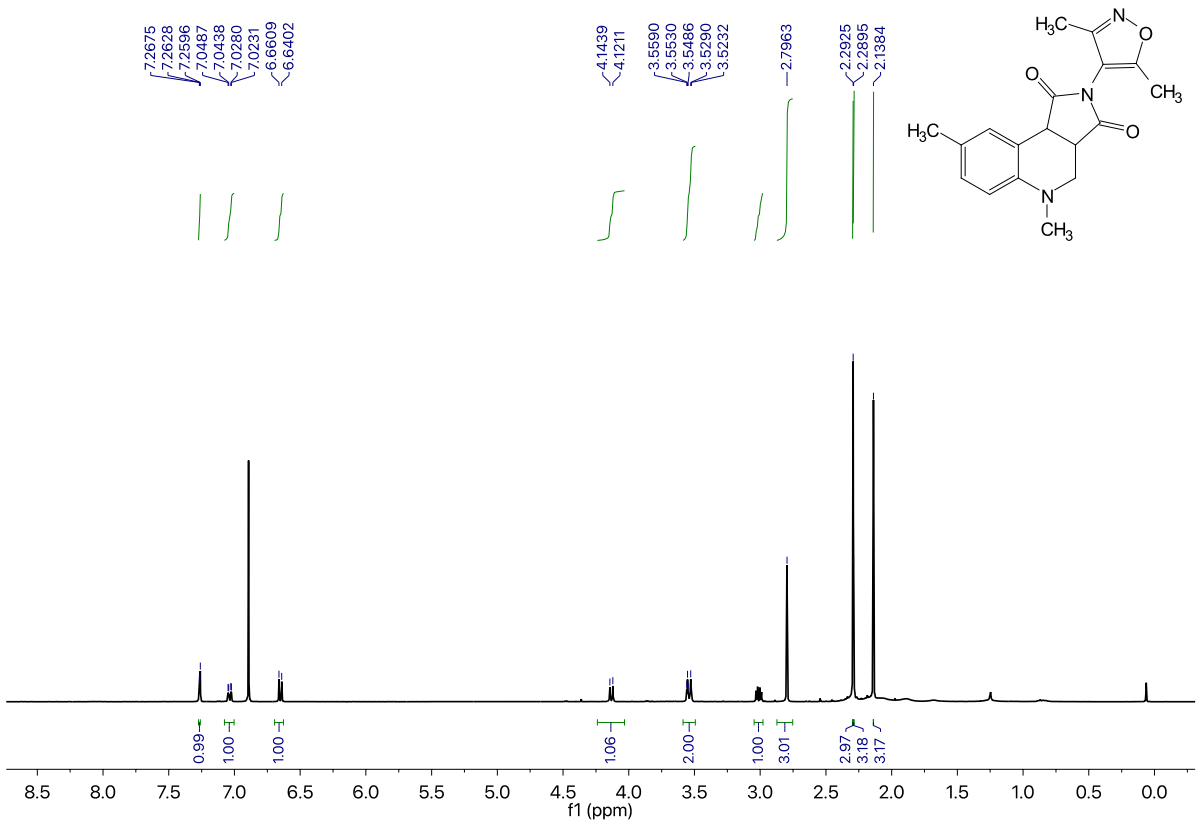
43.9283
42.4397
39.5422
11.4620
10.0197
f1 (ppm)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7.0438
7.0280
7.0231
6.6609
6.6402
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4.1211
3.5590
3.5530
3.5486
3.5290
3.5232
2.7963
2.2925
2.2895
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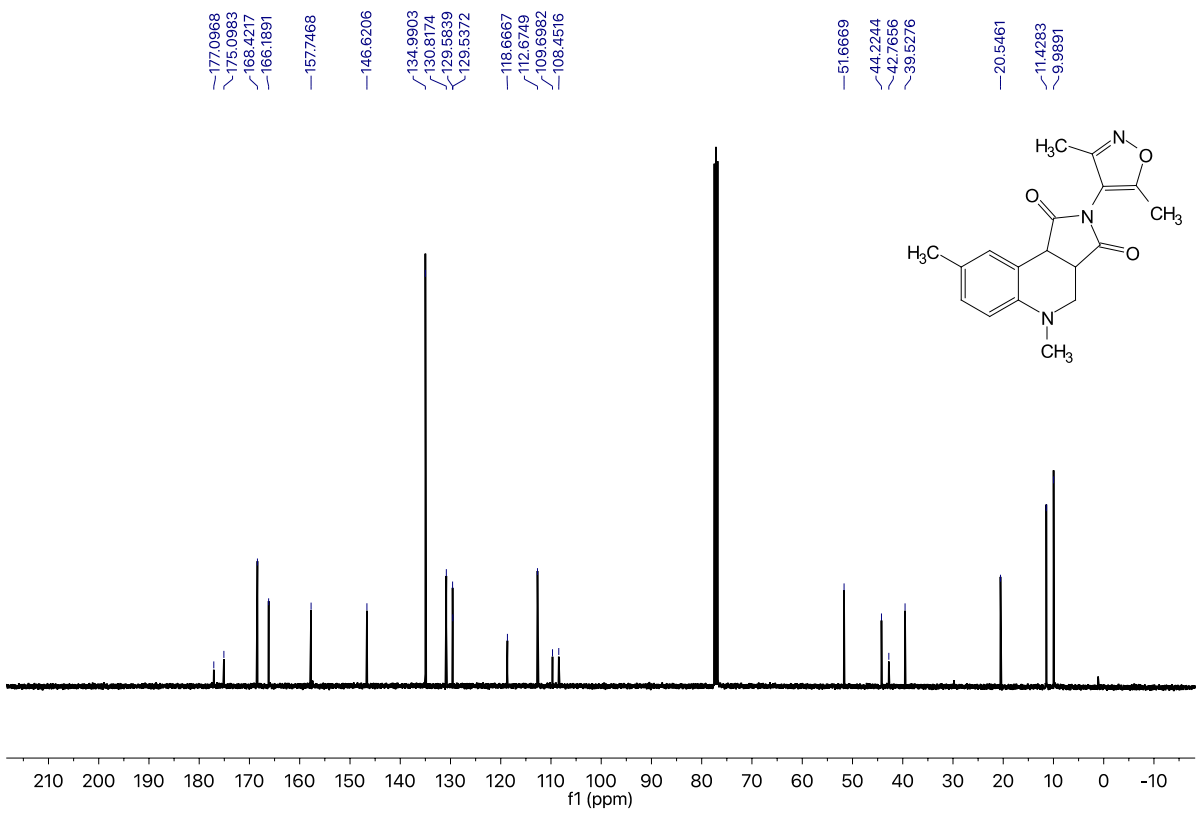
1.00
1.06
2.00
1.00
3.01
2.97
3.18
3.17
f1 (ppm)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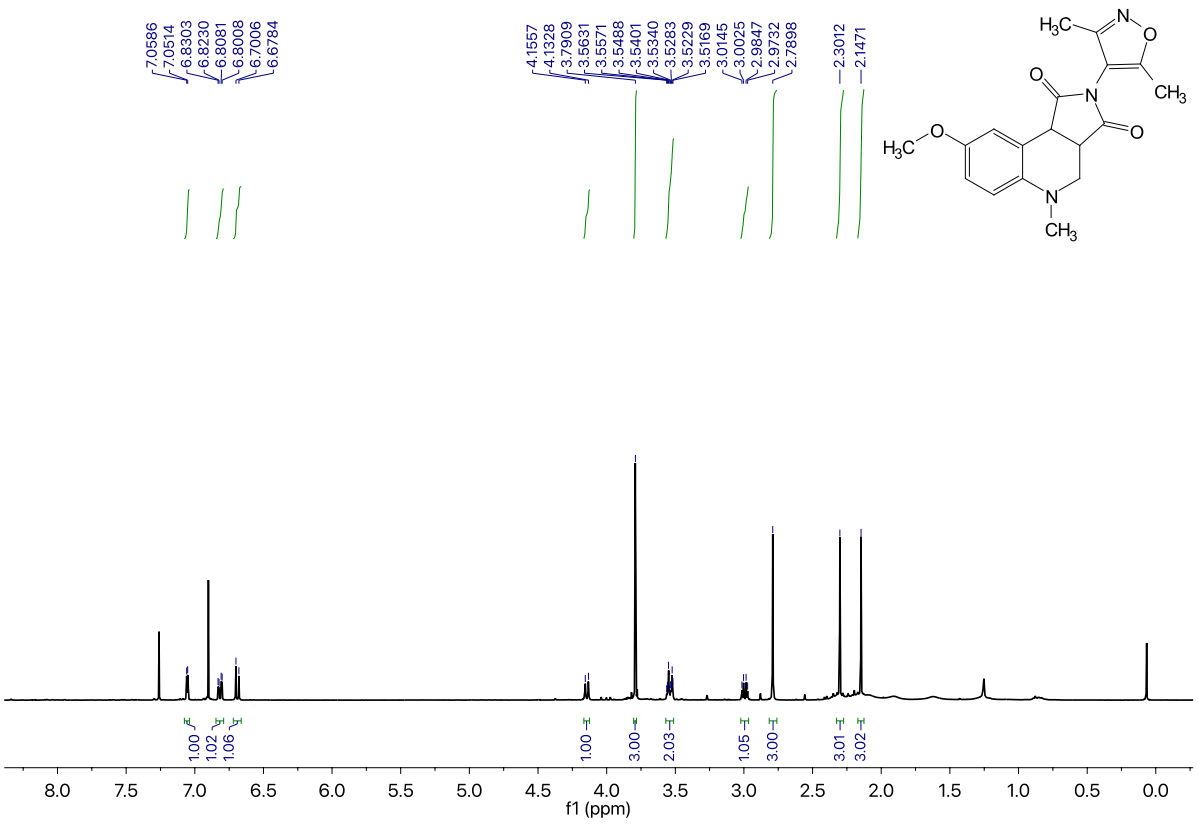
9.9891
f1 (ppm)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3.5340
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1.06
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2.03
1.05
3.00
3.01
3.02
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6.5
6.0
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2.5
2.0
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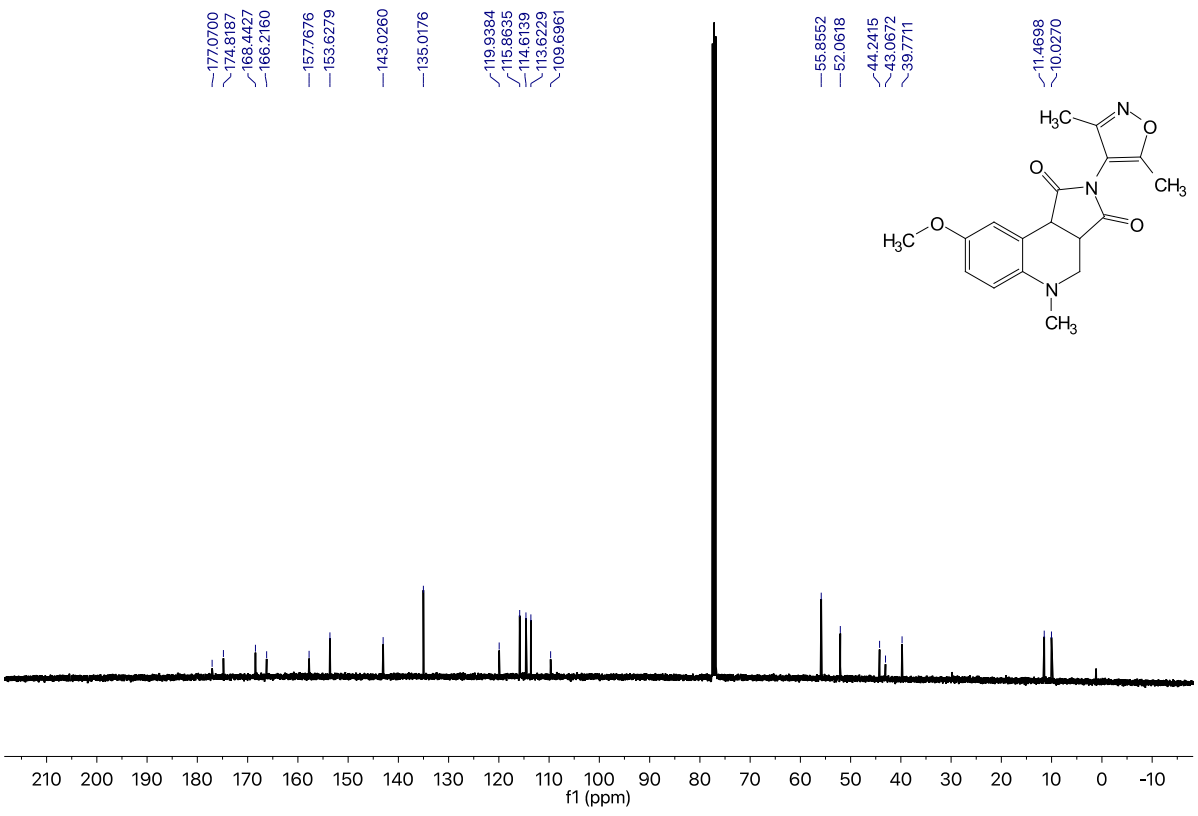
f1 (ppm)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52.0618
44.2415
43.0672
39.7711
11.4698
10.0270
210
200
190
180
170
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120
110
100
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80
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40
30
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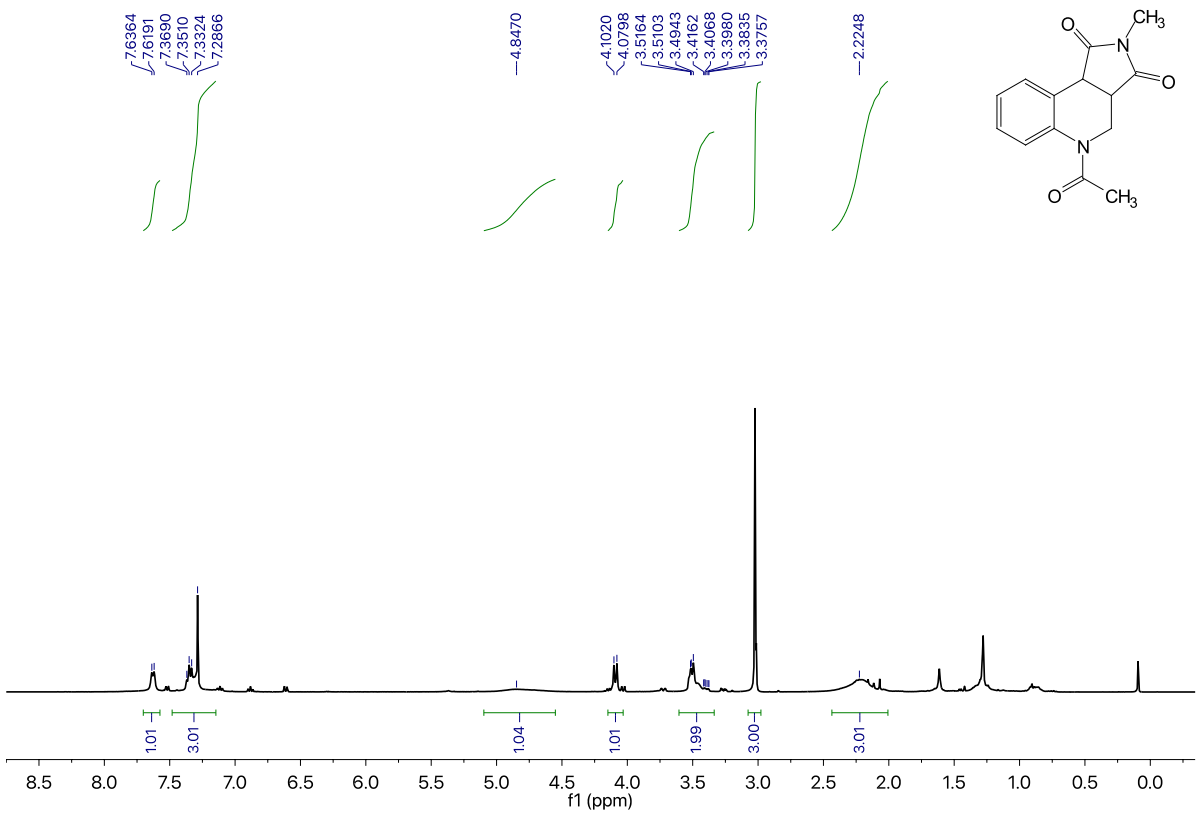
0
-10
f1 (ppm)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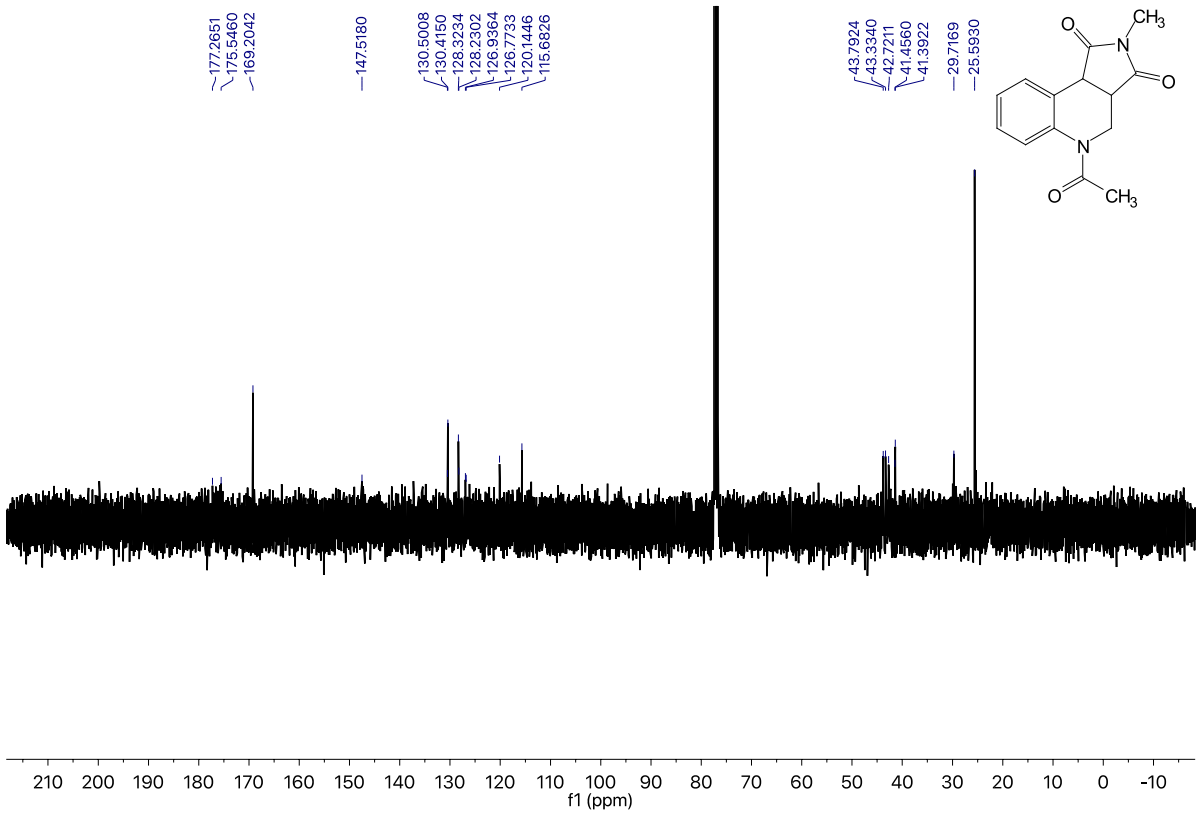
3.01
1.04
1.01
1.99
3.00
3.01
f1 (ppm)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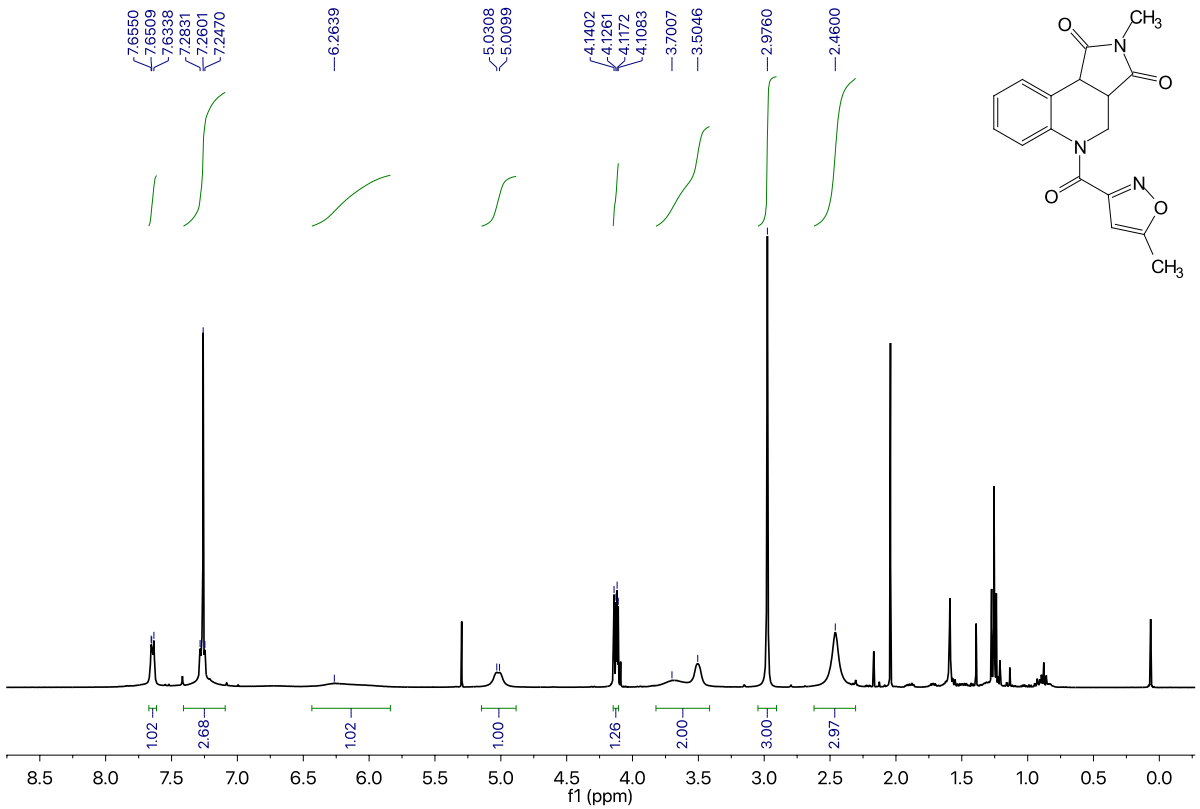
43.3340
42.7211
41.4560
41.3922
29.7169
25.5930
f1 (ppm)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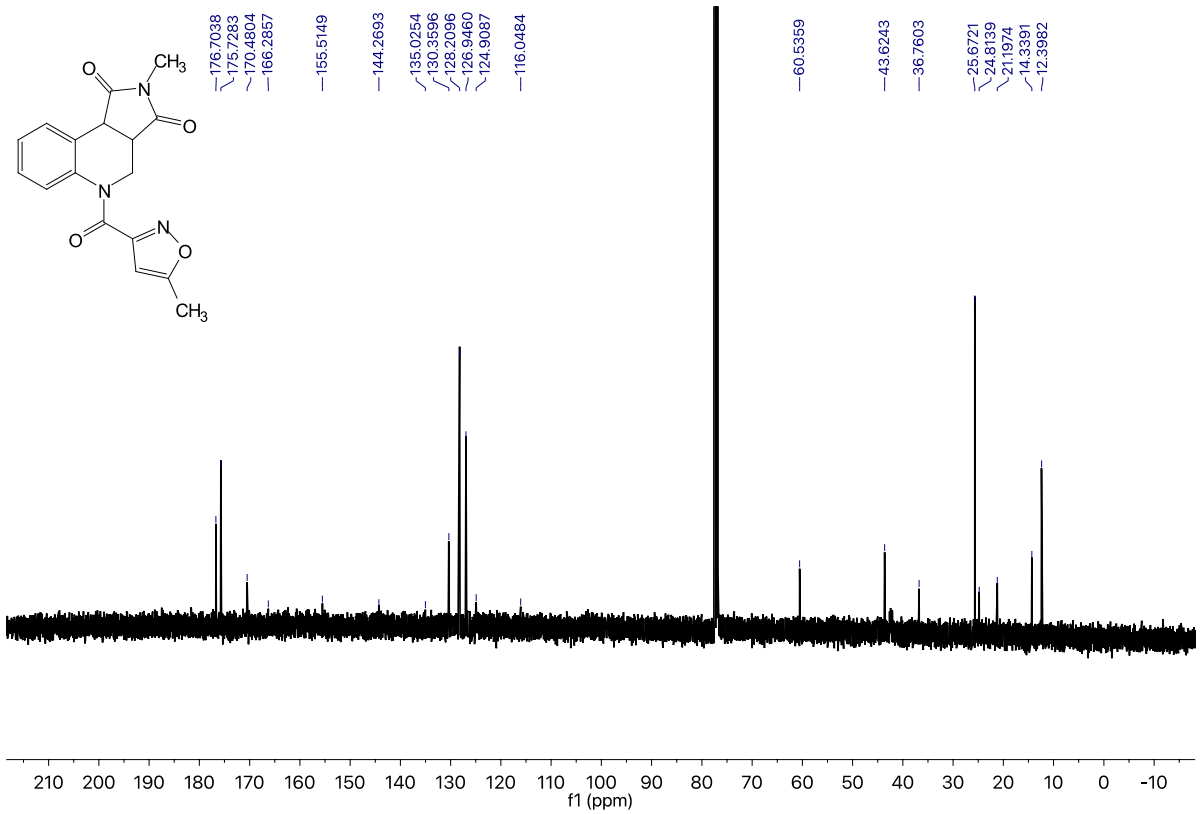
2.97
f1 (ppm)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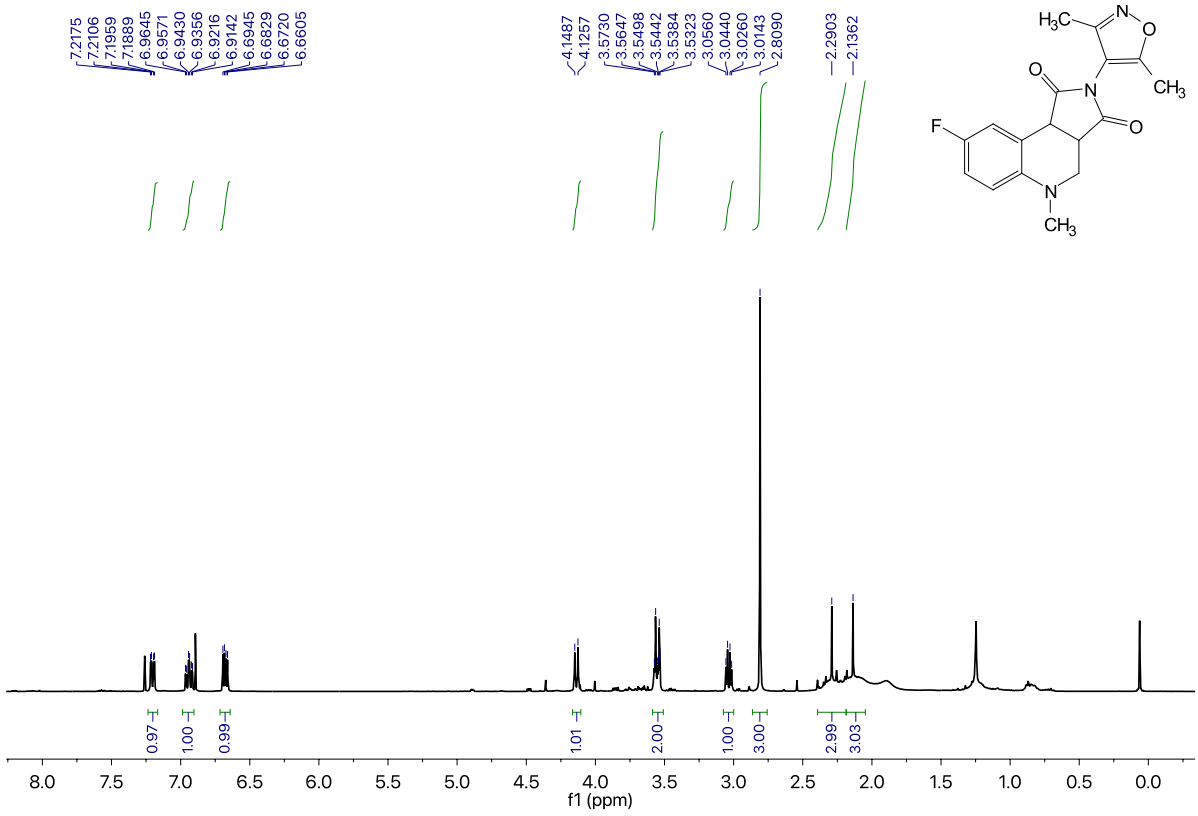
12.3982
f1 (ppm)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3.0260
3.0143
2.8090
2.2903
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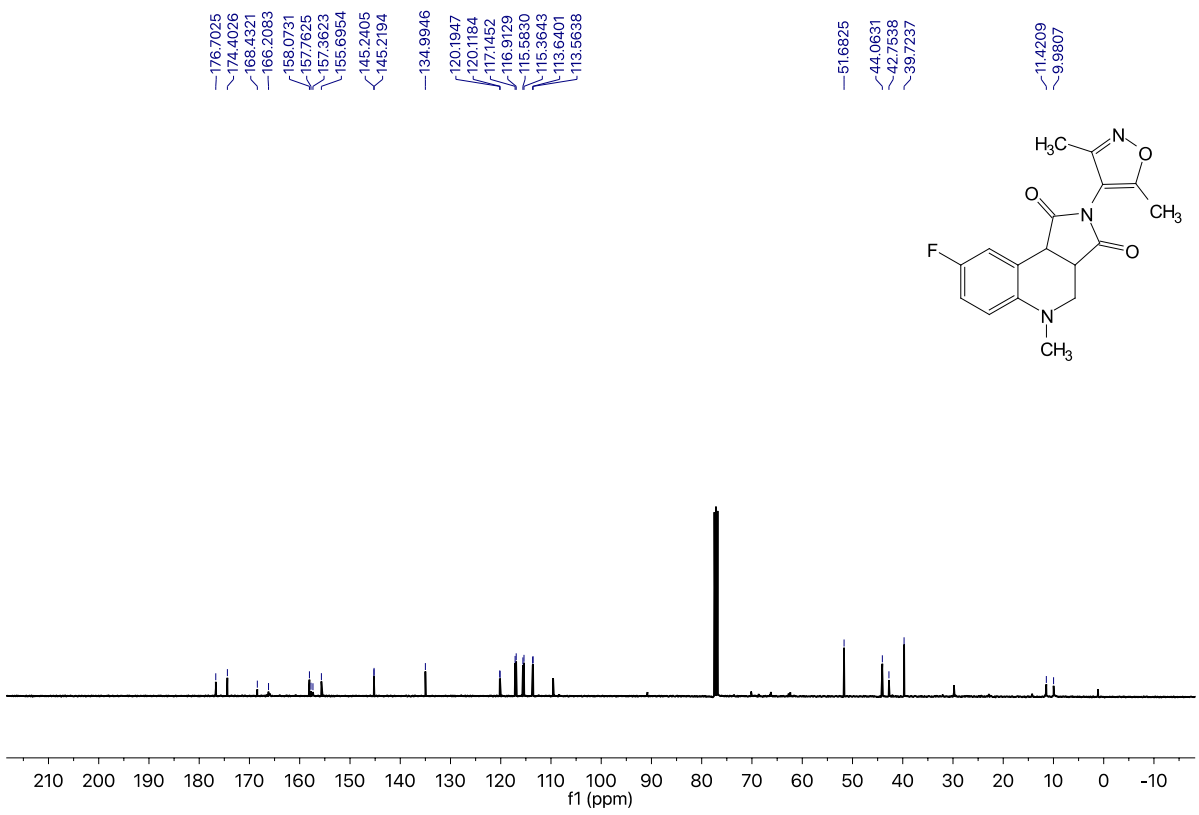
0.99
1.01
2.00
1.00
3.00
2.99
3.03
f1 (ppm)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120.1947
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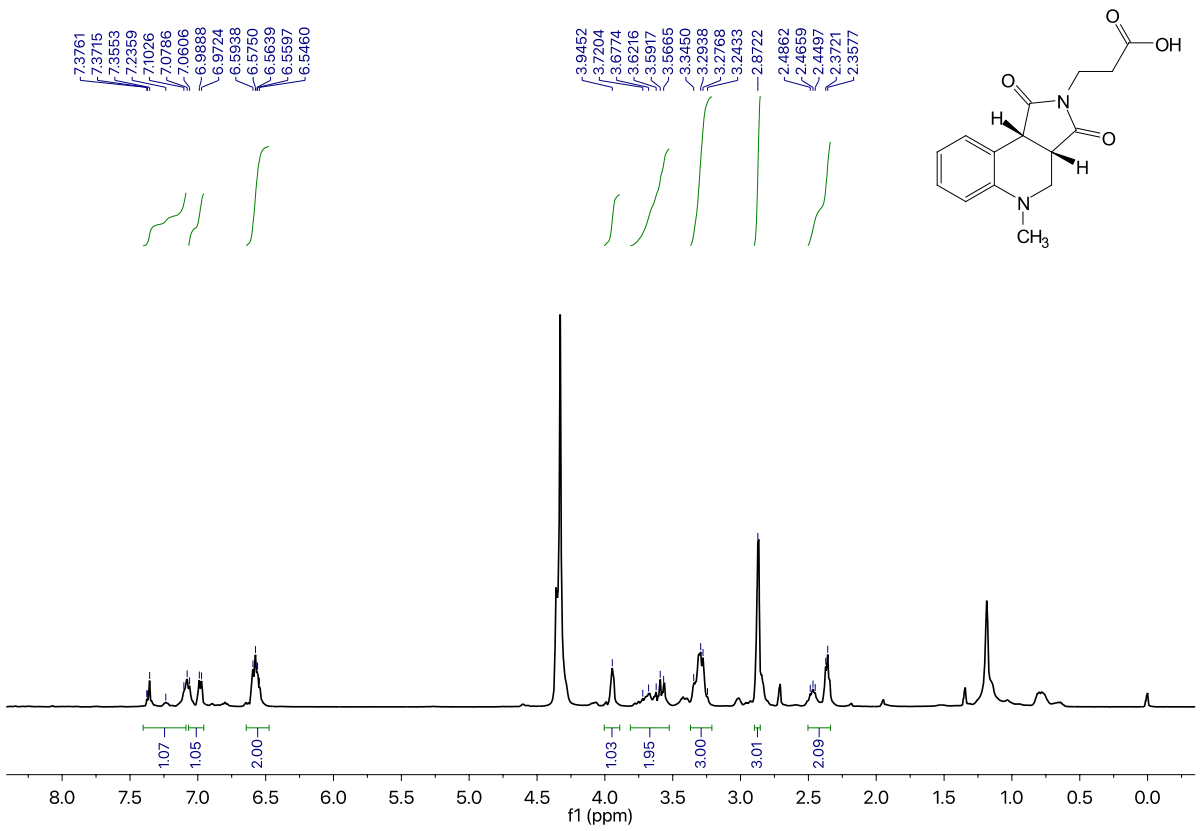
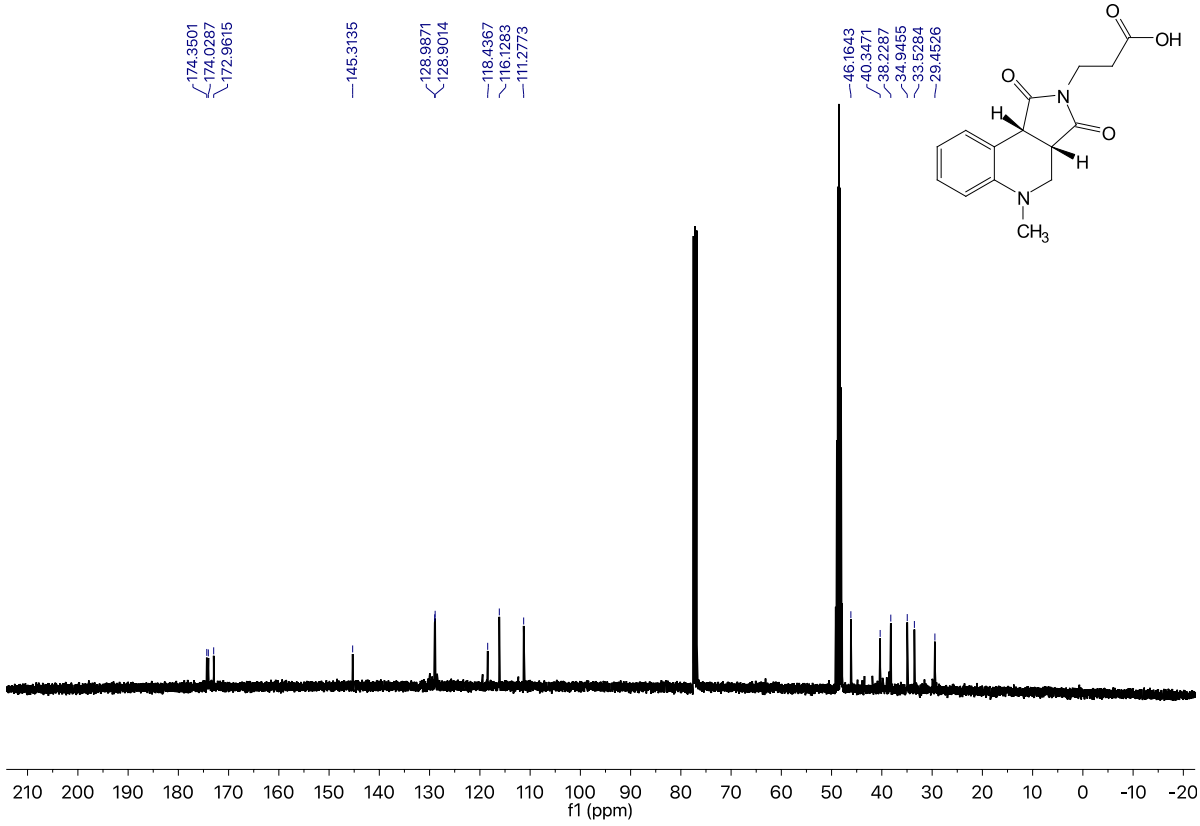
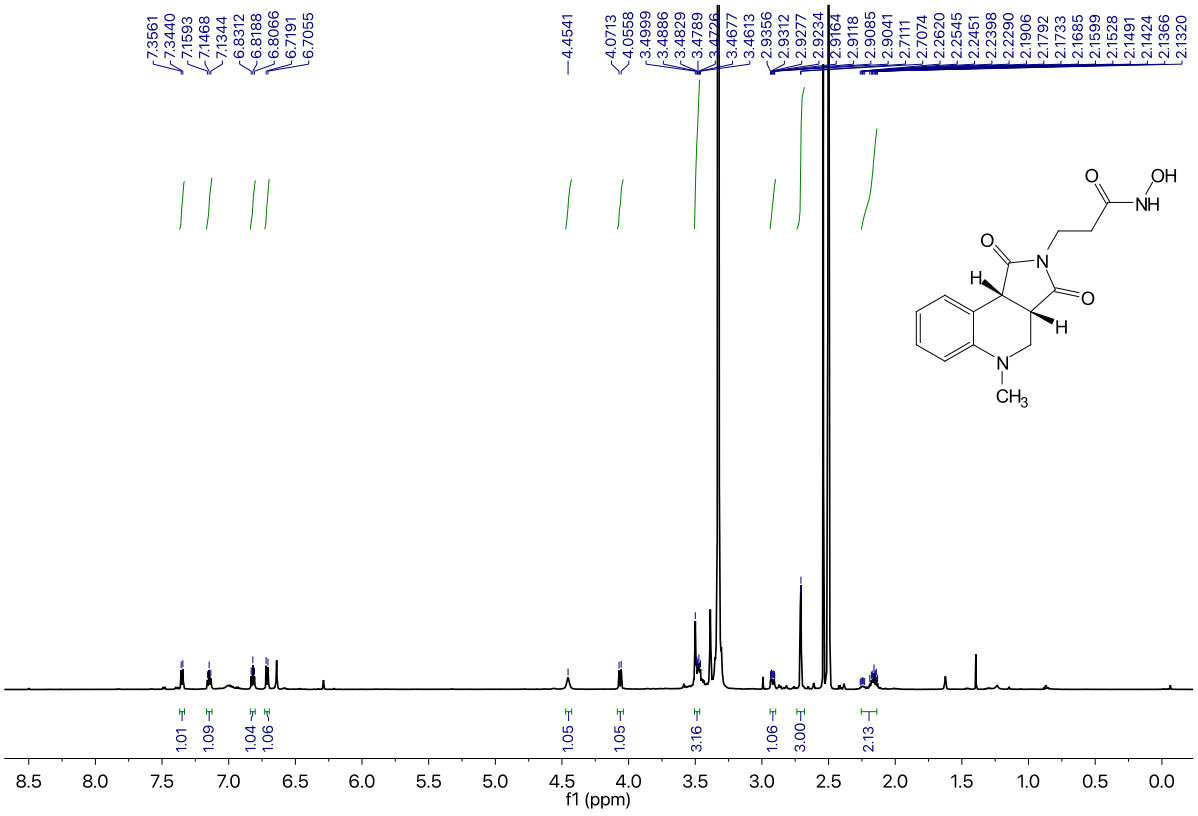
115.3643
113.6401
113.5638
51.6825
44.0631
42.7538
39.7237
11.4209
9.9807
f1 (ppm)


7.3761
7.3715
7.3553
7.2359
7.1026
7.0786
7.0606
6.9888
6.9724
6.5938
6.5750
6.5639
6.5597
6.5460
3.9452
3.7204
3.6774
3.6216
3.5917
3.5665
3.3450
3.2938
3.2768
3.2433
2.8722
2.4862
2.4659
2.4497
2.3721
2.3577
1.07
1.05
2.00
1.03
1.95
3.00
3.01
2.09
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)
O
OH
N
H
CH3


174.3501
174.0287
172.9615
145.3135
128.9871
128.9014
118.4367
116.1283
111.2773
46.1643
40.3471
38.2287
34.9455
33.5284
29.4526
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)
O
OH
N
H
CH3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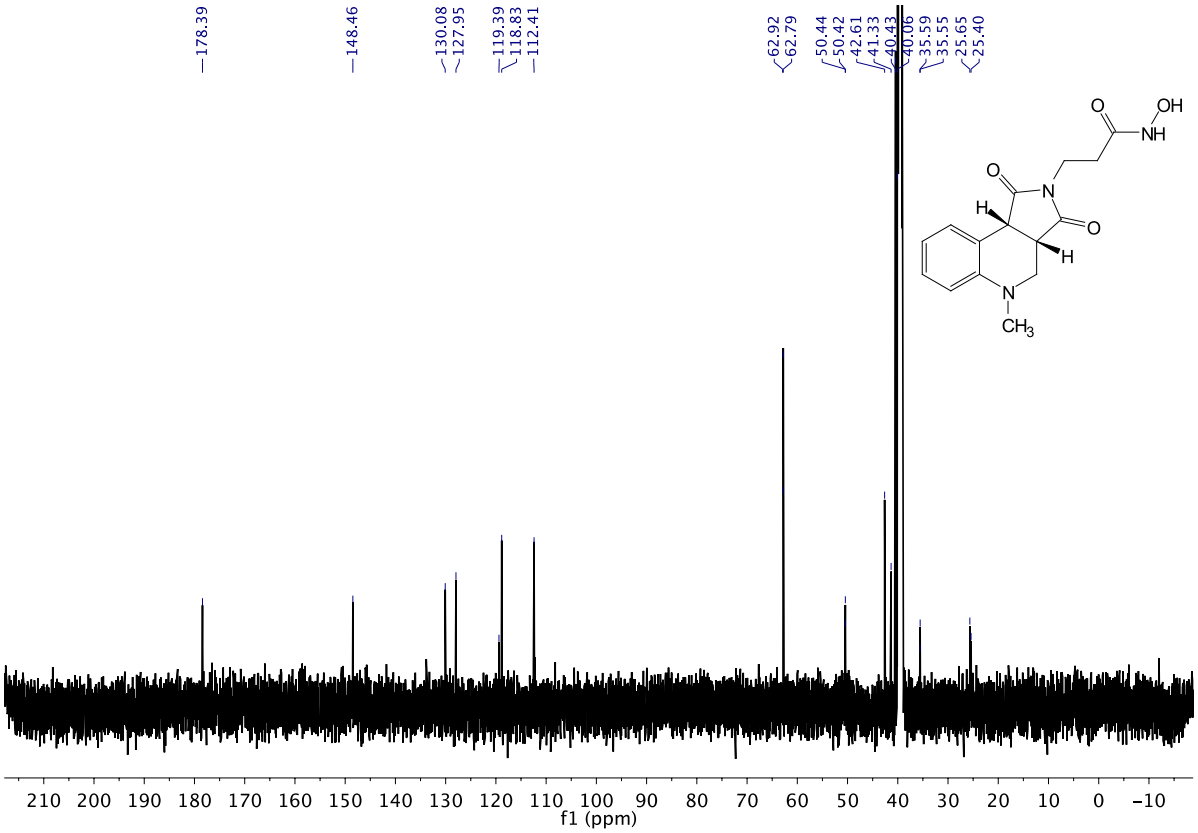
7.3440
7.1593
7.1468
7.1344
6.8312
6.8188
6.8066
6.7191
6.7055
4.4541
4.0713
4.0558
3.4999
3.4886
3.4829
3.4789
3.4726
3.4677
3.4613
2.9356
2.9312
2.9277
2.9234
2.9164
2.9118
2.9085
2.9041
2.7111
2.7074
2.2620
2.2545
2.2451
2.2398
2.2290
2.1906
2.1792
2.1733
2.1685
2.1599
2.1528
2.1491
2.1424
2.1366
2.1320
1.01
1.09
1.04
1.06
1.05
1.05
3.16
1.06
3.00
2.13
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)
O
OH
NH
O
N
H
O
H
N
CH3


178.39
148.46
130.08
127.95
119.39
118.83
112.41
62.92
62.79
50.44
50.42
42.61
41.33
40.43
40.06
35.59
35.55
25.65
25.40
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)
O
OH
NH
O
N
H
O
H
N
CH3

References

1 C.-W. Hsu and H. Sundén, *Org. Lett.*, 2018, **20**, 2051–2054.
2 R. C. Clevenger and K. D. Turnbull, *Synthetic Communications*, 2000, **30**, 1379–1388.