Supporting Information

Selective synthesis of three product classes from imine and carboxylic acid precursors via direct imine acylation

James Rossi-Ashton, Richard J. K. Taylor* and William P. Unsworth*

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General Information

Except where stated, all reagents were purchased from commercial sources and used without further purification. Except where stated, all experimental procedures were carried out under an atmosphere of argon. Anhydrous CH_2Cl_2 was obtained from an Innovative Technology Inc. PureSolv® solvent purification system. ^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL ECX400 or JEOL ECS400 spectrometer, operating at 400 MHz and 100 MHz, respectively. All spectral data was acquired at 295 K unless stated. Chemical shifts (δ) are quoted in parts per million (ppm). The residual solvent peak, δ_H 7.26 and δ_C 77.0 for $CDCl_3$ was used as a reference. Coupling constants (*J*) are reported in Hertz (Hz) to the nearest 0.1 Hz. The multiplicity abbreviations used are: s singlet, d doublet, t triplet, q quartet, m multiplet. Signal assignment was achieved by analysis of DEPT, COSY, NOESY, HMBC and HSQC experiments where required. Infrared (IR) spectra were recorded on a PerkinElmer UATR two spectrometer as a thin film. Mass-spectra (low and high-resolution) were obtained by the University of York Mass Spectrometry Service, using electrospray ionisation (ESI) on a Bruker Daltonics, Micro-tof spectrometer. Melting points were determined using Gallenkamp apparatus and are uncorrected. Thin layer chromatography was carried out on Merck silica gel $60F_{254}$ pre-coated aluminium foil sheets and were visualised using UV light (254 nm) and stained with basic aqueous potassium permanganate. Flash column chromatography was carried out using slurry packed Fluka silica gel (SiO_2), 35–70 μm, 60 Å, under a light positive pressure, eluting with the specified solvent system.

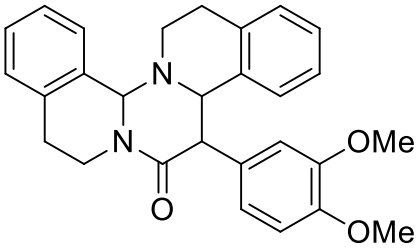
General procedure A. To a solution of imine **1** (100 mg, 0.762 mmol, 1 equiv.) and the appropriate carboxylic acid **2** (0.915 mmol, 1.2 equiv.) in $CHCl_3$ (4 mL) was added DIPEA (1.410 mmol, 1.85 equiv.) followed by T3P (1.14 mmol, 1.5 eq, 50% weight solution in THF). The resulting solution was then stirred at rt, 45 °C, or 70 °C as indicated, for 20 h, before $BF_3.Et_2O$ (1.525 mmol, 2.0 equiv.) was added and the reaction mixture was stirred for a further 1 h at rt, 45 °C or 70 °C as indicated, before being quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL). The aqueous layer was extracted with DCM (3 x 10 mL), dried ($MgSO_4$) and concentrated under reduced pressure.

General procedure B. To a solution of imine **1** (100 mg, 0.762 mmol, equiv.) and carboxylic acid **2** (1.2 equiv.) in $CHCl_3$ (5 mL) was added DIPEA (1.85 equiv.) followed by T3P (1.5 eq, 50% weight solution in THF). The resulting solution was stirred at 70 °C for 20 hr, before being quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL). The aqueous layer was extracted with DCM (3 x 10 mL), dried ($MgSO_4$) and concentrated under reduced pressure.

General procedure C. To a solution of carboxylic acid (1 equiv.) in $CHCl_3$ (7 mL) was added T3P (1.5 equiv., 50% weight solution in THF) followed by imine **1** (3 equiv.). The resulting solution was stirred at 70 °C for 20 hr, before being quenched by the addition of saturated aqueous NH_4Cl (10 mL). The aqueous layer was extracted with DCM (3 x 10 mL), dried ($MgSO_4$) and concentrated under reduced pressure.

For the syntheses of compounds **4a** and **5a** see a) W. P. Unsworth, G. Coulthard, C. Kitsiou R. J. K. Taylor, *J. Org. Chem*. 2014, **79**, 1368 and b) G. Coulthard, W. P. Unsworth, R. J. K. Taylor, *Tetrahedron Lett.* 2015, **56**, 3113.

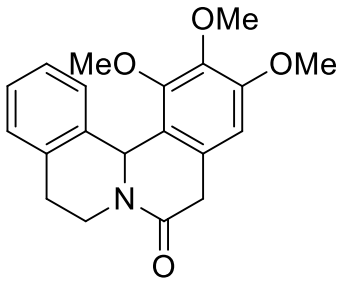
5-(3,4-Dimethoxyphenyl)-4b,5,8,9,15,16-hexahydropyrimido[2,1-a:4,3-a'] diisoquinolin-6(13bH)-one (6a)



The title compound **6a** was synthesised using general procedure C from acid **2a** (100 mg, 0.510 mmol) and imine **1** (202 mg, 1.530 mmol). The unpurified reaction mixture contained a mixture of 4 diastereoisomers in a roughly 10:3:3:2 ratio (A:B:C:D) based on analysis of the unpurified product by ^{1}H NMR spectroscopy. The product was then purified by column chromatography (6:4 ethyl acetate:hexane), affording the *title compound* **6a** (169 mg, 75% overall) as a mixture of three diastereoisomers in a ratio of roughly 6:2:1 (A:B:C). From this mixture, the major isomer was isolated cleanly as an orange oil (114 mg, 51%), with spectral data for the major isomer provided: R_f = 0.20 (7:3 ethyl acetate:hexane); ν_{max} (thin film)/cm^{-1} 2931, 1639, 1514, 1462, 1262, 1237, 1028, 909, 728; δ_H (400 MHz, $CDCl_3$) 7.53 – 7.49 (1 H, m), 7.36 – 7.20 (4 H, m), 7.14 (1 H, t, *J* 7.0), 7.09 (1 H, t, *J* 7.0), 7.02 (1 H, d, *J* 7.5), 6.68 – 6.61 (2 H, m), 6.51 (1 H, d, *J* 8.0), 5.27 (1 H, s), 4.70 (1 H, d, *J* 4.5), 4.22 (1 H, d, *J* 4.5), 3.90 (1 H, ddd, *J* 13.0, 10.5, 6.0), 3.71 (3 H, s), 3.74 – 3.66 (1 H, m), 3.49 (3 H, s), 3.39 (1 H, dt, *J* 11.5, 4.5), 3.15 – 2.93 (3 H, m), 2.72 (1 H, app. dt, *J* 16.0, 4.0), 2.59 (1 H, ddd, *J* 11.5, 10.0, 4.0); δ_C (101 MHz, $CDCl_3$) 169.7 (C), 147.7 (C), 147.5 (C), 137.4 (C), 135.9 (C), 135.3 (C), 134.5 (C), 129.5 (C), 129.1 (CH), 128.2 (CH), 127.9 (CH), 126.9 (CH), 126.7 (CH), 126.6 (CH), 125.8 (CH), 124.5 (CH), 123.1 (CH), 113.6 (CH), 110.3 (CH), 74.2 (CH), 60.9 (CH), 55.7 (CH_3), 55.6 (CH_3), 52.1 (CH), 46.5 (CH_2), 41.7 (CH_2), 29.0 (CH_2), 27.6 (CH_2). HRMS (ESI$^+$): Found: 441.2141; $C_{28}H_{29}N_2O_3^+$ (MH^+) Requires 441.2173 (4.0 ppm error)

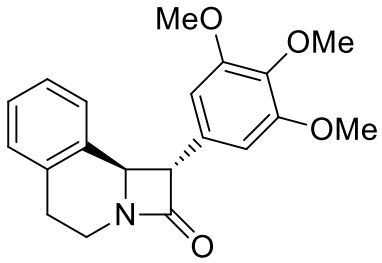
The diastereoisomeric ratio was calculated based on integration of the diamino singlets (NCHC) identified from the unpurified ^{1}H NMR spectra: {6.17 (1 H, s, B), 5.51 (1 H, s, C), 5.63 (1 H, s, D), 5.32 (1 H, s, A)} (3:3:2:10)

1,2,3-Trimethoxy-8,9-dihydro-5H-isoquinolino[1,2-a]isoquinolin-6(13bH)-one (4b)



The title compound **4b** was synthesised using procedure A from imine **1** (100 mg, 0.762 mmol) and acid **2b** (207 mg, 0.915 mmol) with the addition of $BF_3.OEt_2$ after 40 mins stirring at room temperature. Purification by column chromatography (7:3 ethyl acetate:hexane) afforded the *title compound* **4b** as an off white solid (127 mg, 49%): M.p 185–188 °C; R_f = 0.37 (100% ethyl acetate); ν_{max} (thin film)/cm^{-1} 2939, 2840, 1652, 1459, 1415, 1355, 1126, 1110, 736; δ_H (400 MHz, $CDCl_3$) 7.23 – 7.14 (2 H, m), 7.07 (1 H, td, *J* 8.0, 2.0), 6.71 (1 H, d, *J* 8.0), 6.46 (1 H, s), 5.77 (1 H, s), 4.65 (1 H, ddd, *J* 13.0, 8.0, 5.0), 3.95 (3 H, s), 3.92 (3 H, s), 3.89 (3 H, s), 3.49 (1 H, d, *J* 20.0), 3.48 – 3.39 (1 H, m), 3.35 (1 H, d, *J* 20.0), 3.34 – 3.21 (1 H, m), 2.98 (1 H, ddd, *J* 16.5, 7.0, 5.0); δ_C (101 MHz, $CDCl_3$) 169.3 (C), 154.0 (C), 150.5 (C), 140.1 (C), 138.0 (C), 135.2 (C), 128.9 (CH), 128.1 (C), 127.7 (CH), 126.1 (CH), 124.6 (CH), 117.4 (C), 106.0 (CH), 61.1 (2 × CH_3), 61.1 (CH_3), 56.2 (CH), 42.1 (CH_2), 36.7 (CH_2), 27.4 (CH_2); HRMS (ESI^+): Found: 362.1361; $C_{20}H_{21}NNaO_4^+$ (MNa^+) Requires 362.1363 (0.6 ppm error); Found: 340.1539; $C_{20}H_{22}NO_4^+$ (MH^+) Requires 340.1543 (1.2 ppm error).

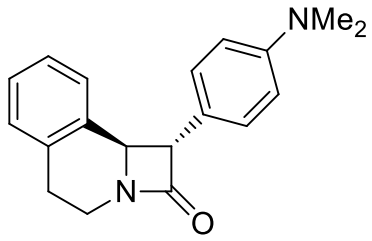
1-(3,4,5-Trimethoxyphenyl)-4,5-dihydro-1H-azeto[2,1-a]isoquinolin-2(9bH)-one (5b)



The title compound **5b** was synthesised using procedure B from imine **1** (100 mg, 0.762 mmol) and acid **2b** (207 mg, 0.915 mmol). Purification by column chromatography (4/6 ethyl acetate/ n-hexane) afforded the *title compound* **5b** as a yellow solid (139 mg, 54%): M.p 88–90 °C; R_f = 0.53 (100% ethyl acetate); ν_{max} (thin film)/cm^{-1} 2939, 1749, 1588, 1508, 1455, 1423, 1349, 1242, 1126; δ_H (400 MHz, $CDCl_3$) 7.32 – 7.16 (4 H, m), 6.60 (2 H, s), 4.56 (1 H, s), 4.15 –

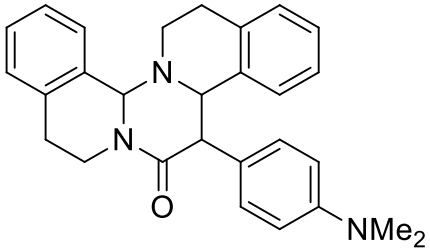
4.02 (2 H, m), 3.90 (6 H, s), 3.85 (3 H, s), 3.22 (1 H, ddd, *J* 12.0, 9.0, 4.0), 3.13 (1 H, ddd, *J* 16.0, 9.0, 6.0), 2.81 (1 H, ddd, *J* 16.0, 4.0); δ_C (100 MHz, $CDCl_3$) 169.5 (C), 153.9 (C), 137.7 (2 × C), 135.1 (C), 134.0 (C), 130.9 (C), 129.8 (CH), 127.7 (CH), 127.2 (CH), 126.2 (CH), 104.5 (2 × CH), 64.2 (CH), 61.0 (CH_3), 57.3 (CH), 56.4 (2 × CH_3), 38.0 (CH_2), 28.4 (CH_2); HRMS (ESI^+): Found: 362.1354; $C_{20}H_{21}NNaO_4^+$ (MNa^+) Requires 362.1363 (2.5 ppm error).

1-(4-(Dimethylamino)phenyl)-4,5-dihydro-1H-azeto[2,1-a]isoquinolin-2(9bH)-one (5c)



The title compound **5c** was synthesised using general procedure B from imine **1** (100 mg, 0.762 mmol) and acid **2c** (164 mg 0.915 mmol). Purification by column chromatography (4:6 ethyl acetate:hexane) afforded the *title compound* **5c** as a red oil as a single diastereoisomer (113 mg, 51%): R_f = 0.24 (4:6 ethyl acetate:hexane); ν_{max} (thin film)/cm^{-1} 2800, 1748, 1623, 1454, 1179, 1164, 1057, 761, 596; δ_H (400 MHz, $CDCl_3$) 7.32 – 7.14 (6 H, m), 6.77 (2 H, d, *J* 8.7), 4.50 (1 H, s), 4.10 (1 H, d, *J* 2.1), 4.06 (1 H, ddd, *J* 9.1, 5.9, 4.0), 3.25 – 3.04 (2 H, m), 2.97 (6 H, s), 2.79 (1 H, ddd, *J* 8.6, 4.0, 4.0); δ_C (100 MHz, $CDCl_3$) 170.4 (C), 150.3 (C), 135.5 (C), 133.9 (C), 129.7 (CH), 128.4 (2 × CH), 127.5 (CH), 127.1 (CH), 126.3 (CH), 123.0 (C), 113.1 (2 × CH), 63.6 (CH), 57.7 (CH), 40.8 (2 × CH_3), 37.8 (CH_2), 28.4 (CH_2); HRMS (ESI^+): Found: 293.1639; $C_{19}H_{21}N_2O^+$ (MH^+) Requires 293.1648 (3.1 ppm error)

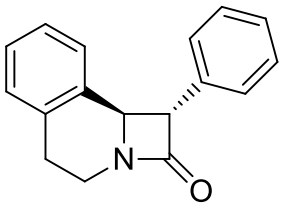
5-(4-Dimethylamino)phenyl)-4b,5,8,9,15,16-hexahydropyrimido[2,1-a:4,3-a']diisoquinolin-6(13bH)-one (6c)



The title compound **6c** was synthesised using general procedure C from acid **2c** (100 mg, 0.588 mmol) and imine **1** (220 mg 1.674 mmol). The unpurified reaction mixture contained a mixture of 3 diastereoisomers in a roughly 5:2:1 ratio (A:B:C) based on analysis of the unpurified product by ^{1}H NMR spectroscopy. The product was then purified by column chromatography (7:3 ethyl acetate:hexane), affording the *title compound* **6c** (85 mg, 36% overall) as a mixture of two diastereoisomers in a ratio of roughly 5:2 (A:B). From this mixture, the major isomer was isolated cleanly as a red oil (60 mg, 25%), with spectral data for the major isomer provided: R_f = 0.19 (9:1 ethyl acetate:hexane); ν_{max} (thin film)/cm^{-1} 2926, 1672, 1610, 1520, 1315, 1143, 947, 745, 699; δ_H (400 MHz, $CDCl_3$) 7.53 (1 H, d, *J* 6.5), 7.38 – 7.29 (2 H, m), 7.27 (1 H, d, *J* 8.0), 7.23 (1 H, d, *J* 8.0), 7.14 (1 H, t, *J* 7.0), 7.07 (1 H, t, *J* 7.0), 7.00 (1 H, d, *J* 7.5), 6.93 (2 H, d, *J* 8.5), 6.36 (2 H, d, *J* 8.5), 5.27 (1 H, s), 4.66 (1 H, d, *J* 4.5), 4.18 (1 H, d, *J* 4.5), 3.90 (1 H, ddd, *J* 13.0, 10.0, 5.5), 3.67 (1 H, app. dt, *J* 13.0, 5.0), 3.38 (1 H, app. dt, *J* 11.5, 5.0), 3.18 – 2.90 (3 H, m), 2.76 (6 H, s), 2.69 (1 H, app. dt, 16.0, 4.0), 2.56 (1 H, ddd, *J* 11.5, 9.0, 4.0); δ_C (100 MHz, $CDCl_3$) 170.3 (C), 162.7 (C), 137.4 (C), 136.0 (C), 135.2 (C), 134.7 (C), 131.2 (2 × CH), 129.0 (CH), 128.0 (CH), 127.8 (2 × CH), 127.0 (CH), 126.8 (CH), 126.4 (CH), 125.8 (CH), 124.8 (CH), 112.1 (2 × CH), 74.3 (CH), 61.0 (CH), 51.7 (CH), 46.1 (CH_2), 41.5 (CH_2), 40.8 (2 × CH_3), 29.0 (CH_2), 27.7 (CH_2); HRMS (ESI$^+$): Found: 424.2375; $C_{28}H_{30}N_3O^+$ (MH^+) Requires 424.2383 (–2.0 ppm error).

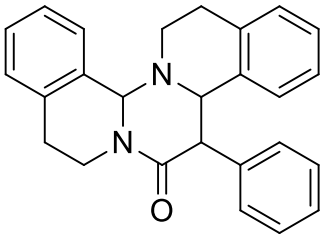
The diastereoisomeric ratio was calculated based on integration of the diamino singlets (NCHC) identified from the unpurified ^{1}H NMR spectra: {6.14 (1 H, s, C), 5.47 (1 H, s, B), 5.25 (1 H, s, A)} (1:2:5)

1-Phenyl-4,5-dihydro-1H-azeto[2,1-a]isoquinolin-2(9bH)-one (5d)



The title compound **5d** was synthesised using general procedure B from imine **1** (100 mg, 0.762 mmol) and acid **2d** (125 mg 0.915 mmol). Purification by column chromatography (4/6 ethyl acetate/ n-hexane) afforded the *title compound* **5d** as a yellow oil (172 mg, 47%) as a single diastereoisomer; R_f = 0.36 (4:6 ethyl acetate:hexane); ν_{max} (thin film)/cm^{-1} 3027, 2926, 1744, 1496, 1454, 1356, 750, 697; δ_H (400 MHz, $CDCl_3$) 7.45 – 7.18 (9 H, m), 4.57 (1 H, s), 4.20 (1 H, d, *J* 2.0) 4.07 (1 H, ddd, *J* 9.5, 6.0, 4.0), 3.27 – 3.09 (2 H, m), 2.81 (1 H, app. dt, *J* 9.0, 4.0); δ_C (100 MHz, $CDCl_3$) 169.5 (C), 135.3 (C), 135.2 (C), 134.0 (C), 129.7 (CH), 129.2 (2 × CH), 127.9 (CH), 127.7 (2 × CH), 127.6 (CH), 127.2 (CH), 126.3 (CH), 63.9 (CH), 57.2 (CH), 37.9 (CH_2), 28.4 (CH_2); HRMS (ESI$^+$): Found: 272.1048; $C_{17}H_{15}NNaO^+$ (MNa^+) Requires 272.1046 (0.7 ppm error).

5-Phenyl-4b,5,8,9,15,16-hexahydropyrimido[2,1-a:4,3-a']diisoquinolin-6(13bH)-one (6d)

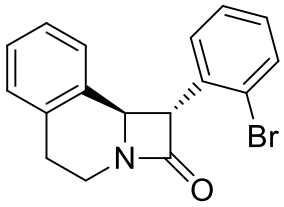


The title compound **6d** was synthesised using general procedure C from acid **2d** (100 mg, 0.734 mmol) and imine **1** (289 mg 2.203 mmol). The unpurified reaction mixture contained a mixture of 3 diastereoisomers in a roughly 7:2:1 ratio (A:B:C) based on analysis of the unpurified product by ^{1}H NMR spectroscopy. The product was then purified by column chromatography (4:6 ethyl acetate:hexane), affording the *title compound* **6c** (191 mg, 69% overall) as a mixture of 3 diastereoisomers in a ratio of roughly 10:6:3 (A:B:C). From this mixture, the major isomer was isolated cleanly as an orange oil (101 mg, 36%), with spectral data for the major isomer provided: R_f = 0.20 (1:1 ethyl acetate:hexane); ν_{max} (thin film)/cm−1 3028, 2931, 1640, 1453, 1316, 910, 729, 690; δ_H (400 MHz, $CDCl_3$) 7.54 – 7.48 (1 H, m), 7.38 – 7.27 (3 H, m), 7.22 (1 H, d, *J* 7.5), 7.16 – 7.03 (4 H, m), 7.02 – 6.91 (4 H, m), 5.32 (1 H, s), 4.74 (1 H, d, *J* 5.0), 4.28

(1 H, d, *J* 5.0), 3.94 (1 H, ddd, *J* 13.0, 10.0, 6.0), 3.69 (1 H, app. dt, *J* 13.0, 5.0), 3.36 (1 H, app. dt, *J* 11.5, 5.0), 3.15 – 2.98 (2 H, m), 2.97 – 2.86 (1 H, m), 2.70 (1 H, app. dt, *J* 16.0, 4.5), 2.57 (1 H, ddd, *J* 11.5, 9.0, 4.0); δ_C (100 MHz, $CDCl_3$) 169.7 (C), 137.4 (C), 137.0 (C), 135.6 (C), 135.2 (C), 134.3 (C), 130.7 (2 × CH), 128.9 (CH), 128.1 (CH), 127.9 (CH), 127.5 (2 × CH), 127.0 (CH), 126.9 (CH), 126.5 (CH), 126.5 (CH), 125.8 (CH), 124.8 (CH), 74.2 (CH), 60.9 (CH), 52.8 (CH), 45.6 (CH_2), 41.5 (CH_2), 28.8 (CH_2), 27.7 (CH_2); HRMS (ESI^+): Found: 403.1760; $C_{26}H_{24}N_2NaO^+$ (MNa^+) Requires 403.1781 (5.2 ppm error)

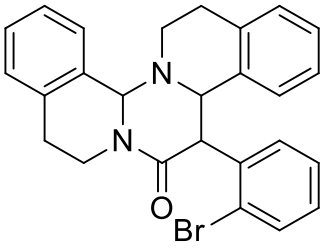
The diastereoisomeric ratio was calculated based on integration of the diamino singlets (NCHC) identified from the unpurified ^1H NMR spectra: {6.17 (1 H, s, C): 5.50 (1 H, s, B): 5.37 (1 H, s, A)} (1:2:7).

1-(2-Bromophenyl)-4,5-dihydro-1H-azeto[2,1-a]isoquinolin-2(9bH)-one (5e)



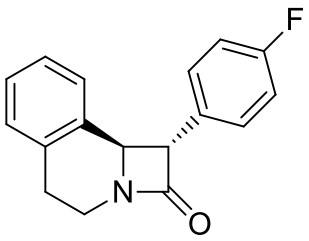
The title compound **5e** was synthesised using general procedure B from imine **1** (100 mg, 0.762 mmol) and acid **2e** (197 mg 0.915 mmol). Purification by column chromatography (4/6 ethyl acetate/ n-hexane) afforded the *title compound* **5e** as a yellow oil (172 mg, 69%) as a single diastereoisomer: R_f = 0.32 (4:6 ethyl acetate:hexane); ν_{max} (thin film)/cm^{-1} 3062, 2935, 1746, 1354, 1296, 1026, 751, 690; δ_H (400 MHz, $CDCl_3$) 7.64 (1 H, dd, *J* 8.0, 1.0), 7.55 – 7.50 (2 H, m), 7.38 (1 H, td, *J* 7.5, 1.0), 7.33 – 7.25 (2 H, m), 7.23 – 7.18 (2 H, m), 4.68 (1 H, d, *J* 2.0), 4.46 (1 H, s), 4.11 – 4.04 (1 H, m), 3.27 – 3.10 (2 H, m), 2.81 (1 H, app. dt, *J* 9.0, 4.0); δ_C (101 MHz, $CDCl_3$) 169.1 (C), 135.5 (C), 134.6 (C), 134.1 (C), 133.2 (CH), 129.6 (CH), 129.5 (CH), 129.0 (CH), 128.4 (CH), 127.79 (CH), 127.2 (CH), 127.1 (CH), 124.6 (CH), 63.1 (CH), 58.1 (CH), 38.1 (CH_2), 28.5 (CH_2); HRMS (ESI^+): Found: 350.0152; $C_{17}H_{14}{}^{79}BrNNaO^+$ (MNa^+) Requires 350.0151 (0.3 ppm error).

5-(2-Bromophenyl)-4b,5,8,9,15,16-hexahydropyrimido[2,1-a:4,3-a']diisoquinolin-6(13bH)-one (6e)



The compound was synthesised using general procedure C from acid **2e** (100 mg, 0.465 mmol) and imine **1** (190 mg 1.395 mmol). Purification by column chromatography (4/6 ethyl acetate/ n-hexane) afforded the *title compound* **6e** as a single diastereoisomer, as an orange oil (120 mg, 56%): R_f = 0.48 (1:1 ethyl acetate:hexane); ν_{max} (thin film)/cm^{-1} 3064, 2923, 1639, 1419, 908, 725, 674; δ_H (400 MHz, $CDCl_3$) 7.66 – 7.62 (1 H, m), 7.45 – 7.40 (1 H, m), 7.39 – 7.30 (2 H, m), 7.26 (1 H, dd, *J* 5.7, 2.8), 7.10 – 7.06 (1 H, m), 6.99 – 6.92 (2 H, m), 6.88 – 6.79 (4 H, m), 5.63 (1 H, s), 5.13 (1 H, d, *J* 9.3), 5.09 (1 H, d, *J* 9.3), 3.94 – 3.71 (2 H, m), 3.07 – 2.80 (5 H, m), 2.68 (1 H, ddd, 11.8, 5.2, 5.4); δ_C (100 MHz, $CDCl_3$) 169.7 (C), 137.4 (C), 137.4 (C), 134.2 (C), 134.1 (C), 134.0 (C), 132.3 (2 × CH), 128.3 (CH), 128.2 (CH), 128.1 (CH), 128.0 (CH), 127.9 (CH), 127.3 (C), 127.2 (CH), 126.8 (CH), 126.5 (CH), 126.4 (CH), 125.4 (CH), 73.4 (CH), 61.1 (CH), 51.2 (CH_2), 41.4 (CH), 40.8 (CH_2), 28.7 (CH_2), 28.4 (CH_2); HRMS (ESI$^+$): Found: 481.0847; $C_{26}H_{23}{}^{79}BrN_2NaO^+$ (MNa^+) Requires 481.0886 (8.1 ppm error)

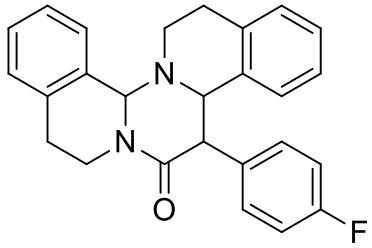
1-(4-Fluorophenyl)-4,5-dihydro-1H-azeto[2,1-a]isoquinolin-2(9bH)-one (5f)



The title compound **5f** was synthesised using general procedure B from imine **1** (100 mg, 0.762 mmol) and acid **2f** (141 mg 0.915 mmol). Purification by column chromatography (4/6 ethyl acetate/ n-hexane) afforded the *title compound* **5f** as a white solid (124 mg, 61%) as a single diastereoisomer: M.p 96–98 °C; R_f = 0.26 (4:6 ethyl acetate:hexane); ν_{max} (thin film)/cm^{-1} 3020, 2936, 1745, 1509, 1354, 1221, 1159, 739, 520; δ_H (400 MHz, $CDCl_3$) 7.36 (2 H, dd, *J* 9.0, 5.5), 7.30 – 7.16 (4 H, m), 7.08 (2 H, t, *J* 9.0). 4.53 (1 H, s), 4.16 (1 H, d, *J* 2.0), 4.06 (1 H,

ddd, *J* 12.0, 6.0, 4.0), 3.26 – 3.07 (2 H, m), 2.81 (1 H, app. dt, *J* 9.0, 4.0); δ_C (100 MHz, $CDCl_3$) 169.3 (C), 162.42 (d, *J* 246.3, C), 135.0 (C), 133.9 (C), 131.1 (d, *J* 3.2, C), 129.8 (CH), 129.2 (d, *J* 8.1, 2 × CH), 127.8 (CH), 127.2 (CH), 126.2 (CH), 116.1 (d, *J* 21.3, 2× CH), 63.1 (CH), 57.3 (CH), 37.9 (CH_2), 28.4 (CH_2); HRMS (ESI^+): Found: 268.1127; $C_{17}H_{15}FNO^+$ (MH^+) Requires 268.1132 (1.9 ppm error); Found: 290.0951; $C_{17}H_{14}FNNaO^+$ (MNa^+) Requires 290.0952 (0.3 ppm error).

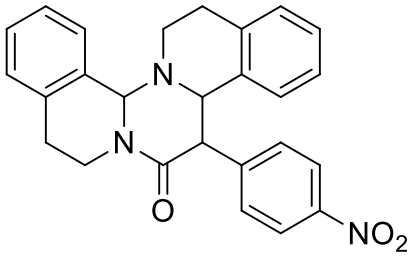
5-(4-Fluorophenyl)-4b,5,8,9,15,16-hexahydropyrimido[2,1-a:4,3-a']diisoquinolin-6(13bH)-one (6f)



The title compound **6f** was synthesised using general procedure C from acid **2f** (100 mg, 0.649 mmol) and imine **1** (257mg 1.946 mmol). The unpurified reaction mixture contained a mixture of 3 diastereoisomers in a roughly 9:2:1 ratio (A:B:C) based on analysis of the unpurified product by ^{1}H NMR spectroscopy. The product was then purified by column chromatography (4:6 ethyl acetate:hexane), affording the *title compound* **6c** (181 mg, 70% overall) as a mixture of 3 diastereoisomers in a ratio of roughly 12:5:1 (A:B:C). From this mixture, the major isomer was isolated cleanly as an orange oil (119 mg, 46%), with spectral data for the major isomer provided: R_f = 0.27 (1:1 ethyl acetate:hexane); ν_{max} (thin film)/cm^{-1} 2932, 1642, 1604, 1508, 1461, 1314, 1222, 1160, 746, 733; δ_H (400 MHz, $CDCl_3$) 7.51 – 7.47 (1 H, m), 7.39 – 7.27 (3 H, m), 7.22 – 6.99 (6 H, m), 6.65 (2 H, t, *J* 8.8), 5.27 (1 H, s), 4.71 (1 H, d, *J* 4.7), 4.26 (1 H, d, *J* 4.7), 3.85 (1 H, ddd, *J* 12.9, 10.7, 5.7), 3.71 (1 H, ddd, *J* 13.0, 5.8, 4.2), 3.37 (1 H, dt, *J* 11.5, 4.6), 3.17 – 2.91 (3 H, m), 2.70 (1 H, dt, *J* 16.0, 4.0), 2.58 (1 H, ddd, *J* 11.5, 9.7, 3.9); δ_C (100 MHz, $CDCl_3$) 169.4 (C), 161.6 (d, *J* 244.6, C), 137.4 (C), 135.7 (C), 135.2 (C), 134.1 (C), 132.7 (d, *J* 3.4, C), 132.1 (d, *J* 7.9, 2 × CH), 129.1 (CH), 128.3 (CH), 127.9 (CH), 127.0 (CH), 126.7 (CH), 126.6 (CH), 125.9 (CH), 124.5 (CH), 114.3 (d, *J* 21.1, 2 × CH), 74.1 (CH), 60.8 (CH), 52.1 (CH_2), 46.3 (CH), 41.7 (CH_2), 28.9 (CH_2), 27.6 (CH_2); HRMS (ESI^+): Found: 421.1666; $C_{26}H_{23}FN_2NaO^+$ (MNa^+) Requires 421.1687 (5.0 ppm error).

The diastereoisomeric ratio was calculated based on integration of the diamino singlets (NCHC) identified from the unpurified ^{1}H NMR spectra: {6.15 (1 H, s, C), 5.49 (1 H, s, B), 5.31 (1 H, s, A)} (1:2:9).

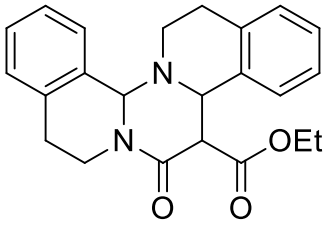
5-(4-Nitrophenyl)-4b,5,8,9,15,16-hexahydropyrimido[2,1-a:4,3-a']diisoquinolin-6(13bH)-one (6g)



The title compound **6g** was synthesised using general procedure C from acid **2g** (100 mg, 0.552 mmol) and imine **1** (217 mg 1.656 mmol). The unpurified reaction mixture contained a mixture of 3 diastereoisomers in a roughly 3:1:1 ratio (A:B:C) based on analysis of the unpurified product by ^{1}H NMR spectroscopy. The product was then purified by column chromatography (4:6 ethyl acetate:hexane), affording the *title compound* **6g** (142 mg, 60% overall) as a mixture of 3 diastereoisomers in a ratio of roughly 3:1:1 (A:B:C). From this mixture, the major isomer was isolated cleanly as an orange solid (85 mg, 36%), with spectral data for the major isomer provided: M.p 161–163 °C; R_f = 0.24 (7:3 ethyl acetate:hexane); ν_{max} (thin film)/cm^{-1} 3064, 1642, 1516, 1344, 1315, 1016, 744, 732; δ_H (400 MHz, $CDCl_3$) 7.83 – 7.78 (2 H, m), 7.49 – 7.44 (1 H, m), 7.35 (2 H, dt, *J* 10.9, 3.8), 7.32 – 7.23 (3 H, m), 7.18 (1 H, d, *J* 7.4), 7.12 (1 H, td, *J* 7.6, 1.6), 7.08 (1 H, td, *J* 7.4, 1.6), 7.01 (1 H, d, *J* 7.3), 5.26 (1 H, s), 4.77 (1 H, d, *J* 4.5), 4.40 (1 H, d, *J* 4.5), 3.88 – 3.67 (2 H, m), 3.36 (1 H, dt, *J* 11.6, 4.5), 3.19 – 2.90 (3 H, m), 2.70 (1 H, dt, *J* 16.1, 3.8), 2.59 (1 H, ddd, *J* 11.6, 9.9, 3.7); δ_C (100 MHz, $CDCl_3$) 168.2 (C), 146.5 (C), 144.7 (C), 137.2 (C), 135.4 (C), 135.1 (C), 133.3 (C), 131.6 (2 × CH), 129.2 (CH), 128.5 (CH), 127.9 (CH), 127.2 (CH), 126.9 (CH), 126.4 (CH), 126.1 (CH), 124.2 (CH), 122.6 (2 × CH), 74.0 (CH), 60.6 (CH), 52.6 (CH), 46.4 (CH_2), 41.9 (CH_2), 28.7 (CH_2), 27.4 (CH_2); HRMS (ESI$^+$): Found: 426.1807; $C_{26}H_{24}N_3O_3^+$ (MH^+) Requires 426.1812 (1.3 ppm error).

The diastereoisomeric ratio was calculated based on integration of the diamino singlets (NCHC) identified from the unpurified ^{1}H NMR spectra: {6.19 (1 H, s, C), 5.53 (1 H, s, B), 5.31 (1 H, s, A)} (1:1:3).

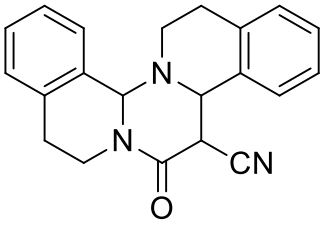
Ethyl 6-oxo-4b,5,6,8,9,13b,15,16-octahydropyrimido[2,1-a:4,3-a']diisoquinoline-5-carboxylate (6h)



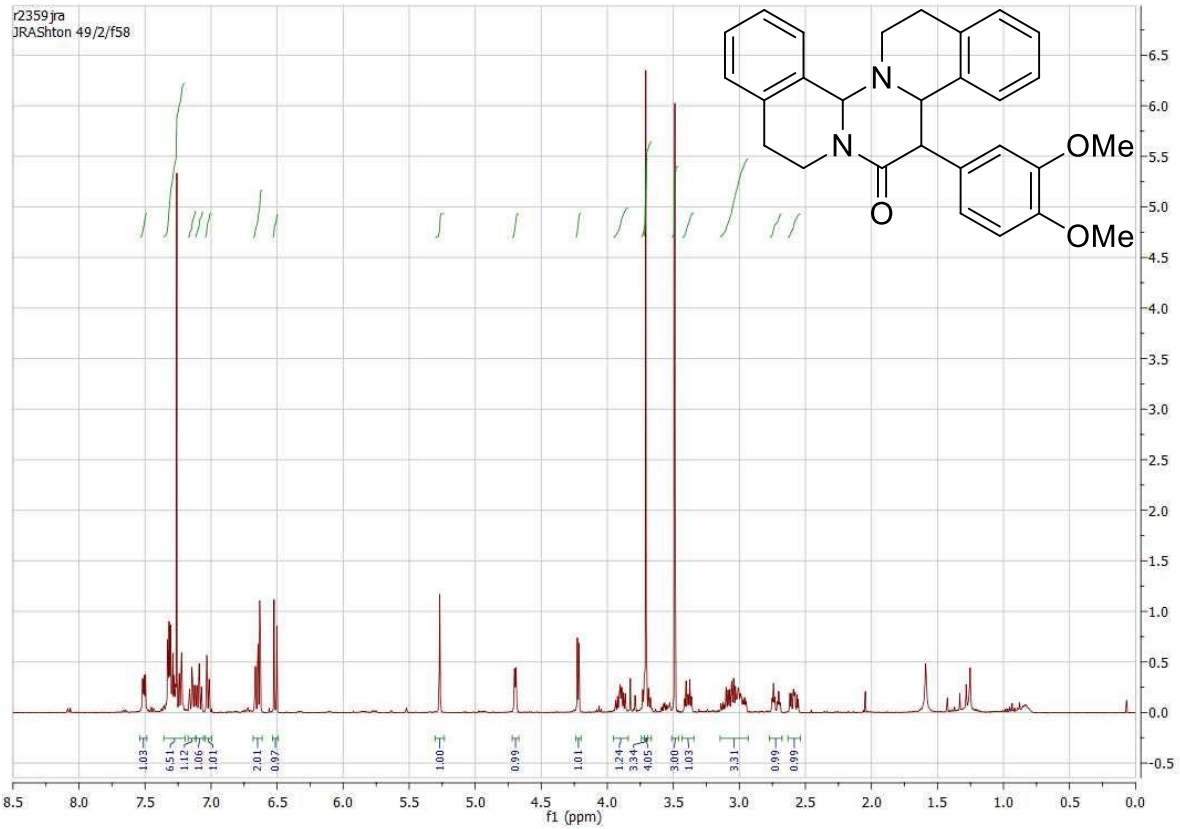
The title compound **6h** was synthesised using general procedure C from acid **2h** (100 mg, 0.757 mmol) and imine **1** (298 mg 2.271 mmol). The unpurified reaction mixture contained a mixture of 2 diastereoisomers in a roughly 3:1 ratio (A:B) based on analysis of the unpurified product by ^{1}H NMR spectroscopy. The product was then purified by column chromatography (4:6 ethyl acetate:hexane), affording the *title compound* **6h** (247 mg, 87% overall) as a mixture of 2 diastereoisomers in a ratio of roughly 11:5 (A:B). From this mixture, the major isomer was isolated cleanly as a white solid (172 mg, 60%), with spectral data for the major isomer provided: M.p 140–142 °C; R_f = 0.28 (6:4 ethyl acetate:hexane); ν_{max} (thin film)/cm^{-1} 2923, 1735, 1648, 1431, 1154, 1096, 1034, 752, 597; δ_H (400 MHz, $CDCl_3$) 7.48 (1 H, dd, *J* 5.2, 3.7), 7.32 – 7.22 (3 H, m), 7.22 – 7.04 (4 H, m), 5.78 (1 H, s), 4.93 (1 H, d, *J* 9.2), 4.74 (1 H, dt, *J* 12.9, 4.1), 3.97 (1 H, d, *J* 9.4), 3.70 (1 H, dq, *J* 10.8, 7.1), 3.59 (1 H, dq, *J* 10.8, 7.1), 3.32 (1 H, td, *J* 11.6, 4.2), 3.24 – 3.10 (1 H, m), 3.02 – 2.71 (3 H, m), 2.63 (1 H, dd, *J* 16.6, 3.5), 2.43 (1 H, dd, *J* 11.5, 6.7), 0.83 (3 H, t, *J* 7.1); δ_C (101 MHz, $CDCl_3$) 169.5 (C), 165.7 (C), 137.0 (C), 135.0 (C), 133.6 (C), 132.6 (C), 129.1 (CH_2), 128.5 (CH_2), 128.0 (CH_2), 127.8 (CH_2), 127.6 (CH_2), 127.4 (CH_2), 127.3 (CH_2), 125.4 (CH_2), 74.5 (CH), 61.2 (CH_2), 58.4 (CH), 53.3 (CH), 38.7 (CH_2), 35.9 (CH_2), 28.7 (CH_2), 28.4 (CH_2), 13.7 (CH_3); HRMS (ESI$^+$): Found: 399.1662; $C_{23}H_{24}N_2NaO_3^+$ (MNa^+) Requires 399.1679 (4.3 ppm error).

The diastereoisomeric ratio was calculated based on integration of the diamino singlets (NCHC) identified from the unpurified ^{1}H NMR spectra: {6.00 (1 H, s, B), 5.78 (1 H, s, A)} (1:3).

6-Oxo-4b,5,6,8,9,13b,15,16-octahydropyrimido[2,1-a:4,3-a']diisoquinoline-5-carbonitrile (6i)



The title compound **6i** was synthesised using general procedure C from acid **2i** (100 mg, 1.18 mmol) and imine **1** (463 mg 3.53 mmol). Purification by column chromatography (4/6 ethyl acetate/ n-hexane) afforded the *title compound* (**6i**) as an yellow solid (261 mg, 79%) as a single diastereoisomer: M.p 178–181 °C; R_f = 0.25 (6:4 ethyl acetate:hexane); ν_{max} (thin film)/cm^{-1} 2894, 2248, 1656, 1428, 907, 725; δ_H (400 MHz, $CDCl_3$) 7.57 – 7.51 (1 H, m), 7.51 – 7.45 (1 H, m), 7.33 – 7.22 (4 H, m), 7.22 – 7.17 (1 H, m), 7.17 – 7.14 (1 H, m), 5.94 (1 H, s), 4.88 – 4.80 (1 H, m), 4.81 (1 H, d, *J* 10.5), 3.84 (1 H, d, *J* 10.5), 3.09 (1 H, app. td, *J* 12.5, 3.5), 2.94 (2 H, ddd, *J* 16.0, 12.0, 6.0), 2.80 (1 H, dt, *J* 16.0, 3.0), 2.67 (1 H, d, *J* 16.0), 2.63 – 2.50 (2 H, m); δ_C (100 MHz, $CDCl_3$) 160.7 (C), 136.4 (C), 134.2 (C), 133.2 (C), 131.5 (C), 129.6 (CH), 128.9 (CH), 128.4 (CH), 128.3 (CH), 127.4 (CH), 127.4 (2 × CH), 126.5 (CH), 117.8 (C), 74.8 (CH), 59.7 (CH), 39.0 (CH_2), 38.4 (CH), 36.1 (CH_2), 28.5 (CH_2), 28.5 (CH_2); HRMS (ESI^+): Found 352.1421 [$C_{21}H_{19}N_3NaO^+$] (MNa^+) Requires 352.1420 (0.3 ppm error).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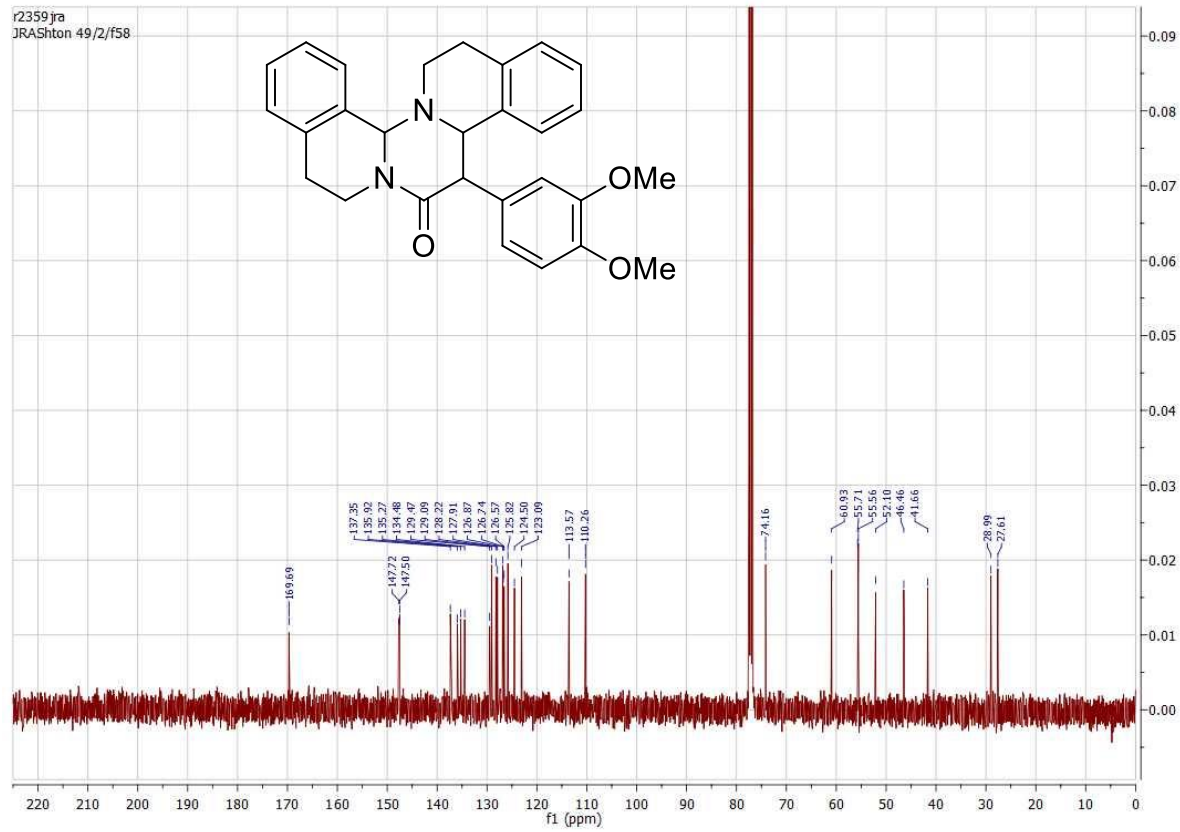
N
N
O
OMe
OMe
f1 (ppm)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O
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OMe
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147.50
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135.92
135.27
134.48
129.47
129.09
128.22
127.91
126.87
126.74
126.57
125.82
124.50
123.09
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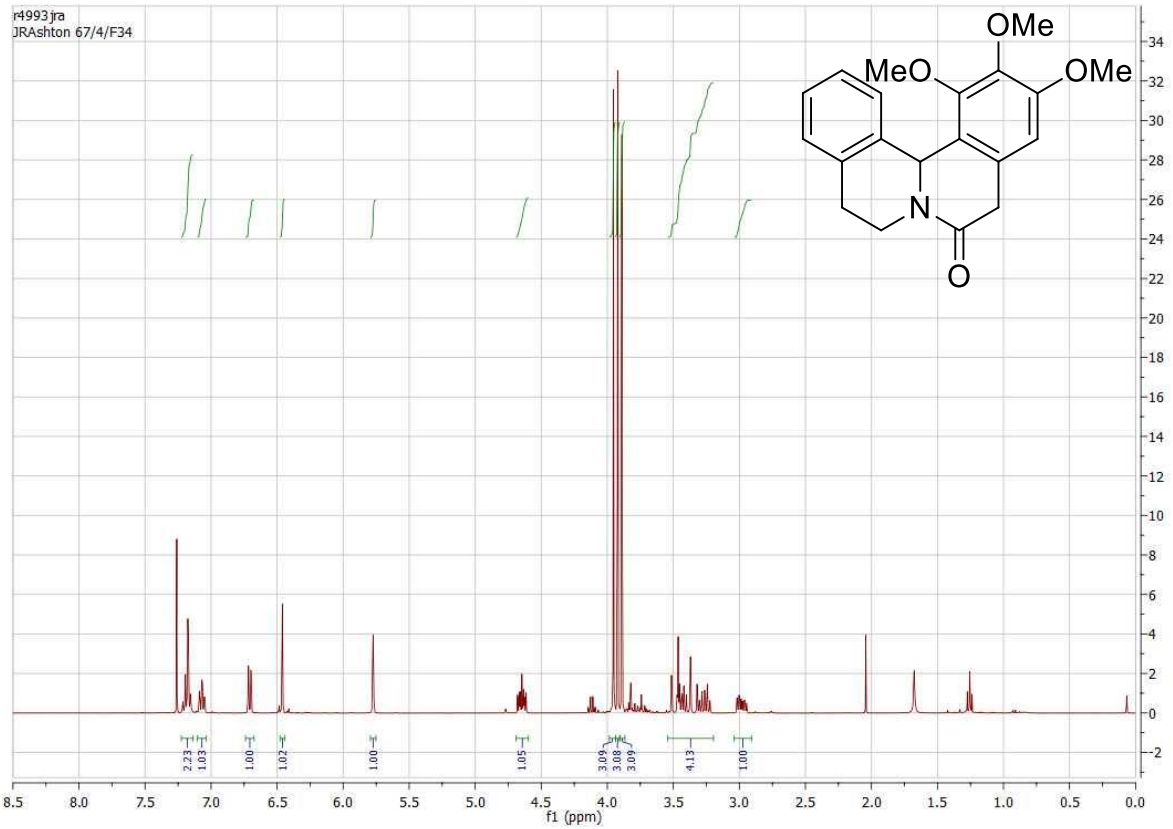
46.46
41.66
28.99
27.61
f1 (ppm)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JRAshton 67/4/F34
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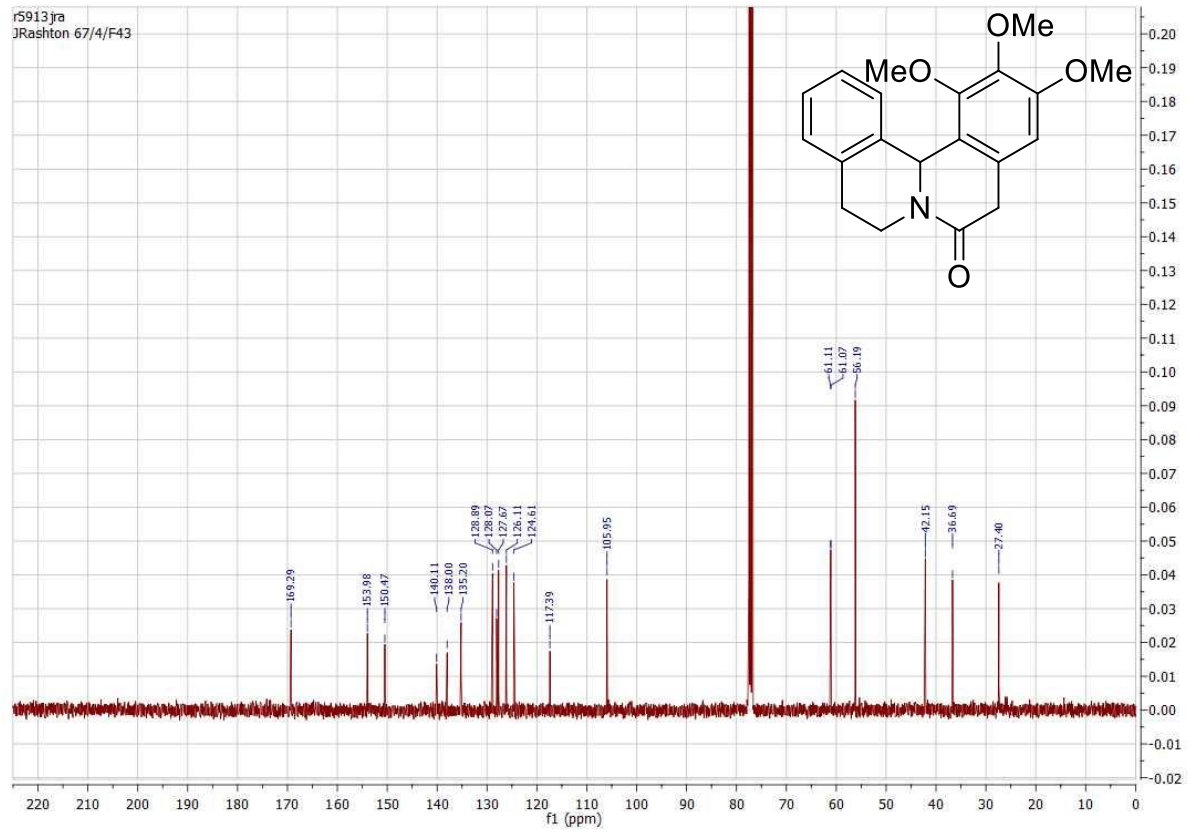
MeO
OMe
N
O
f1 (ppm)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128.07
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61.07
56.19
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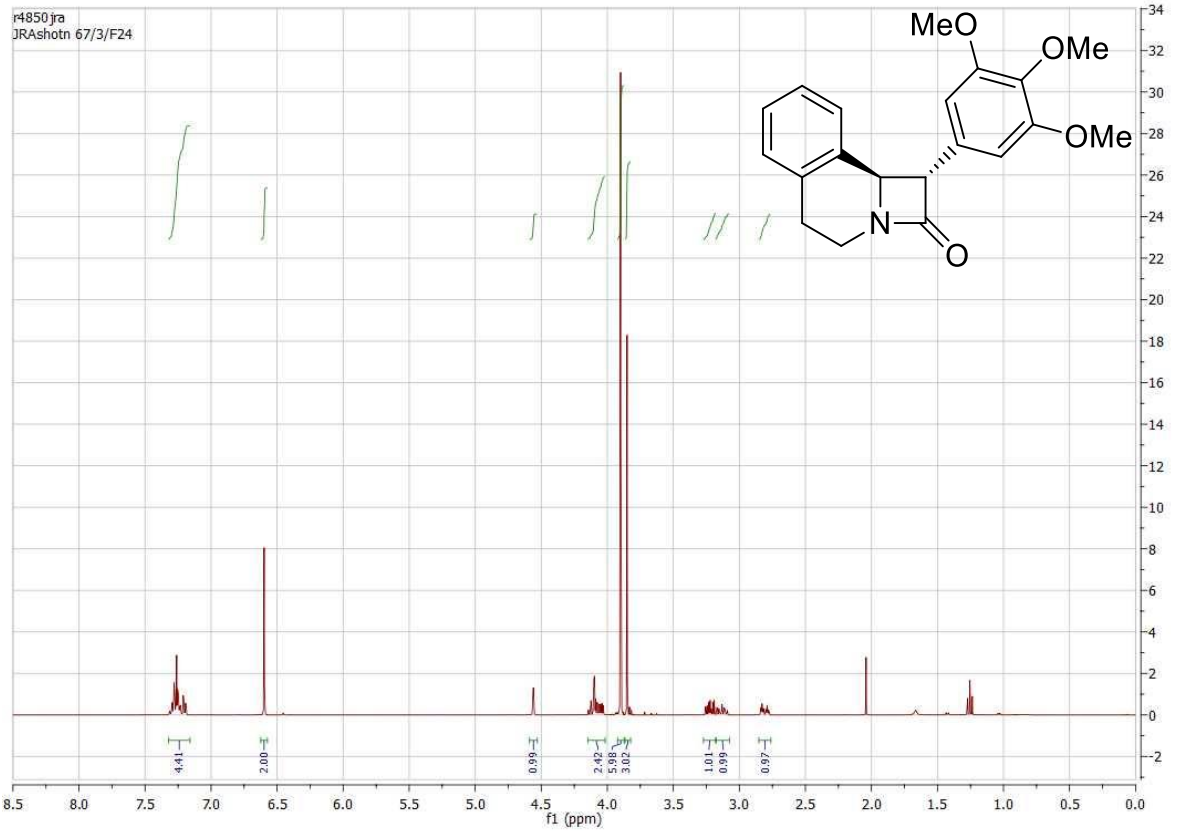
27.40
f1 (ppm)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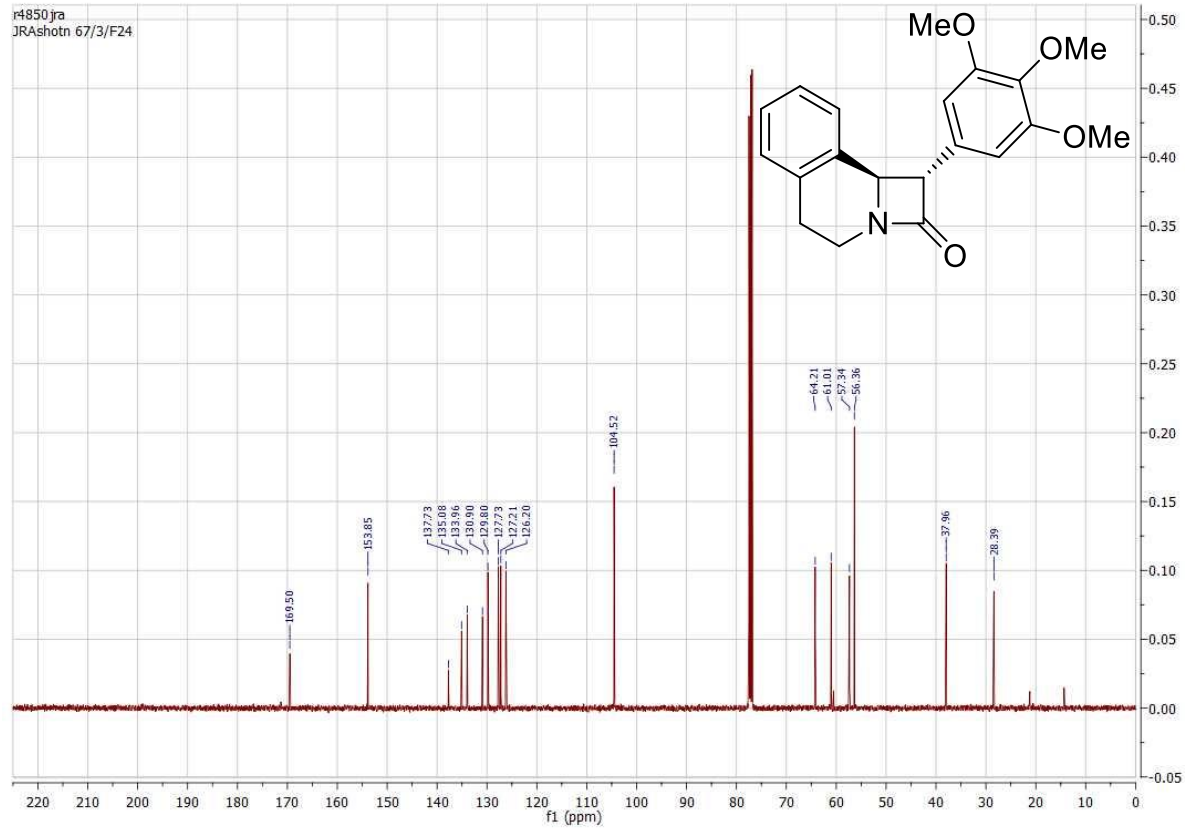
f1 (ppm)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127.73
127.21
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169.50
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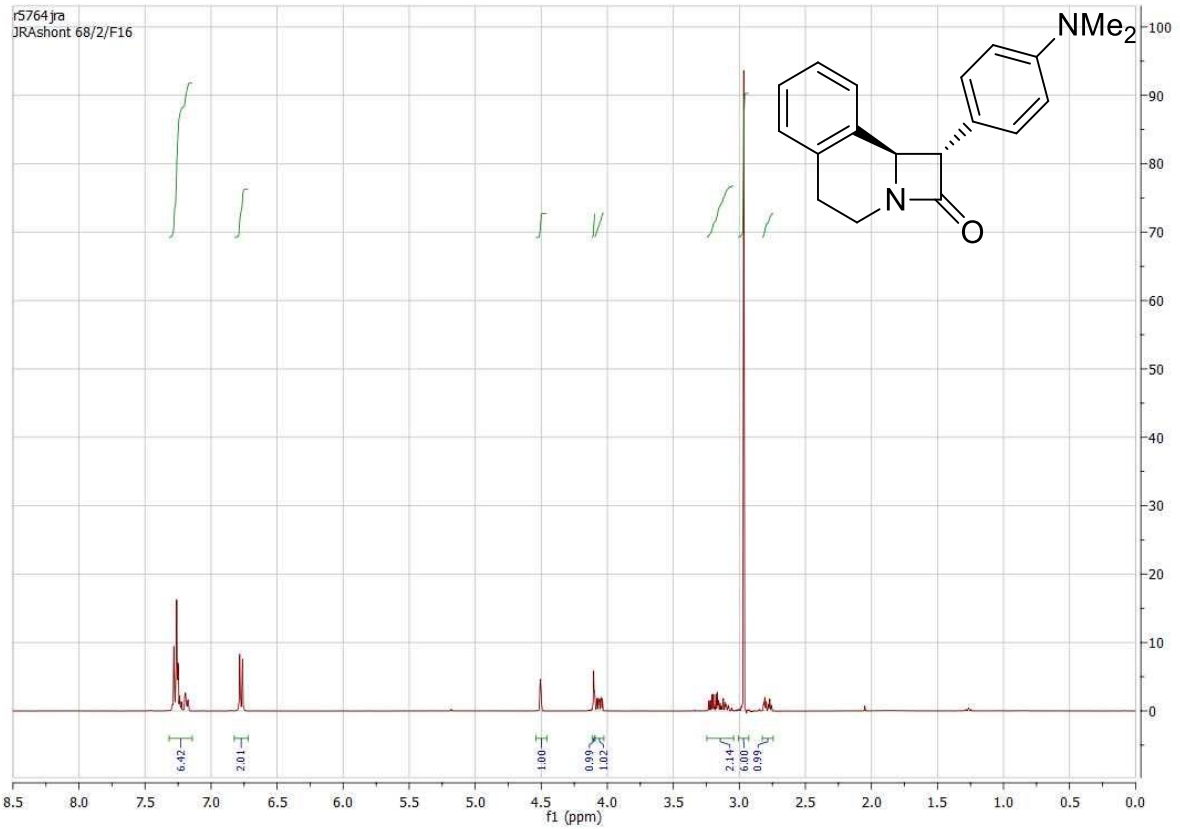
28.39
f1 (ppm)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JRAshont 68/2/F16
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O
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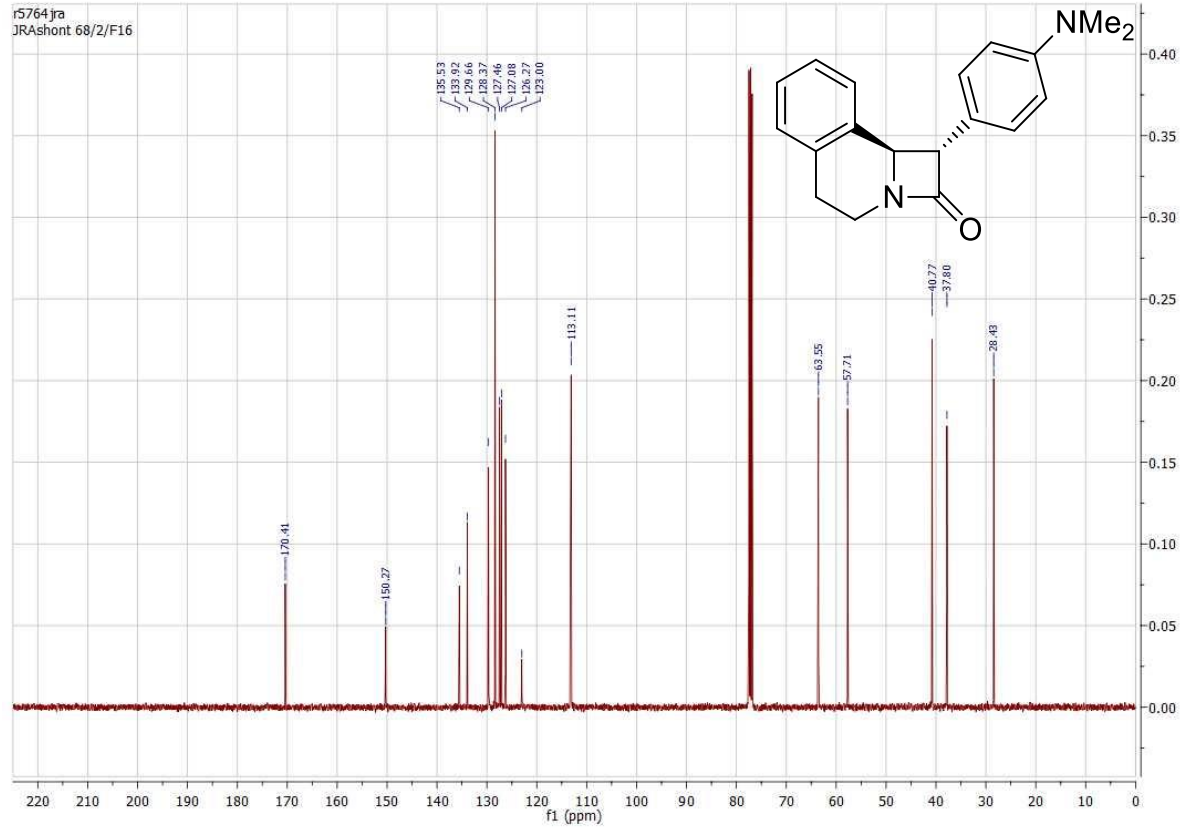
0.99
1.02
2.14
6.00
0.99
f1 (ppm)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O
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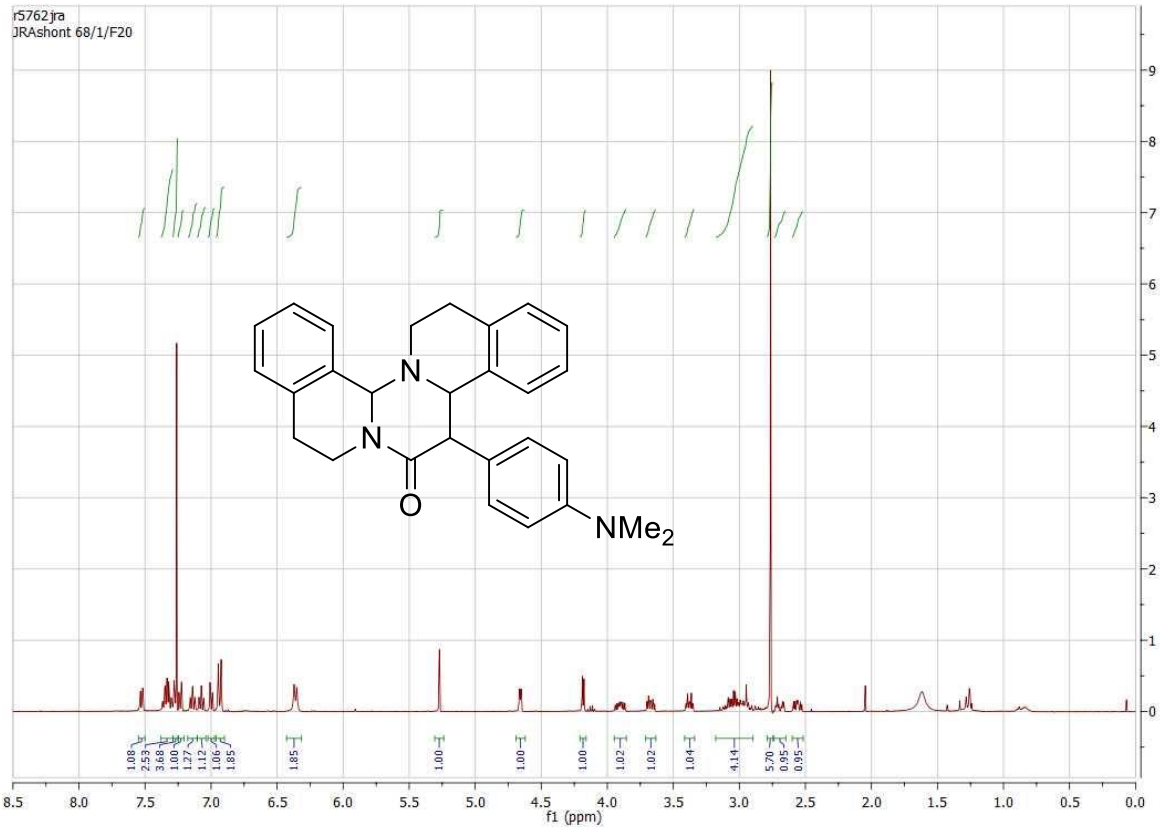
f1 (ppm)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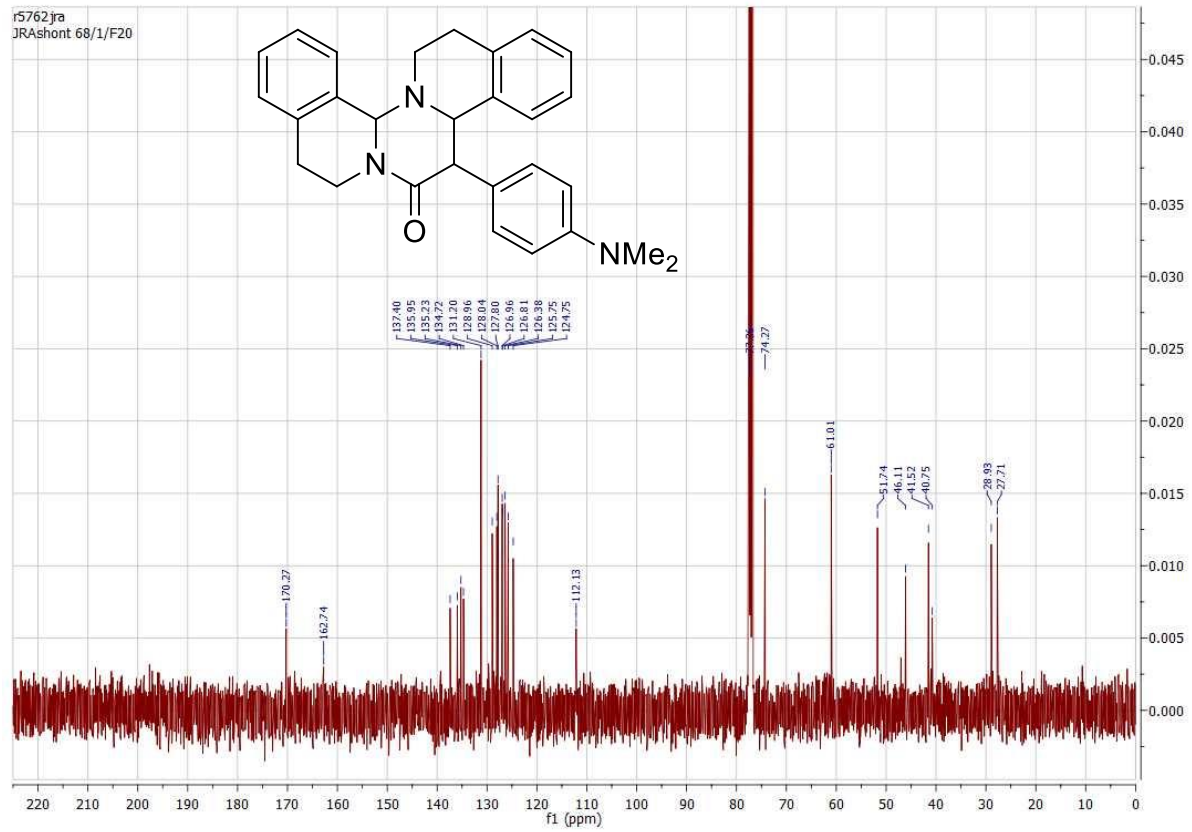
N
O
NMe2
f1 (ppm)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N
O
NMe2
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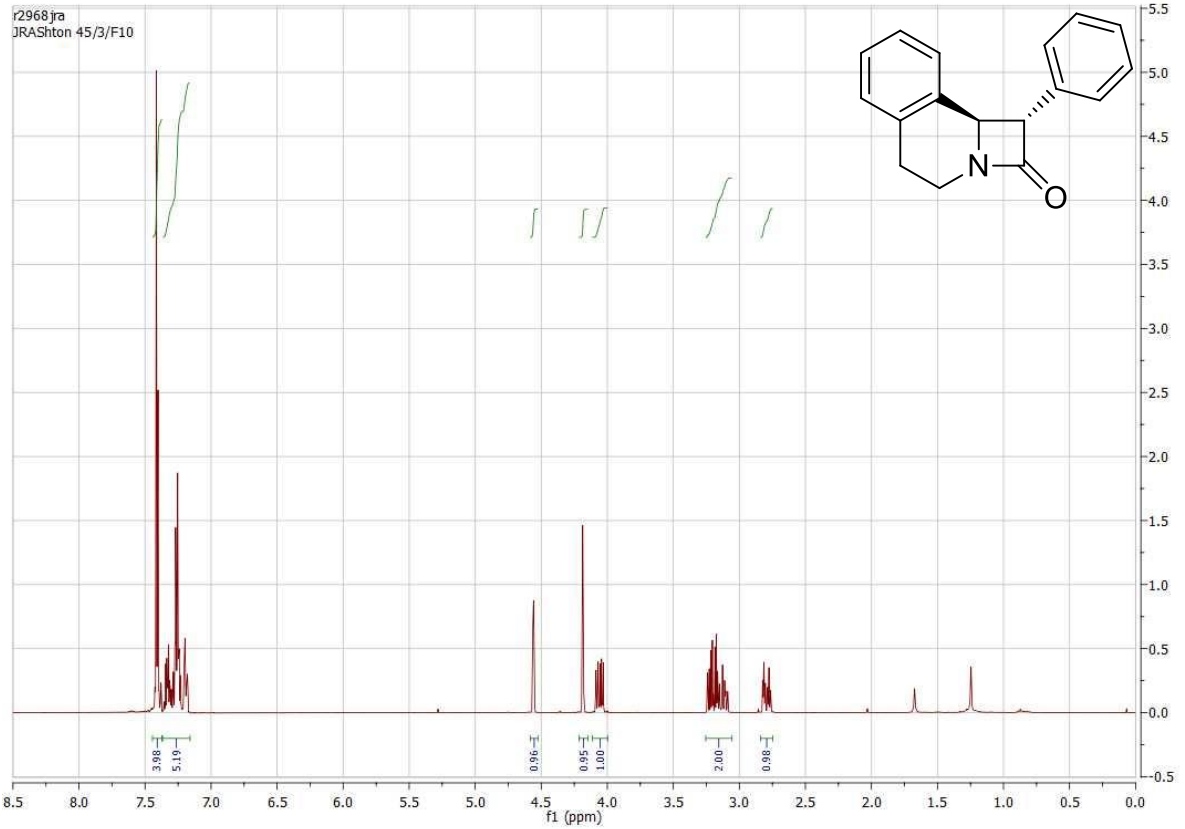
41.52
40.75
28.93
27.71
f1 (ppm)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JRAShton 45/3/F10
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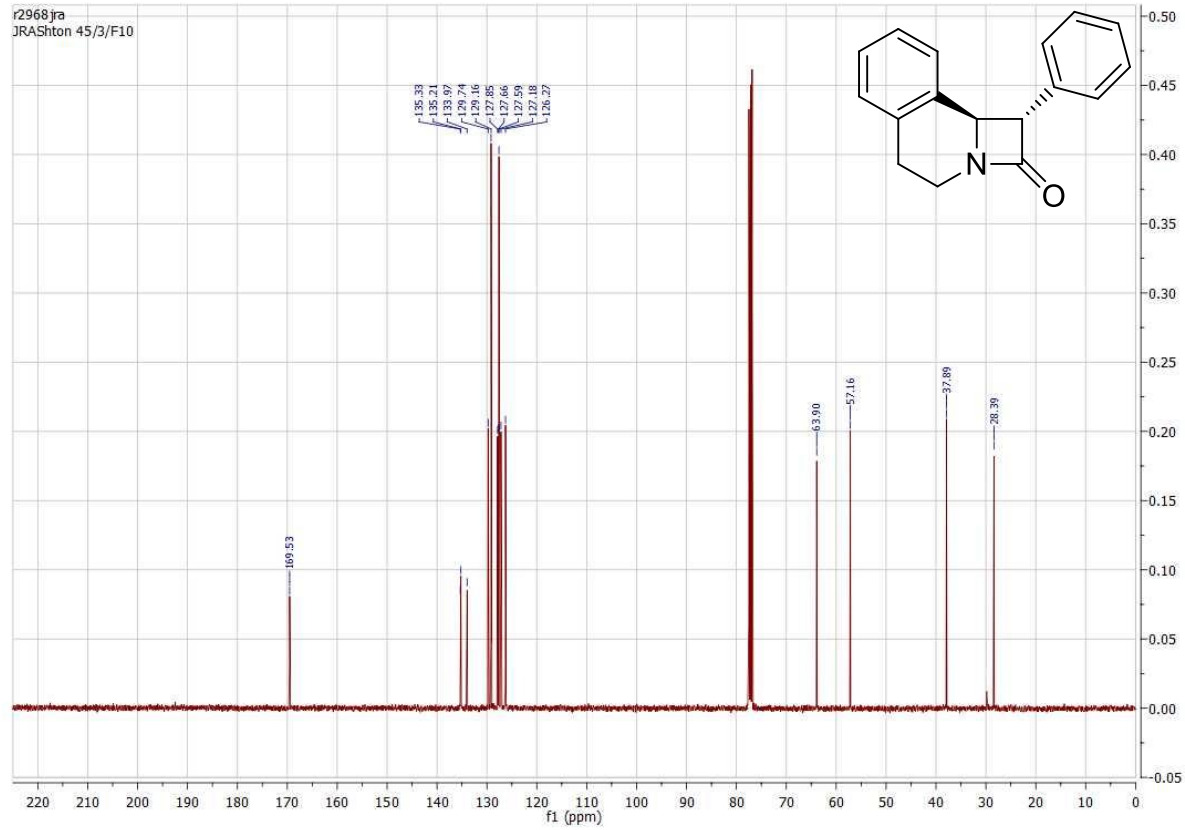
1.00
2.00
0.98
f1 (ppm)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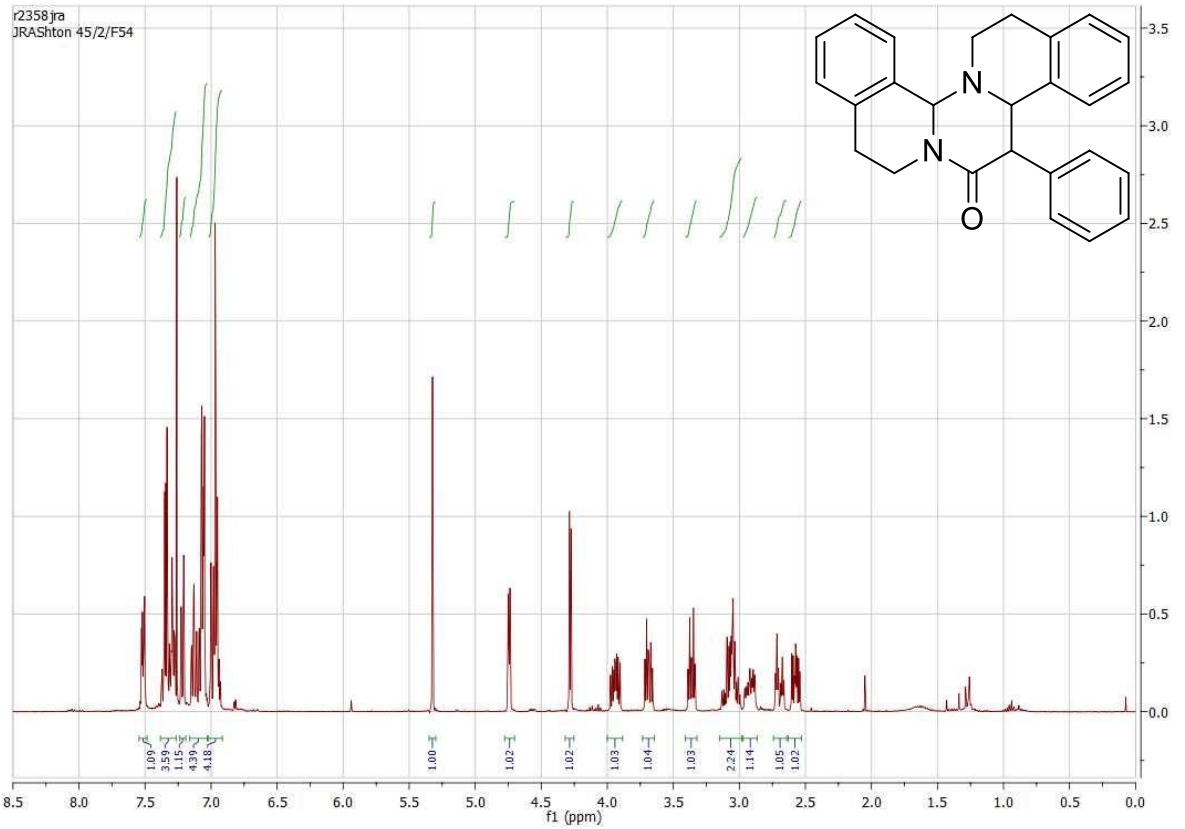
37.89
28.39
N
O
f1 (ppm)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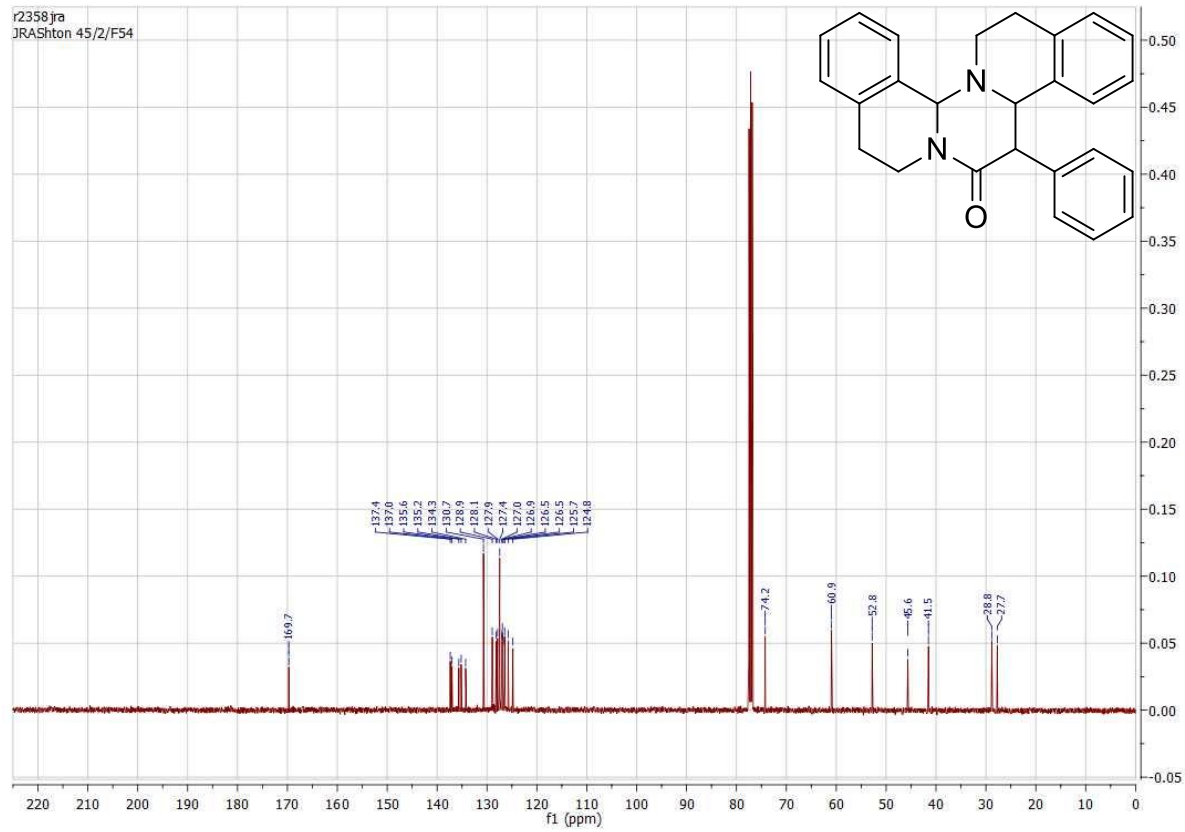
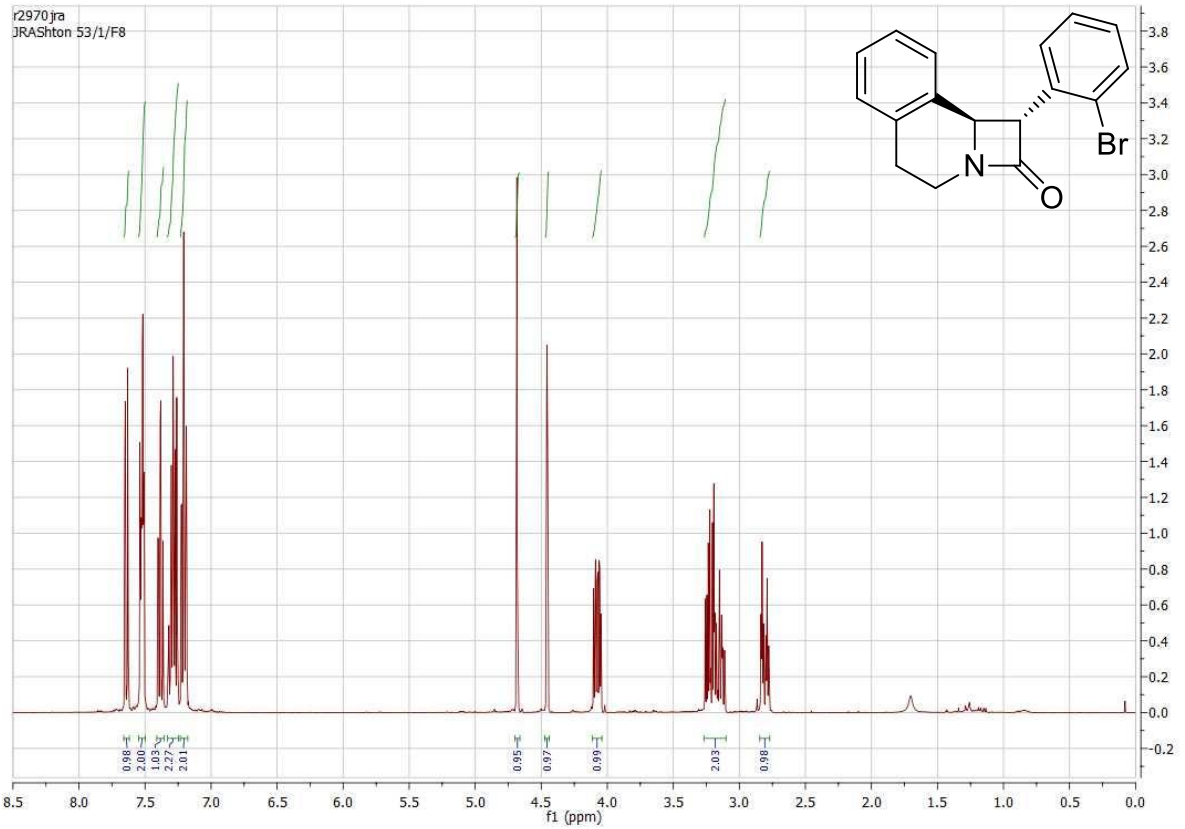
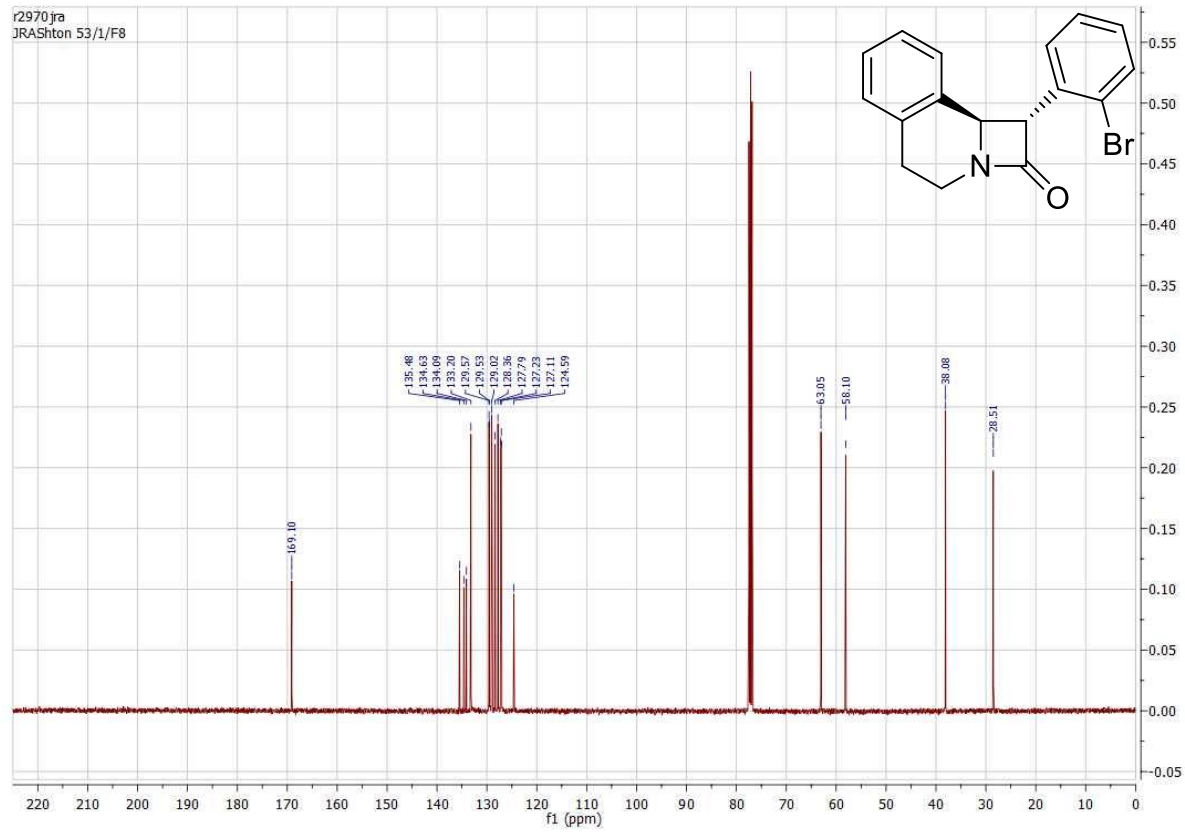
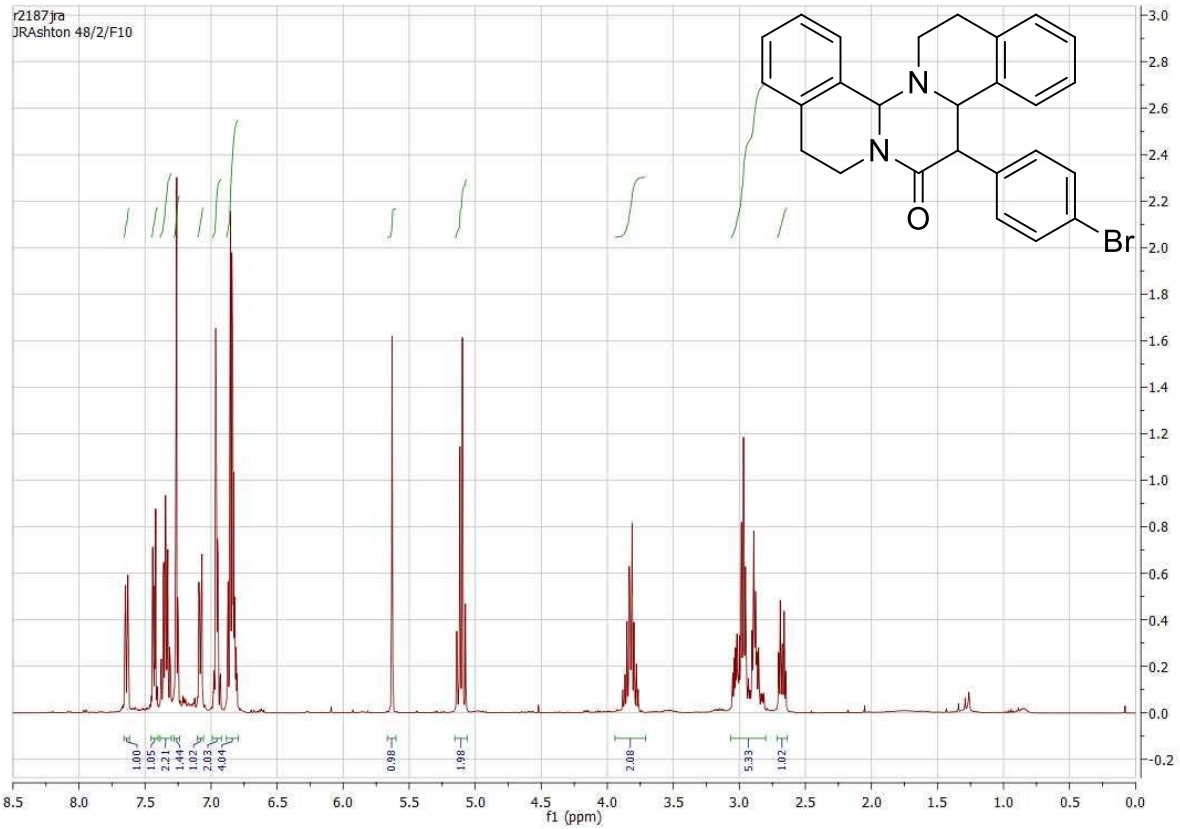
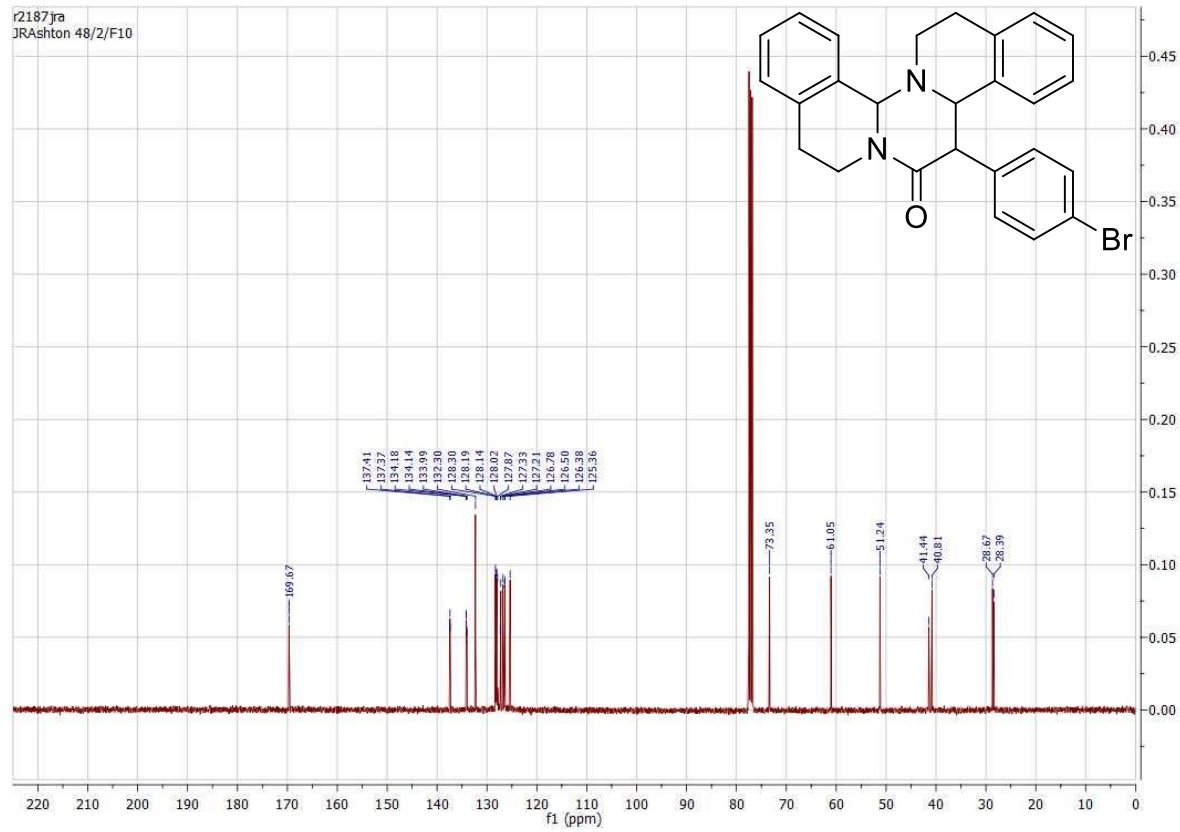
N
O
f1 (ppm)

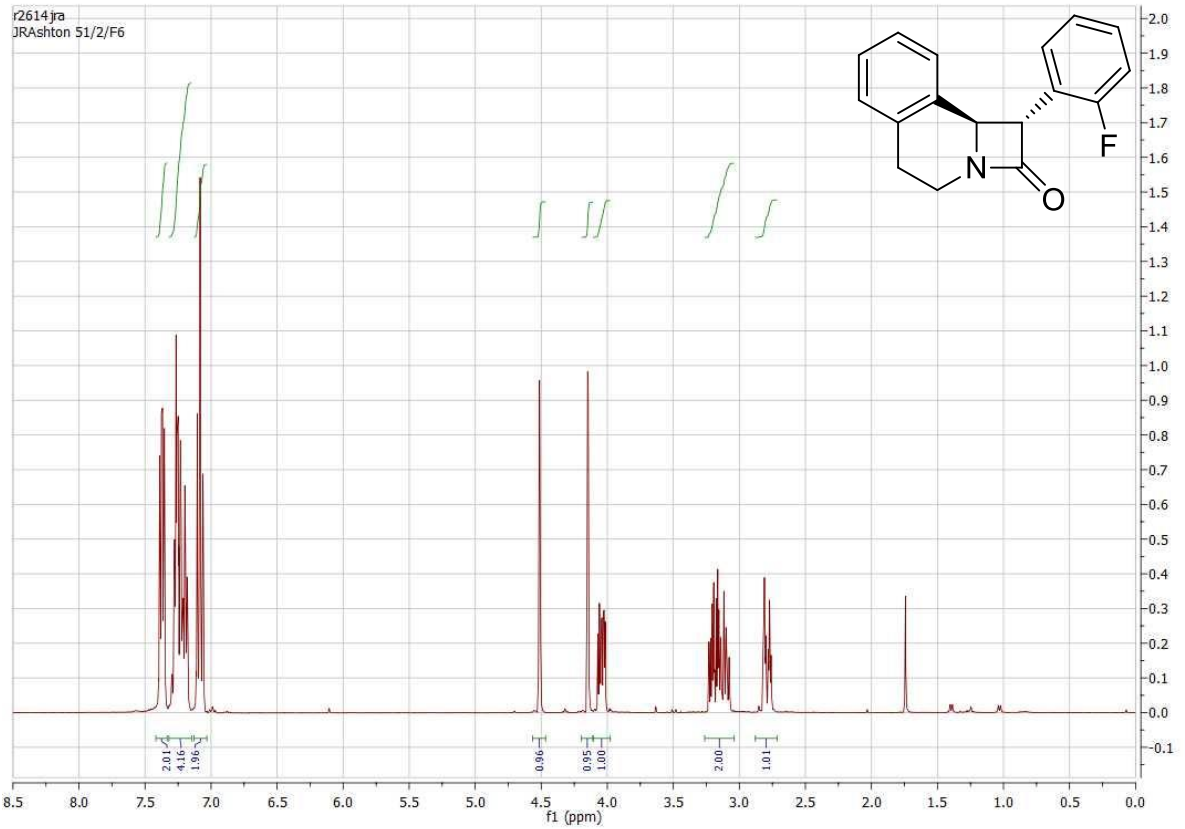

r2358jra
JRAShton 45/2/F54
N
N
O
169.7
137.4
137.0
135.6
135.2
134.3
130.7
128.9
128.1
127.9
127.4
127.0
126.9
126.5
126.5
125.7
124.8
74.2
60.9
52.8
46.6
41.5
28.8
27.7
f1 (ppm)

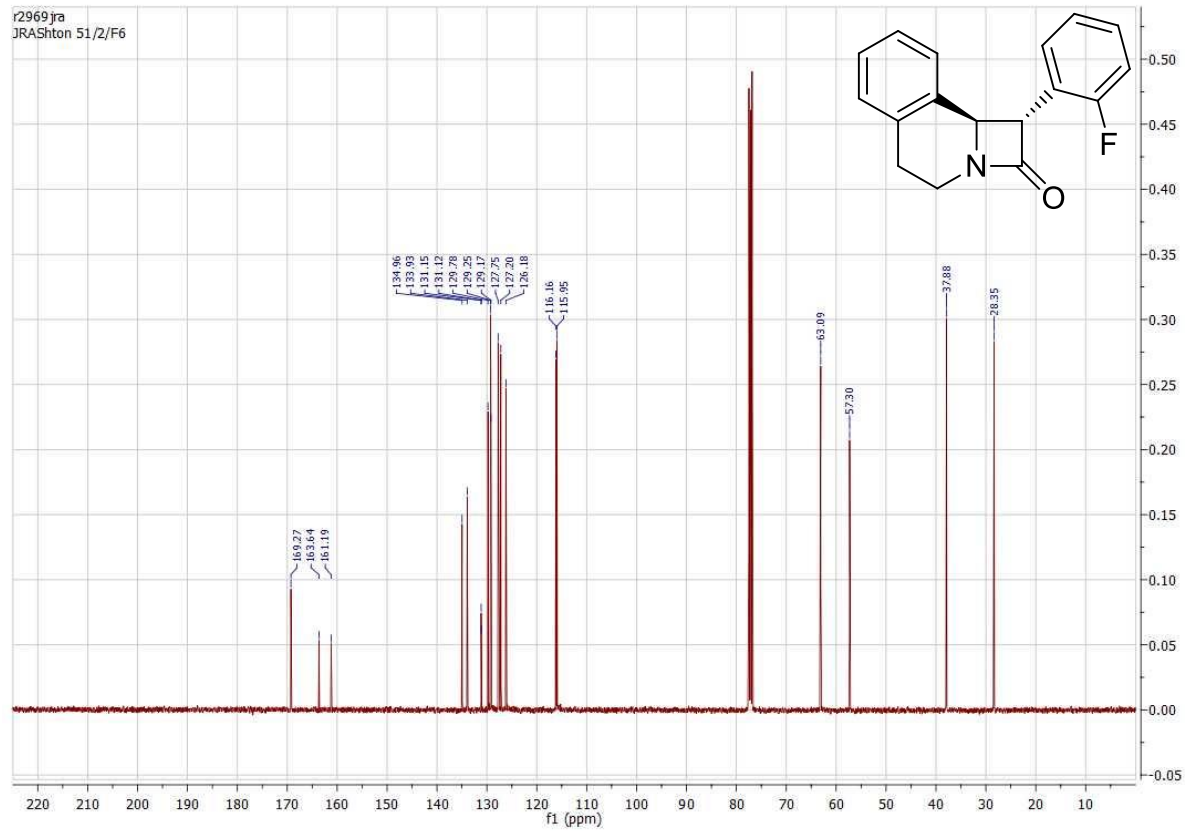

r2970jra
JRAShton 53/1/F8
Br
N
O
f1 (ppm)

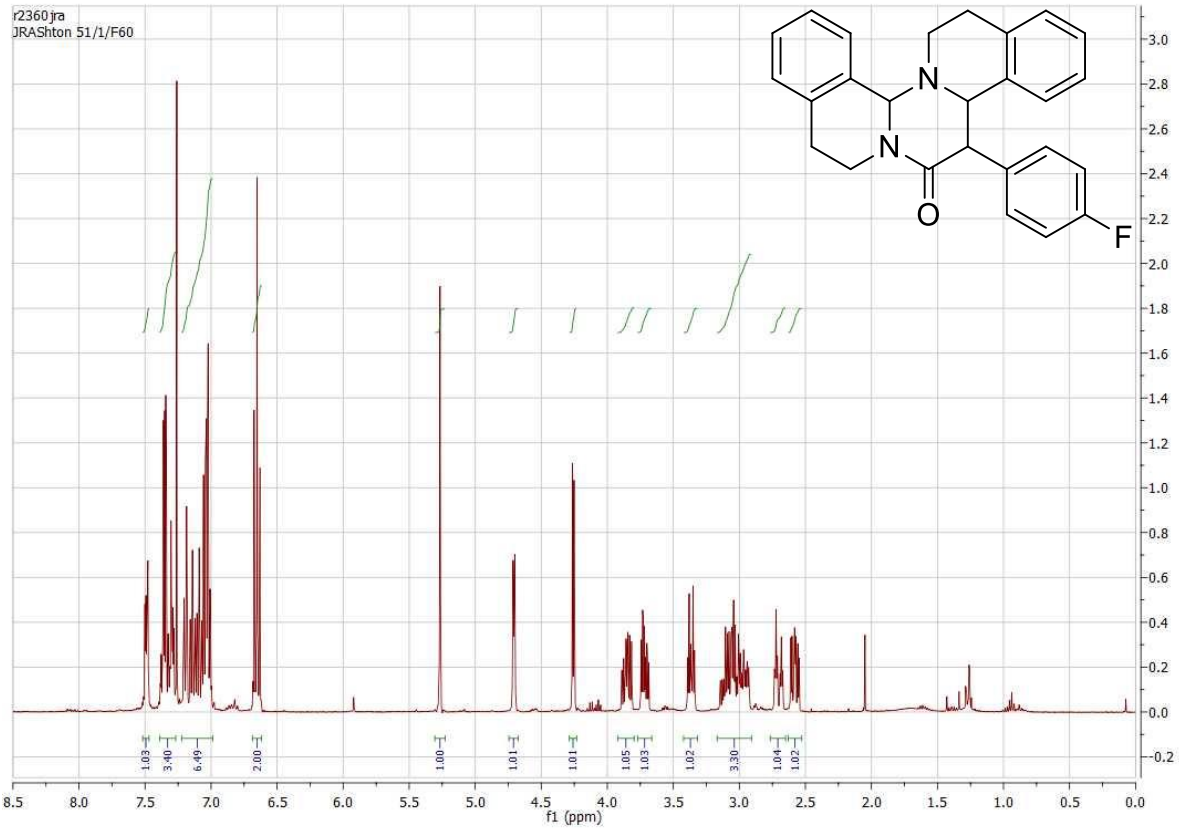

r2970jra
JRAShton 53/1/F8
Br
N
O
135.48
134.63
134.09
133.20
129.57
129.53
129.02
128.36
127.79
127.23
127.11
124.99
169.10
63.05
58.10
38.08
28.51
f1 (ppm)

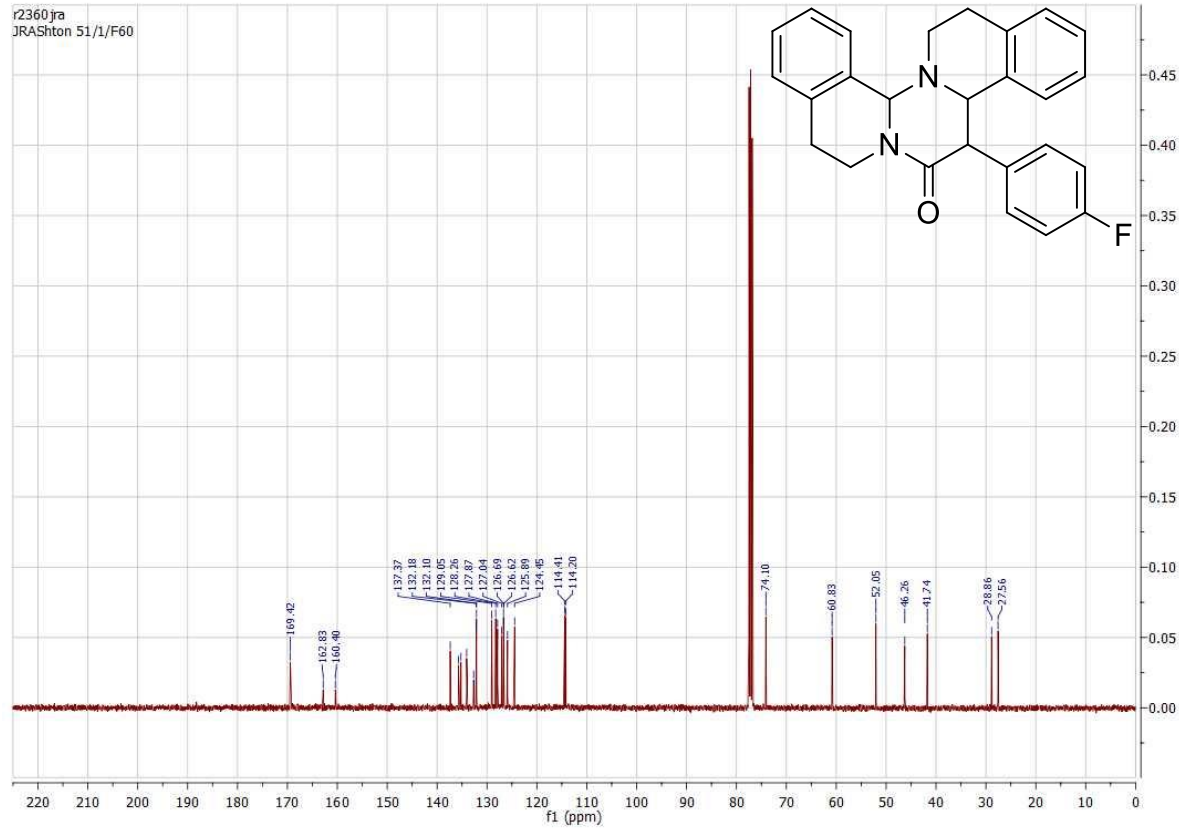

r2187jra
JRAshton 48/2/F10
N
N
O
Br
f1 (ppm)

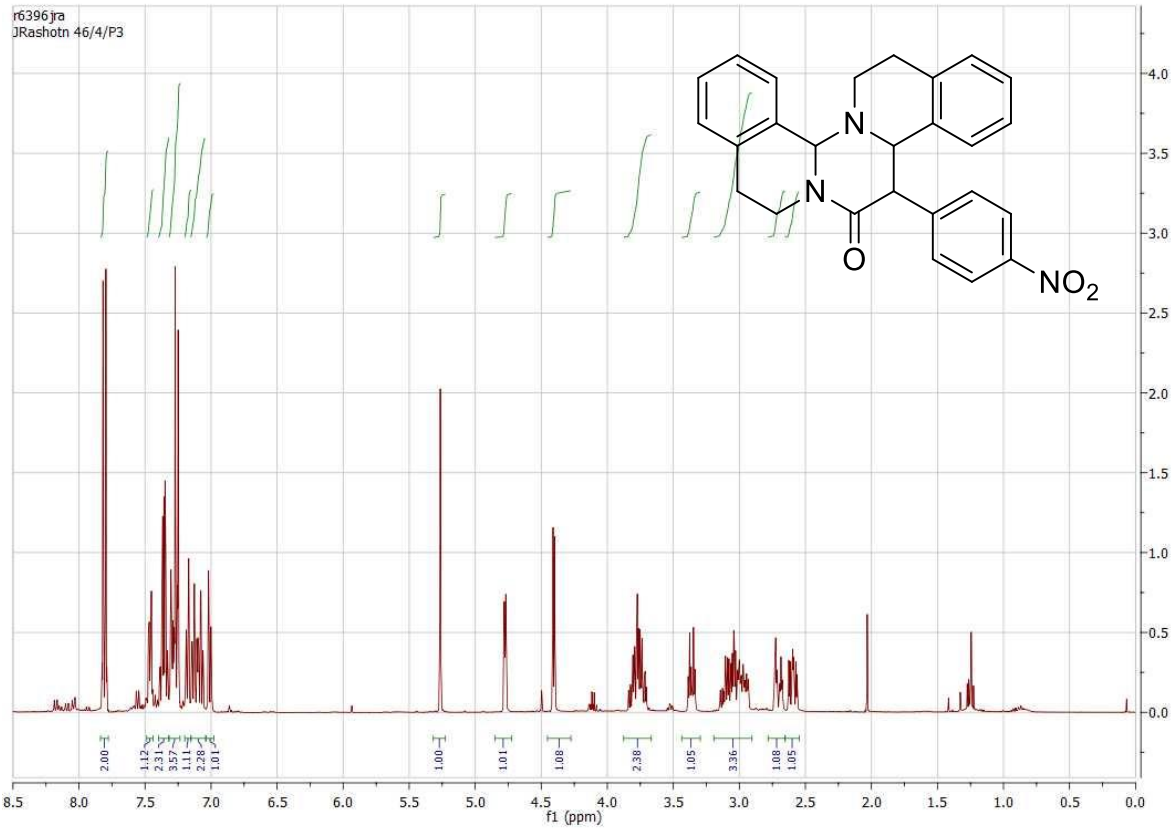

r2187jra
JRAshton 48/2/F10
N
N
O
Br
137.41
137.37
134.18
134.14
133.99
132.30
128.30
128.19
128.14
128.02
127.87
127.33
127.21
126.78
126.50
126.38
125.36
169.67
73.35
61.05
51.24
41.44
40.81
28.67
28.39
f1 (ppm)

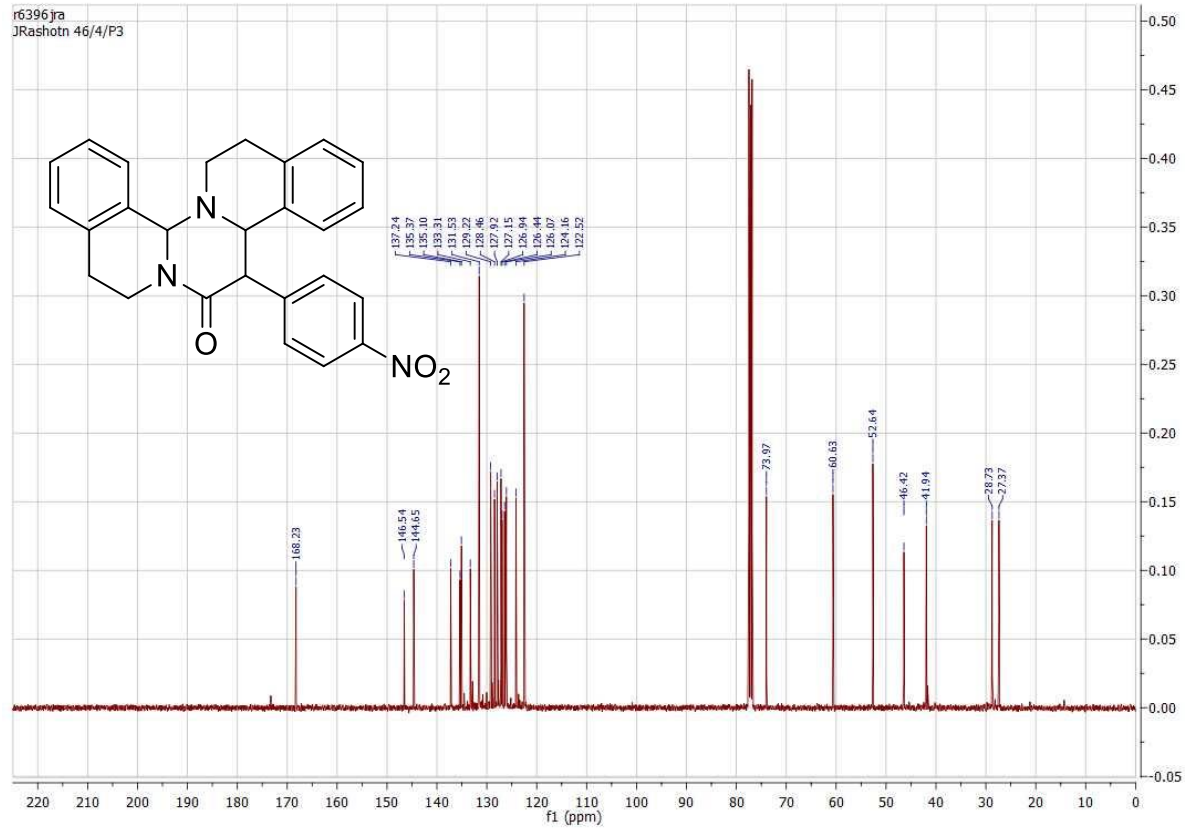

r2614.jra
JRAshton 51/2/F6
F
N
O
f1 (ppm)

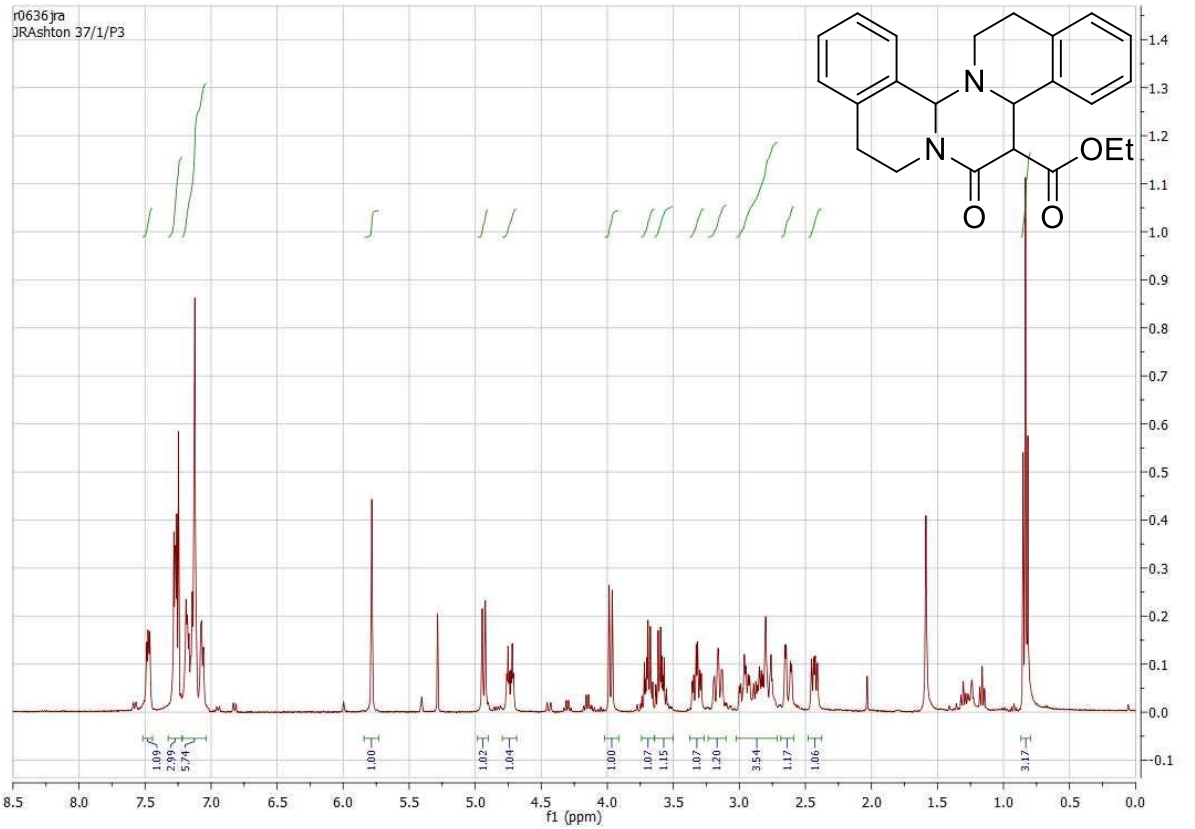

r2969.jra
JRAShton 51/2/F6
F
N
O
134.96
133.93
131.15
131.12
129.78
129.25
129.17
127.75
127.20
126.18
116.16
115.95
169.27
163.64
161.19
63.09
57.30
37.88
28.35
f1 (ppm)

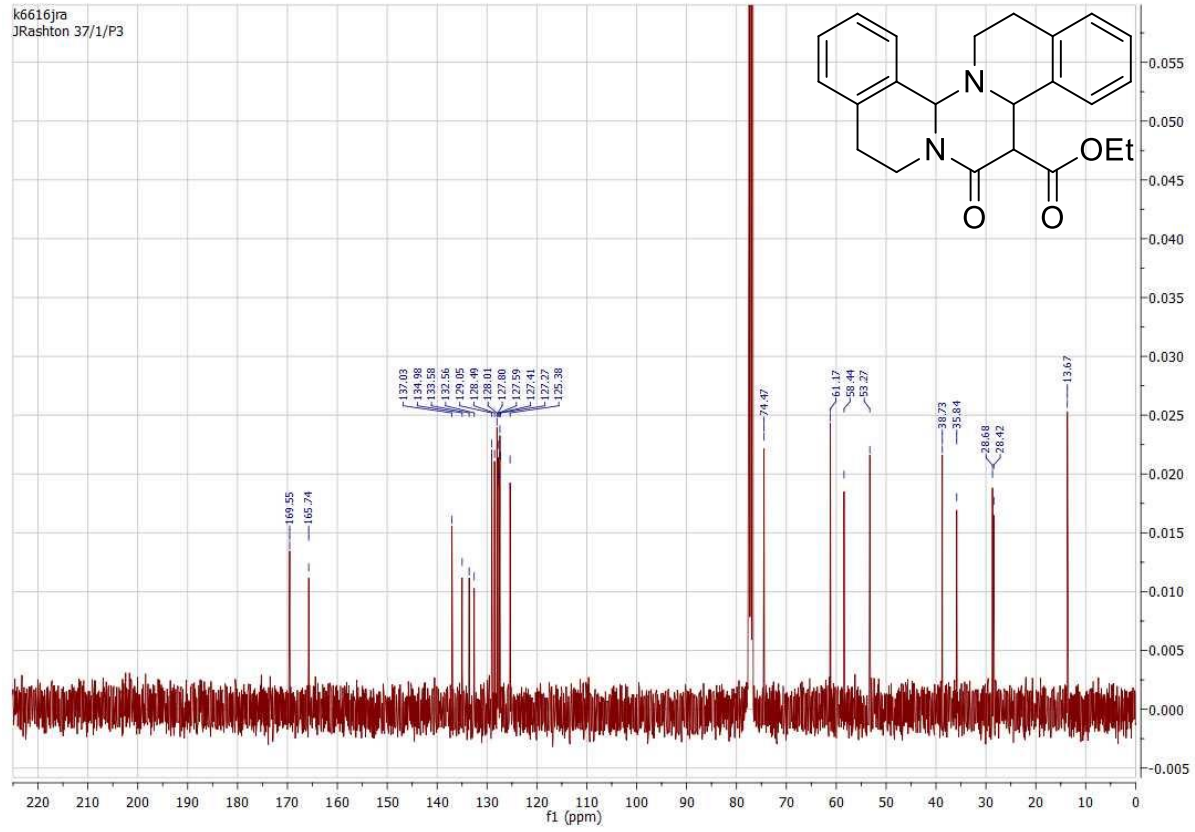

r2360.jra
JRAShton 51/1/F60
N
N
O
F
f1 (ppm)

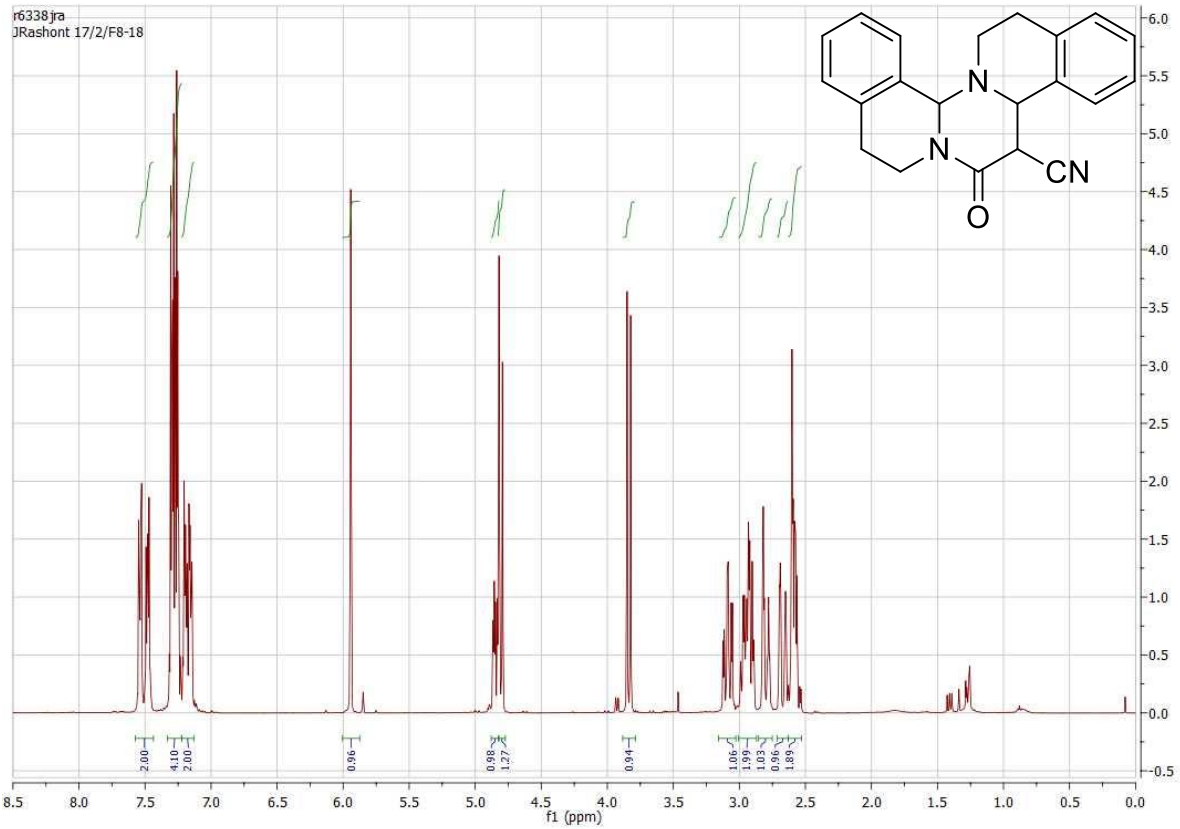

r2360.jra
JRAShton 51/1/F60
N
N
O
F
169.42
162.83
160.40
137.37
132.18
132.10
129.05
128.26
127.87
127.04
126.69
126.62
125.09
124.45
114.41
114.20
74.10
60.83
52.05
46.26
41.74
28.86
27.56
f1 (ppm)

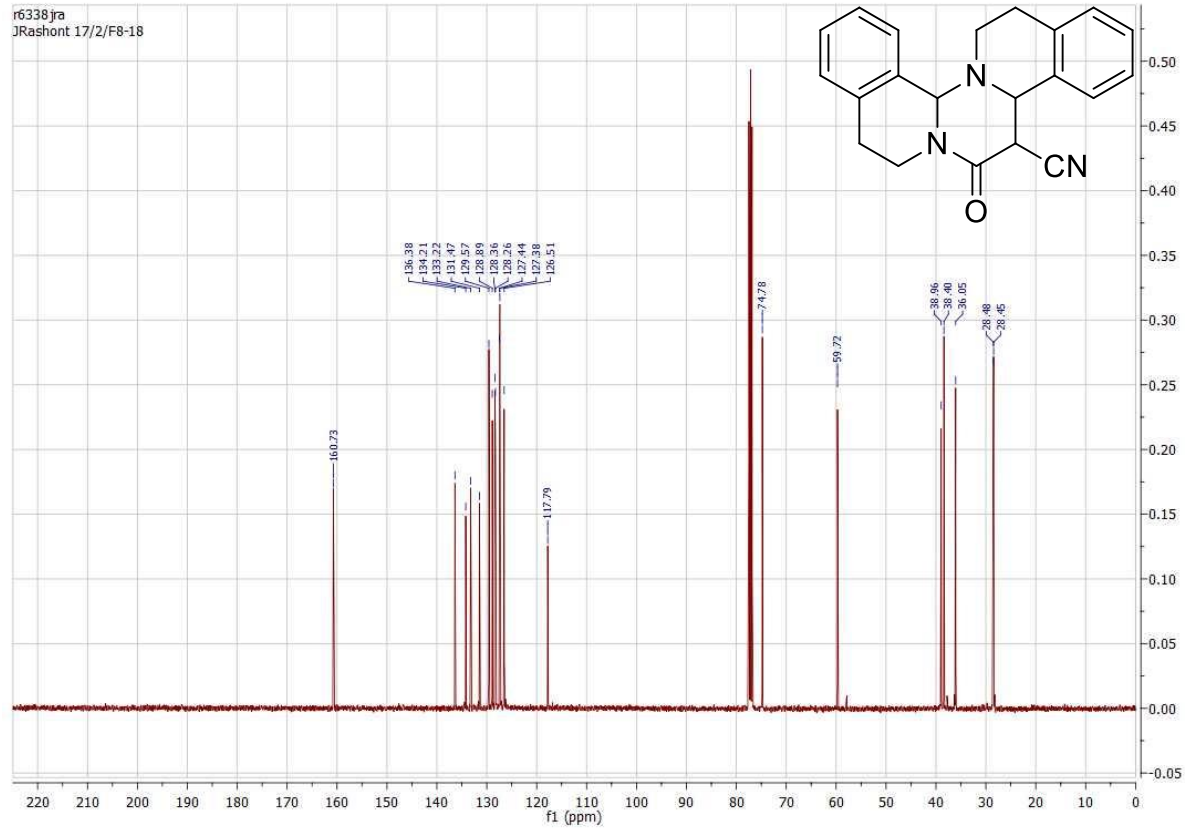

r6396jra
JRashotn 46/4/P3
N
N
O
NO2
f1 (ppm)


r6396jra
JRashotn 46/4/P3
N
N
O
NO2
137.24
135.37
135.10
133.31
131.53
129.22
128.46
127.92
127.15
126.94
126.44
126.07
124.16
122.52
168.23
146.54
144.65
73.97
60.63
52.64
46.42
41.94
28.73
27.37
f1 (ppm)


r0636jra
JRAshton 37/1/P3
N
N
OEt
O
O
f1 (ppm)


k6616jra
JRAshton 37/1/P3
N
N
OEt
O
O
137.03
134.98
133.58
132.56
129.05
128.49
128.01
127.80
127.59
127.41
127.27
125.38
169.55
165.74
74.47
61.17
58.44
53.27
38.73
35.84
28.68
28.42
13.67
f1 (ppm)


r6338jra
JRashont 17/2/F8-18
N
N
CN
O
f1 (ppm)


r6338jra
JRashont 17/2/F8-18
N
N
CN
O
136.38
134.21
133.22
131.47
129.57
128.89
128.36
128.26
127.44
127.38
126.51
160.73
117.79
74.78
59.72
38.96
38.40
36.05
28.48
28.45
f1 (ppm)