

Supplementary Material

Development of Novel and Efficient Processes for the Synthesis of 5-Amino and 5-Iminoimidazo[1,2-*a*]imidazoles via Three-Component Reaction Catalyzed by Zirconium(IV) Chloride

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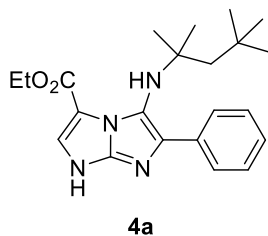
General information

All reagents were purchased from commercial suppliers and were used without further purification. The reactions were monitored by thin-layer chromatography (TLC) analysis using silica gel (60 F254) plates. Compounds were visualized under UV light. Flash column chromatography was performed on silica gel 60 (230–400 mesh, 0.040–0.063 mm). Melting points were measured with Electrothermal IA9100 apparatus and were uncorrected. The infrared spectra of compounds were recorded on a Thermo Scientific Nicolet iS10. Absorption bands are given in cm^{-1} . ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance II 400 MHz (^{13}C , 100.6 MHz) or on a Bruker Avance DPX 250 MHz (^{13}C , 62.9 MHz). Chemical shifts are given in parts per million from tetramethylsilane (TMS) as internal standard. Coupling constants (J) are reported in Hertz (Hz). High-resolution mass spectra (HRMS) were performed on a Maxis Bruker 4G.

General procedure for the synthesis of compounds 4a-f and 5a-i

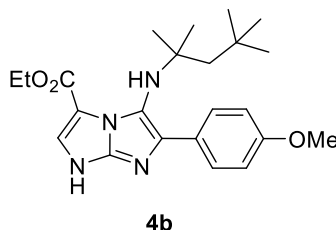
In a closed vessel containing a solution of substituted 2-aminoimidazole **1** or **2** (1.0 mmol) in PEG-400 (1 mL), aldehyde (1.1 mmol) and ZrCl_4 (0.10 mmol) were sequentially added at room temperature followed by the addition of isocyanide (1.1 mmol). The reaction was heated at 75 °C and 55 °C, respectively, for the ethyl 2-aminoimidazole-4-carboxylate **1** and 4,5-dicyano-2-aminoimidazole **2**. Once the reaction was completed (controlled by TLC), the mixture was poured into water (15 mL) then extracted with ethyl acetate (2×15 mL). The extract was washed with water and brine, dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel using petroleum ether/ethyl acetate mixture (3:2 v/v) as eluent to provide the expected pure products **4a-f** and **5a-i**.

Ethyl 6-phenyl-5-((2,4,4-trimethylpentan-2-yl)amino)-1H-imidazo[1,2-a]imidazole-3-carboxylate (**4a**)



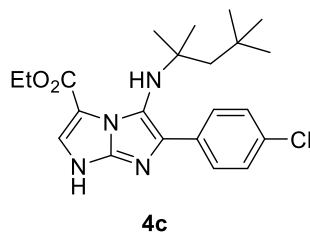
Yellow solid (295 mg, 77%); m.p.: 176-178 °C; IR (neat, cm^{-1}): 3330 (NH), 2955, 2901, 1699 (CO), 1602, 1516, 1249, 1192, 1112; ^1H NMR (400 MHz, DMSO-d_6): δ 12.18 (br s, 1H, NHimidazole), 7.86 (d, $J = 7.3$ Hz, 2H, HAr), 7.71 (s, 1H, Himidazole), 7.42 (t, $J = 7.7$ Hz, 2H, HAr), 7.29 (t, $J = 7.4$ Hz, 1H, HAr), 4.62 (s, 1H, NH), 4.29 (q, $J = 7.1$ Hz, 2H, CH_2ester), 1.46 (s, 2H, CH_2), 1.31 (t, $J = 7.1$ Hz, 3H, CH_3ester), 0.97 (s, 9H, 3CH_3), 0.83 (s, 6H, 2CH_3); ^{13}C NMR (101 MHz, DMSO-d_6): δ 161.1, 147.4, 141.4, 131.7, 128.7, 127.8, 127.5, 123.3, 122.2, 114.1, 61.6, 60.4, 55.5, 32.1, 28.7, 14.9; HRMS (ESI): (m/z) calcd for $\text{C}_{22}\text{H}_{31}\text{N}_4\text{O}_2$ [$\text{M} + \text{H}$] $^+$: 383.2441, found: 383.2439.

Ethyl 6-(4-methoxyphenyl)-5-((2,4,4-trimethylpentan-2-yl)amino)-1*H*-imidazo[1,2-*a*]imidazole-3-carboxylate (4b)



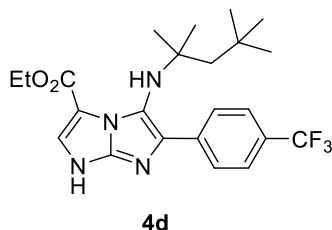
Yellow solid (280 mg, 68%); m.p.: 182-183 °C; IR (neat, cm^{-1}): 3342 (NH), 2956, 2900, 1698 (CO), 1603, 1571, 1248, 1191, 1113; ^1H NMR (400 MHz, DMSO-d_6): δ 12.08 (br s, 1H, NHimidazole), 7.78 (d, $J = 8.8$ Hz, 2H, HAr), 7.68 (s, 1H, Himidazole), 6.99 (d, $J = 8.8$ Hz, 2H, HAr), 4.55 (s, 1H, NH), 4.29 (q, $J = 7.1$ Hz, 2H, CH_2ester), 3.79 (s, 3H, OCH_3), 1.46 (s, 2H, CH_2), 1.30 (t, $J = 7.0$ Hz, 3H, CH_3ester), 0.97 (s, 9H, 3CH_3), 0.83 (s, 6H, 2CH_3); ^{13}C NMR (101 MHz, DMSO-d_6): δ 161.1, 159.0, 147.2, 141.3, 128.9, 124.0, 123.3, 121.3, 114.2, 114.0, 61.4, 60.3, 55.6, 55.5, 32.1, 31.8, 28.7, 15.0; HRMS (ESI): (m/z) calcd for $\text{C}_{23}\text{H}_{33}\text{N}_4\text{O}_3$ [$\text{M} + \text{H}$] $^+$: 413.2547, found: 413.2546.

Ethyl 6-(4-chlorophenyl)-5-((2,4,4-trimethylpentan-2-yl)amino)-1*H*-imidazo[1,2-*a*]imidazole-3-carboxylate (4c)



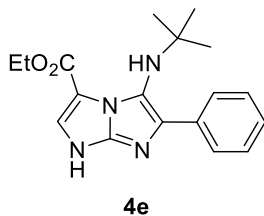
White solid (235 mg, 56%); m.p.: 226-228 °C; IR (neat, cm^{-1}): 3336 (NH), 2954, 2902, 1699 (CO), 1602, 1579, 1512, 1375, 1243, 1188; ^1H NMR (400 MHz, Acetic acid- d_4): δ 8.08–7.87 (m, 3H, 2HAr and Himidazole), 7.48 (t, $J = 9.6$ Hz, 2H, HAr), 4.52–4.40 (m, 2H, CH_2ester), 1.59 (d, $J = 14.8$ Hz, 2H, CH_2), 1.43 (dt, $J = 13.8, 7.2$ Hz, 3H, CH_3ester), 1.05 (s, 9H, 3CH_3), 0.96 (s, 6H, 2CH_3); ^{13}C NMR (101 MHz, Acetic acid- d_4): δ 160.1, 139.8, 134.4, 133.8, 130.0, 129.2, 128.8, 128.7, 128.6, 127.9, 127.8, 126.5, 124.5, 123.8, 120.7, 115.6, 112.1, 61.8, 61.7, 61.6, 60.0, 55.9, 55.3, 31.2, 31.1, 31.0, 27.9, 13.5; HRMS (ESI): (m/z) calcd for $\text{C}_{22}\text{H}_{30}\text{ClN}_4\text{O}_2$ [$\text{M} + \text{H}$] $^+$: 417.2051, found: 417.2047.

Ethyl 6-(4-(trifluoromethyl)phenyl)-5-((2,4,4-trimethylpentan-2-yl)amino)-1*H*-imidazo[1,2-*a*]imidazole-3-carboxylate (4d)



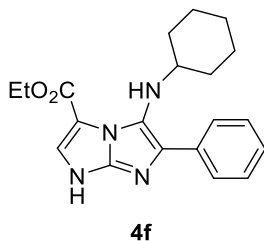
White solid (320 mg, 71%); m.p.: 193-195 °C; IR (neat, cm^{-1}): 3291 (NH), 2962, 2909, 1668 (CO), 1616, 1486, 1320, 1280, 1190; ^1H NMR (400 MHz, Acetic acid- d_4): δ 8.17 (d, $J = 8.2$ Hz, 2H, HAr), 8.01 (s, 1H, Himidazole), 7.78 (d, $J = 8.2$ Hz, 2H, HAr), 4.48 (q, $J = 7.1$ Hz, 2H, CH_2ester), 1.58 (s, 2H, CH_2), 1.45 (t, $J = 7.1$ Hz, 3H, CH_3ester), 1.05 (s, 9H, 3CH_3), 0.98 (s, 6H, 2CH_3); ^{13}C NMR (101 MHz, Acetic acid- d_4): δ 160.2, 140.4, 134.3, 130.5, 129.4 (q, $J = 32.2$ Hz), 128.2, 128.1, 125.5, 125.3 (q, $J = 3.8$ Hz), 124.6, 124.3, 122.8 (q, $J = 271.0$ Hz), 115.6, 61.8, 61.7, 55.4, 31.1, 31.0, 27.8, 13.5; ^{19}F NMR (376 MHz, Acetic acid- d_4): δ -63.4 (s); HRMS (ESI): (m/z) calcd for $\text{C}_{23}\text{H}_{30}\text{F}_3\text{N}_4\text{O}_2$ [$\text{M} + \text{H}$] $^+$: 451.2315, found: 451.2315.

Ethyl 5-(*tert*-butylamino)-6-phenyl-1*H*-imidazo[1,2-*a*]imidazole-3-carboxylate (4e)



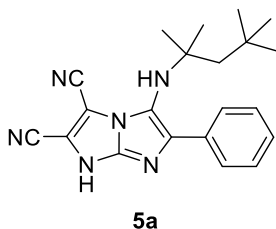
White solid (240 mg, 74%); m.p.: 198-199 °C; IR (neat, cm^{-1}): 3333 (NH), 2959, 2900, 1698 (CO), 1600, 1515, 1249, 1199, 1106; ^1H NMR (400 MHz, DMSO- d_6): δ 12.19 (br s, 1H, NHimidazole), 7.92 (d, $J = 7.5$ Hz, 2H, HAr), 7.72 (s, 1H, Himidazole), 7.41 (t, $J = 7.8$ Hz, 2H, HAr), 7.27 (t, $J = 7.6$ Hz, 1H, HAr), 4.70 (s, 1H, NH), 4.29 (q, $J = 7.0$ Hz, 2H, CH_2ester), 1.30 (t, $J = 7.0$ Hz, 3H, CH_3ester), 0.91 (s, 9H, 3CH_3); ^{13}C NMR (101 MHz, DMSO- d_6): δ 161.0, 147.4, 141.4, 131.5, 128.7, 127.7, 127.2, 123.3, 122.6, 114.0, 60.3, 57.5, 29.5, 14.9; HRMS (ESI): (m/z) calcd for $\text{C}_{18}\text{H}_{23}\text{N}_4\text{O}_2$ [$\text{M} + \text{H}$] $^+$: 327.1816, found: 327.1817.

Ethyl 5-(cyclohexylamino)-6-phenyl-1H-imidazo[1,2-a]imidazole-3-carboxylate (4f)



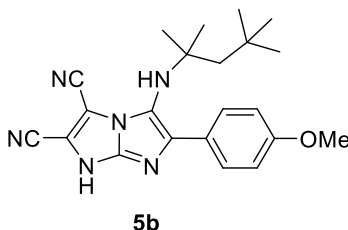
White solid (206 mg, 59%); m.p.: 215-216 °C; IR (neat, cm^{-1}): 3314 (NH), 2931, 2858, 1682 (CO), 1610, 1548, 1418, 1285, 1227, 1109, 1021; ^1H NMR (400 MHz, Acetic acid- d_4): δ 7.99 (s, 1H, Himidazole), 7.90 (d, J = 7.3 Hz, 2H, HAr), 7.48 (t, J = 7.7 Hz, 2H, HAr), 7.36 (t, J = 7.4 Hz, 1H, HAr), 4.46 (q, J = 7.2 Hz, 2H, CH_2ester), 2.91 (ddd, J = 10.4, 6.6, 3.7 Hz, 1H, CH), 1.82–1.90 (m, 2H, CH_2), 1.73–1.64 (m, 2H, CH_2), 1.51–1.57 (m, 1H, $\frac{1}{2}\text{CH}_2$), 1.44 (t, J = 7.2 Hz, 3H, CH_3ester), 1.27–1.10 (m, 5H, $(2+\frac{1}{2})\text{CH}_2$); ^{13}C NMR (101 MHz, Acetic acid- d_4): δ 160.1, 138.9, 129.7, 129.0, 128.7, 128.6, 127.8, 126.5, 126.1, 126.0, 119.3, 115.2, 111.8, 61.8, 56.8, 33.4, 33.1, 25.4, 24.7, 13.4; HRMS (ESI): (m/z) calcd for $\text{C}_{20}\text{H}_{25}\text{N}_4\text{O}_2$ $[\text{M} + \text{H}]^+$: 353.1972, found: 353.1972.

6-Phenyl-5-((2,4,4-trimethylpentan-2-yl)amino)-1H-imidazo[1,2-a]imidazole-2,3-dicarbonitrile (5a)



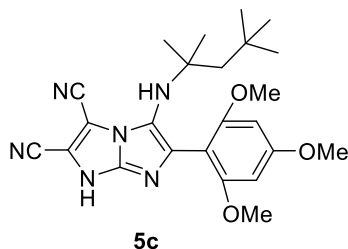
White solid (240 mg, 67%); m.p.: 237-239 °C; IR (neat, cm^{-1}): 3383 (NH), 2956, 2904, 2208 (CN), 1614, 1566, 1382, 1180; ^1H NMR (400 MHz, DMSO- d_6): δ 12.94 (br s, 1H, NHimidazole), 7.84 (d, J = 7.5 Hz, 2H, HAr), 7.49 (t, J = 7.5 Hz, 2H, HAr), 7.46–7.40 (m, 1H, HAr), 4.60 (s, 1H, NH), 1.45 (s, 2H, CH_2), 0.96 (s, 6H, 2CH_3), 0.89 (s, 9H, 3CH_3); ^{13}C NMR (101 MHz, DMSO- d_6): δ 144.8, 130.5, 129.7, 129.2, 129.0, 128.6, 123.4, 121.0, 114.1, 111.3, 97.7, 59.5, 56.2, 31.9, 31.4, 28.7; HRMS (ESI): (m/z) calcd for $\text{C}_{21}\text{H}_{25}\text{N}_6$ $[\text{M} + \text{H}]^+$: 361.2135, found: 361.2137, (m/z) calcd for $\text{C}_{21}\text{H}_{24}\text{N}_6\text{Na}$ $[\text{M} + \text{Na}]^+$: 383.1955, found: 383.1954.

6-(4-Methoxyphenyl)-5-((2,4,4-trimethylpentan-2-yl)amino)-1H-imidazo[1,2-a]imidazole-2,3-dicarbonitrile (5b)



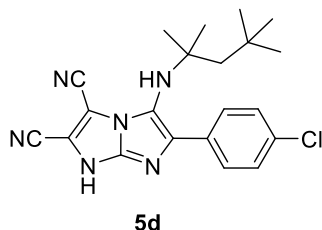
White solid (255 mg, 65%); m.p.: 228-229 °C; IR (neat, cm^{-1}): 3362 (NH), 2951, 2902, 2213 (CN), 1618, 1560, 1370, 1179, 1022; ^1H NMR (400 MHz, DMSO-d_6): δ 12.83 (br s, 1H, NHimidazole), 7.84 (d, $J = 8.3$ Hz, 2H, HAr), 7.05 (d, $J = 8.3$ Hz, 2H, HAr), 4.54 (s, 1H, NH), 3.81 (s, 3H, OCH_3), 1.46 (s, 2H, CH_2), 0.96 (s, 6H, 2CH_3), 0.91 (s, 9H, 3CH_3); ^{13}C NMR (101 MHz, DMSO-d_6): δ 160.1, 144.6, 130.6, 130.0, 123.1, 121.9, 120.3, 114.4, 114.2, 111.4, 97.5, 59.4, 56.2, 55.7, 31.9, 31.4, 28.7; HRMS (ESI): (m/z) calcd for $\text{C}_{22}\text{H}_{27}\text{N}_6\text{O}$ $[\text{M} + \text{H}]^+$: 391.2241, found: 391.2241, (m/z) calcd for $\text{C}_{22}\text{H}_{26}\text{N}_6\text{NaO}$ $[\text{M} + \text{Na}]^+$: 413.2060, found: 413.2063.

6-(2,4,6-Trimethoxyphenyl)-5-((2,4,4-trimethylpentan-2-yl)amino)-1H-imidazo[1,2-a]imidazole-2,3-dicarbonitrile (5c)



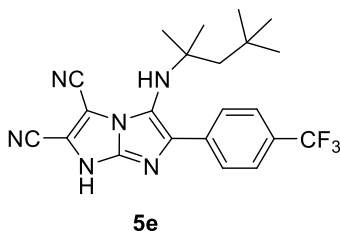
Yellow solid (255 mg, 61%); m.p.: 224-225 °C; IR (neat, cm^{-1}): 3369 (NH), 2954, 2893, 2226 (CN), 1608, 1572, 1253, 1171, 1030; ^1H NMR (400 MHz, DMSO-d_6): δ 12.51 (br s, 1H, NHimidazole), 6.39 (s, 2H, HAr), 3.86 (s, 3H, OCH_3), 3.81 (s, 6H, 2OCH_3), 3.36 (s, 1H, NH), 1.35 (s, 2H, CH_2), 0.94 (s, 6H, 2CH_3), 0.89 (s, 9H, 3CH_3); ^{13}C NMR (101 MHz, DMSO-d_6): δ 163.3, 159.3, 144.8, 123.3, 123.1, 122.5, 114.3, 111.4, 99.1, 96.8, 91.5, 58.6, 56.5, 56.0, 55.7, 31.8, 31.5, 28.5; HRMS (ESI): (m/z) calcd for $\text{C}_{24}\text{H}_{31}\text{N}_6\text{O}_3$ $[\text{M} + \text{H}]^+$: 451.2452, found: 451.2451, (m/z) calcd for $\text{C}_{24}\text{H}_{30}\text{N}_6\text{NaO}_3$ $[\text{M} + \text{Na}]^+$: 473.2272, found: 473.2270.

6-(4-Chlorophenyl)-5-((2,4,4-trimethylpentan-2-yl)amino)-1H-imidazo[1,2-a]imidazole-2,3-dicarbonitrile (5d)



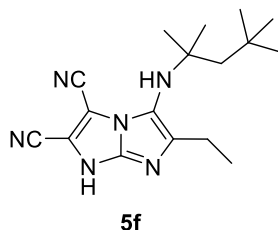
White solid (228 mg, 58%); m.p.: 233-235 °C; IR (neat, cm^{-1}): 3375 (NH), 2945, 2899, 2232 (CN), 1610, 1551, 1186; ^1H NMR (400 MHz, DMSO-d_6): δ 13.02 (br s, 1H, NHimidazole), 7.87 (d, $J = 8.0$ Hz, 2H, HAr), 7.58 (d, $J = 8.0$ Hz, 2H, HAr), 4.63 (s, 1H, NH), 1.45 (s, 2H, CH_2), 0.97 (s, 6H, 2 CH_3), 0.91 (s, 9H, 3 CH_3); ^{13}C NMR (101 MHz, DMSO-d_6): δ 144.8, 133.9, 130.3, 129.4, 129.1, 128.6, 123.6, 121.3, 114.1, 111.3, 97.8, 59.6, 56.2, 31.9, 31.5, 28.7; HRMS (ESI): (m/z) calcd for $\text{C}_{21}\text{H}_{24}\text{ClN}_6$ [$\text{M} + \text{H}$] $^+$: 395.1746, found: 395.1745, (m/z) calcd for $\text{C}_{21}\text{H}_{23}\text{ClN}_6\text{Na}$ [$\text{M} + \text{Na}$] $^+$: 417.1565, found: 417.1563.

6-(4-(Trifluoromethyl)phenyl)-5-((2,4,4-trimethylpentan-2-yl)amino)-1H-imidazo[1,2-a]imidazole-2,3-dicarbonitrile (5e)



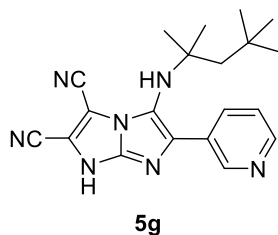
White solid (327 mg, 76%); m.p.: 256-258 °C; IR (neat, cm^{-1}): 3302 (NH), 2955, 2904, 2218 (CN), 1616, 1480, 1331; ^1H NMR (400 MHz, DMSO-d_6): δ 13.16 (br s, 1H, NHimidazole), 8.09 (d, $J = 8.1$ Hz, 2H, HAr), 7.87 (d, $J = 8.1$ Hz, 2H, HAr), 4.73 (s, 1H, NH), 1.44 (s, 2H, CH_2), 0.98 (s, 6H, 2 CH_3), 0.89 (s, 9H, 3 CH_3); ^{13}C NMR (101 MHz, DMSO-d_6): δ 145.0, 133.8, 129.8, 129.5 (q, $J = 32.0$ Hz), 129.0, 129.1, 125.8 (q, $J = 3.7$ Hz), 123.9, 123.1 (q, $J = 272.1$ Hz), 122.1, 113.9, 111.2, 97.9, 70.2, 59.8, 56.2, 31.8, 31.4, 28.6; ^{19}F NMR (376 MHz, DMSO-d_6): δ -61.3 (s); HRMS (ESI): (m/z) calcd for $\text{C}_{22}\text{H}_{24}\text{F}_3\text{N}_6$ [$\text{M} + \text{H}$] $^+$: 429.2009, found: 429.2007, (m/z) calcd for $\text{C}_{22}\text{H}_{23}\text{F}_3\text{N}_6\text{Na}$ [$\text{M} + \text{Na}$] $^+$: 451.1829, found: 451.1824.

6-Ethyl-5-((2,4,4-trimethylpentan-2-yl)amino)-1*H*-imidazo[1,2-*a*]imidazole-2,3-dicarbonitrile (5f)



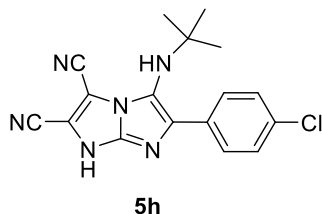
White solid (228 mg, 58%); m.p.: 160-161 °C; IR (neat, cm^{-1}): 3361 (NH), 2958, 2892, 2249 (CN), 1194; ^1H NMR (400 MHz, DMSO-d_6): δ 12.45 (br s, 1H, NHimidazole), 4.29 (s, 1H, NH), 2.63 (q, $J = 7.5$ Hz, 2H, $\text{CH}_2(\text{Et})$), 1.59 (s, 2H, $\text{CH}_2(\text{octyl})$), 1.21 (t, $J = 7.5$ Hz, 3H, $\text{CH}_3(\text{Et})$), 1.14 (s, 6H, 2 CH_3), 1.01 (s, 9H, 3 CH_3); ^{13}C NMR (101 MHz, DMSO-d_6): δ 144.7, 132.6, 122.8, 120.4, 114.2, 111.5, 97.2, 58.2, 55.7, 32.0, 31.7, 28.7, 18.4, 13.5; HRMS (ESI): (m/z) calcd for $\text{C}_{17}\text{H}_{25}\text{N}_6$ [$\text{M} + \text{H}$] $^+$: 313.2135, found: 313.2137, (m/z) calcd for $\text{C}_{17}\text{H}_{24}\text{N}_6\text{Na}$ [$\text{M} + \text{Na}$] $^+$: 335.1955, found: 335.1958.

6-(Pyridin-3-yl)-5-((2,4,4-trimethylpentan-2-yl)amino)-1*H*-imidazo[1,2-*a*]imidazole-2,3-dicarbonitrile (5g)



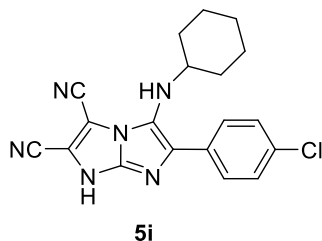
White solid (285 mg, 79%); m.p.: 226-228 °C; IR (neat, cm^{-1}): 3379 (NH), 2955, 2908, 2213 (CN), 1616, 1565, 1383, 1188; ^1H NMR (400 MHz, DMSO-d_6): δ 13.13 (br s, 1H, NHimidazole), 9.05 (d, $J = 1.5$ Hz, 1H, HAr), 8.61 (dd, $J = 4.9, 1.6$ Hz, 1H, HAr), 8.22 (dt, $J = 8.0, 1.9$ Hz, 1H, HAr), 7.54 (dd, $J = 7.5, 4.8$ Hz, 1H, HAr), 4.74 (s, 1H, NH), 1.44 (s, 2H, CH_2), 0.97 (s, 6H, 2 CH_3), 0.89 (s, 9H, 3 CH_3); ^{13}C NMR (101 MHz, DMSO-d_6): δ 150.0, 149.1, 145.1, 135.8, 127.8, 126.0, 123.9, 123.7, 121.8, 114.0, 111.2, 97.8, 59.6, 56.2, 31.8, 31.4, 28.6; HRMS (ESI): (m/z) calcd for $\text{C}_{21}\text{H}_{25}\text{N}_6$ [$\text{M} + \text{H}$] $^+$: 362.2088, found: 362.2089.

5-(*tert*-Butylamino)-6-(4-chlorophenyl)-1*H*-imidazo[1,2-*a*]imidazole-2,3-dicarbonitrile (5h)



White solid (202 mg, 60%); m.p.: 258-260 °C; IR (neat, cm^{-1}): 3354 (NH), 2942, 2906, 2228 (CN), 1609, 1547, 1180; ^1H NMR (400 MHz, DMSO-d_6): δ 13.01 (br s, 1H, NHimidazole), 7.90 (d, $J = 8.6$ Hz, 2H, HAr), 7.57 (d, $J = 8.5$ Hz, 2H, HAr), 4.84 (s, 1H, NH), 0.98 (s, 9H, 3CH_3); ^{13}C NMR (101 MHz, DMSO-d_6): δ 144.8, 133.9, 129.9, 129.1, 129.2, 128.3, 123.5, 121.6, 114.0, 111.1, 97.6, 55.5, 30.0; HRMS (ESI): (m/z) calcd for $\text{C}_{17}\text{H}_{16}\text{ClN}_6$ [$\text{M} + \text{H}$] $^+$: 339.1120, found: 339.1122, (m/z) calcd for $\text{C}_{17}\text{H}_{15}\text{ClN}_6\text{Na}$ [$\text{M} + \text{Na}$] $^+$: 361.0939, found: 361.0942.

6-(4-Chlorophenyl)-5-(cyclohexylamino)-1*H*-imidazo[1,2-*a*]imidazole-2,3-dicarbonitrile (5i)

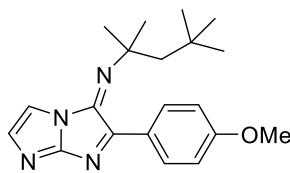


Yellow solid (170 mg, 47%); m.p.: 266-268 °C; IR (neat, cm^{-1}): 3321 (NH), 2930, 2850, 1609, 1570, 1426, 1281, 1224, 1110, 1017; ^1H NMR (400 MHz, DMSO-d_6): δ 12.92 (s, 1H, NHimidazole), 7.94 (d, $J = 8.3$ Hz, 2H, HAr), 7.57 (t, $J = 8.5$ Hz, 2H, HAr), 4.94 (d, $J = 5.1$ Hz, 1H, NH), 3.09–2.83 (m, 1H, CH), 1.84–1.73 (m, 2H, CH_2), 1.62 (dd, $J = 9.9, 3.9$ Hz, 2H, CH_2), 1.49 (d, $J = 7.4$ Hz, 1H, $\frac{1}{2}\text{CH}_2$), 1.21–1.04 (m, 5H, $(2+\frac{1}{2})\text{CH}_2$); ^{13}C NMR (101 MHz, DMSO-d_6): δ 144.8, 133.4, 129.2, 128.5, 128.0, 126.3, 123.4, 123.1, 114.0, 111.0, 97.6, 56.6, 33.2, 25.7, 24.8; HRMS (ESI): (m/z) calcd for $\text{C}_{19}\text{H}_{18}\text{ClN}_6$ [$\text{M} + \text{H}$] $^+$: 365.1276, found: 365.1276.

General procedure for the synthesis of compounds 7a-i

In an open vessel containing a solution of 2-aminoimidazole **3** (1.0 mmol) in EtOH (10 mL), aldehyde (1.1 mmol) and InCl_3 (0.02 mmol) were sequentially added, then the mixture was refluxed at 90 °C. After consumption of the starting material (TLC control), the solvent was removed under reduced pressure, then 2 mL of *n*-butanol were added, followed by ZrCl_4 (0.10 mmol) and isocyanide (1.1 mmol). The mixture was poured in a closed vessel and heated under microwave irradiation at 140 °C for 10 minutes. After cooling to room temperature, the solvent was evaporated and the crude material was extracted with ethyl acetate (15 mL), washed with water and brine dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using petroleum ether/ethyl acetate mixture (4:1 v/v) as eluent, or using dichloromethane/methanol mixture (95:5 v/v) as eluent in the case of **7g** to provide the expected pure products **7a-i**.

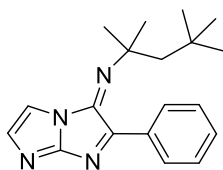
2-(4-Methoxyphenyl)-*N*-(2,4,4-trimethylpentan-2-yl)-3*H*-imidazo[1,2-*a*]imidazol-3-imine (**7a**)



7a

Orange oil (107 mg, 32%); IR (neat, cm^{-1}): 3076, 2958, 2887, 1603, 1572, 1250, 1202, 1121; ^1H NMR (400 MHz, CDCl_3): δ 8.48 (d, J = 8.9 Hz, 2H, HAr), 7.18 (d, J = 1.8 Hz, 1H, Himidazole), 7.04 (d, J = 1.7 Hz, 1H, Himidazole), 6.93 (d, J = 8.9 Hz, 2H, HAr), 3.87 (s, 3H, OCH_3), 1.88 (s, 2H, CH_2), 1.55 (s, 6H, 2 CH_3), 0.98 (s, 9H, 3 CH_3); ^{13}C NMR (101 MHz, CDCl_3): δ 168.9, 164.2, 162.9, 138.2, 133.5, 132.6, 123.9, 116.2, 113.8, 60.2, 55.4, 53.1, 32.0, 31.7, 28.4; HRMS (ESI): (m/z) calcd for $\text{C}_{20}\text{H}_{27}\text{N}_4\text{O}$ [$\text{M} + \text{H}$] $^+$: 339.2124, found: 339.2122.

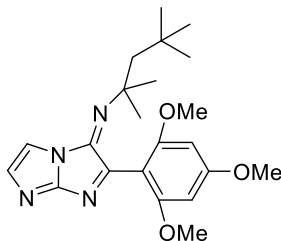
2-Phenyl-*N*-(2,4,4-trimethylpentan-2-yl)-3*H*-imidazo[1,2-*a*]imidazol-3-imine (**7b**)



7b

Yellow oil (73 mg, 24%); IR (neat, cm^{-1}): 3081, 2955, 2896, 1606, 1569, 1268, 1209; ^1H NMR (400 MHz, CDCl_3): δ 8.44 (d, $J = 7.3$ Hz, 2H, HAr), 7.56–7.48 (m, 1H, HAr), 7.44 (t, $J = 7.6$ Hz, 2H, HAr), 7.22 (d, $J = 1.8$ Hz, 1H, Himidazole), 7.09 (d, $J = 1.7$ Hz, 1H, Himidazole), 1.89 (s, 2H, CH_2), 1.56 (s, 6H, 2 CH_3), 0.99 (s, 9H, 3 CH_3); ^{13}C NMR (101 MHz, CDCl_3): δ 169.6, 163.9, 137.8, 133.8, 131.9, 131.1, 130.6, 128.2, 116.4, 60.3, 53.2, 32.0, 31.7, 28.3; HRMS (ESI): (m/z) calcd for $\text{C}_{19}\text{H}_{25}\text{N}_4$ [$\text{M} + \text{H}$] $^+$: 309.2074, found: 309.2073.

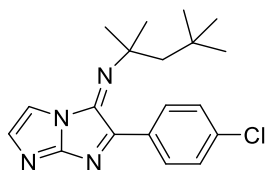
2-(2,4,6-Trimethoxyphenyl)-N-(2,4,4-trimethylpentan-2-yl)-3H-imidazo[1,2-a]imidazol-3-imine (7c)



7c

Yellow oil (141 mg, 35%); IR (neat, cm^{-1}): 3069, 2954, 2898, 1609, 1557, 1263, 1211, 1125; ^1H NMR (400 MHz, CDCl_3): δ 7.18 (d, $J = 1.8$ Hz, 1H, Himidazole), 7.03 (d, $J = 1.7$ Hz, 1H, Himidazole), 6.10 (s, 2H, HAr), 3.82 (s, 3H, OCH_3), 3.69 (s, 6H, 2 OCH_3), 1.63 (s, 2H, CH_2), 1.39 (s, 6H, 2 CH_3), 0.81 (s, 9H, 3 CH_3); ^{13}C NMR (101 MHz, CDCl_3): δ 172.3, 164.6, 163.0, 159.9, 137.8, 132.8, 116.4, 102.8, 90.5, 59.0, 55.8, 55.4, 55.1, 31.8, 31.3, 27.8; HRMS (ESI): (m/z) calcd for $\text{C}_{22}\text{H}_{31}\text{N}_4\text{O}_3$ [$\text{M} + \text{H}$] $^+$: 399.2391, found: 399.2388.

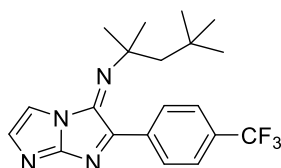
2-(4-Chlorophenyl)-N-(2,4,4-trimethylpentan-2-yl)-3H-imidazo[1,2-a]imidazol-3-imine (7d)



7d

Yellow oil (66 mg, 19%); IR (neat, cm^{-1}): 3085, 2963, 2896, 1601, 1578, 1249, 1202; ^1H NMR (400 MHz, CDCl_3): δ 8.42 (d, $J = 8.2$ Hz, 2H, HAr), 7.41 (d, $J = 8.1$ Hz, 2H, HAr), 7.21 (s, 1H, Himidazole), 7.09 (s, 1H, Himidazole), 1.88 (s, 2H, CH_2), 1.55 (s, 6H, 2CH_3), 0.98 (s, 9H, 3CH_3); ^{13}C NMR (101 MHz, CDCl_3): δ 168.4, 163.7, 138.5, 137.8, 134.0, 131.8, 129.5, 128.6, 116.5, 60.4, 53.2, 32.0, 31.7, 28.3; HRMS (ESI): (m/z) calcd for $\text{C}_{19}\text{H}_{24}\text{ClN}_4$ [$\text{M} + \text{H}$] $^+$: 343.1684, found: 343.1687.

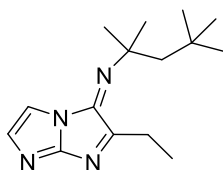
2-(4-(Trifluoromethyl)phenyl)-N-(2,4,4-trimethylpentan-2-yl)-3H-imidazo[1,2-a]imidazol-3-imine (7e)



7e

Orange solid (50 mg, 13%); m.p.: 106-107 $^{\circ}\text{C}$; IR (neat, cm^{-1}): 3080, 2971, 2893, 1608, 1553, 1236, 1192; ^1H NMR (400 MHz, CDCl_3): δ 8.57 (d, $J = 8.1$ Hz, 2H, HAr), 7.70 (d, $J = 8.1$ Hz, 2H, HAr), 7.24 (d, $J = 1.8$ Hz, 1H, Himidazole), 7.13 (d, $J = 1.8$ Hz, 1H, Himidazole), 1.90 (s, 2H, CH_2), 1.57 (s, 6H, 2CH_3), 0.99 (s, 9H, 3CH_3); ^{13}C NMR (101 MHz, CDCl_3): δ 168.0, 163.4, 137.6, 134.2, 134.1, 132.9 (q, $J = 32.5$ Hz), 130.7, 125.1 (q, $J = 3.8$ Hz), 122.4 (q, $J = 272.3$ Hz), 116.7, 60.6, 53.1, 32.0, 31.7, 28.3; ^{19}F NMR (376 MHz, CDCl_3): δ -61.1 (s); HRMS (ESI): (m/z) calcd for $\text{C}_{20}\text{H}_{24}\text{F}_3\text{N}_4$ [$\text{M} + \text{H}$] $^+$: 377.1948, found: 377.1944, (m/z) calcd for $\text{C}_{20}\text{H}_{23}\text{F}_3\text{N}_4\text{Na}$ [$\text{M} + \text{Na}$] $^+$: 399.1767, found: 399.1767.

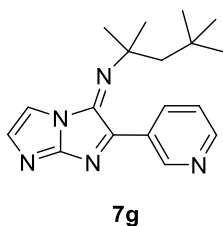
2-Ethyl-N-(2,4,4-trimethylpentan-2-yl)-3H-imidazo[1,2-a]imidazol-3-imine (7f)



7f

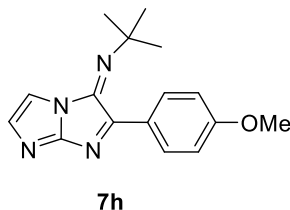
Yellow oil (41 mg, 16%); IR (neat, cm^{-1}): 3083, 2977, 2889, 1602, 1560, 1245; ^1H NMR (400 MHz, CDCl_3): δ 7.12 (d, $J = 1.8$ Hz, 1H, Himidazole), 7.00 (d, $J = 1.8$ Hz, 1H, Himidazole), 2.74 (q, $J = 7.4$ Hz, 2H, $\text{CH}_2(\text{Et})$), 1.77 (s, 2H, CH_2octyl), 1.45 (s, 6H, 2CH_3), 1.30 (t, $J = 7.4$ Hz, 3H, $\text{CH}_3(\text{Et})$), 1.00 (s, 9H, 3CH_3); ^{13}C NMR (101 MHz, CDCl_3): δ 180.7, 164.6, 137.9, 133.0, 116.2, 59.3, 54.7, 32.0, 31.7, 27.8, 22.7, 10.6; HRMS (ESI): (m/z) calcd for $\text{C}_{15}\text{H}_{25}\text{N}_4$ $[\text{M} + \text{H}]^+$: 261.2074, found: 261.2073.

2-(Pyridin-3-yl)-*N*-(2,4,4-trimethylpentan-2-yl)-3*H*-imidazo[1,2-*a*]imidazol-3-imine (7g)



Orange oil (38 mg, 12%); IR (neat, cm^{-1}): 3089, 2943, 2905, 1612, 1560, 1257, 1202; ^1H NMR (400 MHz, CDCl_3): δ 9.63 (s, 1H, HAr), 8.72 (dd, $J = 4.9, 1.7$ Hz, 1H, HAr), 8.66 (dt, $J = 8.1, 2.0$ Hz, 1H, HAr), 7.40 (ddd, $J = 8.0, 4.8, 0.9$ Hz, 1H, HAr), 7.24 (d, $J = 1.8$ Hz, 1H, Himidazole), 7.12 (d, $J = 1.7$ Hz, 1H, Himidazole), 1.89 (s, 2H, CH_2), 1.57 (s, 6H, 2CH_3), 0.98 (s, 9H, 3CH_3); ^{13}C NMR (101 MHz, CDCl_3): δ 167.9, 163.7, 152.1, 151.3, 137.5, 137.2, 134.1, 127.1, 123.2, 116.7, 60.6, 53.2, 32.0, 31.7, 28.4; HRMS (ESI): (m/z) calcd for $\text{C}_{18}\text{H}_{24}\text{N}_5$ $[\text{M} + \text{H}]^+$: 310.2026, found: 310.2027, (m/z) calcd for $\text{C}_{18}\text{H}_{23}\text{N}_5\text{Na}$ $[\text{M} + \text{Na}]^+$: 332.1846, found: 332.1848.

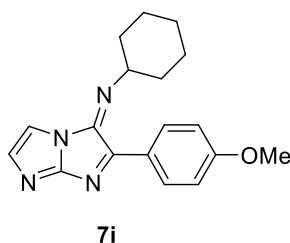
***N*-(*tert*-Butyl)-2-(4-methoxyphenyl)-3*H*-imidazo[1,2-*a*]imidazol-3-imine (7h)**



Orange oil (47 mg, 17%); IR (neat, cm^{-1}): 3088, 2945, 2890, 1606, 1542, 1256, 1211, 1120; ^1H NMR (400 MHz, CDCl_3): δ 8.50 (d, $J = 9.0$ Hz, 2H, HAr), 7.15 (d, $J = 1.8$ Hz, 1H, Himidazole), 7.04 (d, $J = 1.8$ Hz, 1H, Himidazole), 6.94 (d, $J = 9.0$ Hz, 2H, HAr), 3.87 (s, 3H, OCH_3), 1.51 (s, 9H, 3CH_3); ^{13}C

NMR (101 MHz, CDCl₃): δ 169.1, 164.1, 163.0, 139.3, 133.6, 132.5, 123.8, 116.3, 113.9, 56.1, 55.4, 28.2; HRMS (ESI): (m/z) calcd for C₁₆H₁₉N₄O [M + H]⁺: 283.1553, found: 283.1553, (m/z) calcd for C₁₆H₁₈N₄NaO [M + Na]⁺: 305.1373, found: 305.1374.

***N*-Cyclohexyl-2-(4-methoxyphenyl)-3*H*-imidazo[1,2-*a*]imidazol-3-imine (7i)**

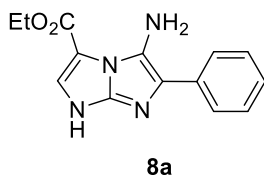


Orange oil (30 mg, 10%); IR (neat, cm⁻¹): 3082, 2951, 2884, 1605, 1562, 1248, 1224, 1129; ¹H NMR (400 MHz, CDCl₃): δ 8.55 (d, *J* = 9.0 Hz, 2H, HAr), 7.04 (dd, *J* = 5.0, 1.8 Hz, 2H, Himidazole), 6.96 (d, *J* = 9.0 Hz, 2H, HAr), 3.88 (s, 3H, OCH₃), 3.82–3.76 (m, 1H, CH), 1.93–1.88 (m, 3H, 3/2CH₂), 1.73–1.62 (m, 4H, 2CH₂), 1.50–1.39 (m, 3H, 3/2CH₂); ¹³C NMR (101 MHz, CDCl₃): δ 167.9, 163.2, 163.0, 142.6, 133.9, 132.2, 123.7, 115.0, 114.0, 60.4, 55.4, 32.5, 25.5, 24.2; HRMS (ESI): (m/z) calcd for C₁₈H₂₁N₄O [M + H]⁺: 309.1710, found: 309.1709, (m/z) calcd for C₁₈H₂₀N₄NaO [M + Na]⁺: 331.1529, found: 331.1529.

General procedure for the synthesis of compounds 8a-d, 9a-g

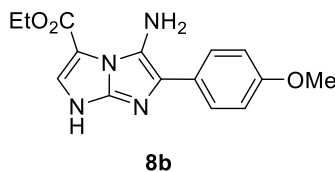
In a closed vessel containing a mixture of DCM/TFA (5 mL, 1:1 v/v), 0.2 mmol of **4a-d** or **5a-g** was added at room temperature. After completion of the reaction (30 min), the solvents were removed under reduced pressure, and the mixture was partitioned between saturated aqueous solution of NaHCO₃ (10 mL) and EtOAc (15 mL). The organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was then purified by flash chromatography on silica gel using petroleum ether/ethyl acetate mixture (1:1 – 1:4 v/v) as eluent to afford the expected pure products **8a-d** and **9a-g**.

Ethyl 5-amino-6-phenyl-1H-imidazo[1,2-a]imidazole-3-carboxylate (**8a**)



Yellow solid (38 mg, 70%); m.p.: 202-204 °C; IR (neat, cm⁻¹): 3420 (NH), 2981, 2899, 1693 (CO), 1596, 1510, 1247, 1196; ¹H NMR (400 MHz, DMSO-d₆): δ 11.80 (br s, 1H, NHimidazole), 7.71 (s, 1H, Himidazole), 7.66 (d, *J* = 7.2 Hz, 2H, HAr), 7.41 (t, *J* = 7.8 Hz, 2H, HAr), 7.19 (t, *J* = 7.4 Hz, 1H, HAr), 5.95 (s, 2H, NH₂), 4.27 (q, *J* = 7.1 Hz, 2H, CH₂ester), 1.30 (t, *J* = 7.1 Hz, 3H, CH₃ester); ¹³C NMR (101 MHz, DMSO-d₆): δ 161.3, 147.4, 142.3, 131.4, 129.1, 125.8, 125.7, 124.4, 113.0, 110.1, 60.4, 14.8; HRMS (ESI): (*m/z*) calcd for C₁₄H₁₅N₄O₂ [*M* + *H*]⁺: 271.1189, found: 271.1186.

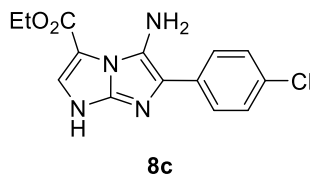
Ethyl 5-amino-6-(4-methoxyphenyl)-1H-imidazo[1,2-a]imidazole-3-carboxylate (**8b**)



Brown solid (44 mg, 74%); m.p.: 104-106 °C; IR (neat, cm⁻¹): 3379 (NH), 2975, 2902, 1698 (CO), 1601, 1502, 1258, 1108; ¹H NMR (250 MHz, DMSO-d₆): δ 11.72 (br s, 1H, NHimidazole), 7.67 (s, 1H, Himidazole), 7.59 (d, *J* = 8.8 Hz, 2H, HAr), 7.00 (d, *J* = 8.8 Hz, 2H, HAr), 5.72 (s, 2H, NH₂), 4.26

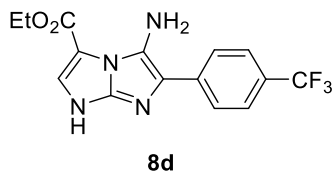
(q, $J = 7.1$ Hz, 2H, CH₂ester), 3.78 (s, 3H, OCH₃), 1.29 (t, $J = 7.1$ Hz, 3H, CH₃ester); ¹³C NMR (62.9 MHz, DMSO-d₆): δ 161.2, 157.8, 146.0, 140.6, 126.2, 124.5, 123.7, 114.7, 113.2, 110.8, 60.6, 55.6, 14.8; HRMS (ESI): (m/z) calcd for C₁₅H₁₇N₄O₃ [M + H]⁺: 301.1295, found: 301.1301.

Ethyl 5-amino-6-(4-chlorophenyl)-1H-imidazo[1,2-a]imidazole-3-carboxylate (8c)



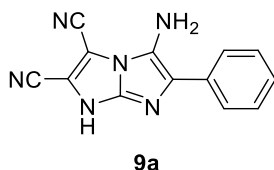
Yellow solid (41 mg, 68%); m.p.: 212-214 °C; IR (neat, cm⁻¹): 3393 (NH), 2989, 2909, 1691 (CO), 1612, 1508, 1270; ¹H NMR (400 MHz, DMSO-d₆): δ 11.86 (br s, 1H, NHimidazole), 7.70 (s, 1H, Himidazole), 7.66 (d, $J = 8.4$ Hz, 2H, HAr), 7.00 (d, $J = 8.3$ Hz, 2H, HAr), 6.01 (s, 2H, NH₂), 4.27 (q, $J = 7.1$ Hz, 2H, CH₂ester), 1.30 (t, $J = 7.1$ Hz, 3H, CH₃ester); ¹³C NMR (100.1 MHz, DMSO-d₆): δ 161.3, 147.4, 142.3, 130.4, 129.8, 129.0, 126.3, 125.9, 113.1, 109.4, 60.5, 14.8; HRMS (ESI): (m/z) calcd for C₁₄H₁₄ClN₄O₂ [M + H]⁺: 305.0800, found: 305.0796.

Ethyl 5-amino-6-(4-(trifluoromethyl)phenyl)-1H-imidazo[1,2-a]imidazole-3-carboxylate (8d)



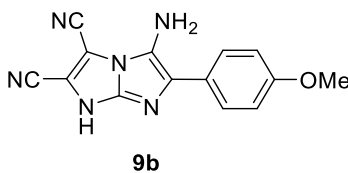
Yellow solid (44 mg, 65%); m.p.: 223-225 °C; IR (neat, cm⁻¹): 3382 (NH), 2990, 2895, 1698 (CO), 1610, 1488, 1254; ¹H NMR (400 MHz, DMSO-d₆): δ 11.86 (br s, 1H, NHimidazole), 7.70 (s, 1H, Himidazole), 7.66 (d, $J = 8.4$ Hz, 2H, HAr), 7.00 (d, $J = 8.3$ Hz, 2H, HAr), 6.01 (s, 2H, NH₂), 4.27 (q, $J = 7.1$ Hz, 2H, CH₂ester), 1.30 (t, $J = 7.1$ Hz, 3H, CH₃ester); ¹³C NMR (100.1 MHz, DMSO-d₆): δ 161.3, 147.6, 142.6, 135.6, 127.8, 125.9 (q, $J = 3.9$ Hz), 125.0 (q, $J = 32.0$ Hz), 124.3, 123.6 (q, $J = 271.4$ Hz), 113.2, 108.9, 60.6, 14.8; ¹⁹F NMR (376 MHz, CDCl₃): δ -60.7 (s); HRMS (ESI): (m/z) calcd for C₁₅H₁₄F₃N₄O₂ [M + H]⁺: 339.1063, found: 339.1064.

5-Amino-6-phenyl-1*H*-imidazo[1,2-*a*]imidazole-2,3-dicarbonitrile (9a)



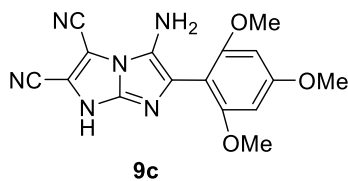
Yellow solid (29 mg, 59%); m.p.: 260-262 °C; IR (neat, cm^{-1}): 3396 (NH), 2954, 2909, 2214 (CN), 1627, 1567, 1389; ^1H NMR (400 MHz, DMSO-d_6): δ 12.66 (s, 1H, NHimidazole), 7.79 (d, $J = 7.2$ Hz, 2H, HAr), 7.49 (t, $J = 7.7$ Hz, 2H, HAr), 7.37 (t, $J = 7.4$ Hz, 1H, HAr), 4.90 (s, 2H, NH_2); ^{13}C NMR (101 MHz, DMSO-d_6): δ 144.3, 129.4, 129.3, 128.2, 126.6, 123.1, 122.8, 121.8, 114.2, 110.9, 96.9; HRMS (ESI): (m/z) calcd for $\text{C}_{13}\text{H}_9\text{N}_6$ $[\text{M} + \text{H}]^+$: 249.0883, found: 249.0881, (m/z) calcd for $\text{C}_{13}\text{H}_8\text{N}_6\text{Na}$ $[\text{M} + \text{Na}]^+$: 271.0703, found: 271.0701.

5-Amino-6-(4-methoxyphenyl)-1*H*-imidazo[1,2-*a*]imidazole-2,3-dicarbonitrile (9b)



Yellow solid (34 mg, 61%); m.p.: 227-229 °C; IR (neat, cm^{-1}): 3403 (NH), 2949, 2912, 2225 (CN), 1618, 1560, 1398, 1134; ^1H NMR (400 MHz, DMSO-d_6): δ 12.57 (s, 1H, NHimidazole), 7.74 (d, $J = 8.5$ Hz, 2H, HAr), 7.06 (d, $J = 8.5$ Hz, 2H, HAr), 4.73 (s, 2H, NH_2), 3.81 (s, 3H, OCH_3); ^{13}C NMR (101 MHz, DMSO-d_6): δ 159.4, 144.1, 128.2, 122.8, 122.7, 121.7, 121.5, 114.7, 114.2, 110.9, 96.8, 55.7; HRMS (ESI): (m/z) calcd for $\text{C}_{14}\text{H}_{10}\text{N}_6\text{O}$ $[\text{M} + \text{H}]^+$: 279.0989, found: 279.0988.

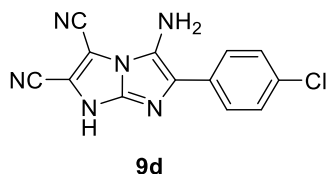
5-Amino-6-(2,4,6-trimethoxyphenyl)-1*H*-imidazo[1,2-*a*]imidazole-2,3-dicarbonitrile (9c)



Yellow solid (22 mg, 32%); m.p.: 262-264 °C; IR (neat, cm^{-1}): 3392 (NH), 2964, 2906, 2217 (CN), 1611, 1552, 1420, 1102; ^1H NMR (400 MHz, DMSO-d_6): δ 12.04 (s, 1H, NHimidazole), 6.35 (s, 2H,

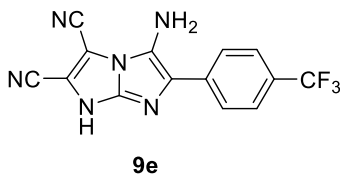
HAr), 4.31 (s, 2H, NH₂), 3.85 (s, 3H, OCH₃), 3.77 (s, 6H, 2OCH₃); ¹³C NMR (101 MHz, DMSO-d₆): δ 162.8, 159.6, 144.0, 124.4, 122.4, 114.4, 113.3, 111.2, 98.2, 95.9, 91.3, 56.3, 56.0; HRMS (ESI): (m/z) calcd for C₁₆H₁₅N₆O₃ [M + H]⁺: 339.1200, found: 339.1200, (m/z) calcd for C₁₆H₁₄N₆NaO₃ [M + Na]⁺: 361.1020, found: 361.1019.

5-Amino-6-(4-chlorophenyl)-1H-imidazo[1,2-a]imidazole-2,3-dicarbonitrile (9d)



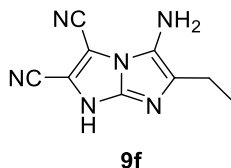
Yellow solid (34 mg, 57%); m.p.: 268-270 °C; IR (neat, cm⁻¹): 3403 (NH), 2949, 2912, 2225 (CN), 1618, 1560, 1398, 1134; ¹H NMR (400 MHz, DMSO-d₆): δ 12.70 (s, 1H, NHimidazole), 7.81 (d, *J* = 8.7 Hz, 2H, HAr), 7.56 (d, *J* = 8.6 Hz, 2H, HAr), 4.95 (s, 2H, NH₂); ¹³C NMR (101 MHz, DMSO-d₆): δ 144.4, 132.7, 129.3, 128.3, 128.2, 123.3, 123.2, 120.8, 114.1, 110.8, 97.0; HRMS (ESI): (m/z) calcd for C₁₃H₈ClN₆ [M + H]⁺: 283.0493, found: 283.0492.

5-Amino-6-(4-(trifluoromethyl)phenyl)-1H-imidazo[1,2-a]imidazole-2,3-dicarbonitrile (9e)



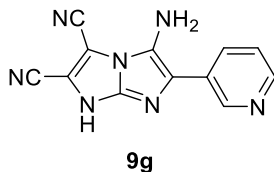
Yellow solid (50 mg, 79%); m.p.: 247-249 °C; IR (neat, cm⁻¹): 3384 (NH), 2963, 2905, 2221 (CN), 1626, 1545, 1410, 1117; ¹H NMR (400 MHz, DMSO-d₆): δ 12.80 (s, 1H, NHimidazole), 7.98 (d, *J* = 8.2 Hz, 2H, HAr), 7.84 (d, *J* = 8.2 Hz, 2H, HAr), 5.15 (s, 2H, NH₂); ¹³C NMR (101 MHz, DMSO-d₆): δ 144.6, 133.5, 127.6 (q, *J* = 32.0 Hz), 126.8, 126.1 (q, *J* = 3.9 Hz), 124.6, 123.7, 122.4 (q, *J* = 271.8 Hz), 119.5, 114.0, 110.7, 97.1; ¹⁹F NMR (376 MHz, CDCl₃): δ -61.0 (s); HRMS (ESI): (m/z) calcd for C₁₄H₇F₃N₆ [M + H]⁺: 317.0757, found: 317.0758.

5-Amino-6-ethyl-1*H*-imidazo[1,2-*a*]imidazole-2,3-dicarbonitrile (9f)



Colorless oil (16 mg, 41%); IR (neat, cm^{-1}): 3403 (NH), 2949, 2912, 2225 (CN), 1618, 1560, 1398, 1134; ^1H NMR (400 MHz, DMSO-d_6): δ 12.13 (s, 1H, NHimidazole), 4.45 (s, 2H, NH_2), 2.58 (q, $J = 7.5$ Hz, 2H, CH_2), 1.16 (t, $J = 7.5$ Hz, 3H, CH_3); ^{13}C NMR (101 MHz, DMSO-d_6): δ 173.5, 143.9, 124.4, 121.8, 114.3, 111.0, 96.1, 17.4, 13.8; HRMS (ESI): (m/z) calcd for $\text{C}_9\text{H}_9\text{N}_6$ [$\text{M} + \text{H}$] $^+$: 200.0924, found: 200.0921.

5-Amino-6-(pyridin-3-yl)-1*H*-imidazo[1,2-*a*]imidazole-2,3-dicarbonitrile (9g)

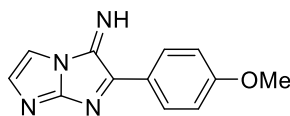


Yellow solid (13 mg, 26%); m.p.: 255-257 $^{\circ}\text{C}$; IR (neat, cm^{-1}): 3374 (NH), 2966, 2900, 2219 (CN), 1632, 1548, 1365; ^1H NMR (400 MHz, DMSO-d_6): δ 12.83 (br s, 1H, NHimidazole), 9.01 (s, 1H, HAr), 8.54 (dd, $J = 4.9, 1.6$ Hz, 1H, HAr), 8.16 (dt, $J = 8.1, 1.9$ Hz, 1H, HAr), 7.52 (dd, $J = 8.1, 4.8$ Hz, 1H, HAr), 5.04 (s, 2H, NH_2); ^{13}C NMR (101 MHz, DMSO-d_6): δ 148.8, 147.4, 144.9, 133.7, 125.9, 124.1, 123.8, 123.4, 119.1, 114.1, 110.8, 96.9; HRMS (ESI): (m/z) calcd for $\text{C}_{12}\text{H}_8\text{N}_7$ [$\text{M} + \text{H}$] $^+$: 250.0836, found: 250.0834.

General procedure for the synthesis of compounds 10a, 10b, 10d, 10e, 10g

In a closed vessel containing a mixture of DCM/TFA (5 mL, 4:1 v/v), 0.15 mmol of **7a**, **7b**, **7d**, **7e** or **7g** was added. The solution was stirred at room temperature for 10 min. After completion of the reaction, TFA and DCM were evaporated under reduced pressure. The mixture was then partitioned between saturated aqueous solution of NaHCO₃ (10 mL) and EtOAc (15 mL). The organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using petroleum ether/ethyl acetate mixture (3:2 v/v) as eluent, or using dichloromethane/methanol mixture (96:4 v/v) as eluent in the case of **10g** to afford the desired pure products **10a**, **10b**, **10d**, **10e** and **10g**.

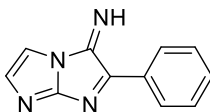
2-(4-Methoxyphenyl)-3H-imidazo[1,2-a]imidazol-3-imine (10a)



10a

Yellow solid (25 mg, 74%); m.p.: 180-182 °C; IR (neat, cm⁻¹): 3261 (NH), 3084, 2938, 2873, 1592, 1224, 1116; ¹H NMR (400 MHz, CDCl₃): δ 12.79 (s, 1H, NH), 8.02 (d, *J* = 8.5 Hz, 2H, HAr), 7.38 (s, 1H, Himidazole), 7.17 (d, *J* = 8.9 Hz, 3H, Himidazole+2HAr), 3.88 (s, 3H, OCH₃); ¹³C NMR (101 MHz, CDCl₃): δ 163.3, 147.5, 131.7, 129.9, 127.2, 120.0, 115.3, 113.2, 56.2; HRMS (ESI): (m/z) calcd for C₁₂H₁₁N₄O [M + H]⁺: 227.0928, found: 227.0927, (m/z) calcd for C₁₂H₁₀N₄NaO [M + Na]⁺: 249.0747, found: 249.0746.

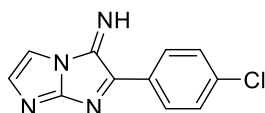
2-Phenyl-3H-imidazo[1,2-a]imidazol-3-imine (10b)



10b

Yellow solid (25 mg, 85%); m.p.: 185-187 °C; IR (neat, cm^{-1}): 3273 (NH), 2934, 2836, 1604, 1510, 1463, 1247; ^1H NMR (400 MHz, CDCl_3): δ 12.97 (s, 1H, NH), 8.07 (dd, $J = 7.9, 1.8$ Hz, 2H, HAr), 7.67–7.59 (m, 3H, HAr), 7.35 (s, 2H, Himidazole); ^{13}C NMR (101 MHz, CDCl_3): δ 147.2, 134.5, 132.9, 131.6, 129.8, 127.8, 113.2; HRMS (ESI): (m/z) calcd for $\text{C}_{11}\text{H}_9\text{N}_4$ $[\text{M} + \text{H}]^+$: 197.0822, found: 197.0823, (m/z) calcd for $\text{C}_{11}\text{H}_8\text{N}_4\text{Na}$ $[\text{M} + \text{Na}]^+$: 219.0641, found: 219.0641.

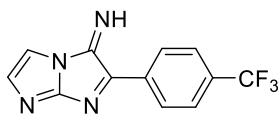
2-(4-Chlorophenyl)-3H-imidazo[1,2-a]imidazol-3-imine (10d)



10d

Yellow solid (28 mg, 82%); m.p.: 156-158 °C; IR (neat, cm^{-1}): 3296 (NH), 3080, 2946, 2871, 1564, 1226; ^1H NMR (400 MHz, CDCl_3): δ 13.01 (s, 1H, NH), 8.04 (d, $J = 8.7$ Hz, 2H, HAr), 7.68 (d, $J = 8.7$ Hz, 2H, 2HAr), 7.56–7.19 (m, 2H, Himidazole); ^{13}C NMR (101 MHz, CDCl_3): δ 147.0, 137.6, 133.5, 130.2, 129.9, 129.4, 113.1; HRMS (ESI): (m/z) calcd for $\text{C}_{11}\text{H}_8\text{ClN}_4$ $[\text{M} + \text{H}]^+$: 231.0539, found: 231.0537.

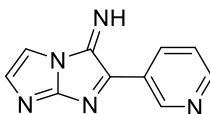
2-(4-(Trifluoromethyl)phenyl)-3H-imidazo[1,2-a]imidazol-3-imine (10e)



10e

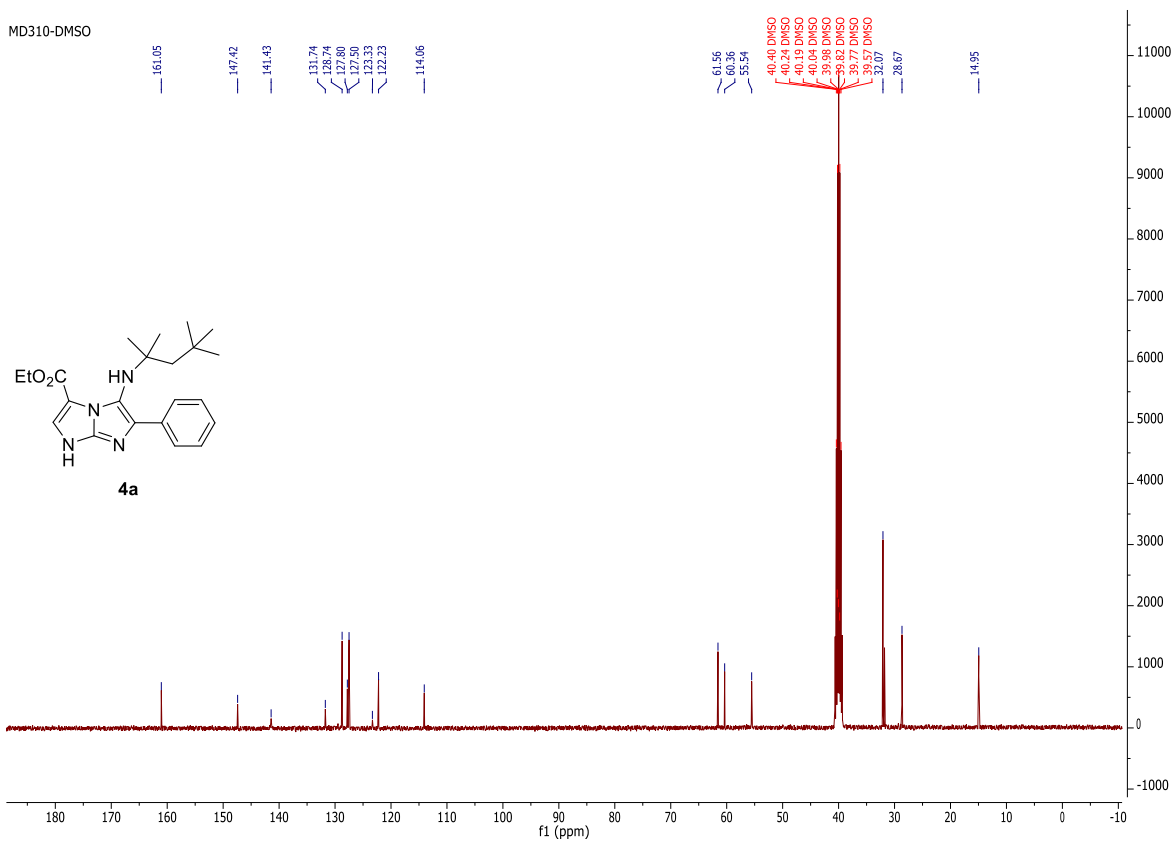
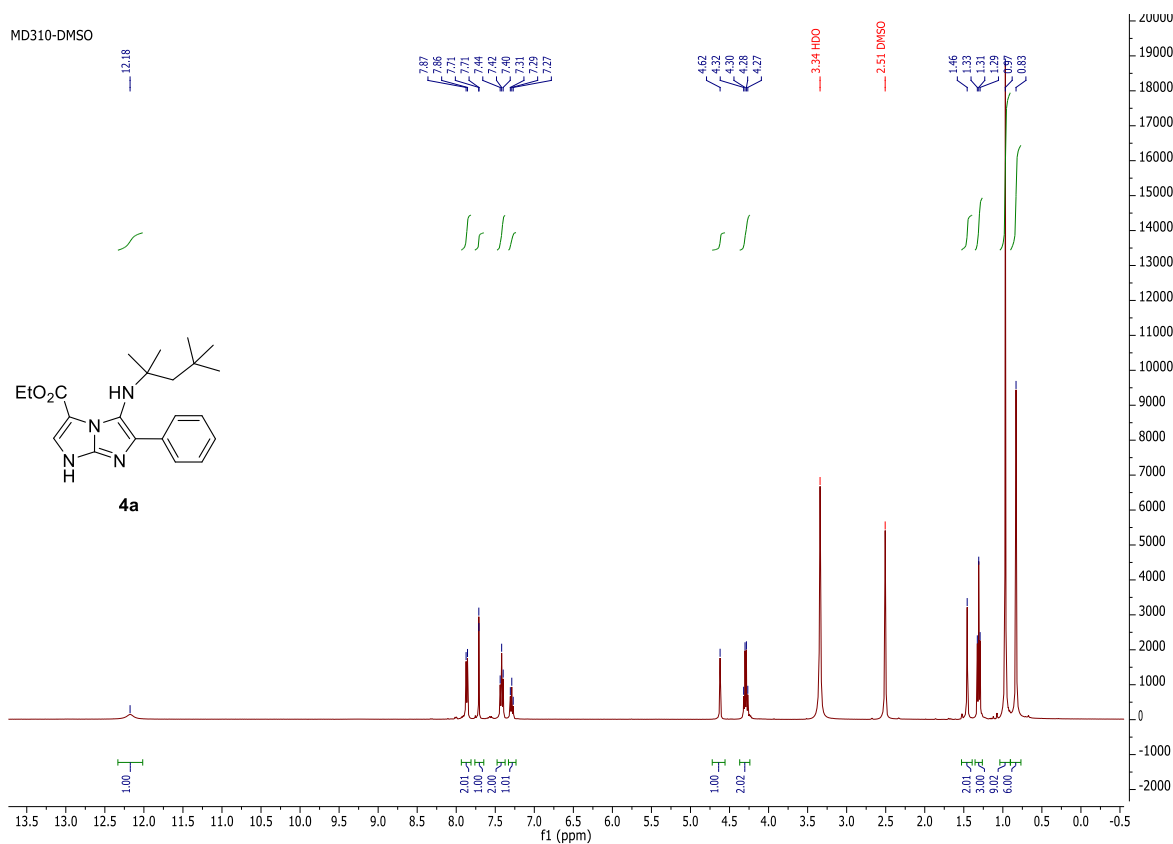
Yellow solid (25 mg, 63%); m.p.: 185-186 °C; IR (neat, cm^{-1}): 3305 (NH), 3079, 2950, 2866, 1553, 1216; ^1H NMR (400 MHz, CDCl_3): δ 13.15 (s, 1H, NH), 8.24 (d, $J = 8.2$ Hz, 2H, HAr), 7.68 (d, $J = 8.3$ Hz, 2H, 2HAr), 7.43 (s, 2H, Himidazole); ^{13}C NMR (101 MHz, CDCl_3): δ 146.9, 138.2, 138.2, 131.7 (q, $J = 32.2$ Hz), 129.6, 129.3, 128.5, 126.6 (q, $J = 3.9$ Hz), 122.1 (q, $J = 272.4$ Hz), 113.2; ^{19}F NMR (376 MHz, CDCl_3): δ -61.5 (s); HRMS (ESI): (m/z) calcd for $\text{C}_{12}\text{H}_8\text{F}_3\text{N}_4$ $[\text{M} + \text{H}]^+$: 265.0696, found: 265.0697, (m/z) calcd for $\text{C}_{12}\text{H}_7\text{F}_3\text{N}_4\text{Na}$ $[\text{M} + \text{Na}]^+$: 287.0515, found: 287.0520.

2-(Pyridin-3-yl)-3*H*-imidazo[1,2-*a*]imidazol-3-imine (10g)

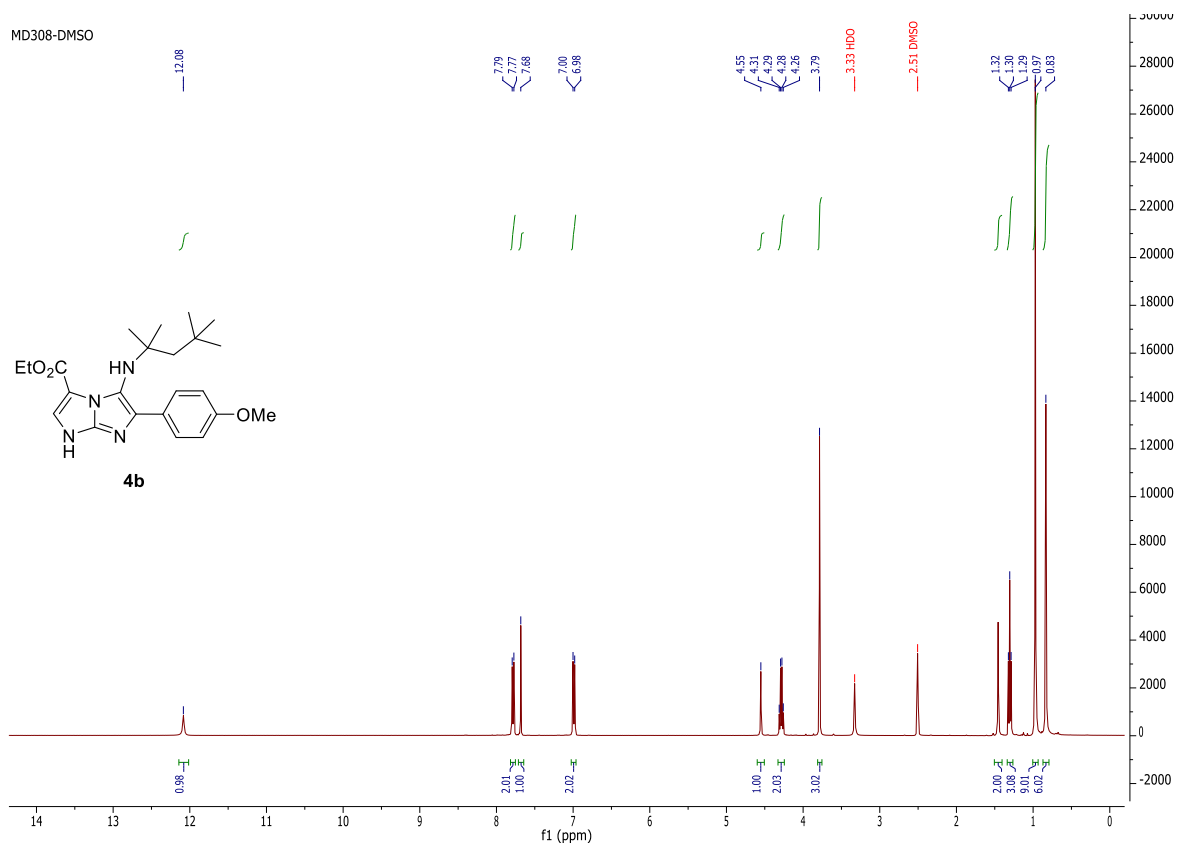


10g

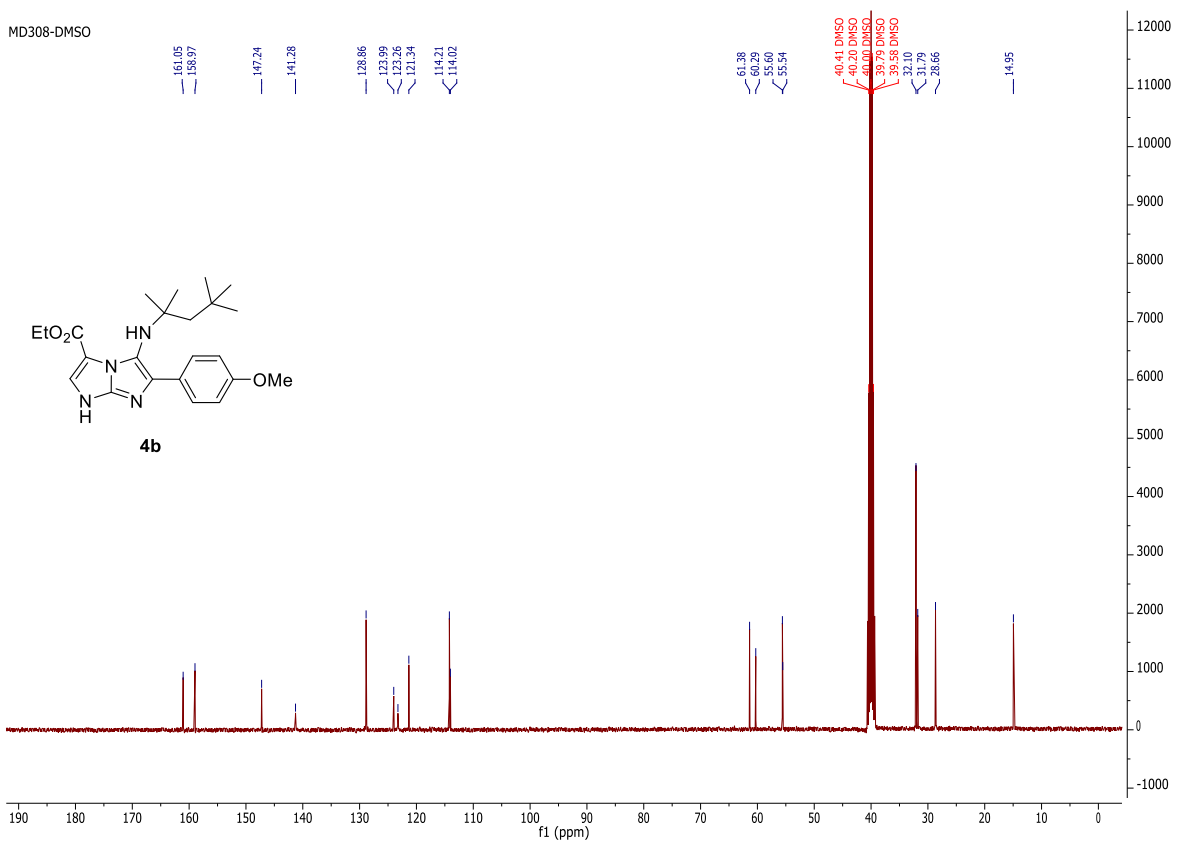
Yellow solid (19 mg, 64%); m.p.: 176-178 °C; IR (neat, cm⁻¹): 3286 (NH), 2977, 2861, 1609, 1523, 1438, 1259; ¹H NMR (400 MHz, CDCl₃): δ 13.10 (br s, 1H, NH), 9.18 (d, *J* = 1.5 Hz, 1H, , HAr), 8.78 (dd, *J* = 4.8, 1.6 Hz, 1H, HAr), 8.34 (ddd, *J* = 8.1, 2.4, 1.6 Hz, 1H, , HAr), 7.64 (ddd, *J* = 8.1, 4.8, 0.9 Hz, 1H, HAr), 7.39 (s, 2H, Himidazole); ¹³C NMR (101 MHz, CDCl₃): δ 152.8, 148.6, 147.1, 135.2, 130.6, 129.2, 124.6, 112.9; HRMS (ESI): (m/z) calcd for C₁₀H₈N₅ [M + H]⁺: 198.0774, found: 198.0769, (m/z) calcd for C₁₀H₇N₅Na [M + Na]⁺: 220.0594, found: 220.0588.

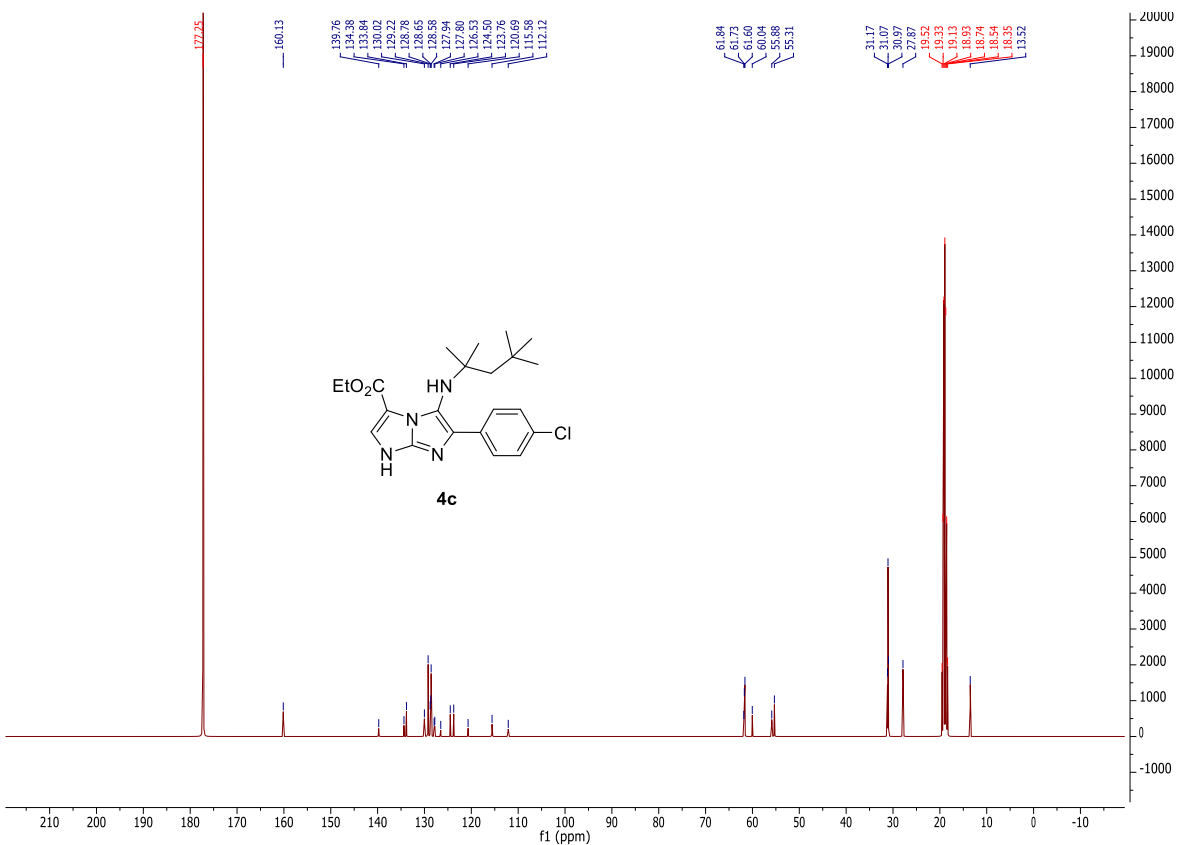
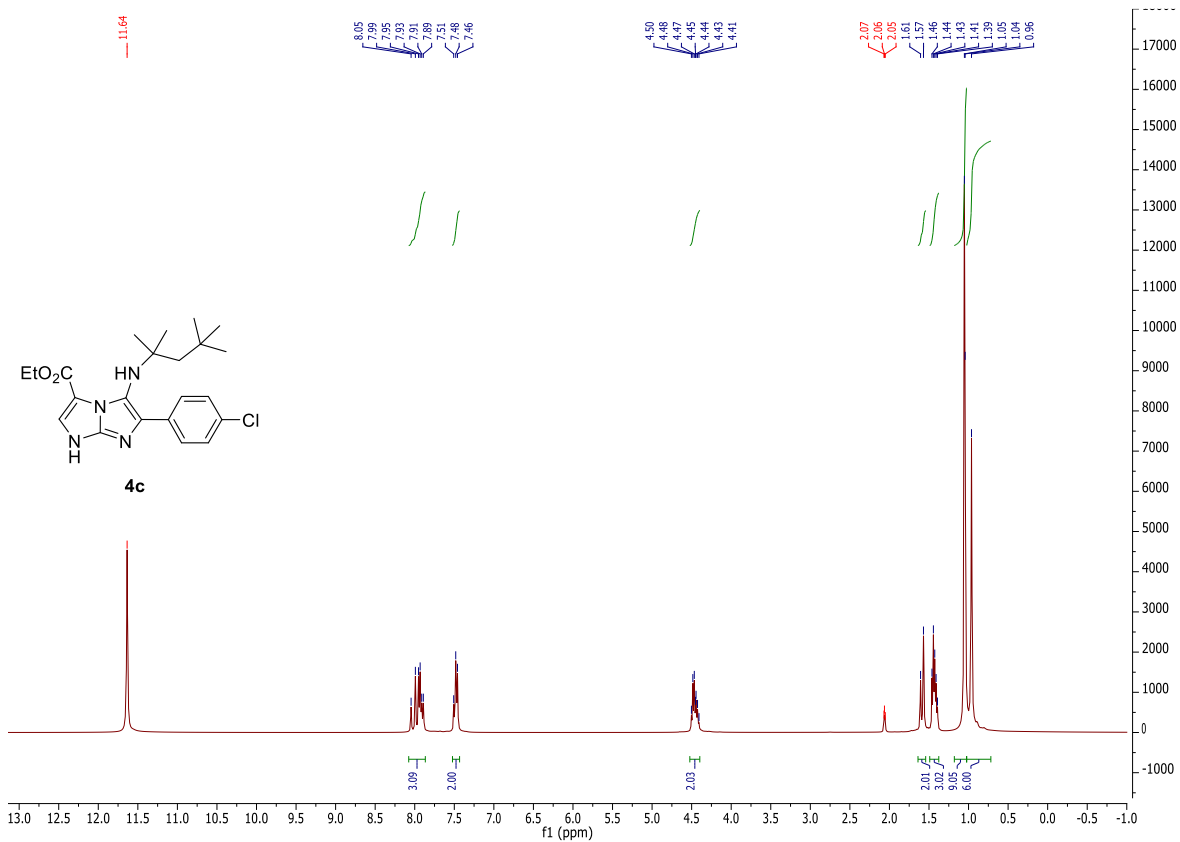


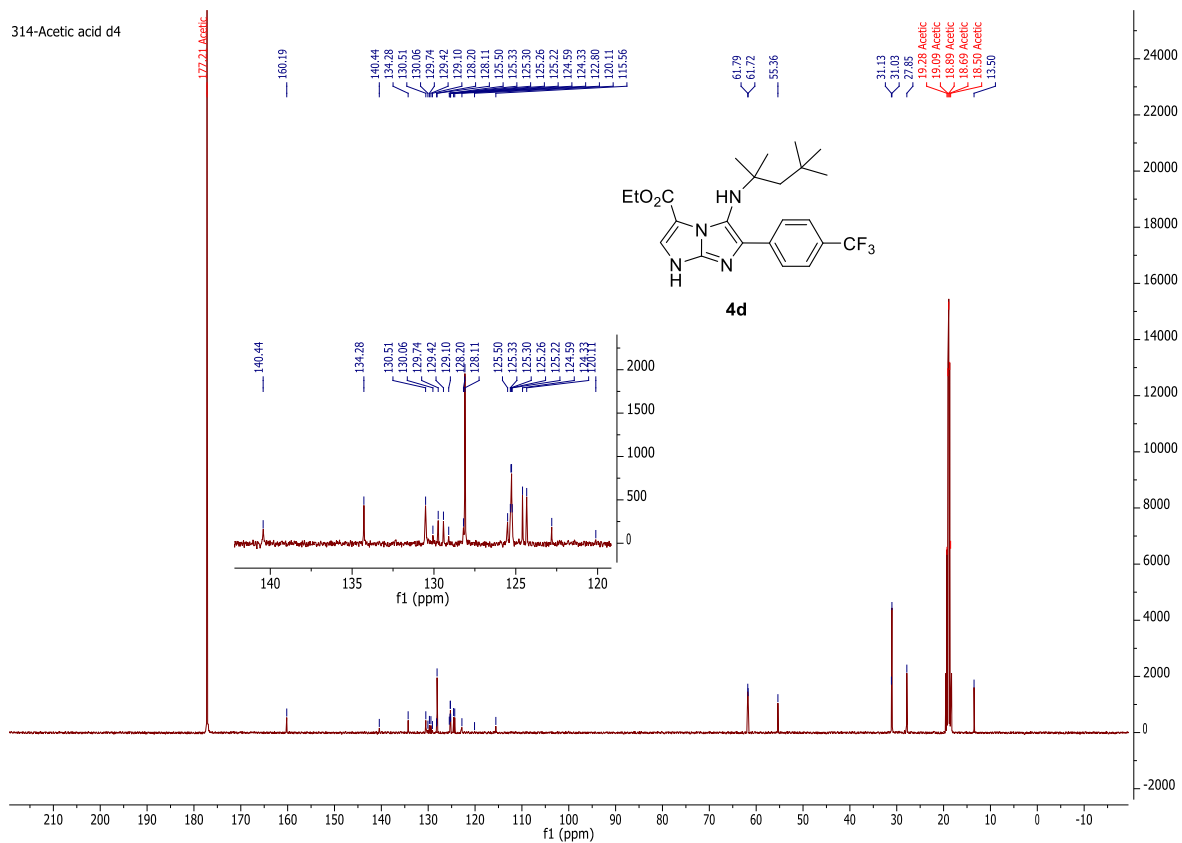
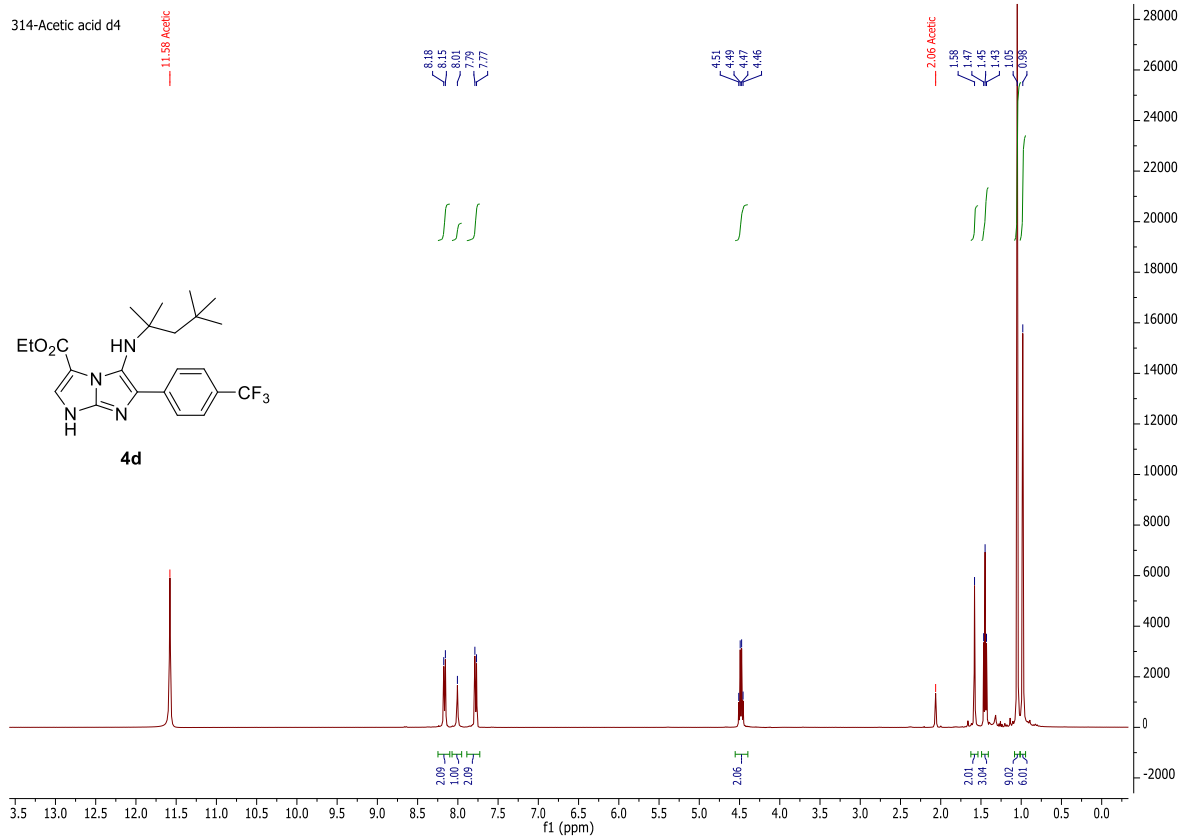
MD308-DMSO



MD308-DMSO

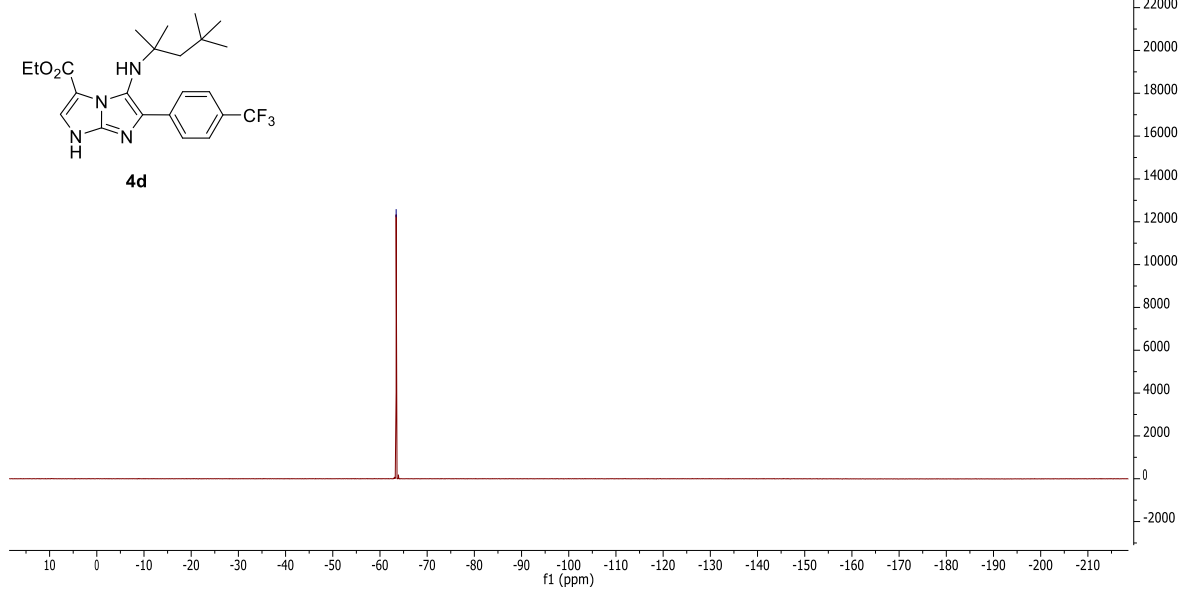


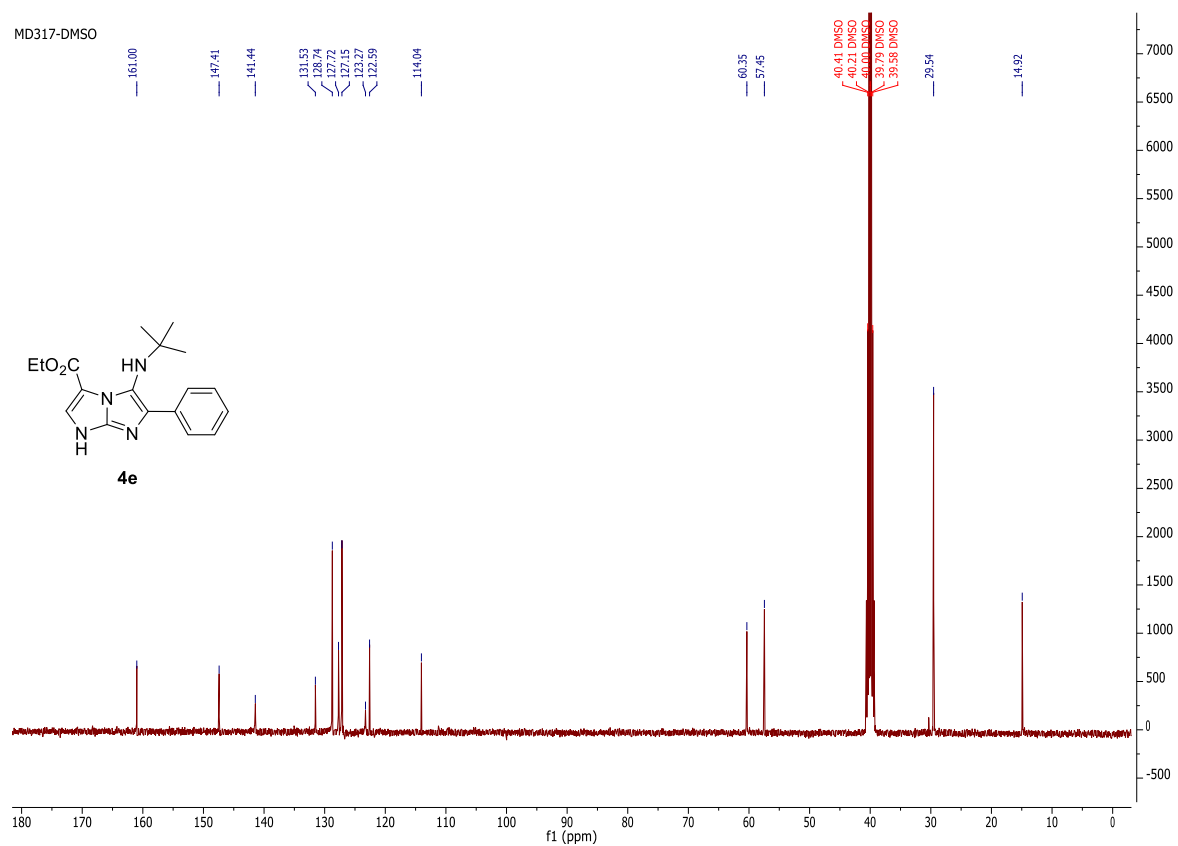
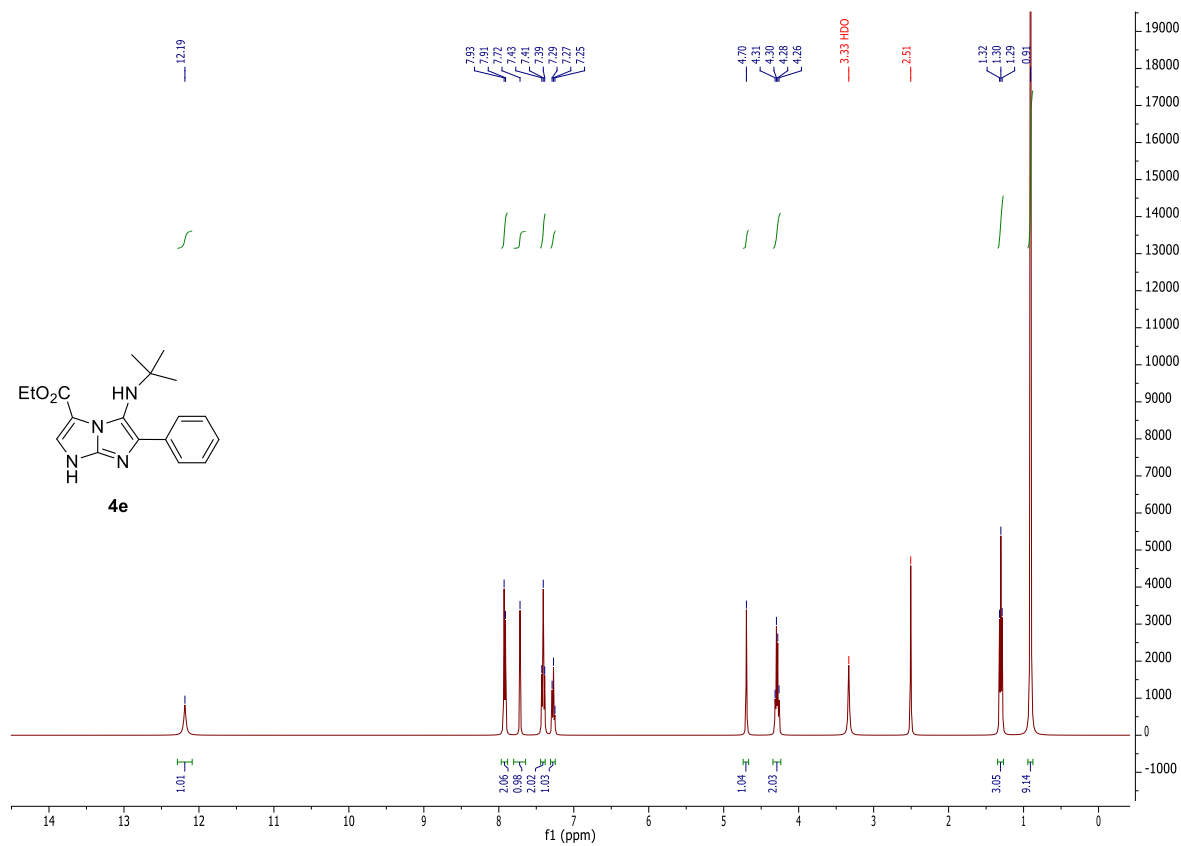


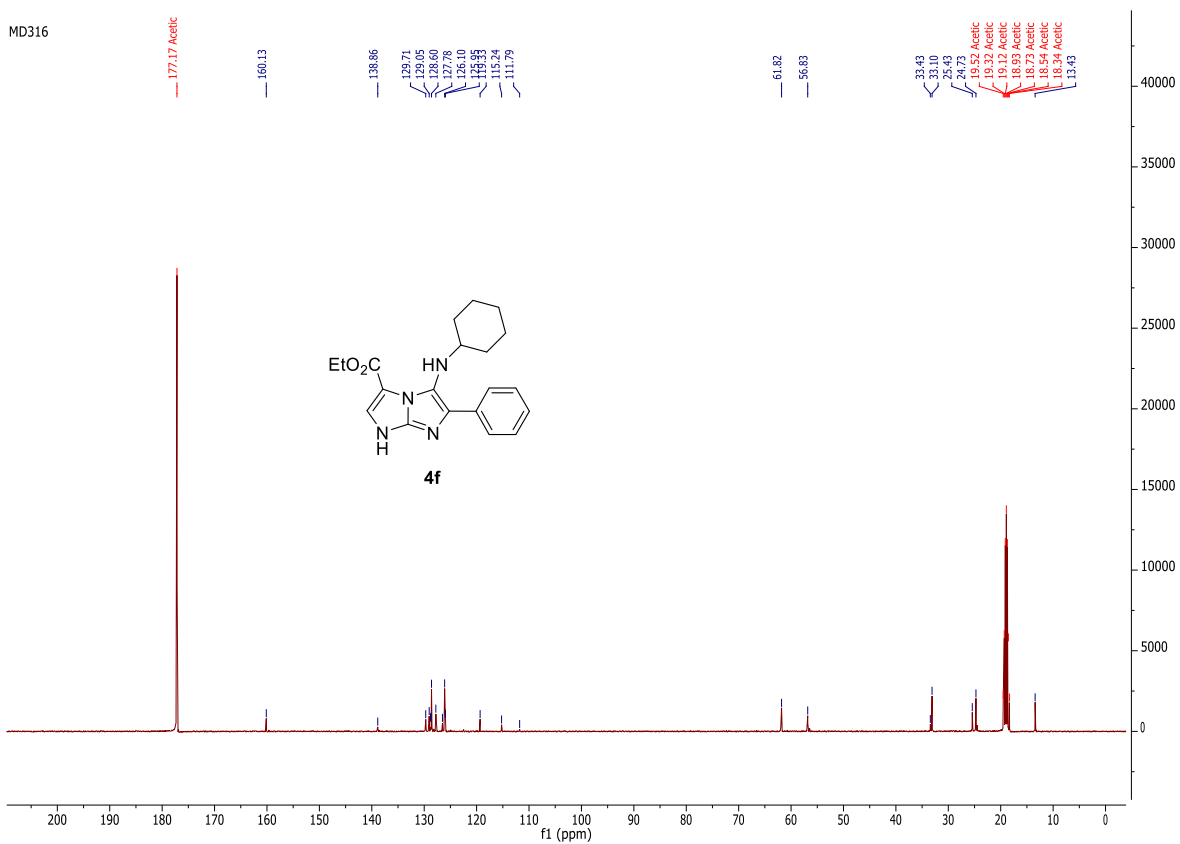
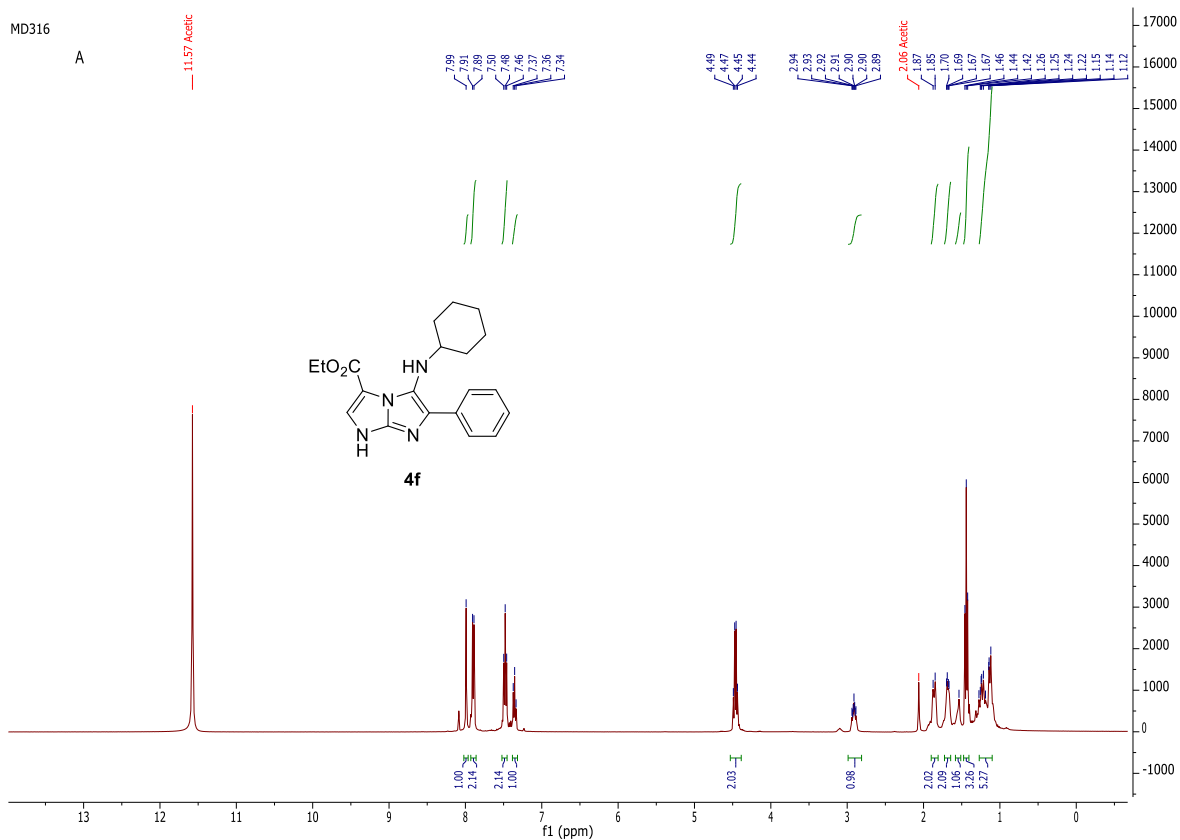


314-Acetic acid d4

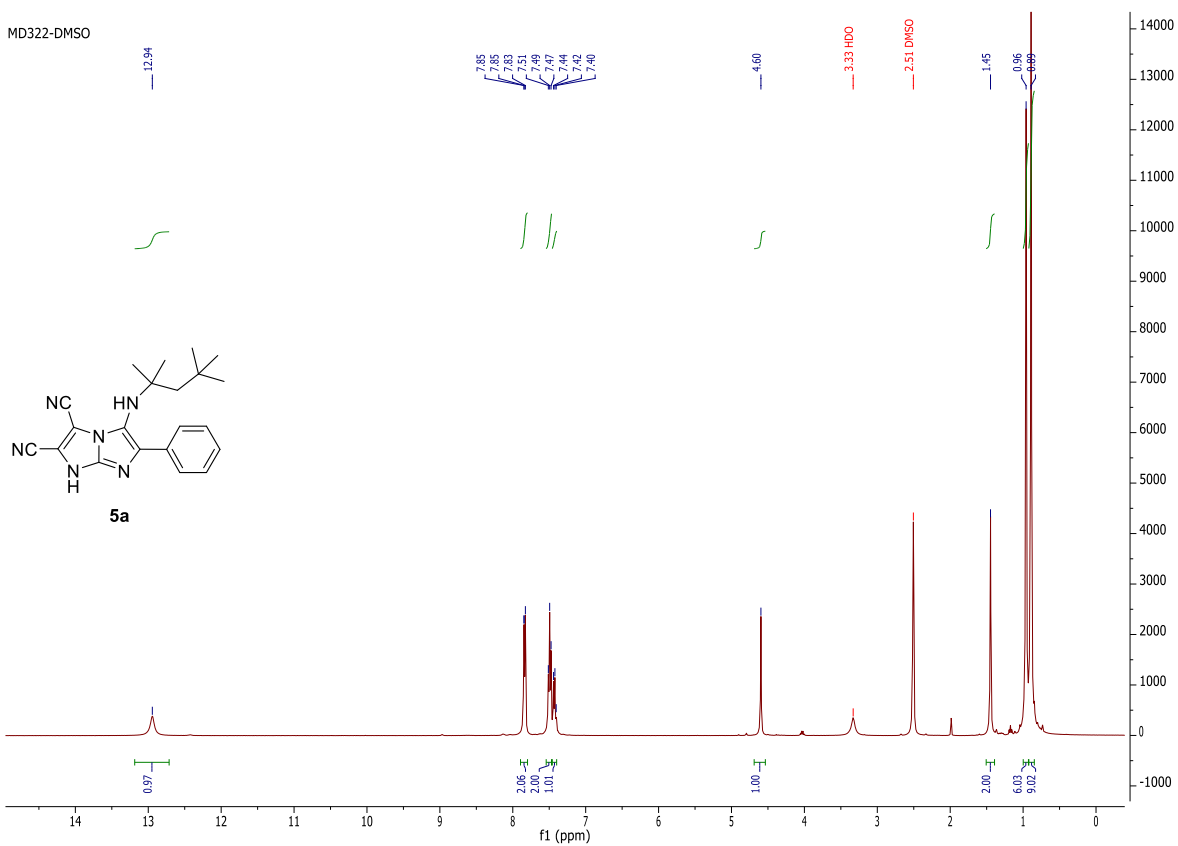
63.43



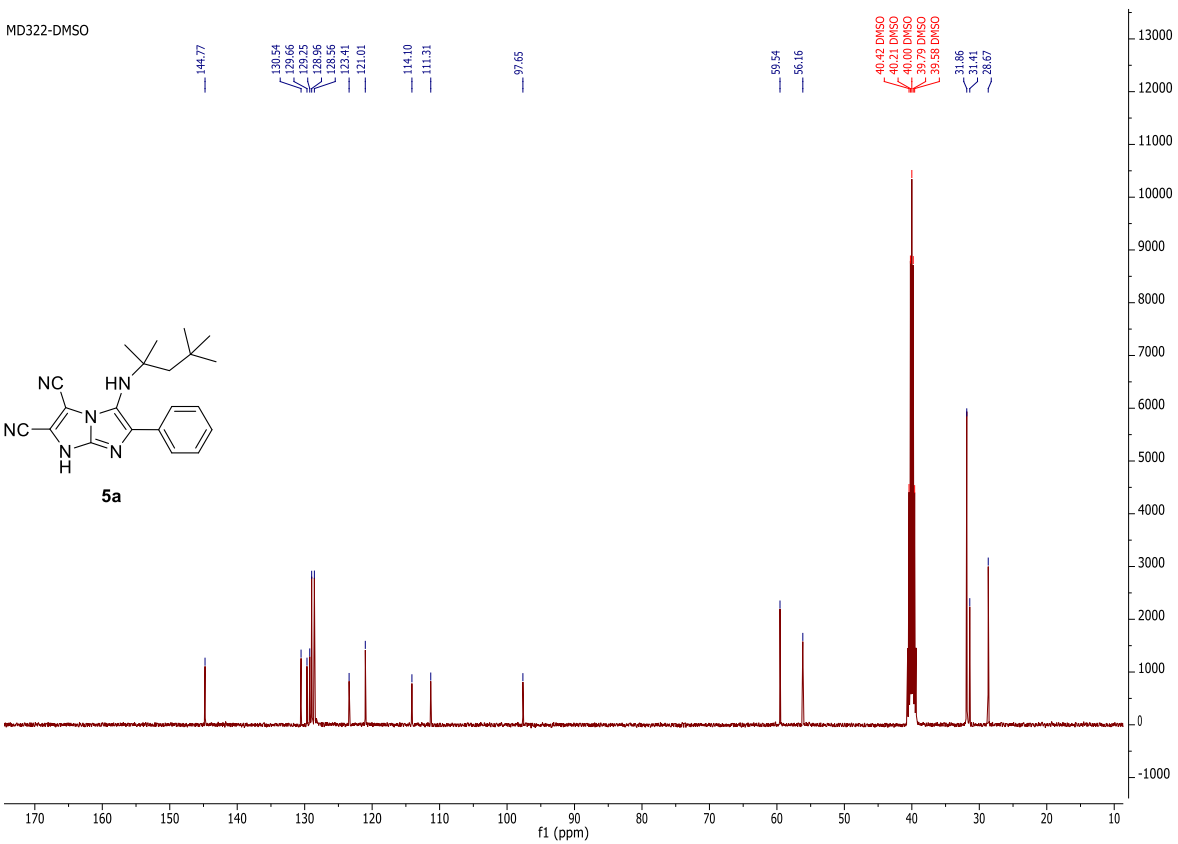


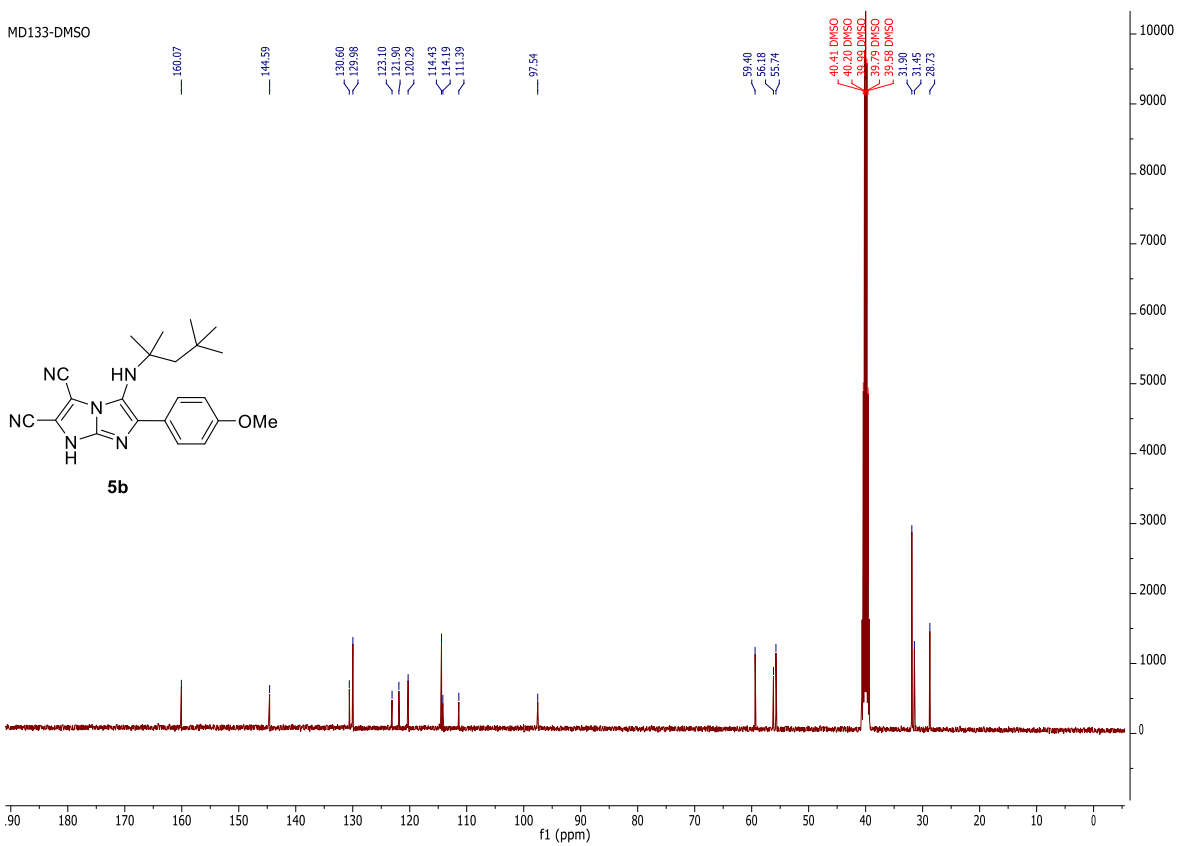
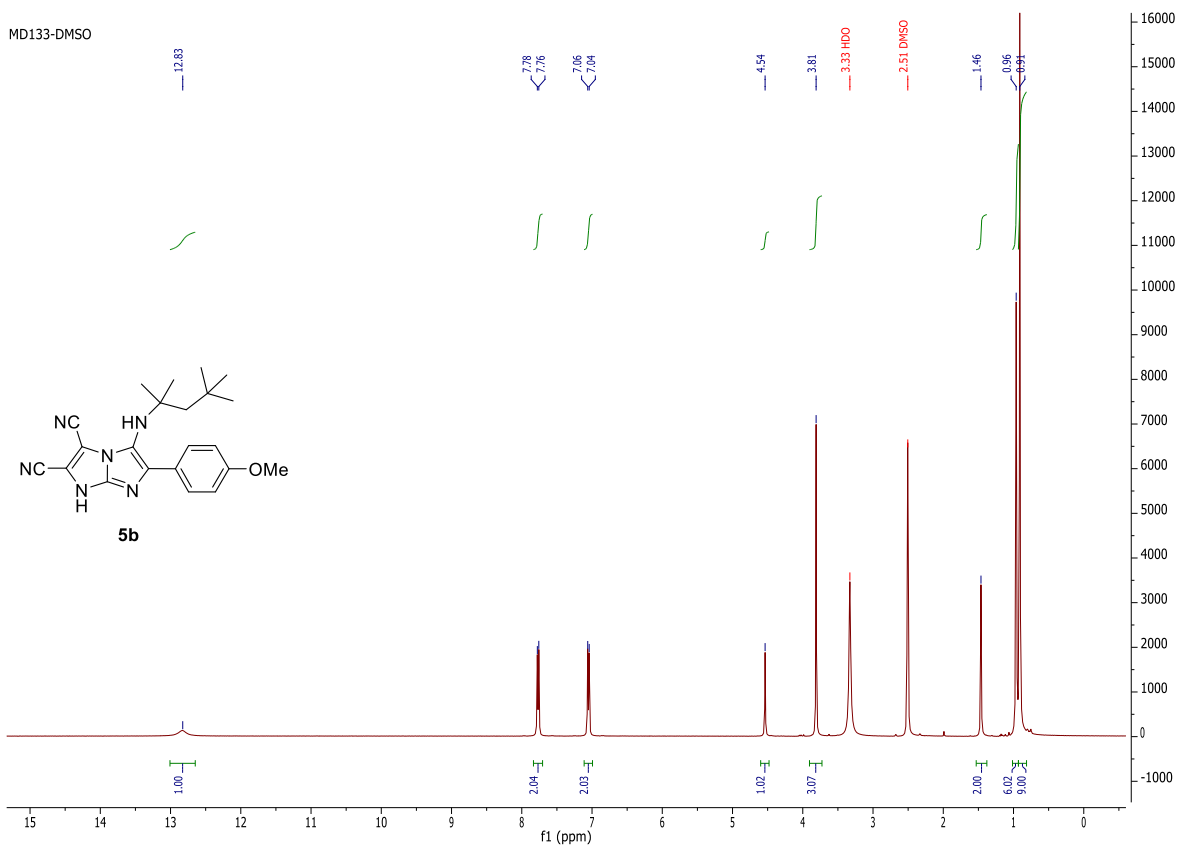


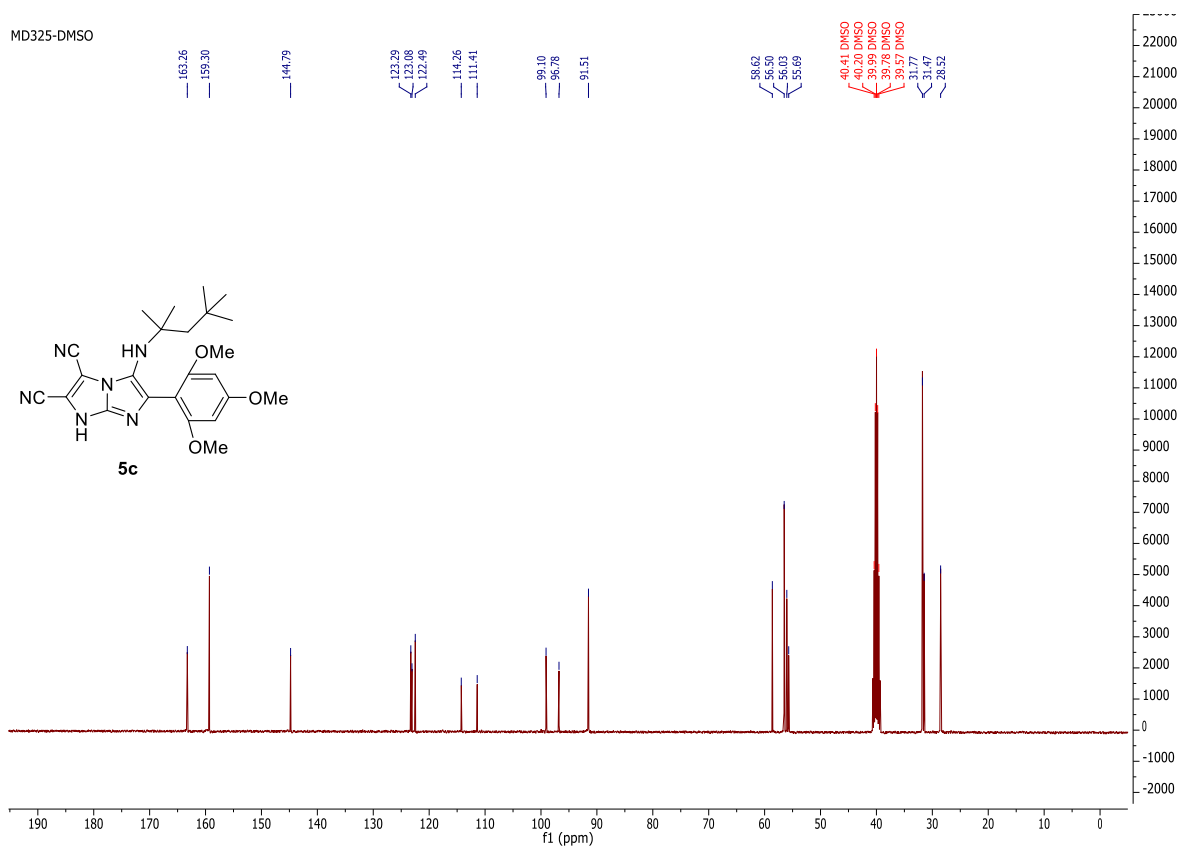
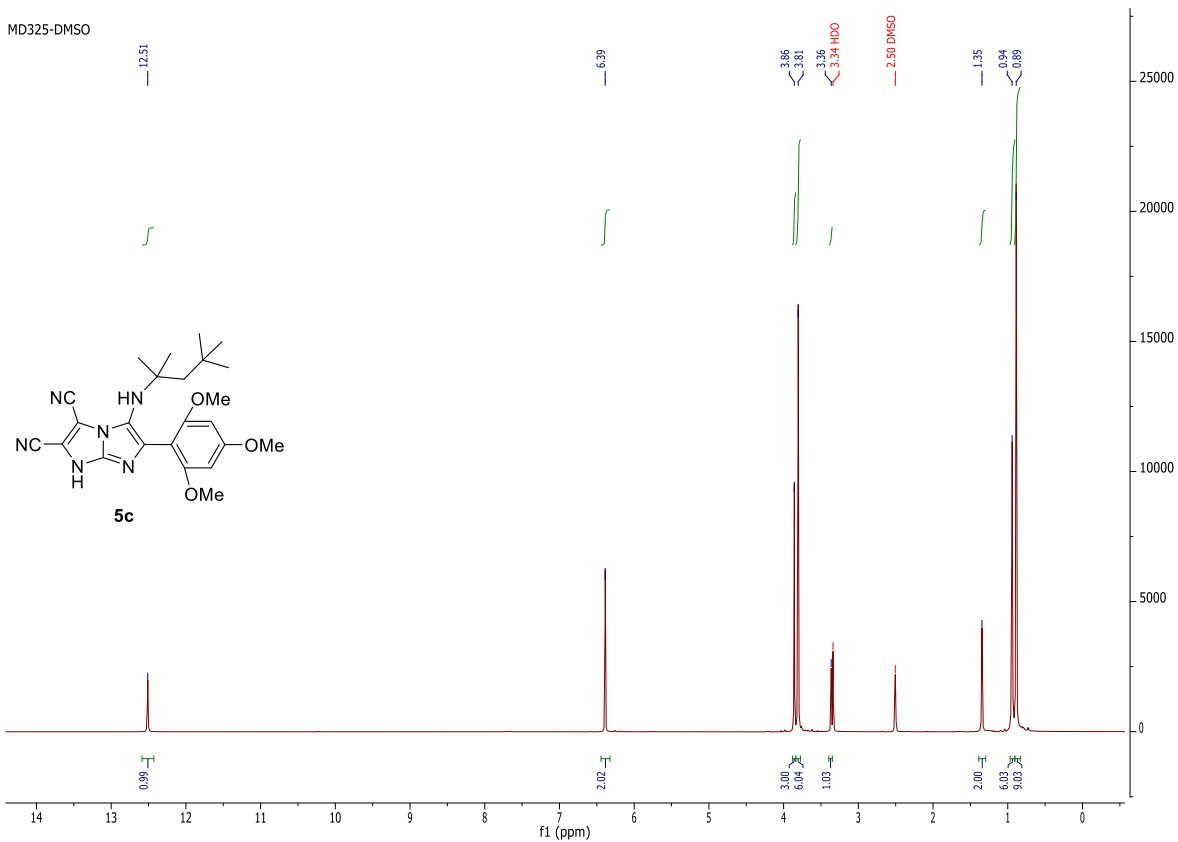
MD322-DMSO

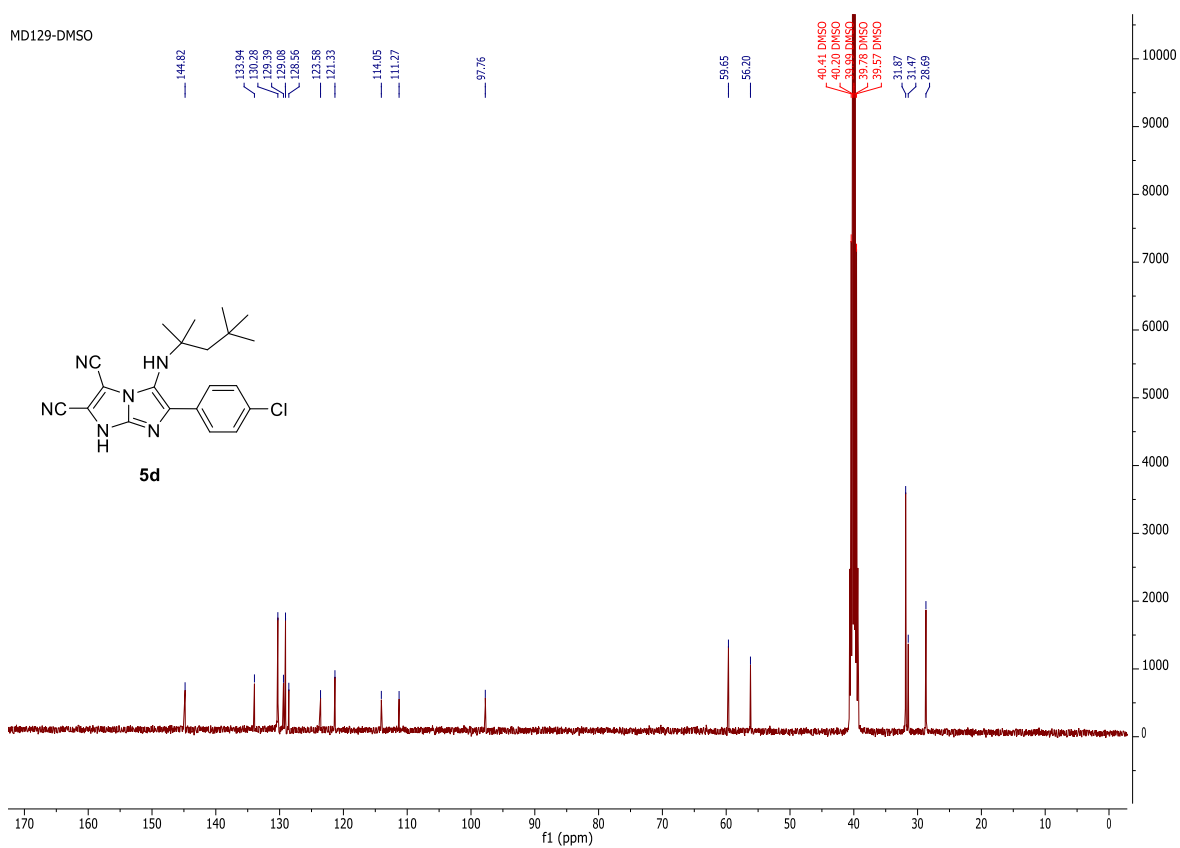
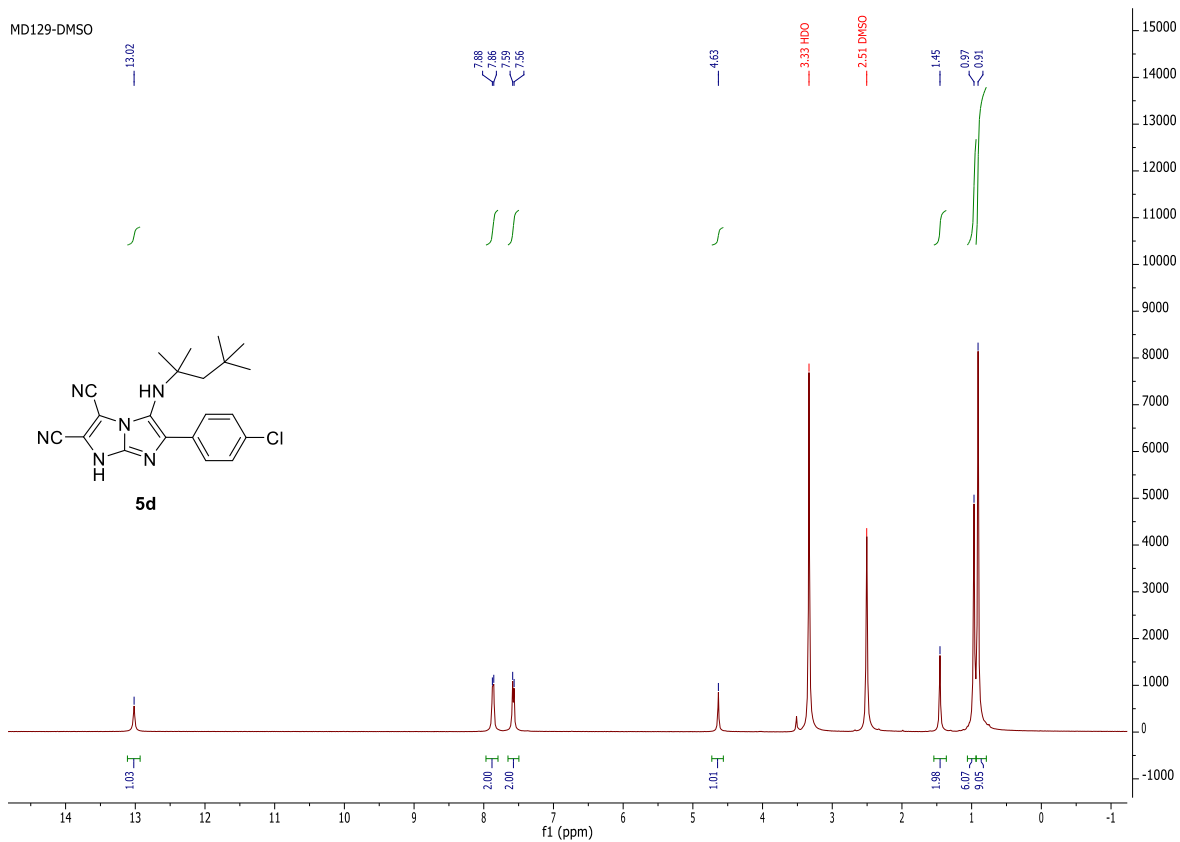


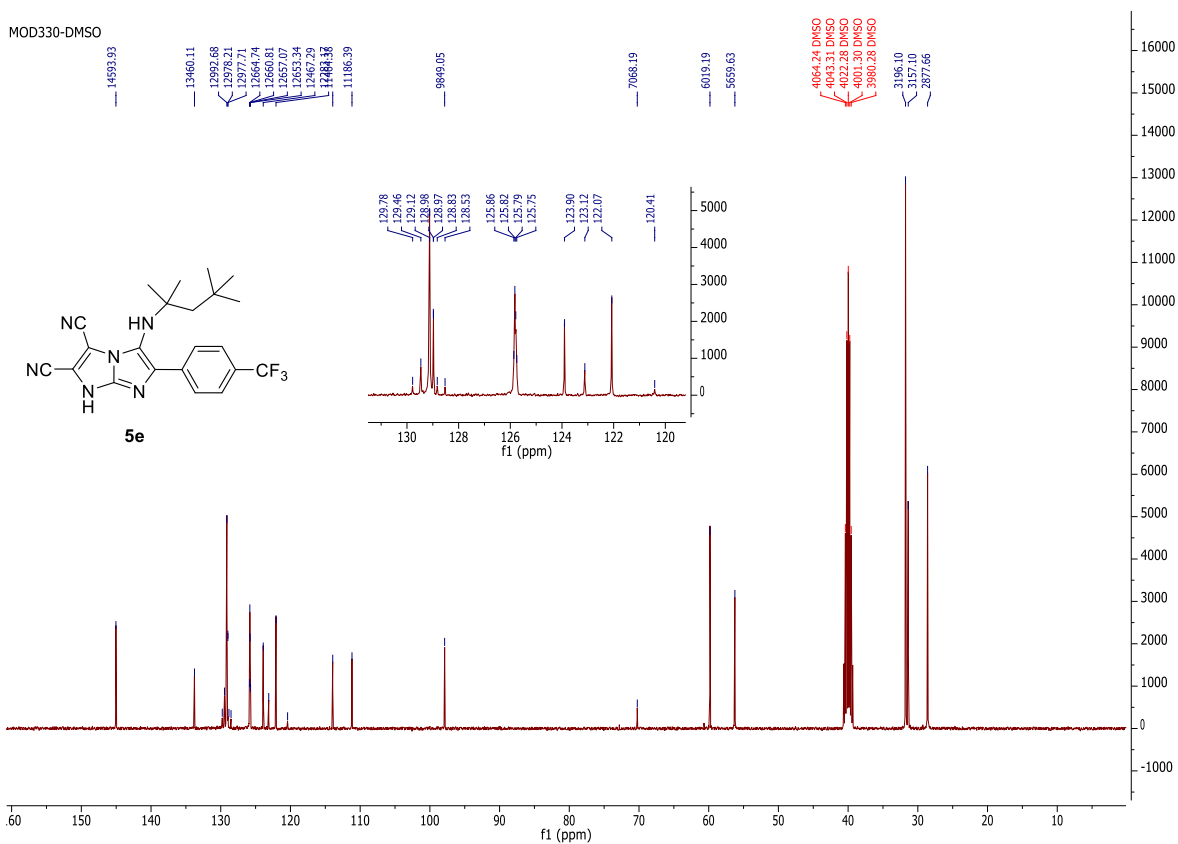
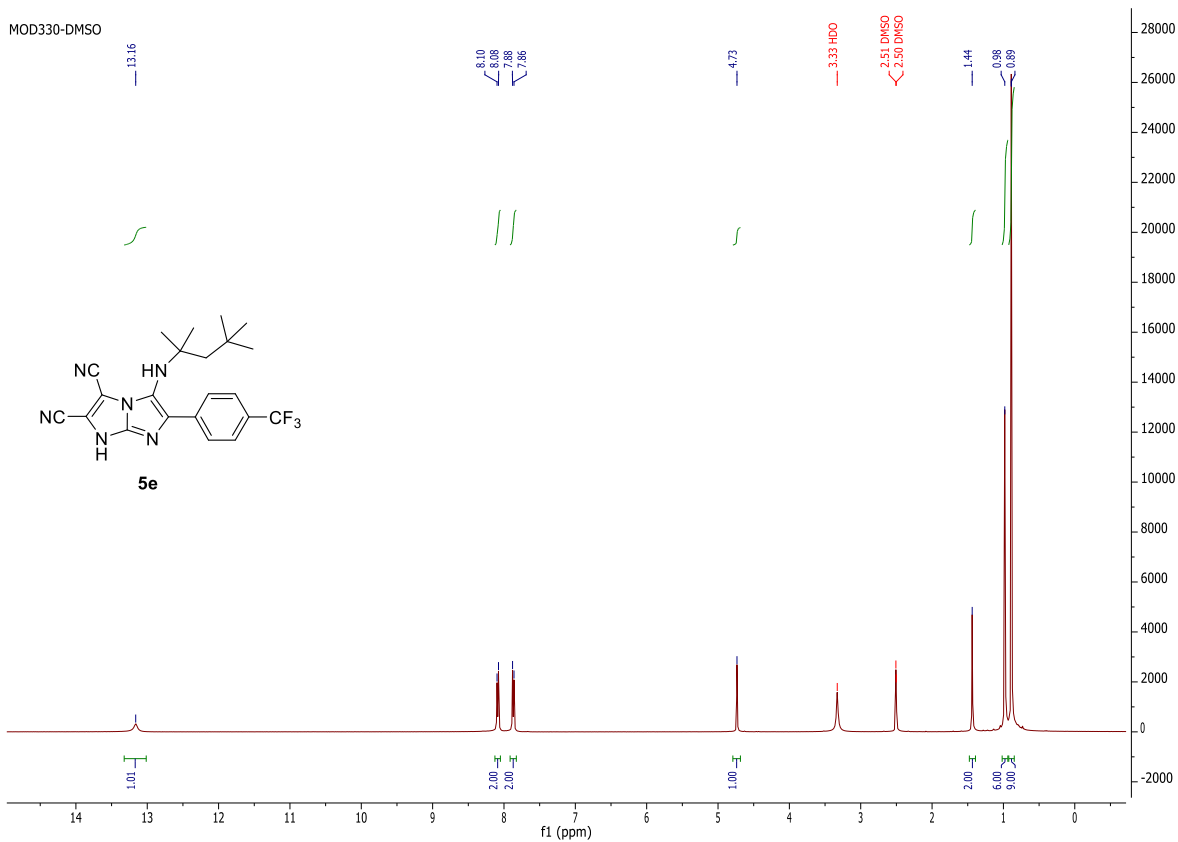
MD322-DMSO



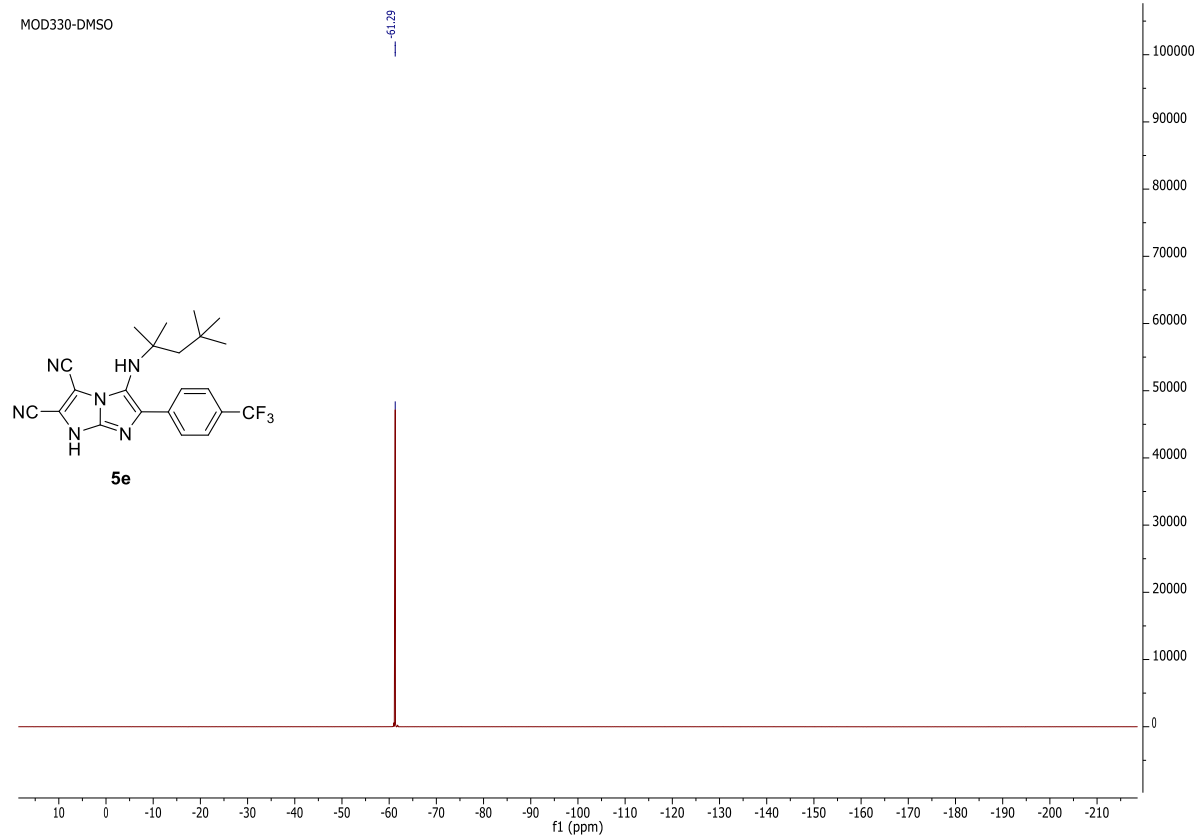


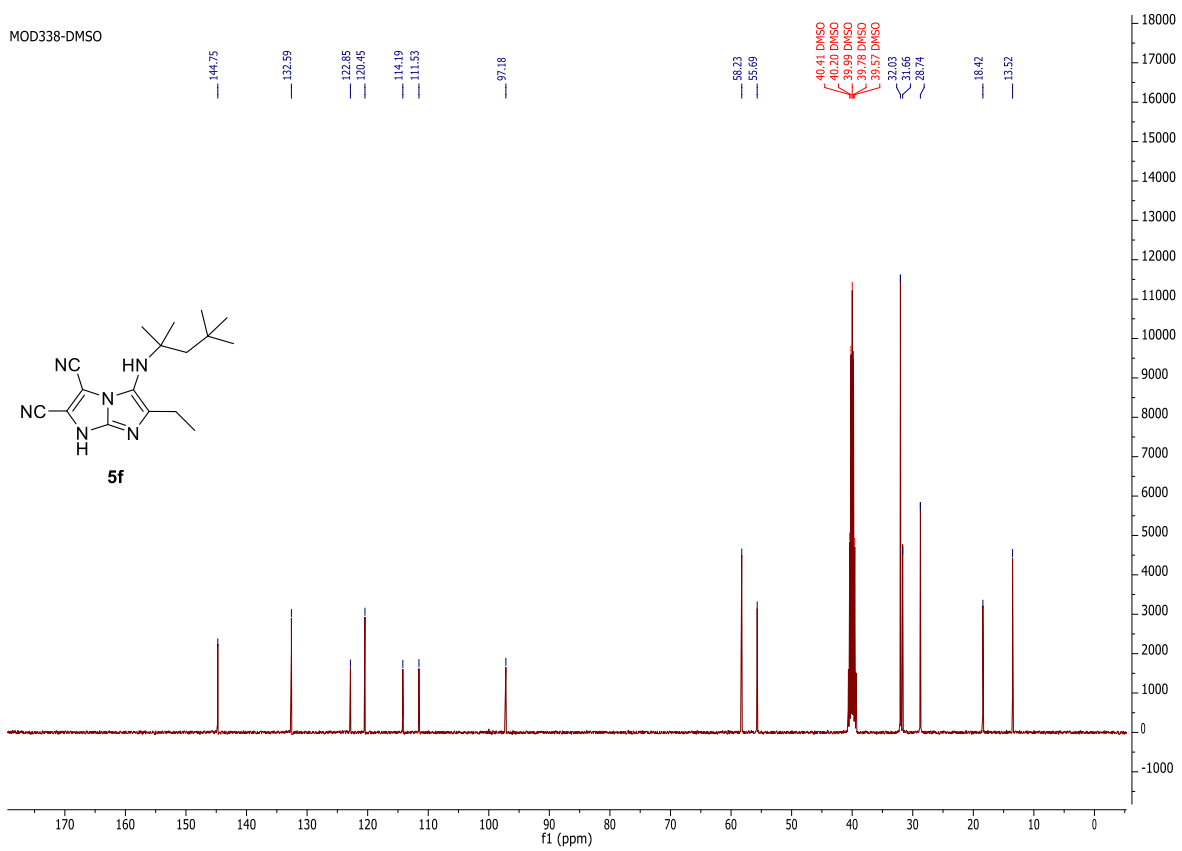
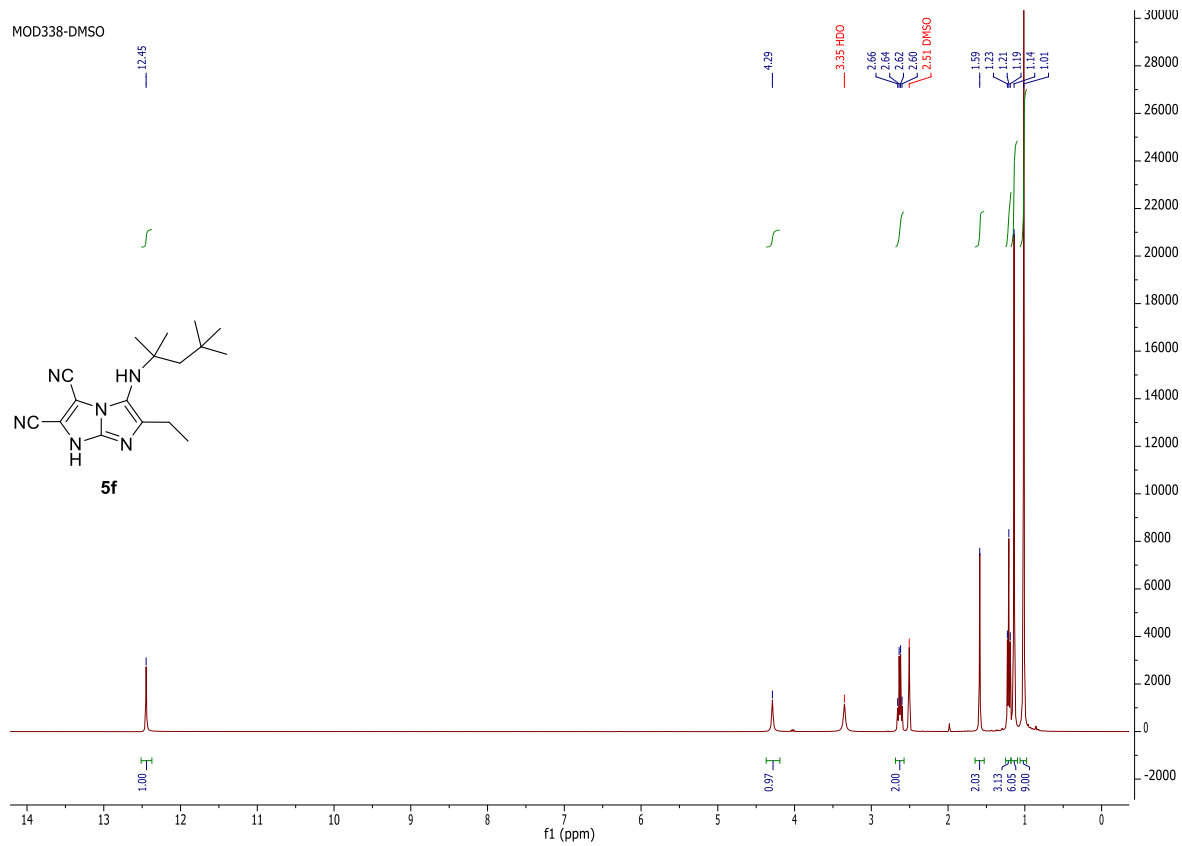


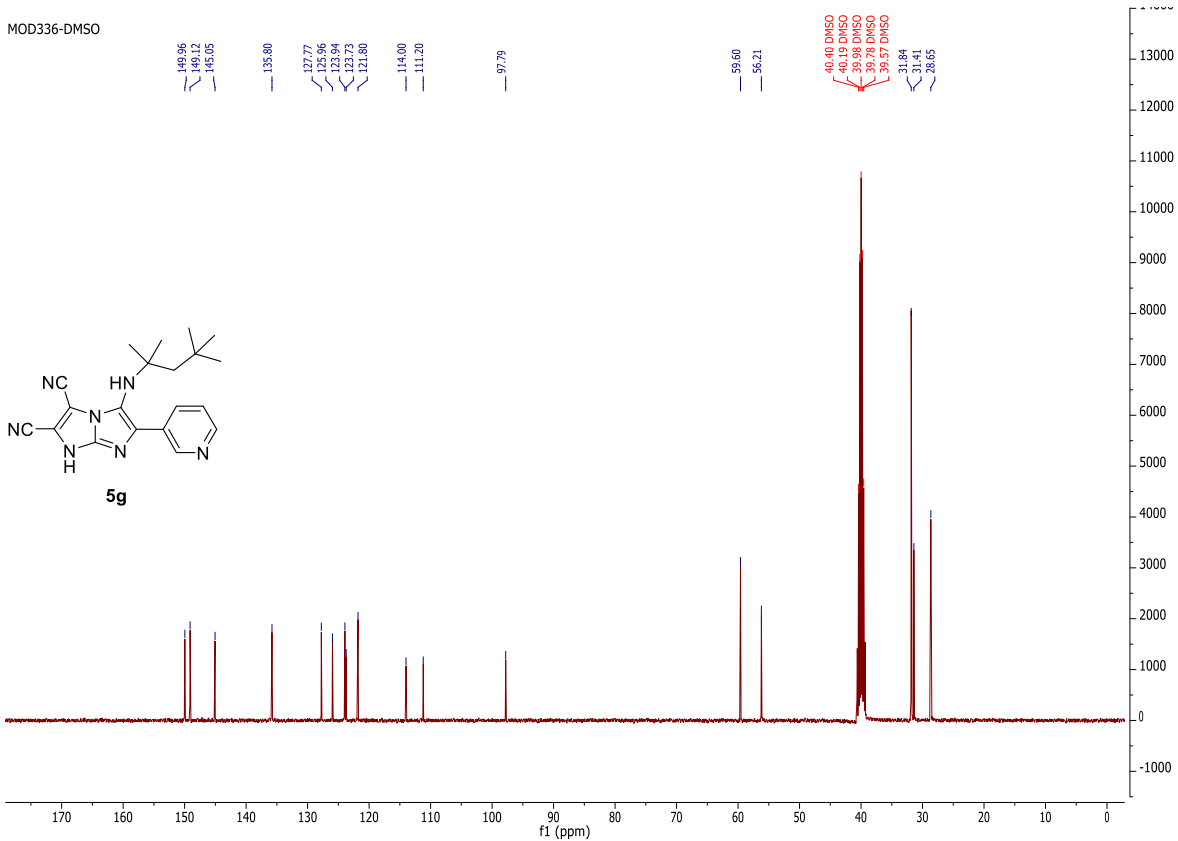
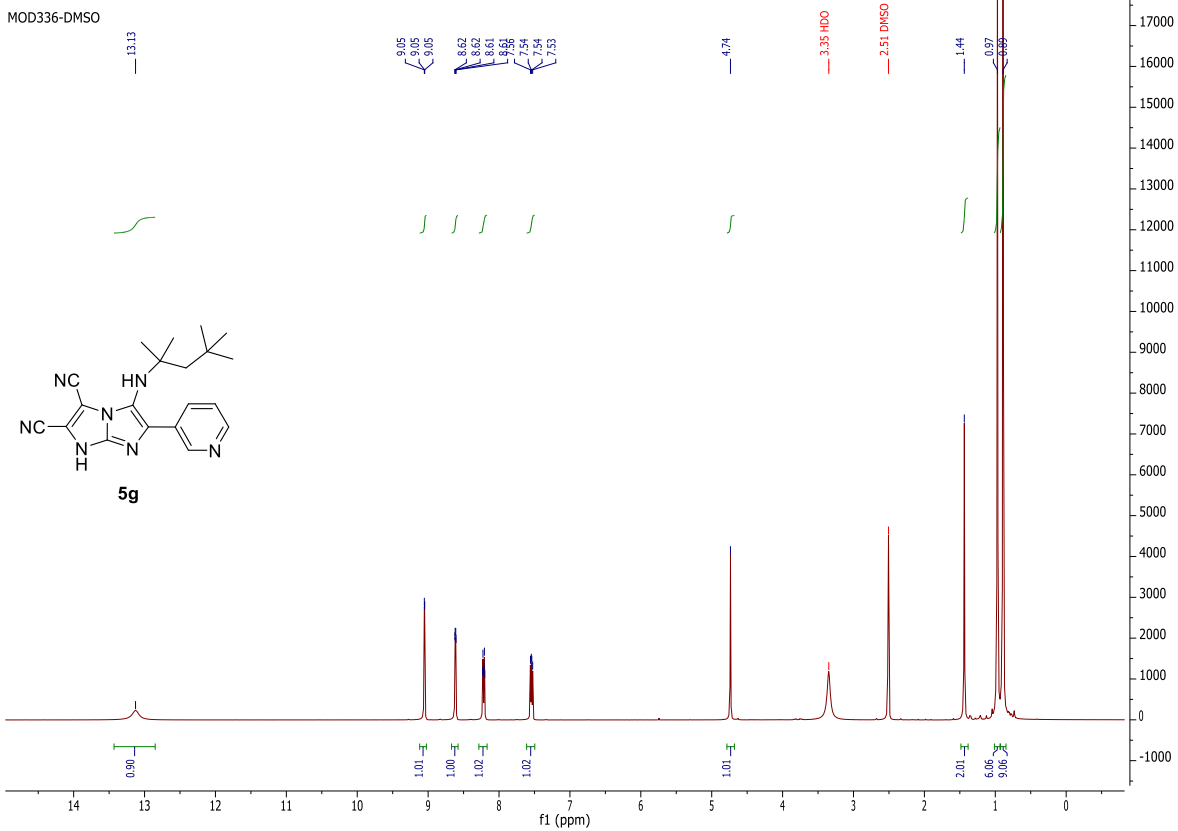


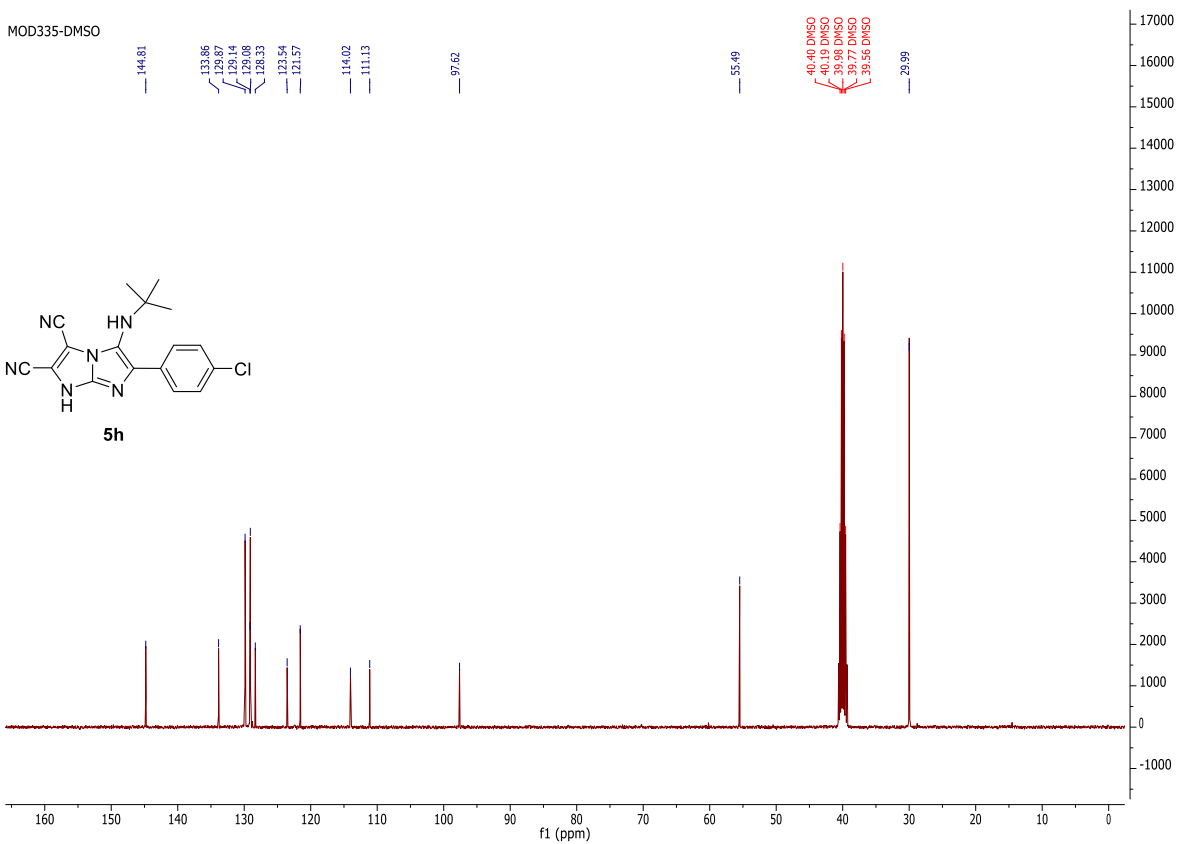
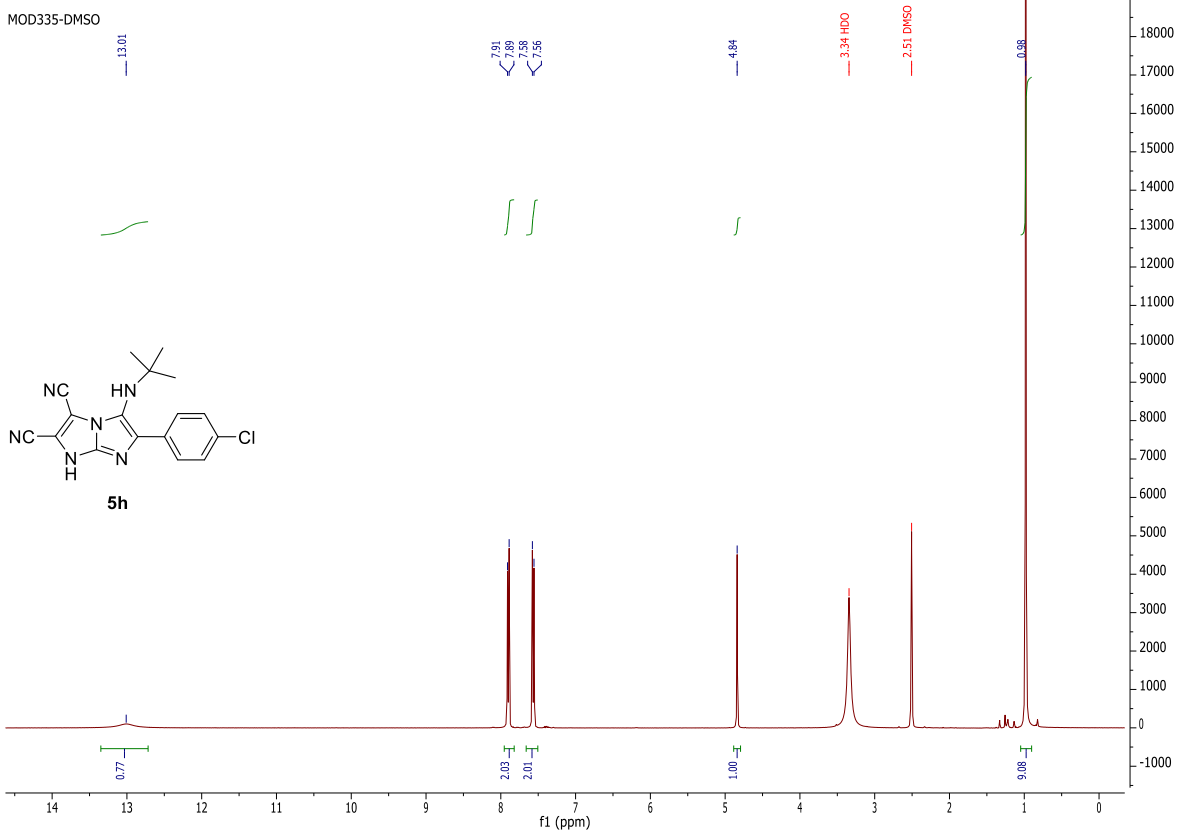


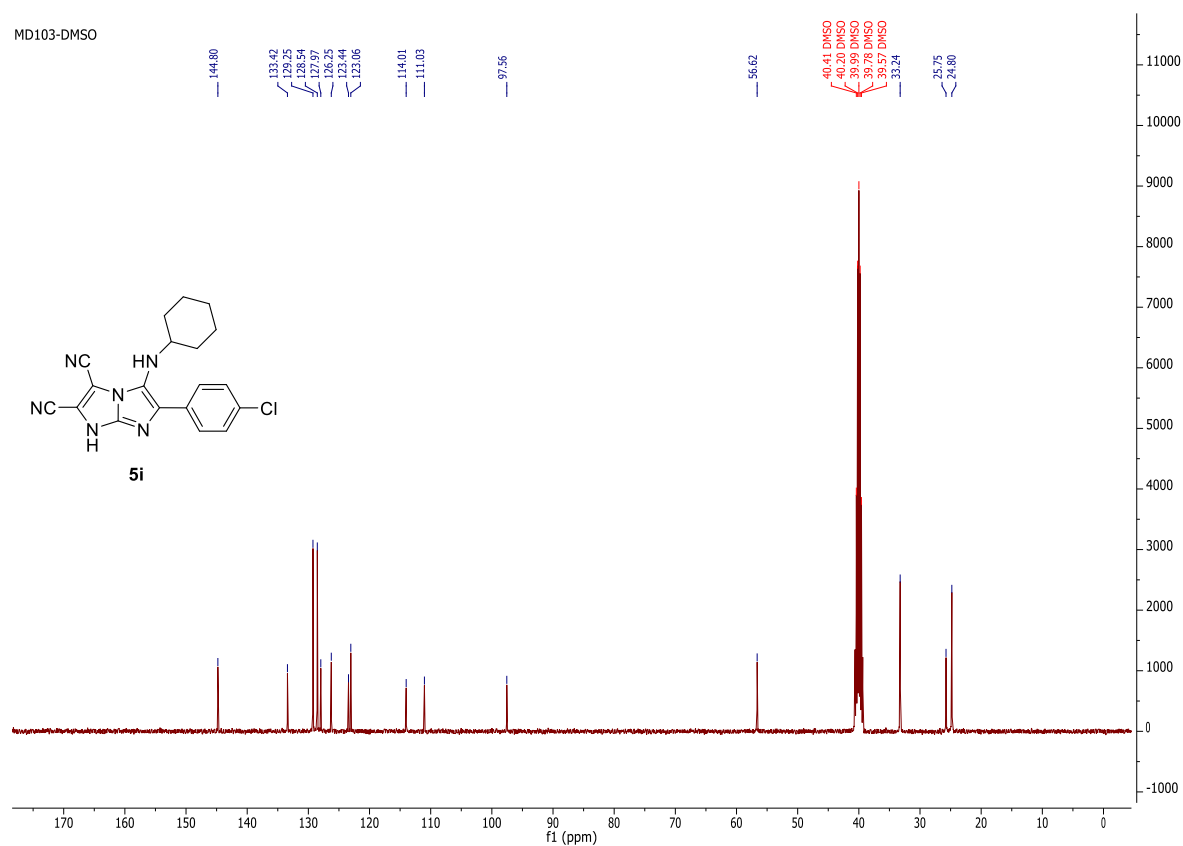
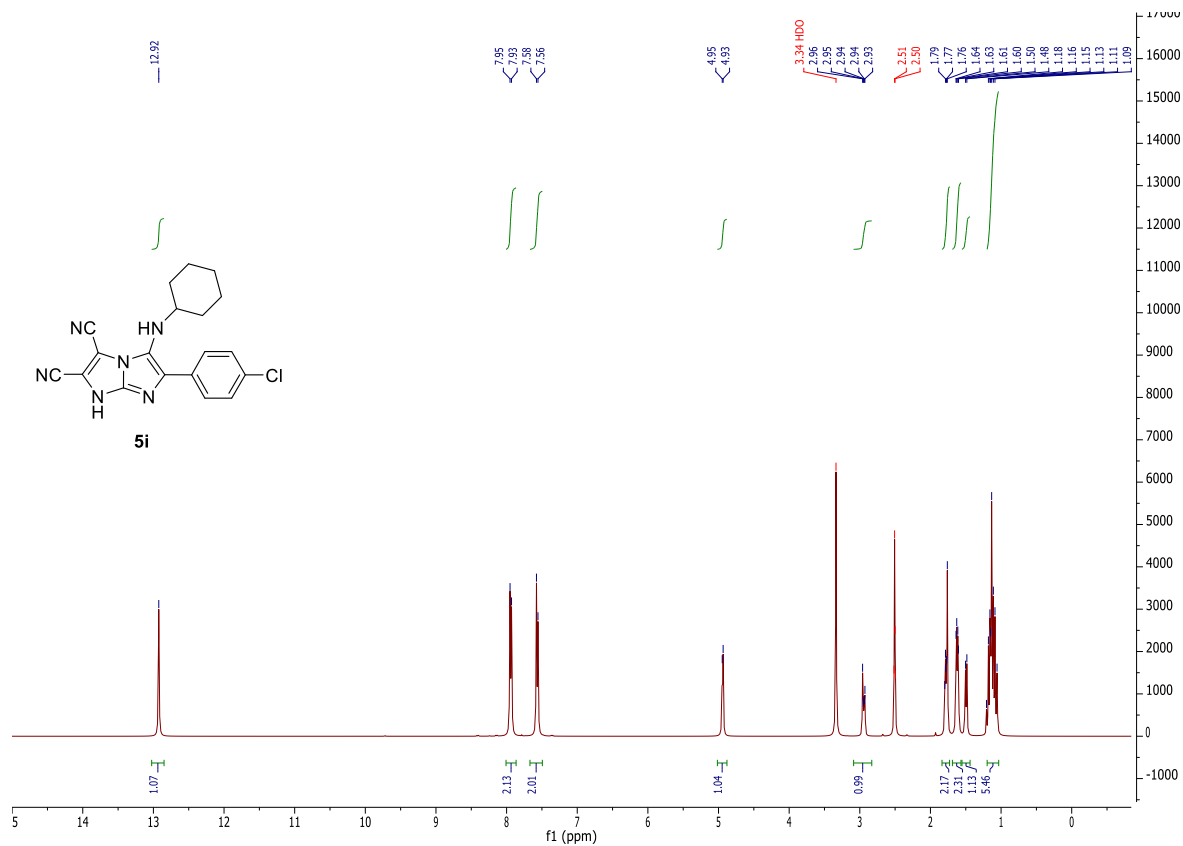
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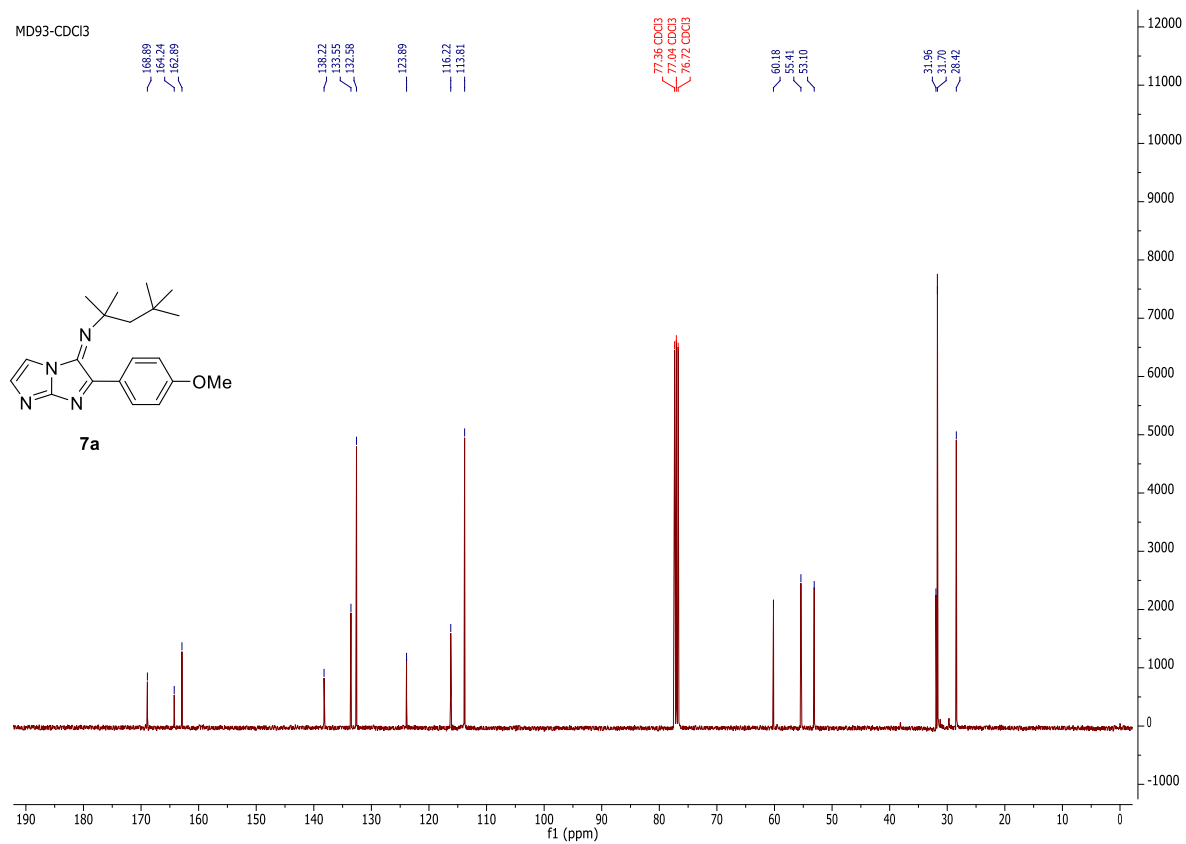
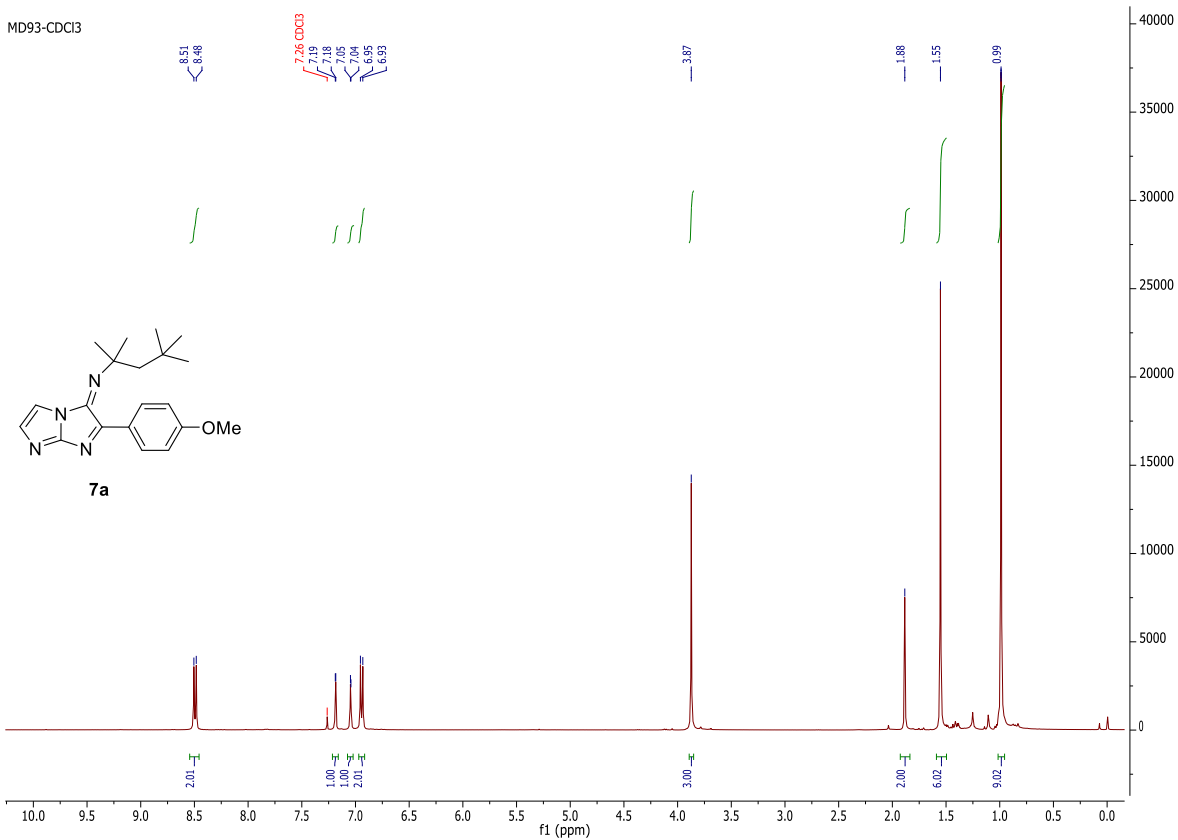




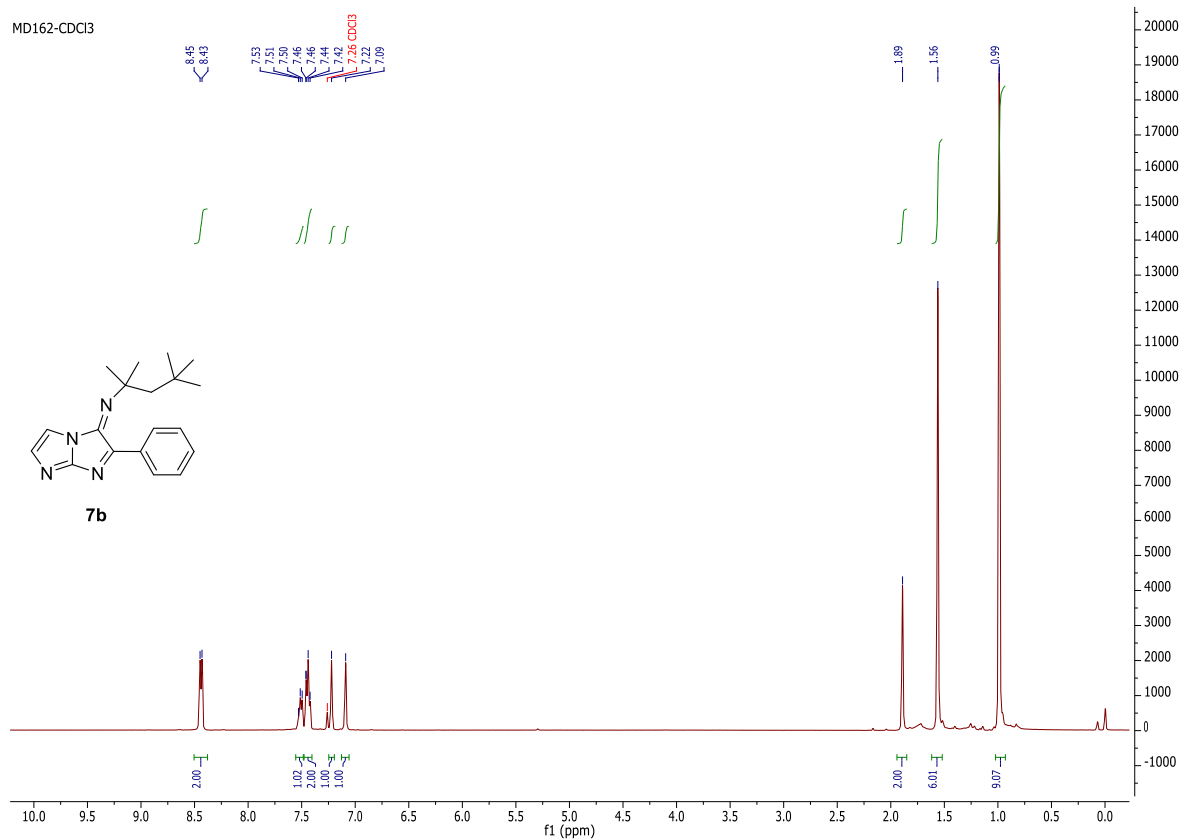




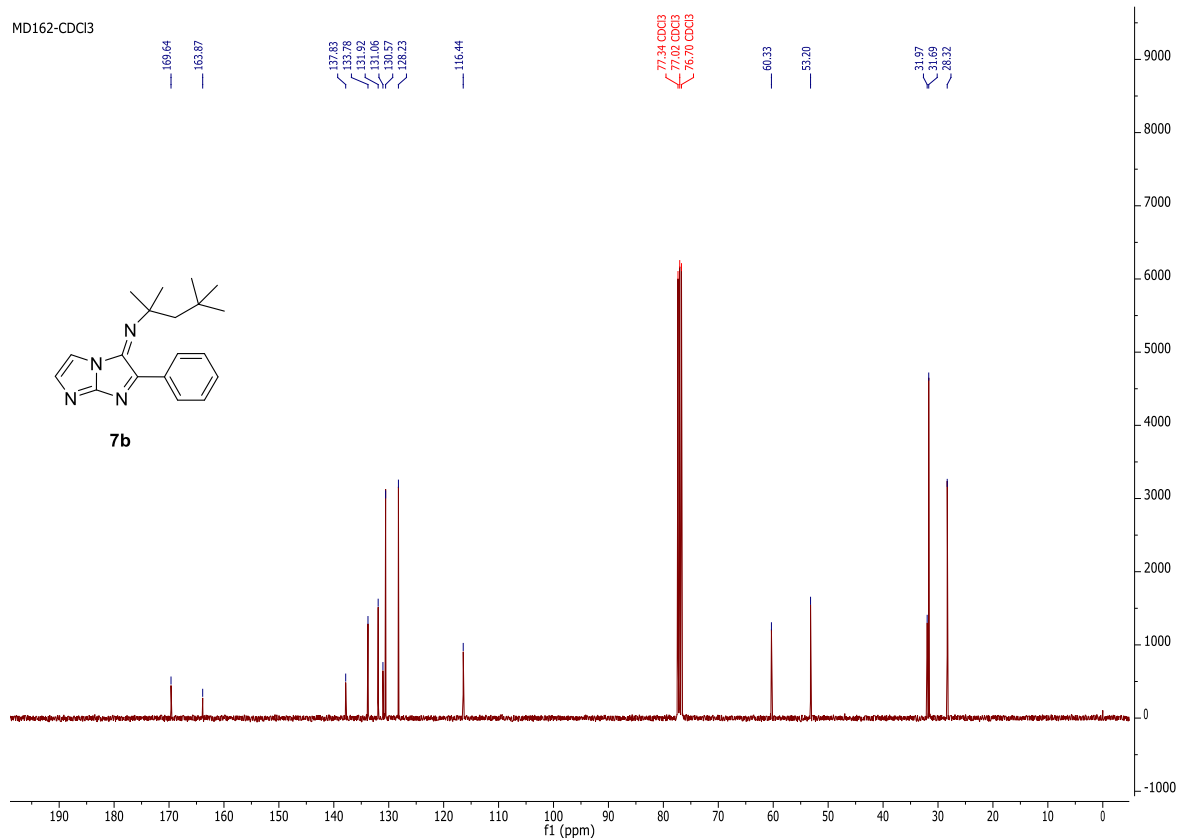


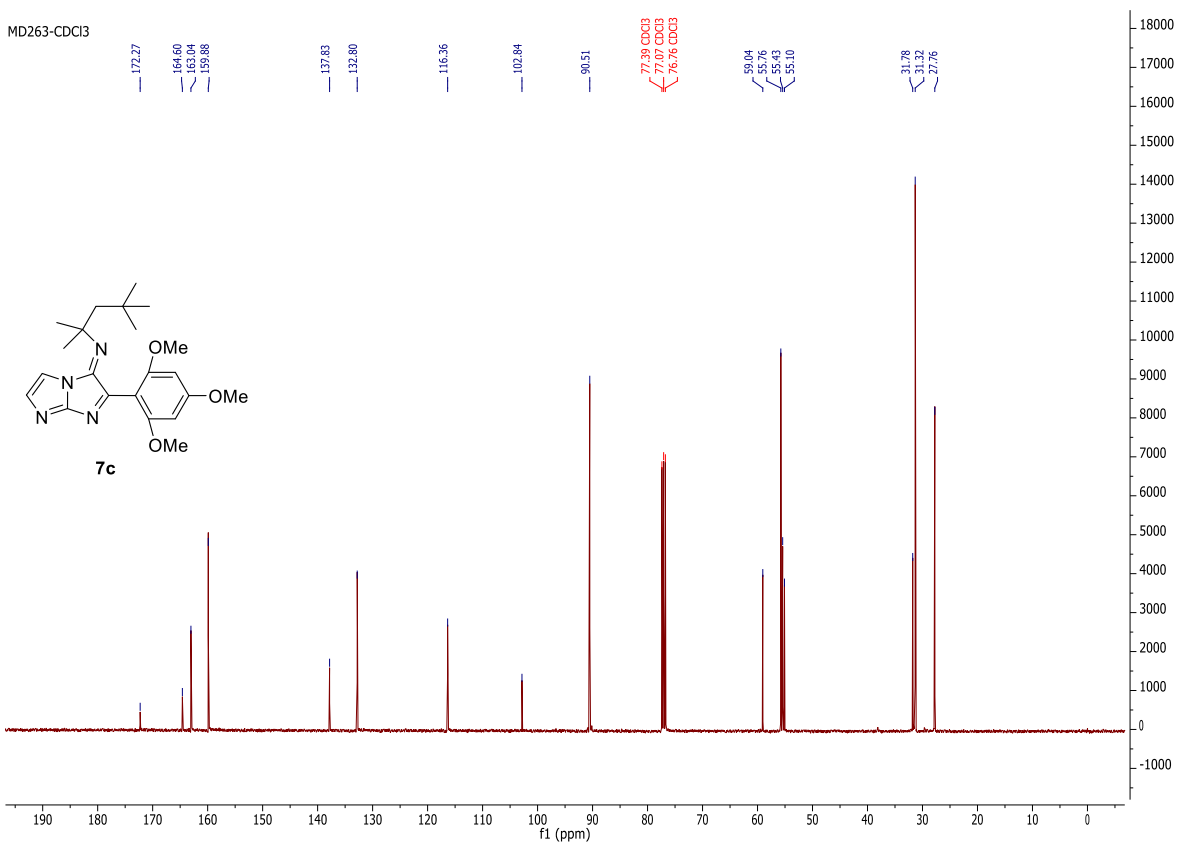
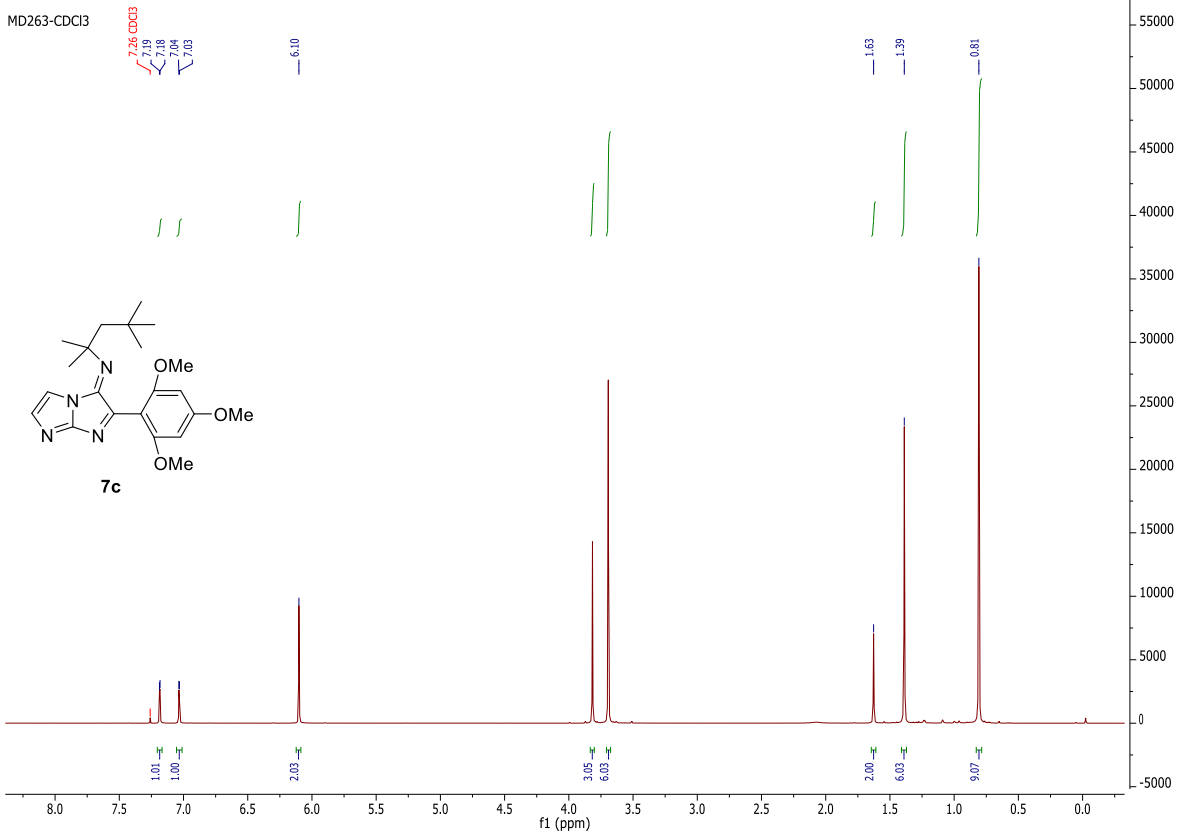


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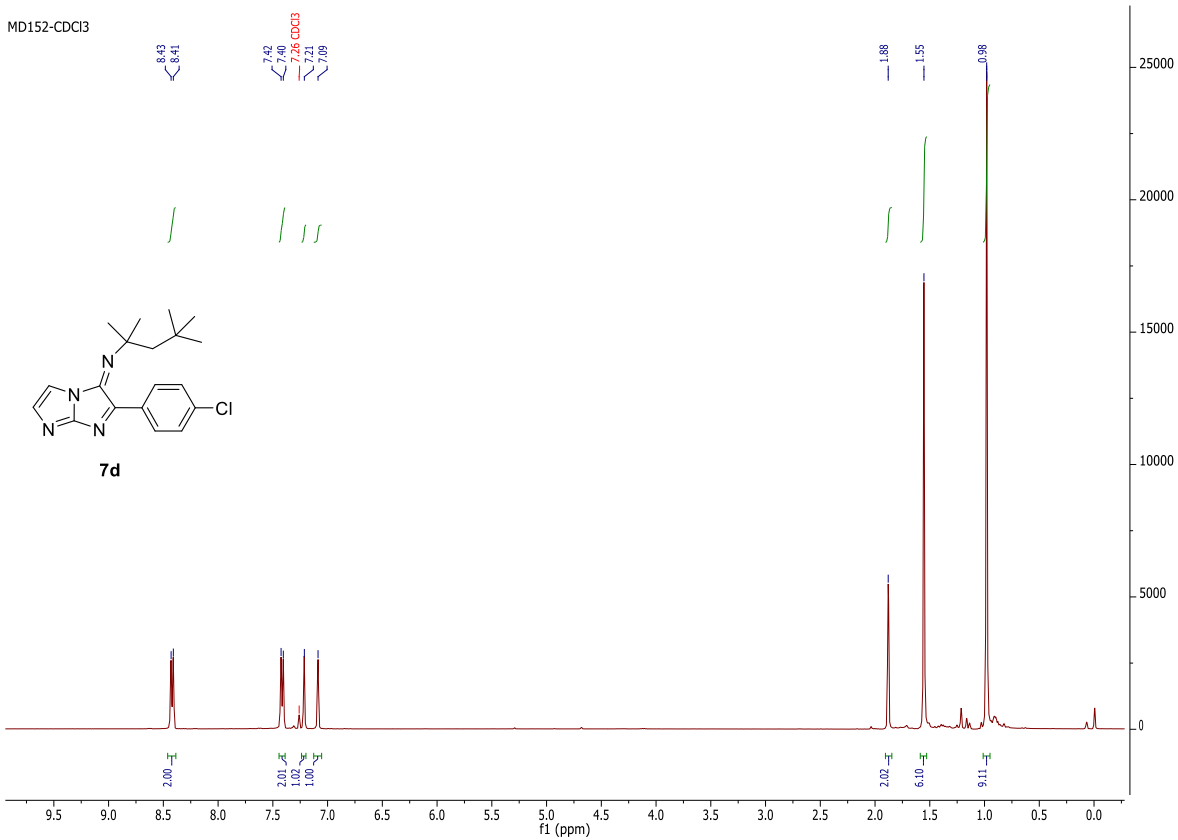


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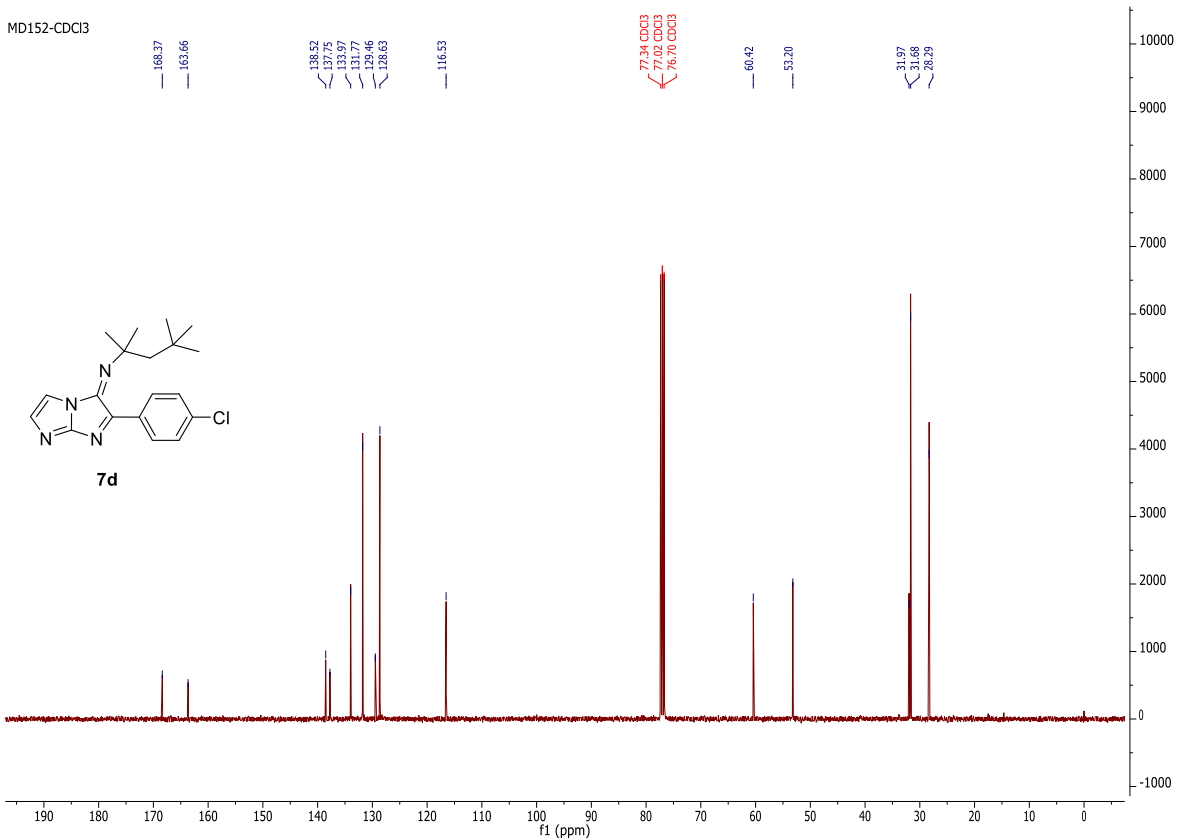


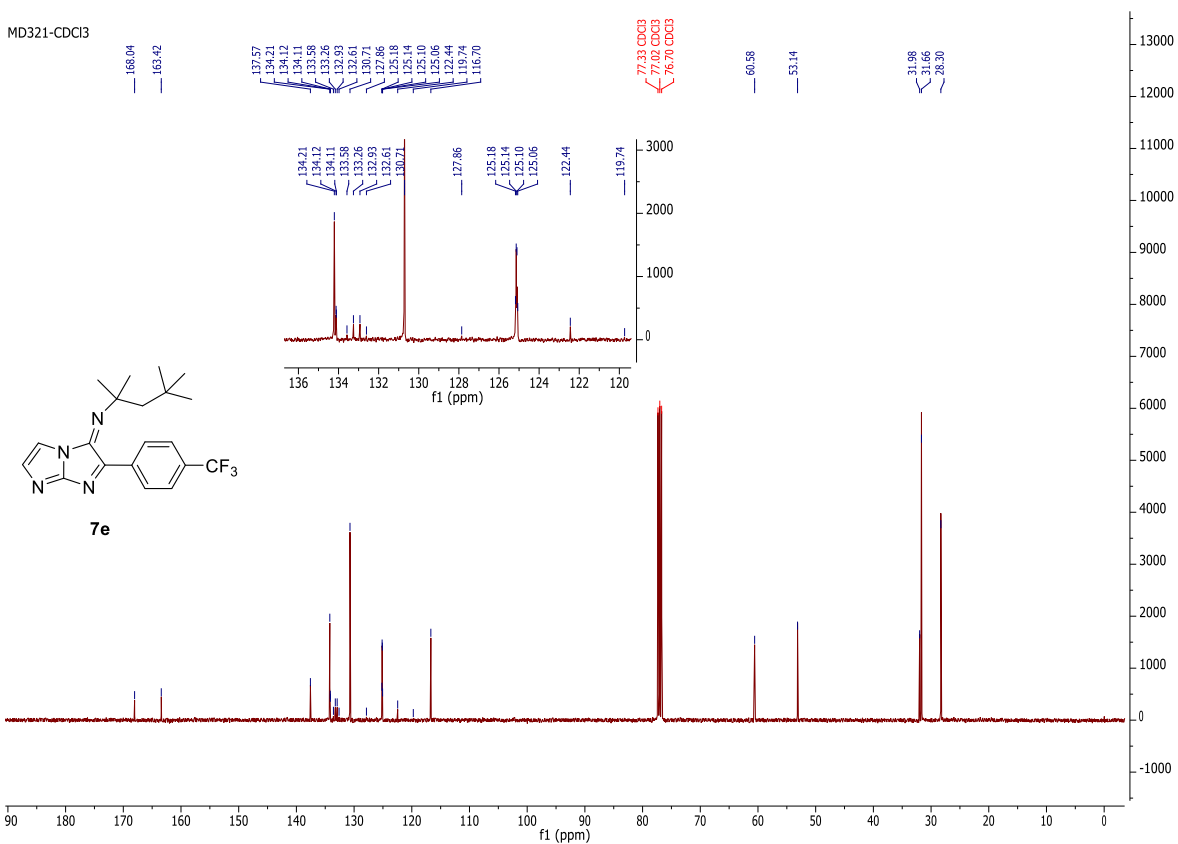
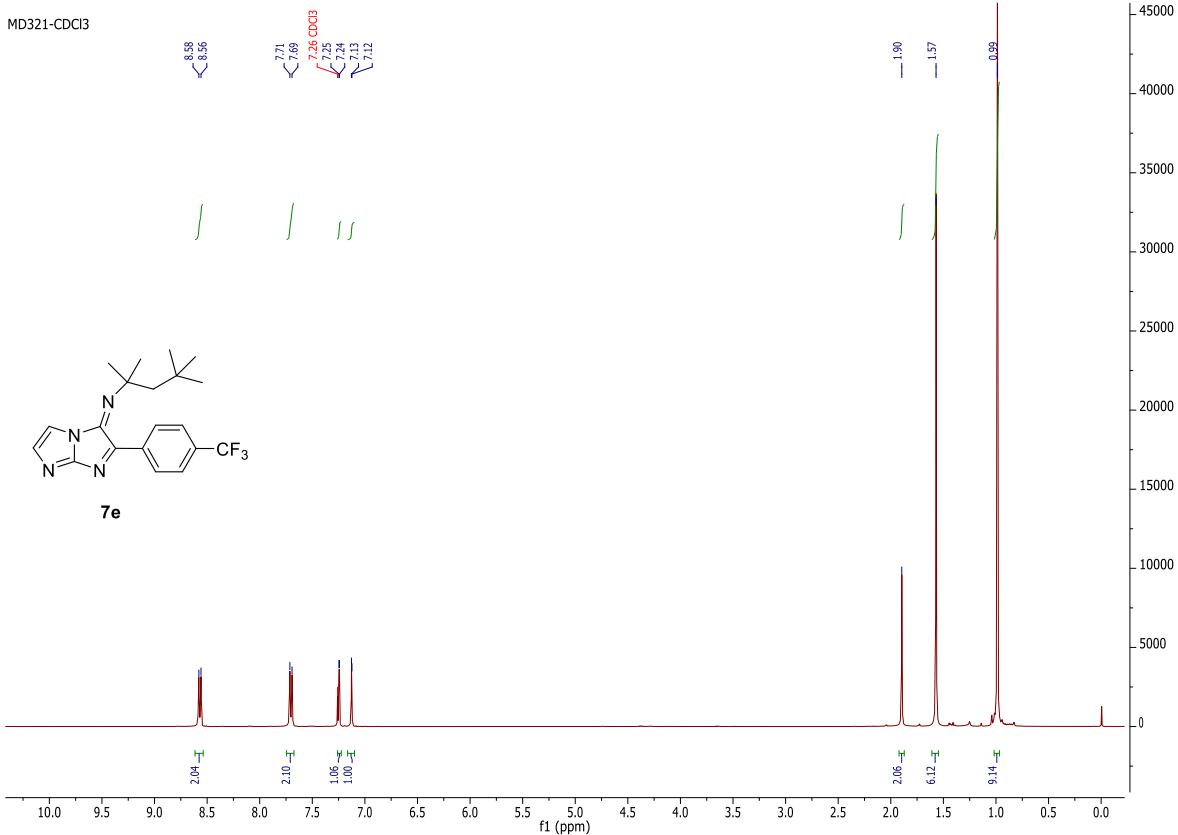


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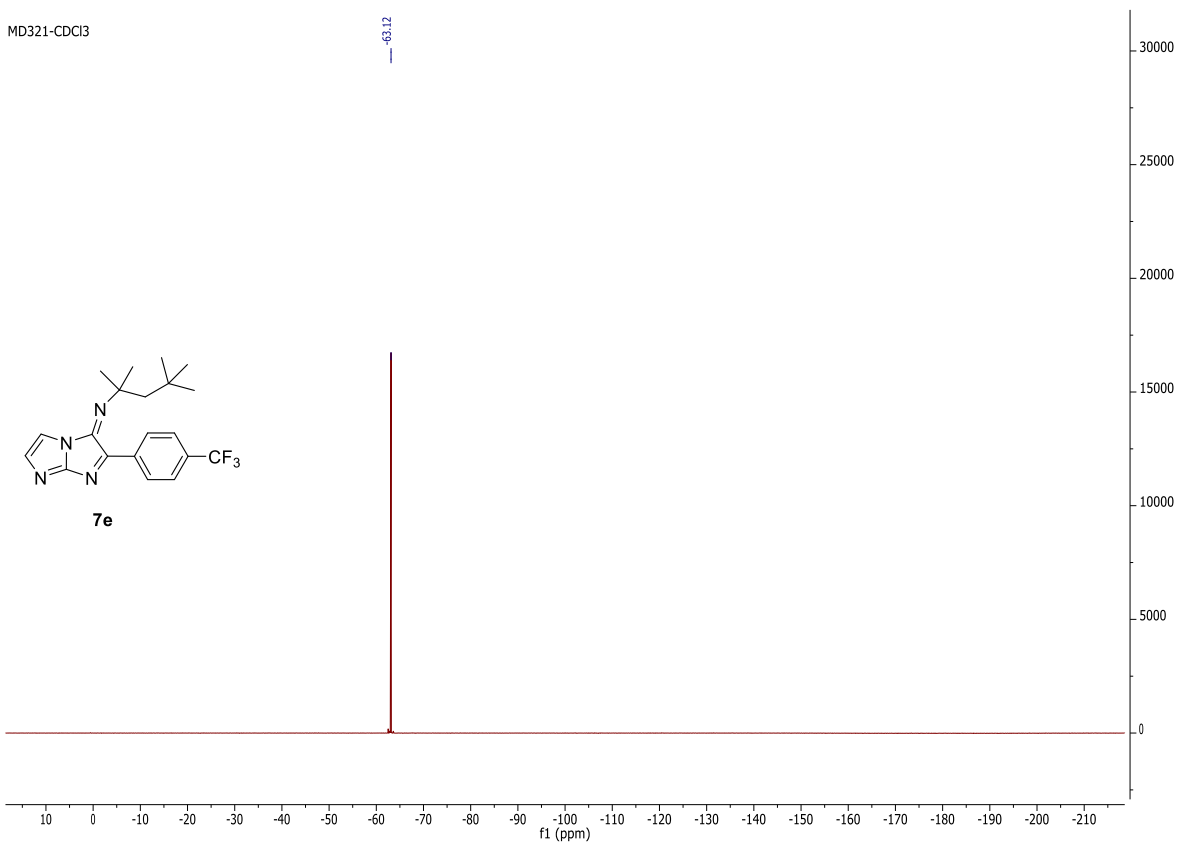


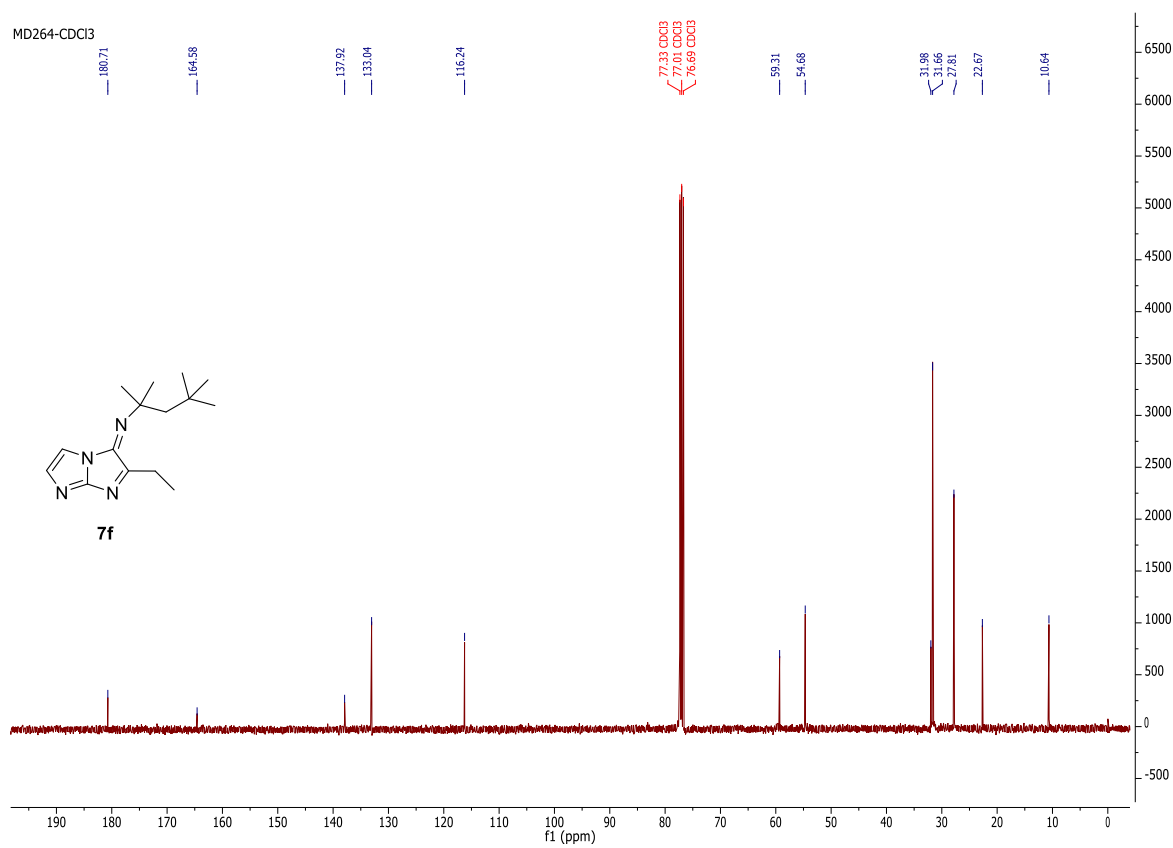
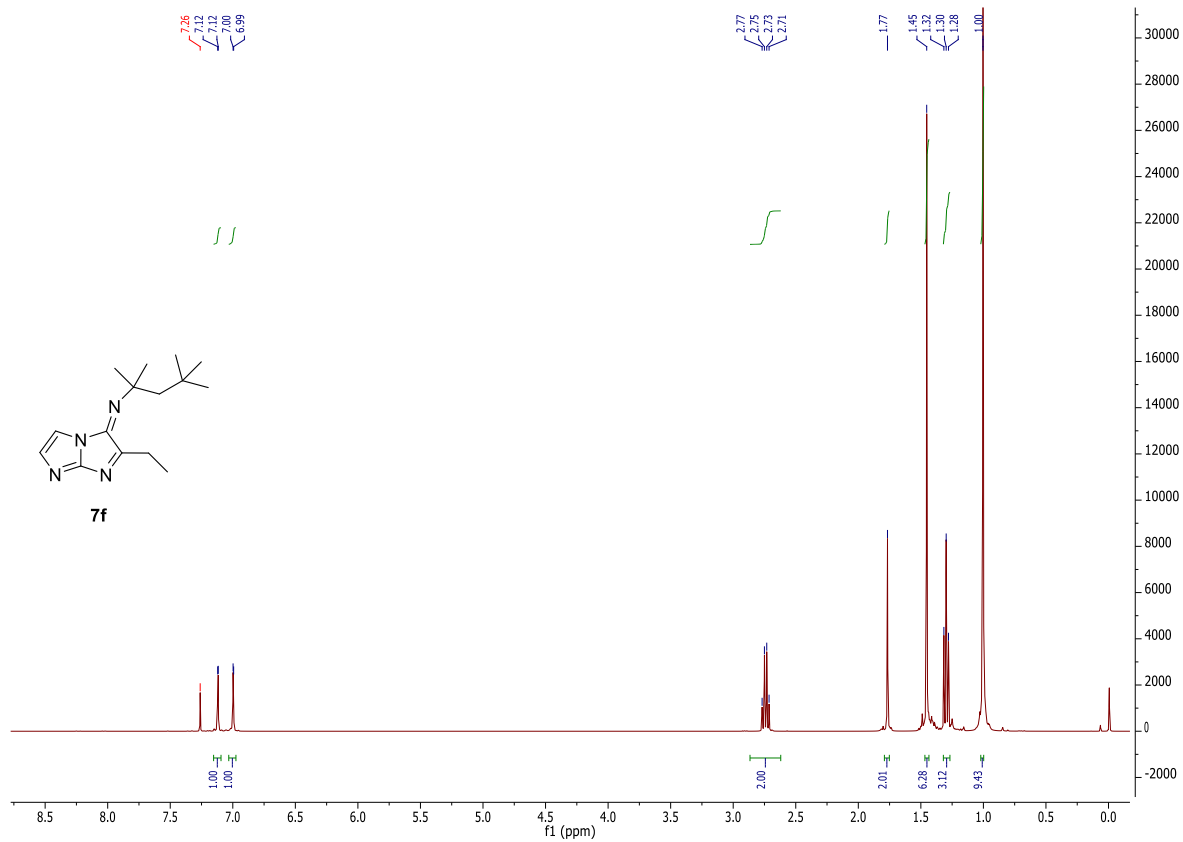
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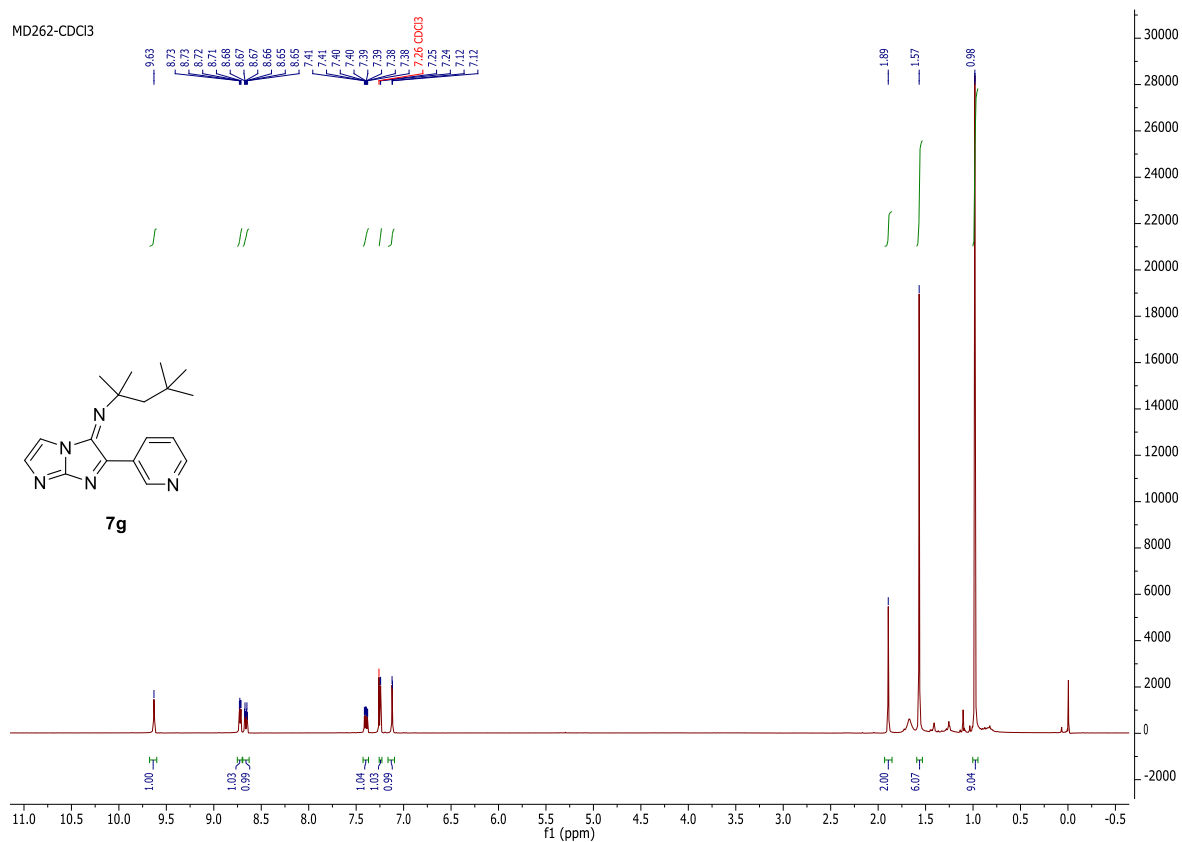


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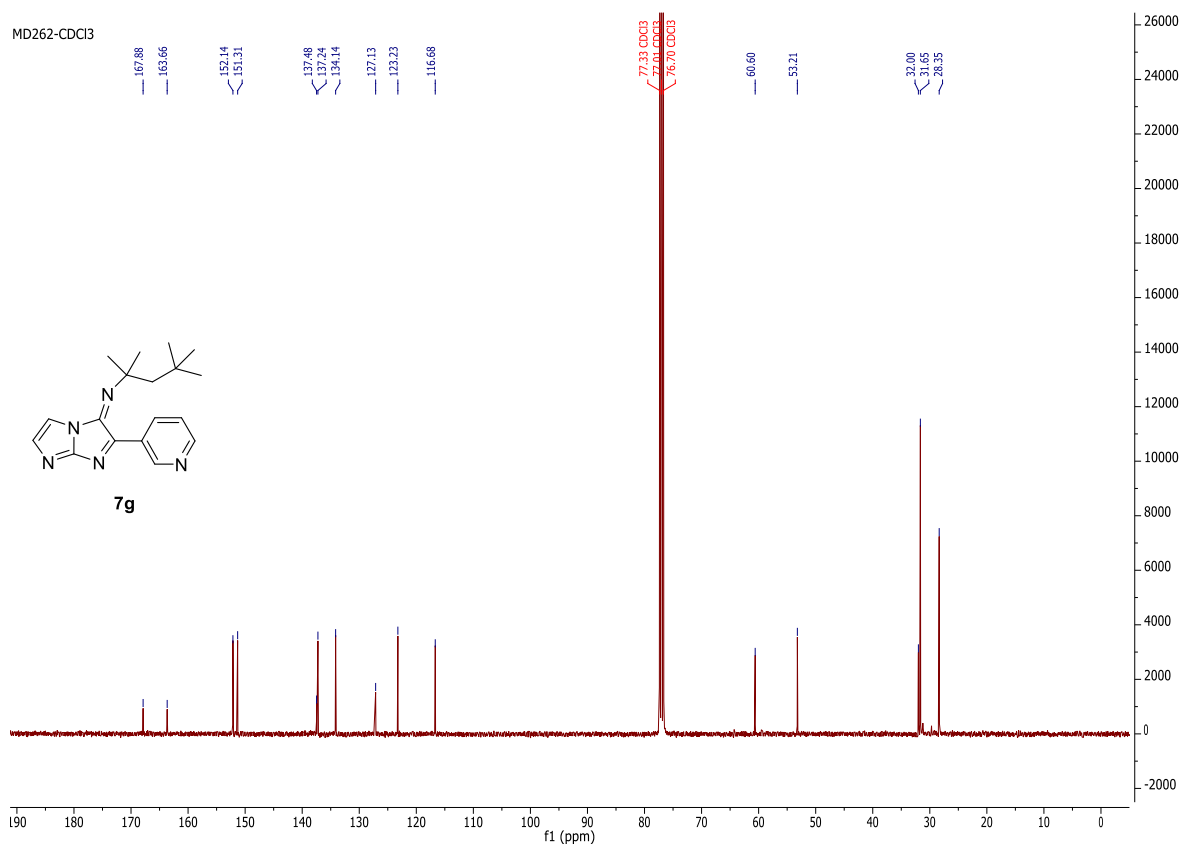




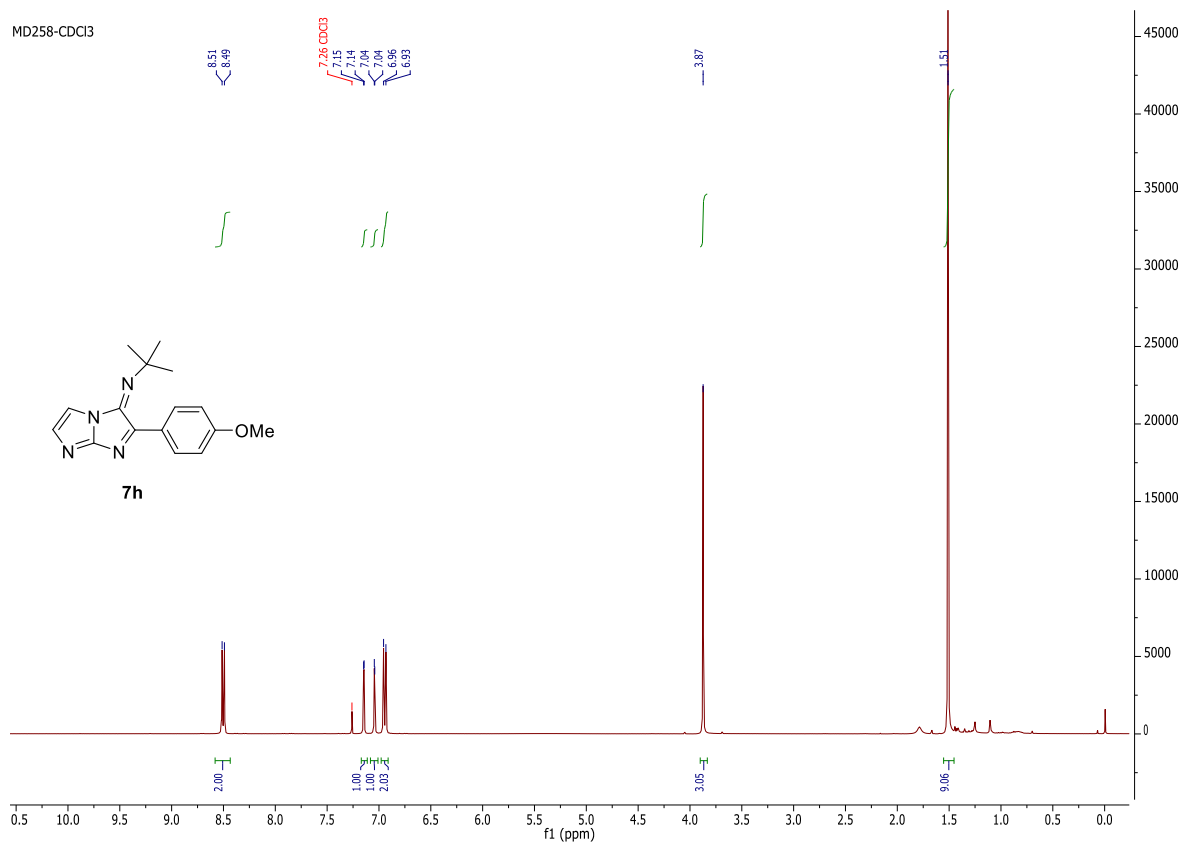
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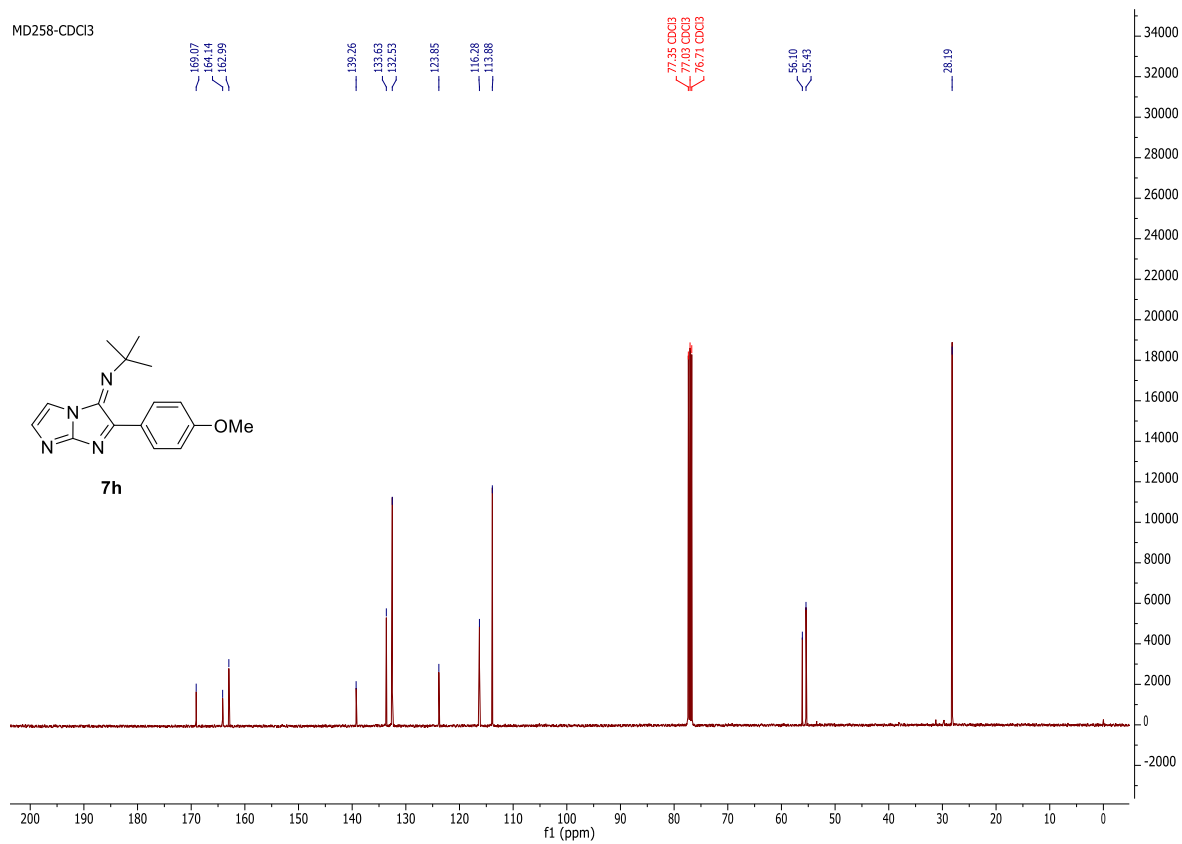
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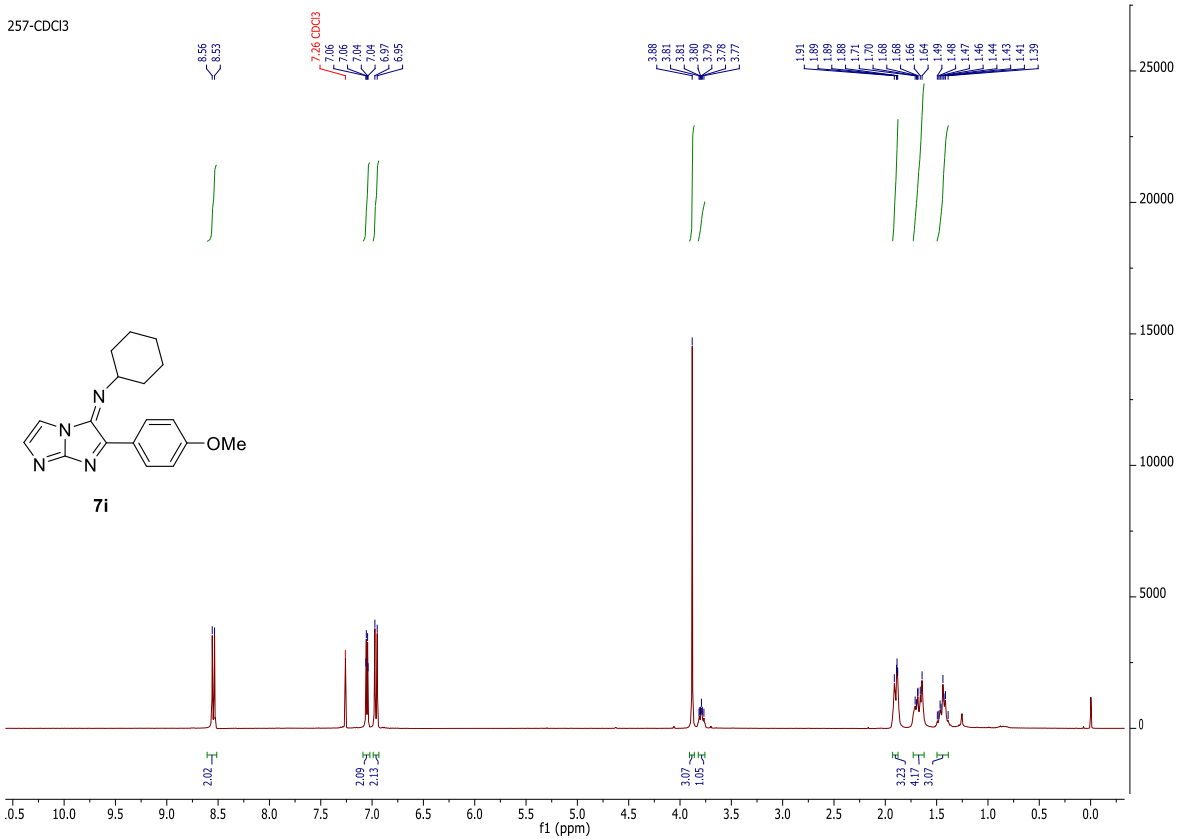
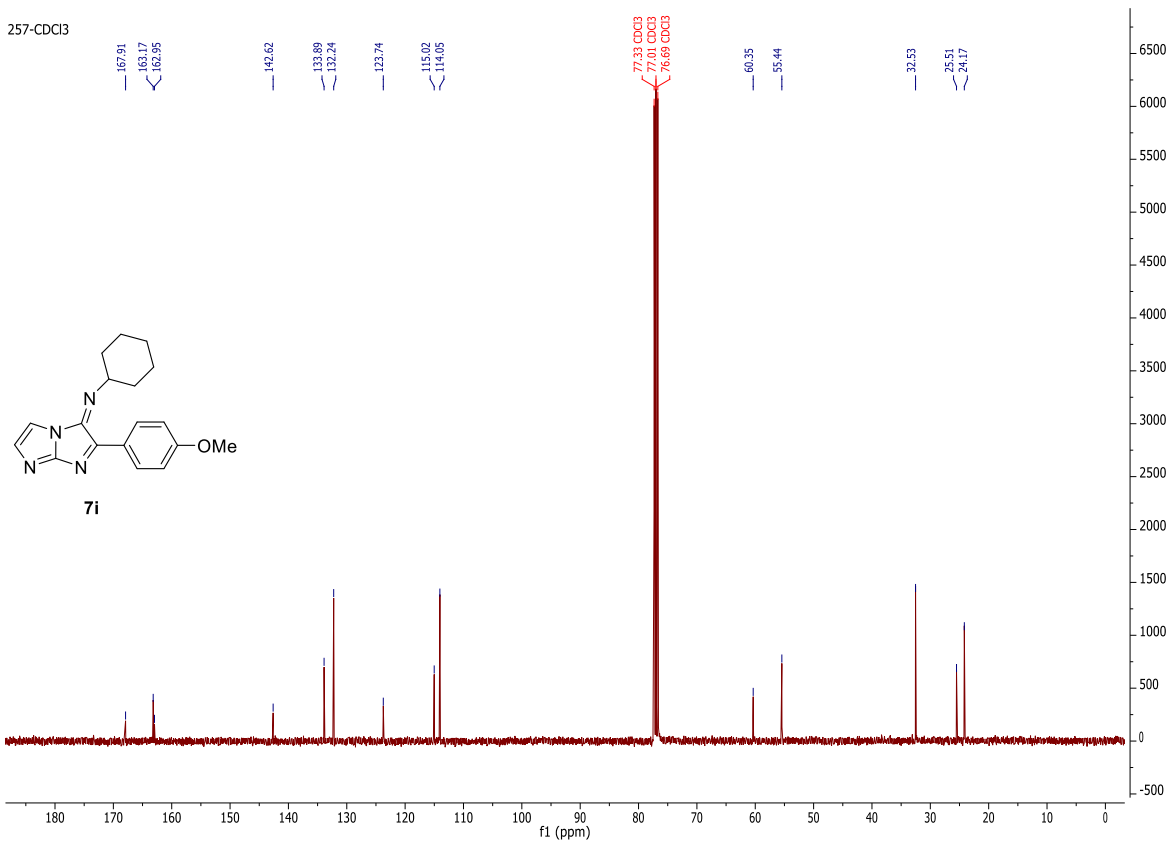


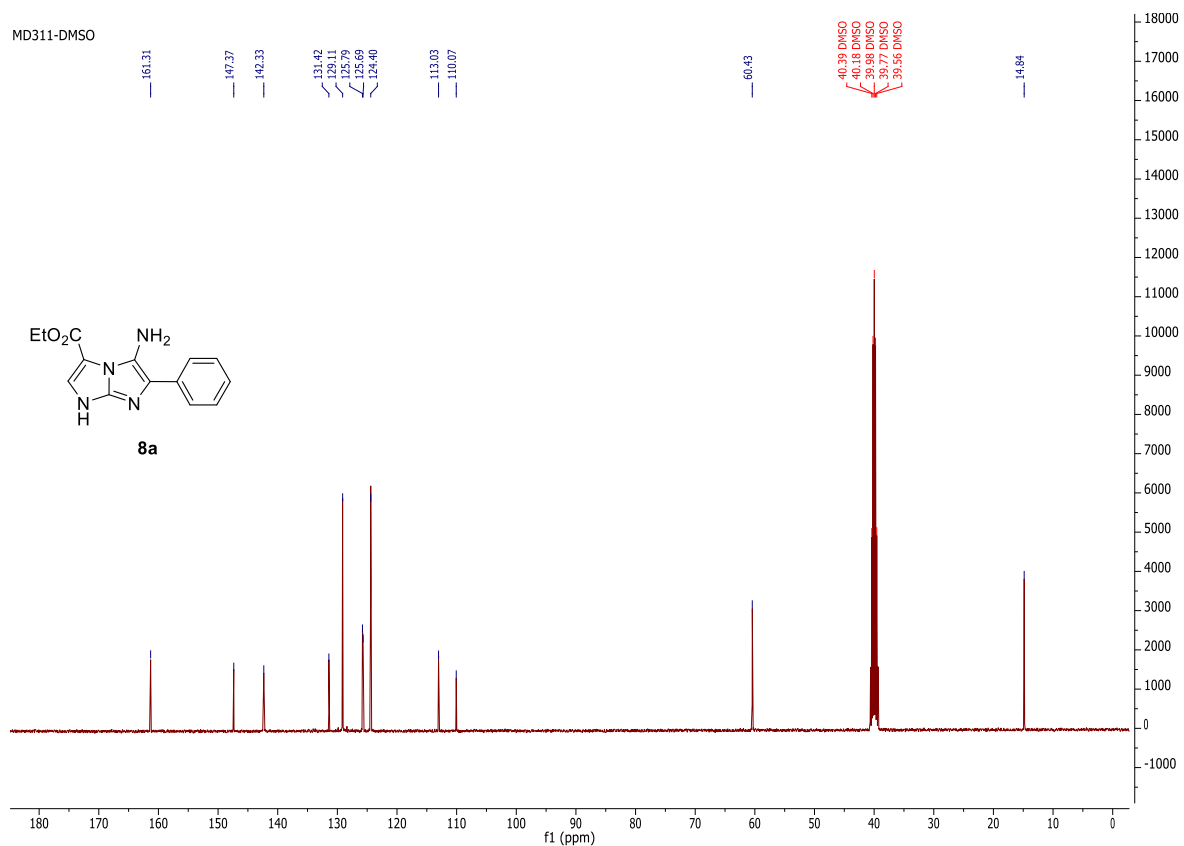
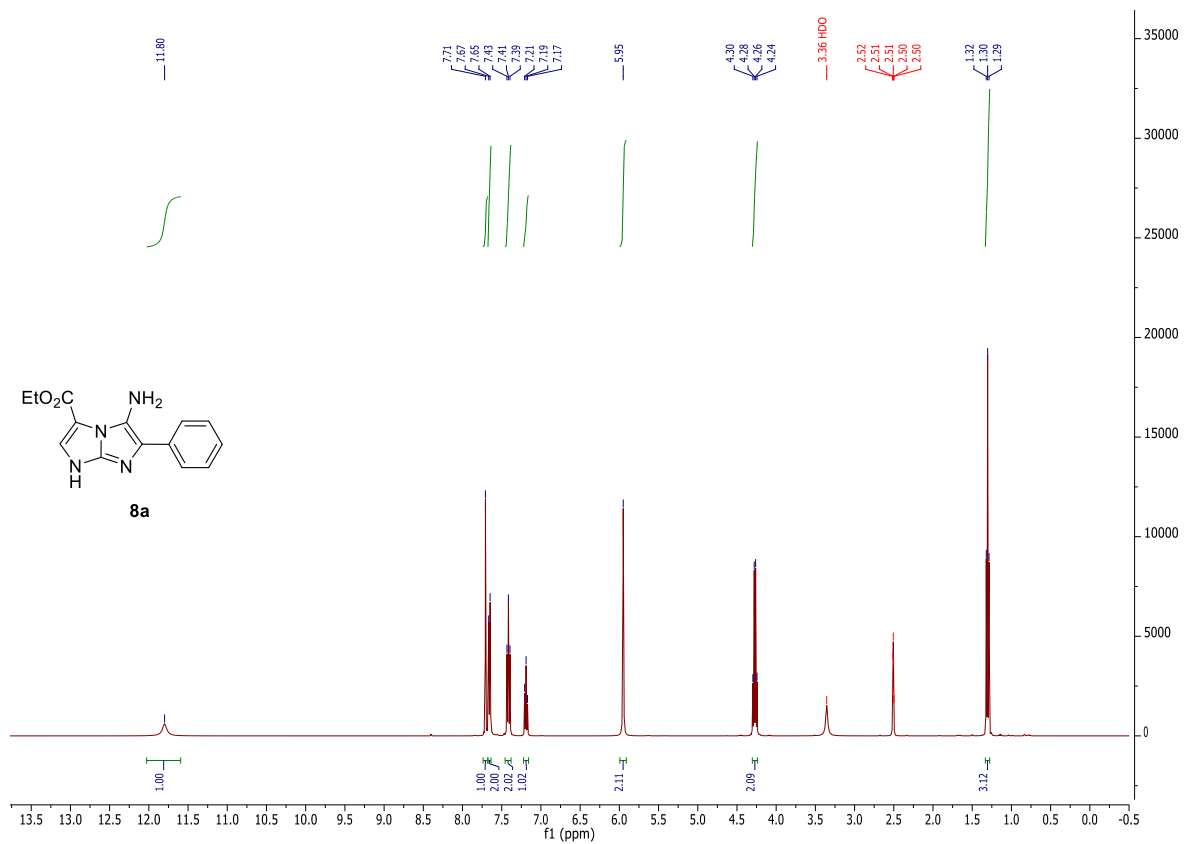
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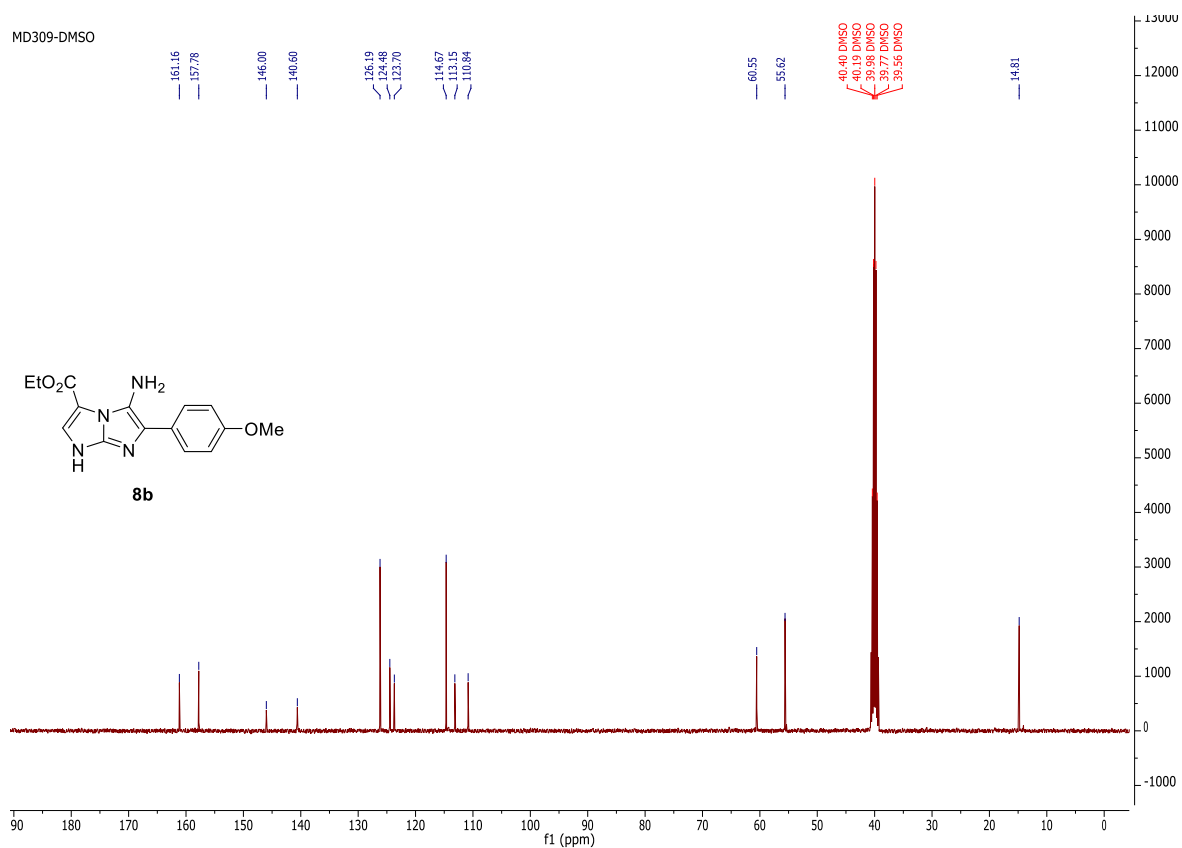
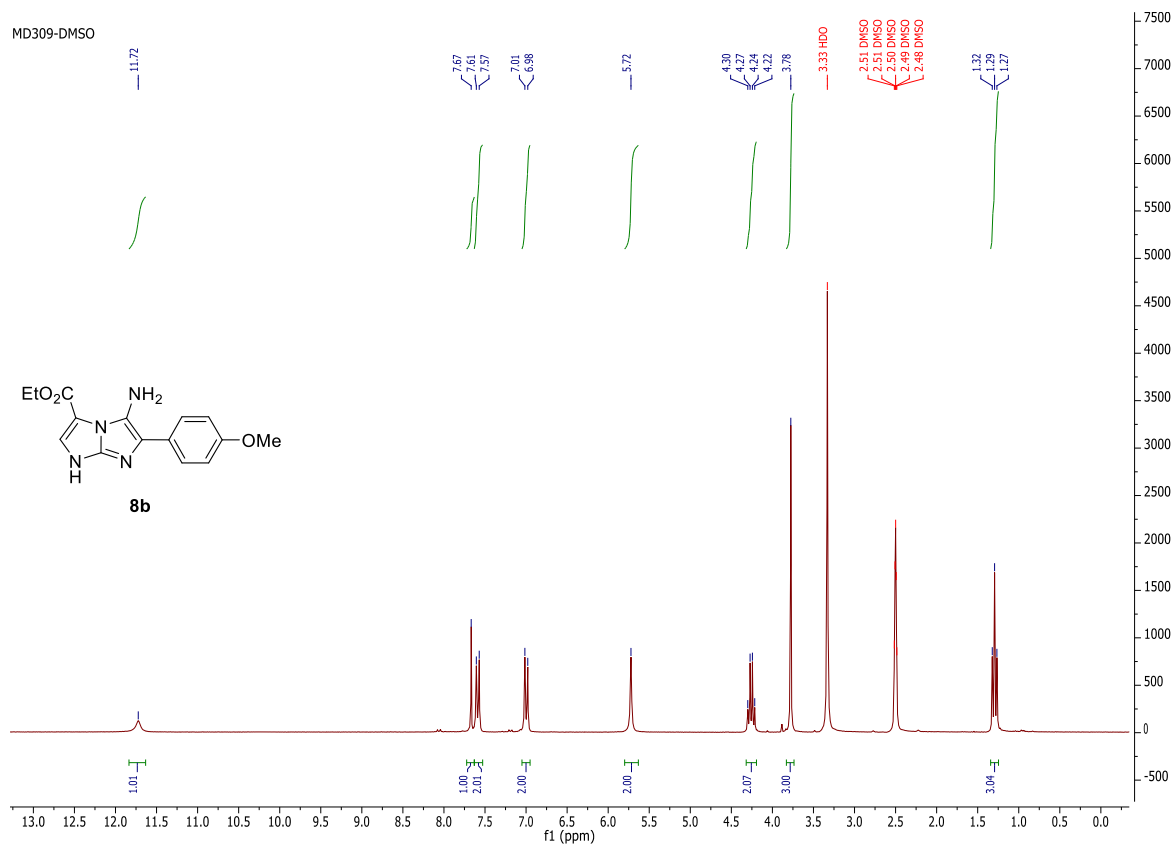


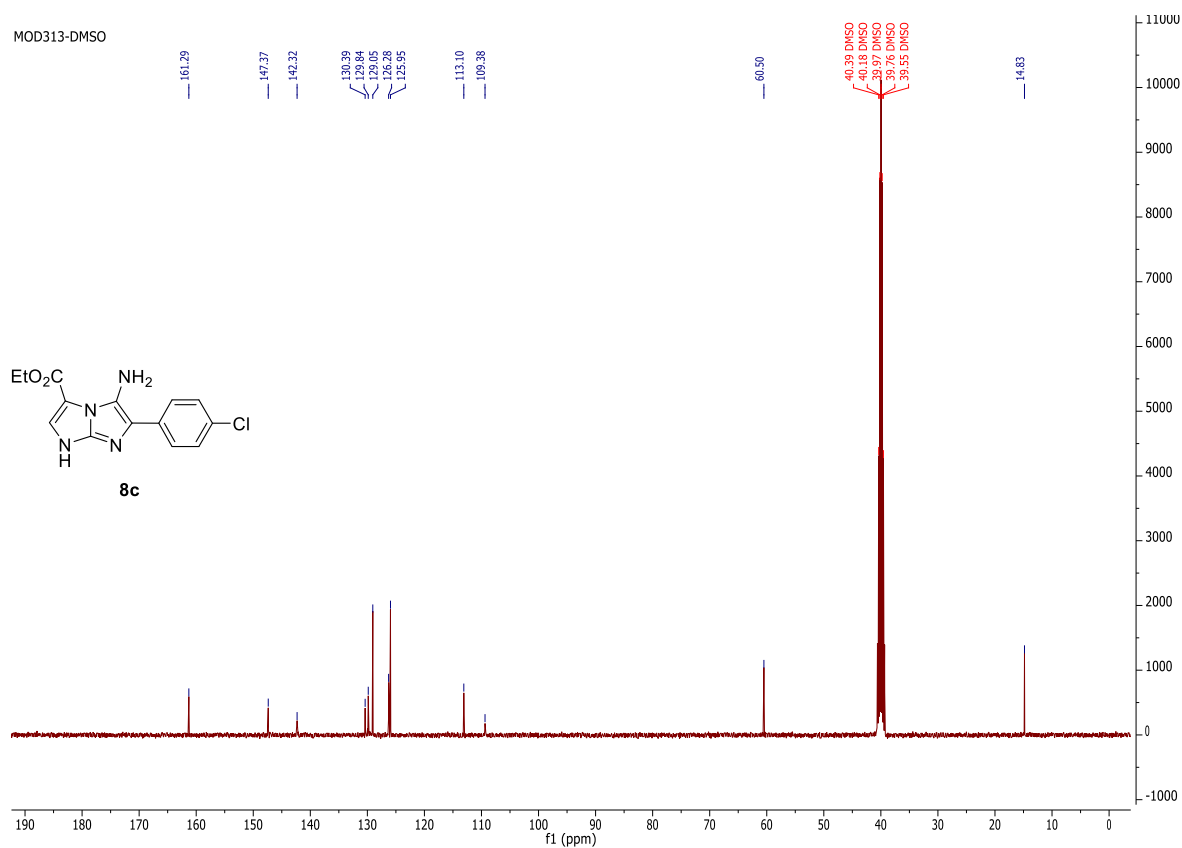
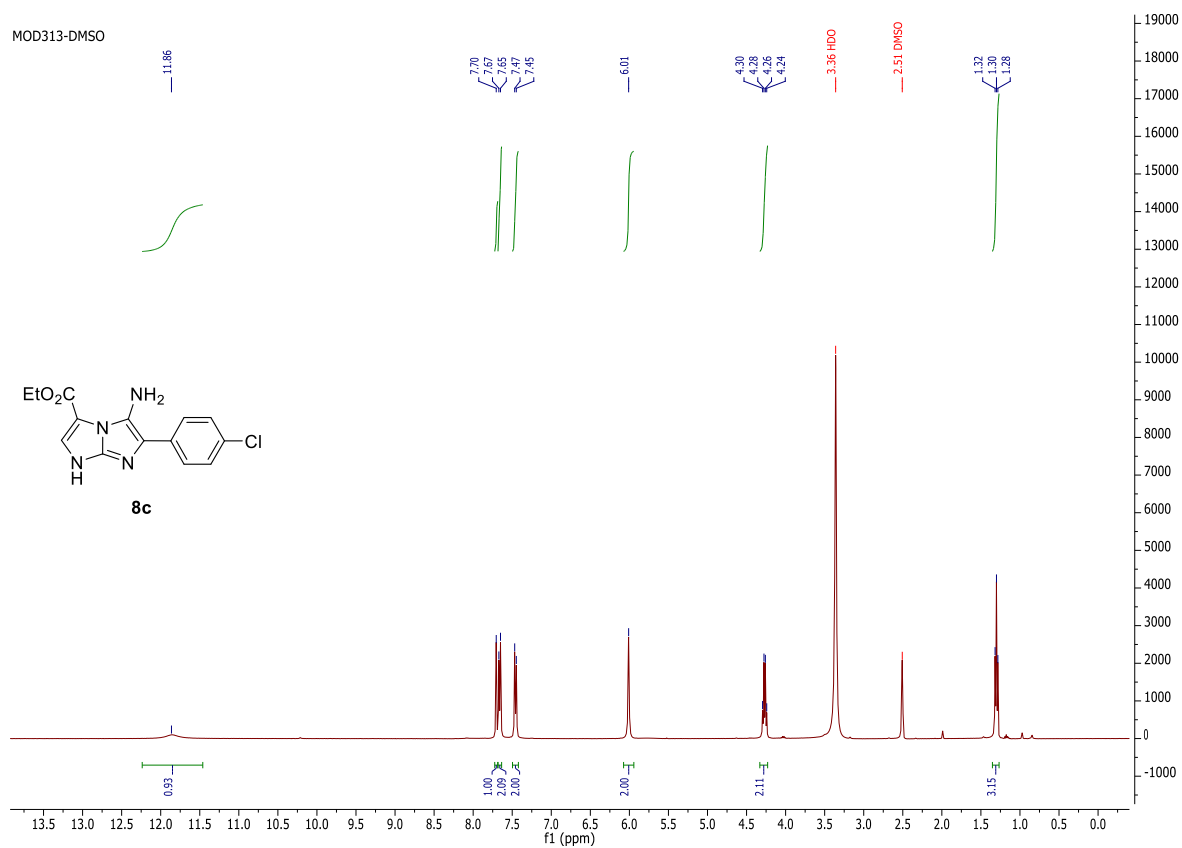
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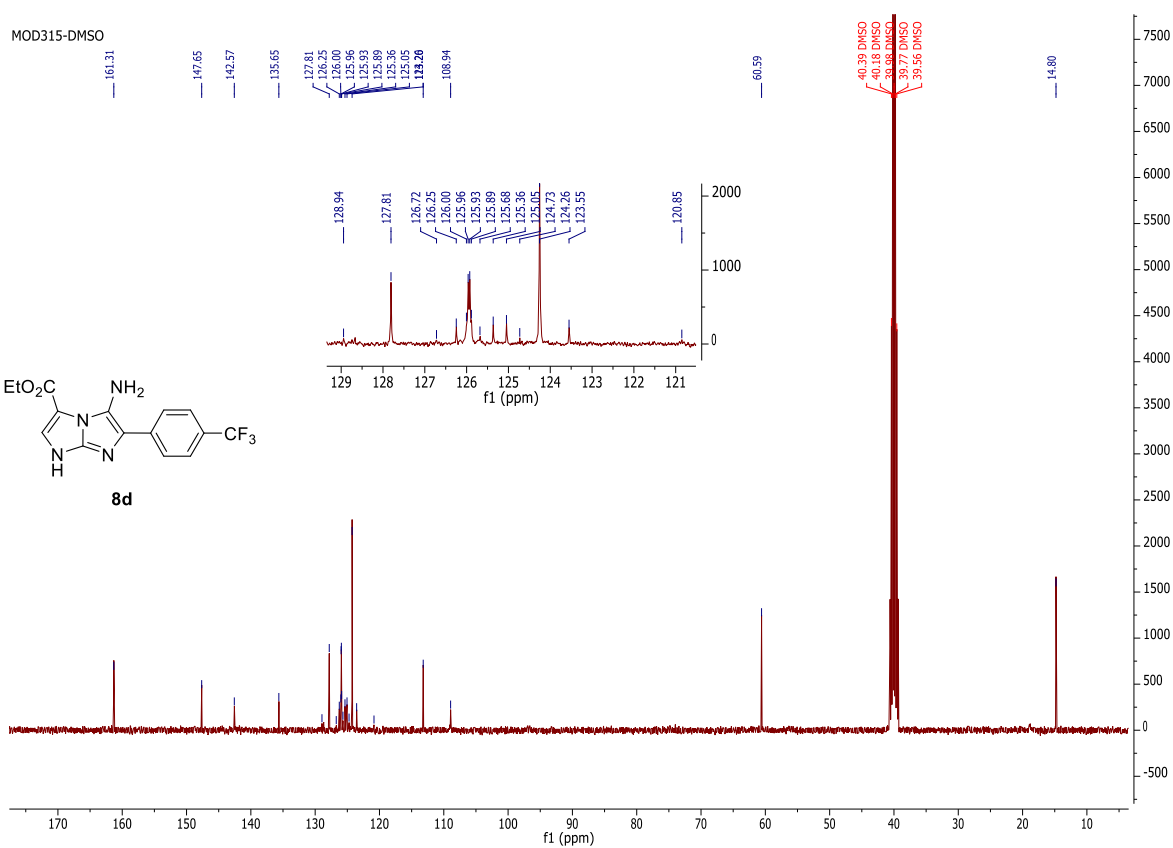


257-CDCl₃257-CDCl₃

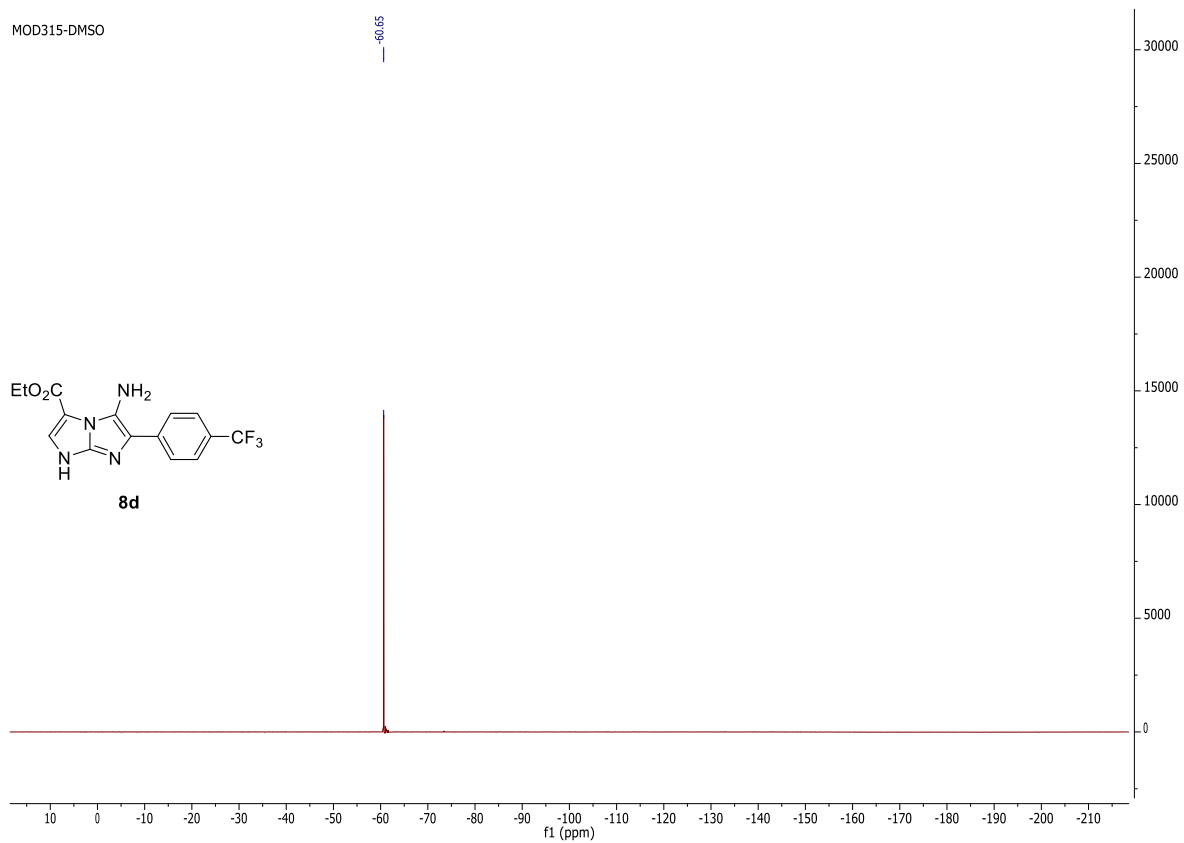




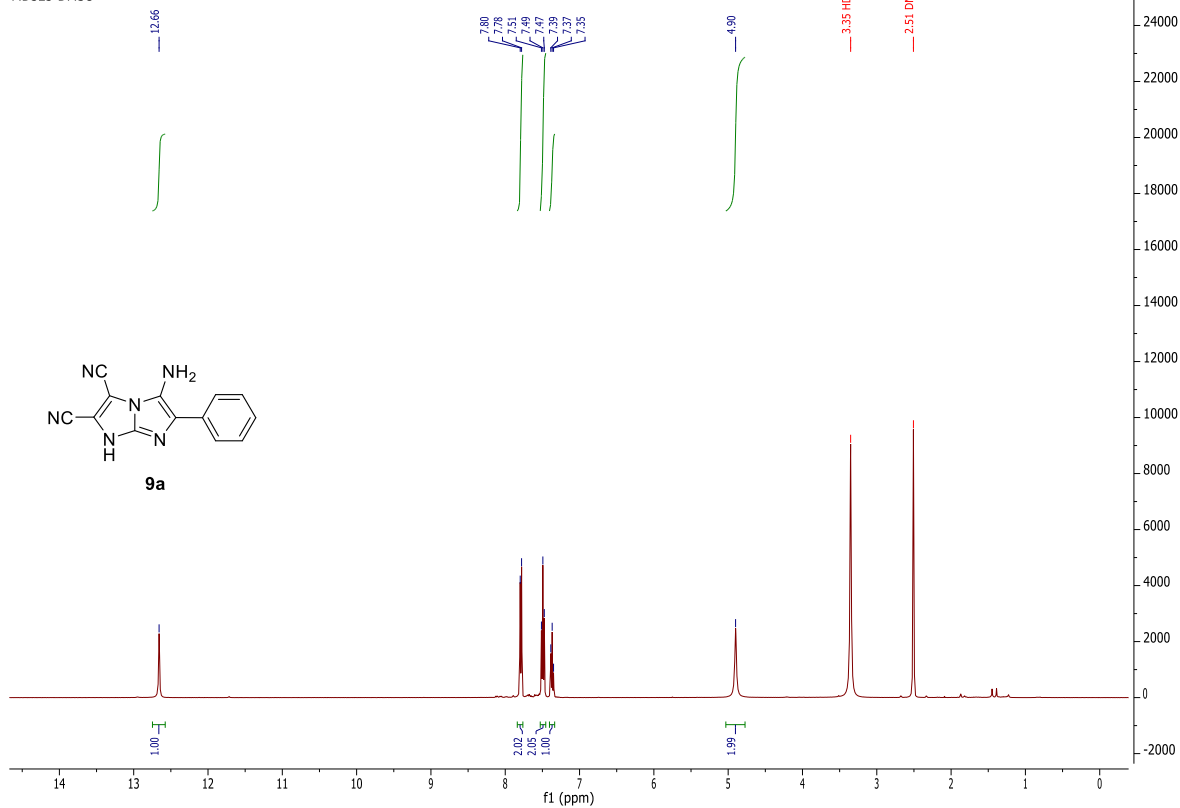




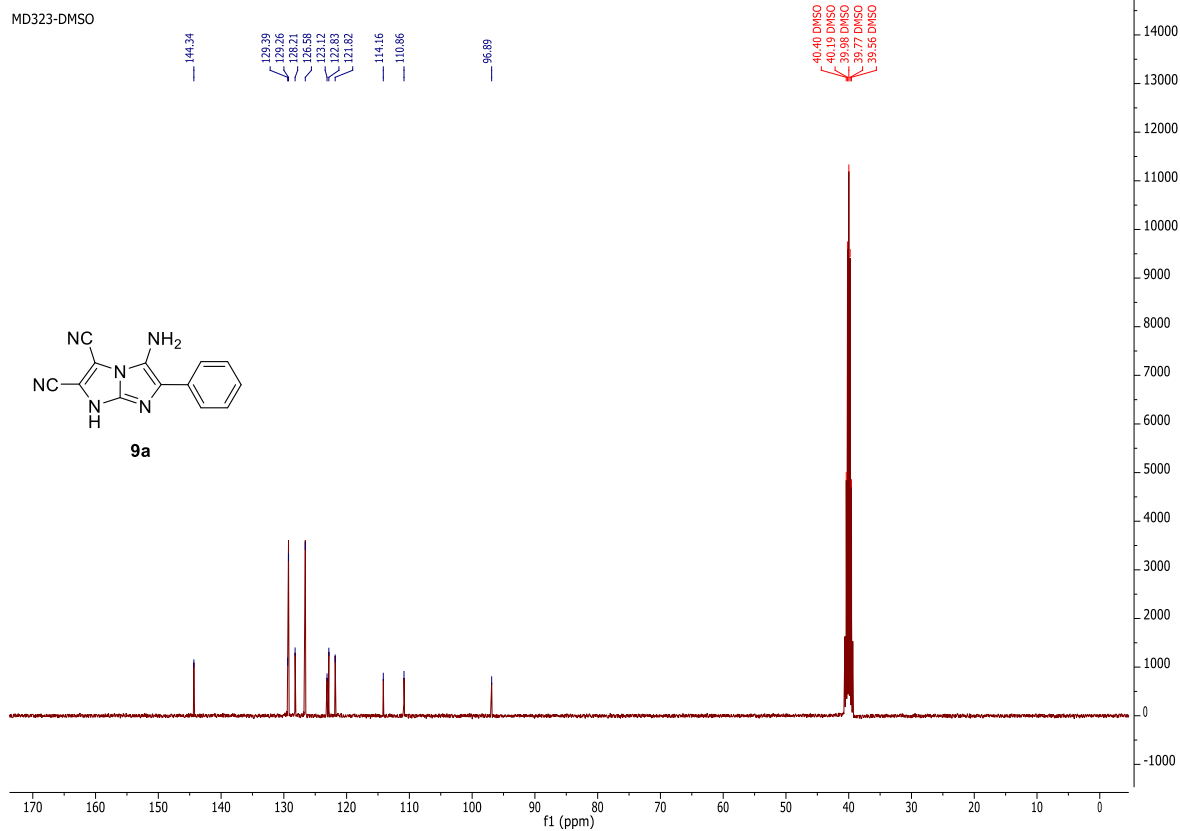
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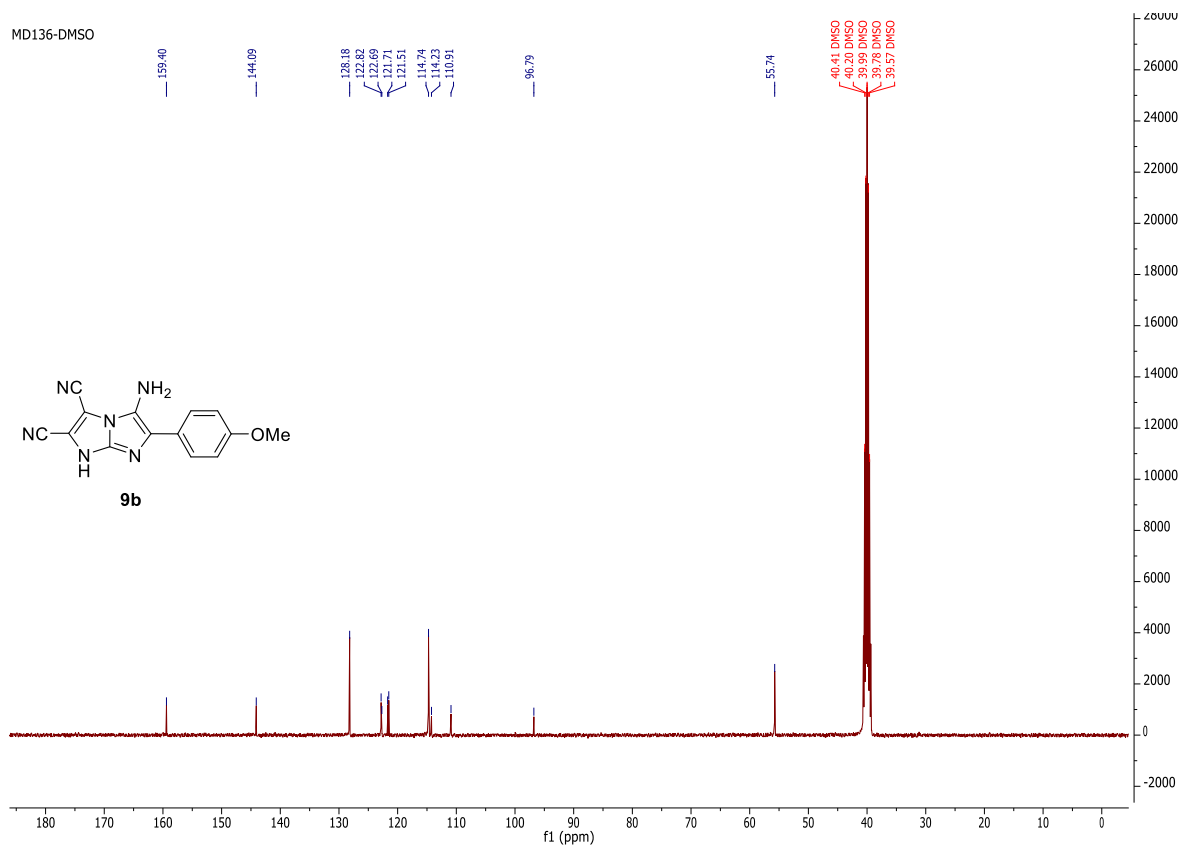
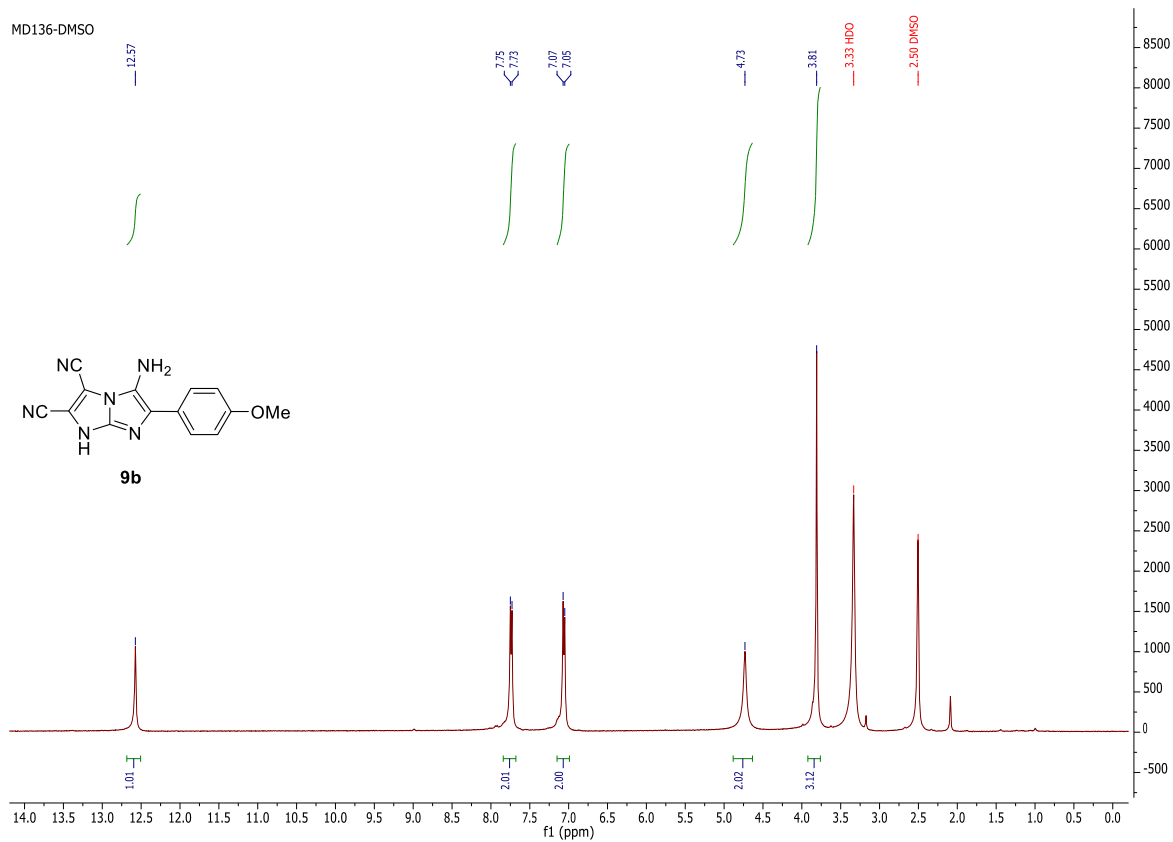


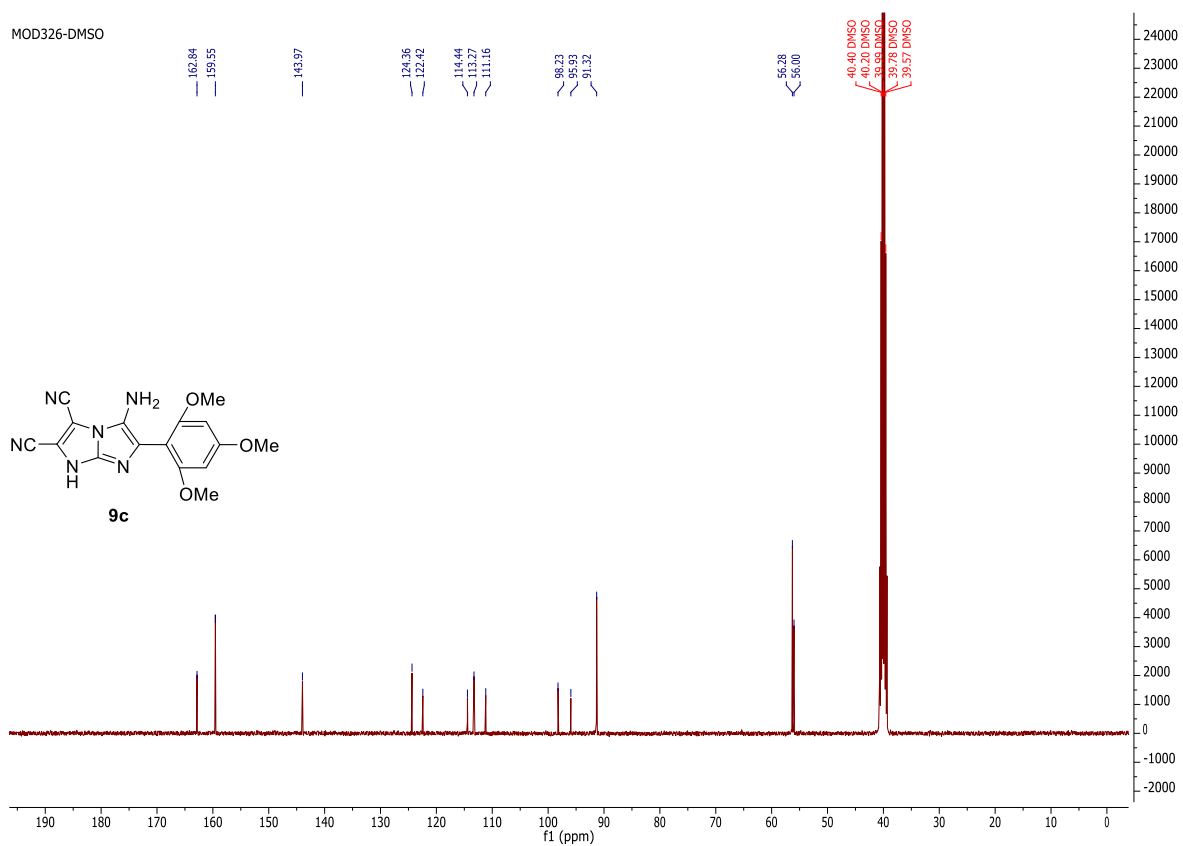
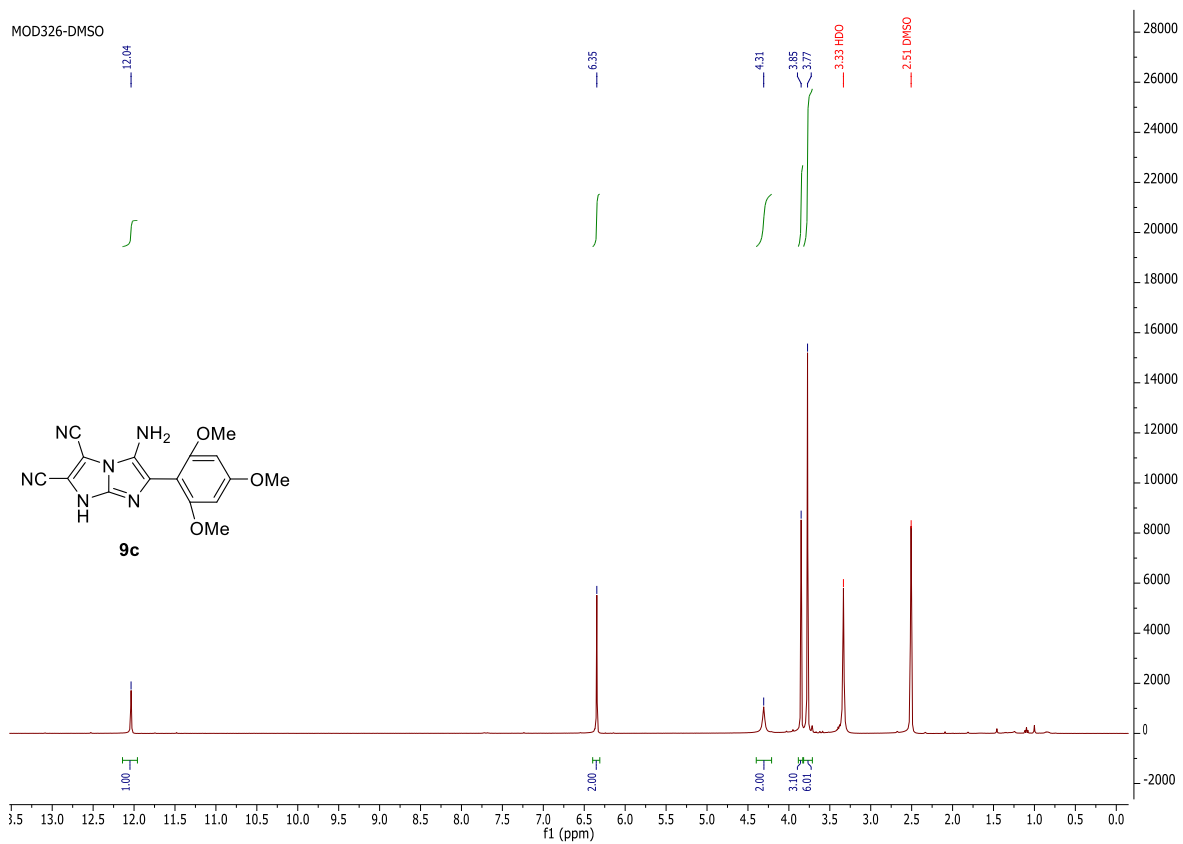
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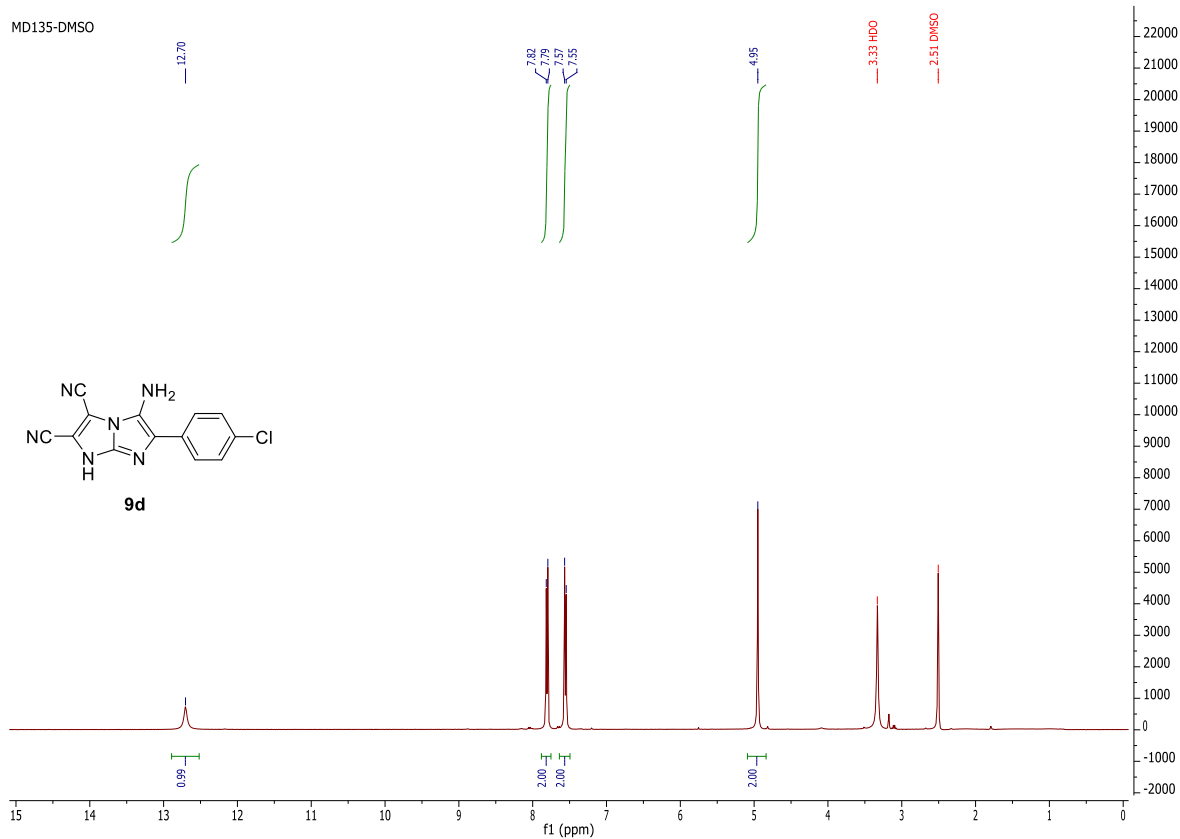
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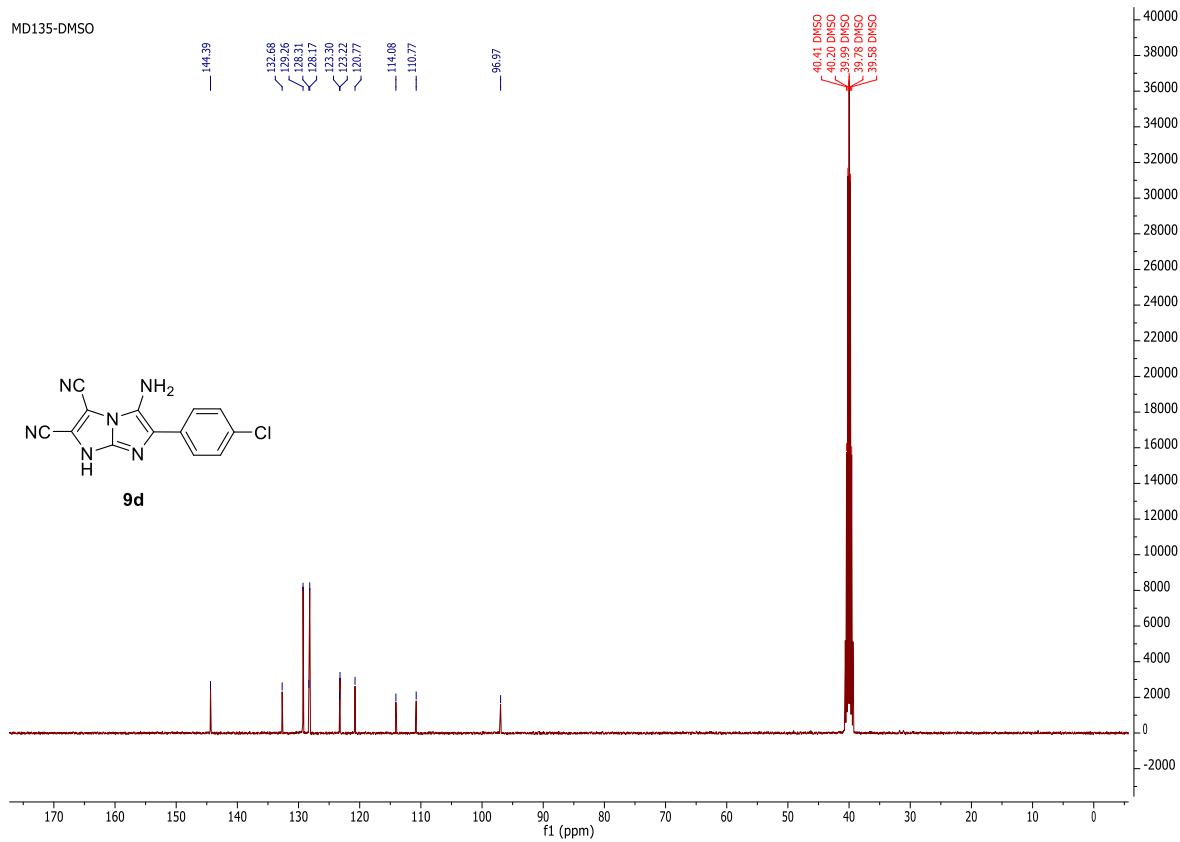


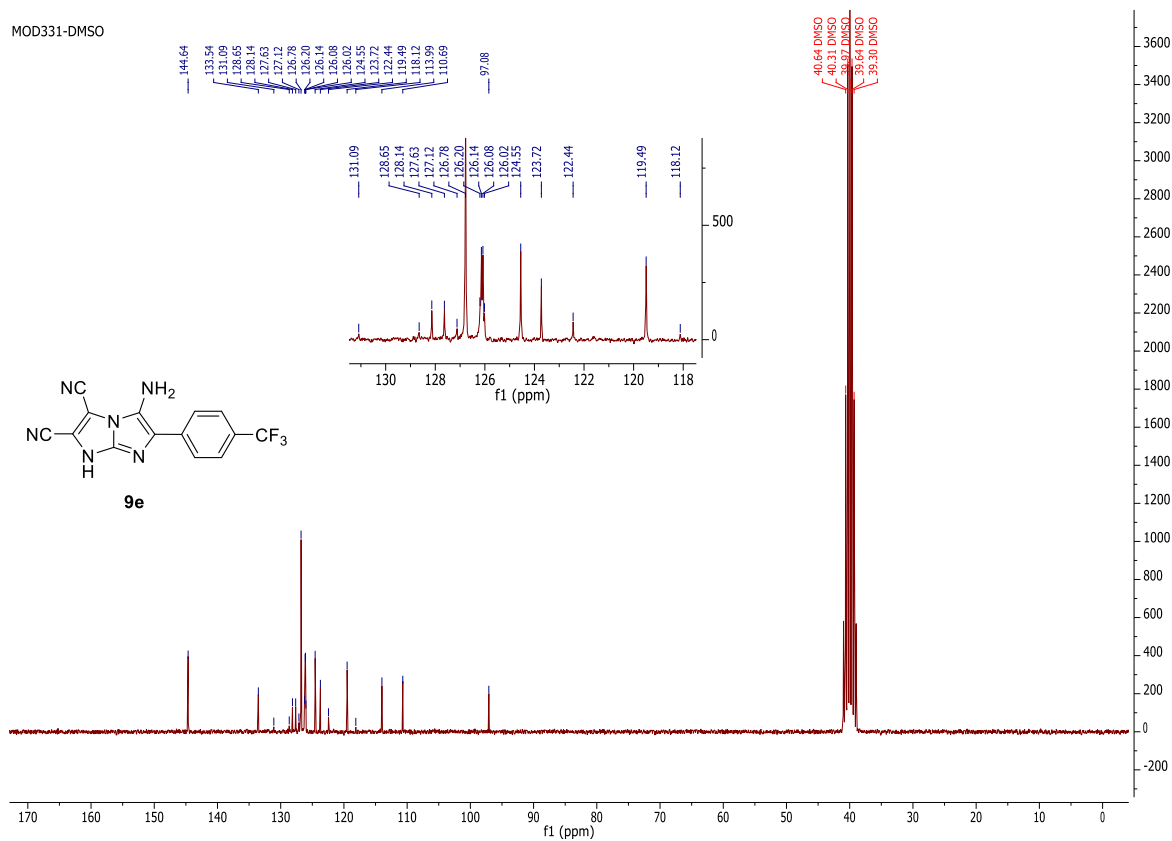
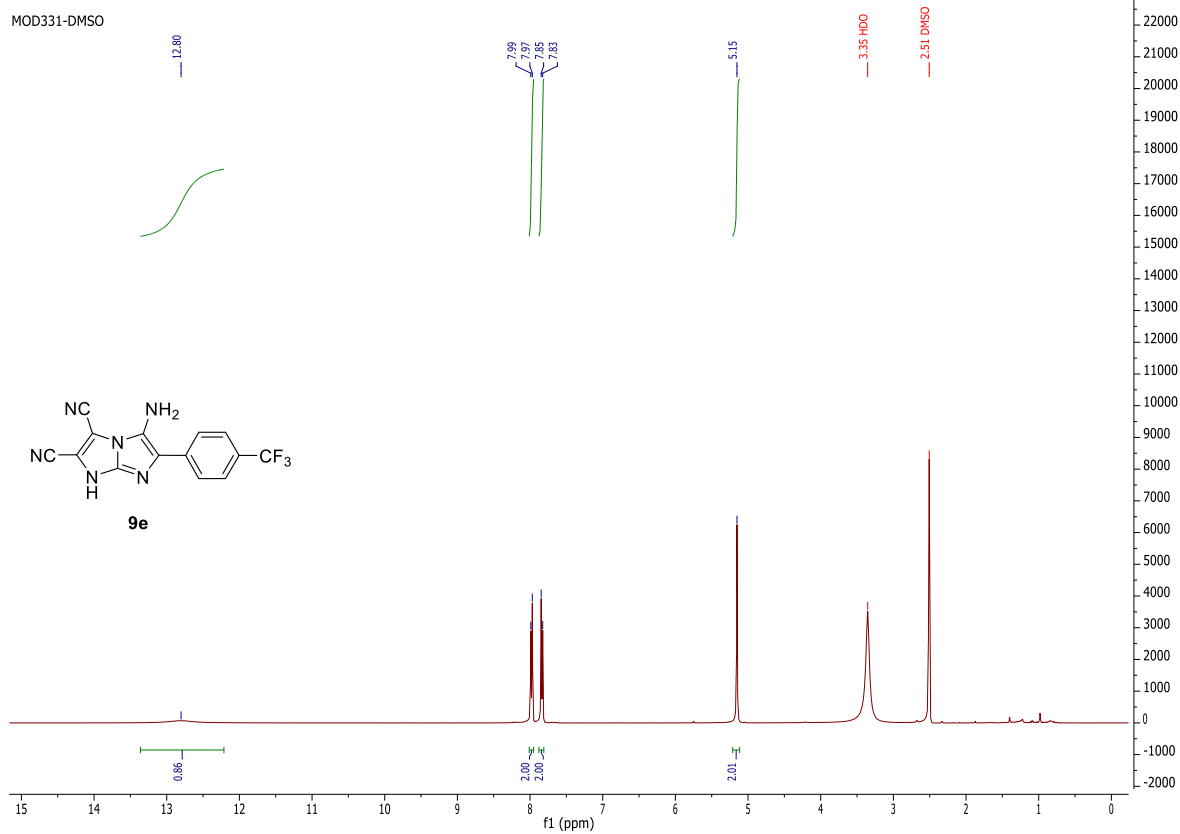


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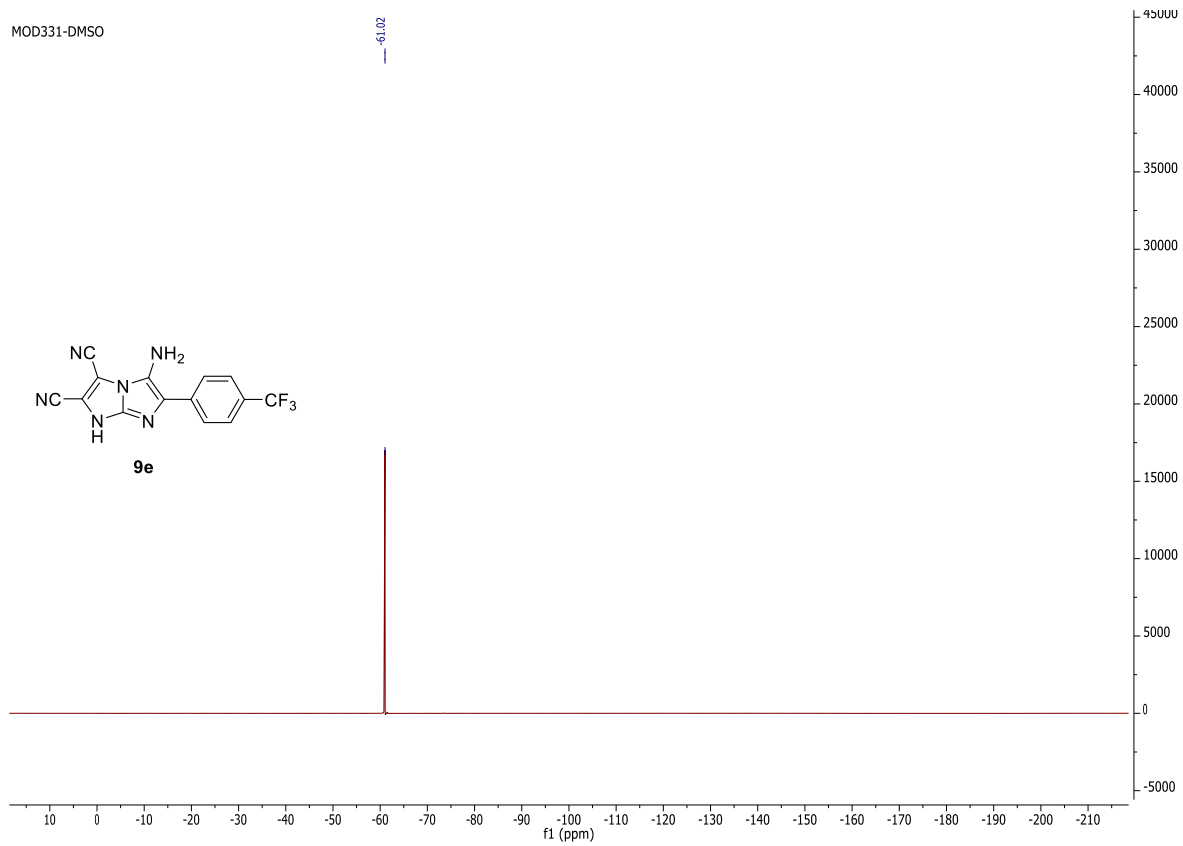


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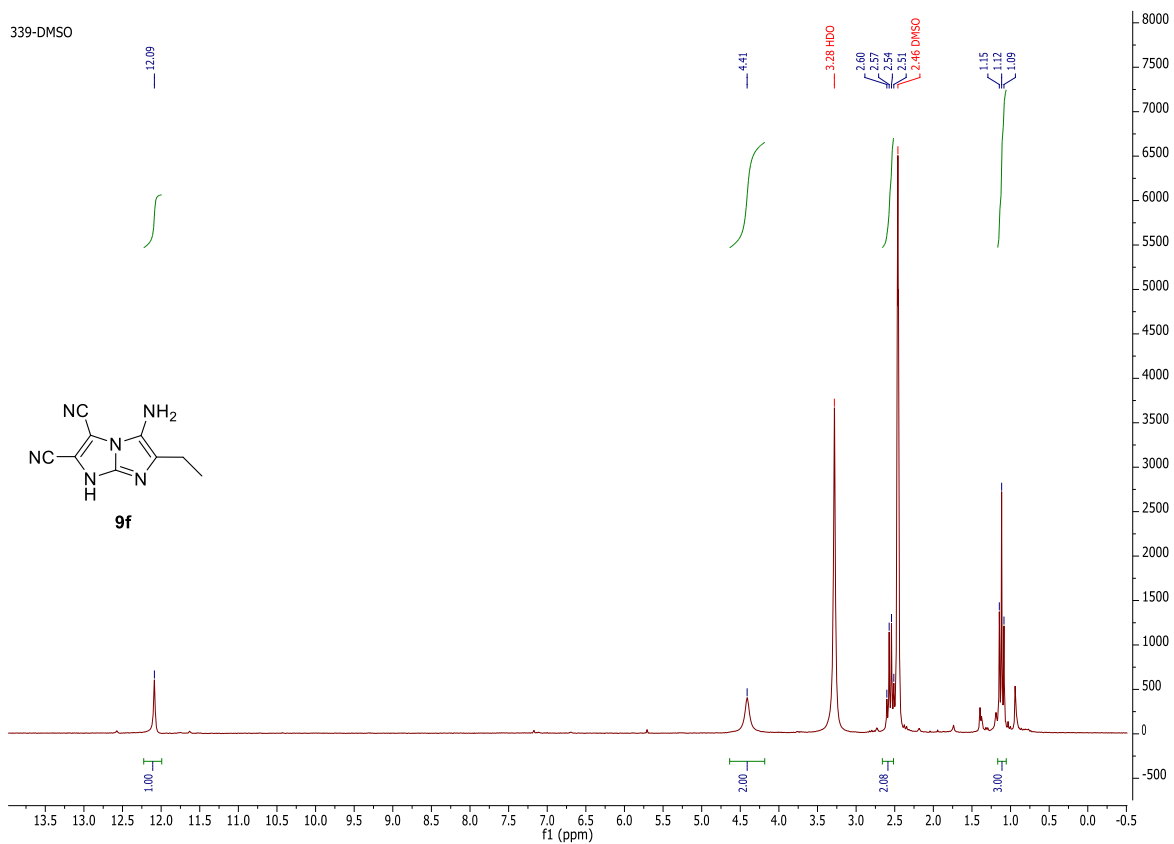




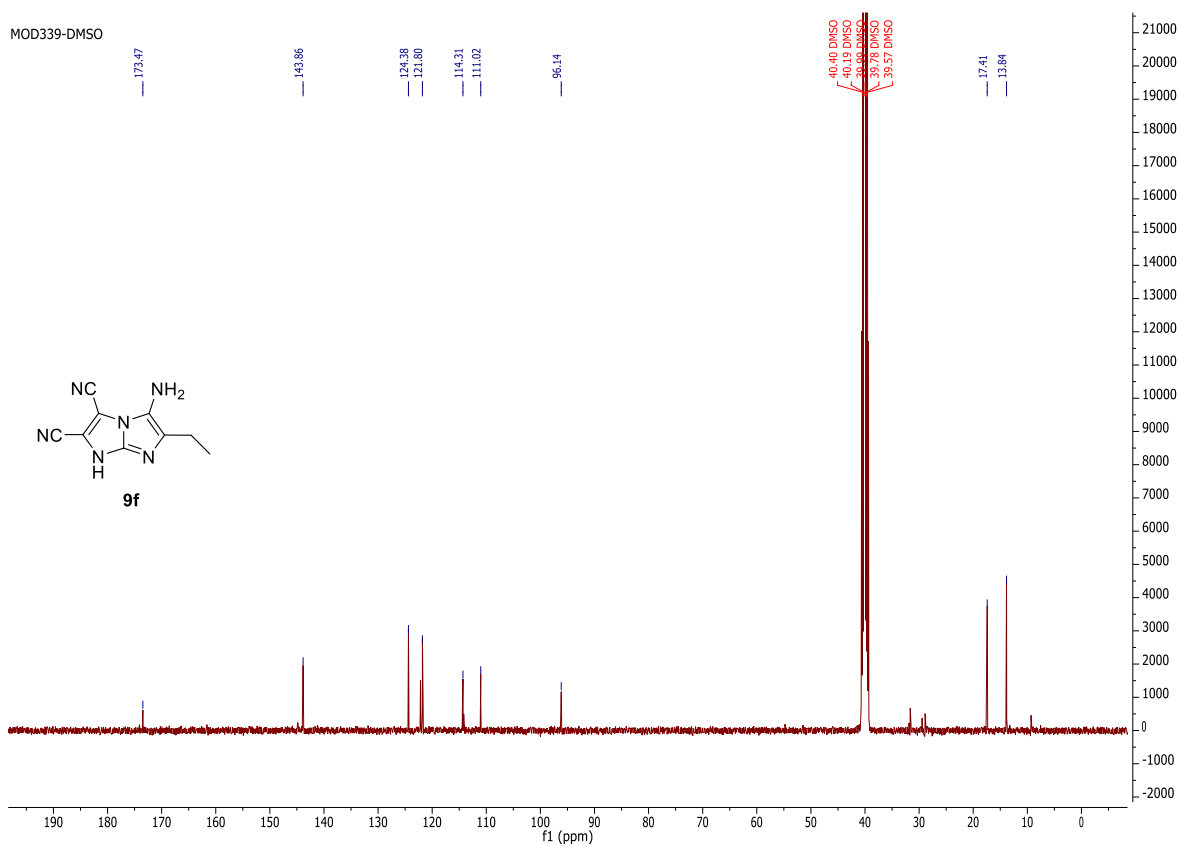
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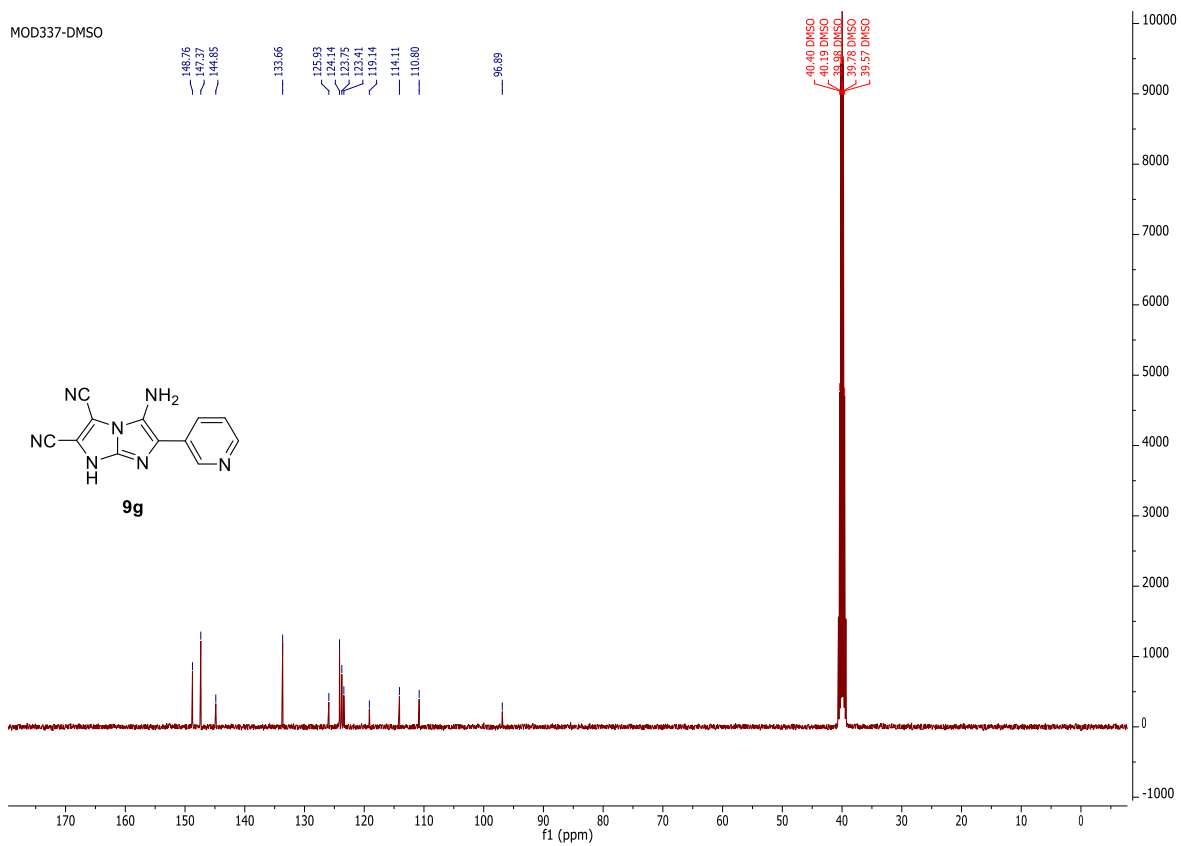
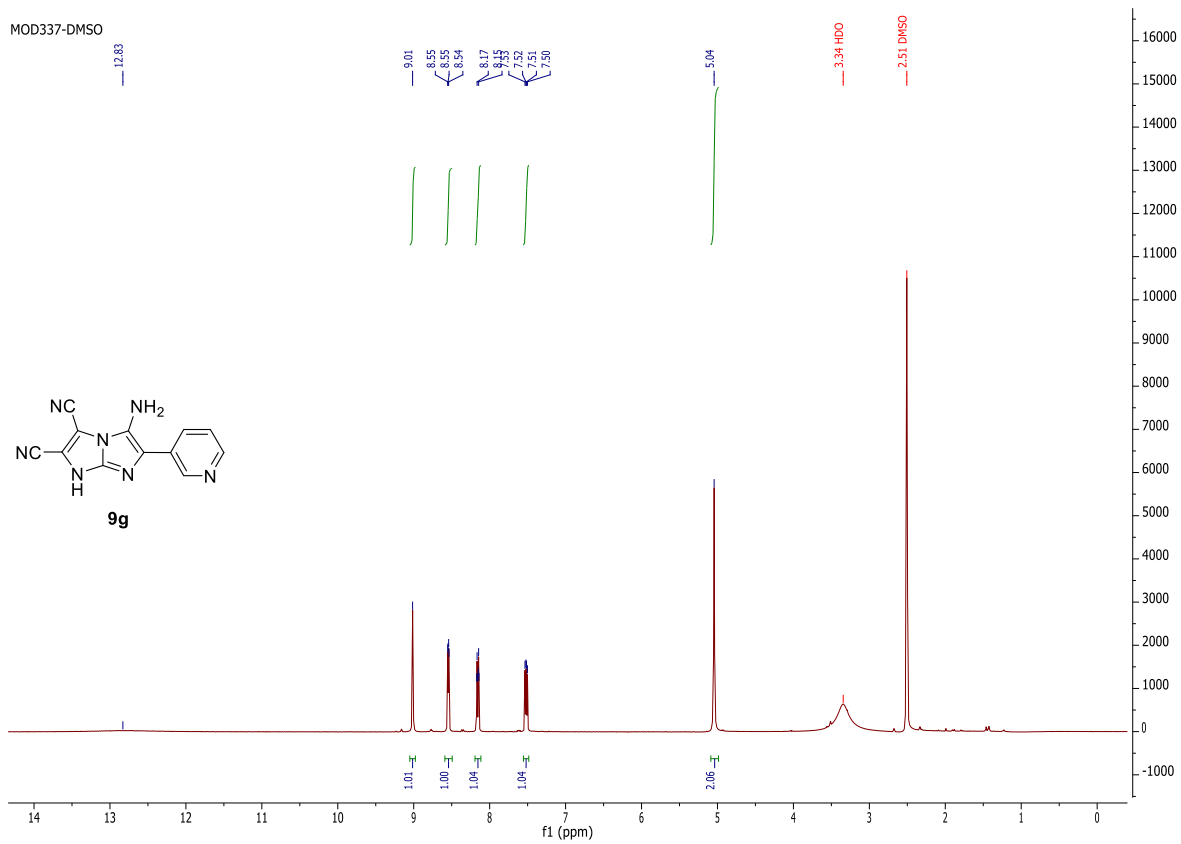


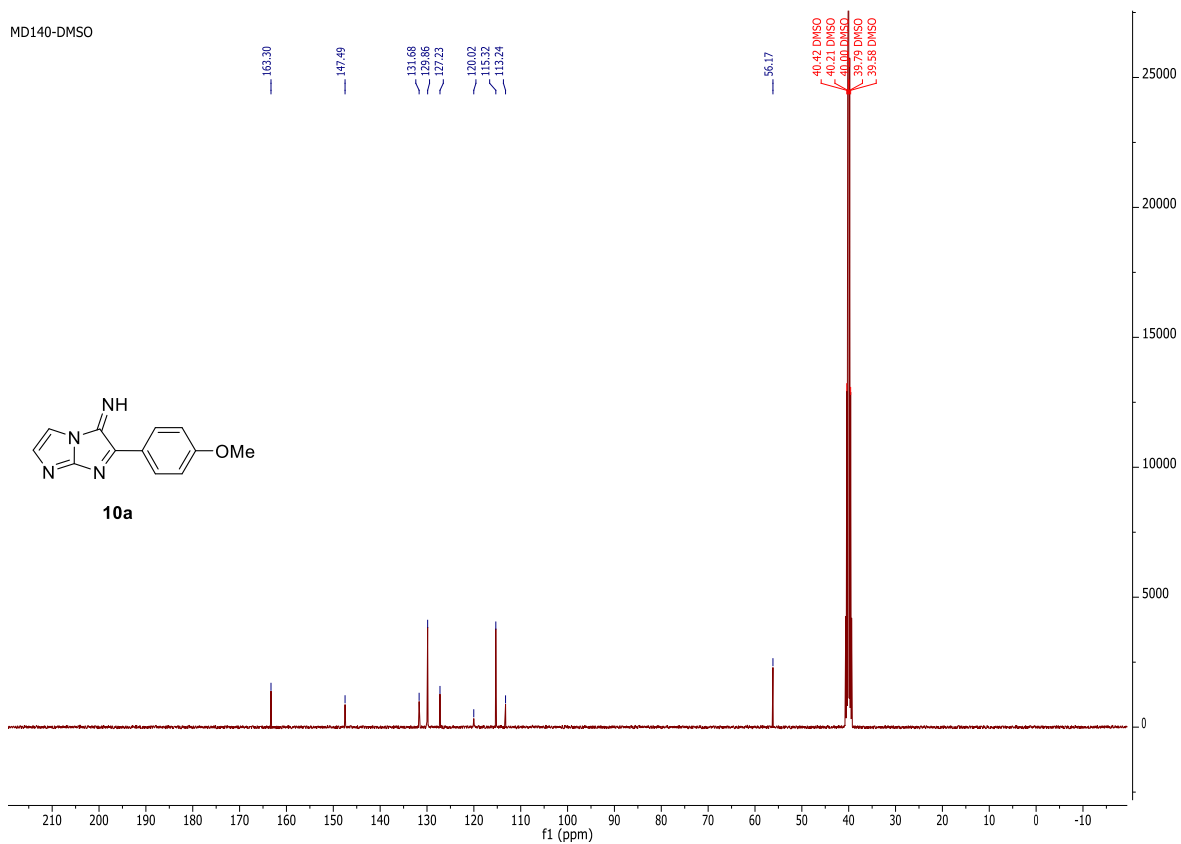
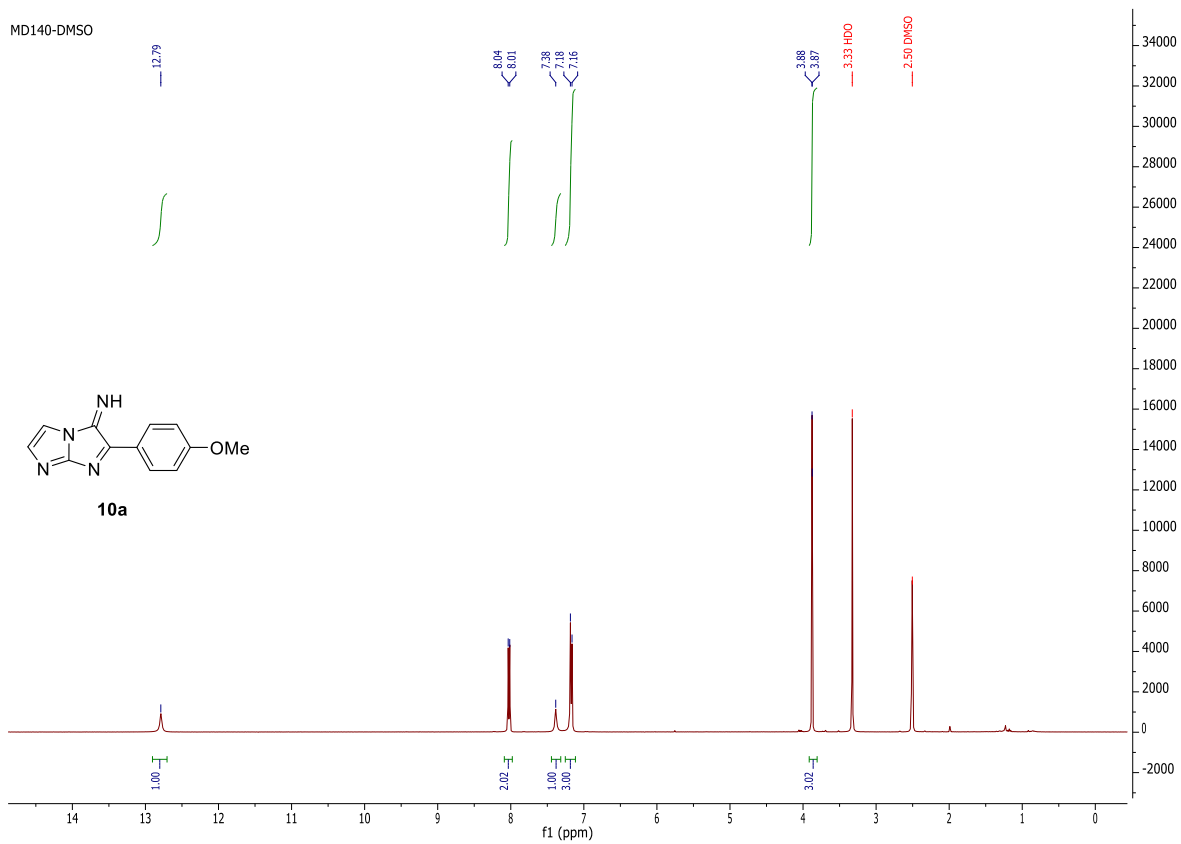
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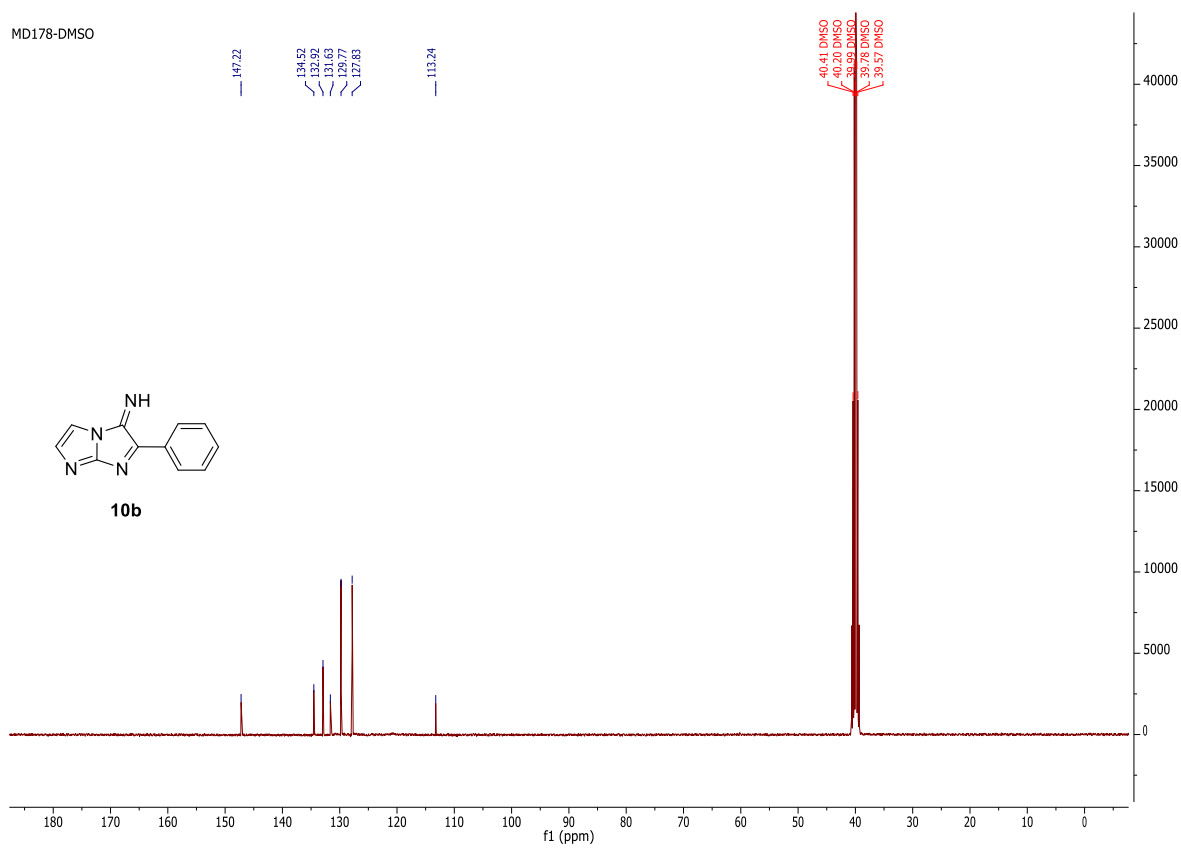
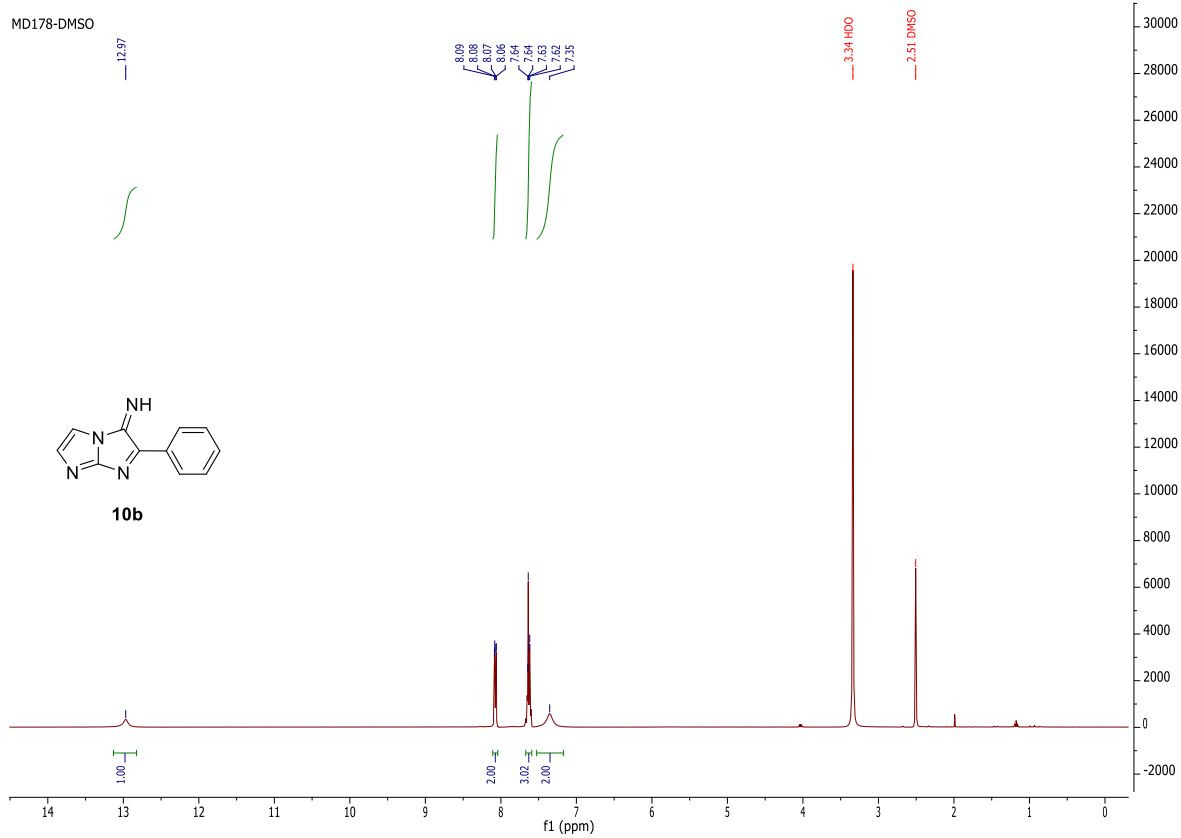


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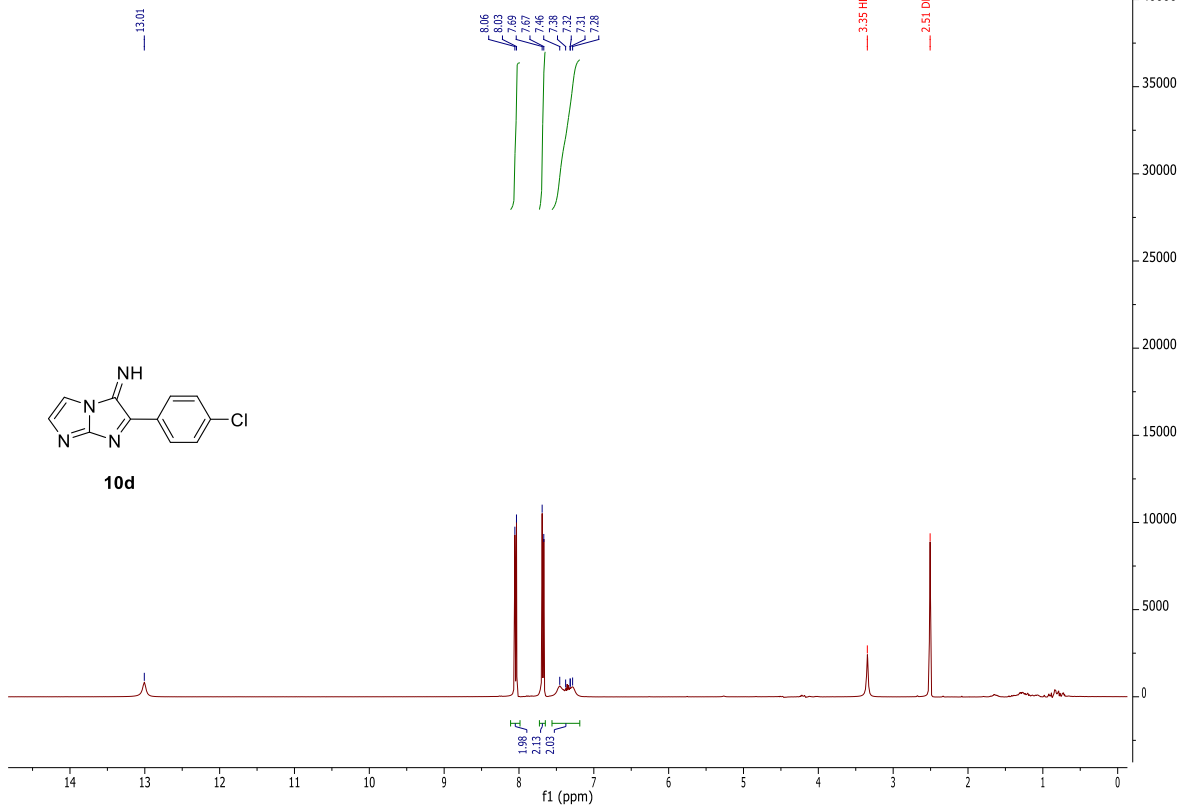




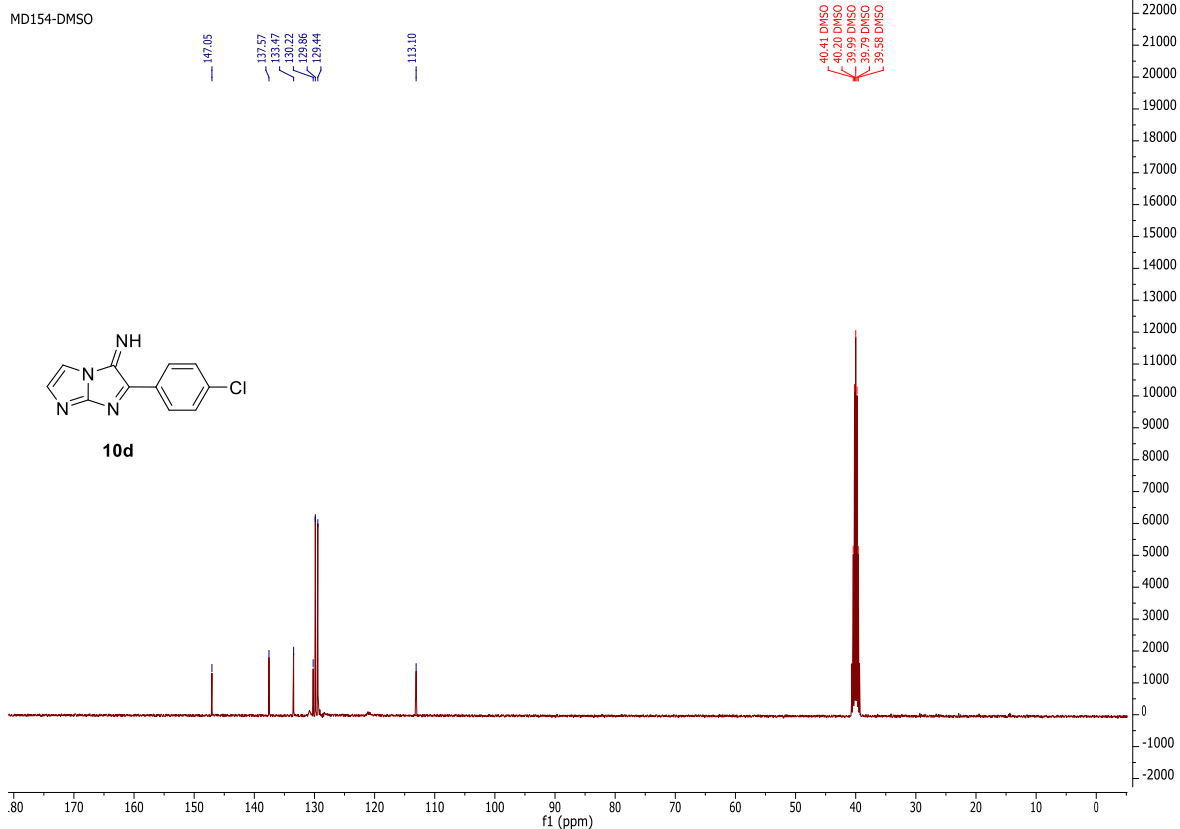


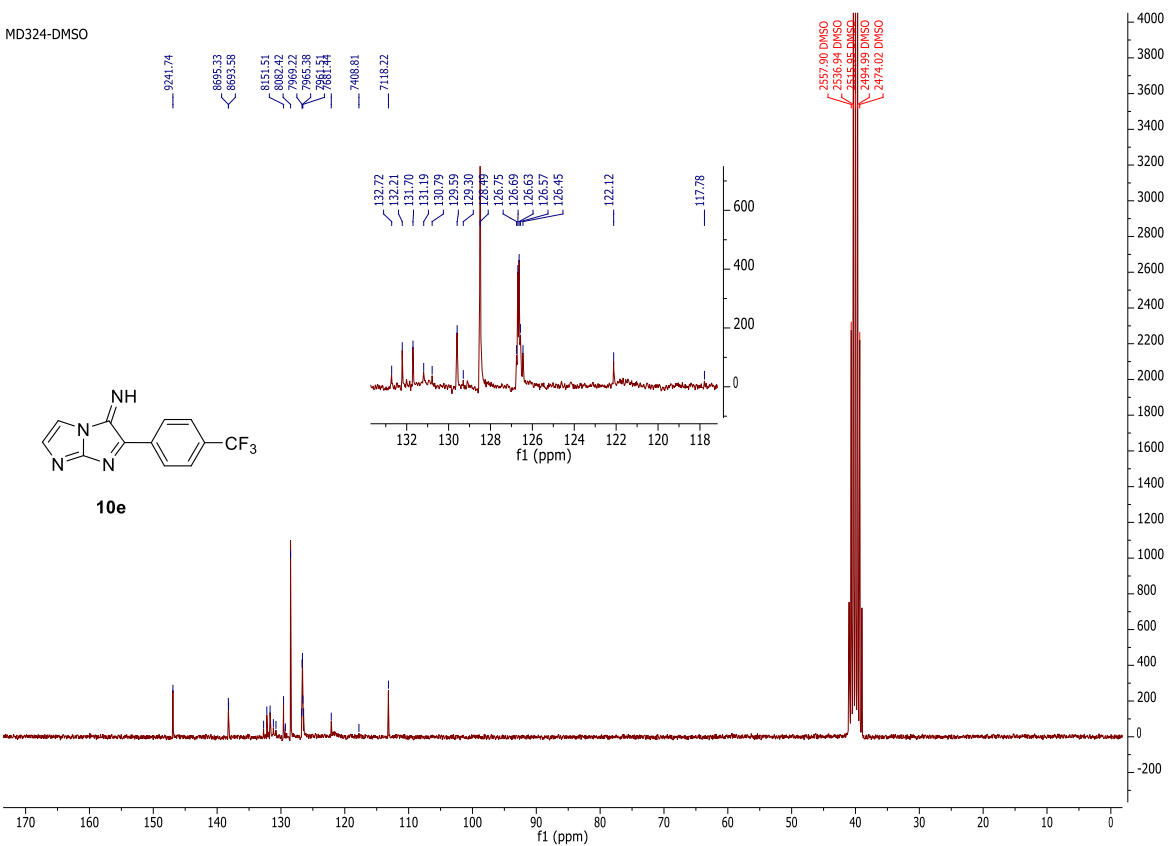
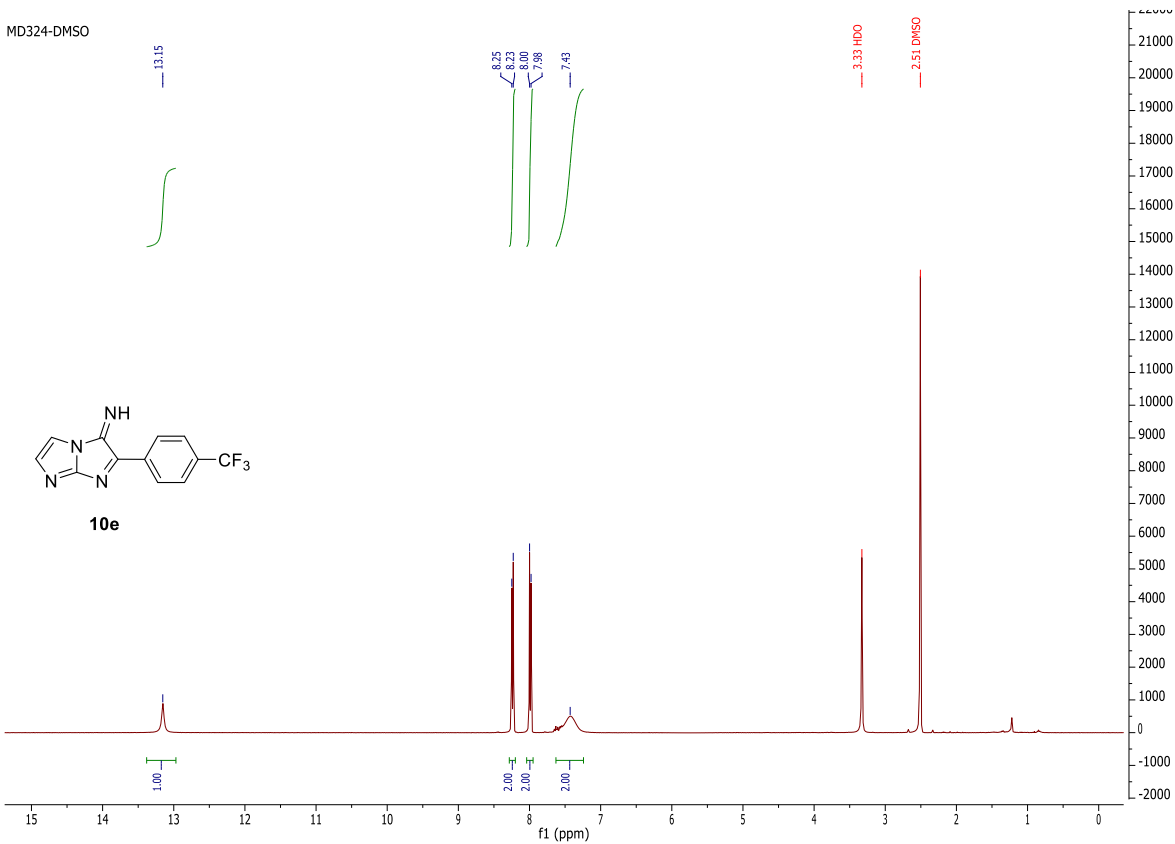


MD154-DMSO

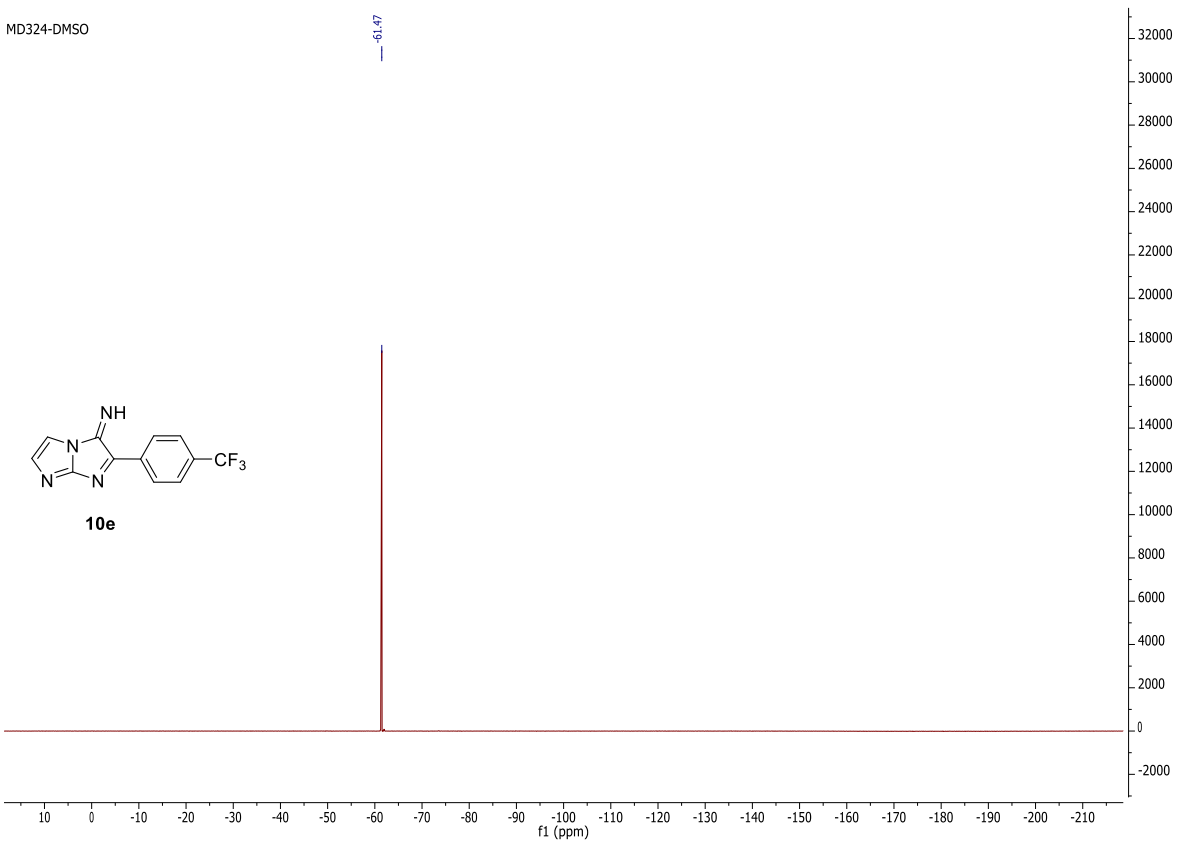


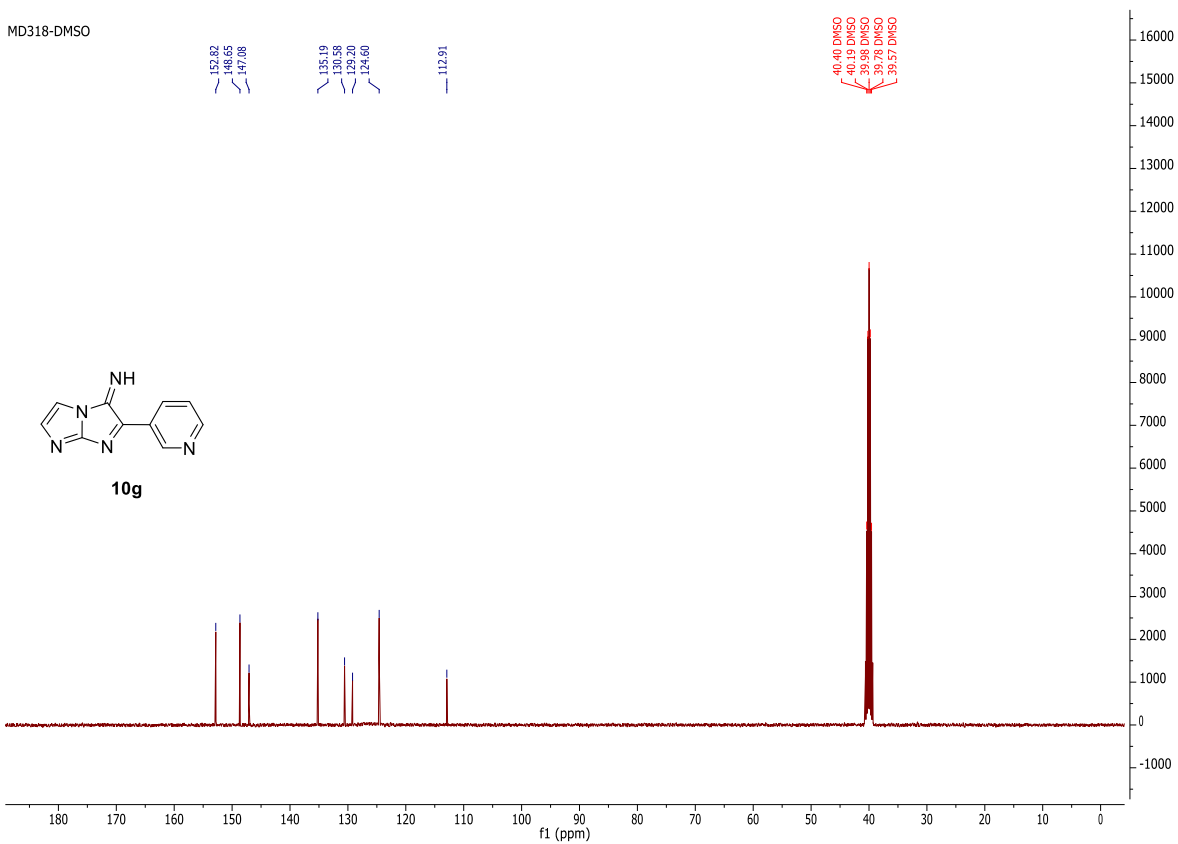
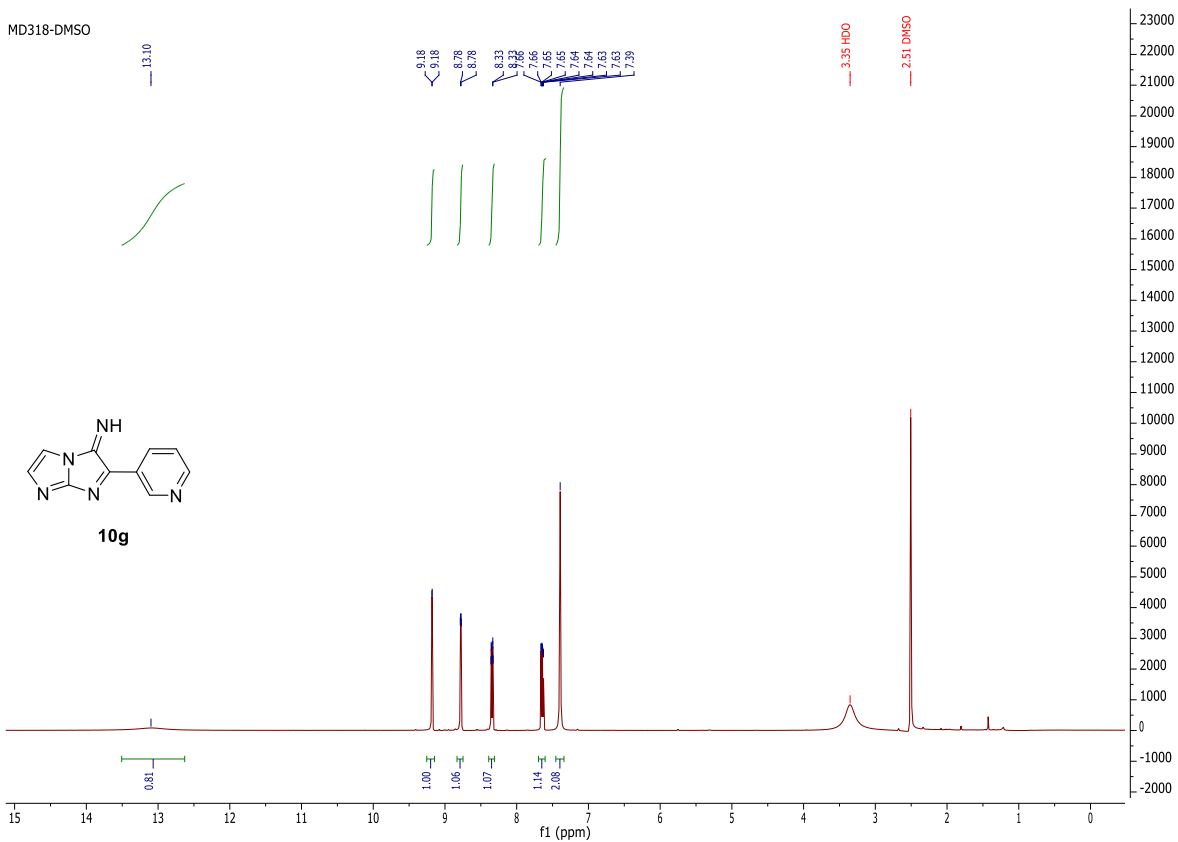
MD154-DMSO





MD324-DMSO





X-ray analysis of compound 4a

Slow evaporation of an ethanol solution of **4a** yielded single crystals suitable for X-ray crystallography.

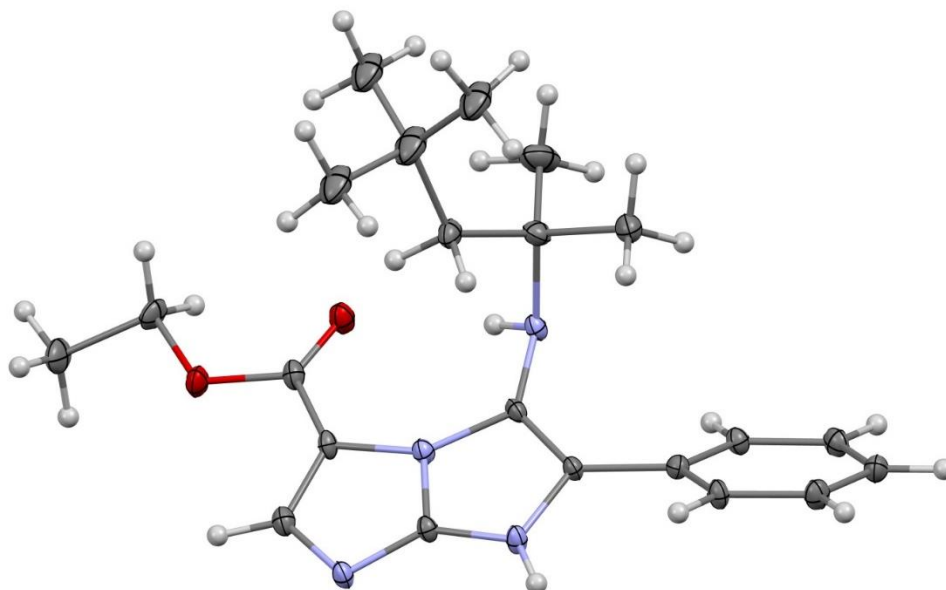


Fig. S01. An ORTEP drawing of compound **4a**. Thermal ellipsoids are shown at the 30% level.

Disorder in *t*-octyl is omitted for clarity.

X-ray diffraction data for compound **4a** was collected by using a VENTURE PHOTON100 CMOS Bruker diffractometer with Micro-focus IuS source Cu K α radiation. Crystals were mounted on a CryoLoop (Hampton Research) with Paratone-N (Hampton Research) as cryoprotectant and then flashfrozen in a nitrogen-gas stream at 100 K. For compounds, the temperature of the crystal was maintained at the selected value by means of a 700 series Cryostream cooling device to within an accuracy of ± 1 K. The data were corrected for Lorentz polarization, and absorption effects. The structures were solved by direct methods using SHELXS-97¹ and refined against F^2 by full-matrix least-squares techniques using SHELXL-2018² with anisotropic displacement parameters for all non-hydrogen atoms. Hydrogen atoms were located on a difference Fourier map and introduced into the calculations as a riding model with isotropic thermal parameters. All calculations were performed by using the Crystal Structure crystallographic software package WINGX.³

The *t*-octyl is disordered over two orientations; the final refined occupancy factors of the two components of disorder are 0.694(4) and 0.306(4).

The crystal data collection and refinement parameters are given in Table S1.

¹ Sheldrick, G. M. SHELXS-97, Program for Crystal Structure Solution, University of Göttingen, Göttingen, Germany, **1997**.

² Sheldrick, G. M. *Acta Crystallogr., Sect. A: Found. Crystallogr.*, **2008**, 64, 112-122.

³ Farrugia, L. J. *J. Appl. Cryst.* **1999**, 32, 837.

CCDC 1916259 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via <http://www.ccdc.cam.ac.uk/Community/Requestastructure>.

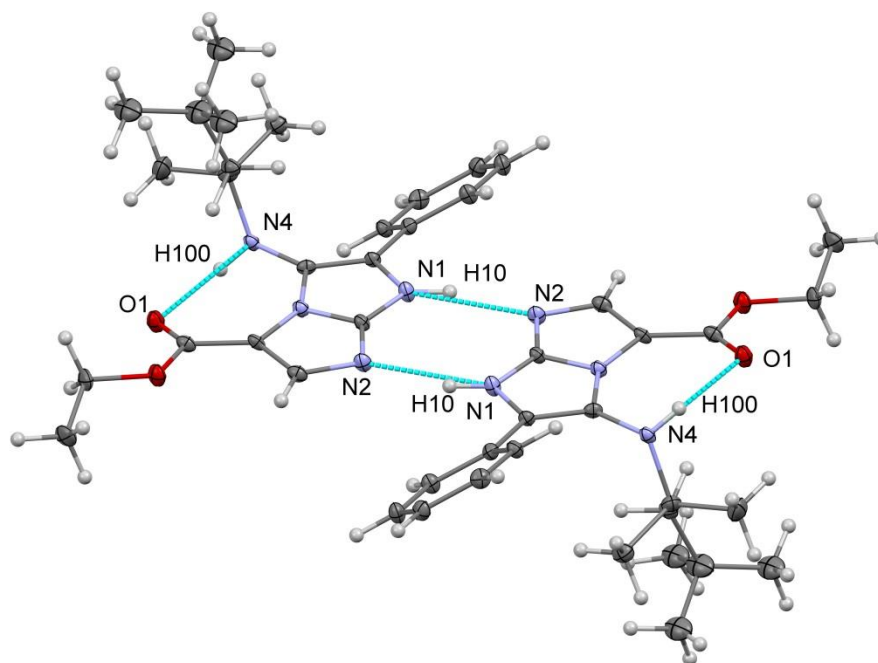


Fig. S02. Part of the crystalline structure of **4a** showing the formation of hydrogen bonds. The intramolecular and intermolecular hydrogen bonds are drawn in blue dashed lines.

The crystal structure of compound **4a** is further stabilized by two N-H...X interactions (table S2).

Table S1. Crystallographic data and structure refinement details.

Compound	4a
Empirical Formula	C ₂₂ H ₃₀ N ₄ O ₂
<i>M_r</i>	382.50
Crystal size, mm ³	0.35 x 0.02 x 0.02
Crystal system	monoclinic
Space group	<i>C</i> 2/ <i>c</i>
<i>a</i> , Å	29.4080(12)
<i>b</i> , Å	6.4911(2)
<i>c</i> , Å	26.8178(9)
α , °	90
β , °	122.192(2)

$\gamma, ^\circ$	90
Cell volume, $\text{\AA}^3$	4332.3(3)
$Z ; Z'$	8 ; 1
T, K	100 (1)
Radiation type ; wavelength $\text{\AA}$	CuK α ; 1.54178
F_{000}	1648
μ, mm^{-1}	0.609
θ range, $^\circ$	3.552 - 59.053
Reflection collected	27 162
Reflections unique	3 114
R_{int}	0.0906
GOF	1.031
Refl. obs. ($I > 2\sigma(I)$)	1 961
Parameters / restraints	257 / 11
w R_2 (all data)	0.1715
R value ($I > 2\sigma(I)$)	0.0657
Largest diff. peak and hole ($\text{e}^- \cdot \text{\AA}^{-3}$)	0.442 ; -0.673

Table S2. Geometric parameters ($\text{\AA}$, degree) for intra- and intermolecular interactions

Donor-H....Acceptor	$D - H$	$H \dots A$	$D \dots A$	$D - H \dots A$
N1-H10...N2 ⁽ⁱ⁾	0.88	1.93	2.7837(1)	162
N4-H100..O1	0.85	2.21	2.9606(1)	149

Symmetry codes: $i = 1-x, -y, -z$