Supporting Information

Ru(II)-catalyzed Regioselective Carbene Insertion to β-Carbolines and Isoquinolines

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Contents

1. General Information

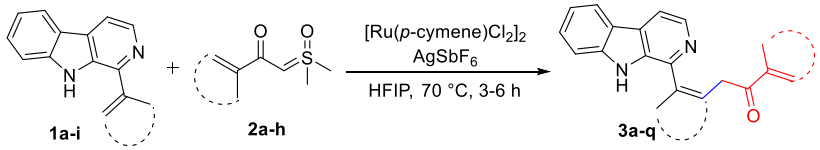
All the chemicals, starting materials, reagents and solvents were procured from commercial sources and were used without further purification. The ^{1}H NMR spectra were recorded on NMR Bruker instrument operated at 500 MHz. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: δ = 7.25 ppm and DMSO-d_6: δ = 2.50 ppm). ^{13}C NMR spectra were recorded on NMR Bruker instrument operated at 125 MHz with complete proton decoupling. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: δ = 77.16 ppm and DMSO-d_6: δ = 39.52 ppm). The following abbreviations were used for ^{1}H NMR spectra to indicate the signal multiplicity: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet) and dt (doublet of triplet). HRMS was measured in ESI-MS mass spectrophotometer. Thin layer chromatography was performed on MERCK precoated silica gel 60F-254 (0.5 mm) aluminum plates and visualized under UV light at 254 nm. Column chromatography was performed using silica gel #60-120 and #100-200 mesh.

2. Synthesis of substrates

2.1. General procedure for synthesis of starting material

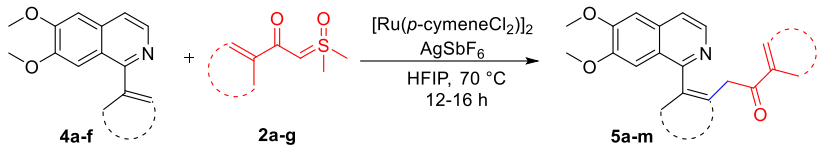
The starting material **1a-i** and **4a-f** were synthesized using the previous literature reports.[1] Similarly, the sulfoxonium ylides (**2a-h**) were prepared using the typical procedure reported in the literature.[2]

2.2. General procedure for acylmethylation of β-carbolines (3a-q)



A pressure tube was charged with [Ru(*p*-cymene)Cl_2]$_2$ (5 mol%), $AgSbF_6$ (20 mol%), substituted β-carbolines (**1**, 70 mg, 1 equiv.), sulfoxonium ylide (**2**, 1.5 equiv.) and HFIP (2 mL). The mixture was stirred at 70 °C for 3-6 h. After reaction completion the solvent was removed under reduced pressure and the crude was subjected to column chromatography to obtain the desired products **3a-q** using 10-20% EA/hexane. All the synthesized compounds were thoroughly characterized by IR, ^{1}H, ^{13}C NMR and HRMS (ESI).

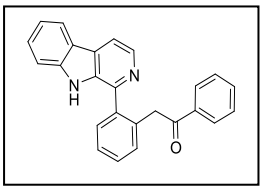
2.3. General procedure for acylmethylation of 3, 4-dimethoxyisoquinolines (5a-m)



A pressure tube was charged with $[Ru(p\text{-cymene})Cl_2]_2$ (5 mol%), $AgSbF_6$ (20 mol%), substituted 3, 4-dimethoxyisoquinolines (**4**, 70 mg, 1 equiv.), sulfoxonium ylide (**2**, 1.5 equiv.) and HFIP (2 mL). The mixture was stirred at 70 °C for 12-16 h. After reaction completion, the solvent was removed under reduced pressure and the crude was subjected to column chromatography to obtain the desired products **5a-m** using 30-40% EA/hexane. All the synthesized compounds were thoroughly characterized by IR, ^1H, ^{13}C NMR and HRMS (ESI).

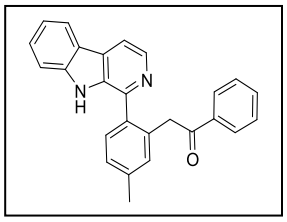
3. Characterization data

2-(2-(9H-Pyrido[3,4-b]indol-1-yl)phenyl)-1-phenylethan-1-one (**3a**). 81% yield (84.1 mg),



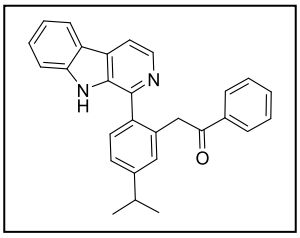
yellow solid, mp: 118-120 °C, FT-IR $(cm)^{-1}$: 3058, 2879, 1751, 1607, 1565; ^1H NMR (500 MHz, DMSO-d_6): δ 11.33 (s, 1H), 8.16 (m, 1H), 7.97 (dd, J = 10.0, 6.4 Hz, 1H), 7.69 (d, J = 7.7 Hz, 3H), 7.60 (d, J = 8.4 Hz, 1H), 7.55 – 7.47 (m, 6H), 7.37 (t, J = 7.5 Hz, 2H), 7.24 (t, J = 7.4 Hz, 1H), 4.53 (s, 2H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ 167.3, 152.2, 148.6, 142.4, 139.4, 135.1, 134.3, 133.2, 132.5, 132.4, 130.1, 129.3, 128.9, 128.2, 127.6, 125.8, 124.6, 114.3, 112.8, 108.7, 108.4, 102.6, 43.2. ppm; HRMS (ESI-QTOF): m/z $[M+H]^+$ calcd. for $C_{25}H_{19}N_2O$ 363.1492 found 363.1491.

2-(2-(9H-Pyrido[3,4-b]indol-1-yl)phenyl)-1-(p-tolyl)ethan-1-one (**3b**). 72% yield (73.4 mg),



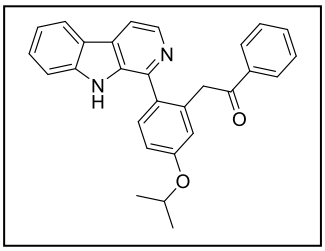
light brown solid, mp: 112-114 °C, FT-IR $(cm)^{-1}$: 2876, 1726, 1678, 1565, 1447; ^1H NMR (500 MHz, DMSO-d_6): δ 11.28 (s, 1H), 8.21 (d, J = 8.3 Hz, 1H), 8.13–8.09 (m, 1H), 7.97 (s, 1H), 7.70–7.67 (m, 2H), 7.57 (dd, J = 23.3, 14.4 Hz, 4H), 7.39–7.28 (m, 4H), 7.28–7.22 (m, 1H), 4.48 (s, 2H), 2.44 (s, 3H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ 197.7, 143.6, 141.4, 137.9, 137.7, 137.2, 135.1, 134.9, 134.3, 133.2, 133.1, 129.9, 128.9, 128.5, 128.2, 128.1, 122.0, 121.3, 119.7, 114.0, 112.8, 43.1, 21.3 ppm; HRMS (ESI-QTOF): m/z $[M+H]^+$ calcd. for $C_{26}H_{21}N_2O$ 377.1648 found 377.1646.

2-(5-Isopropyl-2-(9H-pyrido[3,4-b]indol-1-yl)phenyl)-1-phenylethan-1-one (**3c**). 75% yield



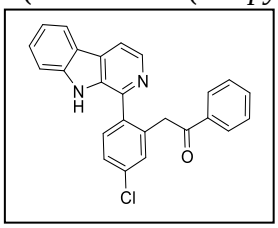
(74.1 mg), yellow solid, mp: 98-100 °C, FT-IR $(cm)^{-1}$: 3059, 2867, 1726, 1625, 1497; ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.30 (s, 1H), 8.20 (d, J = 7.9 Hz, 1H), 8.09 (d, J = 5.2 Hz, 1H), 7.95 (d, J = 5.2 Hz, 1H), 7.71–7.65 (m, 2H), 7.61 (dd, J = 8.0, 3.7 Hz, 3H), 7.55–7.49 (m, 2H), 7.41–7.33 (m, 3H), 7.24 (t, J = 7.4 Hz, 1H), 4.55 (s, 2H), 3.04-2.97 (m, 1H), 1.32 (d, J = 6.9 Hz, 6H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ 197.7, 148.7, 143.7, 141.4, 137.7, 137.3, 135.6, 135.0, 134.2, 133.1, 130.8, 129.9, 129.0, 128.9, 128.4, 128.2, 125.3, 122.0, 121.3, 119.7, 113.9, 112.8, 43.3, 33.8, 24.4 ppm; HRMS (ESI-QTOF): *m/z* $[M+H]^+$ calcd. for $C_{28}H_{25}N_2O$ 405.1961 found 405.1992.

2-(5-Isopropoxy-2-(9H-pyrido[3,4-b]indol-1-yl)phenyl)-1-phenylethan-1-one (**3d**). 79% yield



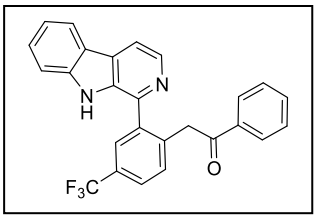
(76.9 mg), yellow solid, mp: 90-92 °C, FT-IR $(cm)^{-1}$: 3058, 2877, 1722, 1678, 1566; ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.29 (s, 1H), 8.20 (d, J = 7.4 Hz, 1H), 8.07 (d, J = 4.1 Hz, 1H), 7.94 (d, J = 4.2 Hz, 1H), 7.71 (d, J = 7.0 Hz, 2H), 7.70-7.59 (m, 2H), 7.53-7.39 (m, 2H), 7.38 (t, J = 6.8 Hz, 2H), 7.26–7.22 (m, 1H), 7.04 (s, 2H), 4.74–4.72 (m, 1H), 4.49 (s, 2H), 1.36 (d, J = 5.3 Hz, 6H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ 197.5, 157.7, 143.54, 141.4, 137.6, 137.2, 136.7, 134.3, 133.2, 131.2, 128.9, 128.4, 128.2, 122.0, 121.3, 119.73, 114.0, 113.7, 112.8, 69.7, 43.3, 22.4 ppm; HRMS (ESI-QTOF): *m/z* $[M+H]^+$ calcd. for $C_{28}H_{25}N_2O_2$ 421.1911 found 421.1924.

2-(5-Chloro-2-(9H-pyrido[3,4-b]indol-1-yl)phenyl)-1-phenylethan-1-one (**3e**). 66% yield (65.8

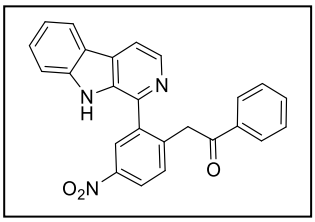


mg), yellow solid, mp: 95-97 °C, FT-IR $(cm)^{-1}$: 3057, 2868, 1722, 1677, 1566; ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.37 (s, 1H), 8.21 (d, J = 6.9 Hz, 1H), 8.08 (d, J = 2.7 Hz, 1H), 8.07-7.95 (m, 1H), 7.71-7.69 (m, 2H), 7.61-7.58 (m, 6H), 7.54-7.39 (m, 2H), 7.26-7.22 (m, 1H), 4.56 (s, 2H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ 197.0, 142.3, 141.5, 137.8, 137.7, 137.0, 136.8, 133.3, 133.1, 132.4, 131.7, 129.7, 129.2, 129.0, 129.0, 128.6, 128.2, 127.4, 122.1, 121.2, 119.9, 114.4, 112.7, 42.8 ppm. HRMS (ESI-QTOF): *m/z* $[M+H]^+$ calcd. for $C_{25}H_{18}N_2O$ 397.1102 found 397.1080.

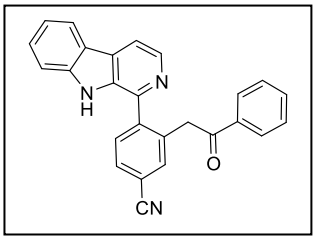
2-(2-(9H-Pyrido[3,4-b]indol-1-yl)-6-(trifluoromethyl)phenyl)-1-phenylethan-1-one (**3f**). 70% yield (67.5 mg), yellow solid, mp: 140-143 °C, FT-IR (cm)$^{-1}$: 3368, 2876, 1730, 1625, 1563; ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.52 (s, 1H), 8.23 (d, J = 7.8 Hz, 1H), 8.14 (d, J = 5.1 Hz, 1H), 8.03 (d, J = 5.1 Hz, 1H), 7.92 (s, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.76 (d, J = 7.9 Hz, 1H), 7.68 (d, J = 7.7 Hz, 2H), 7.60 –7.52 (m, 3H), 7.38 (t, J = 7.6 Hz, 2H), 7.26 (t, J = 7.3 Hz, 1H), 4.63 (s, 2H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ 196.9, 141.9, 141.5, 140.0, 138.9, 137.9, 136.9, 134.3, 133.6, 133.4, 129.4, 129.0, 128.7, 128.2, 126.5 (q, J = 3.3 Hz), 125.5, 125.4 (q, J = 4.2), 124.7 (q, J = 270.0), 122.2, 121.2, 119.9, 114.7, 112.7, 43.0 ppm; ^{19}F NMR (470 MHz, DMSO-d_6): δ -60.7 ppm; HRMS (ESI-QTOF): *m/z* $[M+H]^+$ calcd. for $C_{26}H_{18}F_3N_2O$ 431.1366 found 431.1370.



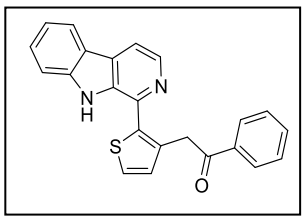
2-(2-Nitro-6-(9H-pyrido[3,4-b]indol-1-yl)phenyl)-1-phenylethan-1-one **(3g)**. 60% yield, (59.1mg), yellow solid, mp: 148-150 °C, FT-IR (cm)$^{-1}$: 2878, 2239, 1734, 1679, 1566; ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.57 (s, 1H), 8.47 (s, 1H), 8.39 (d, J = 8.4 Hz, 1H), 8.24 (d, J = 7.8 Hz, 1H), 8.10 (d, J = 5.0 Hz, 1H), 8.04 (d, J = 5.0 Hz, 1H), 7.82 (d, J = 8.4 Hz, 1H), 7.73 (d, J = 7.5 Hz, 2H), 7.58–7.43 (m, 3H), 7.41 (t, J = 7.5 Hz, 2H), 7.28–7.26 (m, 1H), 4.75 (s, 2H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ 196.5, 147.0, 143.4, 141.4, 141.0, 138.9, 137.8, 136.8, 134.3, 133.4, 129.5, 129.0, 128.9, 128.2, 124.8, 123.3, 122.25, 121.2, 120.0, 114.9, 112.6, 43.2 ppm; HRMS (ESI-QTOF): *m/z* $[M+H]^+$ calcd. for $C_{25}H_{18}N_3O_3$ 408.1343 found 408.1338.



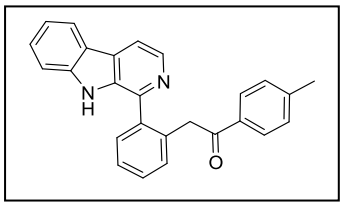
3-(2-Oxo-2-phenylethyl)-4-(9H-pyrido[3,4-b]indol-1-yl)benzonitrile (**3h**). 63% yield (63.4 mg), yellow solid, mp: 94-96 °C, FT-IR (cm)$^{-1}$: 3058, 2868, 2229, 1726, 1679; ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.46 (s, 1H), 8.22 (d, J = 7.8 Hz, 1H), 8.08 (d, J = 5.2 Hz, 1H), 8.04–7.98 (m, 3H), 7.90 (d, J = 7.9 Hz, 1H), 7.74–7.69 (m, 2H), 7.57 (ddd, J = 9.9, 4.7, 2.1 Hz, 3H), 7.41 (t, J = 7.7 Hz, 2H), 7.26 (ddd, J = 7.9, 6.7, 1.3 Hz, 1H), 4.64 (s, 2H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ 196.7, 142.6, 141.6, 141.5, 137.8, 137.0, 136.9, 136.3, 134.2, 133.4, 131.4, 131.0, 129.5, 129.00, 128.8, 128.1, 122.5, 121.1, 119.9, 119.3, 114.9, 112.7, 111.1, 42.7 ppm; HRMS (ESI-QTOF): *m/z* $[M+H]^+$ calcd. for $C_{26}H_{18}F_3N_2O$ 388.1444 found 388.1437.



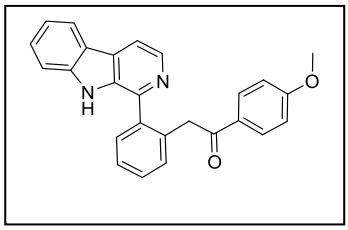
2-(2-(9H-pyrido[3,4-b]indol-1-yl)thiophen-3-yl)-1-phenylethan-1-one **(3i)**. 70% yield (72.1 mg), yellow solid, mp: 210-212 °C, FT-IR (cm)$^{-1}$: 3058, 2868, 1718, 1683, 1624; ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.37 (s, 1H), 8.26 (d, J = 7.0 Hz, 2H), 8.09 (d, J = 4.1 Hz, 1H), 7.84 (d, J = 7.0 Hz, 2H), 7.78 (d, J = 4.3 Hz, 1H), 7.67 (d, J = 7.8 Hz, 1H), 7.56 (s, 2H), 7.44-7.42 (m, 2H), 7.28 (t, J = 6.9 Hz, 1H), 7.21 (d, J = 4.1 Hz, 1H), 4.61 (s, 2H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ 197.4, 141.4, 138.4, 137.2, 137.0, 135.5, 134.6, 134.1, 133.4, 131.4, 129.5, 129.0, 128.8, 128.4, 126.2, 125.6, 122.1, 121.3, 120.1, 114.5, 113.0, 46.0 ppm; HRMS (ESI-QTOF): *m/z* $[M+H]^+$ calcd. for $C_{23}H_{17}N_2OS$ 369.1056 found 369.1114.



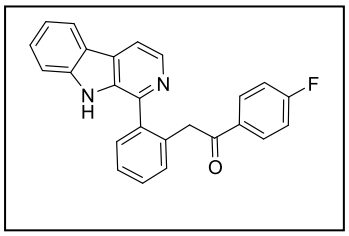
2-(2-(9H-pyrido[3,4-b]indol-1-yl)phenyl)-1-(m-tolyl)ethan-1-one **(3j)**. 68% yield (73.3 mg), yellow solid, mp: 115-118°C, FT-IR (cm)$^{-1}$: 3062, 1672, 1615, 1543, 1458; ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.29 (s, 1H), 8.22 (d, J = 7.9 Hz, 1H), 8.15 (d, J = 5.2 Hz, 1H), 7.99 (d, J = 5.2 Hz, 1H), 7.65 (s, 2H), 7.58-7.55 (m, 4H), 7.52–7.47 (m, 3H), 7.24 (t, J = 7.4 Hz, 1H), 7.14 (d, J = 7.8 Hz, 1H), 4.49 (s, 2H), 2.28 (s, 3H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ 197.2, 143.5, 141.4, 137.6, 135.1, 134.5, 134.2, 132.4, 130.0, 129.8, 129.6, 129.4, 129.1, 128.7, 128.5, 128.3, 127.5, 122.0, 121.2, 119.8, 114.1, 112.77, 43.0, 21.4 ppm; HRMS (ESI-QTOF): *m/z* $[M+H]^+$ calcd. for $C_{26}H_{21}N_2O$ 377.1648 found 377.1643.



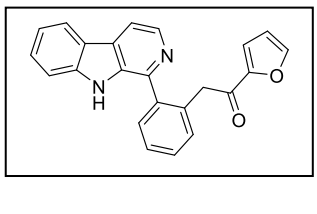
2-(2-(9H-pyrido[3,4-b]indol-1-yl)phenyl)-1-(4-methoxyphenyl)ethan-1-one (**3k**). 72% yield (80.9 mg), yellow solid, mp: 98-100 °C, FT-IR (cm)$^{-1}$: 3057, 2877, 2743, 1718, 1677; ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.28 (s, 1H), 8.28 – 8.16 (m, 2H), 8.01 (s, 1H), 7.69–7.57 (m, 4H), 7.54-7.48 (m, 4H), 7.25 (d, J = 8.0 Hz, 1H), 6.83 (d, J = 8.2 Hz, 2H), 4.46 (s, 2H), 3.75 (s, 3H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ 196.0, 163.2, 143.6, 141.4, 138.0, 137.8, 135.2, 134.3, 132.2, 131.1, 130.5, 130.0, 129.9, 129.04, 128.6, 128.4, 127.4, 122.0, 121.2, 119.7, 114.1, 114.0, 112.7, 55.8, 42.6 ppm; HRMS (ESI-QTOF): *m/z* $[M+H]^+$ calcd. for $C_{26}H_{21}N_2O_2$ 393.1598 found 393.1652.



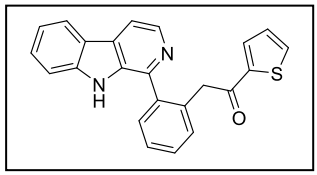
2-(2-(9H-pyrido[3,4-b]indol-1-yl)phenyl)-1-(3-fluorophenyl)ethan-1-one (**3l**). 63% yield (68.6 mg), yellow solid, mp: 98-100 °C, FT-IR (cm)$^{-1}$: 2868, 1712, 1682, 1596, 1477; ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.33 (s, 1H), 8.23 (s, 1H), 8.11 (s, 1H), 8.00 (s, 1H), 7.80 (s, 2H), 7.73–7.68 (m, 1H), 7.61-7.53 (m, 4H), 7.26-7.20 (m, 4H), 4.52 (s, 2H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ 196.2, 141.4, 137.9, 137.7, 135.0, 134.3, 133.8 (d, J = 2.3 Hz), 132.6, 131.2, 131.1 (d, $J_{C\text{-}F}$ = 9.1 Hz), 130.0, 129.1, 128.7, 128.5, 127.6, 122.0, 121.3, 119.8, 115.9, 115.8 (d, $J_{C\text{-}F}$ = 21.8 Hz), 114.1, 112.8, 43.2 ppm; ^{19}F NMR (470 MHz, DMSO-d_6): δ -106.7 ppm; HRMS (ESI-QTOF): *m/z* [M+H]$^+$ calcd. for $C_{25}H_{18}FN_2O$ 381.1398 found 381.1378.



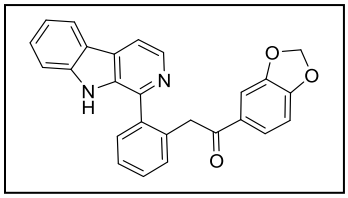
2-(2-(9H-pyrido[3,4-b]indol-1-yl)phenyl)-1-(furan-3-yl)ethan-1-one (**3m**). 69% yield (69.6 mg), yellow solid, mp: 126-128 °C, FT-IR (cm)$^{-1}$: 3062, 2225, 1728, 1543, 1458; ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.29 (s, 1H), 8.27 (s, 1H), 8.23 (d, J = 5.5 Hz, 2H), 8.03 (d, J = 5.2 Hz, 1H), 7.65 (d, J = 6.0 Hz, 2H), 7.59 (d, J = 8.1 Hz, 1H), 7.55–7.48 (m, 4H), 7.25 (t, J = 7.4 Hz, 1H), 6.55 (s, 1H), 4.32 (s, 2H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ 192.2, 149.0, 145.1, 143.6, 141.4, 138.1, 137.8, 134.6, 134.3, 132.4, 130.0, 129.1, 128.7, 128.5, 127.6, 127.4, 122.0, 121.3, 119.8, 114.2, 112.8, 108.8, 44.7 ppm; HRMS (ESI-QTOF): *m/z* [M+H]$^+$ calcd. for $C_{23}H_{17}N_2O_2$ 353.1285 found 353.1280.



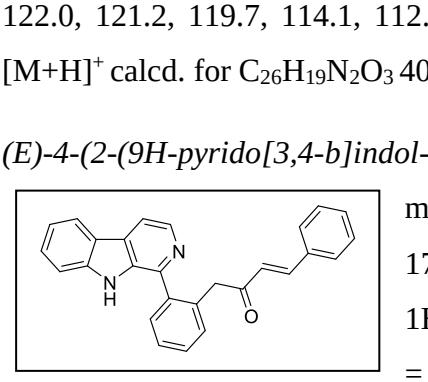
2-(2-(9H-pyrido[3,4-b]indol-1-yl)phenyl)-1-(thiophen-2-yl)ethan-1-one (**3n**). 62% yield (65.4 mg), yellow solid, mp: 120-122 °C, FT-IR (cm)$^{-1}$: 3057, 2867, 1734, 1624, 1497; ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.30 (s, 1H), 8.22 (d, J = 7.9 Hz, 1H), 8.18 (d, J = 5.2 Hz, 1H), 8.01 (d, J = 5.2 Hz, 1H), 7.85 (d, J = 4.9 Hz, 1H), 7.66 (dd, J = 6.8, 2.5 Hz, 1H), 7.62–7.60 (m, 1H), 7.58 (s, 1H), 7.52 (dd, J = 13.0, 5.2 Hz, 4H), 7.25 (t, J = 7.4 Hz, 1H), 7.09–7.06 (m, 1H), 4.46 (s, 2H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ 190.6, 144.0, 143.5, 141.5, 138.1, 137.8, 134.8, 134.6, 134.3, 133.2, 132.5, 130.1, 129.1, 128.8, 128.7, 128.5, 127.7, 122.0, 121.3, 119.8, 114.2, 112.8, 43.5 ppm; HRMS (ESI-QTOF): *m/z* [M+H]$^+$ calcd. for $C_{23}H_{17}N_2OS$ 369.1056 found 369.1050.



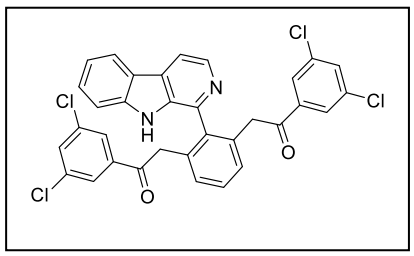
2-(2-(9H-pyrido[3,4-b]indol-1-yl)phenyl)-1-(benzo[d][1,3]dioxol-5-yl)ethan-1-one **(3o)**. 73% yield (85.0 mg), yellow solid, mp: 115-117 °C, FT-IR $(cm)^{-1}$: 3057, 2870, 1726, 1620, 1562; ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.20 (s, 1H), 8.27–8.19 (m, 2H), 8.01 (s, 1H), 7.64–7.53 (m, 2H), 7.50-7.47 (m, 4H), 7.34–7.22 (m, 2H), 7.13 (s, 1H), 6.82 (d, J = 7.9 Hz, 1H), 6.03 (s, 2H), 4.42 (s, 2H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ 195.7, 151.4, 148.0, 143.6, 141.4, 137.9, 137.7, 135.2, 134.3, 132.3, 131.6, 130.0, 129.0, 128.6, 128.4, 127.4, 124.55, 122.0, 121.2, 119.7, 114.1, 112.7, 108.2, 107.7, 102.3, 42.8 ppm; HRMS (ESI-QTOF): *m/z* $[M+H]^+$ calcd. for $C_{26}H_{19}N_2O_3$ 407.1390 found 407.1405.

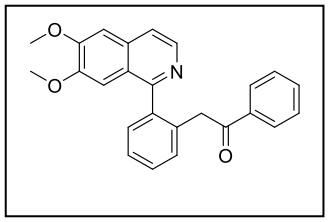


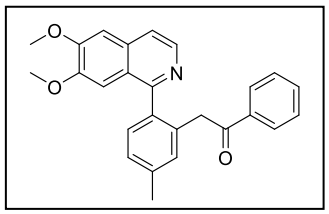
(E)-4-(2-(9H-pyrido[3,4-b]indol-1-yl)phenyl)-1-phenylbut-2-en-1-one **(3p)**. 80% yield (89.0 mg), yellow solid, mp: 128-130 °C, FT-IR $(cm)^{-1}$: 2878, 2239, 1734, 1679, 1566; ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.36 (s, 1H), 8.37 (d, J = 5.2 Hz, 1H), 8.25 (d, J = 7.9 Hz, 1H), 8.09 (d, J = 5.2 Hz, 1H), 7.65 (dd, J = 5.7, 3.1 Hz, 1H), 7.58 (d, J = 8.1 Hz, 1H), 7.55 (d, J = 7.7 Hz, 1H), 7.53–7.47 (m, 3H), 7.41 (d, J = 7.2 Hz, 2H), 7.35 (t, J = 7.3 Hz, 1H), 7.28-7.24 (m, 4H), 6.59 (d, J = 16.2 Hz, 1H), 4.17 (s, 2H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ 197.1, 143.7, 142.2, 141.5, 138.1, 138.0, 134.8, 134.6, 134.4, 132.2, 130.8, 130.2, 129.3, 129.1, 128.9, 128.6, 128.5, 127.6, 126.2, 122.1, 121.3, 119.8, 114.3, 112.8, 45.3 ppm; HRMS (ESI-QTOF): *m/z* $[M+H]^+$ calcd. for $C_{27}H_{21}N_2O$ 389.1648 found 389.1652.

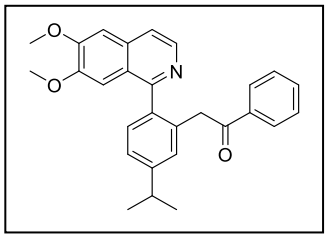


2,2'-(2-(9H-pyrido[3,4-b]indol-1-yl)-1,3-phenylene)bis(1-(3,5-dichlorophenyl)ethan-1-one) (**3q**). 68% yield (120.17 mg), yellow solid, mp: 208-210 °C, FT-IR $(cm)^{-1}$: 3068, 2867, 1714, 1563, 1478; ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.94 (s, 1H), 8.17 (d, J = 5.2 Hz, 1H), 8.11 (d, J = 7.9 Hz, 1H), 7.89 (d, J = 5.2 Hz, 1H), 7.59 (t, J = 1.7 Hz, 2H), 7.52–7.46 (m, 3H), 7.43 (d, J = 7.6 Hz, 2H), 7.21 (d, J = 1.8 Hz, 5H), 4.13 (d, J = 15.9 Hz, 2H), 3.95 (d, J = 15.9 Hz, 2H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ 195.8, 141.8, 141.4, 139.5, 138.1, 135.3, 134.9, 134.7, 132.1, 130.4, 129.0, 128.9, 128.5, 126.5, 122.1, 122.0, 121.0, 120.5, 119.8, 117.3, 116.6, 114.6, 113.8, 113.5, 112.6, 43.1 ppm; HRMS (ESI-QTOF): *m/z* $[M+H]^+$ calcd. for $C_{33}H_{21}Cl_4N_2O_2$ 617.0352 found 617.0339.

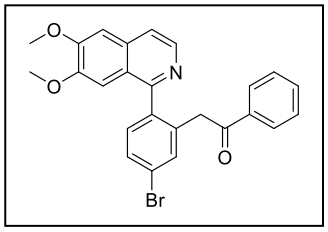


2-(2-(6,7-Dimethoxyisoquinolin-1-yl)phenyl)-1-phenylethan-1-one **(5a)** 76% yield (76.8 mg), 
buff-white solid, mp: 127-129 °C, FT-IR (cm)$^{-1}$: 3058, 2868, 1729, 1618, 1558; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.24 (d, J = 5.2 Hz, 1H), 7.58 (d, J = 6.6 Hz, 3H), 7.49-7.43 (m, 4H), 7.37-7.34 (m, 1H), 7.33 (d, J = 9.0 Hz, 3H), 6.82 (s, 1H), 4.20 (s, 2H), 3.90 (s, 3H), 3.65 (s, 3H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ 197.5, 157.6, 152.9, 150.0, 140.9, 139.7, 136.9, 134.5, 133.4, 133.2, 132.1, 130.1, 128.8, 128.5, 128.0, 126.9, 123.2, 119.3, 105.71, 105.2, 56.1, 55.5, 42.9 ppm; HRMS (ESI-QTOF): *m/z* $[M+H]^+$ calcd. for $C_{25}H_{22}NO_3$ 384.1592 found 384.1617.

2-(2-(6,7-Dimethoxyisoquinolin-1-yl)-5-methylphenyl)-1-phenylethan-1-one **(5b)**. 75% yield 
(74.7 mg), buff-white solid, mp: 135-138 °C, FT-IR (cm)$^{-1}$: 3057, 2818, 1700, 1565, 1625; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.22 (s, 1H), 7.58 (d, J = 8.3 Hz, 3H), 7.49 (d, J = 7.2Hz, 1H), 7.32 (s, 3H), 7.26 (s, 3H), 6.86 (s, 1H), 4.17 (s, 2H), 3.90 (s, 3H), 3.66 (s, 3H), 2.42 (s, 3H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ 197.6, 157.7, 152.8, 150.0, 140.9, 137.6, 137.0, 136.9, 134.4, 133.3, 133.2, 132.7, 130.1, 128.8, 128.1, 127.5, 123.2, 119.1, 105.7, 105.3, 56.18, 55.6, 42.9, 21.3 ppm; HRMS (ESI-QTOF): *m/z* $[M+H]^+$ calcd. for $C_{26}H_{24}NO_3$ 398.1751 found 398.1770.

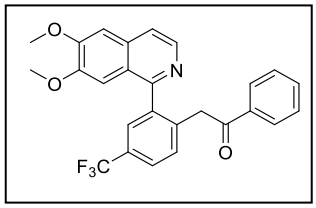
2-(2-(6,7-Dimethoxyisoquinolin-1-yl)-5-isopropylphenyl)-1-phenylethan-1-one **(5c)**. 78% yield 
(75.5 mg), buff-white solid, mp: 155-158 °C, FT-IR (cm)$^{-1}$: 3006, 2868, 2324, 1616, 1558; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.19 (s, 1H), 7.58 (d, J = 7.8 Hz, 3H), 7.50 (d, J = 7.9 Hz, 1H), 7.32 (d, J = 15.4 Hz, 6H), 6.89 (s, 1H), 4.22 (s, 2H), 3.91 (s, 3H), 3.66 (s, 3H), 3.00 (s, 1H), 1.29 (s, 6H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ 197.7, 157.8, 152.9, 150.0, 148.4, 140.9, 137.4, 137.1, 134.5, 133.4, 133.2, 130.2, 128.9, 128.1, 124.7, 123.2, 119.1, 105.8, 105.5, 56.2, 55.7, 43.2, 33.6, 24.3 ppm; HRMS (ESI-QTOF): *m/z* $[M+H]^+$ calcd. for $C_{28}H_{28}NO_3$ 426.2064 found 426.2070.

2-(5-Bromo-2-(6,7-dimethoxyisoquinolin-1-yl)phenyl)-1-phenylethan-1-one **(5d)**. 68% yield



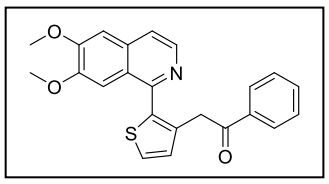
(63.7 mg), buff-white solid, mp: 143-145 °C, FT-IR $(cm)^{-1}$: 3007, 2877, 1730, 1560, 1413; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.21 (d, J = 4.1 Hz, 1H), 7.72 (s, 1H), 7.64 (d, J = 7.2 Hz, 1H), 7.59-7.56 (m, 3H), 7.54-7.52 (m, 1H), 7.36-7.35 (m, 4H), 6.81 (s, 1H), 4.24 (s, 2H), 3.90 (s, 3H), 3.70 (s, 3H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ 197.1, 156.4, 153.0, 150.2, 140.9, 139.1, 137.4, 136.7, 135.0, 133.5, 133.4, 132.2, 129.9, 129.0, 128.1, 123.0, 121.6, 119.5, 105.8, 104.9, 56.2, 55.7, 42.5 ppm; HRMS (ESI-QTOF): *m/z* $[M+H]^+$ calcd. for $C_{25}H_{21}BrNO_3$ 462.0699 found 462.0706.

2-(2-(6,7-Dimethoxyisoquinolin-1-yl)-6-(trifluoromethyl)phenyl)-1-phenylethan-1-one (**5e**).



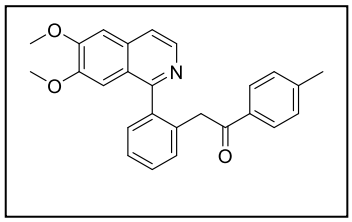
65% yield (61.6mg), buff-white solid, mp: 155-158 °C, FT-IR $(cm)^{-1}$: 2997, 1619, 1597, 1476, 1307; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.25 (d, J = 5.5 Hz, 1H), 7.89 (d, J = 7.9 Hz, 1H), 7.71–7.64 (m, 2H), 7.62-7.60 (m, 3H), 7.54 (t, J = 7.3 Hz, 1H), 7.38-7.35 (m, 3H), 6.75 (s, 1H), 4.33 (s, 2H), 3.90 (s, 3H), 3.67 (s, 3H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ 197.0, 155.9, 153.0, 150.4, 141.1, 140.7, 139.6, 136.7, 133.6, 133.5, 133.5, 129.0, 128.1, 126.8, 126.7 (q, J = 3.7), 125.2, 125.1 (q, J = 3.6), 124.7 (q, J = 271.1), 123.0, 119.8, 105.9, 104.6, 56.3, 55.6, 42.8 ppm; ^{19}F NMR (470 MHz, DMSO-d_6): δ -60.8 ppm HRMS (ESI-QTOF): *m/z* $[M+H]^+$ calcd. for $C_{26}H_{21}F_3NO_3$ 452.1468 found 452.1457.

2-(2-(6,7-Dimethoxyisoquinolin-1-yl)thiophen-3-yl)-1-phenylethan-1-one (**5f**). 70% yield (70.3



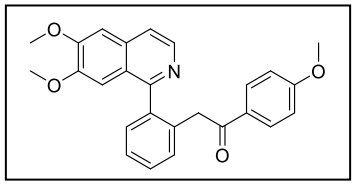
mg), buff-white solid, mp: 150-153 °C, FT-IR $(cm)^{-1}$: 3167, 2278, 1738, 1566, 1424; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.35 (s, 1H), 7.80 (s, 2H), 7.71 (d, J = 19.3 Hz, 2H), 7.58 (s, 1H), 7.41 (s, 3H), 7.15 (s, 2H), 4.26 (s, 2H), 3.92 (s, 3H), 3.73 (s, 3H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ 197.5, 153.1, 150.7, 141.4, 137.3, 136.7, 134.2, 133.7, 133.6, 130.8, 129.1, 128.4, 126.5, 123.7, 119.9, 106.0, 104.6, 56.3, 55.7 ppm; HRMS (ESI-QTOF): *m/z* $[M+H]^+$ calcd. for $C_{23}H_{20}NO_3S$ 390.1158 found 390.1164.

2-(2-(6,7-Dimethoxyisoquinolin-1-yl)phenyl)-1-(p-tolyl)ethan-1-one (**5g**). 71% yield (74.4 mg),



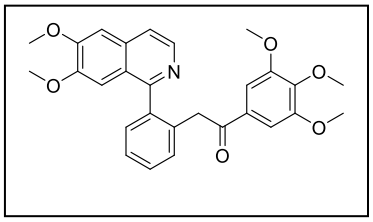
buff-white solid, mp: 130-132 °C, FT-IR (cm)$^{-1}$: 2999, 2323, 1747, 1559, 1456; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.26 (d, J = 5.5 Hz, 1H), 7.60 (d, J = 5.6 Hz, 1H), 7.50–7.41 (m, 5H), 7.36–7.32 (m, 2H), 7.11 (d, J = 8.0 Hz, 2H), 6.77 (s, 1H), 4.15 (s, 2H), 3.90 (s, 3H), 3.63 (s, 3H), 2.28 (s, 3H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ 197.1, 157.7, 152.8, 150.0, 143.6, 140.9, 139.8, 134.6, 134.4, 133.3, 132.1, 130.1, 129.4, 128.5, 128.23, 126.8, 123.22, 119.2, 105.7, 105.2, 56.2, 55.5, 42.8, 21.4 ppm; HRMS (ESI-QTOF): *m/z* [M+H]$^{+}$ calcd. for $C_{26}H_{24}NO_3$ 398.1751 found 398.1747.

2-(2-(6,7-Dimethoxyisoquinolin-1-yl)phenyl)-1-(4-methoxyphenyl)ethan-1-one (**5h**). 72% yield



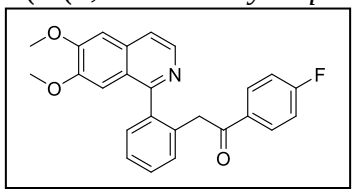
(78.5 mg), buff-white solid, mp: 150-153 °C, FT-IR (cm)$^{-1}$: 3128, 2289, 1718, 1656, 1545; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.28 (d, J = 5.5 Hz, 1H), 7.61 (d, J = 5.5 Hz, 1H), 7.54 (d, J = 8.7 Hz, 2H), 7.51–7.46 (m, 1H), 7.45–7.40 (m, 2H), 7.34 (d, J = 6.9 Hz, 2H), 6.83 (d, J = 8.8 Hz, 2H), 6.77 (s, 1H), 4.11 (s, 2H), 3.91 (s, 3H), 3.77 (s, 3H), 3.63 (s, 3H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ 196.1, 163.3, 157.8, 152.9, 150.0, 140.9, 139.7, 134.73, 133.4, 132.0, 130.4, 130.1, 129.7, 128.6, 126.9, 123.2, 119.4, 114.0, 105.7, 105.2, 56.2, 55.8, 55.5, 42.5 ppm; HRMS (ESI-QTOF): *m/z* [M+H]$^{+}$ calcd. for $C_{26}H_{24}NO_4$ 414.1700 found 414.1700.

2-(2-(6,7-Dimethoxyisoquinolin-1-yl)phenyl)-1-(3,4,5-trimethoxyphenyl)ethan-1-one (**5i**). 69%



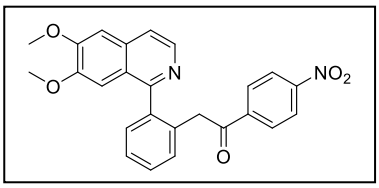
yield (86.2 mg), buff-white solid, mp: 166-169 °C, FT-IR (cm)$^{-1}$: 3123, 2688, 1720, 1688, 1567; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.30 (d, J = 5.2 Hz, 1H), 7.59 (d, J = 5.1 Hz, 1H), 7.49 (s, 2H), 7.44 (d, J = 5.6 Hz, 1H), 7.35 (d, J = 7.2 Hz, 1H), 7.30 (s, 1H), 6.77 (s, 2H), 6.68 (s, 1H), 4.15 (d, J = 16.4 Hz, 2H), 3.89 (s, 3H), 3.68 (s, 9H), 3.61 (s, 3H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ 196.8, 157.6, 152.8, 152.7, 150.0, 141.8, 140.9, 139.6, 135.0, 133.3, 132.2, 131.9, 130.1, 128.7, 126.9, 123.2, 119.3, 105.6, 105.1, 60.4, 56.2, 56.1, 55.4, 42.8 ppm; HRMS (ESI-QTOF): *m/z* [M+H]$^{+}$ calcd. for $C_{28}H_{28}NO_6$ 474.1911 found 474.1904.

2-(2-(6,7-Dimethoxyisoquinolin-1-yl)phenyl)-1-(4-fluorophenyl)ethan-1-one **(5j)**. 65% yield



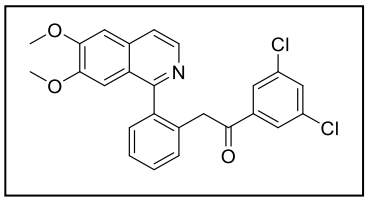
(68.8 mg), buff-white solid, mp: 125-128 °C, FT-IR (cm)$^{-1}$: 3474, 2868, 1730, 1618, 1559; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.22 (d, J = 5.6 Hz, 1H), 7.66–7.62 (m, 2H), 7.58 (d, J = 5.5 Hz, 1H), 7.52–7.42 (m, 3H), 7.37 (dd, J = 7.4, 0.9 Hz, 1H), 7.33 (s, 1H), 7.15 (t, J = 8.8 Hz, 2H), 6.78 (s, 1H), 4.18 (s, 2H), 3.91 (s, 3H), 3.64 (s, 3H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ 196.2, 166.2, 164.2, 157.6, 152.9, 150.0, 140.9, 139.7, 134.5, 133.4, 132.3, 131.1 (d, $J_{C\text{-}F}$ = 9.6 Hz), 131.0, 130.1, 128.6, 127.0, 123.2, 119.3, 115.9, 115.8 (d, $J_{C\text{-}F}$ = 21.9 Hz), 105.7, 105.2, 56.2, 55.6, 42.9 ppm; ^{19}F NMR (470 MHz, DMSO-d_6): δ -106.5 ppm; HRMS (ESI-QTOF): *m/z* [M+H]$^{+}$ calcd. for $C_{25}H_{21}FNO_3$ 402.1500 found 402.1525.

2-(2-(6,7-Dimethoxyisoquinolin-1-yl)phenyl)-1-(4-nitrophenyl)ethan-1-one **(5k)**. 62% yield



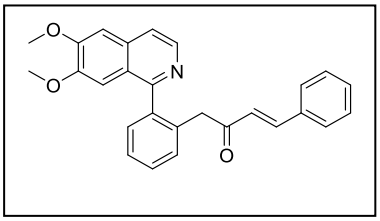
(70.0 mg), light yellow solid, mp: 172-175 °C, FT-IR (cm)$^{-1}$: 3030, 2868, 1683, 1599, 1434; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.16-8.11 (m, 3H), 7.75 (d, J = 8.7 Hz, 2H), 7.56 (d, J = 5.6 Hz, 1H), 7.54–7.50 (m, 2H), 7.48–7.44 (m, 1H), 7.39 (d, J = 7.4 Hz, 1H), 7.31 (s, 1H), 6.77 (s, 1H), 4.27 (s, 2H), 3.90 (s, 3H), 3.64 (s, 3H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ 197.0, 157.4, 152.9, 150.1, 149.9, 141.7, 140.8, 139.4, 134.2, 133.5, 132.5, 130.3, 129.4, 128.8, 127.2, 123.9, 123.0, 119.4, 105.7, 105.0, 56.2, 55.5, 43.5 ppm; HRMS (ESI-QTOF): *m/z* [M+H]$^{+}$ calcd. for $C_{25}H_{21}NO_5$ 429.1445 found 429.1385.

1-(3,5-Dichlorophenyl)-2-(2-(6,7-dimethoxyisoquinolin-1-yl)phenyl)ethan-1-one **(5l)** 66% yield



(78.8 mg), buff-white solid, mp: 138-140 °C, FT-IR (cm)$^{-1}$: 3055, 2879, 1692, 1622, 1523; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.20 (d, J = 5.5 Hz, 1H), 7.75 (t, J = 1.7 Hz, 1H), 7.57 (d, J = 5.5 Hz, 1H), 7.51 (d, J = 3.3 Hz, 2H), 7.47–7.43 (m, 1H), 7.39 (t, J = 5.7 Hz, 3H), 7.33 (s, 1H), 6.72 (s, 1H), 4.18 (s, 2H), 3.92 (s, 3H), 3.64 (s, 3H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ 195.9, 157.3, 152.9, 150.1, 140.8, 139.8, 134.8, 134.4, 133.4, 132.3, 130.2, 128.8, 127.1, 126.6, 123.0, 119.4, 105.7, 104.9, 56.2, 55.6, 43.3 ppm; HRMS (ESI-QTOF): *m/z* [M+H]$^{+}$ calcd. for $C_{25}H_{20}Cl_2NO_2$ 452.0815 found 452.0801.

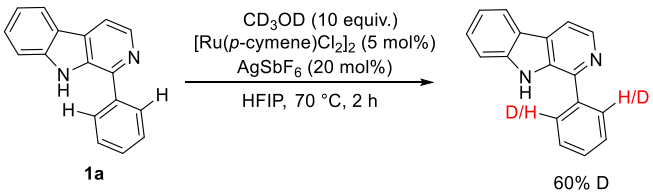
(E)-1-(2-(6,7-Dimethoxyisoquinolin-1-yl)phenyl)-4-phenylbut-3-en-2-one (**5m**). 71% yield



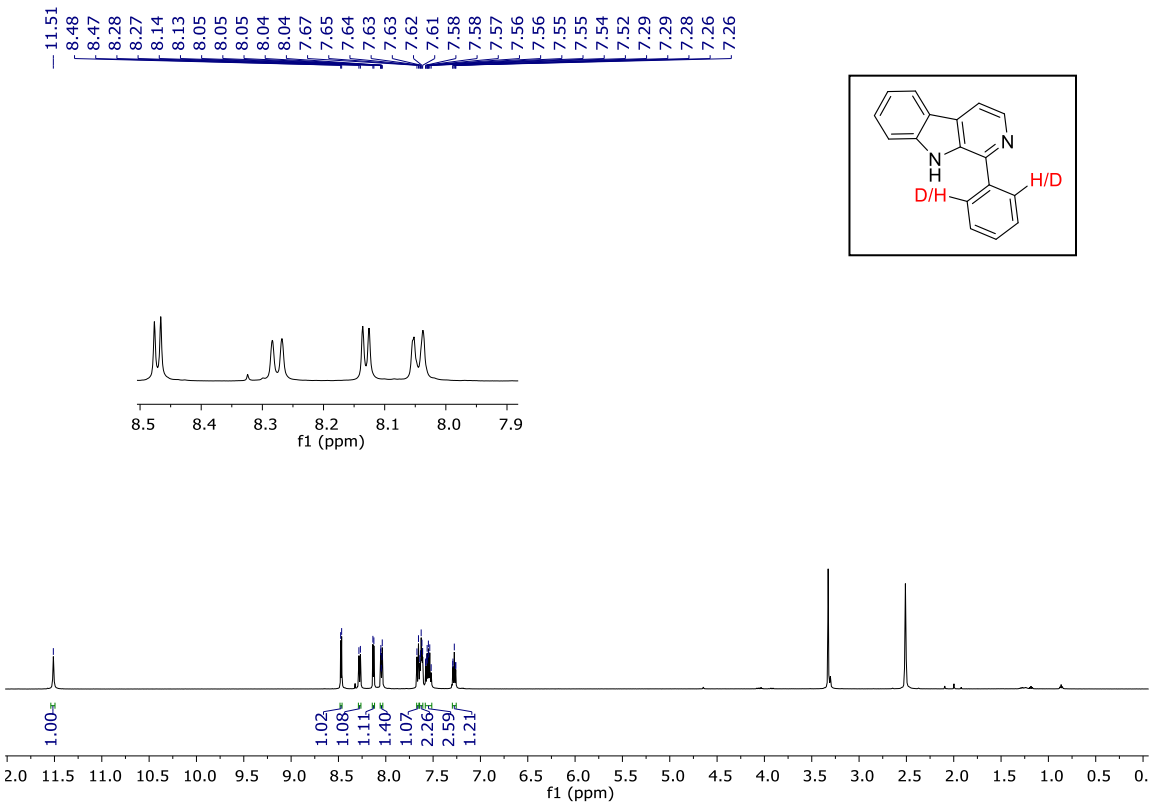
(76.7 mg), buff-white solid, mp: 155-158 °C, FT-IR $(cm)^{-1}$: 3024, 2890, 1729, 1670, 1588; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.38 (d, J = 5.5 Hz, 1H), 7.66 (d, J = 5.5 Hz, 1H), 7.51-7.42 (m, 6H), 7.41-7.35 (m, 5H), 7.20 (d, J = 16.2 Hz, 1H), 6.80 (s, 1H), 6.54 (d, J = 16.2 Hz, 1H), 3.89 (s, 3H), 3.61 (s, 3H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ 197.1, 157.8, 153.0, 150.1, 142.3, 141.1, 139.8, 134.6, 134.4, 133.5, 132.0, 130.9, 130.2, 129.3, 128.7, 127.0, 126.3, 123.3, 119.4, 105.8, 105.2, 56.2, 55.6, 45.0 ppm; HRMS (ESI-QTOF): *m/z* $[M+H]^+$ calcd. for $C_{27}H_{24}NO_3$ 410.1751 found 410.1751.

4. Control Experiments

4.1. H/D Exchange Experiment



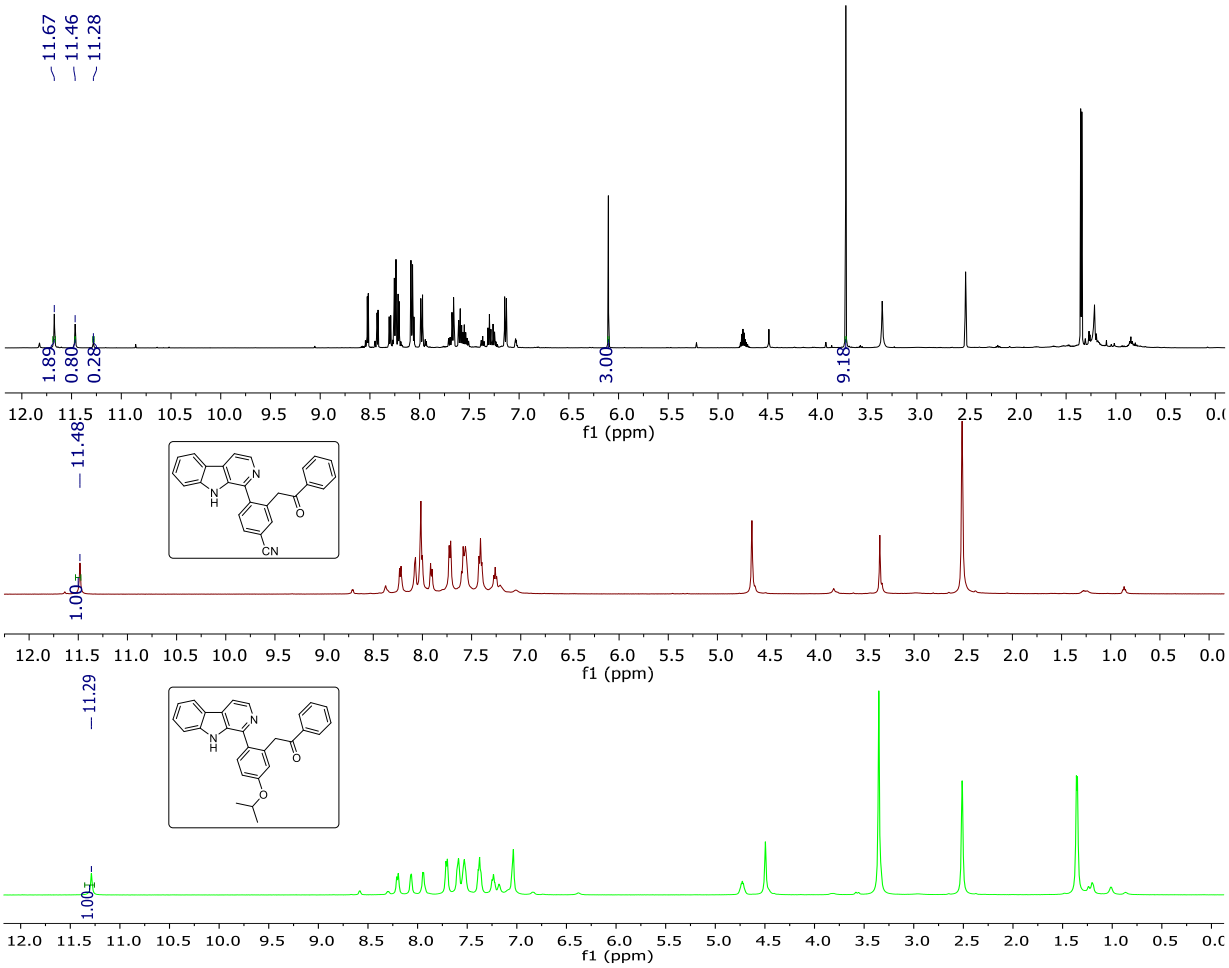
A pressure tube was charged with [Ru(*p*-cymene)Cl_2]$_2$ (5 mol%), $AgSbF_6$ (20 mol%), *β*-carboline (**1a**, 1 equiv.), CD_3OD (10 equiv.), and HFIP (2 mL). The reaction mixture was stirred at 70 °C for 3 h. After that, the solvent was removed under reduced pressure and the residue was purified by silica gel chromatography using EA/hexane to afford the deuterated compound, which was characterized by ^{1}H NMR spectroscopy. ^{1}H NMR analysis of **1a** revealed 60% deuteration at the *ortho*-position of phenyl ring of *β*-carboline.



^{1}H NMR of compound **1a** (500 MHz, $CDCl_3$)

4.2. Intermolecular Competitive Experiment

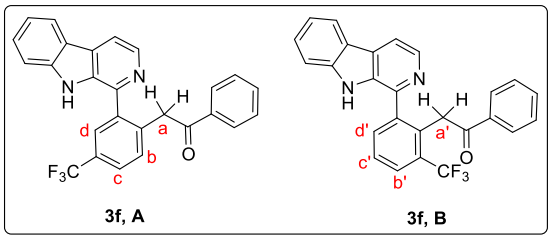
A pressure tube with a magnetic stir bar was charged with **1d** (1.0 equiv.), **1h** (1.0 equiv.), **2a** (1.5 equiv.), $[Ru(p\text{-cymene})Cl_2]_2$ (5.0 mol%) and $AgSbF_6$ (20 mol%) and HFIP (2.0 mL) was added. The resulting mixture was stirred under reflux for 2 h. After that, in reaction mixture trimethoxy benzene (1.0 equiv.) was added as the standard. The reaction mixture was evaporated under reduced pressure and the crude product containing mixture of the product **3d** and **3h** was directly submitted for ^{1}H NMR analysis. The ^{1}H NMR analysis demonstrated that the compounds **3h**/**3d** have been formed with the ratio of 0.80/0.28. It indicated that, the reaction for formation of **3h** proceeds faster than **3d**.



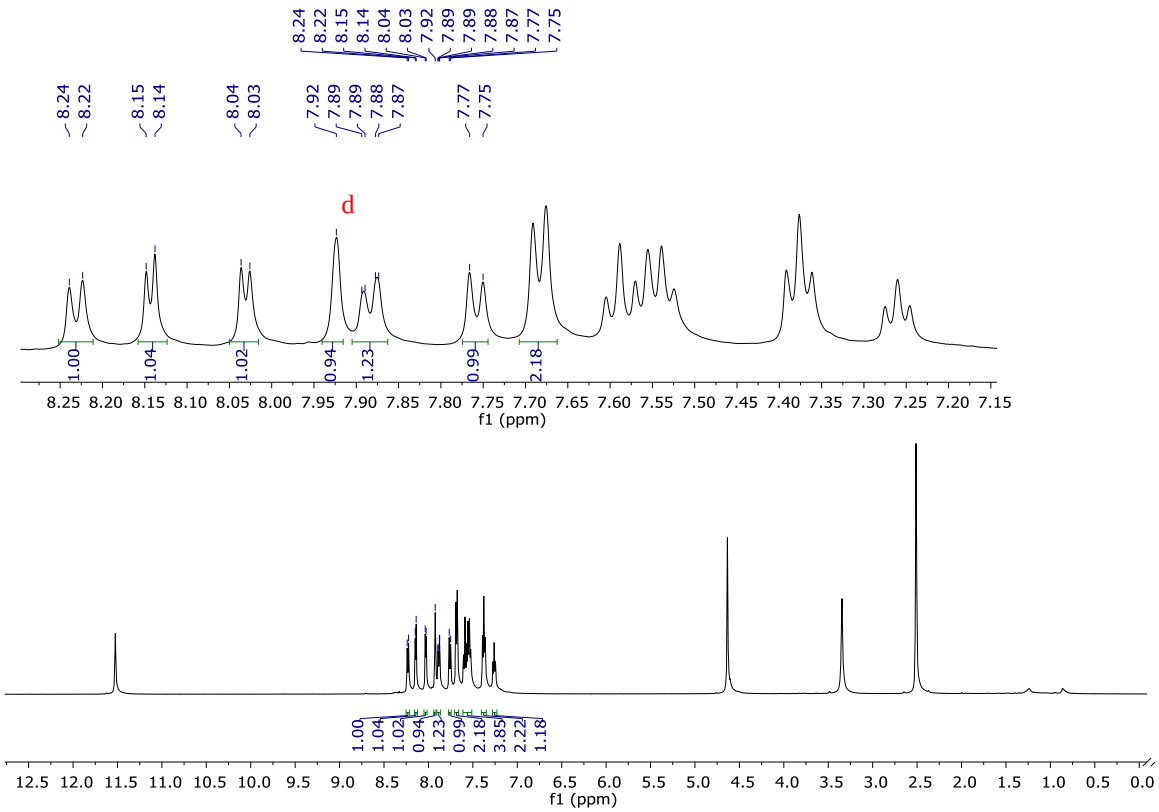
^{1}H NMR overlay of competitive reaction, ^{1}H NMR of **3d** and **3h** ($CDCl_3$, 500 MHz)

4.3. Reaction Selectivity

Selectivity of the reaction protocol has been established based on a series of 2D NMR studies performed for representative compounds. For compound **3f**, formation of two regio isomers is a high possibility. The 2D NMR studies evidences that only one regio-isomer is selectively formed at the less hindered position.



Initially, an analysis of the ^{1}H NMR with a singlet at 7.92 ppm hints the formation of the **A** isomer since in the case of **B** isomer there is no possibility of a singlet formation.



^{1}H NMR (500 MHz, DMSO-d_6) of compound **3f**.

Additionally, the 2D NMR such as HMBC, COSY and NOSY equally support the formation of the **A** isomer for compound **3f**. In HMBC a three-bond correlation was observed for methylene carbon at 43.0 ppm with doublet at 7.76 ppm which is corresponds to 'b' position in the aromatic ring as depicted. Similarly, proton at 7.87 ppm shows correlation with the CF_3 carbon at 126.5 and 140.0 ppm, respectively. The COSY spectra of the same compound showcase the proton-proton correlation present at 7.87 and 7.76 ppm which are doublets, it is not possible in case of **B** isomer formation. Finally, the NOSY study indicating the through space correlation of the protons clearly revealed the correlation between NH proton at 11.52 ppm with singlet at 7.92 ppm. All the above stated correlations unveiled the selective formation of the **A** isomer over **B** for compound **3f** (**Fig S.1**).

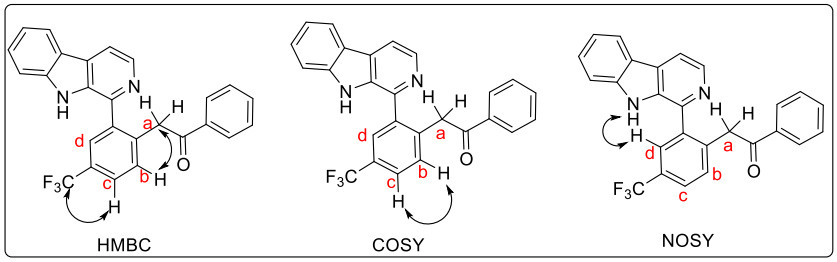
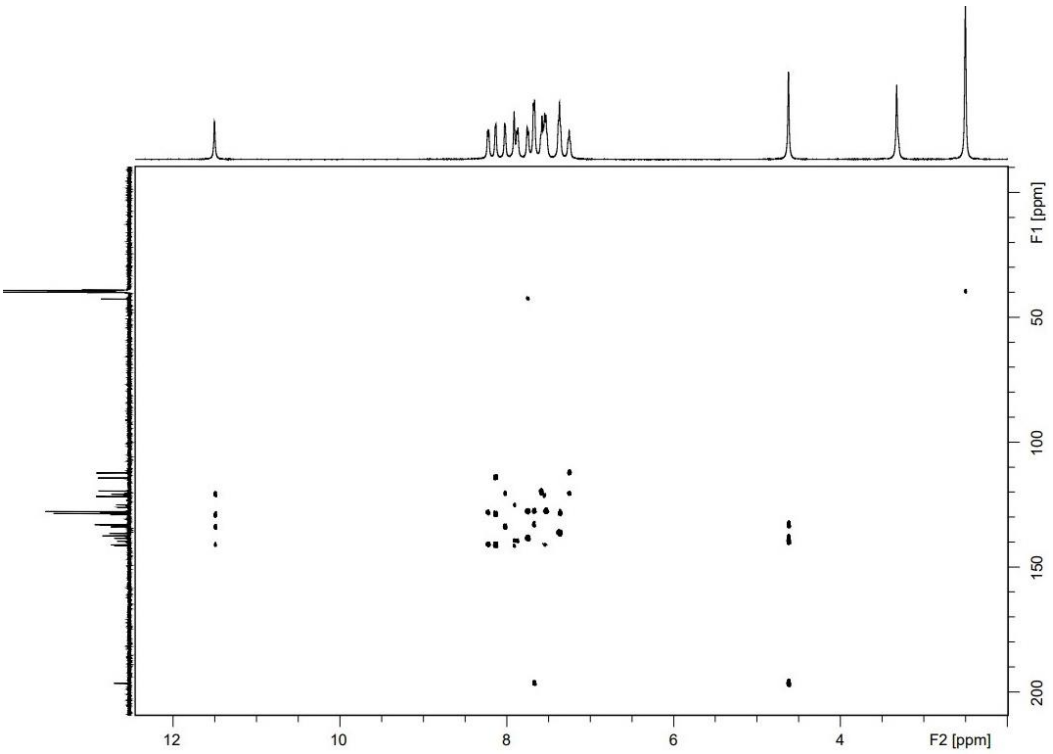
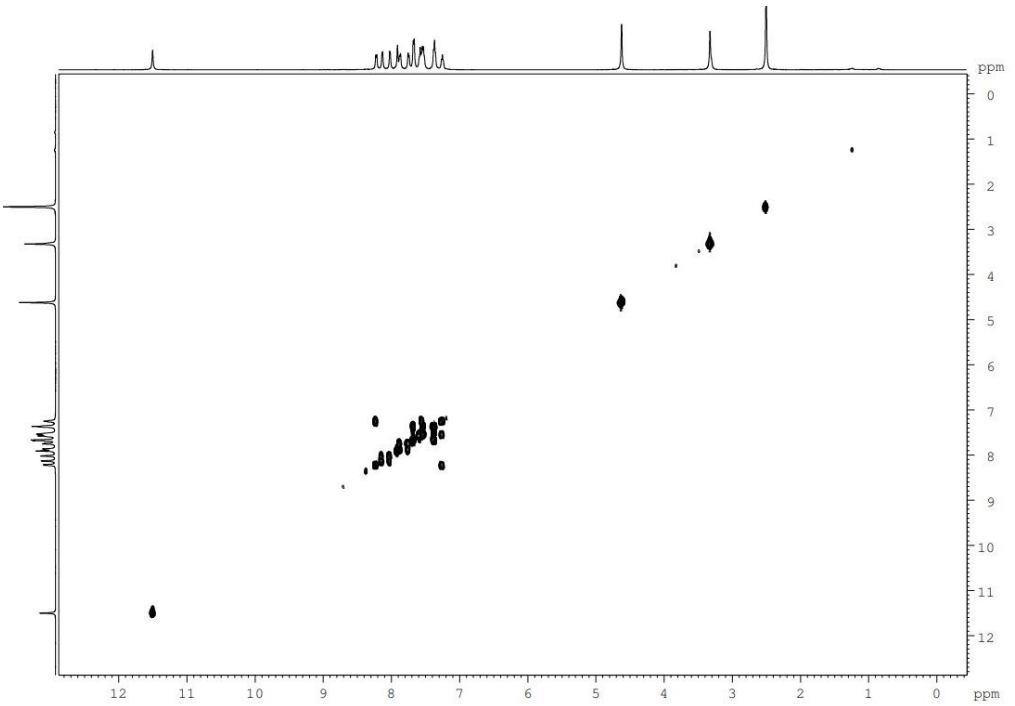


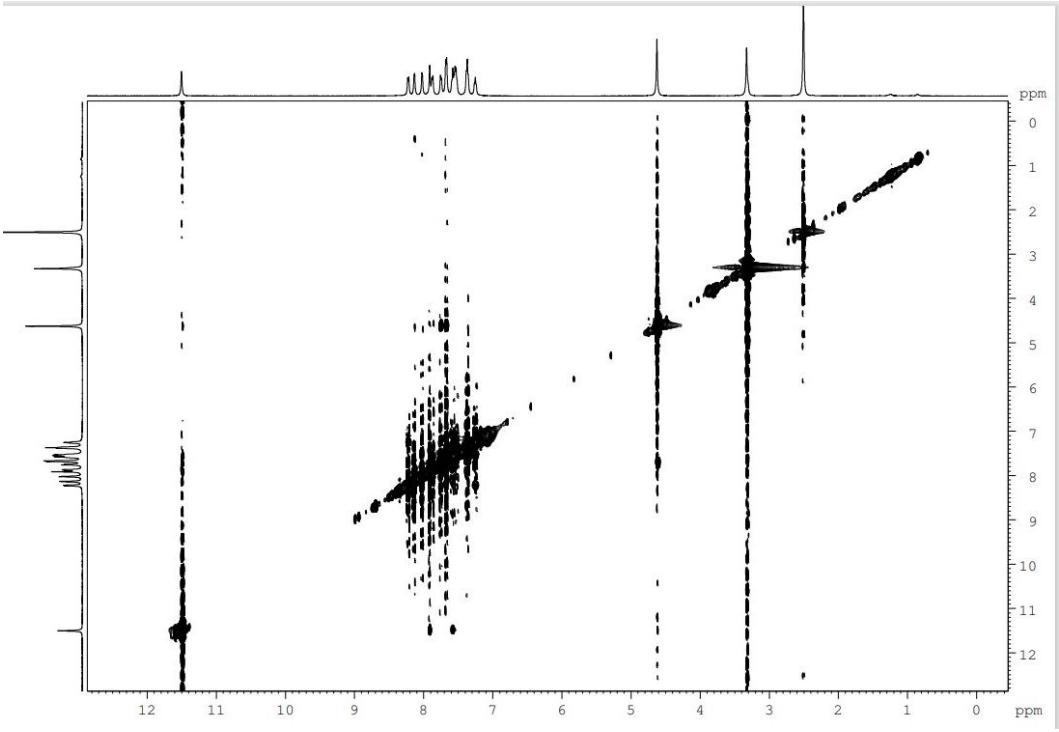
Fig S.1. Correlations established by HMBC, COSY and NOSY for compound **3f**.



HMBC of compound **3f**

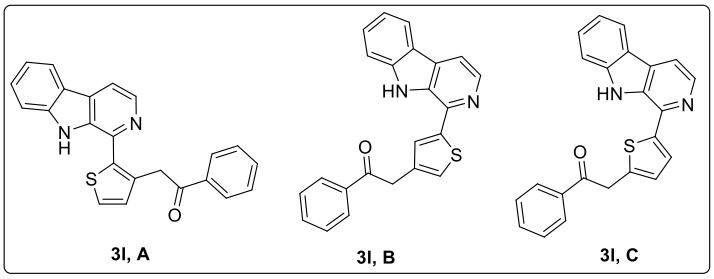


COSY of compound **3f**



NOSY of compound **3f**

For compound **3l**, the formation of three regio-isomers is a possibility. The 2D NMR studies evidence that only one regio-isomer is selectively formed in the protocol.



Initially, an analysis of the ^{1}H NMR revealed no formation of singlet in the spectra which eliminates the possibility of the regio-isomer **3l**, **B**. The possibility of formation of **3l**, **C** was also eliminated as in HMBC correlation of the methylene protons was observed with the de-shielded carbon 131.42 ppm at c position. The formation of regio-isomer **A** can be established with the HMBC, HSQC, NOSY and COSY data. In HMBC the methylene protons at 4.61 ppm showed correlation with the carbon at 131.4 and 126.2 ppm corresponding to the carbons at c and b position, respectively. The HSQC data revealed the carbon-proton correlation at position c and b wherein proton at 7.77 ppm correlated with carbon at 126.2 ppm attributing to c position and proton at 7.21 ppm correlated with carbon at 131.4 ppm attributing to position b. The COSY experiment showed correlation of the protons at b and c position. Interestingly, the NOSY experiment showed correlation of the NH protons at 11.37 ppm with methylene protons at 4.67 ppm which supports that **3l**, **C** (correlation won't be observed due to distance) is not formed and a probable indication of spatial arrangement. Additionally, the study also showed correlation of the methylene protons with protons at b and c positions.

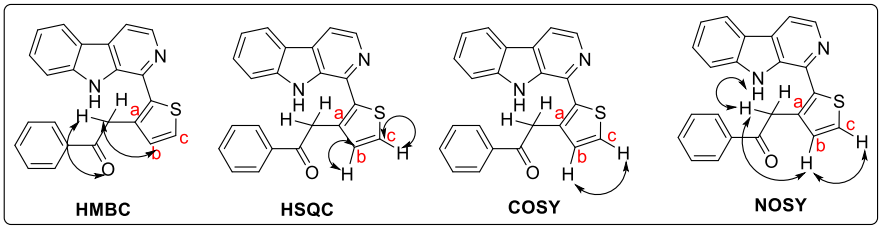
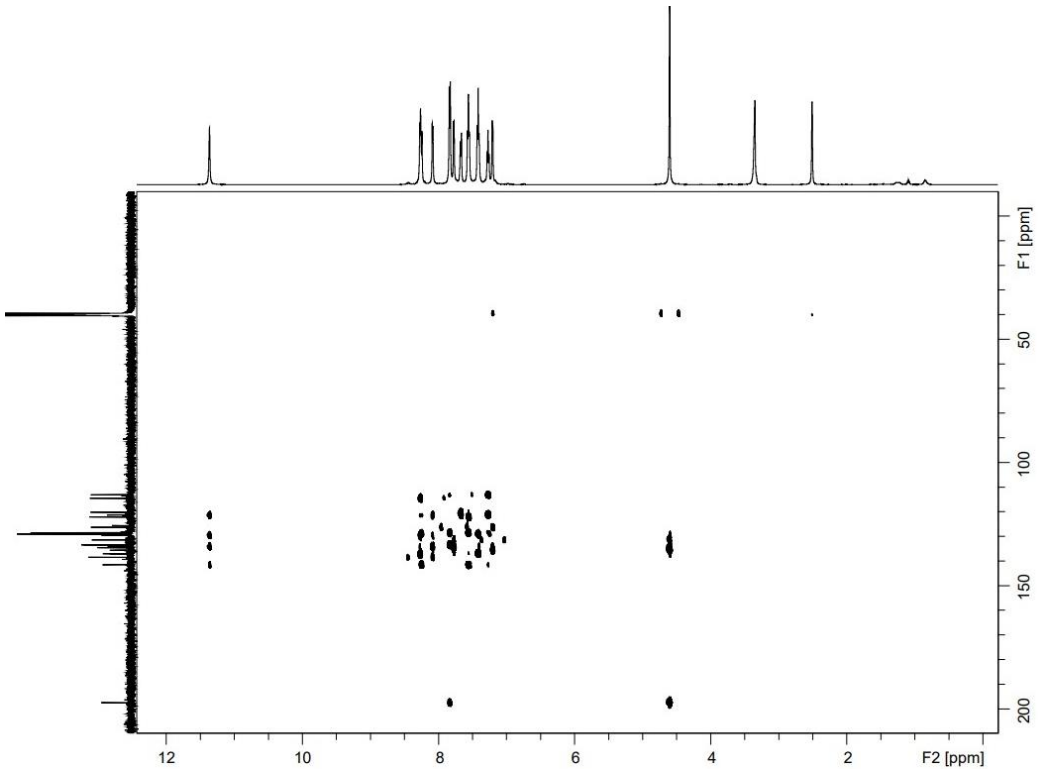
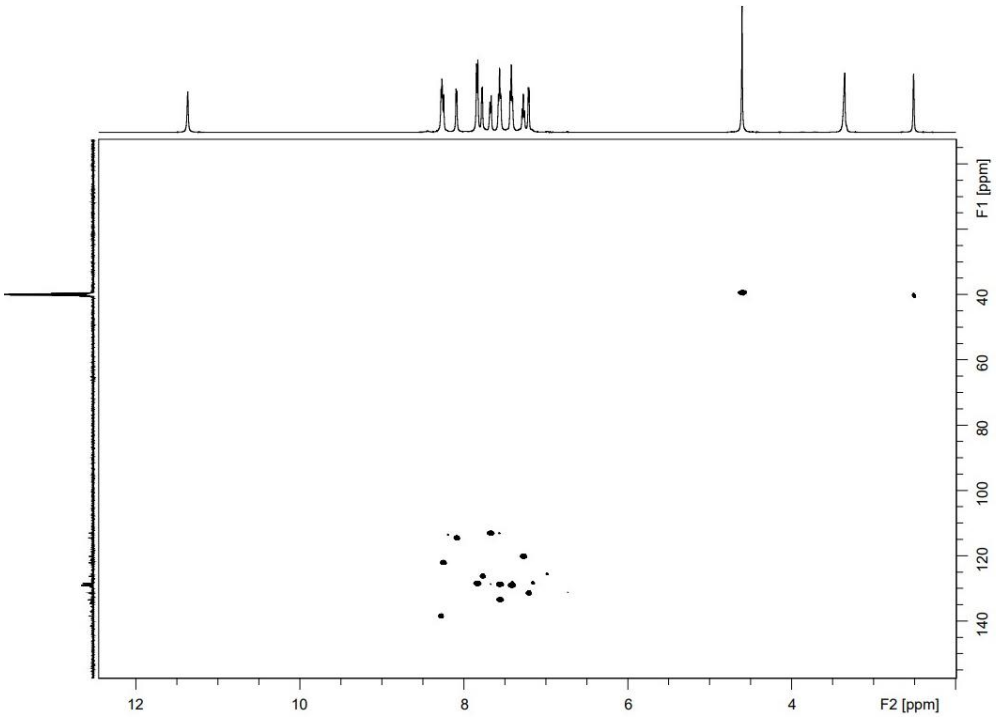


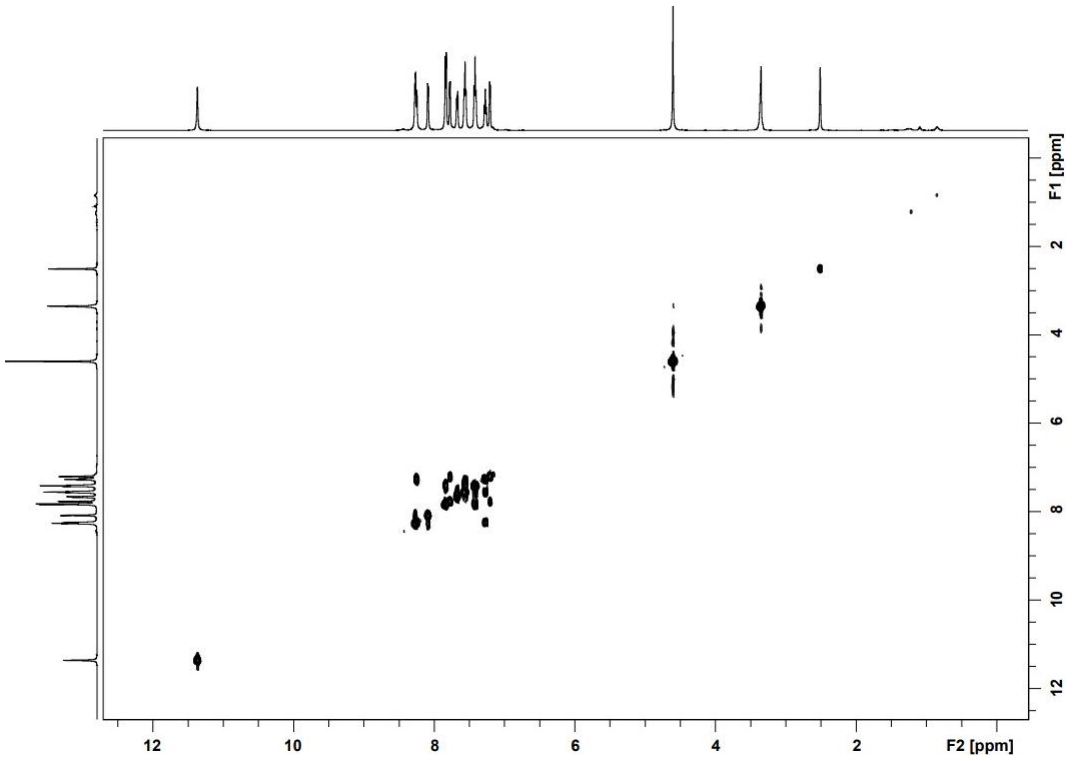
Fig S.2. Correlations established by HMBC, COSY and NOSY for **3l** compound.



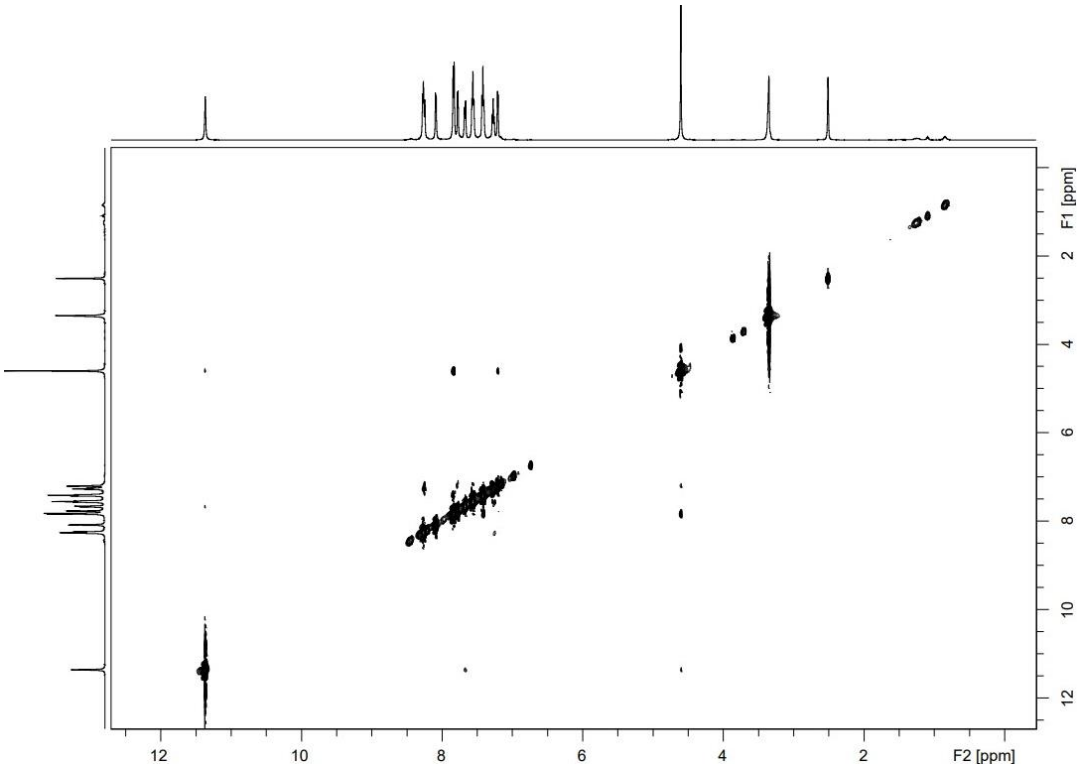
HMBC of compound **3l**



HSQC of compound **3l**

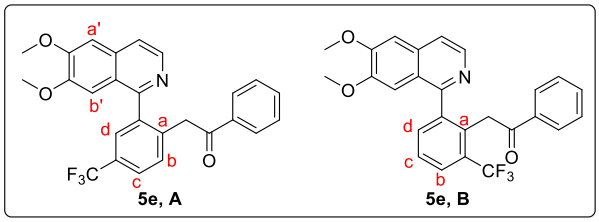


COSY of compound **3l**

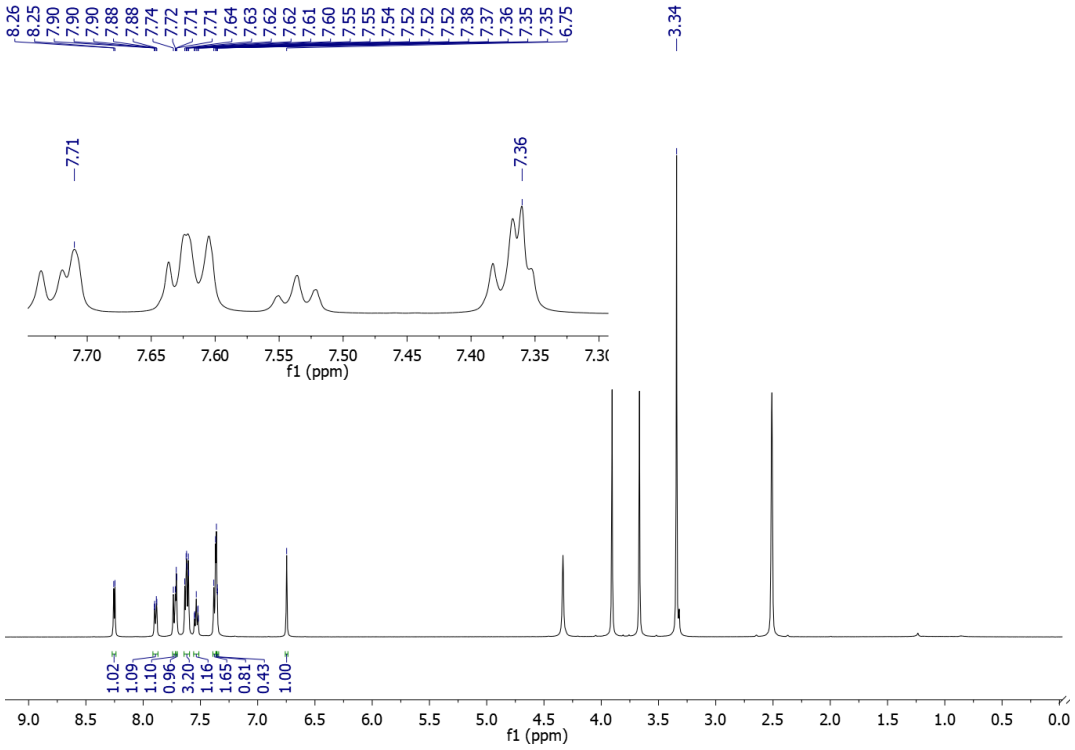


NOSY of compound **3l**

For compound **5e**, formation of two regio-isomers is a possibility. The 2D NMR studies evidence that only one regio-isomer is selectively formed.



The presence of 3 singlet protons in the ^{1}H NMR of compound **5e** eliminates the possibility of the **5e**, **B** regio-isomer. The singlet protons at 6.75, 7.36 and 7.71 ppm correspond to position a', b' and d.



^{1}H NMR (500 MHz, DMSO-d_6) of compound **5e**.

The HMBC experiment performed for **5e** reveals the correlation of the methylene protons at 4.33 ppm with the carbonyl carbon at 196.9 ppm and carbon at 133.5 ppm corresponding to position b. The two doublets of position b and c was obtained at 7.73 and 7.89, respectively. The correlation was established between these both protons using COSY experiment. Whereas the carbon and proton correlation in HSQC allocated the carbon-proton at b and c position.

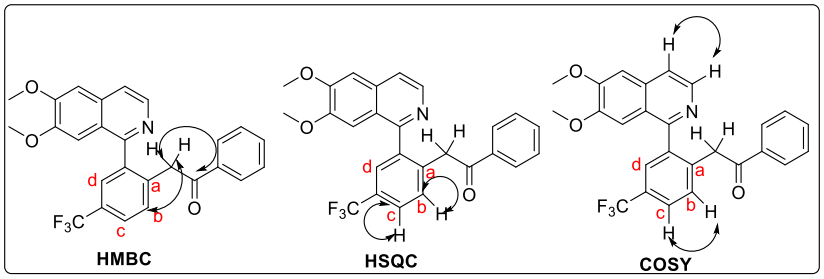
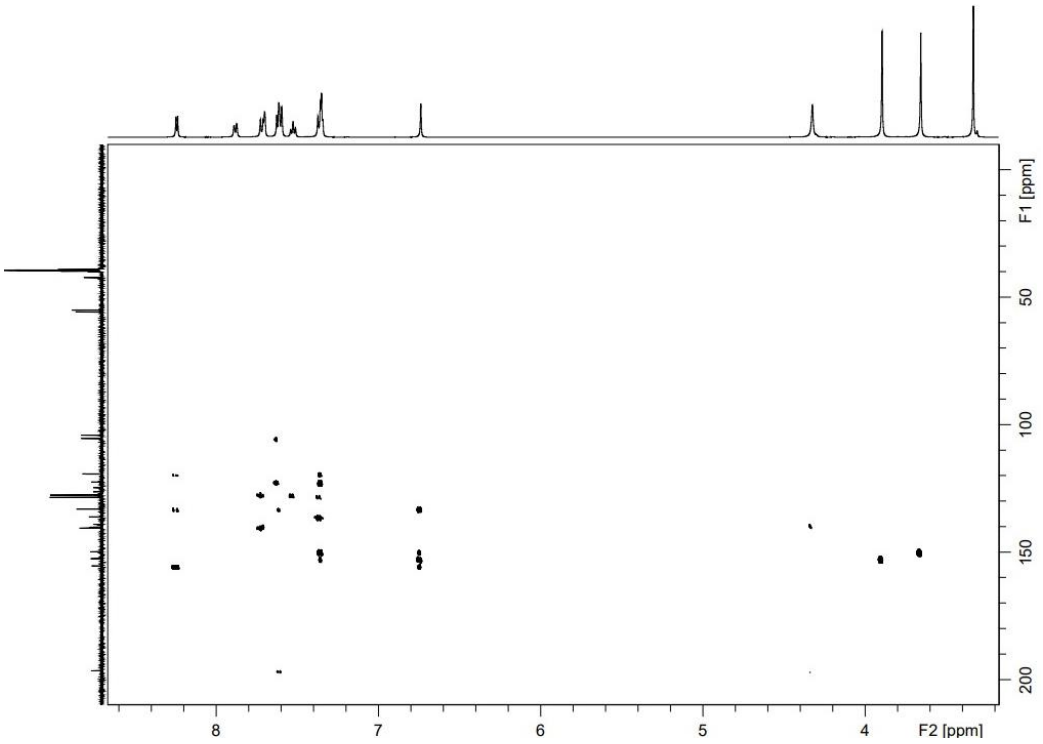
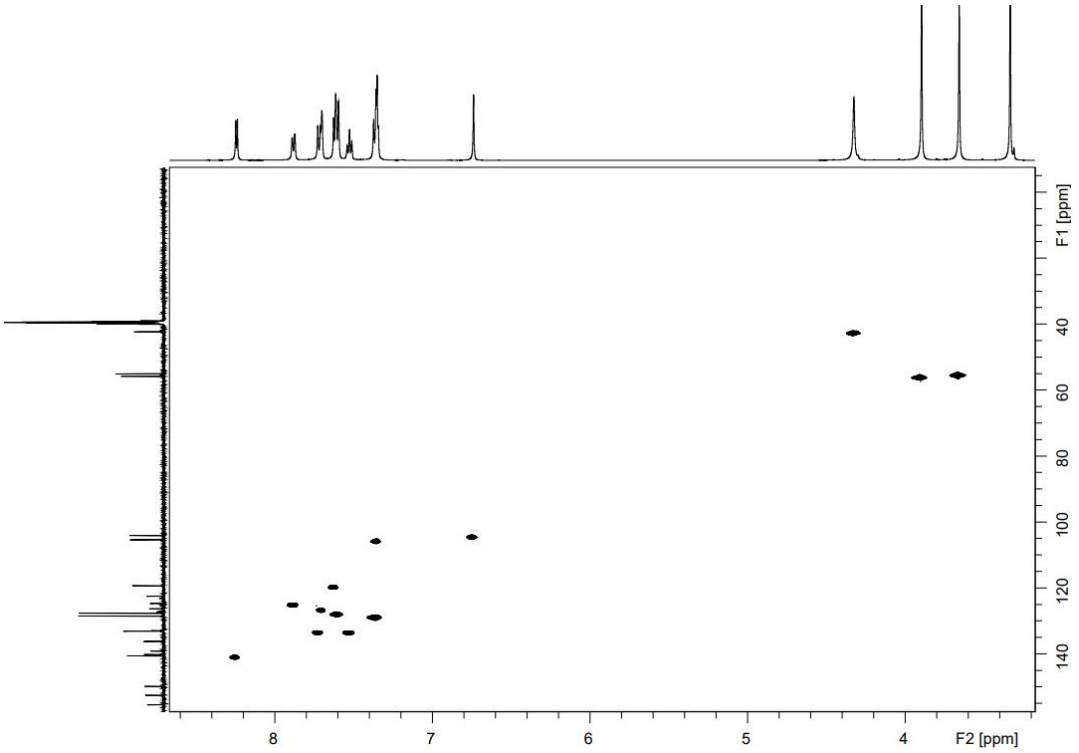


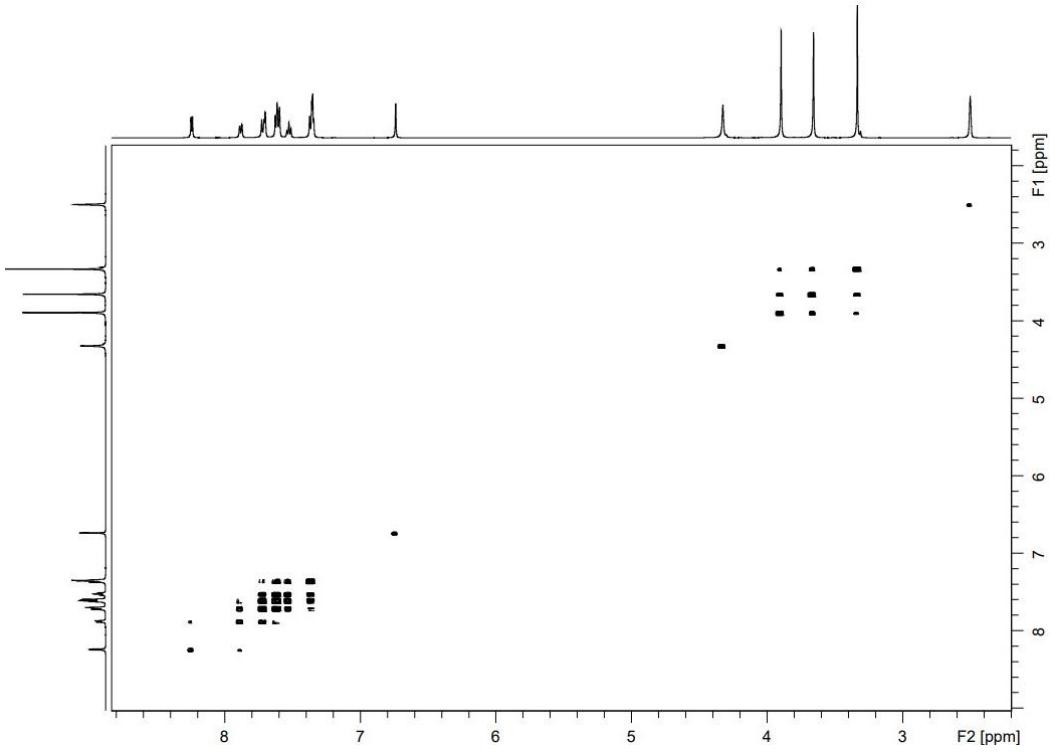
Fig S.3. Correlations established by HMBC, HSQC and COSY for **5e** compound.



HMBC of compound **5e**



HSQC of compound **5e**



COSY of compound **5e**

4.4. Carbene insertion

A pressure tube was charged with [Ru(*p*-cymene)Cl_2]$_2$ (5 mol%), $AgSbF_6$ (20 mol%), substituted 2-phenyl β-carboline (**1a**, 20 mg, 1 equiv.), sulfoxonium ylide (**2a**, 1.5 equiv.) and HFIP (2 mL). The reaction mixture was stirred at 70 °C for 2 h. Without further purification, the reaction mixture was analyzed for ^{1}H NMR.

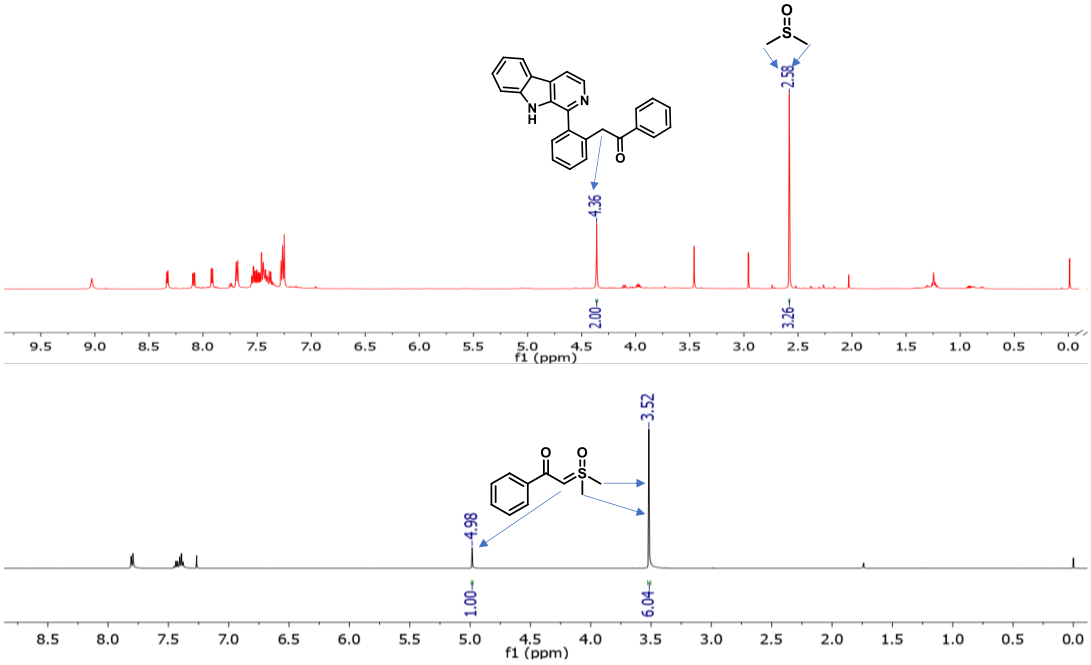


Fig. S. 4. ^{1}H NMR of reaction mixture and phenyl sulfoxonium ylide ($CDCl_3$, 500 MHz).

5. Gram-Scale Preparation and Transformations

5.1. Gram-Scale Synthesis

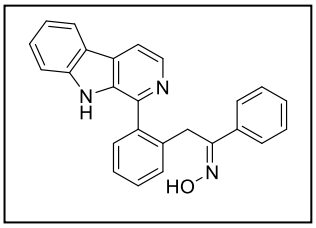
To demonstrate the scalability of the regioselective acylmethylation, a gram-scale synthesis was performed using **1a** (1.0 g, 1.0 equiv.) and **2a** (1.5 equiv.) under the optimized conditions, as discussed in the general procedure. The reaction proceeded efficiently to give the desired product **3a** (1.10 g) in 75% yield.

5.2. Synthesis of *β*-carboline hydroxime

A reaction vessel was charged with **3a** (70 mg,1 equiv.), hydroxyl amine hydrochloride (2 equiv.), catalytic amount of acetic acid and was refluxed in EtOH:H_2O (1:1). After completion of reaction, the solvent was removed under reduced pressure. The crude product was extracted using ethyl acetate and water. The organic layer thus obtained was dried over Na_2SO_4 the solvent

was removed and the crude was subjected to column chromatography. The desired product was obtained in 30% EA/hexane.

2-(2-(9H-pyrido[3,4-b]indol-1-yl)phenyl)-1-phenylethan-1-one oxime (**6**). 68% yield (49.5 mg),

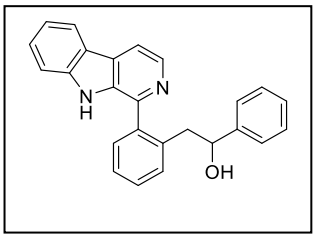


buff-white solid, mp: 118-120 °C, FT-IR $(cm)^{-1}$: 3512, 2866, 1718, 1566, 1625; ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.42 (s, 1H), 11.29 (s, 1H), 8.49 (d, J = 5.2 Hz, 1H), 8.29 (d, J = 8.0 Hz, 1H), 8.17 (d, J = 5.2 Hz, 1H), 7.58 (t, J = 8.6 Hz, 2H), 7.54 (d, J = 7.4 Hz, 2H), 7.41 (d, J = 7.0 Hz, 5H), 7.28 (d, J = 7.3 Hz, 1H), 7.25 (d, J = 6.6 Hz, 1H), 7.19 (d, J = 7.0 Hz, 1H), 7.13 (t, J = 7.5 Hz, 2H), 4.07 (s, 2H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ 155.2, 143.7, 141.5, 138.3, 137.9, 136.2, 136.1, 134.6, 130.3, 129.0, 128.6, 126.9, 126.1, 122.2, 121.3, 119.9, 114.4, 112.7, 28.6 ppm; HRMS (ESI-QTOF): *m/z* $[M+H]^+$ calcd. for $C_{25}H_{20}N_3O$ 378.1601 found 378.1603.

5.3. Reduction

A reaction vessel was charged with **3a** (70 mg, 1 equiv.), $NaBH_4$ (2 equiv.) was stirred in MeOH at rt for 1 h. After completion of reaction, the solvent was removed under reduced pressure. The crude was then subjected to column chromatography. The desired product was obtained in 20% EA/hexane.

2-(2-(9H-pyrido[3,4-b]indol-1-yl)phenyl)-1-phenylethan-1-ol (**7**). 90% yield (63.3 mg), buff-

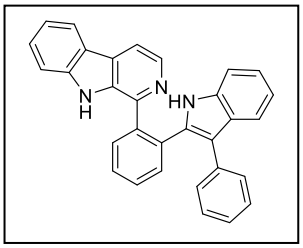


white solid, mp: 158-160 °C, FT-IR $(cm)^{-1}$: 3058, 2975, 1722, 1604, 1566; ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.32 (s, 1H), 8.51 (d, J = 5.3 Hz, 1H), 8.30 (d, J = 7.9 Hz, 1H), 8.22 (d, J = 5.3 Hz, 1H), 7.61–7.57 (m, 2H), 7.57–7.54 (m, 1H), 7.52 (dd, J = 8.4, 6.4 Hz, 1H), 7.48–7.43 (m, 2H), 7.29–7.26 (m, 1H), 7.19 (t, J = 7.5 Hz, 2H), 7.11 (dd, J = 12.0, 7.2 Hz, 3H), 6.53 (s, 1H), 4.64 (dd, J = 9.3, 3.9 Hz, 1H), 2.96 (dd, J = 13.5, 4.0 Hz, 1H), 2.78 (dd, J = 13.5, 9.5 Hz, 1H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ 147.0, 143.6, 141.6, 138.7, 137.8, 137.6, 134.6, 131.8, 130.1, 129.4, 128.8, 128.7, 128.3, 126.9, 126.8, 125.8, 122.2, 121.2, 120.0, 114.6, 112.8, 74.1, 43.6 ppm; HRMS (ESI-QTOF): *m/z* $[M+H]^+$ calcd. for $C_{25}H_{21}N_2O$ 365.1648 found 365.1641.

5.4. Synthesis of *β*-carboline-indole conjugate

A reaction vessel was charged with **3a** (70 mg, 1 equiv.), phenyl hydrazine (1.5 equiv.), catalytic amount of H_2SO_4 was refluxed in EtOH for 8 h. After completion of reaction, the solvent was removed under reduced pressure. The crude product obtained was extracted using ethyl acetate- water. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The mixture was then purified using column chromatography at 30% EA/hexane.

1-(2-(3-Phenyl-1H-indol-2-yl)phenyl)-9H-pyrido[3,4-b]indole (**8**). 65% yield (54.6 mg), buff-white solid, mp: 178-180 °C, FT-IR $(cm)^{-1}$: 3062, 1672, 1615, 1543, 1458; ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.22 (s, 1H), 11.07 (s, 1H), 8.14 (d, J = 7.8 Hz, 1H), 7.95 (d, J = 5.2 Hz, 1H), 7.81–7.72 (m, 2H), 7.64 – 7.53 (m, 5H), 7.49 (d, J = 7.3 Hz, 1H), 7.42 (d, J = 6.6 Hz, 2H), 7.29 (d, J = 8 Hz, 1H), 7.22-7.19 (m, 2H), 7.17-7.14 (m, 2H), 6.69 (t, J = 7.0 Hz, 1H), 6.92 (s, 1H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ 144.4, 141.2, 139.0, 137.7, 136.2, 135.7, 135.7, 135.5, 134.9, 134.2, 133.2, 132.7, 130.8, 129.0, 128.9, 128.4, 128.0, 127.8, 127.3, 127.0, 121.7, 121.6, 121.4, 119.4, 119.1, 119.0, 113.6, 113.3, 112.5, 111.4 ppm; HRMS (ESI-QTOF): *m/z* $[M+H]^+$ calcd. for $C_{31}H_{22}N_3$436.1808 found 436.1799.



6. MTT Assay

MTT assay is a colorimetric assay based on the conversion of MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) into insoluble formazan by succinate dehydrogenase enzyme (mitochondrial enzyme). The viability of cells is indicated by the ability of the live cells to reduce MTT level. The assay initiates with the seeding of cells in 96-well plates (density = 1000-4000 cell/well) in 100 µL of medium and grown for 24 h. The media was replaced with fresh media and cells were treated with 50 µM concentration of compounds and standard for 48 h period. After 48 h of incubation media removal was followed by the addition of 100 µL of MTT solution in media (0.5 mg/mL) and incubated for 4 h at 37 °C. The whole media was removed and 100 µL of DMSO was added to dissolve formazan crystal and kept for 20 min at 37 °C. The amount of formazan was determined utilizing spectrophotometric microtiter plate reader at 570 nm wavelength.

Table S1. Percentage inhibition on cancer cell lines (HCT-116 and MCF-7) at 50 µM after 48 h

Compounds	Percentage Inhibition		
	HCT-116	MCF-7	HaCaT
3a	83.90	83.65	30.44
3c	29.65	30.76	33.80
3e	57.29	78.72	25.77
3f	55.77	27.11	27.34
3g	40.90	50.05	20.78
3h	49.64	69.37	23.90
3i	80.32	64.55	15.99
3j	73.64	53.85	36.90
3k	32.40	87.66	21.44
3l	81.31	88.03	40.89
3o	24.44	83.20	17.77
3p	83.61	93.02	10.33
Harmine	90.22	78.30	26.80

*****HCT-116: human colon cancer cell line, MCF-7: human breast cancer cell

7. Molecular Docking

The docking for the DNA intercalation studies was performed using duplex DNA obtained from protein data bank (PDB ID: 209D). The receptor model was prepared using the protein preparation tool (Schrödinger 2017-1). The missing side chains and loops were added with removal of water molecules with a distance of more than 5Å away from the active pocket. The receptor grid was generated with 20Å distance equally in each direction X, Y and Z. The Ligprep model of Schrödinger suite was used to sketch the potent ligand **3p** along with different conformer generation. The ligand was docked using GLIDE-XP 7.4 (Extra Precision) mode.

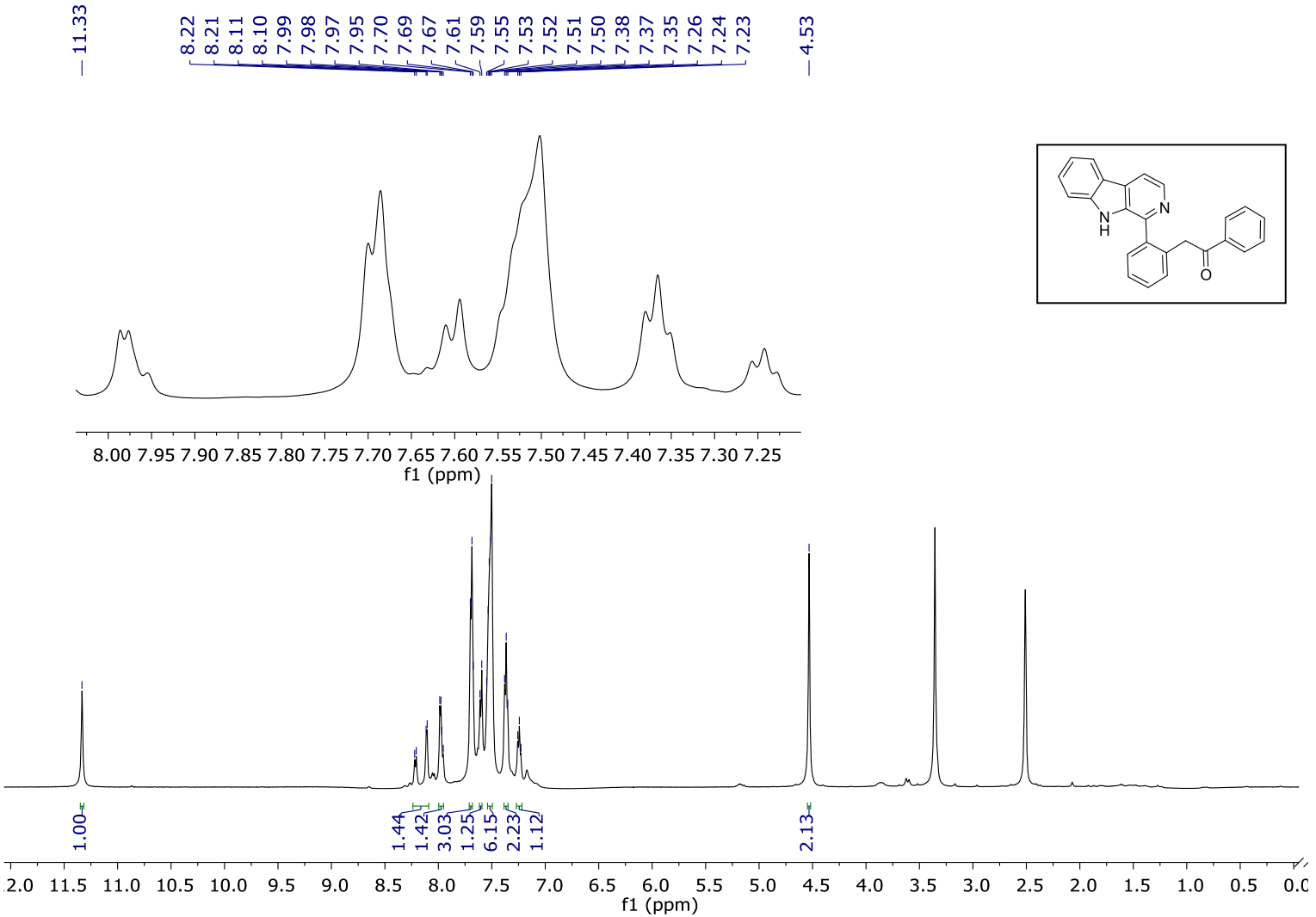
8. Photophysical Study

The fluorescence intensity experiment was performed using EnVision® Multimode Plate Reader using 200 µM concentration of the tested compounds in pure ACN.

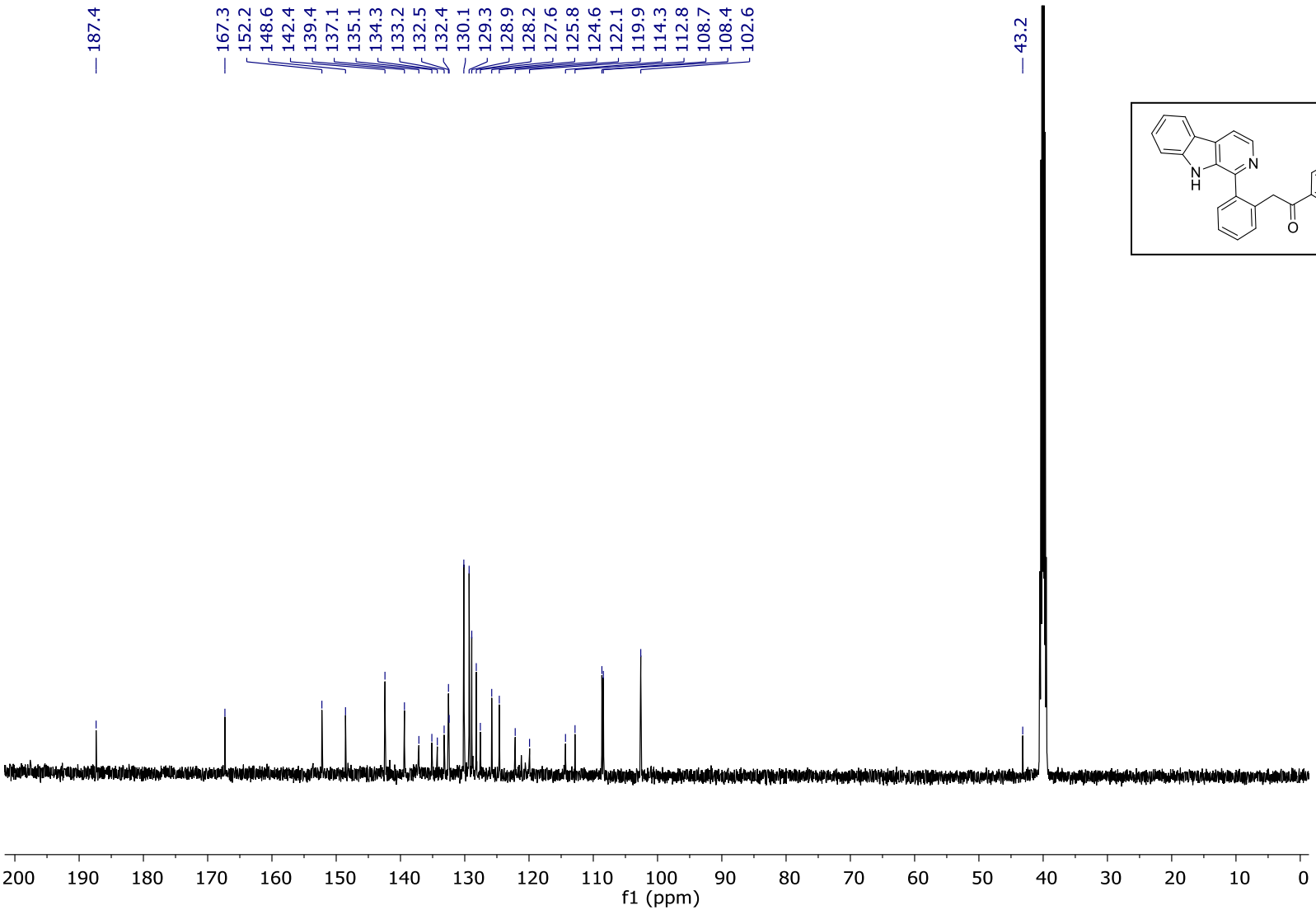
9. References

1. Tokala, R.; Bora, D.; Sravani, S.; Nachtigall, F. M.; Santos, L. S.; Shankaraiah, N. Ru(II)-Catalyzed Regioselective Hydroxymethylation of β-Carbolines and Isoquinolines *via* C-H Functionalization: Probing the Mechanism by Online ESI-MS/MS Screening. *J. Org. Chem.* **2019**, *84*, 5504-5513.
2. Xu, Y.; Yang, X.; Zhou, X.; Kong, L.; Li, X. Rhodium(III)-Catalyzed Synthesis of Naphthols *via* C-H Activation of Sulfoxonium Ylides. *Org. Lett.*, **2017**, *19*, 4307–4310.

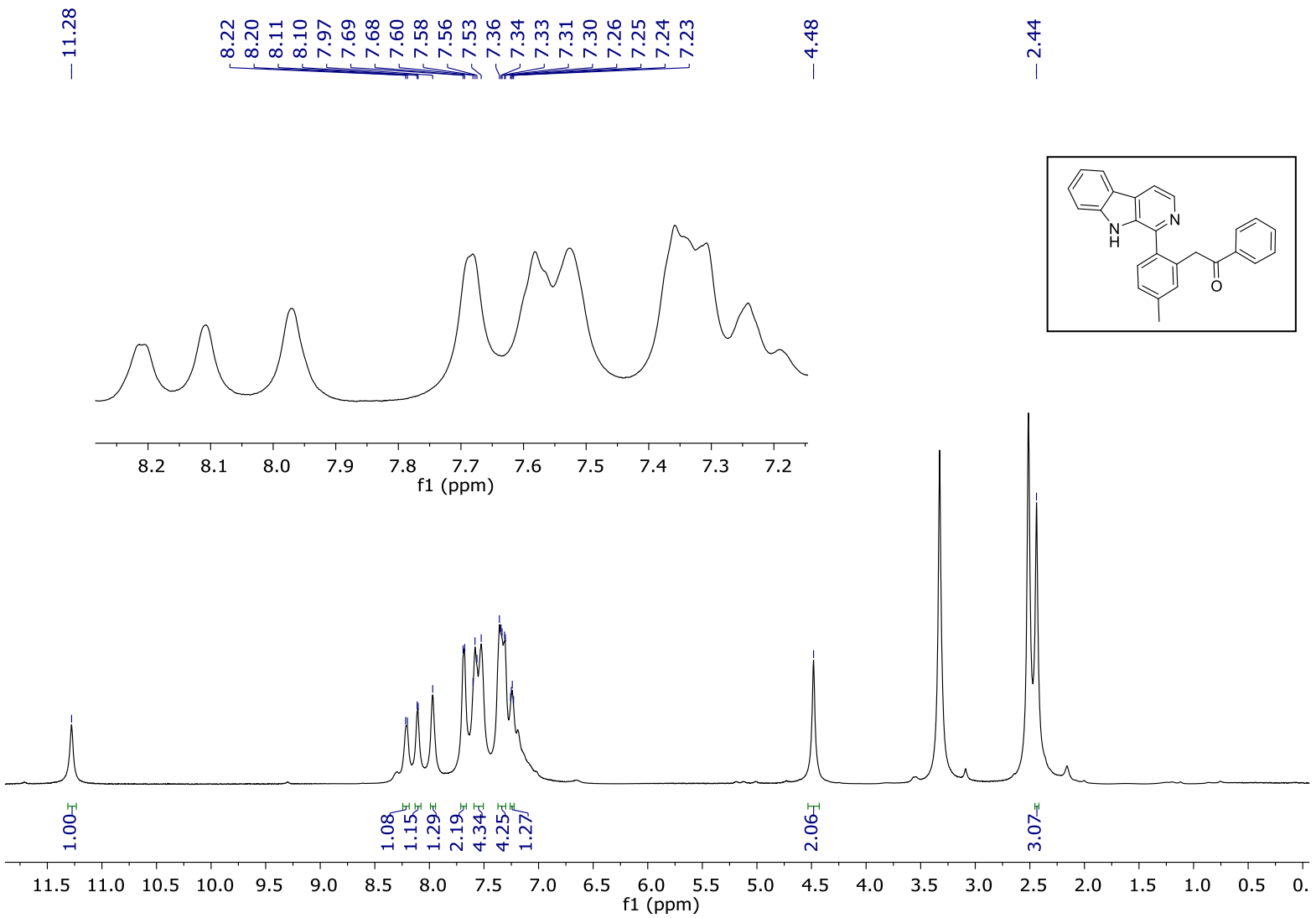
10. Copy of ^{1}H and ^{13}C Spectra



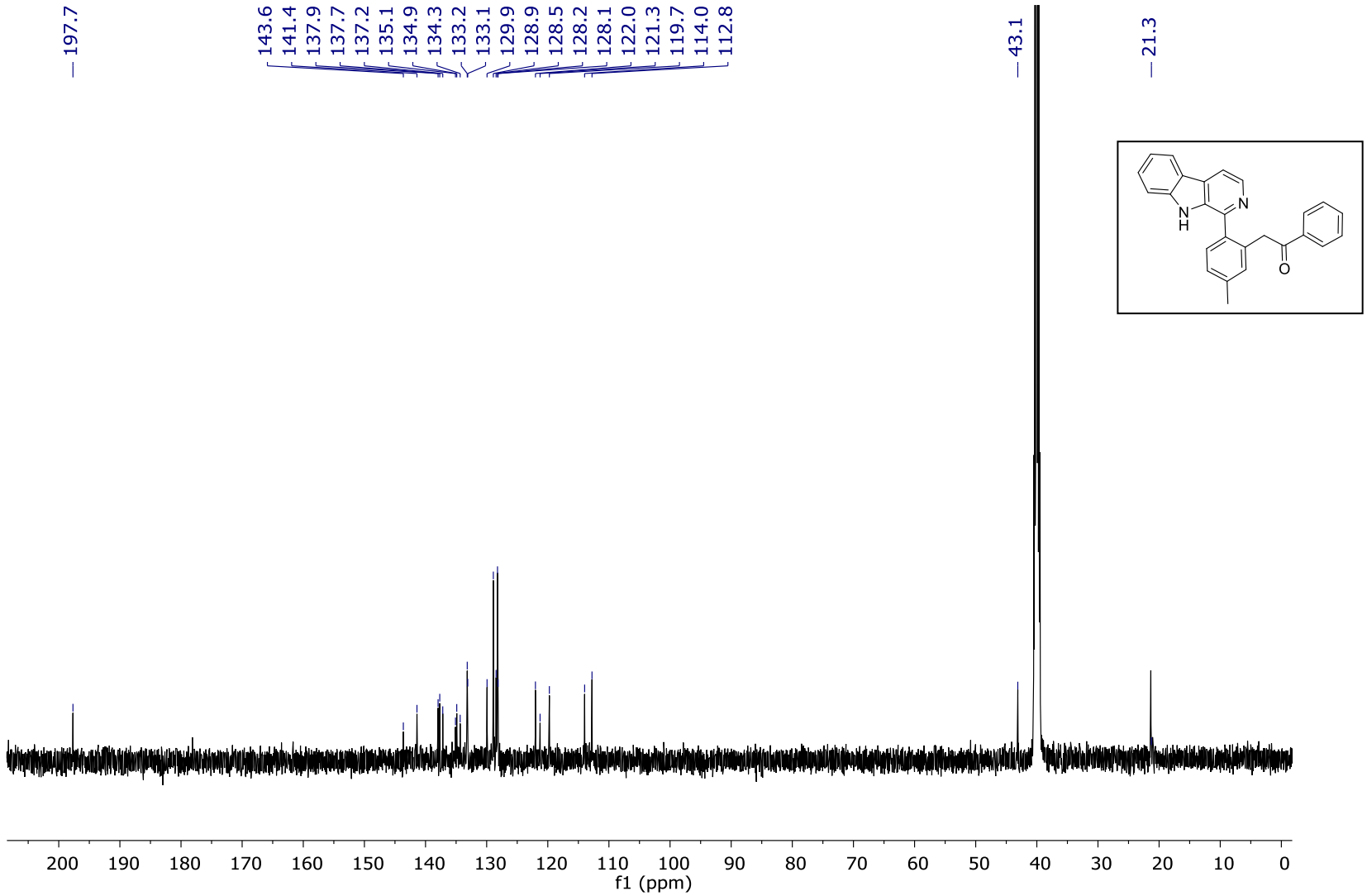
^{1}H NMR (500 MHz, DMSO-d_6) of compound **3a**



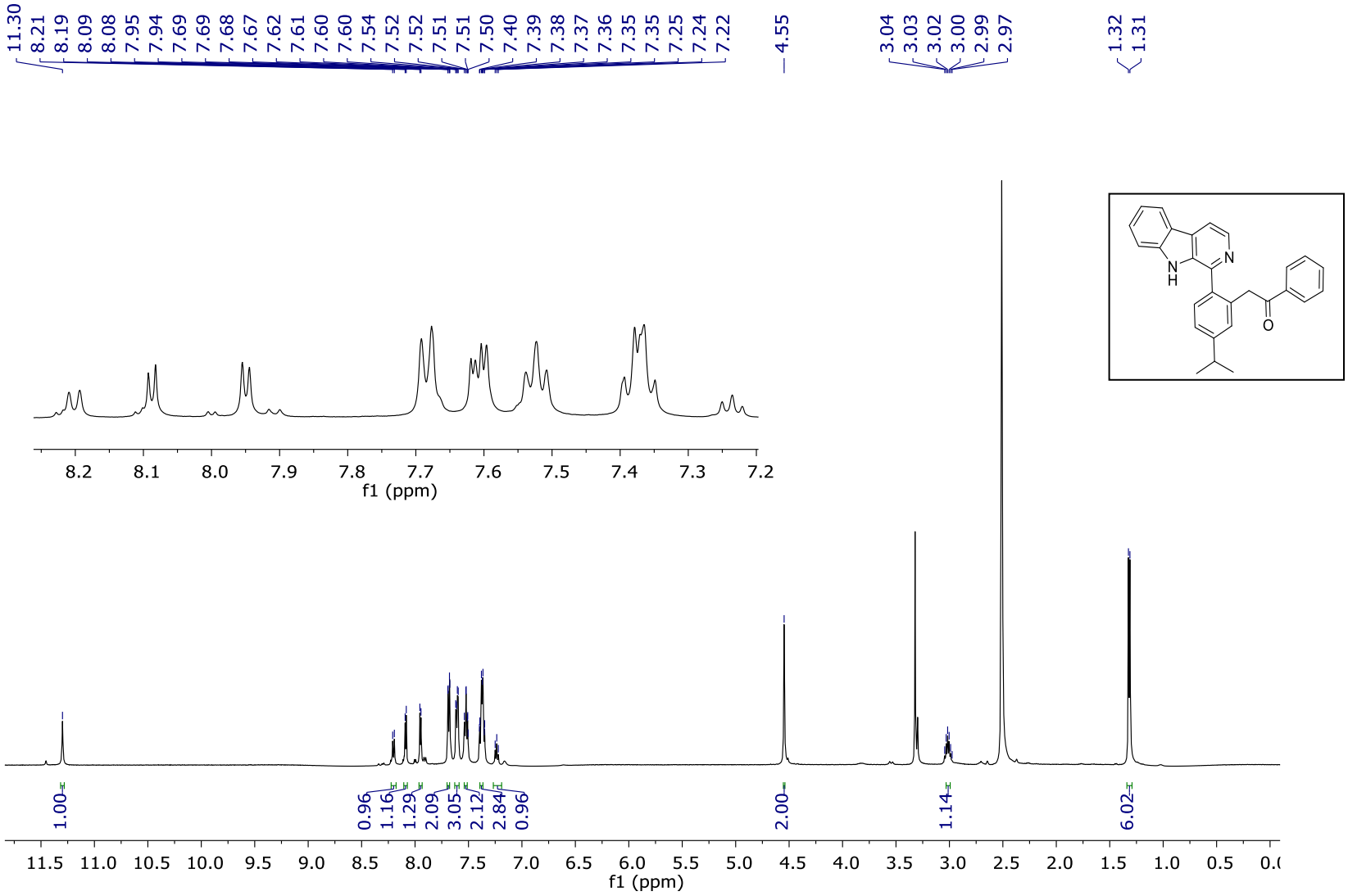
^{13}C NMR (125 MHz, DMSO-d_6) of compound **3a**



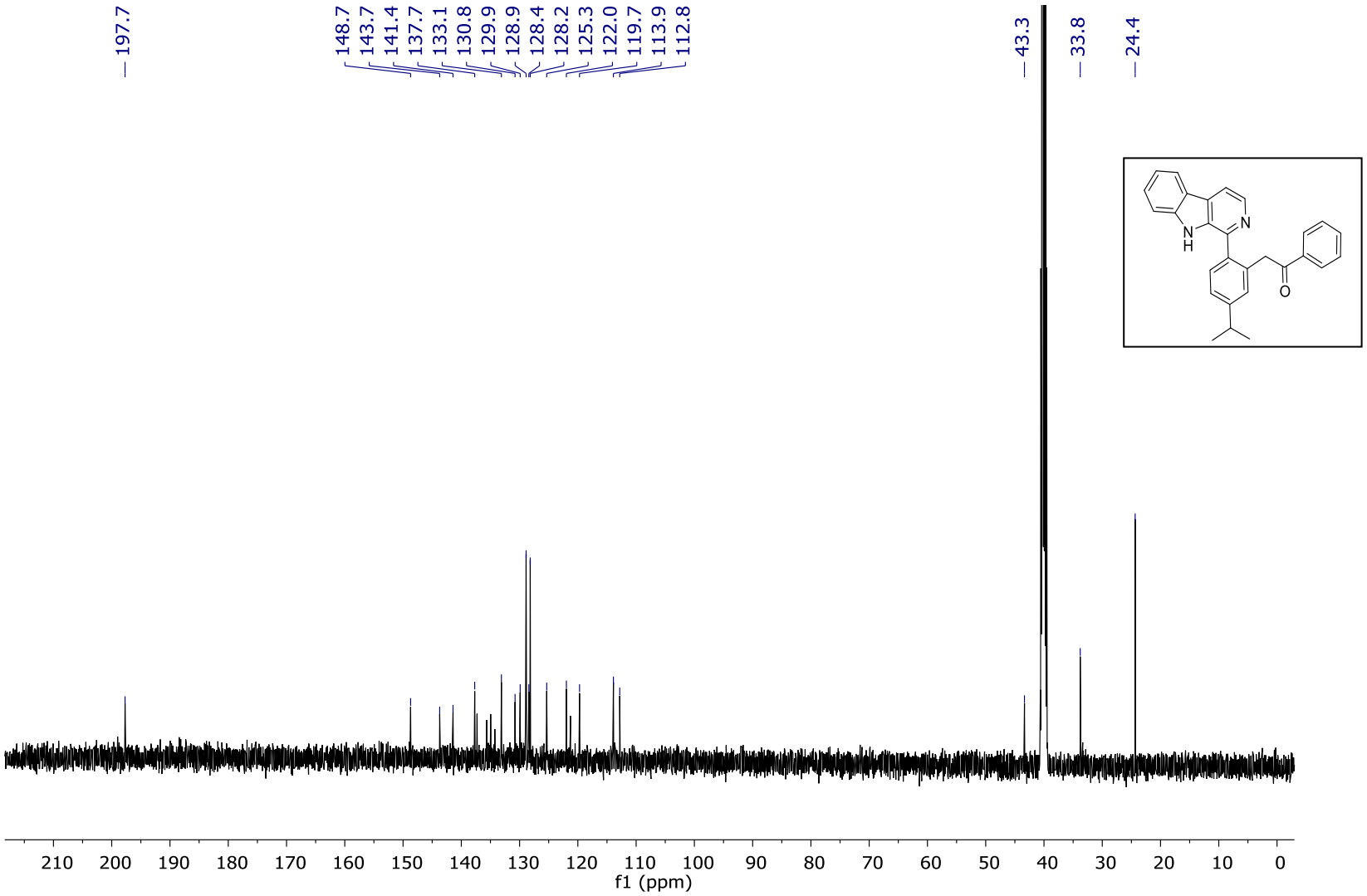
^{1}H NMR (500 MHz, DMSO-d_6) of compound **3b**



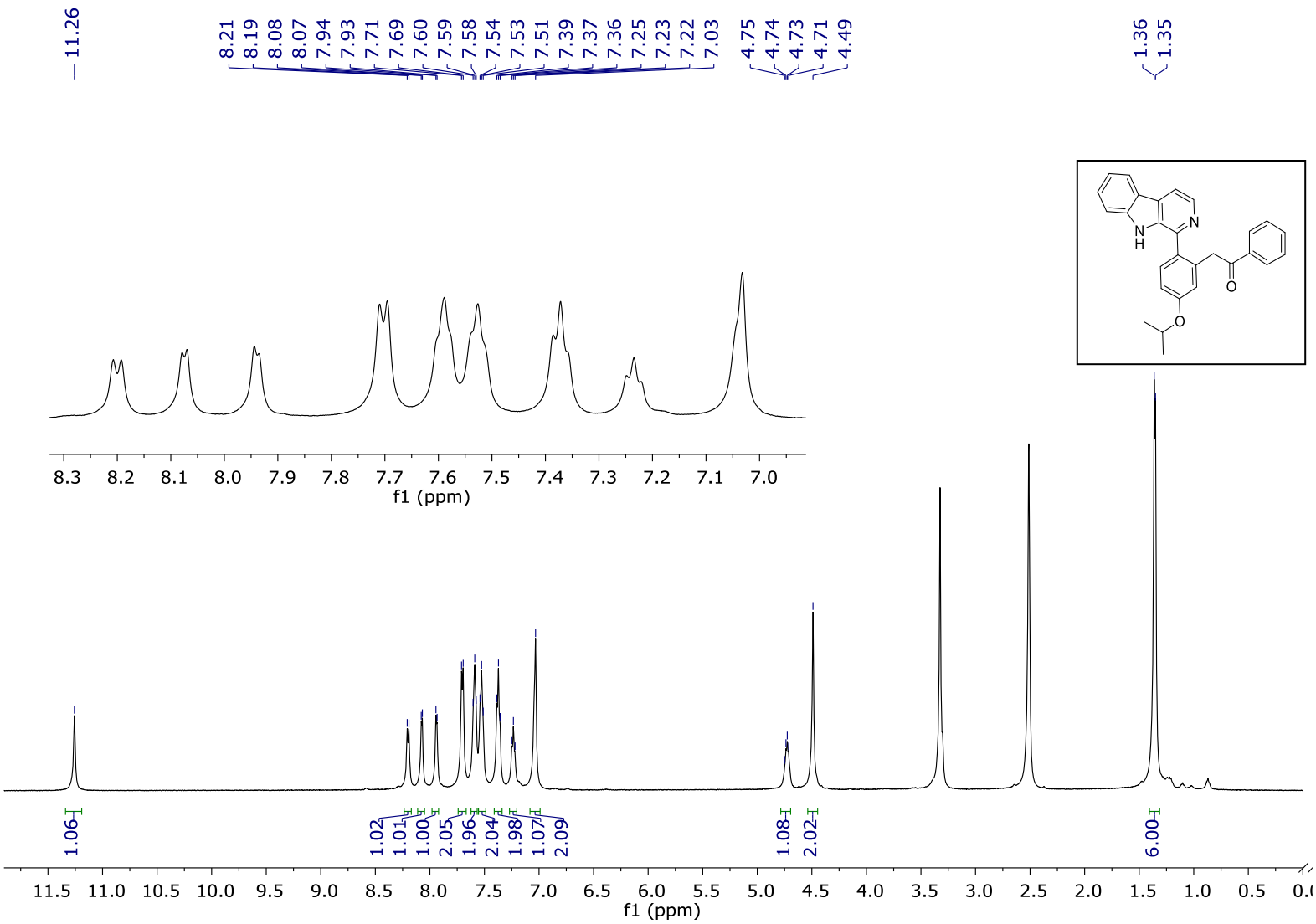
^{13}C NMR (125 MHz, DMSO-d_6) of compound **3b**



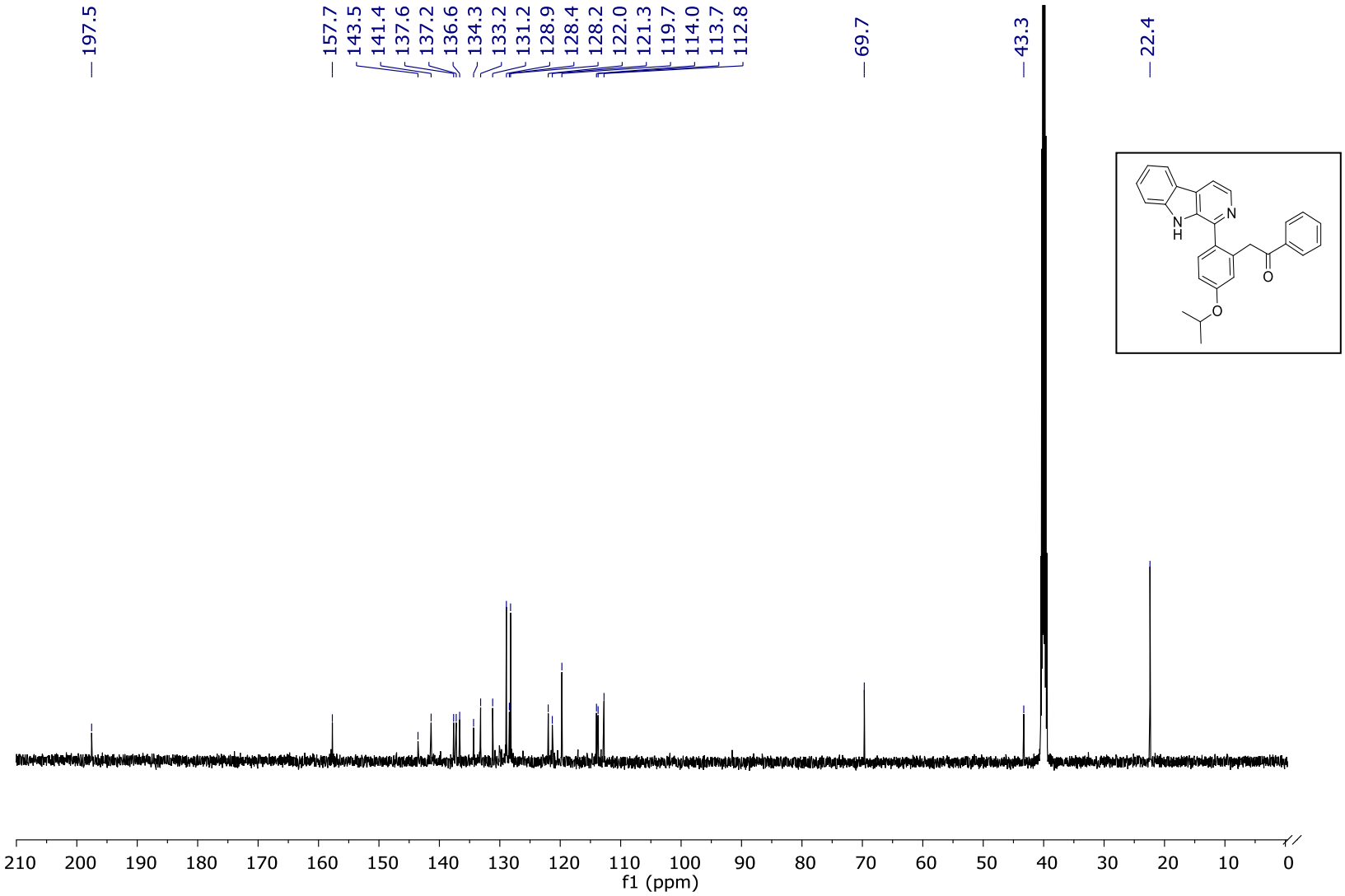
^{1}H NMR (500 MHz, DMSO-d_6) of compound **3c**



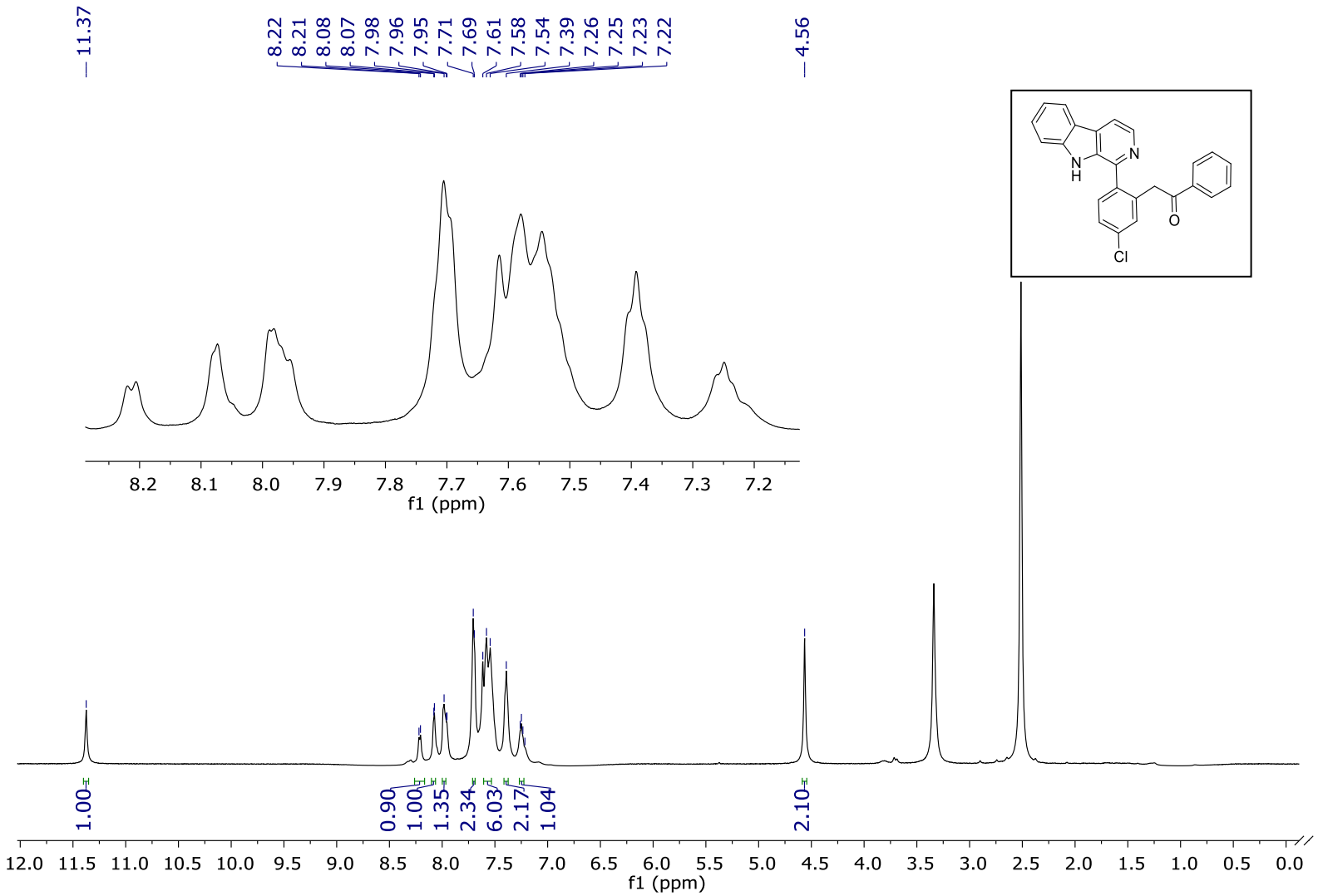
^{13}C NMR (125 MHz, DMSO-d_6) of compound **3c**



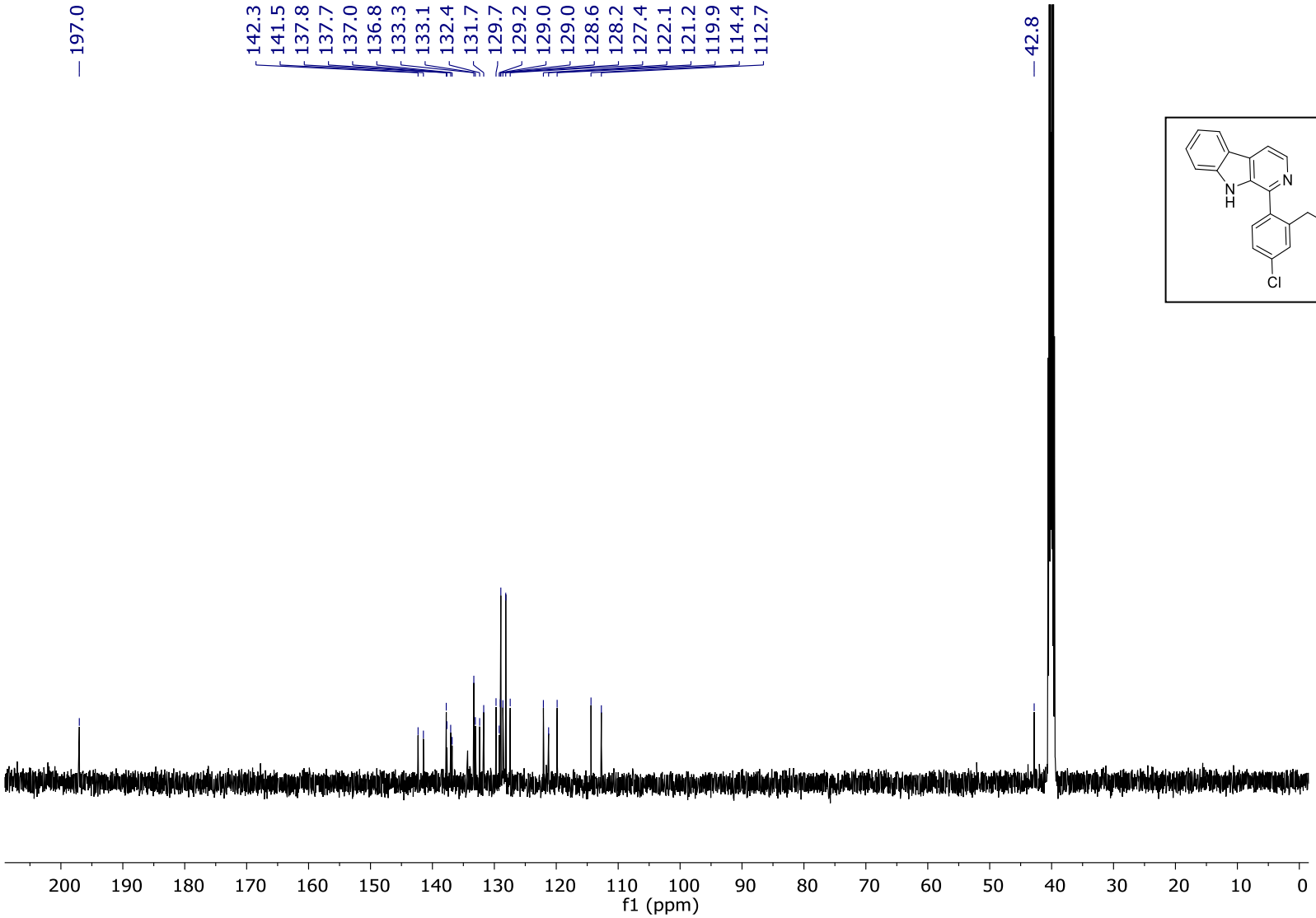
^{1}H NMR (500 MHz, DMSO-d_6) of compound **3d**



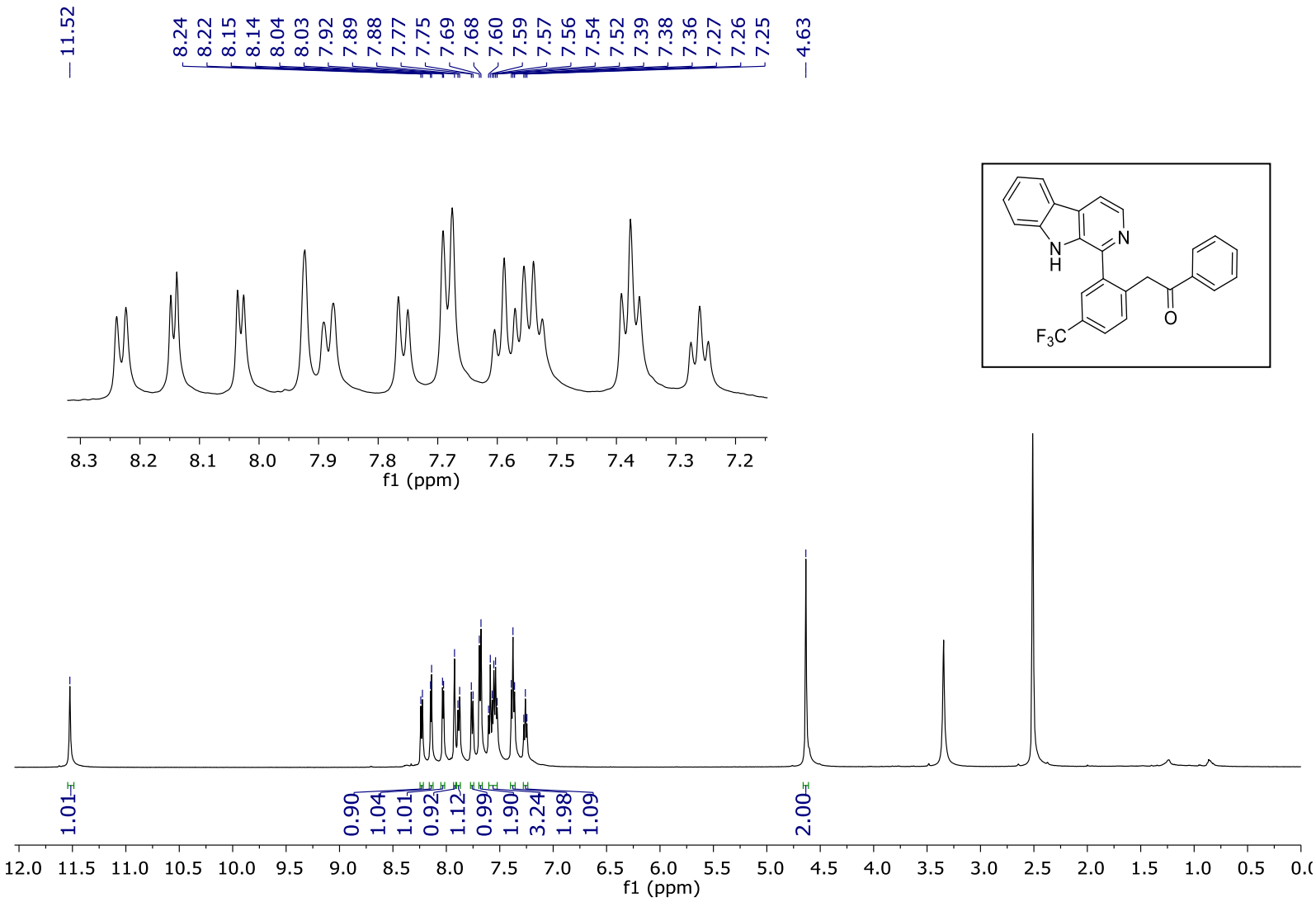
^{13}C NMR (125 MHz, DMSO-d_6) of compound **3d**



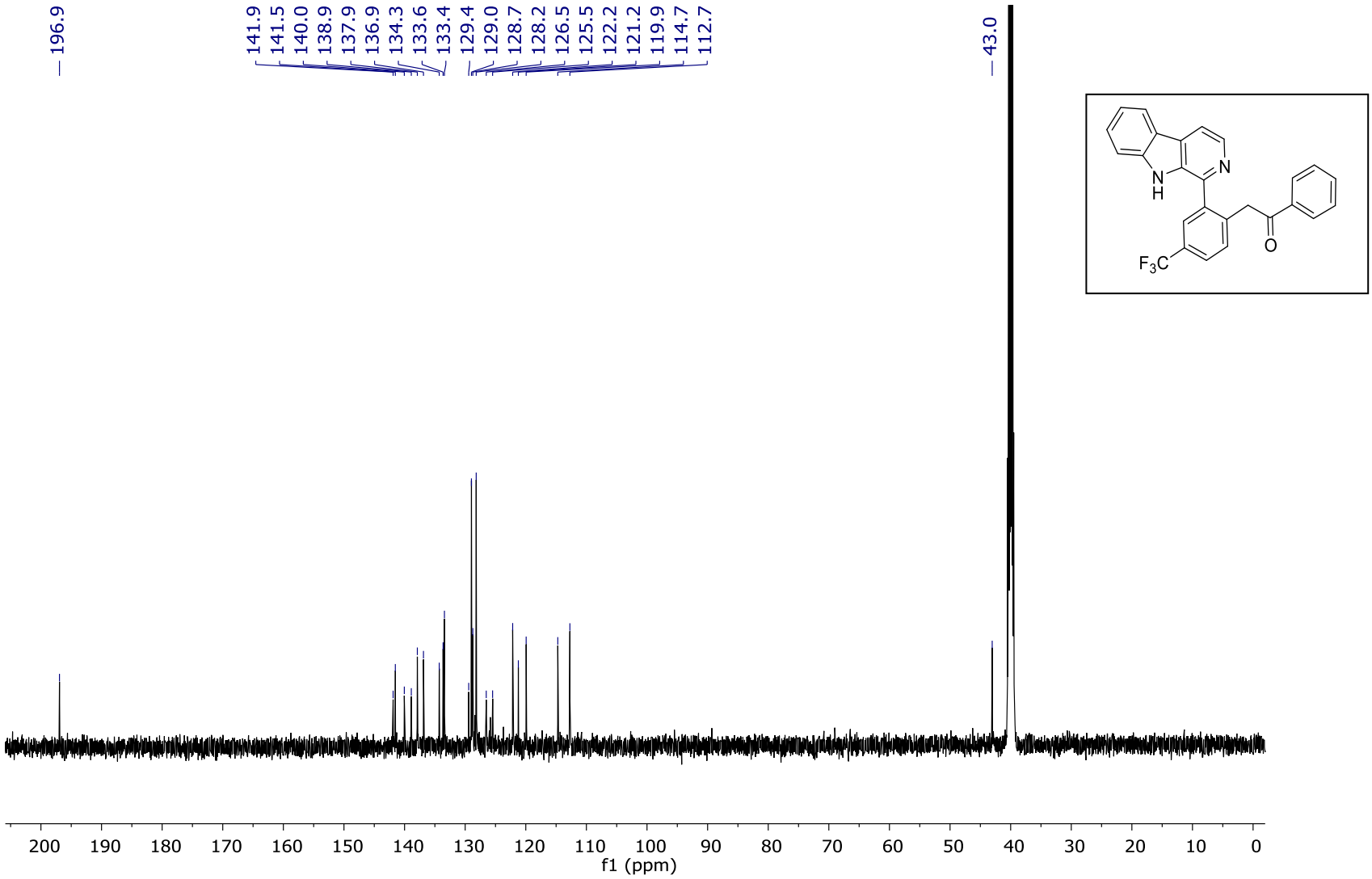
^{1}H NMR (500 MHz, DMSO-d_6) of compound **3e**



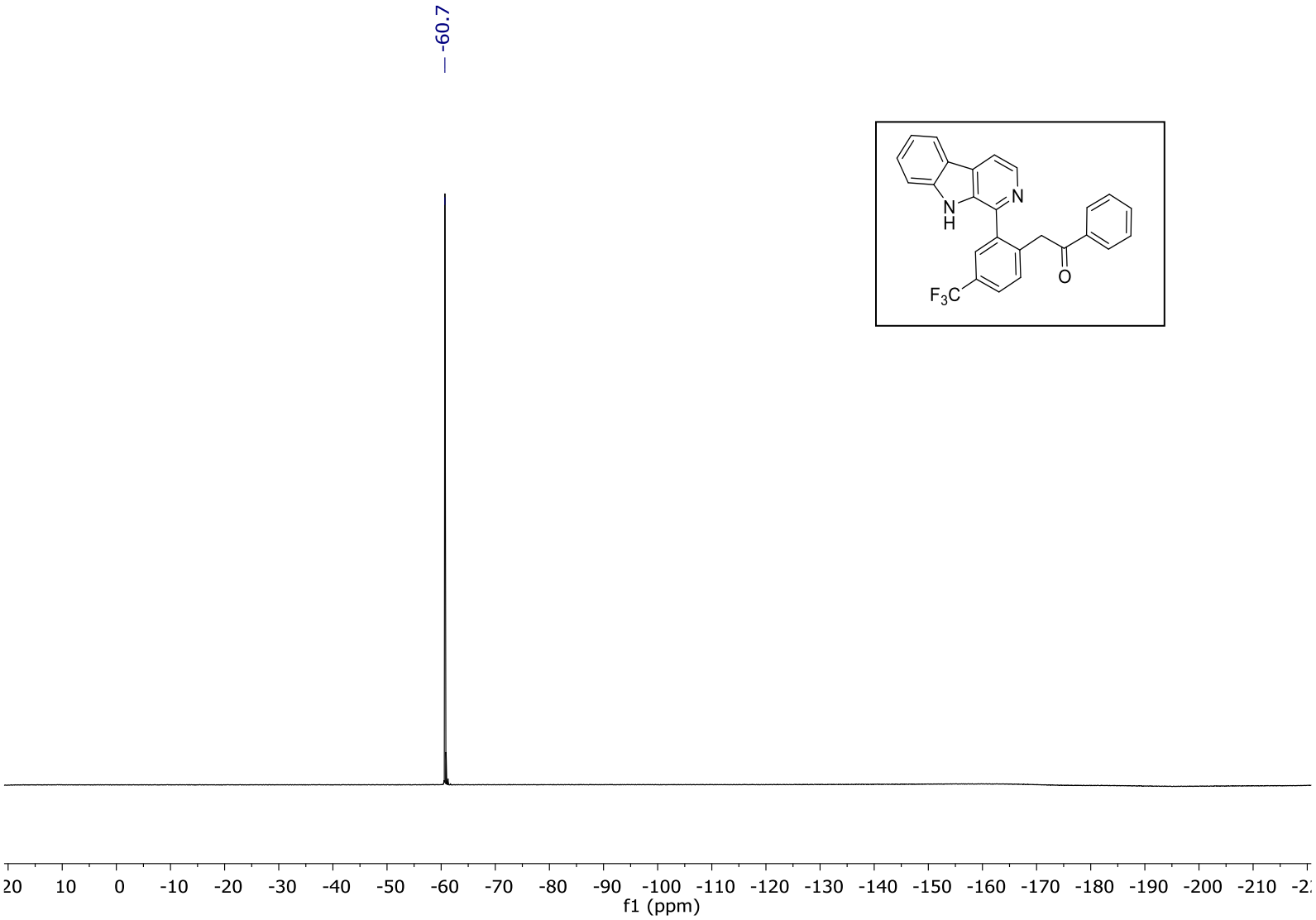
^{13}C NMR (125 MHz, DMSO-d_6) of compound **3e**



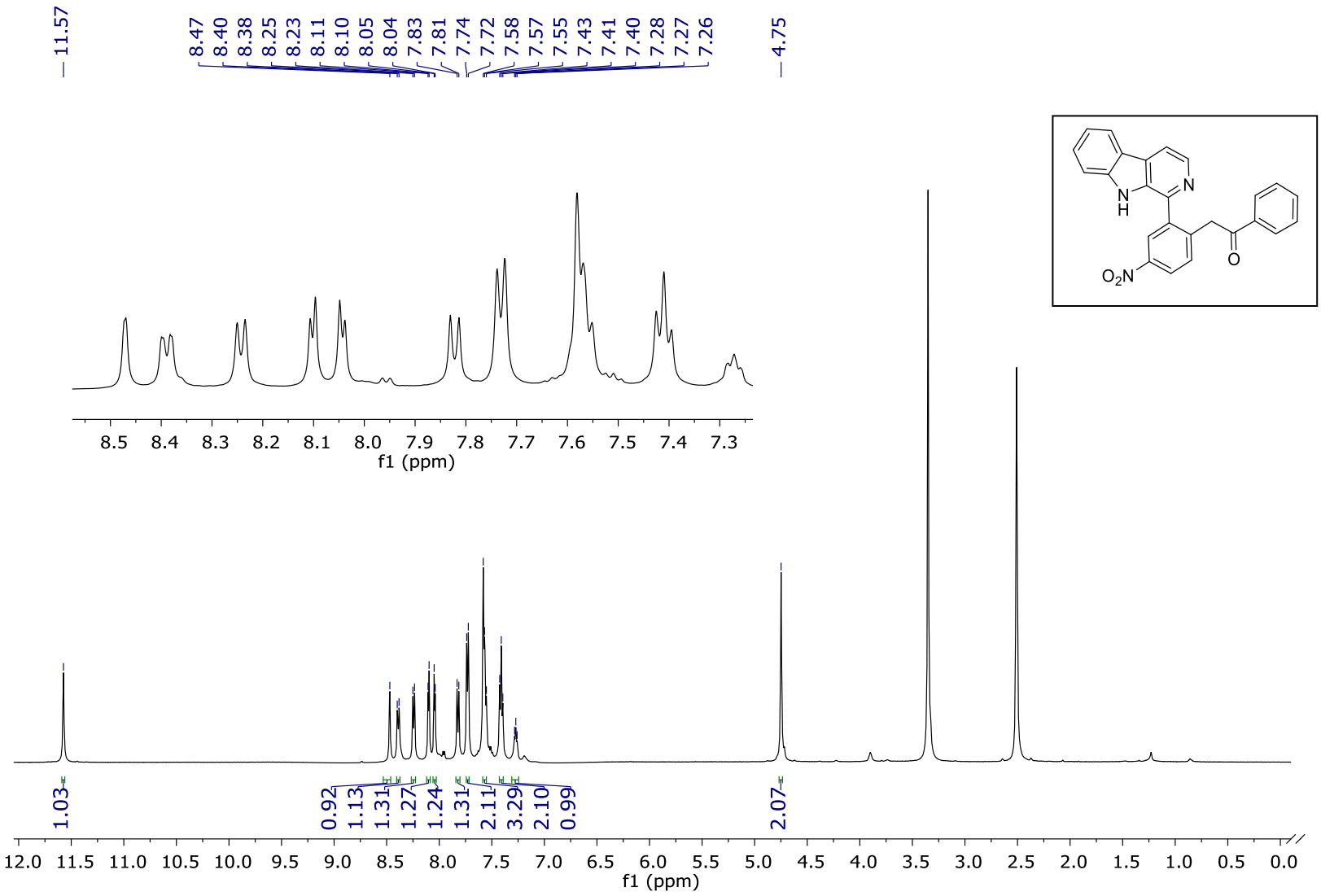
^{1}H NMR (500 MHz, DMSO-d_6) of compound **3f**



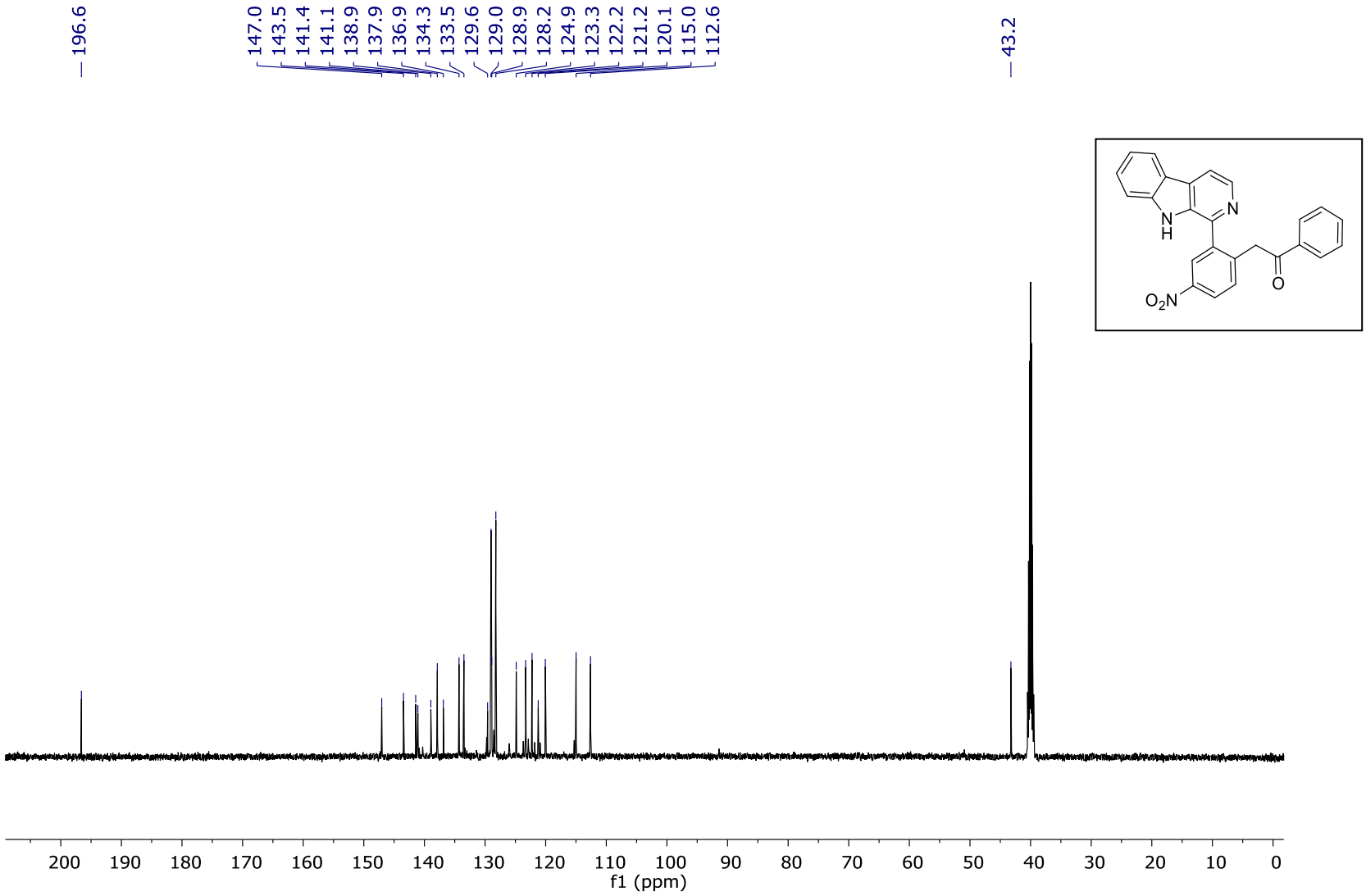
^{13}C NMR (125 MHz, DMSO-d_6) of compound **3f**



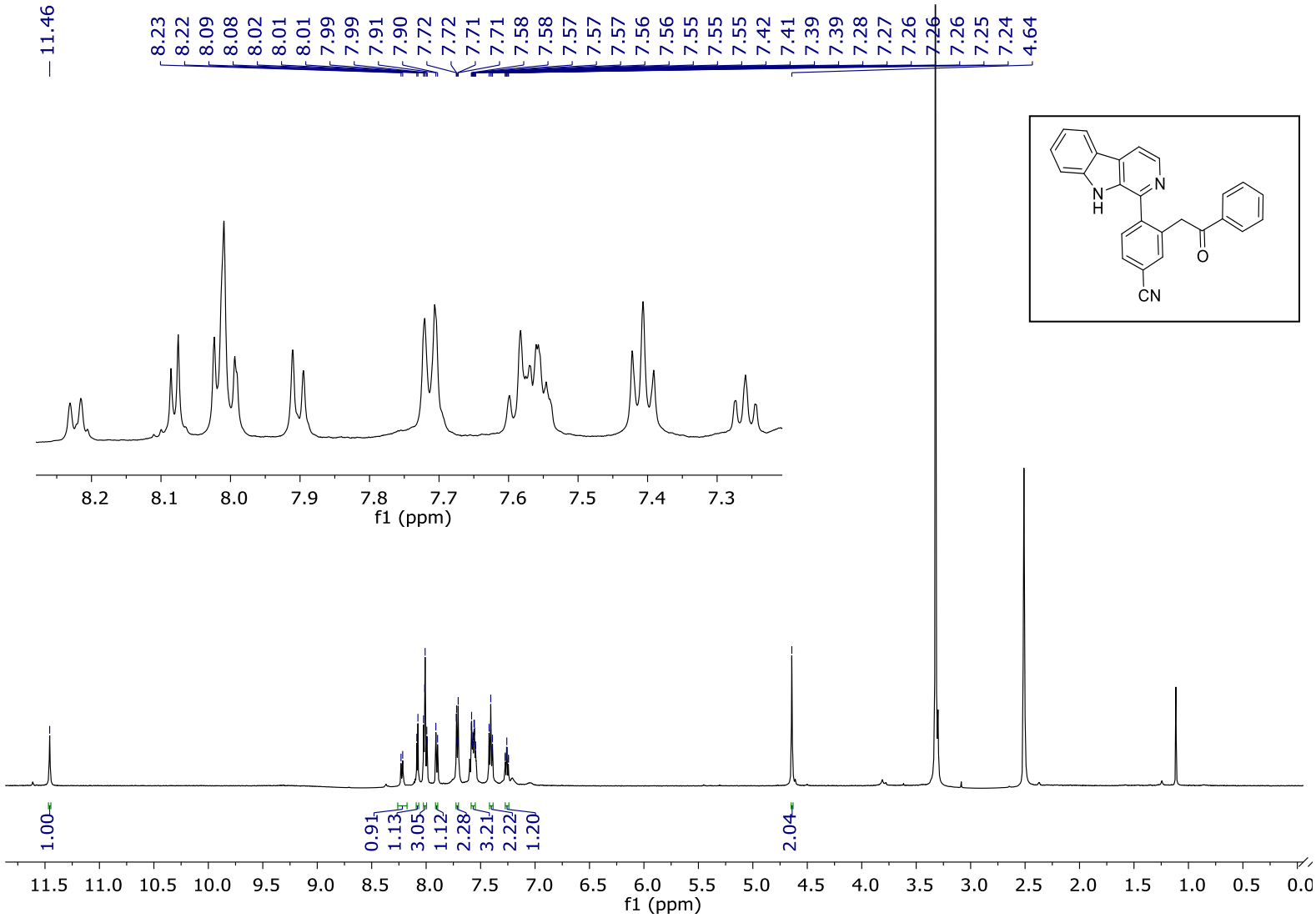
^{19}F NMR (470 MHz, DMSO-d_6) of compound **3f**



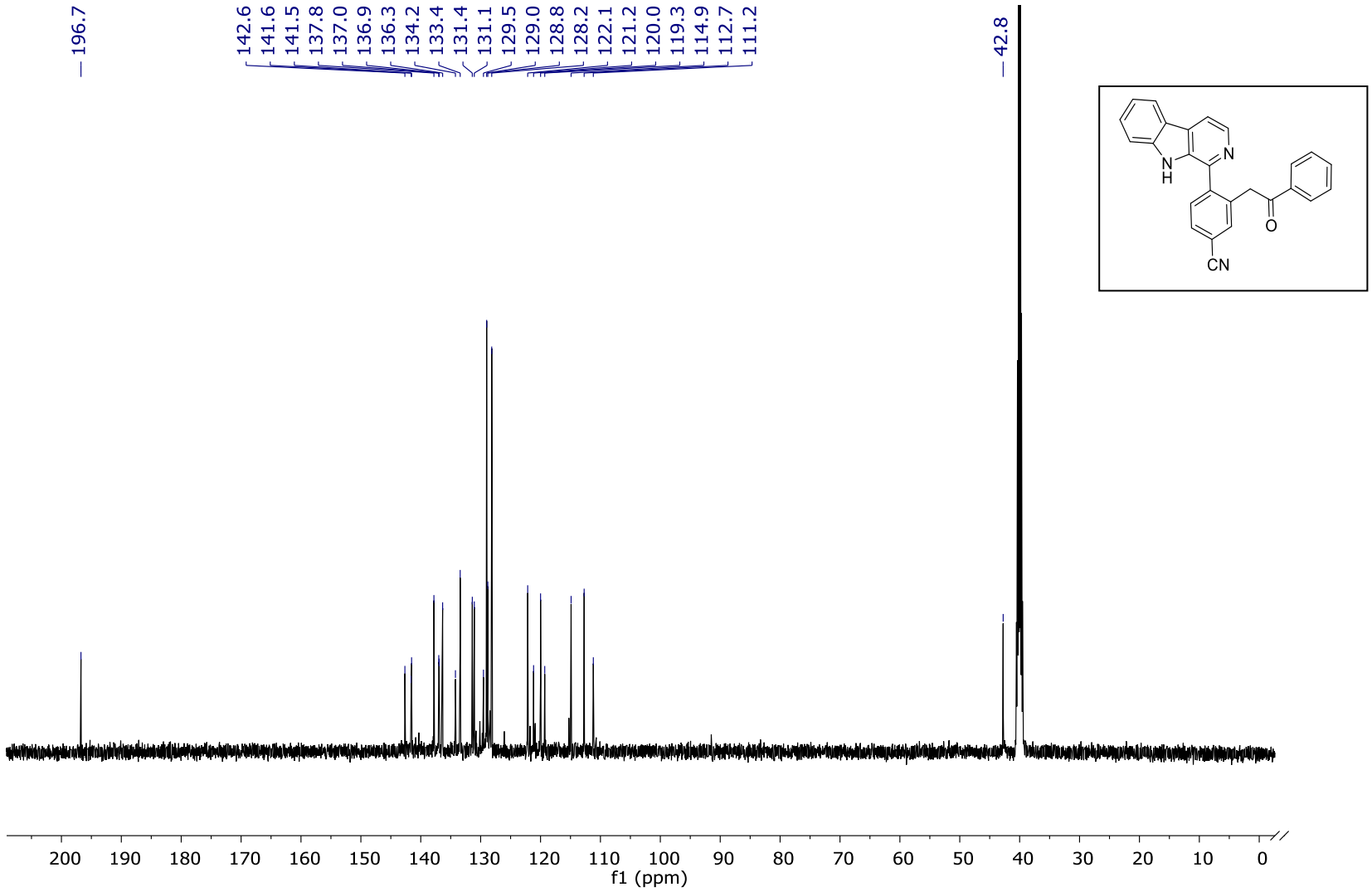
^{1}H NMR (500 MHz, DMSO-d_6) of compound **3g**



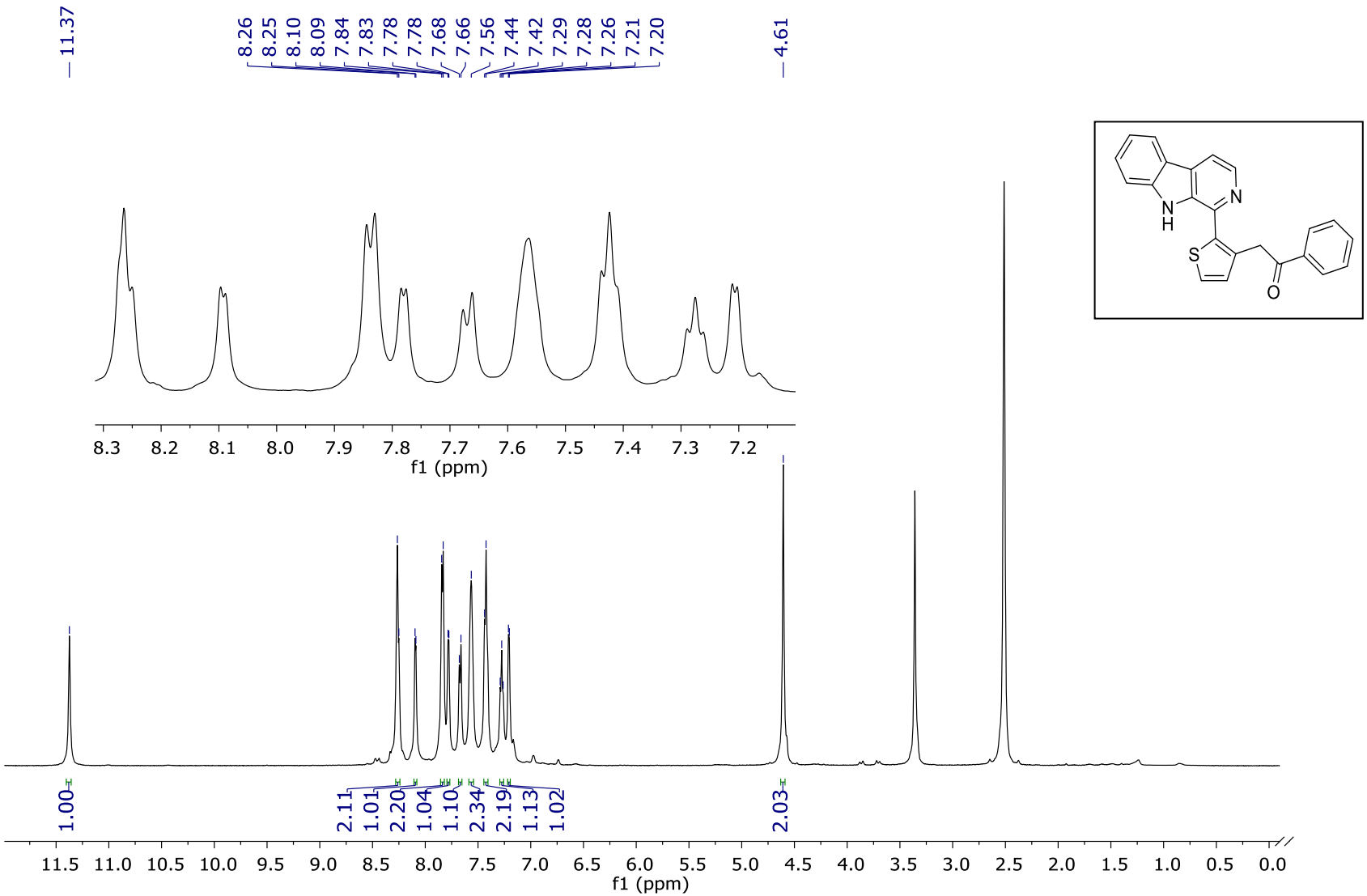
^{13}C NMR (125 MHz, DMSO-d_6) of compound **3g**



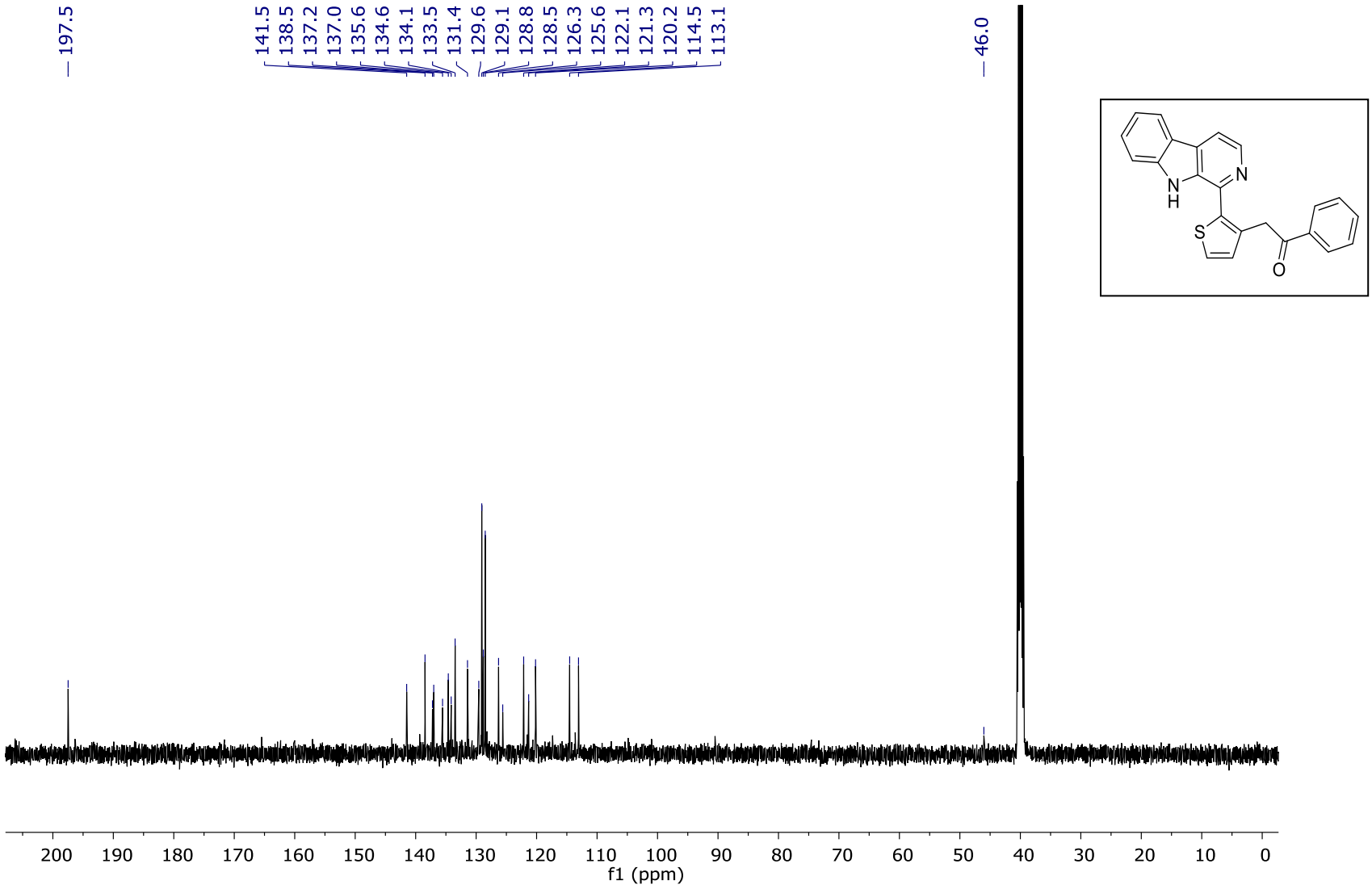
^{1}H NMR (500 MHz, DMSO-d_6) of compound **3h**



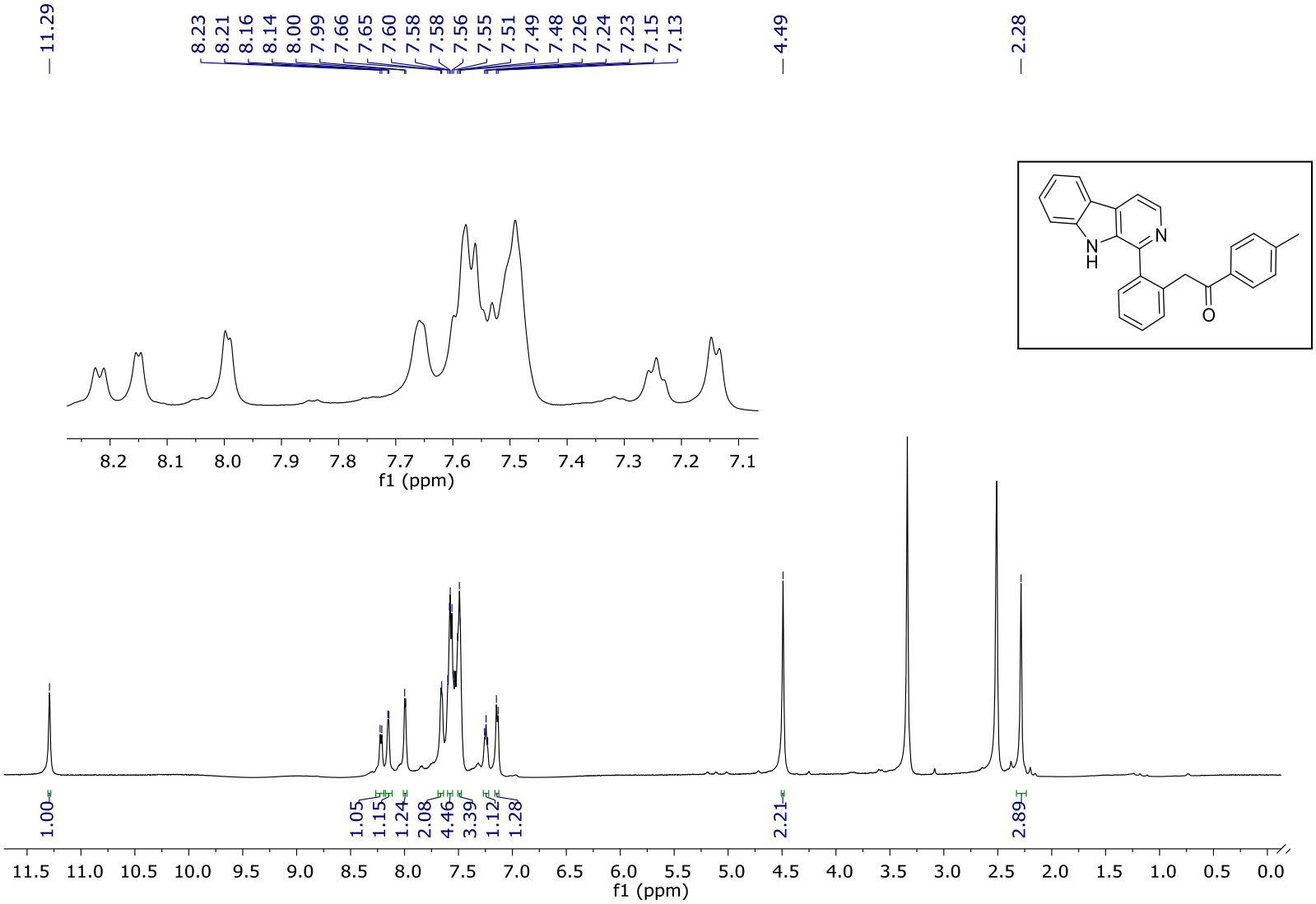
^{13}C NMR (125 MHz, DMSO-d_6) of compound **3h**



^{1}H NMR (500 MHz, DMSO-d_6) of compound **3i**



^{13}C NMR (125MHz, DMSO-d_6) of compound **3i**



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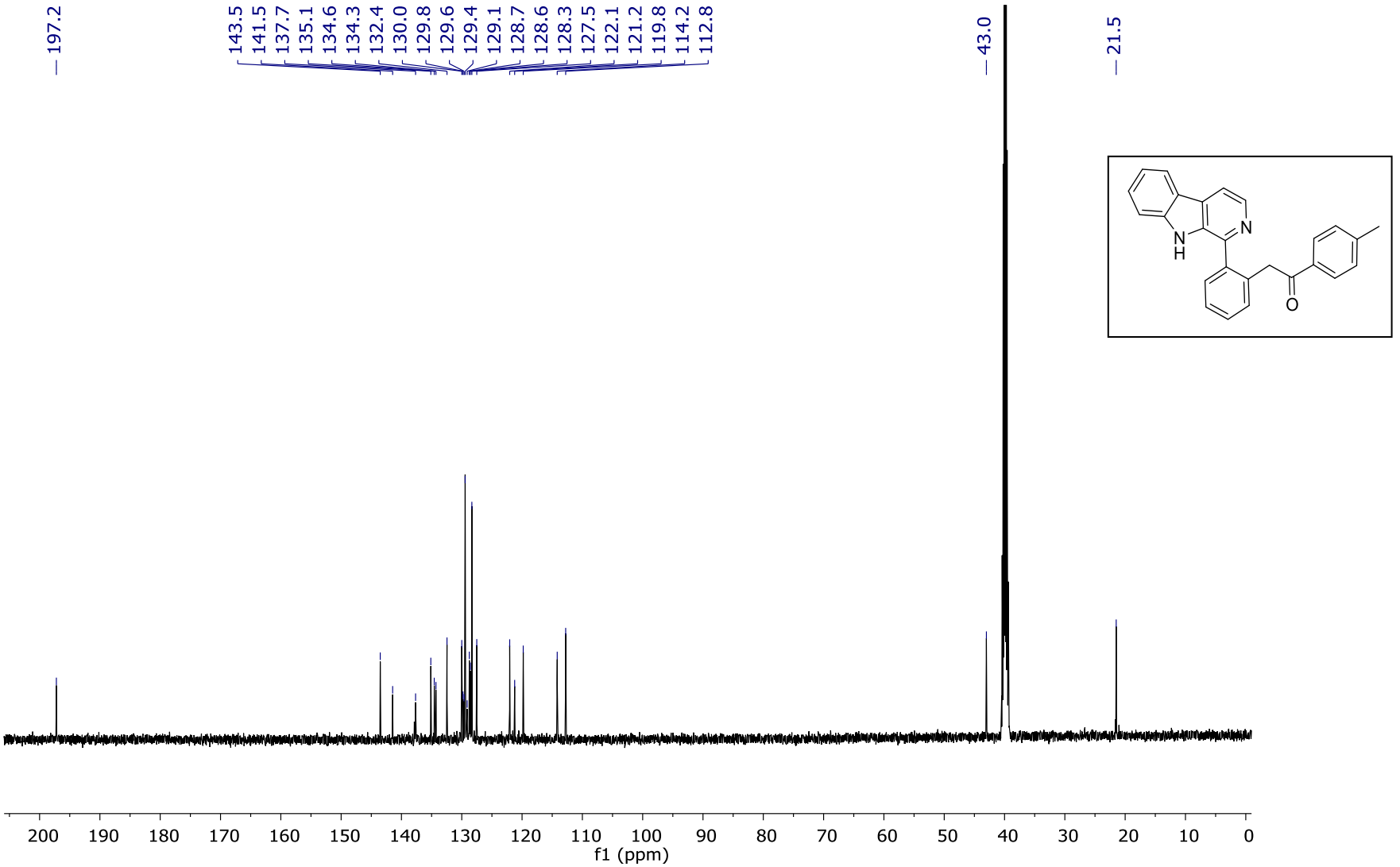
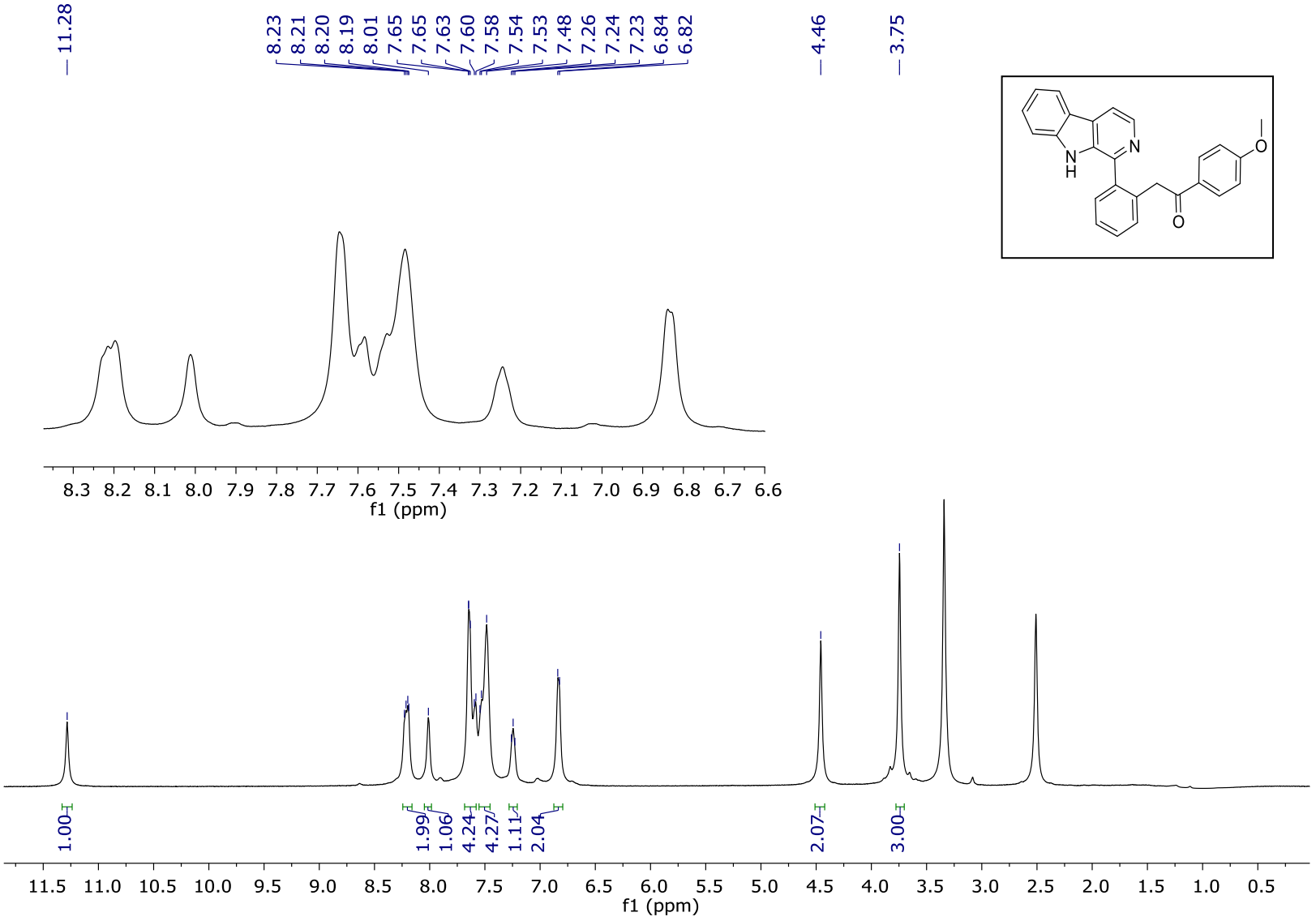


^{13}C NMR (125MHz, DMSO-d_6) of compound **3j**



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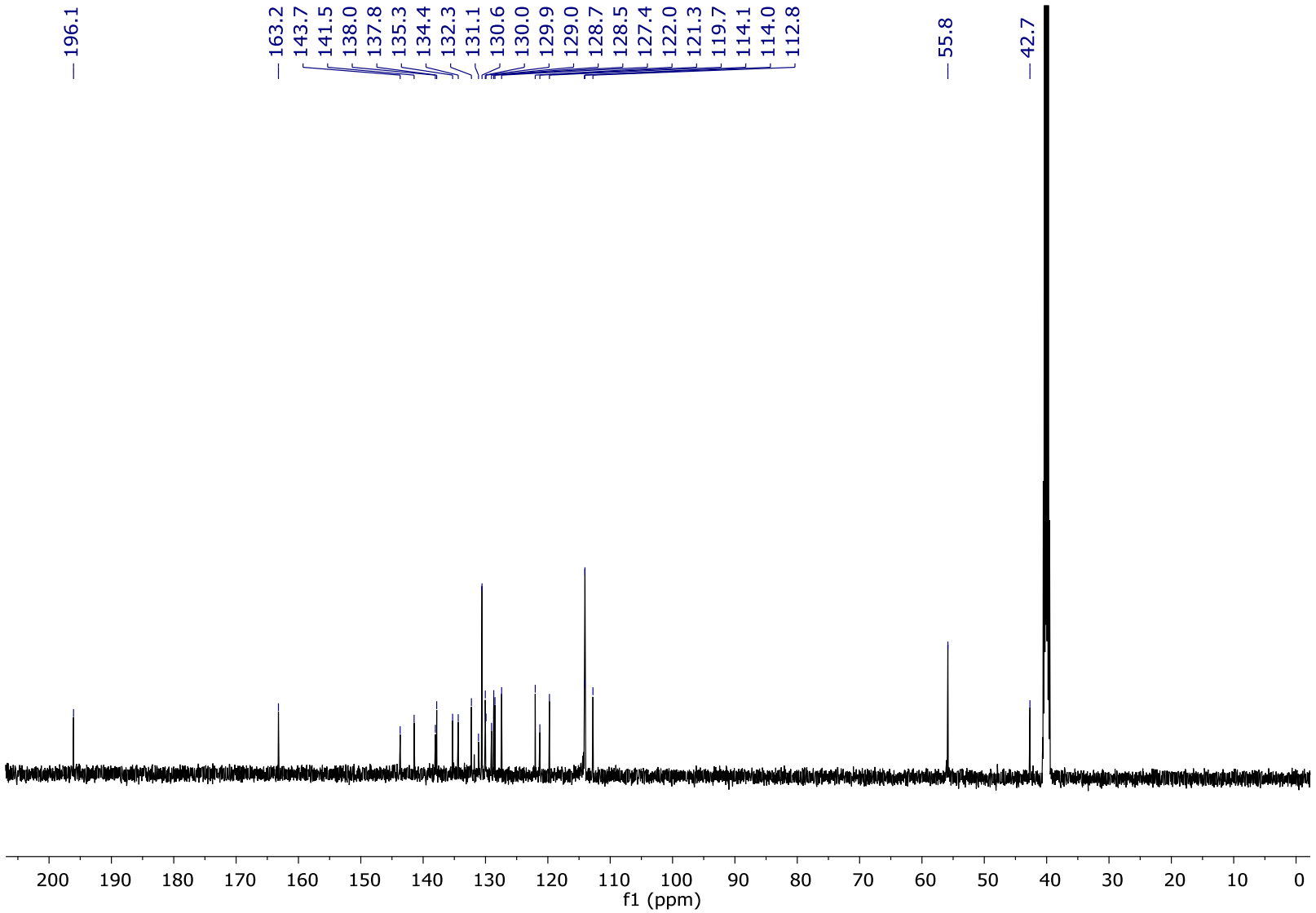
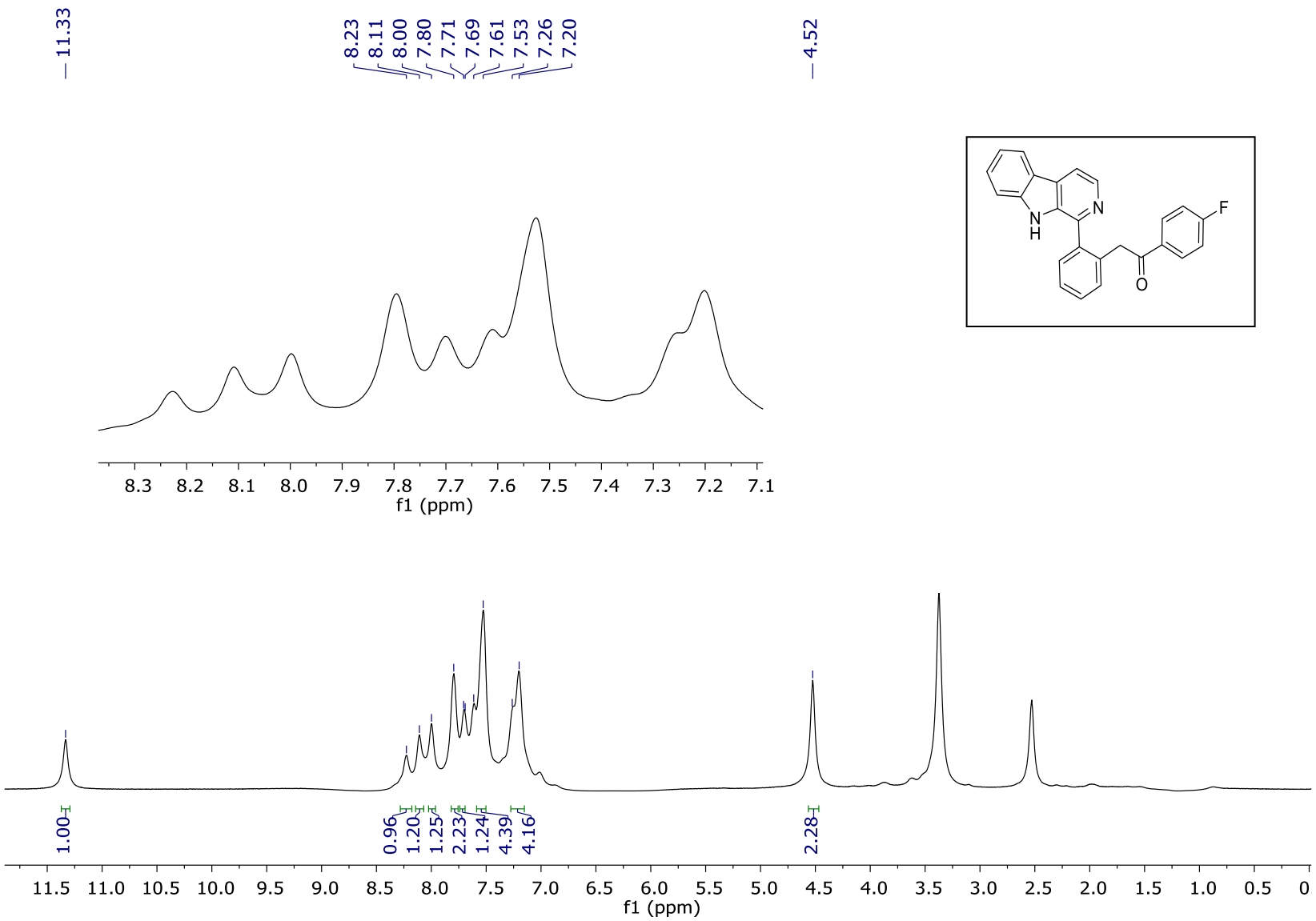


^{13}C NMR (125 MHz, DMSO-d_6) of compound **3k**



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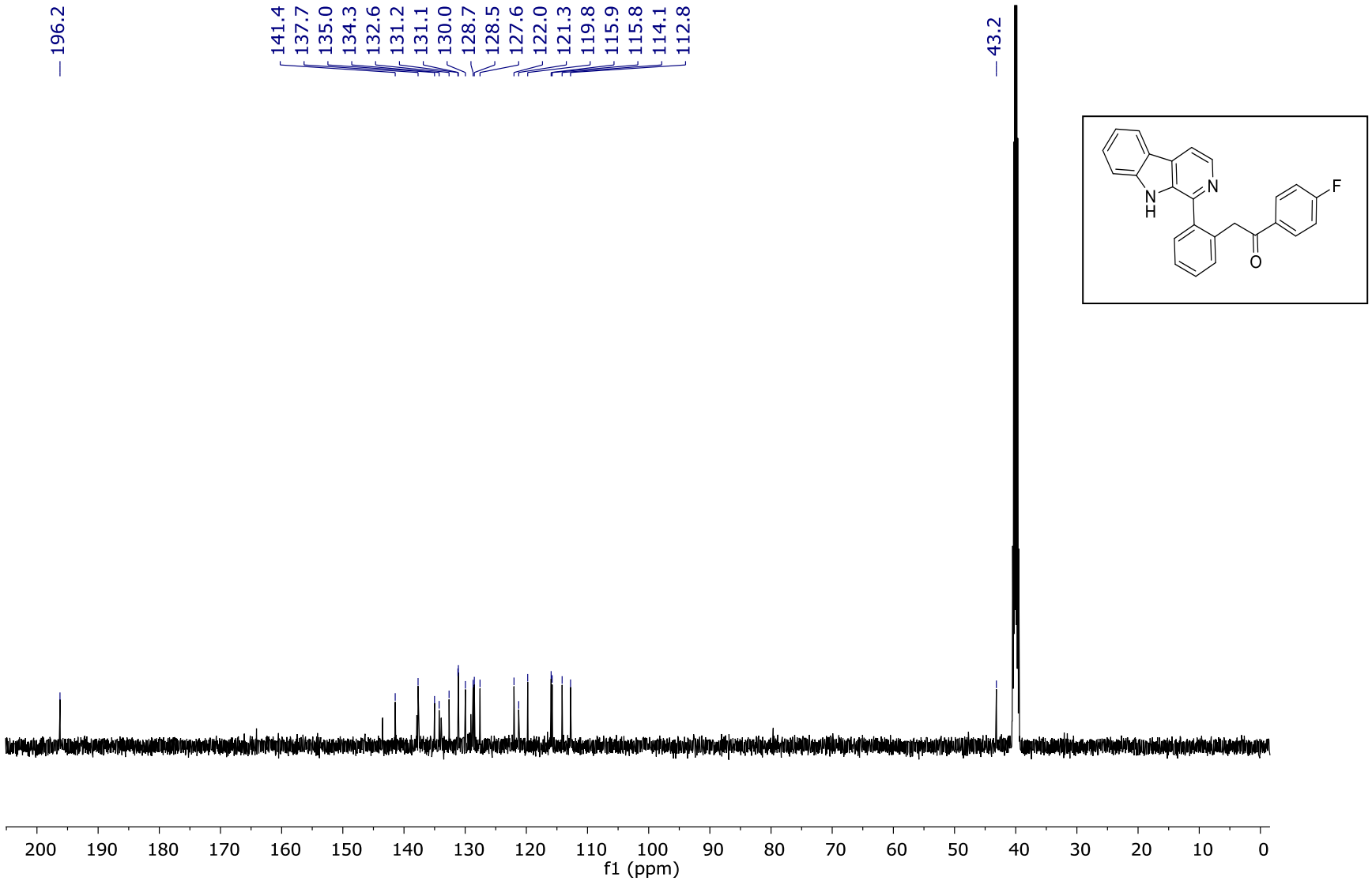
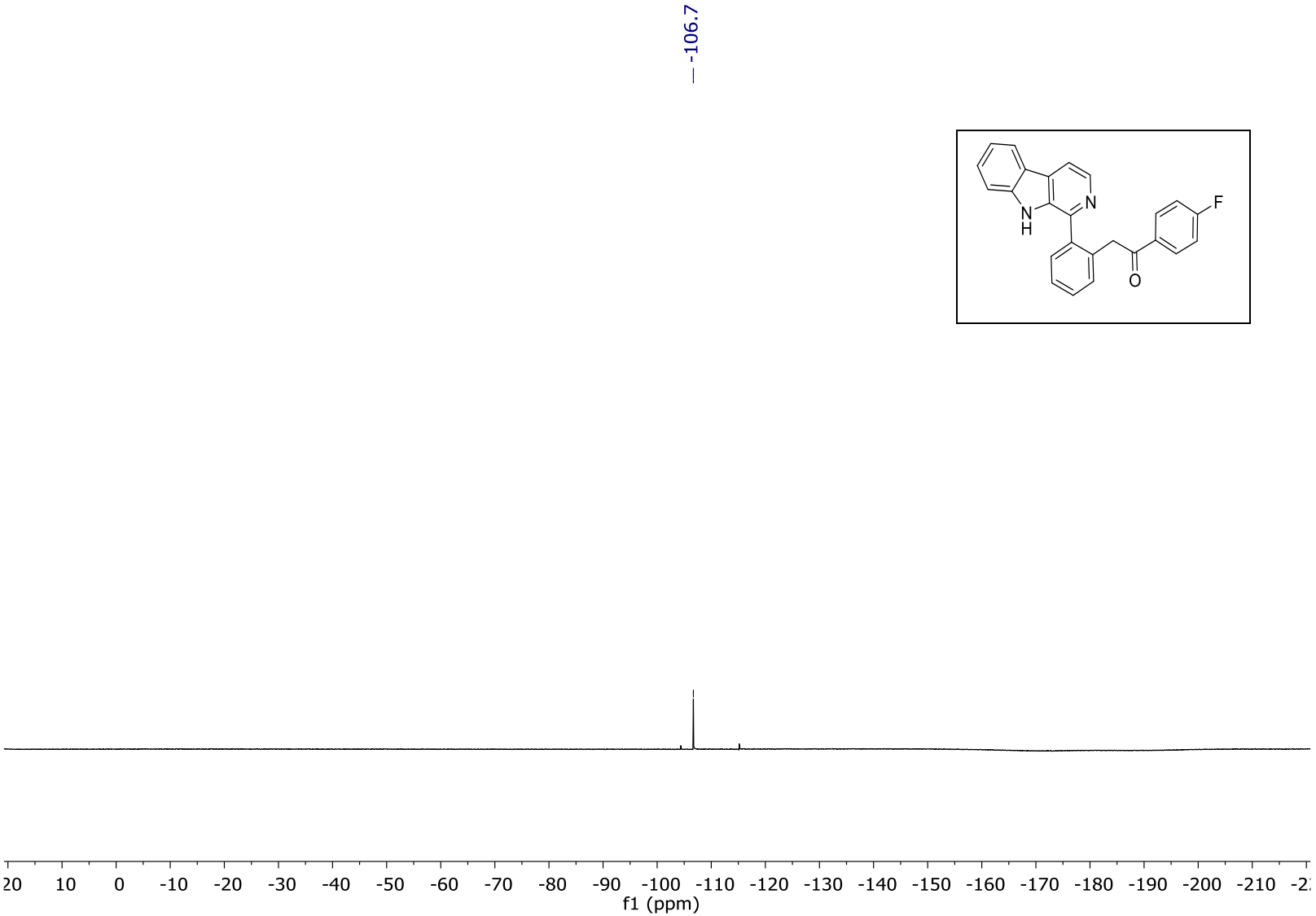
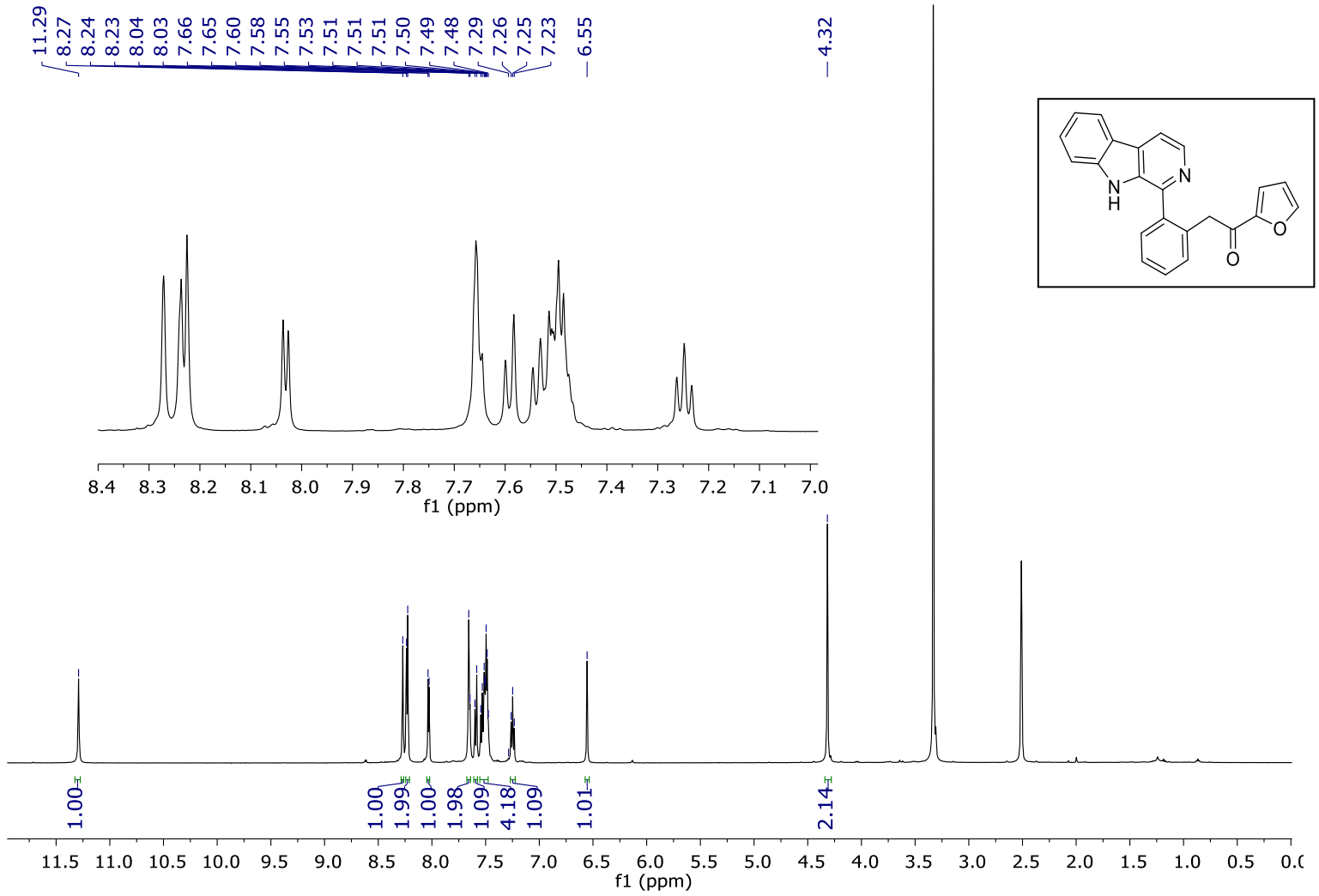


^{13}C NMR (125 MHz, DMSO-d_6) of compound **3l**



^{19}F NMR (470 MHz, DMSO-d_6) of compound **3l**



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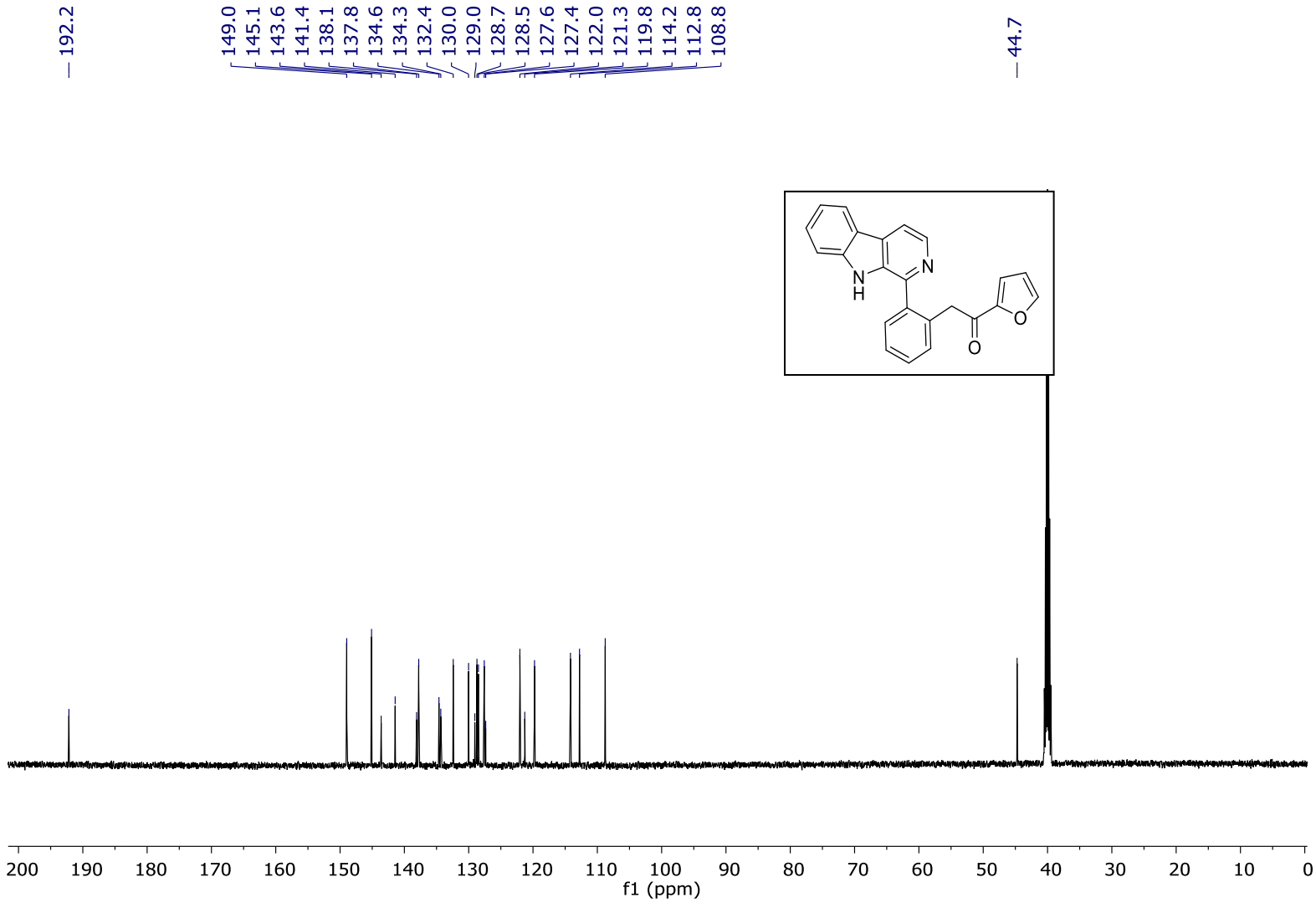

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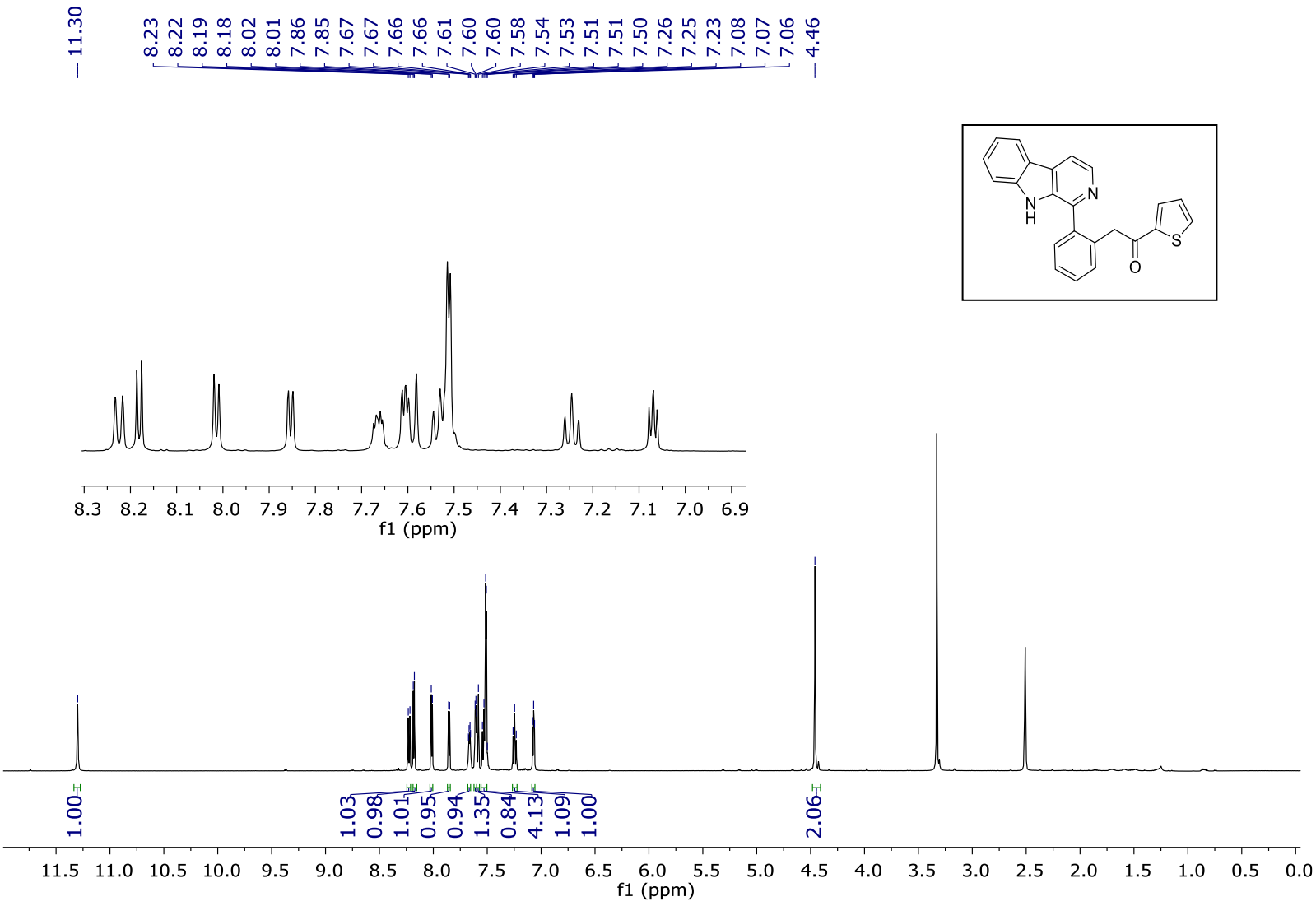

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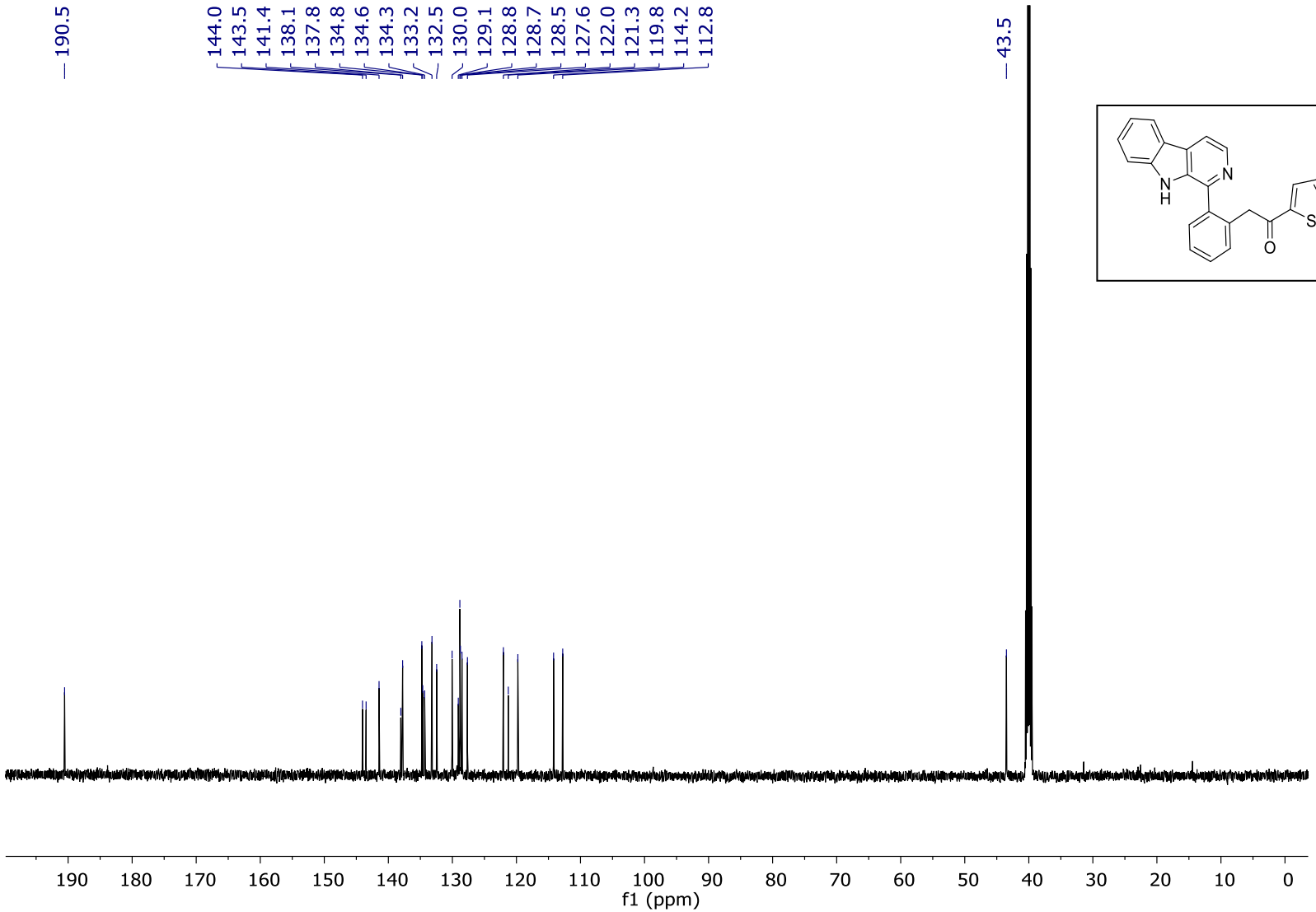

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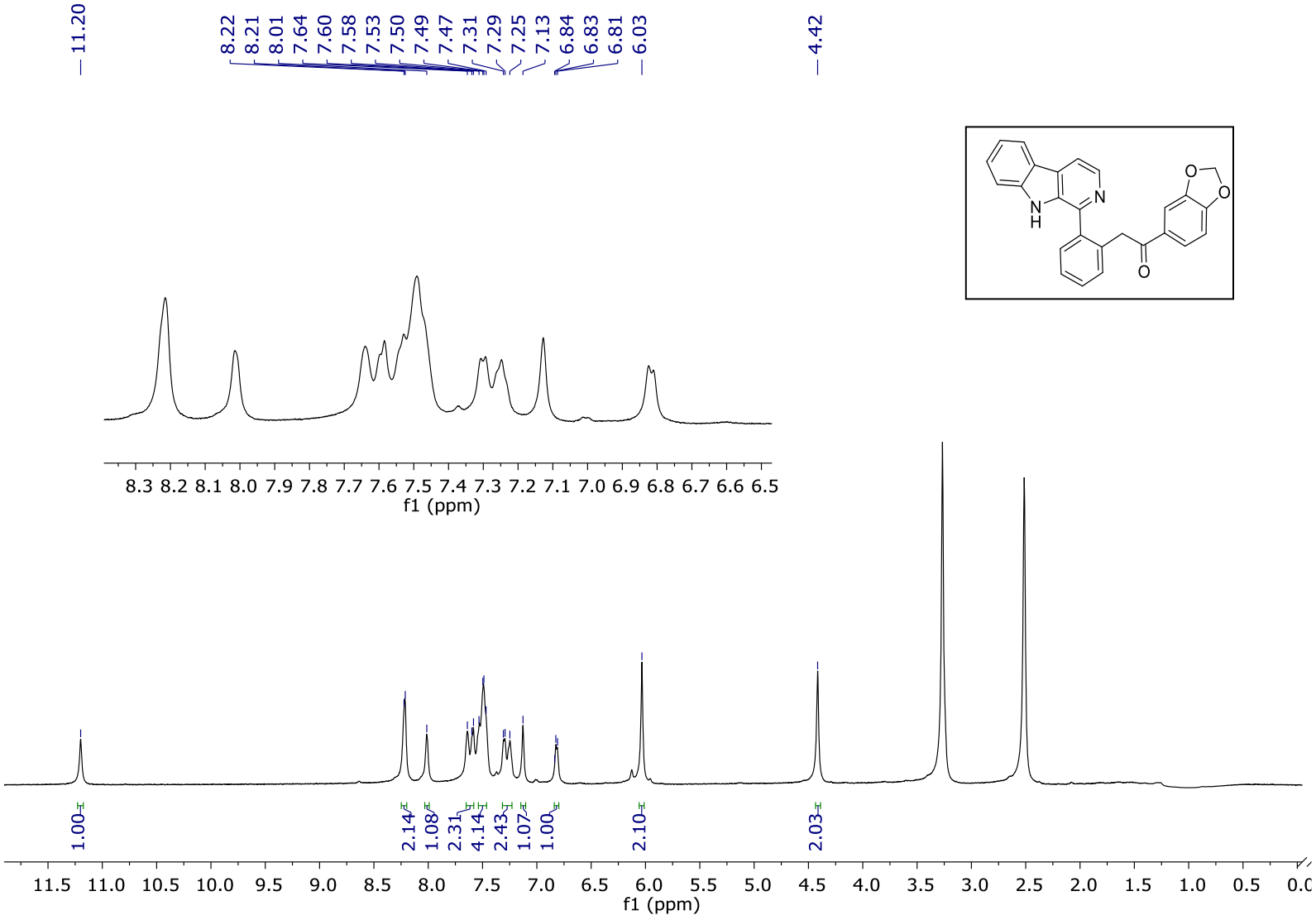

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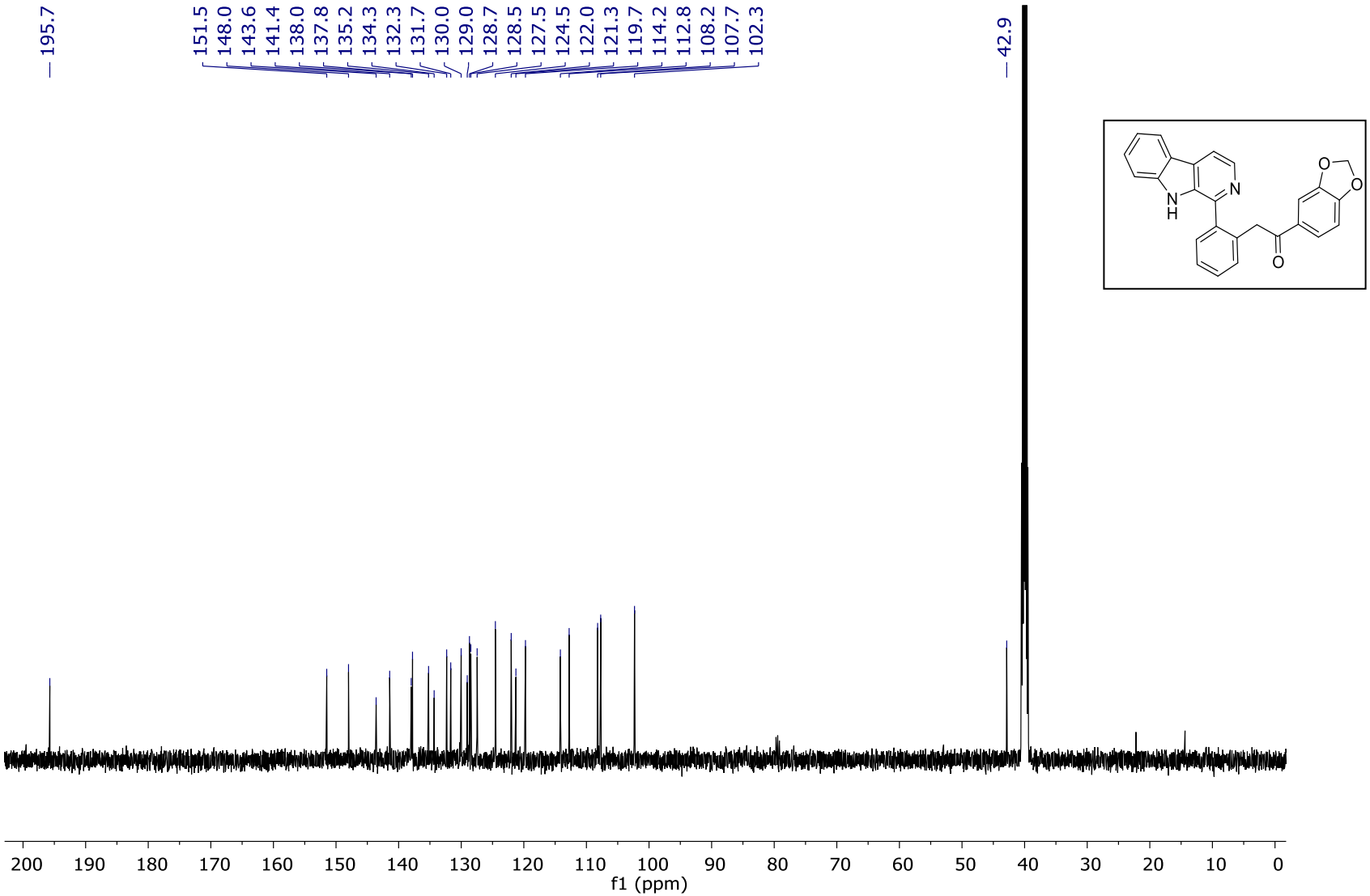

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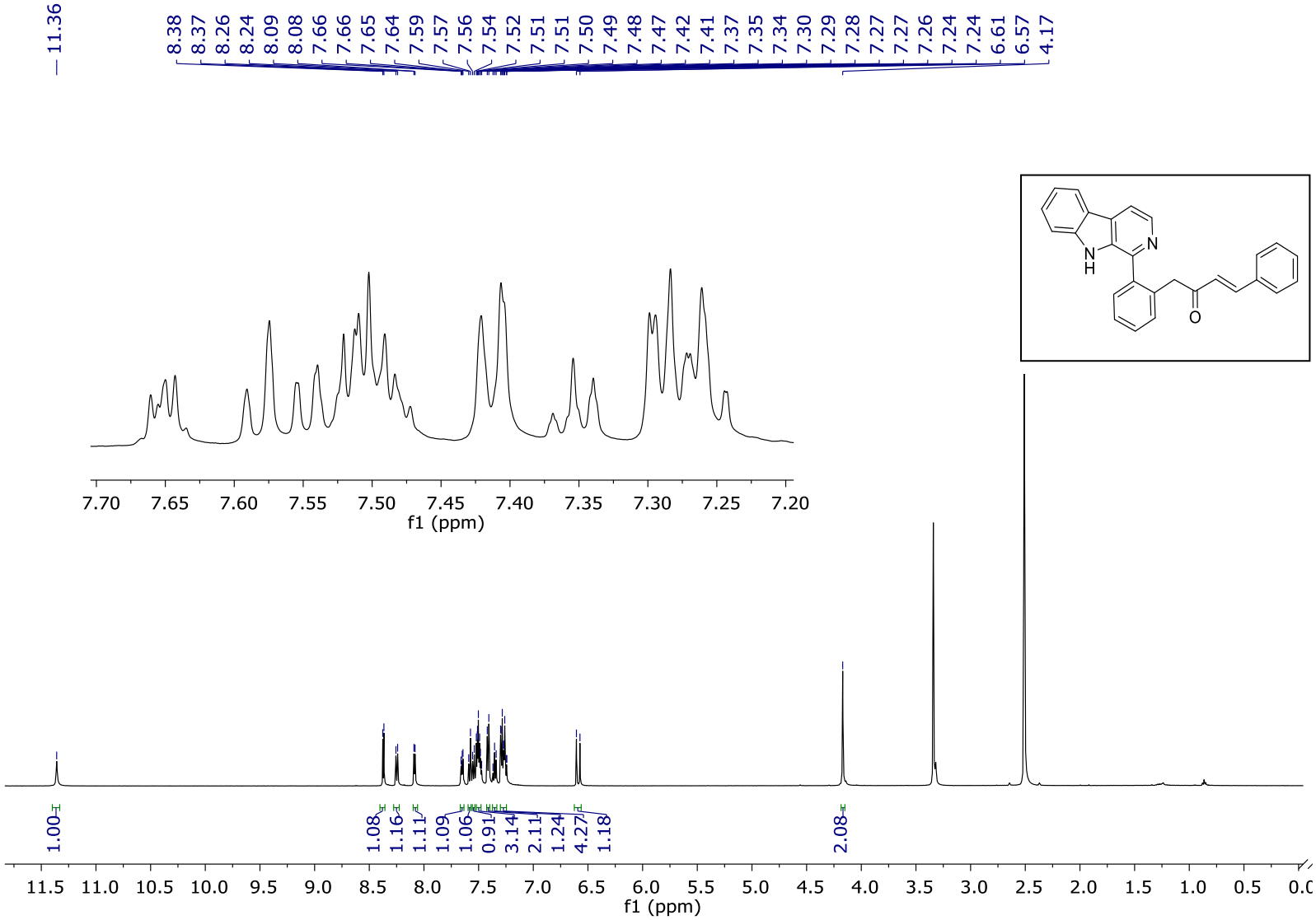

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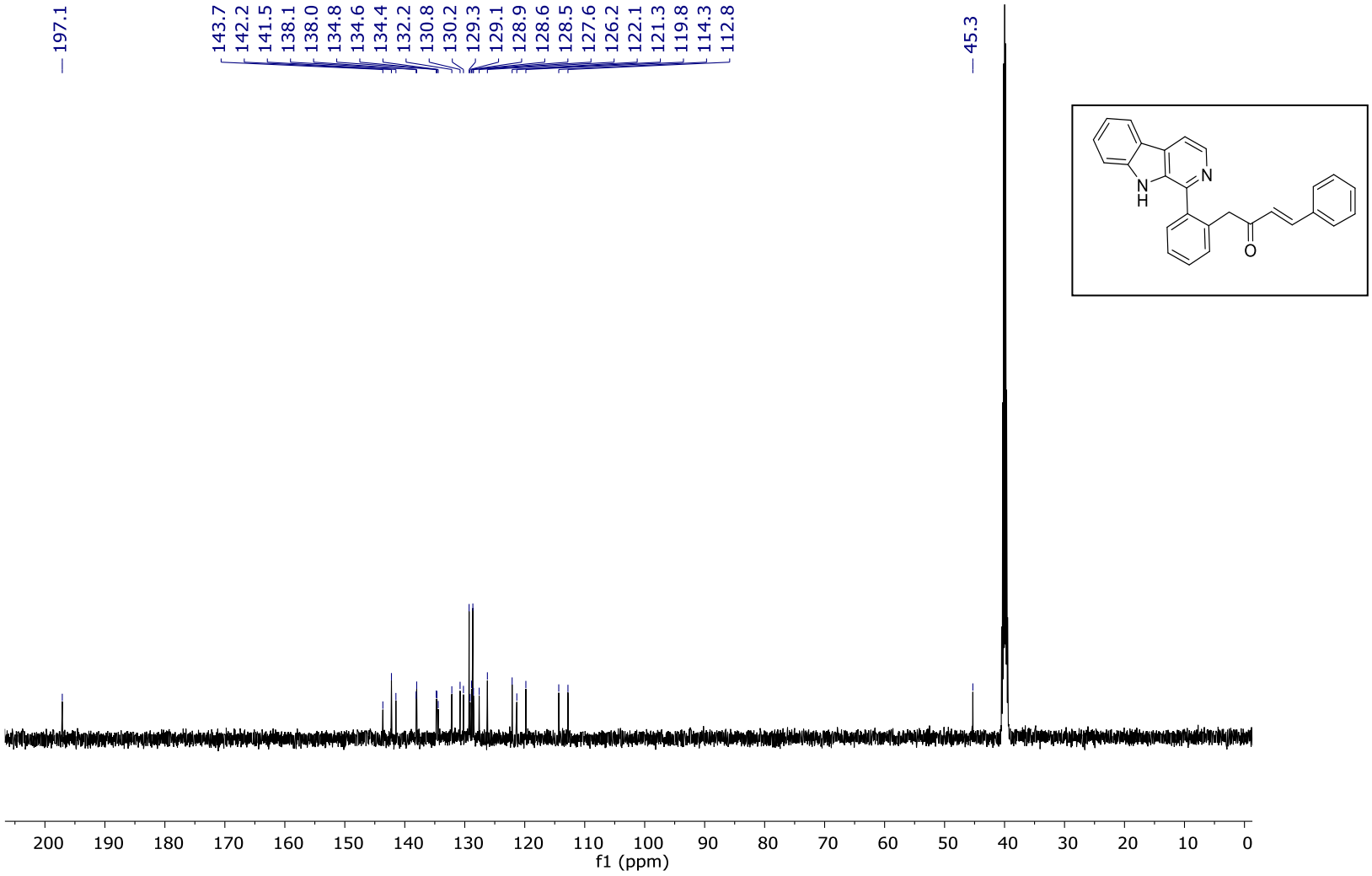

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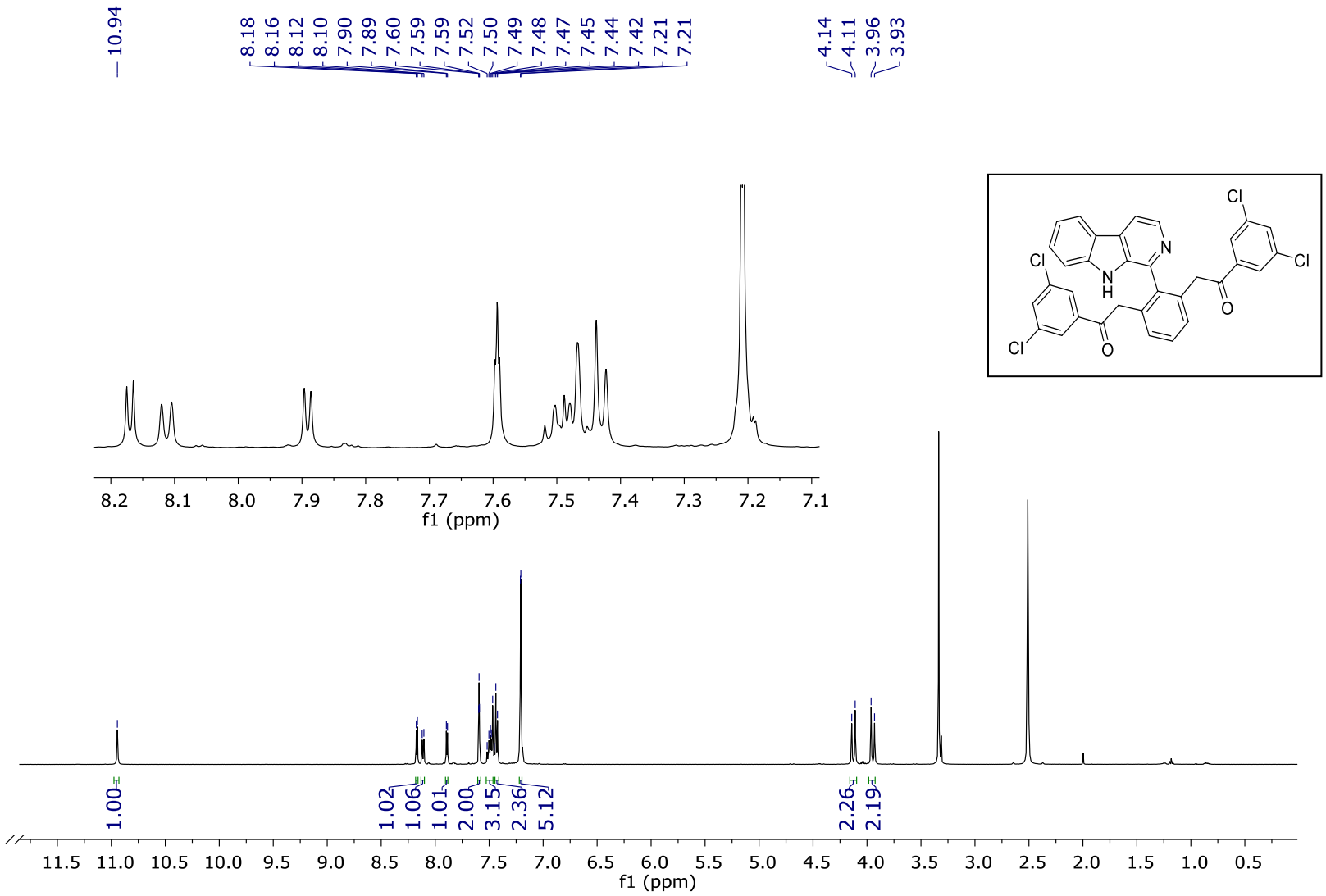
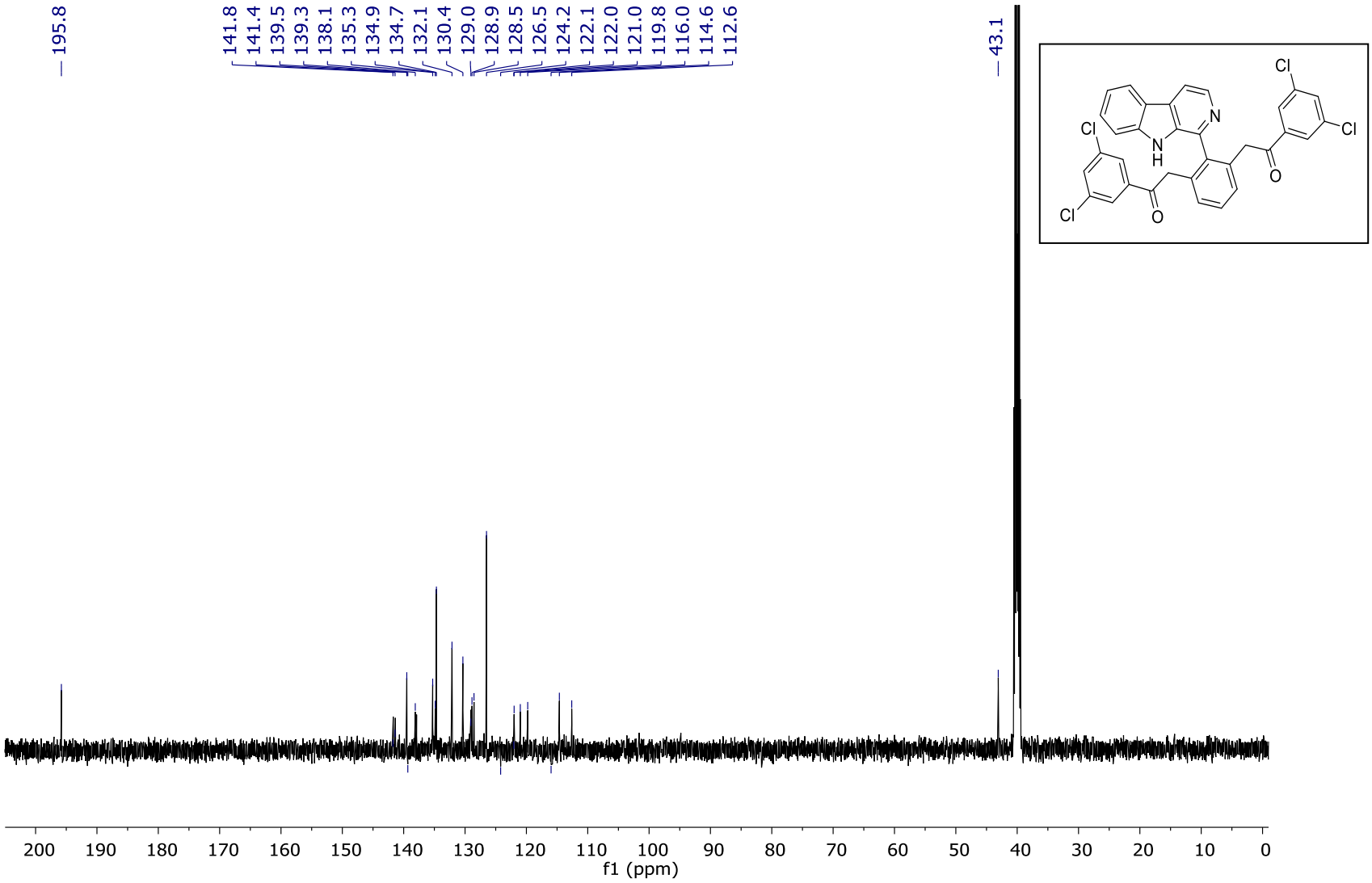
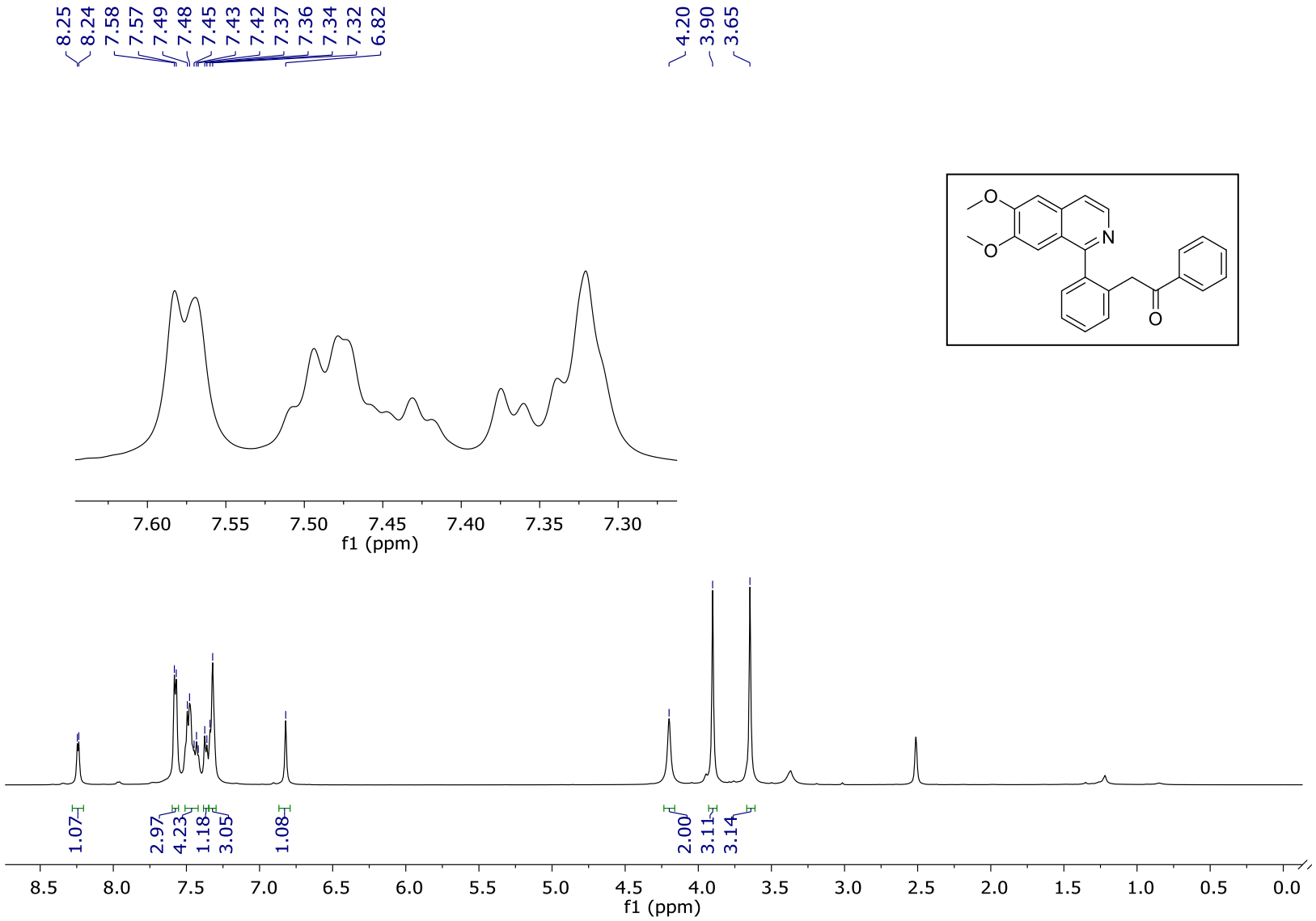


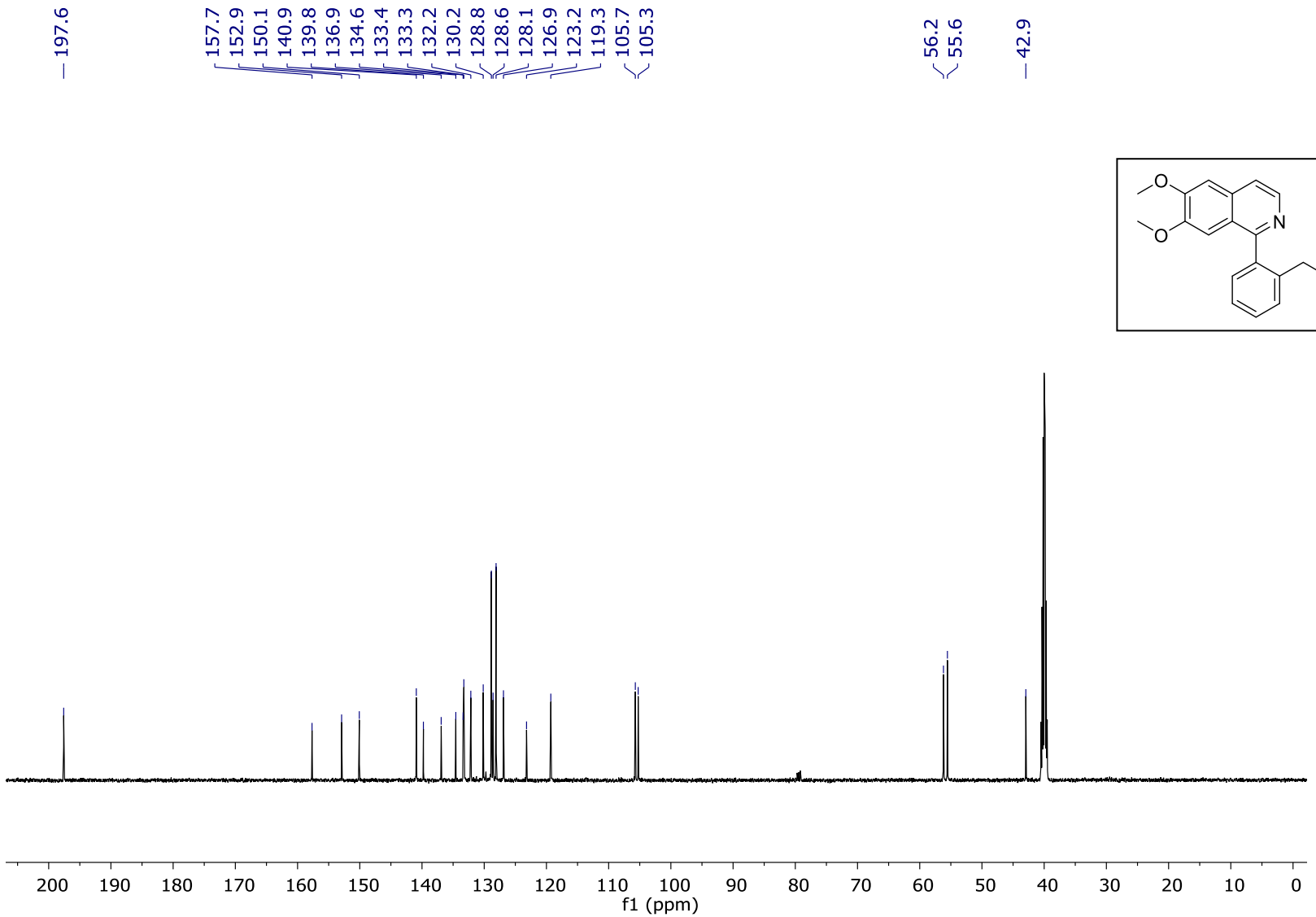
^{1}H NMR (500 MHz, DMSO-d_6) of compound **3q**



^{13}C NMR (125 MHz, DMSO-d_6) of compound **3q**



^{1}H NMR (500 MHz, DMSO-d_6) of compound **5a**



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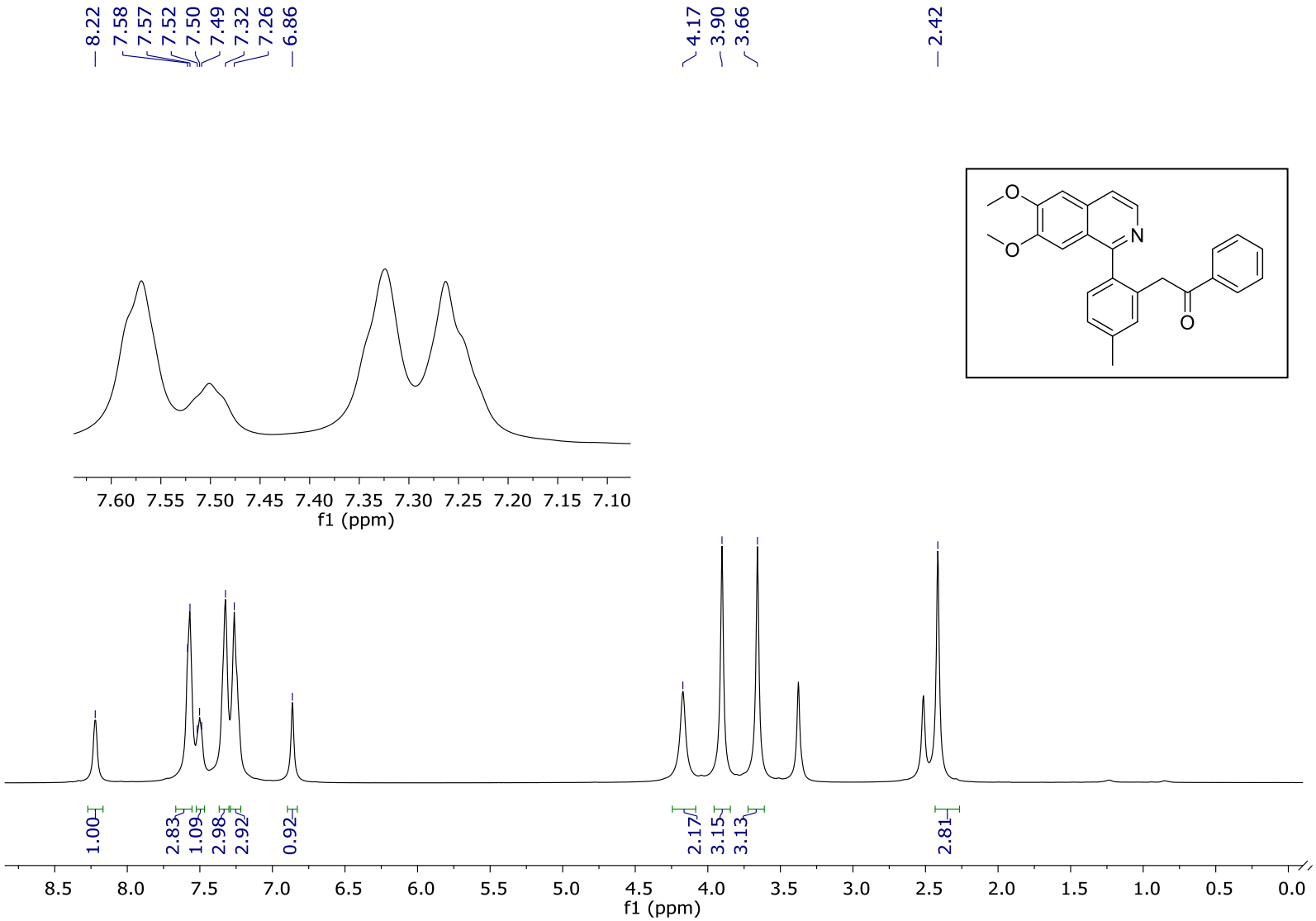
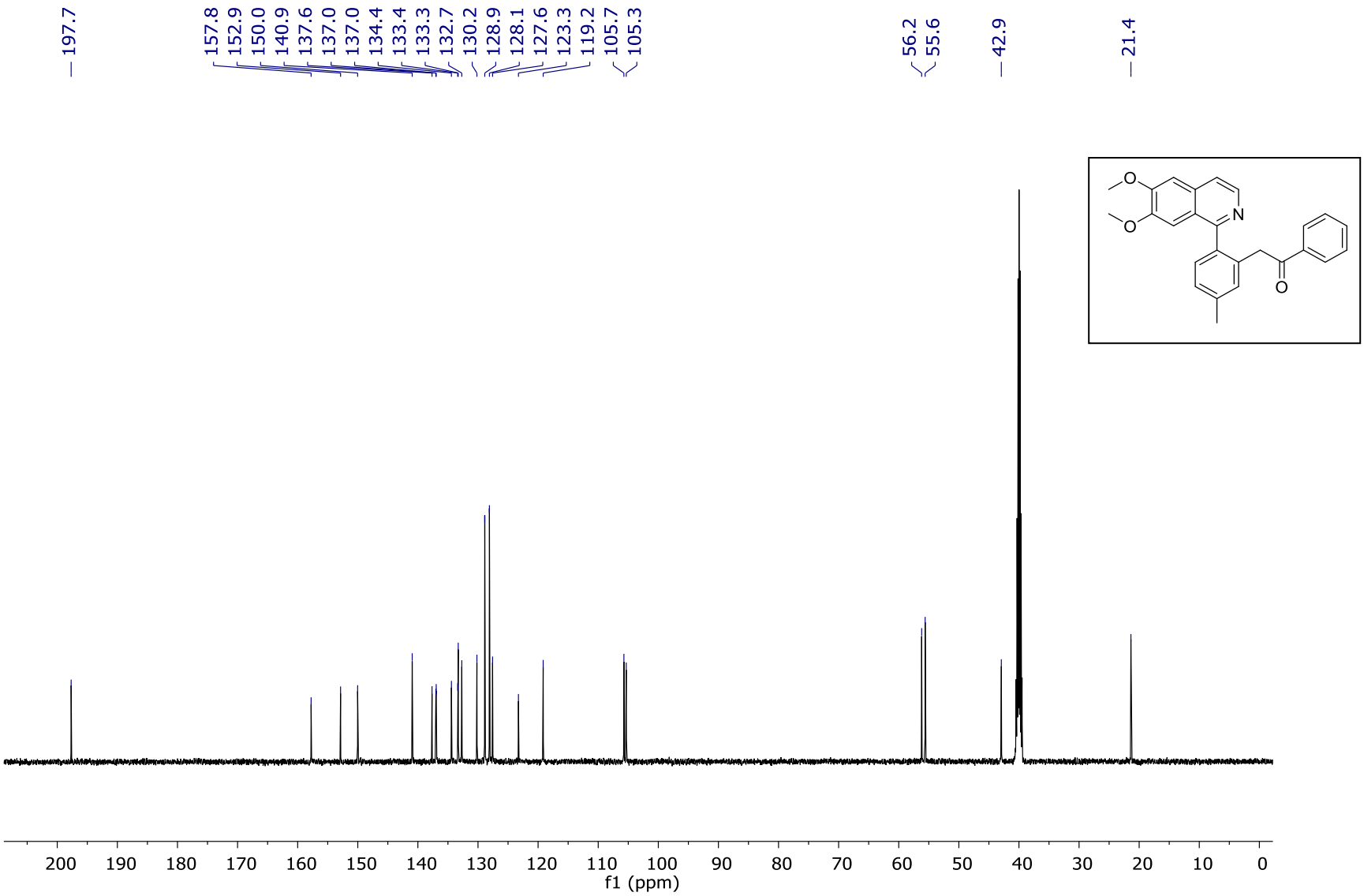
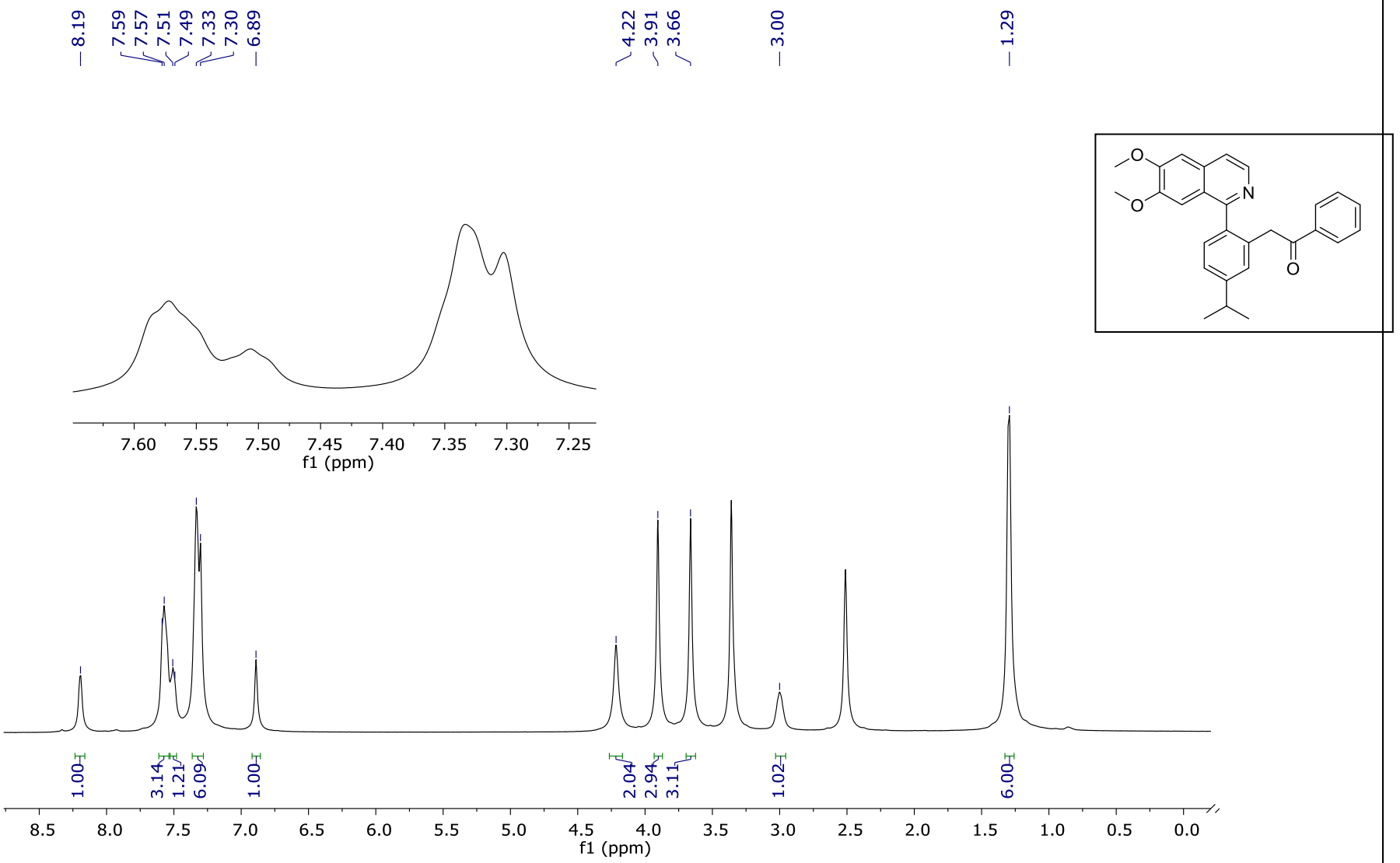


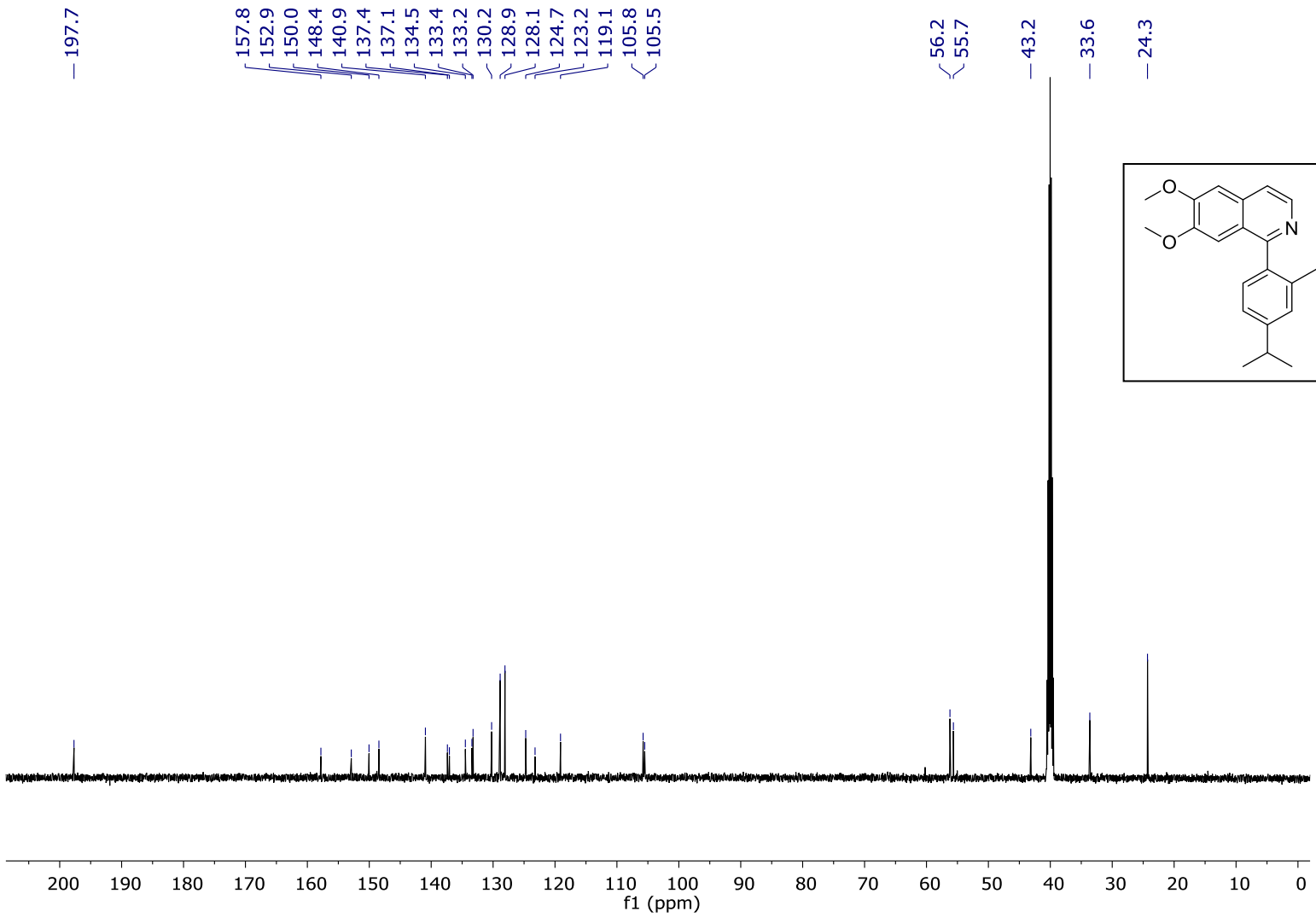
^{1}H NMR (500 MHz, DMSO-d_6) *o*f compound **5b**



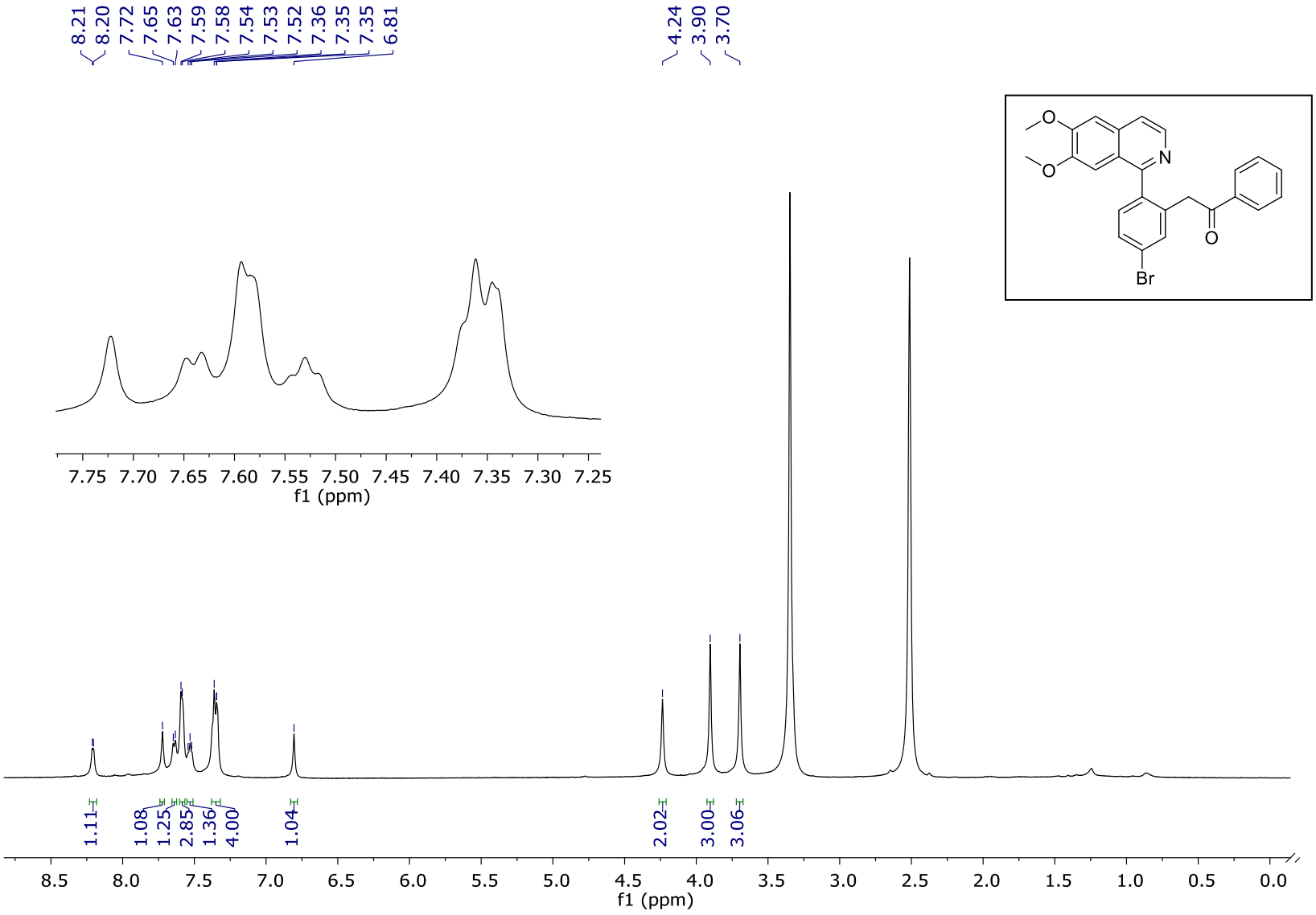
^{13}C NMR (125 MHz, DMSO-d_6) of compound **5b**



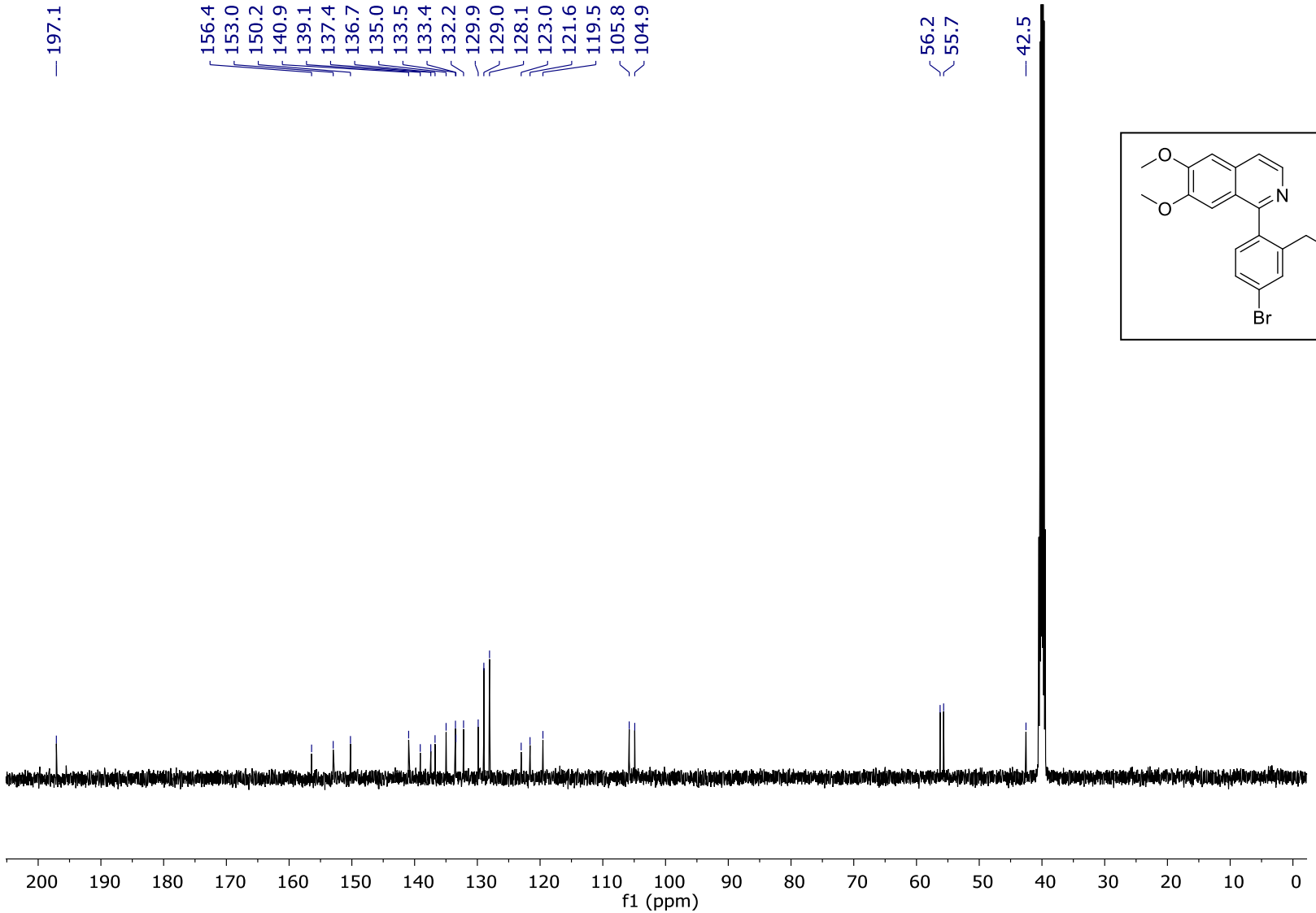
^{1}H NMR (500 MHz, DMSO-d_6) of compound **5c**



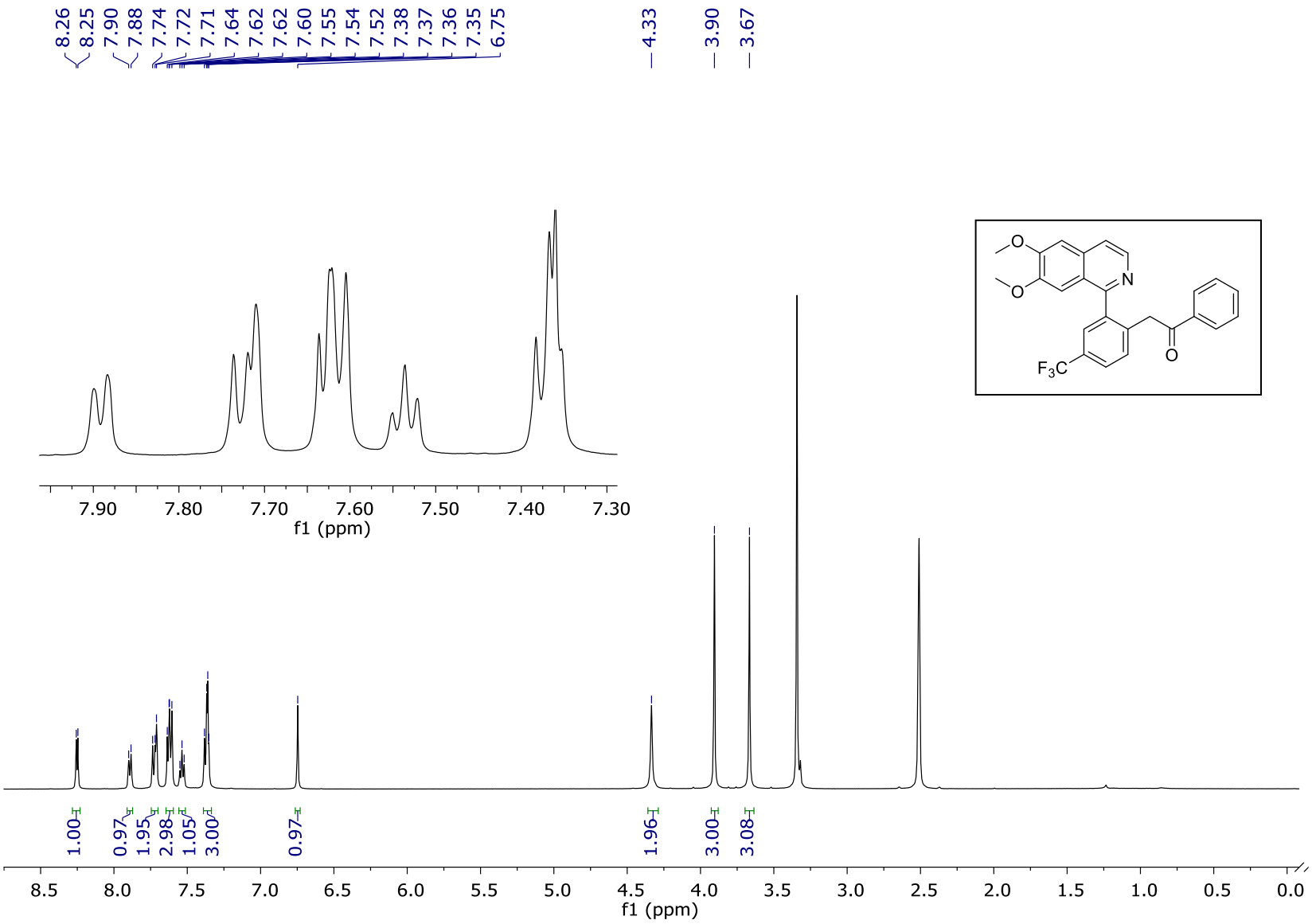
^{13}C NMR (125 MHz, DMSO-d_6) of compound **5c**



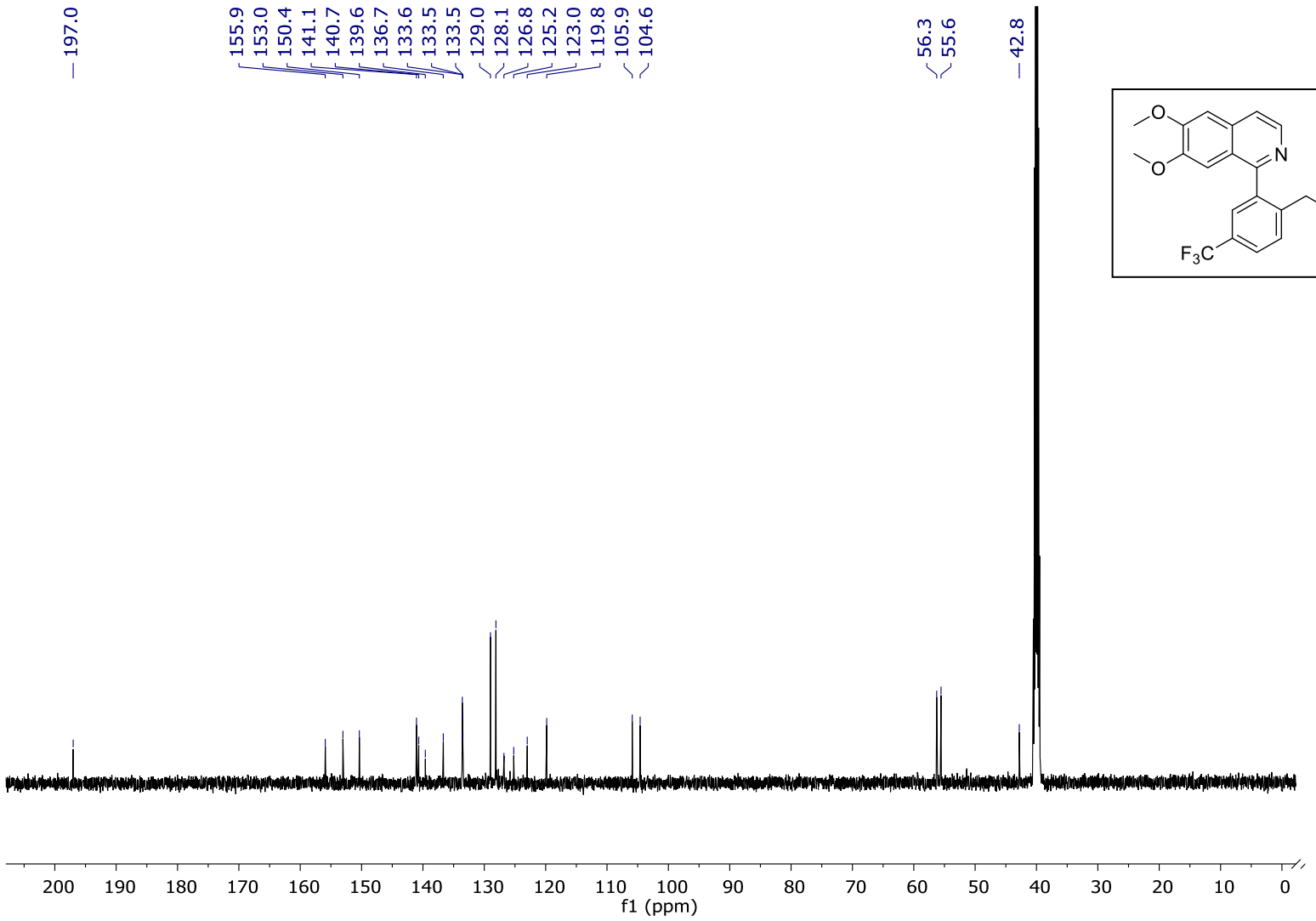
^{1}H NMR (500 MHz, DMSO-d_6) of compound **5d**



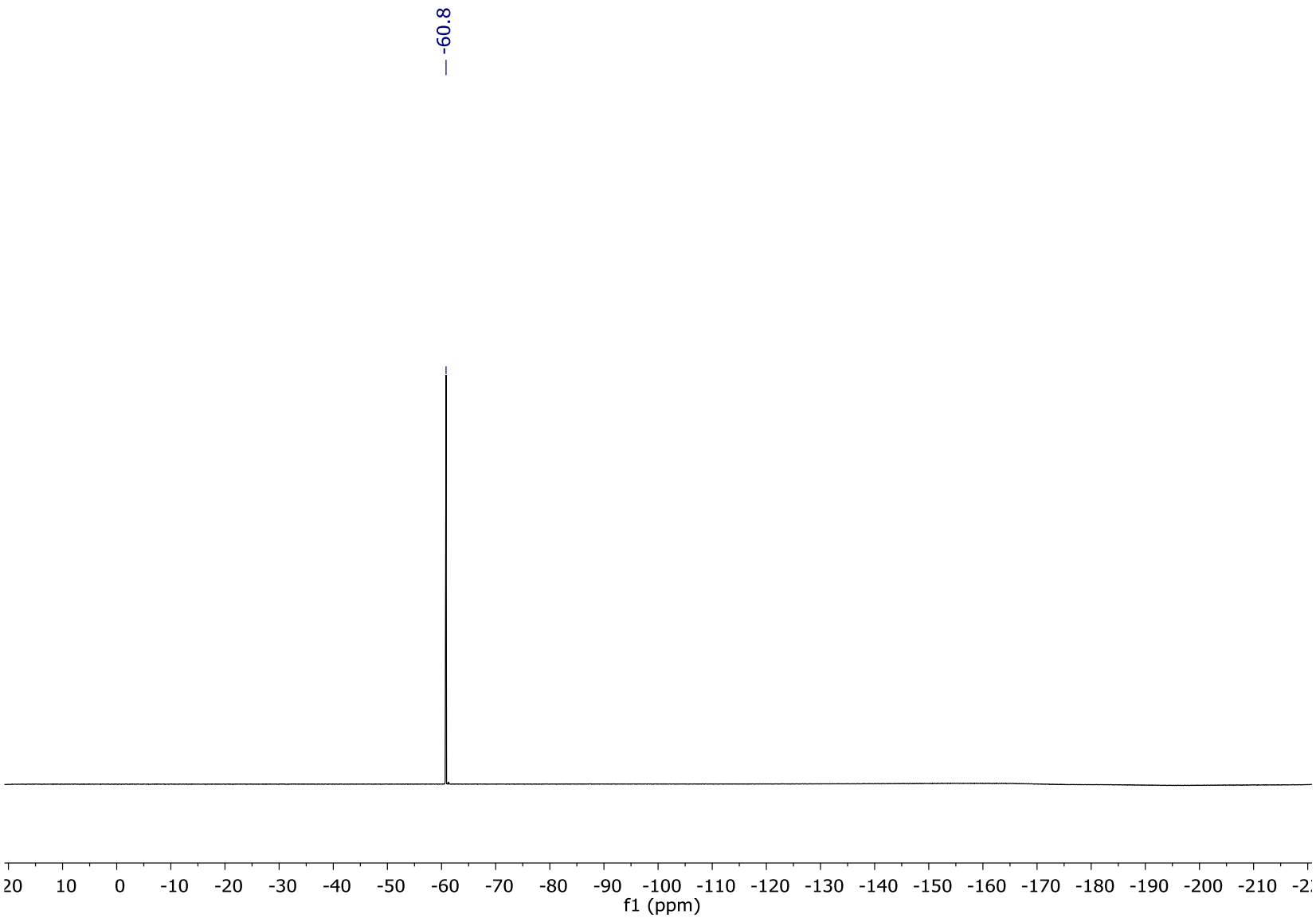
^{13}C NMR (125 MHz, DMSO-d_6) of compound **5d**



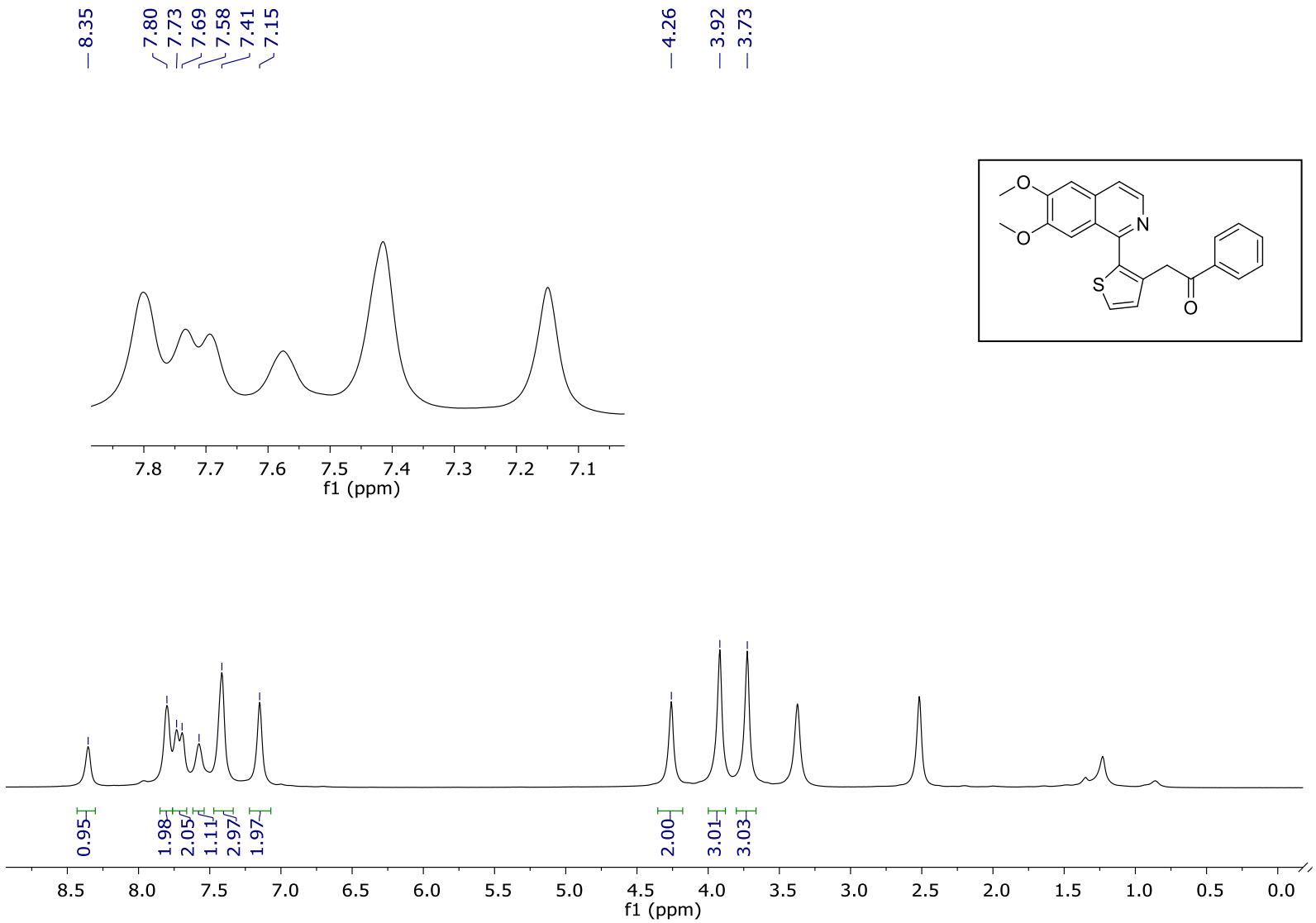
^{1}H NMR (500 MHz, DMSO-d_6) of compound **5e**



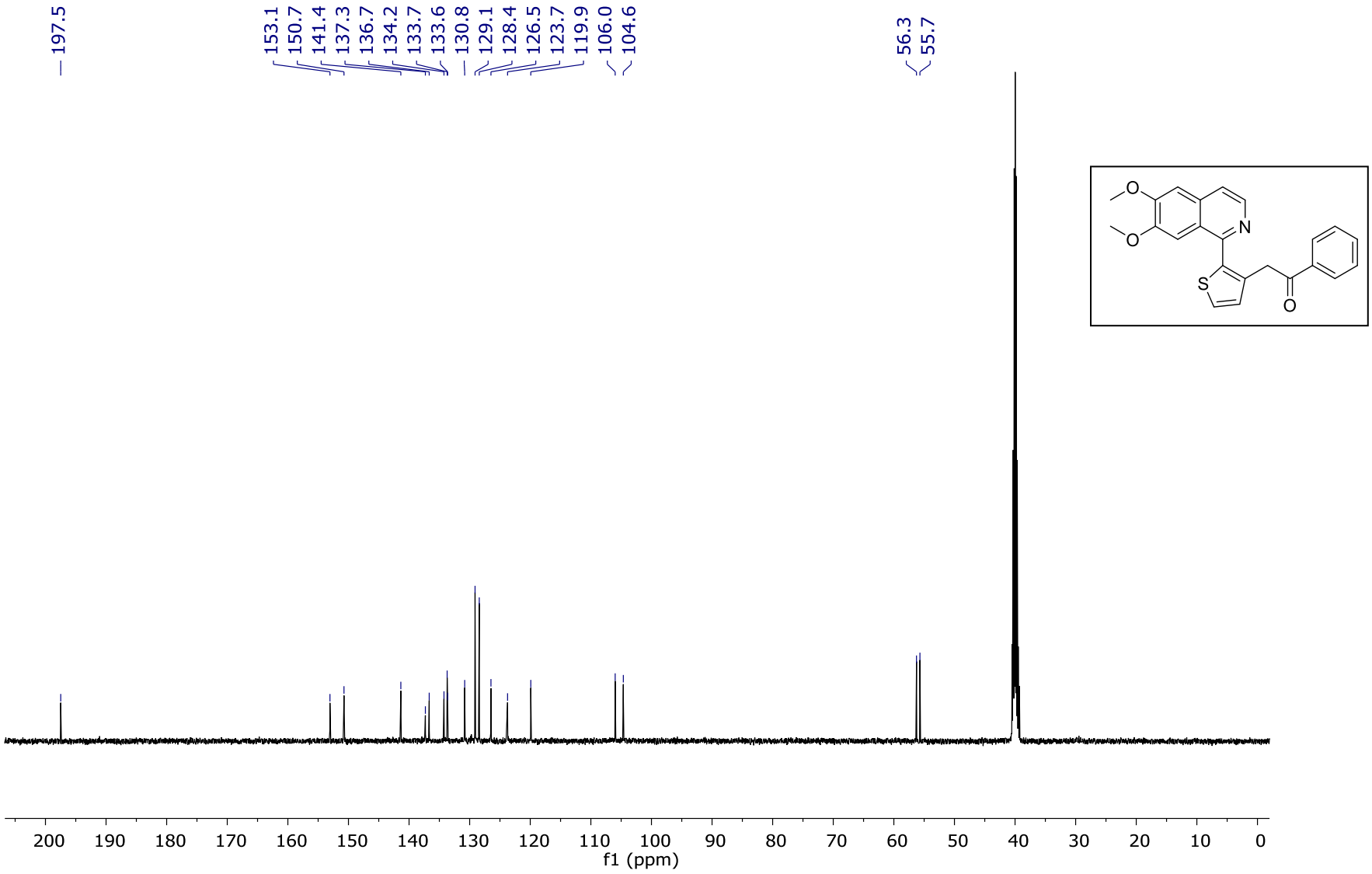
^{13}C NMR (125 MHz, DMSO-d_6) of compound **5e**



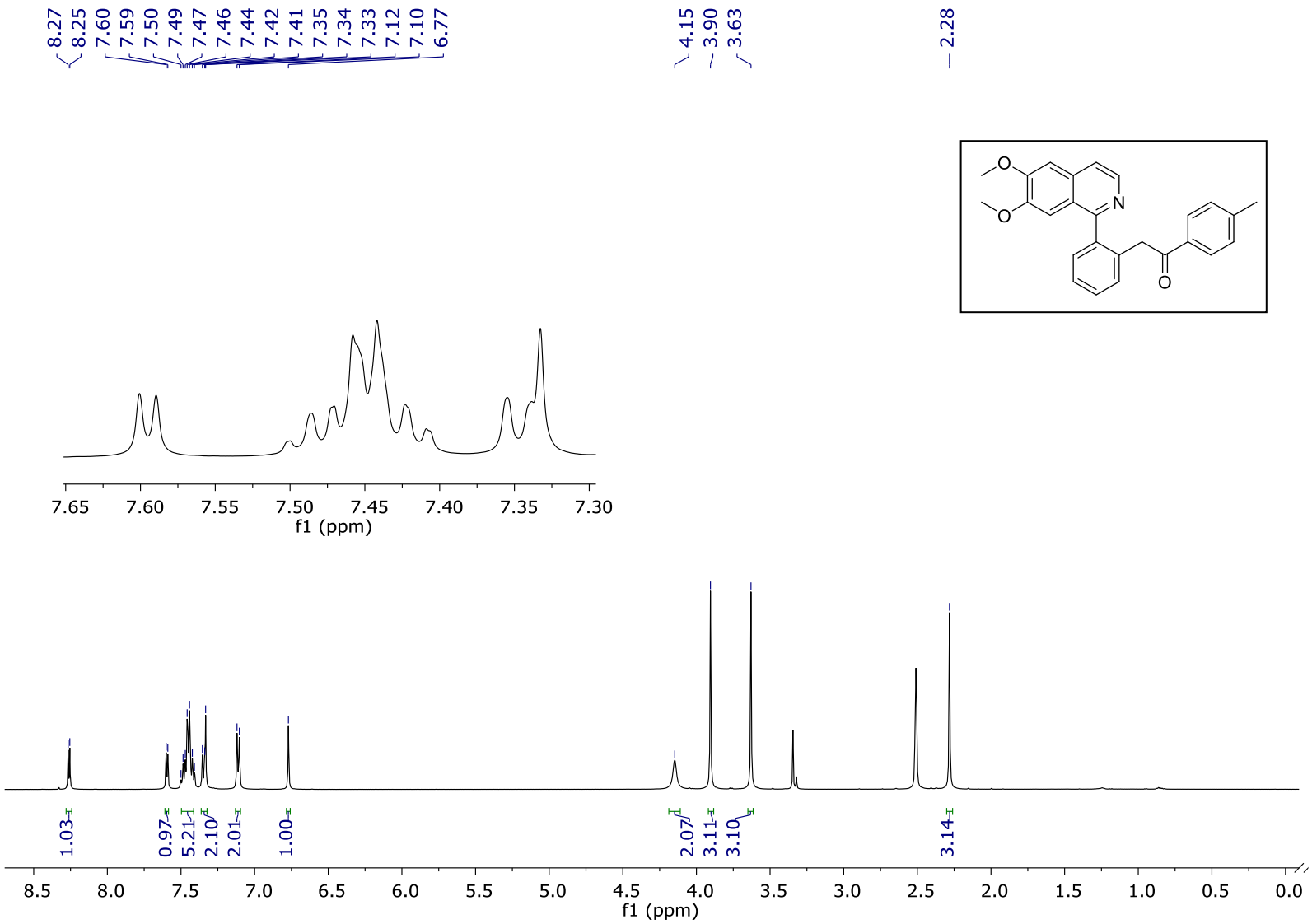
^{19}F NMR (470 MHz, DMSO-d_6) of compound **5e**



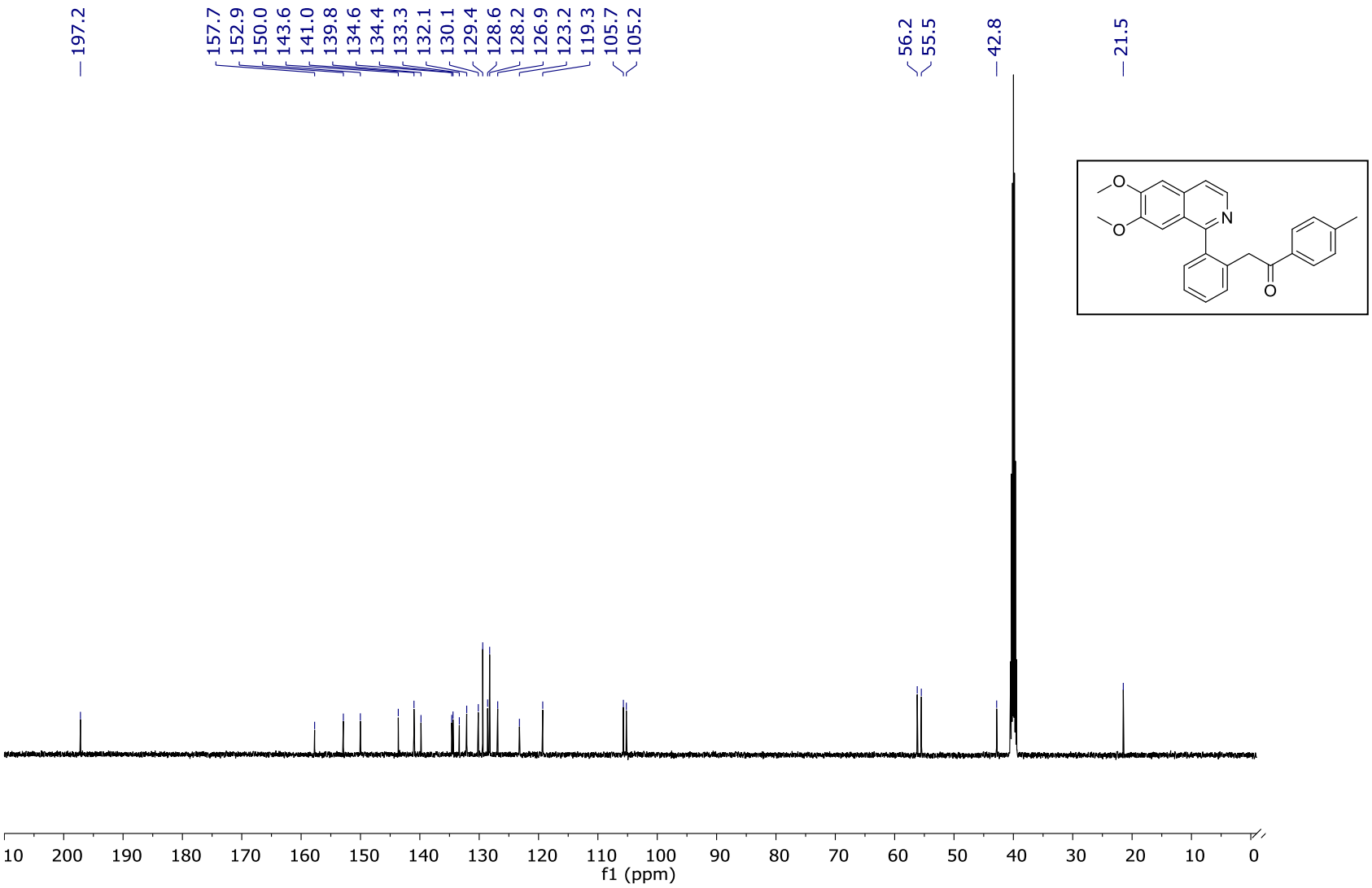
^{1}H NMR (500 MHz, DMSO-d_6) of compound **5f**



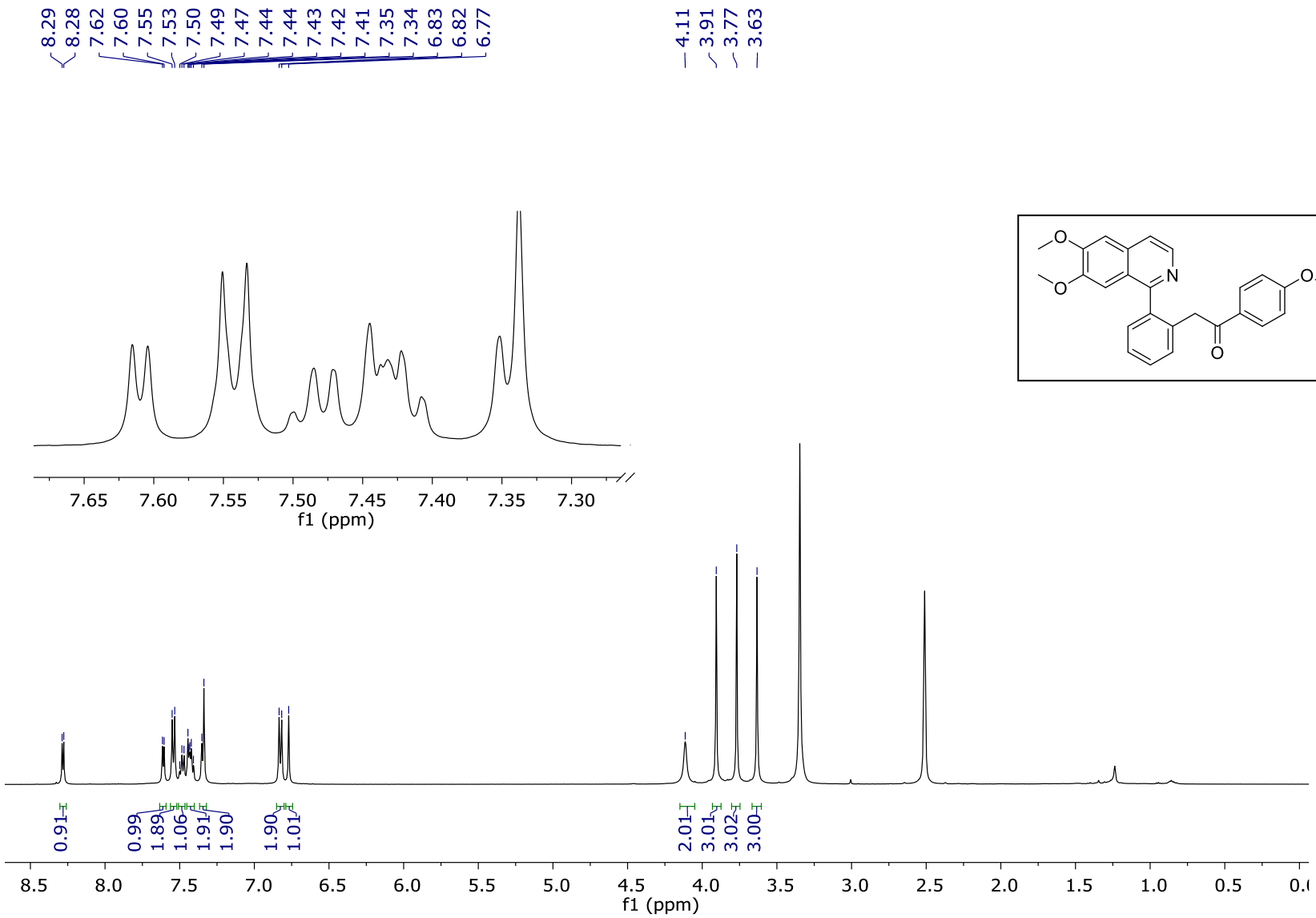
^{13}C NMR (125 MHz, DMSO-d_6) of compound **5f**



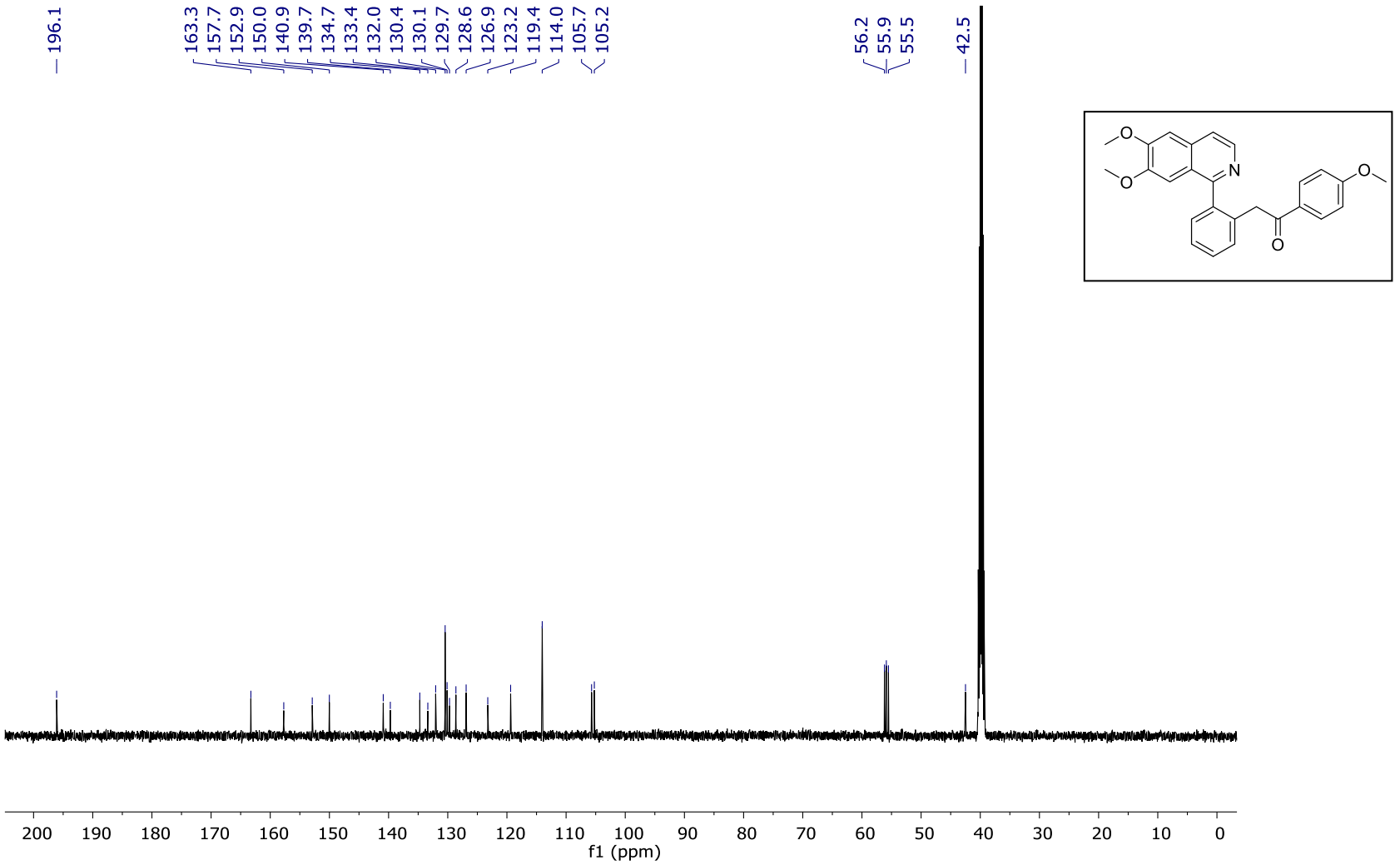
^{1}H NMR (500 MHz, DMSO-d_6) of compound **5g**



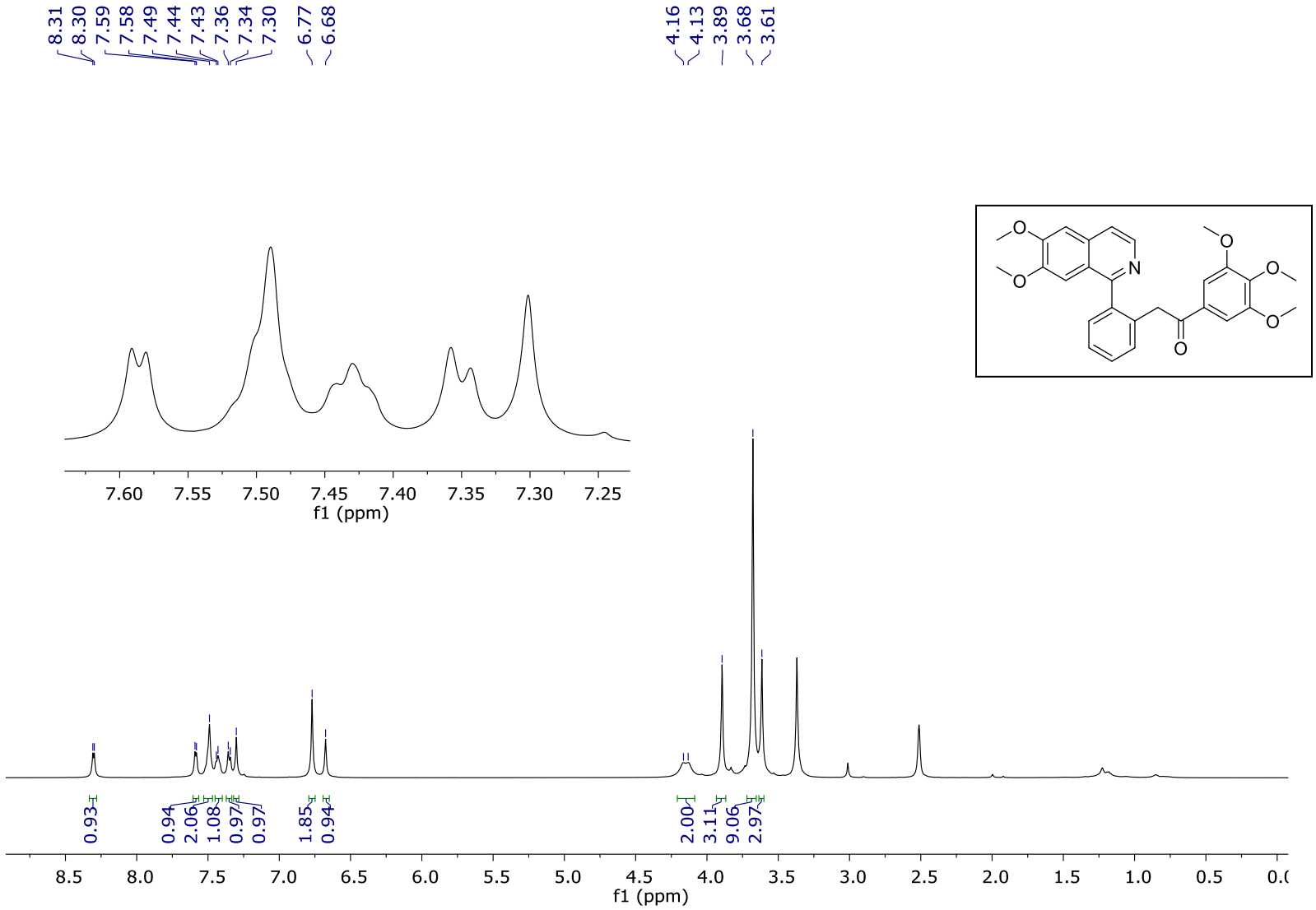
^{13}C NMR (125 MHz, DMSO-d_6) of compound **5g**



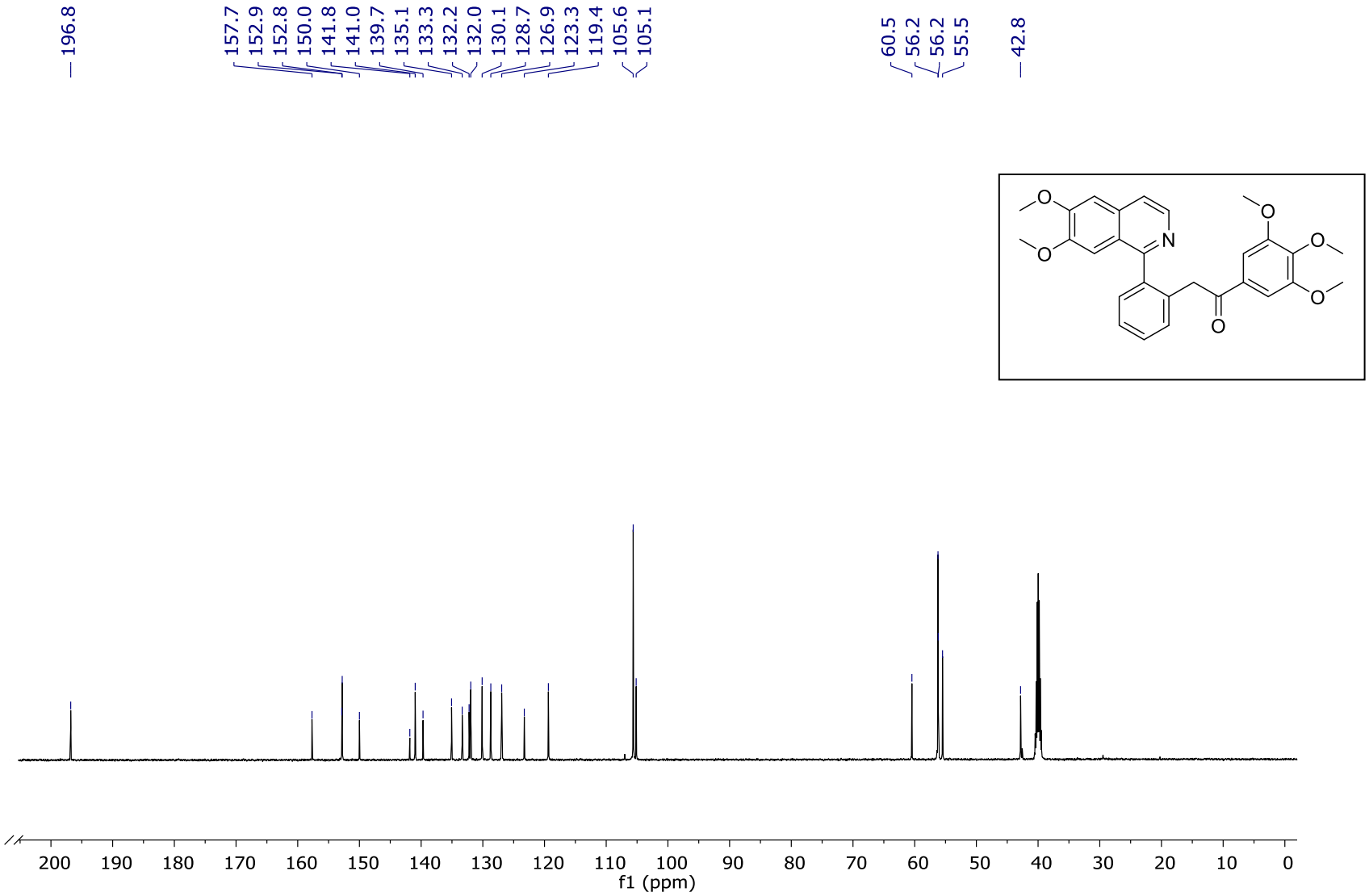
^{1}H NMR (500 MHz, DMSO-d_6) of compound **5h**



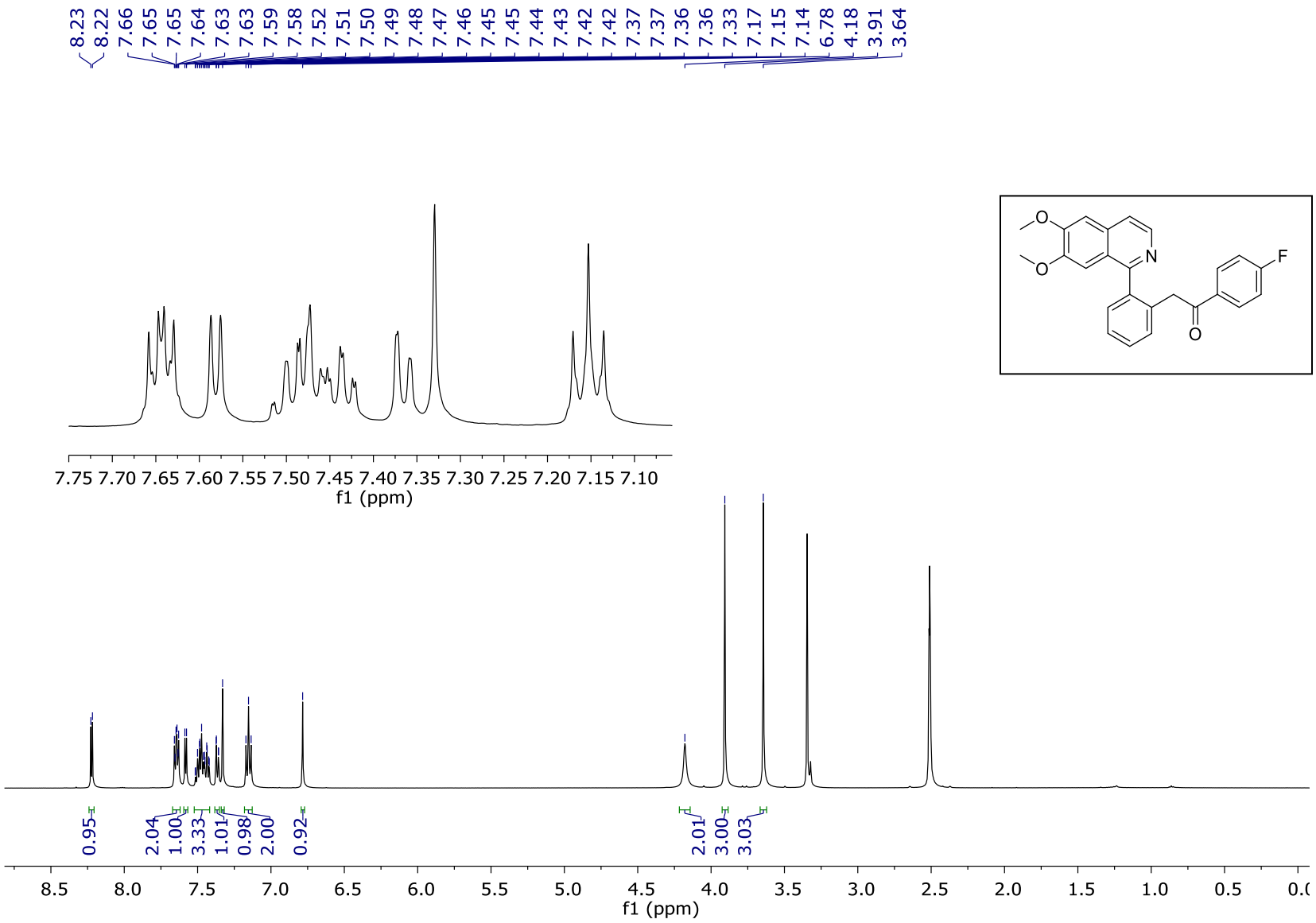
^{13}C NMR (125 MHz, DMSO-d_6) of compound **5h**



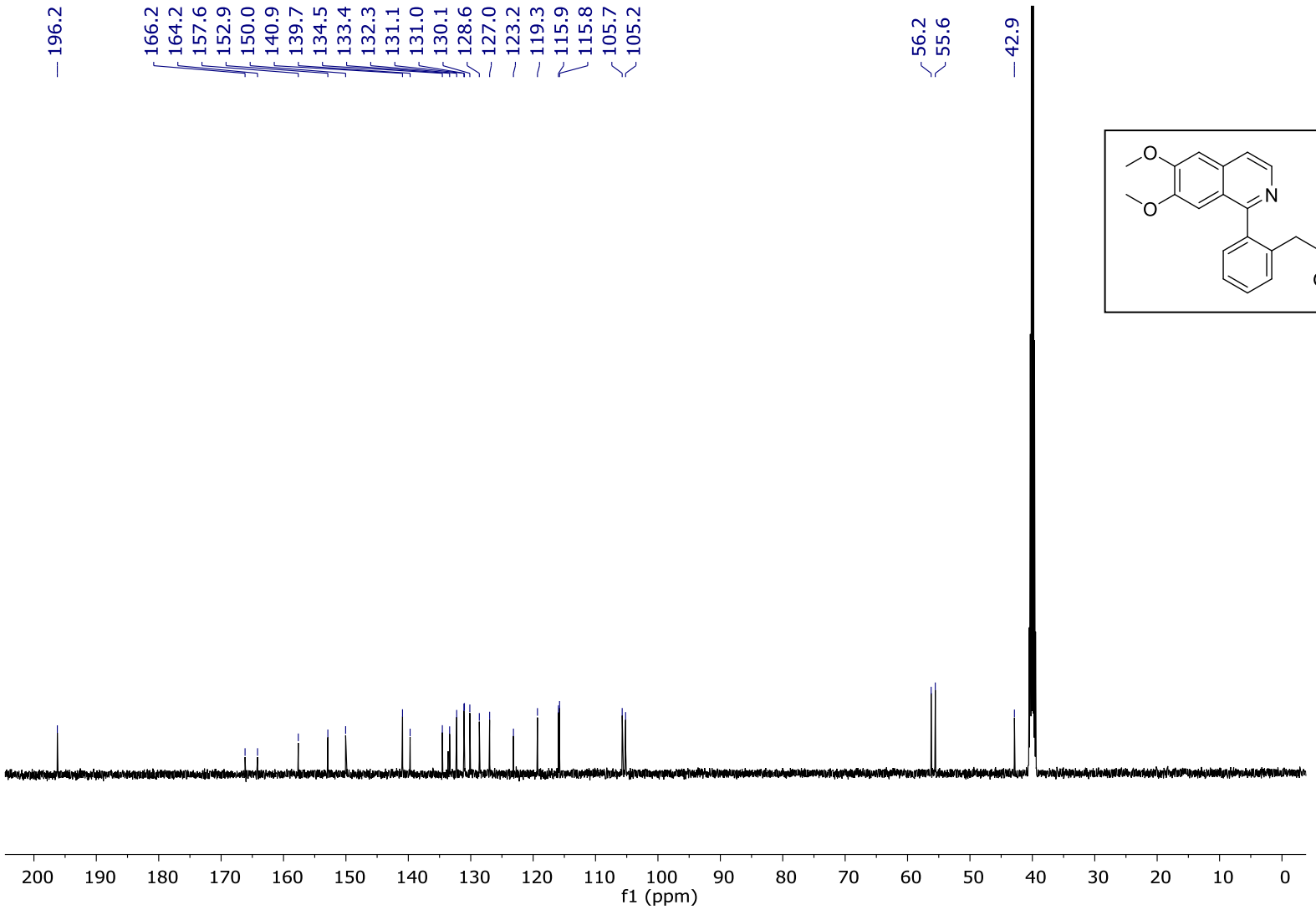
^{1}H NMR (500 MHz, DMSO-d_6) of compound **5i**



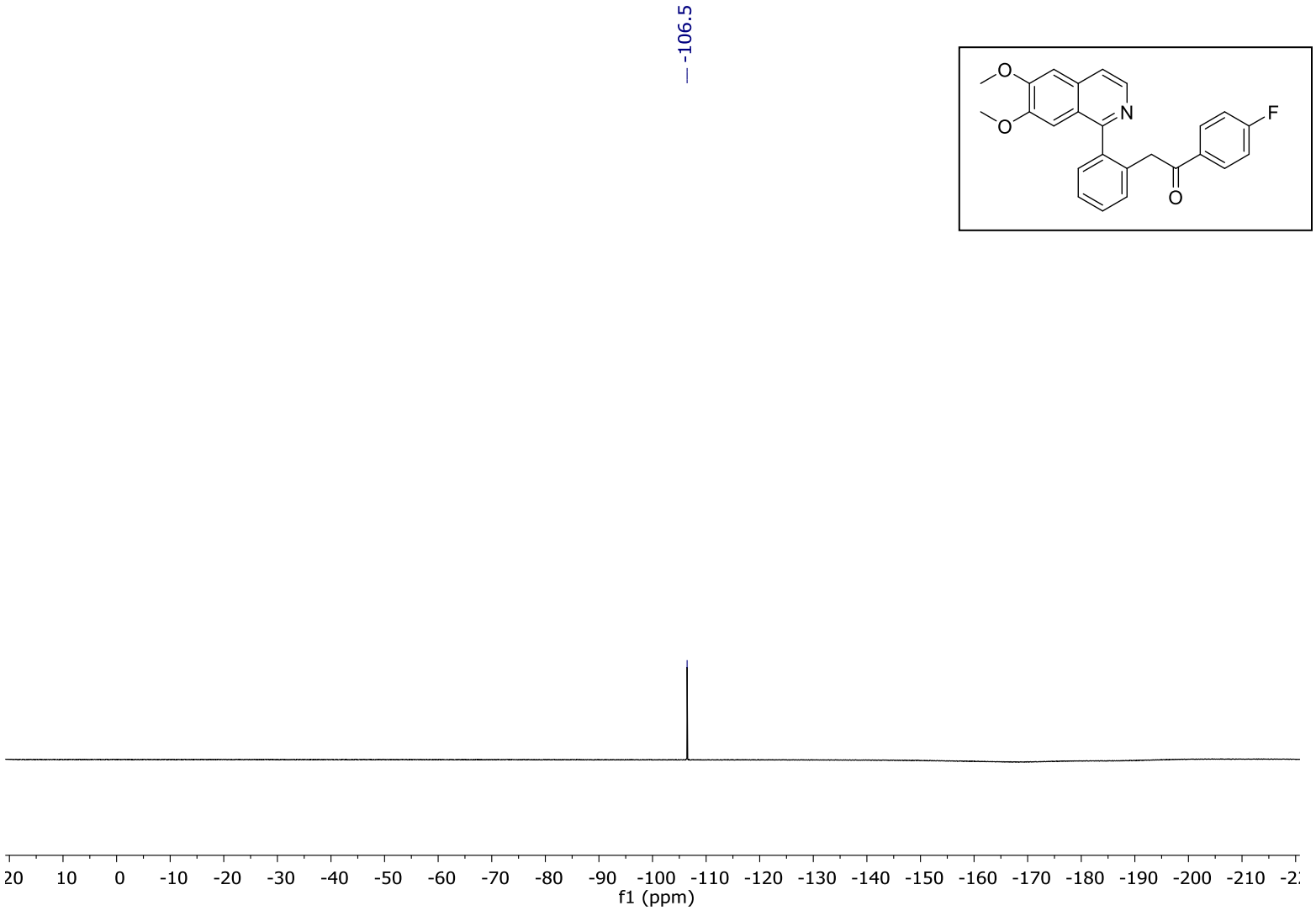
^{13}C NMR (125 MHz, DMSO-d_6) of compound **5i**



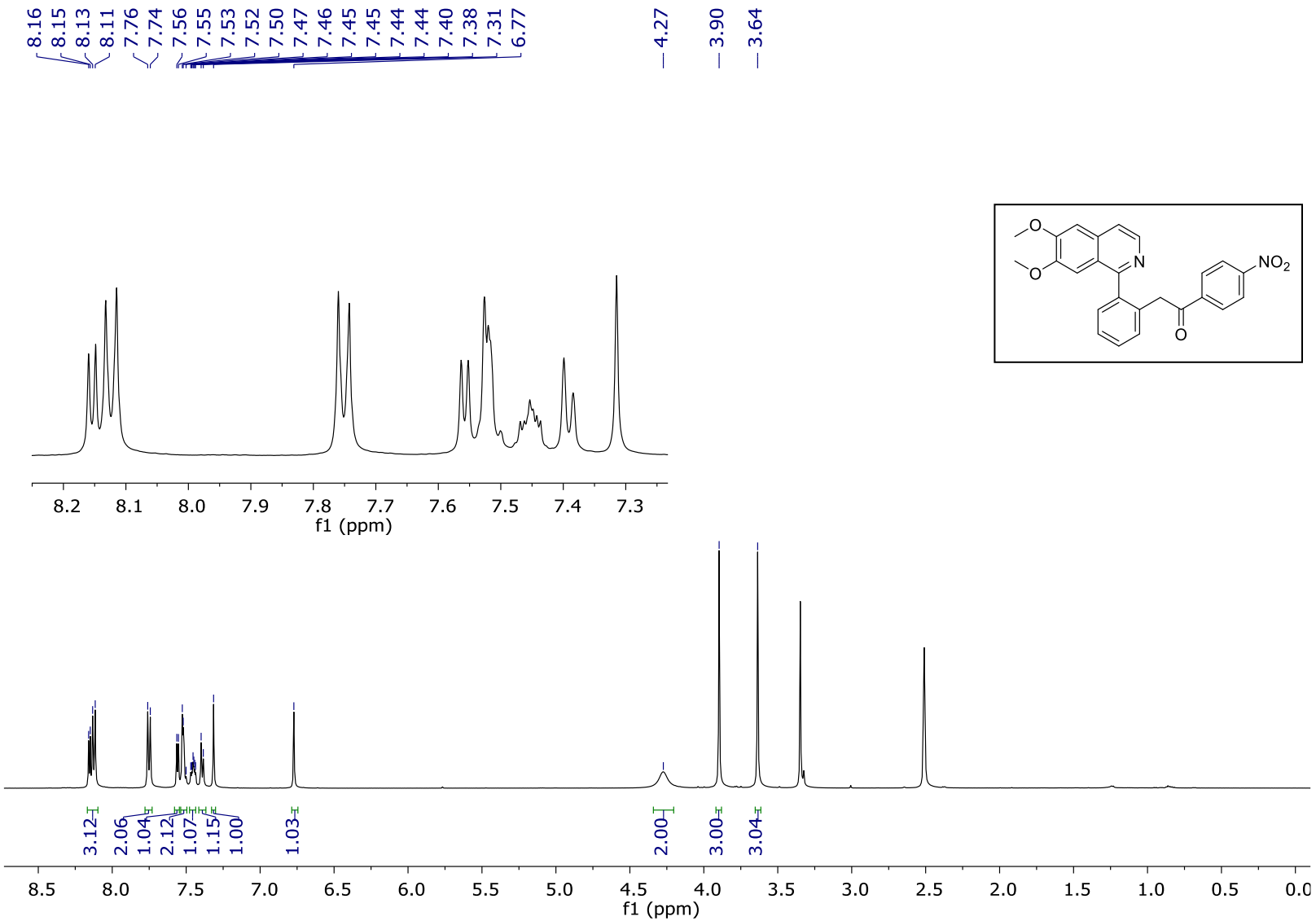
^{1}H NMR (500 MHz, DMSO-d_6) of compound **5j**



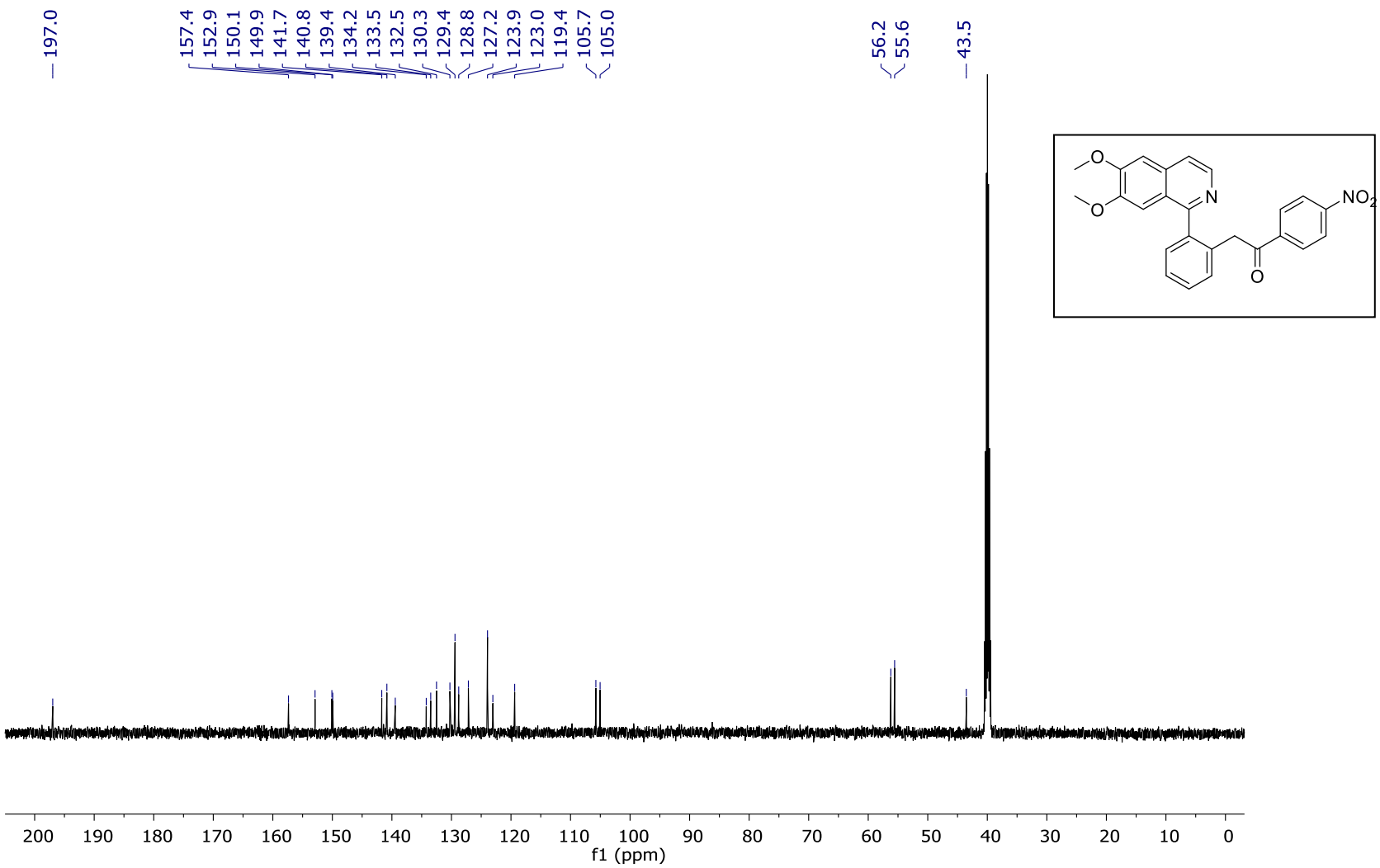
^{13}C NMR (125 MHz, DMSO-d_6) of compound **5j**



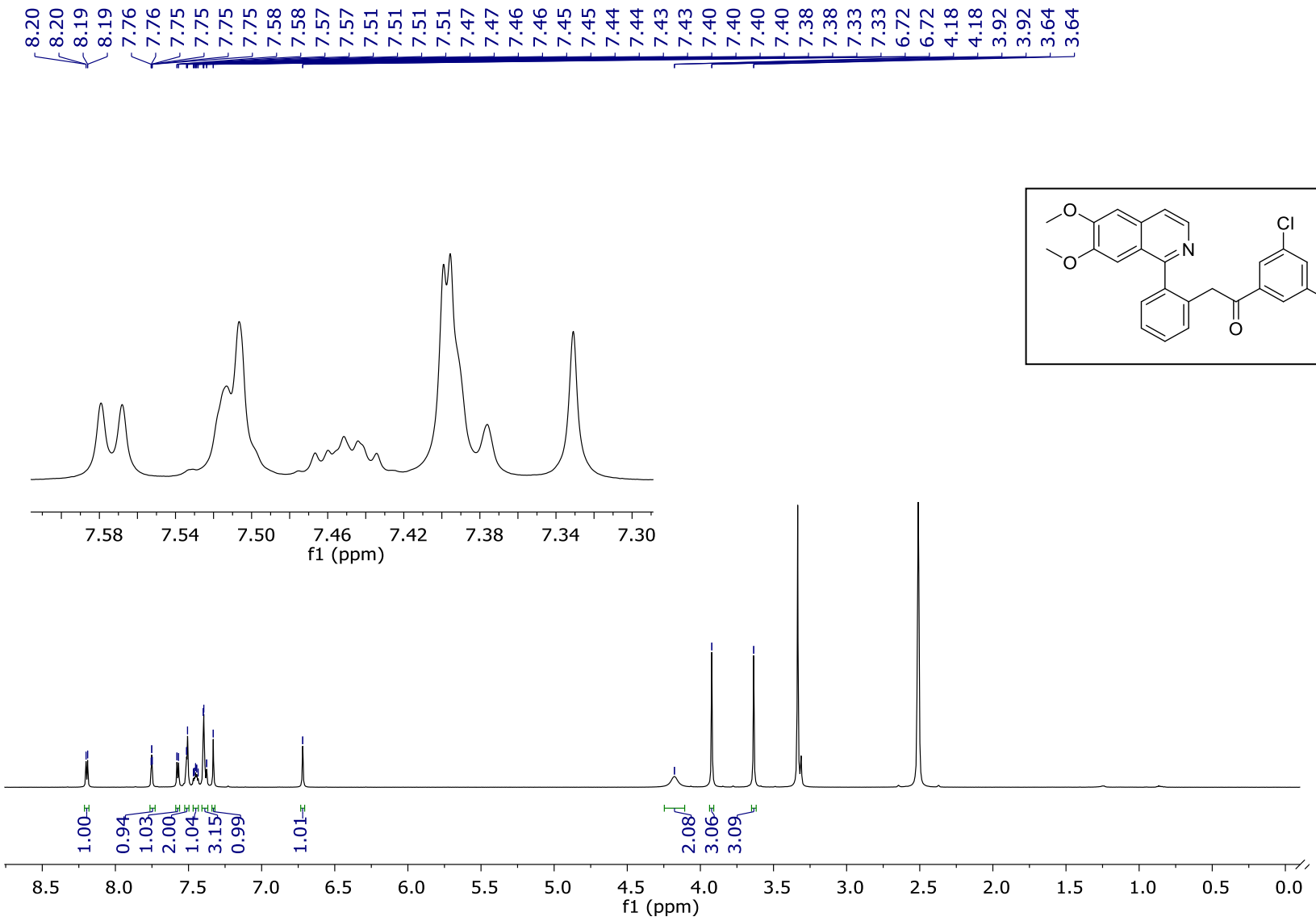
^{19}FNMR (470 MHz, , DMSO-d_6) of compound **5j**



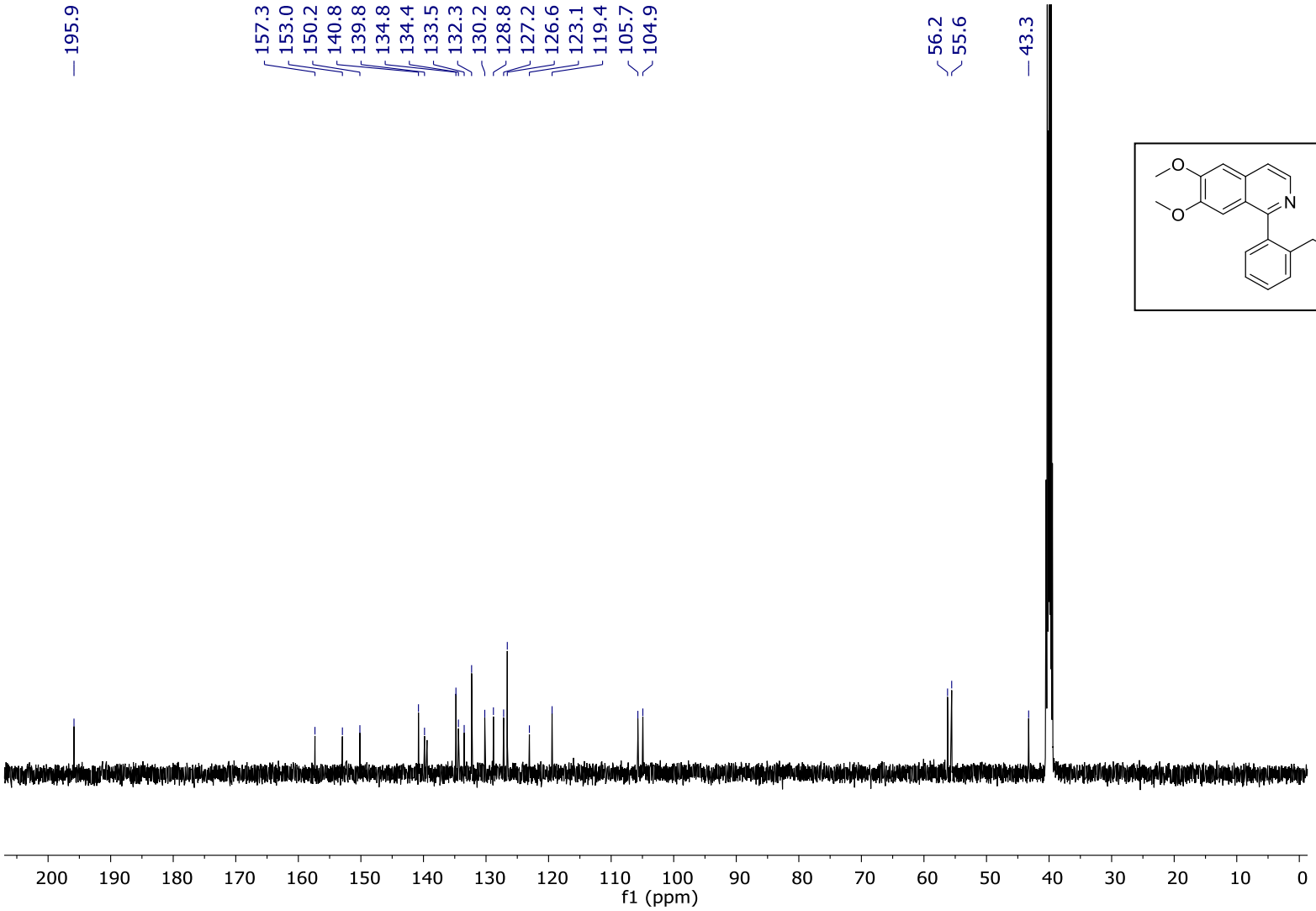
^{1}H NMR (500 MHz, DMSO-d_6) of compound **5k**



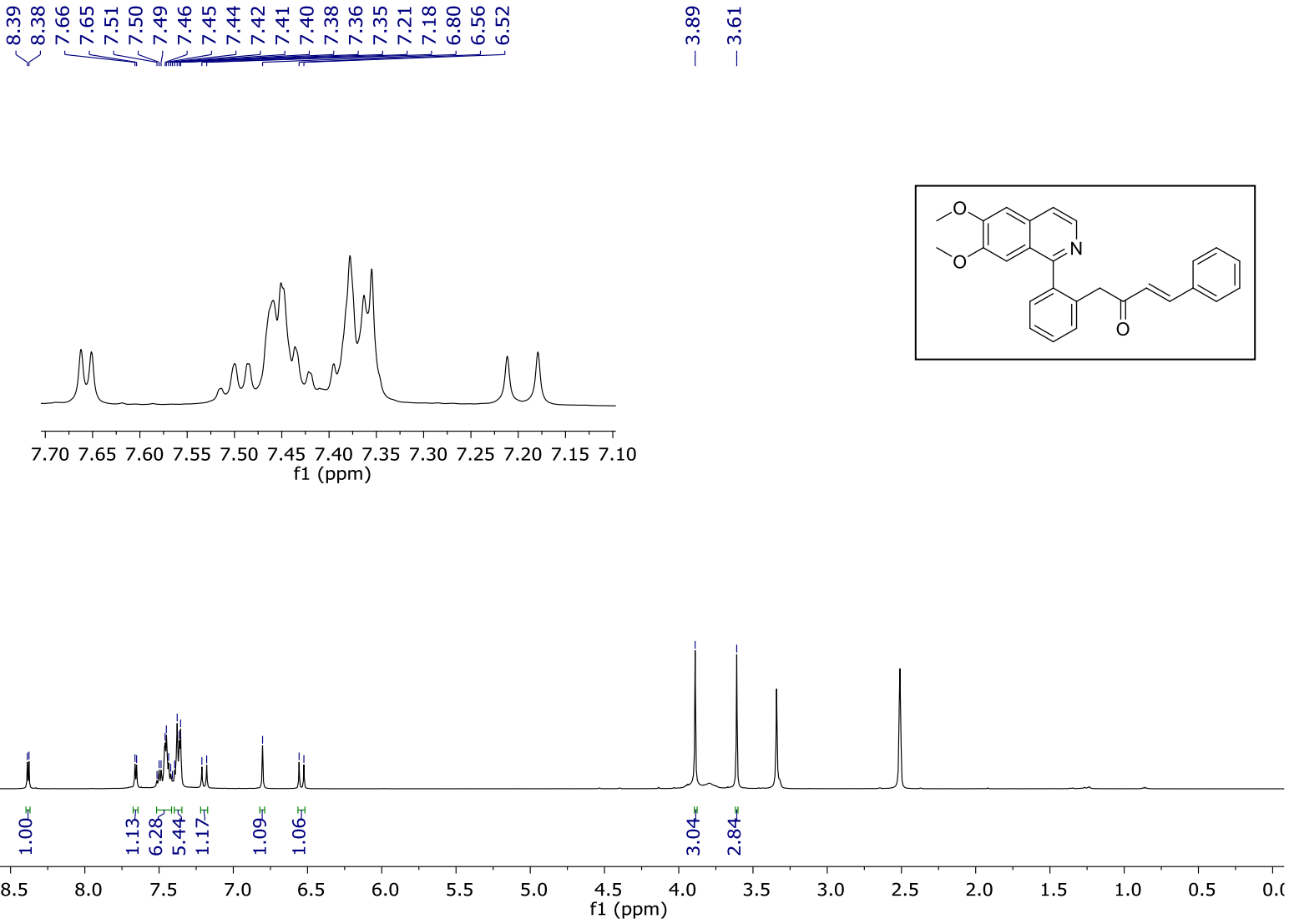
^{13}C NMR (125 MHz, DMSO-d_6) of compound **5k**



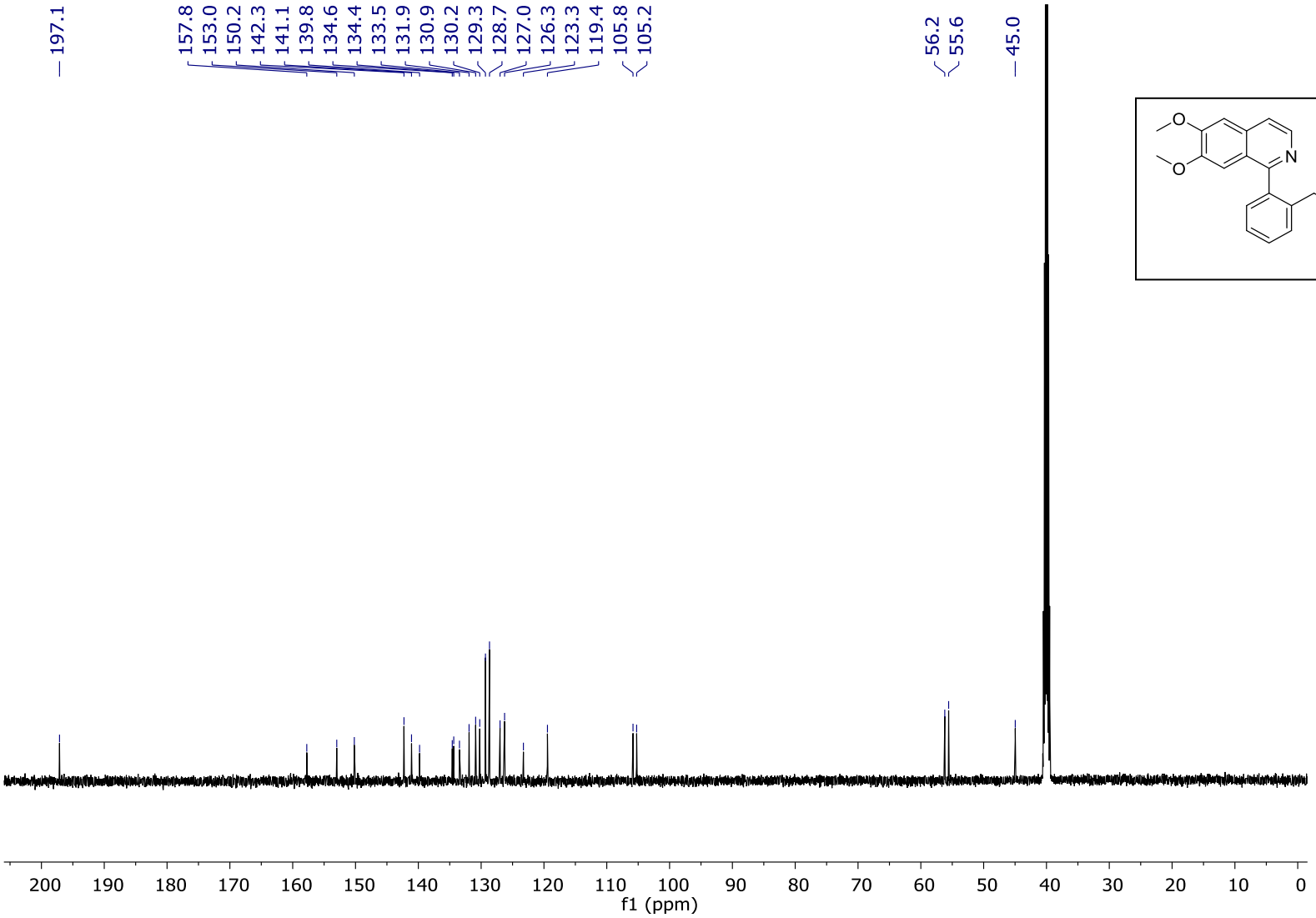
^{1}H NMR (500 MHz, DMSO-d_6) of compound **5l**



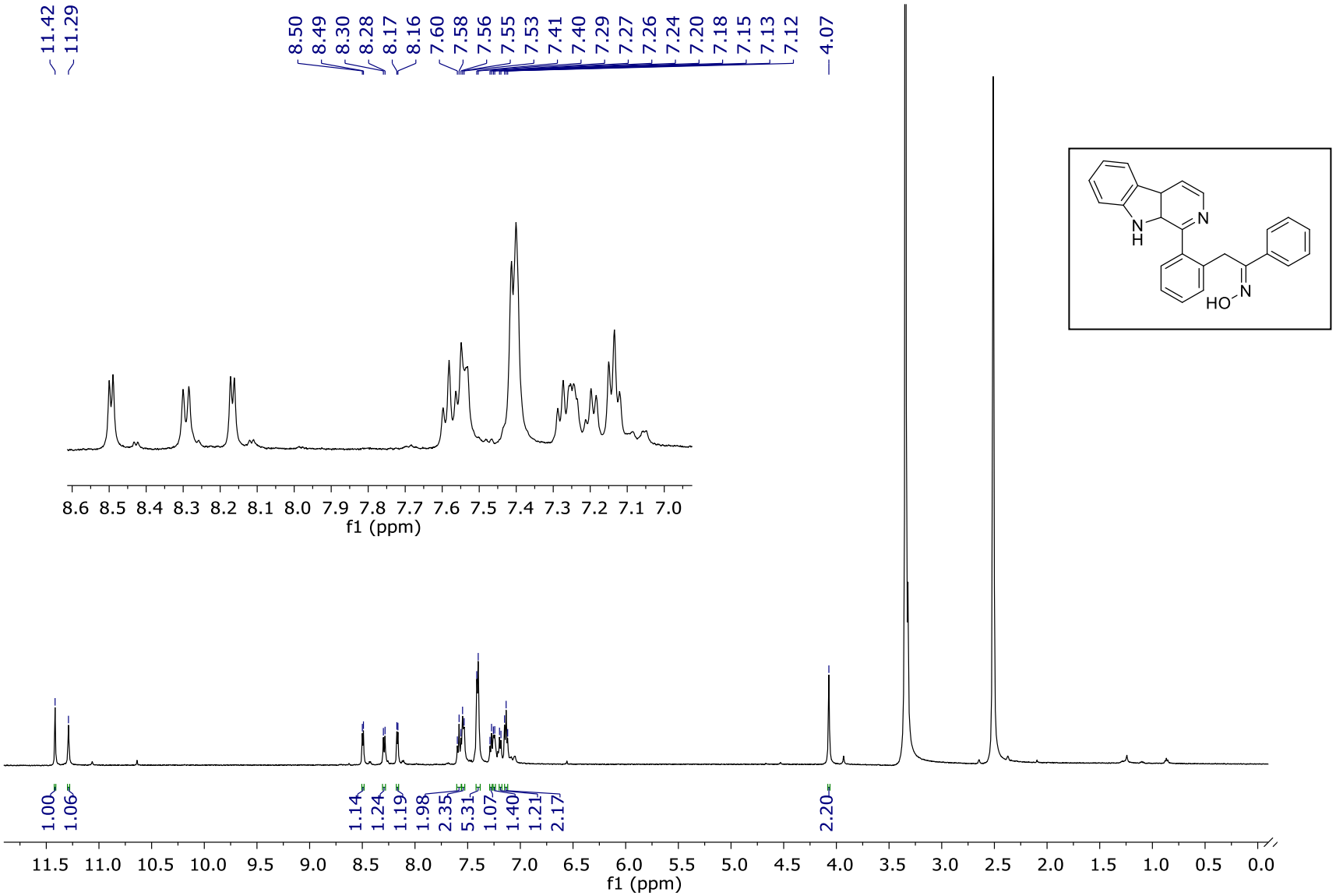
^{13}C NMR (125 MHz, DMSO-d_6) of compound **5l**



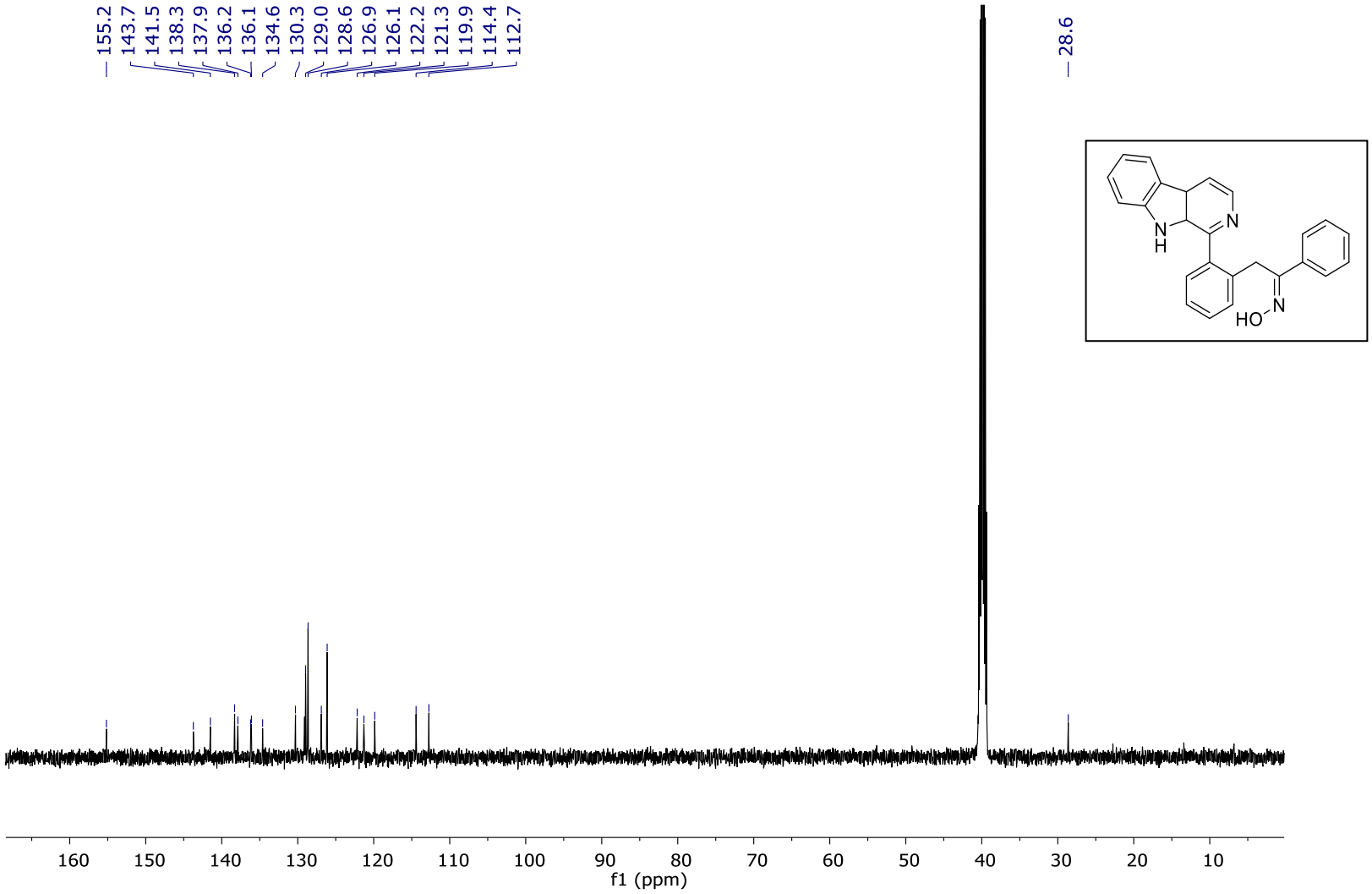
^{1}H NMR (500 MHz, DMSO-d_6) of compound **5m**



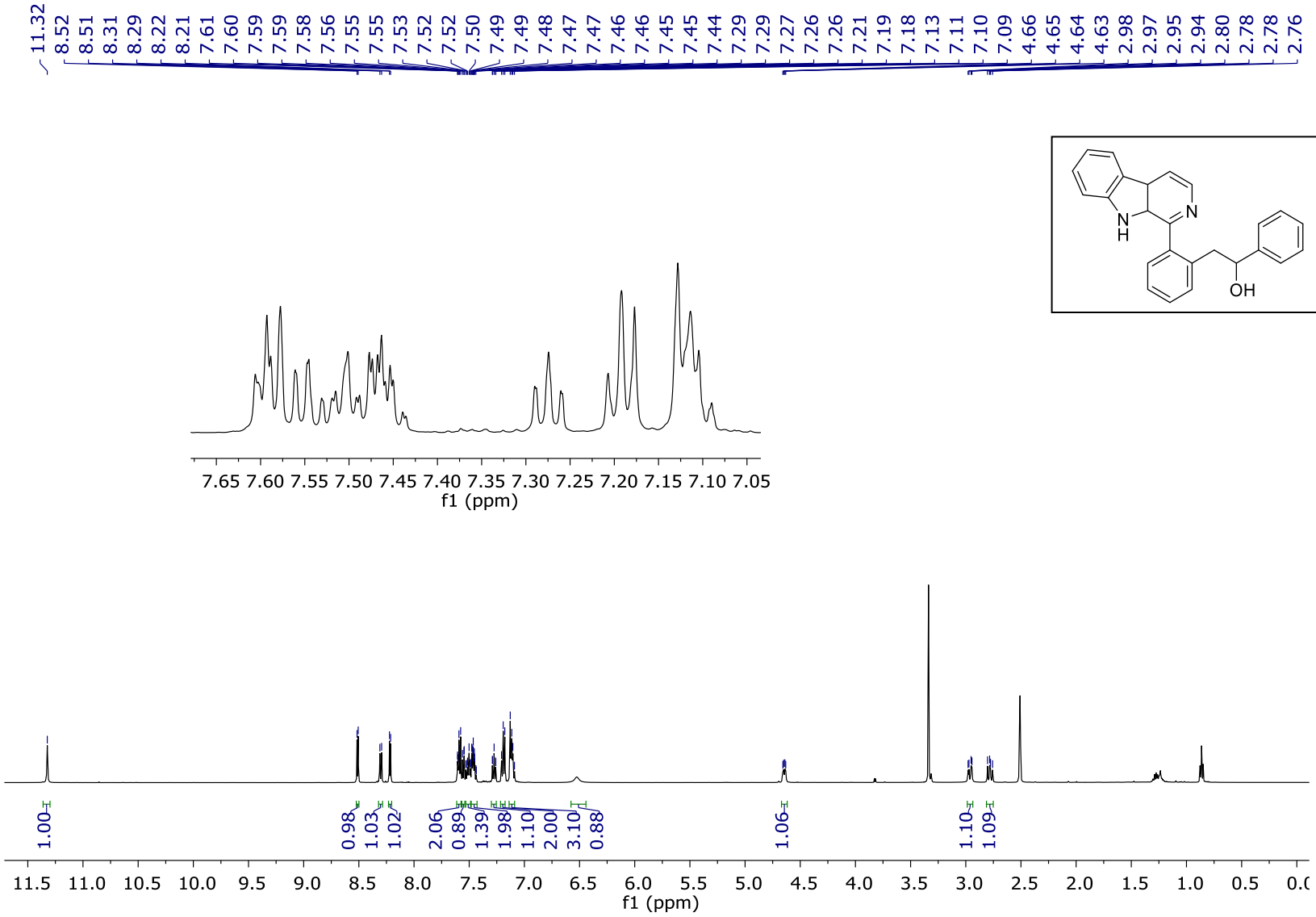
^{13}C NMR (125 MHz, DMSO-d_6) of compound **5m**



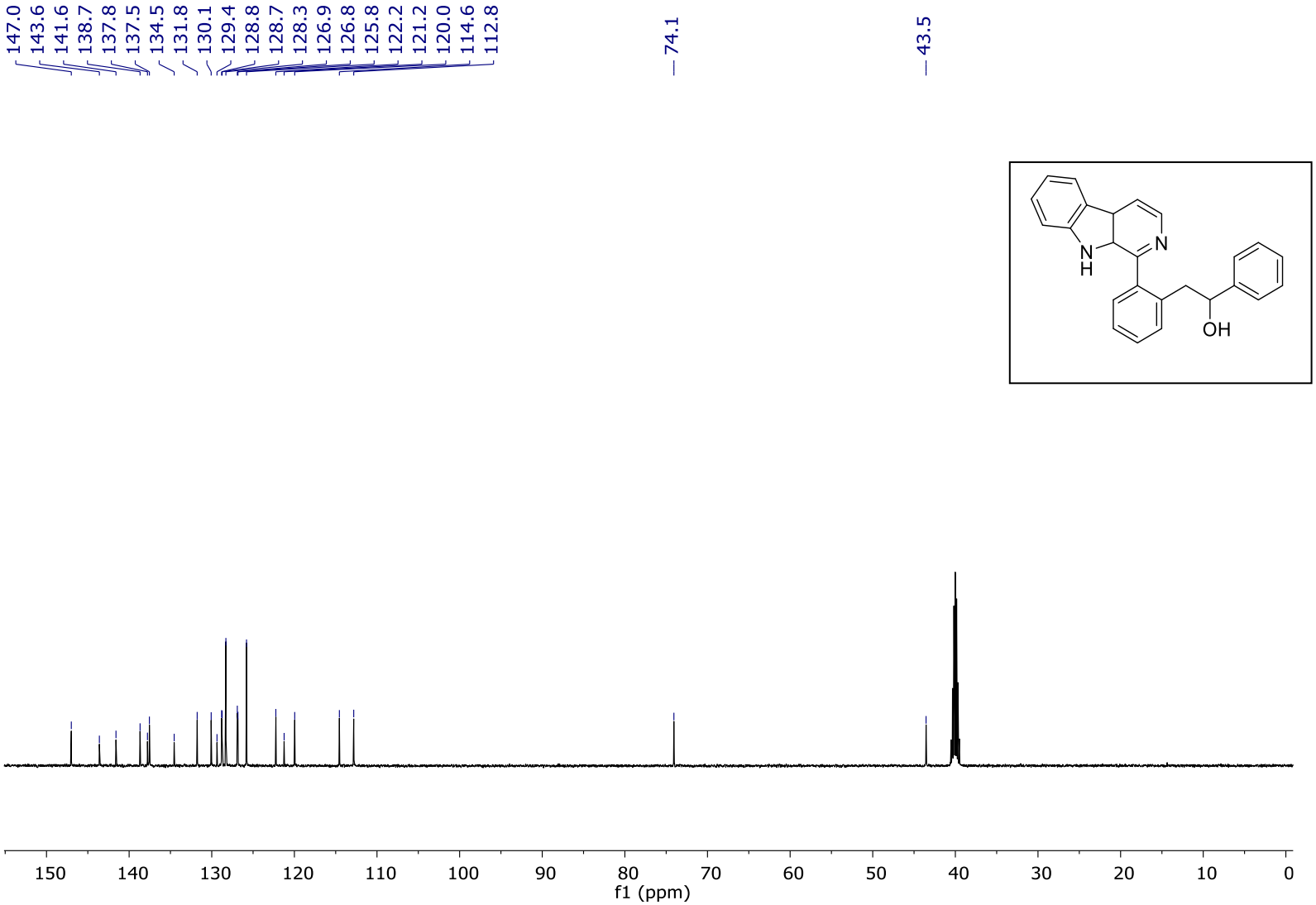
^{1}H NMR (500 MHz, DMSO-d_6) of compound**6**



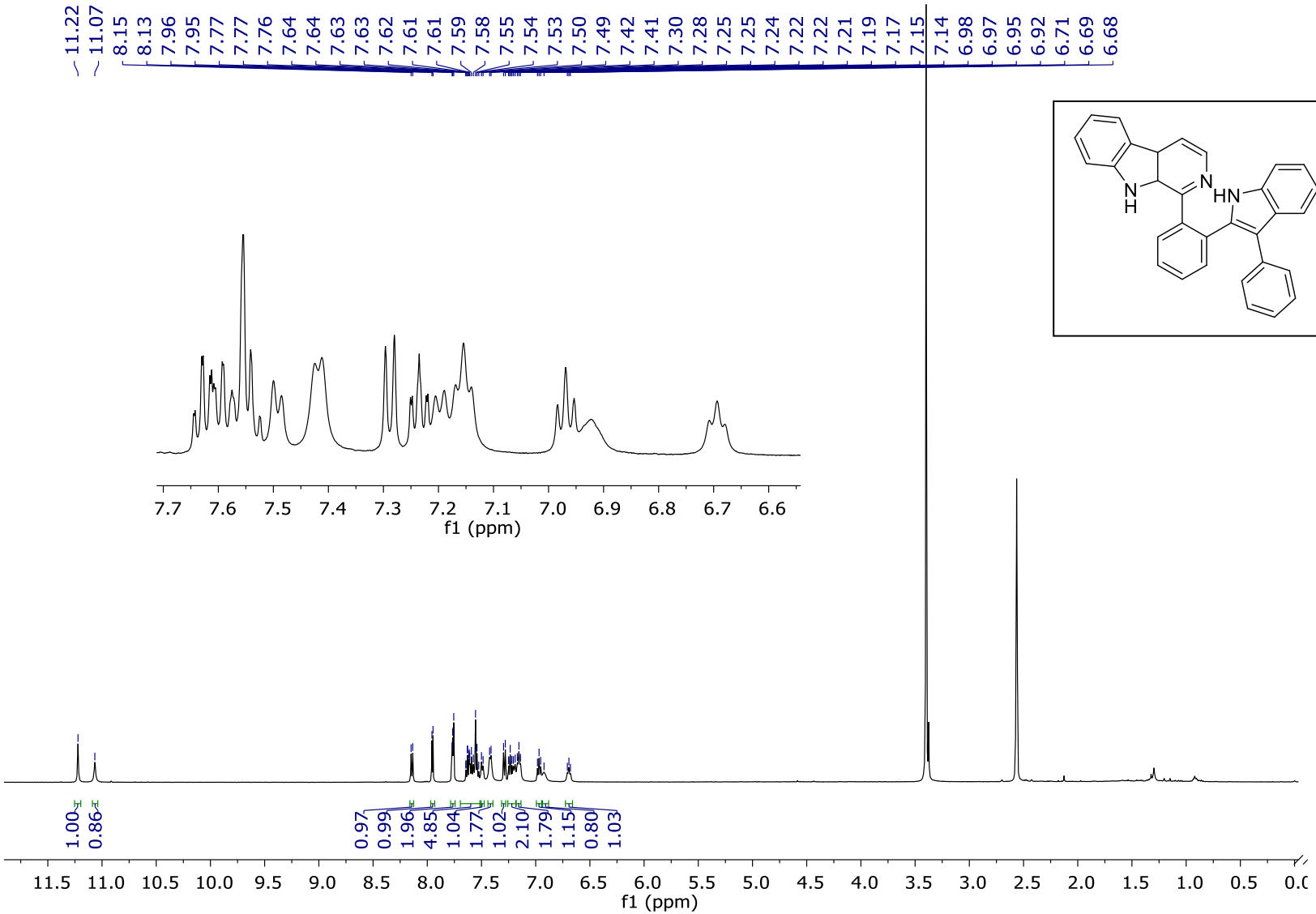
^{13}C NMR (125 MHz, DMSO-d_6) of compound **6**



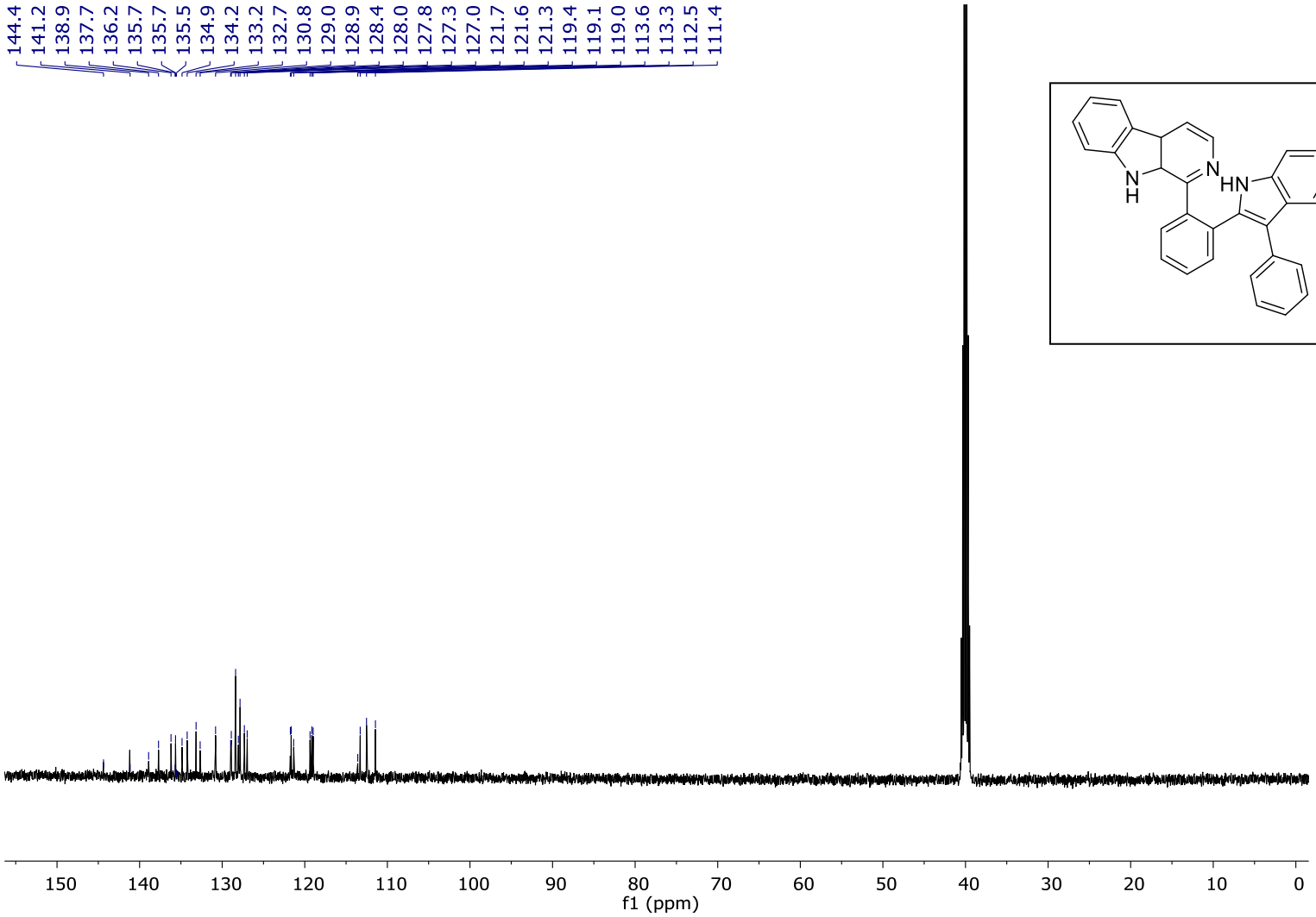
^{1}H NMR (500 MHz, DMSO-d_6) of compound **7**



^{13}C NMR (125 MHz, DMSO-d_6) of compound **7**



^{1}H NMR (500 MHz, DMSO-d_6) of compound **8**



^{13}C NMR (125 MHz, DMSO-d_6) of compound **8**