Supporting Information

MCR Synthesis and Biological Evaluation of Novel Praziquantel Derivatives

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1 CHEMISTRY

Experimental Section

General procedure (I) for the Ugi reaction: A mixture of aldehyde (1.2 eq.), amine (1.0 mmol) and carboxylic acid (1.0 eq.) in anhydrous MeOH was treated with isocyanide (1.0 eq.) at 0 ^{o}C. After being stirred at room temperature overnight, the reaction mixture was concentrated in vacuo to give Ugi-4CR product, which was used directly in the next step without further purification.

General procedure (II) for the Pictet-Spengler reaction: A mixture of above Ugi product (1.0 eq.) and anhydrous $MgSO_4$ (2.0 eq.) in anhydrous 1,2-dichloroethane was treated with MsOH (6.0 eq.) slowly under argon at room temperature. The mixture was then kept at 80 ^{o}C with stirring until the reaction was complete by TLC. After completion, the reaction was quenched by cold aq. $NaHCO_3$ solution and extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by flash column chromatography.

2-(Cyclohexanecarbonyl)-10-methoxy-2,3,6,7-tetrahydro-1*H*-pyrazino [2,1-a]isoquinolin-4(11b*H*)-one (8a): According to general procedure II was obtained as a white solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.27 (m, 3H), 1.52 (m, 2H), 1.81 (m, 5H), 2.47 (tt, *J* = 3.0, 11.4 Hz, 1H), 2.71 (d, *J* = 14.4 Hz, 1H), 2.85 (m, 3H), 3.79 (s, 3H), 4.07 (d, *J* = 17.4 Hz, 1H), 4.46 (d, *J* = 17.4 Hz, 1H), 4.75 (1dd, *J* = 4.3, 10.8 Hz, 1H), 4.80 (dd, *J* = 4.2, 12.0 Hz, 1H), 5.14 (dd, *J* = 3.0, 16.8 Hz, 1H), 6.79 (S, 1H), 6.80 (dd, *J* = 1.8, 8.4 Hz, 1H), 7.08 (d, *J* = 8.4 Hz, 1H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 174.82, 164.36, 158.51, 133.69, 130.26, 126.67, 114.08, 110.05, 55.43, 55.08, 49.02, 45.18, 40.79, 39.36, 29.24, 29.01, 27.90, 25.70 ppm. HRMS (EI) calcd for $C_{20}H_{26}N_2O_3$ $[M]^+$: 342.1943, found: 342.1943.

2-(Cyclohexanecarbonyl)-9,10-dimethoxy-2,3,6,7-tetrahydro-1*H*-pyrazino[2,1-a]isoquinolin-4(11b*H*)-one (8b): According to general procedure II was obtained as a white solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.28 (3H, m), 1.55 (2H, m), 1.76 (5H, m), 2.47 (1H, tt, *J* = 3.0, 12.0 Hz), 2.68 (1H, d, *J* = 15.0 Hz), 2.78 (1H, dd, *J* = 11.2, 13.8 Hz), 2.84 (1H, ddd, *J* = 2.4, 12.6, 12.6 Hz), 2.92 (1H, ddd, *J* = 4.2, 15.6, 15.6 Hz), 3.86 (3H, s), 3.87 (3H, s), 4.08 (1H, d, *J* = 17.4 Hz), 4.87 (1H, d, *J* = 17.4 Hz), 4.72 (1H, dd, *J* = 3.6, 10.2 Hz), 4.85 (1H, m), 5.12 (1H, dd, *J* = 3.0, 13.2 Hz), 6.64 (1H, s), 6.72 (1H, s) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 174.86, 164.33,

148.26, 148.06, 126.89, 124.38, 111.62, 108.00, 56.09, 55.92, 54.80, 49.00, 45.35, 40.77, 39.12, 29.24, 29.01, 28.26, 25.70, 25.68, 25.66 ppm. HRMS (ESI) calcd for $C_{21}H_{28}N_2O_4Na$ $[M+Na]^+$: 395.1947, found: 395.1947.

Compound 8c: According to general procedure II was obtained as a white solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.27 (m, 3H), 1.54 (m, 2H), 1.80 (m, 5H), 2.45 (tt, *J* = 11.4, 3.0 Hz, 1H), 2.71 (dd, *J* = 11.4, 13.2 Hz, 1H), 2.94 (m, 3H), 4.05 (d, *J* = 17.4 Hz, 1H), 4.48 (d, *J* = 17.4 Hz, 1H), 4.70 (d, *J* = 9.6 Hz, 1H), 5.03 (dd, *J* = 4.8, 13.2 Hz, 1H), 5.14 (dd, *J* = 2.4, 13.8 Hz, 1H), 6.89 (d, *J* = 4.8 Hz, 1H), 7.19 (d, *J* = 4.8 Hz, 1H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 174.69, 164.40, 135.07, 131.81, 124.46, 123.71, 54.44, 49.10, 44.20, 40.62, 39.32, 29.55, 28.97, 25.69, 25.66, 24.66 ppm. HRMS (EI) calcd for $C_{17}H_{12}N_2O_2S$ $[M]^+$: 318.1402, found: 318.1399.

Methyl 2-(cyclohexanecarbonyl)-4-oxo-2,3,4,6,7,11b-hexahydro-1*H*-pyrazino[2,1-a]isoquinoline-6-carboxylate (8d): According to general procedure II was obtained as a wax. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.28 (m, 3H), 1.54 (m, 2H), 1.58-1.87 (m, 5H), 2.49 (t, *J* = 11.4 Hz, 1H), 2.97 (ddd, *J* = 3.0, 12.0, 12.0 Hz, 1H), 3.17 (dd, *J* = 6.0, 15.6 Hz, 1H), 3.28 (m, 1H), 3.63 (s, 3H), 4.20 (d, *J* = 17.4 Hz, 1H), 4.51 (d, *J* = 17.4 Hz, 1H), 4.96 (m, 2H), 5.63 (dd, *J* = 3.6, 5.4 Hz, 1H), 7.18-7.28 (m, 4H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 174.92, 170.48, 165.41, 131.71, 131.56, 129.13, 127.82, 127.48, 125.68, 53.39, 52.67, 50.28, 48.77, 45.73, 40.87, 30.51, 29.12, 28.97, 25.71 ppm. HRMS (ESI) calcd for $C_{21}H_{26}N_2O_4Na$ $[M+Na]^+$: 393.1790, found: 393.1801.

2-(Cyclohexanecarbonyl)-3-methyl-2,3,6,7-tetrahydro-1*H*-pyrazino [2,1-a]isoquinolin-4(11b*H*)-one (9a): According to general procedure II was obtained as a wax. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.25-1.79 (m, 13H), 2.36 (m, 1H), 2.81-3.13 (m, 3H), 3.51 (m, 0.4H), 3.79 (m, 0.6H), 4.00 (m, 0.4H), 4.27 (m, 0.6H), 4.48 (m, 0.6H), 4.58 (m, 0.6H), 4.77 (m, 1H), 4.82 (m, 0.4H), 4.94 (m, 0.4H), 7.17-7.30 (m, 4H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 175.36, 168.54, 135.19, 133.66, 128.87, 127.77, 126.92, 125.01, 54.44, 53.98, 41.83, 40.73, 40.43, 29.92, 29.04, 28.22, 25.61, 19.92 ppm. HRMS (ESI) calcd for $C_{20}H_{26}N_2O_2Na$ $[M+Na]^+$: 349.1892, found: 349.1876.

2-(Cyclohexanecarbonyl)-3-cyclopropyl-2,3,6,7-tetrahydro-1*H*-pyrazino[2,1-a]isoquinolin-4(11b*H*)-one (9b): According to general procedure II was obtained a wax. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.67 (m, 4H), 1.25-1.82 (m, 11H), 2.42 (m, 1H), 2.82 (dd, *J* = 3.0, 12.0 Hz, 1H), 2.93-3.08 (m, 2H), 3.50 (dd, *J* = 8.4, 8.4 Hz, 0.5H), 3.93 (d, *J* = 12.6 Hz, 0.5H), 3.99 (d, *J* = 8.4 Hz, 0.5H), 4.04 (dd, *J* = 9.6, 24.0 Hz, 0.5H), 4.17 (d, *J* = 4.8 Hz, 0.5H), 4.60 (d, *J* = 12.0 Hz, 0.5H), 4.65 (d, *J* = 6.0 Hz, 0.5H), 4.80 (m, 0.5H), 4.95 (m, 0.5H), 5.12 (m, 0.5H), 7.18-7.31

(m, 4H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 175.82, 167.30, 135.08, 133.19, 128.87, 127.62, 126.88, 125.21, 61.08, 53.30, 44.87, 40.60, 39.74, 29.80, 29.26, 28.41, 25.85, 14.80, 4.46, 3.34 ppm. HRMS (EI) calcd for $C_{22}H_{28}N_2O_2$ $[M]^+$: 352.2151, found: 352.2148.

2-(Cyclohexanecarbonyl)-3-isopropyl-2,3,6,7-tetrahydro-1*H*-pyrazino[2,1-a]isoquinolin-4(11b*H*)-one (9c): According to general procedure II was obtained as a white solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.03 (d, *J* = 6.6 Hz, 1.5H), 1.07 (d, *J* = 6.6 Hz, 1.5H), 1.12 (d, *J* = 6.6 Hz, 1.5H), 1.17 (d, *J* = 6.6 Hz, 1.5H), 1.24 (m, 4H), 1.49-1.47 (m, 2H), 1.67-1.80 (m, 5H), 2.10 (m, 0.5H), 2.24 (m, 0.5H), 2.78-3.06 (m, 3H), 3.50 (dd, *J* = 10.8, 10.8 Hz, 0.5H), 3.72 (dd, *J* = 5.4, 14.4 Hz, 0.5H), 3.98 (dd, *J* = 4.2, 11.4 Hz, 0.5H), 4.10 (d, *J* = 9.0 Hz, 0.5H), 4.16 (dd, *J* = 8.4, 13.8 Hz, 0.5H), 4.63 (m, 0.5H), 4.81 (dd, *J* = 3.0, 13.2 Hz, 0.5H), 4.85 (d, *J* = 9.6 Hz, 0.5H), 4.89 (dd, *J* = 4.8, 9.8 Hz, 0.5H), 5.02 (dd, *J* = 3.6, 9.6 Hz, 0.5H), 7.16 (m, 1H), 7.23 (m, 2H), 7.29 (m, 1H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 176.13, 175.71, 168.68, 167.93, 135.81, 135.00, 134.44, 132.49, 129.51, 128.92, 127.76, 127.56, 126.93, 126.83, 125.98, 125.42, 64.62, 61.00, 53.24, 53.01, 50.21, 44.72, 41.12, 40.70, 39.83, 38.62, 32.19, 31.63, 29.99, 29.92, 29.71, 29.06, 28.50, 28.42, 26.00, 25.69, 25.62, 25.47, 20.21, 20.05 ppm. HRMS (ESI) calcd for $C_{22}H_{30}N_2O_2Na$ $[M+Na]^+$: 377.2205, found: 377.2217.

(3R,11bS)-2-(Cyclohexanecarbonyl)-3-isobutyl-2,3,6,7-tetrahydro-1*H*-pyrazino[2,1-a]isoquinolin-4(11b*H*)-one (9d): According to general procedure II was obtained as a white solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.96 (d, *J* = 6.0 Hz, 1.5H), 0.99 (d, *J* = 6.0 Hz, 1.5H), 1.07 (d, *J* = 6.0 Hz, 3H), 1.22 (m, 2H), 1.72 (m, 10.5H), 1.92 (m, 0.5H), 2.39 (tt, *J* = 3.0, 11.4 Hz, 1H), 2.80 (m, 1H), 2.98 (m, 2H), 3.57 (dd, *J* = 9.6, 12.0 Hz, 0.5H), 3.78 (dd, *J* = 4.2, 13.8 Hz, 0.5H), 3.97 (dd, *J* = 3.6, 12.0 Hz, 0.5H), 4.13 (dd, *J* = 7.2, 13.8 Hz, 0.5H), 4.43 (dd, *J* = 7.8, 7.8 Hz, 0.5H), 4.62 (m, 0.5H), 4.82 (m, 1H), 4.98 (dd, *J* = 3.6, 9.0 Hz, 0.5H), 5.04 (dd, *J* = 7.2, 7.2 Hz, 0.5H), 7.14 (d, *J* = 6.6 Hz, 0.5H), 7.23 (m, 2H), 7.29 (m, 1.5H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 175.45, 174.98, 169.18, 168.09, 135.96, 135.15, 133.39, 132.44, 129.56, 128.86, 127.77, 127.61, 126.90, 126.81, 125.90, 125.44, 57.24, 54.68, 53.79, 53.61, 49.28, 43.43, 43.40, 42.22, 41.04, 40.63, 40.09, 38.97, 29.97, 29.70, 29.60, 29.04, 28.97, 28.82, 28.60, 28.40, 25.95, 25.92, 25.68, 25.60, 25.02, 24.64, 23.12, 22.42, 22.21, 22.09 ppm. HRMS (ESI) calcd for $C_{23}H_{32}N_2O_2Na$ $[M+Na]^+$: 391.2361, found: 391.2352.

2-(Cyclohexanecarbonyl)-3-neopentyl-2,3,6,7-tetrahydro-1*H*-pyrazino[2,1-a]isoquinolin-4(11b*H*)-one (9e): According to general procedure II was obtained as a white solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.03 (s, 5.4H), 1.07 (s, 3.6H), 1.25 (m, 4H), 1.44 (m, 1H), 1.74 (m, 6.6H), 1.99 (dd, *J* = 8.4, 14.4 Hz, 0.4H), 2.35 (tt, *J* = 3.0, 11.4 Hz, 0.6H), 2.48 (tt, *J* = 3.0, 11.4 Hz, 0.4H), 2.78 (dd, *J* = 15.6, 15.6 Hz, 1H), 2.86 (ddd, *J* = 3.0, 12.0, 12.0 Hz,

0.8H), 2.98 (m, 1.2H), 3.74 (dd, *J* = 8.4, 12.6 Hz, 0.6H), 3.84 (dd, *J* = 4.8, 13.8 Hz, 0.4H), 3.90 (dd, *J* = 8.4, 13.8 Hz, 0.4H), 4.01 (dd, *J* = 4.8, 12.6 Hz, 0.6H), 4.57 (dd, *J* = 5.4, 8.4 Hz, 0.4H), 4.67 (m, 0.4H), 4.81 (ddd, *J* = 2.4, 4.8, 13.2 Hz, 0.6H), 4.98 (dd, *J* = 4.8, 8.4 Hz, 0.4H), 5.03 (dd, *J* = 4.8, 7.8 Hz, 0.6H), 5.28 (dd, *J* = 6.6, 6.6 Hz, 0.6H), 7.26 (m, 4H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 174.61, 170.20, 136.60, 132.73, 129.66, 127.75, 126.80, 125.80, 53.75, 53.50, 48.14, 46.30, 40.89, 39.37, 30.94, 29.70, 29.52, 29.06, 28.56, 25.95, 25.66, 25.56 ppm. HRMS (ESI) calcd for $C_{24}H_{34}N_2O_2Na$ $[M+Na]^+$: 405.2518, found: 405.2530.

2-(Cyclohexanecarbonyl)-3-(4-fluorophenyl)-2,3,6,7-tetrahydro-1*H*-pyrazino[2,1-a]isoquinolin-4(11b*H*)-one (9f): According to general procedure II was obtained as a white solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.89-1.27 (m, 4H), 1.44-1.88 (m, 6H), 2.26 (m, 1H), 2.83 (m, 1H), 2.95 (m, 2H), 3.52 (dd, *J* = 12.0, 12.0 Hz, 1H), 4.15 (d, *J* = 12.0 Hz, 1H), 4.62 (m, 2H), 5.67 (s, 1H), 7.06-7.18 (m, 3H), 7.24 (m, 3H), 7.36-7.47 (m, 2H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 176.61, 166.78, 162.23, 134.85, 131.95, 128.96, 127.91, 127.24, 127.18, 127.03, 126.20, 116.25, 61.72, 51.87, 49.03, 41.16, 38.95, 29.94, 29.71, 29.06, 28.73, 25.75, 25.34 ppm. HRMS (ESI) calcd for $C_{25}H_{27}N_2O_2FNa$ $[M+Na]^+$: 429.1954, found: 429.1953.

2-(Cyclohexanecarbonyl)-3-(hydroxymethyl)-2,3,6,7-tetrahydro-1*H*-pyrazino[2,1-a]isoquinolin-4(11b*H*)-one (9g): According to general procedure II was obtained as a wax. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.10 (m, 3H), 1.20 (m, 2H), 1.51 (m, 1H), 1.58 (m, 2H), 1.69 (m, 2H), 2.02 (br s, 1H), 2.12 (tt, *J* = 3.6, 10.8 Hz, 1H), 2.69 (ddd, *J* = 3.0, 3.0, 16.2 Hz, 1H), 2.81 (ddd, *J* = 3.6, 12.0, 12.0 Hz, 1H), 2.91 (ddd, *J* = 4.8, 11.4, 16.2 Hz, 1H), 3.15 (dd, *J* = 8.4, 13.2 Hz, 1H), 3.45 (dd, *J* = 4.8, 13.2 Hz, 1H), 3.76 (dd, J = 3.0, 7.8 Hz, 1H), 4.20 (dd, *J* = 3.0, 10.8 Hz, 1H), 4.43 (dd, *J* = 7.2, 11.4 Hz, 1H), 4.72 (dd, *J* = 4.8, 8.4 Hz, 1H), 4.78 (ddd, *J* = 2.4, 5.4, 13.2 Hz, 1H), 7.08 (m, 1H), 7.09 (m, 1H), 7.16 (m, 2H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 175.66, 166.77, 135.09, 134.28, 129.38, 127.16, 126.66, 124.52, 64.54, 57.21, 57.01, 45.54, 43.04, 39.72, 28.89, 28.85, 25.63, 25.38, 25.34 ppm. HRMS (ESI) calcd for $C_{20}H_{26}N_2O_3Na$ $[M+Na]^+$: 365.1841, found: 365.1834.

2-(Cyclopropanecarbonyl)-2,3,6,7-tetrahydro-1*H*-pyrazino[2,1-a] isoquinolin-4(11b*H*)-one (10a): According to general procedure II was obtained as a white solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.88 (m, 2H), 1.01 (m, 1H), 1.11 (m, 1H), 1.71 (m, 1H), 2.92 (m, 4H), 4.21 (d, *J* = 17.4 Hz, 1H), 4.70 (d, *J* = 17.4 Hz, 1H), 4.83 (d, *J* = 4.8 Hz, 2H), 5.13 (d, *J* = 17.4 Hz, 1H), 7.18 (d, *J* = 7.2 Hz, 1H), 7.26 (m, 3H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 172.34, 164.46, 134.81, 132.65, 129.30, 127.45, 126.97, 125.58, 54.87, 48.95, 45.58, 39.01, 28.75, 11.22, 8.39, 8.08 ppm. HRMS (EI) calcd for $C_{16}H_{18}N_2O_2$ $[M]^+$: 270.1368, found: 270.1367.

2-Benzoyl-2,3,6,7-tetrahydro-1*H*-pyrazino[2,1-a]isoquinolin-4(11b*H*)-one (10b): According to general procedure II was obtained a a white solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.81 (dd, *J* = 2.4, 16.2 Hz, 1H), 2.91 (ddd, *J* = 3.0, 12.0, 12.0 Hz, 1H), 3.00 (ddd, *J* = 4.2, 15.6, 15.6 Hz, 1H), 3.08 (m, 1H), 4.10 (m, 1H), 4.37 (m 1H), 4.82 (m, 1H), 5.00 (m, 1H), 5.28 (m, 1H), 7.22-7.60 (m, 9H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.33, 164.22, 134.83, 134.18, 132.73, 130.74, 129.45, 128.76, 127.56, 126.99, 125.50, 54.69, 51.45, 45.95, 39.04, 28.75 ppm. HRMS (EI) calcd for $C_{19}H_{18}N_2O_2$ $[M]^+$: 306.1368, found: 306.1363.

2-(2,4-Dimethylbenzoyl)-2,3,6,7-tetrahydro-1*H*-pyrazino[2,1-a] isoquinolin-4(11b*H*)-one (10c): According to general procedure II was obtained as a white solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.27 (s, 3H), 2.31 (s, 3H), 2.78-3.08 (m, 4H), 3.92 (d, *J* = 18.0 Hz, 1H), 4.10 (d, *J* = 18.0 Hz, 1H), 4.82 (d, *J* = 10.8 Hz, 1H), 4.97 (dd, *J* = 4.2, 10.2 Hz, 1H), 5.32 (d, *J* = 11.4 Hz, 1H), 7.05-7.40 (m, 7H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.38, 164.30, 139.70, 134.78, 132.72, 131.95, 131.48, 129.39, 127.56, 127.03, 126.86, 126.08, 125.51, 125.06, 55.13, 50.27, 45.09, 39.19, 28.73, 21.25, 18.95 ppm. HRMS (ESI) calcd for $C_{21}H_{22}N_2O_2Na$ $[M+Na]^+$: 357.1579, found: 357.1549.

2-(4-Fluoro-3-nitrobenzoyl)-2,3,6,7-tetrahydro-1*H*-pyrazino[2,1-a] isoquinolin-4(11b*H*)-one (10d): According to general procedure II was obtained as a white solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.82 (dd, *J* = 2.4, 15.6 Hz, 1H), 2.93 (ddd, *J* = 3.0, 12.6, 12.6 Hz, 1H), 3.01 (ddd, *J* = 4.2, 12.0, 12.0 Hz, 1H), 3.13 (m, 1H), 4.23 (m, 2H), 4.83 (m, 1H), 5.01 (d, *J* = 7.2 Hz, 1H), 5.20 (m, 1H), 7.22 (m, 2H), 7.29 (m, 2H), 7.44 (dd, *J* = 9.0, 9.0 Hz, 1H), 7.83 (m, 1H), 8.28 (dd, *J* = 2.4, 7.2 Hz, 1H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 166.72, 161.10, 156.07,137.27, 134.83 132.20, 131.09, 129.57, 128.75, 127.79, 127.12, 126.04, 125.35, 119.29, 54.49, 51.28, 46.37, 39.16, 28.68 ppm. HRMS (EI) calcd for $C_{19}H_{16}N_3O_4F$ $[M]^+$: 369.1125, found: 369.1136.

2-(4-Methoxyquinoline-2-carbonyl)-2,3,6,7-tetrahydro-1*H*-pyrazino [2,1-a]isoquinolin-4(11b*H*)-one (10e): According to general procedure II was obtained as a white solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.82 (m, 1H), 2.94 (m, 1H), 3.04 (m, 1H), 3.14 (dd, *J* = 10.8, 13.2 Hz, 0.5H), 3.25 (dd, *J* = 10.8, 13.2 Hz, 0.5H), 4.03 (d, *J* = 18.0 Hz, 0.5H), 4.12 (s, 1.5H), 4.20 (s, 1.5H), 4.43 (d, *J* = 18.0 Hz, 0.5H), 4.83 (ddd, *J* = 2.4, 4.8, 12.6 Hz, 0.5H), 4.99 (m, 0.5H), 5.00 (d, *J* = 17.4 Hz, 0.5H), 5.06 (dd, J = 4.2, 10.8 Hz, 0.5H), 5.13 (d, *J* = 18.0 Hz, 0.5H), 5.32 (m, 1H), 5.52 (dd, *J* = 3.6, 11.2 Hz, 0.5H), 7.09 (d, *J* = 7.8 Hz, 0.5H), 7.17 (m, 0.5H), 7.21 (m, 1H), 7.25 (s, 0.5H), 7.30-7.35 (m, 2H), 7.41 (d, *J* = 7.8 Hz, 0.5H), 7.60 (dd, *J* = 7.2, 7.2 Hz, 0.5H), 7.63 (dd, *J* = 7.2, 7.2 Hz, 0.5H), 7.76 (dd, *J* = 7.8, 7.8 Hz, 0.5H), 7.80 (dd, *J* = 7.8, 7.8 Hz, 0.5H), 8.06 (dd, *J* = 8.4 Hz, 1H), 8.23 (d, *J* = 8.4 Hz, 0.5H), 8.29 (dd, *J* = 8.4 Hz, 0.5H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 167.67, 166.80, 164.87, 164.84, 163.51, 163.46,

153.50, 153.18, 147.43, 147.34, 135.15, 134.92, 132.79, 132.71, 130.69, 130.56, 129.54, 129.41, 129.36, 129.14, 127.54, 127.32, 127.17, 127.14, 127.04, 126.85, 125.63, 125.33, 122.10, 121.82, 121.70, 121.46, 100.81, 100.22, 56.15, 56.13, 56.09, 54.64, 51.17, 51.08, 47.64, 46.51, 38.99, 38.81, 28.95, 28.77 ppm. HRMS (EI) calcd for $C_{23}H_{21}N_3O_3$ $[M]^+$: 387.1583, found: 387.1585.

2-(1-Ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carbonyl)-2,3,6,7-tetrahydro-1*H*-pyrazino[2,1-a]isoquinolin-4(11b*H*)-one (10f): According to general procedure II was obtained as a white wax. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.52 (m, 3H), 2.70 (s, 1.65H), 2.72 (s, 1.35H), 2.79 (m, 1H), 2.91 (m, 1H), 2.98 (m, 1H), 3.13 (m, 1H), 3.99 (d, J = 18.6 Hz, 0.55H), 4.27 (d, *J* = 12.0 Hz, 0.45H), 4.32 (s, 1H), 4.45 (m, 1H), 4.56 (m, 1H), 4.81 (m, 0.55H), 4.95 (m, 1H), 5.00 (dd, *J* = 3.0, 10.8 Hz, 0.45H), 5.17 (dd, *J* = 3.0, 13.2 Hz, 0.55H), 5.50 (d, *J* = 8.4 Hz, 0.45H), 7.11-7.39 (m, 5H), 8.21(s, 0.55H), 8.29 (s, 0.45H), 8.60 (d, *J* = 8.4 Hz, 0.55H), 8.70 (d, *J* = 8.4 Hz, 0.45H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 174.16, 173.69, 166.15, 165.65, 165.50, 165.04, 163.13, 163.04, 148.61, 148.60, 146.99, 146.04, 136.54, 136.50, 135.16, 134.88, 132.92, 132.84, 129.30, 129.23, 127.45, 127.12, 126.98, 126.63, 125.83, 125.66, 121.24, 121.12, 120.42, 120.25, 117.75, 117.41, 56.01, 54.68, 53.77, 51.51, 50.78, 47.39, 46.64, 46.53, 38.95, 38.65, 31.76, 29.26, 29.01, 28.79, 25.22 ppm. HRMS (ESI) calcd for $C_{24}H_{24}N_4O_3Na$ $[M+Na]^+$: 439.1746, found: 439.1707.

2-(2-(Pyridin-4-ylthio)acetyl)-2,3,6,7-tetrahydro-1*H*-pyrazino[2,1-a] isoquinolin-4(11b*H*)-one (10g): According to general procedure II was obtained as a yellow wax. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.79-2.99 (m, 4H), 3.89 (s, 2H), 4.21 (d, *J* = 17.4 Hz, 1H), 4.48 (d, *J* = 17.4 Hz, 1H), 4.83 (m, 2H), 5.06 (ddd, *J* = 1.8, 4.2, 13.2 Hz, 1H), 7.29 (m, 6H), 8.44 (d, *J* = 4.2 Hz, 2H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 166.09, 163.44, 149.49, 146.99, 134.74, 132.17, 129.39, 127.68, 125.42, 121.09, 54.72, 49.48, 45.69, 39.18, 33.40, 28.64 ppm. HRMS (EI) calcd for $C_{19}H_{19}N_3O_2S$ $[M]^+$: 353.1198, found: 353.1203.

1-(4-Oxo-3,4,6,7-tetrahydro-1*H*-pyrazino[2,1-a]isoquinolin-2(11b*H*)-yl) -2-phenylethane-1,2-dione (10h): According to general procedure II was obtained as a white wax. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.80 (ddd, *J* = 1.5, 18.8, 18.8 Hz, 1H), 2.87-3.01 (m, 2H), 3.18 (dd, *J* = 11.2, 13.2 Hz, 0.5H), 3.30 (dd, *J* = 10.8, 13.8 Hz, 0.5H), 4.80 (m, 0.5H), 4.89 (m, 0.5 H), 5.00 (m, 1.5H), 5.14 (dd, *J* = 4.2, 13.8 Hz, 0.5H), 6.93 (d, *J* = 7.8 Hz, 0.5H), 7.18 (m, 1H), 7.22 (dd, *J* = 7.2, 7.2 Hz, 1H), 7.33 (m, 2H), 7.51 (dd, *J* = 8.4, 8.4 Hz, 1H), 7.55 (dd, *J* = 7.2, 7.2 Hz, 1H), 7.69 (m, 1H), 7.95 (d, *J* = 8.4 Hz, 1H), 8.04 (d, *J* = 7.8 Hz, 1H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 190.46, 190.25, 165.12, 164.71, 163.84, 163.22, 135.31, 135.26, 135.08, 134.89, 132.92, 132.60, 132.17, 131.56, 130.02, 129.84, 129.54, 129.51, 129.19, 127.80, 127.70, 127.11, 126.94, 125.42, 125.26, 55.68, 54.92, 49.63,

48.64, 45.49, 44.61, 39.26, 38.89, 28.75, 28.63 ppm. HRMS (EI) calcd for $C_{20}H_{18}N_2O_3$ $[M]^+$: 334.1317, found: 334.1321.

General procedure (III) for the amidation of compound 8d: To a mixture of **8d** (1.0 eq.) and amine (1.5 eq.) was added TBD (0.2 eq.). The mixture was heated at 60 ^oC for 2h and the mixture was purified by flash column chromatography directly to give **11(a-b)**.

2-(Cyclohexanecarbonyl)-N-(2-methoxyethyl)-4-oxo-2,3,4,6,7,11b-hexahydro-1*H*-pyrazino[2,1-a]isoquinoline-6-carboxamide (11a): According to general procedure III was obtained as a white solid. ^1H NMR (600 MHz, $CDCl_3$): δ = 1.28 (m, 3H), 1.31-1.85 (m, 7H), 2.45 (m, 1H), 3.08 (dd, *J* = 6.0, 15.6 Hz, 1H), 3.26-3.46 (m, 9H), 3.69 (dd, *J* = 7.8, 13.8 Hz, 1H), 4.25 (d, *J* = 18.0 Hz, 1H), 4.40 (d, *J* = 18.0 Hz, 1H), 4.83 (dd, *J* = 3.6, 7.8 Hz, 1H), 5.24 (dd, *J* = 6.0, 6.0 Hz, 1H), 6.50 (br s, 1H), 7.26 (m, 4H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 174.82, 169.37, 165.84, 132.95, 132.90, 128.73, 128.01, 127.15, 124.46, 70.93, 58.83, 53.47, 52.03, 48.94, 43.54, 40.83, 39.32, 29.76, 29.07, 28.99, 25.69 ppm. HRMS (EI) calcd for $C_{23}H_{31}N_3O_4$ $[M]^+$: 413.2314, found: 413.2306.

2-(Cyclohexanecarbonyl)-6-(morpholine-4-carbonyl)-2,3,6,7-tetrahydro -1*H*-pyrazino[2,1-a]isoquinolin-4(11b*H*)-one (11b): According to general procedure III was obtained as a white solid. ^1H NMR (600 MHz, $CDCl_3$): δ = 1.27 (m, 3H), 1.79 (m, 7H), 2.44 (tt, *J* = 3.0, 11.4 Hz, 1H), 3.10 (m, 2H), 3.69 (m, 9H), 4.18 (d, *J* = 17.4 Hz, 1H), 4.38 (d, *J* = 17.4 Hz, 1H), 4.69 (dd, *J* = 3.6, 13.8 Hz, 1H), 5.04 (dd, *J* = 4.2, 8.4 Hz, 1H), 5.50 (dd, *J* = 6.0, 6.0 Hz, 1H), 7.20 (m, 2H), 7.31 (m, 2H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 174.76, 169.20, 165.12, 133.73, 132.13, 128.31, 127.88, 127.39, 124.33, 66.89, 66.70, 53.53, 48.98, 48.77, 46.40, 43.59, 42.57, 40.81, 30.91, 29.07, 25.69 ppm. HRMS (EI) calcd for $C_{24}H_{31}N_3O_4$ $[M]^+$: 425.2314, found: 425.2307.

General procedure (IV) for the amidation of 10c: To a mixture of **10c** (1.0 eq.) and K_2CO_3 (1.0 eq.) in DMF was added amine (1.0 eq.). After being stirred at room temperature overnight, the reaction mixture was diluted with H_2O and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography affording **11(c-g)**.

2-(4-(Cyclopropylmethylamino)-3-nitrobenzoyl)-2,3,6,7-tetrahydro-1*H*-pyrazino[2,1-a]isoquinolin-4(11b*H*)-one (11c): According to general procedure IV was obtained as an orange solid. ^1H NMR (600 MHz, $CDCl_3$): δ =

0.36 (m, 2H), 0.68 (m, 2H), 1.21 (m, 1H), 2.79 (ddd, *J* = 2.4, 2.4, 15.6 Hz, 1H), 2.92 (ddd, *J* = 3.0, 12.6, 12.6 Hz, 1H), 2.99 (ddd, *J* = 4.8, 12.0, 15.6 Hz, 1H), 3.11 (m, 1H), 3.22 (m, 2H), 4.17 (m, 1H), 4.54 (m, 1H), 4.83 (d, *J* = 10.8 Hz, 1H), 5.01 (dd, *J* = 4.8, 10.2 Hz, 1H), 5.03 (m, 1H), 6.90 (d, *J* = 9.0 Hz, 1H), 7.19 (d, *J* = 7.2 Hz, 1H), 7.26 (m, 3H), 7.64 (dd, *J* = 1.2, 8.4 Hz, 1H), 8.36 (t, *J* = 4.8 Hz, 1H), 8.42 (d, *J* = 1.8 Hz, 1H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 168.57, 164.21, 146.50, 135.69, 134.91, 132.45, 130.64, 129.45, 127.56, 127.35, 127.00, 125.44, 120.28, 114.24, 54.76, 48.21, 38.99, 28.75, 10.24, 3.50 ppm. HRMS (EI) calcd for $C_{23}H_{24}N_4O_4$ $[M]^+$: 420.1798, found: 420.1797.

2-(4-Morpholino-3-nitrobenzoyl)-2,3,6,7-tetrahydro-1*H*-pyrazino [2,1-a]isoquinolin-4(11b*H*)-one (11d): According to general procedure IV was obtained as an orange solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.80 (ddd, *J* = 3.0, 3.0, 15.6 Hz, 1H), 2.90 (ddd, *J* = 3.0, 12.0, 12.0 Hz, 1H), 3.00 (ddd, *J* = 4.8, 11.4, 22.8 Hz, 1H), 3.16 (m, 5H), 3.87 (dd, *J* = 4.8, 4.8 Hz, 4H), 4.17 (m, 1H), 4.40 (m, 1H), 4.82 (m, 1H), 4.99 (dd, *J* = 4.2, 10.8 Hz, 1H), 5.15 (m, 1H), 7.15 (d, *J* = 8.4 Hz, 1H), 7.20 (d, *J* = 7.2 Hz, 1H), 7.28 (m, 3H), 7.65 (d, *J* = 7.8 Hz, 1H), 8.01 (d, *J* = 1.8 Hz, 1H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 167.93, 163.88, 147.41, 141.06, 134.91, 133.09, 129.50, 127.66, 127.05, 126.64, 126.30, 125.40, 120.17, 66.51, 51.36, 39.06, 28.72 ppm. HRMS (EI) calcd for $C_{23}H_{24}N_4O_5$ $[M]^+$: 436.1747, found: 436.1741.

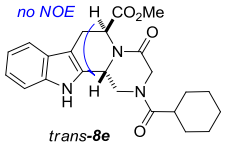
2-(4-(3-Methoxypropylamino)-3-nitrobenzoyl)-2,3,6,7-tetrahydro-1*H*-pyrazino[2,1-a]isoquinolin-4(11b*H*)-one (11e): According to general procedure IV was obtained as an orange solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.02 (m, 2H), 2.79 (ddd, *J* = 2.4, 2.4, 15.6 Hz, 1H), 2.90 (ddd, *J* = 3.6, 12.0, 12.0 Hz, 1H), 2.99 (ddd, *J* = 4.8, 12.0, 15.6 Hz, 1H), 3.11 (m, 1H), 3.40 (s, 3H), 3.49 (m, 2H), 3.56 (dd, *J* = 6.0, 6.0 Hz, 2H), 4.18 (m, 1H), 4.55 (m, 1H), 4.82 (d, *J* = 10.8 Hz, 1H), 5.02 (dd, *J* = 3.0, 10.2 Hz, 1H), 5.03 (m, 1H), 6.95 (d, *J* = 9.0 Hz, 1H), 7.19 (d, *J* = 7.2 Hz, 1H), 7.26 (m, 3H), 7.65 (dd, *J* = 1.2, 9.0 Hz, 1H), 8.41 (d, *J* = 2.4 Hz, 1H), 8.60 (t, *J* = 4.2 Hz, 1H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 168.65, 164.27, 146.73, 135.67, 134.91, 132.44, 130.73, 129.45, 127.56, 127.40, 127.01, 125.45, 120.11, 114.08, 70.44, 58.88, 54.84, 50.85, 41.23, 39.00, 28.74 ppm. HRMS (EI) calcd for $C_{23}H_{26}N_4O_5$ $[M]^+$: 438.1903, found: 438.1911.

2-(4-(2-Morpholinoethylamino)-3-nitrobenzoyl)-2,3,6,7-tetrahydro-1*H*-pyrazino[2,1-a]isoquinolin-4(11b*H*)-one (11f): According to general procedure IV was obtained as an orange solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.55 (m, 4H), 2.77 (m, 3H), 2.90 (ddd, *J* = 3.0, 12.6, 12.6 Hz, 1H), 2.99 (ddd, *J* = 3.6, 12.0, 15.6 Hz, 1H), 3.11 (m, 1H), 3.42 (m, 2H), 3.77 (m, 4H), 4.17 (m, 1H), 4.54 (m, 1H), 4.82 (d, *J* = 11.4 Hz, 1H), 5.02 (dd, *J* = 3.0, 10.8 Hz, 1H), 5.03 (m, 1H), 6.89 (d, *J* = 9.0 Hz, 1H), 7.20 (d, *J* = 10.8 Hz, 1H), 7.26 (m, 3H), 7.66 (d, *J* = 8.4 Hz, 1H), 8.42

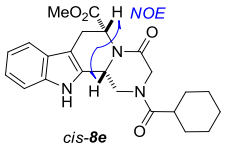
(d, *J* = 1.8 Hz, 1H), 8.81 (t, *J* = 4.2 Hz, 1H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 168.59, 164.22, 146.36, 135.68, 134.91, 132.44, 130.88, 129.45, 127.56, 127.39, 127.00, 125.43, 120.24, 114.41, 66.99, 55.71, 54.76, 53.10, 39.38, 38.99, 28.71 ppm. HRMS (EI) calcd for $C_{25}H_{29}N_5O_5$ $[M]^+$: 479.2169, found: 479.2171.

5-(Dimethylamino)-N-(2-(2-nitro-4-(4-oxo-2,3,4,6,7,11b-hexahydro-1*H*-pyrazino[2,1-a]isoquinoline-2-carbonyl)phenylamino)ethyl) naphthalene-1-sulfonamide (11g): According to general procedure IV was obtained as an orange solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.81(ddd, *J* = 3.0, 3.0, 15.6 Hz, 1H), 2.88 (s, 6H), 2.92 (ddd, *J* = 3.0, 12.6, 12.6 Hz, 1H), 3.01 (ddd, *J* = 4.8, 12.0, 15.6 Hz, 1H), 3.13 (m, 1H), 3.24 (dd, *J* = 6.0, 12.0 Hz, 2H), 3.44 (dd, *J* = 6.0, 12.0 Hz, 2H), 4.20 (m, 1H), 4.54 (m, 1H), 4.84 (d, *J* = 11.4 Hz, 1H), 5.04 (dd, *J* = 4.2, 10.8 Hz, 1H), 5.71 (t, *J* = 6.0 Hz, 1H), 6.78 (d, *J* = 8.4 Hz, 1H), 7.21 (d, *J* = 6.6 Hz, 1H), 7.24 (d, *J* = 6.6 Hz, 1H), 7.26 (m, 3H), 7.51 (m, 2H), 7.57 (d, *J* = 8.4 Hz, 1H), 8.19 (t, *J* = 4.8 Hz, 1H), 8.26 (m, 2H), 8.32 (d, *J* = 1.2 Hz, 1H), 8.52 (d, *J* = 8.4 Hz, 1H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 168.32, 164.29, 152.09, 146.01, 143.21, 135.63, 134.90, 134.28, 132.44, 131.09, 130.86, 129.87, 129.64, 129.45, 129.40, 128.71, 127.59, 127.37, 127.05, 125.48, 123.13, 120.98, 119.37, 118.34, 115.35, 113.79, 45.40, 42.69, 41.80, 39.05, 28.76 ppm. HRMS (EI) calcd for $C_{33}H_{34}N_6O_6S$ $[M]^+$: 642.2260, found: 642.2238.

2 2D NOESY studies of 8e, 9b, 9d, 9f, 9g.



*trans-**8e***



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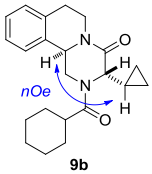
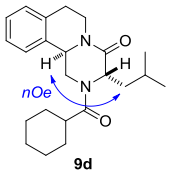
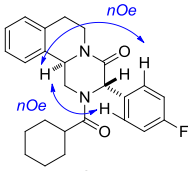


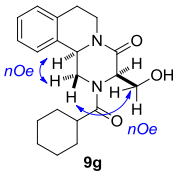
9b



9d

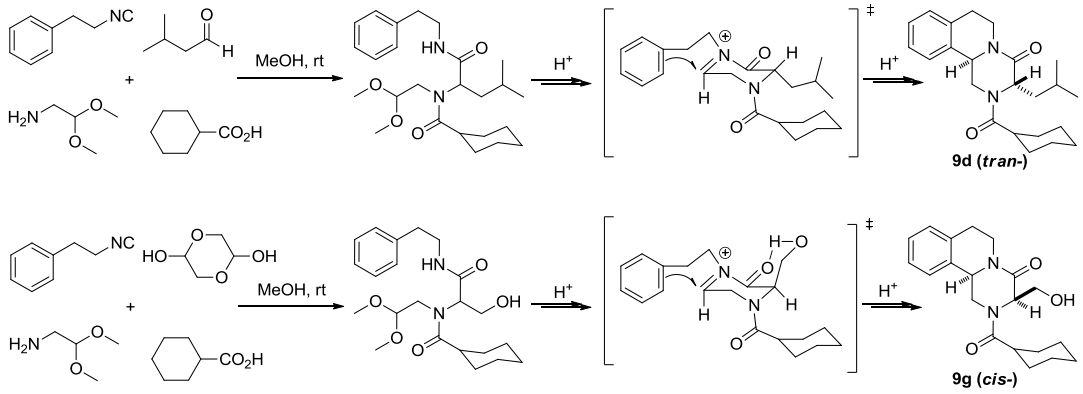


9f



9g

3 A plausible mechanism for the Pictet-Spengler cyclization leading to 9d and 9g



4 X-ray data for 9e

Crystal Structure Determinationof 9e

Operator:	*** Herdtweck ***
Molecular Formula:	C_{24} H_{34} N_2 O_2
Crystal Color / Shape	Colorless needle
Crystal Size	Approximate size of crystal fragment used for data collection: 0.05 × 0.05 × 0.36 mm
Molecular Weight:	382.53 a.m.u.
F_{000}:	416
Systematic Absences:	none
Space Group:	Triclinic $P\bar{1}$ (I.T.-No.: 2)
Cell Constants:	Least-squares refinement of 9897 reflections with the programs "APEX suite" and "SAINT" [1,2]; theta range 1.30° < θ < 25.45°; Mo(K$\bar{\alpha}$); λ = 71.073 pm
	a = 586.18(2) pm α = 89.293(3)°
	b = 1191.92(5) pm β = 82.239(2)°
	c = 1579.91(7) pm γ = 76.332(2)°
	V = 1062.55(8)· 10^6 pm^3; Z = 2; D_{calc} = 1.196 g cm^{-3}; Mos. = 0.75
Diffractometer:	Kappa APEX II (Area Diffraction System; BRUKER AXS); rotating anode; graphite monochromator; 60 kV; 40 mA; λ = 71.073 pm; Mo(K$\bar{\alpha}$)
Temperature:	(-120±1) °C; (153±1) K
Measurement Range:	1.30° < θ < 25.45°; h: -6/6, k: -14/14, l: -19/19
Measurement Time:	2 × 10 s per film
Measurement Mode:	measured: 7 runs; 2821 films / scaled: 7 runs; 2821 films
	φ– and ω–movement; Increment: $\Delta\varphi/\Delta\omega$ = 0.50°; dx = 35.0 mm
LP - Correction:	Yes [2]
Intensity Correction	No/Yes; during scaling [2]
Absorption Correction:	Multi-scan; during scaling; μ = 0.076 mm^{-1} [2]
	Correction Factors: T_{min} = 0.5976 T_{max} = 0.7452
Reflection Data:	31067 reflections were integrated and scaled
	31067 reflections to be merged
	3771 independent reflections
	0.050 R_{int}: (basis F_o^2)
	3771 independent reflections (all) were used in refinements
	3305 independent reflections with $I_o > 2\sigma(I_o)$
	95.8 % completeness of the data set
	389 parameter full-matrix refinement
	9.7 reflections per parameter
Solution:	Direct Methods [3]; Difference Fourier syntheses
Refinement Parameters:	In the asymmetric unit:
	28 Non-hydrogen atoms with anisotropic displacement parameters
	34 Hydrogen atoms with isotropic displacement parameters
Hydrogen Atoms:	All hydrogen atom positions were found in the difference map calculated from the model containing all non-hydrogen atoms. The hydrogen positions were refined with individual isotropic displacement parameters.
Atomic Form Factors:	For neutral atoms and anomalous dispersion [4]
Extinction Correction:	no
Weighting Scheme:	$w^{-1} = \sigma^2(F_o^2)+(a*P)^2+b*P$
	with a: 0.0318; b: 0.4210; P: [Maximum(0 or F_o^2)+2*F_c^2]/3
Shift/Err:	Less than 0.001 in the last cycle of refinement:
Resid. Electron Density:	+0.21 $e_{0;}^-$/Å^3; -0.18 $e_{0;}^-$/Å^3
R1:	$\Sigma(\|\|F_o\|-\|F_c\|\|)/\Sigma\|F_o\|$
[$F_o > 4\sigma(F_o)$; N=3305]:	= 0.0349
[all reflctns; N=3771]:	= 0.0412
wR2:	$[\Sigma w(F_o^2-F_c^2)^2/\Sigma w(F_o^2)^2]^{1/2}$
[$F_o > 4\sigma(F_o)$; N=3305]:	= 0.0837
[all reflctns; N=3771]:	= 0.0890

Goodness of fit: $[\Sigma w(F_o^2-F_c^2)^2/(NO-NV)]^{1/2}$ = 1.038
Remarks: Refinement expression $\Sigma w(F_o^2-F_c^2)^2$
Programs: The program system "WinGX32" [7] with the programs: "PLATON" [6], "SHELXL-97" [5], "SIR92" [3]

Table S1 - Bond Distances (Angstrom) for **9e**

O5	-C4	1.2313(15)	C11	-C12	1.389(2)
O17	-C16	1.2327(15)	C12	-C13	1.3854(19)
N2	-C1	1.4538(16)	C13	-C14	1.3967(17)
N2	-C3	1.4660(15)	C14	-C15	1.5283(18)
N2	-C16	1.3677(15)	C16	-C18	1.5183(17)
N6	-C4	1.3524(17)	C18	-C19	1.5325(18)
N6	-C7	1.4635(17)	C18	-C23	1.5366(18)
N6	-C15	1.4663(16)	C19	-C20	1.526(2)
C1	-C15	1.5325(17)	C20	-C21	1.527(2)
C3	-C4	1.5257(17)	C21	-C22	1.526(2)
C3	-C24	1.5407(18)	C22	-C23	1.531(2)
C7	-C8	1.522(2)	C24	-C25	1.5452(18)
C8	-C9	1.516(2)	C25	-C26	1.526(2)
C9	-C10	1.3985(19)	C25	-C27	1.531(2)
C9	-C14	1.4029(17)	C25	-C28	1.5355(19)
C10	-C11	1.382(2)			

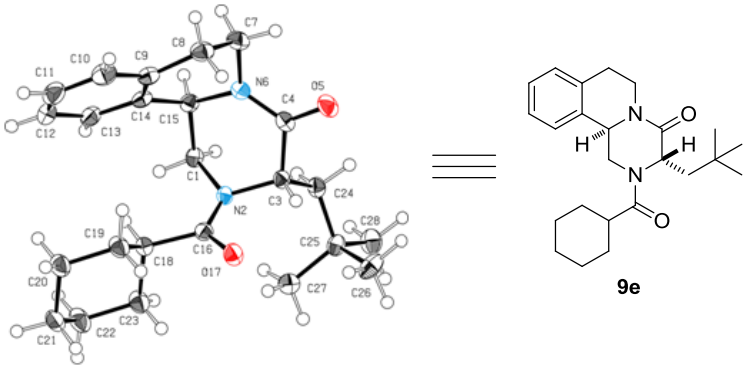
C1	-H11	0.968(13)	C21	-H211	1.028(18)
C1	-H12	0.993(14)	C21	-H212	0.989(17)
C3	-H31	0.964(12)	C22	-H221	1.010(18)
C7	-H71	1.032(17)	C22	-H222	1.010(17)
C7	-H72	0.981(17)	C23	-H231	0.978(17)
C8	-H81	1.000(18)	C23	-H232	1.002(18)
C8	-H82	0.992(15)	C24	-H241	0.988(14)
C10	-H101	0.990(17)	C24	-H242	0.997(18)
C11	-H111	0.981(17)	C26	-H261	1.001(17)
C12	-H121	0.963(17)	C26	-H262	1.008(19)
C13	-H131	0.971(16)	C26	-H263	1.006(17)
C15	-H151	0.994(12)	C27	-H271	0.990(17)
C18	-H181	0.957(17)	C27	-H272	0.988(17)
C19	-H191	0.987(18)	C27	-H273	0.988(18)
C19	-H192	0.992(17)	C28	-H281	1.017(18)
C20	-H201	1.019(18)	C28	-H282	1.015(17)
C20	-H202	0.992(16)	C28	-H283	0.985(17)

Table S2 - Bond Angles (Degrees) for **9e**

C1	-N2	-C3	111.62(9)	C9	-C14	-C15	121.22(11)
C1	-N2	-C16	126.53(10)	C13	-C14	-C15	119.40(11)
C3	-N2	-C16	118.69(10)	N6	-C15	-C1	109.69(10)
C4	-N6	-C7	119.50(12)	N6	-C15	-C14	110.40(10)
C4	-N6	-C15	126.85(10)	C1	-C15	-C14	114.87(10)
C7	-N6	-C15	113.26(11)	O17	-C16	-N2	120.93(11)
N2	-C1	-C15	110.75(10)	O17	-C16	-C18	119.61(10)
N2	-C3	-C4	110.08(10)	N2	-C16	-C18	119.35(10)
N2	-C3	-C24	114.94(10)	C16	-C18	-C19	110.16(11)
C4	-C3	-C24	111.55(10)	C16	-C18	-C23	108.79(10)
O5	-C4	-N6	122.31(11)	C19	-C18	-C23	110.88(10)
O5	-C4	-C3	119.04(11)	C18	-C19	-C20	111.12(13)
N6	-C4	-C3	118.59(10)	C19	-C20	-C21	111.17(12)
N6	-C7	-C8	107.60(10)	C20	-C21	-C22	111.14(12)
C7	-C8	-C9	111.06(13)	C21	-C22	-C23	110.82(13)
C8	-C9	-C10	120.18(12)	C18	-C23	-C22	111.05(11)
C8	-C9	-C14	121.09(11)	C3	-C24	-C25	117.31(10)
C10	-C9	-C14	118.69(12)	C24	-C25	-C26	110.23(11)
C9	-C10	-C11	121.43(14)	C24	-C25	-C27	112.24(11)

C10	-C11	-C12	119.70(13)	C24	-C25	-C28	106.66(11)
C11	-C12	-C13	119.65(14)	C26	-C25	-C27	109.57(12)
C12	-C13	-C14	121.07(12)	C26	-C25	-C28	108.84(11)
C9	-C14	-C13	119.30(11)	C27	-C25	-C28	109.21(11)
N2	-C1	-H11	111.8(7)	C21	-C20	-H202	109.8(9)
N2	-C1	-H12	107.5(7)	H201	-C20	-H202	108.3(13)
C15	-C1	-H11	111.3(7)	C20	-C21	-H211	108.3(9)
C15	-C1	-H12	107.8(8)	C20	-C21	-H212	108.9(9)
H11	-C1	-H12	107.4(10)	C22	-C21	-H211	109.2(9)
N2	-C3	-H31	105.3(8)	C22	-C21	-H212	111.2(10)
C4	-C3	-H31	104.3(8)	H211	-C21	-H212	107.9(13)
C24	-C3	-H31	110.0(8)	C21	-C22	-H221	110.4(10)
N6	-C7	-H71	108.4(9)	C21	-C22	-H222	108.9(10)
N6	-C7	-H72	107.7(9)	C23	-C22	-H221	109.7(10)
C8	-C7	-H71	110.3(8)	C23	-C22	-H222	110.2(10)
C8	-C7	-H72	113.1(9)	H221	-C22	-H222	106.8(14)
H71	-C7	-H72	109.7(13)	C18	-C23	-H231	109.6(9)
C7	-C8	-H81	108.6(9)	C18	-C23	-H232	108.5(9)
C7	-C8	-H82	110.2(9)	C22	-C23	-H231	109.9(10)
C9	-C8	-H81	109.7(9)	C22	-C23	-H232	109.9(9)
C9	-C8	-H82	109.2(10)	H231	-C23	-H232	107.8(13)
H81	-C8	-H82	108.1(14)	C3	-C24	-H241	107.2(8)
C9	-C10	-H101	118.4(9)	C3	-C24	-H242	109.4(8)
C11	-C10	-H101	120.2(9)	C25	-C24	-H241	107.1(8)
C10	-C11	-H111	119.9(10)	C25	-C24	-H242	108.5(8)
C12	-C11	-H111	120.4(10)	H241	-C24	-H242	106.8(11)
C11	-C12	-H121	120.3(9)	C25	-C26	-H261	111.3(10)
C13	-C12	-H121	120.1(9)	C25	-C26	-H262	111.3(11)
C12	-C13	-H131	118.9(9)	C25	-C26	-H263	110.6(10)
C14	-C13	-H131	120.1(9)	H261	-C26	-H262	109.1(15)
N6	-C15	-H151	106.9(7)	H261	-C26	-H263	106.3(14)
C1	-C15	-H151	107.3(7)	H262	-C26	-H263	108.2(15)
C14	-C15	-H151	107.3(7)	C25	-C27	-H271	112.2(10)
C16	-C18	-H181	110.9(9)	C25	-C27	-H272	109.9(10)
C19	-C18	-H181	108.6(9)	C25	-C27	-H273	111.9(10)
C23	-C18	-H181	107.4(9)	H271	-C27	-H272	106.8(14)
C18	-C19	-H191	108.2(8)	H271	-C27	-H273	107.9(14)
C18	-C19	-H192	108.3(10)	H272	-C27	-H273	107.9(14)
C20	-C19	-H191	110.3(8)	C25	-C28	-H281	111.2(9)
C20	-C19	-H192	111.6(10)	C25	-C28	-H282	110.1(10)
H191	-C19	-H192	107.2(14)	C25	-C28	-H283	111.7(10)
C19	-C20	-H201	109.3(9)	H281	-C28	-H282	108.1(14)
C19	-C20	-H202	109.3(10)	H281	-C28	-H283	107.1(14)
C21	-C20	-H201	108.9(9)	H282	-C28	-H283	108.3(14)

Figure F1 –ORTEP drawing with 50% ellipsoids for **9e**



9e

5 BIOLOGY

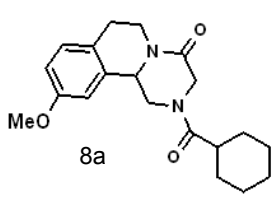
Material and Methods

Syrian golden hamsters (*Mesocrietus auratus*) 100-120 gm each, were obtained from the Schistosome Biological Supply Center (SBSC), Theodor Bilharz Research Institute. They were fed on a standard pelleted diet containing 24% protein, 4% fat and 4-5% fiber and water. *Schistosoma mansoni* cercariae shed from *Biomphalariae alexandrina* snails were used to infect Syrian golden (*Mesocrietus auratus*) hamsters weighing 100-120 g with 350 cercariae each using abdominal skin exposure. Compounds (PZQ derivatives) were prepared as 5 mM stock solutions in DMSO. At day of sacrifice, the stock solution was diluted with complete medium to produce concentrations ranging from 0.4 to 100 µM.

In vitro schistosome worm killing assay: The mother PZQ (Shin Poong Pharmaceutical Co., South Korea) and PZQ derivatives were prepared as 5 mM stock solutions. Immediately before use, the stock solutions were diluted with complete medium to diminishing concentrations of 100, 75, 50, 25, 12.5, 6.0, 30, 1.5, 0.8, 0.4 µM. *S. mansoni* infected hamsters were sacrificed and worms harvested from the portomesenteric vessels to recover adult schistosomes. Worms was cultured on duplicate Petri dishes with a density of 12 to 16 worms per dish with RPMI 1640 medium (glutamine, 20% fetal calf serum, and antibiotics [streptomycin, penicillin and gentamicin] containing the indicated concentration of test compound was added. The worms were incubated overnight in a CO_2 incubator, washed twice with FBS, and fresh medium without drug was added and the incubation was continued overnight. On the second day, worm motility was observed and the medium was changed again and the incubation continued. On day 5 the numbers of living and dead worms were recorded. Negative controls using pure medium alone or medium with DMSO and positive control media containing various concentrations of PZQ were similarly evaluated. At the end of observation period, worms were examined in a laminar flow hood for their motility and appearance using a stereomicroscope and the final recording of percent mortality was assessed (the number of dead worms [contracted and opaque] relative to the number of worms). The percentages of *Schistosoma mansoni* worm killing in vitro under the influences of different test PZQ derivatives in different concentrations versus untreated and DMSO negative controls and positive controls treated with the mother drug PZQ were determined. Different compounds EC_{50}'s were computed using computerized program "Pharm/PCS" Version 4.2 (Pharmacologic calculation system) by a plot of the percent of worms mortality (versus living worms) against the concentration of the drug.

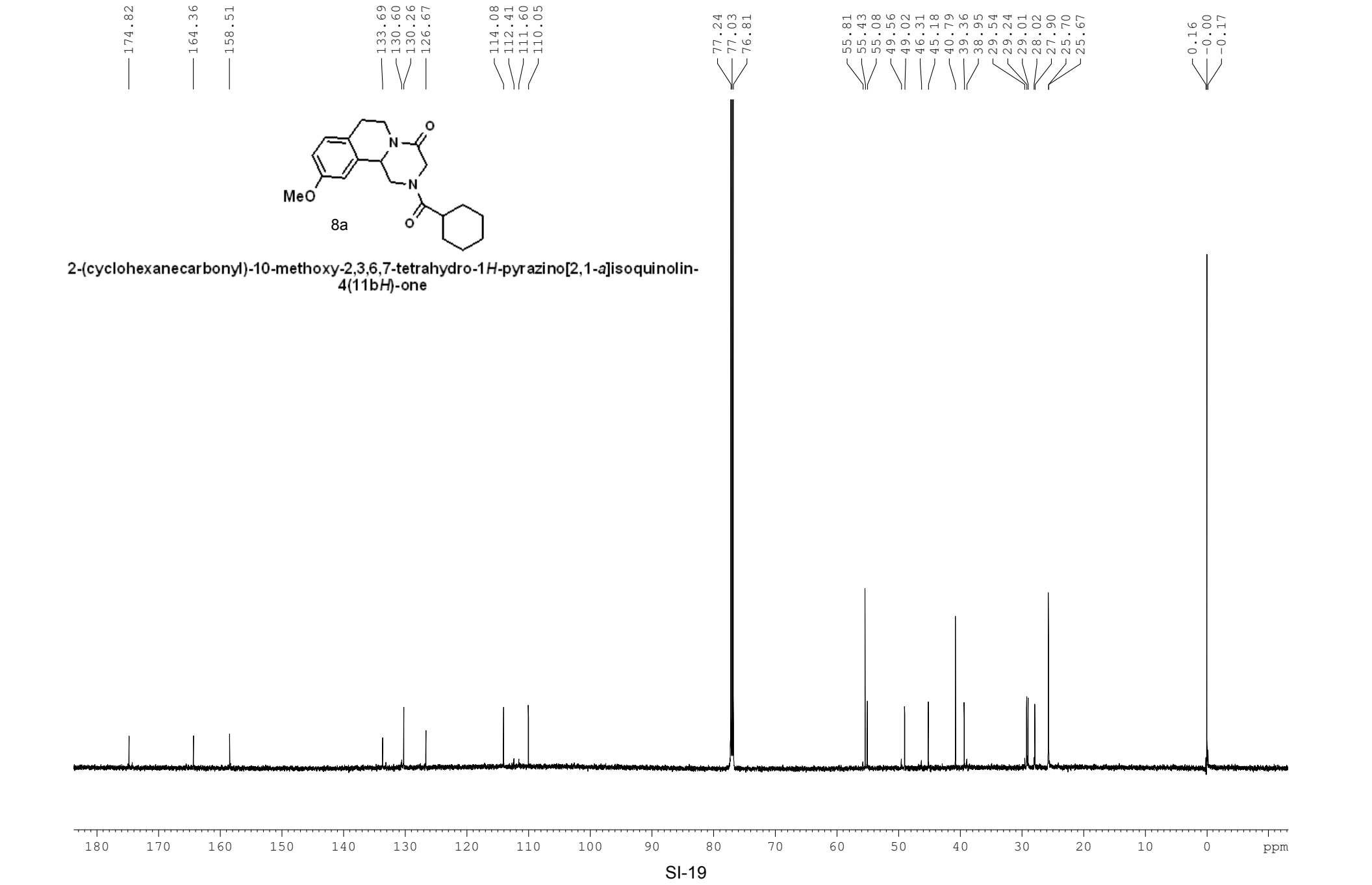
6 Copies of NMR spectra

LHX-69, CDCl3, 600 MHz



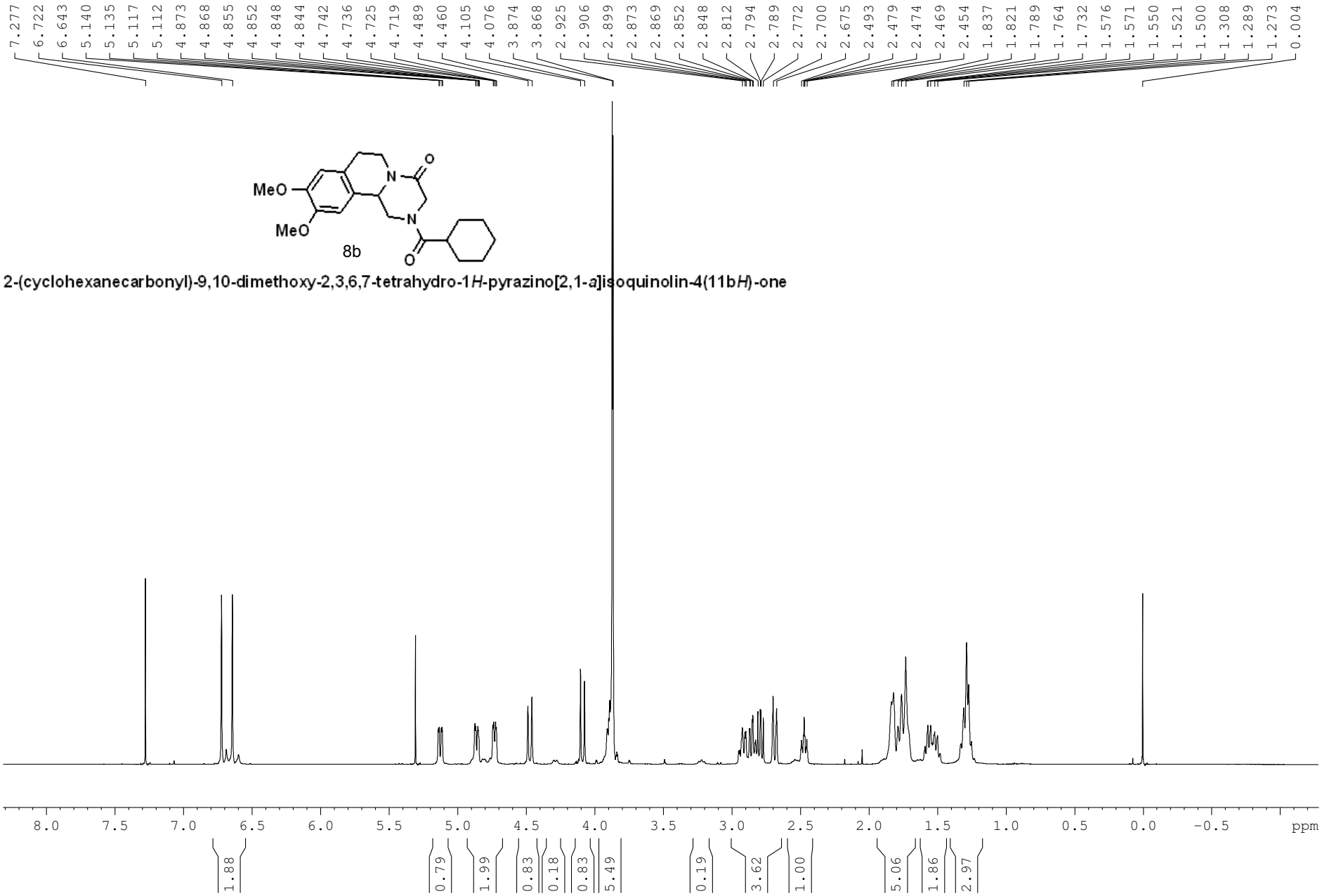
2-(cyclohexanecarbonyl)-10-methoxy-2,3,6,7-tetrahydro-1*H*-pyrazino[2,1-*a*]isoquinolin-4(11b*H*)-one

LHX-69, CDCl3, 600 MHz



2-(cyclohexanecarbonyl)-10-methoxy-2,3,6,7-tetrahydro-1*H*-pyrazino[2,1-*a*]isoquinolin-4(11b*H*)-one

LHX-134, CDCl3, 600 MHz



LHX-134, CDCl3, 600 MHz

174.86
164.33
148.26
148.06
126.89
124.38
111.62
108.00
77.26
77.05
76.83
56.09
55.92
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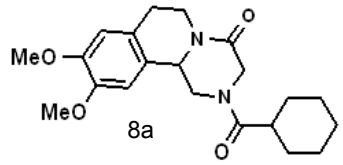
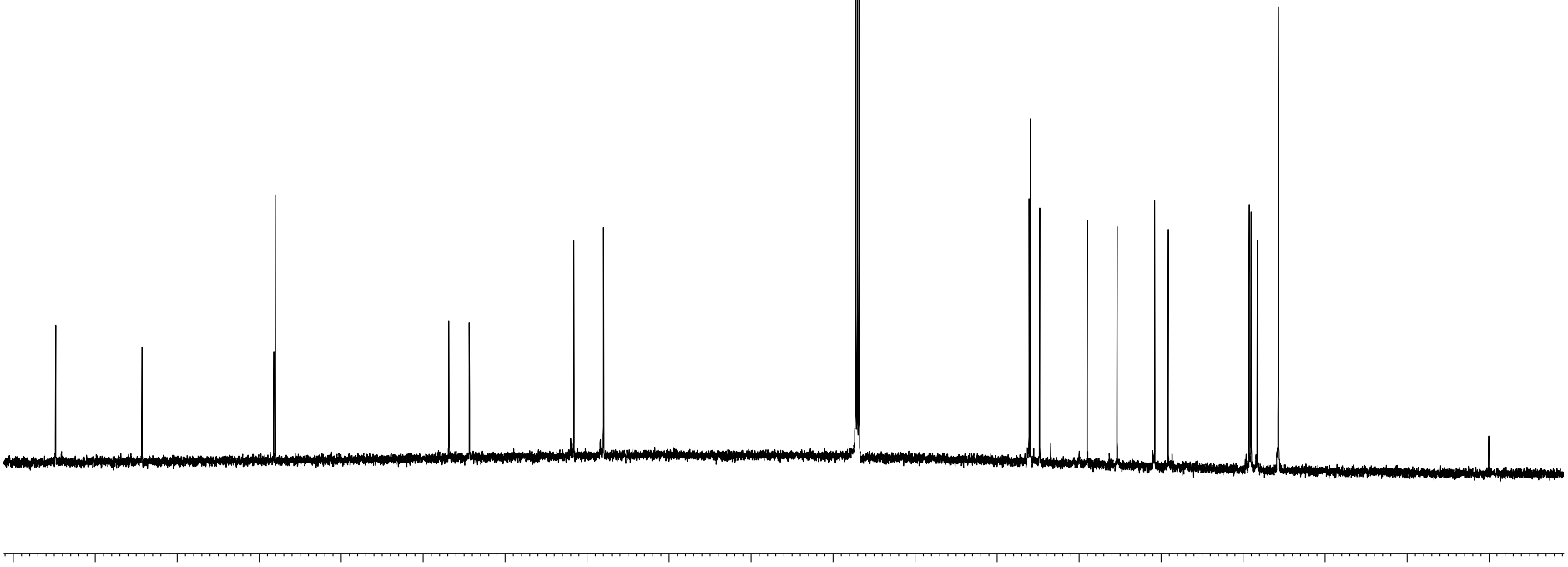
29.24
29.01
28.26
25.70
25.68
25.66

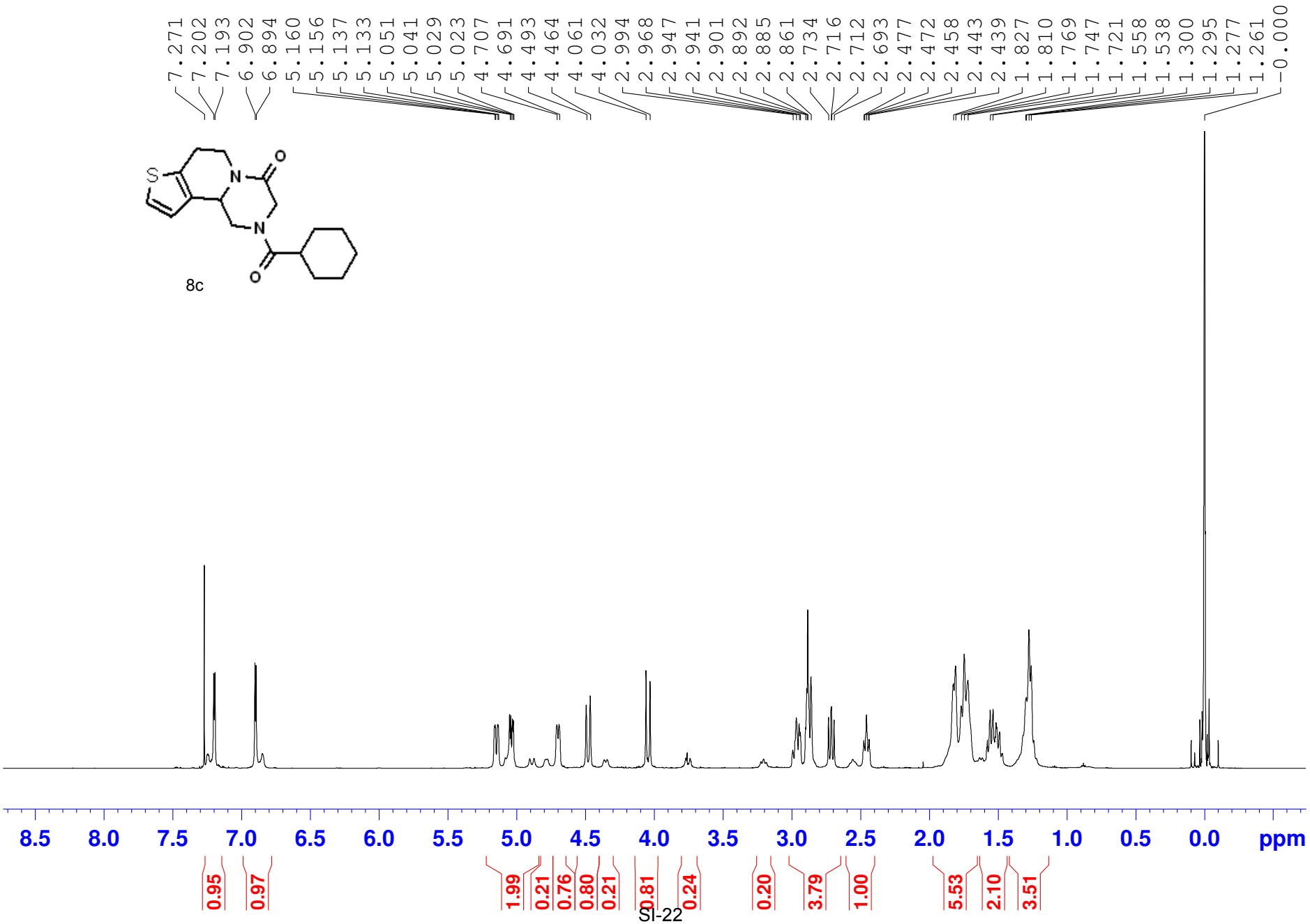


8a

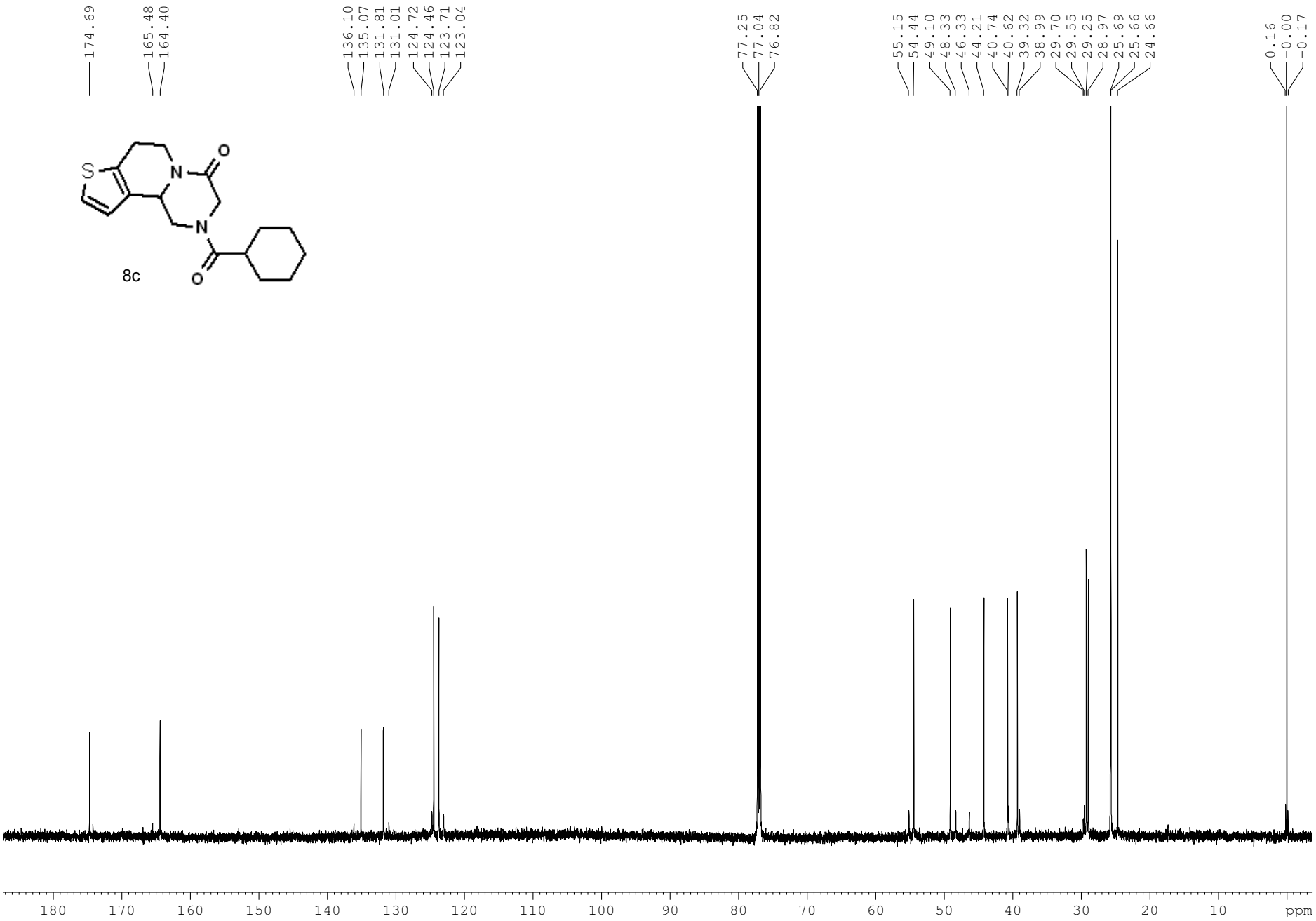
2-(cyclohexanecarbonyl)-9,10-dimethoxy-2,3,6,7-tetrahydro-1*H*-pyrazino[2,1-*a*]isoquinolin-4(11b*H*)-one



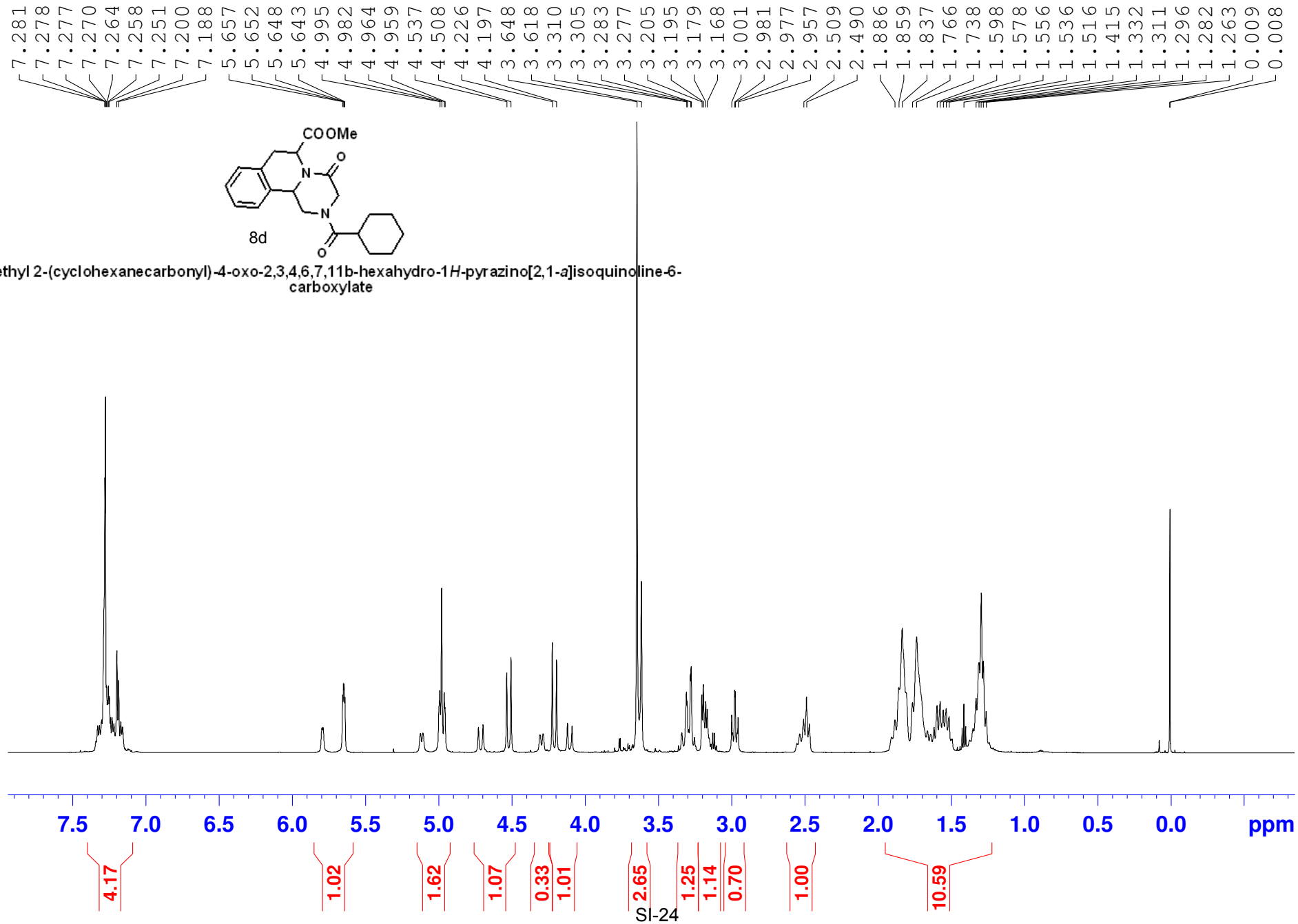
LHX-71, CDCl3, 600 MHz



LHX-71, CDCl3, 600 MHz

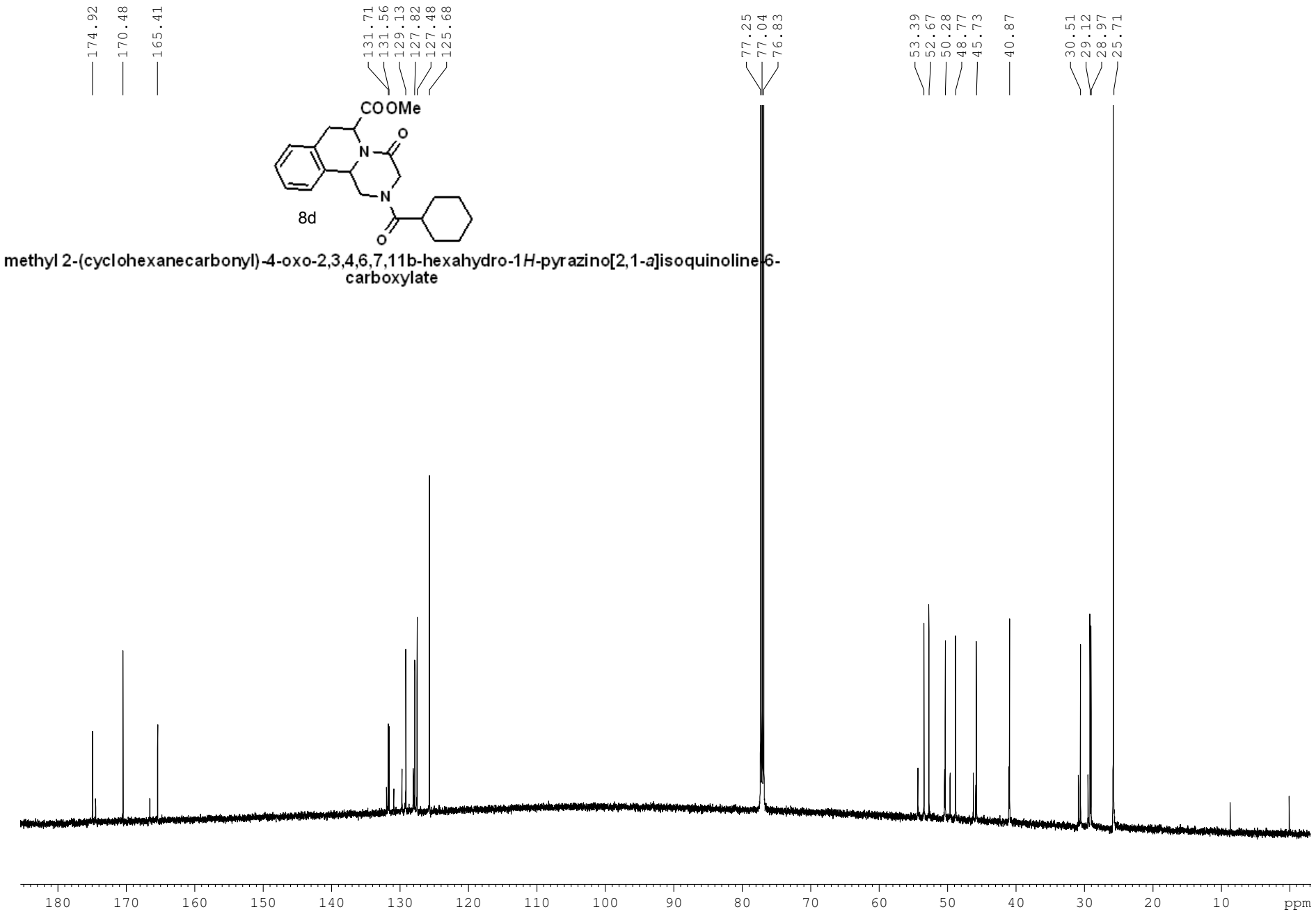


LHX-78, CDCl3, 600 Mz



methyl 2-(cyclohexanecarbonyl)-4-oxo-2,3,4,6,7,11b-hexahydro-1*H*-pyrazino[2,1-*a*]isoquinoline-6-carboxylate

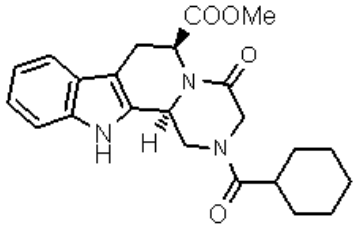
LHX-78, CDCl3, 600 MHz



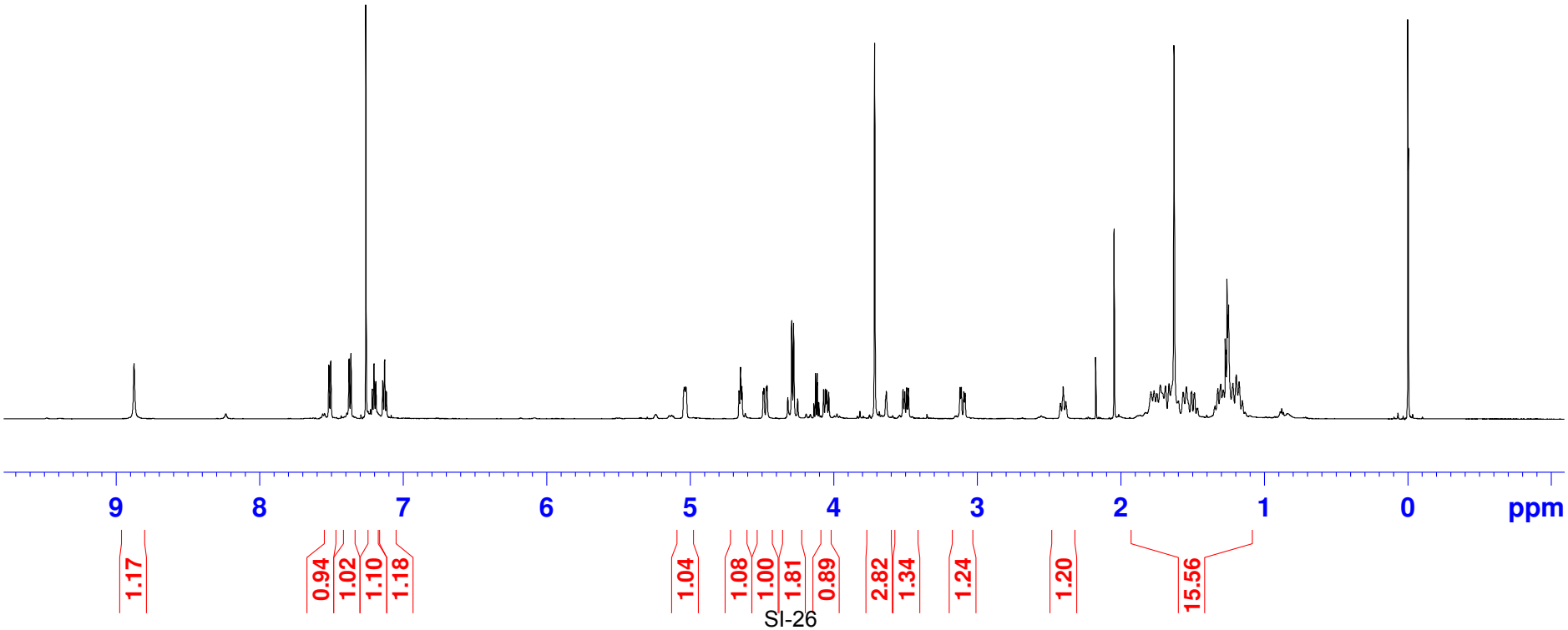
methyl 2-(cyclohexanecarbonyl)-4-oxo-2,3,4,6,7,11b-hexahydro-1*H*-pyrazino[2,1-*a*]isoquinoline-6-carboxylate

LHX-124b, CDCl3, 600 MHz

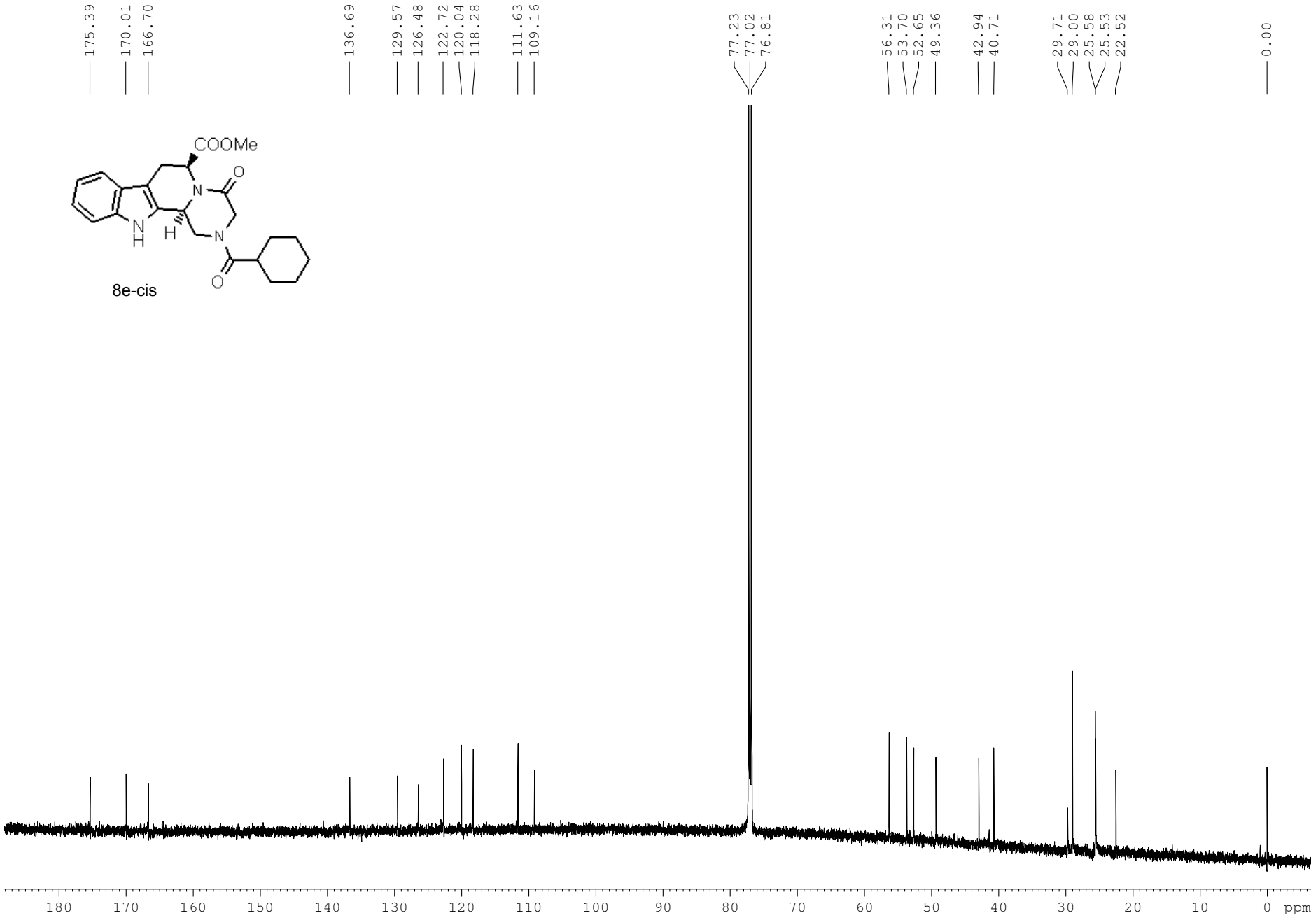
8.877
7.519
7.506
7.379
7.365
7.263
7.260
7.218
7.205
7.192
7.144
7.131
5.043
5.033
4.662
4.651
4.641
4.488
4.471
4.466
4.295
4.281
4.129
4.127
4.117
4.115
4.072
4.059
4.050
3.717
3.519
3.493
3.481
3.121
3.112
2.403
1.770
1.726
1.690
1.665
1.630
1.545
1.325
1.305
1.289
1.273
1.271
1.261
1.259
1.253
1.250
1.247
1.220
1.197
1.176



8e-cis

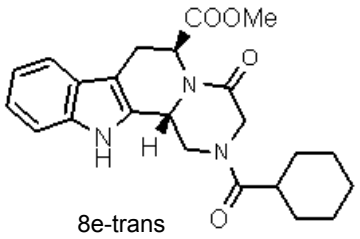


LHX-124b, CDCl3, COSY

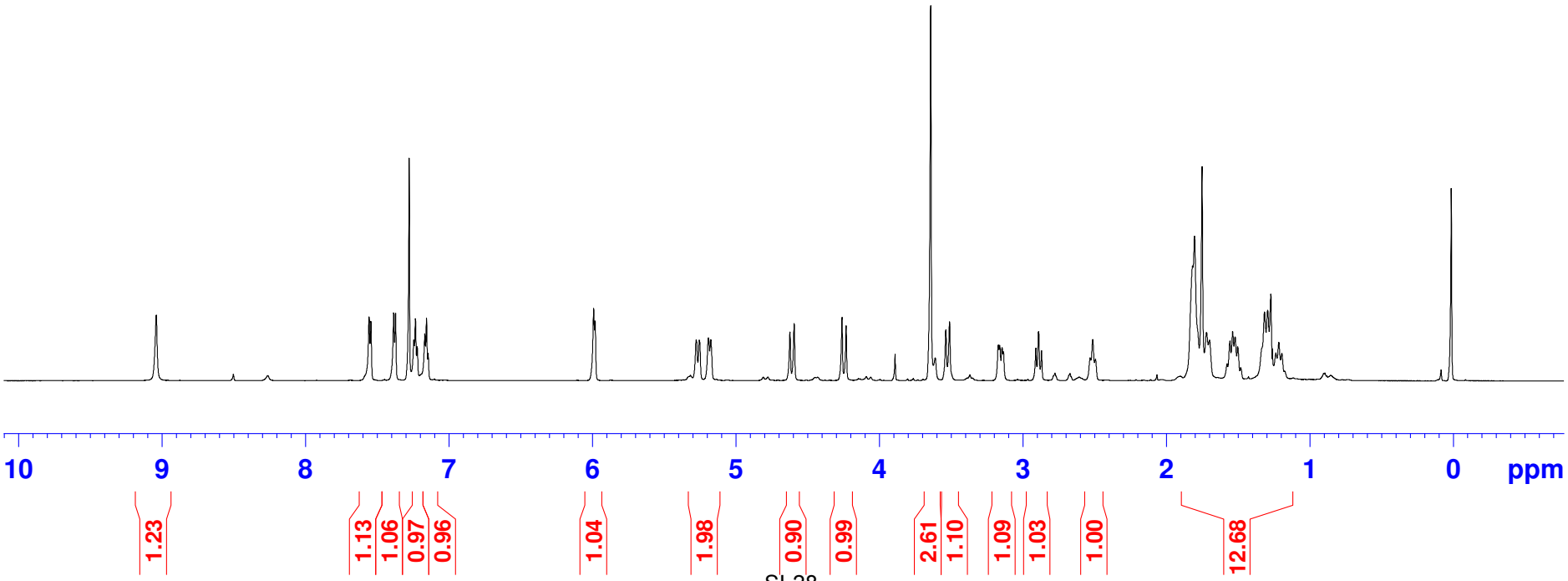


LHX-124a, CDCl3, 600 MHz

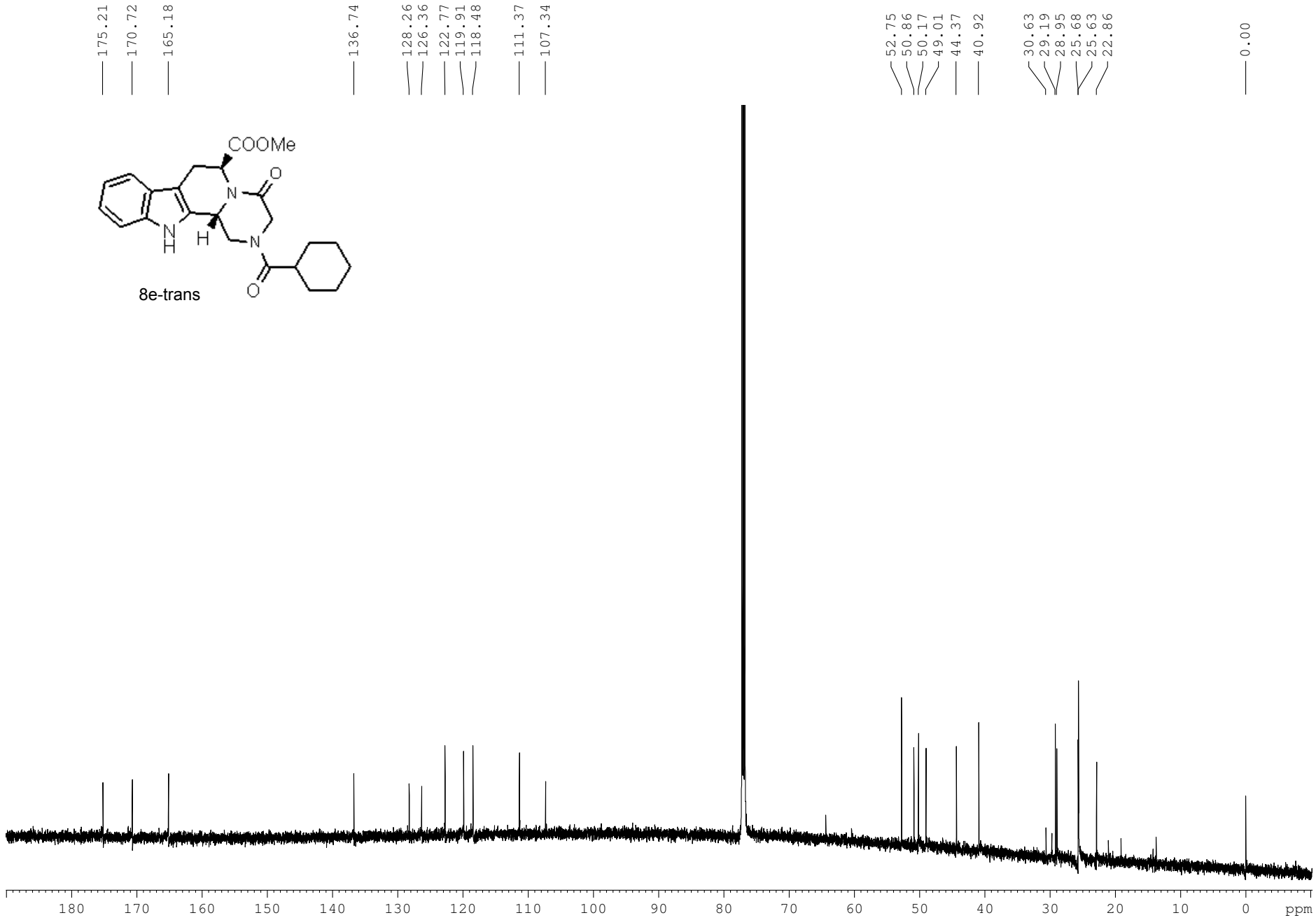
9.039
7.556
7.543
7.385
7.372
7.277
7.245
7.233
7.168
7.156
5.990
5.981
5.276
5.254
5.191
5.174
4.622
4.593
4.260
4.230
3.641
3.536
3.510
3.169
3.161
3.143
3.135
2.909
2.889
2.869
2.511
1.815
1.802
1.749
1.718
1.697
1.537
1.519
1.314
1.293
1.270
0.016



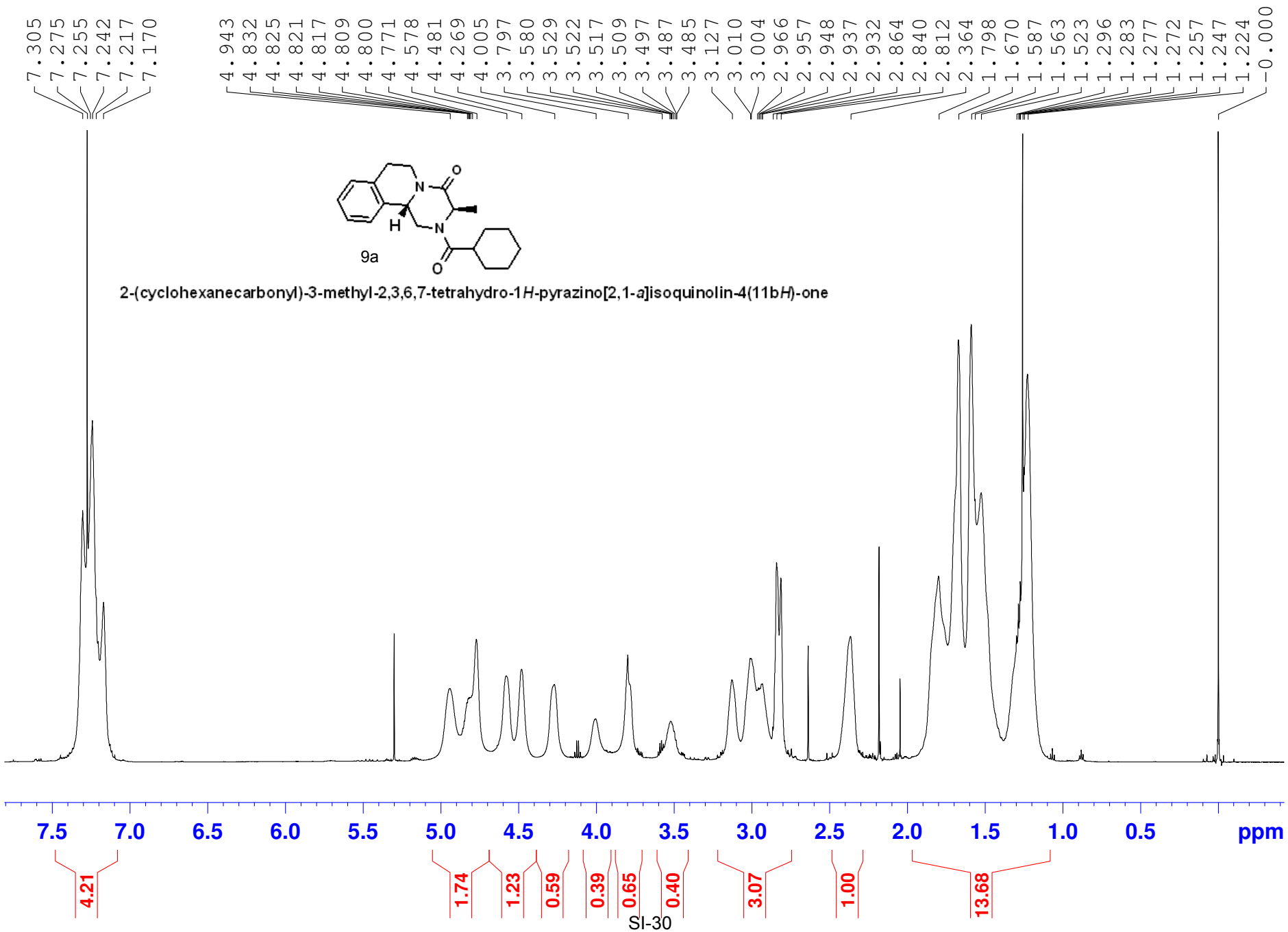
8e-trans



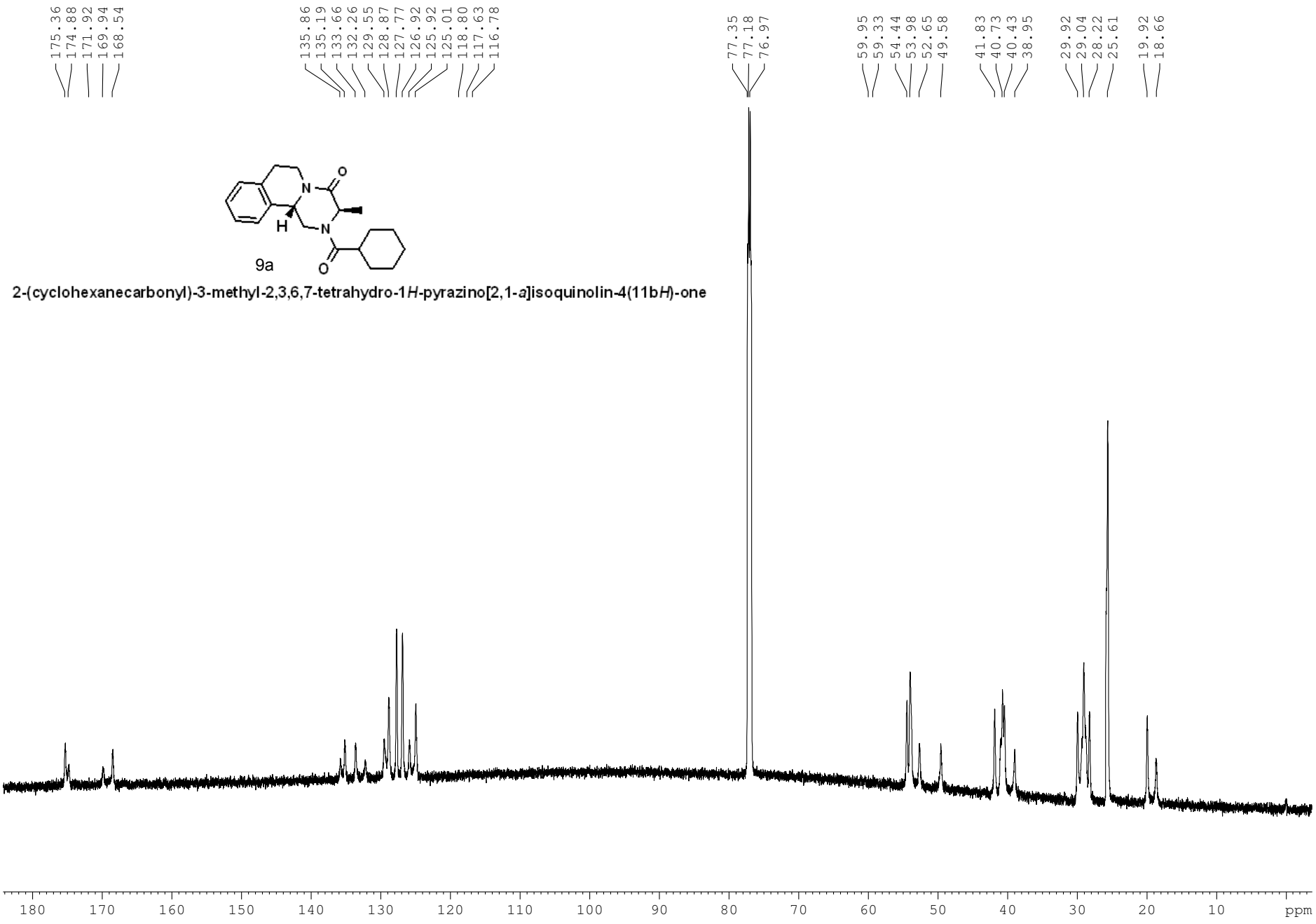
LHX-124a, CDCl3, COSY



LHX-103, CDCl3, 600 MHz



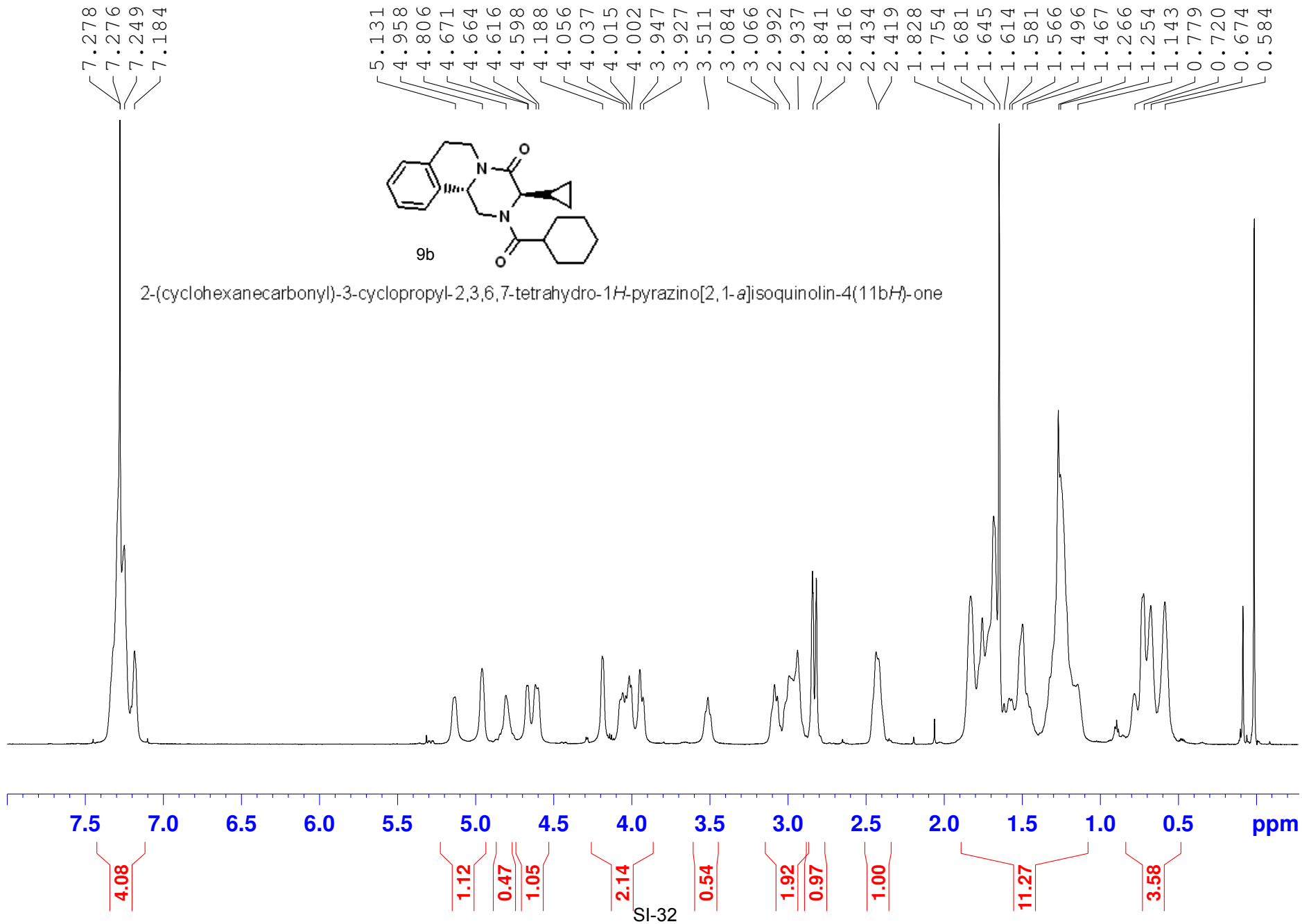
LHX-103, CDCl3, 600 MHz



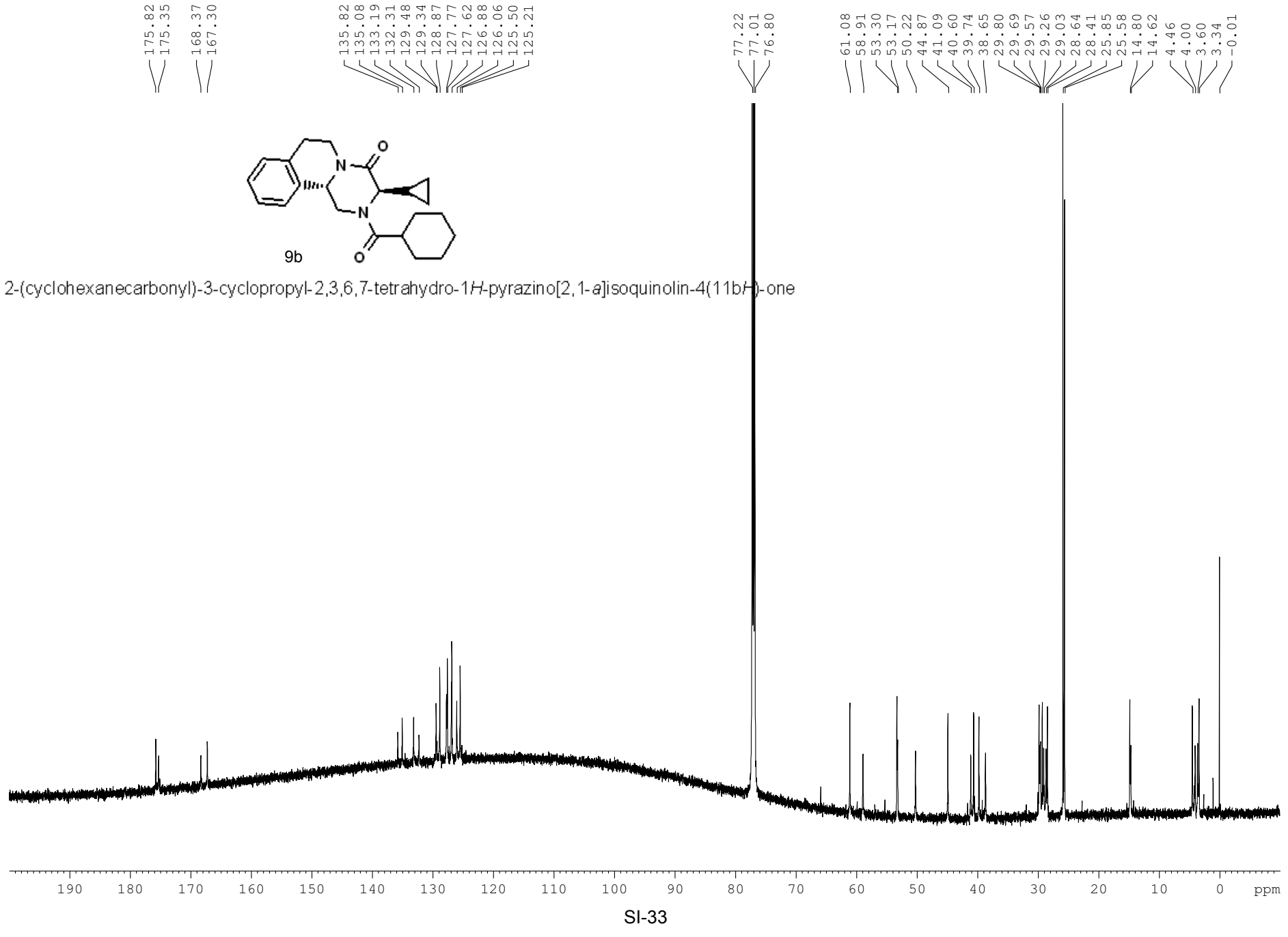
9a

2-(cyclohexanecarbonyl)-3-methyl-2,3,6,7-tetrahydro-1*H*-pyrazino[2,1-*a*]isoquinolin-4(11b*H*)-one

LHX_74, CDCl3, 600 MHz



LHX-74, CDCl3, NMR600

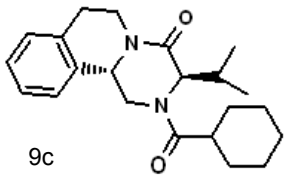


9b

2-(cyclohexanecarbonyl)-3-cyclopropyl-2,3,6,7-tetrahydro-1*H*-pyrazino[2,1-*a*]isoquinolin-4(11b*H*)-one

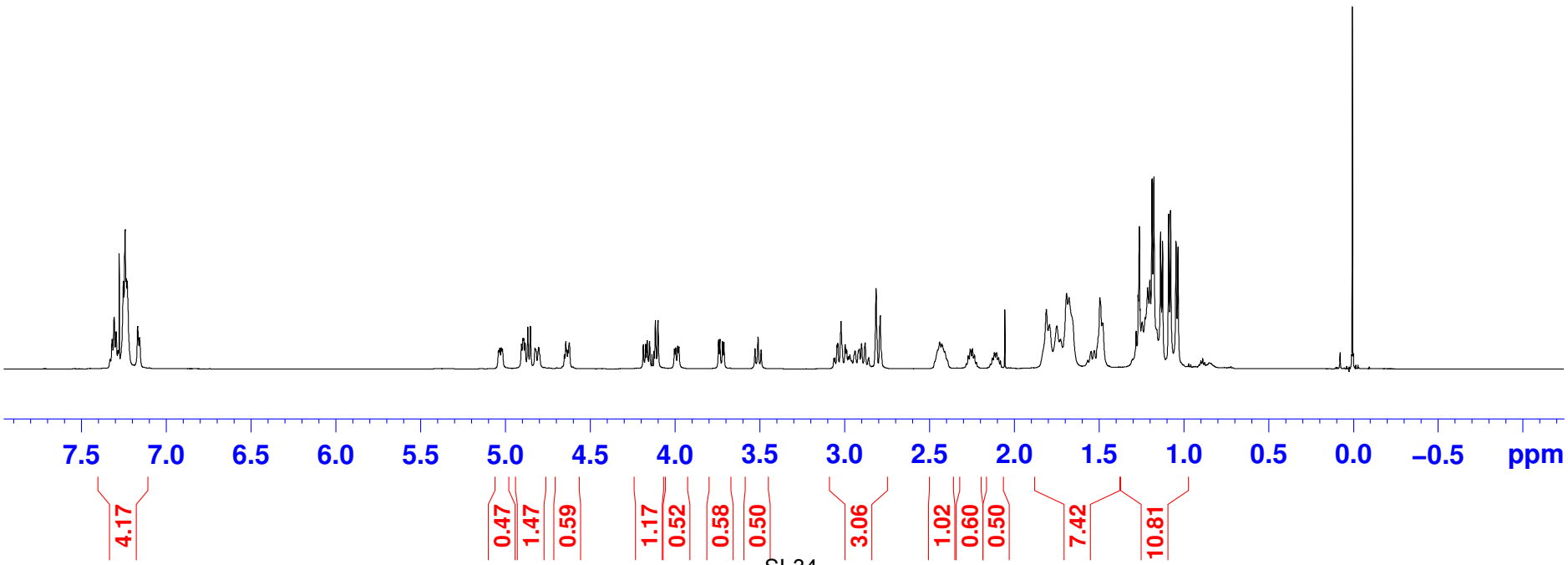
LX-128, CDCl3, 600 MHz

7.306
7.295
7.277
7.252
7.242
7.235
7.230
7.168
4.896
4.891
4.883
4.867
4.851
4.643
4.623
4.163
4.149
4.114
4.099
3.742
3.734
3.719
3.710
3.509
3.020
2.877
2.813
2.789
2.438
1.809
1.790
1.747
1.725
1.689
1.675
1.493
1.480
1.475
1.279
1.267
1.260
1.256
1.243
1.226
1.211
1.198
1.186
1.175
1.135
1.124
1.087
1.076
1.044
1.033
0.007

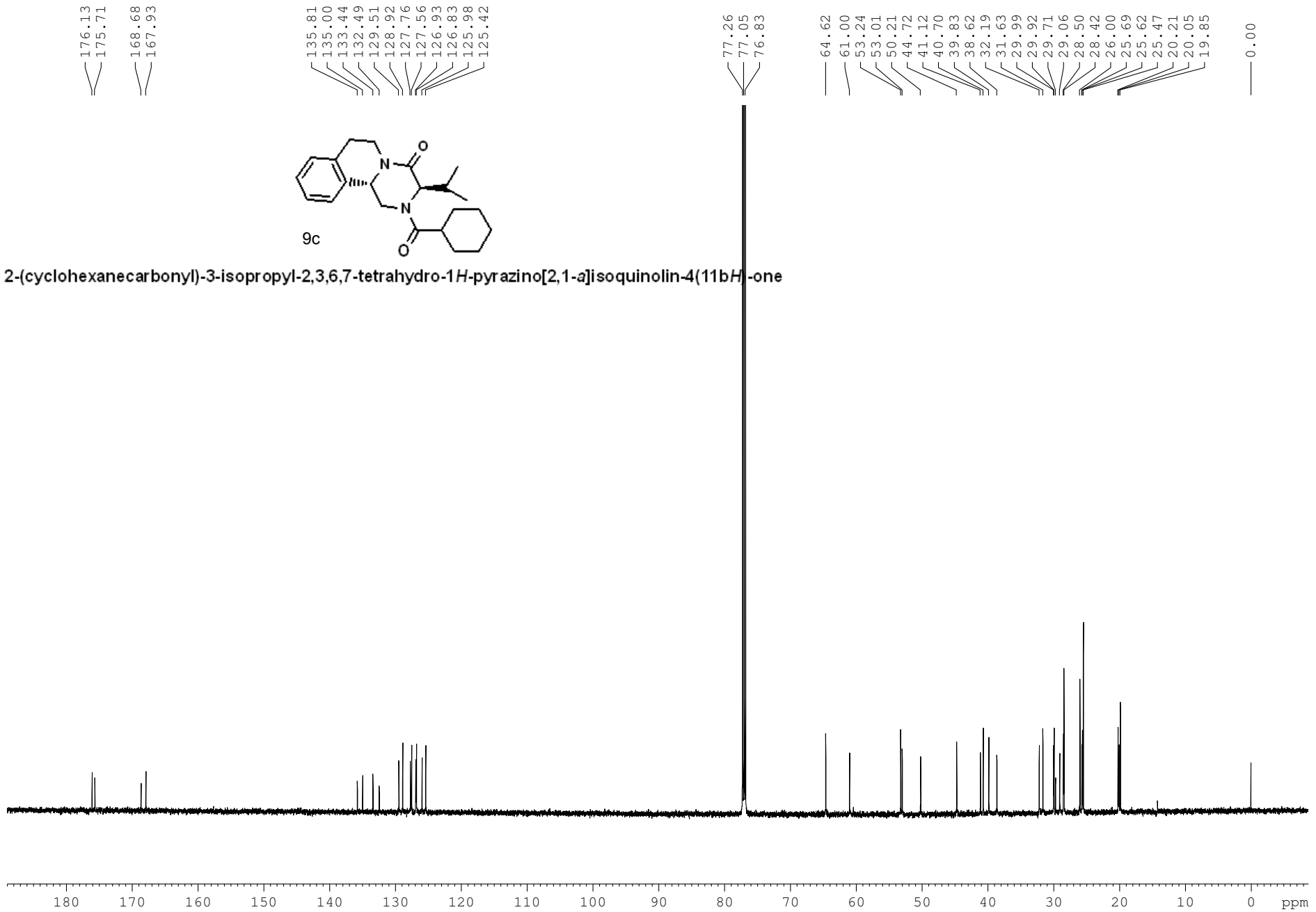


9c

2-(cyclohexanecarbonyl)-3-isopropyl-2,3,6,7-tetrahydro-1*H*-pyrazino[2,1-*a*]isoquinolin-4(11b*H*)-one



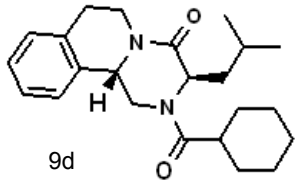
LX-128, CDCl3, 600 MHz



2-(cyclohexanecarbonyl)-3-isopropyl-2,3,6,7-tetrahydro-1*H*-pyrazino[2,1-*a*]isoquinolin-4(11b*H*)-one

LX-106, CDCl3, 600 MHz

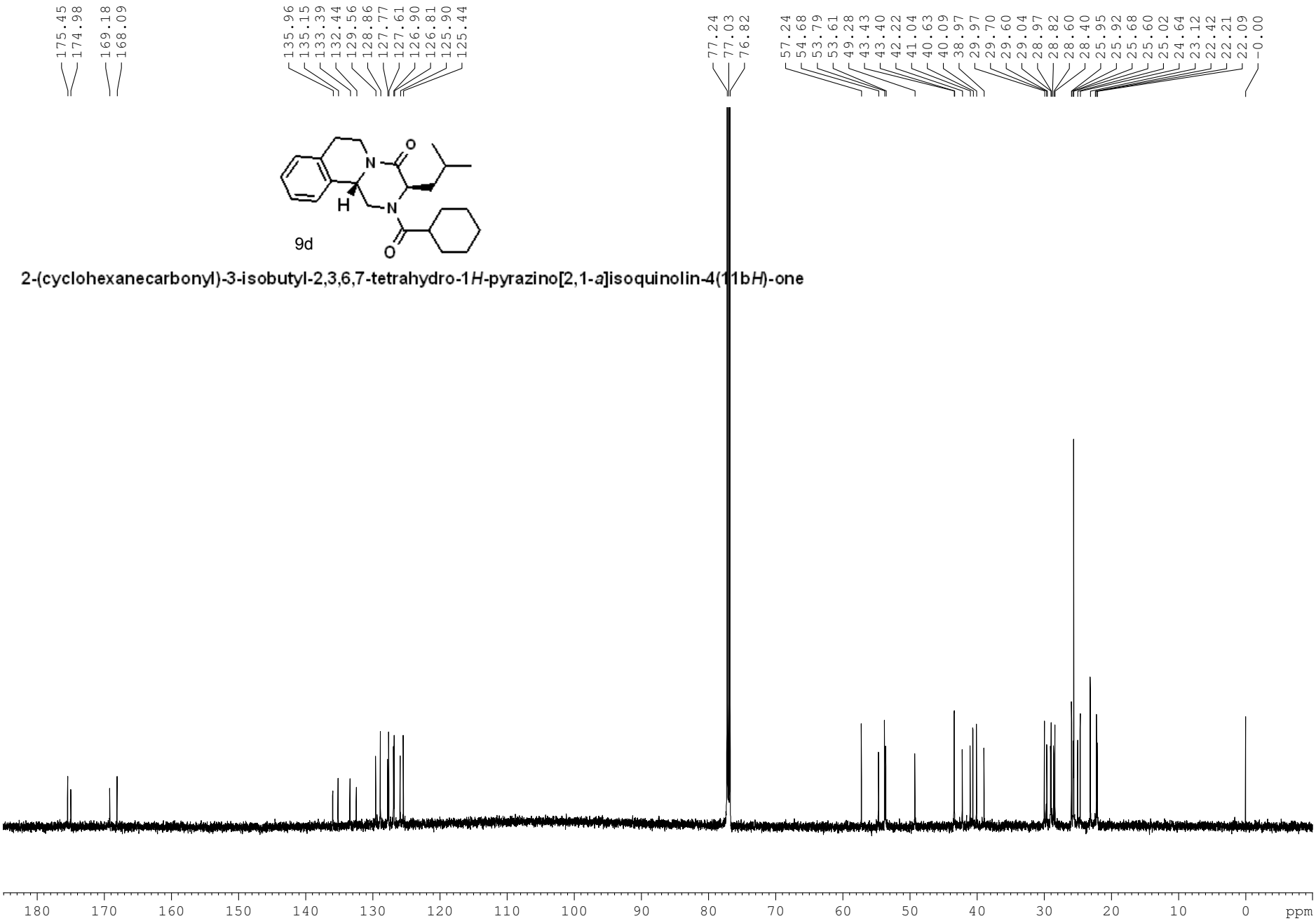
7.310 7.299 7.293 7.284 7.267 7.249 7.237 7.231 7.221 7.208 7.157 7.147 5.055 4.831 4.631 4.611 4.441 4.429 4.416 4.144 4.133 4.121 3.806 3.799 3.782 3.775 3.577 3.574 3.046 3.031 3.026 2.994 2.871 2.815 2.808 2.800 2.388 2.383 1.807 1.708 1.697 1.677 1.673 1.665 1.652 1.453 1.449 1.254 1.213 1.084 1.073 1.067 1.003 0.992 -0.000



9d

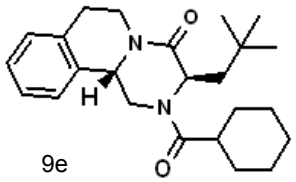
2-(cyclohexanecarbonyl)-3-isobutyl-2,3,6,7-tetrahydro-1*H*-pyrazino[2,1-*a*]isoquinolin-4(11b*H*)-one

LX-106, CDCl3, 600 MHz



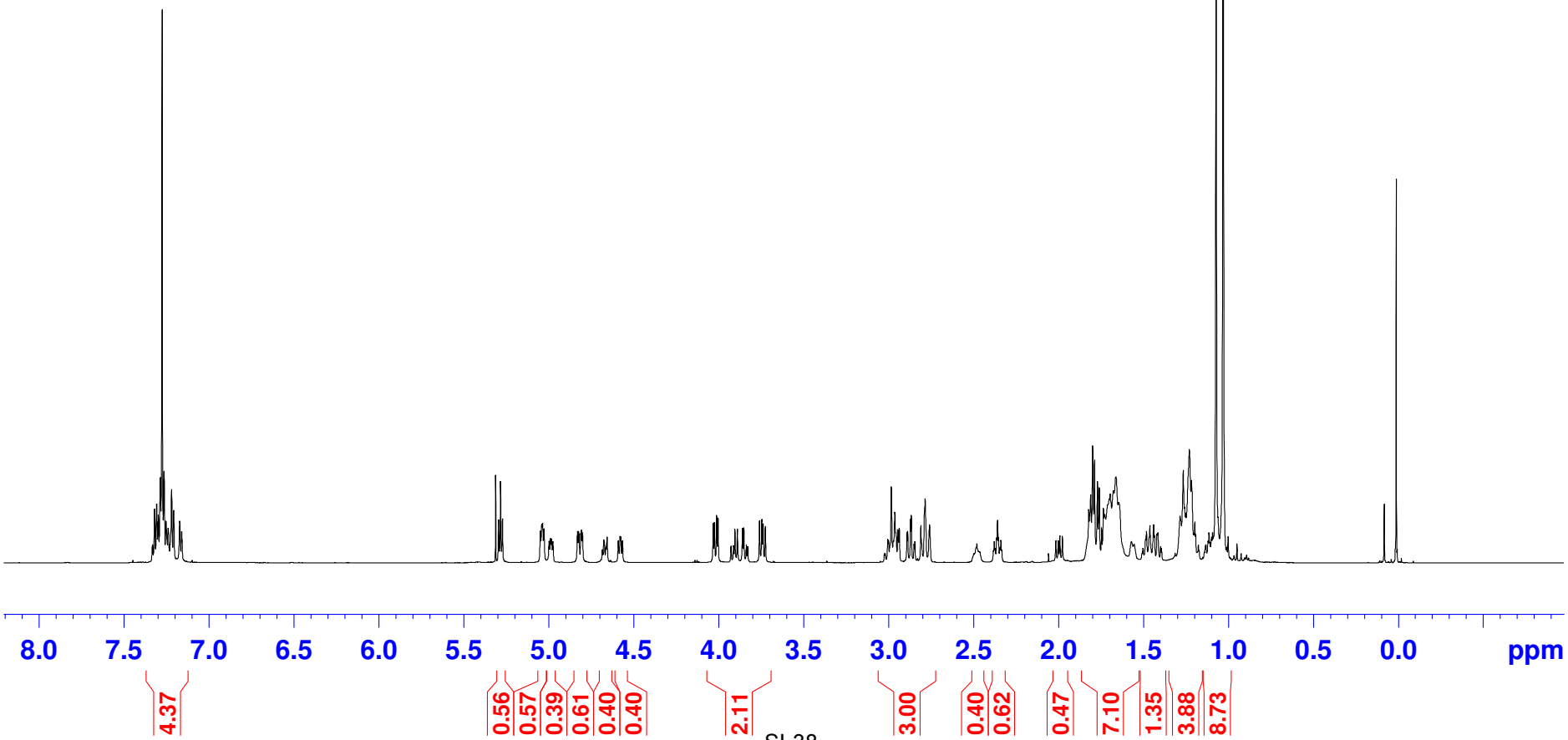
LHX-123, CDCl3, 600 MHz

7.322 7.310 7.299 7.287 7.266 7.254 7.221 7.209 7.174 5.314 5.296 5.285 5.274 5.043 5.038 5.034 4.026 4.013 4.005 3.761 3.747 3.740 3.726 2.985 2.964 2.872 2.867 2.811 2.786 2.760 2.359 1.811 1.799 1.788 1.771 1.760 1.736 1.729 1.697 1.678 1.662 1.646 1.462 1.441 1.285 1.266 1.258 1.252 1.231 1.218 1.198 1.073 1.061 1.031 0.012

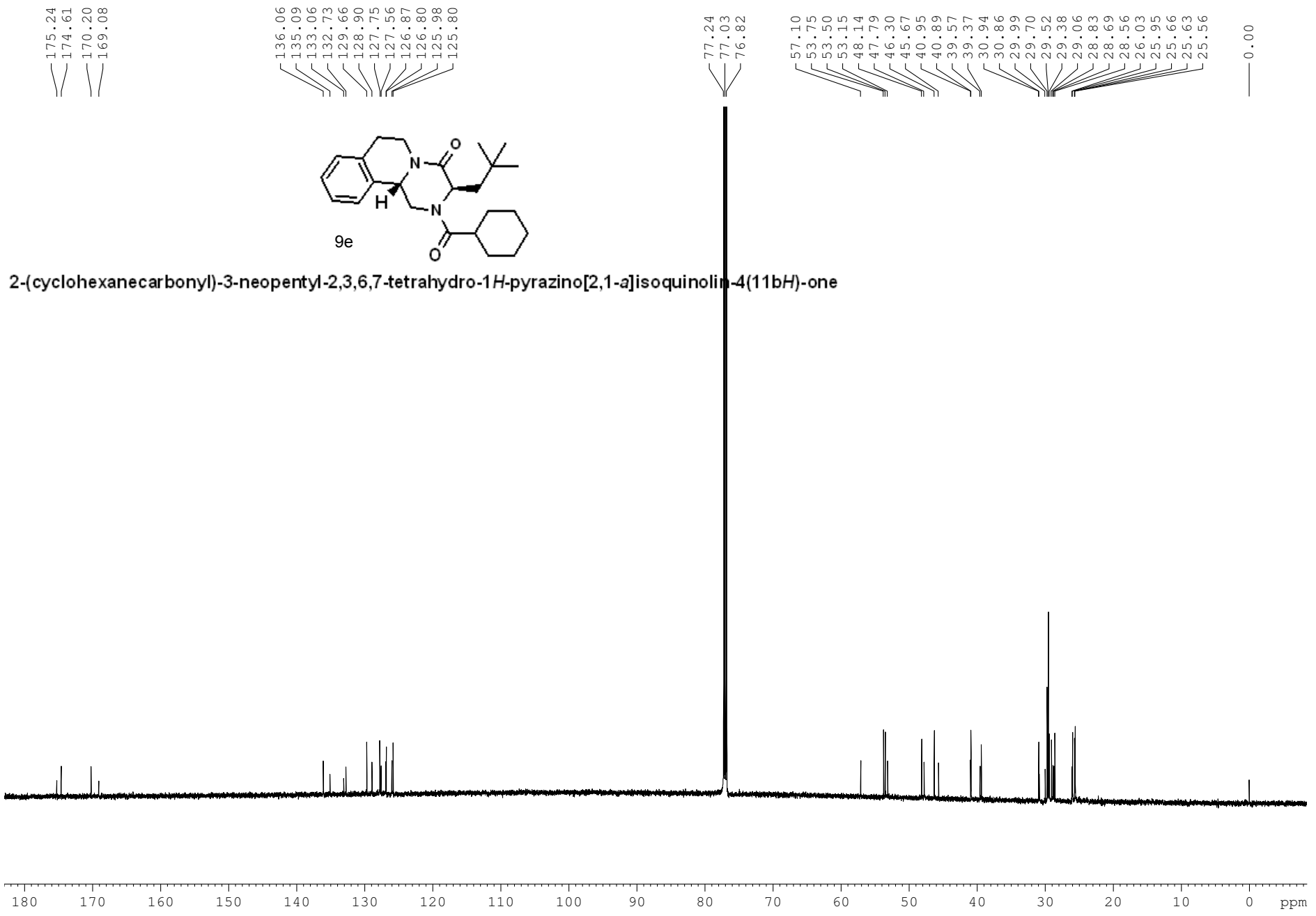


9e

2-(cyclohexanecarbonyl)-3-neopentyl-2,3,6,7-tetrahydro-1*H*-pyrazino[2,1-*a*]isoquinolin-4(11b*H*)-one

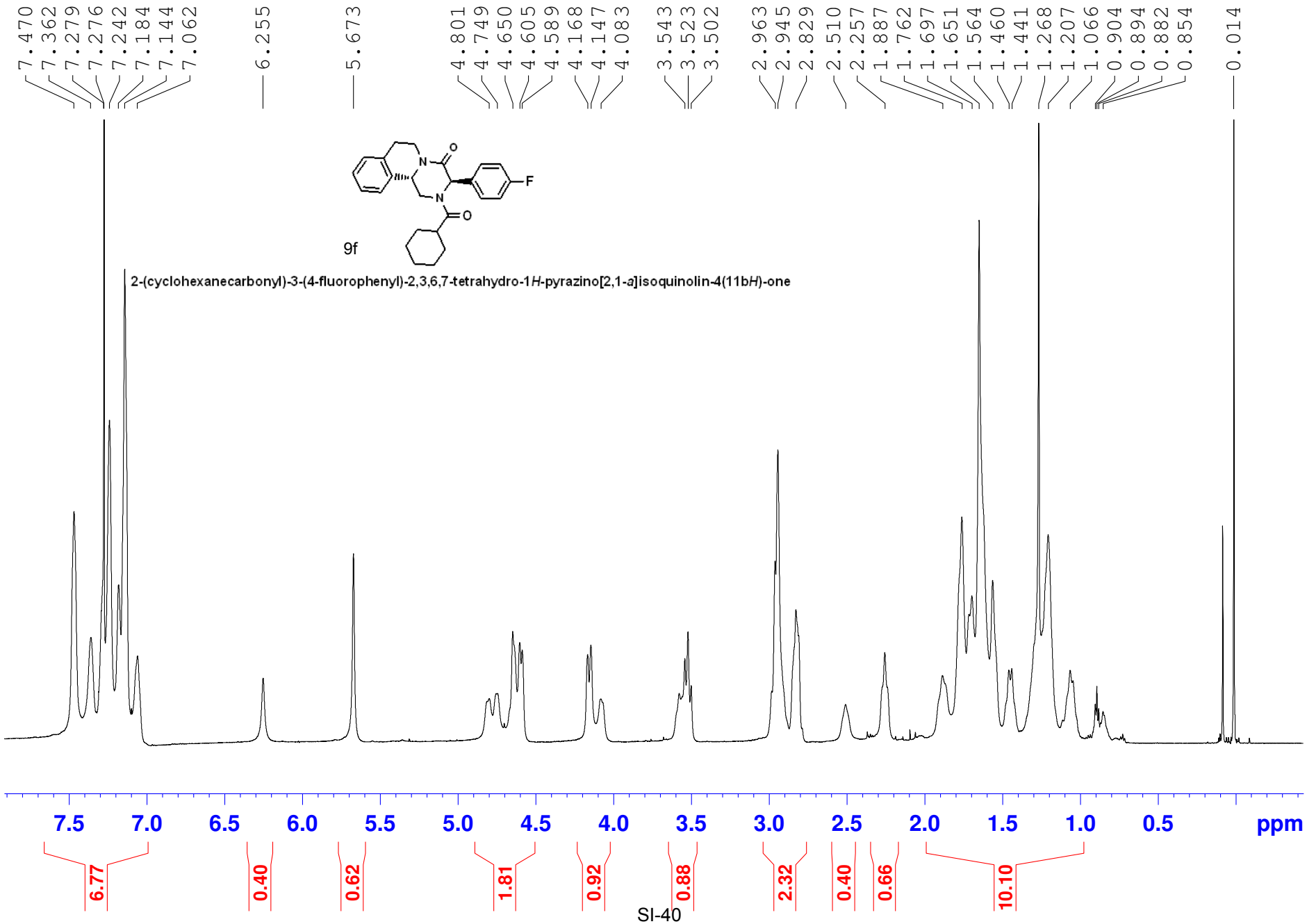


LHX-123, CDCl3, 600 MHz

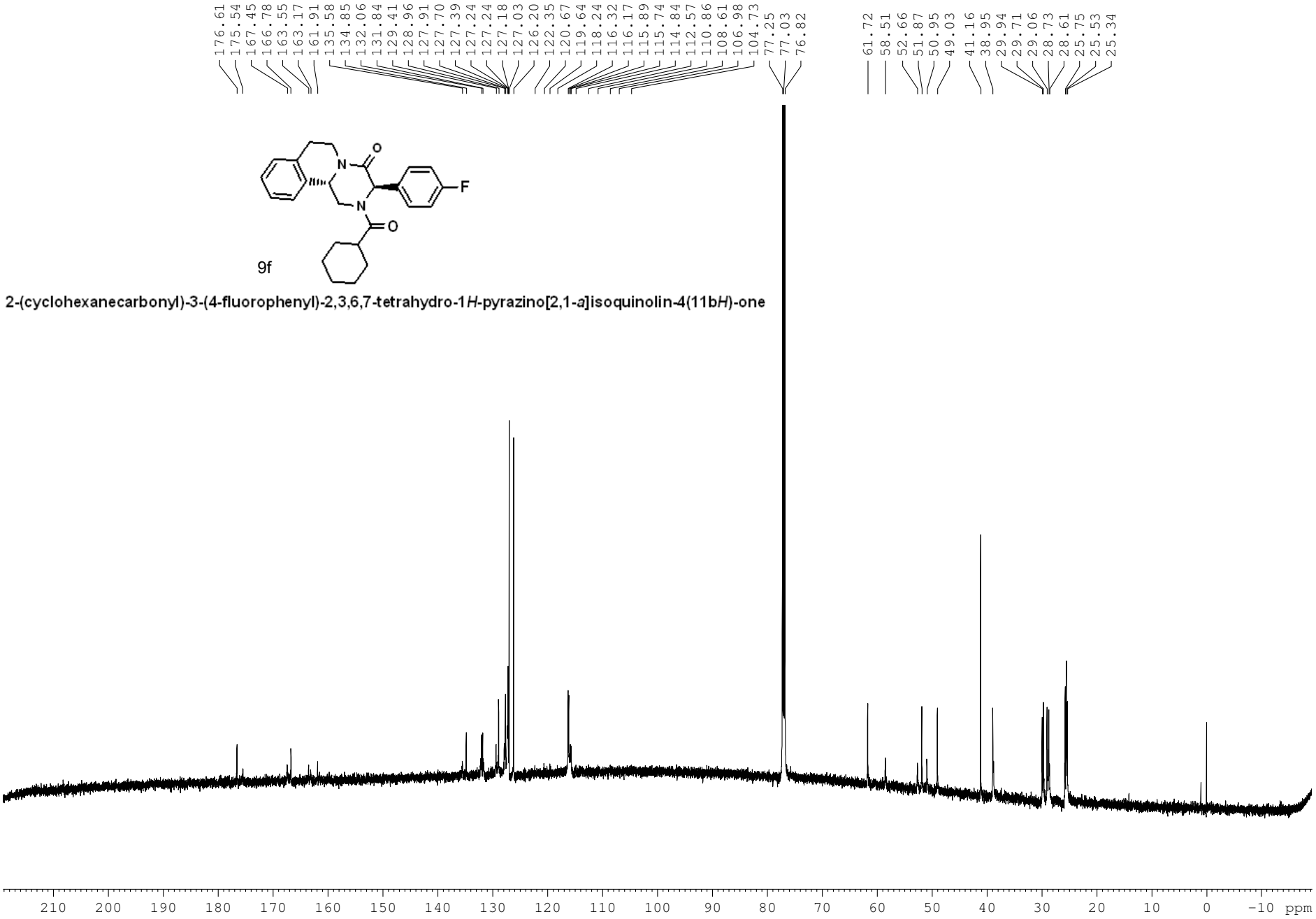


2-(cyclohexanecarbonyl)-3-neopentyl-2,3,6,7-tetrahydro-1*H*-pyrazino[2,1-*a*]isoquinolin-4(11b*H*)-one

LHX-127, CDCl3, 600 MHz



LHX-127, CDCl3, 600 MHz

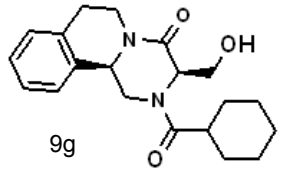


9f

2-(cyclohexanecarbonyl)-3-(4-fluorophenyl)-2,3,6,7-tetrahydro-1*H*-pyrazino[2,1-*a*]isoquinolin-4(11b*H*)-one

LHX-130

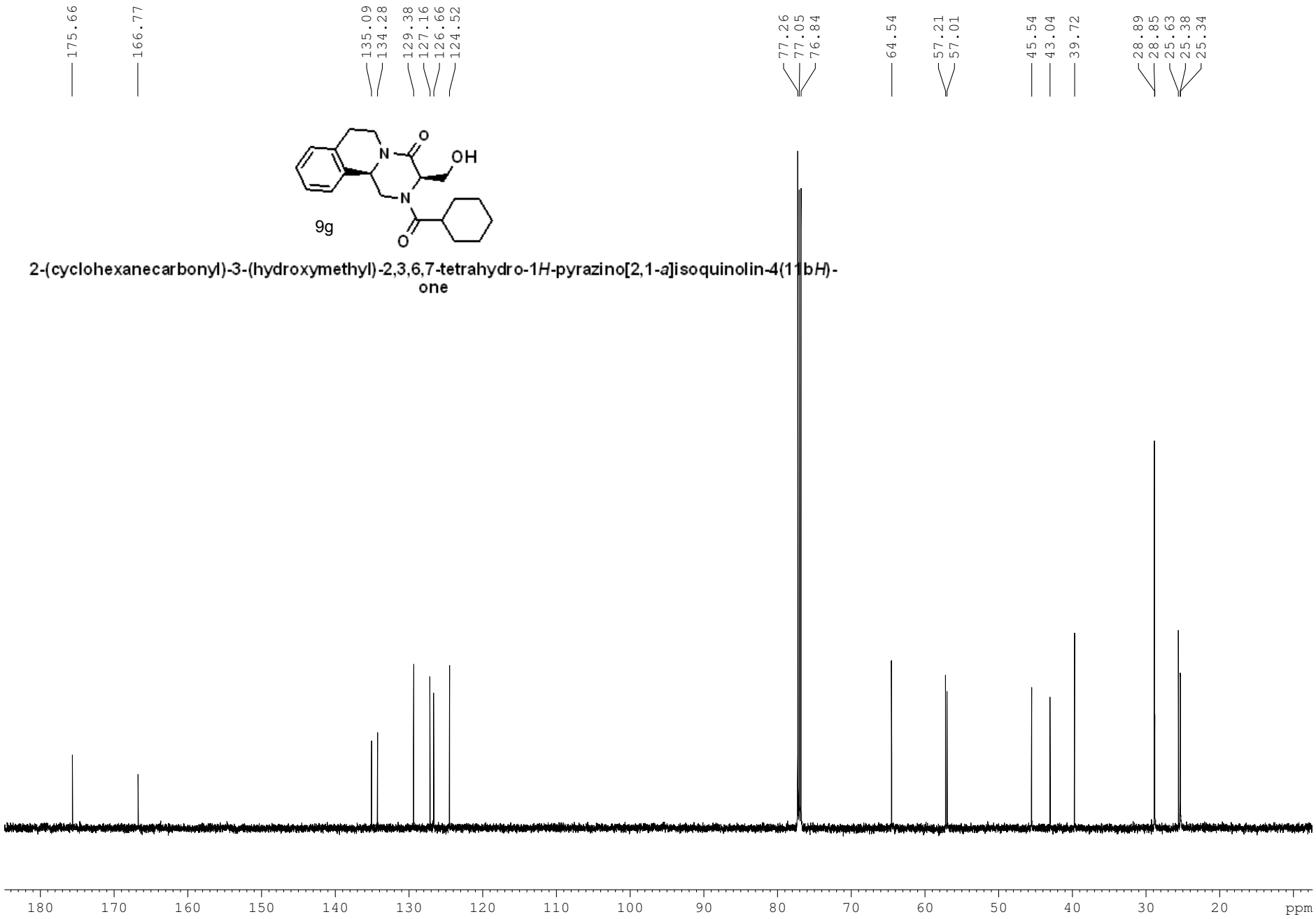
7.197 7.168 7.165 7.162 7.158 7.153 7.150 7.147 7.108 7.097 7.093 7.082 7.078 7.068 4.456 4.444 4.437 4.425 4.221 4.216 4.203 4.198 3.782 3.777 3.769 3.765 3.472 3.464 3.450 3.442 3.179 3.164 3.156 3.142 2.825 2.819 2.713 2.126 2.107 1.695 1.692 1.587 1.584 1.578 1.572 1.220 1.215 1.200 1.195 1.185 1.120 1.115 1.099 1.094 1.075



9g

2-(cyclohexanecarbonyl)-3-(hydroxymethyl)-2,3,6,7-tetrahydro-1*H*-pyrazino[2,1-*a*]isoquinolin-4(11b*H*)-one

LHX-130,carbon

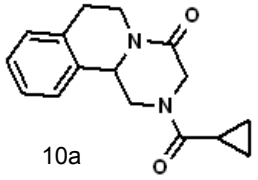


2-(cyclohexanecarbonyl)-3-(hydroxymethyl)-2,3,6,7-tetrahydro-1*H*-pyrazino[2,1-*a*]isoquinolin-4(11b*H*)-one

LHX-70, CDCl3, 600 MHz

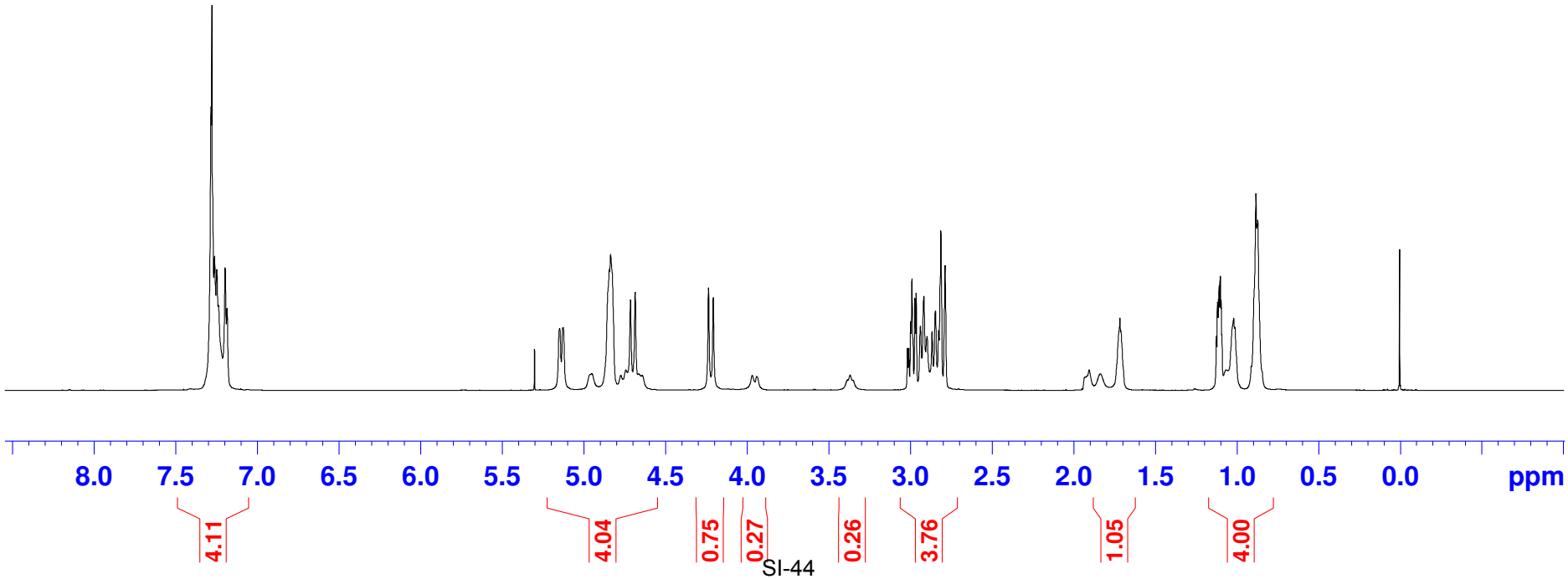
7.282 7.277 7.261 7.248 7.237 7.196 7.184

5.146 5.127 4.951 4.843 4.835 4.713 4.684 4.235 4.206 3.967 3.938 3.383 3.367 3.016 3.008 2.997 2.989 2.970 2.963 2.937 2.916 2.896 2.866 2.846 2.825 2.812 2.786 1.835 1.715 1.123 1.118 1.110 1.107 1.102 1.100 1.095 1.018 1.011 0.882 0.871 0.002

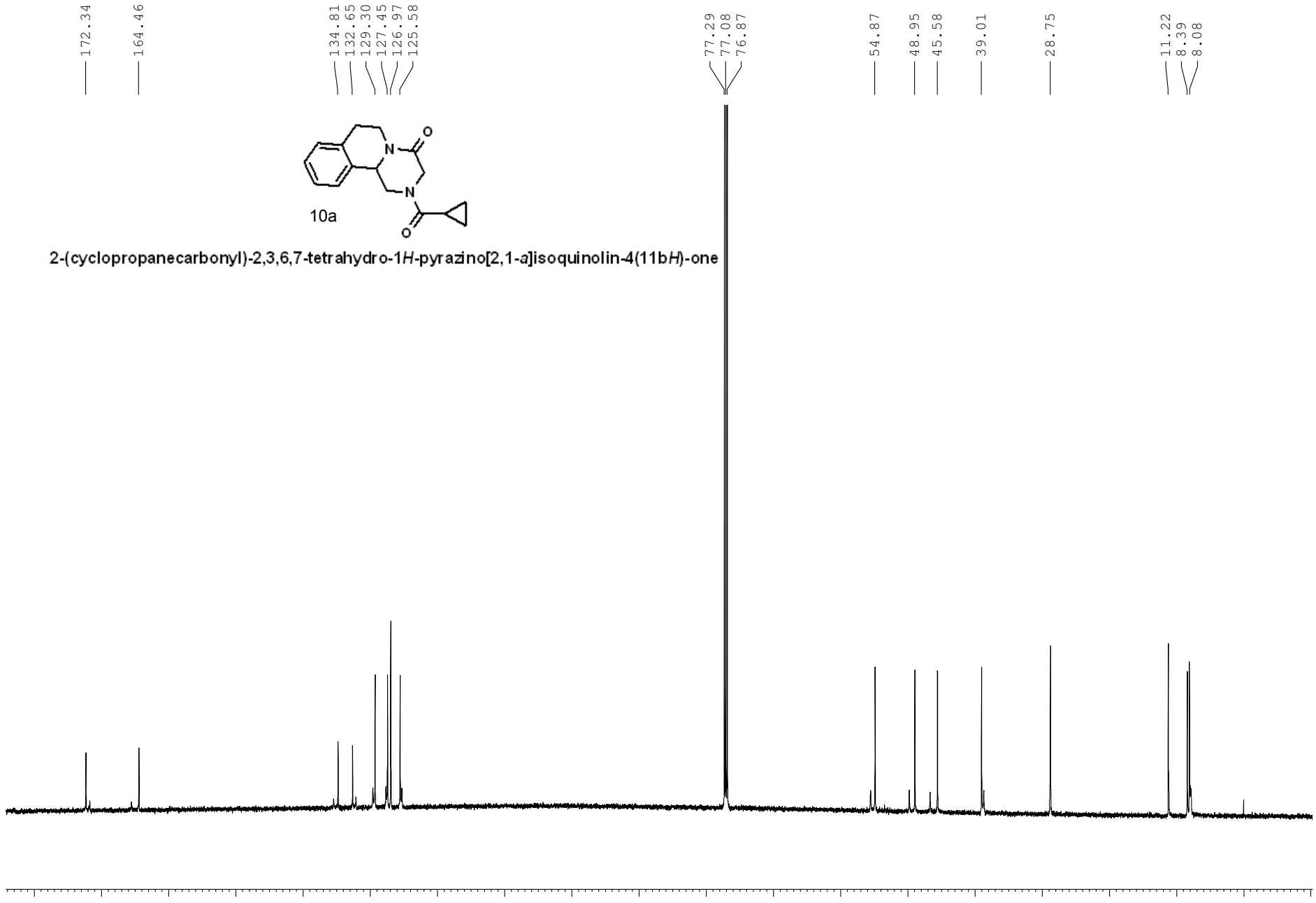


10a

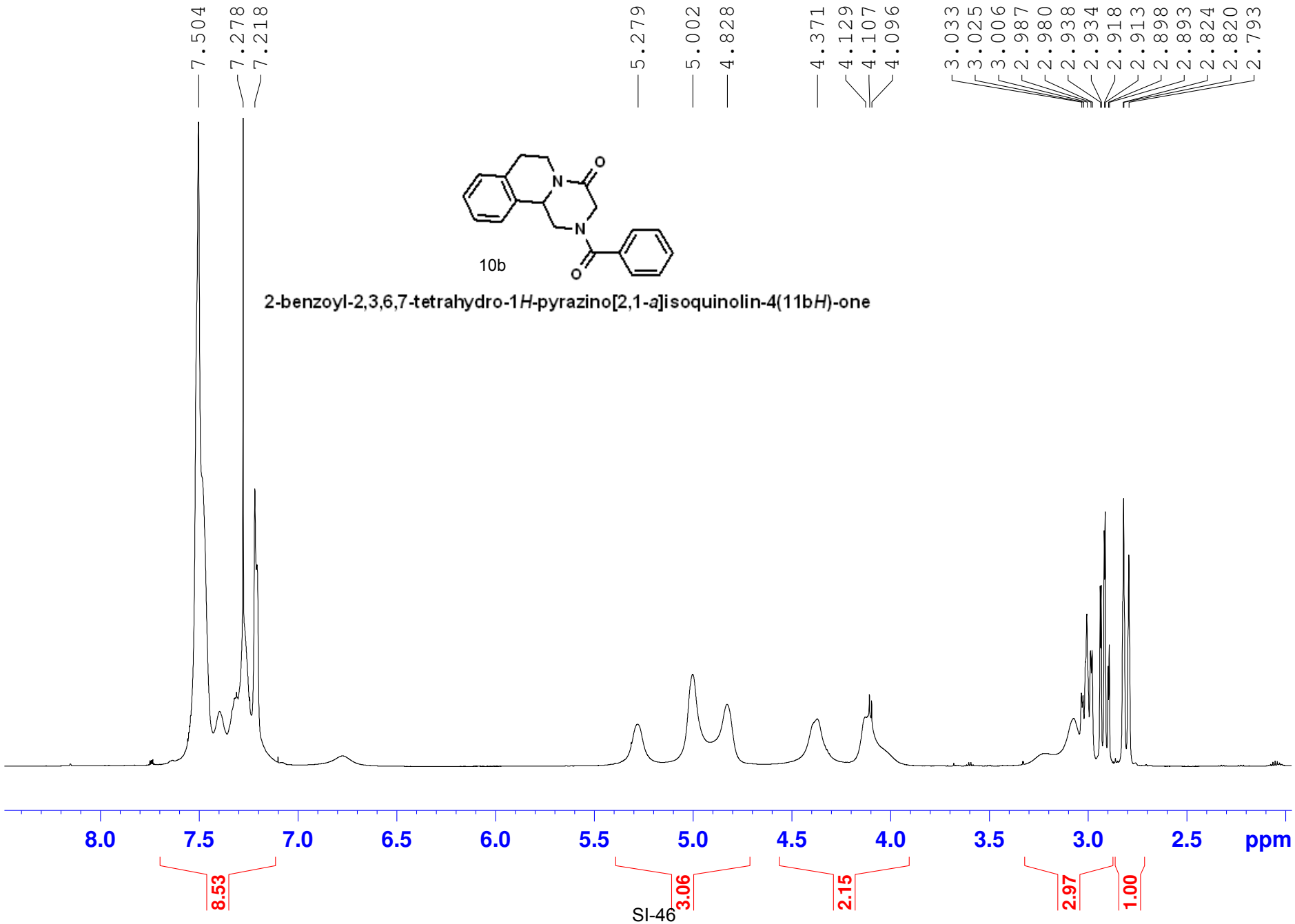
2-(cyclopropanecarbonyl)-2,3,6,7-tetrahydro-1*H*-pyrazino[2,1-*a*]isoquinolin-4(11b*H*)-one



LHX-70, CDCl3, 600 MHz



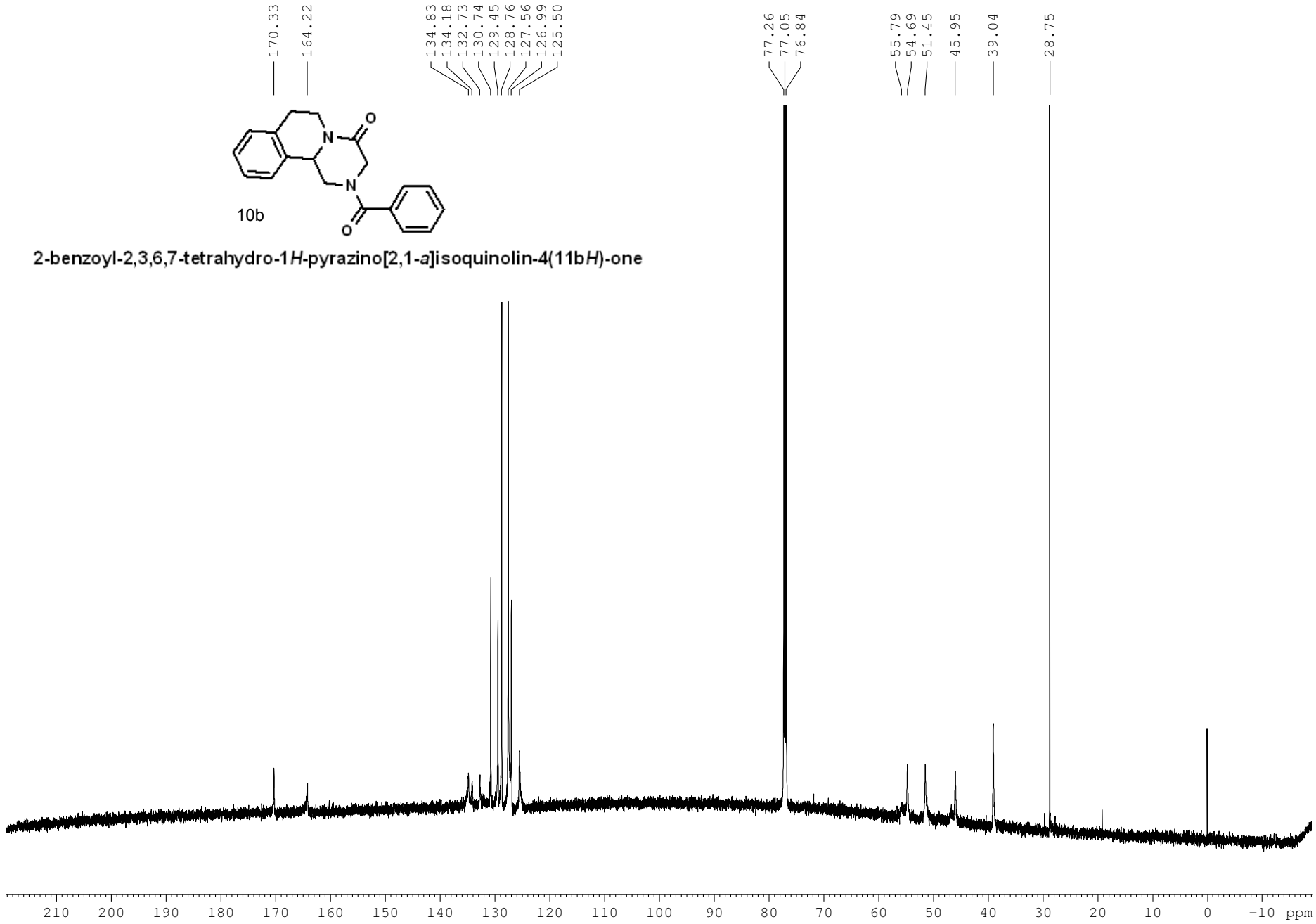
LHX-72, CDCl3, 600 MHz



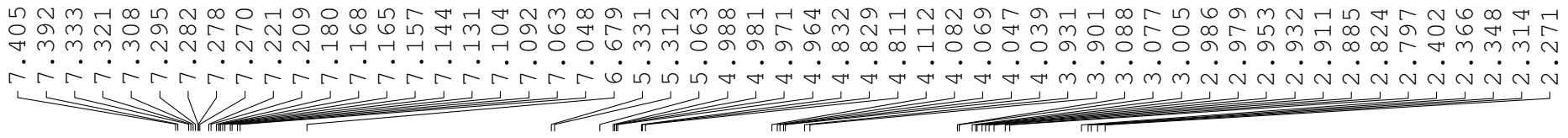
10b

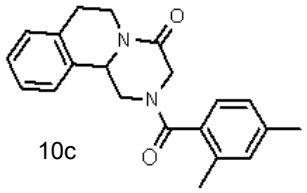
2-benzoyl-2,3,6,7-tetrahydro-1*H*-pyrazino[2,1-*a*]isoquinolin-4(11b*H*)-one

LHX-72, CDCl3, 600 MHz



LHX-101, CDCl3, NMR600

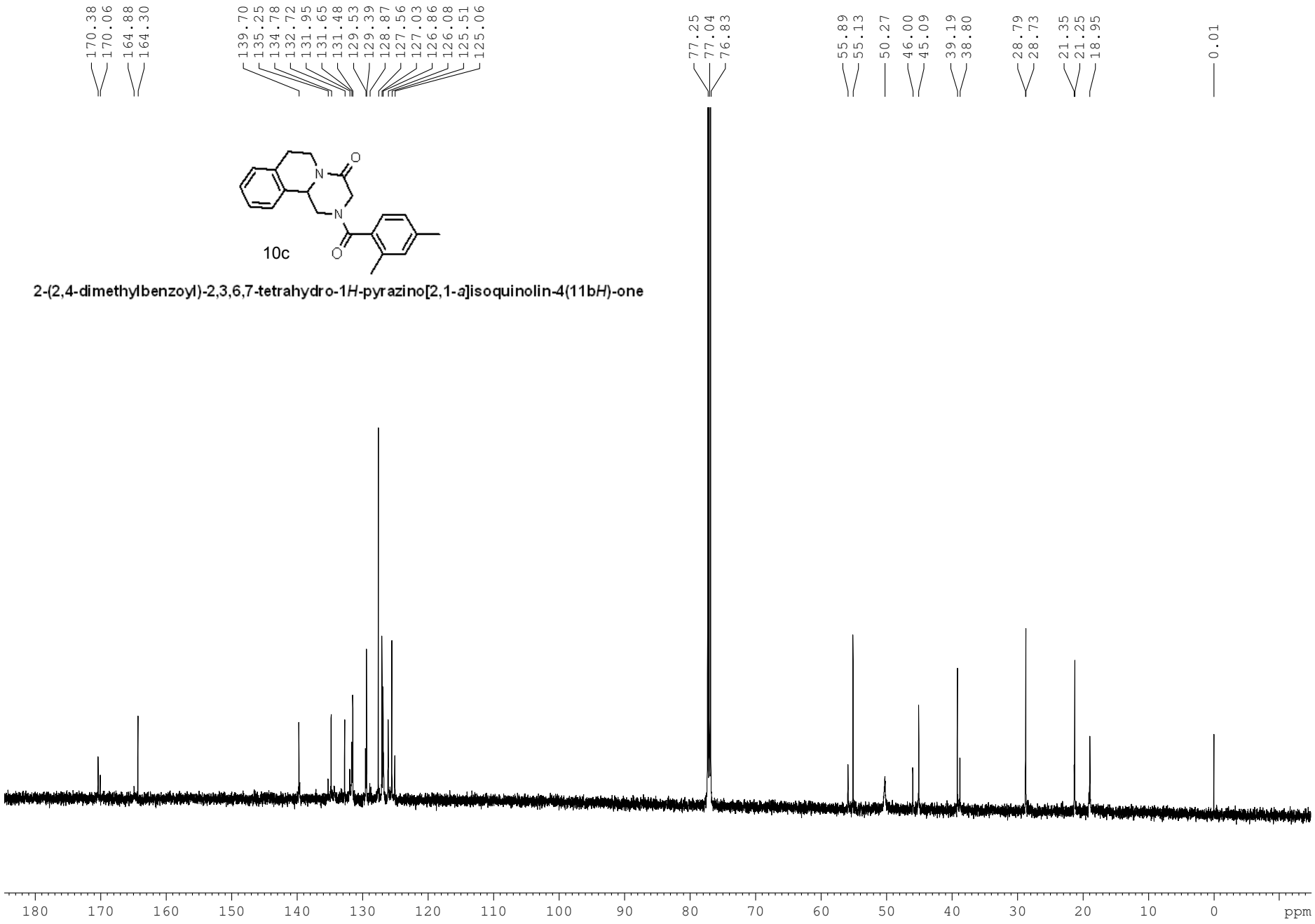




10c

2-(2,4-dimethylbenzoyl)-2,3,6,7-tetrahydro-1*H*-pyrazino[2,1-*a*]isoquinolin-4(11b*H*)-one

LHX-101, CDCl3, NMR600

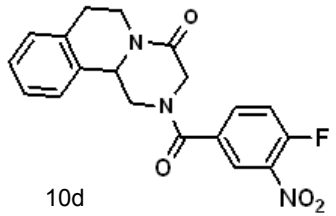


LHX-118, CDCl3, 600 MHz

8.283 8.280 8.271 8.268 7.836 7.832 7.824 7.458 7.443 7.428 7.323 7.291 7.278 7.237 7.227 7.223

5.314 5.200 5.024 5.012 4.830

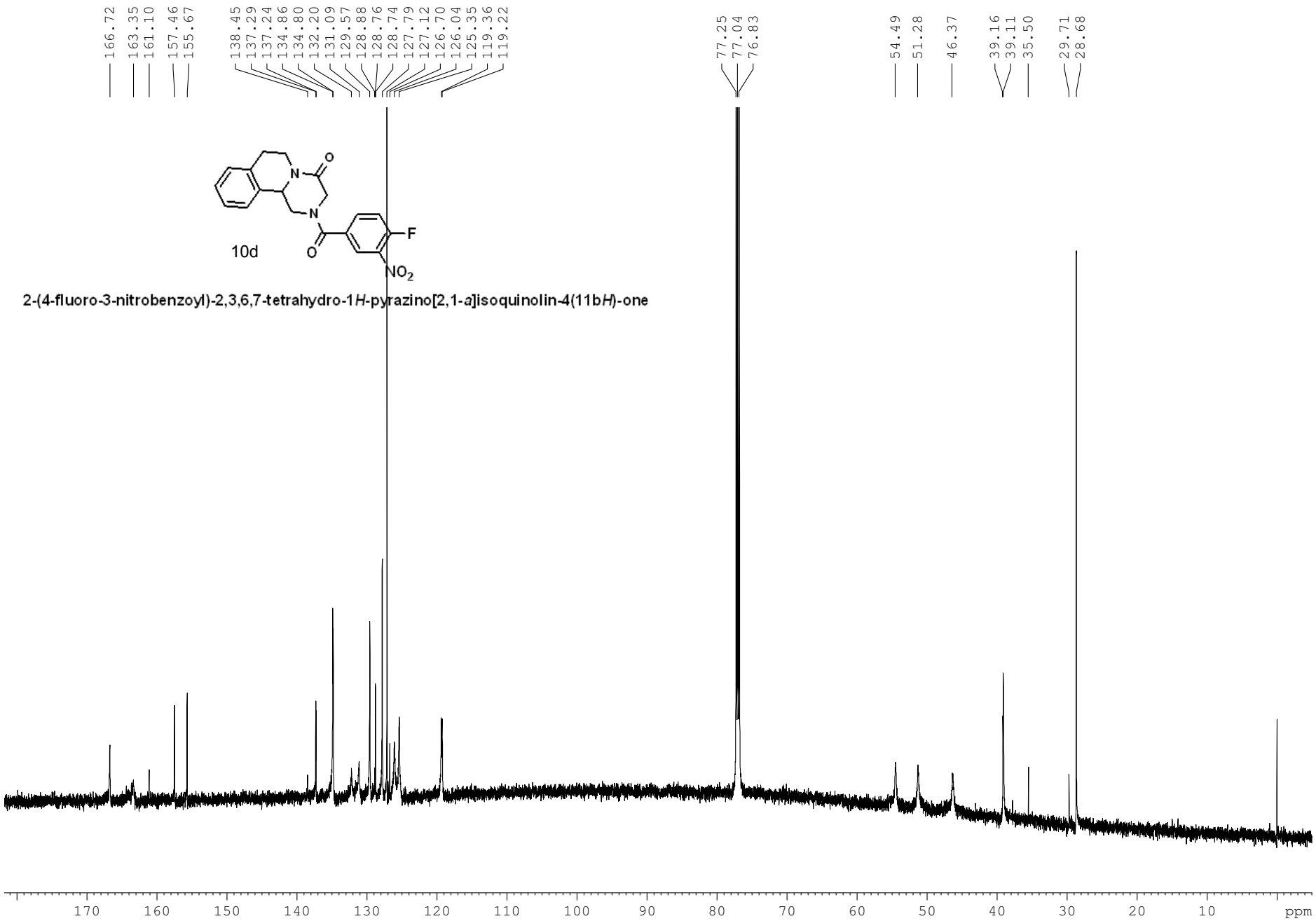
4.272 4.201 3.135 3.041 3.033 3.021 3.014 2.995 2.988 2.957 2.952 2.936 2.931 2.916 2.911 2.876 2.865 2.853



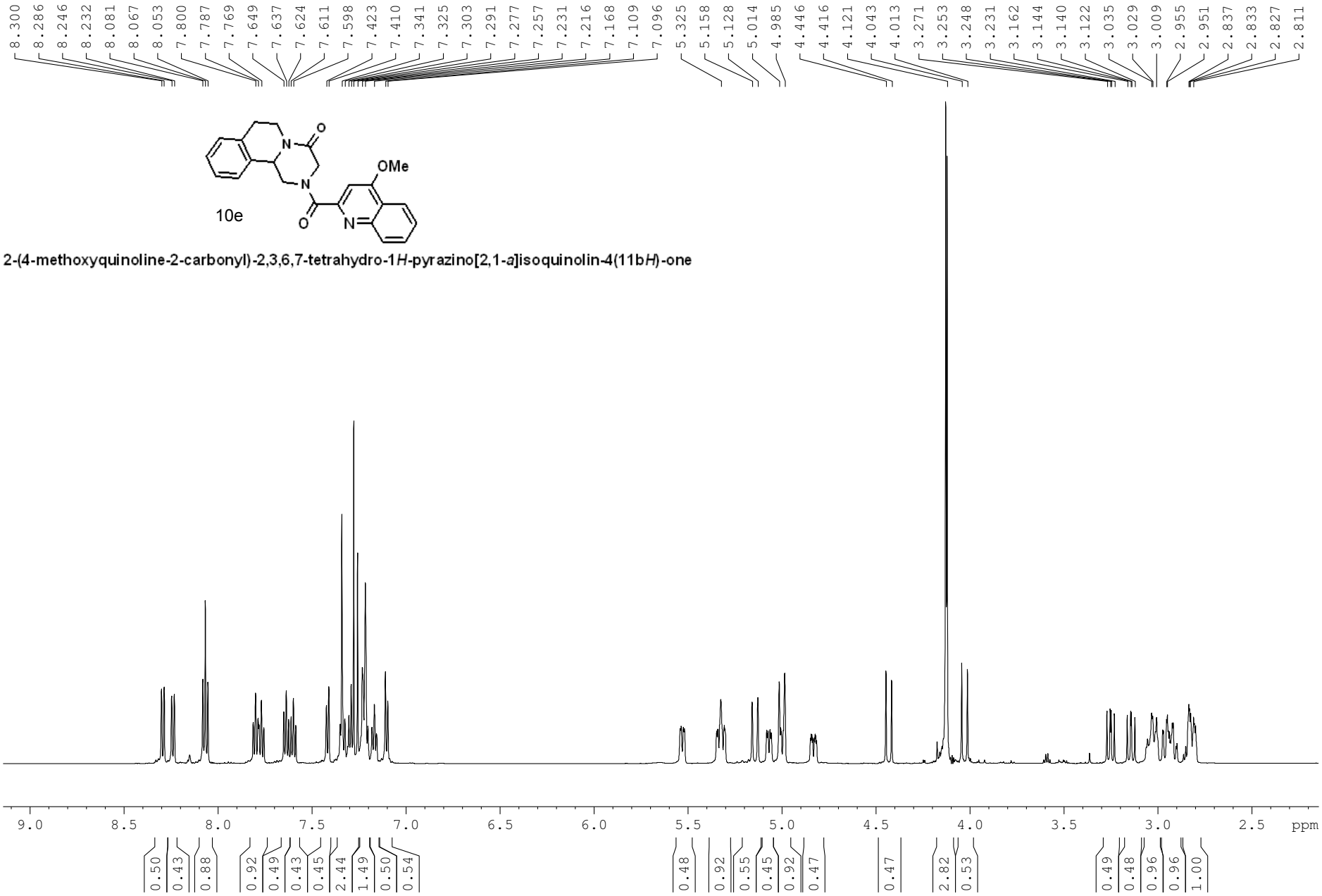
10d

2-(4-fluoro-3-nitrobenzoyl)-2,3,6,7-tetrahydro-1*H*-pyrazino[2,1-*a*]isoquinolin-4(11b*H*)-one

LHX-118, CDCl3, 600 MHz



LHX-140, CDCl3, 600 MHz



2-(4-methoxyquinoline-2-carbonyl)-2,3,6,7-tetrahydro-1*H*-pyrazino[2,1-*a*]isoquinolin-4(11b*H*)-one

LHX-140, CDCl3, 600 MHZ

167.66
166.79
164.87
164.83
163.51
163.45
153.51
153.19
147.43
147.34
135.15
134.92
132.79
132.72
130.69
130.55
129.54
129.41
129.37
129.15
127.54
127.33
127.17
127.04
126.85
125.62
125.33
122.10
121.83
121.70
121.46
100.81
100.22
77.30
77.09
76.87
56.15
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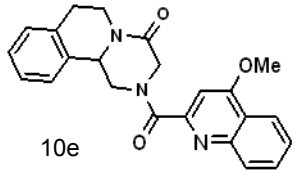
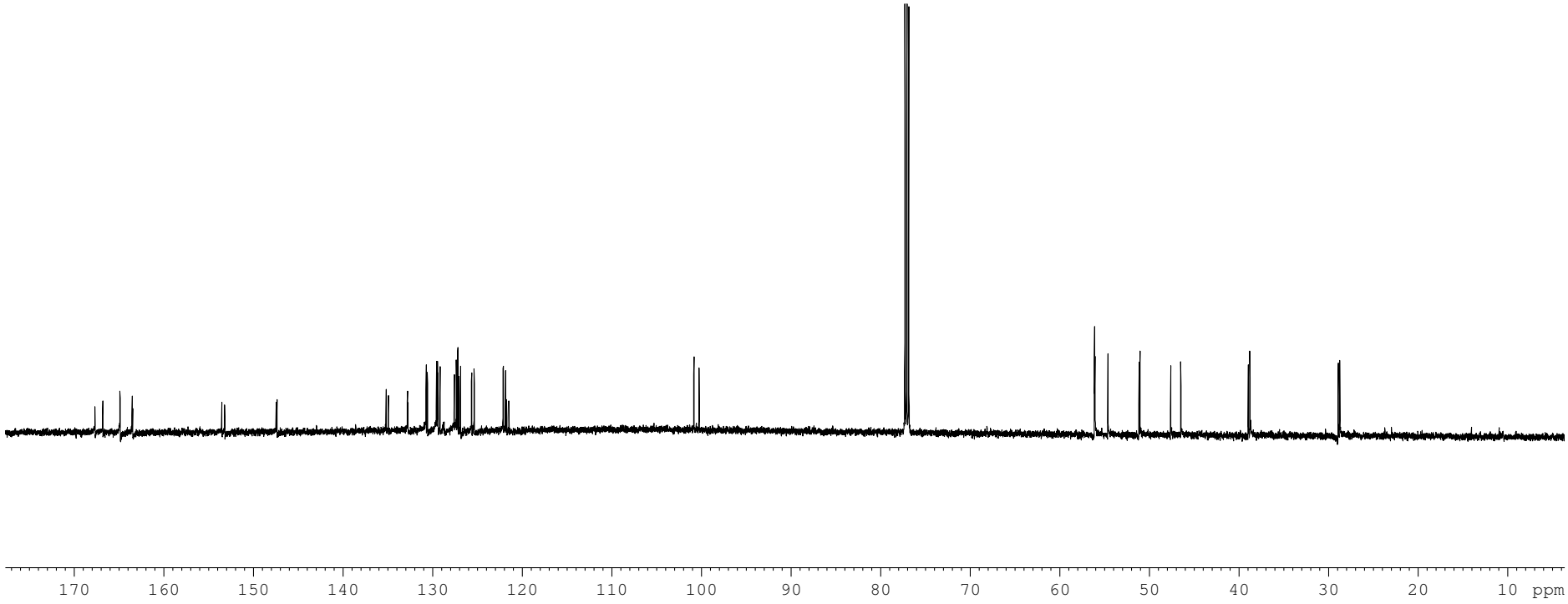
56.09
54.64
51.17
51.08
47.63
46.51
38.98
38.80
28.95
28.77



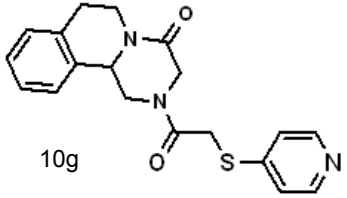
10e

2-(4-methoxyquinoline-2-carbonyl)-2,3,6,7-tetrahydro-1*H*-pyrazino[2,1-*a*]isoquinolin-4(11b*H*)-one



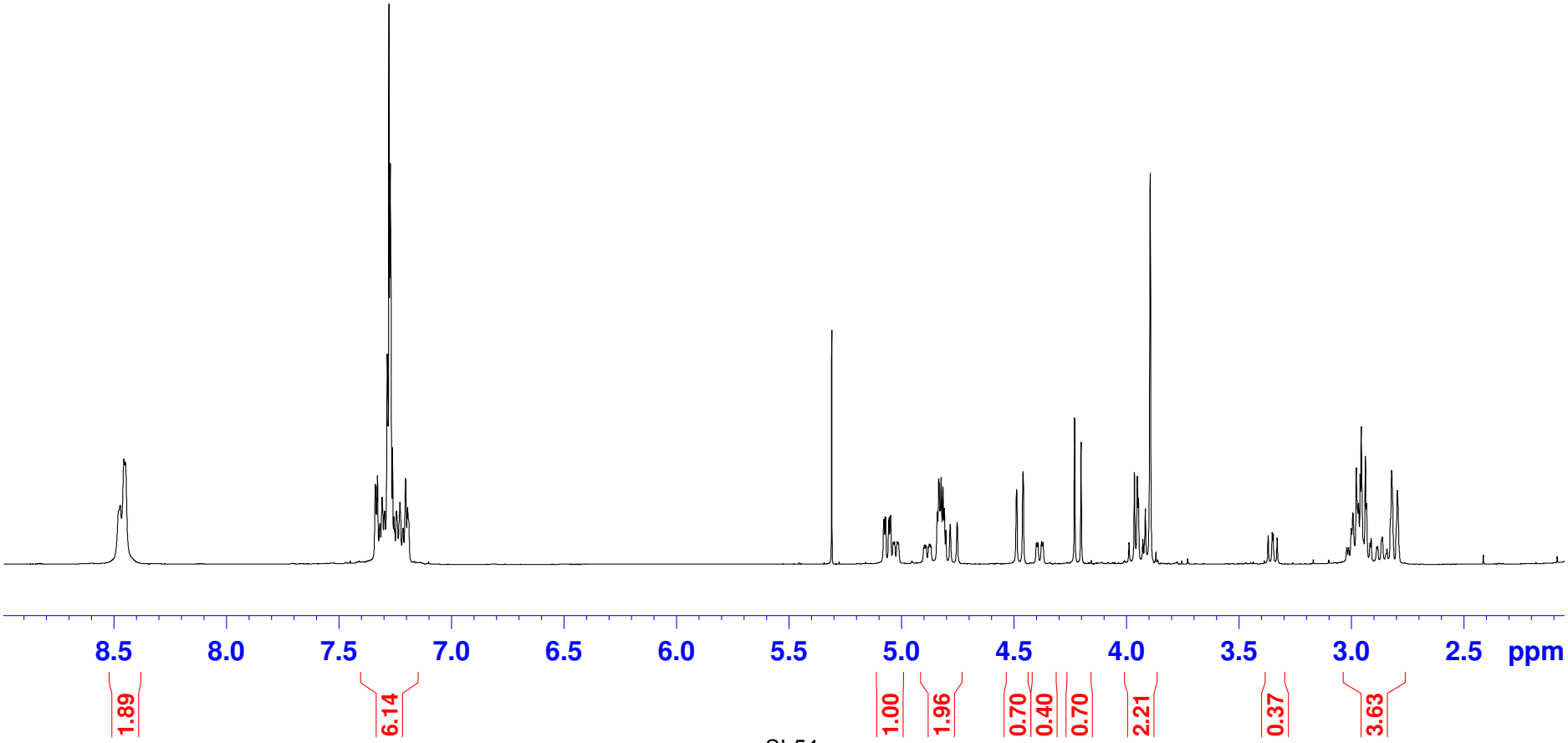
LHX-141, CDCl3, 600 MHz

8.478 8.472 8.455 8.448 7.338 7.328 7.317 7.307 7.296 7.285 7.277 7.271 7.261 7.255 7.244 7.228 7.214 7.203 7.194 5.309 5.079 5.076 5.072 5.069 5.056 5.054 5.049 5.047 4.840 4.833 4.827 4.823 4.815 4.809 4.782 4.752 4.488 4.459 4.229 4.201 3.963 3.951 3.946 3.915 3.894 2.993 2.978 2.968 2.960 2.955 2.938 2.932 2.825 2.821 2.795

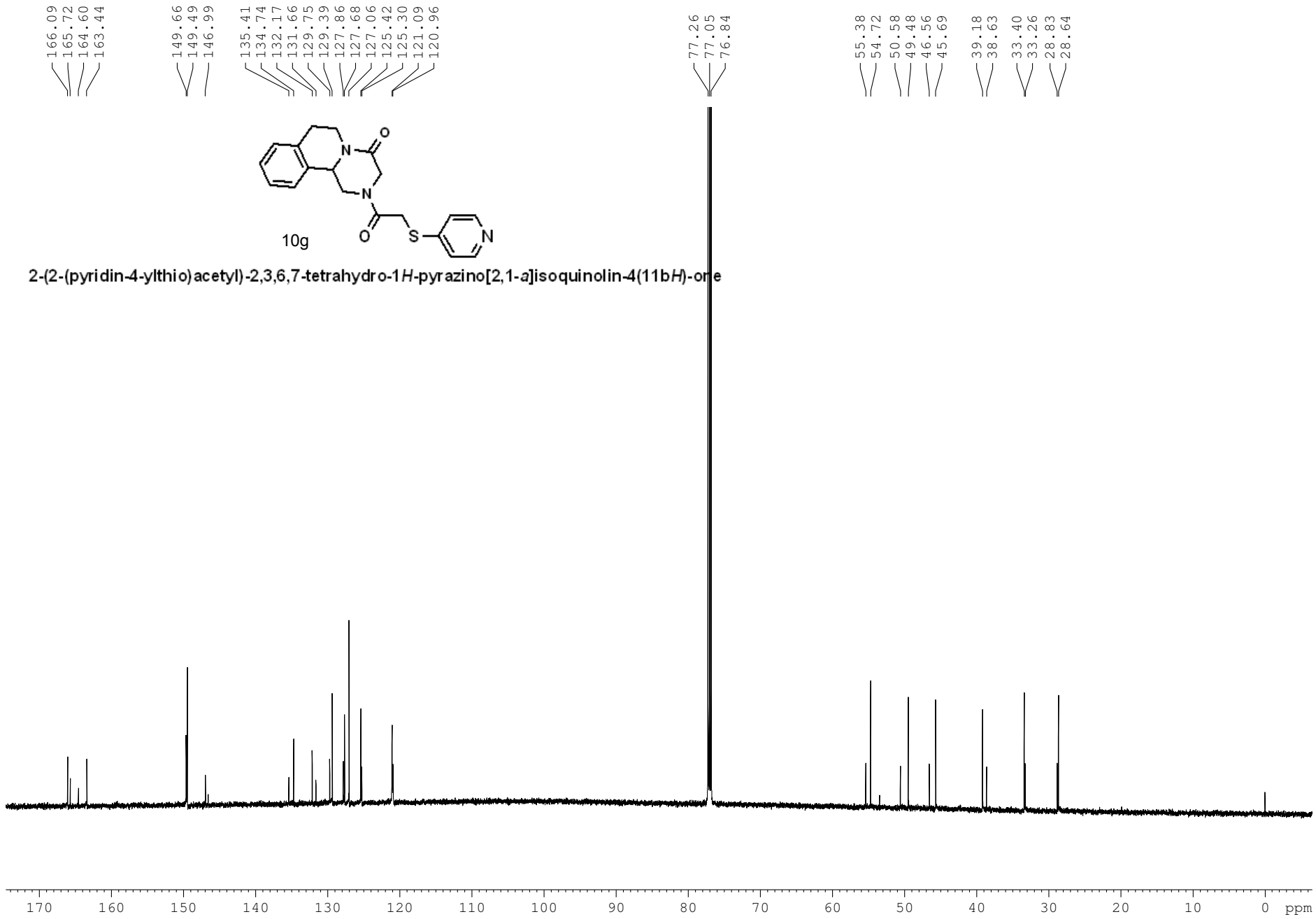


10g

2-(2-(pyridin-4-ylthio)acetyl)-2,3,6,7-tetrahydro-1*H*-pyrazino[2,1-*a*]isoquinolin-4(11b*H*)-one

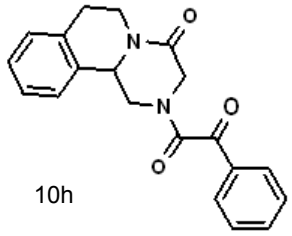


LHX-141, CDCl3, 600 MHz



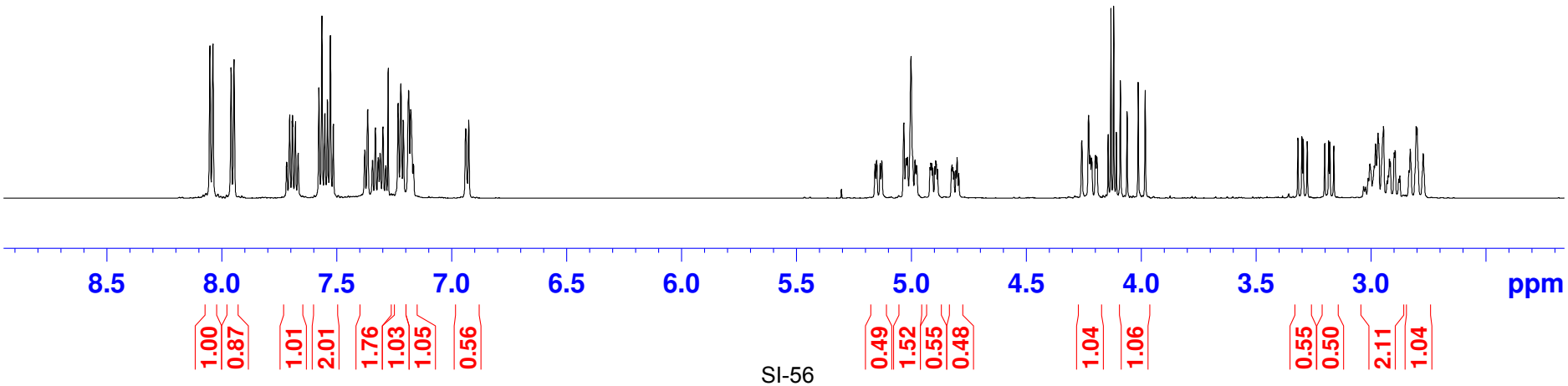
LHX-88, CDCl3, 600 MHz

8.053 8.052 8.040 7.961 7.947 7.707 7.706 7.694 7.693 7.681 7.681 7.578 7.552 7.541 7.529 7.515 7.379 7.366 7.333 7.300 7.277 7.234 7.222 7.211 7.188 7.179 6.939 6.926 5.033 5.002 4.259 4.230 4.144 4.132 4.120 4.108 4.092 4.062 4.014 3.983 3.319 3.301 3.296 3.278 3.202 3.185 3.180 3.163 2.981 2.971 2.947 2.896 2.830 2.805 2.800

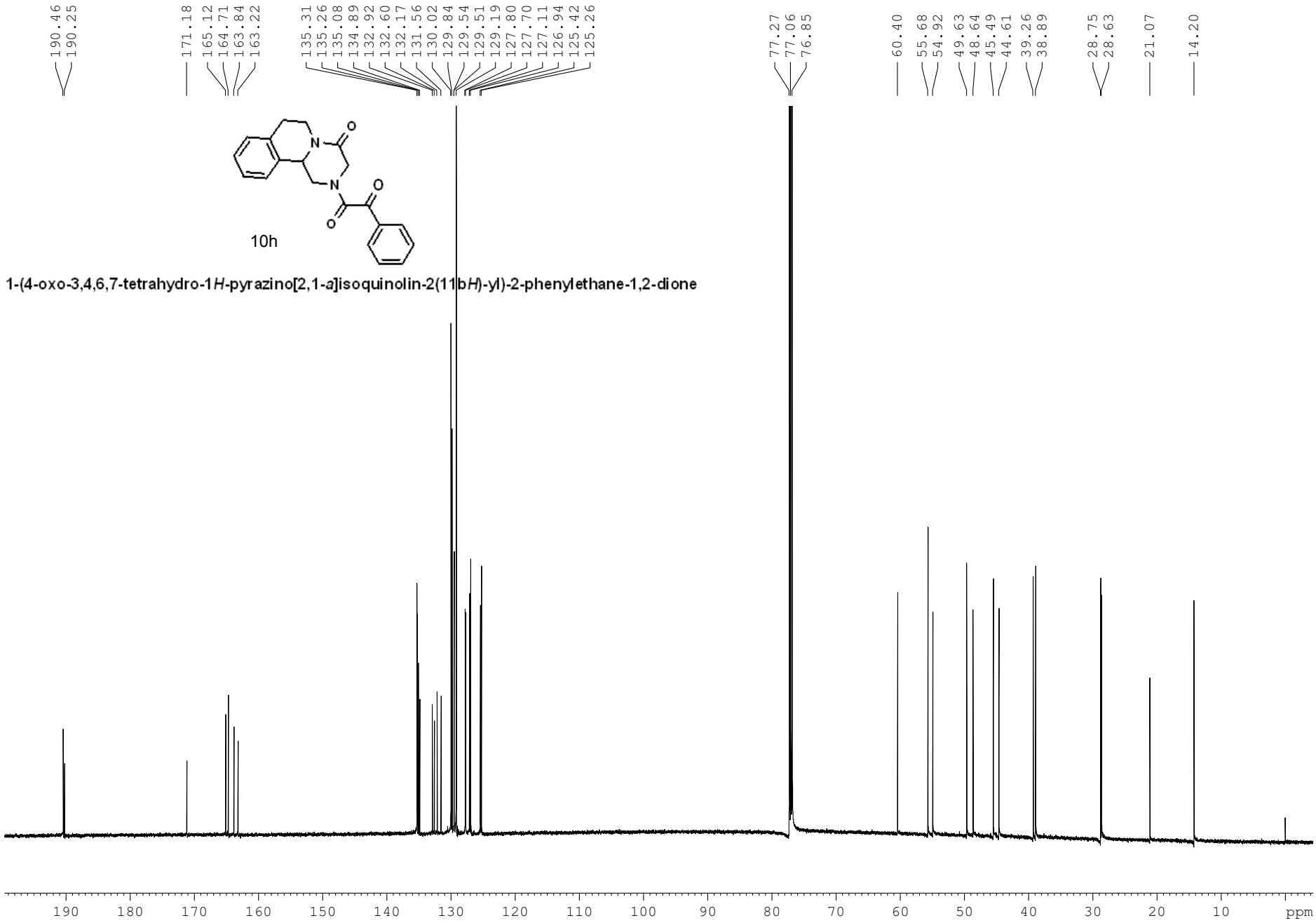


10h

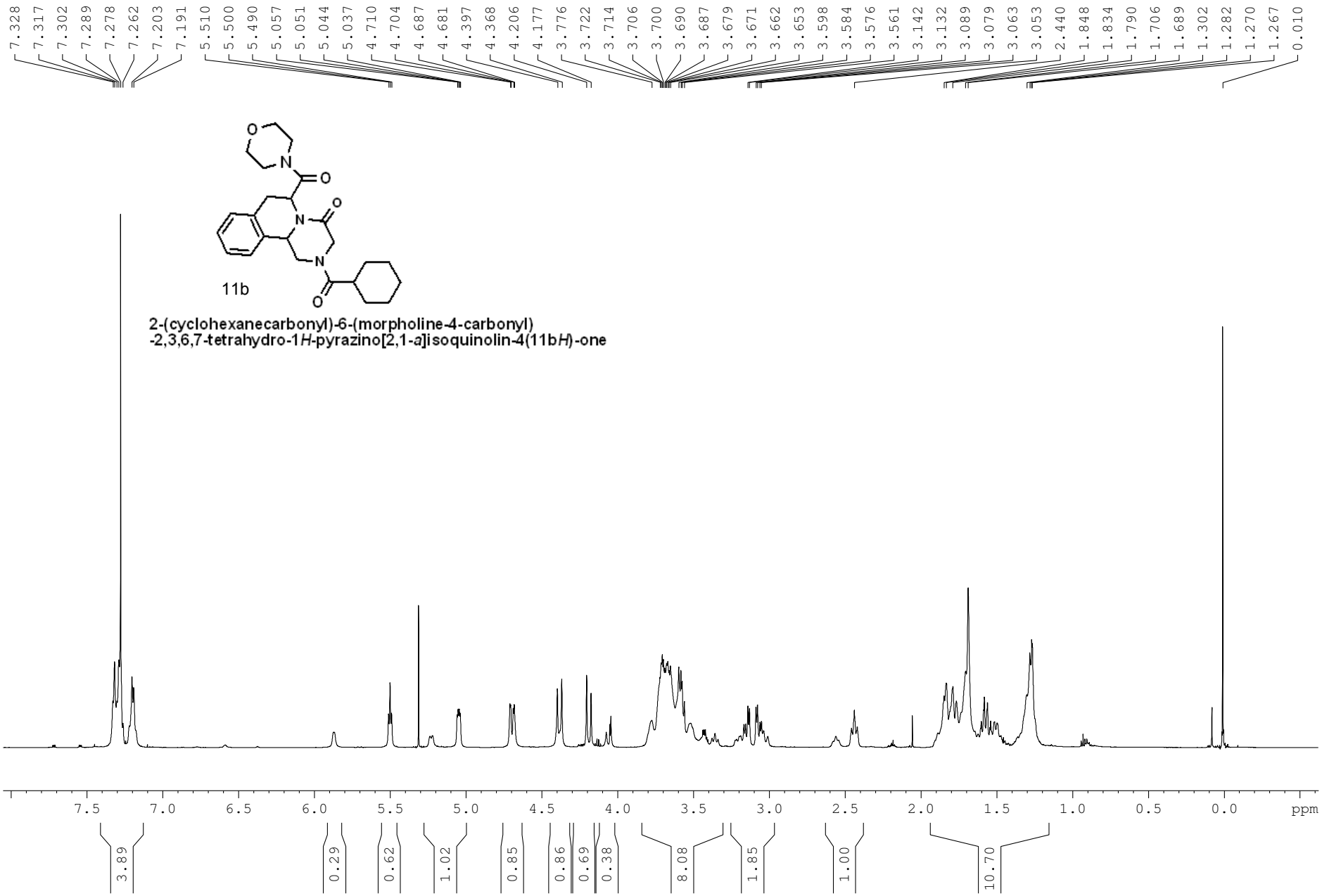
1-(4-oxo-3,4,6,7-tetrahydro-1*H*-pyrazino[2,1-*a*]isoquinolin-2(11b*H*)-yl)-2-phenylethane-1,2-dione



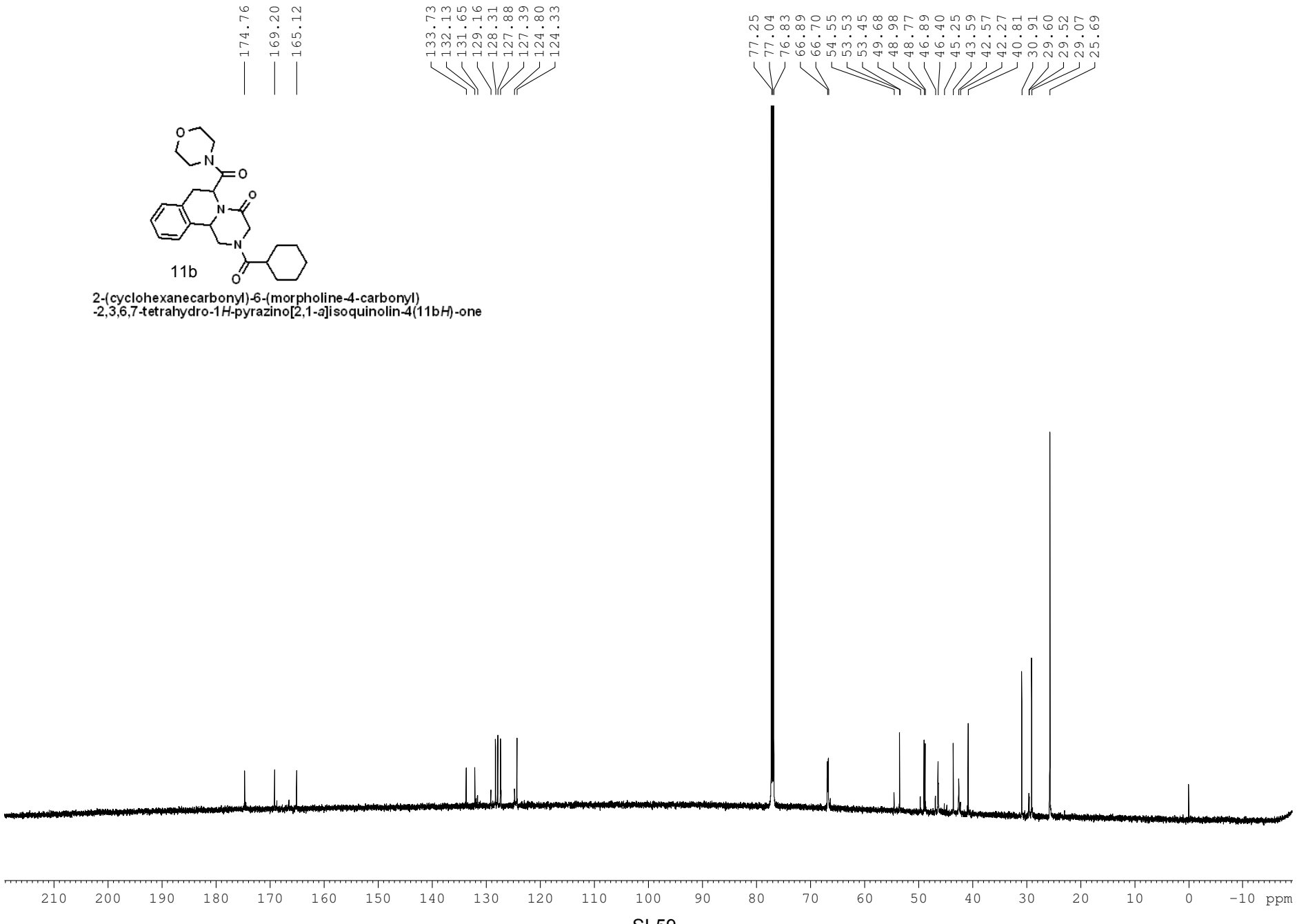
LHX-88, CDCl3, 600 MHz



LHX-142, CDCl3, 600 MHz

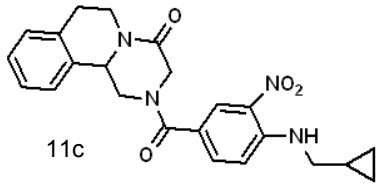


LHX-142, CDCl3, 600 MHz



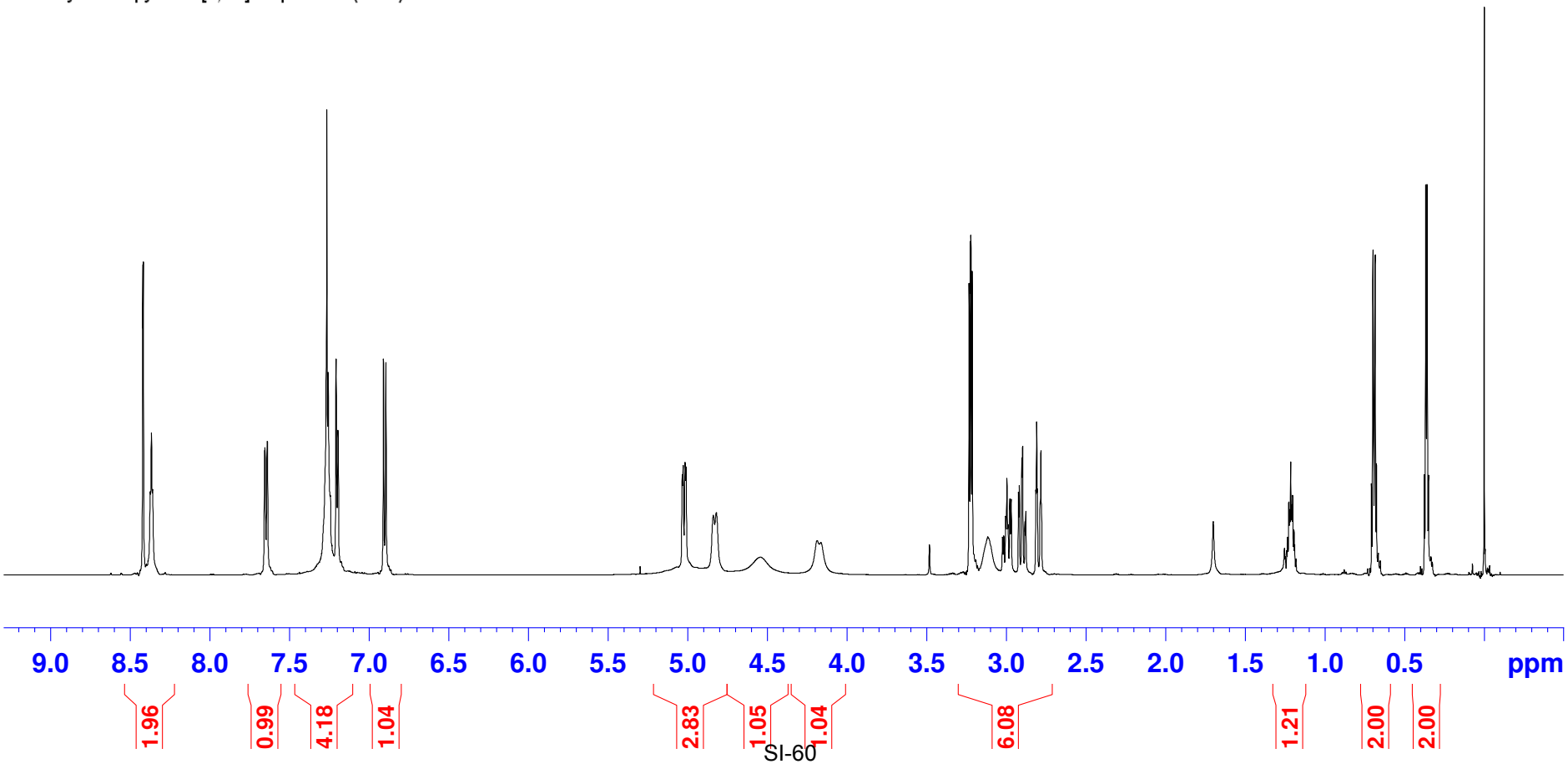
LHX-KK108, CDCl3, NMR600

8.423 8.420 8.376 8.369 8.361 7.657 7.655 7.643 7.641 7.268 7.259 7.209 7.197 6.911 6.896 5.035 5.029 5.018 5.012 4.840 4.822 3.234 3.226 3.223 3.214 3.004 2.997 2.978 2.970 2.924 2.919 2.903 2.898 2.878 2.815 2.810 2.806 2.788 2.784 2.780 1.227 1.222 1.214 1.209 1.206 1.202 0.707 0.698 0.685 0.676 0.375 0.367 0.358 0.349 -0.000

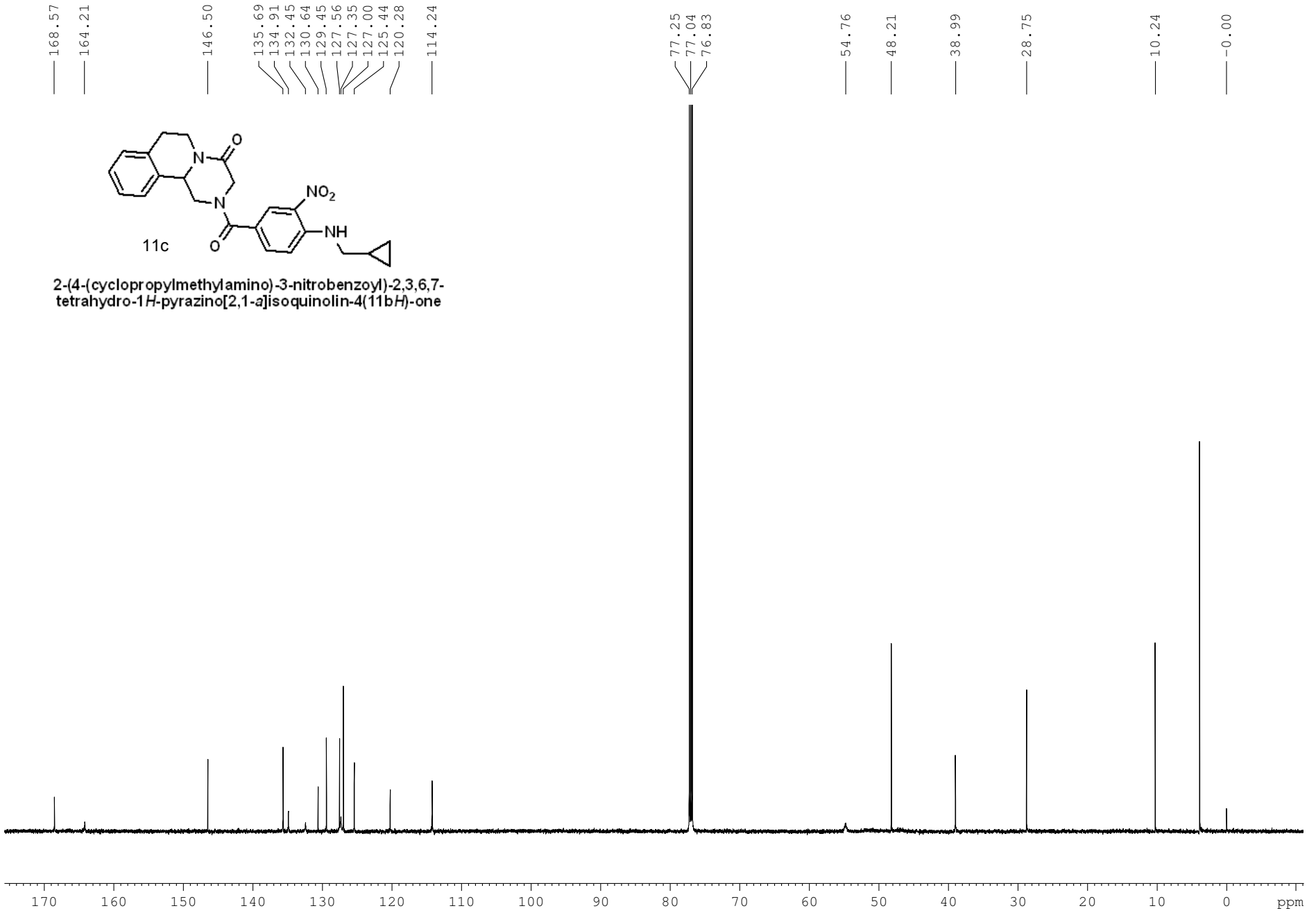


11c

2-(4-(cyclopropylmethylamino)-3-nitrobenzoyl)-2,3,6,7-tetrahydro-1*H*-pyrazino[2,1-*a*]isoquinolin-4(11b*H*)-one



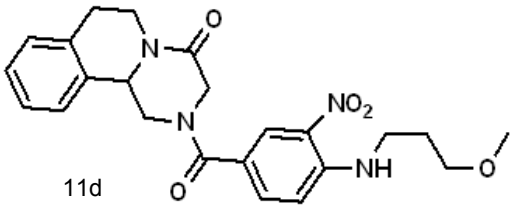
LHX-KK108, CDCl3, NMR600



2-(4-(cyclopropylmethylamino)-3-nitrobenzoyl)-2,3,6,7-tetrahydro-1*H*-pyrazino[2,1-*a*]isoquinolin-4(11b*H*)-one

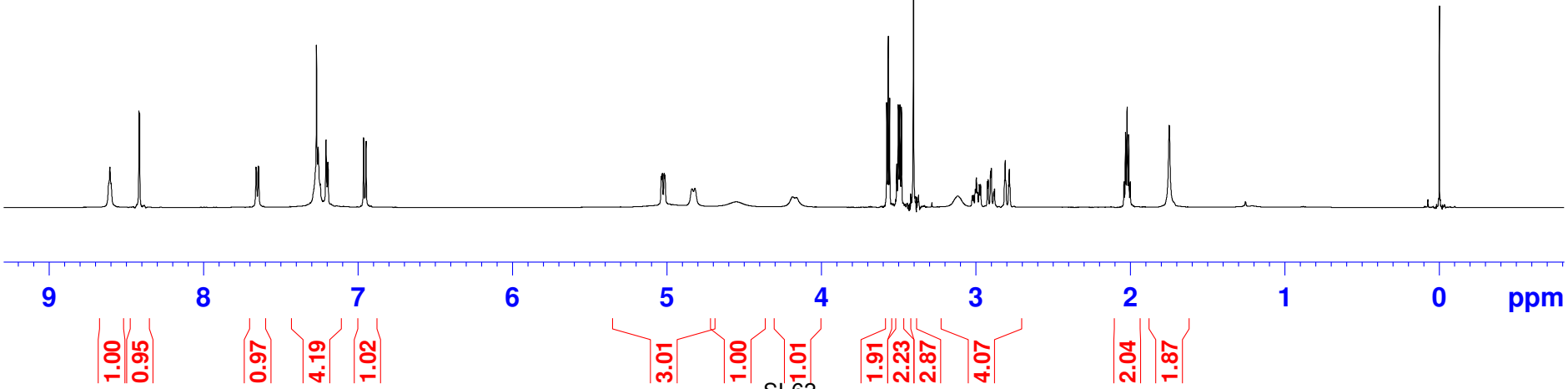
LHX-KK106, CDCl3, NMR600

8.616 8.608 8.601 8.420 8.416 7.662 7.660 7.647 7.645 7.271 7.260 7.245 7.209 7.197 6.965 6.950 5.037 5.032 5.020 5.014 4.839 4.821 3.578 3.568 3.559 3.513 3.503 3.494 3.482 3.405 3.118 3.025 3.017 3.005 2.997 2.991 2.979 2.971 2.926 2.921 2.906 2.901 2.886 2.880 2.815 2.811 2.807 2.789 2.785 2.042 2.031 2.022 2.012 2.002 1.749

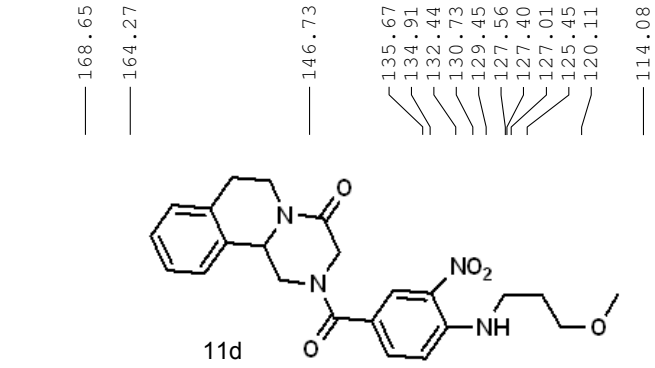


11d

2-(4-(3-methoxypropylamino)-3-nitrobenzoyl)-2,3,6,7-tetrahydro-1*H*-pyrazino[2,1-*a*]isoquinolin-4(11b*H*)-one



LHX-KK106, CDCl3, NMR600

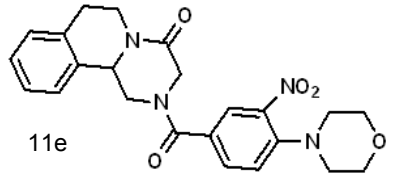


2-(4-(3-methoxypropylamino)-3-nitrobenzoyl)-2,3,6,7 -tetrahydro-1*H*-pyrazino[2,1-*a*]isoquinolin-4(11b*H*)-one

LHX-KK105, CDCl3, NMR600

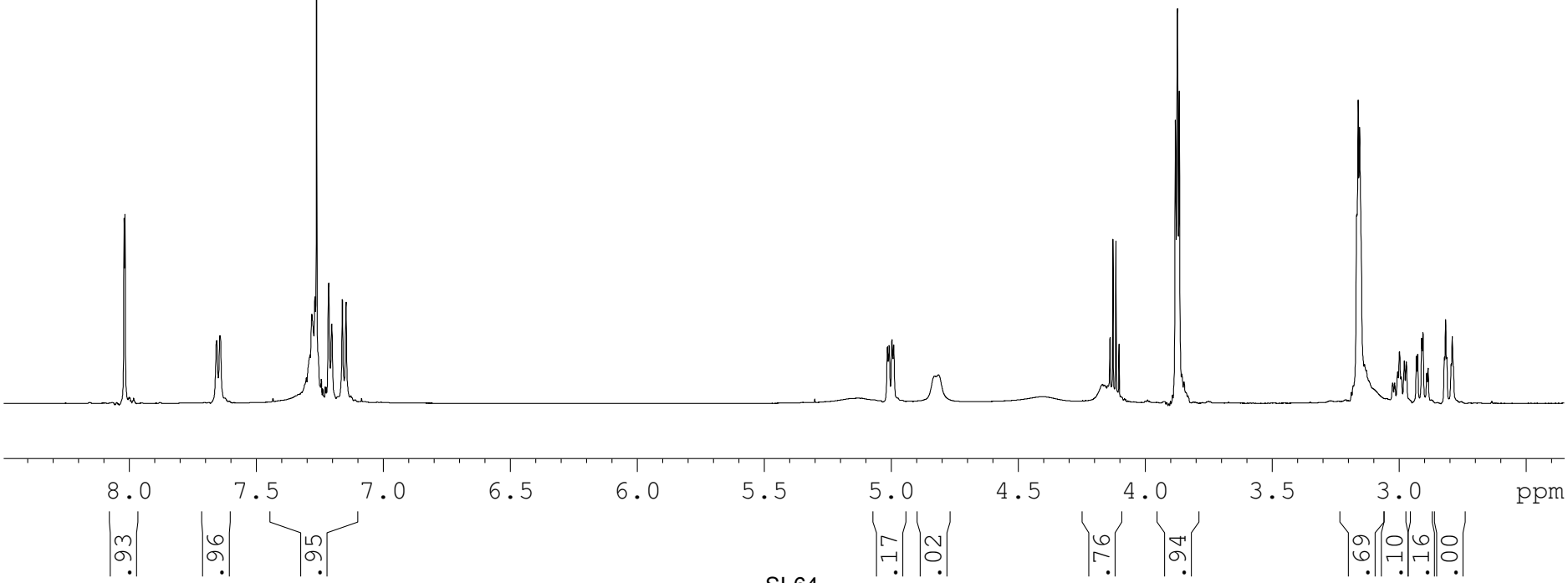
8.021 8.018 7.657 7.644 7.282 7.270 7.263 7.216 7.204 7.162 7.148

5.015 5.009 4.998 4.991 4.830 4.815 4.168 4.161 4.149 3.882 3.874 3.866 3.182 3.168 3.162 3.157 3.137 3.130 3.120 3.026 3.018 3.007 2.999 2.992 2.980 2.973 2.932

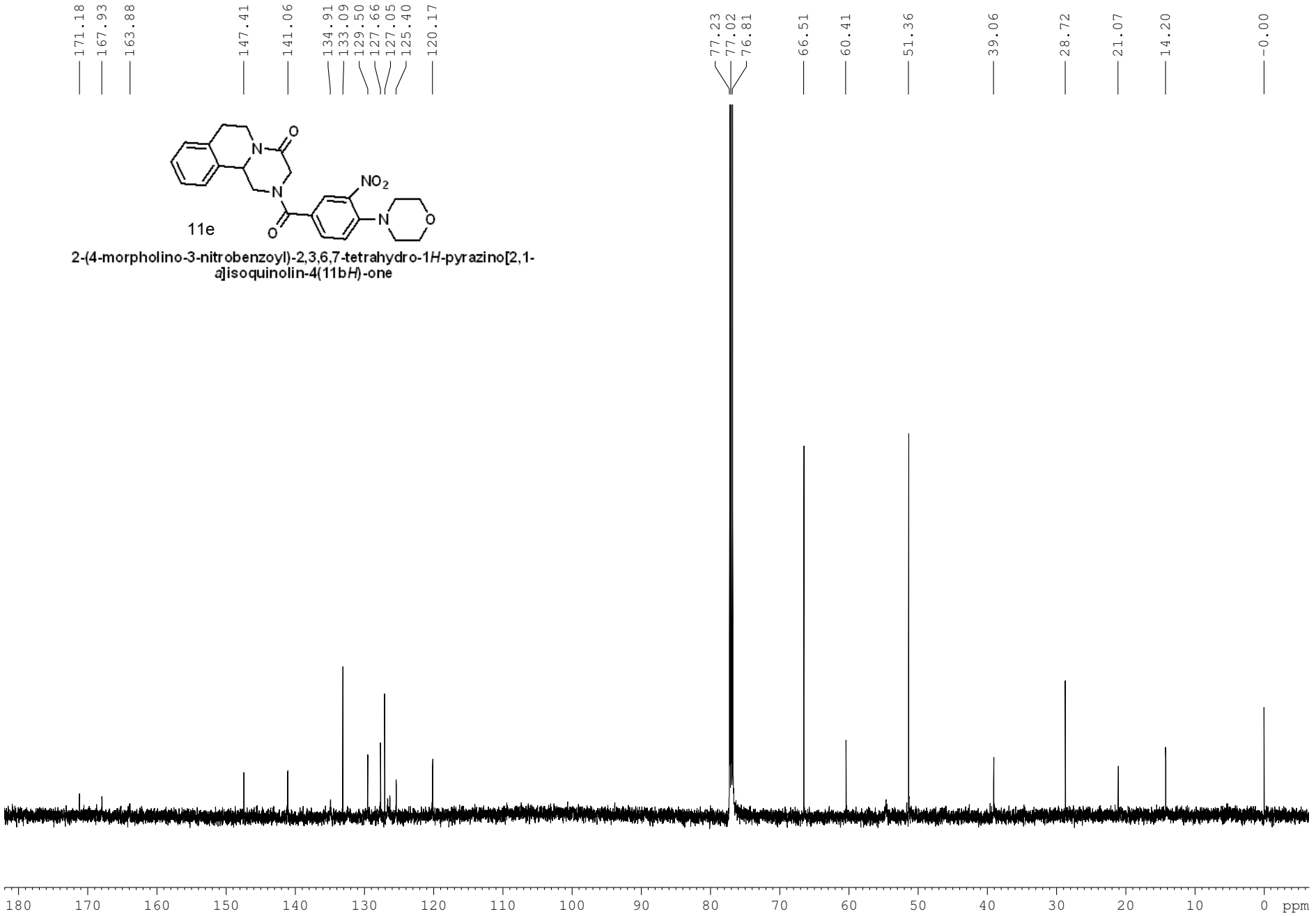


11e

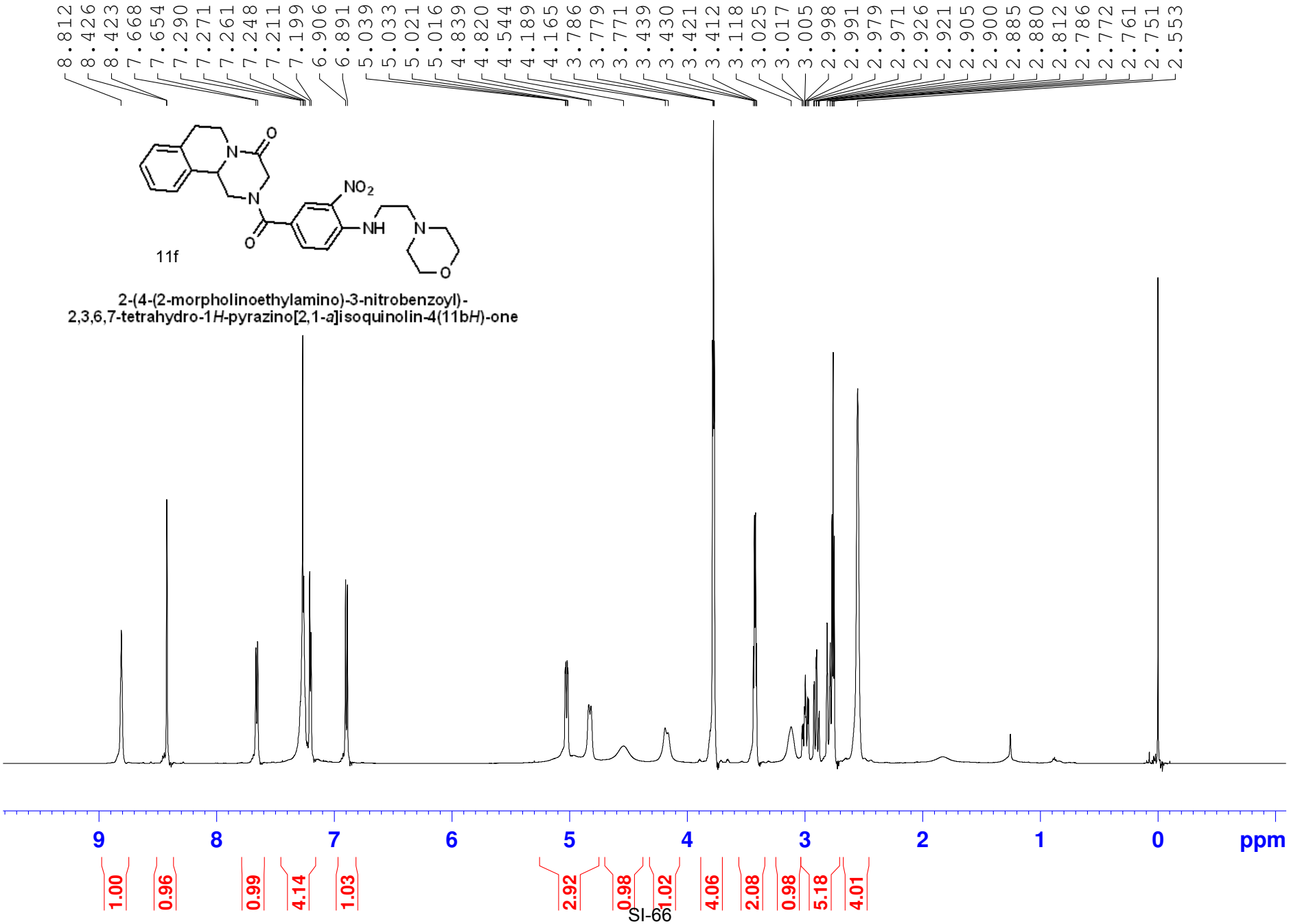
2-(4-morpholino-3-nitrobenzoyl)-2,3,6,7-tetrahydro-1*H*-pyrazino[2,1-*a*]isoquinolin-4(11b*H*)-one



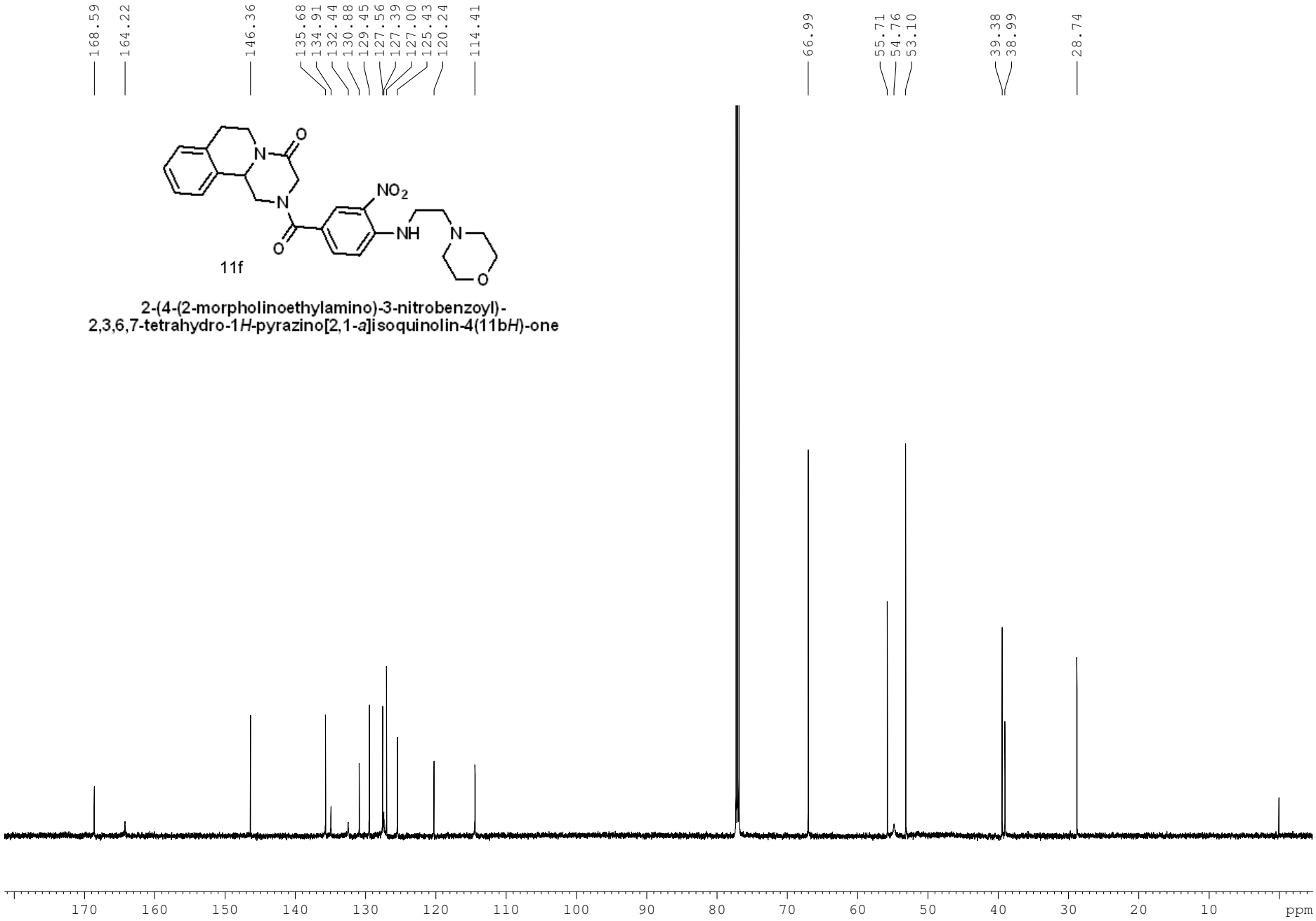
LHX-KK105, CDCl3, NMR600



LHX-KK107, CDCl3, NMR600

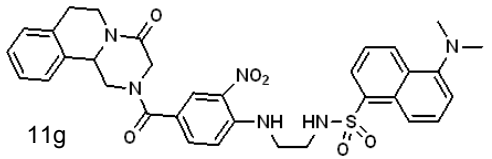


LHX-KK107, CDCl3, NMR600



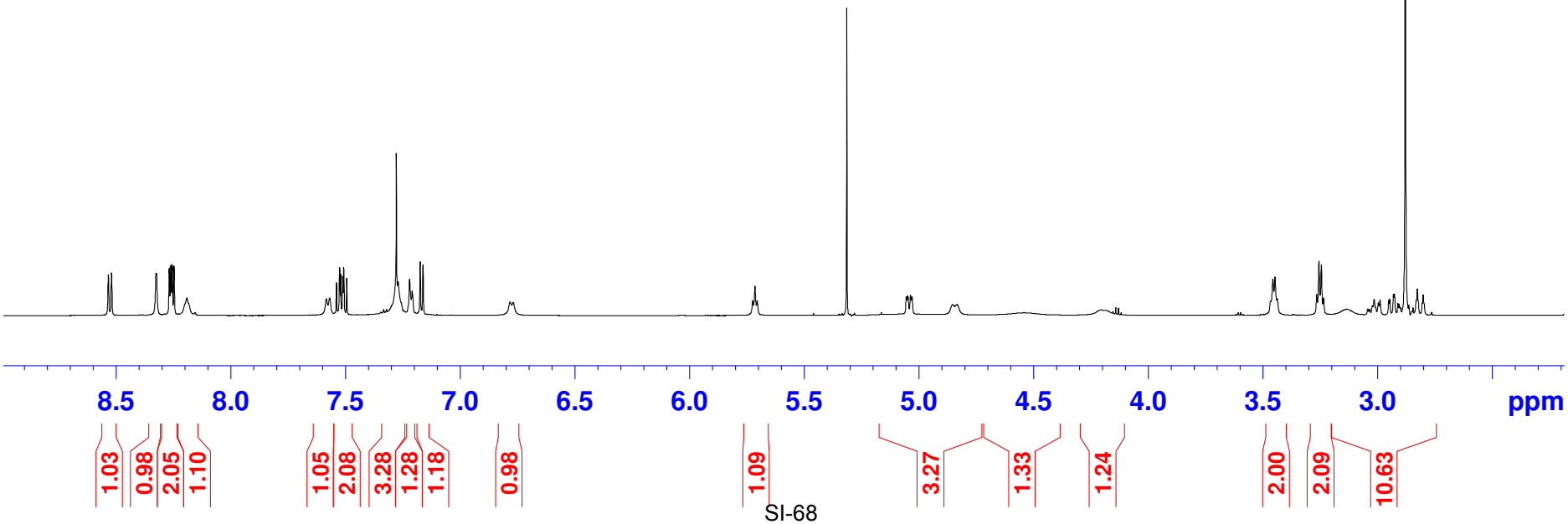
LHX-153, CDCl3, 600 MHz

8.533 8.519 8.326 8.324 8.268 8.267 8.261 8.256 8.255 8.247 8.191 7.583 7.569 7.539 7.526 7.520 7.512 7.508 7.506 7.494 7.278 7.269 7.220 7.209 7.174 7.161 6.782 5.724 5.714 5.704 5.053 5.047 5.036 5.029 3.466 3.456 3.446 3.437 3.265 3.255 3.245 3.235 3.015 2.996 2.989 2.951 2.946 2.930 2.926 2.878 2.831 2.826 2.823 2.805 2.800

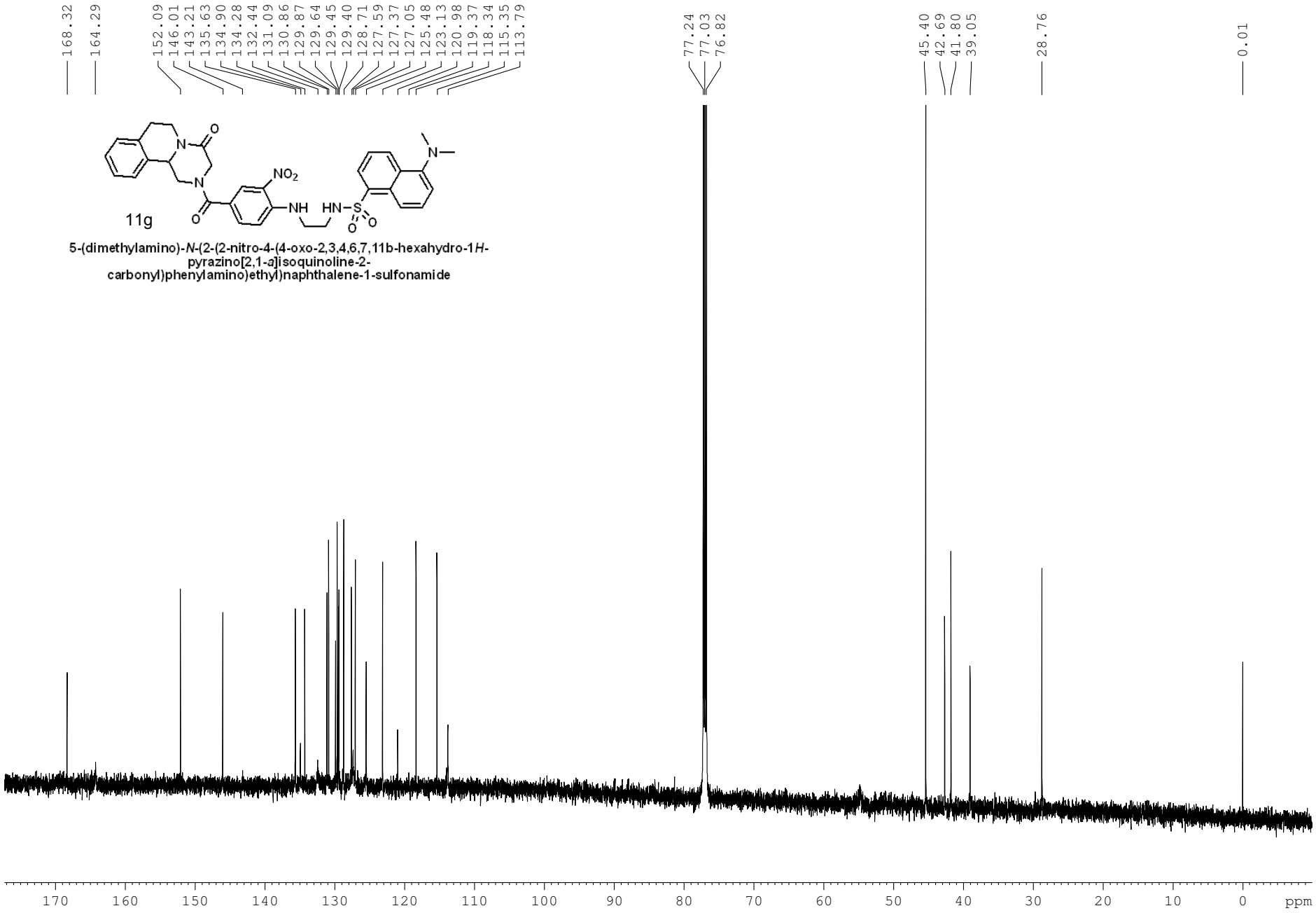


11g

5-(dimethylamino)-*N*-(2-(2-nitro-4-(4-oxo-2,3,4,6,7,11b-hexahydro-1*H*-pyrazino[2,1-*a*]isoquinoline-2-carbonyl)phenylamino)ethyl)naphthalene-1-sulfonamide



LHX-153, CDCl3, NMR600



11g

5-(dimethylamino)-*N*-(2-(2-nitro-4-(4-oxo-2,3,4,6,7,11b-hexahydro-1*H*-pyrazino[2,1-*a*]isoquinoline-2-carbonyl)phenylamino)ethyl)naphthalene-1-sulfonamide