Supporting Information

New 5-unsubstituted-dihydropyridines with improved $Ca_V1.3$ selectivity as potential neuroprotective agents against ischemic injury

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1. EXPERIMENTAL PROTOCOLS

1.1. SYNTHESIS

General experimental information

All reagents (Aldrich, Fluka, SDS, Probus) and solvents (SDS), were of commercial quality and were used as received. Reactions were monitored by thin layer chromatography, on aluminum plates coated with silica gel with fluorescent indicator (SDS CCM221254). Separations by flash chromatography were performed on silica gel (SDS 60 ACC 40-63 μm) or neutral alumina (Merck S22). Melting points were measured on a Reichert 723 hot stage microscope, and are uncorrected. Infrared spectra were recorded on a Perkin Elmer Paragon 1000 FT-IR spectrophotometer, with all compounds examined as KBr pellets or as a thin film on NaCl disks. NMR spectra were obtained on a Bruker Avance 250 spectrometer operating at 250 MHz for ^{1}H and 63 MHz for ^{13}C (CAI de Resonancia Magnética Nuclear, Universidad Complutense). Elemental analyses were determined by CAI de Microanálisis Elemental, Universidad Complutense, using a Leco 932 CHNS combustion microanalyzer. The purity of new compounds was determined by CHNS elemental analysis, and all values were verified to be within 0.4 % of theoretical data.

General procedure for the synthesis of 1,4-dihydropyridine derivatives (3) and 4,6,7,8-tetrahydroquinolin-5(1*H*)-ones (5)

To a stirred solution of 1,3-diphenyl-2-propen-1-one derivatives (1 equiv, 2 mmol), 1,3-dicarbonyl compounds (1.1 equiv, 2.2 mmol) and ammonium acetate (3 equiv, 6 mmol) in ethanol (3 mL) was added Ceric Ammonium Nitrate (CAN, 10% mol) and the resulting mixture was refluxing for 4 hours. After this time, ammonium acetate (1.5 equiv, 3 mmol) was again added and stirring was continued at the same condition for 4 hours more. After completion of the reaction (checked by TLC), the mixture was allowed to cool to room temperature, diluted with CH_2Cl_2 (20 mL) and washed with water to remove CAN and the excess of ammonium acetate. The organic layer is then washed with brine and dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude residue was crystallized from EtOH or purified by silica column chromatography using petroleum ether-ethyl acetate mixture (12:1 v/v) as eluent to give pure compounds (**3a-u** or **5a-b**). Characterization data for all final compounds follow.

Ethyl 2-methyl-4,6-diphenyl-1,4-dihydropyridine-3-carboxylate (3a)

Yellow solid, mp 244-246 °C; ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 1.28 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 2.56 (s, 3H, C-2CH_3), 4.17 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 4.84 (d, J = 5.5 Hz, 1H,

C-4*H*), 5.34 (dd, *J* = 1.8, 5.5 Hz, 1H, C-5*H*), 5.73 (bs, 1H, N*H*), 7.30-7.33 (m, 1H, Ar*H*), 7.38-7.52 (m, 9H, Ar*H*); ^{13}C-NMR ($CDCl_3$, 63 MHz) δ 14.7 (OCH_2CH_3), 21.1 (C-2CH_3), 41.4 (*C*-4), 59.7 (OCH_2CH_3), 99.5 (*C*-3), 105.5 (*C*-5), 125.5 (2x*C*HAr), 126.5 (*C*HAr), 128.2 (2x*C*HAr), 128.6 (2x*C*HAr), 128.9 (*C*HAr), 129.2 (2x*C*HAr), 134.7, 136.3 (C-6*C*Ar, *C*-6), 147.3, 149.3 (C-4*C*Ar, *C*-2), 168.8 (*C*OOR); IR (NaCl) ν 2984, 1717, 1666, 1481, 1382 cm^{-1}; elemental analysis calcd (%) for $C_{21}H_{21}NO_2$: C 78.97, H 6.63, N 4.39; found: C 78.87, H 6.71, N 4.42.

Ethyl 2-ethyl-4,6-diphenyl-1,4-dihydropyridine-3-carboxylate (3b)

White solid, mp 143-145 °C; ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 1.28 (t, *J* = 7.2 Hz, 3H, CH_2CH_3), 1.44 (t, *J* = 7.5 Hz, 3H, OCH_2CH_3), 2.97 (dq, *J* = 4.3, 7.2 Hz, 2H, CH_2CH_3), 4.17 (dq, *J* = 0.6, 7.5 Hz, 2H, OCH_2CH_3), 4.84 (d, *J* = 5.6 Hz, 1H, C-4*H*), 5.33 (dd, *J* = 1.9, 5.6 Hz, 1H, C-5*H*), 5.79 (bs, 1H, N*H*), 7.23-7.33 (m, 1H, Ar*H*), 7.38-7.57 (m, 9H, Ar*H*); ^{13}C-NMR ($CDCl_3$, 63 MHz) δ 13.5 (CH_2CH_3), 14.6 (OCH_2CH_3), 27.4 (CH_2CH_3), 41.4 (*C*-4), 59.6 (OCH_2CH_3), 98.6 (*C*-3), 105.4 (*C*-5), 125.5 (2x*C*HAr), 126.4 (*C*HAr), 128.1 (2x*C*HAr), 128.6 (2x*C*HAr), 128.9 (*C*HAr), 129.2 (2x*C*HAr), 134.6, 136.4 (C-6*C*Ar, *C*-6), 149.4, 152.7 (C-4*C*Ar, *C*-2), 168.3 (*C*OOR); IR (NaCl) ν 3325, 2974, 1666, 1487, 1366 cm^{-1}; elemental analysis calcd (%) for $C_{22}H_{23}NO_2$: C 79.25, H 6.95, N 4.20; found: C 78.94, H 6.88, N 4.40.

Ethyl 4,6-diphenyl-2-propyl-1,4-dihydropyridine-3-carboxylate (3c)

Yellow paste; ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 1.08 (t, *J* = 7.3 Hz, 3H, $CH_2CH_2CH_3$), 1.17 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3), 1.69-1.84 (m, 2H, $CH_2CH_2CH_3$) 2.69-2.90 (m, 2H, $CH_2CH_2CH_3$), 4.06 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 4.72-4.75 (d, *J* = 5.6 Hz, 1H, C-4*H*), 5.20-5.23 (dd, *J* = 1.9, 5.6 Hz, 1H, C-5*H*), 5.68 (bs, 1H, N*H*), 7.15-7.43 (m, 10H, Ar*H*); ^{13}C-NMR ($CDCl_3$, 63 MHz) δ 14.60 ($CH_2CH_2CH_3$), 14.64 (OCH_2CH_3), 22.7 ($CH_2CH_2CH_3$), 36.1 ($CH_2CH_2CH_3$), 41.4 (*C*-4), 59.7 (OCH_2CH_3), 99.0 (*C*-3), 105.4(*C*-5), 125.5 (2x*C*HAr), 126.4 (*C*HAr), 128.1 (2x*C*HAr), 128.6 (2x*C*HAr), 128.9 (*C*HAr), 129.2 (2x*C*HAr), 134.6, 136.4 (C-6*C*Ar, *C*-6), 149.4, 151.6 (C-4*C*Ar, *C*-2), 168.5 (*C*OOR); IR (NaCl) ν 3363, 2963, 2933, 2872, 1724, 1602, 1576, 1494, 1448, 1411, 1273, 1216, 1098, 698 cm^{-1}; elemental analysis calcd (%) for $C_{23}H_{25}NO_2$: C 79.51, H 7.25, N 4.03; found: C 79.21, H 6.93, N 3.94.

S-*tert*-butyl 2-methyl-4,6-diphenyl-1,4-dihydropyridine-3-carbothioate (3d)

Yellow solid, mp 158-160 °C; ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 1.44 (s, 9H, $SC(CH_3)_3$), 2.45 (s, 3H, C-2CH_3), 4.87 (d, *J* = 6 Hz, 1H, C-4*H*), 5.30 (dd, *J* = 1.9, 6 Hz, 1H, C-5*H*), 5.68 (bs, 1H, N*H*), 7.20-7.24 (m, 1H, Ar*H*), 7.31-7.40 (m, 9H, Ar*H*); ^{13}C-NMR ($CDCl_3$, 63 MHz) δ 21.7 (C-2CH_3), 30.5 ($SC(CH_3)_3$), 41.4 (*C*-4), 47.6 ($SC(CH_3)_3$), 105.6 (*C*-5), 108.0 (*C*-3), 125.5 (2x*C*HAr), 126.6 (*C*HAr), 127.9 (2x*C*HAr), 128.8 (2x*C*HAr), 129.0 (*C*HAr), 129.2 (2x*C*HAr), 134.5, 136.1 (C-6*C*Ar, *C*-6), 144.7, 147.9 (C-4*C*Ar, *C*-2), 193.1 (*C*OSR); IR (NaCl) ν 3050, 2884, 1630, 1564, 1470, 1376 cm^{-1}; elemental analysis calcd (%) for $C_{23}H_{25}NOS$: C 75.99, H 6.93, N 3.85, S 8.82; found: C 75.86, H 6.74, N 4.05, S 8.57.

1-(2-Methyl-4,6-diphenyl-1,4-dihydropyridin-3-yl)ethanone (3e)

Yellow solid, mp 153-155 °C; ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 2.07 (s, 3H, COC*H*$_3$), 2.48 (s, 3H, C-2C*H*$_3$), 4.74 (d, *J* = 5.6 Hz, 1H, C-4*H*), 5.30 (dd, *J* = 1.9, 5.6 Hz, 1H, C-5*H*), 5.70 (bs, 1H, N*H*), 7.19-7.25 (m, 1H, Ar*H*), 7.30-7.40 (m, 9H, Ar*H*); ^{13}C-NMR ($CDCl_3$, 63 MHz) δ 22.2 (C-2*C*H$_3$), 29.9 (CO*C*H$_3$), 42.5 (*C*-4), 106.3 (*C*-5), 107.8 (*C*-3), 125.4 (2x*C*HAr), 126.8 (*C*HAr), 127.7 (2x*C*HAr), 129.0 (*C*HAr), 129.17 (2x*C*HAr), 129.21 (2x*C*HAr), 134.1, 136.0 (C-6*C*Ar, *C*-6), 147.3, 148.3 (C-4*C*Ar, *C*-2), 199.2 (*C*OCH$_3$); IR (NaCl) ν 3022, 2962, 1637, 1574, 1474, 1289 cm^{-1}; elemental analysis calcd (%) for $C_{20}H_{19}NO$: C 83.01, H 6.62, N 4.84; found: C 82.83, H 6.45, N 4.98.

Ethyl 6-(4-chlorophenyl)-2-methyl-4-phenyl-1,4-dihydropyridine-3-carboxylate (3f)

Yellow solid, mp > 250 °C; ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 1.16 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 2.44 (s, 3H, C-2C*H*$_3$), 4.05 (dq, *J* = 1.6, 7.1 Hz, 2H, OC*H*$_2$CH$_3$), 4.71 (d, *J* = 5.5 Hz, 1H, C-4*H*), 5.19 (dd, *J* = 1.8, 5.5 Hz, 1H, C-5*H*), 5.52 (bs, 1H, N*H*), 7.16-7.22 (m, 1H, Ar*H*), 7.27-7.36 (m, 8H, Ar*H*); ^{13}C-NMR ($CDCl_3$, 63 MHz) δ 14.6 (OCH$_2$*C*H$_3$), 21.1 (C-2*C*H$_3$), 41.3 (*C*-4), 59.7 (O*C*H$_2$CH$_3$), 99.7 (*C*-3), 106.0 (*C*-5), 126.5 (*C*HAr), 126.8 (2x*C*HAr), 128.1 (2x*C*HAr), 128.7 (2x*C*HAr), 129.3 (2x*C*HAr), 133.7, 134.7, 134.8 (C-6*C*Ar, *C*-6, Ar*C*Cl), 147.0, 149.0 (C-4*C*Ar, *C*-2), 168.7 (*C*OOR); IR (NaCl) ν 2981, 2363, 1722, 1586, 1491, 1382 cm^{-1}; elemental analysis calcd (%) for $C_{21}H_{20}ClNO_2$: C 71.28, H 5.70, N 3.96; found: C 70.91, H 5.68, N 4.00.

Ethyl 4,6-bis(4-chlorophenyl)-2-methyl-1,4-dihydropyridine-3-carboxylate (3g)

Yellow solid, mp > 250 °C; ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 1.17 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 2.44 (s, 3H, C-2C*H*$_3$), 4.05 (q, *J* = 7.1 Hz, 2H, OC*H*$_2$CH$_3$), 4.69 (d, *J* = 5.5 Hz, 1H, C-4*H*), 5.15 (dd, *J* = 1.88, 5.5 Hz, 1H, C-5*H*), 5.57 (bs, 1H, N*H*), 7.26 (s, 4H, Ar*H*), 7.35 (s, 4H, Ar*H*); ^{13}C-NMR ($CDCl_3$, 63 MHz) δ 14.7 (OCH$_2$*C*H$_3$), 21.1 (C-2*C*H$_3$), 40.8 (*C*-4), 59.8 (O*C*H$_2$CH$_3$), 99.4 (*C*-3), 105.5 (*C*-5), 126.8 (2x*C*HAr), 128.8 (2x*C*HAr), 129.4 (2x*C*HAr), 129.5 (2x*C*HAr), 132.1, 134.0, 134.6, 134.8 (C-6*C*Ar, *C*-6, 2xAr*C*Cl), 147.3, 147.5 (C-4*C*Ar, *C*-2), 168.5 (*C*OOR); IR (NaCl) ν 3348, 2982, 1724, 1597, 1491, 1270, 1231, 1091, 1015, 757 cm^{-1}; elemental analysis calcd (%) for $C_{21}H_{19}Cl_2NO_2$: C 64.96, H 4.93, N 3.61; found: C 64.78, H 4.84, N 3.43.

Ethyl 4-(4-methoxyphenyl)-2-methyl-6-phenyl-1,4-dihydropyridine-3-carboxylate (3h)

Yellow solid, mp 220-222 °C; ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 1.20 (t, *J* = 7.12 Hz, 3H, OCH$_2$C*H*$_3$), 2.43 (s, 3H, C-2C*H*$_3$), 3.80 (s, 3H, OC*H*$_3$), 4.08 (q, *J* = 7.12 Hz, 2H, OC*H*$_2$CH$_3$), 4.67 (d, *J* = 5.5 Hz, 1H, C-4*H*), 5.21 (dd, *J* = 1.62, 5.5 Hz, 1H, C-5*H*), 5.60 (bs, 1H, N*H*), 6.84 (d, *J* = 8.7 Hz, 2H, C-4Ar-*H*3 and C-4Ar-*H*5), 7.27 (d, *J* = 8.7 Hz, 2H, C-4Ar-*H*2 and C-4Ar-*H*6), 7.35-7.46 (m, 5H, Ar*H*); ^{13}C-NMR ($CDCl_3$, 63 MHz) δ 14.7 (OCH$_2$*C*H$_3$), 21.1 (C-2*C*H$_3$), 40.3 (*C*-4), 55.6 (O*C*H$_3$), 59.7 (O*C*H$_2$CH$_3$), 99.8 (*C*-3), 105.6 (*C*-5), 114.0 (2x*C*HAr), 125.5 (2x*C*HAr), 128.9 (*C*HAr), 129.2 (4x*C*HAr), 134.6, 136.4 (C-6*C*Ar, *C*-6), 141.8, 146.9 (C-4*C*Ar, *C*-2), 158.3

(Ar*C*-OCH_3), 168.9 (*C*OOR); IR (NaCl) ν 3375, 2980, 2935, 1722, 1693, 1610, 1512, 1486, 1274, 1250, 1096, 1034, 760 cm^{-1}; elemental analysis calcd (%) for $C_{22}H_{23}NO_3$: C 75.62, H 6.63, N 4.01; found: C 75.42, H 6.48, N 4.00.

S-*tert*-butyl 4-(4-methoxyphenyl)-2-methyl-6-phenyl-1,4-dihydropyridine-3-carbothioate (3i)

Yellow solid, mp 138-140 °C; ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 1.56 (s, 9H, SC(CH_3)$_3$), 2.55 (s, 3H, C-2CH_3), 3.92 (s, 3H, OCH_3), 4.92 (d, *J* = 6.0 Hz, 1H, C-4*H*), 5.40 (dd, *J* = 1.6, 6.0 Hz, 1H, C-5*H*), 5.78 (bs, 1H, N*H*), 6.97 (d, *J* = 8.6 Hz, 2H, C-4Ar-*H*3 and C-4Ar-*H*5), 7.38 (d, *J* = 8.6 Hz, 2H, C-4Ar-*H*2 and C-4Ar-*H*6), 7.49-7.51 (m, 5H, Ar*H*); ^{13}C-NMR ($CDCl_3$, 63 MHz) δ 21.7 (C-2*C*H_3), 30.6 (SC(*C*H_3)$_3$), 40.5 (*C*-4), 47.6 (S*C*(CH_3)$_3$), 55.6(O*C*H_3), 105.8 (*C*-5), 108.4 (*C*-3), 114.1 (2x*C*HAr), 125.5 (2x*C*HAr), 128.88 (2x*C*HAr), 128.91 (*C*HAr), 129.2 (2x*C*HAr), 134.3, 136.1 (C-6*C*Ar, *C*-6), 140.5, 144.4 (C-4*C*Ar, *C*-2), 158.4 (Ar*C*-OCH_3), 193.2 (*C*OSR); IR (NaCl) ν 2960, 1534, 1506, 1472, 1382 cm^{-1}; elemental analysis calcd (%) for $C_{24}H_{27}NO_2S$: C 73.25, H 6.92, N 3.56, S 8.15; found: C 73.11, H 6.75, N 3.73, S 7.91.

Ethyl 6-(4-chlorophenyl)-4-(3-methoxyphenyl)-2-methyl-1,4-dihydropyridine-3-carboxylate (3j)

Yellow syrup; ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 1.17 (t, *J* = 7.12 Hz, 3H, OCH_2C*H*$_3$), 2.44 (s, 3H, C-2CH_3), 3.81 (s, 3H, OCH_3), 4.08 (q, *J* = 7.12 Hz, 2H, OCH_2CH_3), 4.69 (d, *J* = 5.5 Hz, 1H, C-4*H*), 5.19 (dd, *J* = 1.2, 5.5 Hz, 1H, C-5*H*), 5.54 (bs, 1H, N*H*), 6.72-6.77 (dd, *J* = 2.5, 8.1 Hz, 1H, C-4Ar*H*), 6.89-6.96 (m, 2H, C-4Ar*H*) 7.23 (t, *J* = 7.8 Hz, 1H, C-4Ar*H*), 7.35 (s, 4H, C-6Ar*H*); ^{13}C-NMR ($CDCl_3$, 63 MHz) δ 14.7 (OCH_2C*H*$_3$), 21.1 (C-2*C*H_3), 41.3 (*C*-4), 55.5 (O*C*H_3), 59.7 (O*C*H_2CH_3), 99.6 (*C*-3), 105.9 (*C*-5), 111.4 (*C*HAr), 114.2 (*C*HAr), 120.6 (*C*HAr), 126.8 (2x*C*HAr), 129.3(2x*C*HAr), 129.6 (*C*HAr), 133.8, 134.7, 134.8 (C-6*C*Ar, *C*-6, Ar*C*Cl), 147.1, 150.7 (C-4*C*Ar, *C*-2), 160.0 (Ar*C*-OCH_3), 168.6 (*C*OOR); IR (NaCl) ν 3356, 2980, 1724, 1676, 1596, 1486, 1286, 1266, 1224, 1093, 754 cm^{-1}; elemental analysis calcd (%) for $C_{22}H_{22}ClNO_3$: C 68.83, H 5.78, N 3.65; found: C 68.59, H 5.67, N 3.72.

S-*tert*-butyl 4-(4-bromophenyl)-2-methyl-6-(4-tolyl)-1,4-dihydropyridine-3-carbothioate (3k)

Light yellow solid, mp 164-166 °C; ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 1.56 (s, 9H, SC(CH_3)$_3$), 2.49 (s, 3H, CH_3), 2.55 (s, 3H, CH_3), 4.93 (d, *J* = 5.9 Hz, 1H, C-4*H*), 5.32 (dd, *J* = 1.6, 5.9 Hz, 1H, C-5*H*), 5.79 (bs, 1H, N*H*), 7.28-7.40 (m, 6H, Ar*H*), 7.54 (d, *J* = 8.3 Hz, 2H, Ar*H*); ^{13}C-NMR ($CDCl_3$, 63 MHz) δ 21.3 (*C*H_3), 21.4 (*C*H_3), 30.2 (SC(*C*H_3)$_3$), 40.6 (*C*-4), 47.4 (S*C*(CH_3)$_3$), 104.0 (*C*-5), 107.3 (*C*-3), 120.0 (Ar*C*Br), 125.1 (2x*C*HAr), 129.3 (2x*C*HAr), 129.6 (2x*C*HAr), 131.5 (2x*C*HAr), 132.7, 134.4, 138.8 (C-6*C*Ar, *C*-6, Ar*C*CH_3), 144.7, 146.8 (C-4*C*Ar, *C*-2), 192.5 (*C*OSR); IR (NaCl) ν 3299, 2892, 1612, 1553, 1470, 1387, 1159 cm^{-1}; elemental analysis calcd (%) for $C_{24}H_{26}BrNOS$: C 63.15, H 5.74, N 3.07, S 7.03; found: C 62.98, H 5.78, N 3.36, S 6.99.

S-*tert*-butyl 2-methyl-6-phenyl-4-(4-tolyl)-1,4-dihydropyridine-3-carbothioate (3l)

Yellow solid, mp 172-174 °C; ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 1.45 (s, 9H, SC(CH_3)$_3$), 2.34 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 4.82 (d, *J* = 6.1 Hz, 1H, C-4*H*), 5.31 (dd, *J* = 1.8, 6.1 Hz, 1H, C-5*H*), 5.68 (bs, 1H, N*H*), 7.12 (d, *J* = 8.0 Hz, 2H, C-4Ar*H*), 7.25 (d, *J* = 8.0 Hz, 2H, C-4Ar*H*), 7.33-7.39 (m, 5H C-6Ar*H*); ^{13}C-NMR ($CDCl_3$, 63 MHz) δ 21.5 (*C*H_3), 21.7 (*C*H_3), 30.6 (SC(*C*H_3)$_3$), 40.9 (*C*-4), 47.6 (S*C*(CH$_3$)$_3$), 105.8 (*C*-5), 108.1 (*C*-3), 125.5 (2x*C*HAr), 127.7 (2x*C*HAr), 128.9 (*C*HAr), 129.2 (2x*C*HAr), 129.5 (2x*C*HAr), 134.4, 136.07, 136.10 (C-6*C*Ar, *C*-6, Ar*C*CH$_3$), 144.7 ,145.1 (C-4*C*Ar, *C*-2), 193.1 (*C*OSR); IR (NaCl) ν 3279, 2968, 1612, 1559, 1474, 1379 cm^{-1}; elemental analysis calcd (%) for $C_{24}H_{27}NOS$: C 76.35, H 7.21, N 3.71, S 8.49; found: C 75.92, H 7.10, N 4.01, S 8.11.

S-*tert*-butyl 2-methyl-4,6-di(4-tolyl)-1,4-dihydropyridine-3-carbothioate (3m)

Yellow solid, mp 169-171 °C; ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 1.46 (s, 9H, SC(CH_3)$_3$), 2.35 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 4.82 (d, *J* = 6.1 Hz, 1H, C-4*H*), 5.27 (dd, *J* = 1.7, 6.1 Hz, 1H, C-5*H*), 5.67 (bs, 1H, N*H*), 7.04-7.38 (m, 8H, Ar*H*); ^{13}C-NMR ($CDCl_3$, 63 MHz) δ 21.5 (*C*H_3), 21.6 (*C*H_3), 21.7 (*C*H_3), 30.6 (SC(*C*H_3)$_3$), 40.8 (*C*-4), 47.5 (S*C*(CH$_3$)$_3$), 105.1 (*C*-5), 108.1 (*C*-3), 125.4 (2x*C*HAr), 127.7 (2x*C*HAr), 129.5 (2x*C*HAr), 129.8 (2x*C*HAr), 133.2, 134.3, 136.0, 138.8 (C-6*C*Ar, *C*-6, 2xAr*C*CH$_3$), 144.8, 145.2 (C-4*C*Ar, *C*-2), 193.1 (*C*OSR); IR (NaCl) ν 2959, 2851, 1614, 1550, 1470, 1378 cm^{-1}; elemental analysis calcd (%) for $C_{25}H_{29}NOS$: C 76.68, H 7.46, N 3.58, S 8.19; found: C 76.57, H 7.36, N 3.79, S 8.13.

Ethyl 2-methyl-6-phenyl-4-(4-tolyl)-1,4-dihydropyridine-3-carboxylate (3n)

Yellow solid, mp 233-235 °C; ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 1.31 (t, *J* = 7.1 HZ, 3H, OCH$_2$CH_3), 2.45 (S, 3H, CH_3), 2.55 (s, 3H, CH_3), 4.19 (q, *J* = 7.1 Hz, 2H, OCH_2CH$_3$), 4.81 (d, *J* = 5.5 Hz, 1H, C-4*H*), 5.34 (dd, *J* = 1.9-5.5 Hz, 1H, C-5*H*), 5.75 (bs, 1H, N*H*), 7.24 (d, *J* = 8.0 Hz, 2H, C-4Ar*H*), 7.38 (d, *J* =8.0 Hz, 2H, C-4Ar*H*), 7.45-7.57 (m, 5H, Ar*H*); ^{13}C-NMR ($CDCl_3$, 63 MHz) δ 14.7 (OCH$_2$*C*H$_3$), 21.1 (*C*H$_3$), 21.5 (*C*H$_3$), 40.8 (*C*-4), 59.7 (O*C*H$_2$CH$_3$), 99.7 (*C*-3), 105.6 (*C*-5), 125.5 (2x*C*HAr), 128.1 (2x*C*HAr), 128.8 (*C*HAr), 129.2 (2x*C*HAr), 129.3 (2x*C*HAr), 134.6, 135.9, 136.4 (C-6*C*Ar, *C*-6, Ar*C*CH$_3$), 146.4, 147.0 (C-4*C*Ar, *C*-2), 168.8 (*C*OOR); IR (NaCl) ν 2363, 2341, 1670, 1594, 1488, 1219 cm^{-1}; elemental analysis calcd (%) for $C_{22}H_{23}NO_2$: C 79.25, H 6.95, N 4.20; found: C 79.01, H 6.89, N 4.14.

Allyl 6-(4-chlorophenyl)-2-methyl-4-phenyl-1,4-dihydropyridine-3-carboxylate (3o)

Orange syrup; ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 2.45 (s, 3H, C-2CH_3), 4.52 (dd, *J* = 0.85, 5.3 Hz 2H, OCH_2CH=CH$_2$), 4.74 (d, *J* = 5.58 Hz, 1H, C-4*H*), 5.10-5.23 (m, 3H, C-5*H*, OCH$_2$CH=CH_2), 5.60 (bs, 1H, N*H*) 5.76-5.93 (m, 1H, OCH$_2$C*H*=CH$_2$), 7.17-7.24 (m, 1H, Ar*H*), 7.28-7.38 (m, 8H, Ar*H*); ^{13}C-NMR ($CDCl_3$, 63 MHz) δ 18.8 (C-2*C*H$_3$), 38.8 (*C*-4), 62.1 (O*C*H$_2$CH=CH$_2$), 96.8 (*C*-3), 103.7 (*C*-5), 115.0 (OCH$_2$CH=*C*H$_2$), 124.2 (*C*HAr), 124.4 (2x*C*HAr), 125.6 (2x*C*HAr), 126.3

(2x*C*HAr), 130.9 ($OCH_2CH=CH_2$), 131.2, 132.2, 132.3 (C-6*C*Ar, *C*-6, Ar*C*Cl), 145.2, 146.4 (C-4*C*Ar, *C*-2), 165.8 (*C*OOR); IR (NaCl) ν 3342, 2926, 1678, 1606, 1484, 1221, 1095 cm^{-1}; elemental analysis calcd (%) for $C_{22}H_{20}ClNO_2$: C 72.22, H 5.51, N 3.83; found: C 71.97, H 5.43, N 4.00.

Ethyl 2-methyl-4-(4-nitrophenyl)-6-phenyl-1,4-dihydropyridine-3-carboxylate (3p)

Orange solid, mp 108-110 °C; ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 1.17 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3), 2.48 (s, 3H, C-2CH_3), 4.07 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 4.86 (d, *J* = 5.5 Hz, 1H C-4*H*), 5.14 (dd, *J* = 1.88, 5.5 Hz, 1H, C-5*H*), 5.75 (bs, 1H, N*H*), 7.38-7.44 (m, 5H, Ar*H*), 7.51 (d, *J* = 8.75 Hz, 2H, C-4Ar*H*), 8.18 (d, *J* = 8.75 Hz, 2H, C-4Ar*H*); ^{13}C-NMR ($CDCl_3$, 63 MHz) δ 14.7 (OCH_2CH_3), 21.2 (C-2CH_3), 41.7 (*C*-4), 60.0 (OCH_2CH_3), 98.4 (*C*-3), 103.9 (*C*-5), 124.1 (2x*C*HAr), 125.5 (2x*C*HAr), 128.8 (2x*C*HAr), 129.4 (3x*C*HAr), 135.7, 135.8 (C-6*C*Ar, *C*-6), 146.7, 148.1, 156.4 (C-4*C*Ar, *C*-2, Ar*C*NO_2), 168.2 (*C*OOR); IR (NaCl) ν 3386, 2978, 1723, 1602, 1518, 1486, 1346 cm^{-1}; elemental analysis calcd (%) for $C_{21}H_{20}N_2O_4$: C 69.22, H 5.53, N 7.69; found: C 69.41, H 5.27, N 7.50.

Ethyl 2-methyl-4-(2-nitrophenyl)-6-(4-tolyl)-1,4-dihydropyridine-3-carboxylate (3q)

Yellow syrup; ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 0.98 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3), 2.38 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 3.92 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 5.21 (d, *J* = 5.05 Hz, 1H, C-4*H*), 5.38 (dd, *J* = 1.8, 5.05 Hz, 1H, C-5*H*), 5.67 (bs, 1H, N*H*), 7.19 (d, *J* = 7.95 Hz, 2H, C-6Ar*H*), 7.25-7.33 (m, 3H, Ar*H*), 7.55 (dt, *J* = 1.0, 7.42 Hz, 1H, C-4Ar*H*), 7.66 (dd, *J* = 1.22, 7.87 Hz, 1H, C-4Ar*H*), 7.74 (dd, *J* = 1.0, 8.08 Hz, 1H, C-4Ar*H*); ^{13}C-NMR ($CDCl_3$, 63 MHz) δ 14.3 (OCH_2CH_3), 20.8 (CH_3), 21.6 (CH_3), 31.1 (*C*-4), 59.7 (OCH_2CH_3), 98.5 (*C*-3), 103.6 (*C*-5), 123.5 (*C*HAr), 125.3 (2x*C*HAr), 126.7 (*C*HAr), 129.9 (2x*C*HAr), 131.9 (*C*HAr), 133.0, 133.5, 135.1 (C-6*C*Ar, *C*HAr, *C*-6), 144.1, 148.2, 148.9 (C-4*C*Ar, *C*-2, Ar*C*NO_2), 168.0 (*C*OOR); IR (NaCl) ν 3332, 2976, 1674, 1608, 1524, 1486, 1355, 1221, 1084, 750 cm^{-1}; elemental analysis calcd (%) for $C_{22}H_{22}N_2O_4$: C 69.83, H 5.86, N 7.40; found: C 69.86, H 5.69, N 7.64.

Ethyl 6-(4-chlorophenyl)-2-methyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3-carboxylate (3r)

Yellow syrup; ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 0.97 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3), 2.49 (s, 3H, C-2CH_3), 3.91 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 5.21 (d, *J* = 5.1 Hz, 1H, C-4*H*), 5.40 (dd, *J* = 1.7, 5.1 Hz, 1H, C-5*H*), 5.57 (bs, 1H, N*H*), 7.27-7.34 (m, 1H, Ar*H*), 7.36 (s, 4H, Ar*H*), 7.53-7.66 (m, 2H, Ar*H*), 7.76 (dd, *J* = 1, 8.2 Hz, 1H, C-4Ar*H*); ^{13}C-NMR ($CDCl_3$, 63 MHz) δ 14.3 (OCH_2CH_3), 20.8 (C-2CH_3), 37.2 (*C*-4), 59.8 (OCH_2CH_3), 98.7 (*C*-3), 104.7 (*C*-5), 123.6 (*C*HAr), 126.8 (2x*C*HAr), 127.1 (*C*HAr), 129.4 (2x*C*HAr), 131.8 (*C*HAr), 133.6 (*C*HAr), 134.3, 134.4, 135.0 (C-6*C*Ar, *C*-6, Ar*C*Cl), 143.7, 148.2, 148.7 (C-4*C*Ar, *C*-2, Ar*C*NO_2), 167.8 (*C*OOR); IR (NaCl) ν 3188, 1721, 1651, 1610, 1528, 1482, 1439, 1269, 1094, 826, 747 cm^{-1}; elemental analysis calcd (%) for $C_{21}H_{19}ClN_2O_4$: C 69.22, H 5.53, N 7.69; found: C 69.11, H 5.37, N 7.66.

Ethyl 2-methyl-4-(thiophen-2-yl)-6-(4-tolyl)-1,4-dihydropyridine-3-carboxylate (3s)

Orange syrup; ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 1.30 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3), 2.40 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 4.18 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 5.04 (d, *J* = 5.8 Hz, 1H, C-4*H*), 5.28 (dd, *J* = 1.8, 5.8 Hz, 1H, C-5*H*), 5.76 (bs, 1H, N*H*), 6.92-6.95 (m, 2H, thienyl*H*), 7.14 (dd, *J* = 1.6, 4.7 Hz, 1H, thienyl*H*), 7.22 (d, *J* = 8.0 Hz, 2H, C-4Ar*H*), 7.36 (d, *J* = 8.0 Hz, 2H, C-4Ar*H*); ^{13}C-NMR ($CDCl_3$, 63 MHz) δ 14.8 (OCH_2CH_3), 21.2 (CH_3), 21.6 (CH_3), 35.5 (*C*-4), 59.9 (OCH_2CH_3), 99.6, 103.3 (*C*-3, *C*-5), 123.3 (*C*H-thienyl), 123.9 (*C*H-thienyl), 125.6 (2x*C*HAr), 127.0 (*C*H-thienyl), 129.9 (2x*C*HAr), 133.3, 135.7, 139.1 (C-6*C*Ar, *C*-6, Ar*C*CH_3), 147.1, 153.9 (*C*-thienyl, *C*-2), 168.5 (*C*OOR); IR (NaCl) ν 2978, 1718, 1670, 1584, 1475, 1383 cm^{-1}; elemental analysis calcd (%) for $C_{20}H_{21}NO_2S$: C 70.77, H 6.24, N 4.13, S 9.45; found: C 70.76, H 6.06, N 4.25, S 9.46.

Ethyl 6-(furan-2-yl)-2-methyl-4-(4-tolyl)-1,4-dihydropyridine-3-carboxylate (3t)

Yellow syrup; ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 1.18 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3), 2.32 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 4.05 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 4.64 (d, *J* = 5.65 Hz, 1H, C-4*H*), 5.37 (dd, *J* = 1.58, 5.65 Hz, 1H, C-5*H*), 5.90 (bs, 1H, N*H*), 6.40-6.44 (m, 2H, furanyl*H*), 7.10 (d, *J* = 8.02 Hz, 2H, C-4Ar*H*), 7.23 (d, *J* = 8.02 Hz, 2H, C-4Ar*H*), 7.39-7.40 (m, 1H, furanyl*H*); ^{13}C-NMR ($CDCl_3$, 63 MHz) δ 14.7 (OCH_2CH_3), 21.1 (CH_3), 21.5 (CH_3), 40.1 (*C*-4), 59.7 (OCH_2CH_3), 99.7, 103.4 (*C*-3, *C*-5), 105.1 (*C*H-furanyl), 112.0 (*C*H-furanyl), 126.3 (*C*-6), 128.1 (2x*C*HAr), 129.4 (2x*C*HAr), 136.0 (Ar*C*CH_3), 141.9 (*C*H-furanyl), 146.0, 146.6, 149.1 (C-4*C*Ar, *C*-2, *C*-furanyl), 168.7 (*C*OOR); IR (NaCl) ν 3348, 2980, 1724, 1662, 1604, 1268, 1096, 751 cm^{-1}; elemental analysis calcd (%) for $C_{20}H_{21}NO_3$: C 74.28, H 6.55, N 4.33; found: C 73.99, H 6.37, N 4.22.

S-*tert*-butyl 2-methyl-6-phenyl-4-(1-phenylprop-1-en-2-yl)-1,4-dihydropyridine-3-carbothioate (3u)

Yellow solid, mp 113-115 °C; ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 1.5 (s, 9H, $SC(CH_3)_3$), 1.95 (d, *J* = 1.3 Hz, 3H, $CH=CCH_3$), 2.39 (s, 3H, C-2CH_3) 4.41 (d, *J* = 5.8 Hz, 1H, C-4*H*), 5.19 (dd, *J* = 1.9, 5.8 Hz, 1H, C-5*H*), 5.55 (bs, 1H, N*H*), 6.40 (s, 1H, $CH=CCH_3$), 7.20-7.24 (m, 1H, Ar*H*), 7.27-7.45 (m, 9H, Ar*H*); ^{13}C-NMR ($CDCl_3$, 63 MHz) δ 15.7 ($CH=CCH_3$), 21.3 (C-2CH_3), 30.6 ($SC(CH_3)_3$), 45.7 (*C*-4), 47.4 ($SC(CH_3)_3$), 103.8 (*C*-5), 106.9 (*C*-3), 125.5 (2x*C*HAr), 125.7 (*C*H=CCH_3), 126.2 (*C*HAr), 128.3 (2x*C*HAr), 129.0 (*C*HAr), 129.2 (2x*C*HAr), 129.4 (2x*C*HAr), 135.8, 136.3, 139.2, 142.6, 144.7 (C-6*C*Ar, *C*-6, CH=*C*CH_3, C=CH*C*Ar, *C*-2), 193.7 (*C*OSR); IR (NaCl) ν 3405, 3357, 2343, 1633, 1470, 1373, 1174, 1154 cm^{-1}; elemental analysis calcd (%) for $C_{26}H_{29}NOS$: C 77.38, H 7.24, N 3.47, S 7.95; found: C 77.21, H 7.04, N 3.61, S 7.85.

2,4-Diphenyl-4,6,7,8-tetrahydroquinolin-5(1*H*)-one (5a)

White solid, mp 208-210 °C; ^{1}H-NMR (DMSO-d_6, 250 MHz) δ 1.75-1.99 (m, 2H, C-7*H*), 2.19-2.26 (m, 2H, C-8*H*), 2.55-2.71 (m, 2H, C-6*H*), 4.61 (d, *J* = 5.4 Hz, 1H, C-4*H*), 5.24 (dd, *J* = 1.6, 5.4 Hz, 1H, C-3*H*), 7.08-7.51 (m, 10H, Ar*H*), 8.71 (bs, 1H, N*H*); ^{13}C-NMR (DMSO-d_6, 63 MHz) δ 21.3 (*C*-7), 27.2 (*C*-8), 37.24 (*C*-4), 37.28 (*C*-6), 106.2 (*C*-3), 107.4 (*C*-4a), 125.91 (2x*C*HAr), 125.96 (*C*HAr), 127.7 (2x*C*HAr), 128.5 (2x*C*HAr), 128.7 (*C*HAr), 128.8 (2x*C*HAr), 134.8, 135.5 (C-2*C*Ar, *C*-2), 148.6, 154.6 (C-4*C*Ar, *C*-8a), 194.7 (*C*=O); IR (NaCl) ν 3213, 3167, 1584, 1487, 1389, 1329 cm^{-1}; elemental analysis calcd (%) for $C_{21}H_{19}NO$: C 83.69 H 6.35, N 4.65; found: C 83.45, H 6.01, N 4.51.

7,7-Dimethyl-2,4-diphenyl-4,6,7,8-tetrahydroquinolin-5(1*H*)-one (5b)

Pale yellow solid, mp 204-206 °C; ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 1.05 (s, 3H, C*H*$_3$), 1.14 (s, 3H, C*H*$_3$), 2.16-2.47 (m, 4H, C-6*H*, C-8*H*), 4.78 (d, *J* = 5.2 Hz, 1H, C-4*H*), 5.33 (dd, *J* = 1.78, 5.2 Hz, 1H, C-3*H*), 5.98 (bs, 1H, N*H*), 7.14-7.45 (m, 10H, Ar*H*); ^{13}C-NMR ($CDCl_3$, 63 MHz) δ 27.8 (*C*H$_3$), 29.8 (*C*H$_3$), 32.9 (*C*-7), 38.1 (*C*-4), 42.5 (*C*-8), 51.1 (*C*-6), 107.5 (*C*-3), 108.9 (*C*-4a), 125.5 (2x*C*HAr), 126.5 (*C*HAr), 128.3 (2x*C*HAr), 128.7 (2x*C*HAr), 129.3 (2x*C*HAr), 129.9 (*C*HAr), 134.4, 136.2 (C-2*C*Ar, *C*-2), 148.0, 151.1 (C-4*C*Ar, *C*-8a), 196.0 (*C*=O); IR (NaCl) ν 2954, 1587, 1487, 1386, 1328, 1240, 755 cm^{-1}; elemental analysis calcd (%) for $C_{23}H_{23}NO$: C 83.85; H 7.04; N 4.25; found: C 83.90, H 7.07, N 4.34.

1.2. PHARMACOLOGY

SH-SY5Y neuroblastoma cells culture

SH-SY5Y cells were cultured following supplier instructions in a 1:1 mixture of F12 (Ham 12) and Eagle's MEM supplemented with 15 non-essential amino-acids, 10 % heat-inactivated foetal bovine serum (FBS), 1mM sodium pyruvate, 100 μg/mL streptomycin and 100 units/mL penicillin. Cells were kept at 37 ºC in humidified atmosphere of 95 % air and 5 % CO_2. For experimental procedures, cells were cultured in 48-well plates at density of $1x10^5$ cells/well. Treatments were performed in 1% FBS medium unless other concentration is stated. Cells were used up to 13 passages.

Ca^{2+} signal measurements

Neuroblastoma cells were cultured in bottom-transparent black 96 well plates at density of $5x10^4$ cells/well. After 2 days in culture, cells were loaded with 10 μM Fluo-4/AM for 1 h at 37 ºC in culture media without FBS. After loading period, cells were washed twice with Krebs-HEPES solution and kept at room temperature for 15 min before starting the experiment. Compounds at desired concentration were incubated for 15 min before injecting the stimulus (70 mM KCl). Fluorescence intensity was measured for 12 s at 485 and 520 nm wavelengths of excitation and emission, respectively, in a microplate reader (FLUOstar Optima, BMG, Offenburg, Germany). Once the experiment was finish, 50 μL of Triton (5 %) was added to measure maximum fluorescence (F_{max}), followed by 50 μL of $MnCl_2$ to obtain the minimum fluorescence (F_{min}). Potassium evoked responses were expressed as % of fluorescence at each time point (F) minus minimum fluorescence values, divided by F_{max}-F_{min}. The maximum value of F_{520} obtained for each well was considered as the peak F_{520} value.

Neuroprotection against Ca^{2+} overload induced by high $[K^+]$

Drugs stock solutions were prepared in DMSO at 10^{-2} M concentration and kept at -20 ºC. Compounds were diluted with neuroblastoma cells culture media to the desired concentration (5 μM) and cells were co-incubated for 24 h with the toxic stimulus. Control group was treated with the same amount of DMSO without any drug.

Neuroprotection against oxidative stress induced by rotenone – oligomycin A cocktail

Co-incubation protocol: Compounds were diluted from stock solutions with neuroblastoma cells culture media (1% FBS) containing the rotenone-oligomycin A mixture (30 μM / 10 μM respectively) to the desired concentration (5 μM). Then, cells were co-incubated for 24 h with each treatment and toxic stimulus rot/olig. Control cells were treated with the same concentration

of DMSO without any drug. Melatonin (0.3 μM) and nifedipine (5 μM) were used as positive and reference controls, respectively.

Post-incubation protocol: Cells were cultured for 24 h, culture media was replaced by media containing toxic stimulus cocktail (rot/olig 30/10 μM), and cells were incubated for 8 h at 37 ºC. Thereafter, compounds were diluted from stock solutions with neuroblastoma cells culture media (1% FBS) to the desired concentration (5 μM). Then, cells were incubated for 16 h with each treatment and without toxic stimulus. Control cells were treated with the same concentration of DMSO without any drug. Melatonin and nifedipine were used as positive and reference controls, respectively.

Animal usage and hippocampal slice preparation

The experiments were performed after experimental protocols approval by the institutional Ethic Committee of the Universidad Autónoma de Madrid, Spain according to the European Guideline for the use and care of animals for research. All efforts were made to minimize animal suffering and to reduce the number of animals used in the experiments.

Experiments were completed in hippocampal slices form adult male Sprague-Dawley rats (275-325 gr). Hippocampal slice preparation protocol was similar to that used by Egea *et al.*[1] with slight modifications. After quick decapitation of rats (pentobarbital anesthesia, 60 mg/Kg i.p.) forebrains were rapidly removed and kept in ice-cold Krebs bicarbonate dissection buffer (pH 7.4) (in mM); KCl: 2; NaCl: 120; $CaCl_2$: 0.5; $NaHCO_3$: 26; $MgSO_4$: 10; KH_2PO_4: 1.18; glucose: 11; sucrose: 200. Then, dissected hippocampi were quickly glued down leaning vertically against agar blocks in small chamber, submerged in cold, oxygenated dissection buffer and sectioned in transverse slices of 200 μM thick using a vibratome (Leica, Hidelberg, Germany).

Neuroprotection against oxidative stress induced by oxygen and glucose deprivation (OGD) in hippocampal slices

We have used the same protocol previously described.[1] Solutions were pre-bubbled with either 95 % O_2/ 5 % CO_2 or 95 % N_2 / 5 % CO_2 gas mixtures, for 45 min before slice immersion to ensure O_2 or N_2 saturation. After a stabilization period of 30 min, hippocampal slices of the control group were incubated 15 min in Krebs solution equilibrated with 95 % O_2/ 5 % CO_2 at 37 ºC. OGD was achived by incubating the hippocampal slices in a glucose-free Krebs solution equilibrated with 95 % N_2/ 5 % CO_2 at 37 ºC over 15 min. Glucose was replaced by 2-

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[1] Egea, J.; Rosa, A. O.; Sobrado, M.; Gandía, L.; López, M. G.; García, A. G. *Neuroscience* **2007**, *145*, 866.

deoxyglucose. After 15 min OGD period, slices were re-incubated in oxygenated normal Krebs solution for 60 min (re-oxygenation period) at 37 ºC.

Viability quantification by MTT-reduction in SH-SY5Y neuroblastoma cells and hippocampal slices

Cell viability was measured by MTT-reduction, which measures the mitochondrial activity of living cells, by quantitative colorimetric assay.[2] Briefly, MTT was added to each well at the final concentration of 5 mg/mL and incubated at 37 ºC in the dark for 2 h. Then, culture media is eliminated and the precipitate was dissolved by adding 300 μL/well (48 well plate) of DMSO. Then, 100 μL of the resulting colored solution from each well are transferred to a transparent 96 well plate and optical density was measured in a ELISA reader at 540 nm. Control cells (DMSO) treated were taken as 100 % viability.

Hippocampal cell viability was determined using the same colorimetric probe. Hippocampal slices were immediately transferred to a 96 well plate after re-oxygenation and incubated with MTT at the final concentration of 0.5 mg/mL in Krebs bicarbonate solution for 30 min at 37 ºC. Finally, the precipitated was dissolved with 200 μL DMSO and optical density was measured. Absorbance of control slices was taken as 100 % viability.

[2] Denizot, F.; Lang, R. *J. Immunol. Methods* **1986**, *89*, 271.

Vascular reactivity

Third order branches of mesenteric artery from 6-month-old Wistar Kyoto rats (2 mm length) were mounted in a small-vessel dual chamber myograph to monitor isometric tension. Two steel wires (40 μm diameter) were introduced through the lumen of the segments and mounted as previously described.[3] After a 30 min equilibration period in oxygenated Krebs Henseleit solution (KHS) at 37 ºC (pH 7.4), segments were stretched to their optimal lumen diameter for active tension development.[3] Then, segments were washed with KHS and equilibrated for 30 min. Contractility of segments was then tested by an initial exposure to a high-K^+ solution (120 mM KCl-KHS). The presence of endothelium was determined by the ability of 10 μM acetylcholine to induce relaxation in arteries pre-contracted with phenylephrine at a concentration that produce approximately 50% of the contraction induced by KCl-KHS. In different segments, concentration response curves (0.01-nM-0.1 μM) to nifedipine, **3n**, **3u** and **5b** were performed in arteries pre-contracted with a 70 mM KCl-KHS solution.

Statistical analysis

All values are expressed as mean ± S.E.M. "n" represents the number of different cultures or animals used. The IC_{50} or EC_{50} values were calculated by non-linear regression analysis of each individual concentration-response curve using GraphPad Prism software (San Diego, CA, USA). Results were analyzed using comparisons between experimental and control groups performed by One-way ANOVA followed by Newman-Keuls *post-hoc* test. Differences were considered to be statistically significant when $p \leq 0.05$.

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[3] Mulvany, M. J.; Halpern, W. *Circ. Res.* **1977**, *41*, 19.

1.3. DOCKING CALCULATIONS

The crystal structure of the $Ca_V1.2$ L-subtype CCVD has not been described, and therefore for molecular modeling studies we used the $Ca_V1.2$ L-subtype CCVD model developed by D. Tikhonov and B. S. Zhorov and kindly shared with us by Prof. Zhorov.[4] Docking was performed with the program Molegro Virtual Docker[5] using the molecular docking algorithm Moldock score. Prior to docking, the structure of the nifedipine and **S-36** was built and energy minimized using Gaussian software.[6] Calculations were run in an iMac with a 3.4 GHz-i7 processor and 16 GB DDR3. Ligand binding cavities were identified using the Molegro expanded Van der Waals molecular surface prediction algorithm with a grid resolution of 0.5 Å. A total of 100 docking runs with a population size of 100 were calculated over a 16 Å radius surrounding the predicted DHP binding site cavity with a grid resolution of 0.3, and a maximum of 15,000 iterations per position, a scaling factor of 0.50, crossover rate of 0.90 using the Moldock Score algorithm. Moldock optimizer function was used to more precisely optimize H-Bonds geometries by calculating the position of the hydrogen atoms for any hydrogen donors (both in the ligand and in the proteins). Similar positions were clustered using a root mean squared deviation (r.m.s.d.) of 1.5 Å. Pre-positioned ligands were randomized in the predicted cavity prior to each docking run, and docking was constrained to the predicted DHPs binding site cavity. In order to verify that positions resulting from *in silico* docking represent correctly bound conformations, each position was visually inspected and compared. Positions were also inspected and compared with the rerank score algorithm, protein interaction, hydrogen bonding, and affinity interaction energies and ordered by the energy of interaction protein-ligand. Complexes were optimized using Moloc software[7] (www.moloc.ch) with standard force field and optimization parameters. During energy minimization, the position of amino acid side chains were fixed while allowing all ligand atoms to move. Final images were generated with MacPymol software v 1.6.

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[4] Tikhonov, D. B.; Zhorov, B. S. *J. Biol. Chem.* **2009**, *284*, 19006.

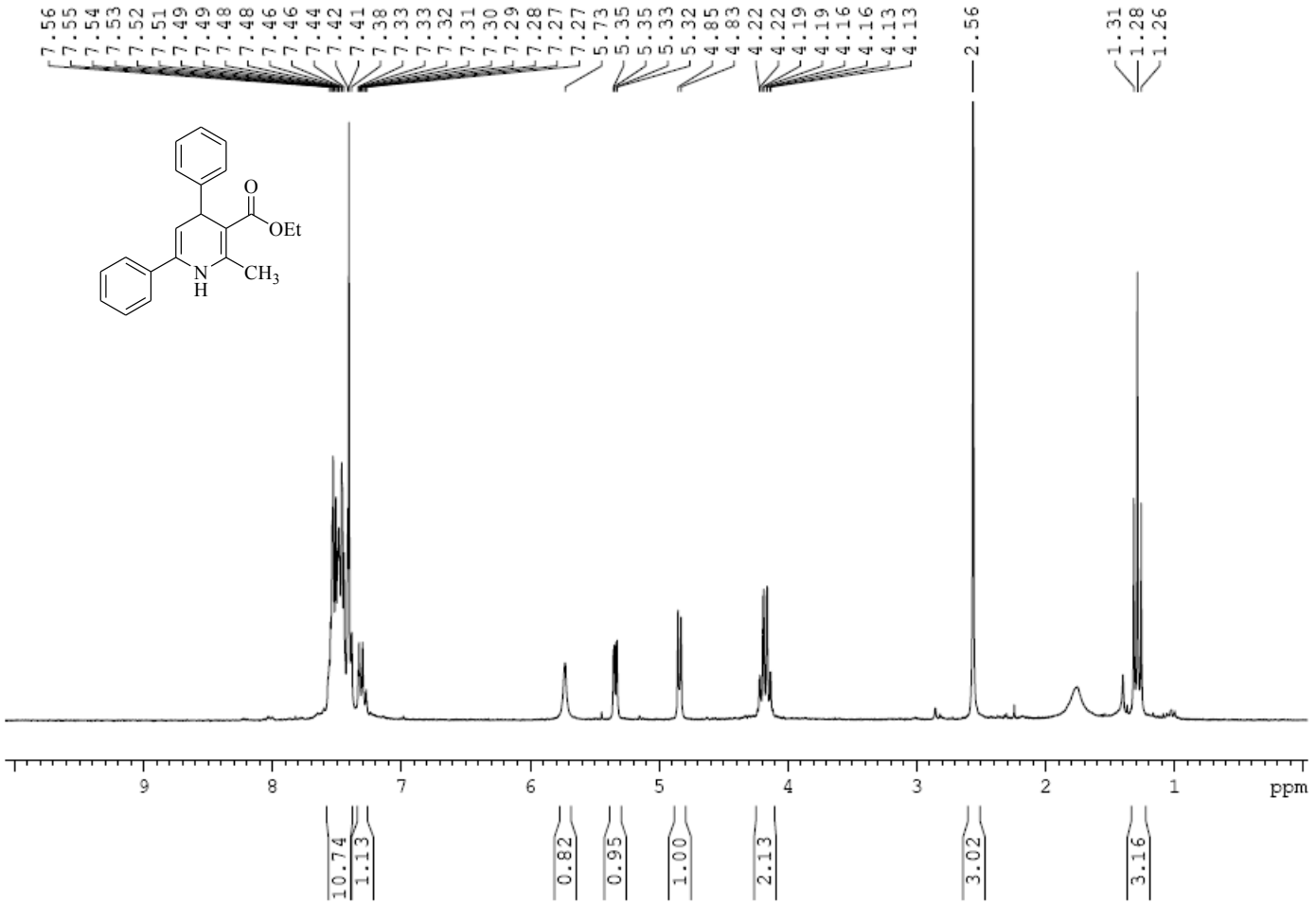
[5] Thomsen, R.; Christensen, M. H. *J. Med. Chem.* **2006**, *49*, 3315.

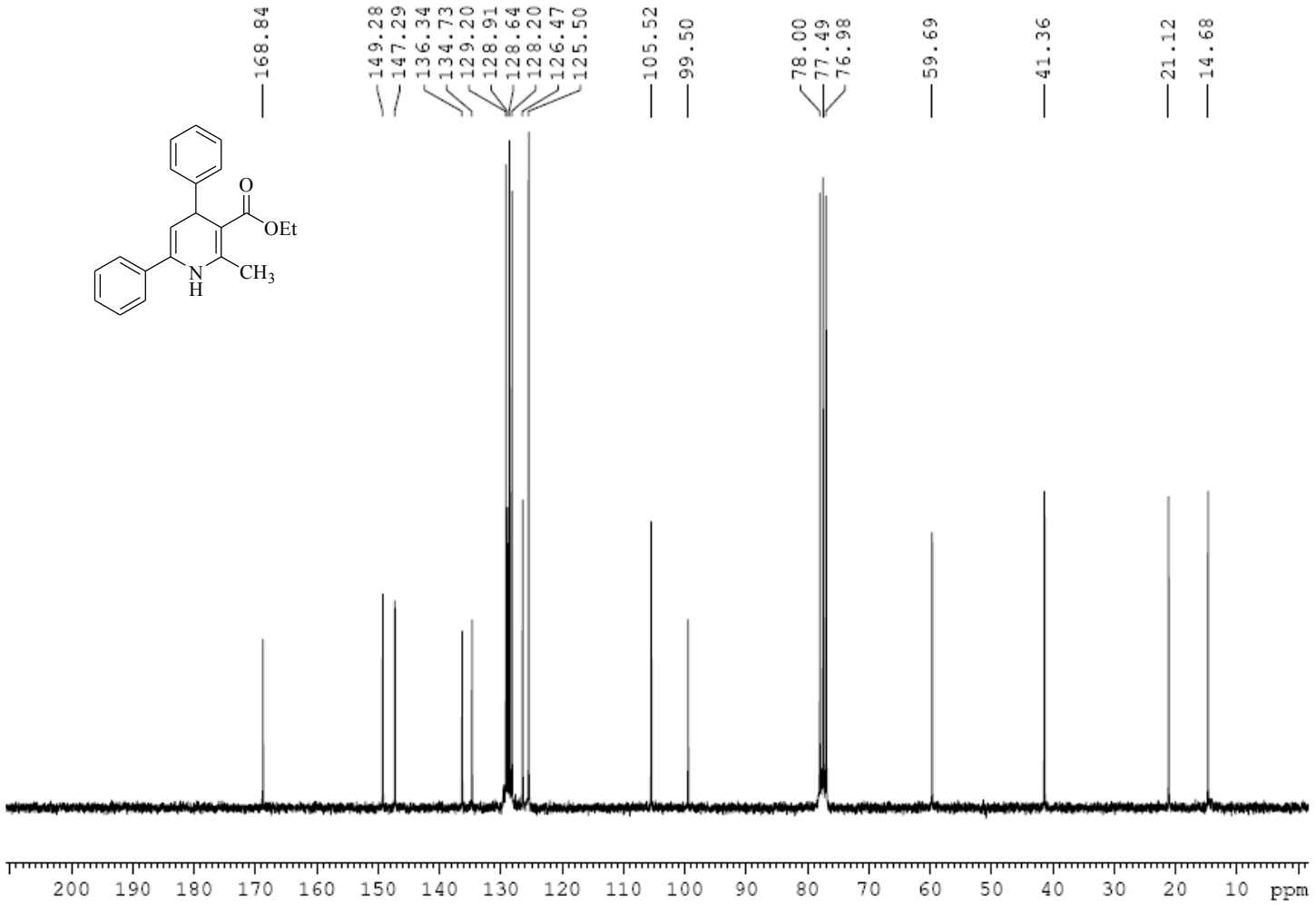
[6] Frisch, M. J. *et. al. Gaussian 03 (Revision B.04)*; Gaussian, Inc: Pittsbusrg, 2003.

[7] Gerber, P. R.; Müller, K. *J. Comput. Aided Mol. Design* **1995**, *9*, 251-268

2. COPIES OF SPECTRA

Ethyl 2-methyl-4,6-diphenyl-1,4-dihydropyridine-3-carboxylate (3a)

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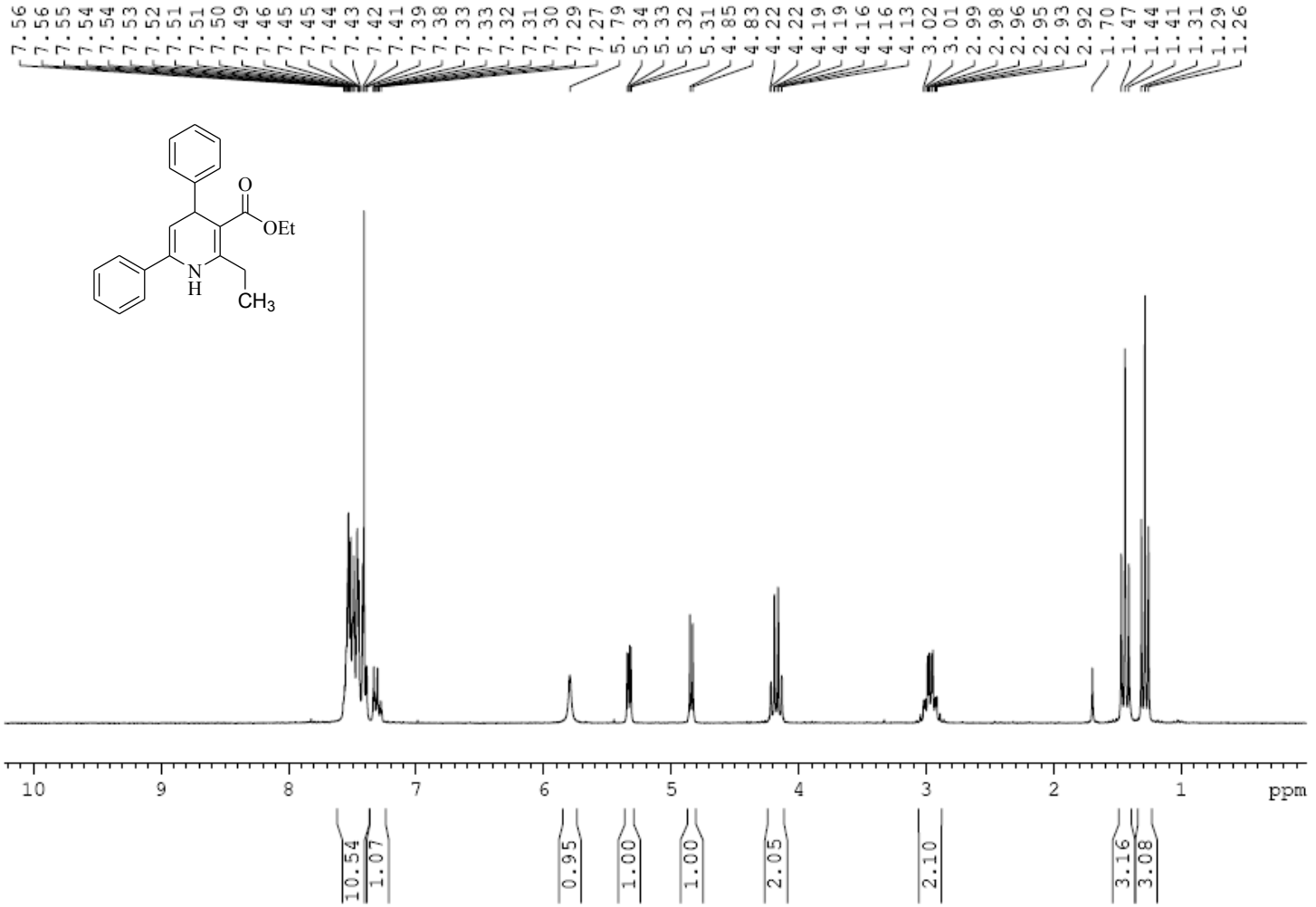
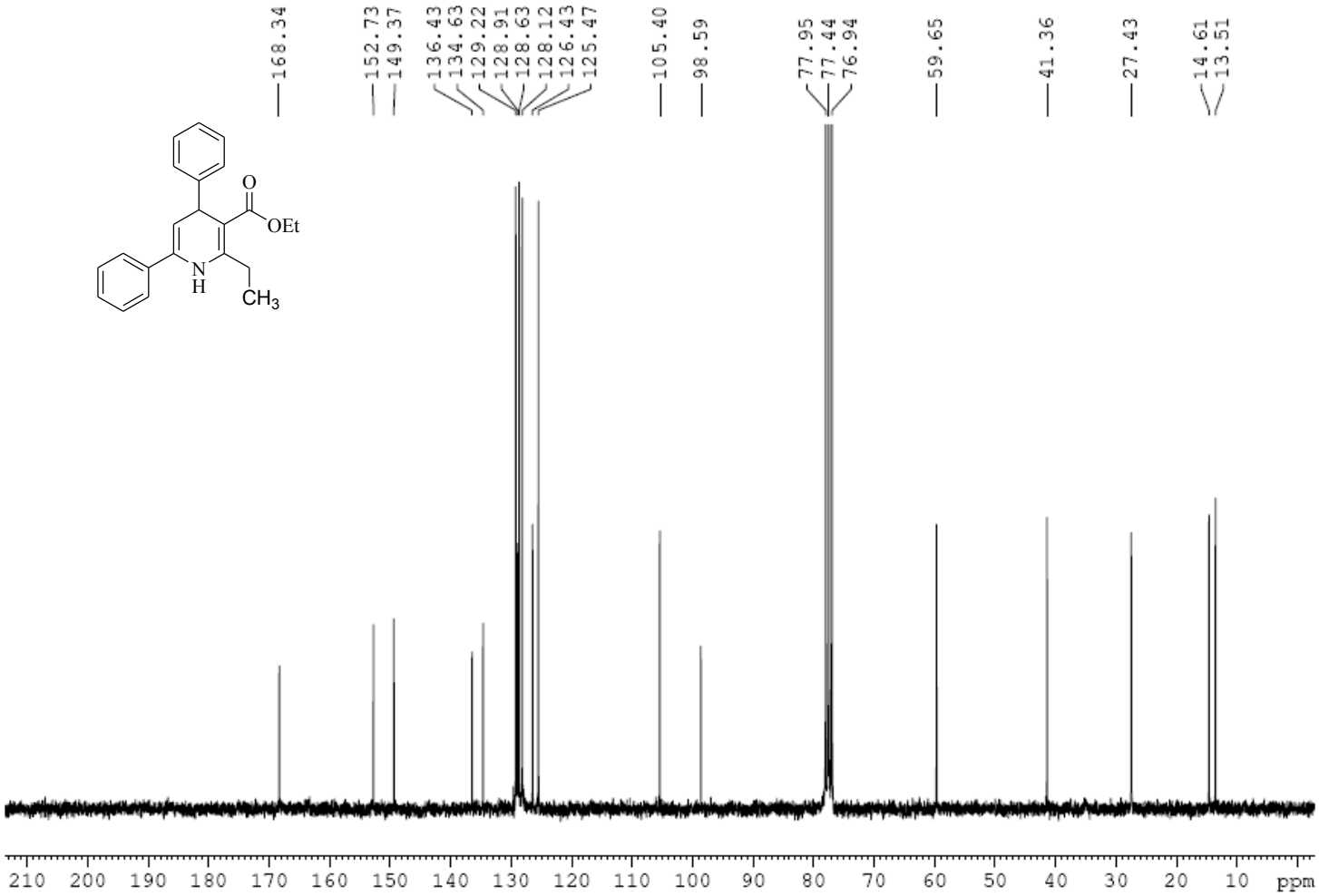
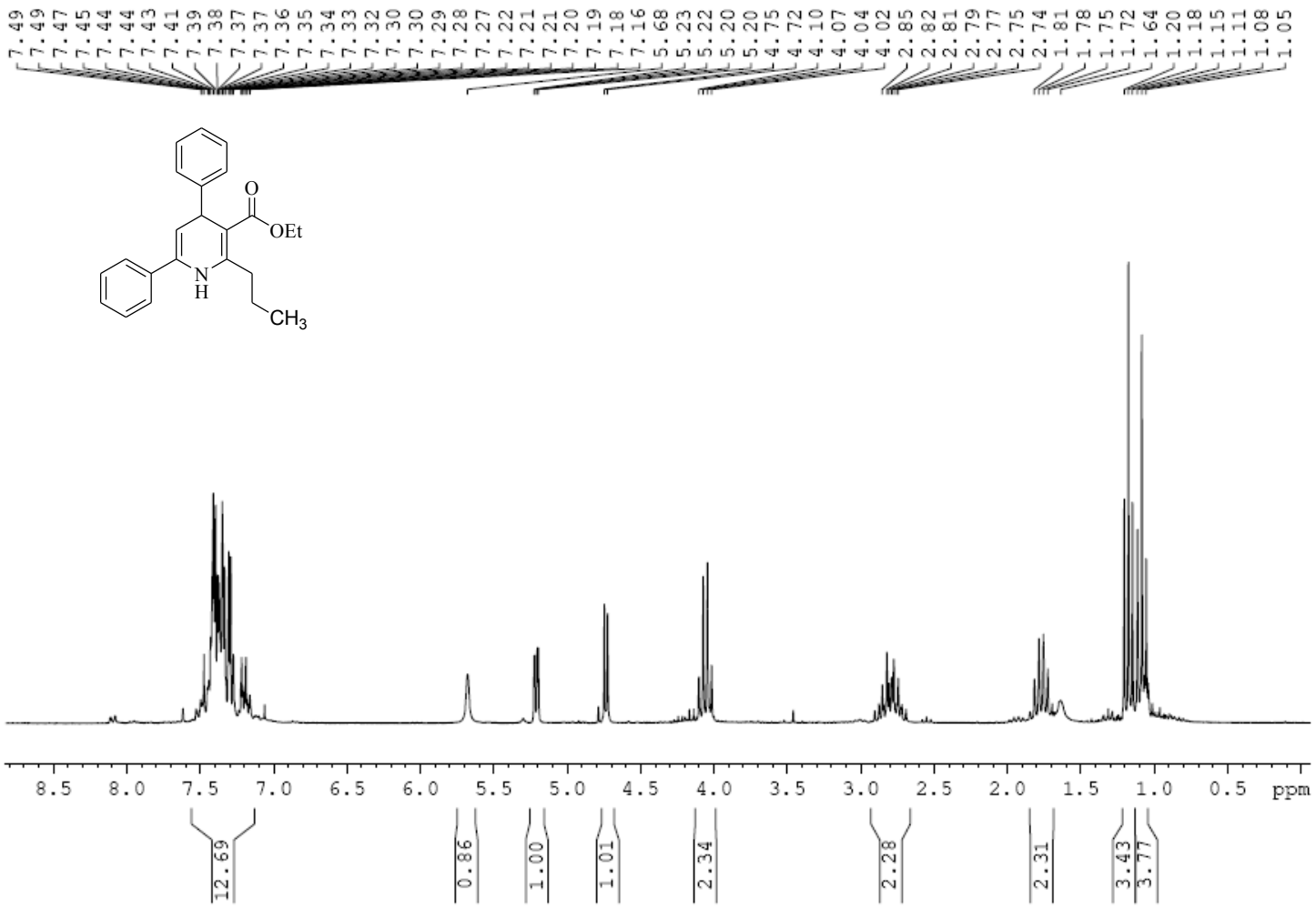
149.28
147.29
136.34
134.73
129.20
128.91
128.64
128.20
126.47
125.50
105.52
99.50
78.00
77.49
76.98
59.69
41.36
21.12
14.68
O
OEt
N
H
CH3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

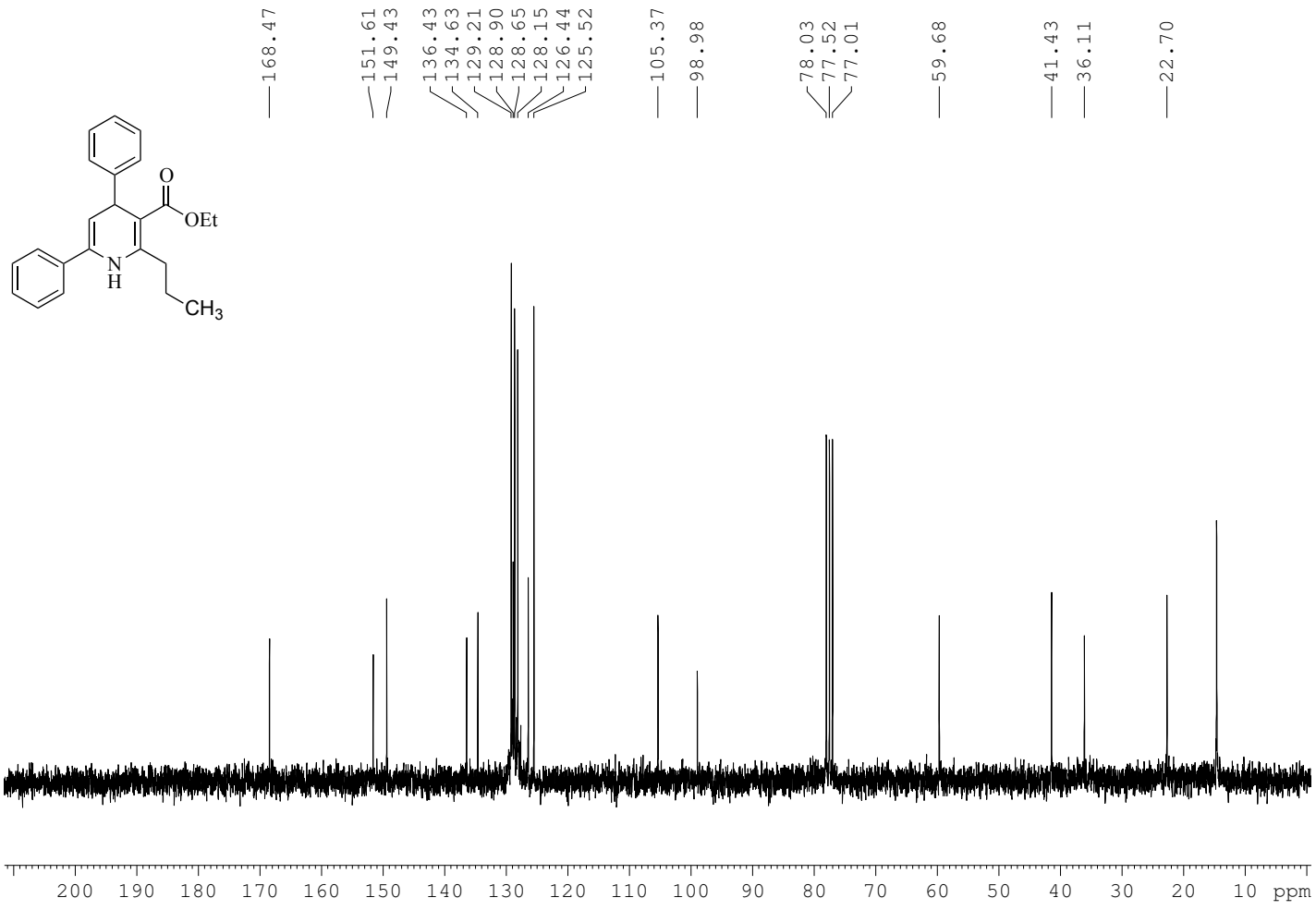
Ethyl 2-ethyl-4,6-diphenyl-1,4-dihydropyridine-3-carboxylate (3b)




168.34
152.73
149.37
136.43
134.63
129.22
128.91
128.63
128.12
126.43
125.47
105.40
98.59
77.95
77.44
76.94
59.65
41.36
27.43
14.61
13.51
O
OEt
N
H
CH3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

Ethyl 4,6-diphenyl-2-propyl-1,4-dihydropyridine-3-carboxylate (3c)

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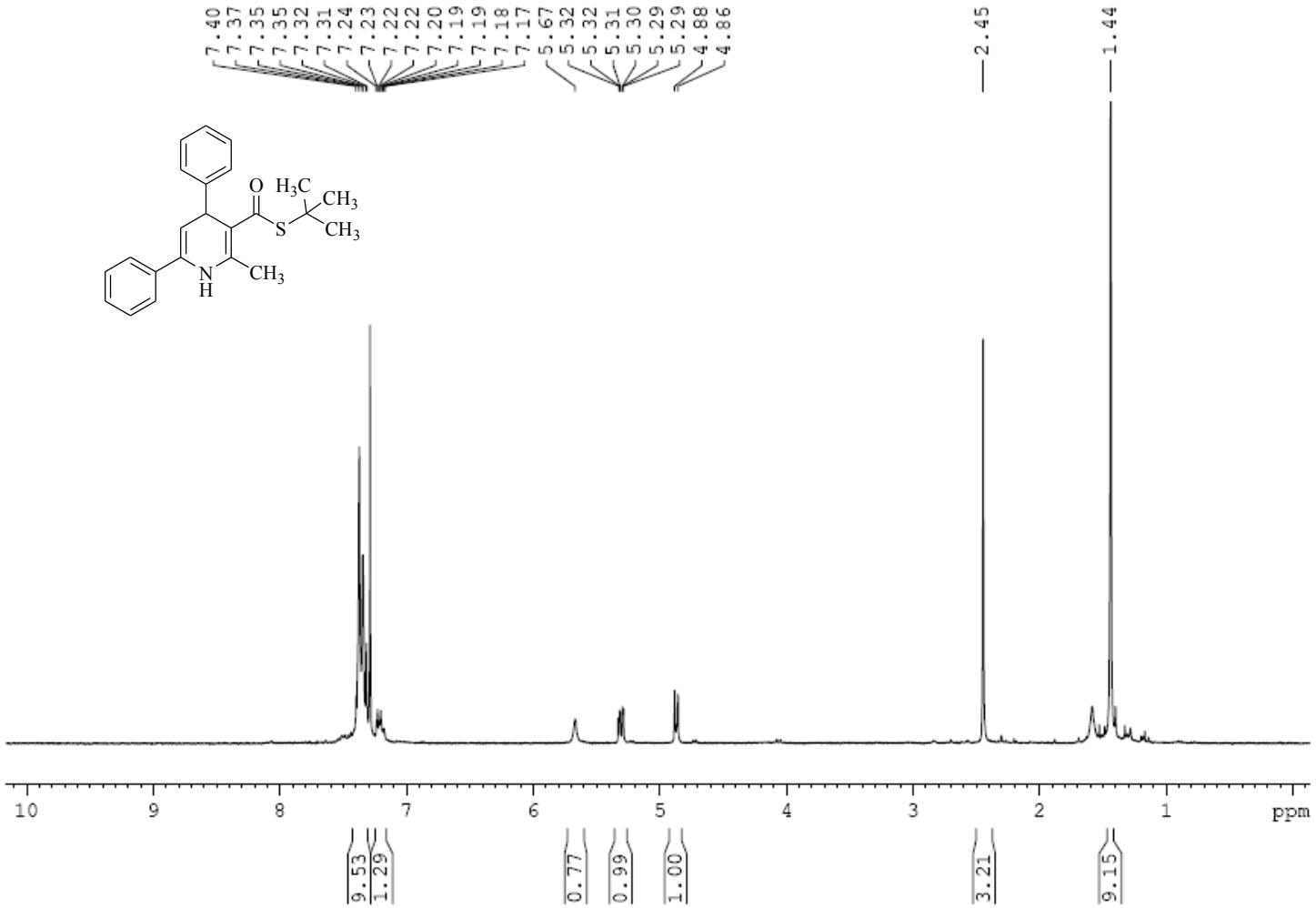
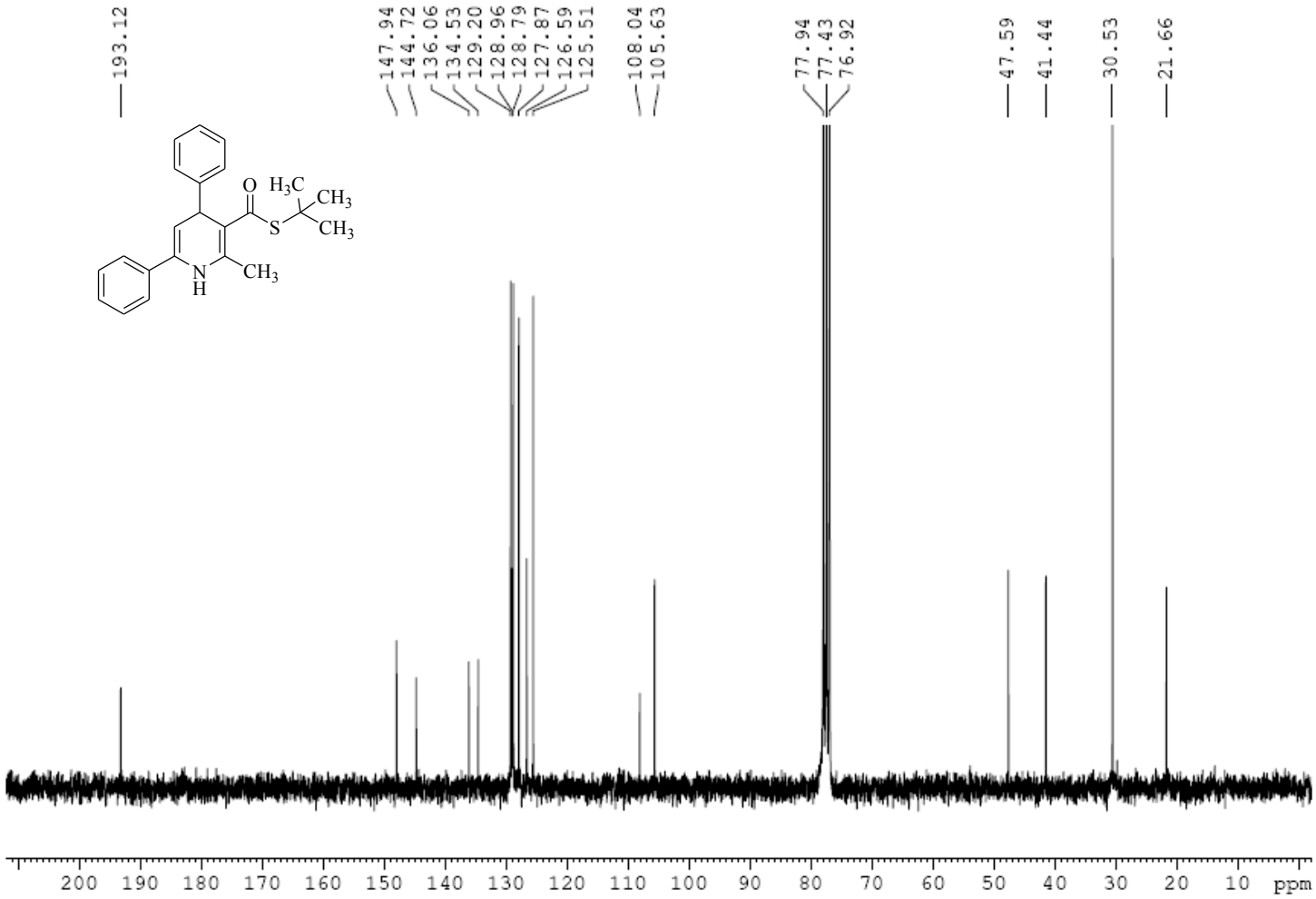
151.61
149.43
136.43
134.63
129.21
128.90
128.65
128.15
126.44
125.52
105.37
98.98
78.03
77.52
77.01
59.68
41.43
36.11
22.70
O
OEt
N
H
CH3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

S-*tert*-butyl 2-methyl-4,6-diphenyl-1,4-dihydropyridine-3-carbothioate (3d)

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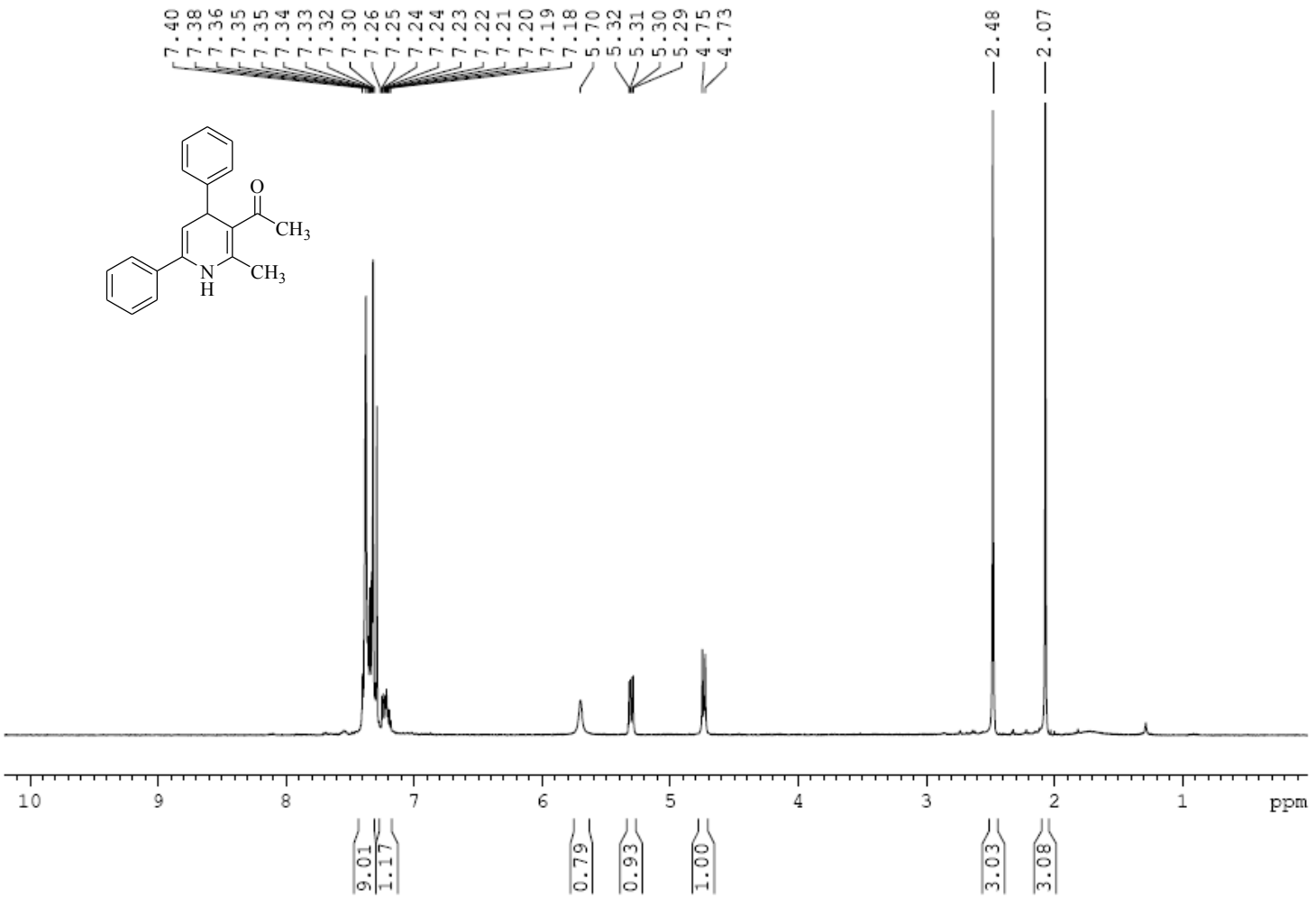
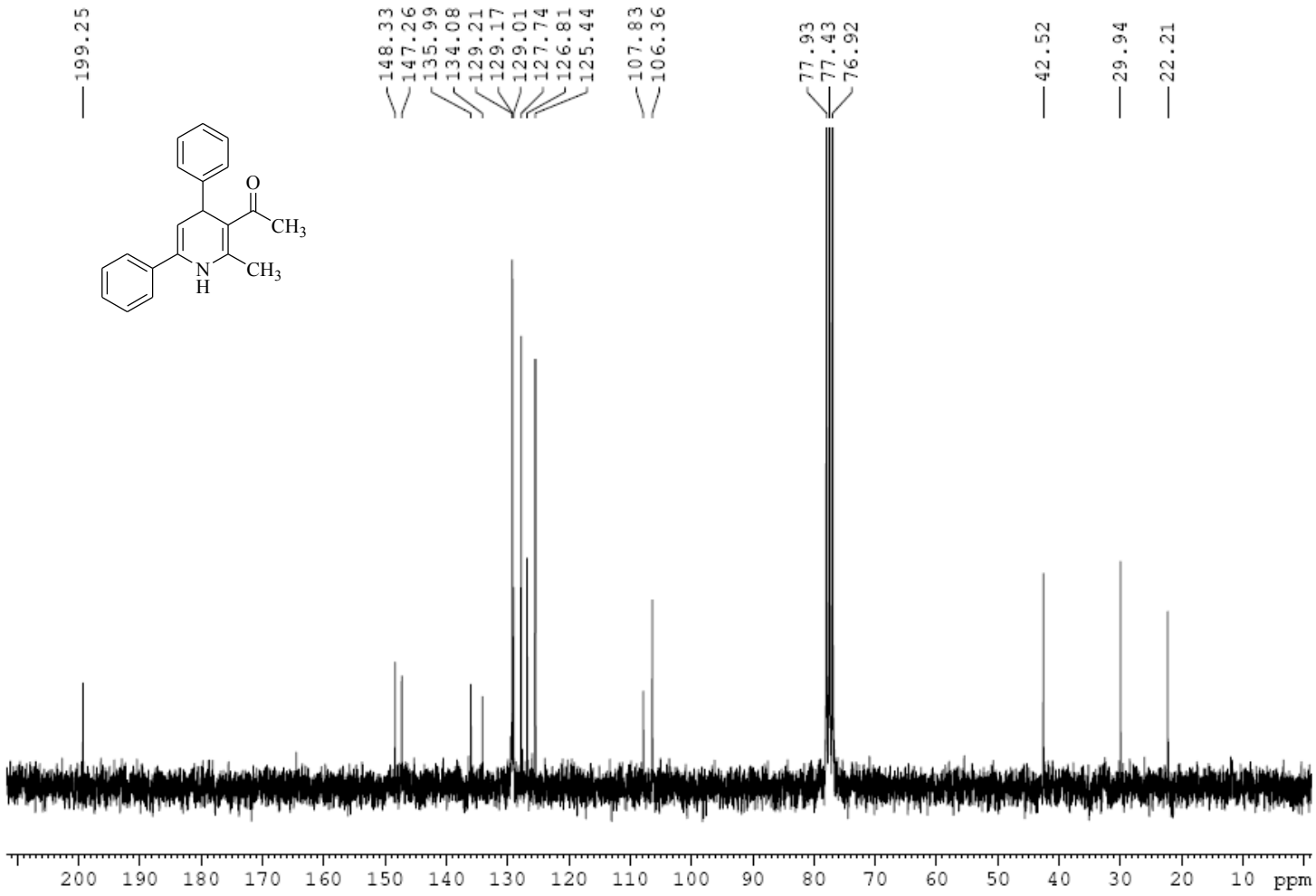
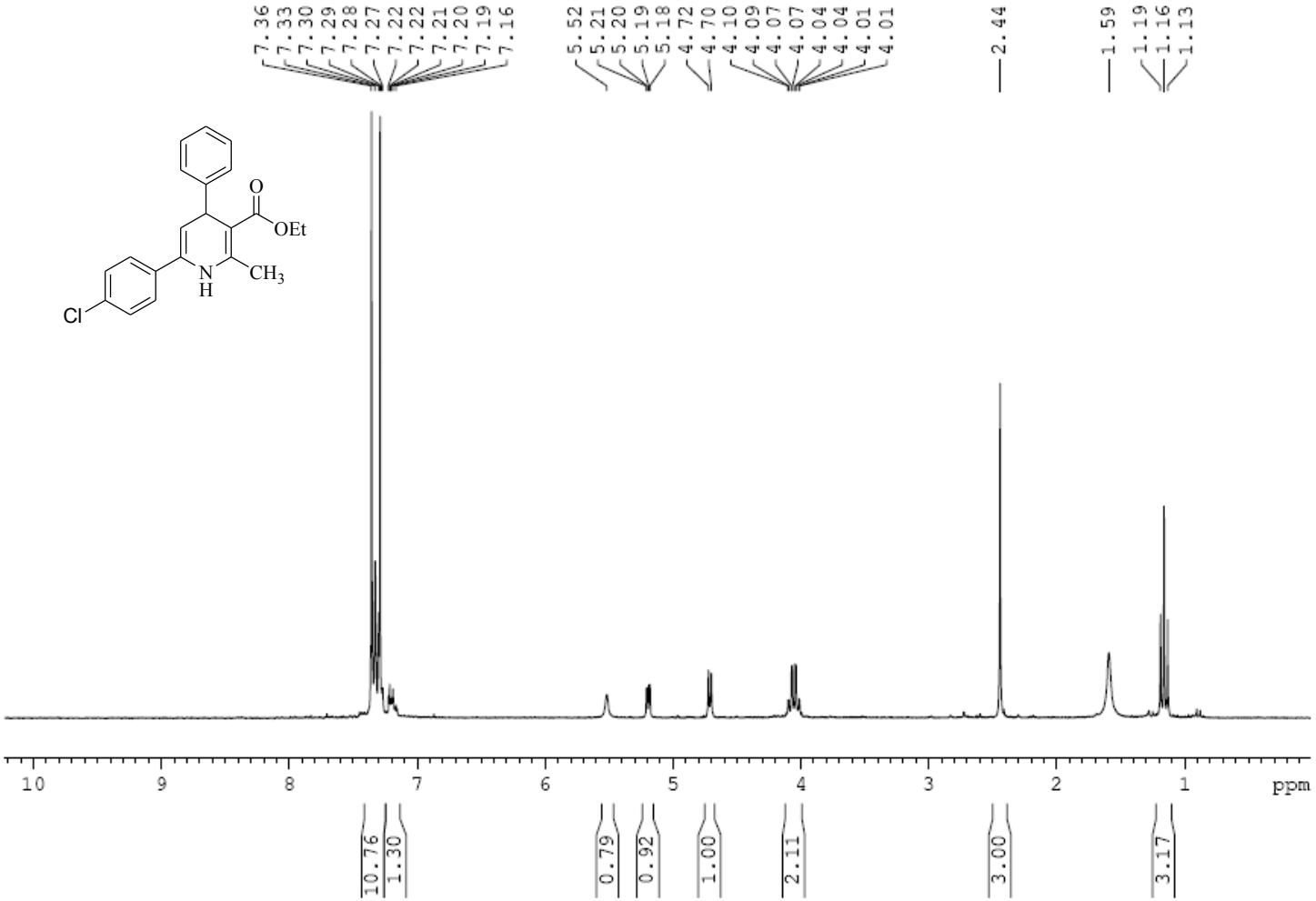
147.94
144.72
136.06
134.53
129.20
128.96
128.79
127.87
126.59
125.51
108.04
105.63
77.94
77.43
76.92
47.59
41.44
30.53
21.66
O
H3C
CH3
CH3
S
N
H
CH3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

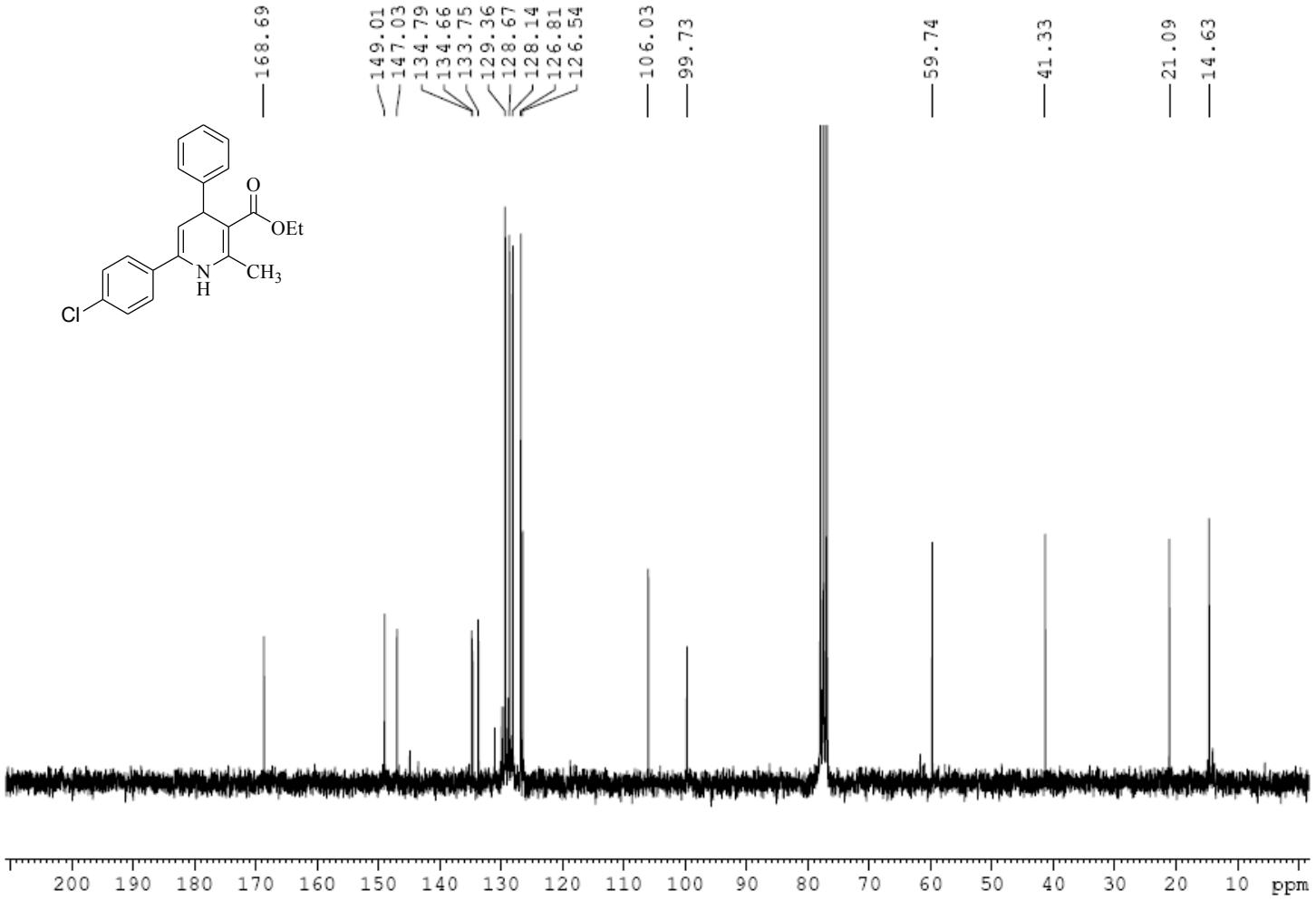
1-(2-methyl-4,6-diphenyl-1,4-dihydropyridin-3-yl)ethanone (3e)




199.25
148.33
147.26
135.99
134.08
129.21
129.17
129.01
127.74
126.81
125.44
107.83
106.36
77.93
77.43
76.92
42.52
29.94
22.21
O
CH3
N
H
CH3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

Ethyl 6-(4-chlorophenyl)-2-methyl-4-phenyl-1,4-dihydropyridine-3-carboxylate (3f)

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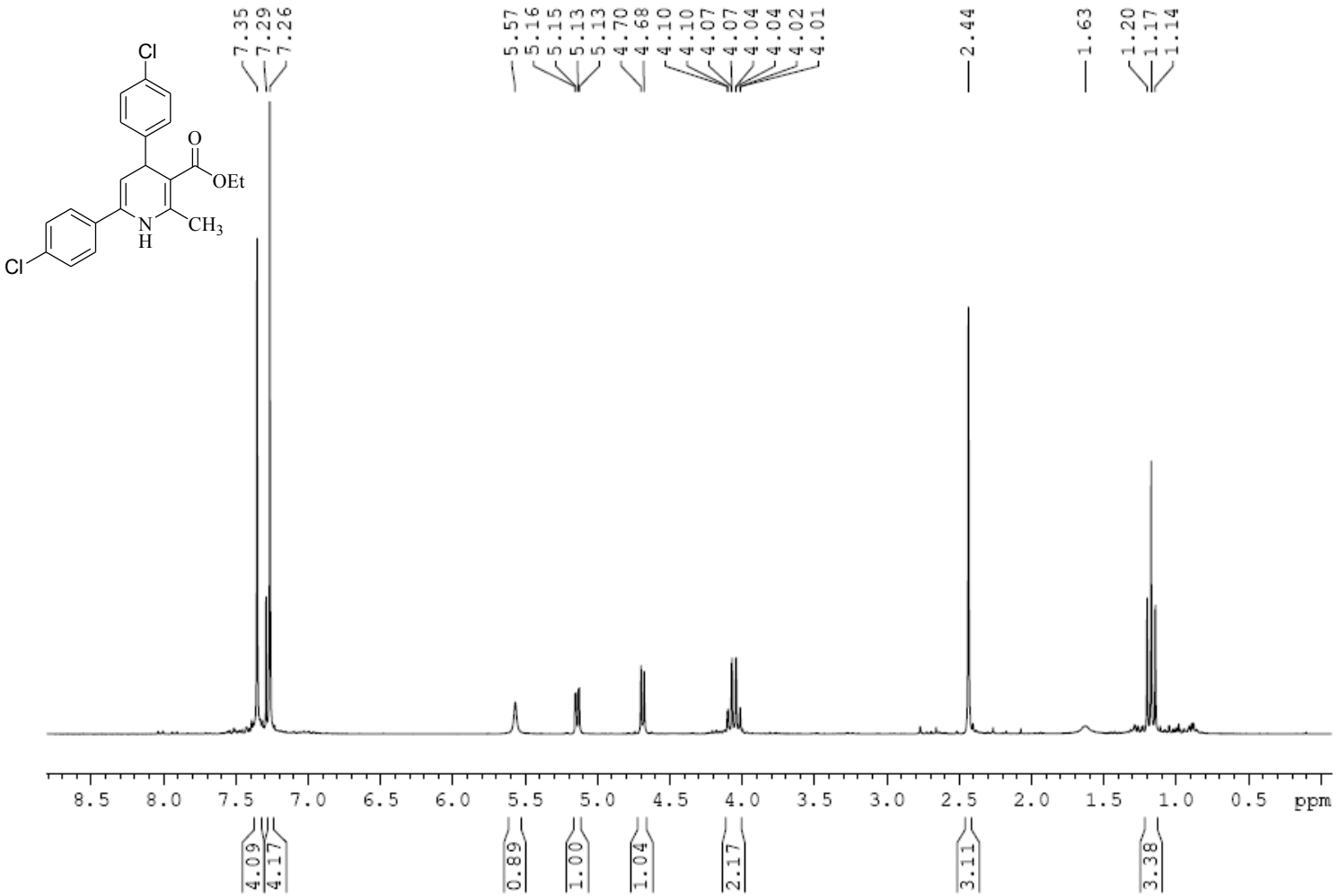
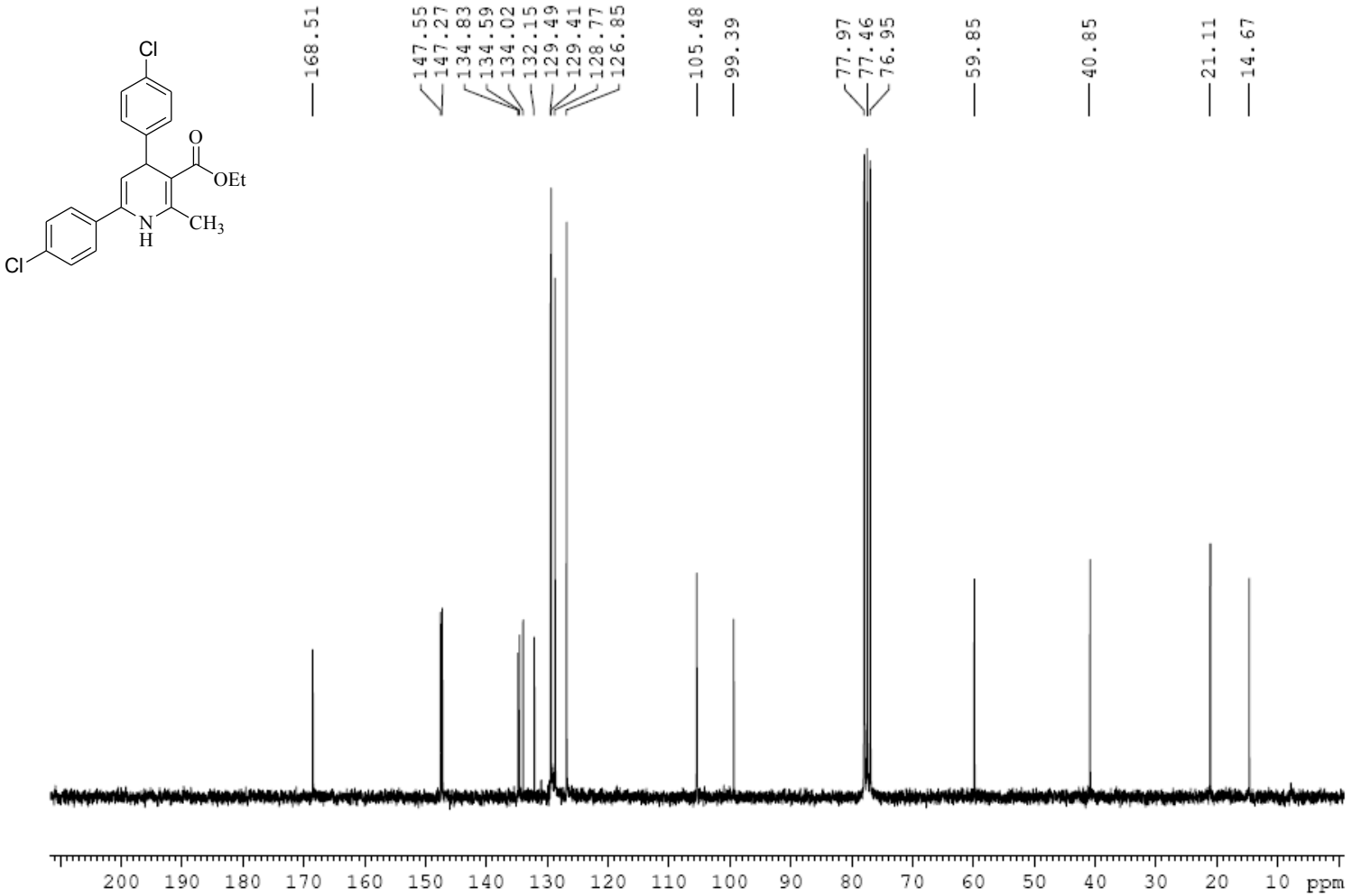
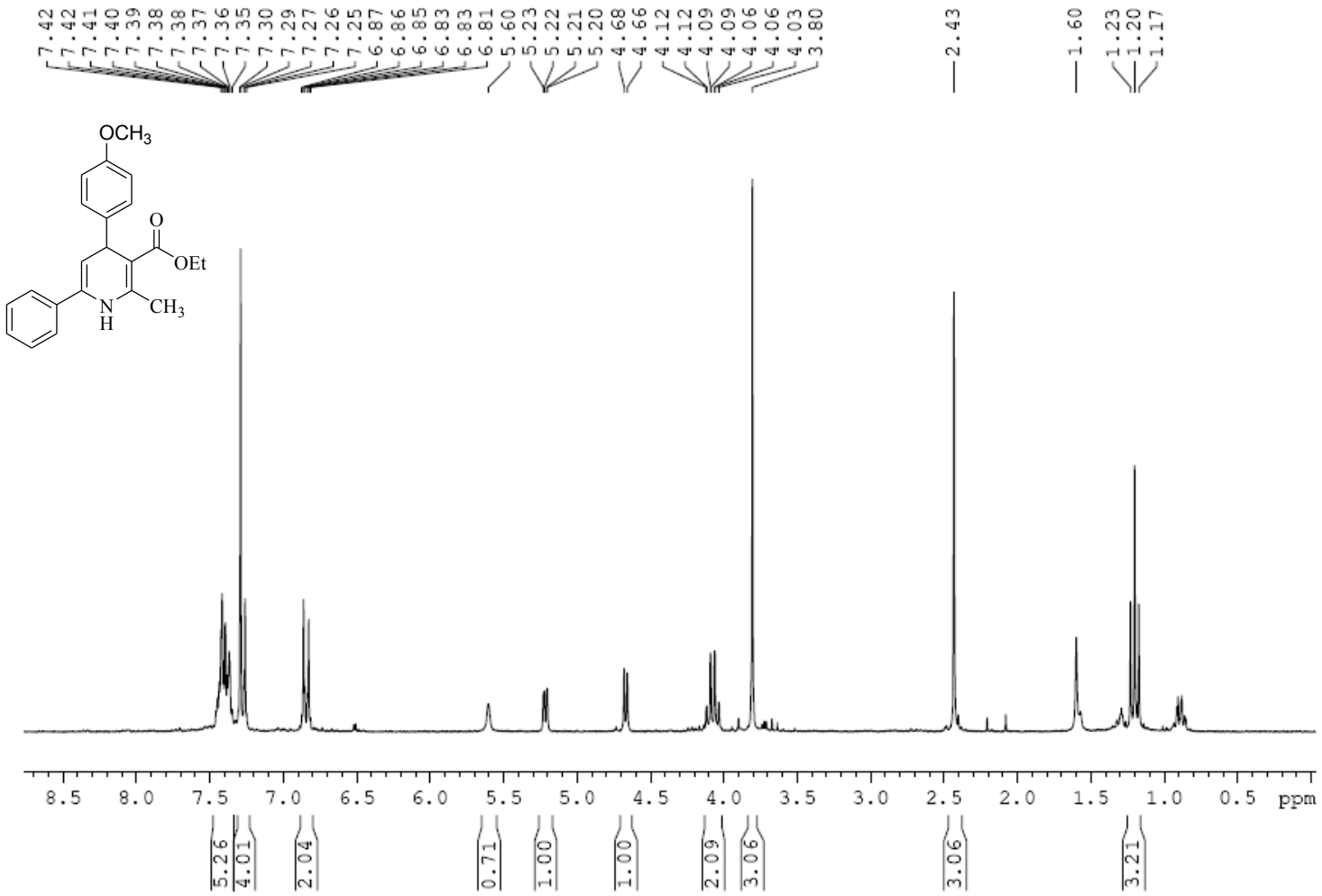
147.03
134.79
134.66
133.75
129.36
128.67
128.14
126.81
126.54
106.03
99.73
59.74
41.33
21.09
14.63
O
OEt
N
H
CH3
Cl
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

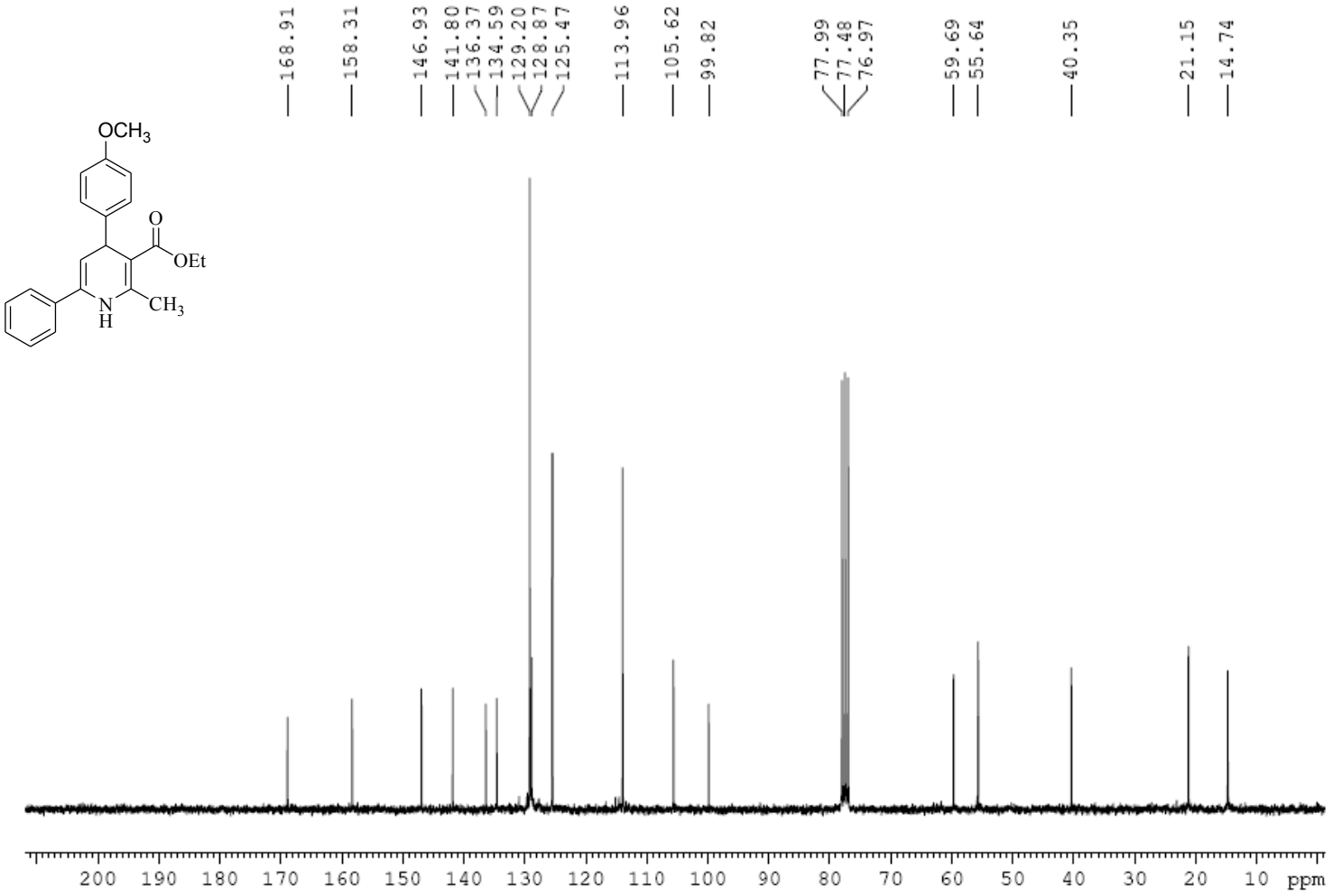
Ethyl 4,6-bis(4-chlorophenyl)-2-methyl-1,4-dihydropyridine-3-carboxylate (3g)



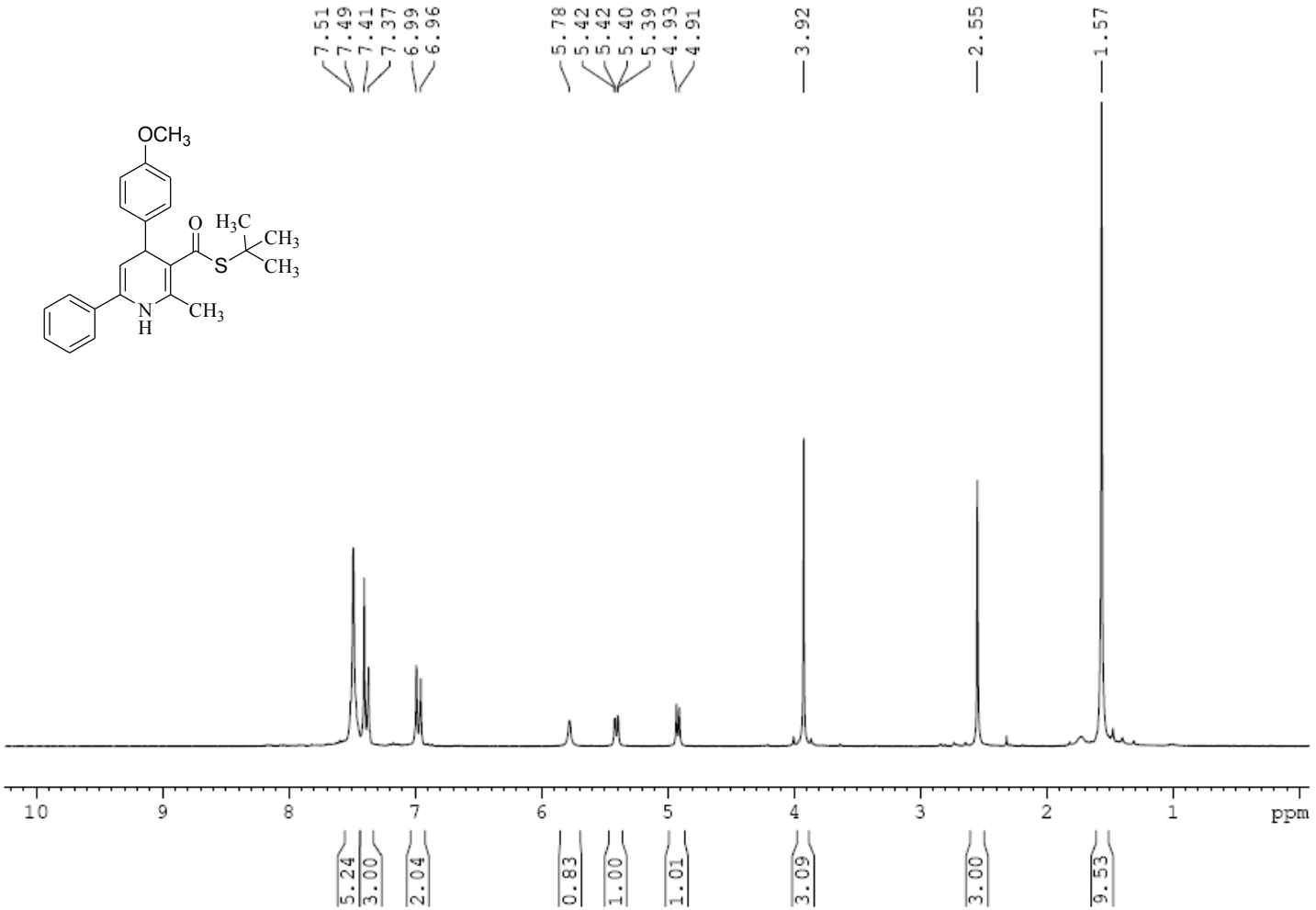

Cl
O
OEt
N
H
CH3
Cl
168.51
147.55
147.27
134.83
134.59
134.02
132.15
129.49
129.41
128.77
126.85
105.48
99.39
77.97
77.46
76.95
59.85
40.85
21.11
14.67
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

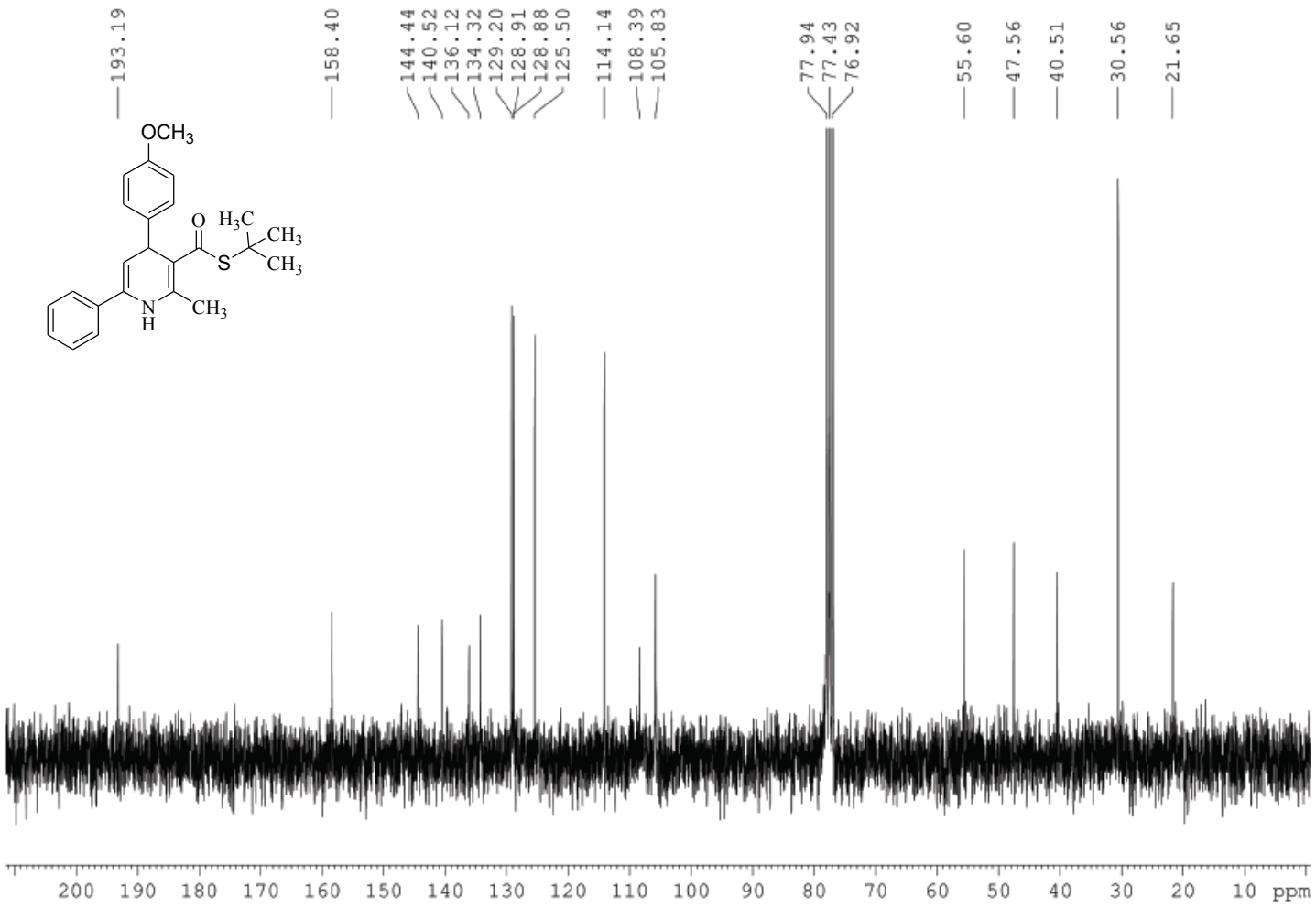
Ethyl 4-(4-methoxyphenyl)-2-methyl-6-phenyl-1,4-dihydropyridine-3-carboxylate (3h)



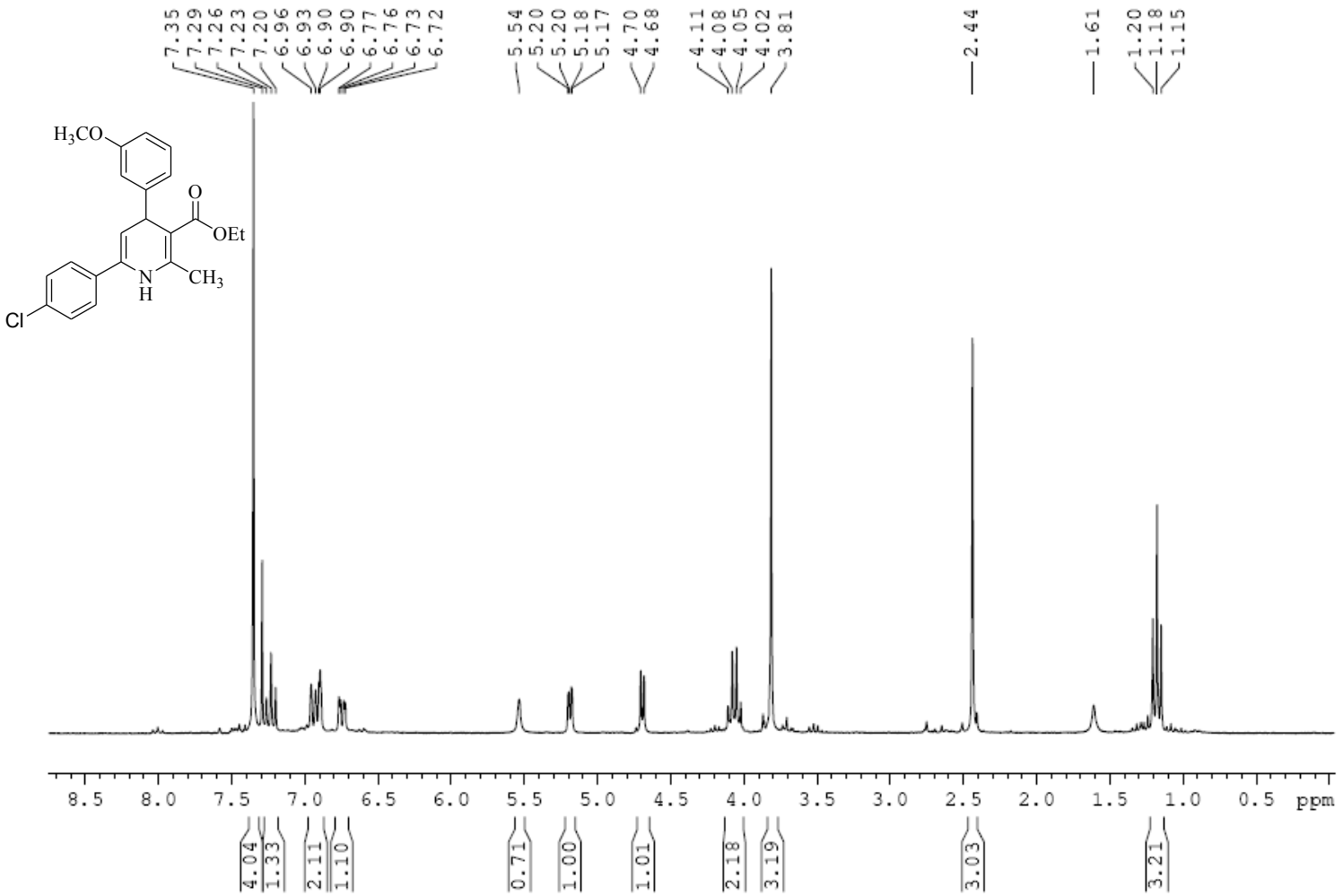

168.91
158.31
146.93
141.80
136.37
134.59
129.20
128.87
125.47
113.96
105.62
99.82
77.99
77.48
76.97
59.69
55.64
40.35
21.15
14.74
OCH3
O
OEt
N
H
CH3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

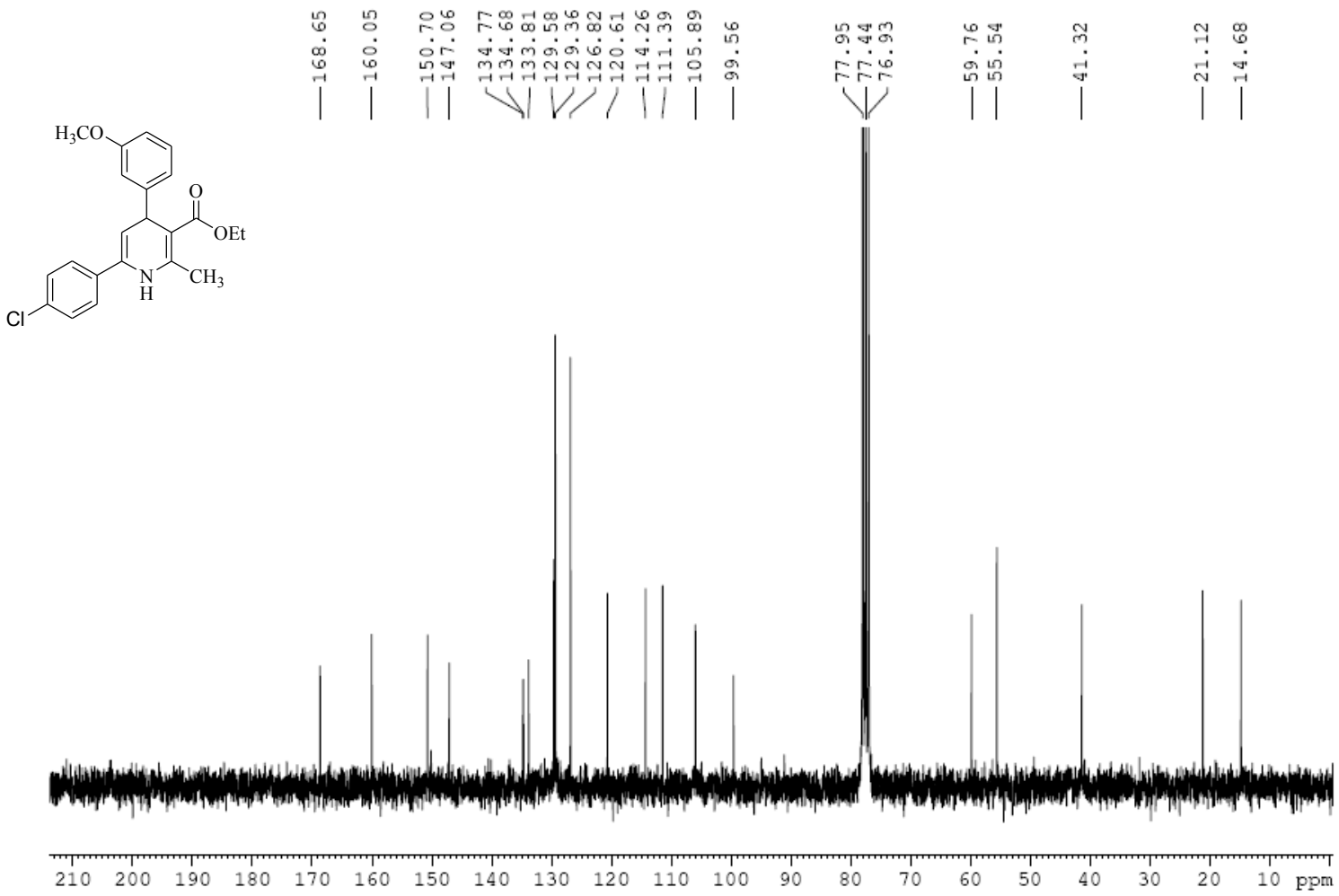
S-*tert*-butyl 4-(4-methoxyphenyl)-2-methyl-6-phenyl-1,4-dihydropyridine-3-carbothioate (3i)



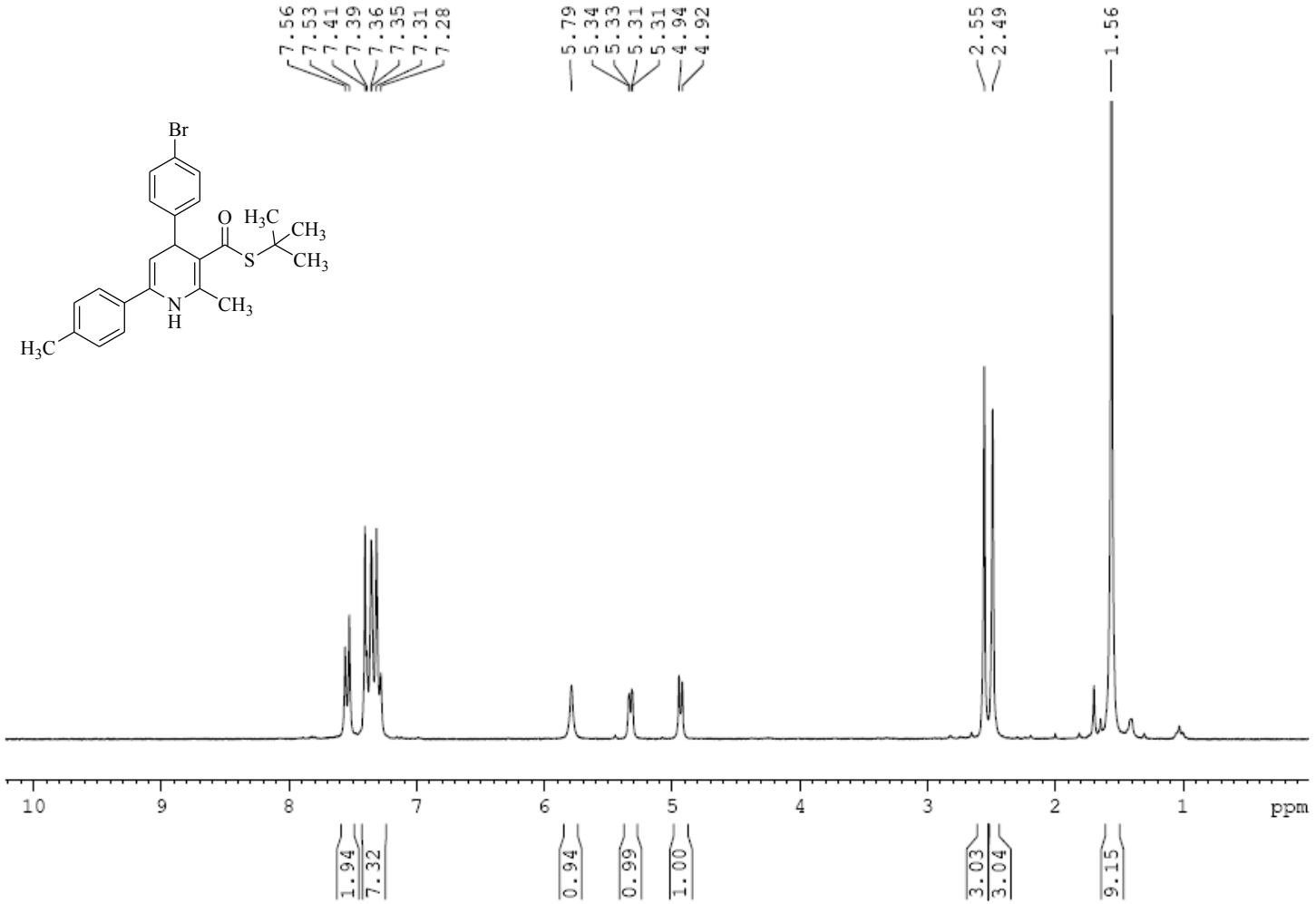

193.19
158.40
144.44
140.52
136.12
134.32
129.20
128.91
128.88
125.50
114.14
108.39
105.83
77.94
77.43
76.92
55.60
47.56
40.51
30.56
21.65
OCH3
O
H3C
CH3
CH3
S
N
H
CH3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

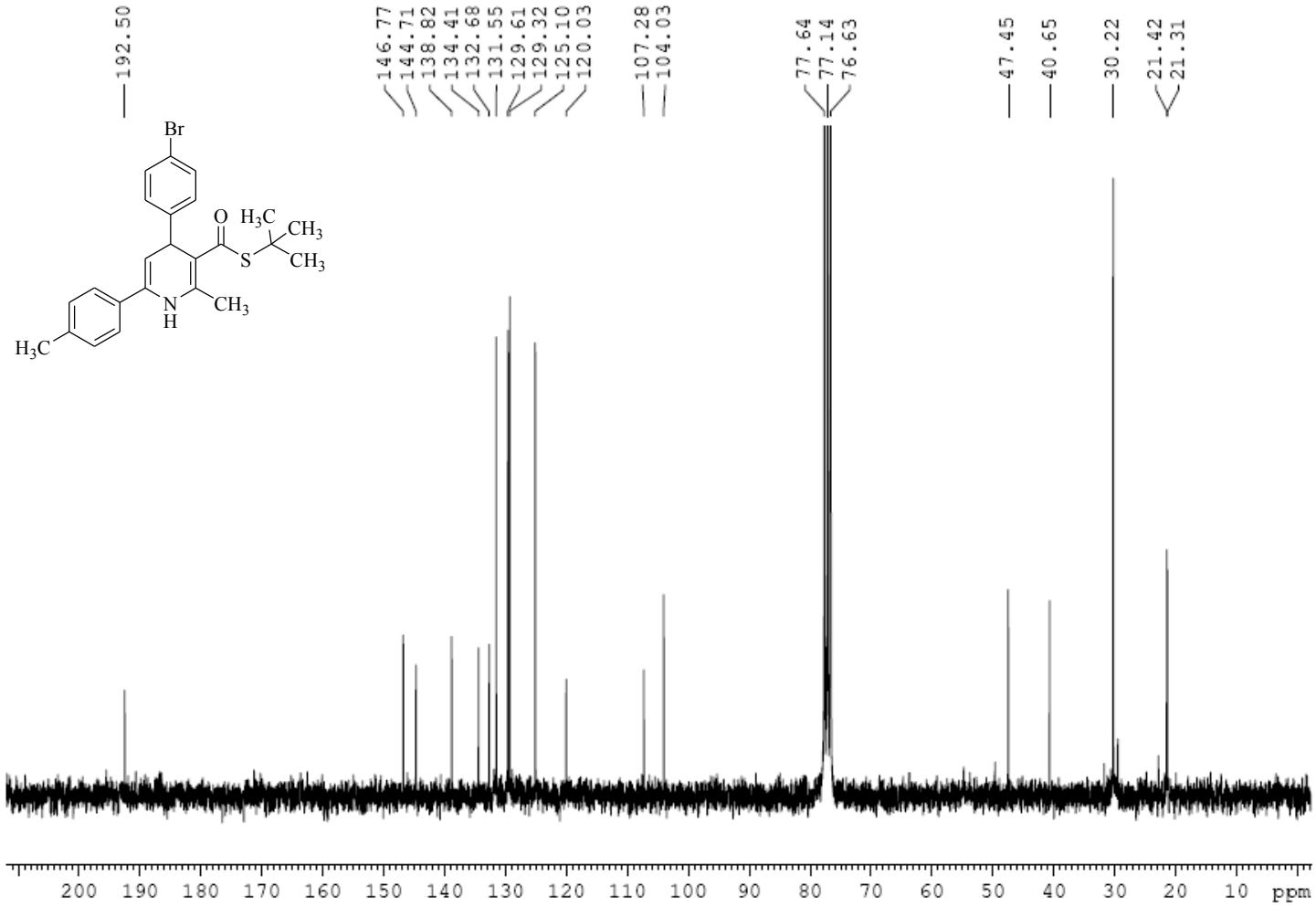
Ethyl 6-(4-chlorophenyl)-4-(3-methoxyphenyl)-2-methyl-1,4-dihydropyridine-3-carboxylate (3j)



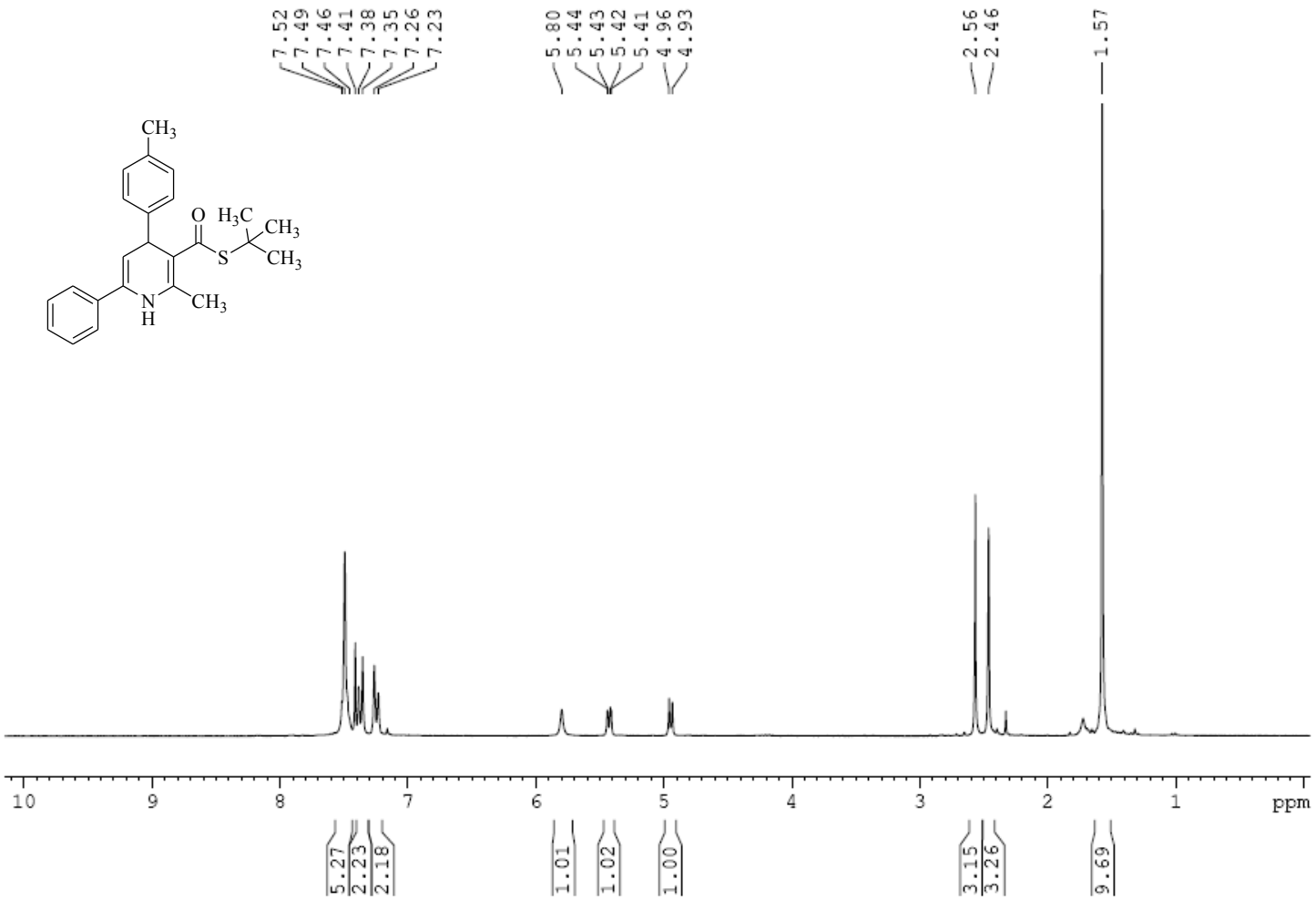

168.65
160.05
150.70
147.06
134.77
134.68
133.81
129.58
129.36
126.82
120.61
114.26
111.39
105.89
99.56
77.95
77.44
76.93
59.76
55.54
41.32
21.12
14.68
H3CO
O
OEt
N
H
CH3
Cl
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

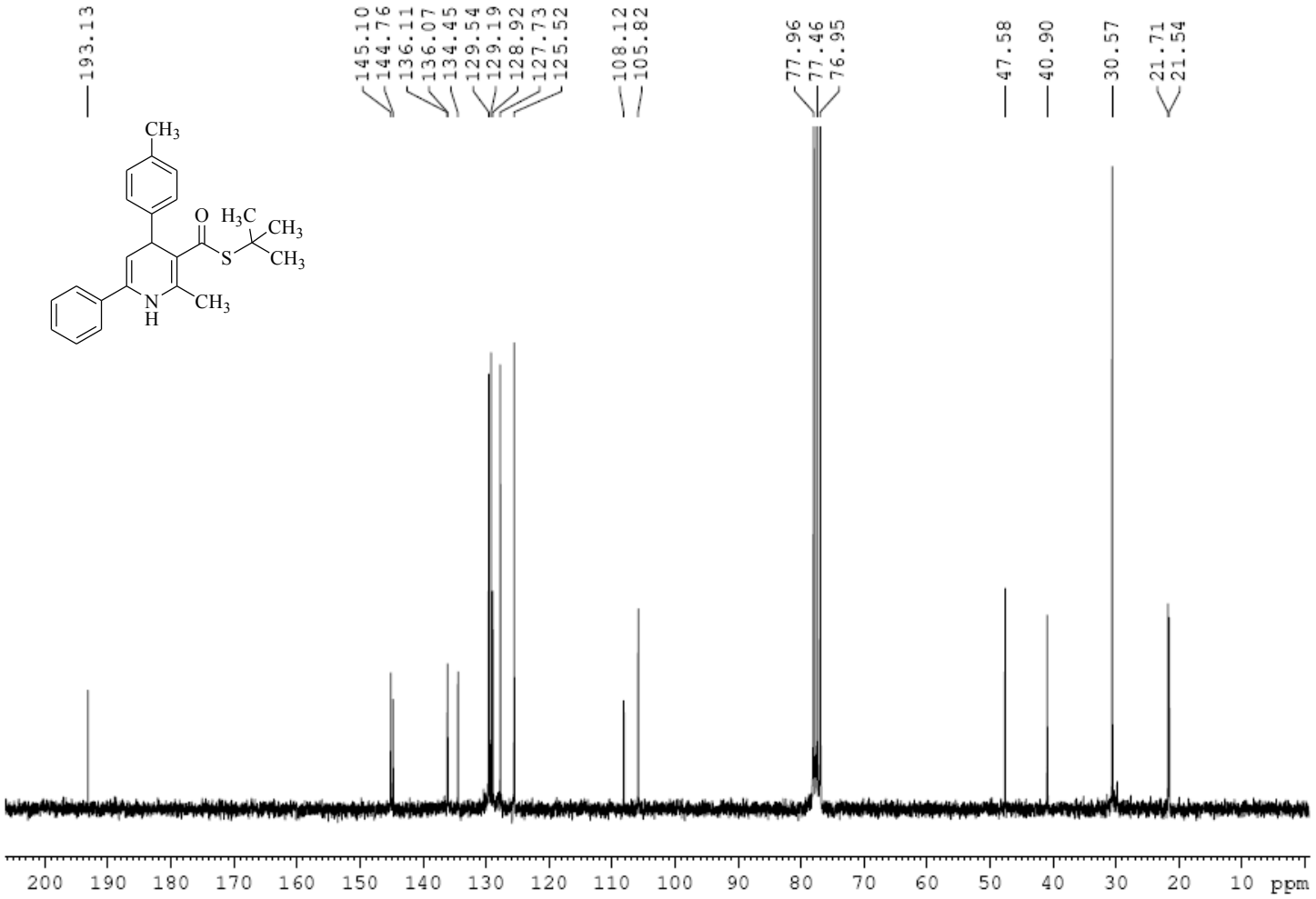
S-*tert*-butyl 4-(4-bromophenyl)-2-methyl-6-p-tolyl-1,4-dihydropyridine-3-carbothioate (3k)




192.50
146.77
144.71
138.82
134.41
132.68
131.55
129.61
129.32
125.10
120.03
107.28
104.03
77.64
77.14
76.63
47.45
40.65
30.22
21.42
21.31
Br
O
H3C
CH3
S
CH3
N
H
CH3
H3C
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

S-*tert*-butyl 2-methyl-6-phenyl-4-p-tolyl-1,4-dihydropyridine-3-carbothioate (3l)

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128.92
127.73
125.52
108.12
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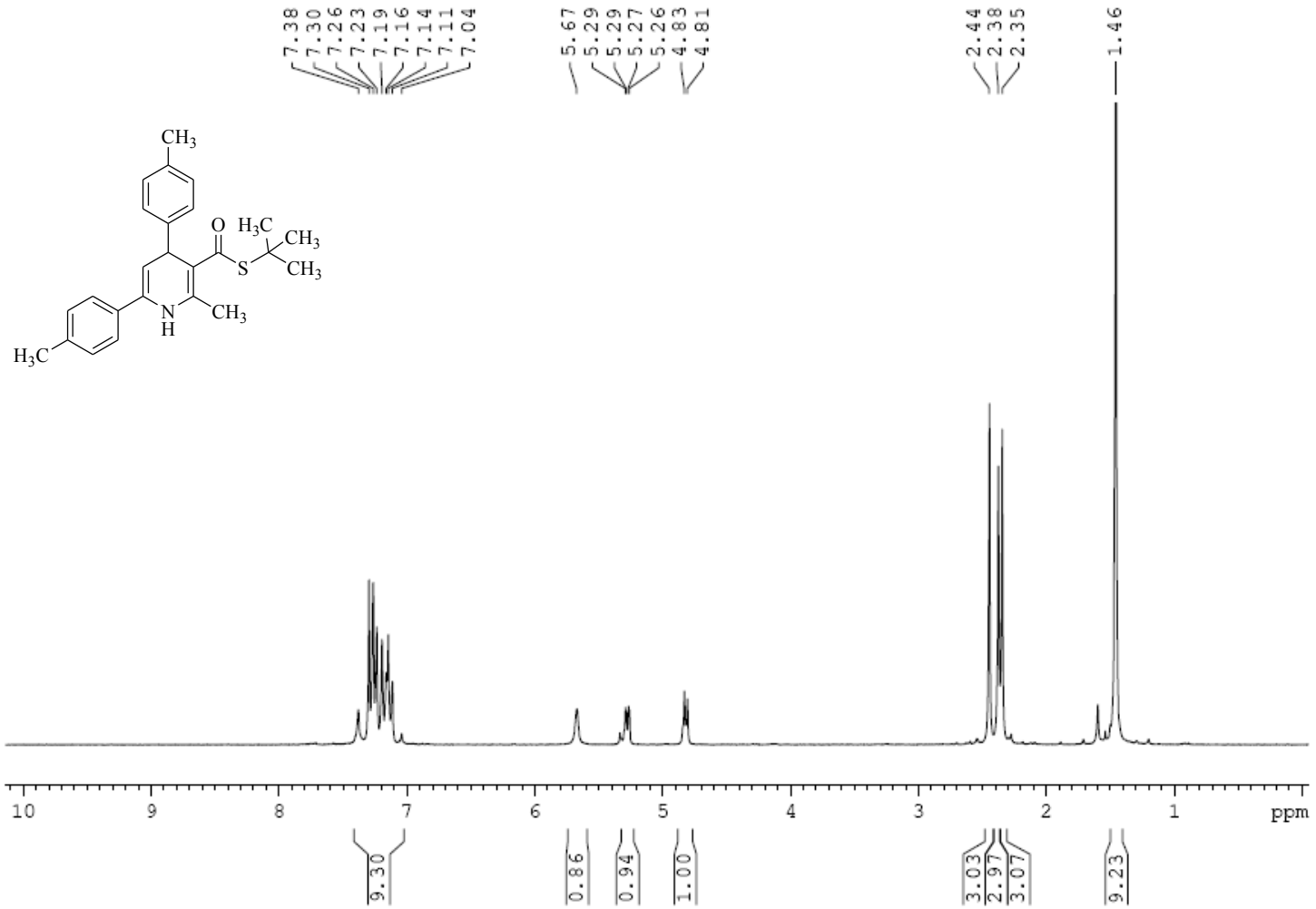
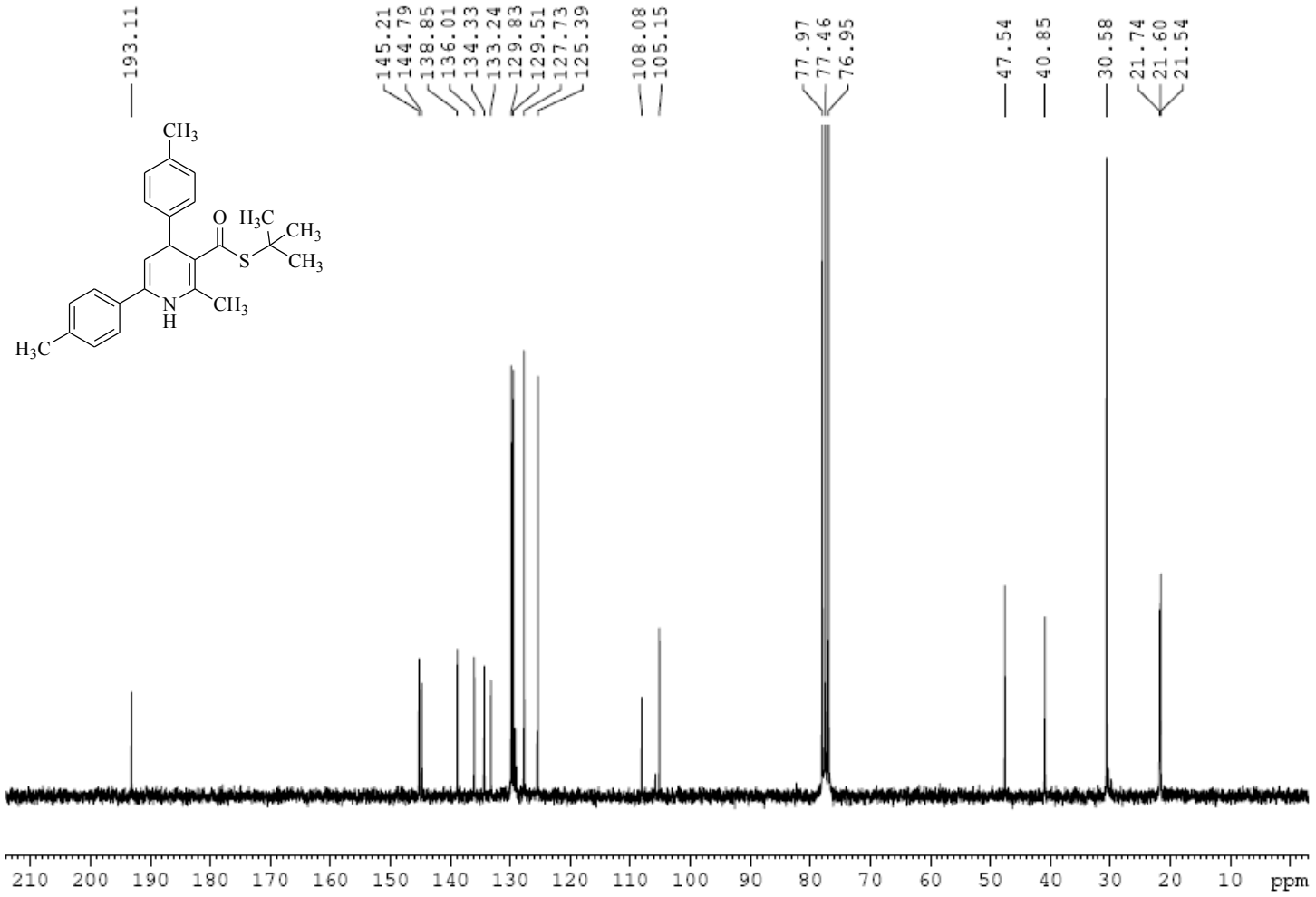
77.96
77.46
76.95
47.58
40.90
30.57
21.71
21.54
CH3
O
H3C
CH3
S
CH3
N
H
CH3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

S-*tert*-butyl 2-methyl-4,6-dip-tolyl-1,4-dihydropyridine-3-carbothioate (3m)

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145.21
144.79
138.85
136.01
134.33
133.24
129.83
129.51
127.73
125.39
108.08
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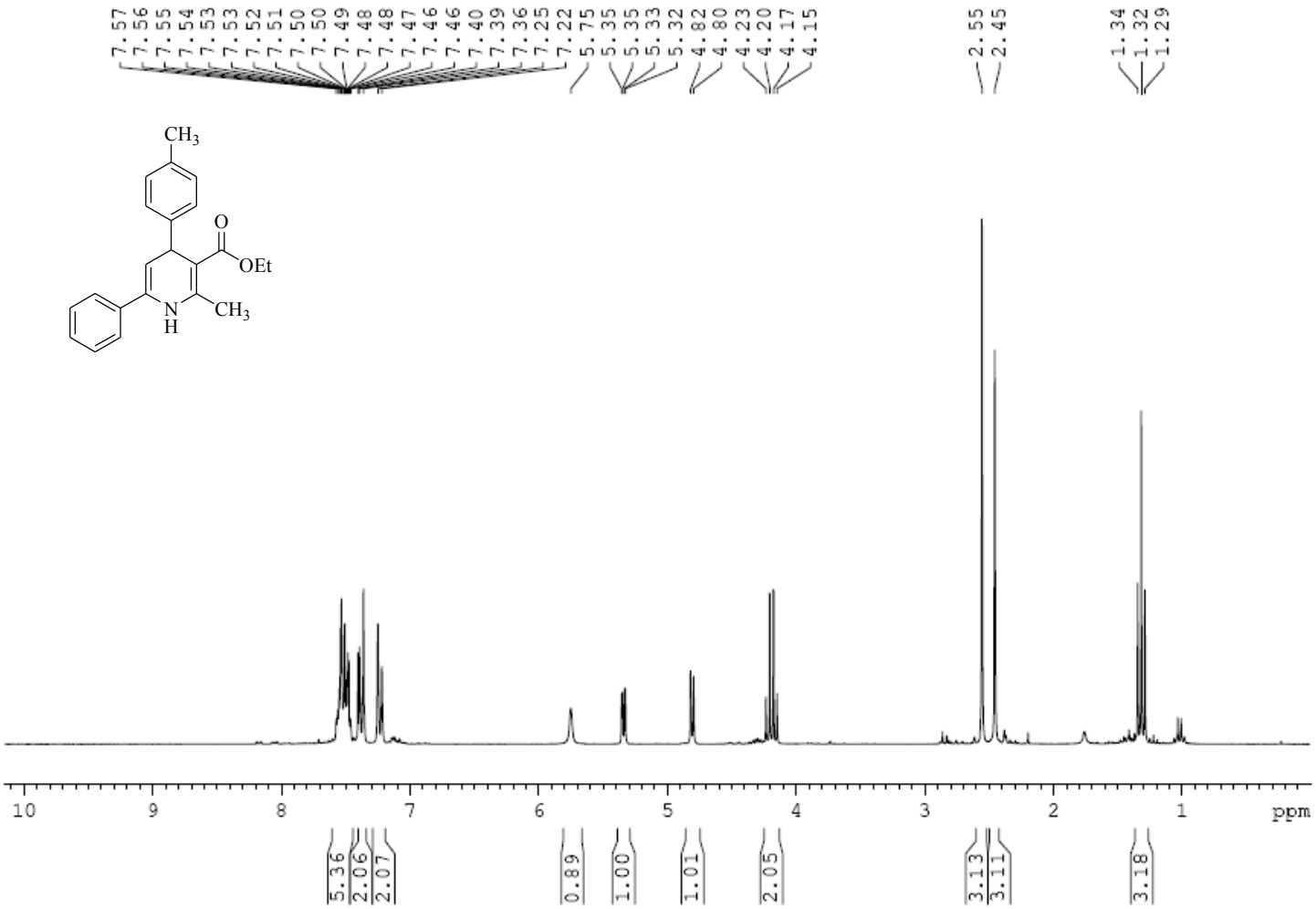
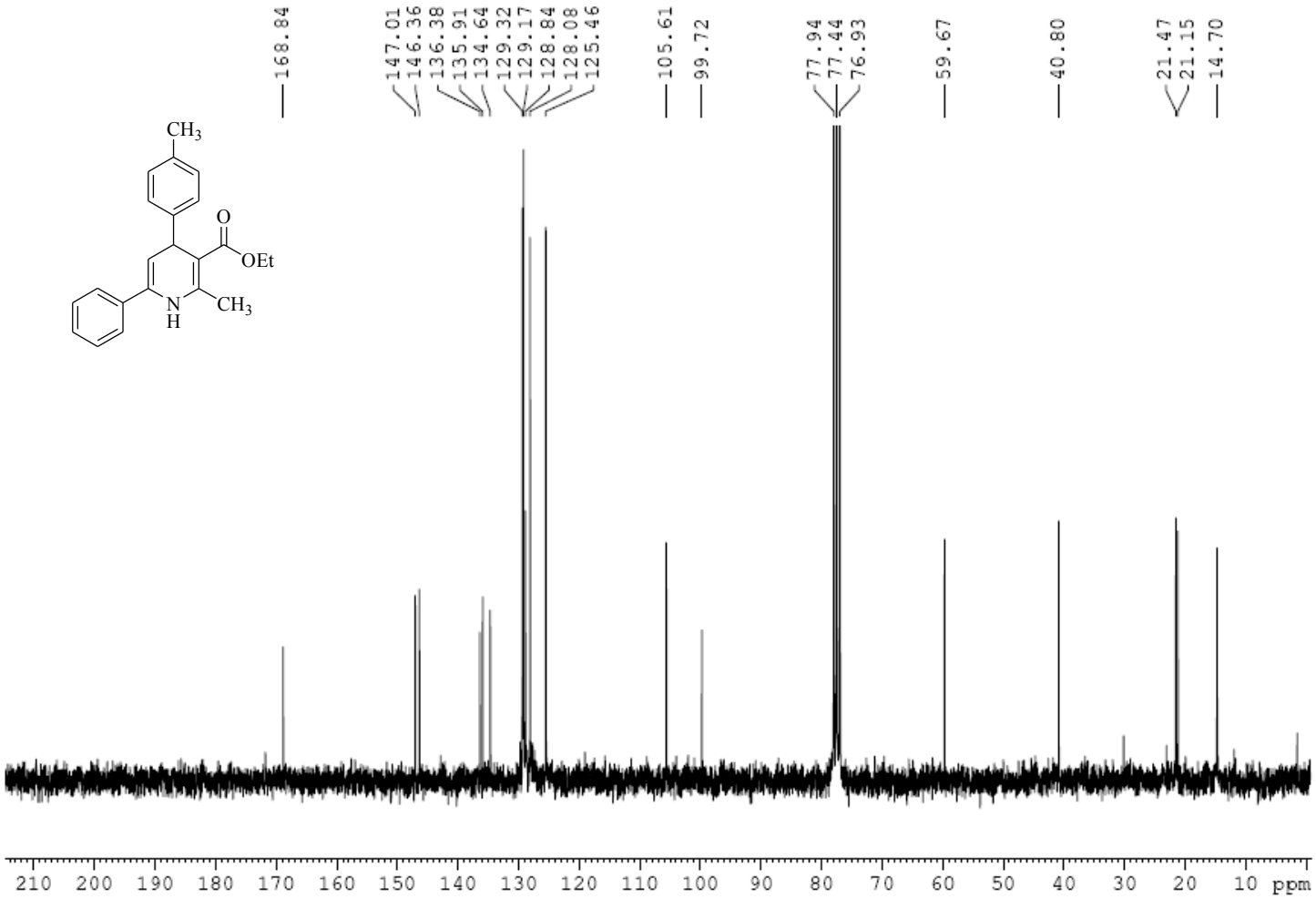
77.97
77.46
76.95
47.54
40.85
30.58
21.74
21.60
21.54
CH3
O
H3C
CH3
S
CH3
N
H
CH3
H3C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

Ethyl 2-methyl-6-phenyl-4-p-tolyl-1,4-dihydropyridine-3-carboxylate (3n)

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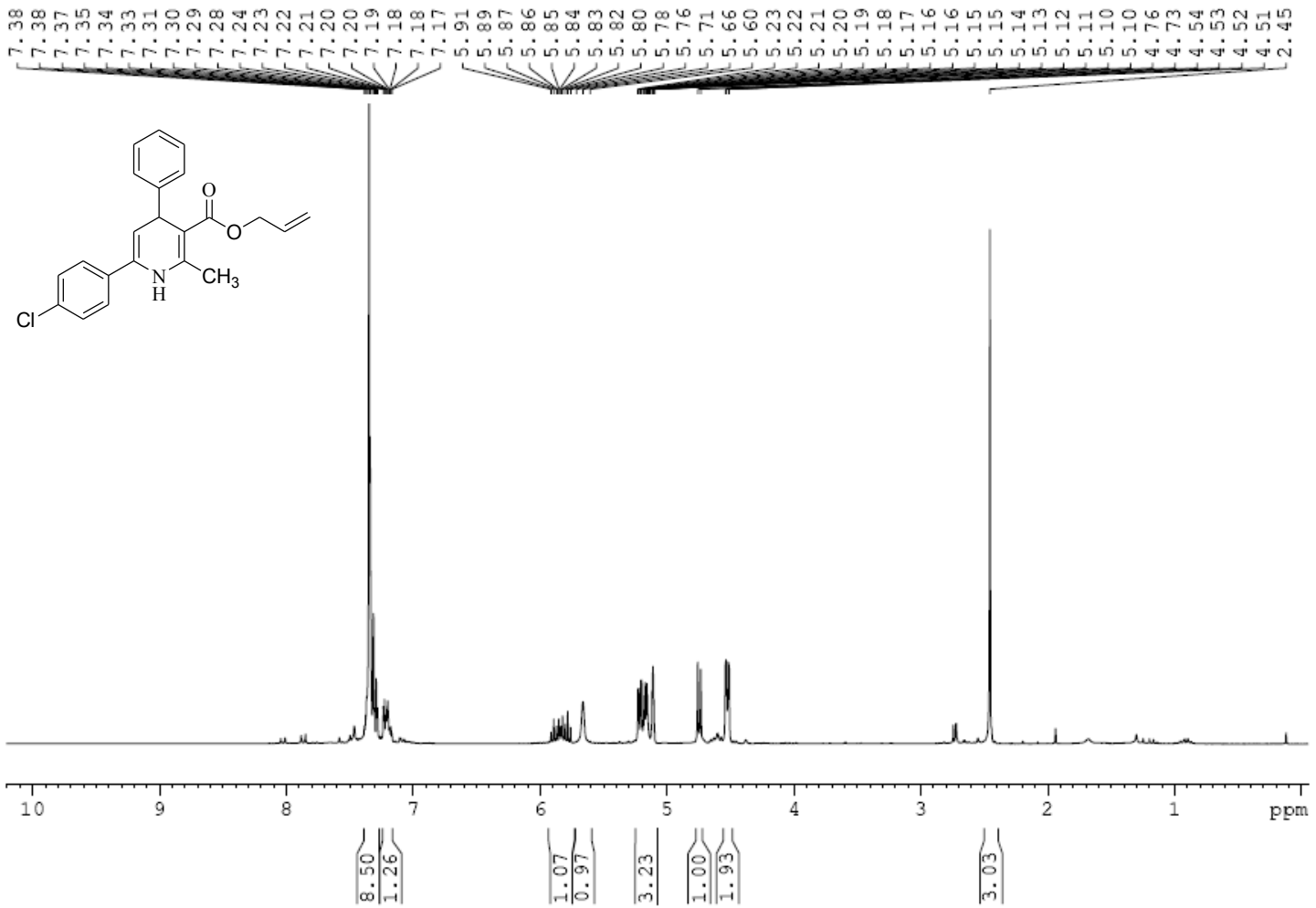
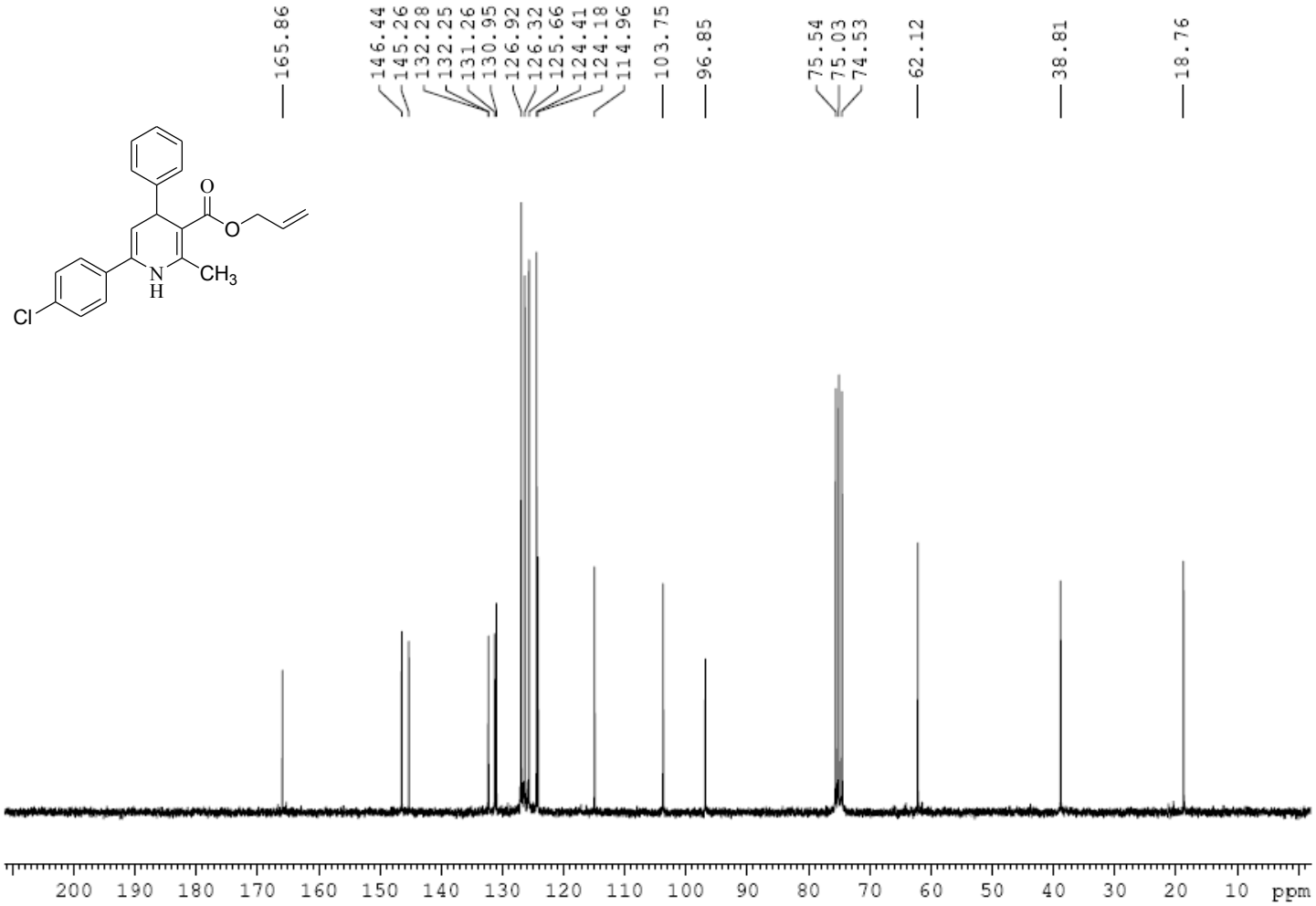
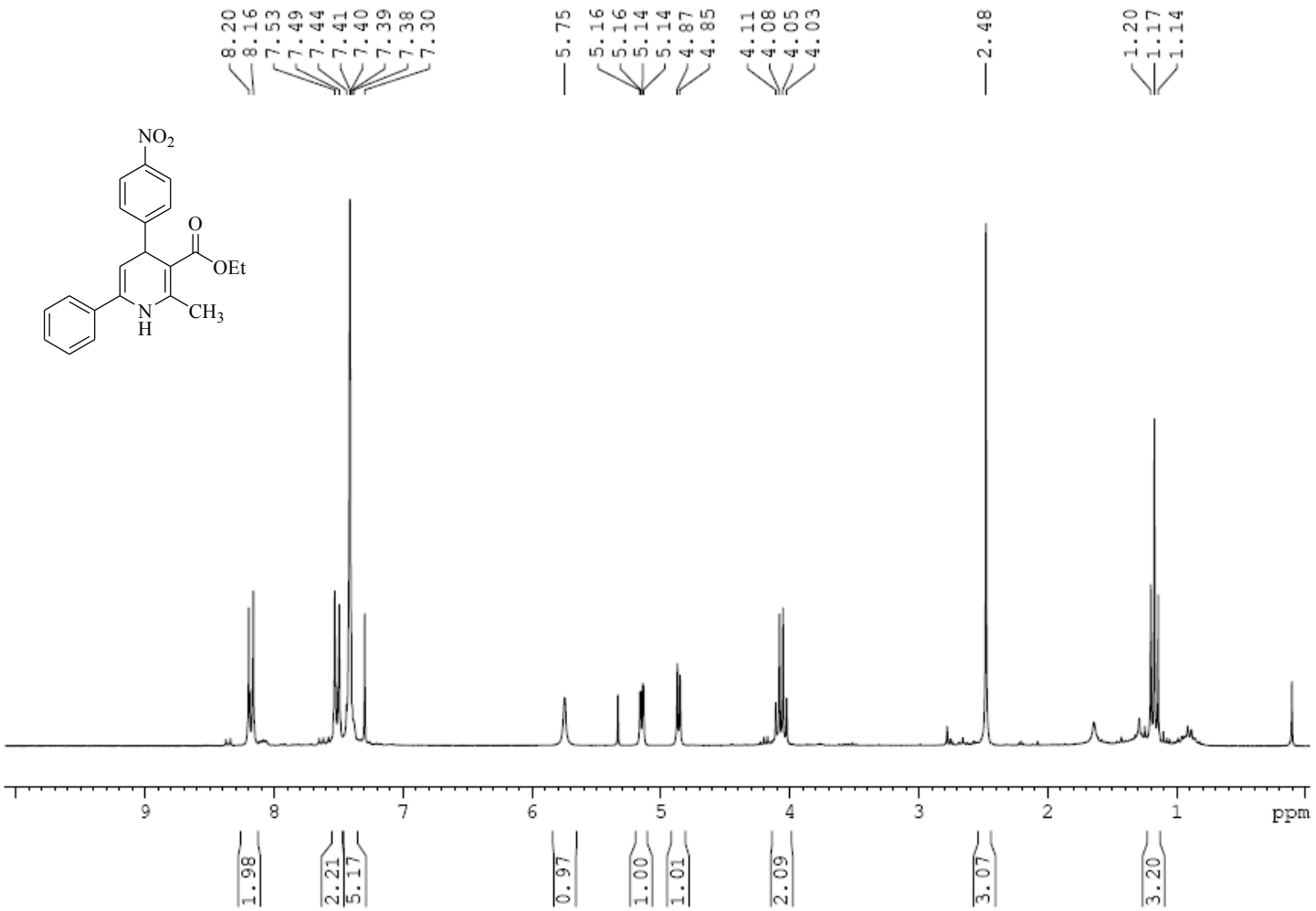
147.01
146.36
136.38
135.91
134.64
129.32
129.17
128.84
128.08
125.46
105.61
99.72
77.94
77.44
76.93
59.67
40.80
21.47
21.15
14.70
CH3
O
OEt
N
H
CH3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

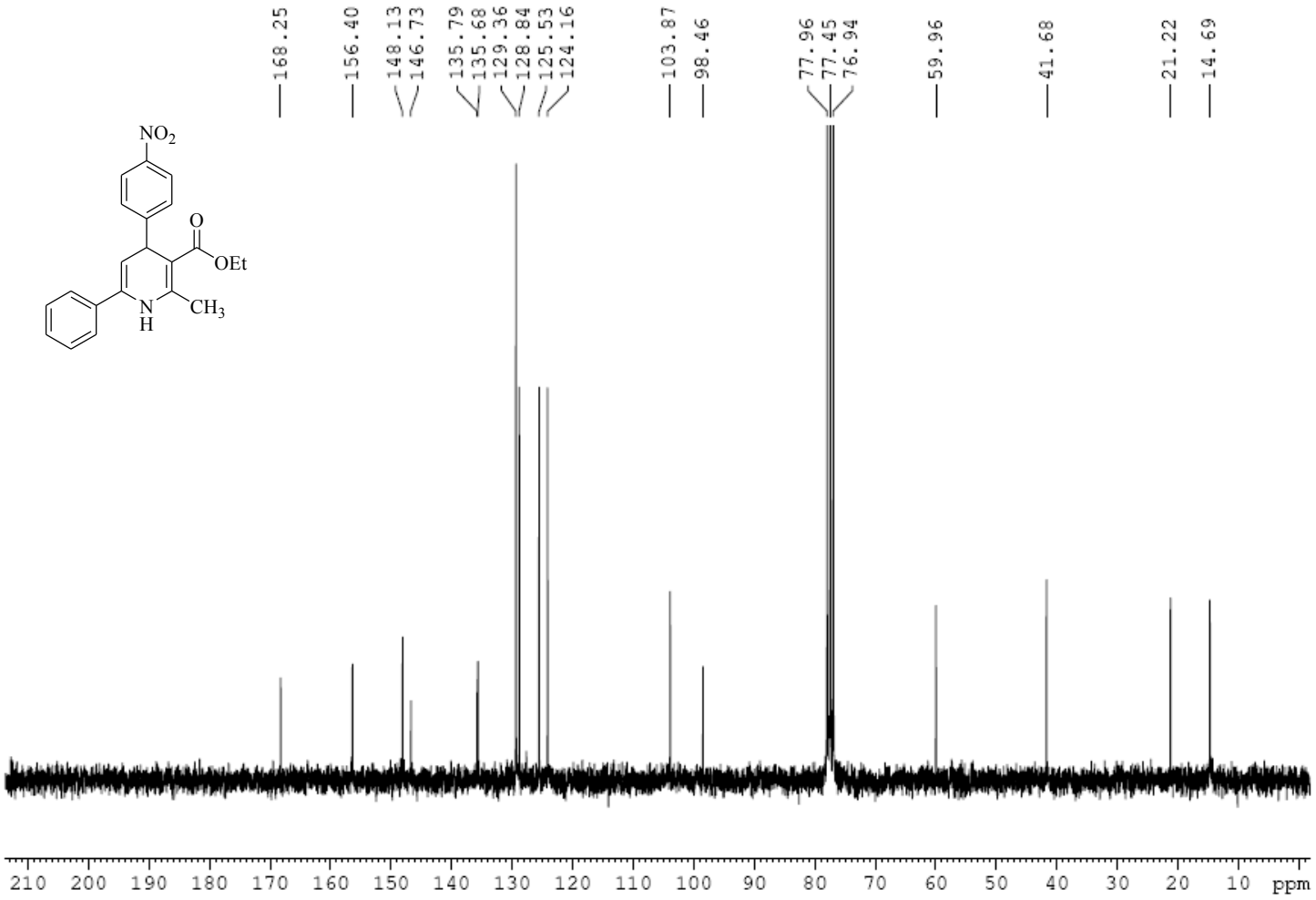
Allyl 6-(4-chlorophenyl)-2-methyl-4-phenyl-1,4-dihydropyridine-3-carboxylate (3o)



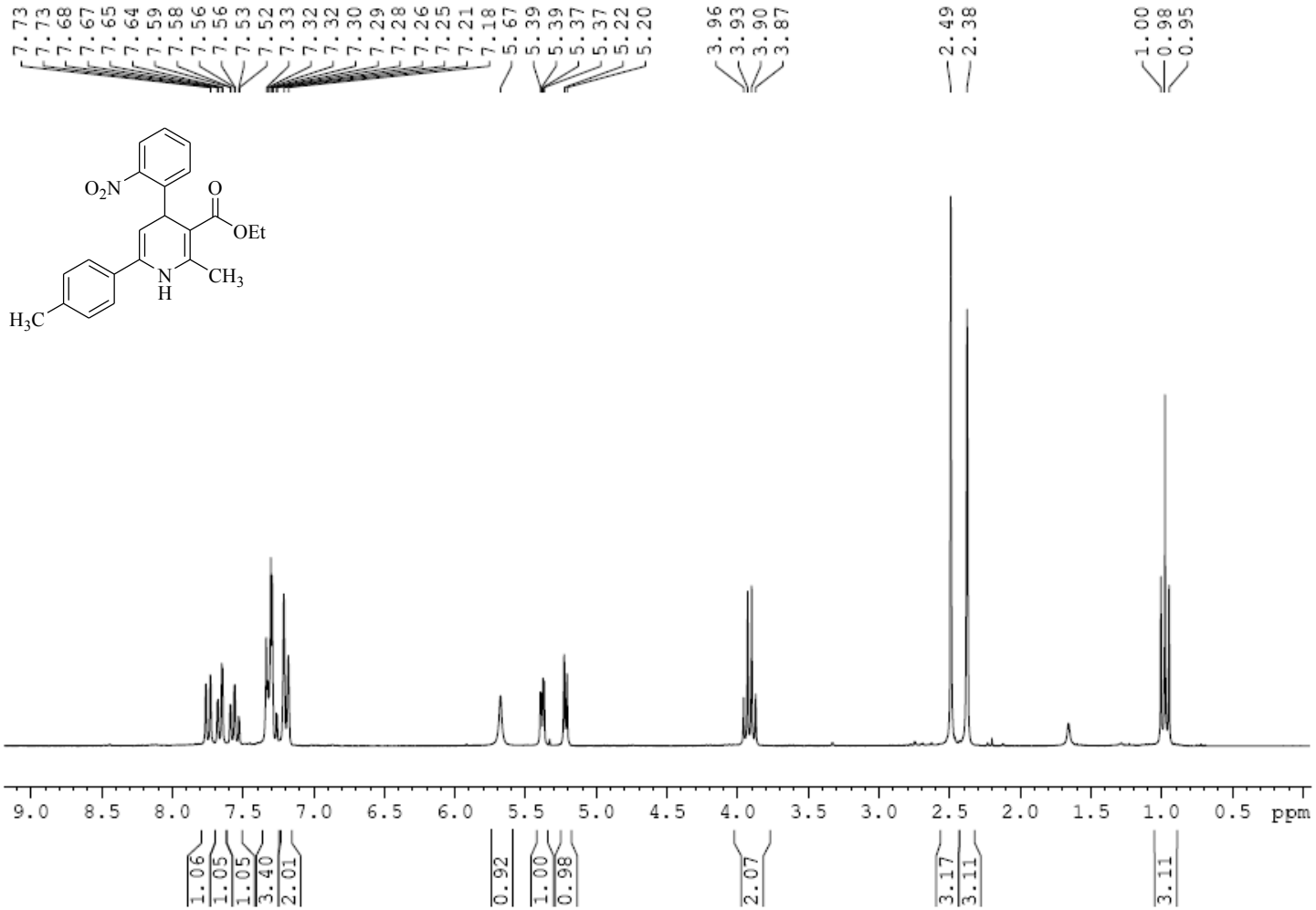

165.86
146.44
145.26
132.28
132.25
131.26
130.95
126.92
126.32
125.66
124.41
124.18
114.96
103.75
96.85
75.54
75.03
74.53
62.12
38.81
18.76
O
O
N
H
CH3
Cl
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

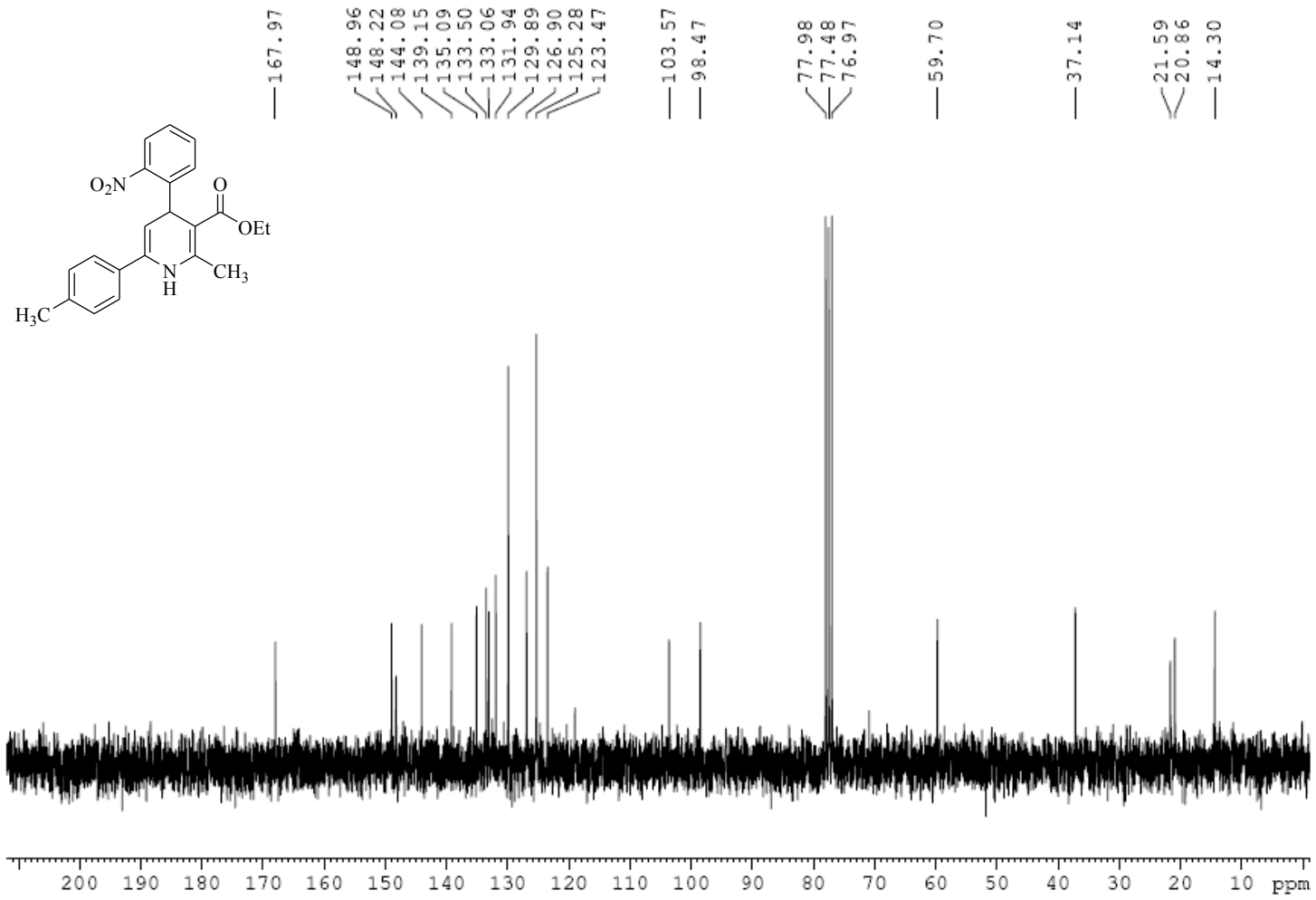
Ethyl 2-methyl-4-(4-nitrophenyl)-6-phenyl-1,4-dihydropyridine-3-carboxylate (3p)



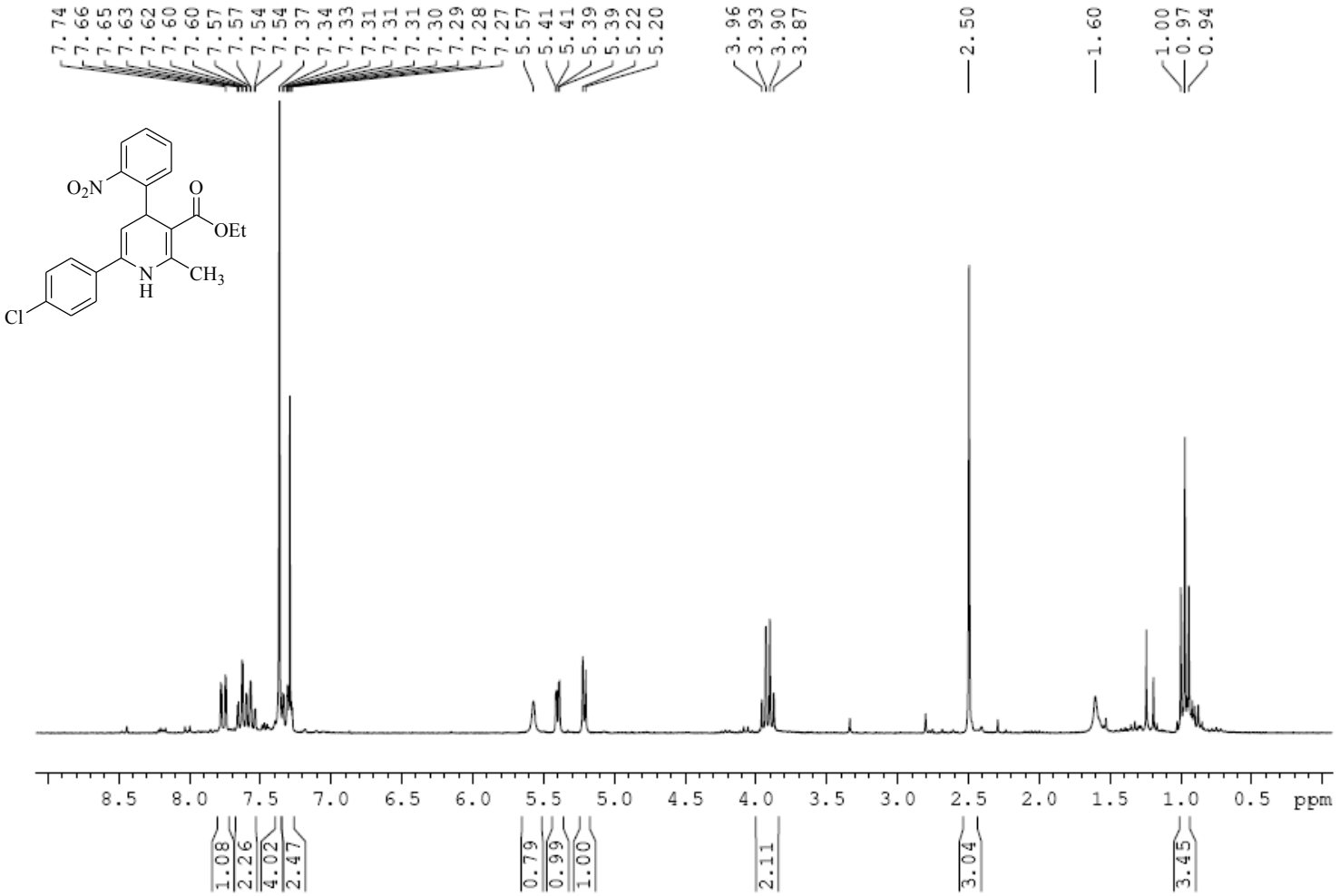

168.25
156.40
148.13
146.73
135.79
135.68
129.36
128.84
125.53
124.16
103.87
98.46
77.96
77.45
76.94
59.96
41.68
21.22
14.69
NO2
O
OEt
N
H
CH3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

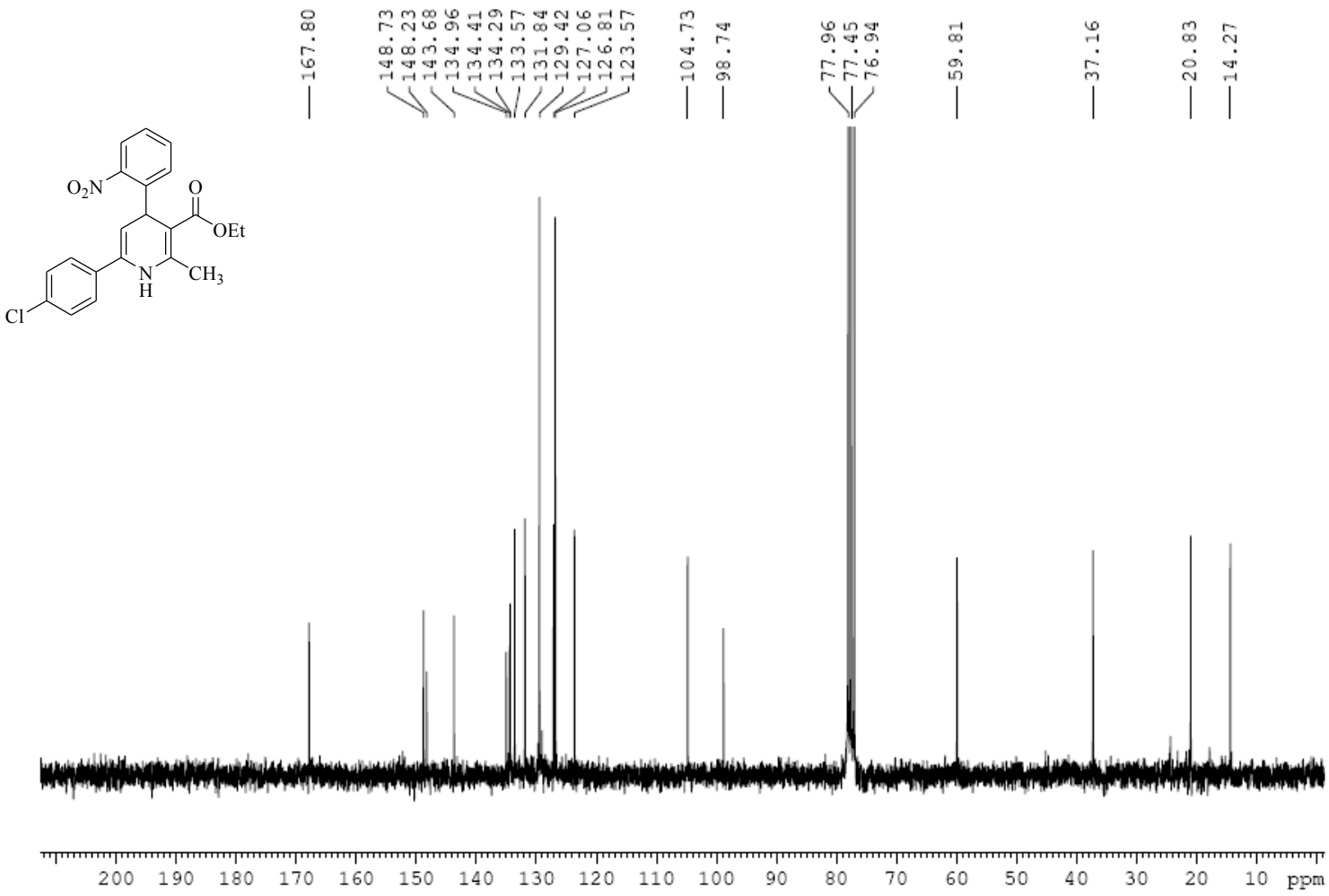
Ethyl 2-methyl-4-(2-nitrophenyl)-6-p-tolyl-1,4-dihydropyridine-3-carboxylate (3q)



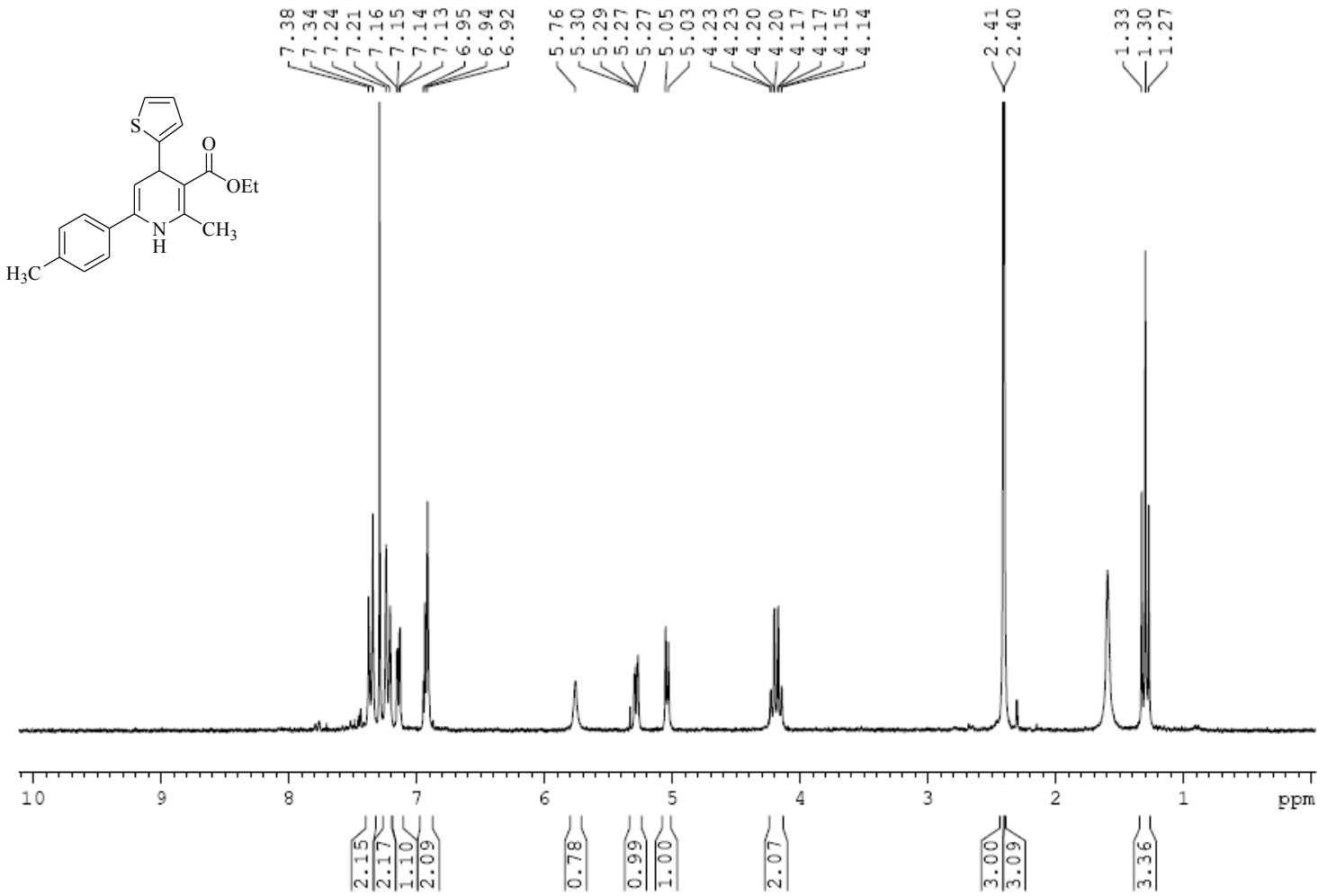

167.97
148.96
148.22
144.08
139.15
135.09
133.50
133.06
131.94
129.89
126.90
125.28
123.47
103.57
98.47
77.98
77.48
76.97
59.70
37.14
21.59
20.86
14.30
O2N
O
OEt
N
H
CH3
H3C
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

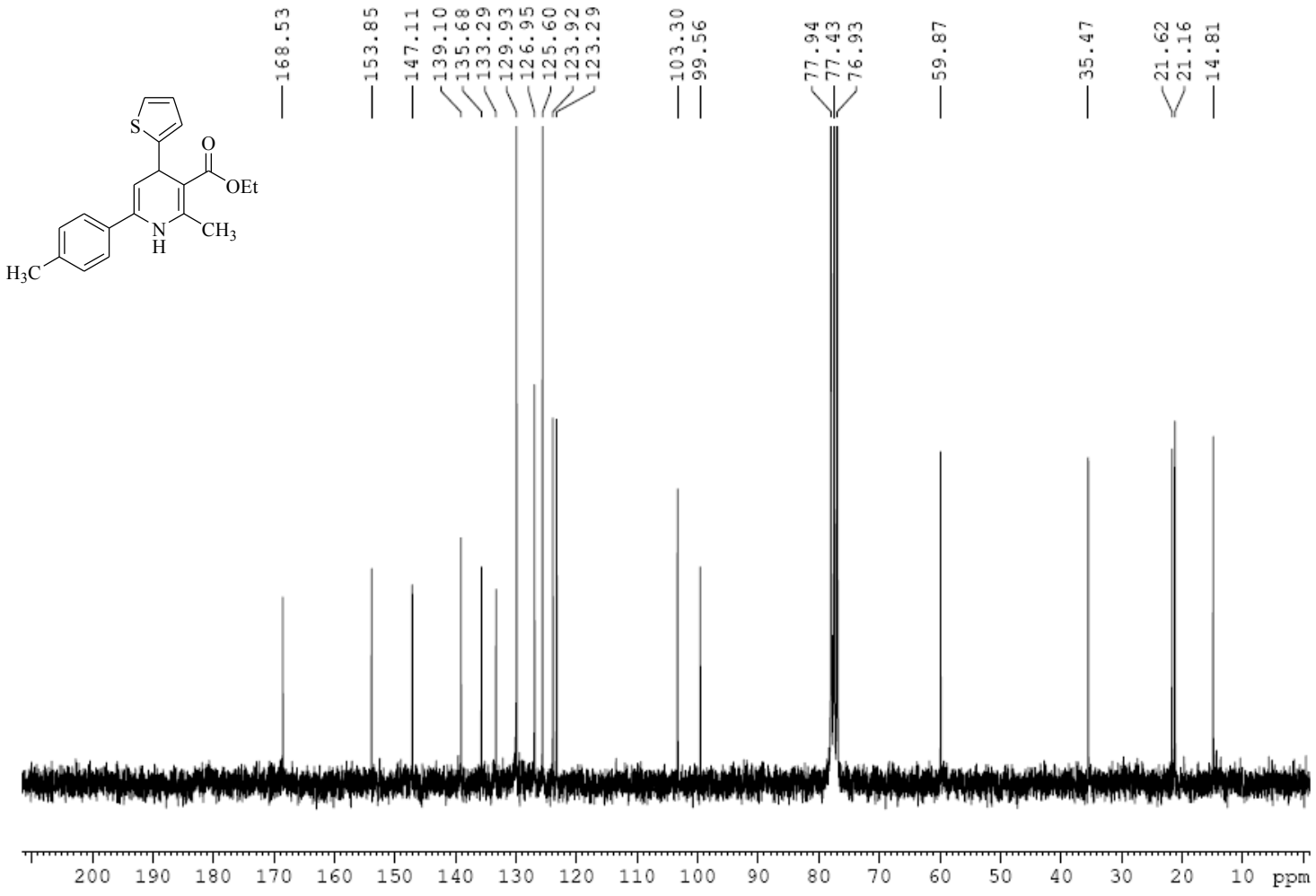
Ethyl 6-(4-chlorophenyl)-2-methyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3-carboxylate (3r)



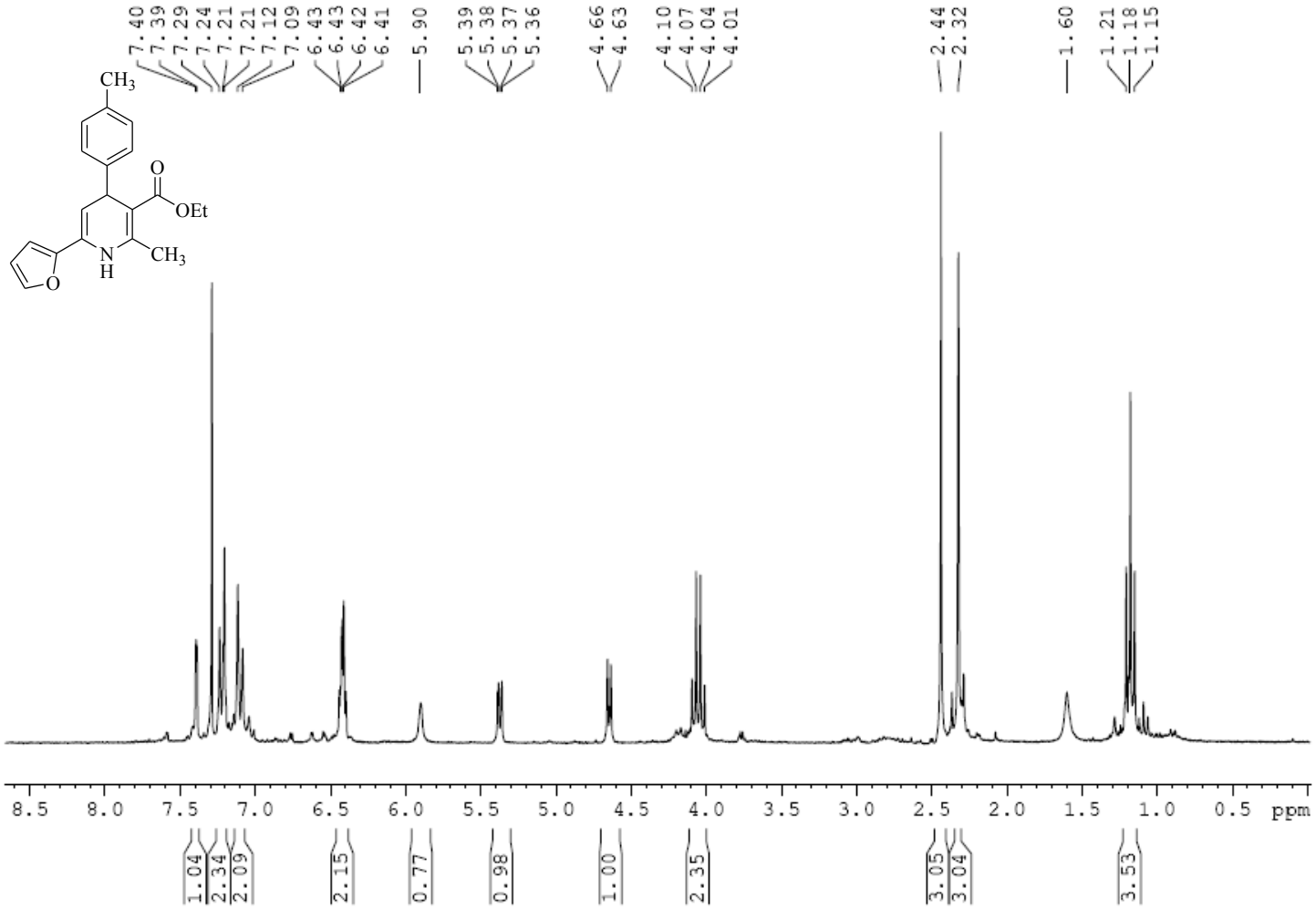

167.80
148.73
148.23
143.68
134.96
134.41
134.29
133.57
131.84
129.42
127.06
126.81
123.57
104.73
98.74
77.96
77.45
76.94
59.81
37.16
20.83
14.27
O2N
O
OEt
CH3
N
H
Cl
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

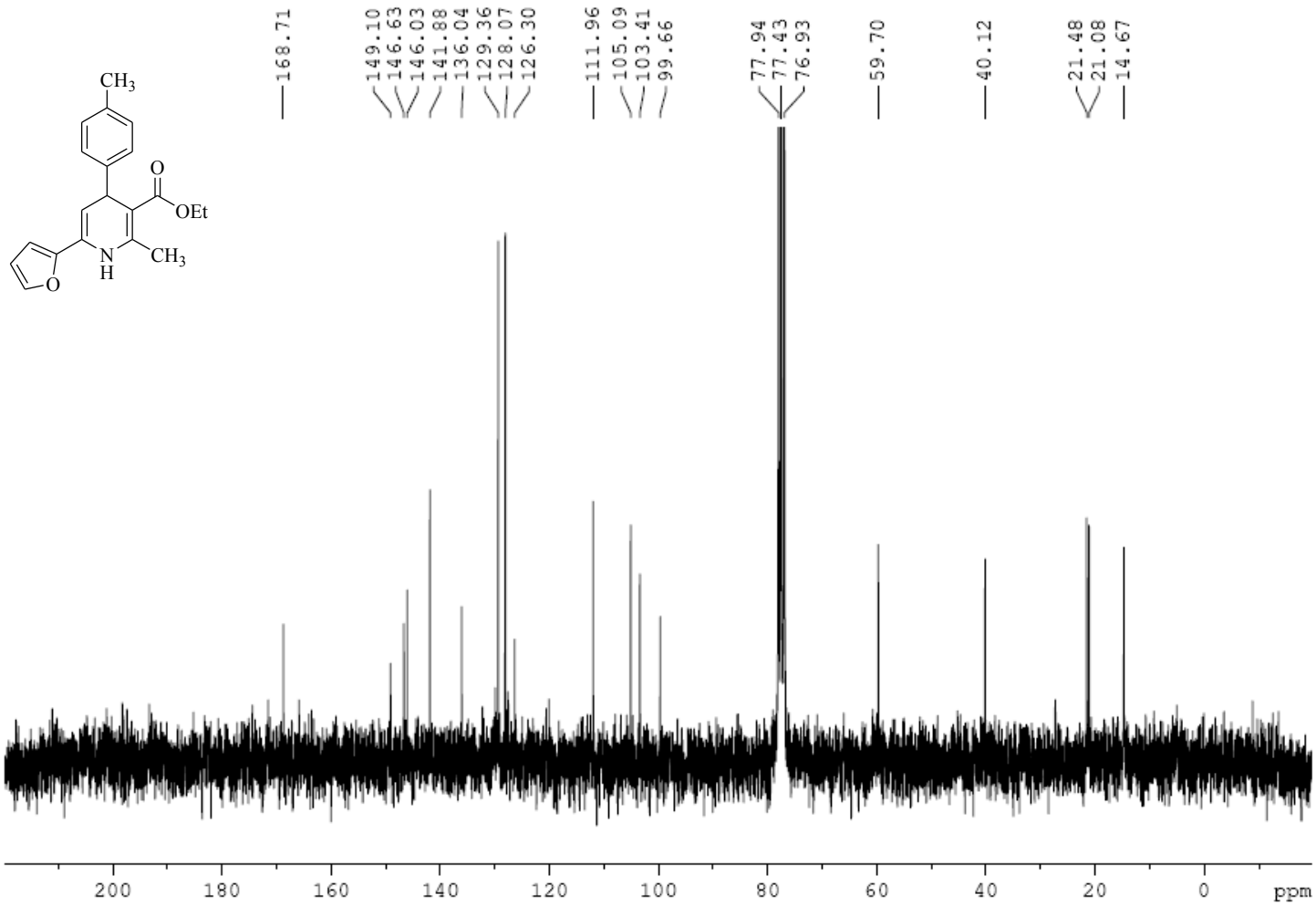
Ethyl 2-methyl-4-(thiophen-2-yl)-6-p-tolyl-1,4-dihydropyridine-3-carboxylate (3s)



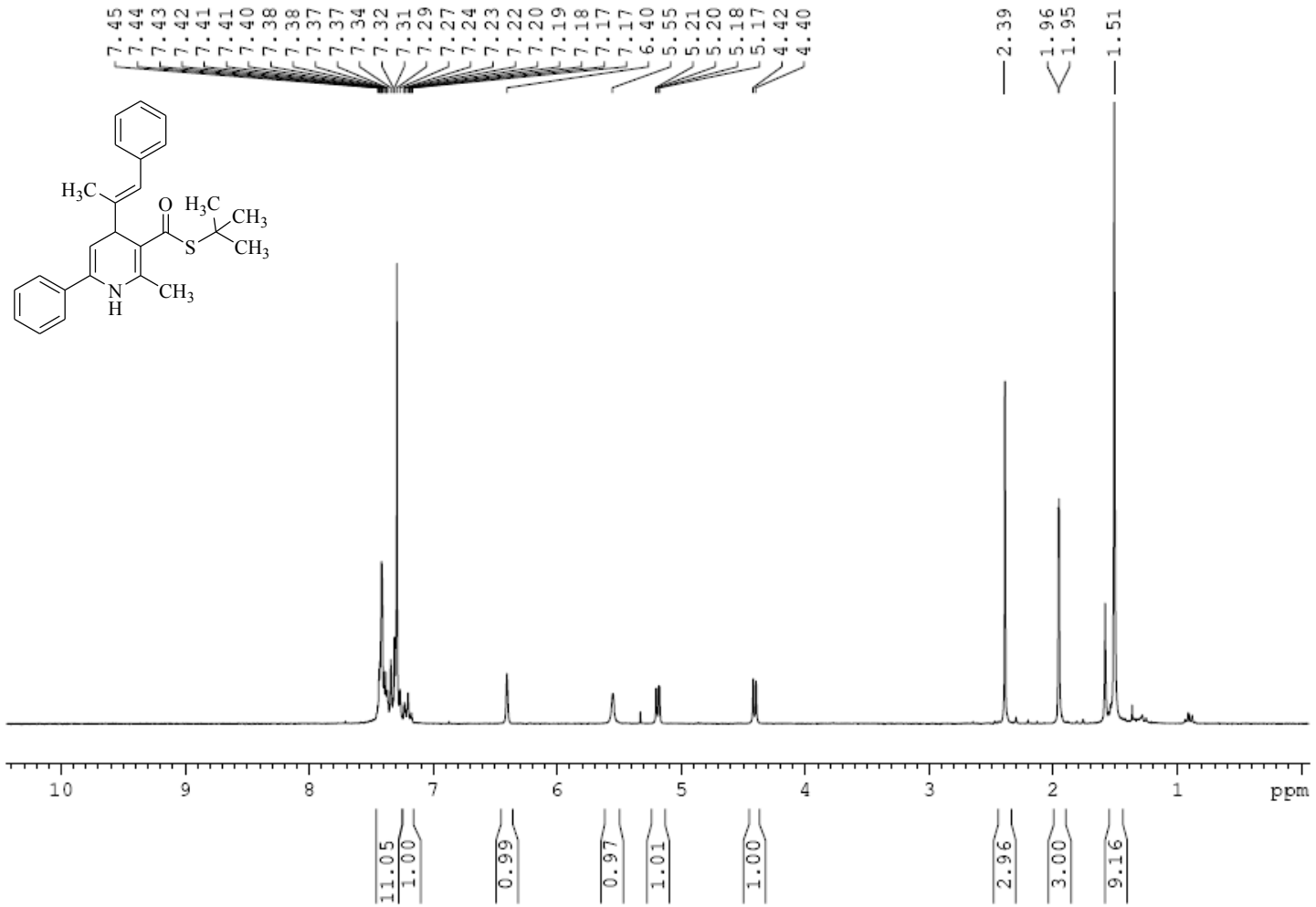

168.53
153.85
147.11
139.10
135.68
133.29
129.93
126.95
125.60
123.92
123.29
103.30
99.56
77.94
77.43
76.93
59.87
35.47
21.62
21.16
14.81
S
O
OEt
N
H
CH3
H3C
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

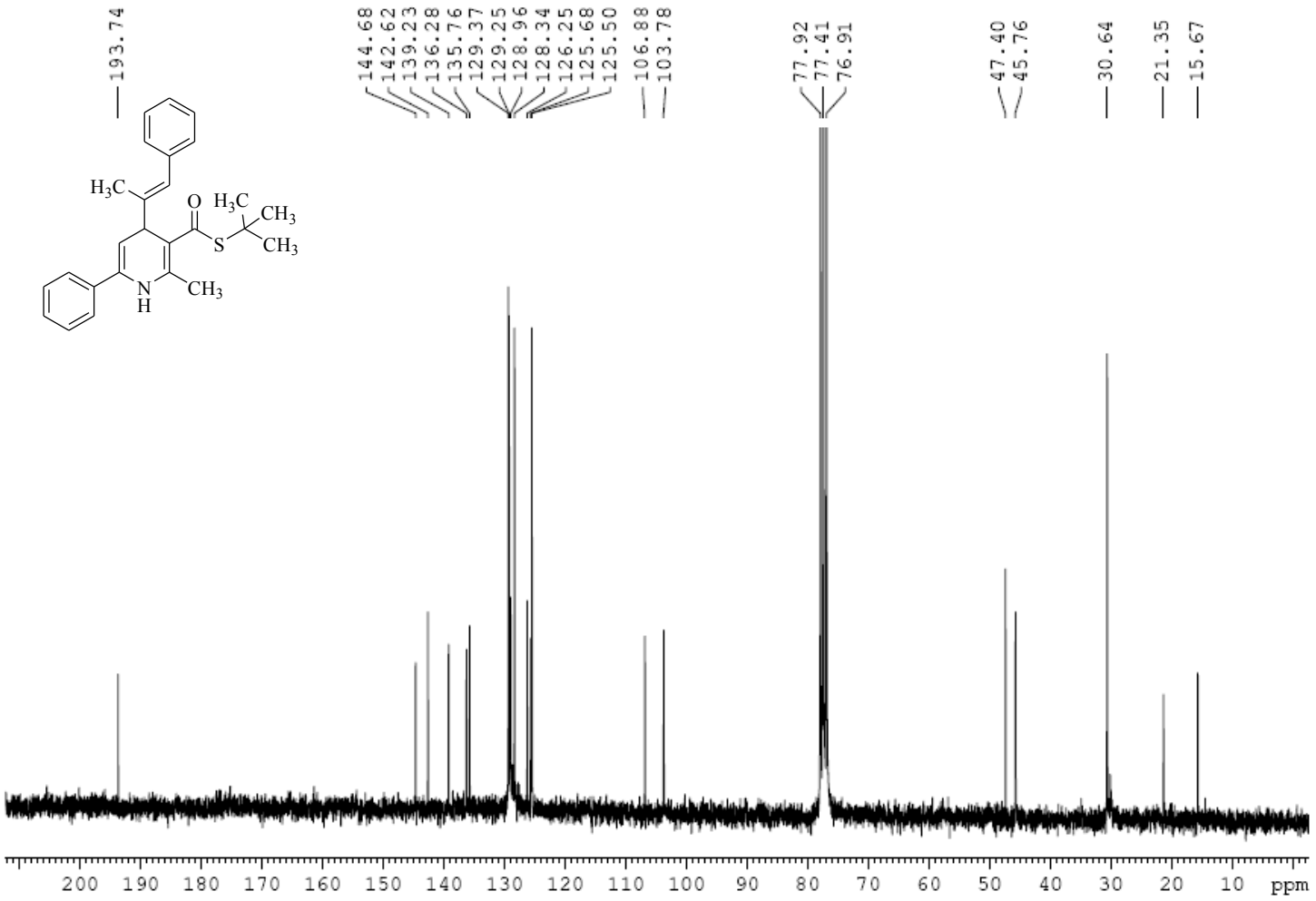
Ethyl 6-(furan-2-yl)-2-methyl-4-p-tolyl-1,4-dihydropyridine-3-carboxylate (3t)



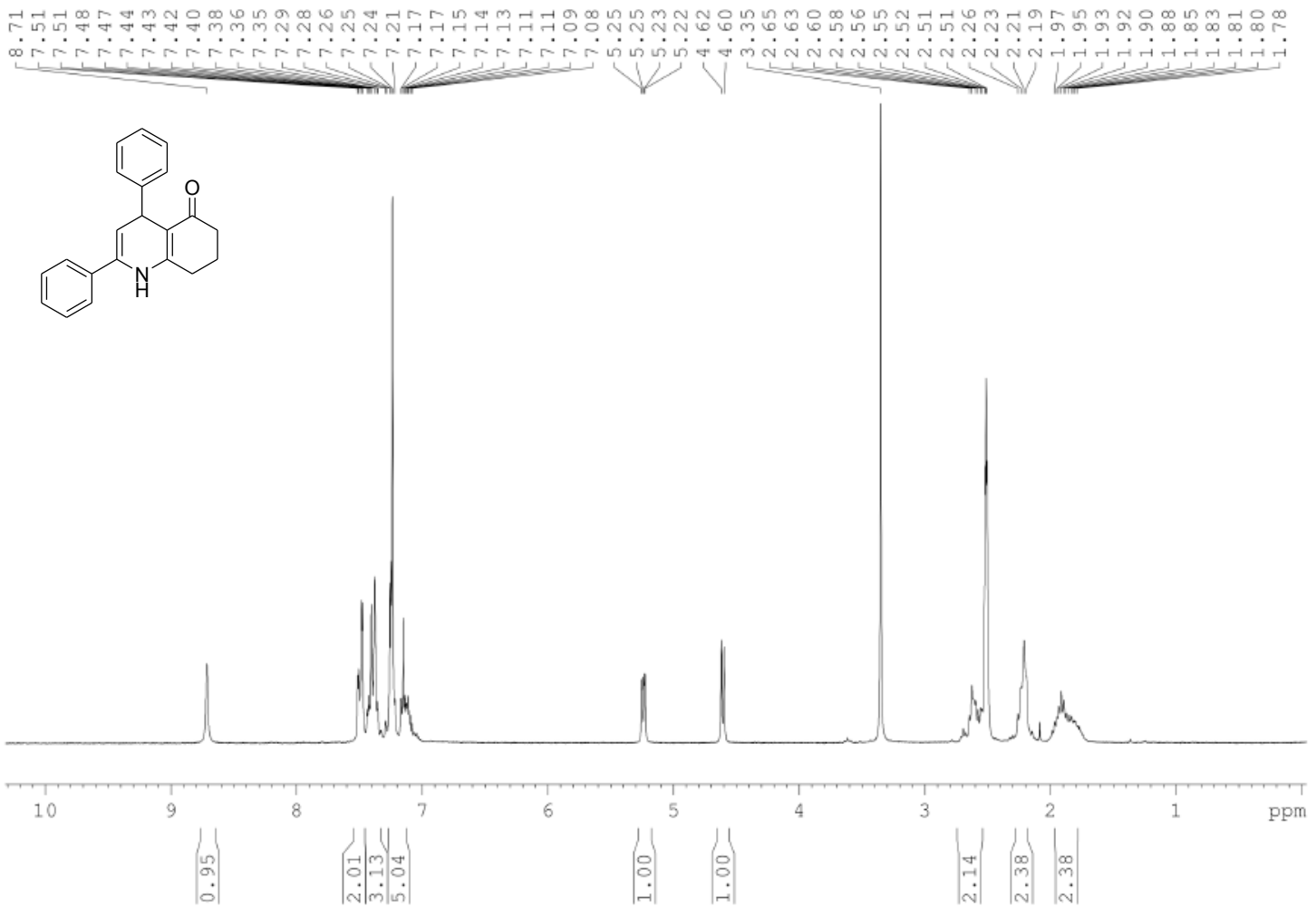

168.71
149.10
146.63
146.03
141.88
136.04
129.36
128.07
126.30
111.96
105.09
103.41
99.66
77.94
77.43
76.93
59.70
40.12
21.48
21.08
14.67
CH3
O
OEt
N
H
CH3
O
200
180
160
140
120
100
80
60
40
20
0
ppm

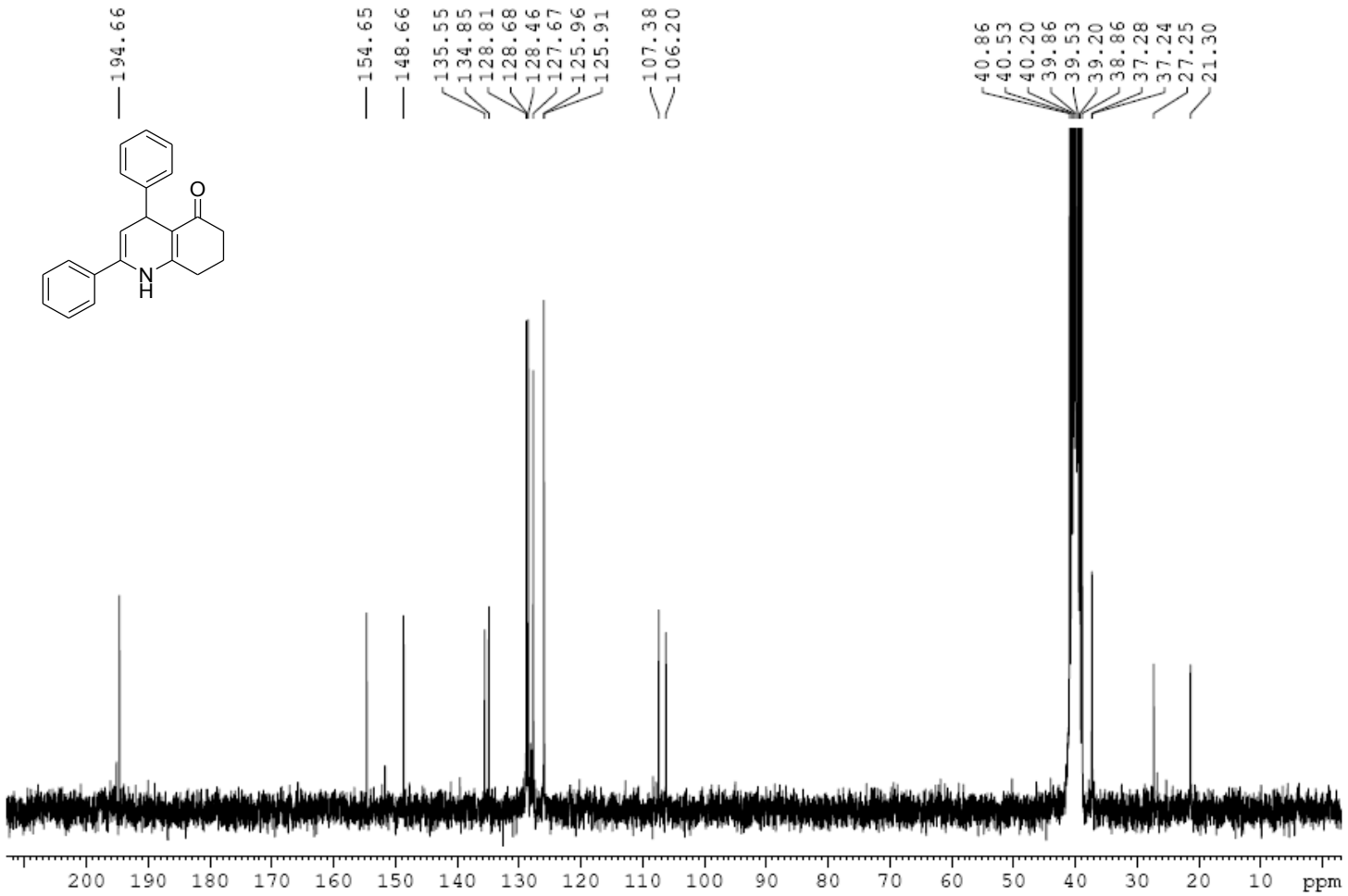
S-*tert*-butyl 2-methyl-6-phenyl-4-(1-phenylprop-1-en-2-yl)-1,4-dihydropyridine-3-carbothioate (3u)



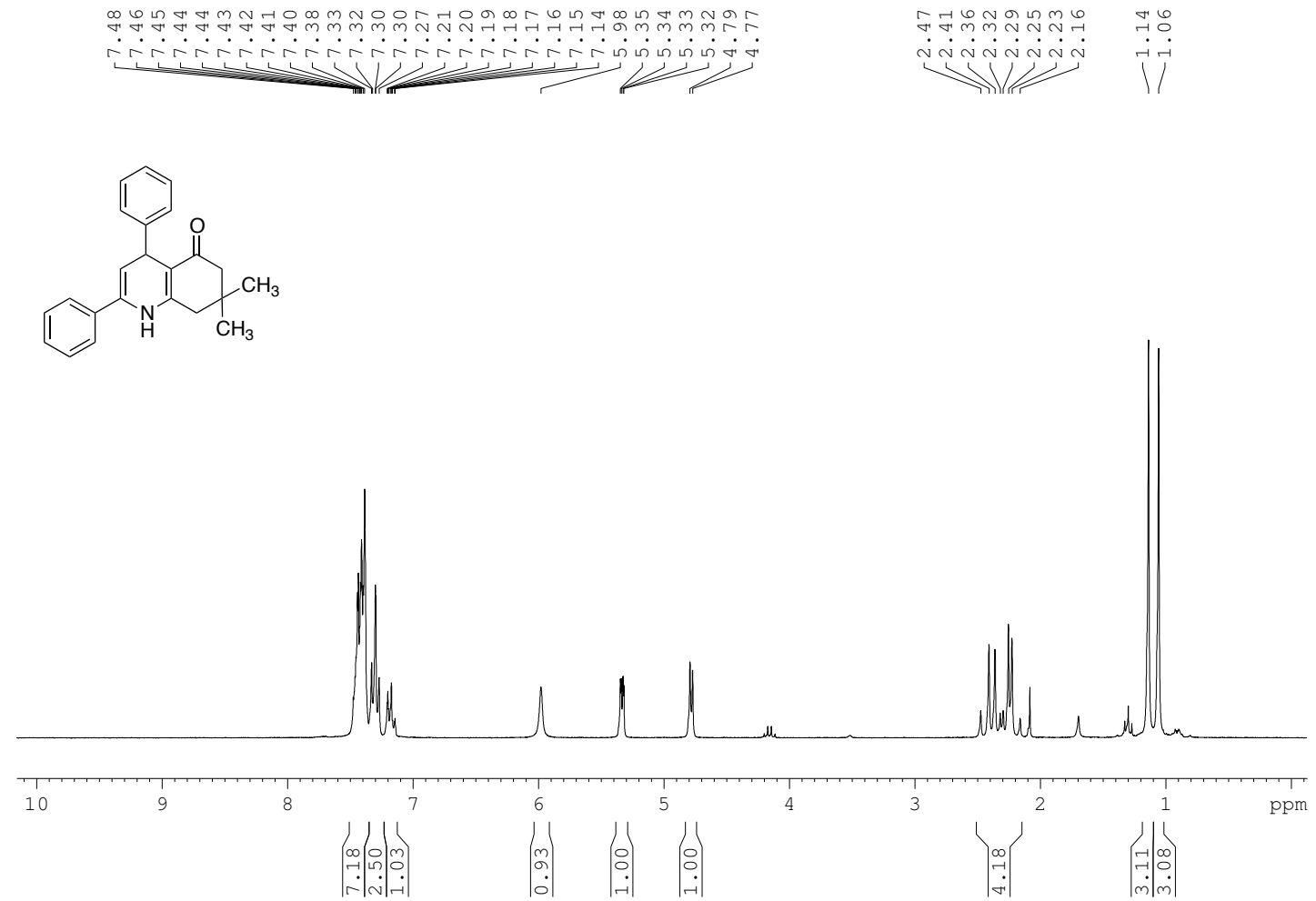

193.74
144.68
142.62
139.23
136.28
135.76
129.37
129.25
128.96
128.34
126.25
125.68
125.50
106.88
103.78
77.92
77.41
76.91
47.40
45.76
30.64
21.35
15.67
H3C
O
H3C
CH3
S
CH3
N
H
CH3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

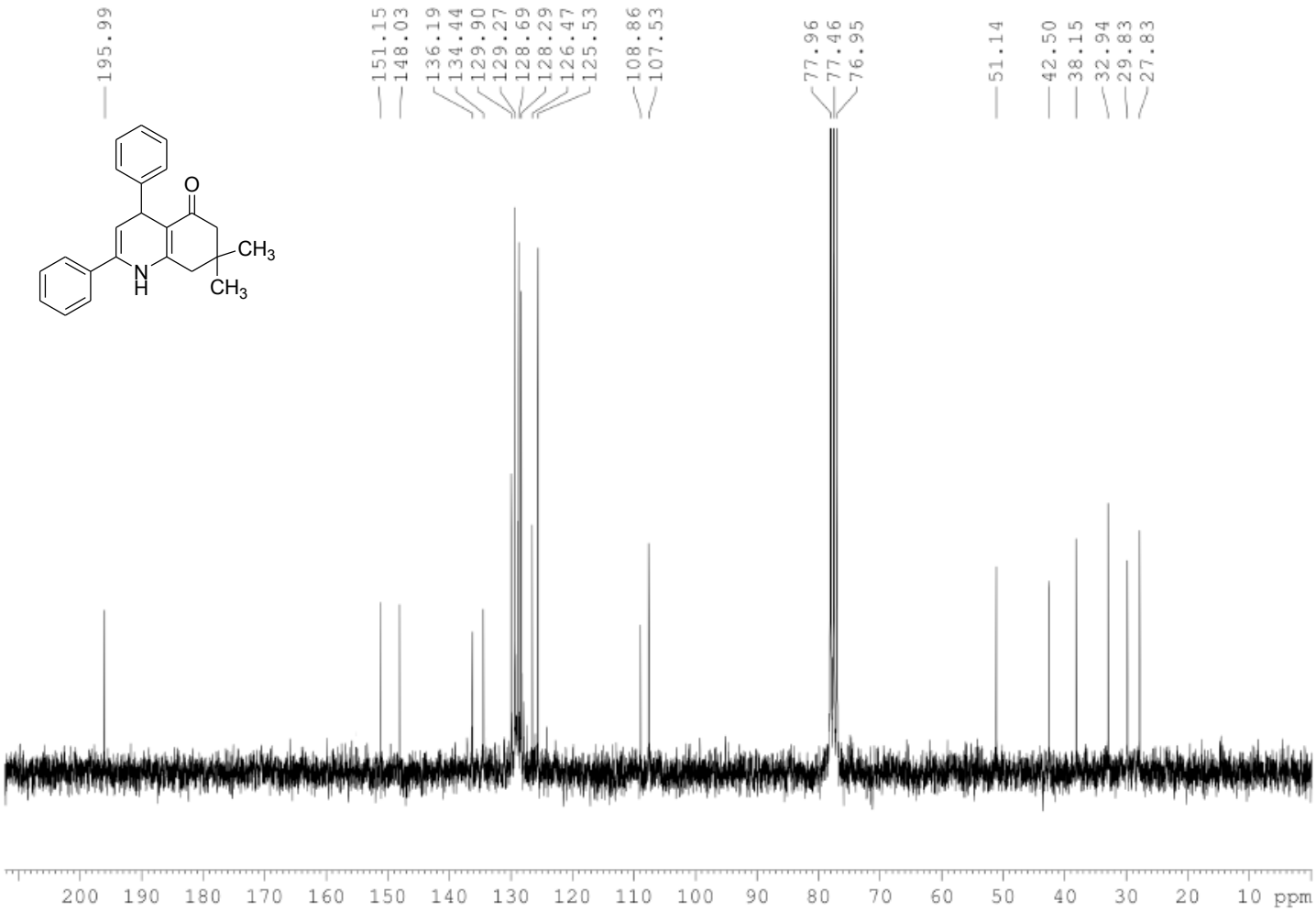
2,4-diphenyl-4,6,7,8-tetrahydroquinolin-5(1*H*)-one (5a)




194.66
154.65
148.66
135.55
134.85
128.81
128.68
128.46
127.67
125.96
125.91
107.38
106.20
40.86
40.53
40.20
39.86
39.53
39.20
38.86
37.28
37.24
27.25
21.30
O
N
H
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

7,7-dimethyl-2,4-diphenyl-4,6,7,8-tetrahydroquinolin-5(1*H*)-one (5b)




195.99
151.15
148.03
136.19
134.44
129.90
129.27
128.69
128.29
126.47
125.53
108.86
107.53
77.96
77.46
76.95
51.14
42.50
38.15
32.94
29.83
27.83
O
CH3
CH3
N
H
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm