Substituted 2-Arylquinoline and 2-Methyl-1,2,3,4-tetrahydroquinoline Derivatives with selective Anticancer Activity: Synthesis, Structure–Activity Relationships, and Molecular Modelling Insights

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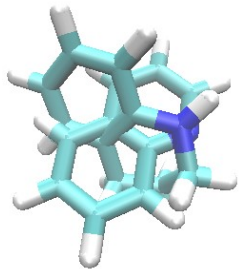


Figure S1. Structural alignment of the cores of IOX1, 2-Arylquinoline derivatives, and 2-Methyl-1,2,3,4-tetrahydroquinoline with RMSD of 0 Å and 2.42 Å, respectively.

3.1 Chemistry

Group F

2-Phenylquinoline (4)

White solid. M.p.: 67-69 °C. Yield 54 %. IR (KBr): ν 1589, 1473, 1439, 849, 748 cm^{-1}. ^{1}H NMR (400 MHz): δ 8.22 (1H, d, *J* = 8.61 Hz, 3-H), 8.19-8.16 (1H, m, 8-H), 8.19-8.16 (2H, m, 2'-H_{Ph} and 6'-H_{Ph}), 7.88 (1H, d, *J* = 8.58 Hz, 4-H), 7.83 (1H, d, *J* = 8.08 Hz, 5-H), 7.73 (1H, ddd, *J* = 7.20, 7.20, 0.72 Hz, 6-H), 7.55-7.52 (1H, m, 7-H), 7.55-7.52 (2H, m, 3'-H_{Ph} and 5'-H_{Ph}), 7.47 (1H, t, *J* = 7.20 Hz, 4'-H_{Ph}); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.3, 148.3, 139.7, 136.7, 129.7, 129.6, 129.2, 128.9 (2C), 127.5 (2C), 127.4, 127.1, 126.2, 118.9. MS *m/z* (EI) 205 (M^+). calcd for $C_{15}H_{11}N$: C, 87.77; H, 5.40; N, 6.82. Found: C, 87.73; H, 5.37; N, 6.79.

6-Ethyl-2-phenylquinoline (5)

White solid. M.p.: 63-66 °C. Yield 51%. IR (KBr): ν 2960, 2895, 1493, 1443 cm^{-1}. ^{1}H NMR (400 MHz): δ 8.17-8.13 (2H, m, 2'-H_{Ph} and 6'-H_{Ph}), 8.15-8.13 (1H, m, 3-H), 8.11 (1H, d, *J* = 9.28 Hz, 8-H), 7.84 (1H, d, *J* = 8.56 Hz, 4-H), 7.61-7.59 (1H, m, 5-H), 7.61-7.59 (1H, m, 7-H), 7.53 (2H, t, *J* = 7.08 Hz, 3'-H_{Ph} and 5'-H_{Ph}), 7.46 (1H, t, *J* = 7.29 Hz, 4'-H_{Ph}), 2.85(2H, q, *J* = 7.59 Hz, CH_3-$\underline{CH_2}$-), 1.36(3H, t, *J* = 7.58 Hz, $\underline{CH_3}$-CH_2-); ^{13}C NMR (100 MHz): δ 156.5, 147.1, 142.3, 139.8, 136.2, 130.8, 129.5, 129.0, 128.7 (2C), 127.4 (2C), 127.2, 124.9, 118.9, 28.8, 15.3. MS *m/z* (EI) 233 (M^+). Calcd for $C_{17}H_{15}N$: C, 87.52; H, 6.48; N, 6.00. Found: C,87.51; H, 6.50; N, 6.02.

6-Nitro-2-phenylquinoline (6)

Brown solid. M.p.: 175-178 °C. Yield 56%. IR (KBr): ν 3456, 1592, 1537, 1476, 873 cm^{-1}. ^{1}H NMR (400 MHz): δ 8.78 (1H, d, *J* = 2.41 Hz, 6-H), 8.47 (1H, dd, *J* = 9.22, 2.45 Hz, 7-H), 8.37 (1H, d, *J* = 8.68 Hz, 3-H), 8.26 (1H, d, *J* = 9.24 Hz, 8-H), 8.22-8.20 (2H, m, 2'-H_{Ph} and 6'-H_{Ph}), 7.56-7.54 (2H, m, 3'-H_{Ph} and 5'-H_{Ph}), 7.48-7.50 (1H, m, 4'-H_{Ph}); ^{13}C NMR (100 MHz): δ 160.6, 150.4, 138.4, 131.4, 130.5, 129.0 (2C), 127.8 (2C), 127.5, 127.4, 124.3, 123.2, 120.6, 77.0. MS *m/z* (EI) 250 (M^+). Calcd for $C_{15}H_{10}N_2O_2$: C, 71.99; H, 4.03; N, 11.19. Found: C, 71.98; H, 4.02; N, 11.22.

6-Fluoro-2-phenylquinoline (7)

Beige solid. M.p.: 128-131 °C. Yield 58 %. IR (KBr): ν 1484, 1231, 831, 750, 686 cm^{-1}. ^{1}H NMR (400 MHz): δ 8.19-8.15 (1H, m, 8-H), 8.19-8.15 (2H, m, 2'-H_{Ph} and 6'-H_{Ph}), 8.15-8.13 (1H, m, 3-H), 7.86 (1H, d, *J* = 8.72 Hz, 4-H), 7.56-7.52 (2H, m, 3'-H_{Ph} and 5'- H_{Ph}), 7.50-7.46 (1H, m, 7-H), 7.50-7.46 (1H, m, 5-H), 7.43 (1H, dd, *J* = 8.80, 2.80 Hz, 4'-H_{Ph})); ^{13}C NMR (100 MHz): δ 161.7, 156.7, 145.5, 139.4, 135.9, 132.2, 129.4, 128.8 (2C), 127.4 (2C), 119.8, 119.6, 110.5, 110.3; MS *m/z* (EI) 223 (M^+). Calcd for $C_{15}H_{10}FN$: C, 80,70; H, 4,51; F, 8,51; N, 6,27. Found: C, 80.73; H, 4.50; F, 8.53; N, 6.29.

6-Chloro-2-phenylquinoline (8)

Beige solid. M.p.: 134-137 °C. Yield 50 %. IR (KBr): ν 1495, 1223, 835, 752, 687 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.16-8.14 (1H, m, 3-H), 8.16-8.14 (1H, m, 8-H), 8.11 (2H, d, *J* = 7.76 Hz, 2'- H_{Ph} and 6'- H_{Ph}), 7.89 (1H, d, *J* = 8.48 Hz, 4-H), 7.80 (1H, d, *J* = 2.30 Hz, 6-H), 7.65 (1H, dd, *J* = 9.02, 2.33 Hz, 7-H), 7.53 (2H, t, *J* = 7.50 Hz, 3'-H_{Ph} and 5'-H_{Ph}), 7.47 (1H, t, *J* = 7.15 Hz, 4'-H_{Ph}); ^{13}C NMR (100 MHz): δ 157.5, 146.6, 139.2, 135.8, 131.9, 131.3, 130.5, 129.5, 128.9 (2C), 127.7 (2C), 127.5, 126.1, 119.7. MS *m/z* (EI) 239 (M^+). Calcd for $C_{15}H_{10}ClN$: C, 75.16; H, 4.21; Cl, 14.79; N, 5.84. Found: C, 75.16; H, 4.23; Cl, 14.81; N, 5.82.

6,7-methylenedioxo-2-Phenylquinoline (10)

Beige solid. M.p.: 109-111 °C. Yield 54%. IR (KBr): ν 1457, 1228, 1029, 849, 748 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.11 (2H, dd, *J* = 7.11, 1.47 Hz, 2'-H_{Ph} and 6'-H_{Ph}), 7.98 (1H, d, *J* = 8.48 Hz, 3-H), 7.69 (1H, d, *J* = 8.49 Hz, 4-H), 7.51 (2H, dd, *J* = 7.12, 1.68 Hz, 3'-H_{Ph} and 5'-H_{Ph}), 7.46 (1H, s, 8-H), 7.03 (1H, s, 5-H), 6.08 (2H, s, -O-CH_2-O-); ^{13}C NMR (100 MHz): δ 155.2, 150.7, 147.6, 146.4, 139.7, 135.4, 128.8, 128.7 (2C), 127.1 (2C), 124.0, 117.1, 106.1, 102.4, 101.6. MS *m/z* (EI) 249 (M^+). Calcd for $C_{16}H_{11}NO_2$: C, 77.10; H, 4.45; N, 5.62. Found: C, 77.13; H, 4.43; N, 5.64.

Group G

2-(Phenyl-3',4'-dioxomethylen)-quinoline (11)

Yellow solid. M.p.: 90-92 °C. Yield 50%. IR (KBr): ν 2884, 1594, 1495, 1248, 1042 cm^{-1}. ^1H NMR (400 MHz): δ 8.16 (1H, d, *J* = 8.56 Hz, 3-H), 8.12 (1H, d, *J* = 8.49 Hz, 4-H), 7.80 (1H, m, 8-H), 7.77 (1H, m, 5-H), 7.74 (1H, d, *J* = 1.71 Hz, 2'-H_{Ph}), 7.70 (1H, ddd, *J*= 8.41, 8.41, 1.45 Hz, 7-H), 7.65 (1H, dd, *J* = 8.07, 1.71 Hz, 6'-H_{Ph}), 7.50 (1H, ddd, *J*= 8.07, 8.07, 1,13 Hz, 6-H), 6.95 (1H, d, *J* = 8.13 Hz, 5'-H_{Ph}), 6.03 (2H, s, -OCH_2O-);^{13}C NMR ($CDCl_3$): δ 156.6, 148.8, 148.4, 148.2, 136.6, 134.1, 129.6, 129.5, 127.4, 127.0, 126.0, 121.7, 118.5, 108.4, 107.9, 101.3. MS *m/z* (EI) 249 (M^+). Calcd for $C_{16}H_{11}NO_2$: C, 77.10; H, 4.45; N, 5.62. Found: C, 77.13; H, 4.44; N, 5.62.

2-(Phenyl-3',4'-dioxomethylen)-6-methylquinoline (12)

Yellow solid. M.p.: 166-168. Yield 41%. IR (KBr): ν 2898, 1587, 1490, 1460, 1246 cm^{-1}. ^1H NMR (400 MHz): δ 8.07 (1H, d, *J* = 8.56 Hz, 3-H), 8.00 (1H, d, *J* = 8.56 Hz, 4-H), 7.74 (1H, d, *J* = 8.56 Hz, 8-H), 7.72 (1H, d, *J* = 1.71 Hz, 2'-H_{Ph}), 7.63 (1H, dd, *J* = 8.31, 1.71 Hz, 6'-H_{Ph}), 6.92 (1H, d, *J* = 8.31 Hz, 5'-H_{Ph}), 7.54 (1H, m, 7-H), 7.52 (1H, d, *J* = 1.71 Hz, 5-H), 6.03 (2H, s,-OCH_2O-), 2.53 (3H, s, 6-CH_3); ^{13}C NMR (100 MHz): δ 155.9, 148.7, 148.4, 146.8, 136.0, 135.9, 134.3, 131.9, 129.3, 127.0, 126.3, 121.6, 118.6, 108.4, 107.9, 101.3, 21.5. MS *m/z* (EI) 263 (M^+). Calcd for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32. Found: C, 77.54; H, 4.97; N, 5.32.

2-(Phenyl-3',4'-dioxomethylen)-6-methoxyquinoline (13)

Brown solid. M.p.: 139-141. Yield 59 %. IR (KBr): ν 2960, 2037, 1612, 1588, 1489 cm^{-1}. ^1H NMR (400 MHz): δ 8.06 (1H, d, *J* = 8.64 Hz, 3-H), 8.02 (1H, d, *J* = 9.21 Hz, 4-H), 7.69 (1H, d, *J* = 1.67 Hz, 2'-H_{Ph}), 7.61 (1H, dd, *J* = 8.12, 1.72 Hz, 6'-H_{Ph}), 7.74 (1H, d, *J* = 8.62 Hz, 8-H), 7.36 (1H, dd, *J* = 9.26, 2.79 Hz, 7-H), 7.07 (1H, s, *J* = 2.75 Hz, 5-H), 6.93 (1H, d, *J* = 8.12 Hz, 5'-H_{Ph}), 6.03 (2H, s, -OCH_2O-), 3.94 (3H, s, 6-OCH_3). MS *m/z* (EI) 279 (M^+). Calcd for $C_{17}H_{13}NO_3$: C, 73.11; H, 4.69; N, 5.02. Found: C, 73.13; H, 4.70; N, 5.04.

2-(Phenyl-3',4'-dioxomethylen)-7-ethylquinoline (14)

Yellow solid. M.p.: 175-177. Yield 40 %. IR (KBr): ν 2959, 2898, 1585, 1490, 1442 cm^{-1}. ^1H NMR (400 MHz): δ 8.16 (1H, d, *J* = 8.60 Hz, 3-H), 8.12 (1H, d, *J* = 8.68 Hz, 4-H), 7.79 (1H, d, *J* = 1.76 Hz, 2'-H_{Ph}), 7.77 (1H, d, *J* = 7.95 Hz, 5-H), 7.68 (1H, dd, *J* = 8.15, 1.74 Hz, 6'-H_{Ph}), 7.50 (1H, d, *J* = 1.55 Hz, 8-H), 7.49 (1H, dd, *J* = 7.98, 1.44 Hz, 6-H), 7.08 (1H, d, *J* = 8.15, 5'-H_{Ph}), 5.94 (2H, s,-OCH_2O-), 1.84 (2H, q, *J* = 7.95 Hz, 8-$\underline{CH_2}CH_3$-), 1.18 (3H, t, *J* = 7.95 Hz, 8-$CH_2\underline{CH_3}$-). MS *m/z* (EI) 277 (M^+). Calcd for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05. Found: C, 77.99; H, 5.46; N, 5.07.

2-(Phenyl-3',4'-dioxomethylen)-6,8-dimethoxyquinoline (15)

Yellow solid. M.p.: 146-148. Yield 62 %. IR (film): ν 2955, 2899, 1607, 1478, 1451 cm^{-1}. ^1H NMR (400 MHz): δ 8.02 (1H, d, *J* = 8.65 Hz, 3-H), 7.76 (1H, d, *J* = 8.62 Hz, 4-H), 7.71 (1H, d, *J* = 1.71 Hz, 2'-H_{Ph}), 7.62 (1H, dd, *J* = 8.13, 1.76 Hz, 6'-H_{Ph}), 6.91 (1H, d, *J* = 8.07 Hz, 5'-H_{Ph}), 6.71 (1H, d, *J* = 2.47 Hz, 5-H), 6.65 (1H, d, *J* = 2.48 Hz, 7-H), 6.01 (2H, s, -OCH_2O-), 4.05 (1H, s, 8-OCH_3), 3.92 (1H, s, 6-H); ^{13}C NMR (100 MHz): δ 158.0, 156.4, 153.3, 148.3, 148.2, 136.6, 135.5, 134.4, 128.6, 121.3, 119.4, 108.3, 107.8, 101.5, 101.2, 96.8, 56.1, 55.5. MS *m/z* (EI) 309 (M^+). Calcd for $C_{18}H_{15}NO_4$: C, 69.89; H, 4.89; N, 4.53; Found: C, 69.88; H, 4.90; N, 4.52.

2-(Phenyl-3',4'-dioxomethylen)-5,8-dimethylquinoline (16)

Yellow solid. M.p.: 170-173. Yield 58 %. IR (KBr): ν 2896, 1591, 1487, 1463, 1251 cm^{-1}. ^1H NMR (400 MHz): δ 8.28 (1H, d, *J* = 8.82 Hz, 3-H), 7.88 (1H, d, *J* = 1.67 Hz, 2'-H_{Ph}), 7.81 (1H, d, *J* = 8.82 Hz, 4-H), 7.73 (1H, dd, *J* = 8.15, 1.68 Hz, 6'-H_{Ph}), 7.44 (1H, d, *J* = 7.09 Hz, 7-H), 7.20 (1H, d, *J* = 7.09 Hz, 6-H), 6.95 (1H, d, *J* = 8.13 Hz, 5'- H_{Ph}), 6.04 (2H, s, -OCH_2O-),

2.84 (3H, s, 5-CH_3), 2.64 (3H, s, 8-CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 154.2, 148.6, 148.3, 147.2, 135.3, 134.4, 133.2, 131.8, 129.2, 126.2, 126.1, 121.4, 117.1, 108.3, 107.8, 101.2, 18.3, 17.8. MS *m/z* (EI) 277 (M^+). Calcd for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05. Found: C, 77.94; H, 5.46; N, 5.03

N-(2-Methyl-1,2,3,4-tetrahydroquinolin-4-yl)acetamide (17)

IR (KBr): ν 3247, 3335, 1640 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.18 (d, *J* = 6.3 Hz, 3 H, 2-CH), 1.39 (q, *J* = 11.5 Hz, 1 H, $H3_{ax}$), 2.02 (s, 3 H, CH3-C=O), 2.22 (ddd, *J* = 12.4, 6.0, 2.3 Hz, 1 H, $H3_{eq}$), 3.50 (ddd, *J* = 11.3, 6.3, 2.3 Hz, 1H, H2), 3.53 (br s, 1 H, NH), 5.27 (ddd, *J* = 11.6, 9.2, 6.2 Hz, 1H, H4), 5.88 (d, *J* = 8.7 Hz, 1 H, HN-C=O), 6.46 (dd, *J* = 8.0, 1.0 Hz, 1H, H8), 6.65 (td, *J* = 7.4, 1.1 Hz, 1 H, H6), 7.00 (td, *J* = 8.8, 1.5 Hz, 1 H, H7), 7.07 (td, *J* = 7.7, 1.1 Hz, 1 H, H5). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.1, 23.4, 37.8, 46.1, 46.6, 114.3, 117.6, 121.4, 126.8, 128.1, 145.1, 170.1. GC-MS (EI) (t_R = 17.39 min): *m/z* (%) = 204 (18, M^+), 130 (100), 144 (73). Anal. Calcd for $C_{12}H_{16}N_2O$: C, 70.56; H, 7.90; N, 13.71. Found: C, 70.65; H, 7.74; N, 13.55.

N-(6-Ethyl-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)acet- amide (18)

IR (KBr): ν 3347, 3309, 1635 cm^{-1}. 1H NMR (200 MHz, $CDCl_3$): δ = 1.01 (d, *J* = 7.9 Hz, 3 H, 2-CH_3), 1.03 (t, *J* = 7.9 Hz, 3 H, 6-CH_2CH_3), 1.09–1.05 (m, 1 H, H3), 1.32 (q, *J* = 11.2 Hz, 1 H, $H3_{ax}$), 1.53 (s, 1 H, NH), 1.94 (s, 3 H, CH_3- C=O), 2.07 (ddd, *J* = 10.4, 6.1, 4.0 Hz, 1 H, H3eq), 2.38 (q, *J* = 7.5 Hz, 2 H, 6-CH_2CH_3), 3.38 – 3.30 (m, 1 H, H2), 5.12 (dd, *J* = 11.2, 2.9 Hz, 1 H, H4), 6.37 6.73 (br s, 1 H, H5), 6.75 (d, *J* = 8.6 Hz, 1 H, H7). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.8, 21.8, 22.7, 28.0, 37.7, 46.0, 46.8, 115.0, 121.9, 126.3, 127.5, 134.2, 142.8, 171.2. CG-EM (EI) (t_R = 18.55 min): *m/z* (%) = 232 (21, M^+). Anal. Calcd for $C_{14}H_{20}N_2O$: C, 72.38; H, 8.68; N, 12.06. Found: C, 72.55; H, 8.47; N, 12.18.

N-(6-Methoxy-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)acet- amide (19)

IR (KBr): ν 3293, 3371, 1639, 1211 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.19 (d, *J* = 6.3 Hz, 3 H, 2-CH_3), 1.41 (q, *J* = 11.4 Hz, 1 H, $H3_{ax}$), 1.61–1.84 (m, 1 H, NH), 2.03 (s, 3H, CH_3-C=O), 2.28 (ddd, J = 12.4, 6.3, 2.1 Hz, 1 H, $H3_{eq}$), 3.43 (ddd, *J* = 11.5, 6.2, 2.1 Hz, 1 H, H2), 3.72 (s, 3 H, OCH_3), 5.31 (ddd, *J* = 11.3, 9.4, 6.1 Hz, 1 H, H4), 5.67 (d, *J* = 8.6 Hz, 1 H, HN-C=O), 6.48 (d, *J* = 8.7 Hz, 1 H, H8), 6.66 (dd, *J* = 8.7, 2.9 Hz, 1 H, H7), 6.70 (d, *J* = 2.7, 0.7

Hz, 1 H, H5). ^{13}C NMR (100 MHz, CDCl3): δ = 22.4, 23.7, 38.4, 46.6, 47.2, 56.0, 112.7, 114.5, 115.8, 123.0, 139.6, 152.4, 170.2. GC-MS (EI) (t_R = 20.60 min): *m/z* (%) = 234 (19, M^+), 160 (100), 174 (54), 161 (20). Anal. Calcd for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74; N, 11.96. Found: C, 66.48; H, 7.90; N, 11.78.

N-(2,5,7-Trimethyl-1,2,3,4-tetrahydroquinolin-4-yl)acetamide (20)

IR (KBr): ν 3347, 3301, 1627 cm^{-1}. 1H NMR (400 MHz, $CDCl_3$): δ = 1.18 (d, *J* = 6.4 Hz, 3 H, 2-CH_3), 1.68 (q, *J* = 11.8 Hz, 1 H, $H3_{ax}$), 2.15 (s, 3 H, 7-CH_3), 2.17 (s, 3 H, 5-CH_3), 2.22 (s, 3 H, CH_3-C=O), 2.28 (ddd, *J* = 11.8, 6.3, 2.1 Hz, 1H, $H3_{eq}$), 3.32–3.40 (m, 1 H, H2), 3.71 (s, 1 H, NH), 5.19 (ddd, *J* = 15.1, 7.7, 7.4 Hz, 1 H, H4), 5.68 (d, *J* = 8.0 Hz, 1 H, HN-C=O), 6.21 (s, 1 H, H8), 6.37 (s, 1 H, H6). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.2, 20.8, 22.3, 22.9, 38.2, 43.9, 46.0, 113.4, 116.6, 121.5, 137.9, 138.2, 146.3, 168.9. CG-EM (EI) (t_R = 19.93 min): *m/z* (%) = 232 (24, M^+), 158 (100), 172 (63). Anal. Calcd for $C_{14}H_{20}N_2O$: C, 72.38; H, 8.68; N, 12.06. Found: C, 72.15; H, 8.83; N, 11.87.

N-(6-Chloro-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)acet- amide (21)

IR (KBr): ν 3383, 3290, 1734, 1635, 1496, 1342, 725 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.16 (d, *J* = 6.3 Hz, 3 H, 2-CH_3), 1.36 (q, *J* = 11.5 Hz, 1 H, H3), 2.03 (s, 3 H, CH3-C=O), 2.16 (ddd, *J* = 12.3, 6.0, 2.3 Hz, 1 H, H3), 3.47 (dqd, *J* = 12.3, 6.2, 2.2 Hz, 1 H, H2), 3.75 (br s, 1 H, NH), 5.15–5.23 (m, 1 H, H4), 6.00 (d, *J* = 9.1 Hz, 1 H, HN-C=O), 6.36 (d, *J* = 8.5 Hz, 1 H, H8), 6.90 (dd, *J* = 8.5, 2.3 Hz, 1 H, H7), 6.99–7.00 (m, 1 H, H5). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.2, 23.5, 38.0, 46.2, 46.7, 114.4, 117.7, 121.6, 127.0, 128.3, 145.3, 170.3. CG-EM (EI) (t_R = 21.09 min): *m/z* (%) = 238 (30, M^+), 164 (100), 177 (51). Anal. Calcd for $C_{12}H_{15}ClN_2O$: C, 60.38; H, 6.33; N, 11.74. Found: C, 66.41; H, 7.24; N, 11.89.

Comment. Although some of these values are outside the expected range for high analytical purity, they are provided to illustrate the best values that could be obtained to date.

N-(2-methyl-6-fluoro- tetrahydroquinolin-4-yl)acet- amide (22)

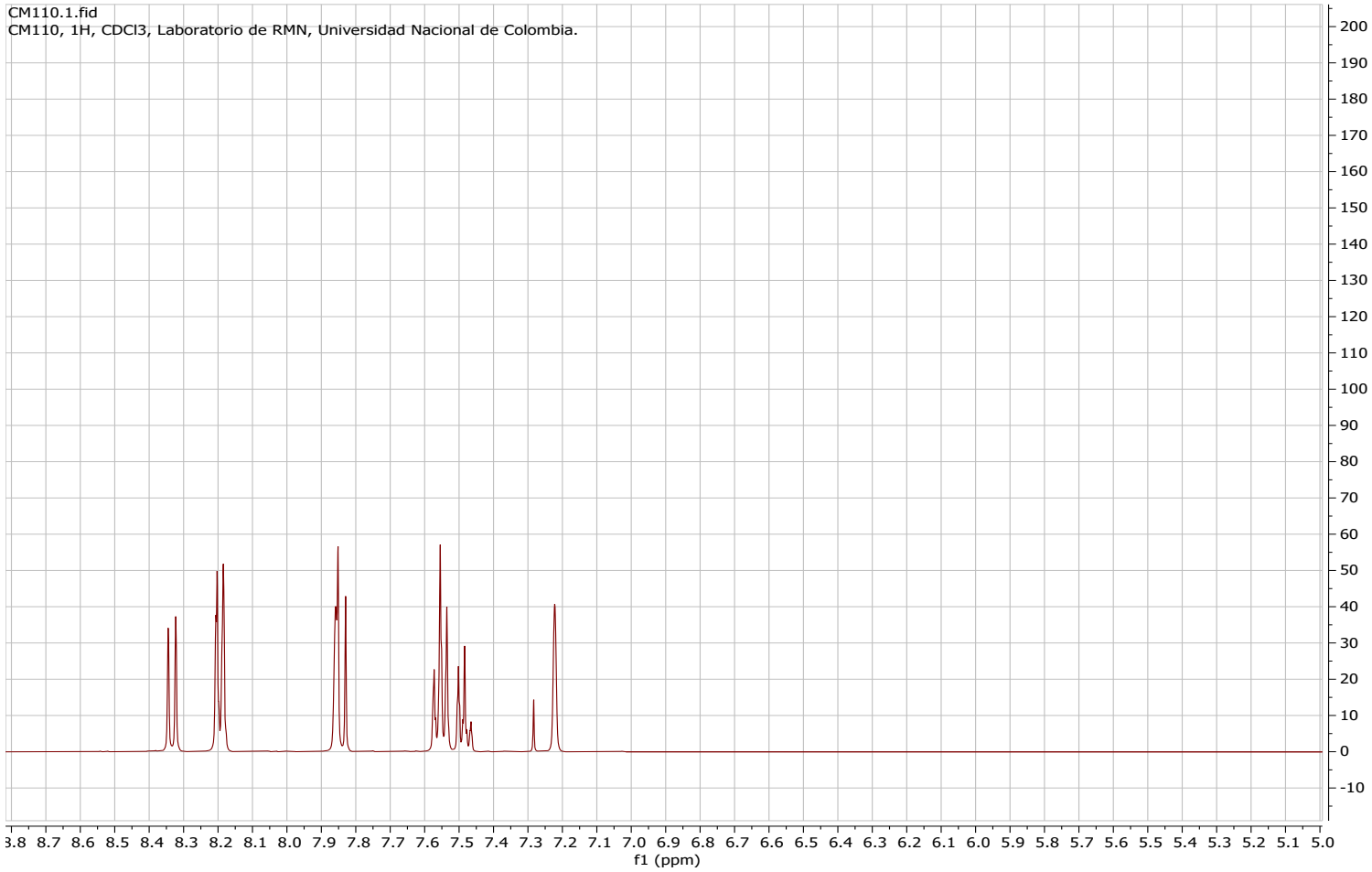
IR (KBr): ν 3343, 3294, 1630 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) = 1.16 (d, *J* = 6.3 Hz, 3H, 2-CH_3), 1.41-1.32 (m, 1H, $H3_{ax}$), 2.02 (3H, s, CH3-C=O), 2.17 (ddd, *J* = 12.4, 6.1, 2.8 Hz, 1

H, $H3_{ec}$), 3.49-3.41 (m, 1 H, 2-H), 3.65 (s.a, 1 H, NH), 6.26-5.19 (m, 1 H, 4-H), 5.95 (d, J = 8.9 Hz, 1 H, NHC(O)), 6.39 (dd, J = 8.7, 4.7 Hz, 1 H, H8), 6.70 (ddd, J = 8.2, 6.7, 2.9 Hz, 1H, 7H), 6.78 (dd, J = 9.5, 2.0 Hz, 1 H, H5), ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.0, 23.2, 37.6, 46.1, 46.8, 113.1, 113.3, 114.7, 114.9, 115.0, 115.1, 122.8, 141.3, 154.5, 156.8, 170.1 ppm; CG-EM t_R: 17.52 min., m/z (%) = 222 (25, $M^{+\cdot}$), 148 (100), 162 (70). Anal. Calcd for $C_{12}H_{15}FN_2O$: C, 64.85; H, 6.80; N, 12.60. Found: C, 66.67; H, 6.93; N, 12.51.

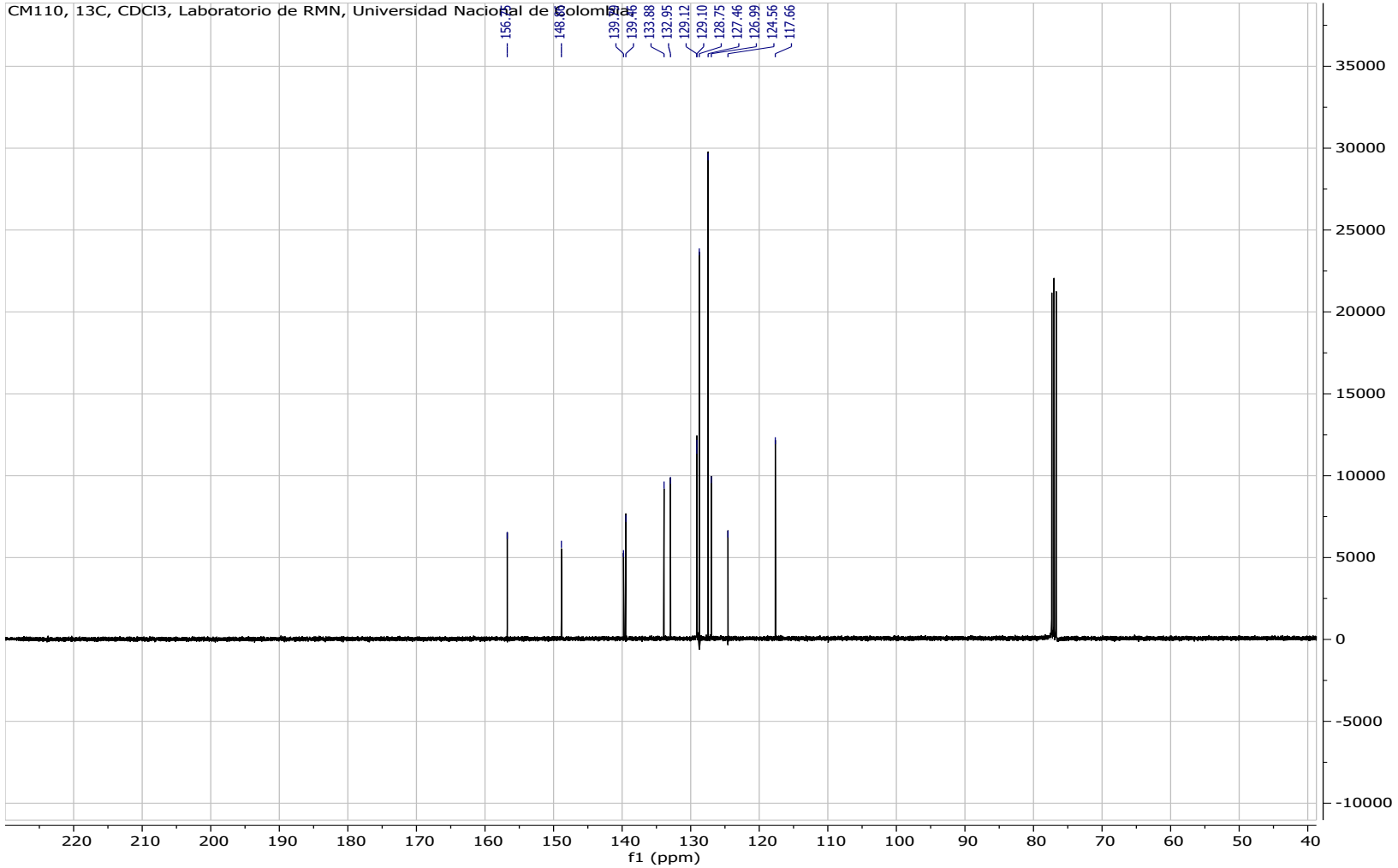
Comment. Although some of these values are outside the expected range for high analytical purity, they are provided to illustrate the best values that could be obtained to date.

NMR spectra

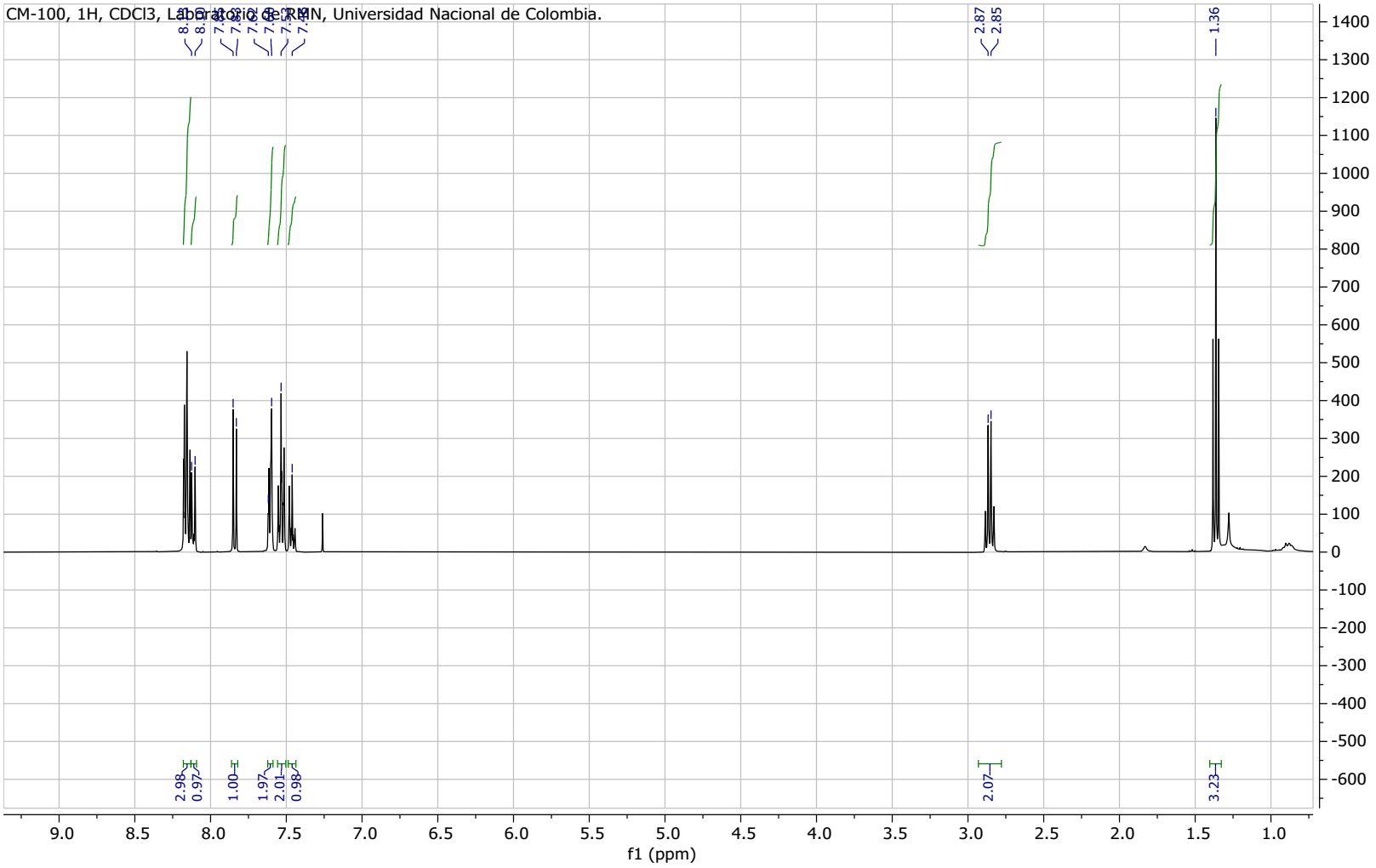
^{1}H NMR of 2-Phenylquinoline (4)



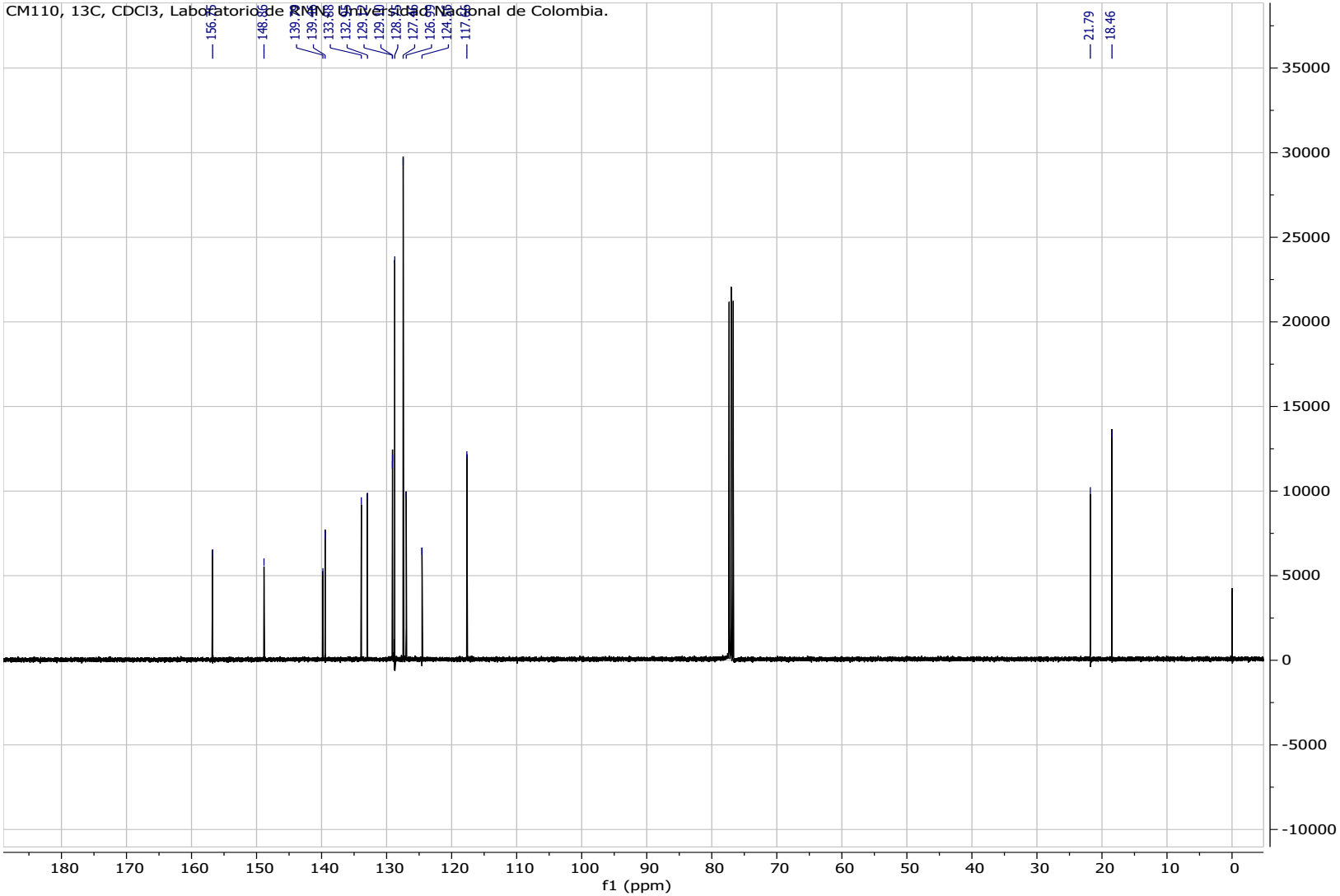
^{13}C NMR of 2-Phenylquinoline (4)



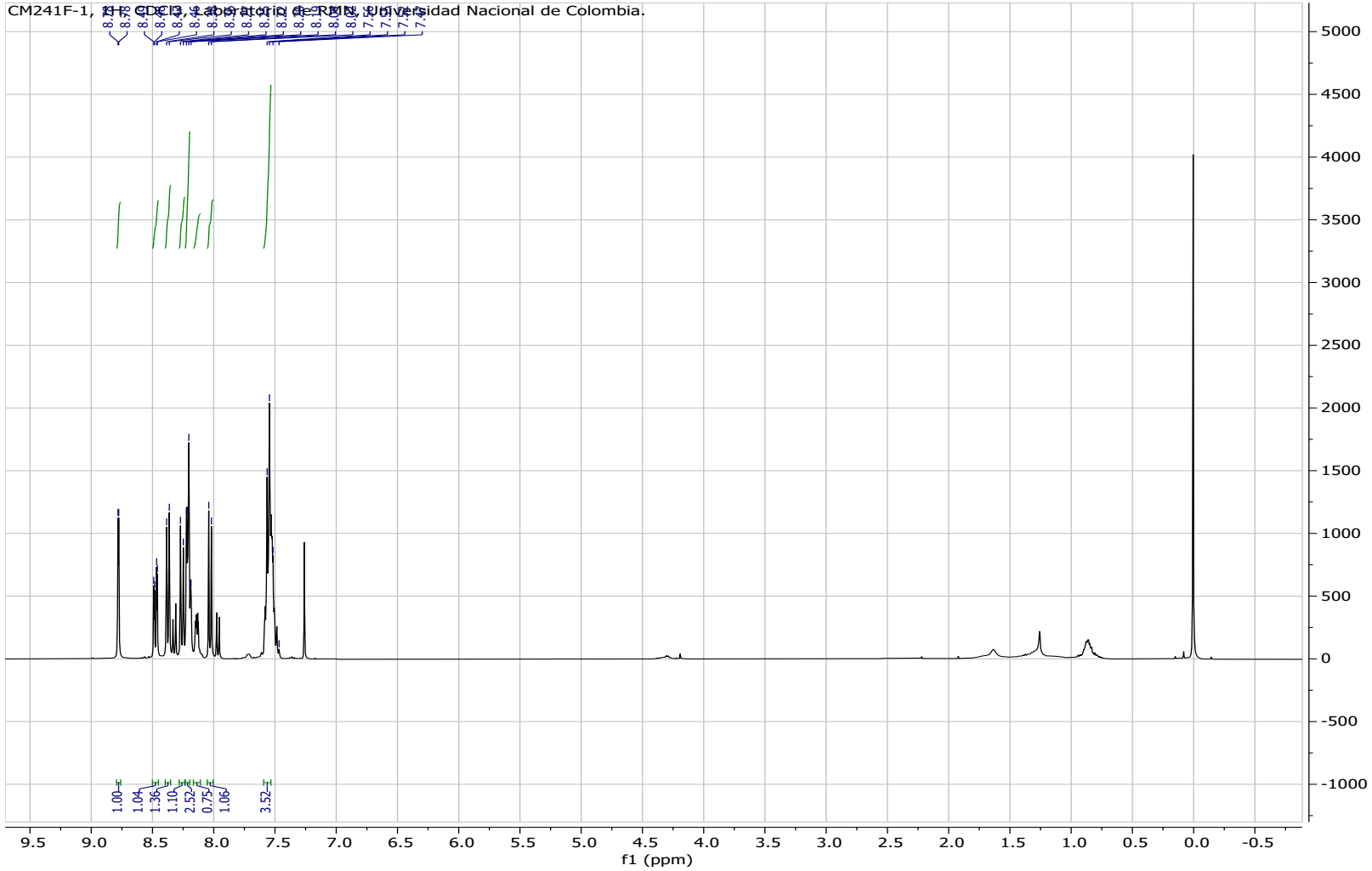
^{1}H NMR spectra of 6-Ethyl-2-phenylquinoline (5)



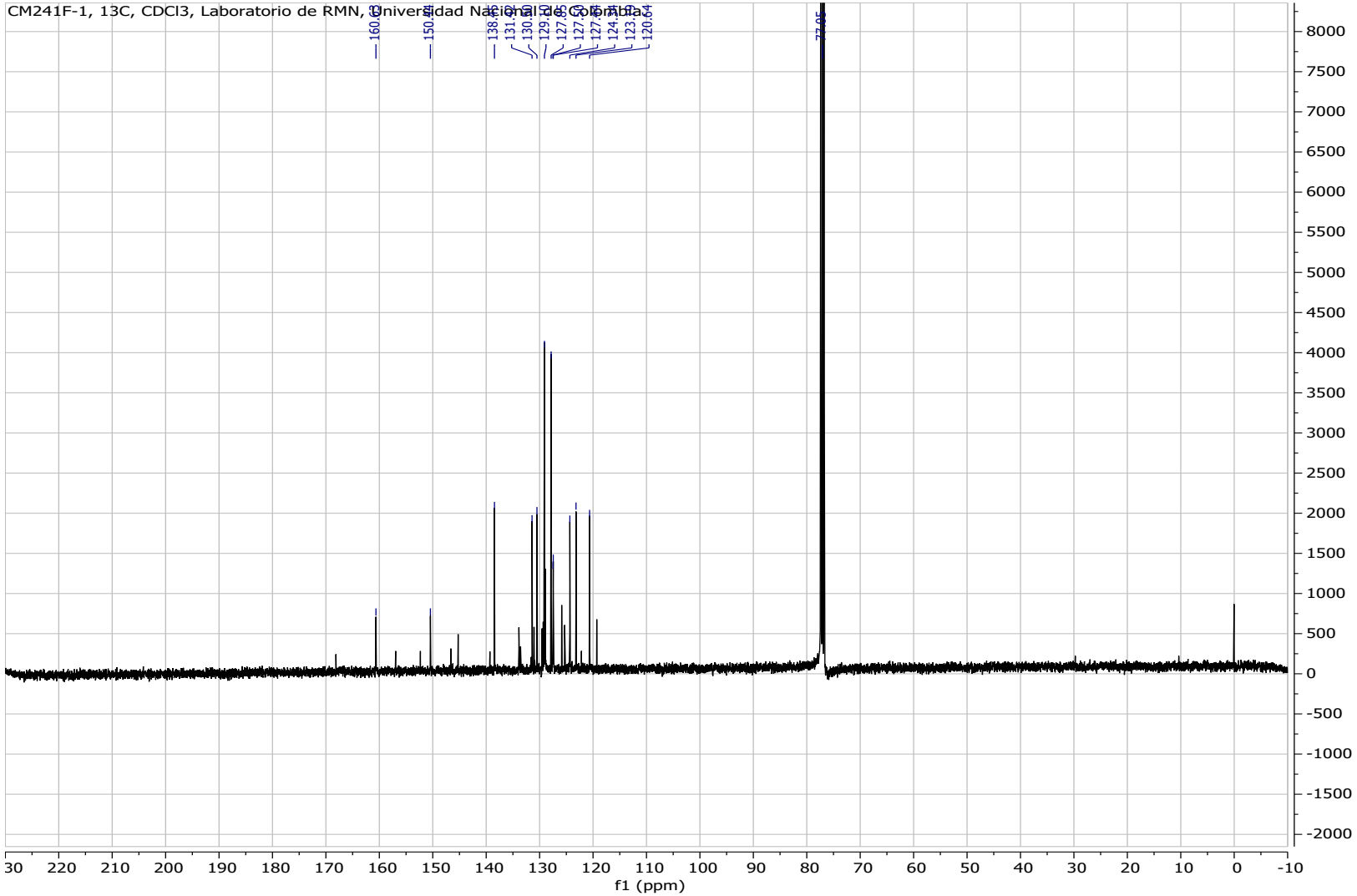
^{13}C NMR spectra of 6-Ethyl-2-phenylquinoline (5)



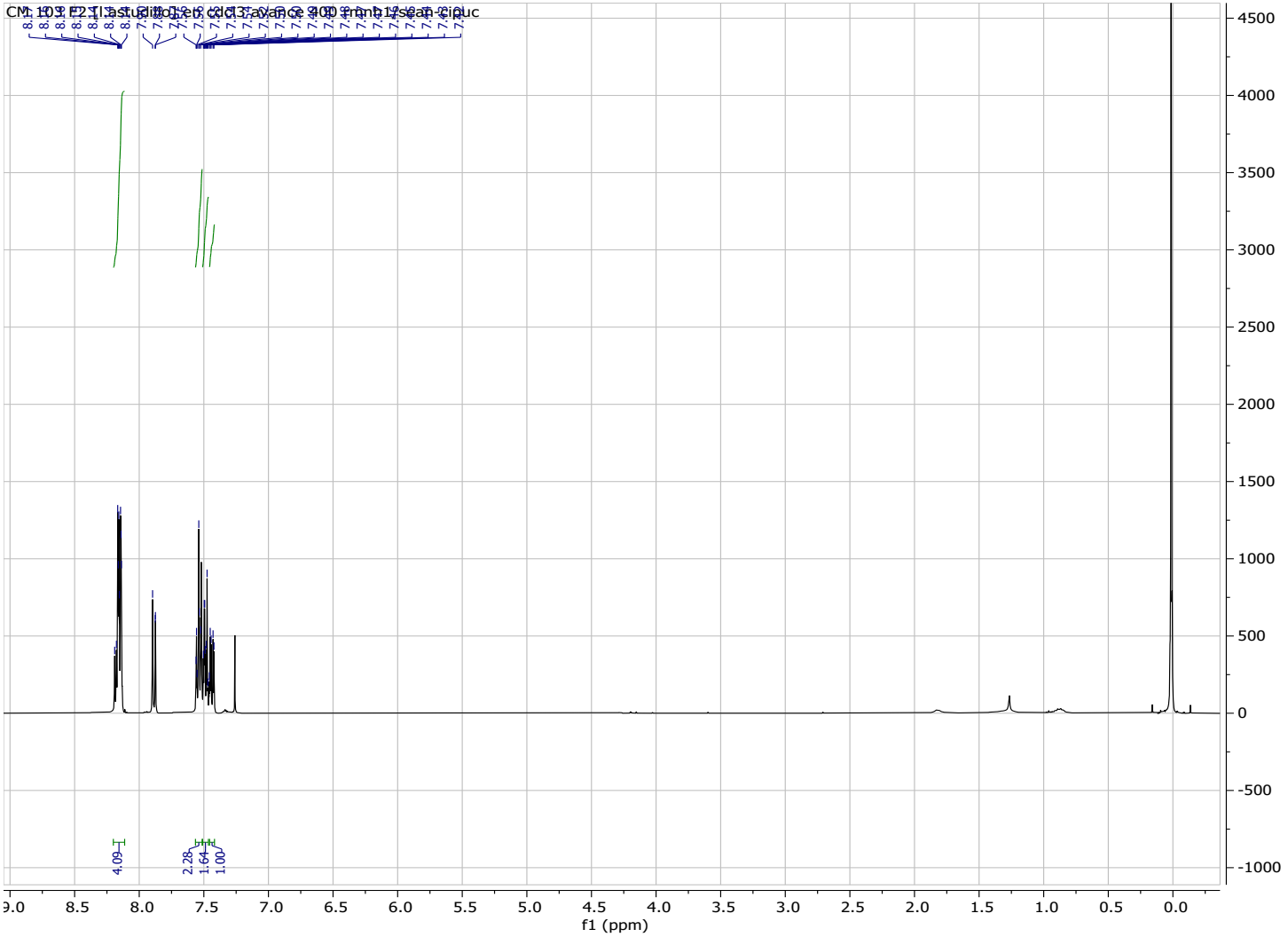
^{1}H NMR spectra of 6-Nitro-2-phenylquinoline (6)



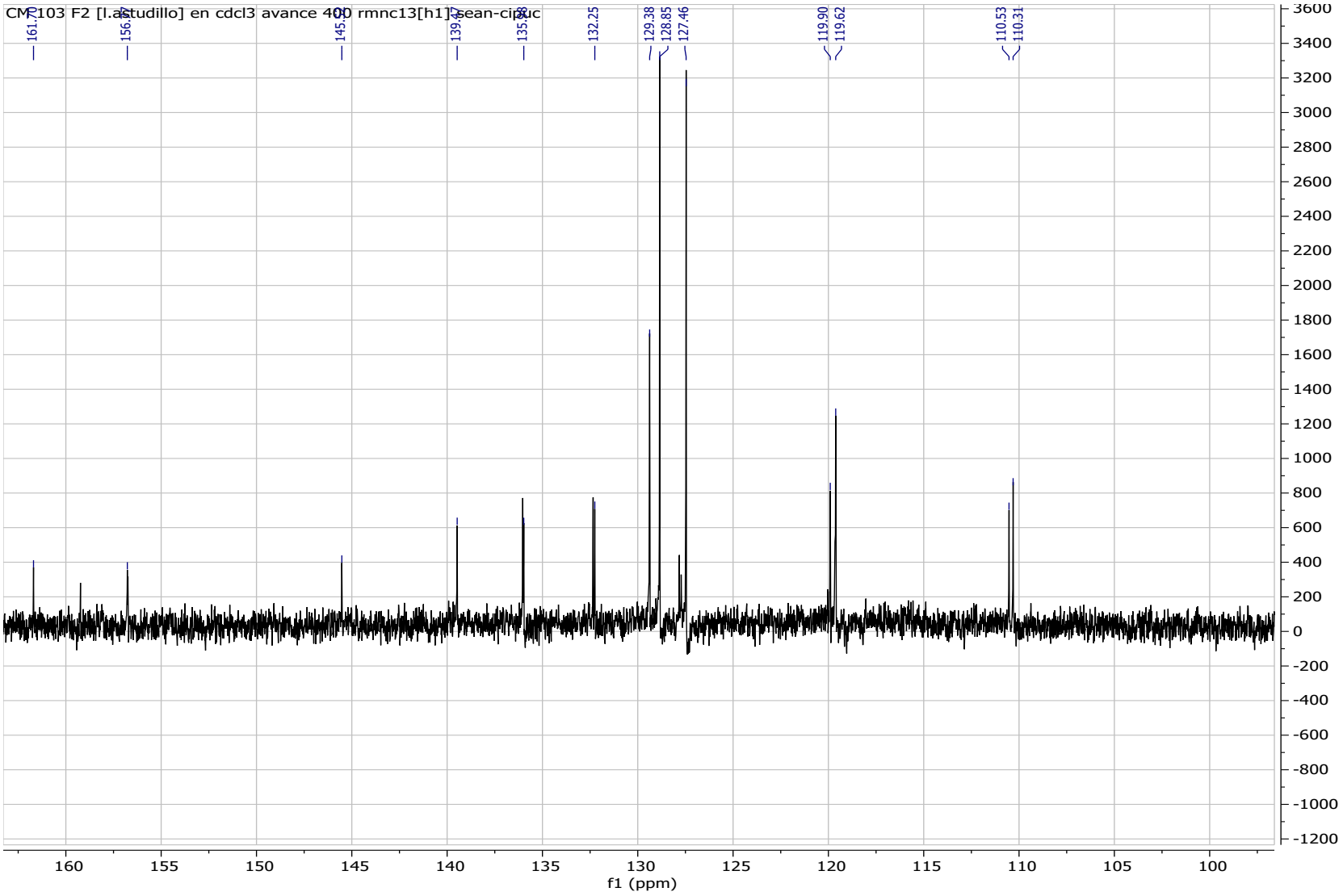
^{13}C NMR spectra of 6-Nitro-2-phenylquinoline (6)



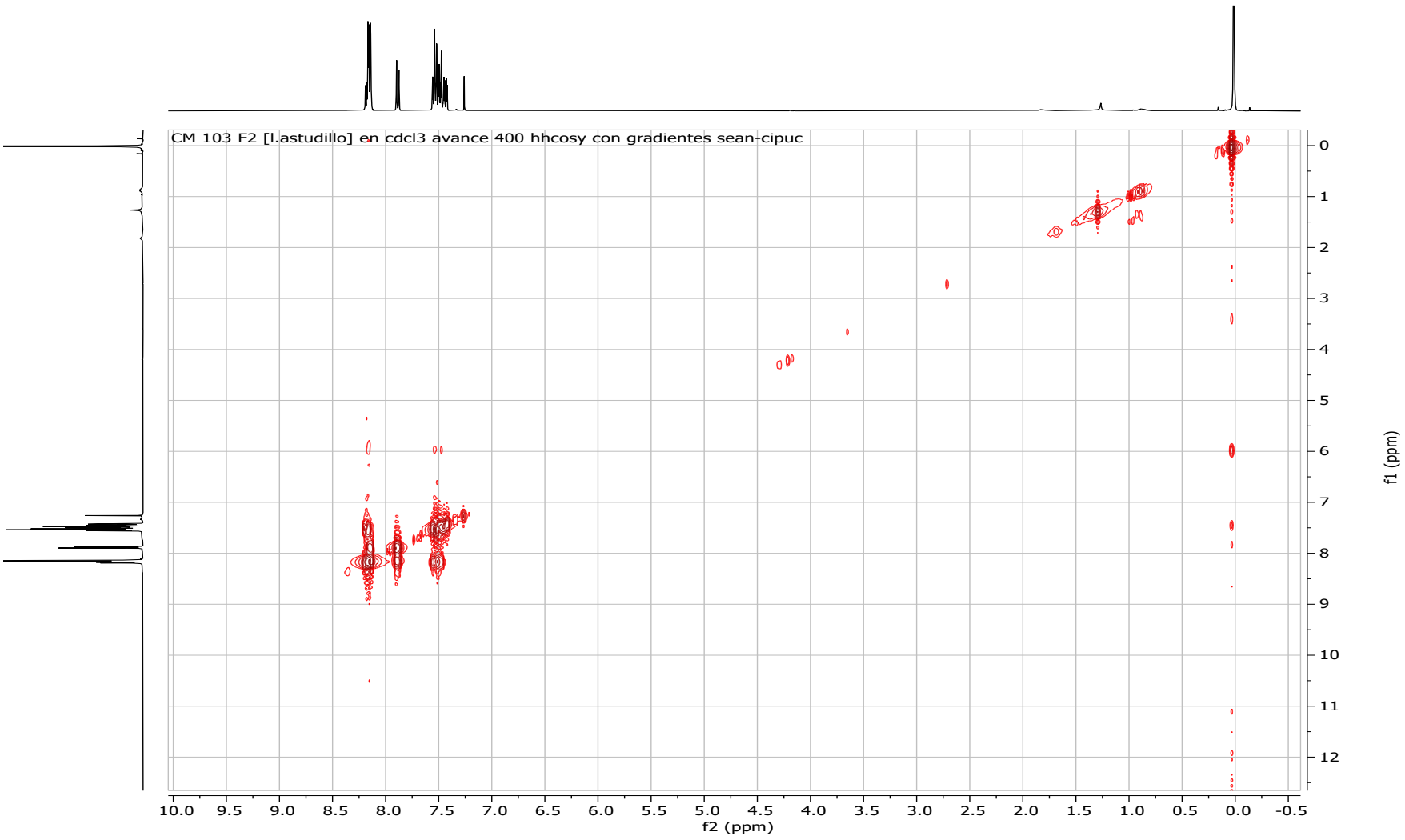
^{1}H NMR spectra of 6-Fluoro-2-phenylquinoline (7)



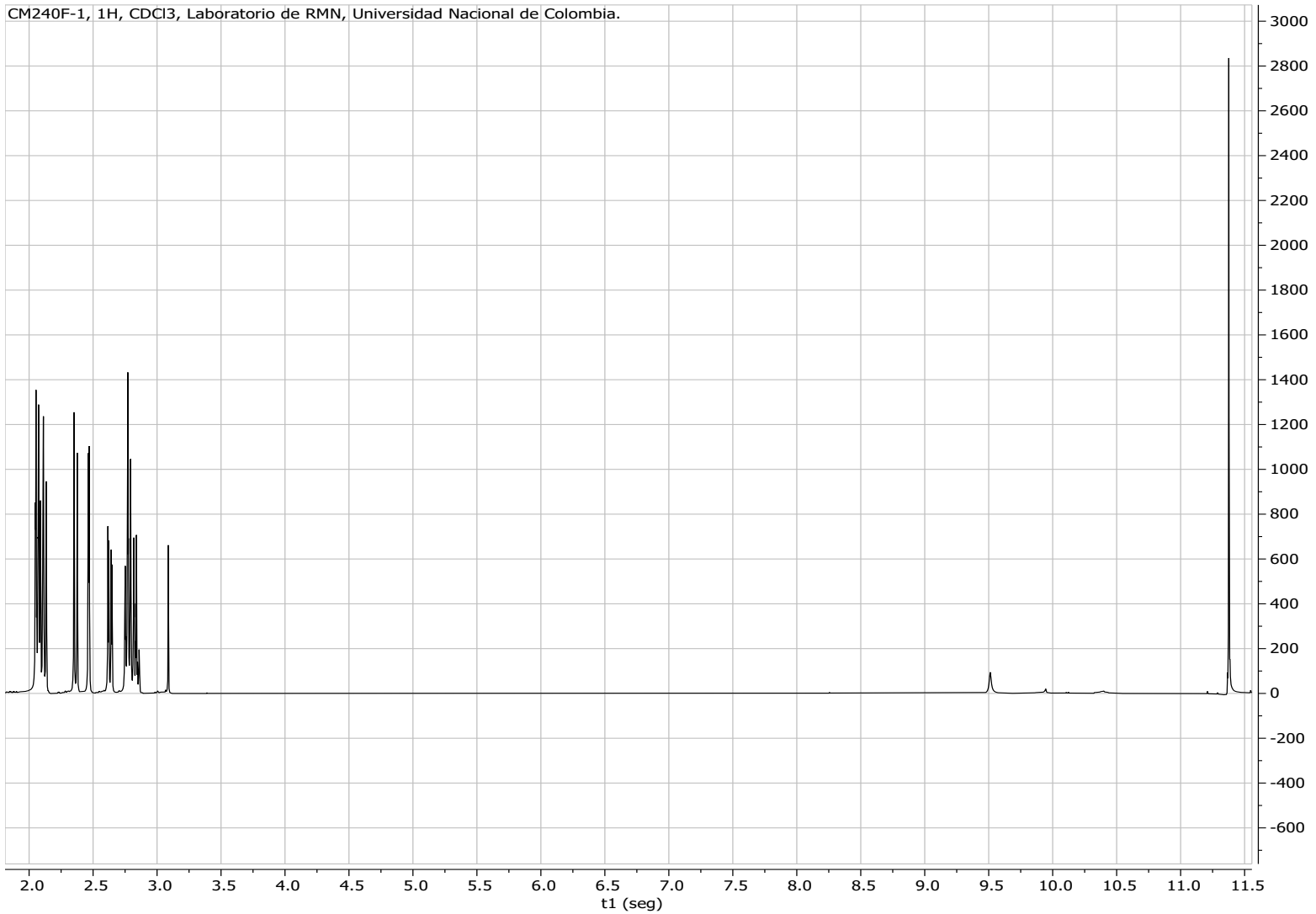
^{13}C NMR spectra of 6-Fluoro-2-phenylquinoline (7)



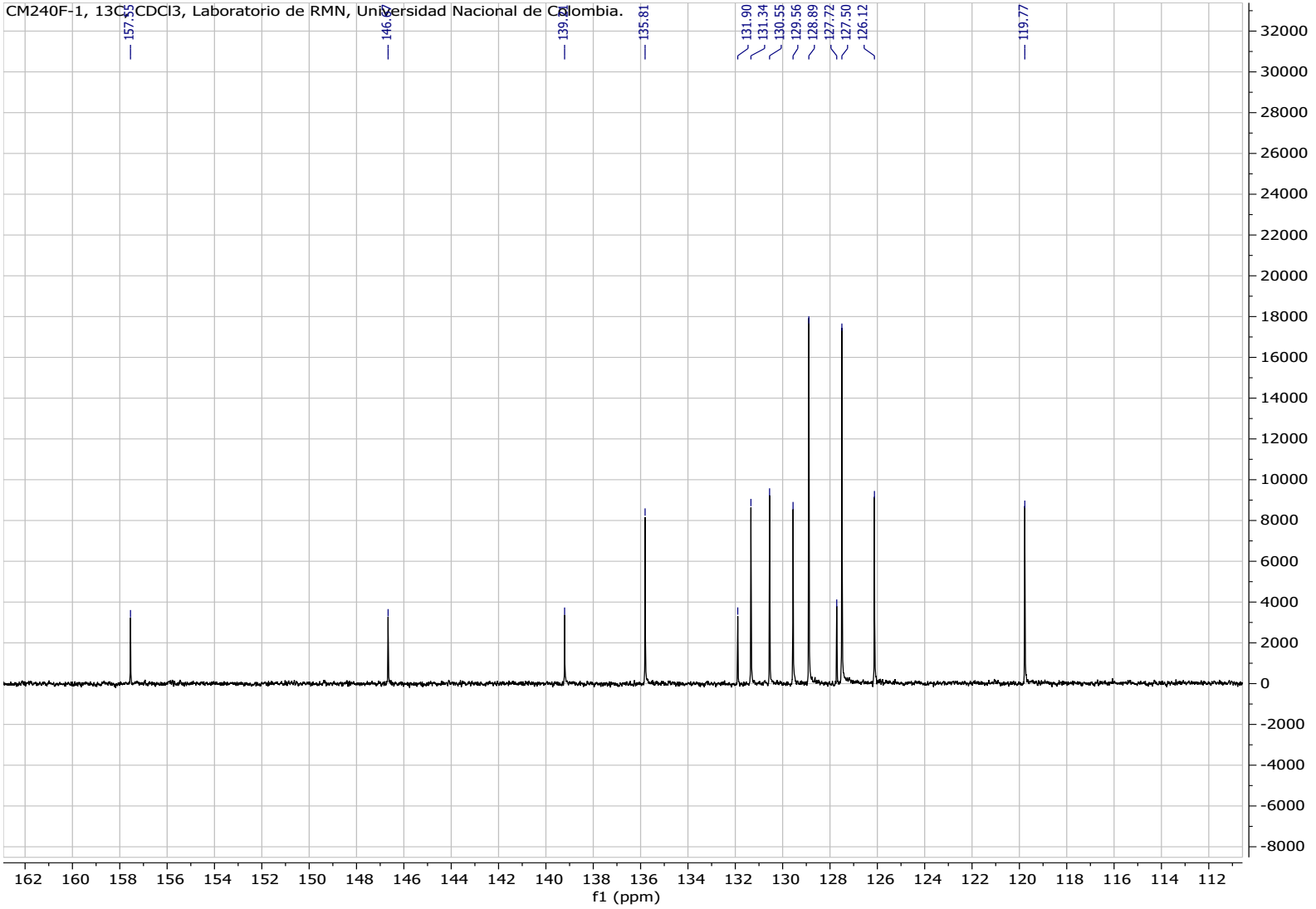
COSY spectra of 6-Fluoro-2-phenylquinoline (7)



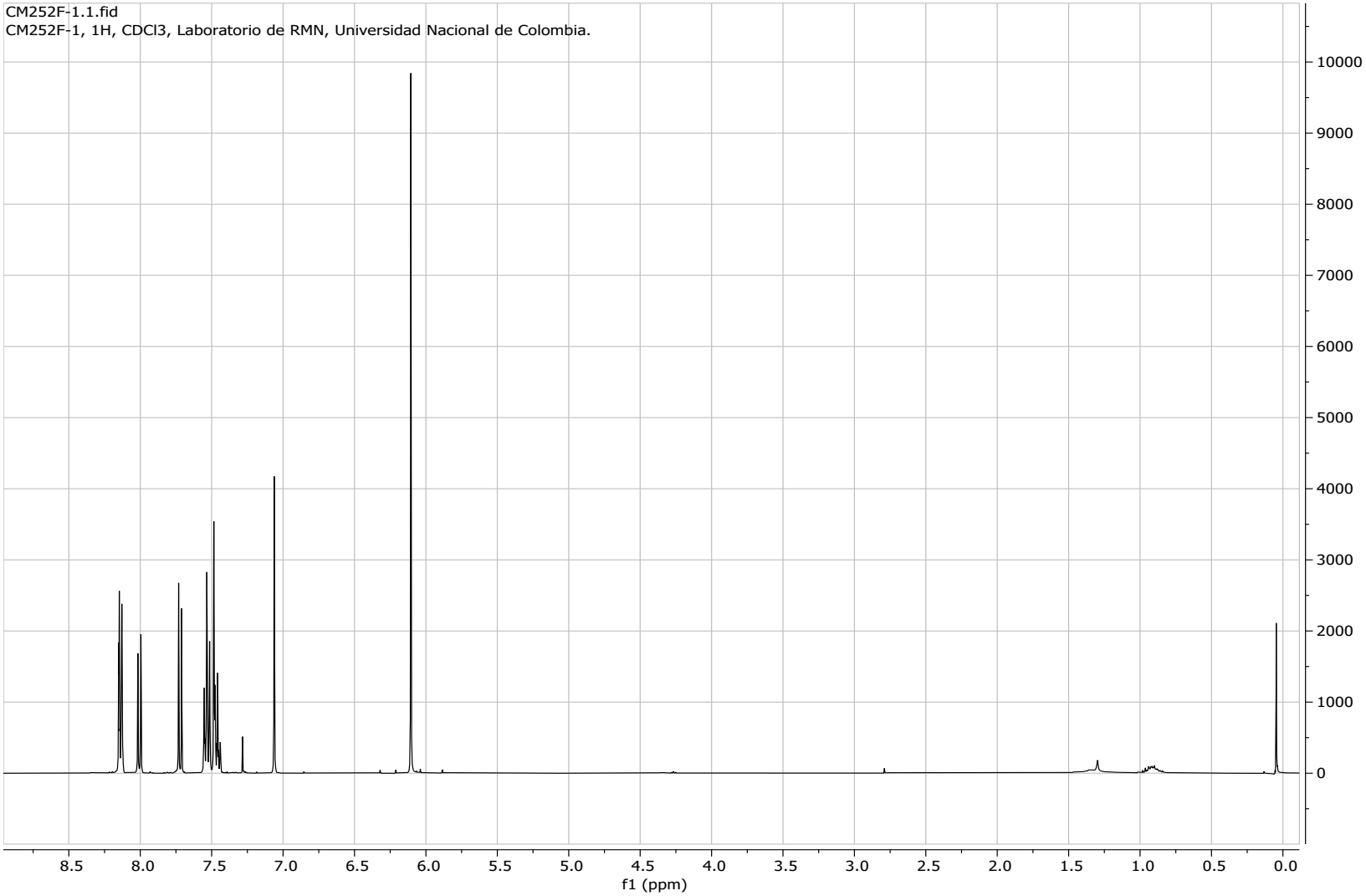
^{1}H NMR spectra of 6-Chloro-2-phenylquinoline (8)



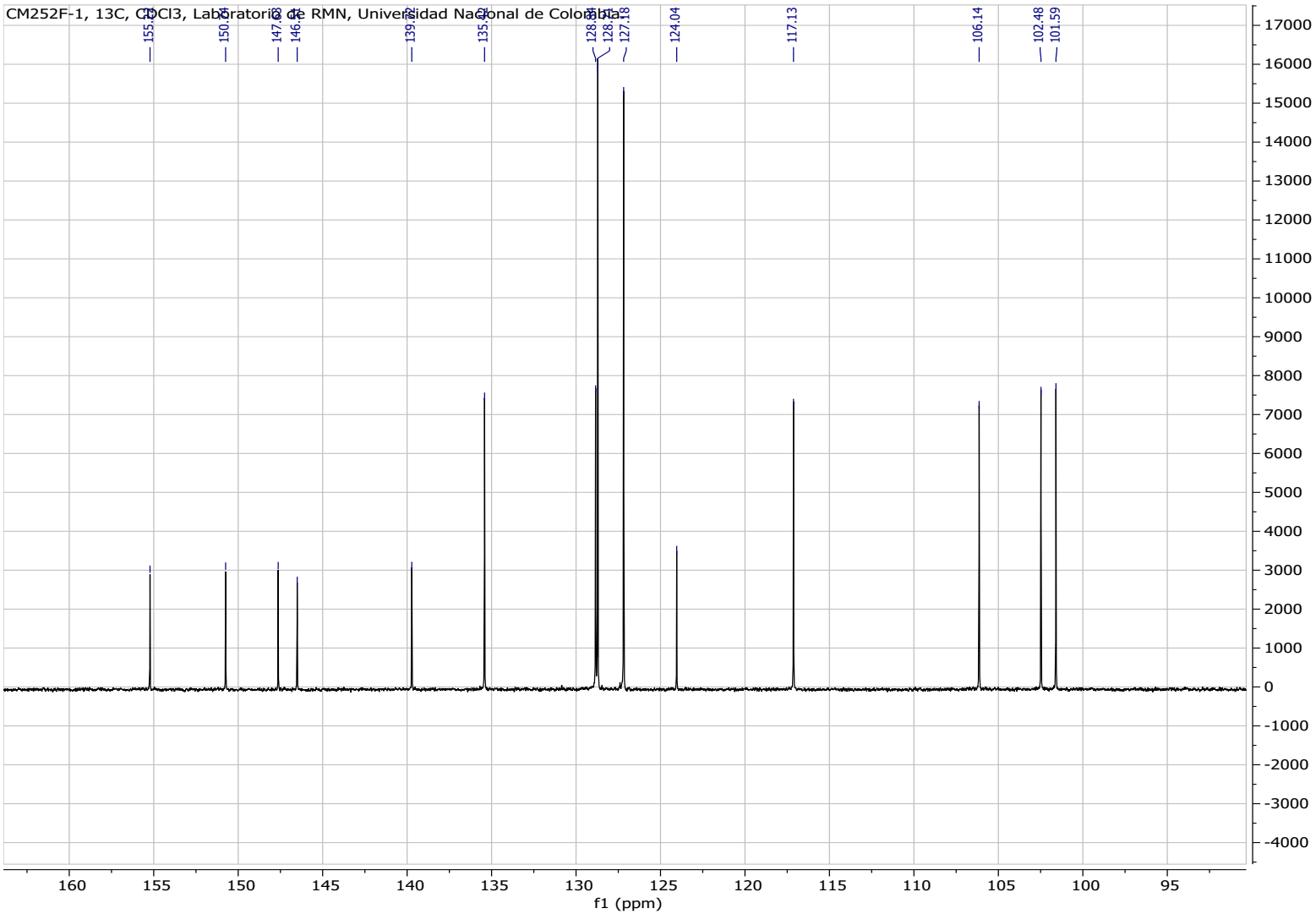
^{13}C NMR spectra of 6-Chloro-2-phenylquinoline (8)


CM240F-1, 13C, CDCl3, Laboratorio de RMN, Universidad Nacional de Colombia.
157.55
146.67
139.41
135.81
131.90
131.34
130.55
129.56
128.89
127.72
127.50
126.12
119.77
32000
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
-4000
-6000
-8000
162 160 158 156 154 152 150 148 146 144 142 140 138 136 134 132 130 128 126 124 122 120 118 116 114 112
f1 (ppm)

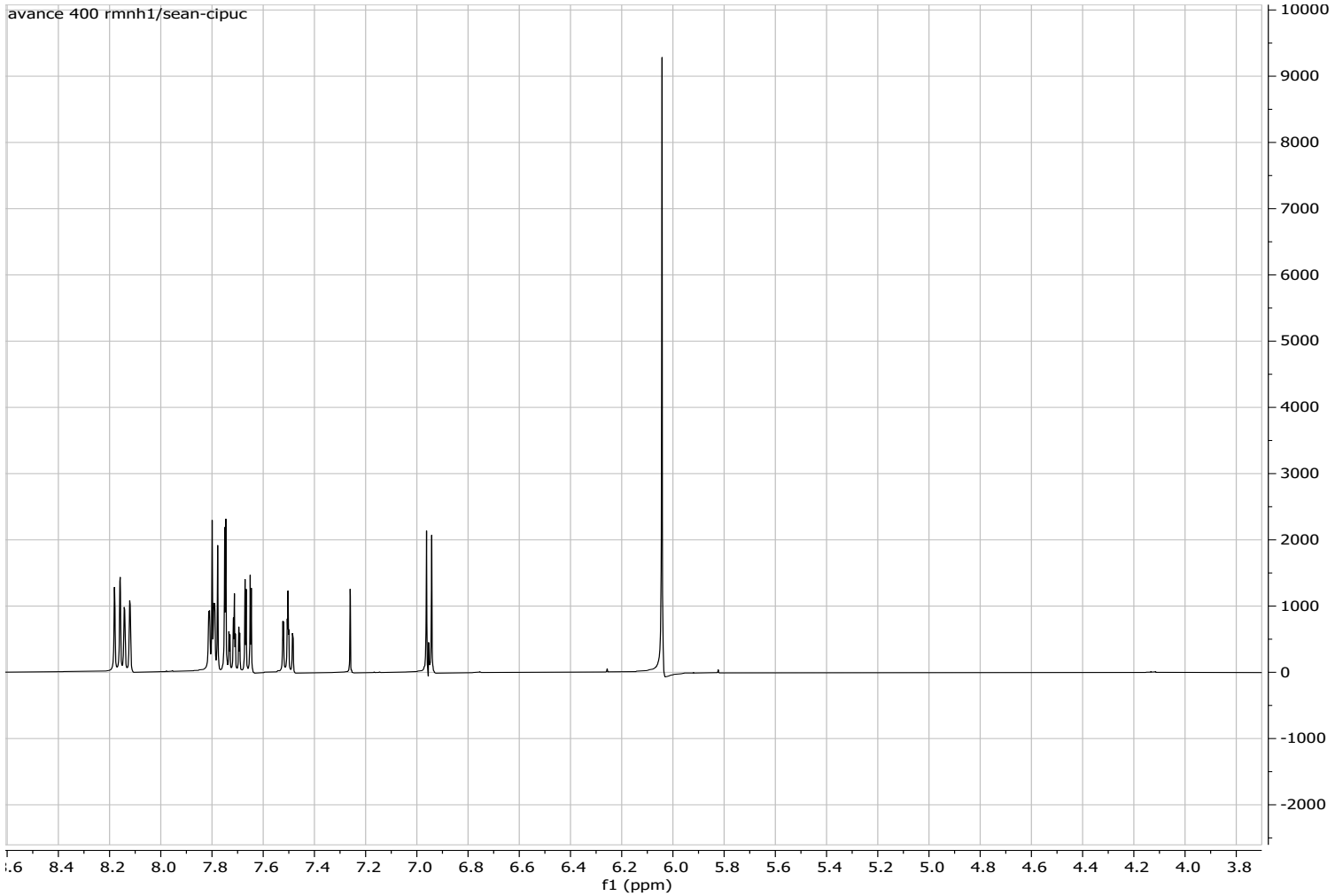
^{1}H NMR spectra of 6,7-methylenedioxo-2-Phenylquinoline (10)



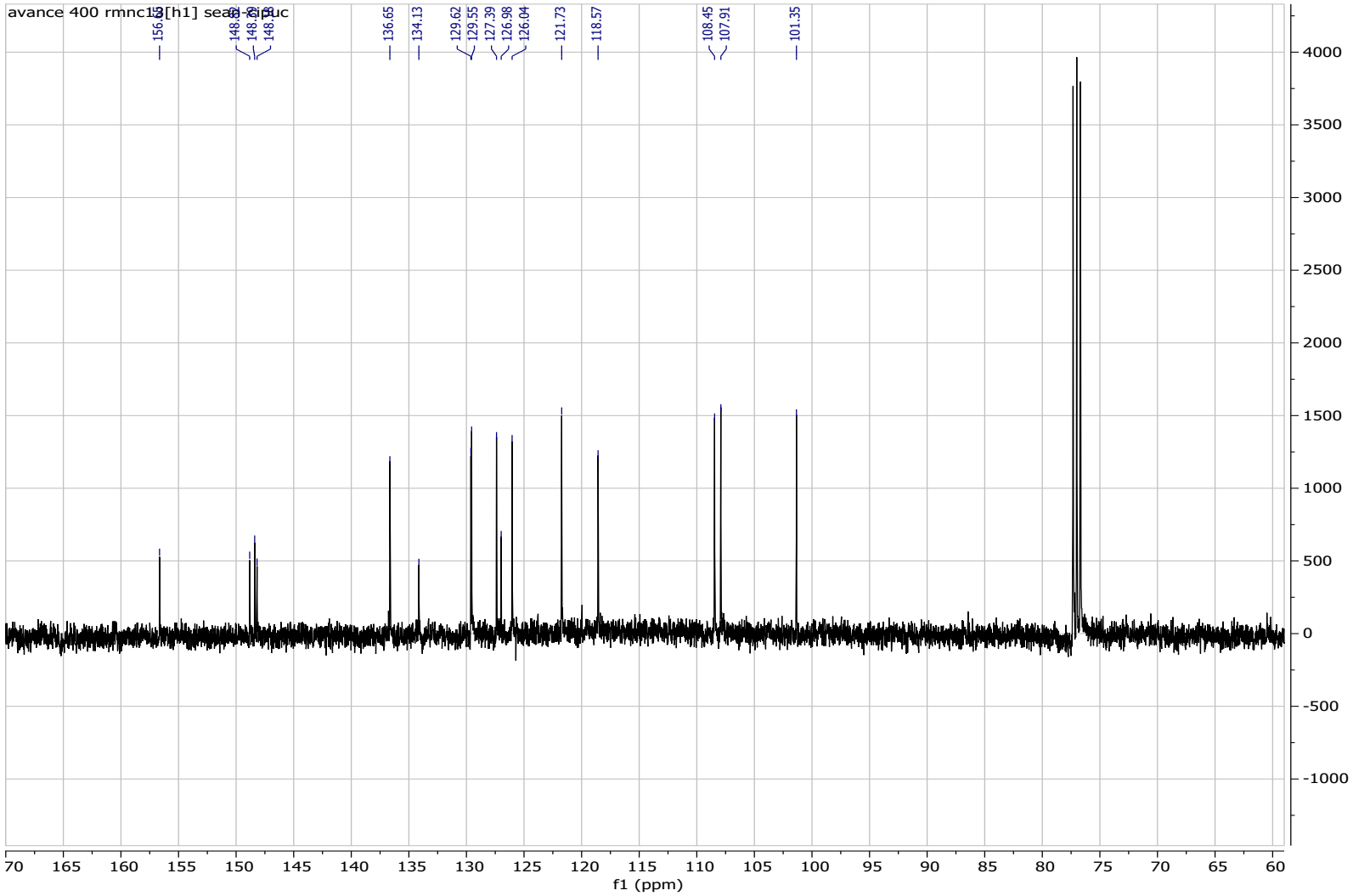
^{13}C NMR spectra of 6,7-methylenedioxo-2-Phenylquinoline (10)



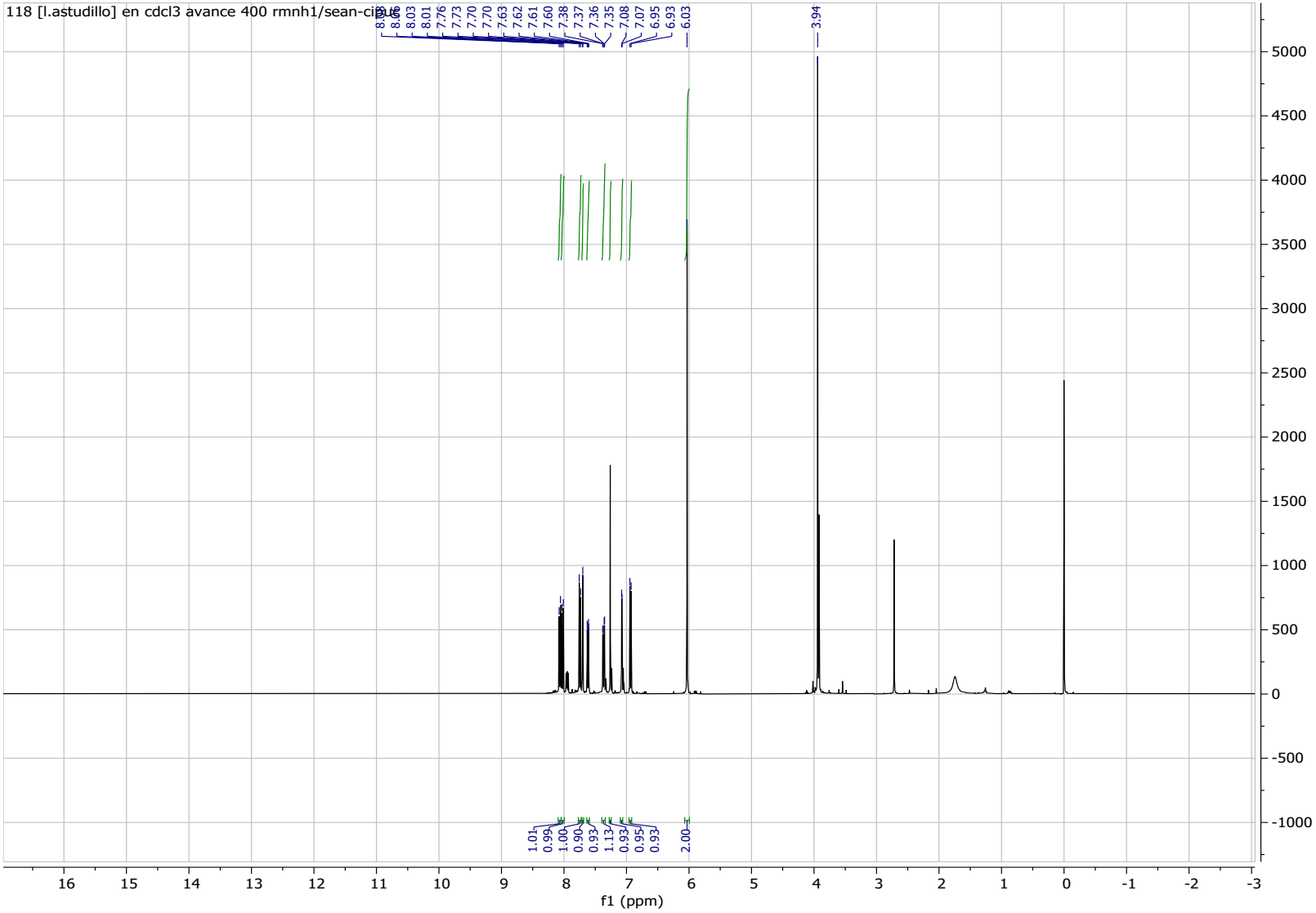
^{1}H NMR spectra of 2-(Phenyl-3',4'-dioxomethylen)-quinoline (11)



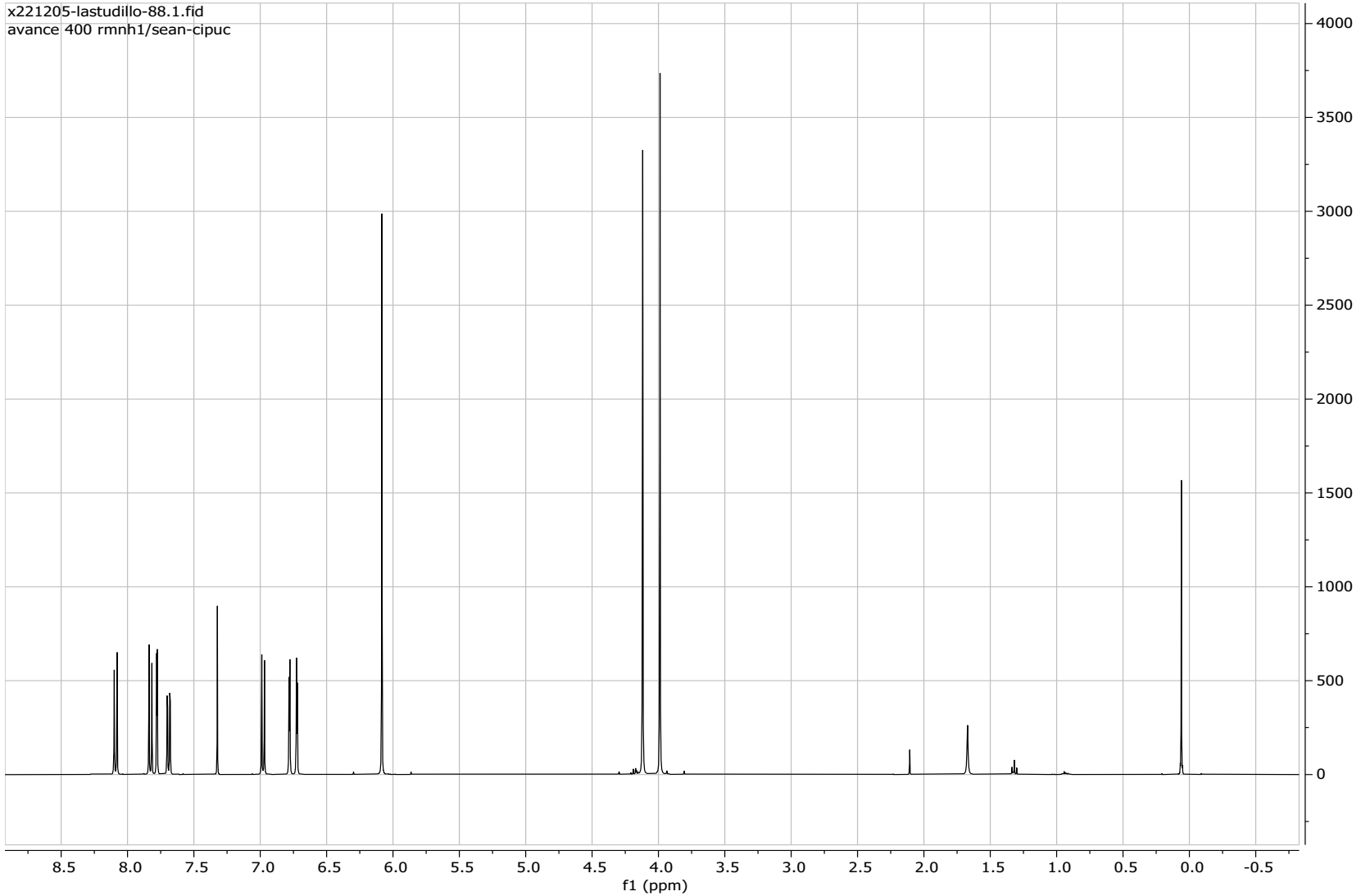
^{13}C NMR spectra of 2-(Phenyl-3',4'-dioxomethylen)-quinoline (11)



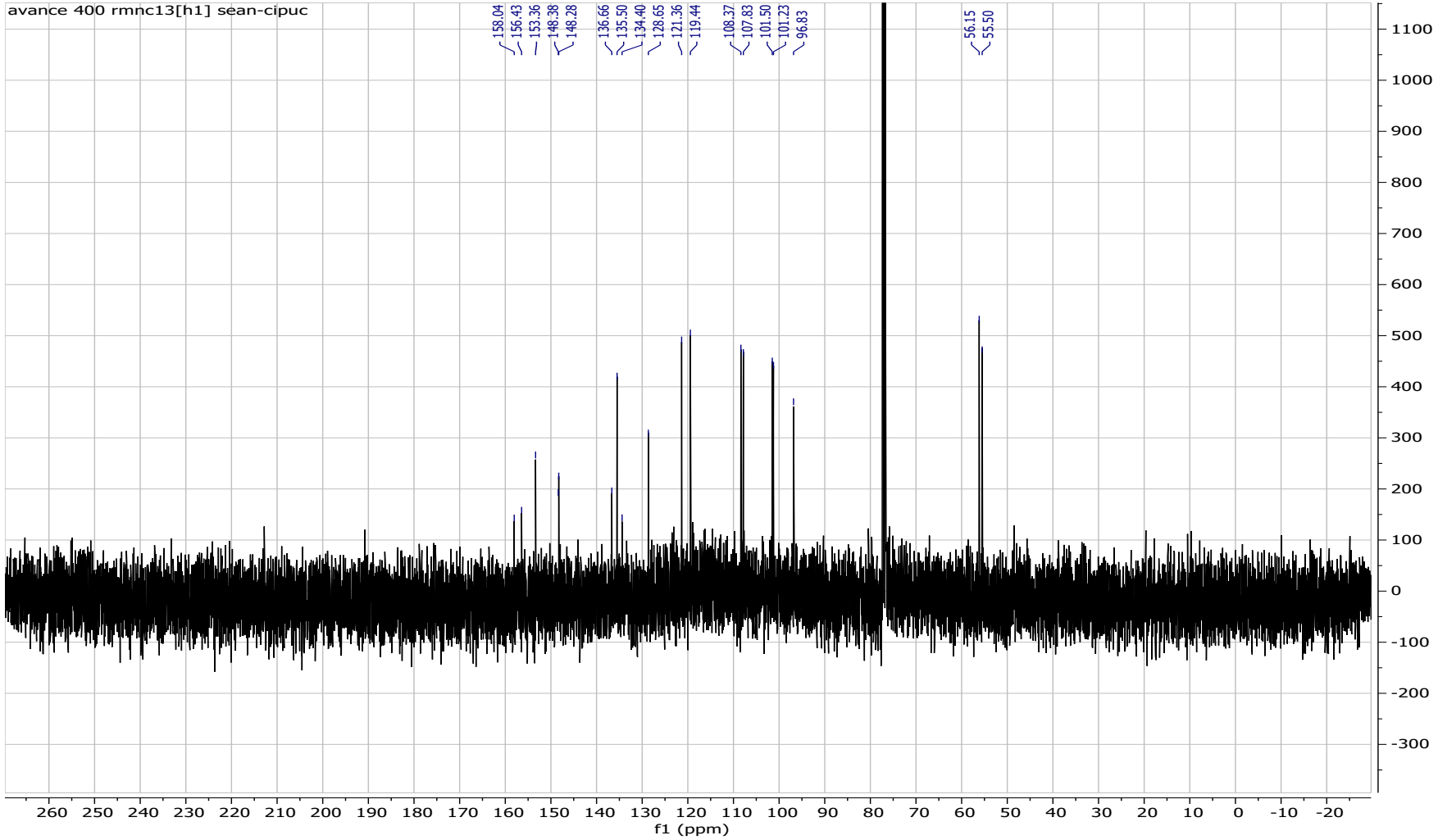
^{1}H NMR spectra of 2-(Phenyl-3',4'-dioxomethylen)-6-methoxyquinoline (13)



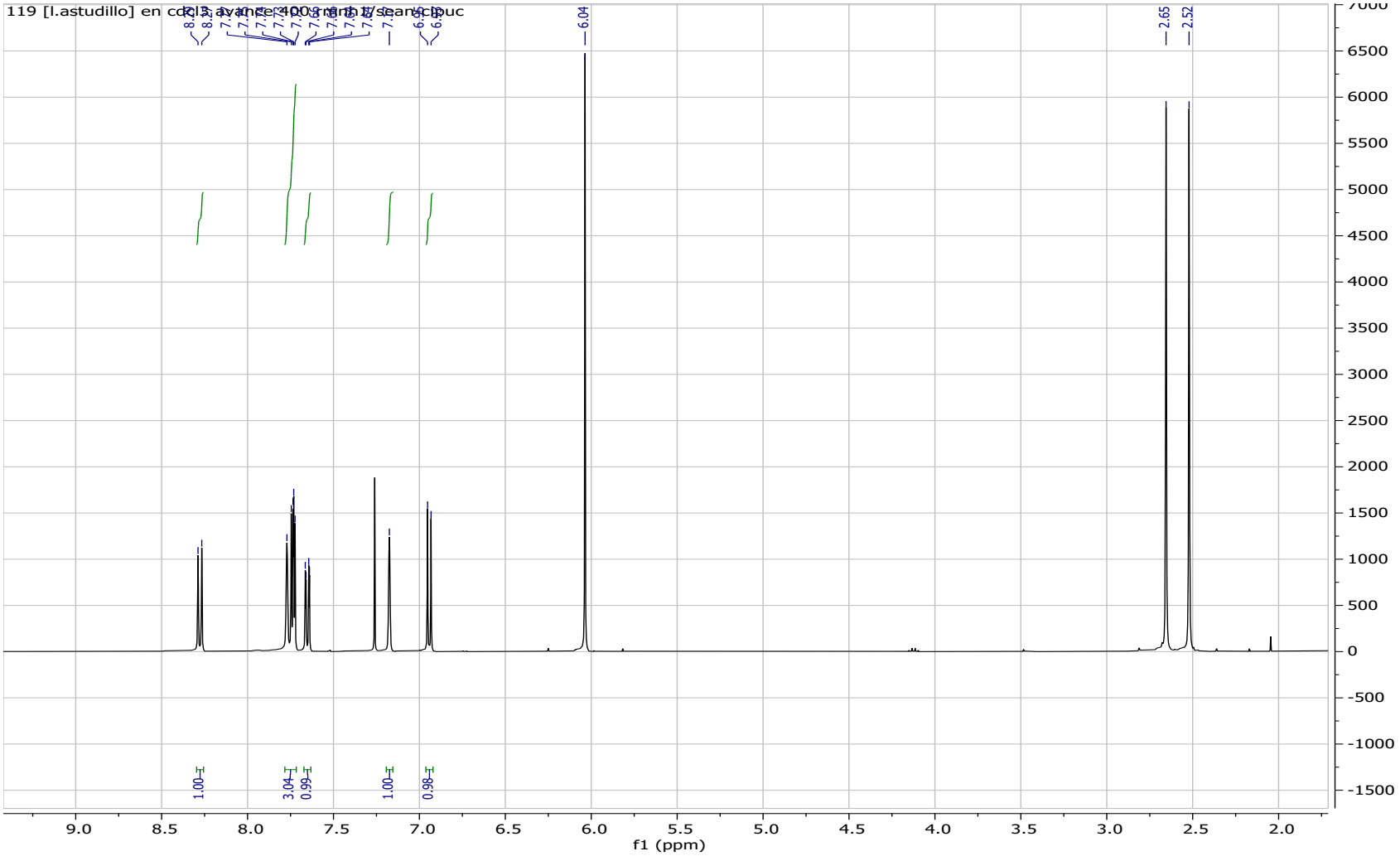
[1]H NMR spectra of 2-(Phenyl-3',4'-dioxomethylen)-6,8-dimethoxyquinoline (15)



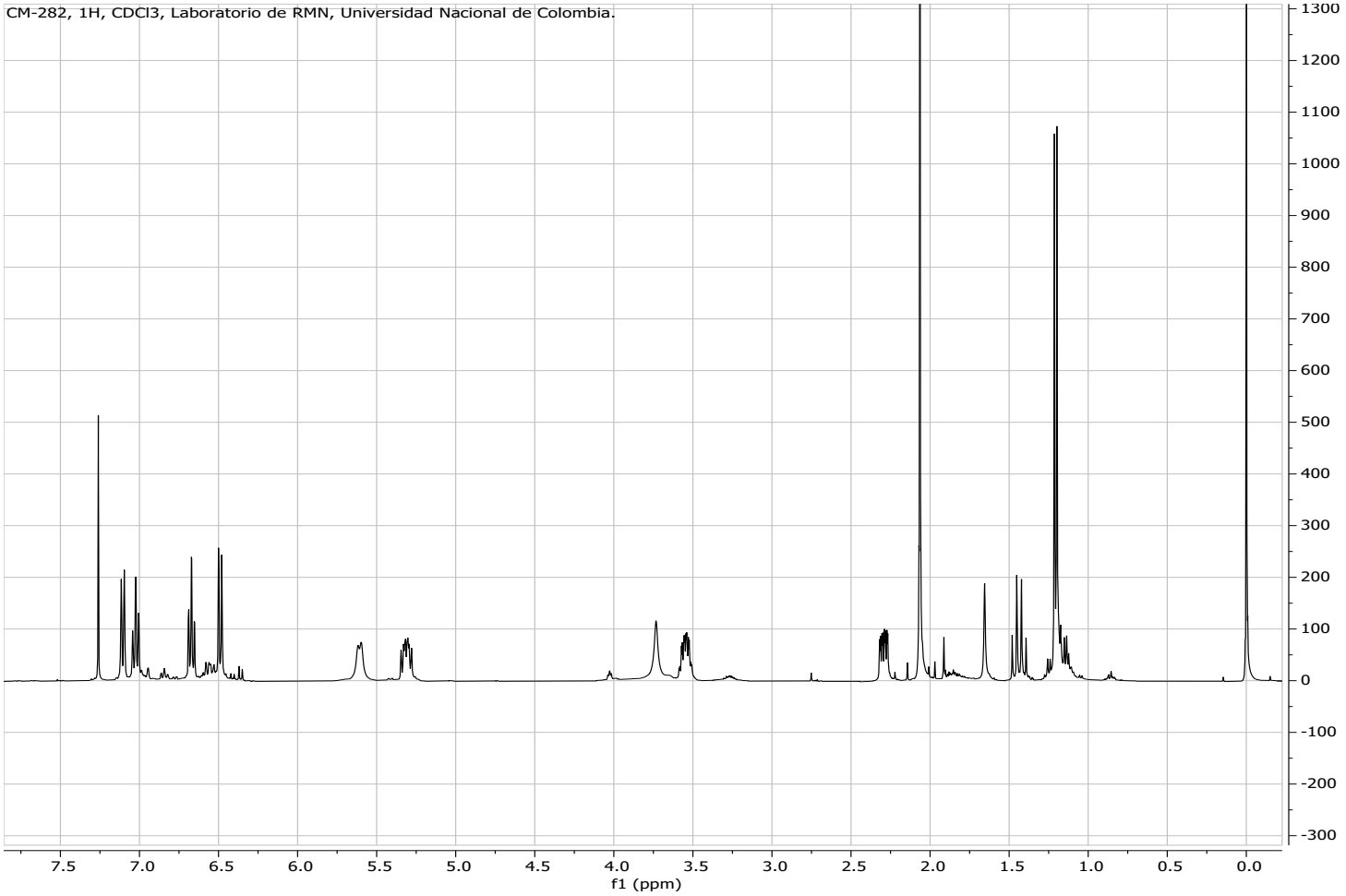
^{13}C NMR spectra of 2-(Phenyl-3',4'-dioxomethylen)-6,8-dimethoxyquinoline (15)


avance 400 rmnc13[h1] sean-cipuc
158.04
156.43
153.36
148.38
148.28
136.66
135.50
134.40
128.65
121.36
119.44
108.37
107.83
101.50
101.23
96.83
56.15
55.50
f1 (ppm)

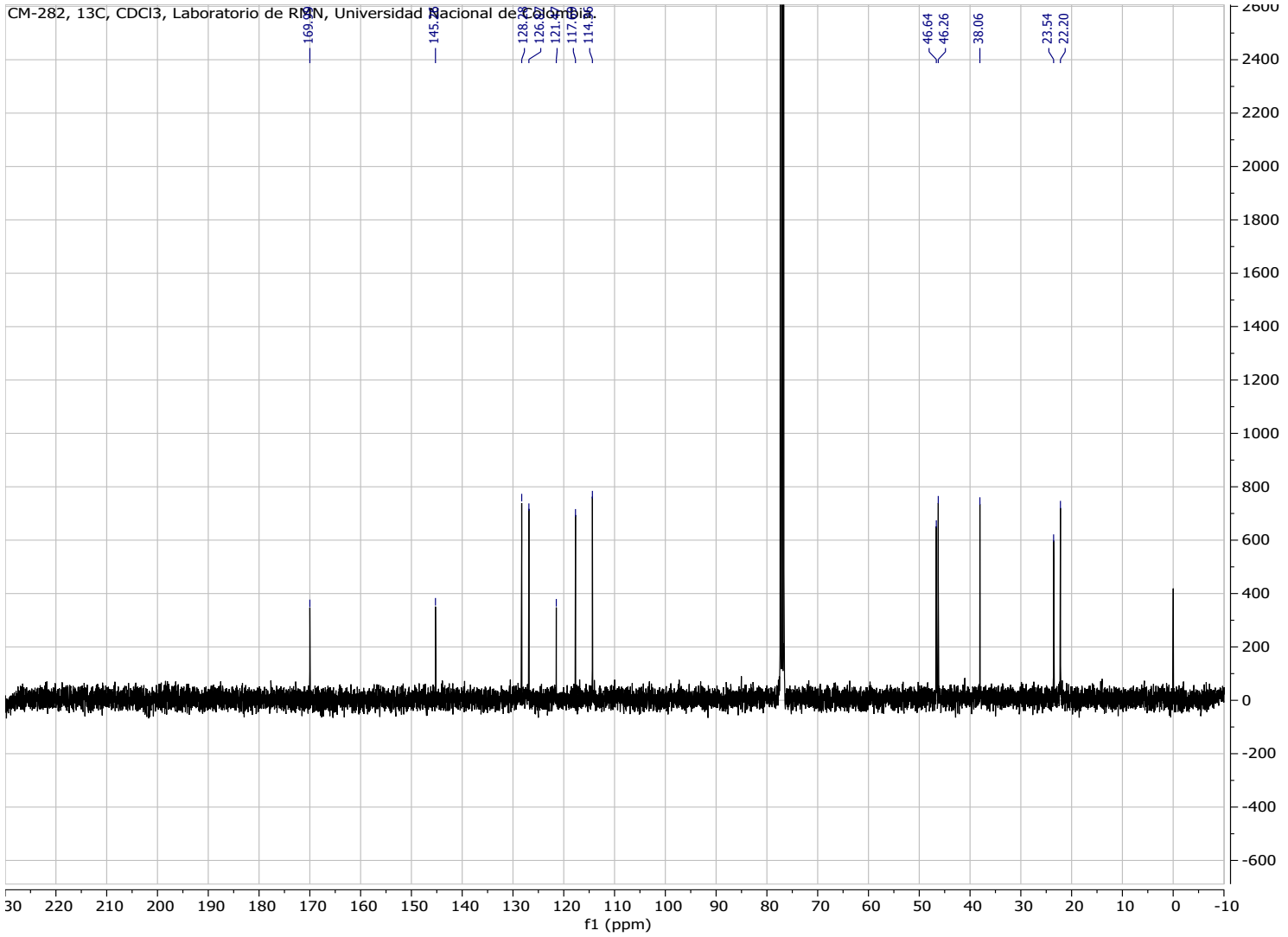
^{1}H NMR spectra of 2-(Phenyl-3',4'-dioxomethylen)-5,8-dimethylquinoline (16)



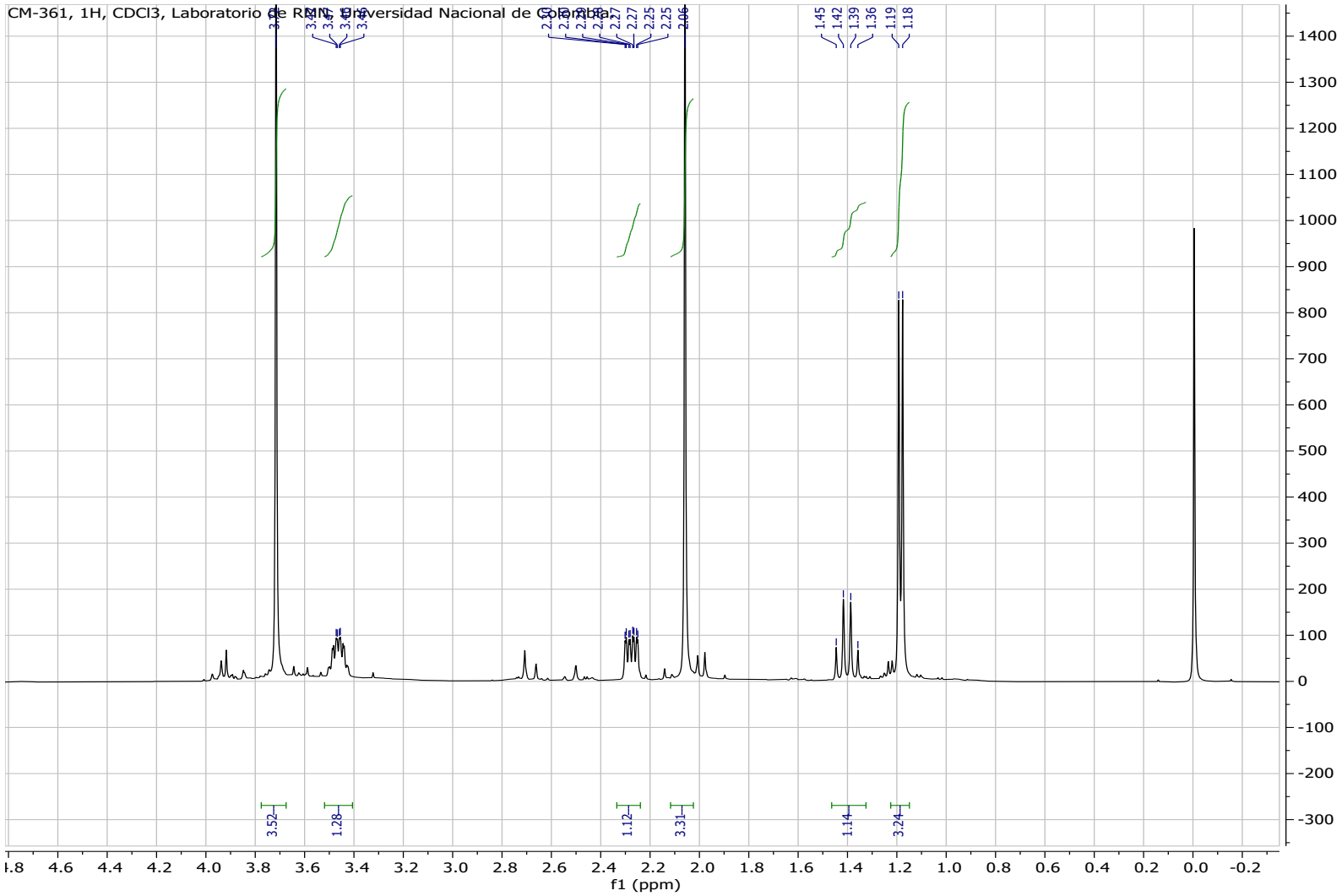
^{1}H NMR spectra of N-(2-Methyl-1,2,3,4-tetrahydroquinolin-4-yl)acetamide (17)



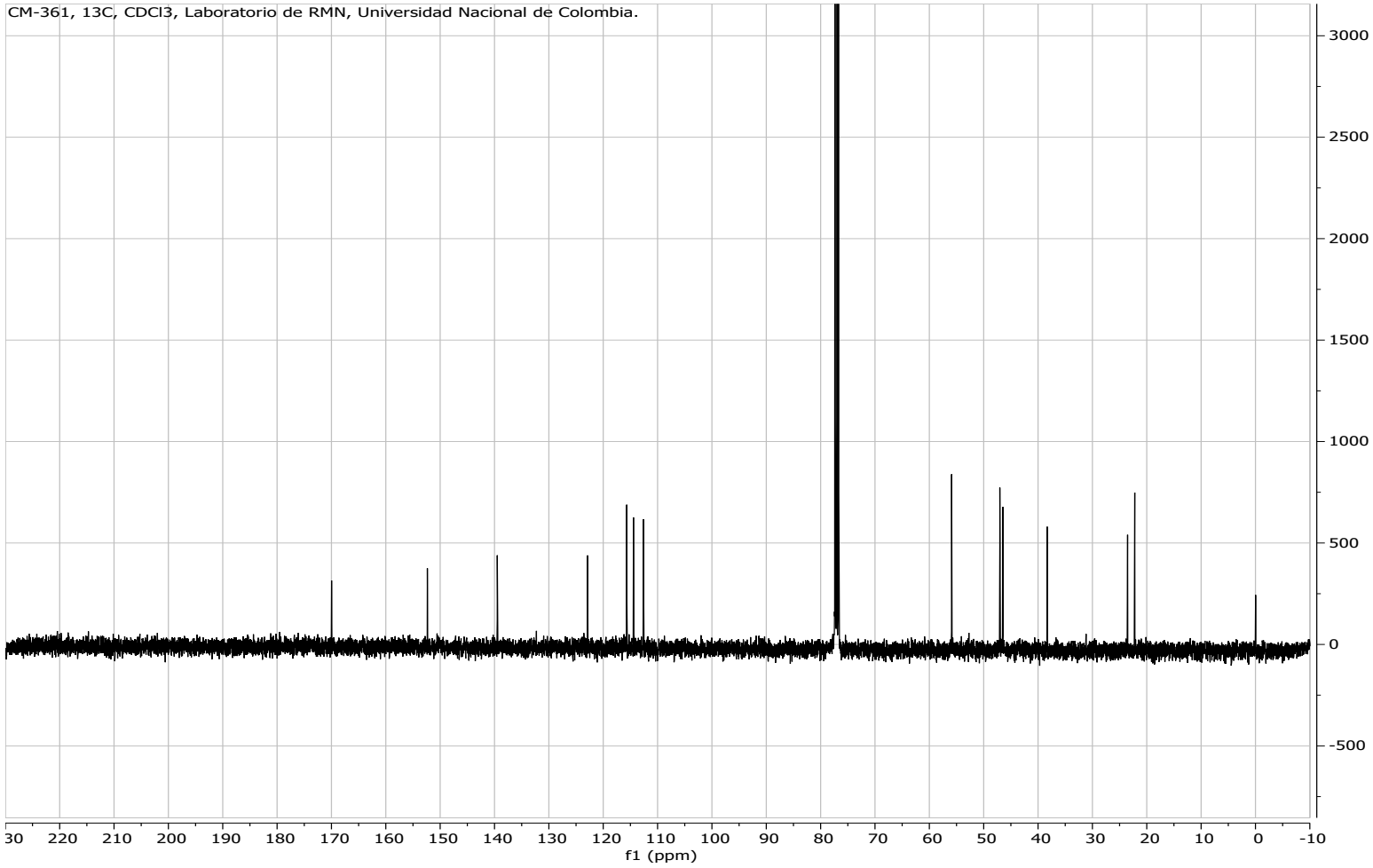
^{13}C NMR spectra of N-(2-Methyl-1,2,3,4-tetrahydroquinolin-4-yl)acetamide (17)



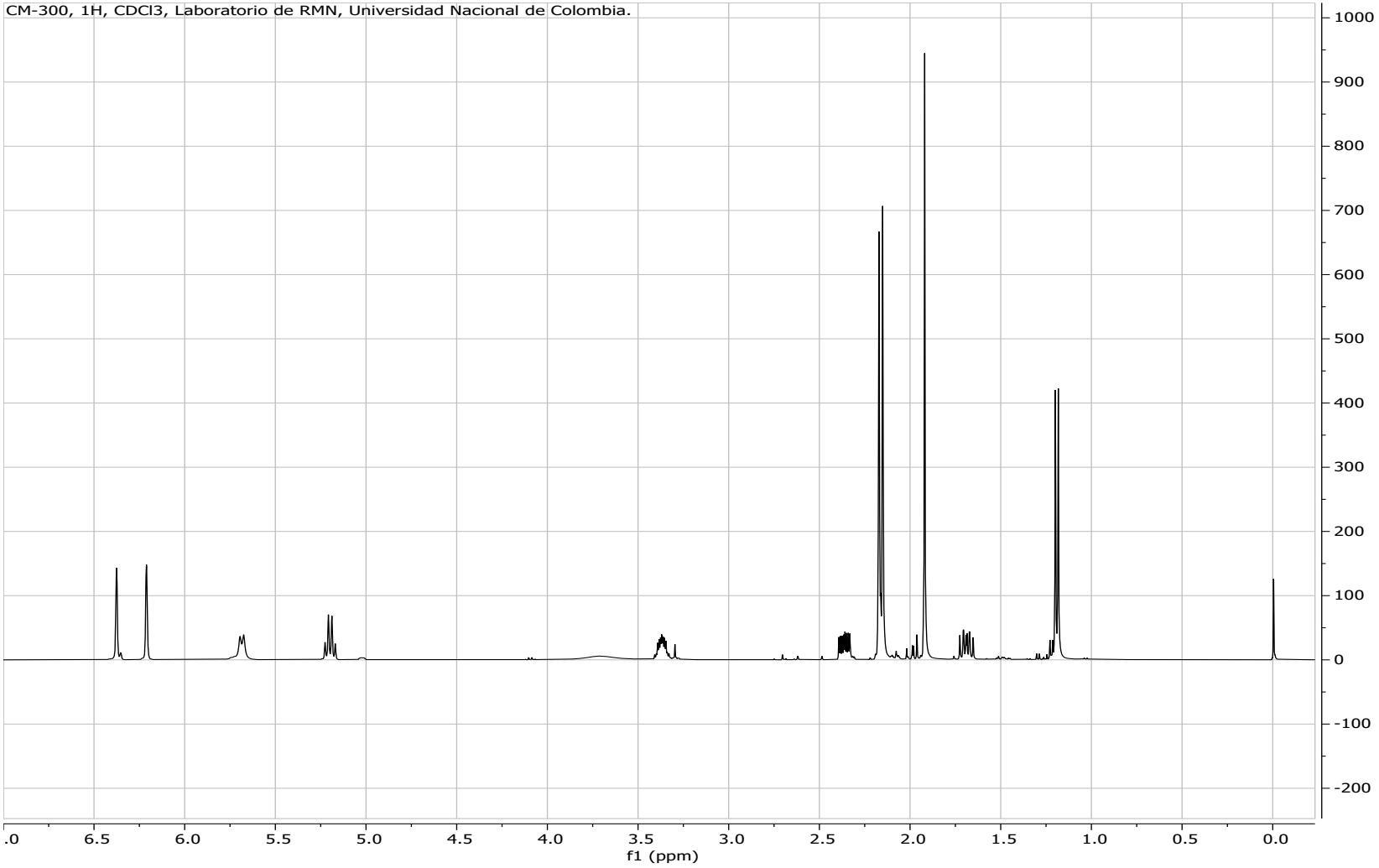
^{1}H NMR spectra of N-(6-Methoxy-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)acet- amide (19)



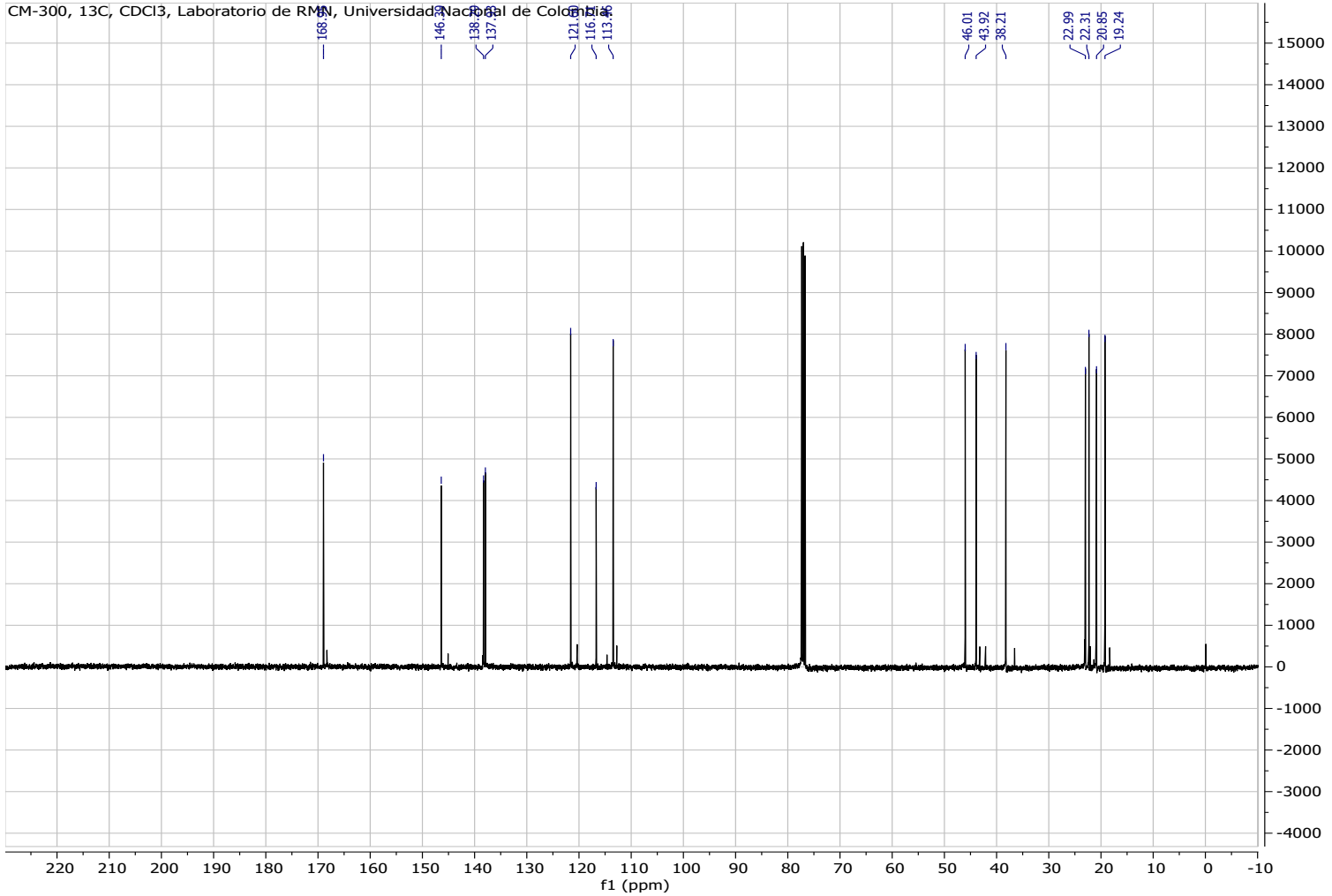
^{13}C NMR spectra of N-(6-Methoxy-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)acet- amide (19)



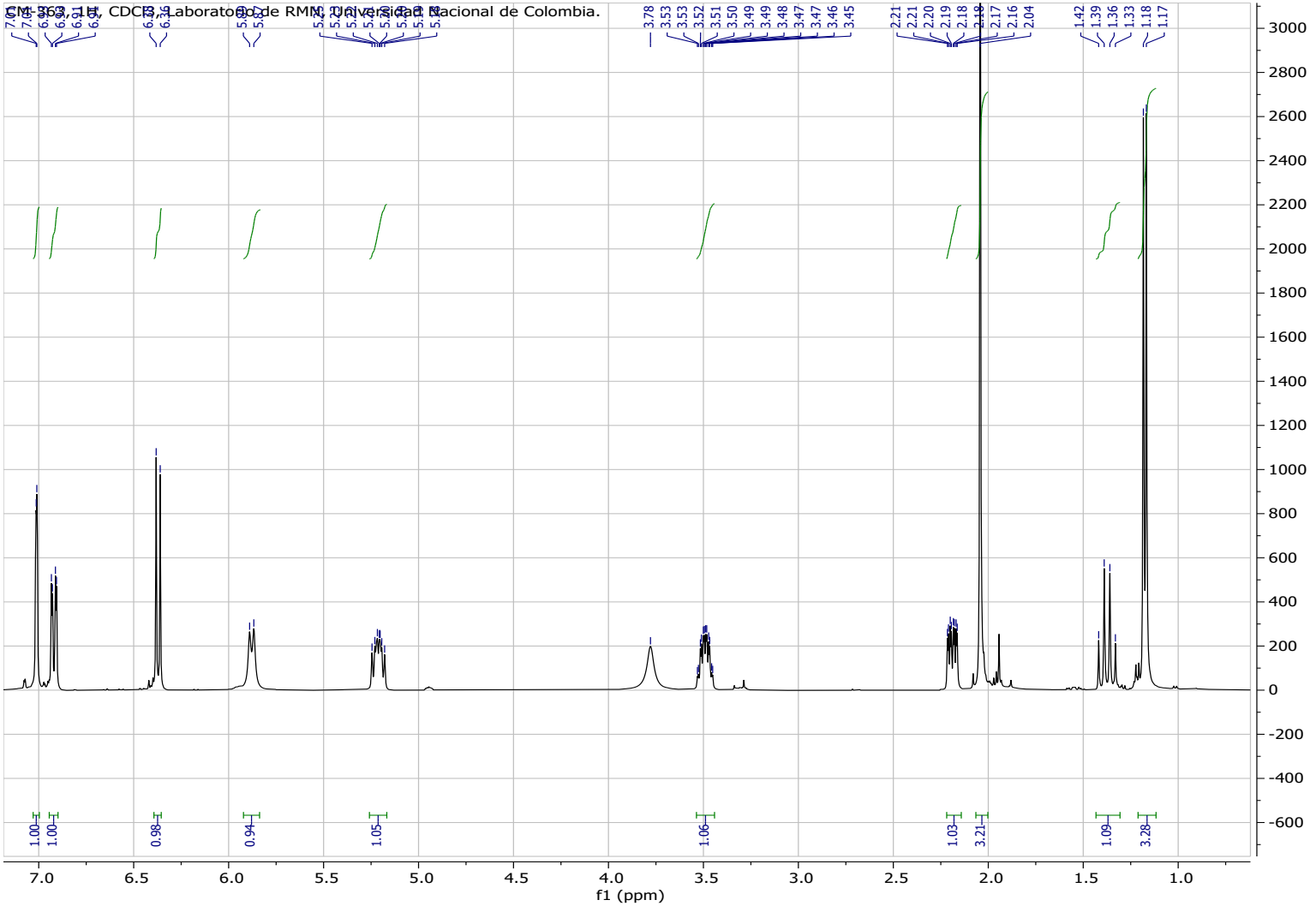
^{1}H NMR spectra of N-(2,5,7-Trimethyl-1,2,3,4-tetrahydroquinolin-4-yl)acetamide (20)



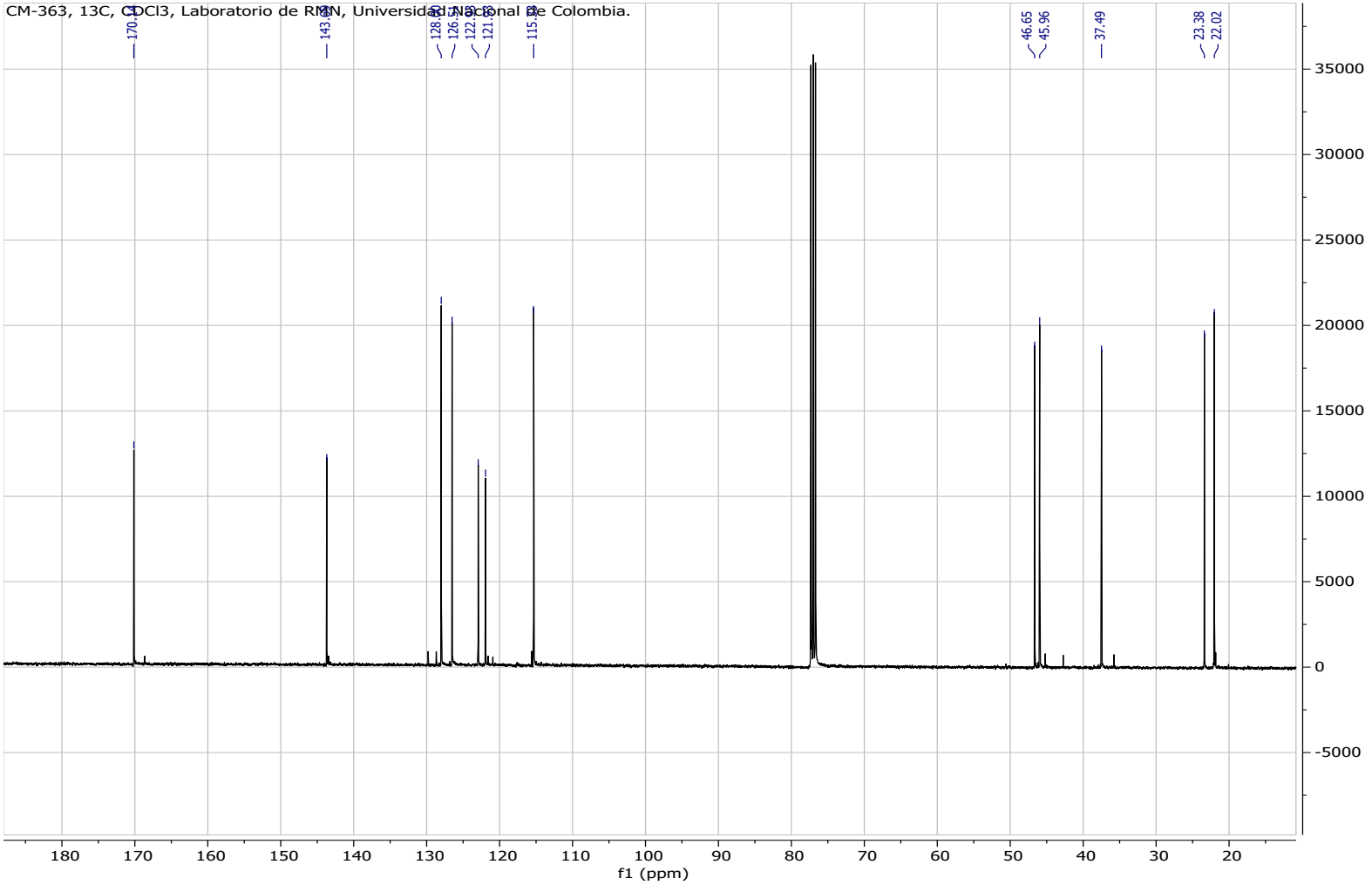
^{13}C NMR spectra of N-(2,5,7-Trimethyl-1,2,3,4-tetrahydroquinolin-4-yl)acetamide (20)



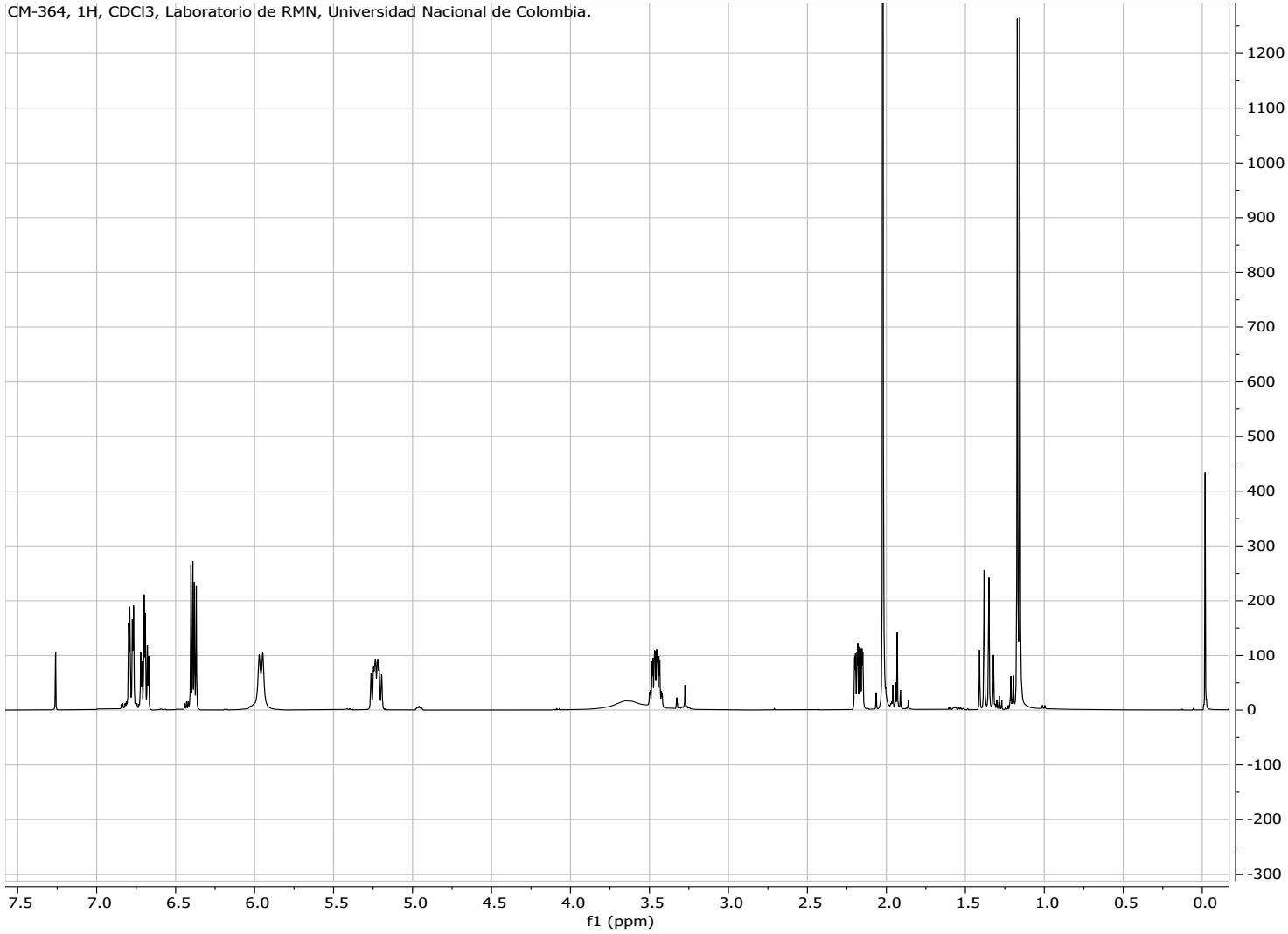
^{1}H NMR spectra of N-(6-Chloro-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)acet- amide (21)



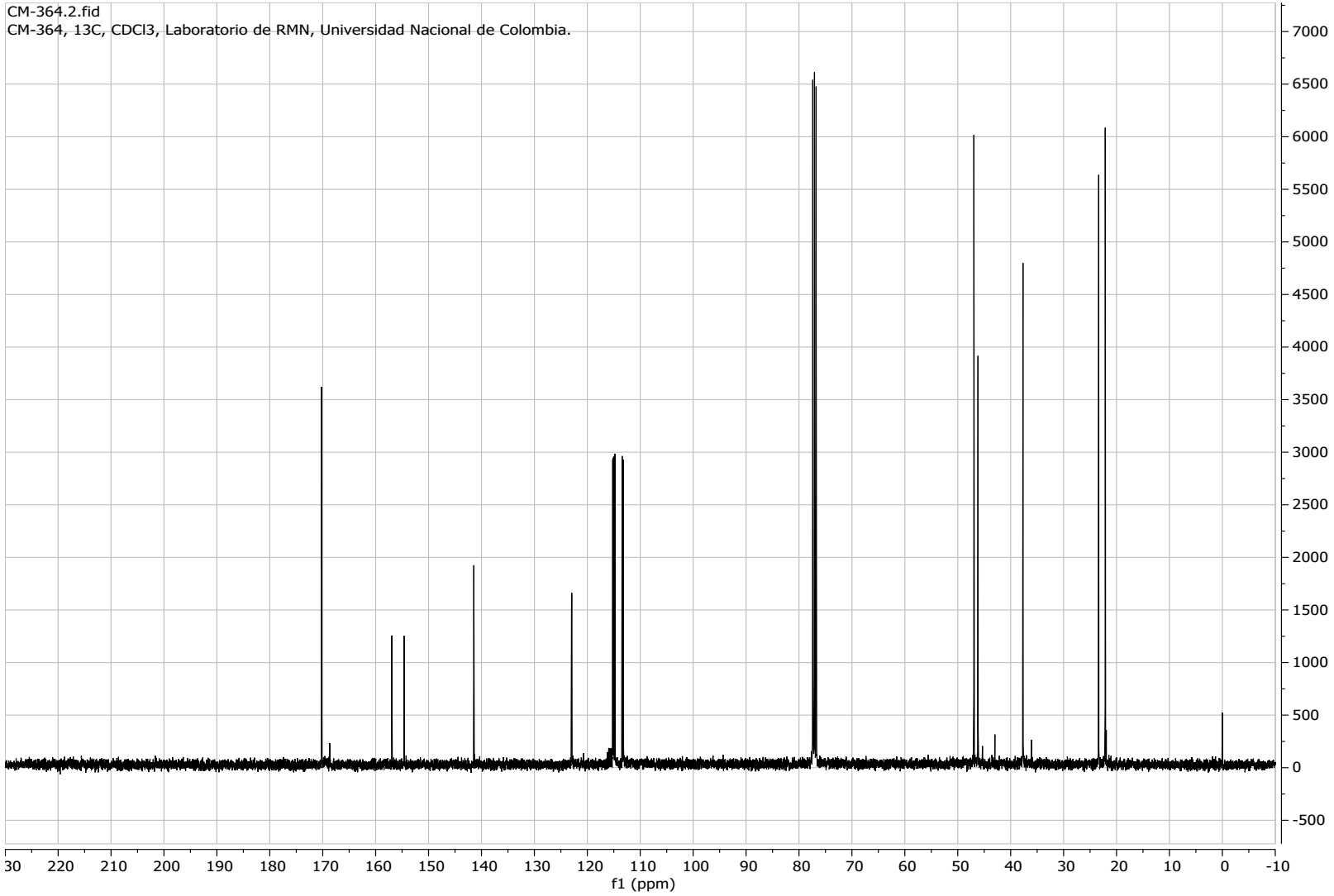
^{13}C NMR spectra of N-(6-Chloro-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)acet- amide (21)



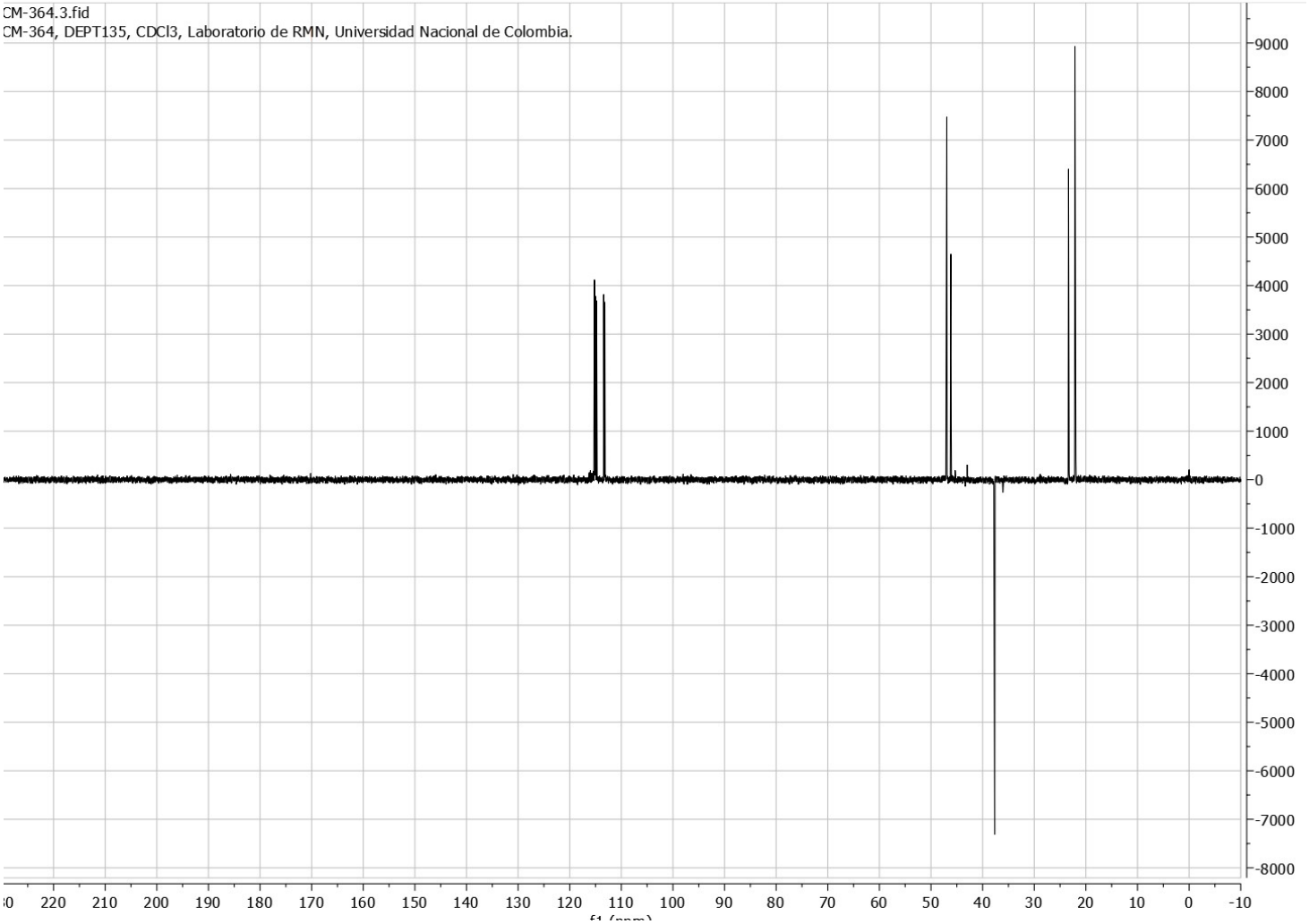
^{1}H NMR spectra of N-(6-Fluor-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)acet- amide (22)



^{13}C NMR spectra of N-(6-Fluor-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)acet- amide (22)



DEPT 135 NMR spectra of N-(6-Fluor-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)acet- amide (22)



2.3 In silico studies

2.3.1 Molecular Docking studies

Table S1
The binding affinity of the 2-substituted (tetrahydro)quinolines **4**–**22** for the different biological targets.

Comp.		Binding affinity (kcal/mol)			
	R	KDM5A	KDM4B	KDM4A	HER-2
4	H	-7.50	-6.51	-7.50	-8.09
5	6-Et	-8.21	-6.89	-8.21	-8.13
6	6-NO_2	-7.81	-7.73	-7.81	-7.67
7	6-F	-7.45	-6.26	-7.45	-7.77
8	6-Cl	-8.02	-6.75	-8.02	-7.88
9	6-OMe	-7.78	-6.59	-7.78	-7.72
10	5,6-OCH_2O	-8.33	-7.03	-8.33	-8.03
11	H	-8.15	-7.19	-8.15	-8.02
12	6-Me	-8.22	-7.50	-8.22	-8.24
13	6-OMe	-7.93	-7.38	-7.93	-8.05
14	Et	-8.15	-7.81	-7.93	-8.63
15	6,8-OMe	-7.88	-7.40	-7.88	-8.22
16	5,7-Me	-8.51	-7.76	-8.51	-8.78
17	H	-5.95	-6.35	-5.95	-6.90
18	Et	-6.43	-6.48	-6.43	-7.04
19	OMe	-6.03	-6.33	-6.03	-6.51
20	5,7-Me	-6.76	-6.72	-6.76	-6.61
21	Cl	-6.32	-6.28	-6.32	-6.81
22	F	-5.87	-6.21	-5.87	-6.65
DOX	-	-9.79	-5.17	-9.79	-7.72

3.4 Molecular dynamics studies

3.4.1 Conformational analysis of the complexes formed by the proteins KDM5A and KDM4B.

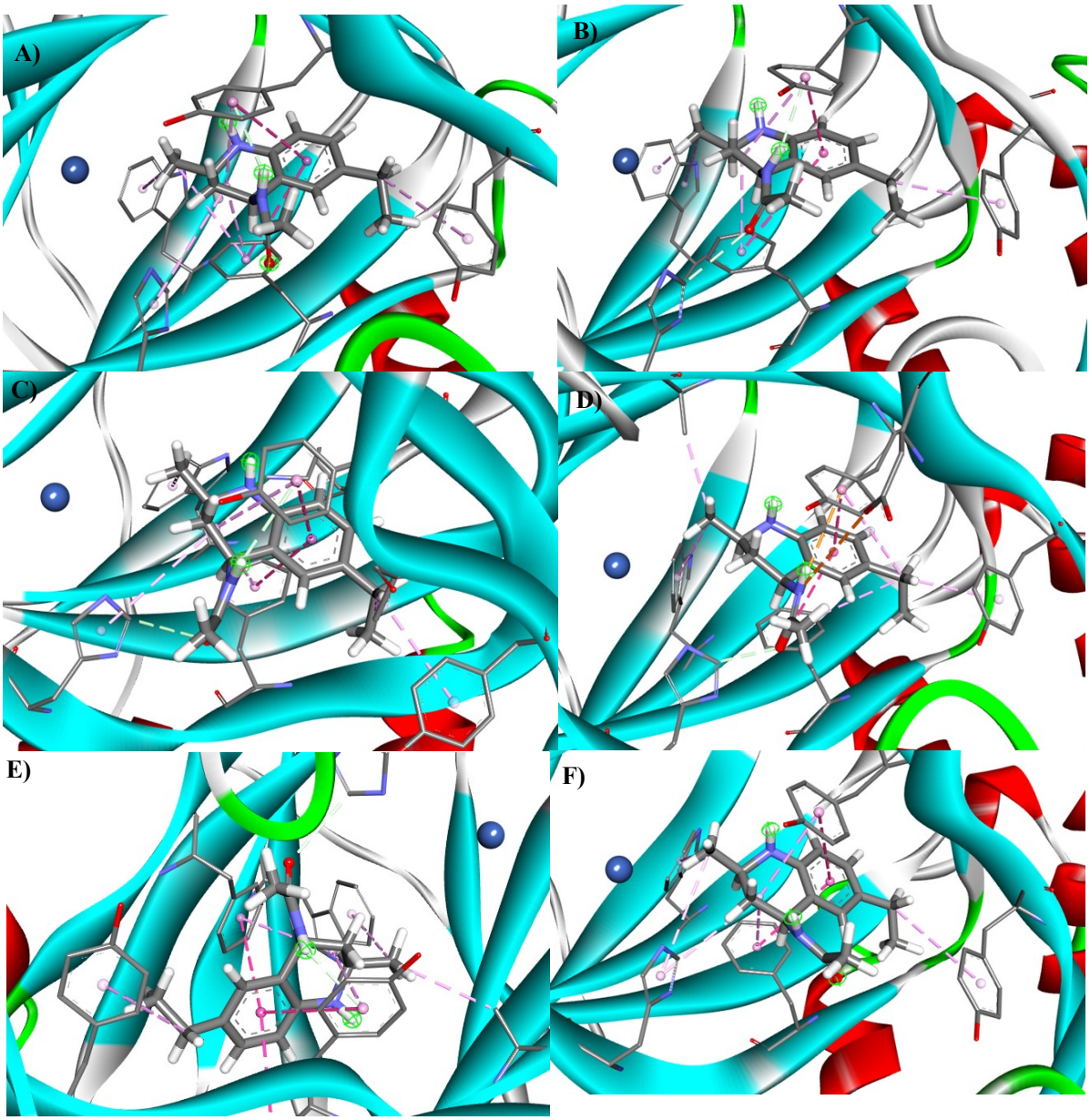


Figure S2. Representative snapshots from the MD simulation at **(A)** 5 ns, **(B)** 10 ns, **(C)** 15 ns, **(D)** 20 ns, **(E)** 25 ns, and **(F)** 30 ns of the molecular dynamics trajectory of 18 with KDM5A.

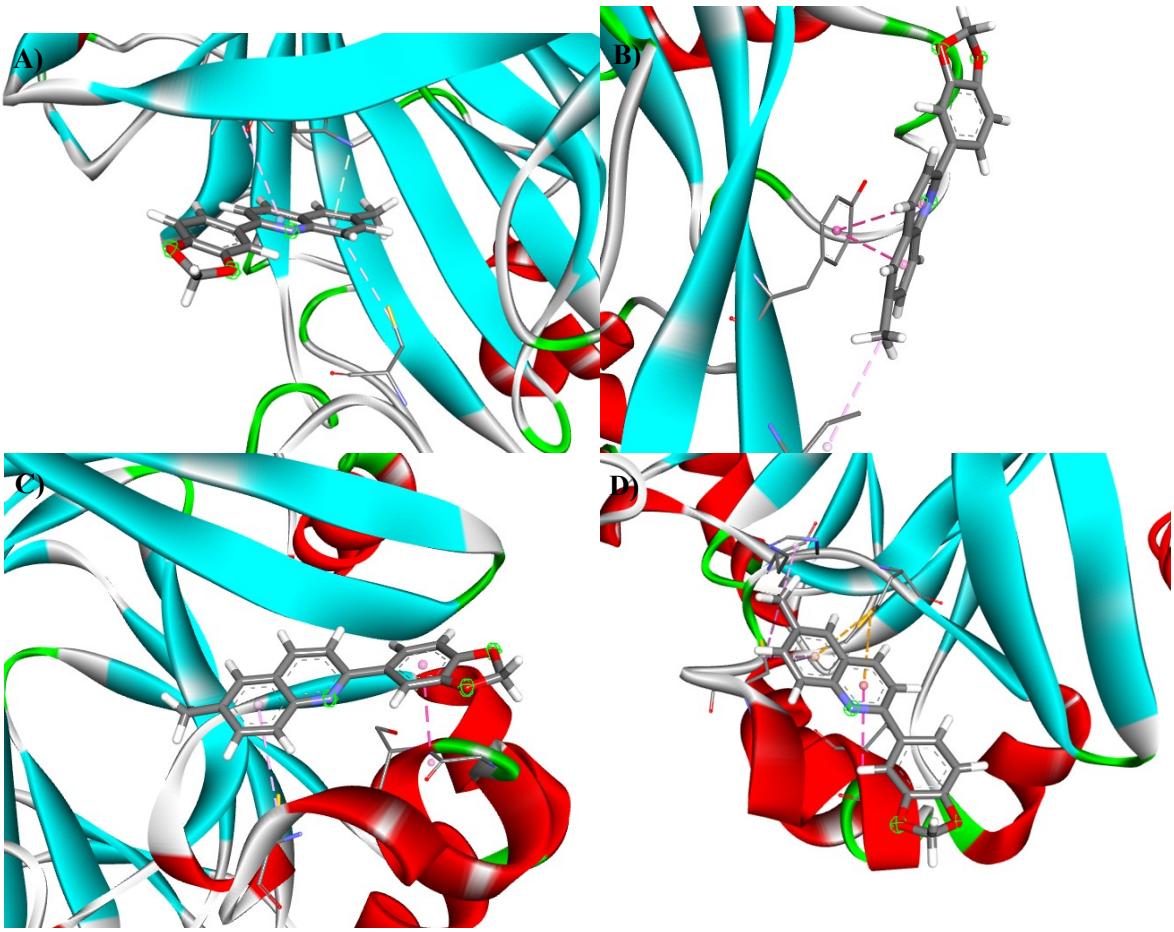


Figure S3. Representative snapshots from the MD simulation at **(A)** 5 ns, **(B)** 10 ns, **(C)** 15 ns, **(D)** 20 - 30 ns, of the molecular dynamics trajectory of 12 with KDM4B.

2.3.3 In-silico ADME properties

Table S2. ADME prediction results of the synthesized 2-substituted (tetrahydro)quinolines **4**–**22.**

Comp.	Group	MW[a]	cLogP[b]	TPSA[c]	HBA[d]	HBD[e]	ROTB[f]	% ABS.[g]	LogS[h]
4	**F**	205.25	3.47	12.89	1	0	1	104.55	-6.22
5	**F**	233.31	4.13	12.89	1	0	2	104.55	-7.02
6	**F**	250.25	3.07	45.82	2	0	2	93.19	-5.97
7	**F**	223.25	3.86	12.89	2	0	1	104.55	-6.50
8	**F**	239.70	4.08	12.89	1	0	1	104.55	-6.84
9	**F**	279.30	3.51	22.12	2	0	2	101.37	-6.35
10	**F**	249.26	3.34	31.35	3	0	1	98.18	-5.98
11	**G**	249.26	3.35	31.35	3	0	1	98.18	-5.98
12	**G**	263.29	3.67	31.35	3	0	1	98.18	-6.36
13	**G**	279.29	3.34	40.58	4	0	2	94.99	-6.10
14	**G**	277.32	3.98	31.35	3	0	3	98.18	-4.84
15	**G**	309.32	3.3	49.81	5	0	3	91.82	-6.21
16	**G**	277.32	4	31.35	3	0	1	98.18	-6.74
17	**H**	204.27	2.23	41.13	1	2	2	94.81	-3.60
18	**H**	232.32	2.98	41.13	1	2	3	94.81	-4.39
19	**H**	234.29	1.56	50.36	2	2	3	91.63	-3.73
20	**H**	232.32	3.02	41.13	1	2	2	94.81	-4.38
21	**H**	238.71	2.9	41.13	1	2	2	94.81	-4.22
22	**H**	222.26	1.91	41.13	2	2	2	94.81	-3.88
DOX	**-**	543.50	0.48	206.08	12	7	5	37.90	-2.67
Lipinski's Rule		< 500	<5	< 140	<10	<5	< 10		

[a] Molecular weight (g/mol); [b] Logarithm of the partition coefficient between n-octanol and water; [c] Polar Surface Area (Å^2), [d] Number of hydrogen-bond acceptors; [e] Number of hydrogen-bond donors; [f] Number of rotatable bonds; [g] Percentage of absorption calculated by % Absorption = 109-(0.345 x TPSA); [h] Logarithm of aqueous solubility.