Electronic Supplementary Material (ESI) for RSC Medicinal Chemistry.


# Supporting Information

## Discovery of aurones bearing two amine functionalities as SHIP2 inhibitors with insulin-sensitizing effect in rat myotubes

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**Characterization data of key intermediates and final compounds**

6-hydroxybenzofuran-3(*2H*)-one: M.p. 245-247 ºC, recrys. solv. MeOH. $^{1}$H NMR (MeOD, 700 MHz): δ 7.49 (d, *J* = 8.55 Hz, H4), 6.58 (dd, $J_1$ = 1.95 Hz, $J_2$ = 8.55 Hz, H5), 6.46 (d, *J* = 1.96, H7), 4.64 (s, 2H); $^{13}$C NMR (MeOD, 175 MHz): δ 200.7, 178.5, 169.2, 126.5, 114.3, 113.5, 99.5, 76.8. HRMS (ESI) *m/z:* [M + 1]$^{+}$ calcd for $C_8H_7O_3^+$ ([M+1]$^{+}$): 151.0395, found 151.0392.

6-methoxybenzofuran-3(*2H*)-one: M.p. 116 -118 °C, recrys. solv. EtOH. $^{1}$H NMR ($CDCl_3$, 700 MHz): δ 7.57 (d, *J* = 8.6 Hz, H4), 6.65 (dd, $J_1$ = 2 Hz, $J_2$ = 8.6 Hz, H5), 6.55 (d, *J* = 2 Hz, H7), 4.63 (s, 2H), 3.89 (s, 3H). $^{13}$C NMR ($CDCl_3$, 175 MHz): δ 197.6, 176.6, 168.2, 125.1, 114.4, 111.7, 96.5, 96.3, 55.9. HRMS (ESI) *m/z:* [M + 1]$^{+}$ calcd for $C_9H_9O_3^+$ 165.0552, found 165.0535.

(*Z*)-6-Hydroxy-2-(4-(2-(piperidin-1-yl)ethoxy)benzylidene)benzofuran-3(*2H*)-one (**1a**): Yellow solid. Yield: 182 mg, 25%. M.p. 261 – 263 °C, recrys. solv. MeOH. $^{1}$H NMR (700 MHz, DMSO-$d_6$): δ 7.90 (d, J = 8.8 Hz, 2H), 7.60 (d, *J* = 8.5 Hz, 1H), 7.07 (d, *J* = 8.8 Hz, 2H), 6.77 (d, J = 2 Hz, 1H), 6.76 (s, 1H, olefinic H), 6.70 (dd, $J_1$ = 2.0 Hz, $J_2$ = 8.5 Hz, 1H), 4.14 (t, *J* = 5.9 Hz, 2H), 2.68 (t, *J* = 5.9 Hz, 2H), 2.44-2.46 (m, 4H), 1.48-1.52 (m, 4H), 1.37-1.4 (m, 2H); $^{13}$C NMR (DMSO-$d_6$, 175 MHz): δ 181.6, 168.2, 167.2, 160.2, 146.7, 133.4, 126.3, 125.1, 115.6, 113.6, 113.3, 111.1, 99.0, 66.2, 57.7, 54.9, 26.0, 24.3. HRMS (ESI) *m/z:* [M + H]$^{+}$ calcd for $C_{22}H_{24}NO_4^+$ 366.1705, found 366.1704.

(*Z*)-6-Hydroxy-2-(4-hydroxybenzylidene)benzofuran-3(*2H*)-one (**1b**): Yellow solid. Yield: 278 mg, 55%. M.p. 291 – 293 °C, recrys. solv. EtOAc. $^{1}$H NMR (700 MHz, DMSO-$d_6$): δ 11.1 (1H, brs, OH), 10.1 (1H, brs, OH), 7.81 (2H, dd, $J_1$ = 1.8 Hz, $J_2$ = 6.9 Hz), 7.60 (1H, d, *J* = 8.4 Hz), 6.88 (2H, dd, $J_1$ = 1.9 Hz, $J_2$ = 6.8 Hz), 6.78 (1H, d, *J* = 1.9 Hz), 6.72 (1H, s, olefinic H), 6.70 (1H, dd, $J_1$ = 2.0 Hz, $J_2$ = 8.4 Hz).$^{13}$C NMR (175 MHz, DMSO-$d_6$): δ 181.2, 167.5, 166.1, 159.3, 145.7, 133.3, 125.7, 123.0, 116.1, 113.2, 112.9, 111.4, 98.5. HRMS (ESI) *m/z:* [M + Na]$^{+}$ calcd for $C_{15}H_{10}NaO_4^+$ 277.0477; found 277.0481.

(*Z*)-2-((1H-Indol-3-yl)methylene)-6-hydroxybenzofuran-3(*2H*)-one (**12e**): Orange solid. Yield: 304 mg, 55%. M.p. 282 – 283 (dec.) °C, recrys. solv. EtOAc. $^{1}$H NMR (700 MHz DMSO-$d_6$): δ 12.0 (brs, 1H), 8.19 (d, J = 2.7 Hz, 1H), 8.01 (d, *J* = 7.9 Hz, 1H), 7.60 (d, J = 8.4 Hz, 1H), 7.50 (d, J = 7.3 Hz, 1H), 7.23 (m, 1H), 7.18 (m, 1H), 7.17 (s, 1H, olefinic H, overlap), 6.83 (d, J = 2.2 Hz, 1H), 6.70 (dd, $J_1$ = 8.5 Hz, $J_2$ = 2.0 Hz, 1H). $^{13}$C NMR (175 MHz, DMSO-$d_6$,): δ 180.2, 166.7, 165.6, 145.1, 136.3, 131.2, 126.7, 125.4, 122.6, 120.8, 118.9, 114.1, 112.6, 112.2,

108.2, 105.2, 98.6. HRMS (ESI) *m/z:* [M + Na]$^+$ calcd for $C_{17}H_{11}NNaO_3^+$ 300.0637; found 300.0639.

(*Z*)-6-Methoxy-2-(4-(2-(piperidin-1-yl)ethoxy)benzylidene)benzofuran-3(*2H*)-one (**2a**): Yellow solid, Yield: 45 mg, 19 %. M.p. 87 - 89 °C, recrys. solv. MeOH. $^1$H NMR ($CDCl_3$): δ 7.85 (d, *J* = 8.8 Hz, 2H), 7.71 (d, *J* = 8.5 Hz, 1H), 6.97 (d, J = 8.5 Hz, 2H), 6.81 (s, 1H, olefinic proton), 6.78 (d, J = 2.0 Hz, 1H), 6.75 (d, $J_1$ = 2.0 Hz, $J_2$ = 8.5 Hz, 1H), 4.17 (t, *J* = 6.1 Hz, 2H), 3.93 (s, 3H), 2.80 (t, *J* = 6.1 Hz, 2H), 2.52 (brs, 4H), 1.60-1.64 (m, 4H), 1.45-1.48 (m, 2H). $^{13}$C NMR (DMSO-$d_6$, 125 MHz): δ 182.9 (CO), 168.3, 167.2, 160.1, 146.8, 133.1, 125.7, 125.2, 115.2, 115.0, 112.2, 112.0, 96.6, 66.1, 57.8, 56.0, 55.1, 25.9, 24.2; HRMS (ESI) *m/z:* [M + H]$^+$ calcd for $C_{23}H_{26}NO_4^+$ 380.1862, found 380.1865.

(*Z*)-2-(4-Methoxybenzylidene)-6-(2-(piperidin-1-yl)ethoxy)benzofuran-3(*2H*)-one (**3a**): Yellow solid. Yield: 114 mg, 46%. M.p. 128-130 ºC, recrys. solv. EtOAc. $^1$H NMR ($CDCl_3$, 700 MHz): δ 7.86 (d, *J* = 8.8 Hz, 2H), 7.69 (d, *J* = 8.4 Hz, 1H), 6.97 (d, *J* = 8.8 Hz, 2H), 6.80 (s, 1H), 6.77 (d, *J* = 2.0 Hz, 1H), 6.75 (dd, $J_1$ = 2.0 Hz, $J_2$ = 8.4 Hz, 1H), 4.21 (t, *J* = 6.0 Hz, 2H), 3.87 (s, 3H), 2.82 (t, *J* = 6.0 Hz, 2H), 2.52 (brs, 4H), 1.60-1.64 (m, 4H), 1.43-1.48 (m, 2H). $^{13}$C NMR ($CDCl_3$, 175 MHz): δ 182.9, 168.2, 166.4, 160.8, 146.8, 133.2, 125.7, 125.2, 115.1, 114.4, 112.5, 112.2, 97.2, 67.0, 57.5, 55.4, 55.1, 25.9, 24.1. HRMS (ESI) *m/z:* [M + H]$^+$ calcd for $C_{23}H_{26}NO_4^+$ 380.1862, found 380.1870.

(*Z*)-6-(2-(Piperidin-1-yl)ethoxy)-2-(3,4,5-trimethoxybenzylidene)benzofuran-3(*2H*)-one (**4a**): Yellow solid. Yield: 198 mg, 69%. M.p. 118-120 ºC, recrys. solv. EtOAc. $^1$H NMR ($CDCl_3$, 700 MHz): δ 7.70 (d, *J* = 8.5 Hz, 1H), 7.15, (s, 2H), 6.77 (dd, $J_1$ = 2.1 Hz, $J_2$ = 8.5 Hz, 1H), 6.75 (d, *J* = 2.1 Hz, 1H), 6.74 (s, 1H), 4.22 (t, *J* = 6.0 Hz, 2H), 3.94 (s, 6H), 3.91 (s, 3H), 2.82 (t, *J* = 6.0 Hz, 2H), 2.50-2.54 (m, 4H), 1.59-1.64 (m, 4H), 1.43 -1.48 (m, 2H); $^{13}$C NMR ($CDCl_3$, 175 MHz): δ 182.8 , 168.3, 166.7, 153.3, 147.4, 139.8, 127.9, 125.8, 114.9, 112.6, 112.1, 108.7, 97.3, 67.1, 61.0, 57.6, 56.2, 55.2, 26.0, 24.1. HRMS (ESI) *m/z:* [M + H]$^+$ calcd for $C_{25}H_{30}NO_6^+$ 440.2073, found 440.2073.

(*Z*)-2-(Naphthalen-1-ylmethylene)-6-(2-(piperidin-1-yl)ethoxy)benzofuran-3(2H)-one (**7a**): Yellow solid. Yield: 86 mg, 33%. M.p. 128 -129 ºC, recrys. solv. EtOAc. $^1$H NMR (700 MHz, DMSO-$d_6$): δ 8.36 (1H, d, *J* = 7.2 Hz), 8.30 (1H, d, *J* = 8.4 Hz), 8.06 (1H, d, *J* = 8.2 Hz), 8.03 (1H, d, J = 7.6 Hz), 7.74 (1H, d, *J* = 8.5 Hz), 7.68 (1H, d, *J* = 8.0 Hz), 7.67 (1H, m), 7.62 (1H, dtd, $J_1$ = 1.0 Hz, $J_2$ = 7.5 Hz), 7.51 (1H, s), 7.19 (1H, d, *J* = 2.1 Hz), 6.88 (1H, dd, $J_1$ = 2.1 Hz,

$J_2$ = 8.5 Hz), 4.26 (2H, t, $J$ = 5.8 Hz), 2.71 (2H, t, $J$ = 5.6 Hz), 2.46 (4H, br s), 1.50 (4H, m), 1.38 (2H, br s).$^{13}$C NMR (175 MHz, DMSO-$d_6$): δ 181.5, 168.3, 166.8, 148.3, 133.4, 131.5, 130.3, 129.6, 128.9, 127.8, 127.4, 126.4, 125.69, 125.67, 123.3, 113.9, 113.3, 106.3, 97.8, 66.9, 56.9, 54.3, 25.4, 23.8. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{26}H_{26}NO_3^+$ 400.1913, found 400.1921.

(*Z*)-2-(4-Chlorobenzylidene)-6-(2-(piperidin-1-yl)ethoxy)benzofuran-3(2H)-one (**8a**): Yellow solid. Yield: 68 mg, 27%. M.p. 143 - 145 ºC, recrys. solv. EtOAc. $^1$H NMR (700 MHz, DMSO-$d_6$): δ 7.98 (2H, d, $J$ = 8.5 Hz), 7.68 (1H, $J$ = 8.5 Hz), 7.57 (2H, d, $J$ = 8.6 Hz), 7.17 (1H, d, $J$ = 2.0 Hz), 6.86 (1H, s), 6.85 (1H, dd, $J_1$ = 2.0 Hz, $J_2$ = 8.7 Hz), 4.26 (2H, t, $J$ = 5.8 Hz), 2.71 (2H, t, $J$ = 5.7 Hz), 2.45 (4h, brs), 1.50 (4H, m), 1.38 (2H, brs). $^{13}$C NMR (175 MHz, DMSO-$d_6$): δ 181.6, 168.1, 166.8, 147.5, 134.4. 132.7, 131.0, 129.1, 125.6, 113.7, 113.3, 109.5, 97.7, 66.9, 56.9, 54.3, 25.5, 23.8. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{22}H_{23}ClNO_3^+$ 384.1366, found 384.1365.

(*Z*)-2-(3,4-Difluorobenzylidene)-6-(2-(piperidin-1-yl)ethoxy)benzofuran-3(2H)-one (**9a**): Yield: 43 mg, 17%. M.p. 127 – 128 ºC, recrys. solv. EtOAc. $^1$H NMR (700 MHz, DMSO-$d_6$): δ 8.03 (1H, m), 7.81 (1H, br s), 7.68 (1H, d, $J$ = 8.5 Hz), 7.58 (1H, dd, $J_1$=8.7 Hz, $J_2$ =19 Hz), 7.22 (1H, d, $J$=1.8 Hz), 6.87 (1H, s), 6.86 (1H, dd, $J_1$=2.3 Hz, $J_2$=8.8 Hz), 4.25 (2H, t, $J$ = 5.8 Hz), 2.71 (2H, t, $J$ = 5.6 Hz), 2.46 (4H, brs), 1.50 (4H, m), 1.38 (2H, brs). $^{13}$C NMR (175 MHz, DMSO-$d_6$): δ 181.6, 168.2, 166.8, 147.5, 129.9, 128.6, 125.6, 119.4, 119.3, 118.3, 118.1, 113.6, 113.4, 108.6, 97.8, 66.9, 56.9, 54.3, 25.5, 23.8. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{22}H_{22}F_2NO_3^+$ 386.1568, found 386.1565.

(*Z*)-2-(4-Fluorobenzylidene)-6-(2-(piperidin-1-yl)ethoxy)benzofuran-3(2H)-one (**10a**): Yellow solid. Yield: 38 mg, 16%. M.p. 132 -134 ºC, recrys. solv. EtOAc. $^1$H NMR (700 MHz, DMSO-$d_6$): δ 8.04 (2H, m), 7.68 (2H, d, $J$ = 8.5 Hz), 7.35 (2H, m), 7.17 (1H, d, $J$ = 2.1 Hz), 6.88 (1H, s), 6.86 (1H, dd, $J_1$ = 2.1 Hz, $J_2$ = 8.5 Hz), 4.25 (2H, t, $J$ = 5.8 Hz), 2.70 (2H, t, $J$ = 5.8 Hz), 2.45 (4H, brs), 1.50 (4H, m), 1.38 (2H, brs). $^{13}$C NMR (175 MHz, DMSO-$d_6$): δ 181.6, 168.0, 166.7, 162.6 (d, $J$ = 248 Hz), 147.0, 133.5 (d, $J$ = 8.7 Hz), 128.7, 125.5, 116.2 (d, $J$ = 22 Hz), 113.8, 113.2, 109.8, 97.7, 66.9, 56.9, 54.3, 25.5, 23.9. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{22}H_{23}FNO_3^+$ 368.1662, found 368.1670.

(*Z*)-2-([1,1'-Biphenyl]-4-ylmethylene)-6-(2-(piperidin-1-yl)ethoxy)benzofuran-3(2H)-one (**11a**): Light yellow solid. Yield: 45 mg, 16%. M.p. 138 -139 ºC, recrys. solv. EtOAc. $^1$H NMR (700 MHz, DMSO-$d_6$): δ 8.07 (2H, d, J = 8.3 Hz), 7.82 (2H, d, J = 8.4 Hz), 7.76 (2H, m), 7.69 (1H, d, $J$ = 8.5 Hz), 7.50 (2H, m), 7.41 (1H, m), 7.20 (1H, d, $J$ = 2.0 Hz), 6.91 (1H, s), 6.87 (1H, dd,

$J_1$ = 2.1 Hz, $J_2$ = 8.5 Hz), 4.27 (2H, t, $J$ = 5.8 Hz), 2.71 (2H, t, $J$ = 5.8 Hz), 2.46 (4H, brs), 1.50 (4H, quin), 1.38 (2H, brs). $^{13}$C NMR (175 MHz, DMSO-$d_6$): δ 181.6, 168.0, 166.7, 147.4, 141.2, 139.1, 131.8, 131.2, 129.1, 128.1, 127.1, 126.8, 110.6, 97.7, 66.9, 57.0, 54.3, 25.5, 23.9. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{28}H_{28}NO_3^+$ 426.2069, found 426.2081.

(*Z*)-6-(2-(Piperidin-1-yl)ethoxy)-2-((1-(2-(piperidin-1-yl)ethyl)-1H-indol-3-yl)methylene)benzofuran-3(2H)-one (**12a**): Light yellow solid. Yield: 101 mg, 31%. M.p. 125 – 126 ºC, recrys. solv. EtOAc. $^1$H NMR (700 MHz, DMSO-$d_6$): δ 8.30 (1H, s), 8.04 (1H, d, J = 7.9 Hz), 7.66 (1H, d, $J$ = 8.5 Hz), 7.60 (1H, d, $J$ = 8.2 Hz), 7.28 (1H, m), 7.22 (1H, s, olefinic proton, overlap), 7.06 (1H, d, $J$ = 2.1 Hz), 6.84 (1H, dd, $J_1$ = 2.1 Hz, $J_2$ = 8.5 Hz), 4.40 (2H, t, $J$ = 6.5 Hz), 4.25 (2H, t, $J$ = 5.9 Hz), 2.72 (2H, t, $J$ = 5.8 Hz), 2.69 (2H, t, $J$ = 6.5 Hz), 2.44 (8H, brs), 1.51 (8H, m), 1.39 (4H, brs). $^{13}$C NMR (175 MHz, DMSO-$d_6$): δ 180.1, 166.5, 165.7, 144.9, 136.3, 134.8, 127.1, 125.0, 122.7, 121.0, 119.2, 115.2, 112.6, 110.7, 107.5, 105.6, 97.2, 66.7, 57.8, 57.0, 54.3, 54.1, 43.8, 25.6, 25.5, 24.0, 23.9. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{31}H_{38}N_3O_3^+$ 500.2913, found 500.2909.

(*Z*)-2-(2,3-dichlorobenzylidene)-6-(2-(piperidin-1-yl)ethoxy)benzofuran-3(*2H*)-one (**18a**): Yellow solid. Yield: 65 mg, 24%. M.p. 162 – 164 ºC, recrys. solv. EtOAc. $^1$H NMR (700 MHz, DMSO-$d_6$): δ 8.22 (1H, dd, $J_1$ = 1.39 Hz, $J_2$ = 7.92 Hz), 7.73 (1H, dd, $J_1$ = 1.39 Hz, $J_2$ = 8.01 Hz), 7.72 (1H, d, $J$ = 8.57 Hz), 7.53 (1H, t, $J$ = 7.97 Hz), 7.18 (1H, d, $J$ = 2.05 Hz), 7.00 (1H, olefinic H, s), 6.89 (1H, dd, $J_1$ = 2.09 Hz, $J_2$ = 8.57 Hz), 4.27 (2H, t, $J$ = 5.75 Hz), 2.73 (2H, m), 2.47 (4H, brs), 1.50 (4H, m), 1.38 (2H, m). $^{13}$C NMR (175 MHz, DMSO-$d_6$): δ 181.5, 168.4, 167.1, 148.8, 132.7, 132.1, 132.0, 131.3, 130.2, 128.6, 125.9, 113.5, 113.4, 104.8, 97.9, 66.9, 56.9, 54.3, 25.4, 23.8. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{22}H_{22}Cl_2NO_3^+$ 418.0977, found 418.0975.

(*Z*)-2-(2,4-dichlorobenzylidene)-6-(2-(piperidin-1-yl)ethoxy)benzofuran-3(*2H*)-one (**20a**): Orange solid. Yield: 110 mg, 40%. M.p. 125 – 126 ºC, recrys. solv. EtOAc. $^1$H NMR (700 MHz, DMSO-$d_6$): δ 8.26 (1H, d, $J$ = 8.57 Hz), 7.81 (1H, d, $J$ = 2.15 Hz), 7.71 (1H, d, J = 8.60 Hz), 7.61 (1H, dd, $J_1$ = 2.01 Hz, $J_2$ = 8.5 Hz), 7.16 (1H, d, J = 2.10 Hz), 6.92 (1H, olefinic H, s), 6.88 (1H, dd, $J_1$ = 2.10 Hz, $J_2$ = 8.56 Hz), 4.26 (2H, t, J = 5.79 Hz), 2.71 (2H, t, J = 5.80 Hz), 2.45 (4H, brs), 1.49 (4H, m), 1.38 (2H, m). $^{13}$C NMR (175 MHz, DMSO-$d_6$): δ 181.4, 168.3, 167.0, 148.5, 135.1, 134.8, 132.6, 129.7, 128.7, 128.1, 125.9, 113.5, 113.4, 103.7, 97.9, 66.8, 56.8, 54.2, 25.4, 23.7. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{22}H_{22}Cl_2NO_3^+$ 418.0977 , found 418.0984.

(*Z*)-2-(4-(benzyloxy)benzylidene)-6-(2-(piperidin-1-yl)ethoxy)benzofuran-3(*2H*)-one (**21a**): Light yellow solid. Yield: 75 mg, 25%. M.p. 117 – 118 ºC, recrys. solv. EtOAc. $^{1}$H NMR (700 MHz, DMSO-$d_6$): δ 7.94 (2H, d, *J* = 8.78 Hz), 7.67 (1H, d, J = 8.39 Hz), 7.47 (2H, d, *J* = 7.25 Hz), 7.41 (2H, t, *J* = 7.56 Hz), 7.35 (1H, t, *J* = 7.21 Hz), 7.17 (1H, d, *J* = 1.96 Hz), 7.14 (2H, d, *J* = 8.82 Hz), 6.85 (1H, dd, $J_1$ = 2.01 Hz, $J_2$ = 8.54 Hz), 6.82 (1H, olefinic H, s), 5.19 (2H, s), 4.27 (2H, t, *J* = 5.44 Hz), 2.79 (2H, brs), 2.51 (4H, m), 1.53 (4H, m), 1.39 (2H, m). $^{13}$C NMR (175 MHz, DMSO-$d_6$): δ 181.5, 167.7, 166.3, 159.7, 146.2, 136.6, 133.1, 128.5, 128.0, 127.8, 125.3, 124.7, 115.5, 115.3, 114.1, 113.0, 111.3, 97.6, 69.5, 56.7, 54.1, 25.2, 23.6. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{29}H_{30}NO_4^+$ 456.2175, found 456.2163.

(*Z*)-2-(3-(benzyloxy)benzylidene)-6-(2-(piperidin-1-yl)ethoxy)benzofuran-3(*2H*)-one (**22a**): Yield: 98 mg, 33%. M.p. 125 – 126 ºC, recrys. solv. EtOAc. $^{1}$H NMR (700 MHz, DMSO-$d_6$): δ 7.69 (1H, d, *J* = 8.54 Hz), 7.62 (1H, s), 7.55 (1H, d, *J* = 7.65 Hz), 7.50 (2H, d, *J* = 7.45 Hz), 7.43 (1H, d, *J* = 8.5 Hz), 7.41 (2H, d, *J* =7.60 Hz), 7.35 (1H, d, *J* = 7.40 Hz), 7.21 (1H, s), 7.12 (1H, dd, $J_1$ = 2.2 Hz, $J_2$ = 8.2 Hz), 6.87 (1H, d, *J* = 8.57 Hz), 6.81 (1H, s), 5.18 (2H, s), 4.34 (2H, brs), 2.94 (2H, brs), 2.69 (4H, m), 1.58 (4H, brs), 1.42 (2H, brs). $^{13}$C NMR (175 MHz, DMSO-$d_6$): δ 181.7, 168.0, 166.4, 158.6, 147.3, 136.9, 133.2, 130.1, 128.5, 128.0, 127.9, 127.6, 125.6, 124.0, 117.2, 116.4, 113.9, 110.9, 97.8, 69.4, 53.8, 52.9, 24.6, 23.1. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{29}H_{30}NO_4^+$ 456.2175, found 456.2165.

(*Z*)-2-(2-methoxybenzylidene)-6-(2-(piperidin-1-yl)ethoxy)benzofuran-3(*2H*)-one (**23a**): Light yellow solid. Yield: 112 mg, 45%. M.p. 131 – 132 ºC, recrys. solv. EtOAc. $^{1}$H NMR (700 MHz, DMSO-$d_6$): δ 8.18 (1H, dd, $J_1$ = 1.57 Hz, $J_2$ = 7.69 Hz), 7.68 (1H, d, *J* = 8.55 Hz), 7.45 (1H, dtd, $J_1$ = 1.7 Hz, $J_2$ = 7.84 Hz), 7.17 (1H, d, *J* = 2.08 Hz), 7.14 (1H, d, *J* = 8.34 Hz), 7.11 (1H, olefinic H, s), 7.10 (1H, d, *J* = 8.30 Hz), 6.85 (1H, dd, $J_1$ = 2.11 Hz, $J_2$ = 8.56 Hz), 4.25 (2H, t, *J* = 5.77 Hz), 3.90 (3H, s), 2.73 (2H, m), 2.48 (4H, brs), 1.51 (4H, m), 1.39 (2H, m). $^{13}$C NMR (175 MHz, DMSO-$d_6$): δ 181.6, 168.0, 166.6, 158.2, 147.3, 131.8, 131.0, 125.5, 120.9, 120.2, 113.9, 113.2, 111.6, 104.3, 97.7, 66.7, 56.9, 55.9, 54.3, 25.4, 23.8. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{23}H_{26}NO_4^+$ 380.1862, found 380.1871.

(*Z*)-2-(2-fluorobenzylidene)-6-(2-(piperidin-1-yl)ethoxy)benzofuran-3(*2H*)-one (**24a**): Orange solid. Yield: 55 mg, 23%. M.p. 139 – 140 ºC, recrys. solv. EtOAc. $^{1}$H NMR (700 MHz, DMSO-$d_6$): δ 8.25 (1H, t, *J* =7.67 Hz), 7.71 (1H, d, *J* = 8.55 Hz), 7.52 (1H, m), 7.34 – 7.39 (2H, m), 7.19 (1H, d, *J* = 1.85 Hz), 6.89 (1H, dd, $J_1$ = 1.91 Hz, $J_2$ = 8.63 Hz), 6.84 (1H, olefinic H, s), 4.28 (2H, t, *J* = 5.78 Hz), 2.73 (2H, *J* = 5.55 Hz), 2.47 (4H, brs), 1.52 (4H, m), 1.40 (2H, m). $^{13}$C NMR (175 MHz, DMSO-$d_6$): δ 181.3, 168.2, 166.9, 160.6 (d, *J* = 250 Hz), 148.2, 131.9 (d, *J* = 8.75 Hz), 131.2, 125.6, 125.0, 119.7 (d, *J* = 12 Hz), 115.8 (d, *J* = 23 Hz), 113.5, 113.3,

100.9, 97.8, 66.9, 56.8, 54.2, 25.4, 23.8. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{22}H_{23}FNO_3^+$ 368.1662, found 368.1663.

(*Z*)-2-((2,3-dihydrobenzofuran-5-yl)methylene)-6-(2-(piperidin-1-yl)ethoxy)benzofuran-3(*2H*)-one (**26a**): Light yellow solid. Yield: 43 mg, 17%. M.p. 160 – 161 ºC, recrys. solv. EtOAc. $^1$H NMR (700 MHz, DMSO-$d_6$): δ 7.91 (1H, s), 7.74 (1H, d, J = 8.30 Hz), 7.66 (1H, d, J = 8.53 Hz), 7.17 (1H, d, J = 1.72 Hz), 6.90 (1H, d, J = 8.40 Hz), 6.84 (1H, dd, $J_1$ = 1.98 Hz, $J_2$ = 8.56 Hz), 6.81 (1H, olefinic H, s), 4.63 (2H, t, J = 8.72 Hz), 4.25 (2H, t, J = 5.75 Hz), 3.26 (2H, t, J = 8.60 Hz), 2.74 (2H, m), 2.48 (4H, brs), 1.51 (4H, m), 1.39 (2H, m). $^{13}$C NMR (175 MHz, DMSO-$d_6$): δ 181.4, 167.6, 166.3, 161.5, 145.8, 132.7, 128.7, 128.1, 125.2, 124.6, 114.2, 113.1, 112.0, 109.7, 97.6, 71.8, 66.7, 56.9, 54.3, 28.7, 25.4, 23.8. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{24}H_{26}NO_4^+$ 392.1862, found 392.1859.

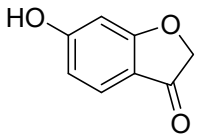
(*Z*)-2-((1-(3-(dimethylamino)propyl)-1H-indol-3-yl)methylene)-6-(2-(piperidin-1-yl)ethoxy)benzofuran-3(*2H*)-one (**12b**): Light yellow solid. Yield: 90 mg, 14%. M.p. 110 – 112 ºC, recrys. solv. EtOAc. $^1$H NMR (700 MHz, DMSO-$d_6$): δ 8.23 (1H, s), 8.07 (1H, d, *J* = 7.87 Hz), 7.66 (1H, d, *J* = 8.49 Hz), 7.62 (1H, d, *J* = 8.32 Hz), 7.30 (1H, t, *J* = 7.37 Hz), 7.24 (1H, d, *J* = 7.56 Hz), 7.23 (1H, olefinic H, s), 7.14 (1H, s), 6.84 (1H, dd, $J_1$ = 1.93 Hz, $J_2$ = 8.56 Hz), 4.35 (2H, t, *J* = 6.87 Hz), 4.26 (2H, t, *J* = 5.84 Hz), 2.72 (2H, t, *J* = 5.83 Hz,), 2.46 (2H, brs), 2.20 (2H, t, *J* = 6.70 Hz), 2.17 (6H, s), 1.96 (2H, m), 1.51 (4H, m), 1.39 (2H, m). $^{13}$C NMR (175 MHz, DMSO-$d_6$): δ 180.2, 166.6, 165.7, 145.0, 136.2, 134.2, 127.2, 124.9, 123.5, 121.0, 119.3, 115.2, 112.6, 110.7, 107.6, 105.4, 97.4, 66.7, 57.0, 55.7, 54.4, 45.1, 44.1, 27.5, 25.6, 23.9. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{29}H_{36}N_3O_3^+$ 474.2757, found 474.2743.

(*Z*)-2-((1-(2-morpholinoethyl)-1H-indol-3-yl)methylene)-6-(2-(piperidin-1-yl)ethoxy)benzofuran-3(*2H*)-one (**12c**): Yellow solid. Yield: 180 mg, 29%. M.p. 158 – 159 ºC, recrys. solv. EtOAc. $^1$H NMR (700 MHz, DMSO-$d_6$): δ 8.30 (1H, s), 8.06 (1H, d, *J* = 7.70 Hz), 7.67 (1H, d, *J* = 8.40 Hz), 7.62 (1H, *J* = 8.00 Hz), 7.29 (1H, t, *J* = 7.28 Hz), 7.23 (1H, J = 8.30 Hz), 7.22 (1H, olefinic H, s), 7.08 (1H, s), 6.84 (1H, *J* = 8.14 Hz), 4.42 (2H, t, *J* = 5.84 Hz), 4.24 (2H, t, *J* = 5.80 Hz), 3.58 (4H, brs), 2.73 (4H, m), 2.48 (8H, m), 1.51 (4H, m), 1.39 (2H, m). $^{13}$C NMR (175 MHz, DMSO-$d_6$): δ 180.1, 166.5, 165.7, 145.0, 136.3, 134.8, 127.1, 125.0, 122.7, 121.0, 119.3, 115.2, 112.5, 110.7, 107.5, 105.5, 97.3, 66.7, 66.2, 57.5, 57.0, 54.3, 53.3, 43.4, 25.5, 23.9. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{30}H_{36}N_3O_4^+$ 502.2706, found 502.2715.

(*Z*)-2-((1H-indol-3-yl)methylene)-6-(2-(piperidin-1-yl)ethoxy)benzofuran-3(*2H*)-one (**12d**): Yellow crystalline solid. Yield: 220 mg, 35%. %. M.p. 148 – 149 ºC, recrys. solv. EtOAc. $^1$H

NMR (700 MHz, DMSO-$d_6$): δ 12.1 (1H, NH, brs), 8.21 (1H, s), 8.07 (1H, d, $J$ = 7.82 Hz), 7.66 (1H, d, $J$ = 8.50 Hz), 7.51 (1H, d, $J$ = 8.03 Hz), 7.25 (1H, t, $J$ = 7.53 Hz), 7.24 (1H, olefinic H, overlap, s), 7.21 (1H, d, $J$ = 7.70 Hz), 7.19 (1H, s), 6.83 (1H, dd, $J_1$ = 1.72 Hz, $J_2$ = 8.51 Hz), 4.25 (2H, t, $J$ = 5.83 Hz), 2.71 (2H, t, $J$ = 5.82 Hz), 2.45 (4H, brs), 1.51 (4H, m), 1.39 (2H, m). $^{13}$C NMR (175 MHz, DMSO-$d_6$): δ 180.2, 166.6, 165.8, 145.0, 136.3, 134.8, 127.1, 125.0, 122.7, 121.0, 119.3, 115.2, 112.5, 110.7, 107.5, 105.5, 97.3, 66.7, 66.2, 57.5, 54.3, 53.3, 43.4, 39.5, 25.5, 23.9. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{24}H_{25}N_2O_3^+$ 389.1865, found 389.1858.

## $^{1}H$ and $^{13}C$ NMR spectra of intermediates and final compounds

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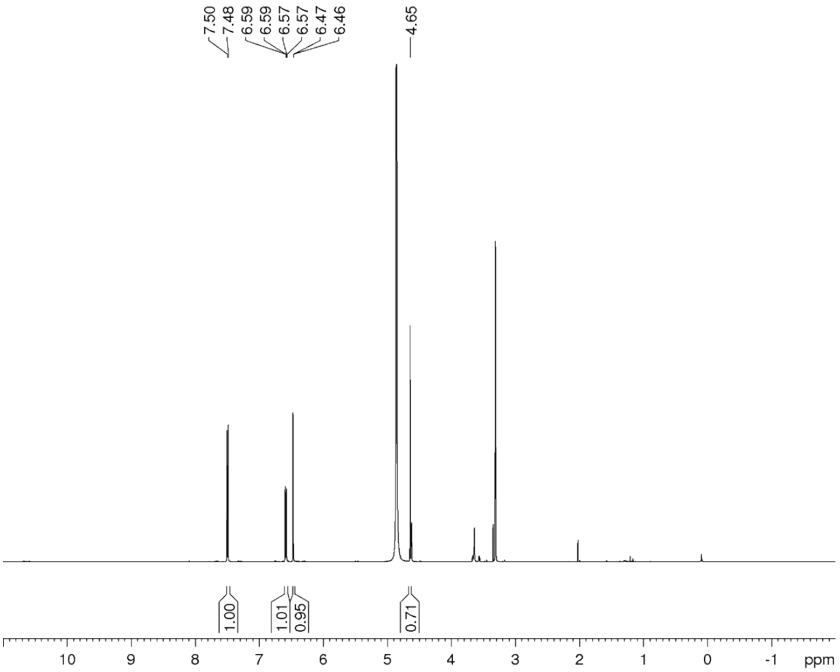


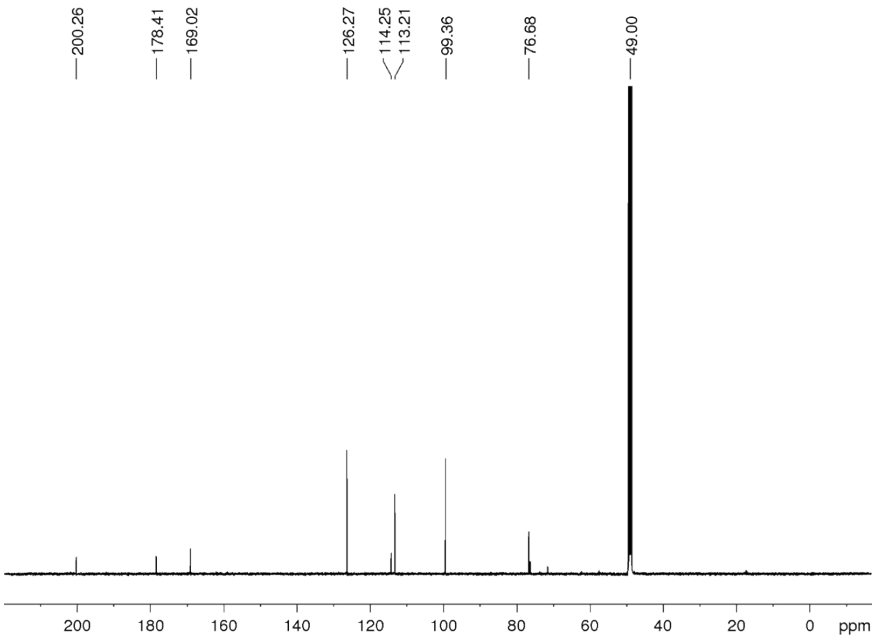

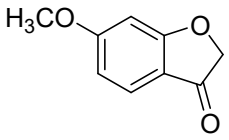


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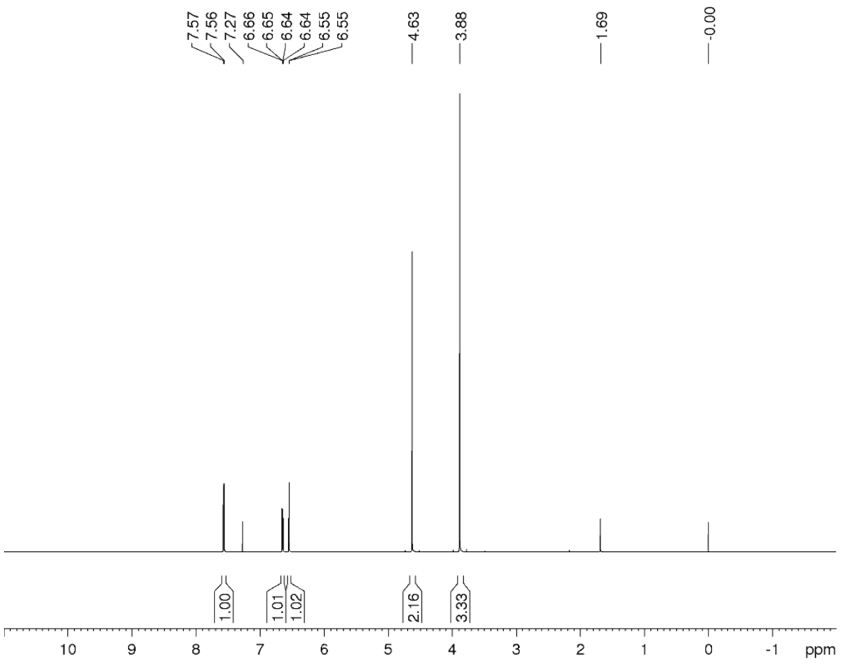


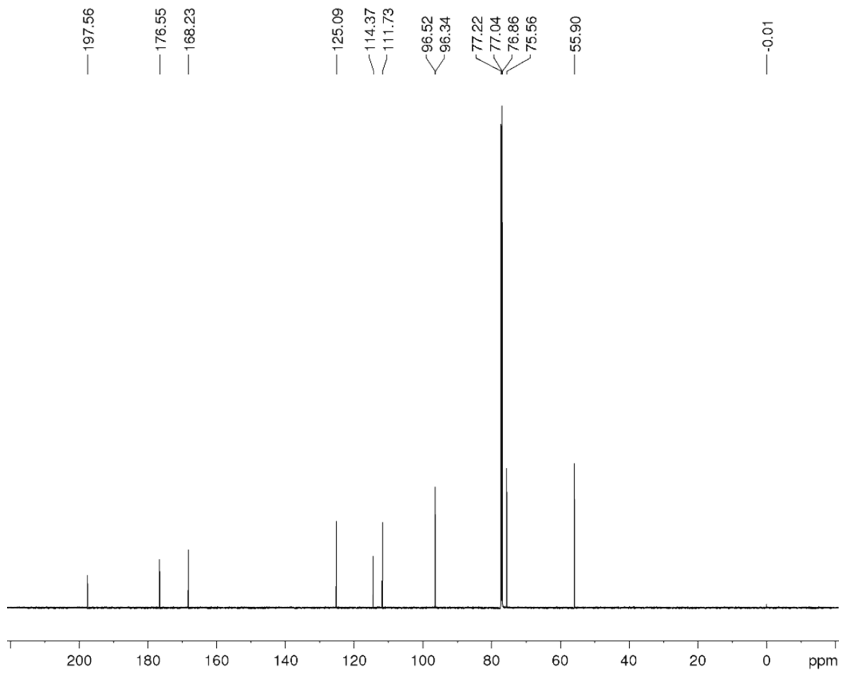

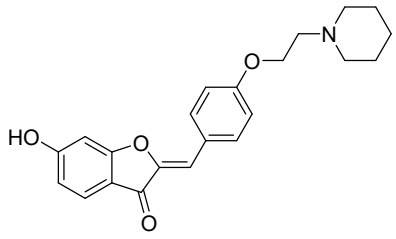
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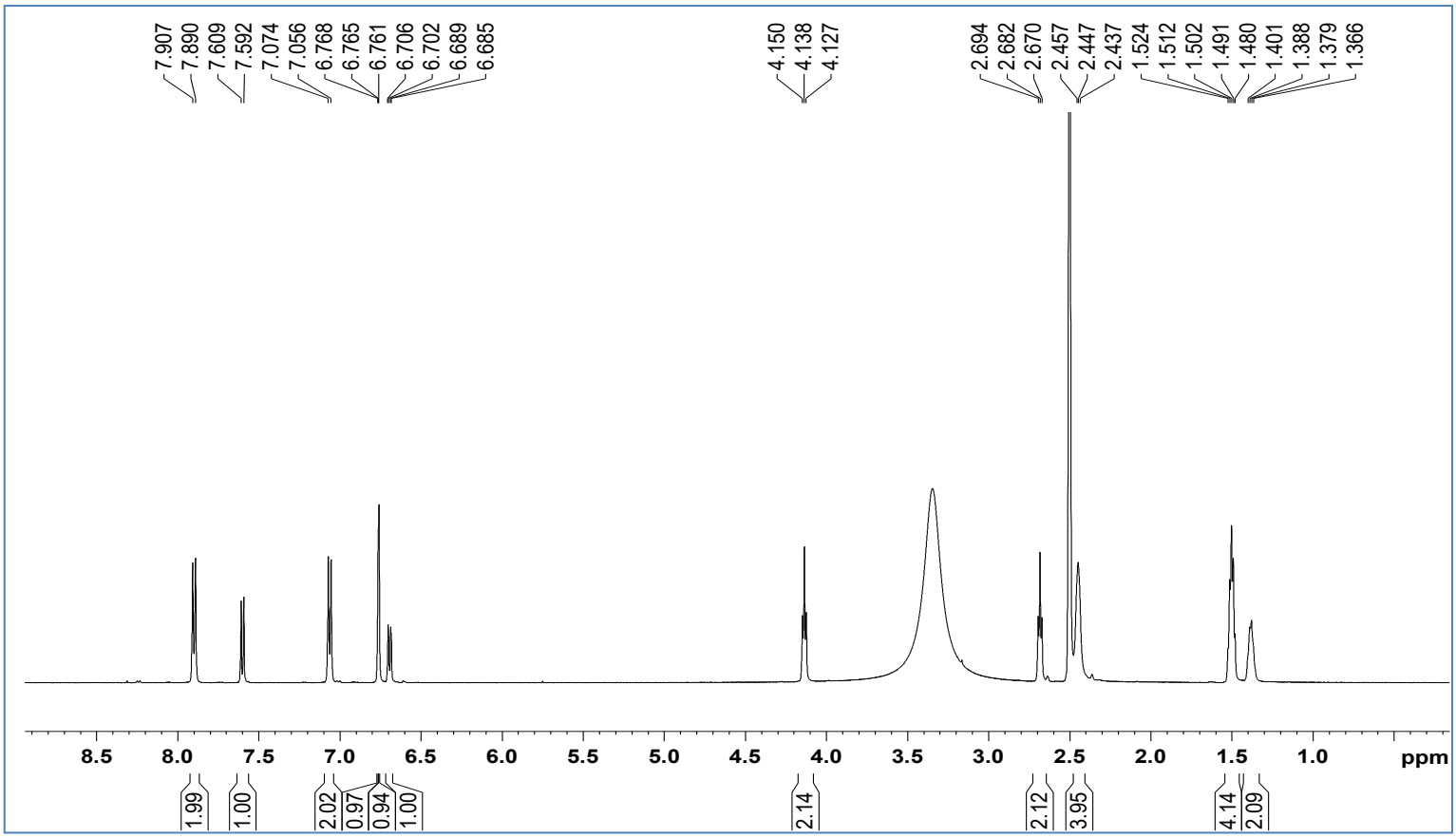
O
N

**1a**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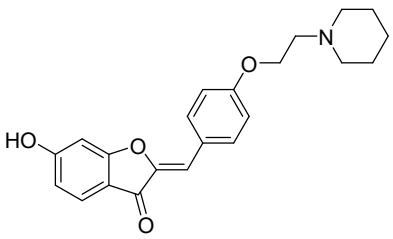
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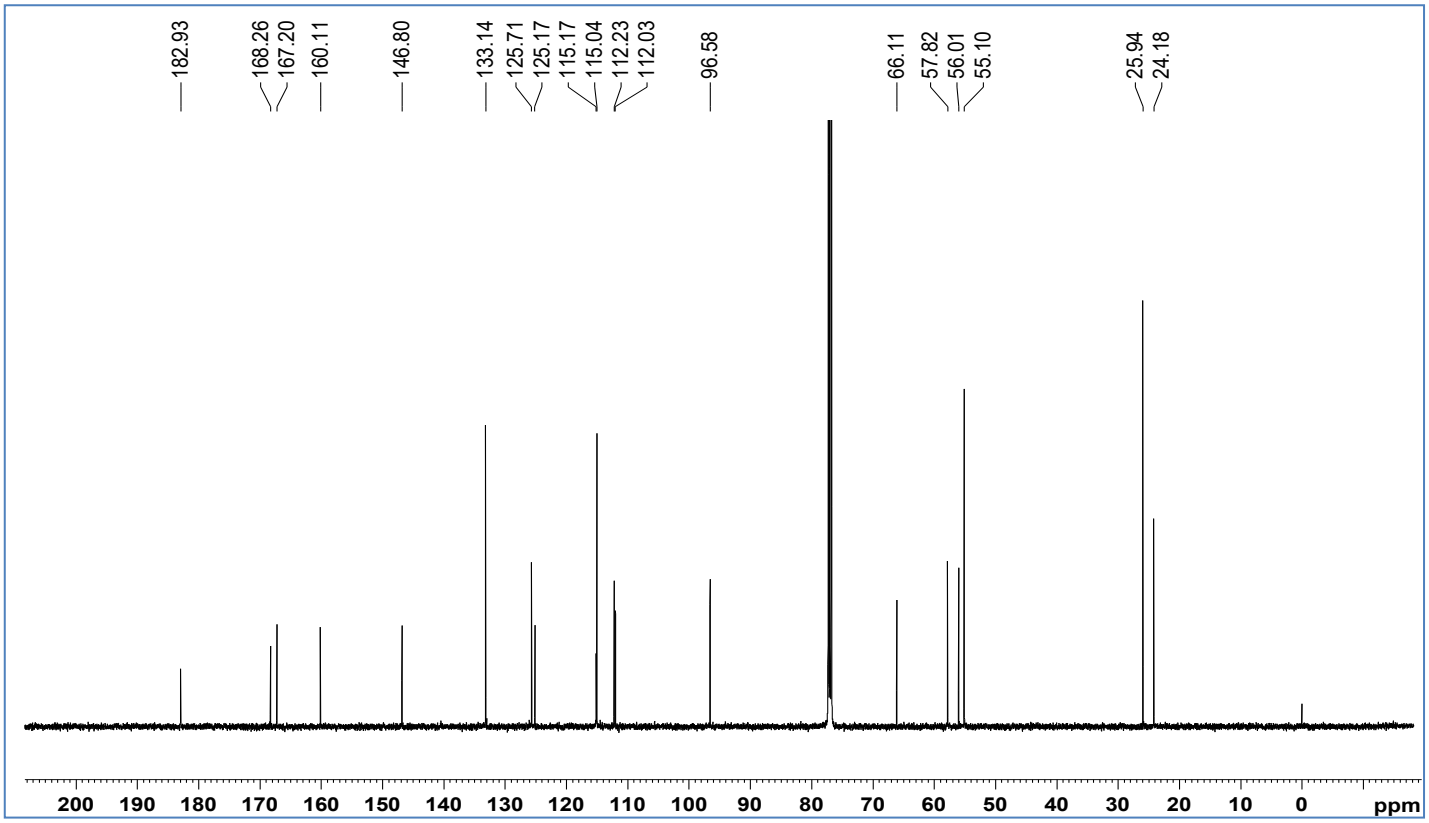
O
O
N

**1a**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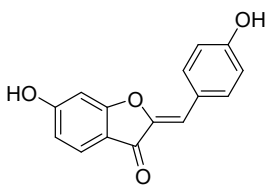
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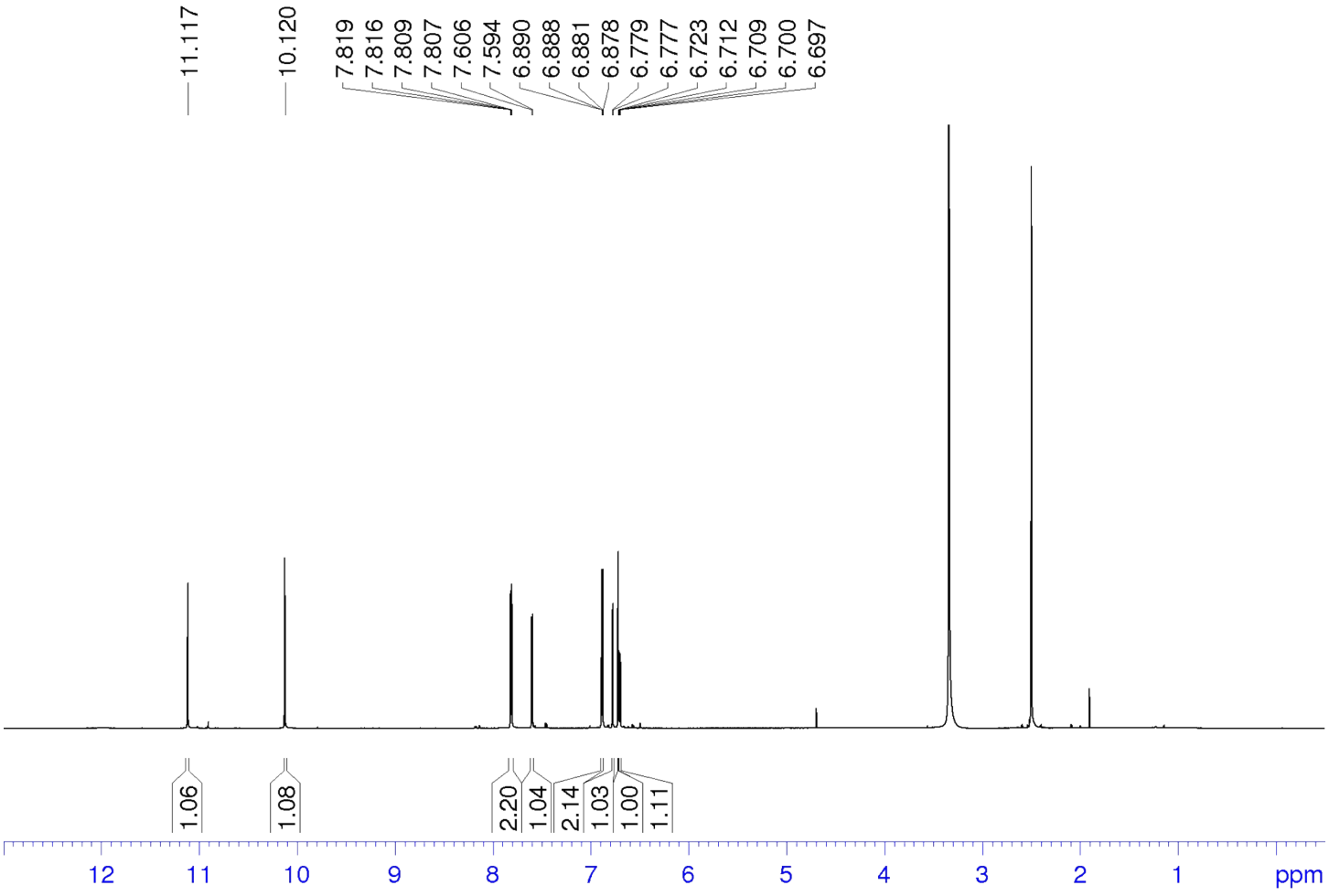
**1b**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6.700
6.697
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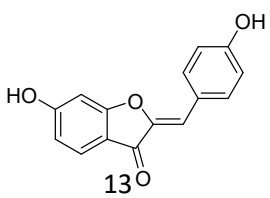
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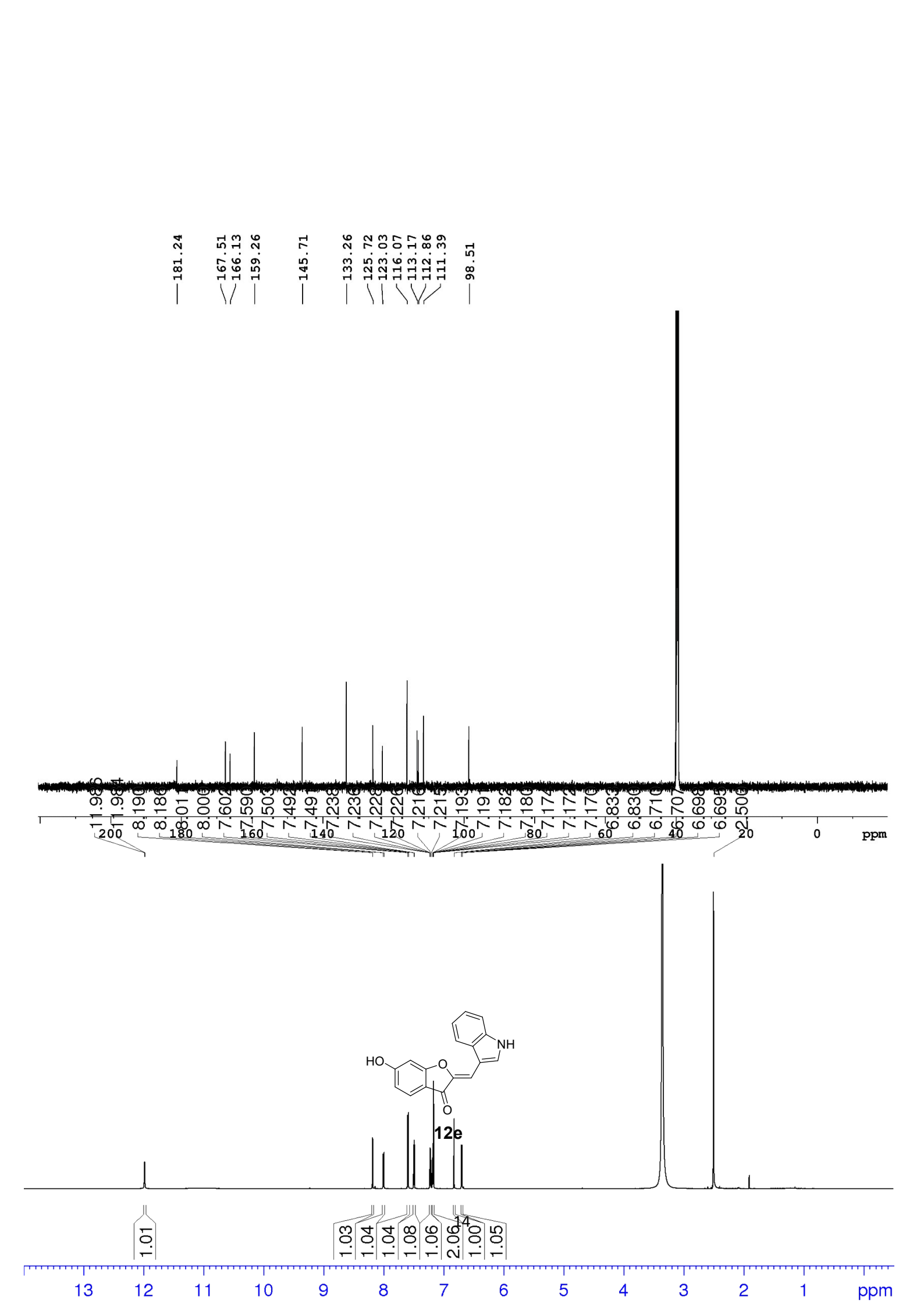
13
O

**1b**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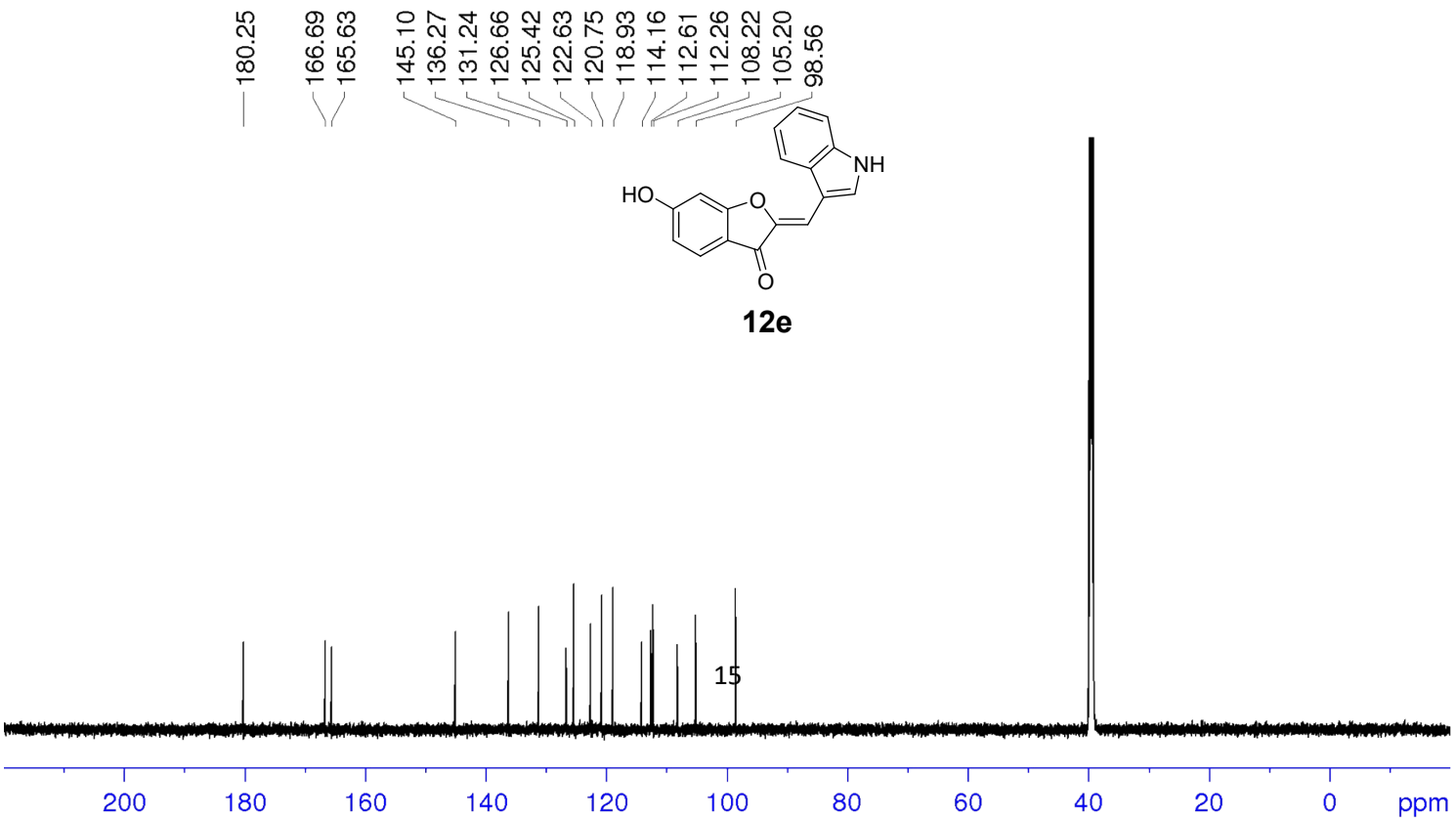
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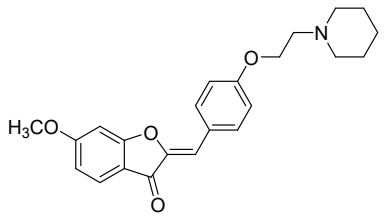


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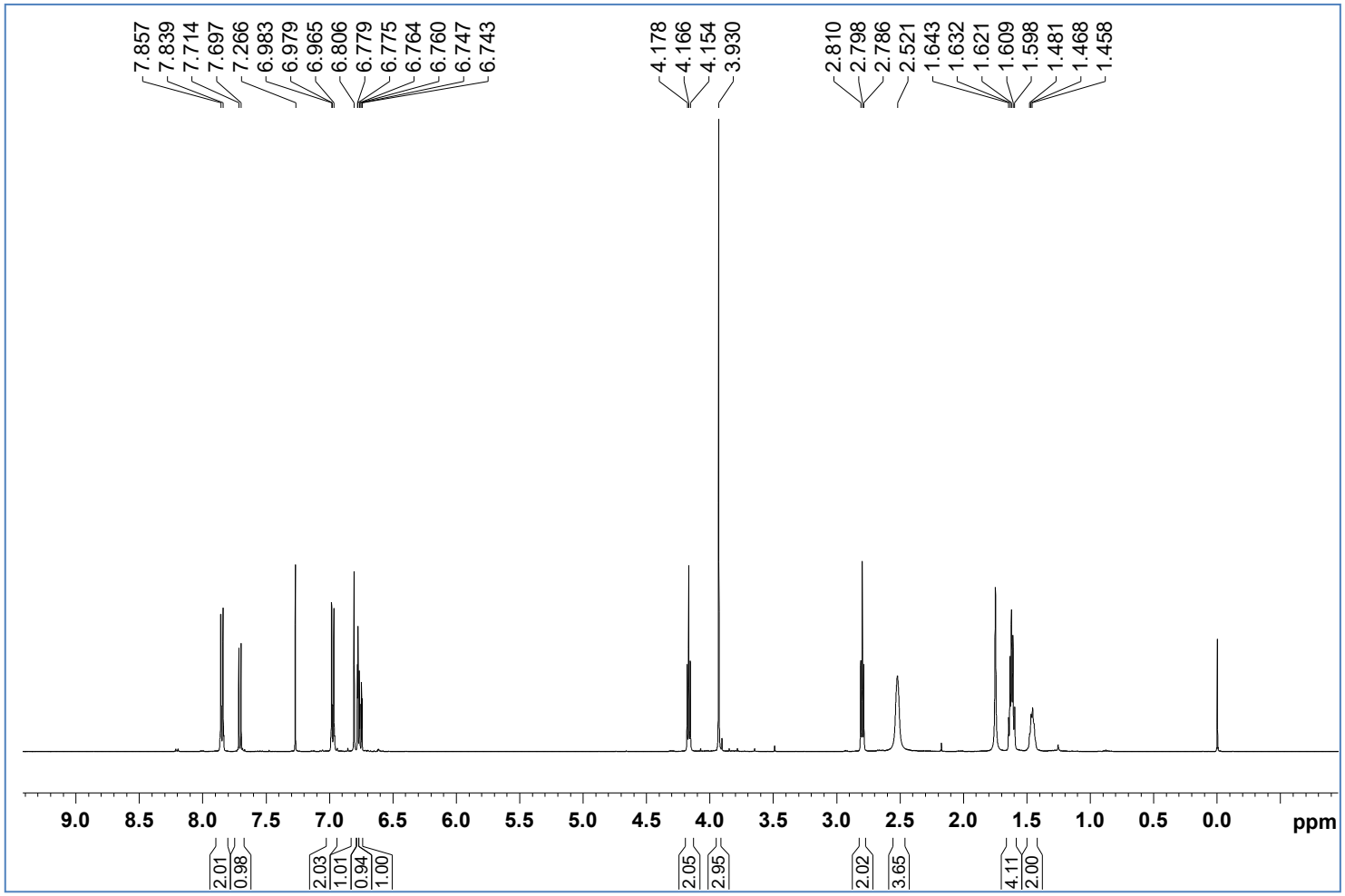
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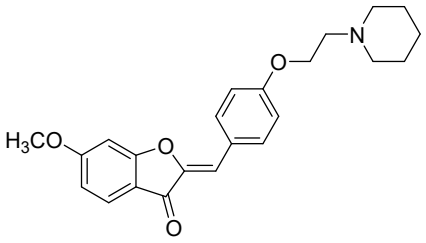
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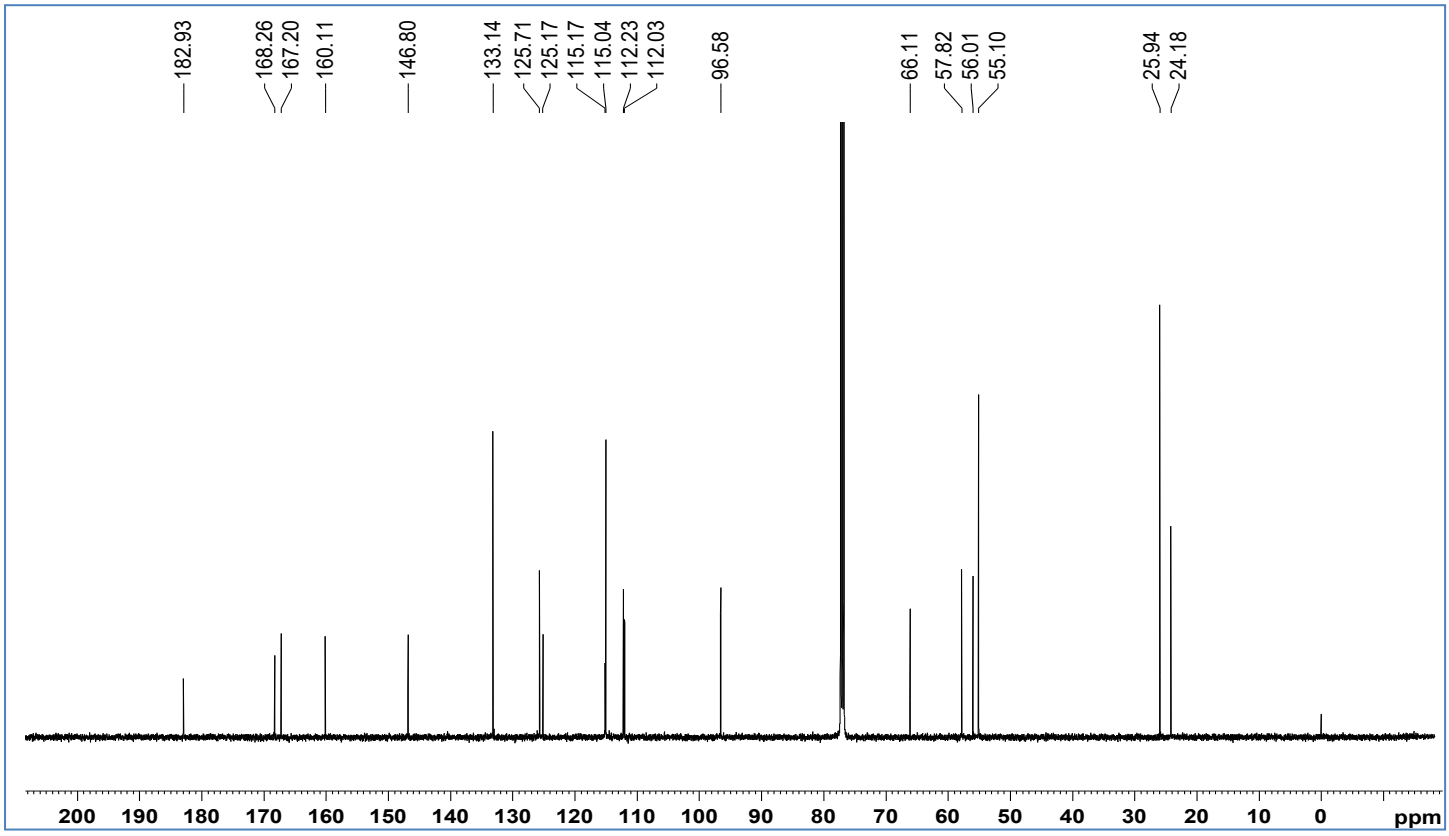
**2a**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112.23
112.03
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56.01
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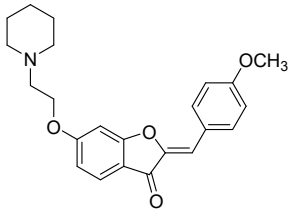
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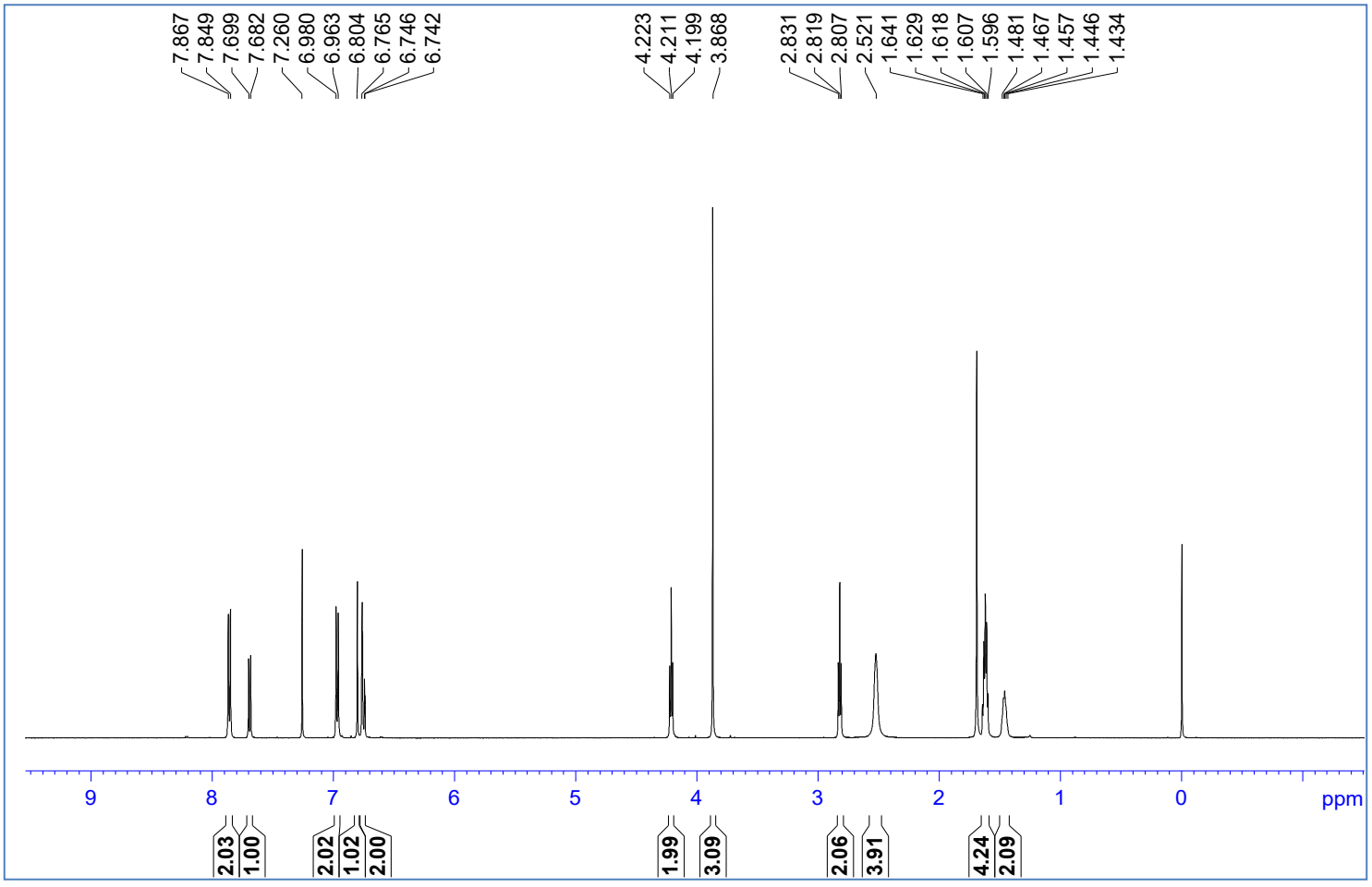
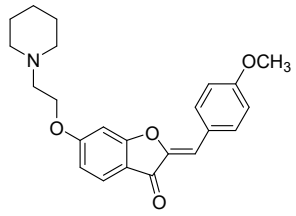
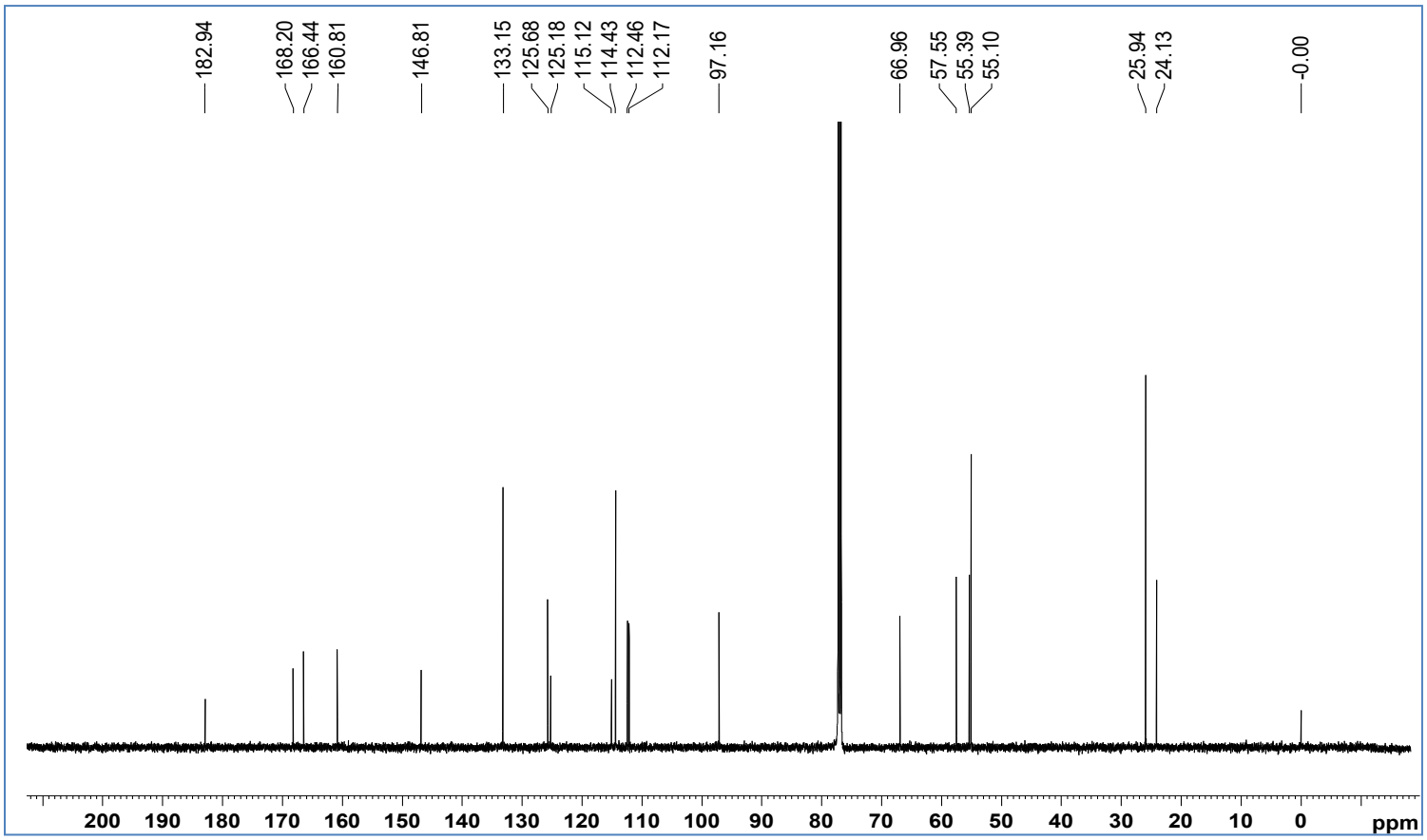
O
OCH3

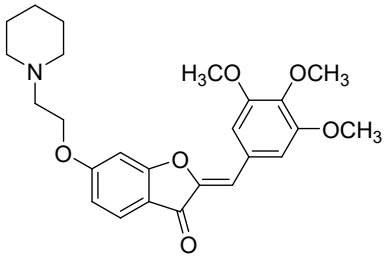
**3a**


7.867
7.849
7.699
7.682
7.260
6.980
6.963
6.804
6.765
6.746
6.742
4.223
4.211
4.199
3.868
2.831
2.819
2.807
2.521
1.641
1.629
1.618
1.607
1.596
1.481
1.467
1.457
1.446
1.434
9
8
7
6
5
4
3
2
1
0
ppm
2.03
1.00
2.02
1.02
2.00
1.99
3.09
2.06
3.91
4.24
2.09

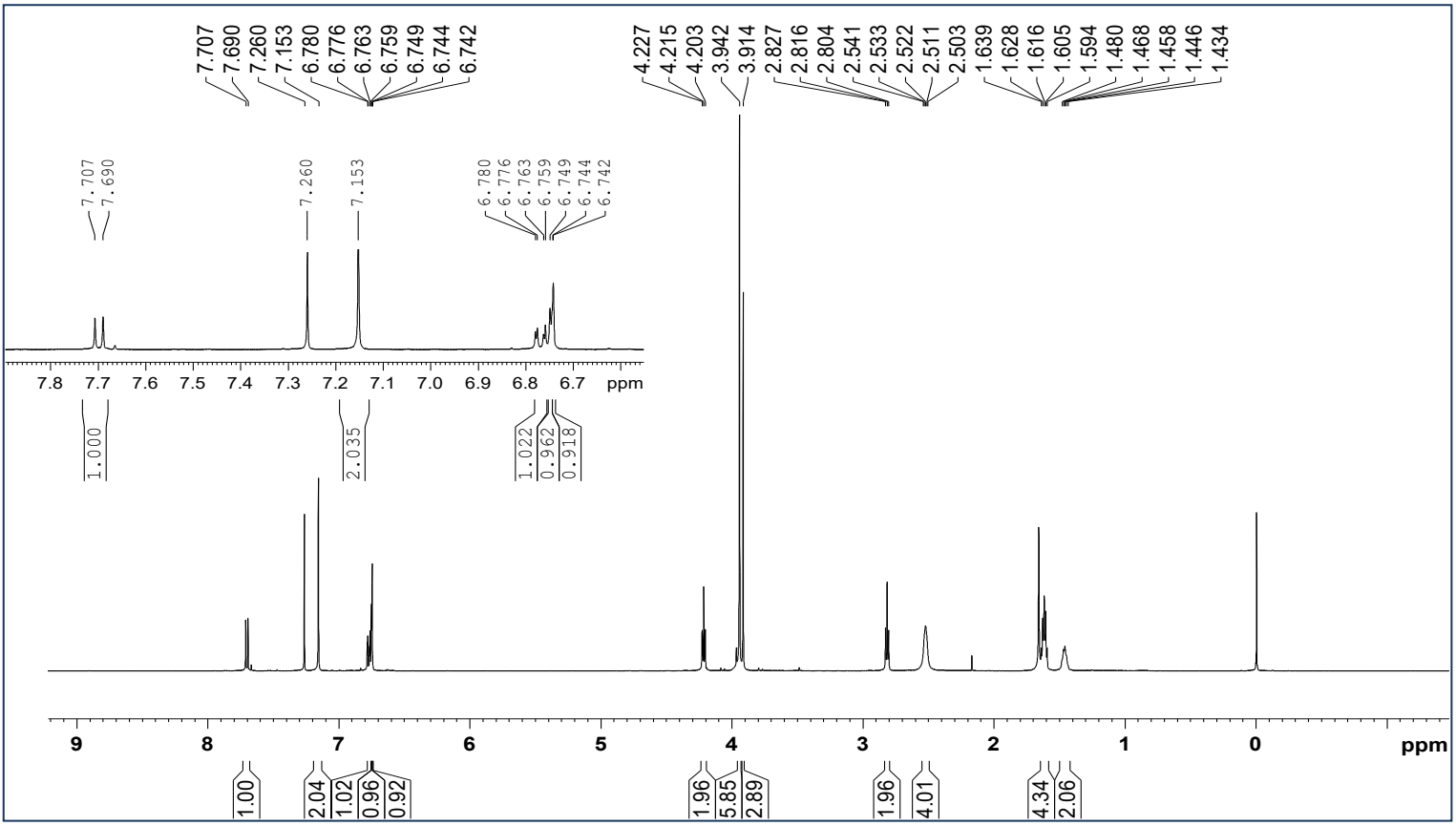

N
OCH3
O
O
O

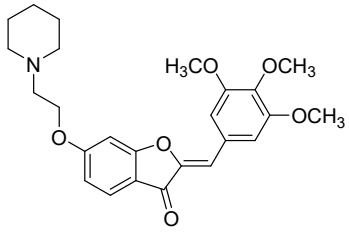
**3a**


182.94
168.20
166.44
160.81
146.81
133.15
125.68
125.18
115.12
114.43
112.46
112.17
97.16
66.96
57.55
55.39
55.10
25.94
24.13
-0.00
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

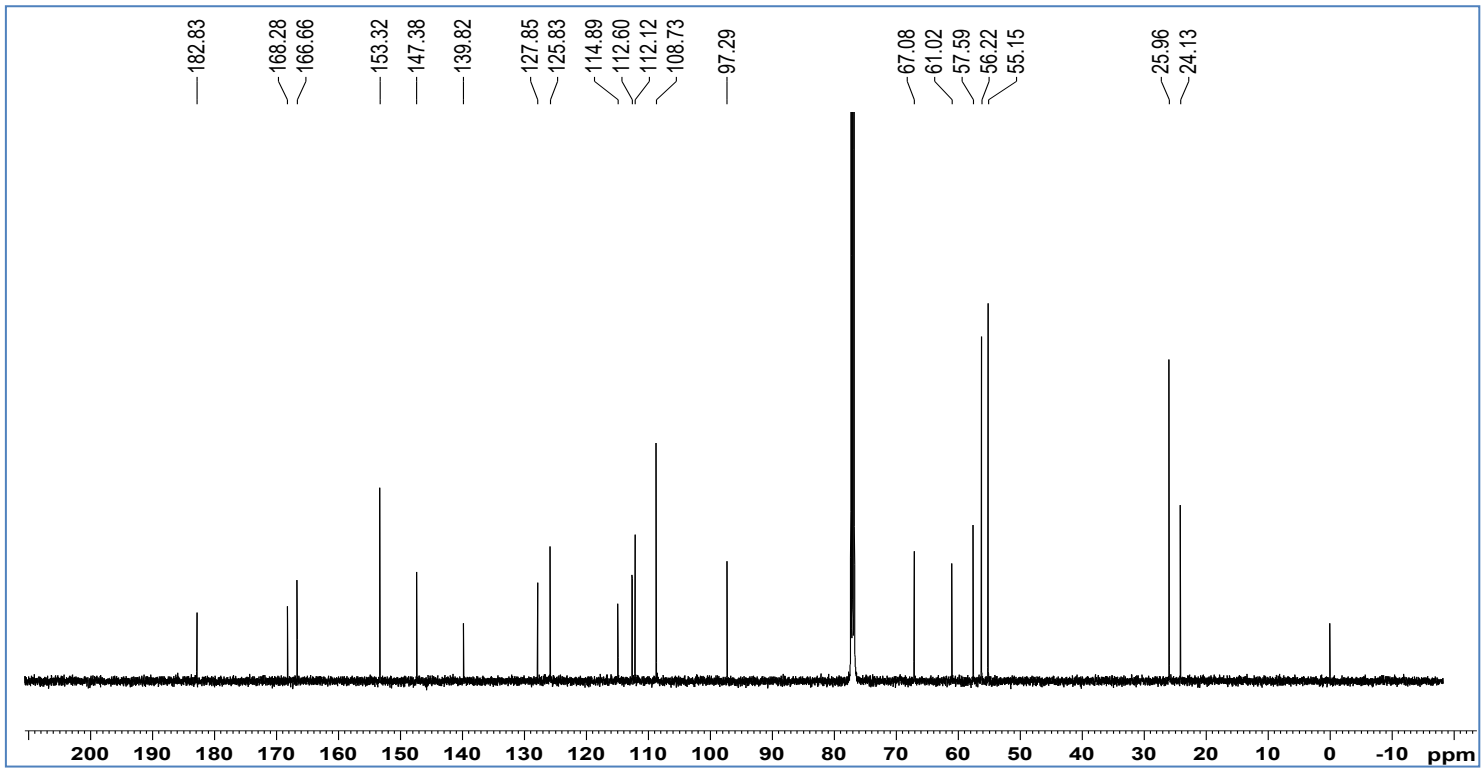

N
O
O
O
H3CO
OCH3
OCH3

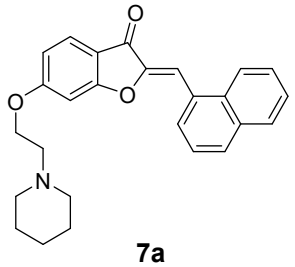
**4a**


7.707
7.690
7.260
7.153
6.780
6.776
6.763
6.759
6.749
6.744
6.742
4.227
4.215
4.203
3.942
3.914
2.827
2.816
2.804
2.541
2.533
2.522
2.511
2.503
1.639
1.628
1.616
1.605
1.594
1.480
1.468
1.458
1.446
1.434
ppm
1.000
2.035
1.022
0.962
0.918
1.00
2.04
1.02
0.96
0.92
1.96
5.85
2.89
1.96
4.01
4.34
2.06

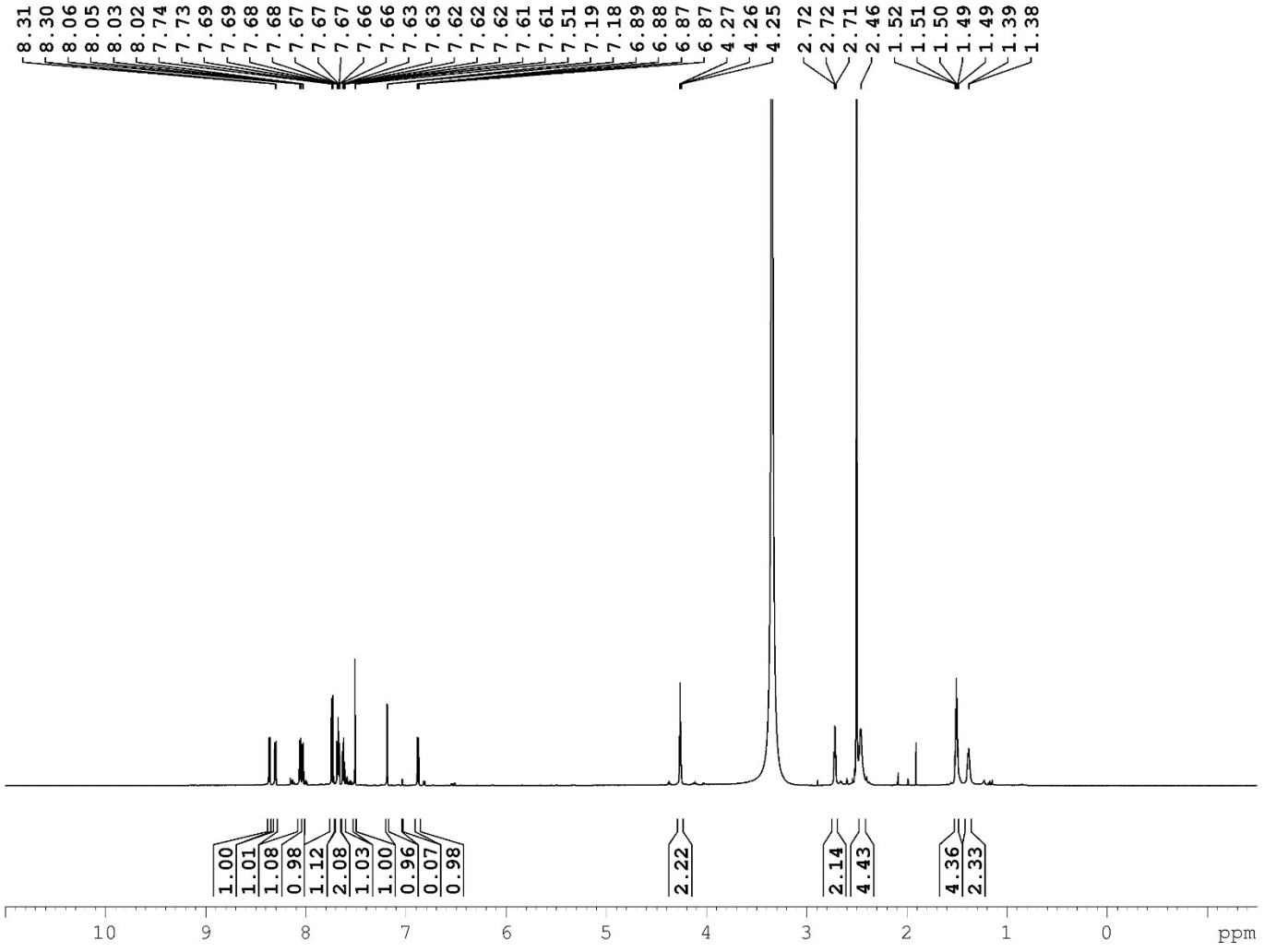

N
O
O
O
H3CO
OCH3
OCH3

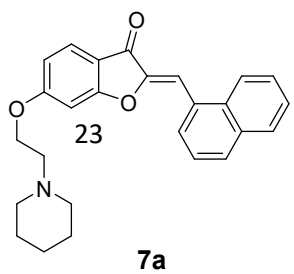
**4a**


182.83
168.28
166.66
153.32
147.38
139.82
127.85
125.83
114.89
112.60
112.12
108.73
97.29
67.08
61.02
57.59
56.22
55.15
25.96
24.13
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 ppm

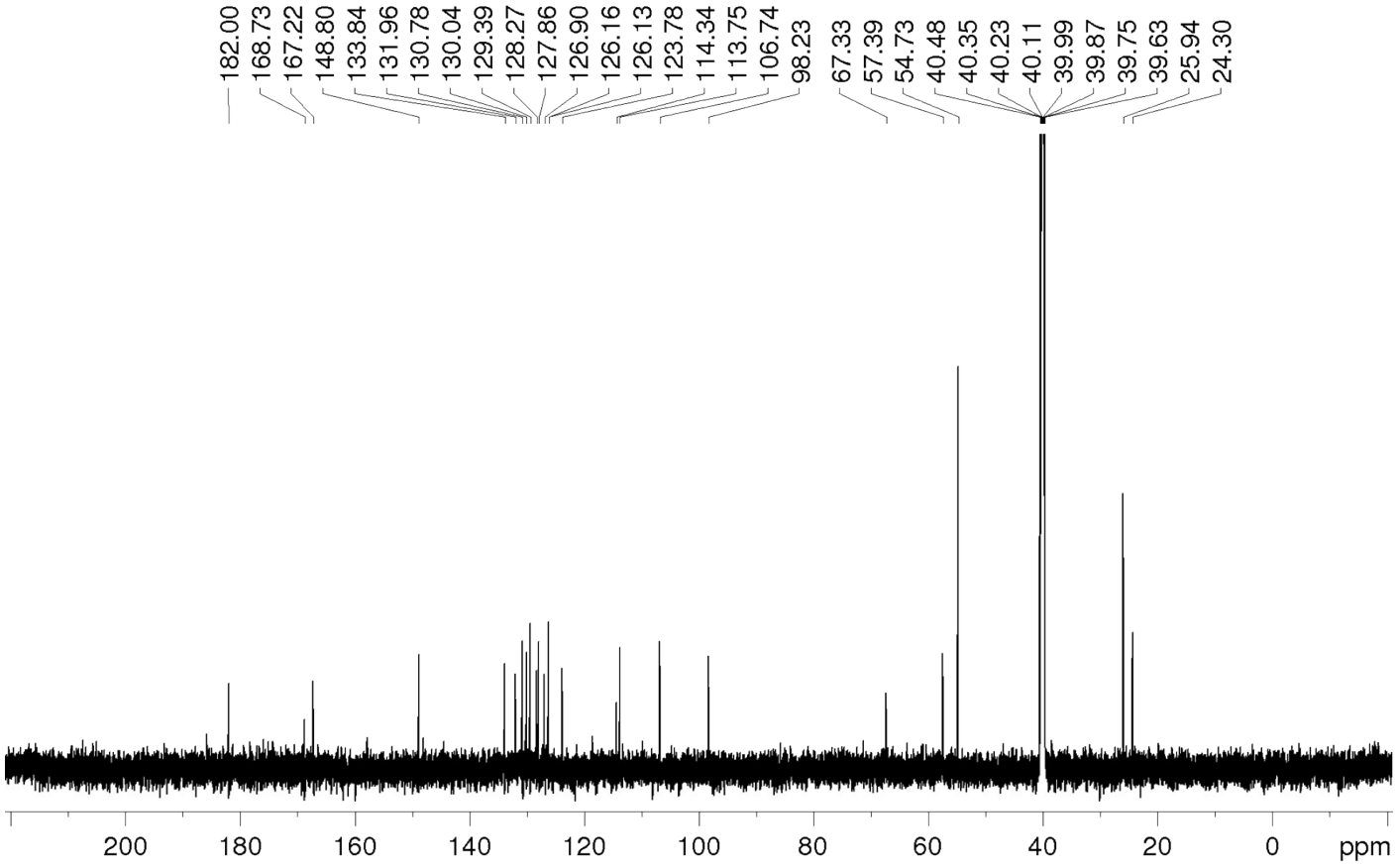


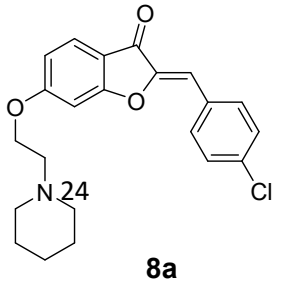
**7a**


8.31
8.30
8.06
8.05
8.03
8.02
7.74
7.73
7.69
7.69
7.68
7.68
7.67
7.67
7.67
7.66
7.66
7.63
7.63
7.62
7.62
7.62
7.61
7.61
7.51
7.19
7.18
6.89
6.88
6.87
6.87
4.27
4.26
4.25
2.72
2.72
2.71
2.46
1.52
1.51
1.50
1.49
1.49
1.39
1.38
1.00
1.01
1.08
0.98
1.12
2.08
1.03
1.00
0.96
0.07
0.98
2.22
2.14
4.43
4.36
2.33
10
9
8
7
6
5
4
3
2
1
0
ppm

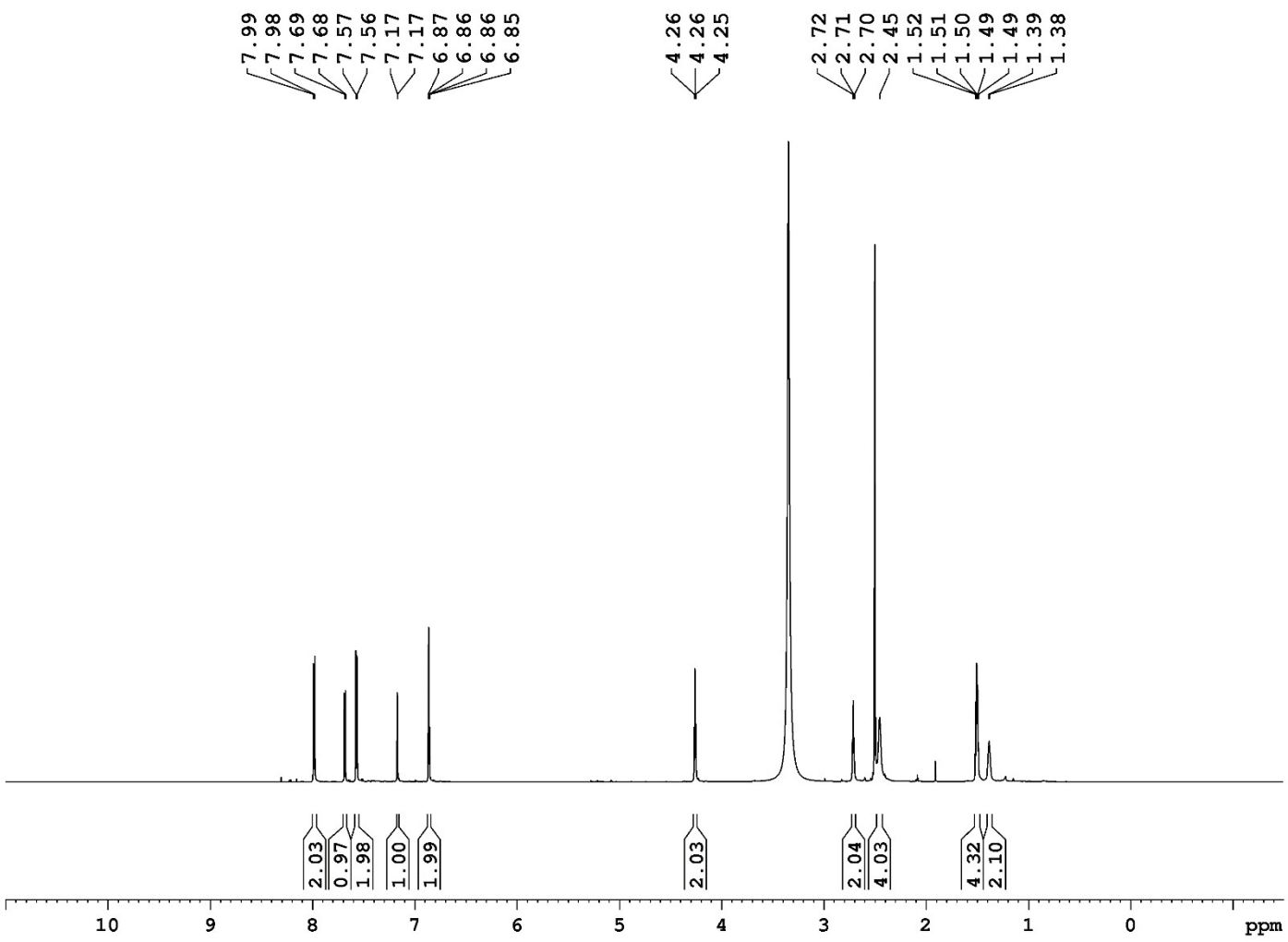

23

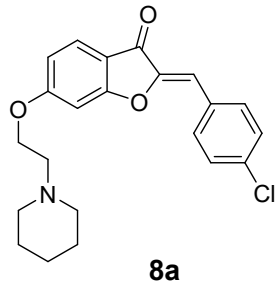
**7a**


182.00
168.73
167.22
148.80
133.84
131.96
130.78
130.04
129.39
128.27
127.86
126.90
126.16
126.13
123.78
114.34
113.75
106.74
98.23
67.33
57.39
54.73
40.48
40.35
40.23
40.11
39.99
39.87
39.75
39.63
25.94
24.30
200
180
160
140
120
100
80
60
40
20
0
ppm

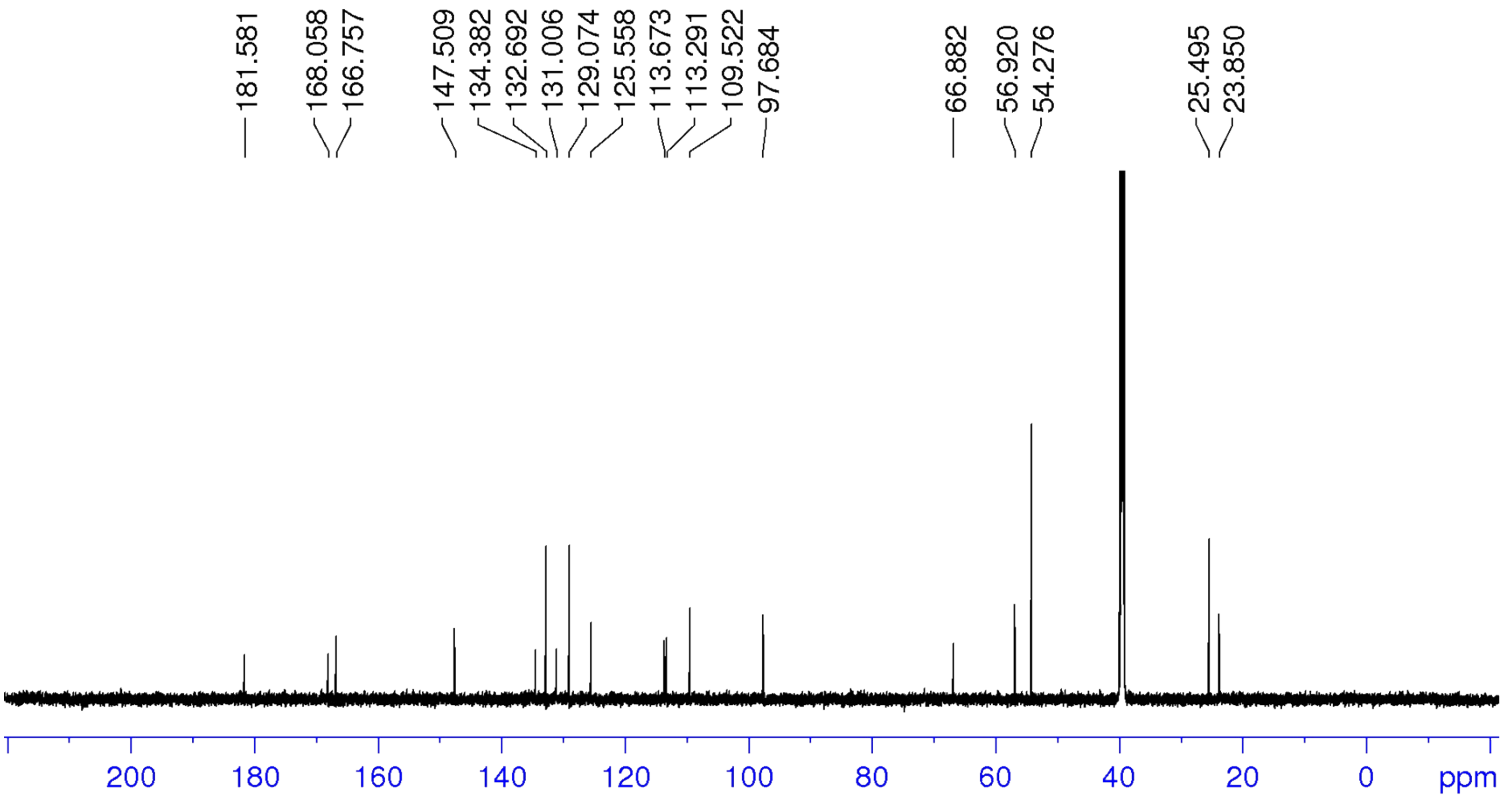

O
O
O
N
24
Cl

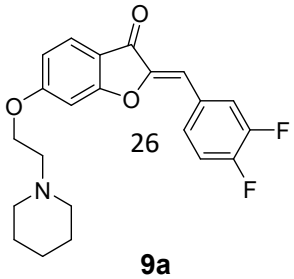
**8a**


7.99
7.98
7.69
7.68
7.57
7.56
7.17
7.17
6.87
6.86
6.86
6.85
4.26
4.26
4.25
2.72
2.71
2.70
2.45
1.52
1.51
1.50
1.49
1.49
1.39
1.38
2.03
0.97
1.98
1.00
1.99
2.03
2.04
4.03
4.32
2.10
10
9
8
7
6
5
4
3
2
1
0
ppm


O
O
O
N
Cl

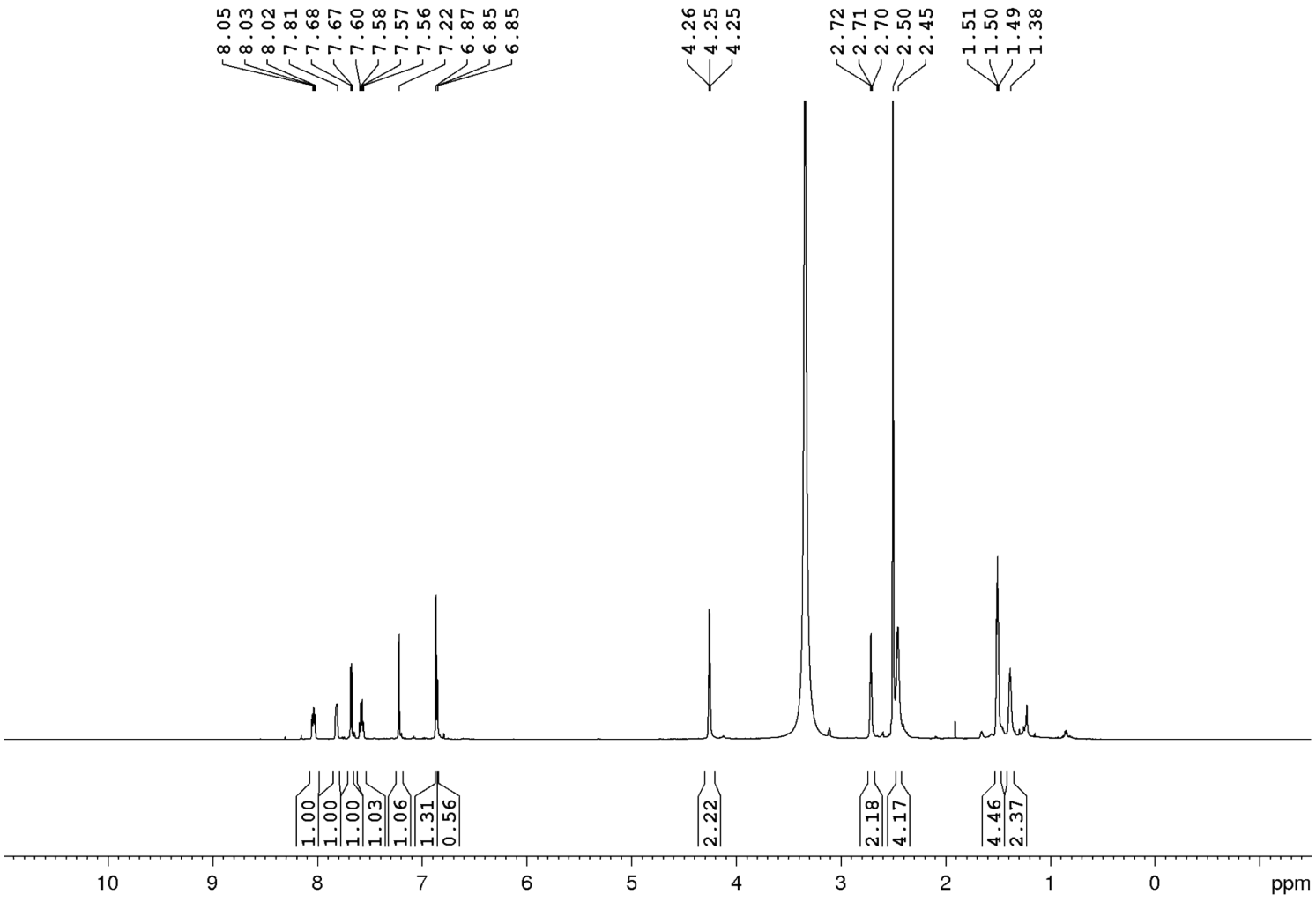
**8a**

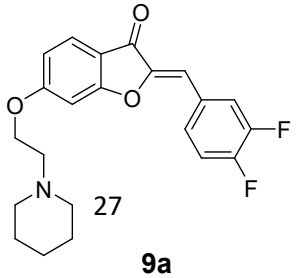

181.581
168.058
166.757
147.509
134.382
132.692
131.006
129.074
125.558
113.673
113.291
109.522
97.684
66.882
56.920
54.276
25.495
23.850
200
180
160
140
120
100
80
60
40
20
0
ppm


O
O
O
N
F
F

26

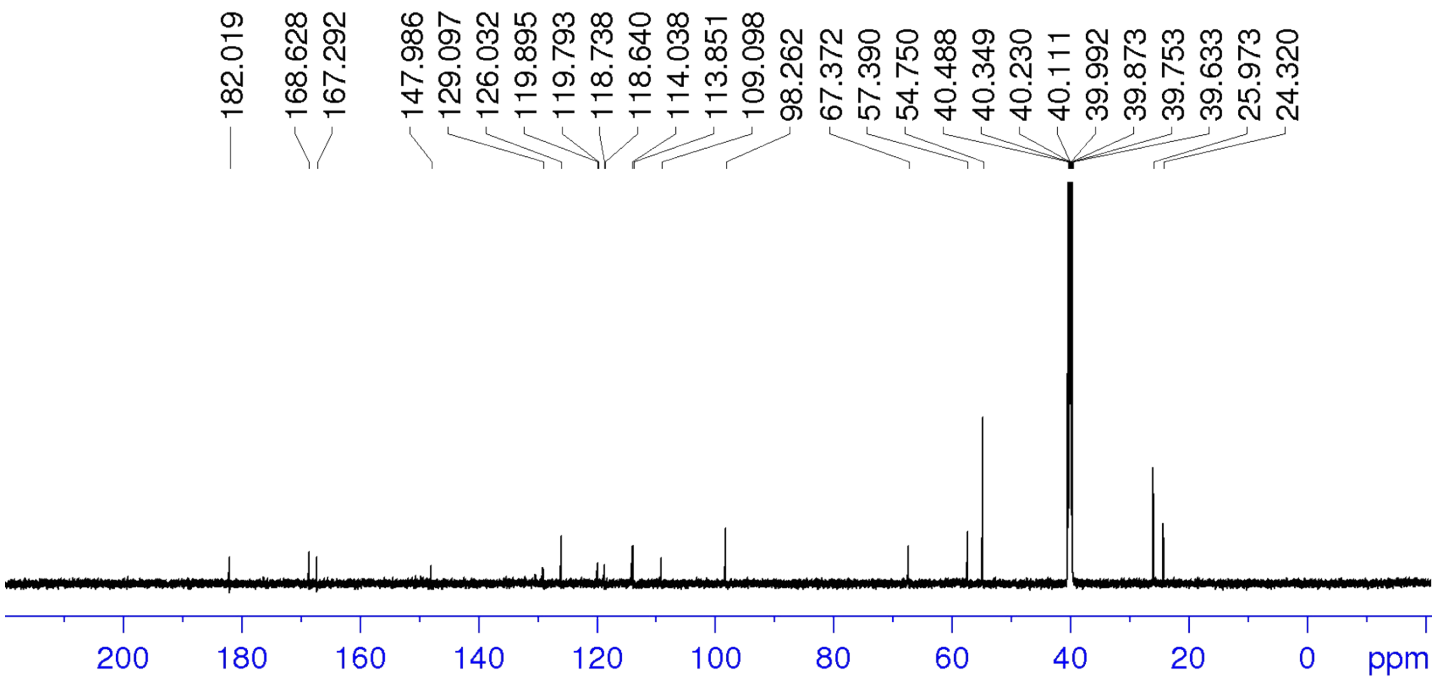
**9a**

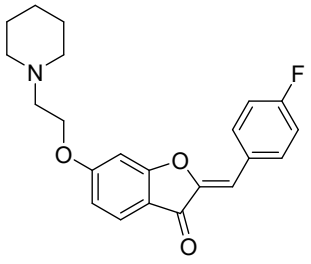

8.05
8.03
8.02
7.81
7.68
7.67
7.60
7.58
7.57
7.56
7.22
6.87
6.85
6.85
4.26
4.25
4.25
2.72
2.71
2.70
2.50
2.45
1.51
1.50
1.49
1.38
1.00
1.00
1.00
1.03
1.06
1.31
0.56
2.22
2.18
4.17
4.46
2.37
10
9
8
7
6
5
4
3
2
1
0
ppm


O
O
O
F
F
N

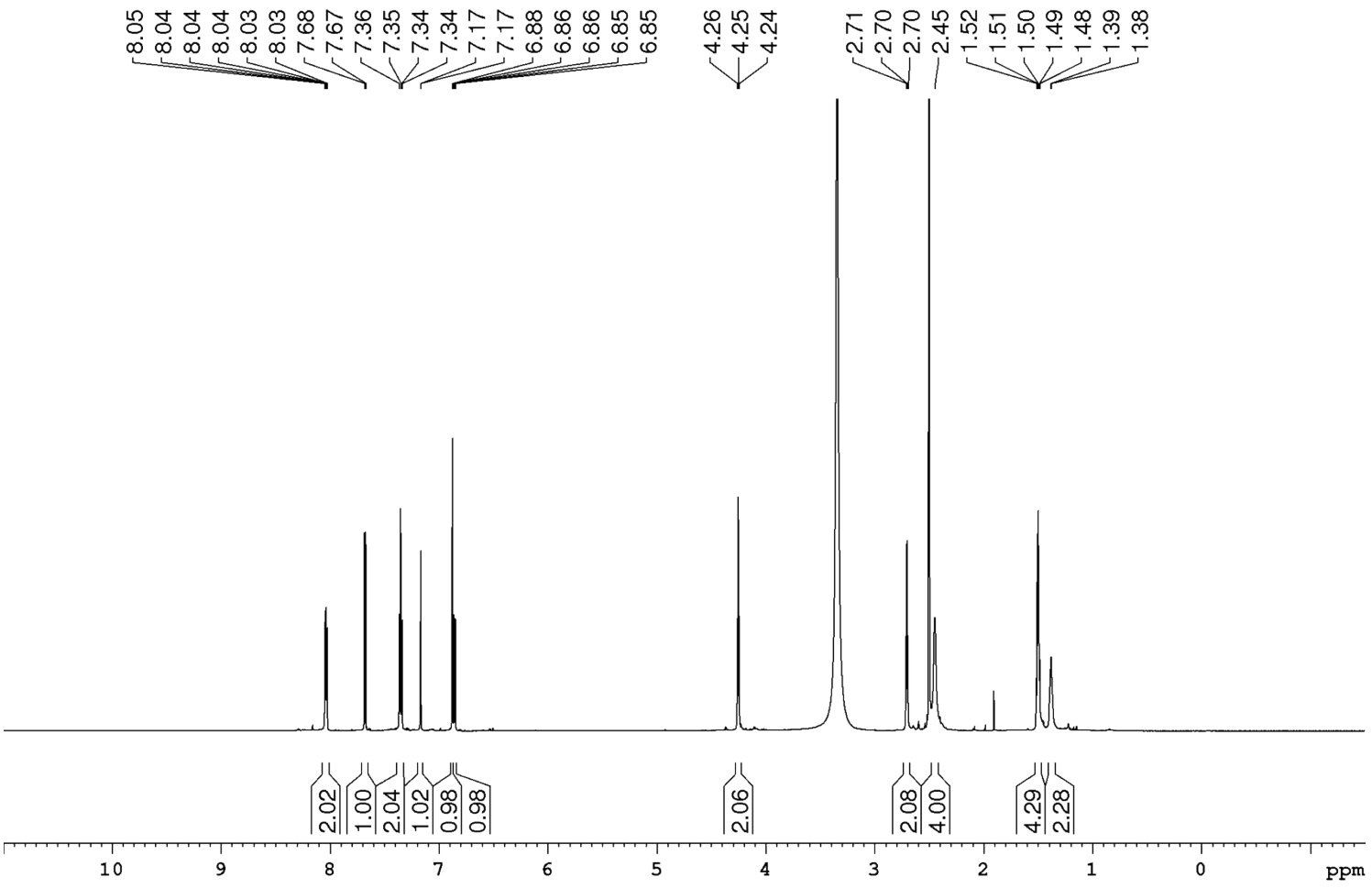
27

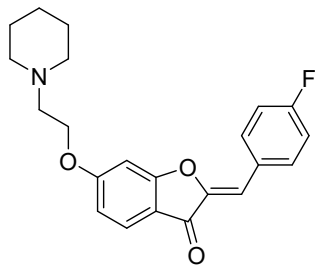
**9a**


182.019
168.628
167.292
147.986
129.097
126.032
119.895
119.793
118.738
118.640
114.038
113.851
109.098
98.262
67.372
57.390
54.750
40.488
40.349
40.230
40.111
39.992
39.873
39.753
39.633
25.973
24.320
200
180
160
140
120
100
80
60
40
20
0
ppm

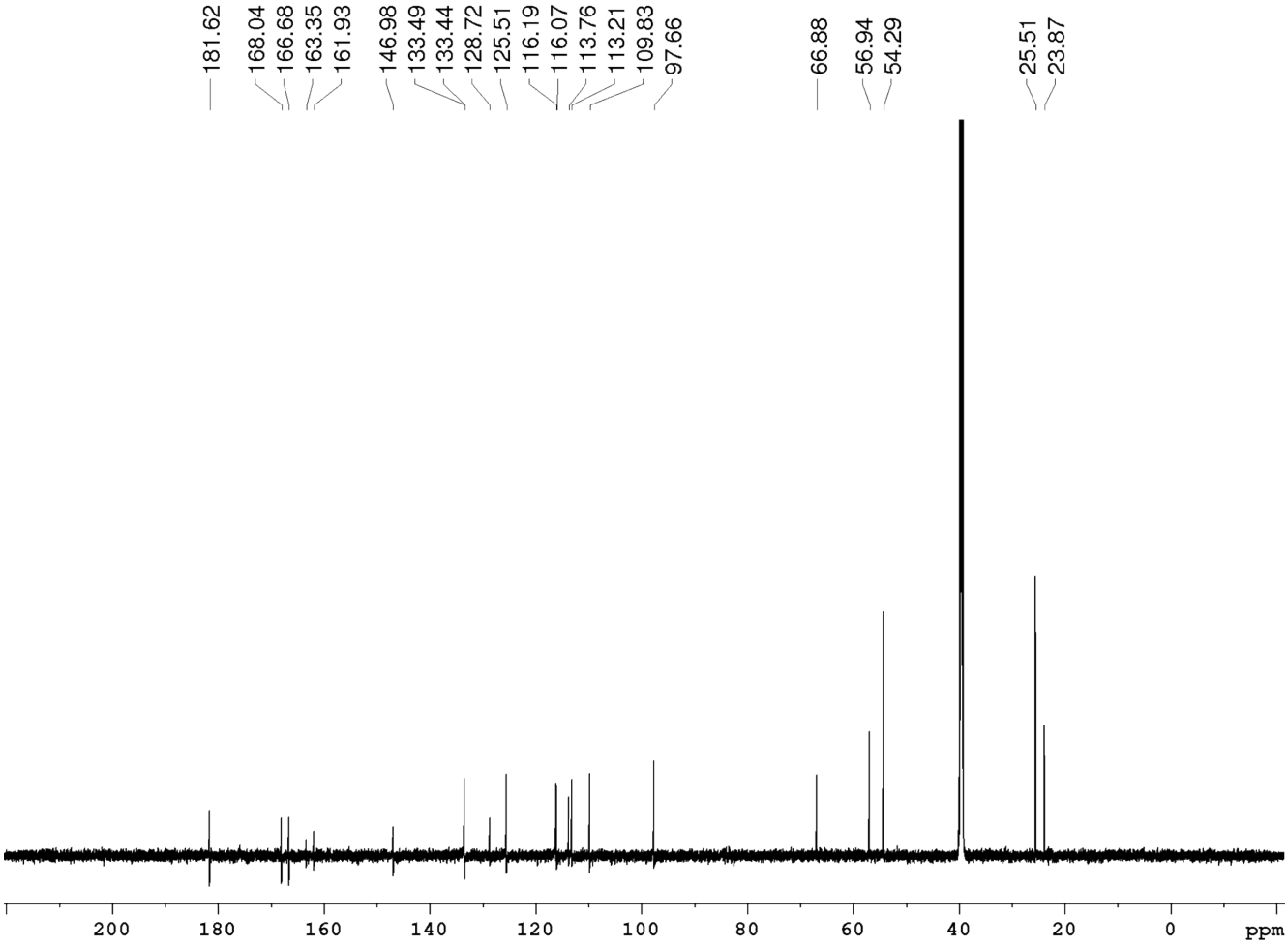

N
O
O
O
F

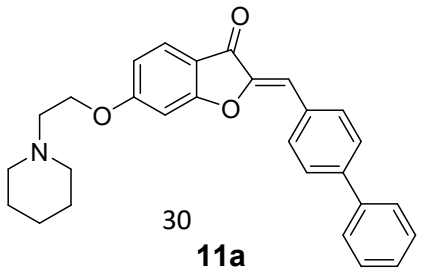
**10a**


8.05
8.04
8.04
8.04
8.03
8.03
7.68
7.67
7.36
7.35
7.34
7.34
7.17
7.17
6.88
6.86
6.86
6.85
6.85
4.26
4.25
4.24
2.71
2.70
2.70
2.45
1.52
1.51
1.50
1.49
1.48
1.39
1.38
2.02
1.00
2.04
1.02
0.98
0.98
2.06
2.08
4.00
4.29
2.28
10
9
8
7
6
5
4
3
2
1
0
ppm


N
F
O
O
O

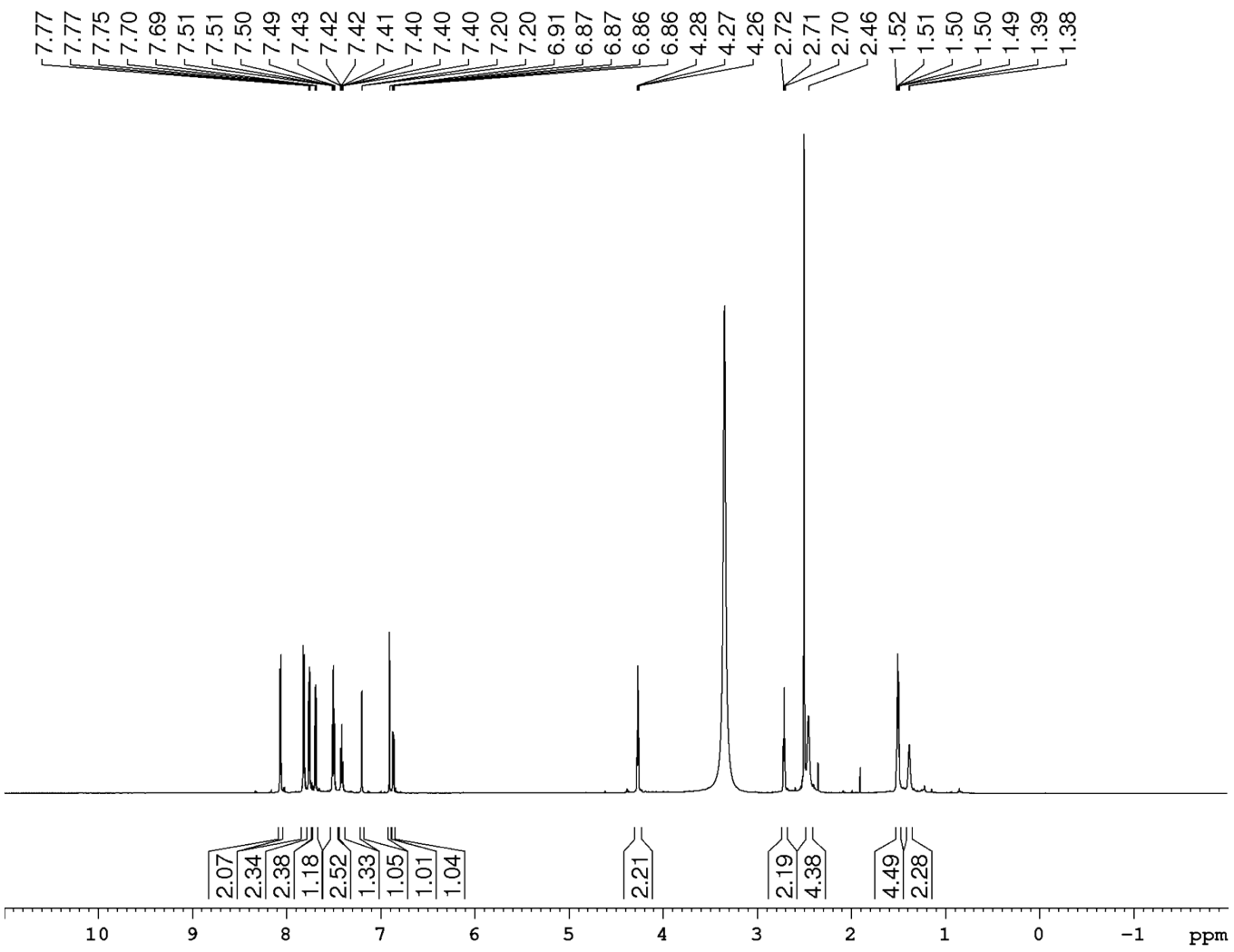
**10a**

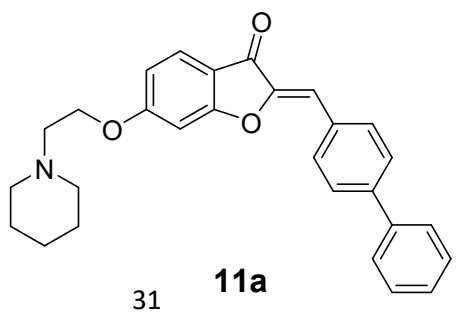

181.62
168.04
166.68
163.35
161.93
146.98
133.49
133.44
128.72
125.51
116.19
116.07
113.76
113.21
109.83
97.66
66.88
56.94
54.29
25.51
23.87
200
180
160
140
120
100
80
60
40
20
0
ppm


O
O
O
N

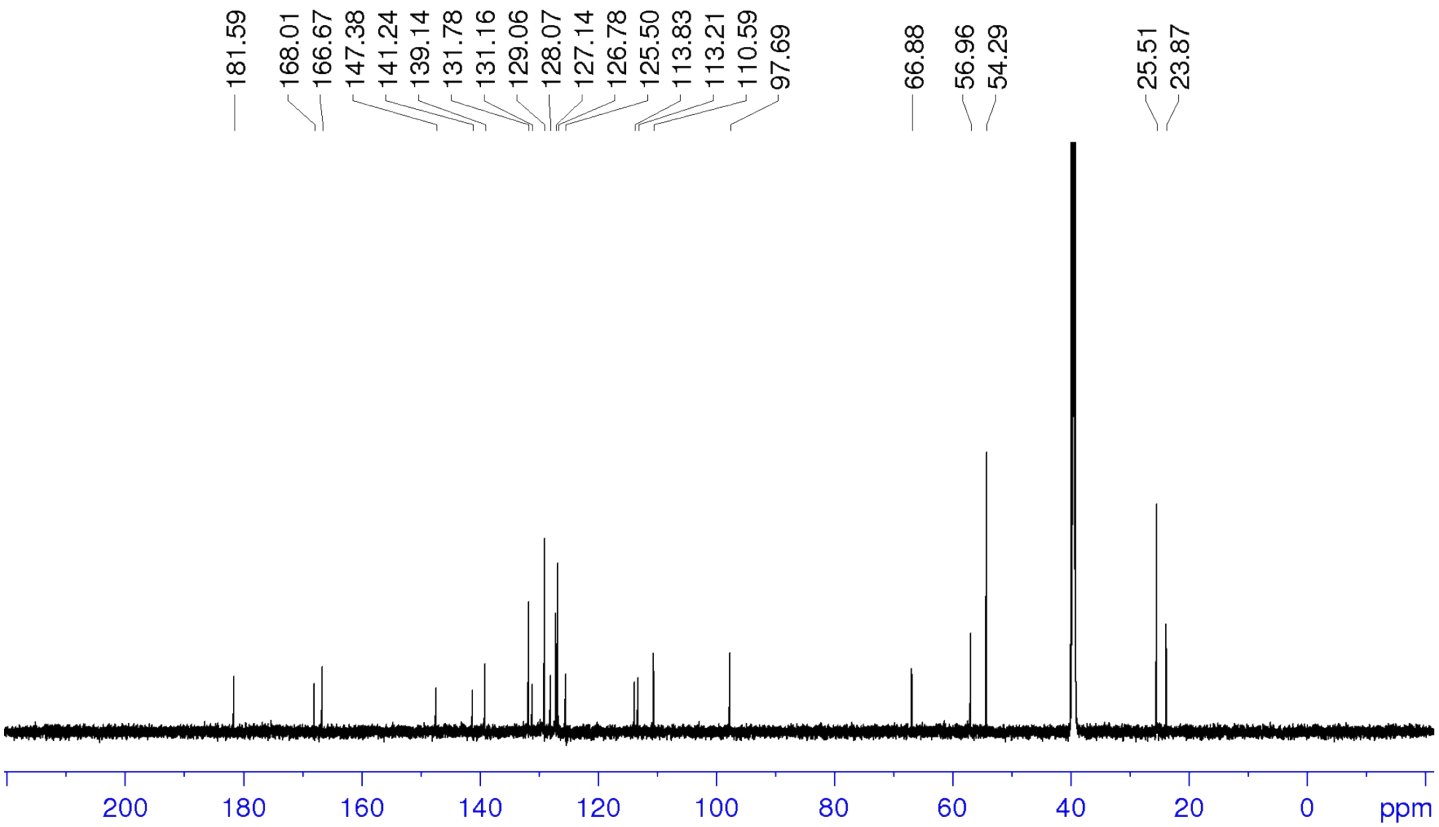


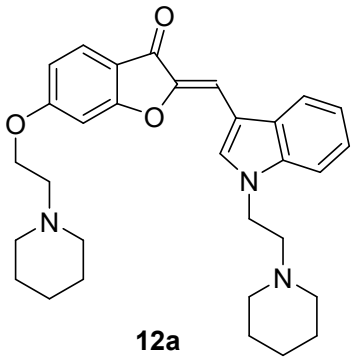
**11a**


7.77
7.77
7.75
7.70
7.69
7.51
7.51
7.50
7.49
7.43
7.42
7.42
7.41
7.40
7.40
7.40
7.20
7.20
6.91
6.87
6.87
6.86
6.86
4.28
4.27
4.26
2.72
2.71
2.70
2.46
1.52
1.51
1.50
1.50
1.49
1.39
1.38
2.07
2.34
2.38
1.18
2.52
1.33
1.05
1.01
1.04
2.21
2.19
4.38
4.49
2.28
10
9
8
7
6
5
4
3
2
1
0
−1
ppm

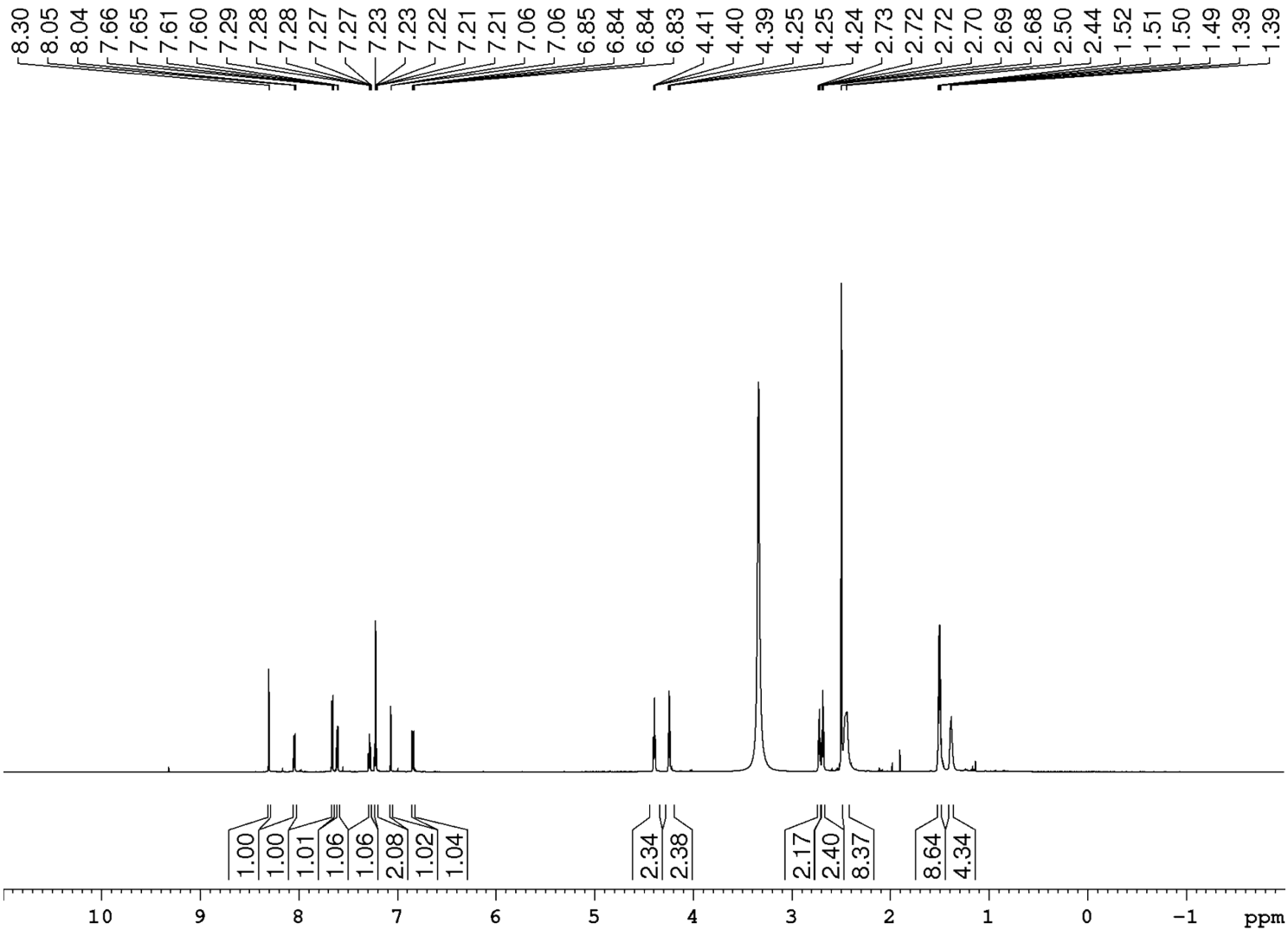

O
O
O
N

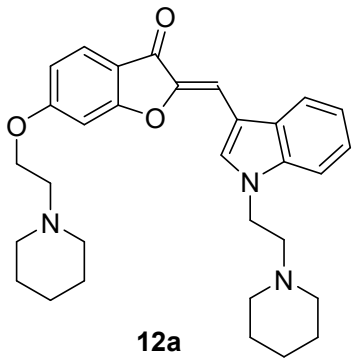
**11a**


181.59
168.01
166.67
147.38
141.24
139.14
131.78
131.16
129.06
128.07
127.14
126.78
125.50
113.83
113.21
110.59
97.69
66.88
56.96
54.29
25.51
23.87
200
180
160
140
120
100
80
60
40
20
0
ppm

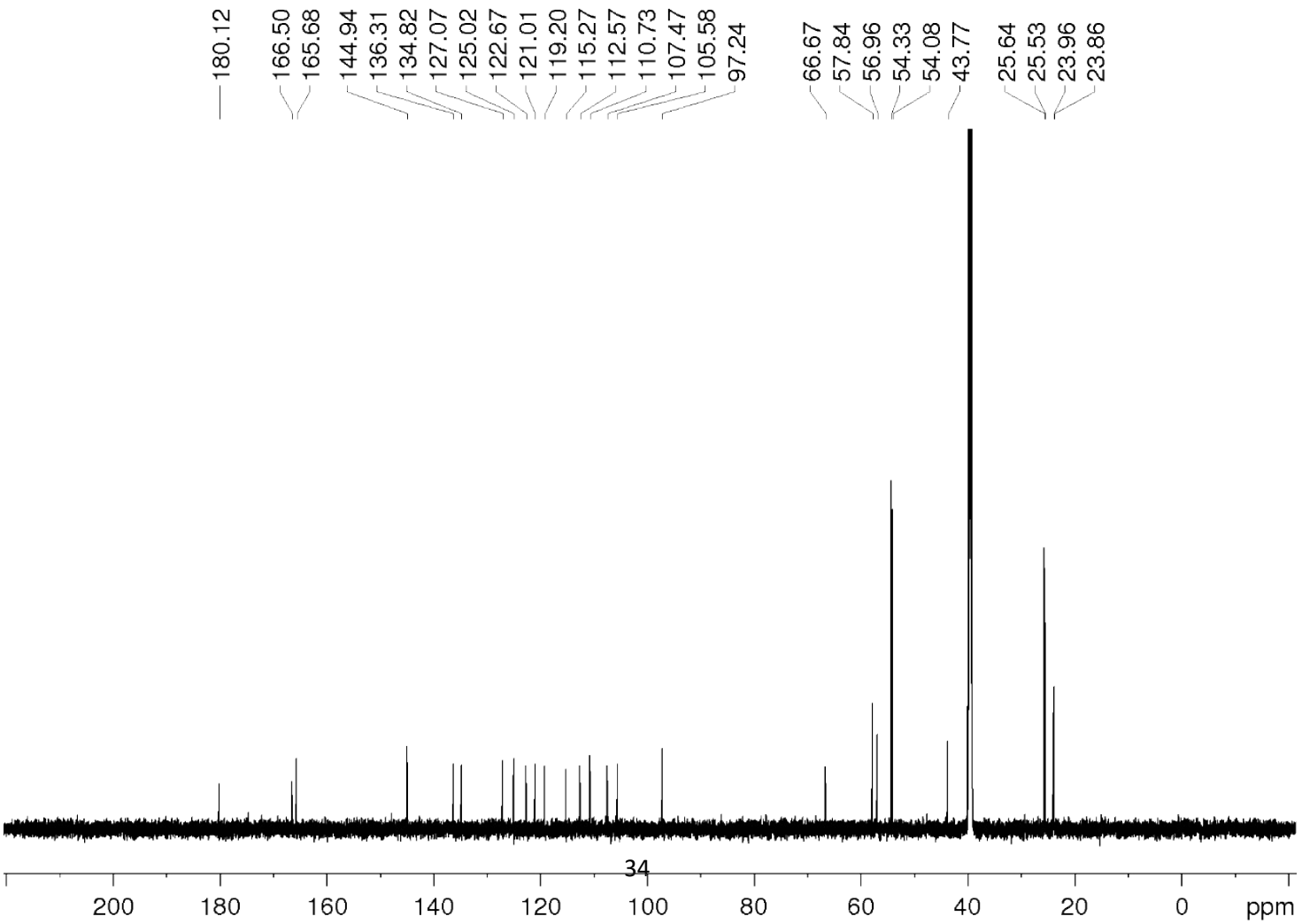

O
O
O
N
N
N

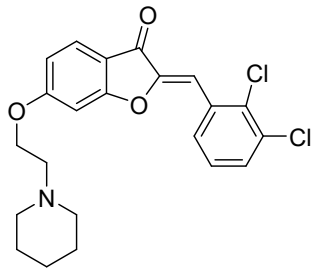
**12a**


8.30
8.05
8.04
7.66
7.65
7.61
7.60
7.29
7.28
7.28
7.27
7.27
7.23
7.23
7.22
7.21
7.21
7.06
7.06
6.85
6.84
6.84
6.83
4.41
4.40
4.39
4.25
4.25
4.24
2.73
2.72
2.72
2.70
2.69
2.68
2.50
2.44
1.52
1.51
1.50
1.49
1.39
1.39
1.00
1.00
1.01
1.06
1.06
2.08
1.02
1.04
2.34
2.38
2.17
2.40
8.37
8.64
4.34
10
9
8
7
6
5
4
3
2
1
0
−1
ppm

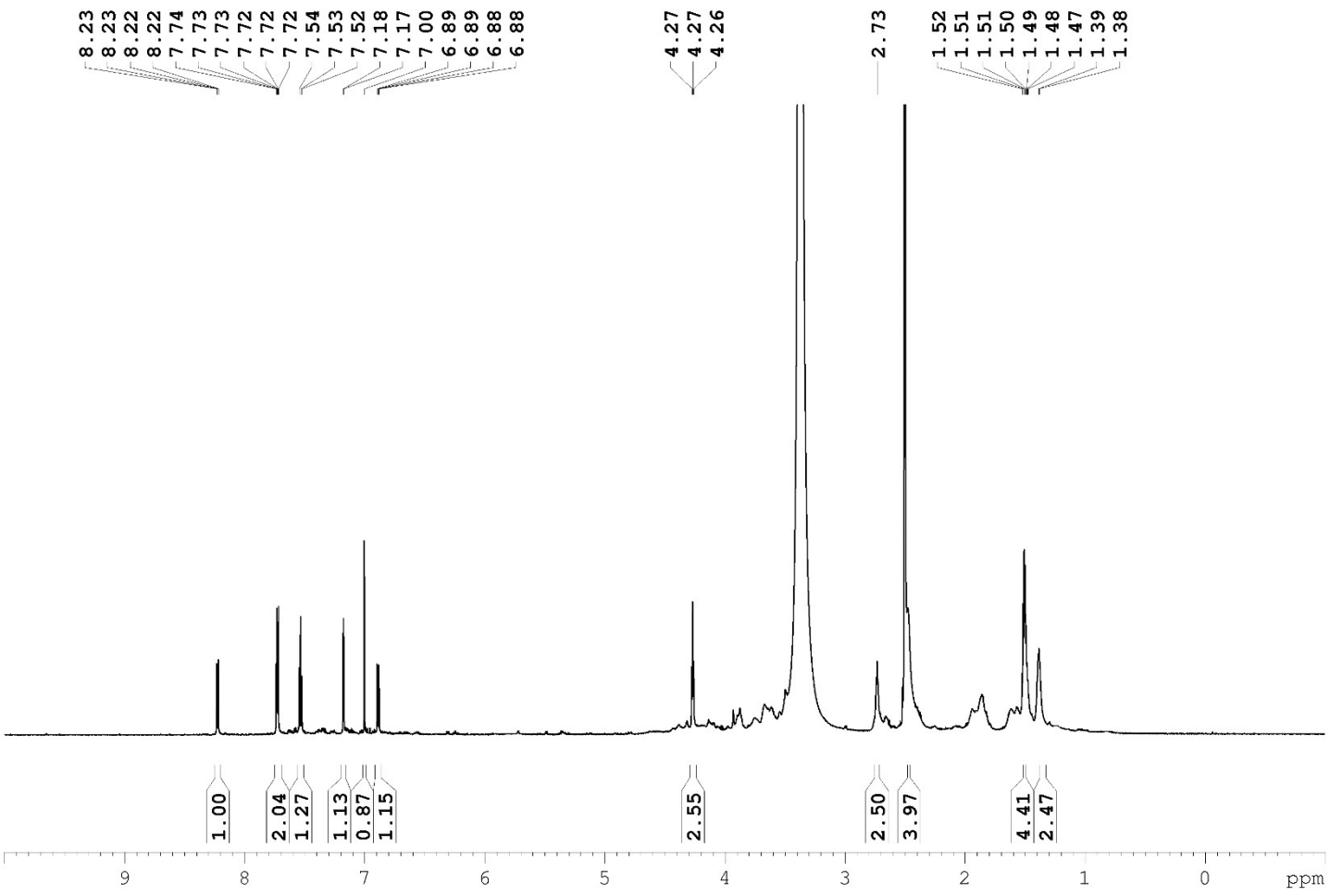


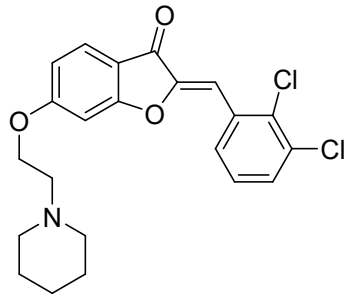
**12a**


180.12
166.50
165.68
144.94
136.31
134.82
127.07
125.02
122.67
121.01
119.20
115.27
112.57
110.73
107.47
105.58
97.24
66.67
57.84
56.96
54.33
54.08
43.77
25.64
25.53
23.96
23.86
200
180
160
140
120
100
80
60
40
20
0
ppm

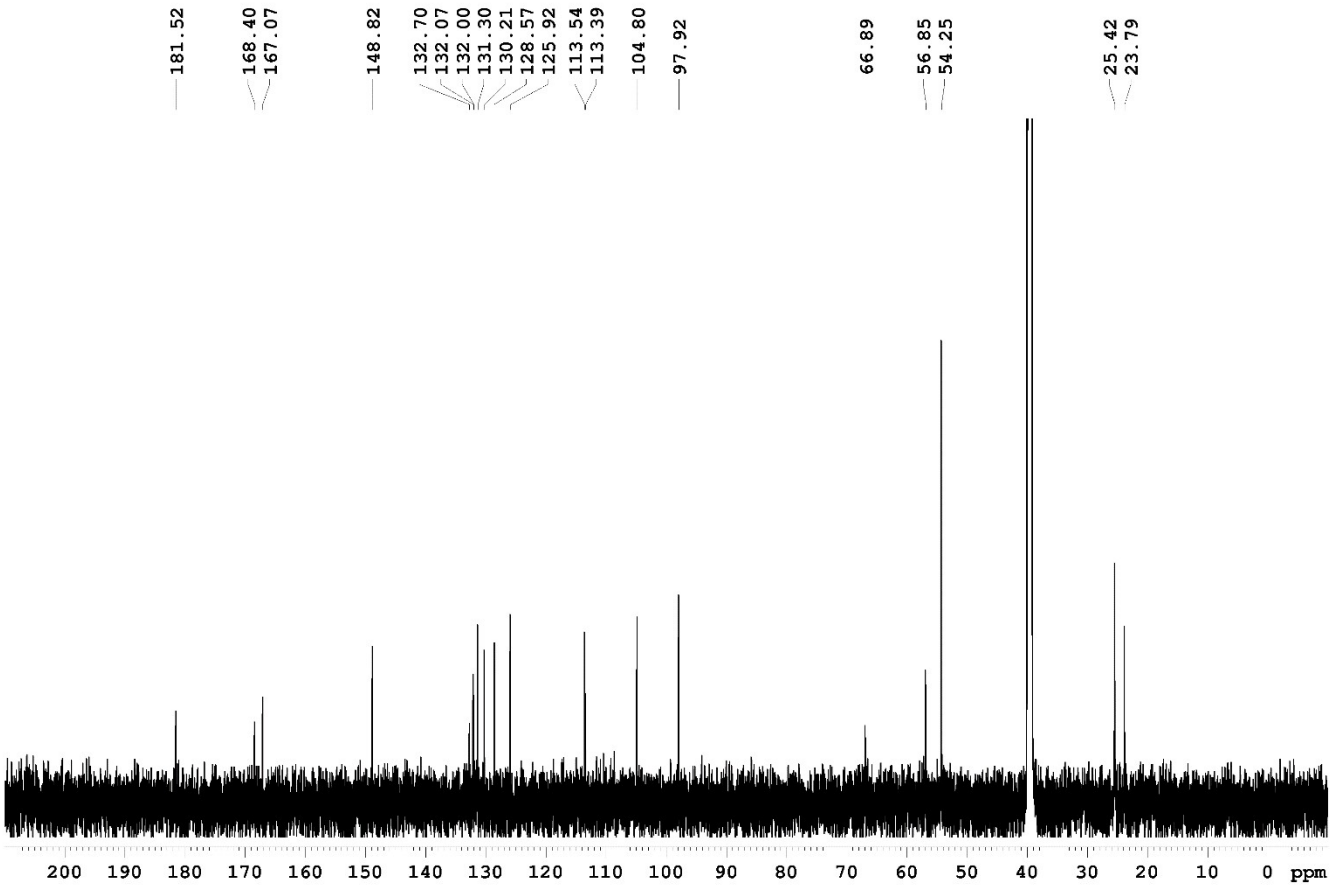

O
Cl
O
O
Cl
N

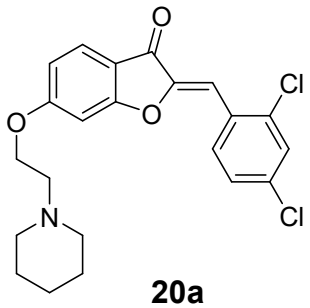
**18a**


8.23
8.23
8.22
8.22
7.74
7.73
7.73
7.72
7.72
7.54
7.53
7.52
7.18
7.17
7.00
6.89
6.89
6.88
6.88
4.27
4.27
4.26
2.73
1.52
1.51
1.51
1.50
1.49
1.48
1.47
1.39
1.38
1.00
2.04
1.27
1.13
0.87
1.15
2.55
2.50
3.97
4.41
2.47
9
8
7
6
5
4
3
2
1
0
ppm

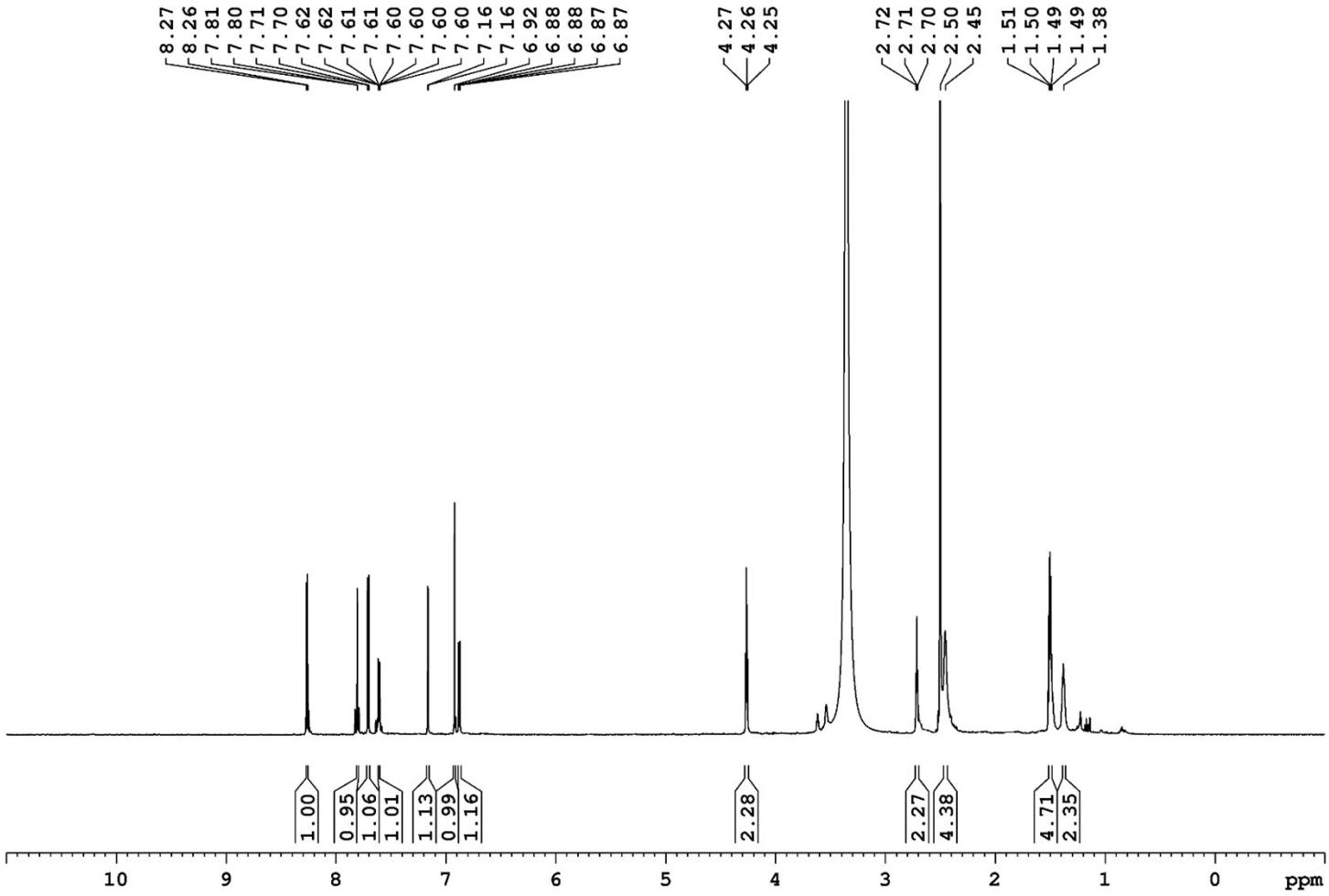

O
Cl
O
O
Cl
N

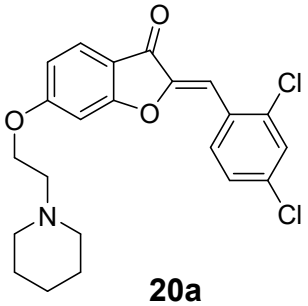
**18a**


181.52
168.40
167.07
148.82
132.70
132.07
132.00
131.30
130.21
128.57
125.92
113.54
113.39
104.80
97.92
66.89
56.85
54.25
25.42
23.79
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

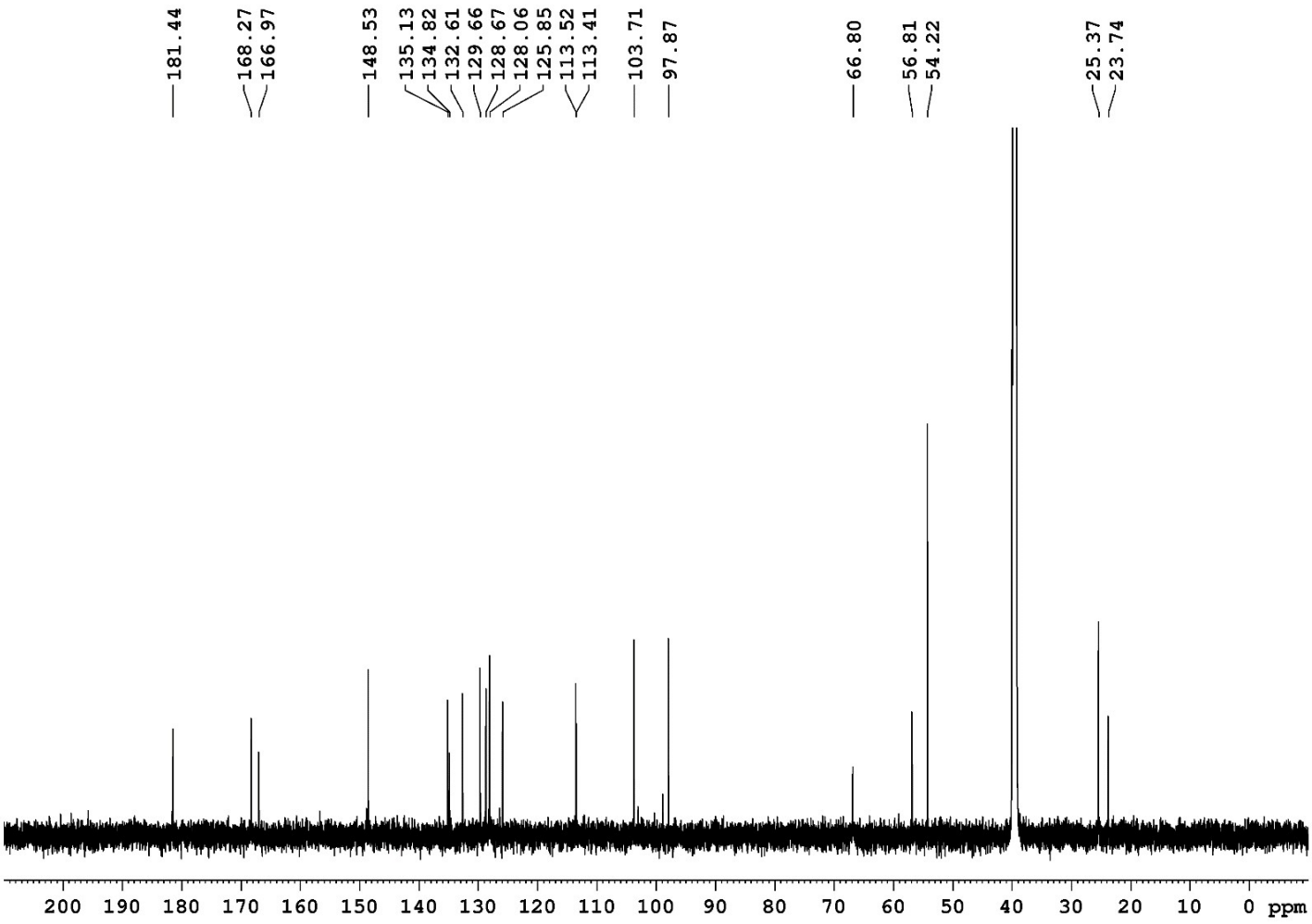

O
O
Cl
O
Cl
N

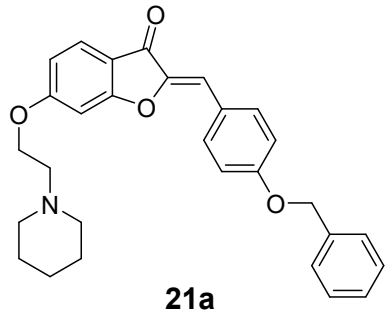
**20a**


8.27
8.26
7.81
7.80
7.71
7.70
7.62
7.62
7.61
7.61
7.60
7.60
7.60
7.60
7.16
7.16
6.92
6.88
6.88
6.87
6.87
4.27
4.26
4.25
2.72
2.71
2.70
2.50
2.45
1.51
1.50
1.49
1.49
1.38
1.00
0.95
1.06
1.01
1.13
0.99
1.16
2.28
2.27
4.38
4.71
2.35
10
9
8
7
6
5
4
3
2
1
0
ppm

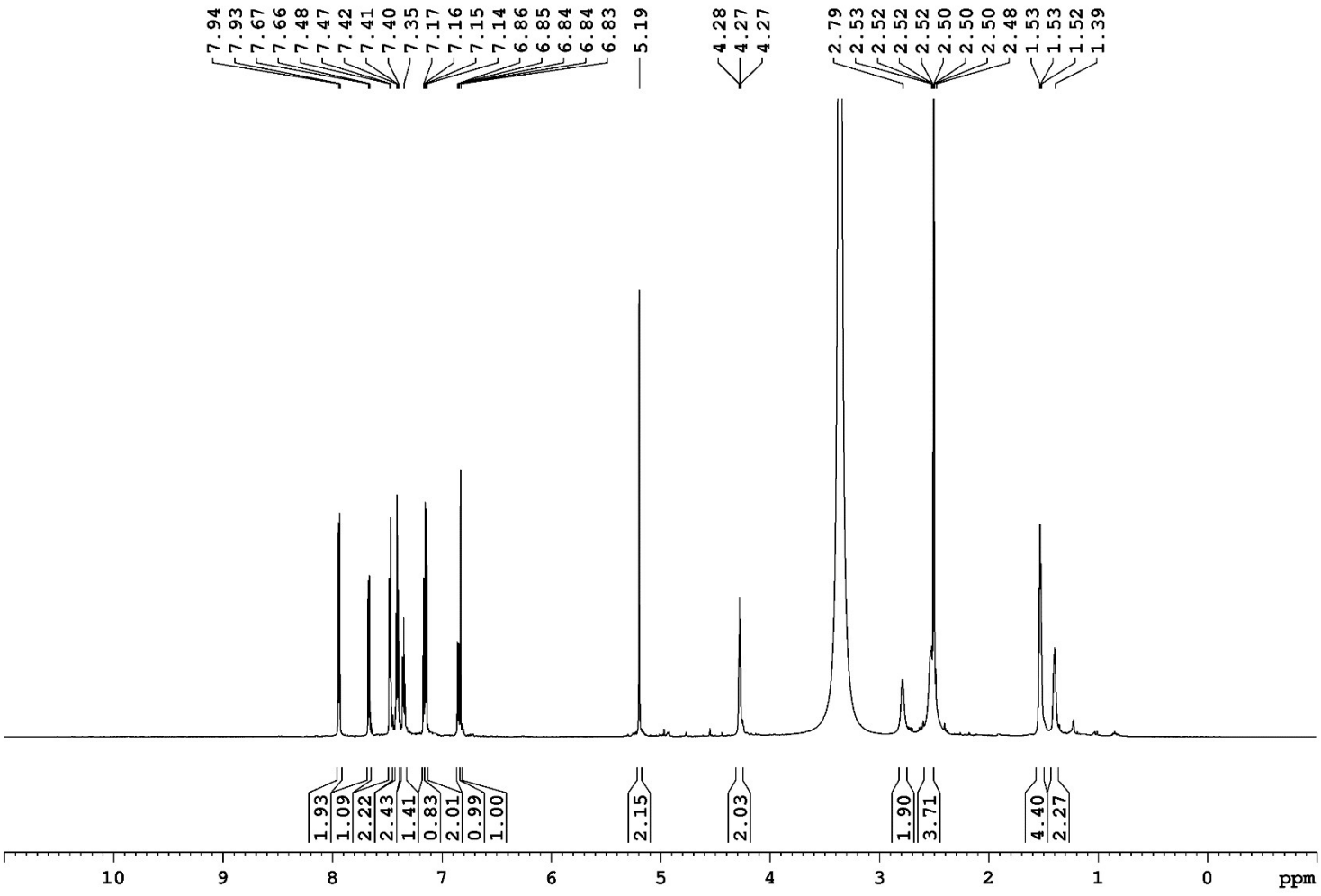

O
O
Cl
O
Cl
N

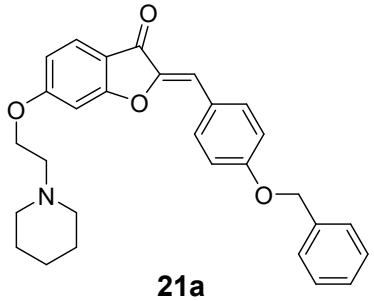
**20a**


181.44
168.27
166.97
148.53
135.13
134.82
132.61
129.66
128.67
128.06
125.85
113.52
113.41
103.71
97.87
66.80
56.81
54.22
25.37
23.74
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

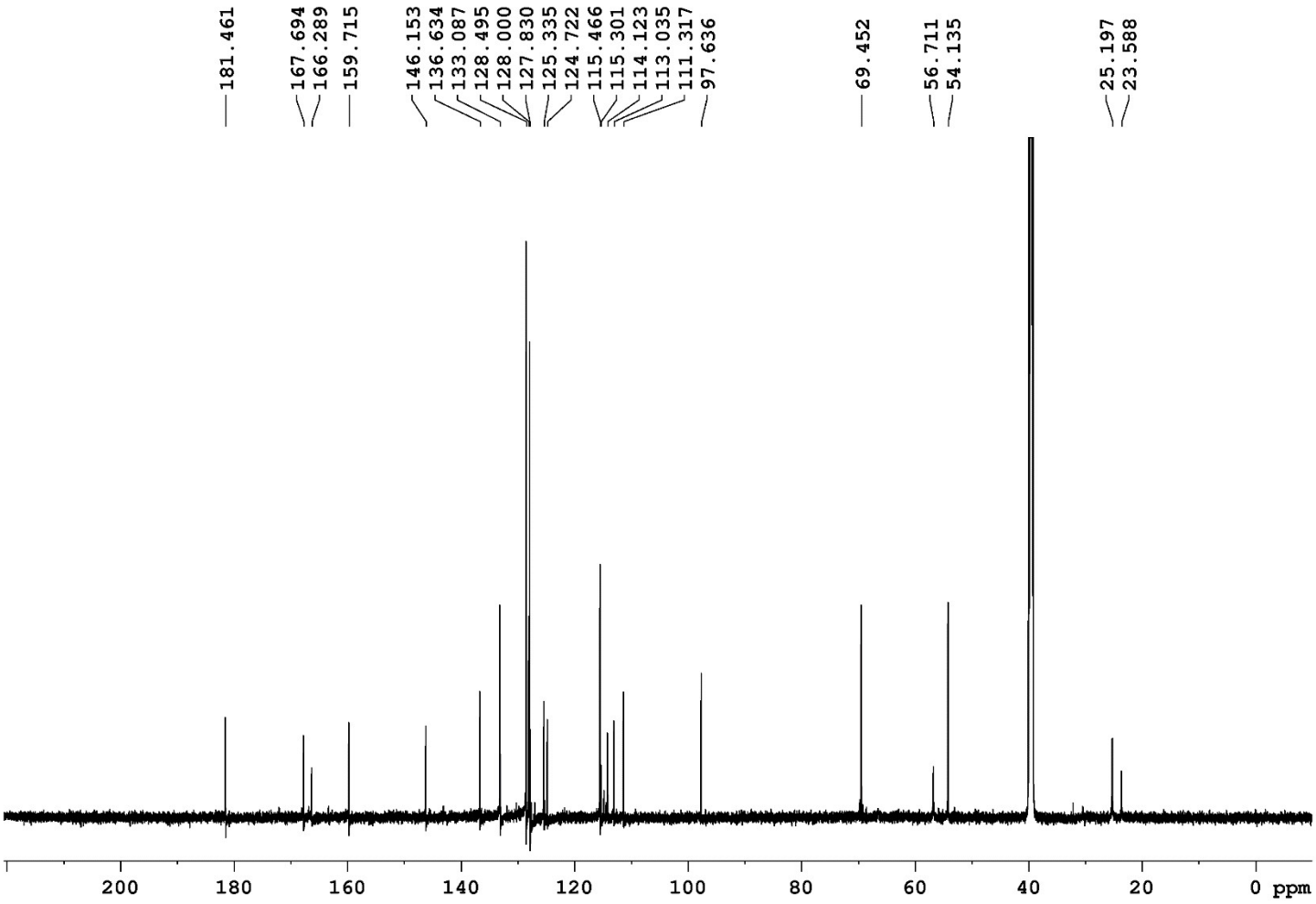


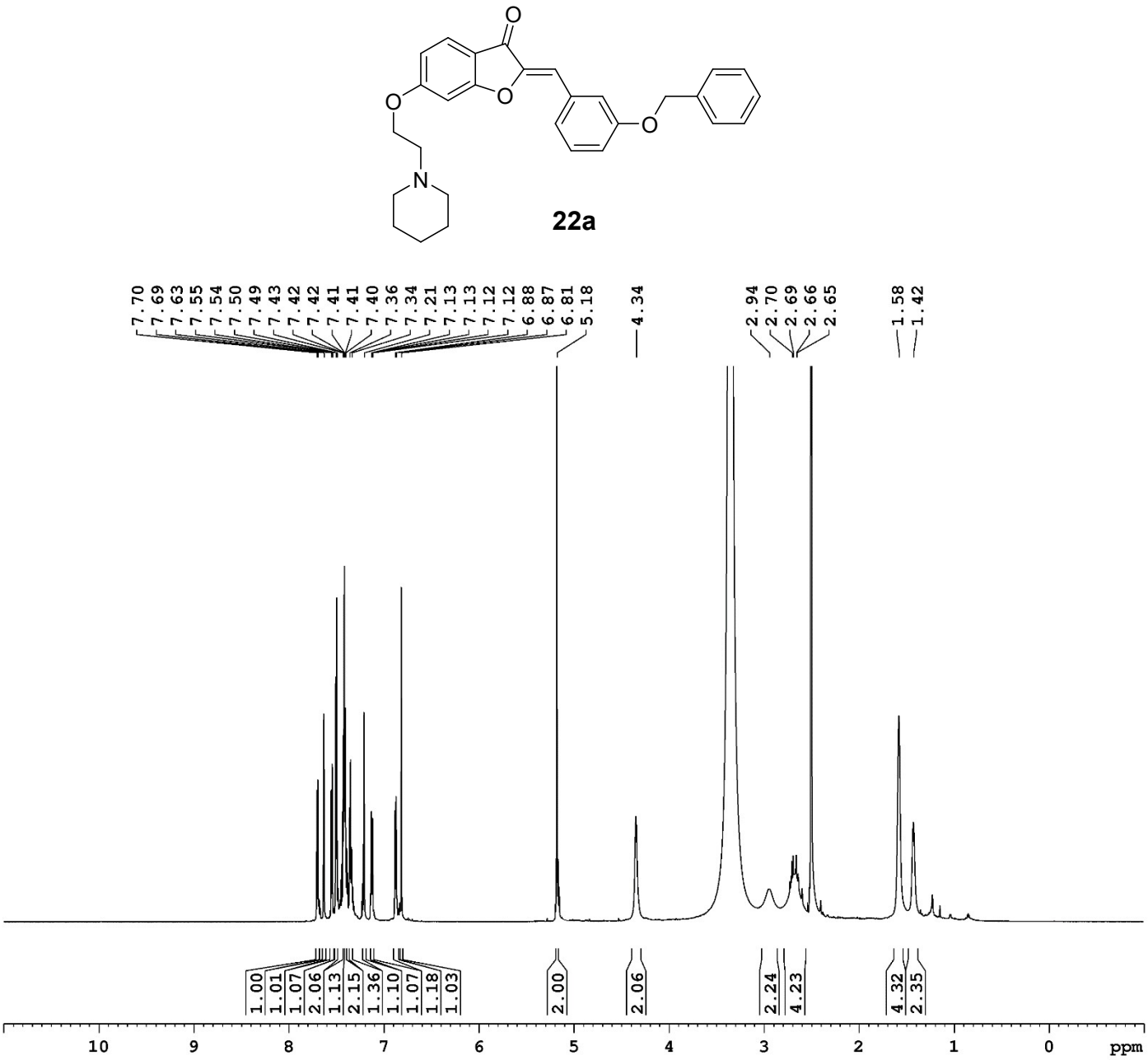
**21a**

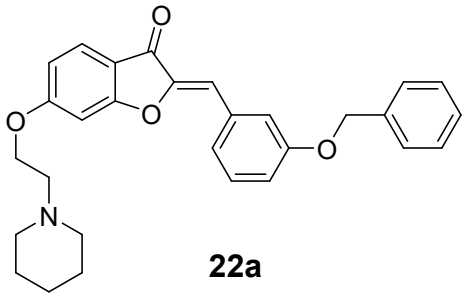

7.94
7.93
7.67
7.66
7.48
7.47
7.42
7.41
7.40
7.35
7.17
7.16
7.15
7.14
6.86
6.85
6.84
6.84
6.83
5.19
4.28
4.27
4.27
2.79
2.53
2.52
2.52
2.52
2.50
2.50
2.50
2.48
1.53
1.53
1.52
1.39
1.93
1.09
2.22
2.43
1.41
0.83
2.01
0.99
1.00
2.15
2.03
1.90
3.71
4.40
2.27
10
9
8
7
6
5
4
3
2
1
0
ppm



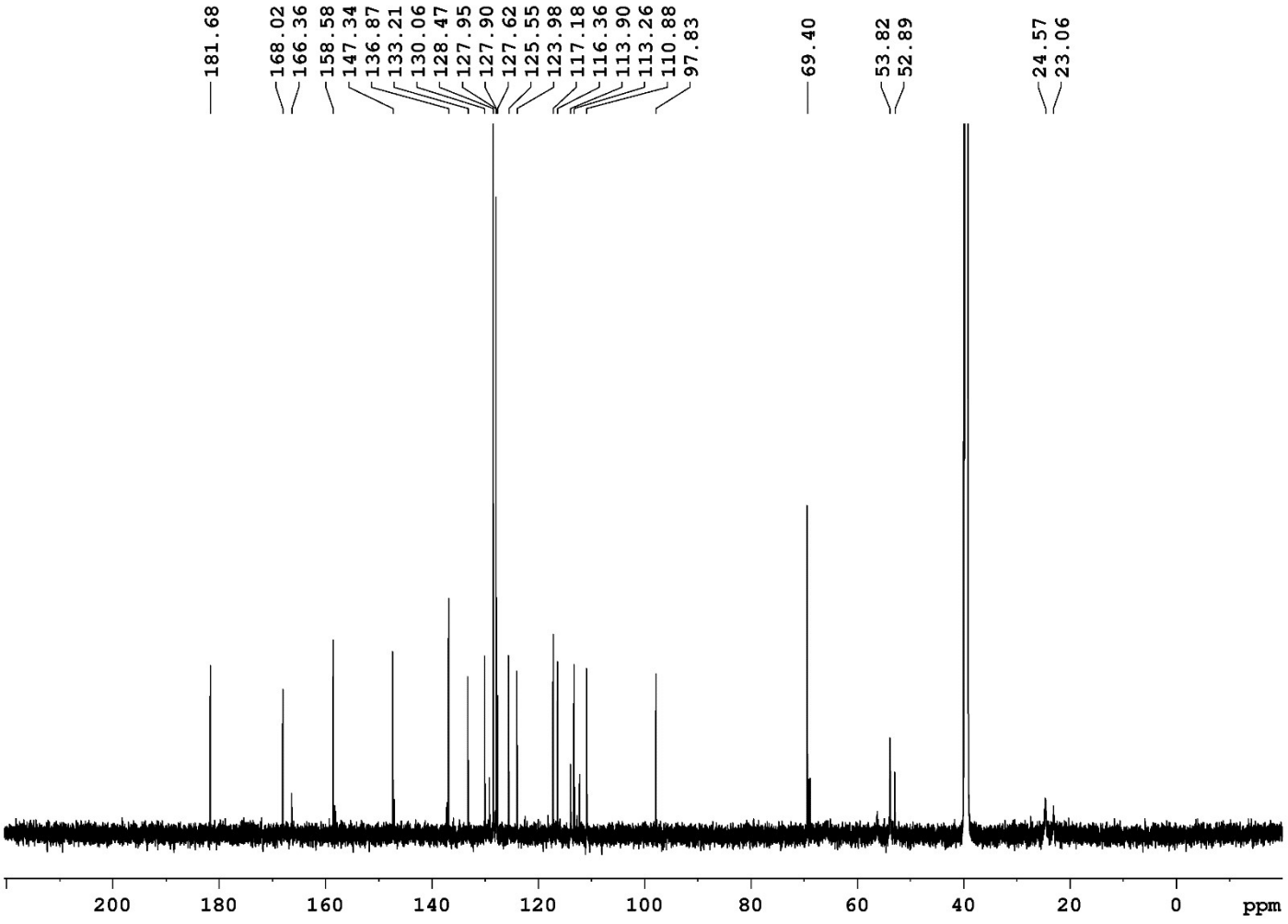
**21a**

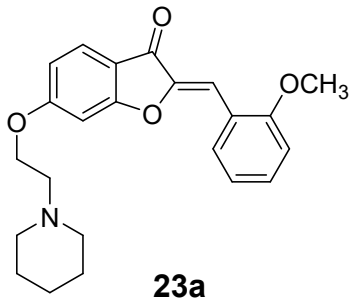

181.461
167.694
166.289
159.715
146.153
136.634
133.087
128.495
128.000
127.830
125.335
124.722
115.466
115.301
114.123
113.035
111.317
97.636
69.452
56.711
54.135
25.197
23.588
200
180
160
140
120
100
80
60
40
20
0 ppm


O
O
O
O
N
22a
7.70
7.69
7.63
7.55
7.54
7.50
7.49
7.43
7.42
7.42
7.41
7.41
7.40
7.36
7.34
7.21
7.13
7.13
7.12
7.12
6.88
6.87
6.81
5.18
4.34
2.94
2.70
2.69
2.66
2.65
1.58
1.42
1.00
1.01
1.07
2.06
1.13
2.15
1.36
1.10
1.07
1.18
1.03
2.00
2.06
2.24
4.23
4.32
2.35
10
9
8
7
6
5
4
3
2
1
0
ppm

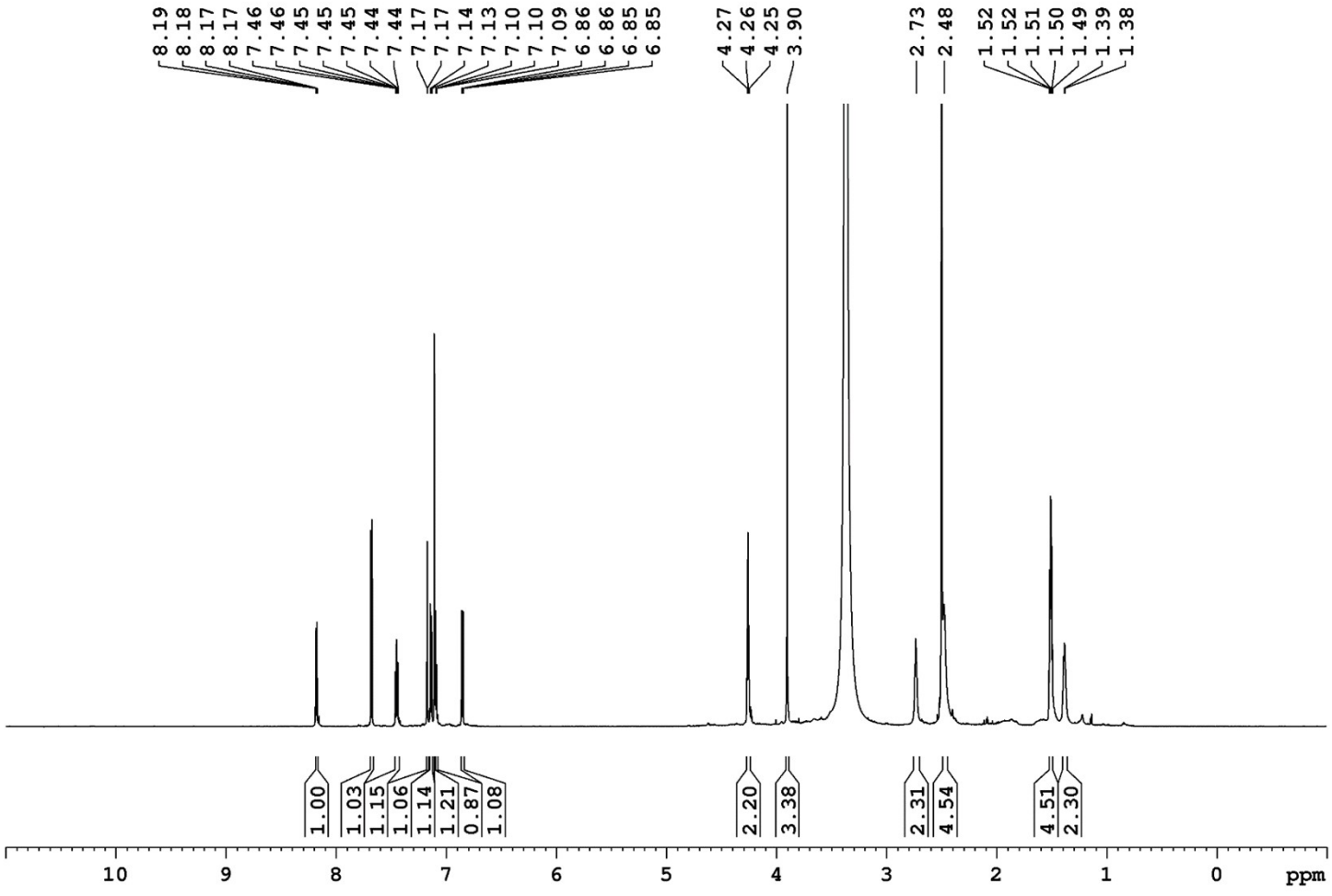


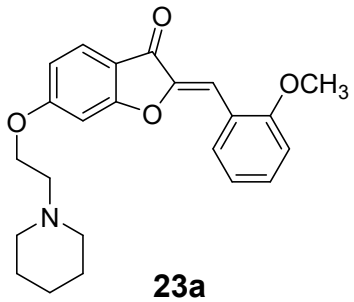
**22a**


181.68
168.02
166.36
158.58
147.34
136.87
133.21
130.06
128.47
127.95
127.90
127.62
125.55
123.98
117.18
116.36
113.90
113.26
110.88
97.83
69.40
53.82
52.89
24.57
23.06
200
180
160
140
120
100
80
60
40
20
0
ppm

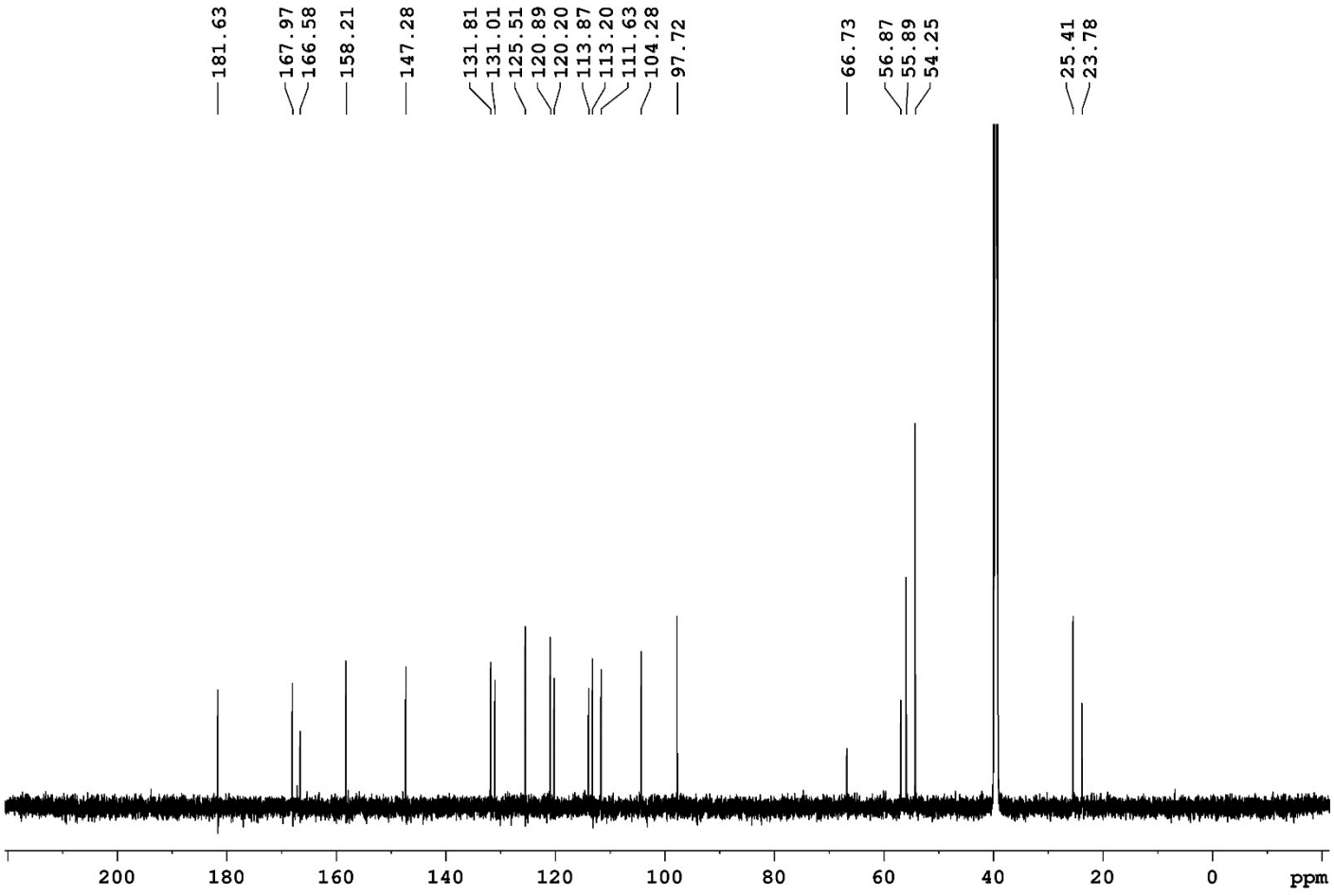

O
OCH3
O
O
N

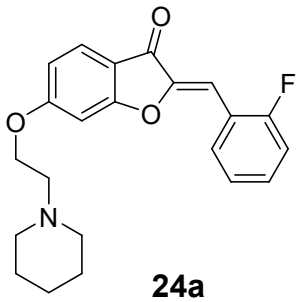
**23a**


8.19
8.18
8.17
8.17
7.46
7.46
7.45
7.45
7.45
7.44
7.44
7.17
7.17
7.14
7.13
7.10
7.10
7.09
6.86
6.86
6.85
6.85
4.27
4.26
4.25
3.90
2.73
2.48
1.52
1.52
1.51
1.50
1.49
1.39
1.38
1.00
1.03
1.15
1.06
1.14
1.21
0.87
1.08
2.20
3.38
2.31
4.54
4.51
2.30
10
9
8
7
6
5
4
3
2
1
0
ppm

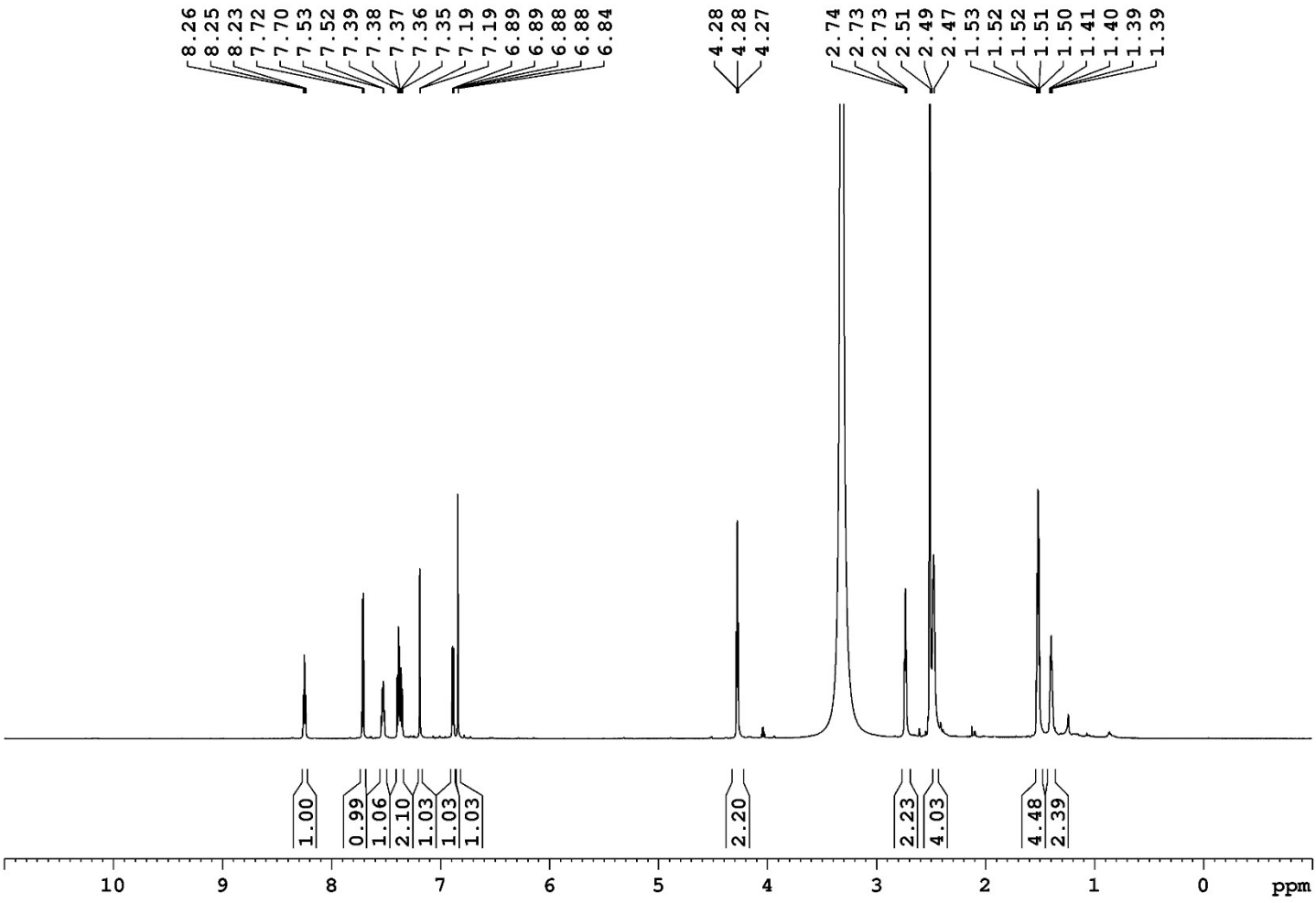

O
OCH3
O
O
N

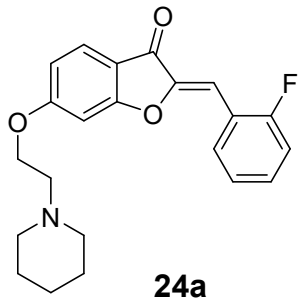
**23a**


181.63
167.97
166.58
158.21
147.28
131.81
131.01
125.51
120.89
120.20
113.87
113.20
111.63
104.28
97.72
66.73
56.87
55.89
54.25
25.41
23.78
200
180
160
140
120
100
80
60
40
20
0
ppm

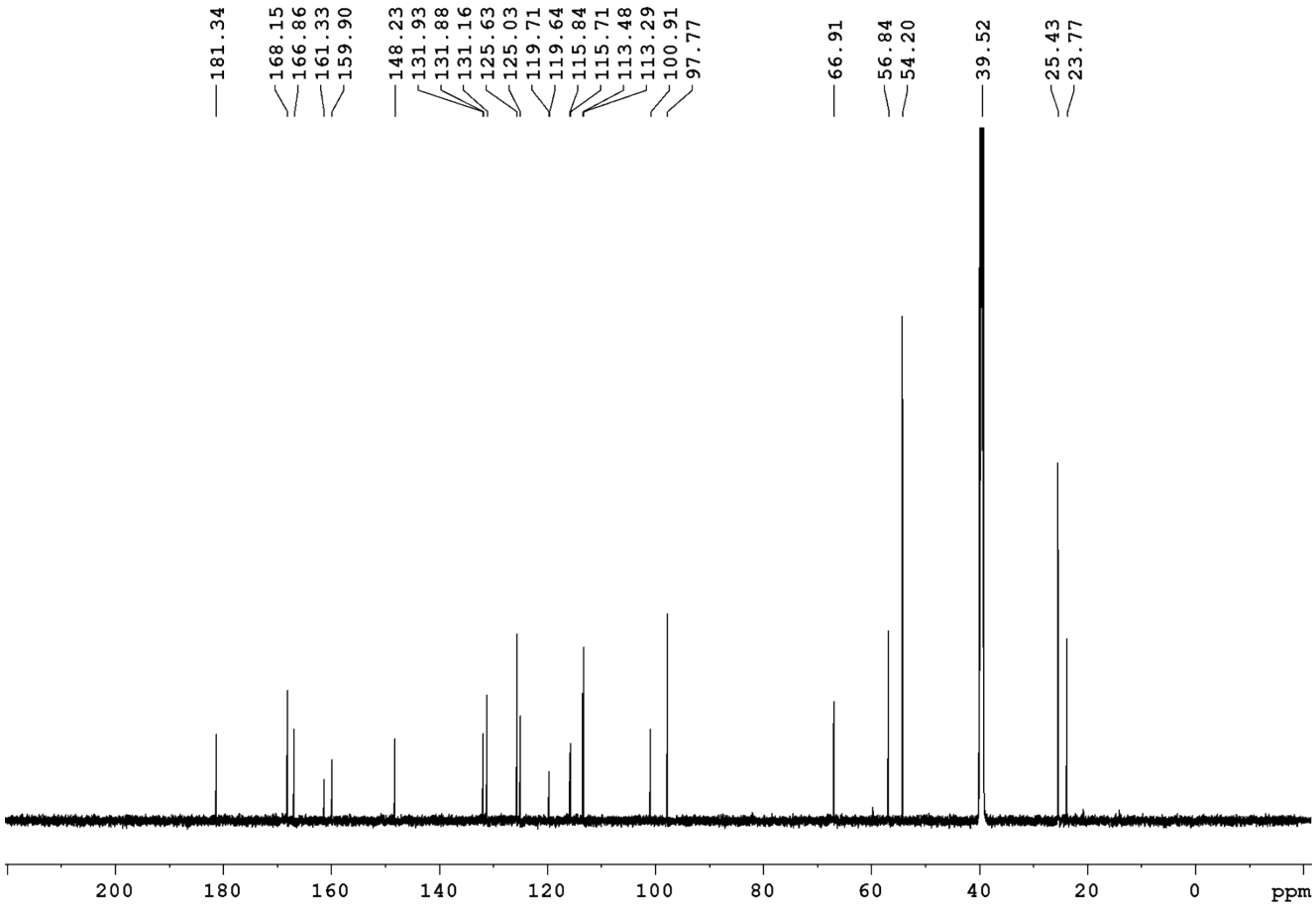

O
F
O
O
N

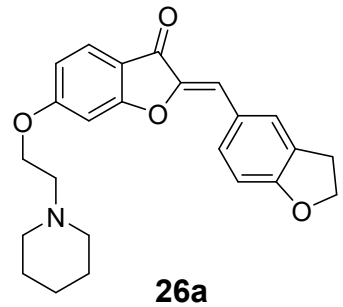
**24a**


8.26
8.25
8.23
7.72
7.70
7.53
7.52
7.39
7.38
7.37
7.36
7.35
7.19
7.19
6.89
6.89
6.88
6.88
6.84
4.28
4.28
4.27
2.74
2.73
2.73
2.51
2.49
2.47
1.53
1.52
1.52
1.51
1.50
1.41
1.40
1.39
1.39
1.00
0.99
1.06
2.10
1.03
1.03
1.03
2.20
2.23
4.03
4.48
2.39
10
9
8
7
6
5
4
3
2
1
0
ppm

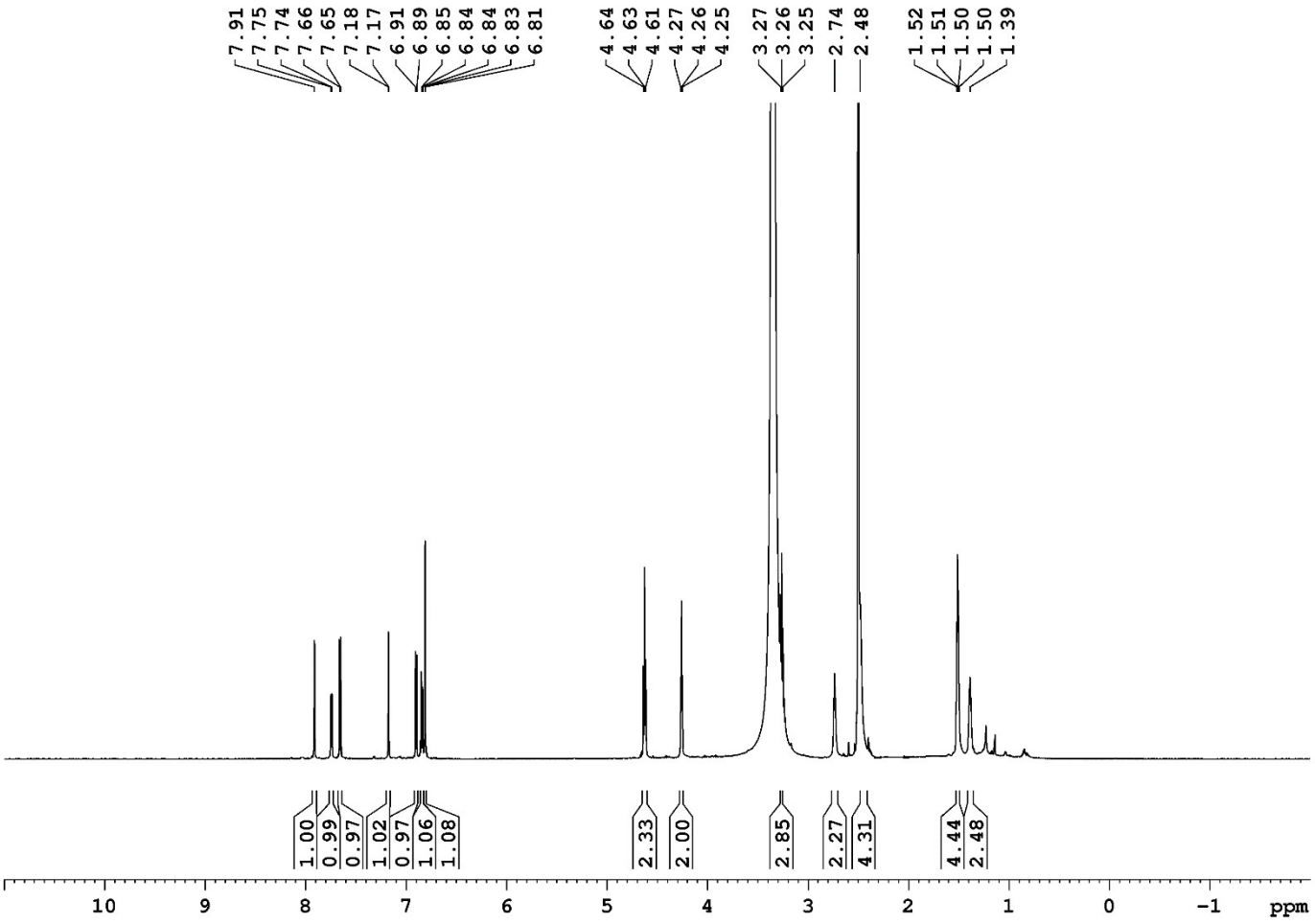

O
F
O
O
N

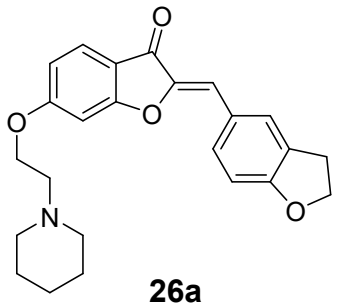
**24a**


181.34
168.15
166.86
161.33
159.90
148.23
131.93
131.88
131.16
125.63
125.03
119.71
119.64
115.84
115.71
113.48
113.29
100.91
97.77
66.91
56.84
54.20
39.52
25.43
23.77
200
180
160
140
120
100
80
60
40
20
0
ppm

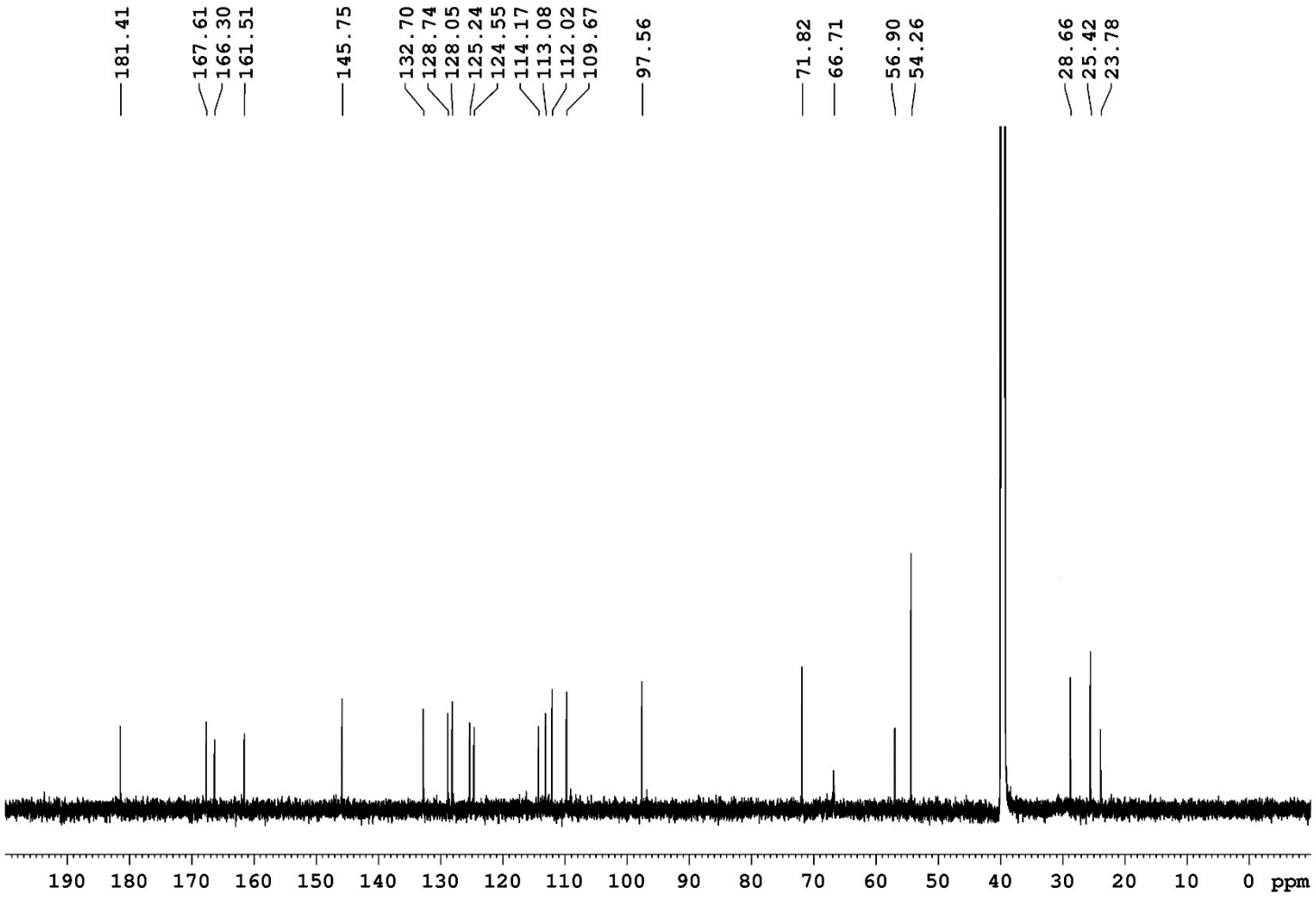


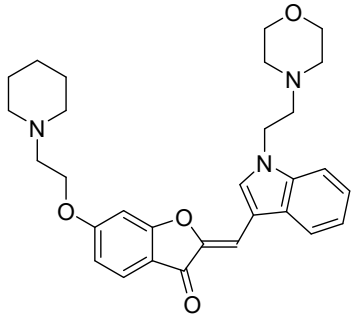
**26a**


7.91
7.75
7.74
7.66
7.65
7.18
7.17
6.91
6.89
6.85
6.84
6.84
6.83
6.81
4.64
4.63
4.61
4.27
4.26
4.25
3.27
3.26
3.25
2.74
2.48
1.52
1.51
1.50
1.50
1.39
1.00
0.99
0.97
1.02
0.97
1.06
1.08
2.33
2.00
2.85
2.27
4.31
4.44
2.48
10
9
8
7
6
5
4
3
2
1
0
-1
ppm

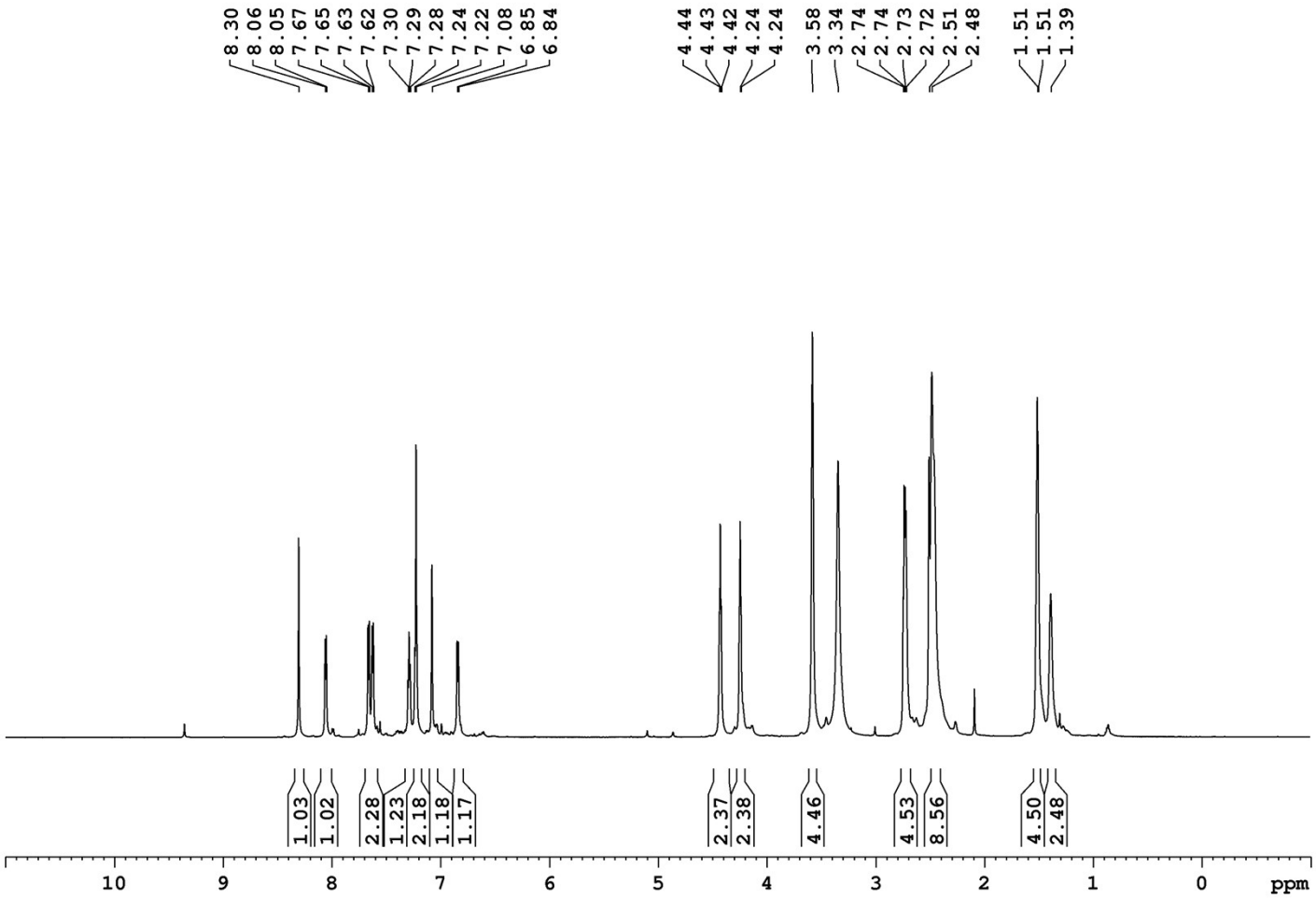


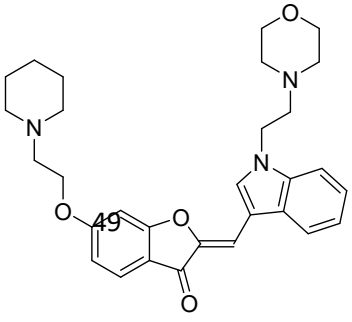
**26a**


181.41
167.61
166.30
161.51
145.75
132.70
128.74
128.05
125.24
124.55
114.17
113.08
112.02
109.67
97.56
71.82
66.71
56.90
54.26
28.66
25.42
23.78
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

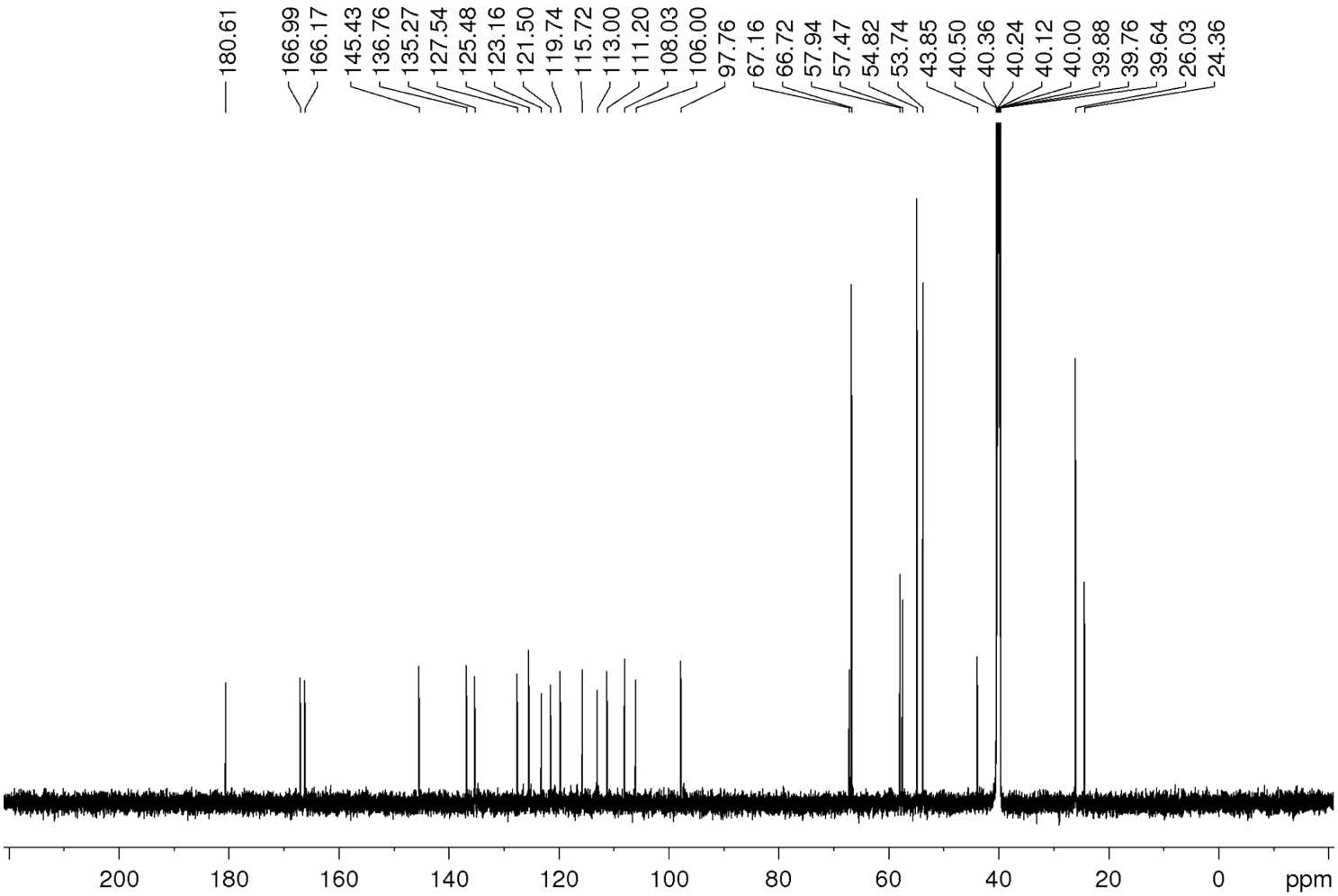


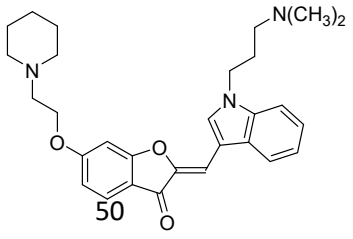
**12c**


8.30
8.06
8.05
7.67
7.65
7.63
7.62
7.30
7.29
7.28
7.24
7.22
7.08
6.85
6.84
4.44
4.43
4.42
4.24
4.24
3.58
3.34
2.74
2.74
2.73
2.72
2.51
2.48
1.51
1.51
1.39
1.03
1.02
2.28
1.23
2.18
1.18
1.17
2.37
2.38
4.46
4.53
8.56
4.50
2.48
10
9
8
7
6
5
4
3
2
1
0
ppm

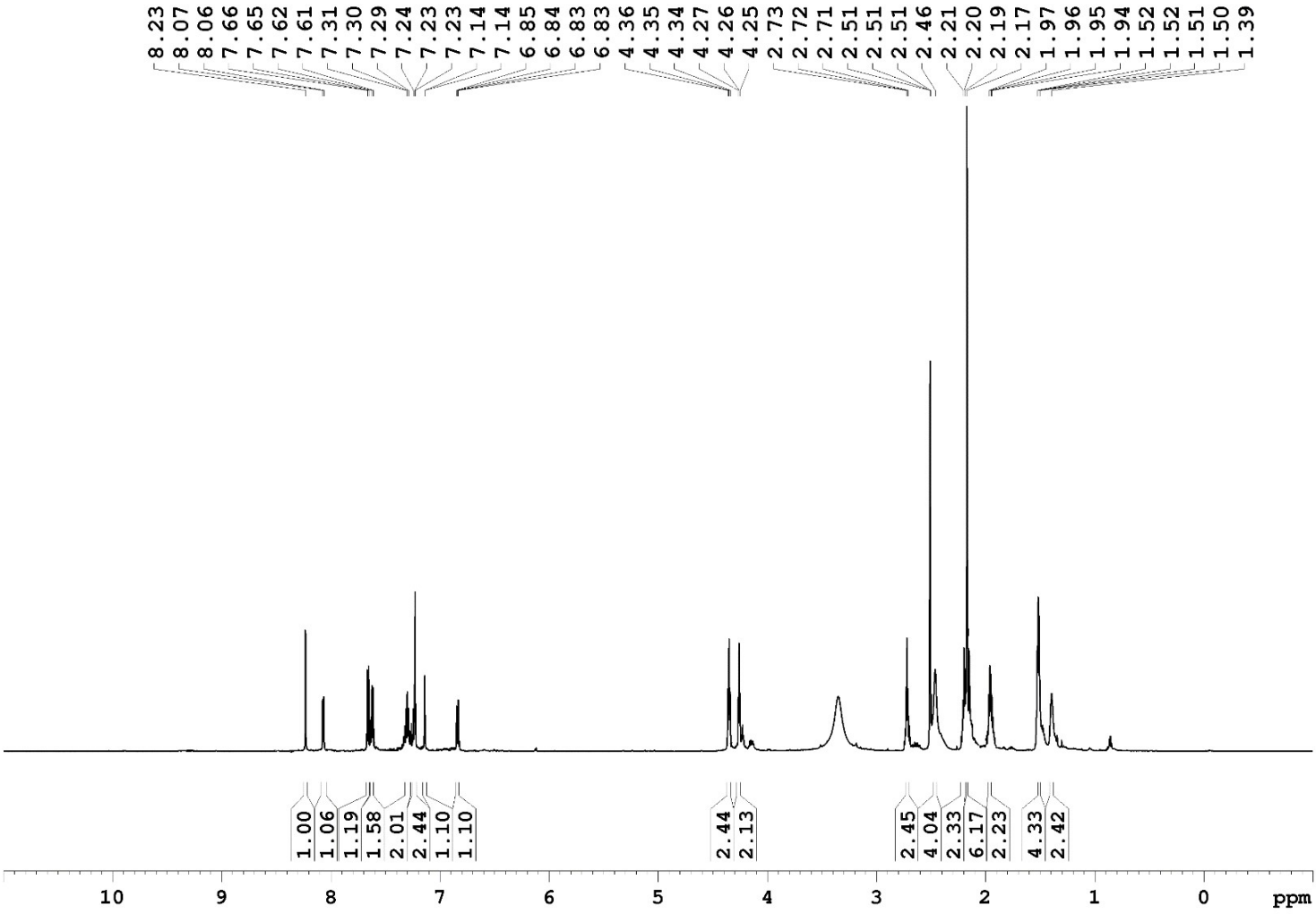


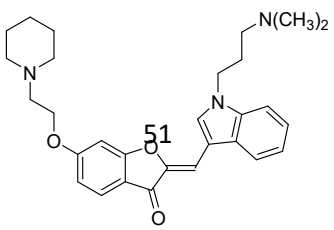
**12c**


180.61
166.99
166.17
145.43
136.76
135.27
127.54
125.48
123.16
121.50
119.74
115.72
113.00
111.20
108.03
106.00
97.76
67.16
66.72
57.94
57.47
54.82
53.74
43.85
40.50
40.36
40.24
40.12
40.00
39.88
39.76
39.64
26.03
24.36
200
180
160
140
120
100
80
60
40
20
0
ppm

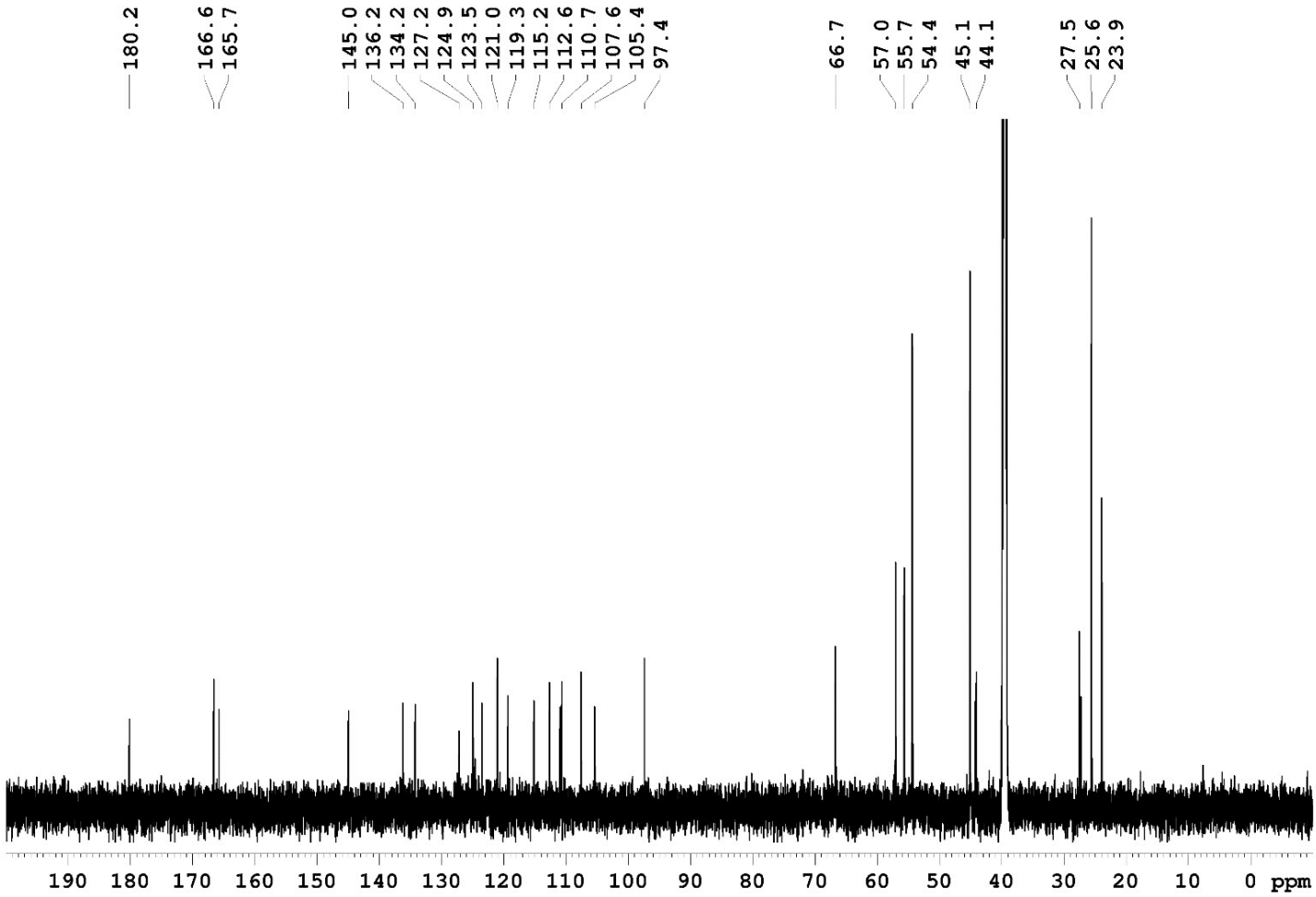

N(CH3)2
N
O
O
N
O
50

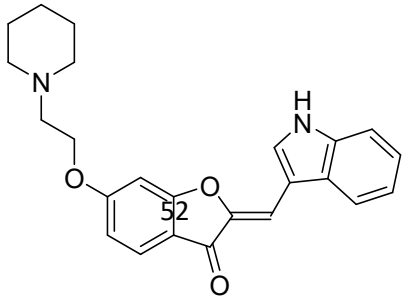
**12b**


8.23
8.07
8.06
7.66
7.65
7.62
7.61
7.31
7.30
7.29
7.24
7.23
7.23
7.14
7.14
6.85
6.84
6.83
6.83
4.36
4.35
4.34
4.27
4.26
4.25
2.73
2.72
2.71
2.51
2.51
2.51
2.46
2.21
2.20
2.19
2.17
1.97
1.96
1.95
1.94
1.52
1.52
1.51
1.50
1.39
1.00
1.06
1.19
1.58
2.01
2.44
1.10
1.10
2.44
2.13
2.45
4.04
2.33
6.17
2.23
4.33
2.42
10
9
8
7
6
5
4
3
2
1
0
ppm


N(CH3)2
N
O
O
N
O

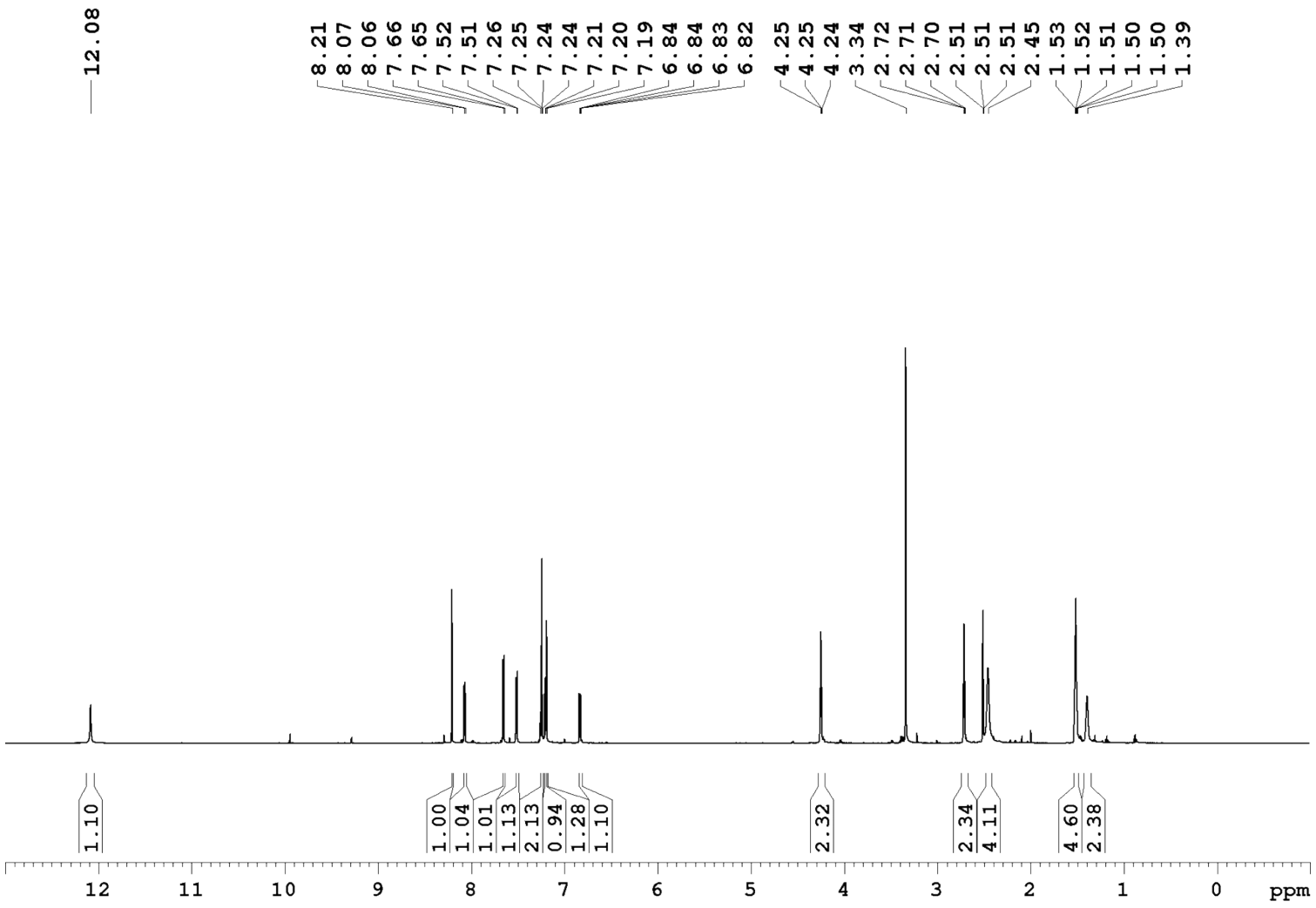
**12b**

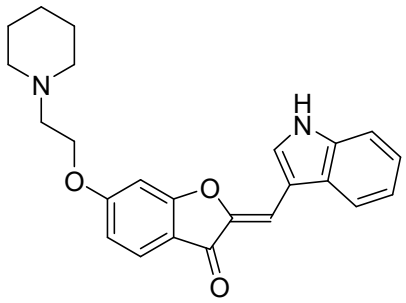

180.2
166.6
165.7
145.0
136.2
134.2
127.2
124.9
123.5
121.0
119.3
115.2
112.6
110.7
107.6
105.4
97.4
66.7
57.0
55.7
54.4
45.1
44.1
27.5
25.6
23.9
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


N
H
N
O
O
O

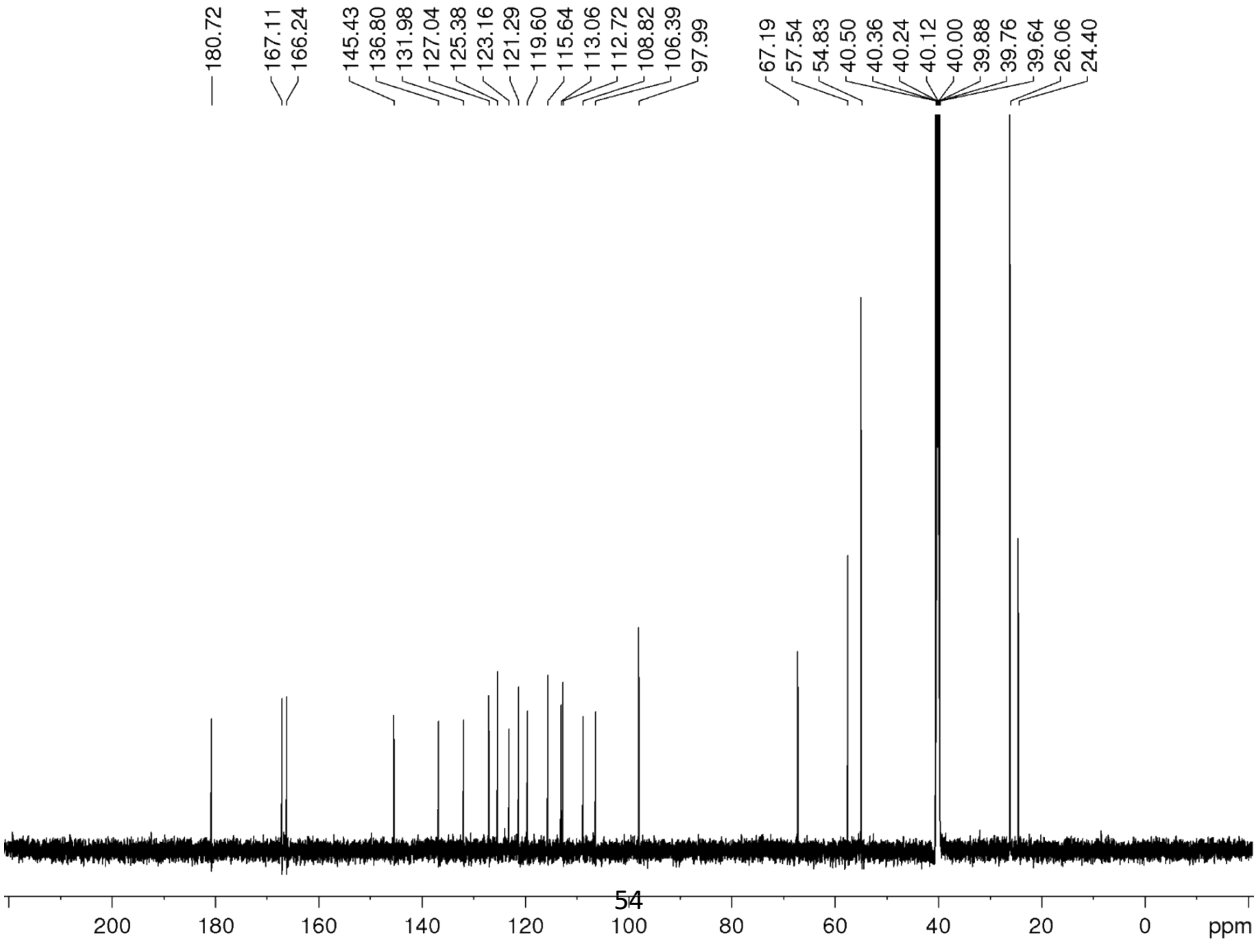
52

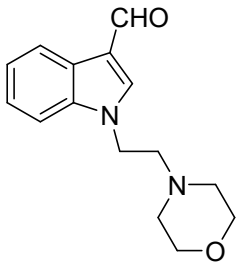
**12d**


12.08
8.21
8.07
8.06
7.66
7.65
7.52
7.51
7.26
7.25
7.24
7.24
7.21
7.20
7.19
6.84
6.84
6.83
6.82
4.25
4.25
4.24
3.34
2.72
2.71
2.70
2.51
2.51
2.51
2.45
1.53
1.52
1.51
1.50
1.50
1.39
1.10
1.00
1.04
1.01
1.13
2.13
0.94
1.28
1.10
2.32
2.34
4.11
4.60
2.38
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

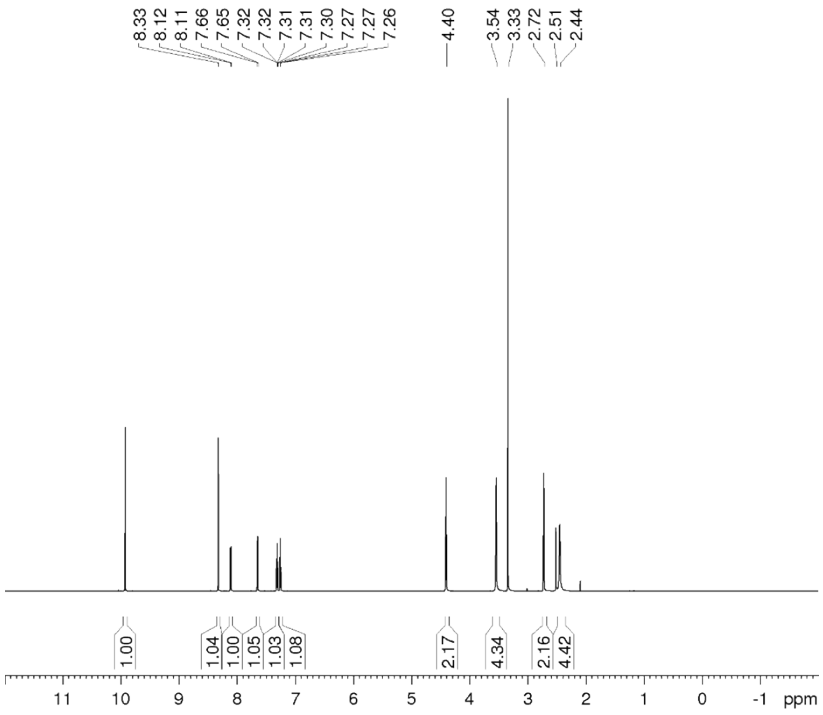


**12d**


180.72
167.11
166.24
145.43
136.80
131.98
127.04
125.38
123.16
121.29
119.60
115.64
113.06
112.72
108.82
106.39
97.99
67.19
57.54
54.83
40.50
40.36
40.24
40.12
40.00
39.88
39.76
39.64
26.06
24.40
200
180
160
140
120
100
80
60
40
20
0
ppm




1-(2-morpholinoethyl)-1*H*-indole-3-carbaldehyde



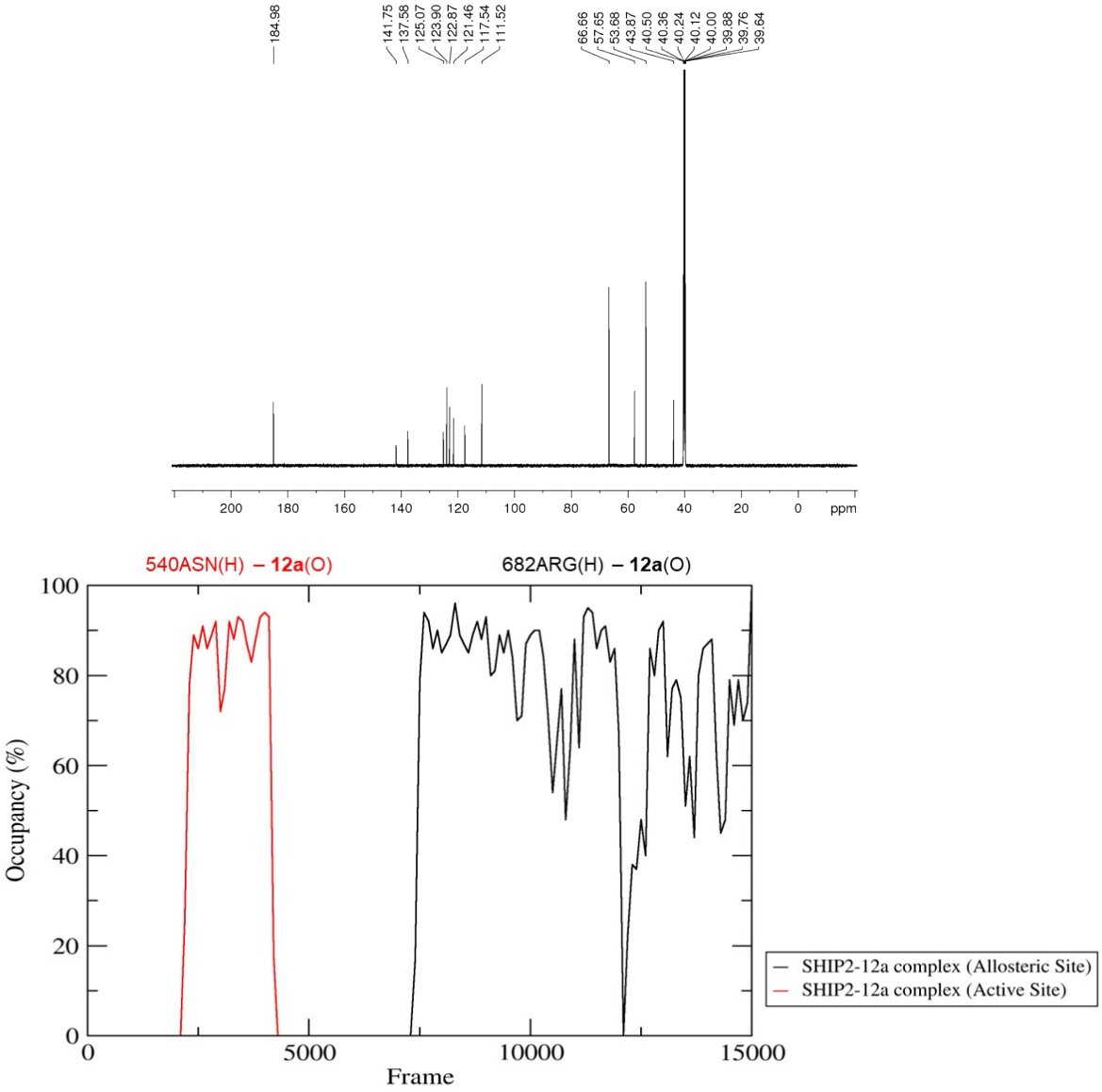



Figure S1. Atom pairs between SHIP2 and **12a** with hydrogen bond occupancy above 10% threshold throughout the 150 ns simulations (10 ps/frame) of the SHIP2-**12a** complex systems. The corresponding atom pair for each system is shown.

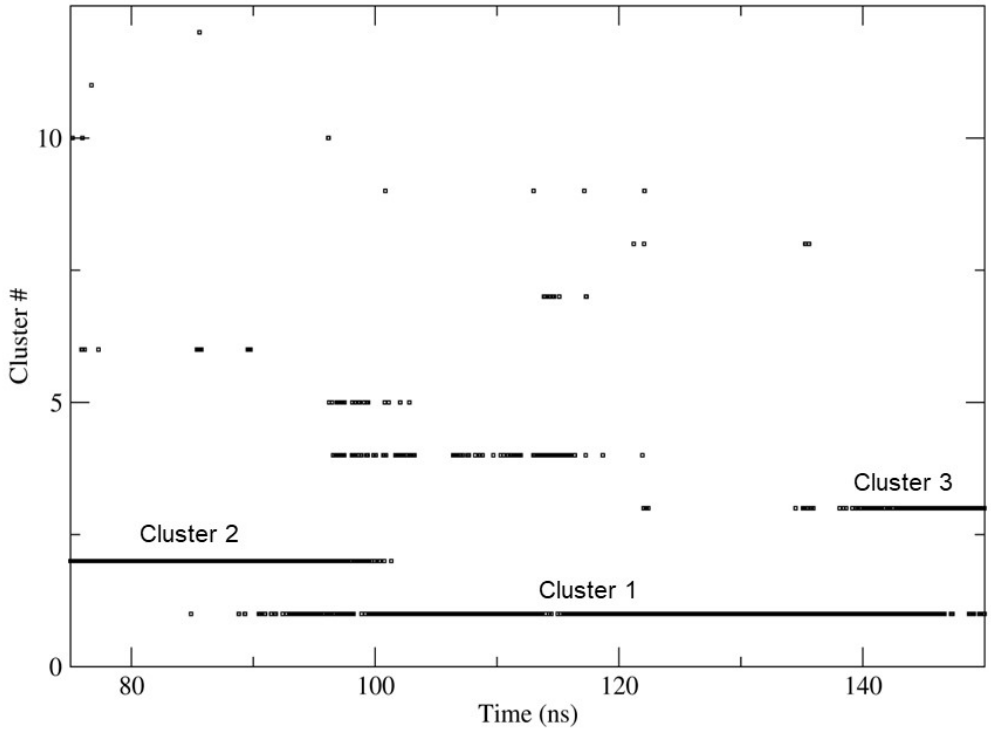



Figure S2. Number of clusters calculated from the stable MD trajectory of SHIP2-**12a** complex (allosteric site) (75-150 ns), using the Gromos clustering algorithm, with an RMSD cut-off value of 1.5 Å.