Aryl Urea based Scaffolds for Multitarget Drug Discovery in Anticancer Immunotherapies

Celia Martín-Beltrán [1], Raquel Gil-Edo [1], German Hernández-Ribelles [1], Raül Agut [1], Pilar Marín-Mezquita [1], Miguel Carda [1,*] and Eva Falomir [1,*]

[1] Depart. de Q. Inorgánica y Orgánica, Univ. Jaume I, E-12071 Castellón, Spain.
* Correspondence: efalomir@uji.es; mcarda@uji.es

Supporting Information

Contents:

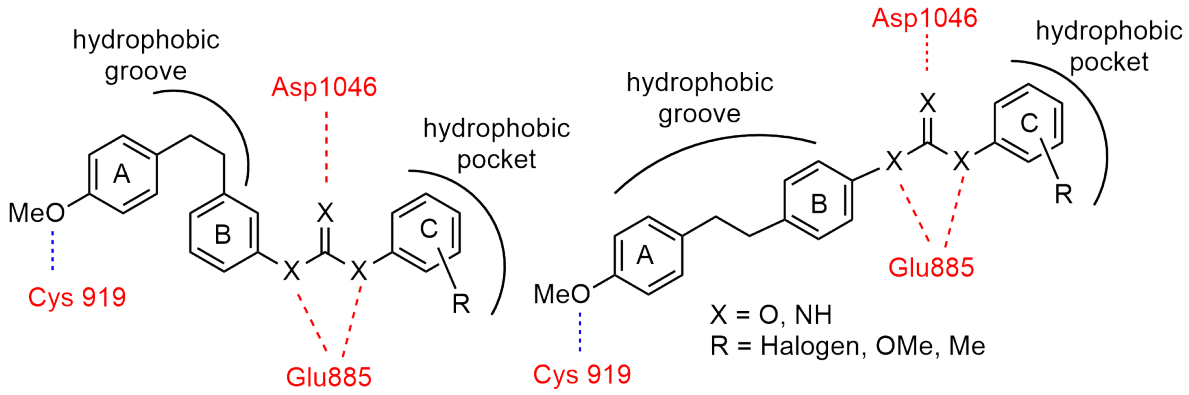


Figure S1. Scaffolds able to interact with the kinase domain of VEGFR-2 and PD-L1.

The hydrogen bonds that these compounds can establish with VEGFR-2 are indicated in red. The regions of the molecules that could interact with the hydrophobic pockets of both binding sites are also indicated.

Analytical NMR spectra

(*Z*)-1-(2-bromophenyl)-3-(3-(4-methoxystyryl)phenyl)urea (14): Yield 41 %; ^{1}H NMR (400 MHz, $DMSO_{d6}$) δ 9.38 (s, 1H); 8.10 (s, 1H); 8.00 (dd, *J* = 8.0, 4.0 Hz, 1H); 7.60 (d, *J* = 4.0 Hz, 1H); 7.30 (d, *J* = 4.0 Hz, 1H); 7.20 (dd, *J* = 8.0, 4.0 Hz, 2H); 7.20-7.17 (m, 3H); 6.94 (dd, *J* = 12.0, 4.0 Hz, 1H); 6.85 (d, *J* = 12.0 Hz, 1H); 6.82 (d, *J* = 8.0 Hz, 2H); 6.55 (d, *J* = 12.0, 8.0 Hz, 2H); 3.70 (s, 3H); ^{13}C NMR (100 MHz, $DMSO_{d6}$) δ 158.4 (C); 152.0 (C); 139.6 (C); 138.0 (C); 137.0 (C); 132.4 (x2 CH); 129.9 (CH); 129,7 (C); 128.9 (C); 128.2 (C); 128.0 (C); 124.0 (C); 122.2 (CH); 118.0 (CH); 113.7 (CH); 113.0 (CH_3) 55.1; IR ν_{max} (cm^{-1}) 3332 (NH), 1555 (CO); HR ESMS *m/z* 423.0675 $[M+Na]^+$. Calc. for $C_{22}H_{19}O_2N_2Br$, 423.0715.

(*Z*)-1-(3-bromophenyl)-3-(3-(4-methoxystyryl)phenyl)urea (15): Yield 62 %, white solid, m. p. 174 °C; ^{1}H NMR (400 MHz, $DMSO_{d6}$) δ 8.78 (s, 1H); 8.65 (s, 1H); 7.83 (s, 1H); 7.39-7.15 (m, 8H); 6.82 (t, *J* = 8.0 Hz, 3H); 6.51 (d, *J* = 12.0 Hz, 1H); 6.50 (d, *J* = 12.0 Hz, 1H); 3.75 (s, 3H); ^{13}C NMR (100 MHz, $DMSO_{d6}$) δ 158.6 (C); 152.4 (C); 140.2 (C); 139.9 (C); 138.6 (C); 131.2 (CHx2); 130.0 (CH); 129.6 (CH); 128.4 (CH); 127.7 (CHx2); 124.9 (CH); 123.2 (CH); 122.8 (CH); 120.1 (CHx2); 118.2 (CH); 117.3 (CH); 113.5 (CHx2); 55.2 (CH_3); IR ν_{max} (cm^{-1}) 3287 (NH), 1649 (CO); HR ESMS *m/z* 423.0711 $[M+H]^+$. Calc. for $C_{22}H_{19}O_2N_2Br$, 423.0715.

(*Z*)-1-(4-bromophenyl)-3-(3-(4-methoxystyryl)phenyl)urea (16): Yield 58 %, white solid, m. p. 173 °C; ^{1}H NMR (400 MHz, $DMSO_{d6}$) δ 8.75 (s, 1H); 8.63 (s, 1H); 7.41(d, *J* = 8.1 Hz, 2H); 7.45-7-39 (m, 3H); 7.28-7.17 (m, 4H); 6.84-6.80 (m, 3H); 6.51 (dd, *J* = 12.0, 8.0 Hz, 2H); 3.72 (s, 3H); ^{13}C NMR (100 MHz, $DMSO_{d6}$) δ 158.5 (C); 152.5 (C); 139.8 (C); 138.6 (C); 137.6 (C); 131.5 (CH x 2); 129.9 (CH); 129.6 (CH); 128.2 (CH); 127.5 (CHx2); 126.0 (CH); 122.5(CH); 122.2 (CH); 120.1 (CHx2); 118.1 (CH); 117.0 (CH); 113.8 (CHx2); 55.0 (CH_3); IR ν_{max} (cm^{-1}) 3291 (NH), 1633 (CO); HR ESMS *m/z* 423.0708 $[M+H]^+$. Calc. for $C_{22}H_{19}O_2N_2Br$, 423.0711.

(*Z*)-1-(2-methoxyphenyl)-3-(3-(4-methoxystyryl)phenyl)urea (17): Yield 31 %; ^{1}H NMR (400 MHz, $DMSO_{d6}$) δ 9.22 (s, 1H); 8.18 (s, 1H); 8.10 (d, *J* = 8.0 Hz, 1H); 7.29 (d, *J* = 8.0 Hz, 1H); 7.20 (s, 1H); 7.18-7.10 (m, 3H); 7.0 (d, *J* = 4.0 Hz, 1H); 6.94-6.86 (m, 3H); 6.83 (d *J* = 4.0 Hz, 1H); 6.51 (dd, *J* = 12.0, 4.0 Hz, 1H); 3.4 (s, 3H); 3.3 (s, 3H); ^{13}C NMR (100 MHz, $DMSO_{d6}$) δ 158.4 (C); 152.3 (C); 147.0 (C); 140.0 (C); 138.1 (C); 129.9 (2xCH); 129.6 (CH); 128.8 (C); 128.8 (CH); 128.2 (CH), 121.8 (CH); 121.7 (CH); 120.5 (CH); 118.2 (CH); 117.7 (CH); 116.7 (CH); 110.7 (CH); 55.7 (CH_3); 55.0 (CH_3); IR ν_{max} (cm^{-1}) 3302 (NH), 1595 (CO); HR ESMS *m/z* 375.1867 $[M+H]^+$. Calc. for $C_{23}H_{22}O_3N_2$, 375.1865.

(*Z*)-1-(3-methoxyphenyl)-3-(3-(4-methoxystyryl)phenyl)urea (18): Yield 61 %; ^{1}H NMR (400 MHz, $DMSO_{d6}$) δ 8.61 (s, 1H); 8.57 (s, 1H); 7.38 (d, *J* = 12.0 Hz, 1H); 7.30 (s, 1H); 7.20-7.14 (m, 5H); 6.90 (d, *J* = 12.0 Hz, 1H); 6.85-6.81 (m, 3H); 6.51 (dd, *J* = 12.0, 8.0 Hz, 3H); 3.7 (s, 3H); 3.3 (s, 3H); ^{13}C NMR (100 MHz, $DMSO_{d6}$) δ 158.4 (C); 152.3 (C); 147.0 (C); 140.0 (C); 138.1 (C); 129.6 (2xCH); 129.4 (CH); 129.2 (C); 128.5 (CH); 128.0 (CH), 121.7 (CH); 117.8 (CH); 116.7 (CH); 113.4 (CH); 110.2 (CH); 107.0 (CH), 103.7 (CH), 54.7 (CH_3); 54.6 (CH_3); IR ν_{max} (cm^{-1}) 3307 (NH), 1595 (CO); HR ESMS *m/z* 375.1887 $[M+H]^+$. Calc. for $C_{23}H_{22}O_3N_2$, 375.1866.

(*Z*)-1-(4-methoxyphenyl)-3-(3-(4-methoxystyryl)phenyl)urea (19): Yield 66 %; ^{1}H NMR (400 MHz, $DMSO_{d6}$) δ 8.60 (s, 1H); 8.51 (s, 1H); 7.65 (s, 1H); 7.56 (d, *J* = 8.0 Hz, 2H); 7.37 (d, *J* = 8.0 Hz, 2H); 7.30-7.20 (m, 3H); 7.15 (d, *J* = 12.0 Hz, 2H); 6.95 (d, *J* = 8.0 Hz, 2H); 6.87 (d, *J* = 12.0 Hz, 2H); 3.78 (s, 3H); 3.72 (s, 3H); ^{13}C NMR (100 MHz, $DMSO_{d6}$) δ 159.0 (C); 154.5 (C); 152.7 (C); 140.2 (C); 137.8 (C); 132.7 (CH); 129.6 (CH); 129.2 (C); 129.0 (CH); 128.0 (2xCH); 127.8 (CH); 126.3 (CH); 120.0 (2xCH); 119.6 (CH); 117,1 (CH); 115.8 (CH); 114.1 (CH); 114.0 (2xCH); 55.1 (2xCH_3); IR ν_{max} (cm^{-1}) 3310 (NH), 1575 (CO); HR ESMS *m/z* 375.1867 $[M+H]^+$. Calc. for $C_{23}H_{22}O_3N_2$, 375.1856.

(*E*)-1-(2-bromophenyl)-3-(3-(4-methoxystyryl)phenyl)urea (21): Yield 13 %, white solid, m. p. 230-232 °C; ^{1}H NMR (400 MHz, $DMSO_{d6}$) δ 9.48 (s, 1H); 8.15 (s, 1H); 8.09 (d, *J* = 8.0 Hz, 1H); 7.68 (s, 1H); 7.62 (d, *J* = 8.0 Hz, 1H); 7.56 (d, *J* = 8.0 Hz, 2H); 7.37-7.21 (m, 4H); 7.10 (d, *J* = 8.0 Hz, 2H); 6.98 (d, *J* = 8.03 Hz, 1H); 6.95 (d, *J* = 12.0 Hz, 2H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $DMSO_{d6}$) δ 159.0 (C); 152.2 (C); 138.8 (C); 138.0 (C); 132,4 (C); 129.5 (C); 129.1 (C); 129.1 (CH); 128.1 (CH); 128,0 (x 2) (CH); 127.8 (CH); 126.1 (CH); 124,0 (CH); 121.9 (CH); 122,2 (CH); 120.1 (CH); 117.3 (CH); 115.9 (CH); 114.1 (x 2) (CH); 113,0, (CH); 55.0 (CH_3); IR ν_{max} (cm^{-1}) 3692 (NH), 1425 (CO); HR ESMS *m/z* 423.0677 $[M+H]^+$. Calc. for $C_{22}H_{19}O_2N_2Br$, 423.0713.

(*E*)-1-(3-bromophenyl)-3-(3-(4-methoxystyryl)phenyl)urea (22): Yield 66 %; ^{1}H NMR (400 MHz, $DMSO_{d6}$) δ 8.88 (s, 1H); 8.74 (s, 1H); 7.89 (s, 1H); 7.68 (s, 1H); 7.56 (d, *J* = 8.0 Hz, 2H); 7.32-7.29 (m, 6H); 7.10 (d, *J* = 12.0 Hz, 2H); 6.94 (d, *J* = 12.0 Hz, 2H); 3.78 (s, 3H); ^{13}C NMR (100 MHz, $DMSO_{d6}$) δ 159.0 (C); 152.4 (C) ; 141.4 (C); 139.7 (C); 137.9 (C); 130.6 (CH); 129.5 (CH); 129.0 (CH); 128.0 (CH); 127.8 (CH); 126.2 (CH); 124.9 (CH); 121.7 (CH); 120.5 (CH); 117.5 (CH); 117.0 (CH); 116.1 (CH); 114.1 (CH); 55.1(CH_3); IR ν_{max} (cm^{-1}) 3544 (NH), 1425 (CO); HR ESMS *m/z* 423.0867 $[M+H]^+$. Calc. for $C_{22}H_{19}O_2N_2Br$, 423.0687.

(*E*)-1-(4-bromophenyl)-3-(3-(4-methoxystyryl)phenyl)urea (23): Yield 82 %; ^{1}H NMR (400 MHz, $DMSO_{d6}$) δ 8.88 (s, 1H); 8.75 (s, 1H); 7.66 (s, 1H); 7.56 (d, *J* = 8.0 Hz, 2H); 7.45 (s, 4H); 7.25-7.21 (m, 3H); 7.12 (dd, *J* = 16.0, 12 Hz, 2H); 6.95 (d, *J* = 12.0 Hz, 2H); 3.78 (s, 3H); ^{13}C NMR (100 MHz, $DMSO_{d6}$) δ 159.0 (C); 152.4 (C); 139.8 (C); 139.1 (C); 137.8 (C); 131.4 (CH); 129.5 (CH); 129.0 (CH); 128.0 (CH); 127.8 (CH); 126.2 (CH); 120.1 (CH); 120.0 (CH); 117.4 (CH); 116.1 (CH); 114.1 (CH); 113.1 (CH); 55.1 (CH_3); IR ν_{max} (cm^{-1}) 3695(NH), 1431 (CO); HR ESMS *m/z* 423.0698 $[M+H]^+$. Calc. for $C_{22}H_{19}O_2N_2Br$, 423.0656.

(*E*)-1-(2-methoxyphenyl)-3-(3-(4-methoxystyryl)phenyl)urea (24): Yield 31 %; ^{1}H NMR (400 MHz, $DMSO_{d6}$) δ 9.33 (s, 1H); 8.25 (s, 1H); 8.15 (d, *J* = 4.0 Hz, 1H); 7.68 (s, 1H); 7.56 (d, *J* = 8.0 Hz, 2H); 7.27 (dd, *J* = 8.0, 4.0 Hz, 2H); 7.25 (d, *J* = 8.0 Hz, 1H); 7.19 (d, *J* = 8.0 Hz, 2H); 7.18-6.90 (m, 5H); 3.89 (s, 3H); 3.78 (s, 3H); ^{13}C NMR (100 MHz, $DMSO_{d6}$) δ 159.0 (C); 152.4 (C); 147.6 (C); 140.0 (C); 137.9 (C); 129.6 (CH); 129.0 (CH); 128.7 (C); 128.0 (CH); 127.8 (x2 CH); 126.3 (CH); 121.8 (CH); 120.5 (CH); 119.7 (CH); 118.5 (CH); 117.0 (CH); 115.7 (CH); 114.5 (CH); 110.7 (CH); 55.7 (CH_3); 55.1 (CH_3); IR ν_{max} (cm^{-1}) 3313 (NH), 1593 (CO); HR ESMS *m/z* 375.1856 $[M+H]^+$. Calc. for $C_{23}H_{22}O_3N_2$, 375.1861.

(*E*)-1-(3-methoxyphenyl)-3-(3-(4-methoxystyryl)phenyl)urea (25): Yield 45 %; ^{1}H NMR (400 MHz, $DMSO_{d6}$) δ 8.73 (s, 1H); 8.69 (s, 1H); 7.65 (s, 1H); 7.56 (d, *J* = 8.0 Hz, 2H); 7.28-7.20 (m, 7H); 6.95 (d, *J* = 8.0 Hz, 3H); 6.56 (d, *J* = 12.0 Hz, 1H); 3.78 (s, 3H); 3.74 (s, 3H); ^{13}C NMR (100 MHz, $DMSO_{d6}$) δ (C) 158.4 (C); 152.3 (C); 147.0 (C); 140.0 (C); 138.1 (C); 129.6 (2xCH); 129.4 (CH); 129.2 (C); 128.5 (CH); 128.0 (CH); 121.7 (CH); 117.8 (CH); 116.7 (CH); 113.4 (CH); 110.2 (CH); 107.0 (CH); 103.7 (CH); 54.7 (CH_3); 54.6 (CH_3); IR ν_{max} (cm^{-1}) 3307 (NH), 1595 (CO); HR ESMS *m/z* 375.1887 $[M+H]^+$. Calc. for $C_{23}H_{22}O_3N_2$, 375.1866.

(*E*)-1-(4-methoxyphenyl)-3-(3-(4-methoxystyryl)phenyl)urea (26): Yield 70 %; ^{1}H NMR (400 MHz, $DMSO_{d6}$) δ 8.55 (s, 1H); 8.45 (s, 1H); 8.23 (s, 1H); 7.99 (d, *J* = 8.0 Hz, 2H); 7.90 (d, *J* = 12.0 Hz, 2H); 7.83 (d, *J* = 12.0 Hz, 1H); 7.67 (t, *J* = 8.0 Hz, 2H); 7.62 (d, *J* = 8.0 Hz, 1H); 7.53 (s, 1H); 7.39 (d, *J* = 8.0 Hz, 2H); 7.32 (d, *J* = 12.0 Hz, 2H); 4.27 (s, 3H); 4.32 (s, 3H); ^{13}C NMR (100 MHz, $DMSO_{d6}$) δ (C) 158,4 (C); 154.4 (C); 152.6 (C); 140.0 (C); 137.7 (C); 132.6 (2xCH); 129.9 (CH); 129.6 (C); 128.9 (CH); 128.7 (CH); 128.3 (CH); 121.6 (CH); 120.0 (2xCH); 117.9 (CH); 116,9 (CH); 114,0 (CH), 113,7 (CH), 55,1 (2xCH_3); IR ν_{max} (cm^{-1}) 3320 (NH), 1565 (CO); HR ESMS *m/z* 375.1869 $[M+H]^+$. Calc. for $C_{23}H_{22}O_3N_2$, 375.1846.

1-(2-bromophenyl)-3-(3-(4-methoxyphenethyl)phenyl)urea (28): Yield 12 %; ^{1}H NMR (400 MHz, $DMSO_{d6}$) δ 9.38 (s, 1H), 8.09 (d, *J* =8.0 Hz 1H); 8.06 (s, 1H); 7.61 (d, *J* = 8.0 Hz, 2H); 7.33 (s, 1H); 7.29 (t, *J* = 8.9 Hz, 2H); 7.28 (d, *J* = 8.0 Hz, 1H); 7.18 (t, *J* = 8.0 Hz, 1H); 7.13 (d, *J* = 8.0 Hz, 2H); 7.02 (t, *J* = 8.0 Hz, 1H); 6.84 (d, *J* = 12.0 Hz, 1H); 6.82 (d, *J* = 8.0 Hz, 2 H); 3.70 (s, 3H); 2.81 (s, 4H); ^{13}C NMR (100 MHz, $DMSO_{d6}$) 157.4 (C); 152.3 (C); 142.2 (C); 141.4 (C); 139.3 (C); 133.3 (C); 130.7 (CH); 129.2 (2xCH); 128.6 (CH); 124.3 (CH); 122.3 (CH); 121.7 (C); 120.3 (CH); 118.3 (CH); 117.0 (CH); 116.0 (CH); 113.6 (2xCH); 54.9 (CH_3); 37.5 (CH_2); 36.1 (CH_2).IR ν_{max} (cm^{-1}) 3301 (NH), 1645 (CO); HR ESMS *m/z* 425.08778$[M+H]^+$. Calc. for $C_{22}H_{21}N_2O_2$, 425.0866.

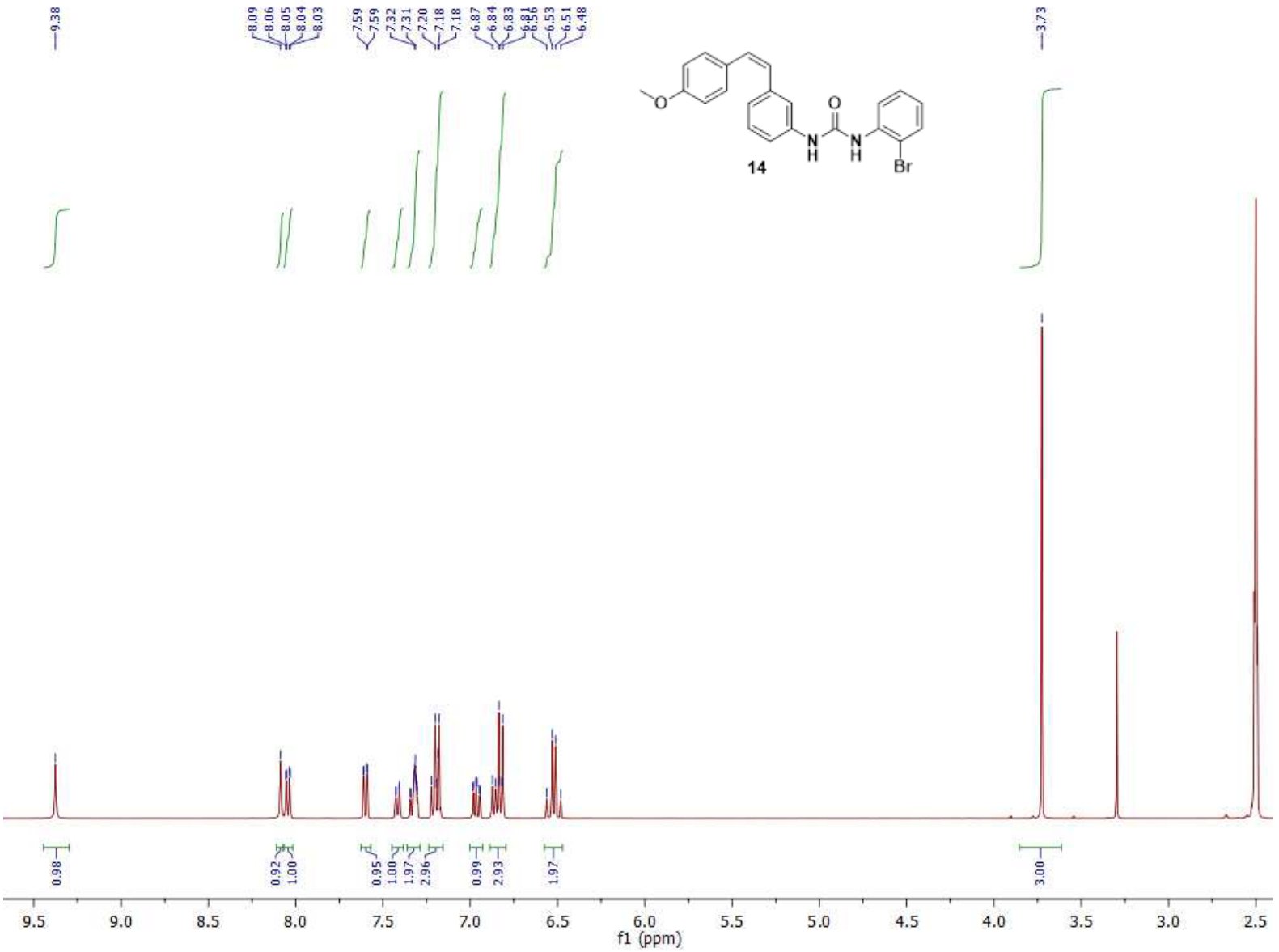
1-(3-bromophenyl)-3-(3-(4-methoxyphenethyl)phenyl)urea (29): Yield 14 %; ^{1}H NMR (400 MHz, $DMSO_{d6}$) δ 8.84 (s, 1H); 8.66 (s, H); 7.87 (t, *J* = 2.1 Hz, 1H); 7.4 (t, *J* = 2.1 Hz, 1H); 7.25-7.12 (m, 7H); 6.84-6.82 (m, 3H); 3.71 (s, 3H); 2.81 (s, 4H); ^{13}C NMR (100 MHz, $DMSO_{d6}$) δ 157.4 (C); 152.3 (C); 142.2 (C); 141.4 (C); 139.3 (C); 133.3 (C); 130.7 (CH); 129.2 (2xCH); 128.6 (CH); 124.3 (CH); 122.3 (CH); 121.7 (C); 120.3 (CH); 118.3 (CH); 117.0 (CH); 116.0 (CH); 113.6 (2xCH); 54.9 (CH_3); 37,5 (CH_2); 36,1 (CH_2).; IR ν_{max} (cm^{-1}) 3304 (NH), 1633 (CO); HR ESMS *m/z* 425.08473 $[M+Na]^+$. Calc. for $C_{22}H_{21}BrN_2O_2$, 425.0865.

1-(4-bromophenyl)-3-(3-(4-methoxyphenethyl)phenyl)urea (30): Yield 27 %; ^{1}H NMR (400 MHz, $DMSO_{d6}$) δ 8.80 (s, 1H); 8.70 (s, 1H); 7.42 (s, 4H); 7.31 (s, 1H); 7.30 (t, *J* = 7.5 Hz, 1H); 7.25 (m, 3H); 7.18 (d, *J* = 7.5 Hz, 3H); 3.71 (s, 3H); 2.81 (s, 4H); ^{13}C NMR (100 MHz, $DMSO_{d6}$) δ 157.4 (C); 152.4 (C); 142.2 (C); 139.4 (C); 139.2 (C); 133.3 (C); 131.5 (CH); 129.3 (2xCH); 128.6 (CH); 122.2 (CH); 122.0 (CH); 120.1 (CH); 118.3 (CH); 115.9 (CH); 113.6 (2xCH); 113.1 (CH); 54.9 (CH_3); 37.4 (CH_2); 36.1 (CH_2).; IR ν_{max} (cm^{-1}) 3290 (NH), 1638 (CO); HR ESMS *m/z* 425.0877 $[M-H]^-$. Calc. for $C_{22}H_{21}BrN_2O_2$, 425.0865.

1-(2-methoxyphenyl)-3-(3-(4-methoxyphenethyl)phenyl)urea (31): Yield 83 %; ^{1}H NMR (400 MHz, $DMSO_{d6}$) δ 9.24 (s, 1H); 8.20 (s, 1H); 8.13 (d, *J* = 8.0 Hz, 1H); 7.33 (s, 1H); 7.26 (d, *J* = 8.10Hz, 1H); 7.17-7.13 (m, 3H); 7.02-6.82 (m, 4H); 3.88 (s, 3H); 3.71 (s, 3H); 2.81 (s, 4H);^{13}C NMR (100 MHz, $DMSO_{d6}$) δ 157.6 (C); 152.6 (C); 147.9 (C); 142.4 (C); 139.8 (C); 133.5 (C); 129.5 (2xCH); 128.9 (CH); 128.8 (C); 122.2 (CH); 122.1 (CH); 120.7 (CH); 118.5 (CH); 118.1 (CH); 115.8 (CH); 113.8 (2xCH); 110.9 (CH); 55.9 (CH_3); 55.1 (CH_3); 37.6 (CH_2); 36.2 (CH_2); IR ν_{max} (cm^{-1}) 3301 (NH), 1645 (CO); HR ESMS *m/z* 377.1867 $[M+H]^+$. Calc. for $C_{23}H_{24}O_3N_2$, 377.1865.

1-(3-methoxyphenyl)-3-(3-(4-methoxyphenethyl)phenyl)urea (32): Yield 69 %; ^{1}H NMR (400 MHz, $DMSO_{d6}$) δ 8.70 (s, 1H); 8.56 (s, 1H); 7.33 (s, 1H); 7.25 (dd, *J* = 8.0, 4.0 Hz, 1H); 7.19-7.13 (m, 5H); 6.93 (d, *J* = 8.0 Hz, 1H); 6.83 (d, *J* = 8.0 Hz, 3H); 6.55 (d, *J* = 8.0 Hz, 1H); 3.73 (s, 3H); 3.71 (s, 3H); 2.80 (s, 4H); ^{13}C NMR (100 MHz, $DMSO_{d6}$) δ 159.7 (C); 157.4 (C); 152.4 (C); 142.2 (C); 141.0 (C); 139.5 (C); 133.4 (C); 129.5 (CH); 129.3 (2xCH); 128.6 (CH); 122.0 (CH); 118.2 (CH); 115.8 (CH); 113.6 (2xCH); 110.5 (CH); 107.2 (CH); 103.9 (CH); 54.9 (2xCH_3); 37.5 (CH_2); 36.1 (CH_2); IR ν_{max} (cm^{-1}) 3304 (NH), 1633 (CO); HR ESMS *m/z* 377.1866 $[M+H]^+$. Calc. for $C_{23}H_{24}N_2O_3$, 377.1865.

1-(4-methoxyphenyl)-3-(3-(4-methoxyphenethyl)phenyl)urea (33): Yield 98 %; ^{1}H NMR (400 MHz, $DMSO_{d6}$) δ 8.5 (s, 1H); 8.4 (s, H); 7.3 (t, *J* = 8.2 Hz, 3H); 7.2 (d, *J* = 8.2 Hz, 1H); 7.1 (t, *J* = 8.3 Hz, 3H); 6.8 (m, 5H); 3.7 (s, 3H); 2.8 (s, 4H); ^{13}C NMR (100 MHz, $DMSO_{d6}$) δ 157.4 (C); 154.4 (C); 152.7 (C); 142.1 (C); 139.8 (C); 133.4 (C); 132.7 (C); 129.2 (2xCH); 128.5 (CH); 121.8 (CH); 119.9 (2xCH); 118.0 (CH); 115.7 (CH); 113.9 (2xCH); 113.6 (2xCH); 55.1 (CH_3); 54.9 (CH_3); 37.5 (CH_2); 36.1 (CH_2); IR ν_{max} (cm^{-1}) 3290 (NH), 1638 (CO); HR ESMS *m/z* 377.1868 $[M-H]^-$. Calc. for $C_{23}H_{24}N_2O_3$, 377.1865.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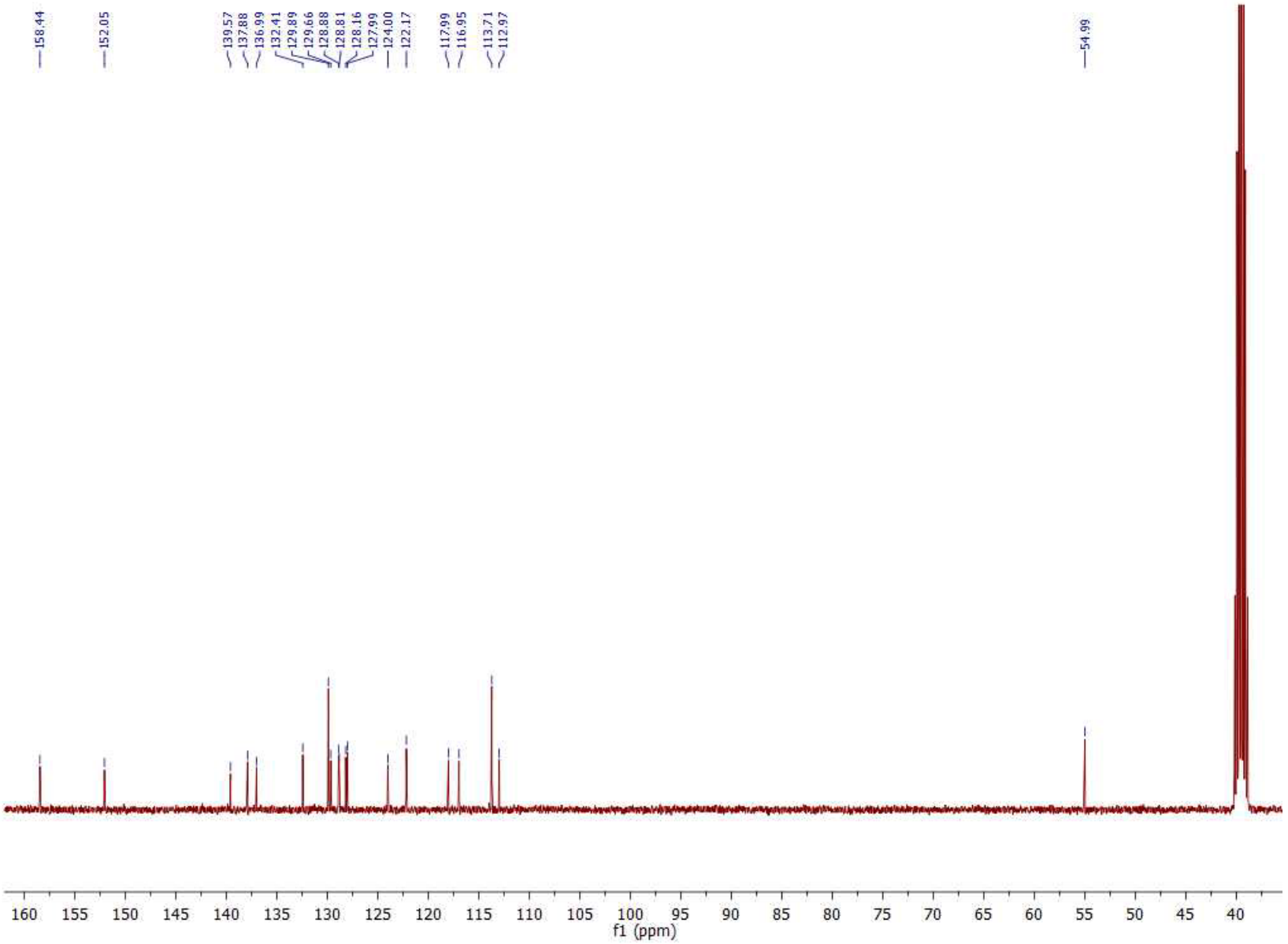
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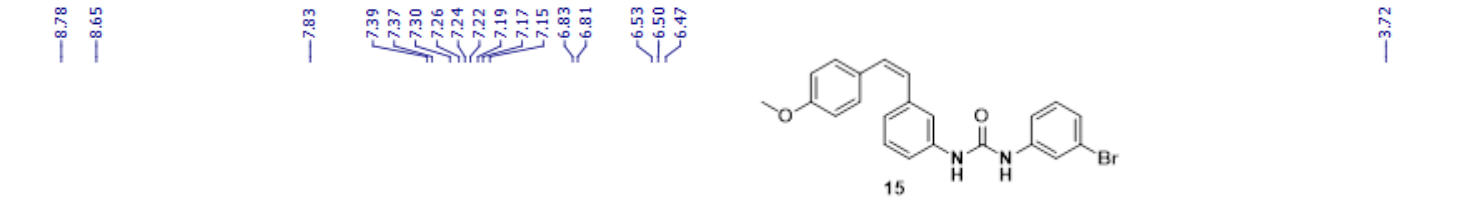
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H
Br
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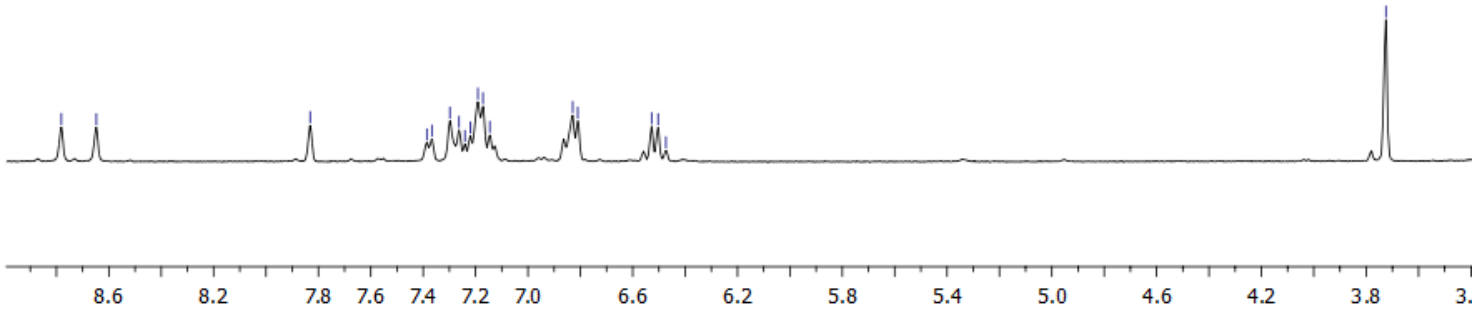
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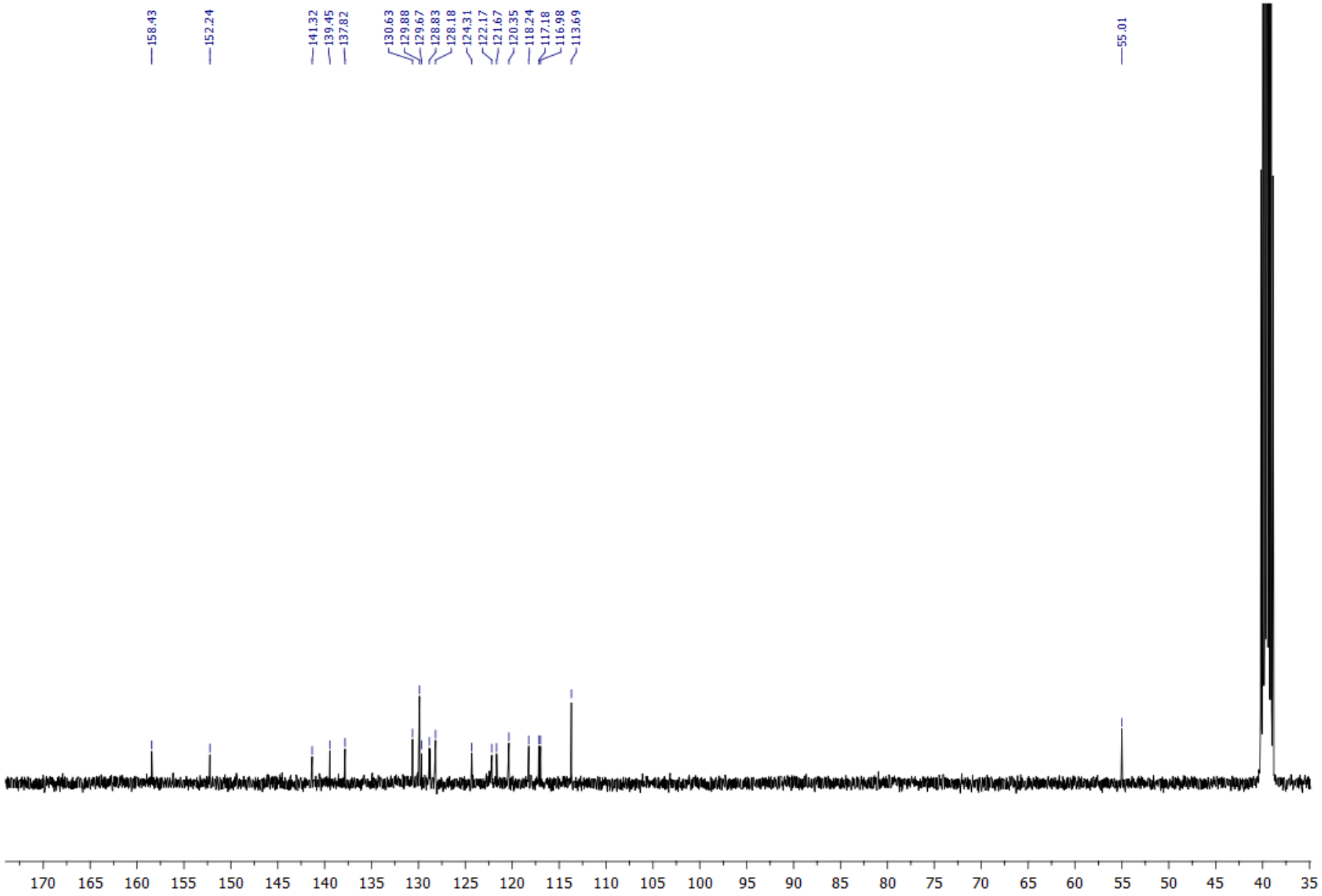
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121.67
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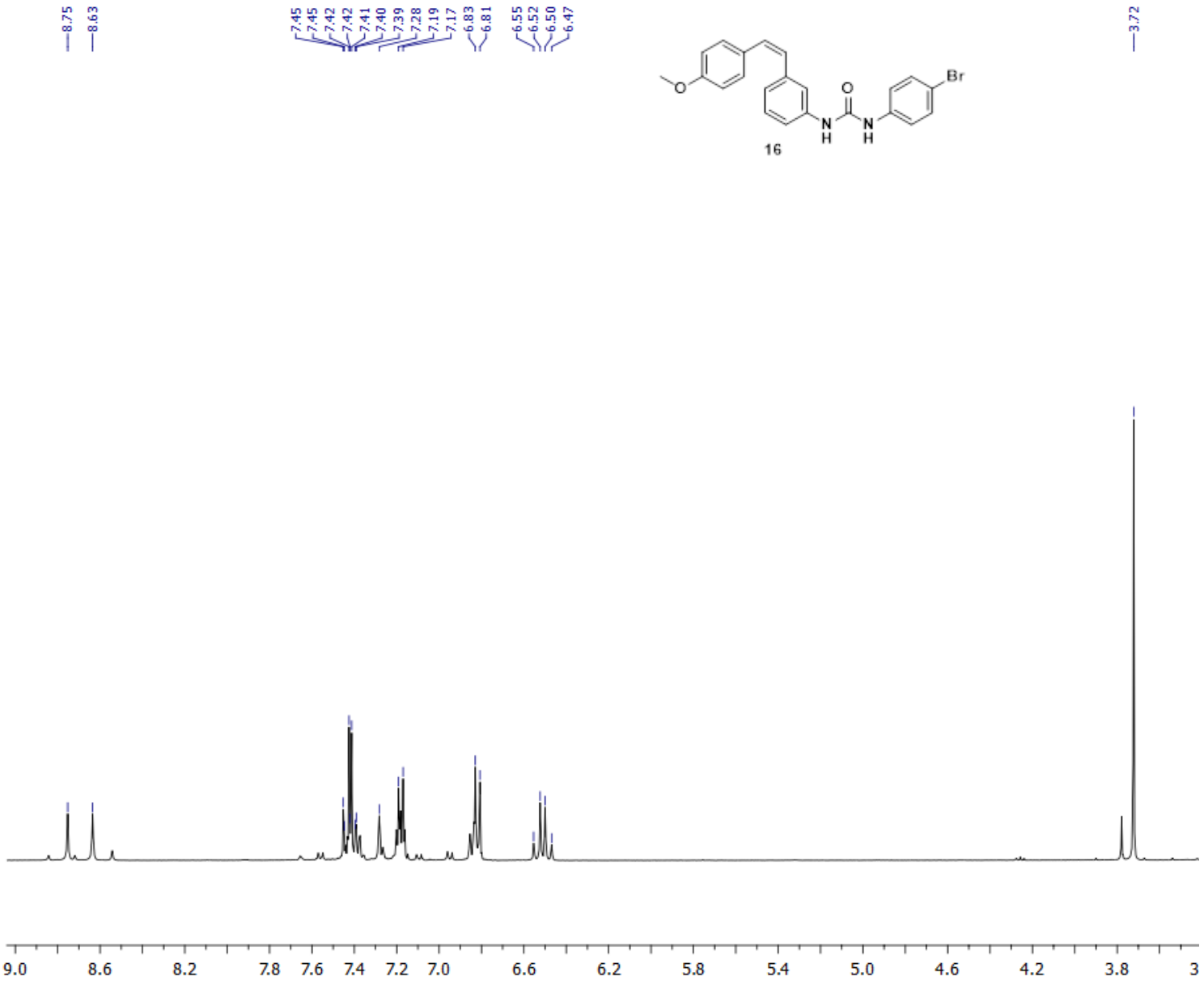
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6.52
6.50
6.47
3.72
O
Br
N
H
O
N
H
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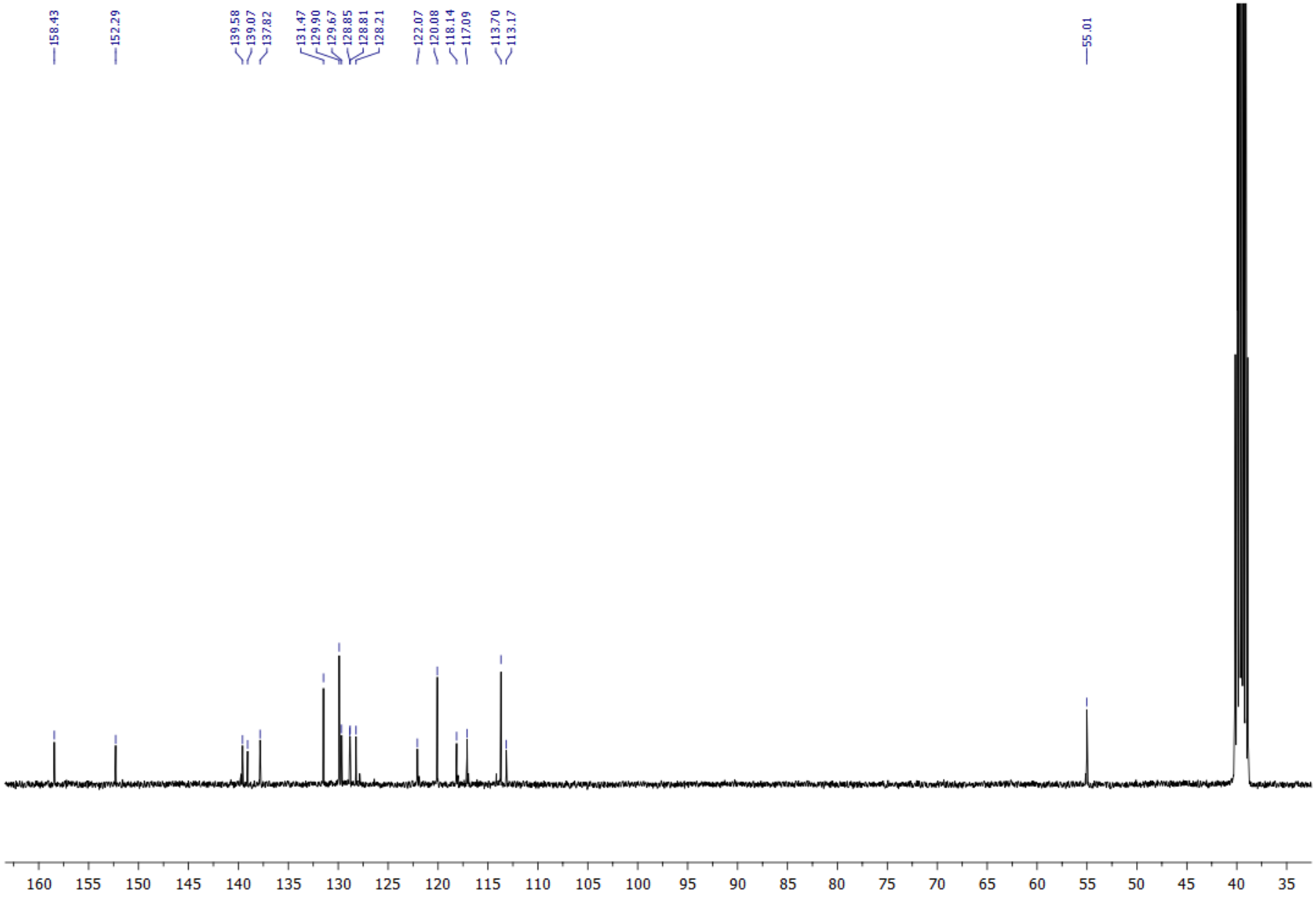
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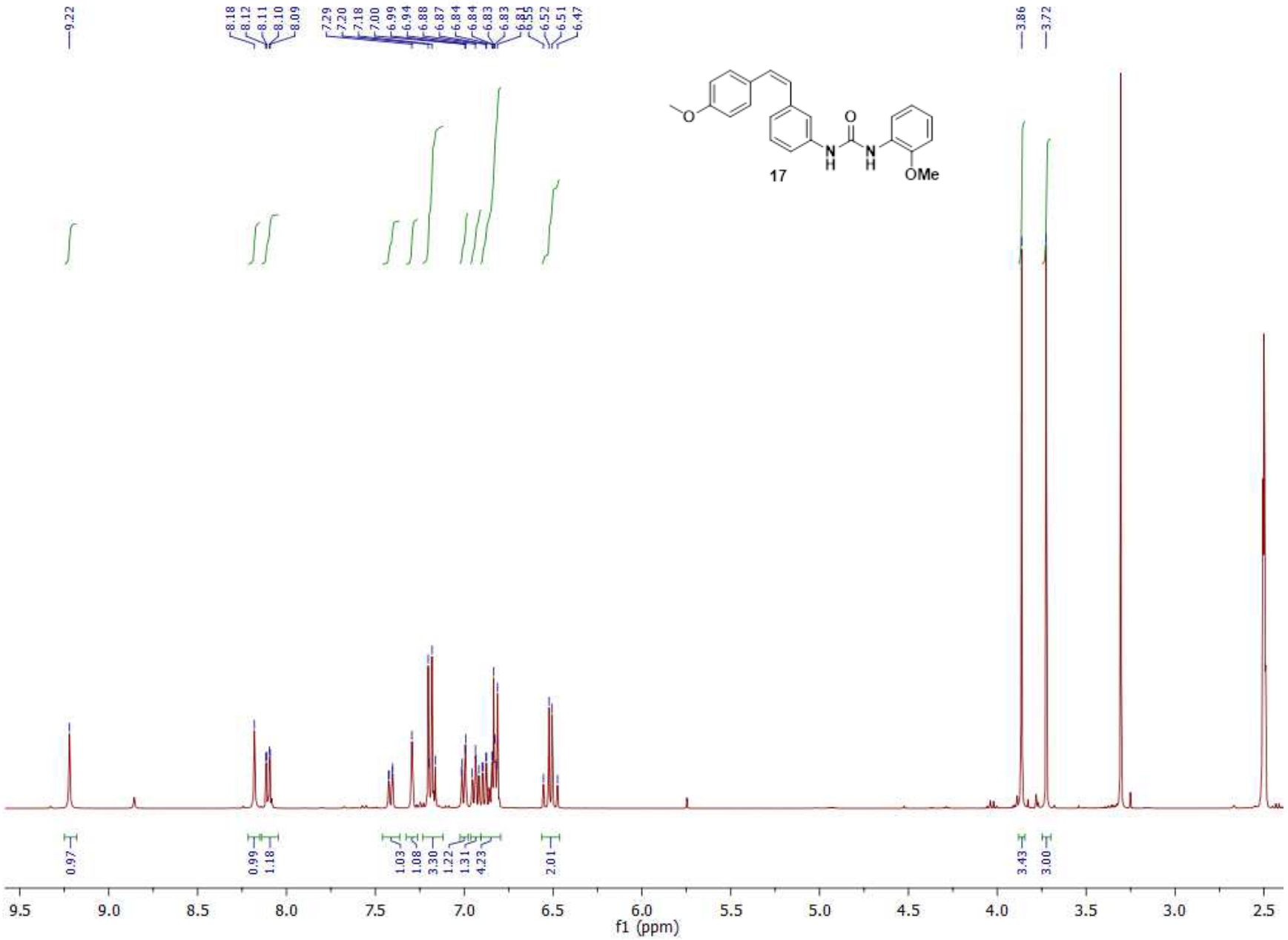
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6.84
6.84
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6.83
6.81
6.55
6.52
6.51
6.47
3.86
3.72
O
O
N
H
N
H
OMe
17
0.97
0.99
1.18
1.03
1.08
3.30
1.22
1.31
4.23
2.01
3.43
3.00
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9.0
8.5
8.0
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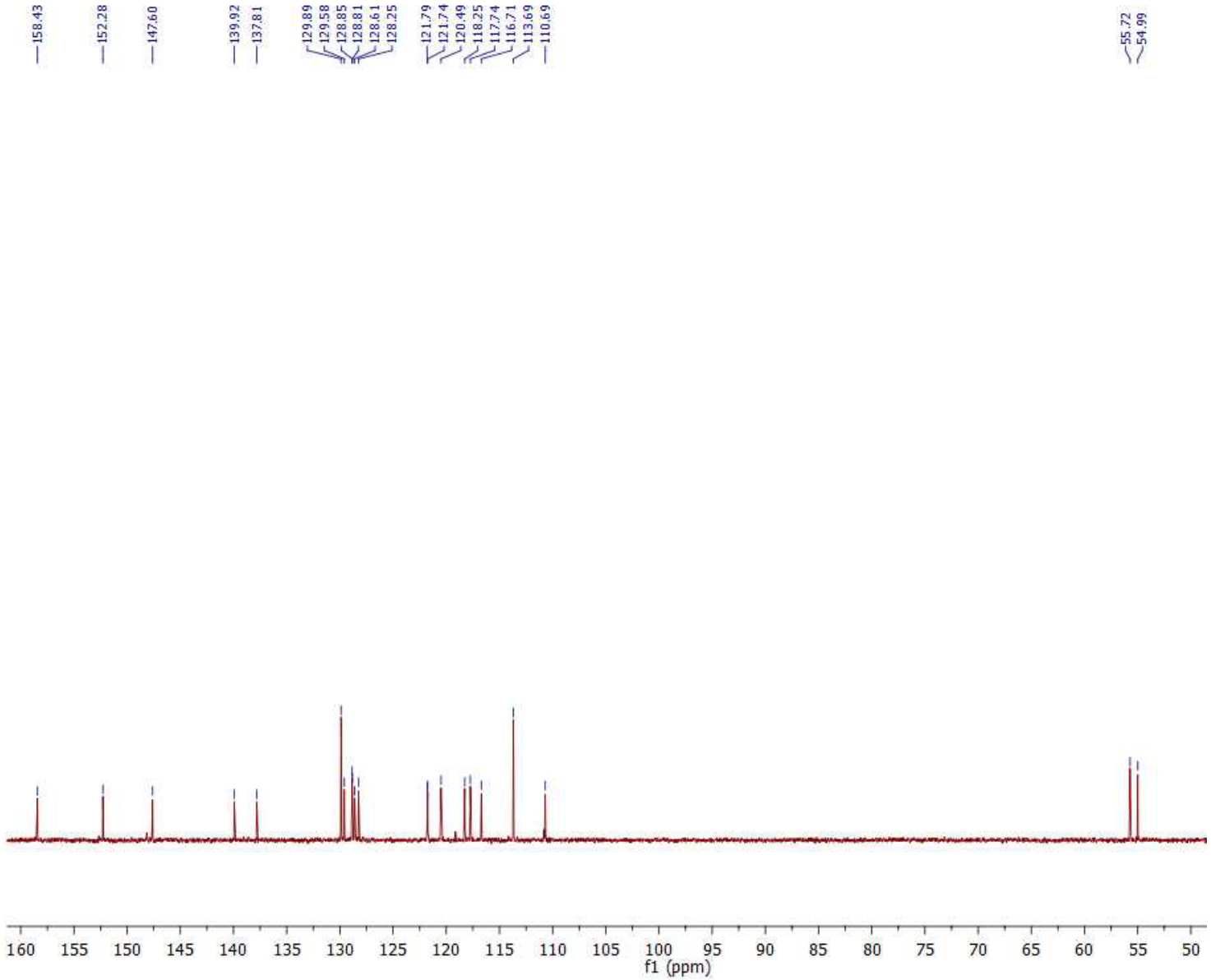
2.5
f1 (ppm)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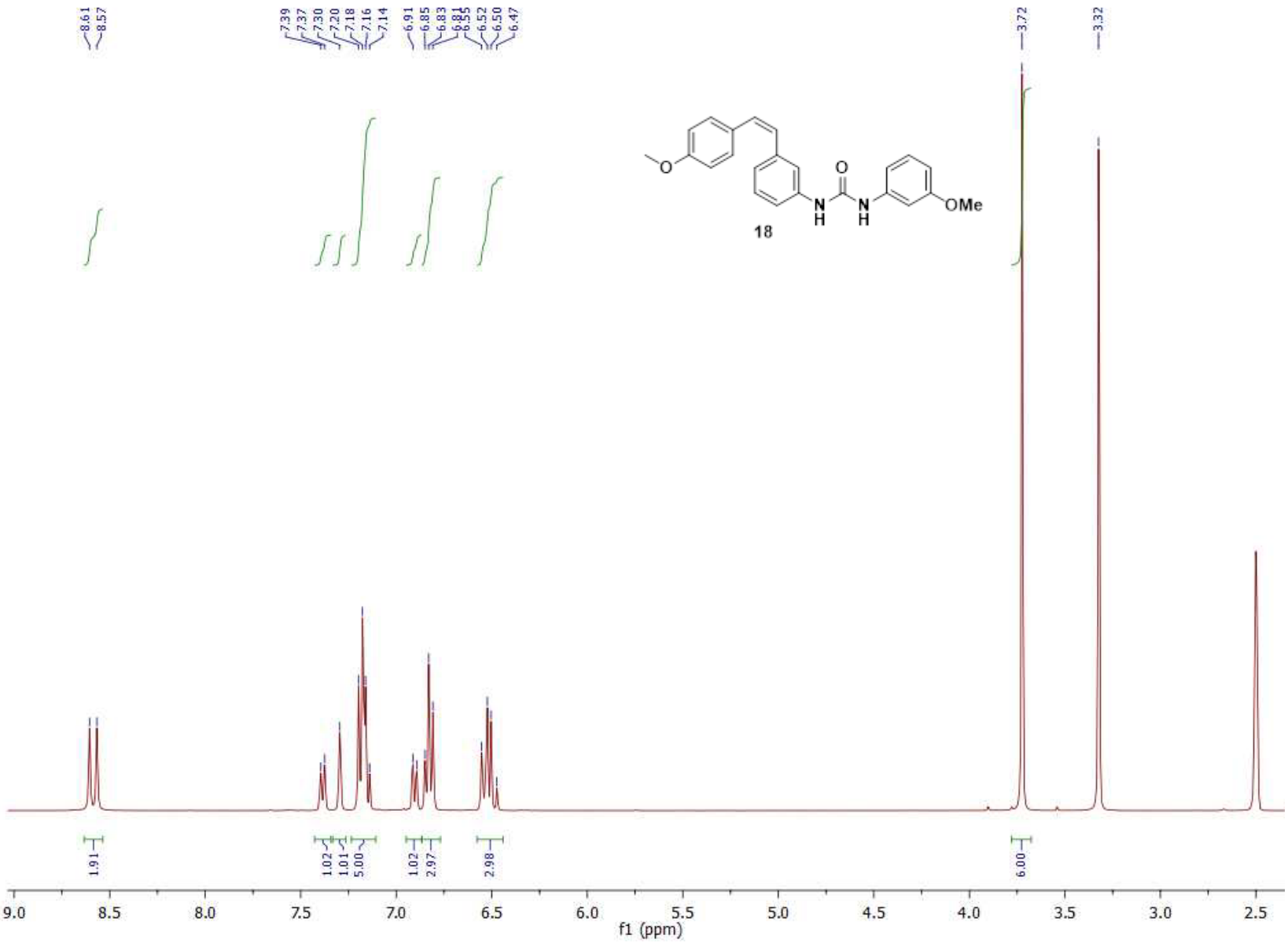
f1 (ppm)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6.81
6.55
6.52
6.50
6.47
3.72
3.32
O
N
H
O
N
H
OMe
18
1.91
1.02
1.01
5.00
1.02
2.97
2.98
6.00
9.0
8.5
8.0
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3.5
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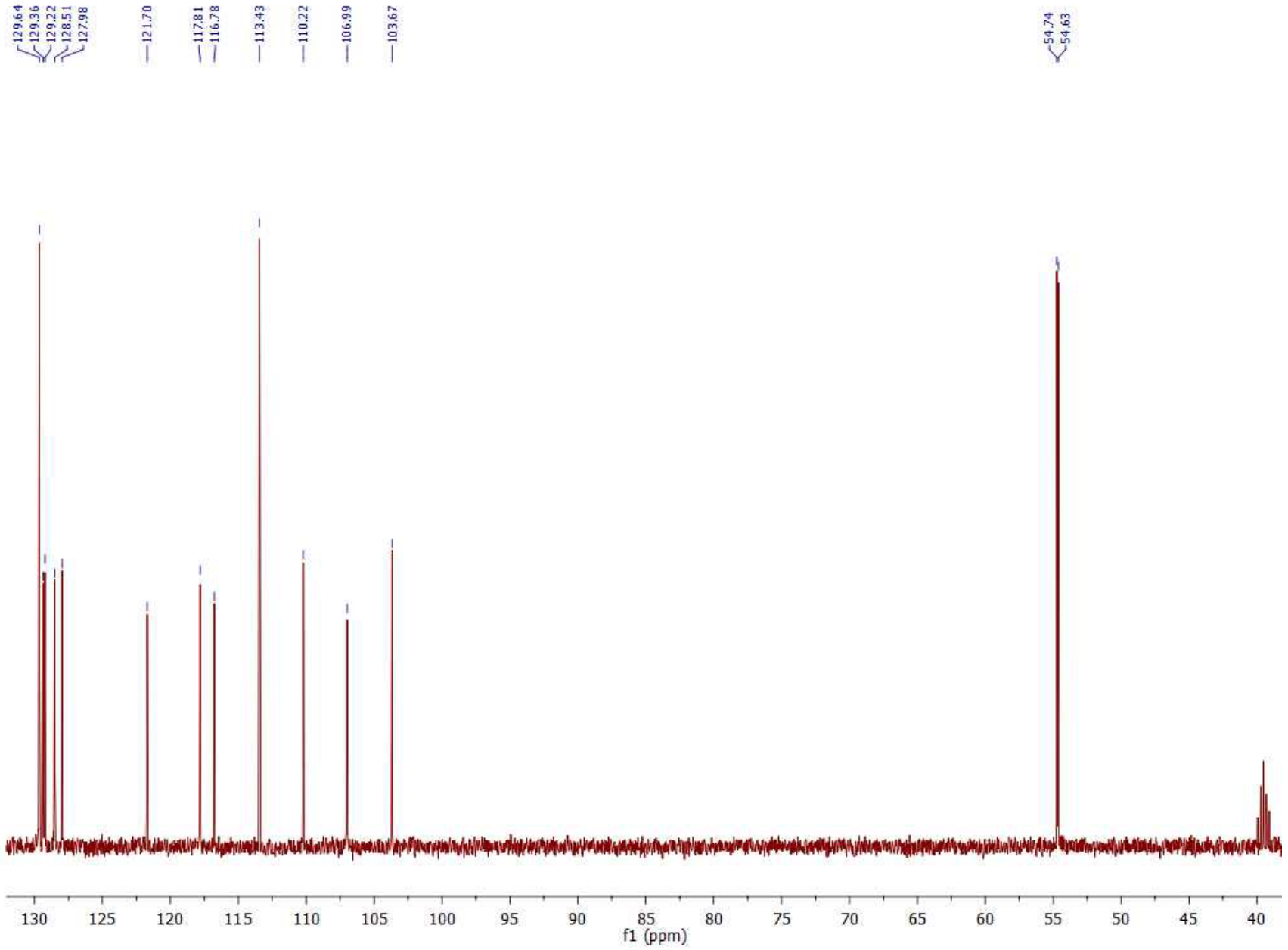
2.5
f1 (ppm)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54.63
130
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100
95
90
85
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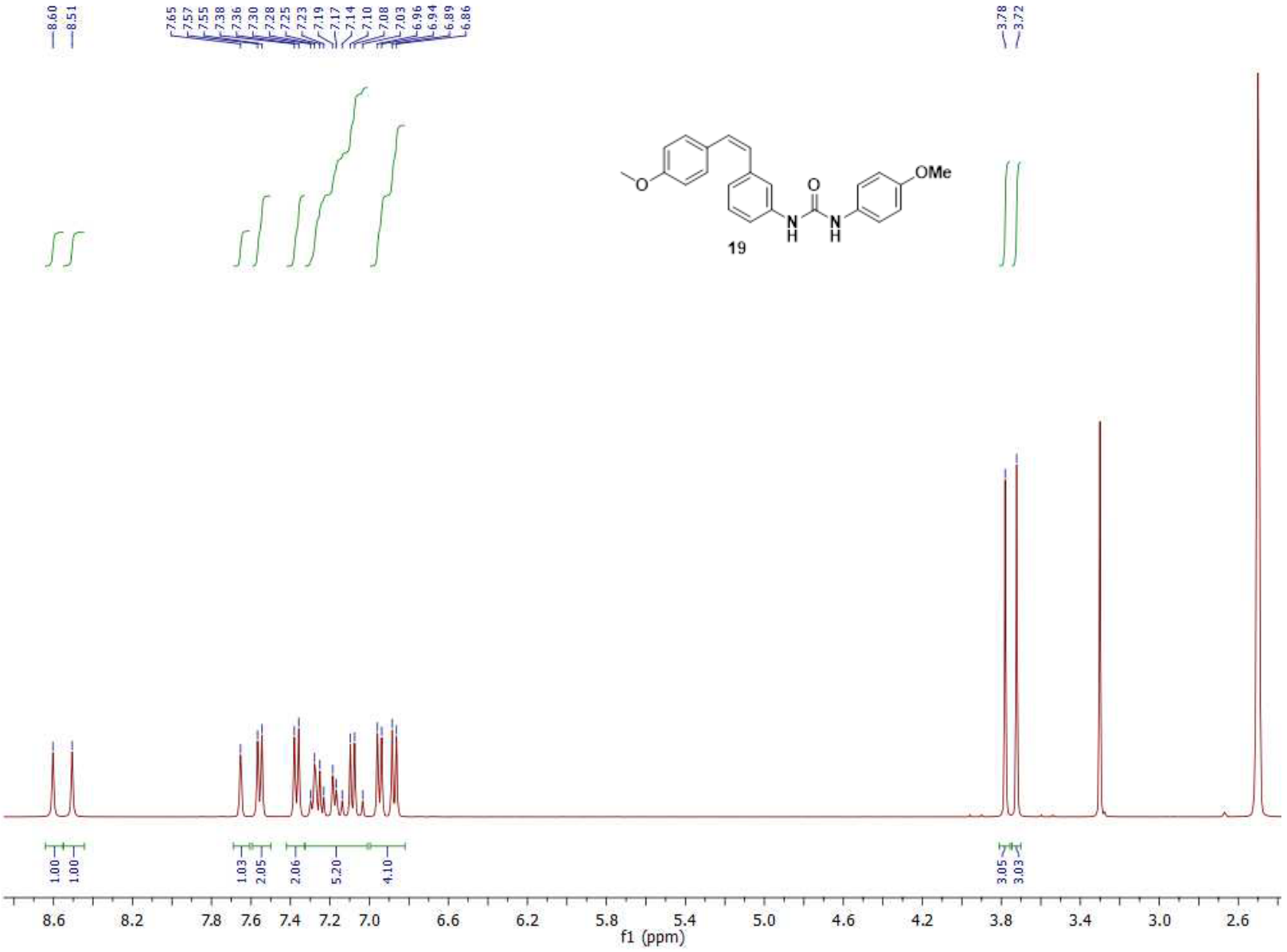
75
70
65
60
55
50
45
40
f1 (ppm)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7.14
7.10
7.08
7.03
6.96
6.94
6.89
6.86
3.78
3.72
O
N
H
O
N
H
OMe
19
1.00
1.00
1.03
2.05
2.06
5.20
4.10
3.05
3.03
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8.2
7.8
7.6
7.4
7.2
7.0
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6.2
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5.4
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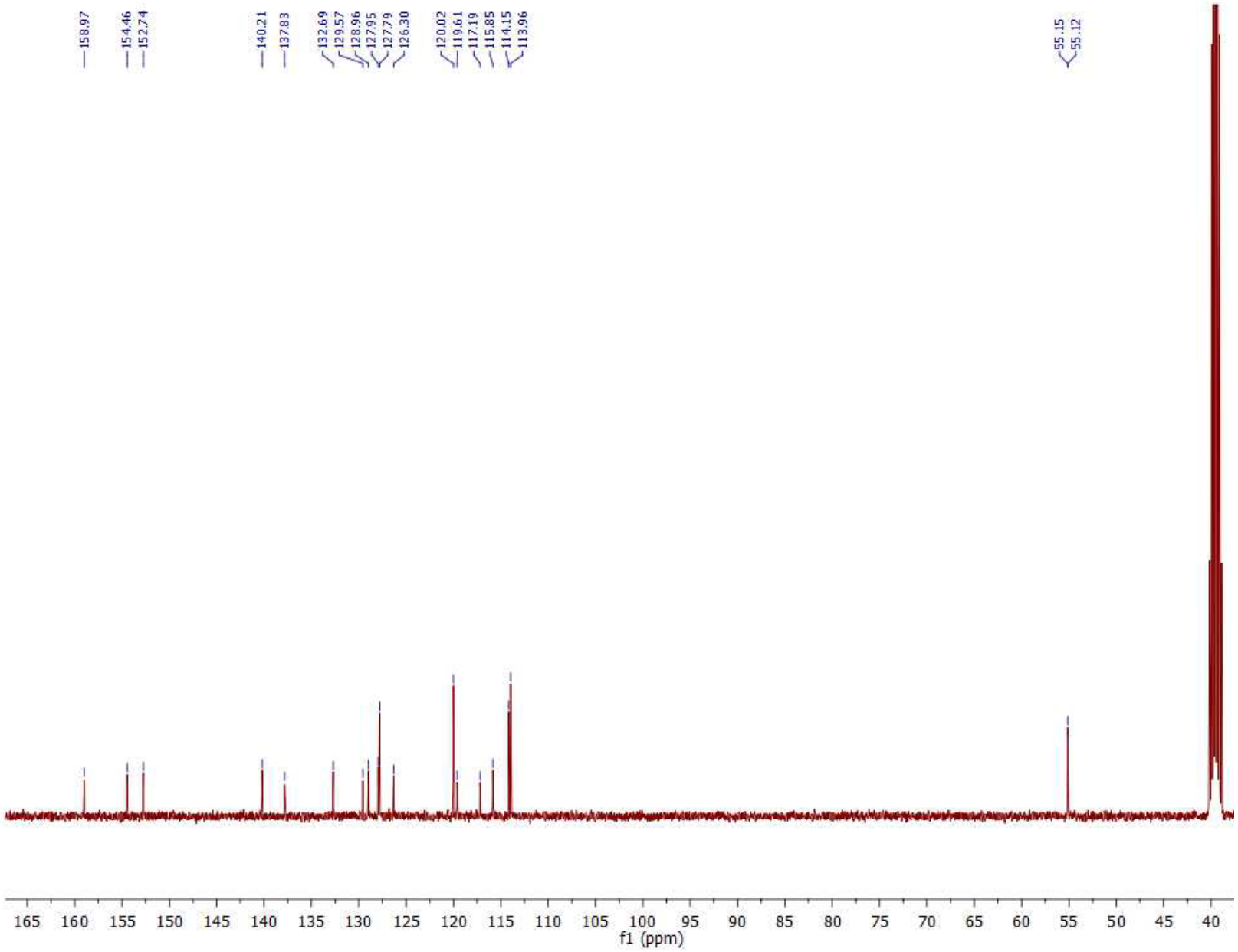
4.6
4.2
3.8
3.4
3.0
2.6
f1 (ppm)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117.19
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55.15
55.12
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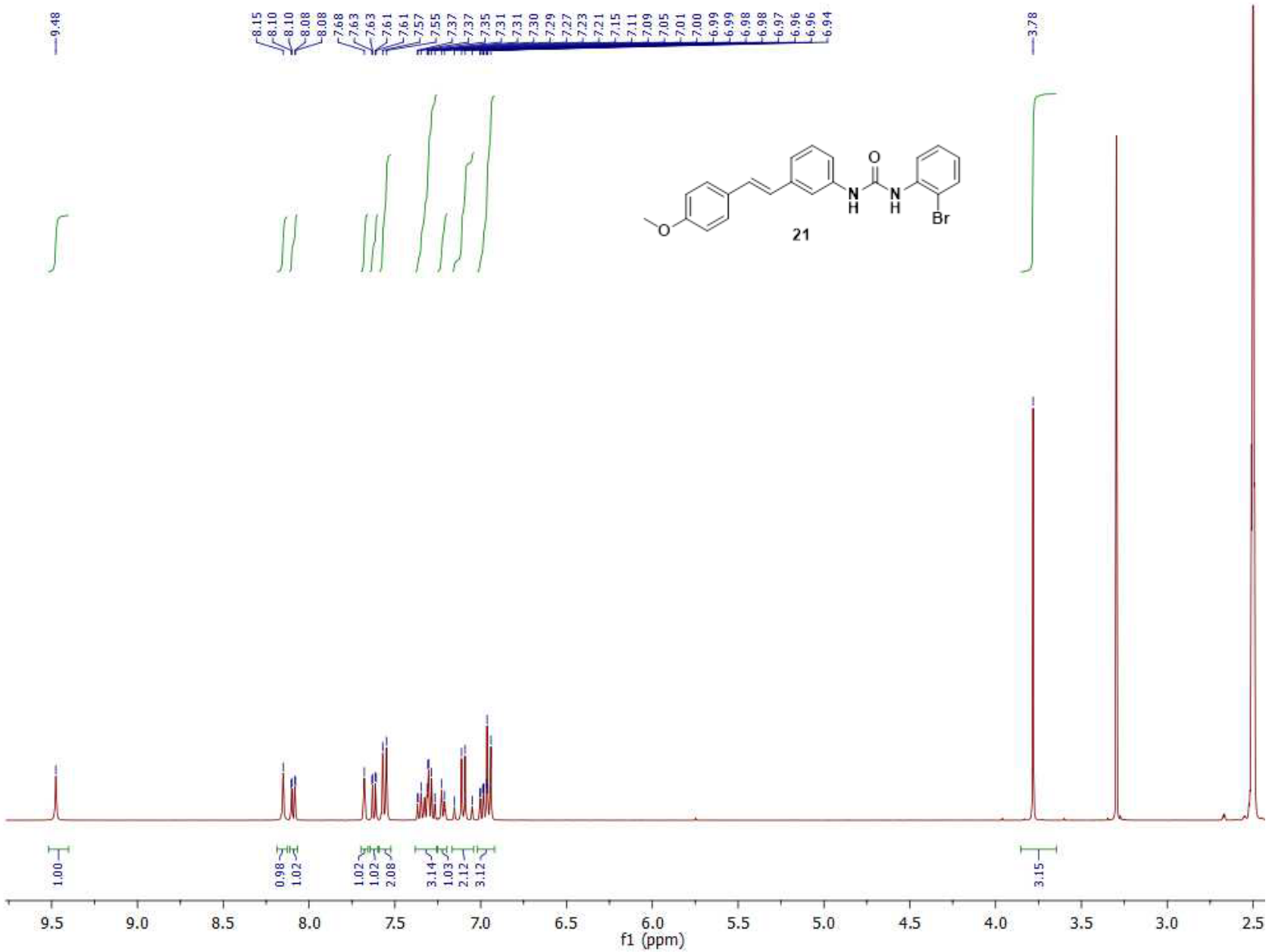
f1 (ppm)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7.05
7.01
7.00
6.99
6.99
6.98
6.98
6.97
6.96
6.96
6.94
3.78
O
N
H
N
H
Br
O
21
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0.98
1.02
1.02
1.02
2.08
3.14
1.03
2.12
3.12
3.15
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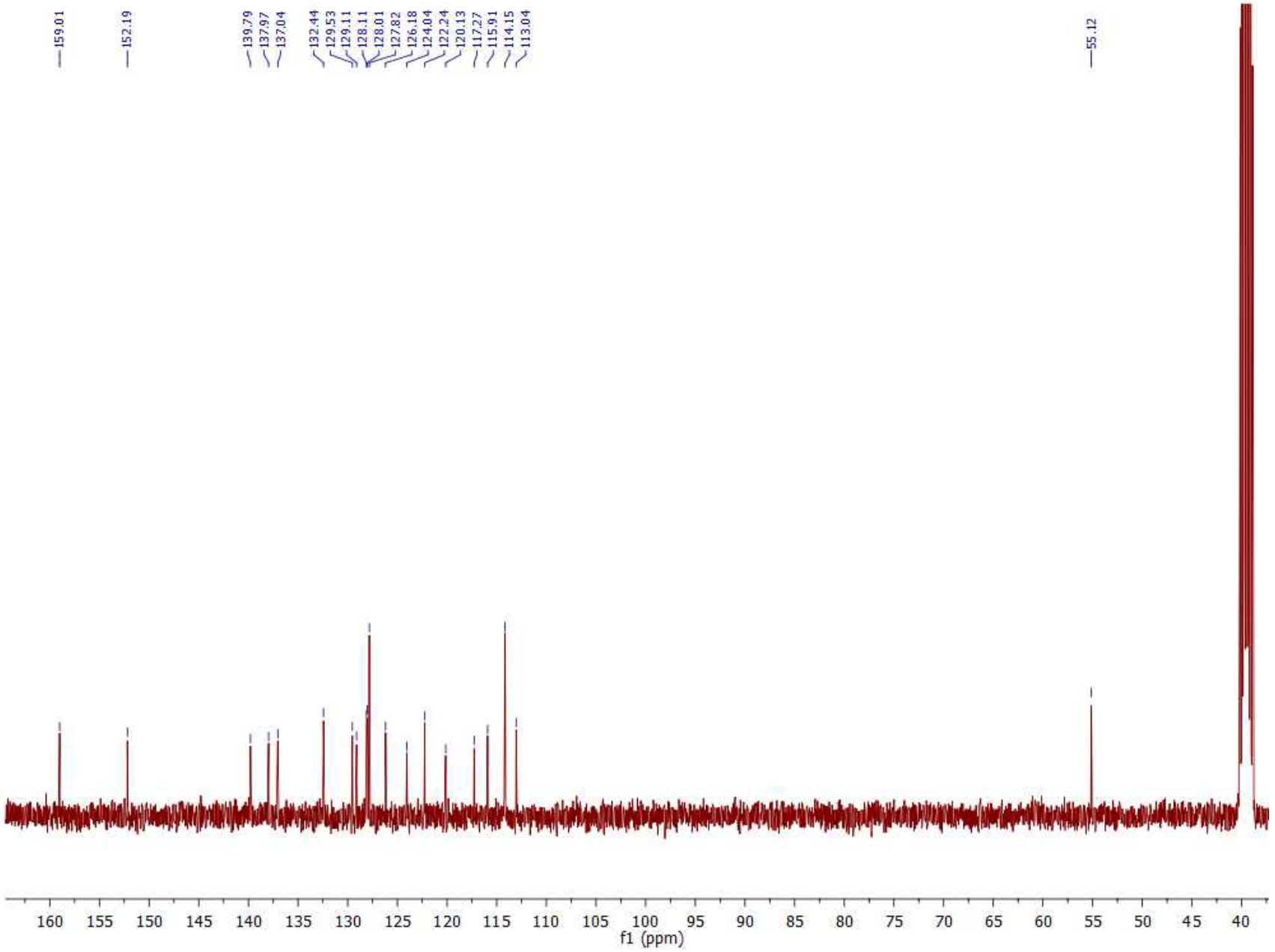
f1 (ppm)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120.13
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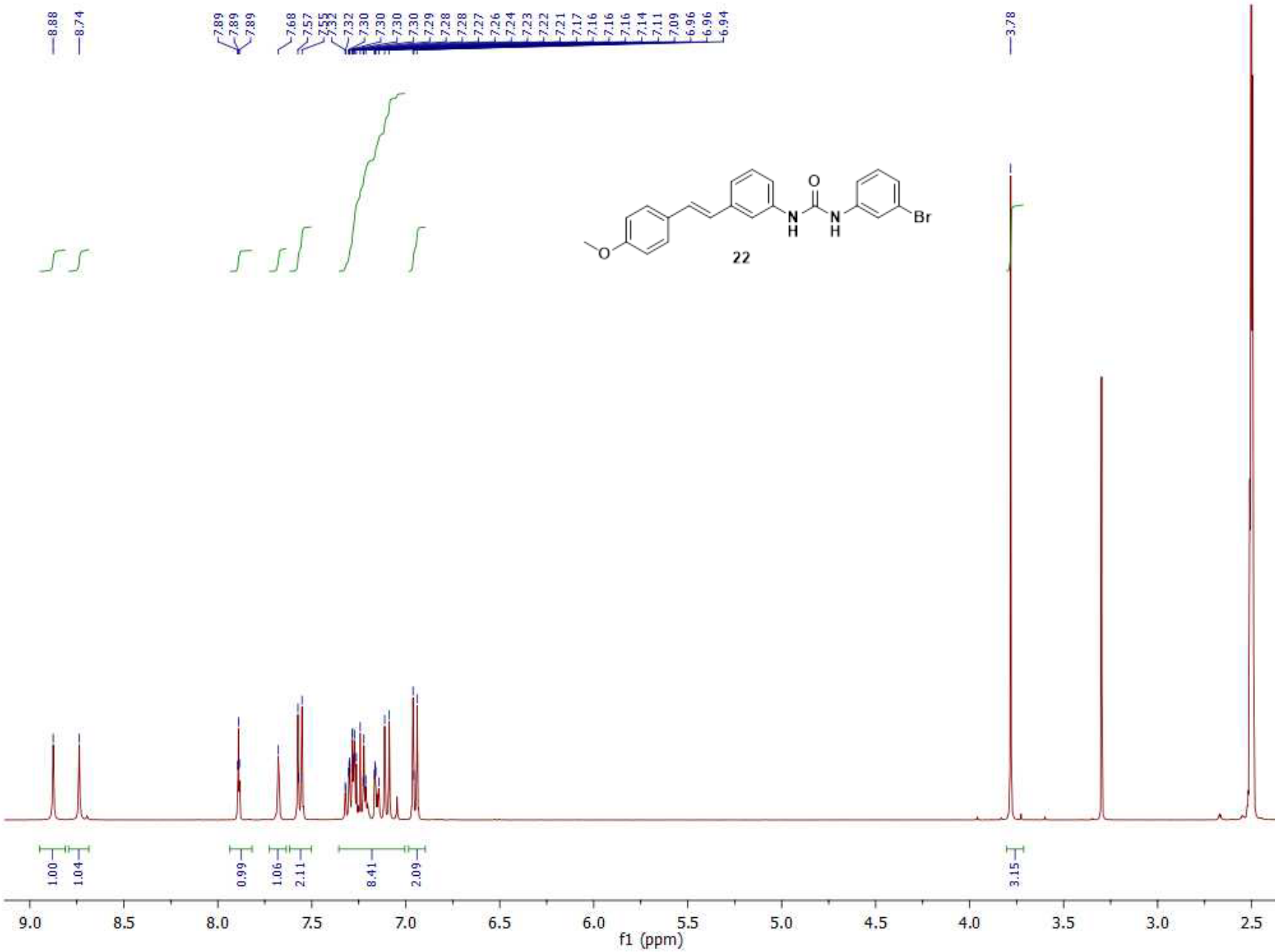
f1 (ppm)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7.27
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7.22
7.21
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7.16
7.14
7.11
7.09
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6.96
6.94
3.78
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H
N
H
Br
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2.09
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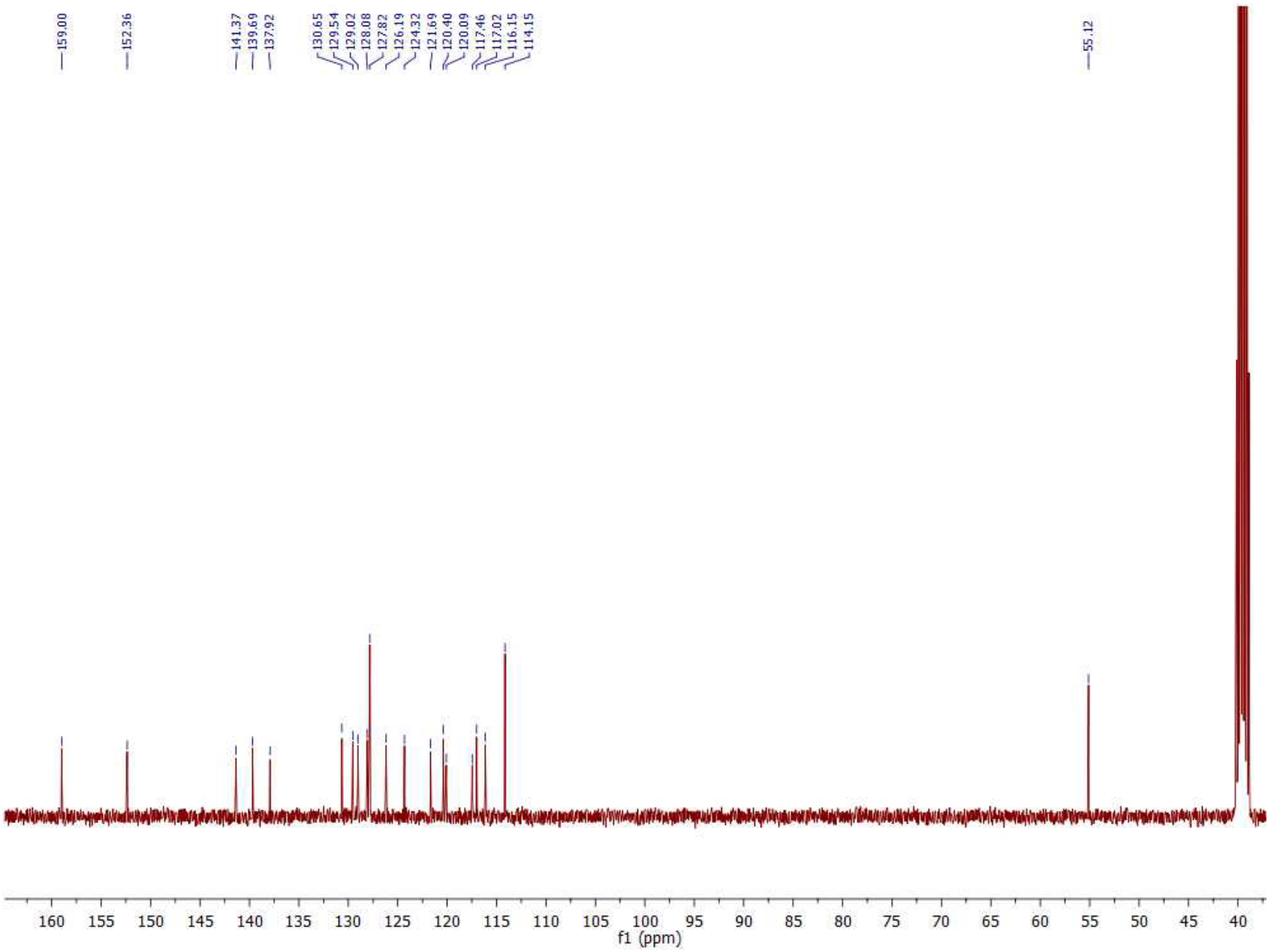
2.5
f1 (ppm)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120.09
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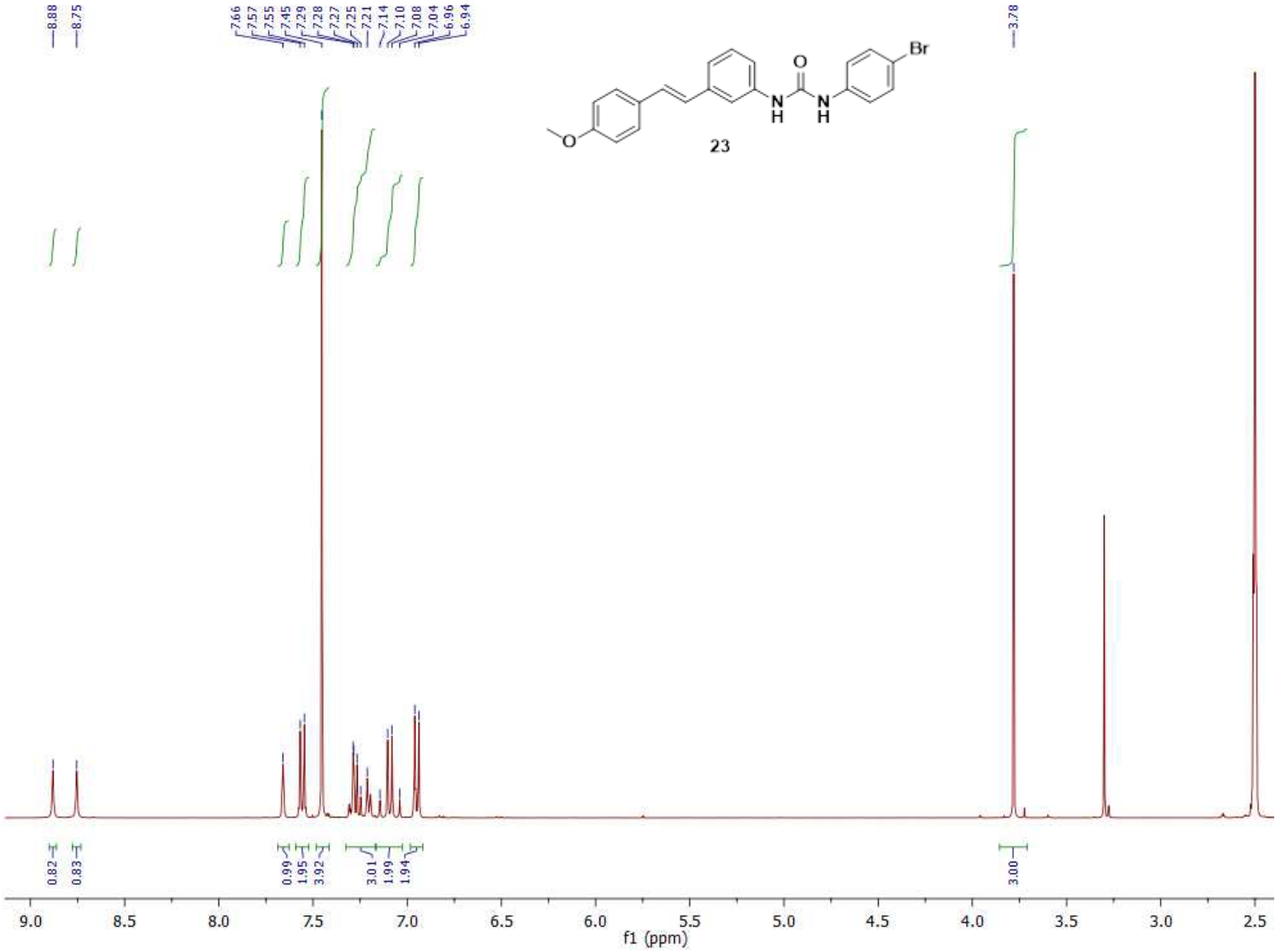
f1 (ppm)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7.08
7.04
6.96
6.94
3.78
Br
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N
H
N
H
O
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0.83
0.99
1.95
3.92
3.01
1.99
1.94
3.00
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8.0
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3.5
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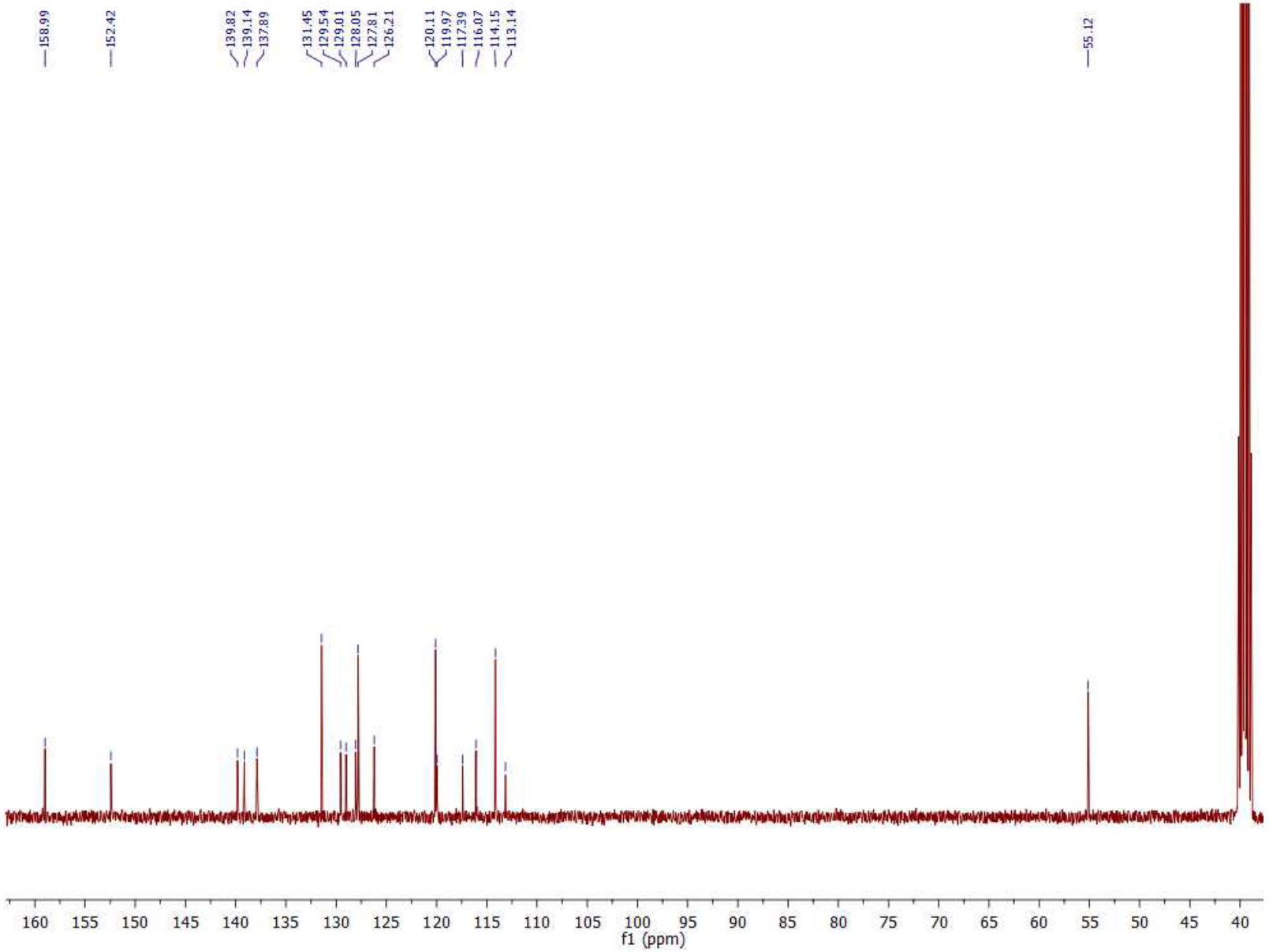
2.5
f1 (ppm)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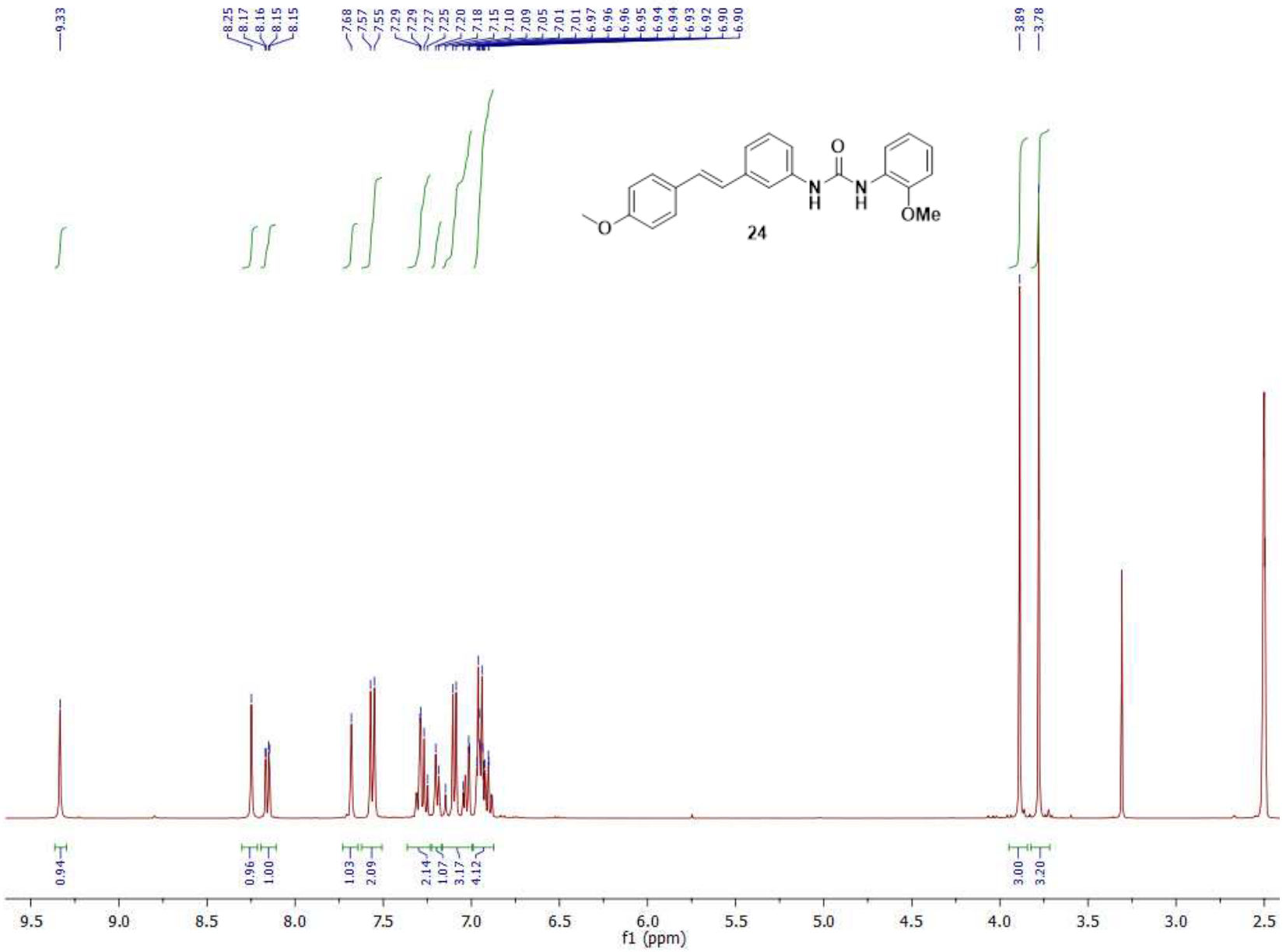
f1 (ppm)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7.18
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7.10
7.09
7.05
7.01
7.01
6.97
6.96
6.96
6.95
6.94
6.94
6.93
6.92
6.90
6.90
3.89
3.78
O
N
H
N
H
OMe
O
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0.96
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1.03
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2.14
1.07
3.17
4.12
3.00
3.20
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8.0
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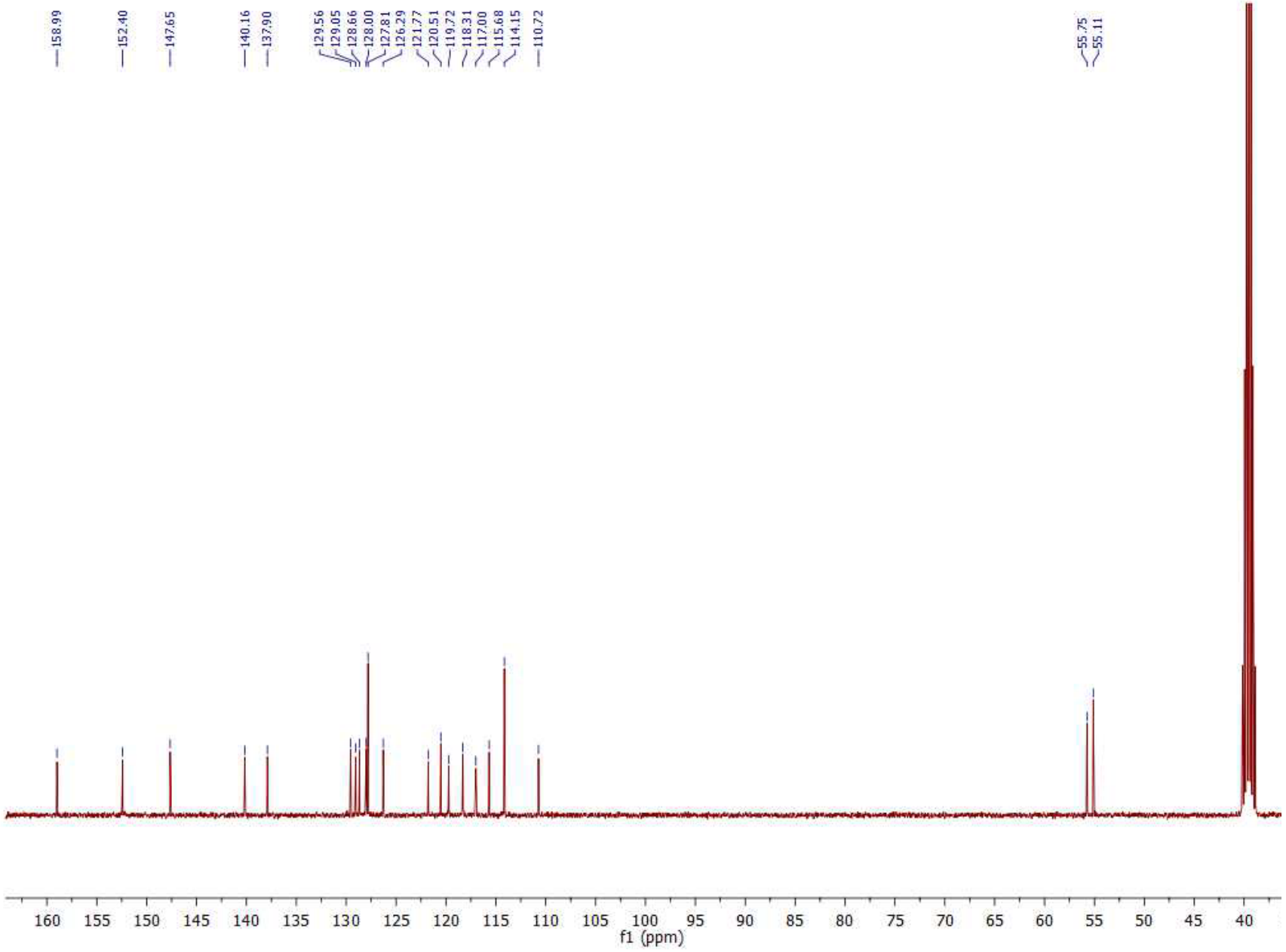
2.5
f1 (ppm)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118.31
117.00
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110.72
55.75
55.11
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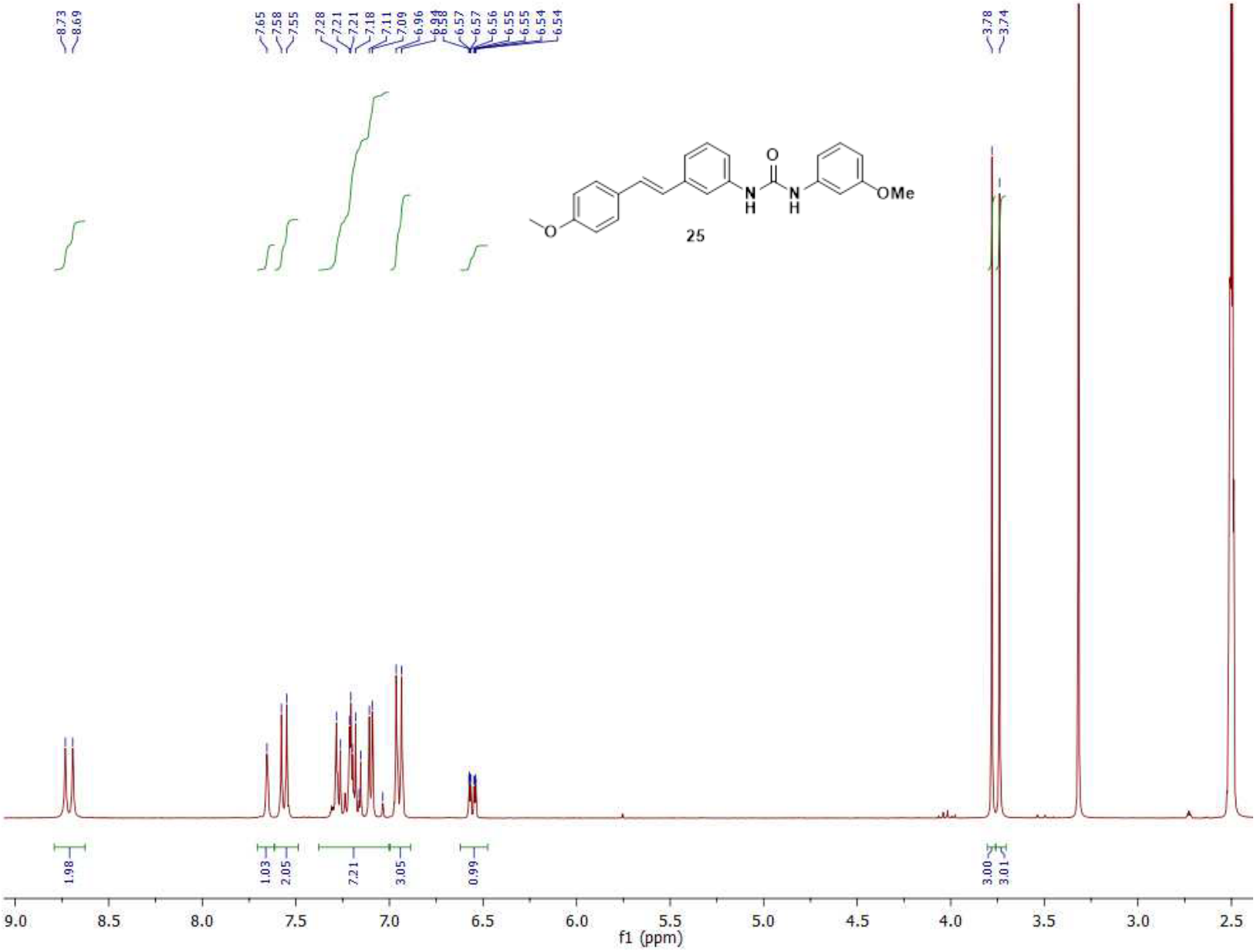
f1 (ppm)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6.58
6.57
6.57
6.56
6.55
6.55
6.54
6.54
3.78
3.74
O
N
H
N
H
OMe
O
25
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1.03
2.05
7.21
3.05
0.99
3.00
3.01
9.0
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8.0
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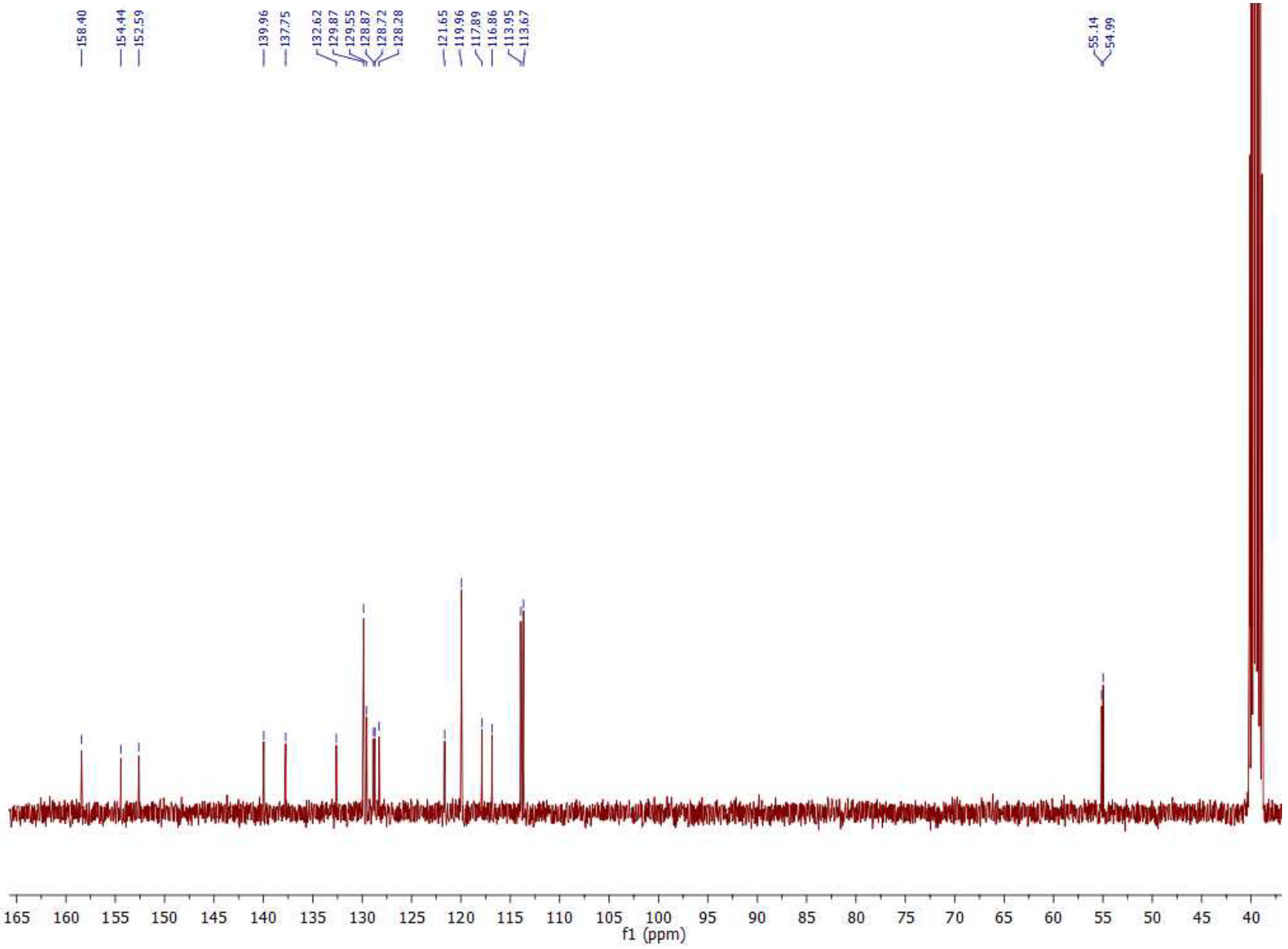
f1 (ppm)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117.89
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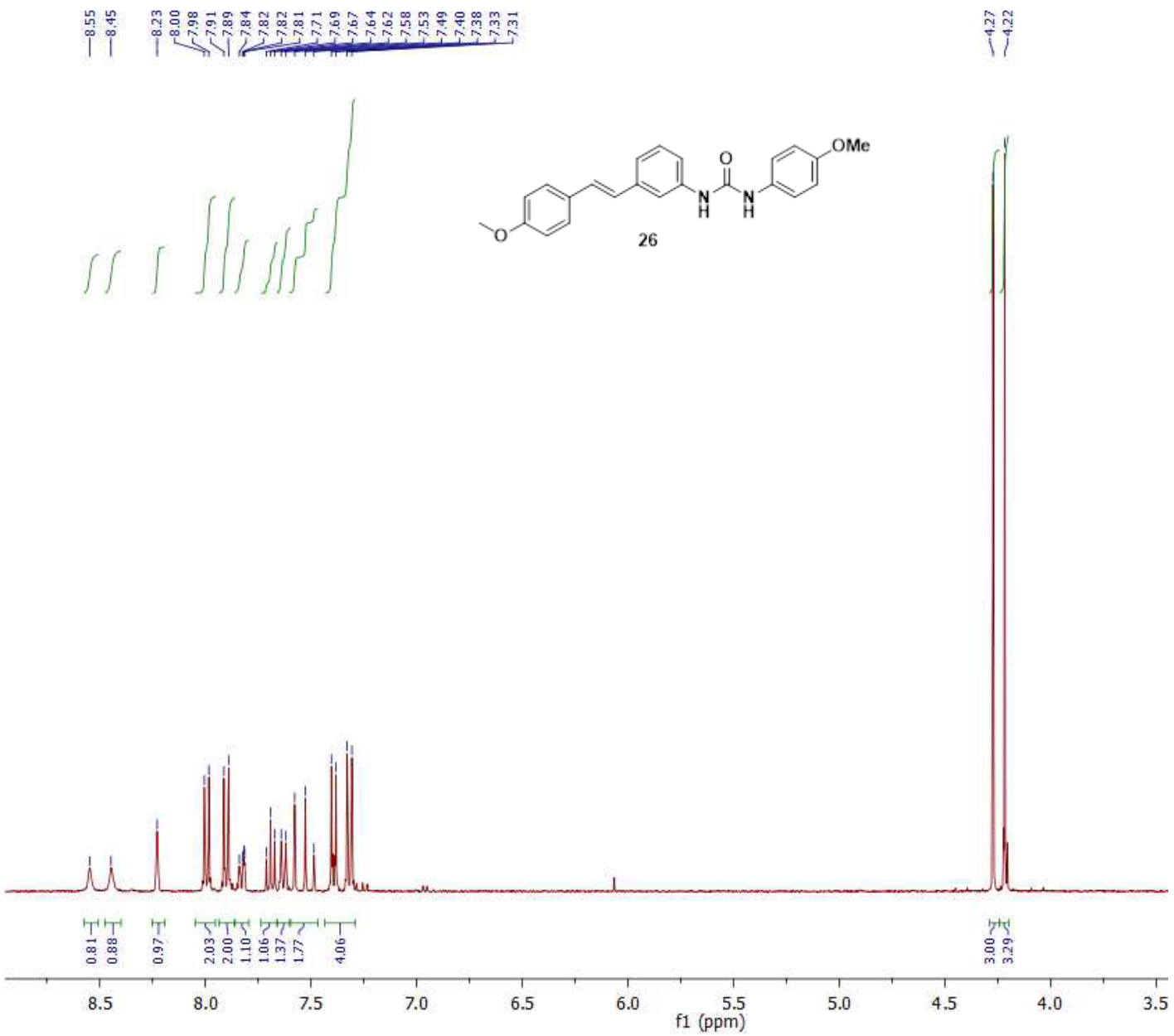
f1 (ppm)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7.53
7.49
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7.38
7.33
7.31
4.27
4.22
OMe
O
N
H
N
H
O
26
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0.88
0.97
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1.10
1.06
1.37
1.77
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3.00
3.29
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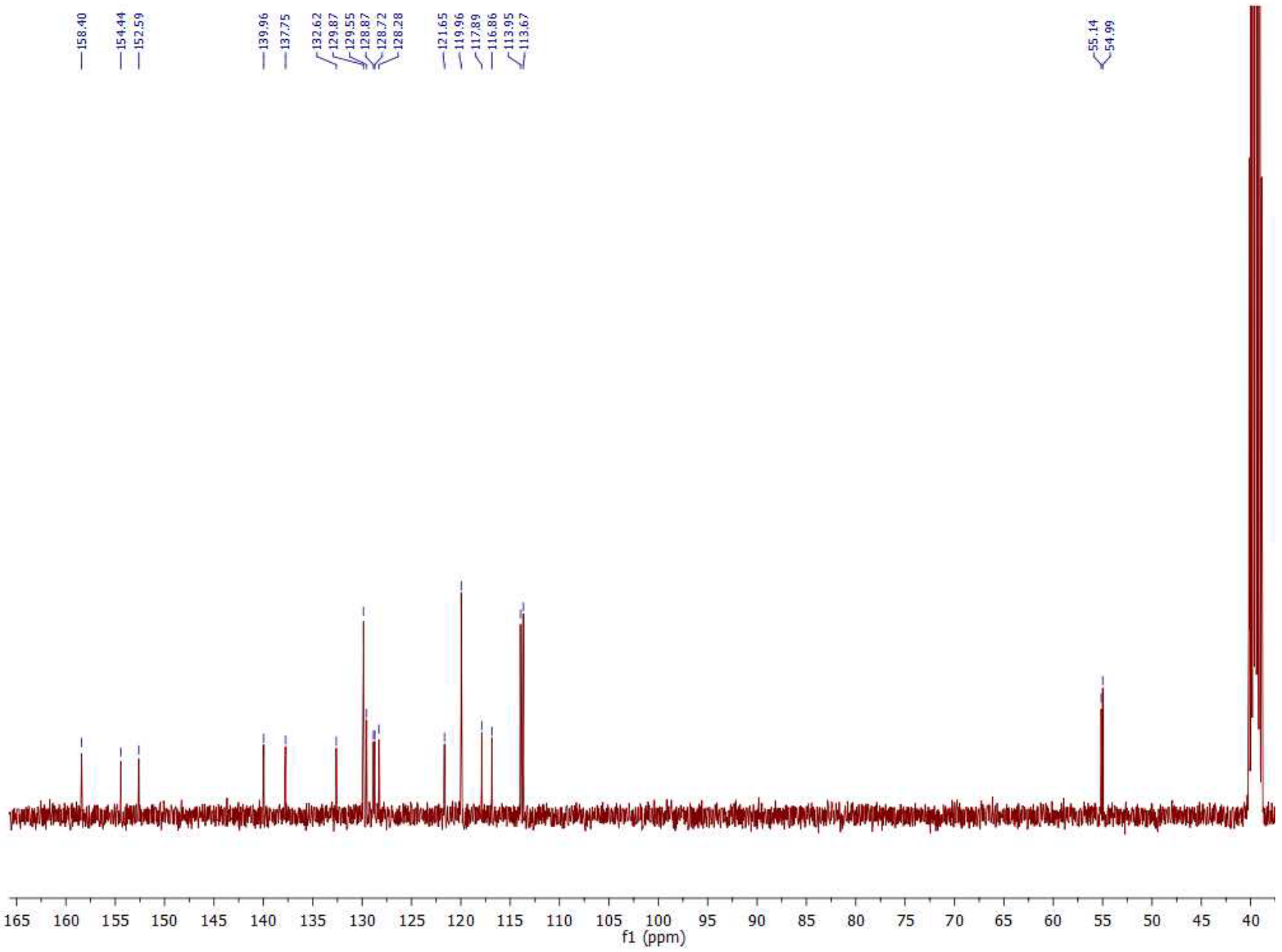
4.5
4.0
3.5
f1 (ppm)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119.96
117.89
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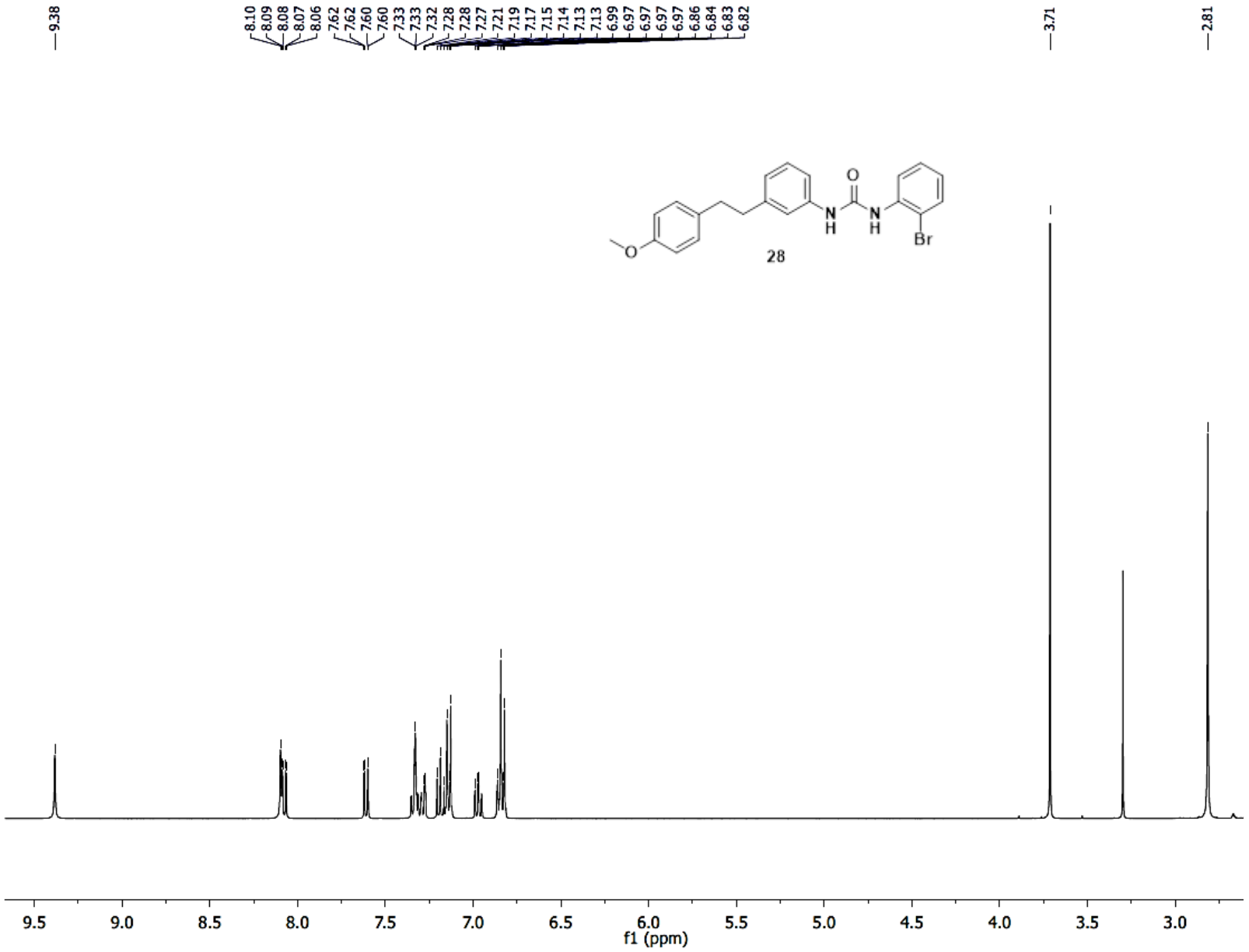
55.14
54.99
165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40
f1 (ppm)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7.13
7.13
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6.97
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6.84
6.83
6.82
3.71
2.81
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O
N
H
Br
28
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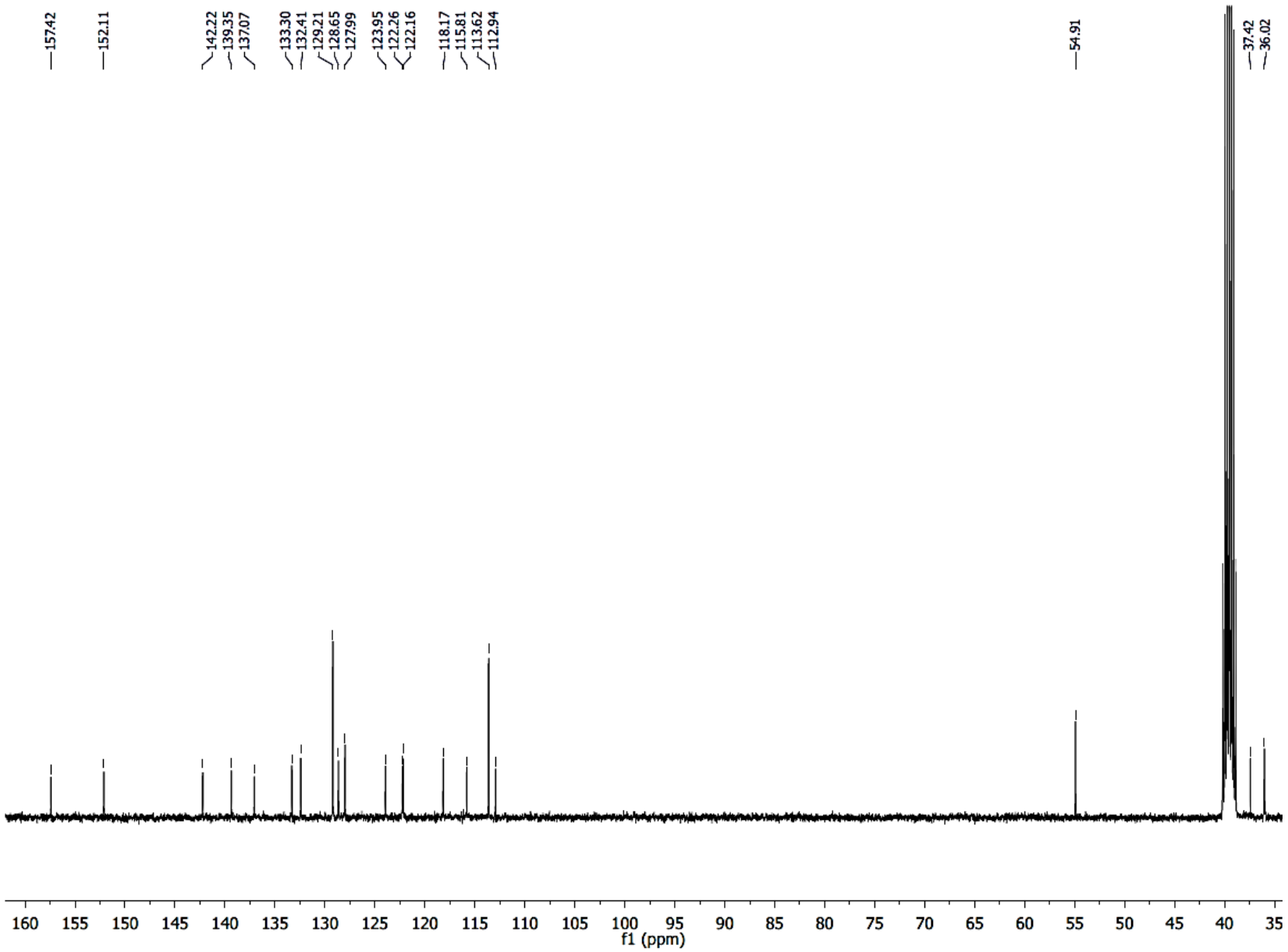
3.0
f1 (ppm)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115.81
113.62
112.94
54.91
37.42
36.02
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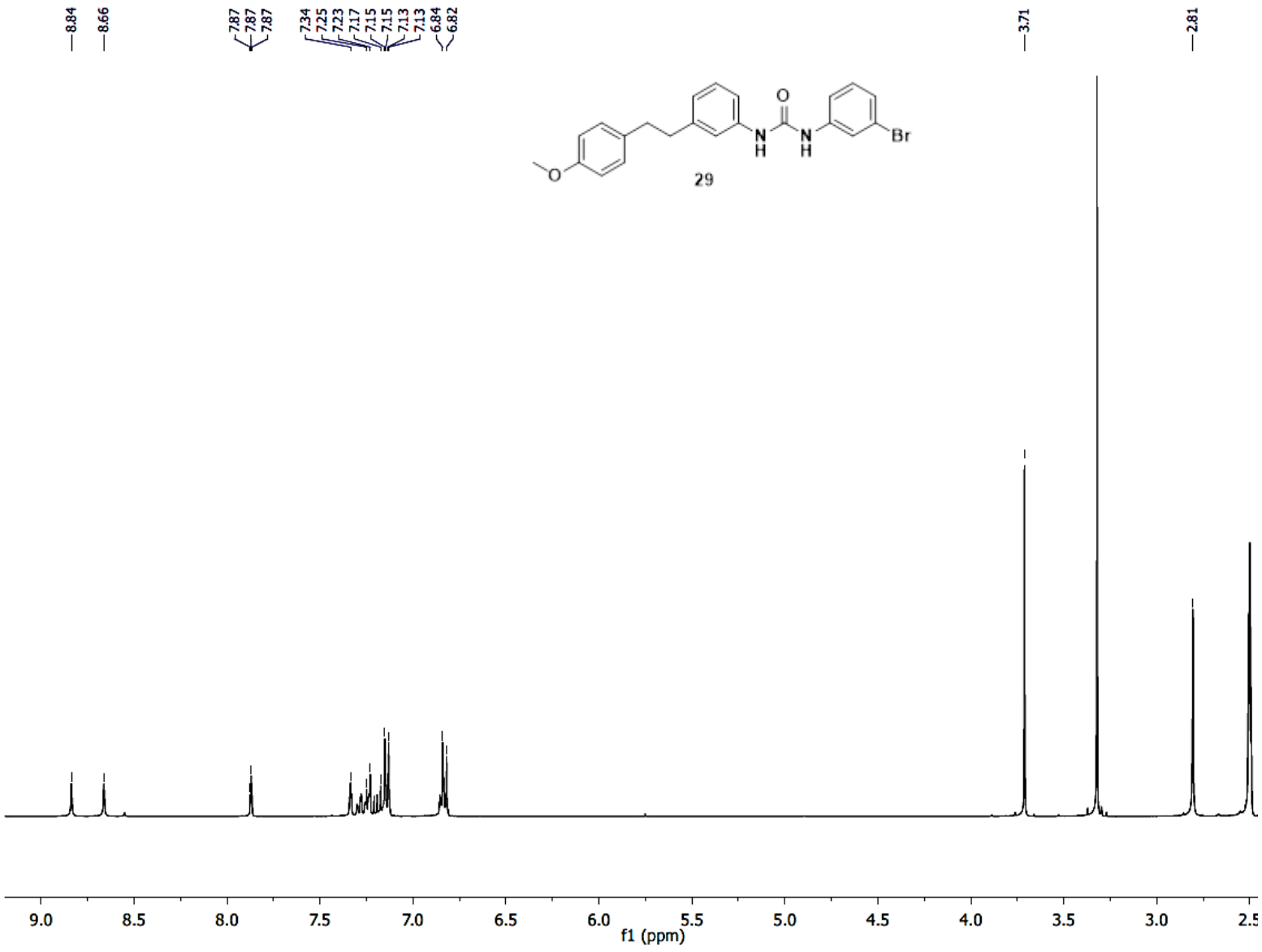
f1 (ppm)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7.15
7.13
7.13
6.84
6.82
3.71
2.81
O
N
H
N
H
Br
O
29
9.0
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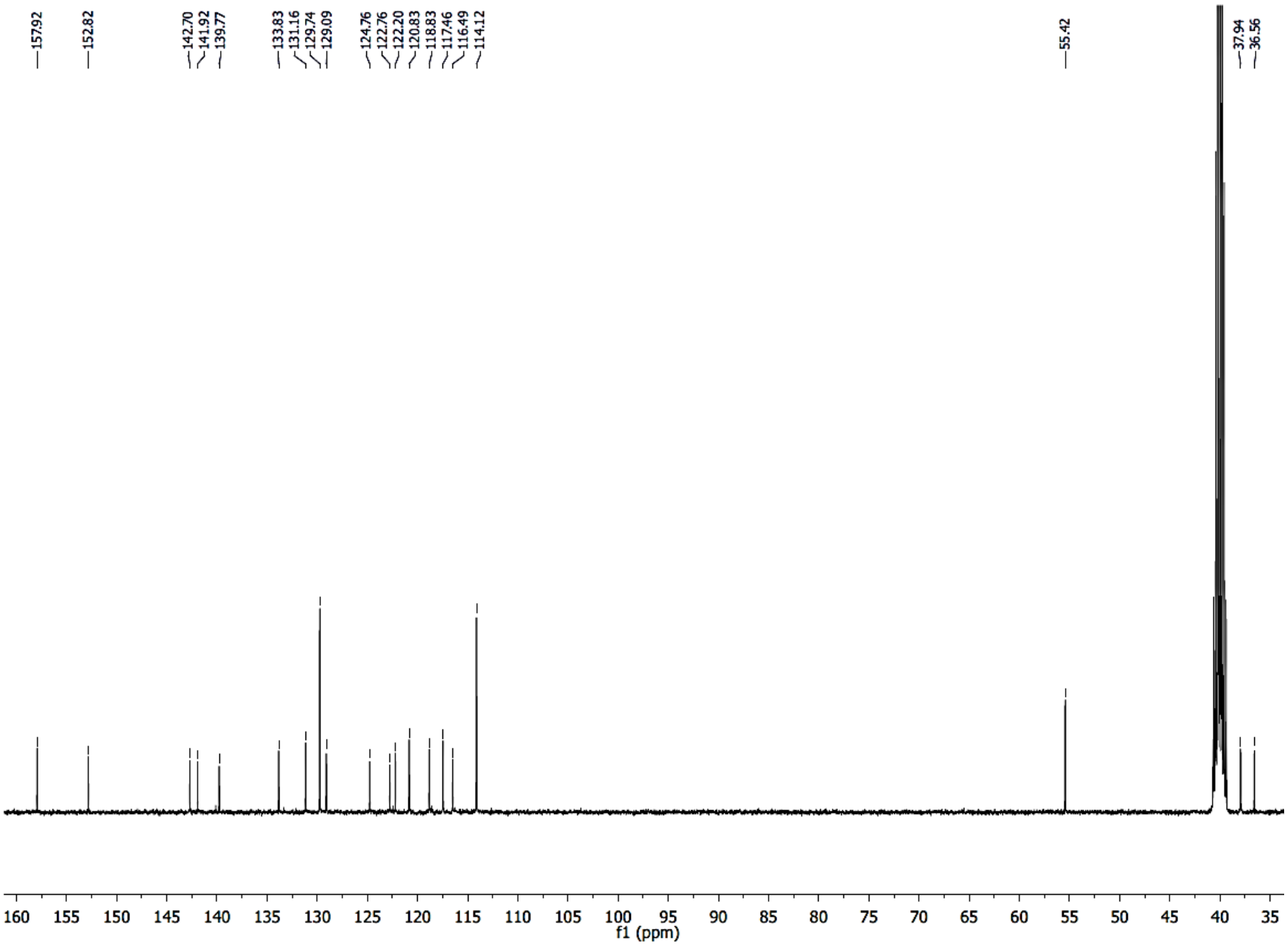
3.0
f1 (ppm)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118.83
117.46
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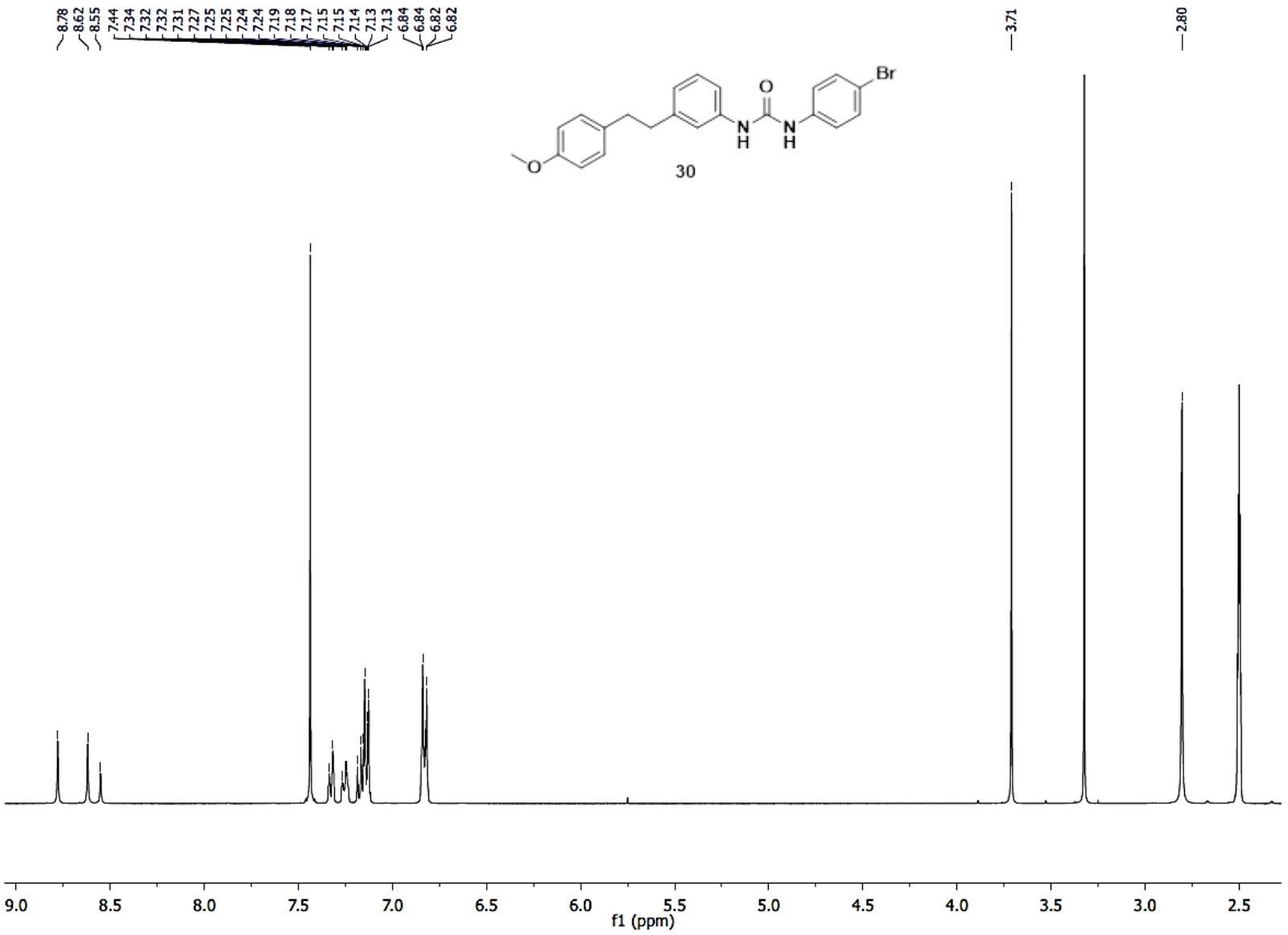
37.94
36.56
160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35
f1 (ppm)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7.24
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7.19
7.18
7.17
7.15
7.15
7.14
7.13
7.13
6.84
6.84
6.82
6.82
3.71
2.80
Br
O
N
H
N
H
O
30
9.0
8.5
8.0
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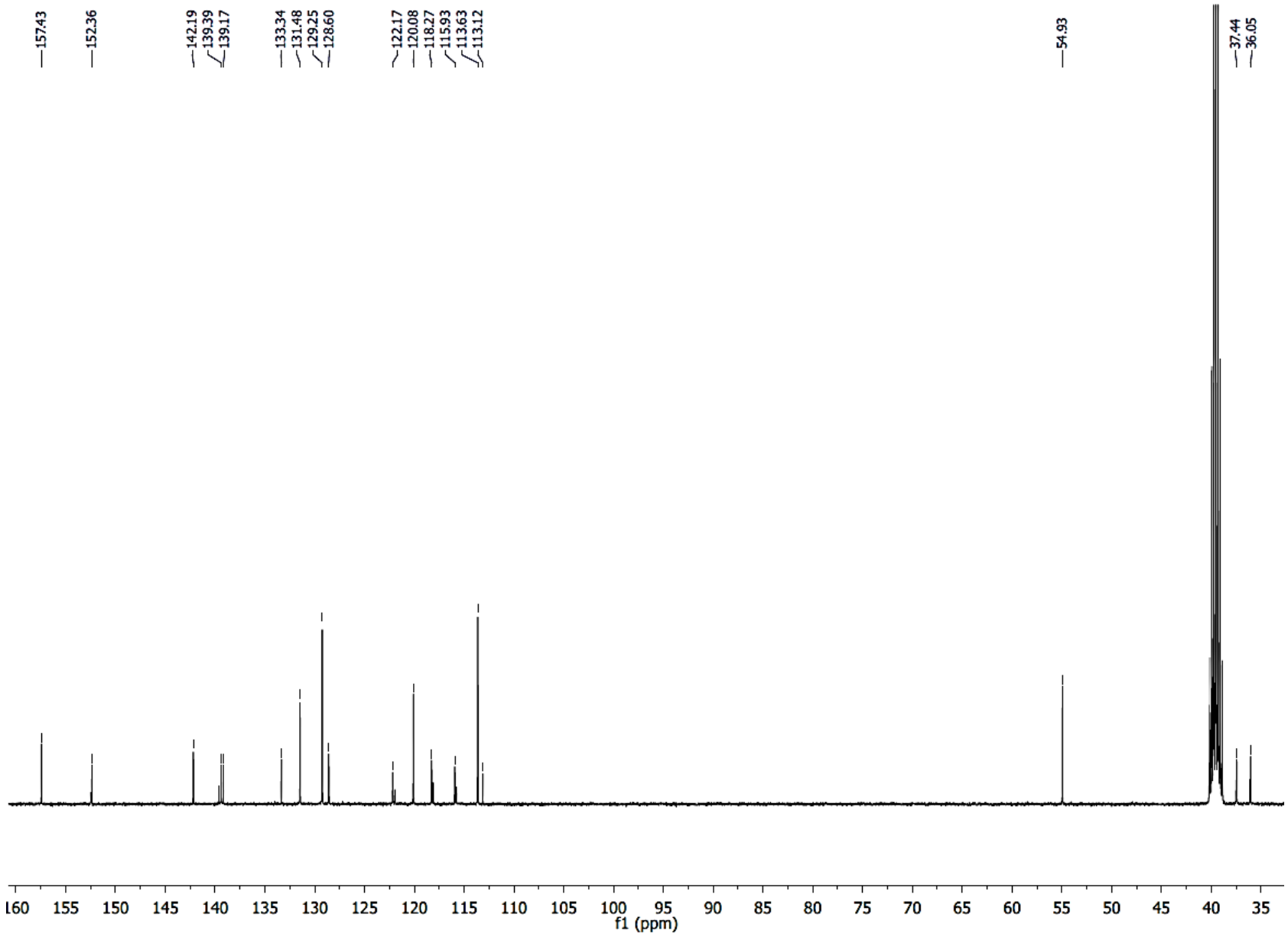
f1 (ppm)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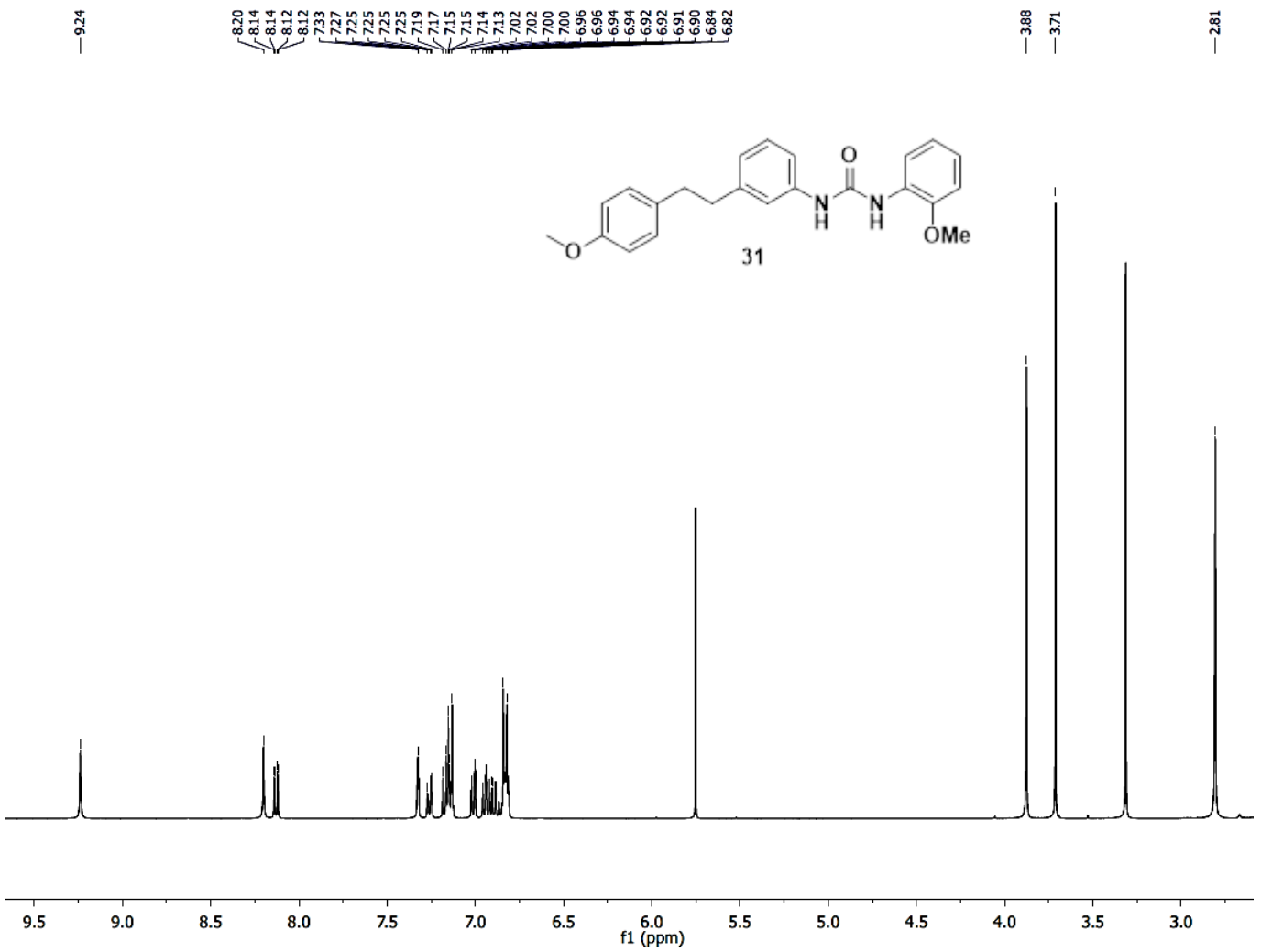
f1 (ppm)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7.15
7.15
7.14
7.13
7.02
7.02
7.00
7.00
6.96
6.96
6.94
6.94
6.92
6.92
6.91
6.90
6.84
6.82
3.88
3.71
2.81
O
N
H
N
H
O
OMe
31
9.5
9.0
8.5
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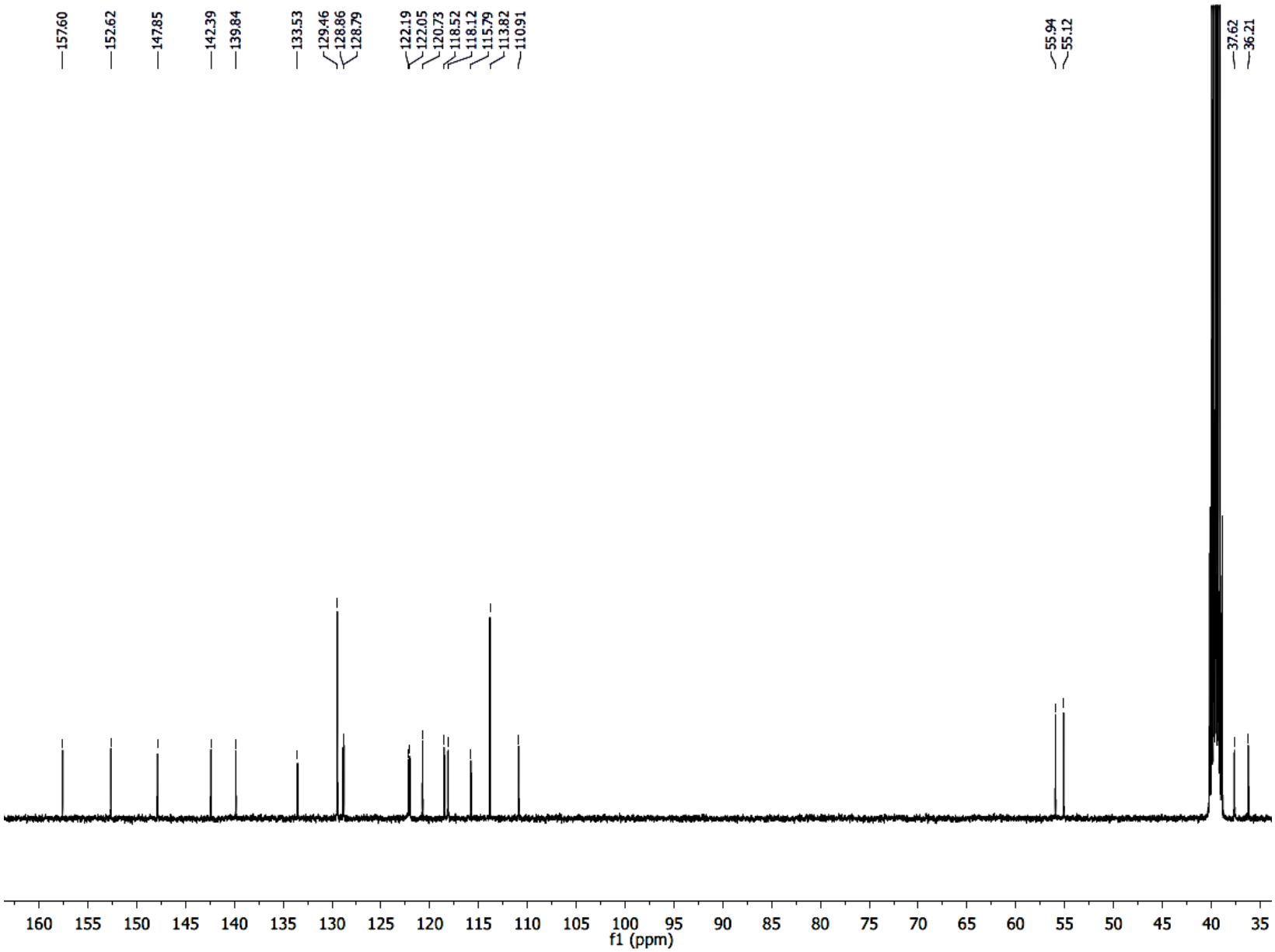
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118.52
118.12
115.79
113.82
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55.12
37.62
36.21
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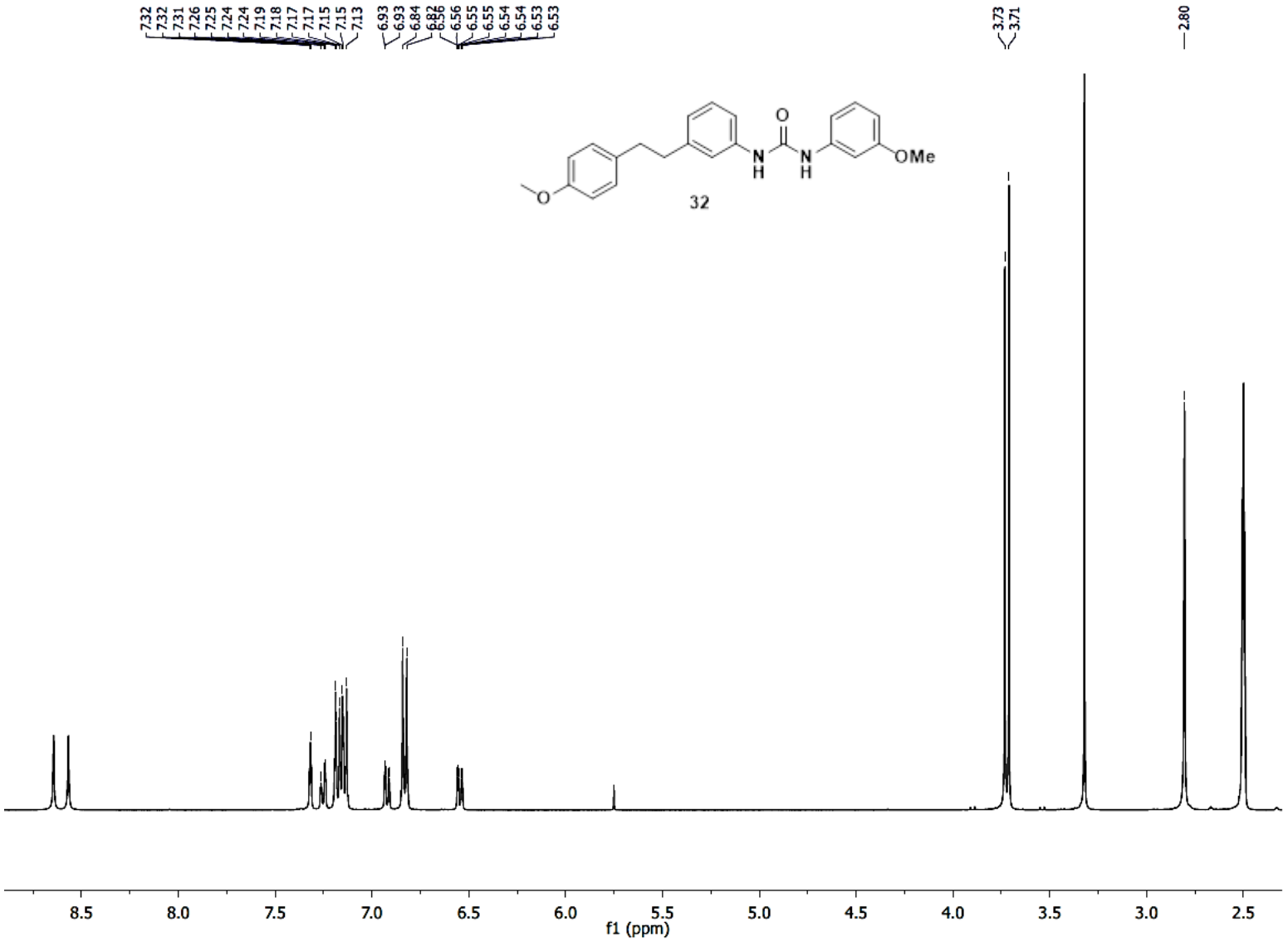
f1 (ppm)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7.19
7.18
7.17
7.17
7.15
7.15
7.13
6.93
6.93
6.84
6.82
6.56
6.55
6.55
6.54
6.54
6.53
6.53
3.73
3.71
2.80
O
N
H
N
H
OMe
O
32
8.5
8.0
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7.0
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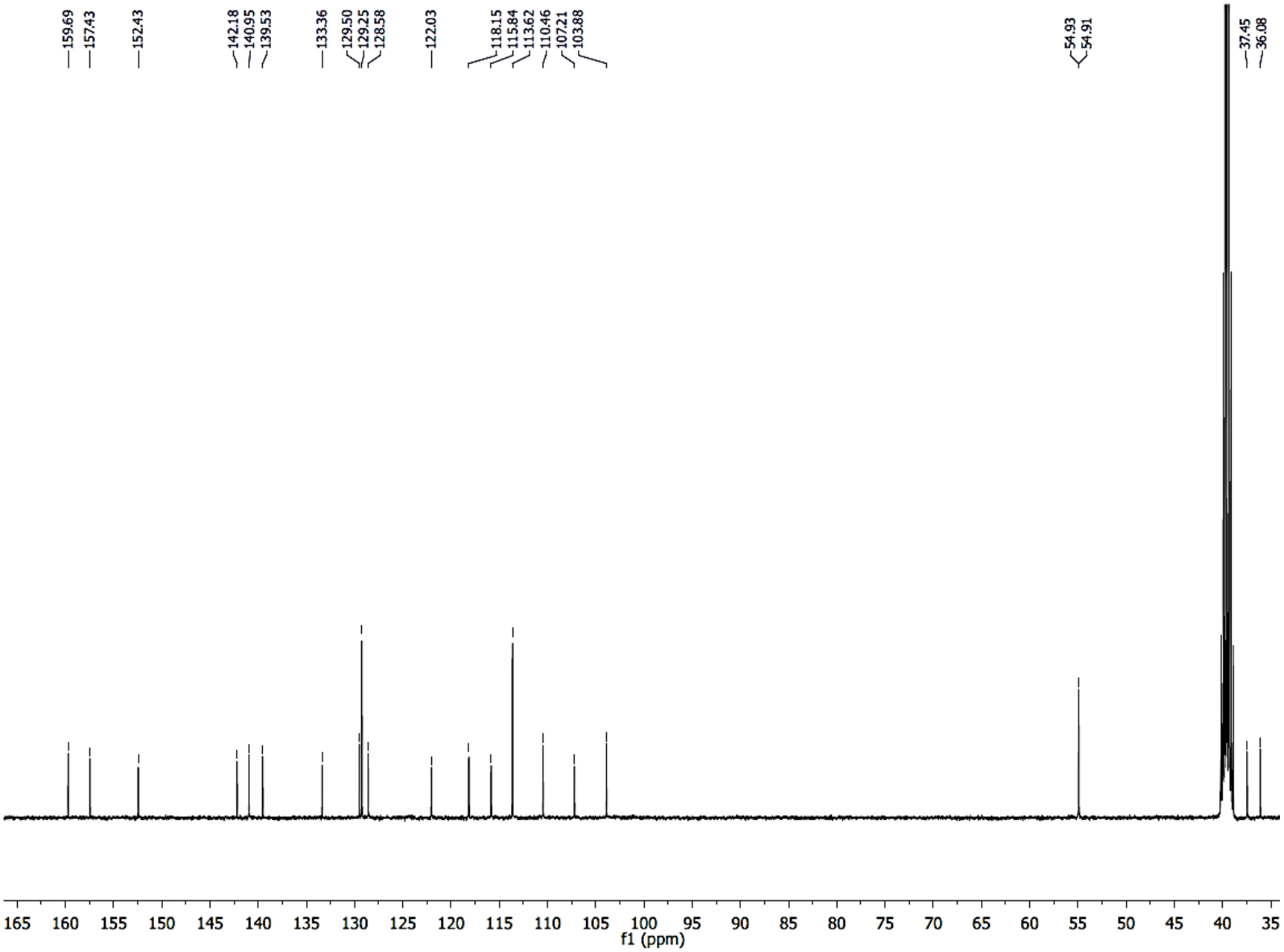
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
f1 (ppm)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142.18
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110.46
107.21
103.88
54.93
54.91
37.45
36.08
165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35
f1 (ppm)