# *In Vitro* $\alpha$-Glucosidase and $\alpha$-Amylase Inhibition, Cytotoxicity and Free Radical Scavenging Profiling of the 6-Halogeno and Mixed 6,8-Dihalogenated 2-Aryl-4-methyl-1,2-dihydroquinazoline 3-oxides

N.M. Magwaza, G.K. More, S. Gildenhuys and M.J. Mphahlele

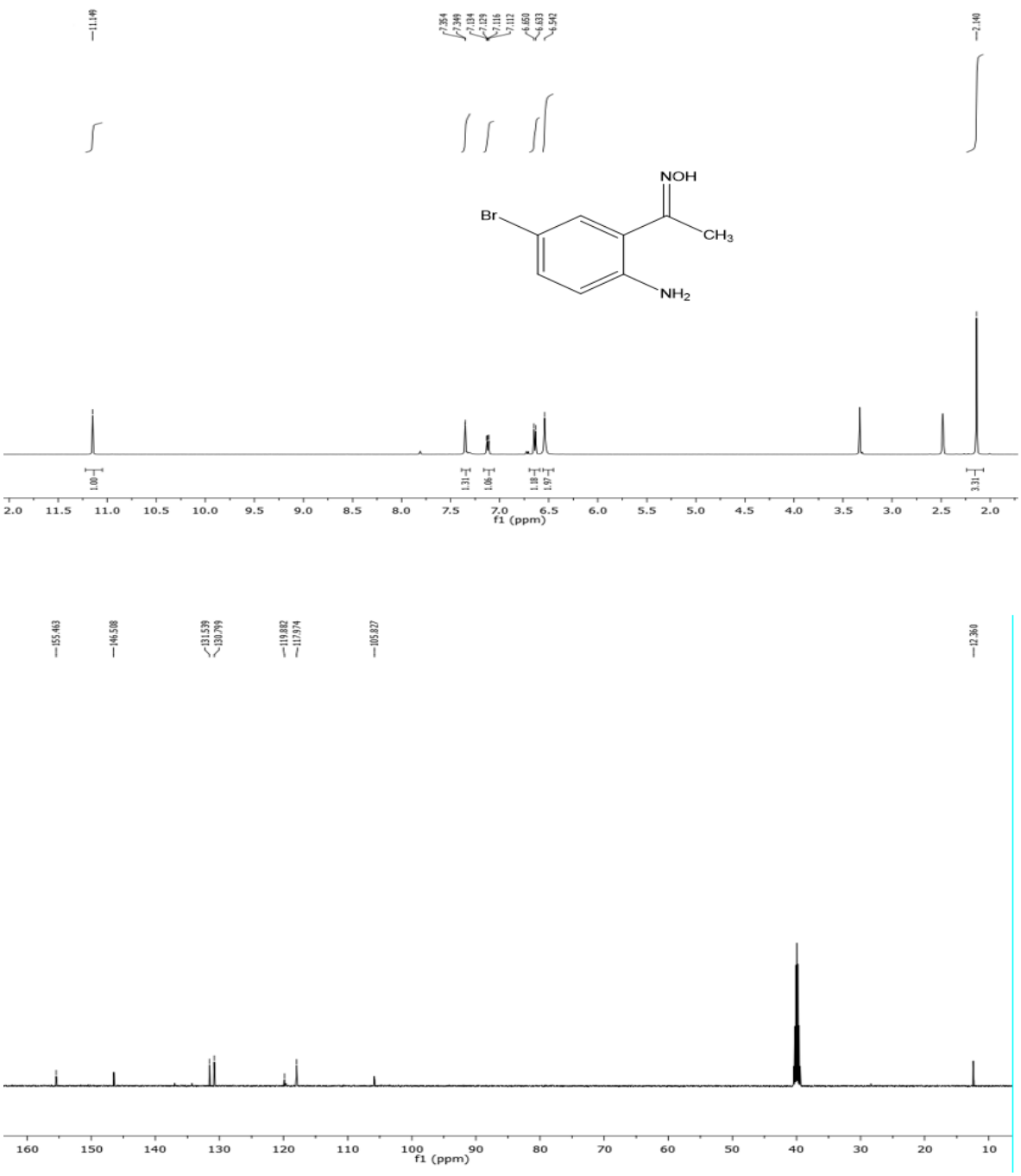



**Figure S1.1**: $^{1}$H- and $^{13}$C-NMR spectra of **2a** in DMSO-$d_6$ at 500 MHz and 125 MHz, respectively

1-(2-Amino-5-bromophenyl)ethan-1-one oxime (**2a**)

White solid (1.85 g, 93%), mp. 159–160 °C (Lit. 161.0–161.5 °C [1]); $\nu_{max}$ (ATR): 822, 1002, 1278, 1396, 1488, 1615, 2810, 3248, 3349 cm$^{-1}$; $^{1}$H-NMR (500 MHz, DMSO-$d_6$): δ 2.30 (s, 3H, -CH3), 6.60 (s, 2H, -NH$_2$), 7.09 (d, $J$ = 6.0 Hz, 1H, H-3), 7.36 (t, $J$ = 7.5 Hz, 1H, H-4), 7.42 (d, $J$ = 6.0 Hz, 1H, H-6), 7.83 (s, 1H, OH); $^{13}$C-NMR (125 MHz, DMSO-$d_6$): δ 12.5, 108.5, 120.6, 131.1, 132.0, 137.2, 144.6, 157.4; HRMS (ES): MH$^+$, calcd for $C_8H_9N_2OBr$: 228.9898; found 228.9974.

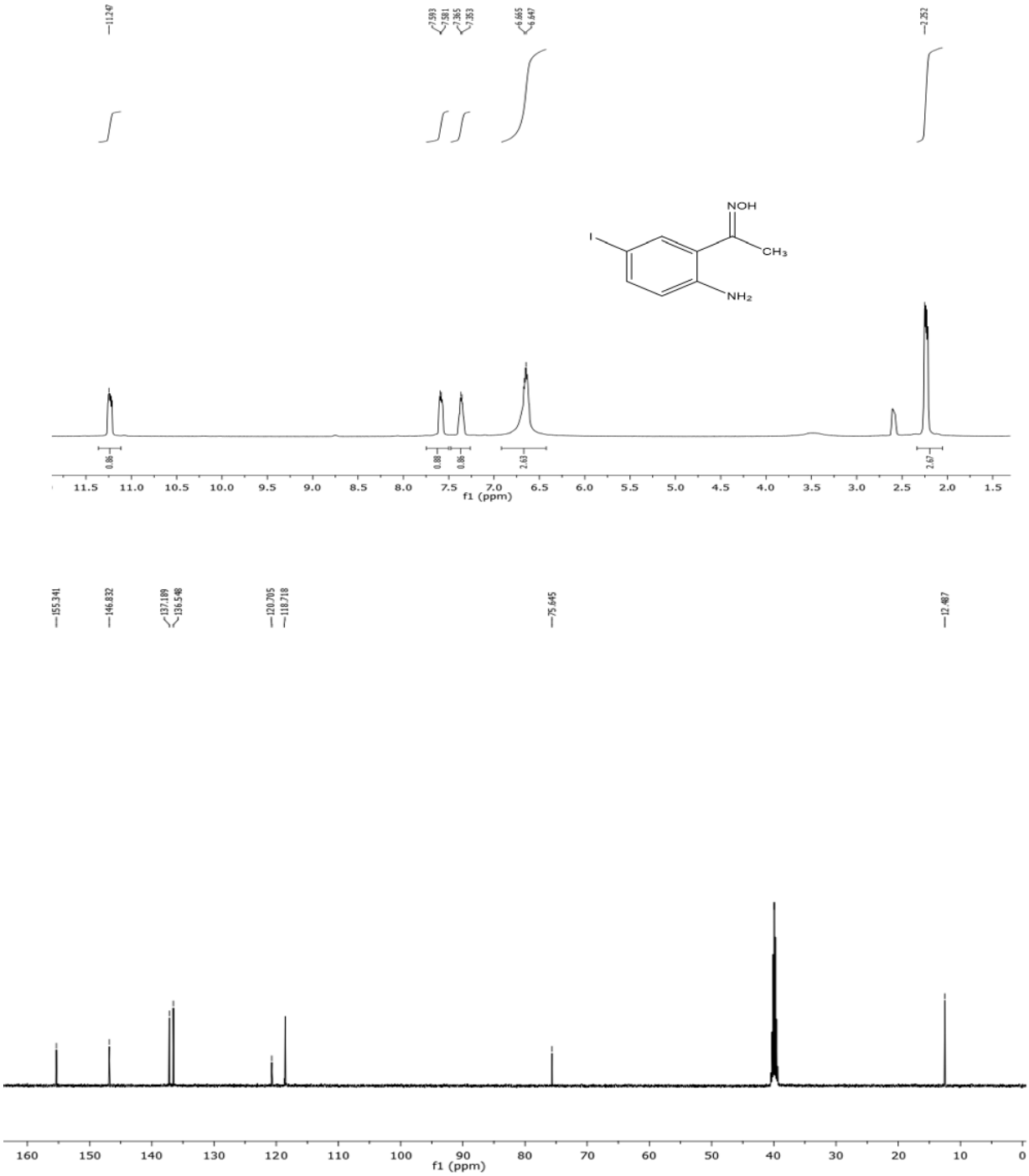



**Figure S1.2**: $^{1}$H- and $^{13}$C-NMR spectra of **2b** in DMSO-$d_6$ at 500 MHz and 125 MHz, respectively.

1-(2-Amino-5-iodophenyl)ethan-1-one oxime (**2b**)

Brown solid (1.78 g, 89%), mp 136–137 °C; $\nu_{max}$ (ATR): 818, 1002, 1058, 1278, 1483, 1610, 2983, 3355, 3673 cm$^{-1}$; $^{1}$H-NMR (500 MHz, DMSO-$d_6$): δ 2.16 (s, 3H, $CH_3$), 6.12 (s, 2H, $NH_2$), 7.45 (d, $J$ = 1.5 Hz, 1H, H-3), 7.59 (d, $J$ = 1.5 Hz, 1H, H-4), 7.35 (s, 1H, H-6), 11.25 (s, 1H, OH); $^{13}$C-NMR (125 MHz, DMSO-$d_6$): δ 12.4, 75.6, 118.6, 120.7, 136.5, 137.2, 146.9, 155.3; HRMS (ES): MH$^+$, calcd for $C_8H_9N_2OI$: 276.9760; found 276.9835.

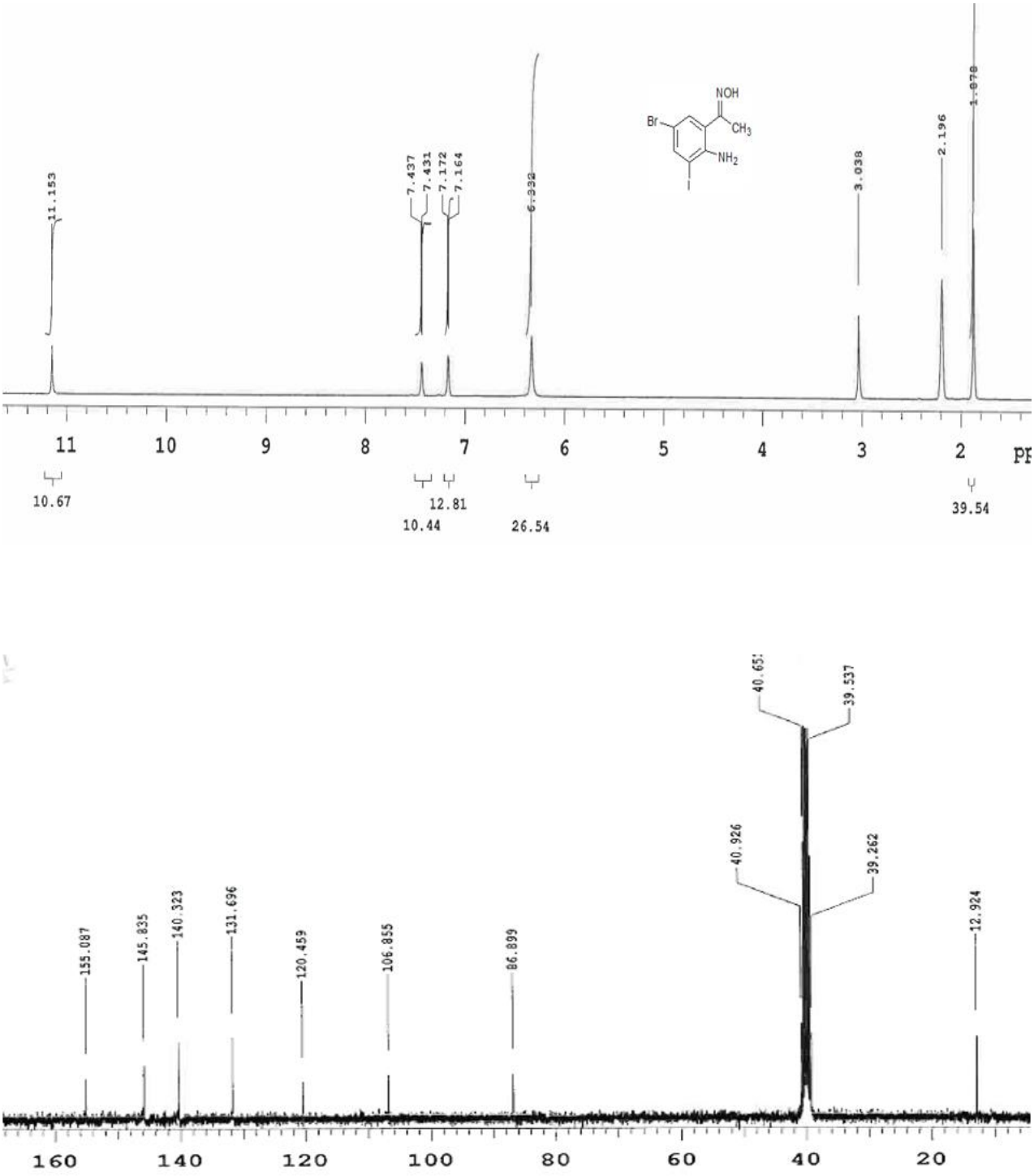



**Figure S1.3**: $^{1}$H- and $^{13}$C-NMR spectra of **2c** in DMSO-$d_6$ at 500 MHz and 125 MHz, respectively.

1-(2-Amino-5-bromo-3-iodophenyl)ethan-1-one oxime (**2c**)

White solid (1.80 g, 90%), mp. 175–176 °C (Lit. 174–176 °C [2]); $\nu_{max}$ (ATR): 680, 755, 860, 1002, 1232, 1364, 1425, 1526, 1738, 2833, 3207, 3364 cm$^{-1}$; $^{1}$H-NMR (500 MHz, DMSO-$d_6$): δ 3.94 (s, 3H, $CH_3$), 6.24 (s, 2H, -$NH_2$), 7.09 (s, 1H, H-4), 7.36 (s, 1H, H-6), 11.06 (s, 1H, NH); $^{13}$C-NMR (125 MHz, DMSO-$d_6$): δ 12.9, 86.9, 106.9, 120.5, 131.7, 140.3, 145.8, 155.1.

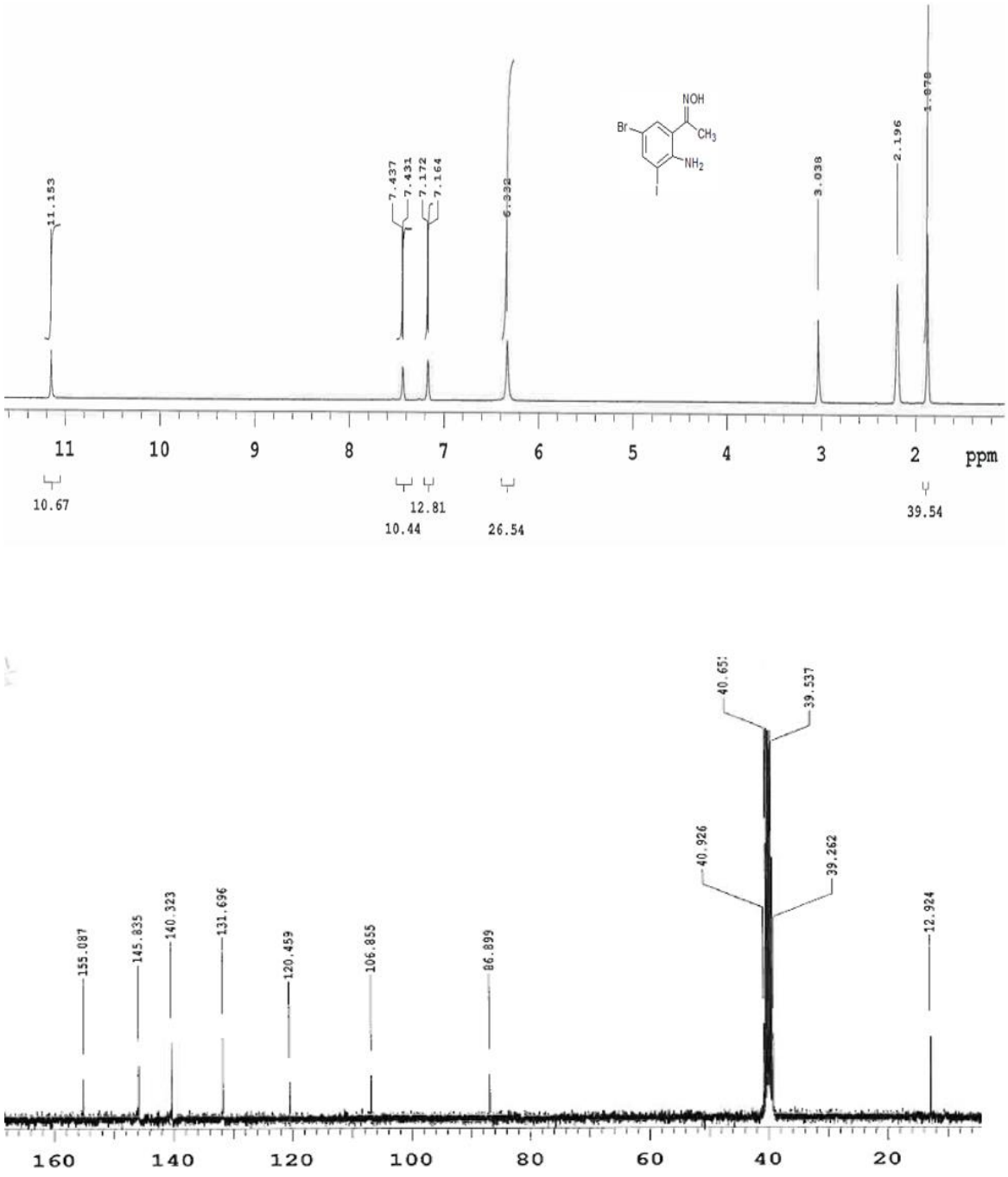



**Figure S1.4**: $^{1}$H- and $^{13}$C-NMR spectra of **2d** in DMSO-$d_6$ at 500 MHz and 125 MHz, respectively.

1-(2-Amino-3-bromo-5-iodophenyl)ethan-1-one oxime (**2d**)

Brown solid (1.78 g, 89%); mp 171–172 °C; $\nu_{max}$ (ATR) 862, 1005, 1067, 1233, 1386, 1531, 2990, 3366 cm$^{-1}$; $^{1}$H-NMR (500 MHz, DMSO-$d_6$): δ 2.16 (s, 3H, $CH_3$), 6.62 (s, 2H, $NH_2$), 7.45 (d, $J$ = 1.5 Hz, 1H, H-4), 7.71(d, $J$ = 1.5 Hz, 1H, H-4), 11.44 (s, 1H, OH); $^{13}$C-NMR (125 MHz, DMSO-$d_6$) 12.6, 86.5, 106.9, 120.5, 131.5, 140.3, 145.4, 154.8; HRMS (ES): $MH^+$, calcd for $C_8H_8N_2OBrI$: 354.8865; found 354.8943.

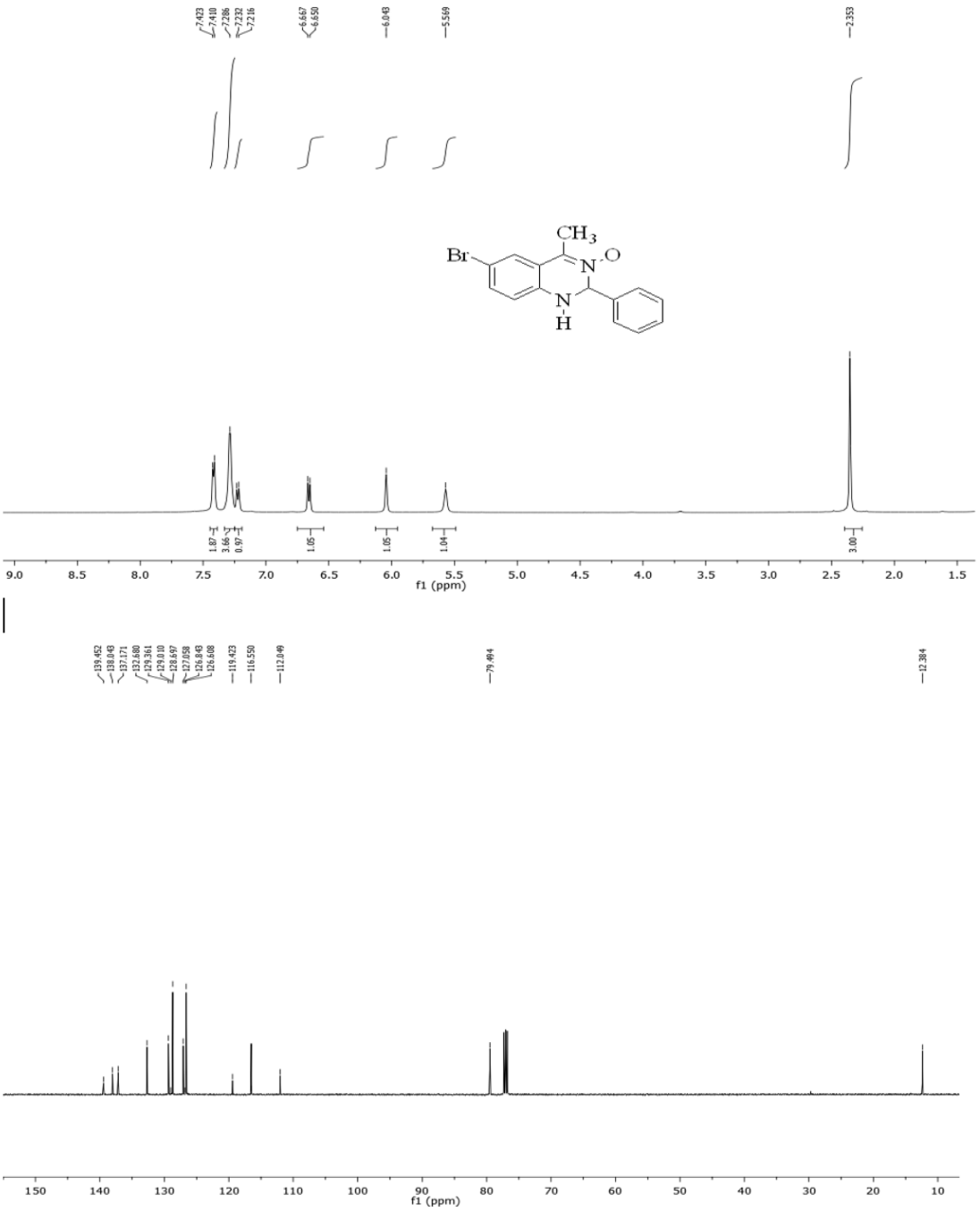



**Figure S1.5**: $^{1}$H- and $^{13}$C-NMR spectra of **3a** in $CDCl_3$ at 500 MHz and 125 MHz, respectively.

6-Bromo-4-methyl-2-phenyl-1,2-dihydroquinazoline 3-oxide (**3a**)

Yellow solid (0.30 g, 62%), $R_f$ (5% EtOAc–toluene) 0.64, mp 158–160 °C (Lit. 160–161°C [1]); $\nu_{max}$ (ATR) 815, 1072, 1199, 1268, 1407, 1492, 1564, 1600, 2987, 3237 cm$^{-1}$; $^{1}$H-NMR (500 MHz, $CDCl_3$): δ 2.35 (s, 3H, -$CH_3$), 5.57 (s, 1H, H-2), 6.04 (s, 1H, NH), 6.65 (d, $J$ = 8.5 Hz, 1H, H-8), 7.22 (d, $J$ = 8.0 Hz, 1H, H-7), 7.23–7.29 (m, 4H, H-2',6' and H-3',5'), 7.42 (d, $J$ = 6.5 Hz, 2H, H-4' and H-5); $^{13}$C-NMR (125 MHz, $CDCl_3$): δ 12.4, 79.5, 112.0, 116.6, 132.0, 119.4, 126.6, 126.8, 127.1, 128.7, 129.0, 129.4, 132.7, 137.2, 138.0, 139.5; HRMS (ES): $MH^+$, calcd for $C_{15}H_{14}N_2OBr$: 317.0211; found 317.0289.

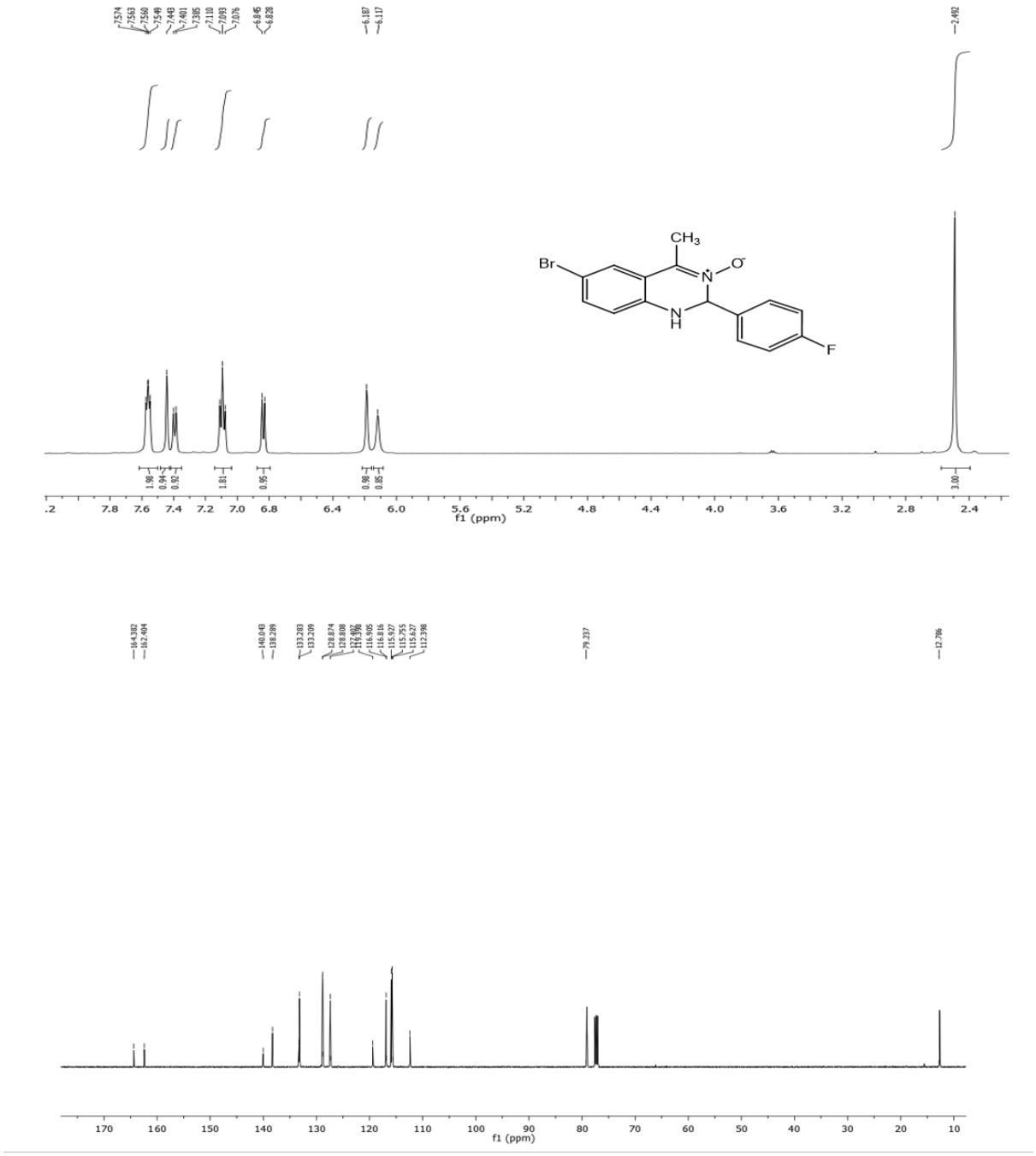



**Figure S1.6**: $^{1}$H- and $^{13}$C-NMR spectra of **3b** in $CDCl_3$ at 500 MHz and 125 MHz, respectively.

6-Bromo-2-(4-fluorophenyl)-4-methyl-1,2-dihydroquinazoline 3-oxide (**3b**)

Yellow solid (0.25 g, 50%), $R_f$ (5% EtOAc–toluene) 0.65; mp 183–185 °C; $\nu_{max}$ (ATR) 817, 1158, 1197, 1501, 1600, 3001, 3057, 3199, 3234 cm$^{-1}$; $^{1}$H-NMR (500 MHz, $CDCl_3$): δ 2.48 (s, 3H, -$CH_3$), 6.10 (s, 1H, H-2), 6.19 (s, 1H, NH), 6.83 (d, $J$ = 8.5 Hz, 1H, H-8), 7.10 (t, $J$ = 8.5 Hz, 2H, H-3',5'), 7.40 (d, $J$ = 8.0 Hz, 1H, H-7), 7.44 (s, 1H, H-5), 7.57 (dd, $J_{HH}$ = 5.5 Hz and $J_{HH}$ = 7.0 Hz, 2H, H-2',6'); $^{13}$C-NMR (125 MHz, $CDCl_3$): δ 12.9, 79.2, 112.4, 115.6 (d, $^{2}J_{CF}$ = 21.5 Hz), 116.8, 116.9, 119.4, 127.4, 128.8 (d, $^{3}J_{CF}$ = 8.3 Hz), 130.9, 132.8 (d, $^{2}J_{CF}$ = 2.7 Hz), 135.3, 138.3, 140.0, 162.4 (d, $^{2}J_{CF}$ = 247.3); HRMS (ES): $MH^+$, calcd for $C_{15}H_{12}N_2OBrF$: 335.0117; found 335.0200.

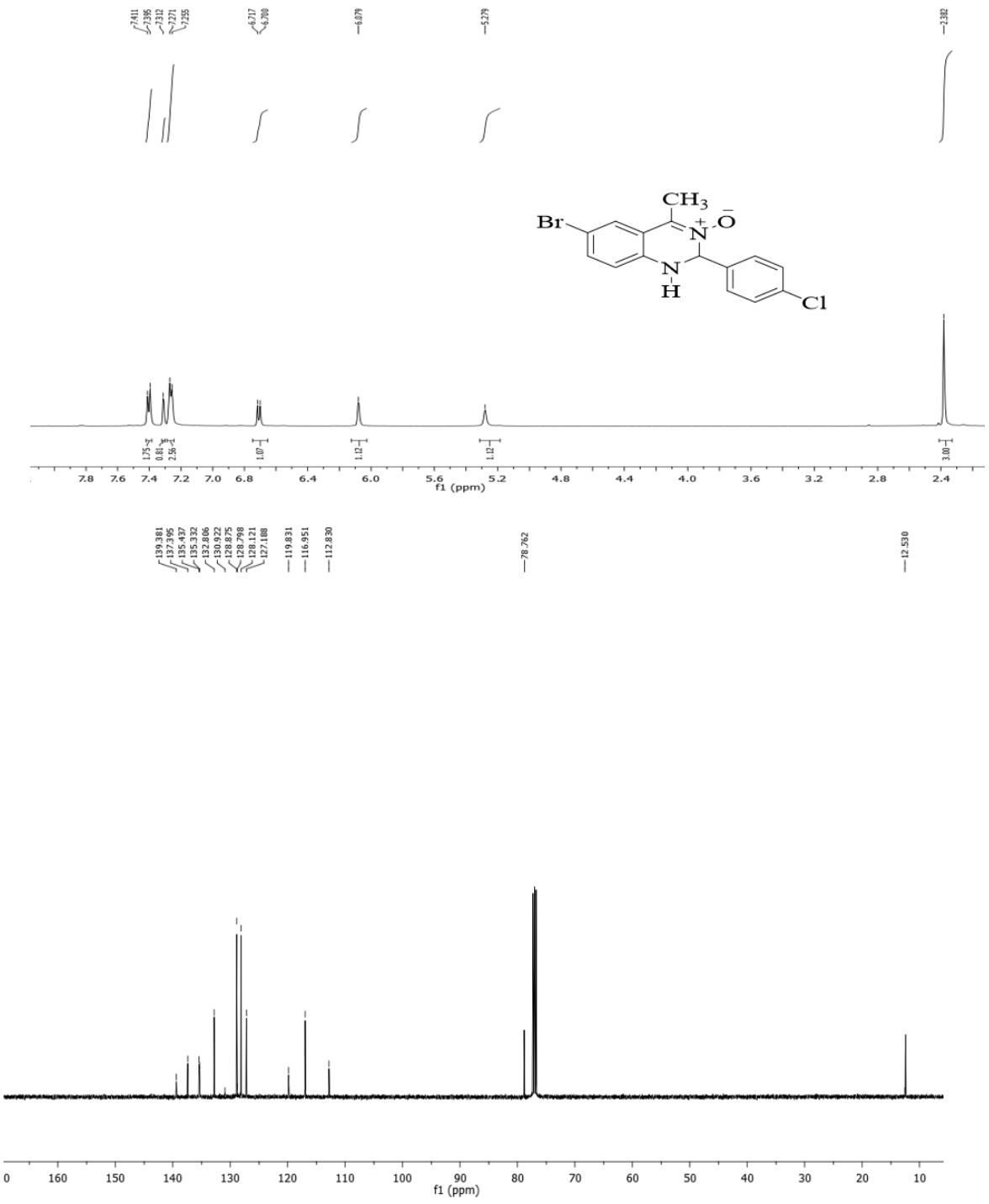



**Figure S1.7**: $^{1}$H- and $^{13}$C-NMR spectra of **3c** in $CDCl_3$ at 500 MHz and 125 MHz, respectively.

6-Bromo-2-(4-chlorophenyl)-4-methyl-1,2-dihydroquinazoline 3-oxide (**3c**)

Yellow solid (0.42 g, 84%), $R_f$ (5% EtOAc–toluene) 0.66, mp. 171–173 °C (Lit. 170–171 °C [1]); $\nu_{max}$ (ATR) 822, 1016, 1093, 1194, 1291, 1489, 1543, 1598, 3271 cm$^{-1}$; $^{1}$H-NMR (500 MHz, $CDCl_3$): δ 2.38 (s, 3H, $CH_3$), 5.28 (s, 1H, H-2), 6.08 (1H, s ,NH), 6.70 (d, $J$ = 8.7 Hz, 1H, H-8), 7.26 (d, $J$ = 8.0 Hz, 3H, H-2',6' and H-7), 7.30 (s, 1H, H-5), 7.40 (d, $J$ = 8.0 Hz, 2H, H-3',5'); $^{13}$C-NMR (125 MHz, $CDCl_3$): δ 12.5, 78.8, 112.8, 116.9, 119.8, 127.2, 128.1, 128.8, 128.9, 130.9, 132.8, 135.3, 135.4, 137.4, 139.4; HRMS (ES): MH$^+$, calcd for $C_{15}H_{13}N_2OBrCl$: 350.9822; found 350.9886.

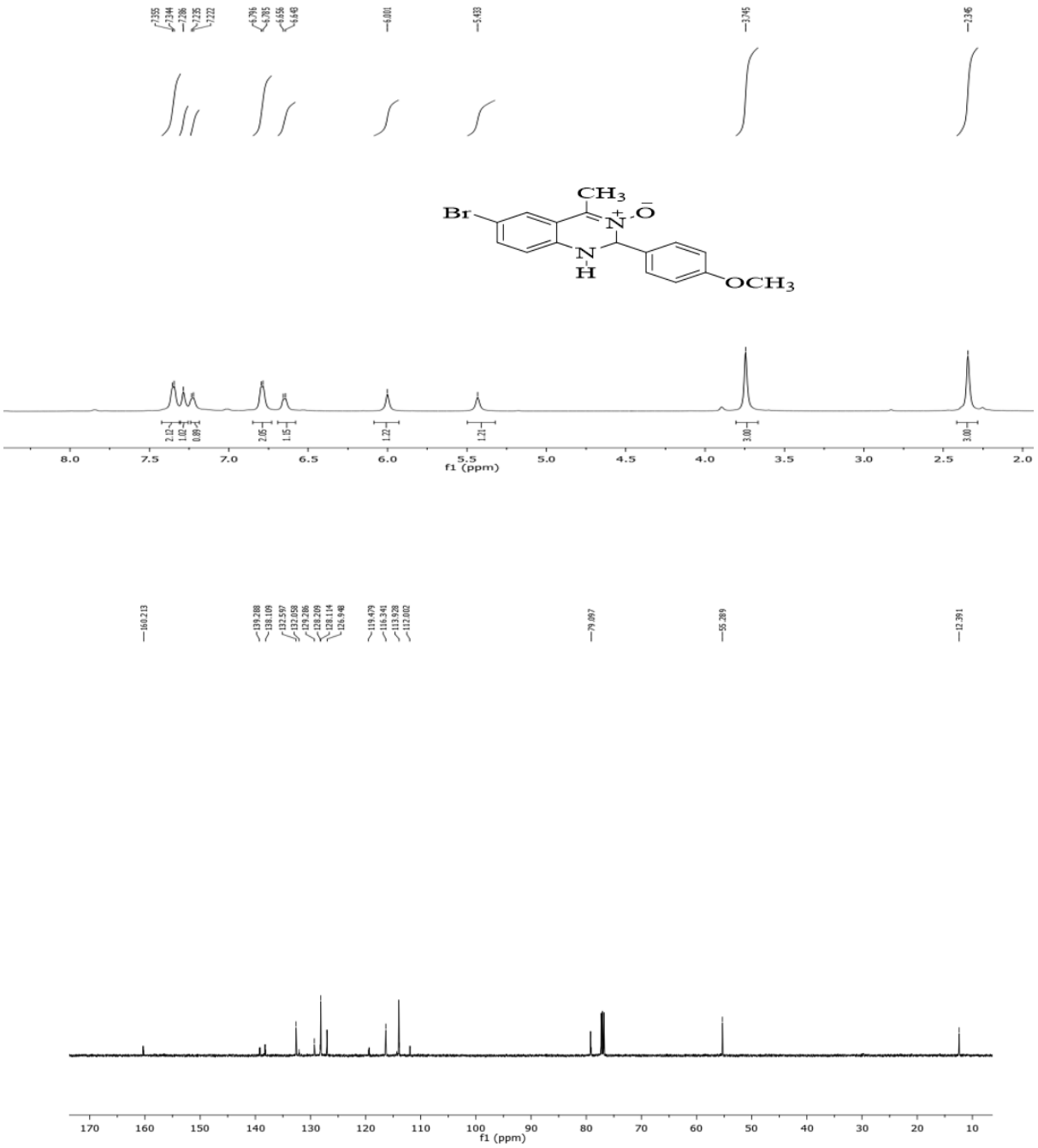



**Figure S1.8**: $^{1}$H- and $^{13}$C-NMR spectra of **3d** in $CDCl_3$ at 500 MHz and 125 MHz, respectively.

6-Bromo-2-(4-methoxyphenyl)-4-methyl-1,2-dihydroquinazoline 3-oxide (**3d**)

Yellow solid (0.45 g, 90%), $R_f$ (5% EtOAc–toluene) 0.62, mp 194–196 °C; $\nu_{max}$ (ATR) 825, 1028, 1199, 1291, 1469, 1517, 1600, 2960, 3281 cm$^{-1}$; $^{1}$H-NMR (500 MHz, $CDCl_3$): δ 2.35 (s, 3H, -$CH_3$), 5.43 (s, 1H, H-2), 6.00 (s 1H, NH), 6.65 (1H, d, $J$ = 6.5 Hz, H-8), 6.79 (2H, d, $J$ = 5.5 Hz, H-3',5'), 7.22 (d, $J$ = 6.5 Hz,1H, H-7), 7.35 (d, $J$ = 5.5 Hz, 2H, H-2',6'); $^{13}$C-NMR (125 MHz, $CDCl_3$): δ 12.4, 55.3, 79.1, 112.0, 113.9, 116.3, 119.5, 126.9, 128.1, 128.2, 129.3, 132.0, 132.6, 138.1, 139.3, 160.2; HRMS (ES): $MH^+$, calcd for $C_{16}H_{16}N_2O_2Br$: 346.0317; found 347.0391.

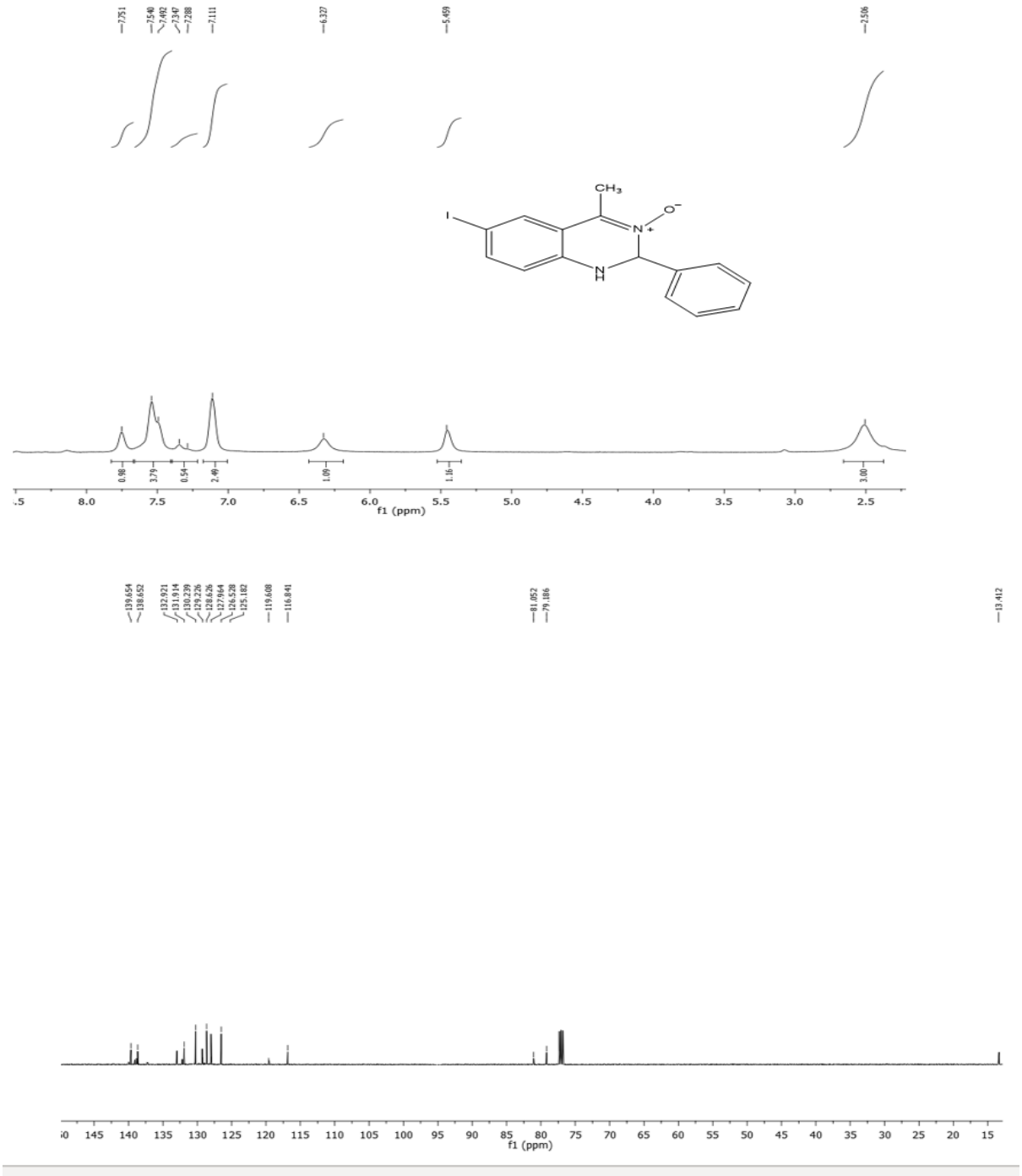



**Figure S1.9**: $^{1}$H- and $^{13}$C-NMR spectra of **3e** in $CDCl_3$ at 500 MHz and 125 MHz, respectively.

6-Iodo-4-methyl-2-phenyl-1,2-dihydroquinazoline 3-oxide (**3e**)

Yellow solid (0.34 g, 68%), $R_f$ (5% EtOAc–toluene) 0.63, mp 184–186 °C; $\nu_{max}$ (ATR) 815, 1028, 1180, 1268, 1489, 1561, 1599, 2987, 3156, 3228 cm$^{-1}$; $^{1}$H-NMR (500 MHz, $CDCl_3$): δ 2.52 (s, 3H, -$CH_3$), 5.36 (s, 1H, H-2), 6.27 (s, 1H, NH), 6.70 (d, 1H, $J$ = 6.5 Hz, H-8), 7.44 (m, 3H, H-4' and H-2',6'), 7.55–7.59 (m, 4H, H-3',5', H-5 and H-7); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 13.4, 79.2, 81.1, 116.8, 119.6, 125.2, 126.5, 127.9, 128.6, 129.2, 130.2, 131.9, 132.9, 138.7, 139.7; HRMS (ES$^+$): m/z $[M + H]^+$ calcd for $C_{15}H_{14}N_2OI$: 365.0073; found 365.0149.

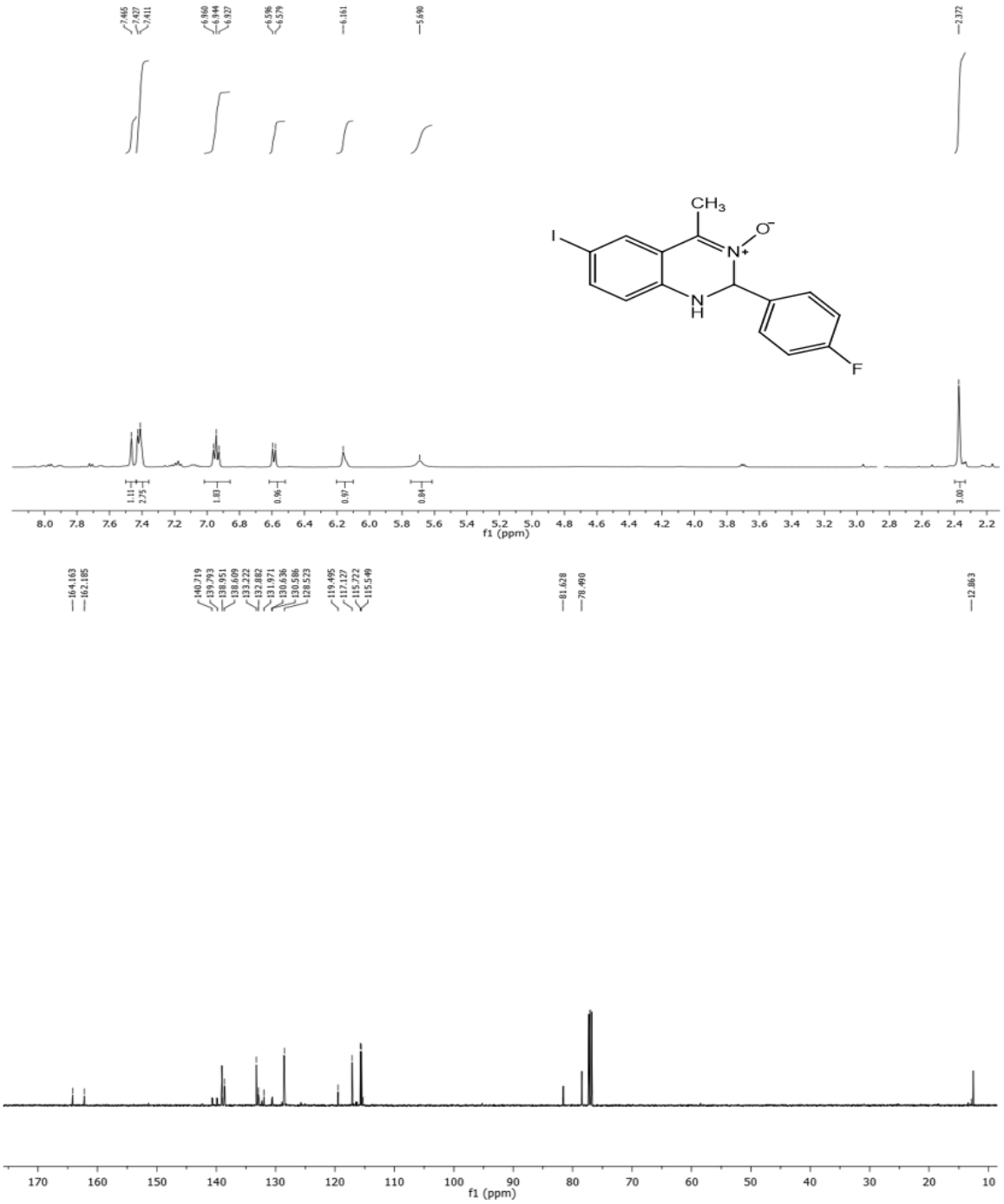



**Figure S1.10**: $^{1}$H- and $^{13}$C-NMR spectra of **3f** in $CDCl_3$ at 500 MHz and 125 MHz, respectively.

2-(4-Fluorophenyl)-6-iodo-4-methyl-1,2-dihydroquinazoline 3-oxide (**3f**)

Yellow solid (0.36 g, 72%), $R_f$ (5% EtOAc–toluene) 0.64; mp 180–182 °C; $\nu_{max}$ (ATR) 813, 1083, 1185, 1286, 1489, 1506, 1596, 1603, 2902, 2974, 3216 cm$^{-1}$; $^{1}$H-NMR (500 MHz, $CDCl_3$): δ 2.37 (s, 3H, -$CH_3$), 5.67 (s, 1H, H-2), 6.16 (s, 1H, NH), 6.56 (d, $J$ = 8.5 Hz, 1H, H-8), 6.94 (t, $J$ = 8.5 Hz, 2H, H-3',5'), 7.41 (d, $J$ = 8.0 Hz, 3H, H-2',6' and H-7), 7.47 (s, 1H, H-5); $^{13}$C-NMR (125 MHz, $CDCl_3$): δ 12.9, 78.5, 81.6, 115.5 (d, $^{2}J_{CF}$ = 21.6 Hz), 117.2, 119.5, 128.5, 130.6 (d, $^{3}J_{CF}$ = 8.2 Hz), 131.9, 132.8 (d, $^{2}J_{CF}$ = 2.7 Hz), 133.2, 138.6, 138.9, 140.7, 163.2 (d, $^{2}J_{CF}$ = 247.3 Hz); HRMS (ES): $MH^+$, calcd for $C_{15}H_{12}N_2OFI$: 382.9978; found 382.9811.

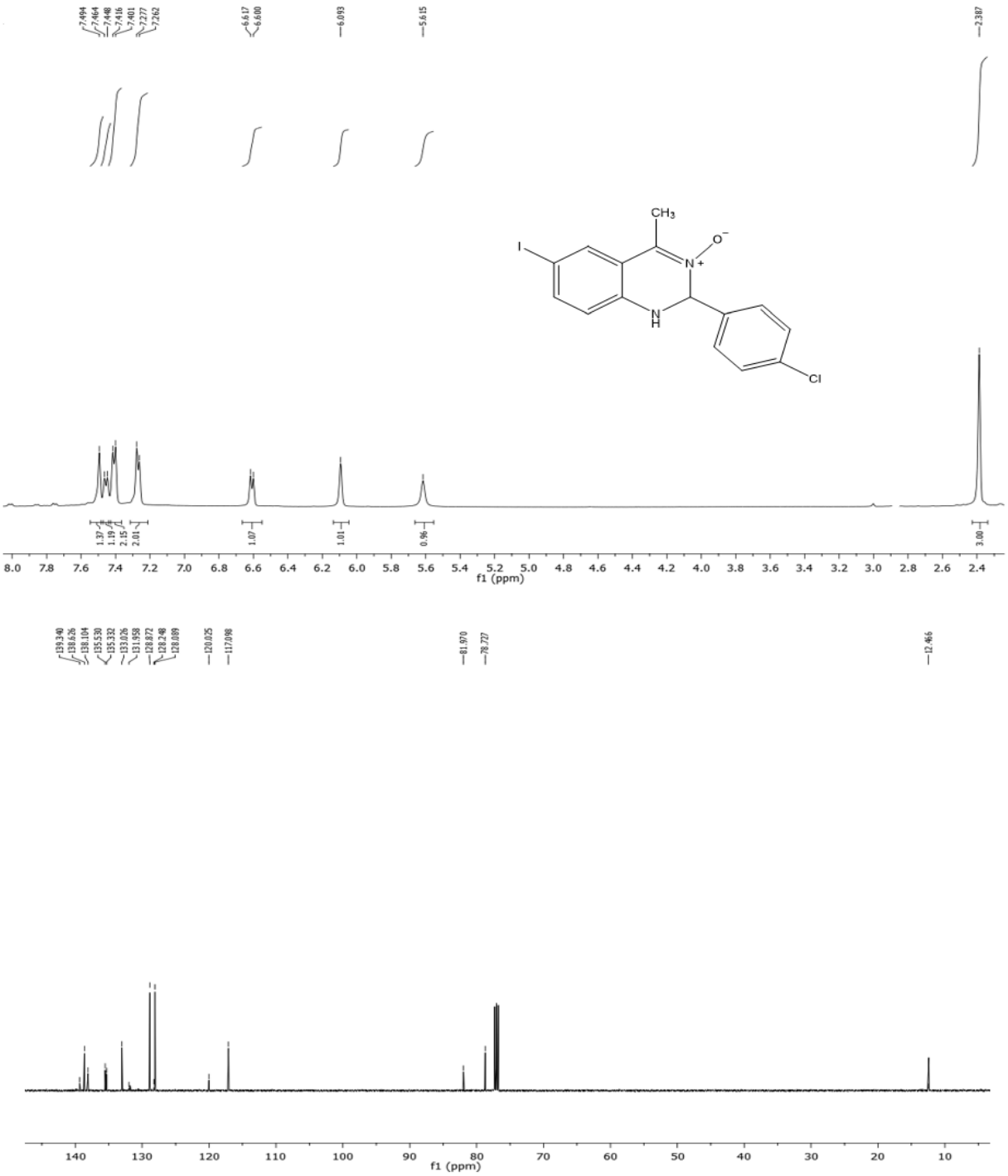



**Fig. S1.11**: $^{1}$H- and $^{13}$C-NMR spectra of **3g** in $CDCl_3$ at 500 MHz and 125 MHz, respectively.

6-Iodo-2-(4-Chlorophenyl)-6-iodo-4-methyl-1,2-dihydroquinazoline 3-oxide (**3g**)

Yellow solid (0.44 g, 88%), $R_f$ (5% EtOAc–toluene) 0.65, mp182–184 °C; $\nu_{max}$ (ATR) 818, 1012, 1092, 1199, 1272, 1404, 1485, 1564, 1601, 2987, 3225 cm$^{-1}$; $^{1}$H-NMR (500 MHz, $CDCl_3$): δ 2.39 (s, 3H, -$CH_3$), 5.62 (s, 1H, H-2), 6.01 (s, 1H, NH), 6.61 (d, *J* = 8.5 Hz, 1H, H-8), 7.26 (d, *J* = 7.5 Hz, 2H, H-2',6'), 7.40 (d, *J* = 7.5 Hz, 2H, H-3',5'), 7.45 (d, *J* = 8.0 Hz, 1H, H-7), 7.49 (s, 1H, H-5); $^{13}$C-NMR (125 MHz, $CDCl_3$): δ 12.6, 78.7, 82.1, 117.3, 119.8, 128.2, 129.1, 130.8, 132.1, 133.1, 134.4, 135.7 138.2, 139.1, 139.8; HRMS (ES): $MH^+$, calcd for $C_{15}H_{13}N_2OClI$: 397.9683; found 398.9760.

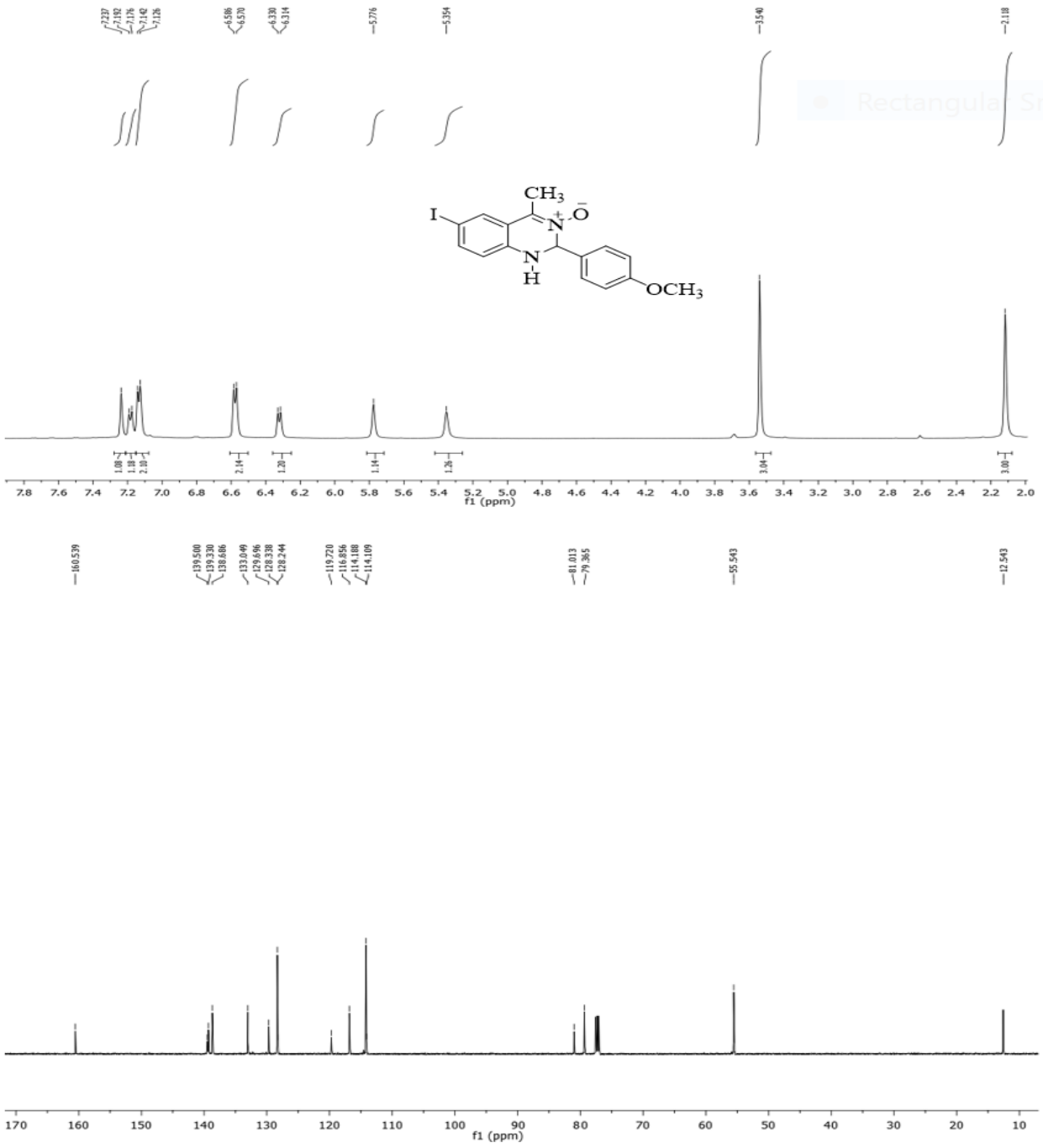



**Fig. S1.12**: $^{1}$H- and $^{13}$C-NMR spectra of **3h** in $CDCl_3$ at 500 MHz and 125 MHz, respectively.

6-Iodo-2-(4-methoxyphenyl)-4-methyl-1,2-dihydroquinazoline 3-oxide (**3h**)

Yellow solid (0.43 g, 86%), $R_f$ (5% EtOAc–toluene) 0.60, mp. 176–179 °C; $\nu_{max}$ (ATR) 822, 1030, 1203, 1293, 1459, 1515, 1596 (C=N), 2974, 3269 (NH) cm$^{-1}$; $^{1}$H-NMR (500 MHz, $CDCl_3$): δ 2.18 (s, 3H, -$CH_3$), 3.54 (s, 3H, -$OCH_3$), 5.35 (s, 1H, H-2), 5.78 (s, 1H, NH), 6.31 (d, $J$ = 8.0 Hz, 1H, H-8), 6.57 (d, $J$ = 8.0 Hz, 2H, H-3',5'), 7.13 (d, $J$ = 8.0 Hz, 2H, H-2',6'), 7.18 (d, $J$ = 8.0 Hz, 1H, H-7), 7.24 (s, 1H, H-5); $^{13}$C-NMR (125 MHz, $CDCl_3$): δ 12.5, 55.5, 79.4, 81.0, 114.1, 114.2, 116.8, 119.7, 128.2, 128.3, 129.7, 133.0, 138.7, 139.3, 139.5, 160.5; HRMS (ES): $MH^+$, calcd for $C_{16}H_{16}N_2O_2I$: 395.0178; found 395.9600.

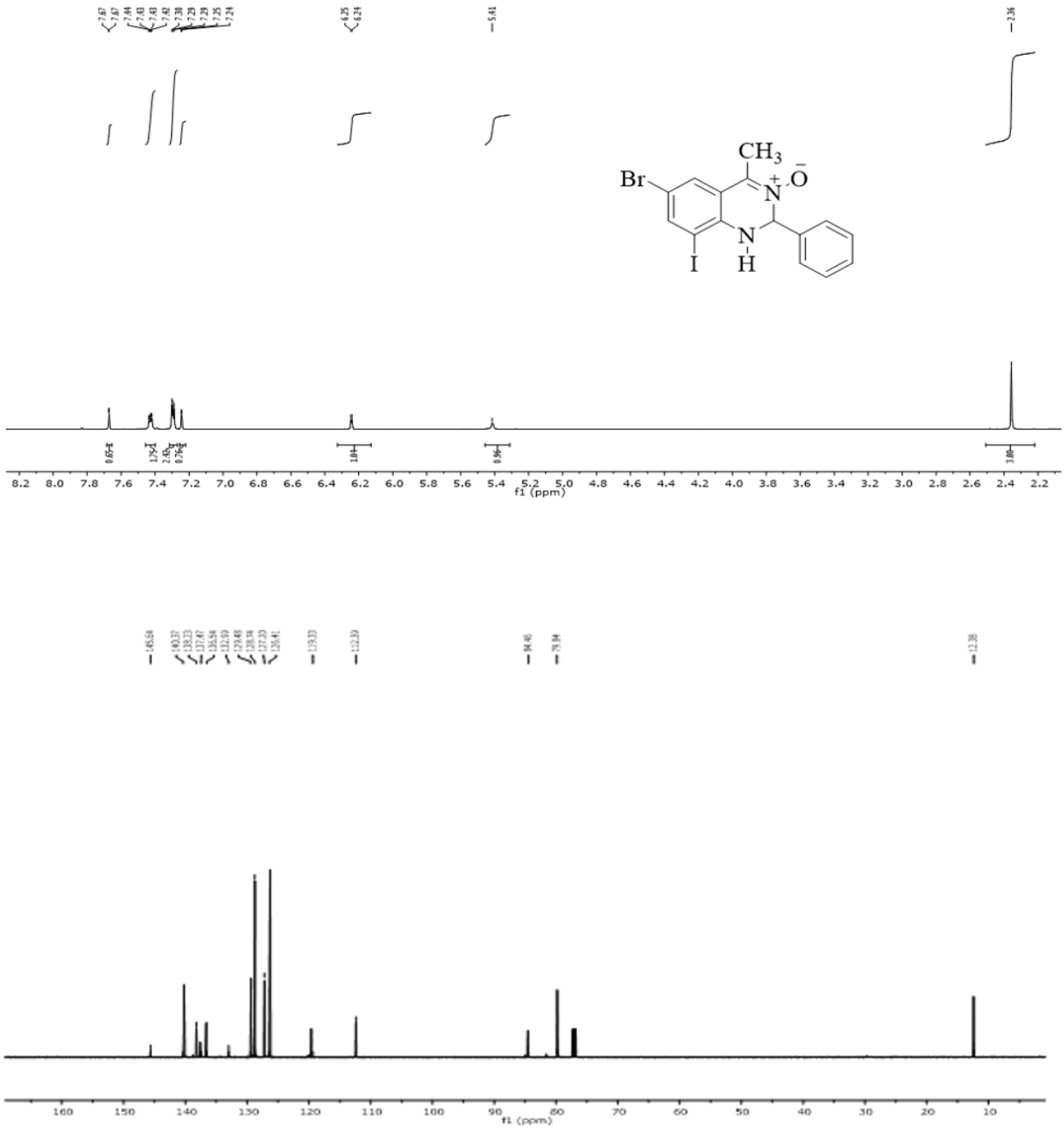



**Fig. S1.13**: $^{1}$H- and $^{13}$C-NMR spectra of **3i** in $CDCl_3$ at 500 MHz and 125 MHz, respectively.

6-Bromo-8-iodo-4-methyl-2-phenyl-1,2-dihydroquinazoline 3-oxide (**3i**)

Yellow solid (0.37 g, 74%); $R_f$ (5% EtOAc–toluene) 0.64, mp. 162–164 °C; $\nu_{max}$ (ATR); 1069, 1231, 1262, 1327, 1478, 1584, 1600, 2921, 3288.3 cm$^{-1}$; $^{1}$H-NMR (500 MHz, $CDCl_3$): δ 2.36 (s, 3H, -$CH_3$), 5.41 (s, 1H, H-2), 6.24 (d, $J$ = 3.5 Hz, 1H, NH), 7.24 (d, $J$ = 2.0 Hz, 1H, H-5), 7.25–7.30 (m, 3H, H-4′ and H-2′,6′), 7.40–7.44 (m, 2H, H-3′,5′), 7.67 (d, $J$ = 2.0 Hz, 1H, H-7); $^{13}$C-NMR (125 MHz, $CDCl_3$): δ 12.4, 79.8, 84.5, 112.3, 119.7, 126.2, 127.2, 128.7, 129.4, 132.9, 136.6, 137.6, 138.3, 140.3, 145.6; HRMS (ES): $MH^+$, calcd for $C_{15}H_{12}N_2OBrI$: 442.9178; found 442.9246.

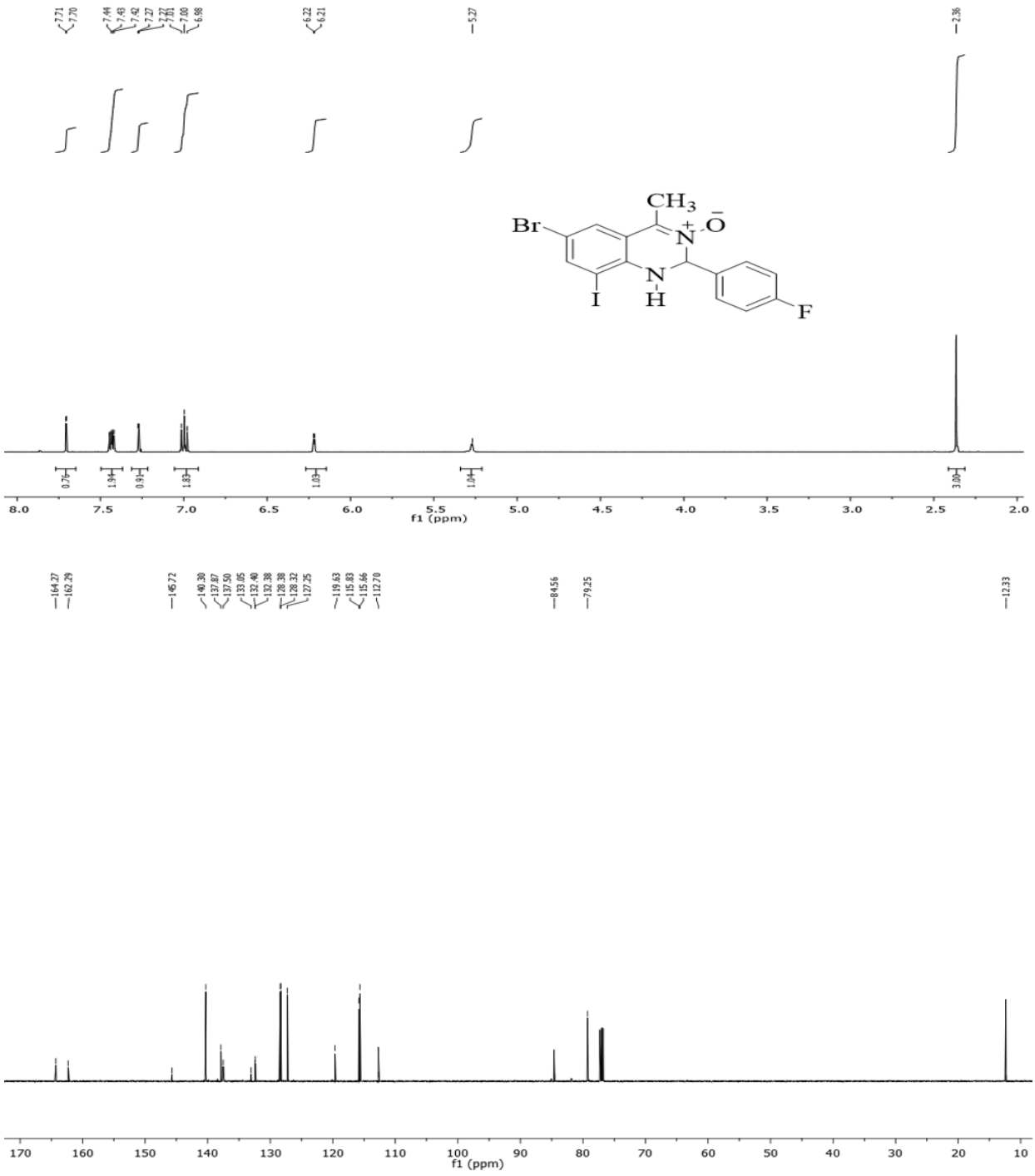



**Fig. S1.14**: $^{1}$H- and $^{13}$C-NMR spectra of **3j** in $CDCl_3$ at 500 MHz and 125 MHz, respectively.

6-Bromo-2-(4-fluorophenyl)-8-iodo-4-methyl-1,2-dihydroquinazoline 3-oxide (**3j**)

Yellow solid (0.30 g, 60%); $R_f$ (5% EtOAc–toluene) 0.66, mp. 170–173 °C; $\nu_{max}$ (ATR) 1010, 1222, 1279, 1404, 1479, 1503, 1602, 2923, 3236, $^{1}$H-NMR (500 MHz, $CDCl_3$): δ 2.37 (s, 3H, -$CH_3$), 5.27 (s, 1H, H-2), 6.22 (d, $J$ = 3.5 Hz, 1H, NH), 6.99 (t, $J$ = 8.5 Hz, 2H, H-3′,5′), 7.27 (d, $J$ = 2.0 Hz, 1H, H-5), 7.43 (dt, $J_{HH}$ = 8.5 Hz and $J_{HF}$ = 5.5 Hz, 2H, H-2′,6′), 7.71 (d, $J$ = 2.0 Hz, 1H, H-7); $^{13}$C-NMR (125 MHz, $CDCl_2$): δ 12.3, 79.3, 84.6, 112.7, 115.7 (d, $^{2}J_{CF}$ = 21.3 Hz), 119.6, 127.3, 128.4 (d, $^{3}J_{CF}$ = 7.7 Hz), 132.4 (d, $^{4}J_{CF}$ = 2.5 Hz), 133.1, 137.5, 137.9, 140.3, 145.7, 162.3 (d, $^{1}J_{CF}$ = 247.5 Hz); HRMS (ES): $MH^+$, calcd for $C_{15}H_{11}N_2OBrFI$: 460.9083; found 460.8727.

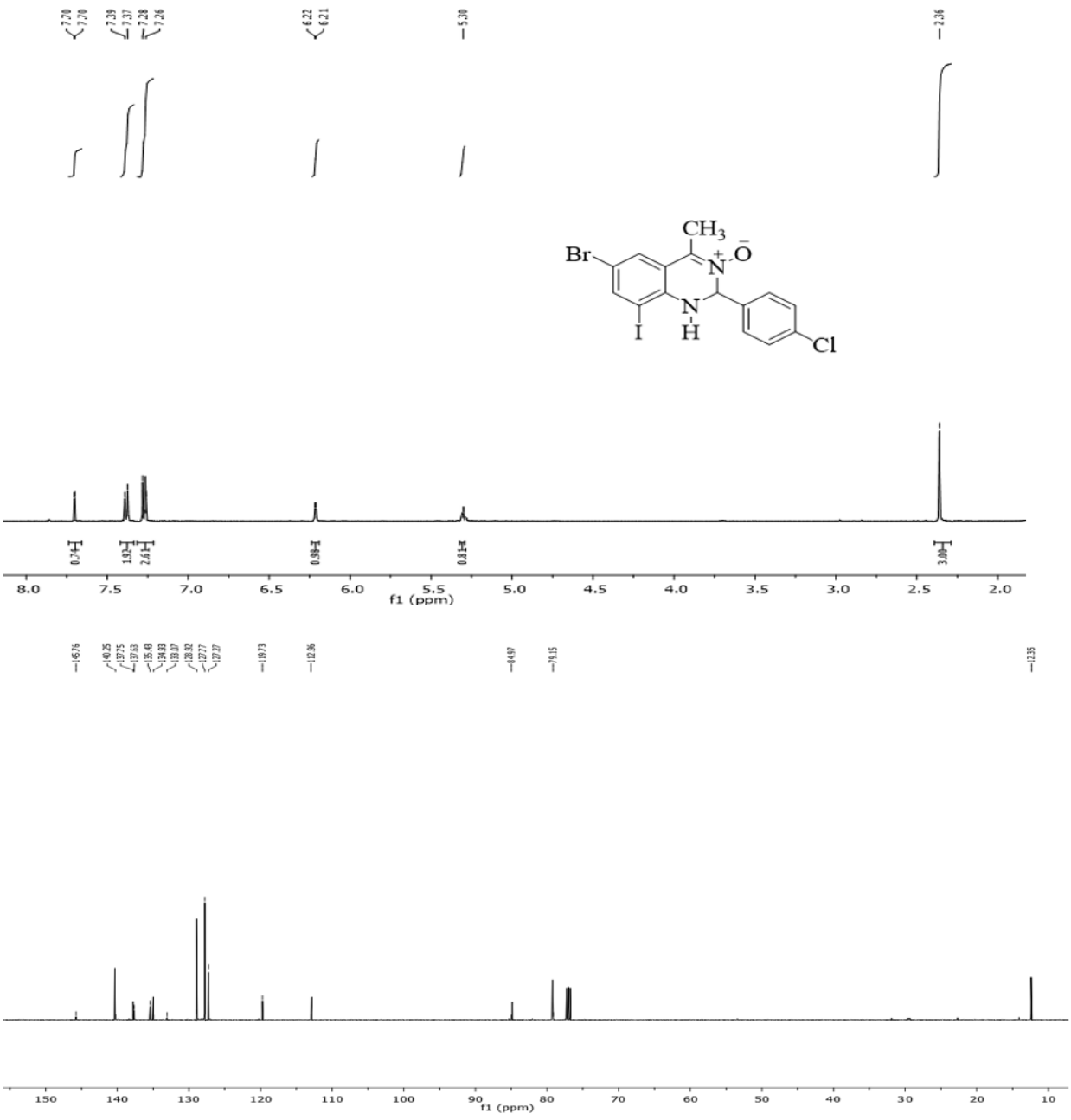



**Fig. S1.15**: $^{1}$H- and $^{13}$C-NMR spectra of **3k** in $CDCl_3$ at 500 MHz and 125 MHz, respectively.

6-Bromo-2-(4-chlorophenyl)-8-iodo-4-methyl-1,2-dihydroquinazoline 3-oxide (**3k**)

Yellow solid (0.40 g, 80%); $R_f$ (5% EtOAc–toluene) 0.70, mp. 168-170 °C; $\nu_{max}$ (ATR) 1172, 1228, 1261, 1399, 1481, 1575, 2916, 2972, 3230; $^{1}$H-NMR (500 MHz, $CDCl_3$): δ 2.36 (s, 3H, -$CH_3$), 5.29 (s, 1H, H-2), 6.21 (d, *J* = 3.5 Hz, 1H, NH), 7.26 (t, *J* = 2.5 Hz, 2H, H-2′,6′), 7.27 (d, *J* = 2.0 Hz, 1H, H-5), 7.28 (d, *J* = 8.0 Hz, 2H, H-3′,5′), 7.70 (d, *J* = 2.0 Hz, 1H, H-7); $^{13}$C-NMR (125 MHz, $CDCl_3$): δ 12.4, 79.2, 85.0, 113.0, 119.7, 127.3, 127.3, 127.8, 128.9, 133.1, 134.9, 135.4, 137.6, 137.8, 140.3, 145.8; HRMS (ES): $MH^+$, calcd for $C_{16}H_{14}N_2O_2BrI$: 472.9283; found 472.9355.

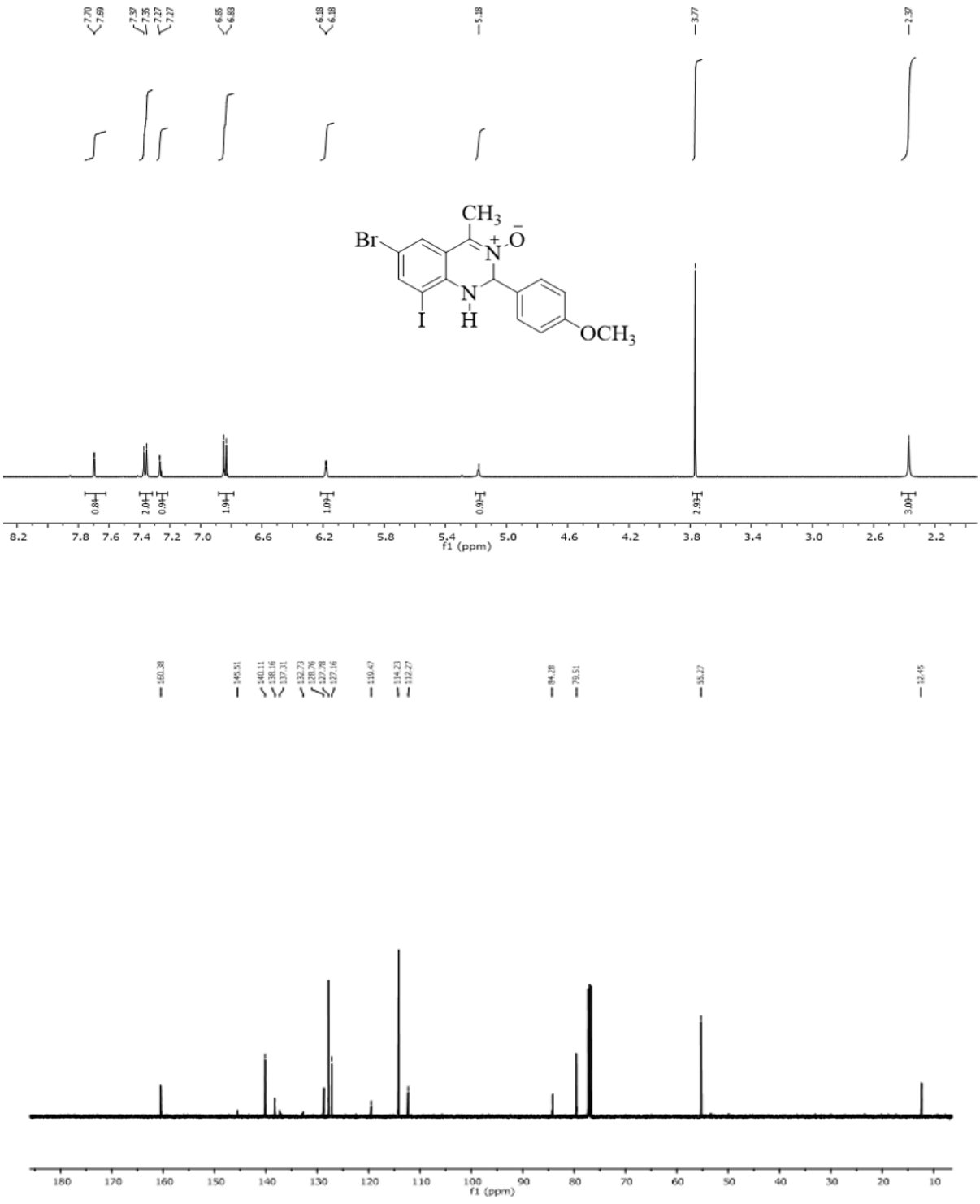



**Fig. S1.16**: $^{1}$H- and $^{13}$C-NMR spectra of **3l** in $CDCl_3$ at 500 MHz and 125 MHz, respectively.

6-Bromo-8-iodo-2-(4-methoxyphenyl)-4-methyl-1,2-dihydroquinazoline 3-oxide (**3l**)

Yellow solid (0.42 g, 84%), $R_f$ (5% EtOAc–toluene) 0.63, mp. 153–155 °C; $\nu_{max}$ (ATR); 1024, 1168, 1230, 1482, 1503, 1575, 1606, 2968, 3223 cm$^{-1}$; $^{1}$H-NMR (500 MHz, $CDCl_3$): δ 2.37 (s, 3H, -$CH_3$), 3.77 (s, 3H, -$OCH_3$), 5.18 (s, 1H, H-2), 6.18 (d, $J$ = 3.0 Hz, 1H, NH), 6.84 (d, $J$ = 9.0 Hz, 2H, H-2′,6′), 7.27 (d, $J$ = 2.0 Hz, 1H, H-5), 7.36 (d, $J$ = 8.5 Hz, 2H, H-3′,5′), 7.70 (d, $J$ = 2.0 Hz, 1H, H-7); $^{13}$C-NMR (125 MHz, $CDCl_3$): δ 12.5, 55.4, 79.5, 84.3, 112.3, 114.2, 119.5, 127.2, 127.4, 128.4, 132.7, 137.3, 138.2, 140.1, 145.5, 160.4; HRMS (ES): $MH^+$, calcd for $C_{16}H_{14}N_2O_2BrI$: 472.9283; found 472.9355.

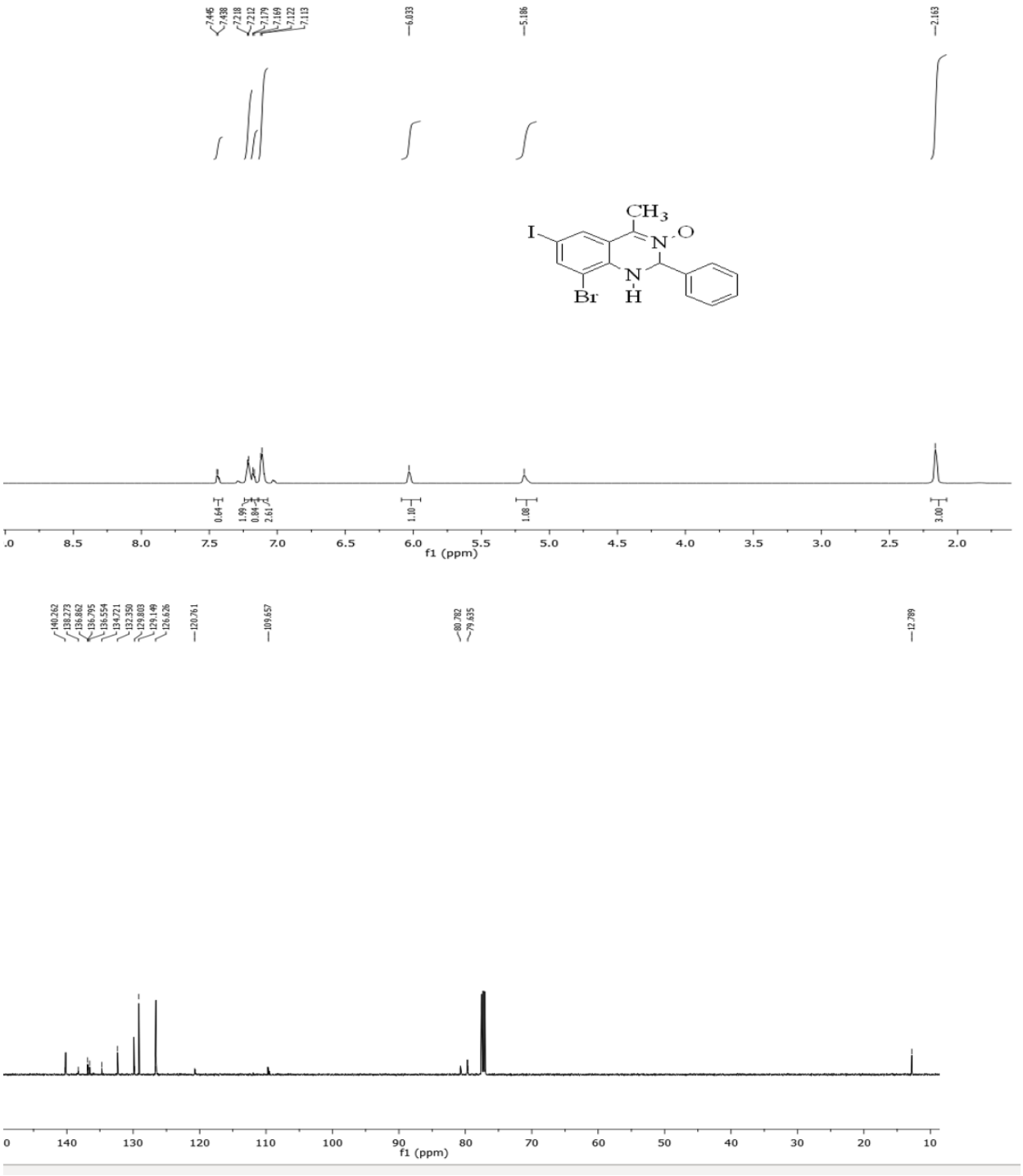



**Fig. S1.17**: $^{1}$H- and $^{13}$C-NMR spectra of **3m** in $CDCl_3$ at 500 MHz and 125 MHz, respectively.

8-Bromo-6-iodo-4-methyl-2-phenyl-1,2-dihydroquinazoline 3-oxide (**3m**)

Yellow solid (0.38 g, 76%), $R_f$ (5% EtOAc–toluene) 0.62, mp. 180–181 °C; $\nu_{max}$ (ATR) 856, 1082, 1184, 1234, 1446, 1485, 1589, 2920, 3250 cm$^{-1}$; $^{1}$H-NMR (500 MHz, $CDCl_3$): δ 2.16 (s, 3H, -$CH_3$), 5.19 (s, 1H, H-2), 6.03 (s, 1H, NH), 7.12 (d, $J$ = 4.5 Hz, 3H, H-4′ and H-2′,6′), 7.18 (d, $J$ = 3.5 Hz, 1H, H-5), 7.21 (d, $J$ = 3.5 Hz, 2H, H-7); $^{13}$CNMR (125 MHz, $CDCl_3$): δ 12.7, 79.6, 80.9, 109.8, 120.6, 126.7, 129.1, 129.9, 132.4, 134.7, 136.6, 136.8, 138.3, 140.3; HRMS (ES): $MH^+$, calcd for $C_{15}H_{13}N_2OBrI$: 442.9178; found 442.9252.

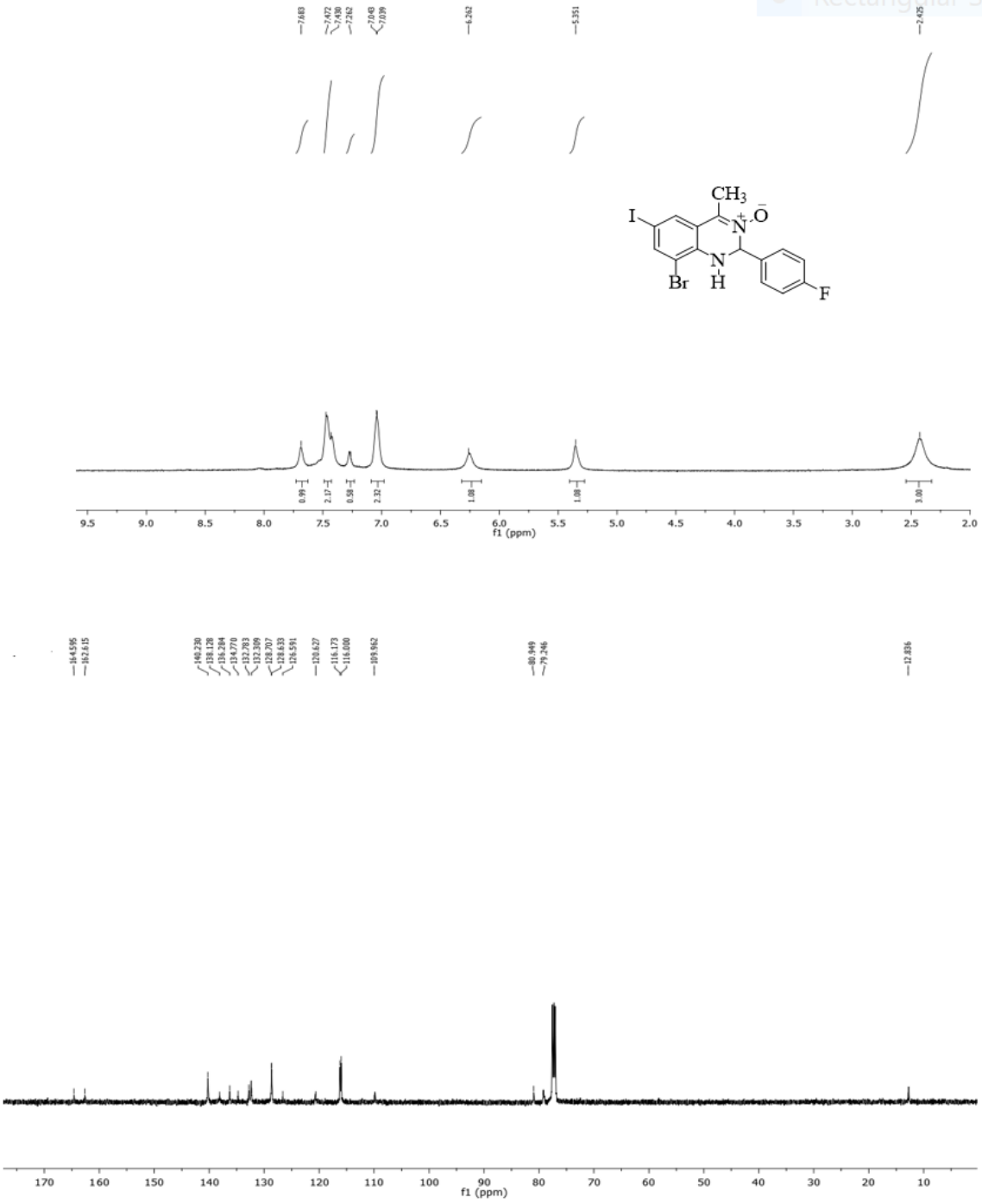



**Fig. S1.18**: $^{1}$H- and $^{13}$C-NMR spectra of **3n** in $CDCl_3$ at 500 MHz and 125 MHz, respectively.

8-Bromo-2-(4-fluorophenyl)-6-iodo-4-methyl-1,2-dihydroquinazoline 3-oxide (**3n**)

Yellow solid (0.30 g, 66%), $R_f$ (5% EtOAc–toluene) 0.64, mp. 125–127 °C; $\nu_{max}$ (ATR) 861, 1095, 1187, 1231, 1487, 1591, 1669, 3057, 3278 cm$^{-1}$; $^{1}$H-NMR (500 MHz, $CDCl_3$): δ 2.43 (s, 3H, $CH_3$), 5.35 (s, 1H, H-2), 6.26 (s, 1H, NH), 7.03 (t, $J$ = 2.0 Hz, 2H, H-3',5'), 7.26 (s, 1H, H-5), 7.43 (2H, d, $J$ = 21.0 Hz, 2H, H-2',6'), 7.68 (s, 1H, H-7); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 12.8, 79.2, 80.9, 109.9, 116.0 (d, $^{2}J_{CF}$ = 21.6 Hz), 120.6, 126.6, 128.6 (d, $^{3}J_{CF}$ = 9.0 Hz), 132.3, 132.7 (d, $^{4}J_{CF}$ = 2.8 Hz), 134.8, 136.3, 138.1, 140.2, 162.6 (d, $^{1}J_{CF}$ = 247.5); HRMS (ES): MH$^{+}$, calcd for $C_{15}H_{12}N_2OBrFI$: 460.9083; found 460.9149.

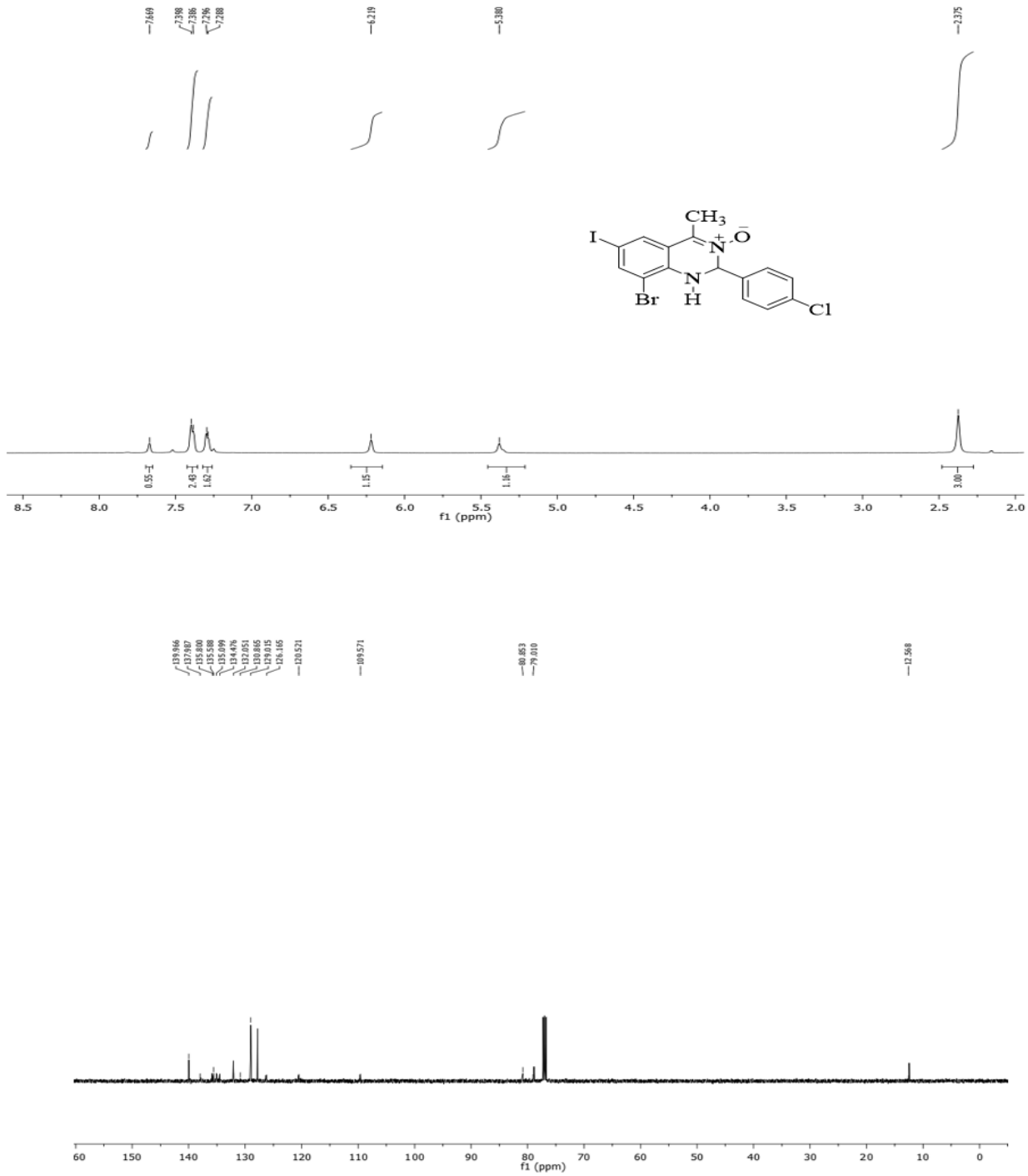



**Fig. S1.19**: $^{1}$H- and $^{13}$C-NMR spectra of **3o** in $CDCl_3$ at 500 MHz and 125 MHz, respectively.

8-Bromo-2-(4-chlorophenyl)-6-iodo-4-methyl-1,2-dihydroquinazoline 3-oxide (**3o**)

Yellow solid (0.49 g, 98%), $R_f$ (5% EtOAc–toluene) 0.65, mp. 140–142 °C; $\nu_{max}$ (ATR) 856, 1082, 1184, 1234, 1446, 1485, 1589, 2920, 3250 cm$^{-1}$; $^{1}$H-NMR (500 MHz, $CDCl_3$): δ 2.38 (s, 3H, $CH_3$), 5.38 (s, 1H, H-2), 6.22 (s, 1H, NH), 7.29 (d, $J$ = 4.0 Hz, 2H, H-2′,6′), 7.39 (d, $J$ = 6.0 Hz, 3H, H-3′,5′ and H-5), 7.69 (s, 1H, H-7); $^{13}$CNMR (125 MHz, $CDCl_2$): δ 12.6, 79.0, 80.8, 109.6, 120.5, 126.2, 129.0, 130.8, 132.1, 134.5, 135.1, 135.6, 135.8, 137.9, 139.9; HRMS (ES): $MH^+$, calcd for $C_{15}H_{12}N_2OBrClI$: 476.8788; found 476.8388.

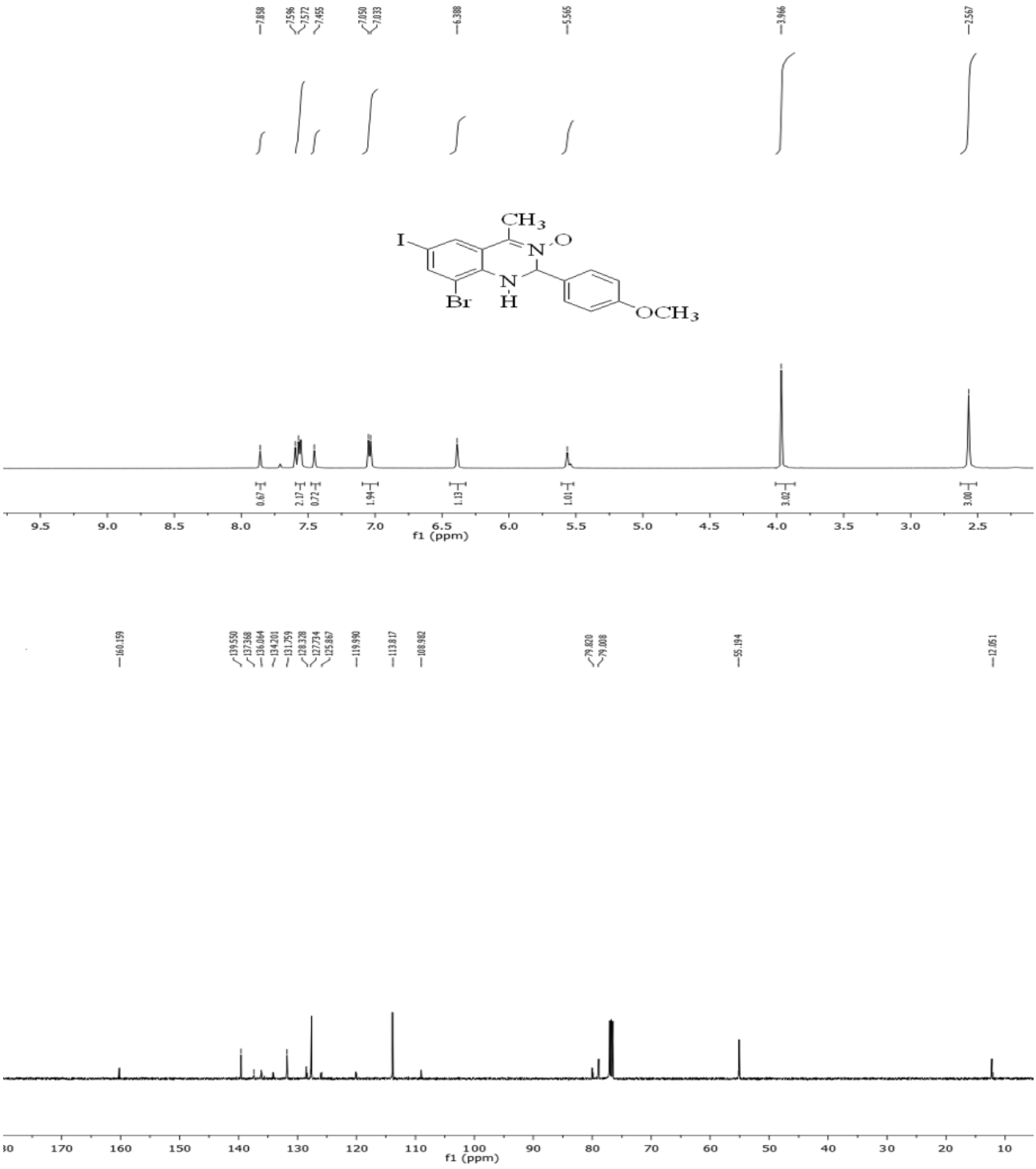



**Fig. S1.20**: $^{1}$H- and $^{13}$C-NMR spectra of **3p** in $CDCl_3$ at 500 MHz and 125 MHz, respectively.

8-bromo-6-iodo-2-(4-methoxyphenyl)-4-methyl-1,2-dihydroquinazoline 3-oxide (**3p**)

Yellow solid (0.47 g, 94%), $R_f$ (5% EtOAc–toluene) 0.60, mp. 173–174 °C; $\nu_{max}$ (ATR) 856, 1082, 1184, 1234, 1446, 1485, 1589, 2920, 3250 cm$^{-1}$; $^{1}$H-NMR (500 MHz, $CDCl_3$): δ 2.57 (s, 3H, $CH_3$), 3.97 (s, 3H, $OCH_3$), 5.57 (s, 1H, H-2), 6.39 (s, 1H, NH), 7.04 (d, $J$ = 10 Hz, 2H, H-3′,5′), 7.46 (s, 1H, H-5), 7.58 (d, $J$ = 12 Hz, 2H, H-2′,6′), 7.86 (s, 1H, H-7); $^{13}$C-NMR (125 MHz, $CDCl_2$): δ 12.1, 55.2, 79.0, 79.8, 108.9, 113.8, 119.9, 125.9, 127.7, 128.3, 131.8, 134.2, 136.1, 137.4, 139.6, 160.2; HRMS (ES): $MH^+$, calcd for $C_{16}H_{15}N_2O_2BrI$: 472.9283; found 472.9385.

**Table S1:** X-ray analysis, crystal data and structure refinement for **3i**

Data collection and refinement of **3i**

Intensity data was determined on a Bruker Venture D8 Photon CMOS diffractometer with graphite-monochromated MoK$\alpha_1$ (l = 0.71073 Å) radiation at 173(2) K using an Oxford Cryostream 600 cooler. Data reduction, empirical absorption corrections and space group assignments were carried out using the program SAINT+ version 6.02, SADABS and XPREP, respectively [3]. The structure was solved in the WinGX [4] Suite of programs, using intrinsic phasing through SHELXT [5] and refined using full-matrix least-squares/difference Fourier techniques on $F^2$ using SHELXL-2017 [6]. All C-bound hydrogen atoms were placed at idealized positions and refined as riding atoms with isotropic parameters 1.2 or 1.5 times those of their parent atoms. The *N*-bound hydrogen atom was located in the difference Fourier Map and fractional coordinates and isotropic displacement parameter refined freely. Diagrams and publication material were generated using ORTEP-3 [4] and PLATON [7].

Crystal data and structure refinement for **3i**

| | **2a** |
|---|---|
| CCDC | 2266298 |
| Empirical formula | $C_{15}H_{12}BrIN_2O$ |
| Formula weight | 443.08 |
| Crystal system | Monoclinic |
| Space group | *P*21/n |
| a, b, c (Å) | 7.5889(3), 8.3516(3), 9.0732(4) |
| β (°) | 90.312(5) |
| Volume (Å$^3$) | 1540.4(3) |
| Z | 4 |
| $\varrho_{calc}$ ($g/cm^3$) | 1.911 |
| μ (mm$^{-1}$) | 4.669 |
| F(000) | 848 |
| Crystal size (mm$^3$) | 0.395 x 0.279 x 0.072 |
| $\theta_{min}/\theta_{max}$ (°) | 2.163/28.000 |
| Index ranges | -14 ≤ h ≤ 14, -10 ≤ k ≤ 10, -24 ≤ l ≤ 24 |
| Reflections collected | 53714 |
| Independent reflections | 3717 [R(int) = 0.0659] |
| Data/restraints/parameters | 3717 / 0 / 186 |
| Goodness-of-fit on $F^2$ | 1.042 |
| Final *R* indexes [$I \geq 2\sigma$ (*I*)] | $R_1$ = 0.0240, wR2 = 0.0622 |
| Final R indexes [all data] | $R_1$ = 0.0263, wR2 = 0.0637 |
| Largest diff. peak/hole ($e.Å^{-3}$) | 1.318 and -1.060 |

**References**


1. Ye, X.; Chen, Z.; Zhang, Z.; Fu, Y.; Deng, Z.; Peng, Y. An convenient approach to 2,4-disubstituted quinazoline-3-oxides using active $MnO_2$ as oxidant. *Canadian J. Chem*. **2019**, *97*, 682–689.
2. Mphahlele, M.J.; Magwaza, N.M.; Gildenhuys, S.; Setshedi, I.B. Synthesis, Synthesis, $\alpha$-glucosidase inhibition, and antioxidant activity of the 7-carbo–substituted 5-bromo-3-methylindazoles. *Bioorg. Chem*. **2020**, *97*, 103702.
3. Bruker, APEX-3, SAINT+, Version 6.02 (Includes XPREP and SADABS), Bruker AXS Inc., Madison, Wisconsin, USA, **2016**.
4. Farrugia, L.J. WinGX and ORTEP for Windows an update. *J. Appl. Crystallogr*. **2012**, *245*, 849–854.
5. Sheldrick, G.M. SHELXT-Integrated space-group and crystal-structure determination. *Acta Cryst*. **2015**, *71*, 3–8.
6. Sheldrick, G.M. SHELXL-2017/1. *Acta Crystallogr*. **2015**, *C71*, 3–8.
7. Spek, A.L. Structure validation in chemical crystallography. *Acta Cryst*. **2009**, *D65*, 148-155.

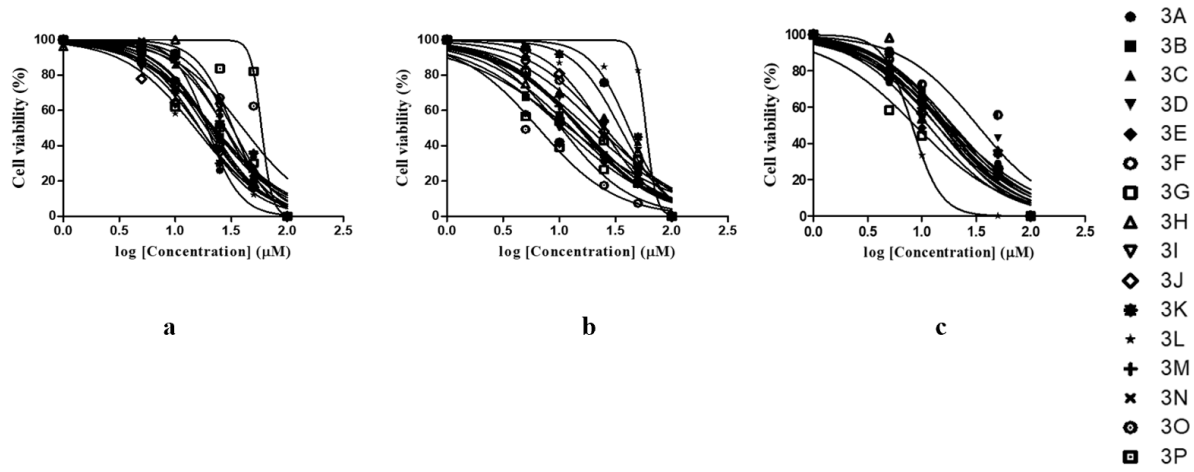



**Fig. S2:** Graphs showing dose-dependent effect on cell viability in MCF-7 (a), A549 (b) and HEK293-T (c).

**Table S2**: Cell viability percentage of compounds **3a–p** against MCF-7 cell line.

| Conc. | 3A | 3B | 3C | 3D | 3E | 3F | 3G | 3H | 3I | 3J | 3K | 3L | 3M | 3N | 3O | 3P |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **50** | 19,6607 | 30,3061 | 37,2256 | 38,6394 | 17,2488 | 23,6814 | 33,9155 | 37,5083 | 18,1803 | 22,7375 | 38,1737 | 17,5102 | 17,6314 | 30,1896 | 23,0428 | 27,8817 |
| **25** | 22,3387 | 33,8157 | 41,6999 | 43,2136 | 19,7272 | 32,649 | 35,8117 | 41,2009 | 19,5775 | 30,7493 | 38,7891 | 35,1896 | 20,6088 | 31,7365 | 38,7891 | 43,212 |
| **10** | 23,187 | 35,1963 | 42,5981 | 44,0286 | 23,6194 | 44,9558 | 36,5769 | 43,1304 | 22,1058 | 40,413 | 39,6041 | 51,5919 | 20,9415 | 31,9528 | 39,6041 | 59,2339 |
| **5** | 26,1144 | 38,34 | 44,7938 | 46,8729 | 22,0559 | 62,4071 | 37,841 | 44,5775 | 22,006 | 53,8289 | 41,6001 | 55,5856 | 24,1517 | 33,2335 | 41,6001 | 70,8112 |
| **1** | 26,2641 | 39,7538 | 46,7898 | 47,0559 | 27,8443 | 69,8879 | 42,0991 | 45,0932 | 24,1184 | 60,354 | 42,1823 | 66,3742 | 25,998 | 34,8969 | 46,2908 | 72,4624 |

**Table S3:** Cell viability percentage of compounds **3a–p** against the A549 cell line.

| Conc. | 3A | 3B | 3C | 3D | 3E | 3F | 3G | 3H | 3I | 3J | 3K | 3L | 3M | 3N | 3O | 3P |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **50** | 30,5771 | 28,8446 | 29,5534 | 39,174 | 30,3184 | 32,7708 | 33,0296 | 38,362 | 23,0847 | 29,7109 | 32,6808 | 45,4944 | 30,0709 | 30,3521 | 39,174 | 39,3879 |
| **25** | 41,1182 | 42,7495 | 41,782 | 44,944 | 40,2408 | 44,212 | 43,0757 | 56,0806 | 43,9195 | 42,6257 | 42,682 | 45,5732 | 42,2995 | 43,4807 | 44,944 | 42,5649 |
| **10** | 54,0443 | 56,1818 | 54,3481 | 46,8555 | 52,0419 | 61,143 | 50,6131 | 64,8667 | 61,098 | 57,7455 | 60,0068 | 60,333 | 61,413 | 62,0205 | 46,8555 | 43,6627 |
| **5** | 57,3068 | 60,8505 | 66,5879 | 66,5487 | 64,338 | 71,9204 | 56,2268 | 86,9389 | 69,8954 | 67,1729 | 73,6416 | 82,1465 | 68,6691 | 73,2703 | 66,5487 | 44,7771 |
| **1** | 66,8354 | 69,0066 | 73,4391 | 67,7876 | 74,9578 | 82,3715 | 72,7416 | 87,7714 | 84,0927 | 79,064 | 78,5578 | 89,6276 | 78,1978 | 79,9753 | 67,7876 | 45,0433 |

**Table S4:** Cell viability percentage of compounds **3a–p** against the HEK293-T cell line.

| Conc. | 3A | 3B | 3C | 3D | 3E | 3F | 3G | 3H | 3I | 3J | 3K | 3L | 3M | 3N | 3O | 3P |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **50** | 19,0443 | 35,7618 | 23,5044 | 17,6402 | 20,0236 | 14,6903 | 17,0502 | 28,1437 | 26,8962 | 19,351 | 24,0118 | 19,7272 | 19,1032 | 20,4602 | 37,658 | 18,3835 |
| **25** | 55,0679 | 38,4731 | 34,1829 | 30,5988 | 31,941 | 36,7198 | 31,41 | 29,6574 | 29,8237 | 33,8879 | 31,5988 | 25,4809 | 41,9705 | 39,5988 | 44,2282 | 74,7257 |
| **10** | 57,8407 | 40,3194 | 50,3009 | 54,1003 | 40,0236 | 47,7522 | 41,062 | 30,7718 | 33,7658 | 54,4779 | 42,5133 | 59,208 | 51,1032 | 54,1003 | 44,3945 | 75,7994 |
| **5** | 63,351 | 41,3007 | 62,9381 | 60,0531 | 60,0118 | 55,2212 | 46,5251 | 32,5682 | 33,8656 | 72,767 | 55,3864 | 69,4229 | 75,0089 | 70,0531 | 44,5609 | 81,4277 |
| **1** | 69,3687 | 41,5502 | 64,6608 | 75,0561 | 69,7463 | 71,9646 | 63,41 | 33,3001 | 34,8969 | 67,5634 | 61,3333 | 80,3803 | 81,2389 | 75,0561 | 45,1763 | 83,4336 |

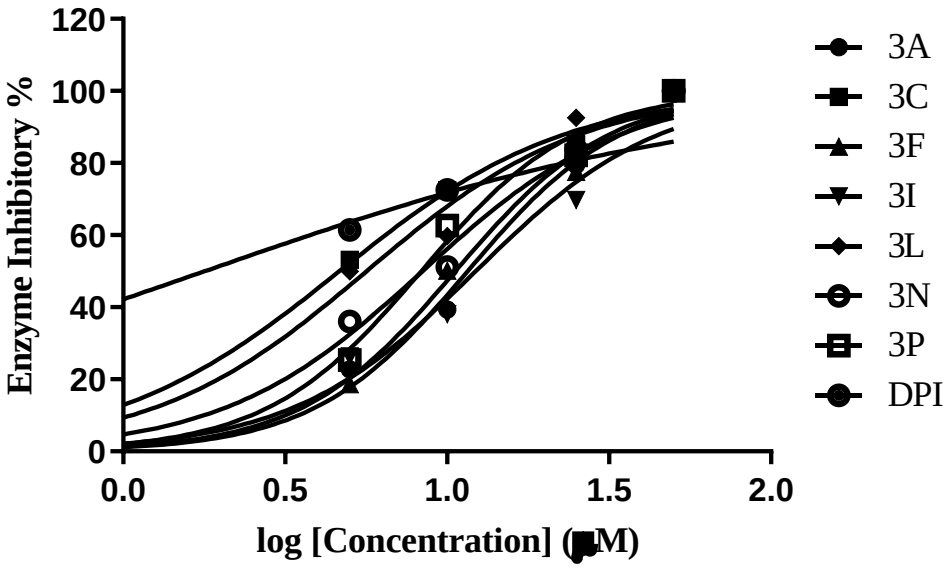
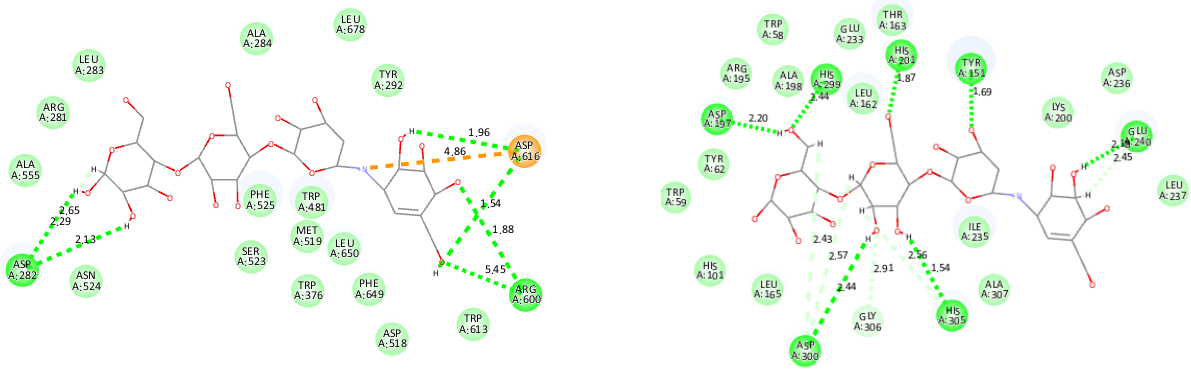



**Fig. S3:** Graphs of % inhibition of SOD used to calculate $IC_{50}$ values.

**Table S5:** Binding energies of **3a, 3c, 3f, 3i, 3l** and **3p** docked into $\alpha$-glucosidase and $\alpha$-amylase

| | Binding energy (kcal/mol) | |
|---|---|---|
| **Compound** | **$\alpha$-glucosidase** | **$\alpha$-amylase** |
| **3a** | -19.5004 | -9.4692 |
| **3c** | -23.5707 | -36.8609 |
| **3f** | -27.3552 | -32.4730 |
| **3i** | -21.2141 | -18.1673 |
| **3l** | -22.5943 | -37.7027 |
| **3p** | -22.5534 | -39.0532 |
| Acarbose | -35.1447 | -25.2018 |



(a) (b)

**Fig. S4:** Docking poses of acarbose against $\alpha$-glucosidase (a) and $\alpha$-amylase (b). Interaction types are marked with dashed lines and are color-coded as follows: Bright green- conventional hydrogen bond; lighter green van der Waals interaction; very light green- carbon-hydrogen bond; orange is a salt bridge or attractive charge or pi-anion.