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# New route to bioactive 2-(hetero)arylethylamines *via* nucleophilic ring opening in fused 7-acyl-2,3-dihydroazepines

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## S1. General Information

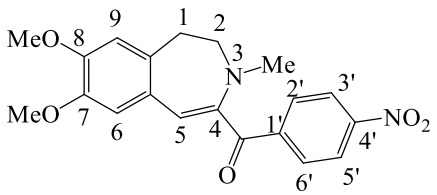
The solvents were purified according to standard procedures. NMR spectra were recorded at 30ºC or 50ºC (for some 2D-spectra) on a Bruker Avance 600 (600 MHz) spectrometer in DMSO-$d_6$. Chemical shifts of nuclei $^1$H and $^{13}$C were measured relatively the signals of deuterated solvent [δ =2.50 (2.49) ppm for residual protons and 39.09 (39.28) ppm for carbon; for 30 (50)ºC, respectively] (see [S1] and literature cited therein), $^{15}$N chemical shifts were given relatively $^{15}NH_3$. Coupling constants (*J*) are reported in Hz. Melting points were determined by using Fisher-Johns Melting Point Apparatus (Fisher Scientific) and are uncorrected. Elemental analysis was performed by the classical method of microanalysis. The reaction and purity of the obtained compounds were monitored by TLC (plates with $Al_2O_3$ III activity grade, eluent $CHCl_3$, development of TLC plates by exposition to iodine vapors in "iodine chamber").

The crystallographic data for structure **2g** were obtained on an Agilent SuperNova diffractometer by using a microfocus X-ray source with copper anode and an Atlas S2 two-dimensional CCD detector. The reflections were collected, unit cell parameters determined and refined by using the CrysAlisPro 1.171.39.46 software suite (Rigaku Oxford Diffraction, 2018) [S2]. The structures were solved by using the ShelXT program (Sheldrick, 2015) [S3] and refined with the ShelXL program (Sheldrick, 2015) [S4] with the following graphical user interfaces of the Olex2 ver. 1.2.10 program [S5]. Molecular graphics: Ortep style plot from Platon [S6]. CCDC 1897576 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk.

Quantum chemical calculations (B3LYP/6-31G**) were performed using quantum chemical program package Firefly 8.0 [S7], which is partially based on the GAMESS (US) [S8] source code.

The starting compounds **1a, c-j** were provided by InterBioscreen Ltd (Russia).

*(7,8-Dimethoxy-3-methyl-1,2-dihydro-3H-benz[d]azepin-4-yl)(4-nitrophenyl)methanone* **1b**.

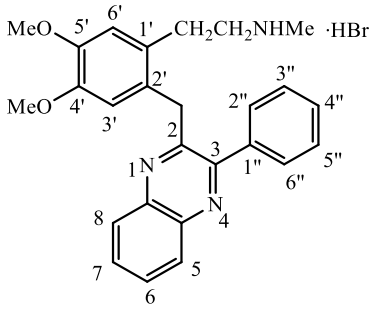



A mixture of 6,7-dimethoxy-2-methyl-3,4-dihydroisoquinolinium iodide (6.7 g; 0.02 mol), 2-bromo-1-(4-nitrophenyl)ethane-1-one (4.9 g; 0.02 mol), suspended in saturated aqueous solution $K_2CO_3$ (15 mL) and $CHCl_3$ (30 mL), was stirred vigorously for 2 h at 25 °C and 1 h at 40°C. The mixture was then cooled, the organic layer was separated, evaporated and the residue was recrystallized from ethyl acetate. The yield was 5.75 g (78%). Red crystals with mp 143-144ºC (EtOAc). $^1$H NMR, δ, ppm: 2.49 (s, 3H, N-Me), 2.92-2.94 (m, 2H, C-$CH_2$), 3.11-3.13 (m, 2H, N-$CH_2$), 3.69 (s, 3H, OMe), 3.76 (s, 3H, OMe), 6.01 (s, 1H, H-5), 6.87 (s, 1H, H-6(9)), 6.90

(s, 1H, H-9(6)), 8.04 (d, 2H, H-2', H-6', *J* 8.8), 8.31 (d, 2H, H-3', H-5', *J* 8.8). $^{13}$C NMR (150 MHz), δ: 34.35, 41.66, 52.11, 55.48, 55.54, 113.12, 115.32, 116.93, 123.45, 126.25, 130.41, 134.35, 143.39, 144.24, 146.71, 147.40, 149.37. Found (%): C, 64.86; H, 5.12; N, 7.31. Calc. for $C_{20}H_{20}N_2O_5$ (%): C, 65.21; H, 5.47; N, 7.60.

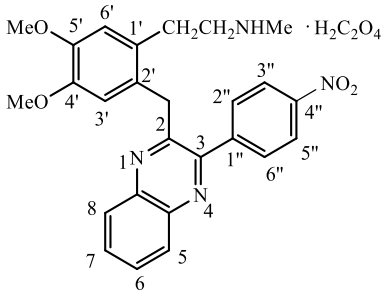
## S2. Synthesis and characterization of [3-(hetero)arylquinoxalin-2-yl]methyl derivatives of β-(hetero)arylethylamines 2a-j.

*2-{4,5-Dimethoxy-2-[(3-phenylquinoxalin-2-yl)methyl]phenyl}-N-methylethan-1-amine hydrobromide* **2a.**




The starting compound was (7,8-dimethoxy-3-methyl-1,2-dihydro-3*H*-benz[*d*]azepin-4-yl)(phenyl)methanone **1a**. The yield was 89%. Colourless crystals with mp 194-196°C (EtOH). $^1$H NMR, δ, ppm: 2.52 (s, 3H, N-Me), 2.84-2.86 (m, 2H, N-CH$_2$), 3.02-3.05 (m, 2H, C-CH$_2$ of fragment CH$_2$-CH$_2$), 3.47 (s, 3H, OMe), 3.72 (s, 3H, OMe), 4.39 (s, 2H, Ar<u>CH$_2$</u>Het), 6.33 (s, 1H, H-6'), 6.81 (s, 1H, H-3'), 7.53-7.57 (m, 3H, H-3"- H-5"), 7.69-7.71 (m, 2H, H-2", H-6"), 7.81-7.84 (m, 2H, H-6, H-7), 8.01-8.03 (m, 1H, H-8), 8.07-8.09 (m, 1H, H-5), 8.48 (s, 2H, $^+$NH$_2$). $^{13}$C NMR (150 MHz,) δ: 28.33 (C-<u>CH$_2$</u> of fragment CH$_2$-CH$_2$), 32.35 (N-Me), 38.37 (Ar<u>CH$_2$</u>Het), 48.80 (N-CH$_2$), 55.30 (OMe), 55.48 (OMe), 113.43 (C-6'), 113.71 (C-3'), 127.76, 128.23, 128.31 (C-3",5"), 128.54, 128.74, 128.87 (C-5), 129.07 (C-2",6"), 129.76, 130.05, 138.56, 140.07, 140.39, 147.19, 147.31, 154.35, 154.71. $^{15}$N, δ: 36.1 (NH), 328.0 (N-1), 329.3 (N-4). Found (%): C, 63.40; H, 5.89; Br, 16.00, N, 8.77. Calc. for $C_{26}H_{27}N_3O_2$·HBr (%): C, 63.16; H, 5.71; Br, 16.16, N, 8.50.

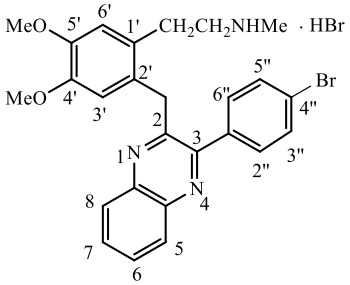
*2-(4,5-Dimethoxy-2-{[3-(4-nitrophenyl)quinoxalin-2-yl]methyl}phenyl)-N-methylethan-1-amine hydrooxalate* **2b**.




The starting compound was (7,8-dimethoxy-3-methyl-1,2-dihydro-3*H*-benz[*d*]azepin-4-yl)(4-nitrophenyl)methanone **1b**. The yield was 72%. Light beige crystals, mp 196-198°C (EtOH). $^1$H NMR, δ, ppm: 2.49 (s, 3H, N-Me), 2.78-2.80 (m, 2H, N-CH$_2$), 2.98-3.00 (m, 2H, C-CH$_2$ of fragment CH$_2$-CH$_2$), 3.47 (s, 3H, OMe), 3.71 (s, 3H, OMe), 4.38 (s, 2H, Ar<u>CH$_2$</u>Het), 6.35 (s, 1H, H-6'), 6.78 (s, 1H, H-3'), 7.83-7.87 (m, 2H, H-6, H-7), 7.98 (d, 2H, H-2", H-6", *J* 8.5), 8.04-8.05 (m, 1H, H-8), 8.10-8.12 (m, 1H, H-5), 8.36 (d, 2H, H-3", H-5", *J* 8.4), 8.62-9.04 (br.s, 2H, $^+$NH$_2$). $^{13}$C NMR (150 MHz,) δ: 28.42 (C-<u>CH$_2$</u> of fragment CH$_2$-CH$_2$), 32.31 (N-Me), 38.42 (Ar<u>CH$_2$</u>Het), 48.78 (N-CH$_2$), 55.30 (OMe), 55.45 (OMe), 113.38 (6'), 113.91 (3'), 123.38, 128.07, 128.11, 128.37 (C-3",5"), 128.85 (C-5), 130.05, 130.59, 130.66 (C-2",6"), 139.89,

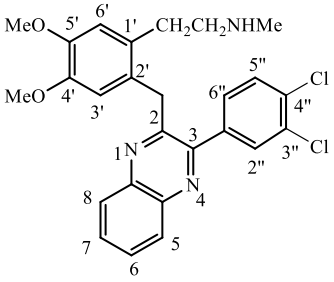
140.72, 144.92, 147.22, 147.43, 147.56, 152.93, 154.15, 154.35. Found (%): C, 61.03; H, 5.00; N, 9.84. Calc. for $C_{26}H_{26}N_4O_4 \cdot (COOH)_2$ (%): C, 61.31; H, 5.15; N, 10.21.

*2-(2-{[3-(4-Bromophenyl)quinoxalin-2-yl]methyl}-4,5-dimethoxyphenyl)-N-methylethan-1-amine hydrobromide* **2c**.



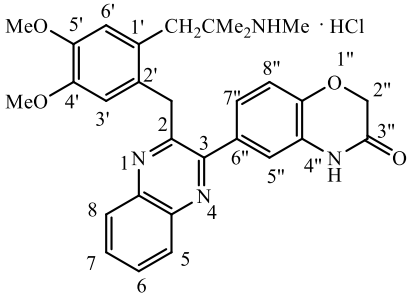

The starting compound was (4-bromophenyl)(7,8-dimethoxy-3-methyl-1,2-dihydro-3*H*-benz[*d*]azepin-4-yl)methanone **1c**. The yield was 92%. Colourless crystals, mp 178-190°C (EtOH). $^1$H NMR, δ, ppm: 2.52 (s, 3H, N-Me), 2.83-2.84 (m, 2H, N-$CH_2$), 3.03 (br.s, 2H, C-$CH_2$ of fragment $CH_2$-$CH_2$), 3.49 (s, 3H, OMe), 3.73 (s, 3H, OMe), 4.38 (s, 2H, Ar$\underline{CH_2}$Het), 6.34 (s, 1H, H-6'), 6.81 (s, 1H, H-3'), 7.66-7.68 (m, 2H, H-3", H-5"), 7.72-7.75 (m, 2H, H-2",6"), 8.01-8.02 (m, 1H, H-8), 8.07-8.09 (m, 1H, H-5), 8.47 (s, 2H, $^+NH_2$). $^{13}$C NMR (150 MHz) δ: 28.32 (C-$\underline{CH_2}$ of fragment $CH_2$-$CH_2$), 32.35 (N-Me), 38.56 (Ar$\underline{CH_2}$Het), 48.77 (N-$CH_2$), 55.26 (OMe), 55.49 (OMe), 113.40 (6'), 113.86 (3'), 122.55, 127.82, 128.26, 128.33 (C-3",5"), 128.74 (C-5'), 129.87, 130.25, 131.27, 131.28, 137.72, 140.01, 140.45, 147.20, 147.35, 153.64, 154.20. $^{15}$N, (DMSO-$d_6$) δ, ppm (from $^{15}$N – $^1$H HMBC spectrum): 35.8 (NMe), 328.0 (N-1), 329.1 (N-4). Found (%): C, 54.26; H, 4.42; Br, 27.40, N, 7.62. Calc. for $C_{26}H_{27}N_3O_2 \cdot HBr$ (%): C, 54.47; H, 4.75; Br, 27.78, N, 7.33.

*2-(2-{[3-(3,4-Dichlorophenyl)quinoxalin-2-yl]methyl}-4,5-dimethoxyphenyl)-N-methylethan-1-amine* **2d**.



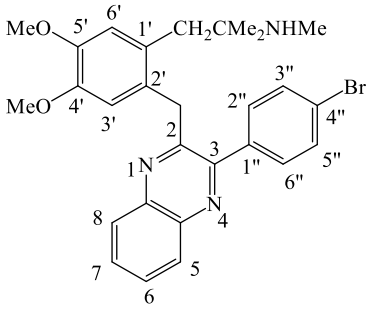

The starting compound was (3,4-dichlorophenyl)(7,8-dimethoxy-3-methyl-1,2-dihydro-3*H*-benz[*d*]azepin-4-yl)methanone **1d.** The yield was 62%. Colourless crystals, mp 45-47°C (EtOH). $^1$H NMR, δ, ppm: 2.04 (s, 3H, N-Me), 2.22 (t, 2H, N-$CH_2$, *J* 7.7), 2.41-2.44 (m, 2H, C-$CH_2$ of fragment $CH_2$-$CH_2$), 3.50 (s, 3H, OMe), 3.68 (s, 3H, OMe), 4.13-4.25 (m, Ar$\underline{CH_2}$Het), 6.22 (s, 1H, H-6'), 6.65 (s, 1H, H-3'), 7.42 (d, 1H, H-6", *J* 8.2), 7.51 (d.d, 1H, H-5", *J* 8.2, 2.1), 7.83-7.89 (m, 1H, H-8), 8.08-8.10 (m, 1H, H-5). $^{13}$C NMR (150 MHz) δ: 32.32 (C-$\underline{CH_2}$-group of fragment $CH_2$-$CH_2$), 35.80 (N-Me), 39.04 (Ar$\underline{CH_2}$Het), 52.70 (N-$CH_2$), 55.13 (OMe), 55.45 (OMe), 113.57 (6'), 114.01 (3'), 126.99, 127.44, 128.42, (C-3",5"), 128.72 (C-5'), 129.91, 130.65, 131.39, 132.09, 133.00, 134.38, 136.15, 139.80, 140.81, 146.45, 147.34, 152.00, 154.85. Found (%): C, 64.59; H, 5.34; Cl, 14.46; N, 8.90. Calc. for $C_{26}H_{25}Cl_2N_3O_2$ (%): C, 64.74; H, 5.22; Cl, 14.70; N, 8.71.

*6-{3-[4,5-Dimethoxy-2-(2-methyl-2-methylaminopropyl)benzyl]quinoxalin-2-yl}-2H-benz[b][1,4]oxazin-3(4H)-one hydrochloride* **2e.**



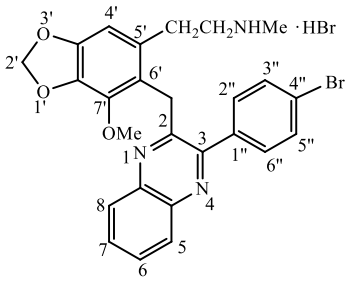
The starting compound was 6-(7,8-dimethoxy-2,2,3-trimethyl-1,2-dihydro-3*H*-benz[*d*]azepin-4-yl-carbonyl)-2*H*-benz[*b*][1,4]oxazin-3(4*H*)-one **1e**. The yield was 71%. Colourless crystals, mp 268-270 ºC (EtOH). $^{1}$H NMR, δ, ppm: 1.17 (s, 6H, C-Me$_2$), 2.47 (s, 3H, N-Me), 2.86 (s, 2H, C-CH$_2$ of fragment CMe$_2$-CH$_2$), 3.47 (s, 3H, OMe), 3.70 (s, 3H, OMe), 4.43 (s, 2H, Ar<u>CH$_2$</u>Het), 4.66 (s, 2H, C"H$_2$), 6.37 (s, 1H, H-6'), 6.76 (s, 1H, H-3'), 7.04-7.05 (m, 1H, H-8"), 7.22-7.24 (m, 2H, H-5", H-7"), 7.79-7.82 (m, 2H, H-6, H-7), 8.00-8.03 (m, 1H, H-8), 8.04-8.06 (m, 1H, H-5), 10.86 (s, 1H, $^{+}$NH$_2$). $^{13}$C NMR (150 MHz), δ: 22.08, 25.85, 38.89, 55.20 (OMe), 55.47 (OMe), 59.30 (CMe$_2$), 66.80, 113.42, 115.20, 115.83, 116.61, 123.86, 126.00, 127.14, 128.30, 128.63, 129.76, 129.84, 129.97, 132.52, 140.04, 140.30, 143.68, 146.73, 147.39, 154.05, 154.72. $^{15}$N, (DMSO-d$_6$) δ, ppm (from $^{15}$N – $^{1}$H HMBC spectrum): 55.3, $^{1}J^{15N\text{-}1H}$ 72,2 Hz ($^{+}$NH$_2$), 130.8, $^{1}J^{15N\text{-}1H}$ 91.6 Hz (N$^{4"}$), 328.0 (N1), 328.8 (N4). Found (%): C, 65.31; H, 5.84; Cl, 6.12; N, 9.89. Calc. for C$_{30}$H$_{32}$N$_4$O$_4$·HCl (%): C, 65.63; H, 6.06; Cl, 6.46, N, 10.20.

*1-(2-{[3-(4-Bromophenyl)quinoxalin-2-yl]methyl}-4,5-dimethoxyphenyl)-N,2-dimethylpropan-2-amine* **2f.**



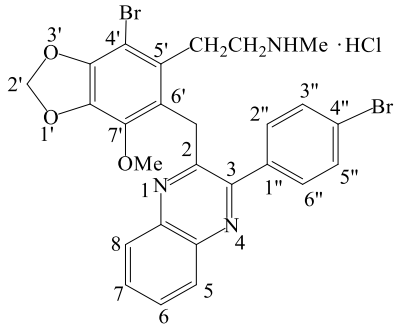
The starting compound was (4-bromophenyl)(7,8-dimethoxy-2,2,3-trimethyl-1,2-dihydro-3*H*-benz[*d*]azepin-4-yl)methanone **1f**. The yield was 65%. Colourless crystals, mp 123-125ºC (EtOH). $^{1}$H NMR, δ, ppm: 1.08 (s, 6H, C-Me$_2$), 2.39 (s, 3H, N-Me), 2.71 (s, 2H, C-CH$_2$ of fragment CMe$_2$-CH$_2$), 3.36 (br. s, 1H, NH), 3.48 (s, 3H, OMe), 3.70 (s, 3H, OMe), 4.41 (s, 2H, Ar<u>CH$_2$</u>Het), 6.40 (s, 1H, H-6'), 6.73 (s, 1H, H-3'), 7.61-7.62 (m, 2H, H-3", H-5"), 7.69-7.70 (m, 2H, H-2",6"), 7.81-7.83 (m, 2H, H-6, H-7), 8.00-8.02 (m, 1H, H-8), 8.06-8.08 (m, 1H, H-5).| $^{13}$C NMR (150 MHz), δ: 22.84, 26.34, 38.94, (Ar<u>CH$_2$</u>Het), 55.19 (OMe), 55.45 (OMe), 58.03 (CMe$_2$), 113.67, 115.18, 122.43, 126.83, 128.34 (3',5'), 128.71 (C-5'), 129.55, 126.82, 130.21, 131.16, 131.18, 137.68, 140.01, 140.50, 146.71, 147.20, 153.75, 154.57. $^{15}$N, δ (DMSO-d$_6$), ppm (from $^{15}$N – $^{1}$H HMBC spectrum): 35.8 (NMe), 328.0 (N-1), 329.1 (N-4). Found (%): C, 64.28; H, 5.49; Br; 15.00, N, 7.72. Calc. for C$_{28}$H$_{30}$BrN$_3$O$_2$ (%): C, 64.62; H, 5.81; Br, 15.35, N, 8.07.

*2-(6-{[3-(4-Bromophenyl)quinoxalin-2-yl]methyl}-7-methoxybenzo[d][1,3]dioxol-5-yl)-N-methylethan-1-amine hydrobromide* **2g.**



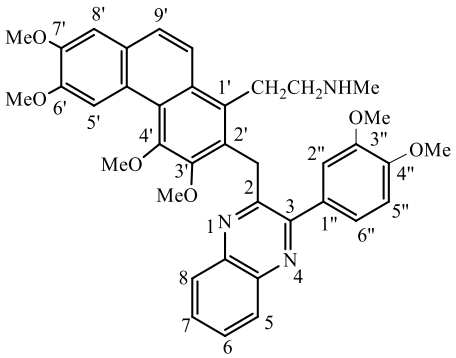
The starting compound was (4-bromophenyl)(10-methoxy-7-methyl-6,7-dihydro-5*H*-[1,3]dioxolo[4',5':4,5]benz[1,2-*d*]azepin-8-yl)methanone **1g**. The yield was 92%. Colourless crystals, mp 178-180ºC (EtOH). $^{1}$H NMR, δ, ppm: 2.55 (s, 3H, N-Me), 2.99-3.01 (m, 2H, N-$CH_2$), 3.20-3.23 (m, 2H, C-$CH_2$ of fragment $CH_2$-$CH_2$), 3.41 (s, 3H, OMe), 4.29 (s, 2H, Ar$\underline{CH_2}$Het), 5.92 (s, 2H, $OCH_2O$), 6.64 (s, 1H, H-4'), 7.76-7.81 (m, 6H, H-6, H-7, H-2", H-3", H-5", H-6"), 7.87-7.90 (m, 1H, H-8), 8.07-8.08 (m, 1H, H-5), 8.49 (s, 2H, $^{+}NH_2$). $^{13}$C NMR (150 MHz) δ: 18.46, 29.31, 32.39, 32.58, 49.02, 55.94, 58.78, 100.94, 103.89, 122.54, 123.38, 128.11, 128.72, 129.59, 129.89, 130.02, 131.26, 131.30, 135.06, 137.81, 139.78, 140.40, 140.76, 147.54, 153.43, 154.90. Found (%): C, 52.72; H, 4.00; Br, 26.86; N, 6.86 .Calc. for $C_{26}H_{24}BrN_3O_3 \cdot HBr$ (%): C, 53.17; H, 4.29; Br, 27.21; N, 7.15 .

*2-(4-Bromo-6-{[3-(4-bromophenyl)quinoxalin-2-yl]methyl}-7-methoxy-benzo[d][1,3]dioxol-5-yl)-N-methylethan-1-amine hydrochloride* **2h**



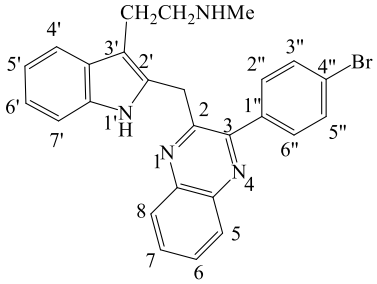
The starting compound was (4-bromo-10-methoxy-7-methyl-6,7-dihydro-5*H*-[1,3]dioxolo[4',5':4,5]benz[1,2-*d*]azepin-8-yl)(4-bromophenyl)methanone **1h**. The yield was 72%. Colorless crystals, mp 209-211ºC (EtOH). $^{1}$H NMR, δ, ppm: 2.52 (s, 3H, N-Me), 2.57 (t, 2H, N-$CH_2$ of fragment $CH_2$-$CH_2$, *J* 7.9), 3.31-3.28 (m, 2H, C-$CH_2$ of fragment $CH_2$-$CH_2$), 3.36 (s, 3H, OMe), 4.49 (s, 2H, Ar$\underline{CH_2}$Het), 6.03 (s, 2H, $OCH_2O$), 7.47 (d, 2H, H-2", H-6", *J* 8.1), 7.73-7.79 (m, 2H, H-6, H-7), 7.86 (d.d, 1H, H-8, *J* 7.9, 1.6), 7.97 (d, 2H, H-3", H-5", *J* 8.3), 8.03 (d.d, 1H, H-5, *J* 7.9, 1.6), 9.34 (s, 2H, $^{+}NH_2$). $^{13}$C NMR (150 MHz), δ: 28.63, 32.07, 33.96, 47.16, 58.28, 95.94, 101.54, 125.74, 128.09, 128.61, 128.68, 129.52, 129.79, 130.65, 135.45, 139.82, 140.03, 140.17, 146.04, 153.77, 154.72. Found (%): C, 50.72; H, 4.00; Br + Cl, 31.14; N, 6.86. Calc. for $C_{26}H_{23}Br_2ClN_3O_3 \cdot$ HCl (%): C, 50.23; H, 3.89; Br + Cl, 31.40; N, 6.76 .

*2-(2-{[3-(3,4-dimethoxyphenyl)quinoxalin-2-yl]methyl}-3,4,6,7-tetramethoxyphenanthren-1-yl)-N-methylethan-1-amine* **2i.**



The starting compound was (3,4-dimethoxyphenyl)(9,10,12,13-tetramethoxy-3-methyl-4,5-dihydro-3*H*-phenanthro[1,2-*d*]azepin-2-yl)methanone **1i.** The yield was 68%. Colourless crystals, mp 108-110ºC (EtOH). $^1$H NMR, δ, ppm: 2.19 (s, 3H, N-Me), 2.60 (t, 2H, N-$CH_2$ of fragment $CH_2$-$CH_2$, *J* 7.9), 3.17 (t, 2H, C-$CH_2$ of fragment $CH_2$-$CH_2$, *J* 7.9), 3.57 (s, 3H, OMe), 3.80 (s, 3H OMe), 3.87 (s, 3H, OMe), 3.89 (s, 3H OMe), 3.92 (s, 3H OMe), 3.93 (s, 3H OMe), 4.70 (s, 2H, $\underline{CH_2}$Het), 7.19 (d, 1H, H-9', *J* 8.3), 7.42 (s, 1H, H-8'), 7.45 (d.d, 1H, H-5", *J* 8.2, 2.0), 7.50 (d, 1H, H-2", *J* 2.0), 7.64-7.76 (m, 4H, H-5 – H-8), 7.89 (d, 1H, H-6", *J* 9.3), 8.07 (d.d, 1H, H-10, *J* 8.2, 2.0), 9.05 (s, 1H, 5). $^{13}$C NMR (DMSO-$d_6$, 150 MHz,) δ: 30.04, 33.81, 35.91, 52.24, 55.24, 55.27, 59.46, 60.12, 108.11, 108.15, 121.09, 123.05, 123.59, 125.55, 127.41, 127.53, 128.10, 128.35, 128.72, 128.97, 12927, 129.45, 129.80, 131.18, 132.14, 138.62, 139.91, 140.44, 148.20, 148.37, 148.49, 149.84, 154.51, 154.91. Found (%): C, 72.24; H, 6.00; N, 6.26. Calc. for $C_{38}H_{39}N_3O_6$ (%): C, 72.02; H, 6.20; N, 6.63.

*2-(2-{[3-(4-Bromophenyl)quinoxalin-2-yl]methyl}-1H-indol-3-yl)-N-methylethan-1-amine* **2j**.



The title compound was prepared from (4-bromophenyl)(3-methyl-1,2,3,6-tetrahydro-azepino[4,5-*b*]indol-4-yl)methanone **1j**. The yield was 55%. Colourless crystals, mp 87-80ºC (EtOH). $^1$H NMR, δ, ppm: 2.14 (s, 3H, N-Me), 2.47 (s, 2H, N-$CH_2$ of fragment $CH_2$-$CH_2$), 2.60 (t, 2H, N-$CH_2$ of fragment $CH_2$-$CH_2$, *J* 7.1), 4.50 (s, 2H, Ar$\underline{CH_2}$Het), 6.90 (t, 1H, H-5', *J* 7.4), 6.95 (t, 1H, H-6', *J* 7.5), 7.17 (d, 1H, H-7', *J* 8.0), 7.39 (d, 1H, H-4', *J* 7.8), 7.61 (d, 2H, H-2", H-6", *J* 8.1), 7.68 (d, 2H, H-3", H-5" *J* 8.2), 7.82-7.84 (m, 2H, H-7, H-8), 8.01-8.03 (m, 1H, H-8), 8.09-8.11 (m, 1H, H-5), 10.42 (s, 1H, NH). $^{13}$C NMR (150 MHz,) δ: 24.12, 33.07, 35.88, 52.14, 109.83 110.67, 117.70, 118.01, 120.21, 122.48, 127.89, 128.34, 128.72, 129.87, 130.14, 131.06, 131.15, 131.89, 135.61, 137.52, 140.23, 140.67, 152.97, 153.55. Found (%): C, 66.02; H, 4.70; Br, 16.56; N, 11.67. Calc. for $C_{26}H_{23}BrN_4$ (%): C, 66.25; H, 4.92; Br, 16.95; N, 11.89.

## S3. Structure and crystal data for compound 2g.

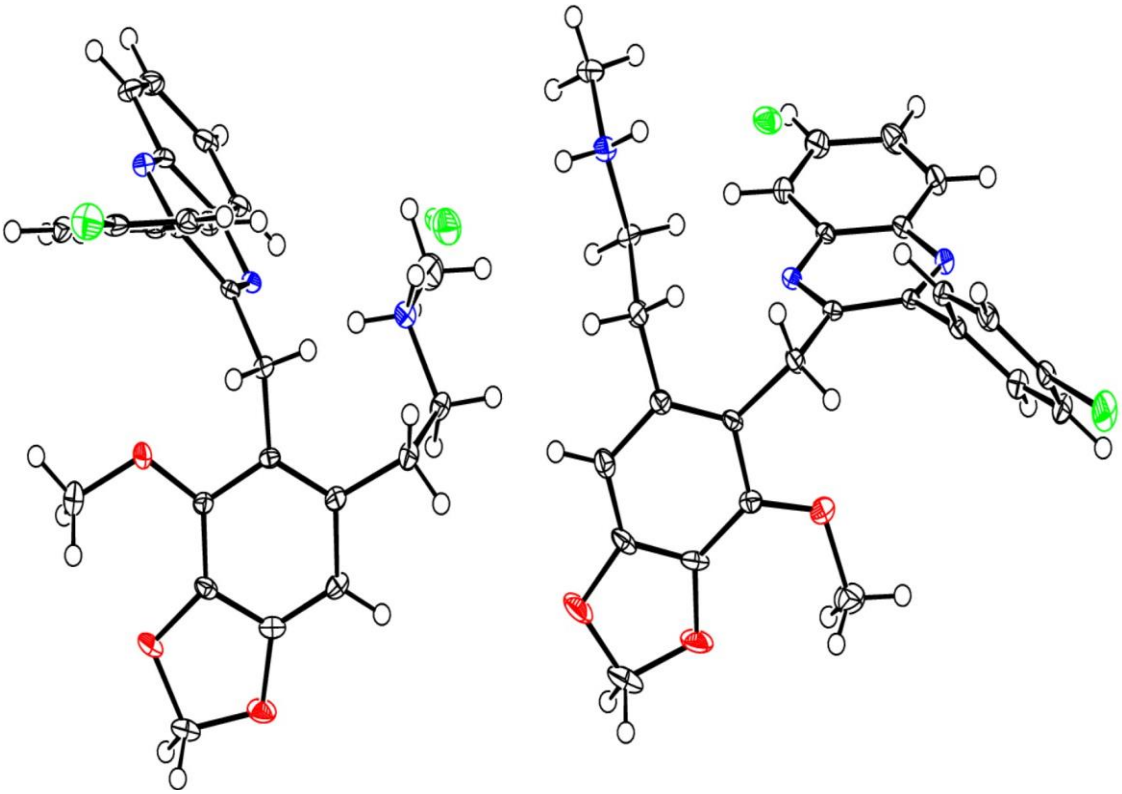


**Figure S1** Structure refinement for compound **2g.**

**Table S1** Crystal data and structure refinement for compound **2g.**

| | |
|---|---|
| CCDC Number | 1897576 |
| Empirical formula | $C_{52}H_{50}Br_4N_6O_6$ |
| Formula weight | 1174.62 |
| Temperature/K | 100.00(10) |
| Crystal system | triclinic |
| Space group | P-1 |
| *a*/Å | 8.75250(10) |
| *b*/Å | 16.5910(3) |
| *c*/Å | 19.9431(4) |
| *α*/° | 70.140(2) |
| *β*/° | 78.5970(10) |
| *γ*/° | 87.9010(10) |
| *V*/Å$^3$ | 2668.53(8) |
| *Z* | 2 |
| $\rho_{calc}$/g cm$^{-3}$ | 1.462 |
| $\mu$/mm$^{-1}$ | 4.105 |
| *F*(000) | 1184.0 |
| Crystal size/mm$^3$ | 0.396 × 0.241 × 0.202 |
| Radiation | CuKα (λ = 1.54184) |
| 2Θ range for data collection/° | 8.59 to 152.502 |
| Index ranges | -8 ≤ h ≤ 11, -20 ≤ k ≤ 20, -25 ≤ l ≤ 25 |

| | |
|---|---|
| Reflections collected | 56701 |
| Independent reflections | 11116 [$R_{int}$ = 0.0543, $R_{sigma}$ = 0.0329] |
| Data/restraints/parameters | 11116/0/657 |
| Goodness-of-fit on $F^2$ | 1.040 |
| Final R indexes [I>=2σ (I)] | $R_1$ = 0.0352, $wR_2$ = 0.0906 |
| Final R indexes [all data] | $R_1$ = 0.0362, $wR_2$ = 0.0916 |
| Largest diff. peak/hole / e $Å^{-3}$ | 0.88/-0.92 |

## S4. References


[S1] http://chem.ch.huji.ac.il/nmr/software/solvent.html.

[S2] *CrysAlisPro, version 1.171.38.41, Rigaku Oxford Diffraction*, Oxford, 2015.

[S3] G. M. Sheldrick, *Acta Crystallogr., Sect. A*: *Found. Adv*. 2015, **71**, 3.

[S4] G. M. Sheldrick, *Acta Crystallogr., Sect. C*: *Struct. Chem*., 2015, **71**, 3.

[S5] O. V. Dolomanov, L. J. Bourhis,; R. J. Gildea, J. A. K. Howard and H. J. Puschmann, *Appl. Crystallogr.*, 2009, **42**, 339.

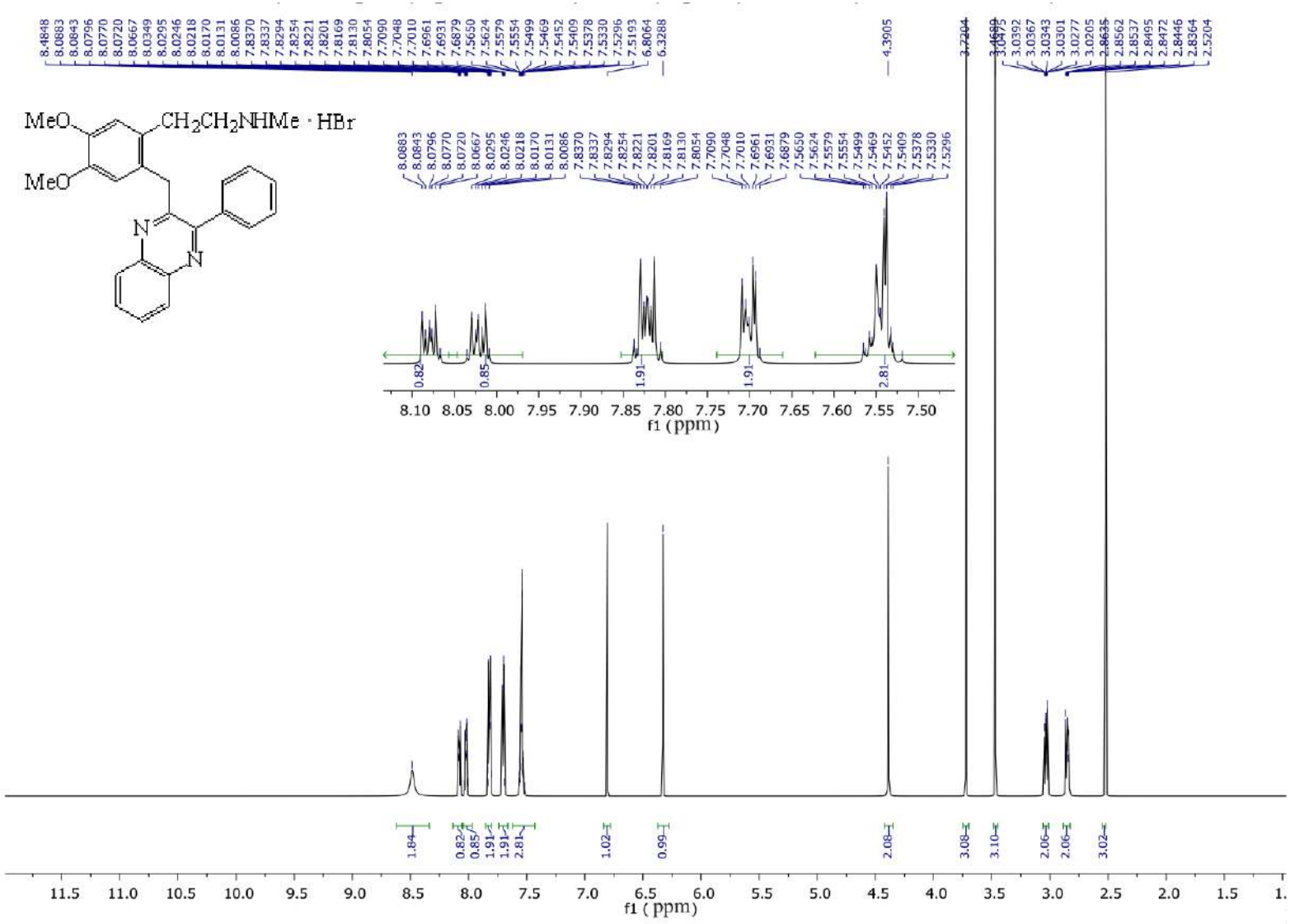
[S6] A. L. Spek, *Acta Crystallogr*., *Sect. D*: *Biol. Crystallogr*., 2009, **65**, 148.

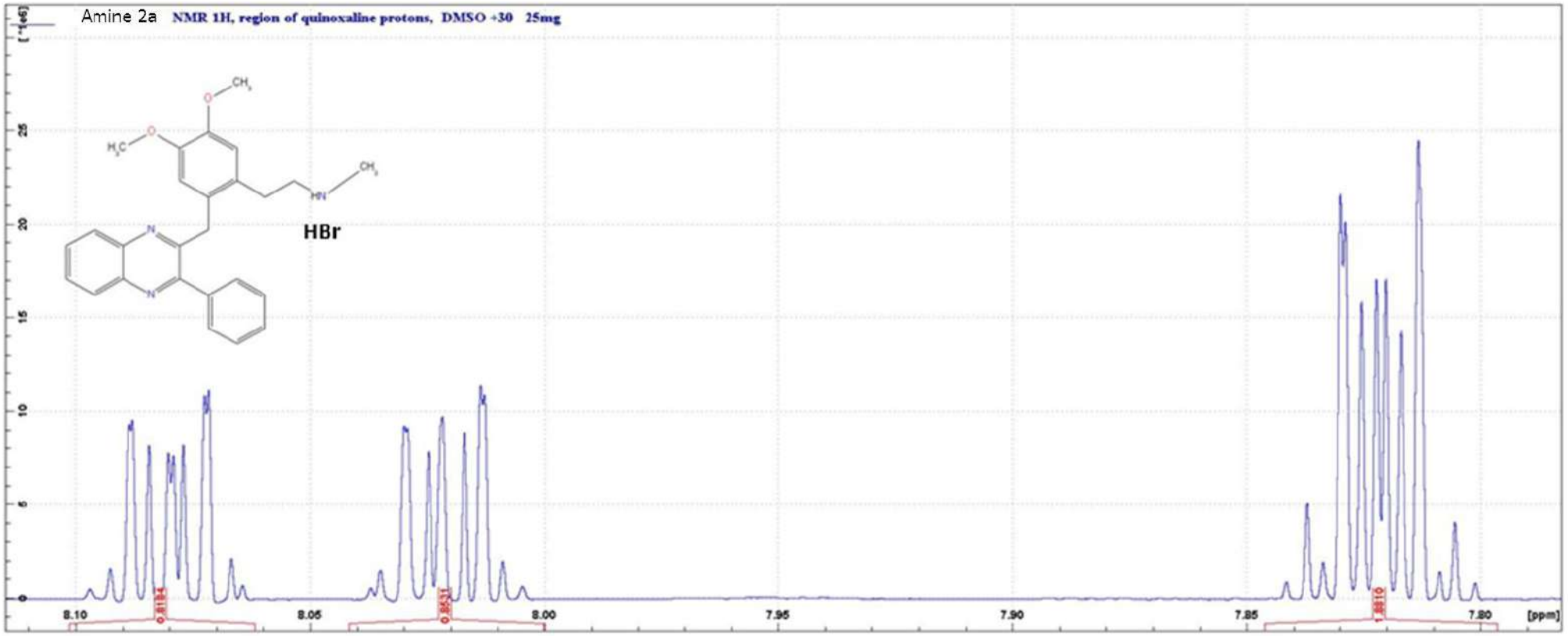
[S7] A. A. Granovsky, *Firefly version 8*, http://classic.chem.msu.su/gran/firefly/index.html.

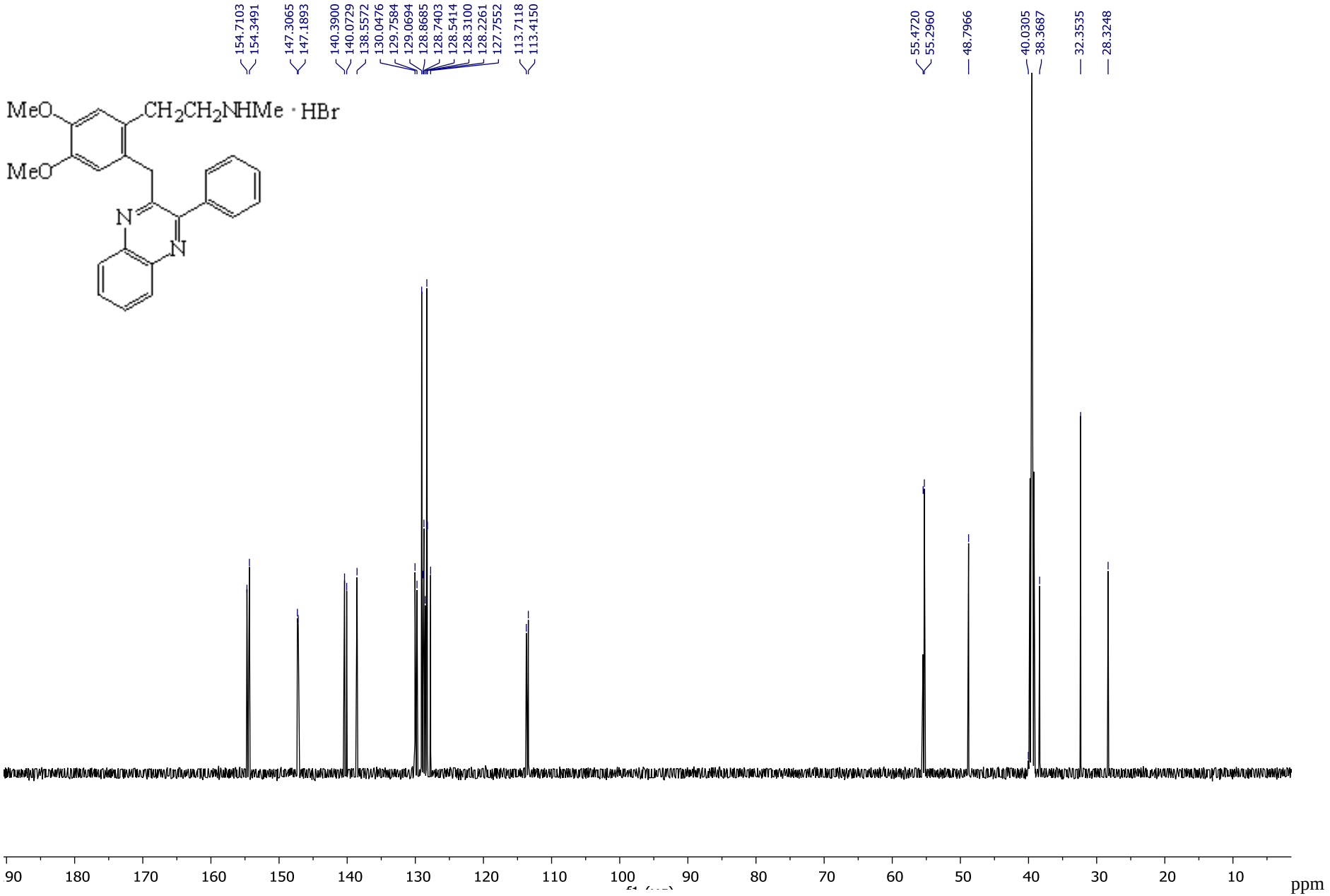
[S8] M. W. Schmidt, K. K. Baldridge, J. A. Boatz, S. T. Elbert, M. S. Gordon, J. H. Jensen, S. Koseki, N. Matsunaga, K. A. Nguyen, S. Su, T. L. Windus, M. Dupuis and J. A. Montgomery, *J.Comput.Chem*. 1993, **14**, 1347.

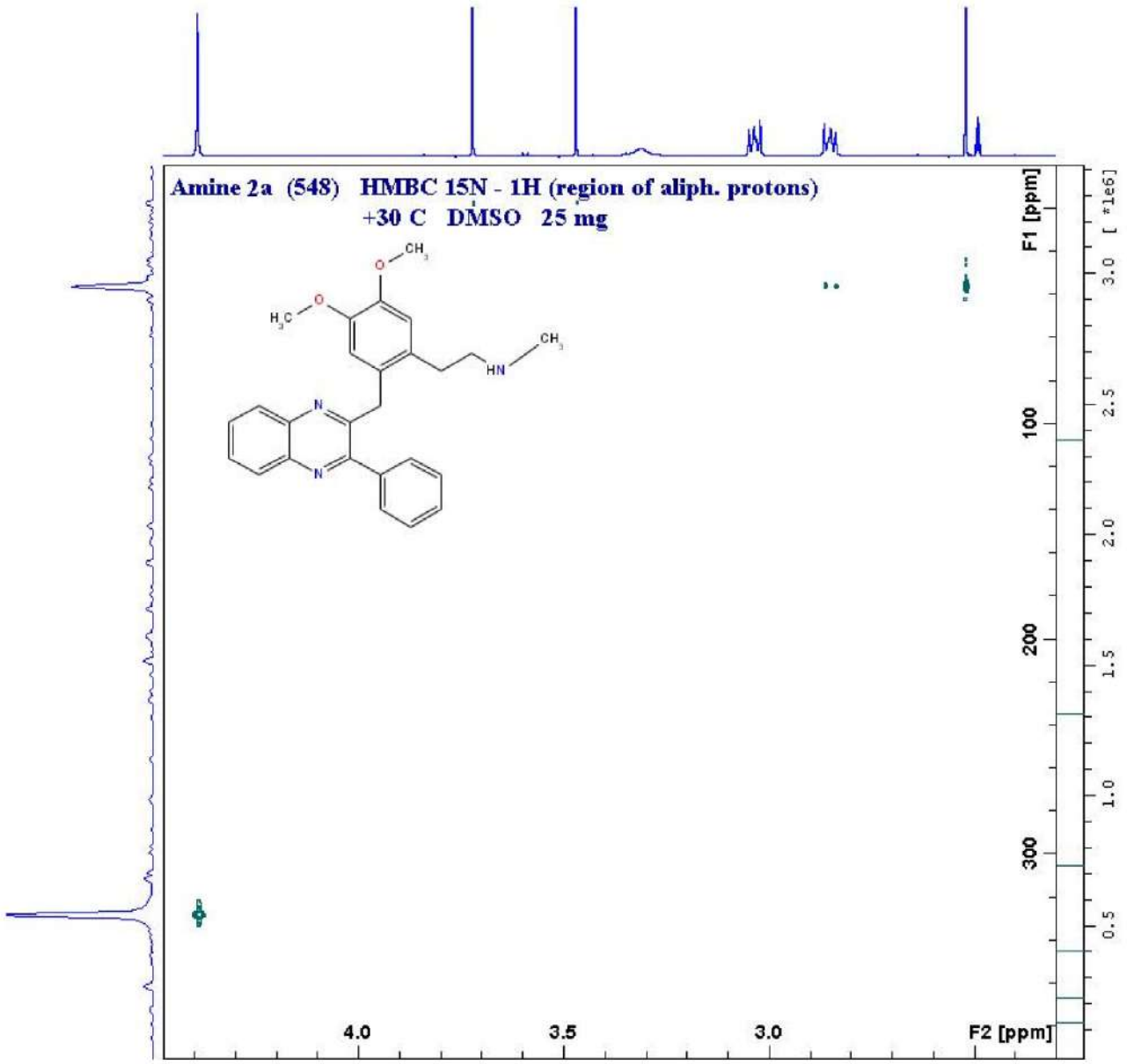
## 4. NMR Spectra of amines 2a-j

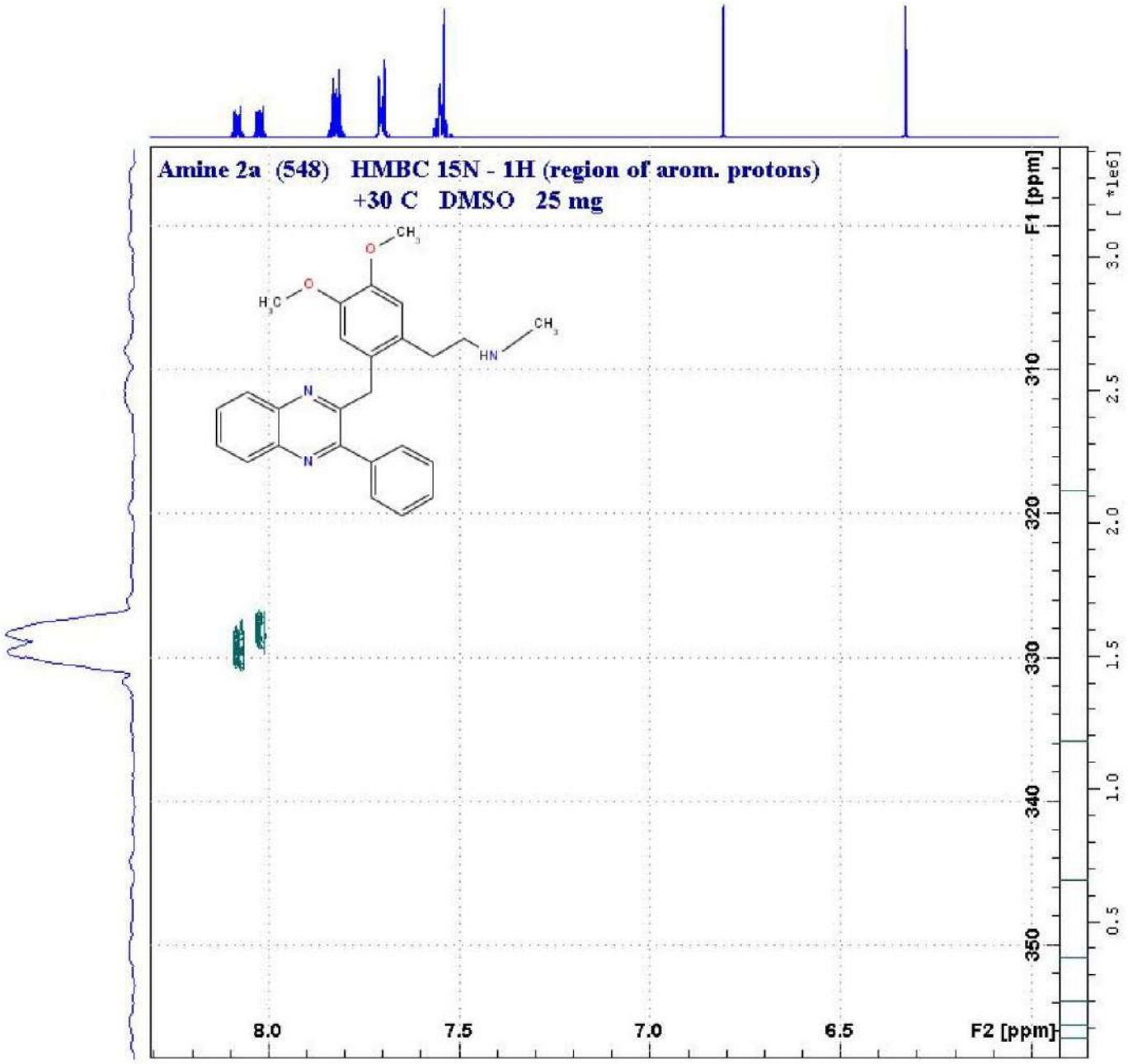
### 2-(4,5-Dimethoxy-2-((3-phenylquinoxalin-2-yl)methyl)phenyl)-N-methylethan-1-amine hydrobromide 2a.



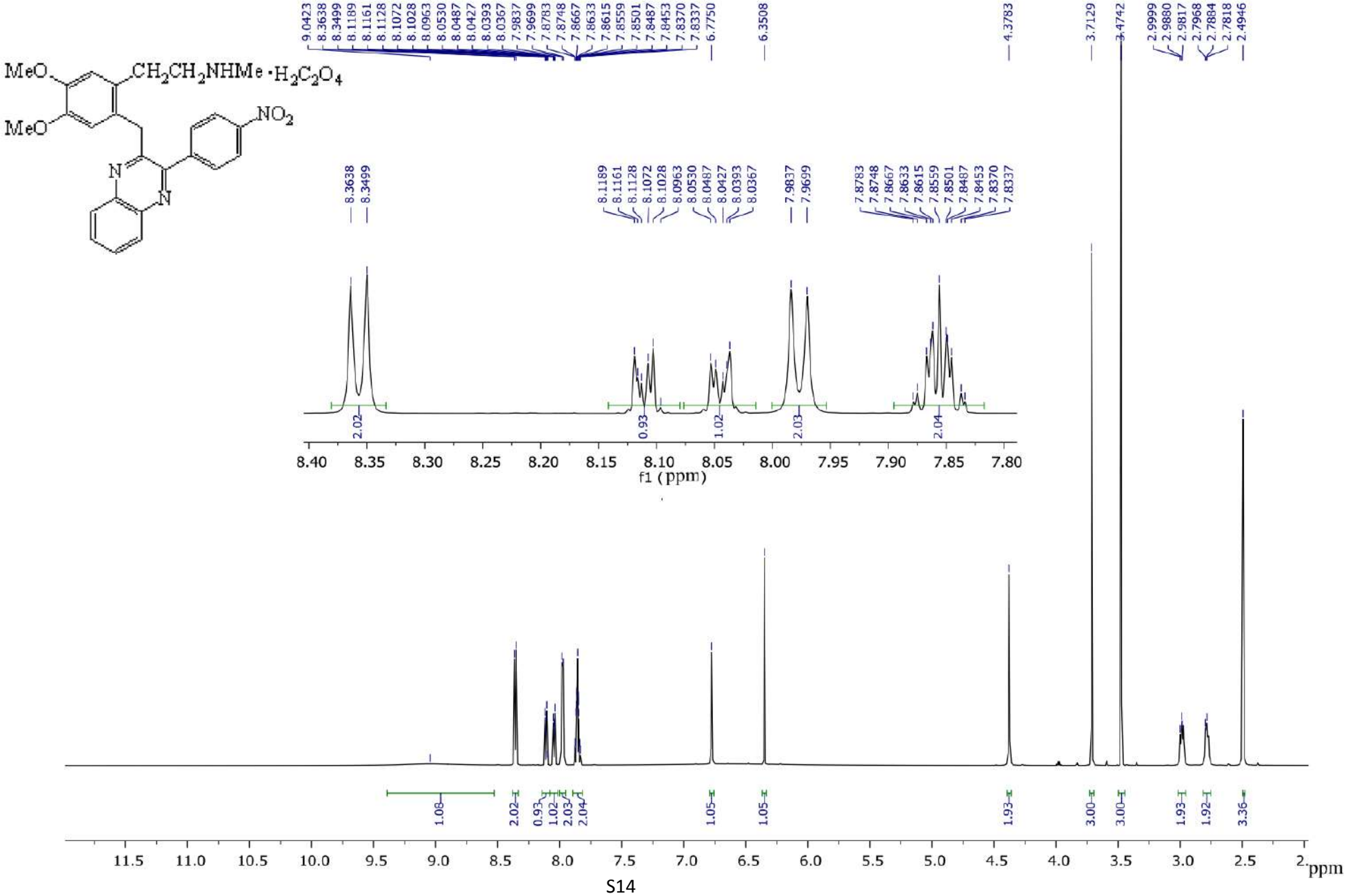

Amine 2a NMR 1H, region of quinoxaline protons, DMSO +30 25mg
HBr
8.10
8.05
8.00
7.95
7.90
7.85
7.80
[ppm]

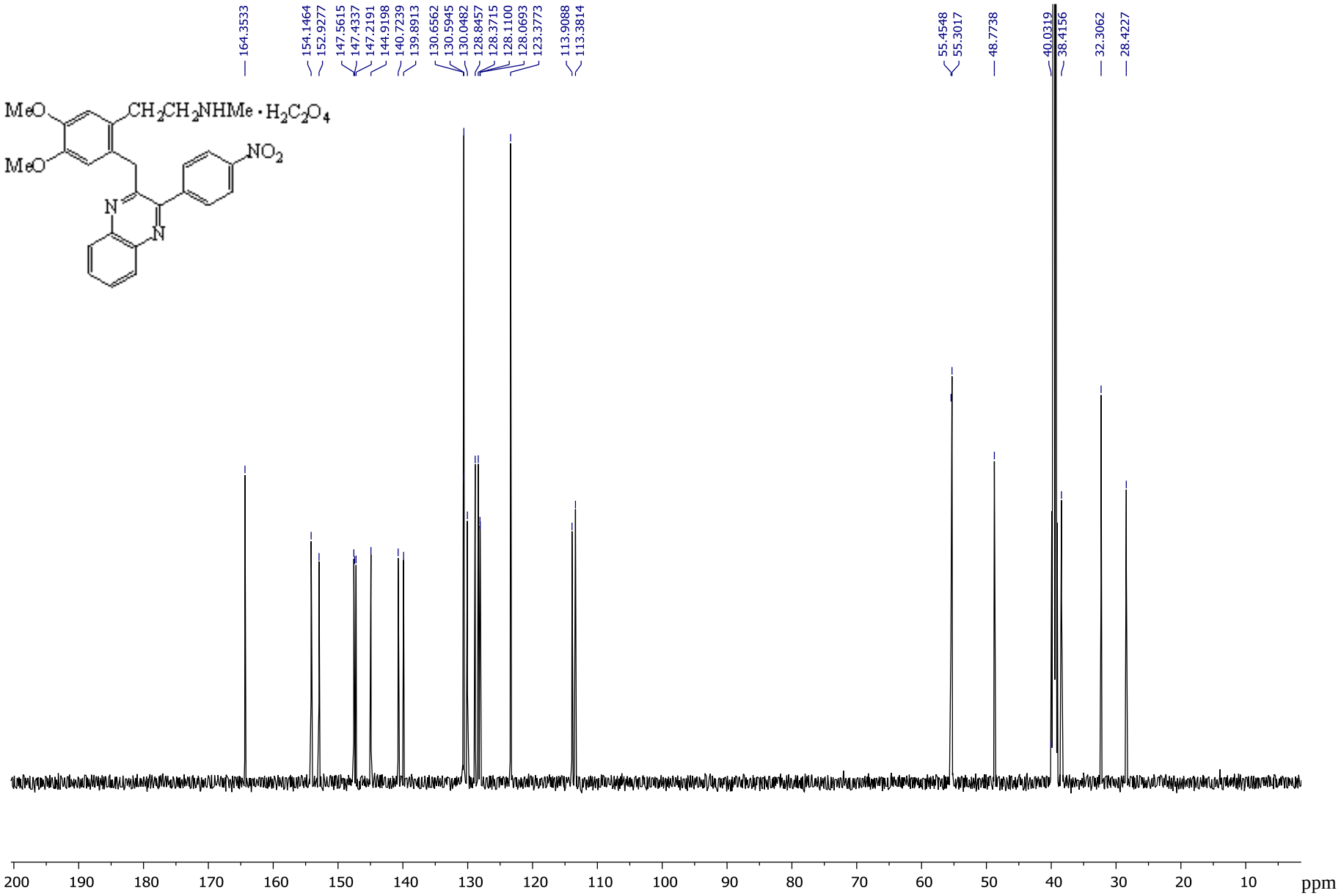

154.7103
154.3491
147.3065
147.1893
140.3900
140.0729
138.5572
130.0476
129.7584
129.0694
128.8685
128.7403
128.5414
128.3100
128.2261
127.7552
113.7118
113.4150
55.4720
55.2960
48.7966
40.0305
38.3687
32.3535
28.3248
MeO
MeO
CH2CH2NHMe · HBr
N
N
90
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

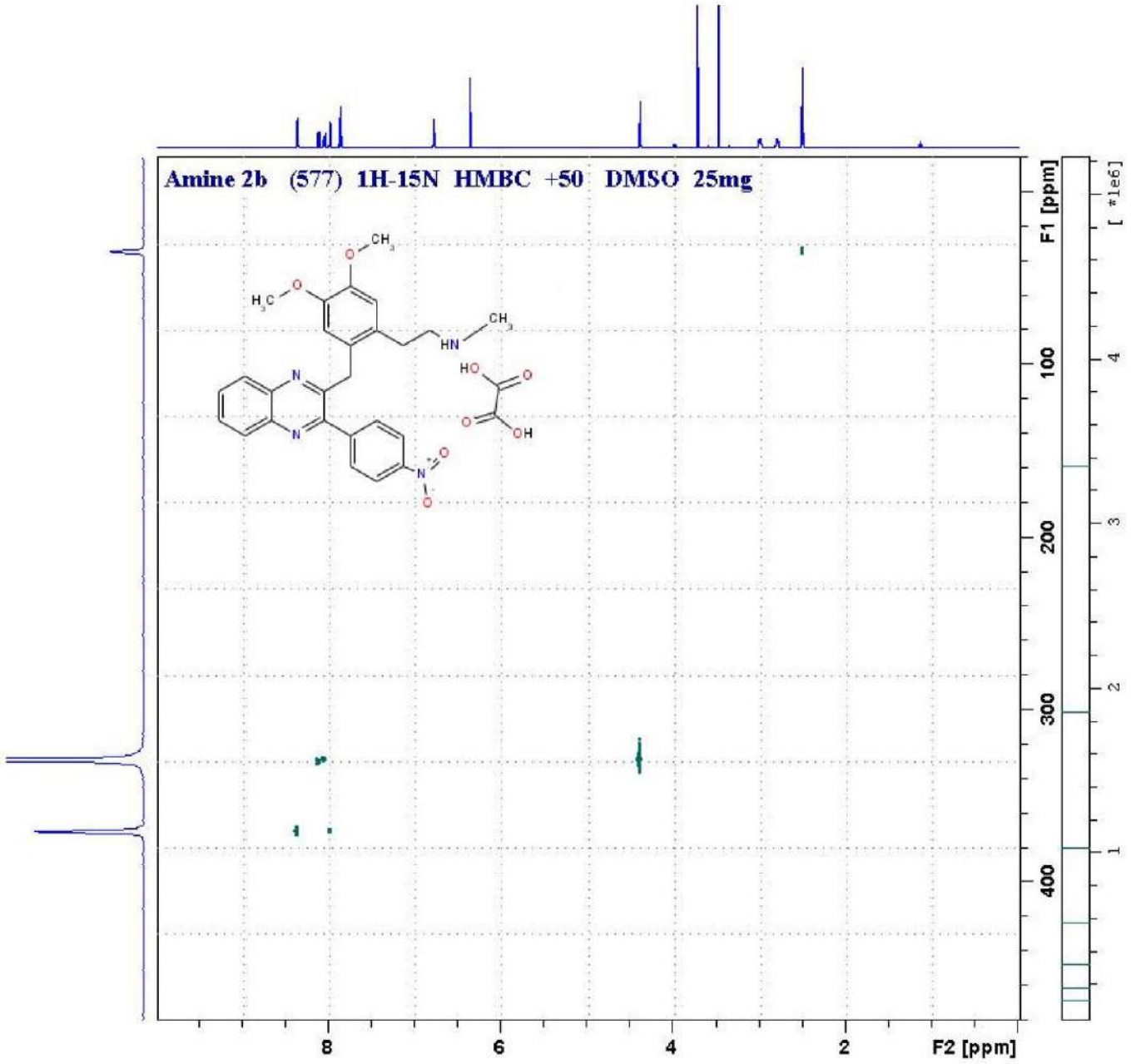

Amine 2a (548) HMBC 15N - 1H (region of aliph. protons)
+30 C DMSO 25 mg
F1 [ppm]
F2 [ppm]
4.0
3.5
3.0
100
200
300
0.5
1.0
1.5
2.0
2.5
3.0
[ *1e6]

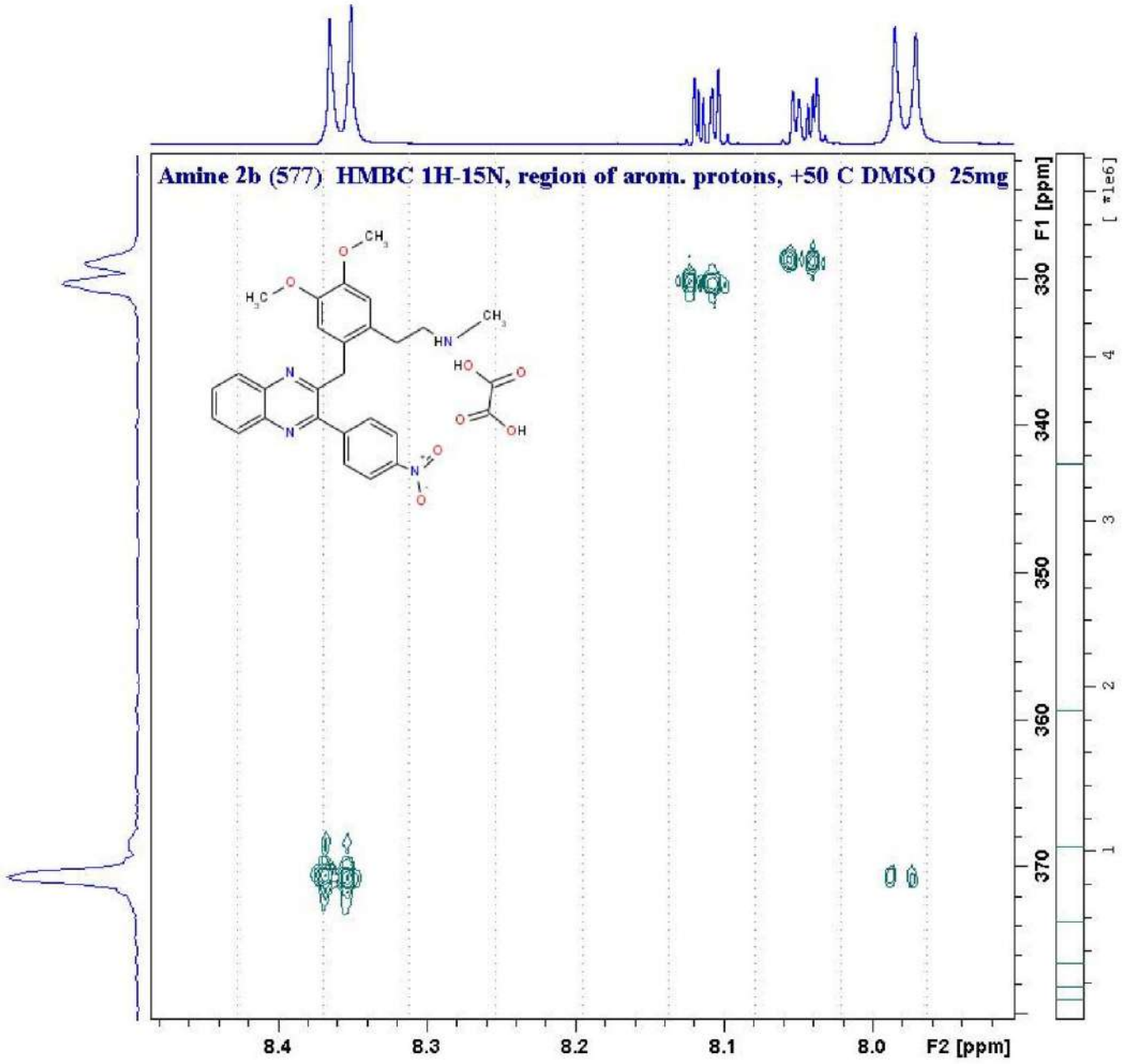

Amine 2a (548) HMBC 15N - 1H (region of arom. protons)
+30 C DMSO 25 mg
F1 [ppm]
310
320
330
340
350
8.0
7.5
7.0
6.5
F2 [ppm]
3.0
2.5
2.0
1.5
1.0
0.5
[ *1e6]

**2-(4,5-Dimethoxy-2-((3-(4-nitrophenyl)quinoxalin-2-yl)methyl)phenyl)-N-methylethan-1-amine oxalate 2b.**

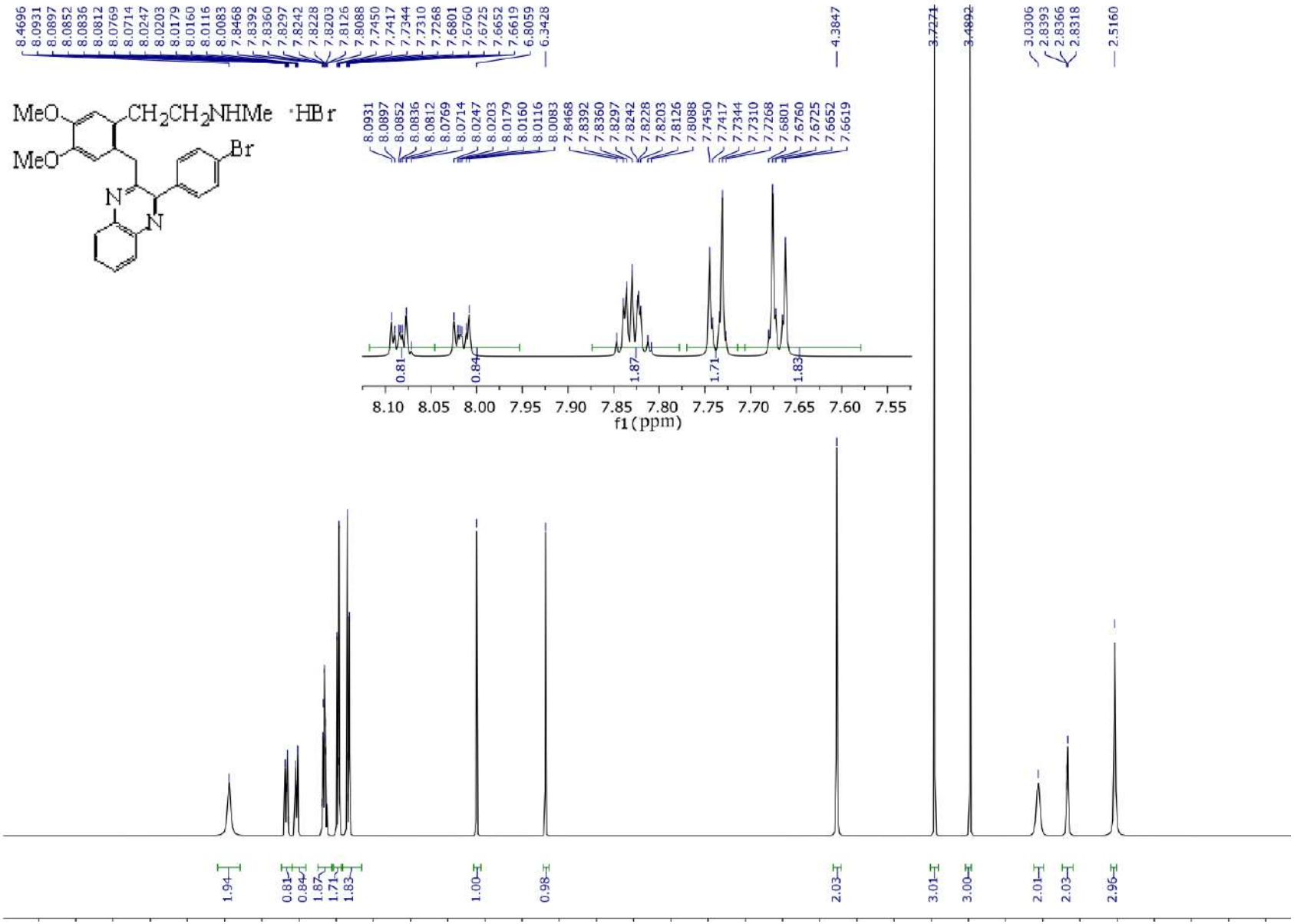


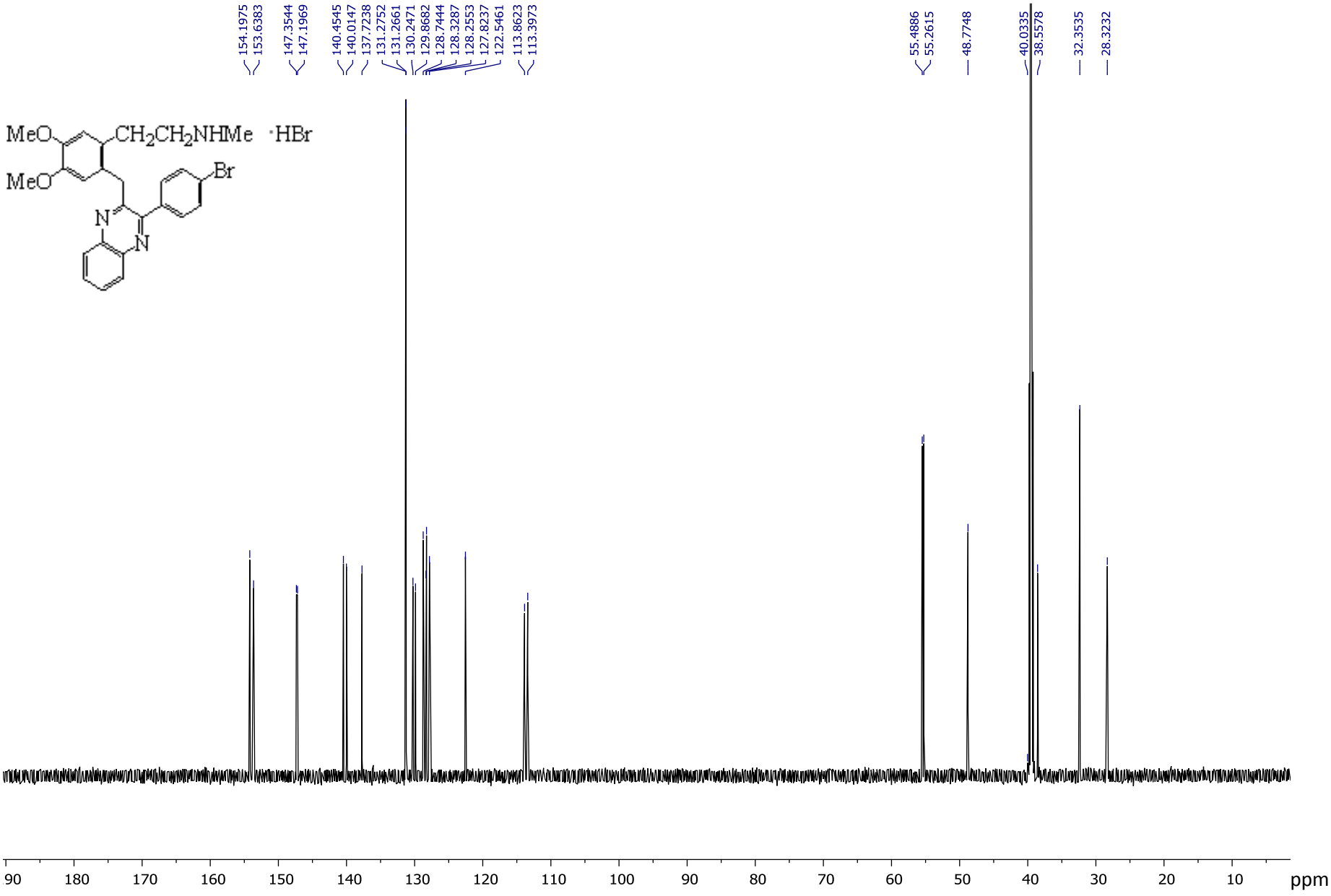

164.3533
154.1464
152.9277
147.5615
147.4337
147.2191
144.9198
140.7239
139.8913
130.6562
130.5945
130.0482
128.8457
128.3715
128.1100
128.0693
123.3773
113.9088
113.3814
55.4548
55.3017
48.7738
40.0319
38.4156
32.3062
28.4227
MeO
MeO
CH2CH2NHMe · H2C2O4
NO2
N
N
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

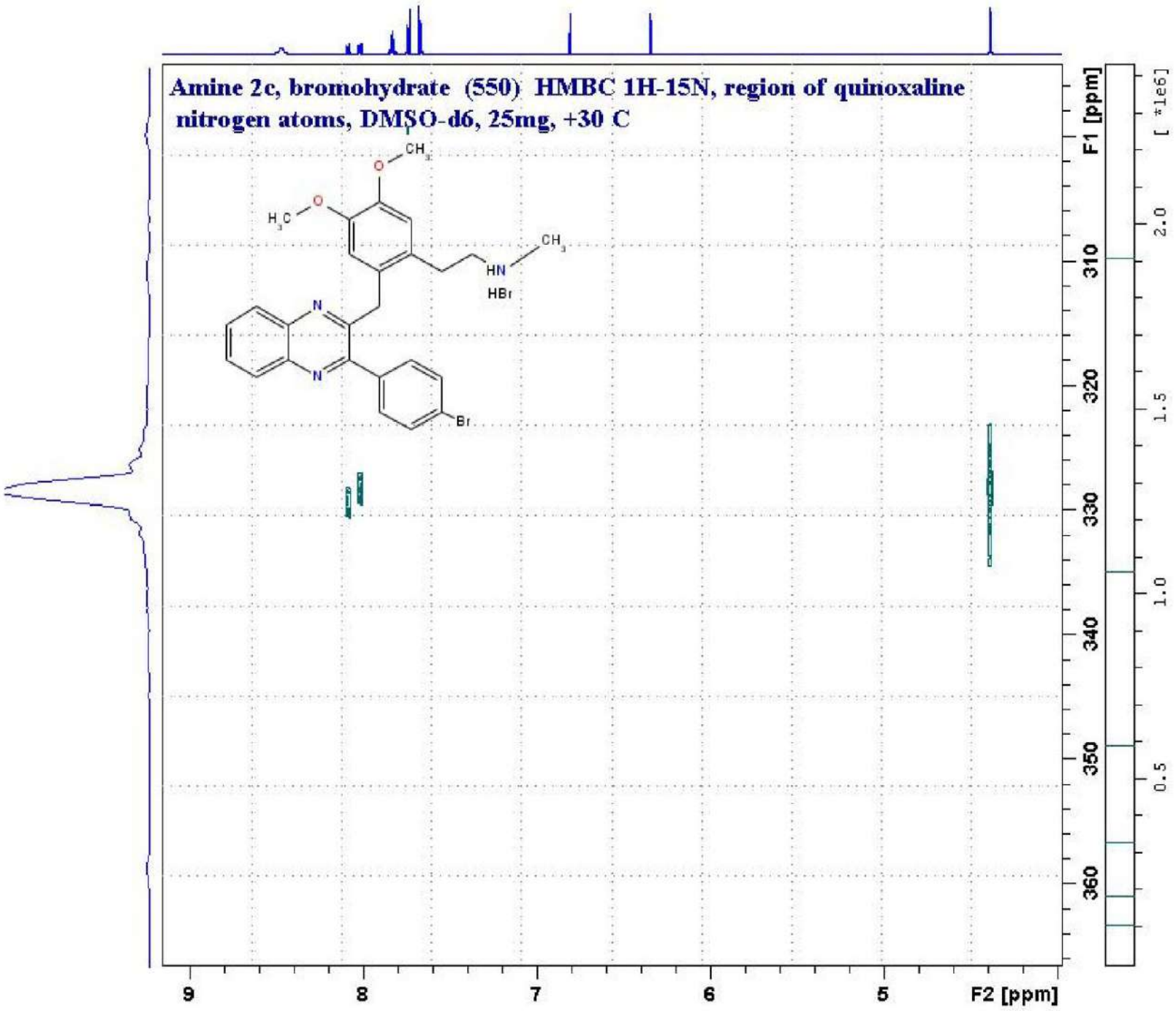

Amine 2b (577) 1H-15N HMBC +50 DMSO 25mg
F1 [ppm]
F2 [ppm]
8
6
4
2
100
200
300
400
[ *1e6]

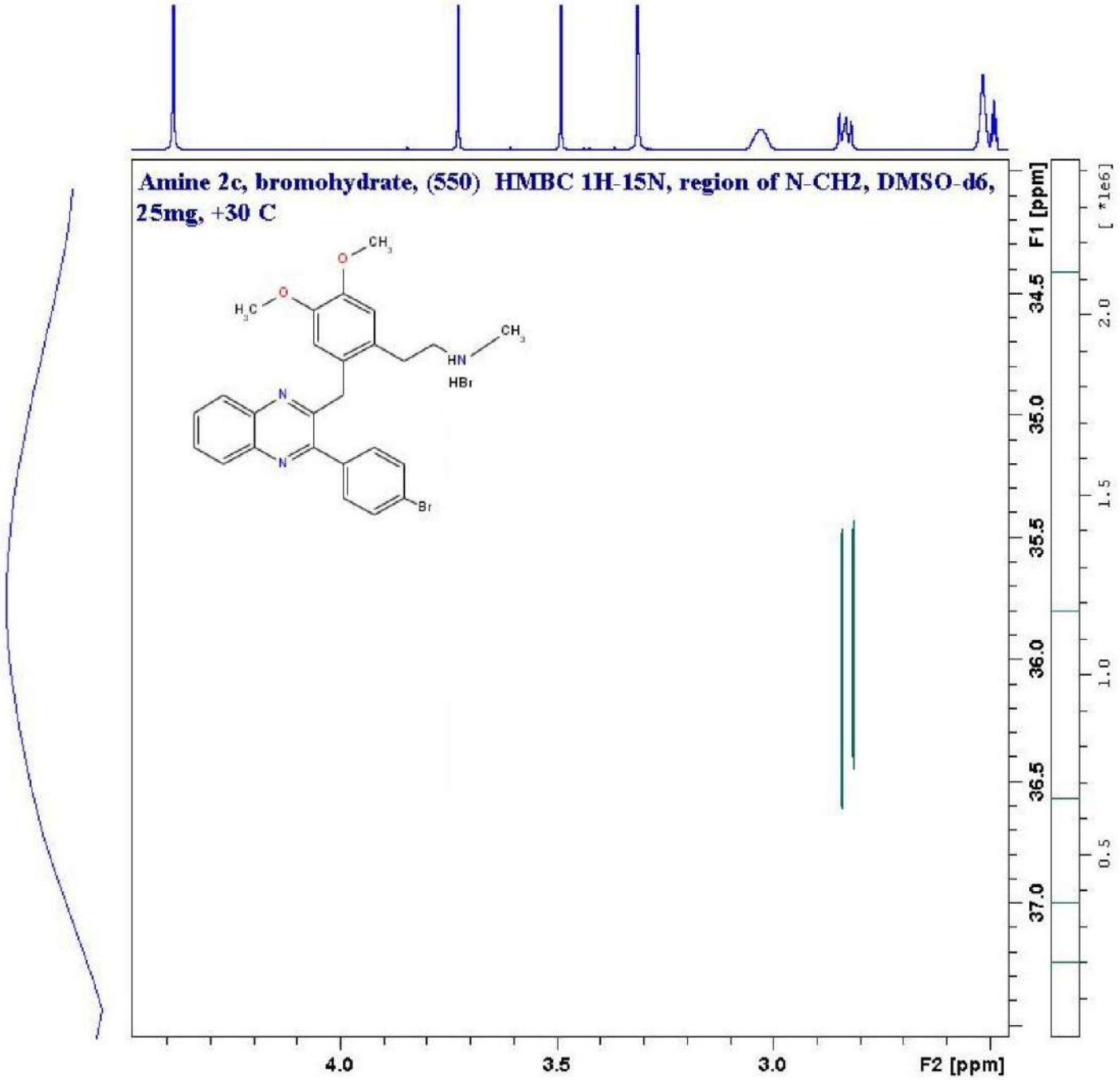

Amine 2b (577) HMBC 1H-15N, region of arom. protons, +50 C DMSO 25mg
F1 [ppm]
330
340
350
360
370
8.4
8.3
8.2
8.1
8.0
F2 [ppm]
[ *1e6]
1
2
3
4

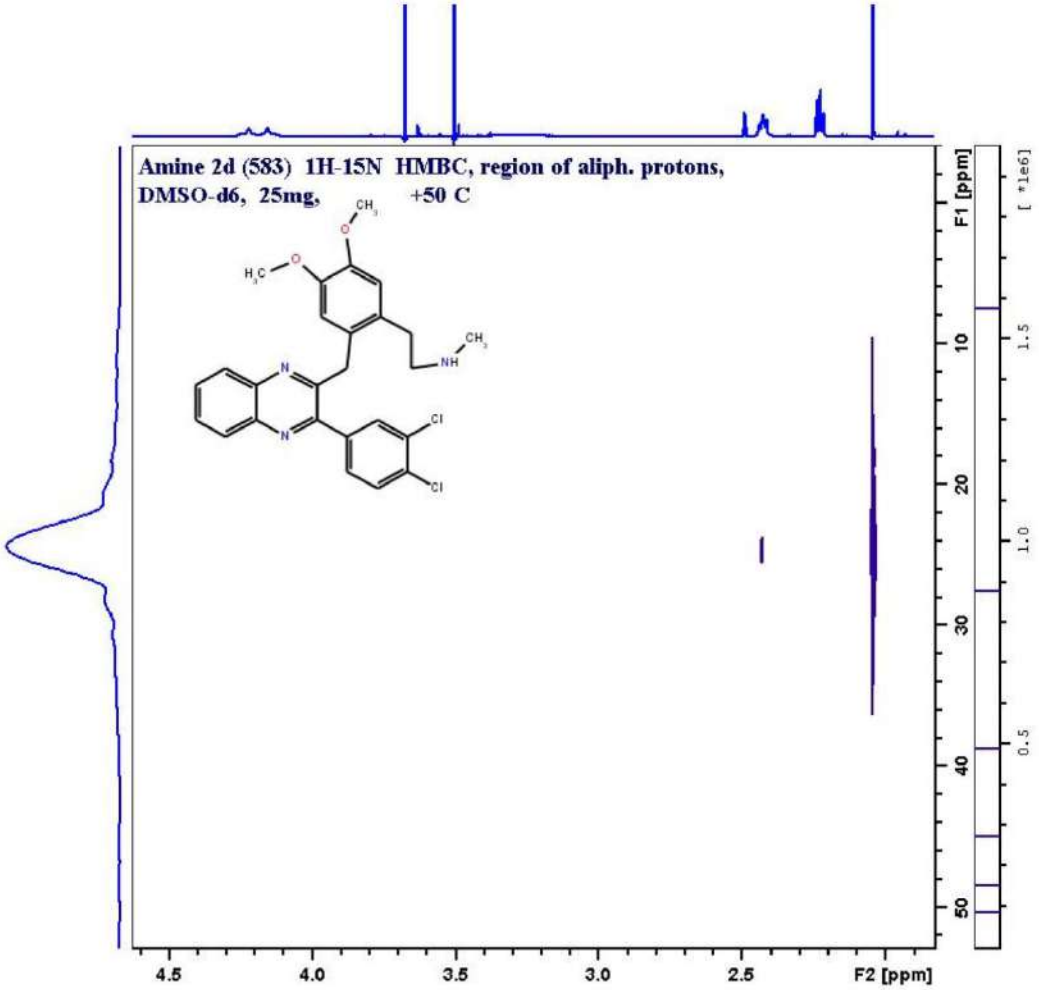
**2-(2-((3-(4-Bromophenyl)quinoxalin-2-yl)methyl)-4,5-dimethoxyphenyl)-N-methylethan-1-amine hydrobromide 2c.**

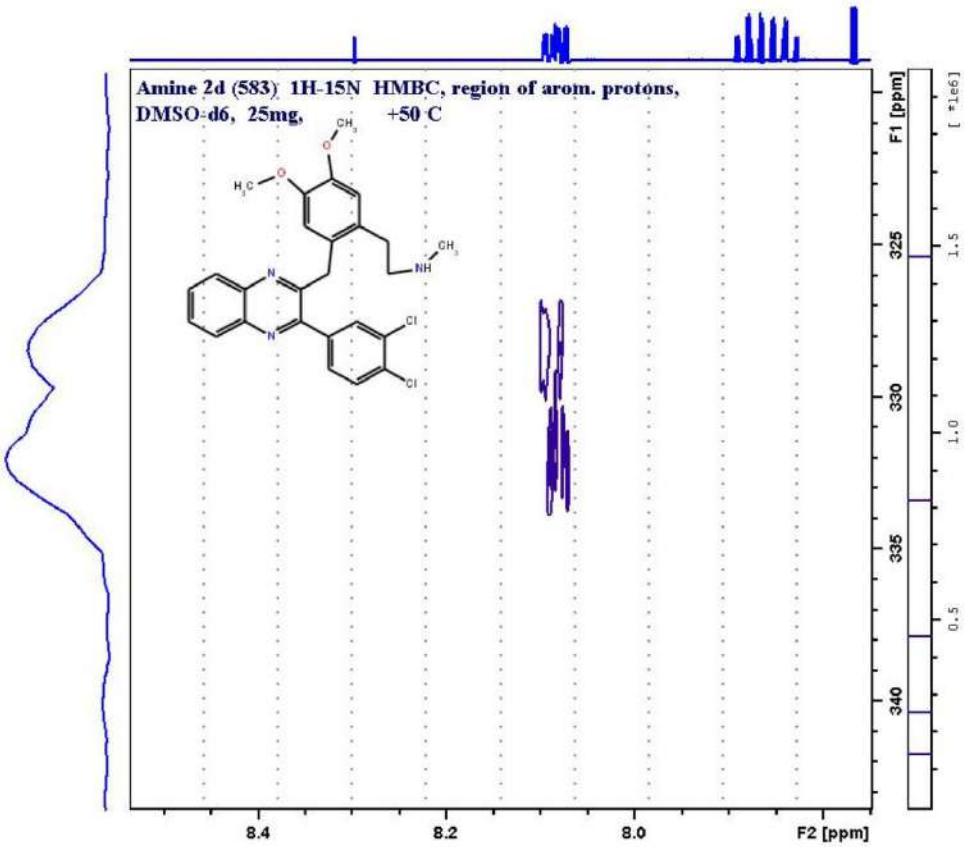



154.1975
153.6383
147.3544
147.1969
140.4545
140.0147
137.7238
131.2752
131.2661
130.2471
129.8682
128.7444
128.3287
128.2553
127.8237
122.5461
113.8623
113.3973
55.4886
55.2615
48.7748
40.0335
38.5578
32.3535
28.3232
MeO
MeO
CH2CH2NHMe ·HBr
Br
N
N
90
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

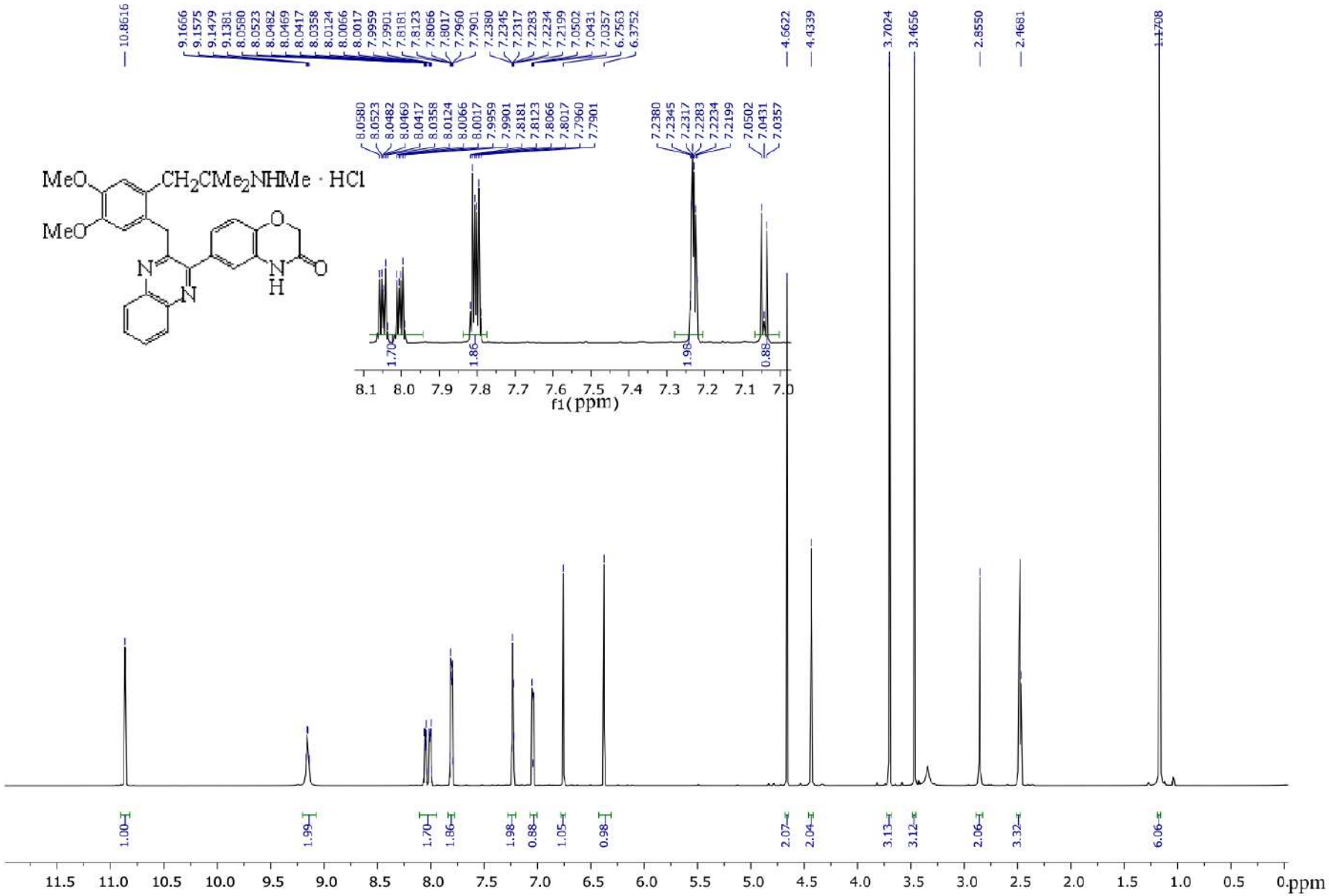

Amine 2c, bromohydrate (550) HMBC 1H-15N, region of quinoxaline nitrogen atoms, DMSO-d6, 25mg, +30 C
F1 [ppm]
F2 [ppm]
9
8
7
6
5
310
320
330
340
350
360
2.0
1.5
1.0
0.5
[ *1e6]
HN
HBr
Br
N
O

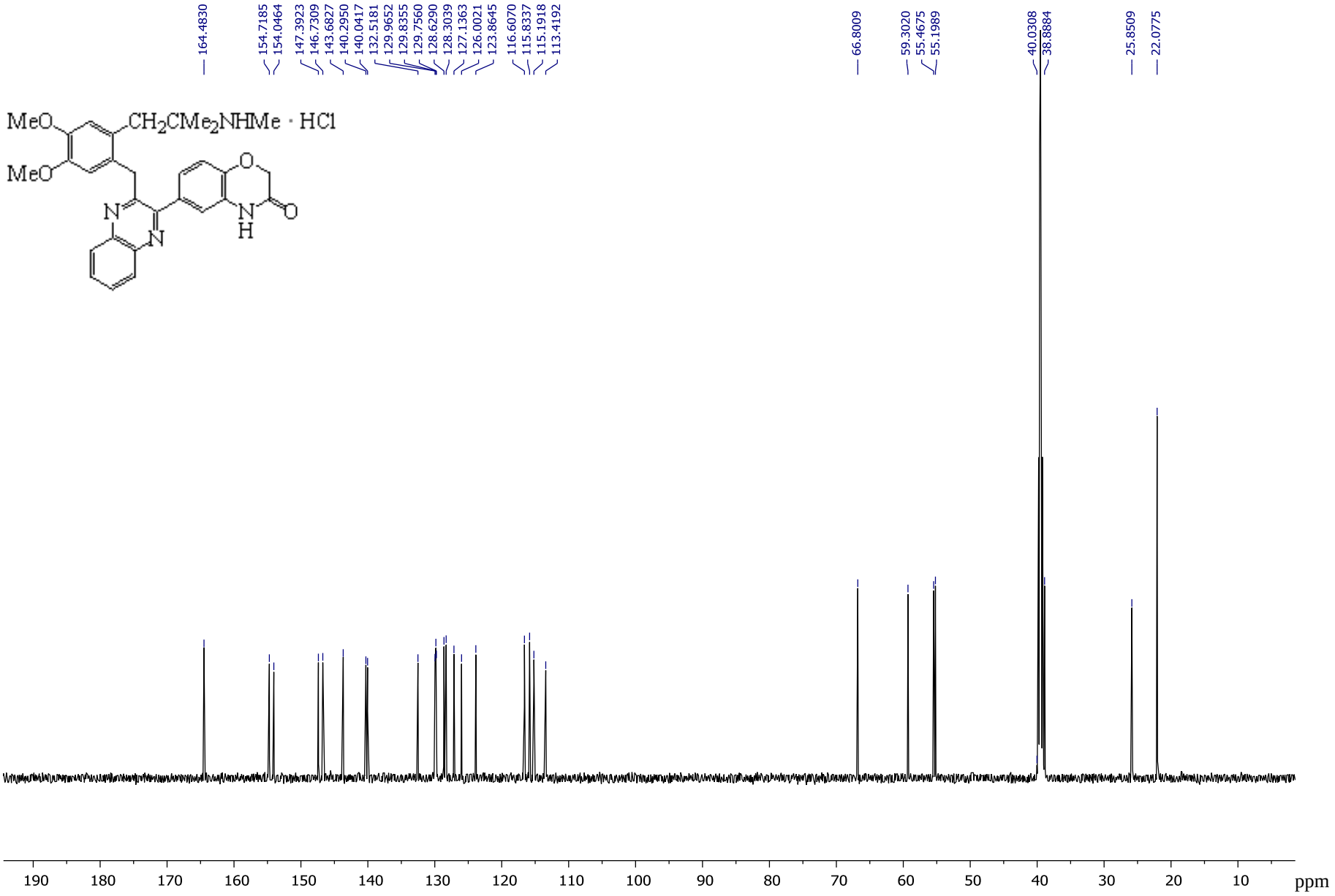

Amine 2c, bromohydrate, (550) HMBC 1H-15N, region of N-CH2, DMSO-d6, 25mg, +30 C
F1 [ppm]
34.5
35.0
35.5
36.0
36.5
37.0
F2 [ppm]
4.0
3.5
3.0
[ *1e6]
2.0
1.5
1.0
0.5
HBr
Br

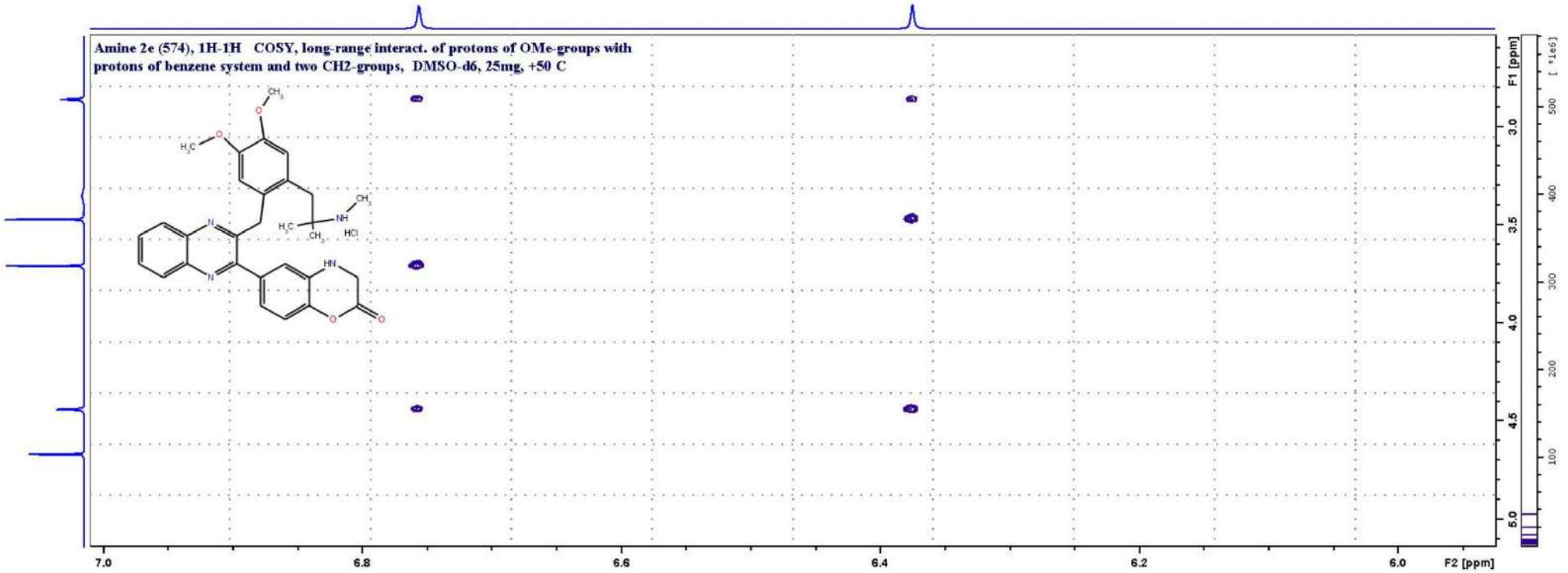

Amine 2d (583) 1H-15N HMBC, region of aliph. protons,
DMSO-d6, 25mg, +50 C
F1 [ppm]
F2 [ppm]
4.5
4.0
3.5
3.0
2.5
10
20
30
40
50

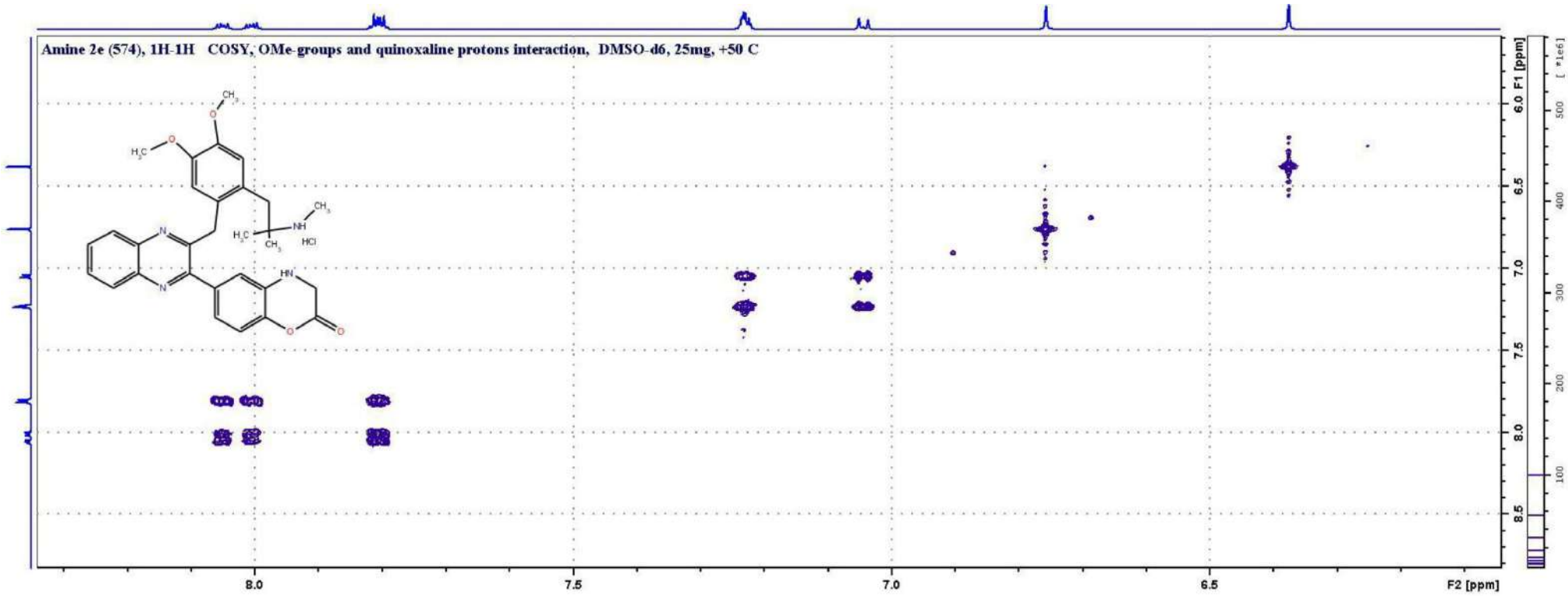

Amine 2d (583) 1H-15N HMBC, region of arom. protons,
DMSO-d6, 25mg, +50 C
F1 [ppm]
F2 [ppm]
8.4
8.2
8.0
325
330
335
340

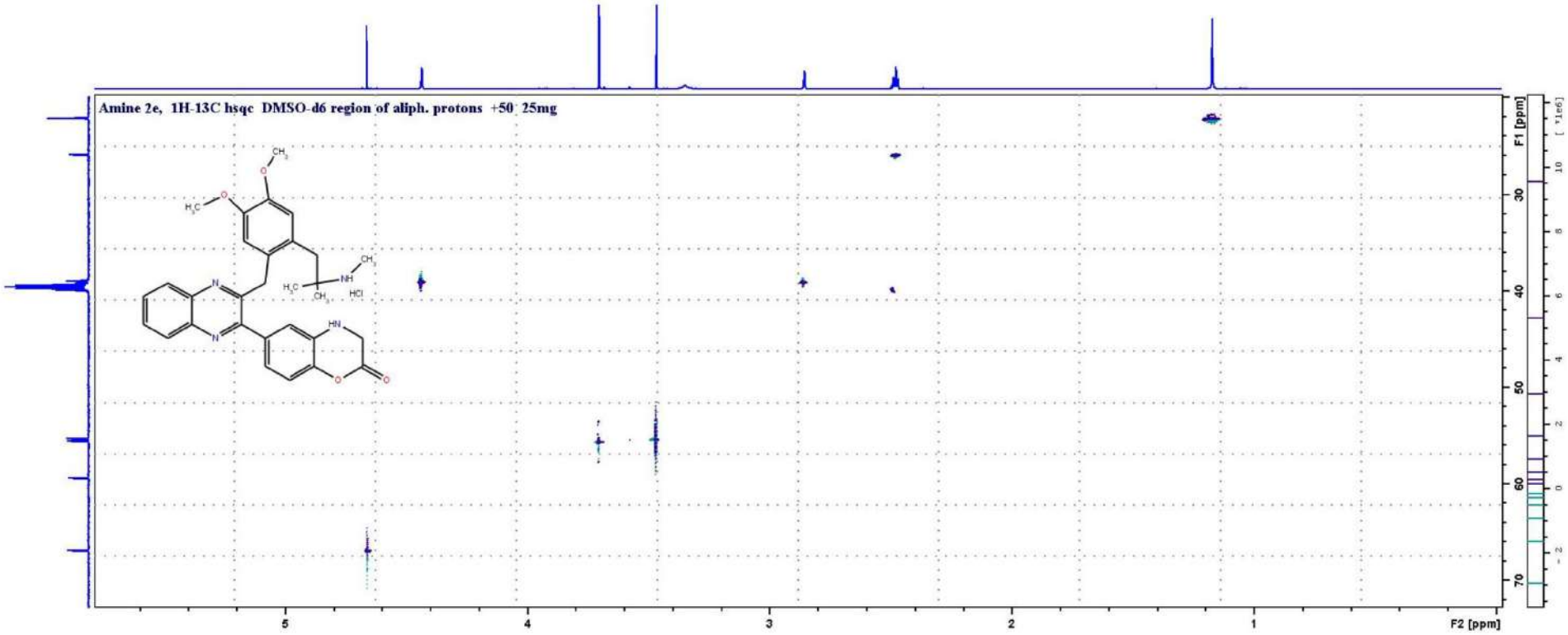
**6-(3-(4,5-Dimethoxy-2-(2-methyl-2-(methylamino)propyl)benzyl)quinoxalin-2-yl)-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one hydrochloride 2e.**

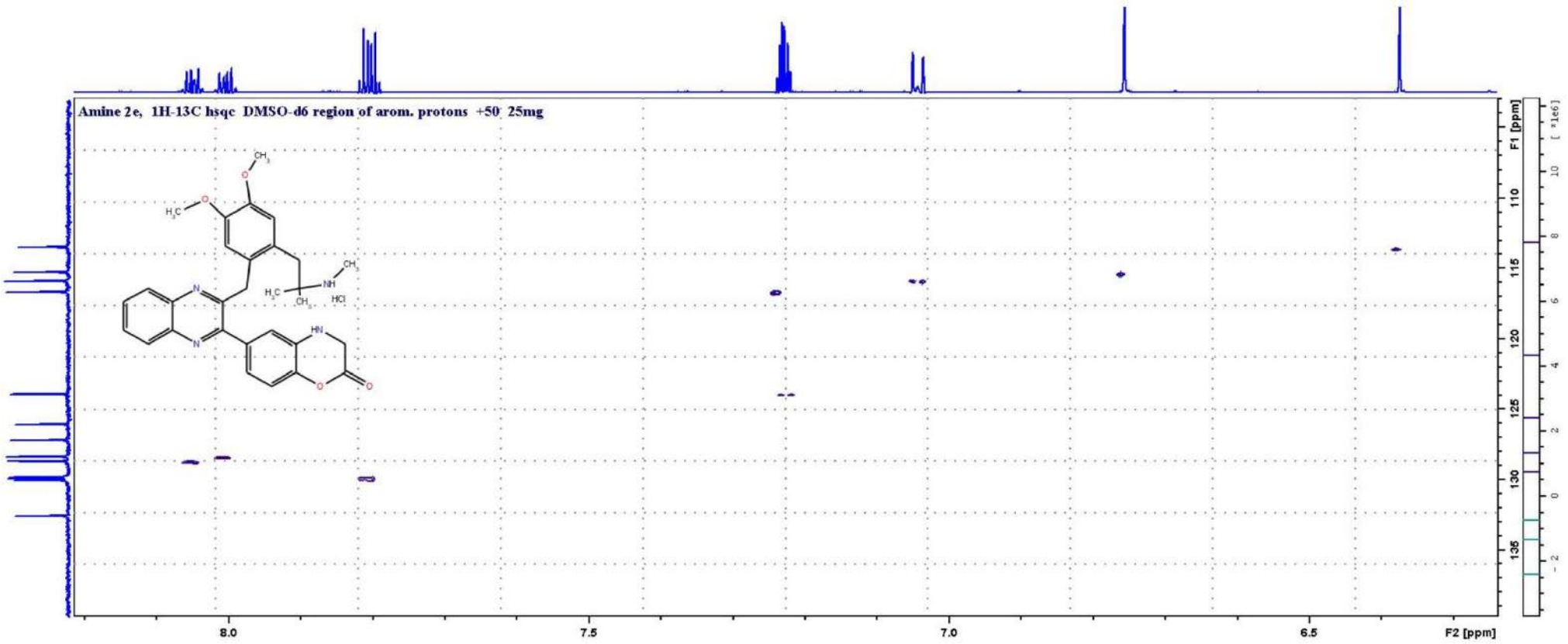


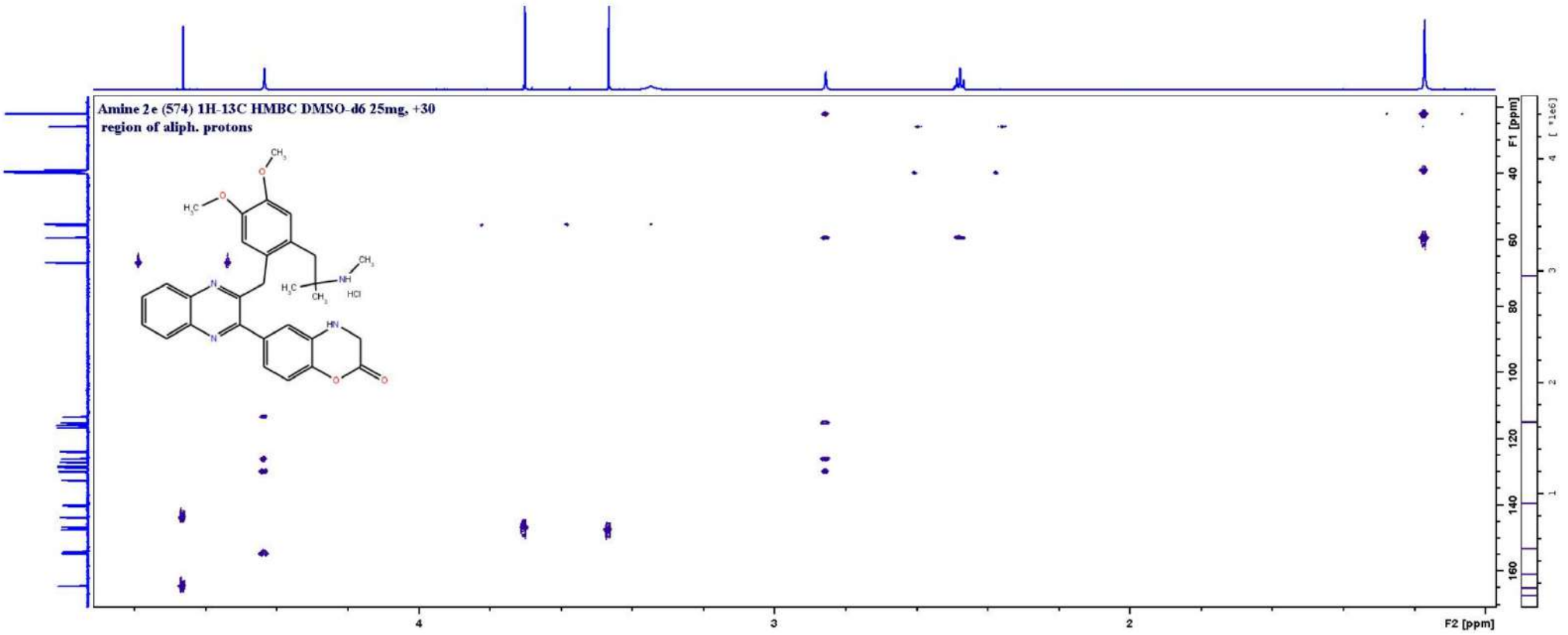

164.4830
154.7185
154.0464
147.3923
146.7309
143.6827
140.2950
140.0417
132.5181
129.9652
129.8355
129.7560
128.6290
128.3039
127.1363
126.0021
123.8645
116.6070
115.8337
115.1918
113.4192
66.8009
59.3020
55.4675
55.1989
40.0308
38.8884
25.8509
22.0775
MeO
MeO
CH2CMe2NHMe · HCl
O
N
N
N
H
O
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

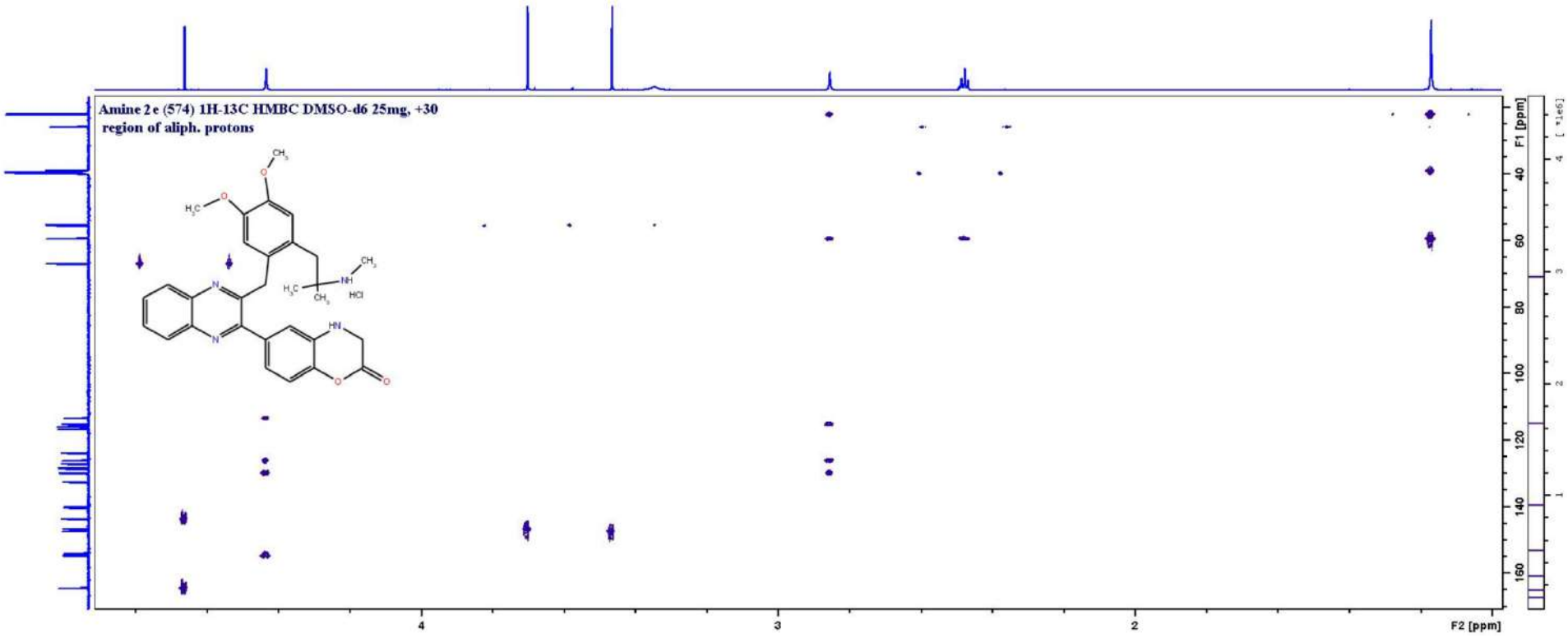

Amine 2e (574), 1H-1H COSY, long-range interact. of protons of OMe-groups with protons of benzene system and two CH2-groups, DMSO-d6, 25mg, +50 C
F1 [ppm]
F2 [ppm]
7.0
6.8
6.6
6.4
6.2
6.0
5.0
4.5
4.0
3.5
3.0
HCl
NH
HN

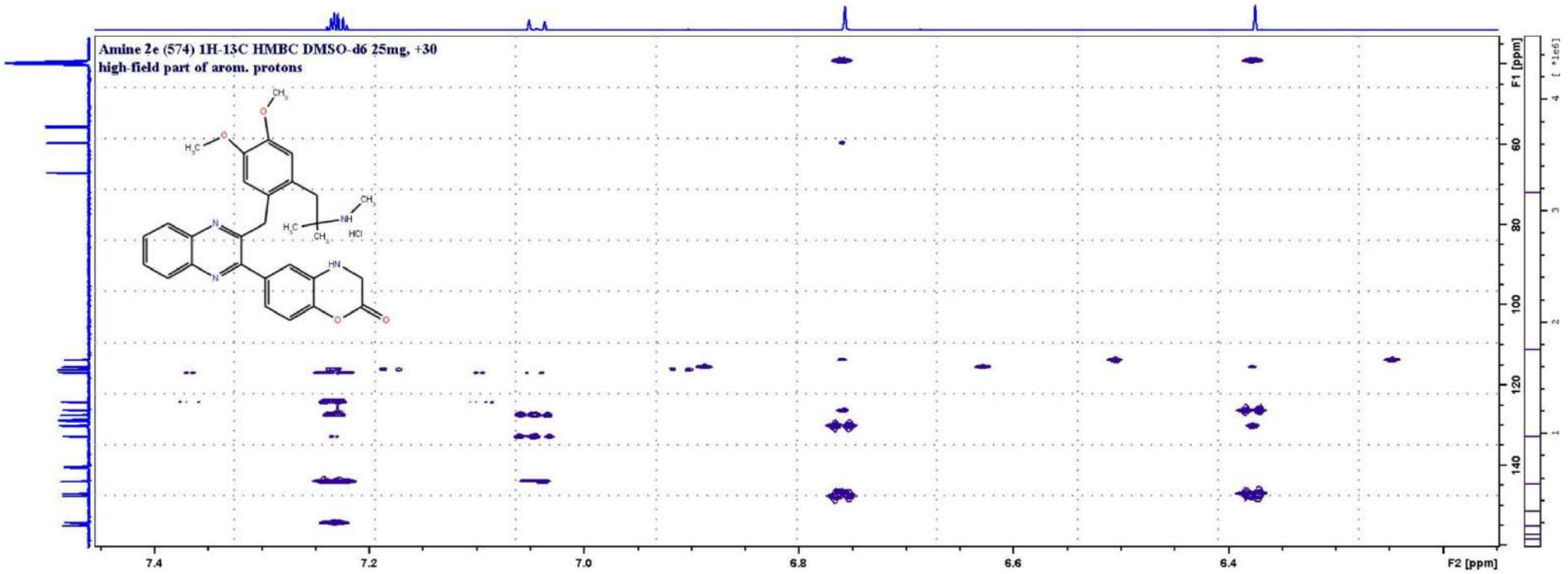

Amine 2e (574), 1H-1H COSY, OMe-groups and quinoxaline protons interaction, DMSO-d6, 25mg, +50 C
8.0
7.5
7.0
6.5
F2 [ppm]
6.0 F1 [ppm]
8.5

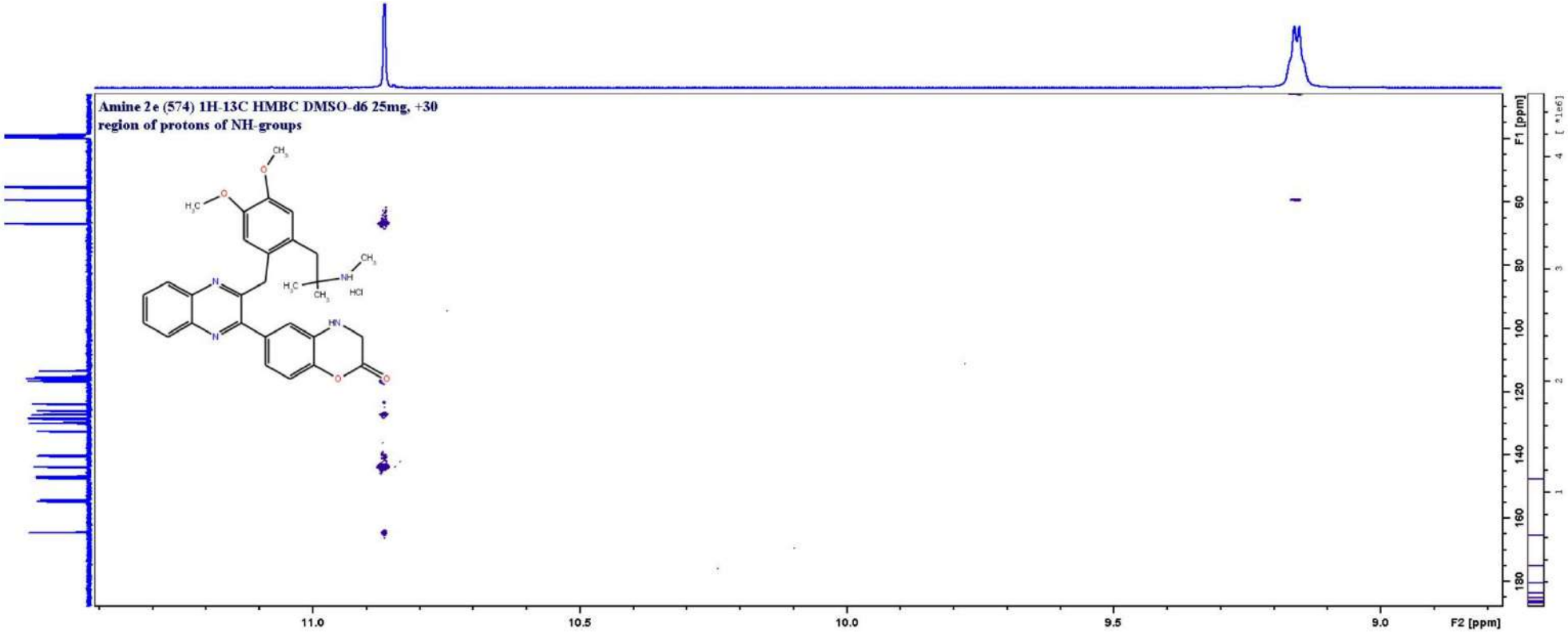

Amine 2e, 1H-13C hsqc DMSO-d6 region of aliph. protons +50 25mg
F1 [ppm]
F2 [ppm]
5
4
3
2
1
30
40
50
60
70
HCl

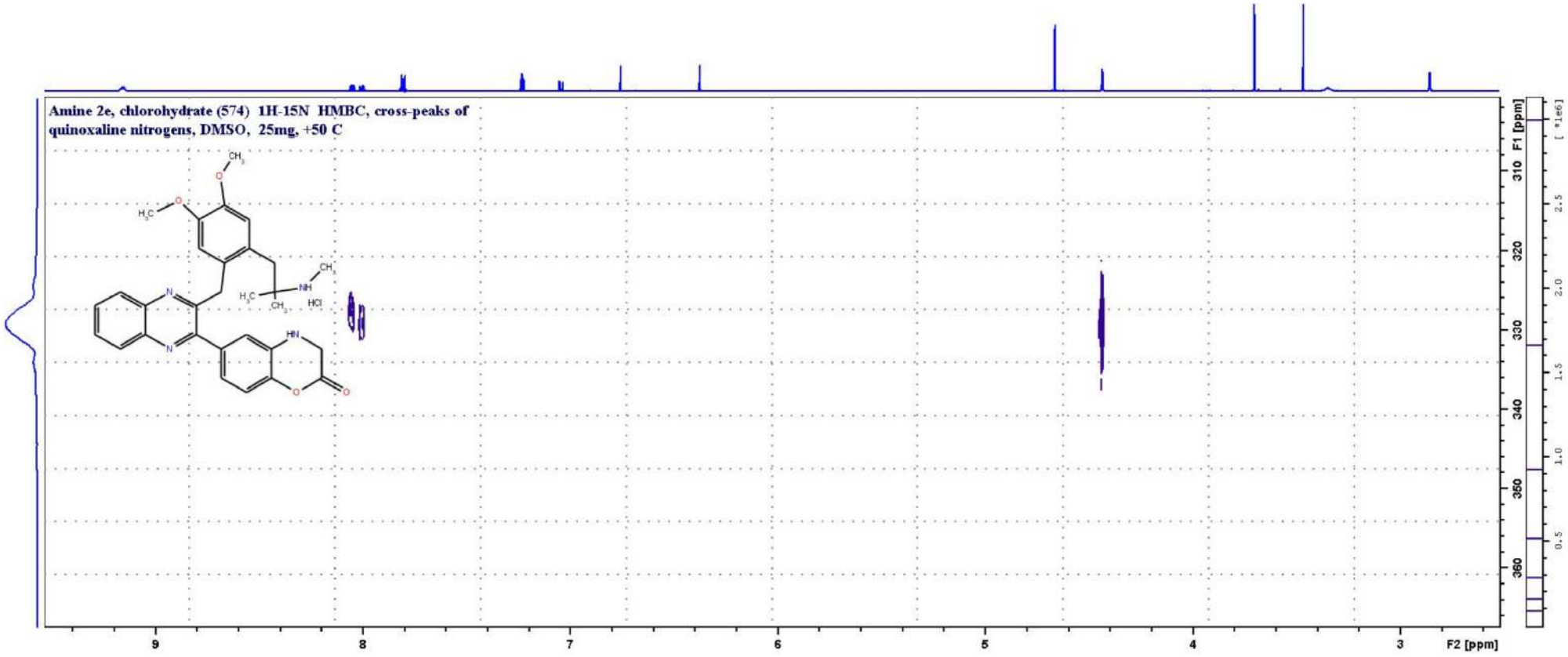

Amine 2e, 1H-13C hsqc DMSO-d6 region of arom. protons +50 25mg
F1 [ppm]
F2 [ppm]
8.0
7.5
7.0
6.5
110
115
120
125
130
135
HCl

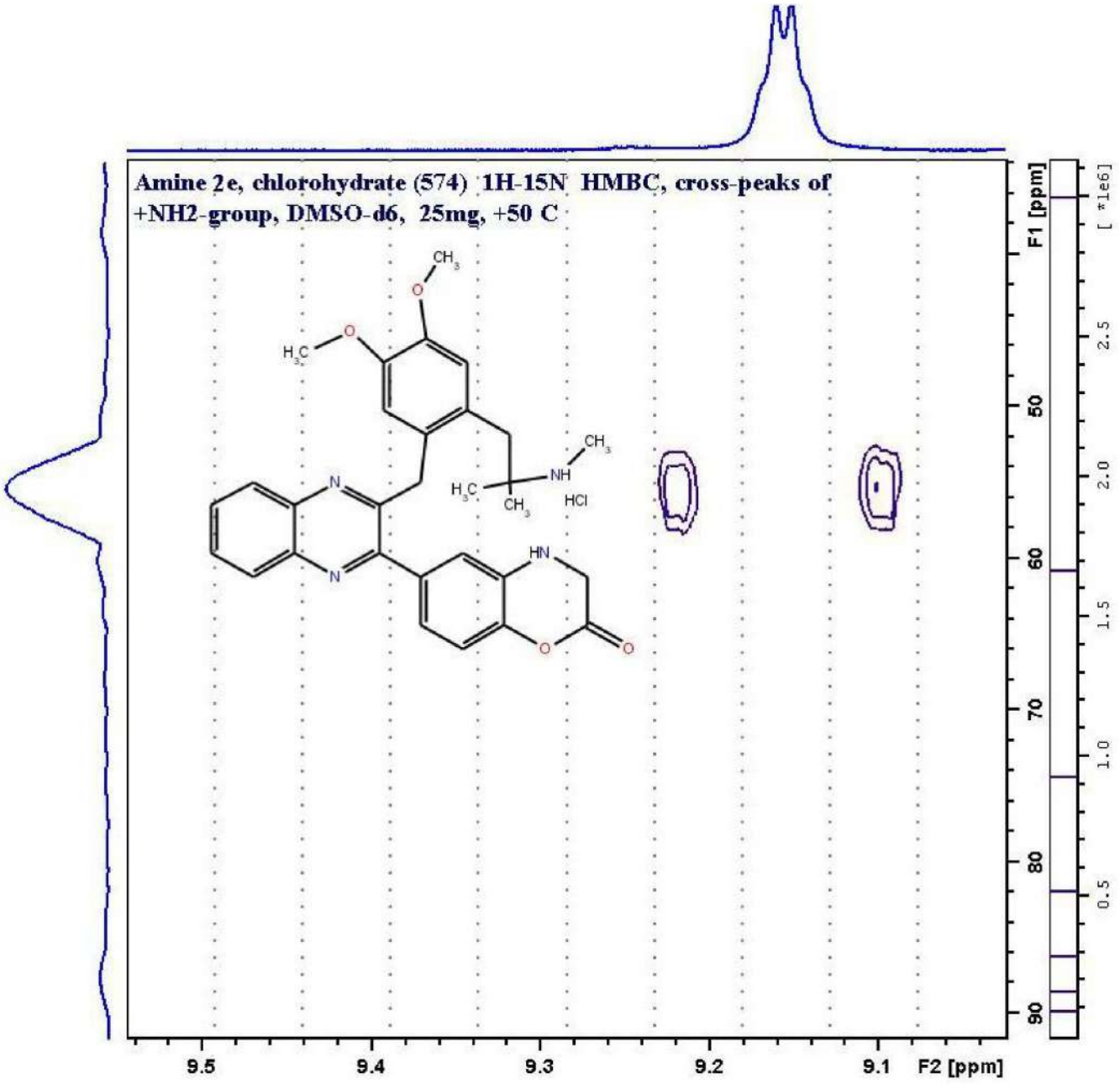

Amine 2e (574) 1H-13C HMBC DMSO-d6 25mg, +30
region of aliph. protons
F1 [ppm]
F2 [ppm]
4
3
2
40
60
80
100
120
140
160

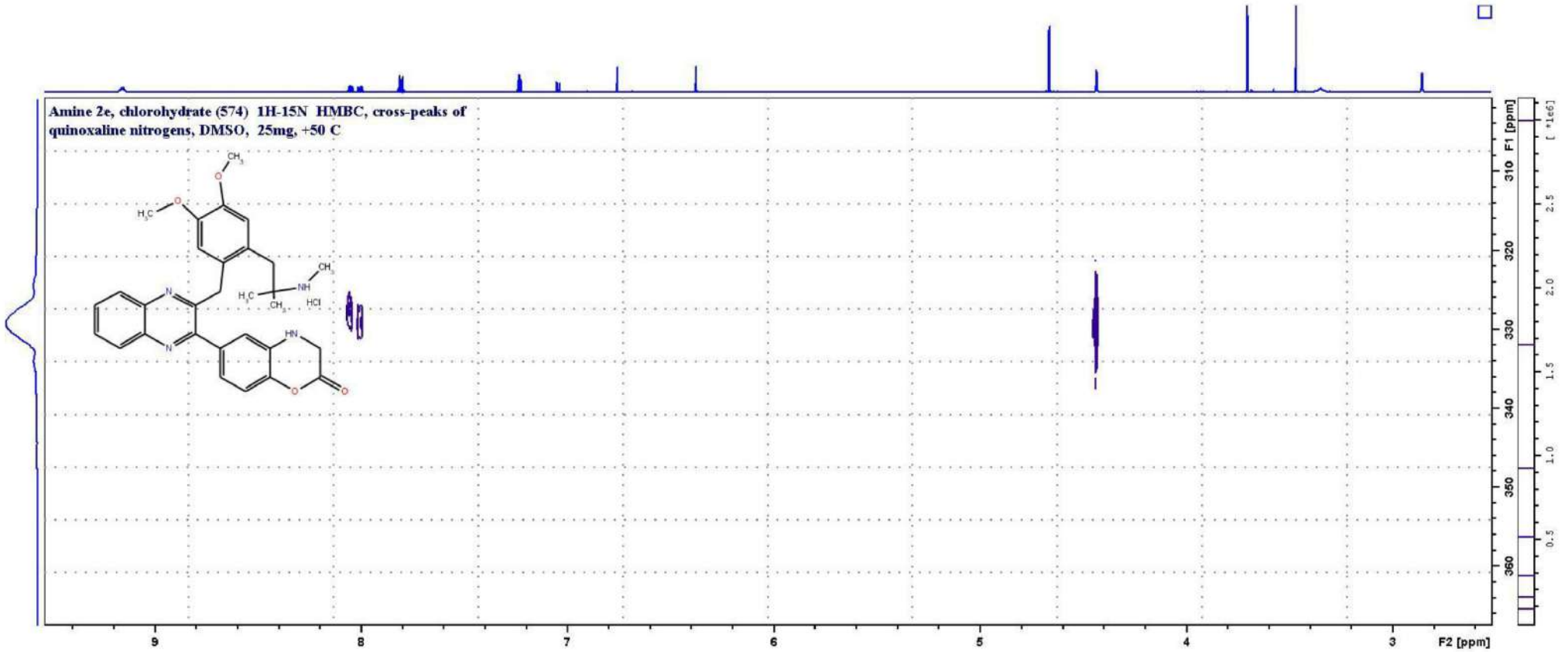

Amine 2 e (574) 1H-13C HMBC DMSO-d6 25mg, +30
region of aliph. protons
F1 [ppm]
F2 [ppm]
4
3
2
40
60
80
100
120
140
160


Amine 2e (574) 1H-13C HMBC DMSO-d6 25mg, +30
high-field part of arom. protons
F1 [ppm]
F2 [ppm]
7.4
7.2
7.0
6.8
6.6
6.4
60
80
100
120
140
HCl

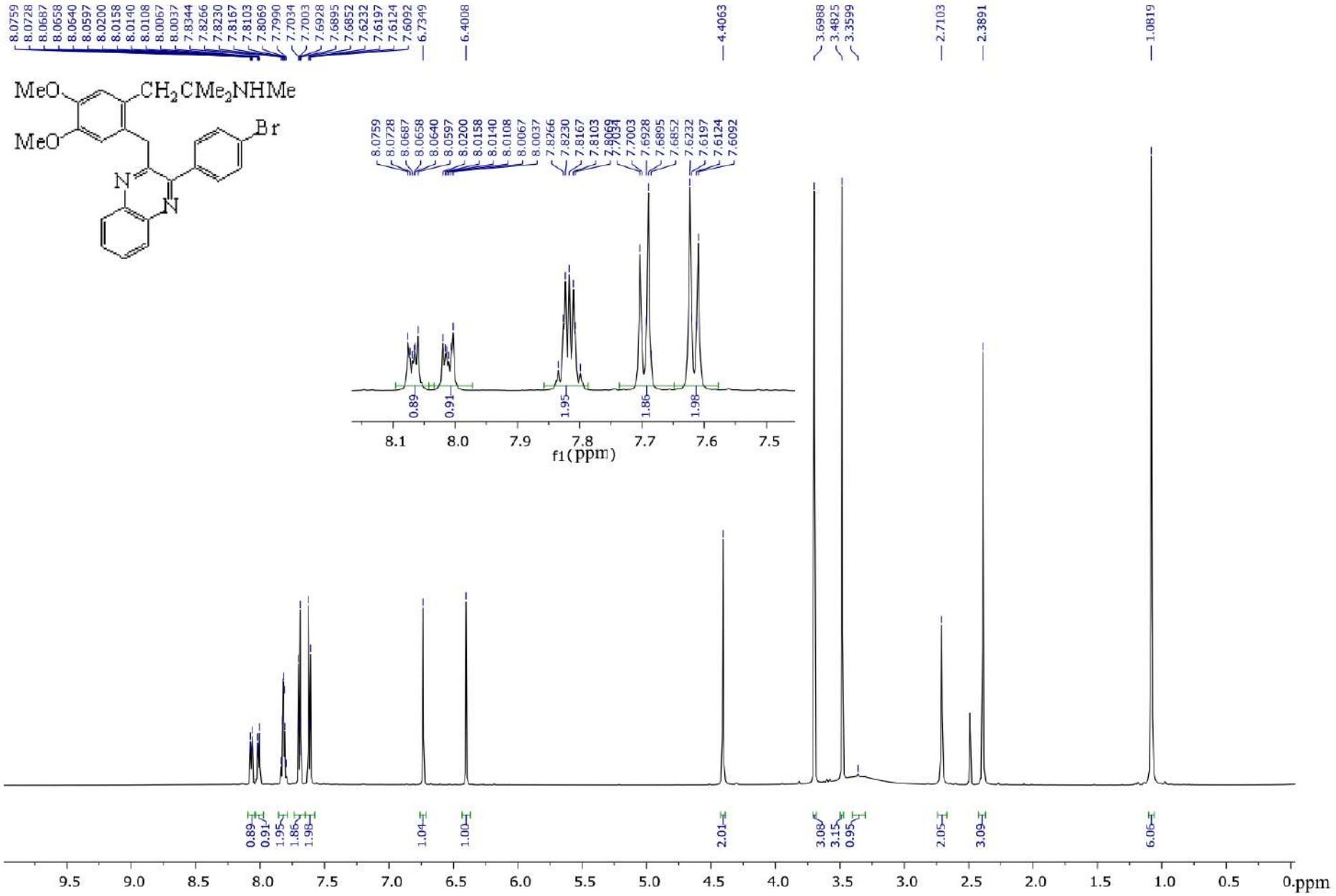

Amine 2e (574) 1H-13C HMBC DMSO-d6 25mg, +30
region of protons of NH-groups
F1 [ppm]
F2 [ppm]
11.0
10.5
10.0
9.5
9.0

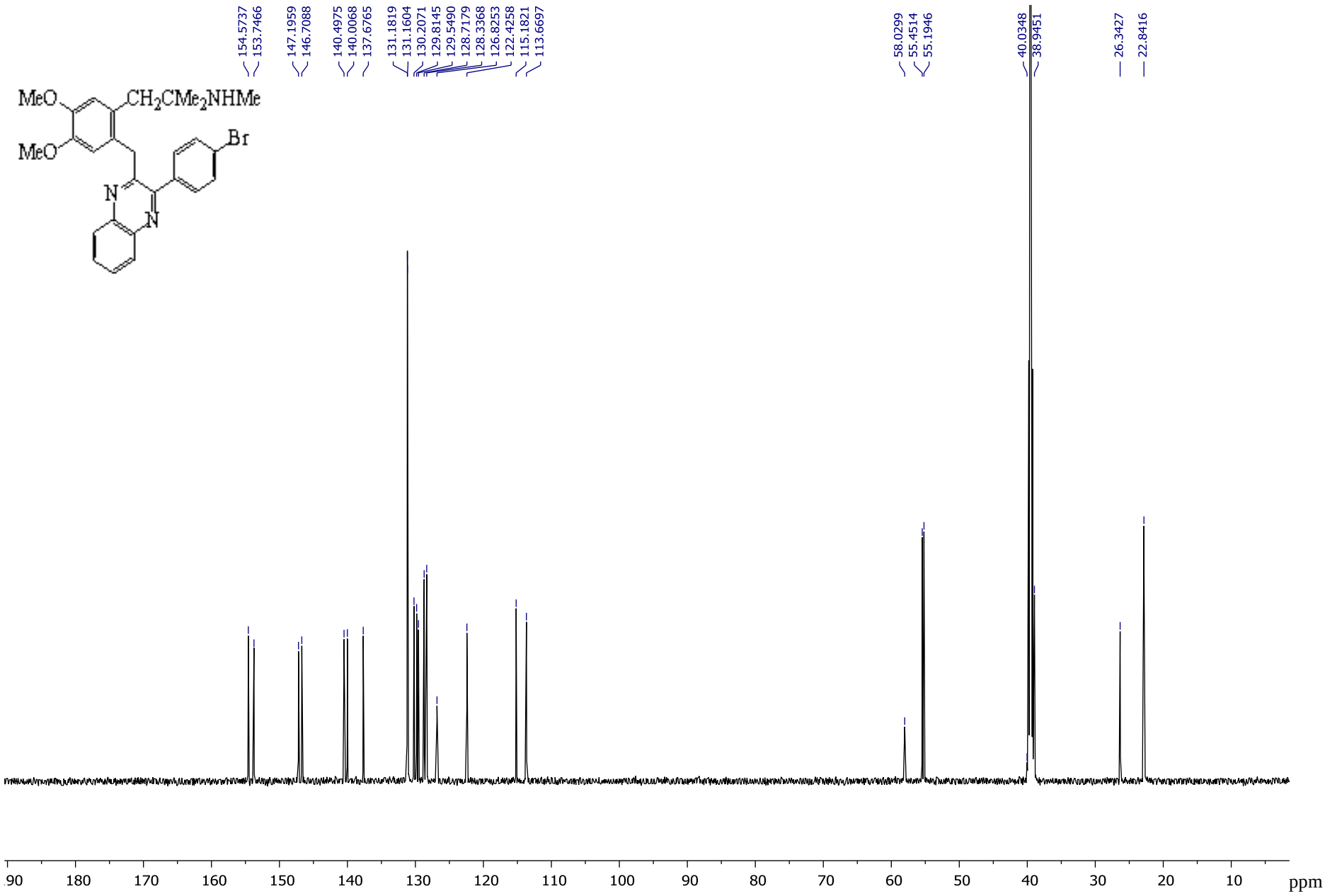

Amine 2e, chlorohydrate (574) 1H-15N HMBC, cross-peaks of quinoxaline nitrogens, DMSO, 25mg, +50 C
F1 [ppm]
F2 [ppm]


Amine 2e, chlorohydrate (574) 1H-15N HMBC, cross-peaks of
+NH2-group, DMSO-d6, 25mg, +50 C
F1 [ppm]
F2 [ppm]
9.5
9.4
9.3
9.2
9.1
50
60
70
80
90
HCl

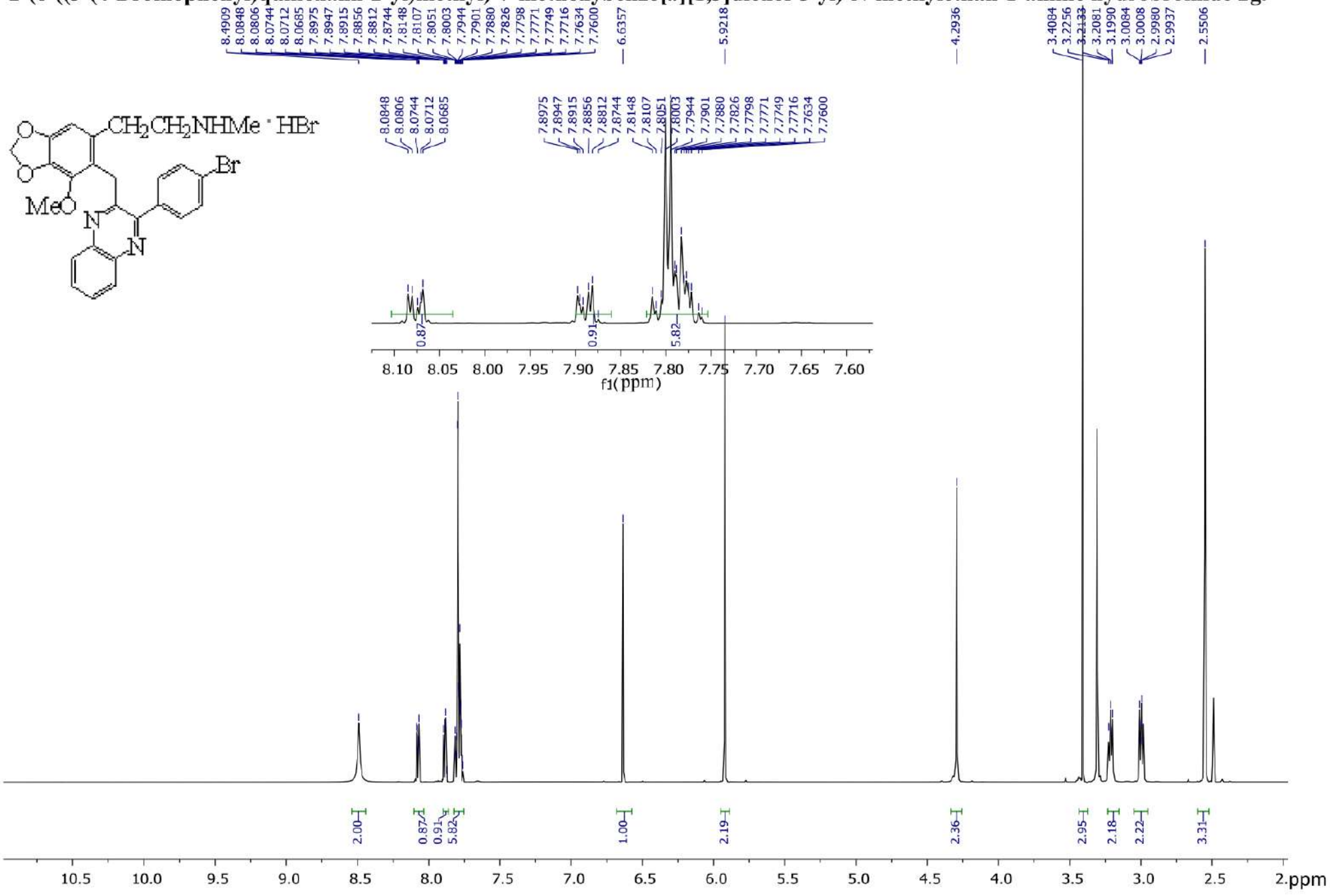

Amine 2e, chlorohydrate (574) 1H-15N HMBC, cross-peaks of quinoxaline nitrogens, DMSO, 25mg, +50 C
F1 [ppm]
F2 [ppm]
9
8
7
6
5
4
3
310
320
330
340
350
360

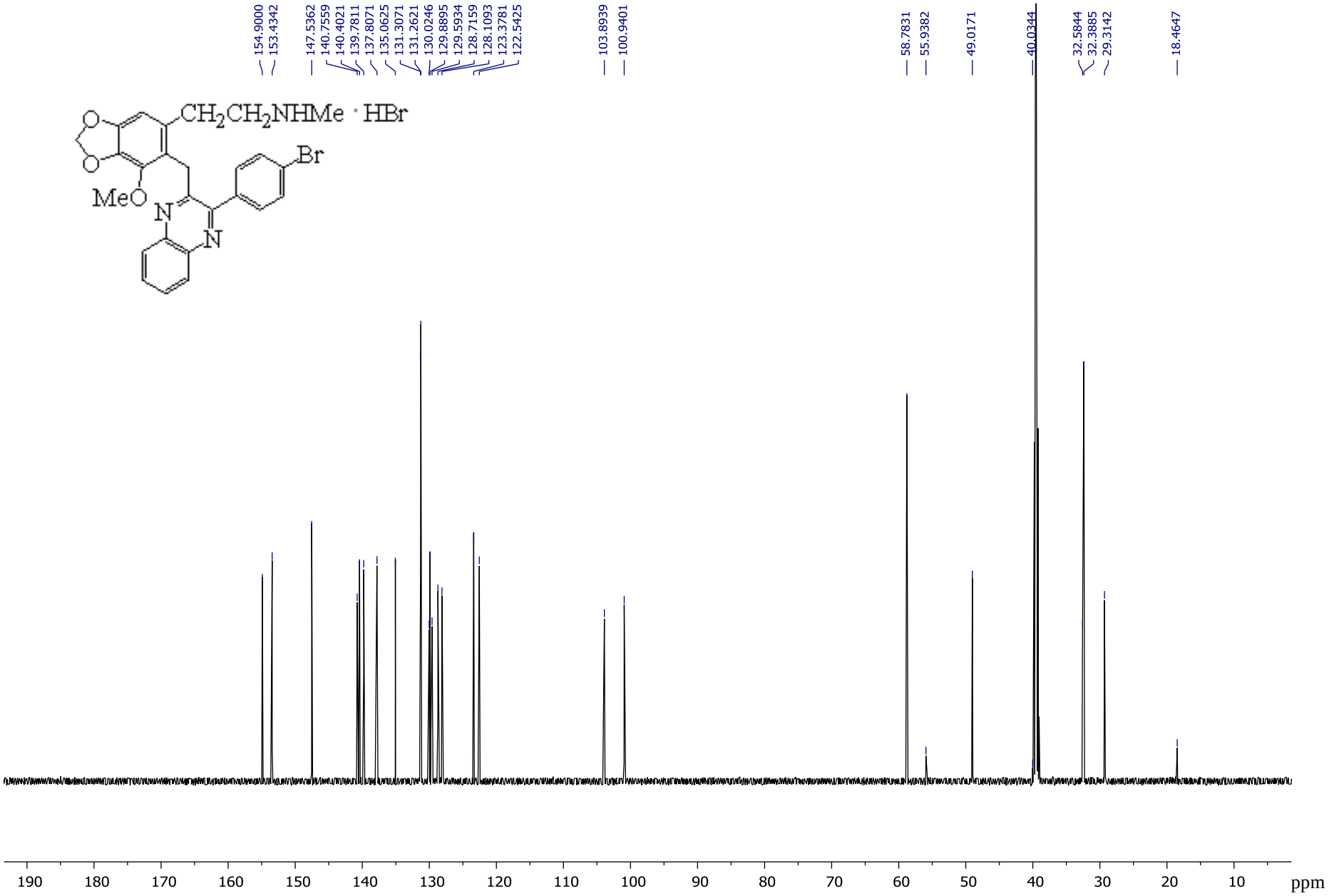
**1-(2-((3-(4-Bromophenyl)quinoxalin-2-yl)methyl)-4,5-dimethoxyphenyl)-N,2-dimethylpropan-2-amine 2f**



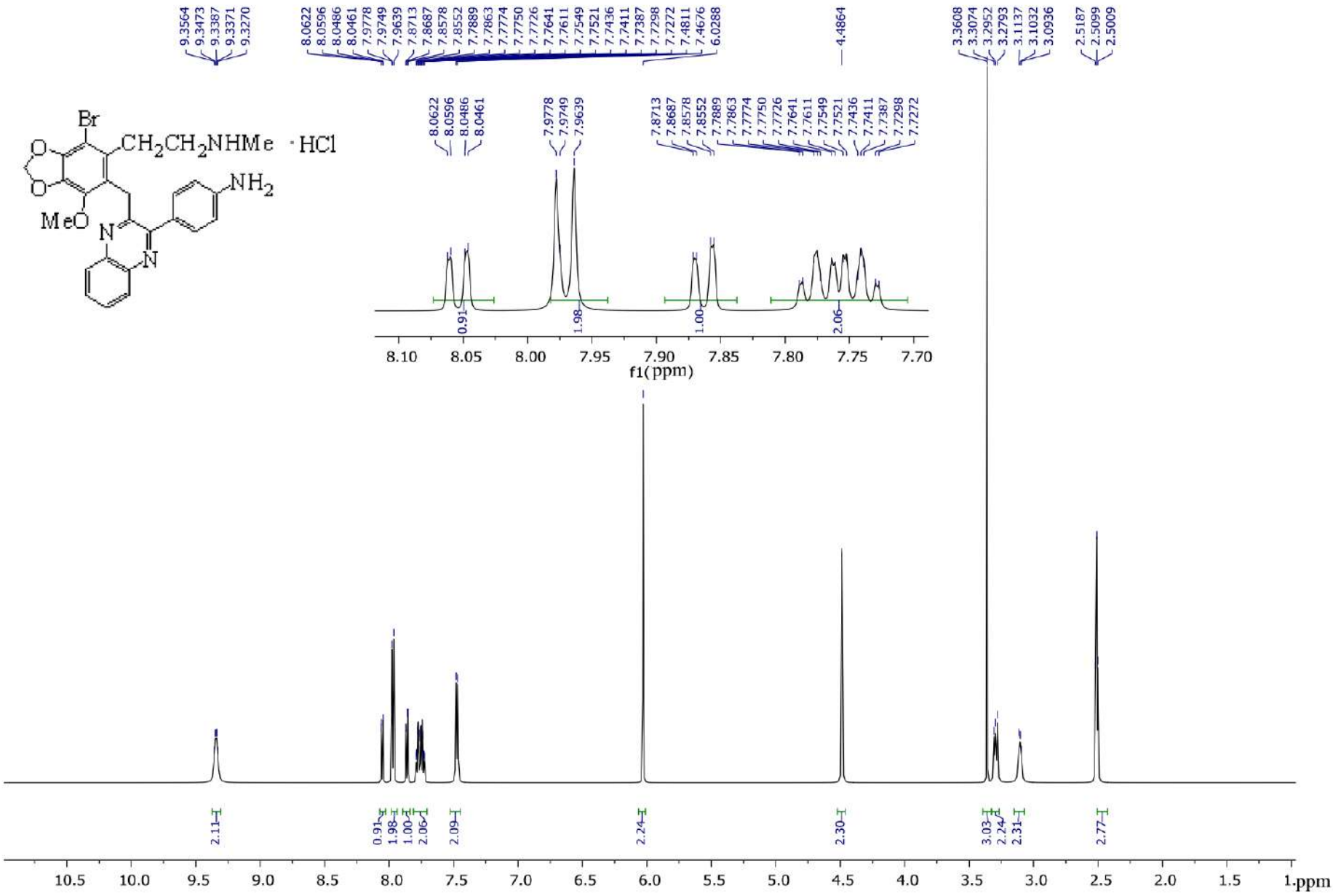

154.5737
153.7466
147.1959
146.7088
140.4975
140.0068
137.6765
131.1819
131.1604
130.2071
129.8145
129.5490
128.7179
128.3368
126.8253
122.4258
115.1821
113.6697
58.0299
55.4514
55.1946
40.0348
38.9451
26.3427
22.8416
MeO
MeO
CH2CMe2NHMe
Br
N
N
90
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

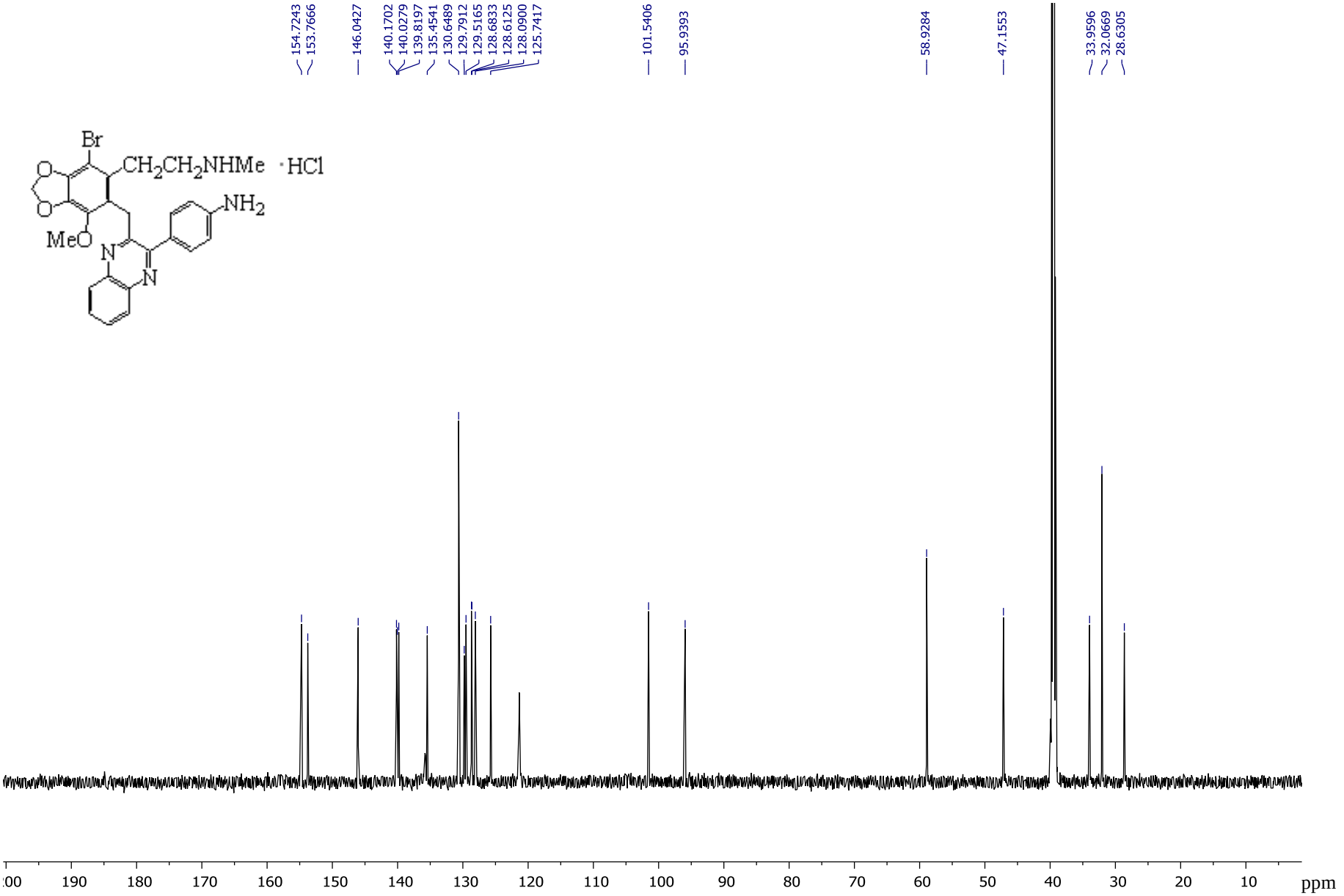
**2-(6-((3-(4-Bromophenyl)quinoxalin-2-yl)methyl)-7-methoxybenzo[*d*][1,3]dioxol-5-yl)-N-methylethan-1-amine hydrobromide 2g.**



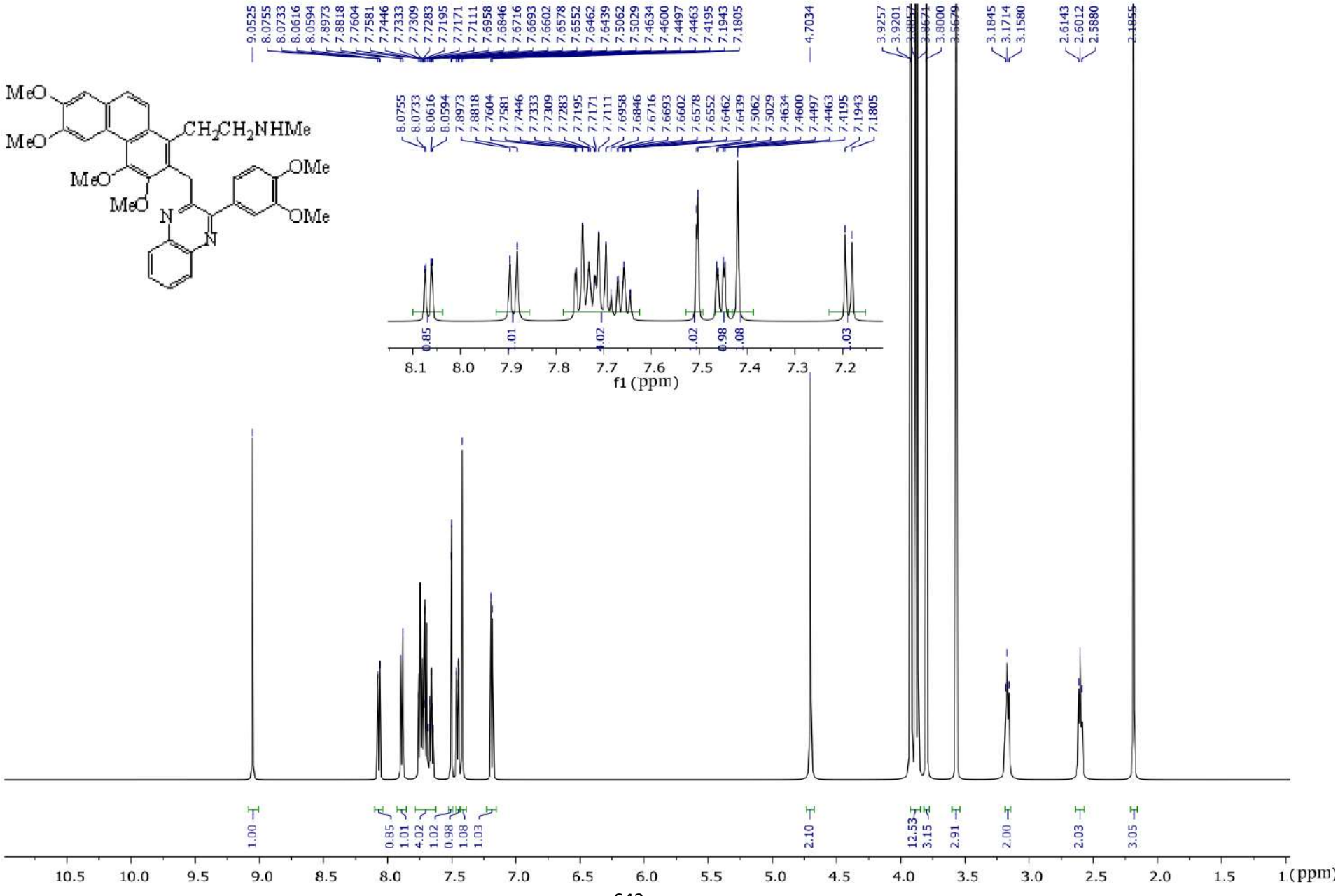

154.9000
153.4342
147.5362
140.7559
140.4021
139.7811
137.8071
135.0625
131.3071
131.2621
130.0246
129.8895
129.5934
128.7159
128.1093
123.3781
122.5425
103.8939
100.9401
58.7831
55.9382
49.0171
40.0344
32.5844
32.3885
29.3142
18.4647
CH2CH2NHMe · HBr
Br
MeO
N
N
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

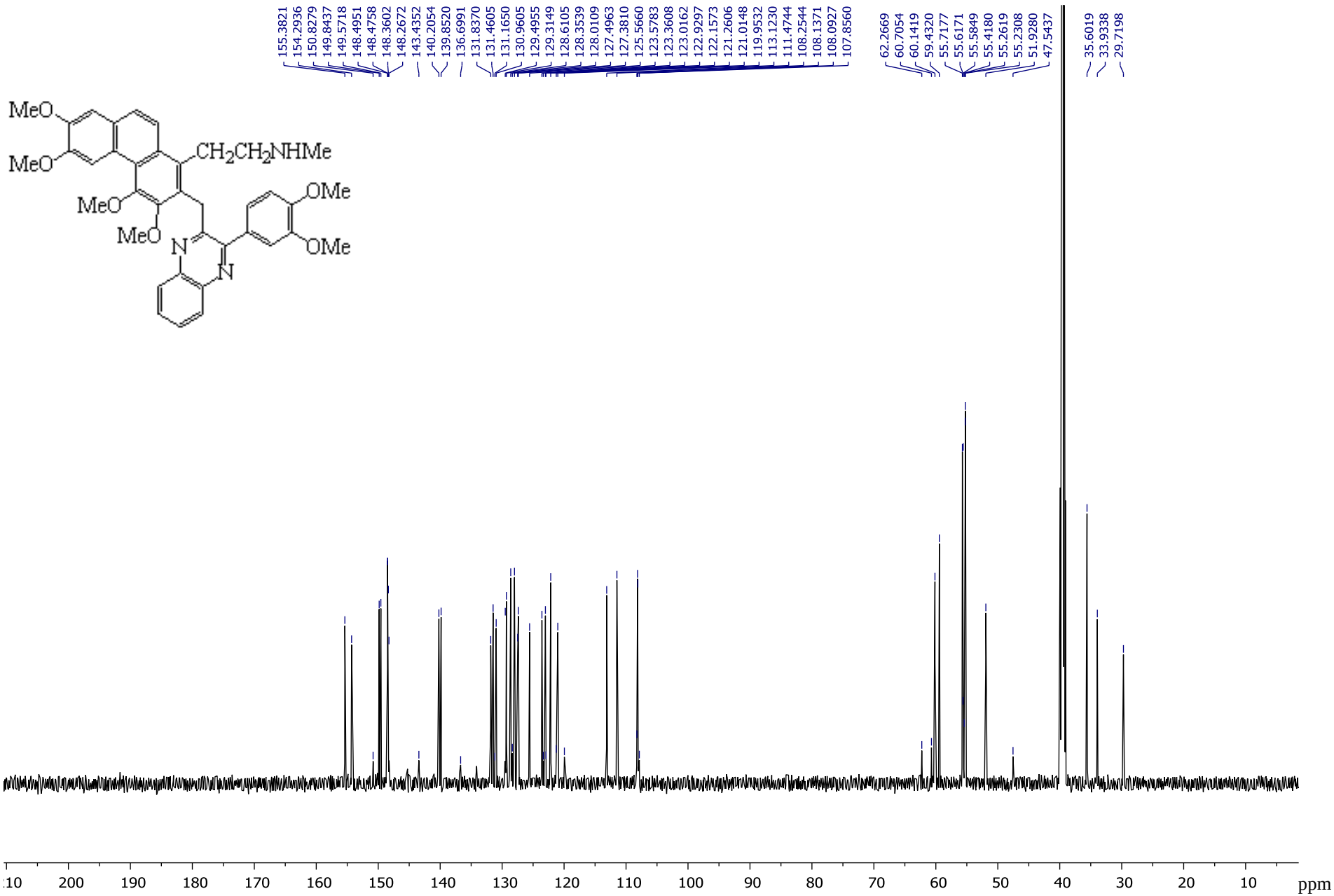
**2-(4-Bromo-6-((3-(4-bromophenyl)quinoxalin-2-yl)methyl)-7-methoxybenzo[d][1,3]dioxol-5-yl)-N-methylethan-1-amine hydrochloride 2h.**



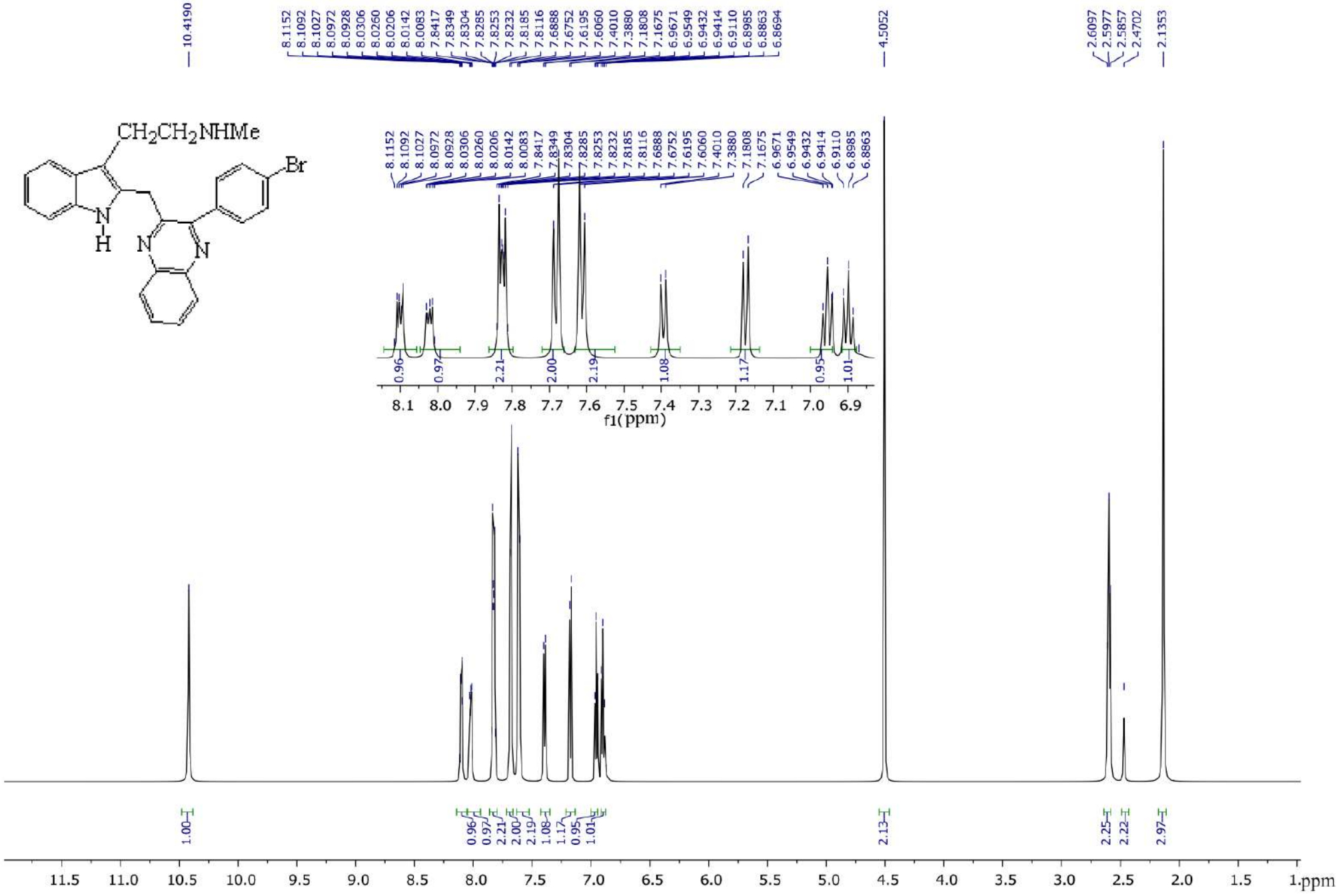

154.7243
153.7666
146.0427
140.1702
140.0279
139.8197
135.4541
130.6489
129.7912
129.5165
128.6833
128.6125
128.0900
125.7417
101.5406
95.9393
58.9284
47.1553
33.9596
32.0669
28.6305
Br
CH2CH2NHMe ·HCl
NH2
MeO
N
N
O
O
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

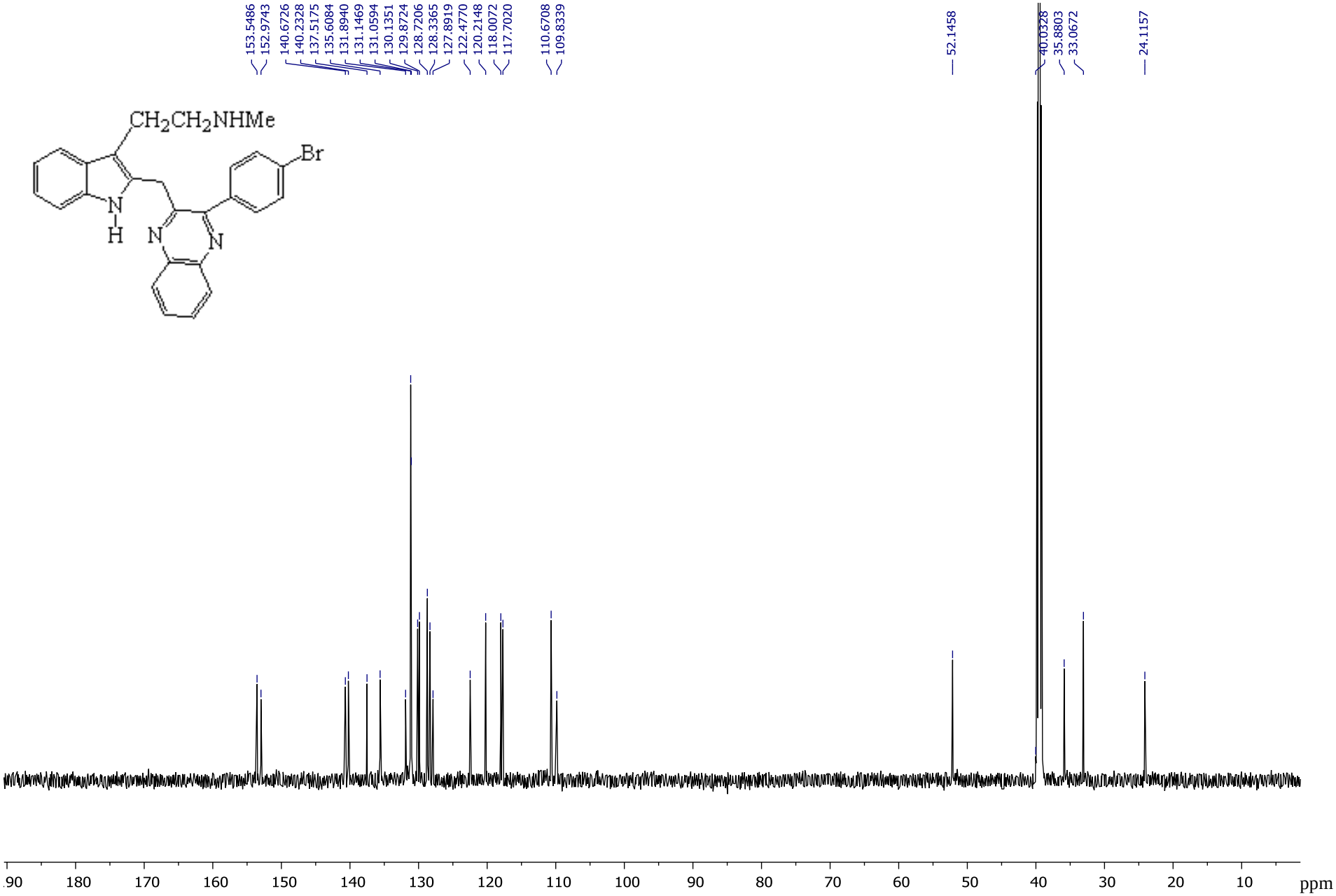
**2-(2-((3-(3,4-dimethoxyphenyl)quinoxalin-2-yl)methyl)-3,4,6,7-tetramethoxyphenanthren-1-yl)-N-methylethan-1-amine 2i.**




155.3821
154.2936
150.8279
149.8437
149.5718
148.4951
148.4758
148.3602
148.2672
143.4352
140.2054
139.8520
136.6991
131.8370
131.4605
131.1650
130.9605
129.4955
129.3149
128.6105
128.3539
128.0109
127.4963
127.3810
125.5660
123.5783
123.3608
123.0162
122.9297
122.1573
121.2606
121.0148
119.9532
113.1230
111.4744
108.2544
108.1371
108.0927
107.8560
62.2669
60.7054
60.1419
59.4320
55.7177
55.6171
55.5849
55.4180
55.2619
55.2308
51.9280
47.5437
35.6019
33.9338
29.7198
MeO
MeO
MeO
MeO
CH2CH2NHMe
OMe
OMe
N
N
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

**2-(2-((3-(4-Bromophenyl)quinoxalin-2-yl)methyl)-1*H*-indol-3-yl)-N-methylethan-1-amine 2j.**




153.5486
152.9743
140.6726
140.2328
137.5175
135.6084
131.8940
131.1469
131.0594
130.1351
129.8724
128.7206
128.3365
127.8919
122.4770
120.2148
118.0072
117.7020
110.6708
109.8339
52.1458
40.0328
35.8803
33.0672
24.1157
CH2CH2NHMe
Br
N
H
N
N
90
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

**5. Quantum chemical data for azepine ring opening in potential N-protonated intermediates of the model reaction between (1,2-dihydro-3*H*-benz[d]azepin-4-yl)phenylmethanone and o-phenylenediamine.**

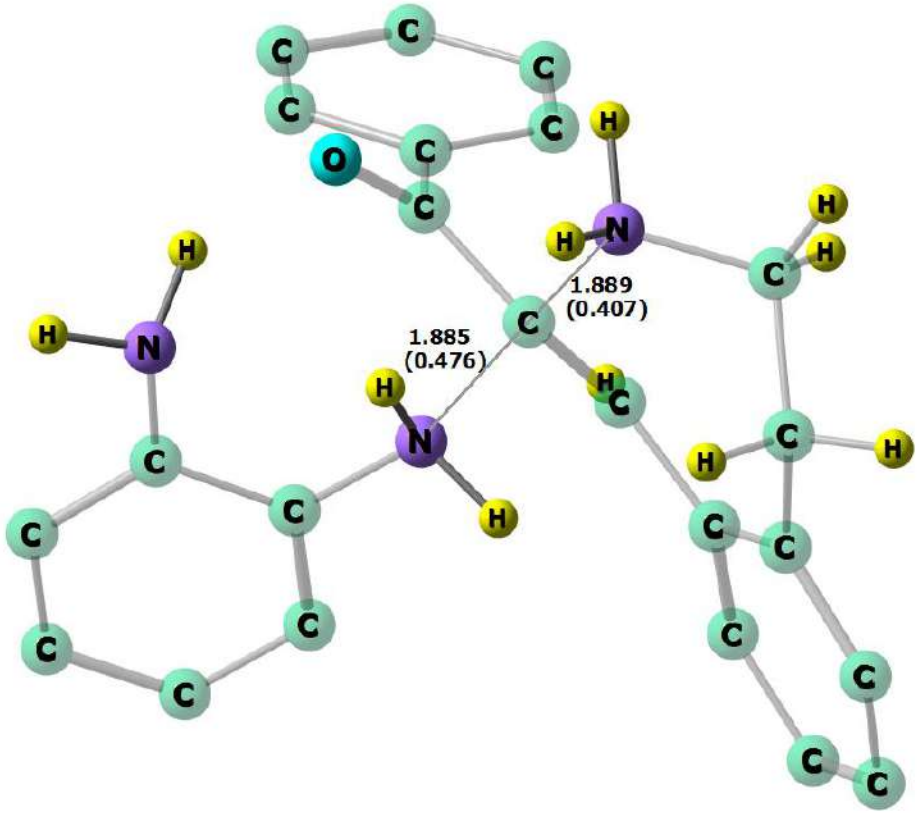



**Figure S2** The transition state **TS1** of the opening reaction of the azepine cycle of the N-protonated form of 4-benzoyl-1,2-dihydrobenz[d]azepine under the influence of a nucleophilic attack with an *o*-phenylenediamine (aromatic protons are not shown); $E_{tot}$ = -1130.13016 a.u. $\lambda\iota = -562$ cm-$^{1}$.

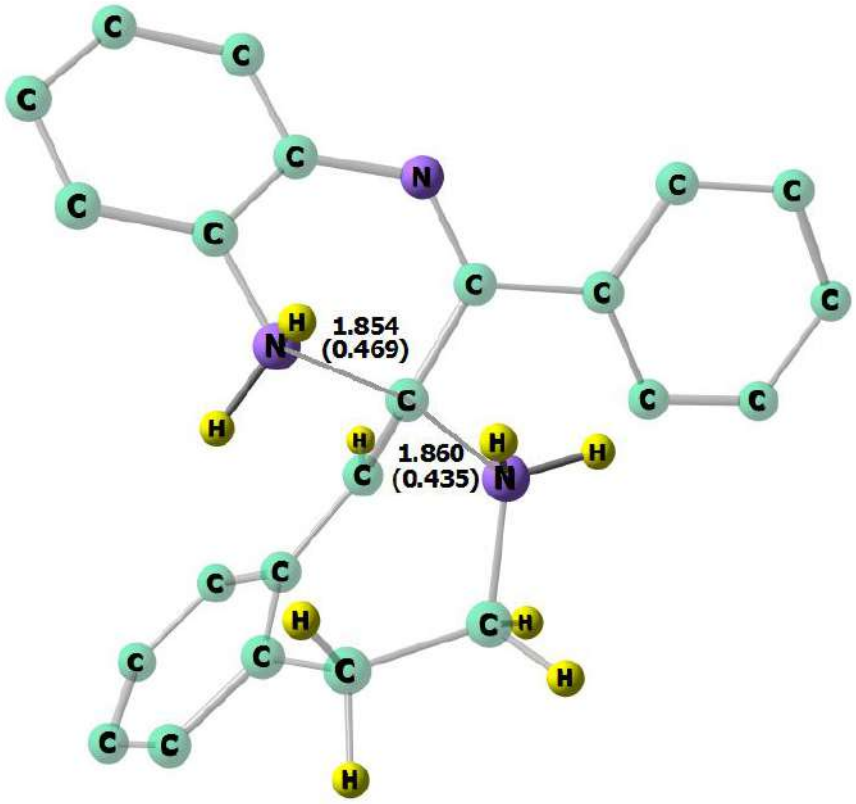



**Figure S3** The transition state **TS2** of the opening reaction of the azepine cycle of the N-protonated form of 4-benzoyl-1,2-dihydrobenz[d]azepine under the influence of a nucleophilic attack with an *o*-phenylenediamine (aromatic protons are not shown); $E_{tot}$ = -1053.67597 a.u.; $\lambda_{\iota}$ = 625 см$^{-1}$

Table S2. Atomic coordinates for transition states TS1 and TS2.**TS1**, Å

| | | | |
|---|---|---|---|
| C | 4.872874860 | -0.536876009 | 1.441211412 |
| C | 3.863126249 | -0.767133833 | 2.376479654 |
| C | 4.558563996 | -0.531770971 | 0.084771085 |
| C | 3.250663070 | -0.727690142 | -0.379867321 |
| C | 2.212192800 | -0.916747583 | 0.569729778 |
| C | 2.559200564 | -0.959183466 | 1.939957447 |
| C | 3.073921151 | -0.784275021 | -1.895684808 |
| C | 1.932271953 | -1.648456480 | -2.434915184 |
| N | 0.656060926 | -0.894799685 | -2.474554138 |
| C | 0.048348730 | -0.512843089 | -0.727679455 |
| C | 0.783079603 | -1.064571475 | 0.269372172 |
| C | -1.431530369 | -0.586767068 | -0.890828028 |
| N | -1.440081251 | 2.980868835 | -1.952999954 |
| C | -2.273126767 | -1.491776988 | -0.065310927 |
| C | -3.571380797 | -1.041938243 | 0.240004511 |
| C | -4.437881759 | -1.844799588 | 0.972664635 |
| C | -4.034338780 | -3.119214206 | 1.382147639 |
| C | -2.761425786 | -3.588781185 | 1.053968908 |
| C | -1.880208213 | -2.781090005 | 0.337976830 |
| C | -1.132773371 | 3.070933598 | -0.579774750 |
| C | -1.690534799 | 4.022022423 | 0.282593575 |
| C | -0.144572535 | 2.210405567 | -0.059016663 |
| C | 0.247143959 | 2.267592721 | 1.278806491 |
| C | -0.336808553 | 3.209646305 | 2.122689178 |
| C | -1.295010039 | 4.091666242 | 1.617270398 |
| N | 0.490698108 | 1.302209188 | -0.982611018 |
| H | 5.898786775 | -0.387681146 | 1.761157040 |
| H | 4.090765983 | -0.800725925 | 3.436930169 |
| H | 5.355789989 | -0.396030207 | -0.641575824 |
| H | 1.771923577 | -1.135143003 | 2.667624874 |
| H | 4.003740336 | -1.178501398 | -2.315749912 |
| H | 2.990148323 | 0.227089124 | -2.327340273 |
| H | 1.769776891 | -2.522834069 | -1.799543613 |
| H | 2.159711829 | -2.002316177 | -3.445458970 |
| H | 0.724178036 | -0.087440102 | -3.094471943 |
| H | 0.187139167 | -1.537283364 | 1.042181579 |
| H | -3.878633878 | -0.057917660 | -0.095924380 |
| H | -5.430221738 | -1.482158135 | 1.220282975 |
| H | -4.715317867 | -3.748675521 | 1.946248727 |
| H | -2.457137371 | -4.588364734 | 1.346994662 |
| H | -0.907043444 | -3.169944899 | 0.060719000 |
| H | -2.442095854 | 4.706122951 | -0.100903265 |
| H | 1.018597249 | 1.598976628 | 1.647180344 |
| H | -0.035190027 | 3.264072593 | 3.162921153 |
| H | -1.743355043 | 4.835581407 | 2.267841527 |
| H | 1.498040091 | 1.277743966 | -0.824482235 |
| H | 0.281801126 | 1.650306291 | -1.925062441 |
| H | -0.100484603 | -1.470659724 | -2.845774429 |
| H | -2.001579073 | 3.758252486 | -2.281234432 |
| H | -1.889175483 | 2.096655427 | -2.188217750 |
| O | -1.940143487 | 0.130876885 | -1.758571790 |

**TS2**, Å

| | | | |
|---|---|---|---|
| C | 4.778871938 | -1.813508725 | 0.752626786 |
| C | 4.166633416 | -1.289440068 | 1.892614495 |
| C | 4.009360638 | -2.053914465 | -0.380849425 |
| C | 2.634977321 | -1.771832482 | -0.423589673 |
| C | 2.018133710 | -1.196740488 | 0.718185378 |
| C | 2.811830740 | -0.988164807 | 1.867520422 |
| C | 1.898992827 | -2.179869371 | -1.698812437 |
| C | 0.432881625 | -2.585776650 | -1.545934761 |
| N | -0.477887714 | -1.411352161 | -1.599998926 |
| C | -0.183659852 | -0.270717899 | -0.160793261 |
| C | 0.612425652 | -0.765175535 | 0.810981845 |
| C | -1.513523563 | 0.397858967 | 0.065673170 |
| N | -1.632245902 | 1.679854390 | 0.130312830 |
| C | -2.734445225 | -0.433810922 | 0.227330333 |
| C | -3.994789224 | 0.147297105 | -0.011232833 |
| C | -5.155872198 | -0.600475377 | 0.148045550 |
| C | -5.085308499 | -1.937078279 | 0.554212984 |
| C | -3.843885815 | -2.521732252 | 0.805526956 |
| C | -2.674284962 | -1.779254028 | 0.640594741 |
| C | -0.547547776 | 2.551855928 | 0.000081685 |
| C | -0.687672668 | 3.843609494 | 0.528999034 |
| C | 0.658587086 | 2.230928222 | -0.645248222 |
| C | 1.693080226 | 3.150487945 | -0.760813678 |
| C | 1.541866953 | 4.424960768 | -0.207272790 |
| C | 0.351226815 | 4.766996049 | 0.436083585 |
| N | 0.757769001 | 0.904456846 | -1.243309901 |
| H | 5.836768358 | -2.054292567 | 0.753508691 |
| H | 4.742754900 | -1.114439991 | 2.795588180 |
| H | 4.477936528 | -2.501181753 | -1.254081739 |
| H | 2.341239975 | -0.566436821 | 2.750956291 |
| H | 2.428242097 | -3.039836784 | -2.119634394 |
| H | 1.976534626 | -1.407521414 | -2.483431915 |
| H | 0.264992159 | -3.074405739 | -0.583808549 |
| H | 0.134145504 | -3.280812927 | -2.336780387 |
| H | -0.463262523 | -0.979937296 | -2.525539515 |
| H | 0.206731204 | -0.649432727 | 1.812864904 |
| H | -4.041070158 | 1.185976604 | -0.317647701 |
| H | -6.120626009 | -0.142116596 | -0.044576999 |
| H | -5.994573999 | -2.516354646 | 0.679130068 |
| H | -3.783961920 | -3.551761648 | 1.142311818 |
| H | -1.715902050 | -2.227765594 | 0.885131939 |
| H | -1.622404854 | 4.091342148 | 1.019606407 |
| H | 2.613010523 | 2.879652212 | -1.271972039 |
| H | 2.351144997 | 5.142951943 | -0.283989056 |
| H | 0.229518170 | 5.757989230 | 0.860357949 |
| H | 1.706459511 | 0.534361936 | -1.151126920 |
| H | 0.521339008 | 0.940257229 | -2.239015245 |
| H | -1.442667356 | -1.704522802 | -1.422990079 |