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A new method for constructing pyrido[3′,2′:4,5]imidazo[1,2-*b*]pyridazine system and preparation of its derivatives

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General Information

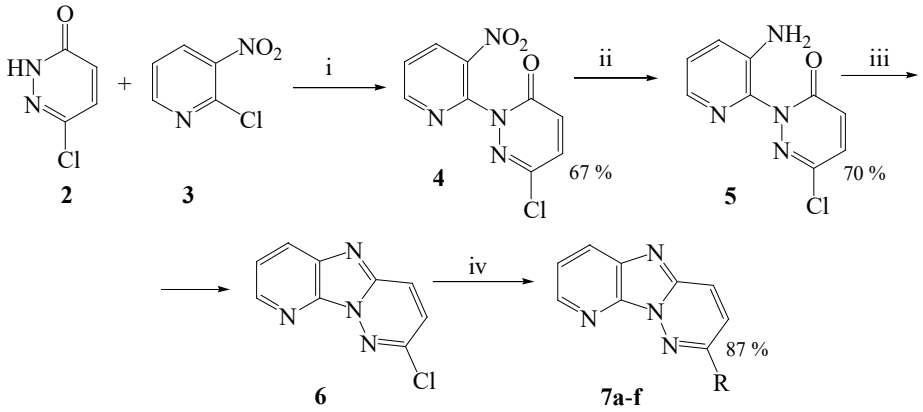
NMR spectra of new compounds **6, 7c–f** were recorded on a spectrometer Bruker Avance 600 (600 MHz), of compounds **4**, **5**, **7a**, **7b** on a spectrometer Varian Unity-300 (300 MHz) in DMSO-d_6. Chemical shifts of nuclei ^{1}H and ^{13}C were measured relatively the residual signals of deuterated solvent (see δ values in Ref. [S1]). 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 using a EuroEA 3000 analyzer by burning a portion of the sample in an oxygen flow followed by chromatography of the combustion gases. ESI mass spectra for compounds **5**,**6** were registered on a Agilent 6470 device. 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).

Quantum-chemical calculations were performed using quantum chemical program packages Gaussian 09 [S2] and Firefly 8.0 [S3], which is partially based on the GAMESS (US) source code [S4] at the DFT level of theory (B3LYP/6-311++G**).

Starting compounds **2** and **3** are commercially available from TCI Shanghai (China) and Chemieliva Pharmaceutical (China), respectively.

2. Synthesis and characterization of compounds 4-7.

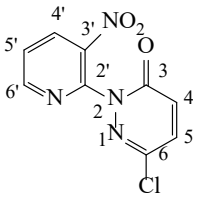
The general scheme:



7: R = MeO (**a**), PhS (**b**), H_2NNH (**c**), 4-Me-piperidinino (**d**), morpholino (**e**), 4-Ph-piperazino (**f**)

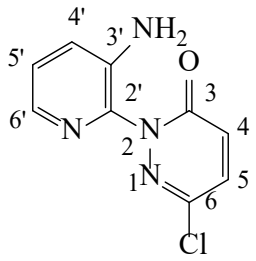
Reagents and conditions: i, K_2CO_3, 60ºC, 3 h; ii, Fe, HCl, reflux, 2 h; iii, $POCl_3$, 100 ºC, 40 min; iv, for **7a**: Na, MeOH, reflux, 1 h, for **7b**: Na, EtOH, PhSH, reflux, 10 min, for **7c**: $N_2H_4 \cdot H_2O$, EtOH, reflux, 1 h, for **7d**: 4-methylpiperidine, $MeO(CH_2)_2OH$, reflux, 4 h, for **7e**: morpholine, $MeO(CH_2)_2OH$, reflux, 1,5 h, for **7f**: 4-Ph-piperazine, tetramethylurea, reflux, 4 h

6-Chloro-2-(3-nitropyridin-2-yl)pyridazin-3(2*H*)-one (4).



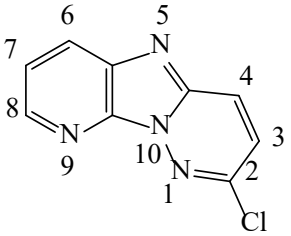
A mixture of 15.8 g (0.1 mol) of chloropyridazinone **2** and chloronitropyridine **3** with 15 g of K_2CO_3 in 50 ml of DMF was heated at 60°C for 1 h with stirring and kept at this temperature for 2 h. The mixture was poured into 250 ml of H_2O, and the precipitate of N-heteroaryl derivative **4** was filtered off and washed with water (3×20 ml). Yield of **4** 16.9 g (67%), mp 176-178°C (EtOH). IR spectrum (powder), ν, cm^{-1}: 1602 s (C=O), 1585 s (C=N), 1534 s (C=N). ^{1}H NMR (300 MHz), δ, ppm: 7.24 (d, *J* 9.8, 1H, H-5), 7.78 (d, *J* 9.9, 1H, H-4), 7.92 (dd, *J* 8.2, 4.7, 1H, H-5'), 8.70 (dd, *J* 8.1, 1.6, 1H, H-4'), 8.97 (dd, *J* 4.8, 1.6, 1H, H-6'). Found, %: C 42.71; H 1.92; Cl 14.18; N 22.12. $C_9H_5ClN_4O_3$. Calcd., %: C 42.79; H 2.00; Cl 14.03; N 22.18.

2-(3-Aminopyridin-2-yl)-6-chloropyridazin-3(2*H*)-one (5).



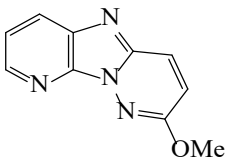
A suspension of 8 g of powdered Fe metal in 100 ml EtOH and 2 ml of conc. HCl was boiled with vigorous stirring for 1 h with portionwise addition of 2.53 g (10 mmol) of pyridazinone **4**, and then the mixture was boiled for another 2 h. The hot reaction mixture was filtered from excess of Fe, the filtrate was evaporated with a water bath to 20 ml volume, and 75 ml of water was added. The resulting crystals of amine **5** were filtered off and washed with water (3x5 ml). Yield 1.56 g (70%), mp 175-176°C (EtOAc : EtOH, 1:1). IR spectrum (powder), ν, cm^{-1}: 3408 m (NH_2), 3329 m (NH_2), 1660 s (C=O), 1577s (C=N). ^{1}H NMR (300 MHz), δ, ppm: 5.51 (s, 2H, NH_2), 7.14 (d, *J* 9.7, 1H, H-5), 7.16-7.24 (m, 2H, H-4', H-5'), 7.62 (d, *J* 9.8, 1H, H-4), 7.67 (dd, *J* 4.8, 1.8, 1H, H-6'). HRMS (ESI): m/z $[M+H]^+$ calcd for $C_9H_7ClN_4O$ 223.63; found: 223.07.

2-Chloropyrido[3',2':4,5]imidazo[1,2-*b*]pyridazine (6).



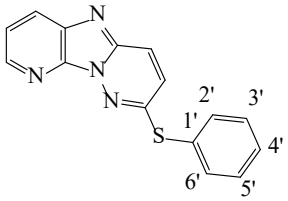
A mixture of 2.05 g (0.01 mmol) of pyridazinone **5** and 12 ml of $POCl_3$ was kept for 40 min at 100°C, then cooled, carefully poured into 120 ml of H_2O and after decomposition of excess of $POCl_3$ at room temperature, it was neutralized with a solution of NH_4OH to pH 7-8. The resulting precipitate of chloro derivative **6** was filtered off and washed with water (5×3 ml). Yield 1.78 g (87%), mp. 242-244°C (EtOAc : EtOH, 1:1). IR spectrum (powder), ν, cm^{-1}: 1577 w (C=N), 1523 m (C=N), 1468 m (C=N). ^{1}H NMR (600 MHz), δ, ppm: 7.66 (1 H, dd, *J* 8.3, 4.5, 7-H), 7.71 (1 H, d, *J* 9.7, 3-H), 8.36 (1 H, d, *J* 9.7, 4-H), 8.39 (1 H, dd, *J* 8.3, 1.4, 6-H), 8.65 (1 H, dd, *J* 4.5, 1.4, 8-H). ^{13}C NMR (600 MHz), δ, ppm: 122.8, 126.2, 129.3, 129.6, 135.8, 141.9, 142.2, 145.6, 146.3. Mass-spectrum (ESI): m/z $[M+H]^+$: calcd for $C_9H_5ClN_4$ 205.62; found: 205.08.

2-Methoxypyrido[3',2':4,5]imidazo[1,2-*b*]pyridazine (7a).



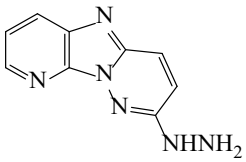
To a solution of 0.23 g (0.01 mol) Na in 10 ml MeOH, 2.05 g (0.01 mol) of chloropyridoimidazopyridazine **6** was added, and this was boiled for 1 h. The reaction mixture was filtered, and the filtrate was evaporated to dryness in vacuum. Yield 1.88 g (94%), m.p. 154-155°C (EtOAc). IR spectrum (powder), ν, cm^{-1}: 1576 m (C=N), 1496 m (C=N), 1496 w (C=N). ^{1}H NMR (300 MHz), δ, ppm: 4.05 (s, 3H, MeO), 7.30 (d, *J* 9.8, 1H, H-3), 7.54 (dd, *J* 8.3, 4.6, 1H, H-7), 8.19 (d, *J* 9.9, 1H, H-4), 8.29 (dd, *J* 8.2, 1.5, 1H, H-6), 8.55 (dd, *J* 4.5, 1.5, 1H, H-8). Found, %: C 59.88; H 3.92; N 27.91. $C_{10}H_8N_4O$. Calcd., %: C 59.99; H 4.03; N 27.99.

2-(Phenylthio)pyrido[3',2':4,5]imidazo[1,2-*b*]pyridazine (7b).



To a solution of 0.23 g (0.01 mol) Na in 150 ml EtOH, 1.10 g (0.01 mol) thiophenol was added followed by 2.05 g (0.01 mol) of chloropyridoimidazopyridazine **6**. The reaction mixture was boiled for 10 min, diluted with 50 ml of water, and phenylthio derivative **6b** was filtered off. Yield 2.11 g (76%), mp. 108-109°C (cyclohexane). IR spectrum (powder), ν, cm^{-1}: 1575 m (C=N), 1526 m (C=N), 1319 s (CS). ^{1}H NMR (300 MHz), δ, ppm: 7.30 (d, *J* 9.7, 1H, H-3), 7.51-7.55 (m, 3H, H-3' – H-5'), 7.60 (dd, *J* 8.3, 4.5, 1H, H-7), 7.68-7.71 (m, 2H, H-2',6'), 8.17 (d, *J* 9.8, 1H, H-4), 8.33 (dd, *J* 8.2, 1.4, 1H, H-6), 8.57 (dd, *J* 4.6, 1.4, 1H, H-8). Found, %: C 64.65; H 3.54; N 20.07; S 11.59. $C_{15}H_{10}N_4S$. Calcd., %: C 64.73; H 3.62; N 20.13; S 11.52

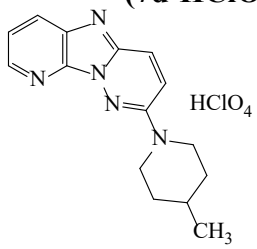
2-Hydrazinopyrido[3',2':4,5]imidazo[1,2-*b*]pyridazine (7c).



A solution of 0.41 g (0.002 mol) chloropyridoimidazopyridazine **6** and 1 ml of hydrazine hydrate in 10 ml of EtOH was boiled for 1 h, evaporated to dryness in a water bath, the residue is treated with 5 ml of water, the reaction product is filtered off and washed with water (3×3 ml). Yield 0.31 g (78%), mp. 276-277°C (MeCN). IR spectrum (powder), ν, cm^{-1}: 3298 m (NH_2), 3262 m (NH), 1587 s (C=N),

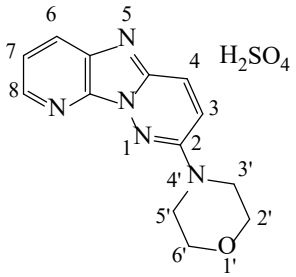
1503 s (C=N). ^{1}H NMR (600 MHz), δ, ppm: 4.37 (s, 2H, NH_2), 7.10 (d, *J* 9.8, 1H, H-3), 7.42 (dd, *J* 8.2, 4.5, 1H, H-7), 7.90 (d, *J* 9.9, 1H, H-4), 8.18 (dd, *J* 8.2, 1.4, 1H, H-6), 8.29 (s, 1H, NH), 8.45 (dd, *J* 4.5, 1.4, 1H, H-8). ^{13}C NMR (600 MHz), δ, ppm: 118.72, 119.87, 126.18, 127.63, 134.44, 141.92, 142.12, 143.30, 155.06. Found, %: C 53.92; H 4.00; N 41.91. $C_9H_8N_6$. Calcd., %: C 53.99; H 4.03; N 41.98.

2-(4-Methylpiperidin-1-yl)pyrido[3',2':4,5]imidazo[1,2-*b*]pyridazine hydroperchlorate (7d·HClO$_4$).



A mixture of 0.41 g (0.002 mol) chloropyridoimidazopyridazine **6**, 2 ml of 4-methylpiperidine and 4 ml of 2-methoxyethanol was boiled for 4 h, 15 ml of water was added, the solid was filtered off and washed with water (3×3 ml). Yield 0.38 g (71%). To convert it into hydroperchlorate, a solution of the base in EtOH was treated with equimolar amount of 60% $HClO_4$, the salt was filtered off, washed with water, mp. 237-238°C (EtOH). IR spectrum (powder), ν, cm^{-1}: 1578 m (C=N), 1498 m (C=N). ^{1}H NMR (600 MHz), δ, ppm: 0.94 (d, *J* 6.5, 3H, Me), 1.23 (m, 2H, H-3',5'-ax), 1.70-1.73 (m, 1H, H-4'), 1.78 (d, *J* 12.9, 2H, H-3',5'-eq), 3.07 (t, *J* 12.1, 2H, H-2',6'-ax), 4.35 (d, *J* 13.2, 2H, H-2',6'-eq), 7.76 (dd, *J* 8.3, 4.6, 1H, H-7), 8.06 (d, *J* 10.2, 1H, H-3), 8.25 (d, *J* 10.2, 1H, H-4), 8.40 (d, *J* 8.2, 1H, H-6), 8.71 (d, *J* 4.6, 1H, H-8), 9.33 (s, 1H, NH). ^{13}C NMR (600 MHz), δ, ppm: 21.50, 30.05, 33.04, 45.58, 122.51, 122.69, 123.42, 124.58, 126.14, 137.85, 139.82, 145.98, 154.99. Found, %: C 48.90; H 4.86; Cl 9.76; N 18.62. $C_{15}H_{17}N_5$·$HClO_4$. Calcd., %: C 48.98; H 4.93; Cl 9.64; N 19.04.

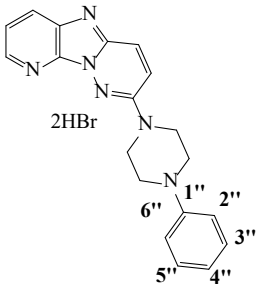
2-(Morpholin-4-yl)pyrido[3',2':4,5]imidazo[1,2-*b*]pyridazine dihydrosulfate (7e·H$_2$SO$_4$).



A mixture of 2.05 g (0.01 mol) of chloropyridoimidazopyridazine **6**, 1.74 g, 1.72 ml (0.02 mol) of morpholine in 8 ml of 2-methoxyethanol was boiled for 1.5 h and diluted 20 ml of water. Sodium bicarbonate (1 g) was added, the mixture was extracted with 15 ml of $CHCl_3$, the extract was dried with Na_2SO_4 and evaporated to dryness to afford 1.81 g (71%) of free base **7e**. To convert the base to dihydrosulfate, its solution in EtOH was treated with sulfuric acid until a weakly acidic reaction, the salt

was filtered and washed with water, mp 234-236°C (EtOH). IR spectrum (powder), ν, cm^{-1}: 1608 m (C=N), 1578 m (C=N). ^1H NMR (600 MHz), δ, ppm: 3.59-3.68 (m, 4H, H-3',5'), 3.77(dd, 4H, H-2',6'), 7.70 (dd, 1H, *J* 8.3, 4.6, H-7), 7.97 (d, *J* 10.2, 1H, H-3), 8.16 (br s, 2H, $2N^+H$), 8.30 (d, *J* 10.2, 1H, H-4), 8.38 (dd, 1H, *J* 8.3, 1.4, H-6), 8.66 (dd, *J* 4.6, 1.4, 1H, H-8). Found, %: C 44.16; H 4.23; N 19.80; S 9.20. $C_{13}H_{13}N_5O{\cdot}H_2SO_4$. Calcd., %: C 44.19; H 4.28; N 19.82; S 9.07

2-(4-Phenylpiperazin-1-yl)pyrido[3',2':4,5]imidazo[1,2-*b*]pyridazine dihydrobromide (7f·2HBr).



A solution of 0.41 g (0.002 mol) of chloropyridoimidazopyridazine **6** and 0.65 g (0.004 mol) of 1-phenylpiperazine in 6 ml of tetramethylurea was boiled for 4 h. After cooling, the reaction mixture was poured into 15 ml of H_2O, the precipitate of free amine **7f** was filtered off, washed with water (3×3 ml) and dried. Yield 0.54 g (82%). To convert it into dihydrobromide, a solution of the base in EtOH was treated with conc. HBr and the precipitated salt was filtered off and washed with water, mp 225-226°C (EtOH). IR spectrum (powder), ν, cm^{-1}: 3478 w ($^+$NH), 3443 w ($^+$NH), 1573 s (C=N), 1485 s (C=N). ^1H NMR (600 MHz), δ, ppm: 3.56 (t, *J* 5.2, 4H, H-2',6'), 4.04 (t, *J* 5.2, 4H, H-3',5'), 7.05-7.13 (m, 1H, H-4''), 7.36-7.39 (m, 4H, H-2'', 3'', 5'', 6''), 7.50 (br s, 2H, 2^+NH), 7.81 (dd, J 8.3, 4.6, 1H, H-7), 8.24 (d, J 10.2, 1H, H-3), 8.45 (d, J 10.1, 1H, H-4), 8.48 (d, J 8.3, 1H, H-6), 8.75 (dd, J 4.6, 1.5, 1H, H-8). ^{13}C NMR (600 MHz), δ, ppm: 44.29, 44.76, 47.73, 49.90, 117.83, 117.95, 122.74, 122.94, 123.77, 124.62, 125.79, 129.37, 131.60, 137.93, 139.66, 146.29, 155.14. Found, %: C 46.31; H 4.06; Br 32.55; N 17.02. $C_{19}H_{18}N_6{\cdot}2HBr$. Calcd., %: C 46.36; H 4.10; Br 32.47; N 17.07.

Quantum chemical data (B3LYP/6-311++G**)

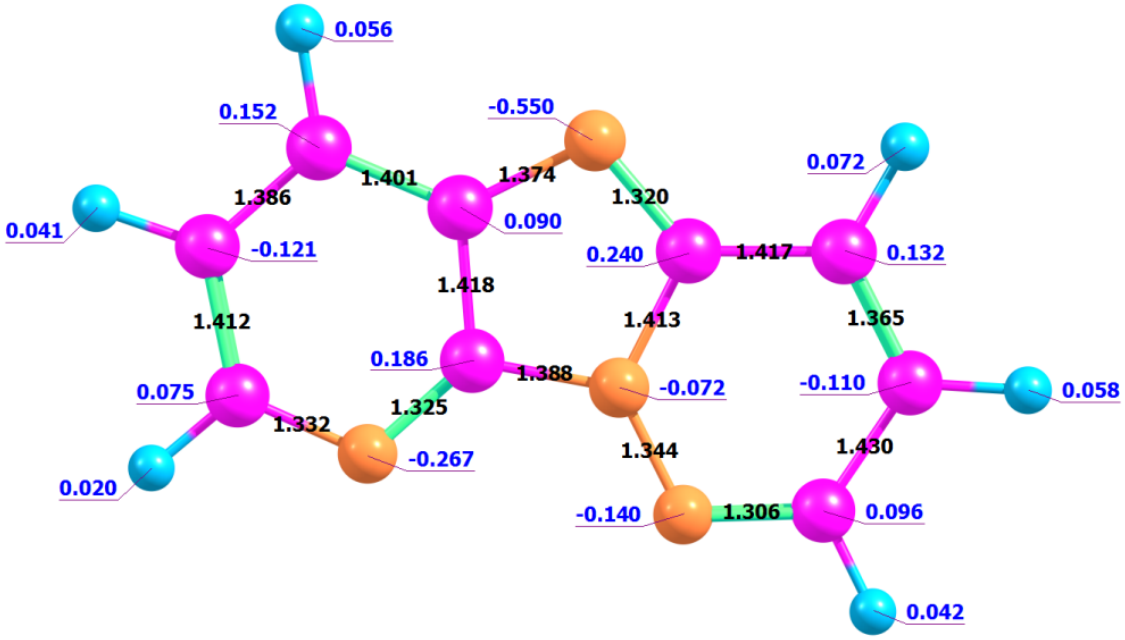


Figure S1. Molecule of tricycle **1**. Here and below, the numbers indicate bond lengths (Å) and atomic charges (APT), respectively.

E_{tot} = -565.691611637 A.U.

symmetry c1

C	-2.809033000	-1.183437000	0.000072000
C	-3.312528000	0.135349000	0.000060000
C	-2.449032000	1.219619000	0.000014000
N	-1.512919000	-1.491501000	0.000025000
C	-0.709372000	-0.438144000	-0.000048000
C	-1.078072000	0.931038000	-0.000040000
N	0.678072000	-0.422513000	-0.000063000
C	1.054054000	0.939605000	0.000026000
N	0.018816000	1.758232000	-0.000161000
N	1.501108000	-1.484675000	-0.000119000
C	2.773946000	-1.191553000	-0.000006000
C	3.300159000	0.137621000	0.000104000
C	2.446371000	1.202541000	0.000114000
H	-3.497710000	-2.022685000	0.000115000
H	-4.385599000	0.285979000	0.000091000
H	-2.804277000	2.243275000	-0.000020000
H	3.436702000	-2.049270000	-0.000048000
H	4.373748000	0.278708000	0.000175000
H	2.782630000	2.231365000	0.000125000

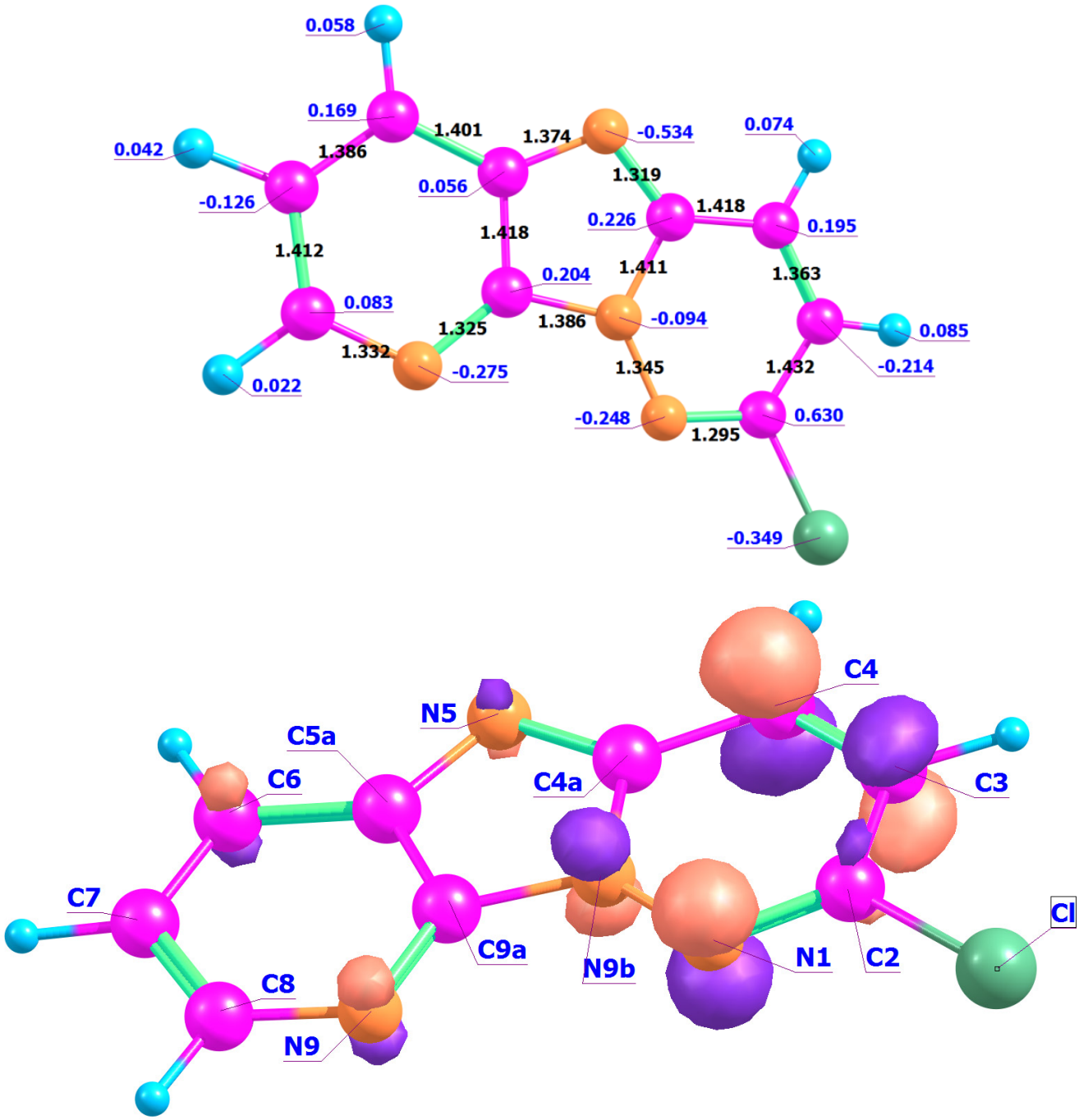


Figure S2. Chloroderivative **6** and its LUMO; light brown color corresponds to a positive sign of the wave function, and purple color corresponds to a negative sign

E_{tot} = -1025.31148626 A.U.

symmetry c1

C	-3.051245000	-1.711078000	0.000020000
C	-3.903903000	-0.585447000	-0.000010000
C	-3.378762000	0.696927000	-0.000040000
N	-1.721049000	-1.644718000	0.000029000
C	-1.245006000	-0.408609000	0.000005000
C	-1.981781000	0.803306000	-0.000031000
N	0.080776000	-0.003430000	0.000021000
C	0.061946000	1.407305000	-0.000003000
N	-1.159677000	1.904177000	-0.000062000
N	1.170685000	-0.791777000	0.000067000
C	2.297928000	-0.154415000	0.000124000
C	2.448680000	1.269990000	0.000063000
C	1.327717000	2.045626000	0.000030000
Cl	3.741266000	-1.140305000	-0.000078000
H	-3.477591000	-2.709403000	0.000046000
H	-4.976118000	-0.741315000	-0.000008000
H	-4.006170000	1.580262000	-0.000073000
H	3.441835000	1.697091000	0.000060000
H	1.367928000	3.127138000	-0.000017000

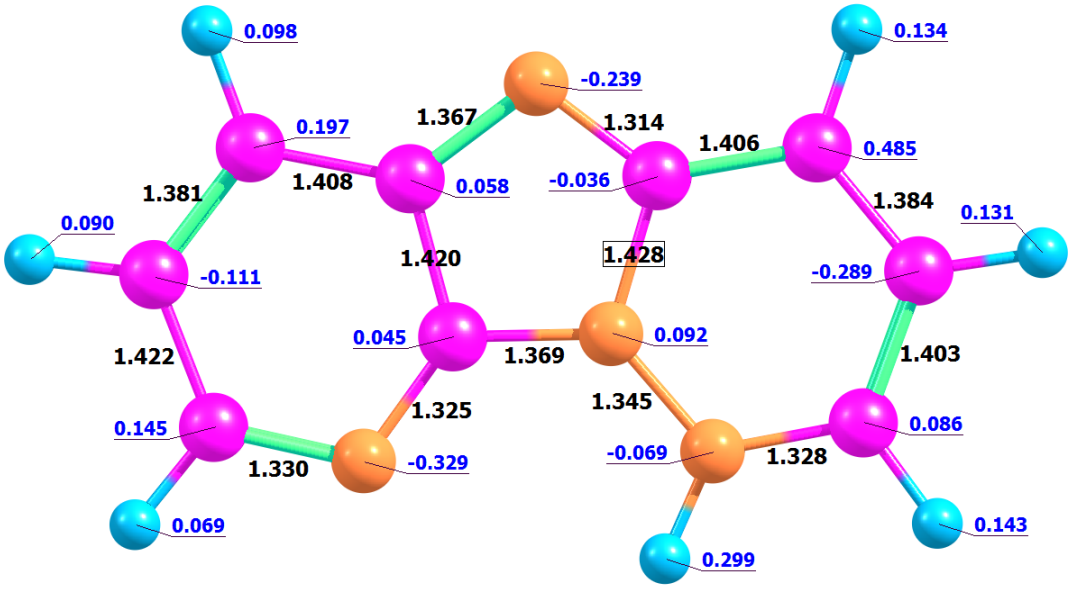


Figure S3. 1H-Protonated form of tricycle **1**.

E_{tot} = -566.038258110 A.U.
symmetry c1

C	2.800787000	-1.204821000	0.000037000
C	3.323608000	0.117628000	0.000016000
C	2.491898000	1.220509000	-0.000010000
N	1.501519000	-1.490663000	0.000024000
C	0.733413000	-0.411583000	-0.000007000
C	1.108200000	0.957877000	-0.000024000
N	-0.635076000	-0.380226000	-0.000007000
C	-1.028605000	0.992421000	-0.000018000
N	0.019709000	1.785399000	-0.000082000
N	-1.518562000	-1.393999000	0.000017000
C	-2.822394000	-1.143485000	0.000030000
C	-3.298134000	0.176089000	0.000019000
C	-2.412942000	1.239383000	-0.000003000
H	3.478606000	-2.051226000	0.000051000
H	4.398998000	0.244005000	0.000016000
H	2.871778000	2.234533000	-0.000035000
H	-1.109863000	-2.328147000	0.000024000
H	-3.467141000	-2.012460000	0.000048000
H	-4.366913000	0.338011000	0.000020000
H	-2.753584000	2.267597000	-0.000028000

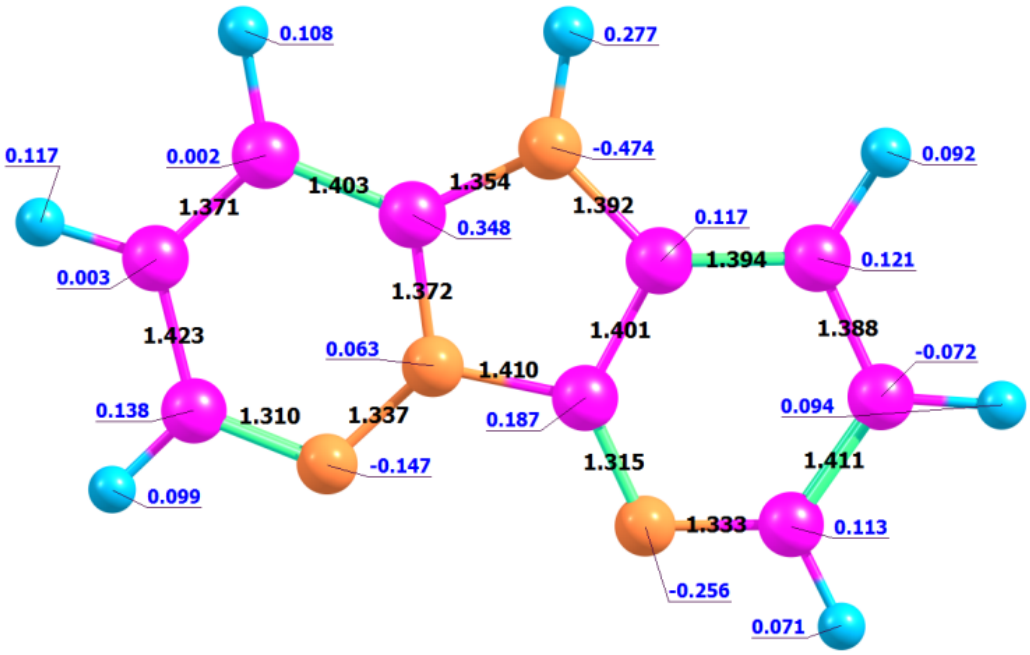


Figure S4. 5H-Protonated form of tricycle **1**

E_{tot} = -566.064423743 A.U.

symmetry c1

C	-2.799500000	-1.226838000	0.000033000
C	-3.330936000	0.080593000	0.000041000
C	-2.494981000	1.188481000	0.000011000
N	-1.494459000	-1.497598000	-0.000007000
C	-0.721406000	-0.434114000	-0.000043000
C	-1.130354000	0.905657000	-0.000045000
N	0.688179000	-0.410554000	-0.000032000
C	1.108740000	0.895680000	-0.000008000
N	0.015581000	1.695028000	-0.000009000
N	1.482380000	-1.486565000	-0.000043000
C	2.767402000	-1.230244000	0.000006000
C	3.319124000	0.081062000	0.000048000
C	2.484629000	1.169051000	0.000036000
H	-3.464870000	-2.082866000	0.000058000
H	-4.405610000	0.211932000	0.000082000
H	-2.882432000	2.199698000	0.000016000
H	0.047134000	2.705425000	-0.000165000
H	3.404565000	-2.106425000	0.000013000
H	4.394479000	0.205696000	0.000106000
H	2.848668000	2.188397000	0.000047000

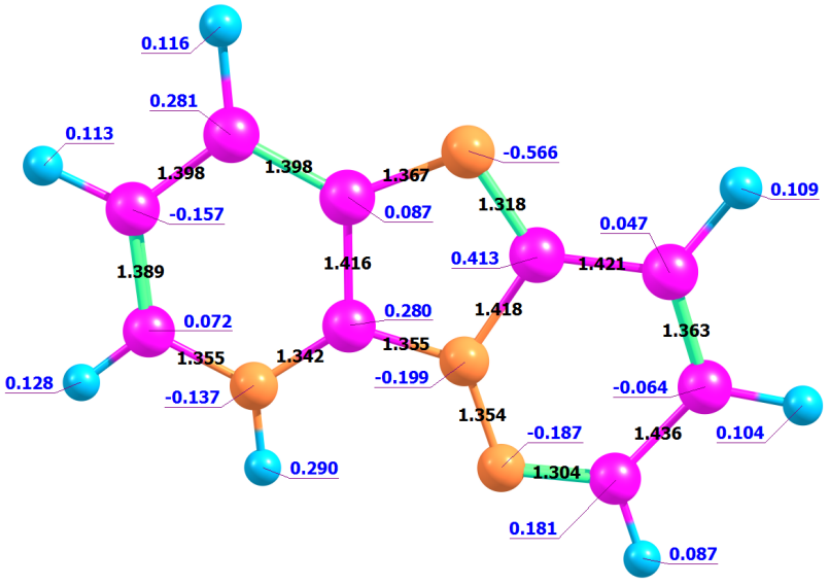


Figure S5. 9H-Protonated form of tricycle **1**.

E_{tot} = -566.062643792 A.U.

symmetry c1

C	-2.858197000	-1.134656000	0.000071000
C	-3.308616000	0.179393000	0.000066000
C	-2.417089000	1.255620000	-0.000004000
N	-1.530034000	-1.404126000	0.000015000
C	-0.655719000	-0.385702000	-0.000083000
C	-1.047975000	0.975301000	-0.000069000
N	0.699526000	-0.393153000	-0.000055000
C	1.086278000	0.970971000	0.000006000
N	0.051294000	1.787767000	-0.000076000
N	1.494034000	-1.489354000	-0.000090000
C	2.768341000	-1.211552000	0.000008000
C	3.311148000	0.117870000	0.000088000
C	2.487509000	1.204267000	0.000074000
H	-3.520192000	-1.989111000	0.000112000
H	-4.376482000	0.352017000	0.000124000
H	-2.771272000	2.279620000	0.000005000
H	-1.190557000	-2.363420000	-0.000016000
H	3.422451000	-2.075462000	0.000012000
H	4.387224000	0.235660000	0.000160000
H	2.851016000	2.223687000	0.000092000

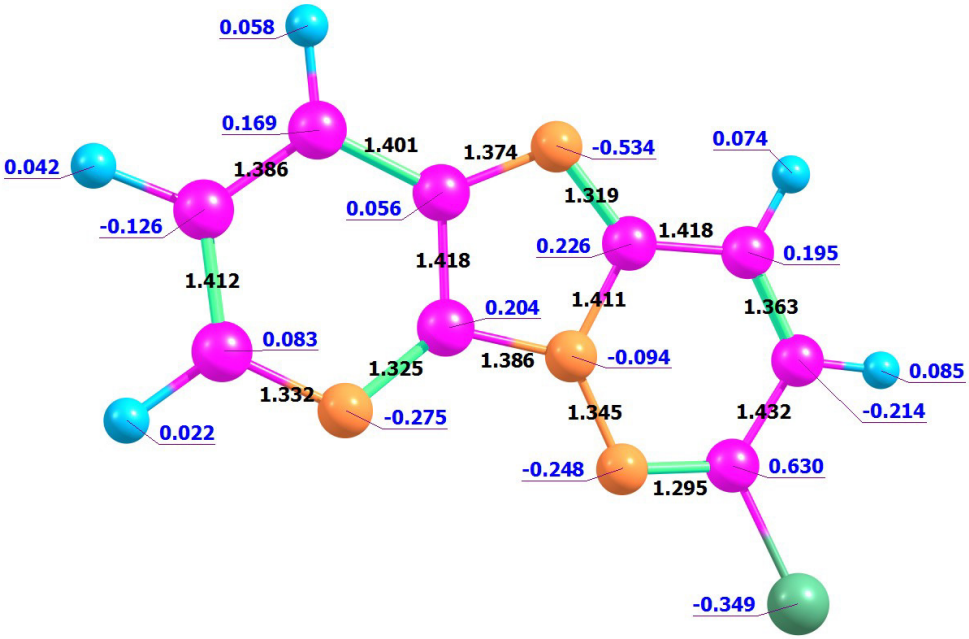


Figure S6. Chloro derivative **6**

E_{tot} = -1025.31148626 A.U.

symmetry c1

C	-3.051245000	-1.711078000	0.000020000
C	-3.903903000	-0.585447000	-0.000010000
C	-3.378762000	0.696927000	-0.000040000
N	-1.721049000	-1.644718000	0.000029000
C	-1.245006000	-0.408609000	0.000005000
C	-1.981781000	0.803306000	-0.000031000
N	0.080776000	-0.003430000	0.000021000
C	0.061946000	1.407305000	-0.000003000
N	-1.159677000	1.904177000	-0.000062000
N	1.170685000	-0.791777000	0.000067000
C	2.297928000	-0.154415000	0.000124000
C	2.448680000	1.269990000	0.000063000
C	1.327717000	2.045626000	0.000030000
Cl	3.741266000	-1.140305000	-0.000078000
H	-3.477591000	-2.709403000	0.000046000
H	-4.976118000	-0.741315000	-0.000008000
H	-4.006170000	1.580262000	-0.000073000
H	3.441835000	1.697091000	0.000060000
H	1.367928000	3.127138000	-0.000017000

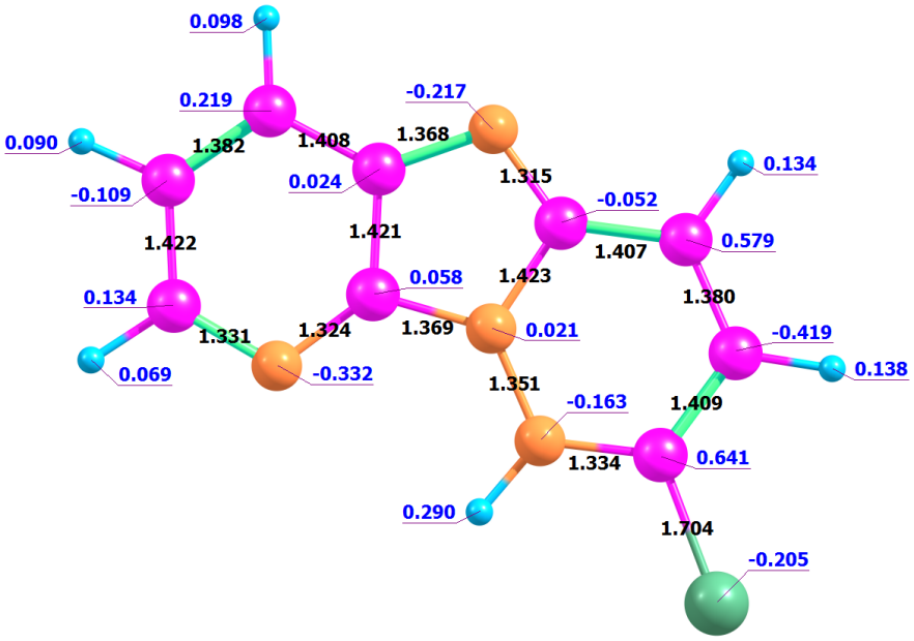


Figure S7. 1H-Protonated form of chloro derivative **6**.

E_{tot} = -1025.65074265 A.U.

symmetry c1

C	-3.036358000	-1.724457000	-0.000013000
C	-3.904354000	-0.598509000	0.000059000
C	-3.409202000	0.691250000	0.000091000
N	-1.708188000	-1.640666000	-0.000063000
C	-1.267595000	-0.392100000	-0.000060000
C	-2.007219000	0.820771000	0.000018000
N	0.037824000	0.019079000	-0.000154000
C	0.036923000	1.441608000	-0.000050000
N	-1.189234000	1.916660000	0.000024000
N	1.168999000	-0.718883000	0.000053000
C	2.357425000	-0.113981000	-0.000029000
C	2.446752000	1.291884000	0.000005000
C	1.300472000	2.060654000	-0.000042000
Cl	3.729109000	-1.124166000	0.000048000
H	-3.453333000	-2.725462000	-0.000022000
H	-4.972831000	-0.774092000	0.000087000
H	-4.054031000	1.561253000	0.000136000
H	1.041621000	-1.731148000	-0.000036000
H	3.429644000	1.741292000	0.000109000
H	1.347213000	3.142924000	0.000019000

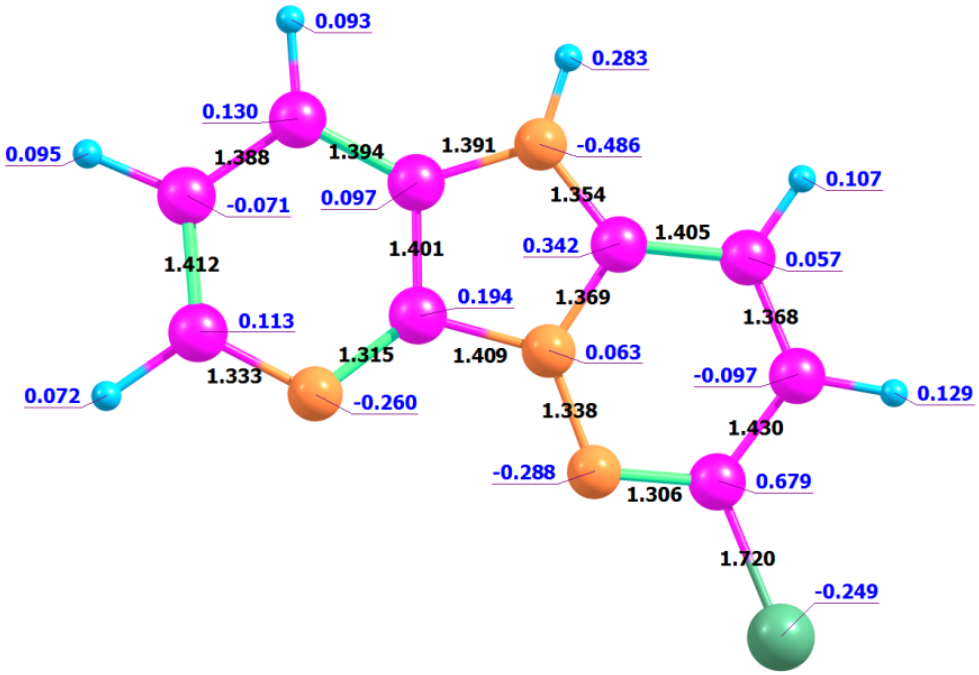


Figure S8. 5H-Protonated form of chloro derivative **6**.

E_{tot} = -1025.67889553 A.U.

symmetry c1

C	-3.001782000	-1.765454000	0.000127000
C	-3.887959000	-0.666171000	-0.000150000
C	-3.407394000	0.635534000	-0.000177000
N	-1.674398000	-1.648546000	0.000328000
C	-1.241027000	-0.407180000	0.000107000
C	-2.018871000	0.758512000	-0.000048000
N	0.100444000	0.022758000	0.000155000
C	0.127229000	1.391399000	0.000005000
N	-1.148968000	1.843907000	-0.000286000
N	1.169784000	-0.782115000	0.000061000
C	2.324417000	-0.171781000	0.000018000
C	2.483269000	1.249231000	0.000277000
C	1.371018000	2.045086000	0.000264000
Cl	3.723101000	-1.173543000	-0.000247000
H	-3.391890000	-2.777029000	0.000307000
H	-4.954859000	-0.850435000	-0.000399000
H	-4.070234000	1.491900000	-0.000366000
H	-1.409232000	2.820818000	-0.000542000
H	3.479093000	1.672145000	0.000495000
H	1.432968000	3.125745000	0.000372000

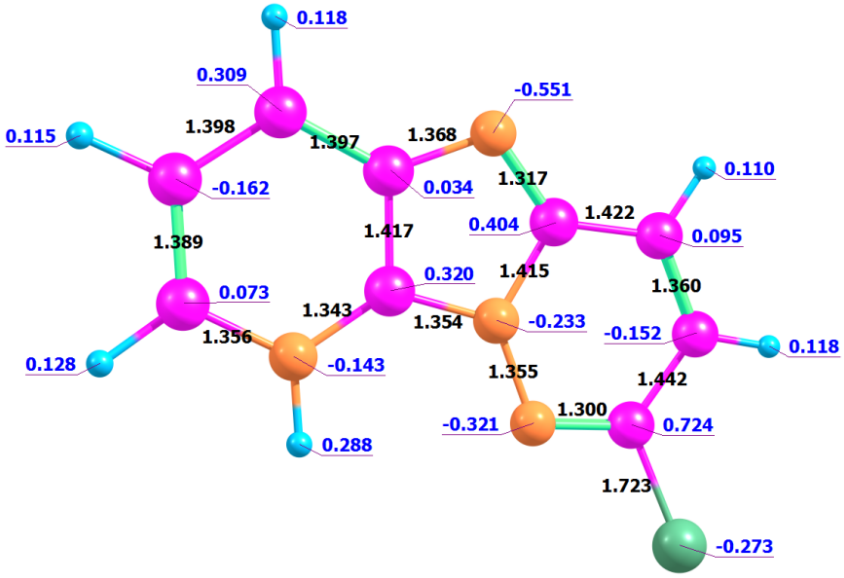


Figure S9. 9H-Protonated form of chloro derivative **6**.

E_{tot} = -1025.67858847 A.U.

symmetry c1

C	-3.096052000	-1.686524000	0.000013000
C	-3.900497000	-0.554473000	-0.000011000
C	-3.350281000	0.730826000	0.000035000
N	-1.745585000	-1.569772000	0.000011000
C	-1.195676000	-0.344695000	-0.000002000
C	-1.958651000	0.849182000	-0.000015000
N	0.104143000	0.034263000	0.000132000
C	0.088898000	1.449450000	-0.000025000
N	-1.133479000	1.940463000	-0.000074000
N	1.175914000	-0.794166000	-0.000055000
C	2.316044000	-0.168713000	-0.000154000
C	2.468903000	1.265488000	0.000024000
C	1.369785000	2.067252000	0.000026000
Cl	3.730939000	-1.151762000	0.000016000
H	-3.489018000	-2.693529000	-0.000009000
H	-4.973506000	-0.691535000	-0.000047000
H	-3.979969000	1.612605000	0.000028000
H	-1.149428000	-2.394449000	0.000020000
H	3.469269000	1.676961000	0.000203000
H	1.434914000	3.147625000	0.000089000

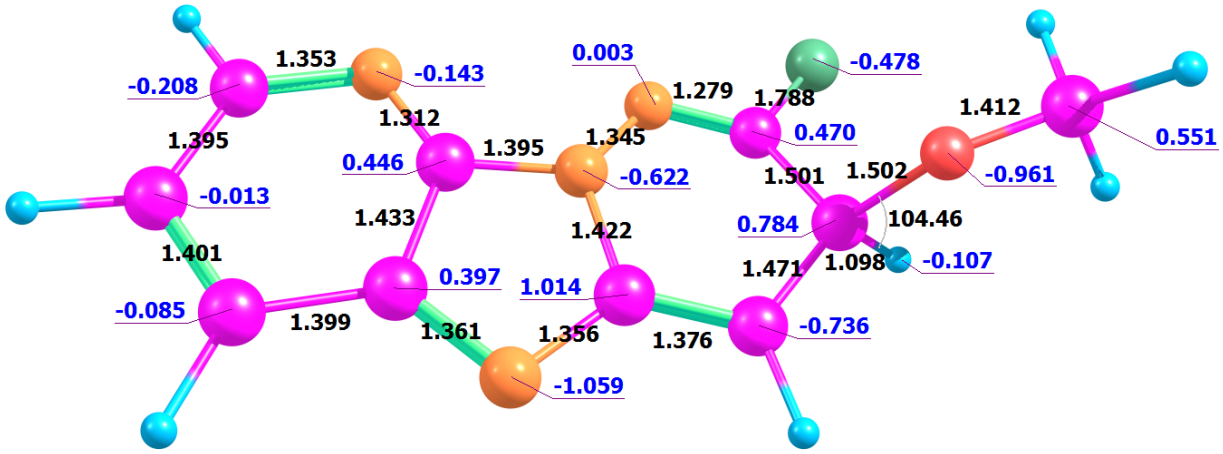


Figure S10. Meisenheimer σ-complex **9** between chloro derivative **6** and MeO^- anion.

E_{tot} = -1140.51293387 A.U.

symmetry c1

C	-3.791085000	1.403328000	0.543804000
C	-4.497704000	0.228164000	0.286444000
C	-3.827069000	-0.945421000	-0.083463000
N	-2.443414000	1.494336000	0.462868000
C	-1.840541000	0.382701000	0.112350000
C	-2.432949000	-0.888495000	-0.184069000
N	-0.473832000	0.151123000	-0.043465000
C	-0.307541000	-1.202351000	-0.446833000
N	-1.508139000	-1.829380000	-0.517965000
N	0.495749000	1.081411000	-0.091712000
C	1.674217000	0.635196000	-0.309427000
C	2.125299000	-0.794696000	-0.376288000
C	0.968587000	-1.629528000	-0.735894000
Cl	2.935672000	1.890886000	-0.477697000
O	2.689860000	-1.218183000	0.949067000
C	4.075218000	-1.008515000	1.122557000
H	-4.312966000	2.312193000	0.829133000
H	-5.579877000	0.232683000	0.375837000
H	-4.360848000	-1.867200000	-0.289165000
H	2.963342000	-0.900183000	-1.077523000
H	1.126893000	-2.637116000	-1.094927000
H	4.651326000	-1.353161000	0.247802000
H	4.329417000	0.044502000	1.302417000
H	4.386259000	-1.596041000	1.991569000

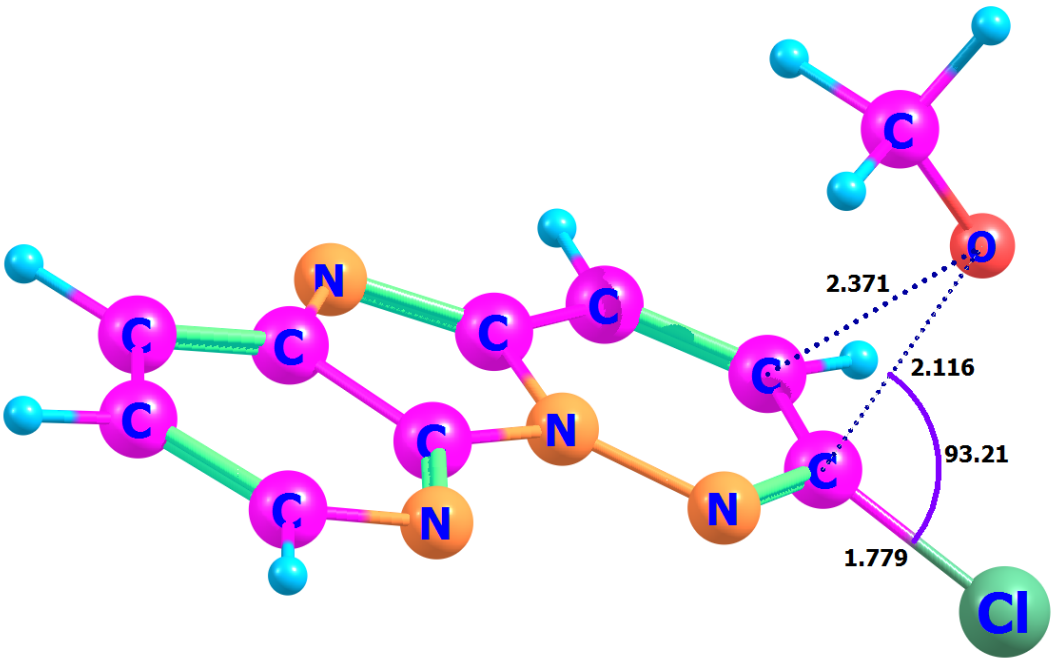


Figure S11. Transition state **TS1** formed in the system **6** – MeO^-.

E_{tot} = -1140.49744278, λ_i = -153.9 cm^{-1}

symmetry c1

C	-3.443980000	-1.641865000	0.374040000
C	-4.275022000	-0.522922000	0.202832000
C	-3.724278000	0.718384000	-0.115291000
N	-2.111117000	-1.619782000	0.254768000
C	-1.608985000	-0.430339000	-0.045472000
C	-2.337658000	0.781689000	-0.249074000
N	-0.289744000	-0.073333000	-0.232675000
C	-0.281995000	1.282063000	-0.537642000
N	-1.499076000	1.823025000	-0.553862000
N	0.796121000	-0.921593000	-0.200329000
C	1.937297000	-0.308766000	-0.364823000
C	2.091042000	1.085084000	-0.721106000
C	0.988173000	1.875897000	-0.797803000
H	-3.881310000	-2.606065000	0.620696000
H	-5.347245000	-0.637388000	0.320983000
H	-4.338123000	1.601659000	-0.255469000
H	3.087784000	1.453665000	-0.907955000
H	1.036959000	2.932812000	-1.022696000
Cl	3.285457000	-1.395309000	-0.774797000
O	2.873613000	0.379700000	1.403087000
C	1.904627000	0.684064000	2.327738000
H	2.337196000	0.801782000	3.341839000
H	1.369383000	1.640213000	2.116357000
H	1.125068000	-0.101987000	2.417390000

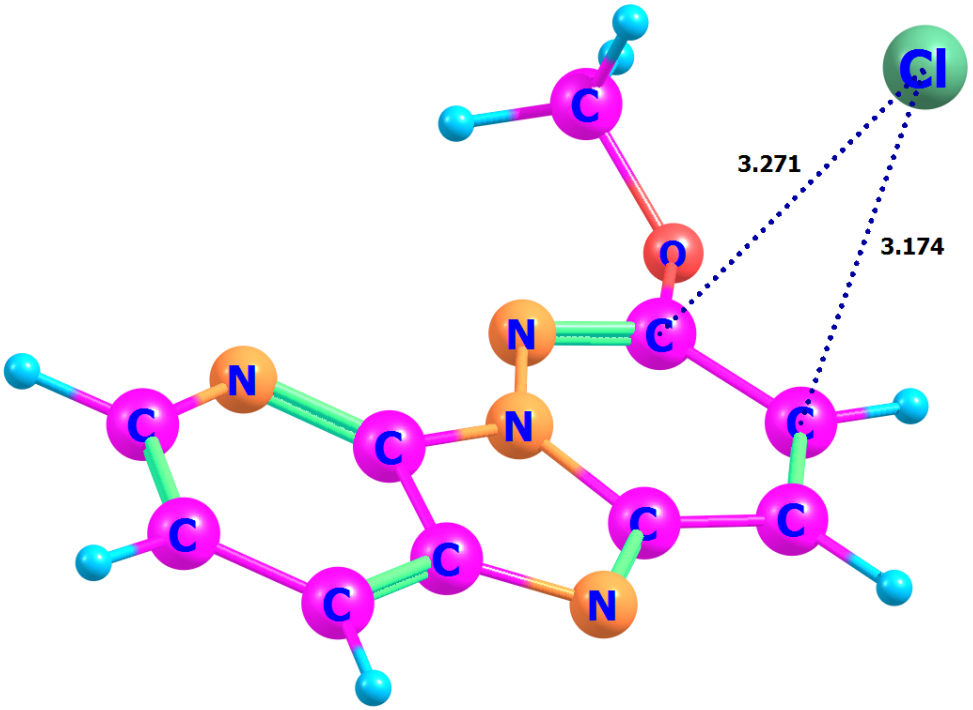


Figure S12. The weak complex between methoxy derivative **7a** and chloride ion formed from transition state **TS1**

E_{tot} = -1140.57802900 A.U.

symmetry c1

C	-3.559312000	1.591040000	0.546649000	C	0.801282000	-1.912190000	-0.881386000
C	-4.365760000	0.438758000	0.584699000	H	-3.994293000	2.561831000	0.768196000
C	-3.822402000	-0.809930000	0.301030000	H	-5.415342000	0.538610000	0.838672000
N	-2.256407000	1.588454000	0.250897000	H	-4.417808000	-1.715930000	0.320795000
C	-1.759913000	0.387898000	-0.008588000	H	2.878122000	-1.453342000	-1.189391000
C	-2.460903000	-0.853009000	-0.012686000	H	0.870695000	-2.987091000	-0.978347000
N	-0.462092000	0.048837000	-0.346910000	O	2.782191000	1.084638000	-1.084461000
C	-0.448203000	-1.334541000	-0.534019000	C	2.936991000	2.276990000	-0.296904000
N	-1.638425000	-1.897600000	-0.340586000	H	3.874093000	2.720643000	-0.631263000
N	0.579130000	0.901840000	-0.513323000	H	2.106929000	2.967384000	-0.459763000
C	1.704418000	0.326226000	-0.831412000	H	3.011690000	1.982968000	0.753153000
C	1.878569000	-1.092859000	-0.999750000	Cl	3.520255000	-0.699599000	1.688076000

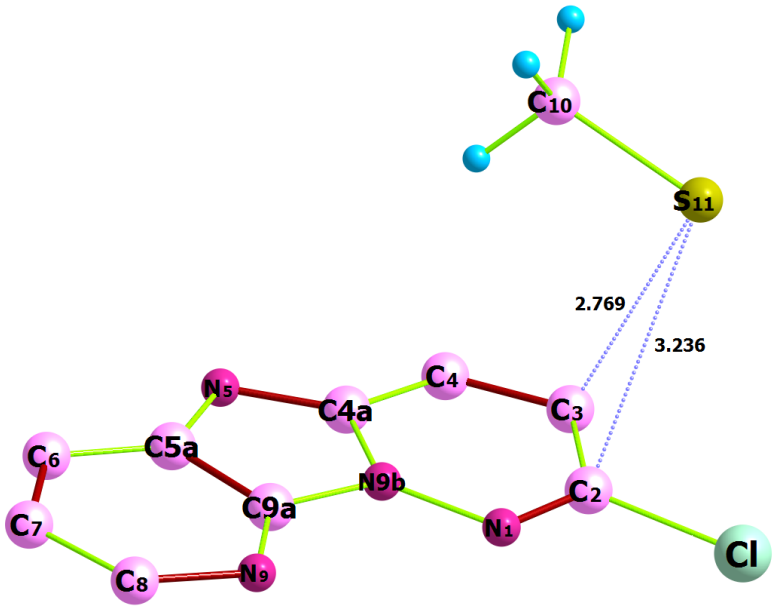


Figure S13. The starting reactant complex **6**·MeS$^-$ from which transition state **TS2** is formed.

E_{tot} = -1463.50996812 A.U.

symmetry c1

Cl	2.635387000	2.387476000	0.158454000
C	0.883106000	-0.979336000	1.451346000
C	1.871836000	-0.072626000	1.100892000
C	1.454905000	1.105728000	0.393836000
N	0.270732000	1.361865000	-0.050411000
N	-1.533822000	-1.500546000	1.103669000
C	-0.420876000	-0.781913000	0.955404000
N	-0.636989000	0.379659000	0.192258000
C	-2.499113000	-0.798989000	0.429913000
C	-1.978910000	0.394094000	-0.152973000
N	-2.637842000	1.298207000	-0.855613000
C	-3.858078000	-1.052141000	0.232177000
C	-4.577298000	-0.113977000	-0.509591000
C	-3.940938000	1.024767000	-1.023023000
H	1.943409000	-2.700619000	-2.017501000
H	1.597252000	-2.523589000	-0.290998000
H	2.995144000	-3.477301000	-0.813431000
C	2.409087000	-2.579507000	-1.034834000
S	3.430937000	-1.072082000	-0.957574000

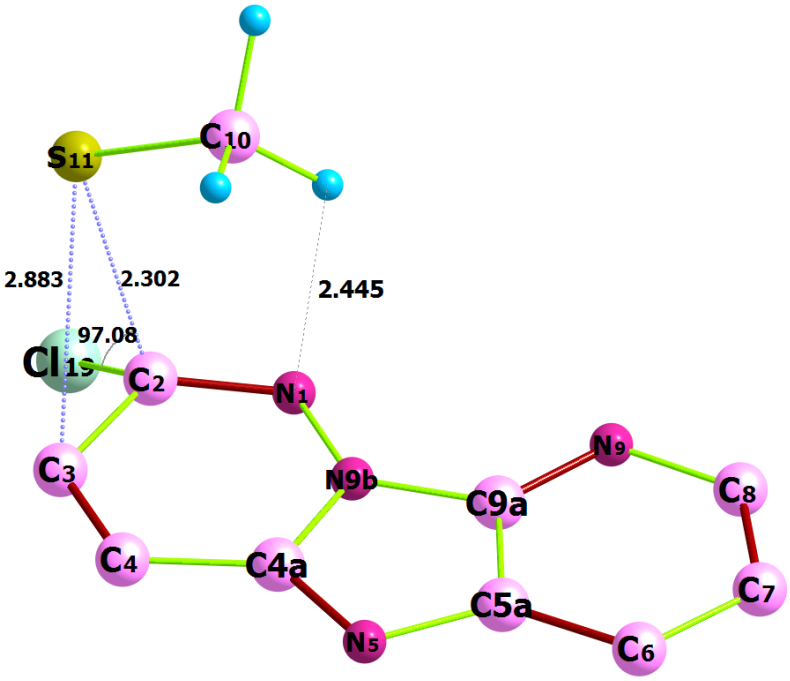


Figure S14. Transition state **TS2** formed in the system **6** – MeS$^-$.

symmetry c1, E^{tot} = -1463.49683586 a.u.,

λ_i = –145 cm^{-1}

C	-3.543848000	-1.619197000	-0.608642000
C	-4.424128000	-0.644139000	-0.105584000
C	-3.933332000	0.584690000	0.330449000
N	-2.220808000	-1.464165000	-0.710628000
C	-1.773448000	-0.286584000	-0.291335000
C	-2.555582000	0.785807000	0.240452000
N	-0.475464000	0.178399000	-0.257966000
C	-0.534058000	1.459471000	0.263351000
N	-1.768789000	1.855181000	0.576344000
N	0.636498000	-0.486402000	-0.727657000
C	1.784185000	0.135930000	-0.475395000
C	1.836157000	1.520091000	0.000966000
C	0.705813000	2.160125000	0.374892000
Cl	3.033688000	-0.157466000	-1.818042000
S	2.985035000	-0.814877000	1.242640000
C	1.500598000	-1.348116000	2.156141000
H	1.742945000	-2.231294000	2.751995000
H	1.113525000	-0.569672000	2.820325000
H	0.729971000	-1.630880000	1.430858000

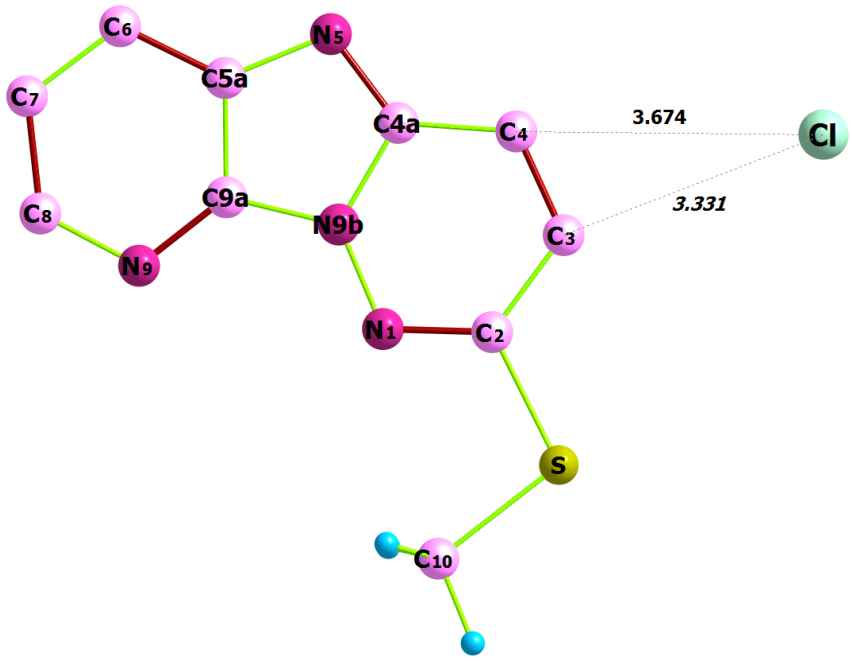


Figure S15. Complex of reaction products in the system **6** – MeS^-

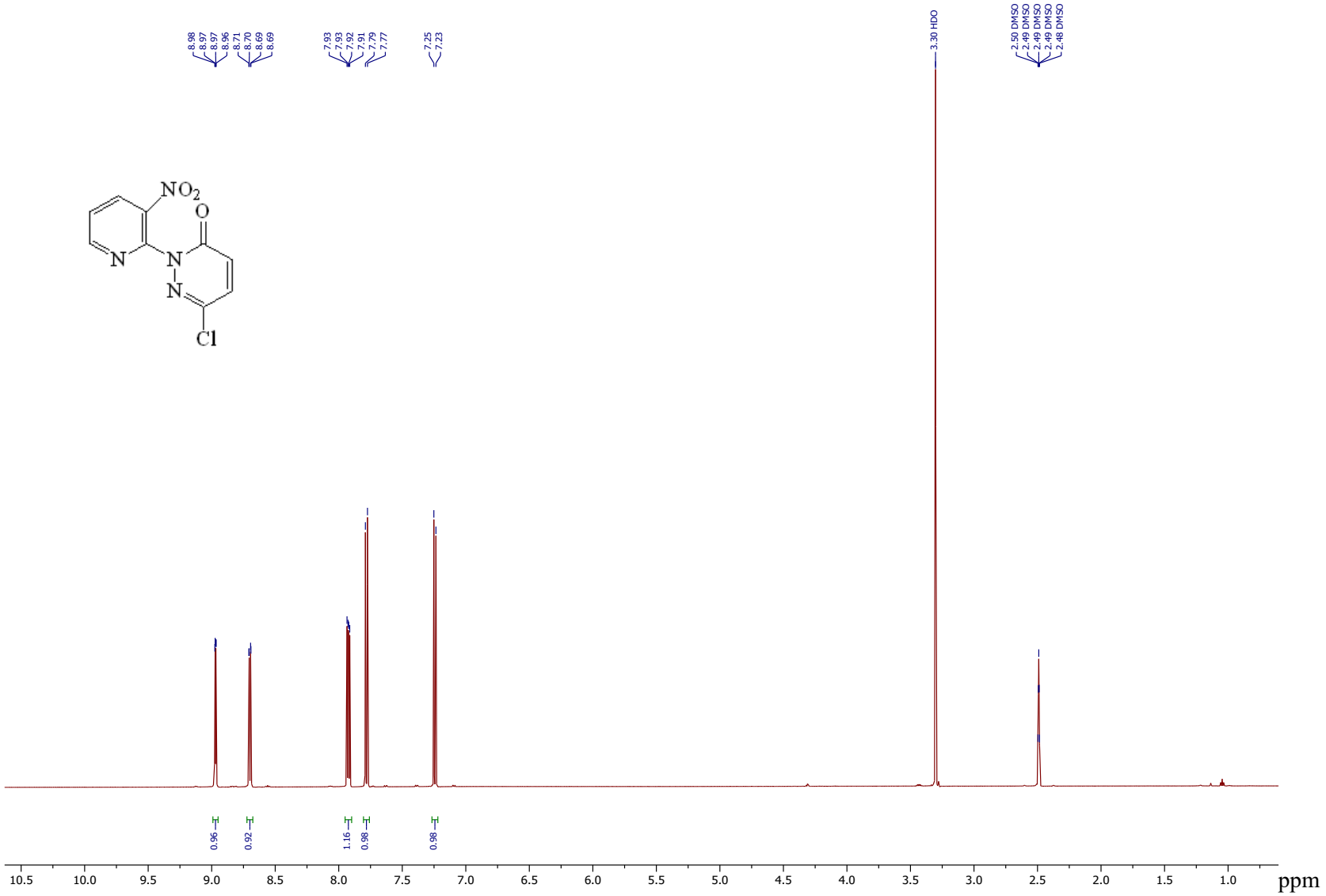
E_{tot} = -1463.56126236 A.U.

symmetry Cs

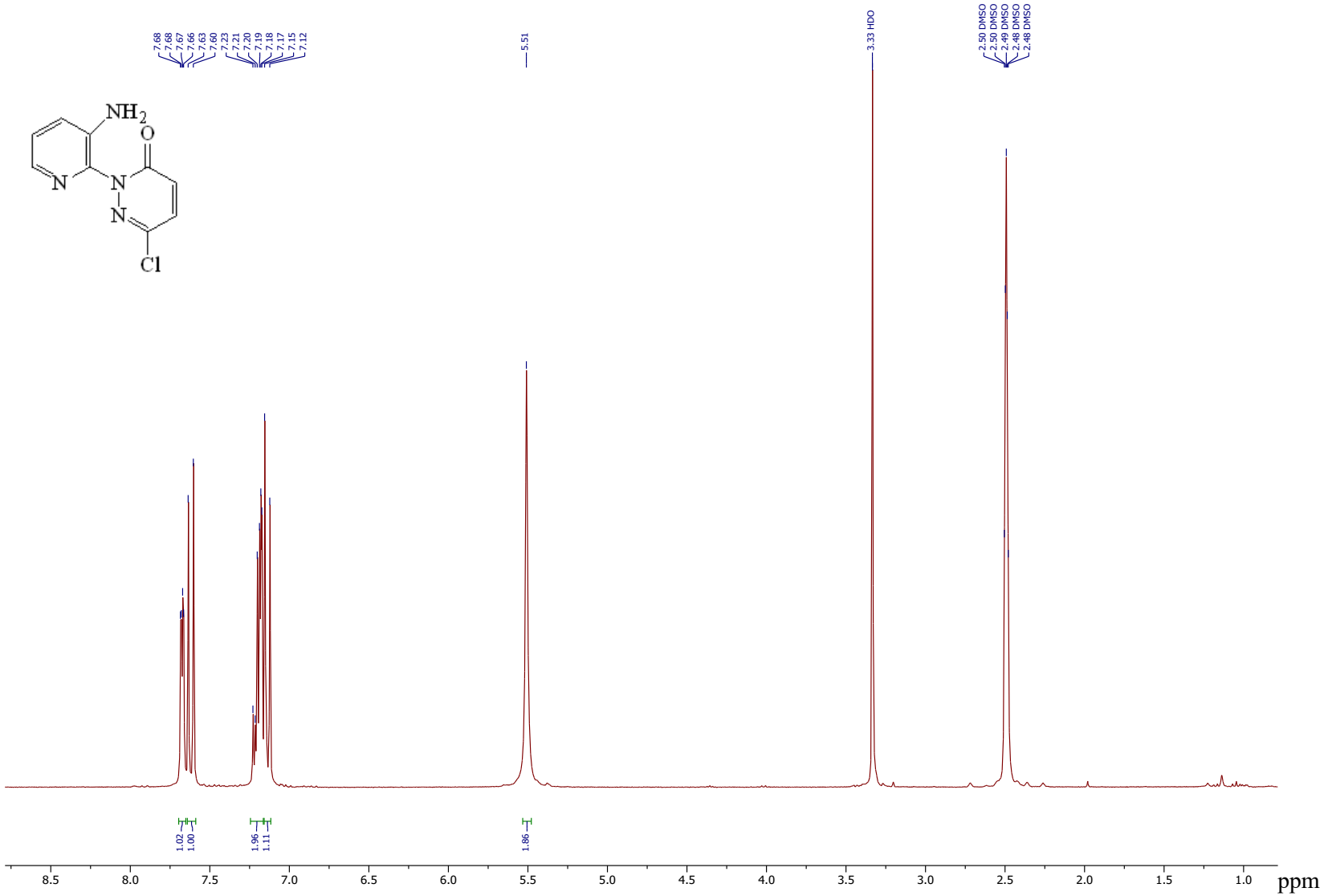
C	-0.283637314	4.341684697	0.000000000
C	1.087478686	4.660709697	0.000000000
C	2.045348686	3.653496697	0.000000000
N	-0.765452314	3.095850697	0.000000000
C	0.166935686	2.154143697	0.000000000
C	1.578741686	2.334871697	0.000000000
N	0.000000686	0.779952697	0.000000000
C	1.286216686	0.219106697	0.000000000
N	2.245004686	1.138573697	0.000000000
N	-1.176558314	0.111063697	0.000000000
C	-1.061442314	-1.191862303	0.000000000
C	0.187001686	-1.906318303	0.000000000
C	1.349894686	-1.199835303	0.000000000
S	-2.543467314	-2.167750303	0.000000000
C	-3.819108314	-0.866584303	0.000000000
H	-4.774924314	-1.392399303	0.000000000
H	-3.734007314	-0.242088303	0.888300000
Cl	1.739675314	-4.853152697	0.000000000

3. NMR Spectra of compounds 4-7.

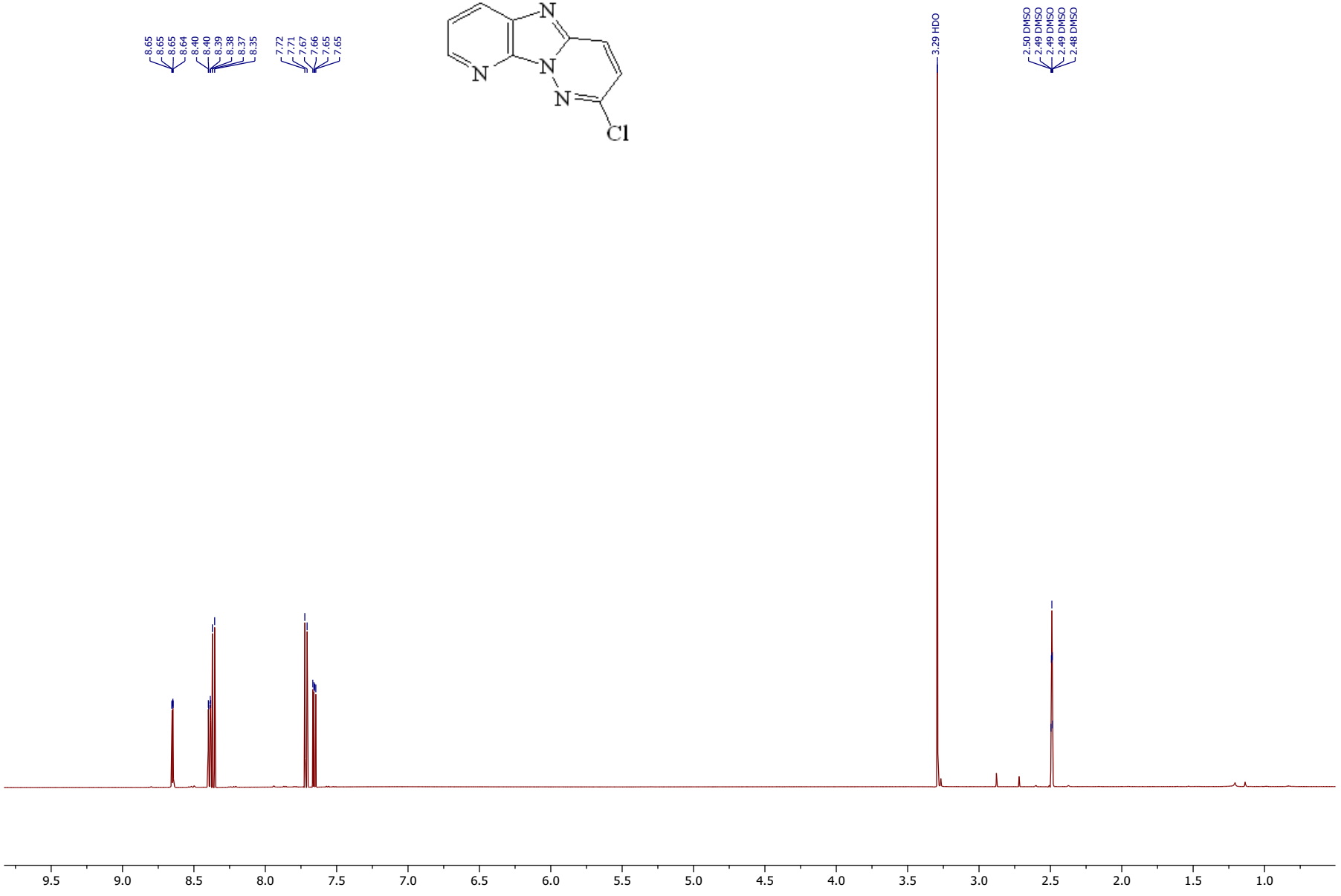
6-Chloro-2-(3-nitropyridin-2-yl)pyridazin-3(2*H*)-one (4).

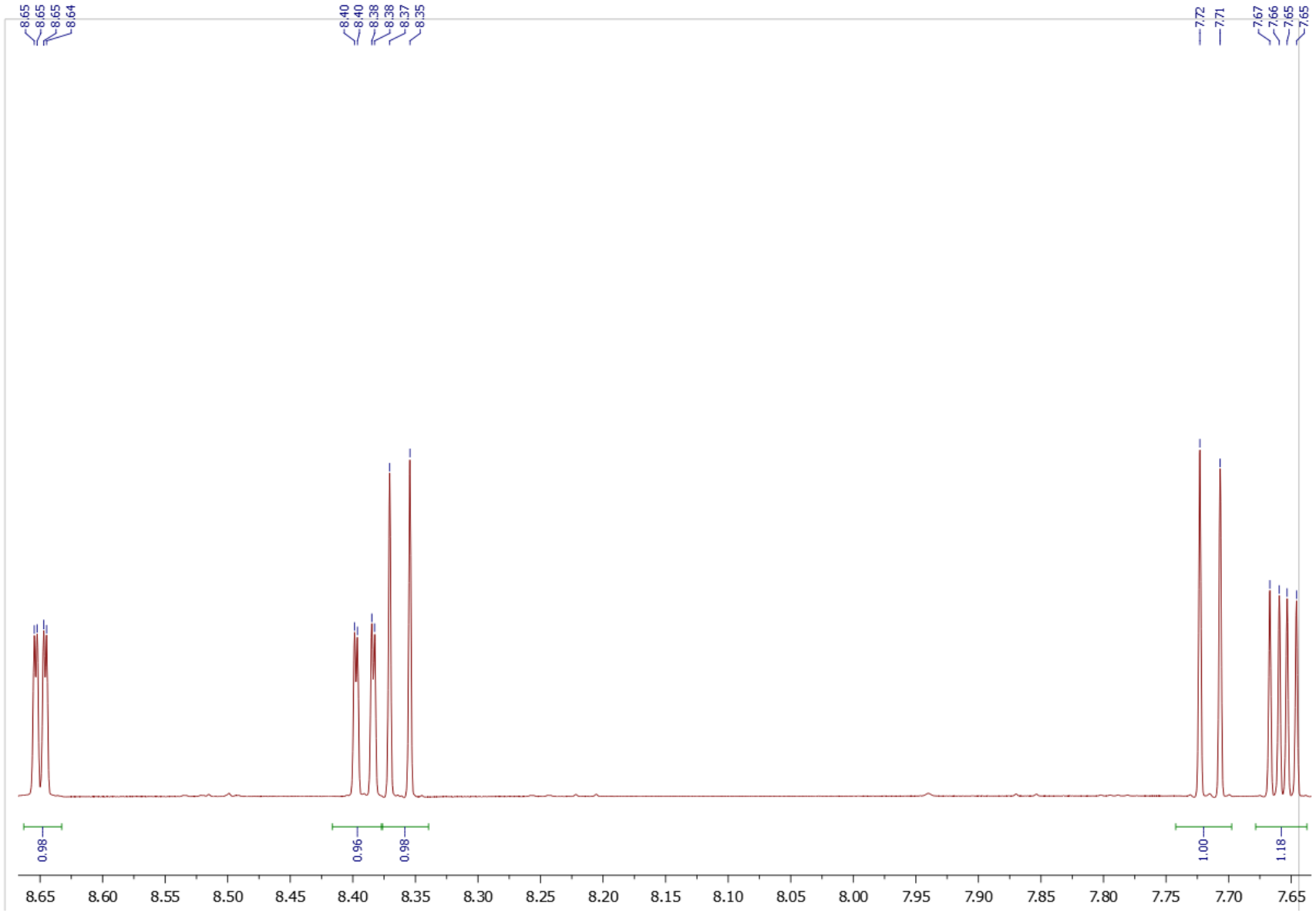


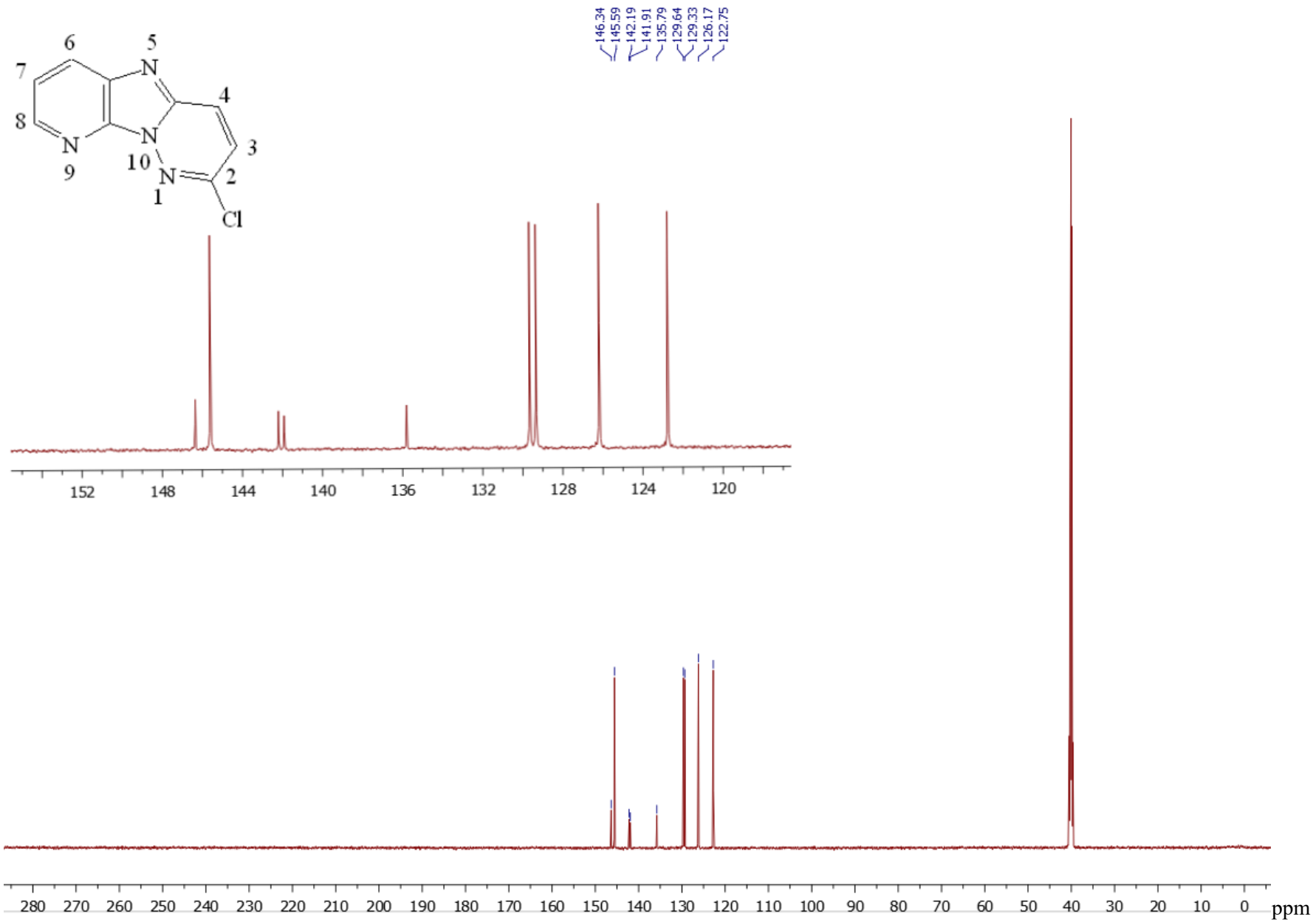
2-(3-Aminopyridin-2-yl)-6-chloropyridazin-3(2*H*)-one (5).



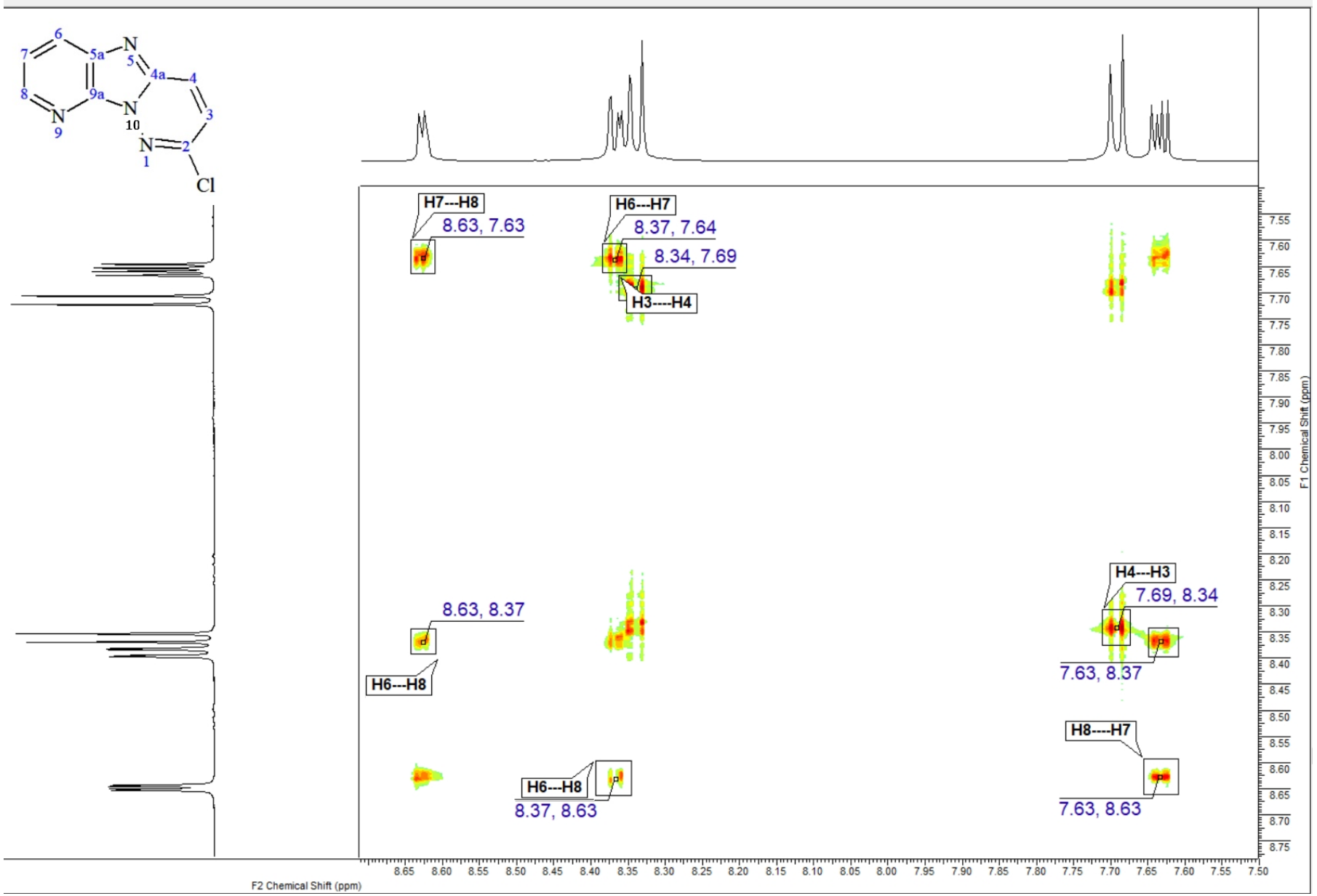
2-Chloropyrido[3',2':4,5]imidazo[1,2-*b*]pyridazine (6).



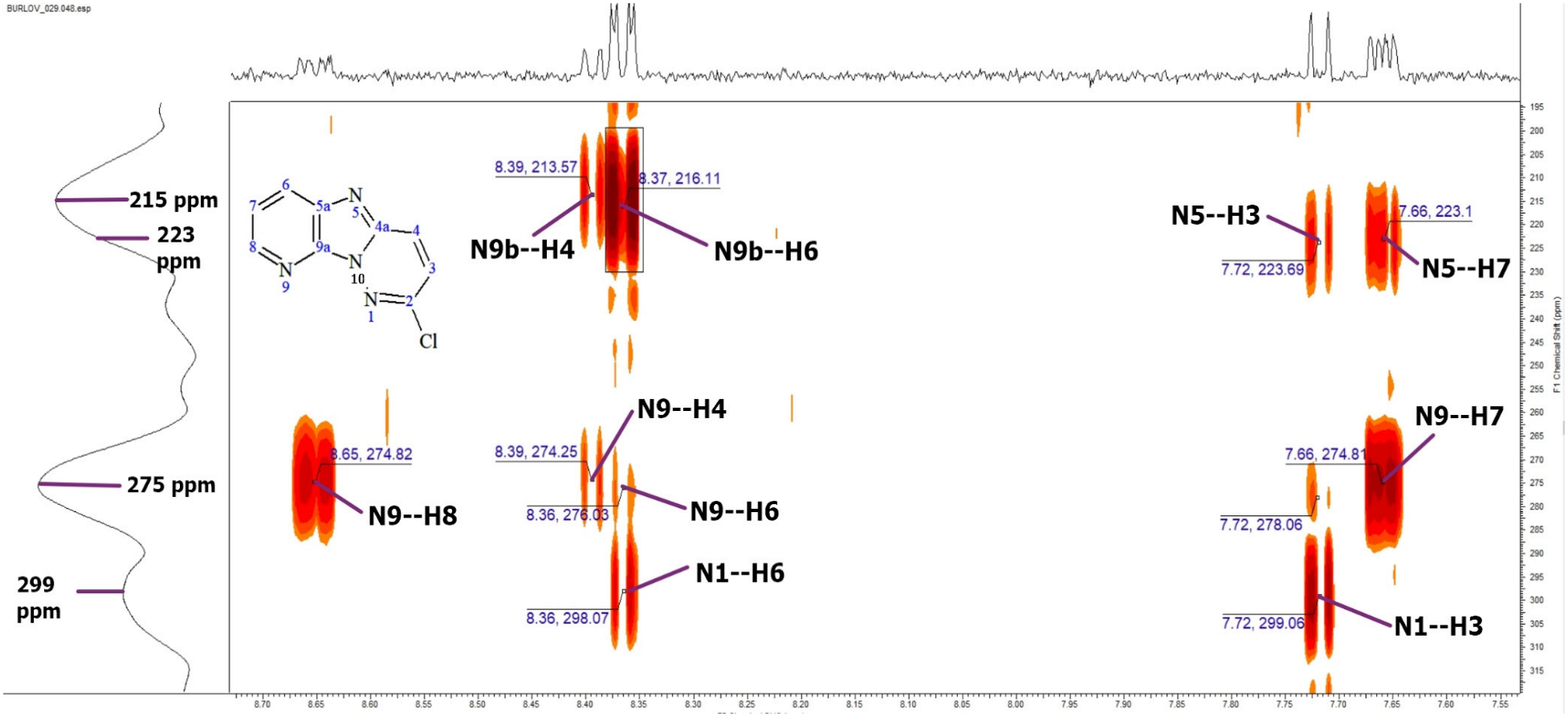

8.65
8.65
8.65
8.64
8.40
8.40
8.38
8.38
8.37
8.35
7.72
7.71
7.67
7.66
7.65
7.65
0.98
0.96
0.98
1.00
1.18
8.65
8.60
8.55
8.50
8.45
8.40
8.35
8.30
8.25
8.20
8.15
8.10
8.05
8.00
7.95
7.90
7.85
7.80
7.75
7.70
7.65


146.34
145.59
142.19
141.91
135.79
129.64
129.33
126.17
122.75
6
5
7
N
4
8
N
N
3
9
10
N
2
1
Cl
152
148
144
140
136
132
128
124
120
280
270
260
250
240
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

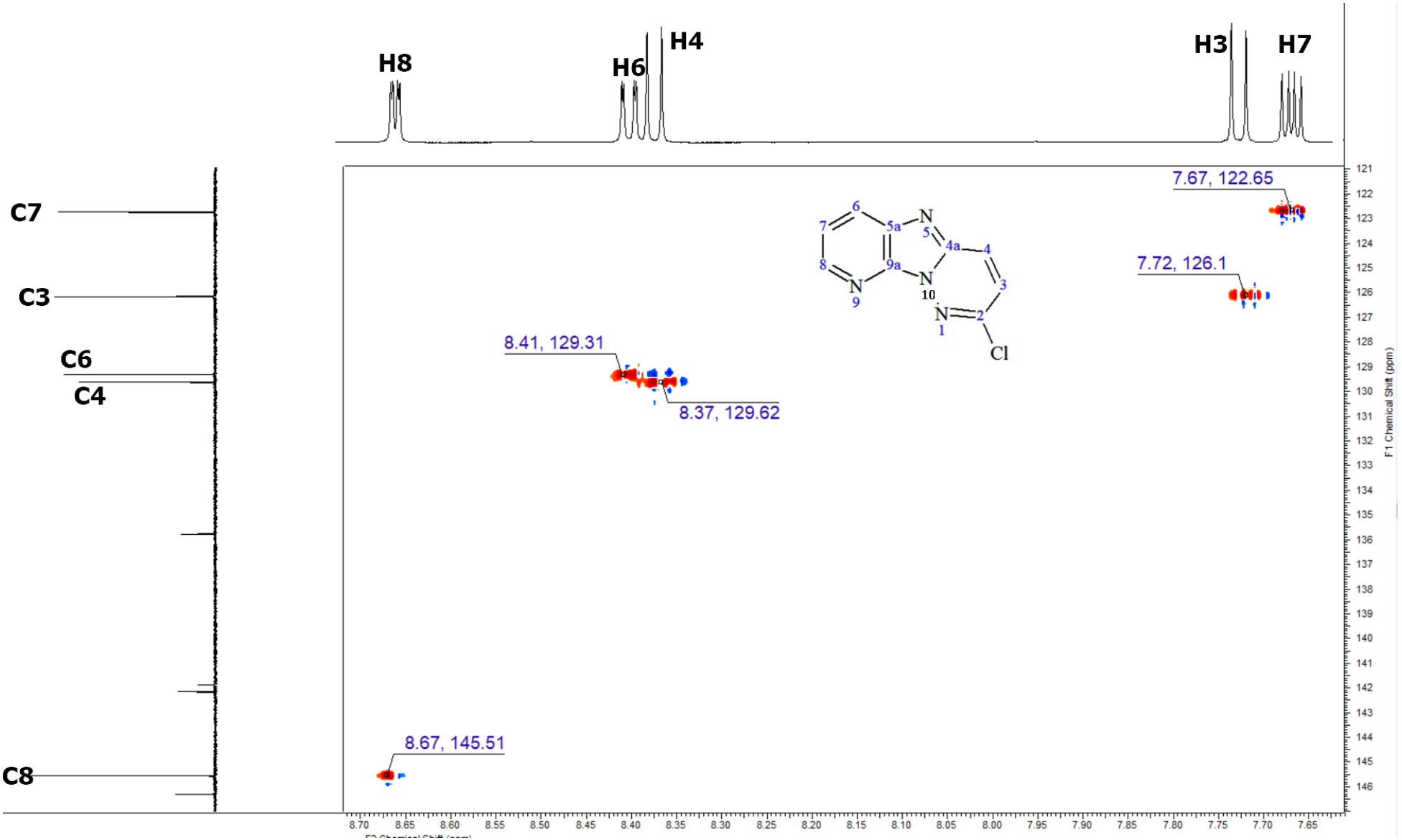
2D NMR Cosy ^{1}H— ^{1}H



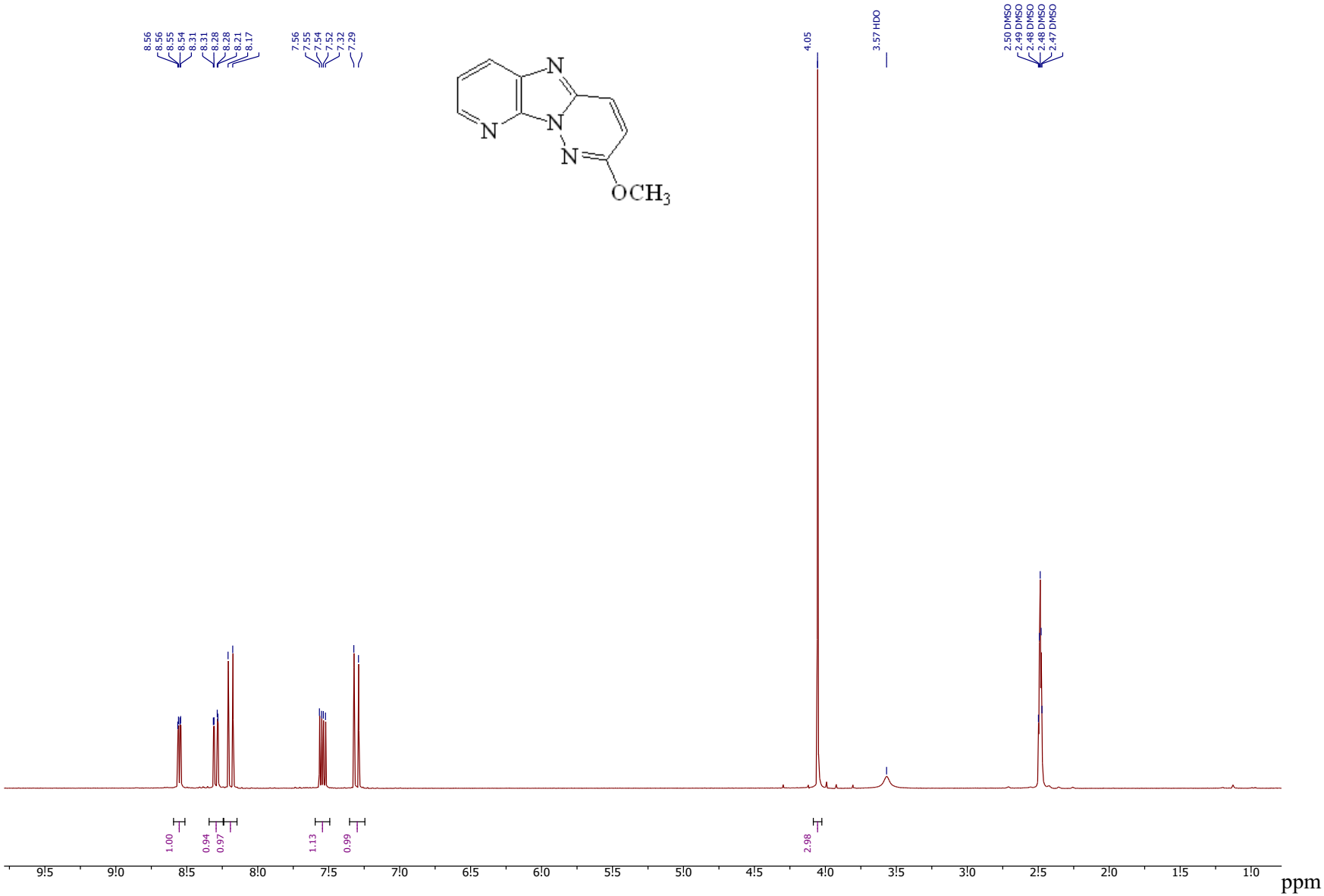
HMBC ^{15}N – ^{1}H


BURLOV_029.048.esp
215 ppm
223 ppm
275 ppm
299 ppm
8.39, 213.57
8.37, 216.11
N9b--H4
N9b--H6
8.65, 274.82
N9--H8
8.39, 274.25
N9--H4
8.36, 276.03
N9--H6
8.36, 298.07
N1--H6
N5--H3
7.72, 223.69
7.66, 223.1
N5--H7
7.66, 274.81
N9--H7
7.72, 278.06
7.72, 299.06
N1--H3
F1 Chemical Shift (ppm)

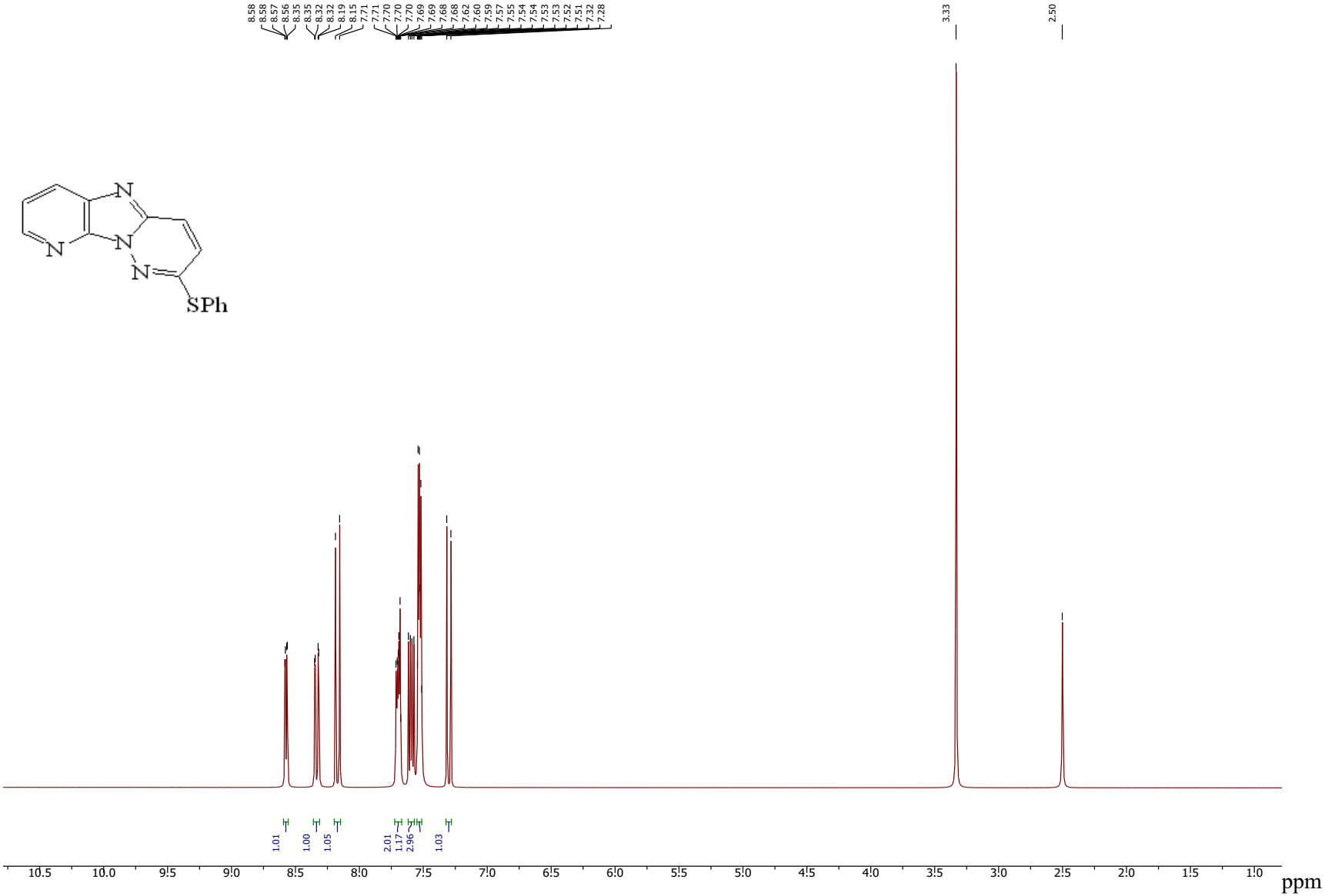
HSQC


H8
H6
H4
H3
H7
C7
C3
C6
C4
C8
7.67, 122.65
7.72, 126.1
8.41, 129.31
8.37, 129.62
8.67, 145.51
Cl
F1 Chemical Shift (ppm)

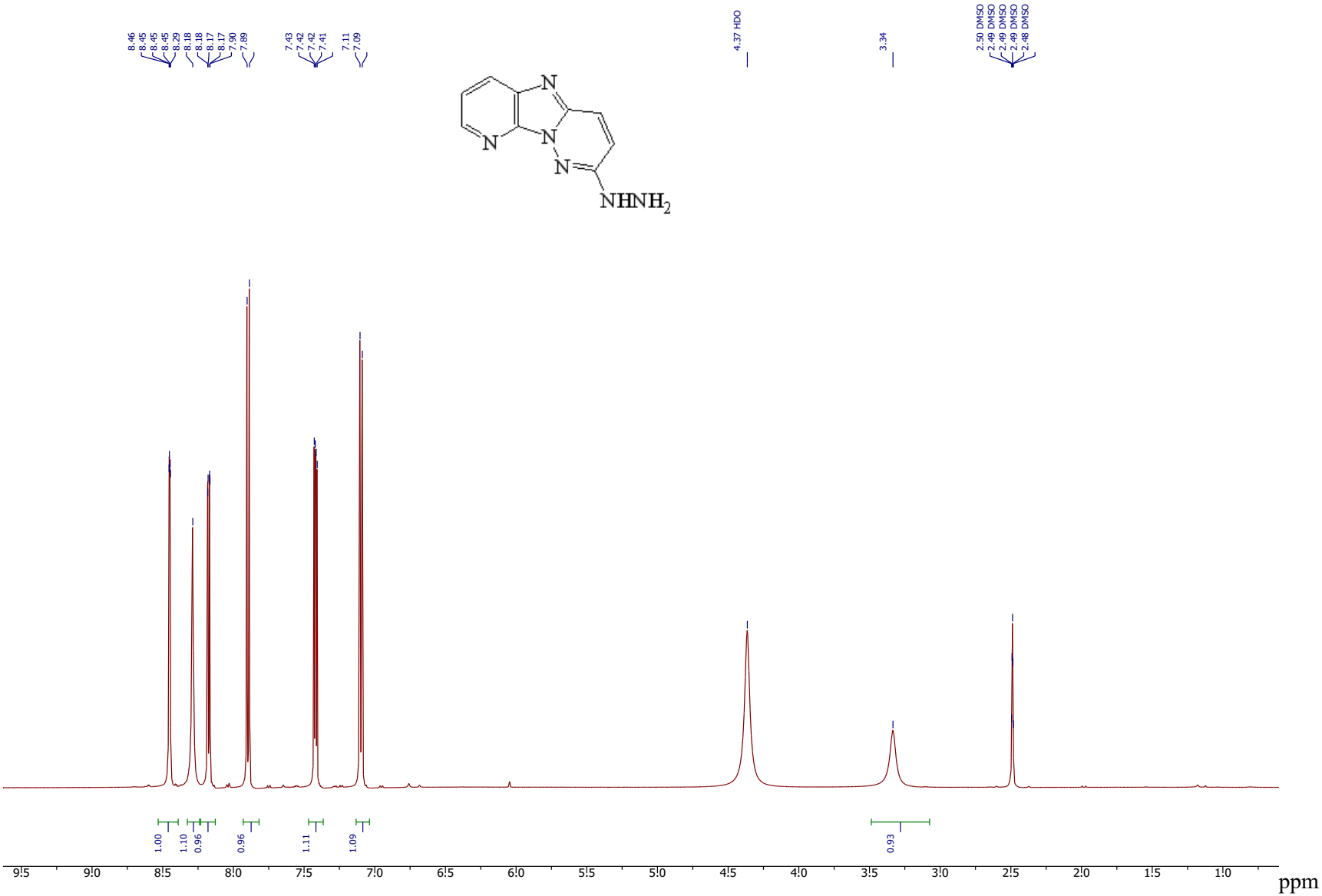
2-Methoxypyrido[3',2':4,5]imidazo[1,2-*b*]pyridazine (7a).

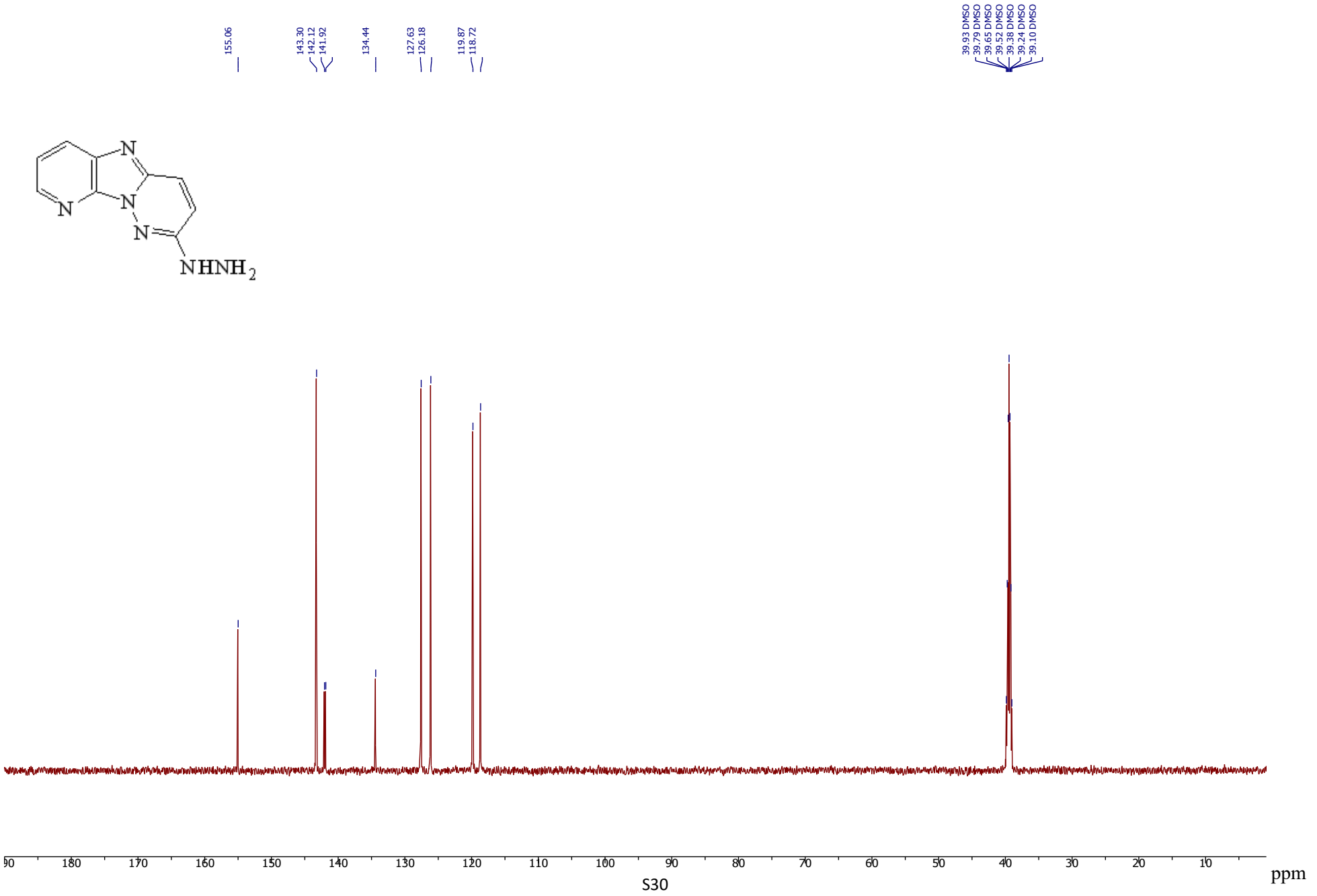


2-(Phenylthio)pyrido[3',2':4,5]imidazo[1,2-*b*]pyridazine (7b).

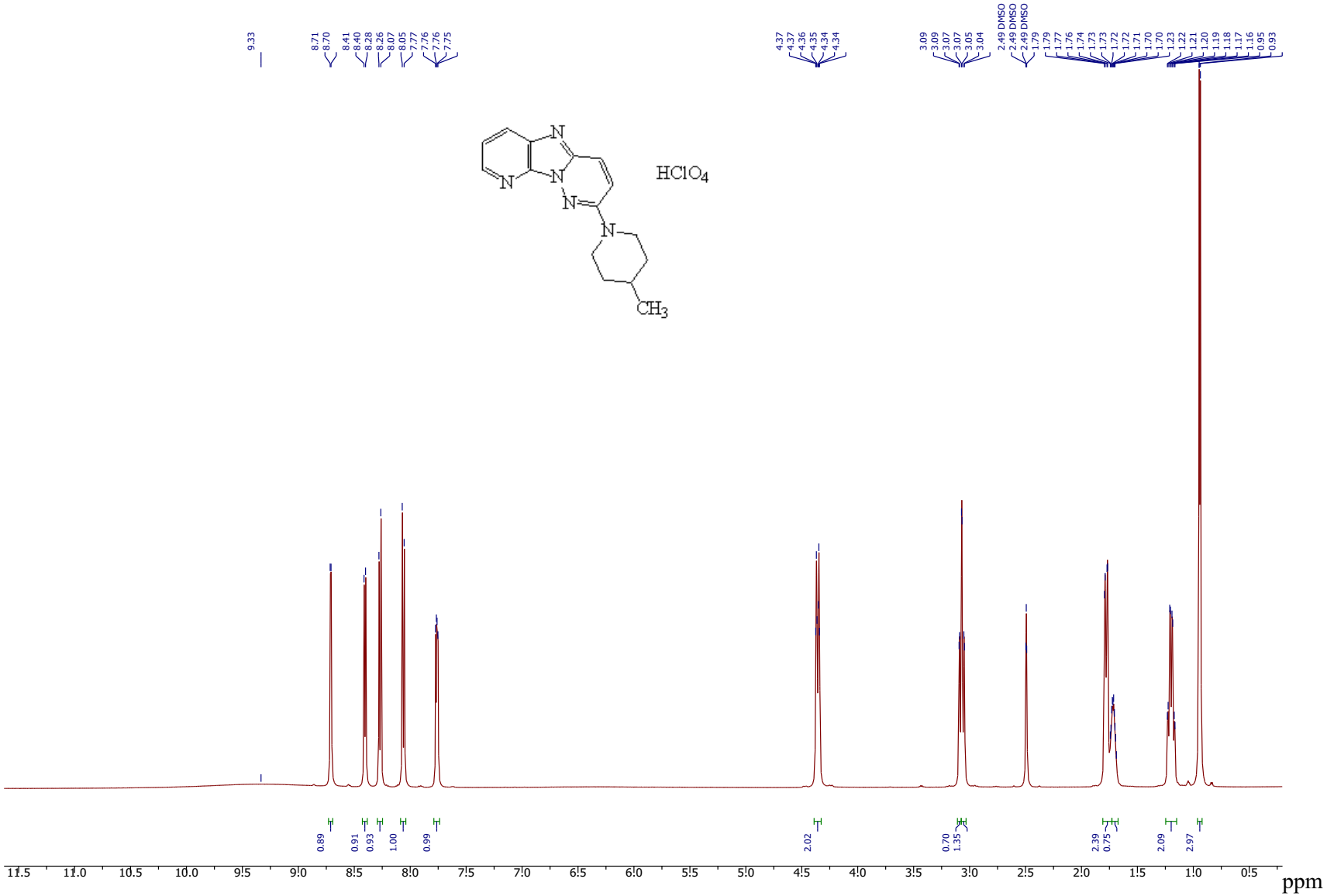


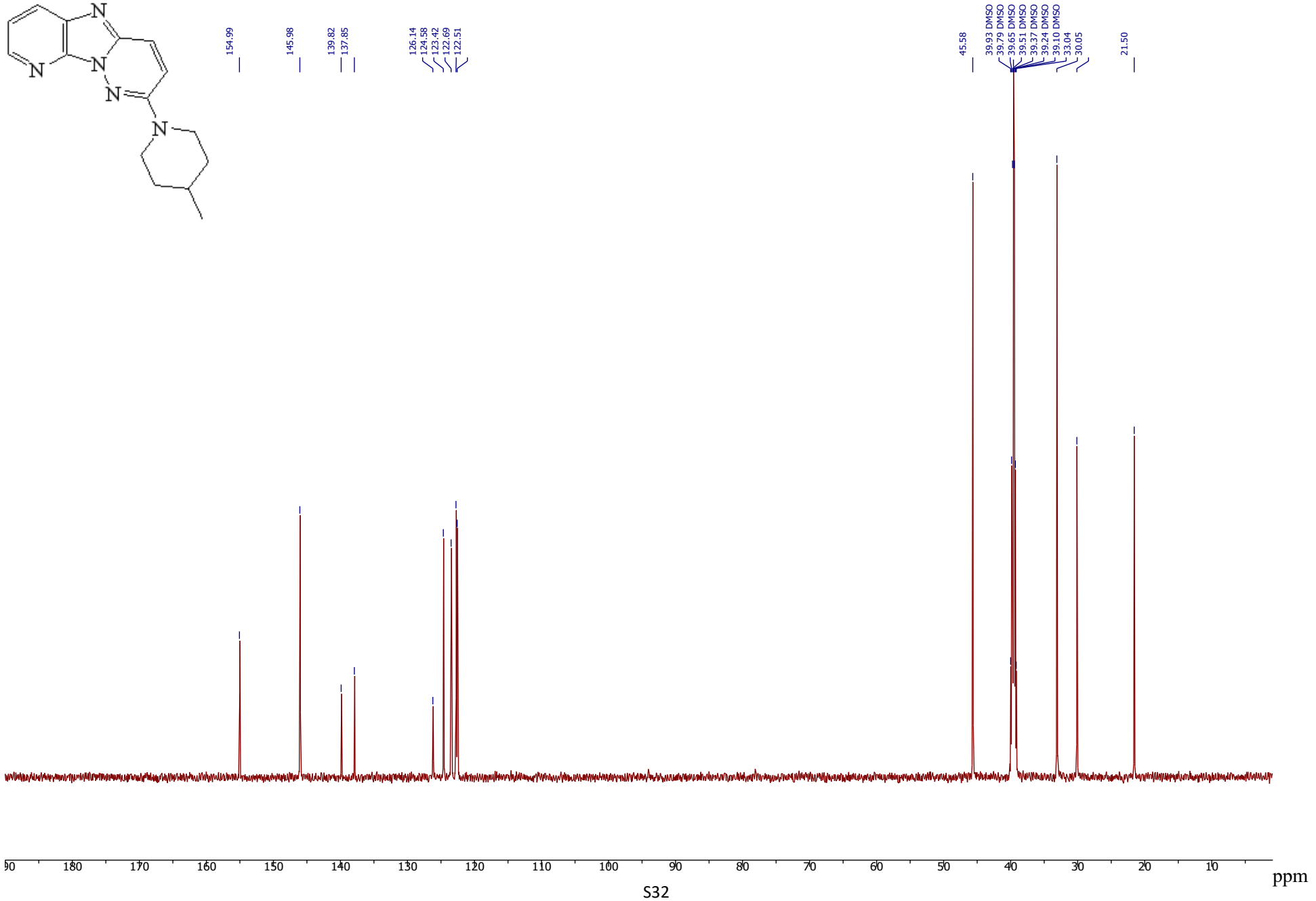
2-Hydrazinylpyrido[3',2':4,5]imidazo[1,2-*b*]pyridazine (7c).



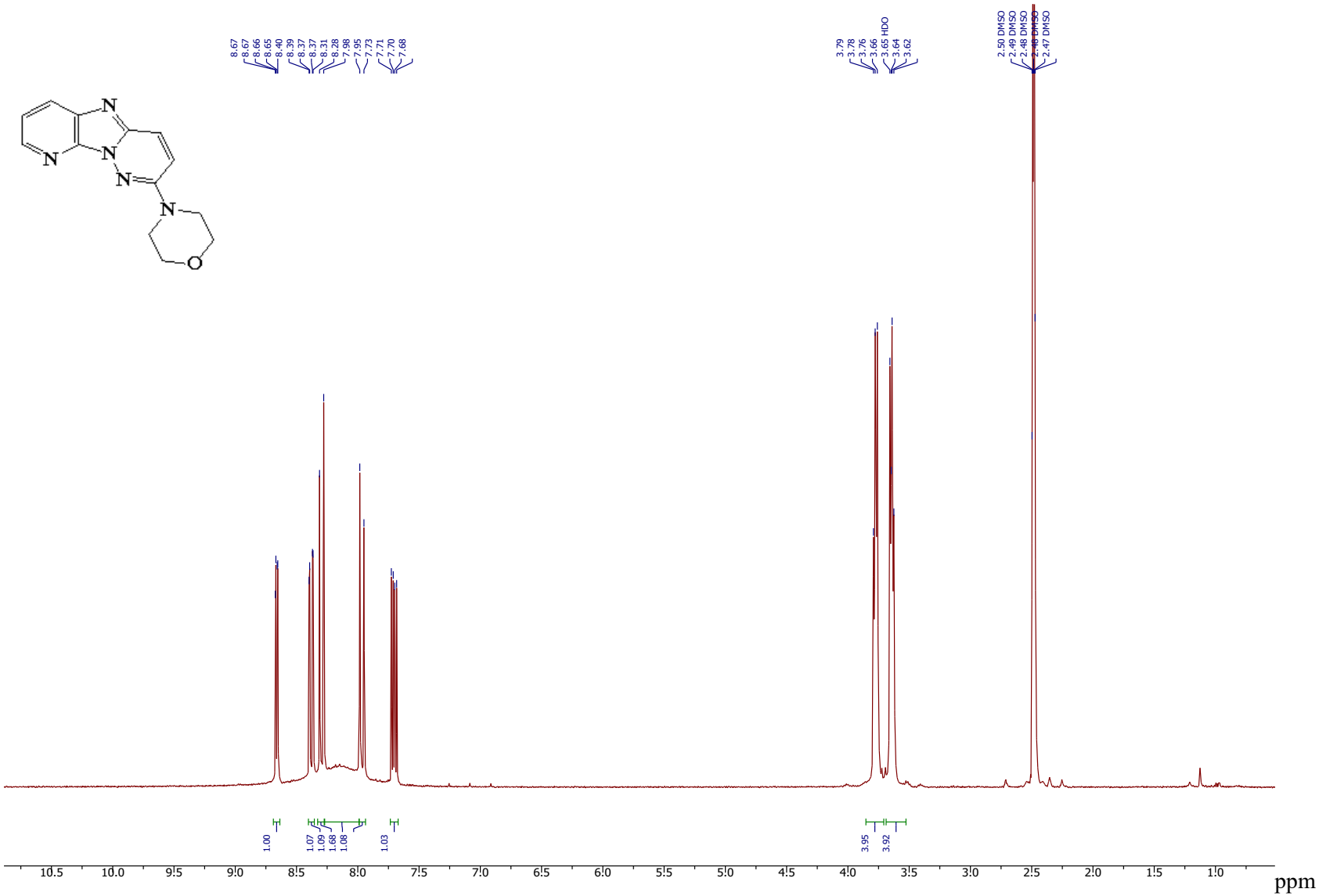

155.06
143.30
142.12
141.92
134.44
127.63
126.18
119.87
118.72
39.93 DMSO
39.79 DMSO
39.65 DMSO
39.52 DMSO
39.38 DMSO
39.24 DMSO
39.10 DMSO
N
N
N
N
NHNH2
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

2-(4-Methylpiperidin-1-yl)pyrido[3',2':4,5]imidazo[1,2-*b*]pyridazine hydroperchlorate (7d·HClO$_4$).

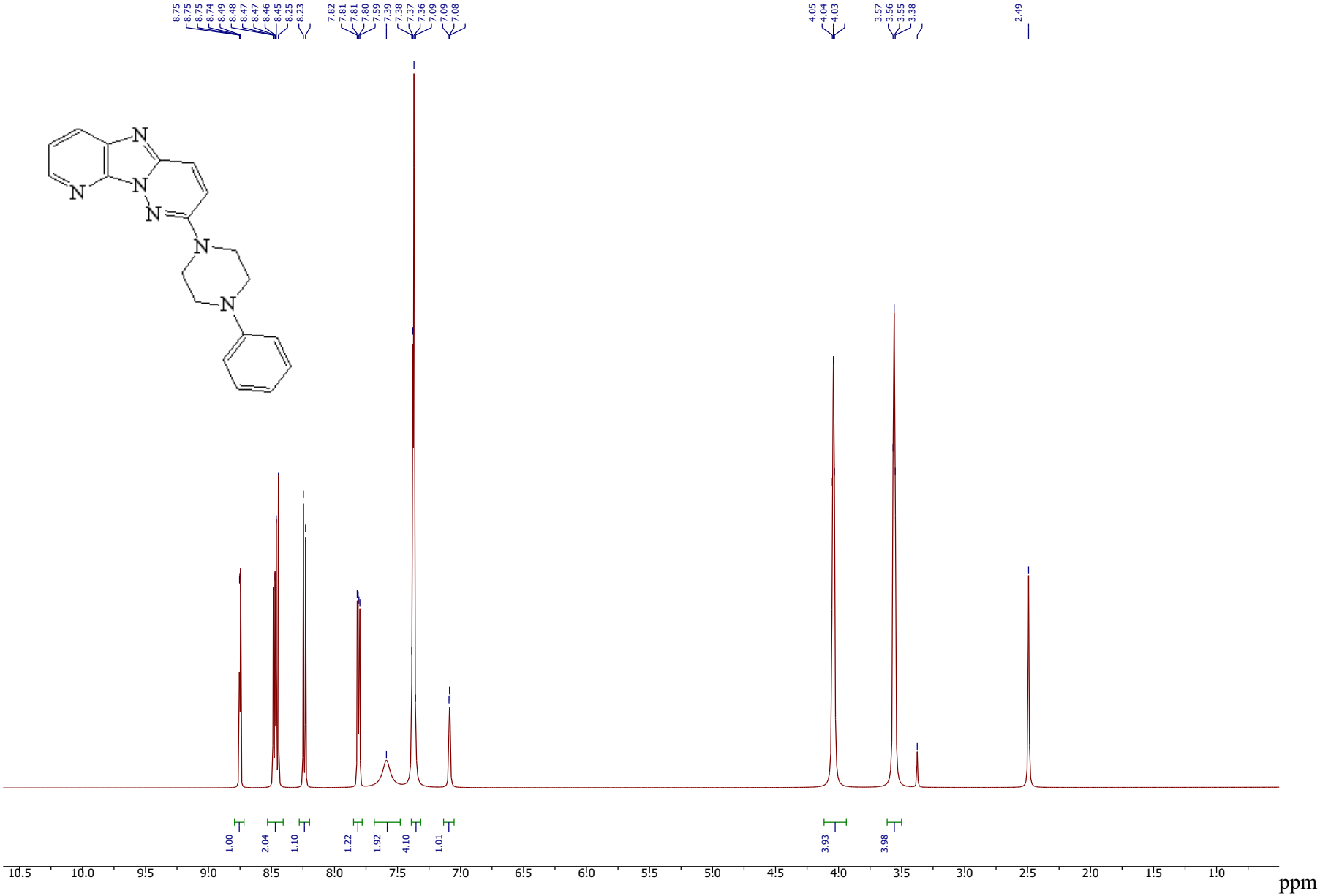


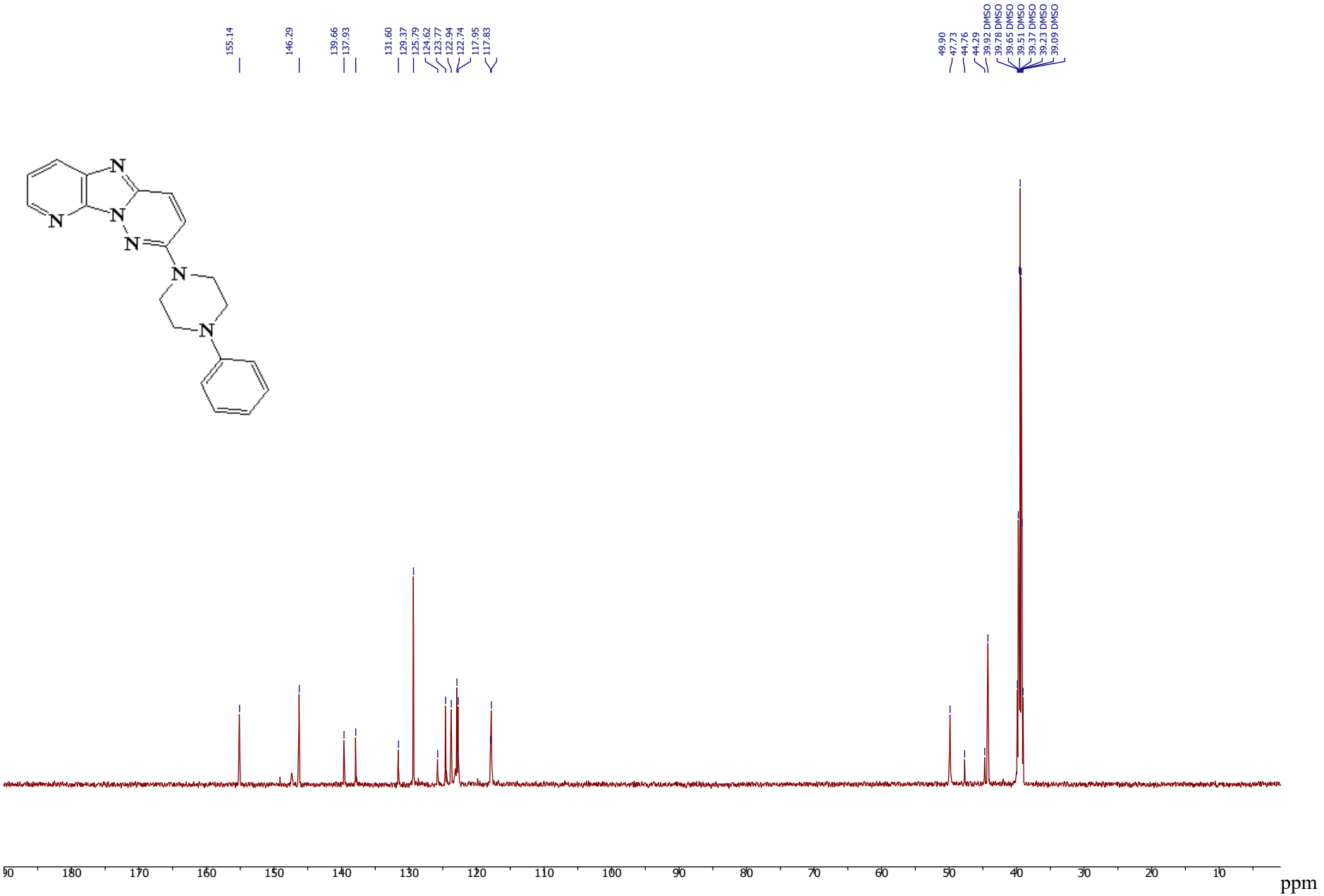

154.99
145.98
139.82
137.85
126.14
124.58
123.42
122.69
122.51
45.58
39.93 DMSO
39.79 DMSO
39.65 DMSO
39.51 DMSO
39.37 DMSO
39.24 DMSO
39.10 DMSO
33.04
30.05
21.50
ppm

2-(Morpholin-4-yl)pyrido[3',2':4,5]imidazo[1,2-*b*]pyridazine dihydrosulfate (7e·H_2SO_4).



2-(4-Phenylpiperazin-1-yl)pyrido[3',2':4,5]imidazo[1,2-*b*]pyridazine dihydrobromide (7f·2HBr).




155.14
146.29
139.66
137.93
131.60
129.37
125.79
124.62
123.77
122.94
122.74
117.95
117.83
49.90
47.73
44.76
44.29
39.92 DMSO
39.78 DMSO
39.65 DMSO
39.51 DMSO
39.37 DMSO
39.23 DMSO
39.09 DMSO
N
N
N
N
N
N
ppm

5. References

S1. *NMR Solvent reference shift*, Version 4.2; http://chem.ch.huji.ac.il/nmr/software/solvent.html.

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S3. A. A. Granovsky, *Firefly*, Version 8; http://classic.chem.msu.su/gran/firefly/index.html.

S4. 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, Jr., *J. Comput. Chem.*, 1993, **14**, 1347; https://doi.org/10.1002/jcc.540141112.