Electronic Supporting Information

2,3-Dicyclohexylsuccinimide as a Directing/Protecting Group for the Regioselective Glycosylation or Alkylation of Purines

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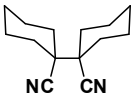
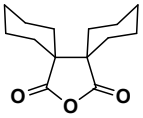
1) Synthesis of 2,3-dicyclosuccinic anhydride and protected nucleobases

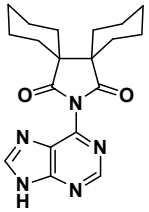
General Procedures: All reactions were carried out under an inert atmosphere with dry solvents under anhydrous conditions unless noted otherwise. Dry tetrahydrofuran (THF), diethyl ether (Et_2O), *N*,*N*-dimethylformamide (DMF), pyridine (pyr), acetonitrile (MeCN), and dichloromethane (DCM) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Dry methanol (MeOH) was obtained by distillation from $Mg(OMe)_2$. Yields refer to chromatographically and spectroscopically (^{1}H-NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm Silicycle TLG-R10011B-323 60 Å plates using UV light as a visualizing agent and/or ceric ammonium molybdate (CAM) stain or 10% sulphuric acid solution (aq.) and heat as developing agents. Silicycle silica gel (SiliaFlash P60, 60 Å, particle size 40-63 μm) was used for flash column chromatography. Difficult separations were carried out using "chromatospec silica gel" (E. Merck Chromatospec silica gel (60 Å, particle size 15-40 μm). NMR spectra were recorded on Varian VNMRS 400, VNMRS 500, VNMRS 600, or INOVA 500 instruments and calibrated using residual undeuterated solvent as an internal reference. High-resolution mass spectra (HRMS) were recorded on a Waters LCT Classic or JEOL AccuTOF mass spectrometer using ESI (electrospray ionization) or DART (direct analysis in real time).



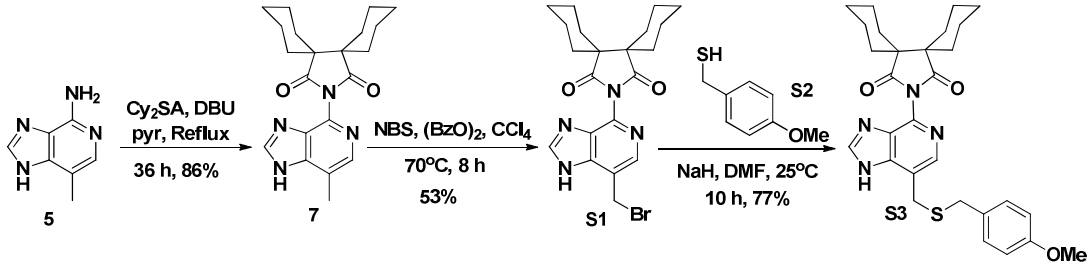
[1,1'-bi(cyclohexane)]-1,1'-dicarbonitrile (2). To a flask containing compound **1** (5.0 g, 20 mmol) was added n-heptane (28 mL). The mixture was heated to 95 ºC for 36 hours. The solution was then allowed to cool to room temperature, the suspension filtered, and the residue washed with hexanes (3×75 mL) to obtain compound **2** as a light yellow solid (4.13 g, 89%): ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 2.12 (d, J = 11.0 Hz, 4H), 1.90 - 1.73 (m, 6H), 1.61 (d, J = 13.3 Hz, 8H), 1.25 - 1.16 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 120.42, 46.45, 31.01, 24.87, 23.16; HRMS (ESI-TOF) calcd for $C_{14}H_{22}N_2O$ $(M+H_2O)^+$ 234.1970, found $(M+H_2O)^+$ 234.1974.

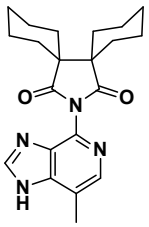


2,3-dicyclohexylsuccinic anhydride (3). A solution of H_2SO_4 (44 mL) in water (19 mL) was prepared, cooled to room temperature, and subsequently added to a flask containing **2** (7.88 g, 36.4 mmol). The mixture was heated to 115 ºC for 75 minutes and then to 125 ºC for 75 minutes. The resulting dark solution was then allowed to cool to room temperature, extracted with diethyl ether (3×200 mL), the combined organic extracts washed with water (3×100 mL), followed by saturated $NaHCO_3$ (3×100 mL), dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The crude residue was purified by flash column chromatography (1:30 ethyl acetate: hexanes) to yield compound **3** as a white amorphous powder (2.88 g, 67%): R_f = 0.42 (silica gel, 1:20 ethyl actate:hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.86 - 1.60 (m, 14H), 1.44 - 1.33 (m, 4H), 1.17 - 1.05 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 174.52, 52.95, 29.12, 25.39, 22.08; HRMS (DART-TOF) calcd for $C_{14}H_{21}O_3$ $(M+H)^+$ 237.1491, found $(M+H)^+$ 237.1491.



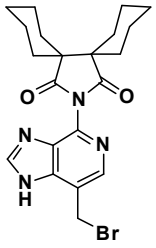
Compound 6. To a flask containing adenine (**4**) (0.25 g, 1.85 mmol) and compound **3** (1.31 g, 5.55 mmol) was added pyridine (20 mL) and DBU (0.83 mL, 5.55 mmol), and the mixture heated to reflux for 20 hours. The solution was cooled to room temperature, all volatiles removed in vacuo, and the residue co-evaporated with toluene (3×10 mL) to remove residual pyridine. The resulting brown oil was purified by flash column chromatography eluting with 1:30 MeOH:DCM to obtain compound **6** as a white amorphous powder (0.582 g, 89%): R_f = 0.42 (silica gel, 1:20 MeOH:DCM); ^{1}H NMR (500 MHz, CD_3OD) δ (ppm) 8.93 (s, 1H), 8.53 (s, 1H), 2.00 - 1.90 (m, 8H), 1.77 - 1.67 (m, 6H), 1.59 (td, *J* = 13.5, 4.1 Hz, 4H), 1.30 - 1.20 (m, 2H); ^{13}C NMR (126 MHz, CD_3OD) δ (ppm) 180.62, 157.71, 153.22, 147.67, 144.63, 128.62, 53.50, 30.87, 26.63, 23.50; HRMS (DART-TOF) calcd for $C_{19}H_{24}N_5O_2$ $(M+H)^+$ 354.1930, found $(M+H)^+$ 354.1935.



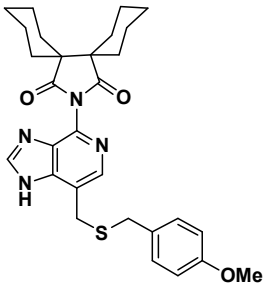


Compound 7. To a flask containing compound **5**[1] (1.20 g, 8.11 mmol) and compound **3** (5.74 g, 24.3 mmol) was added pyridine (80 mL) and DBU (3.63 mL, 24.3 mmol), and the mixture heated to reflux for 36 hours. The solution was cooled to room temperature, all volatiles removed in vacuo, and the residue co-evaporated with toluene (3 x 10 mL) to remove residual pyridine. The resulting brown oil was purified by flash column chromatography eluting with 1:25 MeOH:DCM to obtain compound **7** as a white

amorphous powder (2.55 g, 86%): R_f = 0.32 (silica gel, 1:20 MeOH:DCM); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.00 (s, 1H), 7.36 (s, 1H), 2.21 (s, 3H), 1.98 (dd, *J* = 25.2, 11.7 Hz, 8H), 1.79 - 1.69 (m, 6H), 1.60 - 1.53 (m, 4H), 1.25 - 1.17 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 181.46, 142.94, 140.96, 139.58, 135.77, 135.69, 119.22, 52.07, 30.21, 25.65, 22.47, 14.01; HRMS (DART-TOF) calcd for $C_{21}H_{27}N_4O_2$ $(M+H)^+$ 367.2134, found $(M+H)^+$ 367.2146.

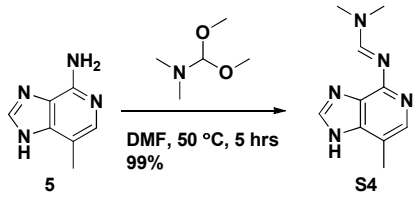


Compound S1. To a flask containing **7** (1.5 g, 4.1 mmol) was added N-bromosuccinimide (1.09 g, 6.14 mmol), benzoyl peroxide (99 mg, 0.41 mmol), and CCl_4 (120 mL, reagent grade). The mixture was heated to reflux with stirring. After five hours, additional portions of NBS (364 mg, 2.05 mmol) and benzoyl peroxide (99 mg, 0.41 mmol) were added. After a total of eight hours, the reaction was allowed to cool to room temperature, filtered, and all volatiles removed in vacuo. The crude residue was purified by flash column chromatography eluting with 3:2 ethyl acetate:hexanes to afford compound **S1** as a white foam (0.966 g, 53%): R_f = 0.23 (silica gel, 1:1 ethyl acetate:hexane); ^{1}H NMR (500 MHz, CD_3OD) δ (ppm) 8.44 (s, 1H), 8.41 (s, 1H), 4.98 (s, 2H), 2.09 – 1.93 (m, 8H), 1.75 – 1.70 (m, 6H), 1.63 (dd, *J* = 13.0, 9.2 Hz, 4H), 1.32 - 127 (m, 2H); ^{13}C NMR (126 MHz, CD_3OD) δ (ppm) 181.59, 146.46, 141.70, 139.16, 122.82, 106.42, 53.17, 31.01, 26.67, 26.08, 23.55; HRMS (DART-TOF) calcd for $C_{21}H_{26}N_4O_2Br$ $(M+H)^+$ 445.1239, found $(M+ H)^+$ 445.1242.

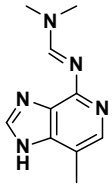


Compound S3. To a flask containing sodium hydride (53 mg, 2.19 mmol) was added DMF (15 mL) and thiol **S2** (0.31 mL, 2.19 mmol). The mixture was stirred at 25 ºC for 30 minutes. Then compound **S1** (0.65 g,

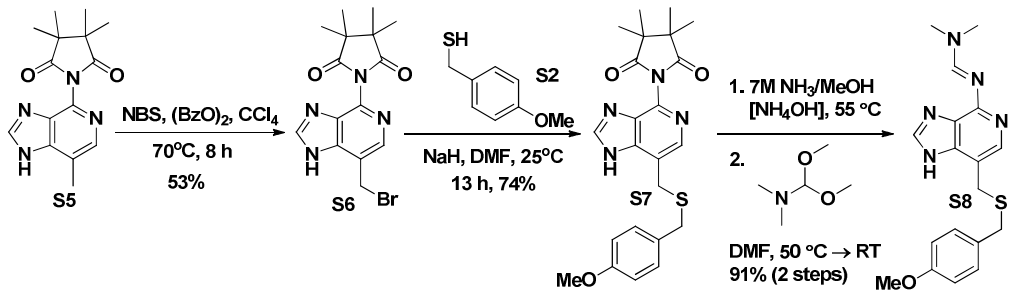
1.46 mmol) was added and allowed to stir for another 10 hours at room temperature. Volatiles were removed in vacuo and the residue purified by flash column chromatography eluting with 1:40 MeOH:DCM to afford compound **S3** as a white foam (0.583 g, 77%): R_f = 0.35 (silica gel, 1:25 MeOH:DCM); ^{1}H NMR (500 MHz, CD_3OD) δ (ppm) 8.33 (s, 1H), 8.14 (s, 1H), 7.16 (d, *J* = 8.5 Hz, 2H), 6.87 – 6.80 (m, 2H), 4.01 (s, 2H), 3.78 (s, 3H), 3.64 (d, *J* = 8.3 Hz, 2H), 2.11 – 1.94 (m, 8H), 1.79 – 1.70 (m, 6H), 1.63 (td, *J* = 13.0, 3.9 Hz, 4H), 1.33 – 1.28 (m, 2H); ^{13}C NMR (126 MHz, CD_3OD) δ (ppm) 180.39, 158.81, 144.46, 139.86, 131.28, 129.66, 129.40, 113.94, 113.47, 54.25, 51.64, 34.69, 29.61, 29.14, 25.27, 22.14; HRMS (DART-TOF) calcd for $C_{29}H_{35}N_4O_3$ $(M+H)^+$ 519.2430, found $(M+H)^+$ 519.2446.

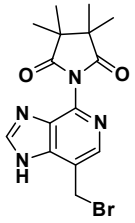


5 S4

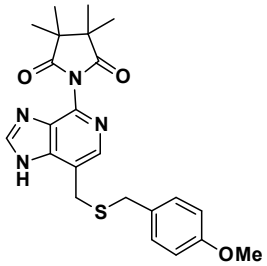


Compound S4. To a suspension of compound **5** (140 mg, 0.945 mmol) in DMF (2.0 mL) was added dimethylformamide dimethyl acetal (170 µL, 1.23 mmol) and the suspension heated to 50 ºC for 5 hours. All solvent was then removed from the following suspension, the resulting solid triturated with DCM, and concentrated again in vacuo to afford compound **S4** as a light tan solid (190 mg, 99%): ^{1}H NMR (500 MHz, CD_3OD) δ (ppm) 8.58 (s, 1H), 8.18 (s, 1H), 7.61 (s, 1H), 3.18 (s, 3H), 3.16 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ (ppm) 158.45, 151.34, 147.98, 146.98, 135.57, 129.37, 117.62, 41.02, 34.79, 13.91; HRMS (DART) calc for $C_{10}H_{14}N_5$ $(M+H)^+$ 204.1244, found 204.1244.

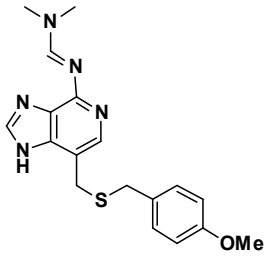




Compound S6. Synthesized using the same procedure as that for compound **S1** with a 53% yield starting from compound **S5**.[1] ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.33 (s, 1H), 7.83 (s, 1H), 4.67 (s, 2H), 1.39 (s, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 182.18, 143.16, 140.79, 138.67, 138.13, 136.46, 119.37, 48.08, 25.59, 21.47; HRMS (ESI-TOF) calcd for $C_{15}H_{18}N_4O_2Br$ $(M+H)^+$ 365.0613, found $(M+H)^+$ 365.0620.



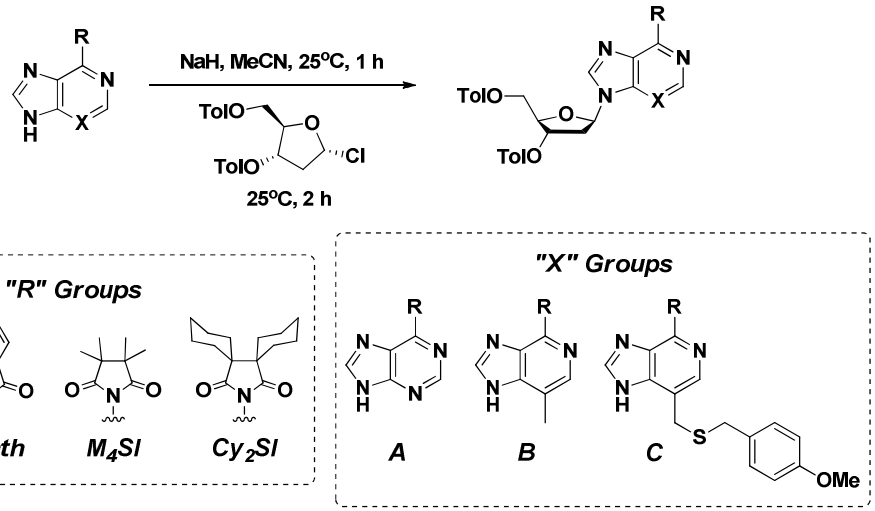
Compound S7. Synthesized using the same procedure as that for compound **S3** with a 74% yield starting from compound **S6**. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.06 (s, 1H), 7.63 (s, 1H), 7.10 (d, J = 8.6 Hz, 2H), 6.80 (d, J = 8.6 Hz, 2H), 3.77 (s, 3H), 3.69 (s, 2H), 3.45 (s, 2H), 1.38 (s, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 182.25, 158.93, 142.82, 140.88, 139.03, 137.47, 136.62, 130.20, 129.11, 119.90, 114.14, 55.41, 48.14, 35.07, 29.41, 21.66; HRMS (DART-TOF) calcd for $C_{23}H_{27}N_4O_3S$ $(M+H)^+$ 439.1787, found $(M+H)^+$ 439.1798.



Compound S8. A solution of compound **S7** (104 mg, 0.237 mmol) in concentrated aqueous ammonium hydroxide (5.0 mL) and 7 M NH_3 in MeOH (5.0 mL) was heated to 55 ºC overnight. The next morning, TLC indicated ~50% conversion at which point another portion of 7M NH_3 in

MeOH (5.0 mL) was added and heating continued at 55 ºC. After a total of 40 hours, the solution was cooled to room temperature and concentrated in vacuo. The crude residue was passed over a short bed of silica gel with 94:6 DCM:MeOH containing 0.4 M NH_3 and concentrated in vacuo. To a solution of this crude product in DMF (1.0 mL) was added dimethylformamide dimethyl acetal (40 µL, 0.29 mmol) and the solution heated to 50 ºC. After 2 hours, the solution was allowed to cool to room temperature and stir overnight. The next morning, the solution was concentrated in vacuo and purified via flash chromatography over a short bed of silica gel with a gradient of 0 → 20% MeOH in DCM to afford compound **S8** as a pale yellow foam over two steps (77 mg, 91%): ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.86 (s, 1H), 8.15 (s, 1H), 7.86 (s, 1H), 7.11 (d, J = 8.2 Hz, 2H), 6.71 (d, J = 8.2 Hz, 2H), 3.90 (s, 2H), 3.69 (s, 3H), 3.53 (s, 2H), 3.04 (s, 3H), 2.93 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 158.53, 157.10, 150.87, 143.88, 143.00, 137.33, 130.05, 129.83, 128.91, 116.43, 113.84, 55.26, 41.07, 35.36, 34.93, 29.47; HRMS (DART) calc for $C_{18}H_{22}N_5OS$ $(M+H)^+$ 356.1540, found 356.1549.

2) Glycosylation reactions



Purine Substrate	R =	X =	Product Number
	Ndmf	A	**S9**
6	Cy_2SI	A	**8**
S4	Ndmf	B	**S10**
7	Cy_2SI	B	**11**
S8	Ndmf	C	**S11**
S7	M_4SI	C	**S12**
S3	Cy_2SI	C	**S13**

General procedure for glycosylation: To a flask containing the protected nucleobase and NaH (1.5 eq.) was added MeCN (0.05 M solution) and the solution stirred for 30 minutes at room temperature. Hoffer's chlorosugar (2-deoxy-3,5-di-*O*-(p-toluoyl)-α-D-*erythro*-pentofuranosyl chloride, 1.8 eq.) was added to the mixture and stirred for another two hours at room temperature. The resulting solution was filtered through celite and rinsed with acetone. The filtrate was concentrated in vacuo and purified by column chromatography. Regioselectivity was determined on an NMR of the crude products and HMBC (2-3 bond ^{1}H-^{13}C correlation) was subsequently used to determine the structures after purification (Figures S1 and S2).

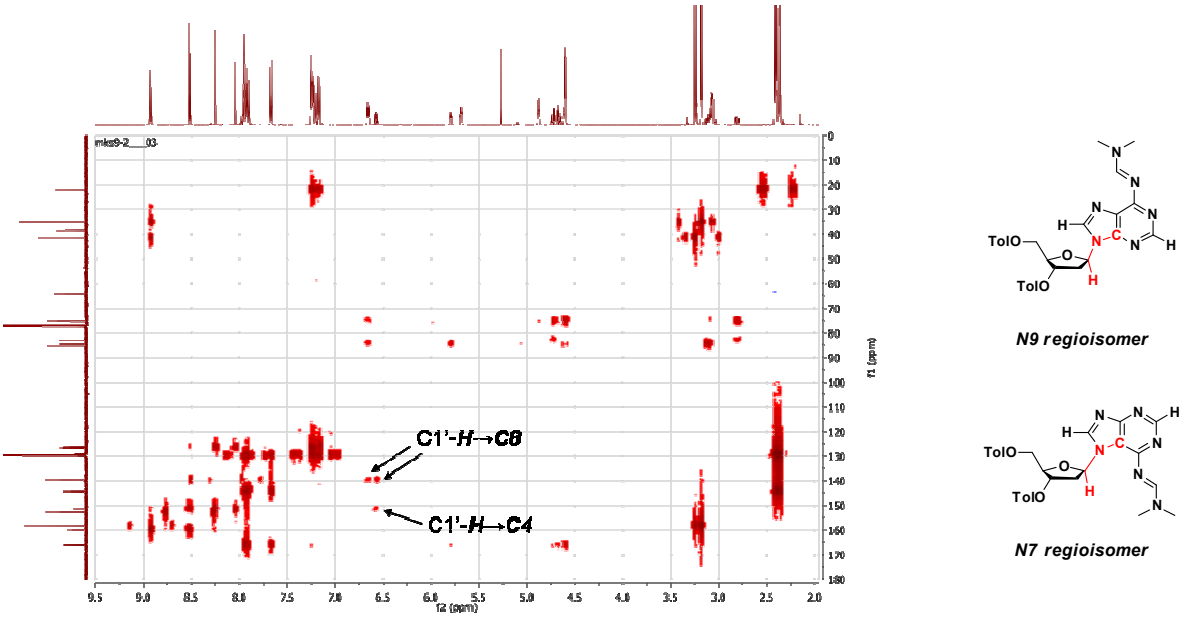


Figure S1. HMBC spectrum for compound **S9** (mixture of β-N9 and β-N7) with the relevant crosspeaks noted. The presence of a crosspeak between the C1'-H (anomeric proton) with C4 (highlighted in red on the structures) indicates the desired N9 regioisomer.

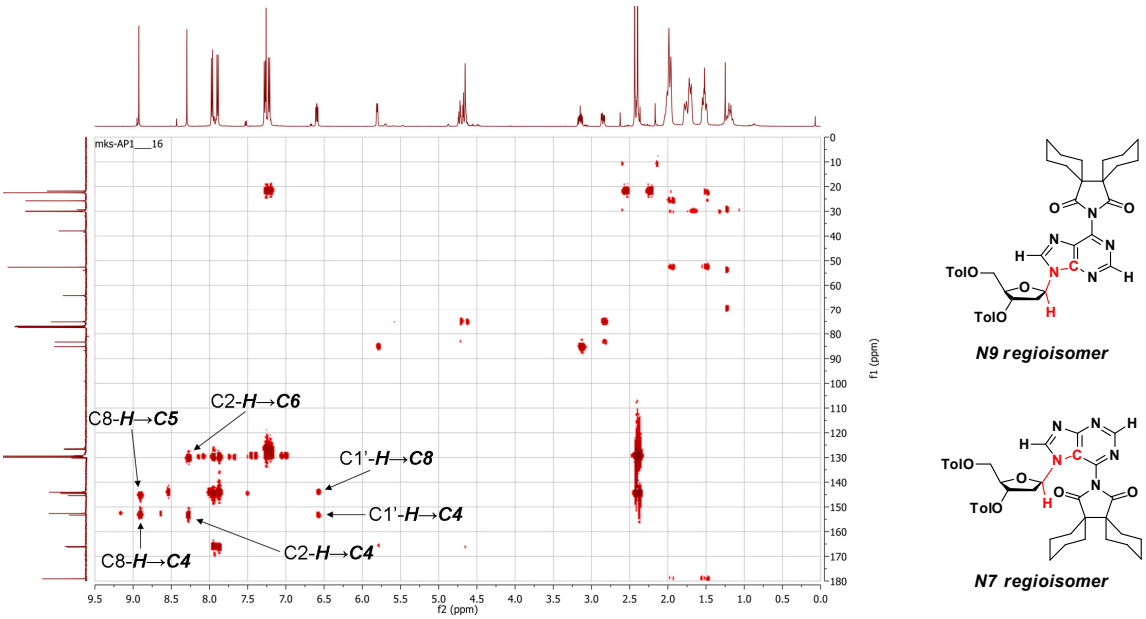
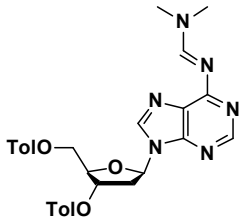
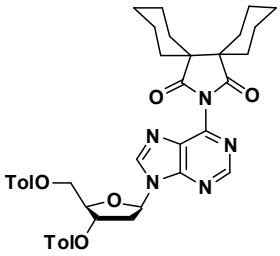


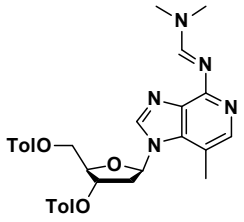
Figure S2. HMBC spectrum for compound **8** with the relevant crosspeaks noted. The presence of a crosspeak between the C1'-H (anomeric proton) with C4 (highlighted in red on the structures) indicates this product is the desired N9 regioisomer.



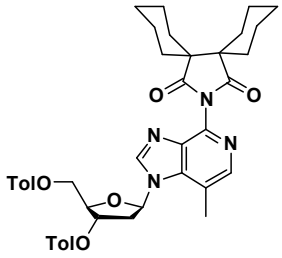
Compound S9. HRMS (DART) calc for $C_{29}H_{31}N_6O_5$ $(M+H)^+$ 543.2350, found 543.2332.



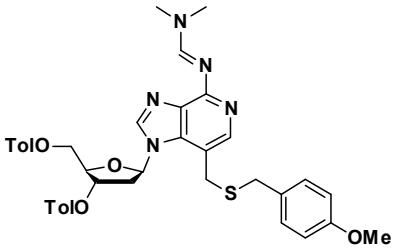
Compound 8. R_f = 2.24 (silica gel, 1:3 ethyl acetate:hexanes); Purified by gradient column chromatography ranging from 1:4 to 3.5:10 ethyl acetate:hexanes; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.93 (s, 1H), 8.29 (s, 1H), 8.00 – 7.95 (m, 2H), 7.92 – 7.88 (m, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.24 (t, *J* = 7.5 Hz, 2H), 6.60 (dd, *J* = 8.4, 5.7 Hz, 1H), 5.81 (d, *J* = 6.2 Hz, 1H), 4.73 (td, *J* = 5.9, 2.9 Hz, 1H), 4.66 (dt, *J* = 7.4, 4.4 Hz, 2H), 3.15 (ddd, *J* = 14.5, 8.5, 6.3 Hz, 1H), 2.85 (ddd, *J* = 14.2, 5.7, 1.9 Hz, 1H), 2.44 (s, 3H), 2.40 (s, 3H), 2.04 – 1.95 (m, 8H), 1.81 – 1.69 (m, 6H), 1.59 – 1.49 (m, 4H), 1.19 (dtd, *J* = 12.7, 9.0, 3.7 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 179.10, 166.28, 166.00, 153.32, 152.67, 145.45, 144.66, 144.25, 144.02, 130.34, 129.94, 129.79, 129.41, 126.79, 126.49, 85.20, 83.30, 75.13, 64.10, 52.63, 37.96, 30.07, 29.94, 25.78, 22.51, 21.86, 21.78; HRMS (ESI-TOF) calcd for $C_{40}H_{43}N_5O_7Na$ $(M+Na)^+$ 728.3060, found $(M+Na)^+$ 728.3028.



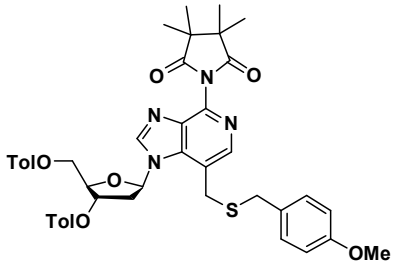
Compound S10. HRMS (DART) calc for $C_{31}H_{34}N_5O_5$ $(M+H)^+$ 556.2554, found 556.2538.



Compound 11. R_f = 2.20 (silica gel, 1:3 ethyl acetate:hexanes); Purified by gradient column chromatography ranging from 1:4 to 2:3 ethyl acetate:hexanes; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.24 (s, 1H), 8.22 (s, 1H), 7.95 – 7.92 (m, 2H), 7.87 – 7.84 (m, 2H), 7.30 – 7.27 (m, 2H), 7.24 – 7.21 (m, 2H), 6.63 (t, *J* = 6.8 Hz, 1H), 5.71 – 5.67 (m, 1H), 4.68 – 4.57 (m, 3H), 2.80 (qd, *J* = 7.9, 4.3 Hz, 2H), 2.70 (d, *J* = 0.7 Hz, 3H), 2.43 (d, *J* = 5.2 Hz, 3H), 2.40 (s, 3H), 2.08 – 1.94 (m, 8H), 1.77 – 1.66 (m, 6H), 1.52 (qd, *J* = 13.1, 3.9 Hz, 4H), 1.18 (tdd, *J* = 12.5, 8.1, 4.4 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 180.31, 166.26, 165.93, 144.80, 144.33, 143.50, 141.74, 139.46, 137.95, 137.21, 129.88, 129.76, 129.48, 126.65, 126.36, 117.80, 85.41, 82.82, 74.62, 63.96, 52.13, 39.54, 30.41, 29.99, 25.90, 22.61, 21.87, 21.78, 15.83; HRMS (ESI-TOF) calcd for $C_{42}H_{46}N_4O_7Na$ $(M+Na)^+$ 741.3264, found $(M+Na)^+$ 741.3242.

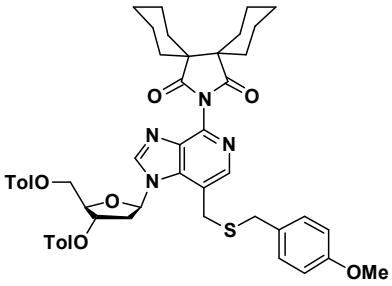


Compound S11. HRMS (DART) calc for $C_{39}H_{42}N_5O_6S$ $(M+H)^+$ 708.2850, found 708.2859.



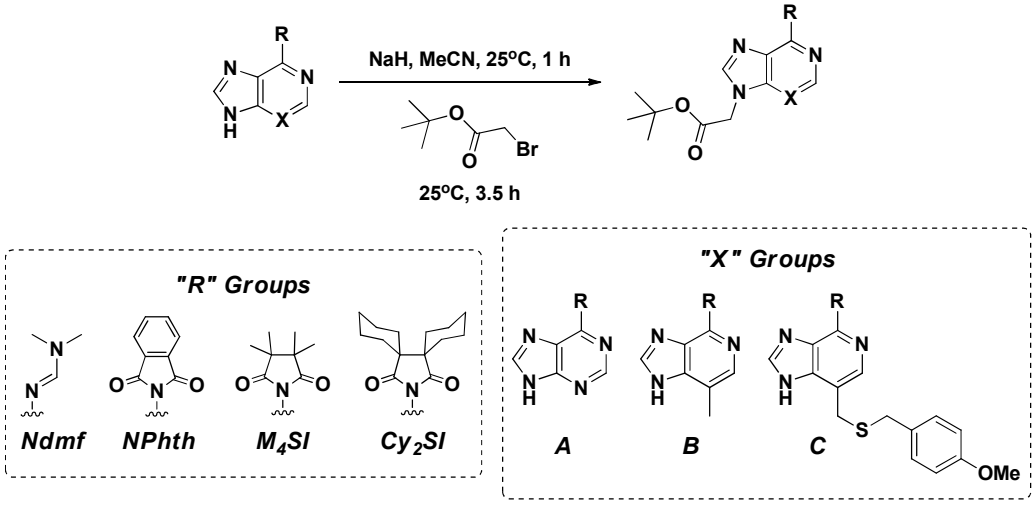
Compound S12. ^{1}H NMR (500 MHz, d_6-acetone) δ (ppm) 8.57 (s, 1H), 8.22 (s, 1H), 8.03 (d, *J* = 8.2 Hz, 2H), 7.87 (d, *J* = 8.2 Hz, 2H), 7.36 – 7.33 (m, 2H), 7.29 – 7.27 (m, 2H), 7.25 (d, *J* = 8.7 Hz, 2H), 6.88 – 6.84 (m, 3H), 5.83 (dt, *J* = 6.3, 3.0 Hz, 1H), 4.61 (s, 3H), 4.39 (d, *J* = 13.3 Hz, 1H), 4.07 (d, *J* = 13.2 Hz, 1H), 3.82 (d, *J* = 3.4 Hz, 2H), 3.80 – 3.77 (m, 1H), 3.76 (s, 2H), 3.22 (ddd, *J* = 14.2, 7.7, 6.5 Hz, 1H), 3.02 (ddd, *J* = 14.1, 5.7, 3.3 Hz, 1H), 2.42 (s, 3H), 2.38 (s, 3H), 1.34 (s, 12H); ^{13}C NMR (126 MHz, d_6-acetone) δ (ppm) 181.76, 181.65, 166.47, 166.32, 159.82, 145.21, 144.76, 144.00, 143.81, 139.84, 139.78, 138.98, 130.99,

130.65, 130.59, 130.38, 130.14, 130.10, 127.98, 127.86, 120.38, 114.77, 86.57, 83.26, 75.27, 64.72, 55.52, 48.48, 38.35, 36.54, 30.68, 21.67, 21.62, 21.58; HRMS (ESI-TOF) calcd for $C_{44}H_{46}N_4O_8SNa$ $(M+Na)^+$ 813.2934, found $(M+Na)^+$ 813.2943.



Compound S13. R_f = 2.26 (silica gel, 1:3 ethyl acetate:hexanes); Purified by gradient column chromatography ranging from 1:5 to 3.2:10 ethyl acetate:hexanes; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.20 (d, *J* = 6.2 Hz, 1H), 8.16 (s, 1H), 7.99 - 7.95 (m, 2H), 7.86 - 7.83 (m, 2H), 7.28 - 7.24 (m, 2H), 7.24 - 7.20 (m, 4H), 6.85 - 6.82 (m, 2H), 6.74 (t, *J* = 6.6 Hz, 1H), 5.69 - 5.65 (m, 1H), 4.61 - 4.53 (m, 2H), 4.50 (dd, *J* = 7.2, 3.9 Hz, 1H), 4.16 (d, *J* = 13.7 Hz, 1H), 3.80 (m, 1H), 3.78 (s, 3H), 3.64 (d, *J* = 1.8 Hz, 2H), 2.82 - 2.76 (m, 2H), 2.44 (s, 3H), 2.40 (s, 3H), 2.03 (dd, *J* = 18.2, 8.0 Hz, 8H), 1.73 (dd, J = 32.1, 12.4 Hz, 6H), 1.56 – 1.48 (m, 4H), 1.22 - 1.17 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 180.25, 166.26, 165.97, 159.00, 144.75, 144.30, 143.52, 142.02, 139.32, 139.16, 137.92, 130.27, 130.01, 129.78, 129.48, 129.27, 126.73, 126.43, 118.77, 114.22, 85.68, 82.52, 74.29, 63.91, 55.42, 52.24, 38.68, 35.43, 30.50, 30.02, 29.94, 25.91, 22.64, 21.89, 21.82; HRMS (ESI-TOF) calcd for $C_{50}H_{54}N_4O_8SNa$ $(M+Na)^+$ 893.3560, found $(M+Na)^+$ 893.3564.

3) Alkylation reactions



Purine Substrate	R =	X =	Product Number
	Ndmf	A	**S14**
6	Cy_2SI	A	**S15**
S4	Ndmf	B	**S16**
7	Cy_2SI	B	**S17**
S8	Ndmf	C	**S18**
S3	Cy_2SI	C	**S19**

General procedure for alkylation: To a flask containing the protected nucleobase and NaH (1.1 eq.), MeCN (0.02 M solution) was added and stirred for 1 hour at room temperature. Then *tert*-butyl bromoacetate (1.1 eq.) was added to the mixture and stirred for an additional 3.5 hours at room temperature. The resulting cloudy solution was filtered through celite and rinsed with acetone. The filtrated was concentrated in vacuo and purified by column chromatography. Regioselectivity was determined on an NMR of the crude products and HMBC (2-3 bond ^{1}H-^{13}C correlation) was subsequently used to determine the structures after purification (Figures S3 and S4).

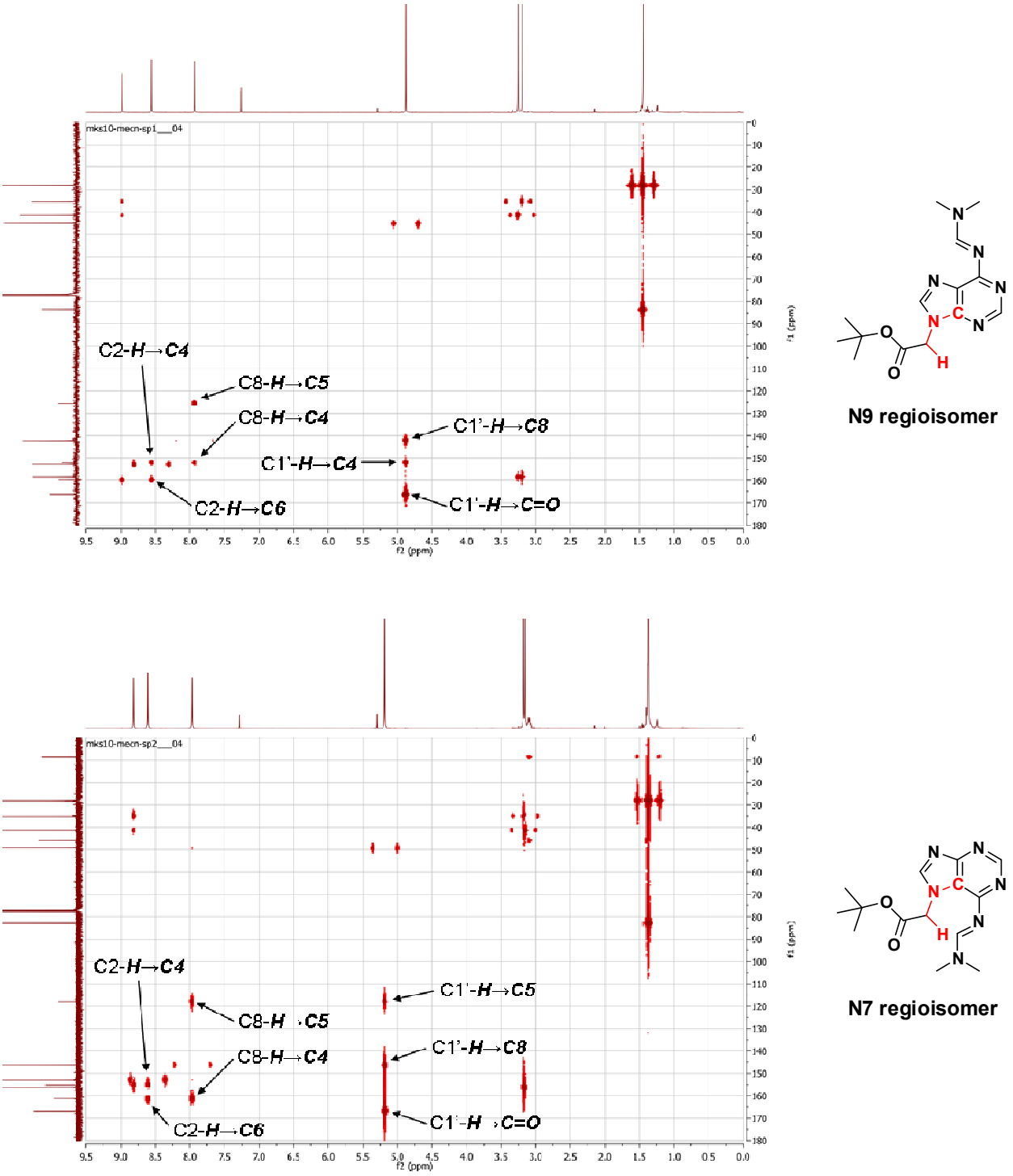


Figure S3. HMBC spectrum for compounds **S14-N9** (top) and **S14-N7** (bottom) with the relevant crosspeaks noted. The presence of a crosspeak between the C1'-H with C4 (highlighted in red on the structures) indicates that compound **S14-N9** is the desired N9 regioisomer while the crosspeak between C1'-H and C5 indicates that compound **S14-N7** is the N7 regioisomer.

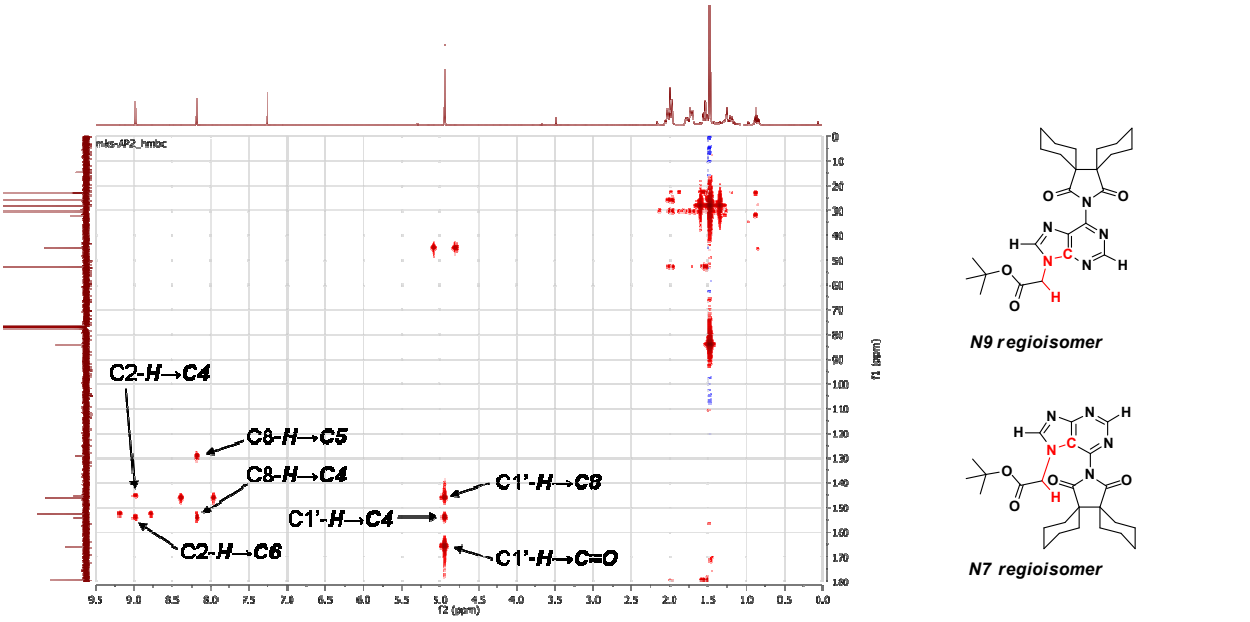
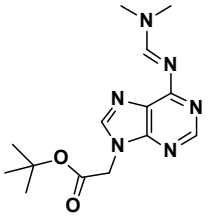
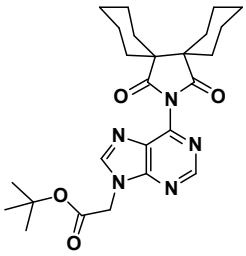


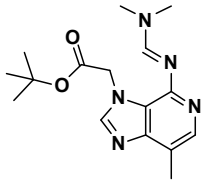
Figure S4. HMBC spectrum for compound **S15** with the relevant crosspeaks noted. The presence of a crosspeak between the C1'-H with C4 (highlighted in red on the structures) indicates that compound **S15** is the desired N9 regioisomer.



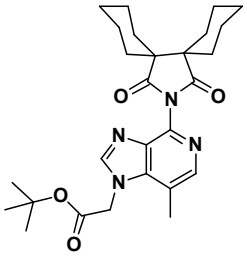
Compound S14. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.98 (s, 1H), 8.55 (s, 1H), 7.94 (s, 1H), 4.88 (s, 2H), 3.25 (s, 3H), 3.20 (s, 3H), 1.45 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 166.23, 159.68, 158.46, 152.81, 152.01, 142.23, 125.45, 83.56, 45.04, 41.41, 35.27, 28.11; HRMS (DART) calc for $C_{14}H_{21}N_6O_2$ $(M+H)^+$ 305.1721, found 305.1713.



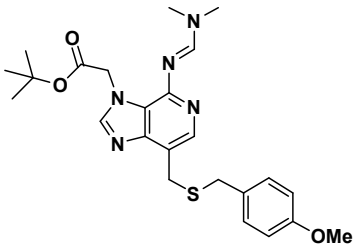
Compound S15. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.98 (s, 1H), 8.17 (s, 1H), 4.94 (s, 2H), 2.07 – 1.96 (m, 8H), 1.81 – 1.68 (m, 6H), 1.58 – 1.49 (m, 4H), 1.47 (s, 9H), 1.28 – 1. 16 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 179.14, 165.58, 154.04, 152.74, 146.16, 145.25, 129.12, 84.10, 52.63, 45.19, 30.04, 28.12, 25.82, 22.54; HRMS (DART-TOF) calcd for $C_{25}H_{34}N_5O_4$ $(M+H)^+$ 468.2605, found $(M+H)^+$ 468.2613.



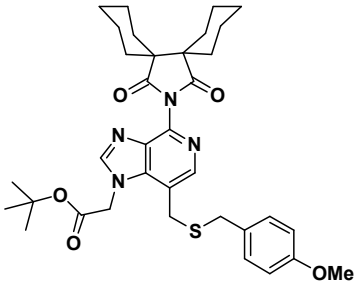
Compound S16 (analytical data for the N7 regioisomer). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.58 (s, 1H), 7.84 (s, 1H), 7.78 (s, 1H), 5.27 (s, 2H), 3.11 (s, 3H), 3.10 (s, 3H), 2.52 (s, 3H), 1.37 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 167.43, 154.63, 149.83, 148.18, 145.31, 138.74, 123.78, 119.69, 82.56, 49.02, 40.80, 34.90, 28.05, 13.61; HRMS (DART) calc for $C_{16}H_{24}N_5O_2$ $(M+H)^+$ 318.1925, found 318.1943.



Compound S17. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.16 (s, 1H), 7.81 (s, 1H), 4.92 (s, 2H), 2.57 (s, 3H), 2.08 – 1.96 (m, 8H), 1.72 (ddt, J = 32.1, 13.5, 3.8 Hz, 6H), 1.52 (td, J = 13.3, 4.3 Hz, 4H), 1.46 (s, 9H), 1.19 (dddd, J = 16.5, 12.6, 8.8, 3.8 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 180.31, 166.39, 146.11, 143.08, 139.96, 138.01, 137.14, 117.57, 84.05, 52.08, 48.50, 30.25, 28.07, 25.93, 22.64, 14.94; HRMS (DART-TOF) calcd for $C_{27}H_{37}N_4O_4$ $(M+H)^+$ 481.2809, found $(M+H)^+$ 481.2816.

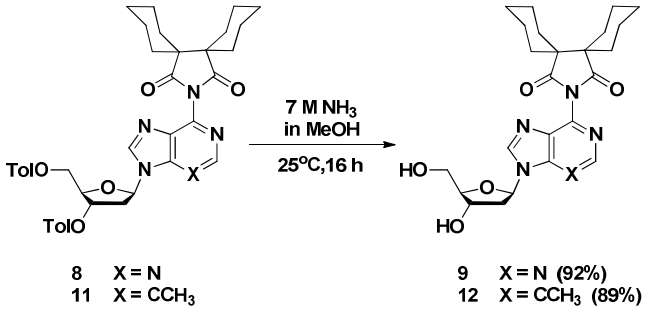


Compound S18 (analytical data for the N7 regioisomer). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.59 (s, 1H), 7.87 (s, 1H), 7.85 (s, 1H), 7.27 (m, 2H), 6.83 (m, 2H), 5.29 (s, 2H), 3.95 (s, 2H), 3.79 (s, 3H), 3.66 (s, 2H), 3.13 (s, 3H), 3.12 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) 167.42, 158.63, 154.71, 149.34, 149.05, 145.47, 139.82, 130.59, 130.28, 124.33, 120.12, 113.97, 82.58, 55.41, 49.03, 40.85, 35.56, 34.97, 28.89, 28.09; HRMS (DART) calc for $C_{24}H_{32}N_5O_3S$ $(M+H)^+$ 470.2220, found 470.2229.

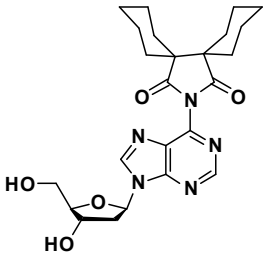


Compound S19. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.11 (s, 1H), 7.85 (s, 1H), 7.25 – 7.20 (m, 2H), 6.89 – 6.81 (m, 2H), 5.10 (s, 2H), 3.80 (d, *J* = 3.1 Hz, 4H), 3.62 (s, 3H), 2.11 – 1.95 (m, 8H), 1.80 – 1.67 (m, 6H), 1.59 – 1.46 (m, 4H), 1.42 (s, 9H), 1.23 (d, *J* = 18.5 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 180.23, 168.94, 166.73, 158.99, 143.01, 139.40, 130.23, 129.07, 118.42, 118.15, 114.25, 83.96, 52.16, 49.02, 35.27, 30.23, 29.86, 29.56, 28.26, 28.07, 25.91, 22.64; HRMS (DART-TOF) calcd for $C_{35}H_{45}N_4O_5S$ $(M+H)^+$ 633.3105, found $(M+H)^+$ 633.3068.

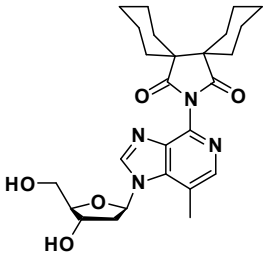
4) Removal of protecting groups after glycosylation



General Procedure for selective removal of toluoyl esters: To a flask containing the nucleoside was added 7 M NH_3 in methanol (0.05 M solution) and the solution stirred at room temperature for 16 hours. The solvent was then removed *in vacuo* and the resulting crude residue was purified by flash column chromatography.

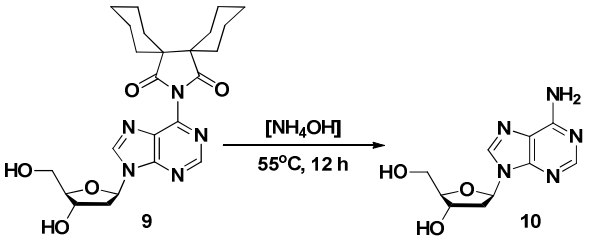


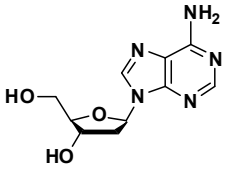
Compound 9. ^{1}H NMR (500 MHz, CD_3OD) δ (ppm) 8.93 (s, 1H), 8.75 (s, 1H), 6.59 (t, *J* = 6.6 Hz, 1H), 4.64 - 4.60 (m, 1H), 4.06 (q, *J* = 3.6 Hz, 1H), 3.83 (dd, *J* = 12.1, 3.5 Hz, 1H), 3.76 (dd, *J* = 12.1, 4.1 Hz, 1H), 2.91 - 2.85 (m, 1H), 2.52 (ddd, *J* = 13.6, 6.4, 3.8 Hz, 1H), 2.01 - 1.91 (m, 8H), 1.72 (dd, *J* = 21.1, 9.7 Hz, 6H), 1.58 (dd, *J* = 20.3, 7.6 Hz, 4H), 1.30 - 1.22 (m, 2H); ^{13}C NMR (101 MHz, CD_3OD) δ (ppm) 179.19, 153.20, 151.69, 144.58, 143.02, 130.36, 88.20, 85.21, 71.05, 61.69, 52.25, 39.90, 29.37, 25.20, 22.07; HRMS (DART-TOF) calcd for $C_{24}H_{32}N_5O_5$ $(M+H)^+$ 470.2398, found $(M+H)^+$ 470.2384.



Compound 12. ^{1}H NMR (500 MHz, CD_3OD) δ (ppm) 8.68 (s, 1H), 8.16 (s, 1H), 6.71 (t, *J* = 6.3 Hz, 1H), 4.58 (dt, *J* = 6.1, 4.3 Hz, 1H), 4.06 (q, *J* =

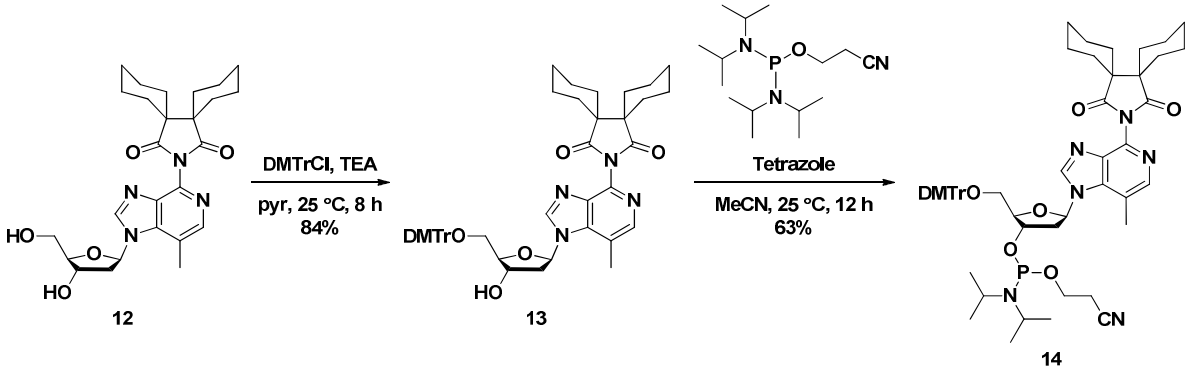
3.6 Hz, 1H), 3.73 (ddd, *J* = 33.6, 12.1, 3.7 Hz, 2H), 2.83 – 2.75 (m, 1H), 2.79 (s, 3H), 2.58 (ddd, *J* = 13.4, 6.0, 4.5 Hz, 1H), 2.16 – 1.92 (m, 8H), 1.72 (dd, *J* = 20.7, 9.2 Hz, 6H), 1.61 (t, *J* = 12.2 Hz, 4H), 1.33 – 1.24 (m, 2H); ^{13}C NMR (101 MHz, CD_3OD) δ (ppm) 180.46, 143.89, 141.74, 139.81, 136.61, 119.61, 87.93, 85.46, 70.59, 61.18, 51.65, 40.44, 29.54, 25.25, 22.13, 14.26; HRMS (DART-TOF) calcd for $C_{26}H_{35}N_4O_5$ $(M+H)^+$ 483.2602, found $(M+H)^+$ 483.2588.

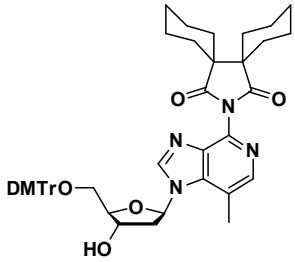




Compound 10. A solution of compound **9** (14 mg, 0.030 mol) in concentrated aqueous ammonium hydroxide (2.0 mL) was heated to 55 ºC for 12 hours. The solvent was then removed *in vacuo* and the obtained crude residue was purified via flash chromatography over silica gel using a gradient from 6→12% MeOH in DCM to obtain **10** as a white solid (6.3 mg, 84%). Analytical data matched that which was previously reported.[2]

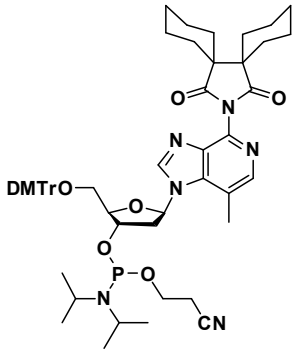
5) Phosphoramidite and oligonucleotide synthesis





Compound 13. To a flask containing compound **12** (35 mg, 0.073 mmol) dissolved in pyridine (0.8 mL) was added Et_3N (14 µL, 0.102 mmol), DMTr-Cl (30 mg, 0.087 mmol), and DMAP (0.9 mg, 0.007 mmol). The reaction was allowed to stir at room temperature for five hours. TLC analysis indicated that some starting material remained, therefore an additional portion of DMTr-Cl (5 mg, 0.015 mmol) was added. TLC after another eight hours indicated complete consumption of starting material at which point all volatiles were removed *in vacuo*. The solid residue was then purified by flash chromatography eluting with 1:50 MeOH:DCM containing 1% TEA to afford compound **13** as a white foam (48 mg, 84%): R_f = 0.23 (silica gel, 1:50 MeOH:DCM); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.16 (s, 1H), 8.11 (s, 1H), 7.41 - 7.35 (m, 2H), 7.30 - 7.18 (m, 7H), 6.81 (dd, J = 8.9, 1.6 Hz, 4H), 6.47 (t, *J* = 6.3 Hz, 1H), 4.51 (dd, *J* = 9.5, 4.3 Hz, 1H), 4.08 (dd, *J* = 8.7, 4.4 Hz, 1H), 3.78 (s, 6H), 3.38 (dd, *J* = 10.2, 4.4 Hz, 1H), 3.28 (dd, *J* = 10.2, 5.1 Hz, 1H), 2.63 (s, 3H), 2.49 (tdd, *J* = 13.1, 11.7, 6.0 Hz, 2H), 2.13 - 1.93 (m, 8H), 1.77 - 1.63 (m, 6H), 1.56 - 1.46 (m, 4H), 1.38 (dd, *J* = 13.9, 6.8 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 180.31, 158.65, 144.42, 143.05, 142.00, 139.33, 137.61, 137.18, 135.52, 135.42, 130.03, 129.98, 128.03, 127.98, 127.01, 117.98, 113.29, 86.75, 85.74, 84.90, 72.18,

63.67, 55.24, 51.99, 41.35, 30.27, 29.93, 25.78, 22.50, 15.73; HRMS (ESI-TOF) calcd for $C_{47}H_{53}N_4O_7$ $(M+H)^+$ 785.3909, found $(M+H)^+$ 785.3941.



Phosphoramidite 14. To a flask containing compound **13** (35 mg, 0.045 mmol) dissolved in MeCN (0.9 mL) was added tetrazole (3 mg, 0.045 mmol) followed by 2-cyanoethyl *N*,*N*,*N'*,*N'*-tetraisopropylphosphordiamidite (30 µL, 0.089 mmol) dropwise. The mixture was allowed to stir at room temperature for 6 hours. Water (0.1 mL) was then added and stirring continued for 10 minutes. The reaction mixture was then diluted with DCM (5 mL) and washed with saturated aq. $NaHCO_3$ (2×2 mL) and brine (1×2 mL). The organic layer was separated and dried with Na_2SO_4, filtered, and dried *in vacuo*. The crude residue was dissolved in DCM (0.2 mL) and hexanes (2 mL) was added to precipitate the desired product. After removing the liquid phase, this process of reverse precipitation was carried out four more times. The resulting white residue was purified further by short flash column chromatography (silica gel washed with 1% TEA in 0.5:9.5 MeOH:DCM) eluting with 0.5:100 MeOH:DCM to afford phosphoramidite **14** as a white foam (28 mg, 63%): R_f = 0.29 (silica gel, 1:50 MeOH:DCM); ^{31}P NMR (202 MHz, $CDCl_3$) δ (ppm) 149.48, 149.07; HRMS (ESI-TOF) calcd for $C_{56}H_{70}N_6O_8P$ $(M+H)^+$ 985.4987, found $(M+H)^+$ 985.4982.

DNA oligonucleotide synthesis. DNA oligonucleotides were prepared on an ABI 394 DNA/RNA synthesizer on a 1 µmole scale. DNA phosphoramidites (A^{Bz}, G^{iPr}, C^{Bz}, T, and **14**) were used at a concentration of 100 mM with a standard protocol for 2-cyanoethyl phosphoramidites, except that the coupling time of phosphoramidite **14** was extended to five minutes. During the synthesis, trityl monitoring indicated that phosphoramidite **14** was

incorporated with greater than 80% efficiency. After the "Trityl ON" synthesis, the resin was incubated with [NH_4OH] at 55 ºC overnight. The next morning, the solution was cooled to room temperature and partially concentrated to remove most of the solvent. The crude oligonucleotide solutions were then purified using C_{18} Sep-Pak columns according to previously reported procedures[3,4] and lyophilized to dryness. MALDI-TOF MS analysis (using 2',4',6'-trihydroacetophenone in 1:1 MeCN:H_2O as the matrix) indicated exclusively the desired oligonucleotides, but with all Cy_2SI protecting groups remaining. Portions of the oligonucleotides were then subjected further to a solution of [NH_4OH] at 55 ºC overnight, a solution of 7 M NH_3 in MeOH at 55 ºC overnight, or a solution of AMA (1:1 mixture of [NH_4OH] and 40% aqueous methylamine) in an unsuccessful attempt to remove the Cy_2SI protecting group from the two oligonucleotides.

Table S1. DNA oligonucleotides synthesized using phosphoramidite **14**.

		Molecular Weight (M^-)[b]		
	Sequence[a]	Calcd (no PGs)	Calcd (free of all PGs *except* Cy_2SI)	Obs.
DNA-1	5'-AAT CGT TGT TT**X** TCT-3'	4560	4778	4777
DNA-2	5'-A**X**T CGT TGT TT**X** TCT-3'	4573	5010	5009

a. The nucleotide "**X**" corresponds to that of 3-deaza-3-methyldeoxyadenosine after incorporation of phosphoramidite **14**. b. Determined using MALDI-TOF MS (negative mode) on the oligonucleotides after Sep-Pak purification.

6) Crystallographic data and structure refinement for compound 7

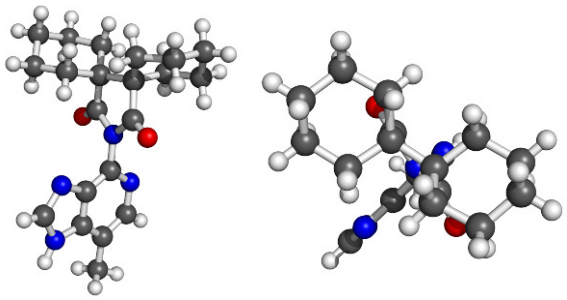


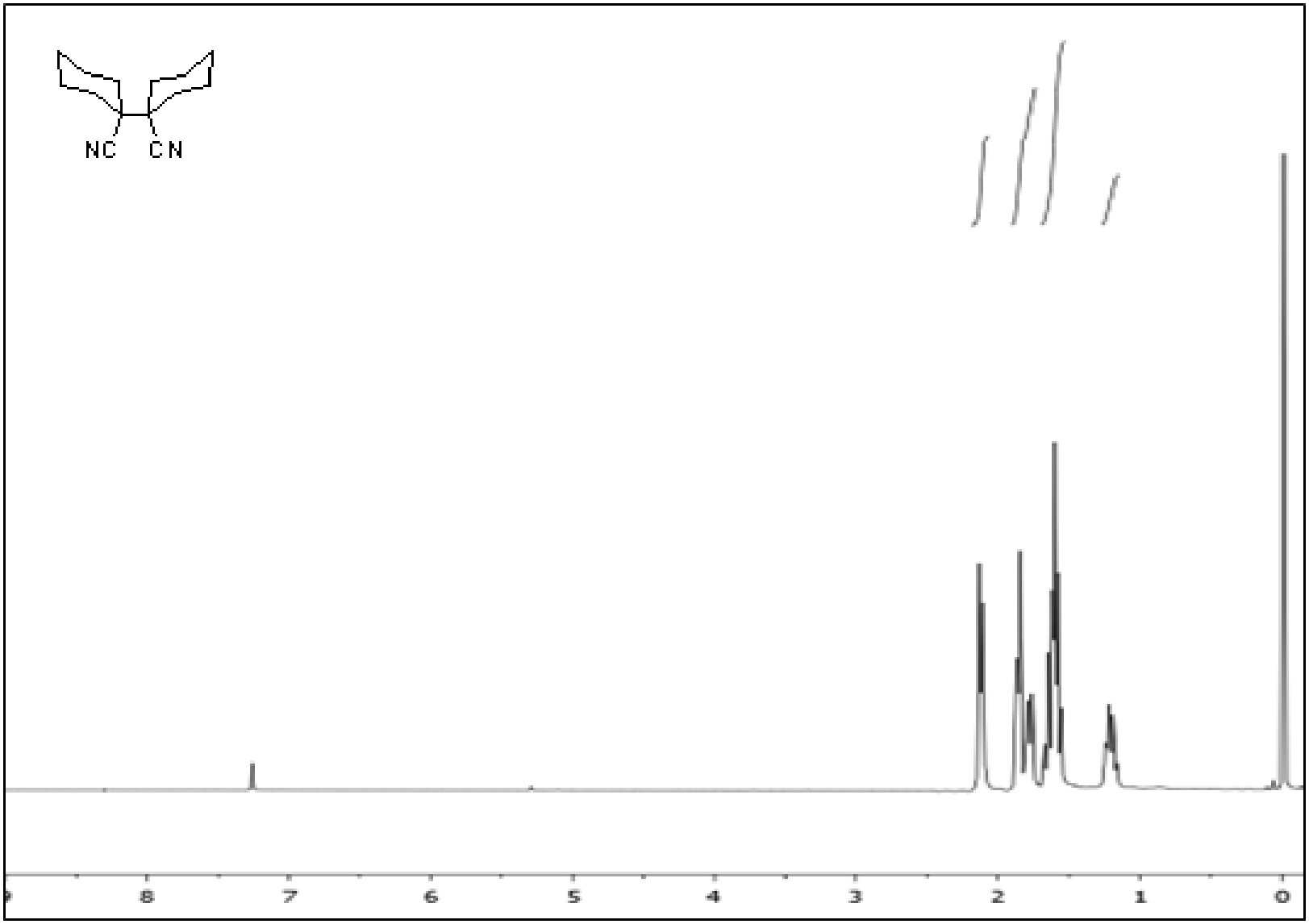
Figure S5. Crystal structure of Cy_2SI protected compound **7** determined via x-ray diffraction: side view (left) and top view (right).

Empirical formula	C29 H41 N4 O5	
Formula weight	525.66	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 1 2(1)/n 1	
Unit cell dimensions	a = 9.1585(13) Å	a= 90°.
	b = 28.601(4) Å	b= 92.664(7)°.
	c = 10.3611(15) Å	g = 90°.
Volume	2711.1(7) $Å^3$	
Z	4	
Density (calculated)	1.288 Mg/m^3	
Absorption coefficient	0.089 mm^{-1}	
F(000)	1132	
Crystal size	0.20 x 0.16 x 0.10 mm^3	
Theta range for data collection	2.09 to 28.43°.	
Index ranges	-12<=h<=12, -38<=k<=38, -13<=l<=13	
Reflections collected	72956	
Independent reflections	6812 [R(int) = 0.0291]	
Completeness to theta = 28.43°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9912 and 0.9825	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6812 / 0 / 354	
Goodness-of-fit on F^2	1.047	
Final R indices [I>2sigma(I)]	R1 = 0.0380, wR2 = 0.0937	
R indices (all data)	R1 = 0.0417, wR2 = 0.0961	
Extinction coefficient	na	
Largest diff. peak and hole	0.385 and -0.210 $e.Å^{-3}$	

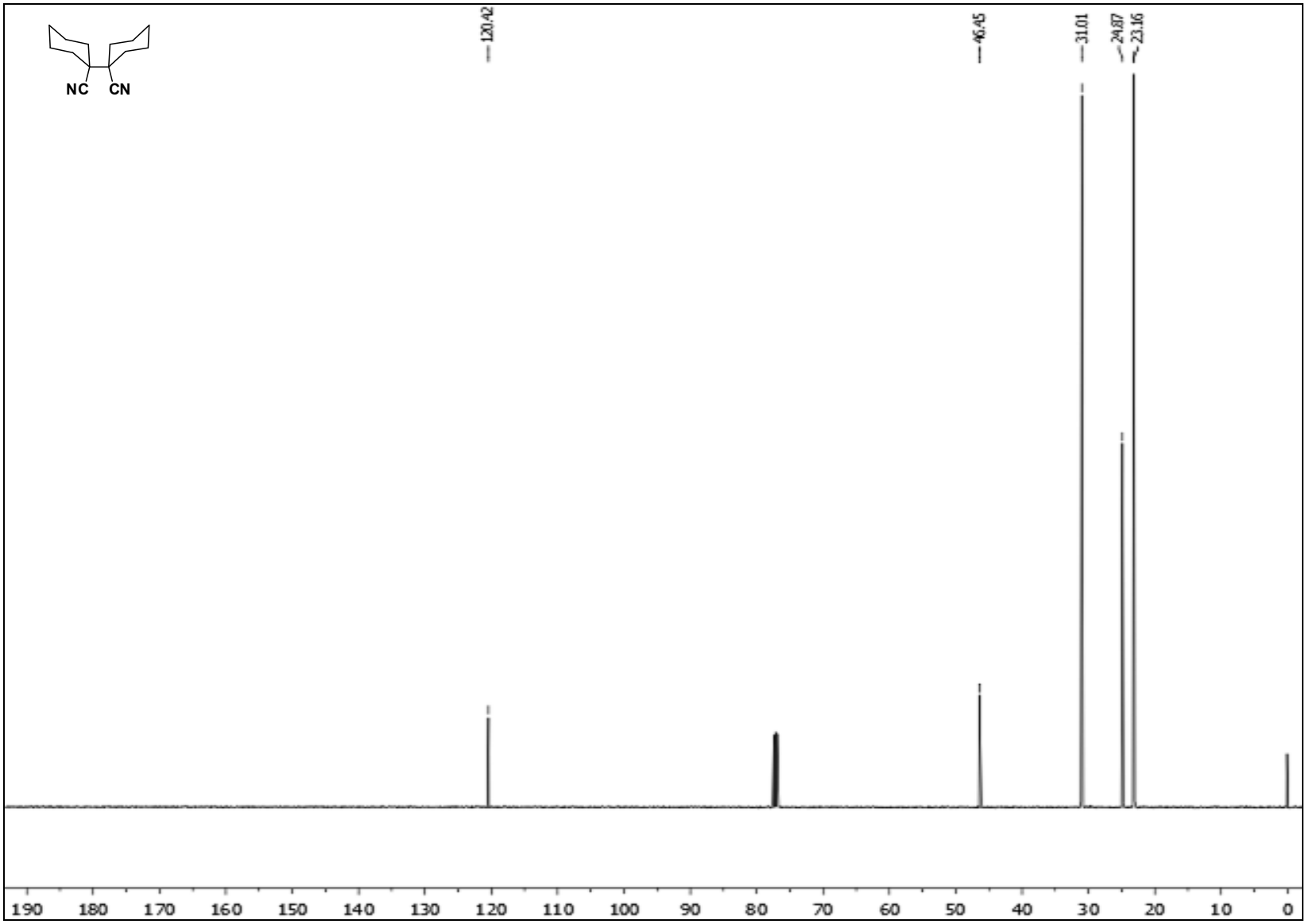
7) References

1. Arico, J. W.; Calhoun, A. K.; Salandria, K. J.; McLaughlin, L. W. *Org. Lett.* **2010**, 12, 120-122.
2. Ciuffreda, P.; Casati, S.; Manzocchi, A. *Magn. Reson. Chem.* **2007**, 45, 781-784.
3. Schlegel, M. K.; Meggers, E. *J. Org. Chem.* **2009**, 74, 4615-4618.
4. Schlegel, M. K.; Hütter, J.; Eriksson, M.; Lepenies, B.; Seeberger, P. H. *ChemBioChem* **2011**, 12, 2791-2800.

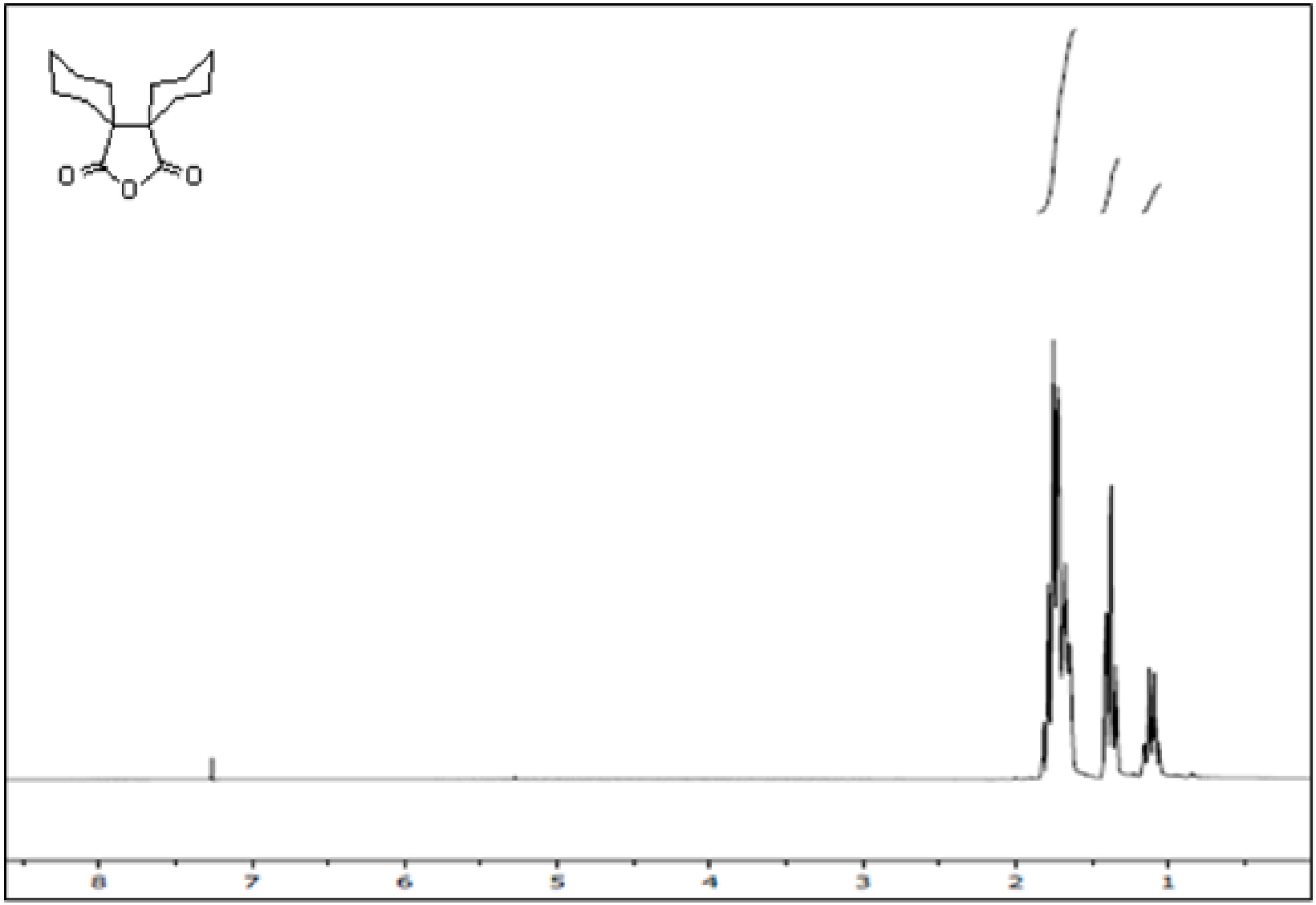
^{1}H NMR of compound **2** (500 MHz, $CDCl_3$)



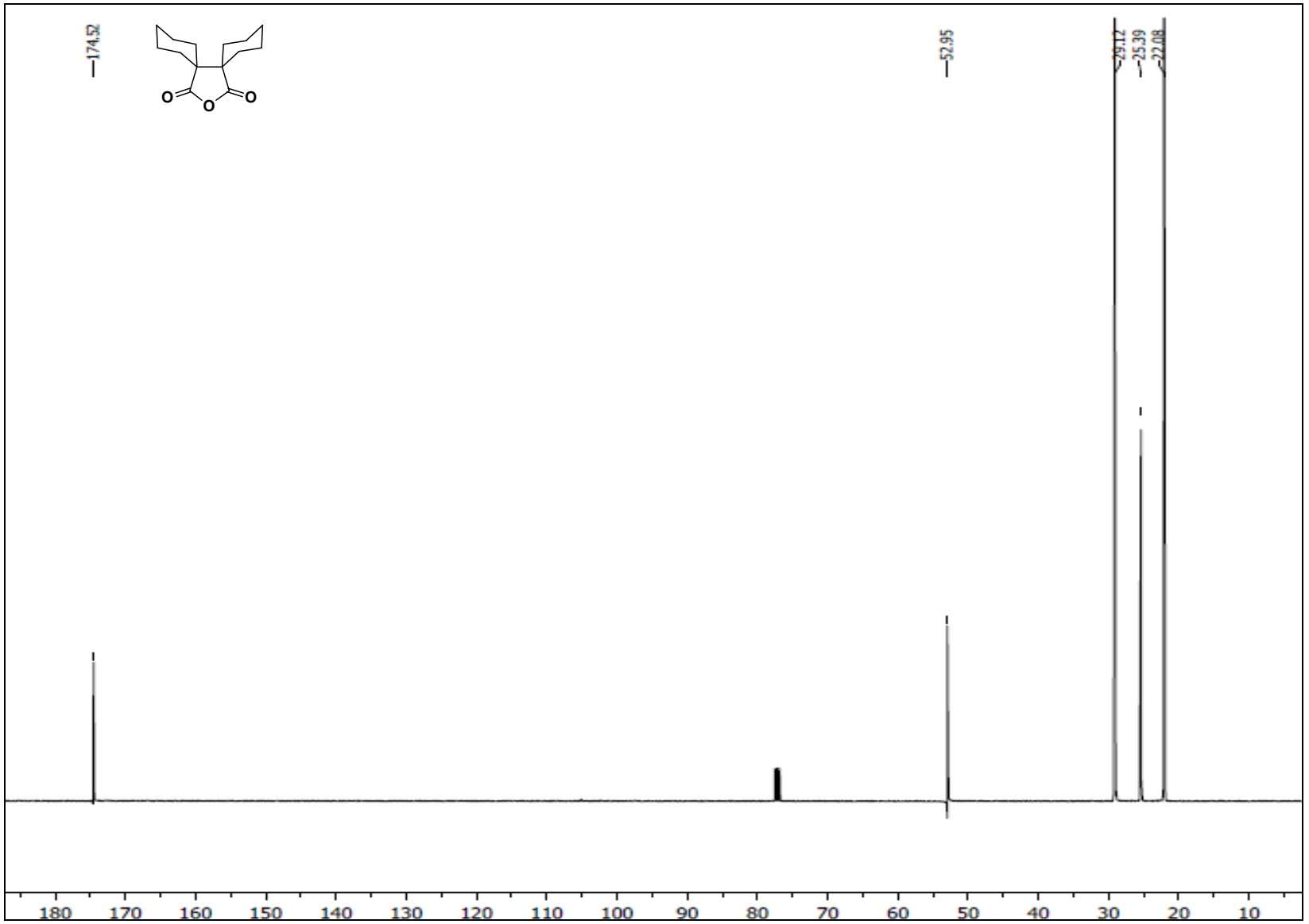
^{13}C NMR of compound **2** (126 MHz, $CDCl_3$)



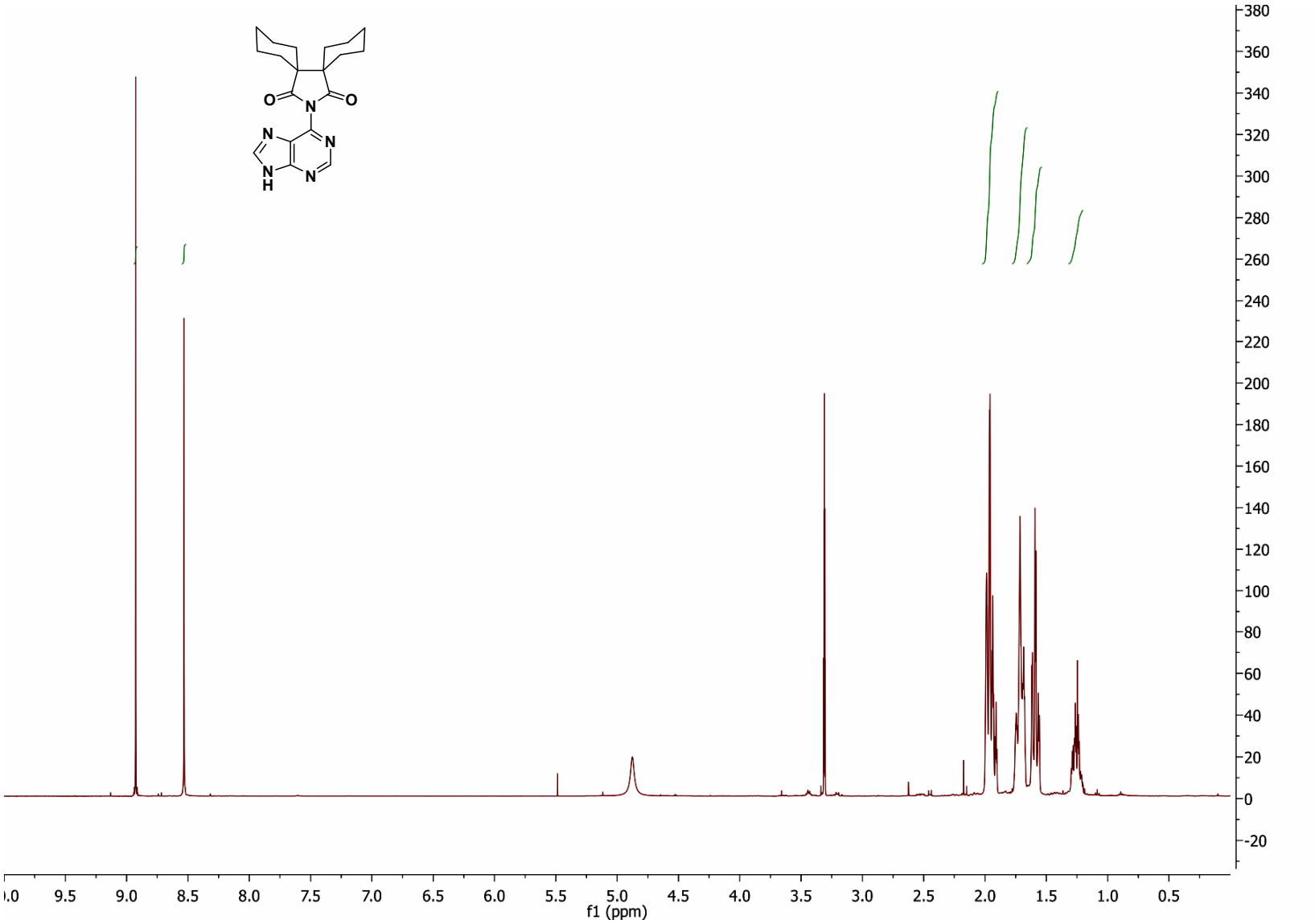
^{1}H NMR of compound **3** (400 MHz, $CDCl_3$)



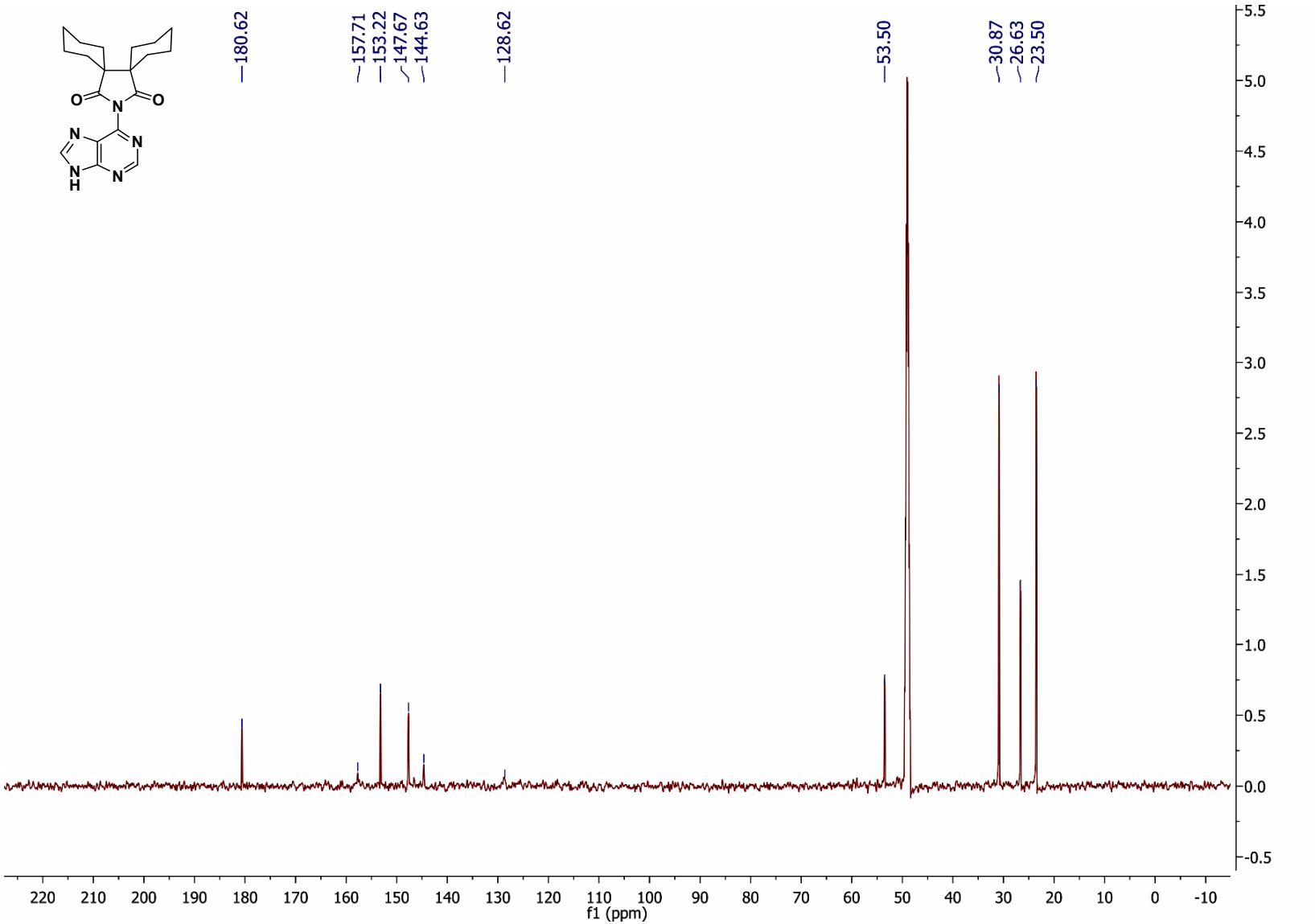
^{13}C NMR of compound **3** (101 MHz, $CDCl_3$)



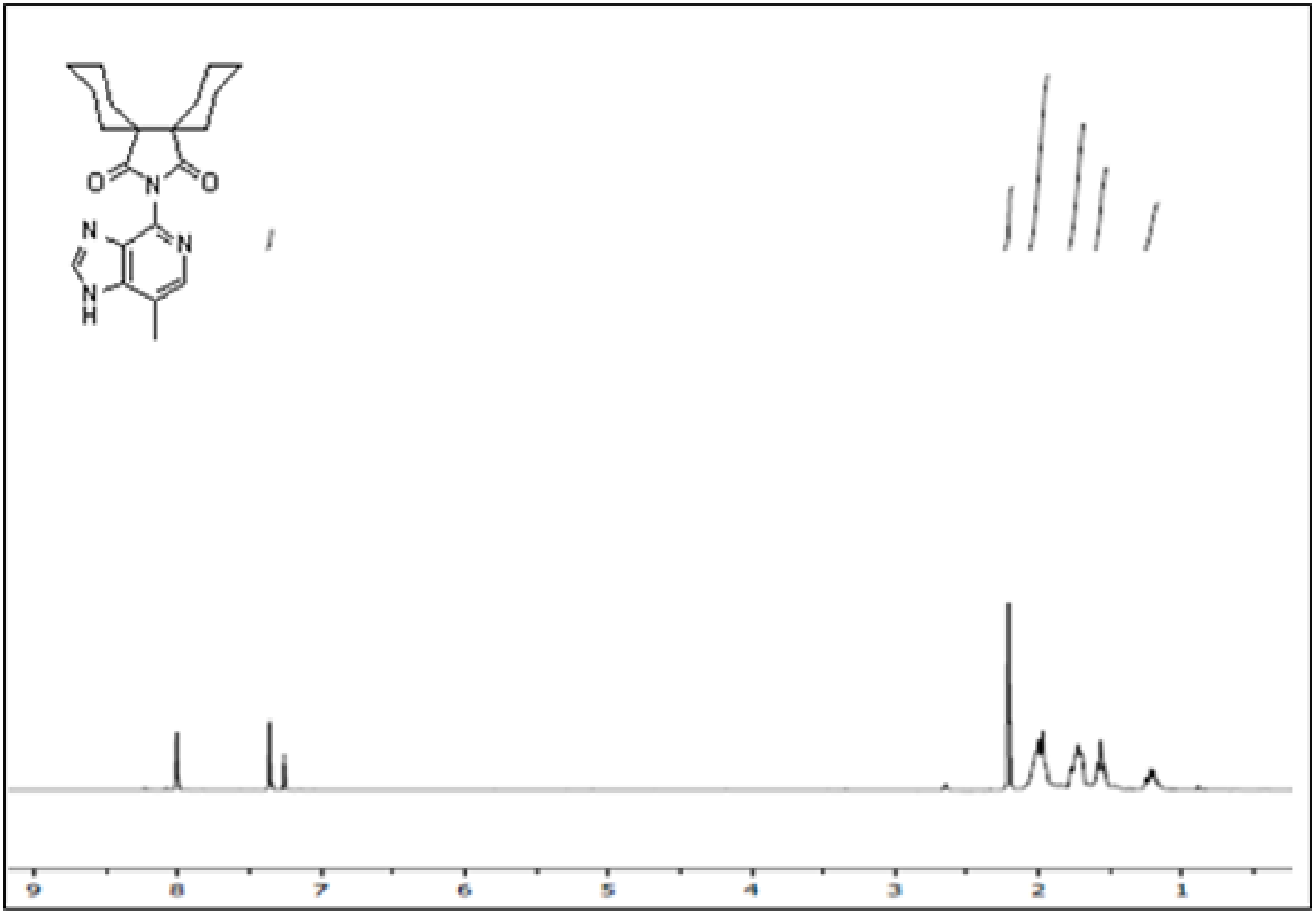
^{1}H NMR of compound **6** (500 MHz, CD_3OD)



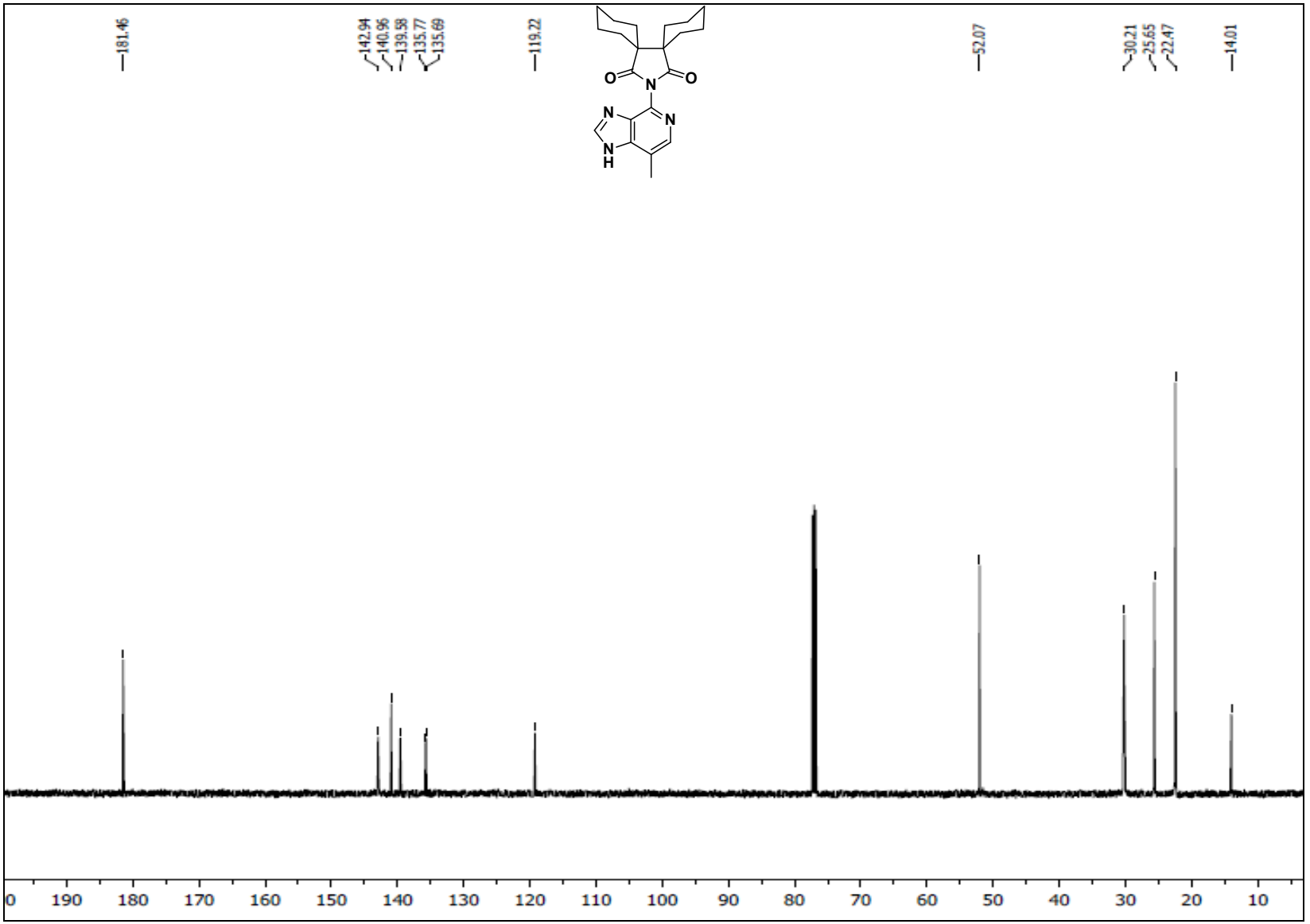
^{13}C NMR of compound **6** (126 MHz, CD_3OD)



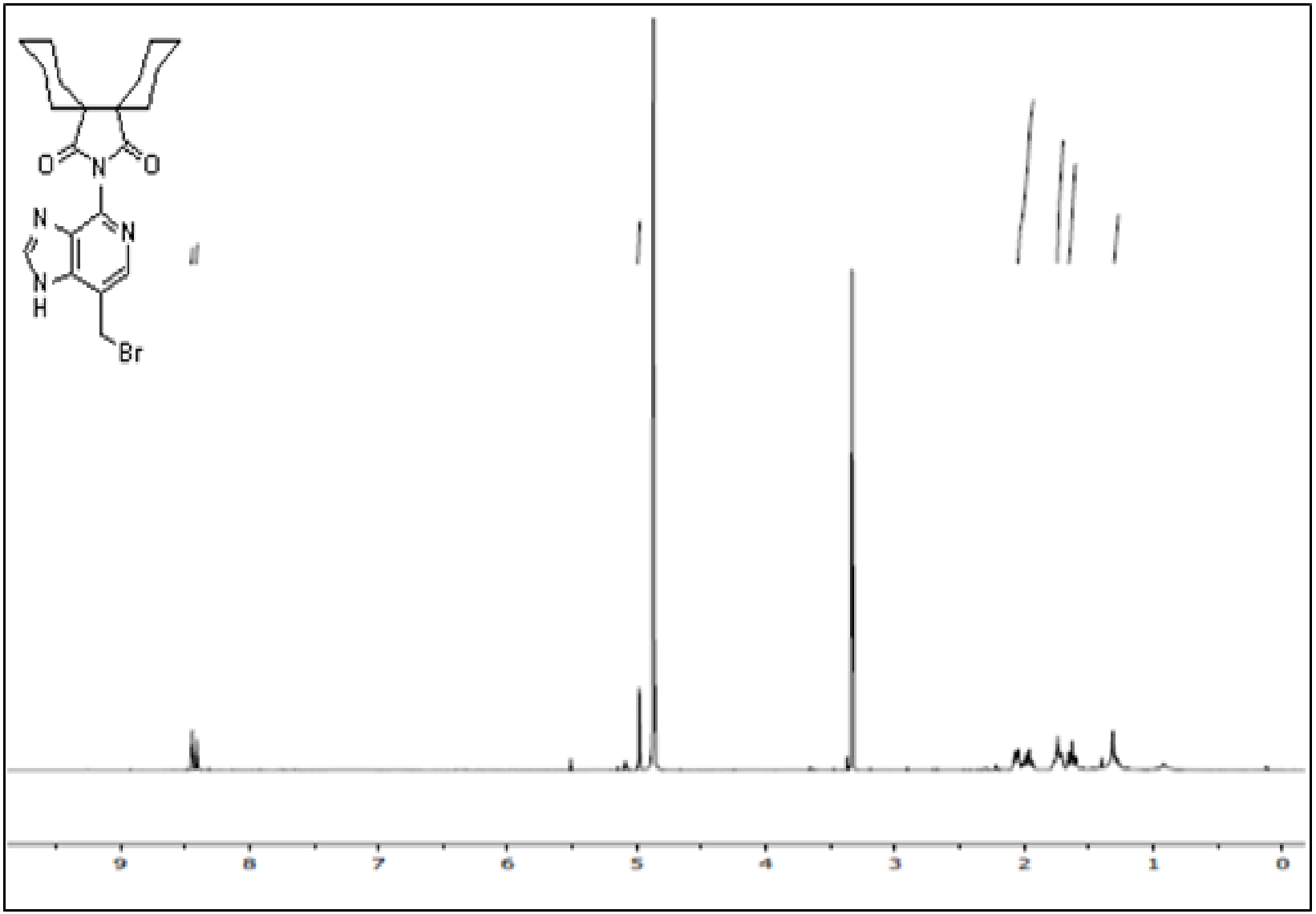
^{1}H NMR of compound **7** (500 MHz, $CDCl_3$)



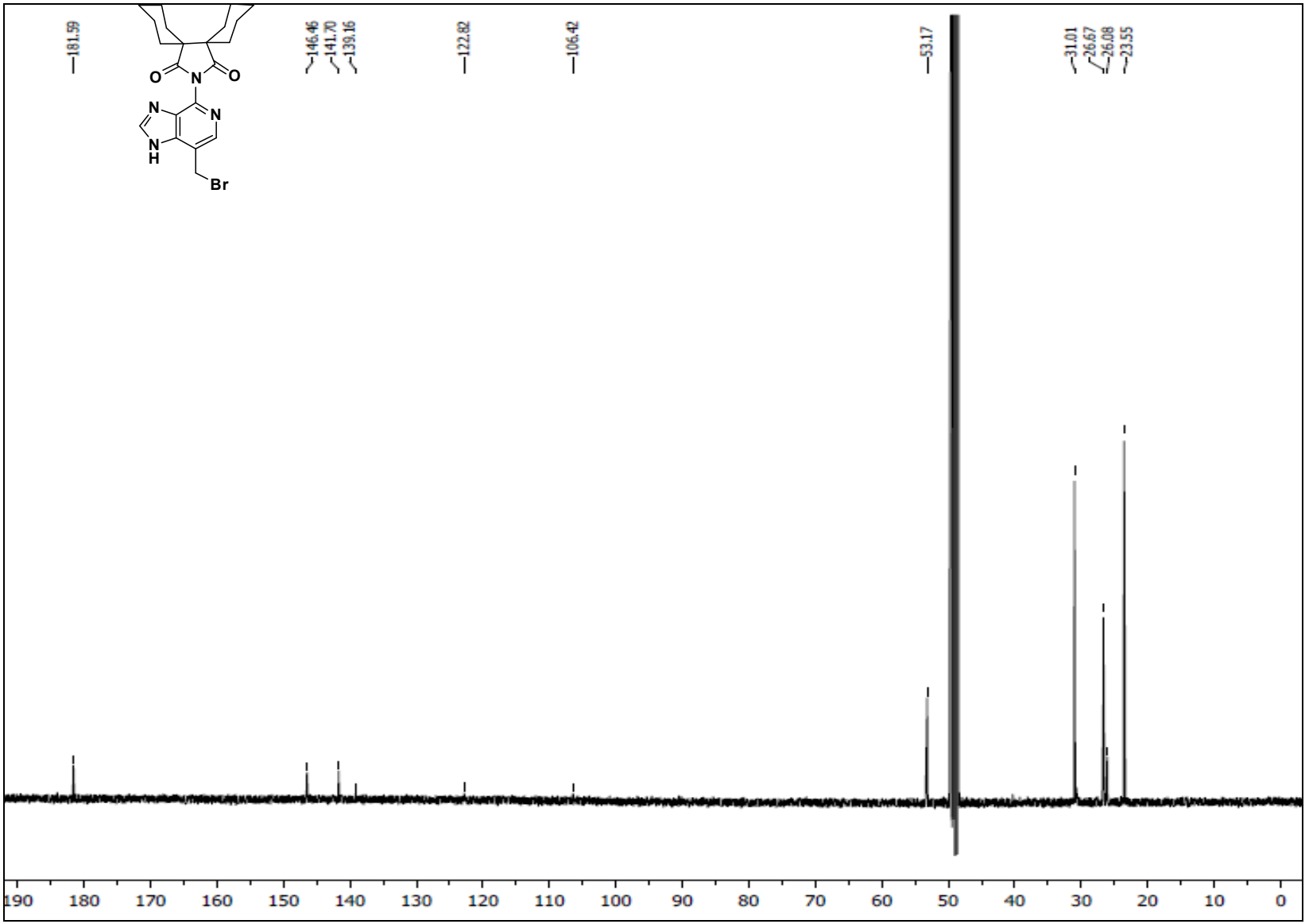
^{13}C NMR of compound **7** (126 MHz, $CDCl_3$)



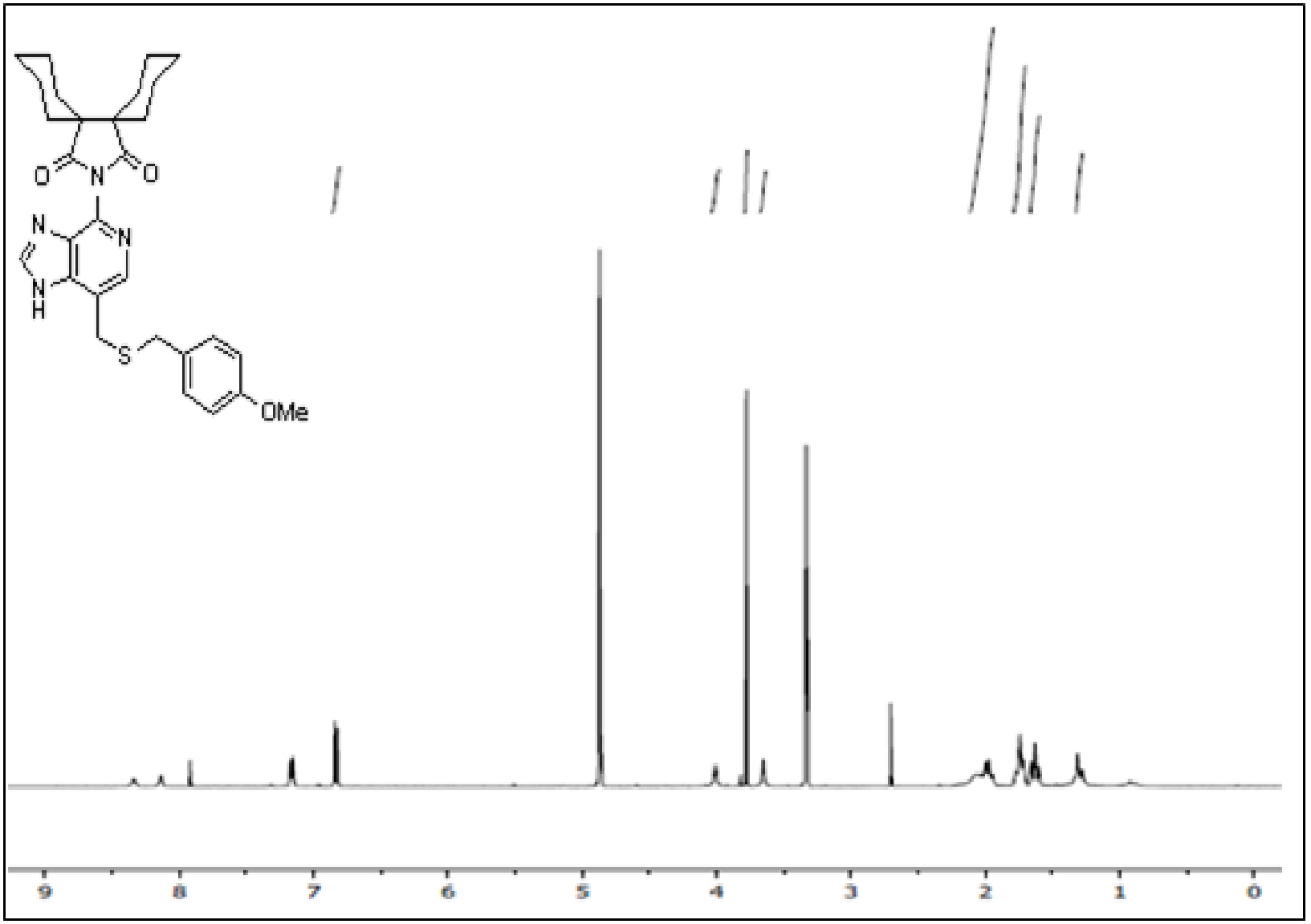
^{1}H NMR of compound **S1** (500 MHz, CD_3OD)



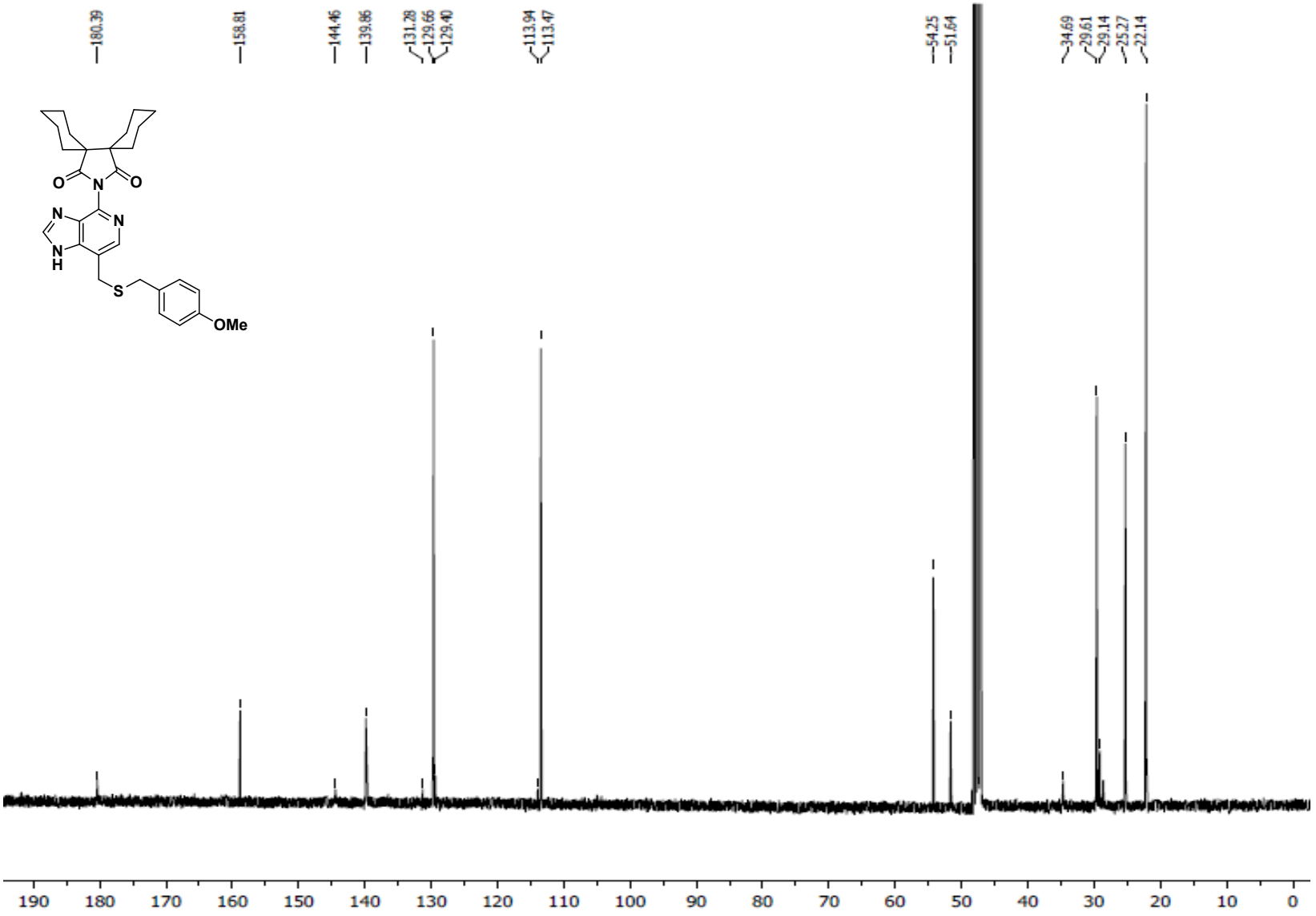
^{13}C NMR of compound **S1** (126 MHz, CD_3OD)



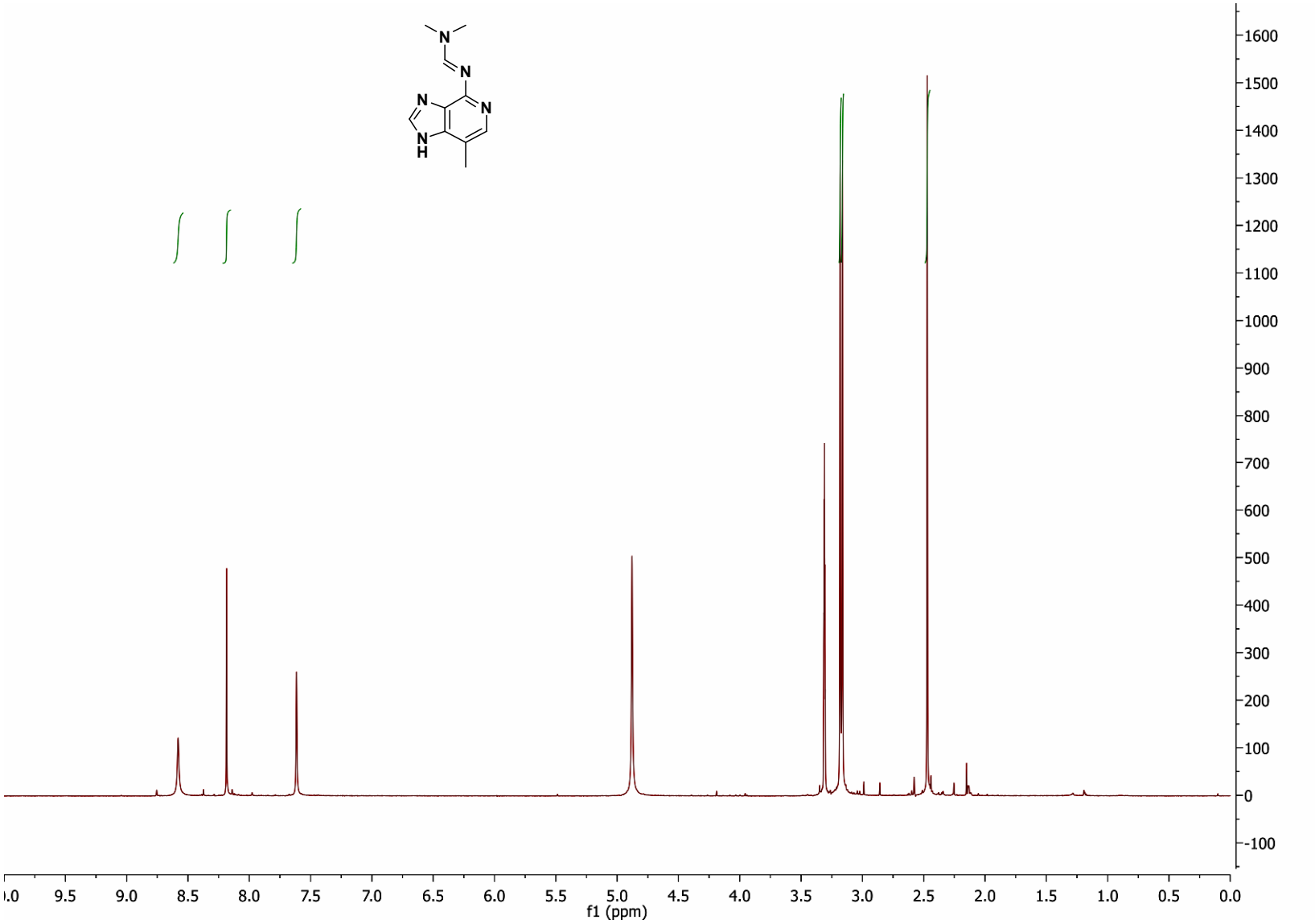
^{1}H NMR of compound **S3** (500 MHz, CD_3OD)



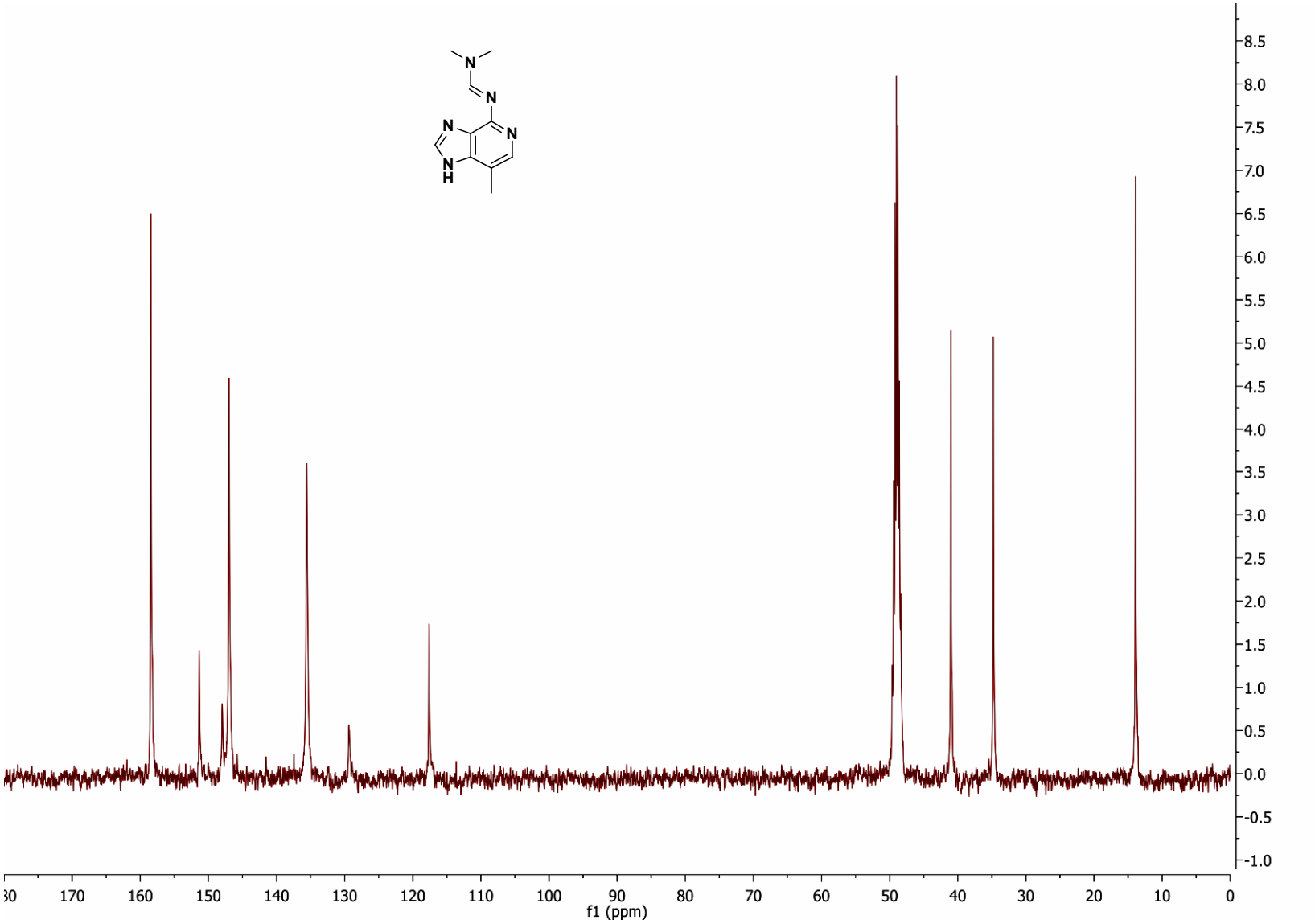
^{13}C NMR of compound **S3** (126 MHz, CD_3OD)



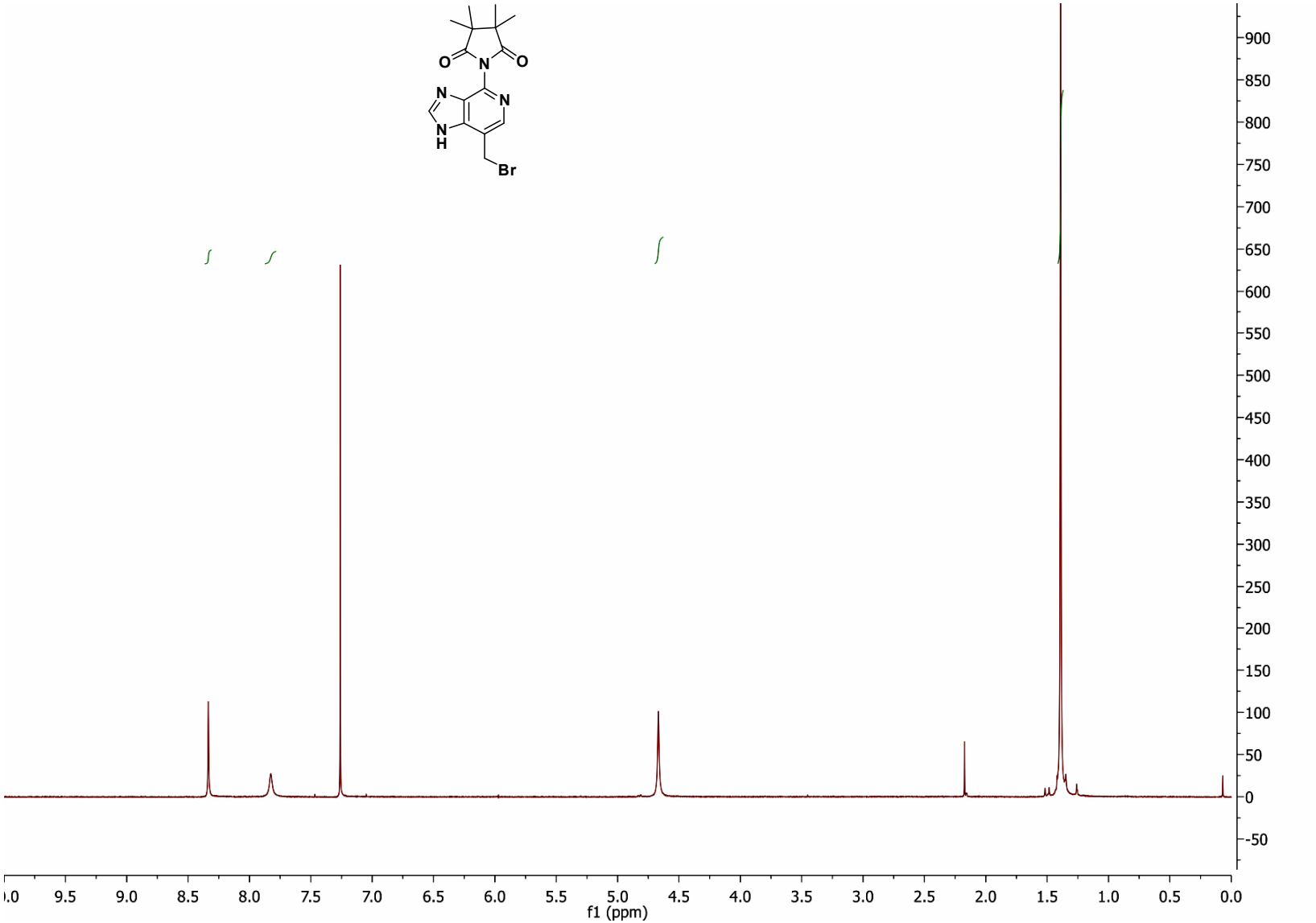
^{1}H NMR of compound **S4** (500 MHz, CD_3OD)



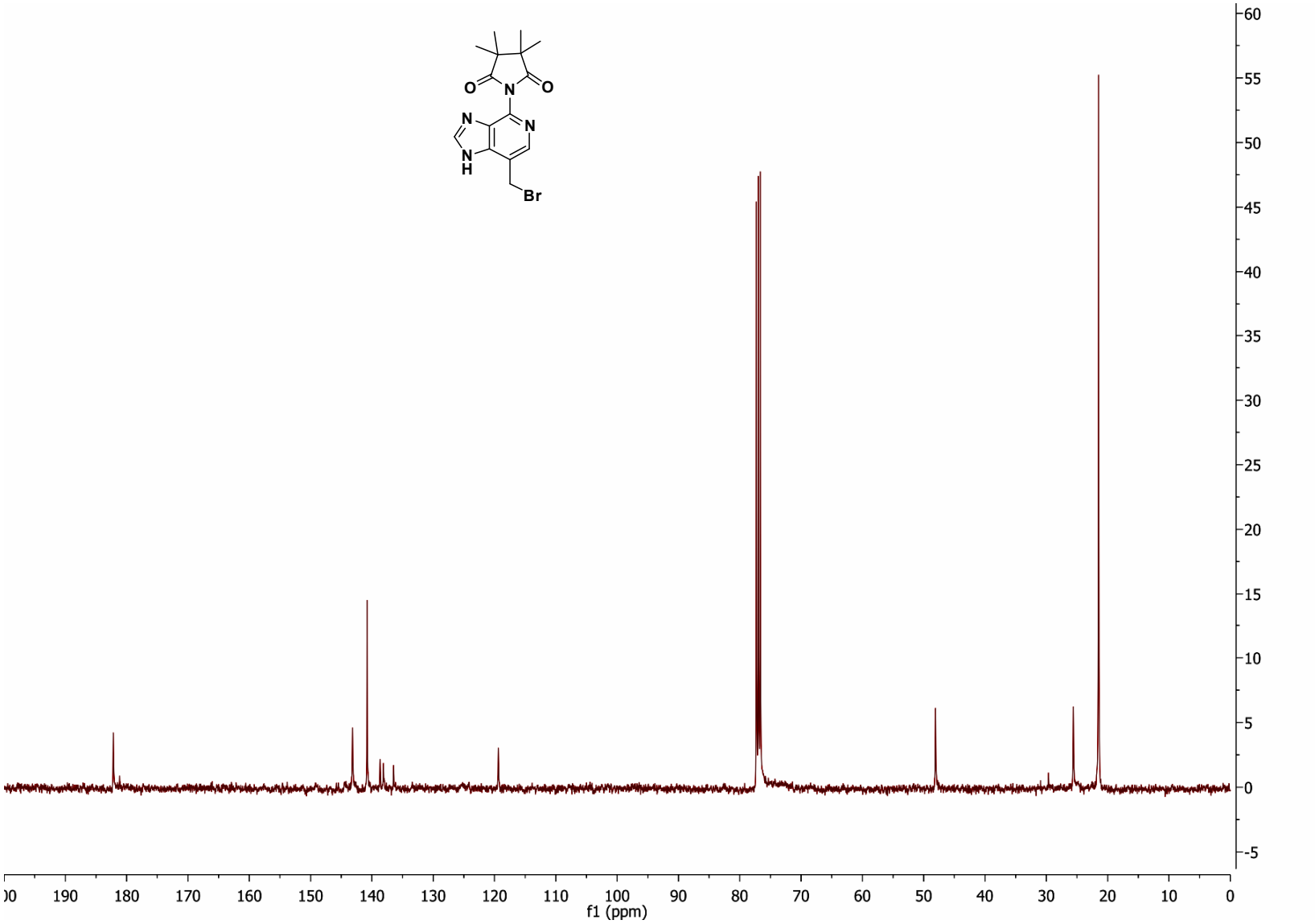
^{13}C NMR of compound **S4** (101 MHz, CD_3OD)



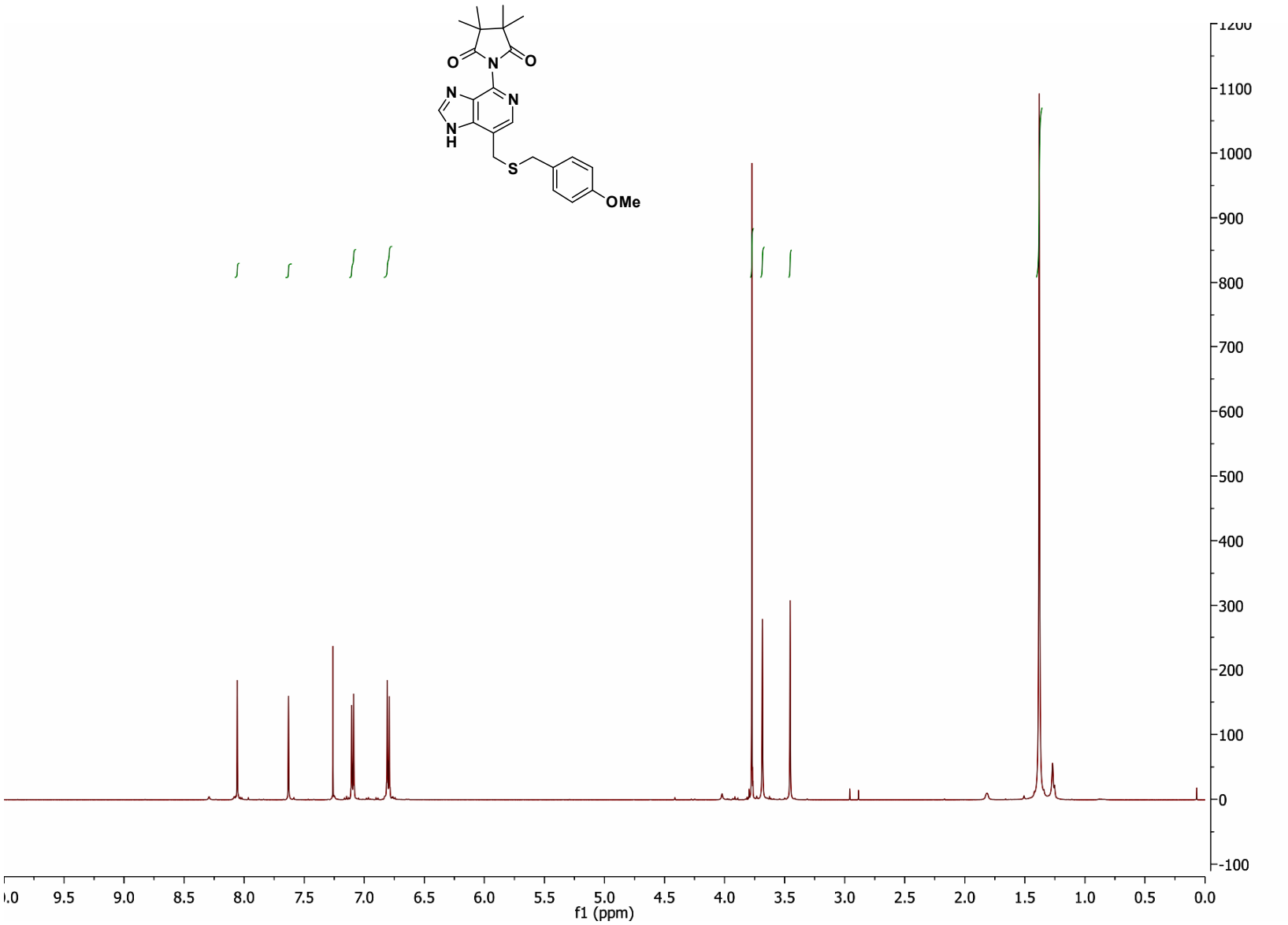
^{1}H NMR of compound **S6** (500 MHz, $CDCl_3$)



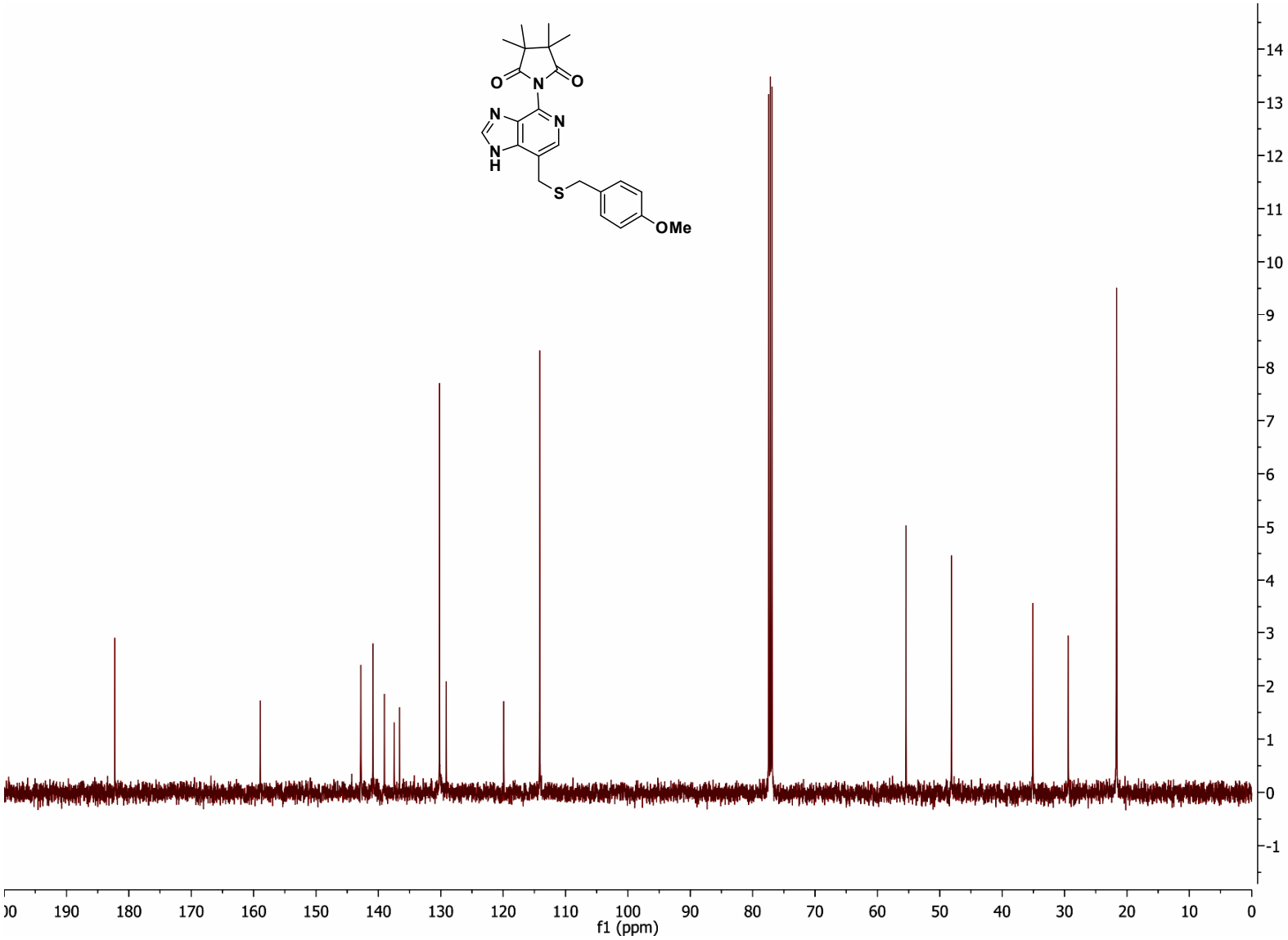
^{13}C NMR of compound **S6** (101 MHz, $CDCl_3$)



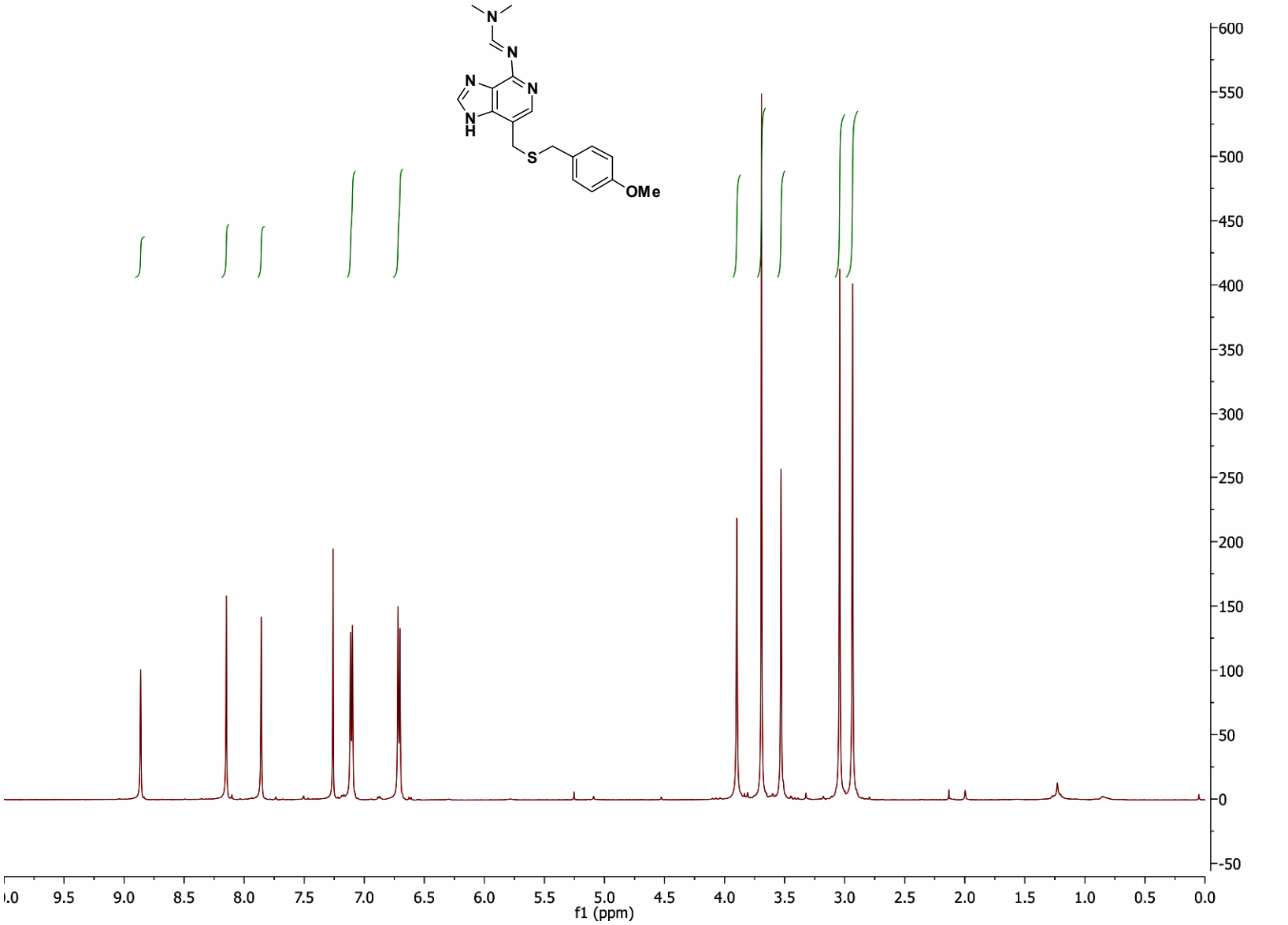
^{1}H NMR of compound **S7** (500 MHz, $CDCl_3$)



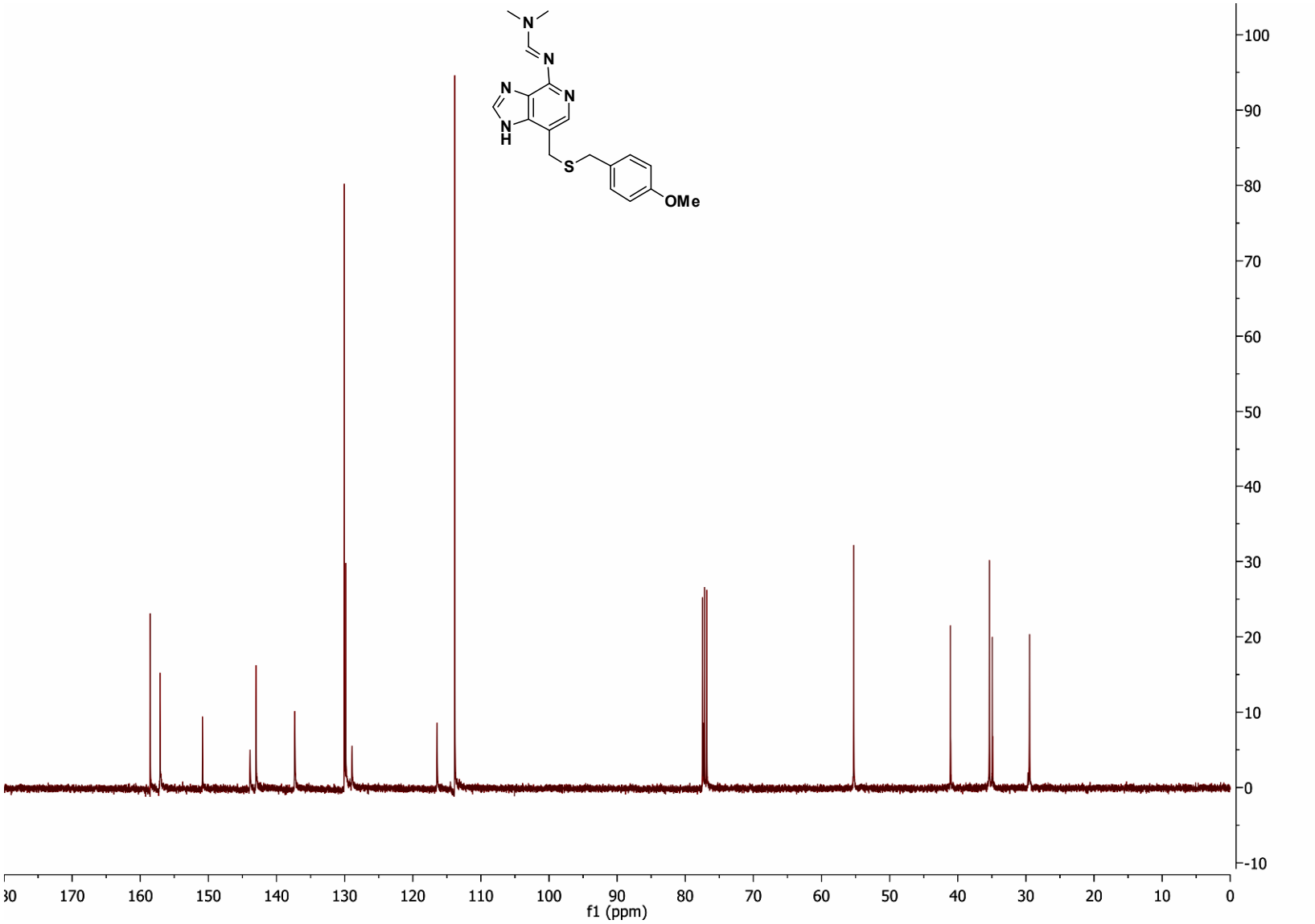
^{13}C NMR of compound **S7** (126 MHz, $CDCl_3$)



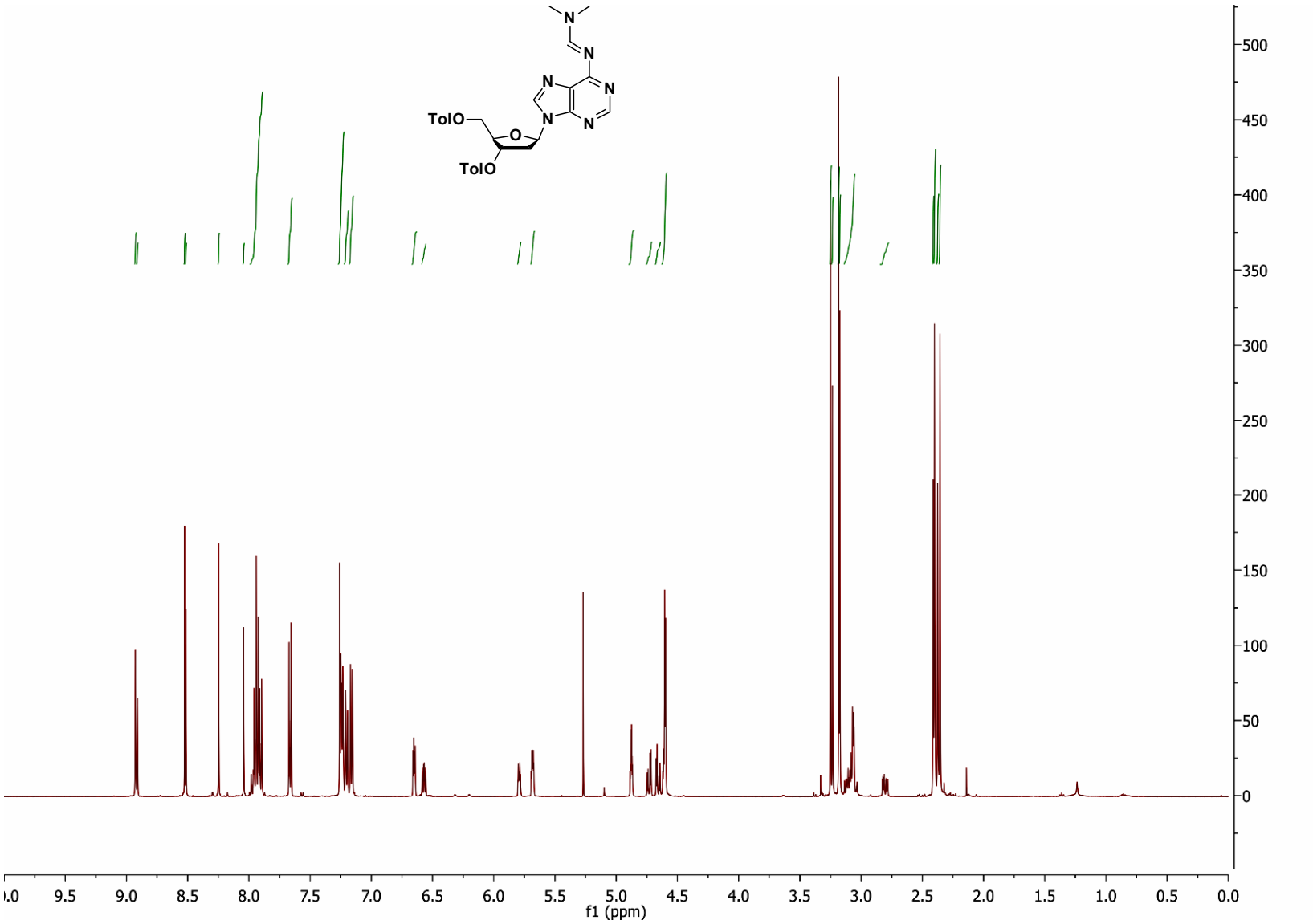
^{1}H NMR of compound **S8** (500 MHz, $CDCl_3$)



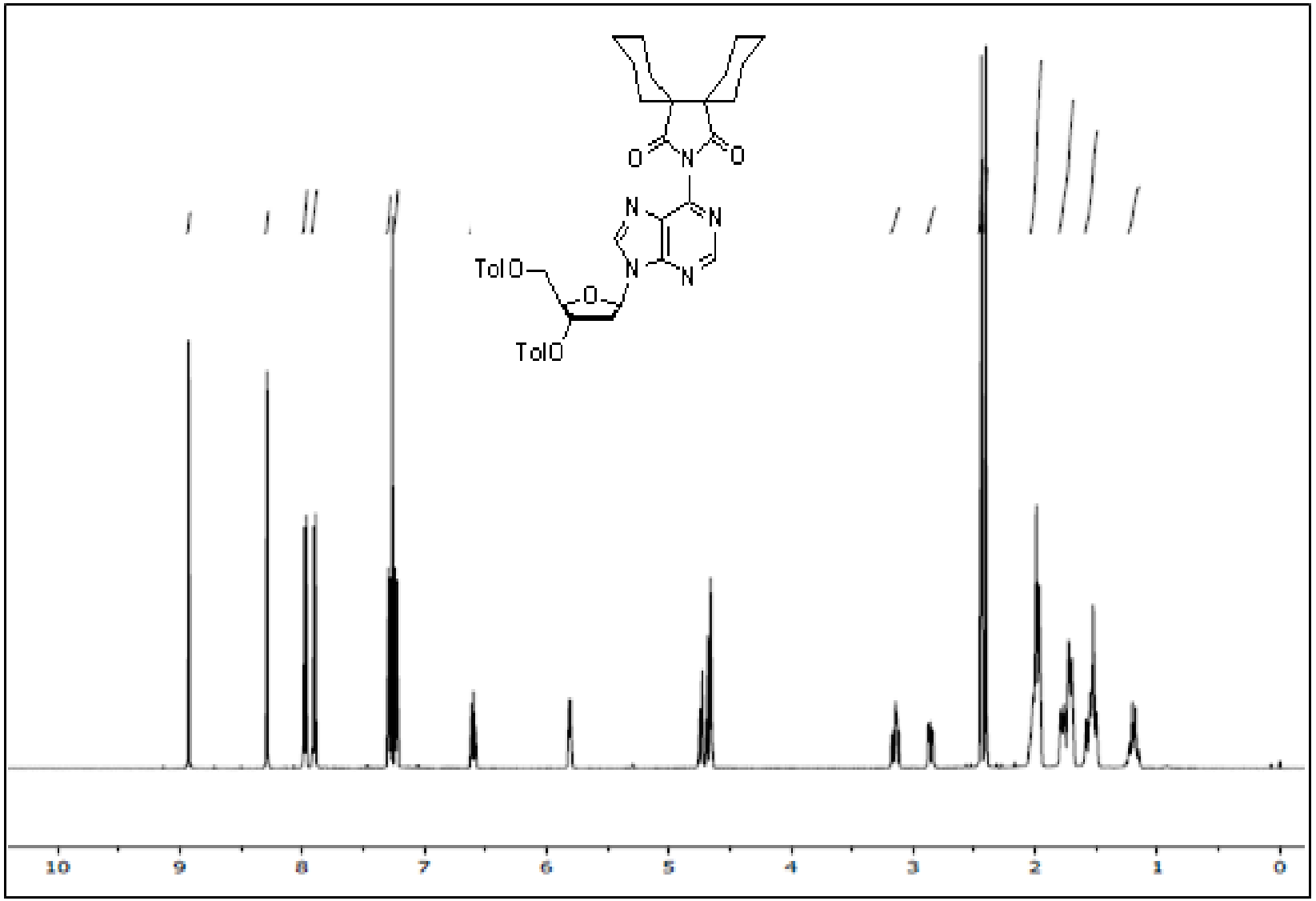
^{13}C NMR of compound **S8** (101 MHz, $CDCl_3$)



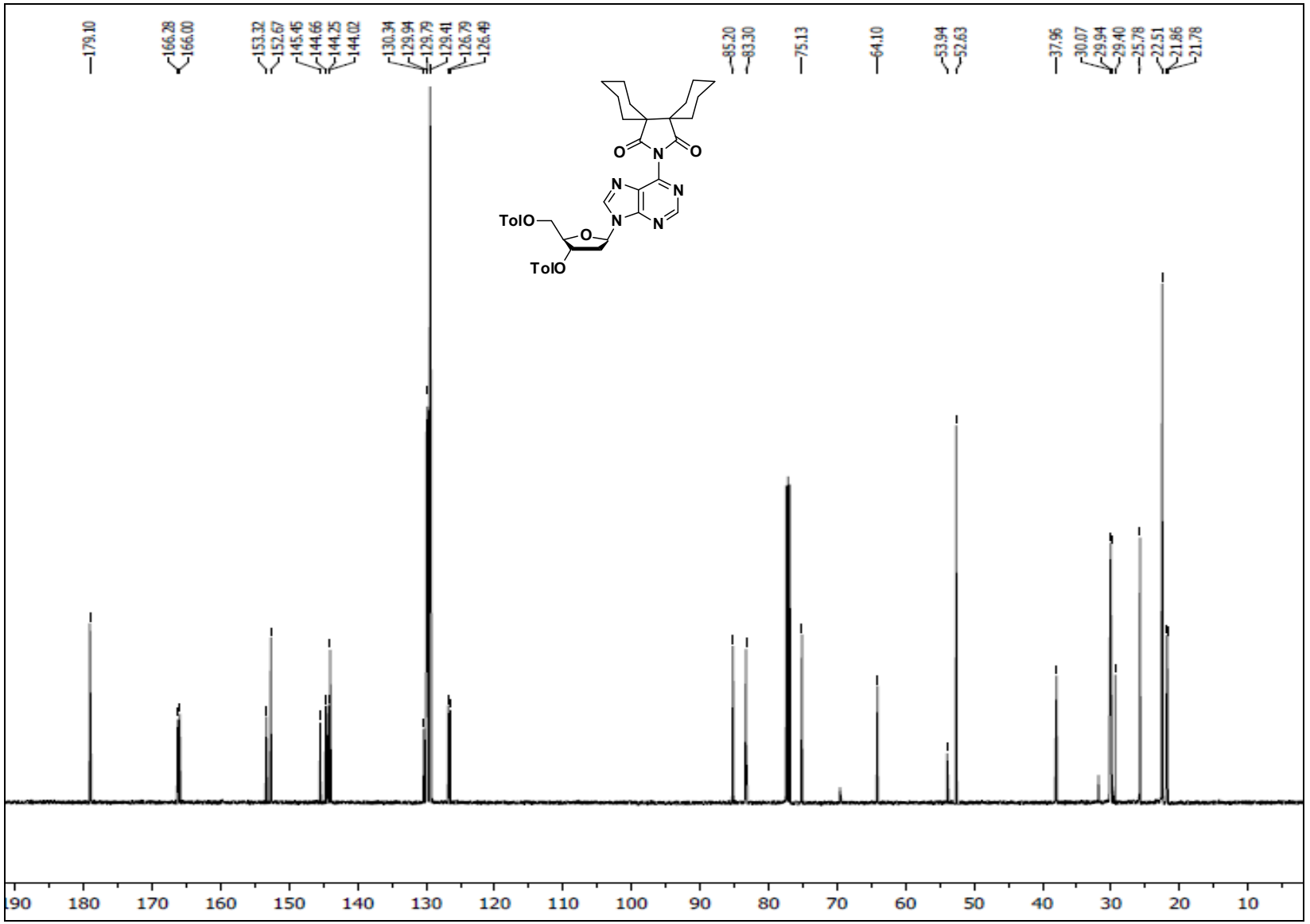
^{1}H NMR of compound **S9** (500 MHz, $CDCl_3$) – mixture of regioisomers



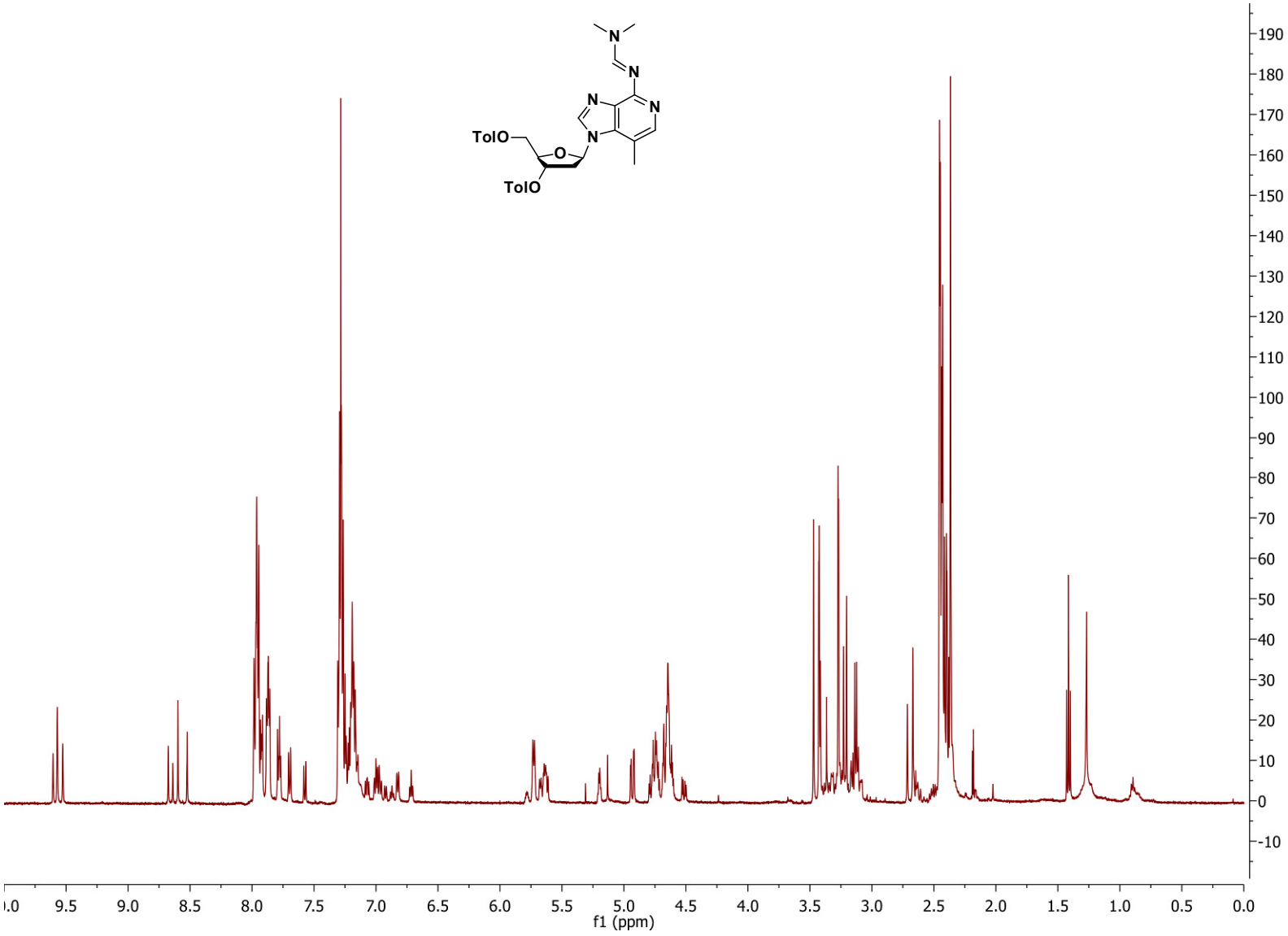
^{1}H NMR of compound **8** (500 MHz, $CDCl_3$)



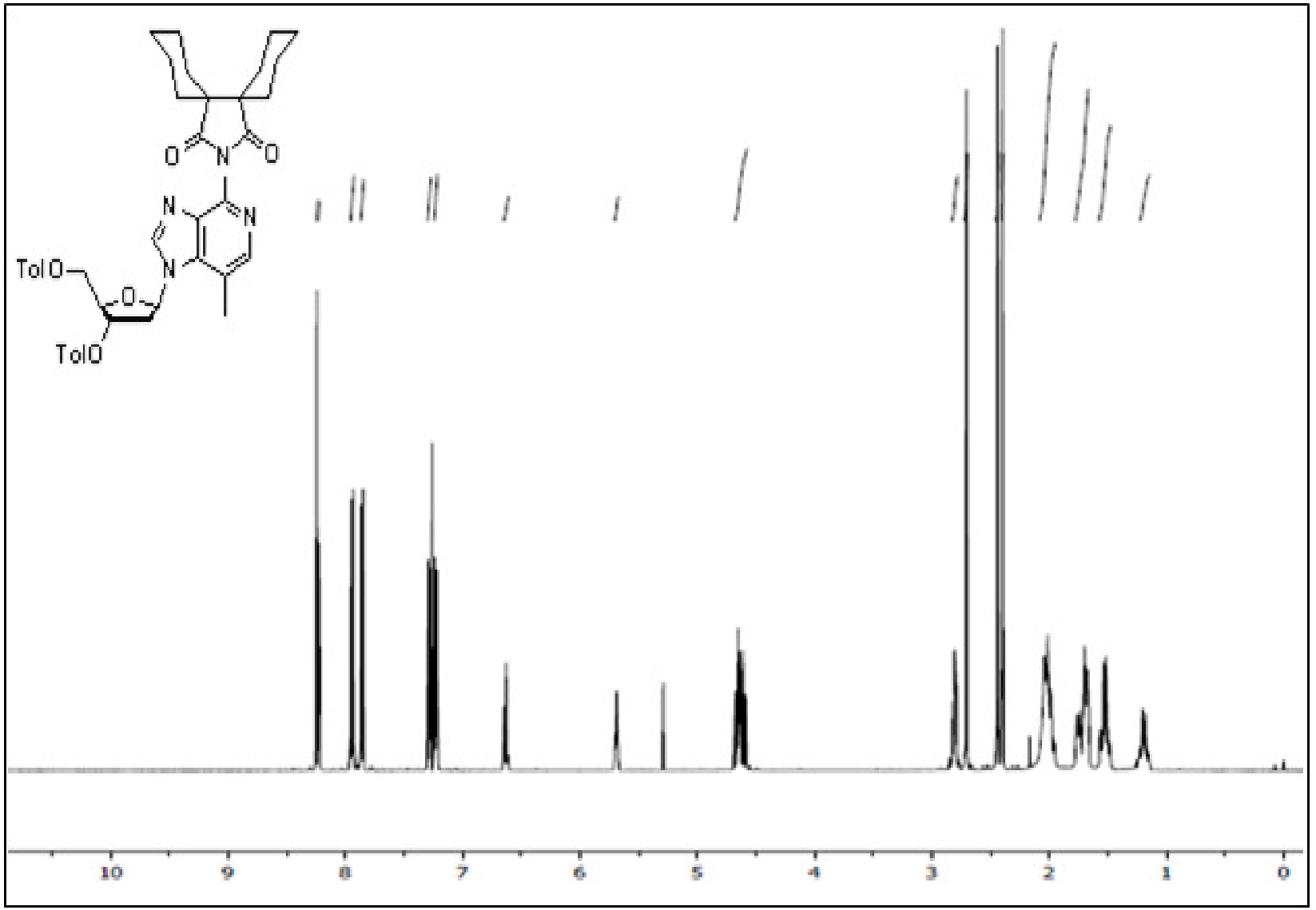
^{13}C NMR of compound **8** (126 MHz, $CDCl_3$)



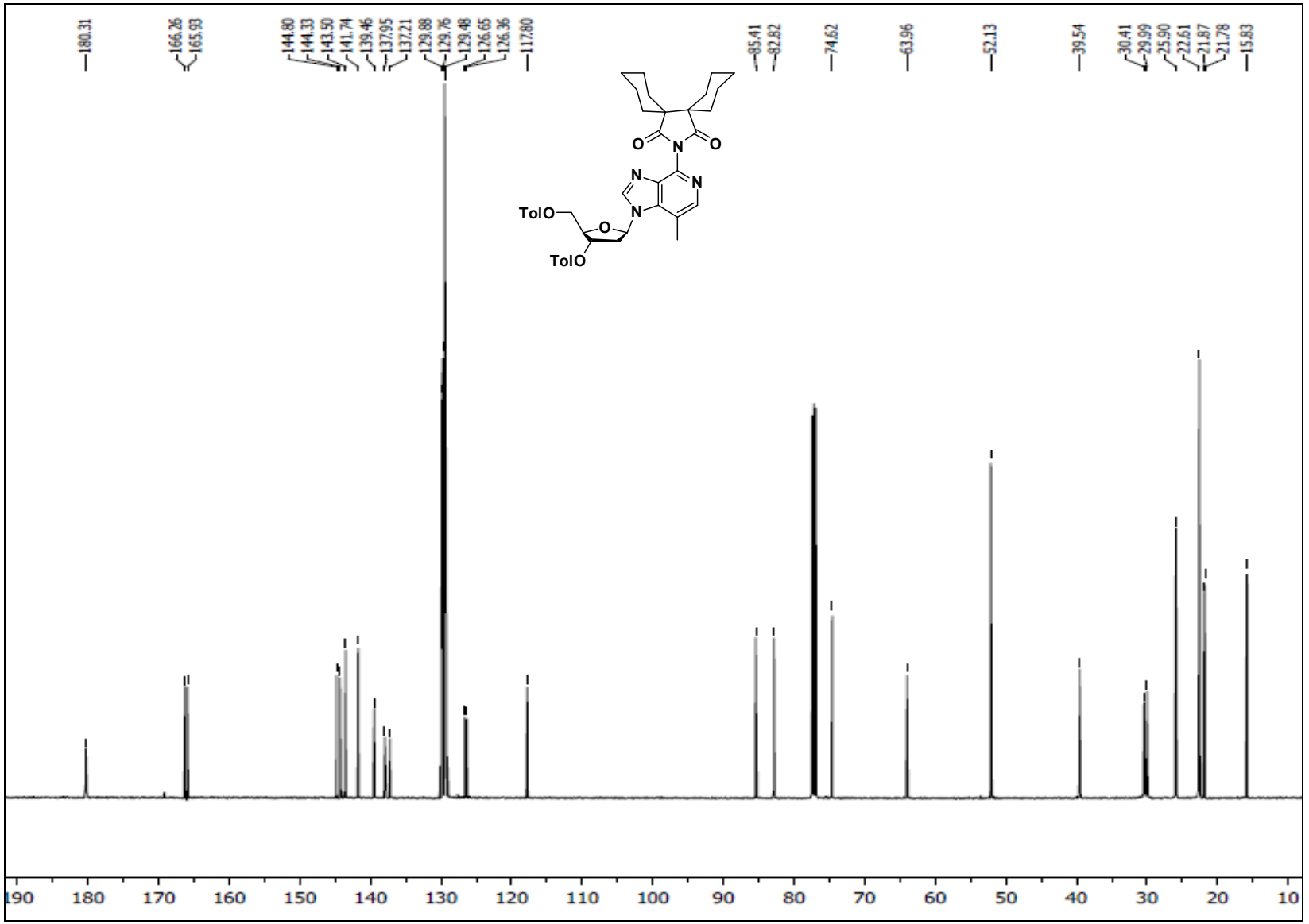
^{1}H NMR of compound **S10** (500 MHz, $CDCl_3$) – mixture of regioisomers



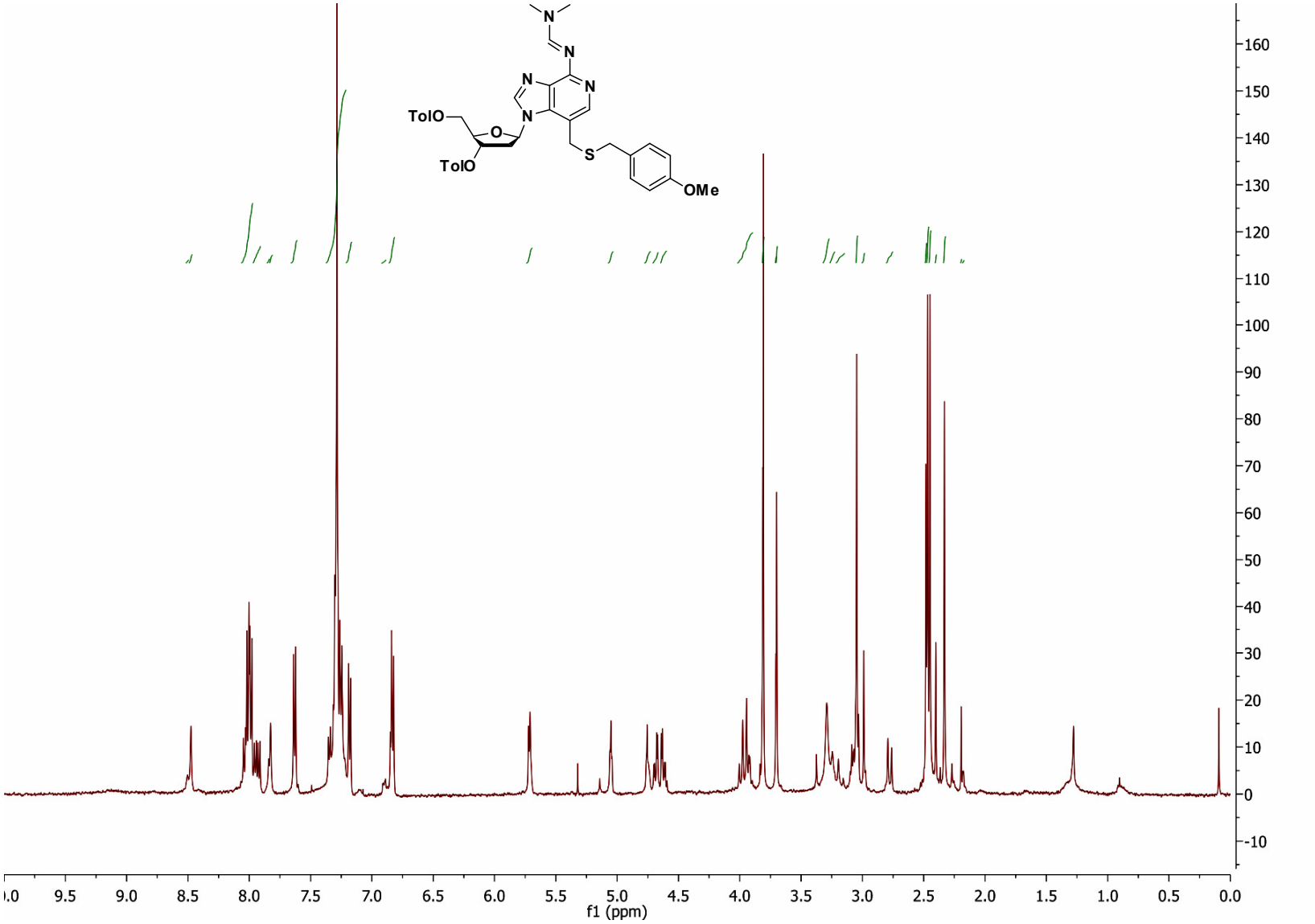
^{1}H NMR of compound **11** (500 MHz, $CDCl_3$)



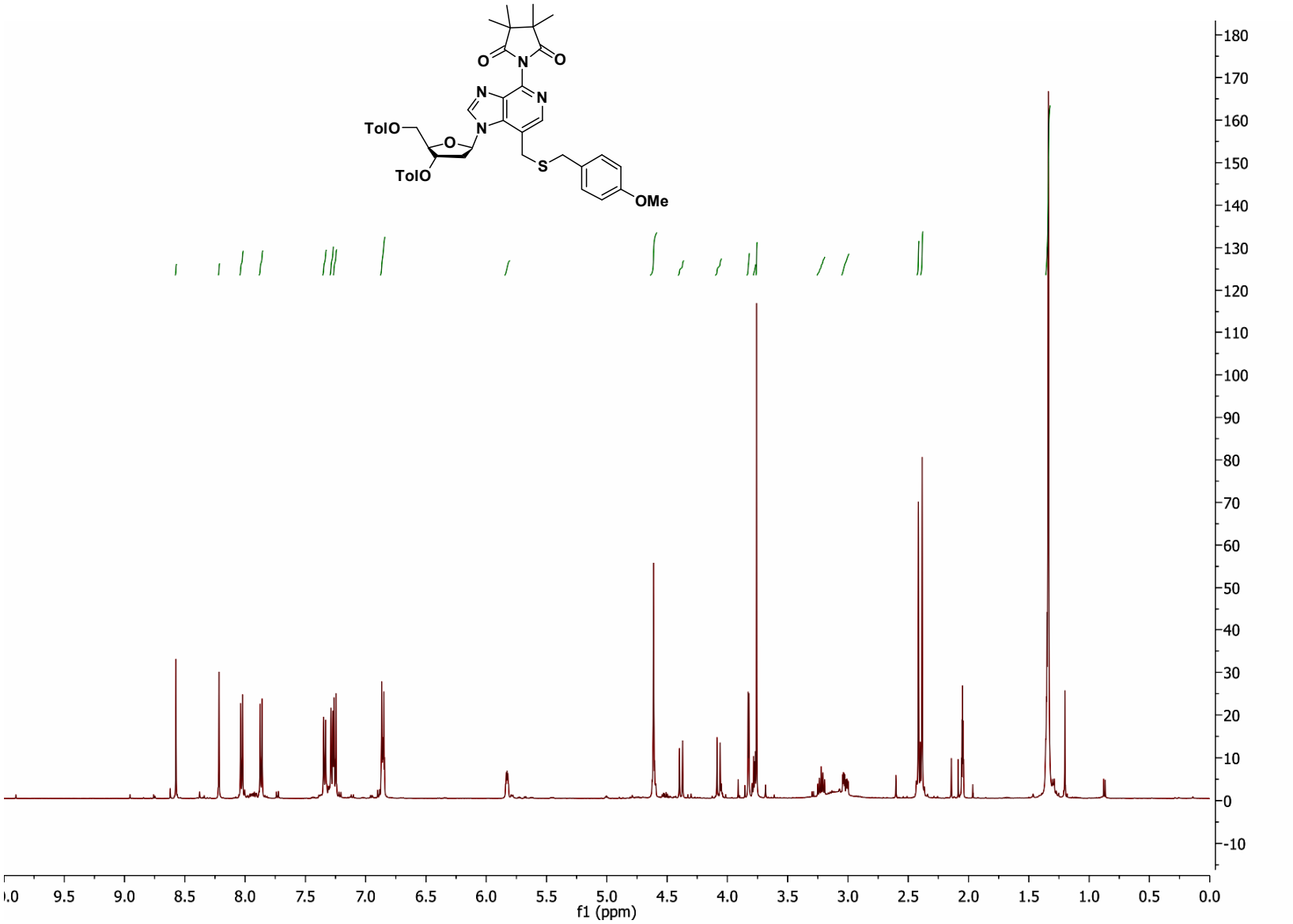
^{13}C NMR of compound **11** (126 MHz, $CDCl_3$)



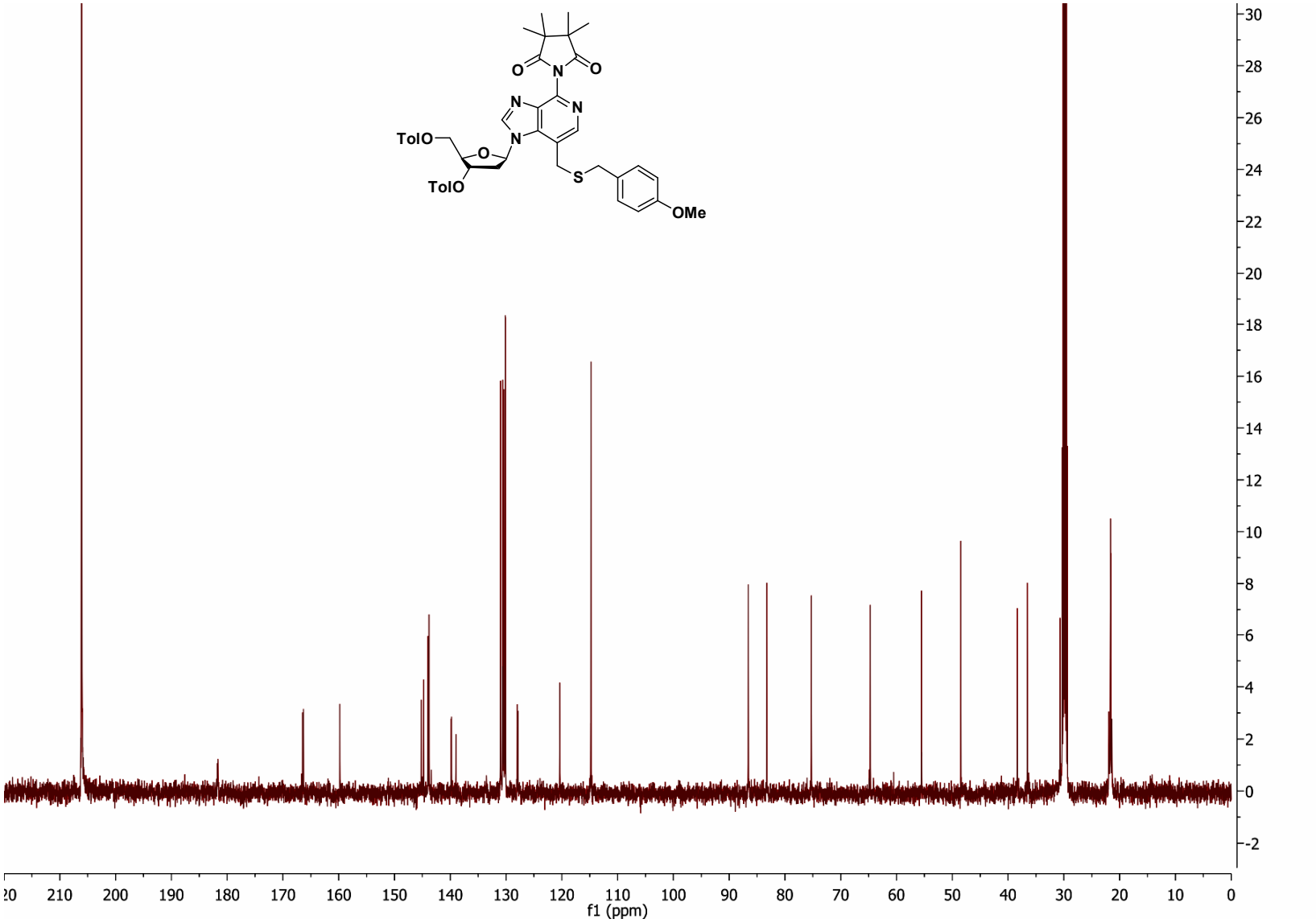
^{1}H NMR of compound **S11** (500 MHz, $CDCl_3$) – mixture of regioisomers



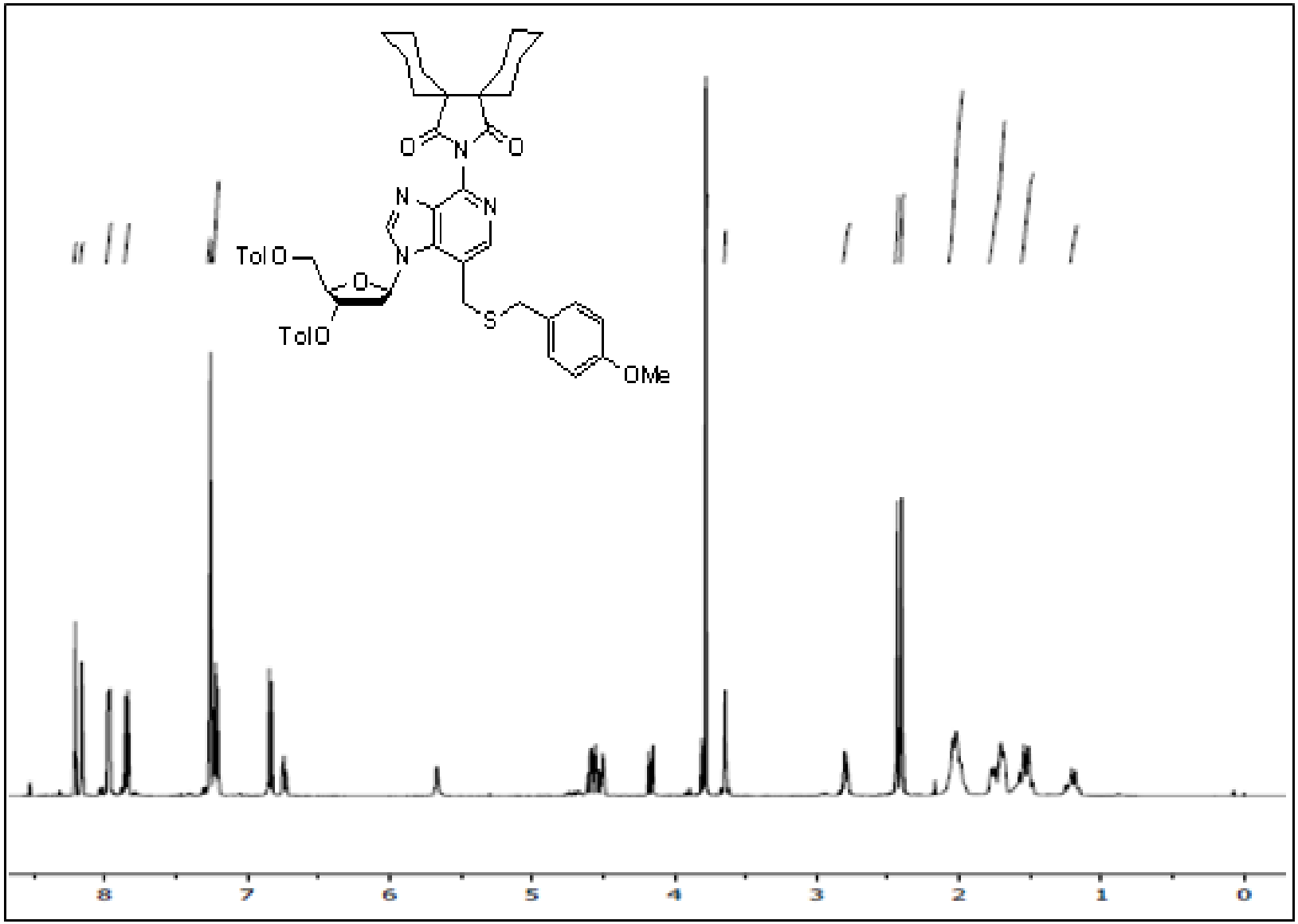
^{1}H NMR of compound **S12** (500 MHz, d_6-acetone)



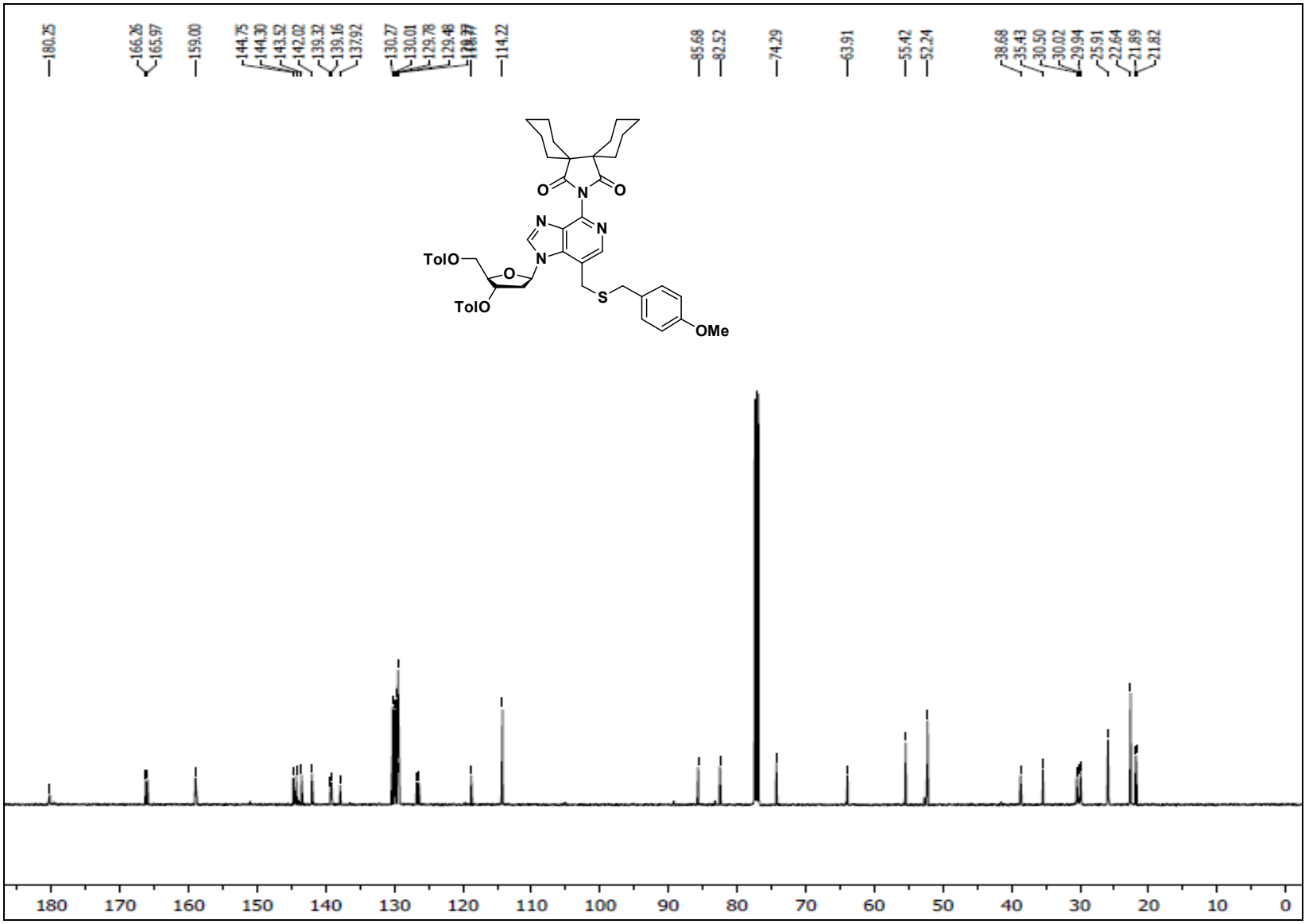
^{13}C NMR of compound **S12** (126 MHz, d_6-acetone)



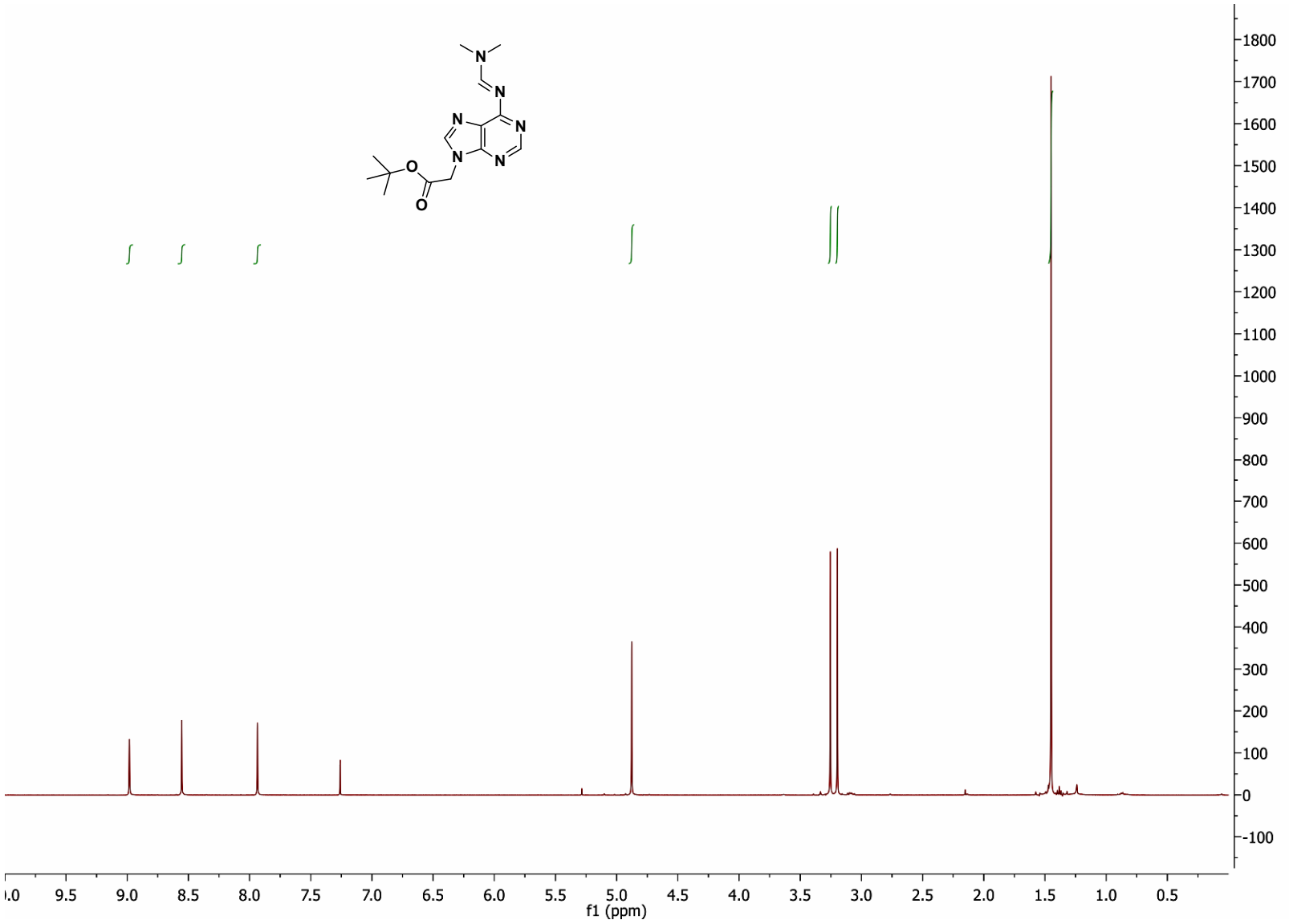
^{1}H NMR of compound **S13** (500 MHz, $CDCl_3$)



^{13}C NMR of compound **S13** (126 MHz, $CDCl_3$)

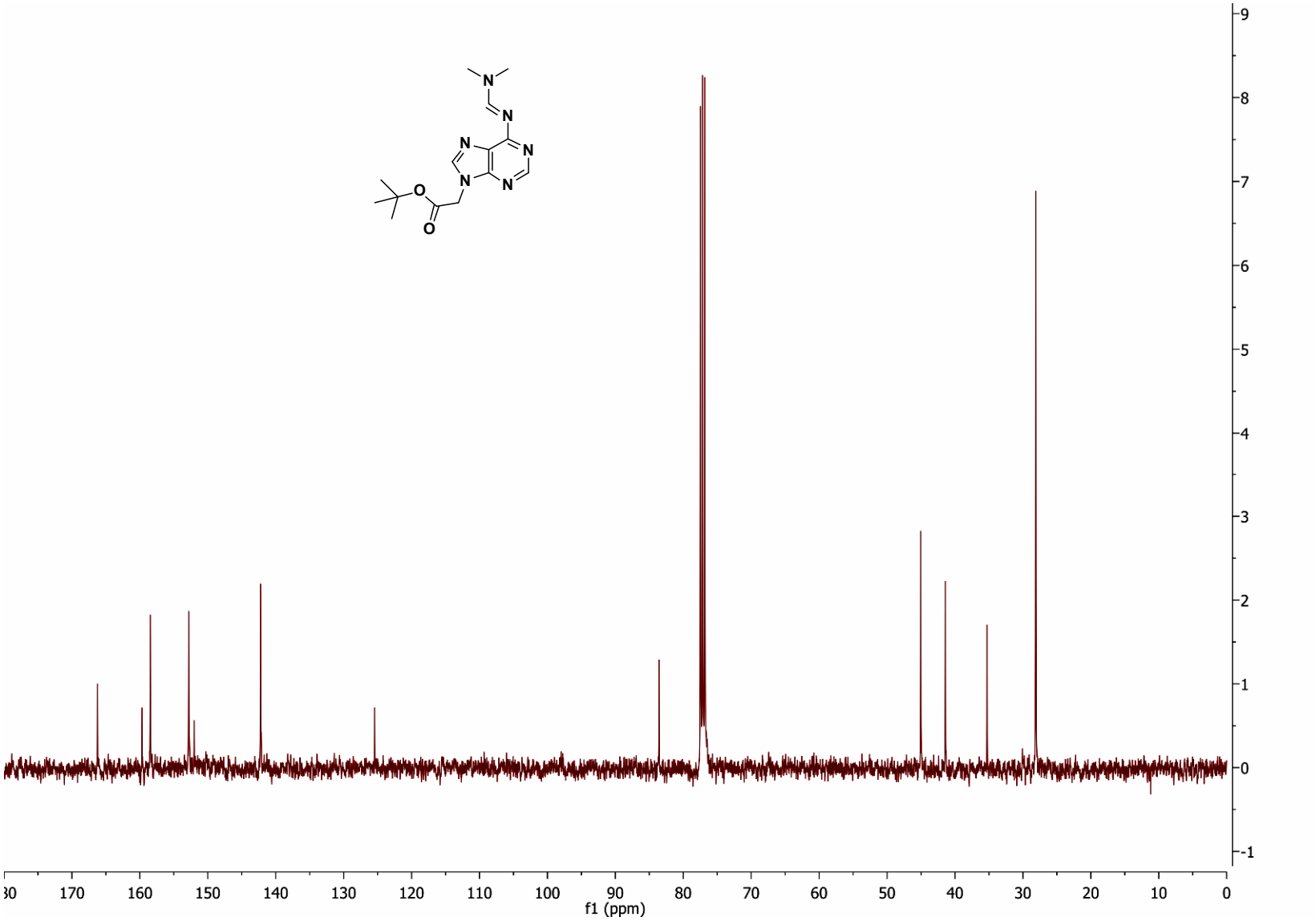


^{1}H NMR of compound **S14** (500 MHz, $CDCl_3$)

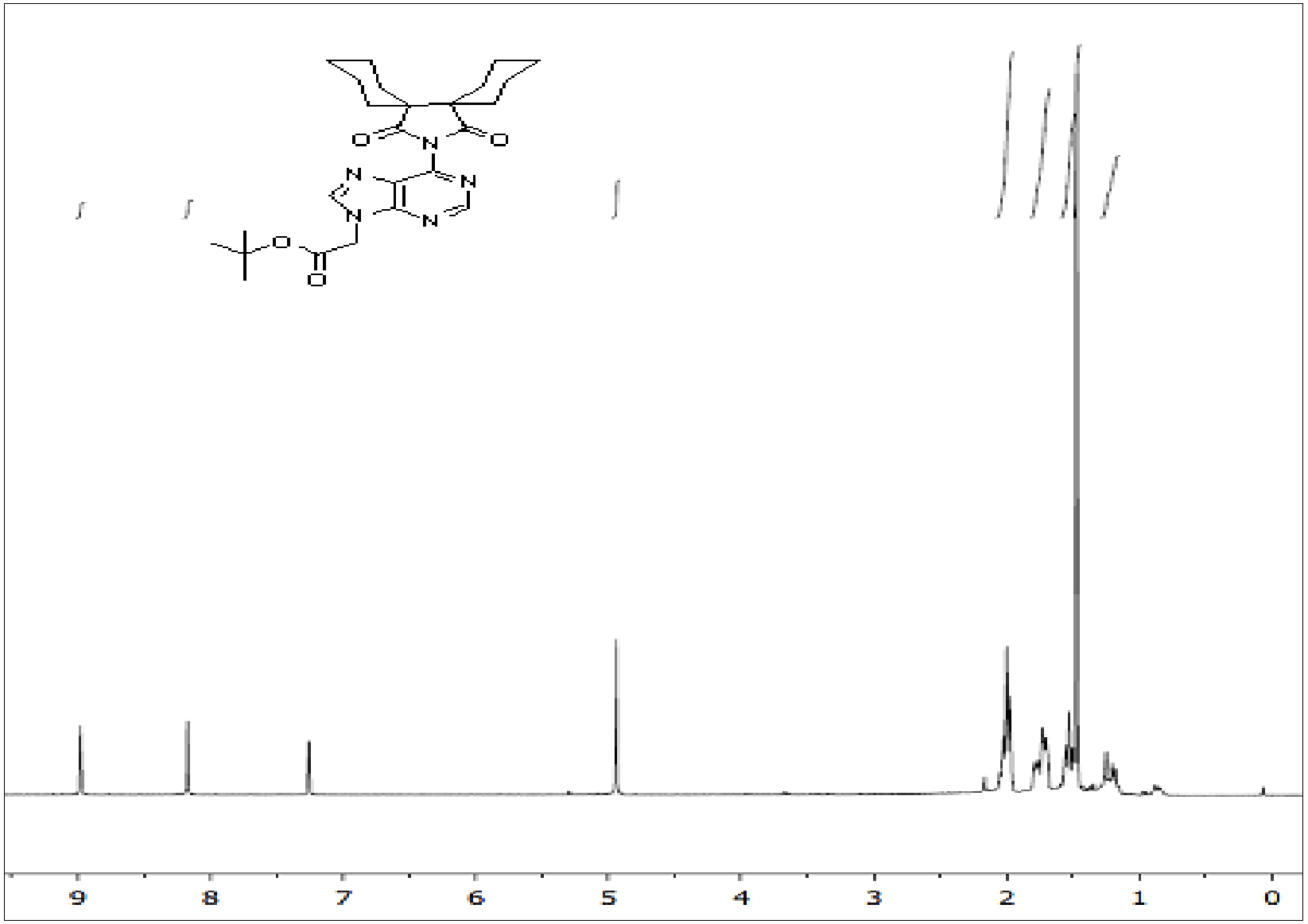


^{13}C

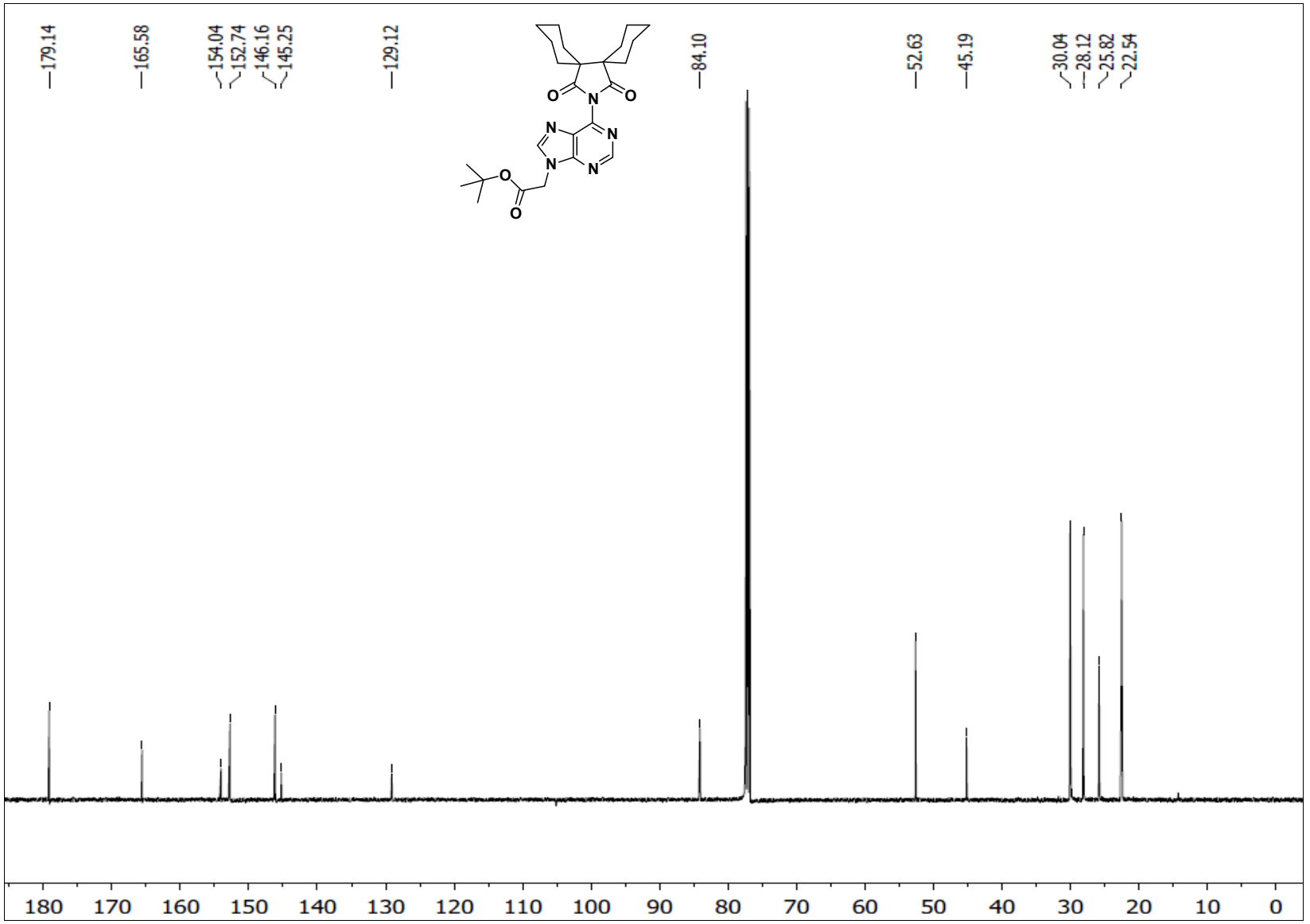
^{13}C NMR of compound **S14** (101 MHz, $CDCl_3$)



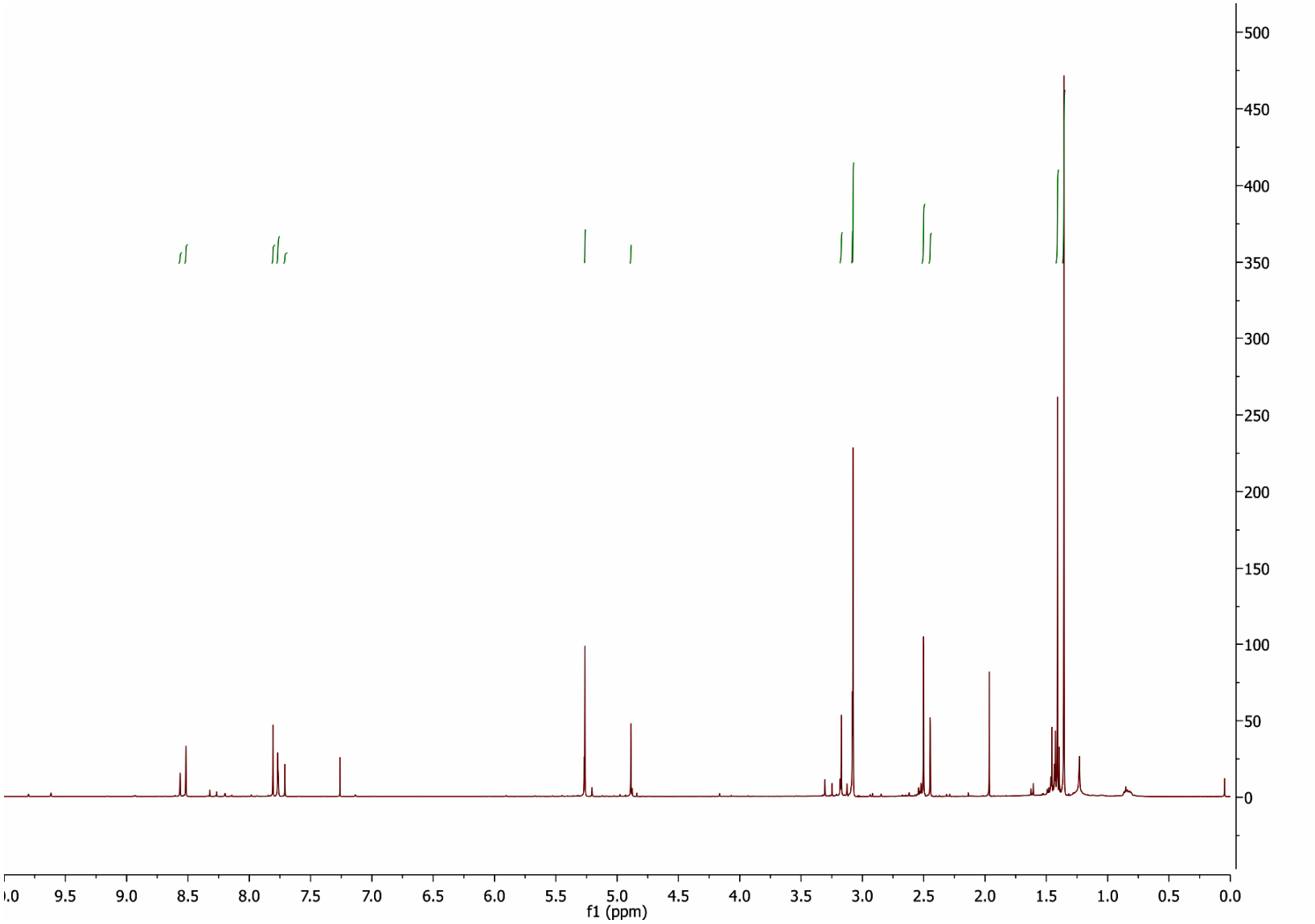
^{1}H NMR of compound **S15** (500 MHz, $CDCl_3$)



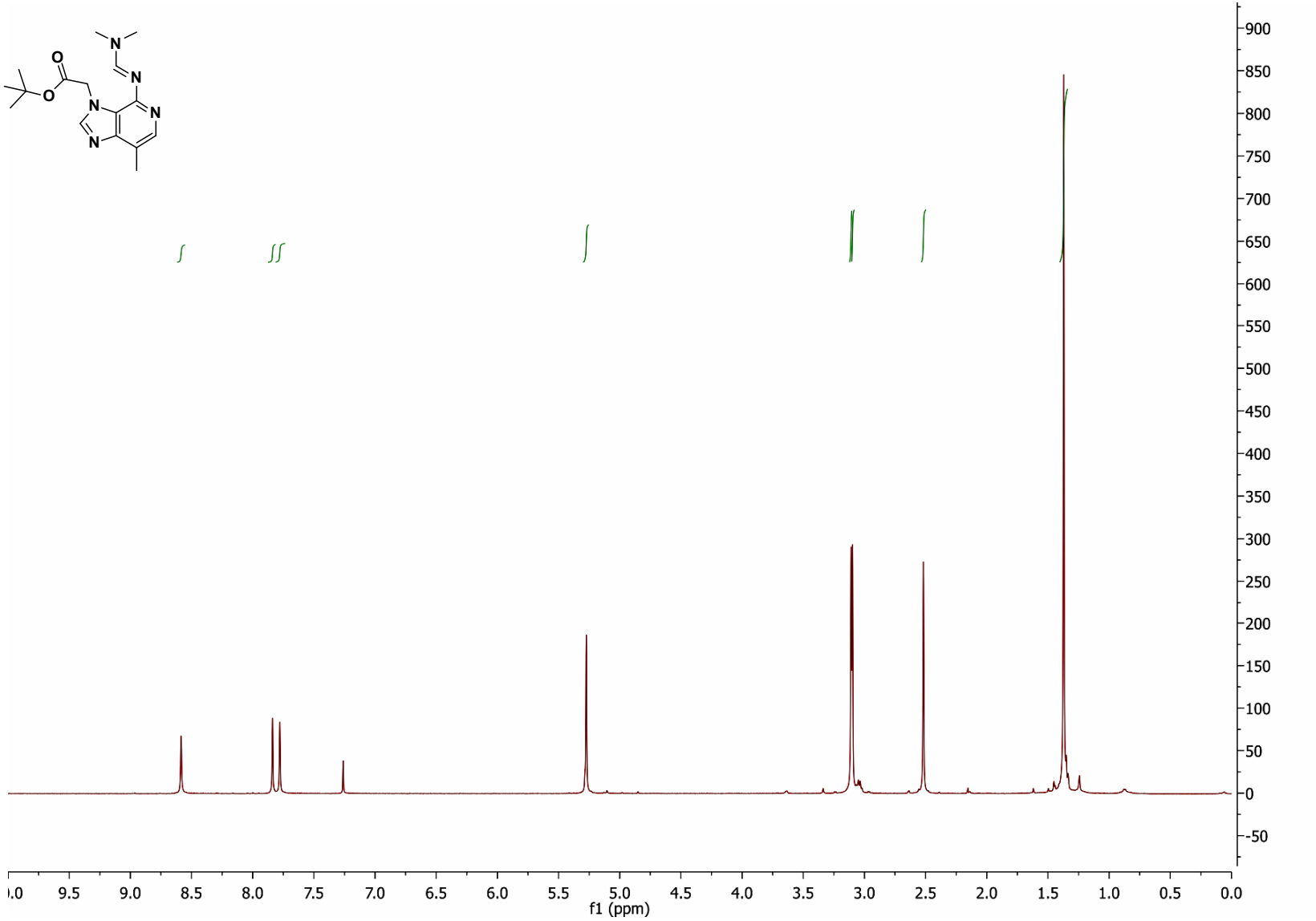
^{13}C NMR of compound **S15** (126 MHz, $CDCl_3$)



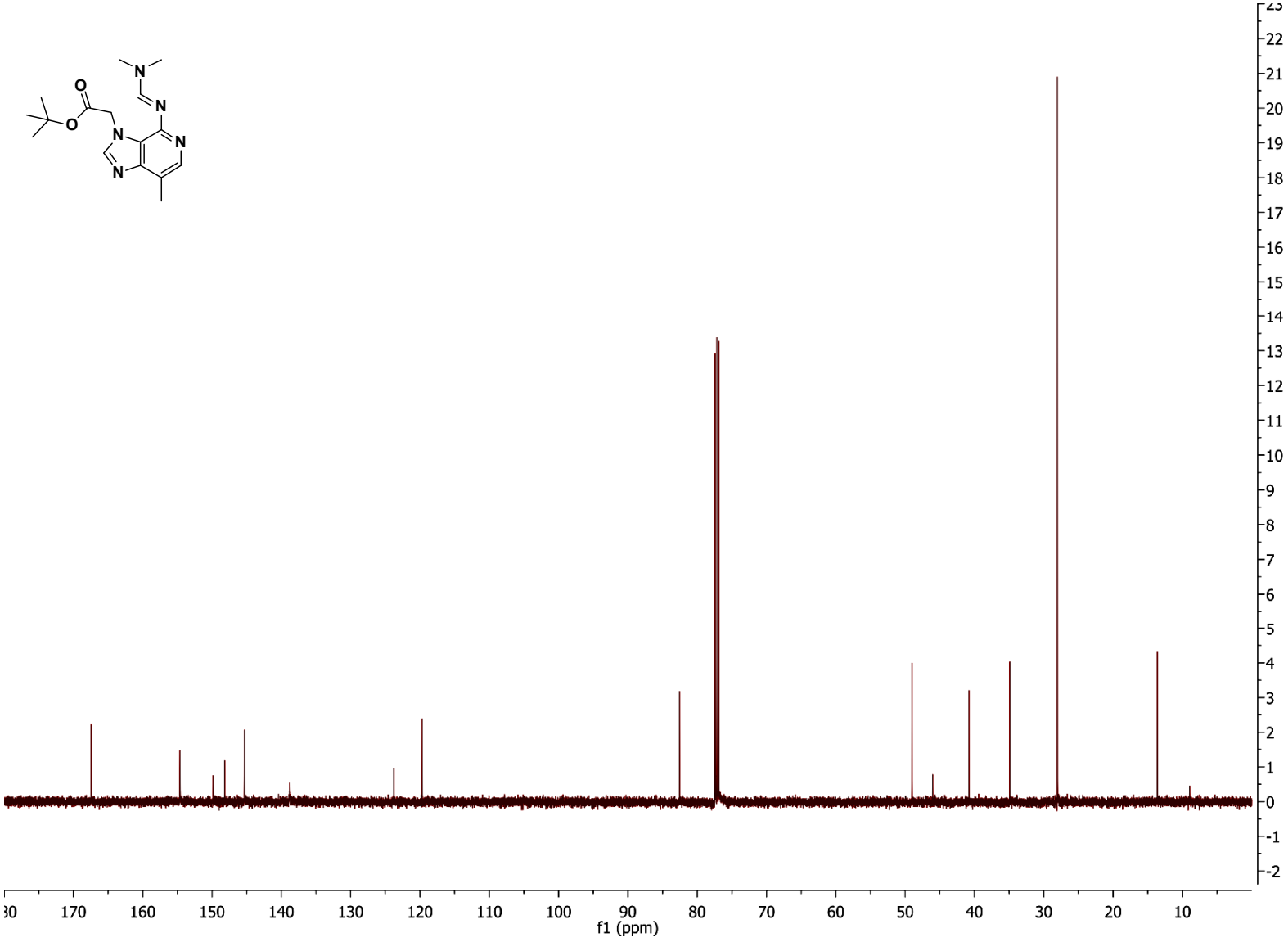
^{1}H NMR of crude reaction mixture for compound **S16** (500 MHz, $CDCl_3$) – both N9 and N7 products



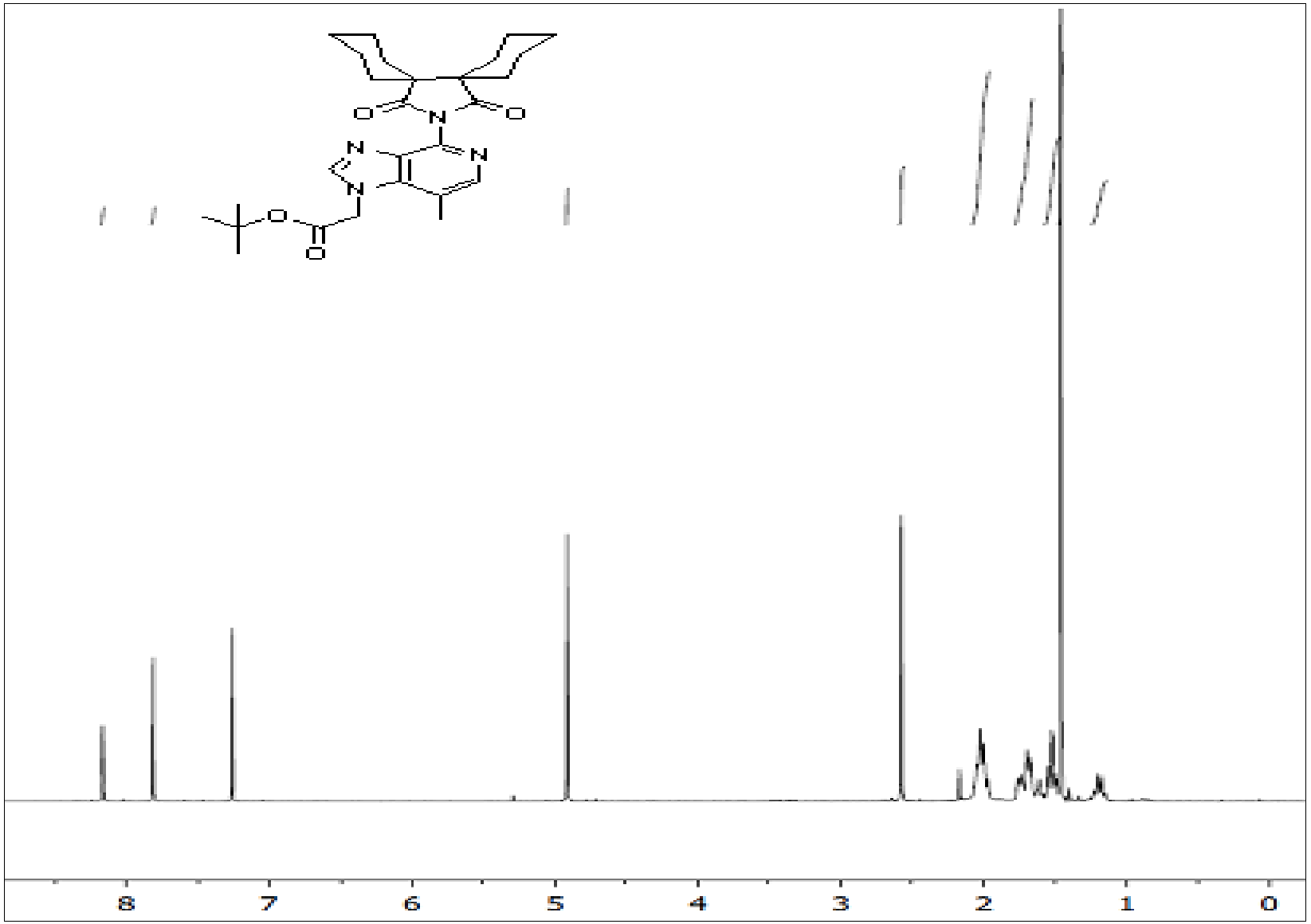
^{1}H NMR of N7 regioisomer of compound **S16** (500 MHz, $CDCl_3$)



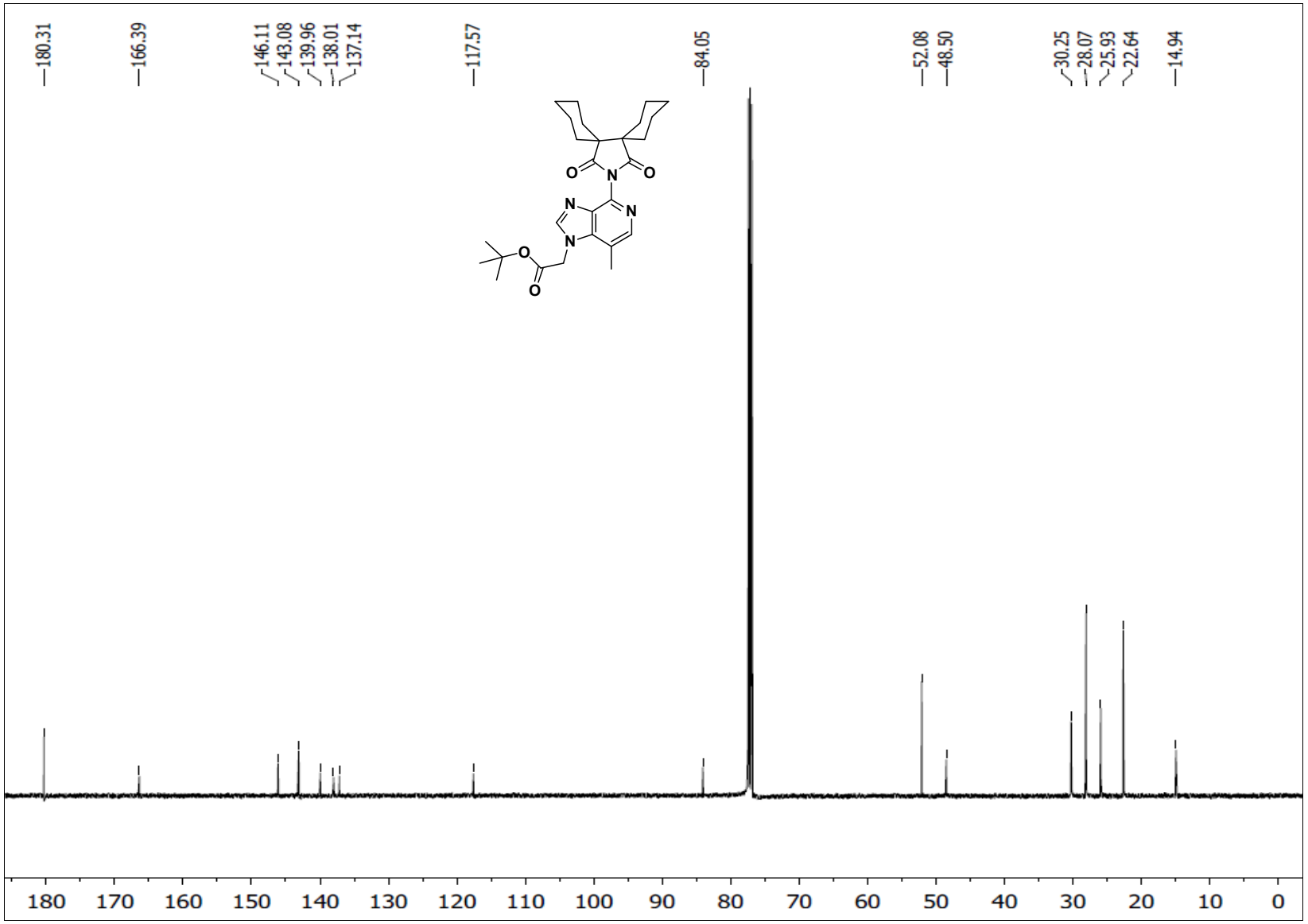
^{13}C NMR of N7 regioisomer of compound **S16** (126 MHz, $CDCl_3$)



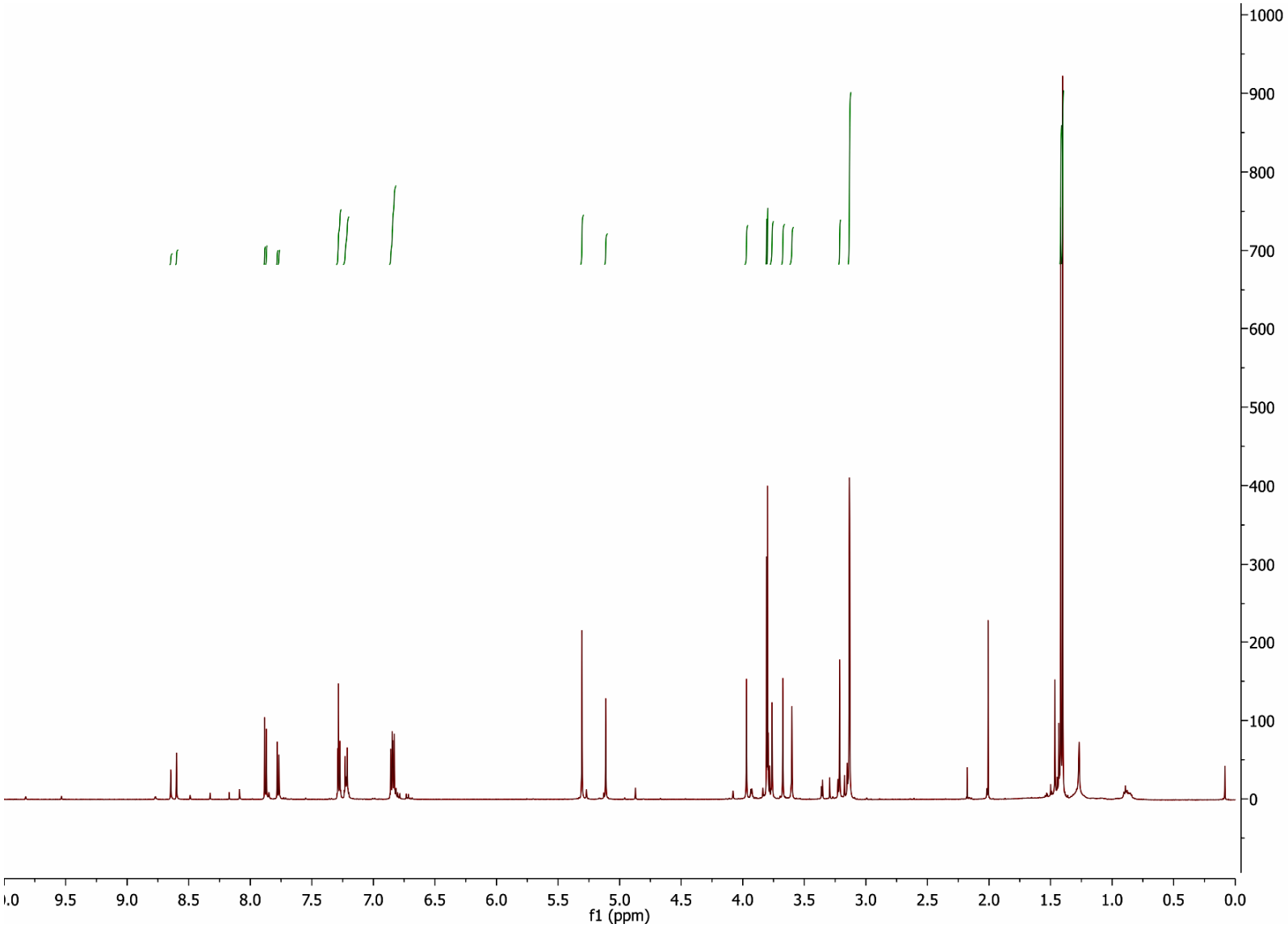
^{1}H NMR of compound **S17** (500 MHz, $CDCl_3$)



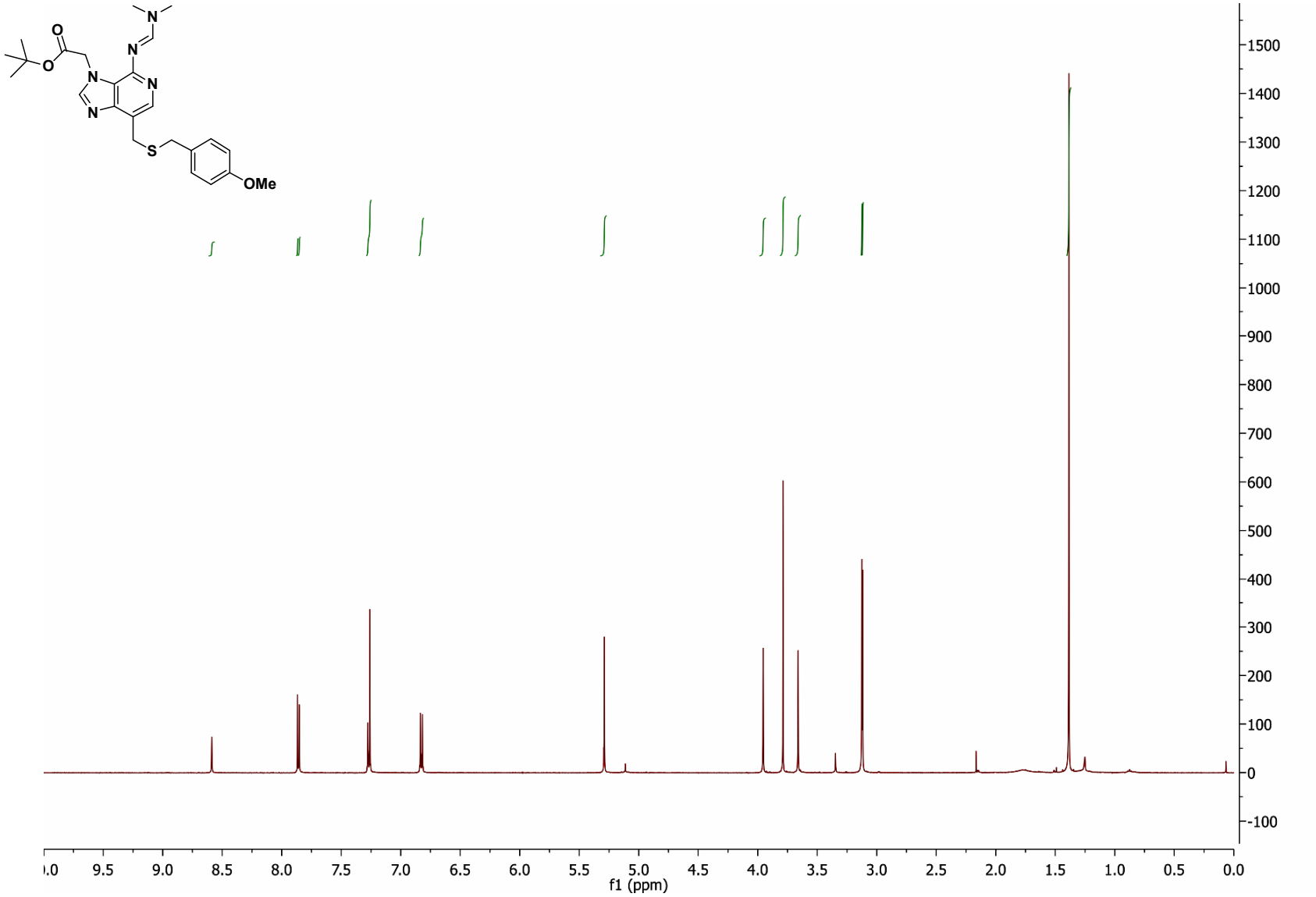
^{13}C NMR of compound **S17** (126 MHz, $CDCl_3$)



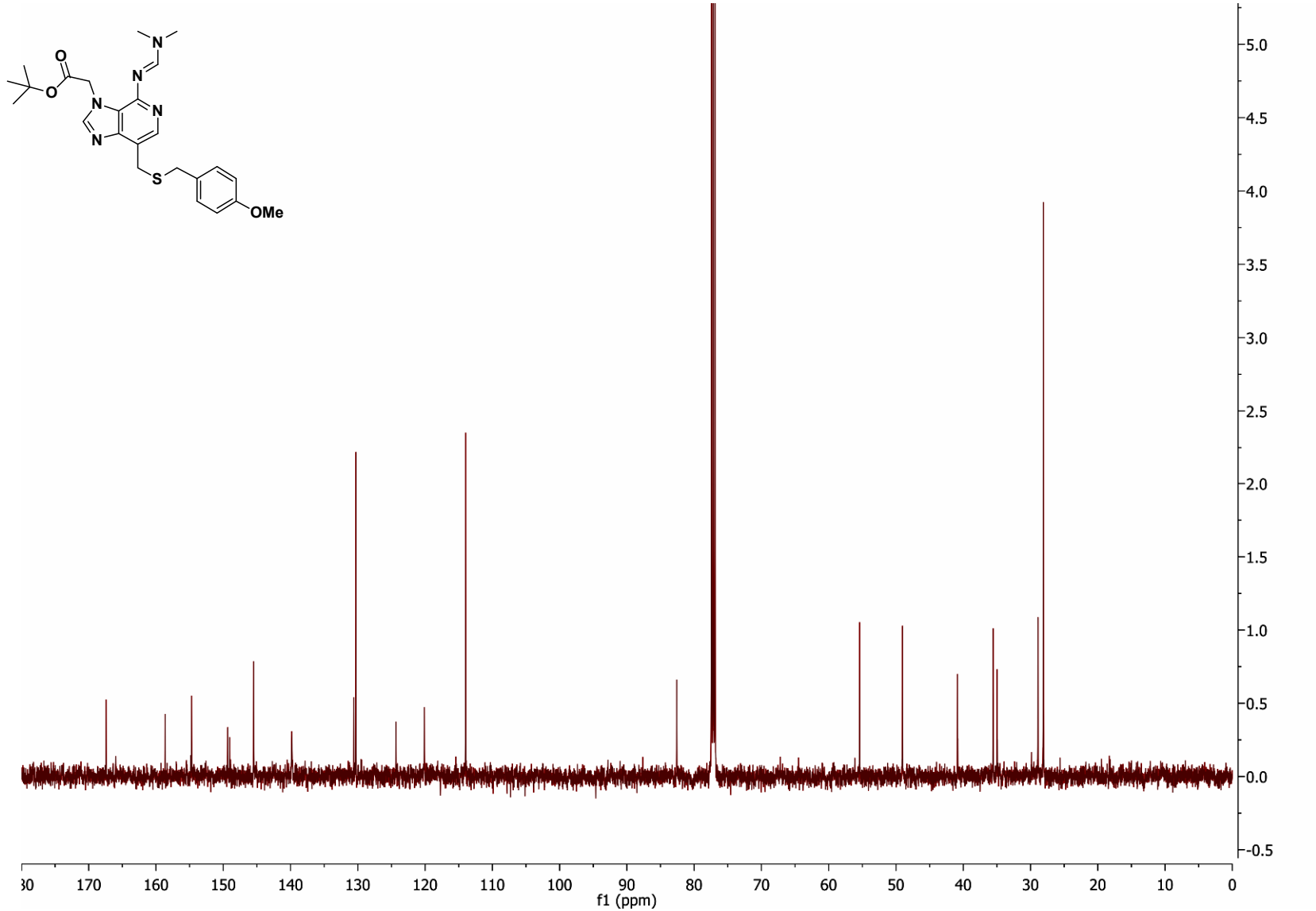
^{1}H NMR of crude reaction mixture for compound **S18** (500 MHz, $CDCl_3$) – both N9 and N7 products



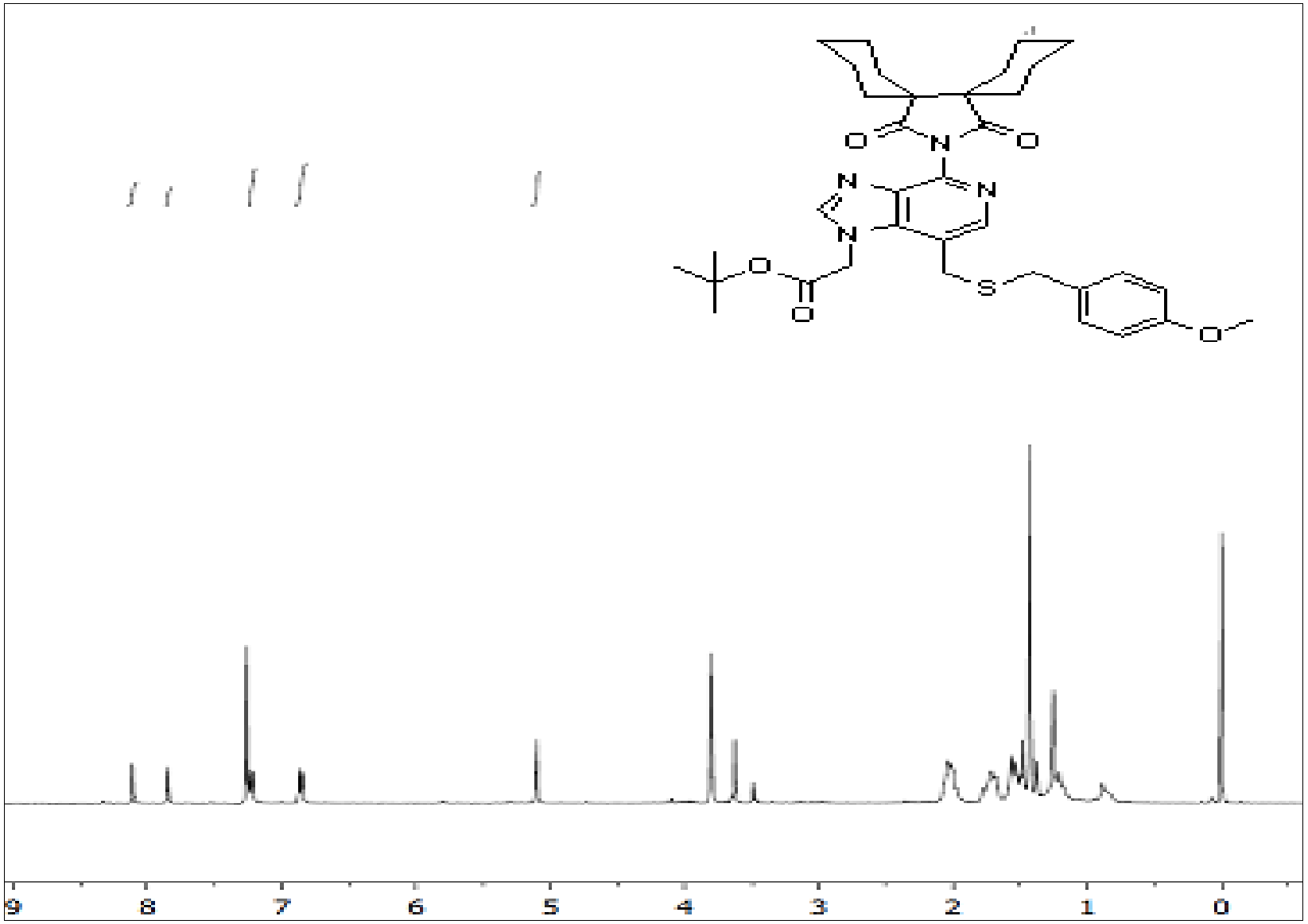
^{1}H NMR of N7 regioisomer of compound **S18** (500 MHz, $CDCl_3$)



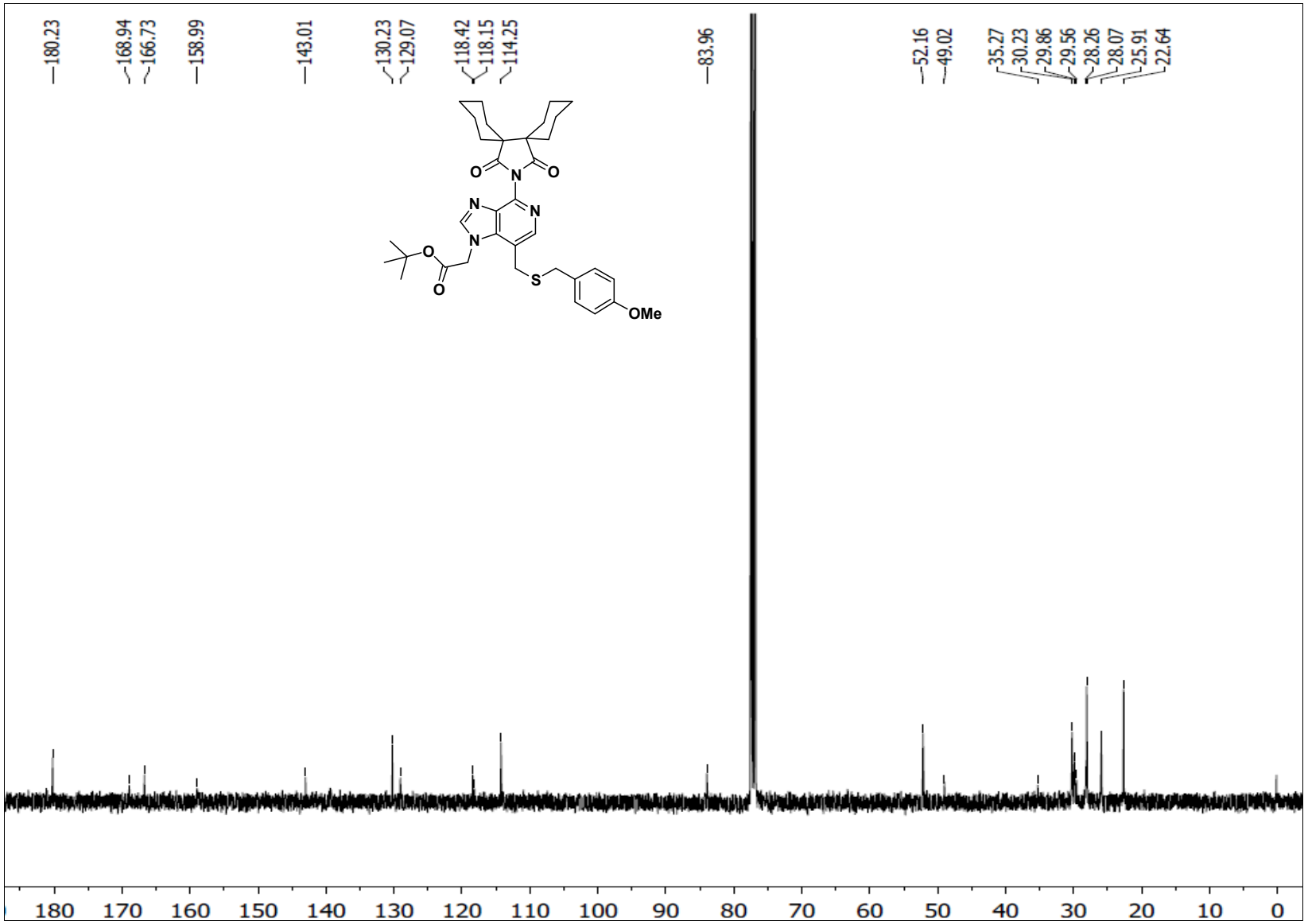
^{13}C NMR of N7 regioisomer of compound **S18** (126 MHz, $CDCl_3$)



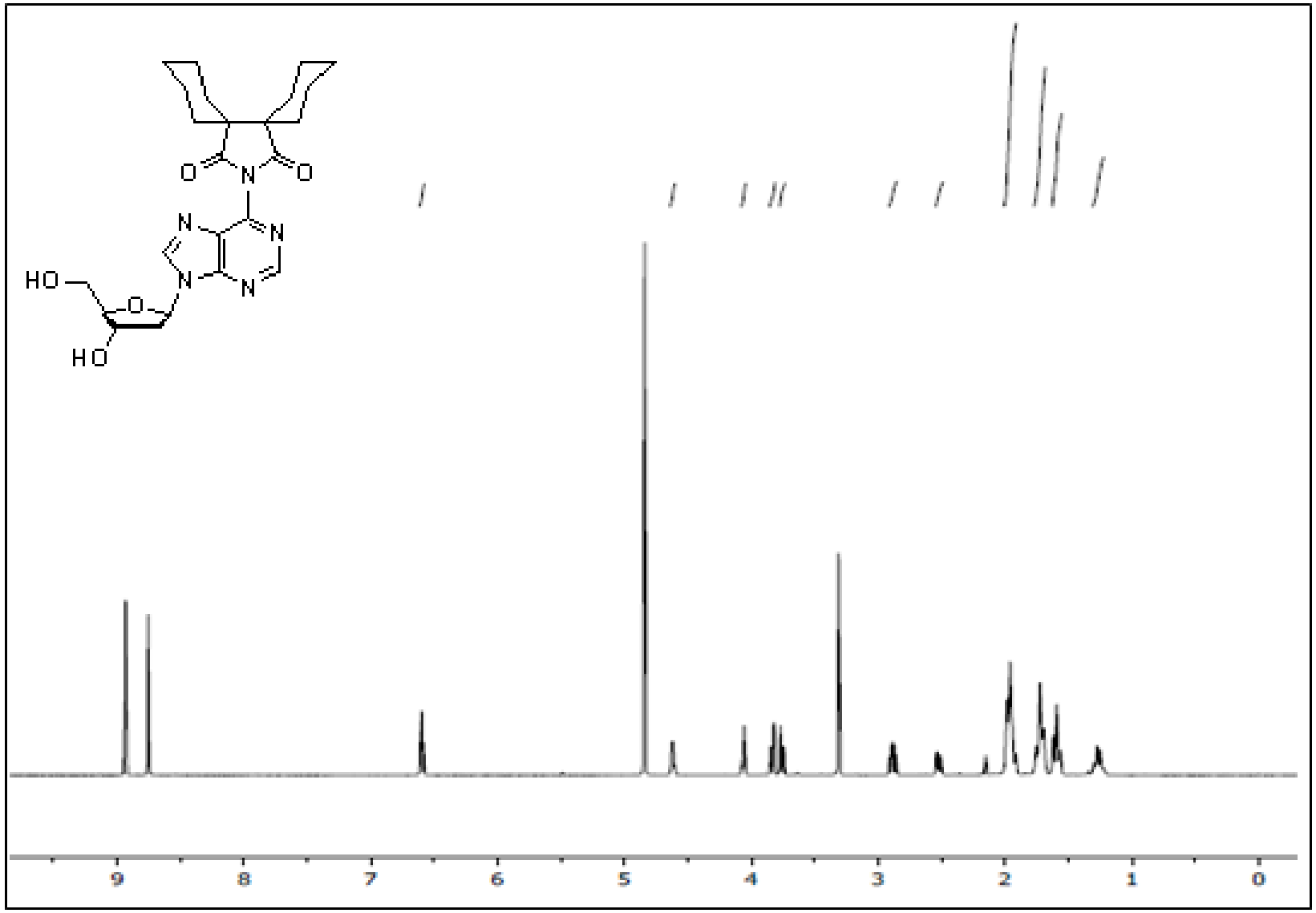
^{1}H NMR of compound **S19** (400 MHz, $CDCl_3$)



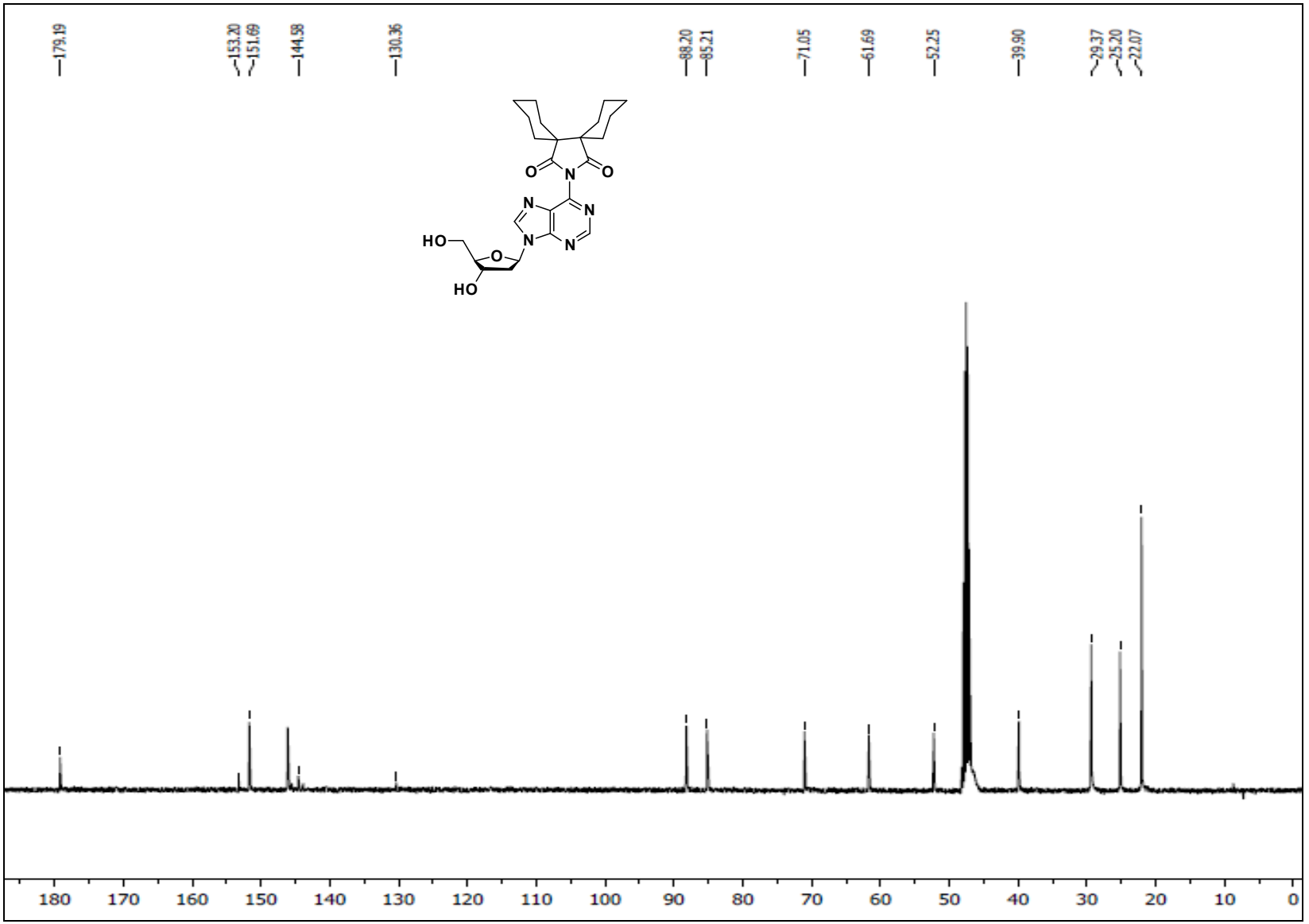
^{13}C NMR of compound **S19** (101 MHz, $CDCl_3$)



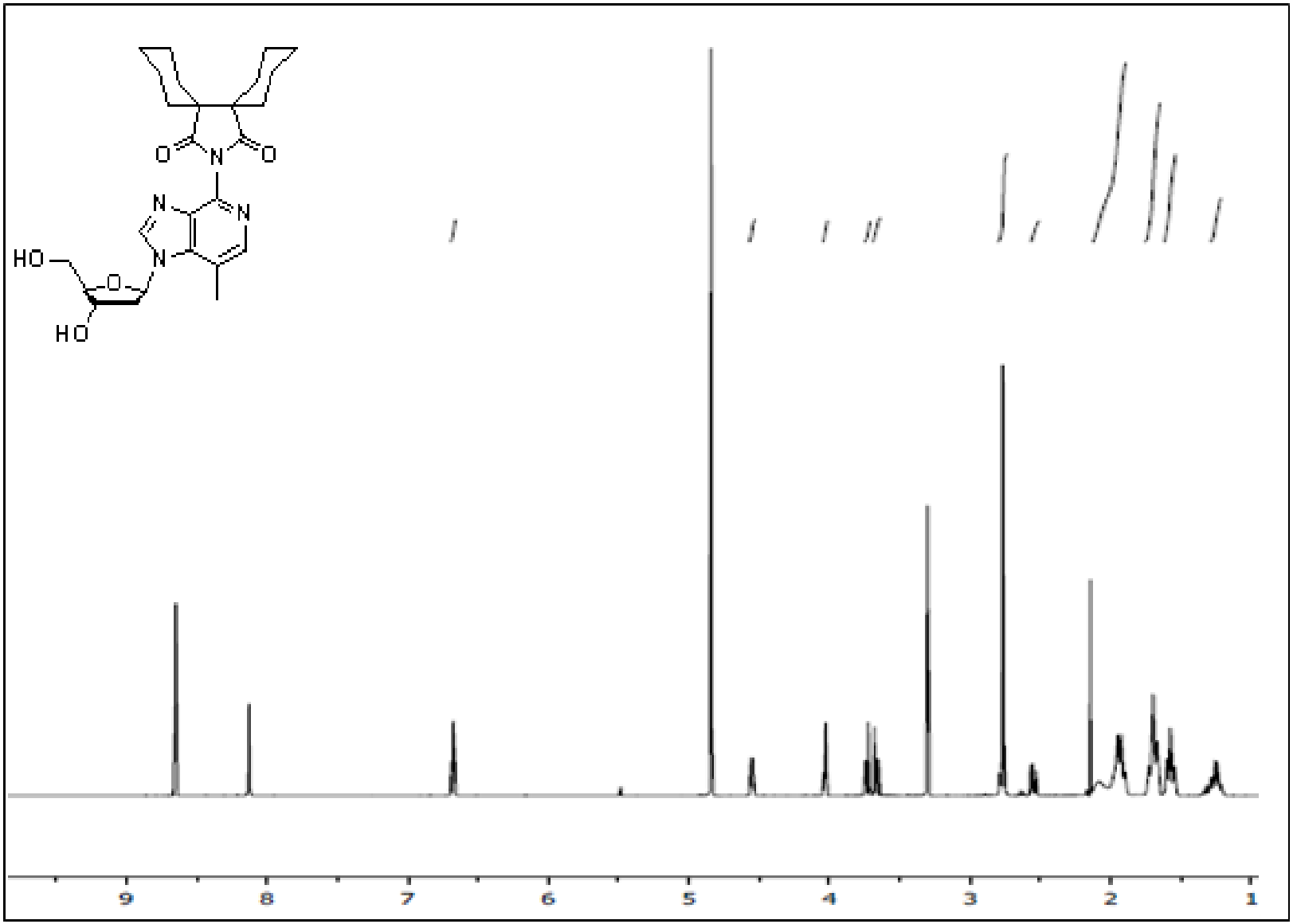
^{1}H NMR of compound **9** (500 MHz, CD_3OD)



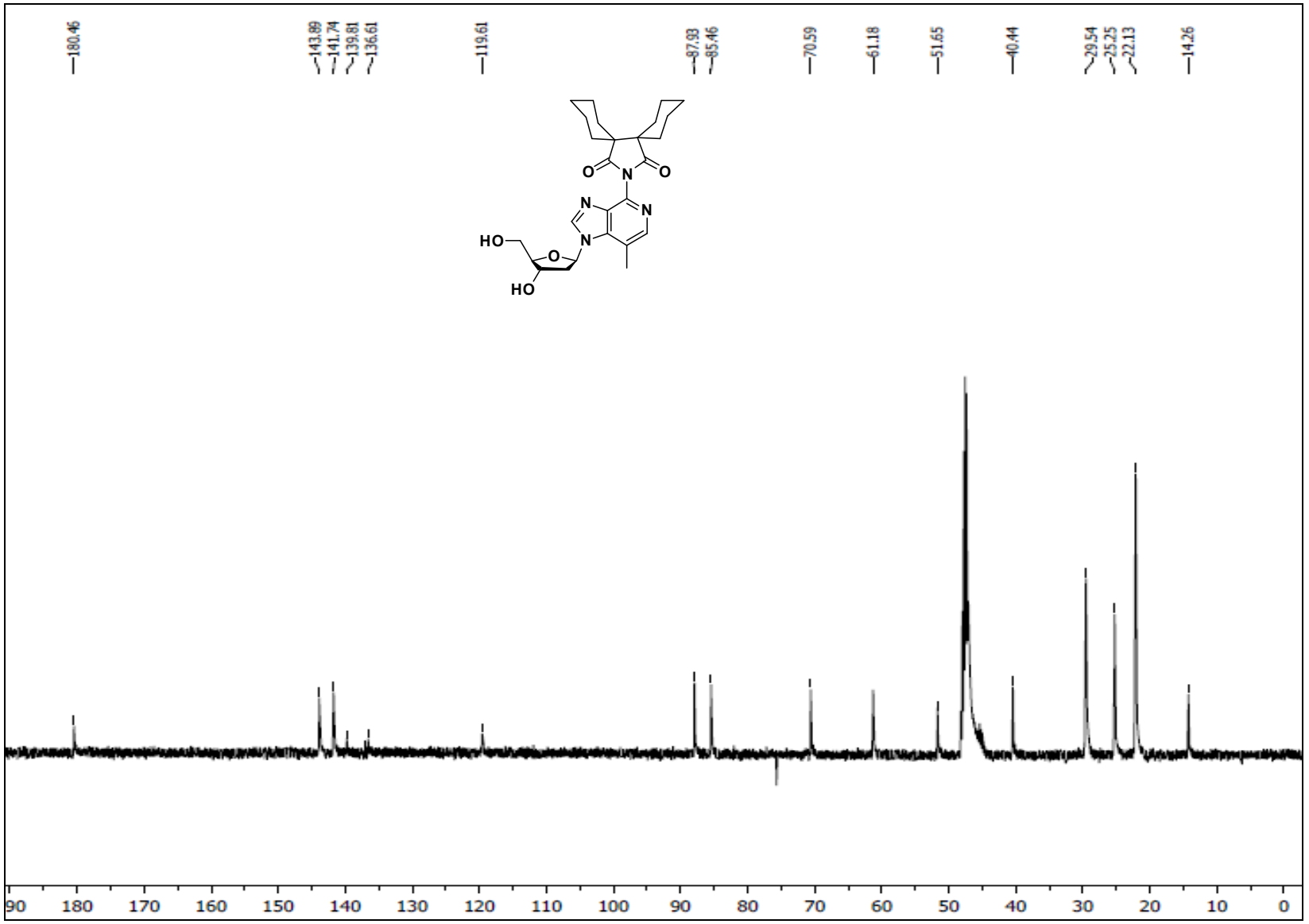
^{13}C NMR of compound **9** (101 MHz, CD_3OD)



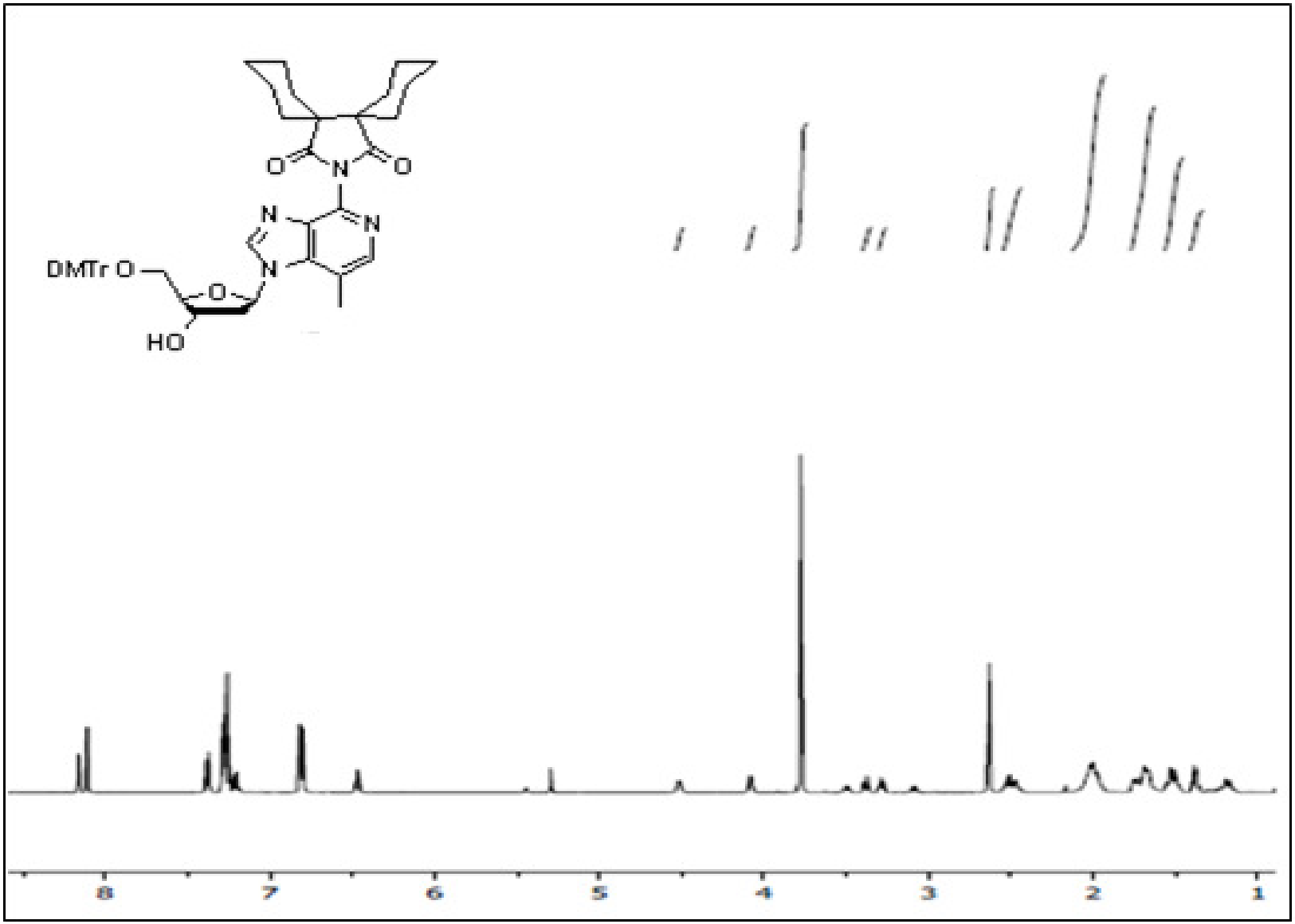
^{1}H NMR of compound **12** (500 MHz, CD_3OD)



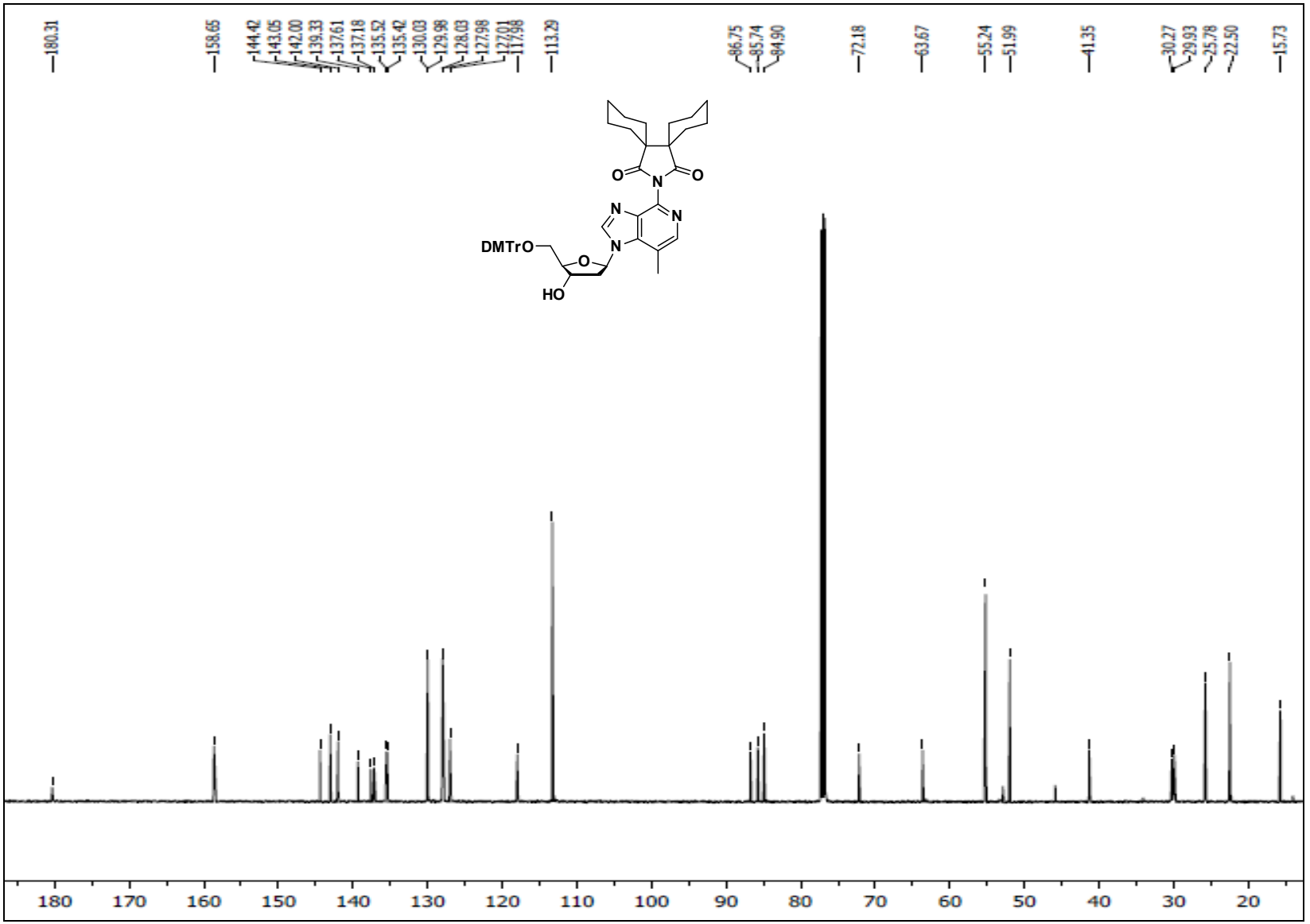
^{13}C NMR of compound **12** (101 MHz, CD_3OD)



^{1}H NMR of compound **13** (500 MHz, $CDCl_3$)



^{13}C NMR of compound **13** (126 MHz, $CDCl_3$)



^{31}P NMR of phosphoramidite **14** (202 MHz, $CDCl_3$)