Supporting Information (I)

Novel homologated-apio adenosine derivatives as A_3 adenosine receptor agonists: design, synthesis and molecular docking studies

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General Information:

All reagents and solvents were from standard commercial sources and used without purification, unless otherwise stated. All moisture sensitive reactions were carried out under argon atmosphere with dry and freshly distilled solvents. Precoated Merck silica gel plates (EM-60-F254) were used for thin-layer chromatography (TLC), and spots were visualized by exposure to UV lamp and/or charring solution (*p*-anisaldehyde) followed by heating. Column chromatography was performed on silica gel (100-200 mesh) and the elution was done with hexane & ethyl acetate and dichloromethane & methanol mixtures. ^{1}H NMR (400 MHz), proton decoupled ^{13}C NMR (100 MHz) and proton decoupled ^{19}F NMR (376.5 MHz) were recorded on a Bruker Avance 400 spectrometer. Samples were generally prepared in $CDCl_3$, CD_3OD & DMSO-d_6. Chemical shifts are expressed in parts per million (δ) scale relative to the residual solvent signals or using tetramethylsilane (Me_4Si) as internal standard. Coupling constants (J), whenever discernible, have been reported in hertz (Hz). The standard abbreviations s, d, t, q, m, br s refer to singlet, doublet, triplet, quartet, multiplet and broad singlet respectively. High resolution mass spectra (HRMS) were recorded on +ESI mode with Q-TOF Micromass spectrometer. UV spectra were recorded on a Perkin Elmer Lambda-35 UV/vis spectrometer.

Experimental:

(1*S*)-1-((3a*S*,6a*S*)-6a-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)ethane-1,2-diol (13). To a stirred solution of **12** (6 g, 13.68 mmol) in 120 ml acetone/water (3:1) were added *N*-methylmorpholine *N*-oxide (2.4 g,

20.55 mmol) and OsO_4 (2.5 % in ^{t}BuOH, 7 ml) successfully. The reaction mixture was stirred at room temperature for 8 h. Then the reaction mixture was treated with 40% aqueous $NaHSO_3$ (15 ml) and the resulting solution was again stirred for another 30 min. The mixture was acidified with saturated aqueous NH_4Cl solution and extracted with EtOAc (4 x 100 ml). The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated. The residue was purified by silica gel column chromatography [Hexane/ EtOAc (3:1)] to afford the diol **13** (5.89 g, 90 %) as a colour less fluid: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.07 (s, 9H), 1.36 (d, 3H, J = 7.6 Hz), 1.51 (d, 3H, J = 3.6), 3.00 (br d, 2H), 3.63-3.75 (m, 4H), 3.82-3.88 (m, 2H), 3.92-4.00 (m, 2H), 4.66 (dd, 1H, J = 1.6 Hz, 2.4 Hz), 7.36-7.43 (m, 6H), 7.67-7.70 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 19.2, 26.8, 27.8, 28.1, 29.7, 63.7, 63.9, 64.9, 65.1, 67.1, 70.2, 70.6, 74.9, 84.1, 84.3, 85.9, 86.7, 92.6, 114.1, 127.8, 129.9, 132.8, 132.9, 135.6, 135.7; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{26}H_{36}O_6SiNa$ 495.2179; found 495.2181.

(3a*S*,6a*S*)-6a-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxole-4-carbaldehyde (14). To a stirred solution of **13** (2 g, 4.24 mmol) in ethyl acetate 40 ml) was added $Pb(OAc)_4$ (2.24 g, 24.6 mmol) at 0 ˚C and the reaction mixture was stirred for 10 min at same temperature. The reaction mixture was filtered, the filtrate was diluted with EtOAc (30 ml), and the organic layer was repeatedly washed with saturated aqueous $NaHCO_3$ solution (3 x 50 ml), dried over anhydrous $NaSO_4$, and evaporated. The residue was purified by silica gel flash column chromatography (hexane/ethyl acetate, 9:1) to give the aldehyde **14** (1.62 g, 88%) as a colourless liquid: IR (film, ν_{max} in cm^{-1}) 2987, 2934, 2860, 1727, 1467, 1428, 1376, 1247, 1214; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.03 (s, 9H), 1.33 (s, 3H), 1.51 (s, 3H), 3.63 (d, 1H, J = 10.4 Hz), 3.71 (d, 1H, J = 10.4 Hz), 3.98 (d, 1H, J = 10

Hz), 4.05 (d, 1H, *J* = 10.4 Hz), 4.46 (s, 1H), 4.89 (d, 1H, *J* = 0.8 Hz), 7.37-7.44 (m, 7H), 7.61-7.64 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 19.3, 27.0, 27.1, 27.8, 28.0, 64.6, 75.8, 84.0, 90.1, 92.6, 114.2, 128.0, 130.2, 132.7, 132.8, 135.8, 135.7, 201.2.

((3a*S*,6a*S*)-6a-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methanol (15). To a solution of aldehyde **14** (1.6 g, 3.62 mmol) in MeOH 20 ml) was added sodium borohydride (0.272 g, 7.24 mmol) portion wise at 0 °C, and the reaction mixture was allowed to stir for 1 h at room temperature and neutralized with glacial AcOH. Solvent was removed and the mixture was partitioned between EtOAc (100 ml) and brine (50 ml). The aqueous layer was extracted using EtOAc (3x 75 ml). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and evaporated. The resulting residue was purified by silica gel column chromatography [hexane/ethylacetate, (3.5:1)] to give **15** as colourless liquid (1.49 g, 93%): IR (film, ν_{max} in cm^{-1}) 3458, 2986, 2934, 2861, 1468, 1428, 1375, 1247, 1214; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* (ppm) 1.07 (s, 9H), 1.37 (s, 3H), 1.53 (s, 3H), 1.95 (t, *J* = 5.5 Hz, 1H), 3.62 (t, *J* = 5.3 Hz, 2H), 3.68 (d, *J* = 10.8 Hz, 1H), 3.81 (d, *J* = 10.8 Hz, 1H), 3.87 (d, *J* = 9.9 Hz, 1H), 3.96 (d, *J* = 9.9 Hz, 1H), 4.15 (td, *J* = 5.7, 2.0 Hz, 1H), 4.49 (d, *J* = 2.1 Hz, 1H), 7.35-7.45 (m, 6H), 7.65-7.70 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 19.4, 27.0, 28.0, 28.2, 61.8, 65.0, 74.5, 84.0, 86.1, 93.0, 114.2, 128.0, 130.1, 132.9, 135.8, 135.9; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{25}H_{34}O_5SiNa$ 465.2073; found 465.2073.

General procedure for the condensation

To a stirred suspension of 6-chloropurine or 2,6 dichloropurine (1.8 eq.) and PPh_3 (2.4 eq.) in anhydrous THF (50 ml) was added DIAD (2.4 eq.) at 0 °C under N_2, and the reaction mixture was stirred for 30 min. To this mixture was added a solution of **15** (1 eq.) in

anhydrous THF (20 ml), and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was evaporated, and the residue was purified by silica gel column chromatography to give the corresponding purine derivatives.

9-(((3a*S*,6a*S*)-6a-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methyl)-6-chloro-9*H*-purine (16). A colour less thick liquid (0.85g, 71%): UV ($CHCl_3$) λ_{max} 265 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.09 (s, 9H), 1.48 (s, 3H), 1.69 (s, 3H), 3.71 (d, 1H, J = 12 Hz), 3.84 (d, 1H, J = 12 Hz), 3.90 (d, 1H, J = 8 Hz), 4.14 (d, 1H, J = 8 Hz), 4.24 (dd, 1H, J = 8 Hz, 16 Hz), 4.37- 4.44 (m, 2H) 4.53 (d, 1H, J = 4Hz), 7.40-7.46 (m, 6H), 7.66-7.69 (m, 4H), 8.05 (s, 1H), 8.73 (s,1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 19.3, 21.9, 27.0, 27.8, 27.9, 43.9, 64.7, 74.0, 83.5, 84.8, 92.6, 114.5, 128.0, 130.1, 130.2, 131.3, 132.6, 135.5, 135.6, 151.1, 152.0.

General procedure for the deprotection of the TBDPS group

To a solution of nucleoside derivatives in THF was added TBAF solution (1.3 eq.) at 0 ˚C and the reaction mixture was allowed to stir at room temperature for 1-2 h. The solvent was removed, the residue was purified by silica gel column chromatography to provide the desilylated compounds.

((3aR,6aS)-6-((6-chloro-9H-purin-9-yl)methyl)-2,2-dimethyldihydrofuro[3,4-d][1,3]dioxol-3a(4H)-yl)methanol (17). A colour less liquid (0.42 g, 92%): ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.38 (s, 3H), 1.51 (s, 3H), 3.07 (brs, 1H), 3.63 (d, 1H, J = 12 Hz), 3.78 (d, 1H, J = 12 Hz), 3.95 (d, 1H, J = 8 Hz), 4.09 (d, 1H, J = 12 Hz), 4.39 (dd, 1H, J = 4 Hz, 8 Hz), 4.46- 4.48 (m, 2H) 4.55 (dd, 1H, J =

4Hz, 12 Hz), 8.22 (s, 1H), 8.77 (s,1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 27.8, 27.9, 44.0, 63.6, 74.6, 83.6, 85.0, 92.5, 114.5, 131..6, 146.0, 151.5, 152.1, 152.2.

General procedure for the deprotection of the isopropylidene group

To a stirred solution of purine derivatives in THF (50 ml) was added 3 *N* HCl at room temperature and the mixture was stirred for 24 h at same temperature. The reaction mixture was neutralized with NH_4OH and evaporated. The residue was purified by flash silica gel column chromatography (CH_2Cl_2/MeOH) to afford the desired products.

(3S,4R)-2-((6-chloro-9H-purin-9-yl)methyl)-4-(hydroxymethyl)tetrahydrofuran-3,4-diol (18). A colour less floppy solid (0.12 g, 90%): UV (MeOH) λ_{max} 265 nm; ^{1}H NMR (400 MHz, CD_3OD) *δ* (ppm) 3.35 (s, 1H), 3.42 (d, 2H, *J* = 8 Hz), 3.70 (dd, 2H, *J* = 4 Hz, 8 Hz), 3.99 (d, 1H, *J* = 12 Hz), 4.10- 4.14 (m, 1H), 4.52 (dd, 1H, *J* = 8 Hz, 12 Hz), 4.67 (dd, 1H, *J* = 4 Hz, 16 Hz), 8.53 (s, 1H), 8.74 (s,1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 47.1, 64.7, 74.6, 76.0, 79.9, 81.6, 132.1, 149.2, 151.3, 153.2, 153.7; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{11}H_{13}ClN_4O_4Na$ 323.0523; found 323.0528.

General procedure for the *N*^{6}-substitution reaction

To a stirred solution of 6-chloropurine derivatives (**16**, **18**) (1 eq.) or 2,6-dichloropurine derivative **19** (1 eq.) and a suitable amine hydrochloride salts or free amines (1.5 eq.) in EtOH (10 ml) was added Et_3N (2 eq.) and the solution was stirred for 24-48 h at room

temperature. After removing the solvent under reduced pressure, the residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH, Hexane/EtOAc) to give the N^6-substituted amine derivatives.

(3S,4R)-2-((6-((3-fluorobenzyl)amino)-9H-purin-9-yl)methyl)-4-(hydroxymethyl)tetrahydrofuran-3,4-diol (6a). A white amorphous solid (0.11 g, 81%): UV (MeOH) λ_{max} 270 nm; ^{1}H NMR (400 MHz, CD_3OD) δ (ppm) 3.42 (d, 2H, J = 4 Hz), 3.69 (d, 2H, J = 12 Hz), 3.97 (d, 2H, J = 12 Hz,), 4.06- 4.10 (m, 1H), 4.38 (dd, 1H, J = 4 Hz, 12 Hz), 4.53 (dd, 1H, J = 4 Hz, 12 Hz), 6.95 (td, 1H, J = 4 Hz, 12 Hz), 7.20 (t, 2H, J = 4 Hz), 7.30 (t, 1H, J = 8 Hz), 8.08 (s, 1H), 8.26 (s,1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 46.5, 64.8, 74.5, 75.9, 80.0, 82.0, 114.8, 115.1, 115.4, 115.8, 116.0, 116.2, 117.0, 124.3, 125.2, 131.3, 131.4, 131.8, 143.3, 154.0, 163.3, 165.8; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{20}FN_5O_4H$ 390.1578; found 390.1580.

(3S,4R)-2-((6-((3-chlorobenzyl)amino)-9H-purin-9-yl)methyl)-4-(hydroxymethyl)tetrahydrofuran-3,4-diol (6b). A colour less solid (0.13 g, 79%): UV (MeOH) λ_{max} 269 nm ^{1}H NMR (400 MHz, CD_3OD) δ (ppm) 3.42 (d, 2H, J = 4 Hz), 3.69 (d, 2H, J = 12 Hz), 3.96 (d, 2H, J = 12 Hz,), 4.05- 4.10 (m, 1H), 4.38 (dd, 1H, J = 4 Hz, 12 Hz), 4.53 (dd, 1H, J = 4 Hz, 12 Hz), 6.95 (d, 1H, J = 4 Hz, 12 Hz), 7.22 (t, 2H, J = 4 Hz), 7.32 (d, 1H, J = 8 Hz), 8.07 (s, 1H), 8.26 (s,1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 45.4, 46.5, 64.9, 74.5, 75.9, 80.1, 82.0, 114.9, 131.2, 135.6, 137.2, 143.4, 154.2, 163.4; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{20}ClN_5O_4H$ 406.1282; found 406.1284.

(3S,4R)-2-((6-((3-bromobenzyl)amino)-9H-purin-9-yl)methyl)-4-(hydroxymethyl)tetrahydrofuran-3,4-diol (6c). A colour less solid (0.1 g, 78%): UV (MeOH) λ_{max} 270 nm; ^{1}H NMR (400 MHz, CD_3OD) δ (ppm) 3.42 (d, 2H, J = 4 Hz), 3.68 (d, 1H, J = 4 Hz),

3.71 (s, 1H), 3.87 (s, 3H), 3.98 (d, 1H, *J* = 8 Hz), 4.06- 4.10 (m, 1H), 4.37 (dd, 1H, *J* = 8 Hz, 16 Hz), 4.52 (dd, 1H, *J* = 4 Hz, 12 Hz), 7.27 (d, 2H, *J* = 8 Hz), 7.43 (d, 1H, *J* = 8Hz), 7.54 (s, 1H), 8.07 (s, 1H), 8.26 (s,1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 51.0, 54.9, 72.0, 82.4, 83.6, 88.0, 89.9, 131.2, 135.9, 137.8, 139.5, 140.0, 141.4, 146.4, 151.0, 161.9; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{20}BrN_5O_4H$ 450.0777; found 450.0709.

(3S,4R)-4-(hydroxymethyl)-2-((6-((3-iodobenzyl)amino)-9H-purin-9-yl)methyl)tetrahydrofuran-3,4-diol (6d). A white floppy solid (0.12 g, 80%): UV (MeOH) λ_{max} 270; nm ^{1}H NMR (400 MHz, CD_3OD) *δ* (ppm) 3.42 (d, 2H, *J* = 4 Hz), 3.68 (s, 1H), 3.70 (d, 1H, *J* = 4 Hz), 3.97 (d, 1H, *J* = 12 Hz), 4.05- 4.10 (m, 1H), 4.38 (dd, 1H, *J* = 8 Hz, 16 Hz), 4.53 (dd, 1H, *J* = 4 Hz, 12 Hz), 7.08 (t, 1H, *J* = 8 Hz), 7.59 (d, 1H, *J* = 8Hz), 7.68 (d, 2H, *J* = 8 Hz), 8.08 (s, 1H), 8.26 (s,1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 45.0, 46.5, 64.9, 74.5, 75.9, 80.0, 82.1, 95.3, 128.0, 128.7, 131.5, 131.8, 137.5, 141.9, 143.3, 154.0; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{20}IN_5O_4H$ 498.0638; found 498.0640.

9-(((3aS,6aS)-6a-(((tert-butyldiphenylsilyl)oxy)methyl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methyl)-2,6-dichloro-9H-purine (19). A colour less thick liquid (0.9 g, 69%): UV ($CHCl_3$ λ_{max} 275nm; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* (ppm) 1.10 (s, 9H), 1.34 (s, 3H), 1.48 (s, 3H), 3.73 (d, 1H, *J* = 12 Hz), 3.85 (d, 1H, *J* = 12 Hz), 3.91 (d, 1H, *J* = 8 Hz), 4.15- 4.23 (m, 2H), 4.32-4.42 (m, 2H), 4.52 (d, 1H, *J* = 4Hz), 7.42-7.45 (m, 6H), 7.67-7.69 (m, 4H), 8.06 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 19.5, 27.2, 27.9, 28.0, 44.0, 64.8, 70.2, 74.1, 83.6, 85.0, 92.7, 114.6, 128.2, 130.3, 132.7, 135.7, 135.8, 146.4, 151.9, 153.2, 153.5, 156.4, 156.6.

9-(((3aS,6aS)-6a-(((tert-butyldiphenylsilyl)oxy)methyl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methyl)-2-chloro-N-(3-fluorobenzyl)-9H-purin-6-amine (20a). A colour less liquid (0.55 g, 76%): ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.09 (s, 9H), 1.33 (s, 3H), 1.47 (s, 3H), 3.71 (d, 1H, *J* = 12 Hz), 3.82 (d, 1H, *J* = 12 Hz), 3.90 (d, 1H, *J* = 12 Hz), 4.04- 4.13 (m, 2H), 4.29 (dd, 1H, *J* = 4Hz, 16Hz), 4.38- 4.41 (m, 1H), 4.50 (d, 1H, *J* = 4 Hz), 4.82 (brs, 1H), 6.38 (brs, 1H), 6.96 (td, 1H, *J* = 4Hz, 8 Hz), 7.07 (dt, 1H, *J* = 4 Hz, 8Hz), 7.15 (d, 1H, *J* = 8 Hz), 7.28-7.33 (m, 1H), 7.39-7.48 (m, 6H), 7.65-7.69 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 19.5, 27.2, 28.0, 43.5, 64.9, 74.0, 83.9, 85.1, 92.8, 114.4, 114.9, 128.2, 130.3, 130.5, 135.8, 135.9, 140.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -112.65 (s).

9-(((3aS,6aS)-6a-(((tert-butyldiphenylsilyl)oxy)methyl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methyl)-2-chloro-N-(3-chlorobenzyl)-9H-purin-6-amine (20b). A colour less liquid (0.46 g, 84%): ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.09 (s, 9H), 1.33 (s, 3H), 1.47 (s, 3H), 3.71 (d, 1H, *J* = 12 Hz), 3.82 (d, 1H, *J* = 12 Hz), 3.90 (d, 1H, *J* = 12 Hz), 4.04- 4.13 (m, 2H), 4.29 (dd, 1H, *J* = 4Hz, 12Hz), 4.37- 4.40 (m, 1H), 4.50 (d, 1H, *J* = 4 Hz), 4.79 (brs, 1H), 6.46 (brs, 1H), 7.25 (d, 2H, *J* = 4 Hz), 7.35 (s, 1H), 7.39-7.44 (m, 6H), 7.64-7.69 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm)19.5, 27.2, 28.0, 43.5, 64.9, 74.0, 83.9, 85.1, 92.8, 114.5, 126.2, 128.0, 130.4, 132.7, 132.9, 135.8, 140.9, 155.2.

N-(3-bromobenzyl)-9-(((3aS,6aS)-6a-(((tert-butyldiphenylsilyl)oxy)methyl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methyl)-2-chloro-9H-purin-6-amine (20c). A colour less liquid (0.49 g, 80%): ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.09 (s, 9H), 1.33 (s, 3H), 1.47 (s, 3H), 3.71 (d, 1H, *J* = 12 Hz), 3.82 (d, 1H, *J* = 12 Hz), 3.90 (d, 1H, *J* = 12 Hz), 4.04- 4.13 (m, 2H), 4.29 (dd, 1H,

J = 4Hz, 12Hz), 4.37- 4.41(m, 1H), 4.50 (d, 1H, *J* = 4 Hz), 4.79 (brs, 1H), 6.42 (brs, 1H), 7.20 (t, 1H, *J* = 8 Hz), 7.30 (d, 1H, *J* = 8 Hz), 7.40-7.46 (m, 7H), 7.52 (t, 1H, *J* = 4 Hz), 7.65-7.69 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm)19.5, 27.2, 28.0, 43.5, 64.9, 74.0, 83.9, 85.1, 92.8, 114.5, 128.2, 130.3, 130.5, 131.0, 135.8, 135.9, 140.9.

9-(((3aS,6aS)-6a-(((tert-butyldiphenylsilyl)oxy)methyl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methyl)-2-chloro-N-(3-iodobenzyl)-9H-purin-6-amine (20d). A colour less liquid (0.55 g, 79%) ^{1}H NMR (400 MHz, $CDCl_3$) *δ* (ppm) 1.09 (s, 9H), 1.33 (s, 3H), 1.47 (s, 3H), 3.71 (d, 1H, *J* = 12 Hz), 3.82 (d, 1H, *J* = 12 Hz), 3.90 (d, 1H, *J* = 12 Hz), 4.04- 4.15 (m, 2H), 4.29 (dd, 1H, *J* = 4Hz, 12Hz), 4.37- 4.41(m, 1H), 4.50 (d, 1H, *J* = 4 Hz), 4.76 (brs, 1H), 6.45 (brs, 1H), 7.06 (t, 1H, *J* = 8 Hz), 7.33 (d, 1H, *J* = 8 Hz), 7.39-7.47 (m, 6H), 7.61-7.72 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm)19.5, 27.2, 28.0, 43.5, 64.9, 74.0, 83.9, 85.1, 92.8, 94.8, 114.4, 128.2, 130.4, 130.6, 132.8, 135.8, 140.9.

((3aR,6aS)-6-((2-chloro-6-((3-iodobenzyl)amino)-9H-purin-9-yl)methyl)-2,2-dimethyldihydrofuro[3,4-d][1,3]dioxol-3a(4H)-yl)methanol (21d). A colour less liquid (0.32 g, 92%): ^{1}H NMR (400 MHz, $CDCl_3$) *δ* (ppm) 1.35 (s, 3H), 1.50 (s, 3H), 3.68 (dd, 1H, *J* = 4 Hz, 12 Hz), 3.88 (dd, 1H, *J* = 4Hz, 12 Hz), 3.98 (d, 1H, *J* = 8 Hz), 4.08- 4.14 (m, 3H), 4.38 (t, 1H, *J* = 8Hz), 4.48- 4.54(m, 2H), 4.78 (brs, 1H), 6.59 (brs, 1H), 7.09 (t, 1H, *J* = 8 Hz), 7.34 (d, 1H, *J* = 8 Hz), 7.63 (d, 1H, *J* = 4 Hz), 7.73 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 27.6, 27.7, 42.9, 63.4, 74.7, 84.0, 85.6, 92.7, 94.8, 113.8, 130.7, 137.1, 140.9.

(3S,4R)-2-((2-chloro-6-((3-fluorobenzyl)amino)-9H-purin-9-yl)methyl)-4-(hydroxymethyl)tetrahydrofuran-3,4-diol (7a). A colour less solid (0.098 g, 88%): UV (DMSO) λ_{max} 274 nm; ^{1}H NMR (400 MHz, DMSO-d_6) *δ* (ppm) 3.16 (d, 1H, *J* = 4Hz), 3.22-

3.28 (m, 2H), 3.51 (d, 1H, *J* = 8Hz), 3.65 (dd, 1H, *J* = 4 Hz, 8 Hz), 3.90 (d, 1H, *J* = 12 Hz), 3.93- 3.97 (m, 1H), 4.10- 4.20 (m, 1H), 4.35 (dd, 1H, *J* = 4Hz, 12 Hz), 4.51 (s, 1H), 4.65 (d, 1H, *J* = 4Hz), 4.81 (t, 1H, *J* = 8Hz), 5.08 (d, 1H, *J* = 4Hz), 7.04 (td, 1H, *J* = 4 Hz, 12 Hz), 7.16 (t, 2H, *J* = 12 Hz), 7.33- 7.38 (m, 1H), 8.09 (s, 1H), 8.32 (t, 1H, *J* = 4Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 42.7, 45.6, 48.6, 57.5, 62.3, 72.8, 74.1, 78.4, 79.6, 113.5, 113.7, 113.9, 114.1, 117.9, 123.3, 130.3, 142.0, 150.1, 152.9, 154.8, 160.9, 163.4; ^{19}F NMR (376 MHz, DMSO-d_6) δ (ppm) -113.49 (s); HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{19}ClFN_5O_4H$ 424.1182; found 424.1191.

(3S,4R)-2-((2-chloro-6-((3-chlorobenzyl)amino)-9H-purin-9-yl)methyl)-4-(hydroxymethyl)tetrahydrofuran-3,4-diol (7b). A colour less floppy solid (0.11 g, 90%): UV (DMSO) λ_{max} 275 nm; ^{1}H NMR (400 MHz, , DMSO-d_6) *δ* (ppm) 3.21-3.27 (m, 2H), 3.49 (d, 1H, *J* = 12 Hz), 3.63 (d, 1H, *J* = 8Hz), 3.88-3.96 (m, 2H), 4.15 (dd, 1H, *J* = 8 Hz, 12 Hz), 4.35 (dd, 1H, *J* = 4Hz, 12Hz), 4.50 (brs, 1H), 4.62 (d, 2H, *J* = 4Hz), 4.81 (brs, 1H), 5.09 (brs, 1H), 7.28- 7.38 (m, 4H), 8.08 (s, 1H), 8.33 (t, 1H, *J* = 4Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 42.7, 45.6, 62.3, 72.8, 74.1, 78.4, 79.6, 126.0, 126.8, 127.2, 130.2, 132.9, 142.0, 154.8; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{19}Cl_2N_5O_4H$ 440.0887; found 440.0882.

(3S,4R)-2-((6-((3-bromobenzyl)amino)-2-chloro-9H-purin-9-yl)methyl)-4-(hydroxymethyl)tetrahydrofuran-3,4-diol (7c). A colour less amorphous solid(0.11 g, 90%): UV (DMSO λ_{max} 275 nm; ^{1}H NMR (400 MHz, DMSO-d_6) *δ* (ppm) 3.16 (d, 1H, *J* = 4Hz), 3.22- 3.29 (m, 2H), 3.51 (d, 1H, *J* = 8Hz), 3.64 (dd, 1H, *J* = 4Hz, 8 Hz), 3.89- 3.97 (m, 2H), 4.11- 4.20 (m, 1H), 4.35 (dd, 1H, *J* = 4Hz, 16 Hz), 4.53 (s, 1H), 4.63 (d, 1H, *J* = 8Hz), 4.83 (t, 1H, *J* = 8Hz), 5.11 (d, 1H, *J* = 8Hz), 7.28 (t, 1H, *J* = 8 Hz), 7.34 (d, 1H, *J* = 8

Hz), 7.43 (d, 1H, *J* = 8Hz), 7.54 (s, 1H), 8.10 (s, 1H), 8.85 (t, 1H, *J* = 8Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 42.7, 45.7, 48.6, 62.3, 72.8, 74.1, 78.4, 79.6, 117.9, 121.6, 126.4, 129.7, 130.1, 130.6, 142.1, 150.1, 153.0, 154.8; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{19}BrClN_5O_4H$ 484.0382; found 484.0381.

(3S,4R)-2-((2-chloro-6-((3-iodobenzyl)amino)-9H-purin-9-yl)methyl)-4-(hydroxymethyl)tetrahydrofuran-3,4-diol (7d). A colour less solid (0.12 g, 89%): UV (DMSO) λ_{max} 275nm ^{1}H NMR (400 MHz, DMSO-d_6) *δ* (ppm) 3.17 (d, 1H, *J* = 4Hz), 3.22- 3.31 (m, 2H), 3.51 (d, 1H, *J* = 8Hz), 3.65 (t, 1H, *J* = 8 Hz), 3.89- 3.97 (m, 2H), 4.09- 4.19 (m, 2H), 4.36 (dd, 1H, *J* = 4Hz, 16 Hz), 4.51 (s, 1H), 4.59 (d, 1H, *J* = 4 Hz), 4.81 (t, 1H, *J* = 8Hz), 5.09 (d, 1H, *J* = 8Hz), 712 (t, 1H, *J* = 8 Hz), 7.35 (d, 1H, *J* = 8 Hz), 7.60 (d, 1H, *J* = 8Hz), 7.74(s, 1H), 8.09 (s, 1H), 8.83 (t, 1H, *J* = 4Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 42.5, 45.6, 48.6, 62.3, 72.8, 74.1, 78.4, 79.6, 94.7, 117.9, 126.8, 130.5, 135.6, 136.0, 142.0, 150.1, 152.9, 154.7; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{19}ClIN_5O_4H$ 532.0243; found 532.0243.

9-(((3aS,6aS)-6a-(((tert-butyldiphenylsilyl)oxy)methyl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methyl)-N-(3-iodobenzyl)-9H-purin-6-amine (22). A colour less thick liquid (0.84 g, 81%): ^{1}H NMR (400 MHz, $CDCl_3$) *δ* (ppm) 1.08 (s, 9H), 1.33 (s, 3H), 1.48 (s, 3H), 3.69 (d, 1H, *J* = 12 Hz), 3.82 (d, 1H, *J* = 8 Hz), 3.90 (d, 1H, *J* = 12 Hz), 4.10- 4.17 (m, 2H), 4.33 (dd, 1H, *J* = 4Hz, 16Hz), 4.41- 4.45(m, 1H), 4.54 (d, 1H, *J* = 4 Hz), 4.83 (brs, 1H), 6.18 (brs, 1H), 7.05 (t, 1H, *J* = 8 Hz), 7.33 (d, 1H, *J* = 8 Hz), 7.38-7.43 (m, 6H), 7.60 (d, 1H, *J* = 8 Hz), 7.66-7.69 (m, 5H), 7.73 (s, 1H), 8.39 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 19.5, 27.2, 28.0, 43.6, 65.0, 74.2, 84.0, 85.1, 92.9, 114.5, 127.1, 128.1, 130.3, 132.8, 135.8, 140.6, 141.3, 153.4, 154.7.

((3aR,6aS)-6-((6-((3-iodobenzyl)amino)-9H-purin-9-yl)methyl)-2,2-dimethyldihydrofuro[3,4-d][1,3]dioxol-3a(4H)-yl)methanol (23). A colour less liquid (0.49 g, 92%): ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.28 (s, 3H), 1.46 (s, 3H), 2.28 (brs, 1H), 3.64 (d, 1H, *J* = 12 Hz), 3.83 (d, 1H, *J* = 12 Hz), 3.94 (d, 1H, *J* =12 Hz), 4.06- 4.11 (m, 2H), 4.20 (d, 1H, *J* = 8Hz), 4.35 (dd, 1H, *J* =4 Hz, 8Hz), 4.44(s, 1H), 4.54 (dd, 1H, *J* = 8 Hz, 12 Hz), 4.79 (brs, 1 H), 5.47 (brs, 1H), 6.79 (s, 1H), 7.02 (t, 1H, *J* = 8 Hz), 7.30(d, 1H, *J* = 8 Hz), 7.57 (d, 1H, *J* = 8 Hz), 7.68 (d, 2H, *J* =4 Hz), 8.35 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 21.2, 27.6, 42.5, 60.6, 63.3, 74.7, 84.1, 85.8, 92.8, 94.8, 113.5, 119.7, 127.0, 130.6, 136.7, 140.6, 141.0, 153.3, 155.1.

(3aR,6aS)-6-((2-chloro-6-((3-iodobenzyl)amino)-9H-purin-9-yl)methyl)-N,2,2-trimethyldihydrofuro[3,4-d][1,3]dioxole-3a(4H)-carboxamide (27). To a solution of **21d** (0.52 g, 0.9 mmol) in dry DMF (12 ml) was added pyridinium dichromate (PDC) (3.4 g, 9 mmol), and the reaction mixture was stirred at room temperature for 20 h. The reaction mixture was poured into water (20 ml) and stirred for another 1 h. The precipitate was filtered off, and the filter cake was washed with water (50 ml) and dried under high vacuum to give acid derivative **25** as a brownish solid (0.33 g) which was used for the next step without further purification.

To a solution of **25** (0.33 g, 0.57 mmol), EDC (0.16g, 0.84 mmol), HOBt (0.11g, 0.84 mmol), and methylamine·HCl (0.06 g, 0.84 mmol) in CH_2Cl_2 (50 ml) was added *N*-*N*-diisopropyl ethyl amine (DIPEA) (0.29 ml, 1.72 mmol), and the mixture was stirred at room temperature for 12 h. The reaction mixture was evaporated, and the residue was purified by a silica gel column chromatography (hexane/EtOAc = 2:1-1:2) to give **27** as a whitish solid mass (0.25 g, 48% for 2 steps): ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.38 (s, 3H), 1.52 (s, 3H), 2.91 (d, 3H, *J* = 4 Hz), 4.05 (d, 1H, *J* = 12 Hz), 4.26 (d, 1H, *J* = 8 Hz), 4.40- 4.52 (m, 2H), 4.66 (dd, 2H, *J* = 8Hz,

12 Hz), 4.77 (brs, 1H), 6.43 (brs, 1H), 6.82 (d, 1H, *J* = 4 Hz), 7.07 (t, 1H, *J* = 8 Hz), 7.34(d, 1H, *J* = 8 Hz), 7.62 (d, 1H, *J* = 8 Hz), 7.73 (d, 1H, *J* =12 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 21.3, 26.2, 26.3, 27.0, 42.1, 60.6, 83.3, 87.7, 92.4, 94.8, 115.0, 130.6, 137.0, 141.3, 171.9.

(3R,4S)-3,4-dihydroxy-5-((6-((3-iodobenzyl)amino)-9H-purin-9-yl)methyl)-N-methyltetrahydrofuran-3-carboxamide (4). A colour less solid (0.081 g, 85%): UV (DMSO) λ_{max} 270 nm ^{1}H NMR (400 MHz, DMSO-d_6) *δ* (ppm) 2.61 (d, 3H, *J* = 4 Hz), 3.65 (d, 1H, *J* = 12 Hz), 3.98- 4.09 (m, 3H), 4.29 (dd, 1H, *J* = 8 Hz, 12 Hz), 4.66 (brs, 1H), 5.38 (s, 1H), 5.60 (d, 1H, *J* = 4 Hz), 7.10(t, 1H, *J* = 8 Hz), 7.36 (d, 1H, *J* = 8 Hz), 7.57 (d, 1H, *J* = 8 Hz), 7.72 (s, 1H), 7.87 (d, 1H, *J* = 4 Hz), 8.09 (s, 1H), 8.21 (s, 1H), 8.35 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 25.8, 45.0, 76.4, 76.6, 79.3, 80.8, 94.7, 126.6, 130.4, 135.3, 135.7, 141.4, 143.0, 152.3, 172.2; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{19}H_{21}IN_6O_4Na$ 547.0561; found 547.0559.

(3R,4S)-5-((2-chloro-6-((3-iodobenzyl)amino)-9H-purin-9-yl)methyl)-3,4-dihydroxy-N-methyltetrahydrofuran-3-carboxamide (5). A white solid (0.09 g, 85%): UV (DMSO) λ_{max} 275 nm ^{1}H NMR (400 MHz, DMSO-d_6) *δ* (ppm) 2.61 (d, 3H, *J* = 4 Hz), 3.66 (d, 1H, *J* = 8 Hz), 3.97 (td, 1H, *J* = 4 Hz, 8 Hz), 4.05 (dd, 2H, *J* = 4 Hz, 8 Hz), 4.24 (dd, 1H, *J* = 8 Hz, 16 Hz), 4.37 (dd, 1H, *J* = 4 Hz, 12 Hz), 4.59 (d, 1H, *J* = 4 Hz), 7.13 (t, 1H, *J* = 8 Hz), 7.35 (d, 1H, *J* = 8 Hz), 7.60 (d, 1H, *J* = 8 Hz), 7.74 (s, 1H), 7.89 (d, 1H, *J* = 4 Hz), 8.11 (s, 1H), 8.85 (t, 1H, *J* = 4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 25.8, 45.3, 76.4, 76.7, 79.1, 80.8, 94.7, 117.9, 126.8, 130.6, 135.6, 136.1, 142.1, 172.2; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{19}H_{20}ClIN_6O_4H$ 559.0352; found 559.0354.

Molecular modelling and docking:

In the current study, the X-ray structure of agonist-bound adenosine A_2A receptor (PDB ID: 2YDO) was identified as a template for A_3AR receptor using Blast.[1] The target template identity was found to be 40% (61% positives) indicating suitability of the template for homology modelling of A_3AR. The alignment between the target and template was done using PROMALS 3D that can utilize 3D structural information for generation of optimal alignment.[2] It has been known that the binding sites of GPCR homology models are often too small to accommodate known ligands, mostly because of misplacement of side-chains of binding site residues during homology model generation. Therefore, the adenosine molecule, which is a natural ligand for A_3AR, co-crystalized with template (A_2AR) was utilized for the homology modeling in the ligand supported homology modeling mode. It is hoped that it will prevent the misplacement of side chains and will preserve orientation of conserved binding site residues. Fifty homology models were generated with quick refinement (refine_fast) as implied in Modeller v9.13. The final model was selected based on lowest molpdf score. The selected model was then imported into protein preparation wizard in Maestro module of Schrodinger v9.3 software prior to docking. The correct bond orders were assigned, hydrogens were added and optimized and the whole complex (A3AR model and adenosine) was then minimized to a gradient of 0.01 Kcal/Mol using OPLS 2005 force field as implied in Maestro.[3]

A number of reported agonists were selected and a few molecules were designed based on reported molecules. These molecules were sketched in Maestro and minimized for proper 3D geometry using OPLS-AA forcefield. The 3D structures were further prepared using LigPrep wizard for generation of tautomers and correct ionization states prior to docking.[4] After ligand

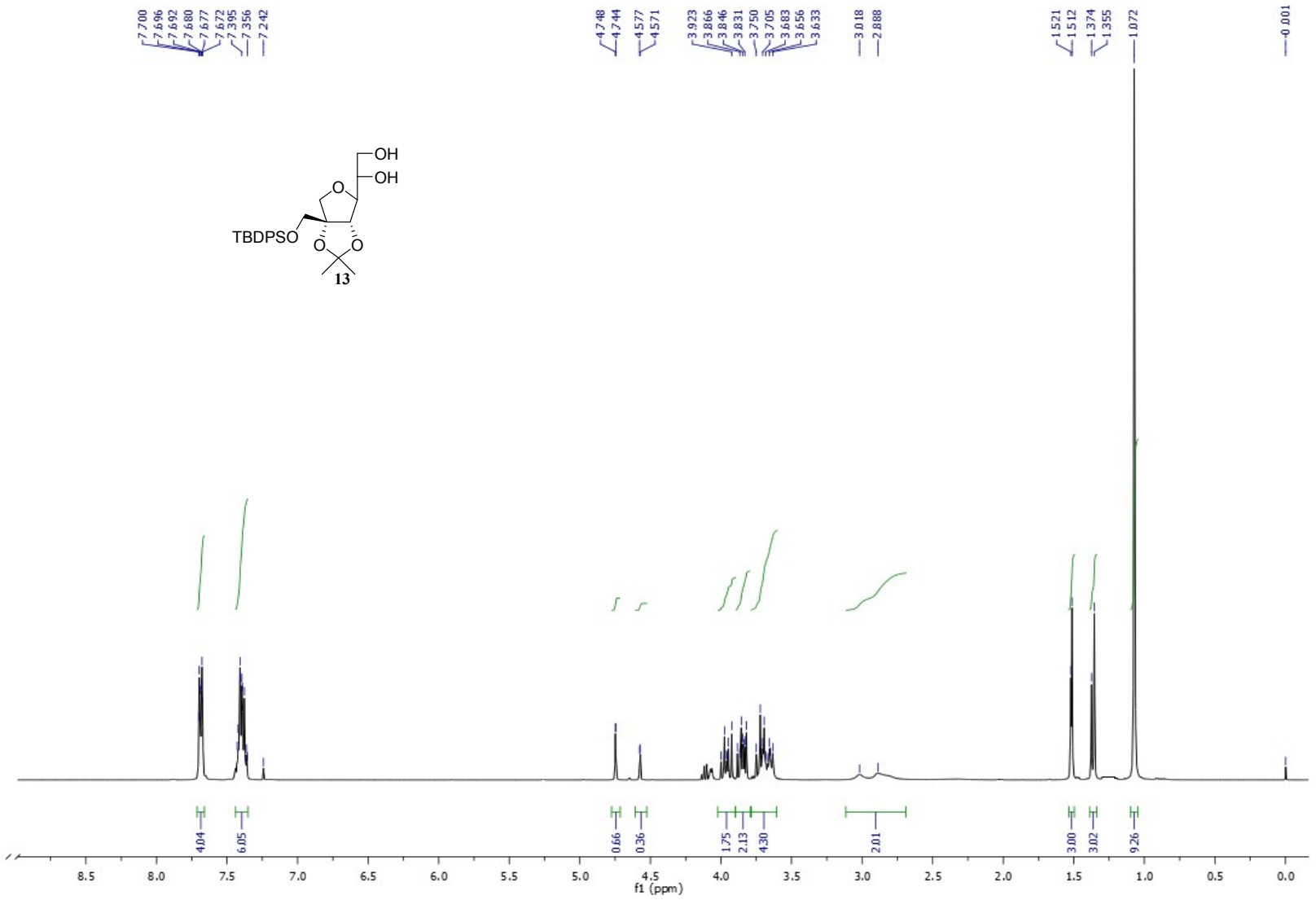
preparation and minimization molecules were preceded further for Glide SP docking at generated receptor grid using Glide module in Schrodinger software. The best complexes were selected on the basis of molecule orientation and docking score. Finally, the selected poses for each of the molecule were further processed for binding affinity calculation using MM/GBSA as implied in Schrodinger v9.3 software.

The binding free energy (MM/GBSA) is calculated as:

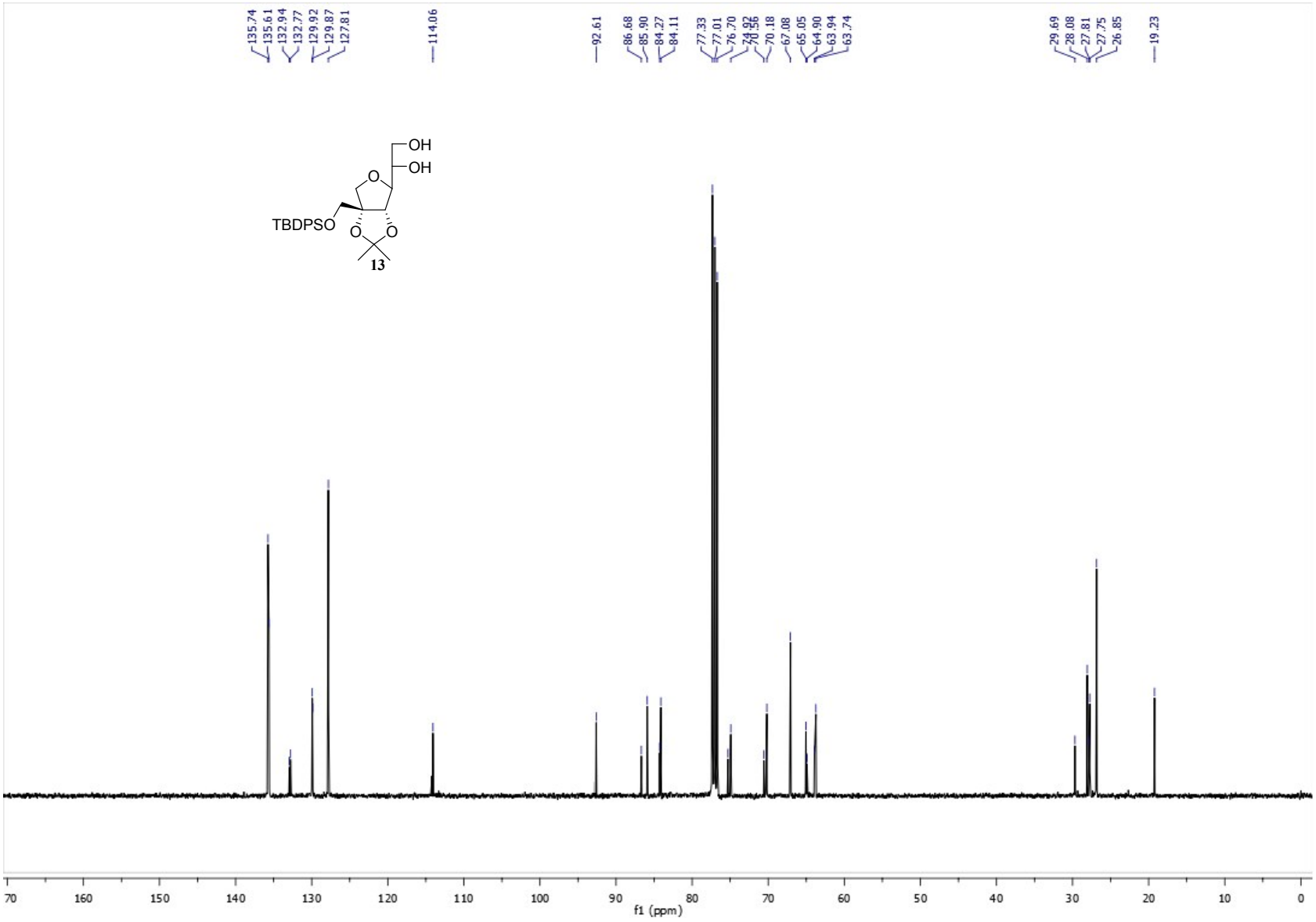
$$\Delta G_{bind} = \Delta E_{MM} + \Delta G_{sol} - T\Delta S$$

Where, ΔG_{bind} is binding free energy of a molecule in the system, ΔE_{MM} corresponds to total molecular mechanics free energy contributed by bonds, angles, dihedrals, van der Waals & electrostatic interactions in gas phase and ΔG_{sol} denotes polar and non-polar contributions to solvent free energy and $T\Delta S$ denotes the change in conformational entropy upon binding. Here, the selected different complexes were estimated for MM/GBSA calculation. Finally, molecules were classified on the basis of docking score, MM/GBSA score and critical interaction with Ser271, Phe168 and Asn250.

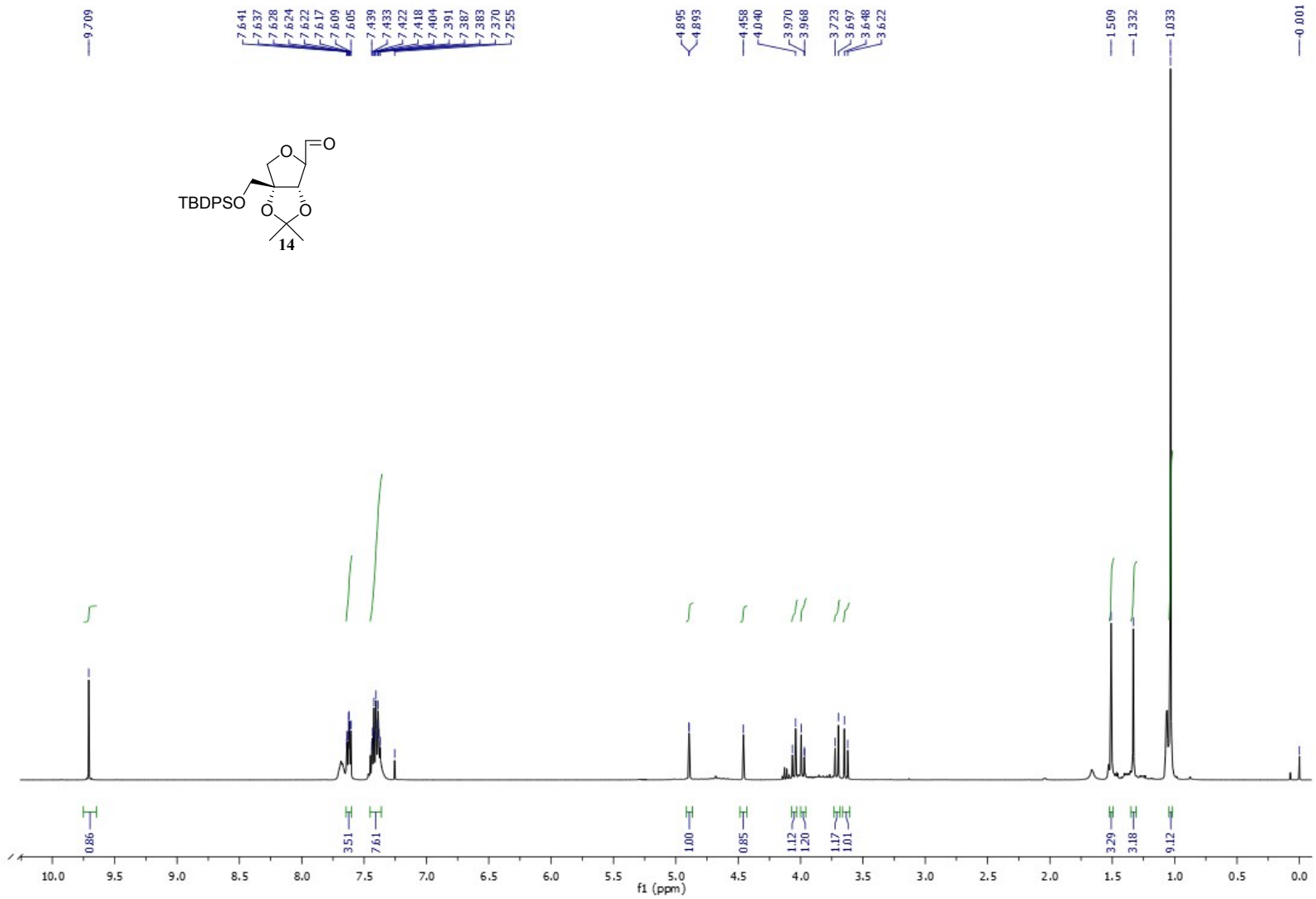
^{1}H spectrum (400 MHz, $CDCl_3$) of compound 13



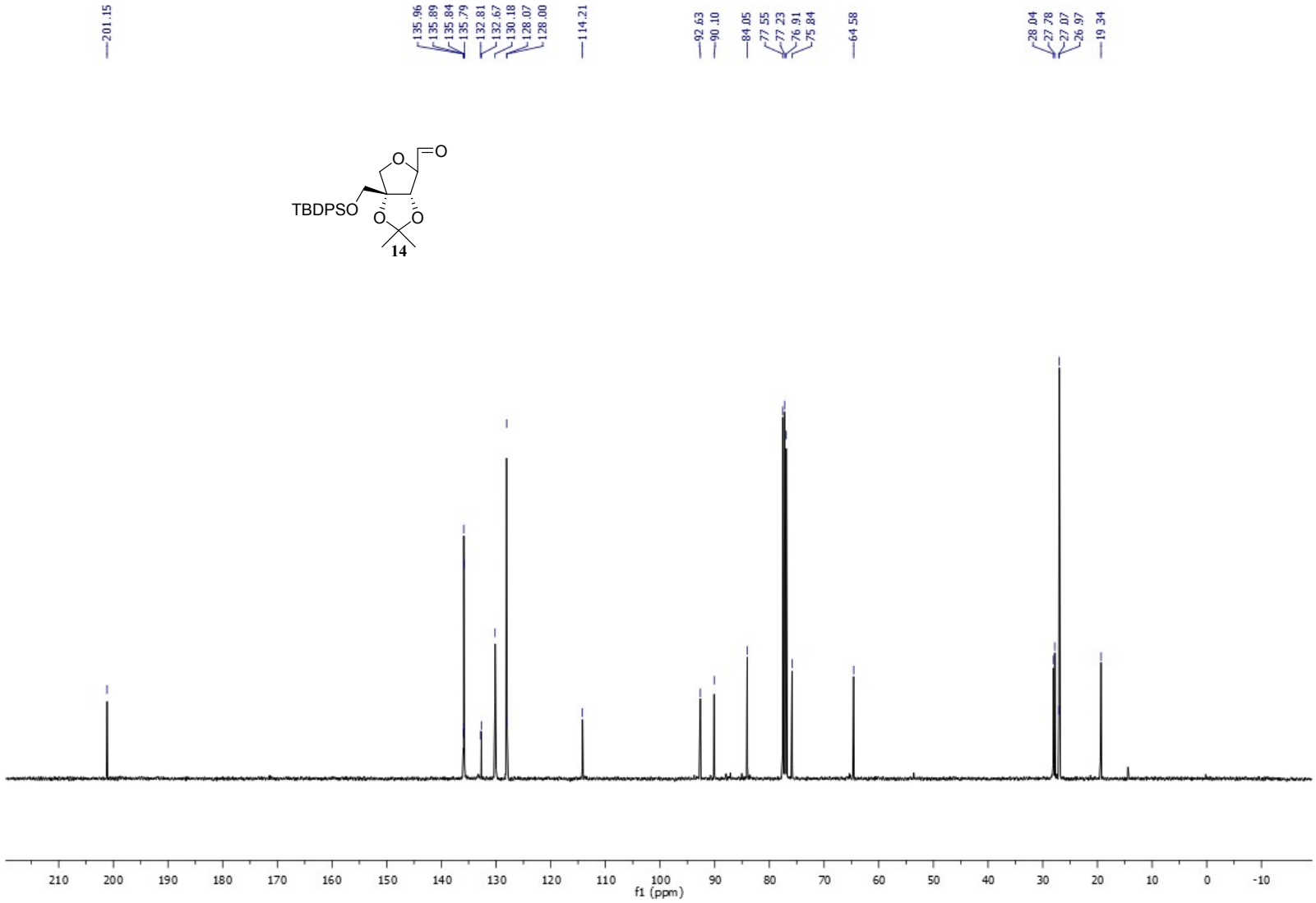
^{13}C spectrum (100 MHz, $CDCl_3$) of compound 13



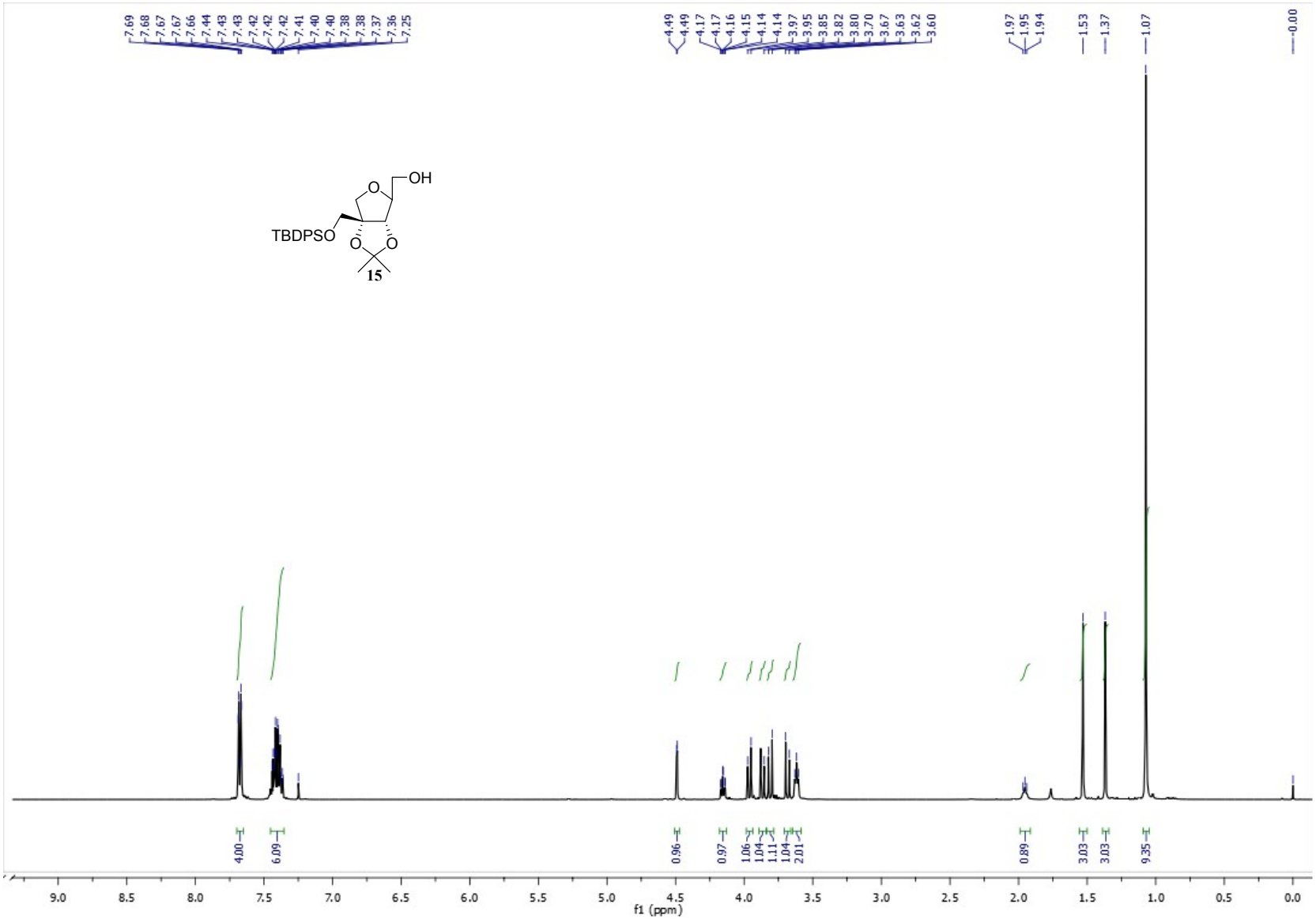
^{1}H spectrum (400 MHz, $CDCl_3$) of compound 14



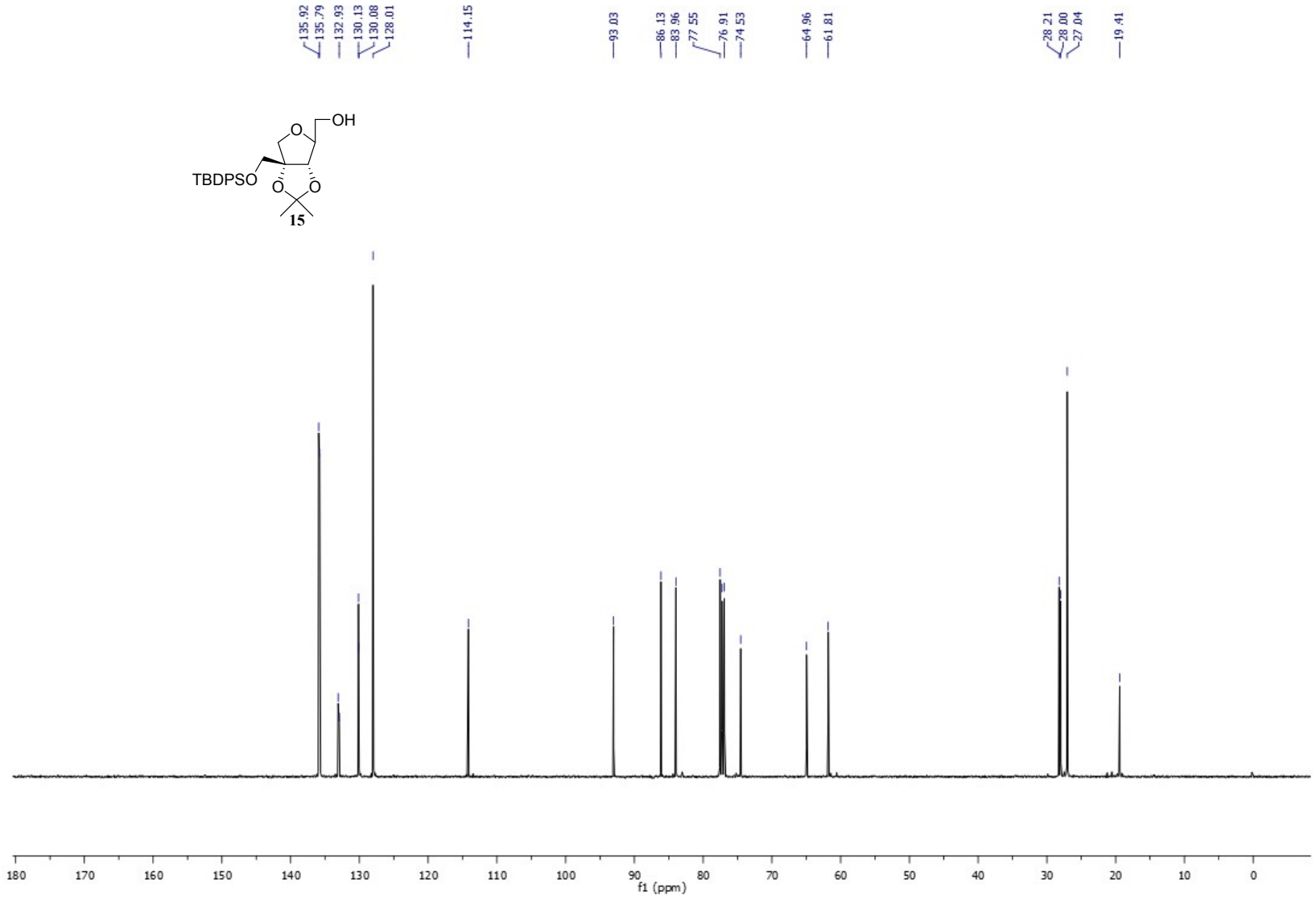
^{13}C spectrum (100 MHz, $CDCl_3$) of compound 14



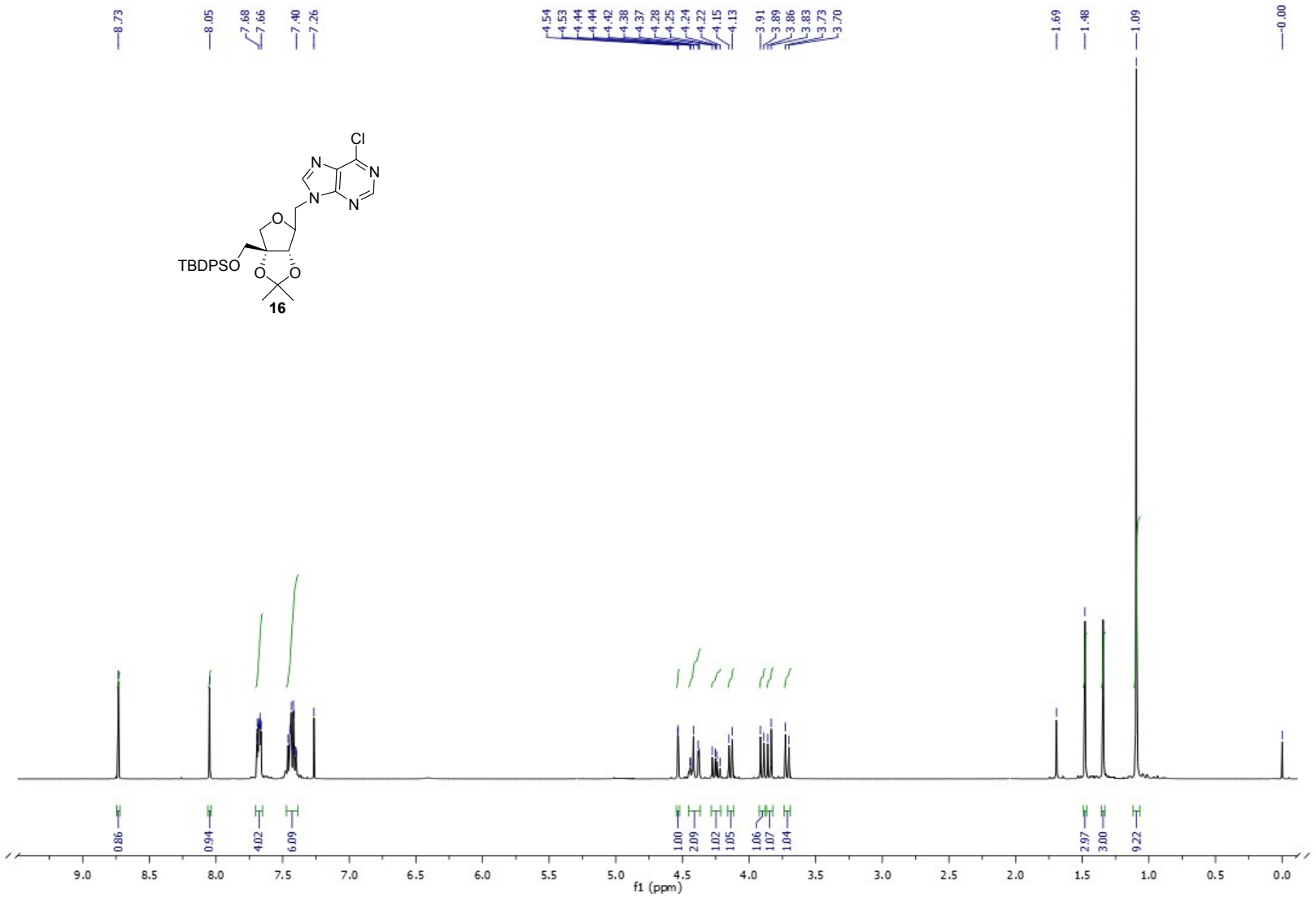
^{1}H spectrum (400 MHz, $CDCl_3$) of compound 15



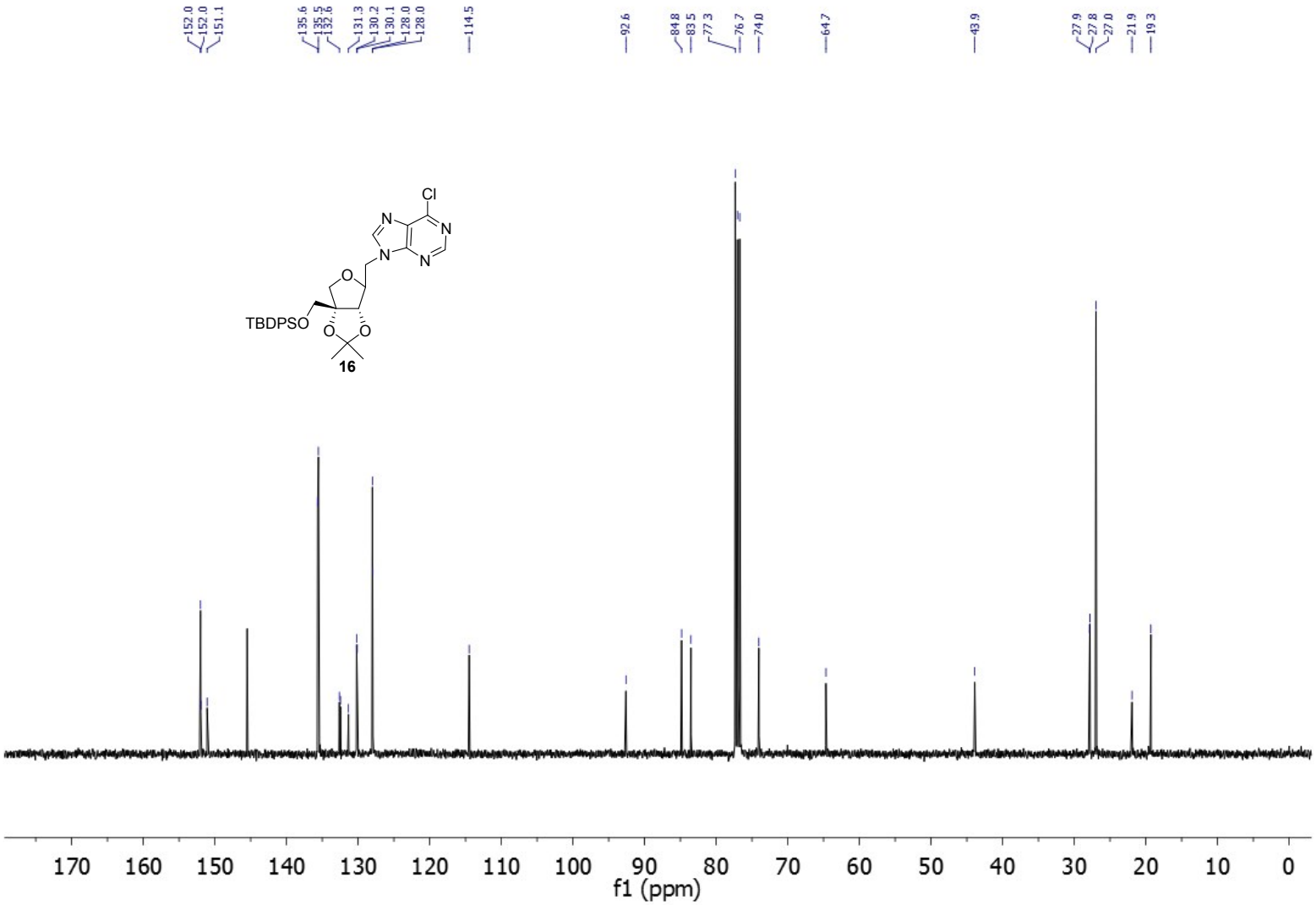
^{13}C spectrum (100 MHz, $CDCl_3$) of compound 15



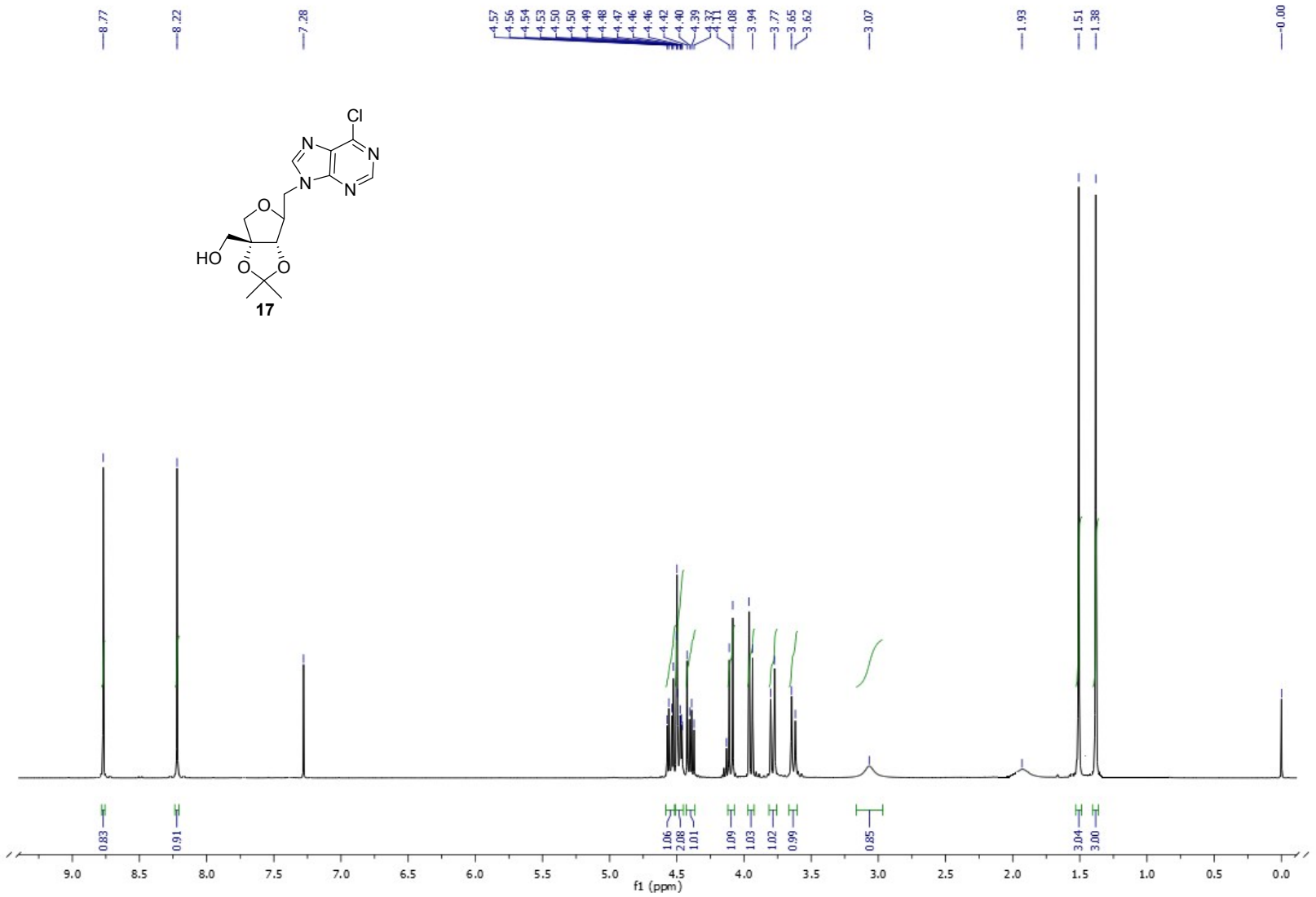
^{1}H spectrum (400 MHz, $CDCl_3$) of compound 16



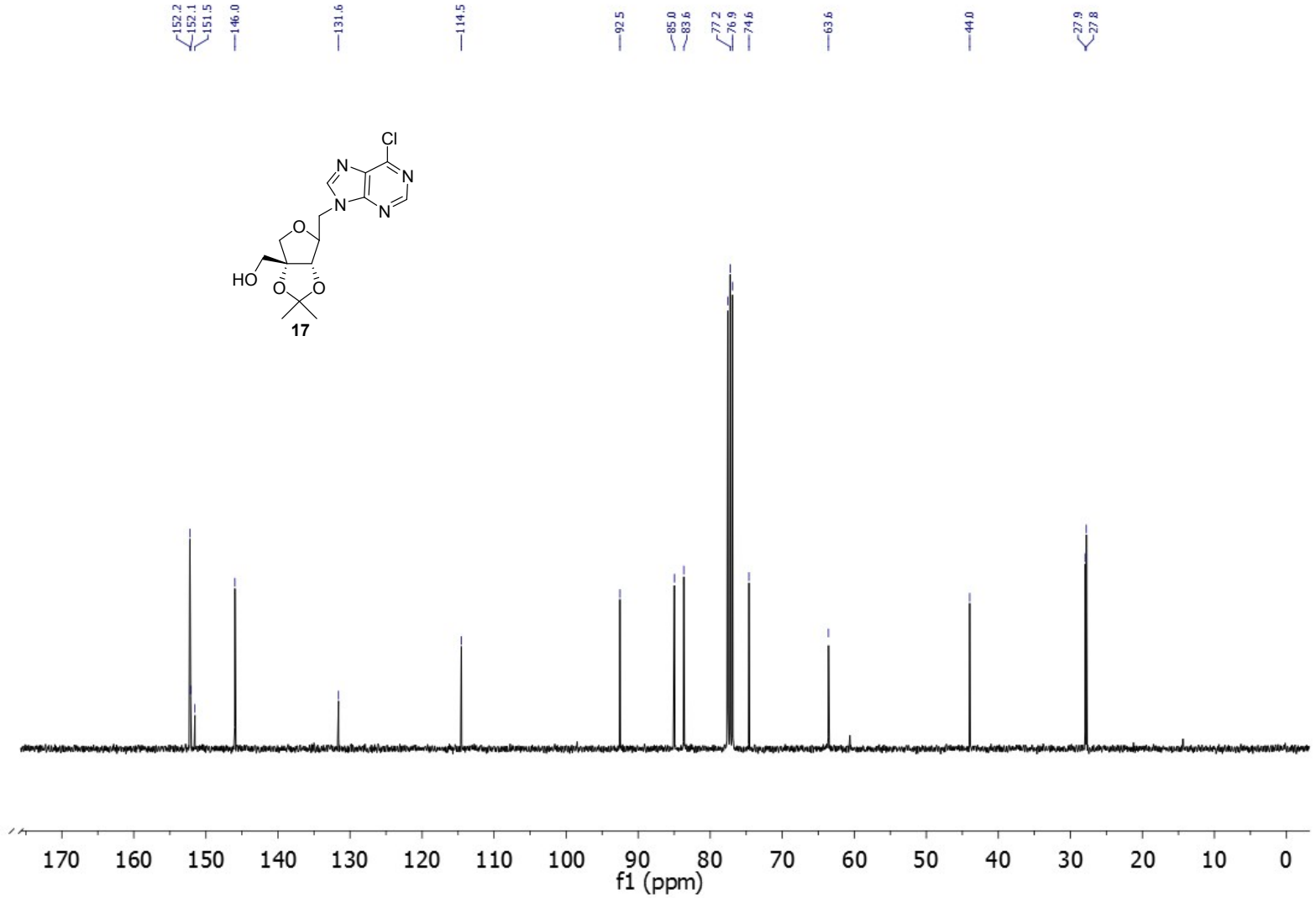
^{13}C spectrum (100 MHz, $CDCl_3$) of compound 16



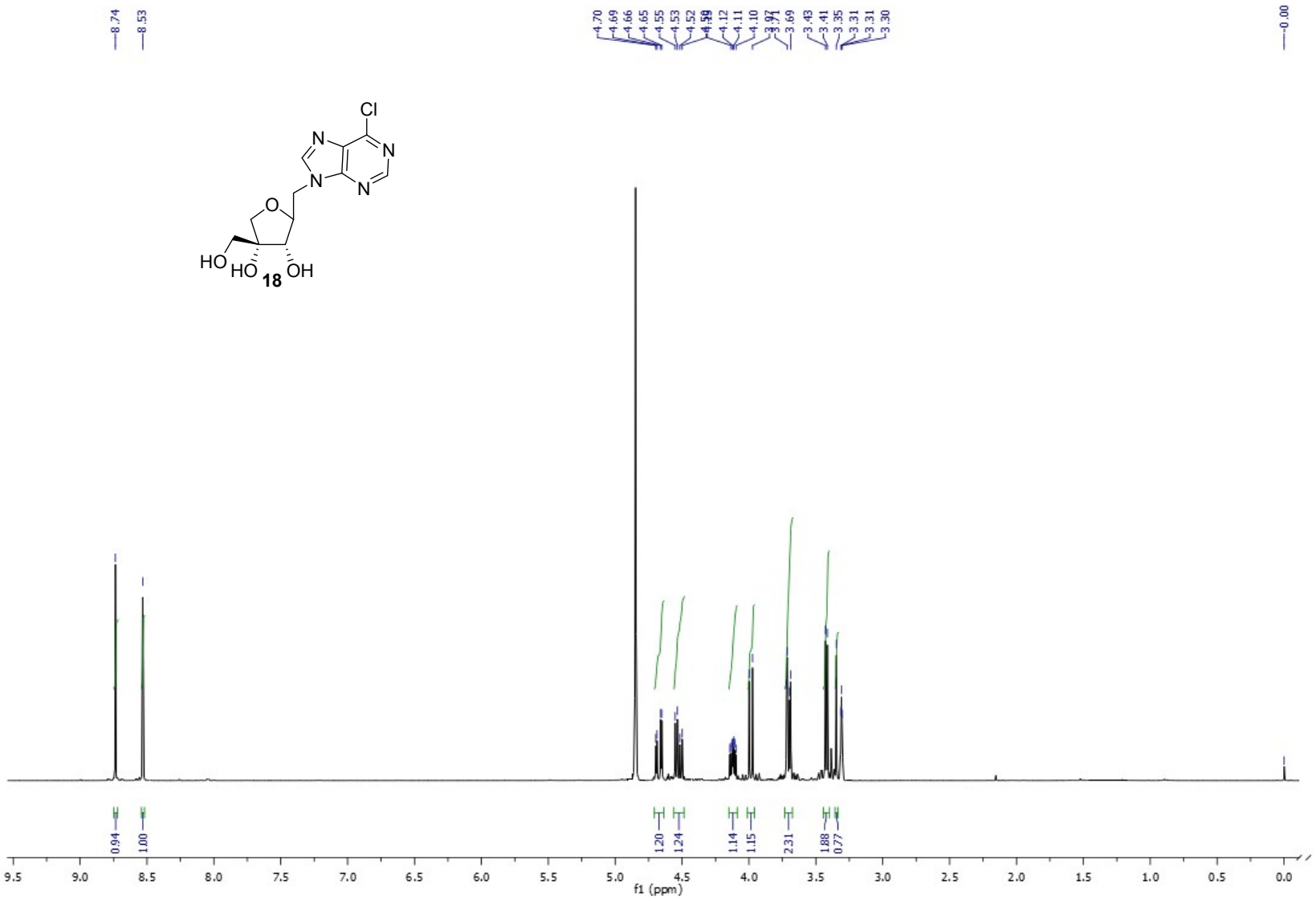
^{1}H spectrum (400 MHz, $CDCl_3$) of compound 17



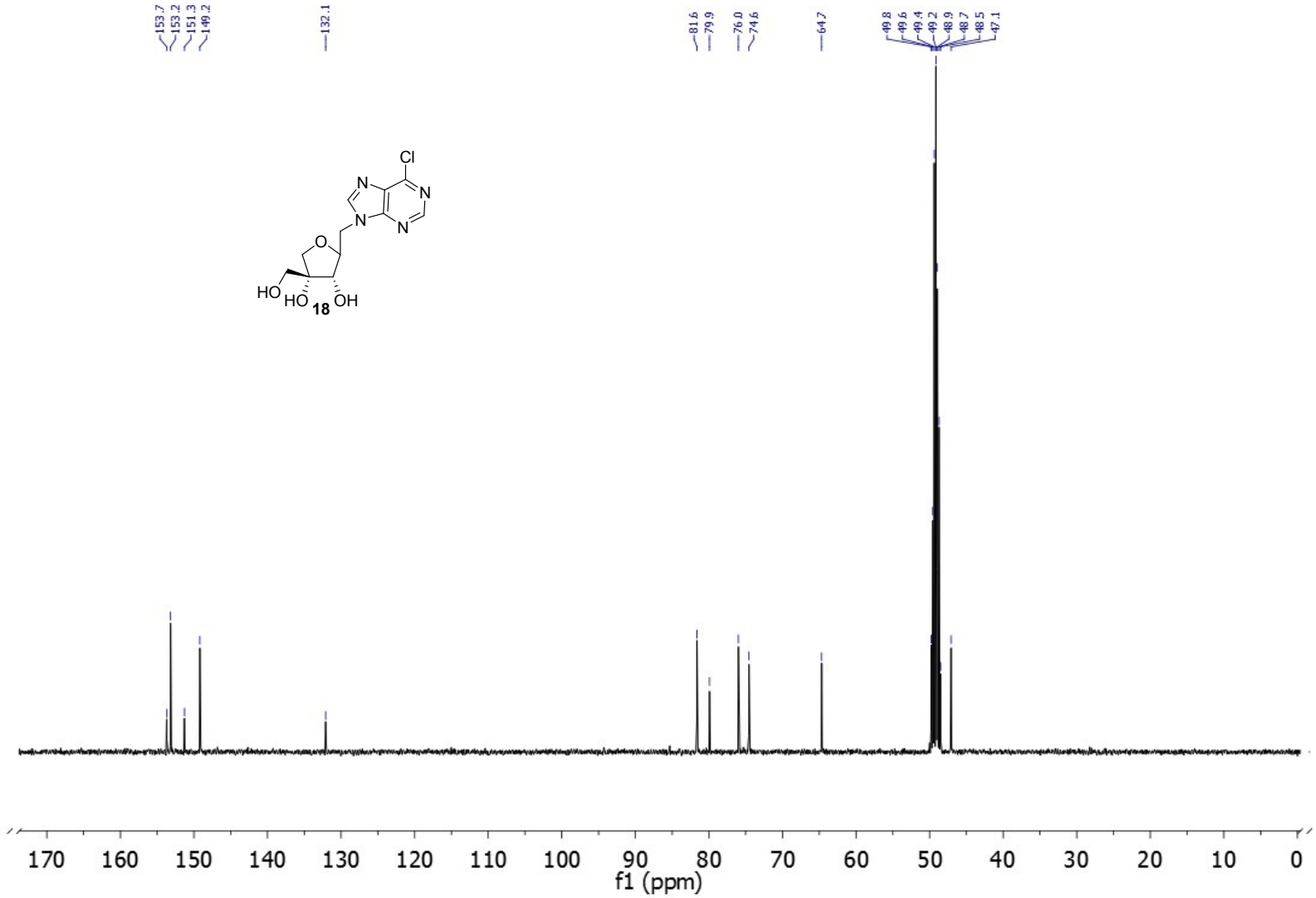
^{13}C spectrum (100 MHz, $CDCl_3$) of compound 17



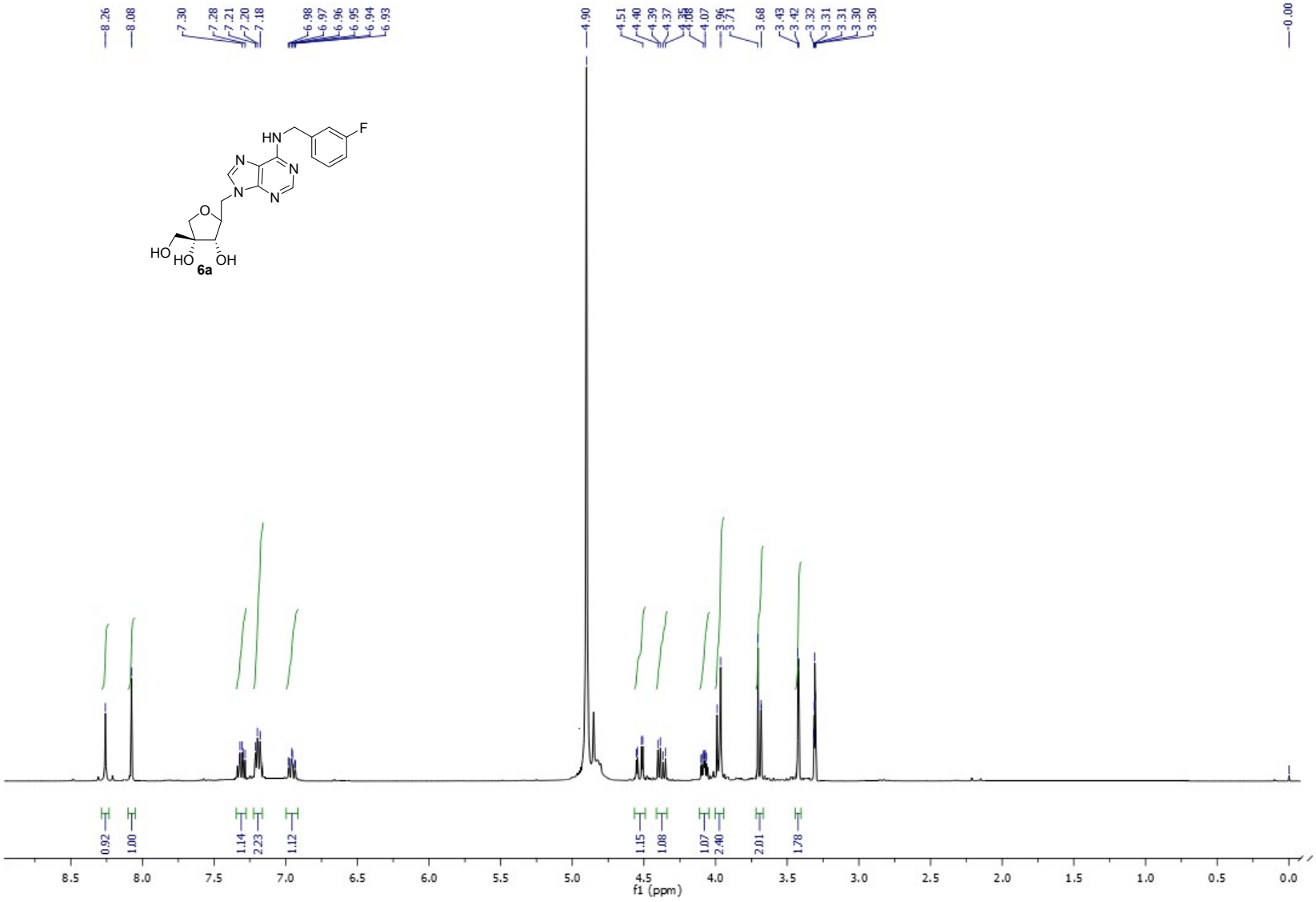
^{1}H spectrum (400 MHz, CD_3OD) of compound 18



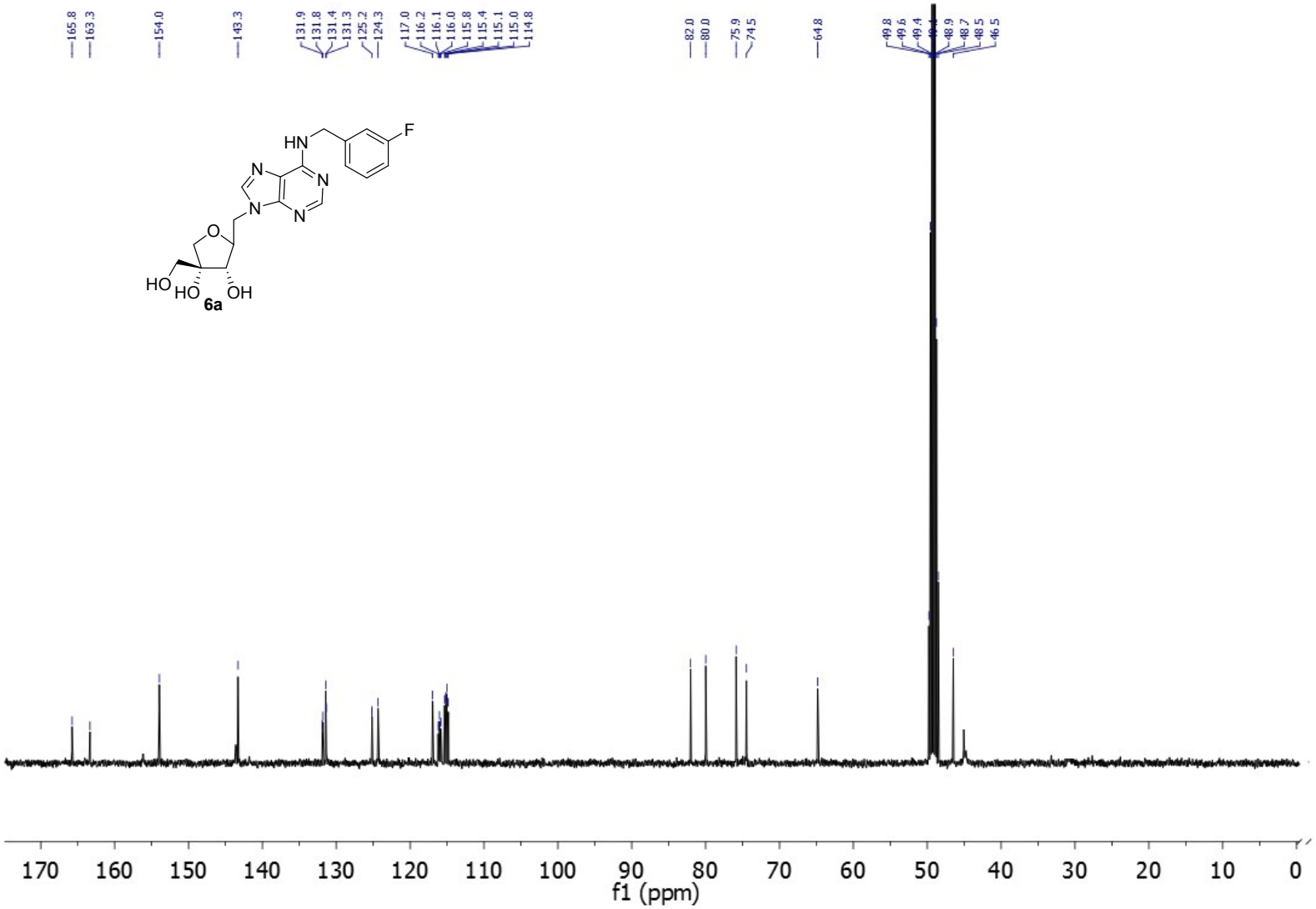
^{13}C spectrum (100 MHz, CD_3OD) of compound 18



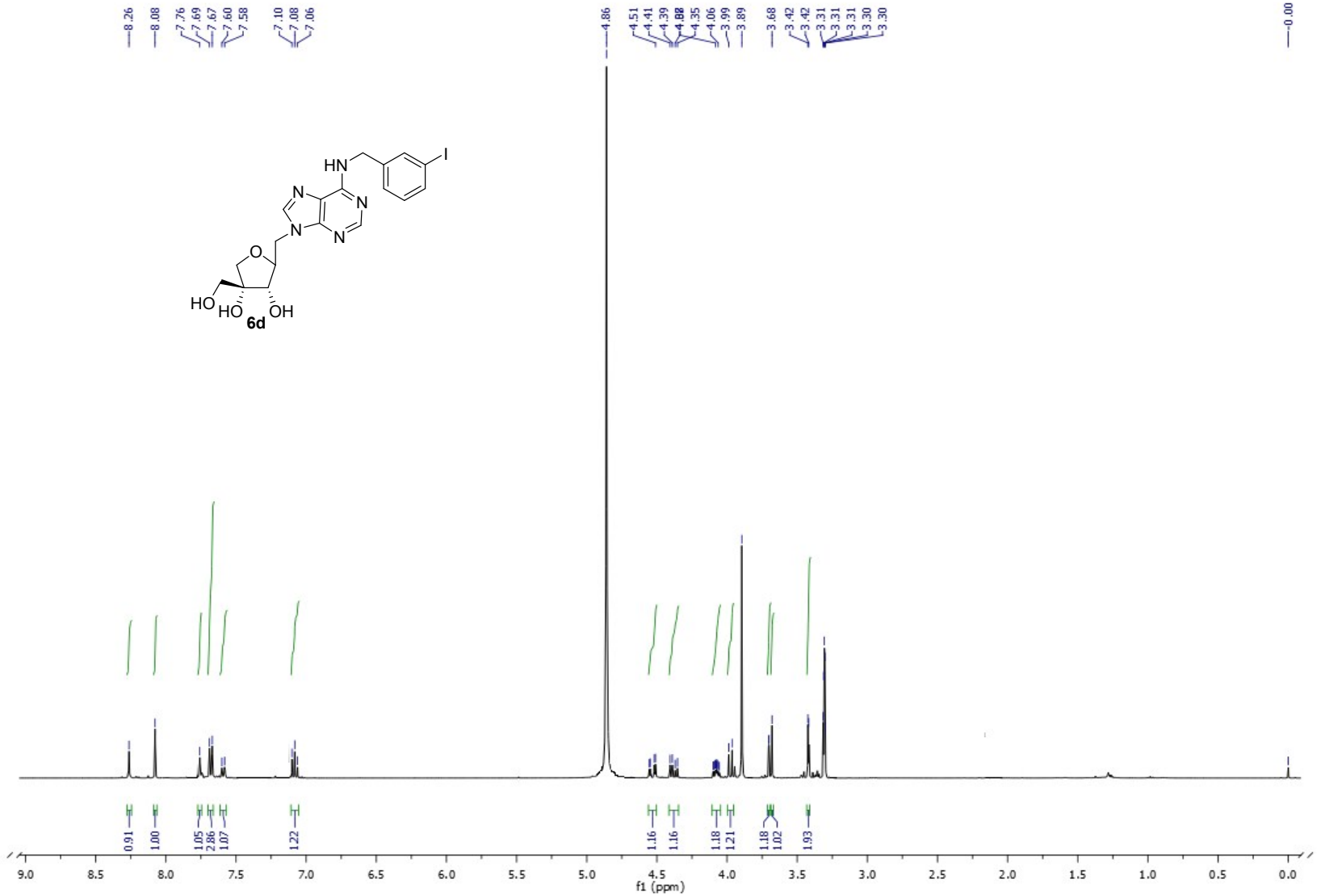
^{1}H spectrum (400 MHz, CD_3OD) of compound 6a



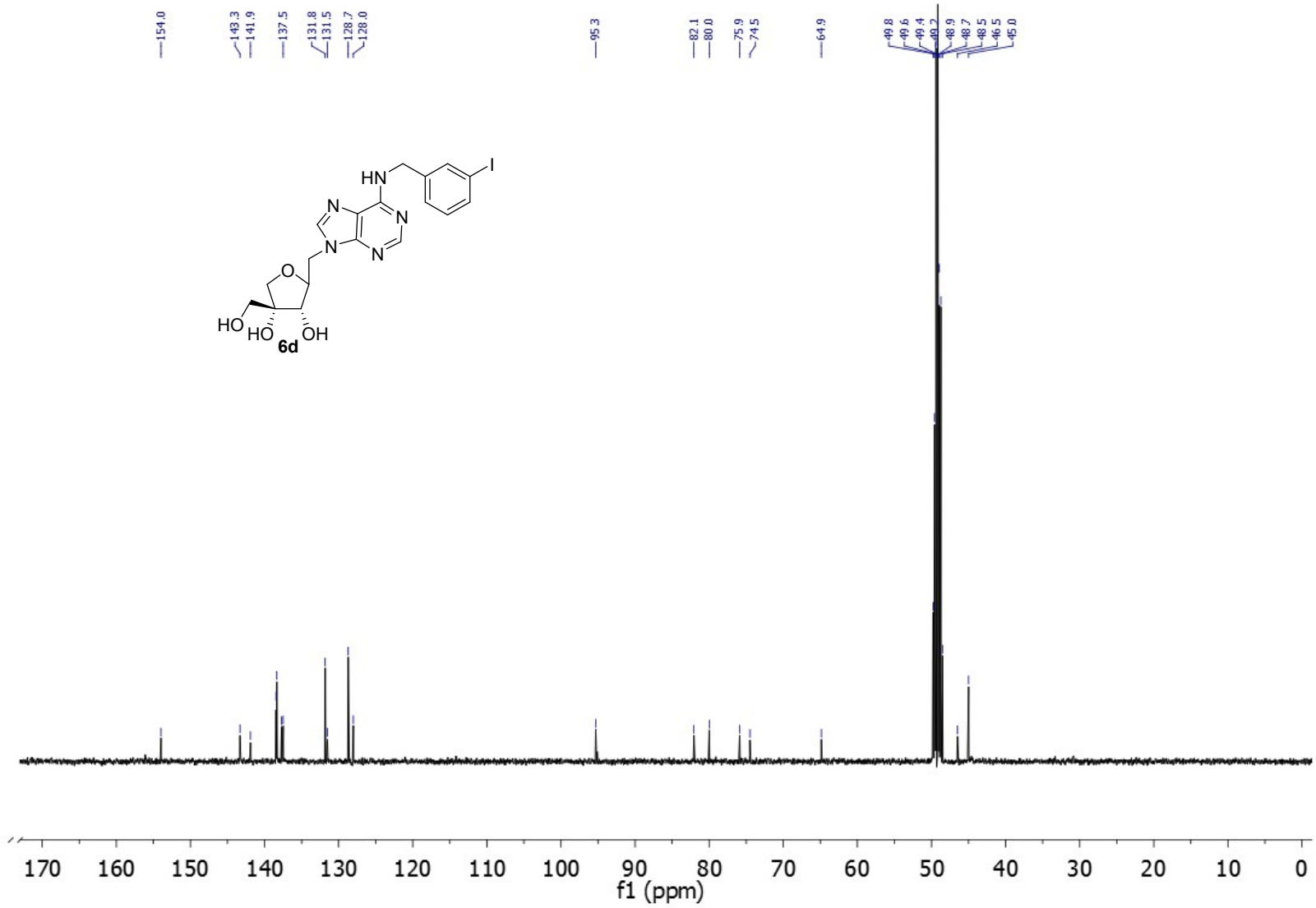
^{13}C spectrum (100 MHz, CD_3OD) of compound 6a



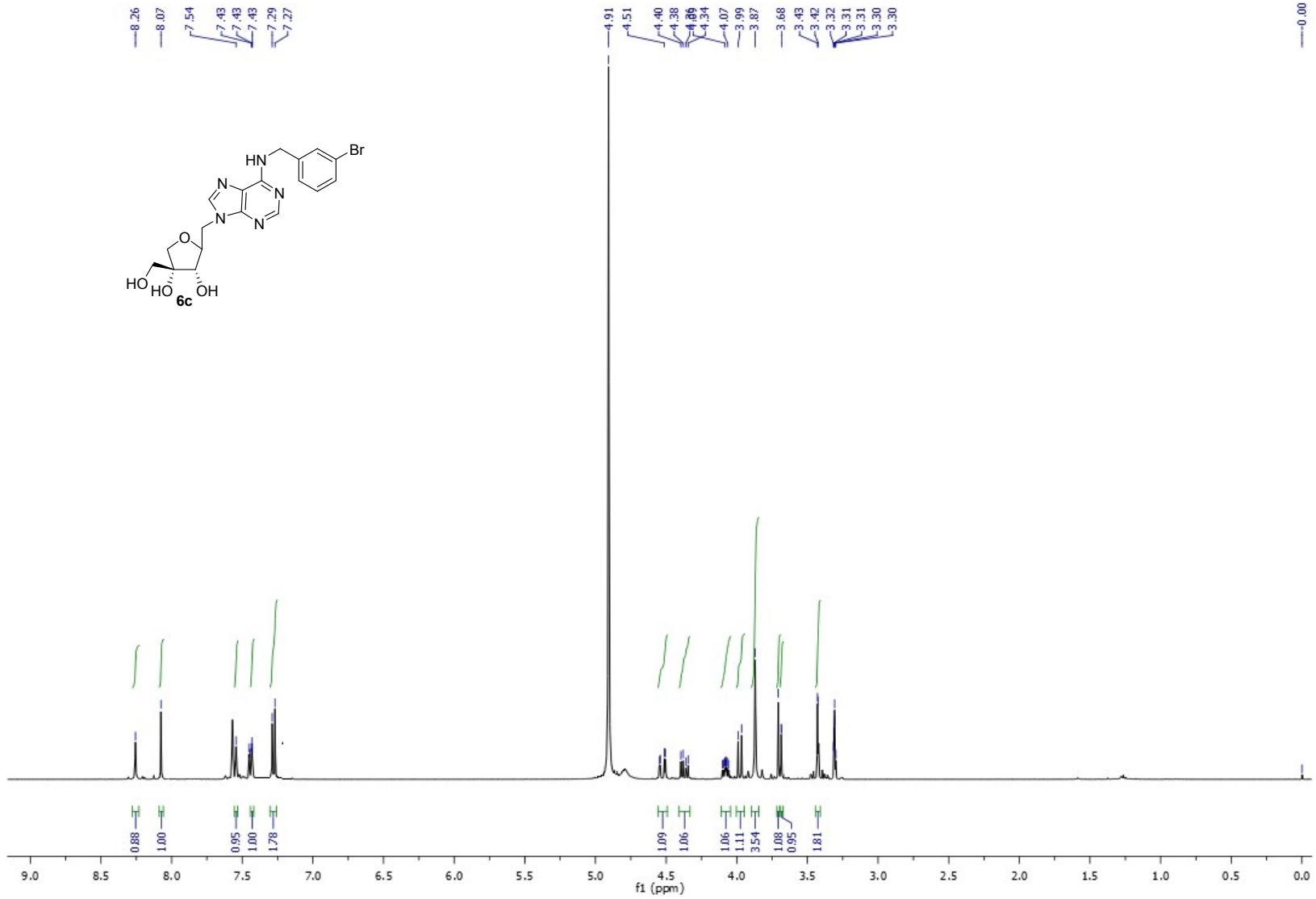
^{1}H spectrum (400 MHz, CD_3OD) of compound 6d



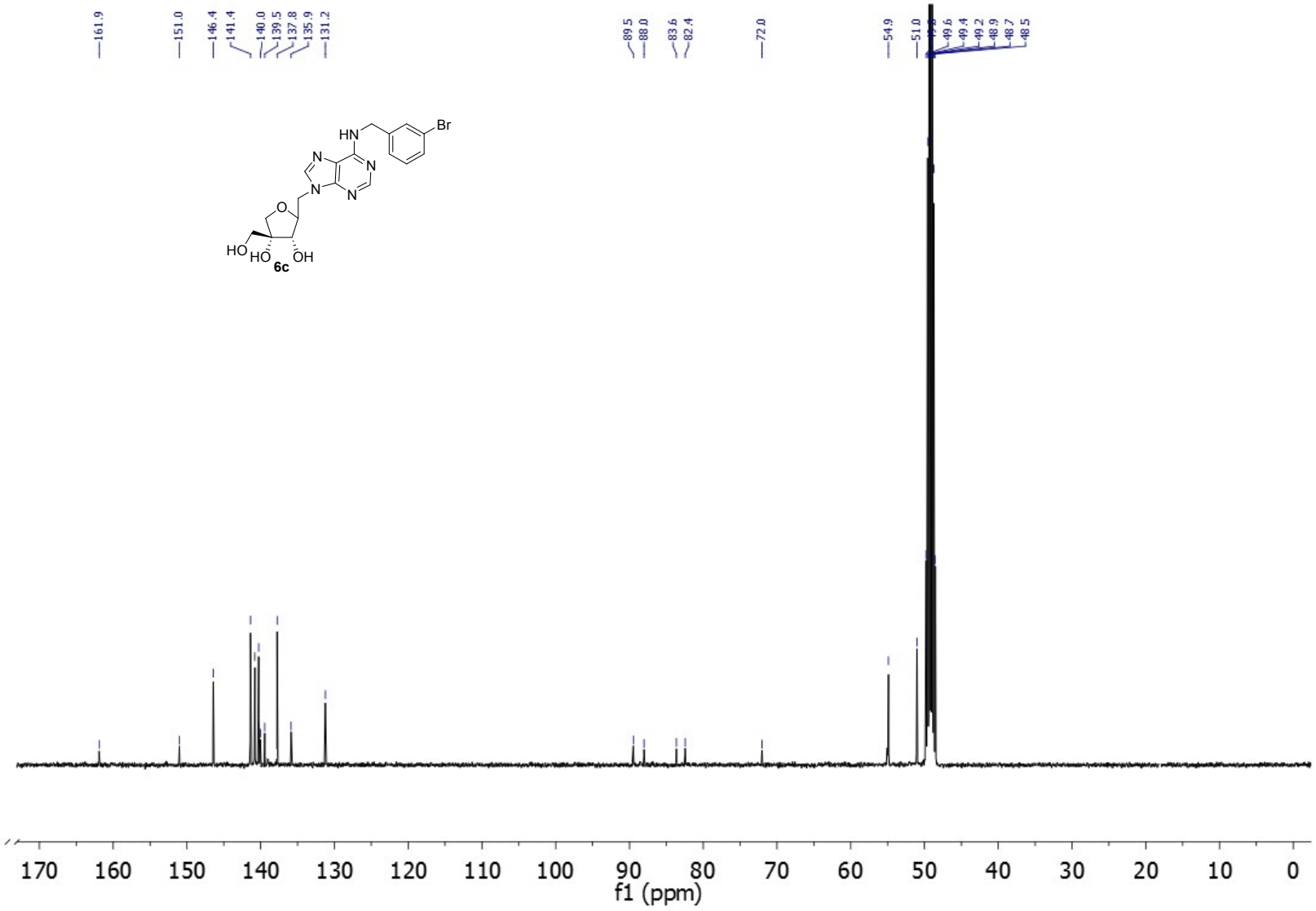
^{13}C spectrum (100 MHz, CD_3OD) of compound 6d



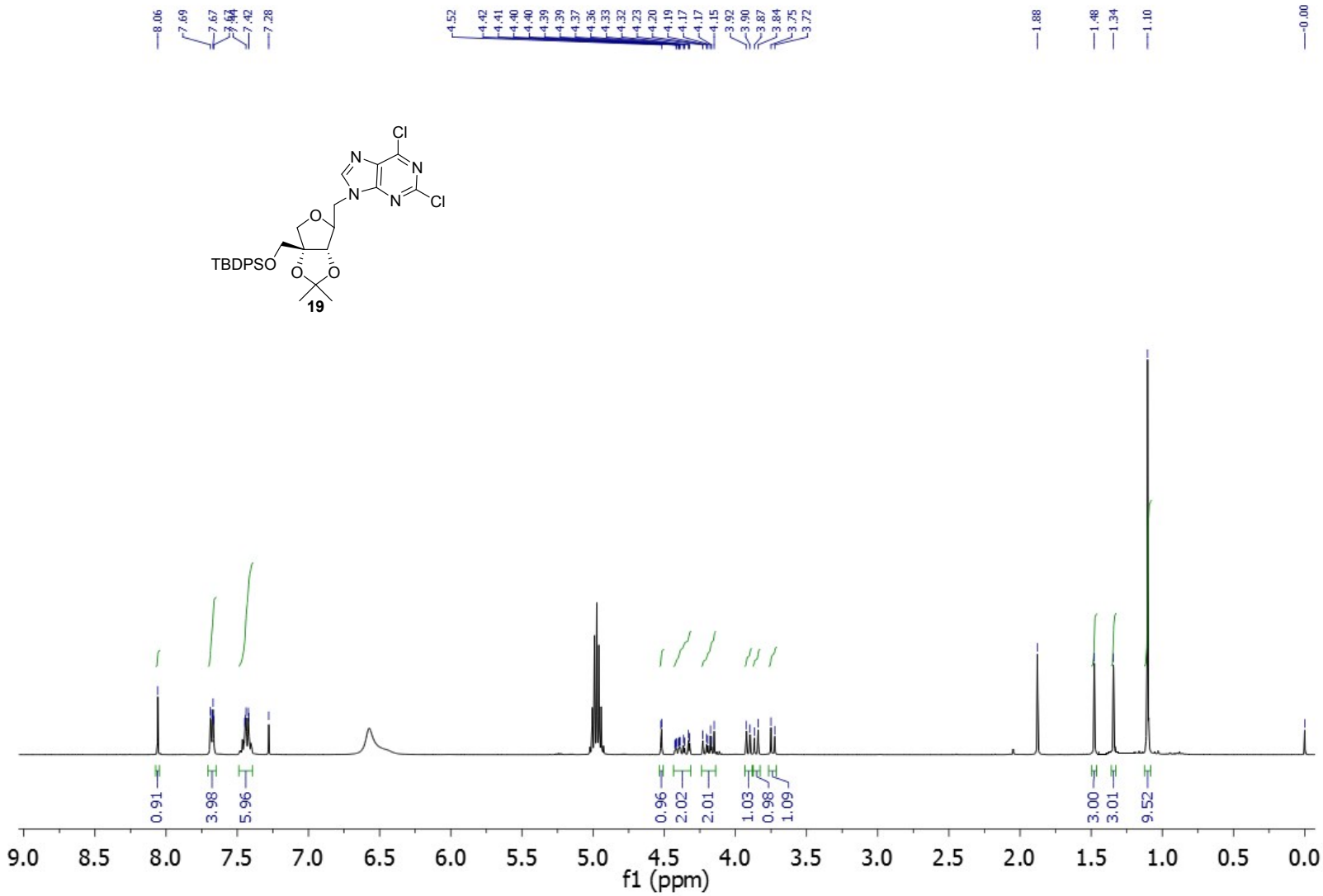
^{1}H spectrum (400 MHz, CD_3OD) of compound 6c



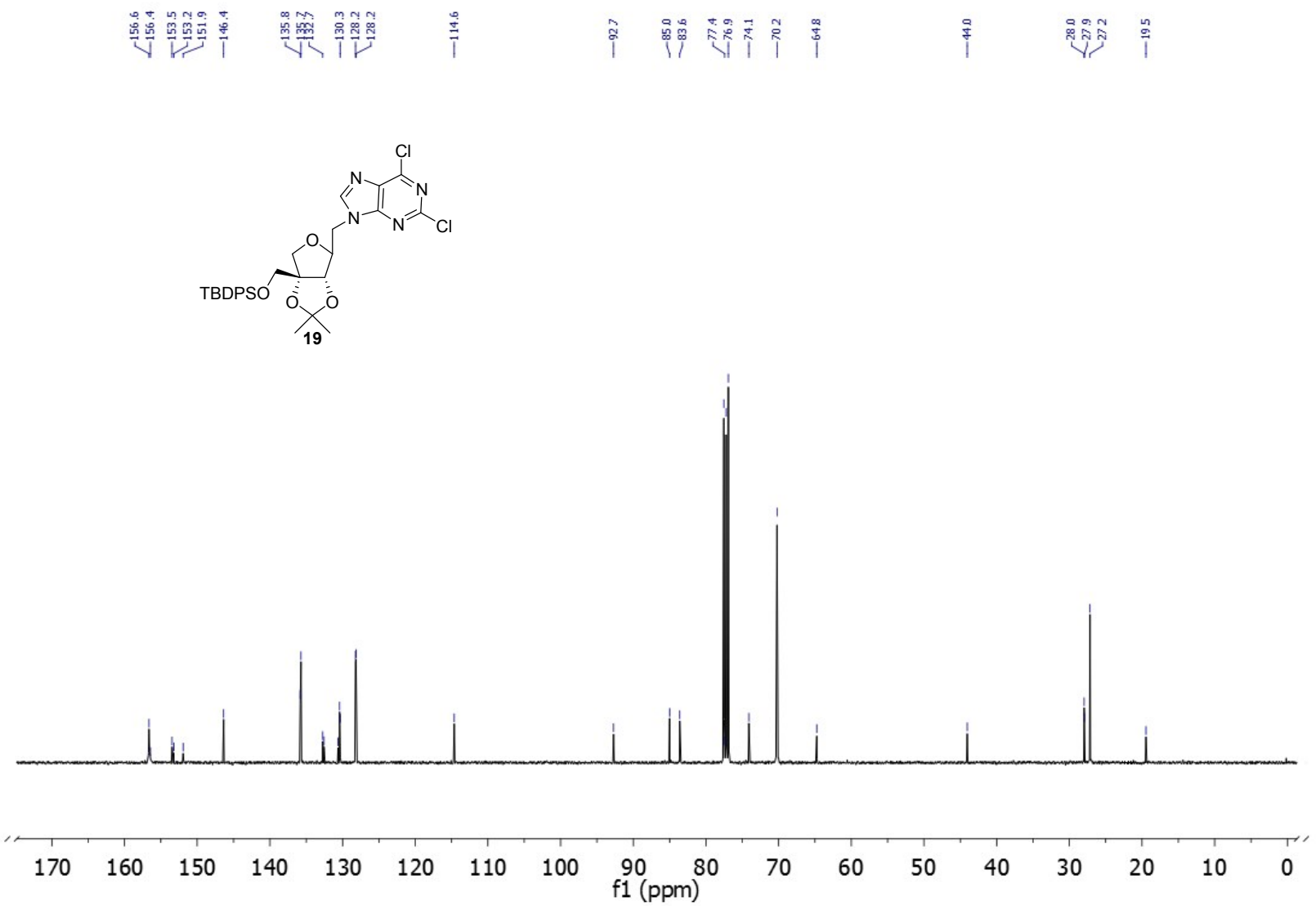
^{13}C spectrum (100 MHz, CD_3OD) of compound 6c



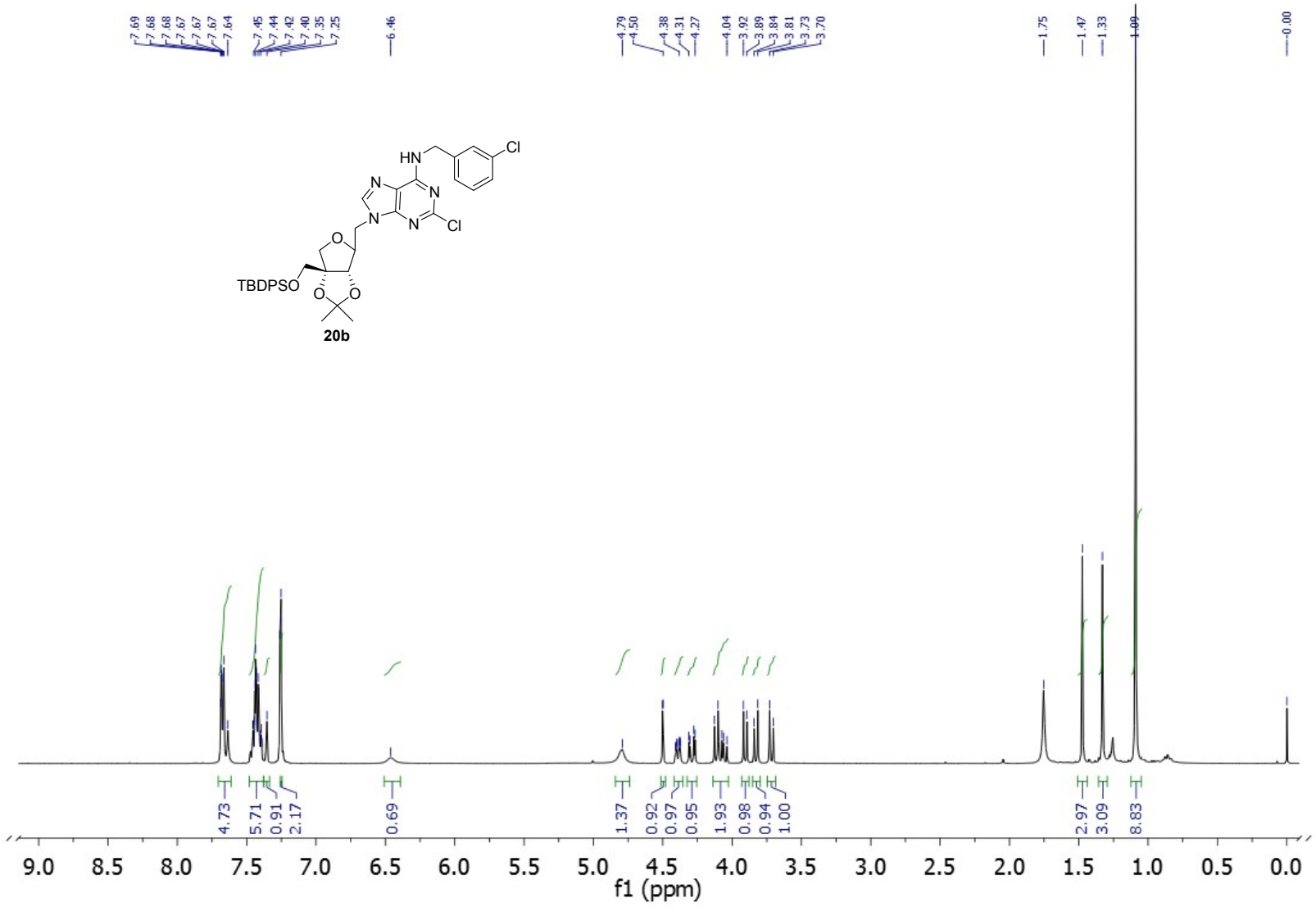
^{1}H spectrum (400 MHz, $CDCl_3$) of compound 19



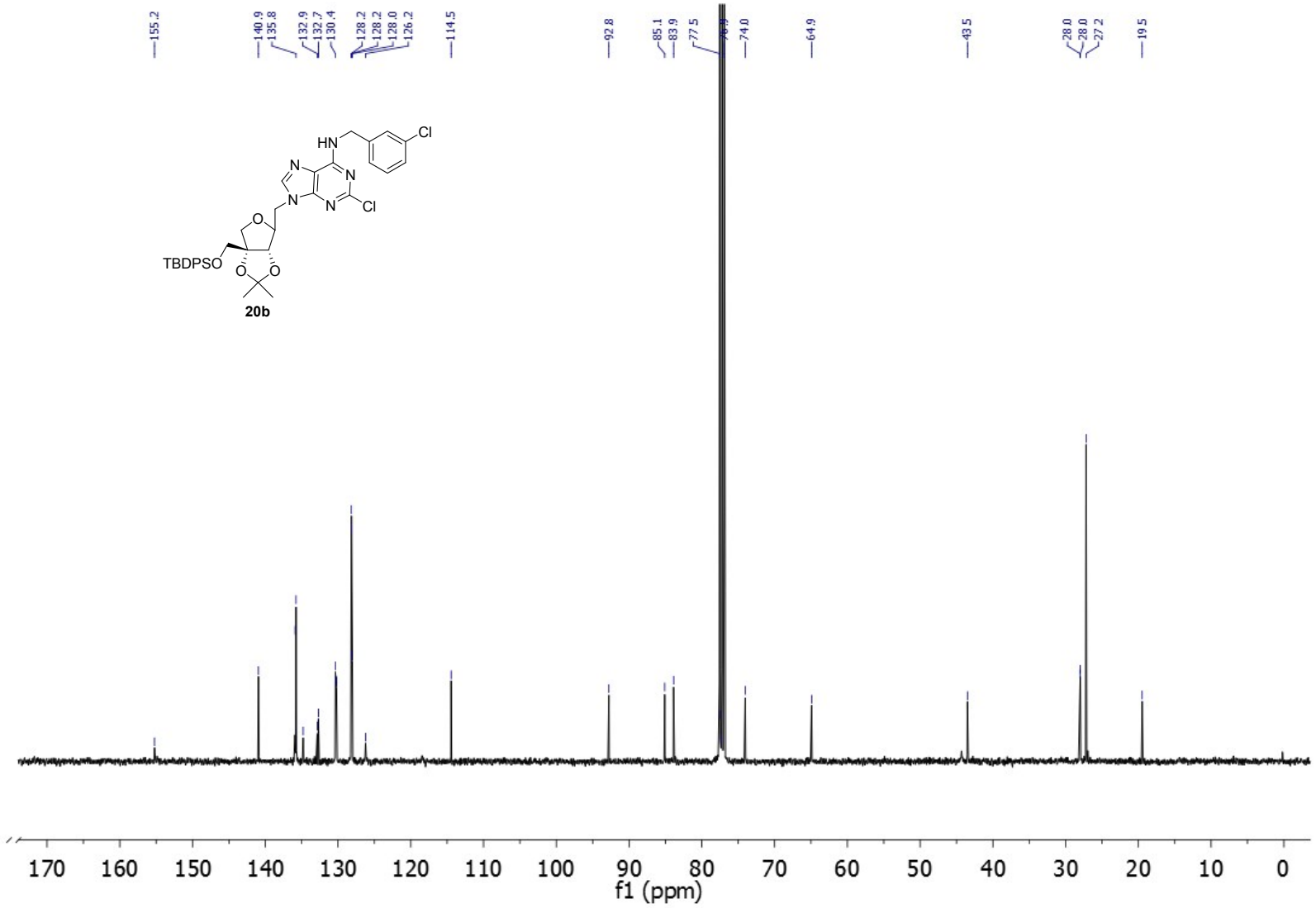
^{13}C spectrum (100 MHz, $CDCl_3$) of compound 19



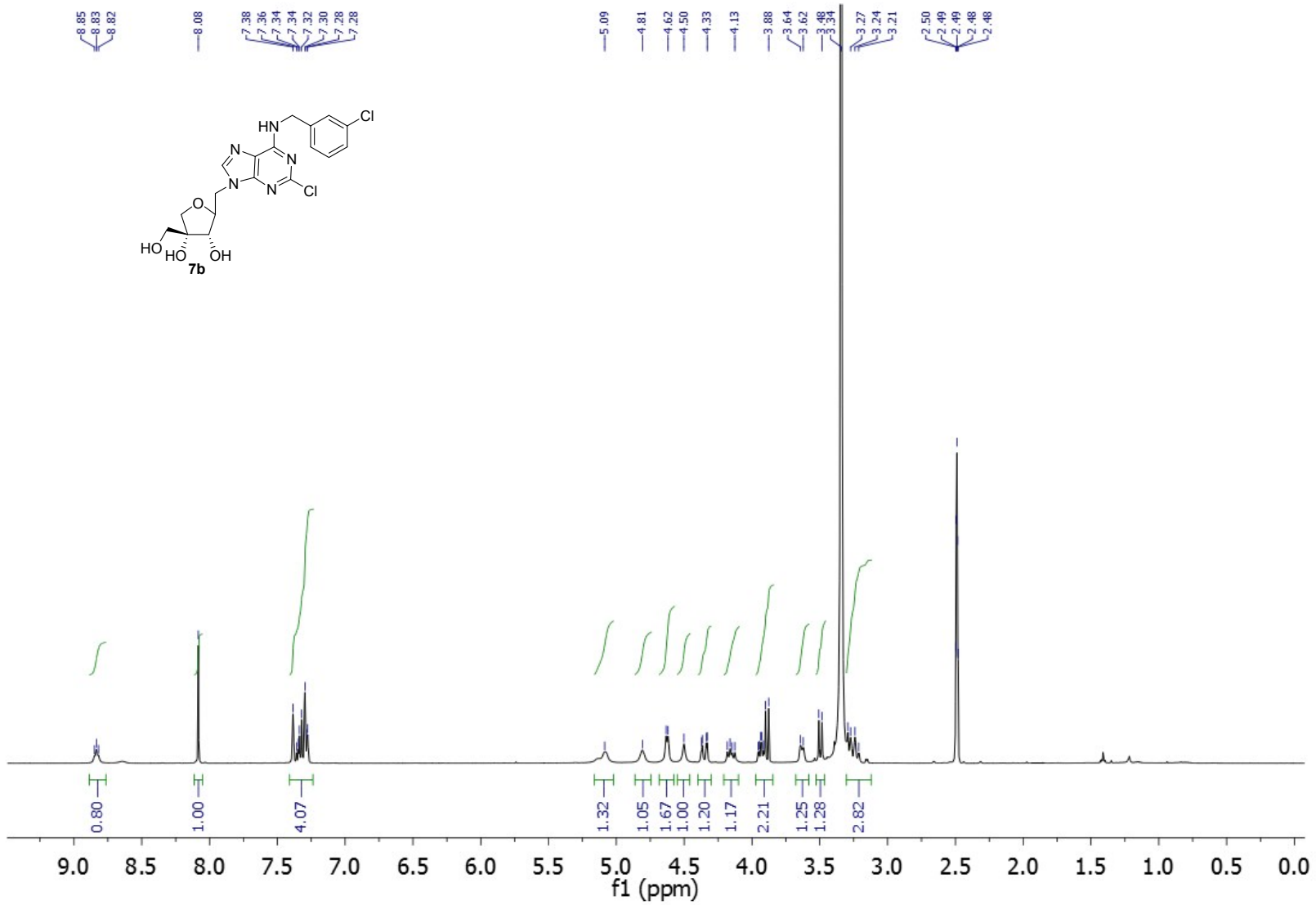
^{1}H spectrum (400 MHz, $CDCl_3$) of compound 20b



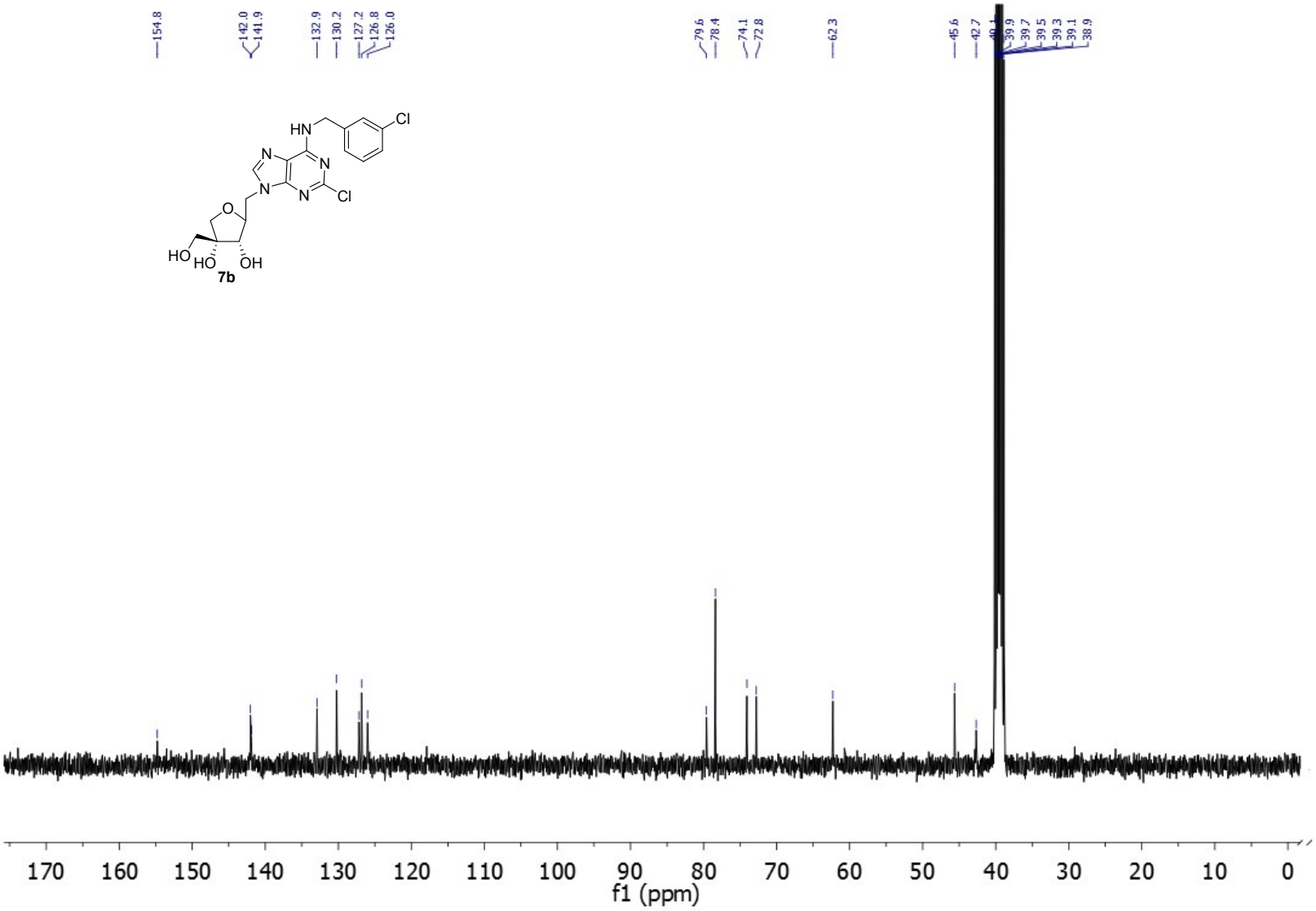
^{13}C spectrum (100 MHz, $CDCl_3$) of compound 20b



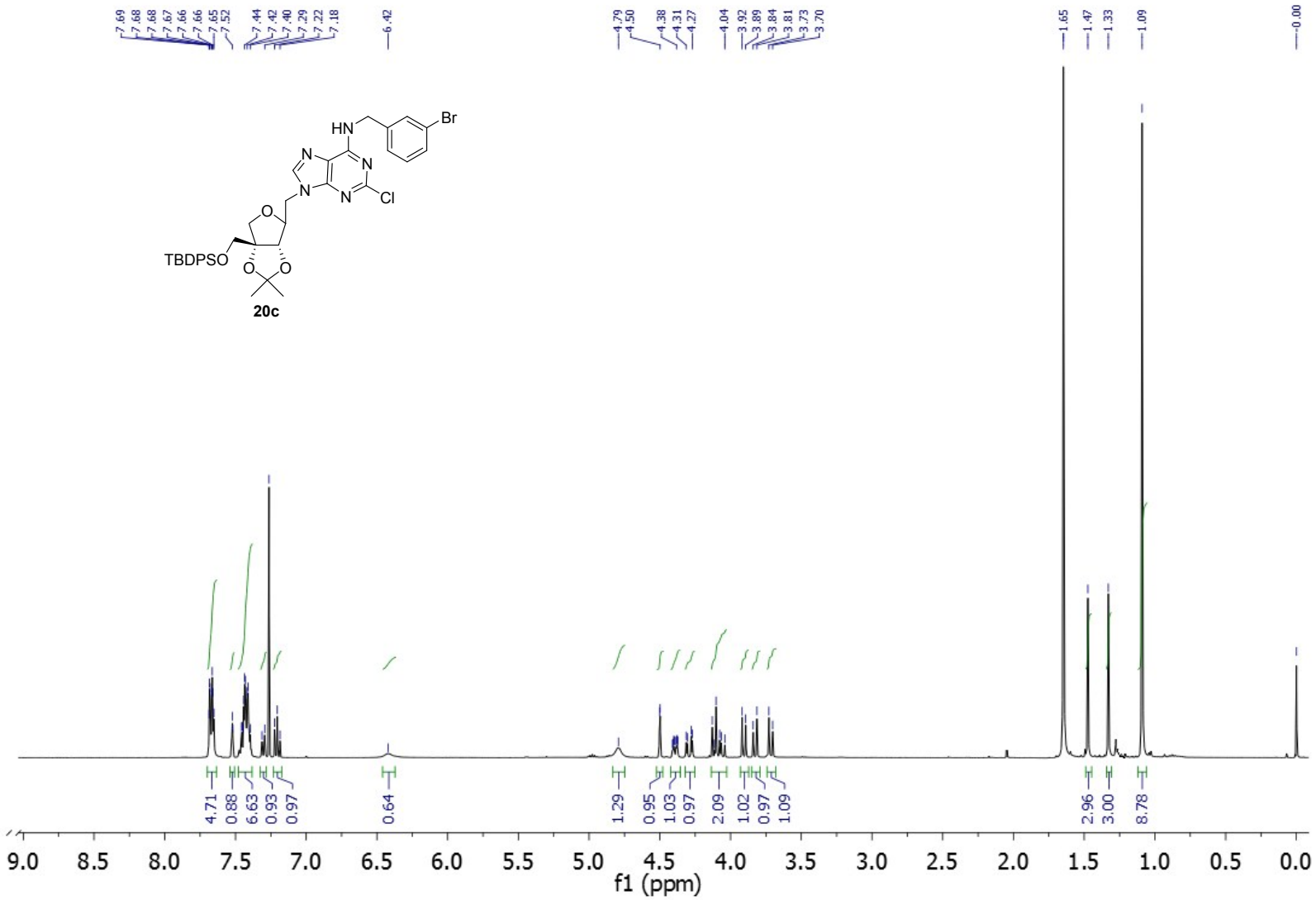
^{1}H spectrum (400 MHz, DMSO-d_6) of compound 7b



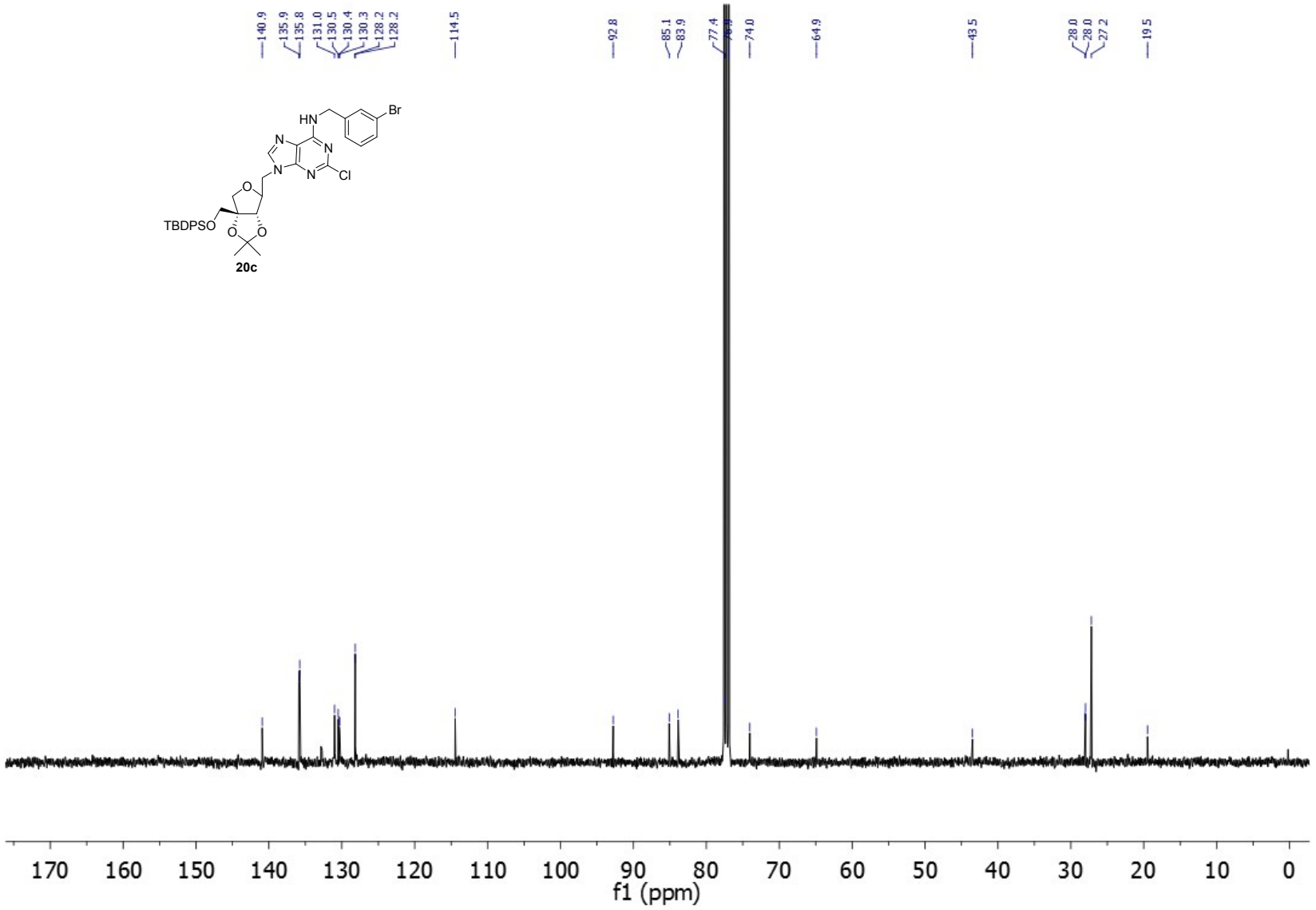
^{13}C spectrum (100 MHz, DMSO-d_6) of compound 7b



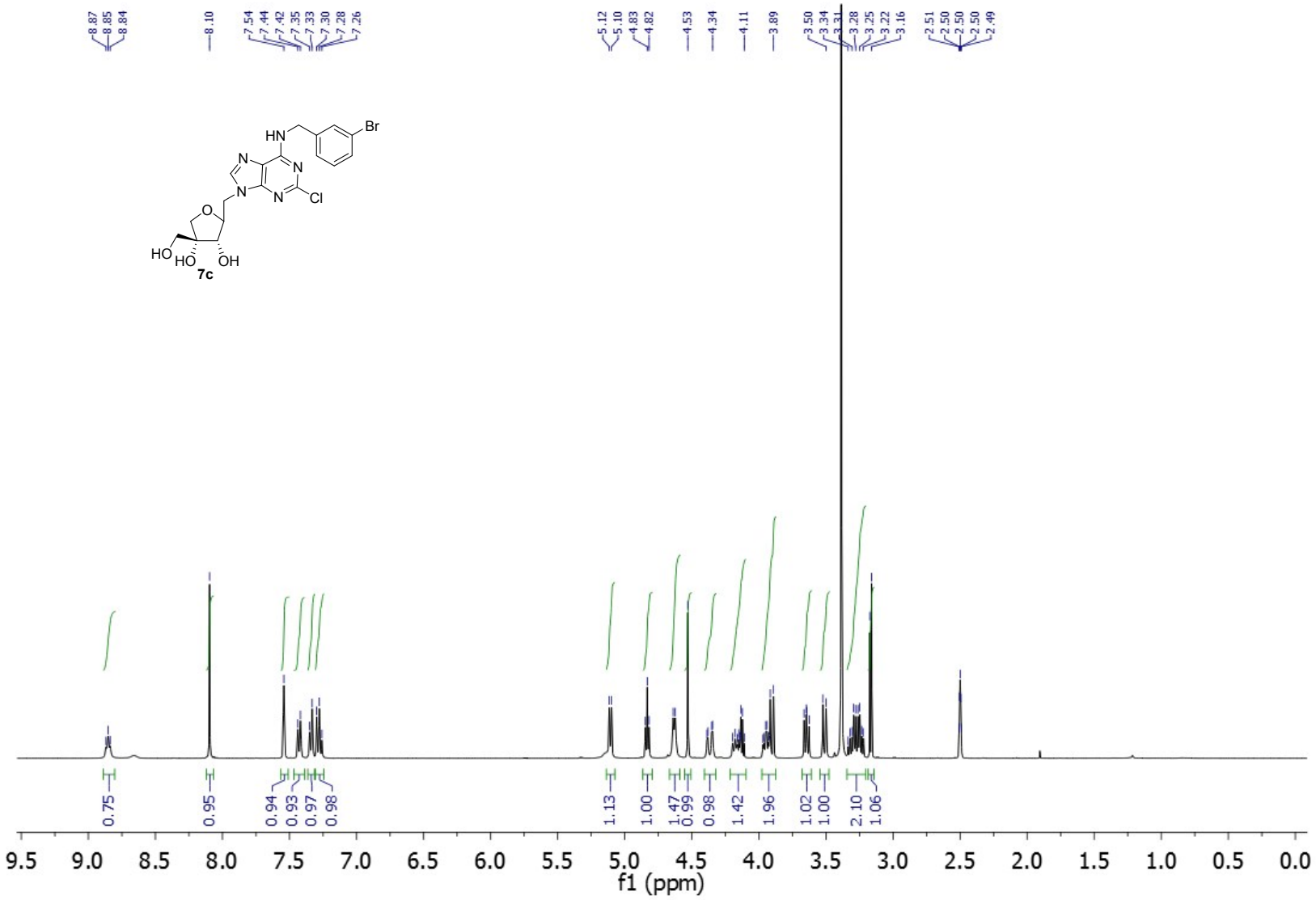
^{1}H spectrum (400 MHz, $CDCl_3$) of compound 20c



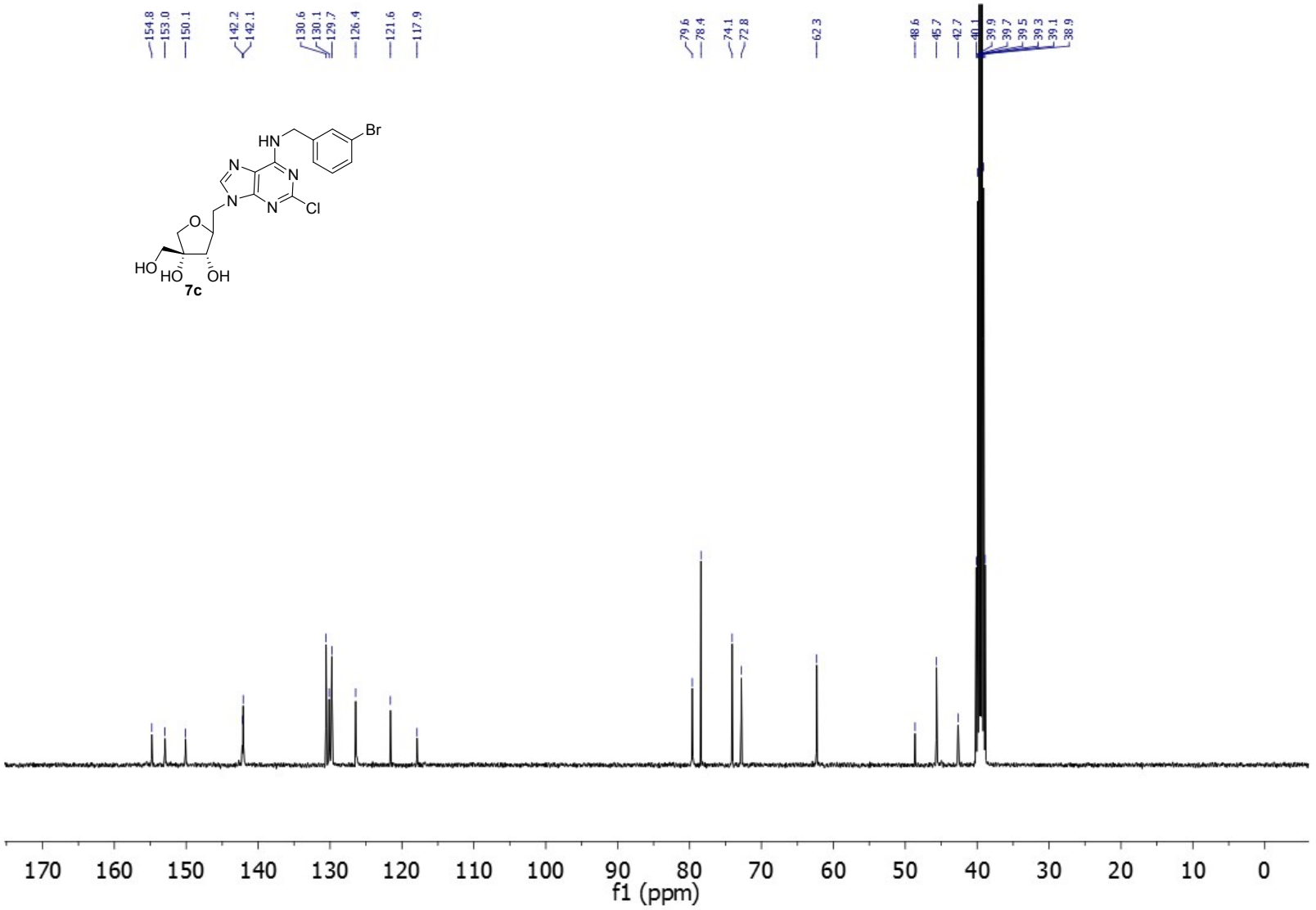
^{13}C spectrum (100 MHz, $CDCl_3$) of compound 20c



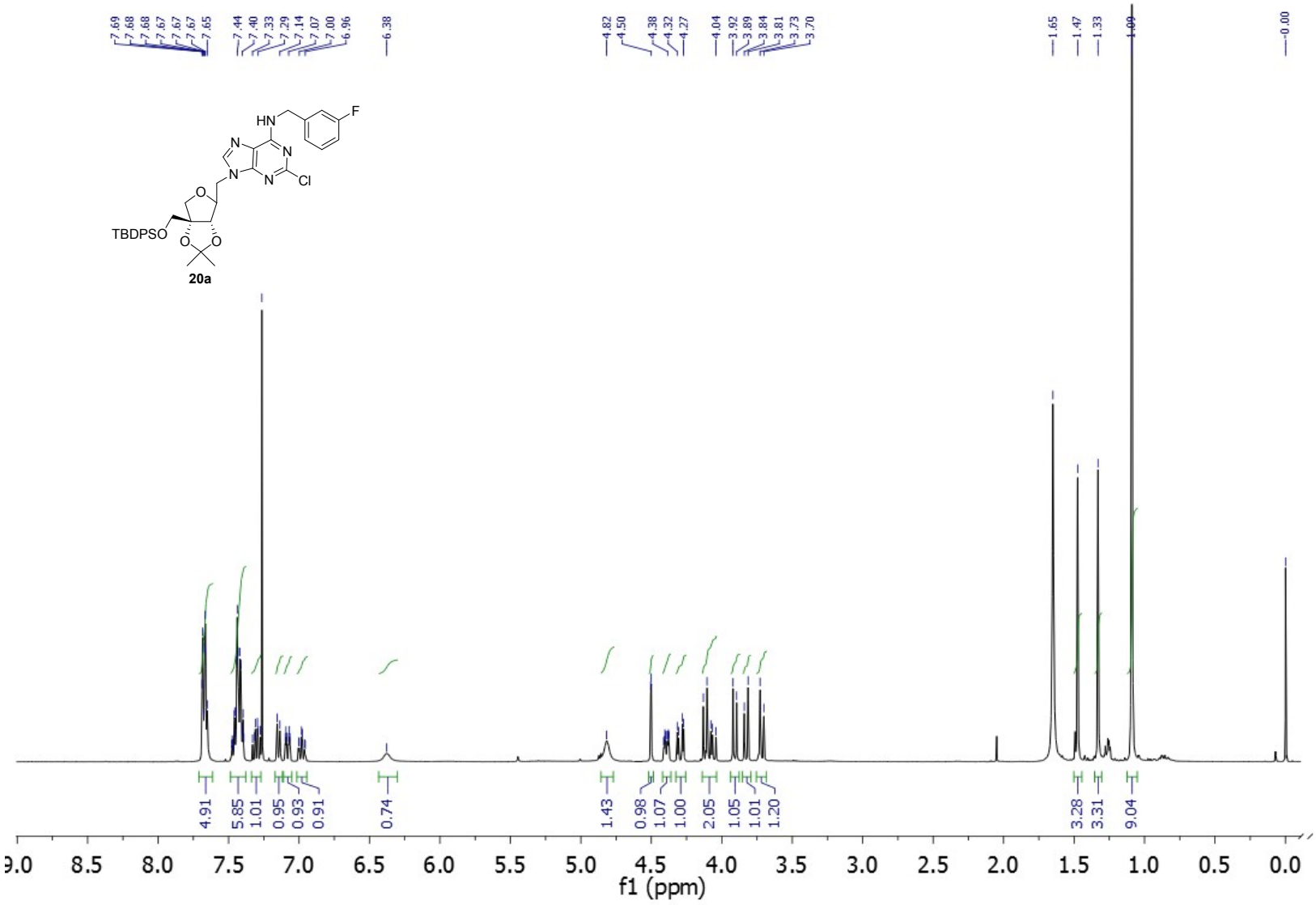
^{1}H spectrum (400 MHz, DMSO-d_6) of compound 7c



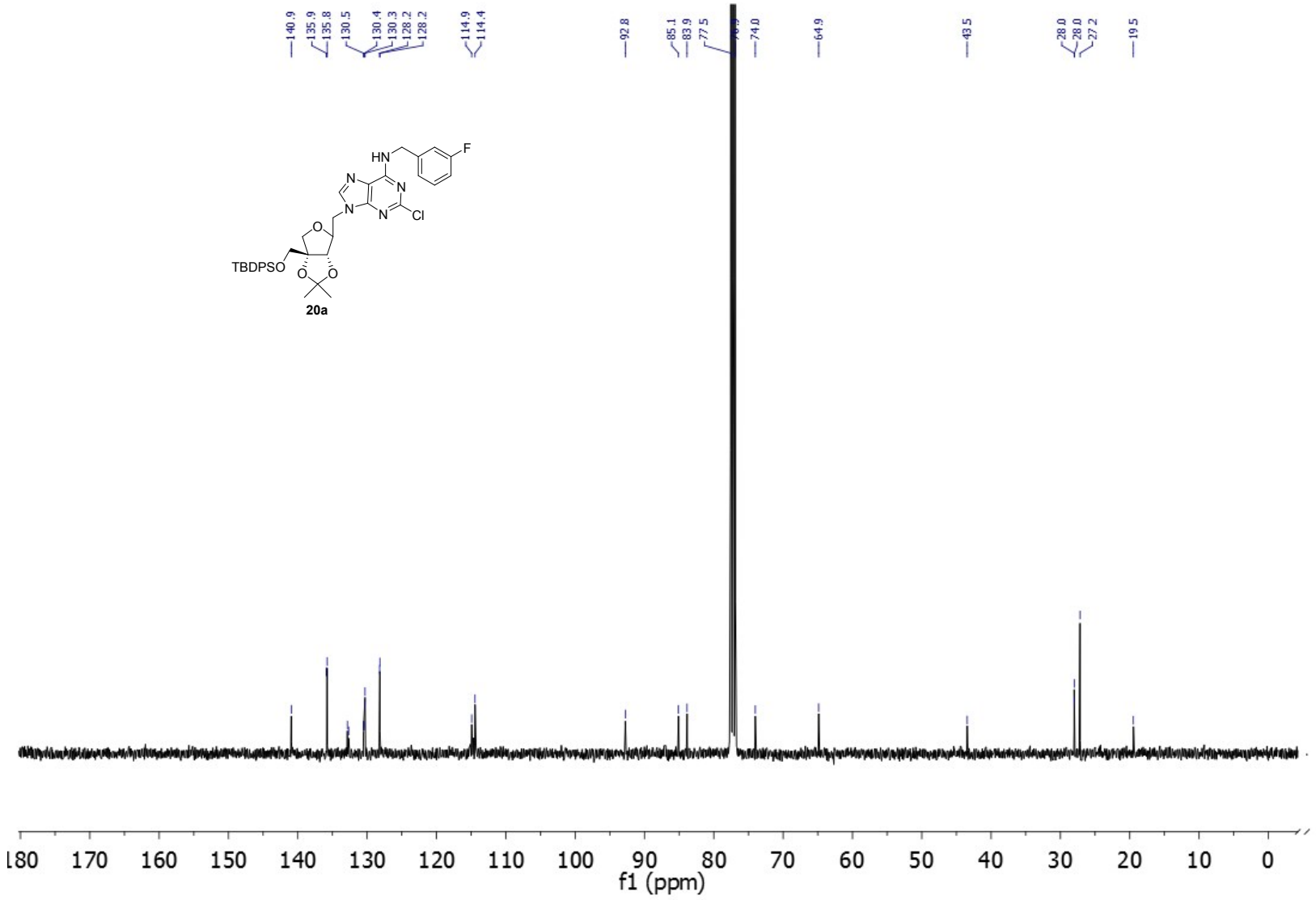
^{13}C spectrum (100 MHz, DMSO-d_6) of compound 7c



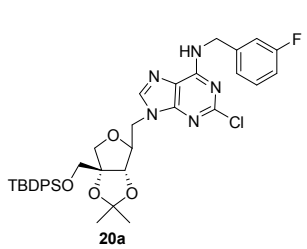
^{1}H spectrum (400 MHz, $CDCl_3$) of compound 20a



^{13}C spectrum (100 MHz, $CDCl_3$) of compound 20a

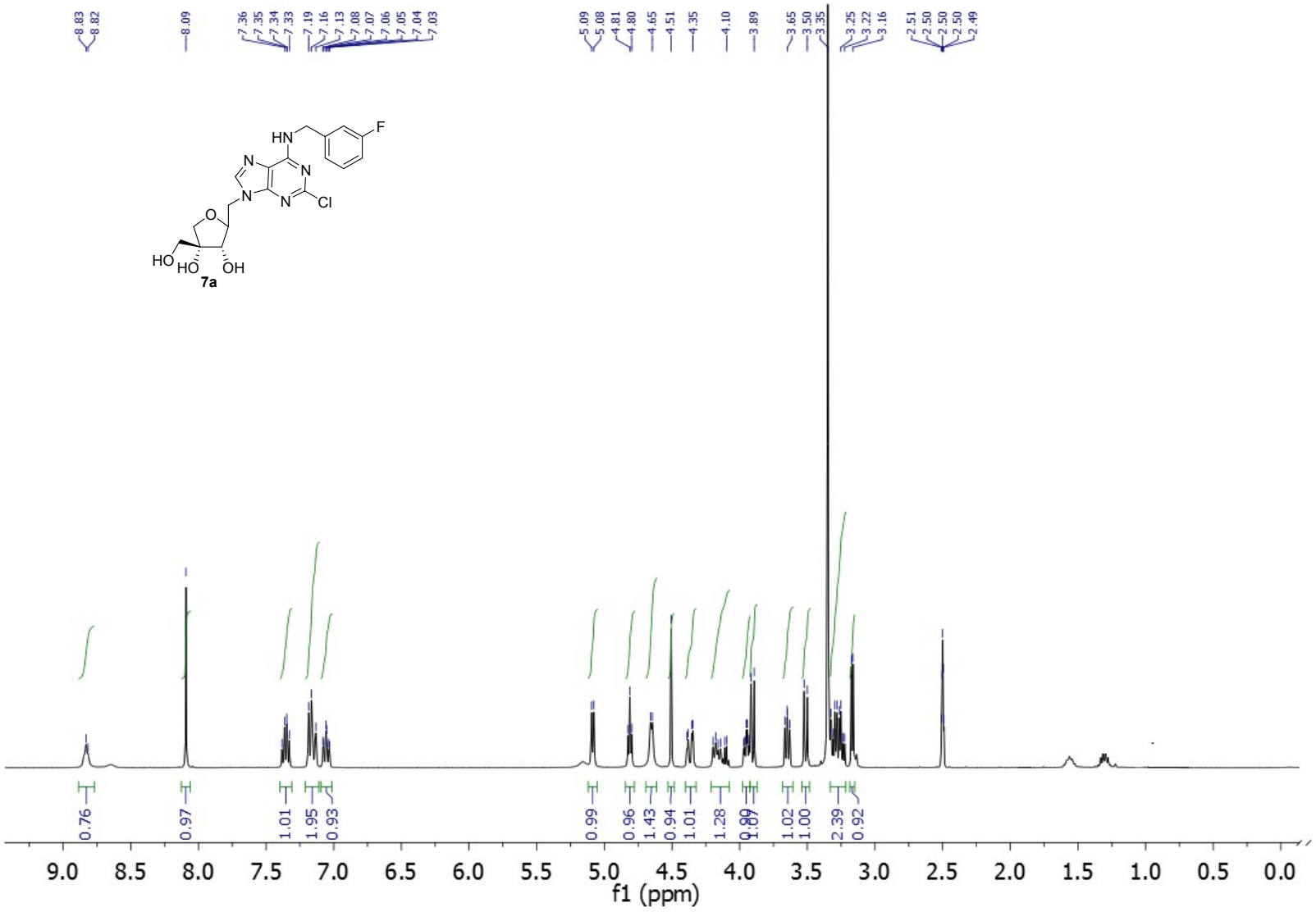


^{19}F spectrum (376 MHz, $CDCl_3$) of compound 20a

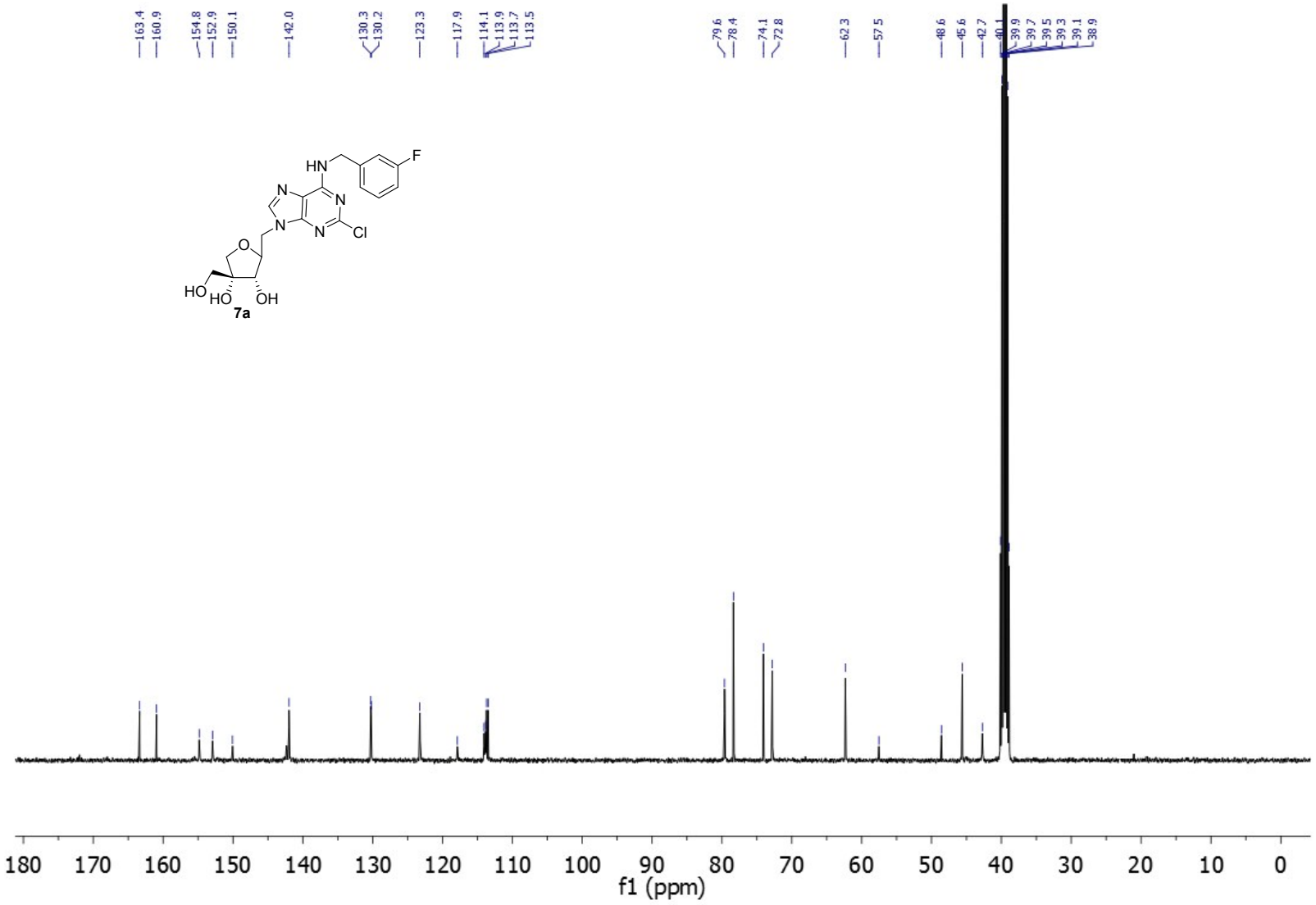


20a

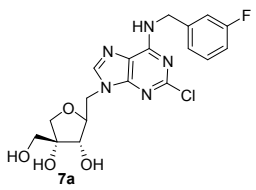
^{1}H spectrum (400 MHz, DMSO-d_6) of compound 7a



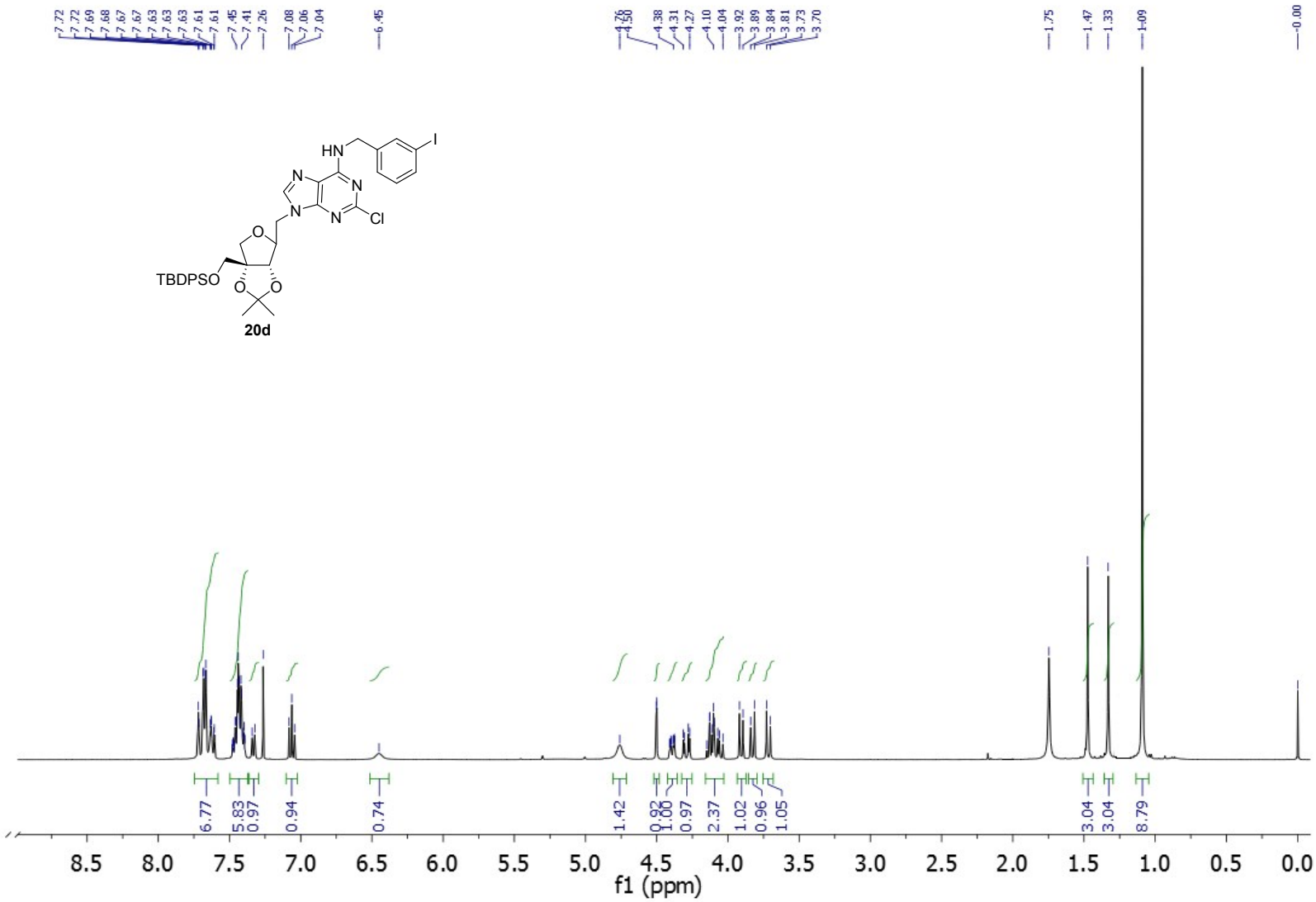
^{13}C spectrum (100 MHz, DMSO-d_6) of compound 7a



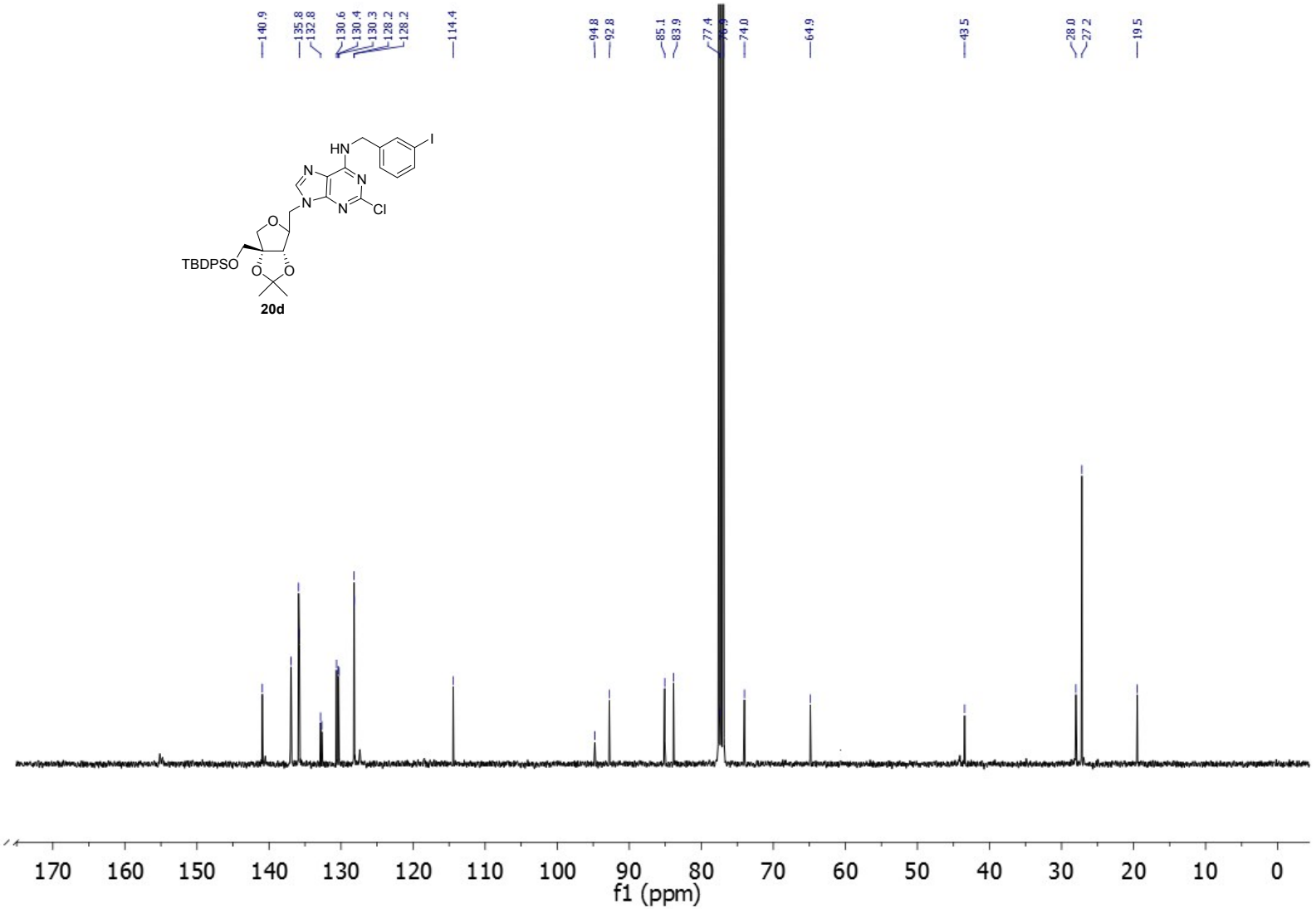
^{19}F spectrum (376MHz, DMSO-d_6) of compound 7a



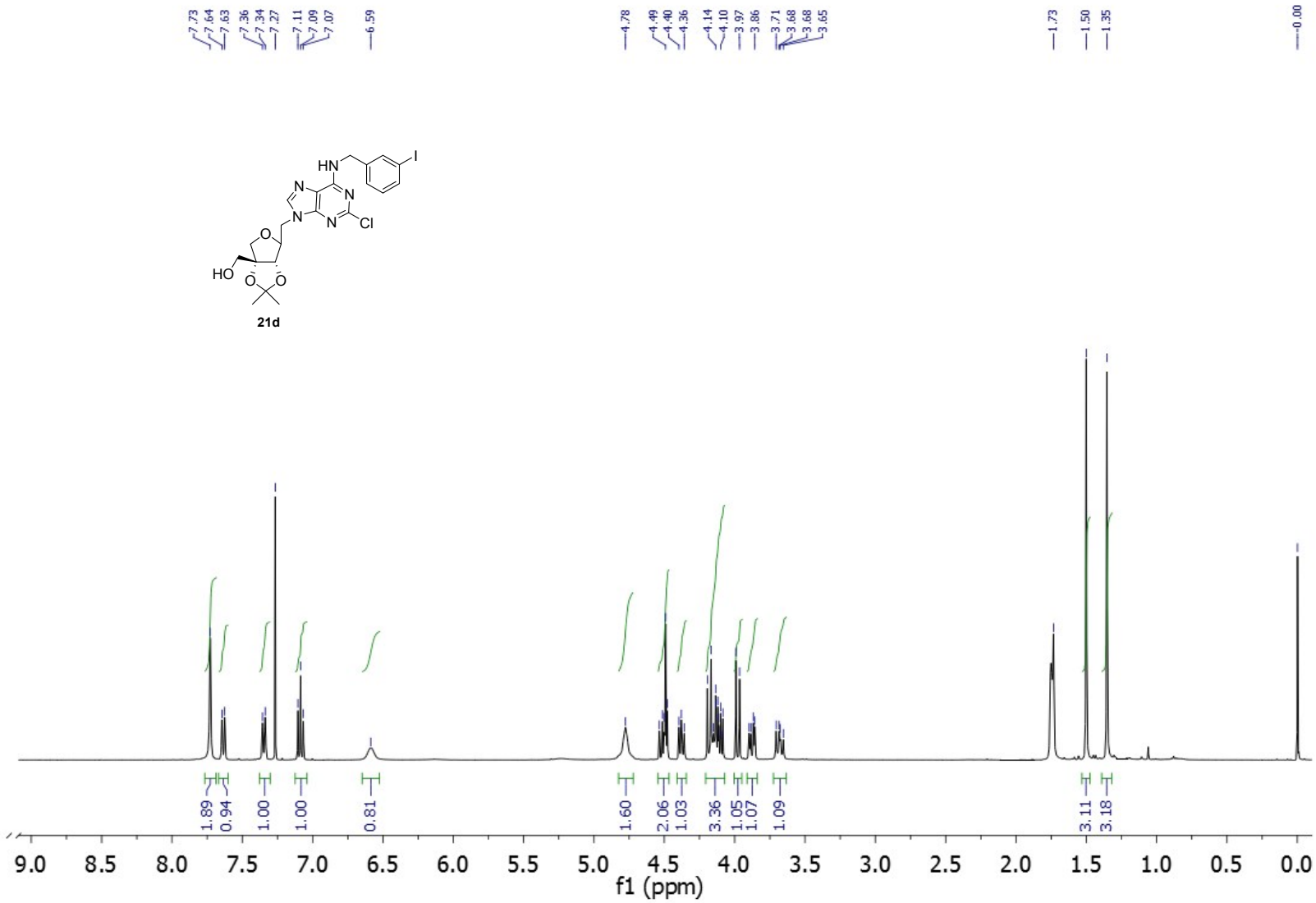
^{1}H spectrum (400 MHz, $CDCl_3$) of compound 20d



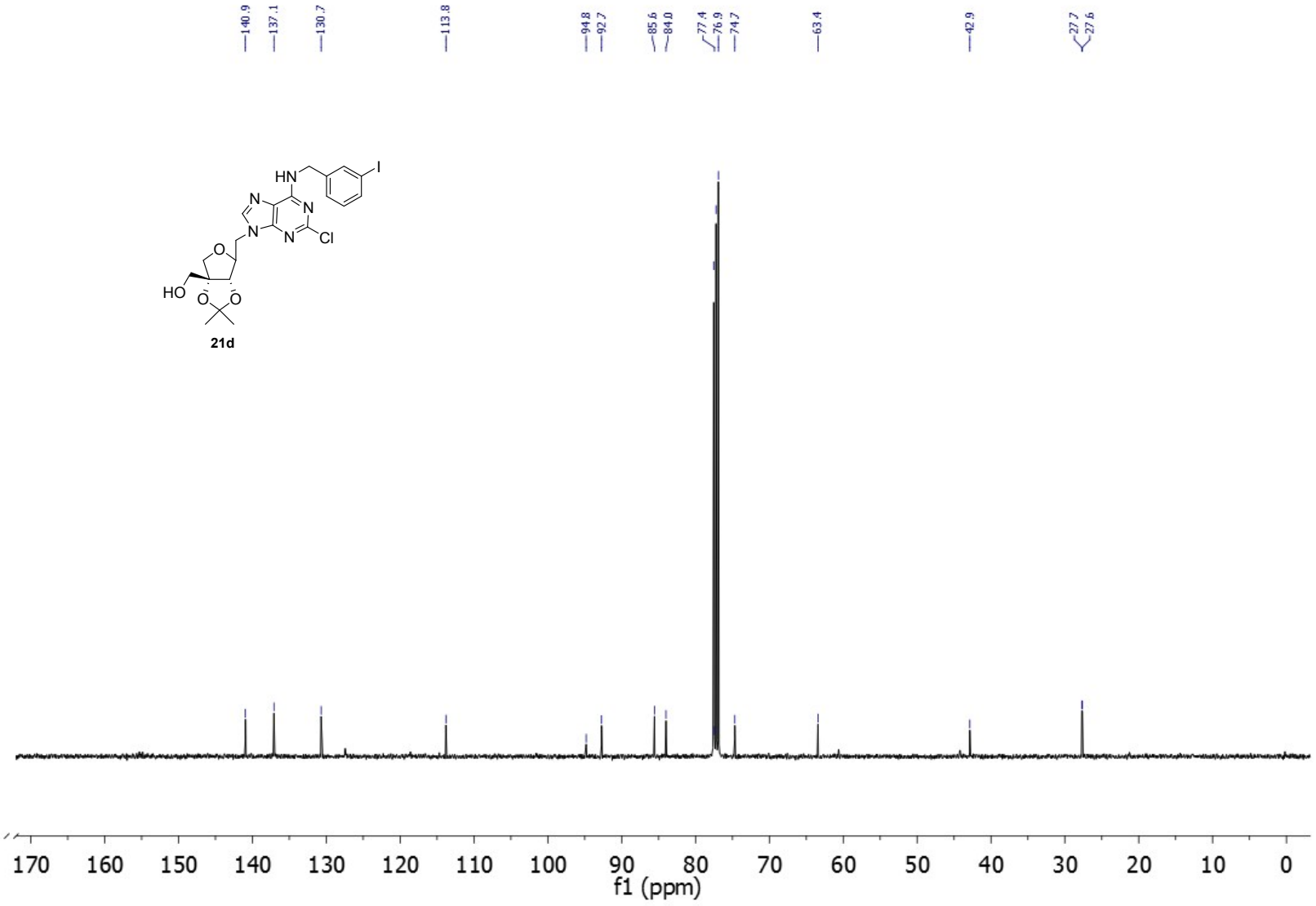
^{13}C spectrum (100 MHz, $CDCl_3$) of compound 20d



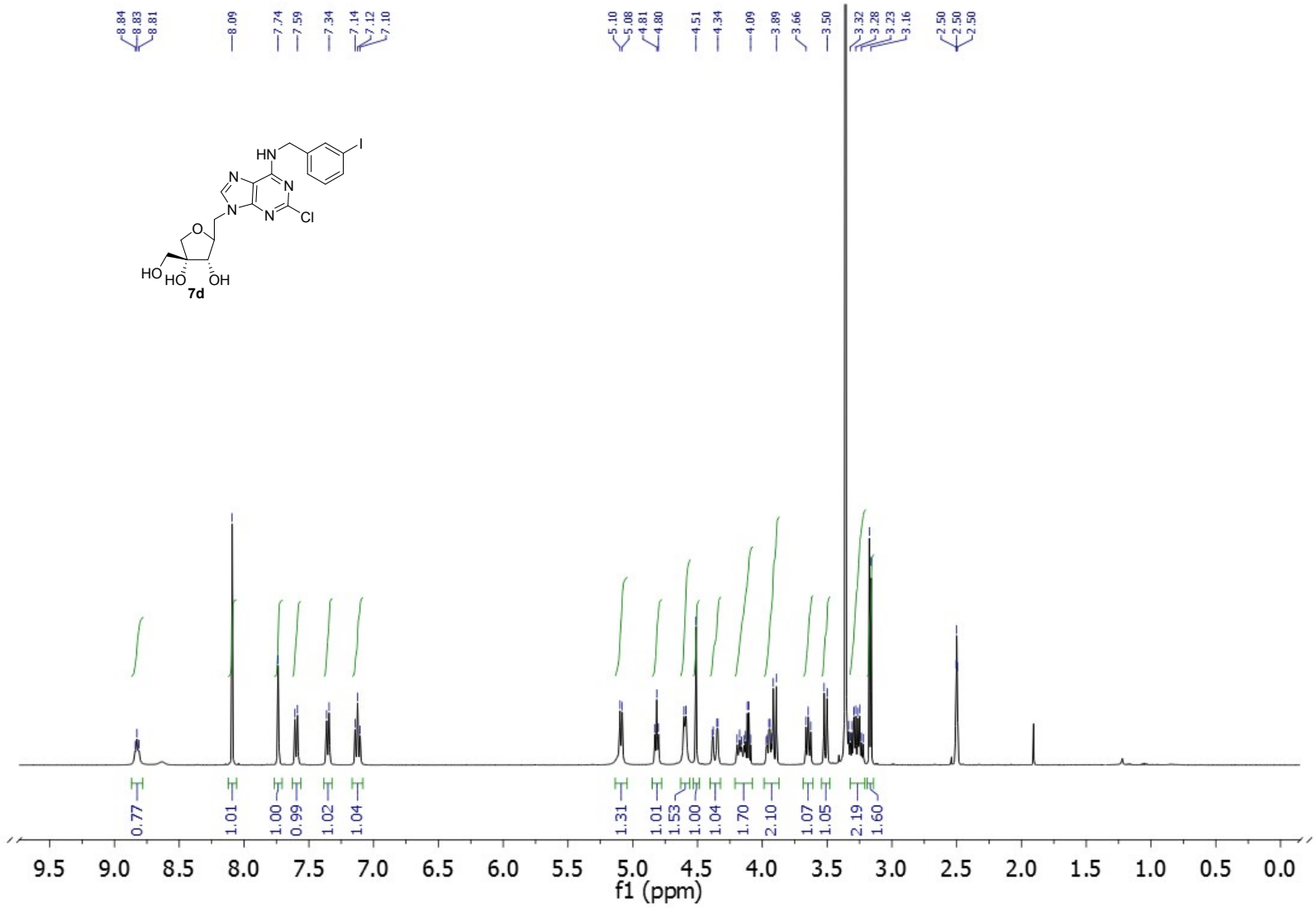
^{1}H spectrum (400 MHz, $CDCl_3$) of compound 21d



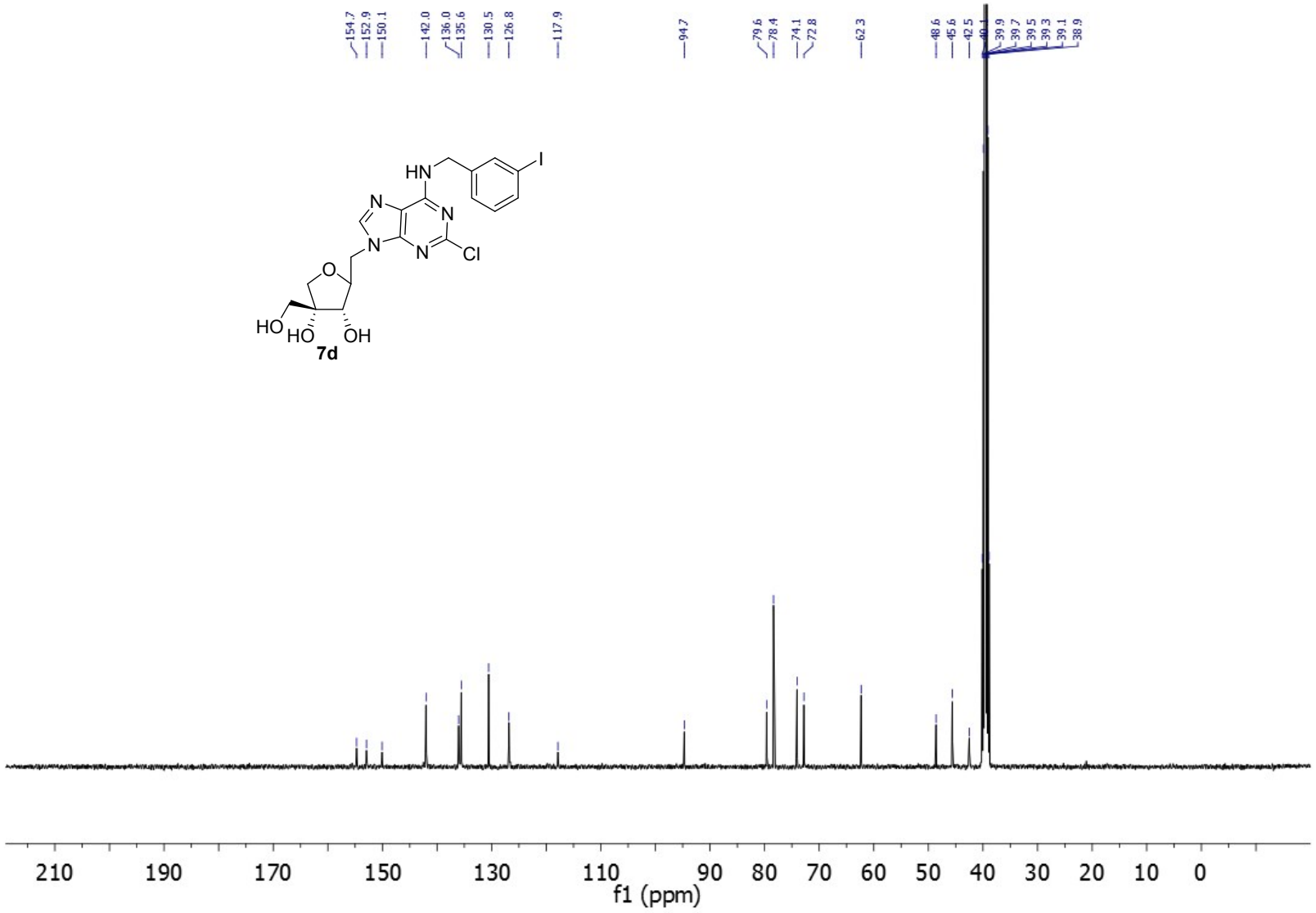
^{13}C spectrum (100 MHz, $CDCl_3$) of compound 21d



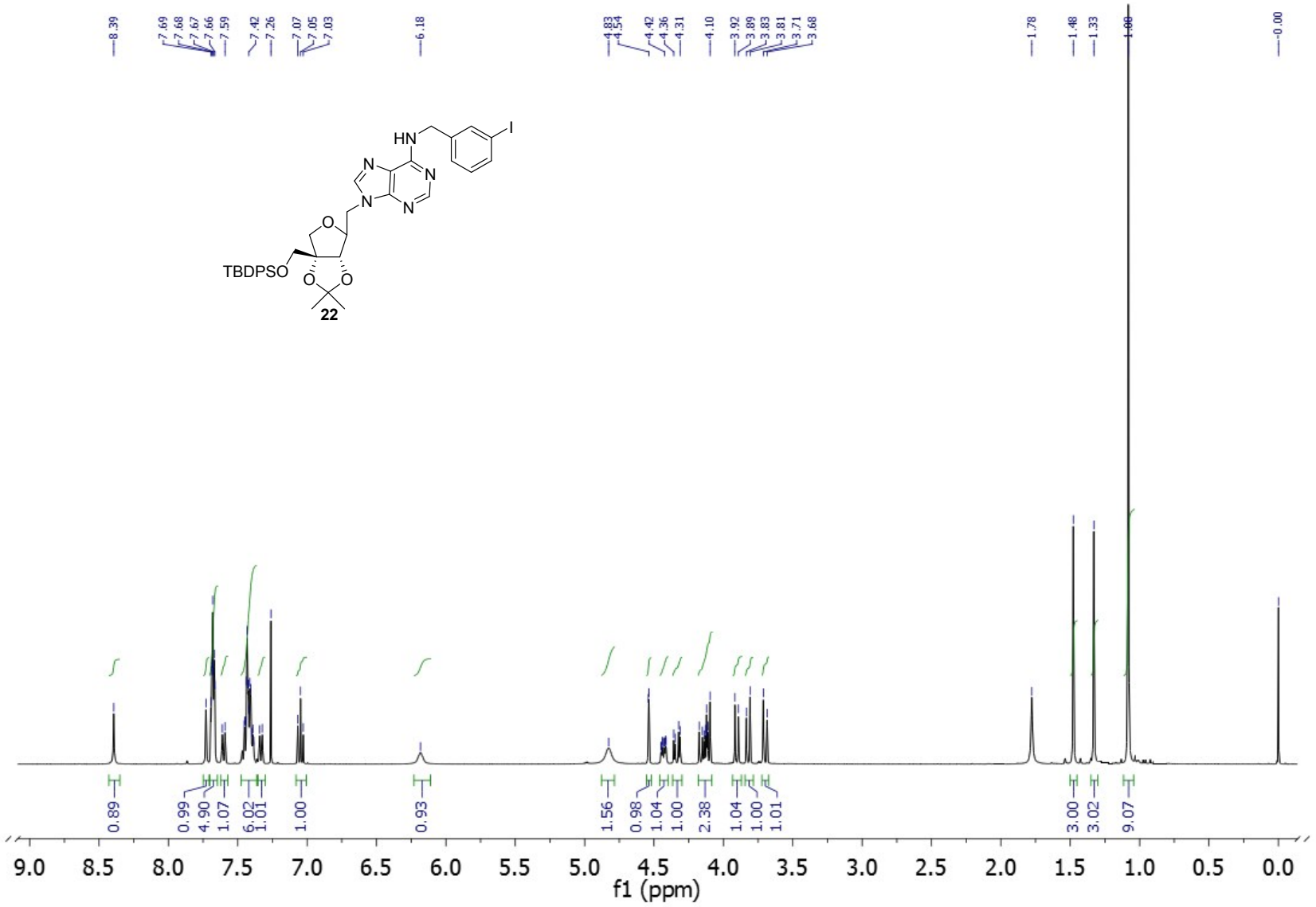
^{1}H spectrum (400 MHz, DMSO-d_6) of compound 7d



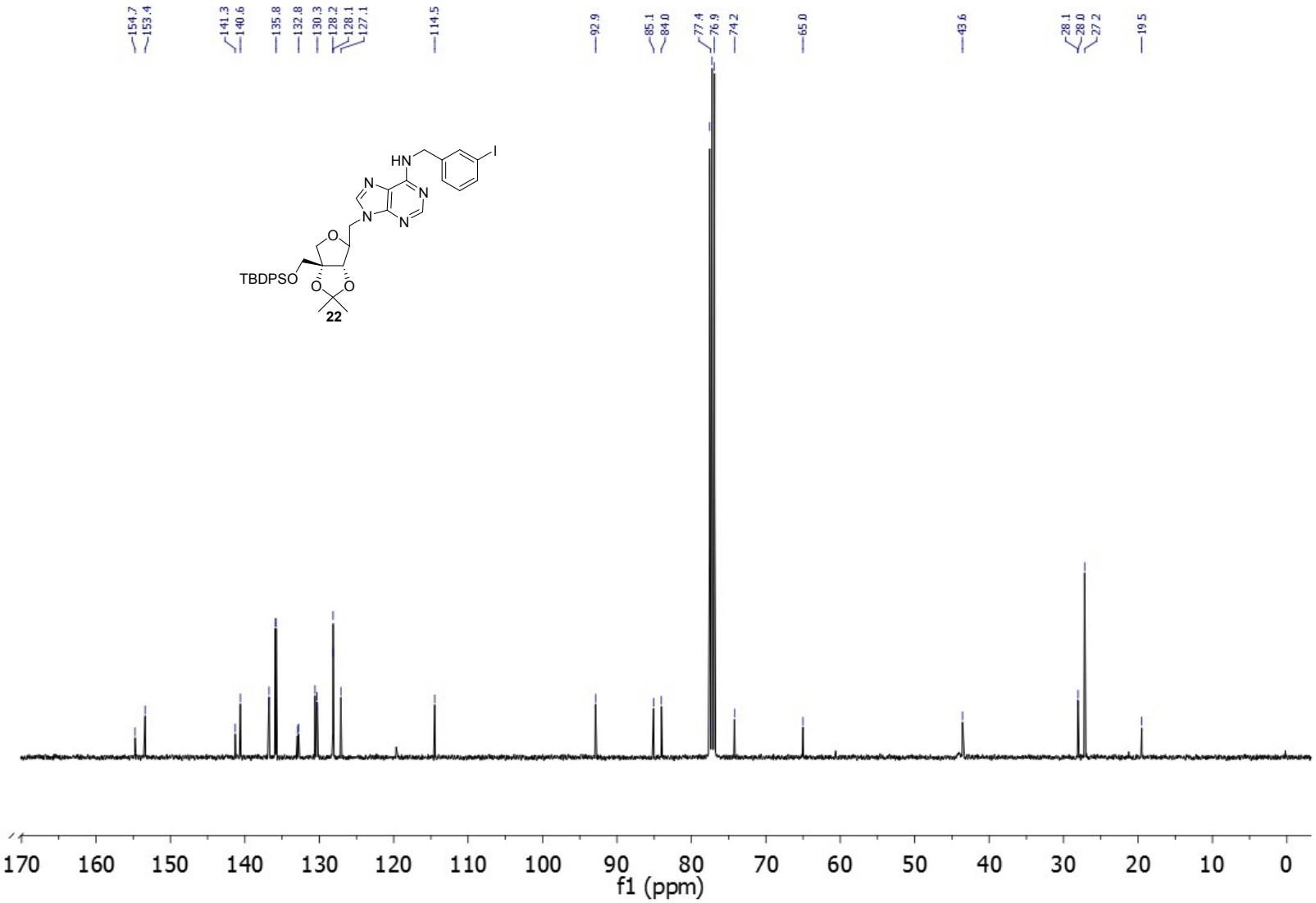
^{13}C spectrum (100 MHz, DMSO-d_6) of compound 7d



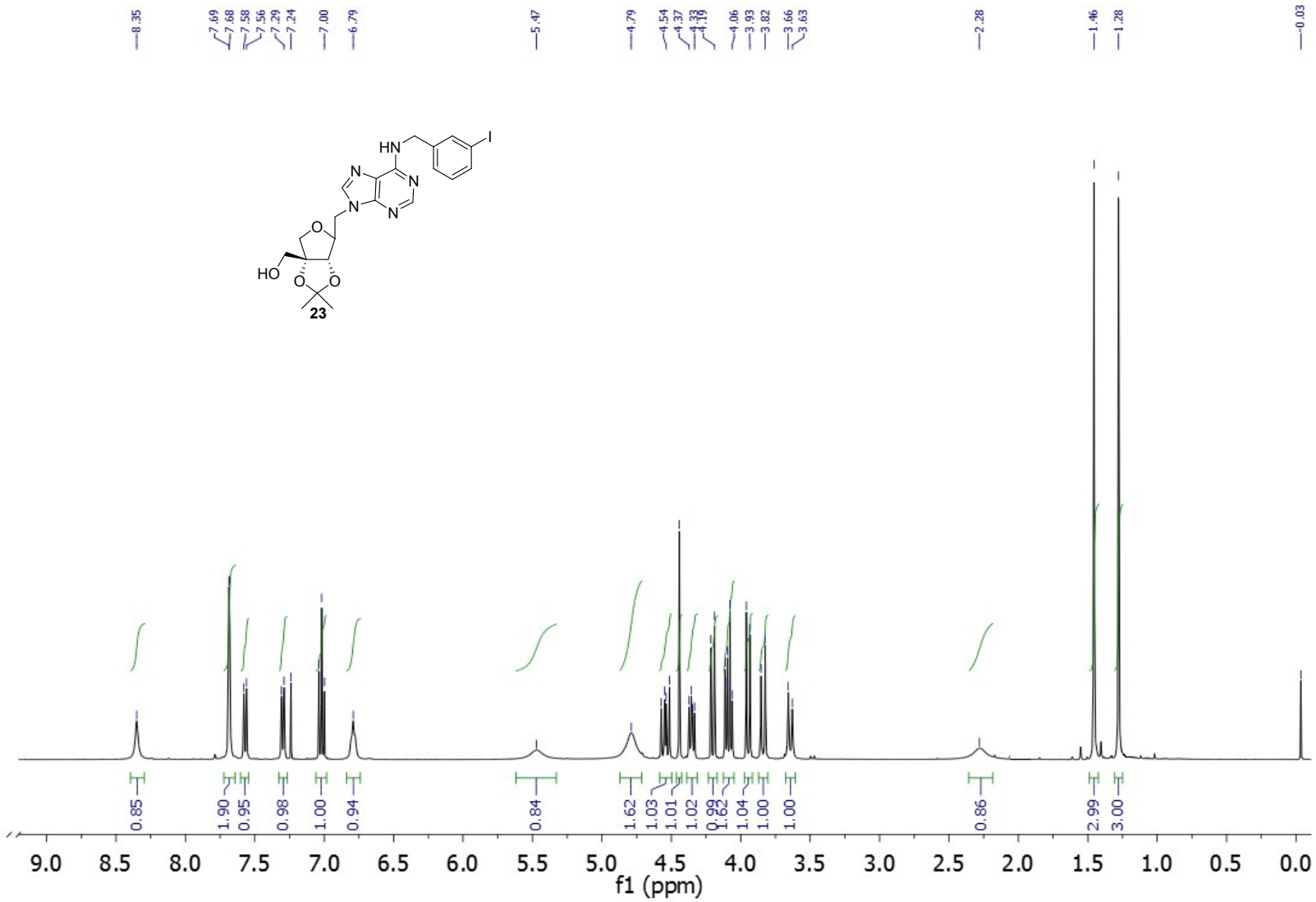
^{1}H spectrum (400 MHz, $CDCl_3$) of compound 22



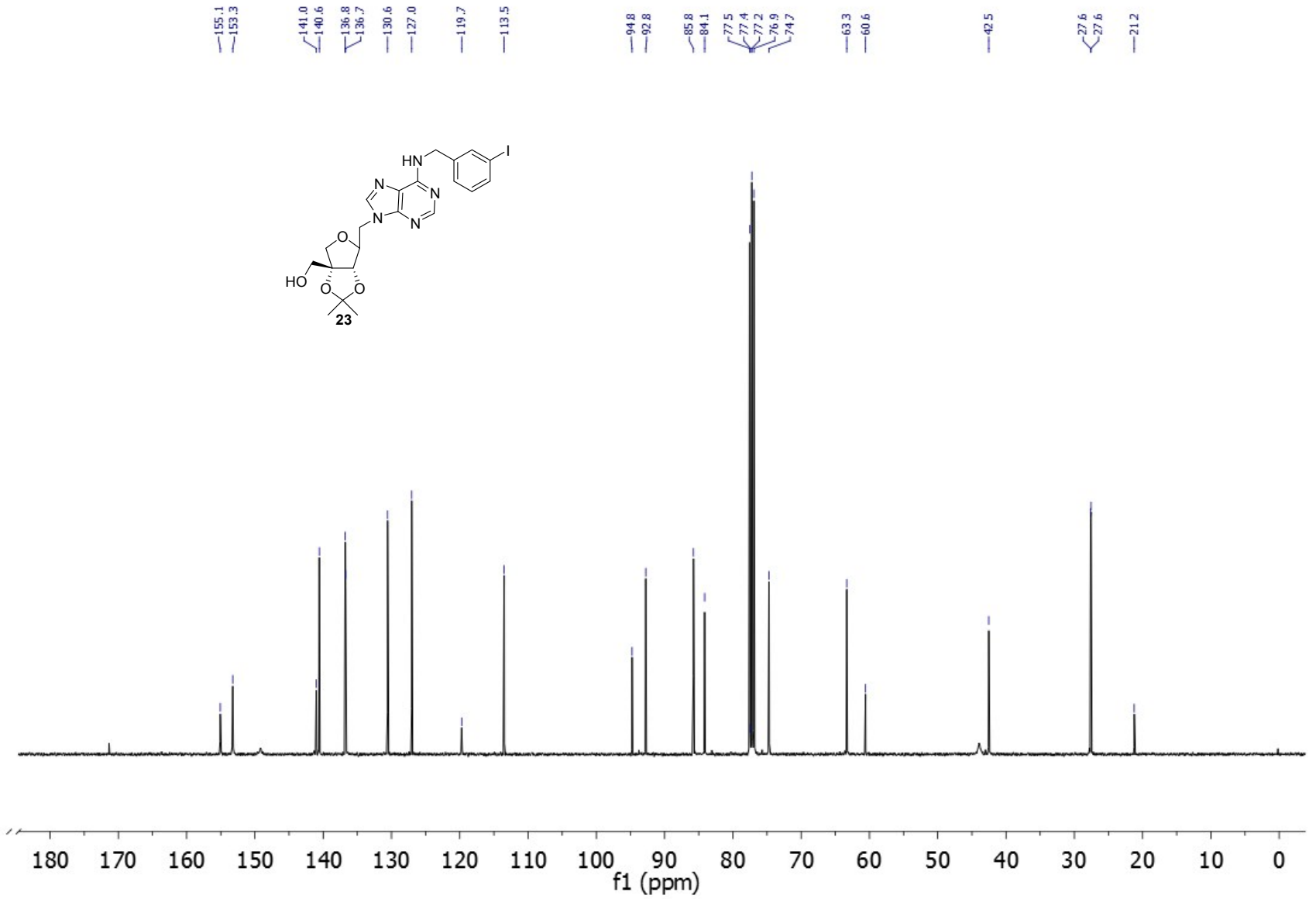
^{13}C spectrum (100 MHz, $CDCl_3$) of compound 22



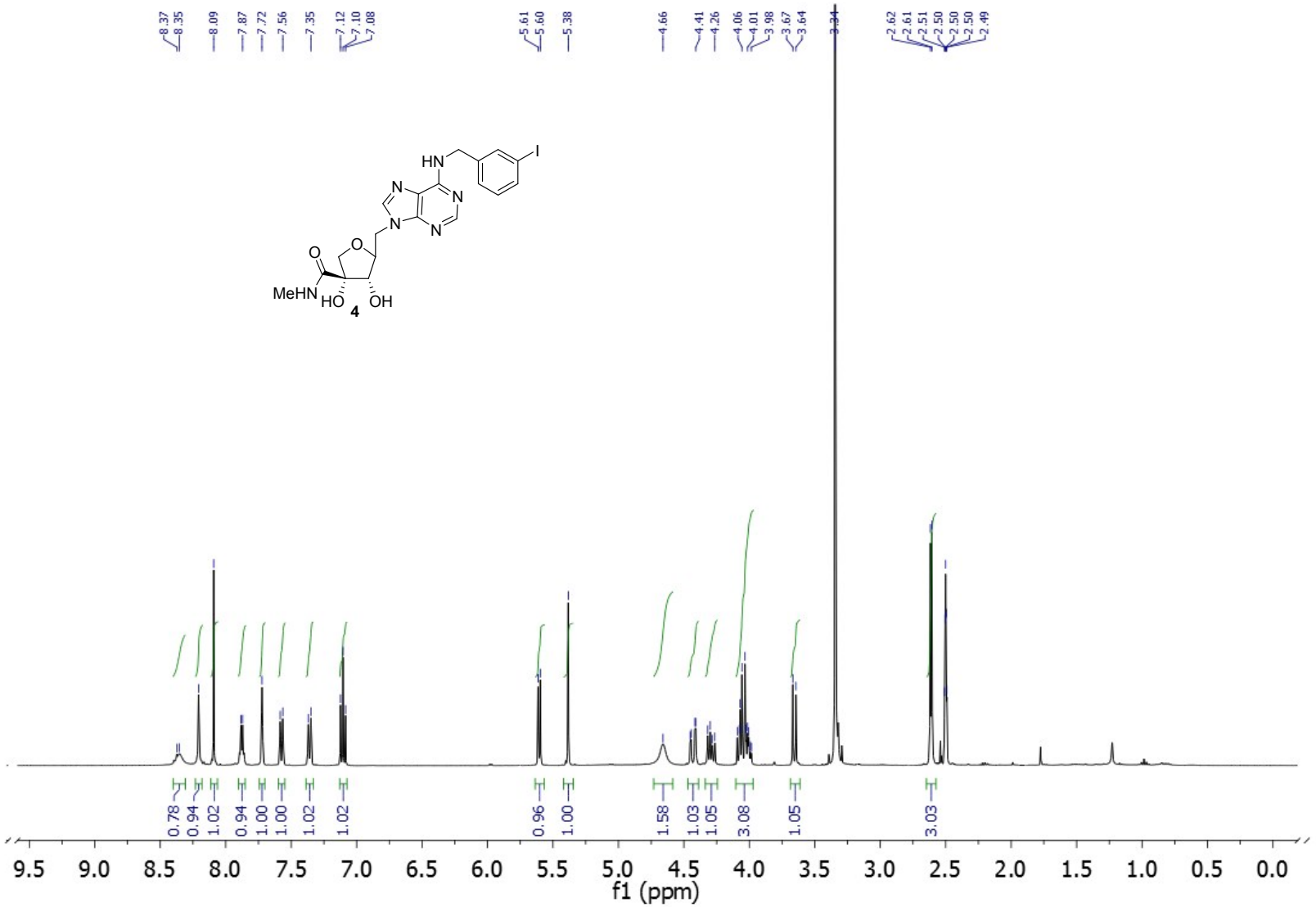
^{1}H spectrum (400 MHz, $CDCl_3$) of compound 23



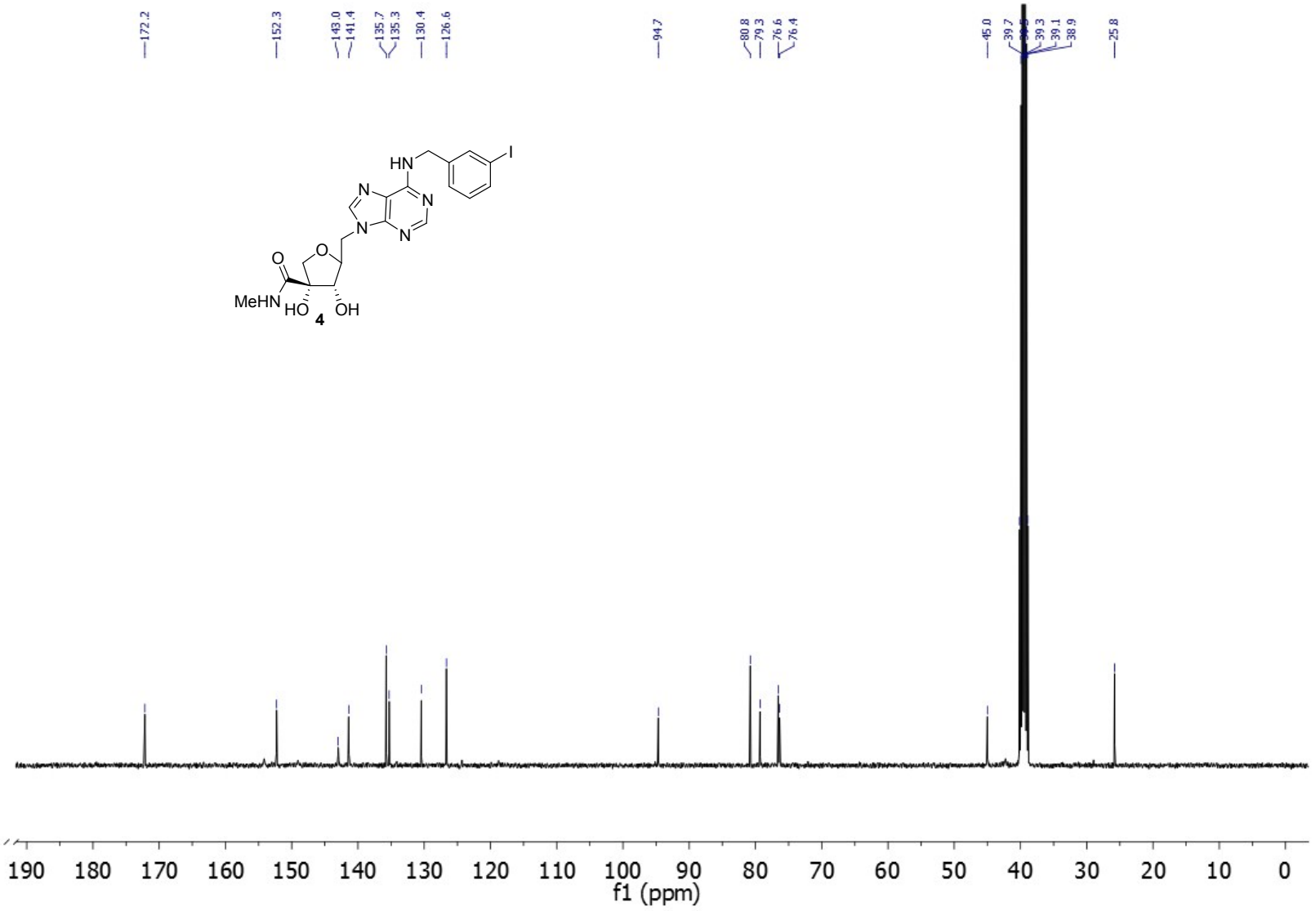
^{13}C spectrum (100 MHz, $CDCl_3$) of compound 23


155.1
153.3
141.0
140.6
136.8
136.7
130.6
127.0
119.7
113.5
94.8
92.8
85.8
84.1
77.5
77.4
77.2
76.9
74.7
63.3
60.6
42.5
27.6
27.6
21.2
HN
I
N
N
N
N
O
HO
O
O
23
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

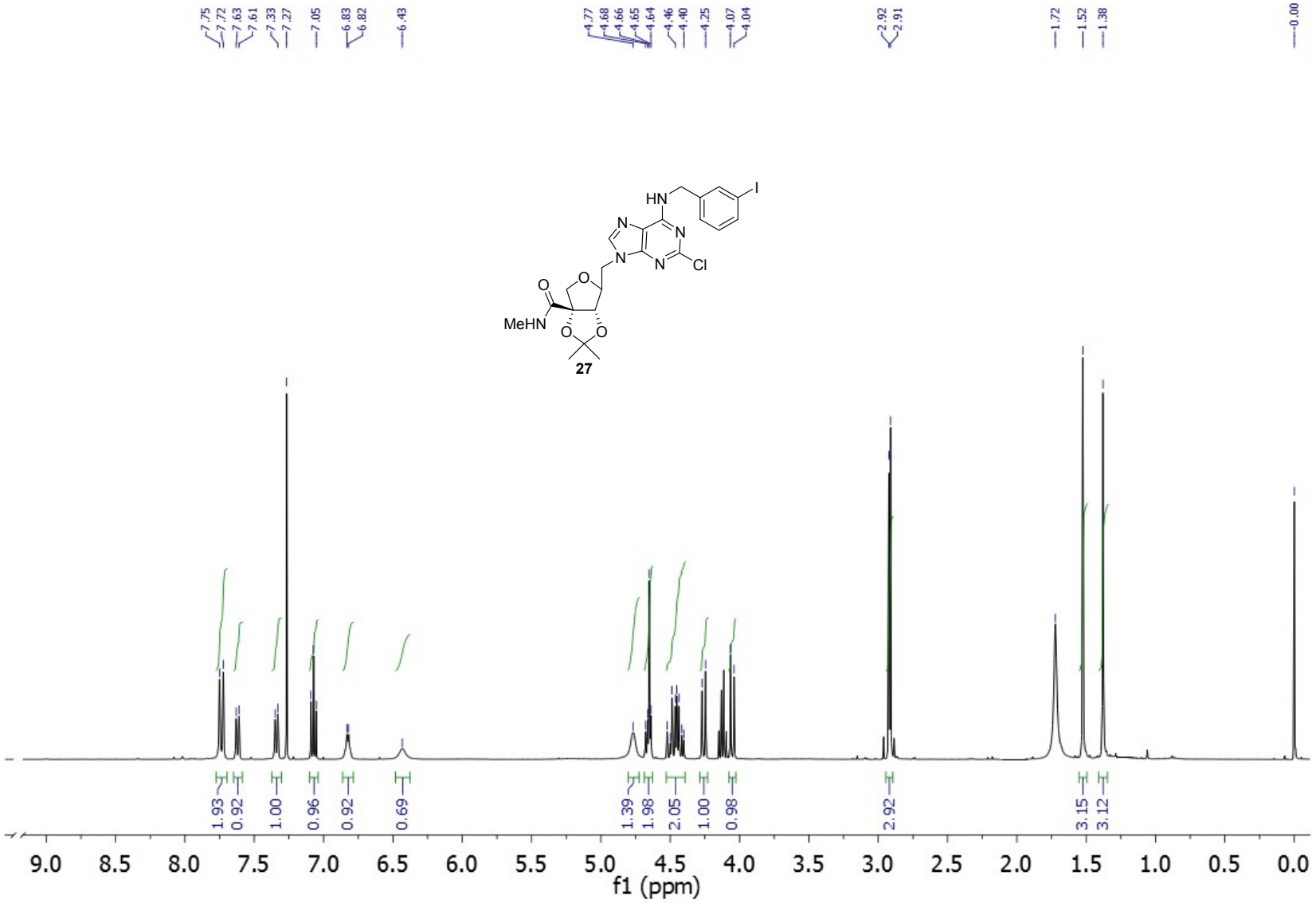
^{1}H spectrum (400 MHz, DMSO-d_6) of compound 4



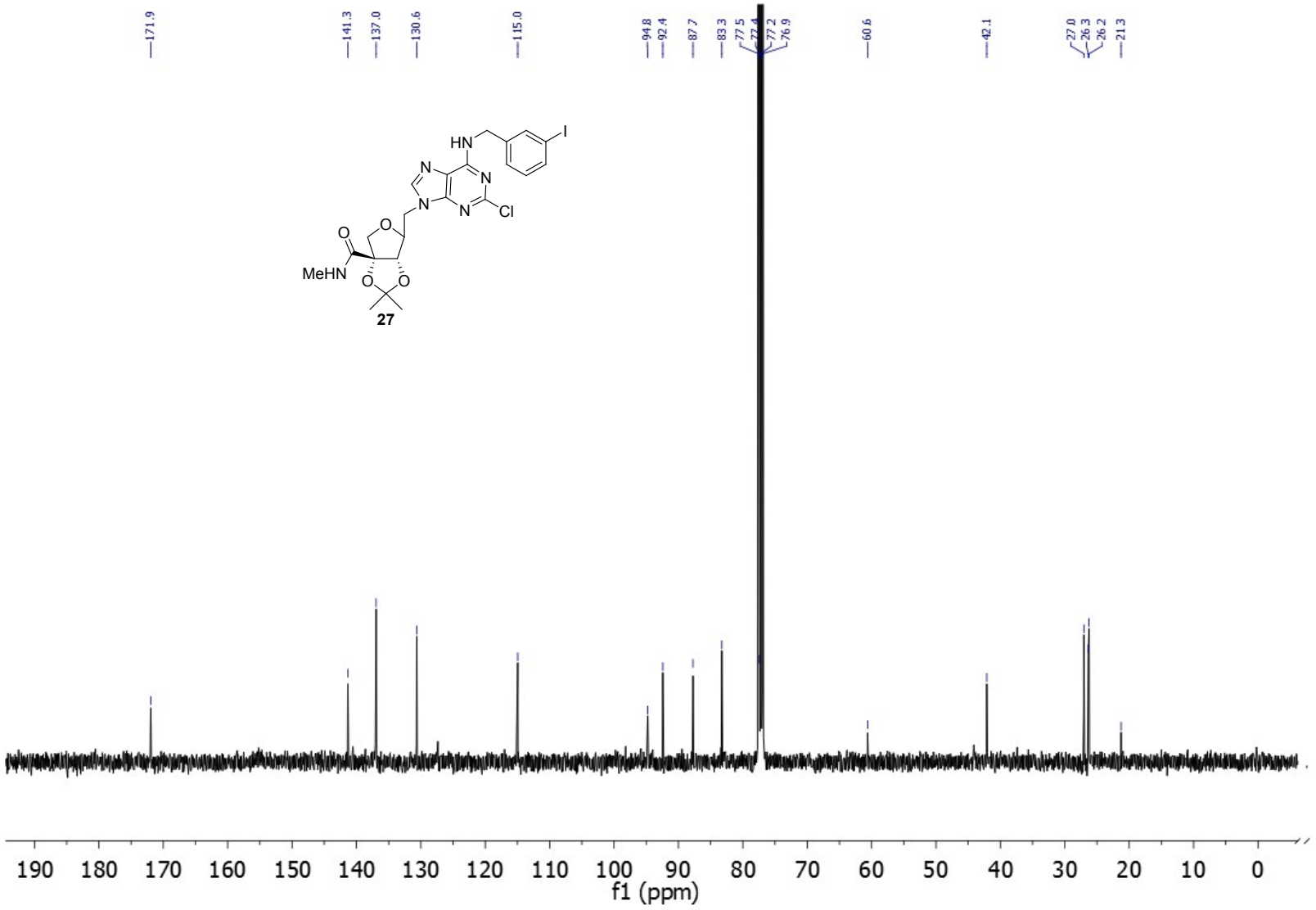
^{13}C spectrum (100 MHz, DMSO-d_6) of compound 4



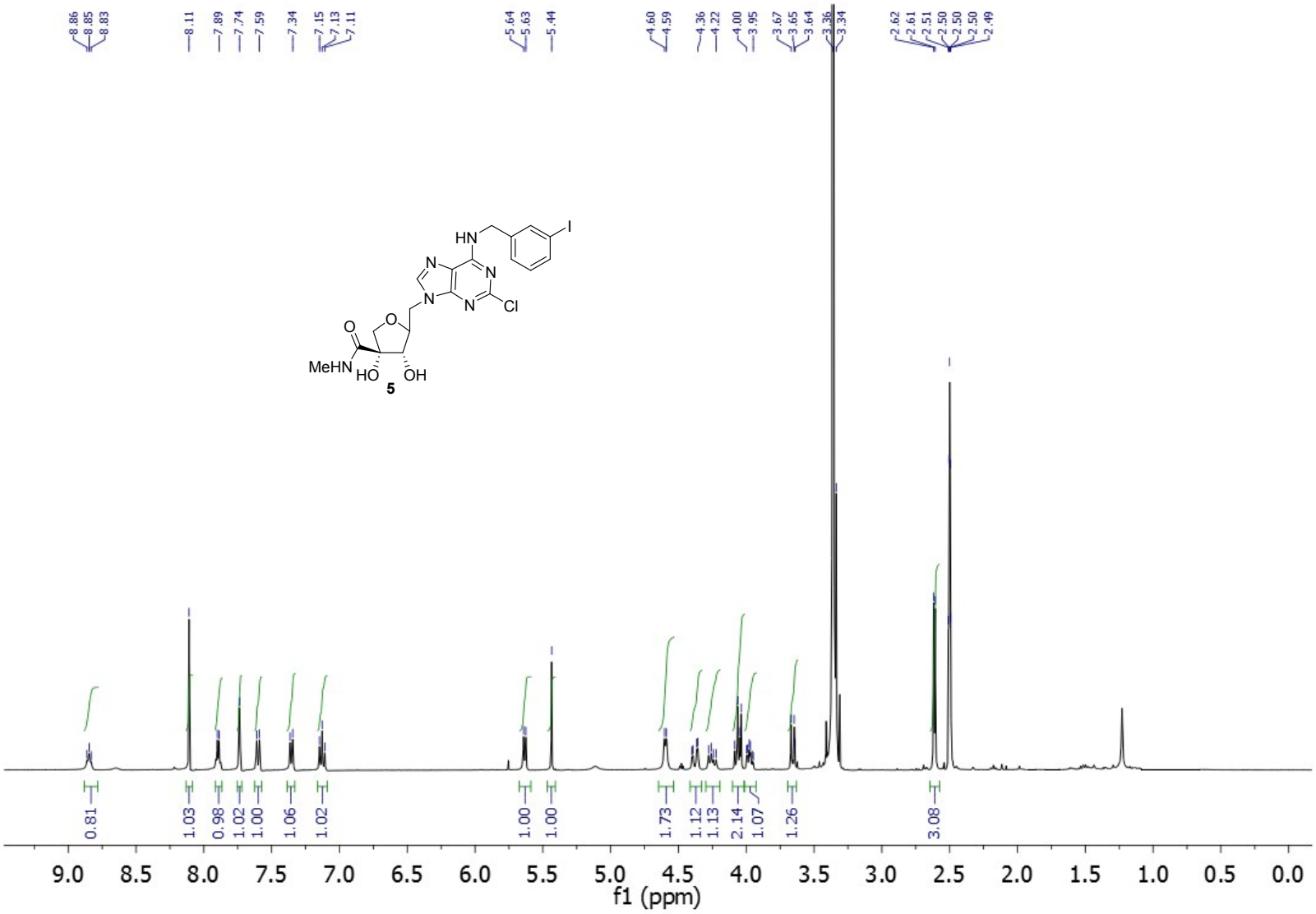
^{1}H spectrum (400 MHz, $CDCl_3$) of compound 27



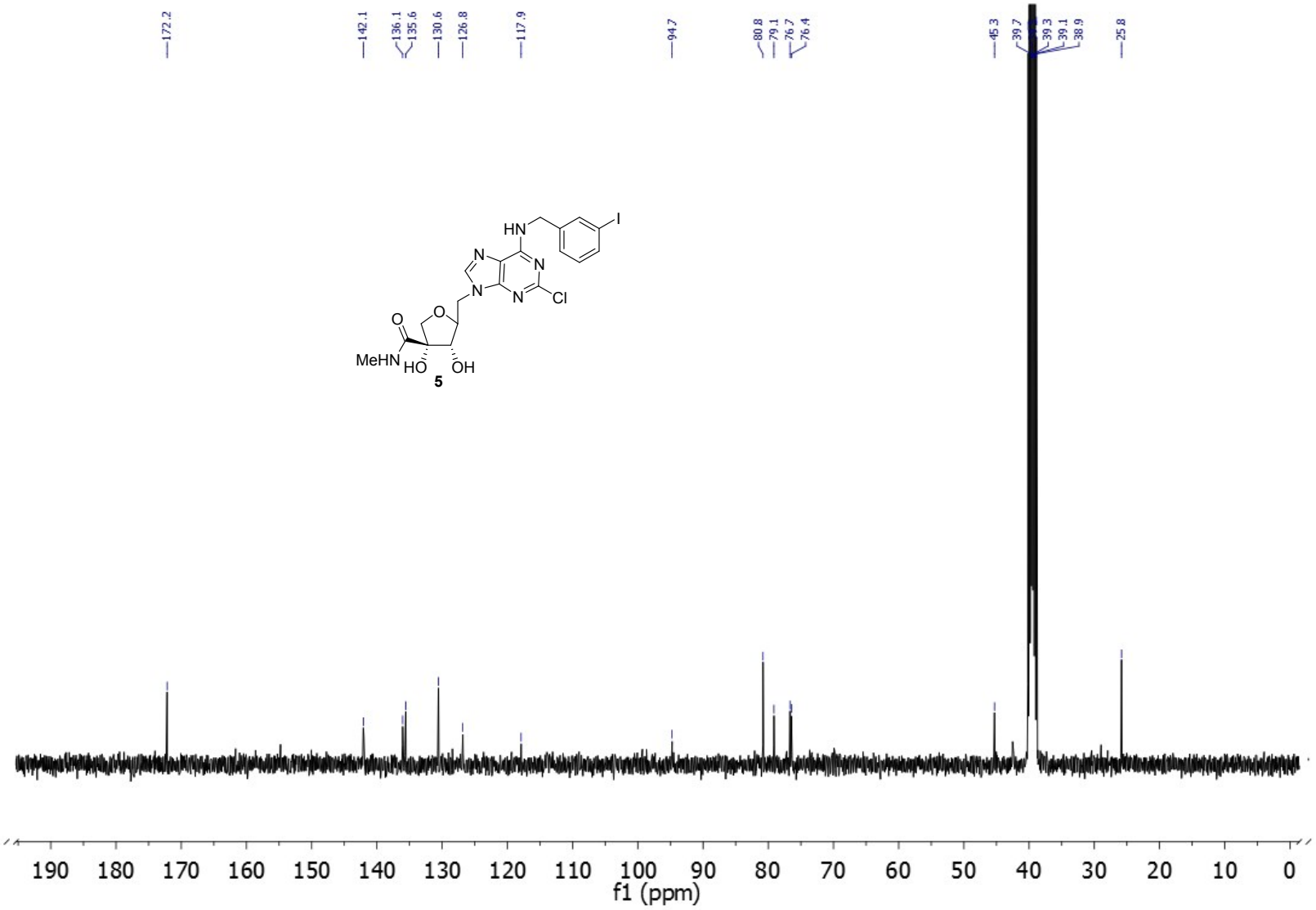
^{13}C spectrum (100 MHz, $CDCl_3$) of compound 27



^{1}H spectrum (400 MHz, DMSO-d_6) of compound 5



^{13}C spectrum (100 MHz, DMSO-d_6) of compound 5



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3 W. L. Jorgensen, D. S. Maxwell and J. Tirado-Rives, *J. Am. Chem. Soc.* 1996, **118**, 11225.

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