



Supporting Information

for

Investigations of amination reactions on an antimalarial 1,2,4-triazolo[4,3-*a*]pyrazine scaffold

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Complete experimental methods, crystallographic data for 2, 7, 10 and 15, characterisation data and 1D/2D NMR spectra (¹H, ¹³C, COSY, HSQC and HMBC) for 2–15

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S1: Experimental methods

General experimental

Melting points were measured using a Cole-Parmer (Chicago, IL, USA) melting point apparatus and were uncorrected. UV spectra were recorded using an Ocean Optics (USB-ISS-UV/VIS) spectrophotometer. NMR spectra were recorded at 25 °C on a Bruker (Billerica, MA, USA) AVANCE III™ HD 500 MHz NMR spectrometer equipped with a cryoprobe. MestreNova™ version 14.3.3 software was used for NMR data analysis. The ^1H and ^{13}C chemical shifts were referenced to solvent peaks for $(\text{CD}_3)_2\text{SO}$ (δ_{H} 2.50, δ_{C} 39.52). LRESIMS data was recorded on a Thermo Scientific (Waltham, MA, USA) UltiMate™ 3000 RS UHPLC coupled to a Thermo Scientific ISQ™ EC single quadrupole ESI mass spectrometer. HRESIMS data were acquired on a Bruker maXis II ETD ESI-qTOF. TLC was carried out on Merck (Kenilworth, NJ, USA) silica gel 60 F254 pre-coated aluminium plates and developed plates were visualised using UV light at 254 and 365 nm.

Reaction mixtures were pre-adsorbed onto Merck silica gel (40–63 μm , 143 Å) and Isolute™ silica (30 × 40 mm, 10 g, 55 μm , 54 Å) SPE cartridges were used for normal-phase small-scale separations. Alltech (Lexington, KY, USA) Davisil™ C₁₈-bonded silica (35–70 μm , 60 Å) were used for pre-adsorption work before reversed-phase HPLC separations. Pre-adsorbed material was packed into an Alltech stainless steel guard cartridge (10 × 30 mm) then attached to an HPLC column prior to fractionation. Thermo Electron Betasil™ C₁₈-bonded silica (5 μm , 100 Å, 150 × 21.2 mm) columns were used for reversed-phase HPLC separations. A Thermo Scientific Dionex Ultimate™ 3000 UHPLC was used for HPLC separations. All solvents used for chromatography and MS were Honeywell Burdick & Jackson (Muskegon, MI, USA) or

RCI Labscan (Bangkok, Thailand) HPLC grade. H₂O was filtered using a Sartorius (Gottingen, Lower Saxony, Germany) Arium™ Pro VF ultrapure water system. Synthetic reagents were purchased from Sigma-Aldrich (St. Louis, MO, USA) and used without further purification. The starting material, 5-chloro-3-(4-chlorophenyl)-[1,2,4]triazolo[4,3-a]pyrazine (**1**), was previously synthesised and purified by the Davis group [1].

Crystallography studies

Intensity data for compounds **2**, **7**, **10** and **15** were collected with an Oxford Diffraction Synergy diffractometer with Cu or Mo K α radiation, and the temperature during data collection was maintained at 100.0(1) K, but 250(1) K for **7**, which underwent a destructive phase change at lower temperatures, using an Oxford Cryosystems cooling device. The structures of **2**, **7**, **10** and **15** were solved by direct methods and difference Fourier synthesis. Hydrogen atoms bound to the carbon atoms were placed at their idealised positions using appropriate HFIX instructions in SHELXL [2] and included in subsequent refinement cycles. The hydrogen atom attached to nitrogen was located from difference Fourier maps and refined freely with isotropic displacement parameters. Thermal ellipsoid plots were generated using the program Mercury [3] integrated within the WINGX suite of programs [4]. Complete crystallographic data for compounds **2** (CCDC 2406262), **7** (CCDC 2420136), **10** (CCDC 2420137) and **15** (CCDC 2420244) have been deposited with the Cambridge Crystallographic Data Centre. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

3-(4-Chlorophenyl)-*N*-phenethyl-[1,2,4]triazolo[4,3-*a*]pyrazin-8-amine (2)

$C_{19}H_{16}ClN_5$, $M = 349.82$, $T = 100.0(1)$ K, $\lambda = 10.71073$ Å, triclinic, space group $P-1$ $a = 9.53590(1)$ Å, $b = 9.6391(2)$ Å, $c = 18.9247(3)$ Å, $\alpha = 91.480(1)$ $\beta = 95.492(1)^\circ$ $\gamma = 103.950(1)^\circ$ $V = 1678.30(5)$ Å³, $Z = 4$, $Z' = 2$, $D_c = 1.384$ mg M^{-3} μ (Mo- $K\alpha$) 0.239 mm⁻¹, $F(000) = 728$, crystal size $0.60 \times 0.27 \times 0.23$ mm³; reflections measured, 21295, $\theta_{max} = 41.17^\circ$, 57839 independent reflections ($R_{int} = 0.0356$); final $R = 0.0455$ [$I > 2\sigma(I)$, 15417 data] and $wR(F^2) = 0.1413$ (all data); GOOF = 1.116.

3-(4-Chlorophenyl)-*N*-isopentyl-[1,2,4]triazolo[4,3-*a*]pyrazin-8-amine (7)

$C_{16}H_{18}ClN_5$, $M = 315.80$, $T = 250.0(1)$ K, $\lambda = 1.54184$ Å, triclinic, space group $P-1$ $a = 6.8541(2)$ Å, $b = 10.4434(3)$ Å, $c = 11.7545(3)$ Å, $\alpha = 92.017(2)$ $\beta = 105.095(2)^\circ$ $\gamma = 93.263(2)^\circ$ $V = 809.95(4)$ Å³, $Z = 2$, $D_c = 1.295$ mg M^{-3} μ (Cu- $K\alpha$) 2.113 mm⁻¹, $F(000) = 332$, crystal size $0.28 \times 0.06 \times 0.04$ mm³; reflections measured, 8861, $\theta_{max} = 79.335^\circ$, 3372 independent reflections ($R_{int} = 0.0339$); final $R = 0.0448$ [$I > 2\sigma(I)$, 2895 data] and $wR(F^2) = 0.1320$ (all data); GOOF = 1.070.

***N*¹-(3-(4-Chlorophenyl)-[1,2,4]triazolo[4,3-*a*]pyrazin-8-yl)-*N*²,*N*²-dimethylethane-1,2-diamine (10)**

$C_{15}H_{17}ClN_6$, $M = 316.79$, $T = 100.0(1)$ K, $\lambda = 1.54184$ Å, triclinic, space group $P-1$ $a = 7.3282(3)$ Å, $b = 12.6354(6)$ Å, $c = 17.5968(7)$ Å, $\alpha = 69.251(4)$ $\beta = 87.931(3)^\circ$ $\gamma = 85.826(3)^\circ$ $V = 1519.56(12)$ Å³, $Z = 4$, $Z' = 2$, $D_c = 1.385$ mg M^{-3} μ (Cu- $K\alpha$) 2.274 mm⁻¹, $F(000) = 664$, crystal size $0.49 \times 0.27 \times 0.06$ mm³; reflections measured, 19842, $\theta_{max} = 80.025^\circ$, 6344 independent reflections ($R_{int} = 0.0463$); final $R = 0.0479$ [$I > 2\sigma(I)$, 15417 data] and $wR(F^2) = 0.1356$ (all data); GOOF = 1.091.

***Tert*-butyl(4-((3-(4-chlorophenyl)-[1,2,4]triazolo[4,3-*a*]pyrazin-8-yl)amino)butyl)carbamate (15)**

C₂₀ H₂₅ Cl N₆ O₂, *M* = 416.91, *T* = 100.0(1) K, λ = 1.54184 Å, triclinic, space group *P*-1 *a* = 9.39890(10) Å, *b* = 10.22800(10) Å, *c* = 22.5357(3) Å, α = 69.251(4)° β = 87.931(3)° γ = 102.5610(10)° *V* = 2050.26(4) Å³, *Z* = 4, *Z'* = 2, *D_c* = 1.351 mg M⁻³ μ (Cu-K α) 1.893 mm⁻¹, *F*(000) = 880, crystal size 0.52 × 0.13 × 0.07 mm³; reflections measured, 24392, $\theta_{\max}$ = 79.437°, 8526 independent reflections (*R*_{int} = 0.0281); final *R* = 0.0638 [*I* > 2 σ (*I*), 7616 data] and *wR*(*F*²) = 0.1811 (all data); GOOF = 1.092.

In vitro antiplasmodial image-based assay

Plasmodium falciparum 3D7 were cultured in RPMI1640 (Life Technologies, Camarillo, CA, USA) supplemented with 2.5 mg/mL Albumax II, 5% AB human serum, 25 mM HEPES, and 0.37mM hypoxanthine. Human red blood cells (RBC) (O+) were supplied by Australian Red Cross LifeBlood in accordance with agreement 23-05QLD-23. Use of human RBC for anti-plasmodial experimentation was in accordance with Griffith University Human Ethics Exemption Approval #03/08/11019. Ring stage parasites were treated with compounds following two rounds of sorbitol synchronisation, as previously described [5]. Puromycin, chloroquine, pyrimethamine, and dihydroartemisinin were used as reference compounds. Following incubation of assay plates for 72 h at 37 °C, and 5% CO₂ and 5% O₂, parasites were stained with 2-(4-amidinophenyl)-1*H*-indole-6-carboxamide (DAPI) and imaged using an Opera PhenixPlus™ High Content Screening System (PerkinElmer, Waltham, MA, USA). Images were analysed using Harmony software (PerkinElmer, Waltham, MA, USA).

In vitro cytotoxicity assay

Human embryonic kidney (HEK293) cells were maintained in DMEM (Life Technologies, Camarillo, CA, USA) containing 10% FBS (Hyclone™ ThermoFisher, Melbourne, Australia). Cytotoxicity testing was undertaken as previously described [6]. In brief, 5 µL of test compound was added to the well of black/clear tissue culture-treated, 384-well plates containing 2000 adherent HEK293 cells/well and incubated for 72 h at 37 °C in 5% CO₂. At 6 h, 5 µL of 600 µM resazurin, diluted in growth media, was added. Plates were further incubated for 6 h and measured for fluorescence at 530 nm excitation and 595 nm emission. The % inhibition was calculated using 0.4% DMSO (no inhibition) and 50 µM puromycin (100% inhibition) data. Puromycin was included as a reference compound to assess assay validity. IC₅₀ values were obtained by plotting % inhibition against log dose using GraphPad Prism v.6 (San Diego, CA, USA) nonlinear regression with a variable slope plot.

Synthesis of 3-(4-chlorophenyl)-*N*-phenethyl-[1,2,4]triazolo[4,3-*a*]pyrazin-8-amine (2) using modified Korsic et al. method [7]

5-Chloro-3-(4-chlorophenyl)-[1,2,4]triazolo[4,3-*a*]pyrazine (**1**, 106 mg, 0.4 mmol), phenethylamine (150 µL, 1.2 mmol, 3.0 equiv), and silica (0.5 g) were dissolved in anhydrous PhCH₃ (2 mL) and the reaction mixture was stirred at room temperature for 6 h then pre-adsorbed to silica (≈1 g) overnight. Purification was performed on a silica Isolute™ SPE cartridge using a 5% stepwise elution from 100% CH₂Cl₂ to 20% MeOH/80% CH₂Cl₂ with five fractions (10 × 5 mL) collected for each flush (50 mL in total). The 25 resulting fractions were all analysed by silica TLC (solvent system: 7.5% MeOH/92.5% CH₂Cl₂) and UV-active (254 nm) samples were further evaluated by ¹H NMR spectroscopy and LCMS to identify product of interest; only fractions containing

the desired product in high purity ($\geq 95\%$) were combined. Some fractions were not of desired purity ($\geq 95\%$) and were subjected to further reversed-phase HPLC separation using a 10% linear gradient from 50% MeOH/50% H₂O/0.1% TFA to 100% MeOH/0.1% TFA over 60 min at a flow rate of 9 mL/min and again analysed by ¹H NMR and LCMS. Pure fractions obtained from reversed-phase HPLC separation were then combined to obtain the desired product, 3-(4-chlorophenyl)-N-phenethyl-[1,2,4]triazolo[4,3-a]pyrazin-8-amine (**2**) as yellow needles (124 mg, 70%).

Modified synthesis of 3-(4-chlorophenyl)-N-phenethyl-[1,2,4]triazolo[4,3-a]pyrazin-8-amine (2**)**

5-Chloro-3-(4-chlorophenyl)-[1,2,4]triazolo[4,3-a]pyrazine (**1**, 106 mg, 0.4 mmol), was dissolved in phenethylamine (500 μ L, 1.6 mmol, 10 equiv) and the reaction mixture stirred at room temperature for 16 h then pre-adsorbed to silica (≈ 1 g) overnight. Purification was performed as described above. Pure fractions ($\geq 95\%$) obtained from reversed-phase HPLC separation were then combined to obtain the desired product, 3-(4-chlorophenyl)-N-phenethyl-[1,2,4]triazolo[4,3-a]pyrazin-8-amine (**2**) as yellow needles (115 mg, 82%).

General method for the synthesis of the aminated triazolopyrazine library (3–15**)**

5-Chloro-3-(4-chlorophenyl)-[1,2,4]triazolo[4,3-a]pyrazine (**1**, 53 mg, 0.20 mmol) was dissolved in excess liquid amine (500 μ L) and the mixture was stirred at room temperature for 16 h. Purification was performed as described above for **2**, and relevant fractions containing high purity product ($\geq 95\%$) were combined.

3-(4-Chlorophenyl)-*N*-phenethyl-[1,2,4]triazolo[4,3-*a*]pyrazin-8-amine (2). Yellow needles (115 mg, 82%), mp 224–226 °C. UV (MeOH) λ_{max} (log ϵ) 250 (4.09), 293 (3.83) nm. ^1H NMR (500 MHz, $(\text{CD}_3)_2\text{SO}$): δ_{H} 8.30 (1H, t, J = 5.8 Hz, H-16), 7.93 (2H, m, H-11, H-15), 7.76 (1H, d, J = 4.8 Hz, H-5), 7.69 (2H, m, H-12, H-14), 7.38 (1H, d, J = 4.8 Hz, H-6), 7.30 (2H, m, H-21, H-23), 7.28 (2H, m, H-20, H-24), 7.20 (1H, tt, J = 6.8, 2.0 Hz, H-22), 3.74 (2H, dt, J = 5.8, 7.3 Hz, H-17), 2.98 (2H, t, J = 7.3 Hz, H-18). ^{13}C NMR (125 MHz, $(\text{CD}_3)_2\text{SO}$) δ_{C} 147.9 (C-8), 146.8 (C-3), 139.7 (C-9), 139.5 (C-19), 135.0 (C-13), 130.3 (C-6), 129.8 (2C, C-11, C-15), 129.4 (2C, C-12, C-14), 128.7 (2C, C-20, C-24), 128.3 (2C, C-21, C-23), 126.1 (C-22), 125.1 (C-10), 106.0 (C-5), 41.6 (C-17), 34.5 (C-18). LRMS (ESI-SQ) m/z : 350 $[\text{M} + \text{H}]^+$, 372 $[\text{M} + \text{Na}]^+$. HRMS (ESI-qTOF) m/z : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{19}\text{H}_{16}^{35}\text{ClN}_5\text{Na}$ 372.0991; Found 372.0991.

3-(4-Chlorophenyl)-*N*-(4-fluorophenethyl)-[1,2,4]triazolo[4,3-*a*]pyrazin-8-amine (3). Yellow amorphous solid (51 mg, 69%). UV (MeOH) λ_{max} (log ϵ) 254 (3.57), 302 (3.56) nm. ^1H NMR (500 MHz, $(\text{CD}_3)_2\text{SO}$) δ_{H} 8.64 (1H, brt, J = 6.1 Hz, H-16), 7.92 (2H, m, H-11, H-15), 7.78 (1H, d, J = 4.9 Hz, H-5), 7.69 (2H, m, H-12, H-14), 7.36 (1H, d, J = 4.9 Hz, H-6), 7.31 (2H, m, H-20, H-24), 7.12 (2H, m, H-21, H-23), 3.74 (2H, dt, J = 6.1, 7.4 Hz, H-17), 2.97 (2H, t, J = 7.4 Hz, H-18). ^{13}C NMR (125 MHz, $(\text{CD}_3)_2\text{SO}$) δ_{C} 160.8 (d, $^1J_{\text{CF}}$ = 241.5 Hz, C-22), 147.6 (C-8), 147.1 (C-3), 139.7 (C-9), 135.5 (C-19), 135.1 (C-13), 130.5 (2C, d, $^3J_{\text{CF}}$ = 8.0 Hz, C-20, C-24), 129.9 (2C, C-11, C-15), 129.4 (2C, C-12, C-14), 128.9 (C-6), 125.0 (C-10), 115.0 (2C, d, $^2J_{\text{CF}}$ = 20.9 Hz, C-21, C-23), 106.4 (C-5), 41.9 (C-17), 33.4 (C-18). LRMS (ESI-SQ) m/z : 368 $[\text{M} + \text{H}]^+$, 390 $[\text{M} + \text{Na}]^+$, 757 $[2\text{M} + \text{Na}]^+$. HRMS (ESI-qTOF) m/z : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{19}\text{H}_{15}^{35}\text{ClFN}_5\text{Na}$ 390.0892; Found 390.0895.

***N*-Benzyl-3-(4-chlorophenyl)-[1,2,4]triazolo[4,3-*a*]pyrazin-8-amine (4).** Yellow amorphous solid (31 mg, 46%). UV (MeOH) λ_{max} (log ϵ) 251 (4.14), 295 (3.83) nm. ^1H NMR (500 MHz, $(\text{CD}_3)_2\text{SO}$) δ_{H} 9.12 (1H, brt, $J = 5.4$ Hz, H-16), 7.93 (2H, m, H-11, H-15), 7.79 (1H, d, $J = 4.9$ Hz, H-5), 7.70 (2H, m, H-12, H-14), 7.38 (2H, m, H-19, H-23), 7.32 (1H, d, $J = 4.9$ Hz, H-6), 7.30 (2H, m, H-20, H-22), 7.23 (1H, tt, $J = 1.3, 7.3$ Hz, H-21), 4.74 (2H, d, $J = 5.4$ Hz, H-17). ^{13}C NMR (125 MHz, $(\text{CD}_3)_2\text{SO}$) δ_{C} 147.6 (C-8), 147.2 (C-3), 139.8 (C-9), 139.1 (C-18), 135.1 (C-13), 129.9 (2C, C-11, C-15), 129.4 (2C, C-12, C-14), 128.9 (C-6), 128.3 (2C, C-20, C-22), 127.2 (2C, C-19, C-23), 126.8 (C-21), 125.0 (C-10), 106.7 (C-5), 43.4 (C-17). LRMS (ESI-SQ) m/z : 336 $[\text{M} + \text{H}]^+$, 358 $[\text{M} + \text{Na}]^+$. HRMS (ESI-qTOF) m/z : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{18}\text{H}_{14}^{35}\text{ClN}_5\text{Na}$ 358.0830; Found 358.0830.

3-(4-Chlorophenyl)-*N*-(4-fluorobenzyl)-[1,2,4]triazolo[4,3-*a*]pyrazin-8-amine (5). Yellow amorphous solid (15 mg, 21%). UV (MeOH) λ_{max} (log ϵ) 253 (4.41), 295 (4.10) nm. ^1H NMR (500 MHz, $(\text{CD}_3)_2\text{SO}$) δ_{H} 8.87 (1H, brt, $J = 6.1$ Hz, H-16), 7.92 (2H, m, H-11, H-15), 7.77 (1H, d, $J = 4.9$ Hz, H-5), 7.69 (2H, m, H-12, H-14), 7.42 (2H, m, H-19, H-23), 7.32 (1H, d, $J = 4.9$ Hz, H-6), 7.13 (2H, m, H-20, H-22), 4.69 (2H, d, $J = 6.1$ Hz, H-17). ^{13}C NMR (125 MHz, $(\text{CD}_3)_2\text{SO}$) δ_{C} 161.1 (d, $^1J_{\text{CF}} = 242.0$ Hz, C-21), 147.7 (C-8), 146.9 (C-3), 139.7 (C-9), 135.7 (d, $^4J_{\text{CF}} = 3.1$ Hz, C-18), 135.0 (C-13), 130.0 (C-6), 129.8 (2C, C-11, C-15), 129.4 (2C, C-12, C-14), 129.2 (2C, $^2J_{\text{CF}} = 8.1$ Hz, C-19, C-23), 125.1 (C-10), 114.8 (2C, $^2J_{\text{CF}} = 21.3$ Hz, C-20, C-22), 106.5 (C-5), 42.5 (C-17). LRMS (ESI-SQ) m/z : 354 $[\text{M} + \text{H}]^+$, 729 $[2\text{M} + \text{Na}]^+$. HRMS (ESI-qTOF) m/z : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{18}\text{H}_{13}^{35}\text{ClFN}_5\text{Na}$ 376.0736; Found 376.0737.

3-(4-Chlorophenyl)-*N*-propyl-[1,2,4]triazolo[4,3-*a*]pyrazin-8-amine (6). Yellow amorphous solid (41 mg, 72%). UV (MeOH) λ_{max} (log ϵ) 251 (3.78), 298 (3.50) nm. ^1H

NMR (500 MHz, (CD₃)₂SO): δ_{H} 8.26 (1H, t, J = 5.7 Hz, H-16), 7.92 (2H, m, H-11, H-15), 7.73 (1H, d, J = 4.9 Hz, H-5), 7.69 (2H, m, H-12, H-14), 7.34 (1H, d, J = 4.9 Hz, H-6), 3.46 (2H, m, H-17), 1.65 (2H, m, H-18), 0.92 (3H, t, J = 7.4 Hz, H-19). ¹³C NMR (125 MHz, (CD₃)₂SO) δ_{C} 148.0 (C-8), 146.8 (C-3), 139.7 (C-9), 134.9 (C-13), 130.3 (C-6), 129.8 (2C, C-11, C-15), 129.4 (2C, C-12, C-14), 125.2 (C-10), 105.8 (C-5), 41.8 (C-17), 21.8 (C-18), 11.4 (C-19). LRMS (ESI-SQ) m/z : 288 [M + H]⁺, 310 [M + Na]⁺. HRMS (ESI-qTOF) m/z : [M + H]⁺ Calcd for C₁₄H₁₅³⁵ClN₅ 288.1010; Found 288.1012; [M + Na]⁺ Calcd for C₁₄H₁₄³⁵ClN₅Na 310.0830; Found 310.0831.

3-(4-Chlorophenyl)-*N*-isopentyl-[1,2,4]triazolo[4,3-*a*]pyrazin-8-amine (7). White needles (56 mg, 89%), mp 193–195 °C. UV (MeOH) λ_{max} (log ϵ) 250 (4.33), 297 (4.05) nm. ¹H NMR (500 MHz, (CD₃)₂SO): δ_{H} 8.22 (1H, brt, J = 5.7 Hz, H-16), 7.93 (2H, m, H-11, H-15), 7.73 (1H, d, J = 4.8 Hz, H-5), 7.69 (2H, m, H-12, H-14), 7.35 (1H, d, J = 4.8 Hz, H-6), 3.52 (2H, m, H-17), 1.65 (1H, m, H-19), 1.54 (2H, m, H-18), 0.92 (6H, d, J = 6.6 Hz, H-20, H-21). ¹³C NMR (125 MHz, (CD₃)₂SO) δ_{C} 148.0 (C-8), 146.8 (C-3), 139.7 (C-9), 134.9 (C-13), 130.3 (C-6), 129.8 (2C, C-11, C-15), 129.3 (2C, C-12, C-14), 125.2 (C-10), 105.7 (C-5), 38.4 (C-17), 37.5 (C-18), 25.4 (C-19), 22.5 (2C, C-20, C-21). LRMS (ESI-SQ) m/z : 316 [M + H]⁺. HRMS (ESI-qTOF) m/z : [M + H]⁺ Calcd for C₁₆H₁₉³⁵ClN₅ 316.1329; Found 316.1323; [M + Na]⁺ Calcd for C₁₆H₁₈³⁵ClN₅Na 338.1143; Found 338.1142; [2M + H]⁺ Calcd for C₃₂H₃₇³⁵Cl₂N₁₀ 631.2580; Found 631.2572.

3-(4-Chlorophenyl)-*N*-cyclohexyl-[1,2,4]triazolo[4,3-*a*]pyrazin-8-amine (8). Yellow amorphous solid (18 mg, 27%). UV (MeOH) λ_{max} (log ϵ) 251 (4.32), 296 (4.02) nm. ¹H NMR (500 MHz, (CD₃)₂SO): δ_{H} 7.98 (1H, d, J = 8.2 Hz, H-16), 7.92 (2H, m, H-11, H-15), 7.72 (1H, d, J = 4.8 Hz, H-5), 7.68 (2H, m, H-12, H-14), 7.34 (1H, d, J = 4.8 Hz,

H-6), 4.07 (1H, m, H-17), 1.91 (2H, m, H-18, H-22), 1.76 (2H, m, H-19, H-21), 1.63 (1H, m, H-20), 1.46 (2H, m, H-18, H-22), 1.33 (2H, m, H-19, H-21), 1.16 (1H, m, H-20). ¹³C NMR (125 MHz, (CD₃)₂SO) δ_c 147.2 (C-8), 146.8 (C-3), 139.6 (C-9), 134.9 (C-13), 130.3 (C-6), 129.8 (2C, C-11, C-15), 129.3 (2C, C-12, C-14), 125.2 (C-10), 105.7 (C-5), 49.0 (C-17), 31.9 (2C, C-18, C-22), 25.3 (C-20), 25.0 (2C, C-19, C-21). LRMS (ESI-SQ) *m/z*: 328 [M + H]⁺. HRMS (ESI-qTOF) *m/z*: [M + H]⁺ Calcd for C₁₇H₁₉³⁵ClN₅ 328.1324; Found 328.1326.

3-(4-Chlorophenyl)-*N*-(2-methoxyethyl)-[1,2,4]triazolo[4,3-*a*]pyrazin-8-amine (9).

Yellow amorphous solid (34 mg, 57%). UV (MeOH) λ_{max} (log ε) 253 (4.37), 294 (4.08) nm. ¹H NMR (500 MHz, (CD₃)₂SO): δ_H 8.13 (1H, t, *J* = 5.8 Hz, H-16), 7.92 (2H, m, H-11, H-15), 7.76 (1H, d, *J* = 4.8 Hz, H-5), 7.69 (2H, m, H-12, H-14), 7.35 (1H, d, *J* = 4.8 Hz, H-6), 3.68 (2H, dt, *J* = 5.8, 6.2 Hz, H-17), 3.57 (2H, t, *J* = 6.2 Hz, H-18), 3.28 (3H, s, H-20). ¹³C NMR (125 MHz, (CD₃)₂SO) δ_c 148.0 (C-8), 146.8 (C-3), 139.7 (C-9), 135.0 (C-13), 130.2 (C-6), 129.8 (2C, C-11, C-15), 129.4 (2C, C-12, C-14), 125.1 (C-10), 106.2 (C-5), 69.8 (C-18), 57.9 (C-20), 39.5 (C-17). LRMS (ESI-SQ) *m/z*: Found 304 [M + H]⁺. HRMS (ESI-qTOF) *m/z*: [M + Na]⁺ Calcd for C₁₄H₁₄³⁵ClN₅NaO 326.0779; Found 326.0776; [2M + Na]⁺ Calcd for C₂₈H₂₈³⁵Cl₂N₁₀NaO₂ 629.1671; Found 629.1662.

***N*¹-(3-(4-Chlorophenyl)-[1,2,4]triazolo[4,3-*a*]pyrazin-8-yl)-*N*²,*N*²-dimethylethane-**

1,2-diamine (10). Pale yellow needles (43 mg, 68%), mp 153–155 °C. UV (MeOH) λ_{max} (log ε) 253 (4.36), 294 (4.08) nm. ¹H NMR (500 MHz, (CD₃)₂SO): δ_H 7.95 (1H, t, *J* = 5.5 Hz, H-16), 7.91 (2H, m, H-11, H-15), 7.74 (1H, d, *J* = 4.8 Hz, H-5), 7.67 (2H, m, H-12, H-14), 7.34 (1H, d, *J* = 4.8 Hz, H-6), 3.60 (2H, dt, *J* = 5.5, 6.6 Hz, H-17), 2.55 (2H, t, *J* = 6.6 Hz, H-18), 2.22 (6H, s, H-20, H-21). ¹³C NMR (125 MHz, (CD₃)₂SO) δ_c

148.0 (C-8), 146.8 (C-3), 139.7 (C-9), 135.0 (C-13), 130.3 (C-6), 129.8 (2C, C-11, C-15), 129.4 (2C, C-12, C-14), 125.1 (C-10), 106.0 (C-5), 57.4 (C-18), 45.1 (2C, C-20, C-21), 37.9 (C-17). LRMS (ESI-SQ) m/z : 317 $[M + H]^+$. HRMS (ESI-qTOF) m/z : $[M + H]^+$ Calcd for $C_{15}H_{18}^{35}ClN_6$ 317.1276; Found 317.1279.

N^1 -(3-(4-Chlorophenyl)-[1,2,4]triazolo[4,3-a]pyrazin-8-yl)- N^2,N^2 -diethylethane-1,2-diamine (11). Pale yellow amorphous solid (19 mg, 27%). UV (MeOH) λ_{max} (log ϵ) 253 (4.38), 292 (4.10) nm. 1H NMR (500 MHz, $(CD_3)_2SO$) δ_H 7.94 (1H, t, J = 5.8 Hz, H-16), 7.92 (2H, m, H-11, H-15), 7.75 (1H, d, J = 4.8 Hz, H-5), 7.68 (2H, m, H-12, H-14), 7.35 (1H, d, J = 4.8 Hz, H-6), 3.57 (2H, dt, J = 5.8, 7.1 Hz, H-17), 2.69 (2H, t, J = 7.1 Hz, H-18), 2.55 (4H, q, J = 7.1 Hz, H-20, H-22), 0.98 (6H, t, J = 7.1 Hz, H-21, H-23). ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ_C 148.0 (C-8), 146.8 (C-3), 139.7 (C-9), 135.0 (C-13), 130.3 (C-6), 129.8 (2C, C-11, C-15), 129.4 (2C, C-12, C-14), 125.1 (C-10), 106.0 (C-5), 50.8 (C-18), 46.6 (2C, C-10, C-22), 38.0 (C-17), 11.9 (2C, C-21, C-23). LRMS (ESI-SQ) m/z : 345 $[M + H]^+$. HRMS (ESI-qTOF) m/z : $[M + H]^+$ Calcd for $C_{17}H_{22}^{35}ClN_6$ 345.1589; Found 345.1599; $[M + Na]^+$ Calcd for $C_{17}H_{21}^{35}ClN_6Na$ 367.1408; Found 367.1409.

N^1 -(3-(4-Chlorophenyl)-[1,2,4]triazolo[4,3-a]pyrazin-8-yl)- N^3,N^3 -dimethylpropane-1,3-diamine (12). Yellow amorphous solid (38 mg, 57%). UV (MeOH) λ_{max} (log ϵ) 253 (4.02), 295 (3.75) nm. 1H NMR (500 MHz $(CD_3)_2SO$): δ_H 8.34 (1H, brt, J = 5.5 Hz, H-16), 7.92 (2H, m, H-11, H-15), 7.75 (1H, d, J = 4.8 Hz, H-5), 7.69 (2H, m, H-12, H-14), 7.35 (1H, d, J = 4.8 Hz, H-6), 3.54 (2H, m, H-17), 2.49 (2H, t, J = 7.1 Hz, H-19), 2.29 (6H, s, H-21, H-22), 1.83 (2H, m, H-18). ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ_C 148.0 (C-8), 146.8 (C-3), 139.7 (C-9), 135.0 (C-13), 130.3 (C-6), 129.8 (2C, C-11, C-15), 129.4 (2C, C-12, C-14), 125.2 (C-10), 105.9 (C-5), 56.5 (C-19), 44.5

(2C, C-21, C-22), 38.4 (C-17), 25.7 (C-18). LRMS (ESI-SQ) m/z : 331 $[M + H]^+$. HRMS (ESI-qTOF) m/z : $[M + H]^+$ Calcd for $C_{16}H_{20}^{35}ClN_6$ 331.1432; Found 331.1441.

***N*¹-(3-(4-Chlorophenyl)-[1,2,4]triazolo[4,3-*a*]pyrazin-8-yl)-*N*³,*N*³-diethylpropane-1,3-diamine (13).** Yellow amorphous solid (62 mg, 87%). UV (MeOH) $\lambda_{\max}$ (log ϵ) 252 (4.50), 292 (4.24) nm. ¹H NMR (500 MHz, (CD₃)₂SO): δ_H 8.44 (1H, t, J = 5.3 Hz, H-16), 7.91 (2H, m, H-11, H-15), 7.73 (1H, d, J = 4.8 Hz, H-5), 7.66 (2H, m, H-12, H-14), 7.33 (1H, d, J = 4.8 Hz, H-6), 3.55 (2H, m, H-17), 2.65 (2H, t, J = 8.0 Hz, H-19), 2.62 (4H, q, J = 7.2 Hz, H-21, H-23), 1.84 (2H, m, H-18), 1.03 (6H, t, J = 7.2 Hz, H-22, H-24). ¹³C NMR (125 MHz, (CD₃)₂SO) δ_C 148.0 (C-8), 146.7 (C-3), 139.7 (C-9), 134.9 (C-13), 130.3 (C-6), 129.7 (2C, C-11, C-15), 129.3 (2C, C-12, C-14), 125.1 (C-10), 105.9 (C-5), 50.1 (C-19), 46.2 (2C, C-21, C-23), 38.9 (C-17), 24.8 (C-18), 10.7 (2C, C-22, C-24). LRMS (ESI-SQ) m/z : 359 $[M + H]^+$. HRMS (ESI-qTOF) m/z : $[M + Na]^+$ Calcd for $C_{18}H_{23}^{35}ClN_6Na$ 381.1565; Found 381.1564.

3-(4-Chlorophenyl)-*N*-(2-(piperazin-1-yl)ethyl)-[1,2,4]triazolo[4,3-*a*]pyrazin-8-amine (14). White amorphous solid (13 mg, 18%). UV (MeOH) $\lambda_{\max}$ (log ϵ) 256 (4.04), 304 (3.86) nm. ¹H NMR (500 MHz, (CD₃)₂SO): δ_H 7.88 (2H, m, H-11, H-15), 7.81 (1H, d, J = 4.7 Hz, H-5), 7.69 (2H, m, H-12, H-14), 7.40 (1H, d, J = 4.7 Hz, H-6), 4.26 (4H, m, H-21, H-23), 2.73 (2H, t, J = 6.4 Hz, H-17), 2.54 (4H, m, H-20, H-24), 2.40 (2H, t, J = 6.4 Hz, H-18). ¹³C NMR (125 MHz, (CD₃)₂SO) δ_C 147.7 (C-8), 146.3 (C-3), 140.6 (C-9), 135.2 (C-13), 130.1 (2C, C-11, C-15), 129.6 (C-6), 129.4 (2C, C-12, C-14), 125.0 (C-10), 107.0 (C-5), 59.6 (C-18), 52.9 (2C, C-20, C-24), 45.8 (2C, C-21, C-23), 38.0 (C-17). LRMS (ESI-SQ) m/z : 358 $[M + H]^+$. HRMS (ESI-qTOF) m/z : $[M + H]^+$ Calcd for $C_{17}H_{21}^{35}ClN_7$ 358.1541; Found 358.1546; $[M + Na]^+$ Calcd for $C_{17}H_{20}^{35}ClN_7Na$ 380.1361; Found 380.1359.

***tert*-Butyl(4-((3-(4-chlorophenyl)-[1,2,4]triazolo[4,3-*a*]pyrazin-8**

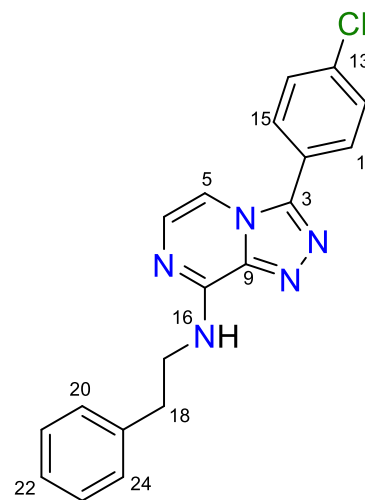
yl)amino)butyl)carbamate (15). Yellow needles (47 mg, 57%), mp 154–156 °C. UV (MeOH) λ_{max} (log ϵ) 250 (4.71), 295 (4.33) nm. ^1H NMR (500 MHz, $(\text{CD}_3)_2\text{SO}$): δ_{H} 8.24 (1H, brt, $J = 5.7$ Hz, H-16), 7.90 (2H, m, H-11, H-15), 7.71 (1H, d, $J = 4.8$ Hz, H-5), 7.66 (2H, m, H-12, H-14), 7.33 (1H, d, $J = 4.8$ Hz, H-6), 6.79 (1H, t, $J = 5.6$ Hz, H-21), 3.48 (2H, m, H-17), 2.94 (2H, m, H-20), 1.61 (2H, m, H-18), 1.44 (2H, m, H-19), 1.35 (9H, s, H-25, H-26, H-27). ^{13}C NMR (125 MHz, $(\text{CD}_3)_2\text{SO}$) δ_{C} 155.7 (C-22), 148.1 (C-8), 146.8 (C-3), 139.8 (C-9), 135.0 (C-13), 130.4 (C-6), 129.8 (2C, C-11, C-15), 129.4 (2C, C-12, C-14), 125.2 (C-10), 105.8 (C-5), 77.4 (C-24), 39.8 (C-17), 39.4 (C-20), 28.3 (3C, C-25, C-26, C-27), 27.2 (C-19), 26.0 (C-18). LRMS (ESI-SQ) m/z : 417 $[\text{M} + \text{H}]^+$. HRMS (ESI-qTOF) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{20}\text{H}_{26}^{35}\text{ClN}_6\text{O}_2$ 417.1800; Found 417.1798; $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{20}\text{H}_{25}^{35}\text{ClN}_6\text{NaO}_2$ 439.1620; Found 439.1616.

S2: Supporting information references

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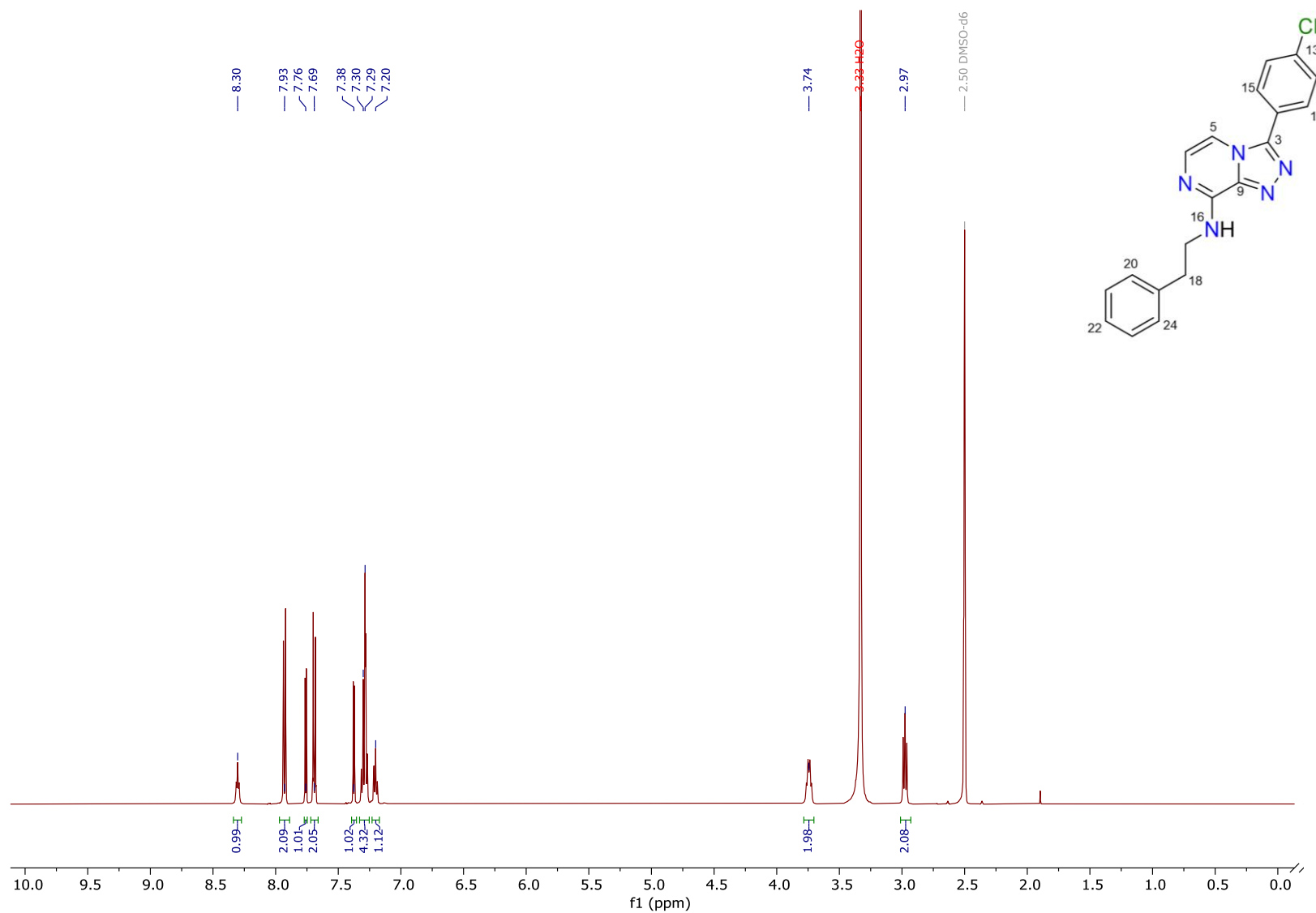
S3: NMR data table for compound 2^a

Position	δ_{H} , mult. (J in Hz), int.	δ_{C} , mult.	COSY	HMBC	ROESY
3		146.8, C			
5	7.76, d (4.8), 1H	106.0, CH	6	3, 6, 9	6, 11, 15
6	7.38, d (4.8), 1H	130.3, CH	5	5, 8	5
8		147.9, C			
9		139.7, C			
10		125.1, C			
11	7.93, m, 1H	129.8, CH	12	3, 13, 15	5, 12
12	7.69, m, 1H	129.4, CH	11	10, 14	11
13		135.0, C			
14	7.69, m, 1H	129.4, CH	15	10, 12	15
15	7.93, m, 1H	129.8, CH	14	3, 11, 13	5, 14
16	8.30, t (5.8), 1H		17	8, 9, 17	17, 18
17	3.74, dt (5.8, 7.3), 2H	41.6, CH ₂	16, 18	8, 18, 19	16, 18
18	2.98, t (7.3), 2H	34.5, CH ₂	17	17, 19, 20, 24	16, 17, 20, 24
19		139.5, C			
20	7.28, m, 1H	128.7, CH	21, 22	18, 21, 22	18, 21
21	7.30, m, 1H	128.3, CH	20, 22	19, 22, 23	20, 22
22	7.20, tt (6.8, 2.0), 1H	126.1, CH	20, 21, 23, 24	20, 21, 23, 24	21, 23
23	7.30, m, 1H	128.3, CH	22, 24	19, 21, 22	22, 24
24	7.28, m, 1H	128.7, CH	22, 23	18, 20, 22	18, 23

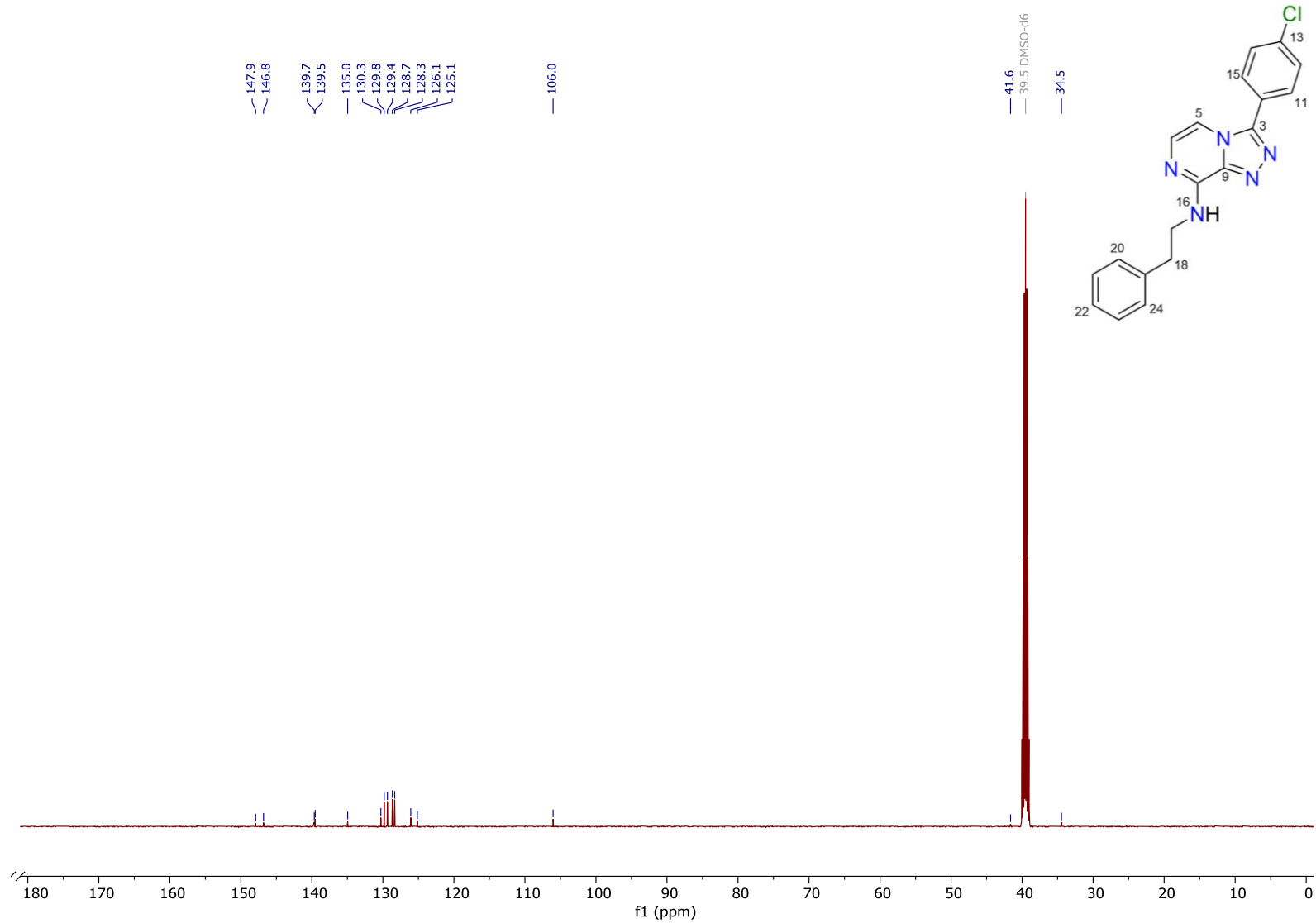


^a Recorded in (CD₃)₂SO 500 MHz (¹H NMR) and 125 MHz (¹³C NMR) at 25 °C.

S4: ^1H NMR spectrum of compound **2** in $(\text{CD}_3)_2\text{SO}$

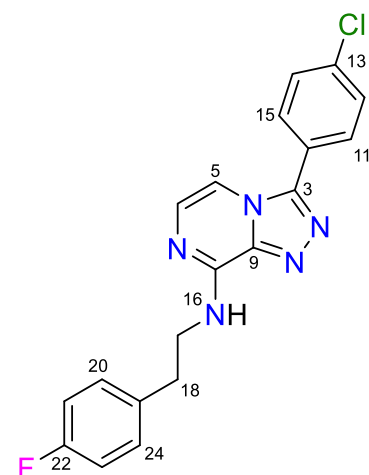


S5: ^{13}C NMR spectrum of compound **2** in $(\text{CD}_3)_2\text{SO}$



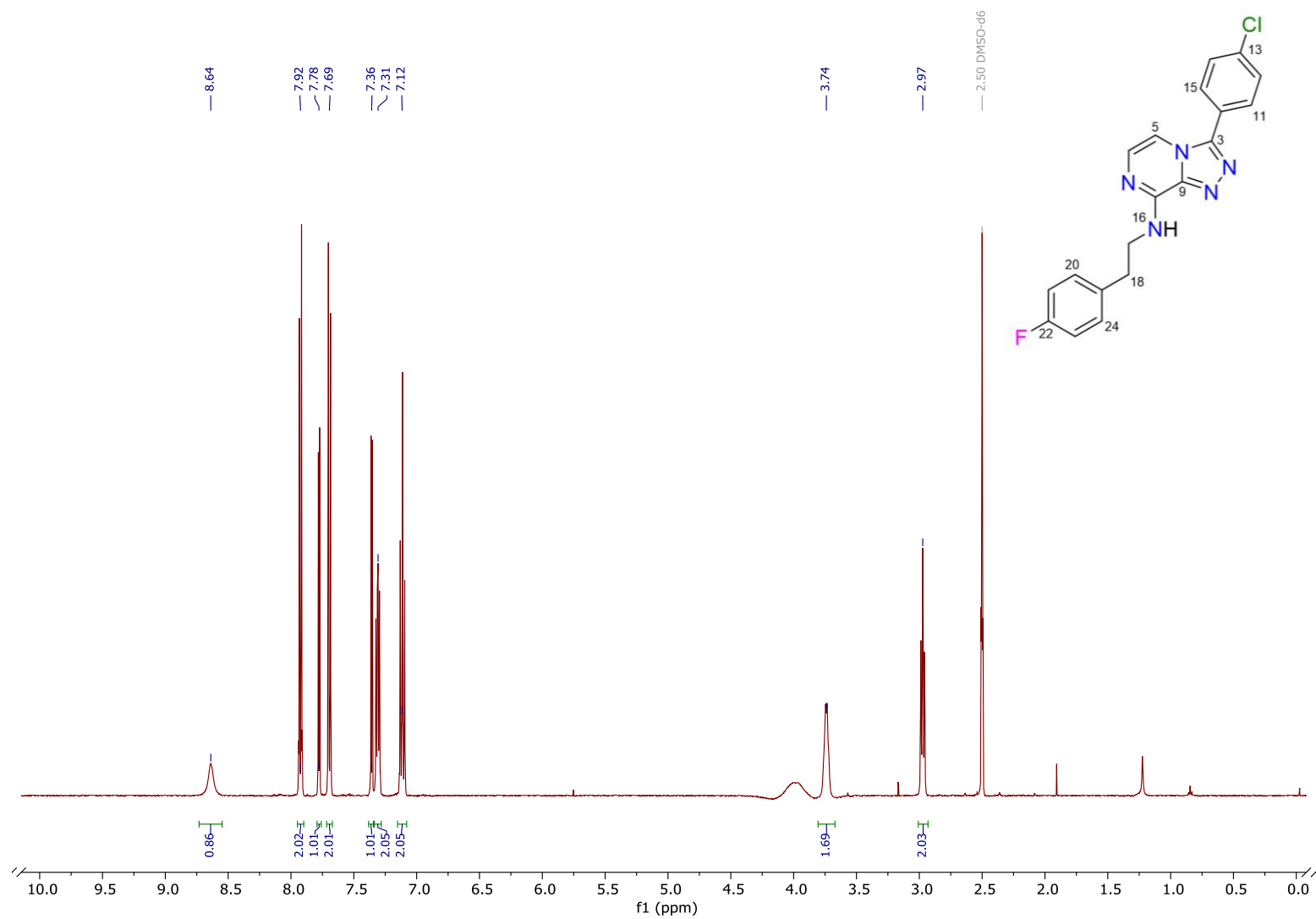
S6: NMR data table for compound **3^a**

Position	δ_{H} , mult. (J in Hz), int.	δ_{C} , mult. (J in Hz)	COSY	HMBC	ROESY
3		147.1, C			
5	7.78, d (4.9), 1H	106.4, CH	6	3, 6, 9	6, 11, 15
6	7.36, d (4.9), 1H	128.9, CH	5	5, 8	5
8		147.6, C			
9		139.7, C			
10		125.0, C			
11	7.92, m, 1H	129.9, CH	12	3, 13, 15	5, 12
12	7.69, m, 1H	129.4, CH	11	10, 14	5, 11
13		135.1, C			
14	7.69, m, 1H	129.4, CH	15	10, 12	5, 15
15	7.92, m, 1H	129.9, CH	14	3, 11, 13	5, 14
16	8.64, brt (6.1), 1H		17		
17	3.74, dt (6.1, 7.4), 2H	41.9, CH ₂	16, 18		18, 20, 24
18	2.97, t (7.4), 2H	33.4, CH ₂	17	17, 19, 20, 24	17, 20, 24
19		135.5, C			
20	7.31, m, 1H	130.5, d (8.0), CH	21	18, 22, 24	17, 18, 21
21	7.12, m, 1H	115.0, d (20.9), CH	20	19, 23	20
22		160.8, d (241.5), C			
23	7.12, m, 1H	115.0, d (20.9), CH	24	19, 21	24
24	7.31, m, 1H	130.5, d (8.0), CH	23	18, 20, 22,	17, 18, 23

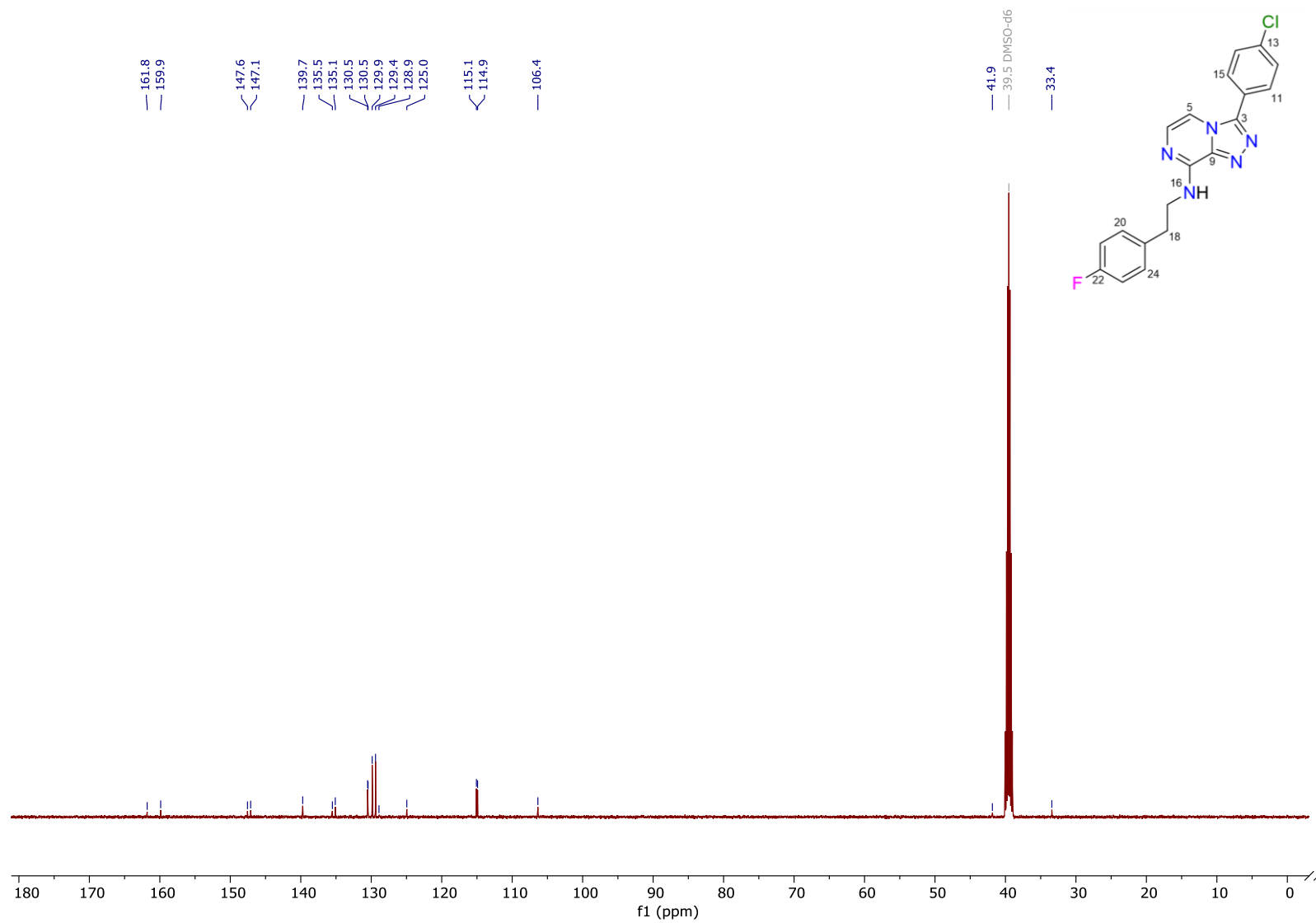


^a Recorded in (CD₃)₂SO 500 MHz (¹H NMR) and 125 MHz (¹³C NMR) at 25 °C.

S7: ^1H NMR spectrum of compound **3** in $(\text{CD}_3)_2\text{SO}$

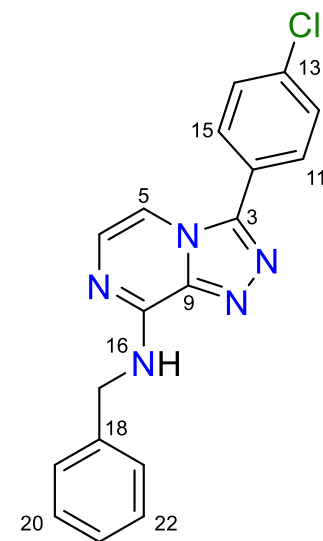


S8: ^{13}C NMR spectrum of compound **3** in $(\text{CD}_3)_2\text{SO}$



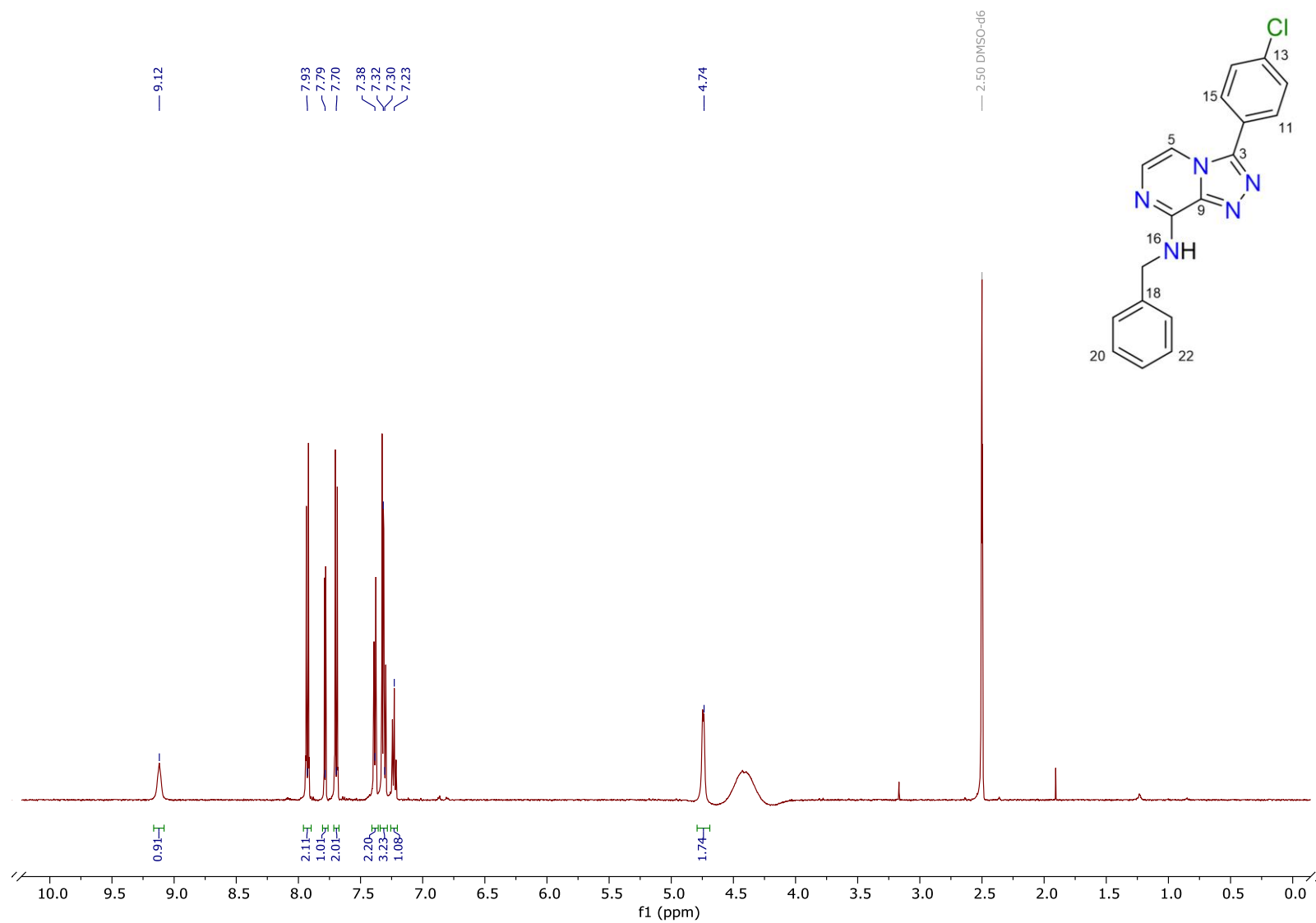
S9: NMR data table for compound **4^a**

Position	δ_{H} , mult. (J in Hz), int.	δ_{C} , mult. (J in Hz)	COSY	HMBC	ROESY
3		147.2, C			
5	7.79, d (4.9), 1H	106.7, CH	6	3, 6, 9	6, 11, 15
6	7.32, d (4.9), 1H	128.9, CH	5	5, 8	5
8		147.6, C			
9		139.8, C			
10		125.0, C			
11	7.93, m, 1H	129.9, CH	12	3, 13, 15	5, 12, 14
12	7.70, m, 1H	129.4, CH	11	10, 14	11
13		135.1, C			
14	7.70, m, 1H	129.4, CH	15	10, 12	15
15	7.93, m, 1H	129.9, CH	14	3, 11, 13	5, 12, 14
16	9.12, brt (5.4), 1H		17		17
17	4.74, d (5.4), 2H	43.4, CH ₂	16		16, 19, 23
18		139.1, C			
19	7.38, m, 1H	127.2, CH	20	17, 21, 23	17, 20
20	7.30, m, 1H	128.3, CH	19, 21	18, 22	
21	7.23, tt (1.3, 7.3), 1H	126.8, CH	19, 20, 22, 23	19, 23	20, 22
22	7.30, m, 1H	128.3, CH	21, 23	18, 20	
23	7.38, m, 1H	127.2, CH	22	17, 19, 21	17, 22

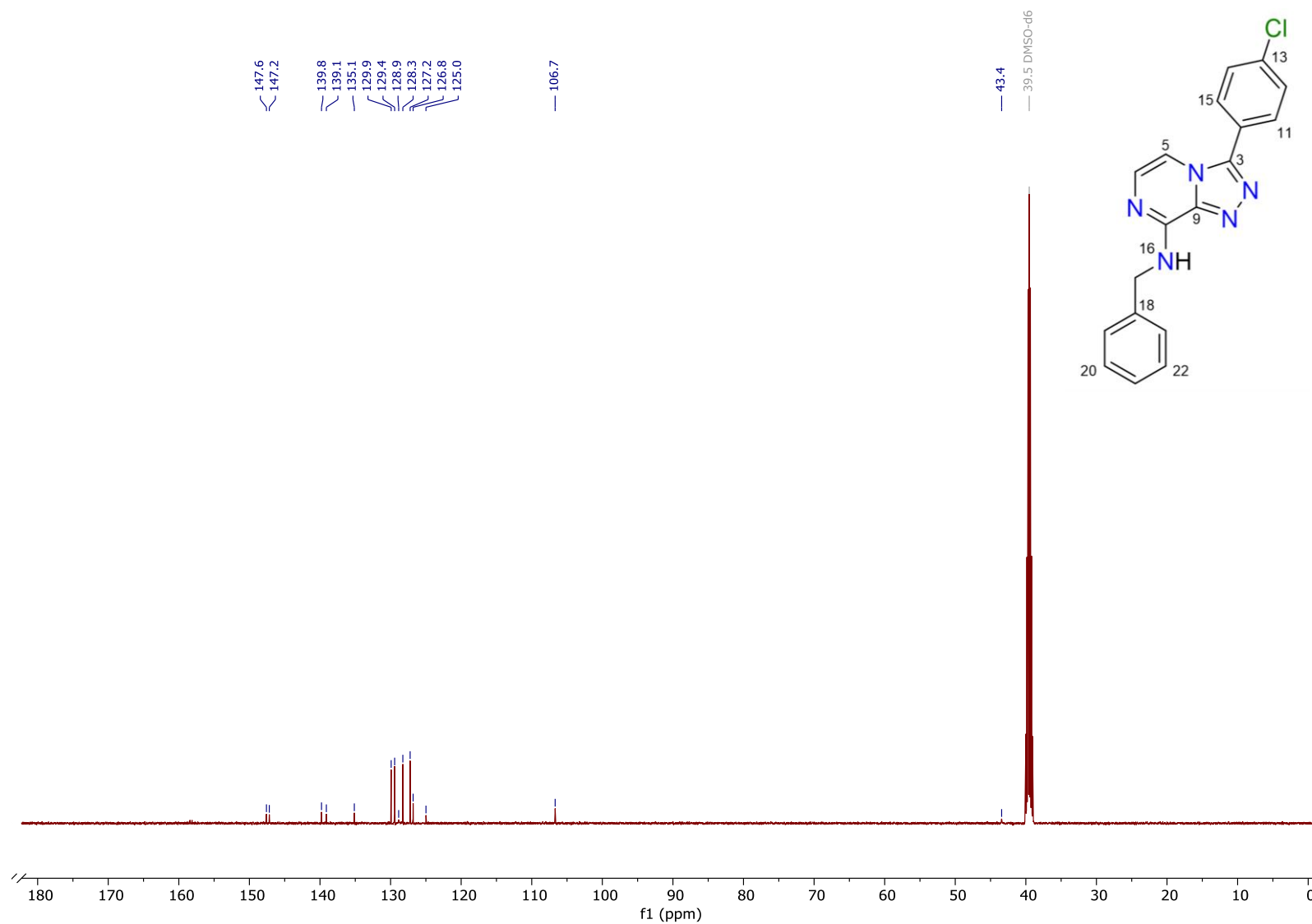


^a Recorded in (CD₃)₂SO 500 MHz (¹H NMR) and 125 MHz (¹³C NMR) at 25 °C.

S10: ^1H NMR spectrum of compound **4** in $(\text{CD}_3)_2\text{SO}$



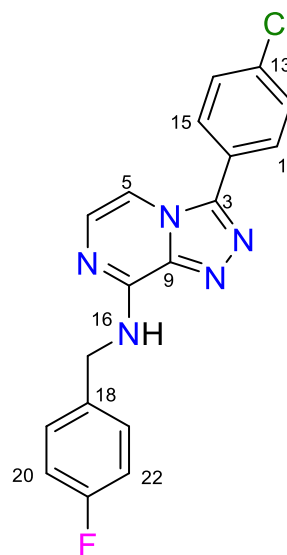
S11: ^{13}C NMR spectrum of compound **4** in $(\text{CD}_3)_2\text{SO}$



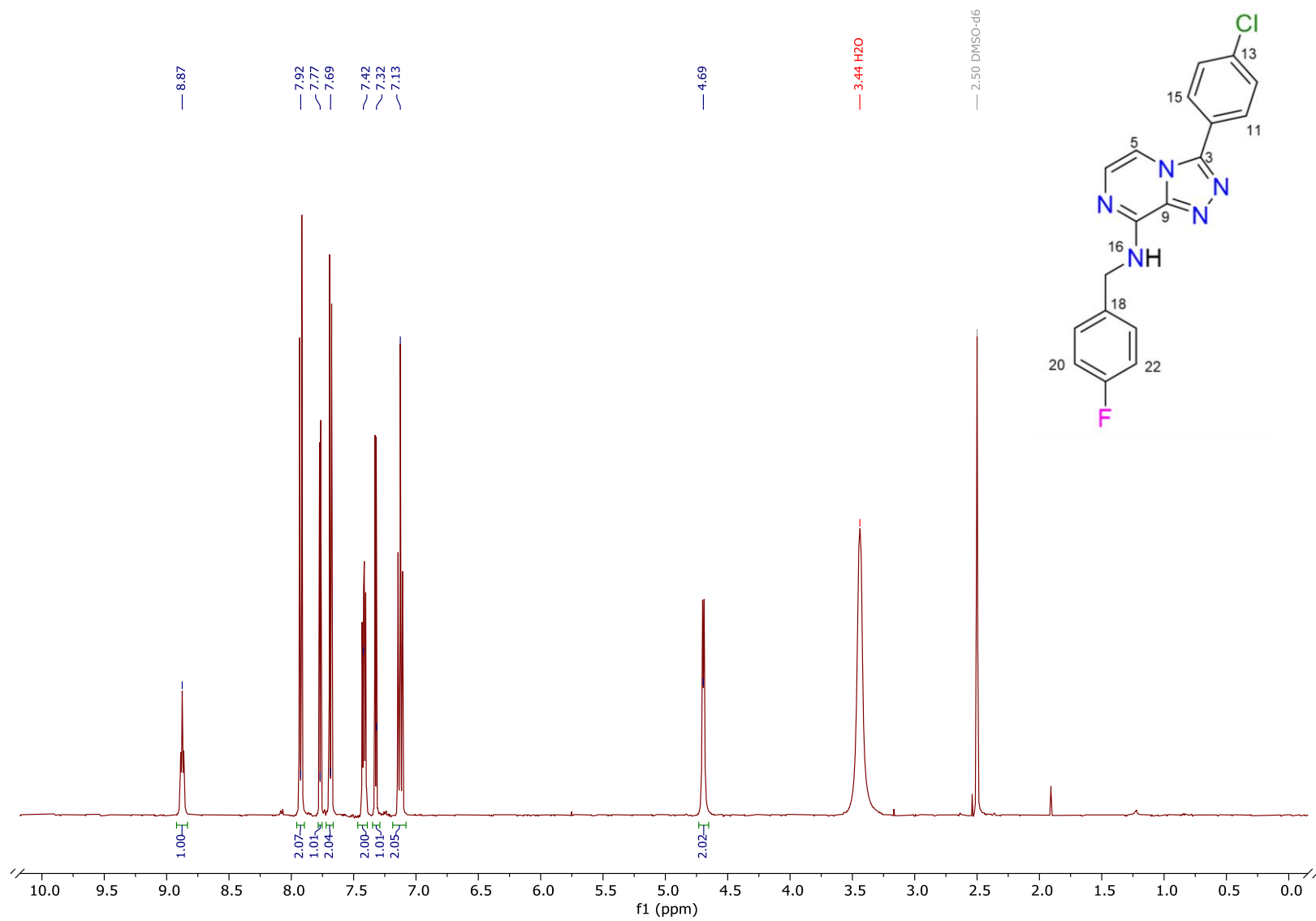
S12: NMR data table for compound **5^a**

Position	δ_{H} , mult. (J in Hz), int.	δ_{C} , mult. (J in Hz)	COSY	HMBC	ROESY
3		146.9, C			
5	7.77, d (4.9), 1H	106.5, CH	6	3, 6, 9	6, 11, 15
6	7.32, d (4.9), 1H	130.0, CH	5	5, 8	5
8		147.7, C			
9		139.7, C			
10		125.1, C			
11	7.92, m, 1H	129.8, CH	12	3, 13, 15	12
12	7.69, m, 1H	129.4, CH	11	10, 14	11
13		135.0, C			
14	7.69, m, 1H	129.4, CH	15	10, 12	15
15	7.92, m, 1H	129.8, CH	14	3, 11, 13	14
16	8.87, brt (6.1), 1H		17		17
17	4.69, d (6.1), 2H	42.5, CH ₂	16	8, 18, 19, 23	16, 19
18		135.7, d (3.1)			
19	7.42, m, 1H	129.2, d (8.1)	20	17, 21, 23	17, 20
20	7.13, m, 1H	114.8, d (21.3)	19	18, 22	19
21		161.1, d (242.0)			
22	7.13, m, 1H	114.8, d (21.3)	23	18, 20	23
23	7.42, m, 1H	129.2, d (8.1)	22	17, 19, 21	17, 22

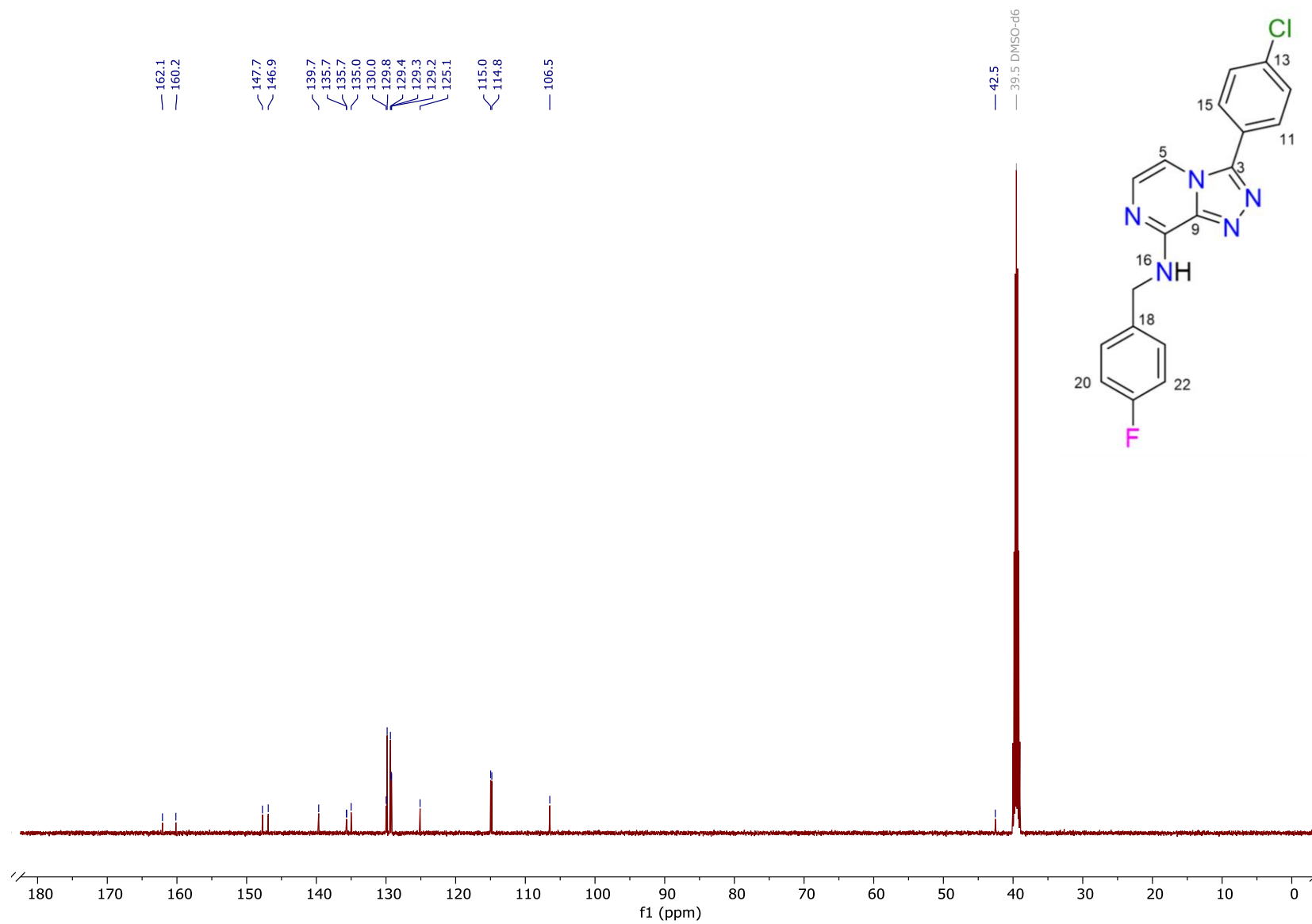
^a Recorded in (CD₃)₂SO 500 MHz (¹H NMR) and 125 MHz (¹³C NMR) at 25 °C.



S13: ^1H NMR spectrum of compound **5** in $(\text{CD}_3)_2\text{SO}$

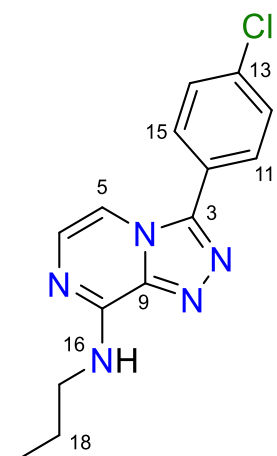


S14: ^{13}C NMR spectrum of compound **5** in $(\text{CD}_3)_2\text{SO}$



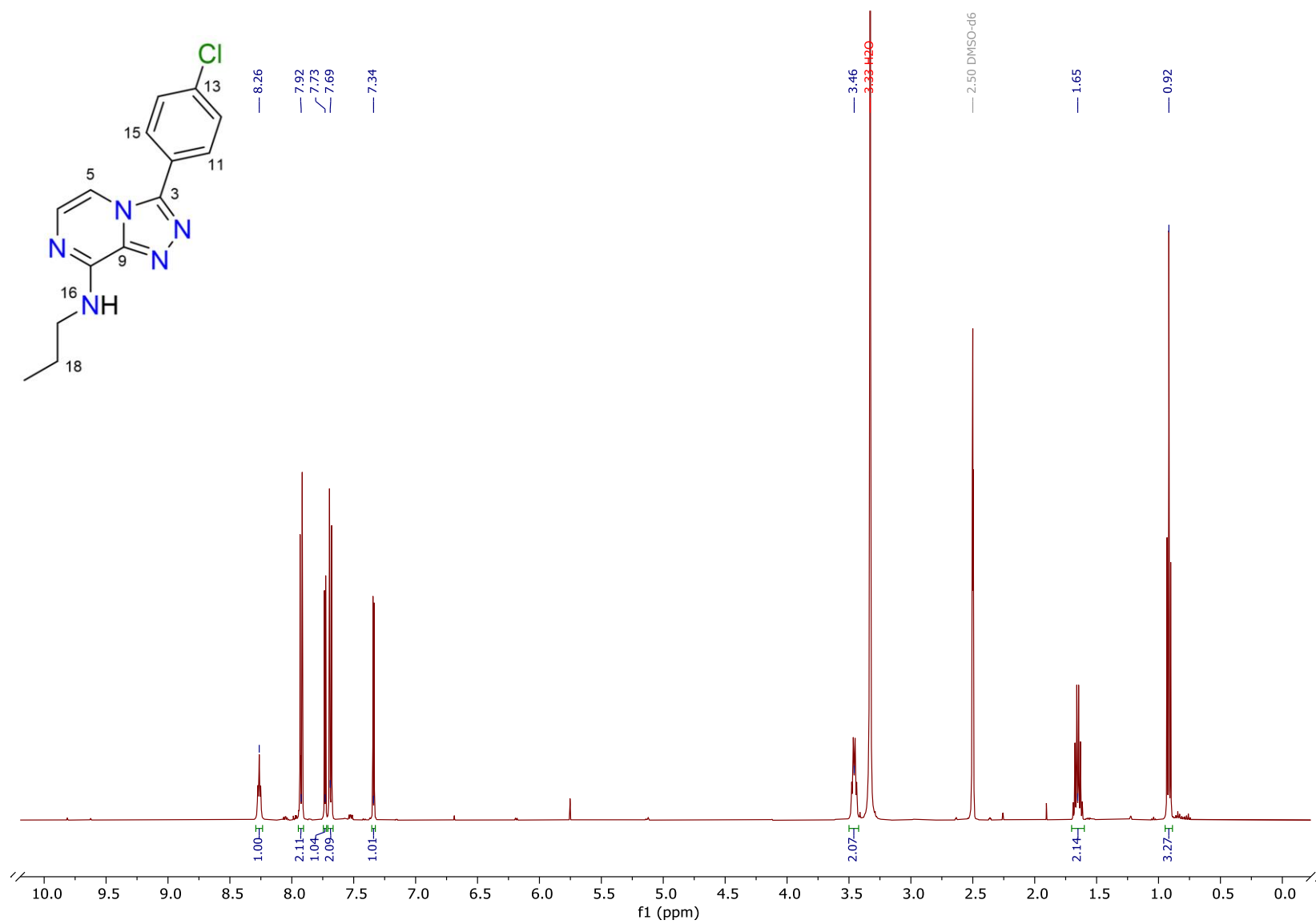
S15: NMR data table for compound **6^a**

Position	δ_{H} , mult. (J in Hz), int.	δ_{C} , mult.	COSY	HMBC	ROESY
3		146.8, C			
5	7.73, d (4.9), 1H	105.8, CH	6	3, 6, 9	6, 11, 15
6	7.34, d (4.9), 1H	130.3, CH	5	5, 8	5
8		148.0, C			
9		139.7, C			
10		125.2, C			
11	7.92, m, 1H	129.8, CH	12	3, 13, 15	5, 12
12	7.69, m, 1H	129.4, CH	11	10, 14	11
13		134.9, C			
14	7.69, m, 1H	129.4, CH	15	10, 12	15
15	7.92, m, 1H	129.8, CH	14	3, 11, 13	5, 14
16	8.26, t (5.7), 1H		17	8, 9	17
17	3.46, m, 2H	41.8, CH ₂	16, 18	8, 18, 19	16, 18, 19
18	1.65, m, 2H	21.8, CH ₂	17, 19	17, 19	17, 19
19	0.92, t (7.4), 3H	11.4, CH ₃	18	17, 18	18

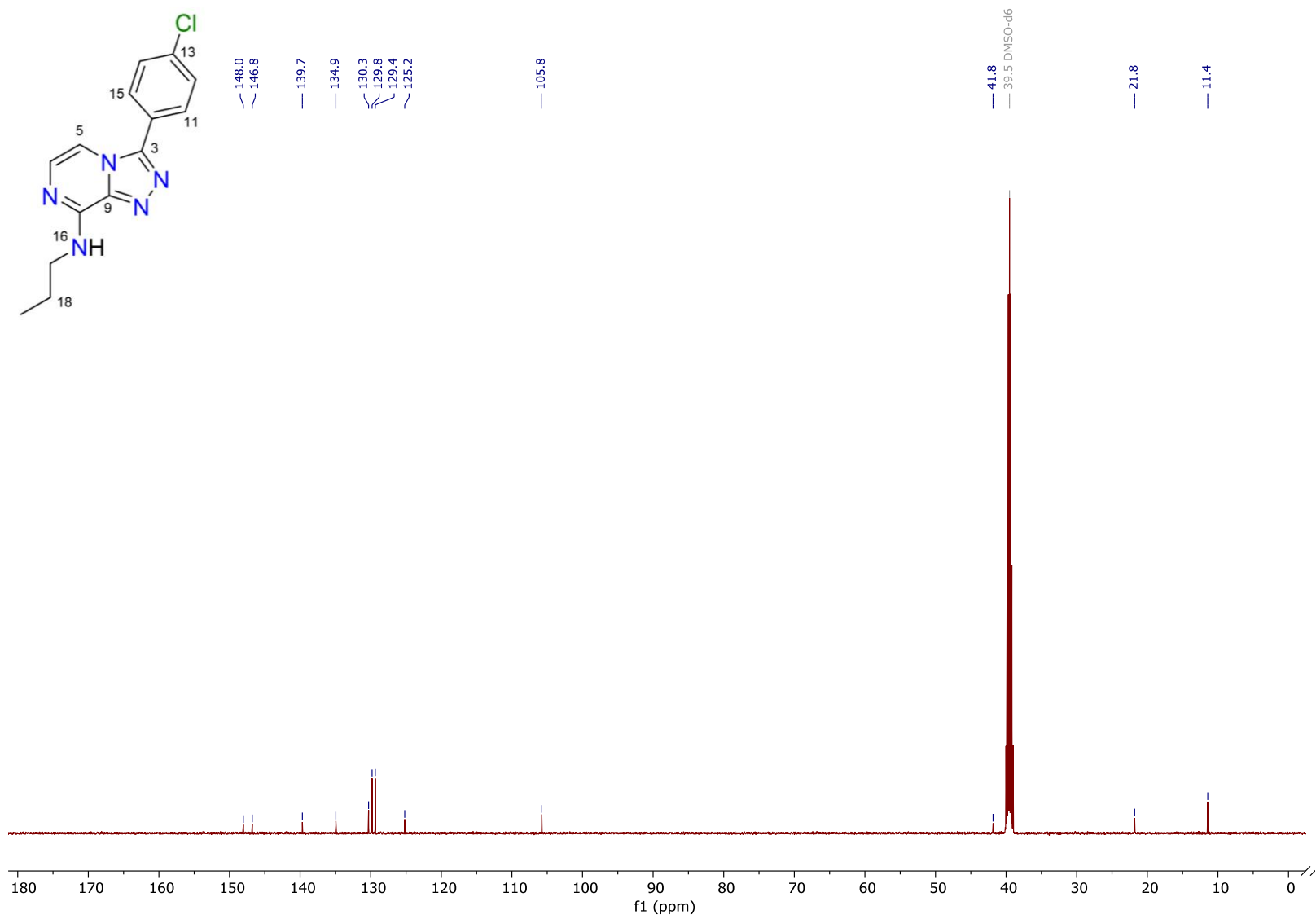


^a Recorded in (CD₃)₂SO 500 MHz (¹H NMR) and 125 MHz (¹³C NMR) at 25 °C.

S16: ^1H NMR spectrum of compound **6** in $(\text{CD}_3)_2\text{SO}$

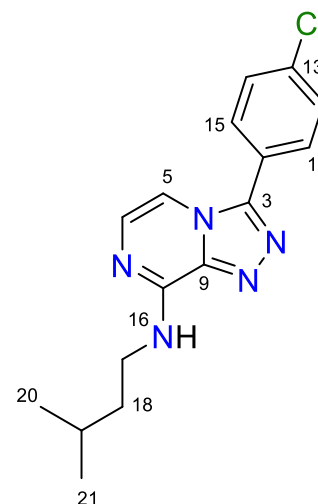


S17: ^{13}C NMR spectrum of compound **6** in $(\text{CD}_3)_2\text{SO}$



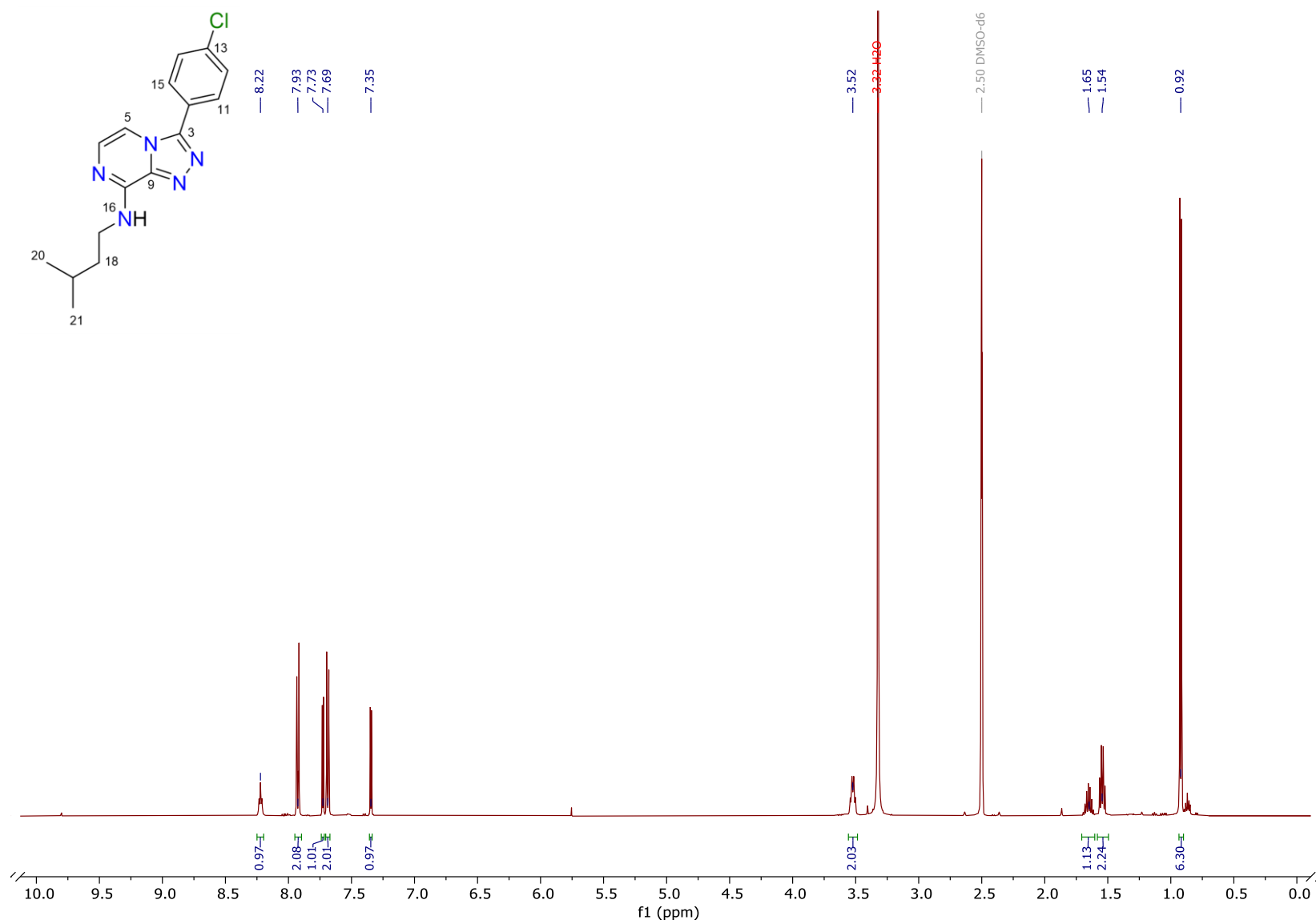
S18: NMR data table for compound **7^a**

Position	δ_{H} , mult. (J in Hz), int.	δ_{C} , mult.	COSY	HMBC	ROESY
3		146.8, C			
5	7.73, d (4.8), 1H	105.7, CH	6	6, 9	6
6	7.35, d (4.8), 1H	130.3, CH	5	5, 8	5
8		148.0, C			
9		139.7, C			
10		125.2, C			
11	7.93, m, 1H	129.8, CH	12	3, 13, 15	12
12	7.69, m, 1H	129.3, CH	11	10, 14	11
13		134.9, C			
14	7.69, m, 1H	129.3, CH	15	10, 12	15
15	7.93, m, 1H	129.8, CH	14	3, 11, 13	14
16	8.22, brt (5.7), 1H		17		17
17	3.52, m, 2H	38.4, CH ₂	16, 18		16, 18, 20, 21
18	1.54, m, 2H	37.5, CH ₂	17, 19	20, 21	17, 20, 21
19	1.65, m, 1H	25.4, CH	18, 20, 21	20, 21	17 ^w , 20, 21
20	0.92, d (6.6), 3H	22.5, CH ₃	19	18, 19, 21	17, 18, 19
21	0.92, d (6.6), 3H	22.5, CH ₃	19	18, 19, 20	17, 18, 19

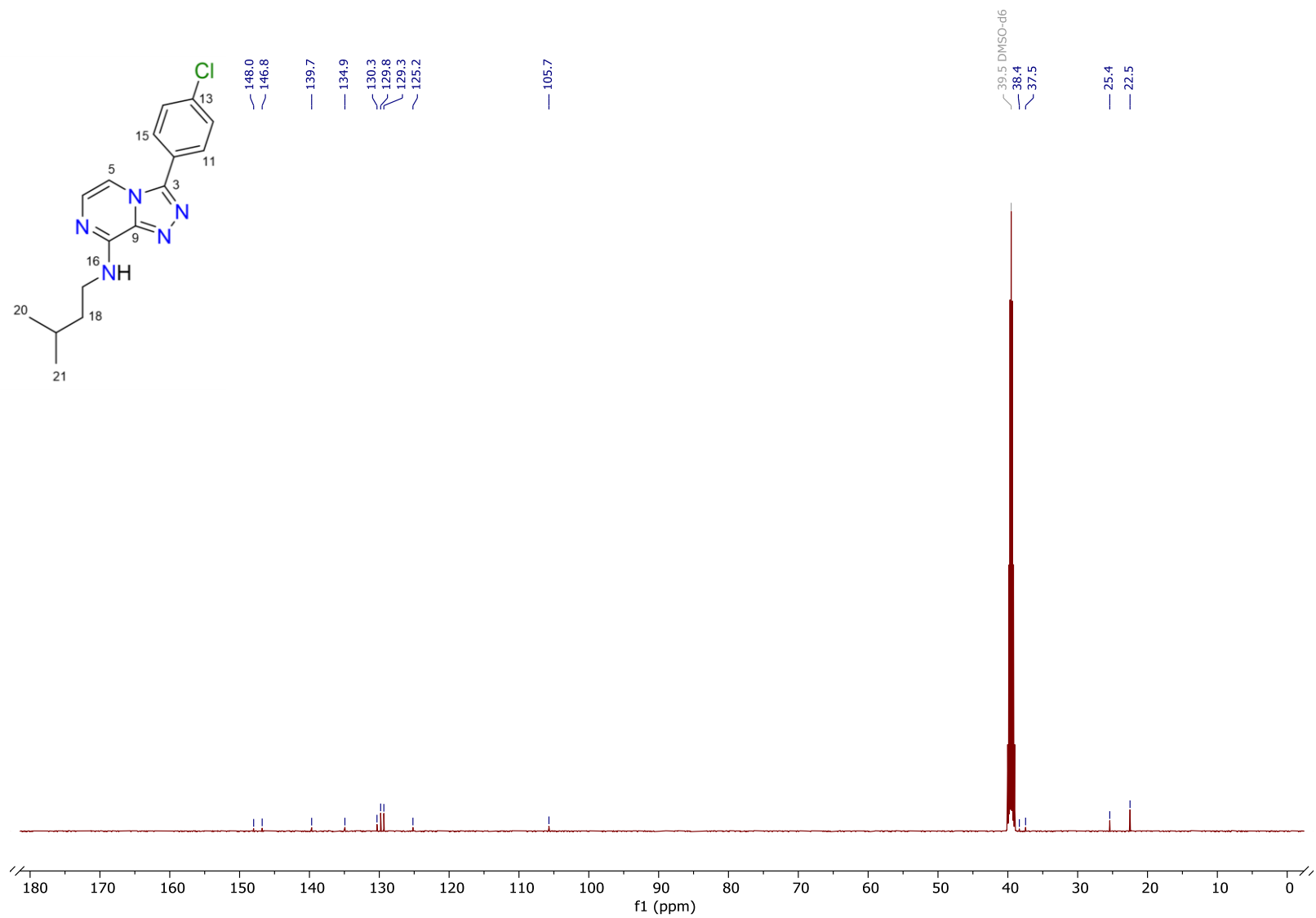


^a Recorded in (CD₃)₂SO 500 MHz (¹H NMR) and 125 MHz (¹³C NMR) at 25 °C; ^wWeak.

S19: ^1H NMR spectrum of compound **7** in $(\text{CD}_3)_2\text{SO}$



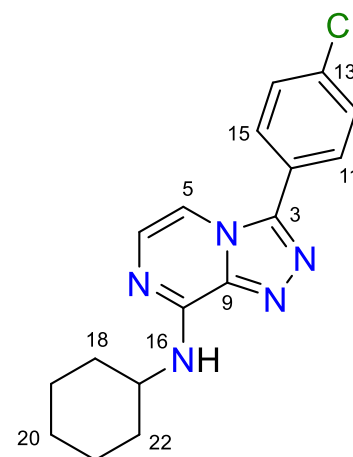
S20: ^{13}C NMR spectrum of compound **7** in $(\text{CD}_3)_2\text{SO}$



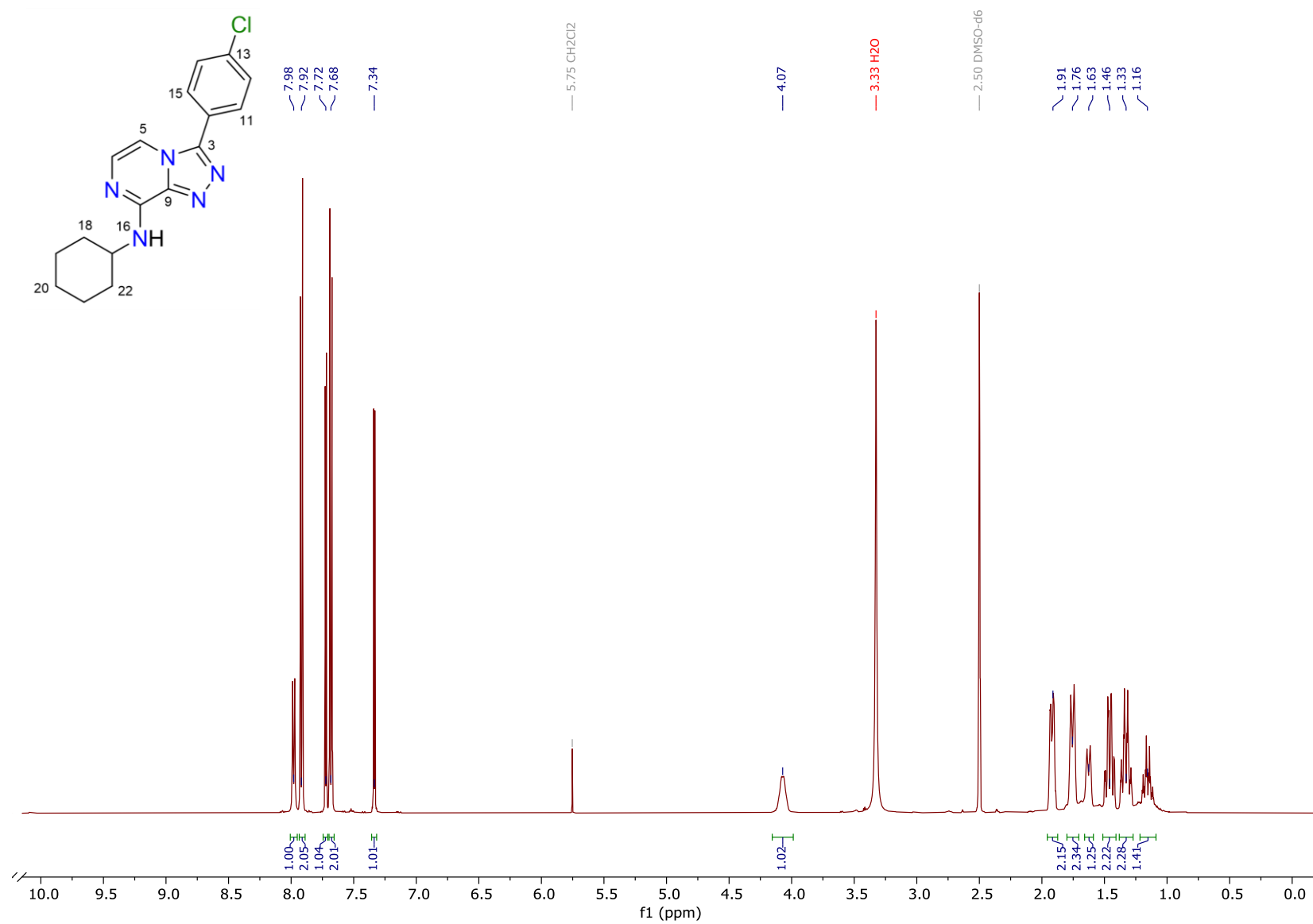
S21: NMR data table for compound **8^a**

Position	δ_{H} , mult. (<i>J</i> in Hz), int.	δ_{C} , mult.	COSY	HMBC	ROESY
3		146.8, C			
5	7.72, d (4.8), 1H	105.7, CH	6	3, 6, 9	6, 11, 15
6	7.34, d (4.8), 1H	130.3, CH	5	5, 8	5
8		147.2, C			
9		139.6, C			
10		125.2, C			
11	7.92, m, 1H	129.8, CH	12	3, 13, 15	12
12	7.68, m, 1H	129.3, CH	11	10, 14	11
13		134.9, C			
14	7.68, m, 1H	129.3, CH	15	10, 12	15
15	7.92, m, 1H	129.8, CH	14	3, 11, 13	14
16	7.98, d (8.2), 1H		17	9, 18 ^w , 22 ^w	17, 18, 22
17	4.07, m, 1H	49.0, CH	16, 18, 22		16, 18, 22
18	1.46, m, 1H	31.9, CH ₂	17, 19	19, 20, 21	19
	1.91, m, 1H	31.9, CH ₂	17, 19	19	19
19	1.33, m, 1H	25.0, CH ₂	18, 20	18, 21, 22	18, 20
	1.76, m, 1H	25.0, CH ₂	18, 20	18, 20	18, 20
20	1.63, m, 1H	25.3, CH ₂	19, 21	18, 19, 21, 22	19, 21
	1.16, m, 1H	25.3, CH ₂	19, 21	22	19
21	1.33, m, 1H	25.0, CH ₂	18, 20	18, 19	18, 20
	1.76, m, 1H	25.0, CH ₂	18, 20	18, 20	18, 20
22	1.46, m, 1H	31.9, CH ₂	17, 23	20	23
	1.91, m, 1H	31.9, CH ₂	17, 23	19	23

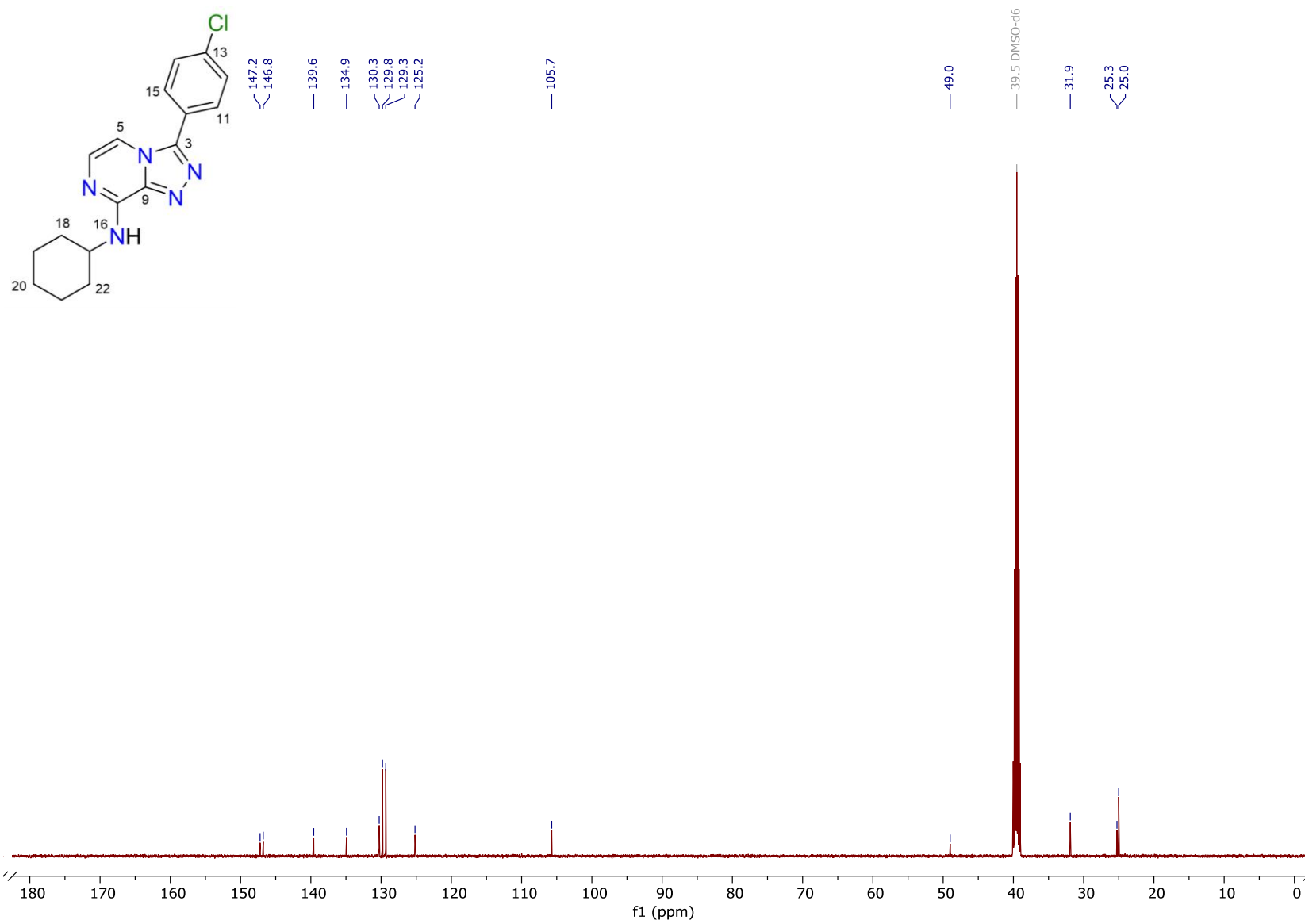
^a Recorded in (CD₃)₂SO 500 MHz (¹H NMR) and 125 MHz (¹³C NMR) at 25 °C; ^wWeak.



S22: ^1H NMR spectrum of compound **8** in $(\text{CD}_3)_2\text{SO}$

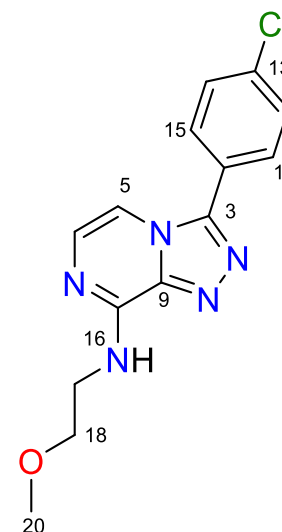


S23: ^{13}C NMR spectrum of compound **8** in $(\text{CD}_3)_2\text{SO}$



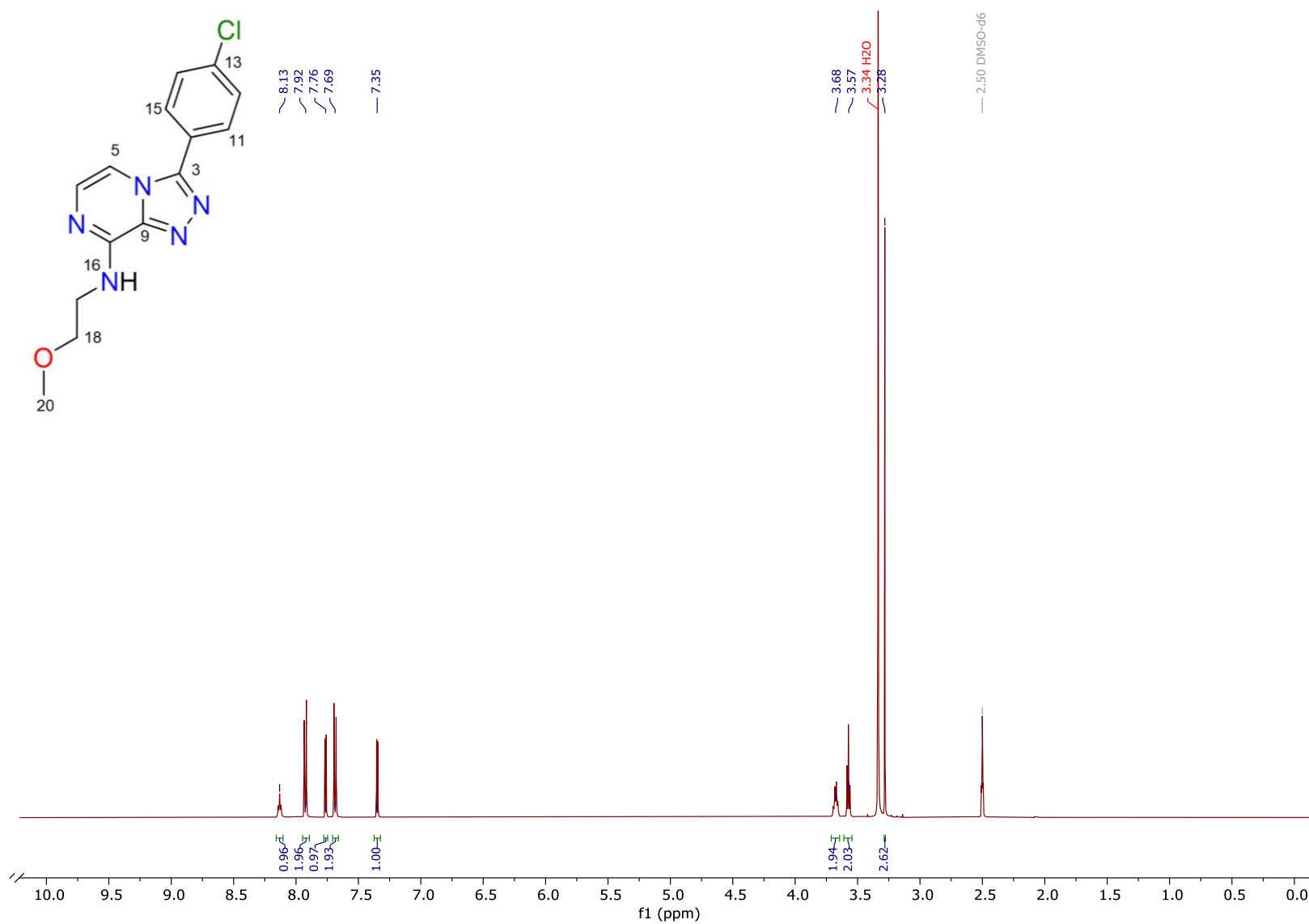
S24: NMR data table for compound **9^a**

Position	δ_{H} , mult. (J in Hz), int.	δ_{C} , mult.	COSY	HMBC	ROESY
3		146.8, C			
5	7.76, d (4.8), 1H	106.2, CH	6	3, 6, 9	6
6	7.35, d (4.8), 1H	130.2, CH	5	5, 8	5
8		148.0, C			
9		139.7, C			
10		125.1, C			
11	7.92, m, 1H	129.8, CH	12	3, 13, 15	12
12	7.69, m, 1H	129.4, CH	11	10, 14	11
13		135.0, C			
14	7.69, m, 1H	129.4, CH	15	10, 12	15
15	7.92, m, 1H	129.8, CH	14	3, 11, 13	14
16	8.13, t (5.8), 1H		17		17
17	3.68, dt (5.8, 6.2), 2H	39.5, CH ₂	16, 18	18 ^w	
18	3.57, t (6.2), 2H	69.8, CH ₂	17	17, 20 ^w	
20	3.28, s, 3H	57.9, CH ₃		18	

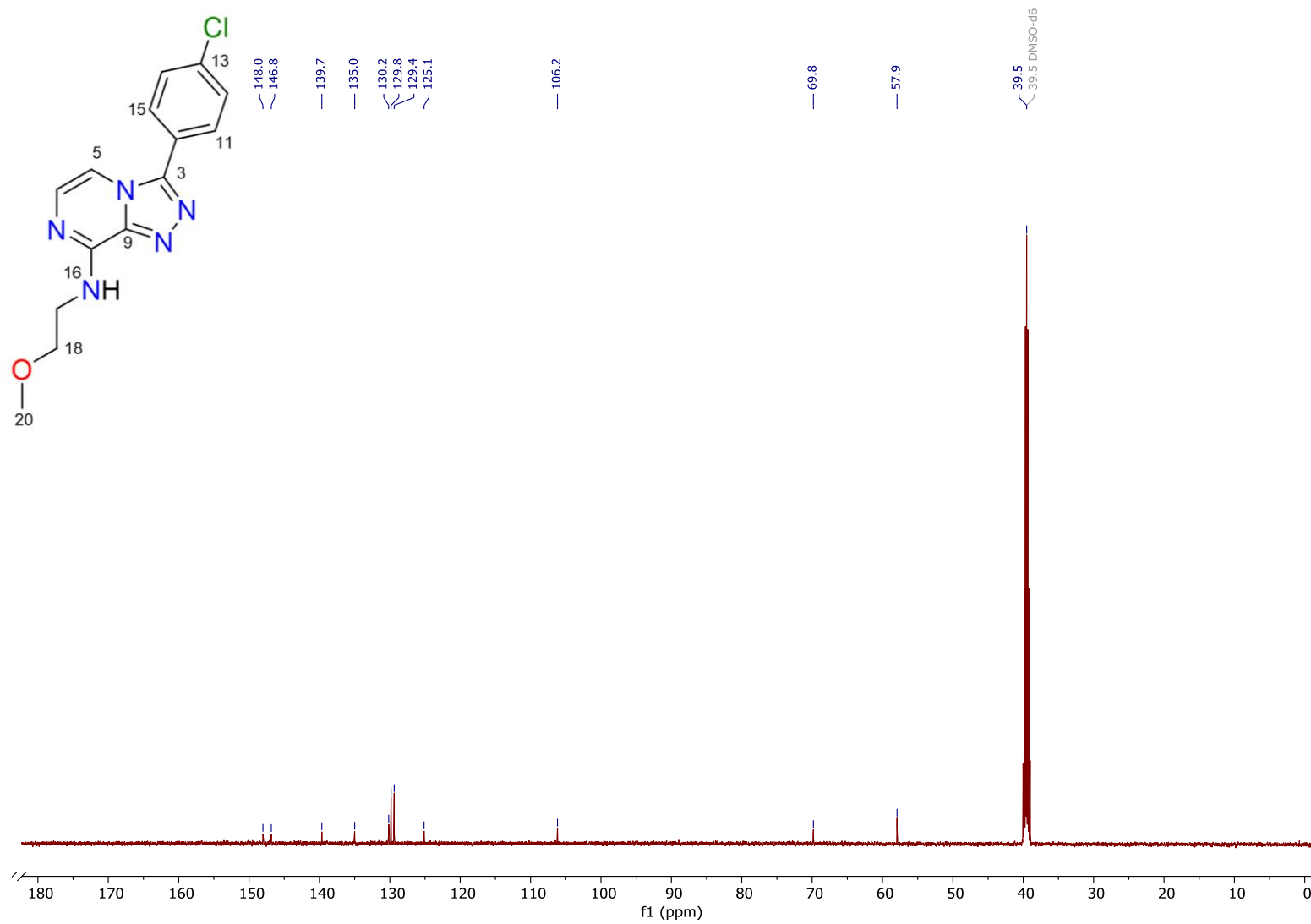


^a Recorded in (CD₃)₂SO 500 MHz (¹H NMR) and 125 MHz (¹³C NMR) at 25 °C; ^wWeak.

S25: ^1H NMR spectrum of compound **9** in $(\text{CD}_3)_2\text{SO}$

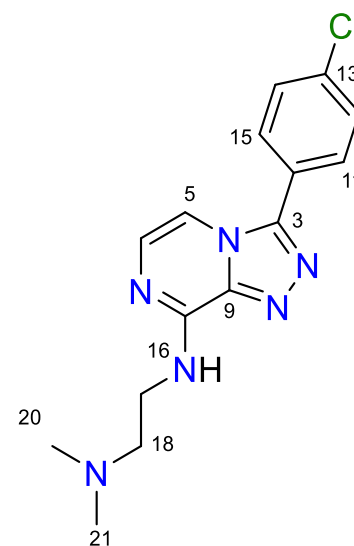


S26: ^{13}C NMR spectrum of compound **9** in $(\text{CD}_3)_2\text{SO}$



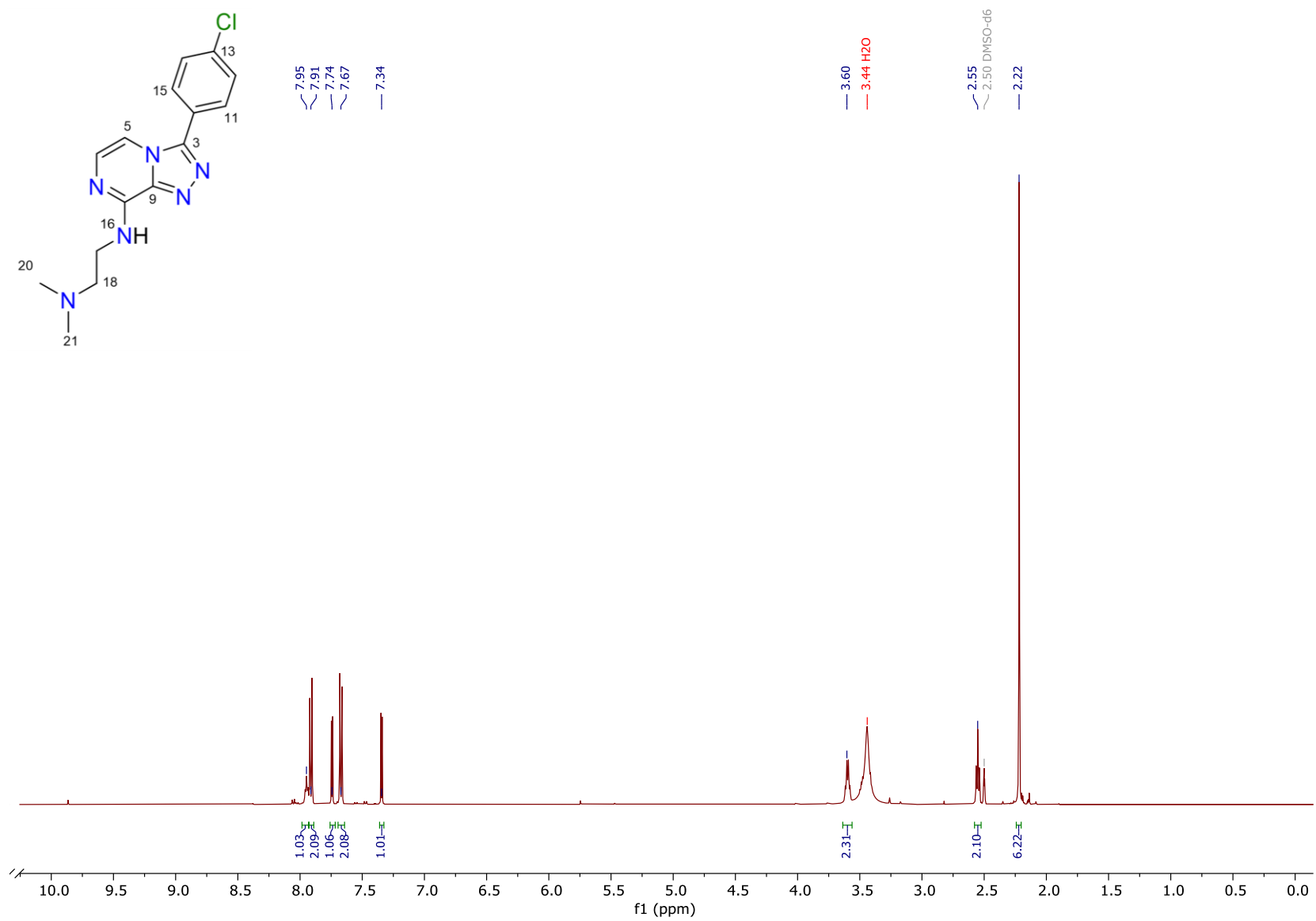
S27: NMR data table for compound **10**^a

Position	δ_{H} , mult. (J in Hz), int.	δ_{C} , mult.	COSY	HMBC	ROESY
3		146.8, C			
5	7.74, d (4.8), 1H	106.0, CH	6	3, 6, 9	6, 11, 15
6	7.34, d (4.8), 1H	130.3, CH	5	5, 8	5
8		148.0, C			
9		139.7, C			
10		125.1, C			
11	7.91, m, 1H	129.8, CH	12	3, 13, 15	5, 12
12	7.67, m, 1H	129.4, CH	11	10, 14	11
13		135.0, C			
14	7.67, m, 1H	129.4, CH	15	10, 12	15
15	7.91, m, 1H	129.8, CH	14	3, 11, 13	5, 12
16	7.95, t (5.5), 1H		17	8, 17 ^w	17
17	3.60, dt (5.5, 6.6), 2H	37.9, CH ₂	16, 18	8, 18	16, 18, 20, 21
18	2.55, t (6.6), 2H	57.4, CH ₂	17	17, 20, 21	17, 20, 21
20	2.22, s, 3H	45.1, CH ₃		18, 21	17, 18
21	2.22, s, 3H	45.1, CH ₃		18, 20	17, 18

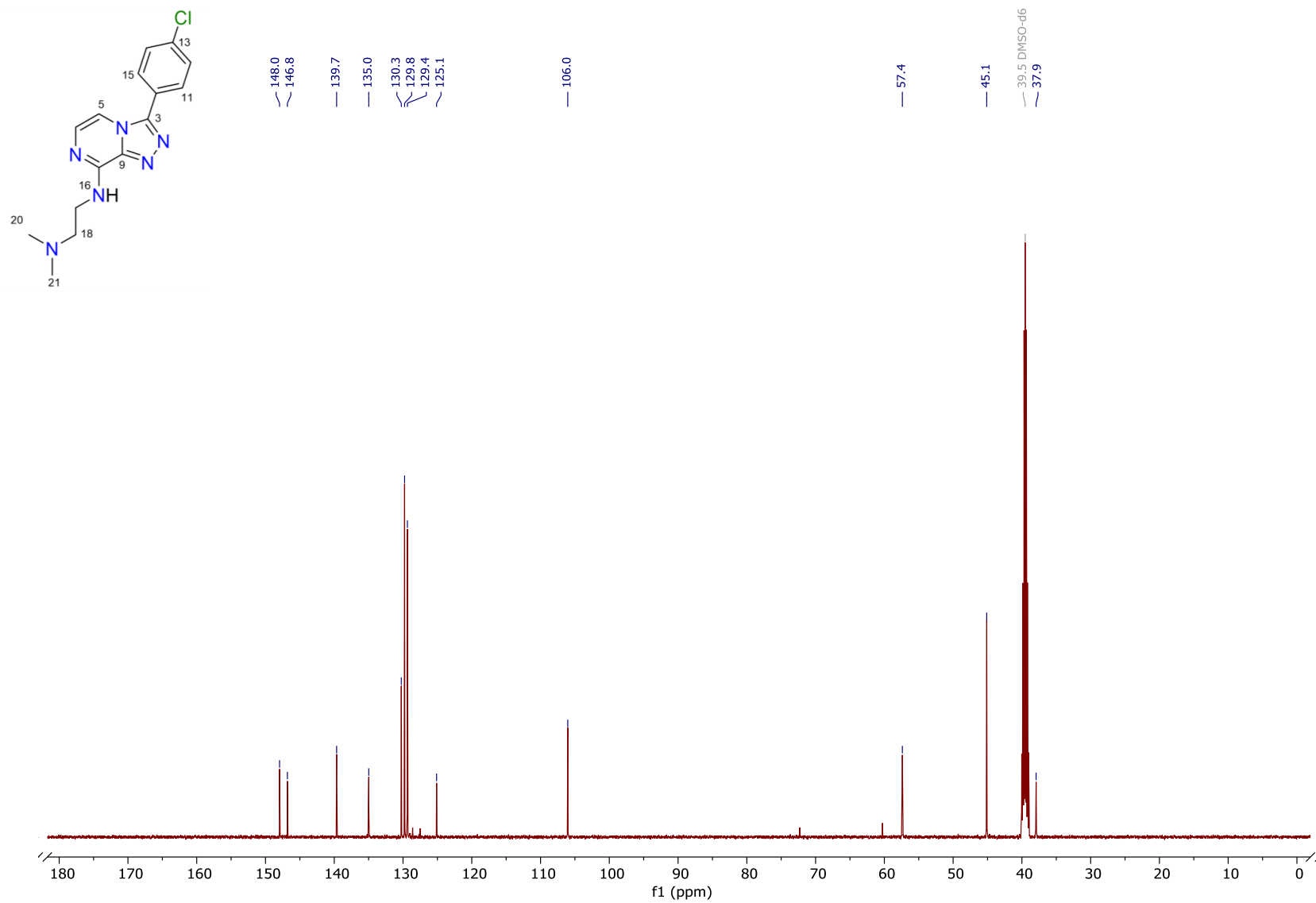


^a Recorded in (CD₃)₂SO 500 MHz (¹H NMR) and 125 MHz (¹³C NMR) at 25 °C; ^wWeak.

S28: ^1H NMR spectrum of compound **10** in $(\text{CD}_3)_2\text{SO}$



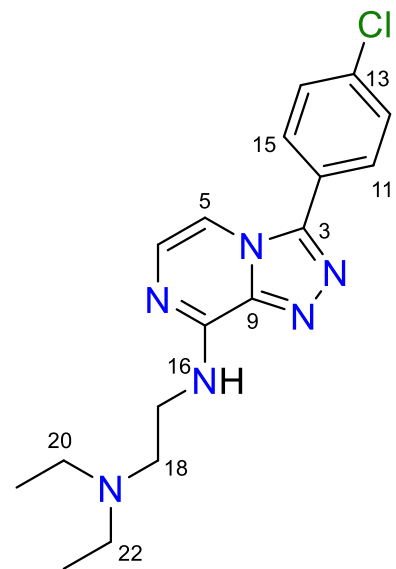
S29: ^{13}C NMR spectrum of compound **10** in $(\text{CD}_3)_2\text{SO}$



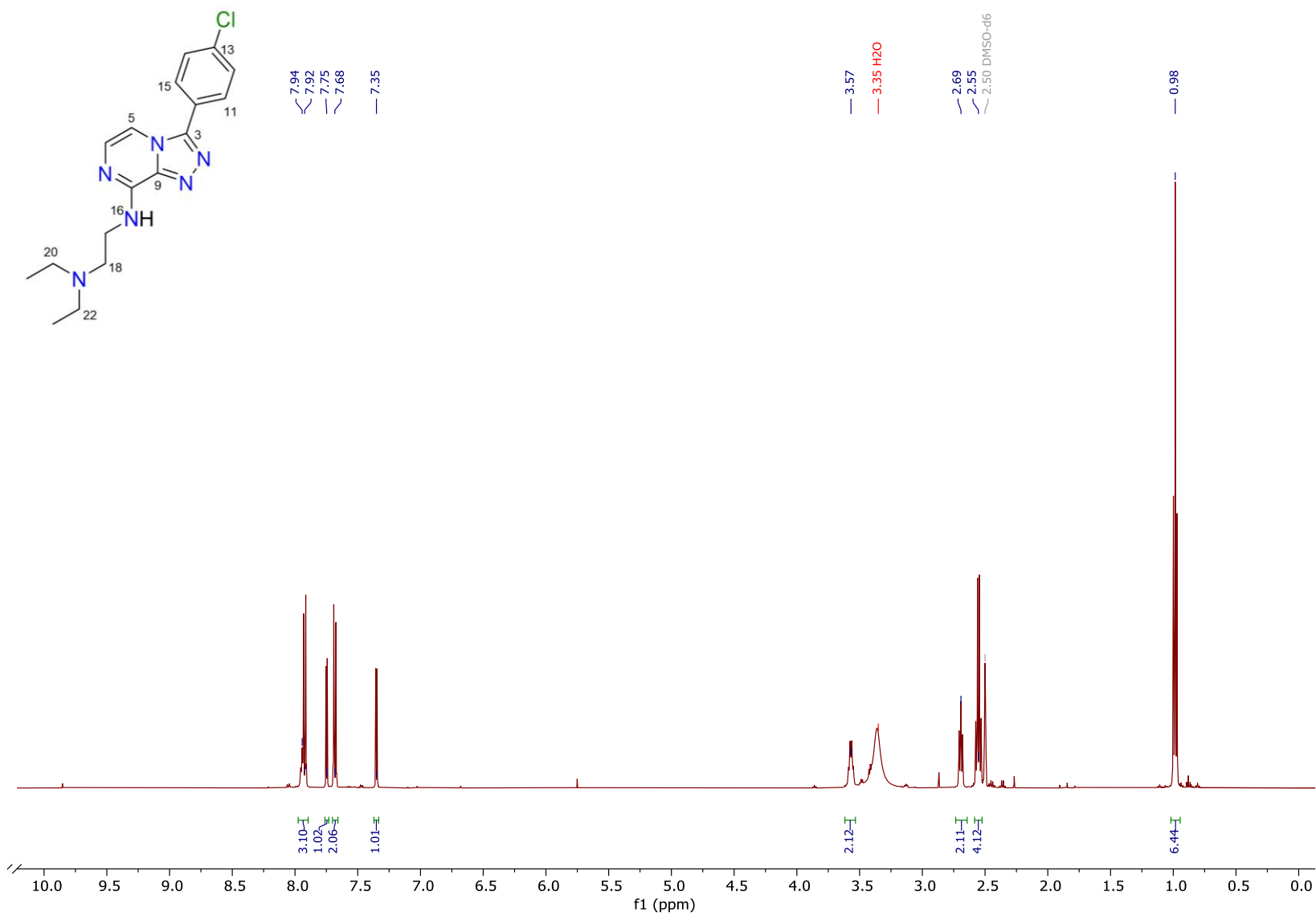
S30: NMR data table for compound **11**^a

Position	δ_{H} , mult. (J in Hz), int.	δ_{C} , mult.	COSY	HMBC	ROESY
3		146.8, C			
5	7.75, d (4.8), 1H	106.0, CH	6	6, 9	6, 11, 15
6	7.35, d (4.8), 1H	130.3, CH	5	5, 8	5
8		148.0, C			
9		139.7, C			
10		125.1, C			
11	7.92, m, 1H	129.8, CH	12	3, 13, 15	12
12	7.68, m, 1H	129.4, CH	11	10, 14	11
13		135.0, C			
14	7.68, m, 1H	129.4, CH	15	10, 12	15
15	7.92, m, 1H	129.8, CH	14	3, 11, 13	14
16	7.94, t (5.8), 1H		17	8, 17 ^w	17, 18
17	3.57, dt (5.8, 7.1), 2H	38.0, CH ₂	16, 18	8, 18	16, 18, 20, 22
18	2.69, t (7.1), 2H	50.8, CH ₂	17	17, 20, 22	16, 17, 20, 21, 22, 23
20	2.55, q (7.1), 2H	46.6, CH ₂	21	18, 21, 22	17, 18, 21
21	0.98, t (7.1), 3H	11.9, CH ₃	20	20	18, 20
22	2.55, q (7.1), 2H	46.6, CH ₂	23	18, 20, 23	17, 18, 23
23	0.98, t (7.1), 3H	11.9, CH ₃	22	22	18, 22

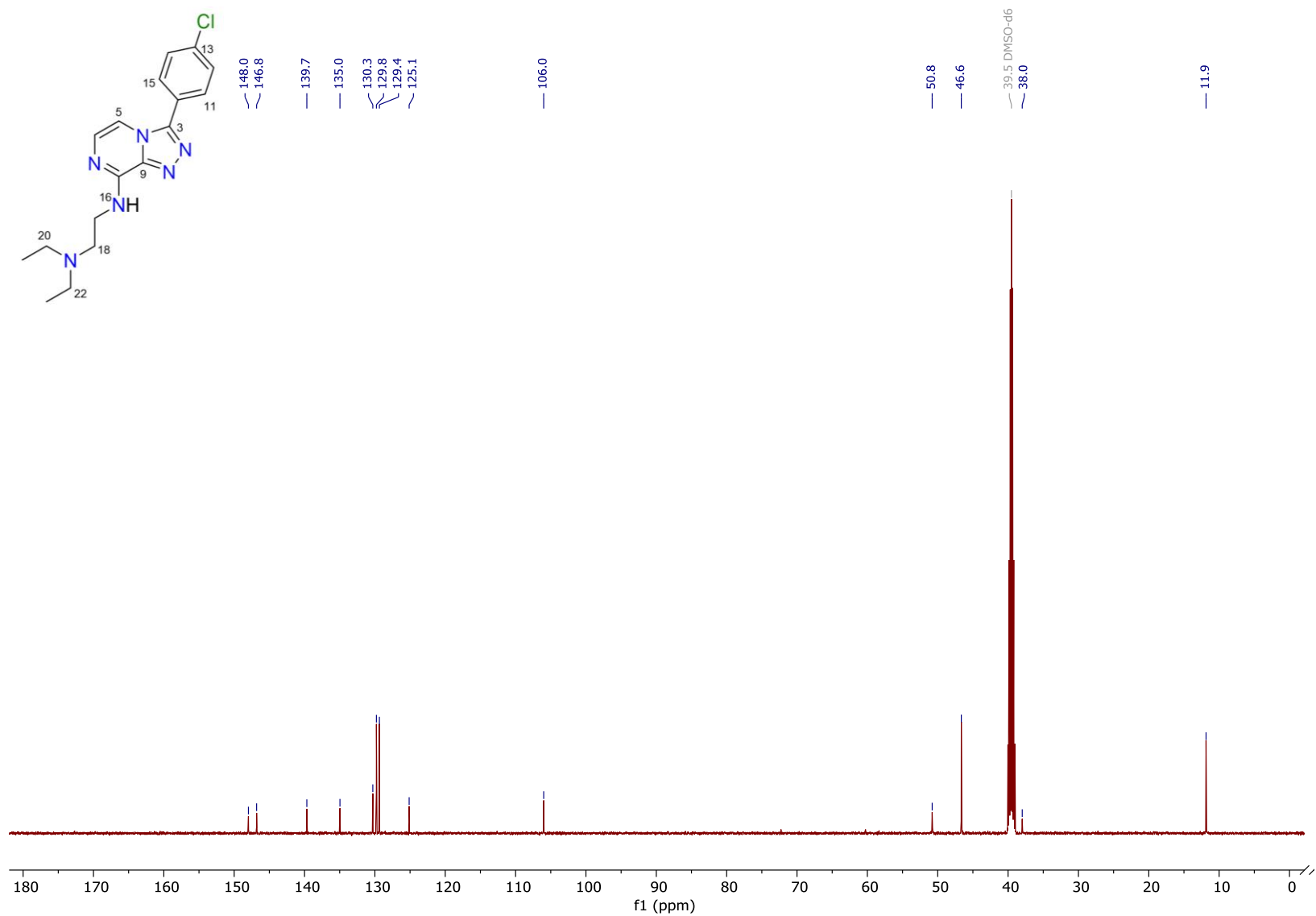
^a Recorded in (CD₃)₂SO 500 MHz (¹H NMR) and 125 MHz (¹³C NMR) at 25 °C; ^wWeak.



S31: ^1H NMR spectrum of compound **11** in $(\text{CD}_3)_2\text{SO}$

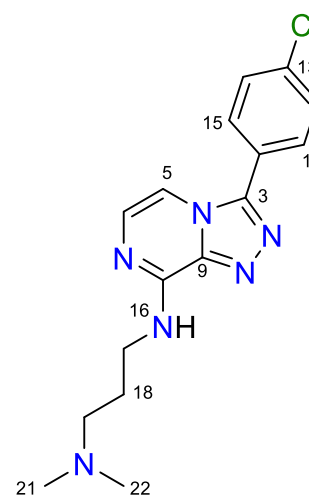


S32: ^{13}C NMR spectrum of compound **11** in $(\text{CD}_3)_2\text{SO}$



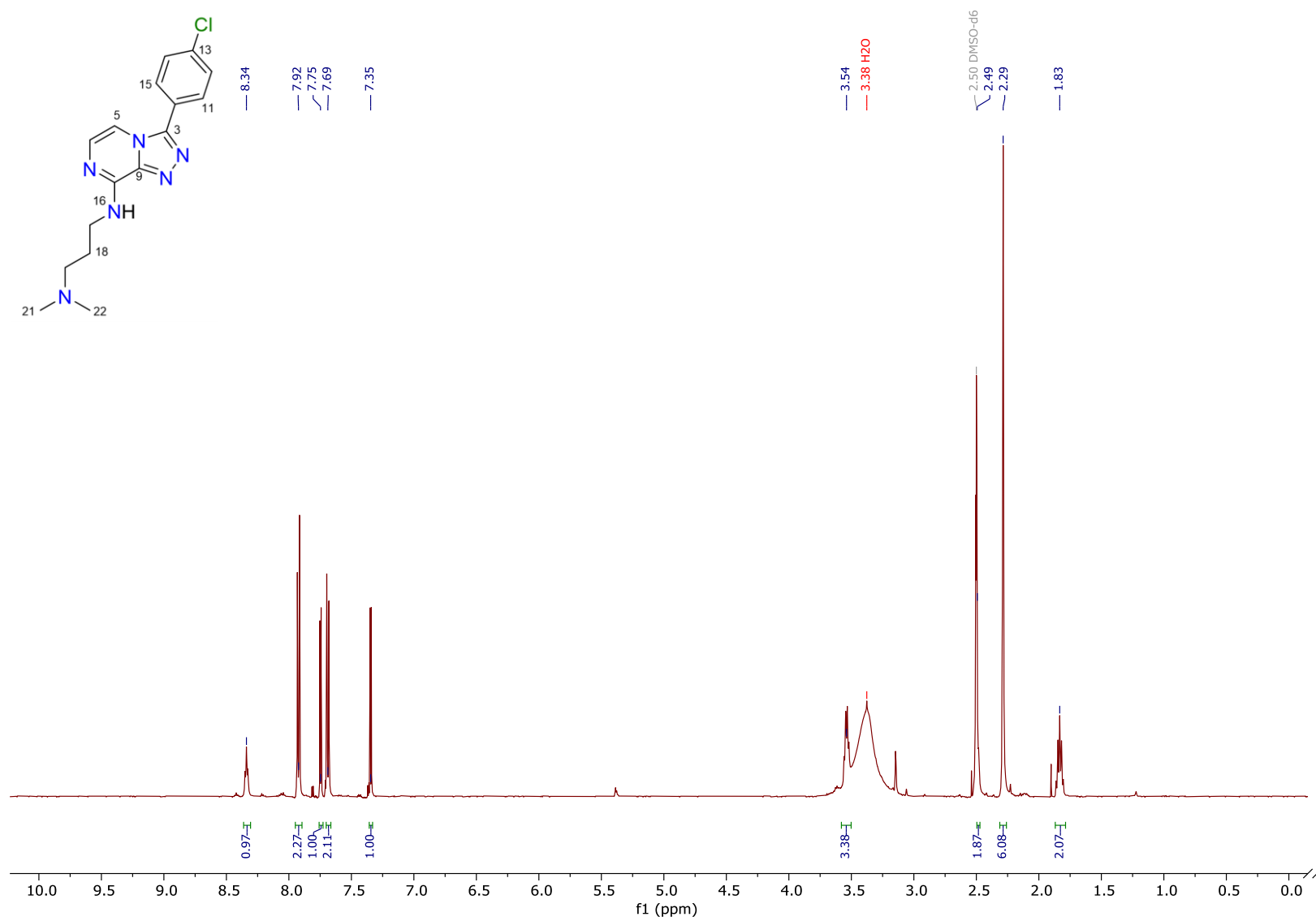
S33: NMR data table for compound **12**^a

Position	δ_{H} , mult. (J in Hz), int.	δ_{C} , mult.	COSY	HMBC	ROESY
3		146.8, C			
5	7.75, d (4.8), 1H	105.9, CH	6	3, 6, 9	6, 11, 15
6	7.35, d (4.8), 1H	130.3, CH	5	5, 8	5
8		148.0, C			
9		139.7, C			
10		125.2, C			
11	7.92, m, 1H	129.8, CH	12	3, 13, 15	12
12	7.69, m, 1H	129.4, CH	11	10, 14	11
13		135.0, C			
14	7.69, m, 1H	129.4, CH	15	10, 12	15
15	7.92, m, 1H	129.8, CH	14	3, 11, 13	14
16	8.34, brt (5.5), 1H		17		17
17	3.54, m, 2H	38.4, CH ₂	16, 18	8, 18 ^w	16, 18
18	1.83, m, 2H	25.7, CH ₂	17, 19	17, 19	17, 19, 21, 22
19	2.49, t (7.1), 2H	56.5, CH ₂	18	17, 18 ^w , 21, 22	18, 21, 22
21	2.29, s, 3H	44.5, CH ₃		19, 22	18, 19
22	2.29, s, 3H	44.5, CH ₃		19, 21	18, 19

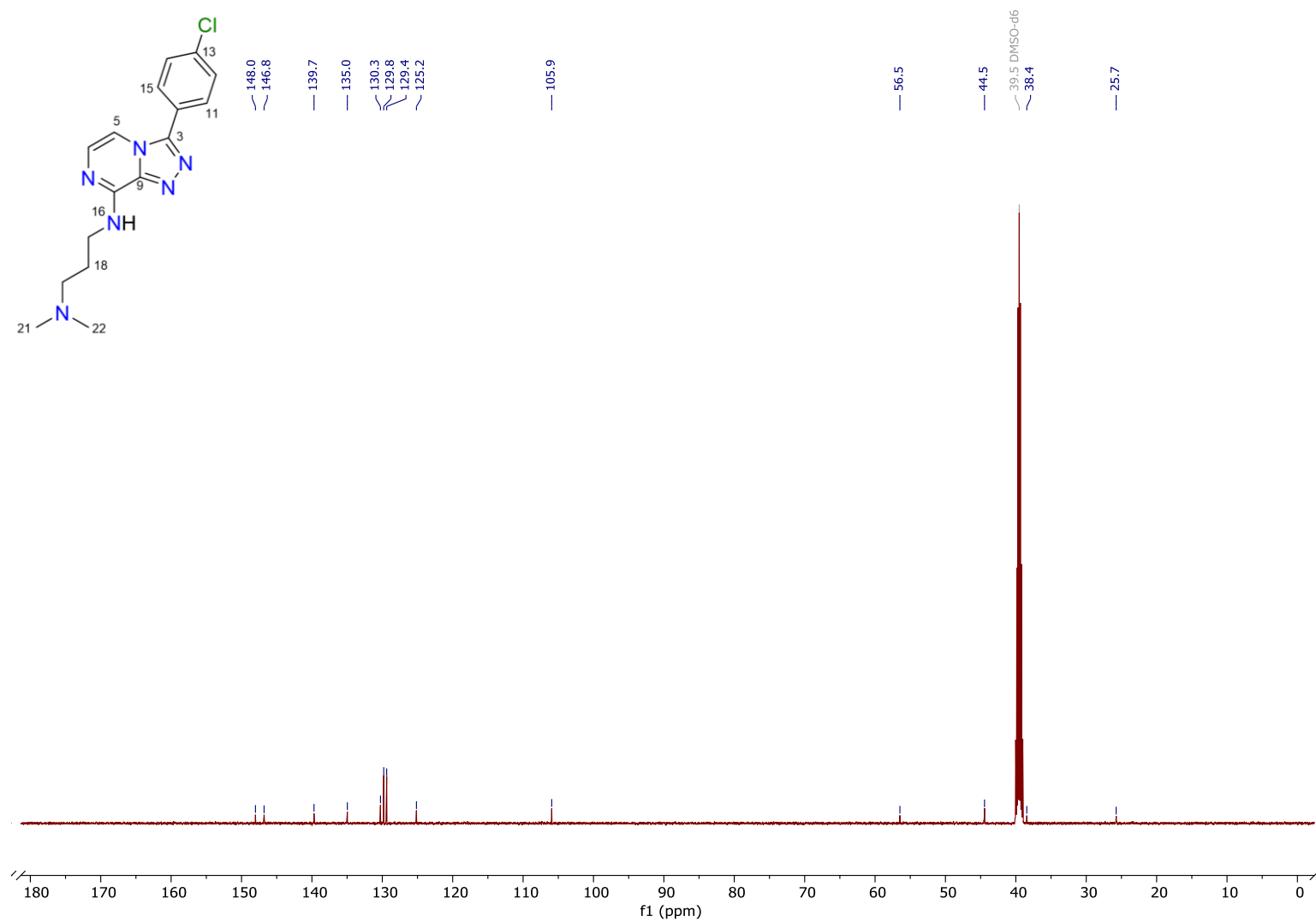


^a Recorded in (CD₃)₂SO 500 MHz (¹H NMR) and 125 MHz (¹³C NMR) at 25 °C; ^wWeak.

S34: ^1H NMR spectrum of compound **12** in $(\text{CD}_3)_2\text{SO}$

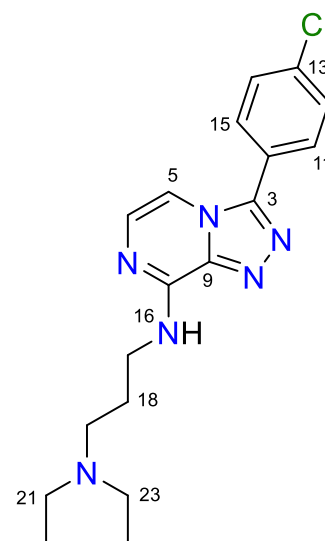


S35: ^{13}C NMR spectrum of compound **12** in $(\text{CD}_3)_2\text{SO}$



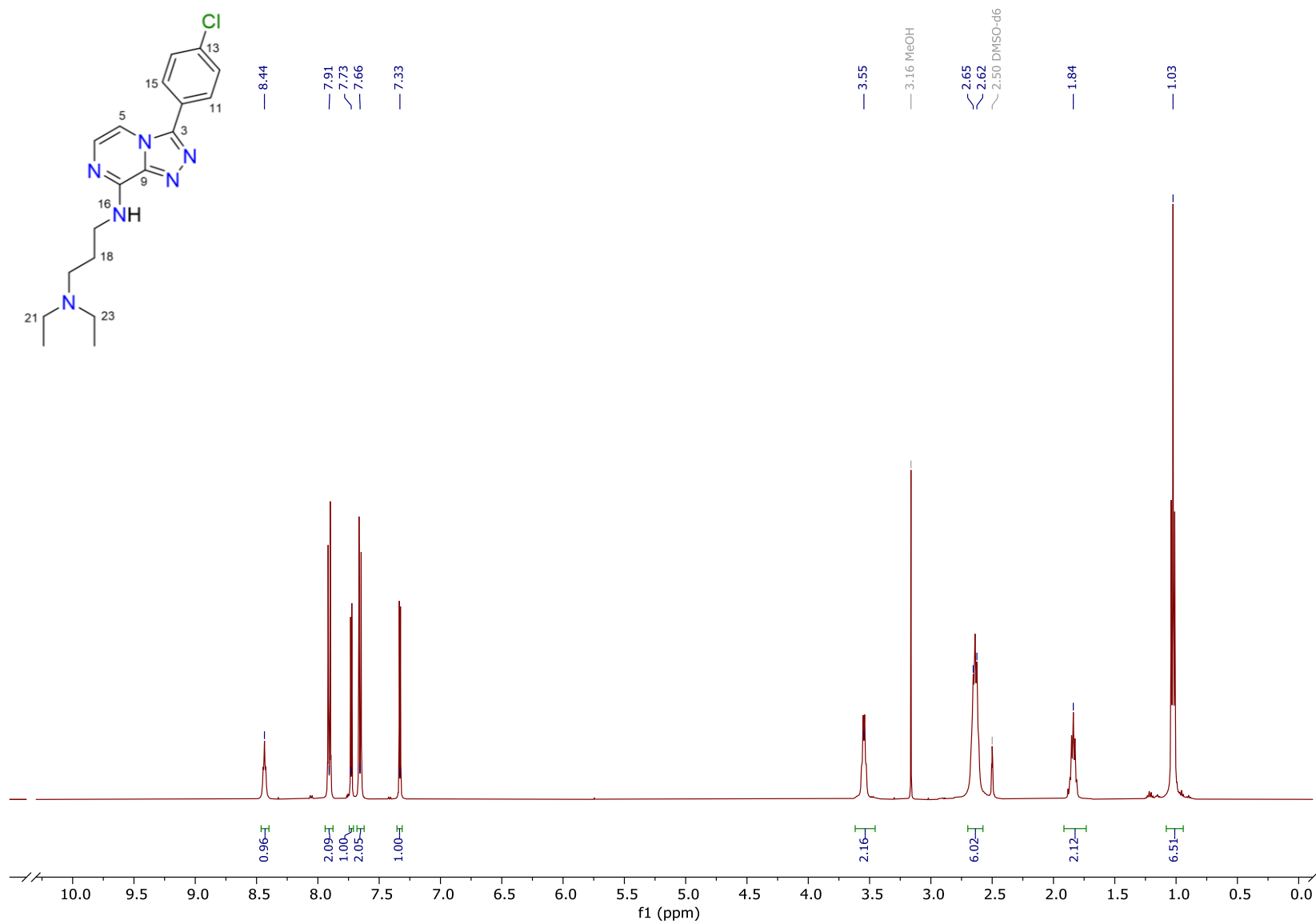
S36: NMR data table for compound **13**^a

Position	δ_{H} , mult. (J in Hz), int.	δ_{C} , mult.	COSY	HMBC	ROESY
3		146.7, C			
5	7.73, d (4.8), 1H	105.9, CH	6	3, 6, 9	6, 11, 15
6	7.33, d (4.8), 1H	130.3, CH	5	5, 8	5
8		148.0, C			
9		139.7, C			
10		125.1, C			
11	7.91, m, 1H	129.7, CH	12	3, 13, 15	5, 12
12	7.66, m, 1H	129.3, CH	11	10,14	11
13		134.9, C			
14	7.66, m, 1H	129.3, CH	15	10, 12	15
15	7.91, m, 1H	129.7, CH	14	3, 11, 13	5, 14
16	8.44, t (5.3), 1H		17	8, 9	17
17	3.55, m, 2H	38.9, CH ₂	16, 18	8, 18, 19	16, 18, 19
18	1.84, m, 2H	24.8, CH ₂	17, 19	17, 19	17, 19, 21, 23
19	2.65, t (8.0), 2H	50.1, CH ₂	18	17 ^w , 18, 21, 23	17, 18
21	2.62, q (7.2), 2H	46.2, CH ₂	22	19, 22, 23	22
22	1.03, t (7.2), 3H	10.7, CH ₃	21	21	21
23	2.63, q (7.2), 2H	46.2, CH ₂	24	19, 21, 24	24
24	1.03, t (7.2), 3H	10.7, CH ₃	23	23	23

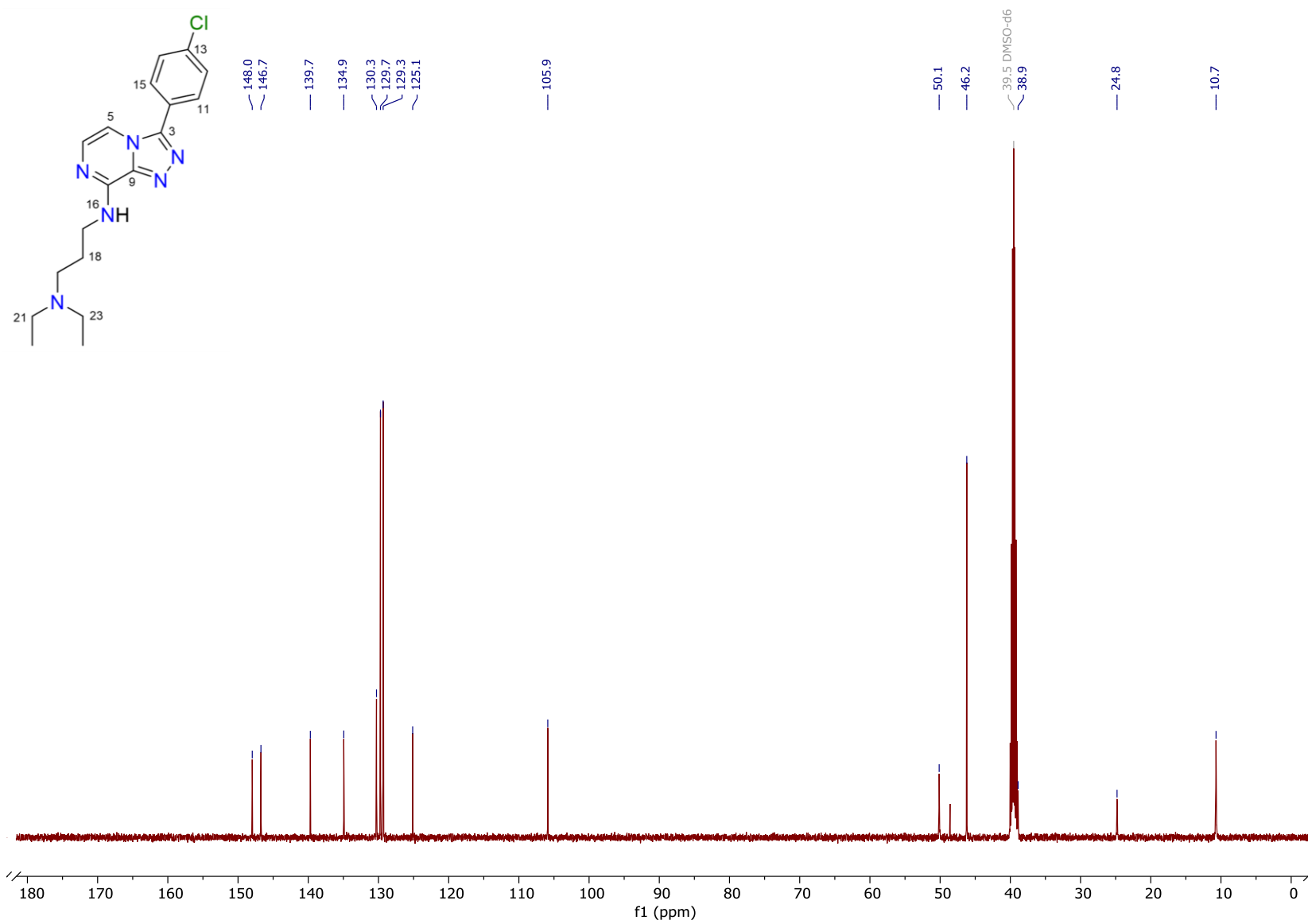


^a Recorded in (CD₃)₂SO 500 MHz (¹H NMR) and 125 MHz (¹³C NMR) at 25 °C; ^wWeak.

S37: ^1H NMR spectrum of compound **13** in $(\text{CD}_3)_2\text{SO}$



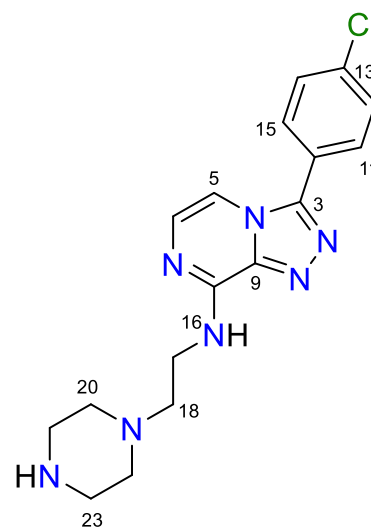
S38: ^{13}C NMR spectrum of compound **13** in $(\text{CD}_3)_2\text{SO}$



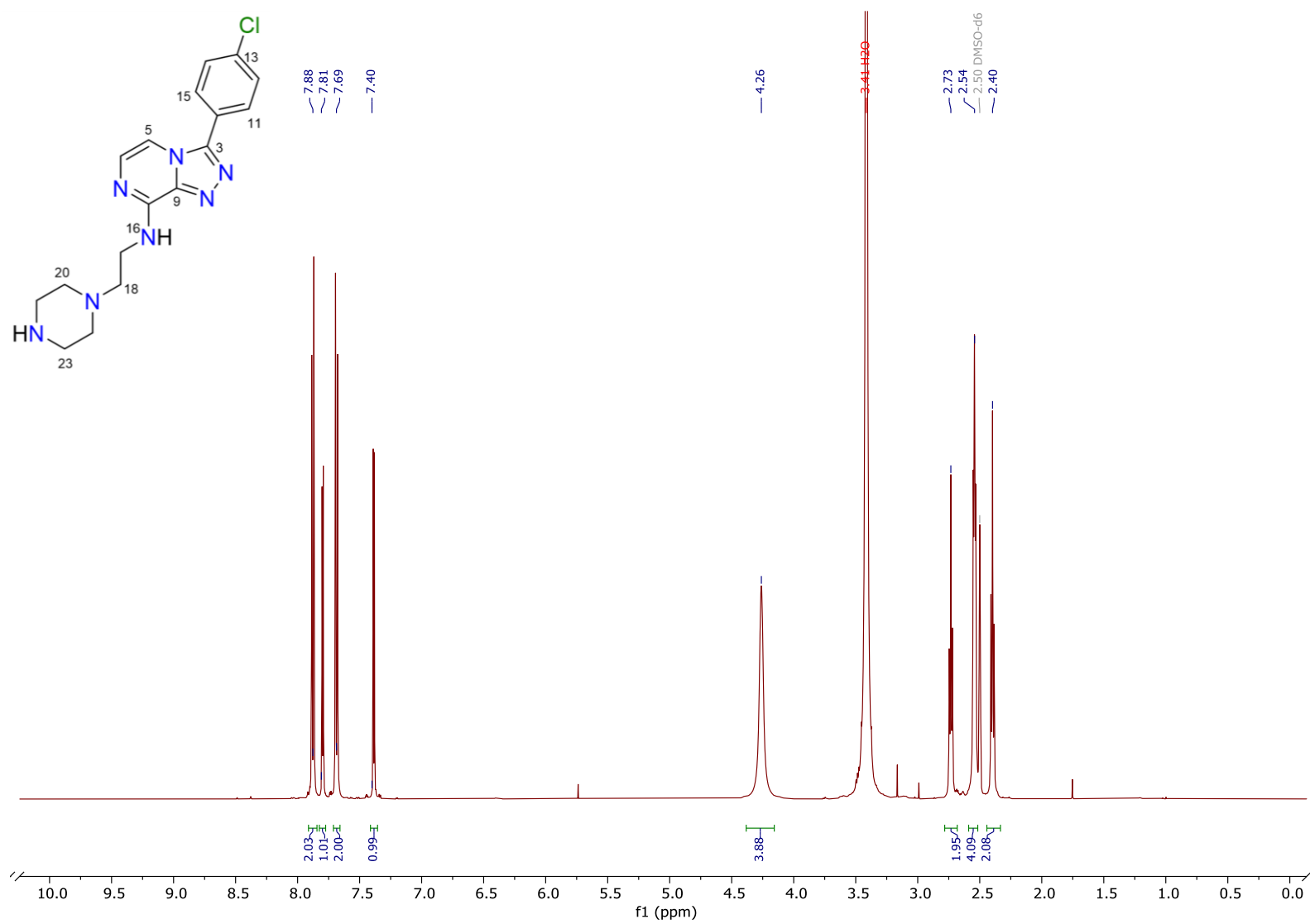
S39: NMR data table for compound **14**^a

Position	δ_{H} , mult. (J in Hz), int.	δ_{C} , mult.	COSY	HMBC	ROESY
3		146.3, C			
5	7.81, d (4.7), 1H	107.0, CH	6	3, 6, 9	6, 11, 15
6	7.40, d (4.7), 1H	129.6, CH	5	5, 8	5
8		147.7, C			
9		140.6, C			
10		125.0, C			
11	7.88, m, 1H	130.1, CH ₂	12	3, 13, 15	12
12	7.69, m, 1H	129.4, CH ₂	11	10, 14	11
13		135.2, C			
14	7.69, m, 1H	129.4, CH ₂	15	10, 12	15
15	7.88, m, 1H	130.1, CH ₂	14	3, 11, 13	14
16	N.O.				
17	2.73, t (6.4), 2H	38.0, CH ₂	18	18	18, 20, 24
18	2.40, t (6.4), 2H	59.6, CH ₂	17	17, 20, 24	17, 20, 24
20	2.54, m, 2H	52.9, CH ₂	21	18, 21	17, 21
21	4.26, m, 2H	45.8, CH ₂	20		20
22	N.O.				
23	4.26, m, 2H	45.8, CH ₂	24		24
24	2.54, m, 2H	52.9, CH ₂	23	18, 21	18, 23

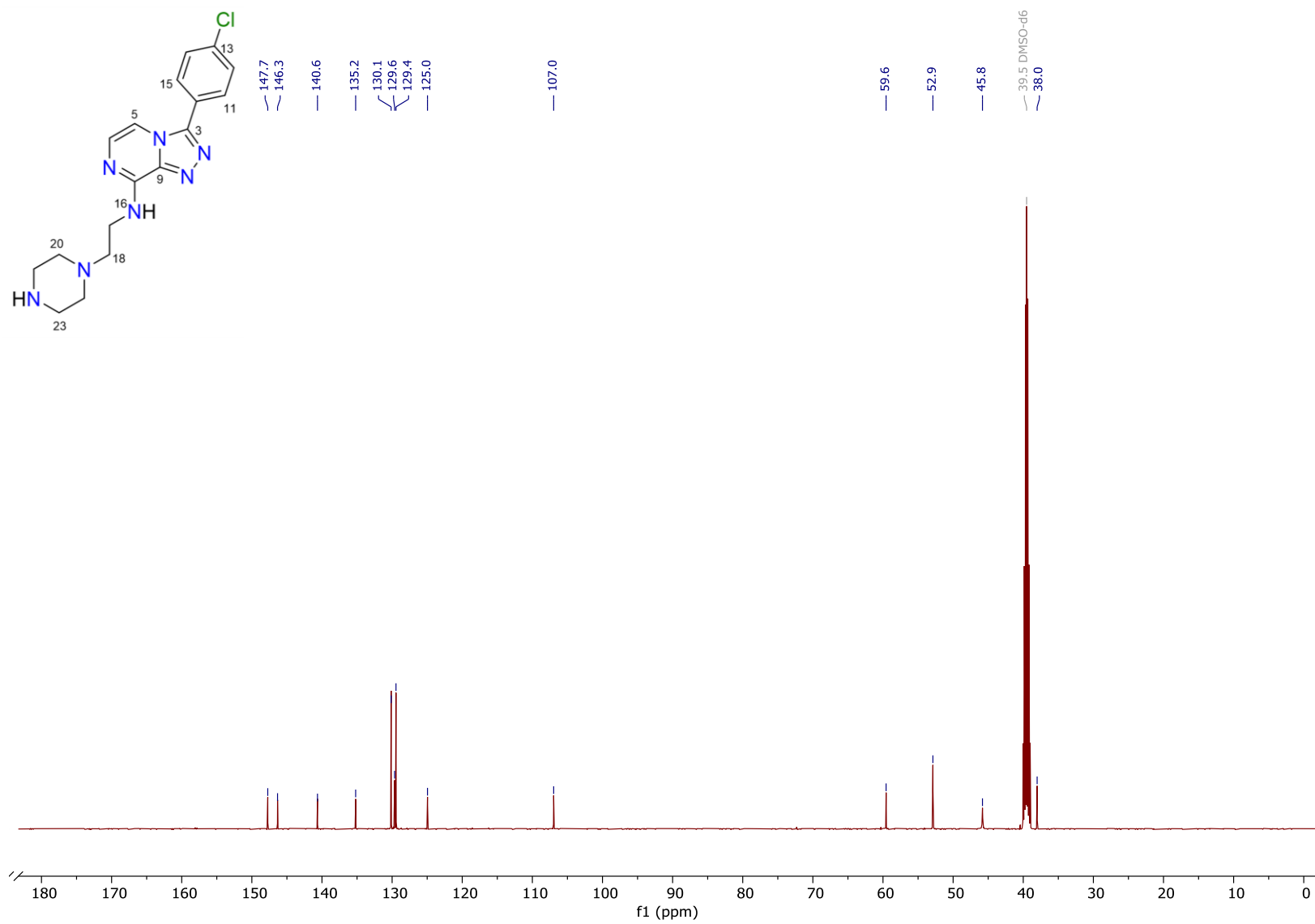
^a Recorded in (CD₃)₂SO 500 MHz (¹H NMR) and 125 MHz (¹³C NMR) at 25 °C.



S40: ^1H NMR spectrum of compound **14** in $(\text{CD}_3)_2\text{SO}$



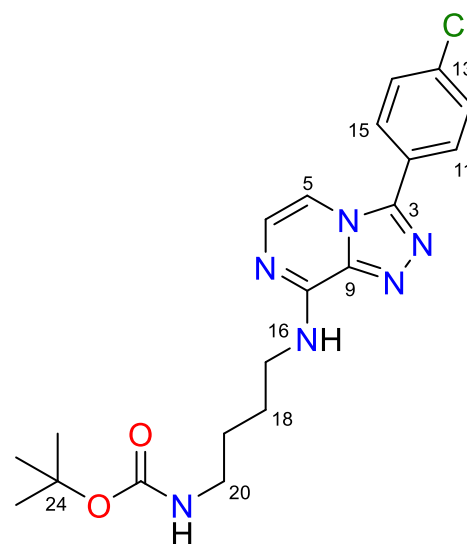
S41: ^{13}C NMR spectrum of compound **14** in $(\text{CD}_3)_2\text{SO}$



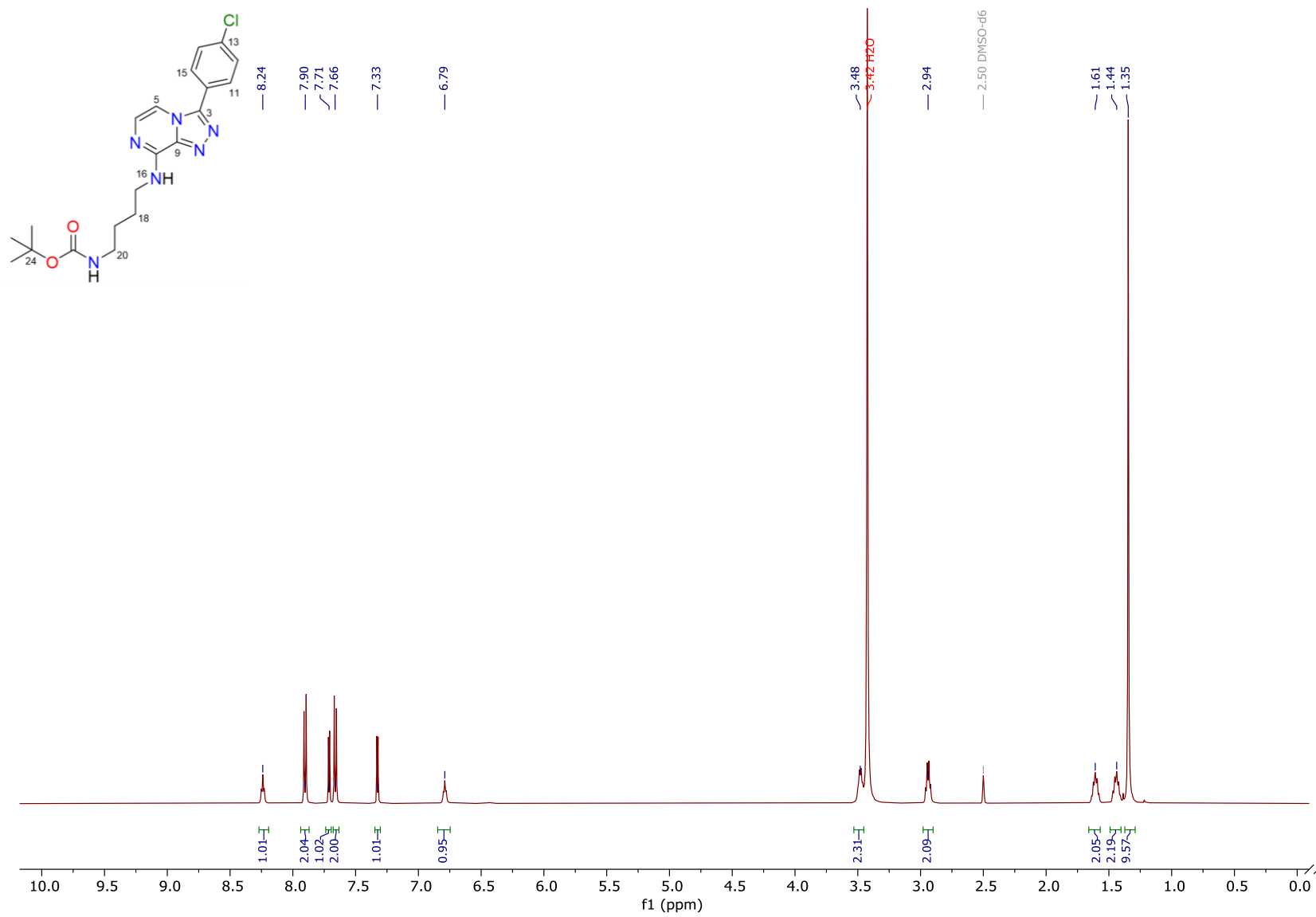
S42: NMR data table for compound **15**^a

Position	δ_H , mult. (J in Hz), int.	δ_C , mult.	COSY	HMBC	ROESY
3		146.8, C			
5	7.71, d (4.8), 1H	105.8, CH	6	3, 6, 9	6
6	7.33, d (4.8), 1H	130.4, CH	5	5, 8	5
8		148.1, C			
9		139.8, C			
10		125.2, C			
11	7.90, m, 1H	129.8, CH	12	3, 13, 15	12
12	7.66, m, 1H	129.4, CH	11	10, 14	11
13		135.0, C			
14	7.66, m, 1H	129.4, CH	15	10, 12	15
15	7.90, m, 1H	129.8, CH	14	3, 11, 13	14
16	8.24, brt (5.7), 1H		17	8	17
17	3.48, m, 2H	39.8, CH ₂	16, 18		
18	1.61, m, 2H	26.0, CH ₂	17, 19		
19	1.44, m, 2H	27.2, CH ₂	18, 20	18, 20	
20	2.94, m, 2H	39.4, CH ₂	19, 21		19
21	6.79, t (5.6), 1H		20		20
22		155.7, C			
24		77.4, C			
25	1.35, s, 3H	28.3, CH ₃		24	
26	1.35, s, 3H	28.3, CH ₃		24	
27	1.35, s, 3H	28.3, CH ₃		24	

^a Recorded in (CD₃)₂SO 500 MHz (¹H NMR) and 125 MHz (¹³C NMR) at 25 °C.



S43: ^1H NMR spectrum of compound **15** in $(\text{CD}_3)_2\text{SO}$



S44: ^{13}C NMR spectrum of compound **15** in $(\text{CD}_3)_2\text{SO}$

