SUPPORTING INFORMATION

Profiling and Application of Photoredox C(sp^3)-C(sp^2) Cross-Coupling in Medicinal Chemistry

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Supplementary Text
NMR Spectra

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I. General Experimental Information

Scaffolds **X1** - **X18** and 6-chloro-4-(2,4-difluorophenyl)picolinonitrile were requested from Merck Sharp & Dohme internal compound collection and used without further purification. All other starting materials and reagents required for the synthesis were commercially available (commercial sources such as Sigma-Aldrich, Acros Organics, Strem Chemicals, etc.).

All reactions were set up under nitrogen atmosphere inside a glove box.
Integrated photoreactor - Royal Blue (450 nm) LED lights, with fan rate: 4700 rpm, stir rate: 1000 rpm, LED light intensity: 100%.
Kessil lamps - Kessil KSH150B Grow Light Blue: Two Kessil lamps were 7 cm away from reaction vessels. Cooling fan - electric fan from ebm-papst 4414FNH – was 6 cm above reaction vessels. Reaction vessels were taped on top of stirring plate, using double sided white Scotch Mounting Squares.
Reaction conversion was calculated based on AUC (area under curve) of LCMS spectra at UV 254 nm. Reaction conversion = AUC of desired product / (AUC of desired product + AUC of by-product(s) + AUC of unreacted starting material)

The abbreviations used in the entire specification may be summarized herein below with their particular meaning.
°C (degree Celsius); % (percentage); rpm (rounds per minute); cm (centimetre); nm (nanometre); HPLC (high-performance liquid chromatography); TLC (thin layer chromatography); LCMS (liquid chromatography mass spectroscopy); HRMS (high resolution mass spectra); R_T (LCMS retention time); AUC (area under curve); ESI (electrospray ionization); mmol (milimoles); M (molar); µL (microlitre); mL (mililitre); mg (miligram); min. (minutes); h (hours); LED (light-emitting diode); Barton's base (2-*tert*-butyl-1,1,3,3-tetramethylguanidine); TTMSS (tris(trimethylsilyl)silane); Boc (*tert*-butyloxycarbonyl); dtbbpy (4,4'-di-*tert*-butyl-2,2'-bipyridine); THP (tetrahydropyran); TFA (trifluoroacetic acid); DMF (*N*,*N*-dimethylformamide); DMSO (dimethyl sulfoxide); DME (1,2-dimethoxyethane); eq. (equivalent); DMSO-d_6 (deuterated DMSO); $CDCl_3$ (deuterated chloroform); TMS (tetramethylsilane).

For compounds purified with semi-preparative reverse phase HPLC (high performance liquid chromatography): Mass Directed purification system. Column - Waters Sunfire C18, 5 µm, 19x100 mm. Gradient conditions - 8 min. run time; flow rate: 25 mL/min.; 8-80% CH_3CN in H_2O (Method A: 0.16% TFA in both CH_3CN and H_2O; Method B: 0.16% Formic Acid in both CH_3CN and H_2O; Method C: 0.16% pH 10 Ammonium Hydroxide in both CH_3CN and H_2O).
For compounds purified with preparative TLC (thin layer chromatography) plate: Silica gel GF UV254 20 x 20 cm, 1000 micron from Analtech, Inc. was used. Elution solvents: low to high % more polar solvent/less polar solvent (e.g., 60% EtOAc/heptane).
For compounds purified with Silica Gel Chromatography: CombiFlash® R_f Flash Chromatography System from Teledyne ISCO was used, with RediSep R_f Gold Silica (20 – 40 µm) Flash Chromatography Column. Gradient conditions: low to high % more polar solvent/less polar solvent (e.g., 15 – 100% EtOAc/hexanes).
For compounds purified with SFC (supercritical fluid chromatography): Instrument: Thar 80 SFC; Column: Chiralpak AS-H, 5 um, 21 x 250 mm; Conditions: 20% MeOH/ACN 1:1 + 0.2% DIPA (diisopropylamine) @ 50 g/min, 120 bar, 40°C, 210 nm
For compounds purified with micro-scale reverse phase HPLC (high performance liquid chromatography): Mass Directed purification system. Waters Auto Purification HPLC/MS system (2545 Binary Gradient Module, 2767 Sample Manager, Waters 3100 Mass detector, 2998 Photodiode Array Detector) equipped with a Waters CSH 5 µm 10 x 50 mm column using gradient chromatography ACN/Water (containing 0.16% TFA modifier or 0.16% NH_4OH), flow rate = 8 mL/min.

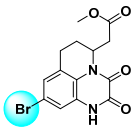
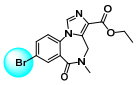
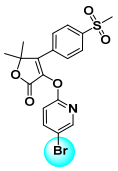
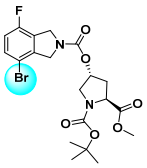
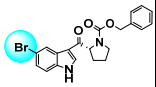
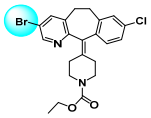
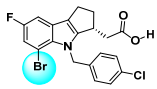
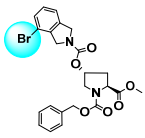
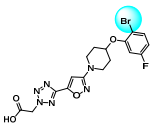
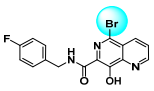
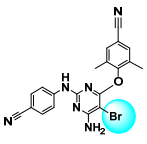
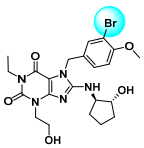
Volatiles were removed with Method A: GeneVac EZ-2 Evaporator or Method B: Buchi R-215 rotavapor system.

Low resolution mass spectra were obtained on a Waters SQ Detector with ESI source, and a photodiode array detector. Method: MS parameters were as follows: Capillary voltage: 3000 V, drying gas flow: 650 L/hr, drying gas temperature: 450°C. Samples were induced via a Waters UPB binary solvent manager. UV absorption was observed at 215 nm and 254 nm with a 4nm bandwidth. Column: Waters Acquity UPLC® HSS C18, 2.1 x 50 mm, 1.8 µm. Gradient conditions: In 2 min. run: 5% to 100% CH_3CN in H_2O (0.1% TFA) over 1.4 min., hold at 100% CH_3CN for 0.4 min., flow rate: 1.0 mL/min., with column temperature at 50°C. In 5 min. run: 5% to 100% CH_3CN in H_2O (0.1% TFA) over 4.4 min., hold at 100% CH_3CN for 0.4 min., flow rate: 1.0 mL/min., with column temperature at 50°C. High resolution mass spectra (HRMS) were obtained on a Waters SQ Detector with ESI source. Column: Waters Acquity UPLC® HSS C18, 2.1 x 50 mm, 1.8 µm. Gradient conditions: 20% to 90% CH_3CN in H_2O (0.05% TFA) over 10 min., hold at 90% CH_3CN in H_2O for 1.5 min., flow rate: 0.3 mL/min., with column temperature at 40°C and auto sampler temperature at 10°C.

All NMR (nuclear magnetic resonance) spectra were recorded on a 500 MHz Bruker NMR spectrometer. ^1H and ^{13}C chemical shifts are reported in δ values in ppm (parts per million) downfield with the deuterated solvent as the internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), integration, coupling constant (Hz). Standard 2D COSY, ROESY, HSQC and HMBC experiments are utilized for the assignment of ^1H and ^{13}C resonances and structure elucidation.

II. Experimental Procedures and Spectroscopic Data of Informer Library

Table 1: Percentage of remaining informer/desired product in crude reaction mixture (reaction time). Reactions were carried out using catalytic photoredox C(sp^3)-C(sp^2) cross-coupling of the informer heterocyclic halides via decarboxylative coupling or cross-electrophile coupling using Integrated Photoreactor or Kessil Lamp.

	Method	LED device	Ir. cat.	X1 	X2 	X3 	X4 	X5 	X6 
	A	KL	1	0/26 (16h)	0/73 (16h)	0/<10 (16h)	0/68 (16h)	0/40 (16h)	0/40 (16h)
	B	IP	1	13/25 (1h)	0/69 (2h)	0/<10 (2h)	0/30 (2h)	0/50 (1h)	0/45 (1h)
	C	KL	1	90/<10 (16h)	64/<10 (16h)	85/0 (16h)	20/0 (16h)	94/0 (16h)	72/<10 (16h)
	D	IP	1	16/<10 (10h)	0/70 (2h)	59/<10 (8h)	52/18 (8h)	100/0 (4h)	0/20 (6h)
	E	IP	2	21/32 (12h)	6/56 (2h)	13/29 (3h)	21/37 (3h)	34/21 (12h)	11/23 (3h)
				X7 	X8 	X9 	X10 	X11 	X12 
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	B	IP	1	0/0 (2h)	0/40 (2h)	0/0 (2h)	0/0 (1h)	0/0 (1h)	0/35 (1h)
	C	KL	1	9/0 (16h)	100/0 (16h)	80/0 (16h)	31/0 (16h)	44/0 (16h)	93/<10 (16h)
	D	IP	1	0/0 (2h)	0/30 (5h)	40/0 (8h)	0/0 (2h)	22/0 (6h)	100/0 (6h)
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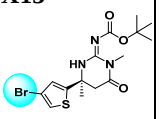
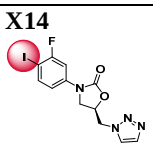
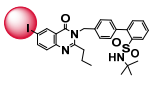
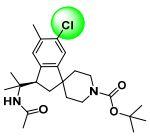
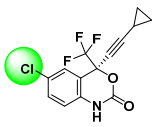
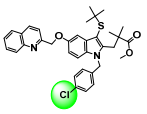
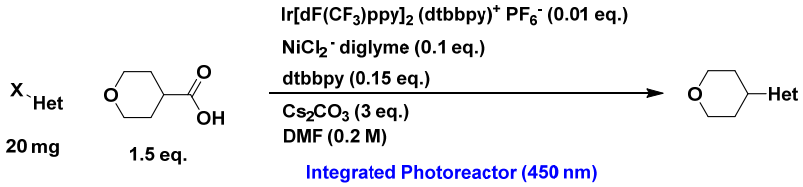
				X13 	X14 	X15 	X16 	X17 	X18 
	A	KL	1	0/26 (16h)	0/0 (16h)	0/0 (16h)	72/0 (16h)	0/0 (16h)	50/<10 (16h)
	B	IP	1	0/31 (1h)	0/0 (1h)	0/35 (1h)	57/0 (14h)	0/0 (2h)	33/<10 (2h)
	C	KL	1	93/<10 (16h)	87/0 (16h)	40/0 (16h)	0/0 (16h)	100/0 (16h)	84/0 (16h)
	D	IP	1	0/20 (10h)	91/0 (4h)	0/<10 (7h)	100/0 (2h)	100/0 (2h)	56/0 (2h)
	E	IP	2	14/20 (8h)	81/<10 (8h)	22/<10 (2h)	61/0 (8h)	100/0 (2h)	38/0 (2h)

KL – Kessil Lamp
IP – Integrated Photoreactor
Photocatalyst 1 - $(Ir[dF(CF_3)ppy]_2(dtbbpy))PF_6$
Photocatalyst 2 - $(Ir[dF(CH_3)ppy]_2(dtbbpy))PF_6$

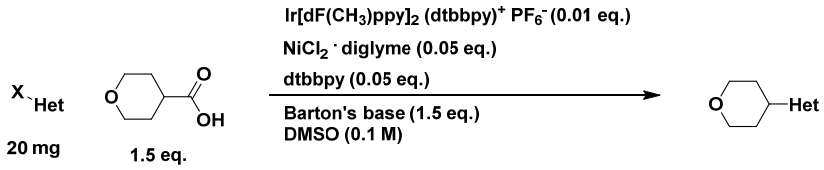
General Scheme 1: Catalytic photoredox C(sp^3)-C(sp^2) cross-coupling of informer heterocyclic halides with THP-COOH in the present of photocatalyst 1 using Integrated Photoreactor



General Procedure 1:

A 2-dram vial equipped with a stir bar was charged with Aryl-halide (20 mg), tetrahydropyran-2-carboxylic acid (1.5 eq.), 4,4'-di-*tert*-butyl-2,2'-bipyridine (0.15 eq.), ($Ir[dF(CF_3)ppy]_2(dtbbpy))PF_6$ (0.01 eq.), nickel(II) chloride ethylene glycol di-methyl ether complex (0.1 eq.) and cesium carbonate (3 eq.). It was transferred into glove box. Anhydrous DMF (0.2 M) was added into the reaction mixture. It was capped and taken out of glove box. Irradiated with Integrated Photoreactor for 0.5 h, Royal Blue (450 nm) LED light. 100% LED light power was applied. Stir rate was 1000 rpm. Fan rate was 4700 rpm. The reaction was checked with LCMS. If the reaction was not complete, let it run till the time indicated in **Table 1**. Reaction conversion was calculated based on AUC (area under curve) of LCMS spectra at 254 nm. Reaction Conversion = AUC of desired product / (AUC of desired product + AUC of by-product(s) + AUC of unreacted starting material). Results were shown in **Table 1**. For high conversion reaction, the following work-up procedure was applied. Reaction mixture was partitioned between EtOAc (2 mL) and water (0.5 mL). Aqueous layer was extracted with EtOAc (2 mL). The combined organic layers was concentrated with GeneVac to dryness. The residue was purified with semi-preparative reverse phase HPLC system, to afford the desired product. To obtain good NMR spectra, the residue could be further purified with prep. TLC and then micro-scale reverse phase HPLC system.

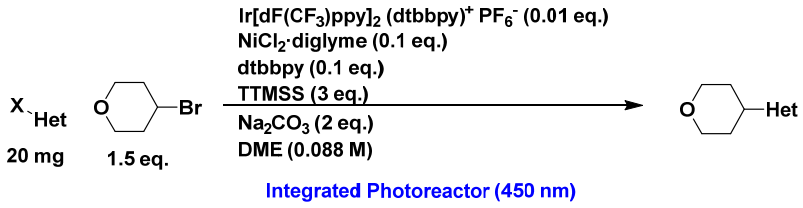
General Scheme 2: Catalytic photoredox C(sp^3)-C(sp^2) cross-coupling of informer heterocyclic halides with THP-COOH in the present of photocatalyst 2 using Integrated Photoreactor



General Procedure 2:

A 2-dram vial equipped with a stir bar was charged with Aryl-halide (20 mg), tetrahydropyran-2-carboxylic acid (1.5 eq.), 4,4'-di-*tert*-butyl-2,2'-bipyridine (0.05 eq.), ($Ir[dF(CH_3)ppy]_2(dtbbpy))PF_6$ (0.01 eq.), and nickel(II) chloride ethylene glycol di-methyl ether complex (0.05 eq.). It was transferred into glove box. Anhydrous DMSO (0.1 M) and Barton's base (1.5 eq.) were added into the reaction mixture. It was capped and taken out of glove box. Irradiated with Integrated Photoreactor for 1 h, Royal Blue (450 nm) LED light. 100% LED light power was applied. Stir rate was 1000 rpm. Fan rate was 4700 rpm. The reaction was checked with LCMS. If the reaction was not complete, let it run till the time indicated in **Table 1**. Reaction conversion was calculated based on AUC (area under curve) of LCMS spectra at 254 nm. Reaction Conversion = AUC of desired product / (AUC of desired product + AUC of by-product(s) + AUC of unreacted starting material). Results were shown in **Table 1**. For high conversion reaction, the following work-up procedure was applied. Reaction mixture was partitioned between EtOAc (2 mL) and water (0.5 mL). Aqueous layer was extracted with EtOAc (2 mL). The combined organic layers was concentrated with GeneVac to dryness. The residue was purified with semi-preparative reverse phase HPLC system, to afford the desired product. To obtain good NMR spectra, the residue could be further purified with prep. TLC and then micro-scale reverse phase HPLC system.

General Scheme 3: Catalytic photoredox C(sp^3)-C(sp^2) cross-coupling of informer heterocyclic halides with THP-Br using Integrated Photoreactor

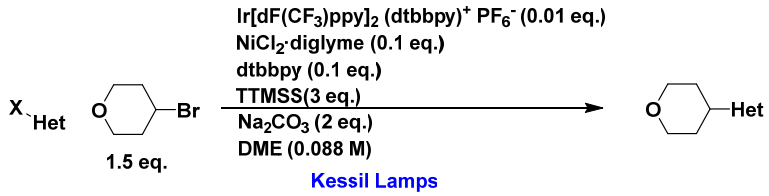


General Procedure 3:

A 2-dram vial equipped with a stir bar was charged with Aryl-halide (20 mg), 4,4'-di-*tert*-butyl-2,2'-bipyridine (0.1 eq.), ($Ir[dF(CF_3)ppy]_2(dtbbpy))PF_6$ (0.01 eq.), nickel(II) chloride ethylene glycol di-methyl ether complex (0.1 eq.) and sodium carbonate (2 eq.). It was transferred into glove box. Anhydrous 1,2-dimethoxyethane (0.088 M), 4-bromotetrahydro-2*H*-pyran (1.5 eq.), and TTMSS (3 eq.) were added into the reaction mixture. It was capped and taken out of glove box. Irradiated with Integrated

Photoreactor for 1 h, Royal Blue (450 nm) LED light. 100% LED light power was applied. Stir rate was 1000 rpm. Fan rate was 4700 rpm. The reaction was checked with LCMS. If the reaction was not complete, let it run for another hour. Reaction conversion was calculated based on AUC (area under curve) of LCMS spectra at 254 nm. Reaction Conversion = AUC of desired product / (AUC of desired product + AUC of by-product(s) + AUC of unreacted starting material). Results were shown in **Table 1**. For high conversion reaction, the following work-up procedure was applied. Reaction mixture was partitioned between EtOAc (2 mL) and water (0.5 mL). Aqueous layer was extracted with EtOAc (2 mL). The combined organic layers was concentrated with GeneVac to dryness. The residue was purified with semi-preparative reverse phase HPLC system, to afford the desired product. To obtain good LCMS and NMR spectra, the residue could be further purified with prep. TLC and then micro-scale reverse phase HPLC system.

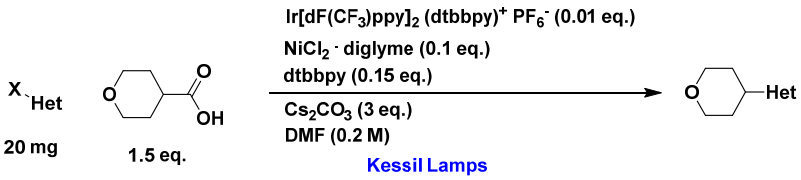
General Scheme 4: Catalytic photoredox C(sp^3)-C(sp^2) cross-coupling of informer heterocyclic halides with THP-Br using Kessil Lamps



General Procedure 4:

A 2-dram vial equipped with a stir bar was charged with Aryl-halide (0.05 mmol), 4,4'-di-*tert*-butyl-2,2'-bipyridine (0.1 eq.), $(Ir[dF(CF_3)ppy]_2(dtbbpy))PF_6$ (0.01 eq.), nickel(II) chloride ethylene glycol di-methyl ether complex (0.1 eq.) and sodium carbonate (2 eq.). It was transferred into glove box. Anhydrous DME (0.088 M), 4-bromotetrahydro-2*H*-pyran (1.5 eq.), and TTMSS (3 eq.) were added into each reaction mixture. It was capped and taken out of glove box. Each four or three reactions were irradiated with two Kessil Lamps for 16 h. Kessil lamps - Kessil KSH150B Grow Light Blue - were 7 cm away from reaction vessels. Cooling fan - electric fan from ebm-papst 4414FNH – was 6 cm above reaction vessels. Reaction vessels were taped on top of stirring plate, using double sided white Scotch Mounting Squares. The reactions were checked with LCMS. Reaction conversion was calculated based on AUC (area under curve) of LCMS spectra at 254 nm. Reaction Conversion = AUC of desired product / (AUC of desired product + AUC of by-product(s) + AUC of unreacted starting material).

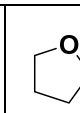
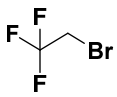
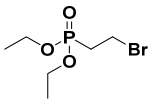
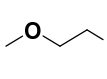
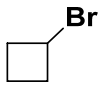
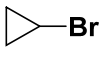
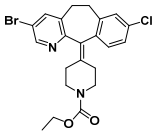
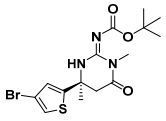
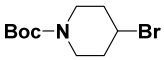
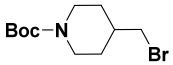
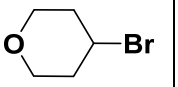
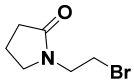
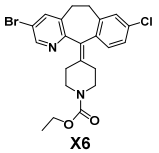
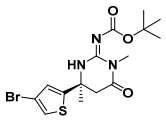
General Scheme 5: Catalytic photoredox C(sp^3)-C(sp^2) cross-coupling of informer heterocyclic halides with THP-COOH in the present of photocatalyst 1 using Kessil Lamps



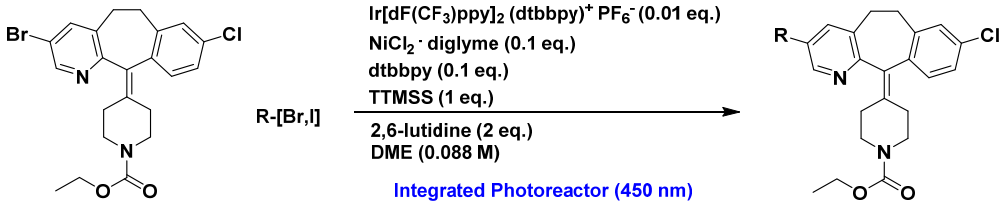
General Procedure 5:

A 2-dram vial equipped with a stir bar was charged with Aryl-halide (20 mg), tetrahydropyran-2-carboxylic acid (1.5 eq.), 4,4'-di-*tert*-butyl-2,2'-bipyridine (0.15 eq.), $(Ir[dF(CF_3)ppy]_2(dtbbpy))PF_6$ (0.01 eq.), nickel(II) chloride ethylene glycol di-methyl ether complex (0.1 eq.) and cesium carbonate (3 eq.). It was transferred into glove box. Anhydrous DMF (0.2 M) was added into the reaction mixture. It was capped and taken out of glove box. Each four or three reactions were irradiated with two Kessil Lamps for 16 h. Kessil lamps - Kessil KSH150B Grow Light Blue - were 7 cm away from reaction vessels. Cooling fan - electric fan from ebm-papst 4414FNH – was 6 cm above reaction vessels. Reaction vessels were taped on top of stirring plate, using double sided white Scotch Mounting Squares. The reactions were checked with LCMS. Reaction conversion was calculated based on AUC (area under curve) of LCMS spectra at 254 nm. Reaction Conversion = AUC of desired product / (AUC of desired product + AUC of by-product(s) + AUC of unreacted starting material).

Table 2. Percentage of desired product in crude reaction mixture for catalytic photoredox C(sp^3)-C(sp^2) cross-electrophile coupling with 12 aliphatic halides using Integrated Photoreactor

						
 X6	65	22	78	65	53	43
 X13	63	<10	74	62	47	33
						
 X6	52	38	45	48	57	40
 X13	55	70	55	77	22	42

General Scheme 6: Catalytic photoredox C(sp^3)-C(sp^2) cross-coupling of heterocyclic halide (X6) with 12 aliphatic halides using Integrated Photoreactor

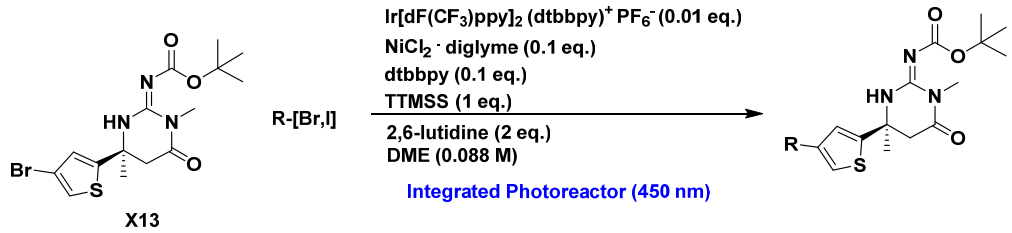


General Procedure 6:

A 2-dram vial equipped with a stir bar was charged with ethyl 4-(3-bromo-8-chloro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11(6*H*)-ylidene)piperidine-1-carboxylate (20 mg, 0.043 mmol), 4,4'-di-*tert*-butyl-2,2'-bipyridine (0.1 eq.), ($Ir[dF(CF_3)ppy]_2(dtbbpy))PF_6$ (0.01 eq.), and nickel(II) chloride ethylene glycol di-methyl ether complex (0.1 eq.). It was transferred into glove box. Anhydrous 1,2-dimethoxyethane (0.088 M), alkyl-halide (1.5 eq.), TTMSS (1 eq.) and 2,6-lutidine (2 eq.) were added into the reaction mixture. It was capped and taken out of glove box. Irradiated with Integrated Photoreactor, Royal Blue (450 nm) LED light for 1 h, with 100% LED light power. Stir rate was 1000 rpm. Fan rate was 4700 rpm. The reaction was checked with LCMS. If the reaction was not complete, the reaction mixture would be irradiated with Integrated Photoreactor for 1 more hour. The reactions were checked with LCMS. Reaction conversion was calculated based on AUC (area under curve) of LCMS spectra at 254 nm. Reaction Conversion = AUC of desired product / (AUC of desired product + AUC of by-product(s) + AUC of unreacted starting material). The following work-up procedure was applied. Reaction mixture was partitioned between EtOAc (2 mL) and water (0.5 mL). Aqueous layer was extracted with EtOAc (2 mL). The combined organic layers was concentrated with GeneVac to dryness. The residue was purified with semi-preparative reverse phase HPLC system, to afford the desired product. It

could be further purified with prep. TLC plate (in 60% EtOAc/heptane or 5% MeOH/EtOAc), followed by micro-scale reverse phase HPLC purification.

General Scheme 7: Catalytic photoredox C(sp^3)-C(sp^2) cross-coupling of heterocyclic halide (X13) with 12 aliphatic halides using Integrated Photoreactor

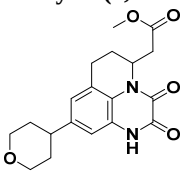


General Procedure 7:

A 2-dram vial equipped with a stir bar was charged with *tert*-butyl (*S*,*Z*)-(4-(4-bromothiophen-2-yl)-1,4-dimethyl-6-oxotetrahydropyrimidin-2(1*H*)-ylidene)carbamate (20 mg, 0.05 mmol), 4,4'-di-*tert*-butyl-2,2'-bipyridine (0.1 eq.), (Ir[dF(CF_3)ppy]$_2$(dtbbpy))PF_6 (0.01 eq.), and nickel(II) chloride ethylene glycol di-methyl ether complex (0.1 eq.). It was transferred into glove box. Anhydrous 1,2-dimethoxyethane (0.088 M), alkyl-halide (1.5 eq.), TTMSS (1 eq.) and 2,6-lutidine (2 eq.) were added into the reaction mixture. It was capped and taken out of glove box. Irradiated with Integrated Photoreactor, Royal Blue (450 nm) LED light for 1 h, with 100% LED light power. Stir rate was 1000 rpm. Fan rate was 4700 rpm. The reaction was checked with LCMS. If the reaction was not complete, the reaction mixture would be irradiated with Integrated Photoreactor for 1 more hour. The reactions were checked with LCMS. Reaction conversion was calculated based on AUC (area under curve) of LC/MS spectra at 254 nm. Reaction Conversion = AUC of desired product / (AUC of desired product + AUC of by-product(s) + AUC of unreacted starting material). The following work-up procedure was applied. Reaction mixture was partitioned between EtOAc (2 mL) and water (0.5 mL). Aqueous layer was extracted with EtOAc (2 mL). The combined organic layers was concentrated with GeneVac to dryness. The residue was purified with semi-preparative reverse phase HPLC system, to afford the desired product. To obtain good NMR spectra, the residue could be further purified with prep. TLC and then micro-scale reverse phase HPLC system.

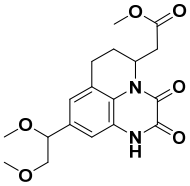
Examples:

methyl 2-(2,3-dioxo-9-(tetrahydro-2*H*-pyran-4-yl)-2,3,6,7-tetrahydro-1*H*,5*H*-pyrido[1,2,3-*de*]quinoxalin-5-yl)acetate (1)



General procedure 3 was followed where **X1**, methyl 2-(9-bromo-2,3-dioxo-2,3,6,7-tetrahydro-1*H*, 5*H*-pyrido[1,2,3-*de*]quinoxalin-5-yl)acetate, was used as aryl-halide. Reaction mixture was partitioned between EtOAc (2 mL) and water (0.5 mL). Aqueous layer was extracted with EtOAc (2 mL). The combined organic layers was concentrated with GeneVac to dryness. General procedure 2 was also applied. The crude materials were combined and purified with prep. TLC plate (in 5% MeOH/EtOAc). R_f = 0.26 (in 5% MeOH/EtOAc). The band containing desired product was scratched off, stirred with 5% MeOH/EtOAc (30 mL) for 0.5 h. Then it was filtered and the filtrate was concentrated with GeneVac. The residue was further purified with Mass Directed HPLC system under TFA condition (0.16% TFA in both CH_3CN and H_2O, 12 min. run, 25 mL/min., 10 – 40% CH_3CN), to afford the title compound **1**, 10.5 mg (98% pure), as off-white solid. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 11.96 (s, 1H), 6.93 (s, 1H), 6.90 – 6.88 (m, 1H), 5.13 – 5.07 (m, 1H), 3.95 (dd, *J* = 11.0, 3.5 Hz, 2H), 3.63 (s, 3H), 3.47 – 3.40 (m, 2H), 2.99 – 2.90 (m, 1H), 2.81 – 2.69 (m, 2H), 2.62 (m, 2H), 2.15 – 2.09 (m, 1H), 1.91 (tt, *J* = 13.8, 4.6 Hz, 1H), 1.72 – 1.56 (m, 4H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 171.21, 154.47, 154.14, 141.46, 126.05, 124.85, 122.17, 121.34, 111.84, 67.72, 52.14, 47.48, 40.42, 35.42, 34.04, 23.31, 21.63. Chemical Formula of $[M+H]^+$: $C_{19}H_{23}N_2O_5^+$; Exact Mass (calculated): 359.1601; **HRMS (ESI$^+$)** (found): 359.1616.

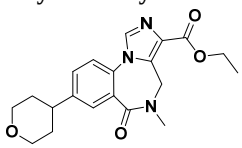
methyl 2-(9-(1,2-dimethoxyethyl)-2,3-dioxo-2,3,6,7-tetrahydro-1*H*, 5*H*-pyrido[1,2,3-*de*]quinoxalin-5-yl)acetate (2)



During the preparation of compound **1**, a by-product, methyl 2-(9-(1,2-dimethoxyethyl)-2,3-dioxo-2,3,6,7-tetrahydro-1*H*, 5*H*-pyrido[1,2,3-*de*]quinoxalin-5-yl)acetate, compound **2**, 1.6 mg (85% pure), as light brown solid, was also isolated. It was formed in General procedure 3 where DME was used as solvent. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.11 (s, 1H), 7.07 (s, 1H), 5.46 – 5.41 (m, 1H), 4.38 (dd, *J* = 7.3, 3.9 Hz, 1H), 3.73 (s, 3H), 3.59 (dd, *J* = 10.0, 7.7 Hz, 1H), 3.46 (dd, *J* = 10.4, 4.0 Hz, 1H), 3.39 (d, *J* =

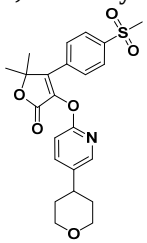
0.7 Hz, 3H), 3.30 (s, 3H), 3.09 – 2.98 (m, 1H), 2.92 – 2.84 (m, 1H), 2.82 (dd, *J* = 15.2, 4.9 Hz, 1H), 2.59 (dd, *J* = 14.9, 9.5 Hz, 1H), 2.36 – 2.31 (m, 1H), 2.03 (ddt, *J* = 14.1, 9.6, 4.7 Hz, 1H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 170.45, 155.45, 154.01, 135.66, 125.12, 124.44, 123.30, 122.42, 113.56, 81.80, 76.51, 59.26, 57.20, 52.16, 48.05, 35.26, 23.15, 21.79. LCMS R_T = 1.26 min. (5 min. run); Chemical Formula of $[M+H]^+$: $C_{18}H_{23}N_2O_6^+$; Exact Mass (calculated): 363.16; **Exact Mass (ESI$^+$)** (found): 363.17.

ethyl 5-methyl-6-oxo-8-(tetrahydro-2*H*-pyran-4-yl)-5,6-dihydro-4*H*-benzo[*f*]imidazo[1,5-*a*][1,4]diazepine-3-carboxylate (3)



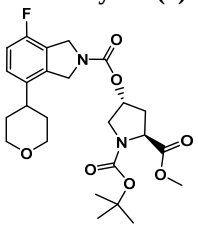
General procedure 3 was followed where **X2**, ethyl 8-bromo-5-methyl-6-oxo-5,6-dihydro-4*H*-benzo[*f*]imidazo[1,5-*a*][1,4]diazepine-3-carboxylate, was used as aryl-halide. Reaction mixture was partitioned between EtOAc (2 mL) and water (0.5 mL). Aqueous layer was extracted with EtOAc (2 mL). The combined organic layers was concentrated with GeneVac to dryness. General procedure 1, 2 and 4 were also applied. The crude materials were combined and purified with Mass Directed HPLC system under TFA condition (0.16% TFA in both CH_3CN and H_2O, 12 min. run, 25 mL/min., 10 – 40% CH_3CN), to afford the title compound **3** as TFA salt, 58 mg (100% pure), colorless oil. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.39 (d, *J* = 2.1 Hz, 1H), 7.78 (d, *J* = 1.5 Hz, 1H), 7.71 – 7.65 (m, 2H), 4.96 (s, 1H), 4.48 (s, 1H), 4.33 (s, 2H), 3.98 (dd, *J* = 10.8, 3.5 Hz, 2H), 3.47 (td, *J* = 11.4, 2.3 Hz, 2H), 3.11 (s, 3H), 2.95 (ddt, *J* = 11.4, 8.3, 4.1 Hz, 1H), 1.79 – 1.67 (m, 4H), 1.35 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 166.21, 162.72, 146.44, 136.83, 135.87, 131.52, 130.50, 130.17, 128.93, 127.78, 123.45, 67.69, 60.59, 42.48, 40.44, 35.59, 33.65, 14.70. Chemical Formula of $[M+H]^+$: $C_{20}H_{24}N_3O_4^+$; Exact Mass (calculated): 370.1761; **HRMS (ESI$^+$)** (found): 370.1772.

5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-3-((5-(tetrahydro-2*H*-pyran-4-yl)pyridine-2-yl)oxy)furan-2(5*H*)-one (4)



General procedure 2 was followed where **X3**, 3-((5-bromopyrifin-2-yl)oxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)furan-2(5*H*)-one, was used as aryl-halide. Reaction mixture was partitioned between EtOAc (2 mL) and water (0.5 mL). Aqueous layer was extracted with EtOAc (2 mL). The combined organic layers was concentrated with GeneVac to dryness. General procedure 1, 3 and 4 were also applied. The crude materials were combined and purified with Mass Directed HPLC system under TFA condition (0.16% TFA in both CH_3CN and H_2O, 12 min. run, 25 mL/min., 25 – 55% CH_3CN), to afford the title compound as TFA salt, 8.4 mg (94% pure), light yellow oil. It was further purified with prep. TLC plate (in 2% MeOH/EtOAc). R_f = 0.54 (in 2% MeOH/EtOAc). The band containing desired product was scratched off, stirred with 2% MeOH/EtOAc (30 mL) for 0.5 h. Then it was filtered and the filtrate was concentrated with GeneVac. Followed by micro-scale HPLC under TFA condition (0.16% TFA in both CH_3CN and H_2O, 12 min. run, 8 mL/min., 25 – 55% CH_3CN), to afford the title compound **4** as TFA salt, less than1 mg (95% pure), colorless oil. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.08 (d, *J* = 2.4 Hz, 1H), 8.04 – 8.01 (m, 2H), 7.88 – 7.86 (m, 2H), 7.80 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.11 (d, *J* = 8.5 Hz, 1H), 3.97 – 3.93 (m, 2H), 3.42 (td, *J* = 11.2, 3.8 Hz, 2H), 3.25 (s, 3H), 2.81 (tt, *J* = 10.8, 6.1 Hz, 1H), 1.72 (s, 6H), 1.68 (m, 4H). Chemical Formula of $[M+H]^+$: $C_{23}H_{26}NO_6S^+$; Exact Mass (calculated): 444.1475; **HRMS (ESI$^+$)** (found): 444.1491. NOTE: Due to low amount of the material, ^{1}H NMR spectra showed peaks of NH_4OH which was induced during HPLC fraction drying down with GeneVac system.

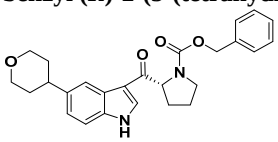
1-(*tert*-butyl) 2-methyl (2*S*,4*R*)-4-4-((4-fluoro-7-(tetrahydro-2*H*-pyran-4-yl)isoindoline-2-carbonyl)oxy)pyrrolidine-1,2-dicarboxylate (5)



General procedure 2 was followed where **X4**, 1-(*tert*-butyl) 2-methyl (2*S*,4*R*)-4-((4-bromo-7-fluoroisoindoline-2-carbonyl)oxy)pyrrolidine-1,2-dicarboxylate, was used as aryl-halide. Reaction mixture was partitioned between EtOAc (2 mL) and water (0.5 mL). Aqueous layer was extracted with EtOAc (2 mL). The combined organic layers was concentrated with GeneVac to dryness. General procedure 1, 3 and 4 were also applied. The crude materials were combined and purified with Mass Directed HPLC system under NH_4OH condition (0.16% NH_4OH in both CH_3CN and H_2O, 12 min. run, 25 mL/min., 25 – 55% CH_3CN), to afford 48 mg (56% pure) of light brown oil. It was further purified with prep. TLC plate (in 2% MeOH/EtOAc). R_f = 0.61 (in 2%

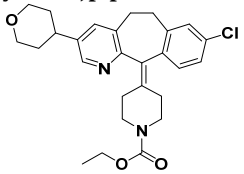
MeOH/EtOAc). The band containing desired product was scratched off, stirred with 2% MeOH/EtOAc (30 mL) for 0.5 h. Then it was filtered and the filtrate was concentrated with GeneVac. Followed by Mass Directed HPLC system under TFA condition (0.16% TFA in both CH_3CN and H_2O, 12 min. run, 25 mL/min., 40 – 75% CH_3CN), to afford the title compound **5**, 3.4 mg (95% pure), light brown oil. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 7.29 – 7.24 (m, 1H), 7.12 (t, *J* = 8.8 Hz, 1H), 5.20 (s, 1H), 4.79 – 4.66 (m, 4H), 4.38 (dq, *J* = 16.9, 8.1 Hz, 1H), 3.94 (d, *J* = 10.1 Hz, 2H), 3.70 (s, 2H), 3.69 – 3.66 (m, 1H), 3.66 – 3.51 (m, 2H), 3.46 (t, *J* = 11.0 Hz, 2H), 2.80 – 2.64 (m, 1H), 2.45 (m, 1H), 2.20 (m, 1H), 1.74 – 1.60 (m, 4H), 1.39 (m, 9H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 173.26, 154.97, 153.78, 138.04, 137.24, 127.46, 123.58, 114.93, 79.94, 73.21, 67.77, 58.01, 52.60, 52.49, 51.91, 49.49, 37.89, 36.58, 33.06, 28.30. Chemical Formula of $[M+H]^+$: $C_{25}H_{34}FN_2O_7^+$; Exact Mass (calculated): 493.2345; **HRMS (ESI$^+$)** (found): 493.2367.

benzyl (*R*)-2-(5-(tetrahydro-2*H*-pyran-4-yl)-1*H*-indole-3-carbonyl)pyrrolidine-1-carboxylate (6)



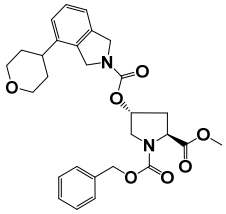
General procedure 3 was followed where **X5**, benzyl (*R*)-2-(5-bromo-1*H*-indole-3-carbonyl)pyrrolidine-1-carboxylate, was used as aryl-halide. Reaction mixture was partitioned between EtOAc (2 mL) and water (0.5 mL). Aqueous layer was extracted with EtOAc (2 mL). The combined organic layers was concentrated with GeneVac to dryness. General procedure 2 was also applied. The crude materials were combined and purified with Mass Directed HPLC system under TFA condition (0.16% TFA in both CH_3CN and H_2O, 8 min. run, 25 mL/min., 30 – 65% CH_3CN), to afford 34.7 mg (56% pure) of off-white solid. It was further purified with prep. TLC plate (in 5% MeOH/EtOAc). R_f = 0.60 (in 5% MeOH/EtOAc). The band containing desired product was scratched off, stirred with 5% MeOH/EtOAc (30 mL) for 0.5 h. Then it was filtered and the filtrate was concentrated with GeneVac. Followed by micro-scale HPLC under NH_4OH condition (0.16% NH_4OH in both CH_3CN and H_2O, 6 min. run, 8 mL/min., 25 – 60% CH_3CN), to afford the title compound **6**, 1.4 mg (95% pure), off-white solid. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 11.93 (d, *J* = 8.1 Hz, 1H), 8.41 (dd, *J* = 11.1, 3.1 Hz, 1H), 8.08 (d, *J* = 22.8 Hz, 1H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.41 – 7.37 (m, 2H), 7.18 – 7.14 (m, 1H), 7.12 – 7.08 (m, 2H), 7.04 – 6.99 (m, 1H), 5.21 (ddd, *J* = 27.0, 8.6, 3.3 Hz, 1H), 5.12 – 5.04 (m, 1H), 5.01 – 4.90 (m, 1H), 3.98 (m, 2H), 3.58 – 3.51 (m, 2H), 3.48 (ddt, *J* = 14.4, 6.9, 3.3 Hz, 2H), 2.86 (ddq, *J* = 15.6, 9.6, 4.9 Hz, 1H), 2.46 – 2.28 (m, 1H), 1.89 (qq, *J* = 12.6, 5.8 Hz, 3H), 1.79 – 1.65 (m, 4H). Chemical Formula of $[M+H]^+$: $C_{26}H_{29}N_2O_4^+$; Exact Mass (calculated): 433.2122; **HRMS (ESI$^+$)** (found): 433.2129.

ethyl 4-(8-chloro-3-(tetrahydro-2H-pyran-4-yl)l-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine-11-ylidene)piperidine-1-carboxylate (7)



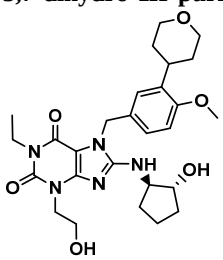
General procedure 6 was followed where 4-bromotetrahydro-2*H*-pyran was used as alkyl-halide. The reaction mixture was purified with prep. TLC plate (in 5% MeOH/EtOAc). R_f = 0.31 (in 5% MeOH/EtOAc). The band containing desired product was scratched off, stirred with 5% MeOH/EtOAc (30 mL) for 0.5 h. Then it was filtered and the filtrate was concentrated with GeneVac. The residue was further purified with SFC (supercritical fluid chromatography) - Instrument: Thar 80 SFC; Column: Chiralpak AS-H, 5um, 21 x 250mm; Conditions: 20% MeOH/ACN 1:1 + 0.2% DIPA (diisopropylamine) @ 50 g/min, 120 bar, 40°C, 210 nm. The fraction containing desired product was concentrated with rotovap, which was purified with Mass Directed HPLC system under TFA condition (0.16% TFA in both CH_3CN and H_2O, 12 min. run, 25 mL/min., 20 – 55% CH_3CN), to afford the title compound **7** as TFA salt, 6.5 mg, light yellow oil. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.54 (s, 1H), 8.21 (s, 1H), 7.43 (d, *J* = 1.9 Hz, 1H), 7.32 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.14 (d, *J* = 8.2 Hz, 1H), 4.06 (q, *J* = 7.0 Hz, 2H), 3.99 – 3.94 (m, 2H), 3.84 – 3.77 (m, 1H), 3.70 (dt, *J* = 10.2, 4.7 Hz, 1H), 3.43 (m, 3H), 3.36 (dq, *J* = 10.4, 5.1 Hz, 1H), 3.13 (s, 2H), 2.99 (ddt, *J* = 21.7, 15.9, 8.2 Hz, 2H), 2.90 (dt, *J* = 15.1, 5.4 Hz, 1H), 2.37 (ddd, *J* = 14.2, 9.6, 4.7 Hz, 1H), 2.27 (m, 2H), 2.16 (dt, *J* = 14.0, 4.0 Hz, 1H), 1.74 (m, 4H), 1.19 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 154.98, 143.15, 140.54, 139.82, 137.13, 136.90, 133.08, 130.88, 129.57, 126.78, 67.47, 61.27, 44.18, 38.05, 32.81, 30.73, 30.22, 15.07. Chemical Formula of $[M+H]^+$: $C_{27}H_{32}ClN_2O_3^+$; Exact Mass (calculated): 467.2096; **HRMS (ESI$^+$)** (found): 467.2110.

1-benzyl 2-methyl (2*S*, 4*R*)-4-((4-(tetrahydro-2*H*-pyran-4-yl)isoindoline-2-carbonyl)oxy)pyrrolidine-1,2-dicarboxylate (8)



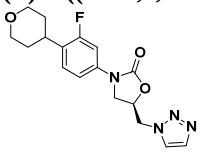
General procedure 3 was followed where **X8**, 1-benzyl 2-methyl (2*S*,4*R*)-4-((4-bromoisoindoline-2-carbonyl)oxy)pyrrolidine-1,2-dicarboxylate, was used as aryl-halide. Reaction mixture was partitioned between EtOAc (2 mL) and water (0.5 mL). Aqueous layer was extracted with EtOAc (2 mL). The combined organic layers was concentrated with GeneVac to dryness. General procedure 2 was also applied. The crude materials were combined and purified with Mass Directed HPLC system under TFA condition (0.16% TFA in both CH_3CN and H_2O, 8 min. run, 25 mL/min., 40 – 75% CH_3CN), to afford 27.7 mg (50% pure) of light brown oil. It was further purified with prep. TLC plate (in 5% MeOH/EtOAc). R_f = 0.70 (in 5% MeOH/EtOAc). The band containing desired product was scratched off, stirred with 5% MeOH/EtOAc (30 mL) for 0.5 h. Then it was filtered and the filtrate was concentrated with GeneVac. Followed by Mass Directed HPLC system under TFA condition (0.16% TFA in both CH_3CN and H_2O, 12 min. run, 25 mL/min., 40 – 70% CH_3CN), to afford the title compound **8**, 9.7 mg (100% pure), colorless oil. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 7.33 (m, 6H), 7.22 – 7.15 (m, 2H), 5.22 (s, 1H), 5.16 – 4.98 (m, 2H), 4.65 (m, 4H), 4.55 – 4.42 (m, 1H), 3.97 – 3.91 (m, 2H), 3.80 – 3.55 (m, 5H), 3.51 – 3.40 (m, 2H), 2.74 (m, 1H), 2.50 – 2.41 (m, 1H), 2.24 (m, 1H), 1.74 – 1.60 (m, 4H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 172.90, 154.53, 153.93, 141.03, 137.23, 136.95, 134.66, 128.80, 127.84, 124.83, 120.94, 73.67, 67.82, 66.75, 57.71, 53.17, 52.97, 52.58, 51.51, 38.43, 35.75, 32.98. Chemical Formula of $[M+H]^+$: $C_{28}H_{33}N_2O_7^+$; Exact Mass (calculated): 509.2282; **HRMS (ESI$^+$)** (found): 509.2297.

1-ethyl-8-(((1*R*,2*R*)-2-hydroxycyclopentyl)amino)-3-(2-hydroxyethyl)-7-(4-methoxy-3-(tetrahydro-2*H*-pyran-4-yl)benzyl)-3,7-dihydro-1*H*-purine-2,6-dione (9)



General procedure 3 was followed where **X12**, 7-(3-bromo-4-methoxybenzyl)-1-ethyl-8-(((1*R*,2*R*)-2-hydroxycyclopentyl)amino)-3-(3-hydroxyethyl)-3,7-dihydro-1*H*-purine-2,6-dione, was used as aryl-halide. Reaction mixture was partitioned between EtOAc (2 mL) and water (0.5 mL). Aqueous layer was extracted with EtOAc (2 mL). The combined organic layers was concentrated with GeneVac to dryness. General procedure 4 was also applied. The crude materials were combined and purified with Mass Directed HPLC system under TFA condition (0.16% TFA in both CH_3CN and H_2O, 15 min. run, 25 mL/min., 13 – 48% CH_3CN), to afford 12.5 mg (55% pure) of off-white solid. It was further purified with prep. TLC plate (in 5% MeOH/EtOAc). R_f = 0.36 (in 5% MeOH/EtOAc). The band containing desired product was scratched off, stirred with 5% MeOH/EtOAc (30 mL) for 0.5 h. Then it was filtered and the filtrate was concentrated with GeneVac. Followed by micro-scale HPLC under NH_4OH condition (0.16% NH_4OH in both CH_3CN and H_2O, 12 min. run, 8 mL/min., 15 – 36% CH_3CN), to afford the title compound **9**, less than1 mg (100% pure), off-white solid. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 7.31 (d, J = 2.1 Hz, 1H), 7.14 (dd, J = 8.4, 2.1 Hz, 1H), 6.97 (d, J = 6.7 Hz, 1H), 6.90 (d, J = 8.5 Hz, 1H), 5.24 (s, 2H), 4.79 (t, J = 5.8 Hz, 1H), 4.76 (d, J = 4.2 Hz, 1H), 3.98 (p, J = 6.8, 6.3 Hz, 3H), 3.94 – 3.85 (m, 5H), 3.75 (s, 3H), 3.62 (q, J = 6.4 Hz, 2H), 3.42 (td, J = 11.2, 5.3 Hz, 2H), 3.12 – 3.02 (m, 1H), 2.06 (td, J = 13.3, 7.8 Hz, 1H), 1.92 – 1.81 (m, 1H), 1.67 (m, 2H), 1.58 (m, 4H), 1.53 – 1.45 (m, 2H), 1.10 (t, J = 7.0 Hz, 3H). Chemical Formula of $[M+H]^+$: $C_{27}H_{38}N_5O_6^+$; Exact Mass (calculated): 528.2817; **HRMS (ESI$^+$)** (found): 528.2839.

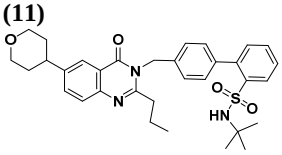
(*R*)-5-((1*H*-1,2,3-triazol-1-yl)methyl)-3-(3-fluoro-4-(tetrahydro-2*H*-pyran-4-yl)phenyl)oxazolidin-2-one (10)



General procedure 2 was followed where **X14**, (*R*)-5-((1*H*-1,2,3-triazol-1-yl)methyl)-3-(3-fluoro-4-iodophenyl)oxazolidin-2-one, was used as aryl-halide. Reaction mixture was partitioned between EtOAc (2 mL) and water (0.5 mL). Aqueous layer was extracted with EtOAc (2 mL). The combined organic layers was concentrated with GeneVac to dryness. The residue was purified with Mass Directed HPLC system under TFA condition (0.16% TFA in both CH_3CN and H_2O, 8 min. run, 25 mL/min., 15 – 50% CH_3CN), to afford 2 mg (57% pure) of brown oil. It was further purified with micro-scale HPLC under NH_4OH condition (0.16% NH_4OH in both CH_3CN and H_2O, 6 min. run, 8 mL/min., 11 – 45% CH_3CN), to afford the title compound **10**, 0.4 mg (100% pure), light yellow oil. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.18 (d, J = 0.8 Hz, 1H), 7.77 (d, J = 0.7 Hz, 1H), 7.42 – 7.32 (m, 2H), 7.21 (dd, J = 8.5,

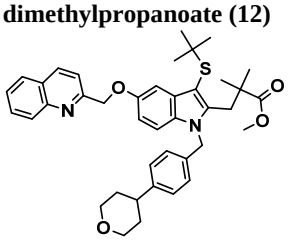
2.2 Hz, 1H), 5.15 (dq, *J* = 10.6, 5.3 Hz, 1H), 4.84 (d, *J* = 5.1 Hz, 2H), 4.24 (t, *J* = 9.2 Hz, 1H), 3.95 (dd, *J* = 10.9, 3.8 Hz, 2H), 3.89 (dd, *J* = 9.4, 5.7 Hz, 1H), 3.46 (td, *J* = 11.6, 1.9 Hz, 2H), 3.02 (tt, *J* = 11.9, 3.8 Hz, 1H), 1.72 (qd, *J* = 12.4, 4.1 Hz, 2H), 1.64 (d, *J* = 10.9 Hz, 2H). Chemical Formula of $[M+H]^+$: $C_{17}H_{20}FN_4O_3^+$; Exact Mass (calculated): 347.1514; **HRMS (ESI$^+$)** (found): 347.1523.

***N*-(*tert*-butyl)-4'-((4-oxo-2-propyl-6-(tetrahydro-2*H*-pyran-4-yl)quinazolin-3(4*H*)-yl)methyl)-[1,1'-biphenyl]-2-sulfonamide (11)**



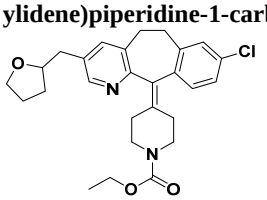
General procedure 3 was followed where **X15**, *N*-(*tert*-butyl)-4'-((6-iodo-4-oxo-2-propylquinazolin-3(4*H*)-yl)methyl)-[1,1'-biphenyl]-2-sulfonamide, was used as aryl-halide. Reaction mixture was partitioned between EtOAc (2 mL) and water (0.5 mL). Aqueous layer was extracted with EtOAc (2 mL). The combined organic layers was concentrated with GeneVac to dryness. The residue was purified with prep. TLC plate (in 5% MeOH/EtOAc). R_f = 0.74 (in 5% MeOH/EtOAc). The band containing desired product was scratched off, stirred with 5% MeOH/EtOAc (30 mL) for 0.5 h. Then it was filtered and the filtrate was concentrated with GeneVac. The residue was further purified with micro-scale HPLC under NH_4OH condition (0.16% NH_4OH in both CH_3CN and H_2O, 12 min. run, 8 mL/min., 40 – 75% CH_3CN), to afford the title compound **11**, 0.2 mg (100% pure), off-white solid. **^{1}H NMR** (500 MHz, DMSO-d_6) δ δ 8.04 (dd, *J* = 7.9, 1.2 Hz, 1H), 8.02 (d, *J* = 2.0 Hz, 1H), 7.78 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.66 – 7.60 (m, 2H), 7.56 (td, *J* = 7.7, 1.4 Hz, 1H), 7.39 (d, *J* = 8.3 Hz, 2H), 7.30 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.21 (d, *J* = 8.2 Hz, 2H), 6.55 (s, 1H), 5.46 (s, 2H), 3.99 (dd, *J* = 10.8, 3.6 Hz, 2H), 3.48 (td, *J* = 11.5, 2.1 Hz, 2H), 3.02 – 2.93 (m, 1H), 2.77 (t, *J* = 7.4 Hz, 2H), 1.83 – 1.66 (m, 6H), 0.96 (s, 9H), 0.94 (t, *J* = 7.4 Hz, 3H). Chemical Formula of $[M+H]^+$: $C_{33}H_{40}N_3O_4S^+$; Exact Mass (calculated): 574.2734; **HRMS (ESI$^+$)** (found): 574.2753.

methyl 3-(3-(*tert*-butylthio)-5-(quinolin-2ylmethoxy)-1-(4-(tetrahydro-2*H*-pyran-4-yl)benzyl)-1*H*-indol-2-yl)2,2-dimethylpropanoate (12)



General procedure 3 was followed where **X18**, methyl 3-(3-(*tert*-butylthio)-1-(4-chlorobenzyl)-5-(quinolin-2-ylmethoxy)-1*H*-indol-2-yl)-2,2-dimethylpropanoate, was used as aryl-halide. Reaction mixture was partitioned between EtOAc (2 mL) and water (0.5 mL). Aqueous layer was extracted with EtOAc (2 mL). The combined organic layers was concentrated with GeneVac to dryness. General procedure 4 was also applied. The crude materials were combined and purified with Mass Directed HPLC system under TFA condition (0.16% TFA in both CH_3CN and H_2O, 8 min. run, 25 mL/min., 45 – 80% CH_3CN), to afford 4 mg (45% pure) of light yellow oil. It was further purified with micro-scale HPLC under NH_4OH condition (0.16% NH_4OH in both CH_3CN and H_2O, 12 min. run, 8 mL/min., 55 – 80% CH_3CN), to afford the title compound **12**, 0.4 mg (100% pure), off-white solid. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.45 (d, *J* = 8.5 Hz, 1H), 8.09 (d, *J* = 8.5 Hz, 1H), 8.02 (d, *J* = 8.3 Hz, 1H), 7.85 – 7.82 (m, 1H), 7.72 (d, *J* = 8.5 Hz, 1H), 7.65 (t, *J* = 7.5 Hz, 1H), 7.29 (d, *J* = 8.9 Hz, 1H), 7.15 – 7.11 (m, 3H), 6.89 (dd, *J* = 8.9, 2.5 Hz, 1H), 6.76 (d, *J* = 8.2 Hz, 2H), 5.43 (s, 2H), 5.41 (s, 2H), 3.90 (dd, *J* = 10.4, 2.9 Hz, 2H), 3.60 (s, 3H), 3.38 (td, *J* = 11.3, 3.2 Hz, 2H), 3.21 (s, 2H), 2.68 (td, *J* = 10.8, 4.8 Hz, 1H), 1.60 (m, 4H), 1.13 (s, 6H), 1.01 (s, 9H). Chemical Formula of $[M+H]^+$: $C_{40}H_{47}N_2O_4S^+$; Exact Mass (calculated): 651.3251; **HRMS (ESI$^+$)** (found): 651.3273.

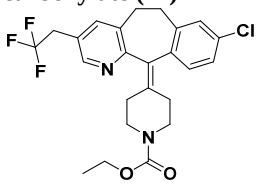
ethyl 4-(8-chloro-3-((tetrahydrofuran-2-yl)methyl)-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine-11-ylidene)piperidine-1-carboxylate (13)



General procedure 6 was followed where 2-(bromomethyl)tetrahydrofuran was used as alkyl-halide. It was purified with Mass Directed HPLC system under TFA condition (0.16% TFA in both CH_3CN and H_2O, 12 min. run, 25 mL/min., 25 – 60% CH_3CN) to afford the title compound **13** as TFA salt, 6.8 mg (91% pure), as colorless oil. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.22 (s, 1H), 7.46 (s, 1H), 7.32 (s, 1H), 7.22 (dd, *J* = 8.1, 2.2 Hz, 1H), 7.09 (d, *J* = 8.2 Hz, 1H), 4.05 (q, *J* = 7.1 Hz, 2H), 3.94 (h, *J* = 6.5 Hz, 1H), 3.79 – 3.73 (m, 1H), 3.65 – 3.54 (m, 3H), 3.31 – 3.24 (m, 2H), 3.18 (m, 2H), 2.84 – 2.77 (m, 2H), 2.74 – 2.66 (m, 2H), 2.37 – 2.32 (m, 1H), 2.32 – 2.25 (m, 1H), 2.20 – 2.16 (m, 2H), 1.95 – 1.86 (m, 1H), 1.85 – 1.73 (m, 2H), 1.49 (dddd, *J* = 13.9, 8.7, 5.6, 2.3 Hz, 1H), 1.18 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (126 MHz, DMSO) δ 155.01, 147.17, 140.76, 138.71, 136.96, 133.74, 133.01, 132.04, 130.97,

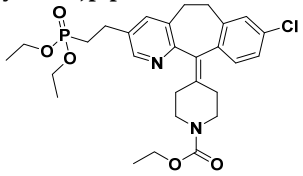
129.30, 126.17, 79.18, 67.41, 61.15, 44.85, 40.03, 38.19, 31.14, 30.65, 25.53, 15.08. Chemical Formula of $[M+H]^+$: $C_{27}H_{32}ClN_2O_3^+$; Exact Mass (calculated): 467.2096; **HRMS (ESI$^+$)** (found): 467.2106.

ethyl 4-(8-chloro-3-(2,2,2-trifluoroethyl)-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine-11-ylidene)piperidine-1-carboxylate (14)



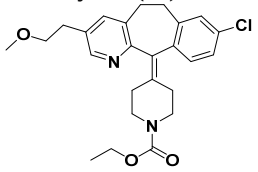
General procedure 6 was followed with larger scale where 2-bromo-1,1,1-trifluoroethane (50 mg) was used as alkyl-halide. It was purified with Mass Directed HPLC system under NH_4OH condition (0.16% NH_4OH in both CH_3CN and H_2O, 12 min. run, 25 mL/min., 50 – 85% CH_3CN) to afford the title compound **14**, 4.0 mg (95% pure), as colorless oil. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.34 (d, *J* = 5.0 Hz, 1H), 7.59 (s, 1H), 7.33 (d, *J* = 2.1 Hz, 1H), 7.23 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.11 (d, *J* = 8.2 Hz, 1H), 4.05 (q, *J* = 7.1 Hz, 2H), 3.72 – 3.54 (m, 4H), 3.37 – 3.28 (m, 2H) (overlap with water peak), 3.23 – 3.17 (m, 2H), 2.92 – 2.78 (m, 2H), 2.37 – 2.27 (m, 2H), 2.23 – 2.13 (m, 2H), 1.18 (t, *J* = 7.1 Hz, 3H). Chemical Formula of $[M+H]^+$: $C_{24}H_{25}ClF_3N_2O_2^+$; Exact Mass (calculated): 465.1551; **HRMS (ESI$^+$)** (found): 465.1564.

ethyl 4-(8-chloro-3-(2-(diethoxyphosphoryl)ethyl)-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine-11-ylidene)piperidine-1-carboxylate (15)



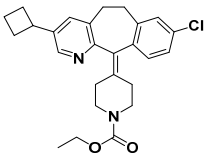
General procedure 6 was followed where diethyl (2-bromoethyl)phosphonate was used as alkyl-halide. It was purified with Mass Directed HPLC system under TFA condition (0.16% TFA in both CH_3CN and H_2O, 12 min. run, 25 mL/min., 25 – 60% CH_3CN) to afford the title compound **15** as TFA salt, 14.9 mg (88% pure), colorless oil. It was further purified with prep. TLC plate (in 60% EtOAc/heptane). The band containing desired product was scratched off, stirred with EtOAc (30 mL) for 1 h. Then it was filtered and the filtrate was concentrated with GeneVac, to afford the title compound 4 mg (95% pure), as colorless oil. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.26 (d, *J* = 1.9 Hz, 1H), 7.50 (d, *J* = 1.8 Hz, 1H), 7.32 (d, *J* = 2.1 Hz, 1H), 7.21 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.08 (d, *J* = 8.2 Hz, 1H), 4.05 (q, *J* = 7.1 Hz, 2H), 3.95 (p, *J* = 7.1 Hz, 4H), 3.62 (tt, *J* = 13.0, 5.1 Hz, 2H), 3.29 - 3.24 (m, 2H), 3.19 – 3.16 (m, 2H), 2.87 – 2.70 (m, 4H), 2.38 – 2.32 (m, 1H), 2.31 – 2.52 (m, 1H), 2.22 – 2.15 (m, 2H), 2.12 – 2.01 (m, 2H), 1.18 (m, 9H). Chemical Formula of $[M+H]^+$: $C_{28}H_{37}ClN_2O_5P^+$; Exact Mass (calculated): 547.2123; **HRMS (ESI$^+$)** (found): 547.2136.

ethyl 4-(8-chloro-3-(2-methoxyethyl)-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine-11-ylidene)piperidine-1-carboxylate (16)



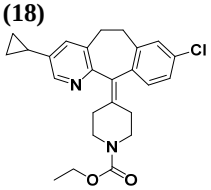
General procedure 6 was followed where diethyl 1-bromo-2-methoxyethane was used as alkyl-halide. It was purified with Mass Directed HPLC system under TFA condition (0.16% TFA in both CH_3CN and H_2O, 12 min. run, 25 mL/min., 25 – 60% CH_3CN) to afford 10.6 mg (82% pure) of colorless oil, as TFA salt. It was further purified with prep. TLC plate (in 60% EtOAc/heptane). The band containing desired product was scratched off, stirred with EtOAc (30 mL) for 1 h. Then it was filtered and the filtrate was concentrated with GeneVac, to afford 4 mg (95% pure) of colorless oil. It was purified with micro-scale HPLC under TFA condition (0.16% TFA in both CH_3CN and H_2O, 6 min. run, 8 mL/min., 25 – 60% CH_3CN), to afford the title compound **16**, 0.7 mg (95% pure), as colorless oil. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.46 (s, 1H), 8.01 (s, 1H), 7.41 (d, *J* = 2.1 Hz, 1H), 7.31 (dd, *J* = 8.1, 2.1 Hz, 1H), 7.13 (d, *J* = 8.2 Hz, 1H), 4.05 (q, *J* = 7.0 Hz, 2H), 3.79 – 3.73 (m, 1H), 3.68 (dd, *J* = 11.7, 6.3 Hz, 1H), 3.58 (t, *J* = 6.4 Hz, 2H), 3.38 (ddt, *J* = 19.9, 14.9, 5.6 Hz, 2H), 3.23 (s, 3H), 3.11 (brs, 2H), 2.98 – 2.84 (m, 4H), 2.36 (ddd, *J* = 14.1, 9.4, 4.8 Hz, 1H), 2.27 (dtt, *J* = 21.6, 9.3, 5.0 Hz, 2H), 2.15 (dt, *J* = 13.8, 4.2 Hz, 1H), 1.18 (t, *J* = 7.1 Hz, 3H). Chemical Formula of $[M+H]^+$: $C_{25}H_{30}ClN_2O_3^+$; Exact Mass (calculated): 441.1939; **HRMS (ESI$^+$)** (found): 441.1948. NOTE: Due to low amount of the material, ^{1}H NMR spectra showed peaks of NH_4OH which was induced during HPLC fraction drying down with GeneVac system.

ethyl 4-(8-chloro-3-cyclobutyl-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine-11-ylidene)piperidine-1-carboxylate (17)



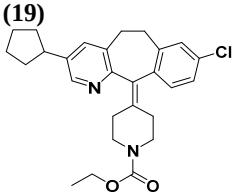
General procedure 6 was followed where bromocyclobutane was used as alkyl-halide. It was purified with Mass Directed HPLC system under TFA condition (0.16% TFA in both CH_3CN and H_2O, 12 min. run, 25 mL/min., 25 – 60% CH_3CN) to afford the compound as TFA salt, 5.2 mg (86% pure), colorless oil. It was further purified with prep. TLC plate (in 60% EtOAc/heptane). The band containing desired product was scratched off, stirred with EtOAc (30 mL) for 1 h. Then it was filtered and the filtrate was concentrated with GeneVac, to afford 2 mg of colorless oil. It was purified with micro-scale HPLC under TFA condition (0.16% TFA in both CH_3CN and H_2O, 6 min. run, 6 mL/min., 25 – 60% CH_3CN), to afford the title compound **17** as TFA salt, 0.8 mg (95% pure), as colorless oil. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.48 (s, 1H), 8.23 (s, 1H), 7.43 (d, J = 2.1 Hz, 1H), 7.34 – 7.32 (m, 1H), 7.14 (d, J = 8.2 Hz, 1H), 4.06 (q, J = 7.0 Hz, 2H) (overlap with water peak), 3.84 – 3.78 (m, 1H), 3.73 – 3.62 (m, 2H), 3.45 (dt, J = 16.5, 5.8 Hz, 1H), 3.36 (ddd, J = 15.0, 10.2, 4.8 Hz, 1H), 3.12 (s, 2H), 3.02 (ddd, J = 16.1, 10.1, 4.7 Hz, 1H), 2.91 (dt, J = 14.5, 5.4 Hz, 1H), 2.40 – 2.24 (m, 5H), 2.23 – 2.11 (m, 3H), 2.07 – 1.97 (m, 1H), 1.89 – 1.82 (m, 1H), 1.18 (t, J = 7.1 Hz, 3H). Chemical Formula of $[M+H]^+$: $C_{26}H_{30}ClN_2O_2^+$; Exact Mass (calculated): 437.1990; **HRMS (ESI$^+$)** (found): 437.2003. NOTE: Due to low amount of the material, ^{1}H NMR spectra showed peaks of NH_4OH which was induced during HPLC fraction drying down with GeneVac system.

ethyl 4-(8-chloro-3-cyclopropyl-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine-11-ylidene)piperidine-1-carboxylate (18)



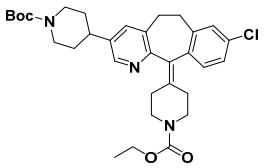
General procedure 6 was followed where bromocyclopropane was used as alkyl-halide. It was purified with Mass Directed HPLC system under TFA condition (0.16% TFA in both CH_3CN and H_2O, 12 min. run, 25 mL/min., 25 – 60% CH_3CN) to afford the compound as TFA salt, 2.7 mg (93% pure), colorless oil. It was further purified with prep. TLC plate (in 60% EtOAc/heptane). The band containing desired product was scratched off, stirred with EtOAc (30 mL) for 1 h. Then it was filtered and the filtrate was concentrated with GeneVac, to afford 1 mg of colorless oil. It was purified with micro-scale HPLC under TFA condition (0.16% TFA in both CH_3CN and H_2O, 6 min. run, 6 mL/min., 25 – 60% CH_3CN), to afford the title compound **18** as TFA salt, 0.3 mg (95% pure), as colorless oil. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.45 (s, 1H), 7.84 (s, 1H), 7.41 (d, J = 2.1 Hz, 1H), 7.32 (dd, J = 8.1, 2.1 Hz, 1H), 7.12 (d, J = 8.2 Hz, 1H), 4.05 (q, J = 7.1 Hz, 2H), 3.79 – 3.70 (m, 2H) (overlap with water peak), 3.42 – 3.30 (m, 2H), 3.11 (brs, 2H), 2.98 – 2.84 (m, 2H), 2.38 – 2.21 (m, 3H), 2.18 – 2.06 (m, 2H), 1.18 (t, J = 7.1 Hz, 3H), 1.09 (d, J = 8.3 Hz, 2H), 0.88 (s, 2H). Chemical Formula of $[M+H]^+$: $C_{25}H_{28}ClN_2O_2^+$; Exact Mass (calculated): 423.1834; **HRMS (ESI$^+$)** (found): 423.1842. NOTE: Due to low amount of the material, ^{1}H NMR spectra showed peaks of NH_4OH which was induced during HPLC fraction drying down with GeneVac system.

ethyl 4-(8-chloro-3-cyclopentyl-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine-11-ylidene)piperidine-1-carboxylate (19)



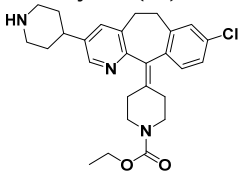
General procedure 6 was followed where bromocyclopentane was used as alkyl-halide. It was purified with Mass Directed HPLC system under TFA condition (0.16% TFA in both CH_3CN and H_2O, 12 min. run, 25 mL/min., 25 – 60% CH_3CN) to afford the title compound **19** as TFA salt, 3.3 mg (90% pure), colorless oil. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.42 (s, 1H), 7.93 (s, 1H), 7.39 (d, J = 2.1 Hz, 1H), 7.29 (dd, J = 8.1, 2.1 Hz, 1H), 7.11 (d, J = 8.2 Hz, 1H), 4.06 (q, J = 7.1 Hz, 2H), 3.69 (ddd, J = 17.7, 12.6, 6.3 Hz, 2H), 3.36 (tq, J = 14.7, 5.8 Hz, 2H), 3.13 (brs, 2H), 3.06 (p, J = 9.4 Hz, 1H), 2.97 – 2.84 (m, 2H), 2.38 – 2.17 (m, 4H), 2.08 – 2.00 (m, 2H), 1.77 (dd, J = 14.7, 4.4 Hz, 2H), 1.65 (ddd, J = 12.5, 7.1, 4.6 Hz, 2H), 1.62 – 1.51 (m, 2H), 1.18 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 158.35, 155.00, 140.65, 137.49, 132.72, 130.88, 129.48, 126.55, 61.23, 44.43, 42.57, 40.02, 34.30, 30.86, 25.49, 15.07. Chemical Formula of $[M+H]^+$: $C_{27}H_{32}ClN_2O_2^+$; Exact Mass (calculated): 451.2147; **HRMS (ESI$^+$)** (found): 451.2157.

***tert*-butyl 4-(8-chloro-11-(1-(ethoxycarbonyl)piperidin-4-ylidene)-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine-3-yl)piperidine-1-carboxylate (20)**



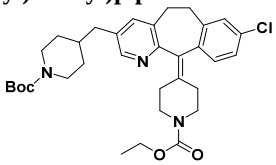
General procedure 6 was followed where *tert*-butyl 4-bromopiperidine-1-carboxylate was used as alkyl-halide. It was purified with Mass Directed HPLC system under TFA condition (0.16% TFA in both CH_3CN and H_2O, 12 min. run, 25 mL/min., 25 – 60% CH_3CN), to afford 7.8 mg (92% pure) of colorless oil. Chemical Formula of $[M+H]^+$: $C_{32}H_{41}ClN_3O_4^+$; Exact Mass (calculated): 566.2780; **HRMS (ESI$^+$)** (found): 566.2794.

ethyl 4-(8-chloro-3-(piperidin-4-yl)-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine-1-carboxylate (21)



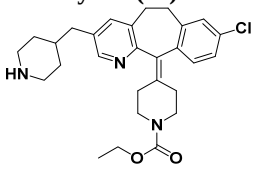
During HPLC purification of compound **20**, Boc-protecting group partially fell off. It was further purified with prep. TLC plate (in 60% EtOAc/heptane). The band containing desired product was scratched off, stirred with EtOAc (30 mL) for 1 h. Then it was filtered and the filtrate was concentrated with GeneVac, to afford 4 mg of colorless oil. It was purified with micro-scale HPLC under TFA condition (0.16% TFA in both CH_3CN and H_2O, 6 min. run, 6 mL/min., 11 – 75% CH_3CN), to afford the de-Boc compound **21**, as TFA salt, 0.1 mg (95% pure), as colorless oil. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.54 – 8.48 (m, 1H), 8.41 (d, J = 1.5 Hz, 1H), 7.81 (s, 1H), 7.39 (d, J = 2.2 Hz, 1H), 7.28 (dd, J = 8.3, 2.3 Hz, 1H), 7.12 (d, J = 8.2 Hz, 1H), 4.05 (q, J = 7.0 Hz, 2H), 3.68 (tt, J = 12.4, 6.3 Hz, 2H), 3.42 – 3.32 (m, 4H), 3.14 (s, 2H), 3.05 – 2.92 (m, 4H), 2.87 (ddd, J = 14.9, 9.2, 3.4 Hz, 1H), 2.35 (ddd, J = 13.9, 9.2, 4.4 Hz, 1H), 2.28 (ddd, J = 13.7, 8.9, 4.7 Hz, 1H), 2.20 (ddt, J = 14.8, 9.8, 4.8 Hz, 2H), 1.99 (d, J = 13.7 Hz, 2H), 1.86 – 1.77 (m, 2H), 1.18 (t, J = 7.1 Hz, 3H). Chemical Formula of $[M+H]^+$: $C_{27}H_{33}ClN_3O_2^+$; Exact Mass (calculated): 466.2256; **HRMS (ESI$^+$)** (found): 466.2267. NOTE: Due to low amount of the material, ^{1}H NMR spectra showed peaks of NH_4OH which was induced during HPLC fraction drying down with GeneVac system.

***tert*-butyl 4-((8-chloro-11-(1-(ethoxycarbonyl)piperidin-4-ylidene)-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine-3-yl)methyl)piperidine-1-carboxylate (22)**



General procedure 6 was followed in a larger scale, 50 mg of ethyl 4-(3-bromo-8-chloro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11(6*H*)-ylidene)piperidine-1-carboxylate. *Tert*-butyl 4-(bromomethyl)piperidine-1-carboxylate was used as alkyl-halide. It was further purified with 2 prep. TLC plates (in 3% MeOH/EtOAc). The band containing desired product was scratched off, stirred with 3% MeOH/EtOAc (30 mL) for 0.5 h. Then it was filtered and the filtrate was concentrated with GeneVac, to afford 22.6 mg of light brown oil. Chemical Formula of $[M+H]^+$: $C_{33}H_{43}ClN_3O_4^+$; Exact Mass (calculated): 580.2937; **HRMS (ESI$^+$)** (found): 580.2953.

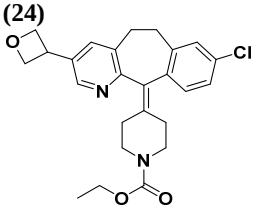
ethyl 4-(8-chloro-3-(piperidin-4-ylmethyl)-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine-1-carboxylate (23)



Tert-butyl 4-((8-chloro-11-(1-(ethoxycarbonyl)piperidin-4-ylidene)-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine-3-yl)methyl)piperidine-1-carboxylate, compound **22**, (22.6 mg, 39 μmol) was dissolved in CH_2Cl_2 (1 mL). Trifluoroacetic acid (0.5 mL) was added to the solution. The reaction mixture was shaked at 240 rpm at r.t. for 1 h. Volatiles were removed with GeneVac. The residue was purified with Mass Directed HPLC system under TFA condition (0.16% TFA in both CH_3CN and H_2O, 12 min. run, 25 mL/min., 10 – 45% CH_3CN), to afford the title compound **23** as TFA salt, 12.6 mg (92% pure), light yellow oil. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.44 (s, 1H), 8.32 (s, 1H), 7.92 (s, 1H), 7.41 (d, J = 2.0 Hz, 1H), 7.30 (dd, J = 8.1, 2.1 Hz, 1H), 7.13 (d, J = 8.2 Hz, 1H), 4.06 (q, J = 7.1 Hz, 2H), 3.70 (ddd, J = 23.3, 11.5, 5.6 Hz, 2H), 3.44 – 3.31 (m, 2H), 3.24 (d, J = 11.9 Hz, 2H), 3.14 (m, 2H), 2.97 – 2.85 (m, 2H), 2.83 – 2.75 (m, 2H), 2.61 (m, 2H), 2.36 (dd, J = 9.4, 4.7 Hz, 1H), 2.25 (tdd, J = 18.7, 9.4, 4.7 Hz, 2H), 2.16 (dt, J = 13.8, 4.0 Hz, 1H), 1.84 (m, 1H), 1.72 (d, J = 13.3 Hz, 2H), 1.32 (q, J = 12.7 Hz, 2H), 1.18 (t, J = 7.1 Hz, 3H). **^{13}C**

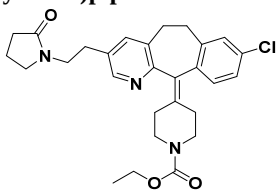
NMR (126 MHz, DMSO-d_6) δ 154.99, 140.61, 137.37, 132.80, 130.94, 129.50, 126.64, 61.25, 44.37, 43.56, 38.02, 34.77, 31.16, 30.83, 30.54, 28.38, 15.07. Chemical Formula of $[M+H]^+$: $C_{28}H_{35}ClN_3O_2^+$; Exact Mass (calculated): 480.2412; **HRMS (ESI$^+$)** (found): 480.2424.

ethyl 4-(8-chloro-3-(oxetan-3-yl)-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine-11-ylidene)piperidine-1-carboxylate (24)



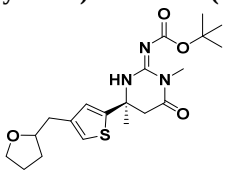
General procedure 6 was followed where 3-iodooxetane was used as alkyl-halide. It was purified with Mass Directed HPLC system under ammonium hydroxide condition (0.16% NH_4OH in both CH_3CN and H_2O, 12 min. run, 25 mL/min., 50 – 85% CH_3CN) to afford the title compound **24**, 2.6 mg (91% pure), as colorless oil. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.32 (d, J = 1.9 Hz, 1H), 7.72 (d, J = 1.8 Hz, 1H), 7.33 (d, J = 2.0 Hz, 1H), 7.22 (dd, J = 8.1, 2.1 Hz, 1H), 7.10 (d, J = 8.2 Hz, 1H), 4.92 (dt, J = 8.3, 5.7 Hz, 2H), 4.62 (dt, J = 9.4, 6.4 Hz, 2H), 4.24 (p, J = 7.6 Hz, 1H), 4.05 (q, J = 7.1 Hz, 2H), 3.63 (ddd, J = 18.8, 13.4, 5.0 Hz, 2H), 3.38 – 3.30 (m, 2H), 3.22 – 3.14 (m, 2H), 2.86 (tdd, J = 13.6, 9.4, 6.1 Hz, 2H), 2.38 – 2.26 (m, 2H), 2.23 – 2.15 (m, 2H), 1.18 (t, J = 7.1 Hz, 3H). Chemical Formula of $[M+H]^+$: $C_{25}H_{28}ClN_2O_3^+$; Exact Mass (calculated): 439.1783; **HRMS (ESI$^+$)** (found): 439.1791.

ethyl 4-(8-chloro-3-(2-(2-oxopyrrolidin-1-yl)ethyl-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine-11-ylidene)piperidine-1-carboxylate (25)



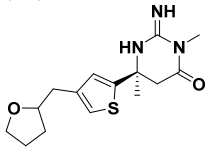
General procedure 6 was followed where 1-(2-bromoethyl)pyrrolidin-2-one was used as alkyl-halide. It was purified with Mass Directed HPLC system under ammonium hydroxide condition (0.16% NH_4OH in both CH_3CN and H_2O, 12 min. run, 25 mL/min., 50 – 85% CH_3CN) to afford the title compound **25**, 5.9 mg (90% pure), as colorless oil. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.23 – 8.21 (m, 1H), 7.46 (s, 1H), 7.32 (d, J = 2.2 Hz, 1H), 7.22 (dd, J = 8.2, 2.2 Hz, 1H), 7.09 (d, J = 8.2 Hz, 1H), 4.05 (q, J = 7.1 Hz, 2H), 3.61 (td, J = 13.2, 6.5 Hz, 2H), 3.41 – 3.37 (m, 2H), 3.31 – 3.24 (m, 4H), 3.18 (m, 2H), 2.81 (td, J = 11.2, 10.5, 5.6 Hz, 2H), 2.73 (t, J = 7.4 Hz, 2H), 2.36 – 2.25 (m, 2H), 2.20 – 2.13 (m, 4H), 1.88 (p, J = 7.7 Hz, 2H), 1.18 (t, J = 7.1 Hz, 3H). Chemical Formula of $[M+H]^+$: $C_{28}H_{33}ClN_3O_3^+$; Exact Mass (calculated): 494.2205; **HRMS (ESI$^+$)** (found): 494.2205.

***tert*-butyl ((4*S*,*Z*)-1,4-dimethyl-6-oxo-4-(4-((tetrahydrofuran-2-yl)methyl)thiophen-2-yl)tetrahydropyrimidin-2(1*H*)-ylidene)carbamate (26)**



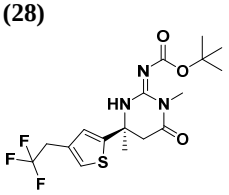
General procedure 7 was followed where 2-(bromomethyl)tetrahydrofuran was used as alkyl-halide. It was purified with Mass Directed HPLC system under TFA condition (0.16% TFA in both CH_3CN and H_2O, 12 min. run, 25 mL/min., 15 – 55% CH_3CN), to afford 10.9 mg of light brown oil. Boc-protecting group partially fell off. LCMS R_T = 1.07 min. (2 min. run); Chemical Formula of $[M+H]^+$: $C_{20}H_{30}N_3O_4S^+$; Exact Mass (calculated): 408.20; **Exact Mass (ESI$^+$)** (found): 408.24.

(6*S*)-2-imino-3,6-dimethyl-6-(4-((tetrahydrofuran-2-yl-methyl)thiophen-2-yl)tetrahydropyrimidin-4(1*H*)-one (27)



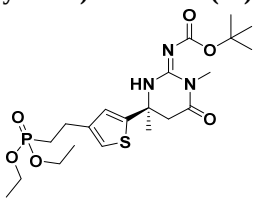
The residue of compound **26** (10.9 mg) was treated with TFA (0.4 mL) in CH_2Cl_2 (0.6 mL), stirred at r.t. for 1 h. Volatiles were removed with GeneVac, to afford the title compound **27**, 9.7 mg (90% pure), light brown solid, as TFA salt. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.66 (s, 2H), 7.16 (s, 1H), 6.97 (d, J = 1.2 Hz, 1H), 3.96 (dtd, J = 13.1, 6.6, 2.3 Hz, 1H), 3.74 (ddt, J = 10.8, 6.8, 3.8 Hz, 1H), 3.64 – 3.55 (m, 1H), 3.32 – 3.18 (m, 2H), 3.14 (s, 3H), 2.68 (t, J = 7.3 Hz, 2H), 1.88 (ddq, J = 14.1, 6.5, 3.4, 2.8 Hz, 1H), 1.82 – 1.72 (m, 2H), 1.69 (s, 3H), 1.45 (dq, J = 11.9, 7.7 Hz, 1H). Chemical Formula of $[M+H]^+$: $C_{15}H_{22}N_3O_2S^+$; Exact Mass (calculated): 308.1427; **HRMS (ESI$^+$)** (found): 308.1431.

***tert*-butyl (*S,Z*)-(1,4-dimethyl-6-oxo-(4-(2,2,2-trifluoroethyl)thiophen-2-yl)tetrahydropyrimidin-2(1*H*)-ylidene)carbamate (28)**



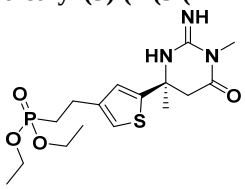
General procedure 7 was followed where 2-bromo-1,1,1-trifluoroethane was used as alkyl-halide. The compound was lost during Mass Directed HPLC purification. LCMS R_T = 1.23 min. (2 min. run); Chemical Formula of $[M+H]^+$: $C_{17}H_{23}F_3N_3O_3S^+$; Exact Mass (calculated): 406.14; **Exact Mass (ESI$^+$)** (found): 406.14.

***tert*-butyl (*S,Z*)-(4-(4-(2-(diethoxyphosphoryl)ethyl)thiophen-2-yl)-1,4-dimethyl-6-oxotetrahydropyrimidin-2(1*H*)-ylidene)carbamate (29)**



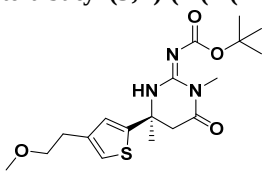
General procedure 7 was followed where diethyl (2-bromoethyl)phosphonate was used as alkyl-halide. It was purified with Mass Directed HPLC system under TFA condition (0.16% TFA in both CH_3CN and H_2O, 12 min. run, 25 mL/min., 15 – 55% CH_3CN), to afford 15.4 mg of light brown oil. Boc-protecting group partially fell off. LCMS R_T = 0.98 min. (2 min. run); Chemical Formula of $[M+H]^+$: $C_{21}H_{35}N_3O_6PS^+$; Exact Mass (calculated): 488.20; **Exact Mass (ESI$^+$)** (found): 488.17.

diethyl (*S*)-(2-(5-(2-imino-1,4-dimethyl-6-oxohexahydropyrimidin-4-yl)thiophen-3-yl)ethyl)phosphonate (30)



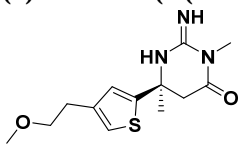
The residue of compound **29** (15.4 mg) was treated with TFA (0.4 mL) in CH_2Cl_2 (0.6 mL), stirred at r.t. for 1 h. Volatiles were removed with GeneVac, to afford the title compound **30**, 13.5 mg (95% pure), light brown solid, as TFA salt. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.65 (s, 2H), 7.22 (s, 1H), 7.05 (d, J = 1.2 Hz, 1H), 4.01 – 3.95 (m, 4H), 3.32 – 3.20 (m, 2H), 3.13 (s, 3H), 2.76 – 2.67 (m, 2H), 2.09 – 1.99 (m, 2H), 1.69 (s, 3H), 1.22 (t, J = 7.0 Hz, 6H). Chemical Formula of $[M+H]^+$: $C_{16}H_{27}N_3O_4PS^+$; Exact Mass (calculated): 388.1454; **HRMS (ESI$^+$)** (found): 388.1462.

***tert*-butyl (*S,Z*)-(4-(4-(2-methoxyethyl)thiophen-2-yl)-1,4-dimethyl-6-oxotetrahydropyrimidin-2(1*H*)-ylidene)carbamate (31)**



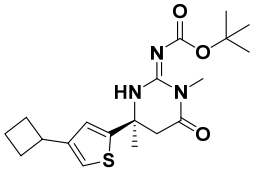
General procedure 7 was followed where diethyl 1-bromo-2-methoxyethane was used as alkyl-halide. It was purified with Mass Directed HPLC system under TFA condition (0.16% TFA in both CH_3CN and H_2O, 12 min. run, 25 mL/min., 15 – 55% CH_3CN), to afford 13 mg of light brown oil. Boc-protecting group partially fell off. LCMS R_T = 1.02 min. (2 min. run); Chemical Formula of $[M+H]^+$: $C_{18}H_{28}N_3O_4S^+$; Exact Mass (calculated): 382.18; **Exact Mass (ESI$^+$)** (found): 382.20.

(*S*)-2-imino-6-(4-(2-methoxyethyl)thiophen-2-yl)-3,6-dimethyltetrahydropyrimidin-4(1*H*)-one (32)



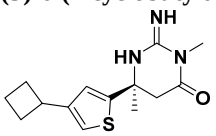
The residue of compound **31** (13 mg) was treated with TFA (0.4 mL) in CH_2Cl_2 (0.6 mL), stirred at r.t. for 1 h. Volatiles were removed with GeneVac, to afford the title compound **32**, 11.1 mg (90% pure), light brown solid, as TFA salt. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 6.93 (s, 1H), 6.78 (s, 1H), 5.91 (brs, 2H), 3.50 (t, J = 6.9 Hz, 2H), 3.25 (s, 3H), 3.02 (s, 3H), 2.77 – 2.65 (m, 4H), 1.41 (s, 3H). Chemical Formula of $[M+H]^+$: $C_{13}H_{20}N_3O_2S^+$; Exact Mass (calculated): 282.1271; **HRMS (ESI$^+$)** (found): 282.1274.

***tert*-butyl (*S*,*Z*)-(4-(4-cyclobutylthiophen-2-yl)-1,4-dimethyl-6-oxotetrahydropyrimidin-2(1*H*)-ylidene)carbamate (33)**



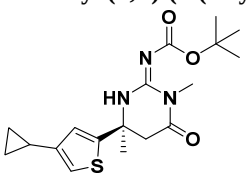
General procedure 7 was followed where bromocyclobutane was used as alkyl-halide. It was purified with Mass Directed HPLC system under TFA condition (0.16% TFA in both CH_3CN and H_2O, 12 min. run, 25 mL/min., 15 – 55% CH_3CN), to afford 7.3 mg of light brown oil. Boc-protecting group partially fell off. LCMS R_T = 1.23 min. (2 min. run); Chemical Formula of $[M+H]^+$: $C_{19}H_{28}N_3O_3S^+$; Exact Mass (calculated): 378.18; **Exact Mass (ESI$^+$)** (found): 378.20.

(*S*)-6-(4-cyclobutylthiophen-2-yl)-2-imino-3,6-dimethyltetrahydropyrimidin-4(1*H*)-one (34)



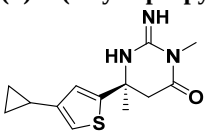
The residue of compound **33** (7.3 mg) was treated with TFA (0.4 mL) in CH_2Cl_2 (0.6 mL), stirred at r.t. for 1 h. Volatiles were removed with GeneVac, to afford the title compound **34**, 6.0 mg (90% pure), light brown solid, as TFA salt. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.59 (brs, 2H), 7.14 (s, 1H), 7.02 (d, J = 1.4 Hz, 1H), 3.45 (p, J = 8.5 Hz, 1H), 3.32 (d, J = 16.4 Hz, 1H), 3.21 (d, J = 16.3 Hz, 1H), 3.13 (s, 3H), 2.25 (dtd, J = 10.5, 7.9, 2.7 Hz, 2H), 2.06 – 1.99 (m, 2H), 1.97 – 1.90 (m, 1H), 1.84 – 1.79 (m, 1H), 1.69 (s, 3H). Chemical Formula of $[M+H]^+$: $C_{14}H_{20}N_3OS^+$; Exact Mass (calculated): 278.1322; **HRMS (ESI$^+$)** (found): 278.1325.

***tert*-butyl (*S*,*Z*)-(4-(4-cyclopropylthiophen-2-yl)-1,4-dimethyl-6-oxotetrahydropyrimidin-2(1*H*)-ylidene)carbamate (35)**



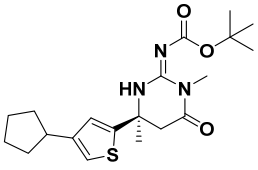
General procedure 7 was followed where bromocyclopropane was used as alkyl-halide. It was purified with Mass Directed HPLC system under TFA condition (0.16% TFA in both CH_3CN and H_2O, 12 min. run, 25 mL/min., 15 – 55% CH_3CN), to afford 3.8 mg of light brown oil. Boc-protecting group partially fell off. LCMS R_T = 1.13 min. (2 min. run); Chemical Formula of $[M+H]^+$: $C_{18}H_{26}N_3O_3S^+$; Exact Mass (calculated): 364.17; **Exact Mass (ESI$^+$)** (found): 364.10.

(*S*)-6-(4-cyclopropylthiophen-2-yl)-2-imino-3,6-dimethyltetrahydropyrimidin-4(1*H*)-one (36)



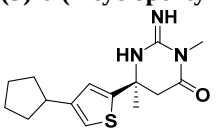
The residue of compound **35** (3.8 mg) was treated with TFA (0.4 mL) in CH_2Cl_2 (0.6 mL), stirred at r.t. for 1 h. Volatiles were removed with GeneVac. The crude material was purified with micro-scale HPLC under TFA condition (0.16% TFA in both CH_3CN and H_2O, 12 min. run, 8 mL/min., 15 – 55% CH_3CN), to afford the title compound **36**, 1.5 mg (100% pure), off-white solid, as TFA salt. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 7.02 (d, J = 1.2 Hz, 1H), 6.85 (d, J = 1.4 Hz, 1H), 3.29 (d, J = 16.3 Hz, 1H), 3.21 (d, J = 16.3 Hz, 1H), 3.13 (s, 3H), 1.87 (ddd, J = 13.4, 8.4, 5.1 Hz, 1H), 1.67 (s, 3H), 0.88 – 0.84 (m, 2H), 0.61 – 0.53 (m, 2H). Chemical Formula of $[M+H]^+$: $C_{13}H_{18}N_3OS^+$; Exact Mass (calculated): 264.1165; **HRMS (ESI$^+$)** (found): 264.1168. NOTE: Due to low amount of the material, ^{1}H NMR spectra showed peaks of NH_4OH which was induced during HPLC fraction drying down with GeneVac system. The two NH protons are exchangeable and don't show up in NMR spectra.

***tert*-butyl (*S*,*Z*)-(4-(4-cyclopentylthiophen-2-yl)-1,4-dimethyl-6-oxotetrahydropyrimidin-2(1*H*)-ylidene)carbamate (37)**



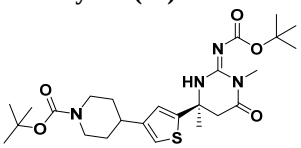
General procedure 7 was followed where bromocyclopentane was used as alkyl-halide. It was purified with Mass Directed HPLC system under TFA condition (0.16% TFA in both CH_3CN and H_2O, 12 min. run, 25 mL/min., 15 – 55% CH_3CN), to afford 9 mg of light brown oil. Boc-protecting group partially fell off. LCMS R_T = 1.29 min. (2 min. run); Chemical Formula of $[M+H]^+$: $C_{20}H_{30}N_3O_3S^+$; Exact Mass (calculated): 392.20; **Exact Mass (ESI$^+$)** (found): 392.24.

(*S*)-6-(4-cyclopentylthiophen-2-yl)-2-imino-3,6-dimethyltetrahydropyrimidin-4(1*H*)-one (38)



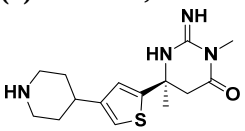
The residue of compound **37** (9 mg) was treated with TFA (0.4 mL) in CH_2Cl_2 (0.6 mL), stirred at r.t. for 1 h. Volatiles were removed with GeneVac, to afford the title compound **38**, 7.4 mg (85% pure), light brown solid, as TFA salt. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.60 (brs, 2H), 7.11 (s, 1H), 7.00 (d, J = 1.4 Hz, 1H), 3.31 (d, J = 16.4 Hz, 1H), 3.21 (d, J = 16.3 Hz, 1H), 3.13 (s, 3H), 3.00 – 2.89 (m, 1H), 2.02 – 1.92 (m, 2H), 1.78 – 1.63 (m, 5H), 1.63 – 1.54 (m, 2H), 1.48 (ddt, J = 11.7, 9.0, 5.7 Hz, 2H). Chemical Formula of $[M+H]^+$: $C_{15}H_{22}N_3OS^+$; Exact Mass (calculated): 292.1478; **HRMS (ESI$^+$)** (found): 292.1479.

***tert*-butyl (*S*,*Z*)-4-(5-(2-((*tert*-butoxycarbonyl)imino)-1,4-dimethyl-6-hexahydropyrimidin-4-yl)thiophen-3-yl)piperidine-1-carboxylate (39)**



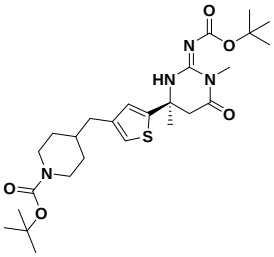
General procedure 7 was followed where *tert*-butyl 4-bromopiperidine-1-carboxylate was used as alkyl-halide. It was purified with Mass Directed HPLC system under TFA condition (0.16% TFA in both CH_3CN and H_2O, 12 min. run, 25 mL/min., 15 – 55% CH_3CN), to afford 15.1 mg of light brown oil. Boc-protecting groups partially fell off. LCMS R_T = 1.25 min. (2 min. run); Chemical Formula of $[M+H]^+$: $C_{25}H_{39}N_4O_5S^+$; Exact Mass (calculated): 507.26; **Exact Mass (ESI$^+$)** (found): 507.22.

(*S*)-2-imino-3,6-dimethyl-6-(4-(piperidin-4-yl)thiophen-2-yl)tetrahydropyrimidin-4(1*H*)-one (40)



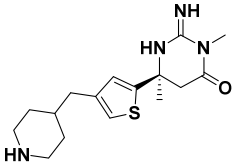
The residue of compound **39** (15.1 mg) was treated with TFA (0.4 mL) in CH_2Cl_2 (0.6 mL), stirred at r.t. for 1 h. Volatiles were removed with GeneVac. The crude material was purified with Mass Directed HPLC system under TFA condition (0.16% TFA in both CH_3CN and H_2O, 12 min. run, 25 mL/min., 15 – 55% CH_3CN), to afford the title compound **40**, 9.8 mg (100% pure), off-white solid, as TFA salt. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.84 (brs, 1H), 8.61 (s, 1H), 8.33 (s, 1H), 7.19 (s, 1H), 7.01 (d, J = 1.4 Hz, 1H), 3.34 (d, J = 12.5 Hz, 2H), 3.30 (d, J = 16.7 Hz, 1H), 3.24 (d, J = 16.3 Hz, 1H), 3.12 (s, 3H), 2.98 (q, J = 12.7 Hz, 2H), 2.83 (ddd, J = 11.8, 8.5, 3.5 Hz, 1H), 2.03 (d, J = 13.9 Hz, 2H), 1.69 (s, 3H), 1.68 – 1.58 (m, 2H). Chemical Formula of $[M+H]^+$: $C_{15}H_{23}N_4OS^+$; Exact Mass (calculated): 307.1587; **HRMS (ESI$^+$)** (found): 307.1590.

***tert*-butyl (*S*,*Z*)-4-((5-(2-((*tert*-butoxycarbonyl)imino)-1,4-dimethyl-6-oxohexahydropyrimidin-4-yl)thiophen-3-yl)methyl)piperidine-1-carboxylate (41)**



General procedure 7 was followed where *tert*-butyl 4-(bromomethyl)piperidine-1-carboxylate was used as alkyl-halide. It was purified with Mass Directed HPLC system under TFA condition (0.16% TFA in both CH_3CN and H_2O, 12 min. run, 25 mL/min., 15 – 55% CH_3CN), to afford 12.6 mg of light brown oil. Boc-protecting groups partially fell off. LCMS R_T = 1.29 min. (2 min. run); Chemical Formula of $[M+H]^+$: $C_{26}H_{41}N_4O_5S^+$; Exact Mass (calculated): 521.28; **Exact Mass (ESI$^+$)** (found): 521.26.

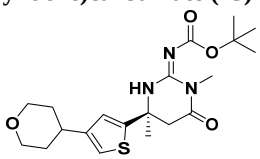
(*S*)-2-imino-3,6-dimethyl-6-(4-(piperidin-4-ylmethyl)thiophen-2-yl)tetrahydropyrimidin-4(1*H*)-one (42)



The residue of compound **41** (12.6 mg) was treated with TFA (0.4 mL) in CH_2Cl_2 (0.6 mL), stirred at r.t. for 1 h. Volatiles were removed with GeneVac. The crude material was purified with Mass Directed HPLC system under TFA condition (0.16% TFA in

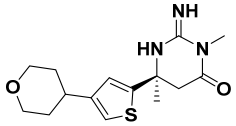
both CH_3CN and H_2O, 12 min. run, 25 mL/min., 15 – 55% CH_3CN), to afford the title compound **42**, 7.2 mg (100% pure), off-white solid, as TFA salt. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.79 (brs, 1H), 8.49 (s, 1H), 8.20 (s, 1H), 7.15 (s, 1H), 6.92 (d, J = 1.2 Hz, 1H), 3.30 – 3.21 (m, 4H), 3.12 (s, 3H), 2.82 (q, J = 11.9 Hz, 2H), 2.48 (d, J = 6.9 Hz, 2H), 1.80 – 1.71 (m, 3H), 1.69 (s, 3H), 1.27 (dd, J = 24.1, 11.3 Hz, 2H). Chemical Formula of $[M+H]^+$: $C_{16}H_{25}N_4OS^+$; Exact Mass (calculated): 321.1744; **HRMS (ESI$^+$)** (found): 321.1749.

***tert*-butyl (*S*,*Z*)-(1,4-dimethyl-6-oxo-4-(4-(tetrahydro-2*H*-pyran-4-yl)thiophen-2-yl)tetrahydropyrimidin-2(1*H*)-ylidene)carbamate (43)**



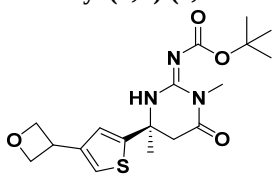
General procedure 7 was followed where 4-bromotetrahydro-2*H*-pyran was used as alkyl-halide. It was purified with Mass Directed HPLC system under TFA condition (0.16% TFA in both CH_3CN and H_2O, 12 min. run, 25 mL/min., 15 – 55% CH_3CN), to afford 12.5 mg of light brown oil. Boc-protecting groups partially fell off. LCMS R_T = 1.03 min. (2 min. run); Chemical Formula of $[M+H]^+$: $C_{20}H_{30}N_3O_4S^+$; Exact Mass (calculated): 408.20; **Exact Mass (ESI$^+$)** (found): 408.24.

(*S*)-2-imino-3,6-dimethyl-6-(4-(tetrahydro-2*H*-pyran-4-yl)thiophen-2-yl)tetrahydropyrimidin-4(1*H*)-one (44)



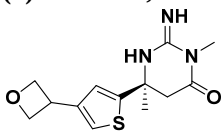
The residue of compound **43** (12.5 mg) was treated with TFA (0.4 mL) in CH_2Cl_2 (0.6 mL), stirred at r.t. for 1 h. Volatiles were removed with GeneVac, to afford the title compound **44**, 10.4 mg (95% pure), light brown solid, as TFA salt. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.63 (s, 2H), 7.15 (s, 1H), 7.06 (d, J = 1.4 Hz, 1H), 3.91 (dd, J = 11.0, 3.7 Hz, 2H), 3.40 (td, J = 11.7, 2.0 Hz, 2H), 3.31 (d, J = 16.4 Hz, 1H), 3.22 (d, J = 16.3 Hz, 1H), 3.13 (s, 3H), 2.76 (tt, J = 11.7, 3.6 Hz, 1H), 1.80 – 1.73 (m, 2H), 1.70 (s, 3H), 1.55 (qdd, J = 12.0, 7.2, 4.4 Hz, 2H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 166.91, 155.21, 147.70, 147.63, 124.63, 119.30, 67.48, 53.85, 44.32, 36.52, 33.56, 29.54, 28.97. Chemical Formula of $[M+H]^+$: $C_{15}H_{22}N_3O_2S^+$; Exact Mass (calculated): 308.1427; **HRMS (ESI$^+$)** (found): 308.1432.

***tert*-butyl (*S*,*Z*)-(1,4-dimethyl-4-(4-(oxetan-3-yl)thiophen-2-yl)-6-oxotetrahydropyrimidin-2(1*H*)-ylidene)carbamate (45)**



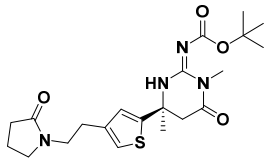
General procedure 7 was followed (with two times the scale) where 3-iodooxetane was used as alkyl-halide. LCMS R_T = 0.90 min. (2 min. run); Chemical Formula of $[M+H]^+$: $C_{18}H_{26}N_3O_4S^+$; Exact Mass (calculated): 380.16; **Exact Mass (ESI$^+$)** (found): 380.19. Reaction mixture was partitioned between EtOAc (4 mL) and water (1 mL). Aqueous layer was extracted with EtOAc (4 mL). The combined organic layers was concentrated with GeneVac to dryness. The residue was purified with Mass Directed HPLC system under formic acid condition (0.16% formic acid in both CH_3CN and H_2O, 15 min. run, 25 mL/min., 25 – 60% CH_3CN). Boc-protecting group totally fell off during the process of drying down solvents using GeneVac. Provided the following compound **46**, (*S*)-2-imino-3,6-dimethyl-6-(4-(oxetan-3-yl)thiophen-2-yl)tetrahydropyrimidin-4(1*H*)-one (5.3 mg, 98% pure), colorless oil, as formic acid salt.

(*S*)-2-imino-3,6-dimethyl-6-(4-(oxetan-3-yl)thiophen-2-yl)tetrahydropyrimidin-4(1*H*)-one (46)



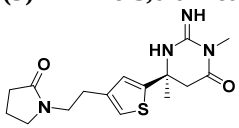
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.22 (s, 1H) (exchangeable NH proton), 7.21 (s, 1H), 7.05 (s, 1H), 4.84 (dd, J = 8.3, 5.8 Hz, 2H), 4.56 (dt, J = 11.2, 6.4 Hz, 2H), 4.20 (p, J = 7.6 Hz, 1H), 3.05 (s, 3H), 2.99 (m, 1H), 2.92 (m, 1H), 1.52 (s, 3H). Chemical Formula of $[M+H]^+$: $C_{13}H_{18}N_3O_2S^+$; Exact Mass (calculated): 280.1114; **HRMS (ESI$^+$)** (found): 280.1112. NOTE: There are fewer H atoms by NMR integration (16) than there are by HRMS $[M+H]^+$ (18) due to there are two exchangeable NH protons.

***tert*-butyl (*S*,*Z*)-(1,4-dimethyl-6-oxo-4-(4-(2-(2-oxopyrrolidin-1-yl)ethyl)thiophen-2-yl)tetrahydropyrimidin-2(1*H*)-ylidene)carbamate (47)**



General procedure 7 was followed where 1-(2-bromoethyl)pyrrolidin-2-one was used as alkyl-halide. Reaction mixture was partitioned between EtOAc (2 mL) and water (0.5 mL). Aqueous layer was extracted with EtOAc (2 mL). The combined organic layers was concentrated with GeneVac to dryness. The residue was purified with Mass Directed HPLC system under TFA condition (0.16% TFA in both CH_3CN and H_2O, 12 min. run, 25 mL/min., 15 – 55% CH_3CN), to afford 7.9 mg of light brown oil. Boc-protecting groups partially fell off. LCMS R_T = 0.88 min. (2 min. run); Chemical Formula of $[M+H]^+$: $C_{21}H_{31}N_4O_4S^+$; Exact Mass (calculated): 435.21; **Exact Mass (ESI$^+$)** (found): 435.33.

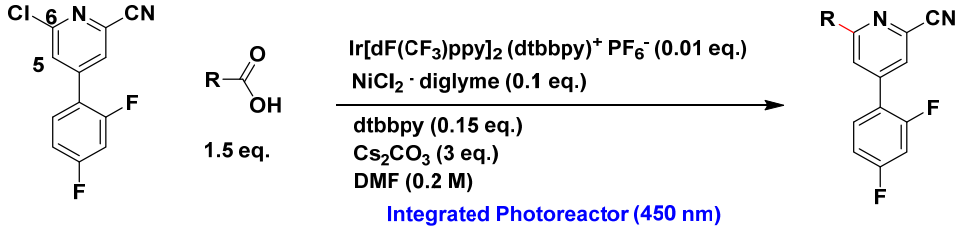
(*S*)-2-imino-3,6-dimethyl-6-(4-(2-(2-oxopyrrolidin-1-yl)ethyl)thiophen-2-yl)tetrahydropyrimidin-4(1*H*)-one (48)



The residue of compound **47** (7.9 mg) was treated with TFA (0.4 mL) in CH_2Cl_2 (0.6 mL), stirred at r.t. for 1 h. Volatiles were removed with GeneVac, to afford the title compound **48**, 6.5 mg (95% pure), light brown solid, as TFA salt. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.68 (s, 2H), 7.19 (s, 1H), 6.96 (s, 1H), 3.46 – 3.29 (m, 2H), 3.28 – 3.19 (m, 4H), 3.13 (s, 3H), 2.71 (t, J = 7.1 Hz, 2H), 2.17 (t, J = 8.1 Hz, 2H), 1.87 (p, J = 7.4 Hz, 2H), 1.68 (s, 3H). Chemical Formula of $[M+H]^+$: $C_{16}H_{23}N_4O_2S^+$; Exact Mass (calculated): 335.1536; **HRMS (ESI$^+$)** (found): 335.1539.

III. Experimental Procedures and Spectroscopic Data of 6-chloro-4-(2,4-difluorophenyl)picolinonitrile Series

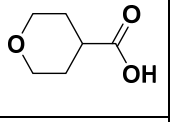
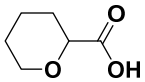
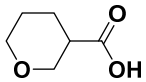
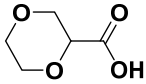
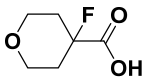
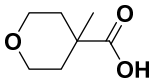
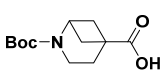
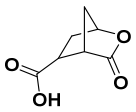
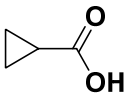
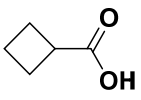
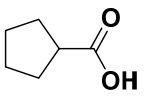
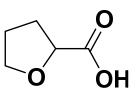
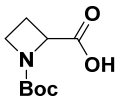
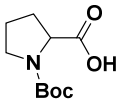
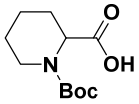
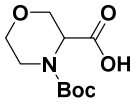
General Scheme 8: 16-member decarboxylative cross-coupling library using Integrated Photoreactor



General Procedure 8:

A 2-dram vial equipped with a stir bar was charged with 6-chloro-4-(2,4-difluorophenyl)picolinonitrile (20 mg, 0.080 mmol), alkyl-carboxylic acid (1.5 eq.), 4,4'-di-*tert*-butyl-2,2'-bipyridine (0.15 eq.), (Ir[dF(CF_3)ppy]$_2$(dtbbpy))PF_6 (0.01 eq.), nickel(II) chloride ethylene glycol di-methyl ether complex (0.1 eq.) and cesium carbonate (3 eq.). It was transferred into glove box. Anhydrous DMF (0.2 M) was added into the reaction mixture. It was capped and taken out of glove box. Irradiated with Integrated Photoreactor, Royal Blue (450 nm) LED light for 1 h, with 100% LED light power. Stir rate was 1000 rpm. Fan rate was 4700 rpm. The reaction was checked with LCMS. If the reaction was not complete, the reaction mixture would be irradiated with Integrated Photoreactor for 1 more hour. The reactions were checked with LCMS. Reaction conversion was calculated based on AUC (area under curve) of LCMS spectra at 254 nm. Reaction Conversion = AUC of desired product / (AUC of desired product + AUC of by-product(s) + AUC of unreacted starting material). The following work-up procedure was applied. Reaction mixture was partitioned between EtOAc (2 mL) and water (0.5 mL). Aqueous layer was extracted with EtOAc (2 mL). The combined organic layers was concentrated with GeneVac to dryness. The residue was purified with Mass Directed semi-preparative HPLC system, to afford the desired product. It could also be purified with prep. TLC plate (in 25% EtOAc/heptane).

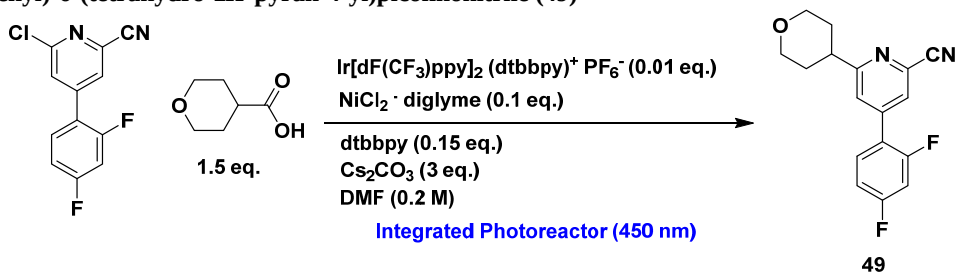
Table 3. Percentage of desired product in crude reaction mixture for catalytic photoredox C(sp^3)-C(sp^2) cross-electrophile coupling with 16 aliphatic carboxylic acids using Integrated Photoreactor and Kessil Lamp

						
Kessil Lamp (16 hrs)	**92**	**58 (5:1)***	**83**	**57 (5:1)***	**0**	**9**
Integrated Photore-actor (1-2 hrs)	**94**	**58 (2:1)***	**92**	**91 (6:1)***	**17**	**13**
						
Kessil Lamp (16 hrs)	**29 (1:1)***	**21 (4:1)***	**6**	**27**	**70**	**76 (5:1)***
Integrated Photore-actor (1-2 hrs)	**64 (1:1)***	**47 (5:1)***	**8**	**57**	**81**	**80 (3:1)***
						
Kessil Lamp (16 hrs)	**87**	**81 (1:1)***	**74 (2:1)***	**71 (7:1)***		
Integrated Photore-actor (1-2 hrs)	**89**	**87 (1:1)***	**86 (1:1)***	**58 (7:1)***		

(6-alkyl:5-alkyl)*

Examples:

4-(2,4-difluorophenyl)-6-(tetrahydro-2*H*-pyran-4-yl)picolinonitrile (49)

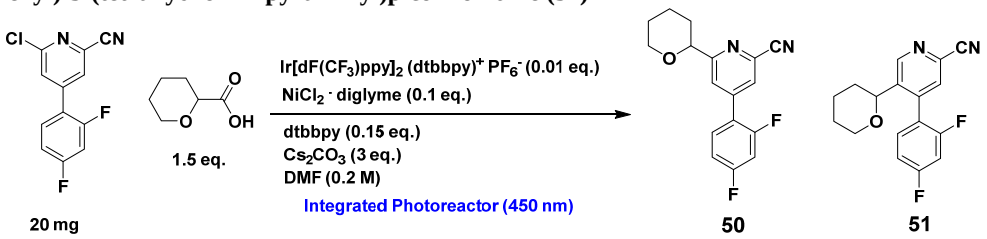


A 2-dram vial equipped with a stir bar was charged with 6-chloro-4-(2,4-difluorophenyl)picolinonitrile (20 mg, 0.080 mmol), tetrahydro-2*H*-pyran-4-carboxylic acid (15.58 mg, 0.120 mmol), 4,4'-di-*tert*-butyl-2,2'-bipyridine (3.21 mg, 0.012 mmol), (Ir[dF(CF_3)ppy]$_2$(dtbbpy))PF_6 (0.895 mg, 0.798 µmol), nickel(II) chloride ethylene glycol dimethyl ether complex (1.753 mg, 7.98 µmol) and cesium carbonate (78 mg, 0.239 mmol). It was transferred into glove box. Anhydrous DMF (399 µl) was added into the reaction mixture. It was taken out of glove box. Irradiated with Integrated Photoreactor, Royal Blue (450 nm) LED light for 30 min., 100% LED light power. Stir rate was 1000 rpm. Fan rate was 4700 rpm. The reaction mixture turned to reddish brown. The reaction mixture was partitioned between EtOAc (2 mL) and water (0.5 mL). Aqueous layer was extracted with EtOAc (2 mL). The combined organic layers was concentrated with rotovap under reduced pressure. The residue was purified with prep. TLC plate (in 25% EtOAc/heptane). The band containing desired product was scratched off, stirred with EtOAc (30 mL) for 0.5 h. Then filtered and the filtrate was concentrated with rotovap under reduced pressure to afford the desired product, compound **49**, 4-(2,4-difluorophenyl)-6-(tetrahydro-2*H*-pyran-4-yl)picolinonitrile, (22.3 mg, 0.074 mmol, 93% yield) as off-white solid. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.12 (s, 1H), 7.86 (s, 1H), 7.85 – 7.80 (m, 1H), 7.51 (ddd, *J* = 11.5, 9.4, 2.5 Hz, 1H), 7.32 (td, *J* = 8.5, 2.4 Hz, 1H), 4.01 – 3.95 (m, 2H), 3.47 (td, *J* = 11.2, 3.4 Hz, 2H), 3.11 (tt, *J* = 10.2, 5.0 Hz, 1H), 1.86 – 1.74 (m, 4H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 167.12, 162.67, 159.04, 144.40, 132.92, 132.79, 126.90, 125.82, 121.21, 118.04, 113.02, 105.44, 67.36, 42.70, 32.00. Chemical Formula of $[M+H]^+$: $C_{17}H_{15}F_2N_2O^+$; Exact Mass (calculated): 301.1147; **HRMS (ESI$^+$)** (found): 301.1145.

200 mg scale: 6-chloro-4-(2,4-difluorophenyl)picolinonitrile (200 mg, 0.80 mmol) was used in a 20 mL vial, following the same procedure. The reaction was complete in 45 min.. Reaction mixture was partitioned between EtOAc (20 mL) and water (5 mL). Aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic layers was concentrated with GeneVac. The residue was purified with ISCO, using silica gel column, 40 g, Gold (20 - 40 µm), 0-40% EtOAc/hex. The fractions containing desired product were combined. Volatiles were removed with rotovap to afford the title compound **49**, 4-(2,4-difluorophenyl)-6-(tetrahydro-2H-pyran-4-yl)picolinonitrile (223.2 mg, 0.74 mmol, 93% yield) as off-white solid. R_f = 0.33 (in 30% EtOAc/hex.).

500 mg scale: 6-chloro-4-(2,4-difluorophenyl)picolinonitrile (500 mg, 2.0 mmol) was used in a 40 mL vial, irradiated with Integrated Photoreactor, Royal Blue (450 nm) LED light for 2.5 h, following the same procedure as shown above. Reaction mixture was partitioned between EtOAc (20 mL) and water (5 mL). Aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic layers was concentrated with GeneVac. The residue was purified with ISCO, using silica gel column, 80 g, Gold (20 - 40 µm), 0-30% EtOAc/hex. The fractions containing desired product were combined. Volatiles were removed with rotovap to afford the title compound **49**, 4-(2,4-difluorophenyl)-6-(tetrahydro-2H-pyran-4-yl)picolinonitrile (538.2 mg, 1.79 mmol, 90% yield) as off-white solid.

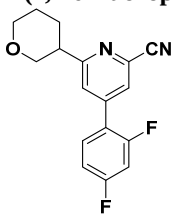
4-(2,4-difluorophenyl)-6-(tetrahydro-2*H*-pyran-2-yl)picolinonitrile (50)
4-(2,4-difluorophenyl)-5-(tetrahydro-2*H*-pyran-2-yl)picolinonitrile (51)



A 2-dram vial equipped with a stir bar was charged with 6-chloro-4-(2,4-difluorophenyl)picolinonitrile (20 mg, 0.080 mmol), 4,4'-di-*tert*-butyl-2,2'-bypyridine (3.21 mg, 0.012 mmol), (Ir[dF(CF_3)ppy]$_2$(dtbbpy))PF_6 (0.895 mg, 0.798 µmol), nickel(II) chloride ethylene glycol dimethyl ether complex (1.753 mg, 7.98 µmol) and cesium carbonate (78 mg, 0.239 mmol). It was transferred into glove box. Tetrahydropyran-2-carboxylic acid (15.58 mg, 0.120 mmol) and anhydrous DMF (399 µl) was added into the reaction mixture. It was taken out of glove box. Irradiated with Integrated Photoreactor, Royal Blue (450 nm) LED light for 2 h, 100% LED light power. Stir rate was 1000 rpm. Fan rate was 4700 rpm. The reaction was checked with LCMS. It was complete. The reaction mixture was partitioned between EtOAc (2 mL) and water (0.5 mL). Aqueous layer was extracted with EtOAc (2 mL). The combined organic layers weas concentrated with GeneVac to dryness. The residue was purified with prep. TLC plate (in 25%

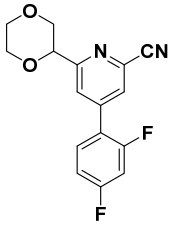
EtOAc/heptane). Two bands containing desired products were scratched off, stirred with EtOAc (30 mL) for 0.5 h, respectively. Then filtered and the filtrates were concentrated with rotovap under reduced pressure to afford compond **50** and **51**. They were further purified with Mass Directed semi-preparative HPLC system under TFA condition (0.16% TFA in both CH_3CN and H_2O, 12 min. run, 25 mL/min., 40 – 80% CH_3CN), to afford 4-(2,4-difluorophenyl)-6-(tetrahydro-2*H*-pyran-2-yl)picolinonitrile, compound **50**, LCMS R_T = 1.12 min. (2 min. run), as TFA salt (8 mg, 0.019 mmol, 24.20 % yield) as brown oil. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.18 (s, 1H), 7.89 (s, 1H), 7.83 (td, *J* = 8.9, 6.6 Hz, 1H), 7.50 (ddd, *J* = 11.5, 9.3, 2.5 Hz, 1H), 7.31 (td, *J* = 8.5, 2.3 Hz, 1H), 4.51 (dd, *J* = 11.2, 2.1 Hz, 1H), 4.09 (d, *J* = 12.0 Hz, 1H), 3.61 (ddd, *J* = 11.3, 8.8, 6.2 Hz, 1H), 2.07 – 2.00 (m, 1H), 1.90 (m, 1H), 1.70 (m, 1H), 1.59 (m, 2H), 1.48 (qd, *J* = 12.7, 3.9 Hz, 1H). Chemical Formula of $[M+H]^+$: $C_{17}H_{15}F_2N_2O^+$; Exact Mass (calculated): 301.1147; **HRMS (ESI$^+$)** (found): 301.1143. NOTE: ^{1}H NMR spectra showed peaks of NH_4OH which was induced during HPLC fraction drying down with GeneVac system. And 4-(2,4-difluorophenyl)-5-(tetrahydro-2*H*-pyran-2-yl)picolinonitrile, compound **51**, LCMS R_T = 1.04 min. (2 min. run), as TFA salt (3.4 mg, 7.71 μmol, 9.67 % yield) as light brown oil. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.92 (s, 1H), 8.03 (s, 1H), 7.57 – 7.46 (m, 2H), 7.29 (td, *J* = 8.4, 2.0 Hz, 1H), 4.23 (d, *J* = 13.0 Hz, 1H), 3.98 (dd, *J* = 11.4, 4.2 Hz, 1H), 3.35 (td, *J* = 11.9, 2.5 Hz, 1H), 1.78 (d, *J* = 12.7 Hz, 1H), 1.61 – 1.44 (m, 4H), 1.44 – 1.31 (m, 1H). Chemical Formula of $[M+H]^+$: $C_{17}H_{15}F_2N_2O^+$; Exact Mass (calculated): 301.1147; **HRMS (ESI$^+$)** (found): 301.1144.

4-(2,4-difluorophenyl)-6-(tetrahydro-2*H*-pyran-3-yl)picolinonitrile (52)



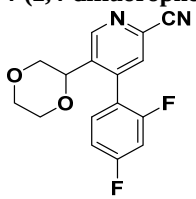
General procedure 8 was followed where tetrahydro-2*H*-pyran-3-carboxylic acid was used as alkyl-carboxylic acid. It was purified with Mass Directed HPLC system under NH_4OH condition (0.16% NH_4OH in both CH_3CN and H_2O, 12 min. run, 25 mL/min., 40 – 75% CH_3CN), to afford 18.2 mg of light brown oil. It was further purified with prep. TLC plate (in 30% EtOAc/heptane), to afford the title compound **52**, 4-(2,4-difluorophenyl)-6-(tetrahydro-2*H*-pyran-3-yl)picolinonitrile (14.4 mg, 95% pure) as colorless oil. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.12 (s, 1H), 7.90 (s, 1H), 7.83 (q, *J* = 8.5 Hz, 1H), 7.51 (t, *J* = 10.3 Hz, 1H), 7.32 (t, *J* = 8.4 Hz, 1H), 4.01 (d, *J* = 10.7 Hz, 1H), 3.88 (d, *J* = 11.0 Hz, 1H), 3.55 (t, *J* = 10.6 Hz, 1H), 3.42 (td, *J* = 10.8, 4.3 Hz, 1H), 3.16 – 3.07 (m, 1H), 2.09 – 2.02 (m, 1H), 1.90 (m, 1H), 1.71 – 1.63 (m, 2H). Chemical Formula of $[M+H]^+$: $C_{17}H_{15}F_2N_2O^+$; Exact Mass (calculated): 301.1147; **HRMS (ESI$^+$)** (found): 301.1147.

4-(2,4-difluorophenyl)-6-(1,4-dioxan-2-yl)picolinonitrile (53)



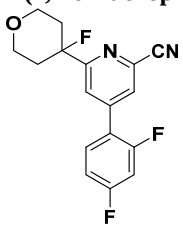
General procedure 8 was followed where 1,4-dioxane-2-carboxylic acid was used as alkyl-carboxylic acid. It was purified with Mass Directed HPLC system under TFA condition (0.16% TFA in both CH_3CN and H_2O, 12 min. run, 25 mL/min., 35 – 70% CH_3CN), to afford the title compound **53**, LCMS R_T = 0.97 min. (2 min. run), 4-(2,4-difluorophenyl)-6-(1,4-dioxan-2-yl)picolinonitrile as TFA salt (17.8 mg, 96% pure), light brown solid. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.24 (t, *J* = 1.4 Hz, 1H), 7.97 – 7.92 (m, 1H), 7.84 (td, *J* = 8.9, 6.5Hz, 1H), 7.51 (ddd, *J* = 11.6, 9.3, 2.6 Hz, 1H), 7.36 – 7.28 (m, 1H), 4.78 (dd, *J* = 9.9, 2.9 Hz, 1H), 4.06 (dd, *J* = 11.5, 3.0 Hz, 1H), 3.96 (dd, *J* = 11.8, 2.7 Hz, 1H), 3.84 (td, *J* = 11.4, 2.7 Hz, 1H), 3.82 – 3.75 (m, 1H), 3.62 (td, *J* = 11.5, 2.9 Hz, 1H), 3.51 (dd, *J* = 11.5, 9.9 Hz, 1H). Chemical Formula of $[M+H]^+$: $C_{16}H_{13}F_2N_2O_2^+$; Exact Mass (calculated): 303.0940; **HRMS (ESI$^+$)** (found): 303.0939.

4-(2,4-difluorophenyl)-5-(1,4-dioxan-2-yl)picolinonitrile (54)



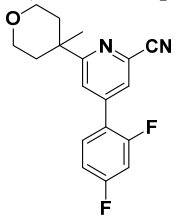
Compound **54** (3.0 mg, TFA salt, off-white solid, LCMS R_T = 0.97 min. in 2 min. run) was obtained in the preparation of compound **53**. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.96 (s, 1H), 8.08 (s, 1H), 7.60 – 7.49 (m, 2H), 7.32 (td, *J* = 8.5, 2.2 Hz, 1H), 4.49 – 4.42 (m, 1H), 3.89 – 3.83 (m, 1H), 3.71 – 3.66 (m, 1H), 3.65 – 3.56 (m, 3H), 3.49 (m, 1H). Chemical Formula of $[M+H]^+$: $C_{16}H_{13}F_2N_2O_2^+$; Exact Mass (calculated): 303.0940; **HRMS (ESI$^+$)** (found): 303.0939.

4-(2,4-difluorophenyl)-6-(4-fluorotetrahydro-2*H*-pyran-4-yl)picolinonitrile (55)



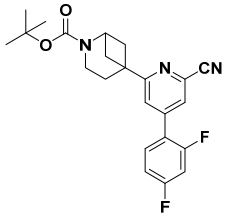
General procedure 8 was followed in a larger scale (80 mg of 6-chloro-4-(2,4-difluorophenyl)picolinonitrile) where 4-fluorotetrahydro-2*H*-pyran-4-carboxylic acid was used as alkyl-carboxylic acid. Irradiated with Royal Blue (450nm) LED light for 4 h. It was purified with ISCO, using silica gel column, 40 g, Gold (20 - 40 μm), 0-30% EtOAc/hex. The fractions containing desired product were combined. Volatiles were removed with rotovap to afford the title compound **55**, 4-(2,4-difluorophenyl)-6-(4-fluorotetrahydro-2*H*-pyran-4-yl)picolinonitrile (10.2 mg, 95% pure) as off-white solid. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.29 (m, 1H), 8.06 (q, *J* = 1.3 Hz, 1H), 7.88 (td, *J* = 8.9, 6.4 Hz, 1H), 7.52 (ddd, *J* = 11.6, 9.3, 2.6 Hz, 1H), 7.37 – 7.29 (m, 1H), 3.95 – 3.88 (m, 2H), 3.72 (td, *J* = 11.9, 2.1 Hz, 2H), 2.38 – 2.15 (m, 2H), 2.02 – 1.90 (m, 2H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 163.97, 145.33, 132.96, 132.84, 128.27, 122.93, 117.66, 113.15, 105.50, 63.14, 35.22, 35.05, 29.41. Chemical Formula of $[M+H]^+$: $C_{17}H_{14}F_3N_2O^+$; Exact Mass (calculated): 319.1053; **HRMS (ESI$^+$)** (found): 319.1050.

4-(2,4-difluorophenyl)-6-(4-methyltetrahydro-2*H*-pyran-4-yl)picolinonitrile (56)



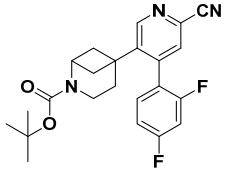
General procedure 8 was followed where 4-methyltetrahydro-2*H*-pyran-4-carboxylic acid was used as alkyl-carboxylic acid. It was purified with Mass Directed HPLC system under TFA condition (0.16% TFA in both CH_3CN and H_2O, 12 min. run, 25 mL/min., 40 – 80% CH_3CN), to afford the title compound **56**, 4-(2,4-difluorophenyl)-6-(4-methyltetrahydro-2*H*-pyran-4-yl)picolinonitrile, as TFA salt (4.2 mg, 90% pure), brown oil. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.11 (m, 1H), 7.95 (m, 1H), 7.85 (td, *J* = 8.9, 6.5 Hz, 1H), 7.50 (ddd, *J* = 11.5, 9.3, 2.6 Hz, 1H), 7.32 (td, *J* = 8.5, 2.5 Hz, 1H), 3.71 (ddd, *J* = 11.1, 7.0, 3.4 Hz, 2H), 3.48 (ddd, *J* = 11.3, 7.6, 3.3 Hz, 2H), 2.24 (ddd, *J* = 13.7, 7.2, 3.4 Hz, 2H), 1.74 (ddd, *J* = 13.6, 7.6, 3.4 Hz, 2H), 1.32 (s, 3H). Chemical Formula of $[M+H]^+$: $C_{18}H_{17}F_2N_2O^+$; Exact Mass (calculated): 315.1303; **HRMS (ESI$^+$)** (found): 315.1307. NOTE: ^{1}H NMR spectra showed peaks of NH_4OH which was induced during HPLC fraction drying down with GeneVac system.

***tert*-butyl 5-(6-cyano-4-(2,4-difluorophenyl)pyridin-2-yl)-2-azabicyclo[3.1.1]heptane-2-carboxylate (57)**



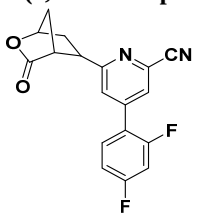
General procedure 8 was followed where 4-methyltetrahydro-2*H*-pyran-4-carboxylic acid was used as alkyl-carboxylic acid. It was purified with Mass Directed HPLC system under TFA condition (0.16% TFA in both CH_3CN and H_2O, 12 min. run, 25 mL/min., 30 – 70% CH_3CN), to afford 4.8 mg (90% pure, TFA salt) of dark brown oil, LCMS R_T = 1.19 min. (2 min. run). It was further purified with prep. TLC plate (in 25% EtOAc/heptane), to afford the title compound **57**, *tert*-butyl 5-(6-cyano-4-(2,4-difluorophenyl)pyridin-2-yl)-2-azabicyclo[3.1.1]heptane-2-carboxylate (2.4 mg, 90% pure) as off-white solid. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.11 (t, *J* = 1.4 Hz, 1H), 7.83 (td, *J* = 8.8, 6.4 Hz, 1H), 7.77 (t, *J* = 1.4 Hz, 1H), 7.51 (ddd, *J* = 11.5, 9.2, 2.5 Hz, 1H), 7.32 (td, *J* = 8.5, 2.6 Hz, 1H), 4.42 (d, *J* = 40.3 Hz, 1H), 3.73 (s, 2H), 2.49 (m, 2H), 2.27 (t, *J* = 7.0 Hz, 2H), 2.08 (m, 2H), 1.46 – 1.41 (s, 9H). Chemical Formula of $[M+H]^+$: $C_{23}H_{24}F_2N_3O_2^+$; Exact Mass (calculated): 412.1831; **HRMS (ESI$^+$)** (found): 412.1837.

***tert*-butyl 5-(6-cyano-4-(2,4-difluorophenyl)pyridin-3-yl)-2-azabicyclo[3.1.1]heptane-2-carboxylate (58)**



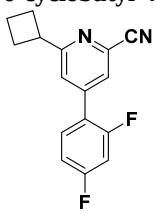
Compound **58** (6.9 mg, TFA salt, light brown solid, LCMS R_T = 1.13 min. in 2 min. run) was obtained in the preparation of compound **57**. It was further purified with prep. TLC plate (in 25% EtOAc/heptane), to afford the title compound **58**, *tert*-butyl 5-(6-cyano-4-(2,4-difluorophenyl)pyridin-3-yl)-2-azabicyclo[3.1.1]heptane-2-carboxylate (3.9 mg, 85% pure) as off-white solid. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.64 (s, 1H), 7.94 (s, 1H), 7.51 – 7.39 (m, 2H), 7.23 (td, *J* = 8.4, 2.3 Hz, 1H), 4.24 (d, *J* = 36.5 Hz, 1H), 3.53 (s, 2H), 2.27 – 2.17 (m, 1H), 2.10 (m, 3H), 1.77 (s, 1H), 1.59 (s, 1H), 1.36 (m, 9H). Chemical Formula of $[M+H]^+$: $C_{23}H_{24}F_2N_3O_2^+$; Exact Mass (calculated): 412.1831; **HRMS (ESI$^+$)** (found): 412.1839.

4-(2,4-difluorophenyl)-6-((1*R*,4*R*)-3-oxo-2-oxabicyclo[2.2.1]heptan-5-yl)picolinonitrile (59)



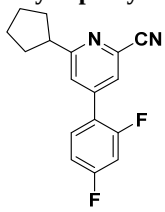
General procedure 8 was followed where 3-oxo-2-oxabicyclo[2.2.1]heptane-5-carboxylic acid was used as alkyl-carboxylic acid. It was purified with Mass Directed HPLC system under TFA condition (0.16% TFA in both CH_3CN and H_2O, 15 min. run, 25 mL/min., 30 – 75% CH_3CN), to afford the title compound **59**, 4-(2,4-difluorophenyl)-6-((1*R*,4*R*)-3-oxo-2-oxabicyclo[2.2.1]heptan-5-yl)picolinonitrile (8.6 mg, 100% pure, LCMS R_T = 0.98 min. in 2 min. run), as TFA salt, light brown solid. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.15 (t, *J* = 1.5 Hz, 1H), 7.99 (m, 1H), 7.84 (td, *J* = 8.9, 6.4 Hz, 1H), 7.48 (ddd, *J* = 11.5, 9.2, 2.6 Hz, 1H), 7.31 (td, *J* = 8.7, 3.0 Hz, 1H), 5.14 (t, *J* = 1.7 Hz, 1H), 3.59 (dd, *J* = 8.8, 4.7 Hz, 1H), 3.13 (s, 1H), 2.42 (ddd, *J* = 13.6, 4.7, 1.9 Hz, 1H), 2.35 – 2.26 (m, 1H), 2.18 – 2.05 (m, 2H). Chemical Formula of $[M+H]^+$: $C_{18}H_{13}F_2N_2O_2^+$; Exact Mass (calculated): 327.0940; **HRMS (ESI$^+$)** (found): 327.0939.

6-cyclobutyl-4-(2,4-difluorophenyl)picolinonitrile (60)



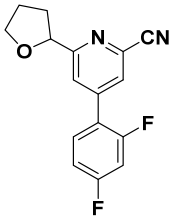
General procedure 8 was followed where cyclobutanecarboxylic acid was used as alkyl-carboxylic acid. It was purified with Mass Directed HPLC system under TFA condition (0.16% TFA in both CH_3CN and H_2O, 15 min. run, 25 mL/min., 45 – 85% CH_3CN), to afford the title compound **60**, 6-cyclobutyl-4-(2,4-difluorophenyl)picolinonitrile (8.9 mg, 90% pure), as TFA salt, colorless oil. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.08 (t, *J* = 1.3 Hz, 1H), 7.82 (td, *J* = 8.9, 6.5 Hz, 1H), 7.78 (t, *J* = 1.3 Hz, 1H), 7.49 (ddd, *J* = 11.6, 9.3, 2.5 Hz, 1H), 7.31 (td, *J* = 8.2, 1.7 Hz, 1H), 3.79 (p, *J* = 8.9 Hz, 1H), 2.33 (td, *J* = 8.9, 6.0 Hz, 4H), 2.09 – 2.00 (m, 1H), 1.93 – 1.84 (m, 1H). Chemical Formula of $[M+H]^+$: $C_{16}H_{13}F_2N_2^+$; Exact Mass (calculated): 271.1041; **HRMS (ESI$^+$)** (found): 271.1042.

6-cyclopentyl-4-(2,4-difluorophenyl)picolinonitrile (61)



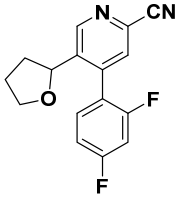
General procedure 8 was followed where cyclopentanecarboxylic acid was used as alkyl-carboxylic acid. It was purified with Mass Directed HPLC system under TFA condition (0.16% TFA in both CH_3CN and H_2O, 12 min. run, 25 mL/min., 26 – 79% CH_3CN), to afford the title compound **61**, 6-cyclopentyl-4-(2,4-difluorophenyl)picolinonitrile (17.2 mg, 100% pure), as TFA salt, colorless oil. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.06 (t, *J* = 1.4 Hz, 1H), 7.82 (dq, *J* = 5.2, 2.7 Hz, 2H), 7.49 (ddd, *J* = 11.6, 9.3, 2.5 Hz, 1H), 7.35 – 7.27 (m, 1H), 3.35 – 3.28 (m, 1H), 2.11 – 2.01 (m, 2H), 1.84 – 1.71 (m, 4H), 1.68 (m, 2H). Chemical Formula of $[M+H]^+$: $C_{17}H_{15}F_2N_2^+$; Exact Mass (calculated): 285.1198; **HRMS (ESI$^+$)** (found): 285.1201.

4-(2,4-difluorophenyl)-6-(tetrahydrofuran-2-yl)picolinonitrile (62)



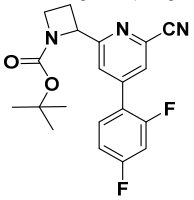
General procedure 8 was followed where tetrahydrofuran-2-carboxylic acid was used as alkyl-carboxylic acid. It was purified with Mass Directed HPLC system under TFA condition (0.16% TFA in both CH_3CN and H_2O, 15 min. run, 25 mL/min., 35 – 80% CH_3CN), to afford the compound **62**, (11.8 mg), as TFA salt, brown oil. LCMS R_T = 1.02 min. (2 min. run). It was further purified with prep. TLC plate (in 25% EtOAc/heptane), to afford the title compound **62**, 4-(2,4-difluorophenyl)-6-(tetrahydrofuran-2-yl)picolinonitrile, 6.4 mg, 95% pure, as off-white solid. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.17 (s, 1H), 7.89 (s, 1H), 7.84 (td, J = 8.9, 6.5 Hz, 1H), 7.50 (ddd, J = 11.6, 9.3, 2.5 Hz, 1H), 7.35 – 7.27 (m, 1H), 5.01 (dd, J = 7.2, 5.6 Hz, 1H), 4.08 – 4.00 (m, 1H), 3.94 – 3.86 (m, 1H), 2.42 – 2.35 (m, 1H), 2.03 – 1.88 (m, 3H). Chemical Formula of $[M+H]^+$: $C_{16}H_{13}F_2N_2O^+$; Exact Mass (calculated): 287.0990; **HRMS (ESI$^+$)** (found): 287.0994.

4-(2,4-difluorophenyl)-5-(tetrahydrofuran-2-yl)picolinonitrile (63)



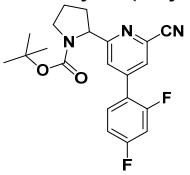
Compound **63** (5.7 mg, TFA salt, brown oil, LCMS R_T = 0.97 min. in 2 min. run) was obtained in the preparation of compound **62**. It was further purified with prep. TLC plate (in 25% EtOAc/heptane), to afford the title compound **63**, *tert*-butyl 5-(6-cyano-4-(2,4-difluorophenyl)pyridin-3-yl)-2-azabicyclo[3.1.1]heptane-2-carboxylate (3.9 mg, 85% pure) as off-white solid. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.90 (s, 1H), 8.02 (s, 1H), 7.55 – 7.46 (m, 2H), 7.31 – 7.26 (m, 1H), 4.74 (t, J = 7.4 Hz, 1H), 4.01 (dt, J = 8.1, 6.7 Hz, 1H), 3.75 (td, J = 7.8, 6.1 Hz, 1H), 2.05 – 1.98 (m, 1H), 1.97 – 1.91 (m, 1H), 1.90 – 1.83 (m, 1H), 1.64 (dq, J = 12.0, 7.9 Hz, 1H). Chemical Formula of $[M+H]^+$: $C_{16}H_{13}F_2N_2O^+$; Exact Mass (calculated): 287.0990; **HRMS (ESI$^+$)** (found): 287.0992.

***tert*-butyl 2-(6-cyano-4-(2,4-difluorophenyl)pyridin-2-yl)azetidine-1-carboxylate (64)**



General procedure 8 was followed where 1-(*tert*-butoxycarbonyl)azetidine-2-carboxylic acid was used as alkyl-carboxylic acid. It was purified with Mass Directed HPLC system under NH_4OH condition (0.16% NH_4OH in both CH_3CN and H_2O, 12 min. run, 25 mL/min., 41 – 71% CH_3CN), to afford the title compound **64**, *tert*-butyl 2-(6-cyano-4-(2,4-difluorophenyl)pyridin-2-yl)azetidine-1-carboxylate (23.8 mg, 100% pure), as light brown oil. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.22 (t, J = 1.3 Hz, 1H), 7.96 (m, 1H), 7.83 (td, J = 8.9, 6.4 Hz, 1H), 7.53 (ddd, J = 11.6, 9.2, 2.6 Hz, 1H), 7.38 – 7.30 (m, 1H), 5.32 (dd, J = 8.9, 5.9 Hz, 1H), 4.05 – 3.89 (m, 2H), 2.70 – 2.59 (m, 1H), 2.25 (m, 1H), 1.20 (brs, 9H). Chemical Formula of $[M+H]^+$: $C_{20}H_{20}F_2N_3O_2^+$; Exact Mass (calculated): 372.1518; **HRMS (ESI$^+$)** (found): 372.1525.

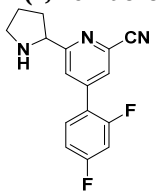
***tert*-butyl 2-(6-cyano-4-(2,4-difluorophenyl)pyridin-2-yl)pyrrolidine-1-carboxylate (65)**



General procedure 8 was followed where (*tert*-butoxycarbonyl)proline was used as alkyl-carboxylic acid. It was purified with Mass Directed HPLC system under TFA condition (0.16% TFA in both CH_3CN and H_2O, 12 min. run, 25 mL/min., 45 – 80% CH_3CN), to afford the compound **65**, (4.7 mg), as TFA salt, light brown oil. LCMS R_T = 1.17 min. (2 min. run). It was further purified with prep. TLC plate (in 25% EtOAc/heptane), followed by microscale purification under TFA condition (0.16% TFA in both CH_3CN and H_2O, 6 min. run, 8 mL/min., 40 – 75% CH_3CN) to afford the title compound **65**, *tert*-butyl 2-(6-cyano-4-(2,4-difluorophenyl)pyridin-2-yl)pyrrolidine-1-carboxylate (0.5 mg, TFA salt, as light brown solid). Chemical Formula of $[M+H]^+$: $C_{21}H_{22}F_2N_3O_2^+$; Exact Mass (calculated): 386.1675; **HRMS (ESI$^+$)** (found): 386.1683. Boc-protecting group partially fell off. The

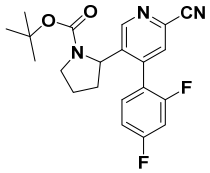
residue was treated with CH_2Cl_2 (0.3 mL) and trifluoroacetic acid (0.2 mL). Shaked at 240 rpm at r.t. for 1 h to remove Boc group. Volatiles were removed with GeneVac to afford compound **66**, 4-(2,4-difluorophenyl)-6-(pyrrolidin-2-yl)picolinonitrile (0.5 mg, 90% pure, TFA salt, reddish brown solid).

4-(2,4-difluorophenyl)-6-(pyrrolidin-2-yl)picolinonitrile (66)



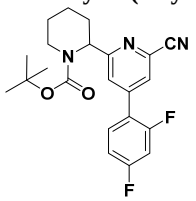
^{1}H NMR (500 MHz, DMSO-d_6) δ 9.01 (brs, 1H), 8.36 (m, 1H), 8.10 (m, 1H), 7.86 (td, J = 8.9, 6.5 Hz, 1H), 7.56 (ddd, J = 11.6, 9.3, 2.5 Hz, 1H), 7.41 – 7.33 (m, 1H), 4.95 (t, J = 7.5 Hz, 1H), 3.47 – 3.32 (m, 2H), 2.56 – 2.52 (m, 1H), 2.13 – 1.98 (m, 3H). Chemical Formula of $[M+H]^+$: $C_{16}H_{14}F_2N_3^+$; Exact Mass (calculated): 286.1150; **HRMS (ESI$^+$)** (found): 286.1163. NOTE: Due to low amount of the material, ^{1}H NMR spectra showed peaks of NH_4OH which was induced during HPLC fraction drying down with GeneVac system.

***tert*-butyl 2-(6-cyano-4-(2,4-difluorophenyl)pyridin-3-yl)pyrrolidine-1-carboxylate (67)**



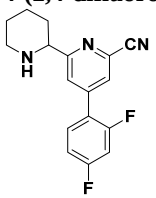
Compound **67** (5.0 mg, TFA salt, light brown oil) was prepared in the preparation of compound **65**. LCMS R_T = 1.14 min. (2 min. run); Chemical Formula of $[M+H]^+$: $C_{21}H_{22}F_2N_3O_2^+$; Exact Mass (calculated): 386.17; **Exact Mass (ESI$^+$)** (found): 386.09. It was lost during HPLC re-purification.

***tert*-butyl 2-(6-cyano-4-(2,4-difluorophenyl)pyridin-2-yl)piperidine-1-carboxylate (68)**



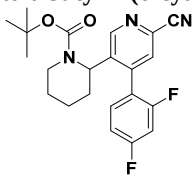
General procedure 8 was followed where 1-(*tert*-butoxycarbonyl)piperidine-2-carboxylic acid was used as alkyl-carboxylic acid. It was purified with Mass Directed HPLC system under TFA condition (0.16% TFA in both CH_3CN and H_2O, 12 min. run, 25 mL/min., 32 – 80% CH_3CN), to afford the compound **68**, (6.1 mg, 93% pure), as TFA salt, light brown oil. LCMS R_T = 1.23 min. (2 min. run). It was further purified with prep. TLC plate (in 25% EtOAc/heptane), followed by microscale purification under TFA condition (0.16% TFA in both CH_3CN and H_2O, 6 min. run, 8 mL/min., 50 – 85% CH_3CN) to afford the title compound **68**, *tert*-butyl 2-(6-cyano-4-(2,4-difluorophenyl)pyridin-2-yl)piperidine-1-carboxylate (0.2 mg, TFA salt, colorless film). Chemical Formula of $[M+H]^+$: $C_{22}H_{24}F_2N_3O_2^+$; Exact Mass (calculated): 400.1831; **HRMS (ESI$^+$)** (found): 400.1841. Boc-protecting group partially fell off. The residue was treated with CH_2Cl_2 (0.3 mL) and trifluoroacetic acid (0.2 mL). Shaked at 240 rpm at r.t. for 1 h to remove Boc group. Volatiles were removed with GeneVac to afford compound **69**, 4-(2,4-difluorophenyl)-6-(piperidin-2-yl)picolinonitrile (0.2 mg, 99% pure, TFA salt, colorless film).

4-(2,4-difluorophenyl)-6-(piperidin-2-yl)picolinonitrile (69)



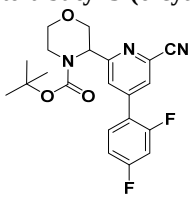
^{1}H NMR (500 MHz, DMSO-d_6) δ 9.06 (brs, 1H), 8.36 (m, 1H), 8.11 (m, 1H), 7.86 (td, J = 8.8, 6.5 Hz, 1H), 7.56 (ddd, J = 11.6, 9.3, 2.5 Hz, 1H), 7.37 (td, J = 8.5, 2.4 Hz, 1H), 4.59 – 4.57 (m, 1H), 3.42 – 3.40 (m, 1H), 3.11 – 3.02 (m, 1H), 2.28 – 2.22 (m, 1H), 1.96 – 1.86 (m, 1H), 1.84 – 1.81 (m, 1H), 1.77 – 1.64 (m, 3H). Chemical Formula of $[M+H]^+$: $C_{17}H_{16}F_2N_3^+$; Exact Mass (calculated): 300.1307; **HRMS (ESI$^+$)** (found): 300.1315. NOTE: Due to low amount of the material, ^{1}H NMR spectra showed peaks of NH_4OH which was induced during HPLC fraction drying down with GeneVac system.

***tert*-butyl 2-(6-cyano-4-(2,4-difluorophenyl)pyridin-3-yl)piperidine-1-carboxylate (70)**



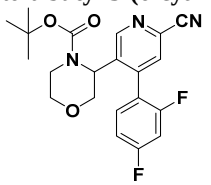
Compound **70** (9.6 mg, 90% pure, TFA salt, light brown oil) was prepared in the preparation of compound **68**. LCMS R_T = 1.17 min. (2 min. run); Chemical Formula of $[M+H]^+$: $C_{22}H_{24}F_2N_3O_2^+$; Exact Mass (calculated): 400.18; **Exact Mass (ESI$^+$)** (found): 399.90. It was lost during HPLC re-purification.

***tert*-butyl 3-(6-cyano-4-(2,4-difluorophenyl)pyridin-2-yl)morpholine-4-carboxylate (71)**



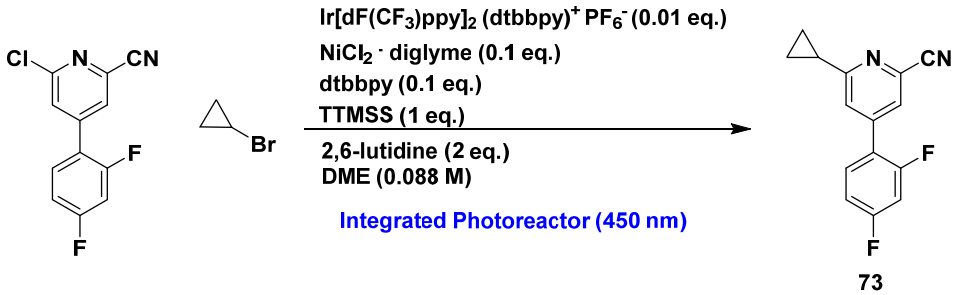
General procedure 8 was followed where 4-(*tert*-butoxycarbonyl)morpholine-3-carboxylic acid was used as alkyl-carboxylic acid. It was purified with Mass Directed HPLC system under NH_4OH condition (0.16% NH_4OH in both CH_3CN and H_2O, 12 min. run, 25 mL/min., 40 – 70% CH_3CN), to afford 8.8 mg (90% pure) of compound **71**, LCMS R_T = 1.09 min. (2 min. run). It was further purified with prep. TLC plate (in 25% EtOAc/heptane), to afford the title compound **71**, *tert*-butyl 3-(6-cyano-4-(2,4-difluorophenyl)pyridin-2-yl)morpholine-4-carboxylate (5.6 mg, 95% pure) as off-white film. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.19 (s, 1H), 7.87 – 7.79 (m, 2H), 7.52 (ddd, *J* = 11.6, 9.3, 2.5 Hz, 1H), 7.37 – 7.29 (m, 1H), 5.09 (s, 1H), 4.48 (d, *J* = 12.1 Hz, 1H), 3.83 (dd, *J* = 12.1, 3.9 Hz, 2H), 3.75 – 3.68 (m, 1H), 3.49 (td, *J* = 11.7, 3.1 Hz, 1H), 3.28 (m, 1H), 1.37 (s, 9H). Chemical Formula of $[M+H]^+$: $C_{21}H_{22}F_2N_3O_3^+$; Exact Mass (calculated): 402.1624; **HRMS (ESI$^+$)** (found): 402.1631.

***tert*-butyl 3-(6-cyano-4-(2,4-difluorophenyl)pyridin-3-yl)morpholine-4-carboxylate (72)**



Compound **72** (0.8 mg, LCMS R_T = 1.04 min. in 2 min. run) was obtained in the preparation of compound **71**. It was further purified with prep. TLC plate (in 25% EtOAc/heptane), to afford the title compound **72**, *tert*-butyl 3-(6-cyano-4-(2,4-difluorophenyl)pyridin-3-yl)morpholine-4-carboxylate (0.4 mg, 95% pure) as off-white film. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.97 (s, 1H), 8.04 (s, 1H), 7.51 – 7.41 (m, 2H), 7.26 (t, *J* = 7.3 Hz, 1H), 4.94 (s, 1H), 3.98 (d, *J* = 12.2 Hz, 1H), 3.83 (dt, *J* = 11.0, 2.3 Hz, 1H), 3.63 (dd, *J* = 12.2, 4.1 Hz, 1H), 3.47 (td, *J* = 11.4, 3.7 Hz, 1H), 3.19 (ddd, *J* = 14.2, 10.8, 3.9 Hz, 1H), 1.26 (s, 9H). Chemical Formula of $[M+H]^+$: $C_{21}H_{22}F_2N_3O_3^+$; Exact Mass (calculated): 402.1624; **HRMS (ESI$^+$)** (found): 402.1631.

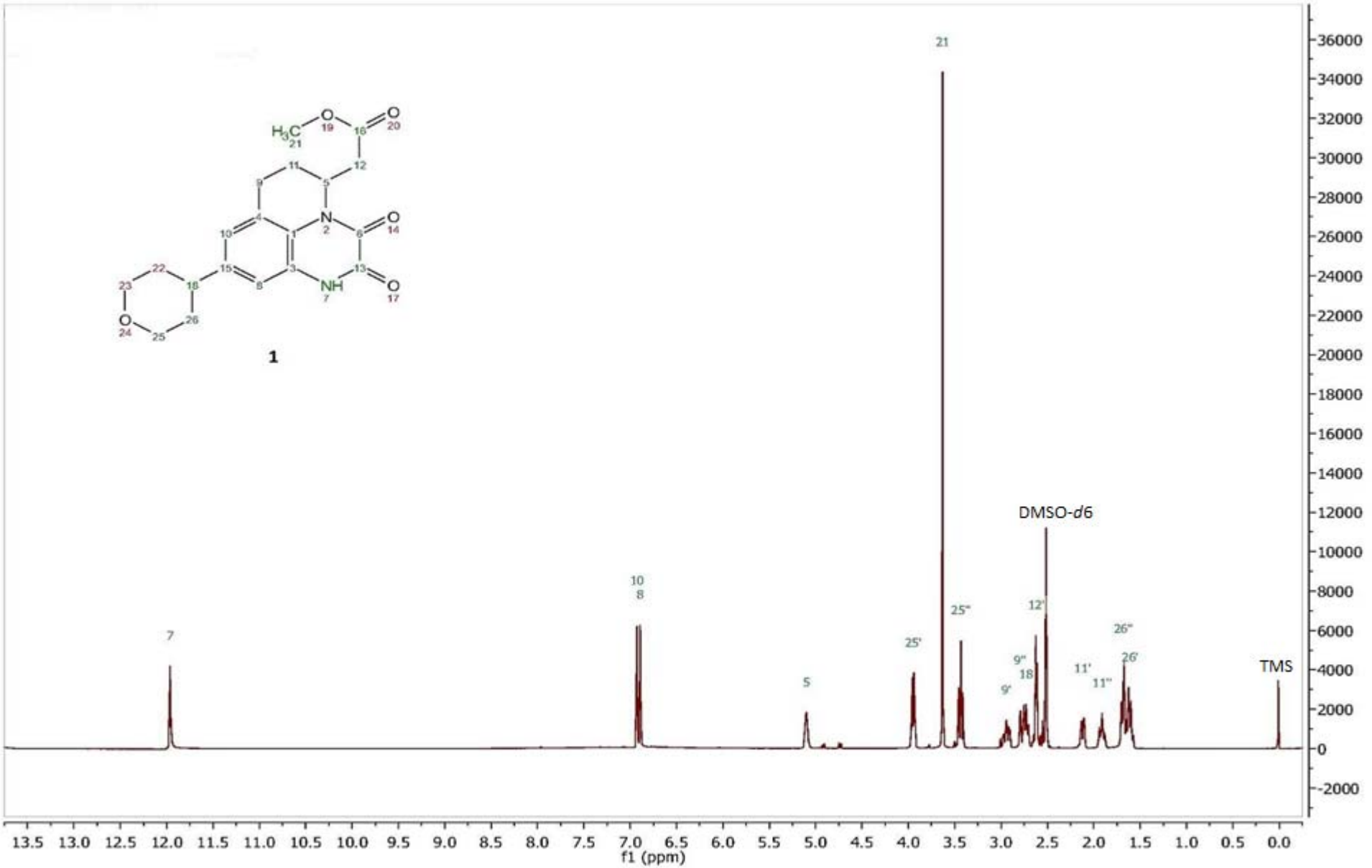
6-cyclopropyl-4-(2,4-difluorophenyl)picolinonitrile (73)



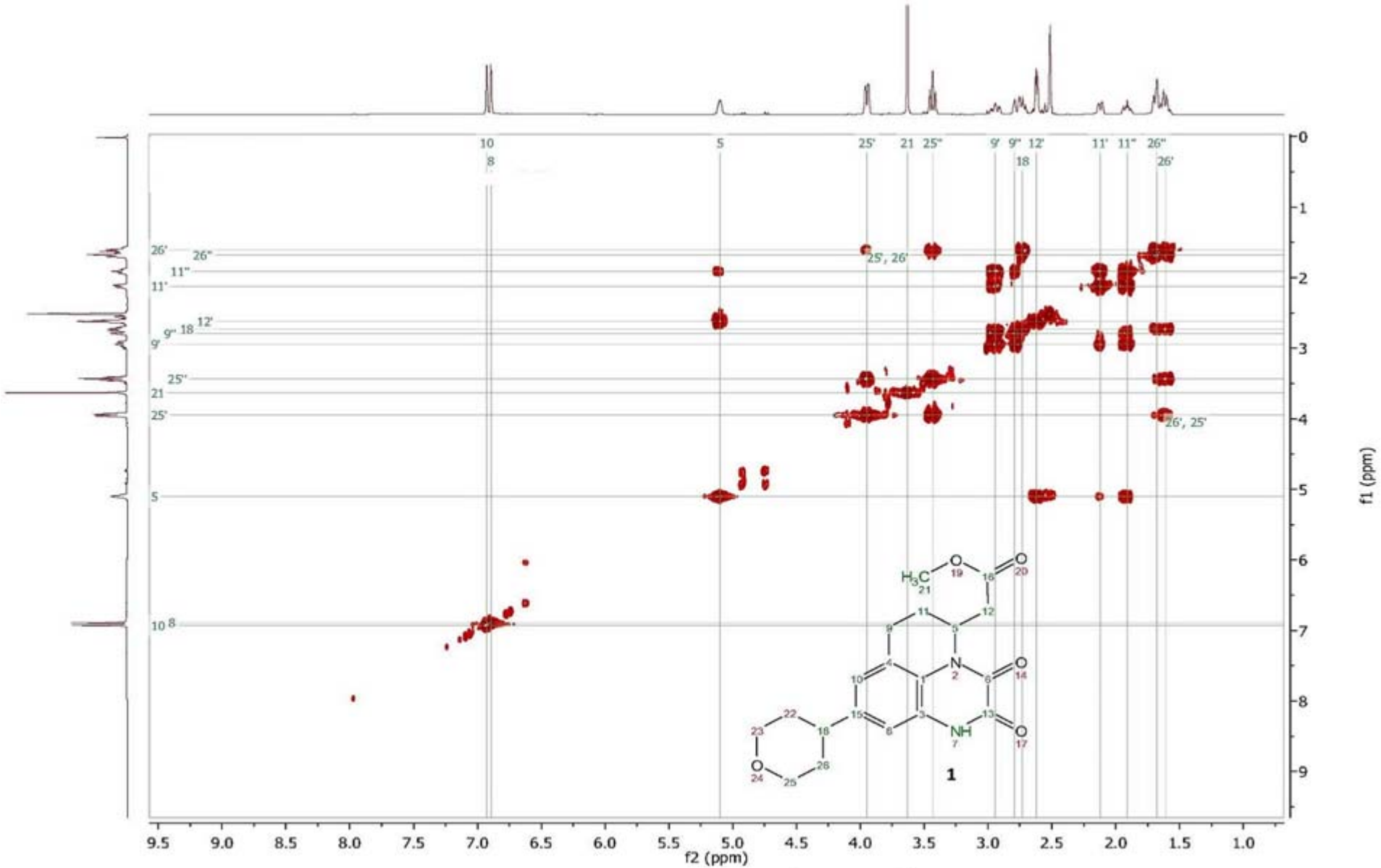
73

General procedure 6 was followed where 6-chloro-4-(2,4-difluorophenyl)picolinonitrile was used as aryl-halide and bromocyclopropane was used as alkyl-halide. It was purified with Mass Directed HPLC system under TFA condition (0.16% TFA in both CH_3CN and H_2O, 8 min. run, 25 mL/min., 50 – 85% CH_3CN) to afford the title compound **73** as TFA salt, 1.9 mg (96% pure), as brown oil. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 7.98 (m, 1H), 7.85 (m, 1H), 7.81 (td, *J* = 8.8, 6.5 Hz, 1H), 7.50 (ddd, *J* = 11.5, 9.3, 2.5 Hz, 1H), 7.31 (td, *J* = 8.5, 2.5 Hz, 1H), 2.29 (tt, *J* = 8.1, 4.8 Hz, 1H), 1.12 – 1.06 (m, 2H), 1.03 (ddd, *J* = 7.3, 5.1, 2.8 Hz, 2H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 165.77, 143.71, 133.03, 132.84, 125.93, 125.67, 121.34, 118.08, 113.17, 105.44, 17.26, 11.36. Chemical Formula of $[M+H]^+$: $C_{15}H_{11}F_2N_2^+$; Exact Mass (calculated): 257.0885; **HRMS (ESI$^+$)** (found): 257.0883.

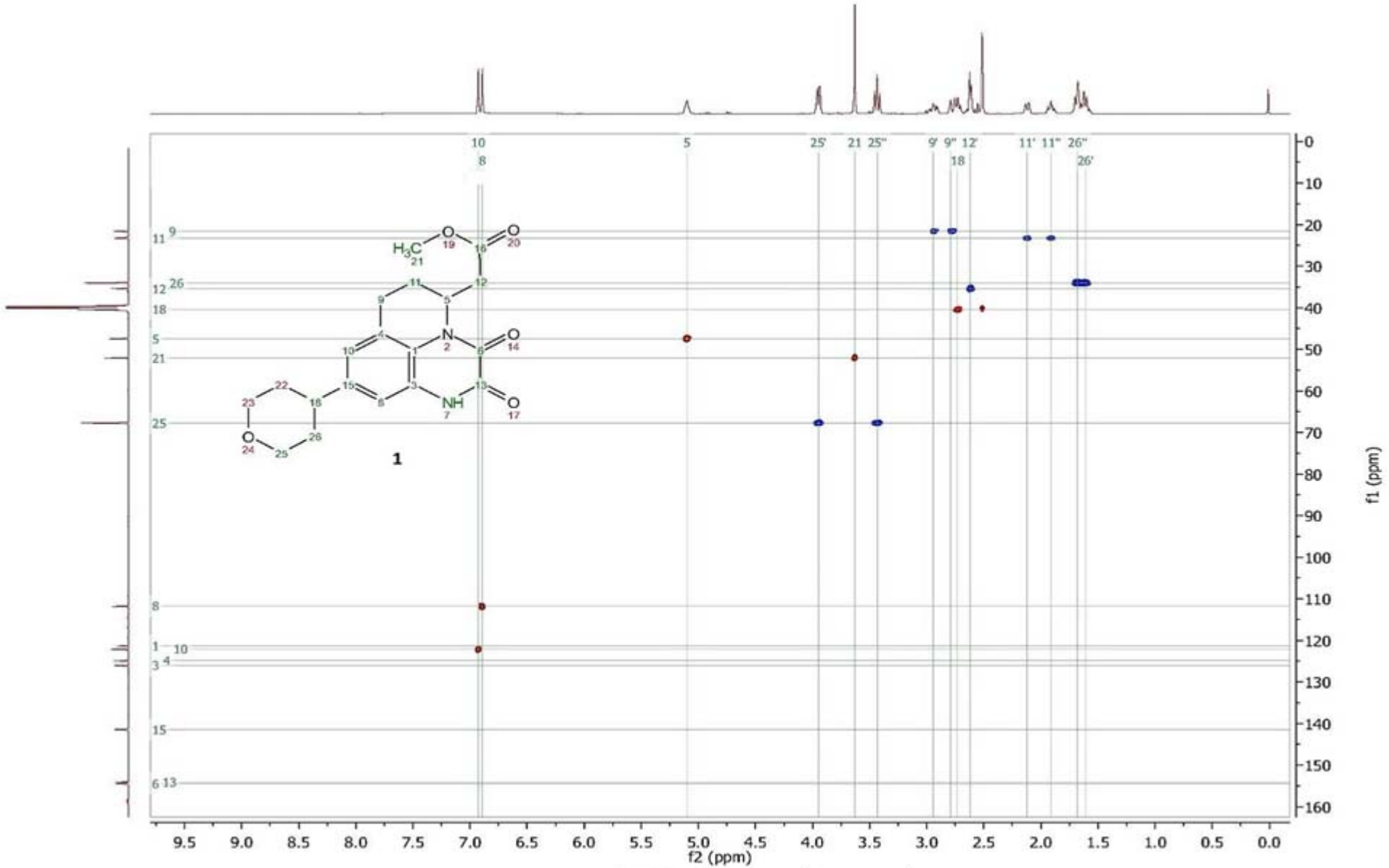
IV. NMR Spectral Data for Novel Compounds



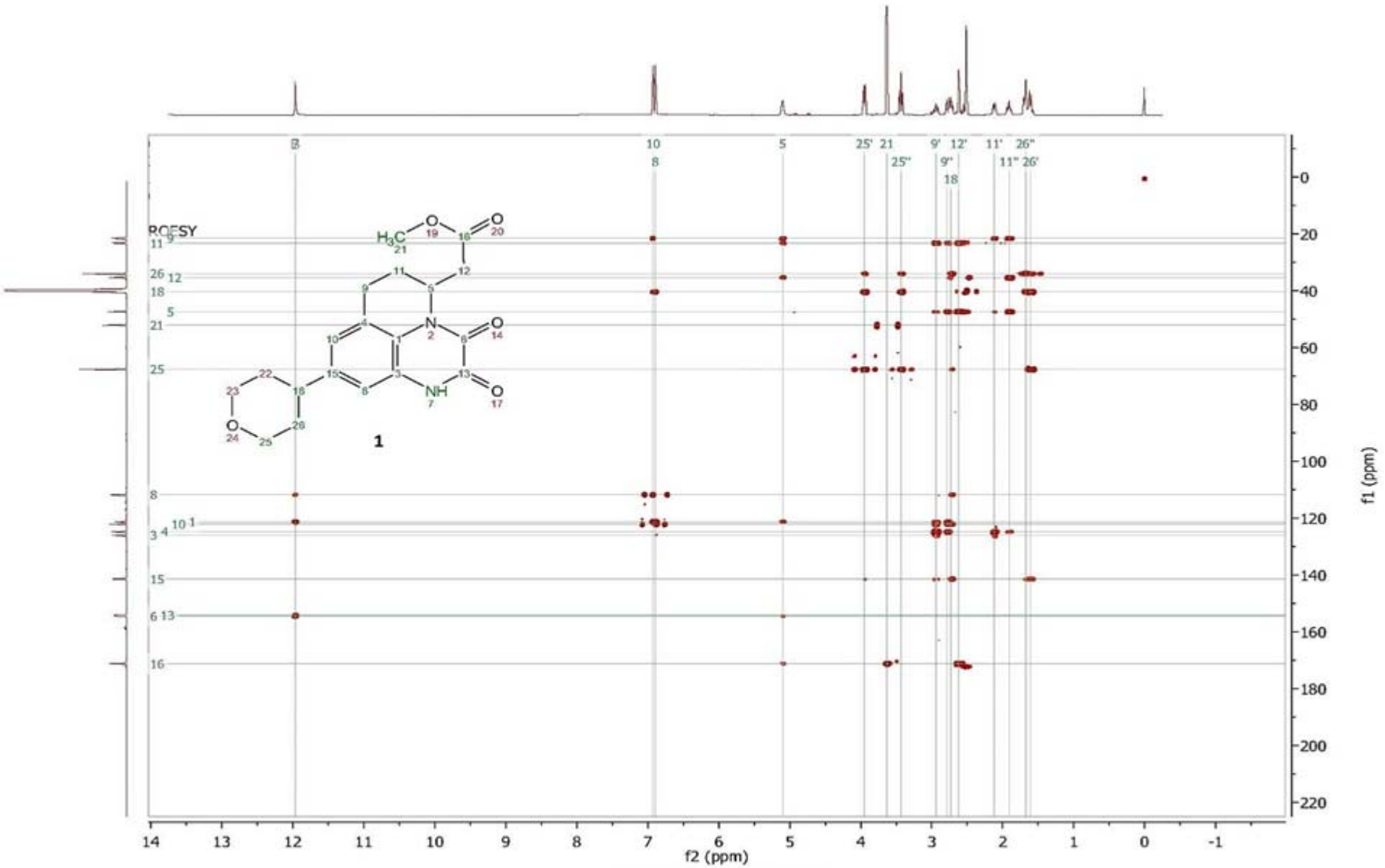
^{1}H NMR of compound **1** in DMSO-*d*6



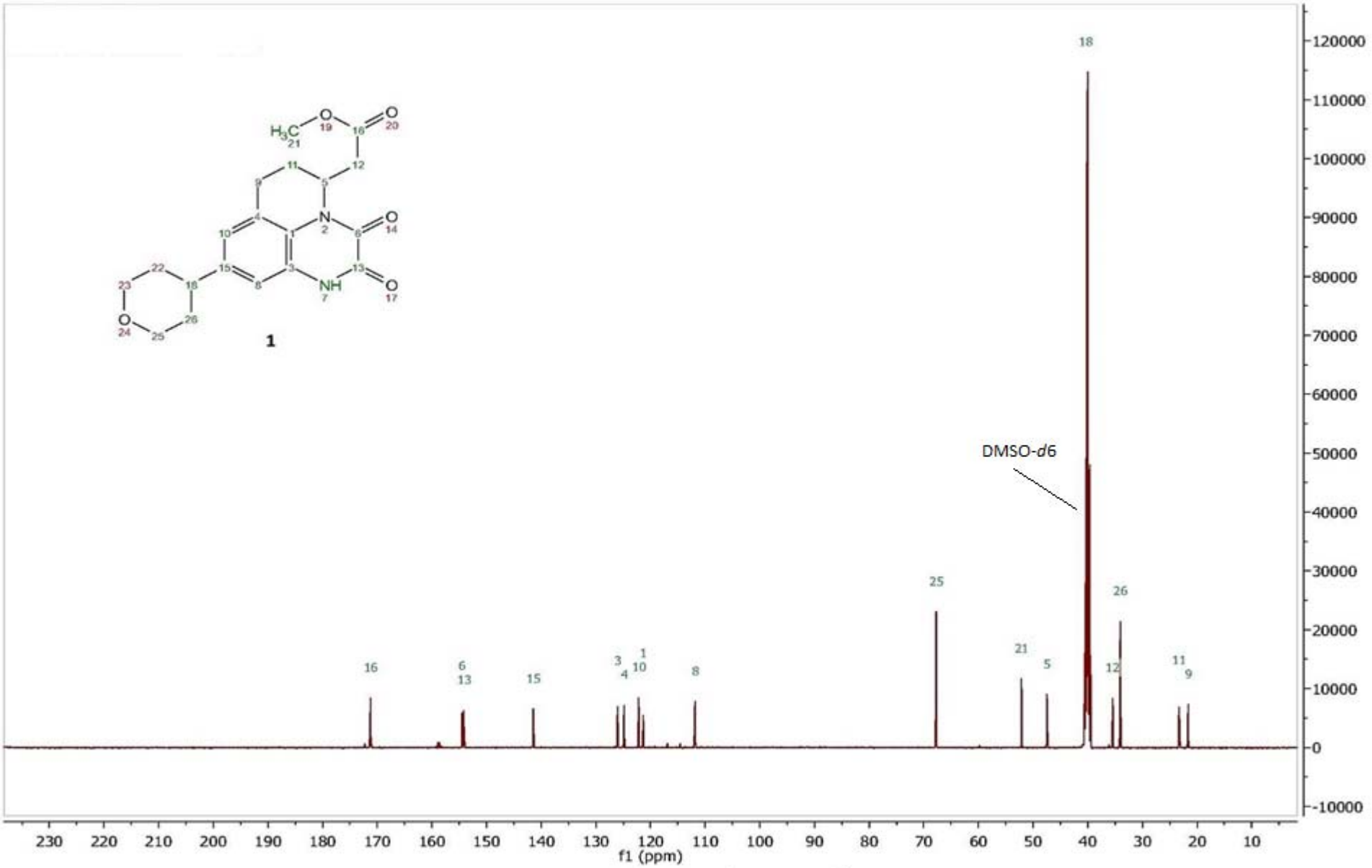
2D COSY of compound **1** in DMSO-*d*6



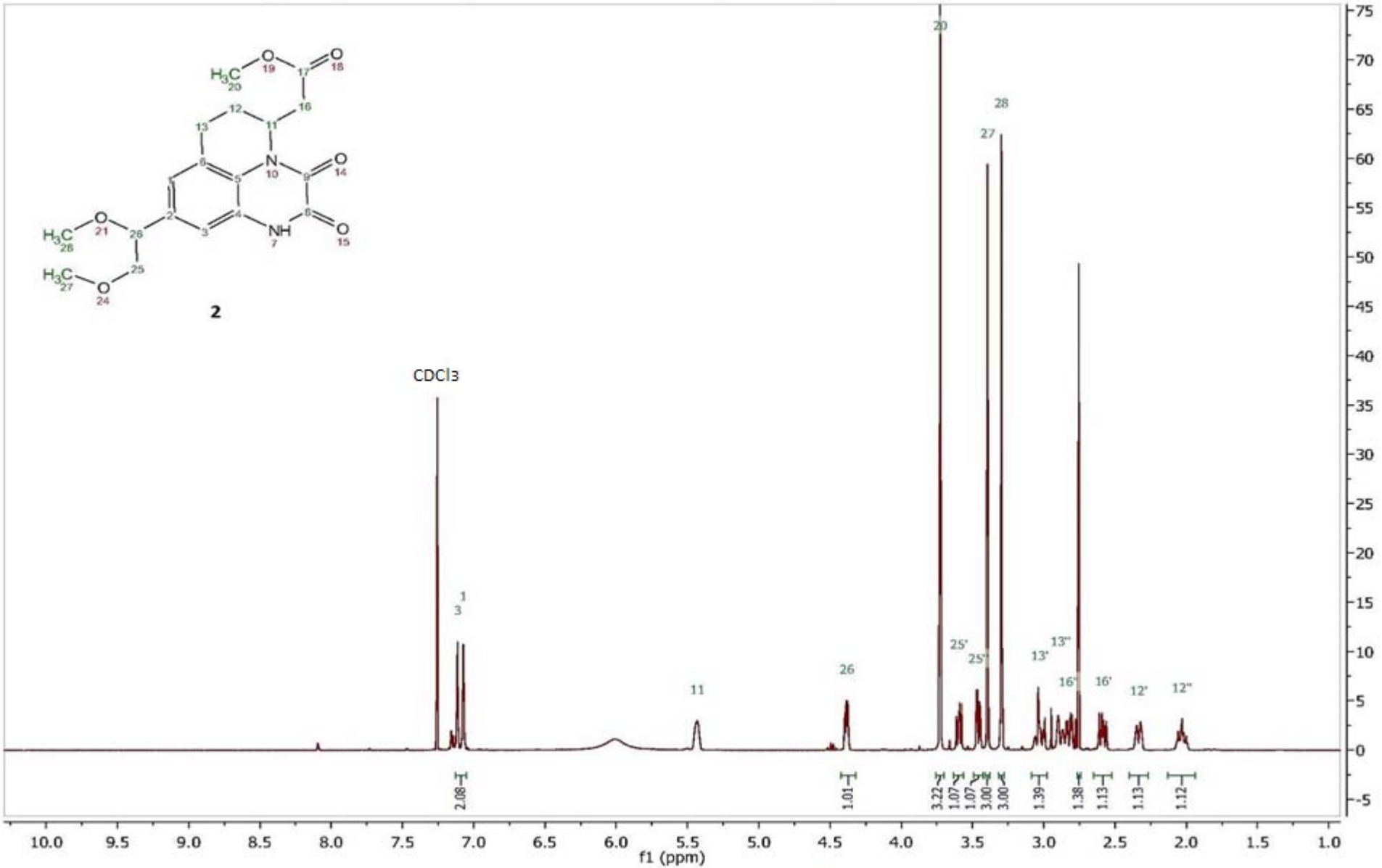
2D HSQC of compound **1** in DMSO-*d*6



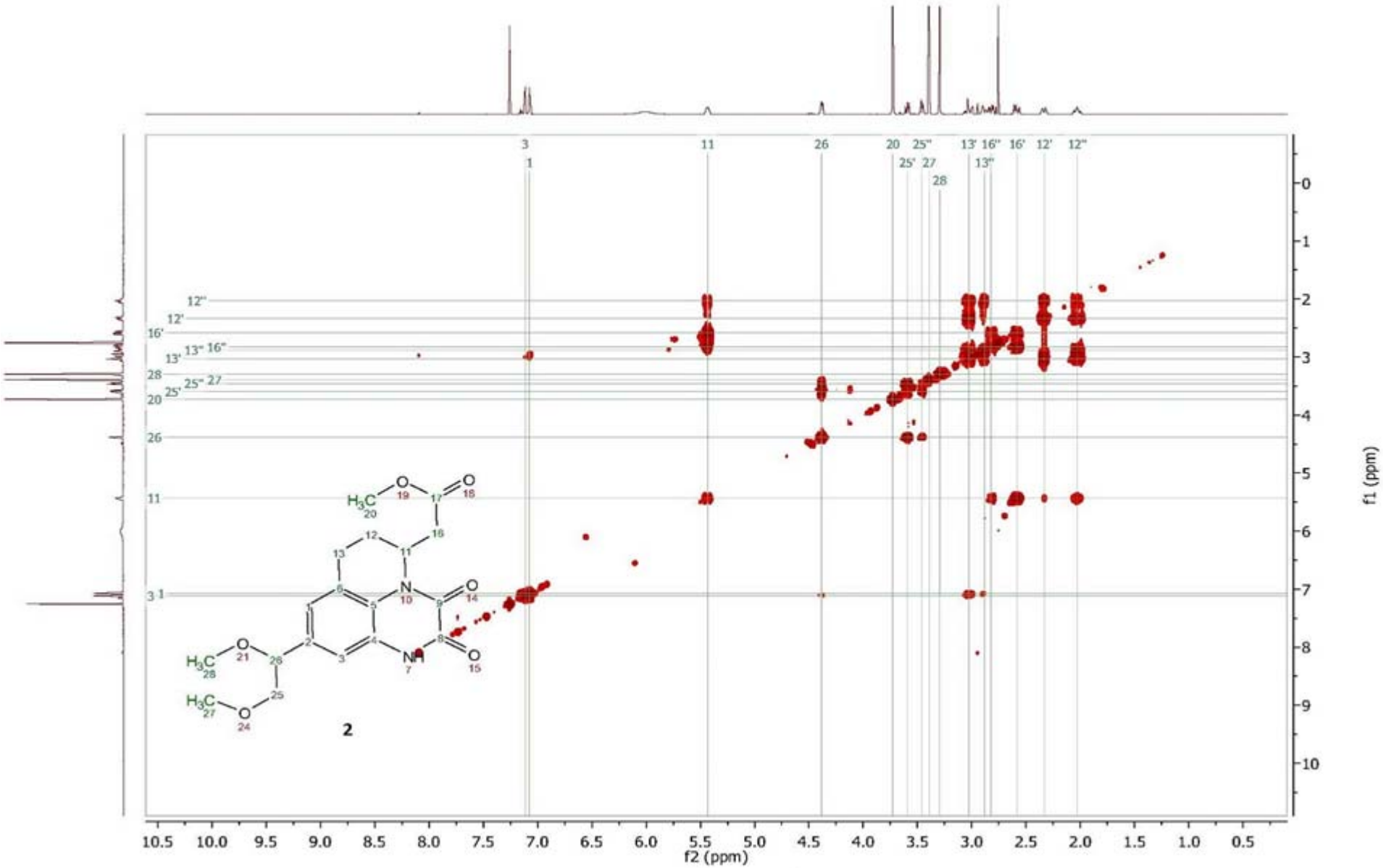
2D ROESY of compound **1** in DMSO-*d*6



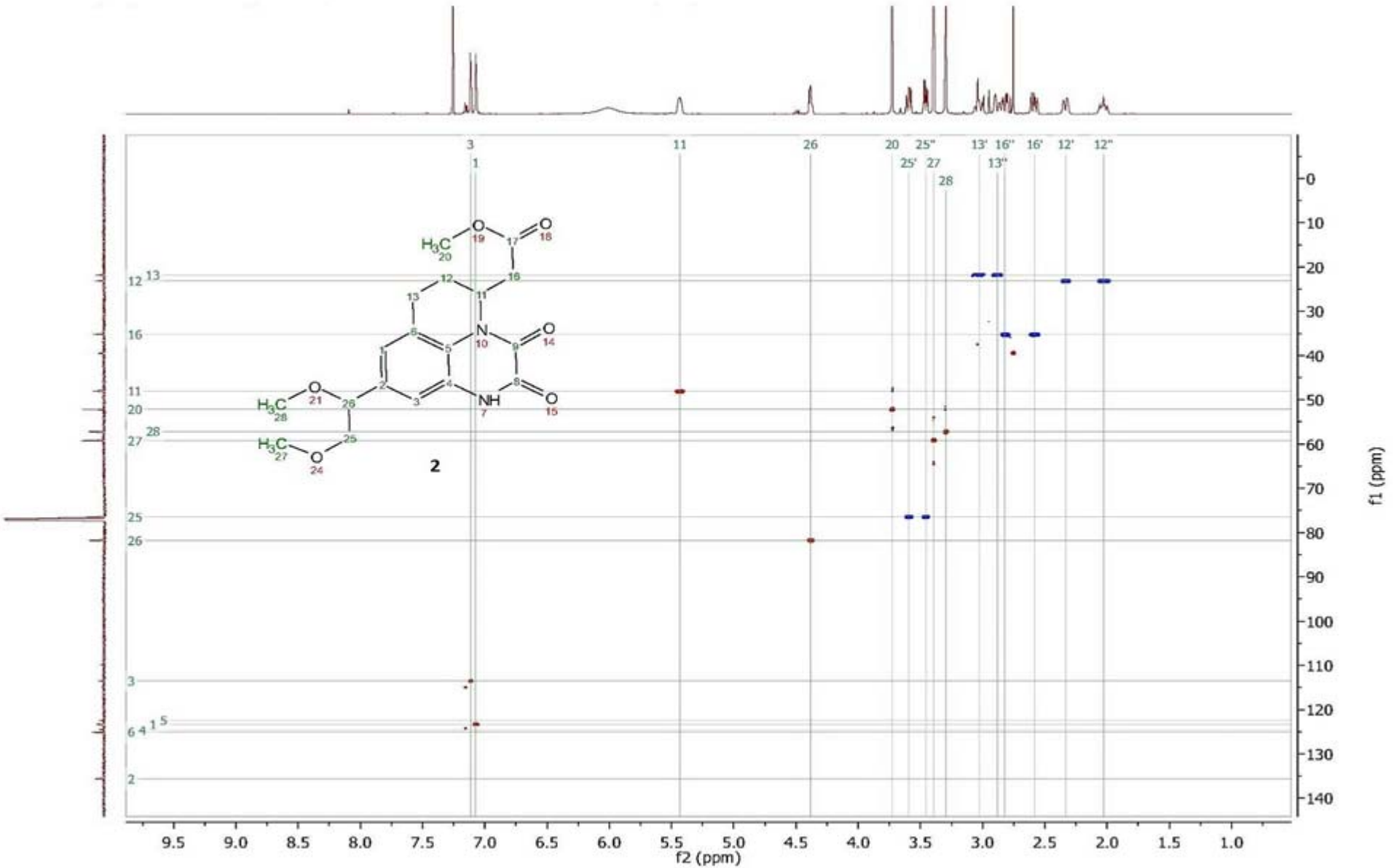
^{13}C NMR of compound **1** in DMSO-*d*6



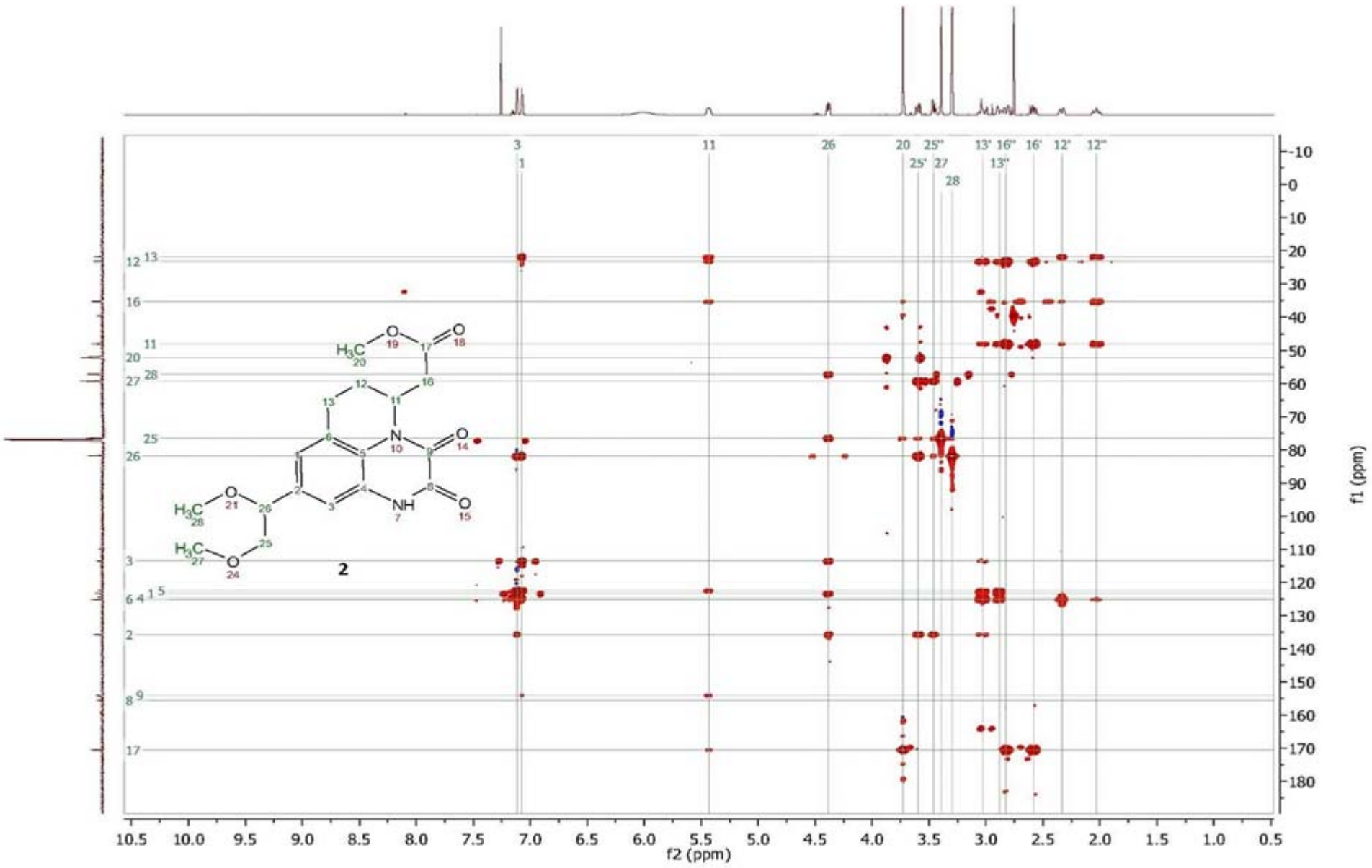
^{1}H NMR of compound **2** in CDCl3



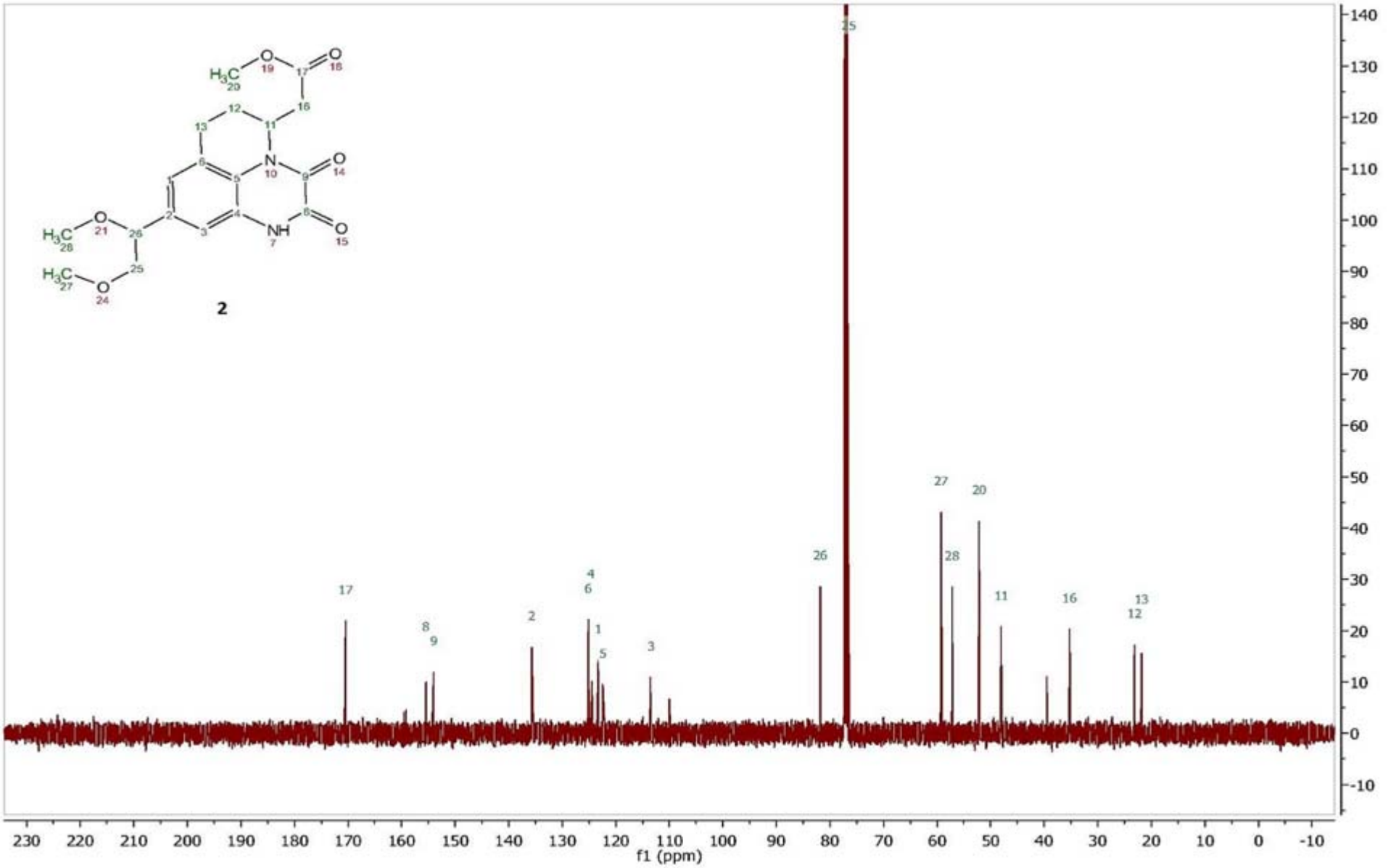
2D COSY of compound **2** in $CDCl_3$



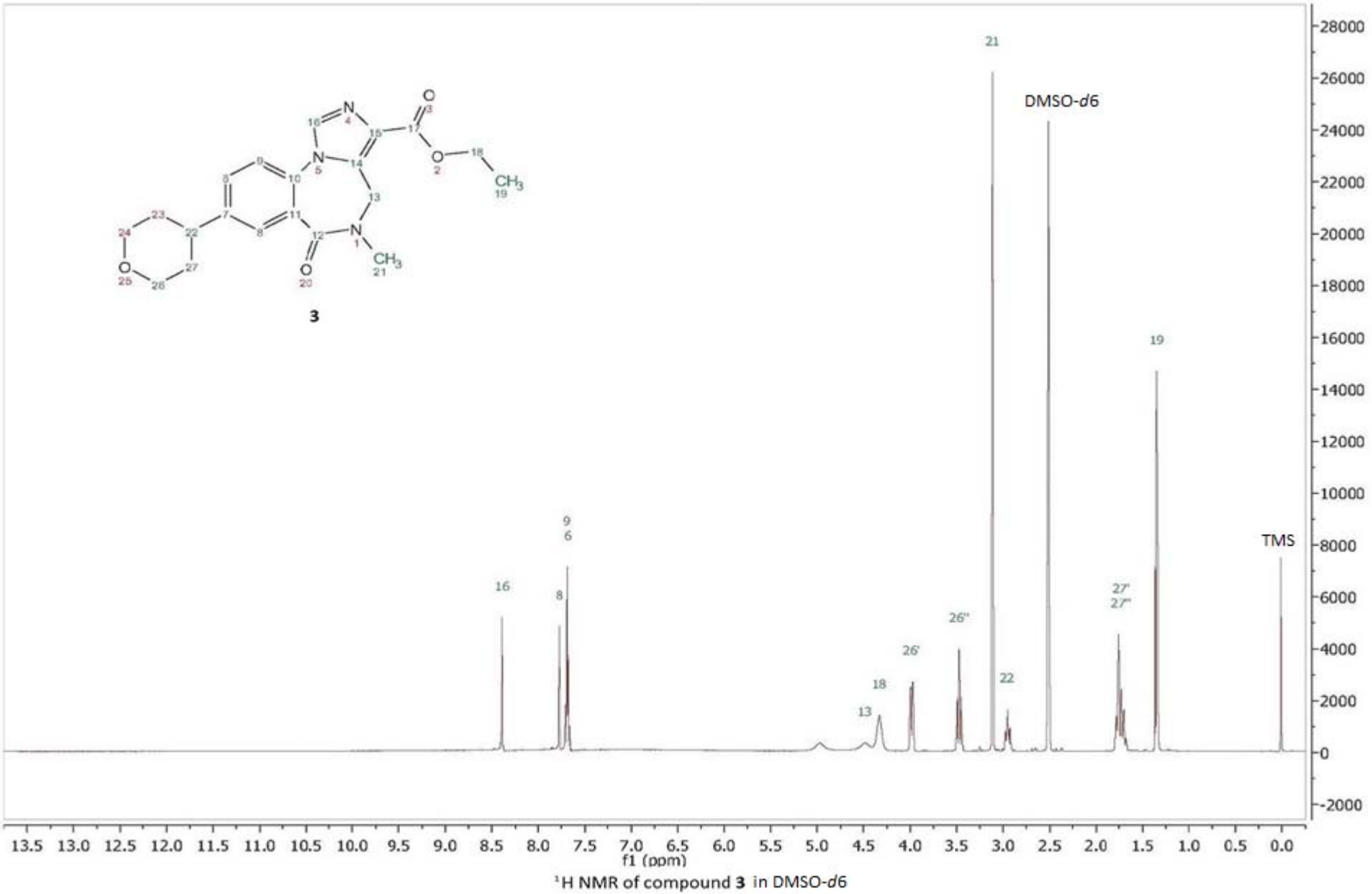
2D HSQC of compound **2** in $CDCl_3$



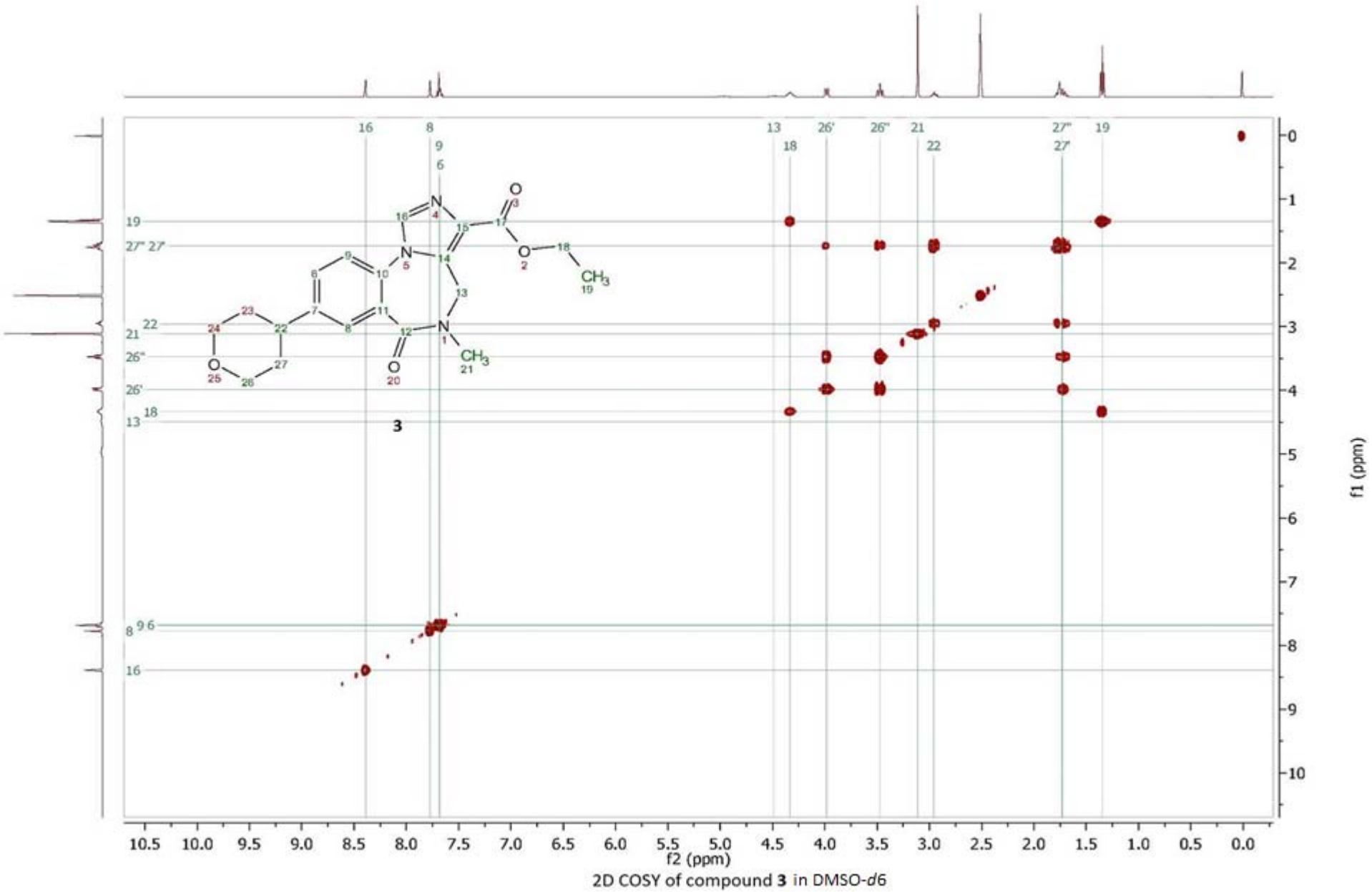
2D HMBC of compound **2** in CDCl3



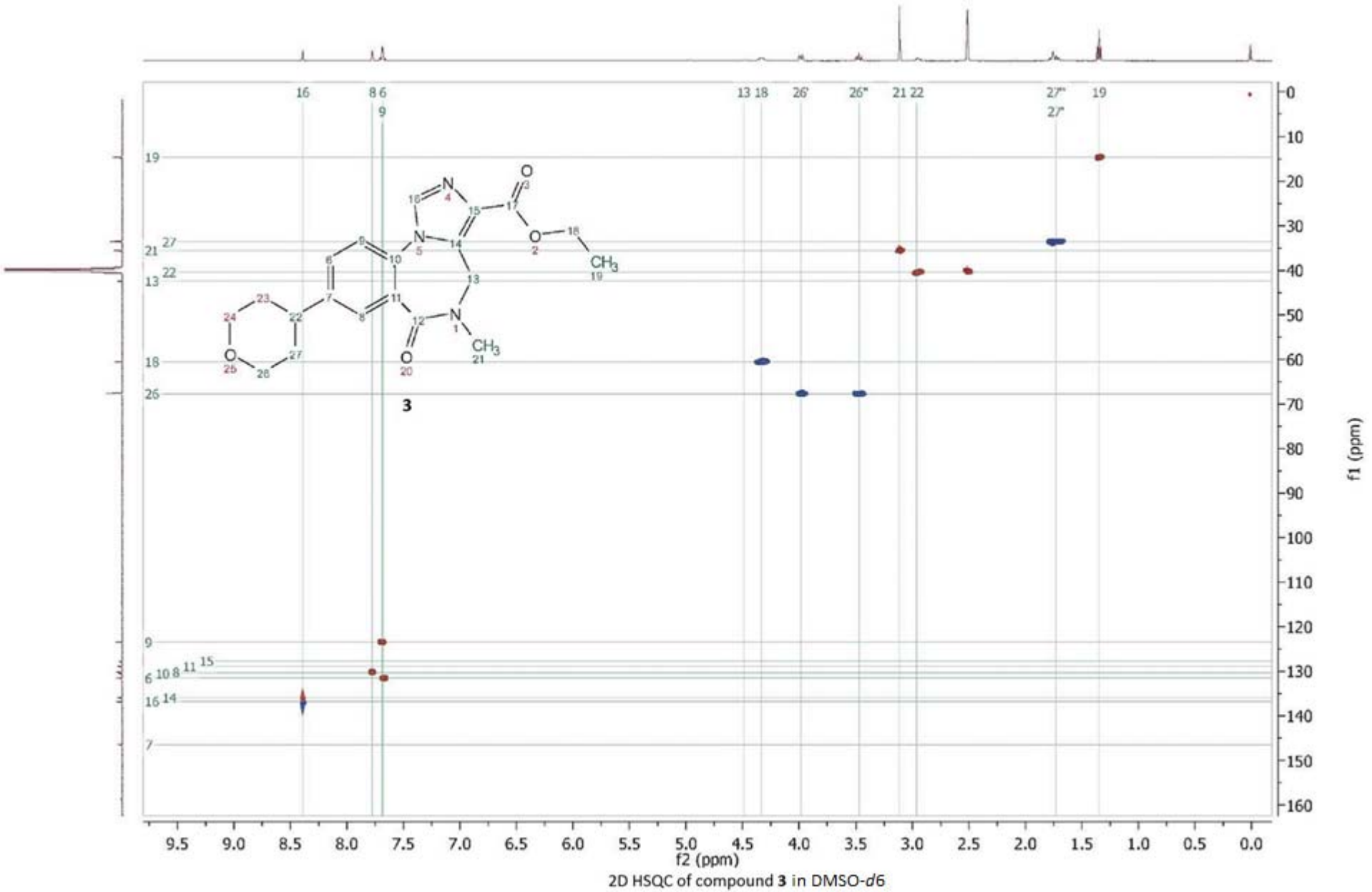
^{13}C NMR of compound **2** in CDCl3



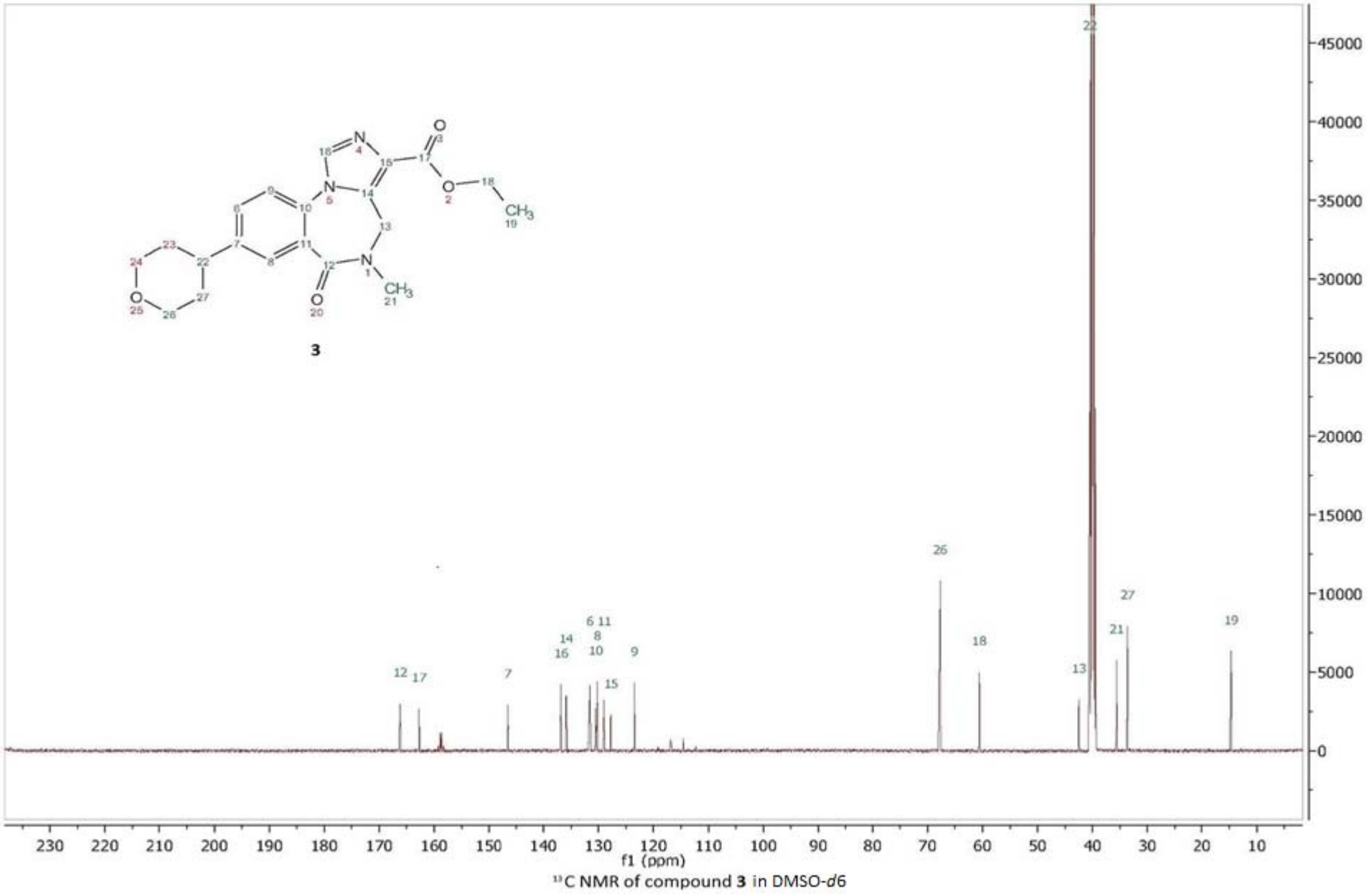
^{1}H NMR of compound **3** in DMSO-*d*6

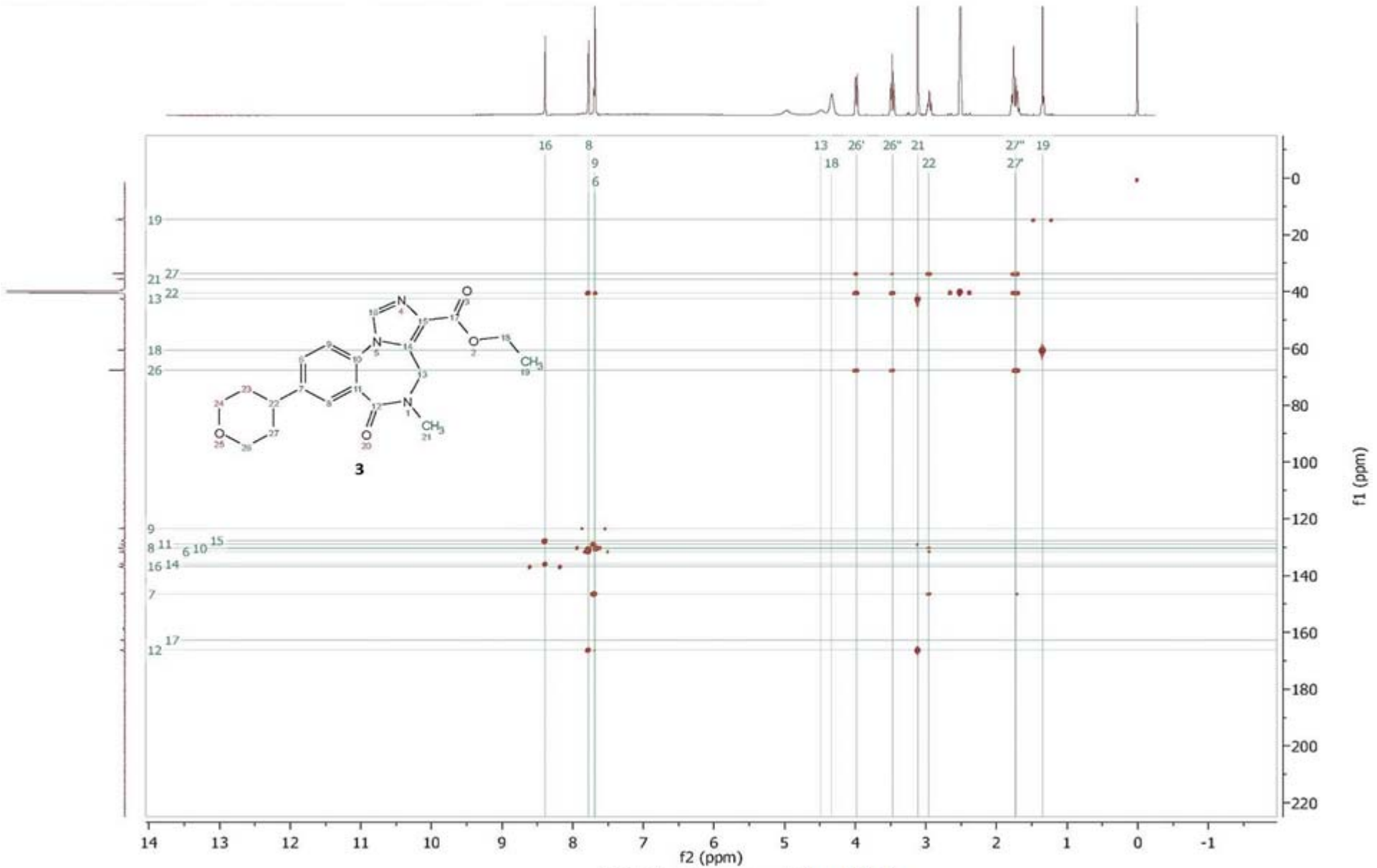


2D COSY of compound **3** in DMSO-*d*6

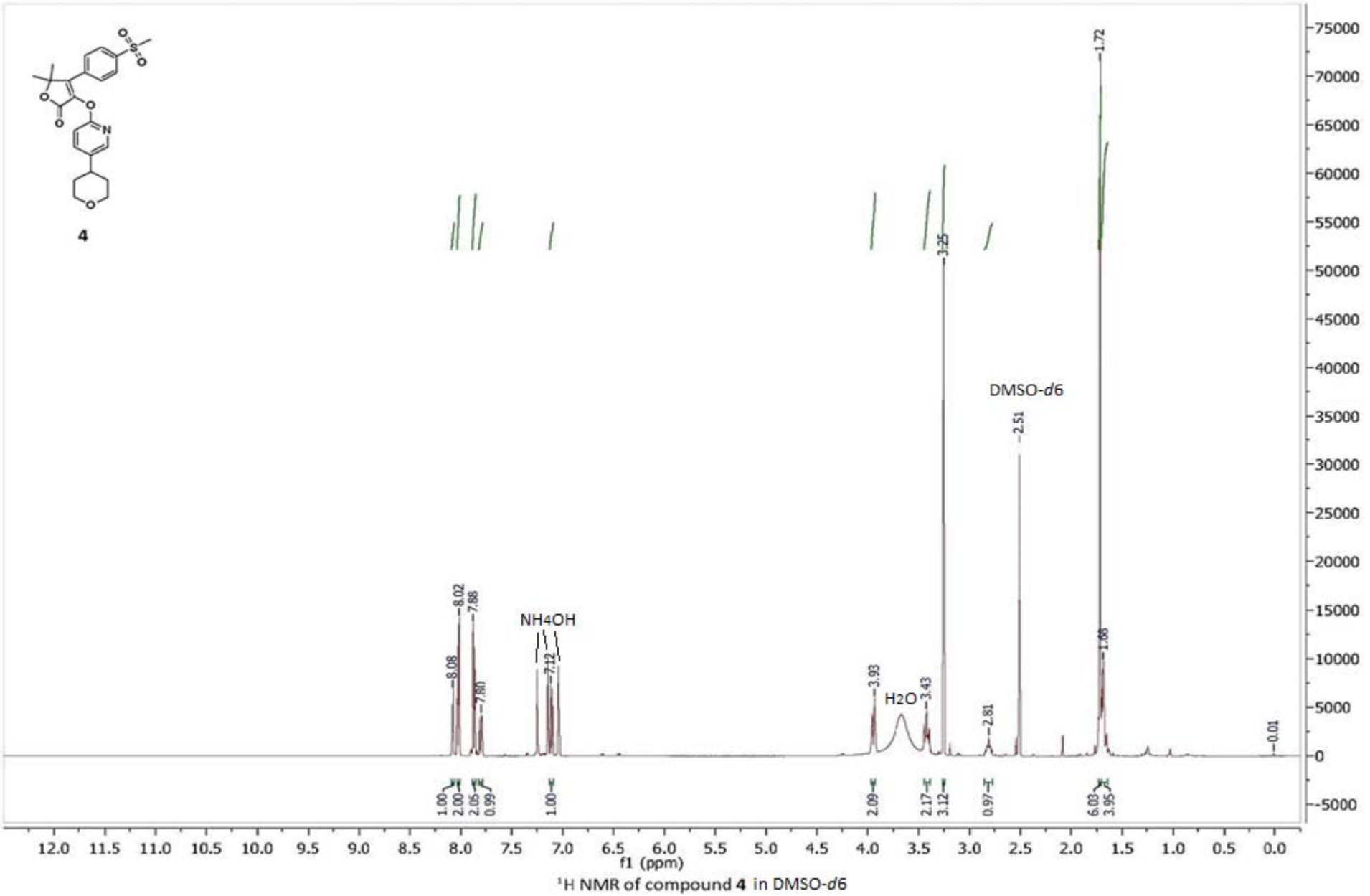


2D HSQC of compound **3** in DMSO-*d6*

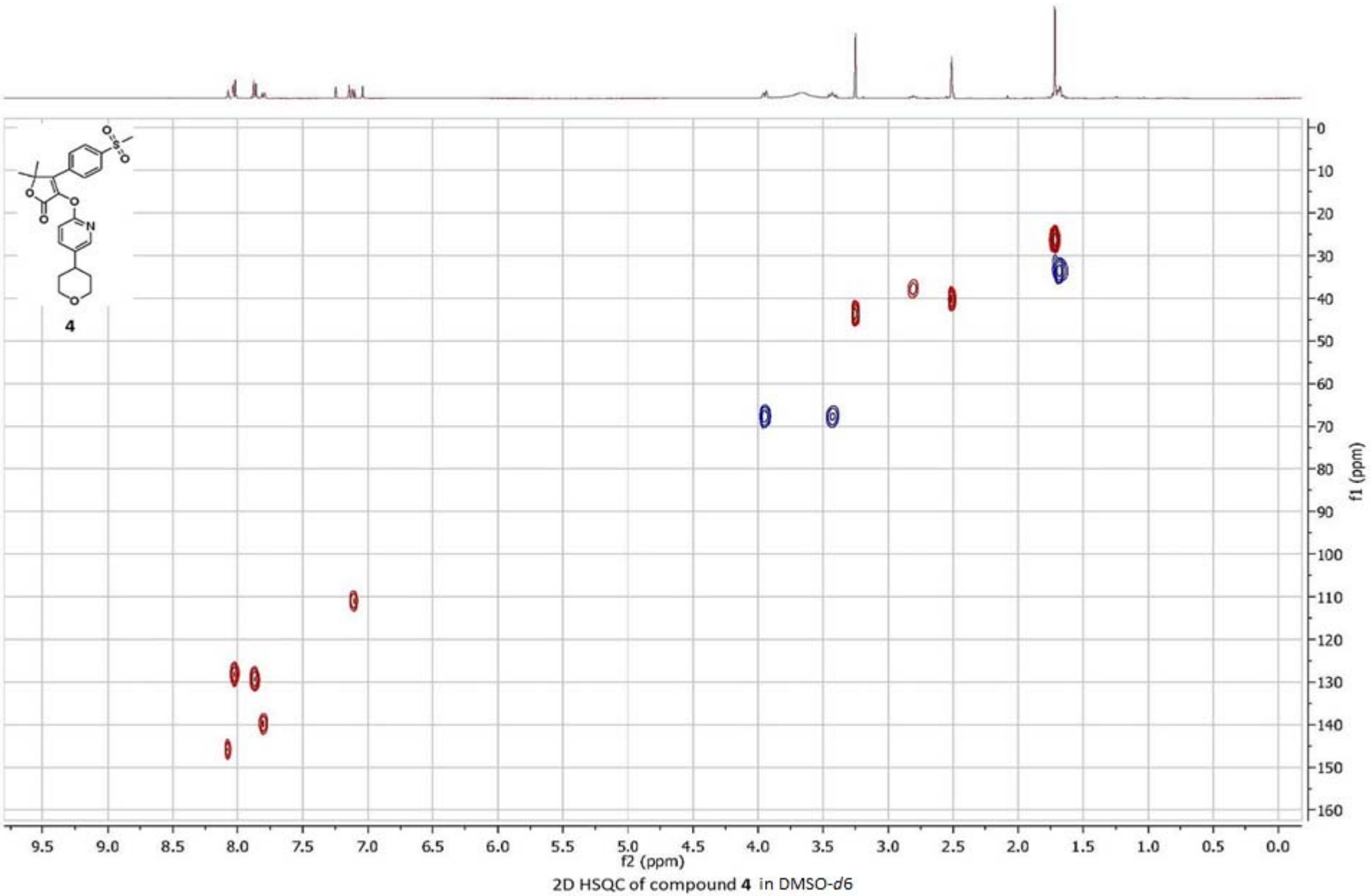

3
f1 (ppm)
13C NMR of compound 3 in DMSO-d6

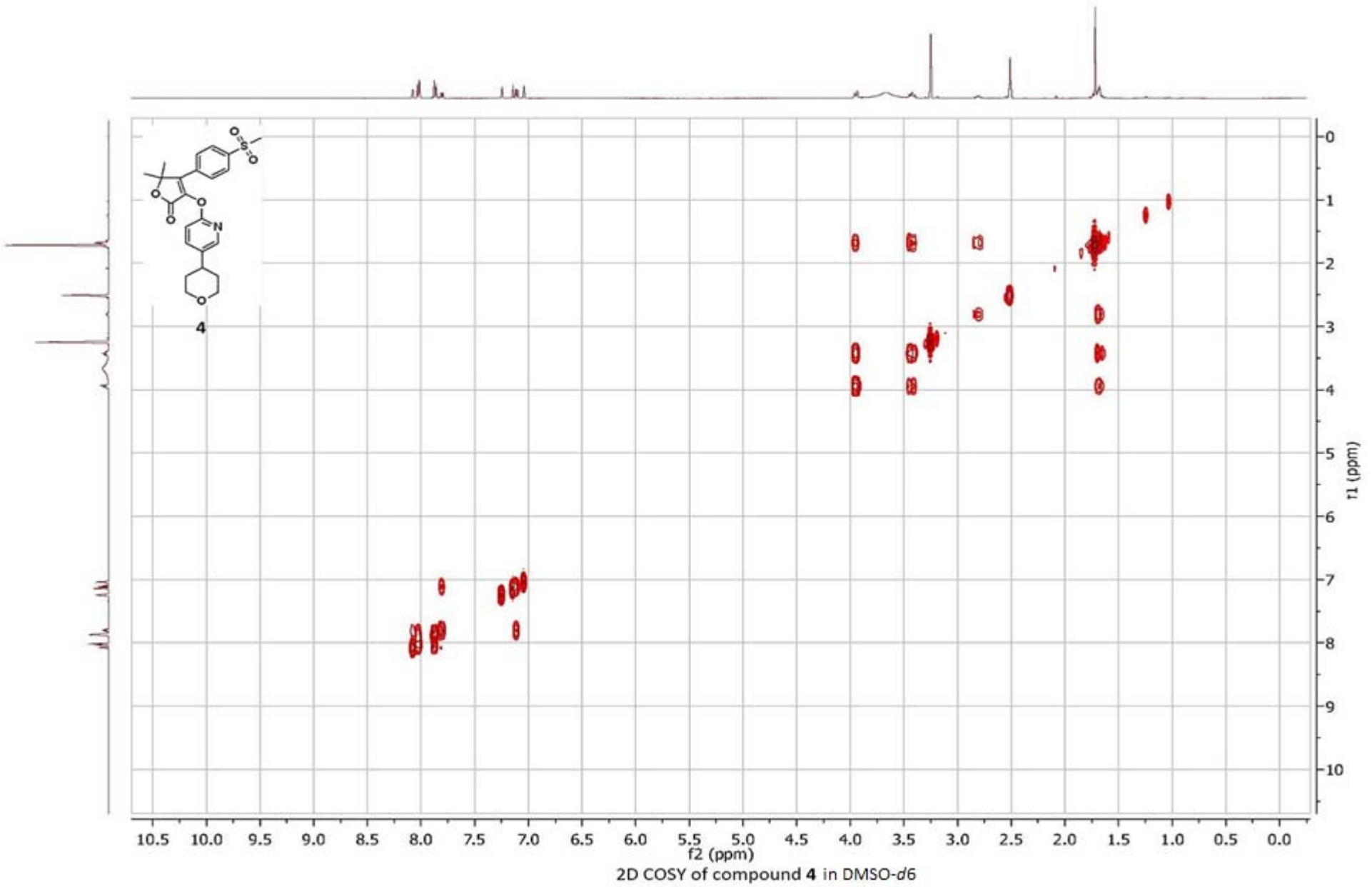


2D HMBC of compound **3** in DMSO-*d*6

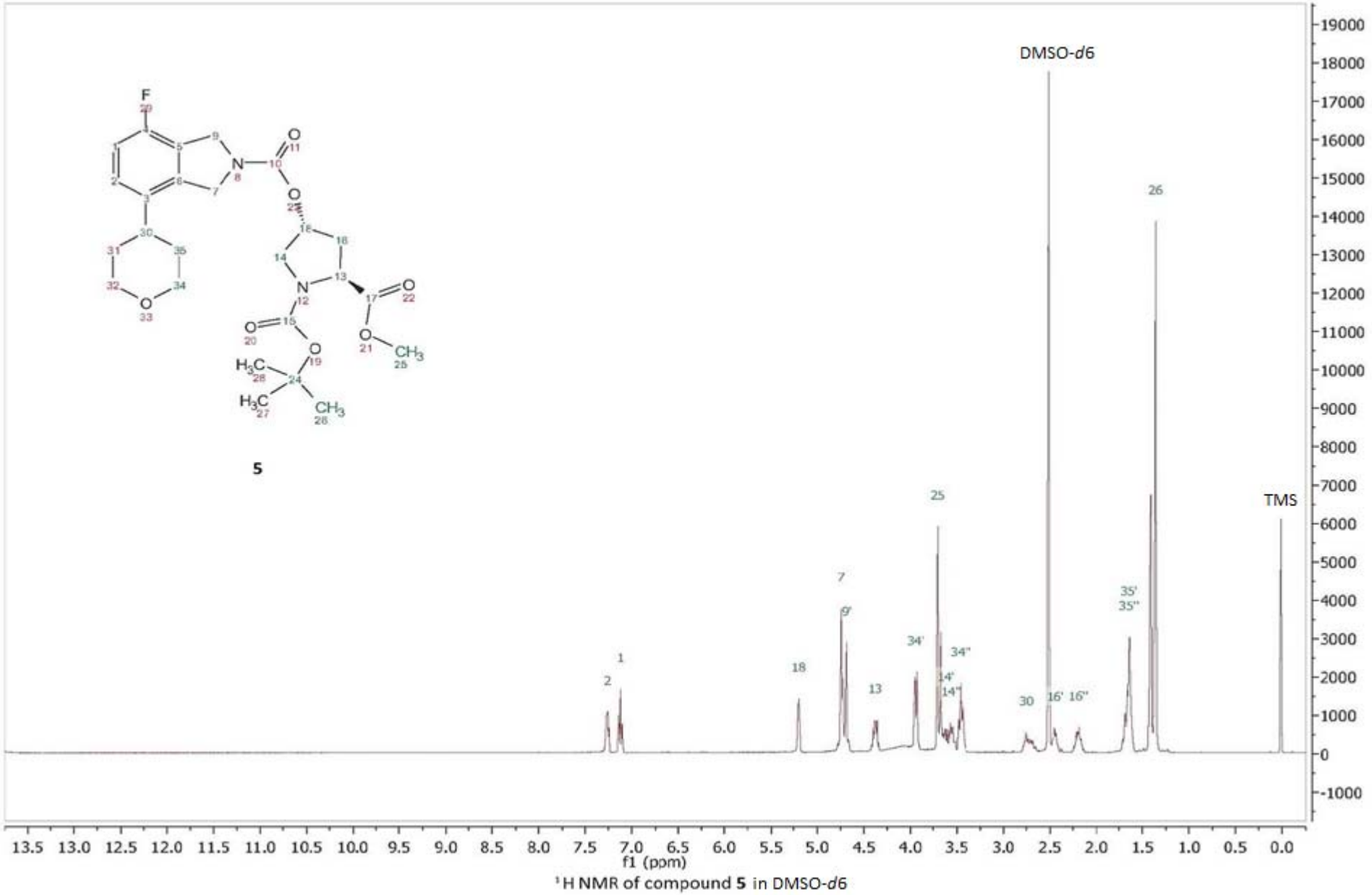


^{1}H NMR of compound **4** in DMSO-*d*6

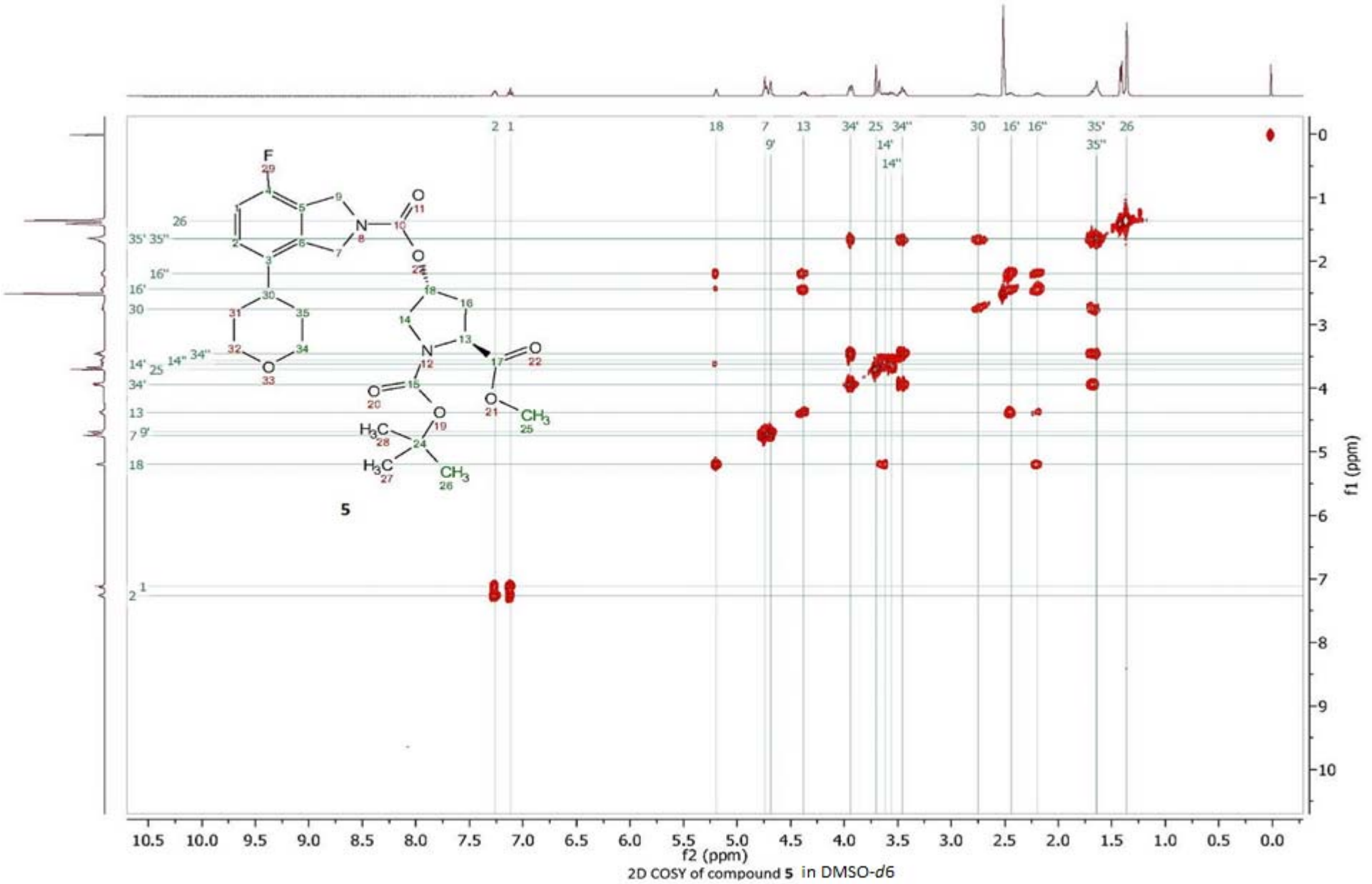

4
f2 (ppm)
f1 (ppm)
2D HSQC of compound 4 in DMSO-d6

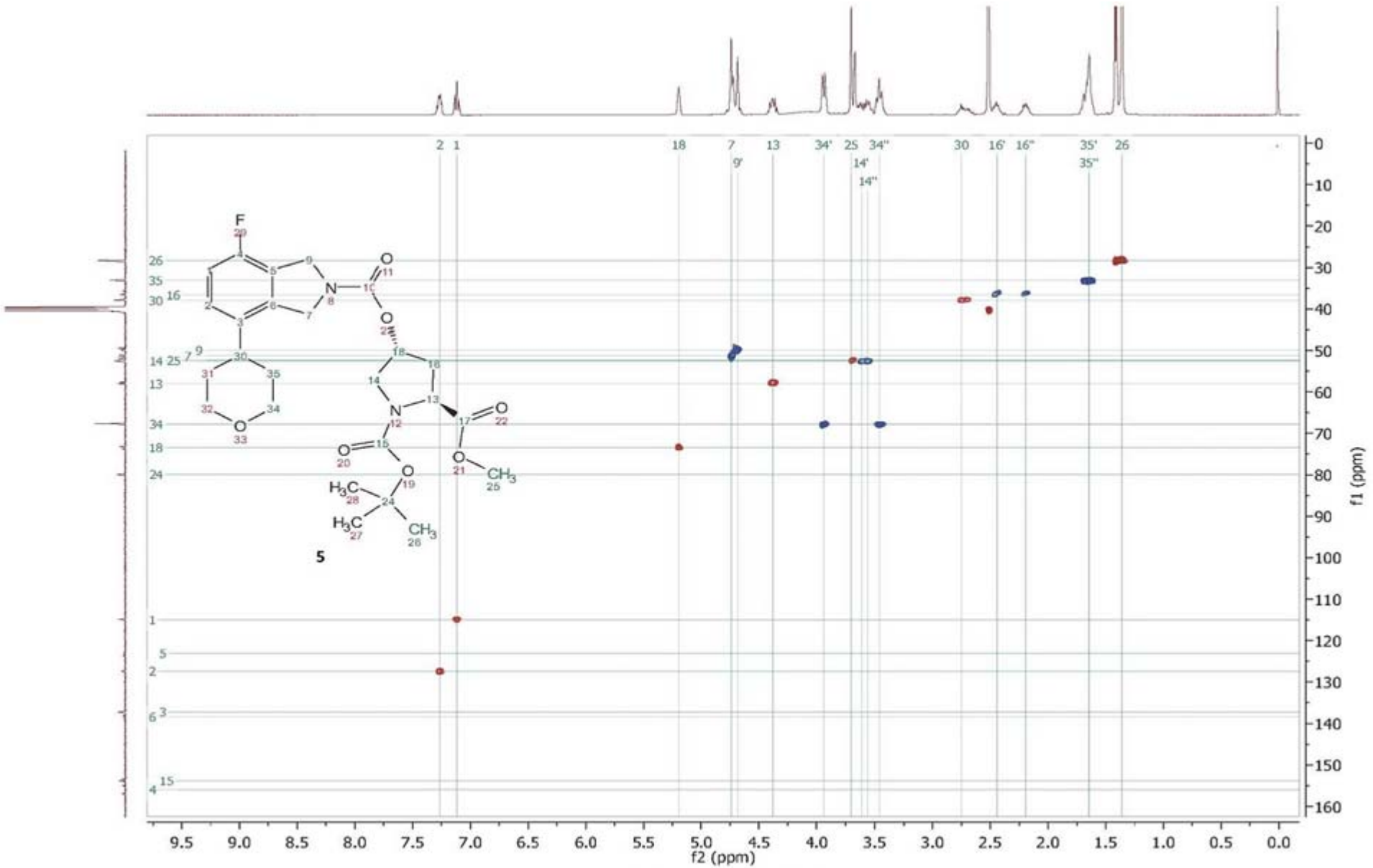


2D COSY of compound **4** in DMSO-*d*6

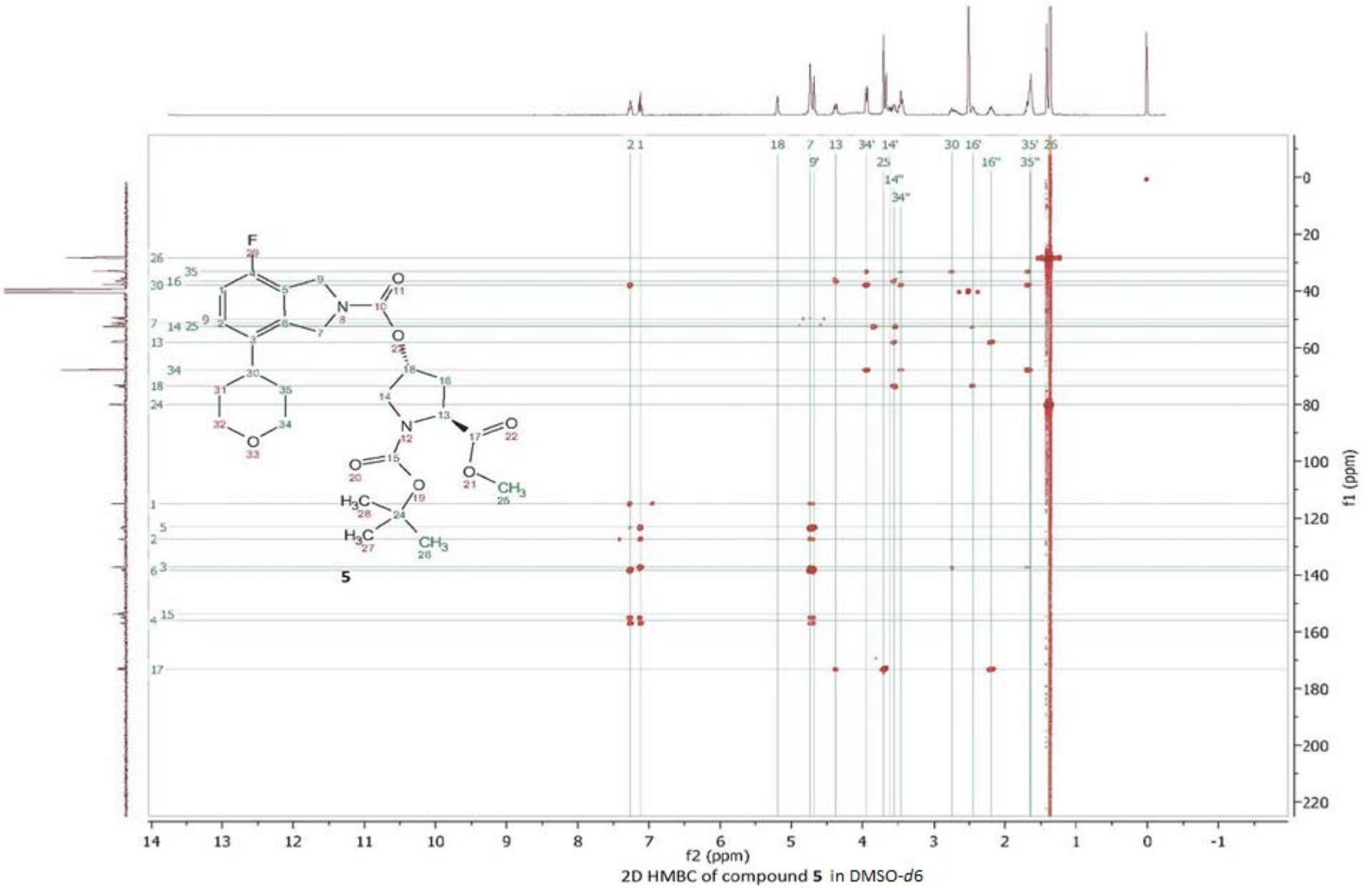


^{1}H NMR of compound **5** in DMSO-*d6*

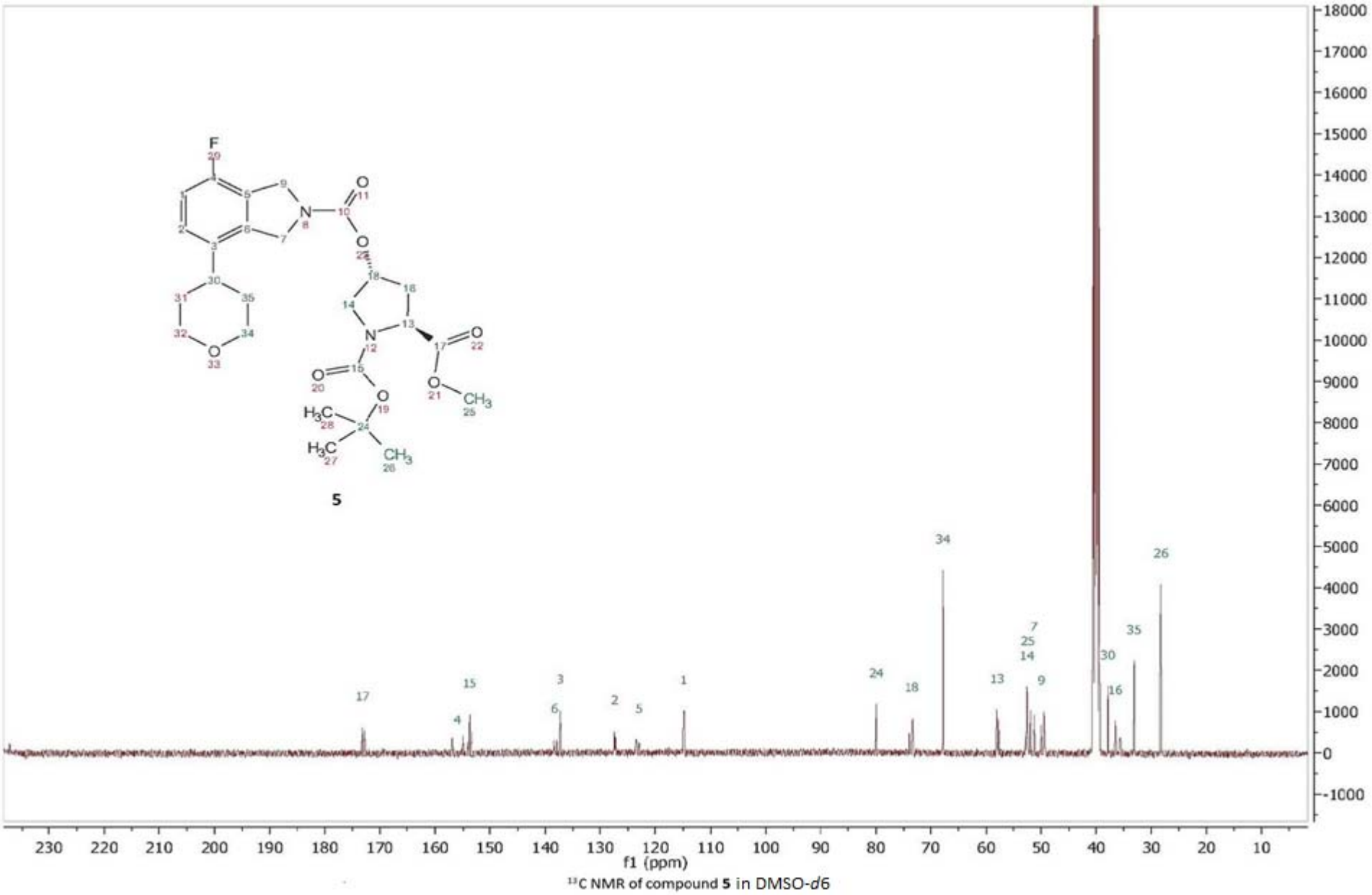

5
f2 (ppm)
f1 (ppm)
2D COSY of compound 5 in DMSO-d6



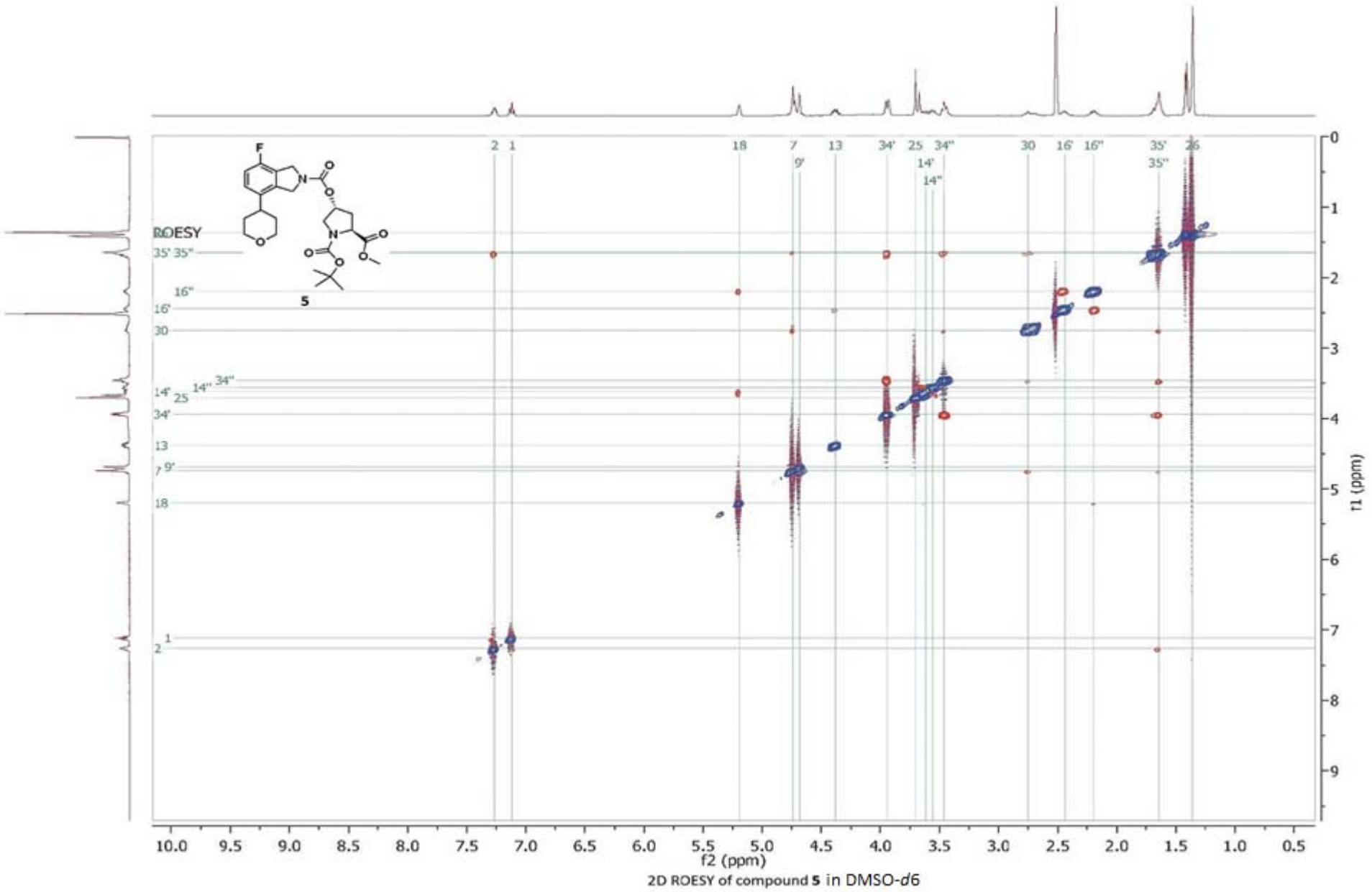
2D HSQC of compound **5** in DMSO-*d*6

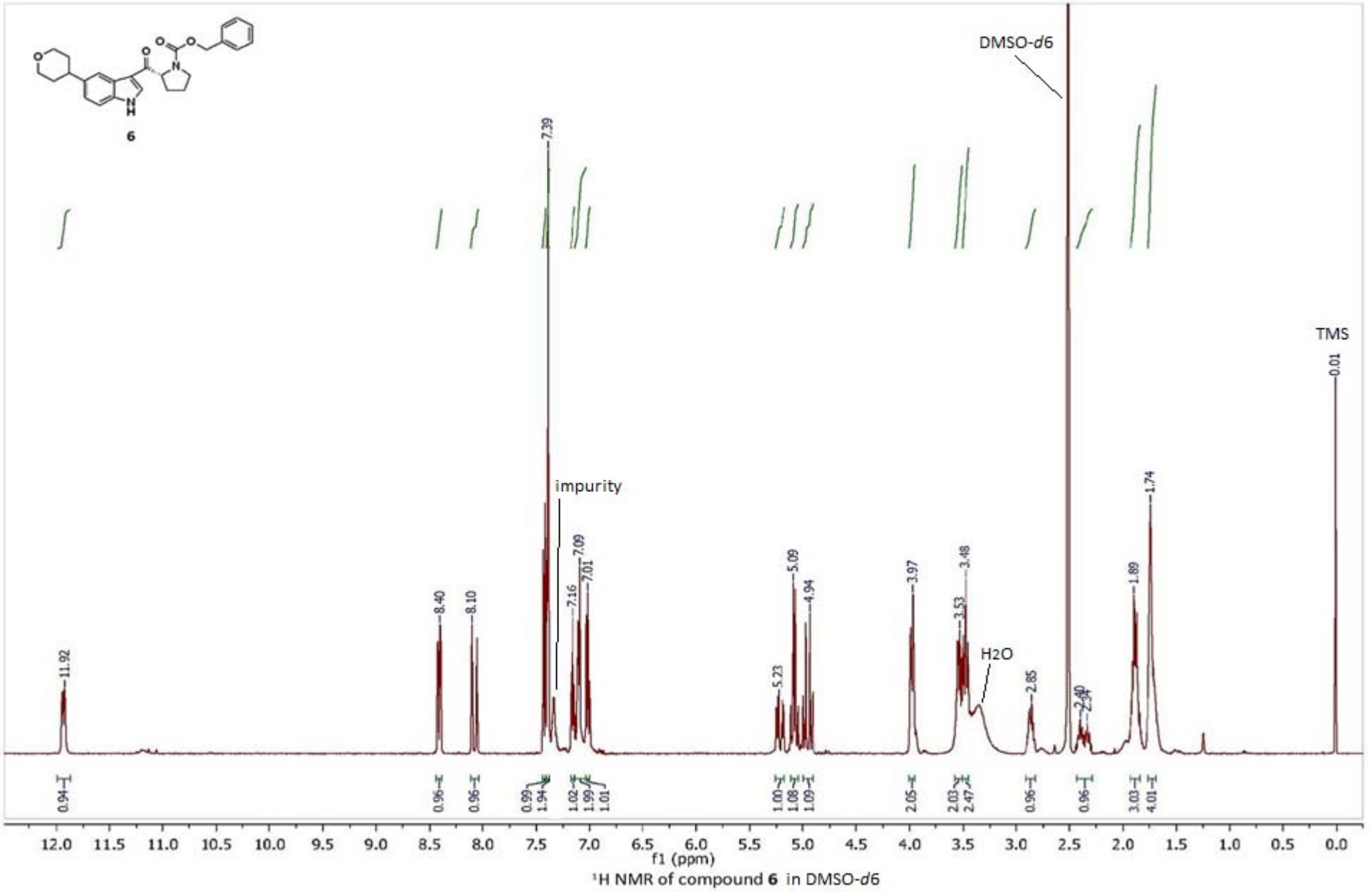


2D HMBC of compound **5** in DMSO-*d*6

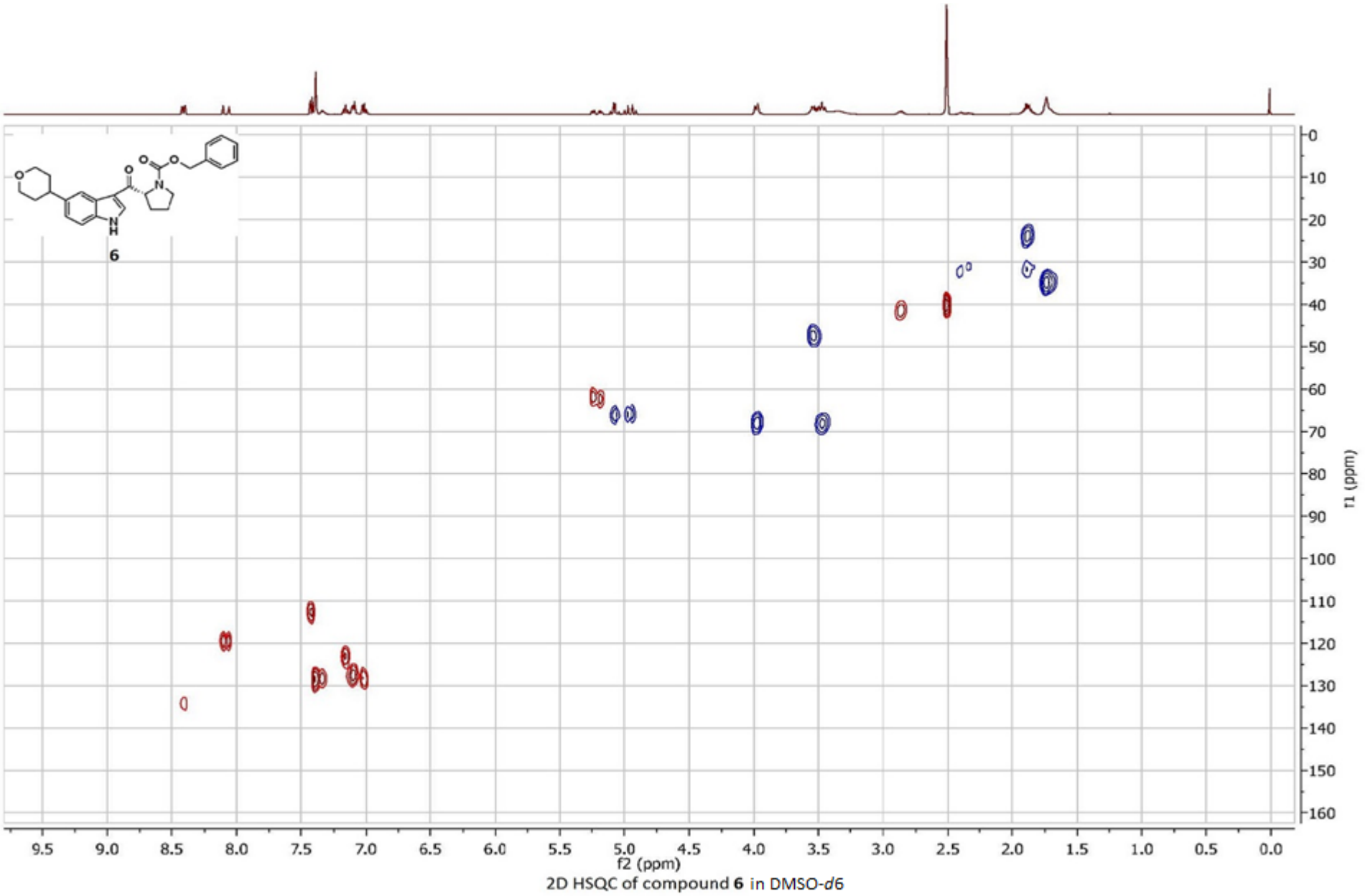


^{13}C NMR of compound **5** in DMSO-*d*6

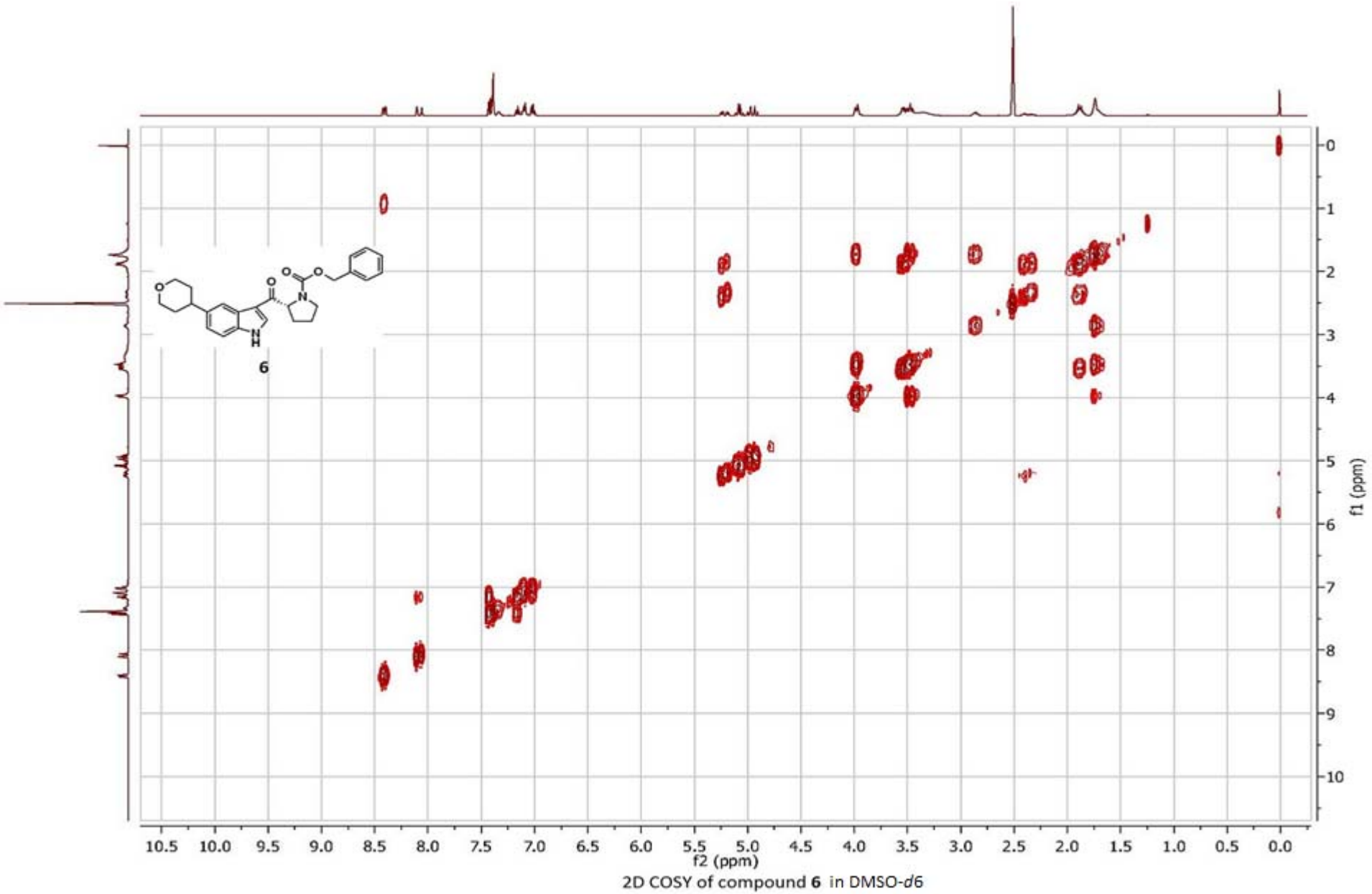

ROESY
5
f2 (ppm)
f1 (ppm)
2D ROESY of compound 5 in DMSO-d6



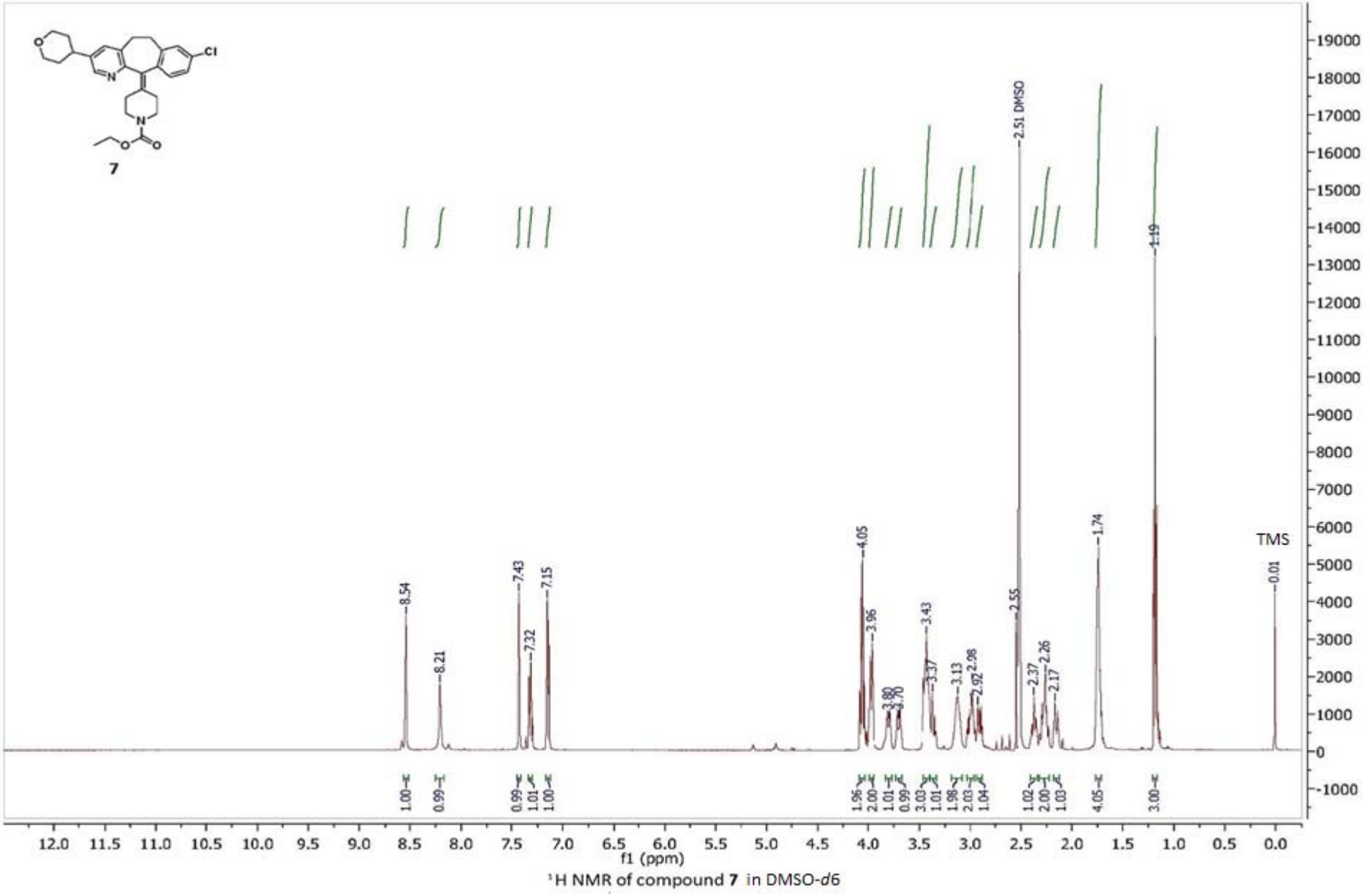
^{1}H NMR of compound **6** in DMSO-*d*6



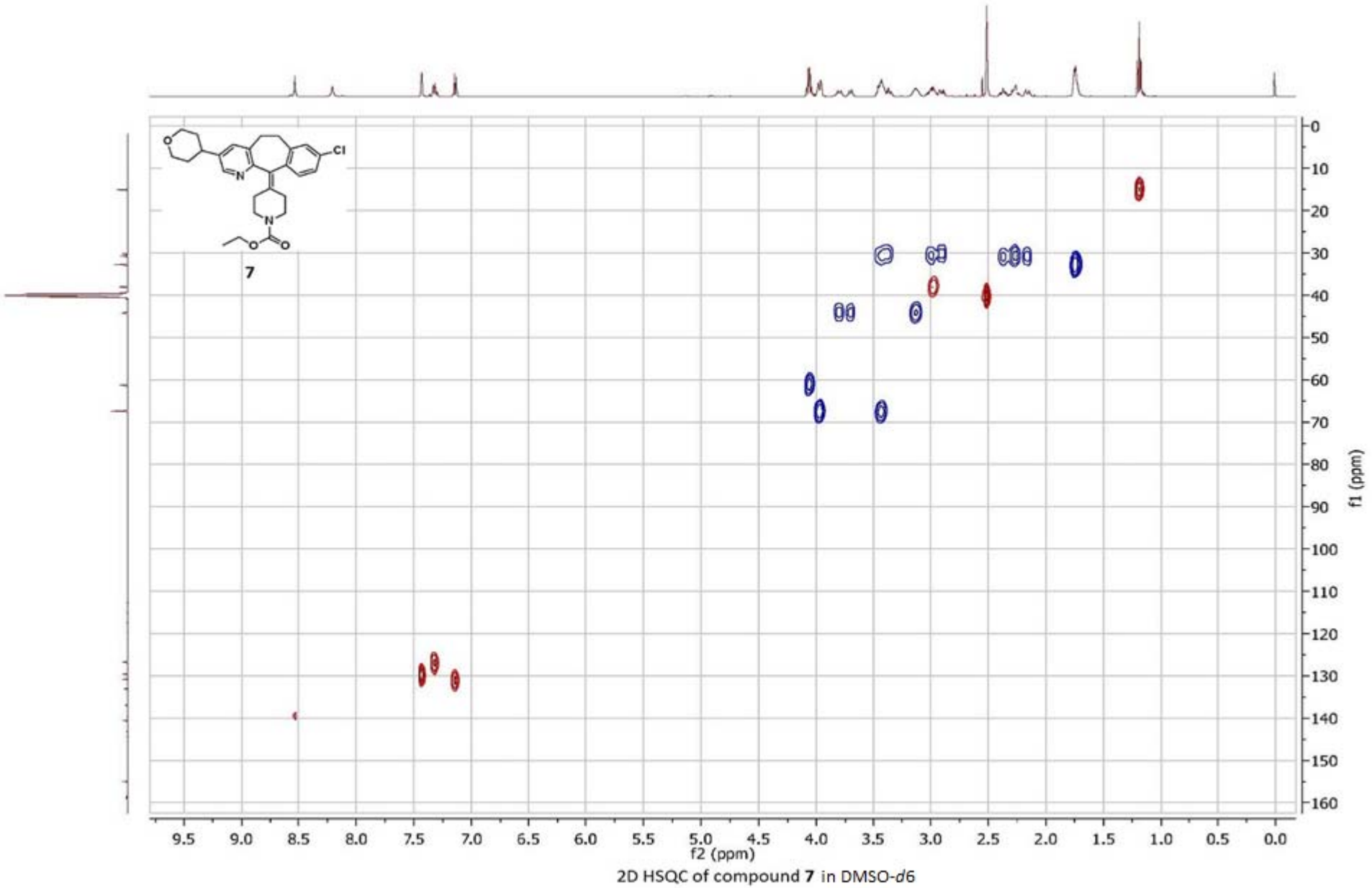
2D HSQC of compound **6** in DMSO-*d*6



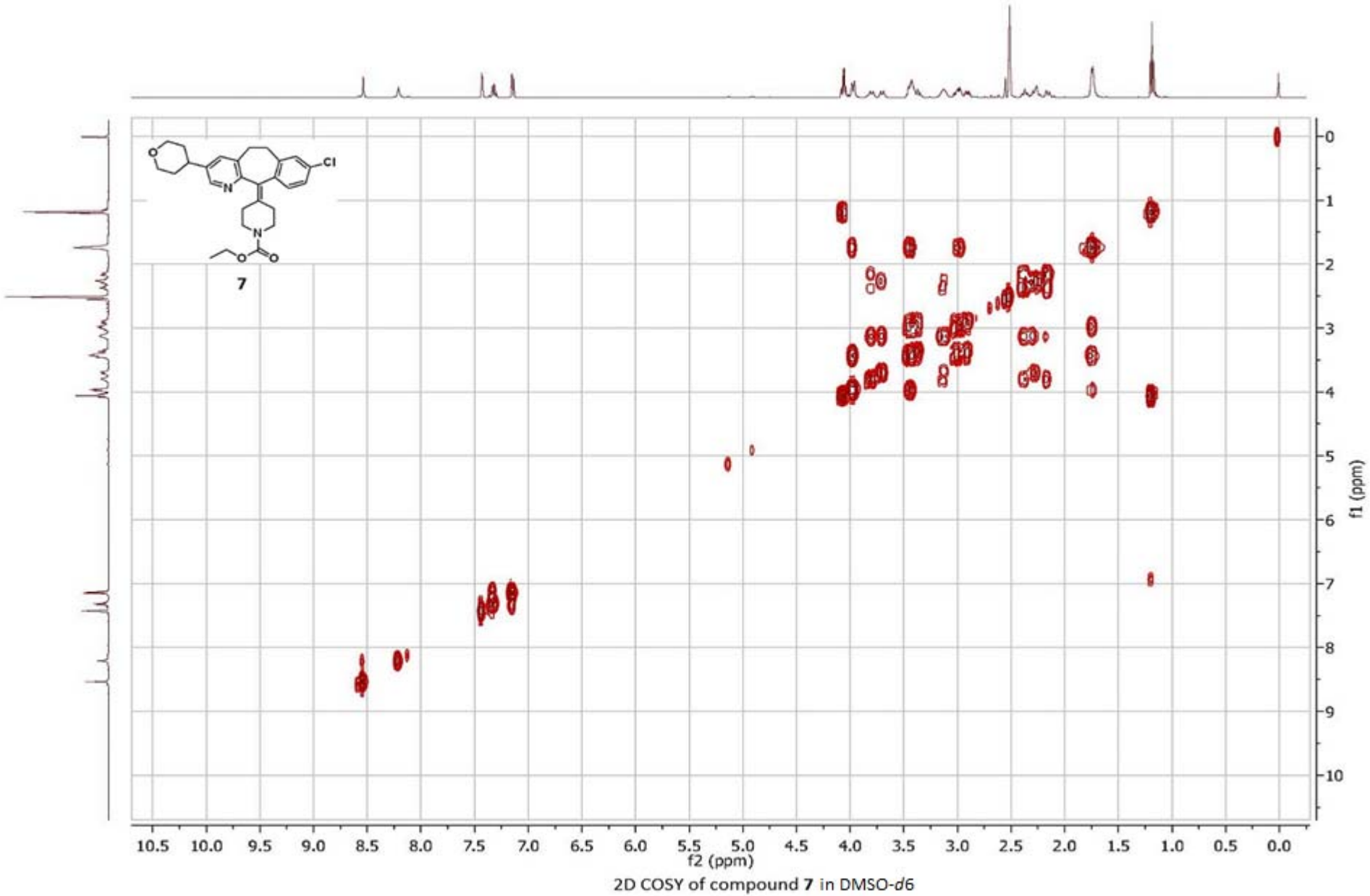
2D COSY of compound **6** in DMSO-*d*6



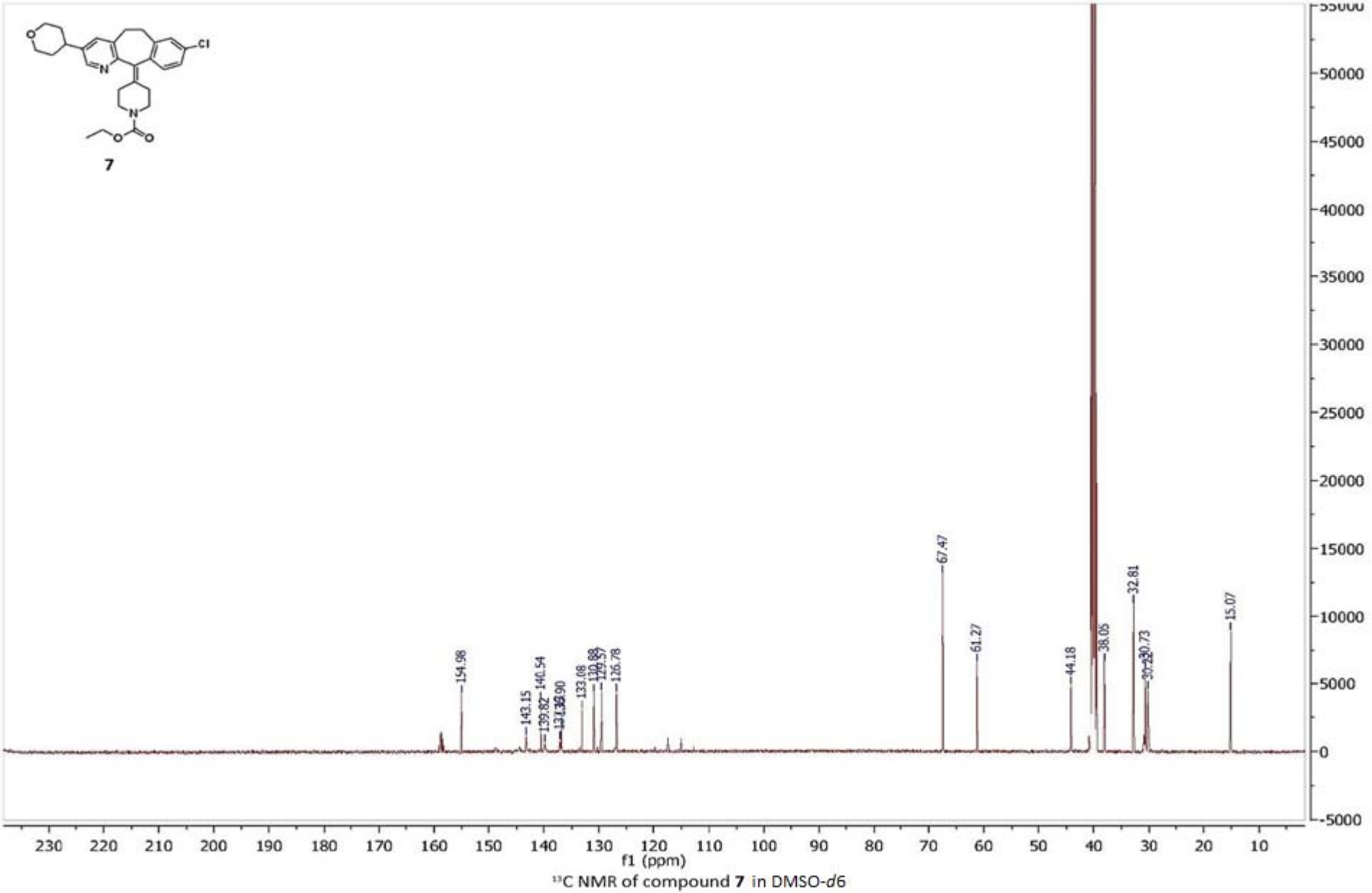
^{1}H NMR of compound **7** in DMSO-*d*6



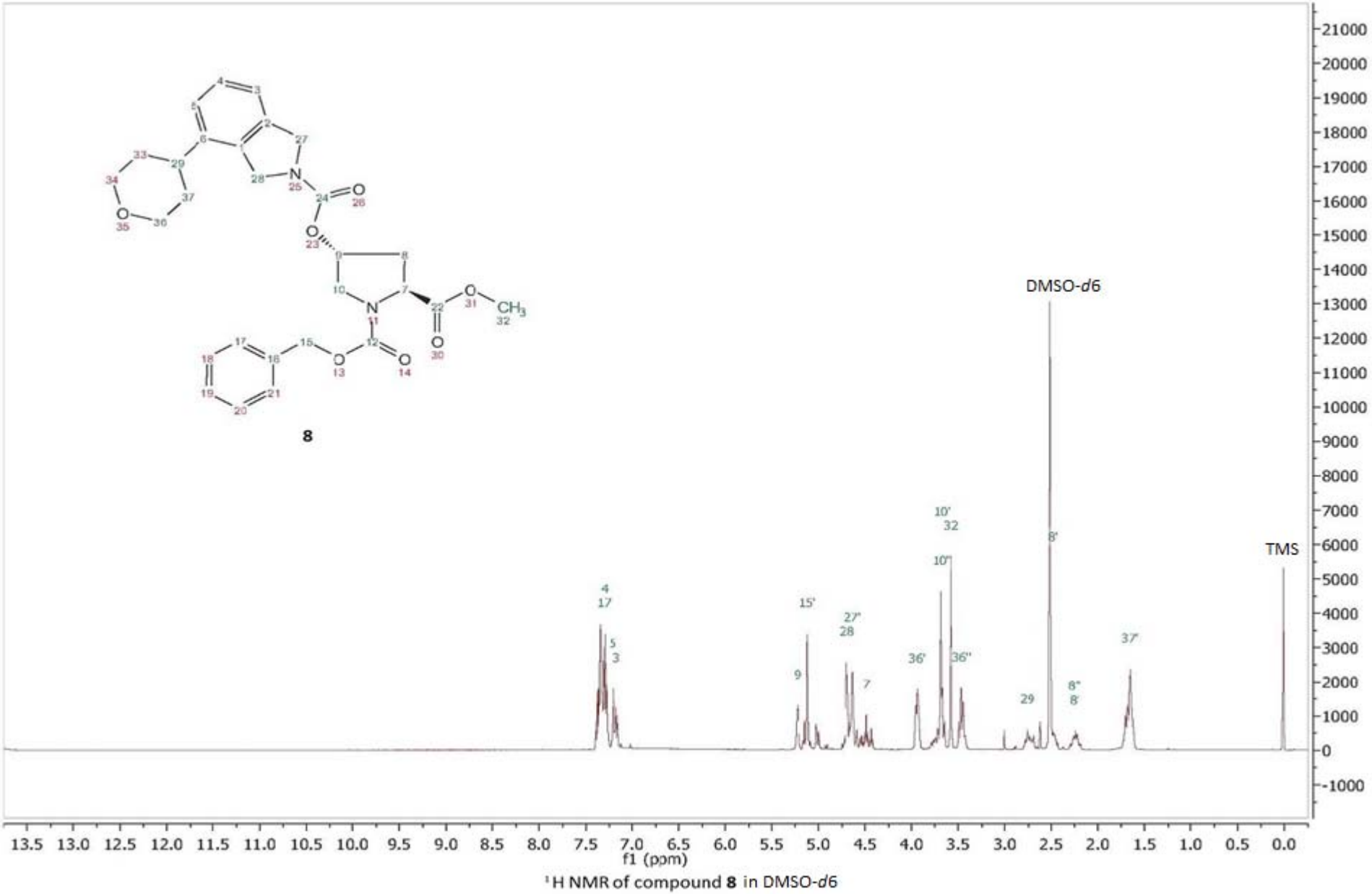
2D HSQC of compound **7** in DMSO-*d*6



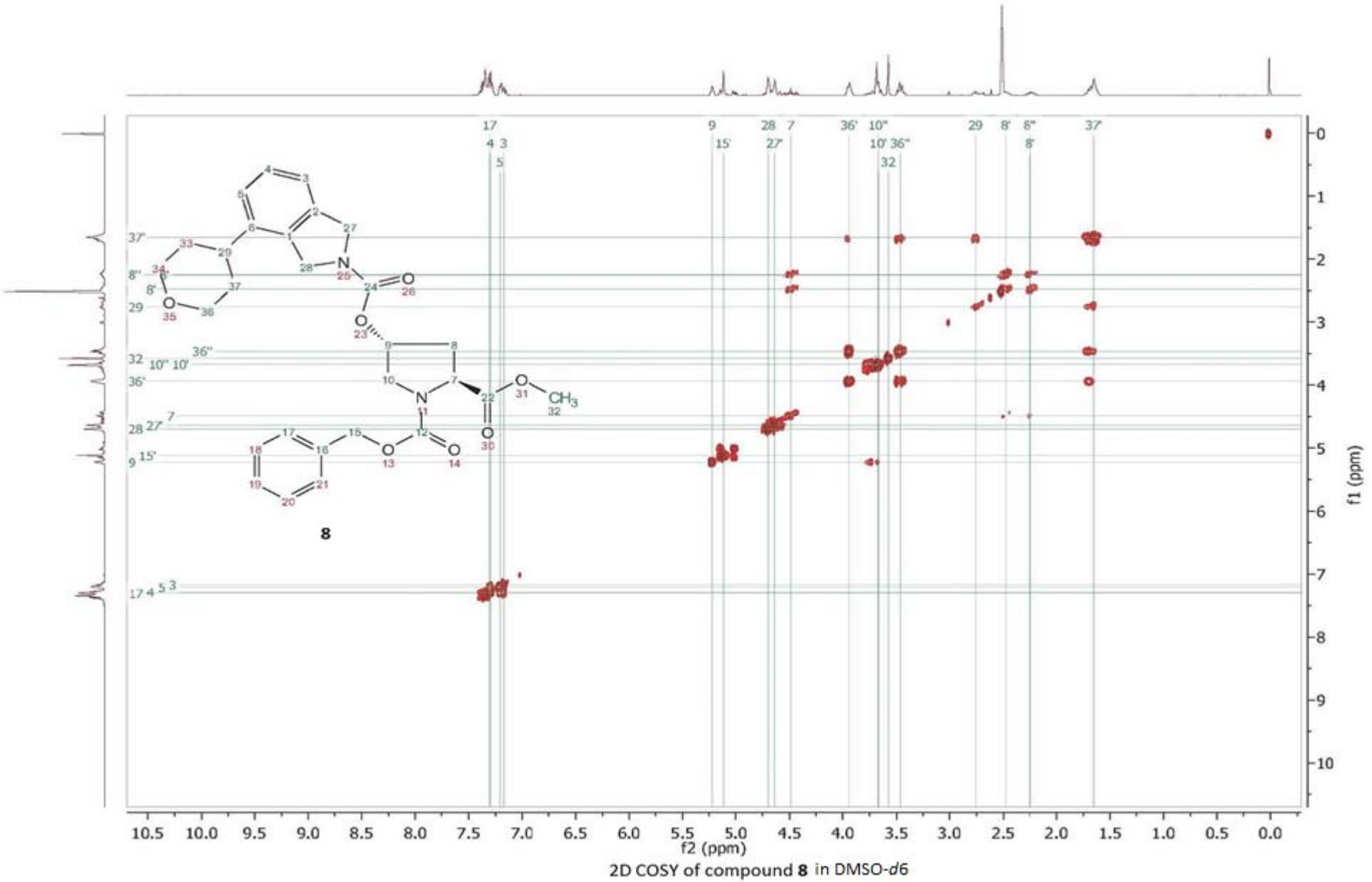
2D COSY of compound **7** in DMSO-*d*6

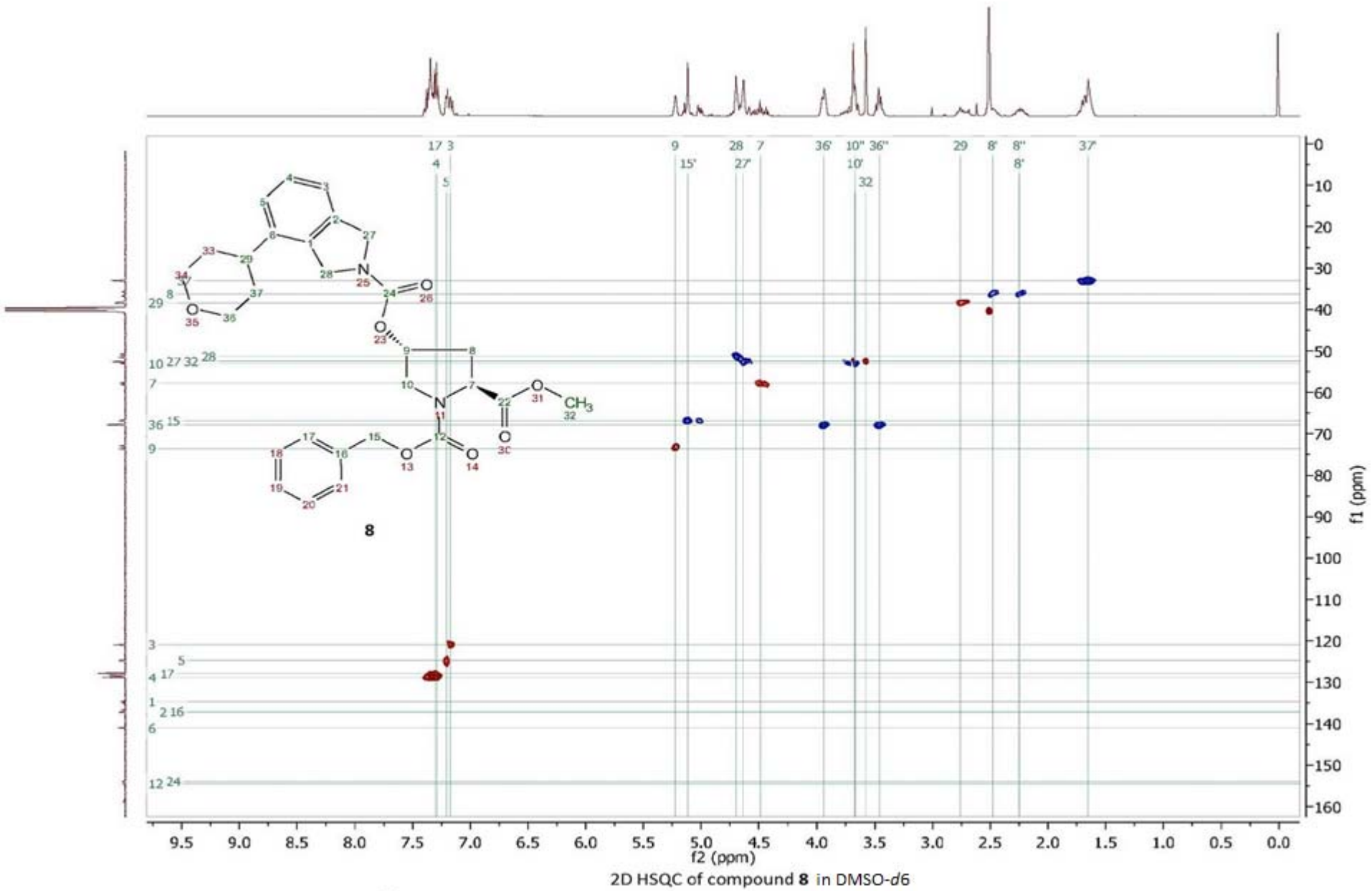


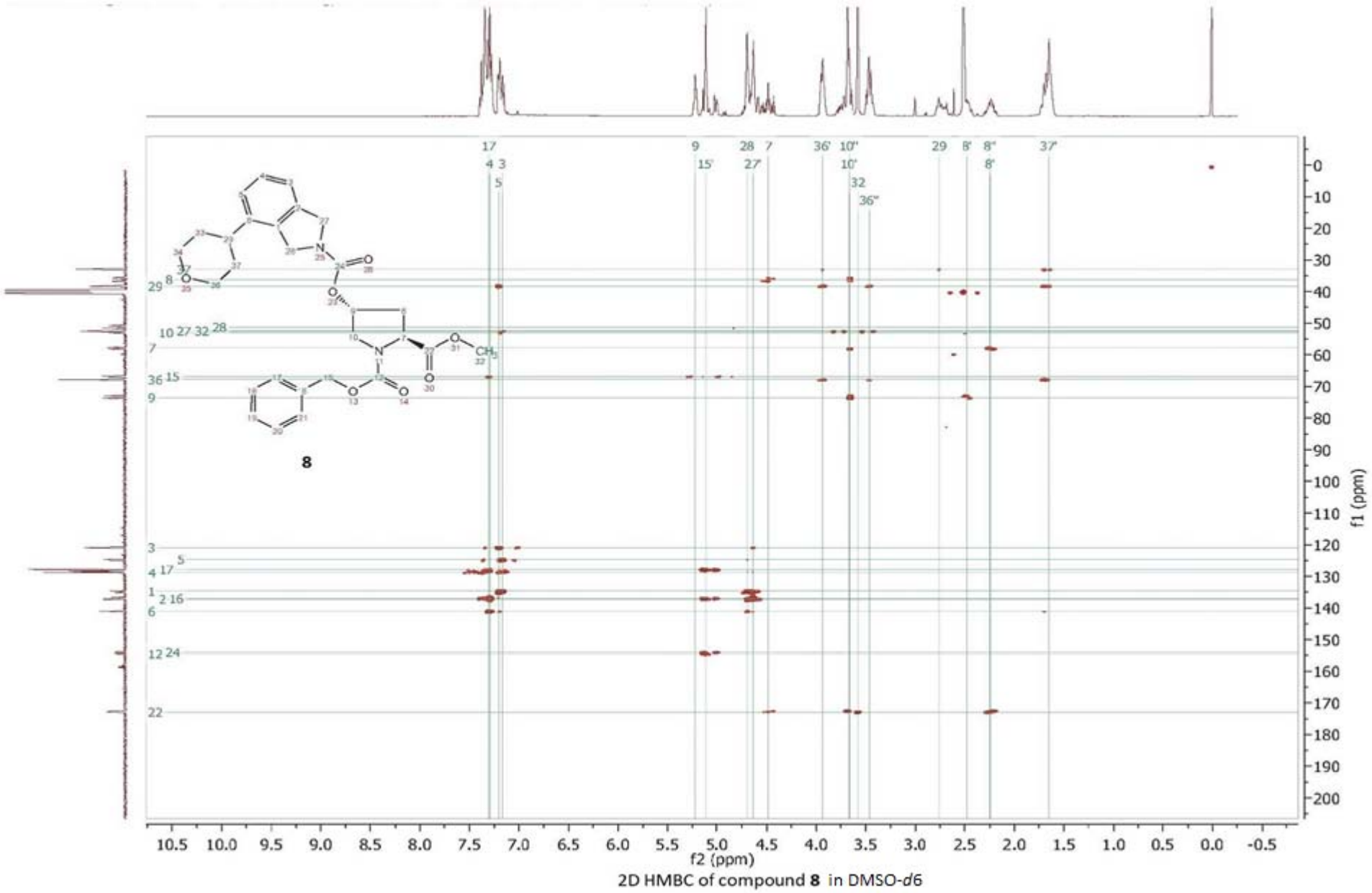
^{13}C NMR of compound **7** in DMSO-*d*6



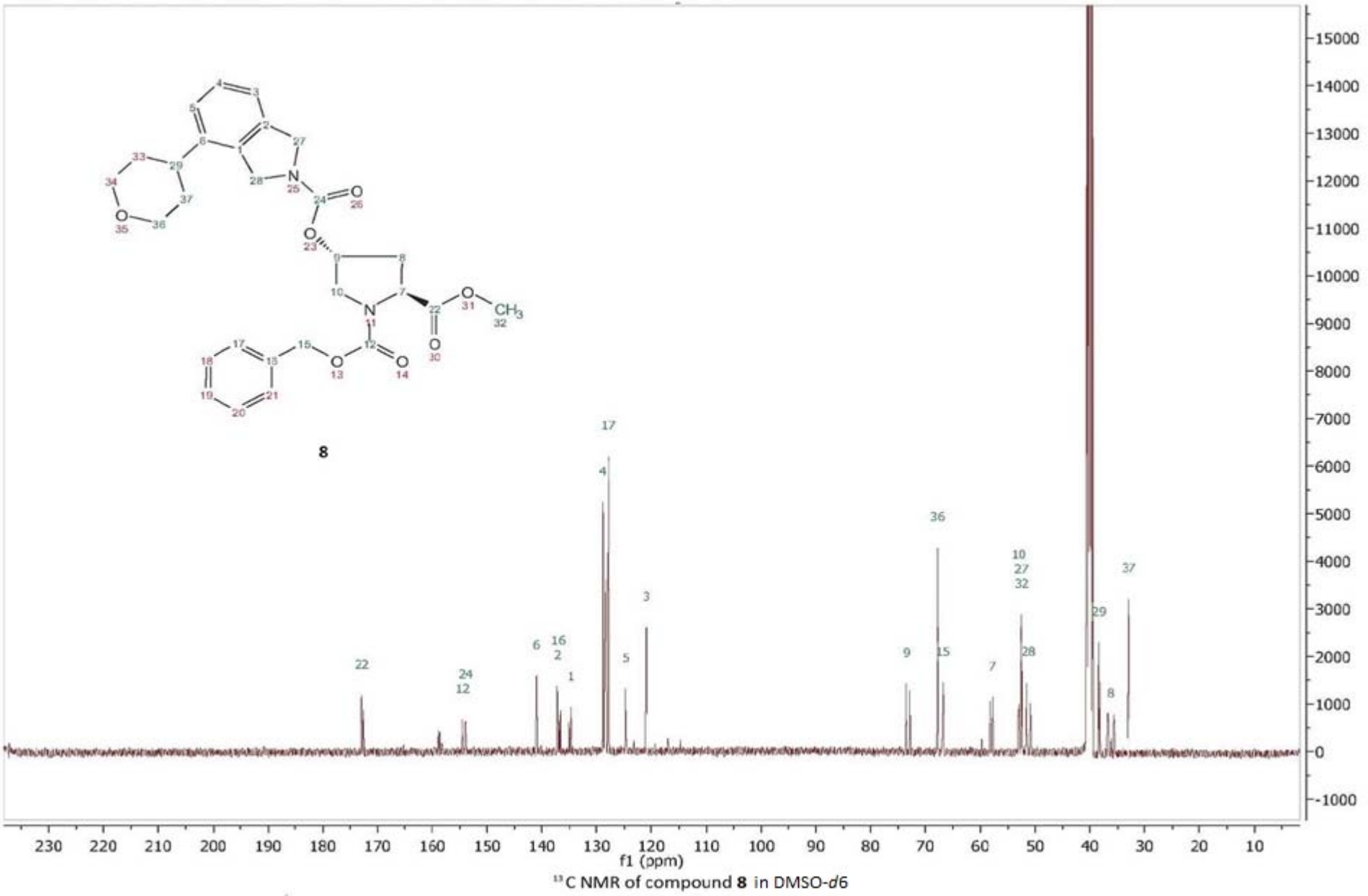
^{1}H NMR of compound **8** in DMSO-*d6*

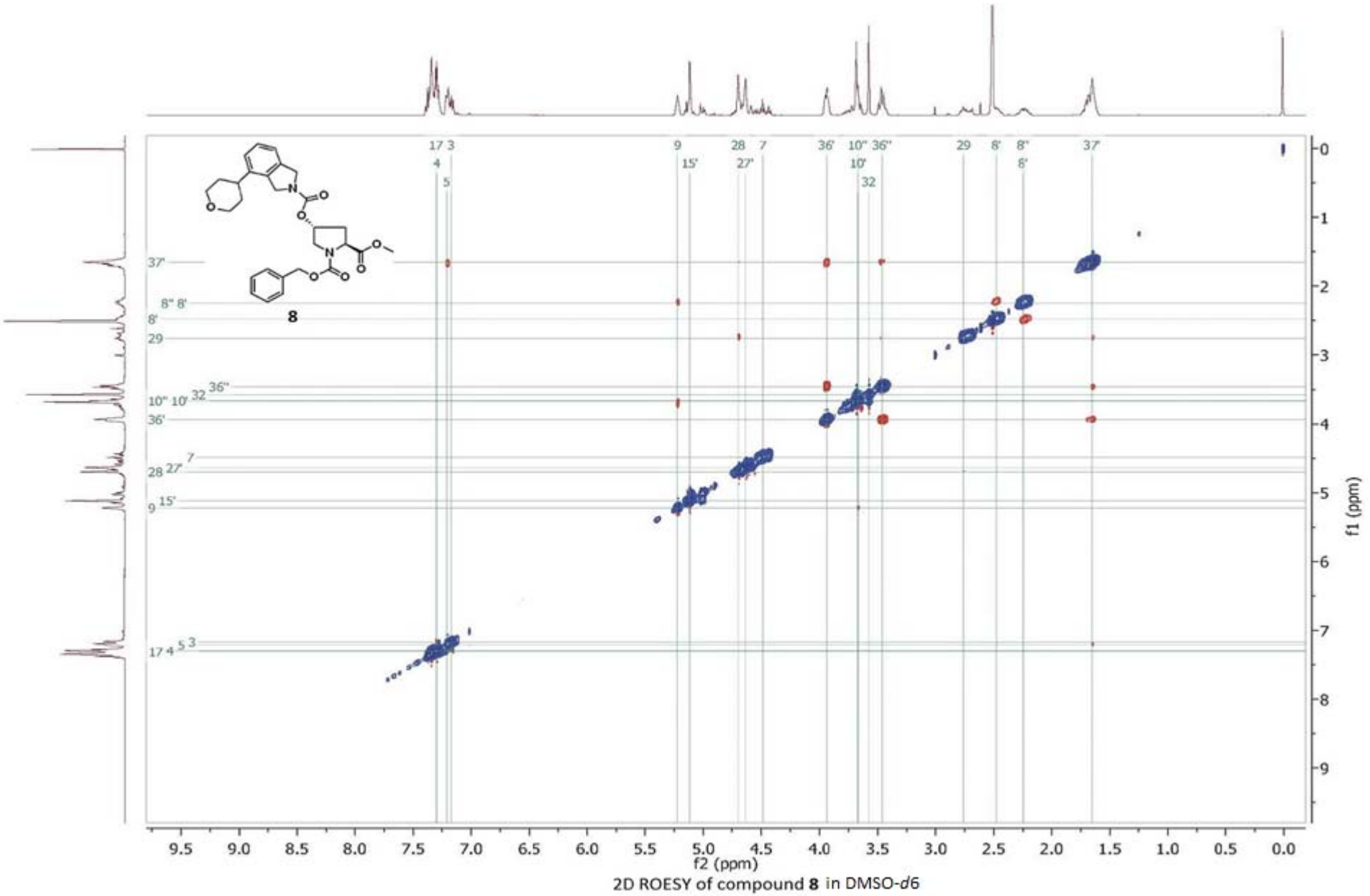

8
f2 (ppm)
f1 (ppm)
2D COSY of compound 8 in DMSO-d6

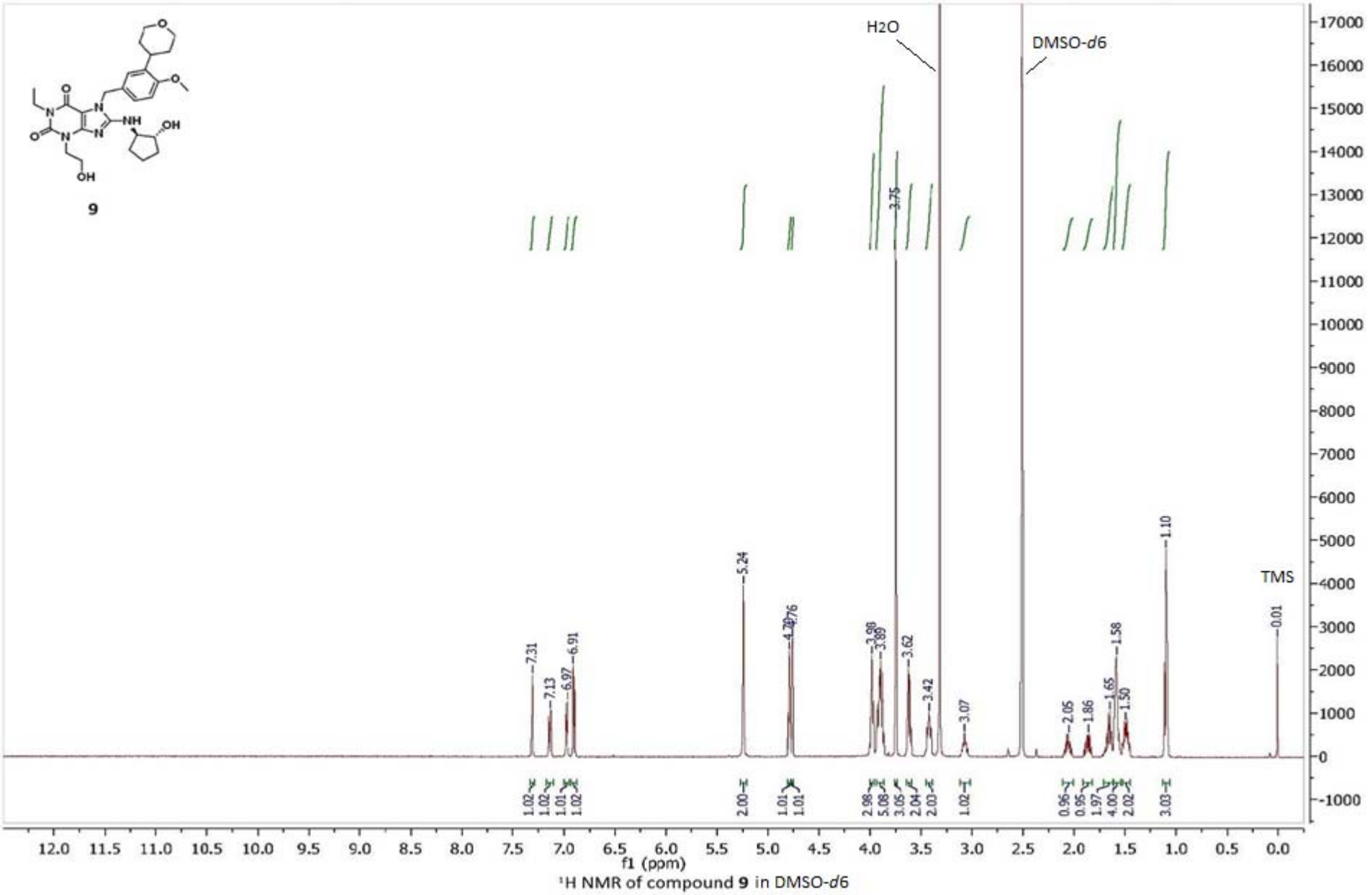

f2 (ppm)
f1 (ppm)
8
2D HSQC of compound 8 in DMSO-d6



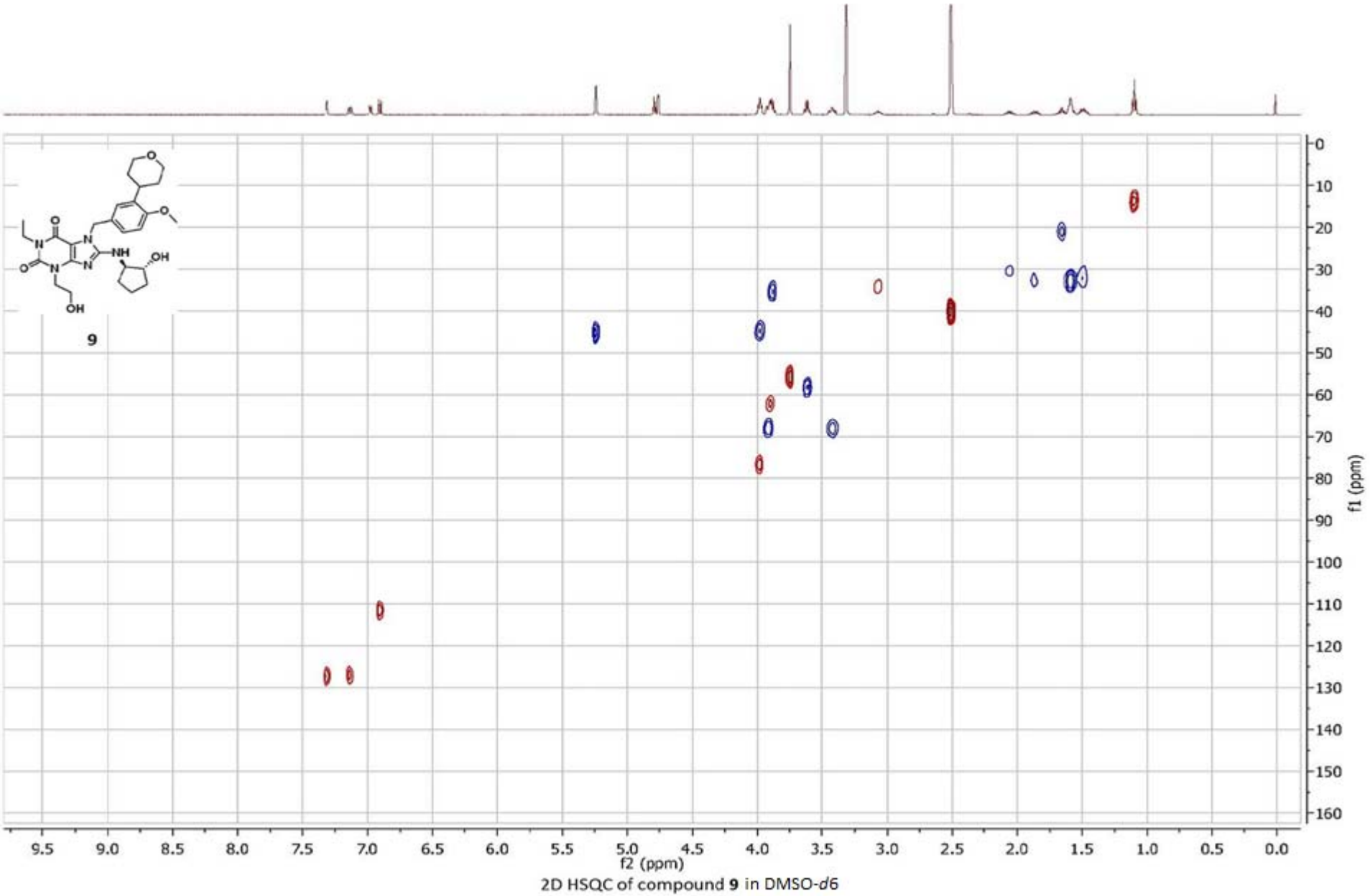
2D HMBC of compound **8** in DMSO-*d6*

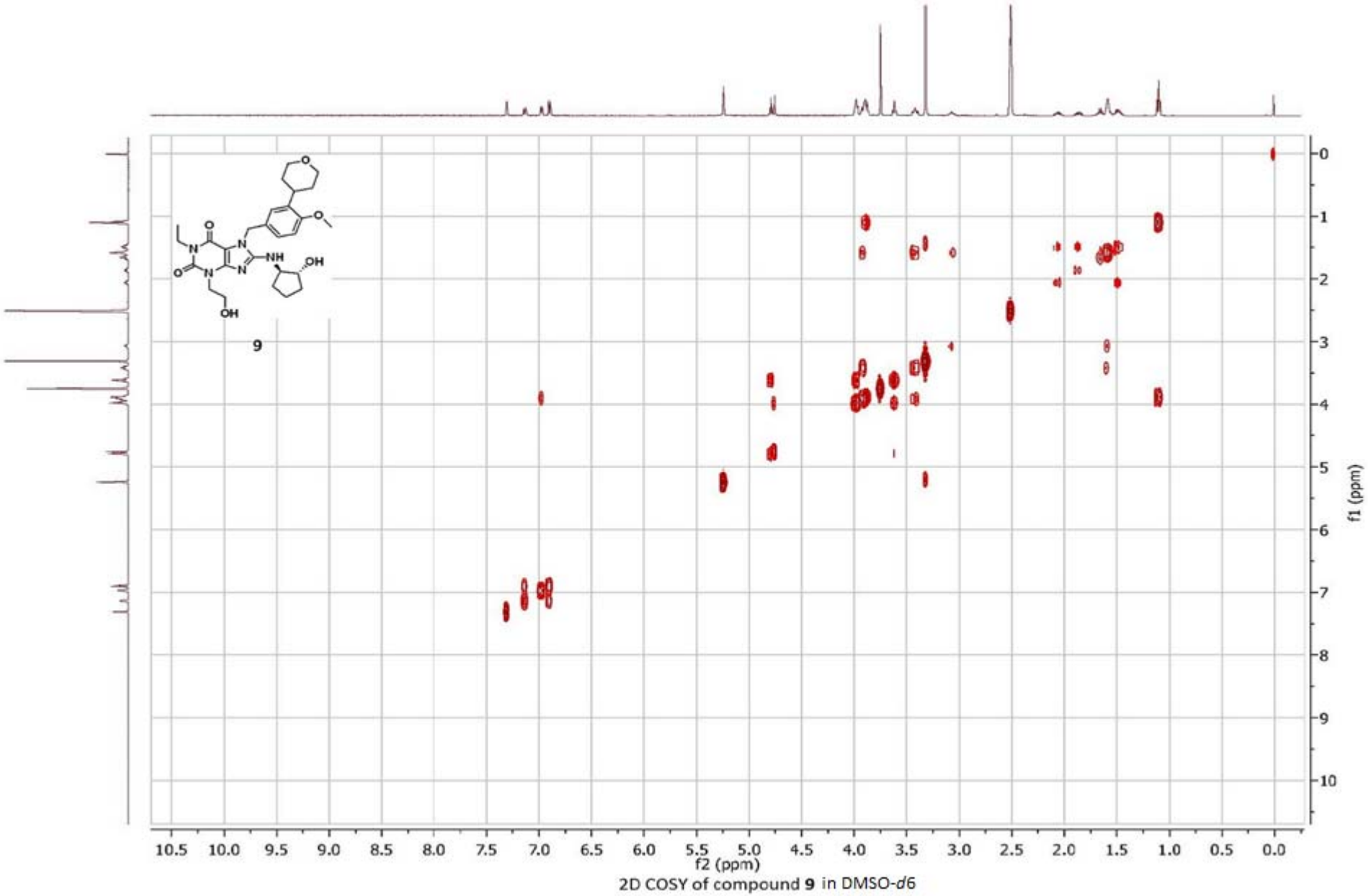

8
f1 (ppm)
13C NMR of compound 8 in DMSO-d6


8
f2 (ppm)
f1 (ppm)
2D ROESY of compound 8 in DMSO-d6

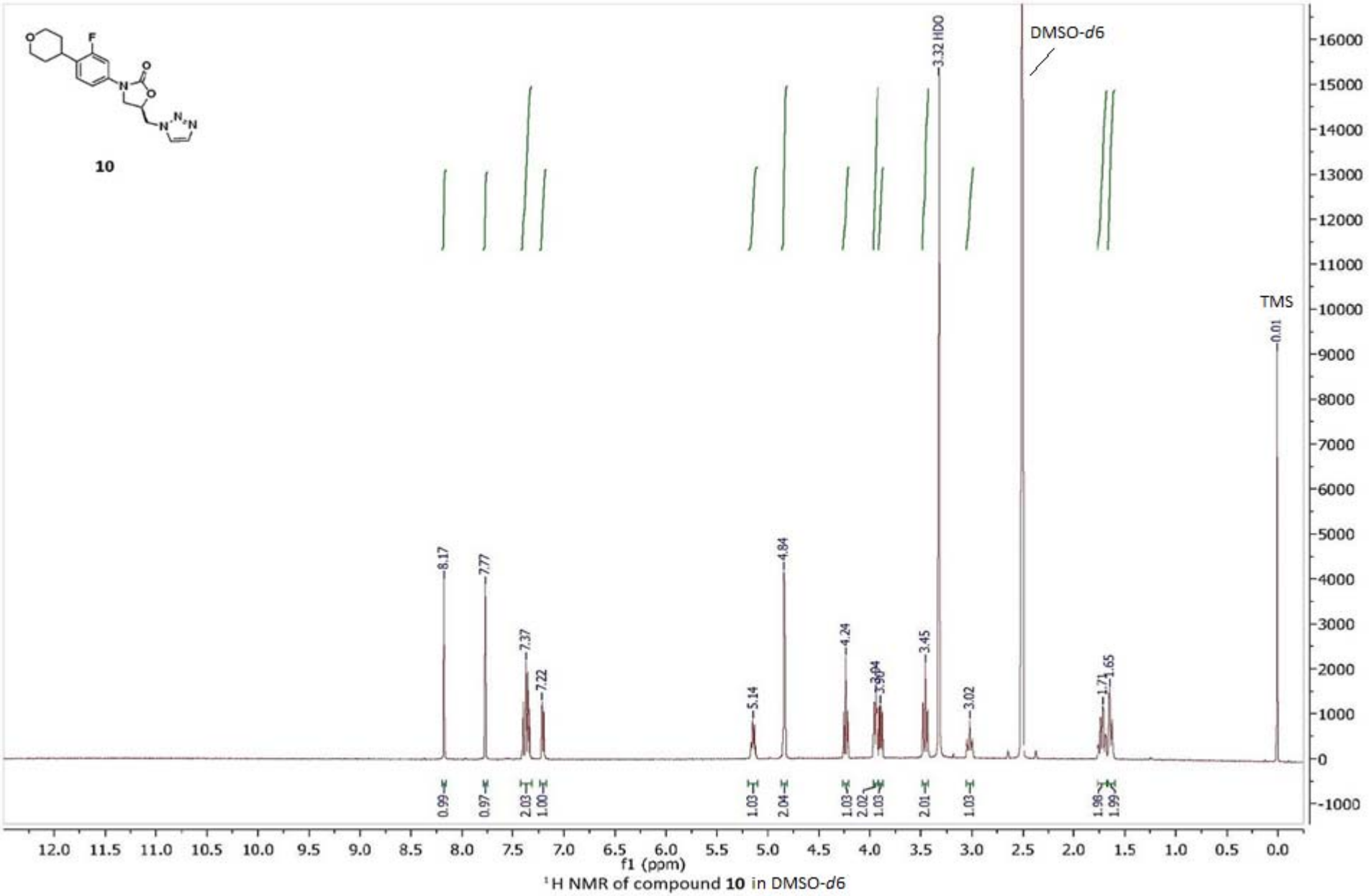


^{1}H NMR of compound **9** in DMSO-*d*6

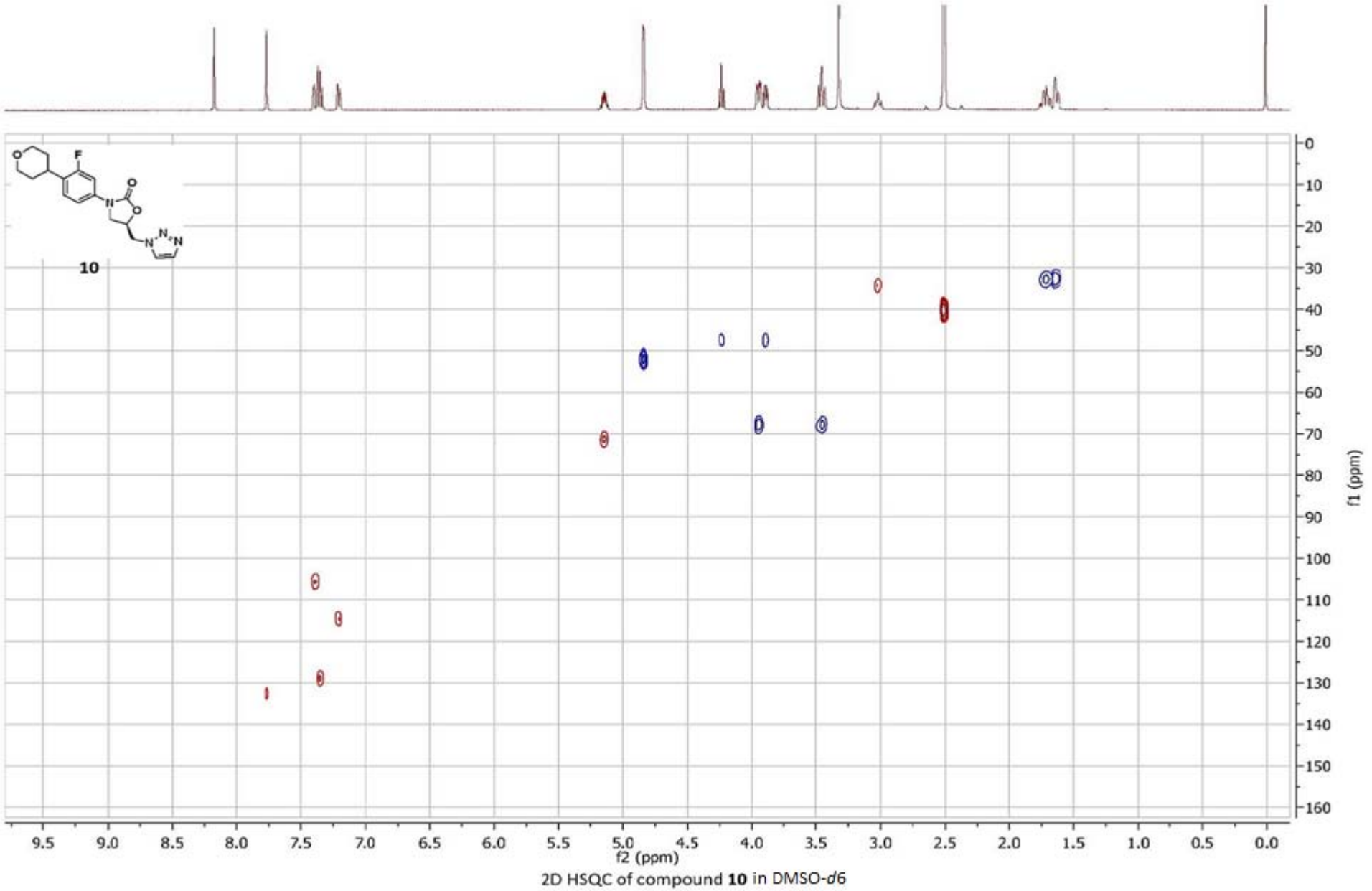

9
f2 (ppm)
f1 (ppm)
2D HSQC of compound 9 in DMSO-d6



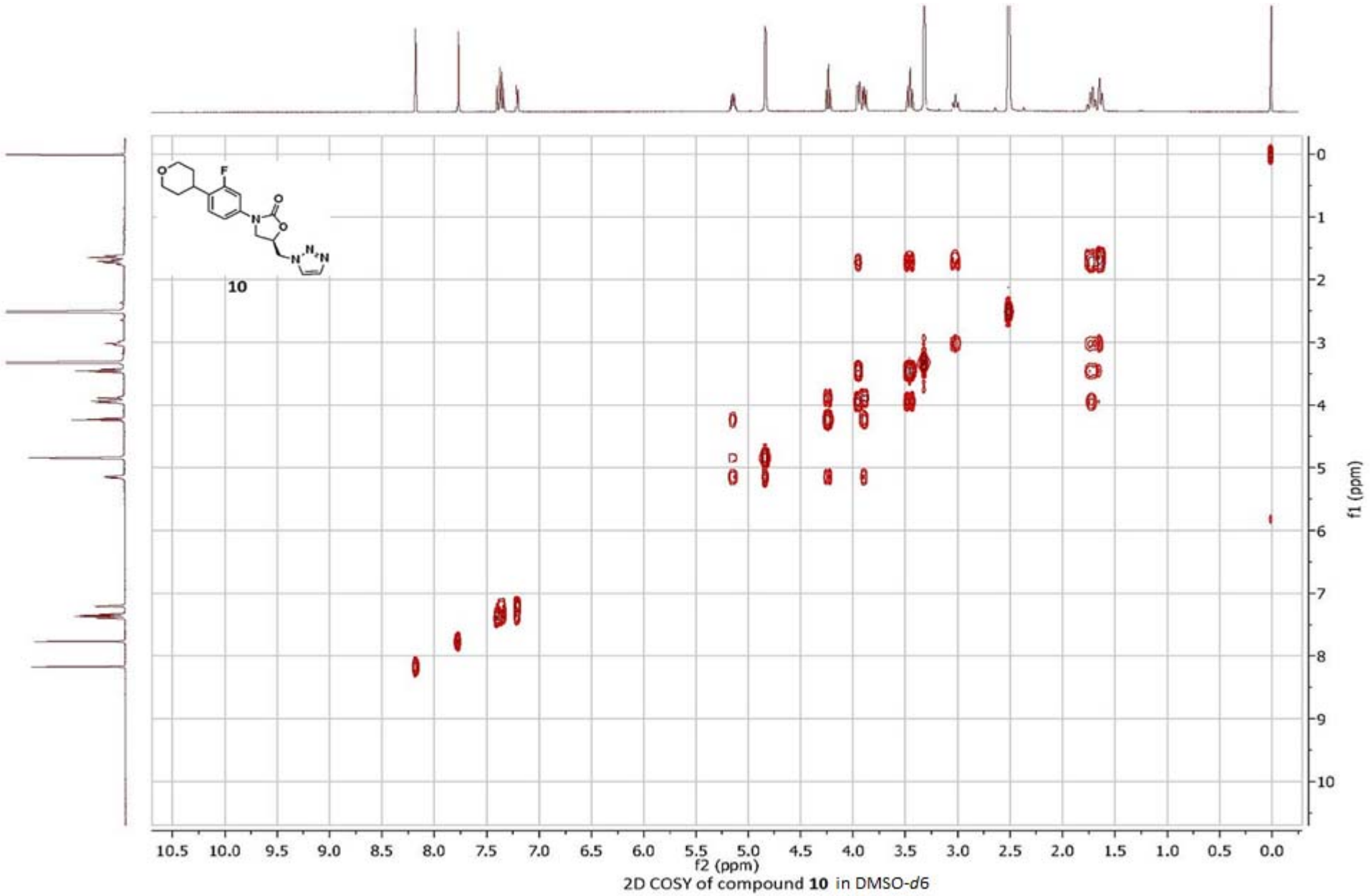
2D COSY of compound **9** in DMSO-*d*6



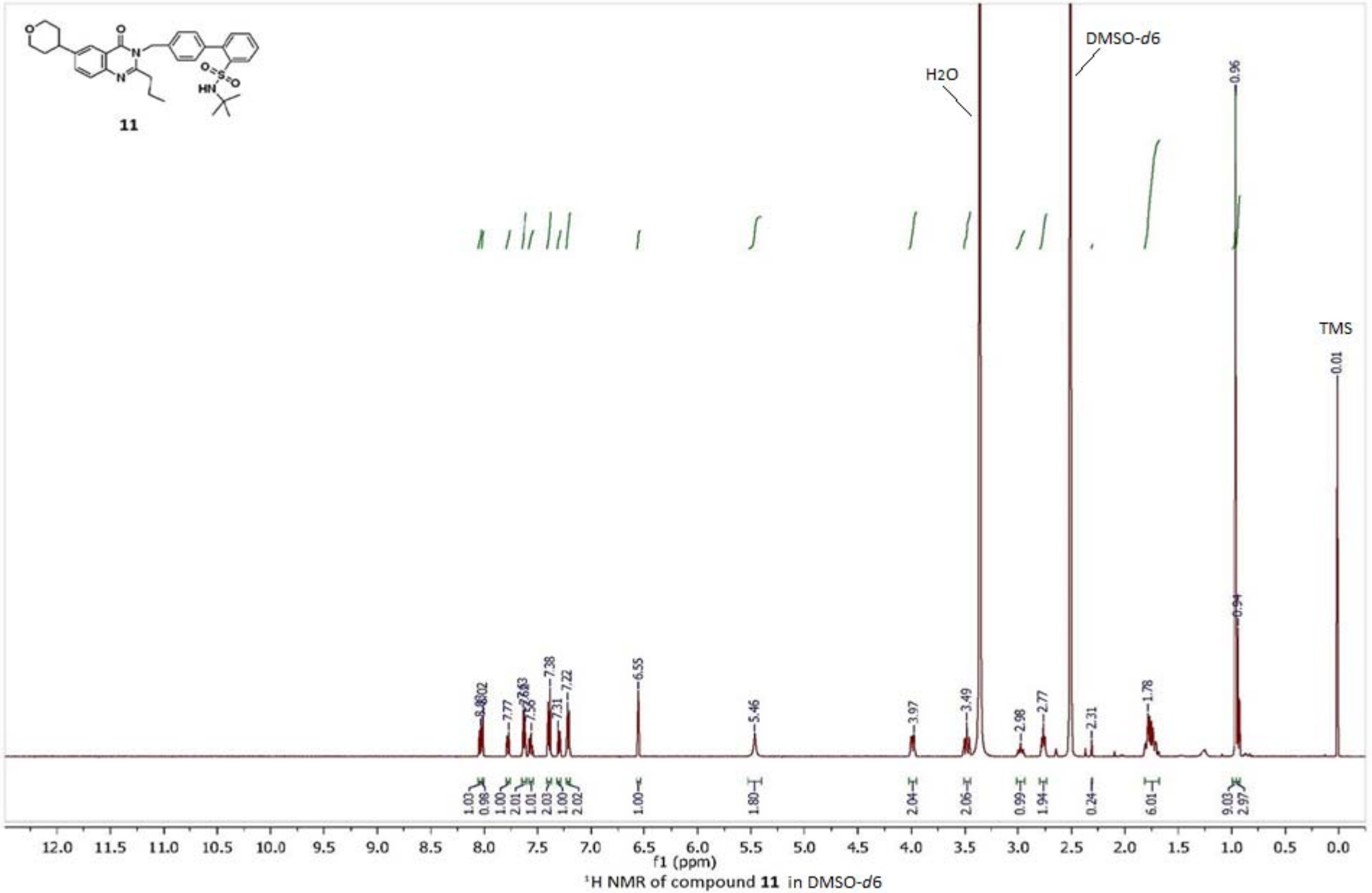
^{1}H NMR of compound **10** in DMSO-*d*6



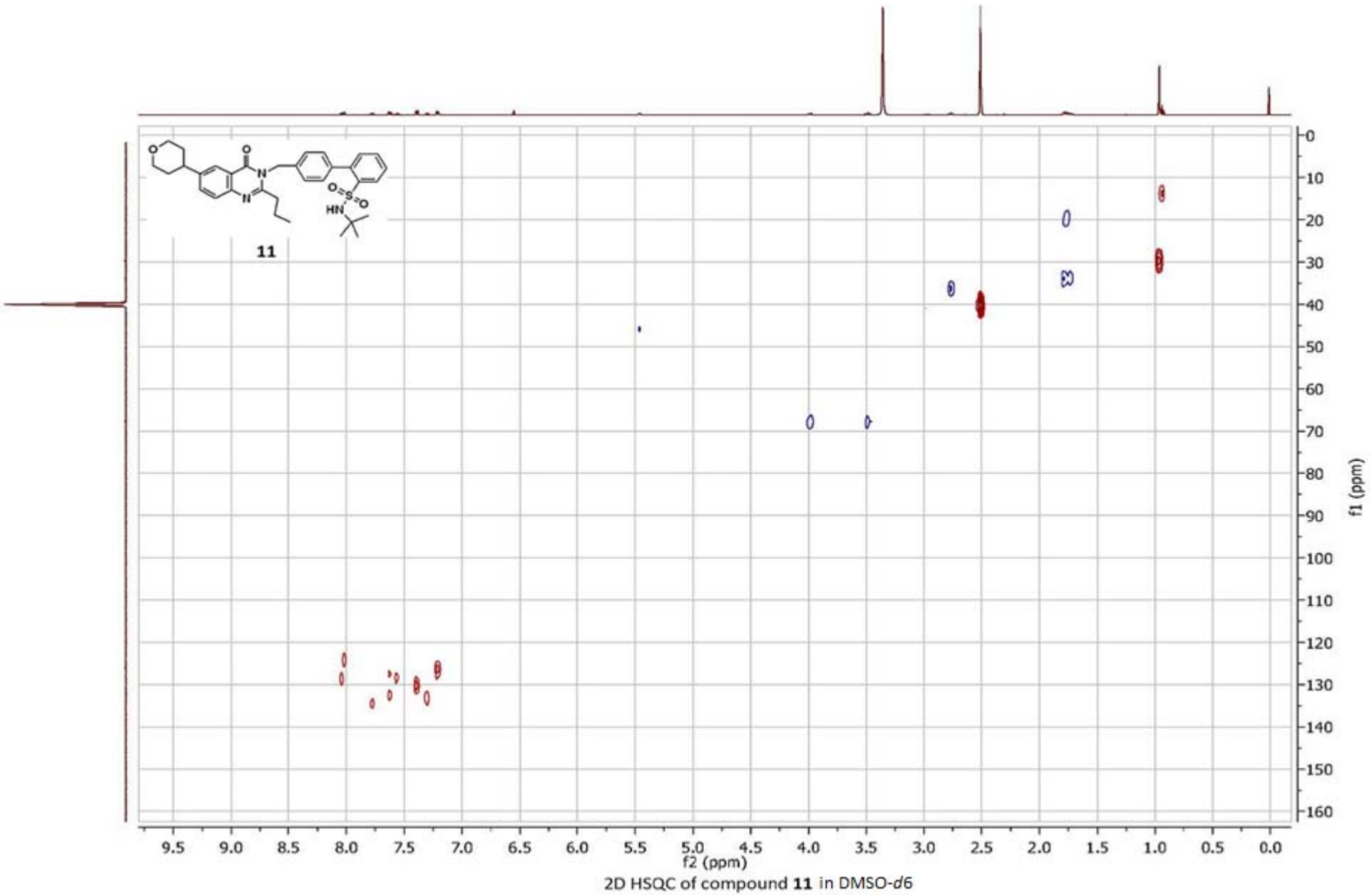
2D HSQC of compound **10** in DMSO-*d6*

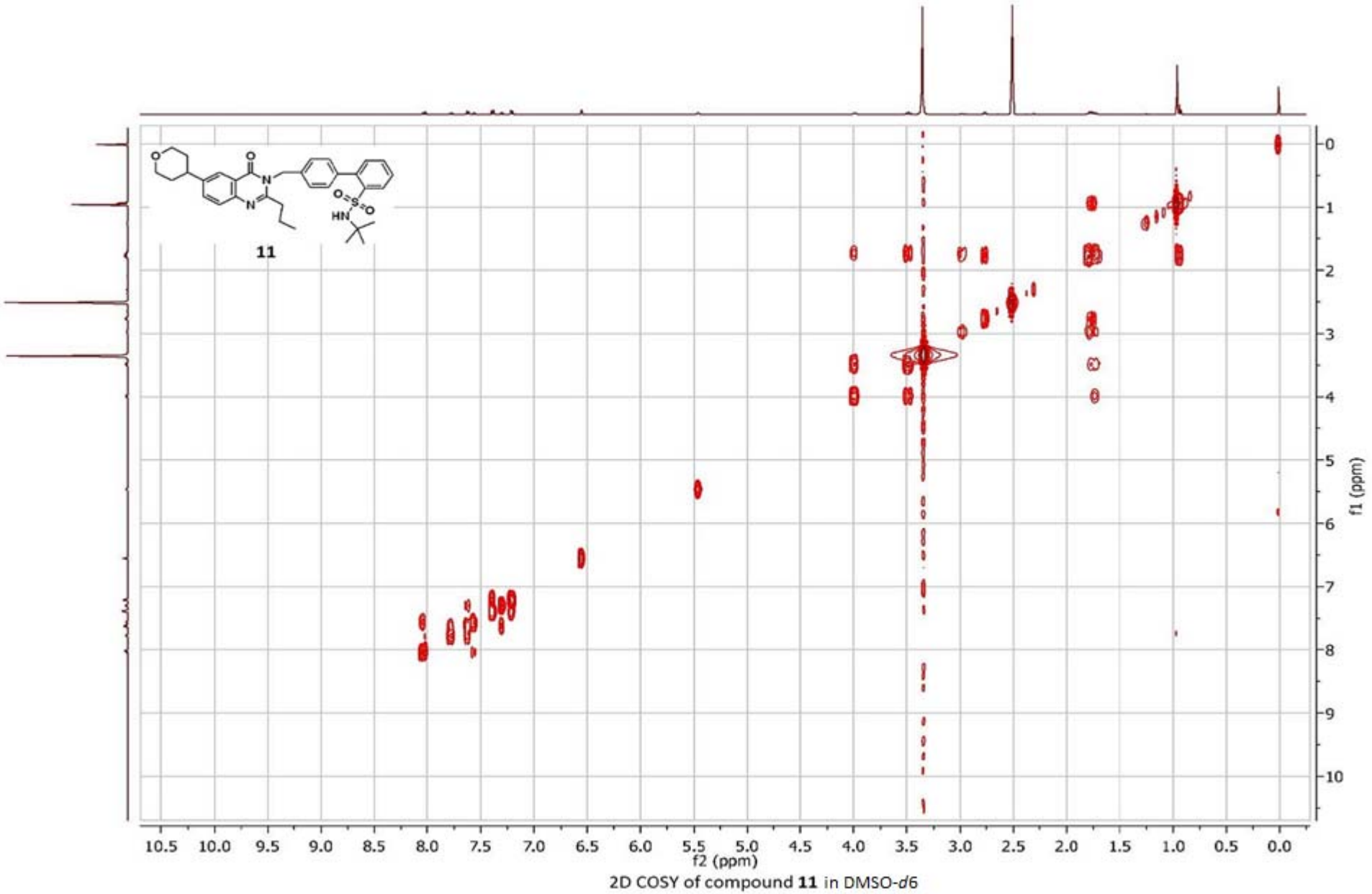


2D COSY of compound **10** in DMSO-*d*6

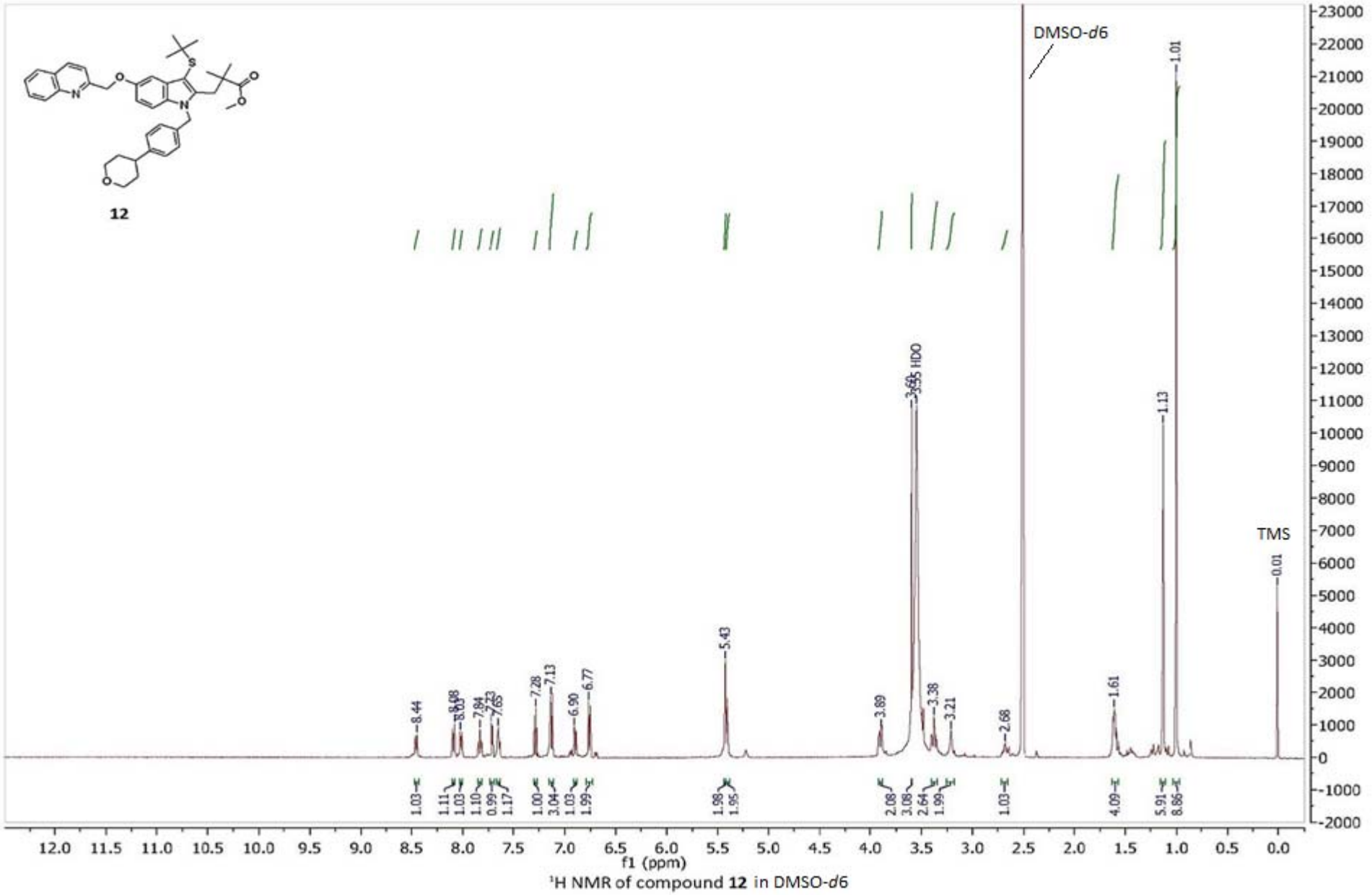


^{1}H NMR of compound **11** in DMSO-*d*6

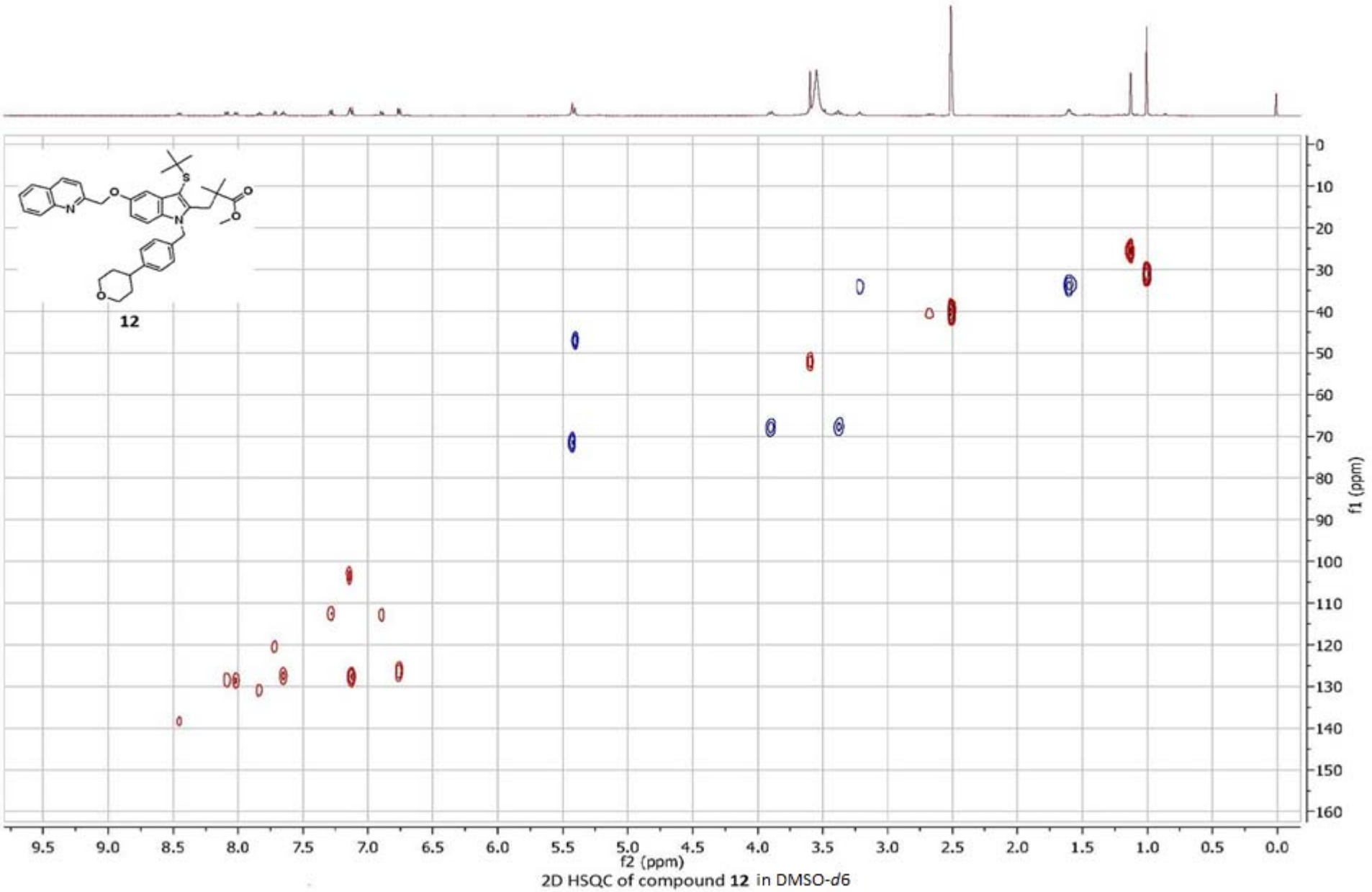

11
f2 (ppm)
f1 (ppm)
2D HSQC of compound 11 in DMSO-d6

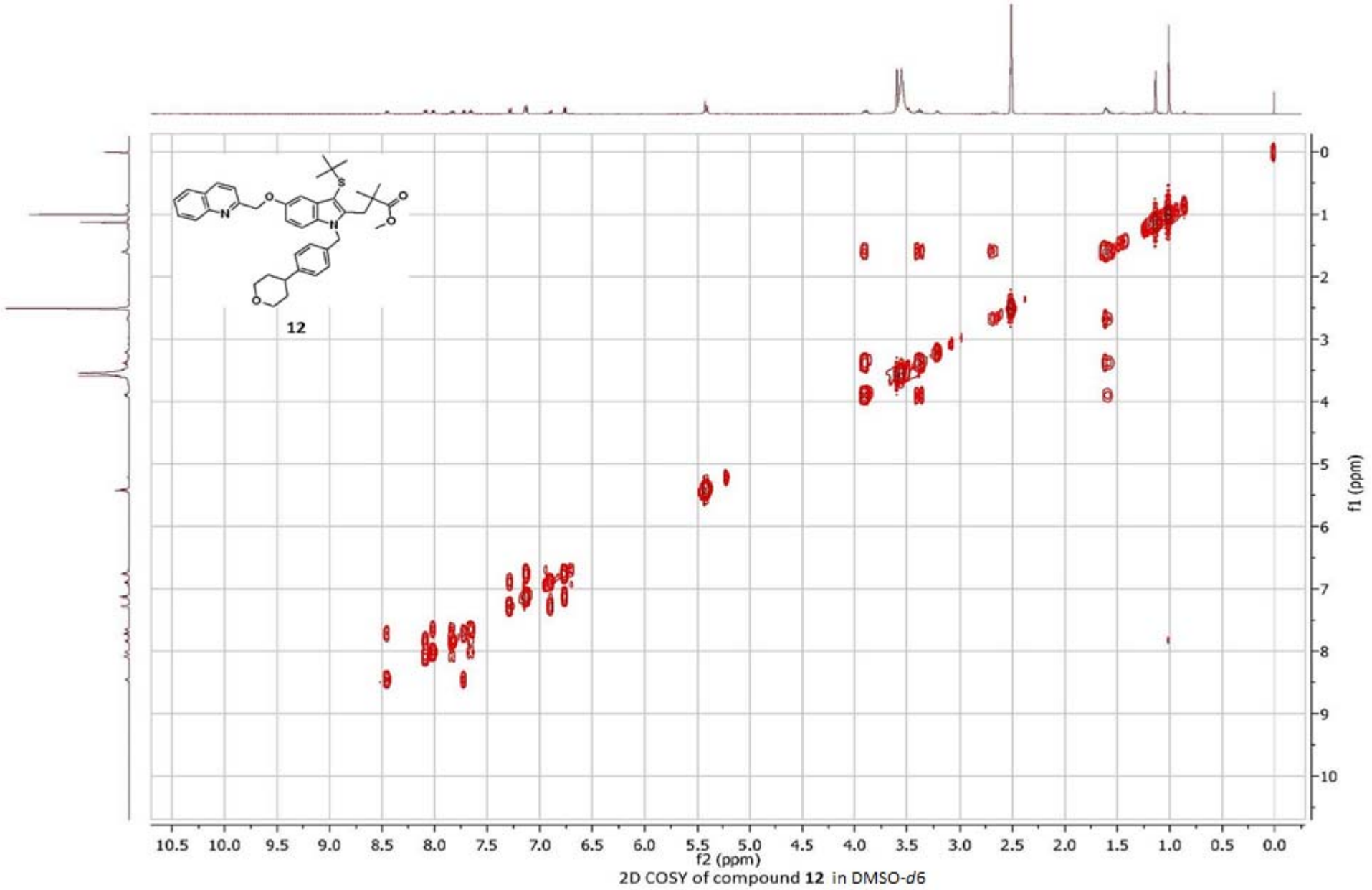


2D COSY of compound **11** in DMSO-*d*6

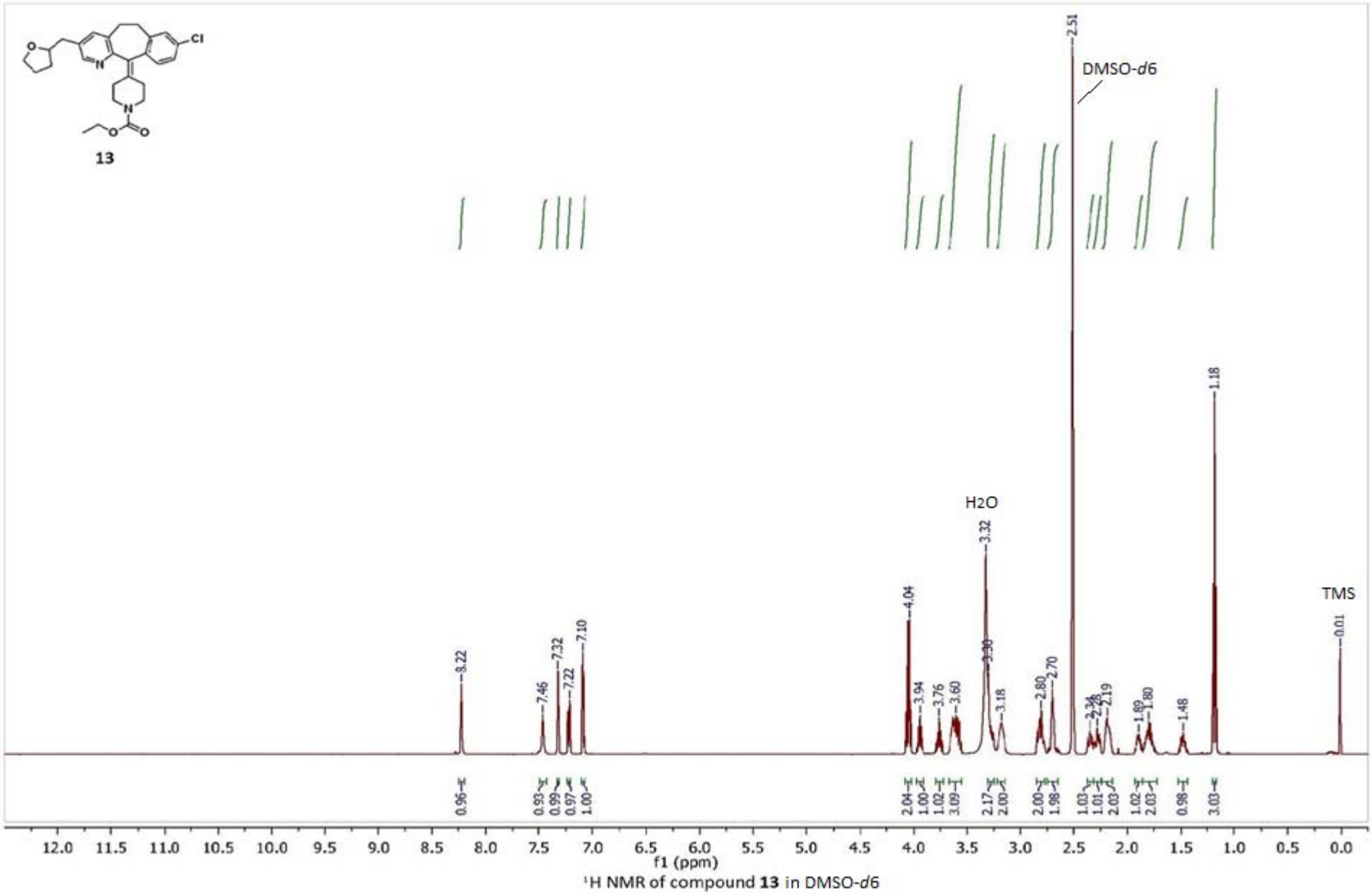


^{1}H NMR of compound **12** in DMSO-*d*6

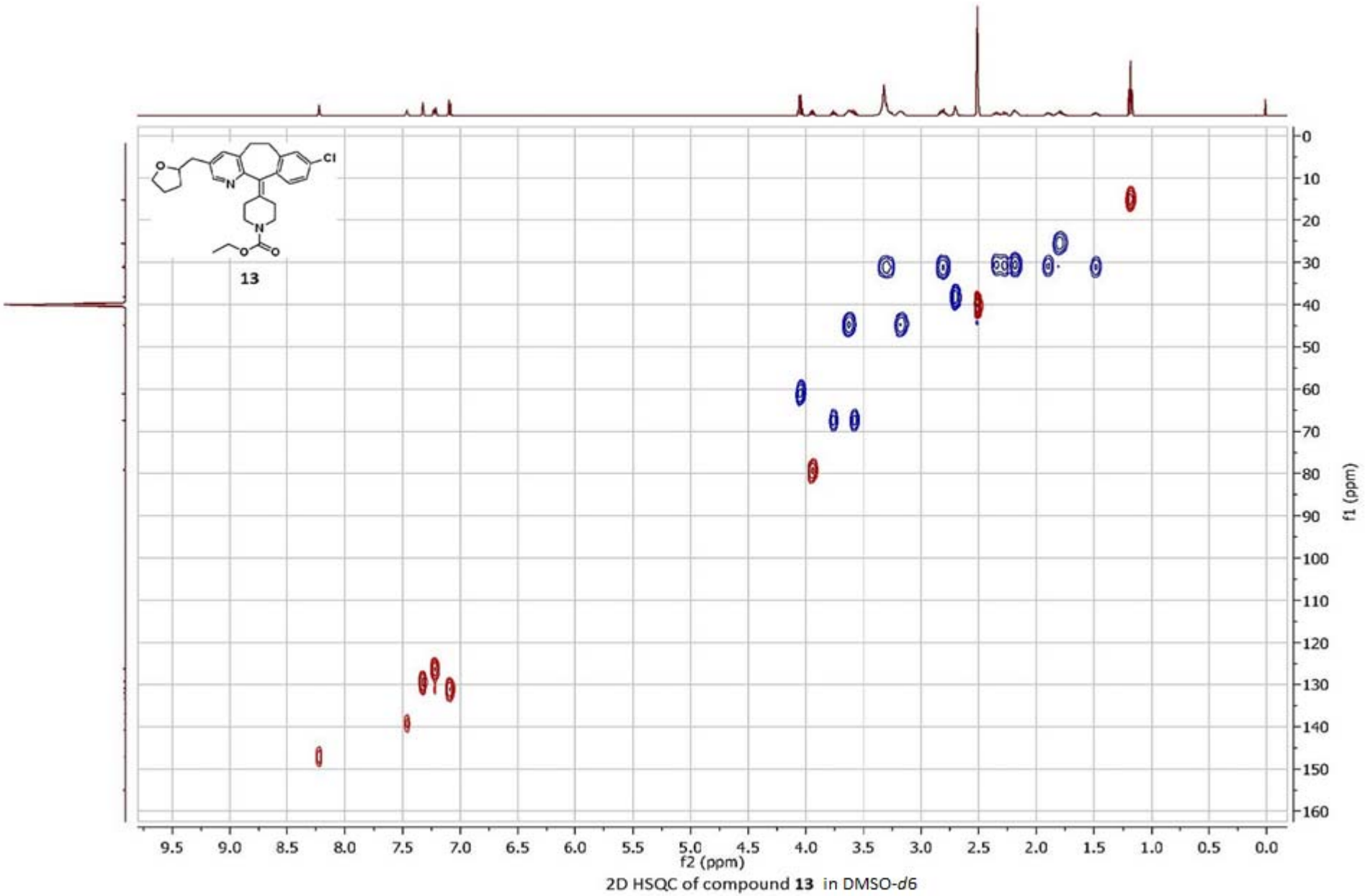

12
f2 (ppm)
f1 (ppm)
2D HSQC of compound 12 in DMSO-d6

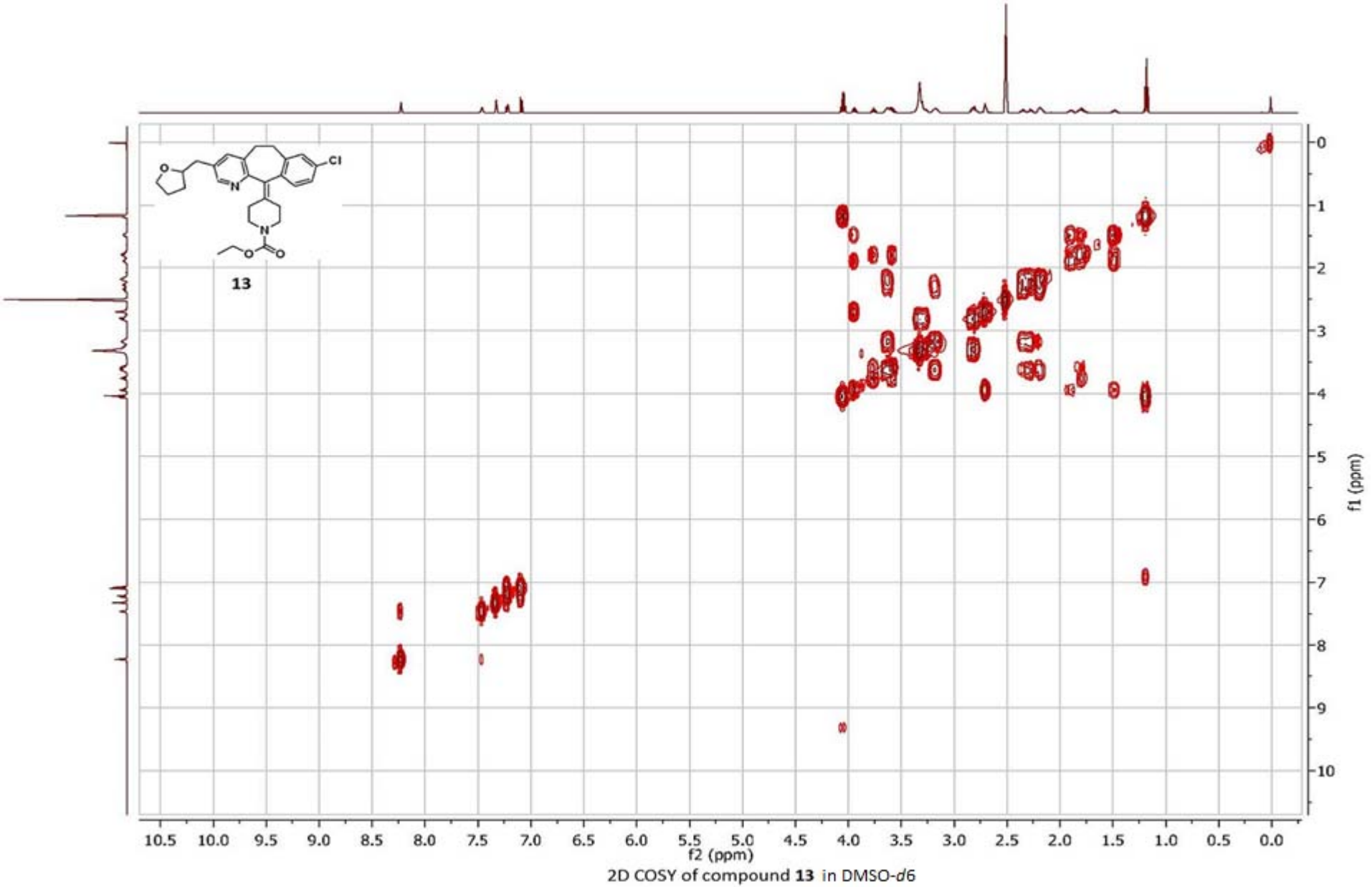


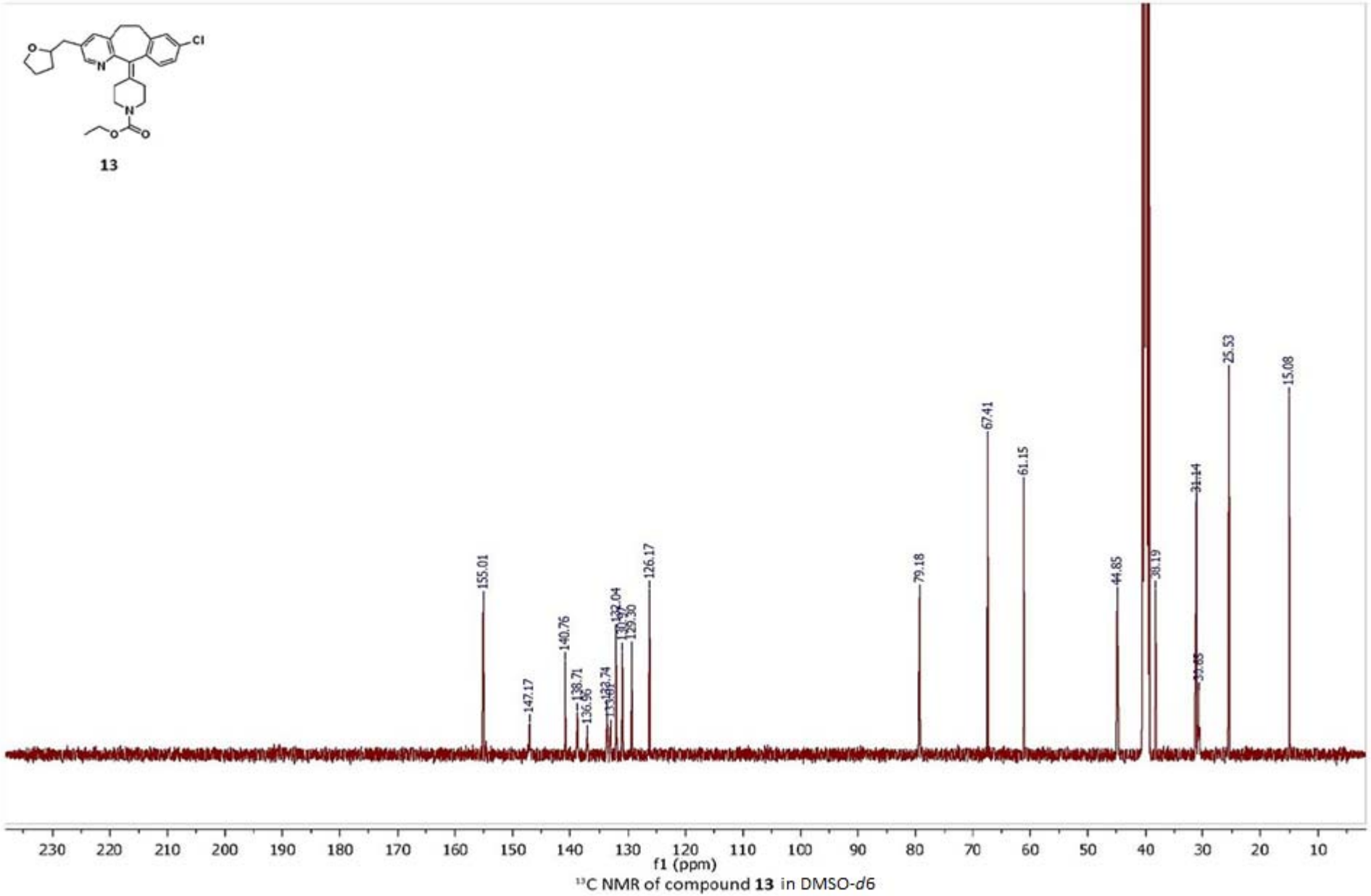
2D COSY of compound **12** in DMSO-*d*6



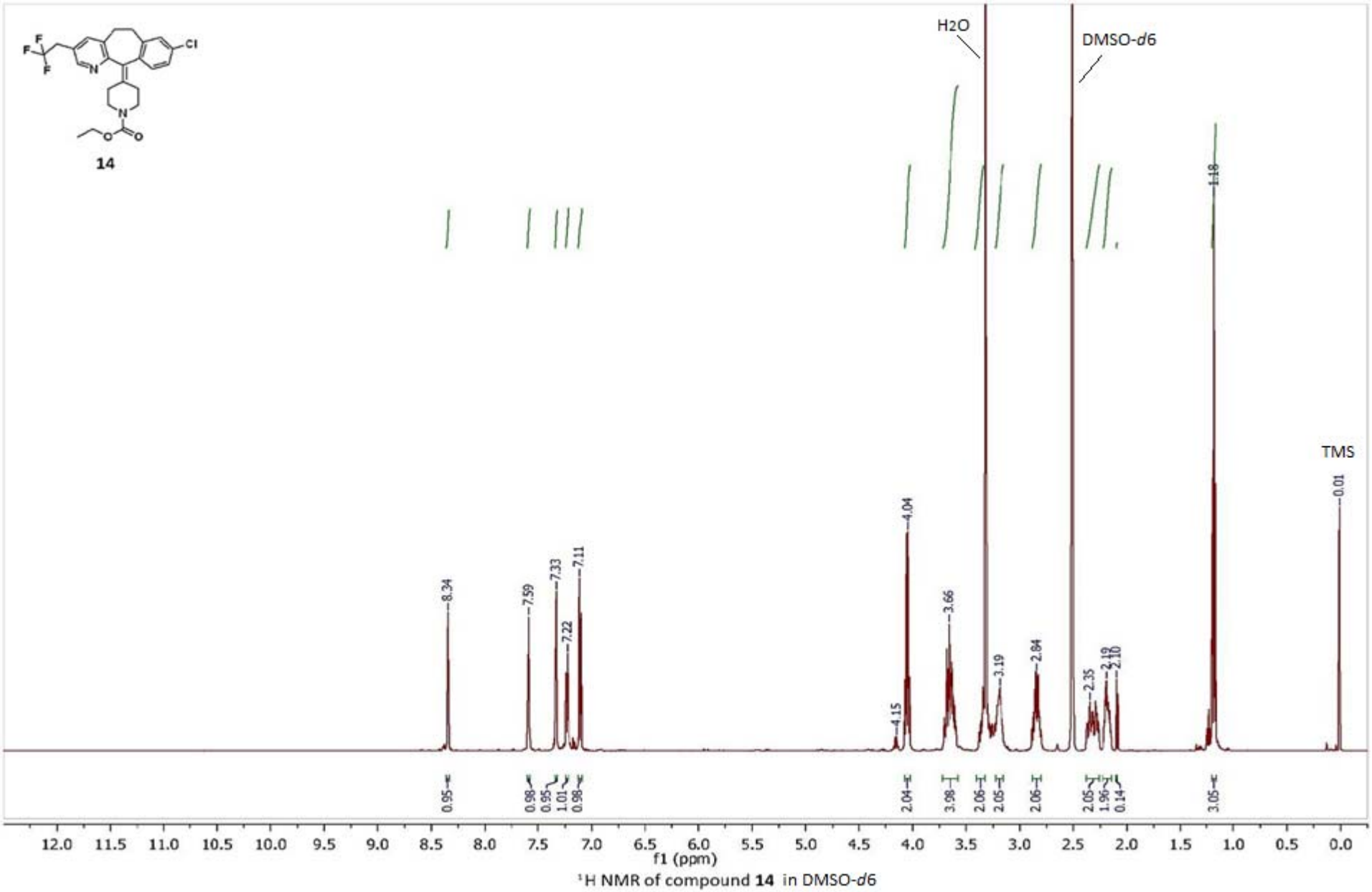
^{1}H NMR of compound **13** in DMSO-*d*6


13
f2 (ppm)
f1 (ppm)
2D HSQC of compound 13 in DMSO-d6

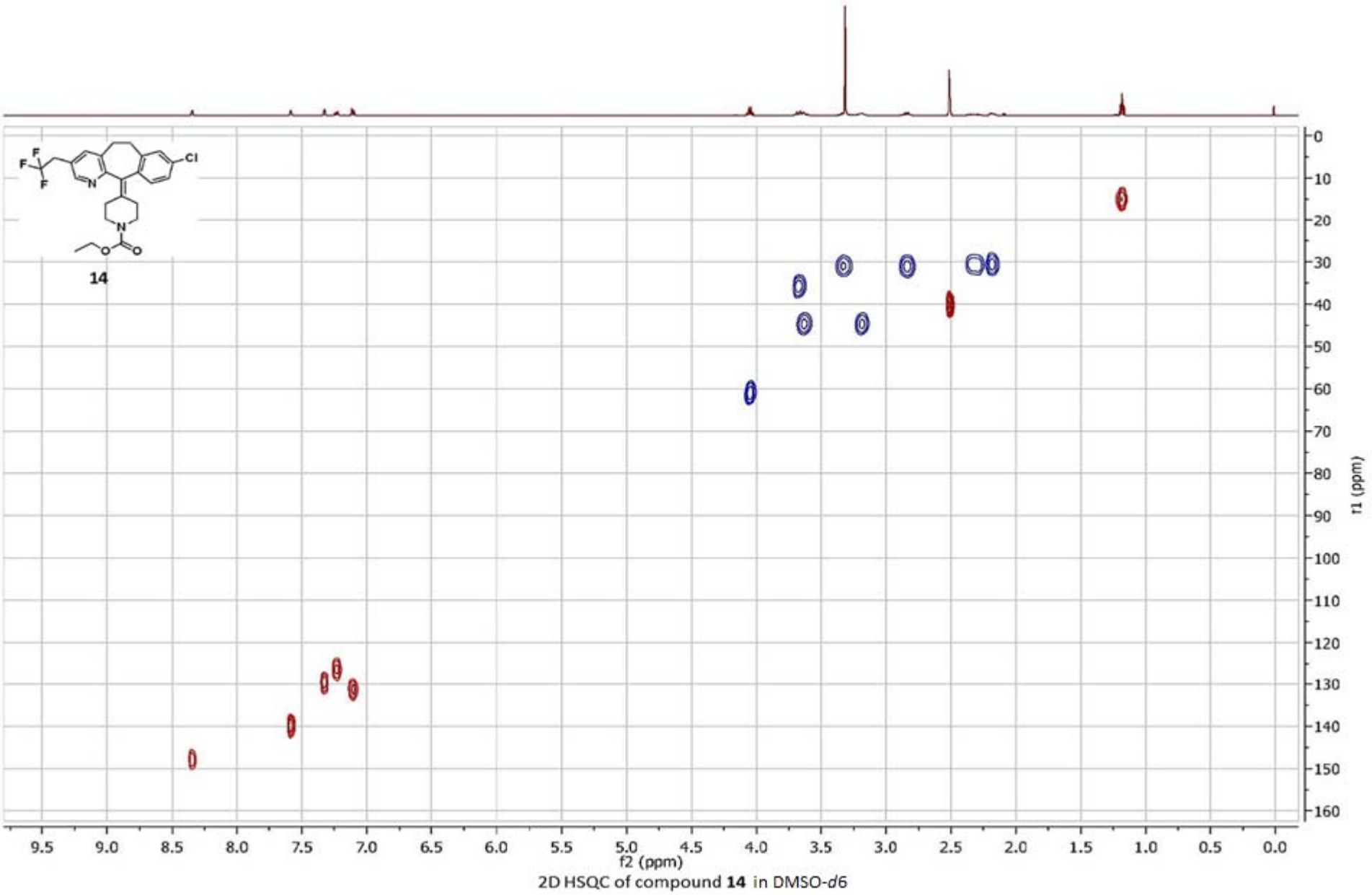

13
f2 (ppm)
f1 (ppm)
2D COSY of compound 13 in DMSO-d6



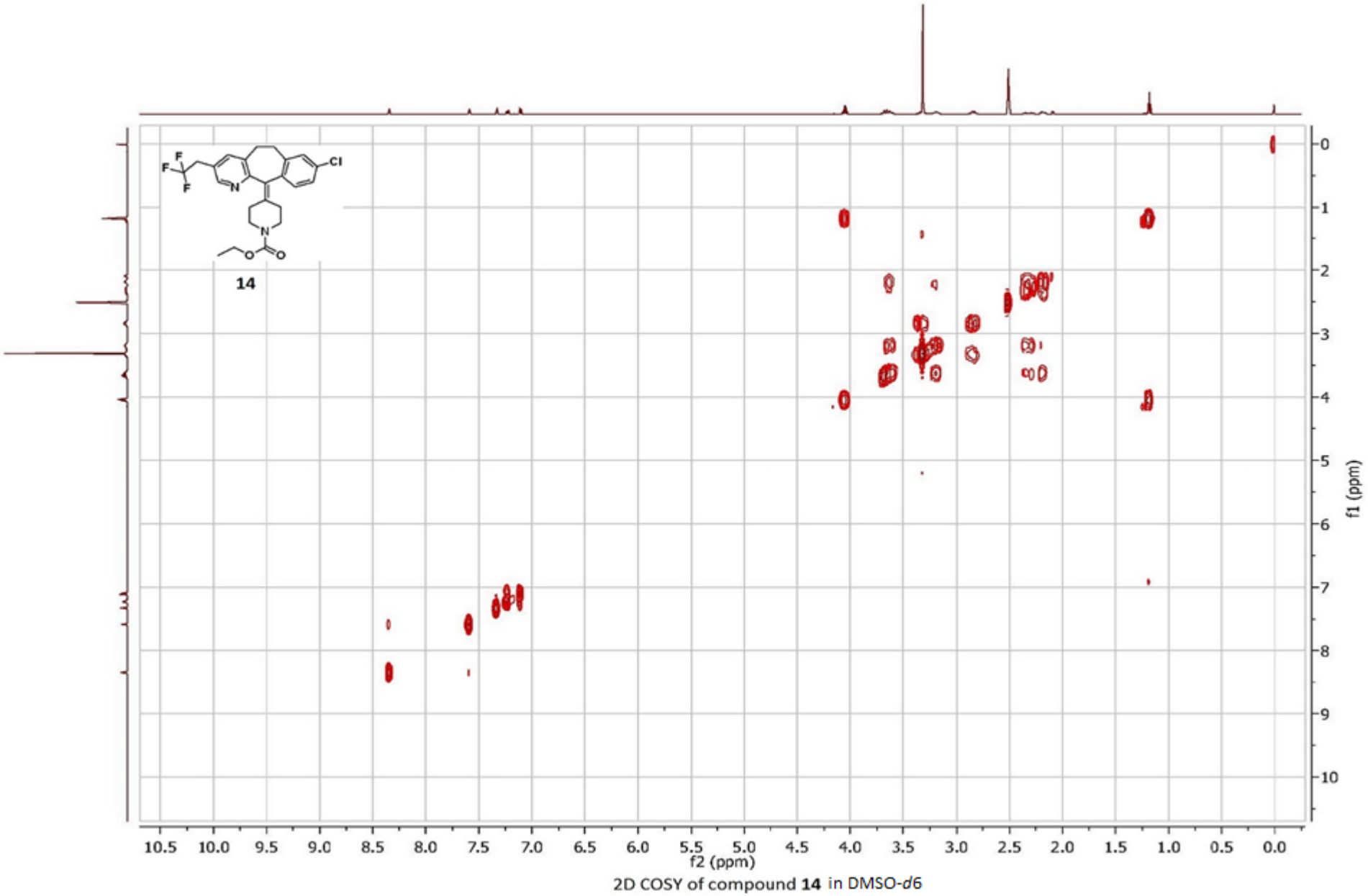
^{13}C NMR of compound **13** in DMSO-*d*6



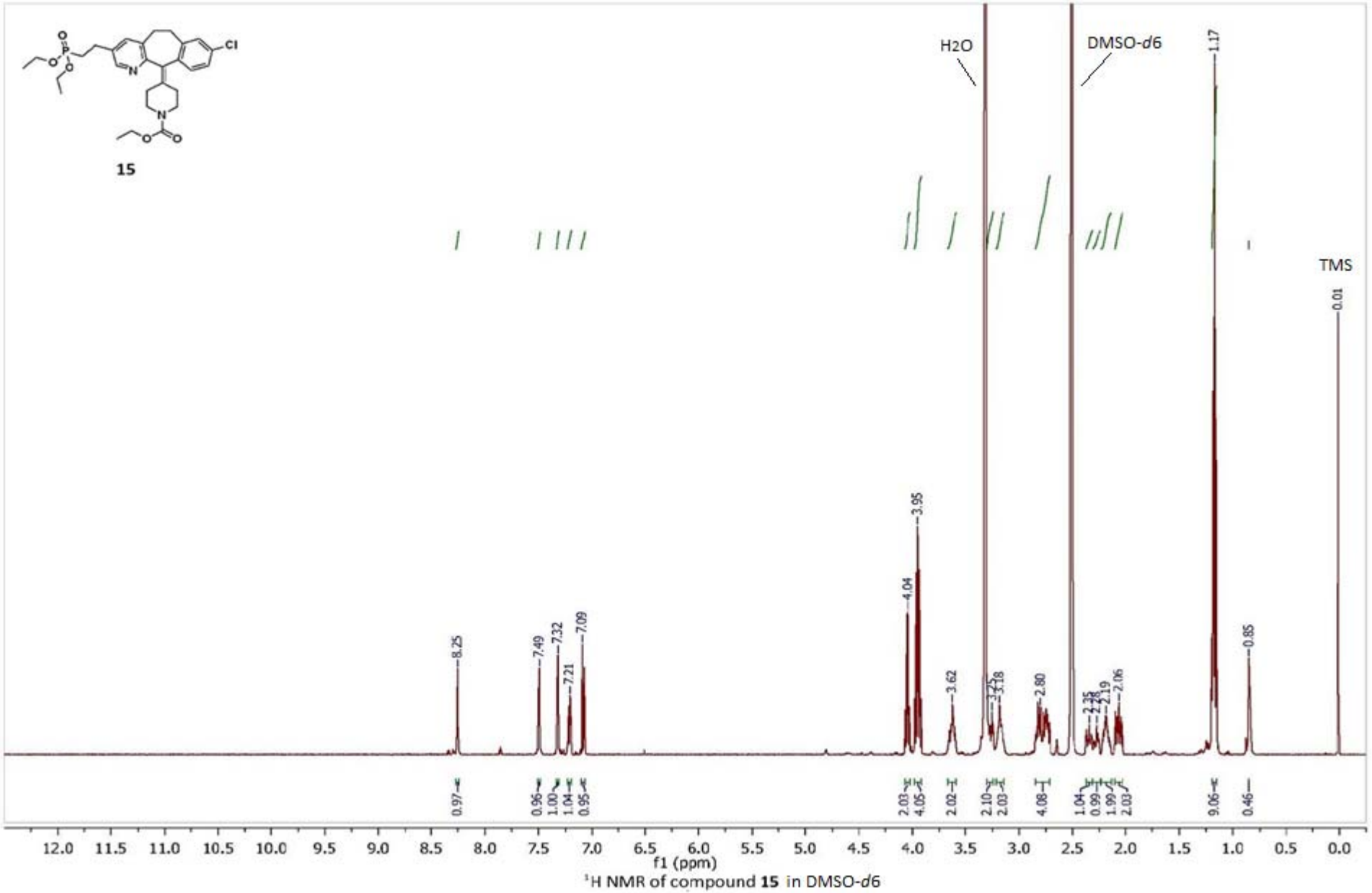
^{1}H NMR of compound **14** in DMSO-*d*6



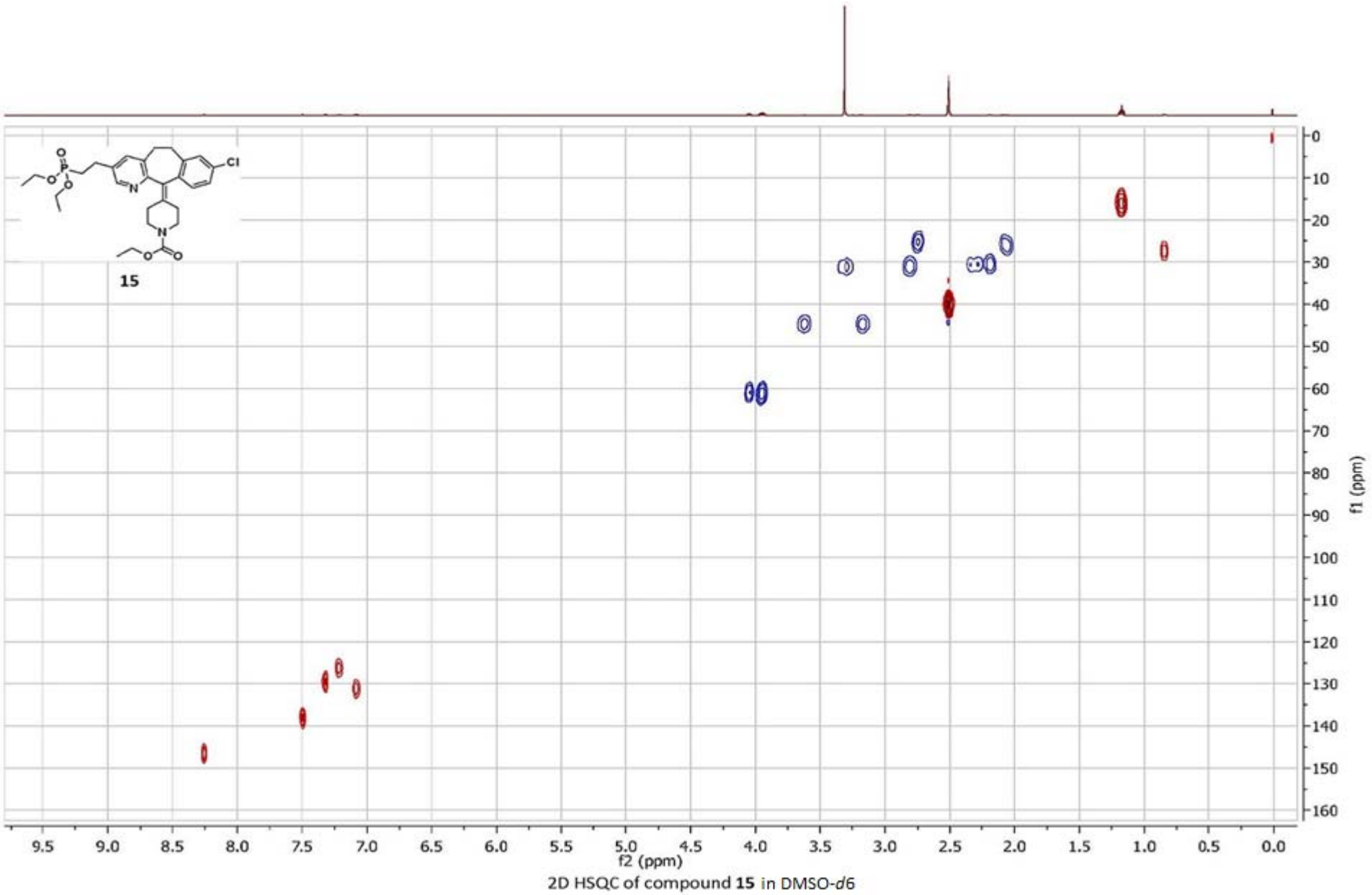
2D HSQC of compound **14** in DMSO-*d*6



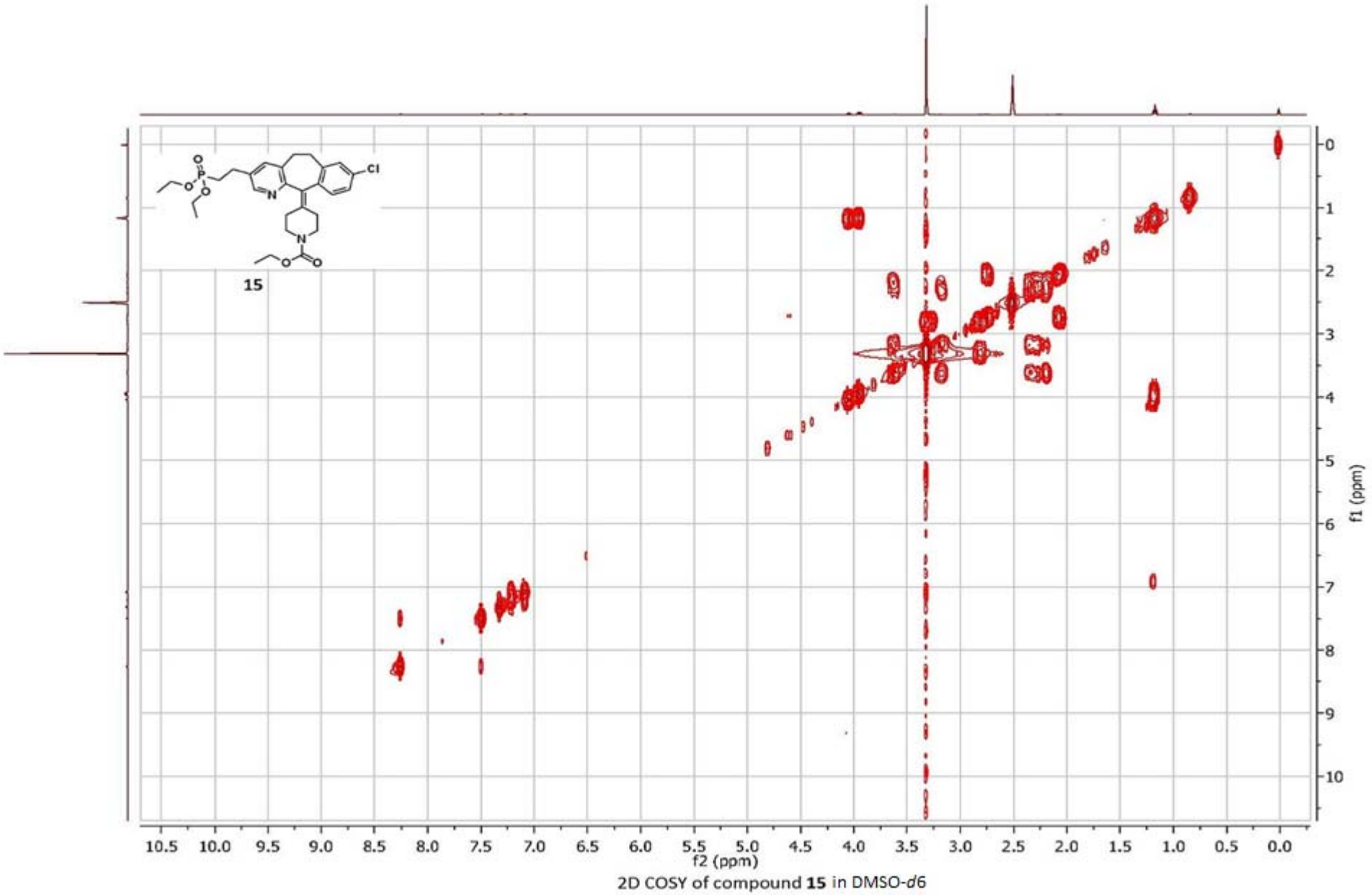
2D COSY of compound **14** in DMSO-*d6*



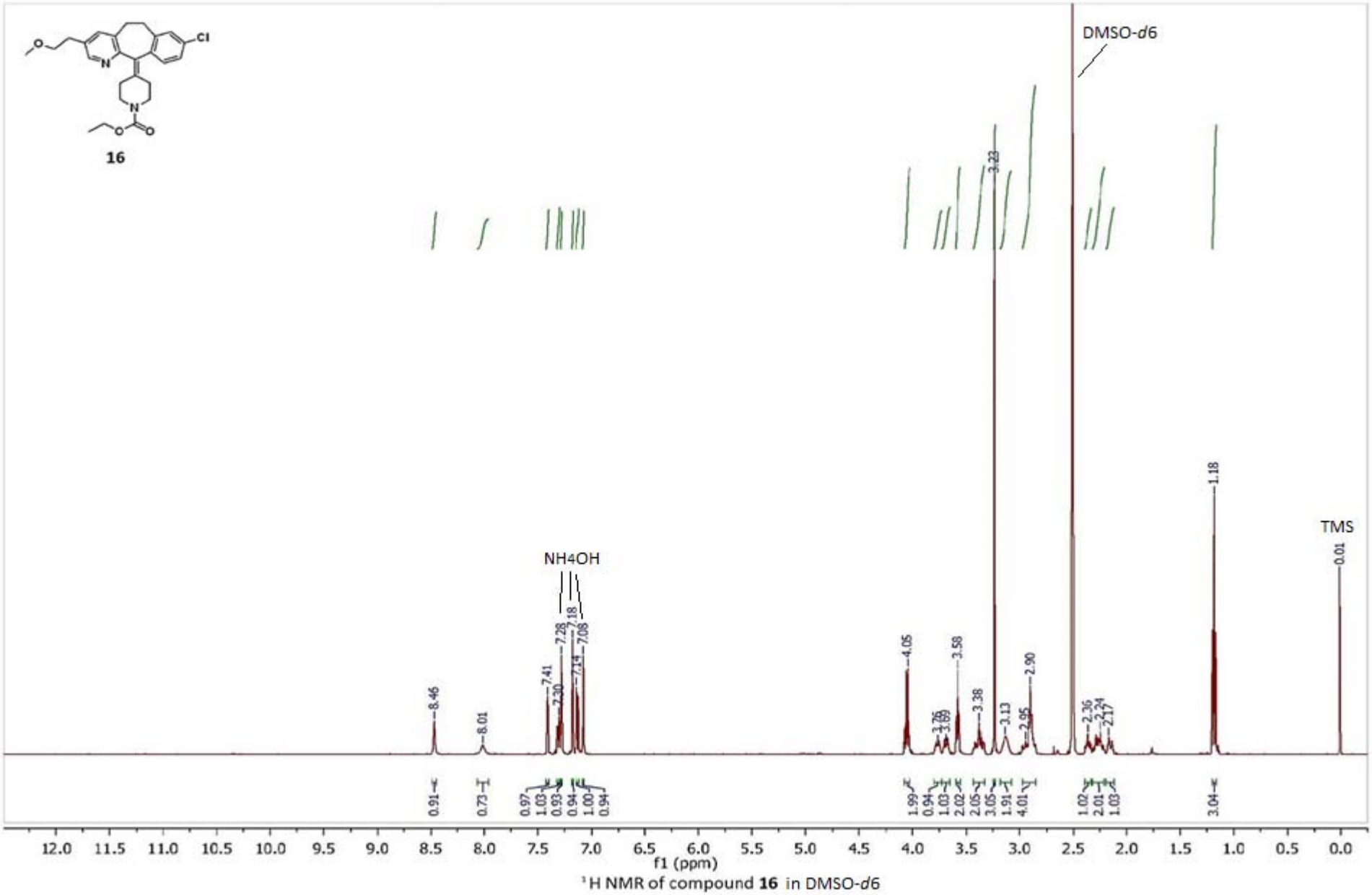
^{1}H NMR of compound **15** in DMSO-*d*6



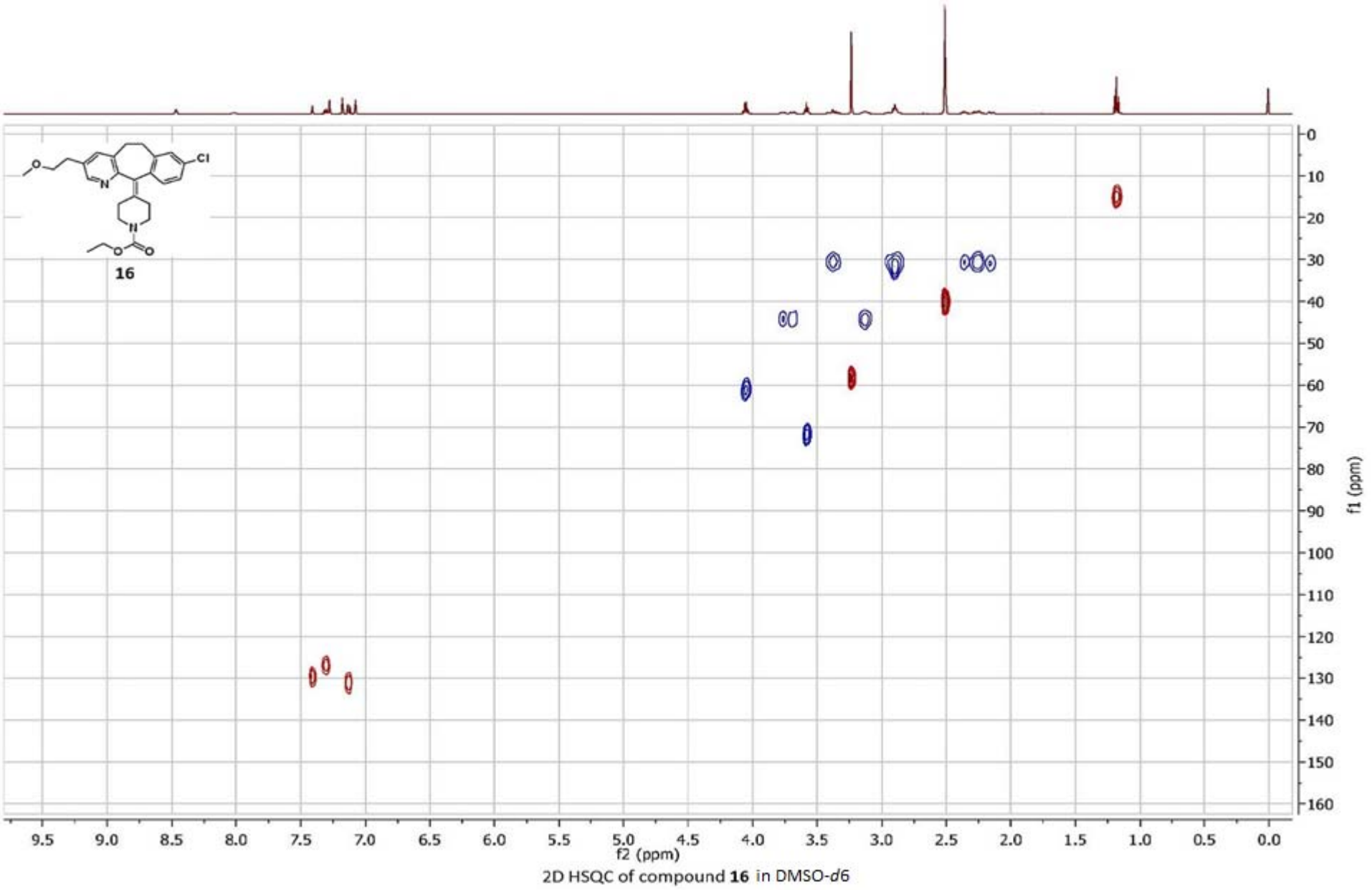
2D HSQC of compound **15** in DMSO-*d6*

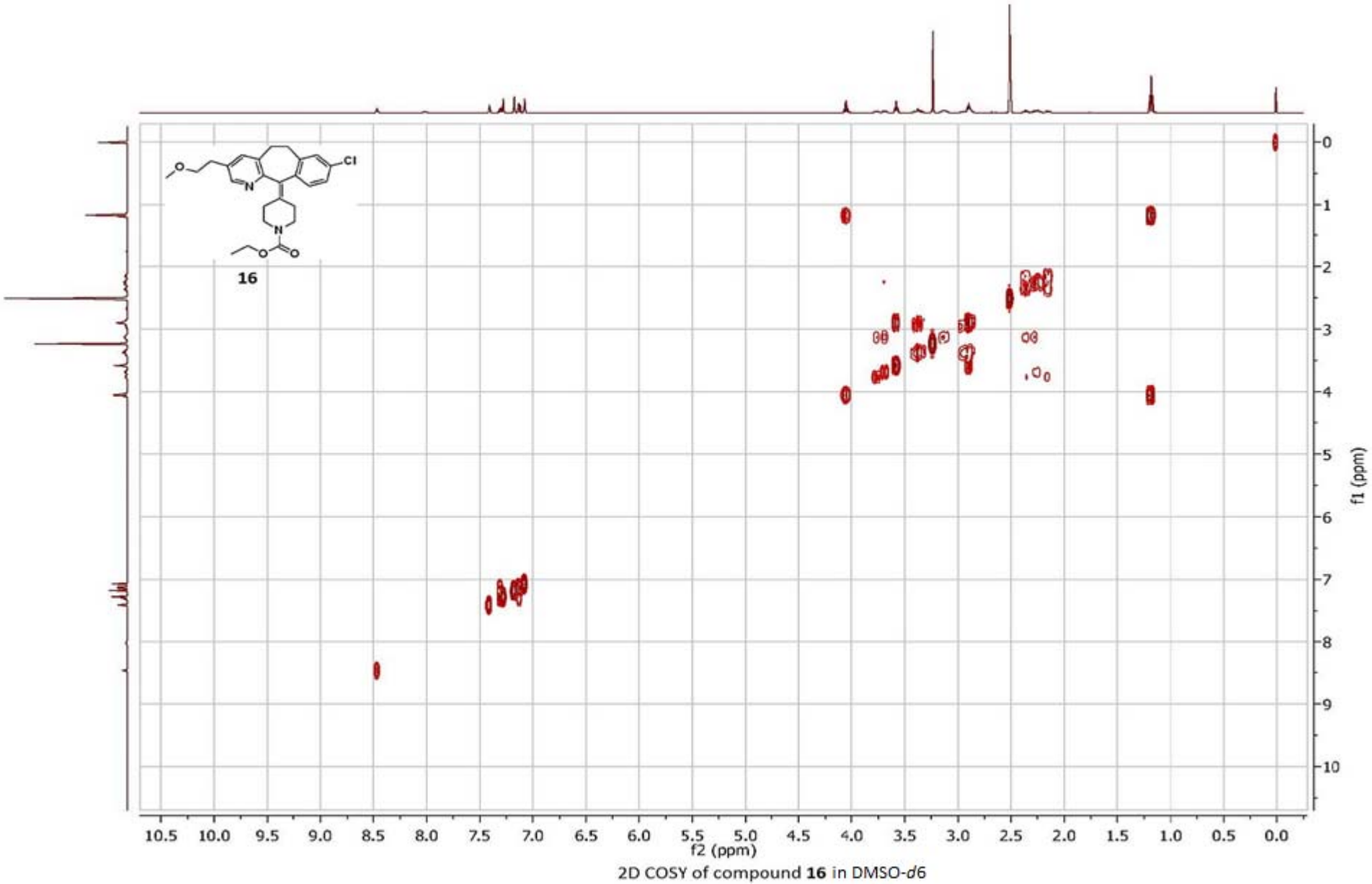


2D COSY of compound **15** in DMSO-*d*6

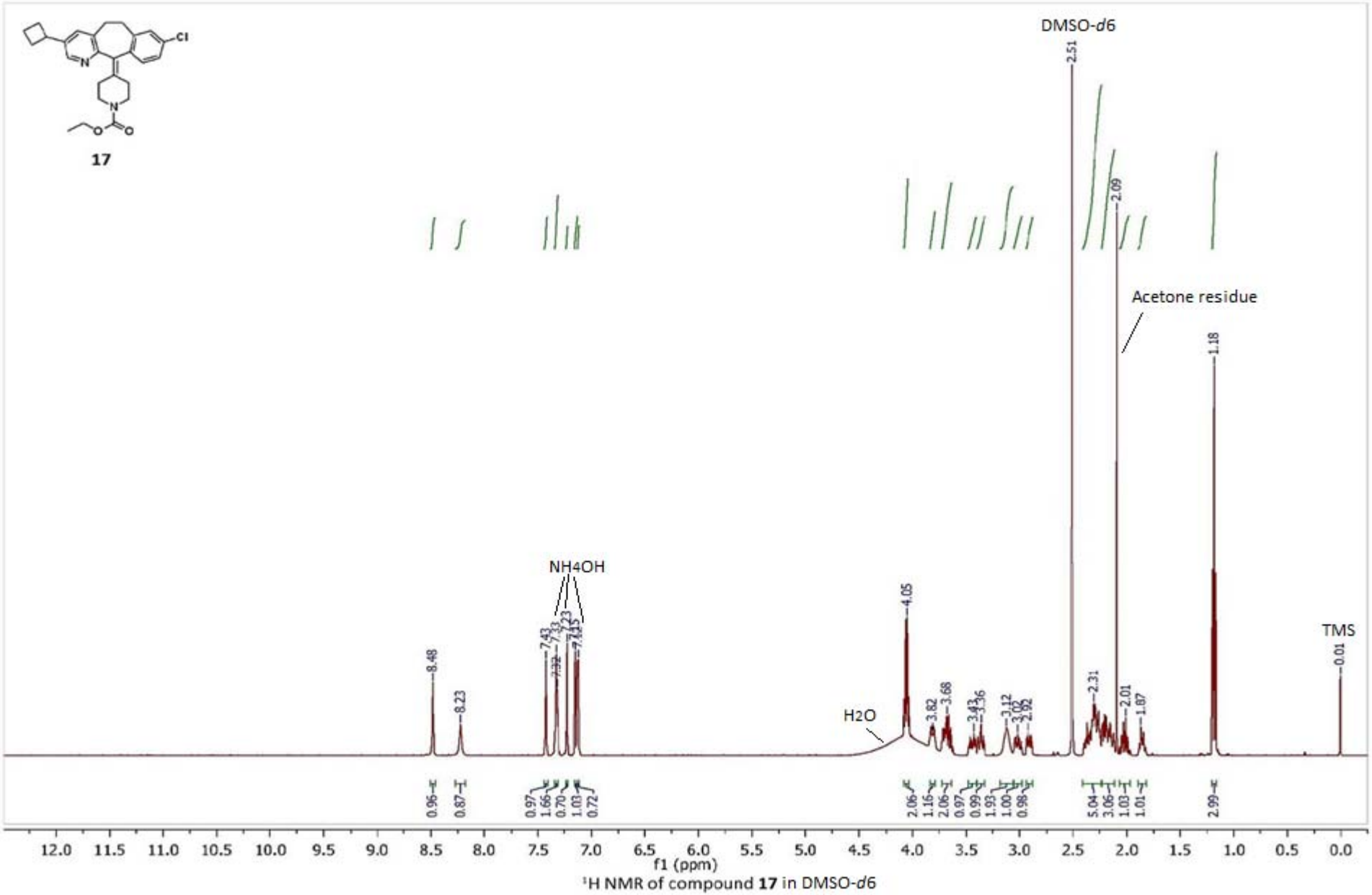


^{1}H NMR of compound **16** in DMSO-*d6*

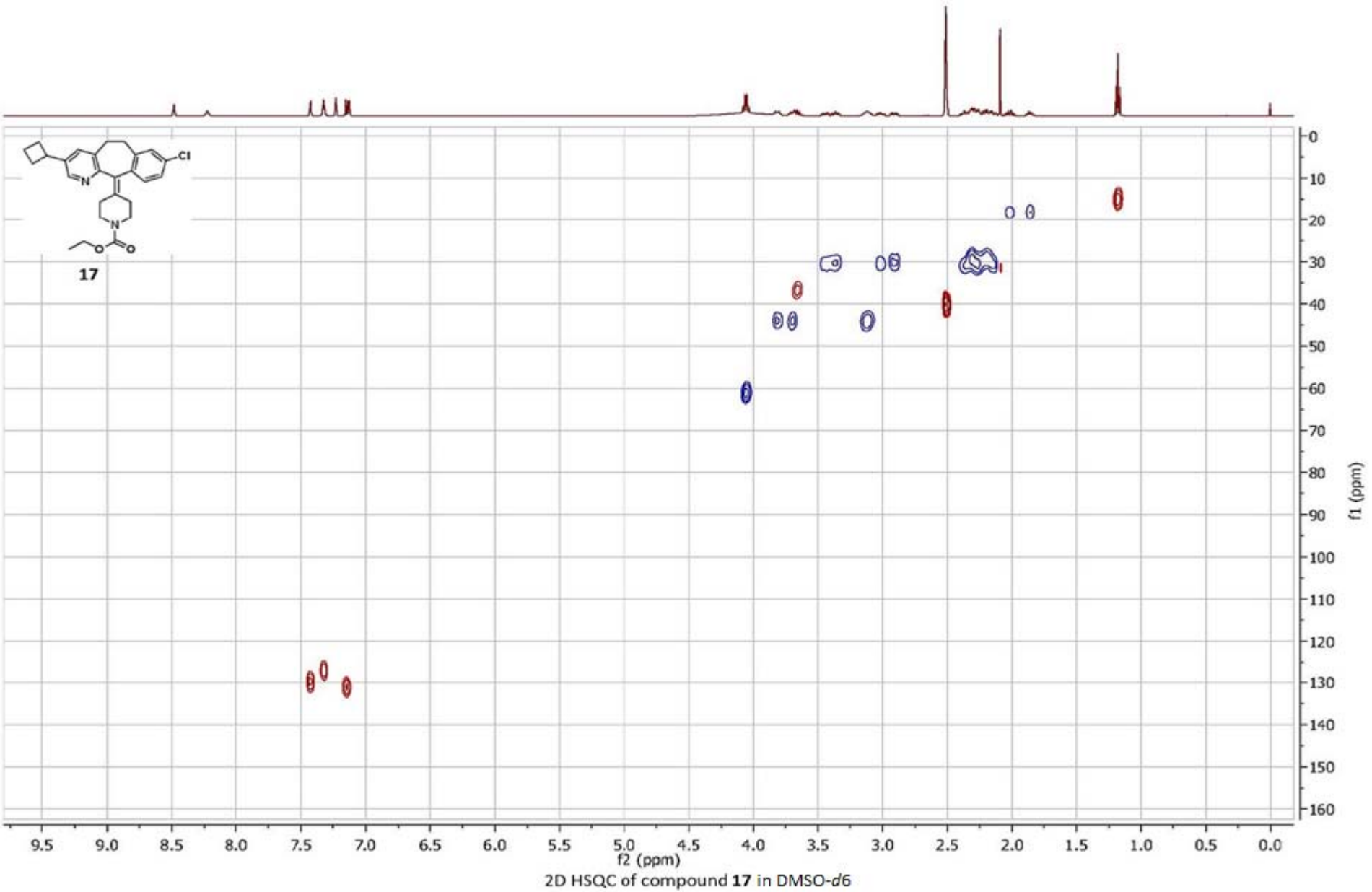

16
f2 (ppm)
f1 (ppm)
2D HSQC of compound 16 in DMSO-d6



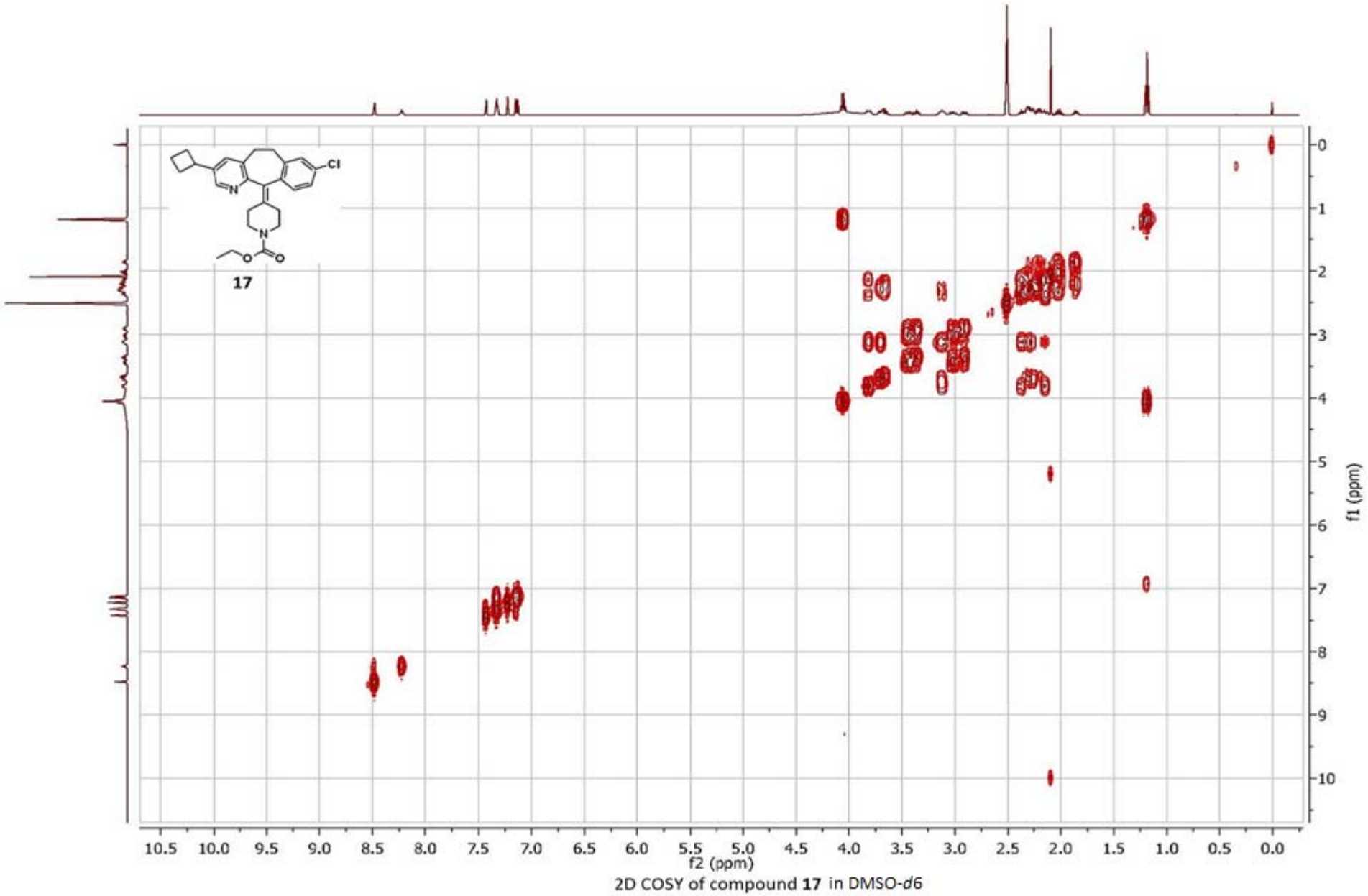
2D COSY of compound **16** in DMSO-*d*6



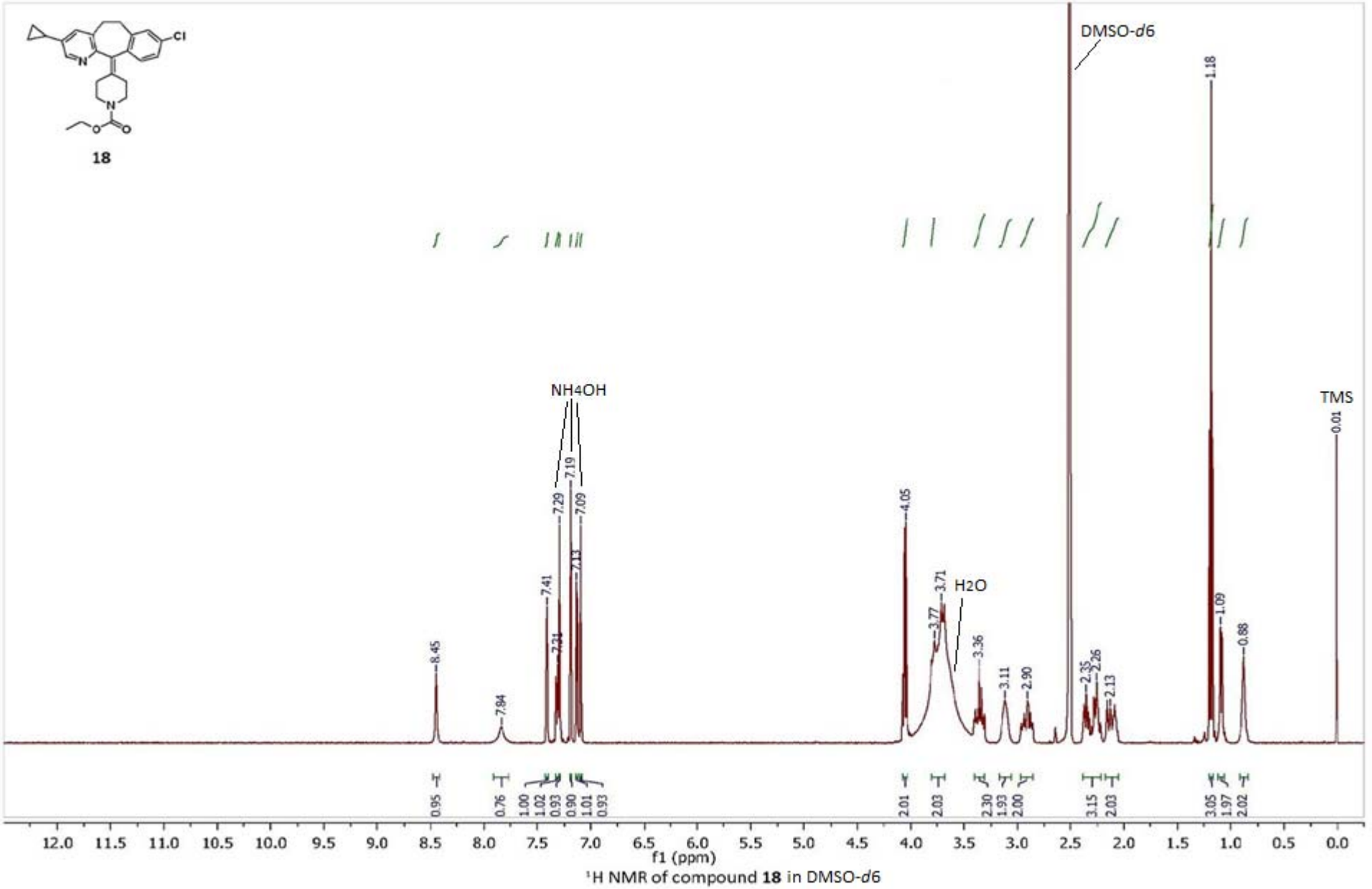
^{1}H NMR of compound **17** in DMSO-*d*6



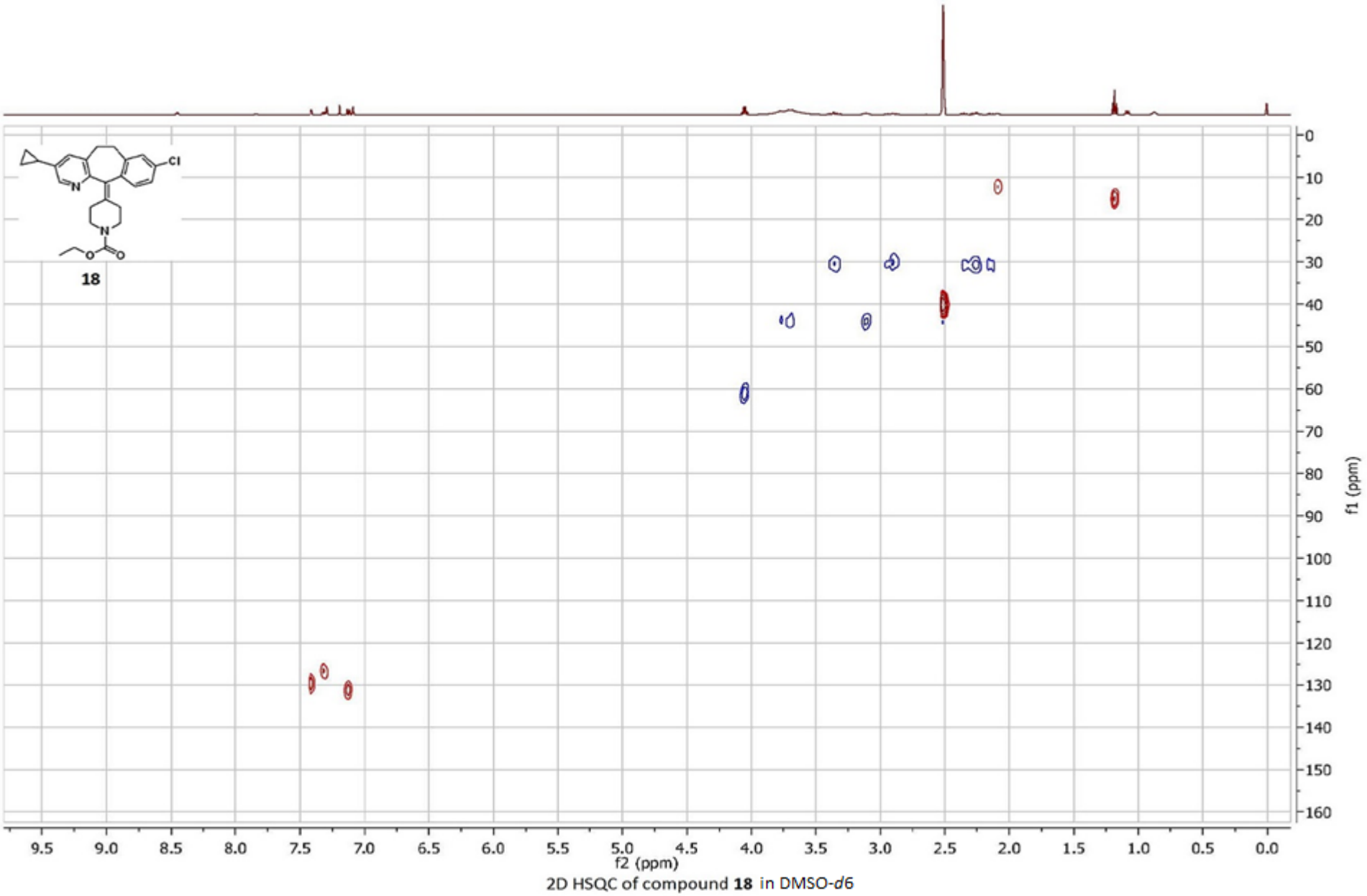
2D HSQC of compound **17** in DMSO-*d6*



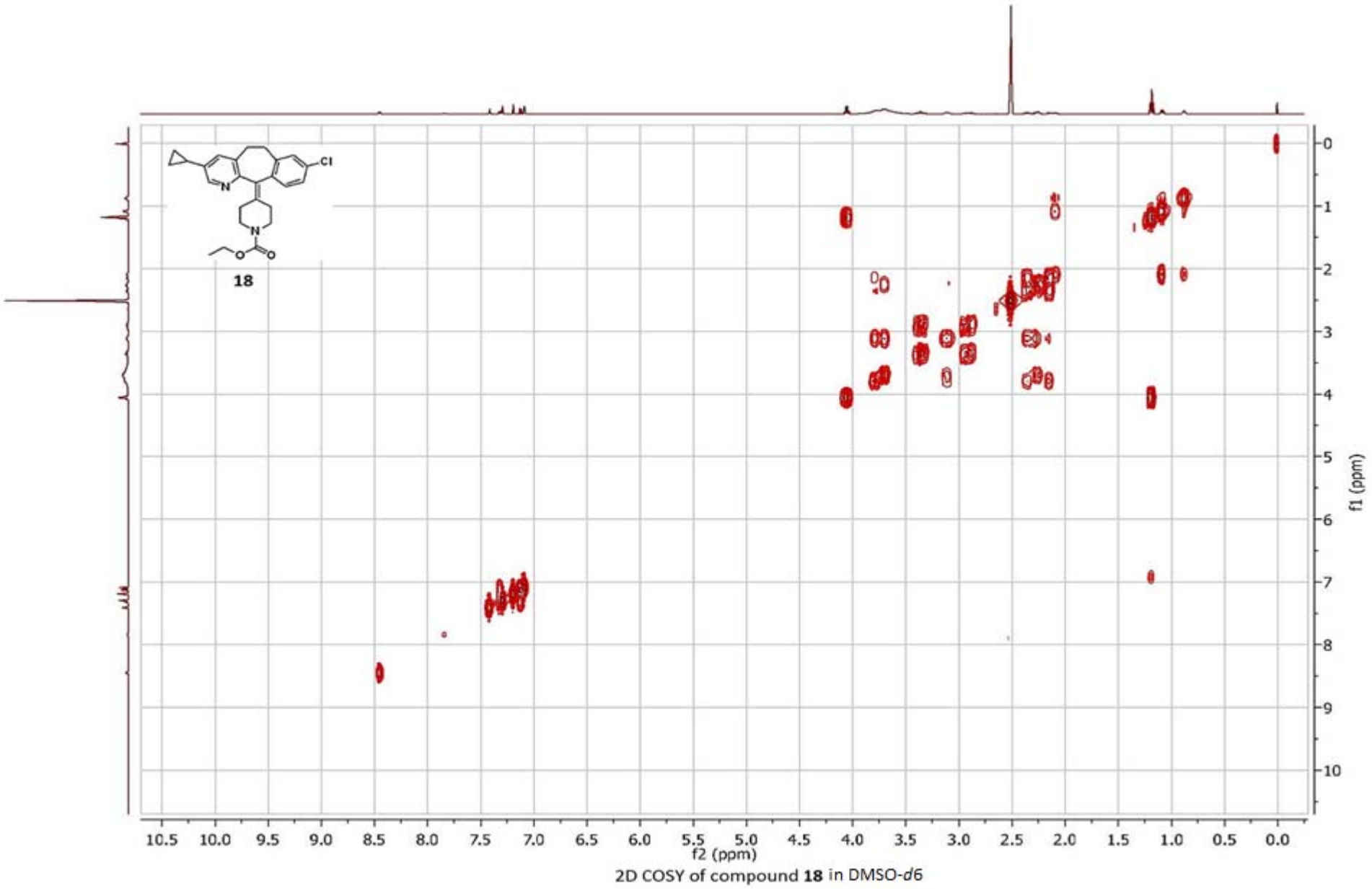
2D COSY of compound **17** in DMSO-*d*6



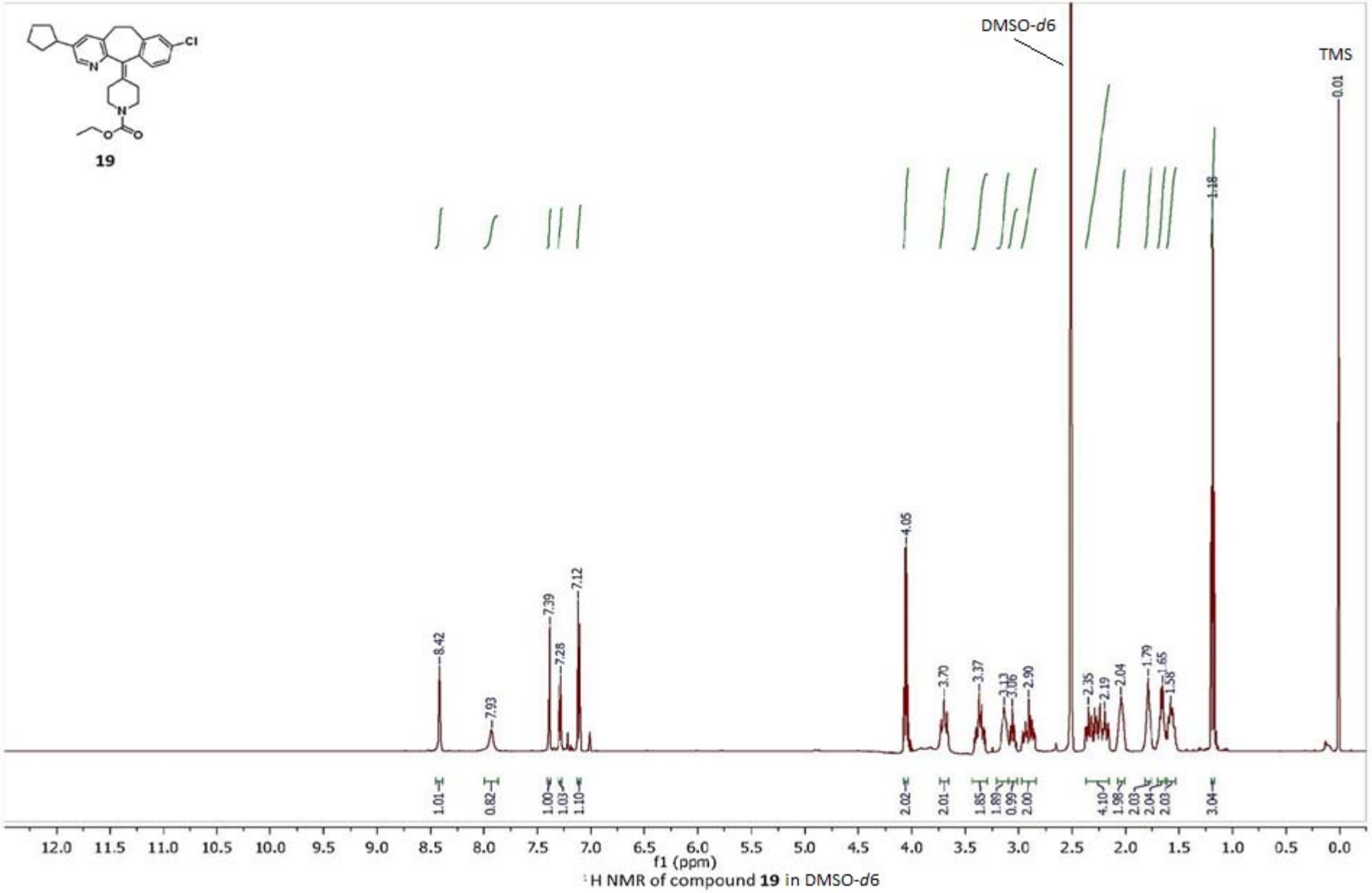
^{1}H NMR of compound **18** in DMSO-*d*6



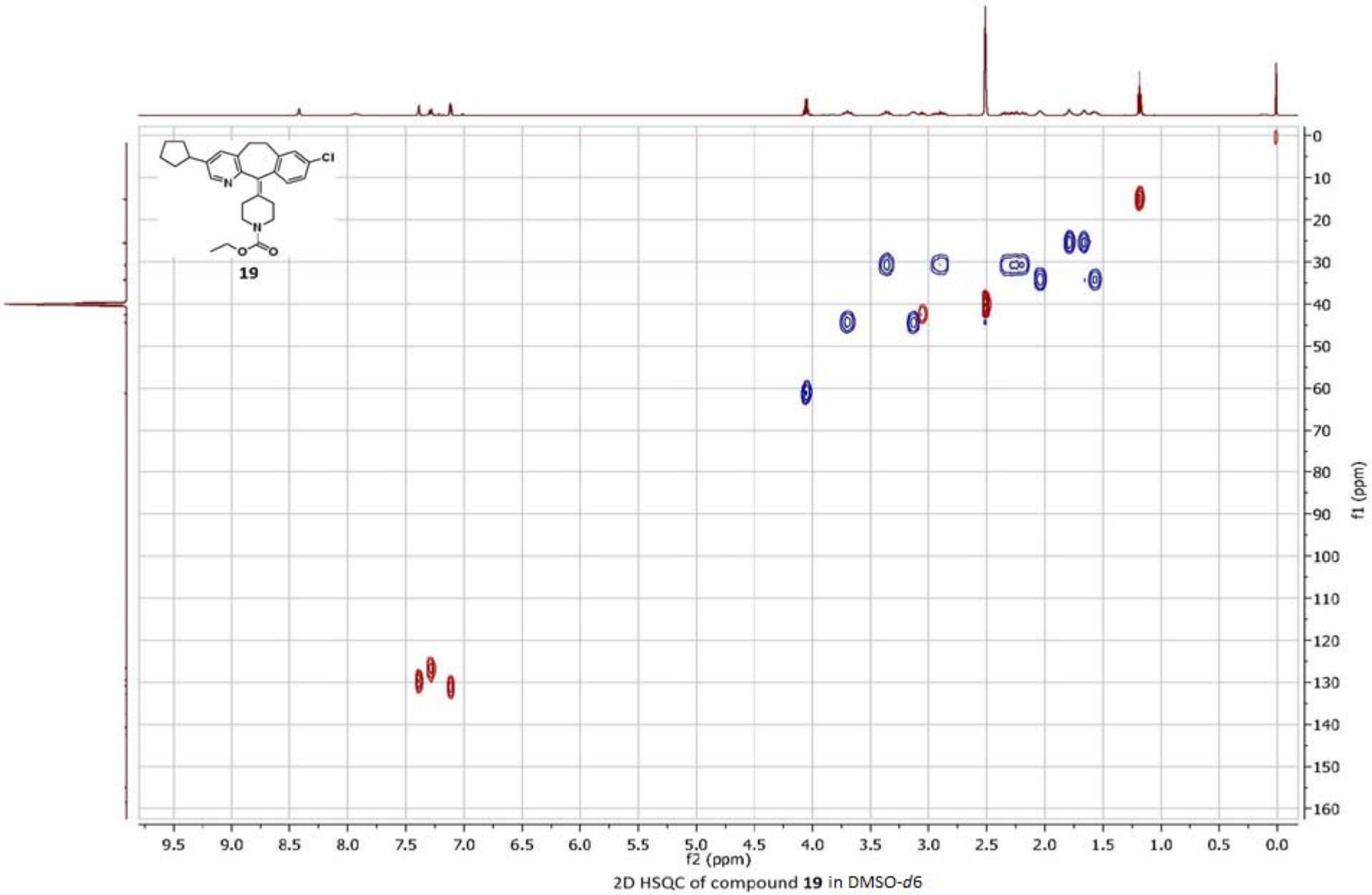
2D HSQC of compound **18** in DMSO-*d6*



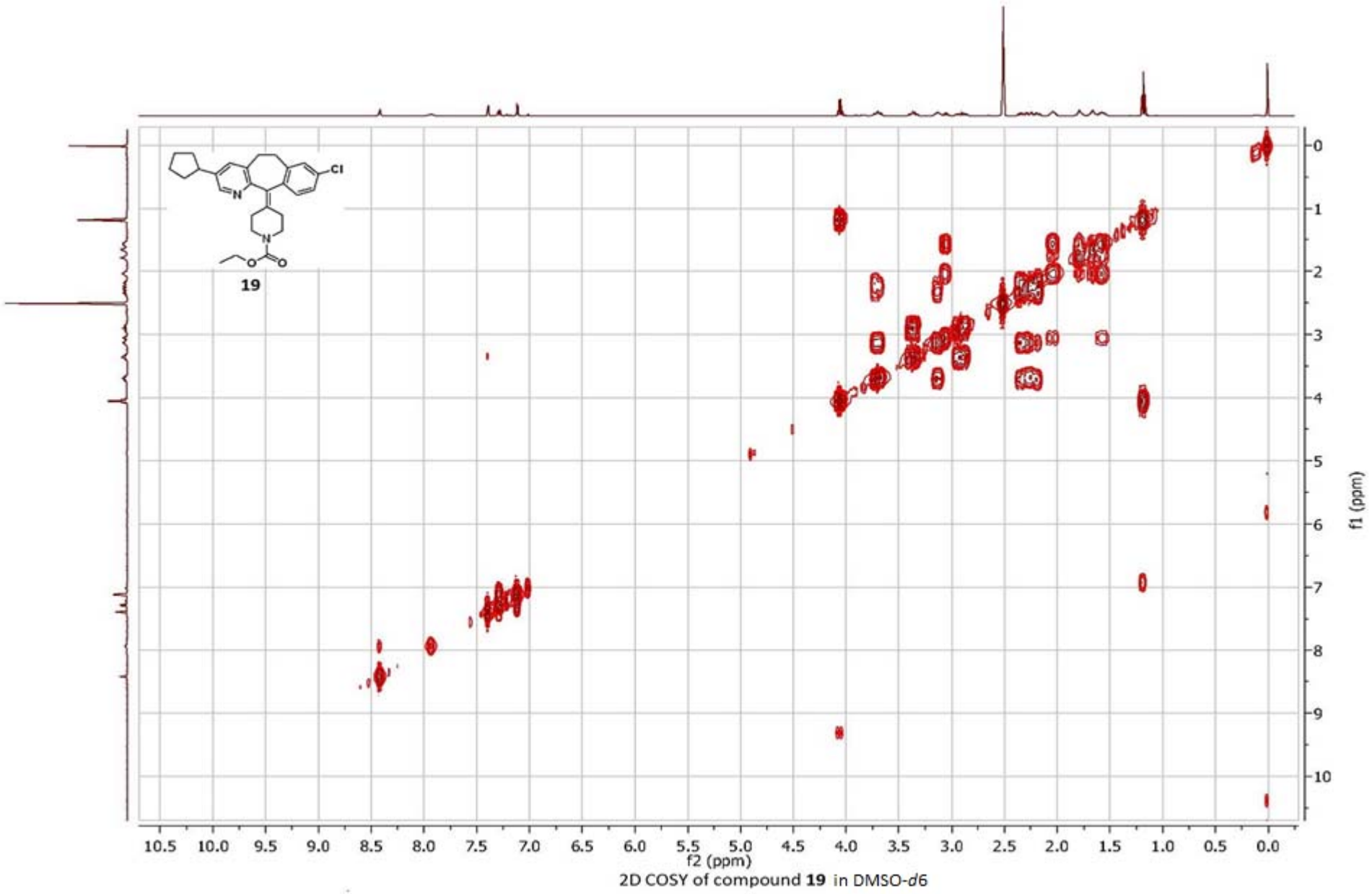
2D COSY of compound **18** in DMSO-*d*6



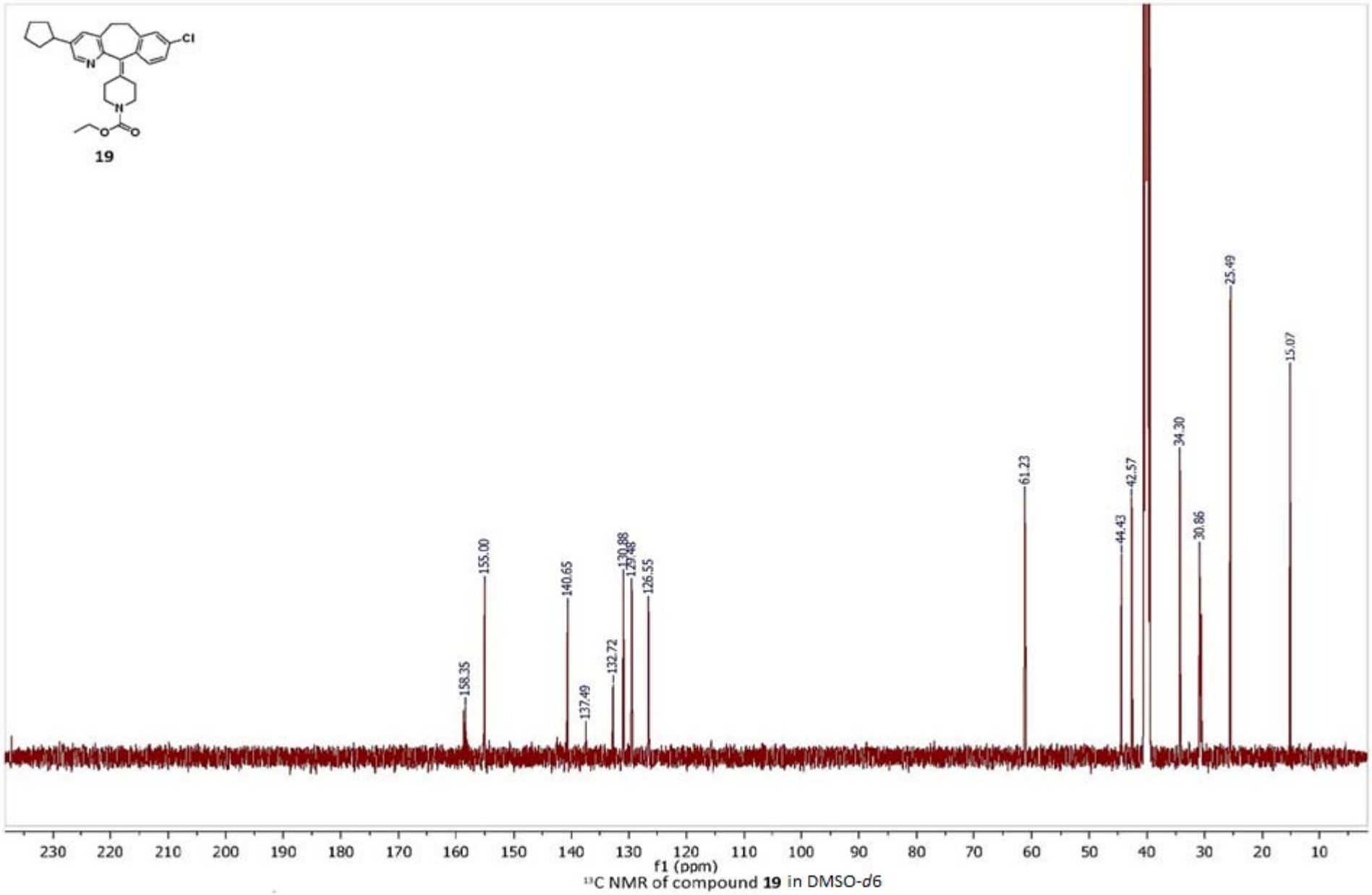
^{1}H NMR of compound **19** in DMSO-*d*6



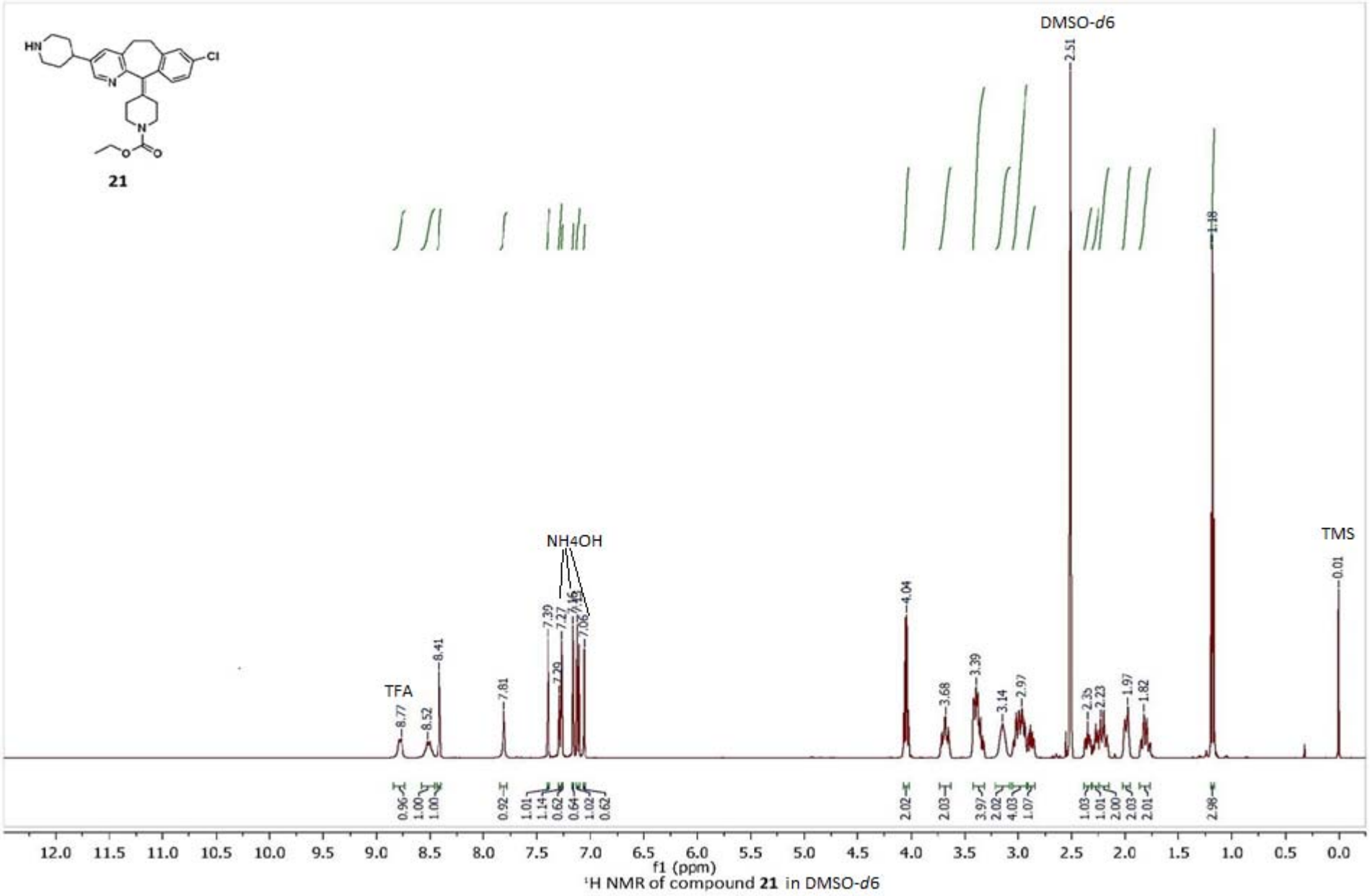
2D HSQC of compound **19** in DMSO-*d*6



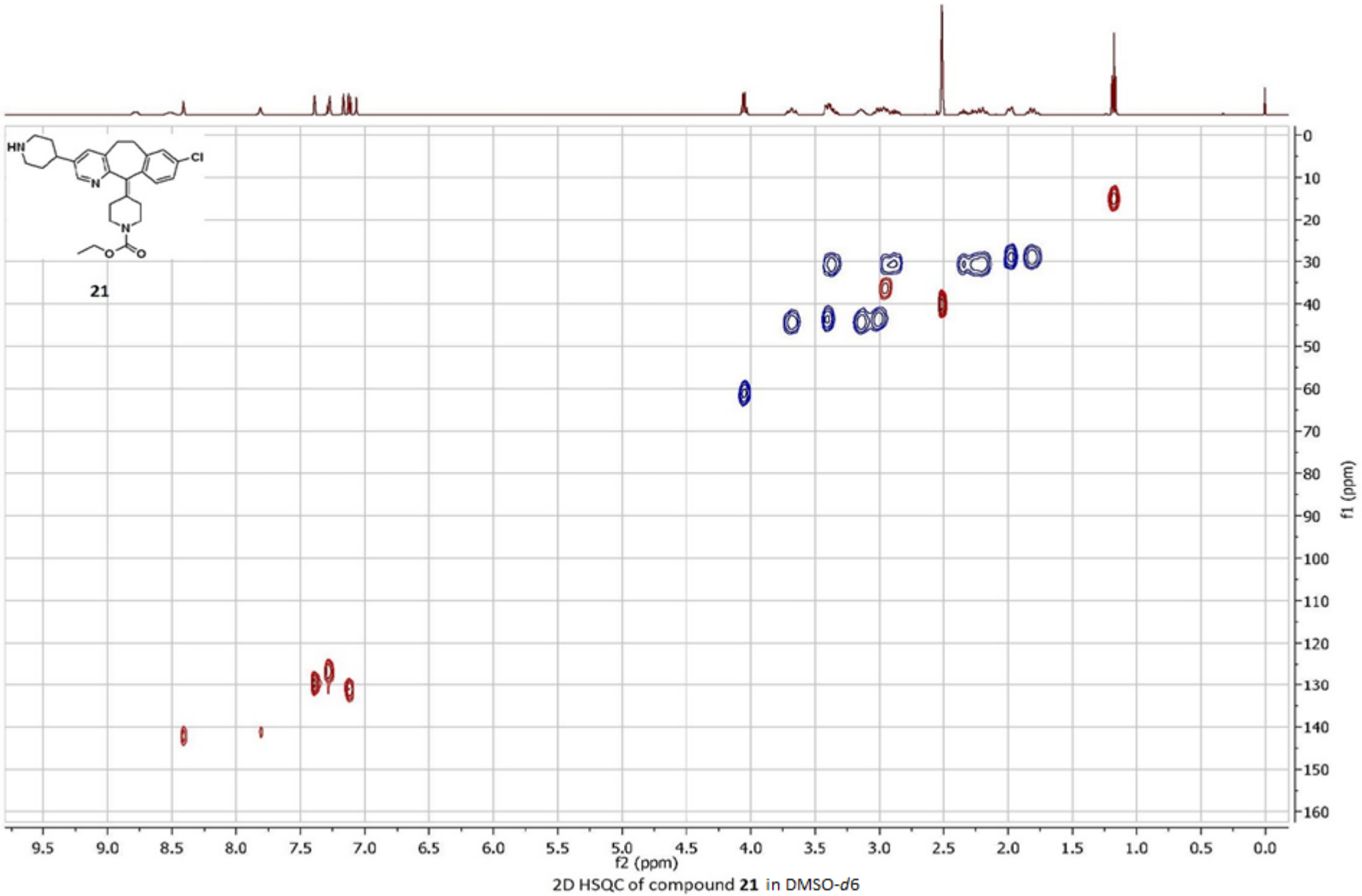
2D COSY of compound **19** in DMSO-*d*6



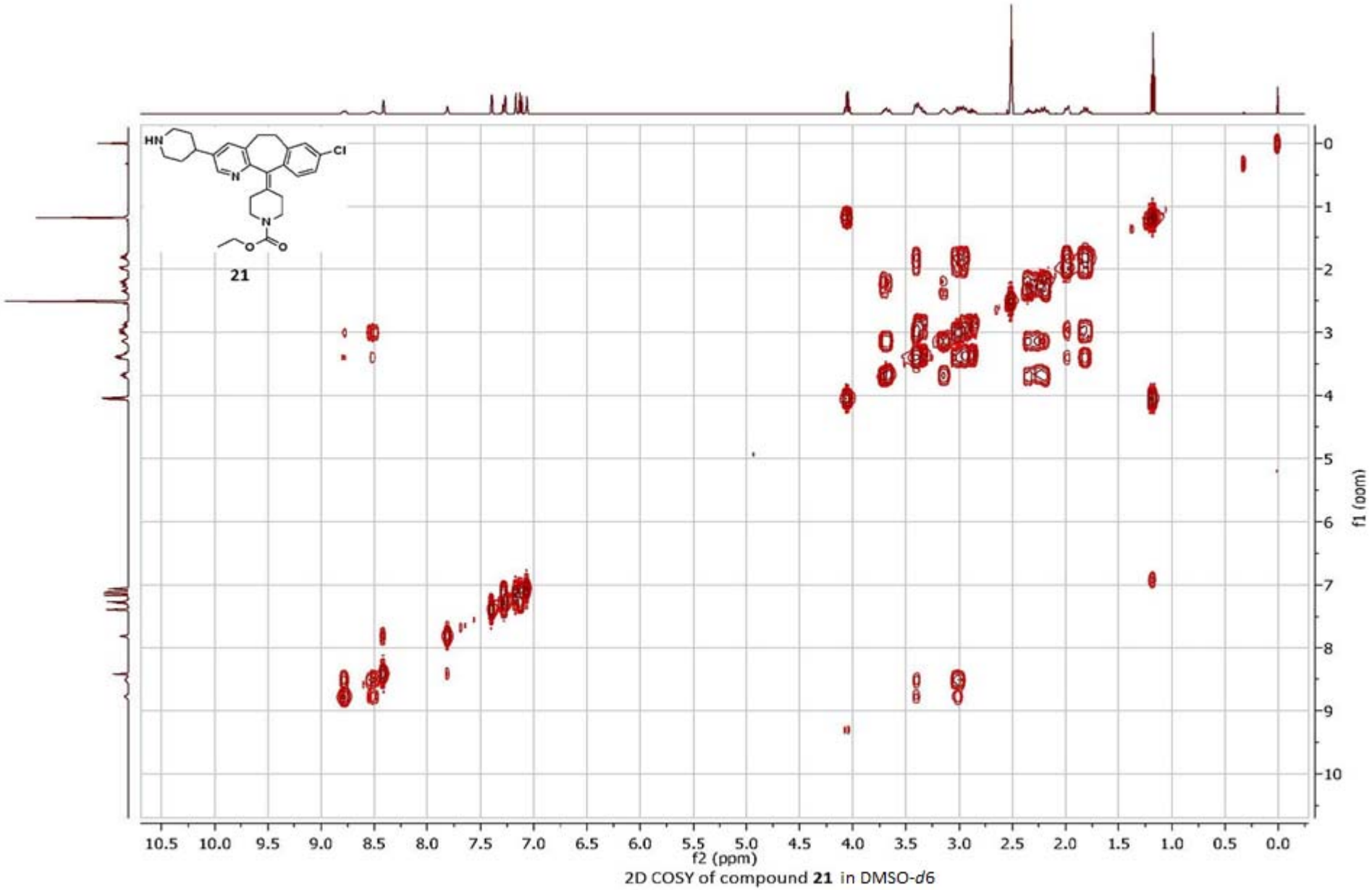
^{13}C NMR of compound **19** in DMSO-*d*6



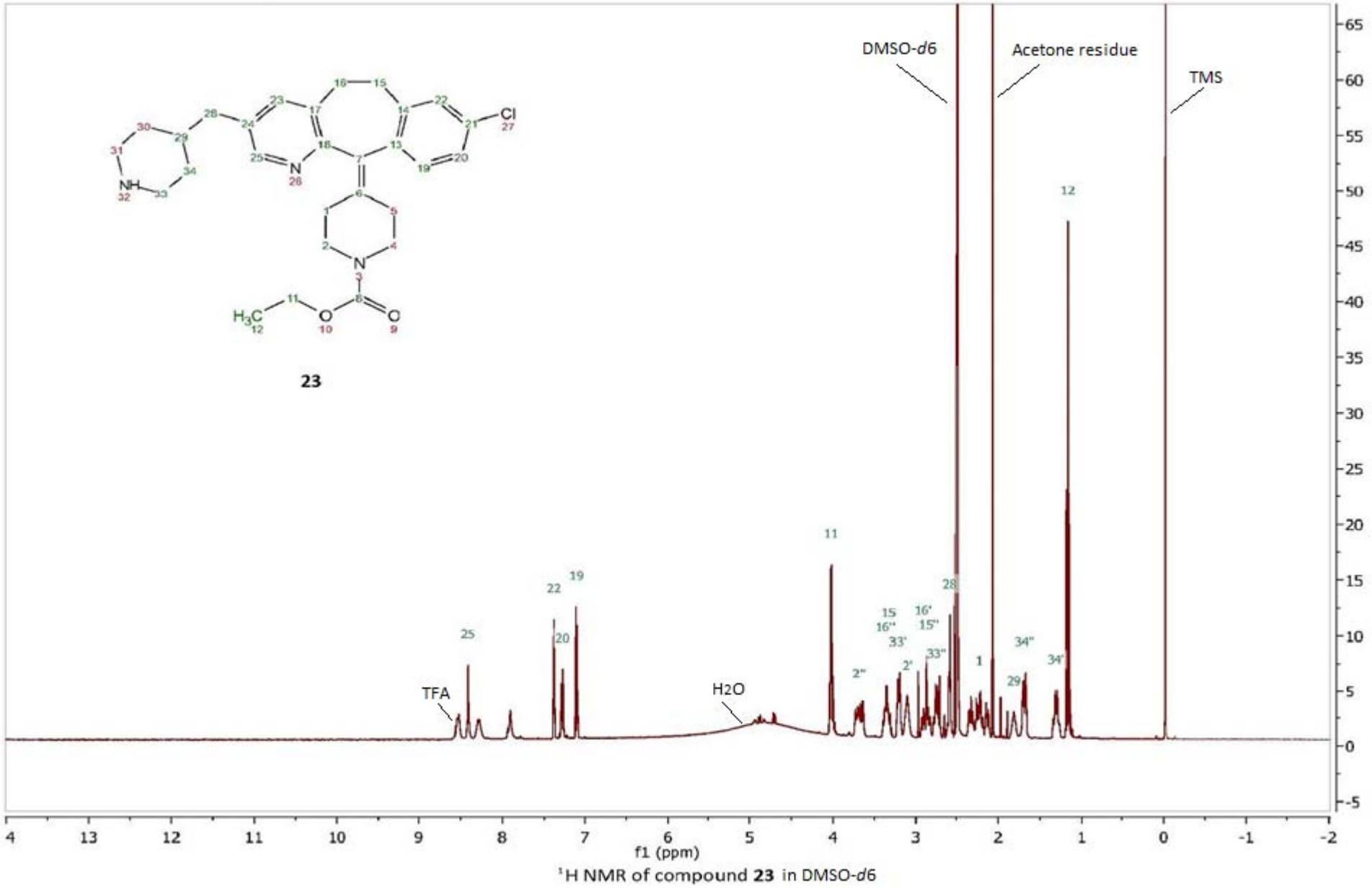
¹H NMR of compound **21** in DMSO-*d*6



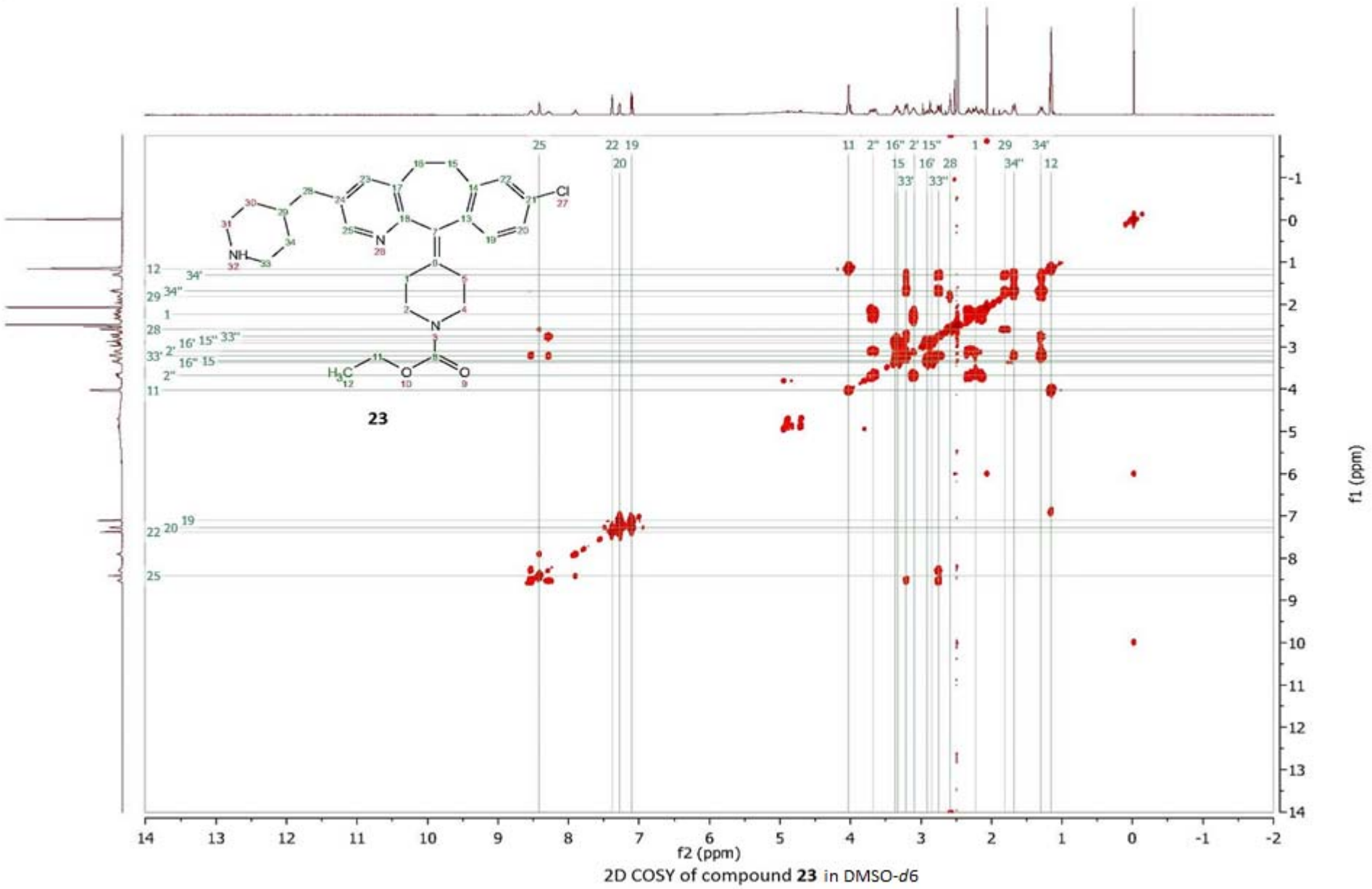
2D HSQC of compound **21** in DMSO-*d6*



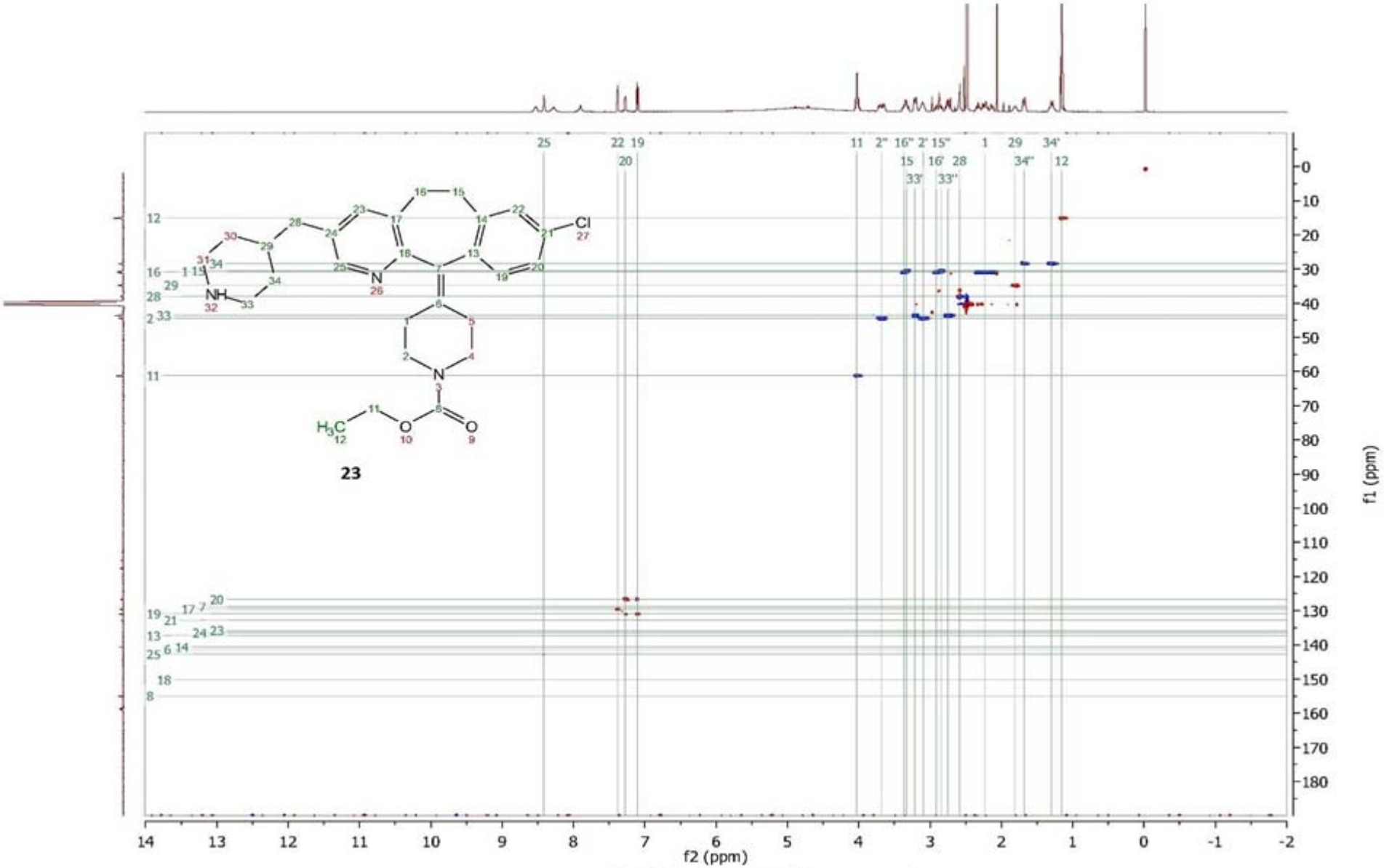
2D COSY of compound **21** in DMSO-*d*6



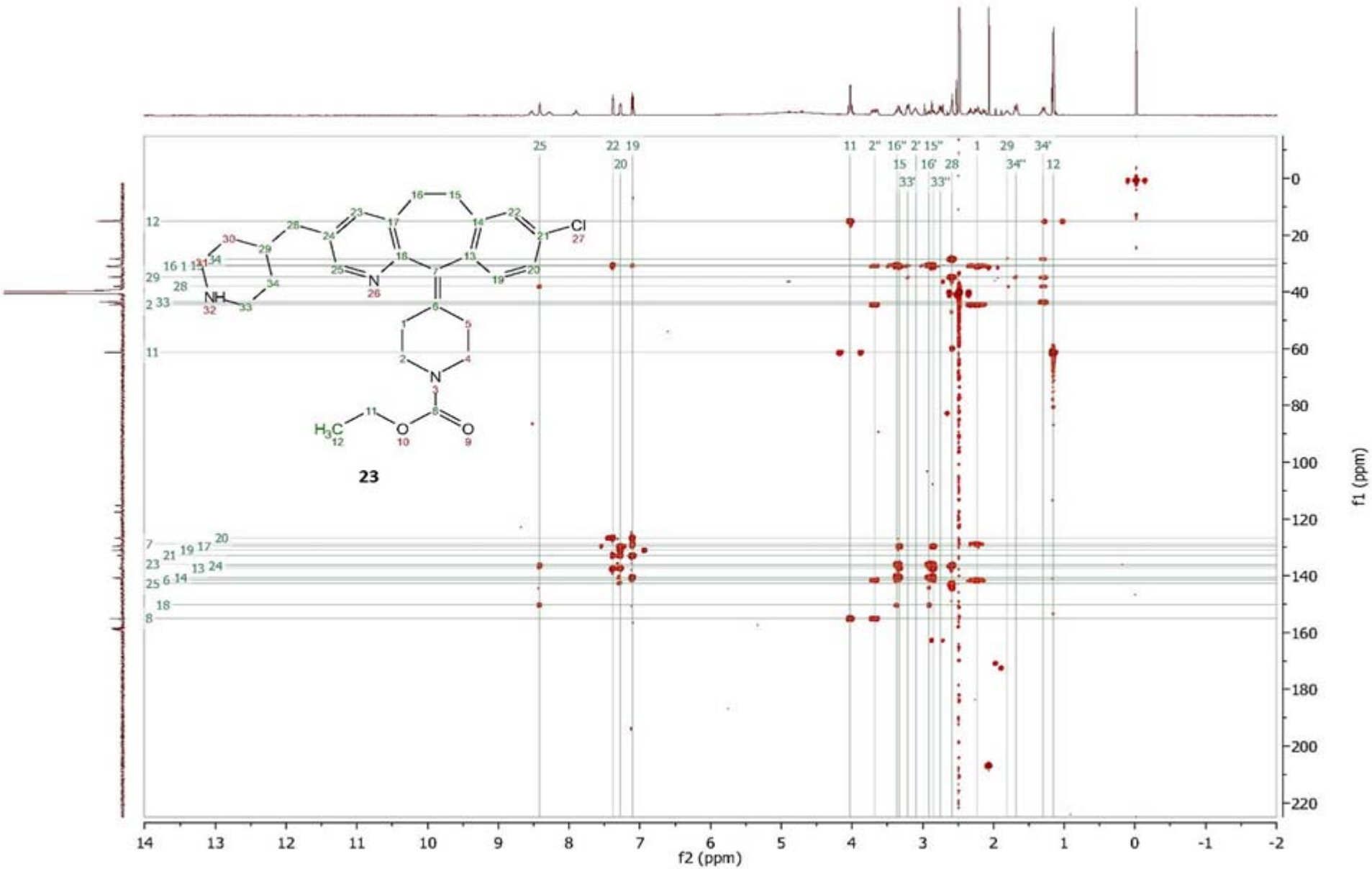
^{1}H NMR of compound **23** in DMSO-*d*6



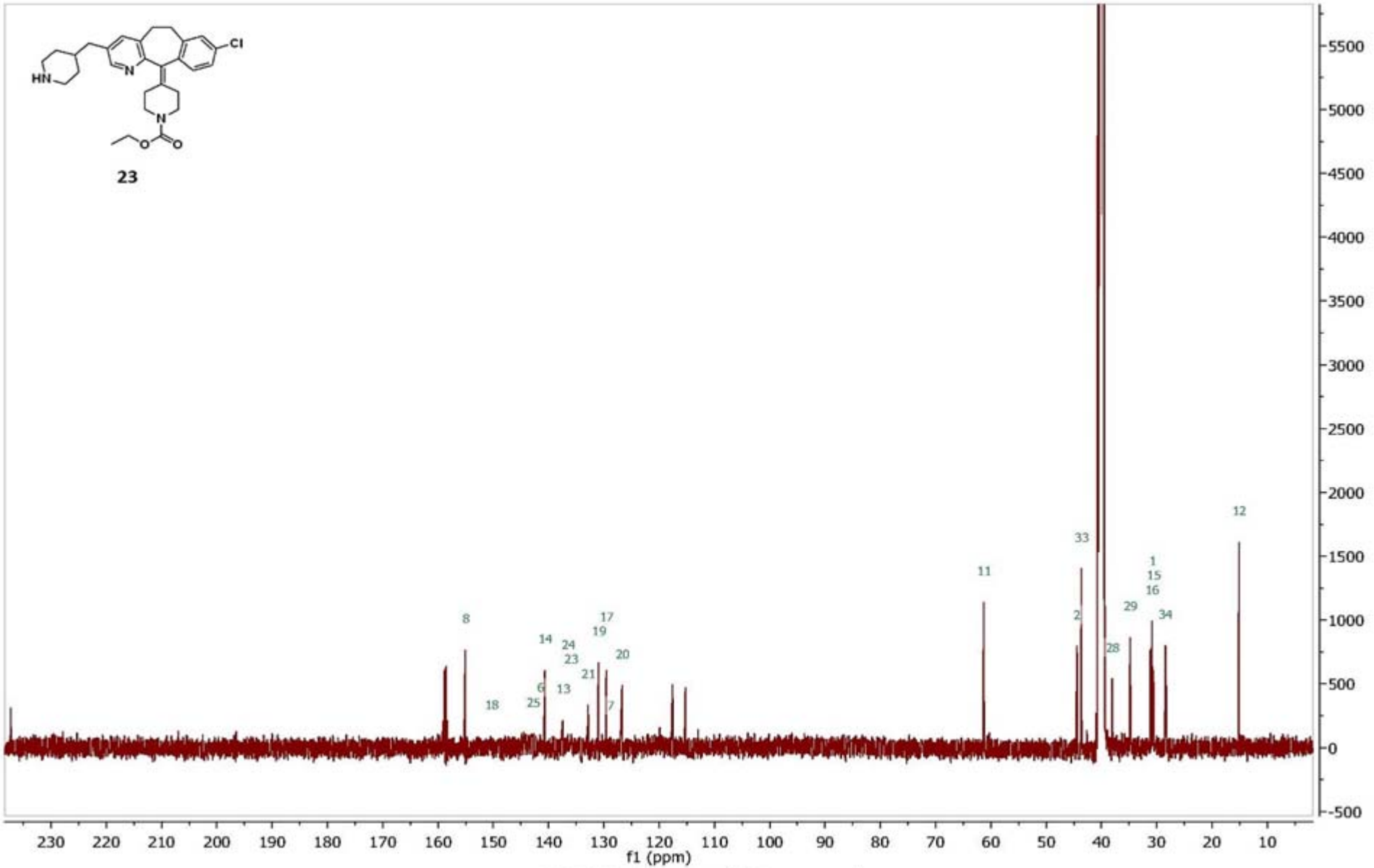
2D COSY of compound **23** in DMSO-*d*6



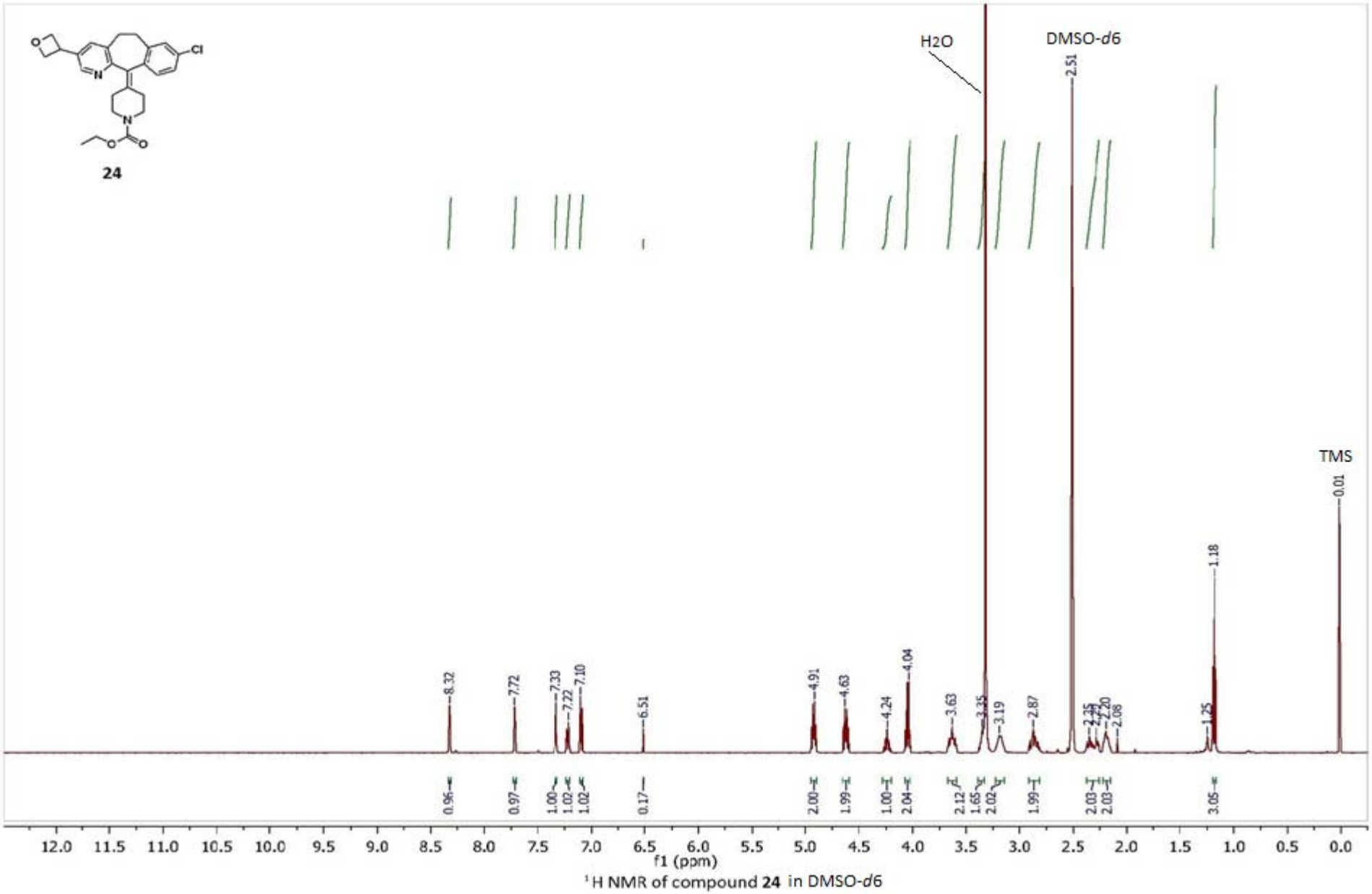
2D HSQC of compound **23** in DMSO-*d*6



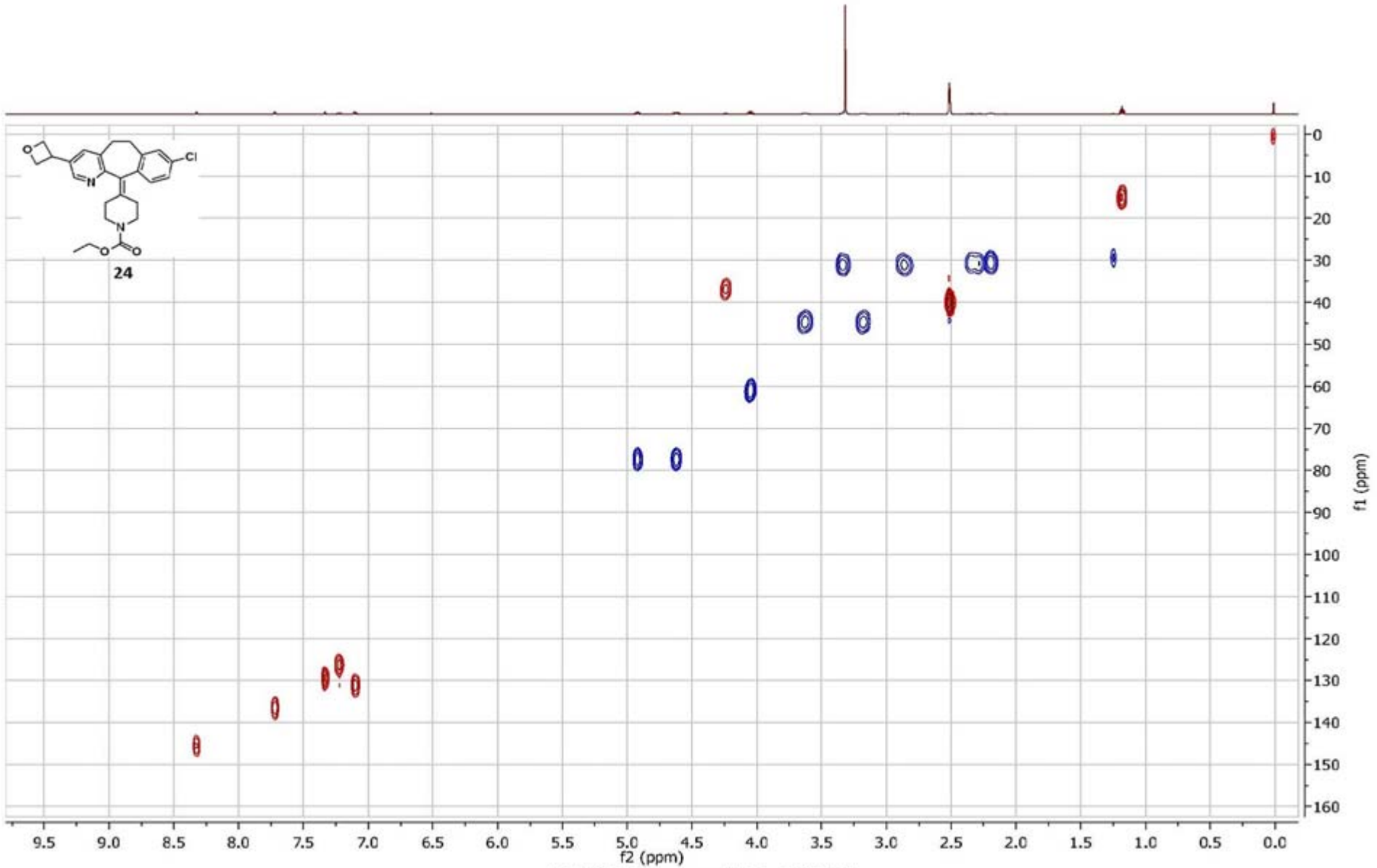
2D HMBC of compound **23** in DMSO-*d*6

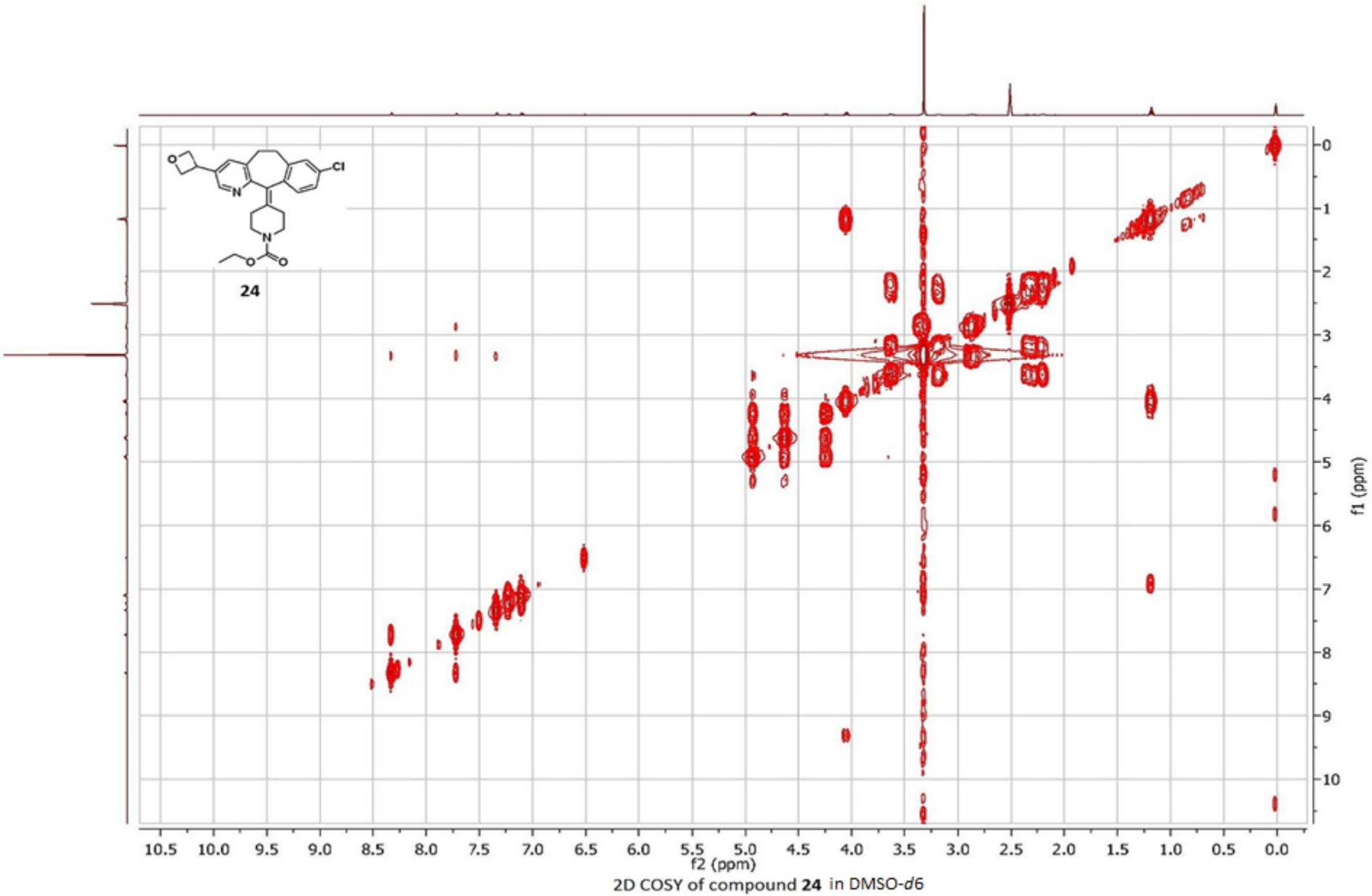


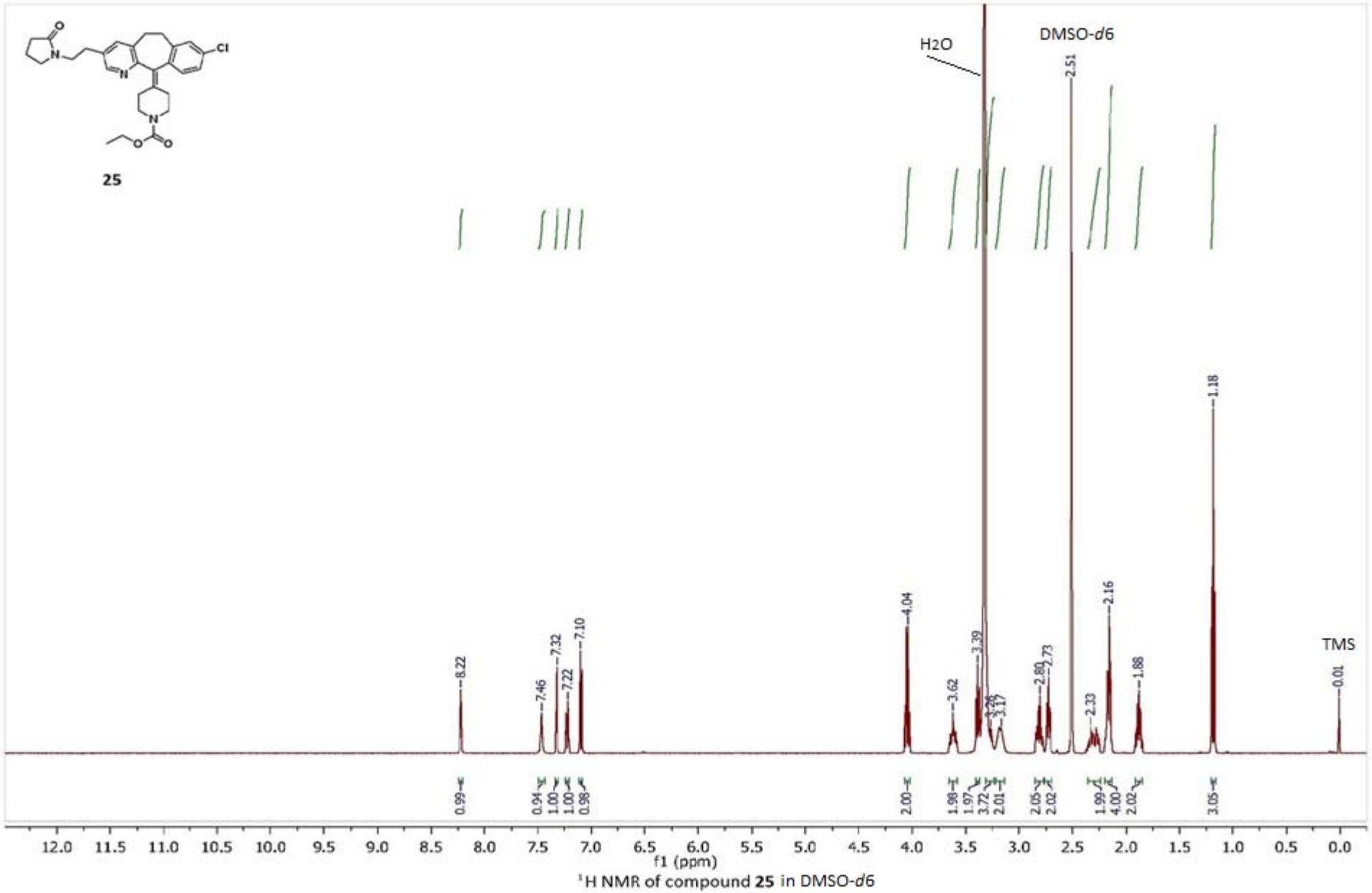
^{13}C NMR of compound **23** in DMSO-*d6*



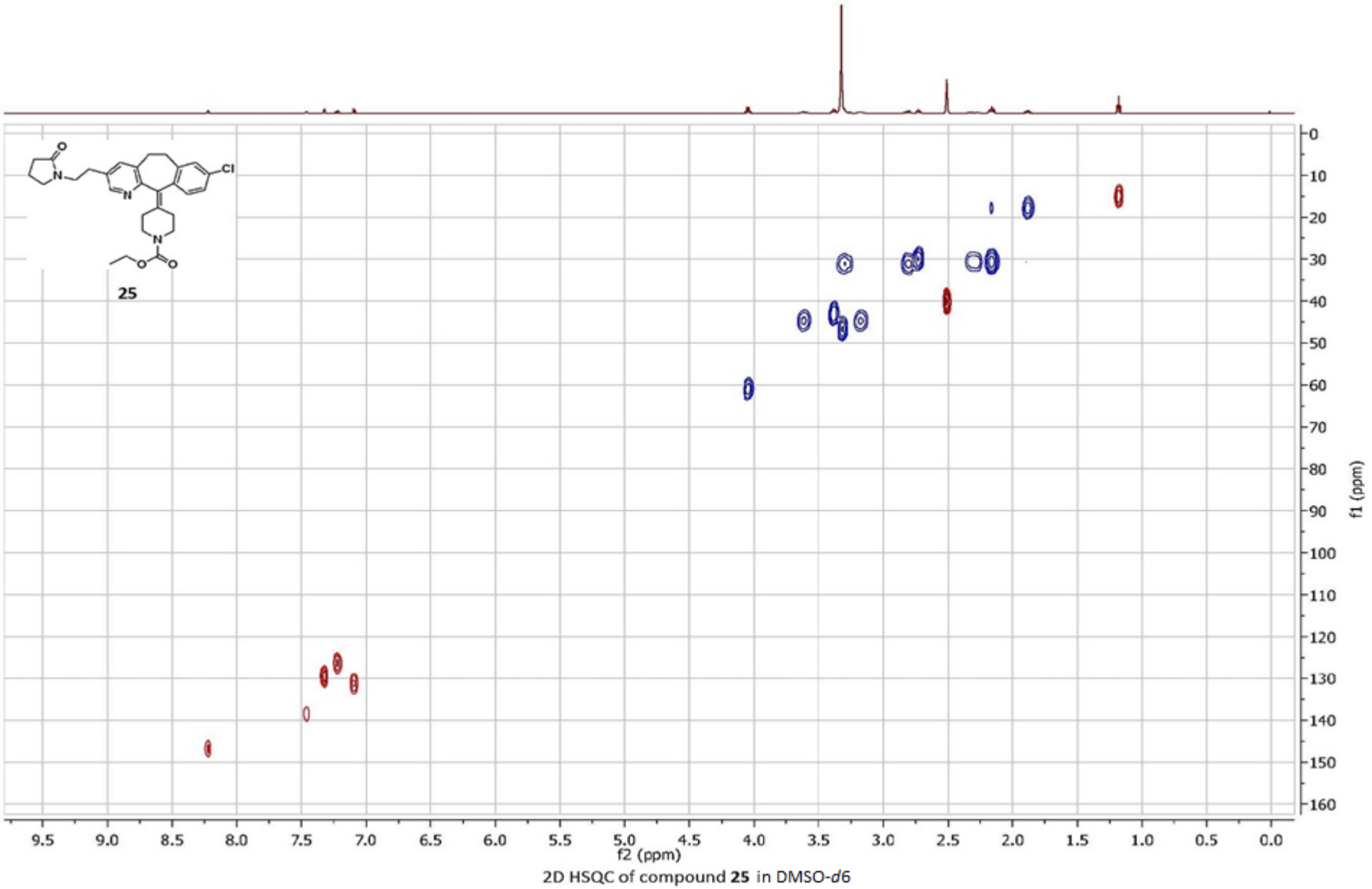
^{1}H NMR of compound **24** in DMSO-*d*6

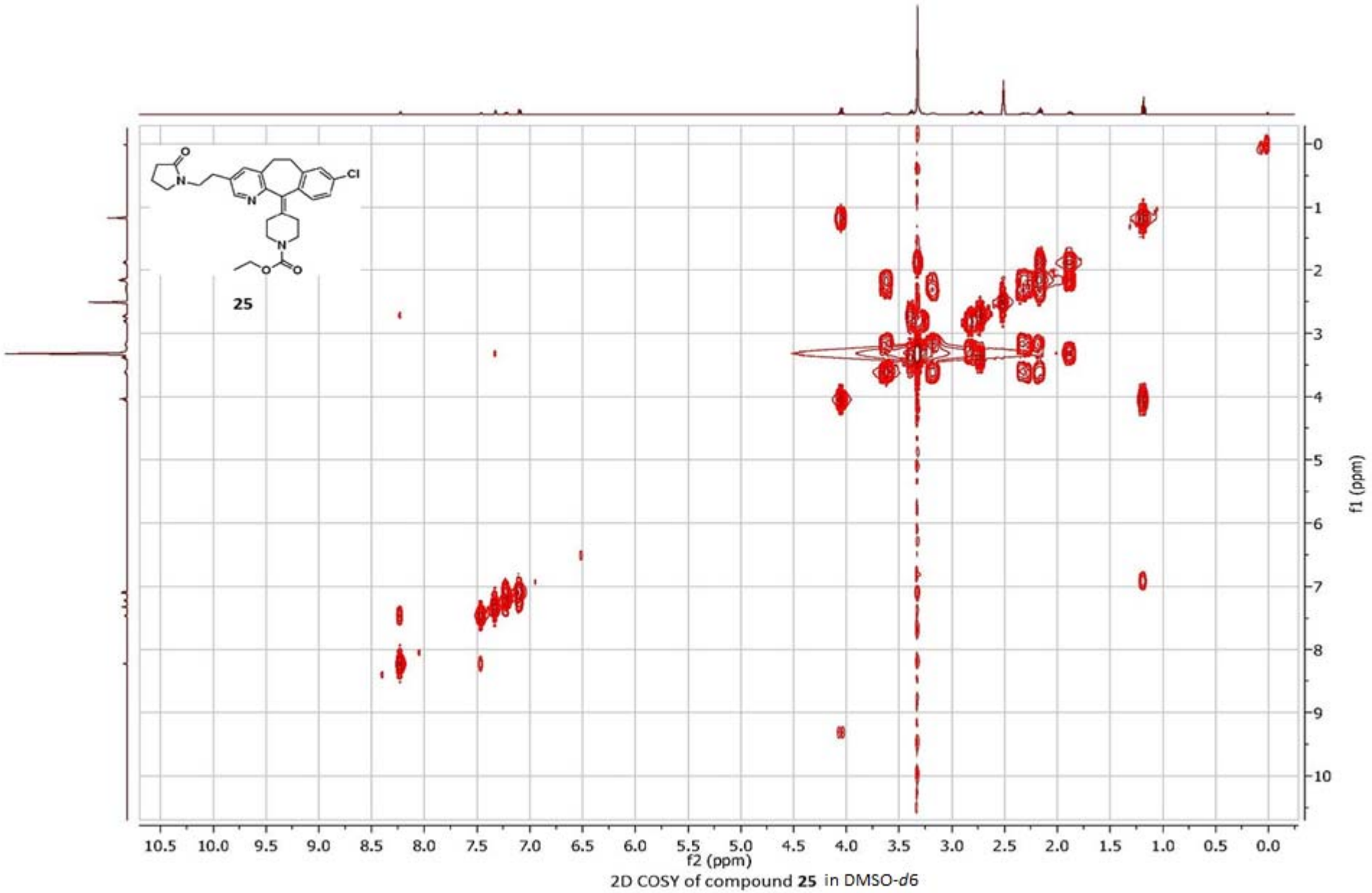

24
f2 (ppm)
f1 (ppm)
2D HSQC of compound 24 in DMSO-d6

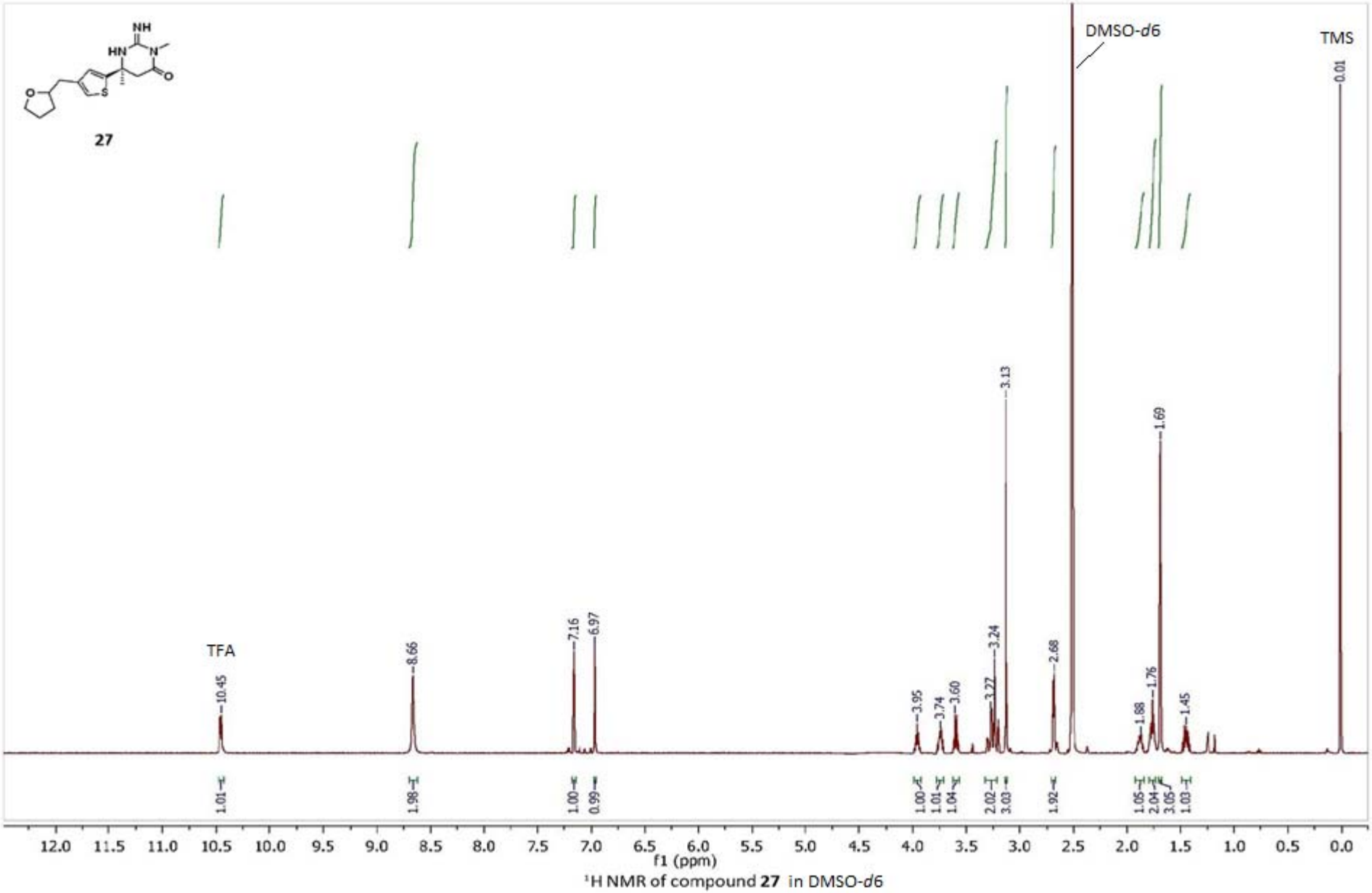

24
f2 (ppm)
f1 (ppm)
2D COSY of compound 24 in DMSO-d6



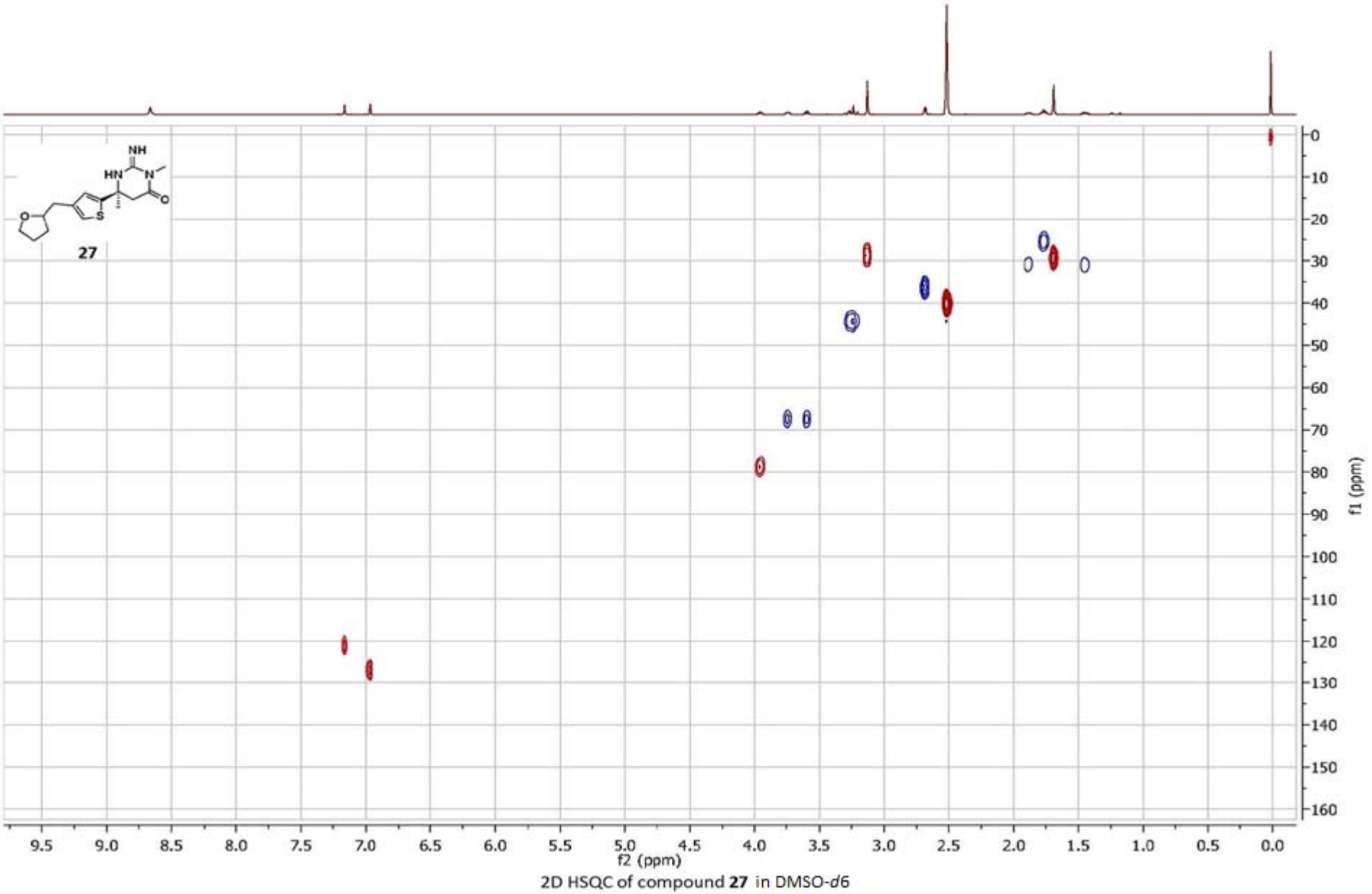
^{1}H NMR of compound **25** in DMSO-*d*6


25
f2 (ppm)
f1 (ppm)
2D HSQC of compound **25** in DMSO-*d6*

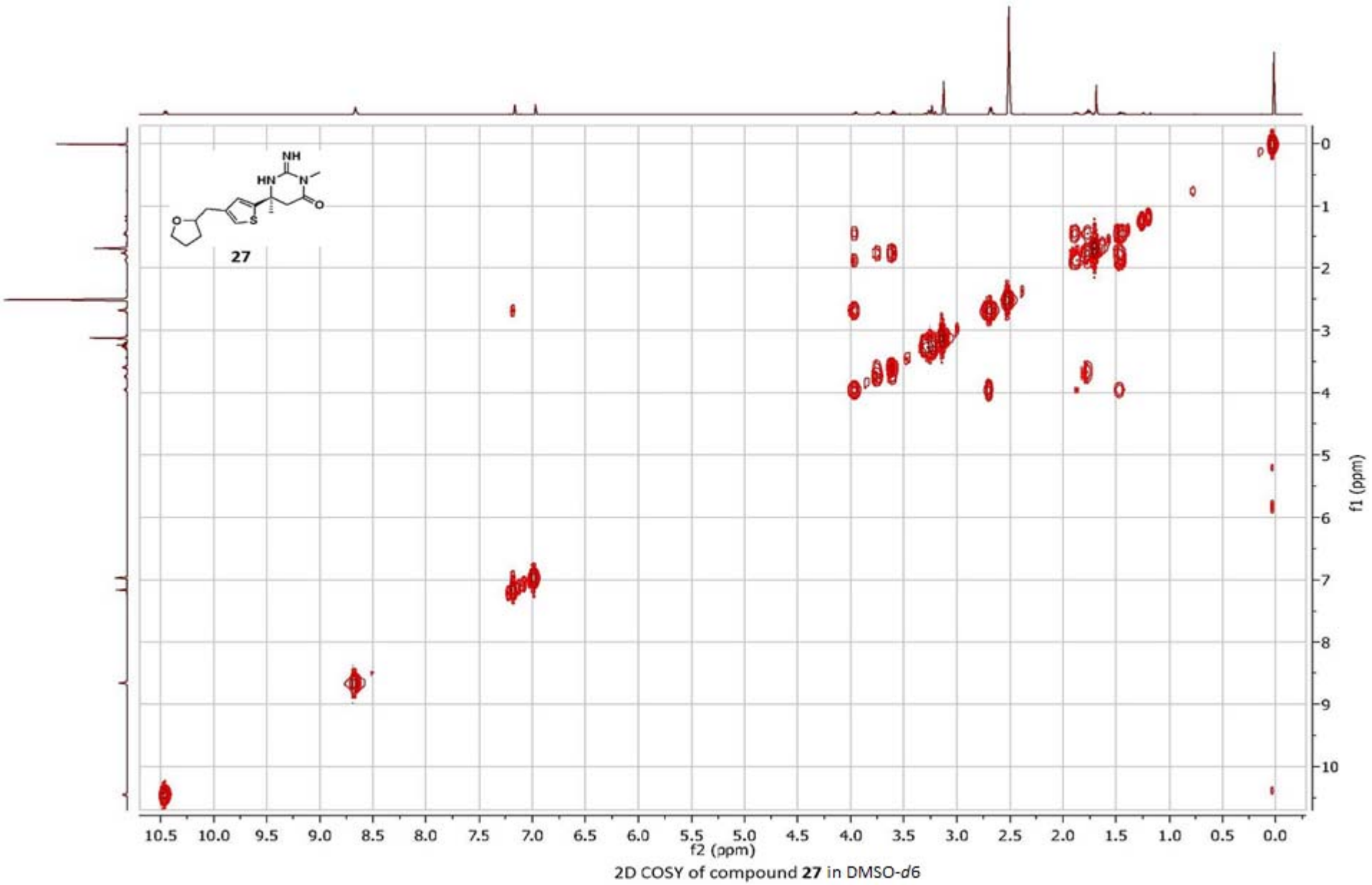

25
f2 (ppm)
f1 (ppm)
2D COSY of compound 25 in DMSO-d6



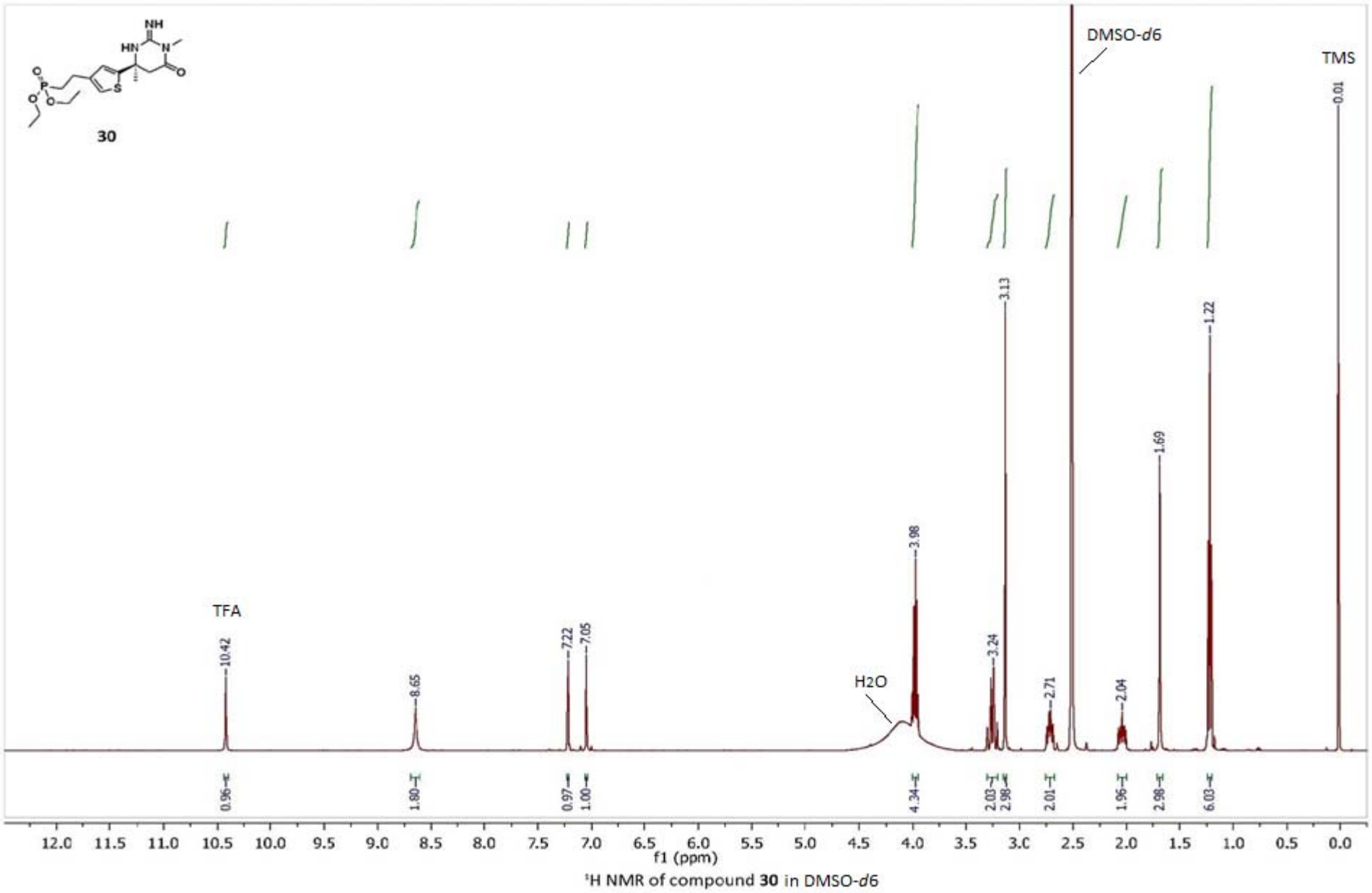
^{1}H NMR of compound **27** in DMSO-*d*6



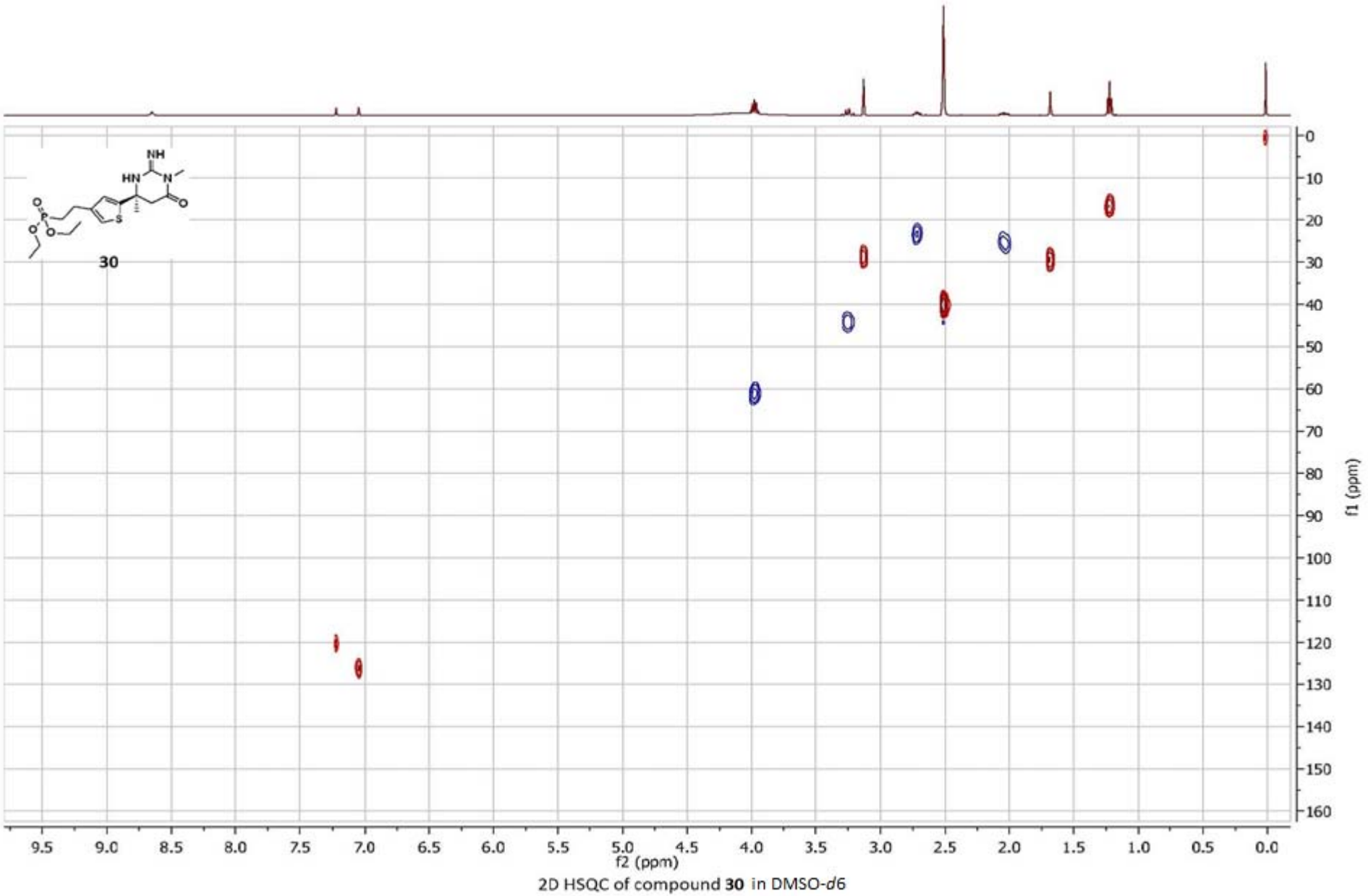
2D HSQC of compound **27** in DMSO-*d*6



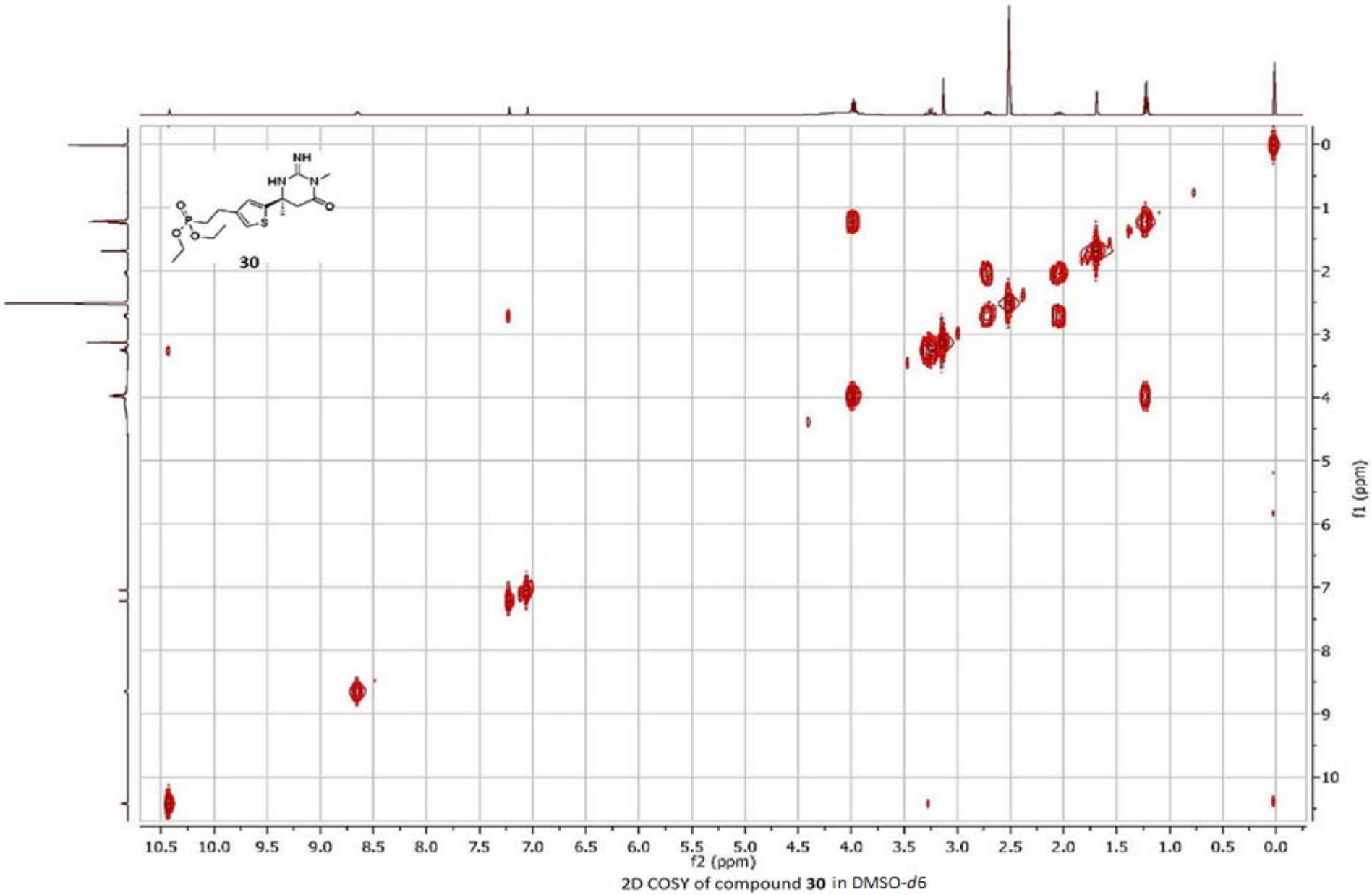
2D COSY of compound **27** in DMSO-*d6*



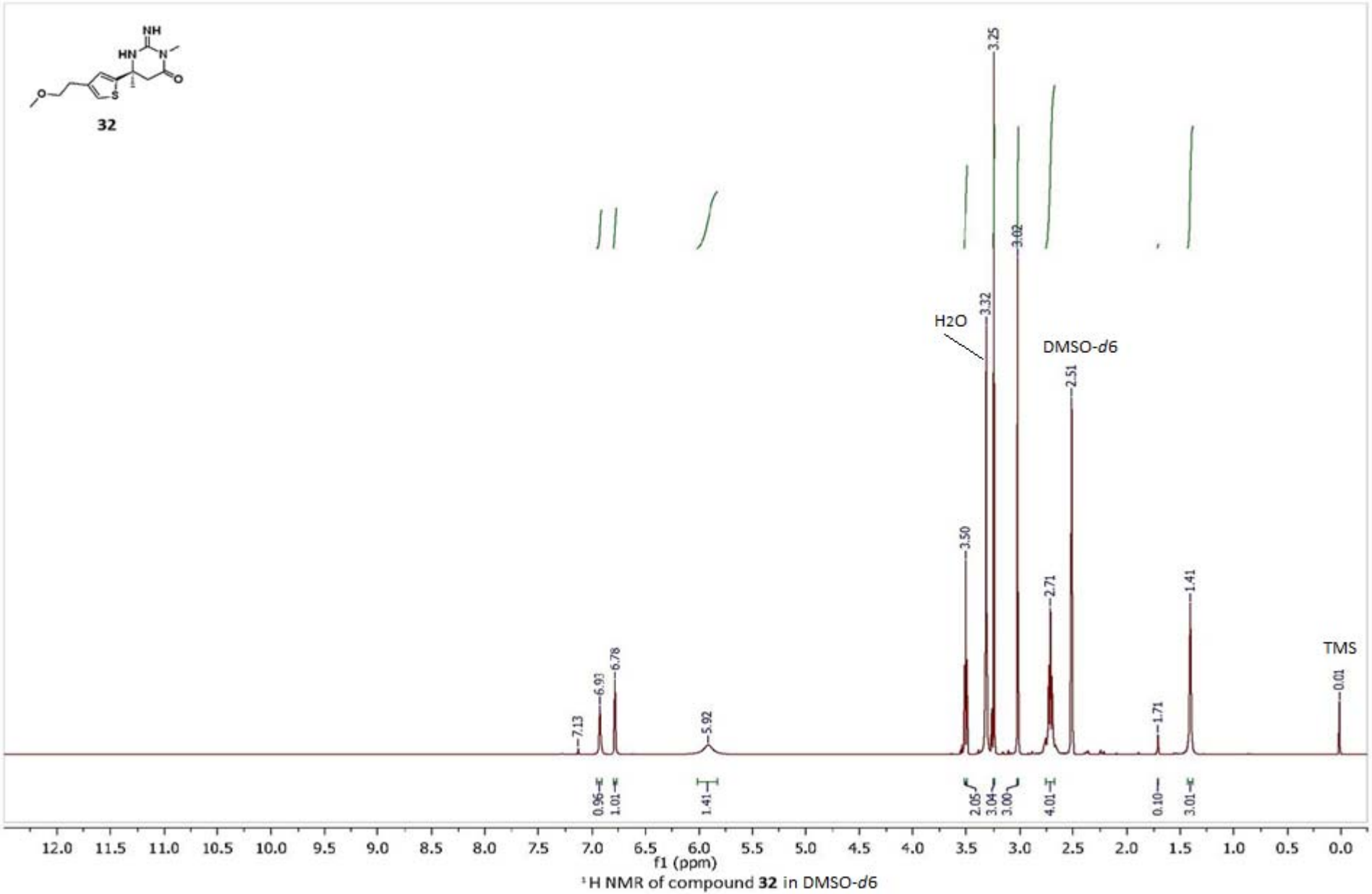
^{1}H NMR of compound **30** in DMSO-*d6*



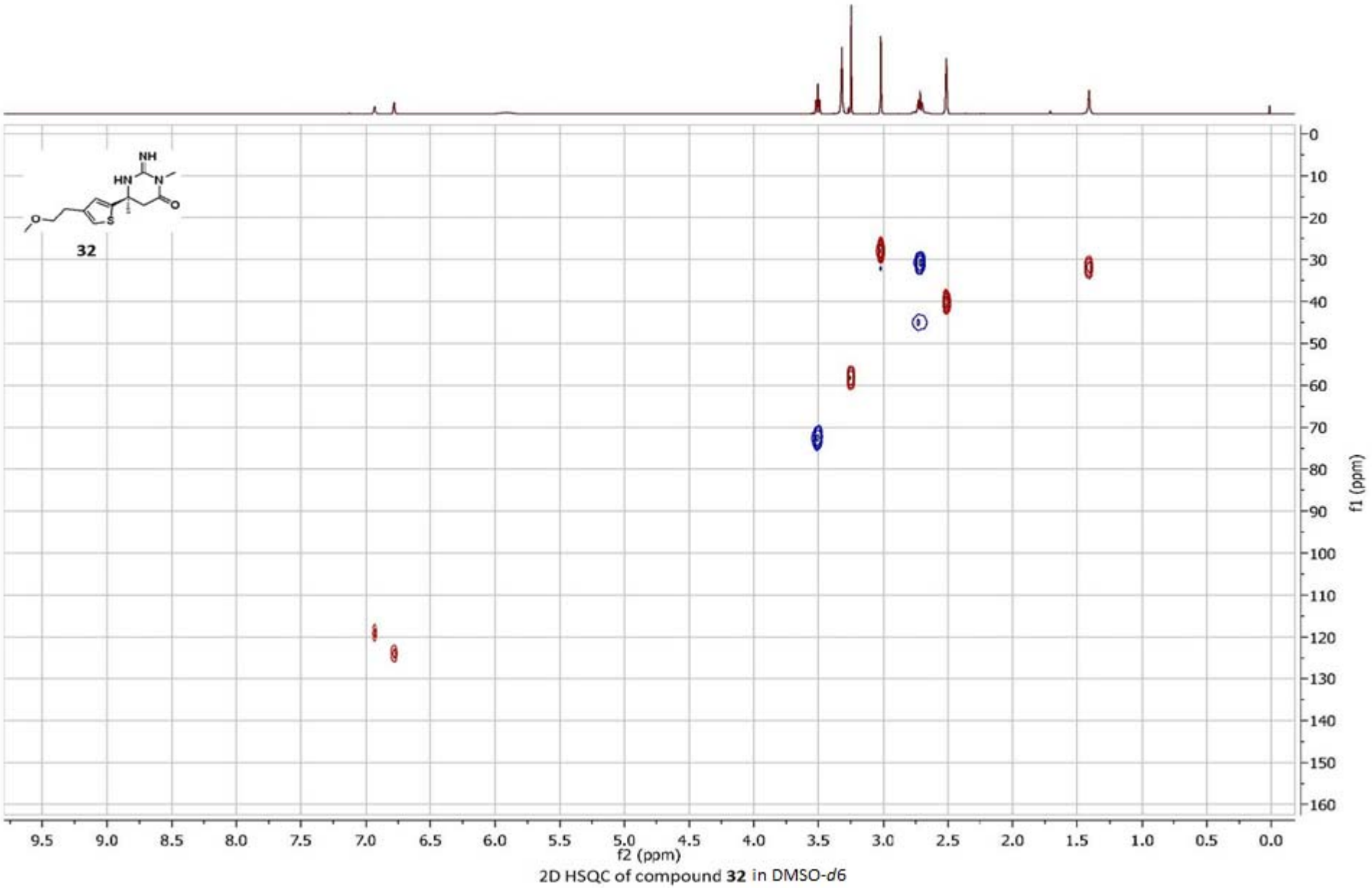
2D HSQC of compound **30** in DMSO-*d*6



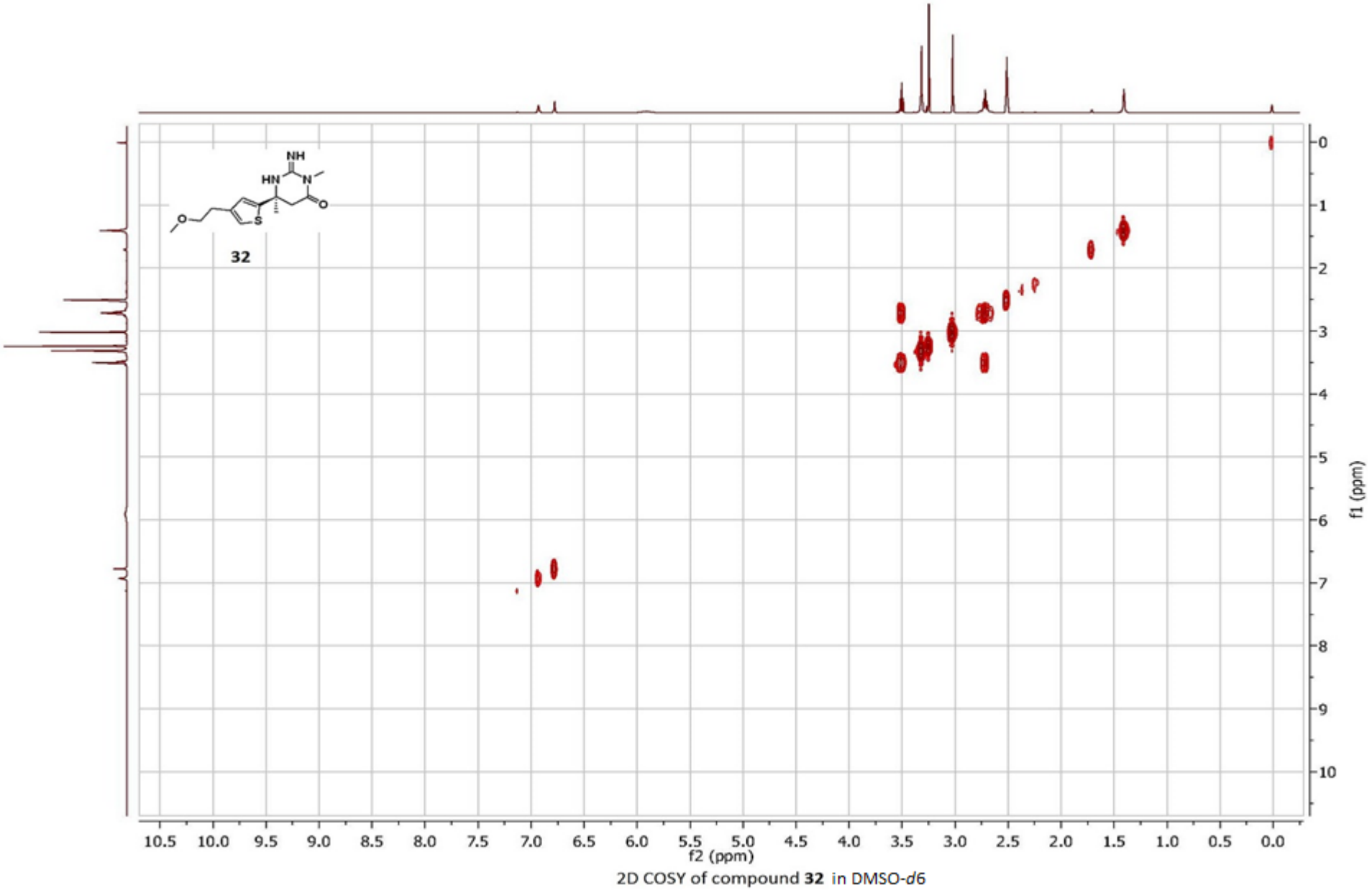
2D COSY of compound **30** in DMSO-*d*6



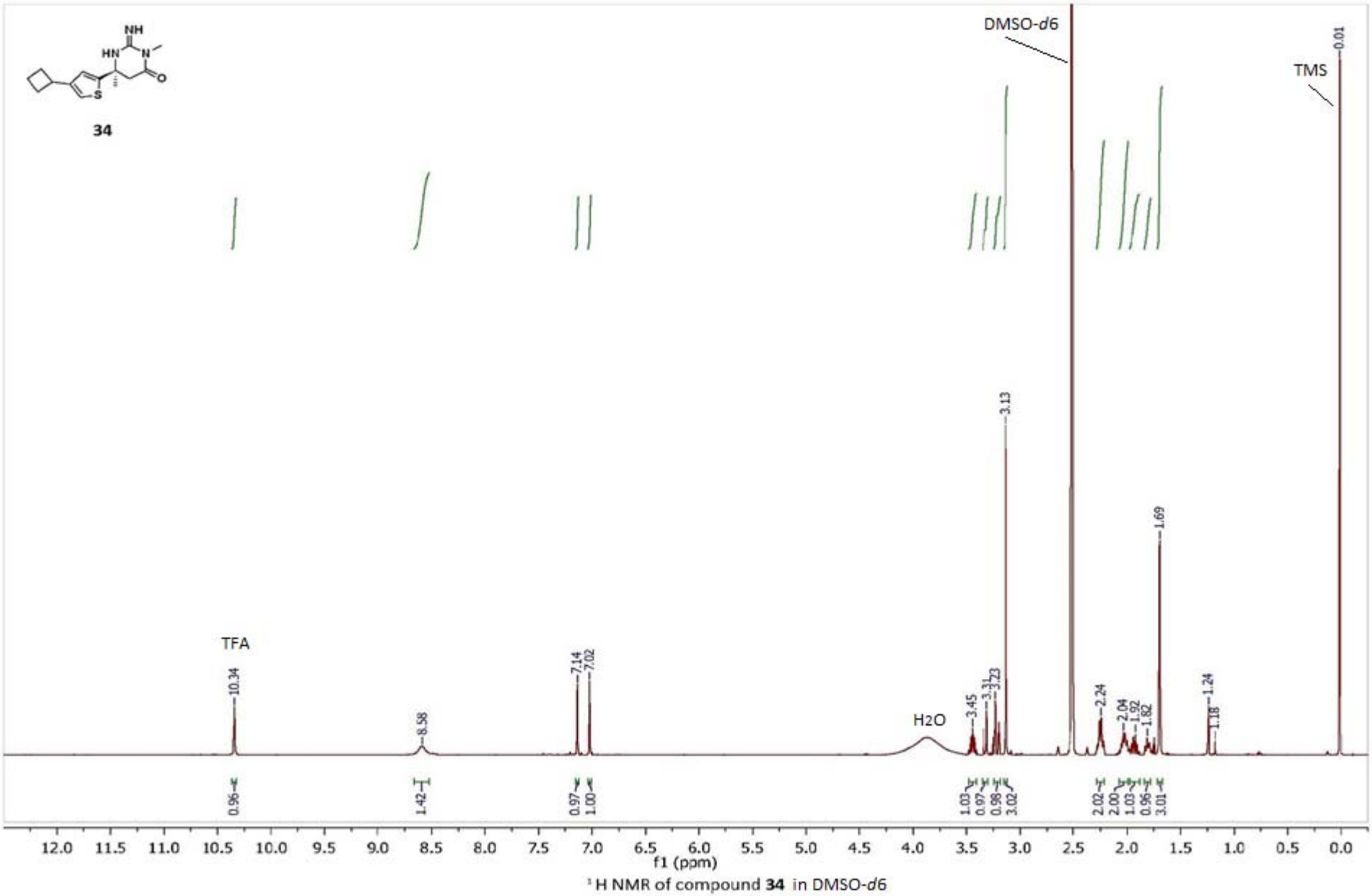
^{1}H NMR of compound **32** in DMSO-*d6*



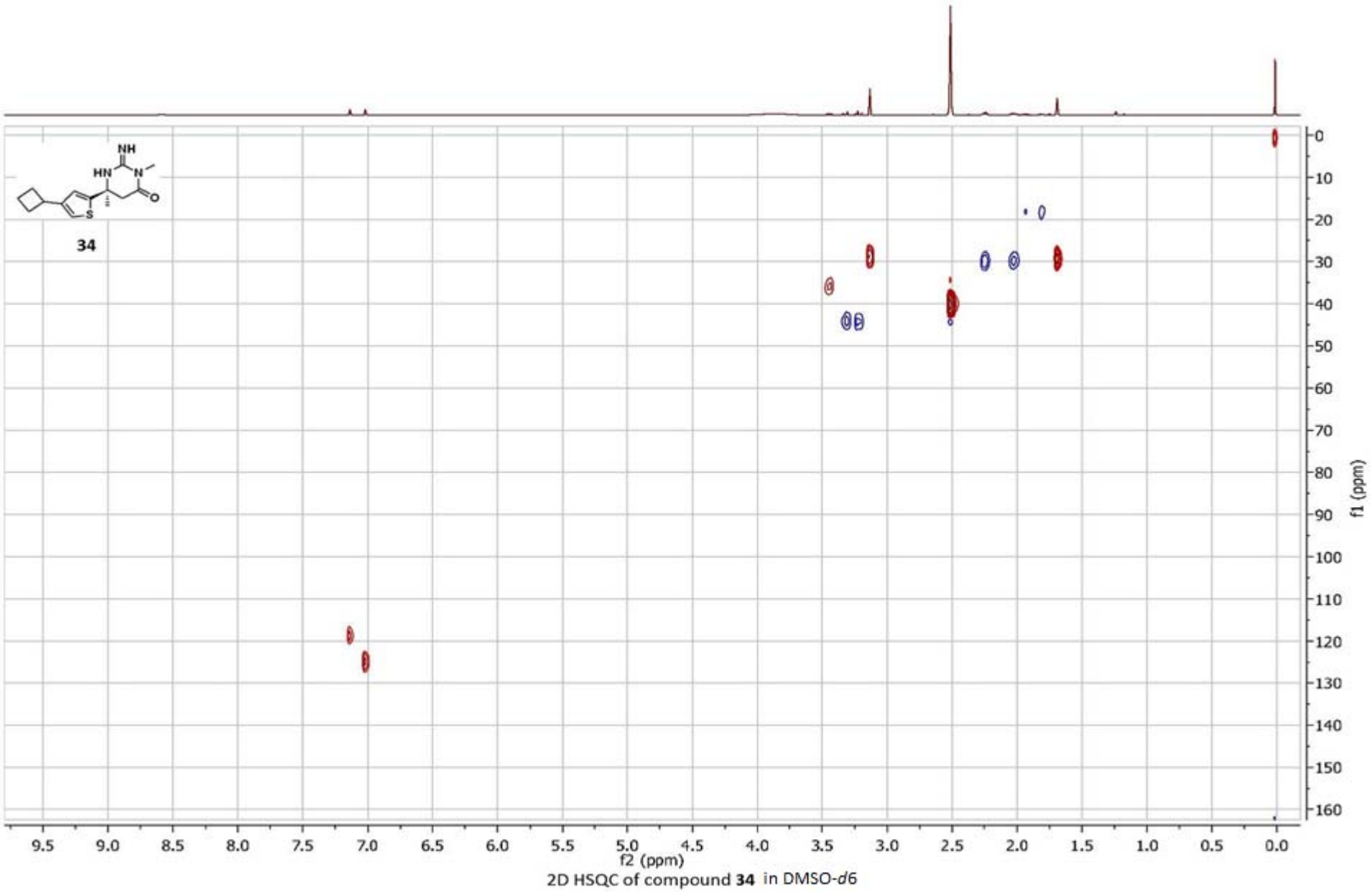
2D HSQC of compound **32** in DMSO-*d*6

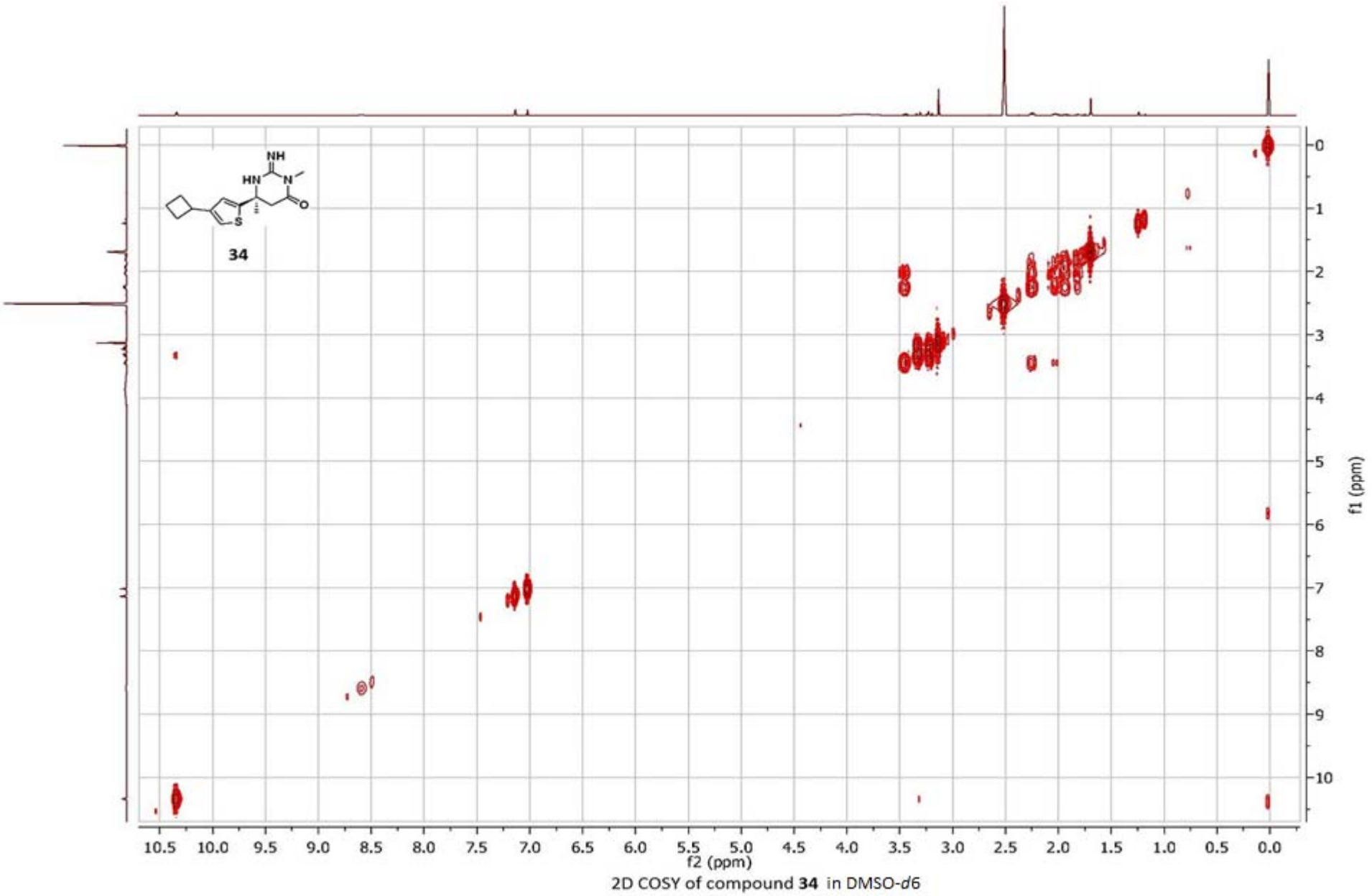


2D COSY of compound **32** in DMSO-*d6*

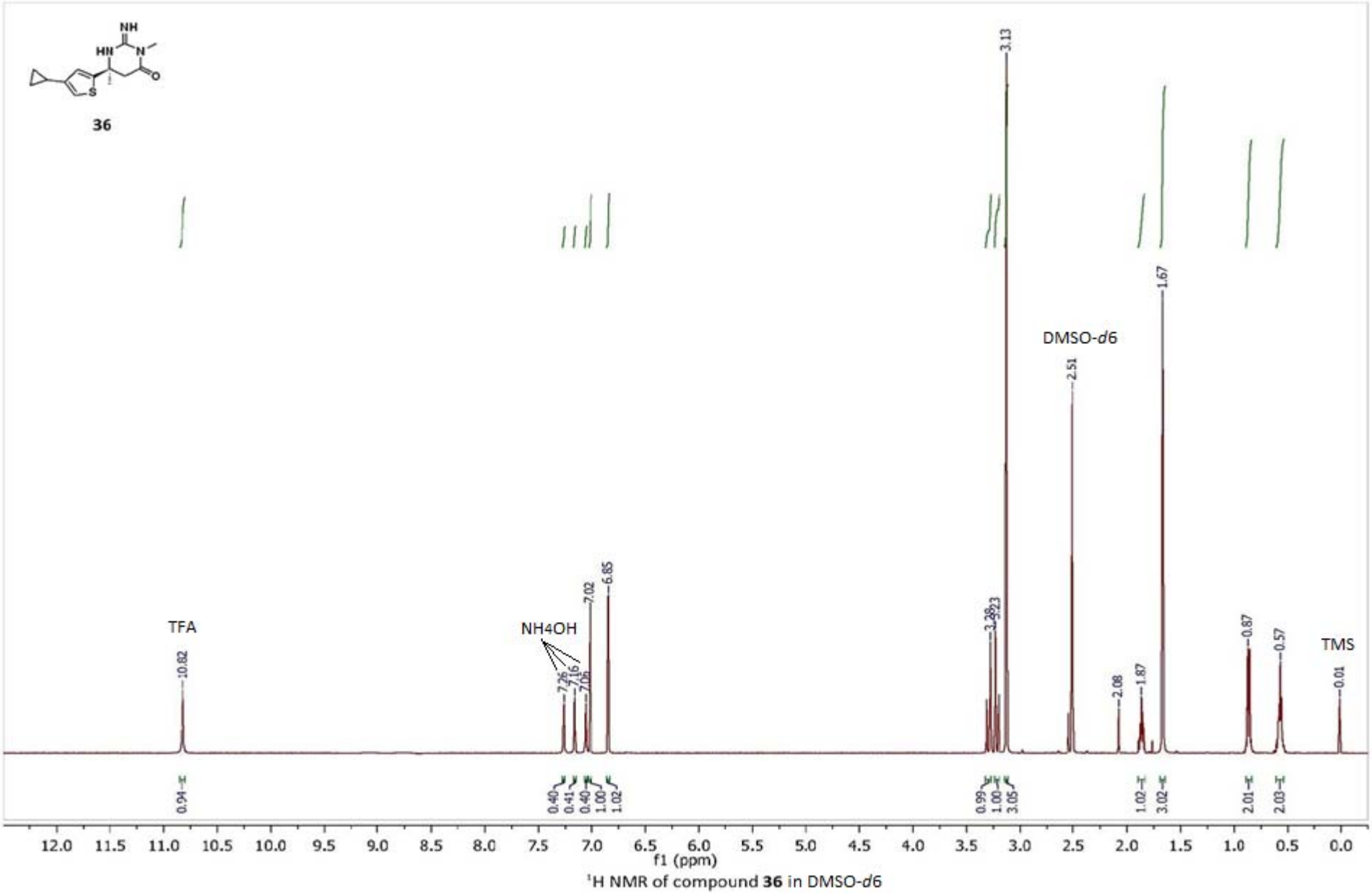


^{1}H NMR of compound **34** in DMSO-*d*6

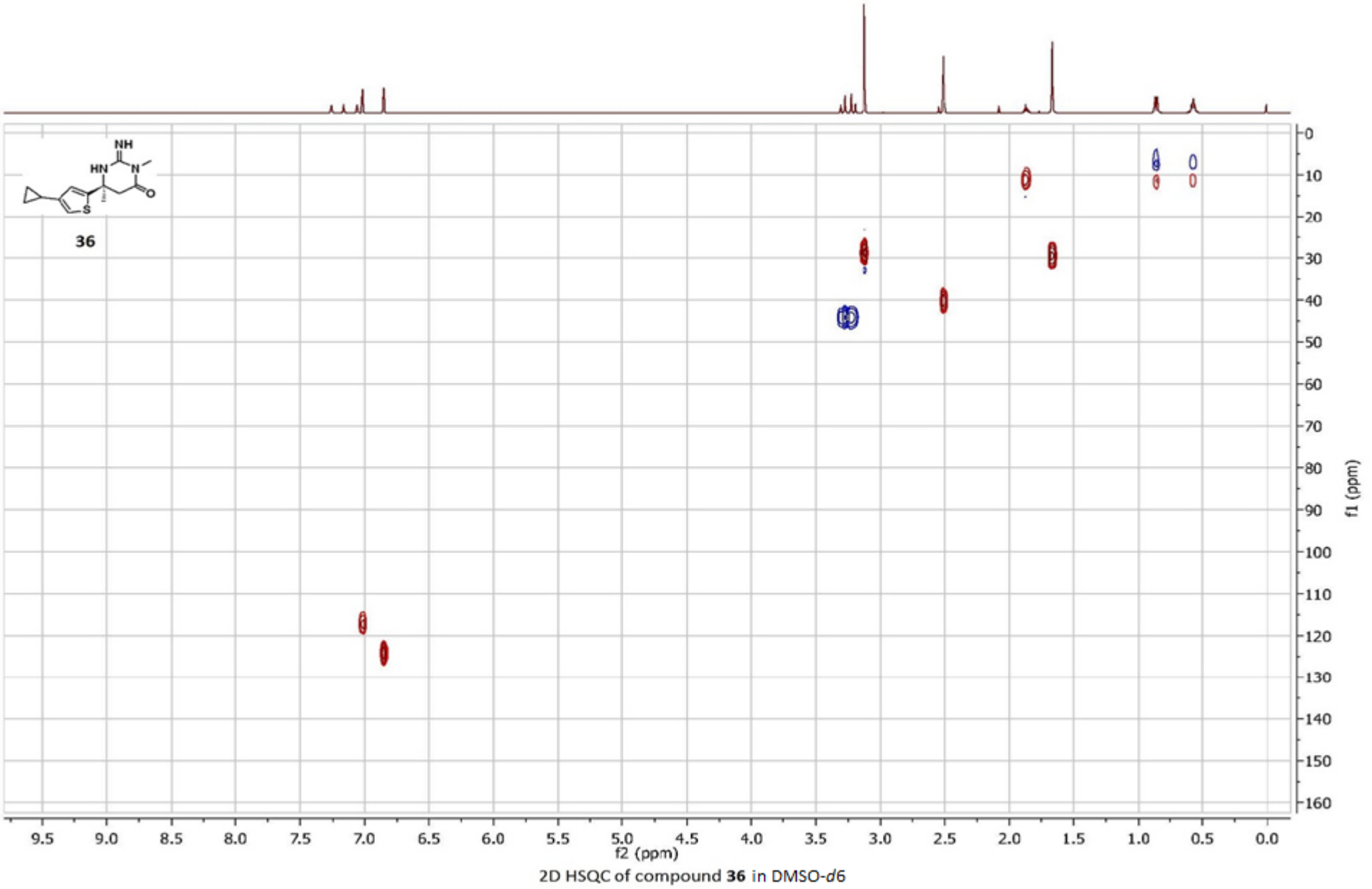

NH
HN
N
O
S
34
f1 (ppm)
f2 (ppm)
2D HSQC of compound 34 in DMSO-d6



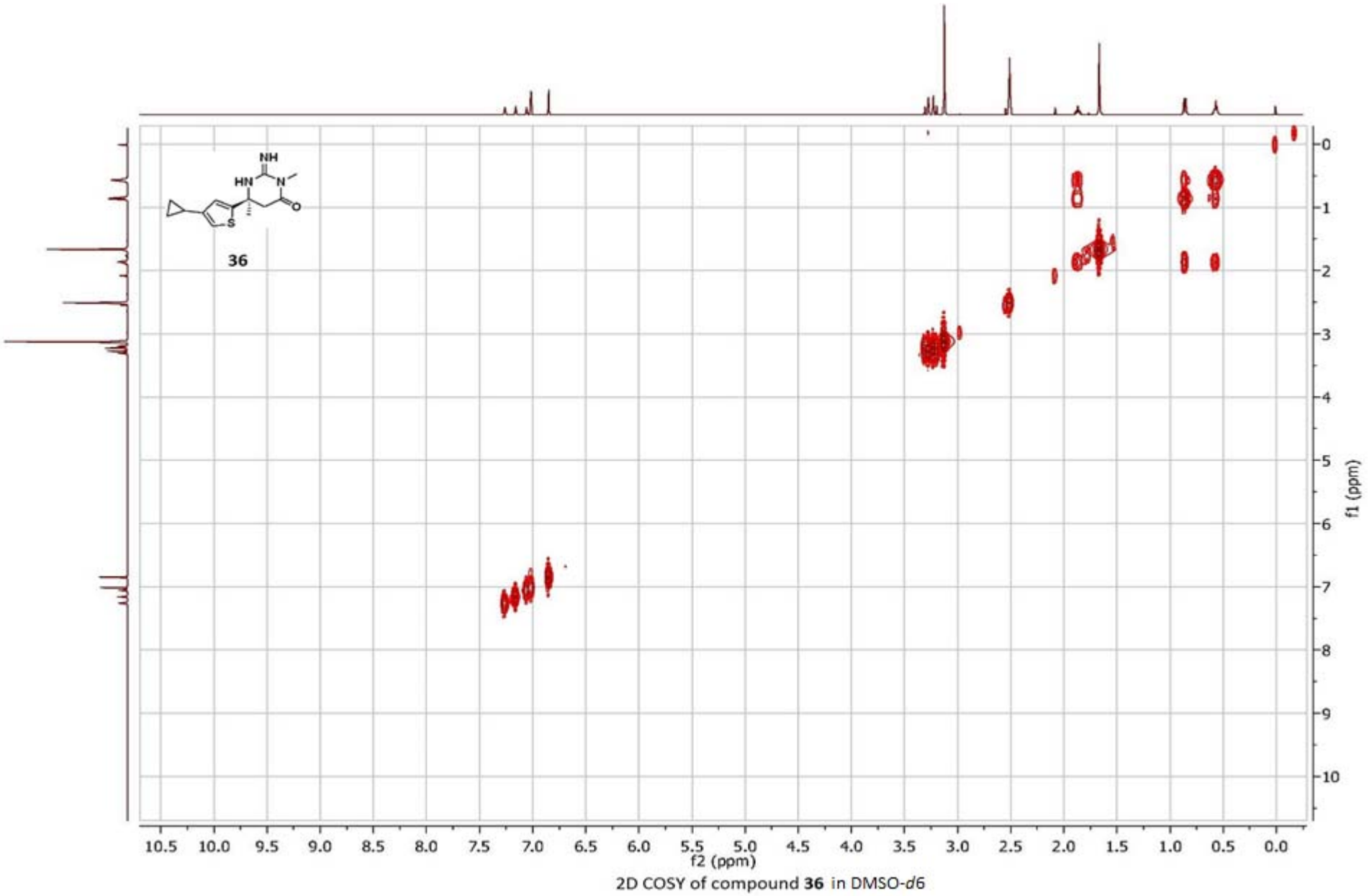
2D COSY of compound **34** in DMSO-*d*6



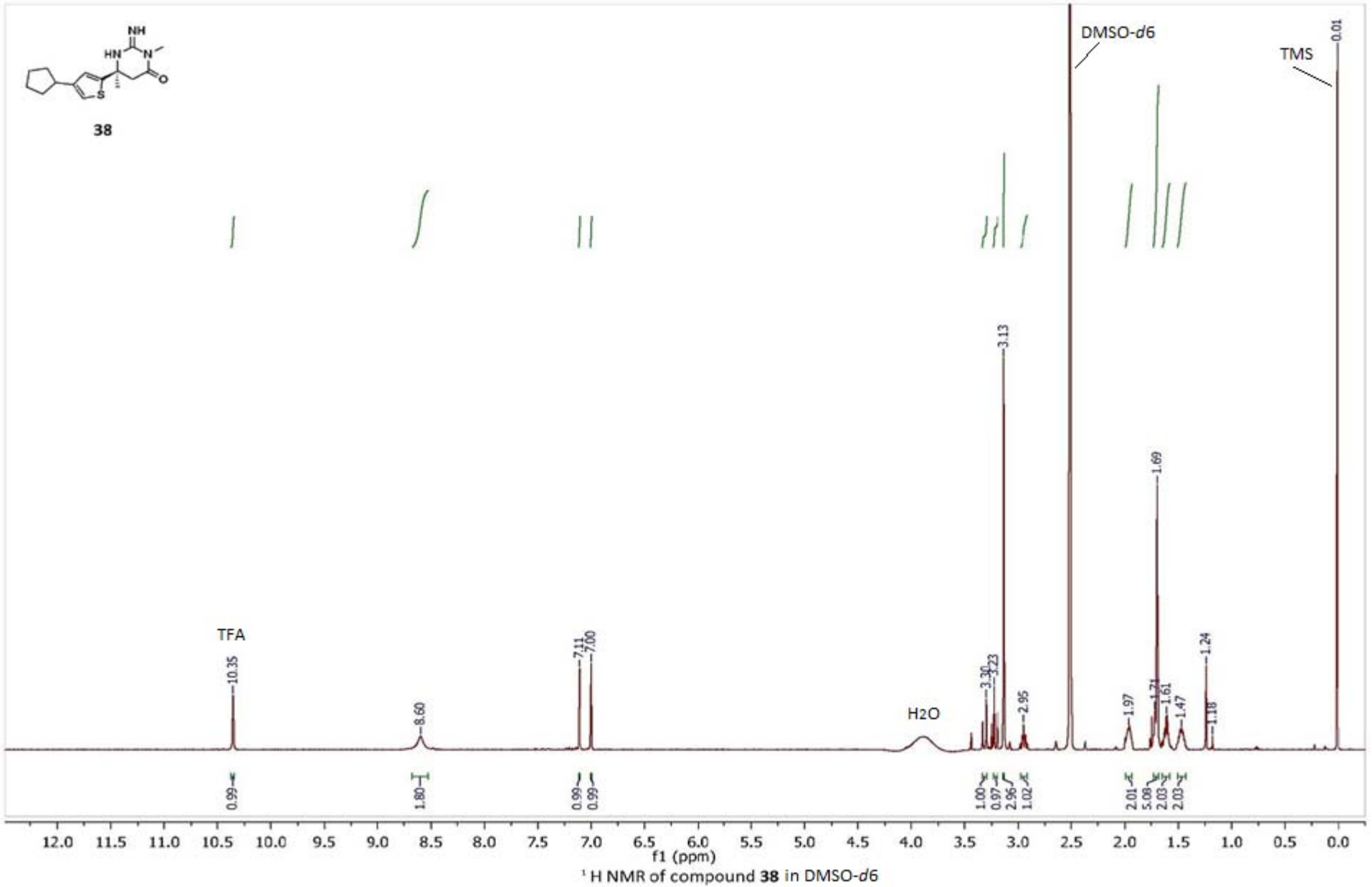
^{1}H NMR of compound **36** in DMSO-*d6*



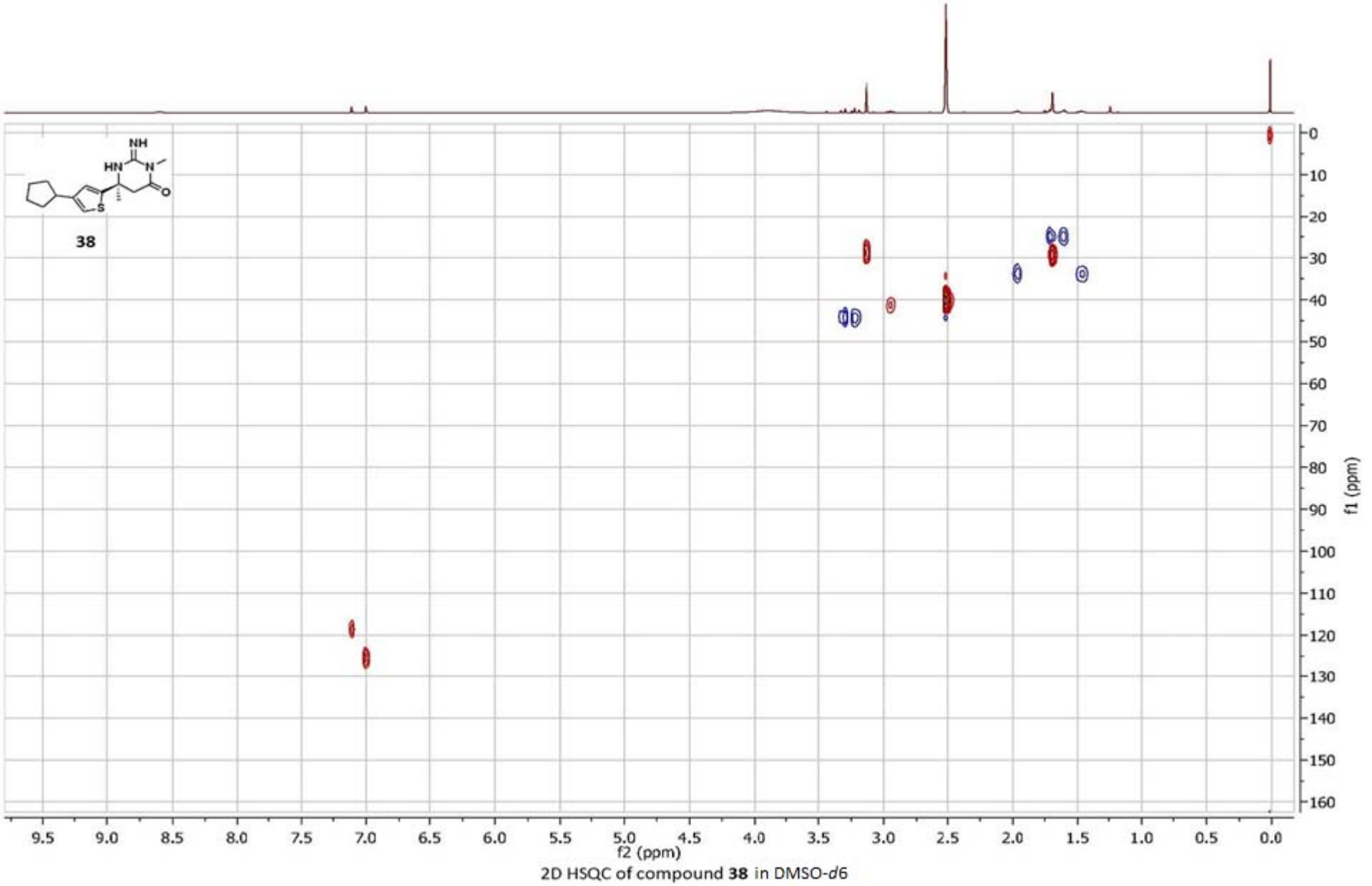
2D HSQC of compound **36** in DMSO-*d*6



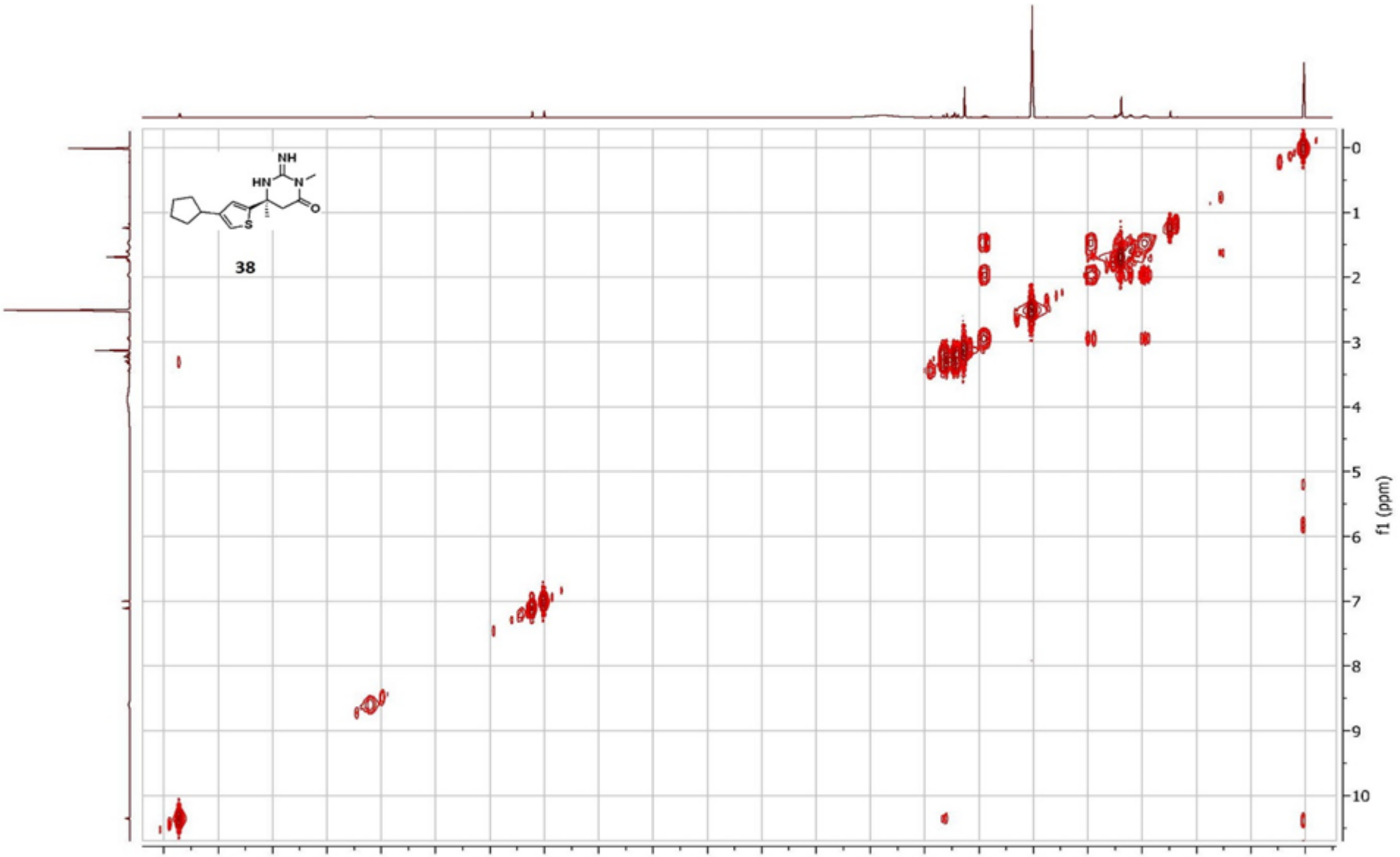
2D COSY of compound **36** in DMSO-*d6*



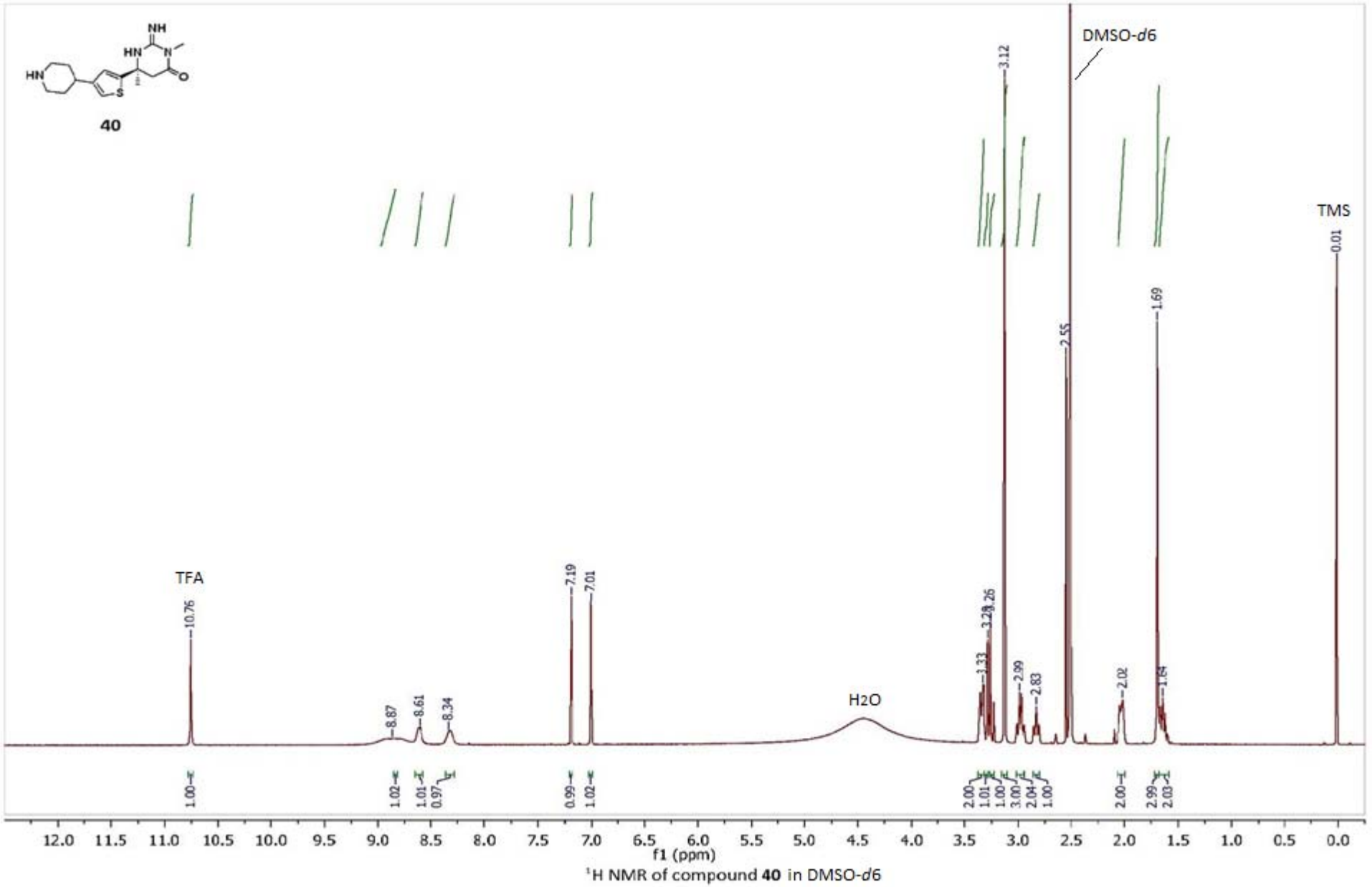
^{1}H NMR of compound **38** in DMSO-*d*6



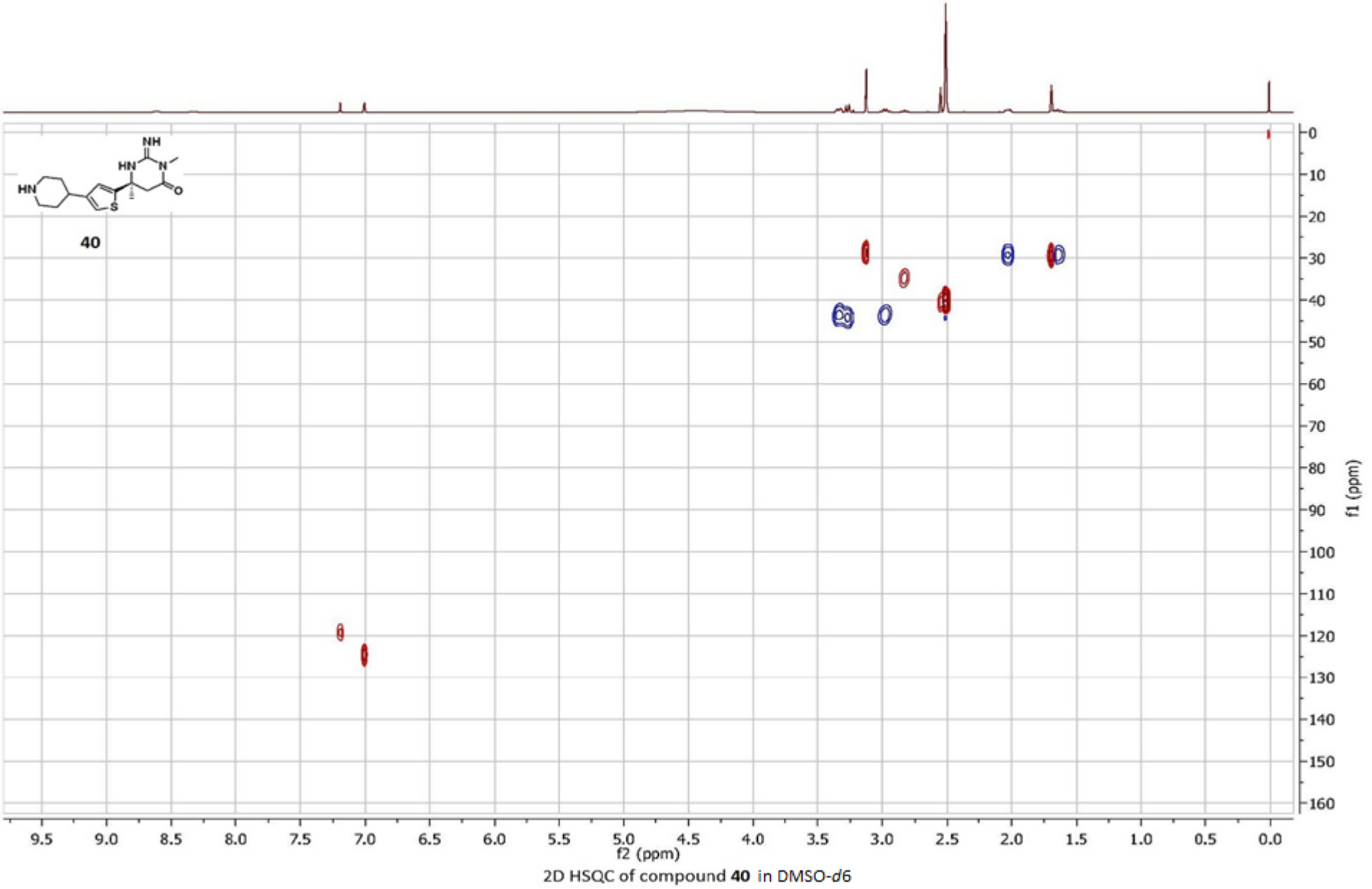
2D HSQC of compound **38** in DMSO-*d*6



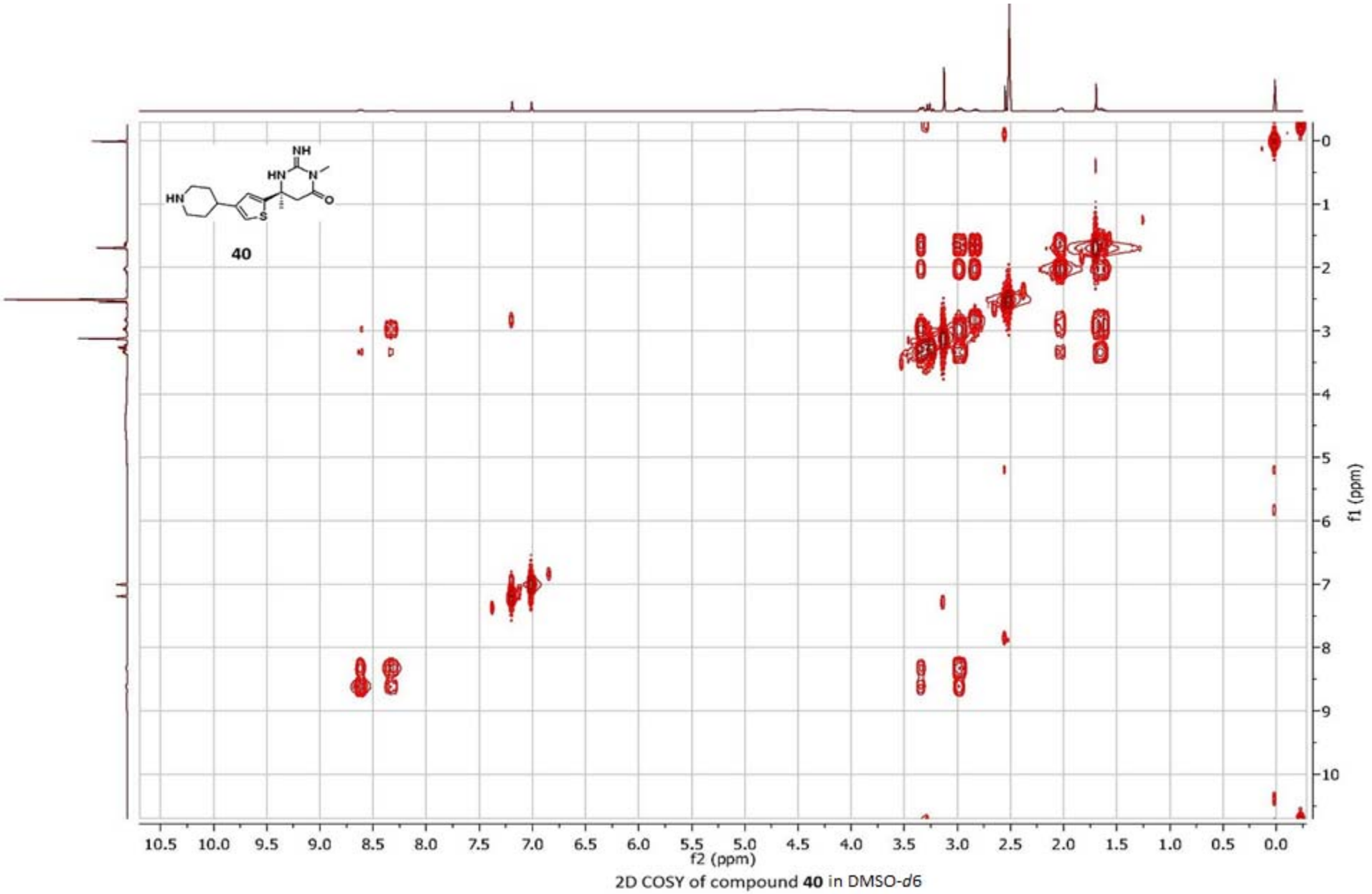
2D COSY of compound **38** in DMSO-*d6*



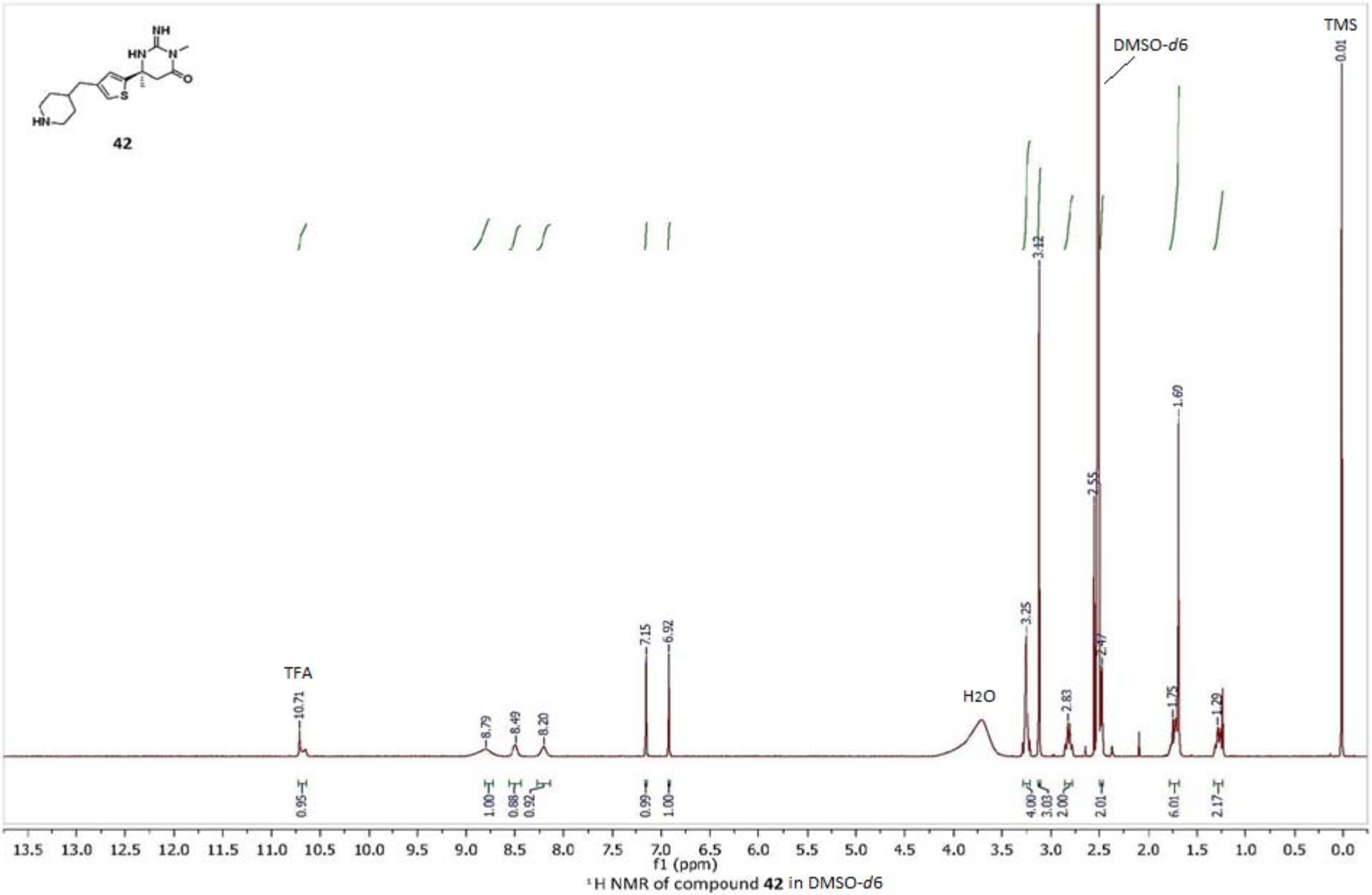
^{1}H NMR of compound **40** in DMSO-*d*6



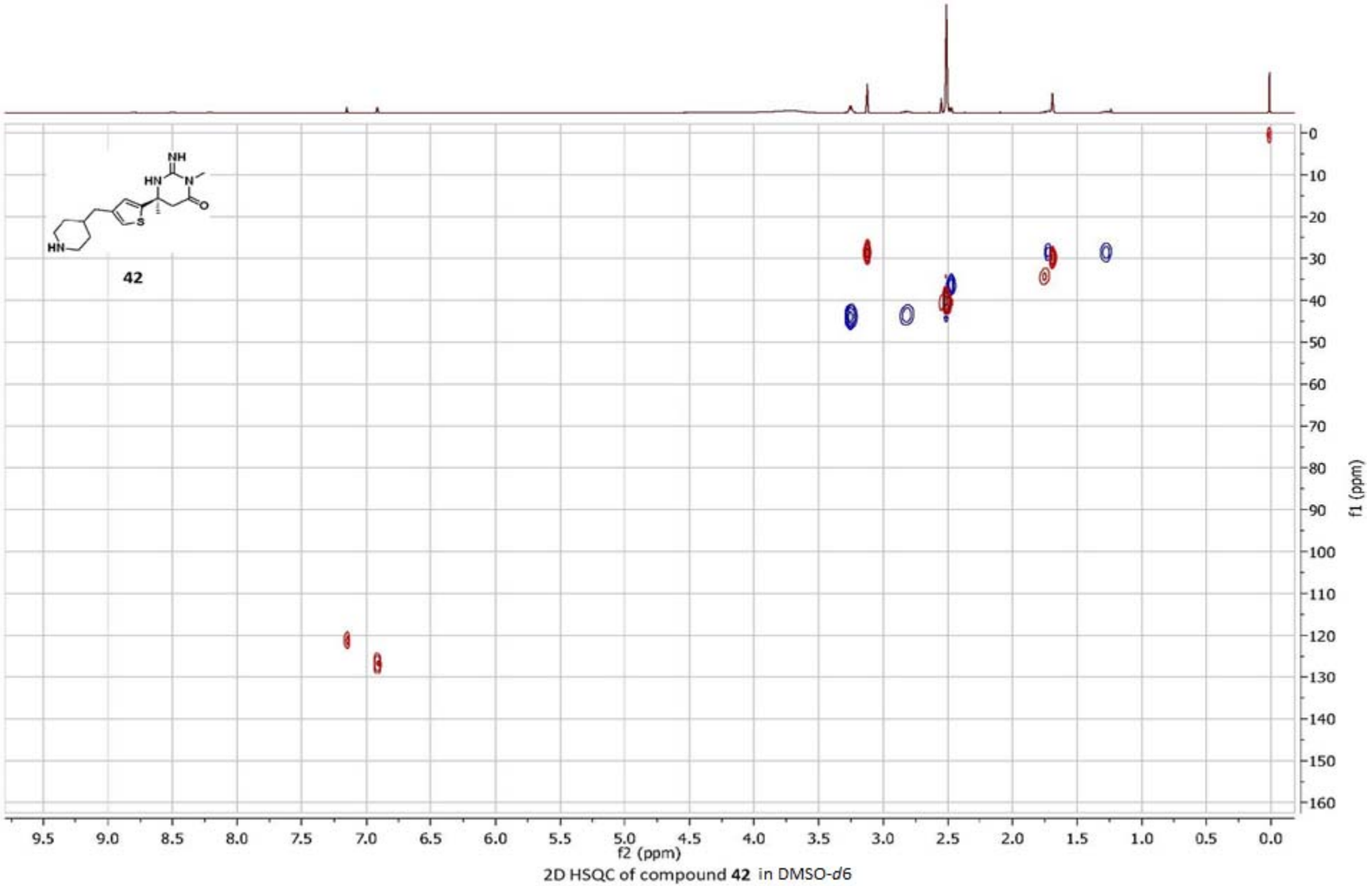
2D HSQC of compound **40** in DMSO-*d6*

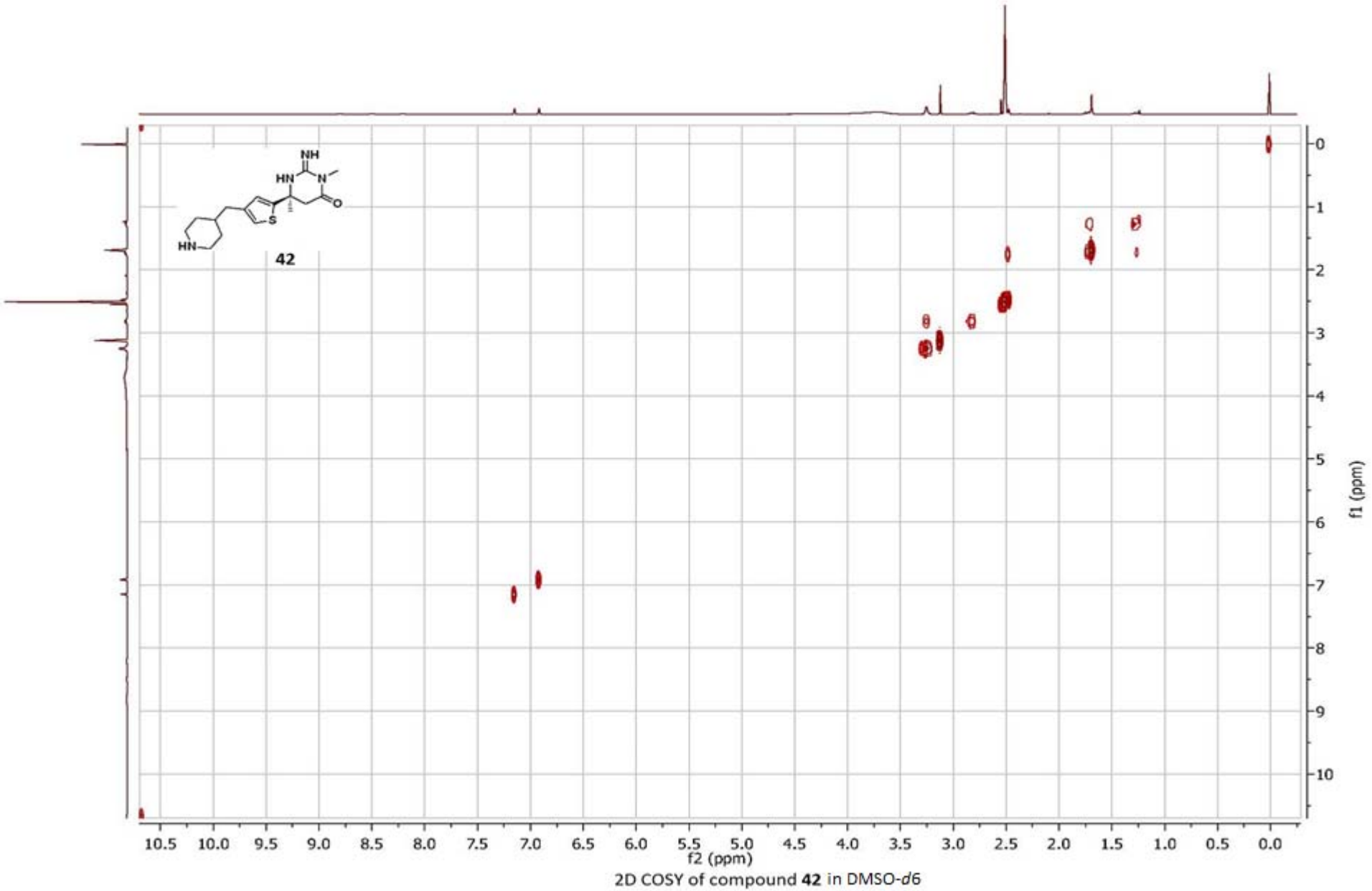


2D COSY of compound **40** in DMSO-*d*6

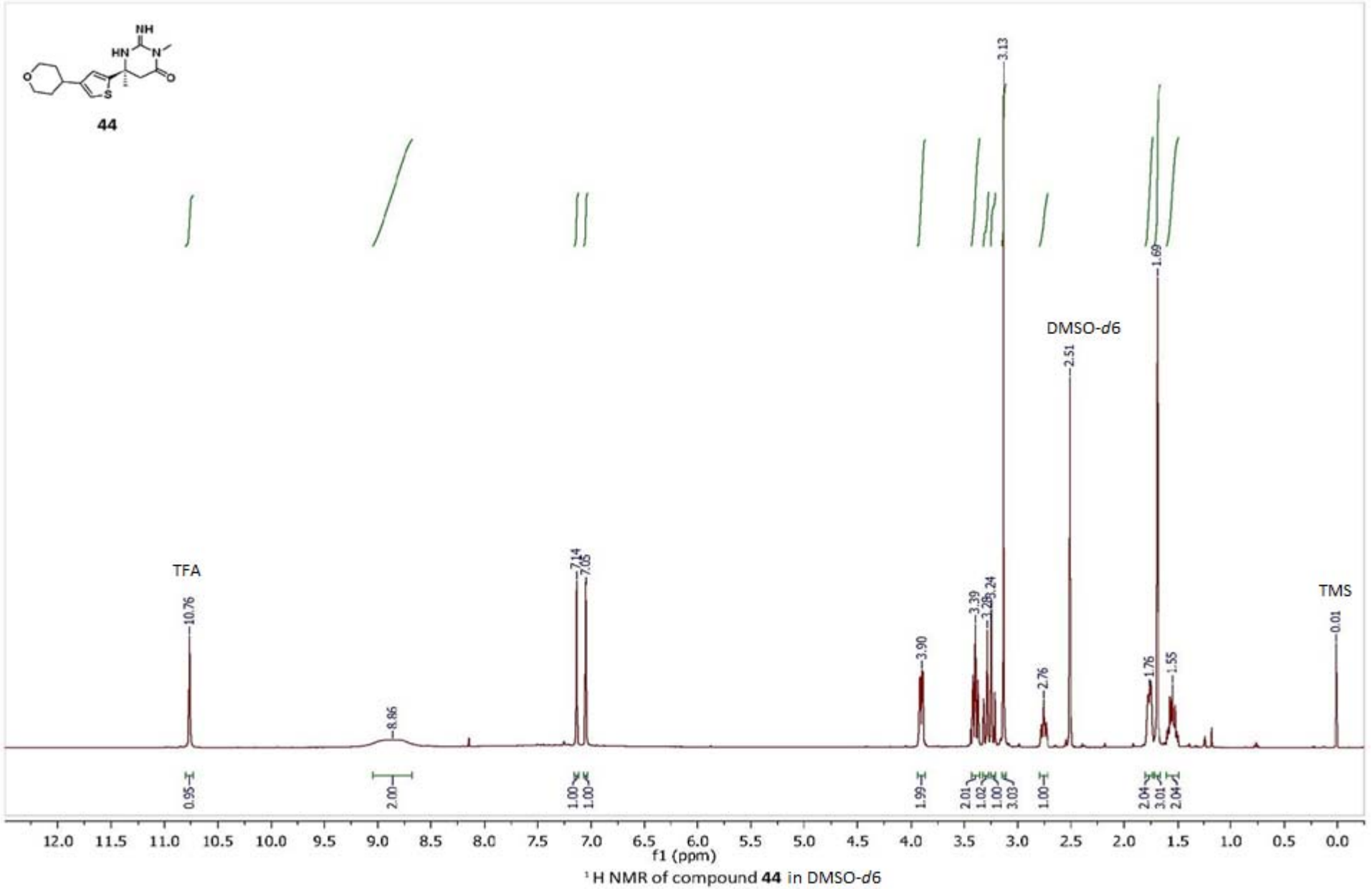


^{1}H NMR of compound **42** in DMSO-*d*6

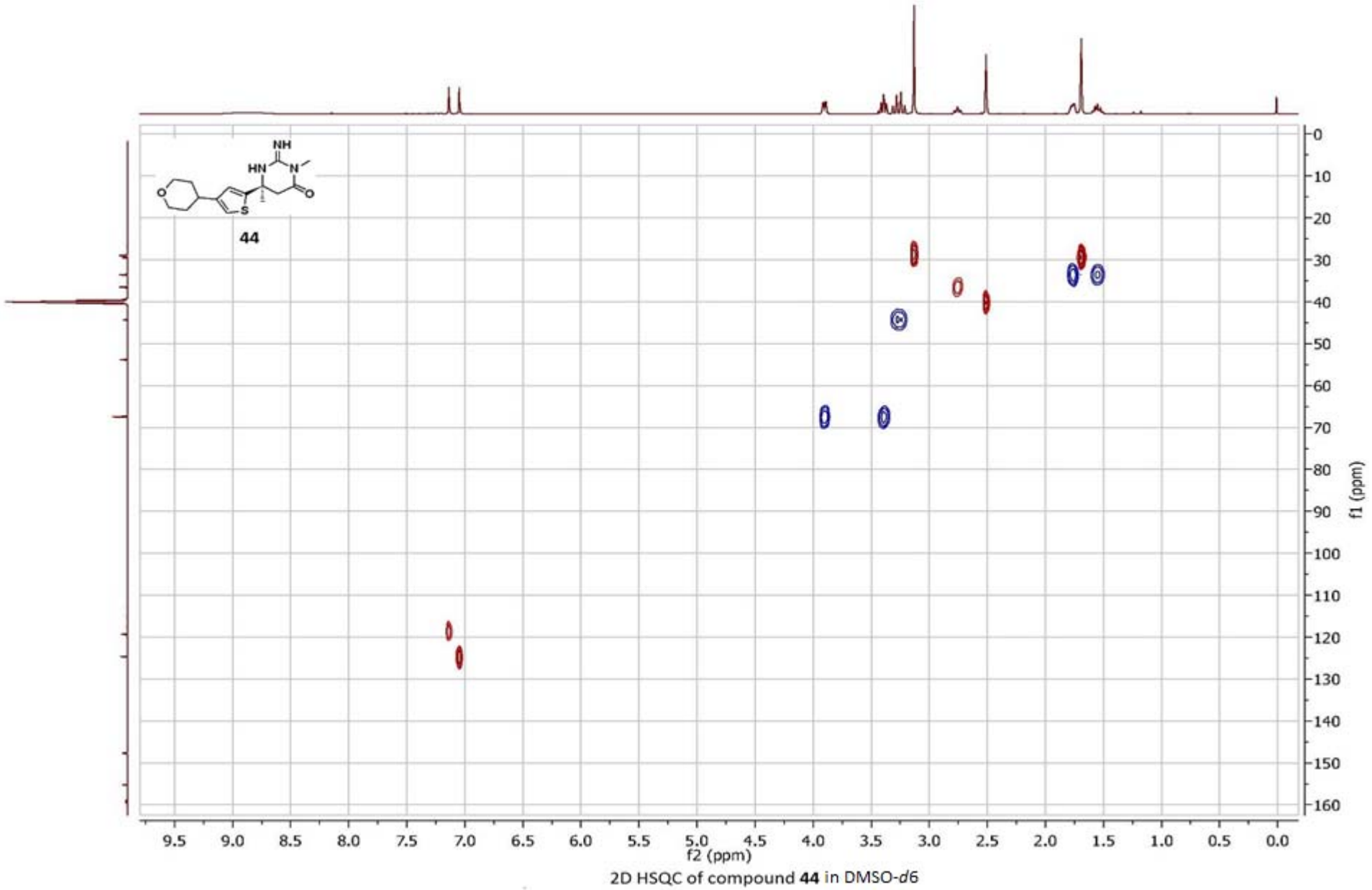

NH
HN
N
O
S
HN
42
f1 (ppm)
f2 (ppm)
2D HSQC of compound 42 in DMSO-d6

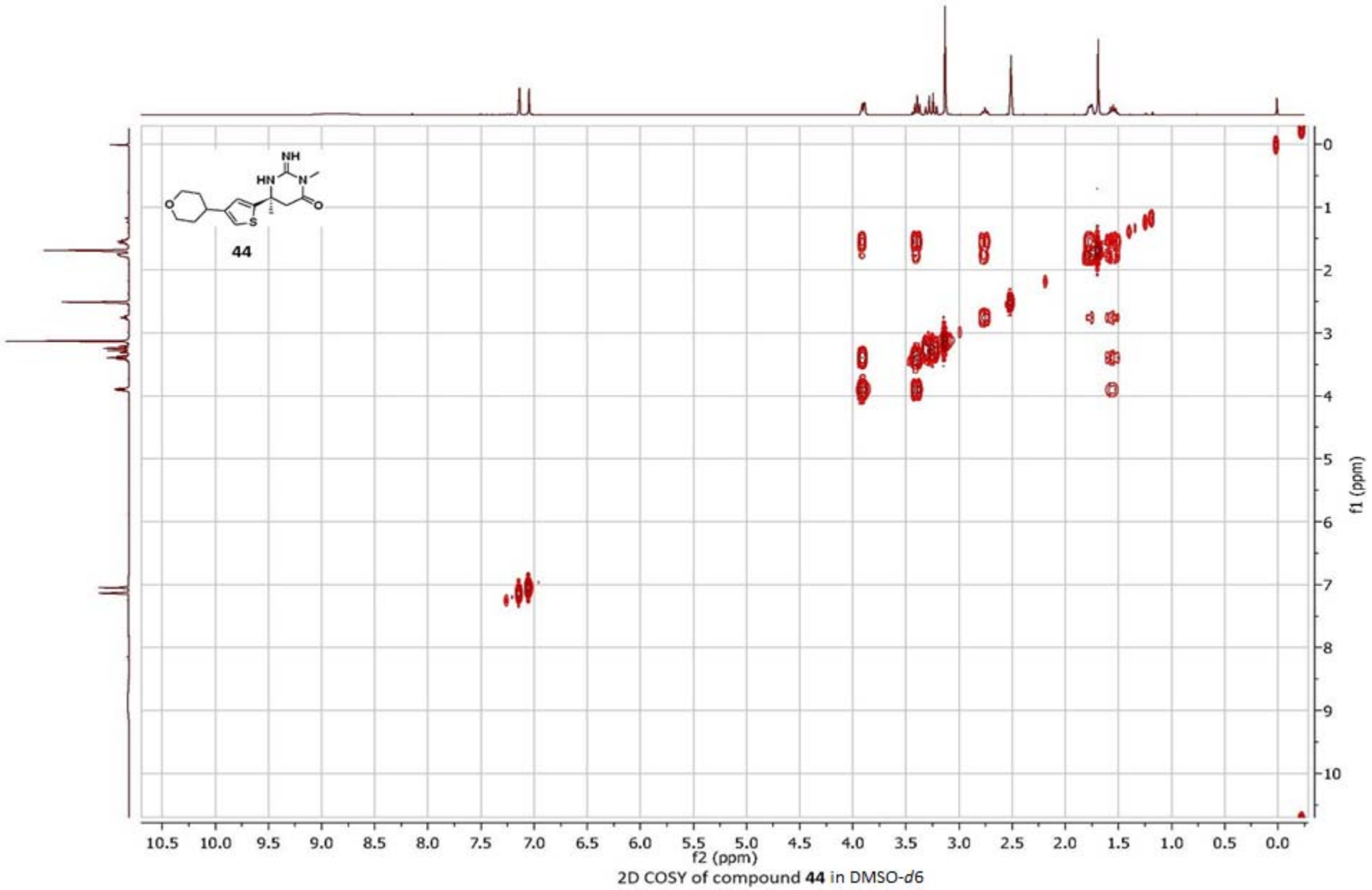


2D COSY of compound **42** in DMSO-*d*6

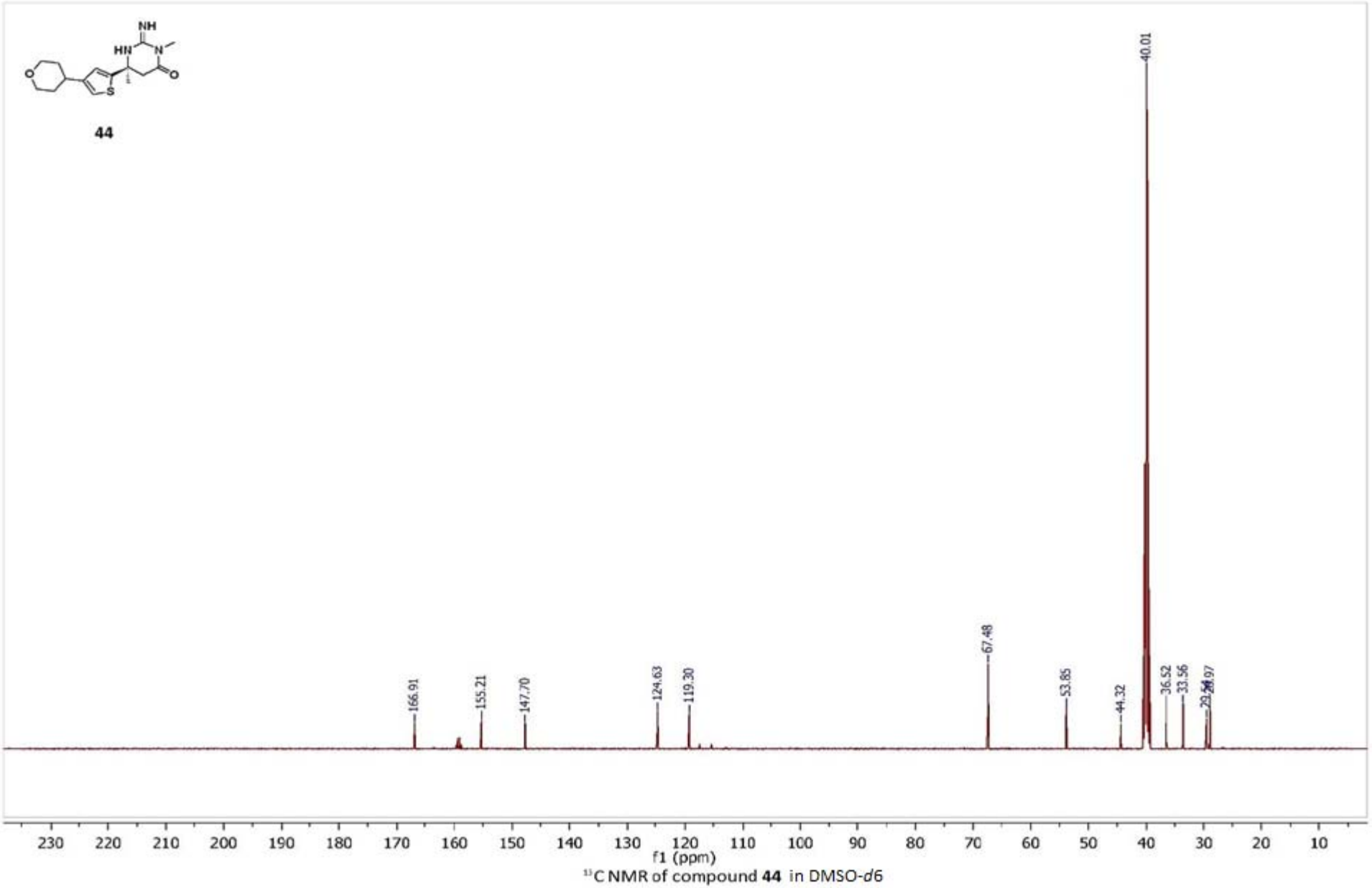


^{1}H NMR of compound **44** in DMSO-*d*6

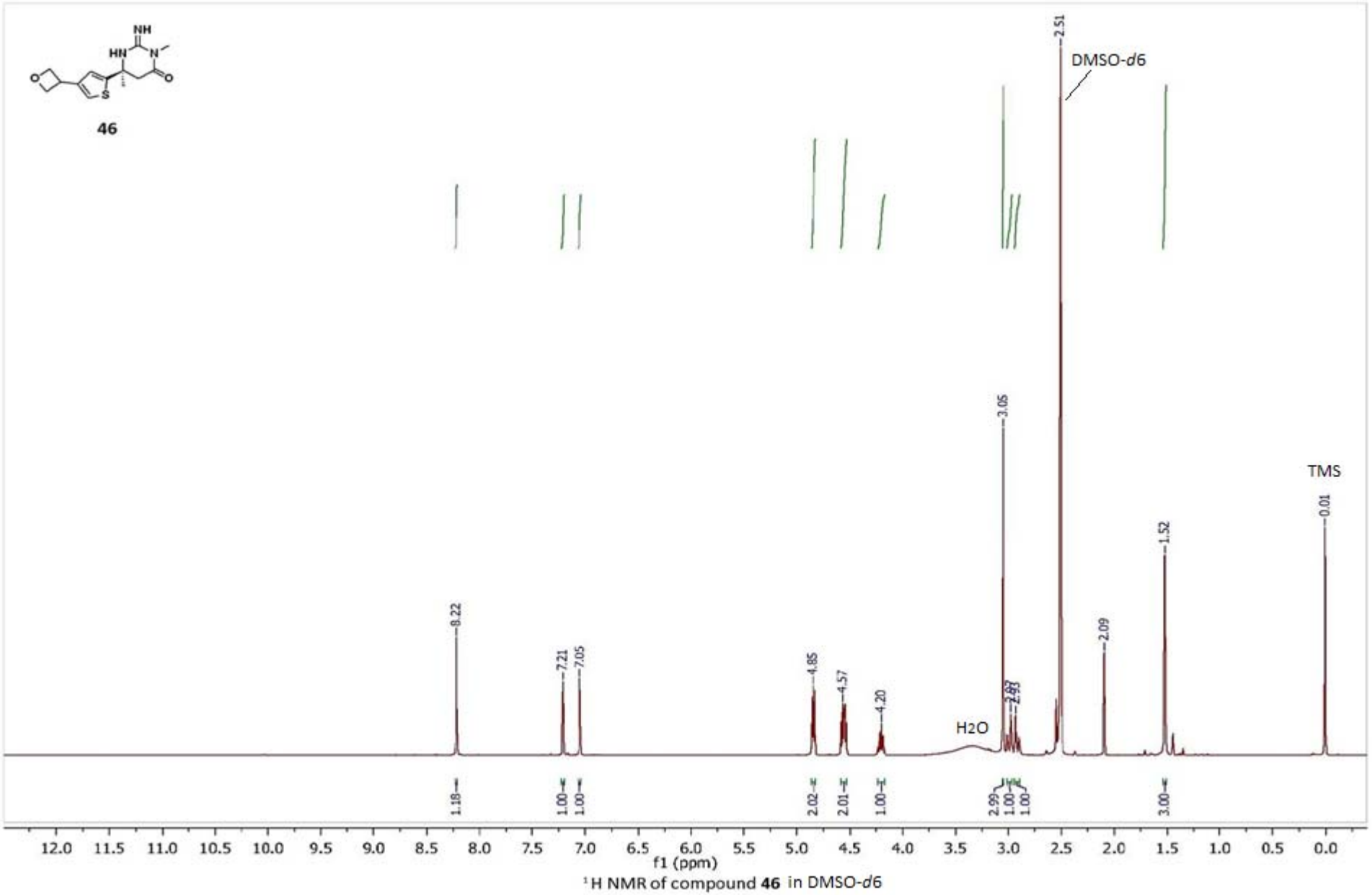

NH
HN
N
O
O
S
44
f2 (ppm)
f1 (ppm)
2D HSQC of compound 44 in DMSO-d6



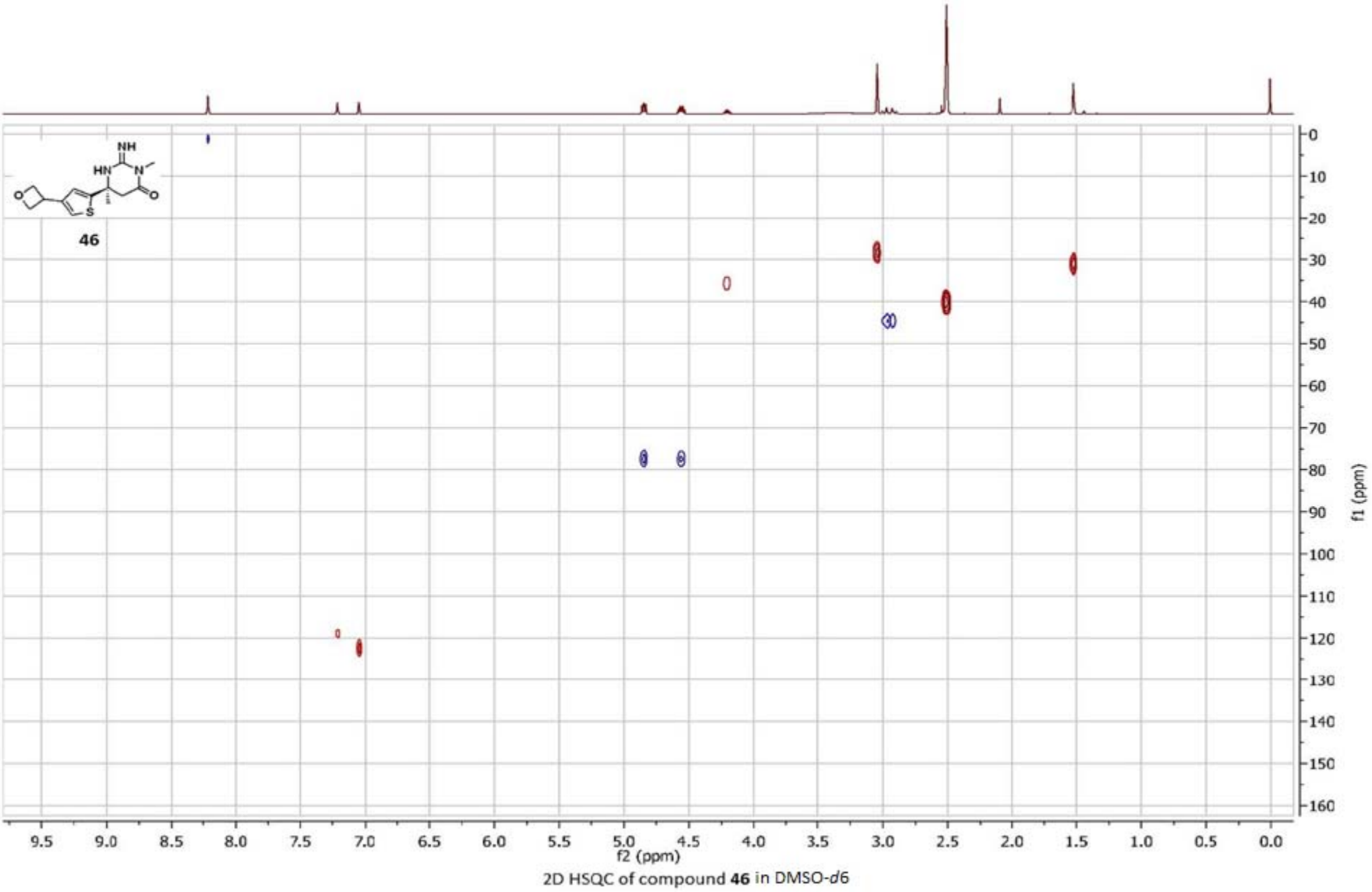
2D COSY of compound **44** in DMSO-*d*6



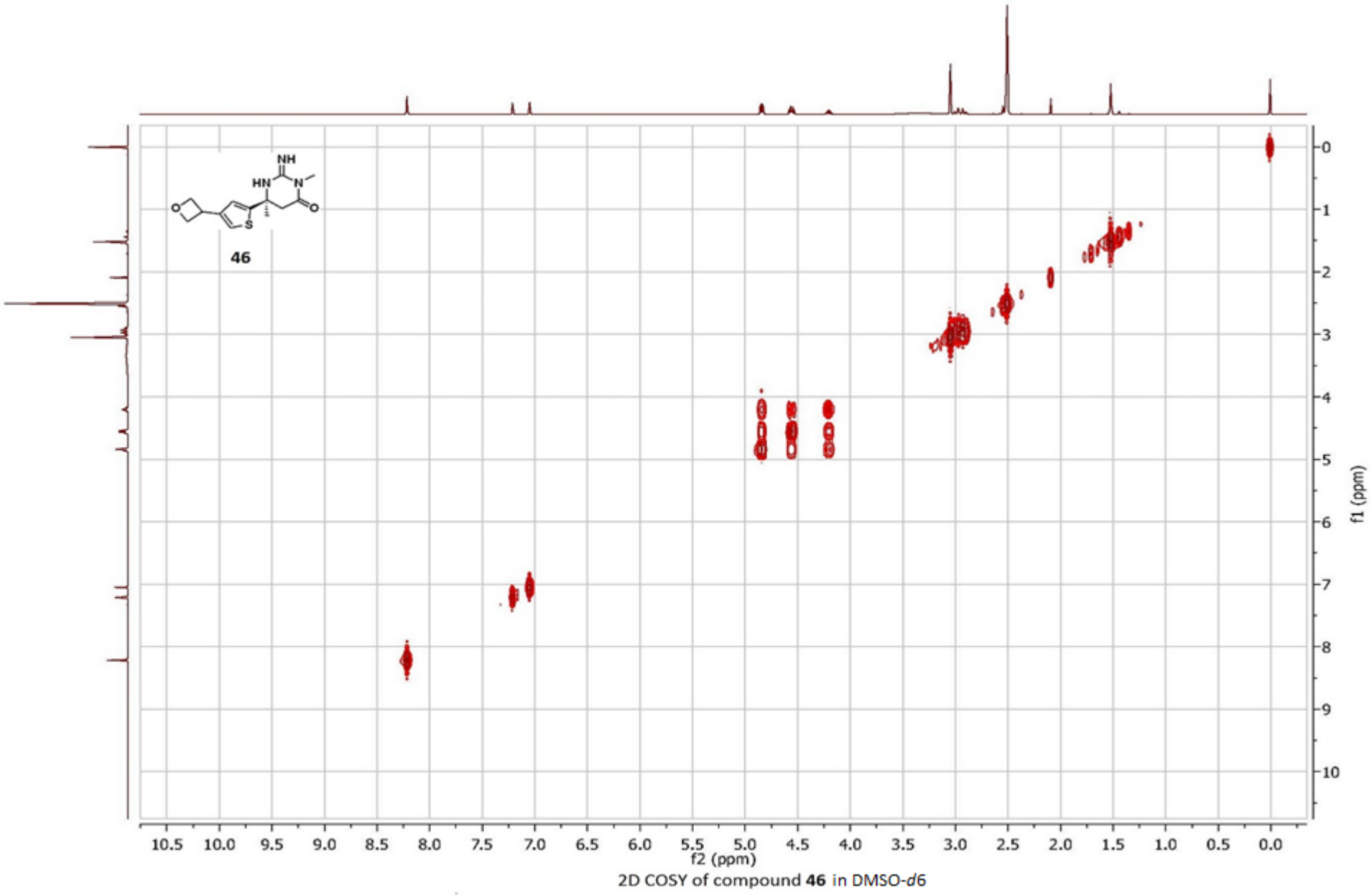
^{13}C NMR of compound **44** in DMSO-*d*6



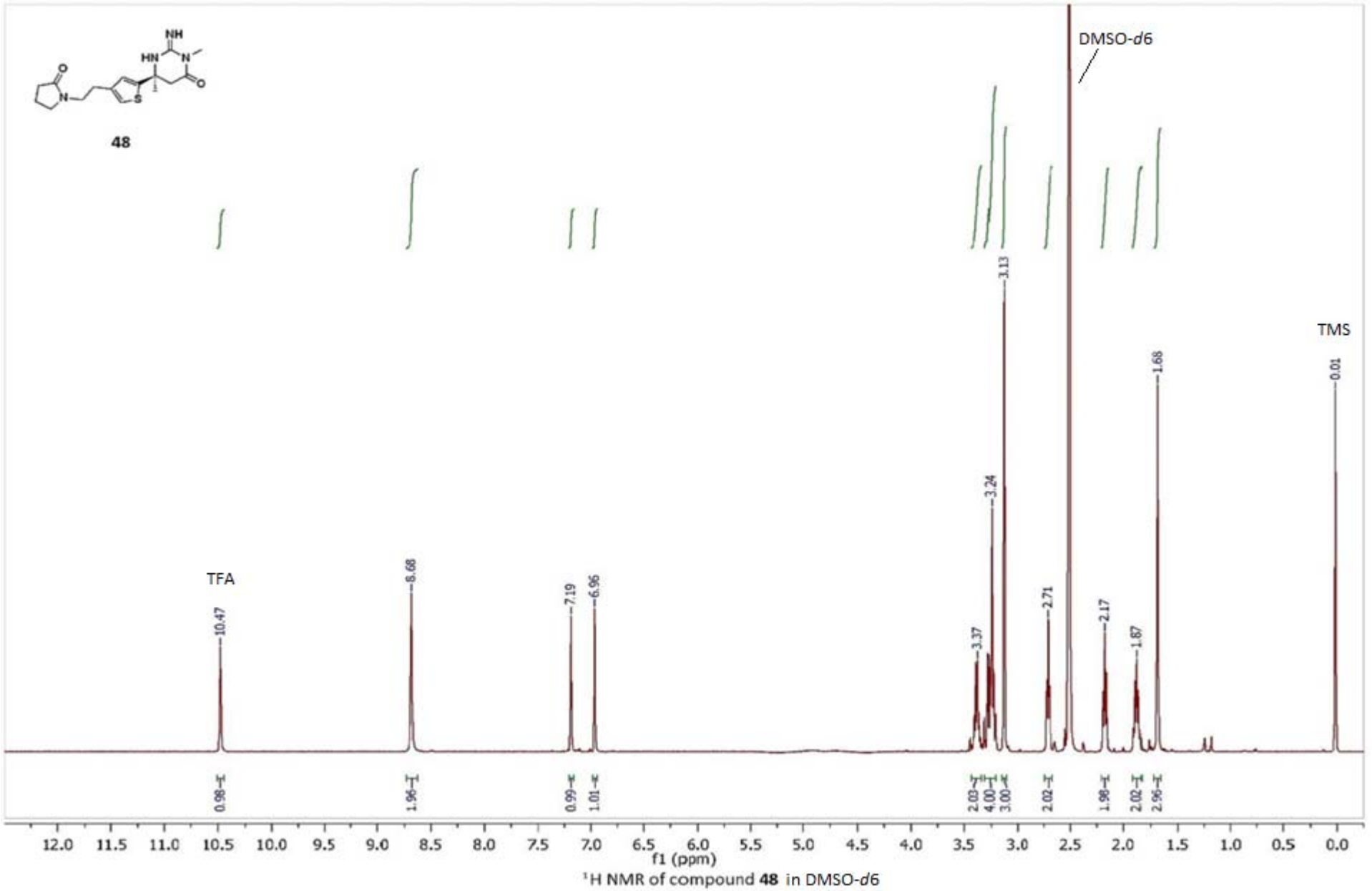
^{1}H NMR of compound **46** in DMSO-*d*6



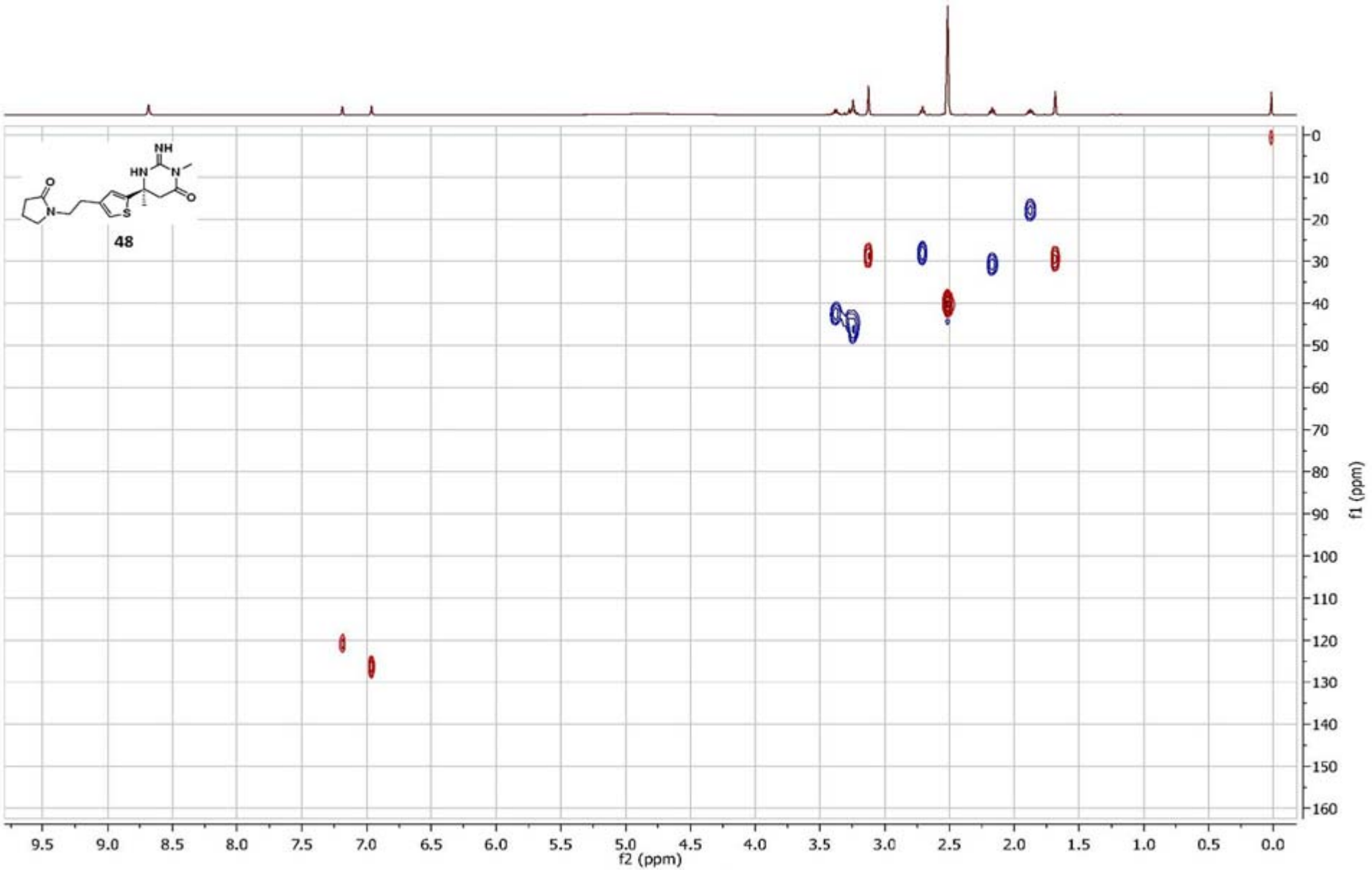
2D HSQC of compound **46** in DMSO-*d*6



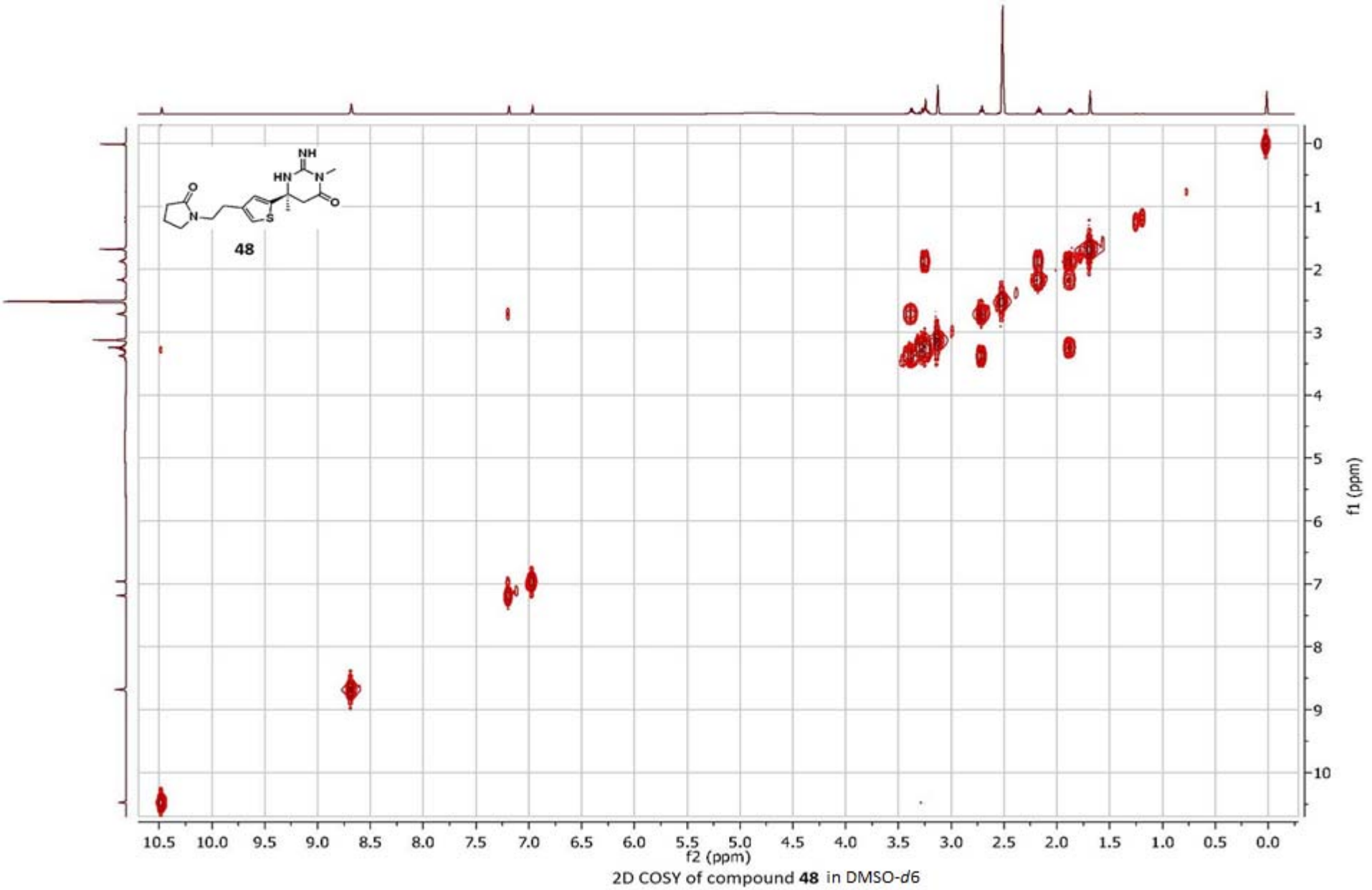
2D COSY of compound **46** in DMSO-*d*6



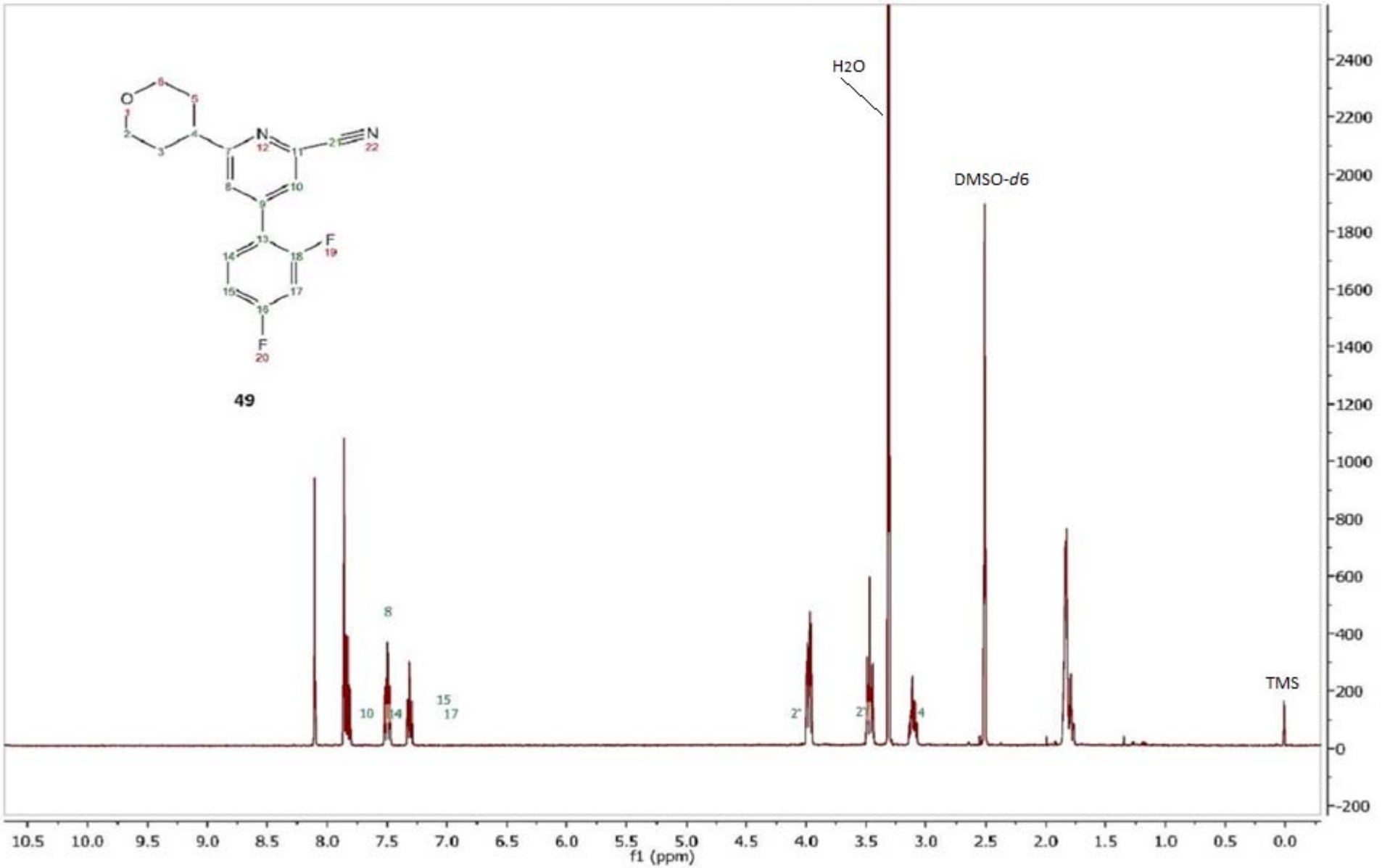
^{1}H NMR of compound **48** in DMSO-*d*6



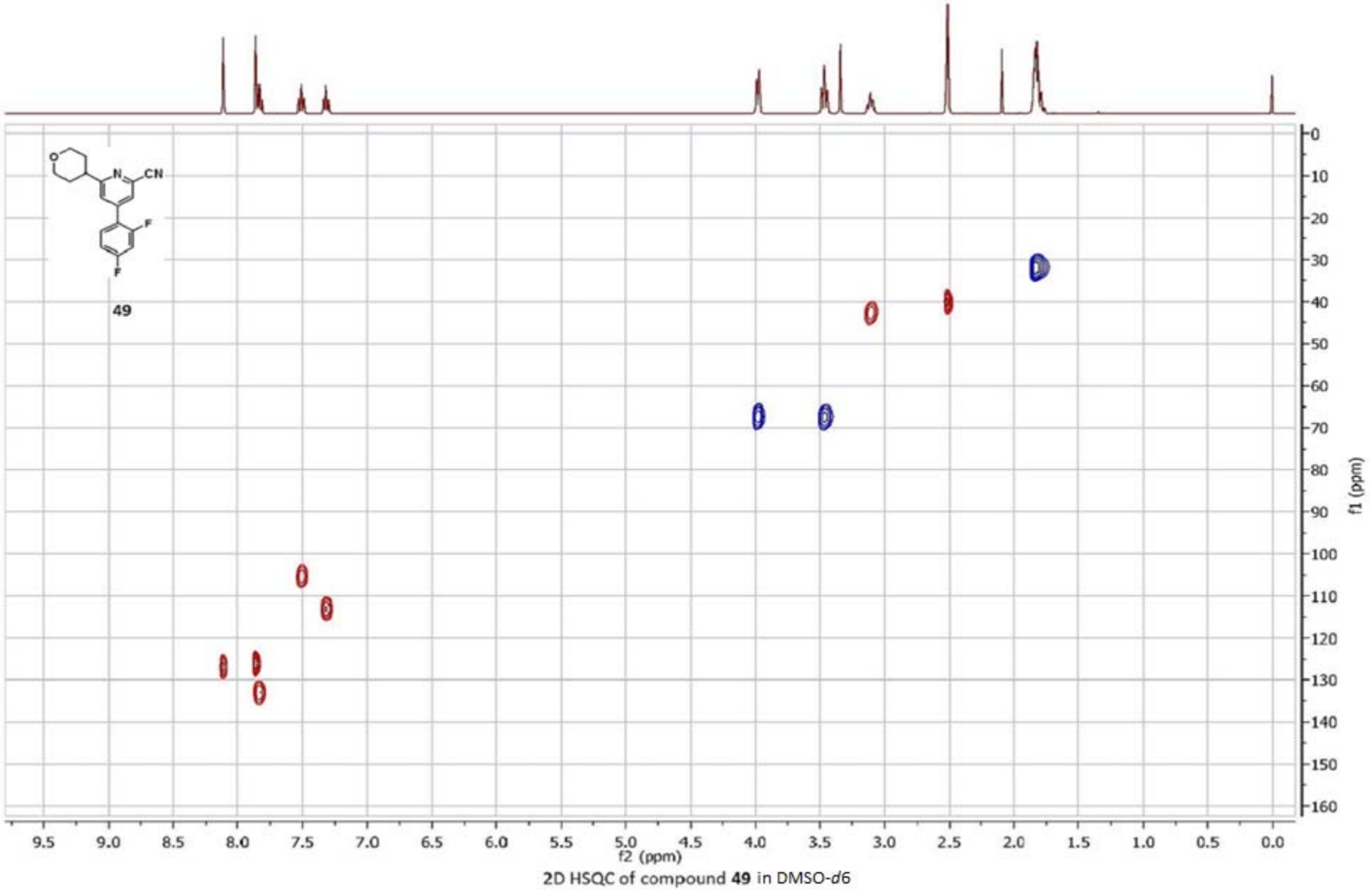
2D HSQC of compound **48** in DMSO-*d*6



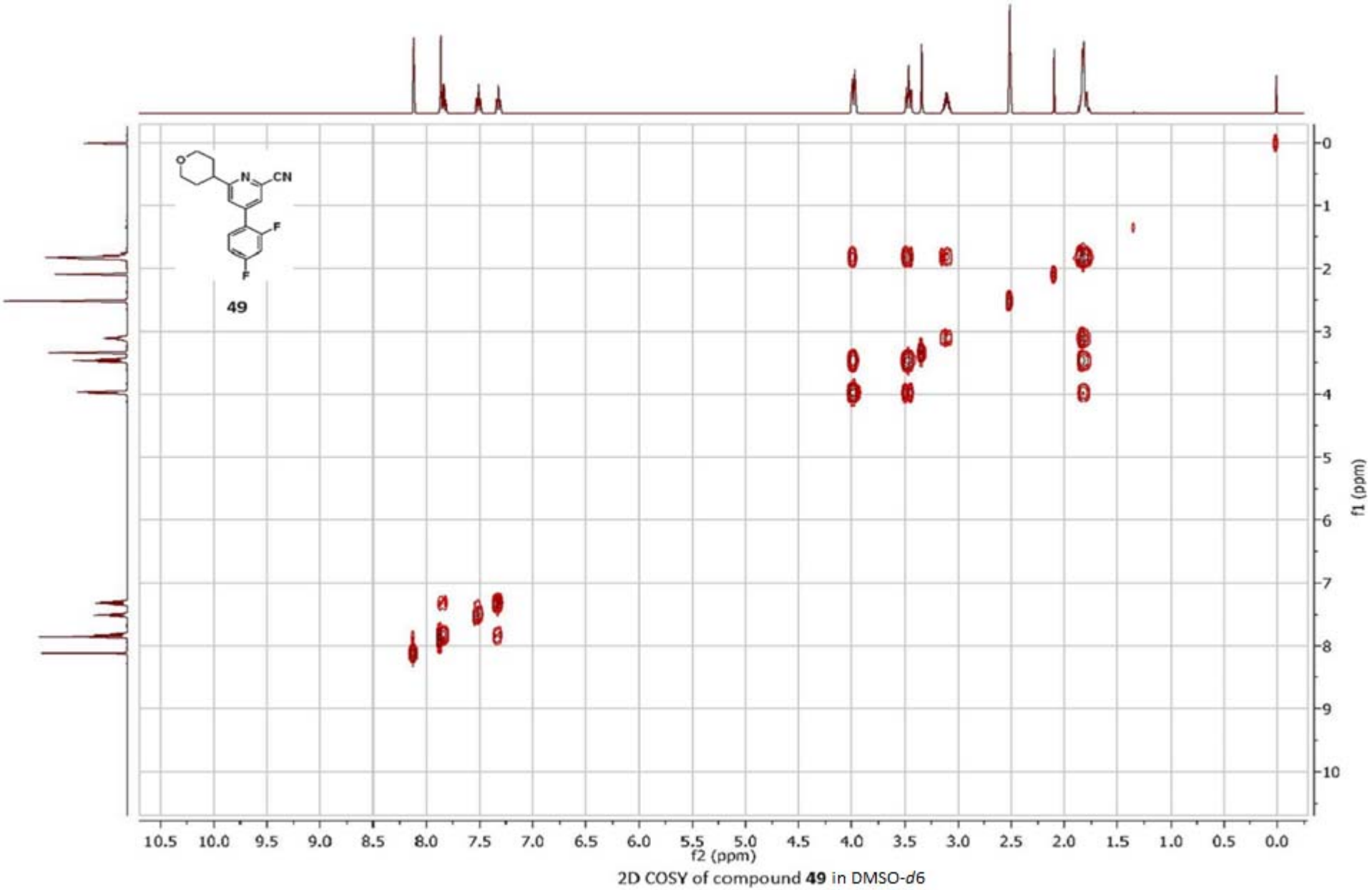
2D COSY of compound **48** in DMSO-*d*6



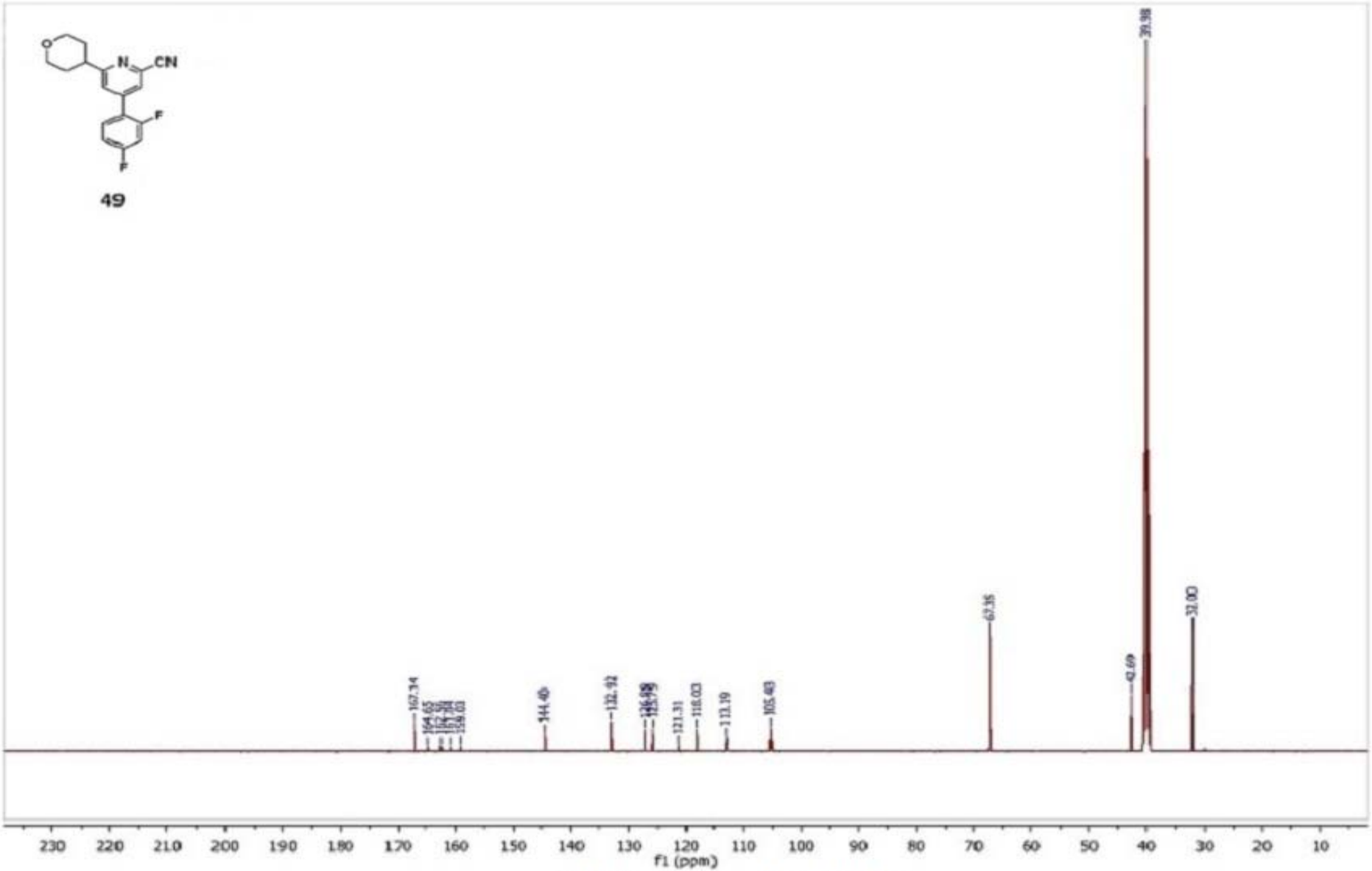
^{1}H NMR of compound **49** in DMSO-*d*6



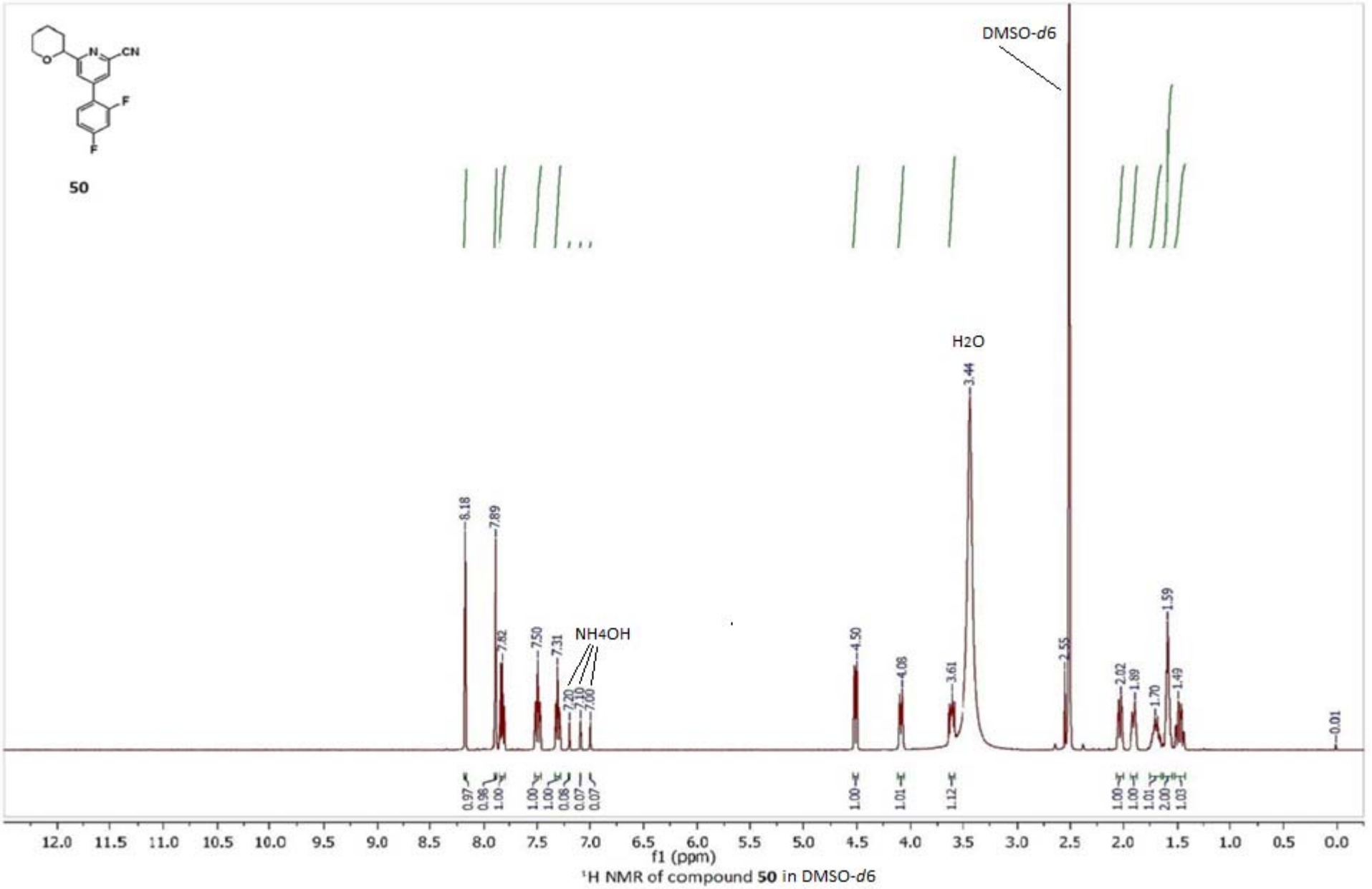
2D HSQC of compound **49** in DMSO-*d6*



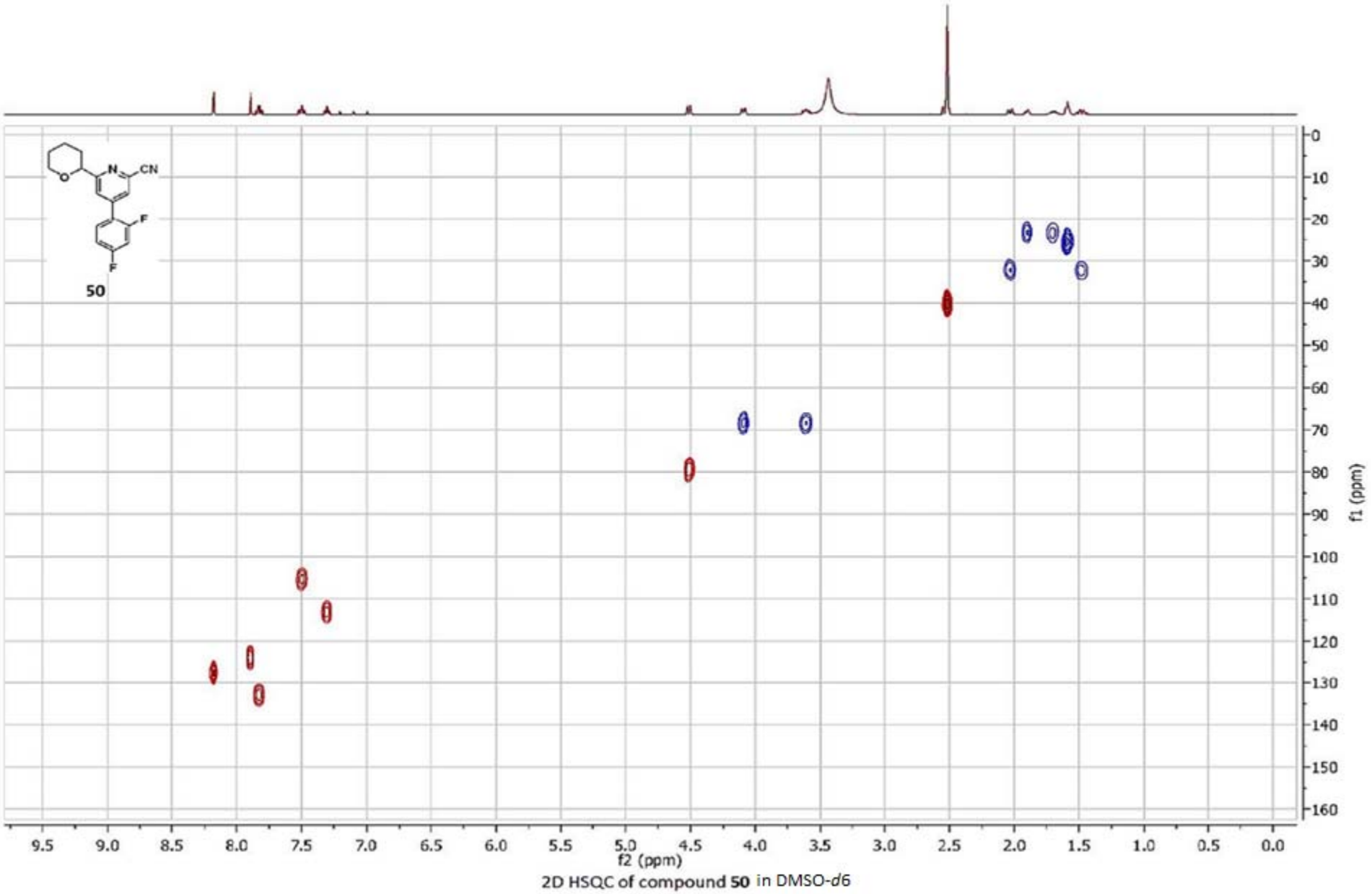
2D COSY of compound **49** in DMSO-*d*6

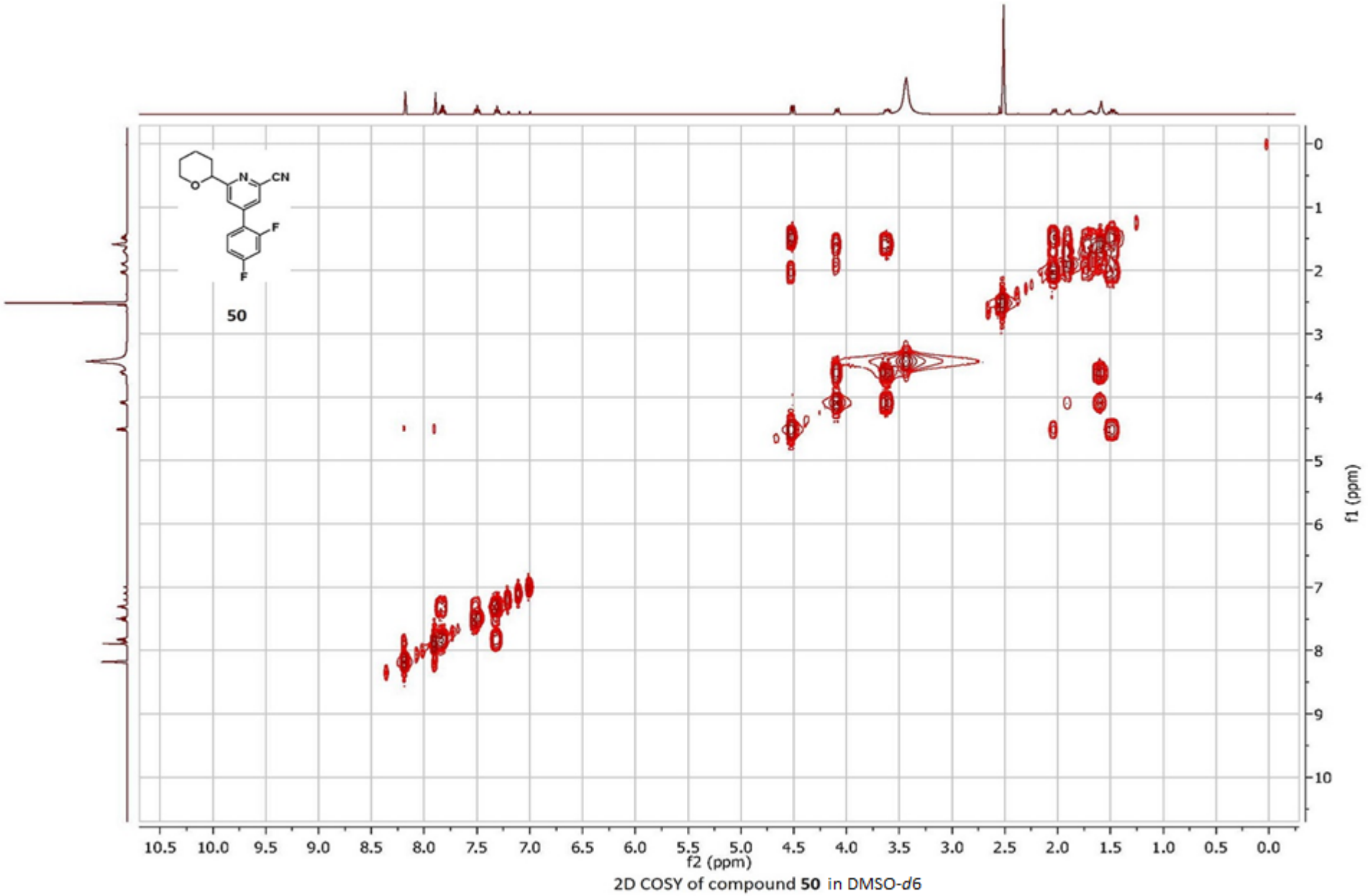


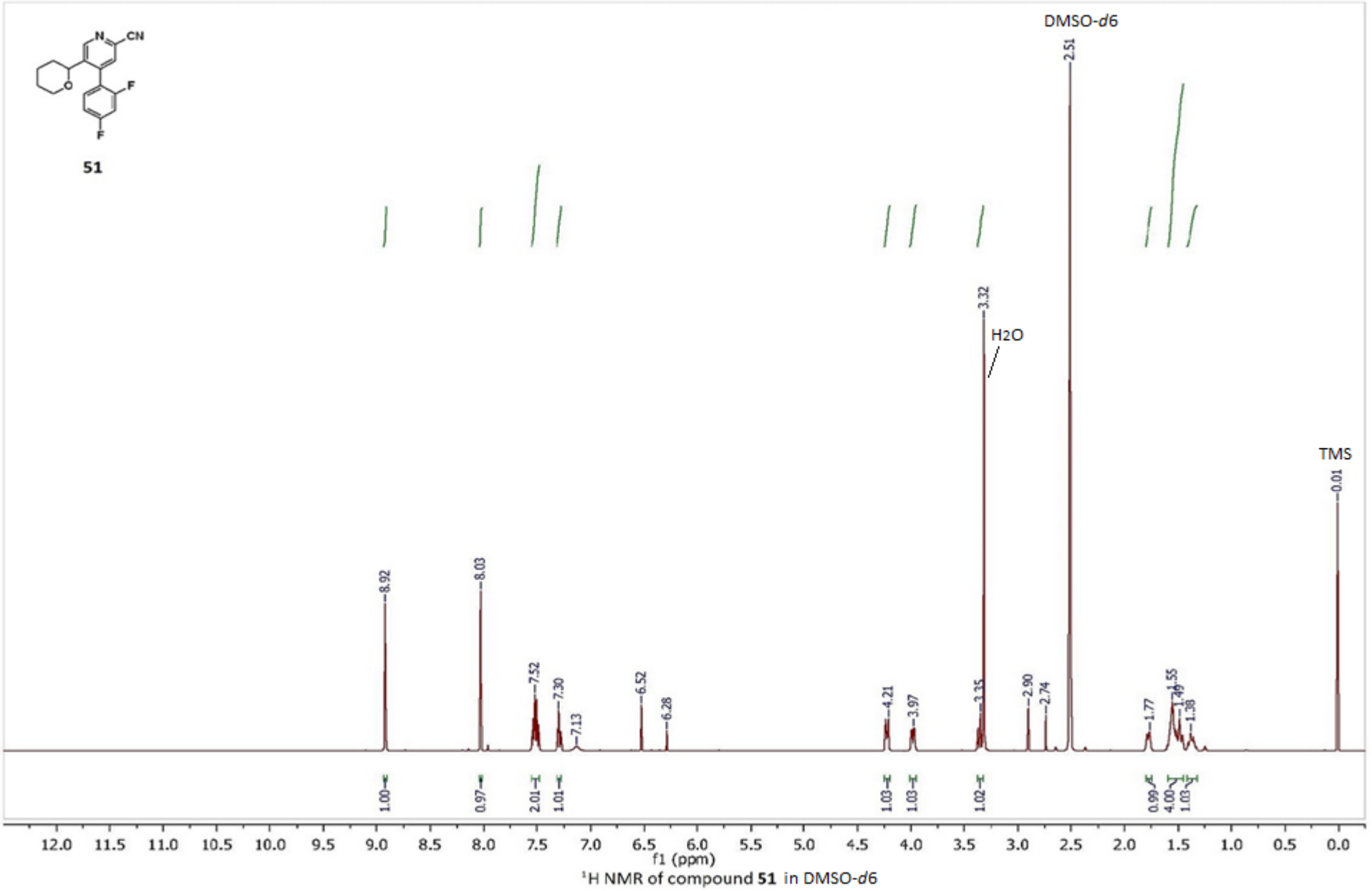
^{13}C NMR of compound **49** in DMSO-*d6*



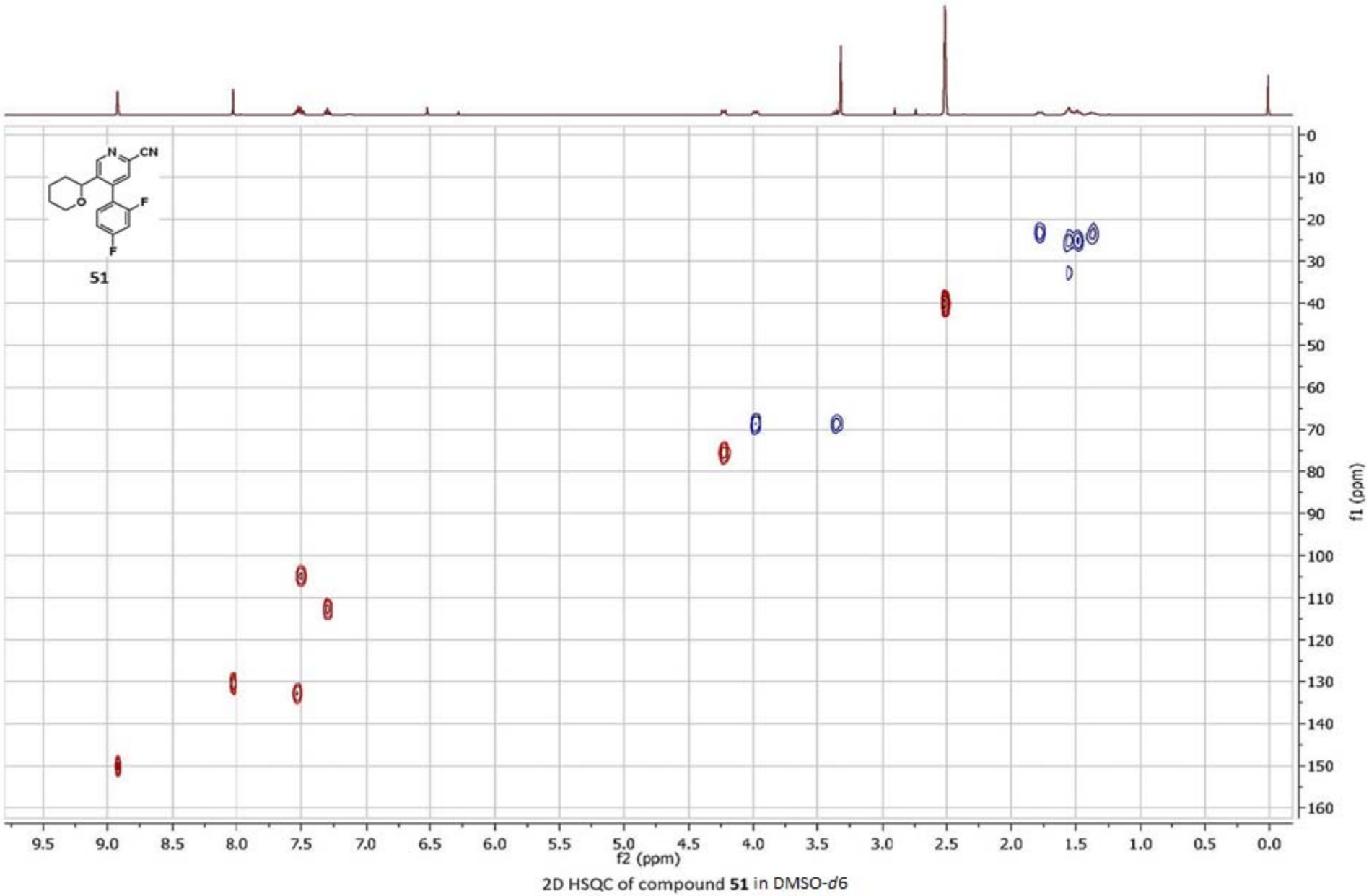
^{1}H NMR of compound **50** in DMSO-*d6*


50
f2 (ppm)
f1 (ppm)
2D HSQC of compound 50 in DMSO-d6

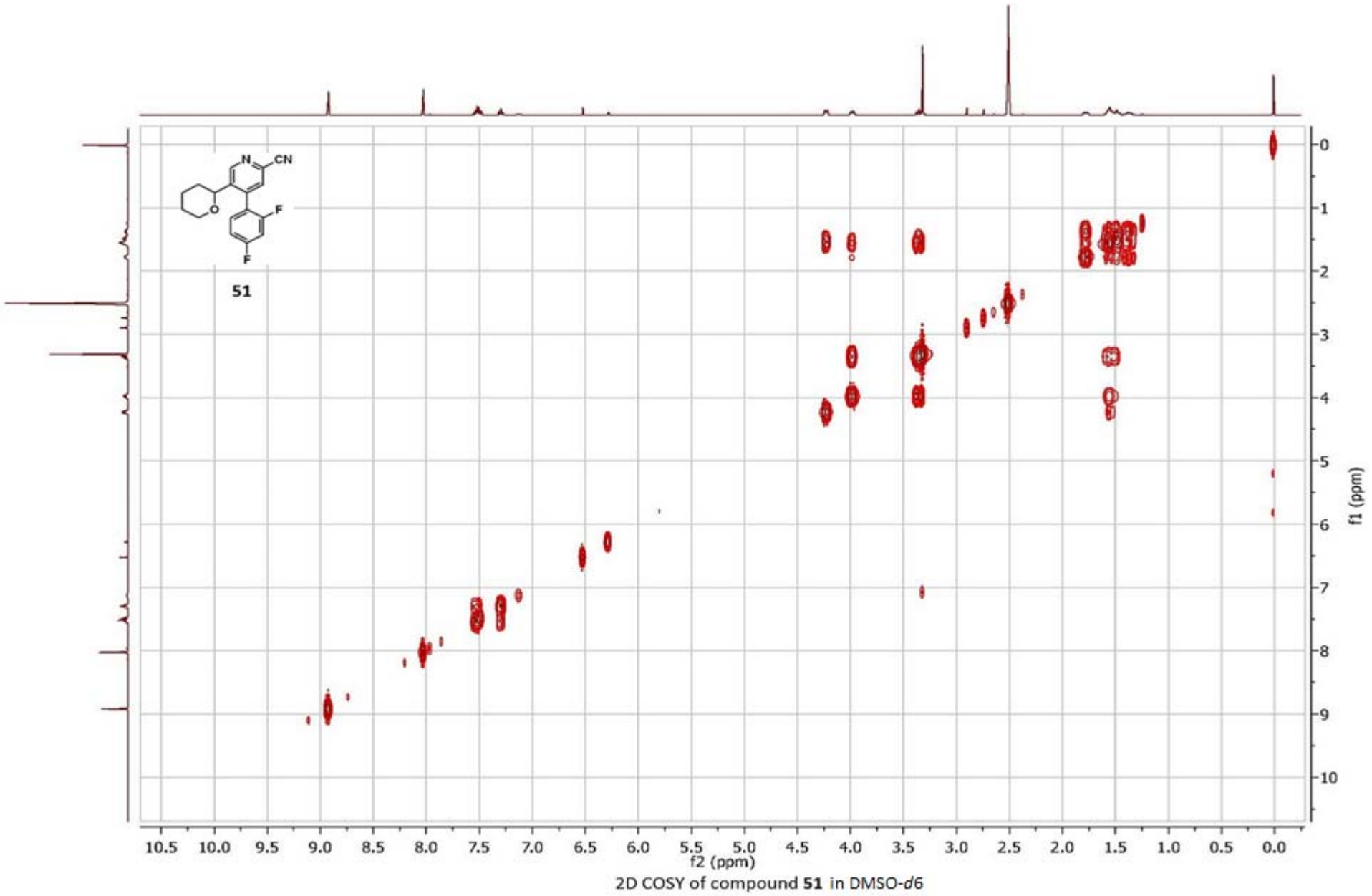

50
f2 (ppm)
f1 (ppm)
2D COSY of compound 50 in DMSO-d6



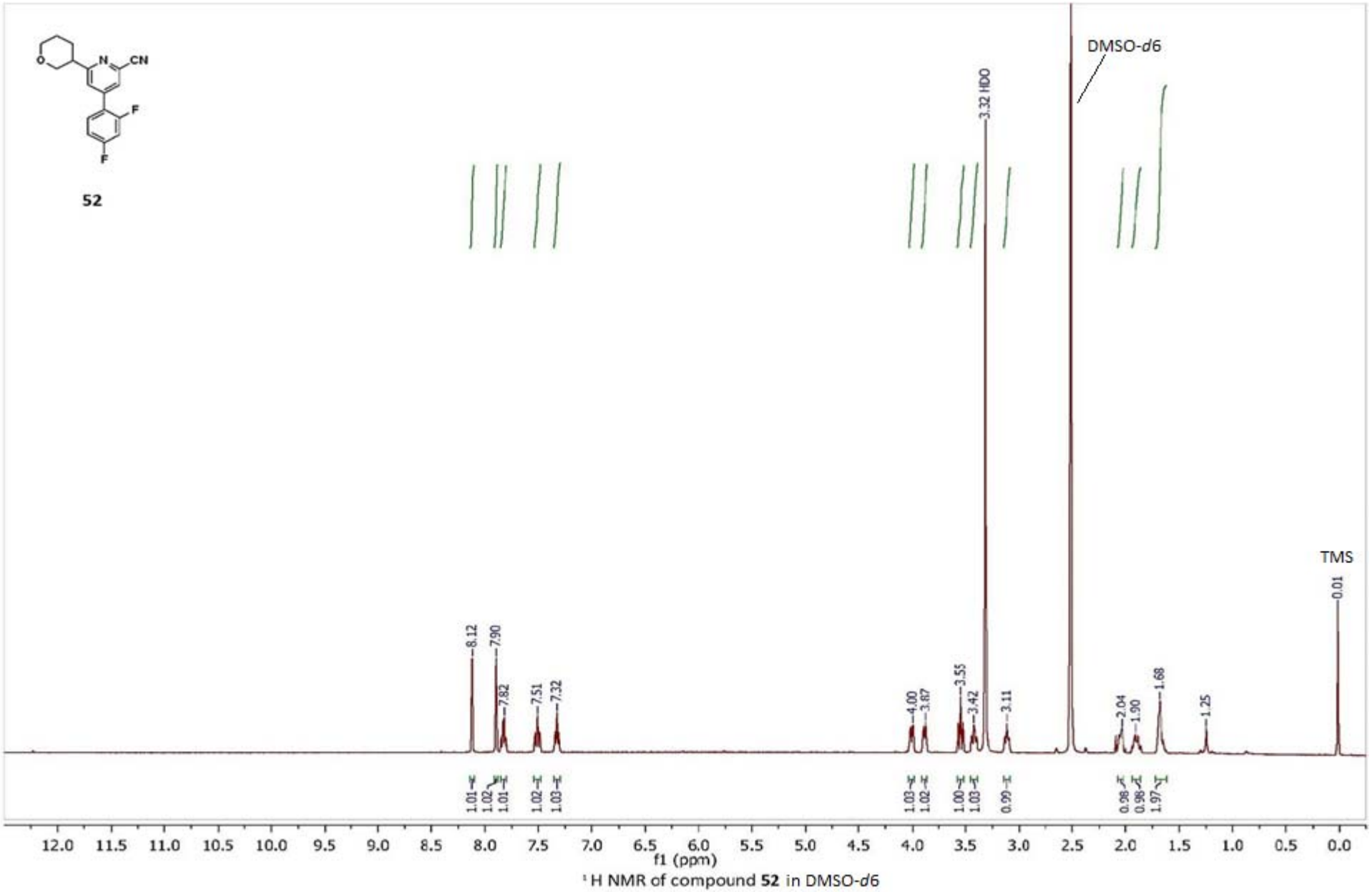
^{1}H NMR of compound **51** in DMSO-*d*6



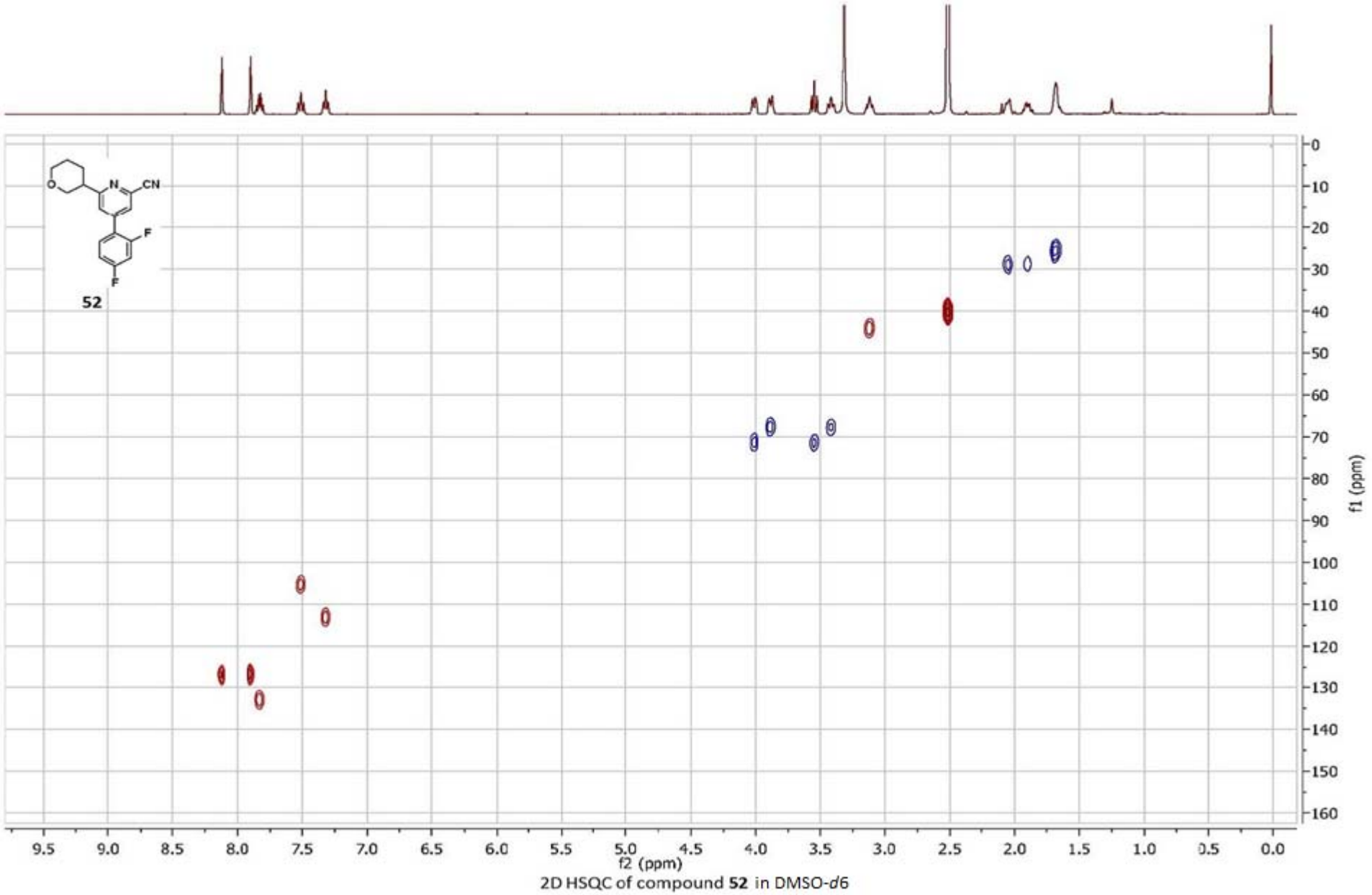
2D HSQC of compound **51** in DMSO-*d*6

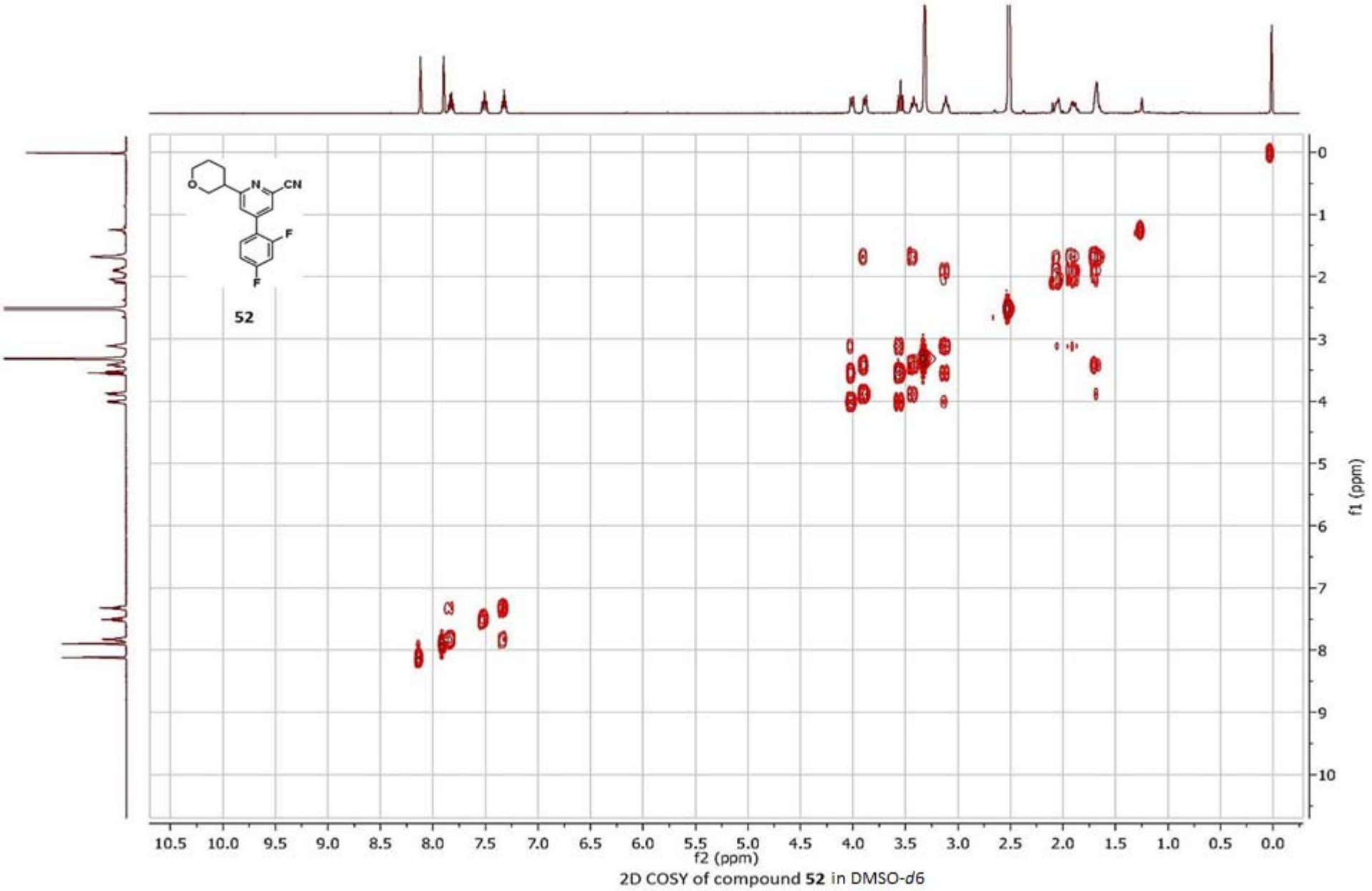


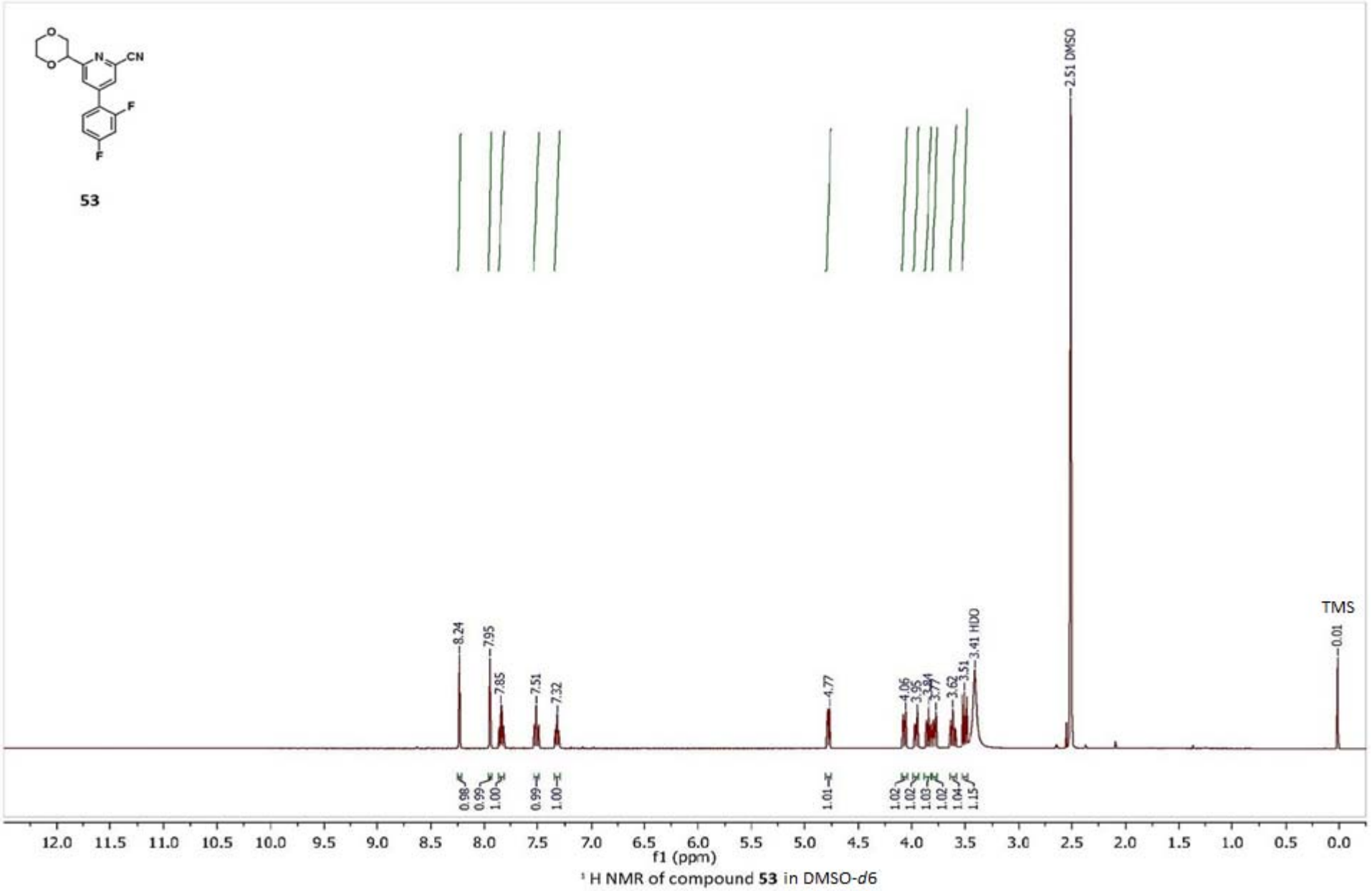
2D COSY of compound **51** in DMSO-*d6*



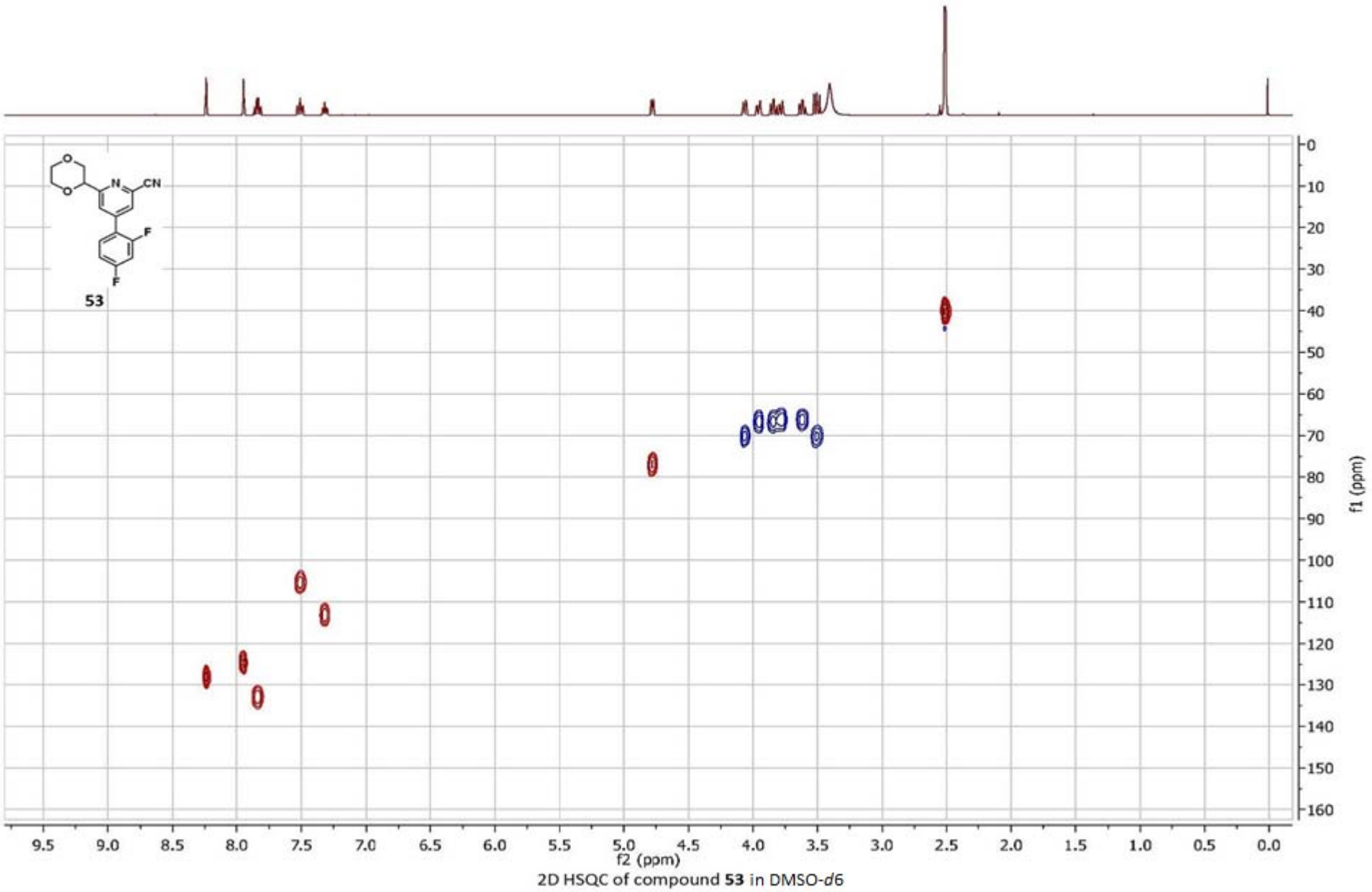
^{1}H NMR of compound **52** in DMSO-*d*6

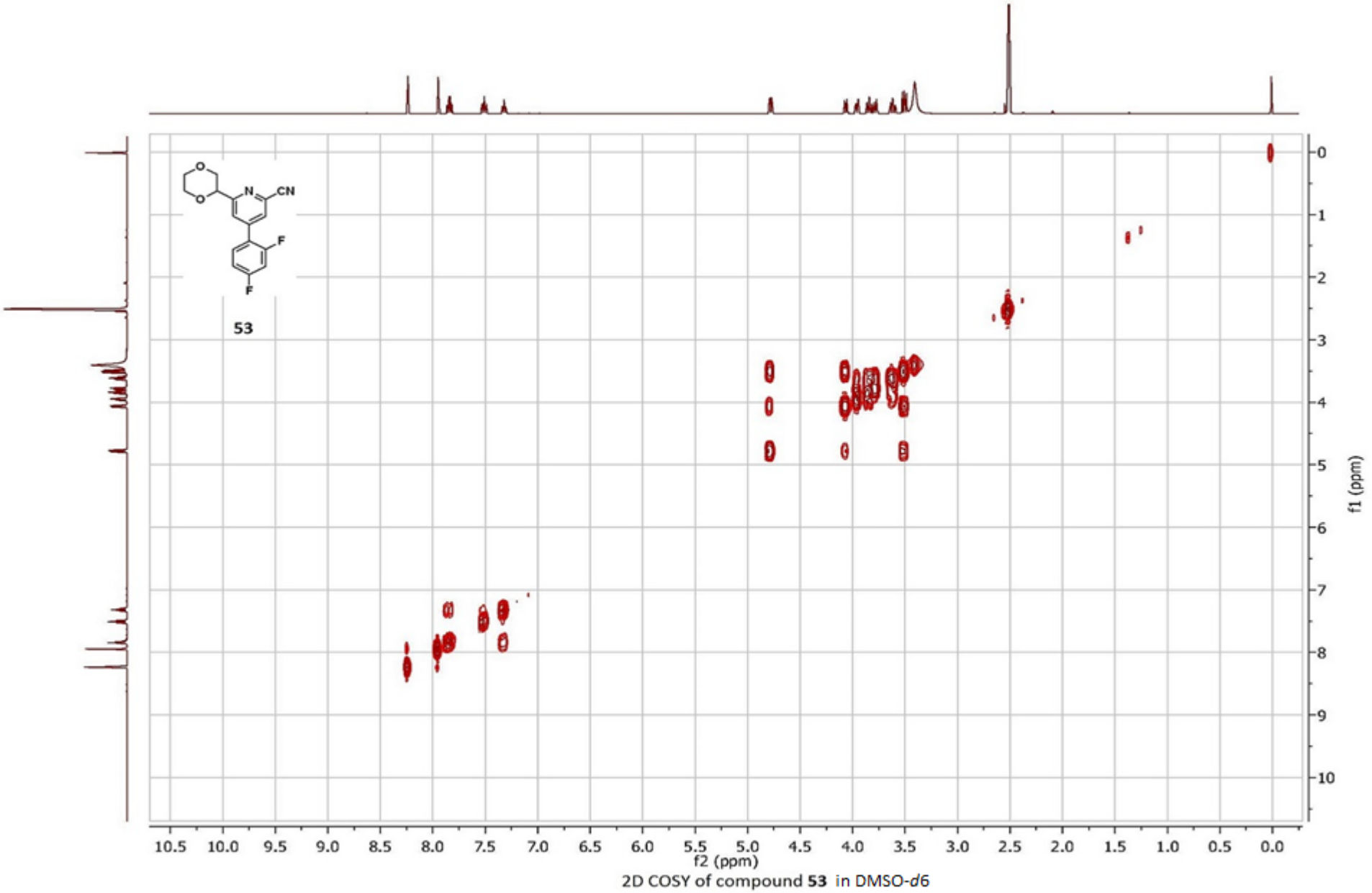

52
f2 (ppm)
f1 (ppm)
2D HSQC of compound 52 in DMSO-d6

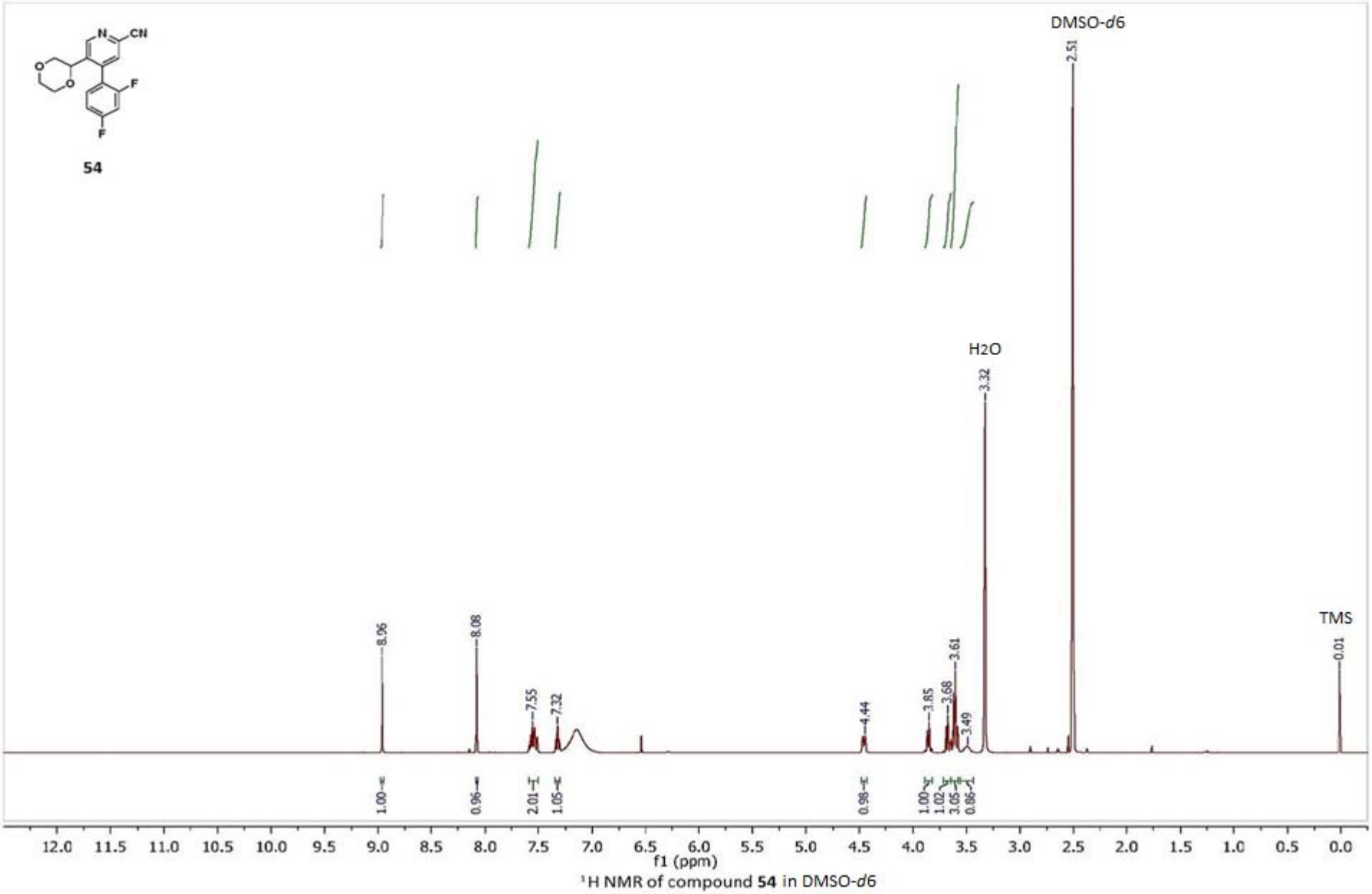

52
f2 (ppm)
f1 (ppm)
2D COSY of compound 52 in DMSO-d6



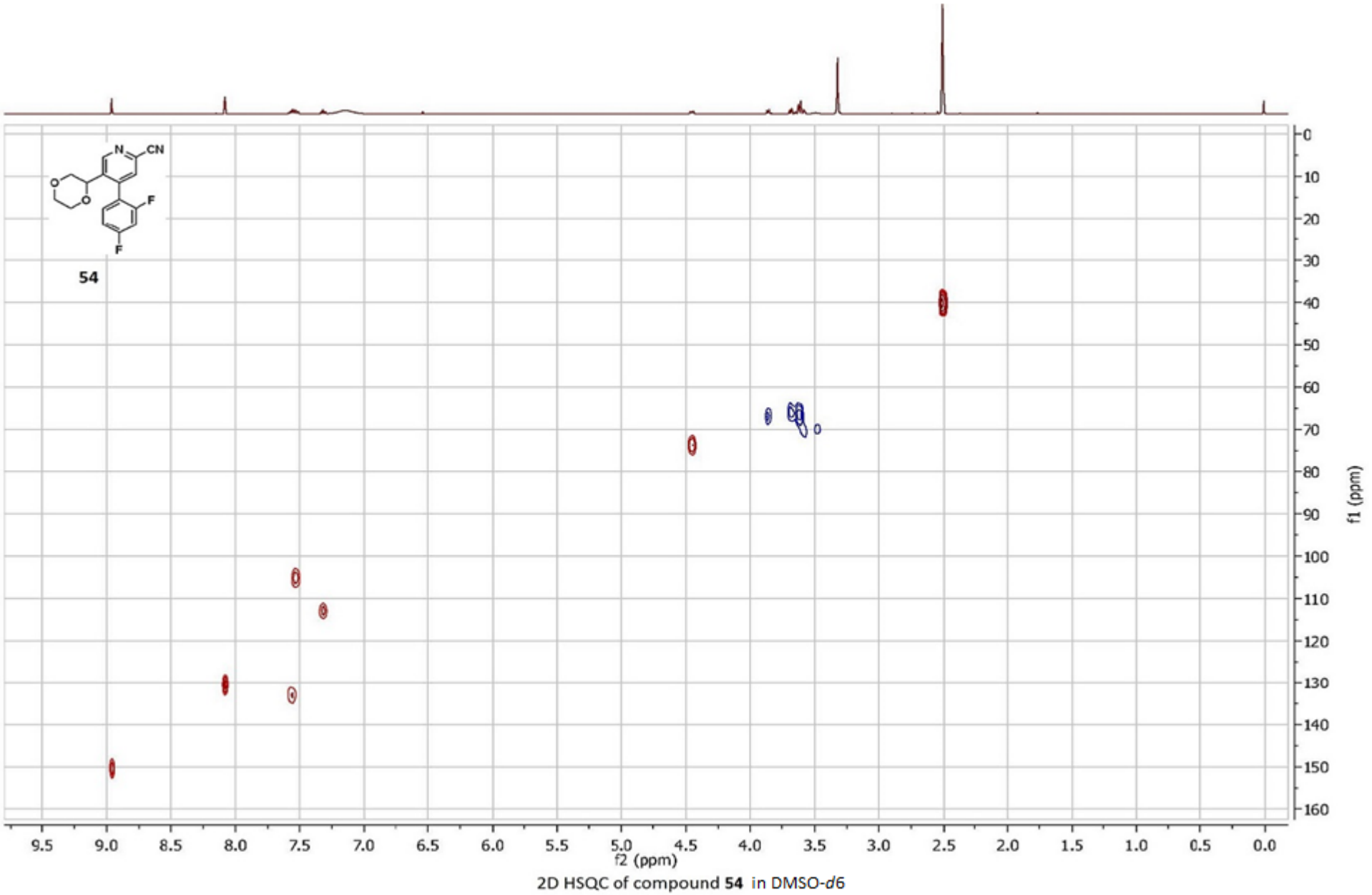
^{1}H NMR of compound **53** in DMSO-*d*6

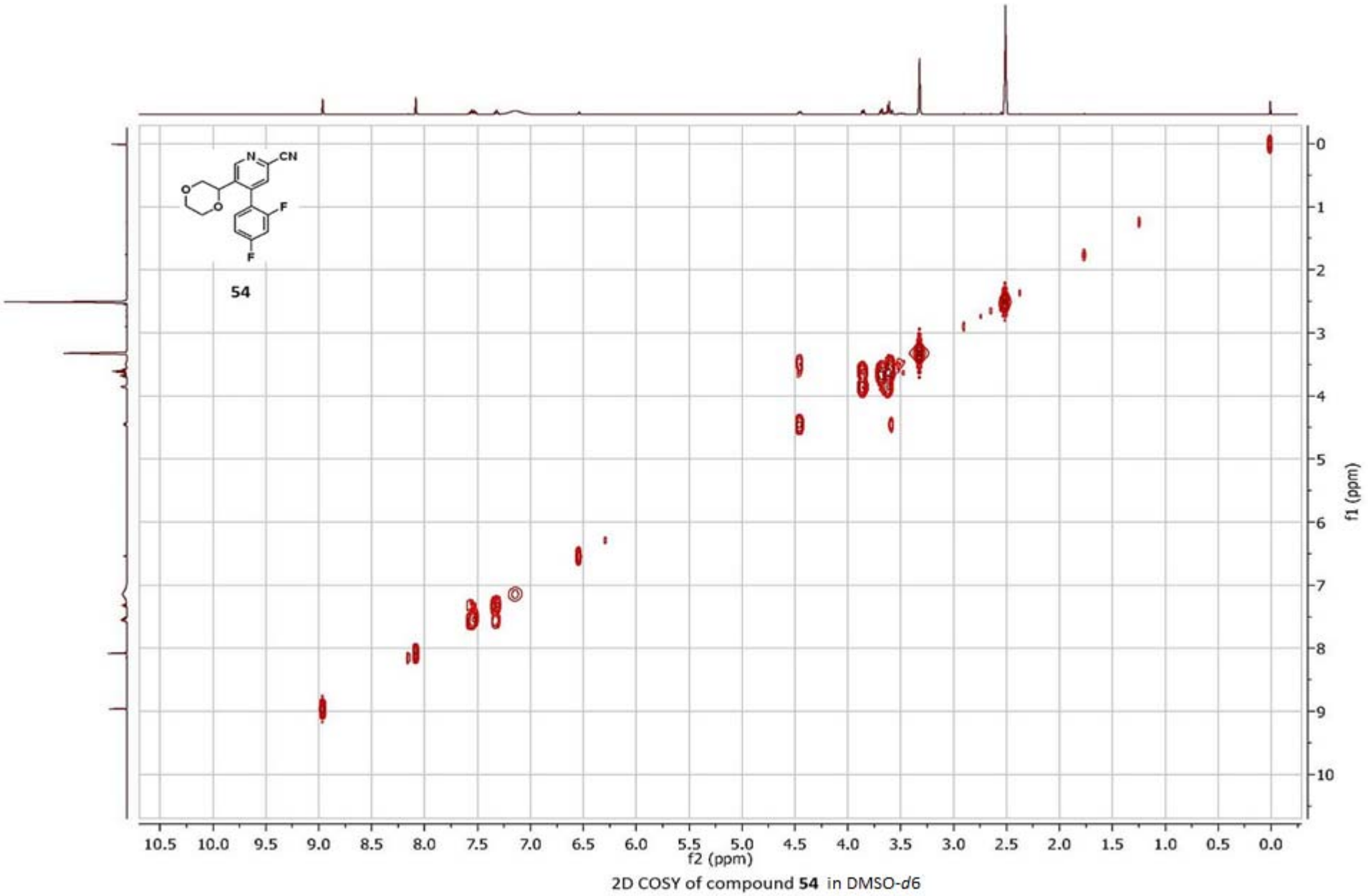

53
f2 (ppm)
f1 (ppm)
2D HSQC of compound 53 in DMSO-d6

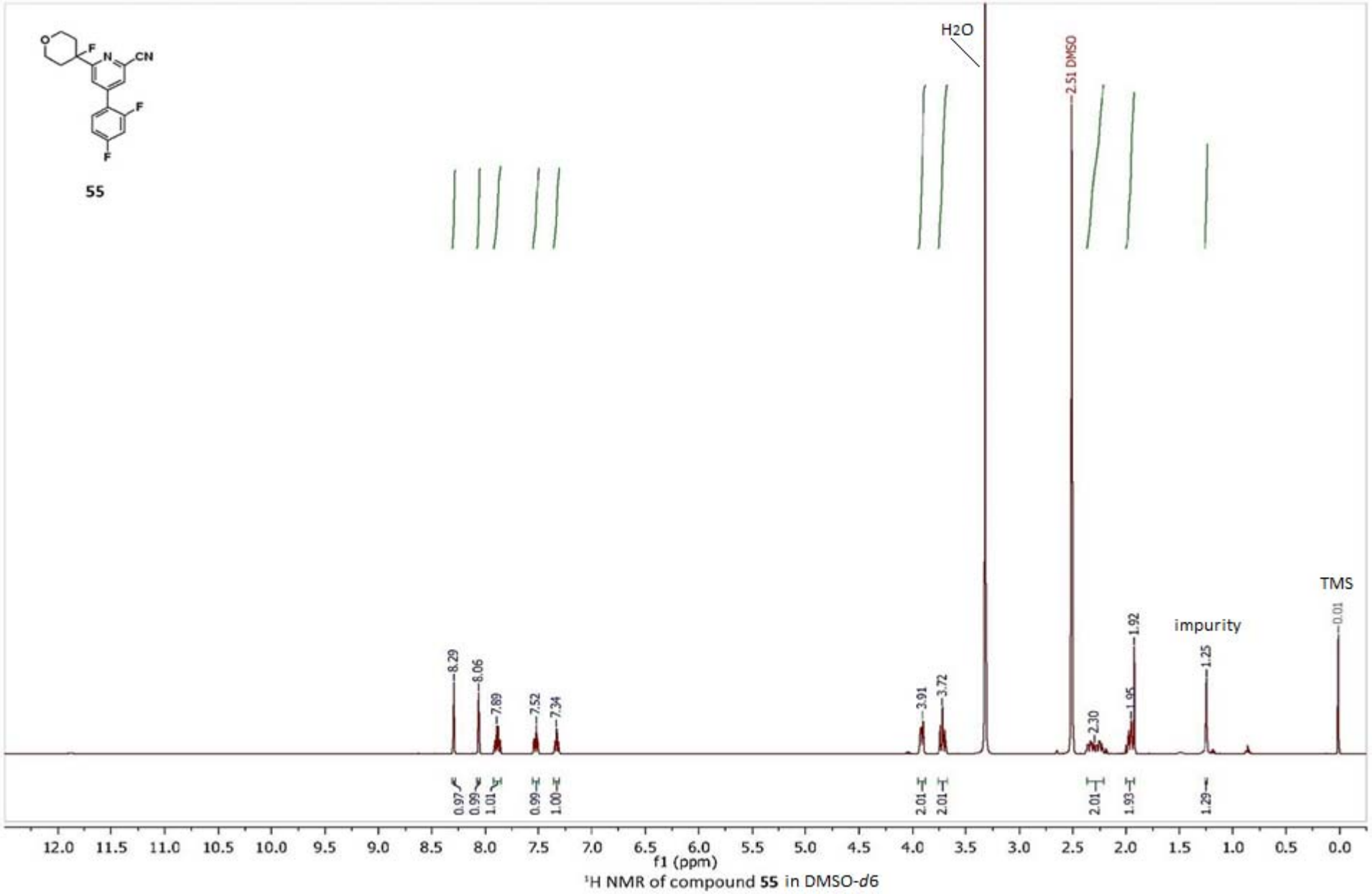

53
f2 (ppm)
f1 (ppm)
2D COSY of compound 53 in DMSO-d6



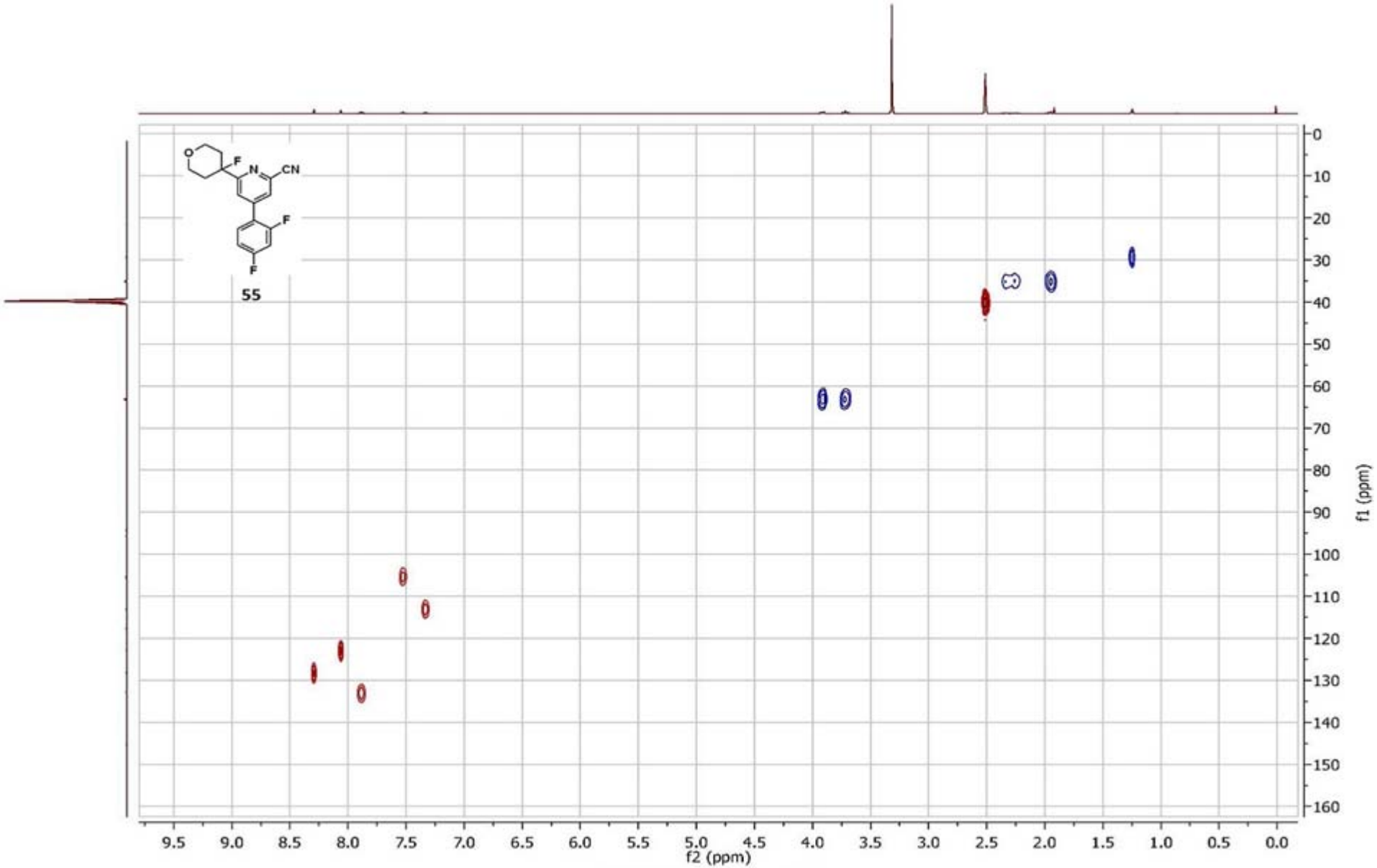
^{1}H NMR of compound **54** in DMSO-*d*6

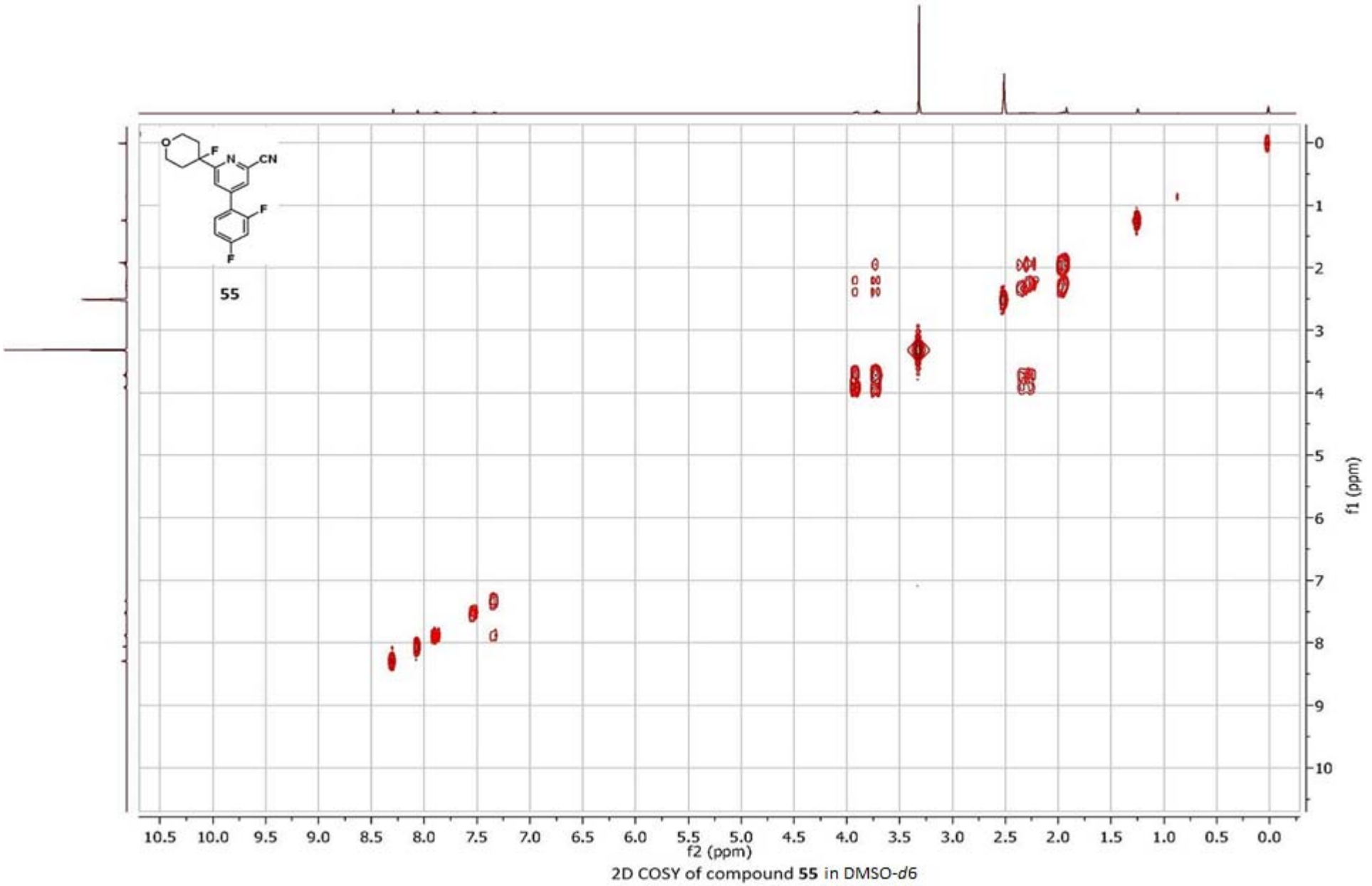

54
f2 (ppm)
f1 (ppm)
2D HSQC of compound 54 in DMSO-d6

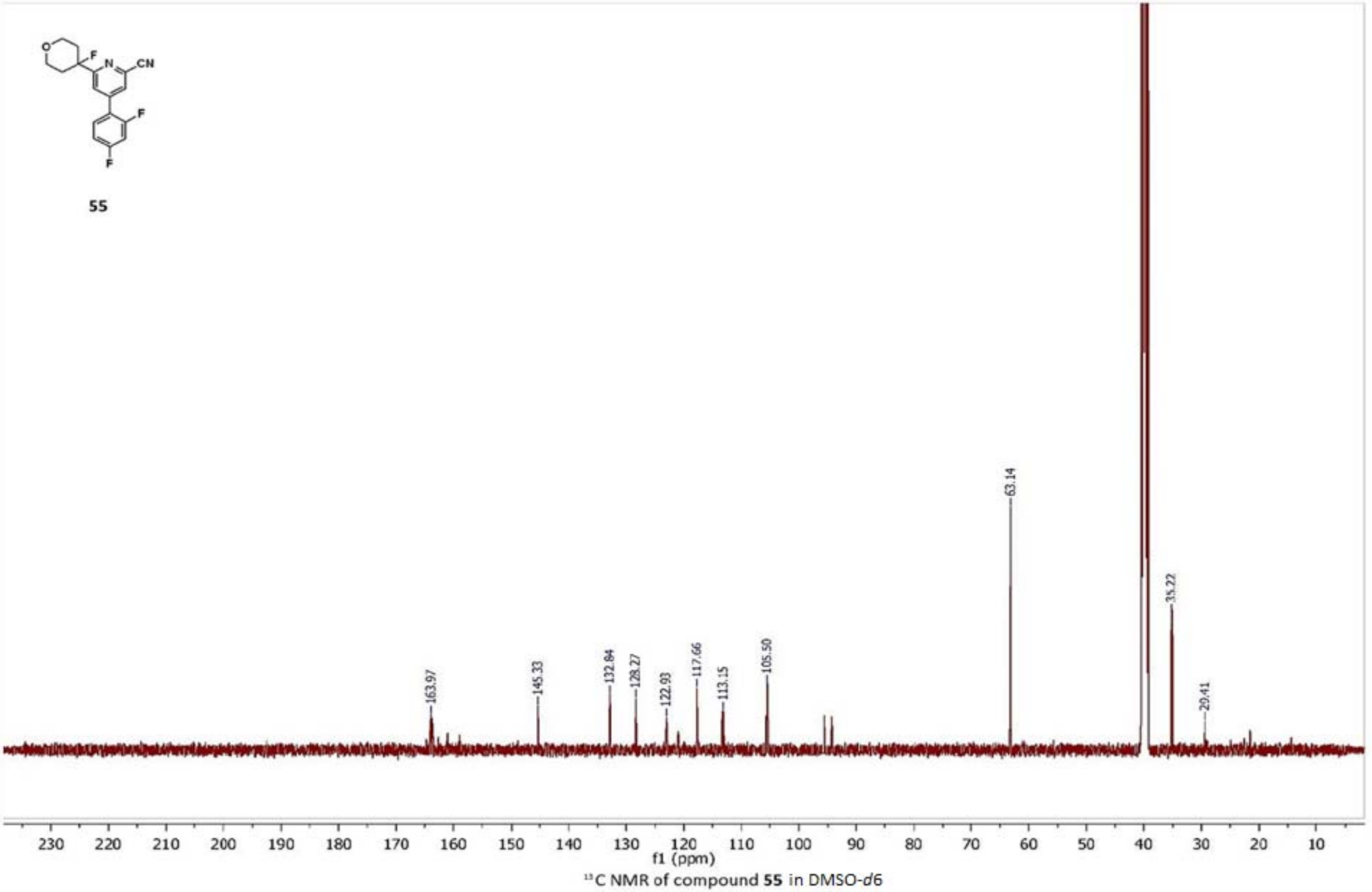

54
f2 (ppm)
f1 (ppm)
2D COSY of compound 54 in DMSO-d6



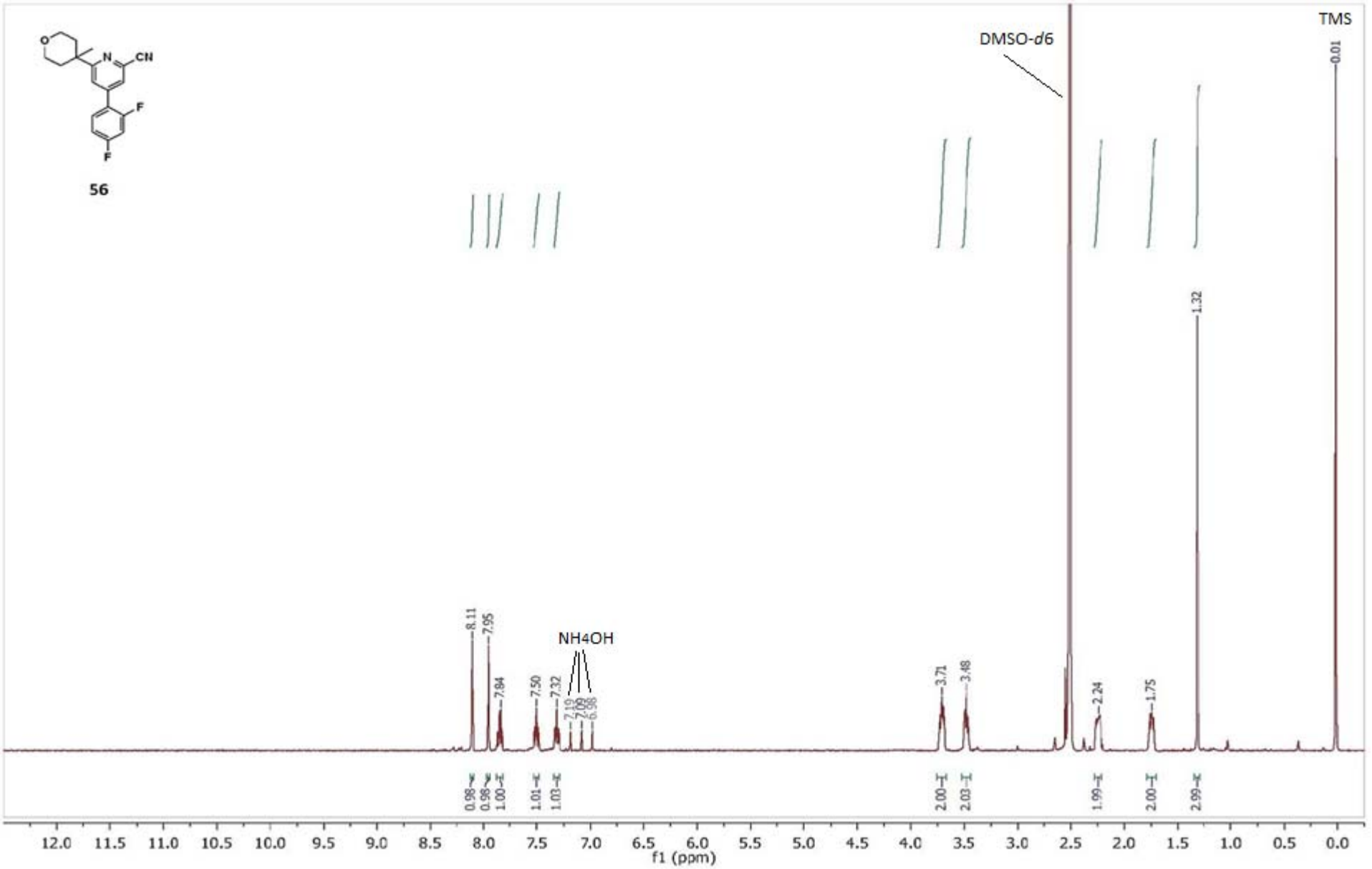
^{1}H NMR of compound **55** in DMSO-*d*6


55
f2 (ppm)
f1 (ppm)
2D HSQC of compound 55 in DMSO-d6

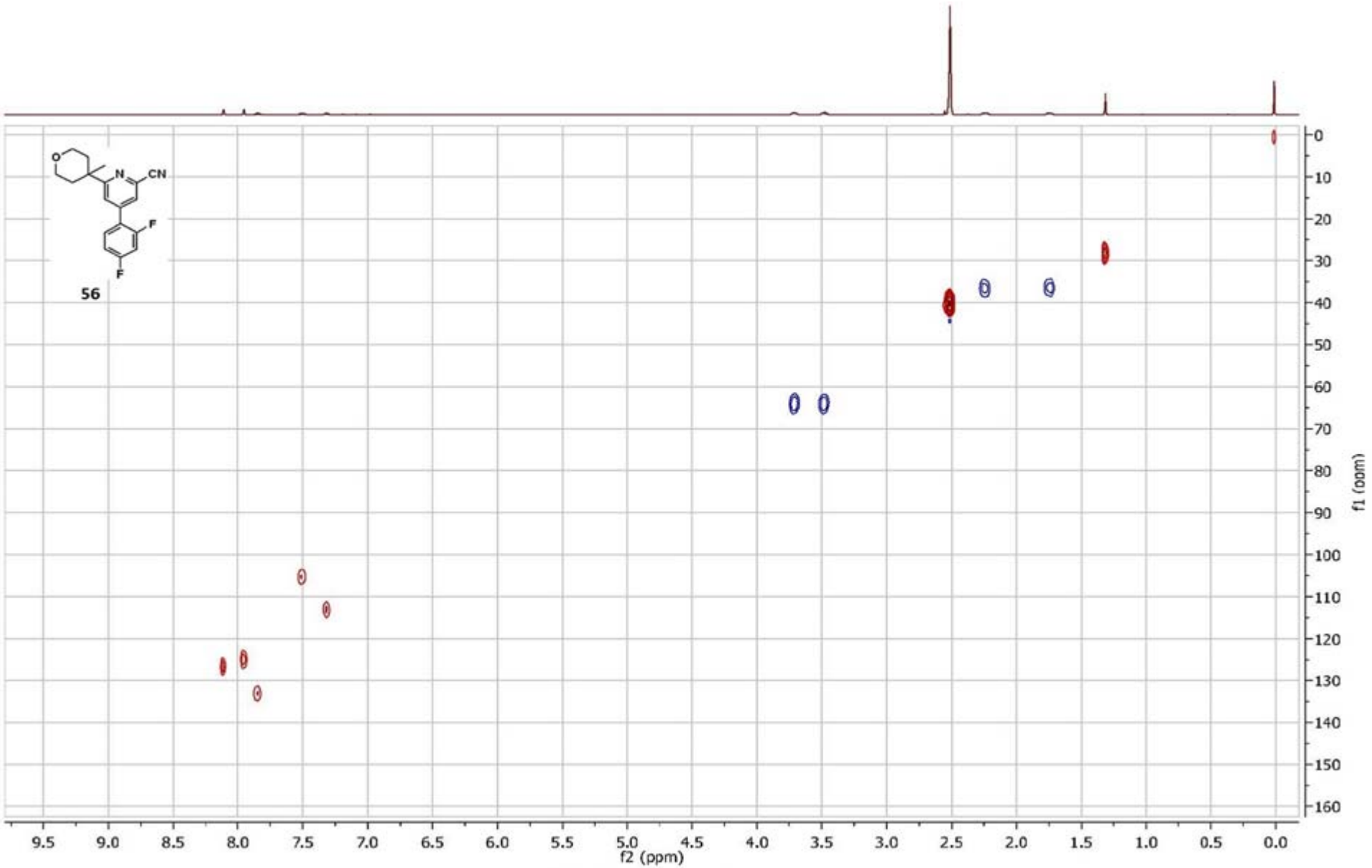

55
f2 (ppm)
f1 (ppm)
2D COSY of compound 55 in DMSO-d6



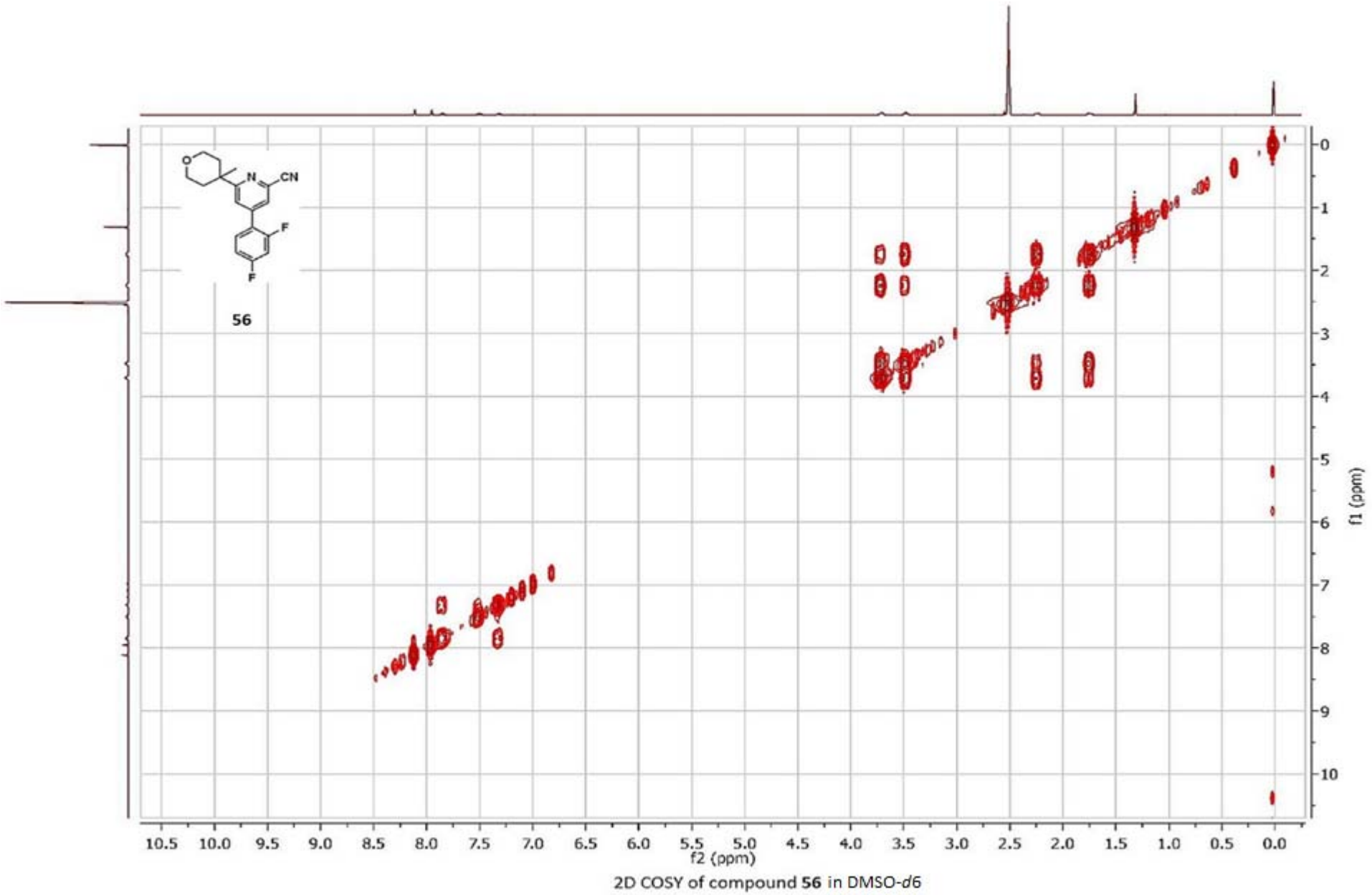
^{13}C NMR of compound **55** in DMSO-*d*6

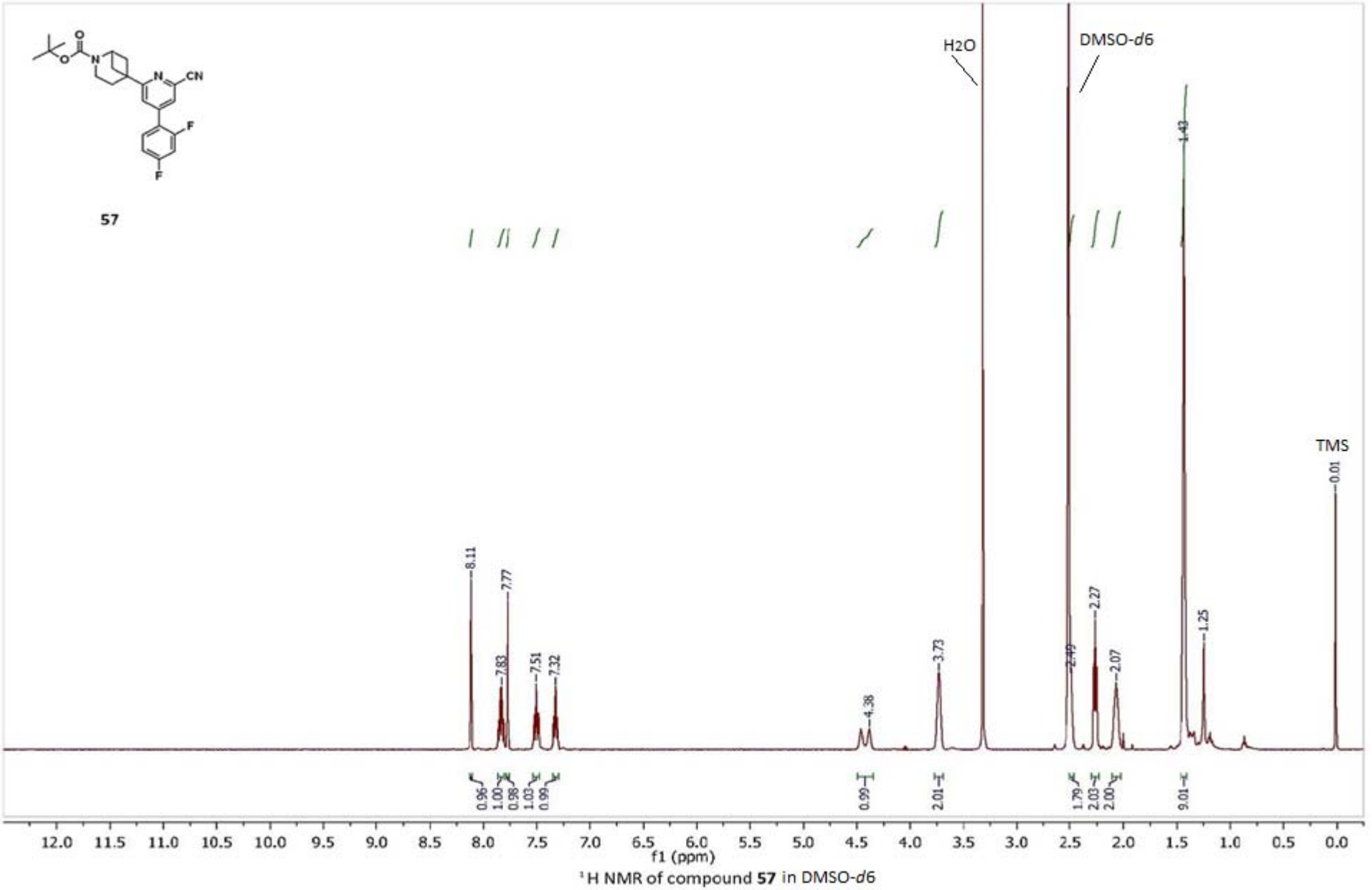


^{1}H NMR of compound **56** in DMSO-*d*6

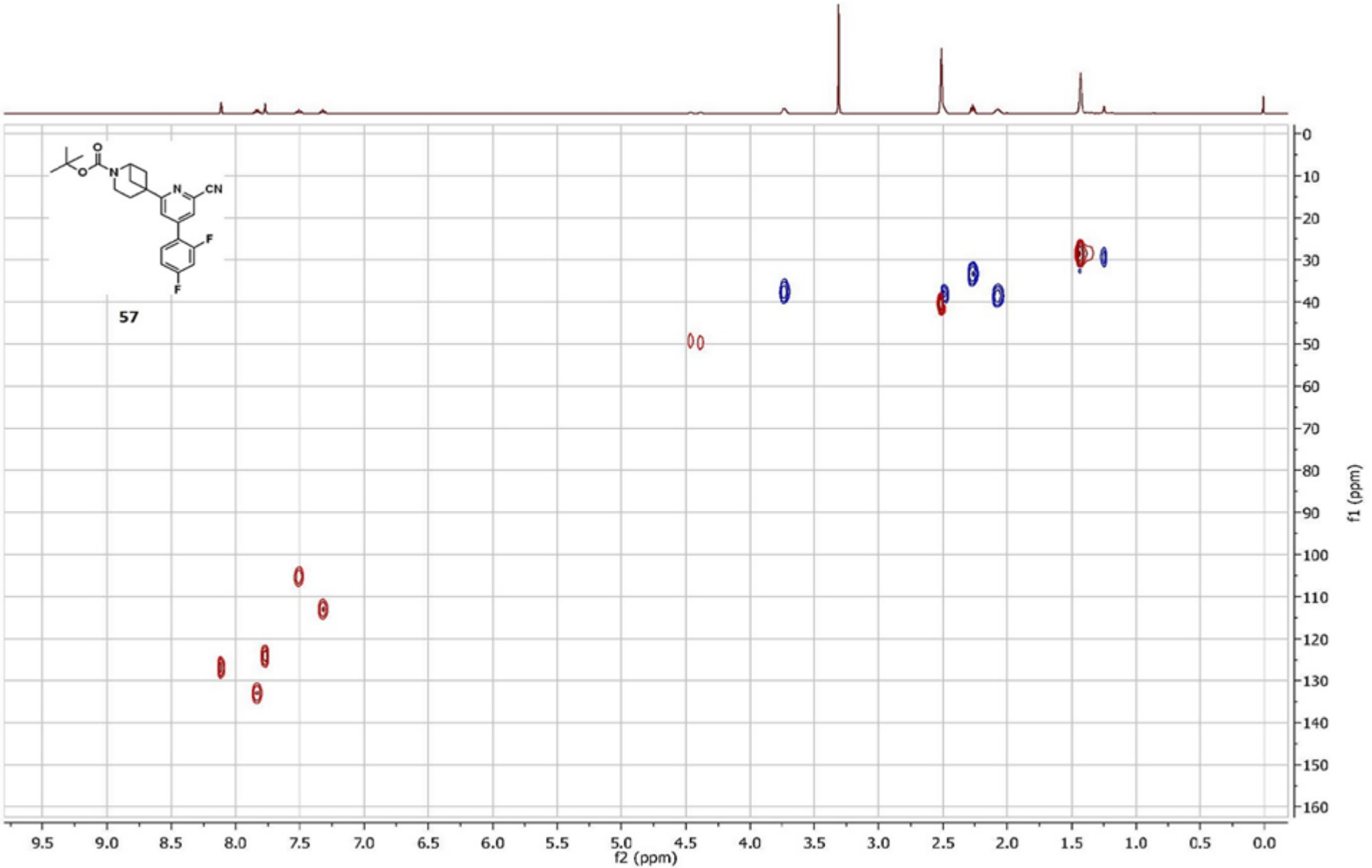


2D HSQC of compound **56** in DMSO-*d*6

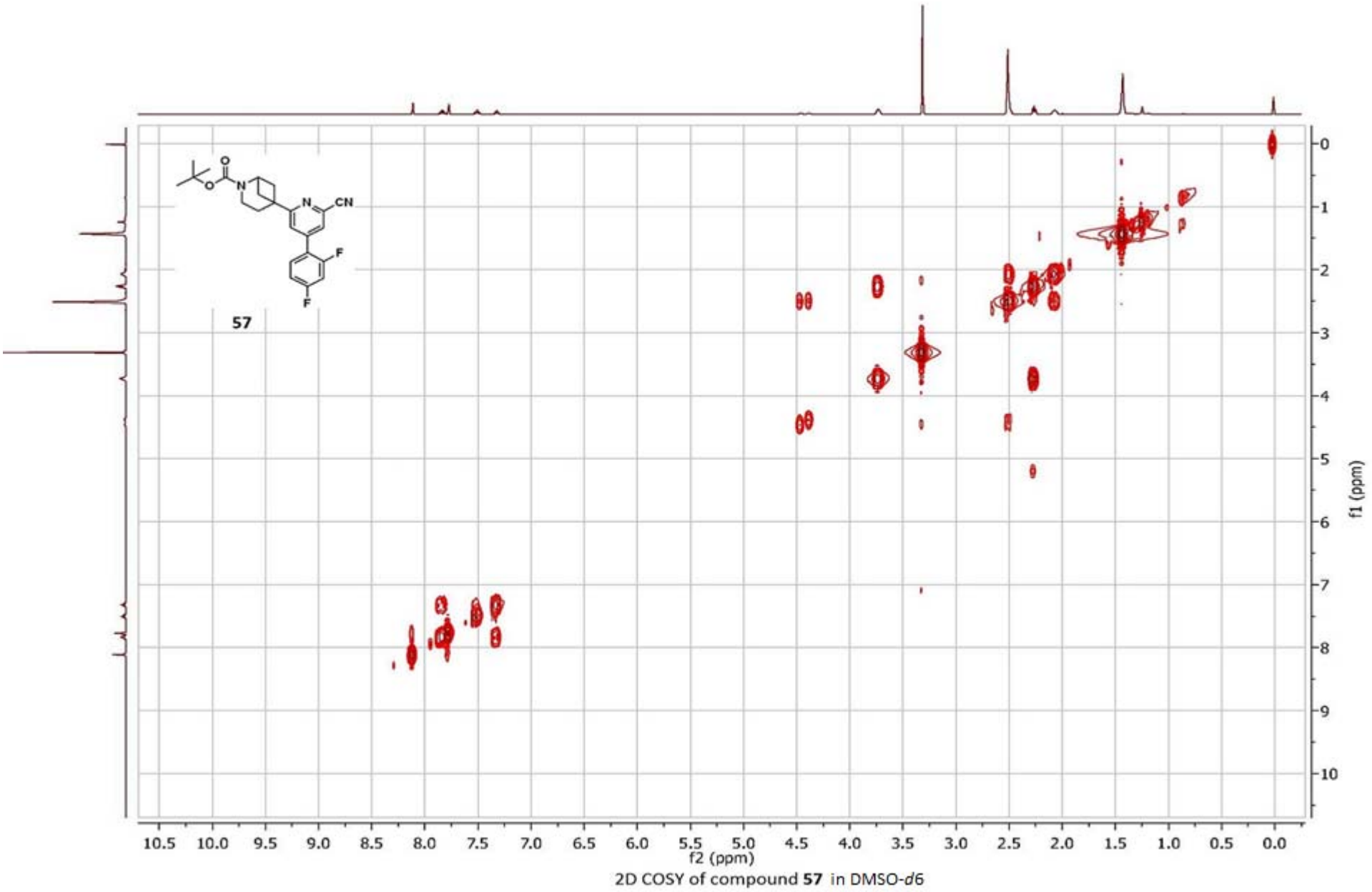

56
f2 (ppm)
f1 (ppm)
2D COSY of compound 56 in DMSO-d6

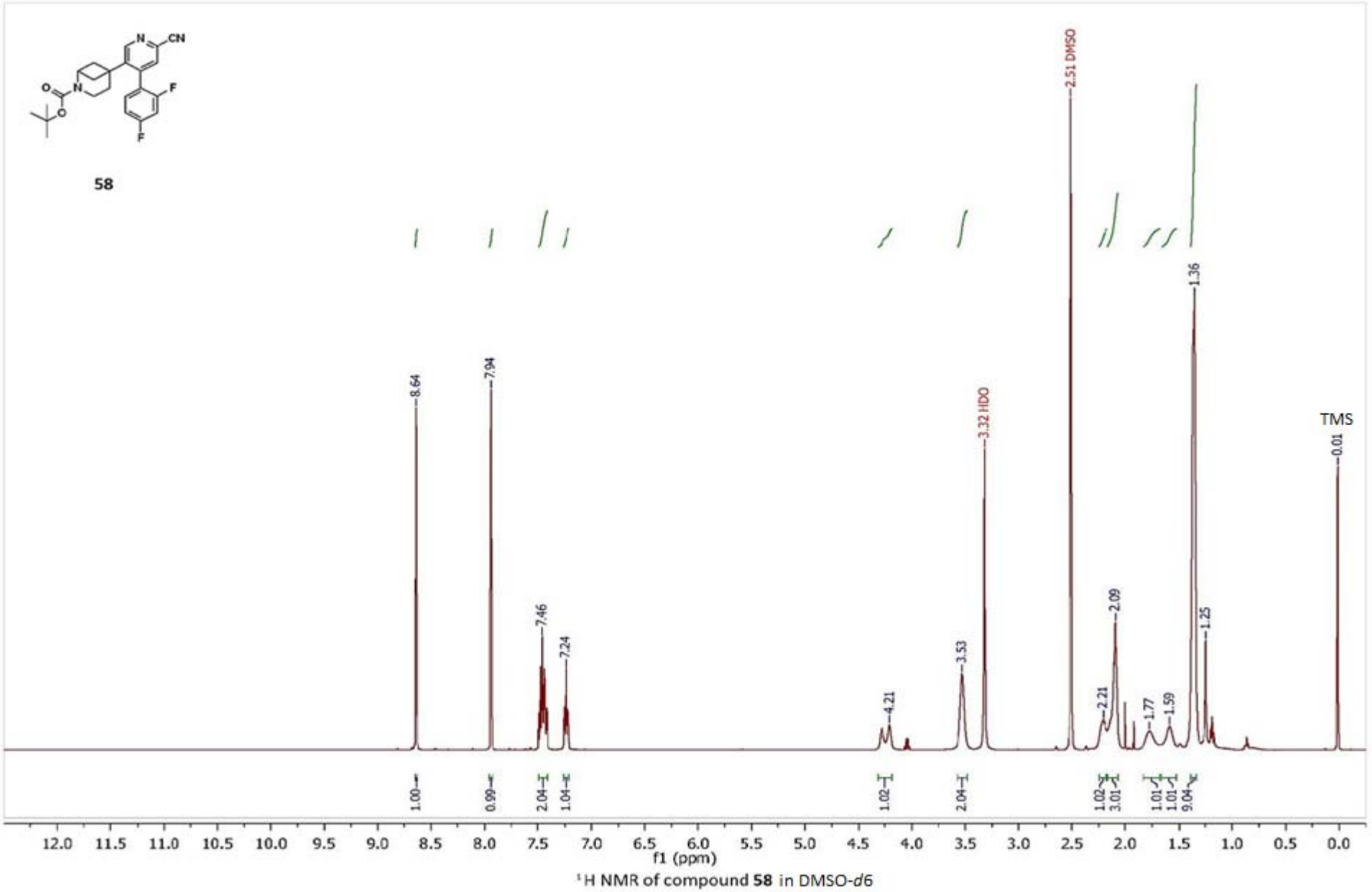


^{1}H NMR of compound **57** in DMSO-*d*6

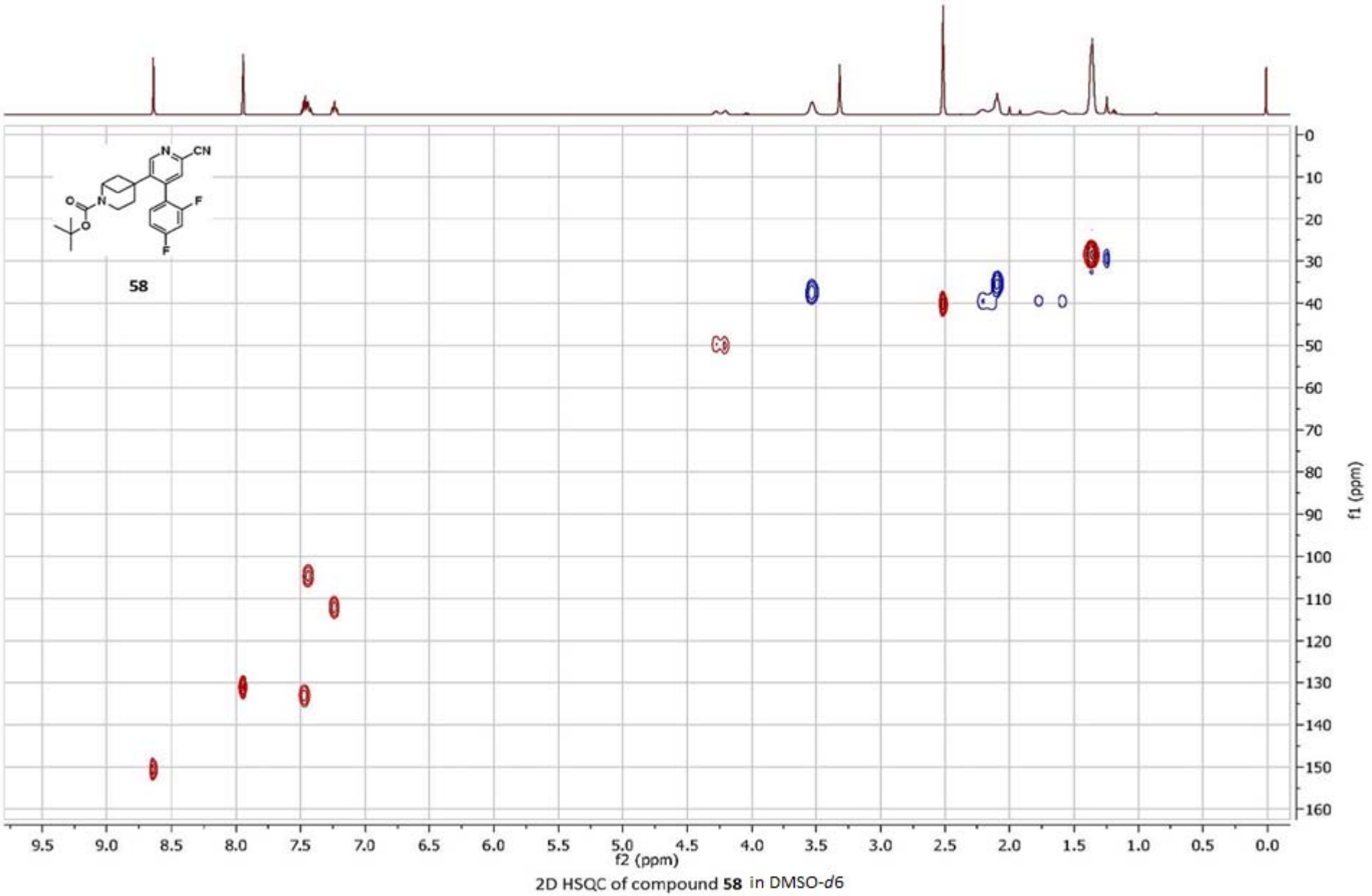


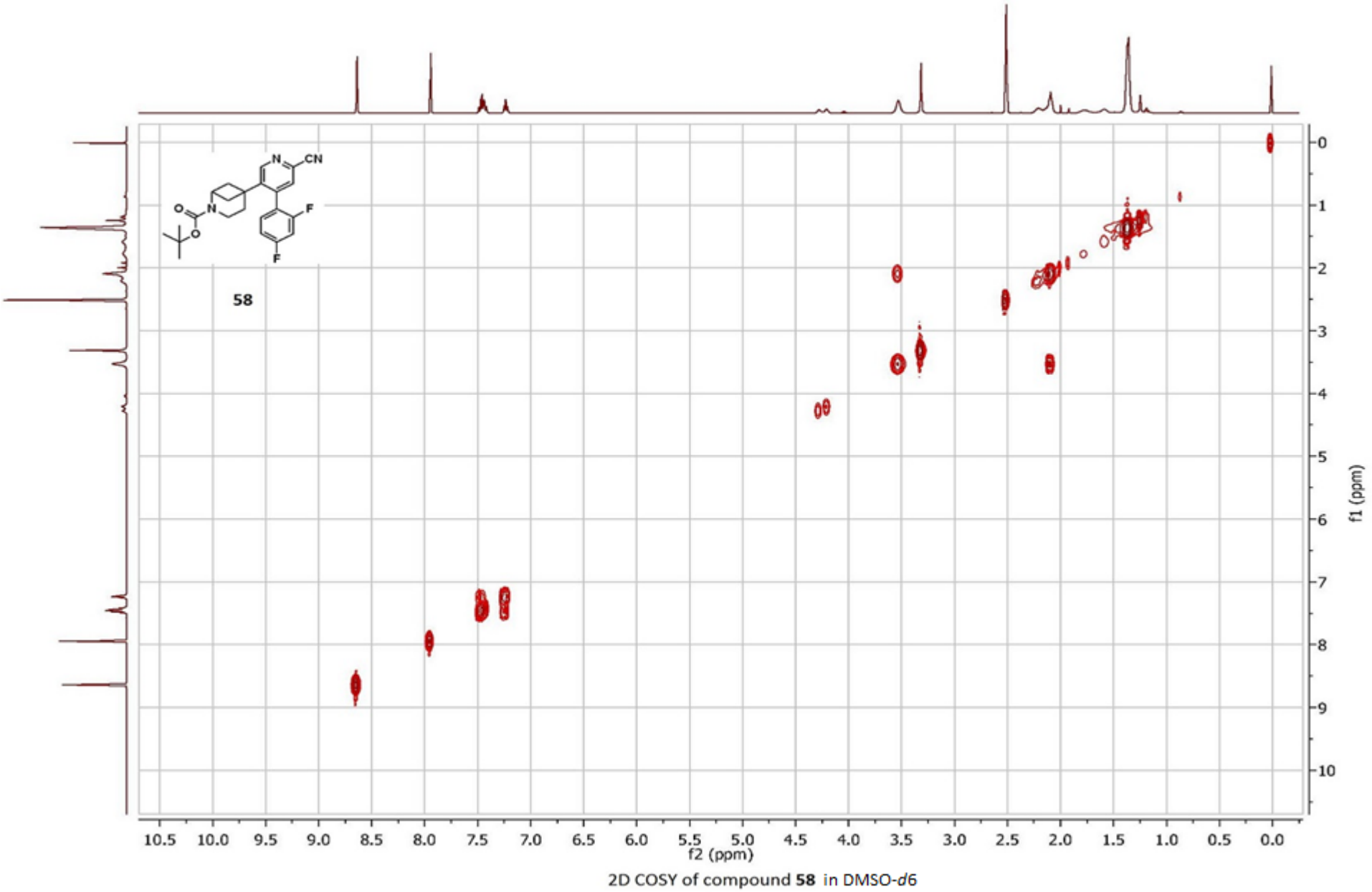
2D HSQC of compound **57** in DMSO-*d6*

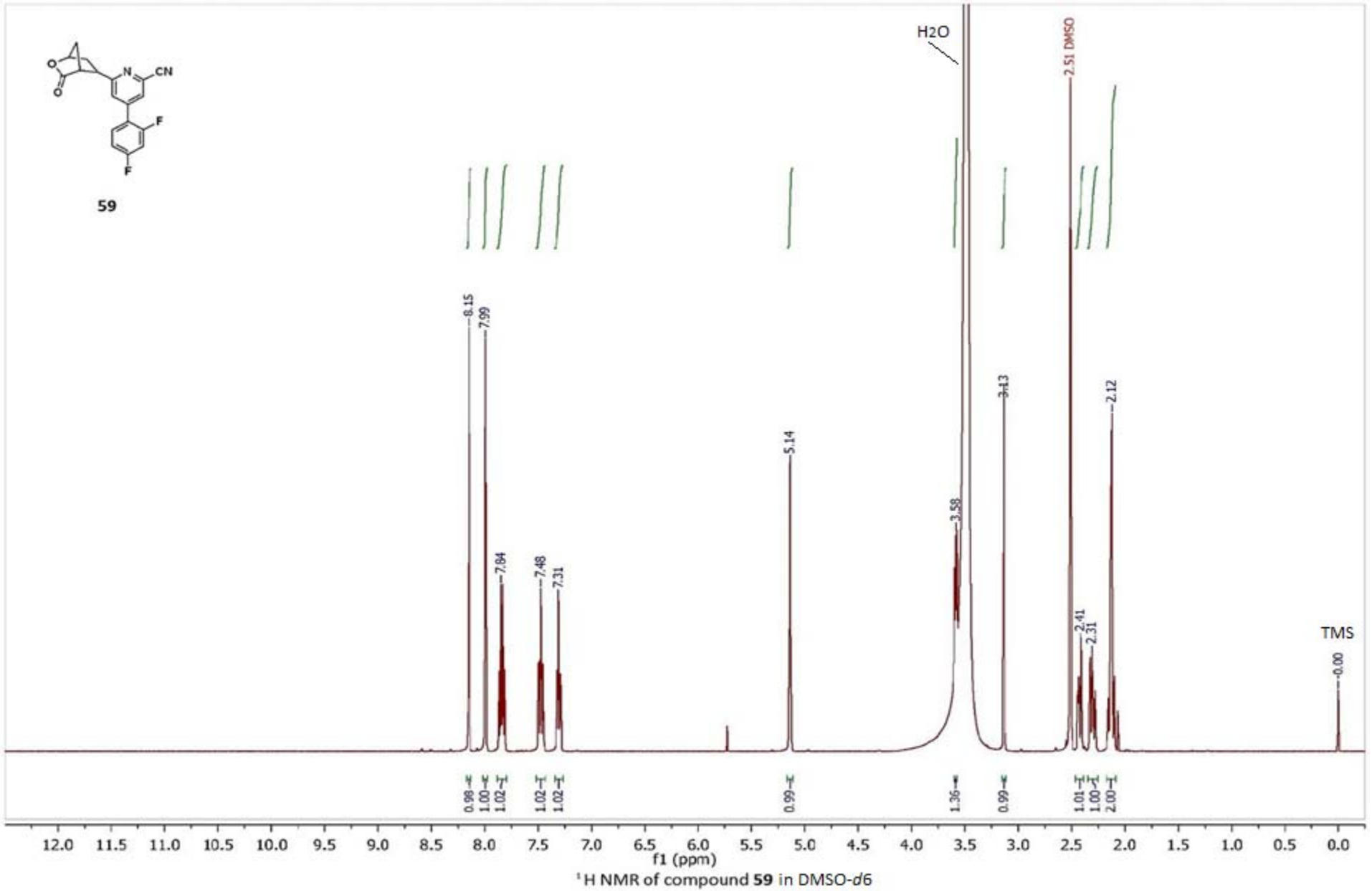

57
f2 (ppm)
f1 (ppm)
2D COSY of compound 57 in DMSO-d6



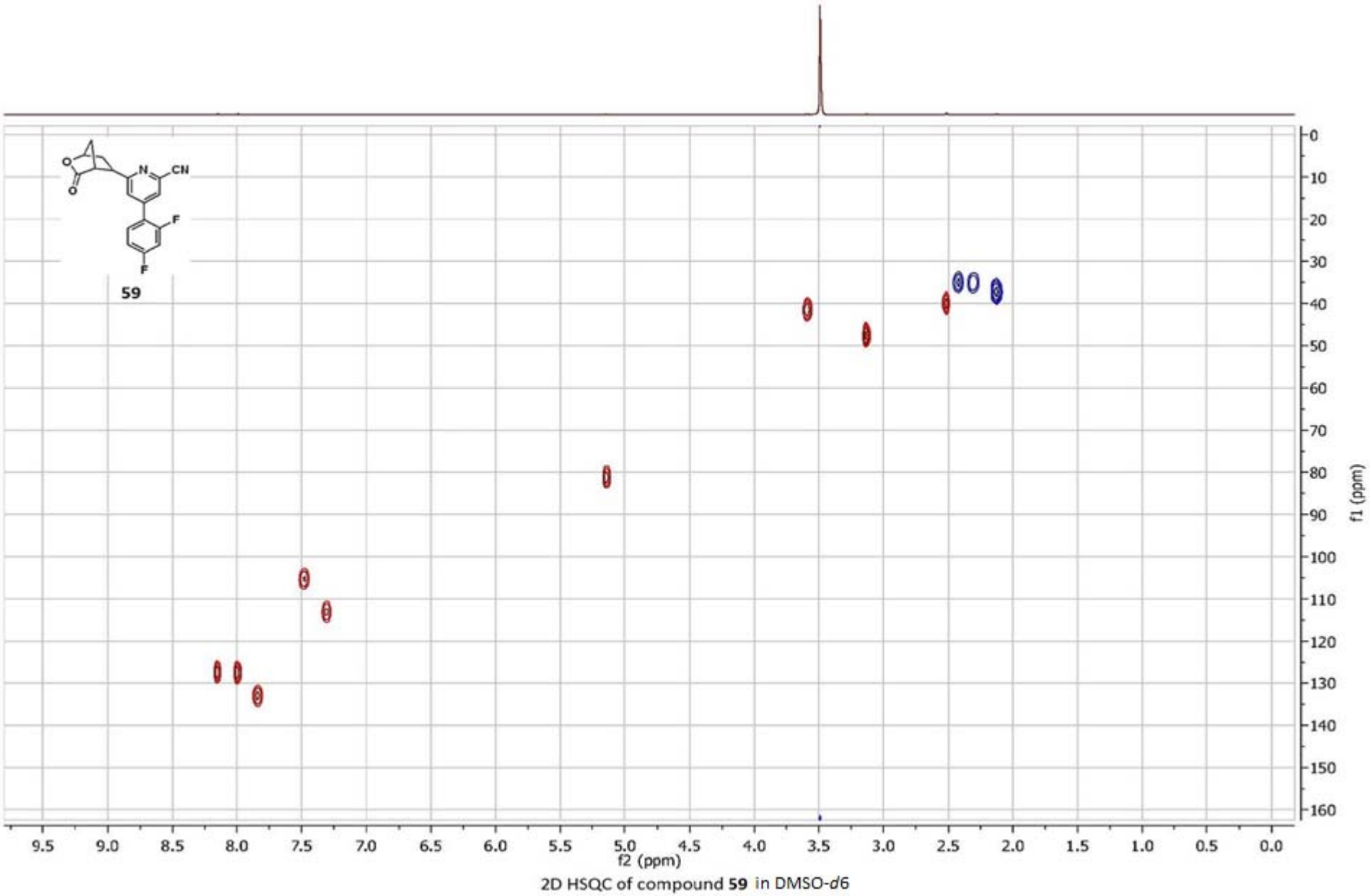
^{1}H NMR of compound **58** in DMSO-*d*6

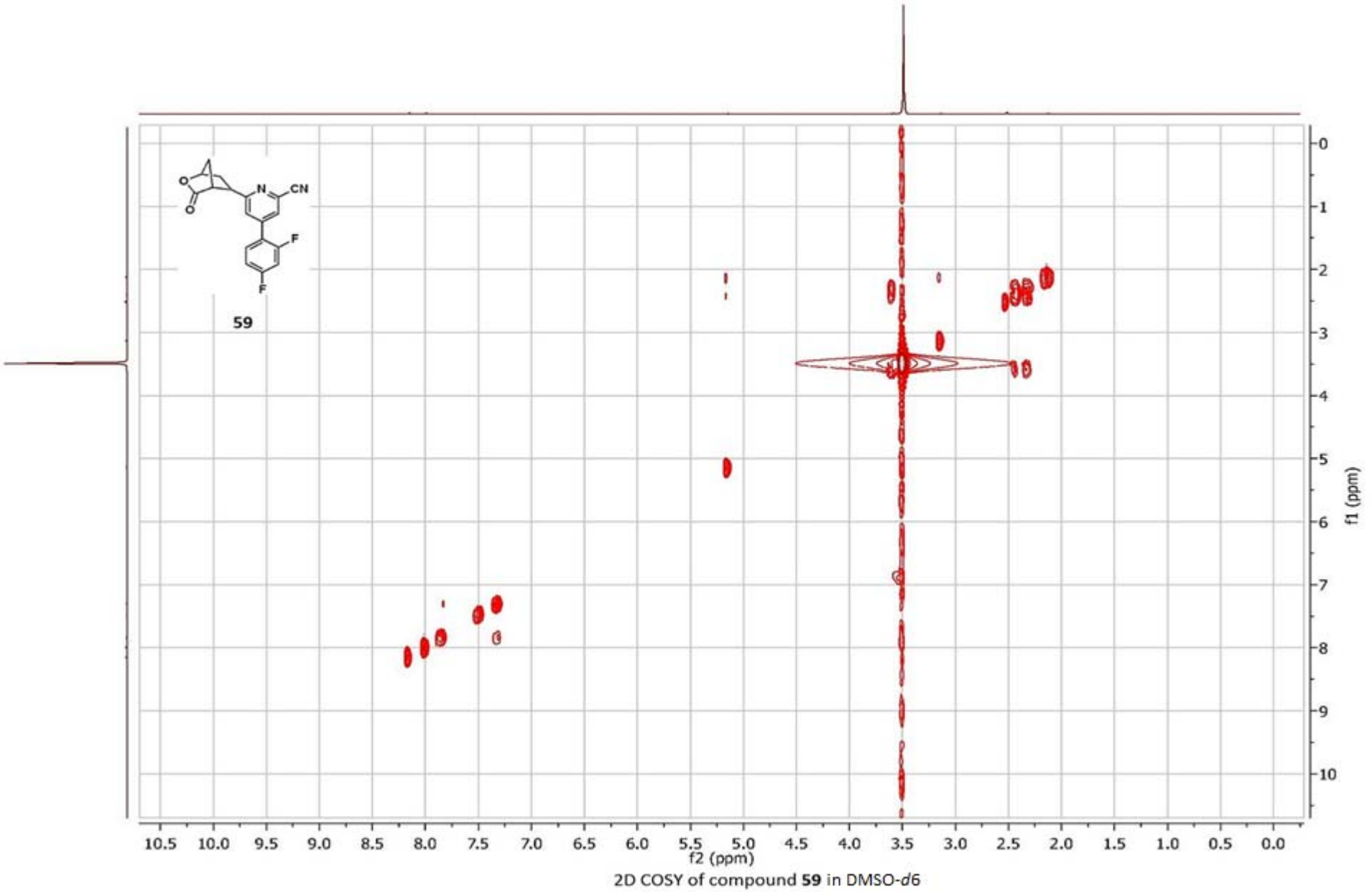

58
f2 (ppm)
f1 (ppm)
2D HSQC of compound 58 in DMSO-d6

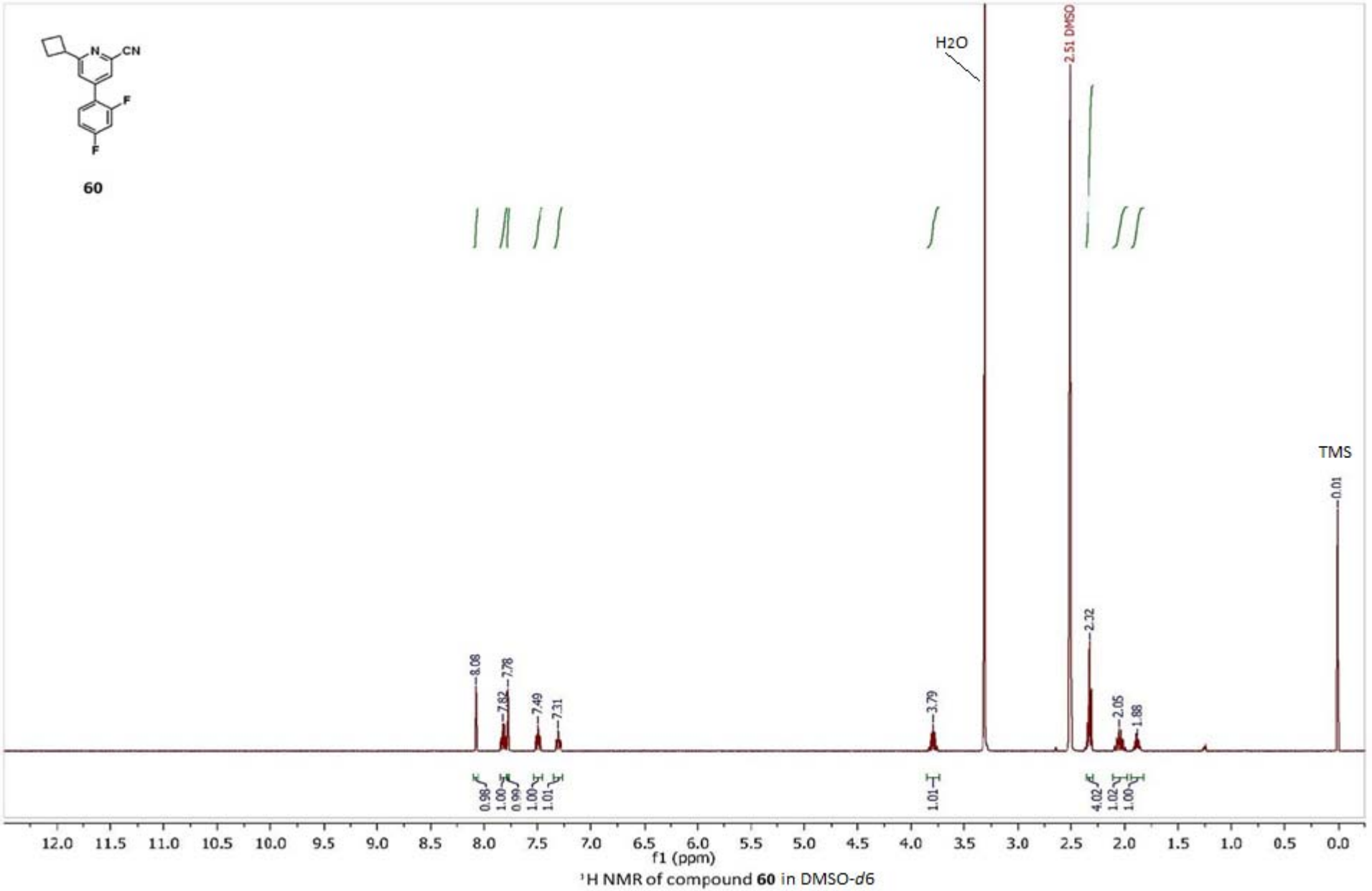

58
f2 (ppm)
f1 (ppm)
2D COSY of compound 58 in DMSO-d6



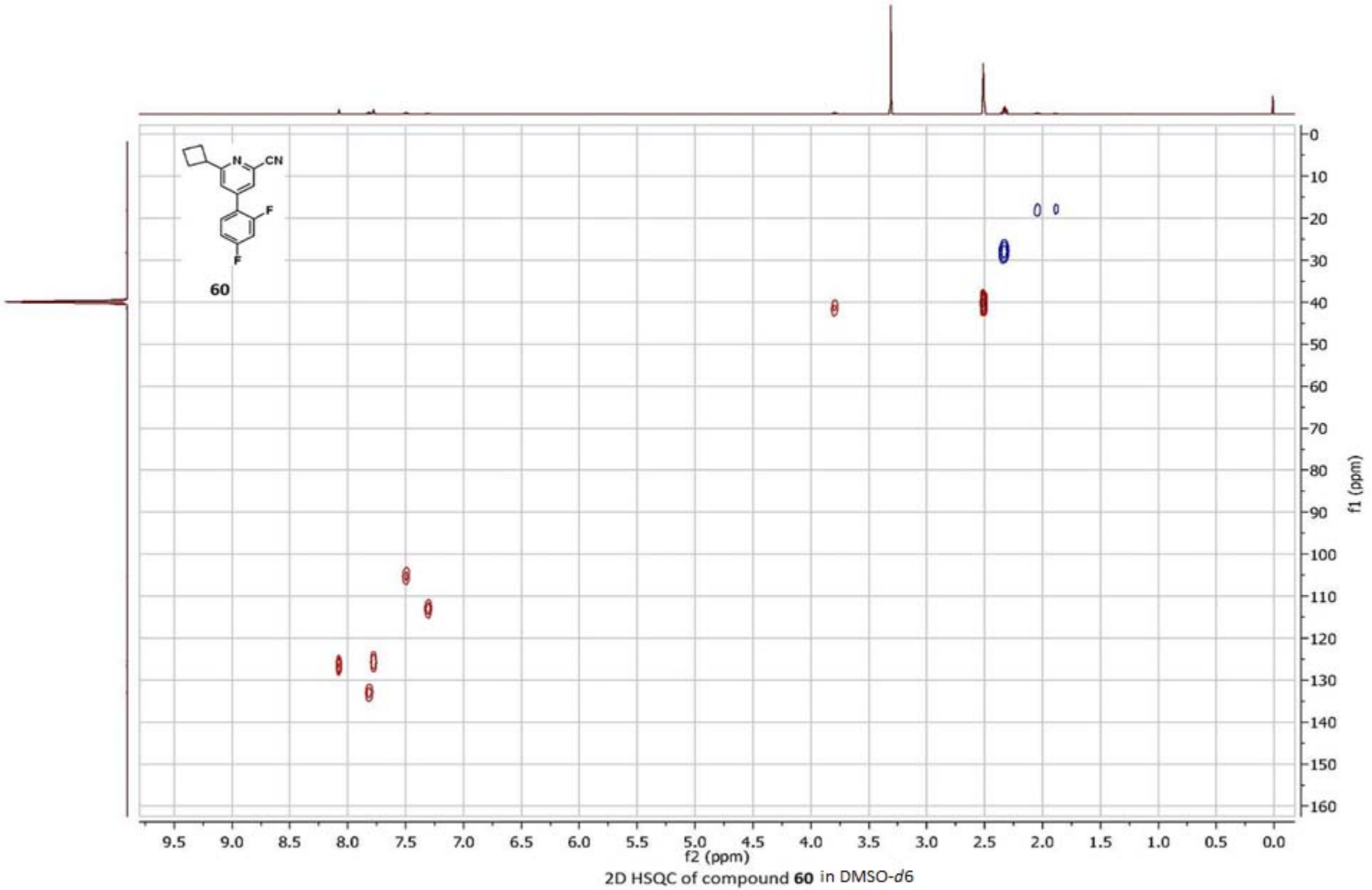
^{1}H NMR of compound **59** in DMSO-*d*6


59
f2 (ppm)
f1 (ppm)
2D HSQC of compound 59 in DMSO-d6

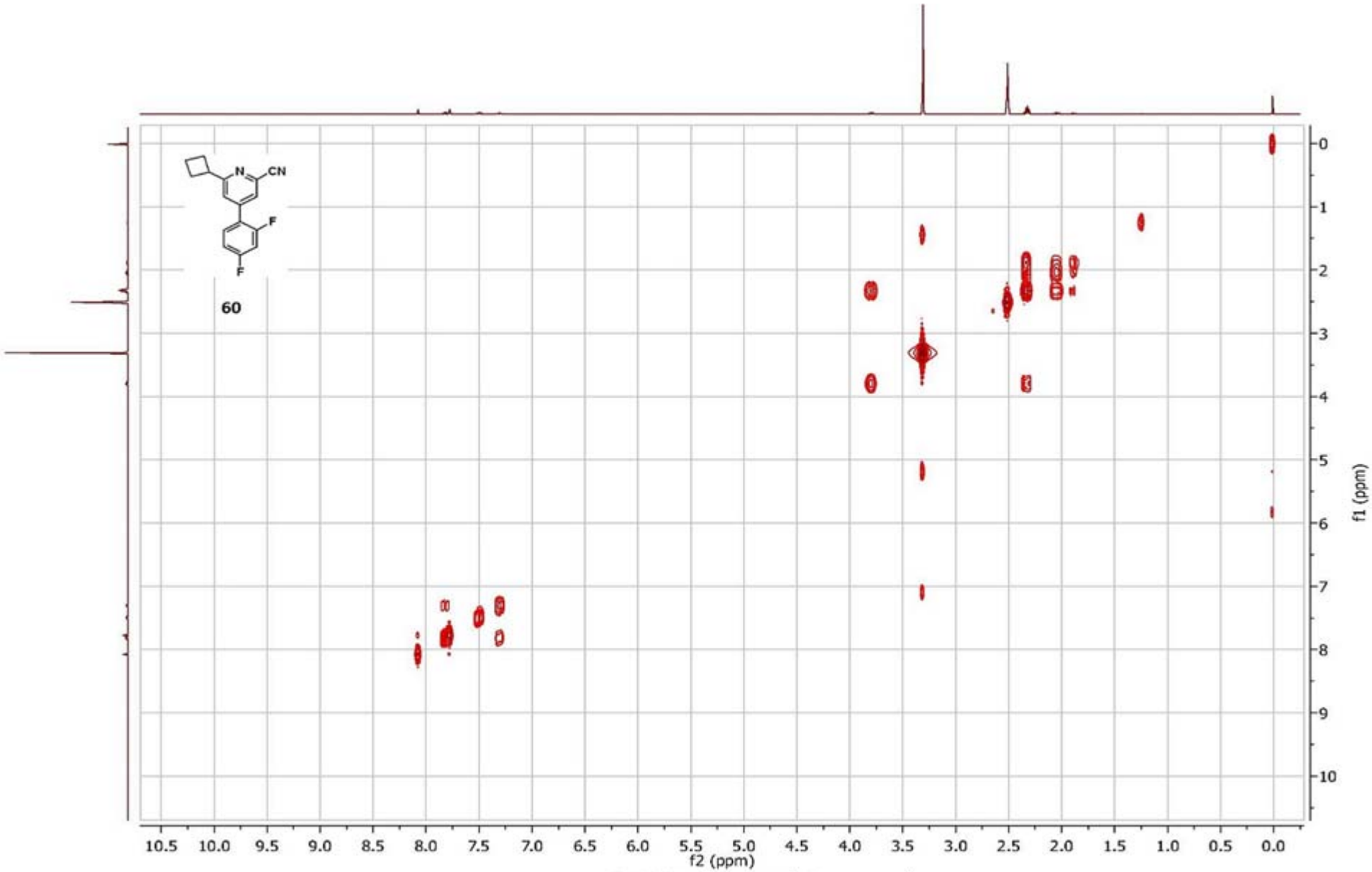

59
f2 (ppm)
f1 (ppm)
2D COSY of compound 59 in DMSO-d6



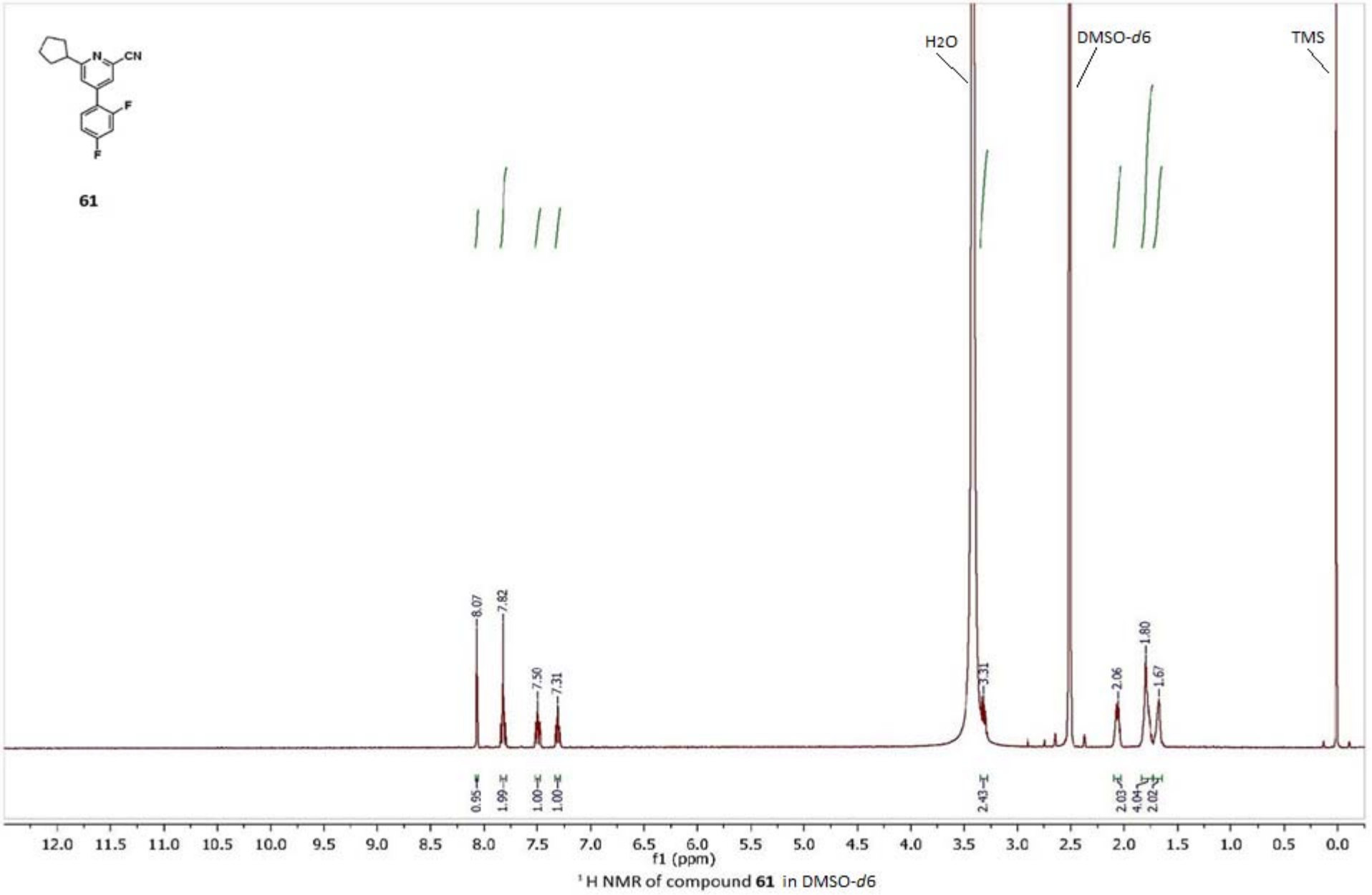
^{1}H NMR of compound **60** in DMSO-*d*6



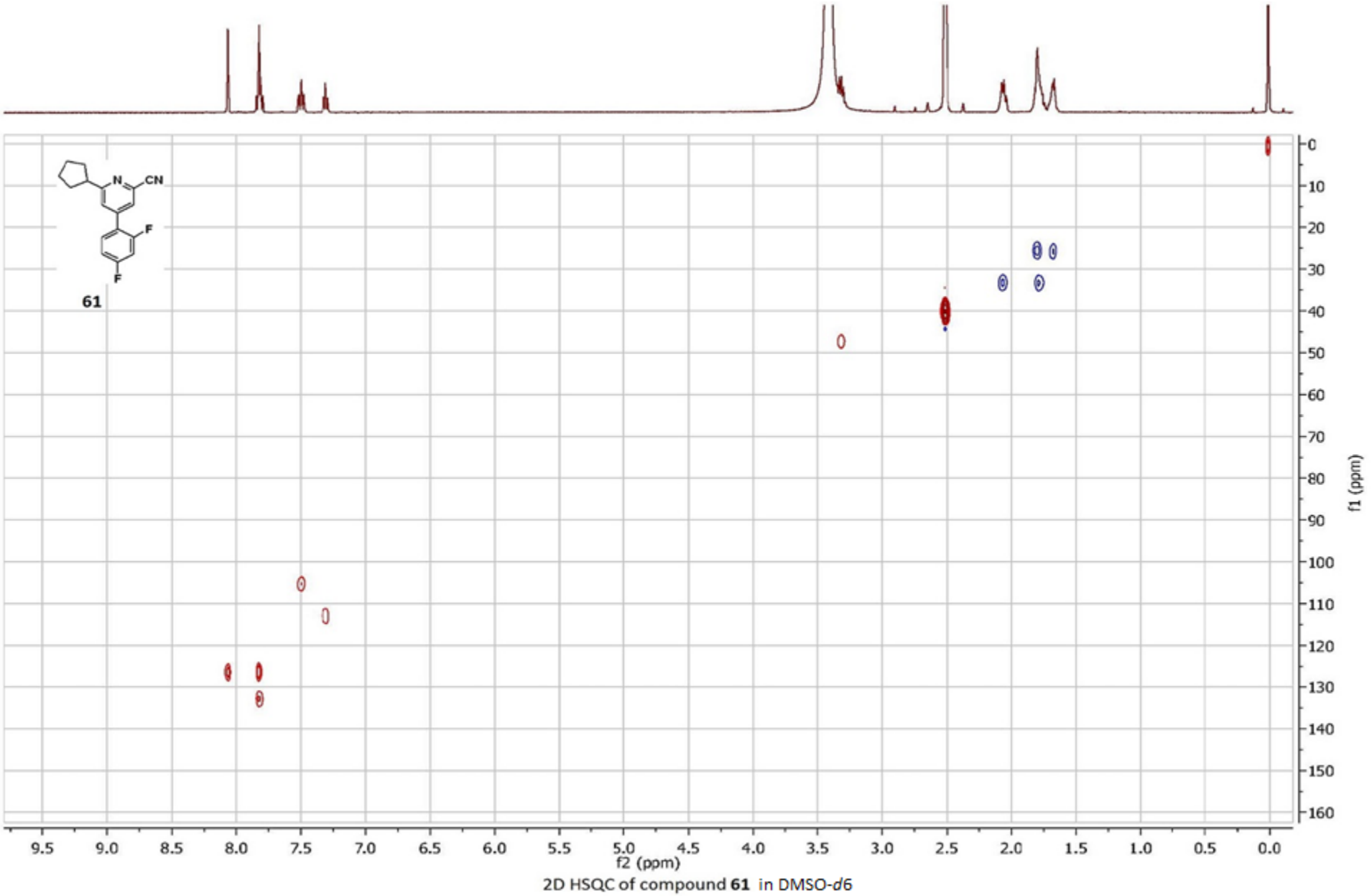
2D HSQC of compound **60** in DMSO-*d*6



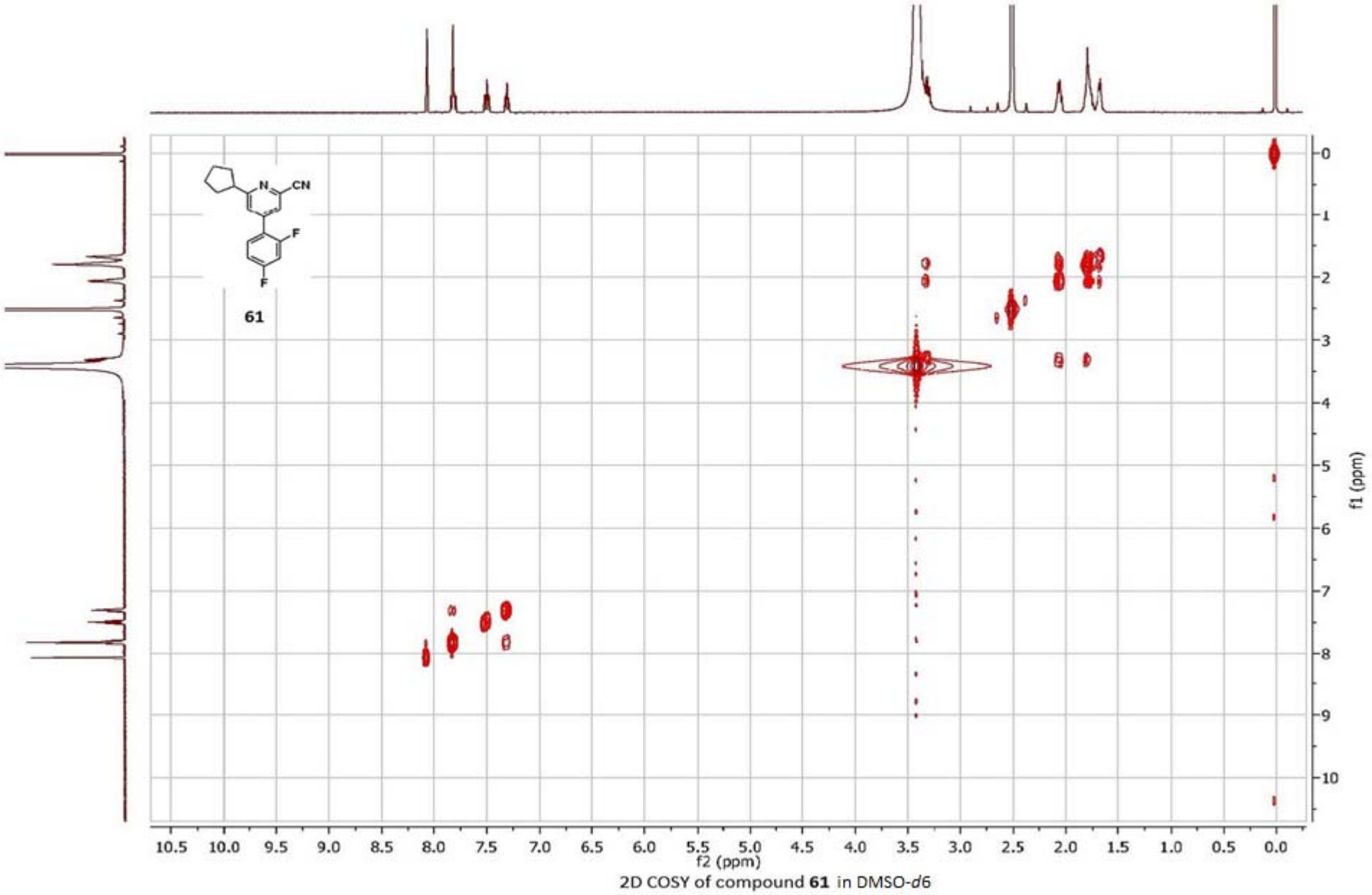
2D COSY of compound **60** in DMSO-*d*6



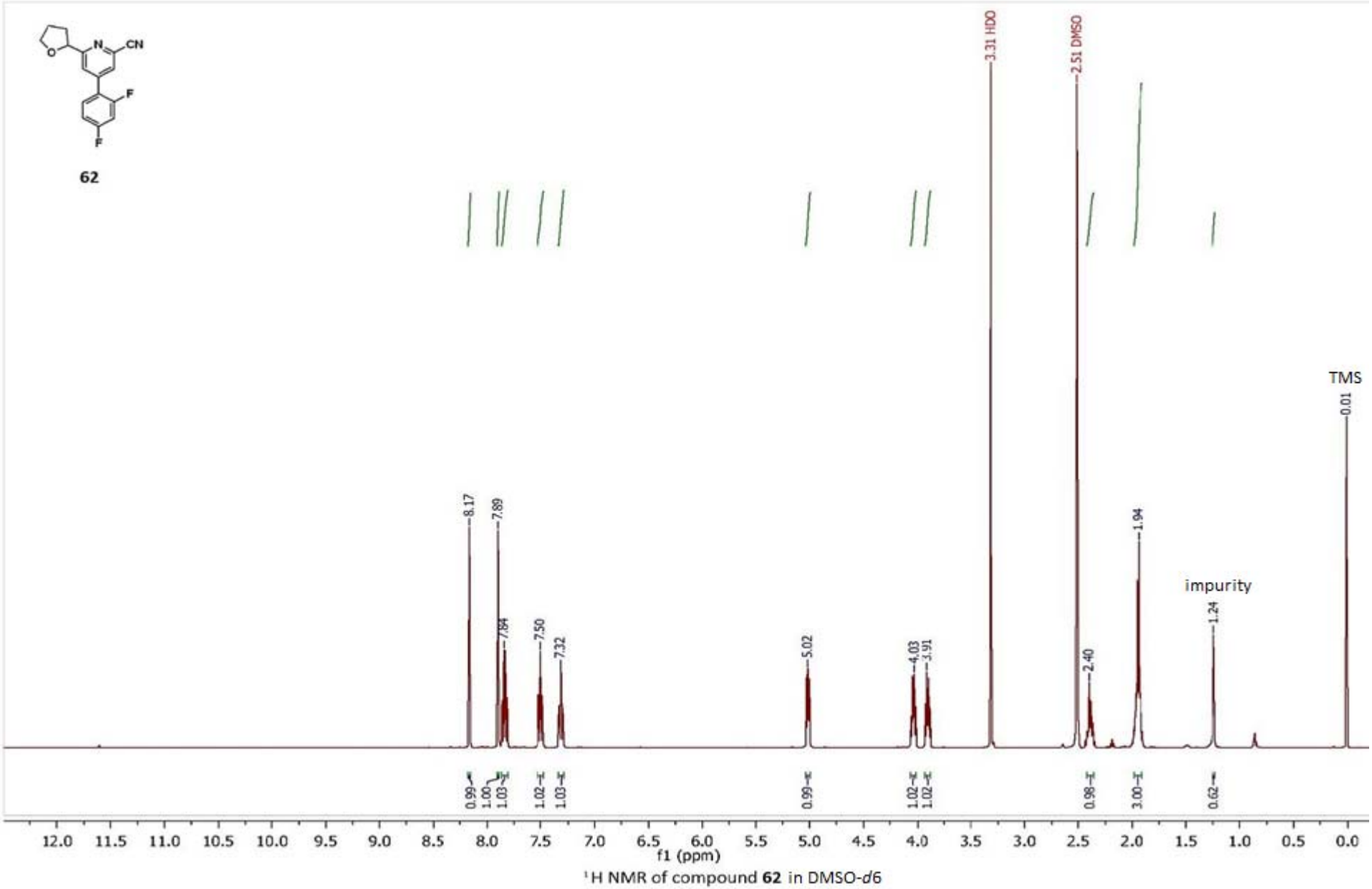
^{1}H NMR of compound **61** in DMSO-*d6*



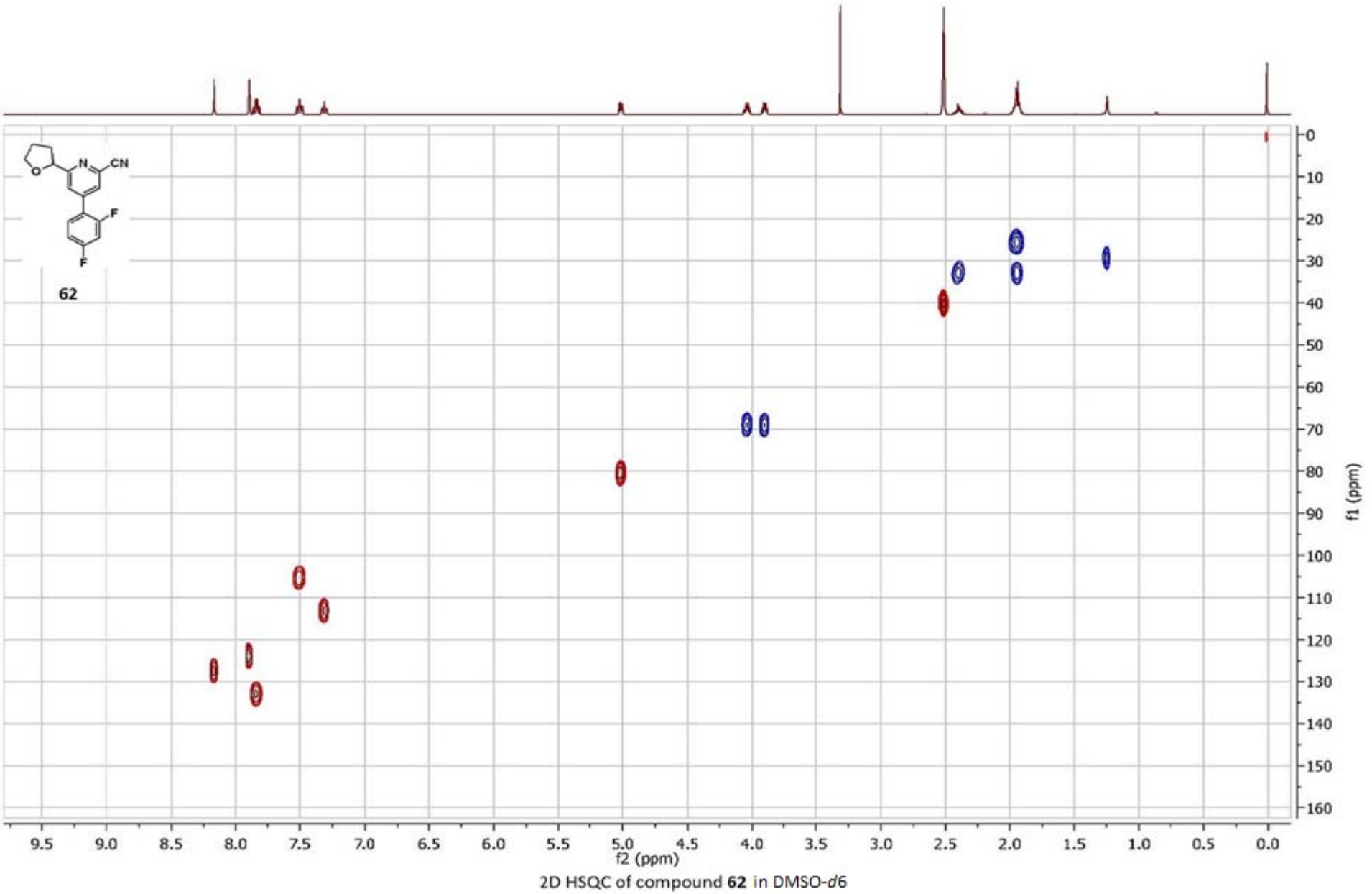
2D HSQC of compound **61** in DMSO-*d*6

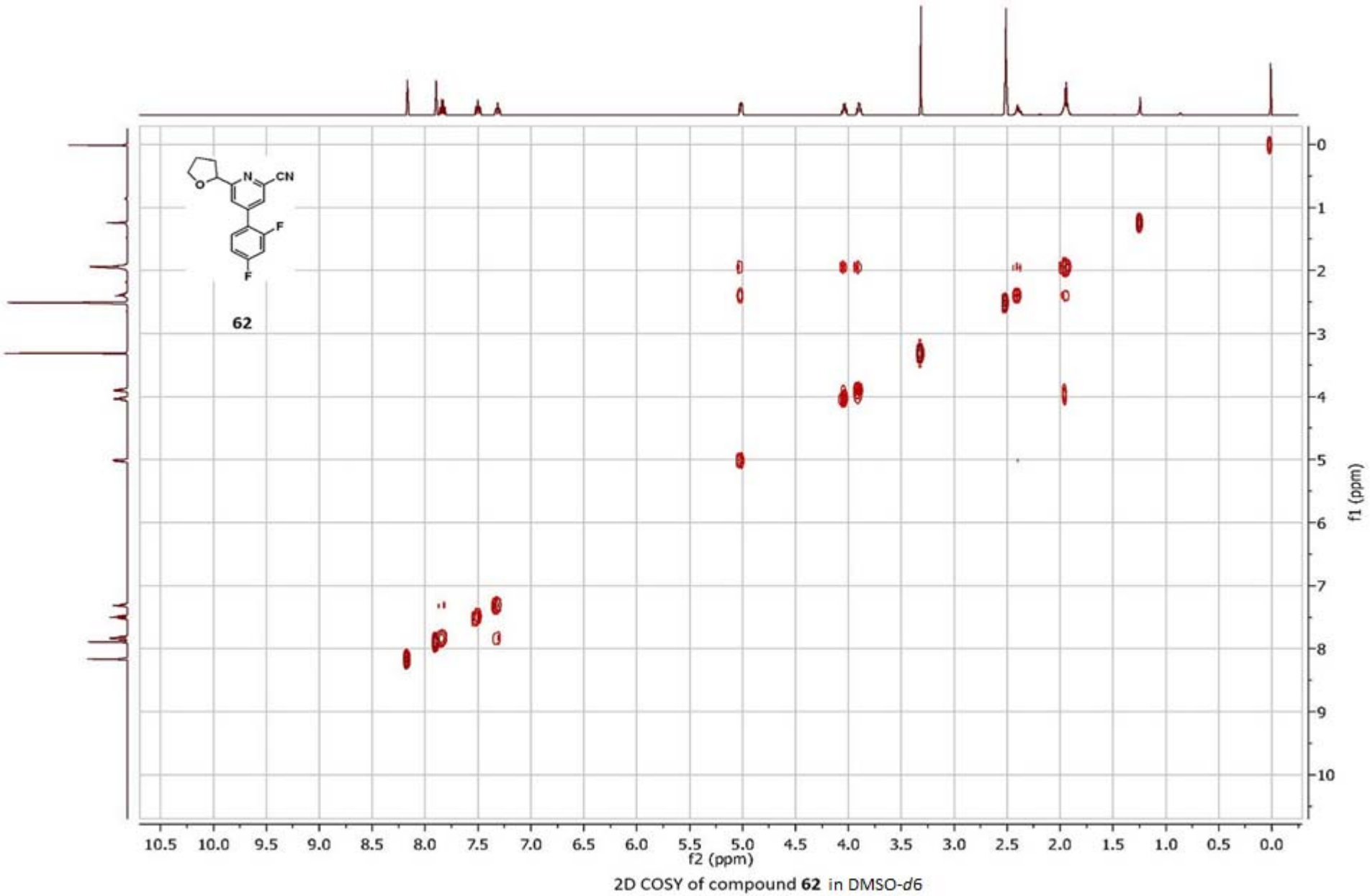


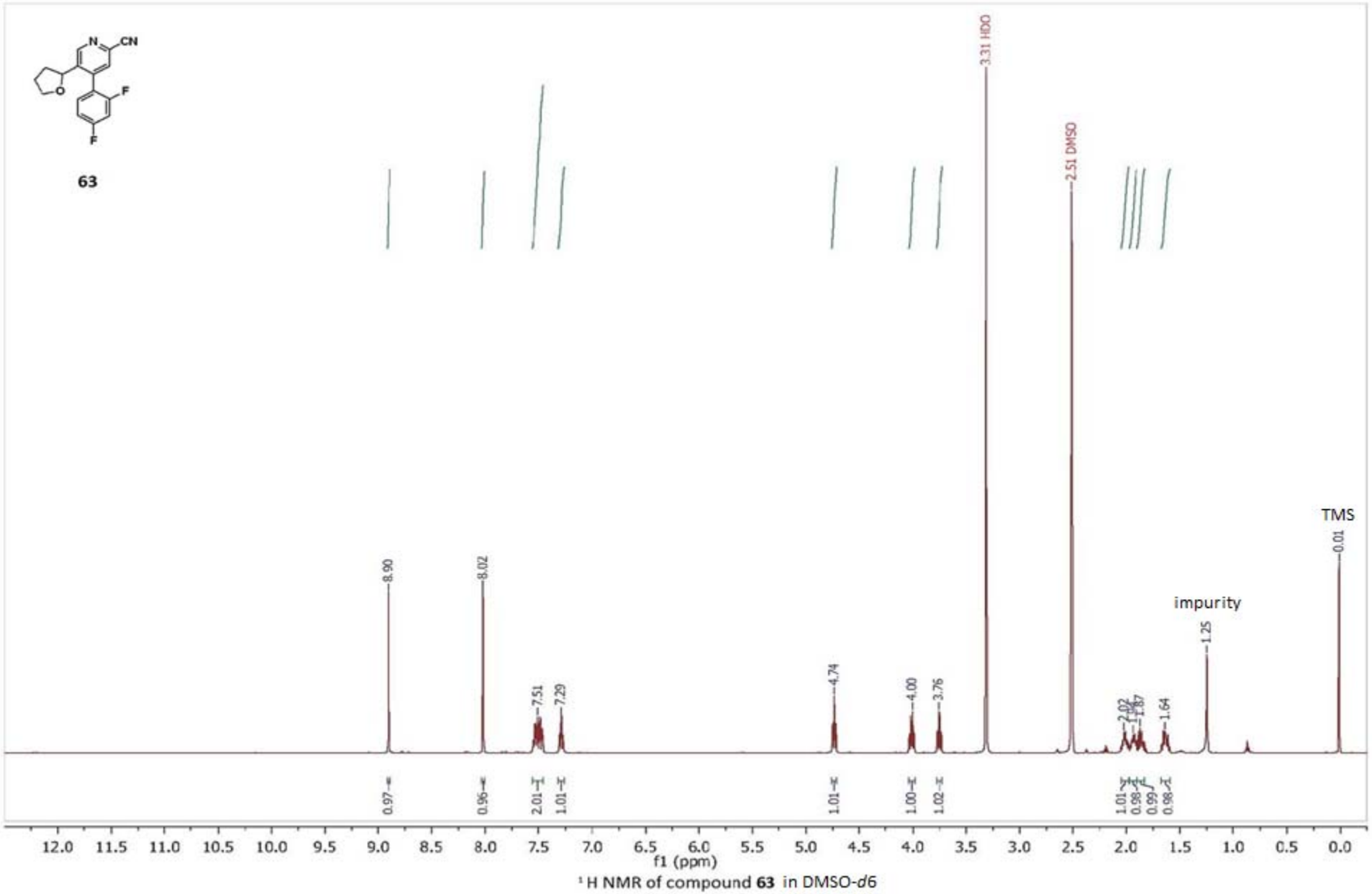
2D COSY of compound **61** in DMSO-*d*6



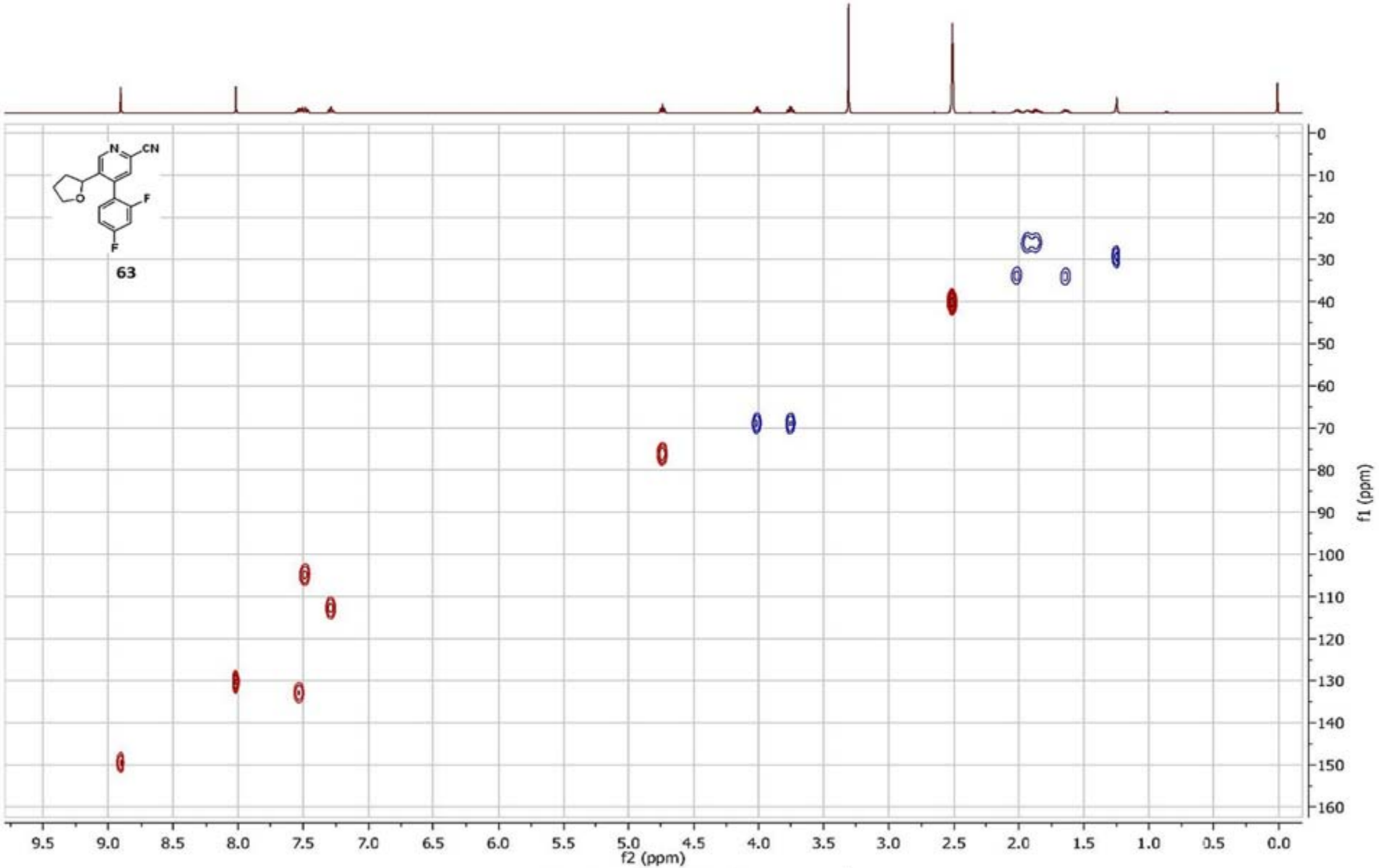
^{1}H NMR of compound **62** in DMSO-*d*6


62
f2 (ppm)
f1 (ppm)
2D HSQC of compound 62 in DMSO-d6

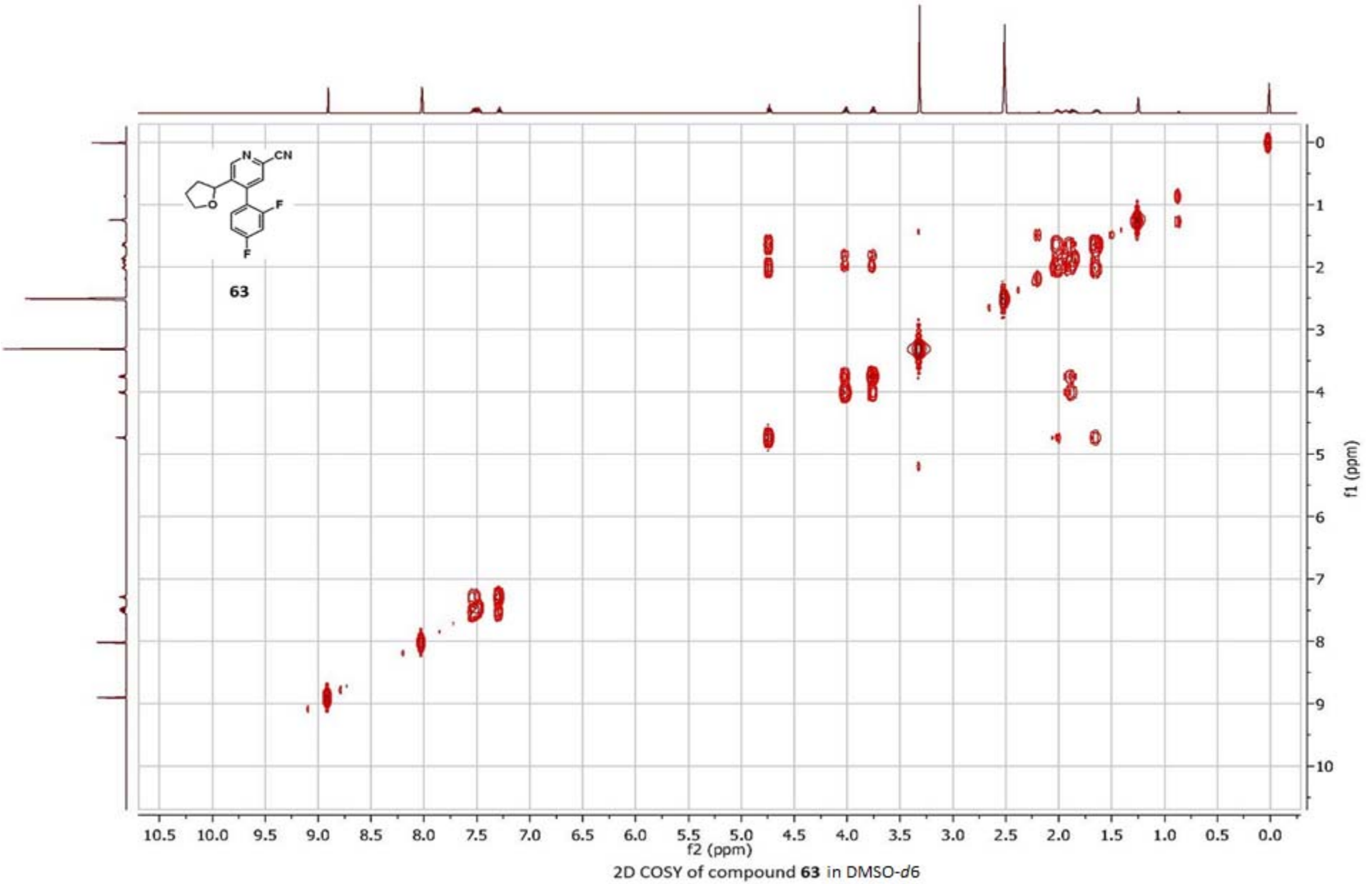

62
f2 (ppm)
f1 (ppm)
2D COSY of compound 62 in DMSO-d6



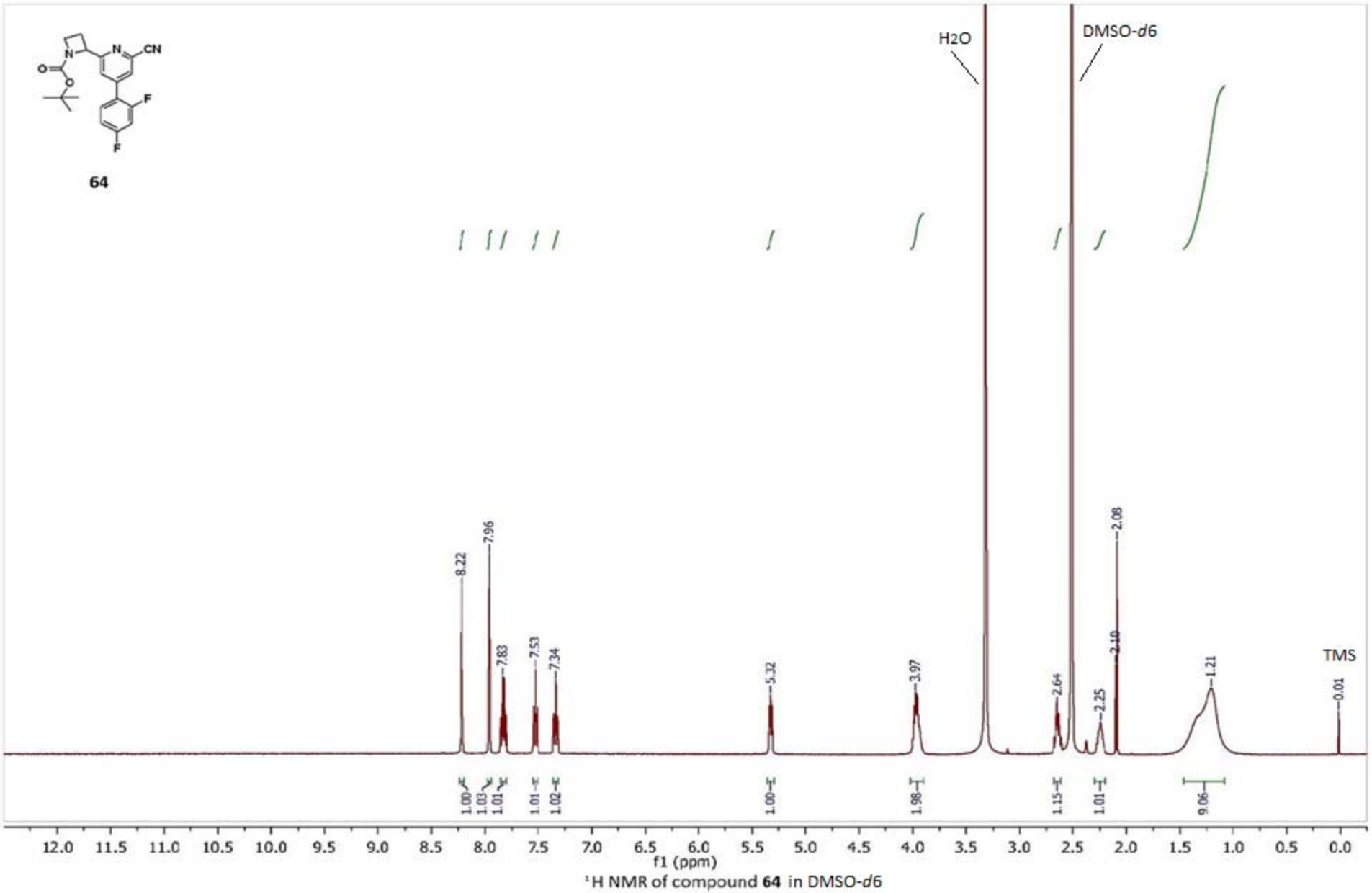
¹H NMR of compound **63** in DMSO-*d*6



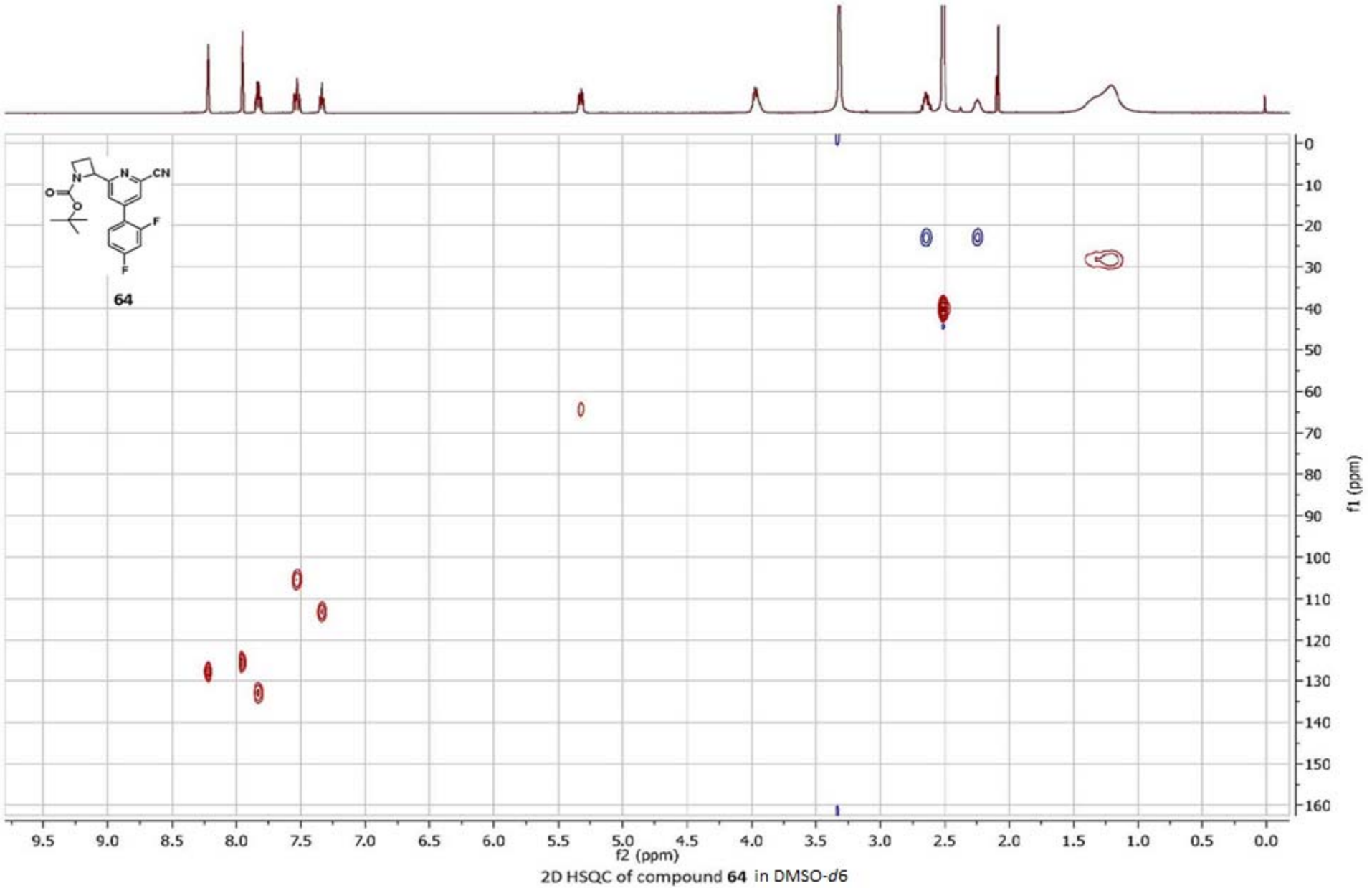
2D HSQC of compound **63** in DMSO-*d6*

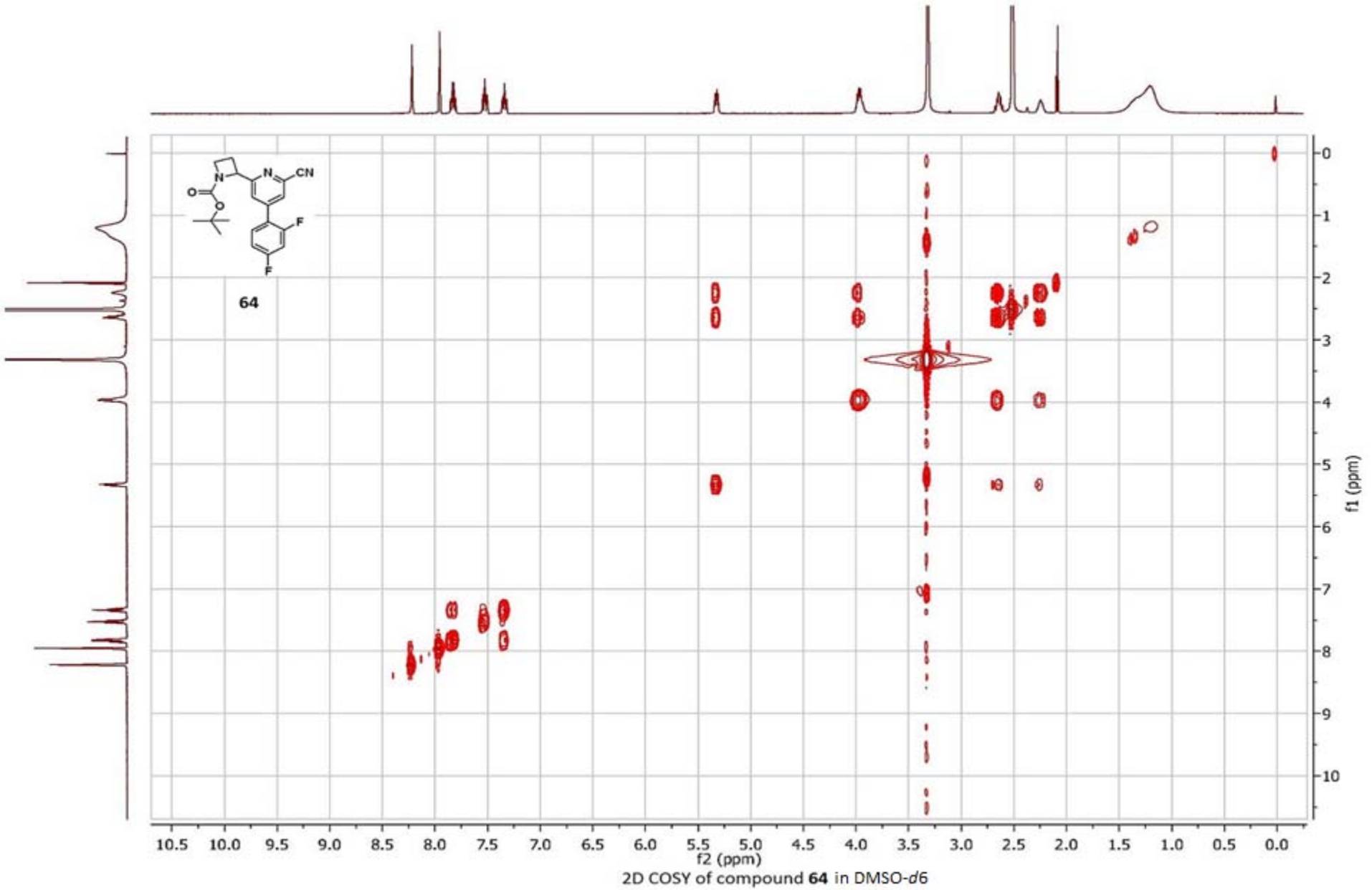


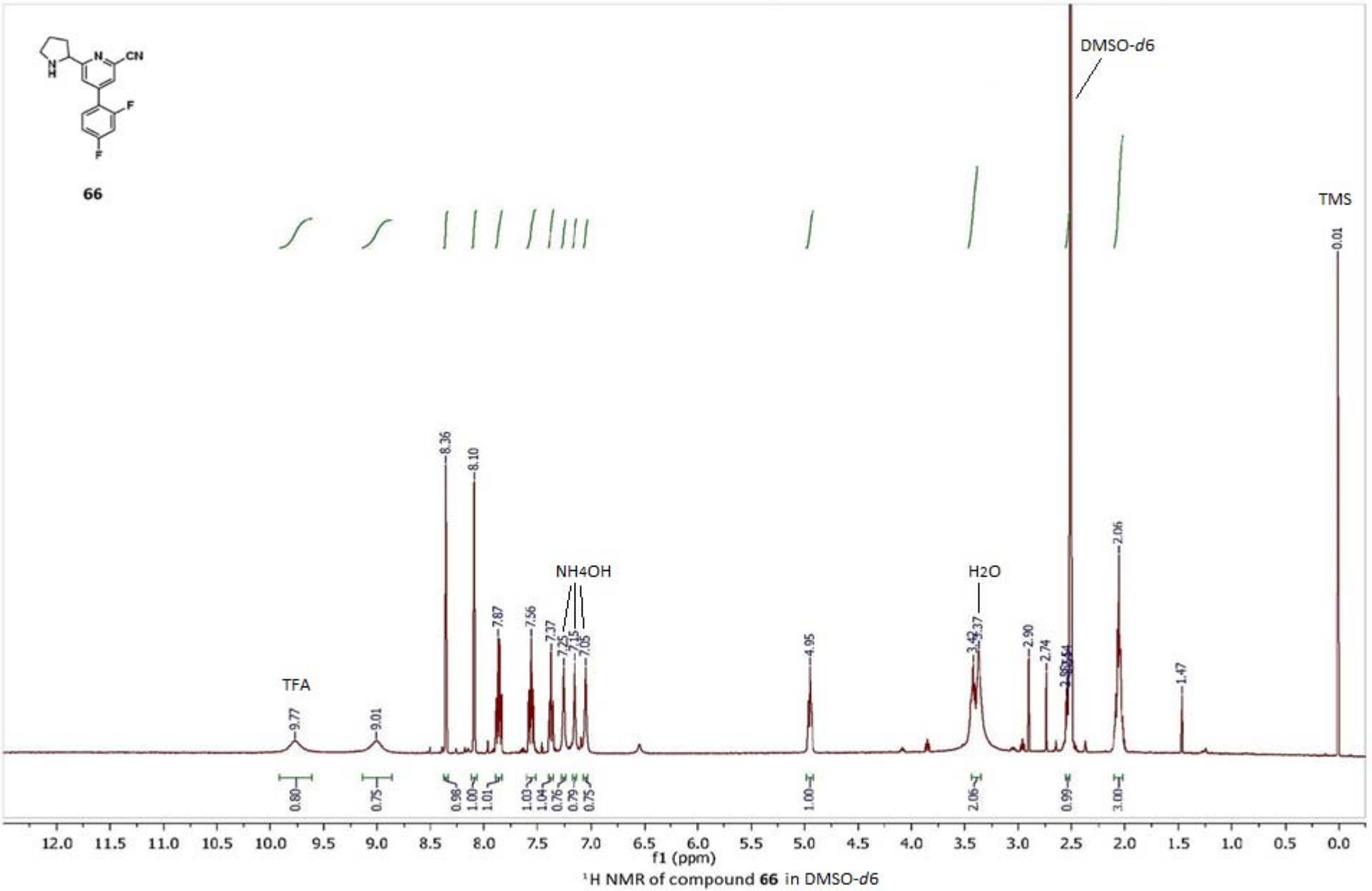
2D COSY of compound **63** in DMSO-*d*6



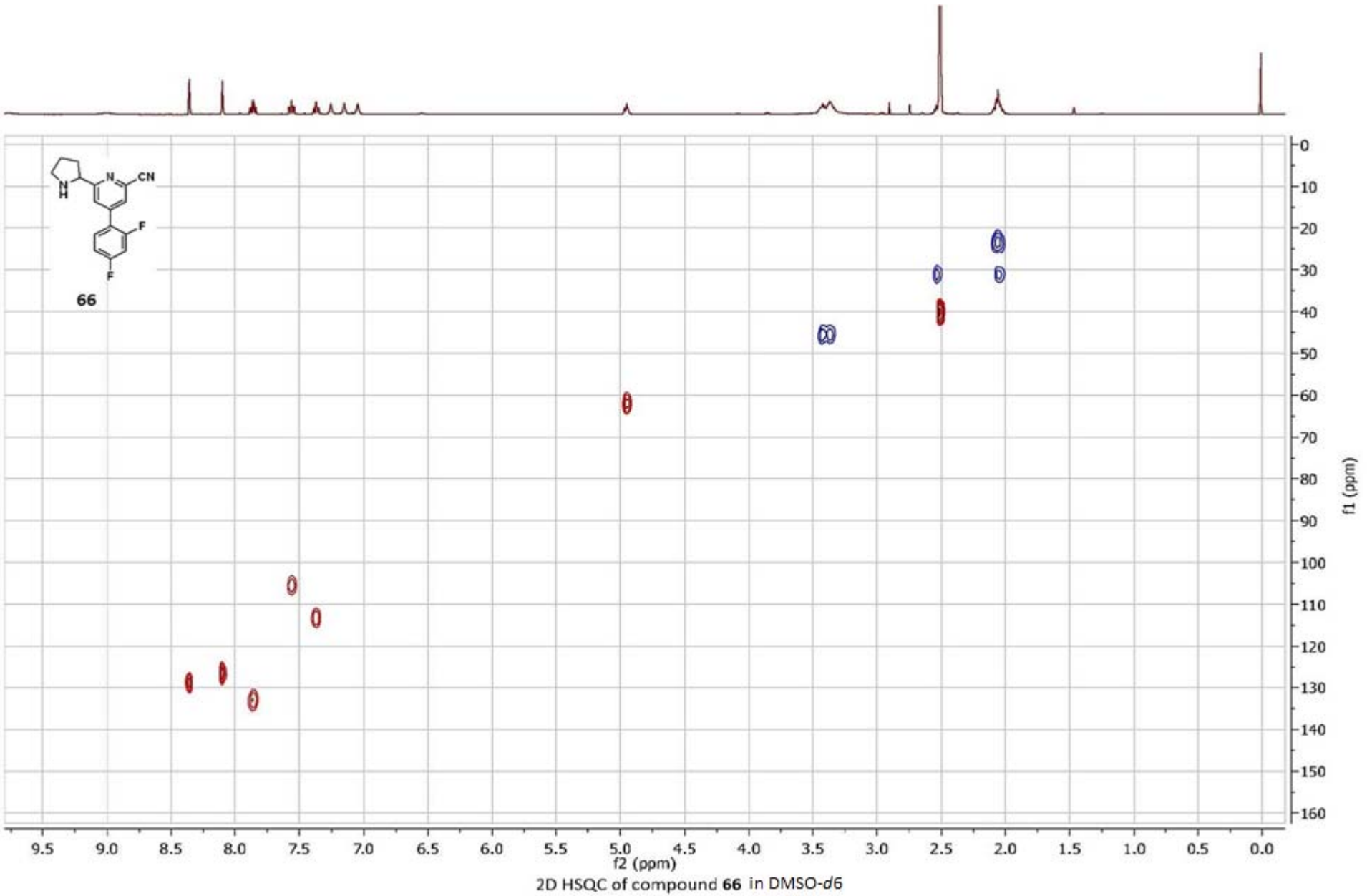
^{1}H NMR of compound **64** in DMSO-*d*6

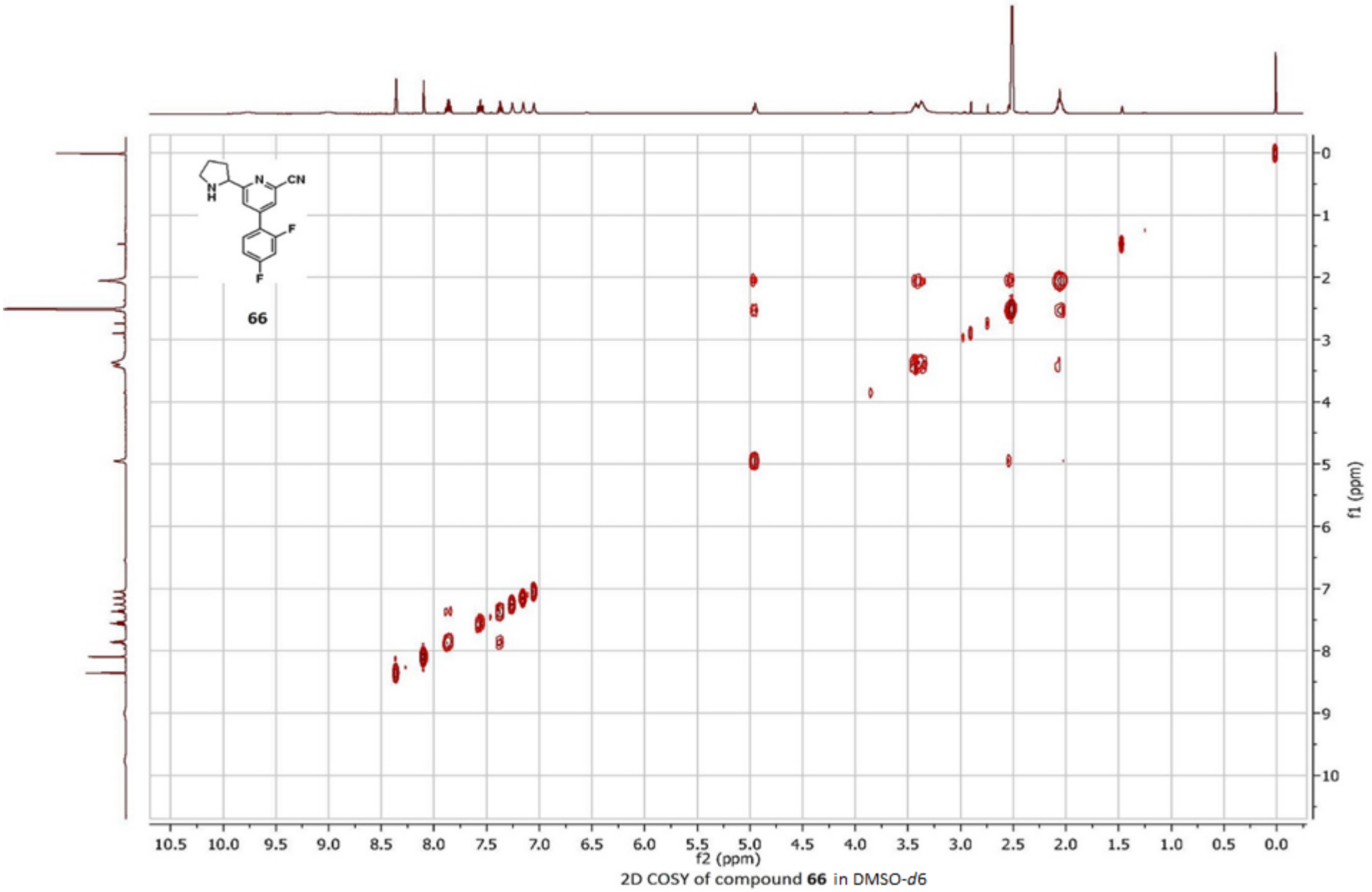

64
f2 (ppm)
f1 (ppm)
2D HSQC of compound 64 in DMSO-d6

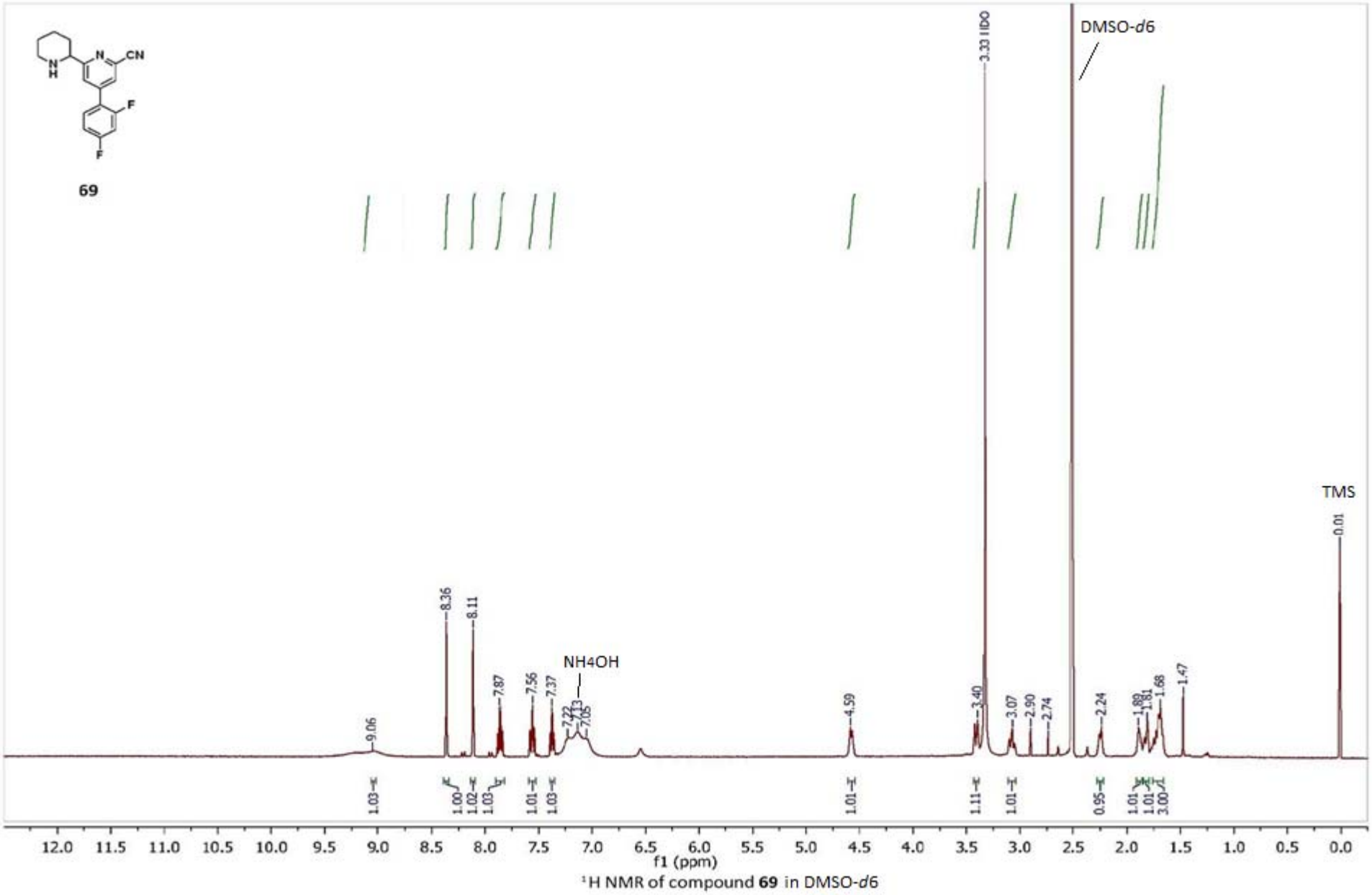

64
f2 (ppm)
f1 (ppm)
2D COSY of compound 64 in DMSO-d6



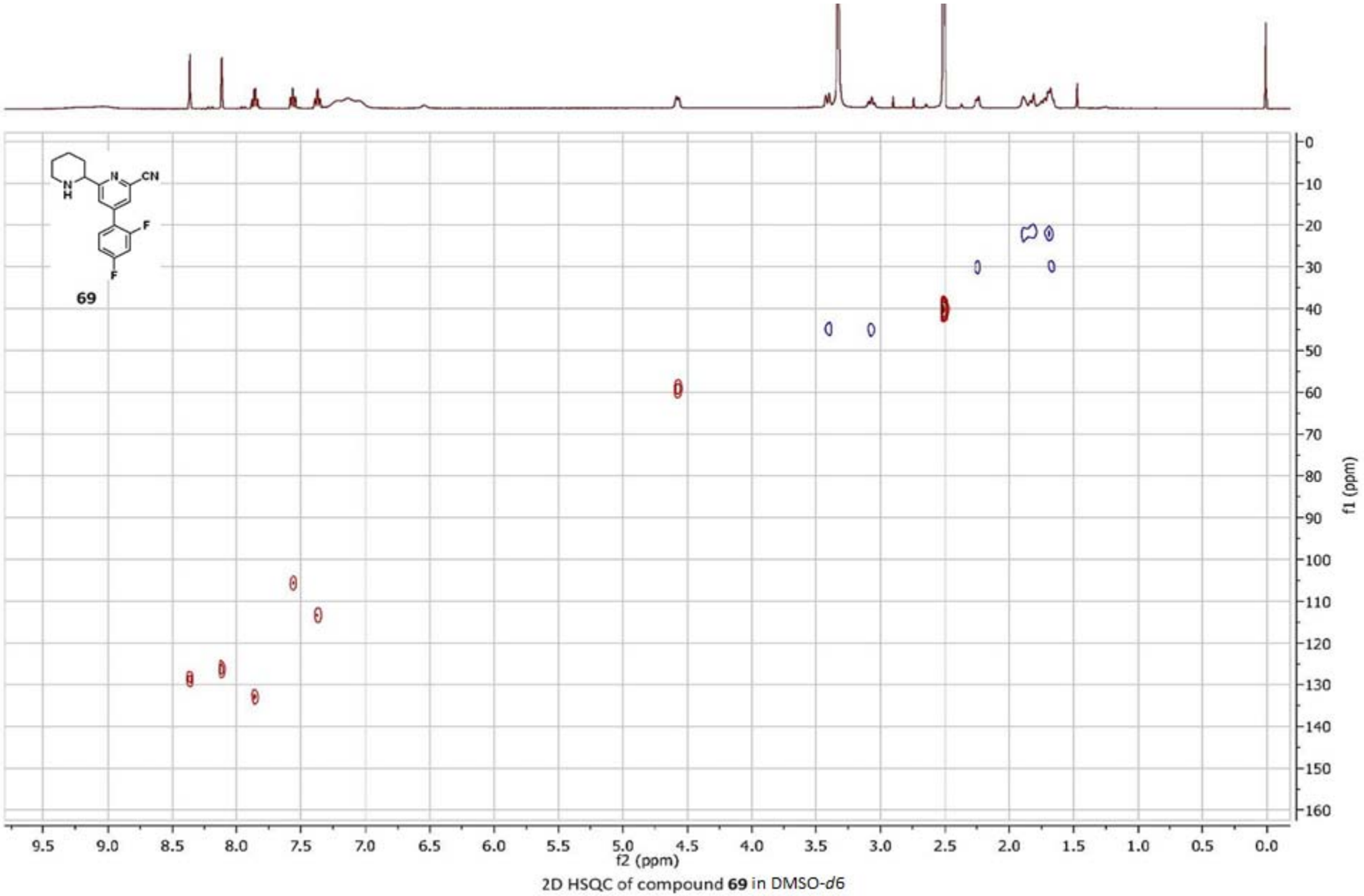
^{1}H NMR of compound **66** in DMSO-*d*6


66
f2 (ppm)
f1 (ppm)
2D HSQC of compound 66 in DMSO-d6

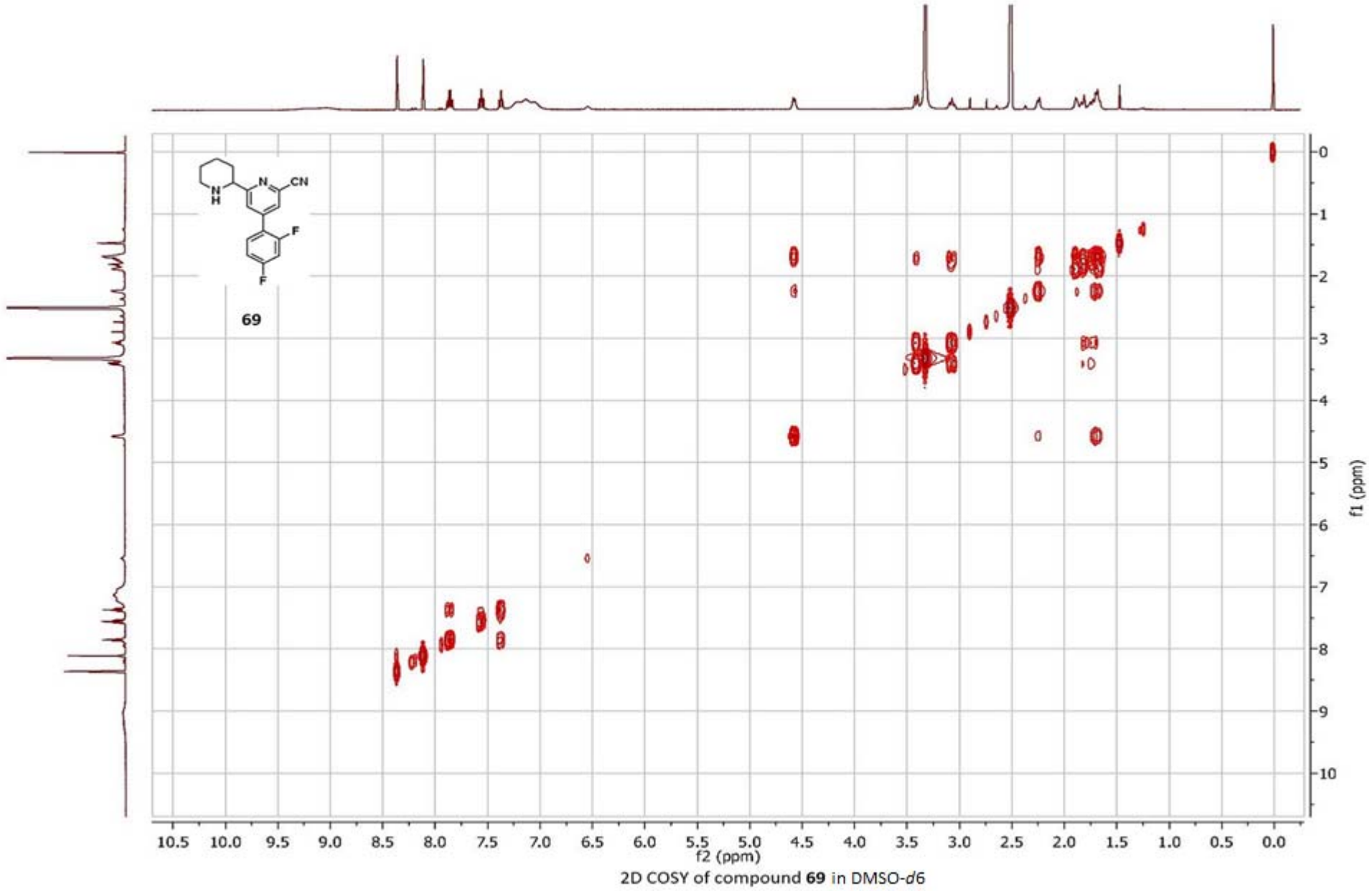

66
f2 (ppm)
f1 (ppm)
2D COSY of compound 66 in DMSO-d6

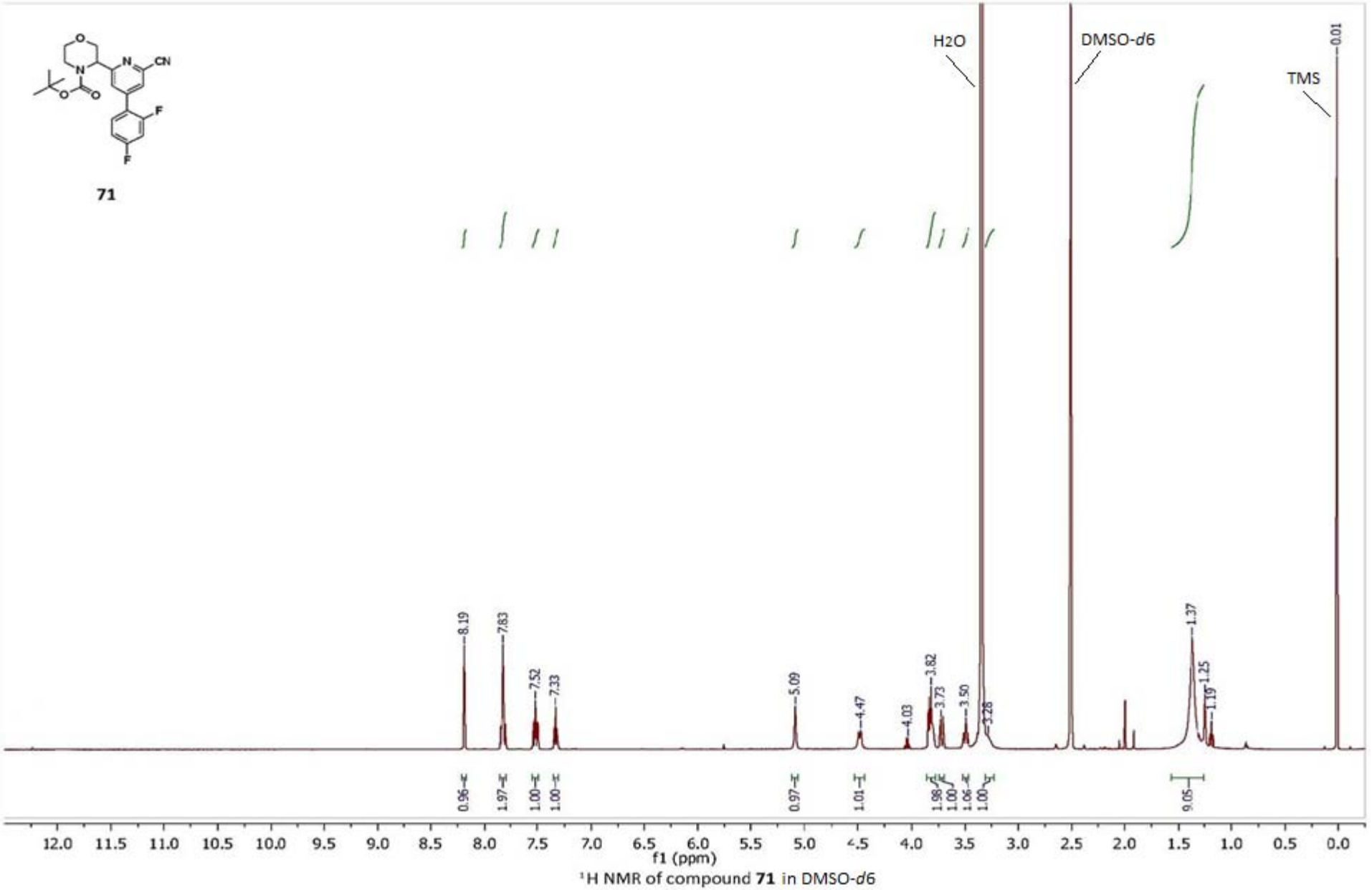


^{1}H NMR of compound **69** in DMSO-*d*6

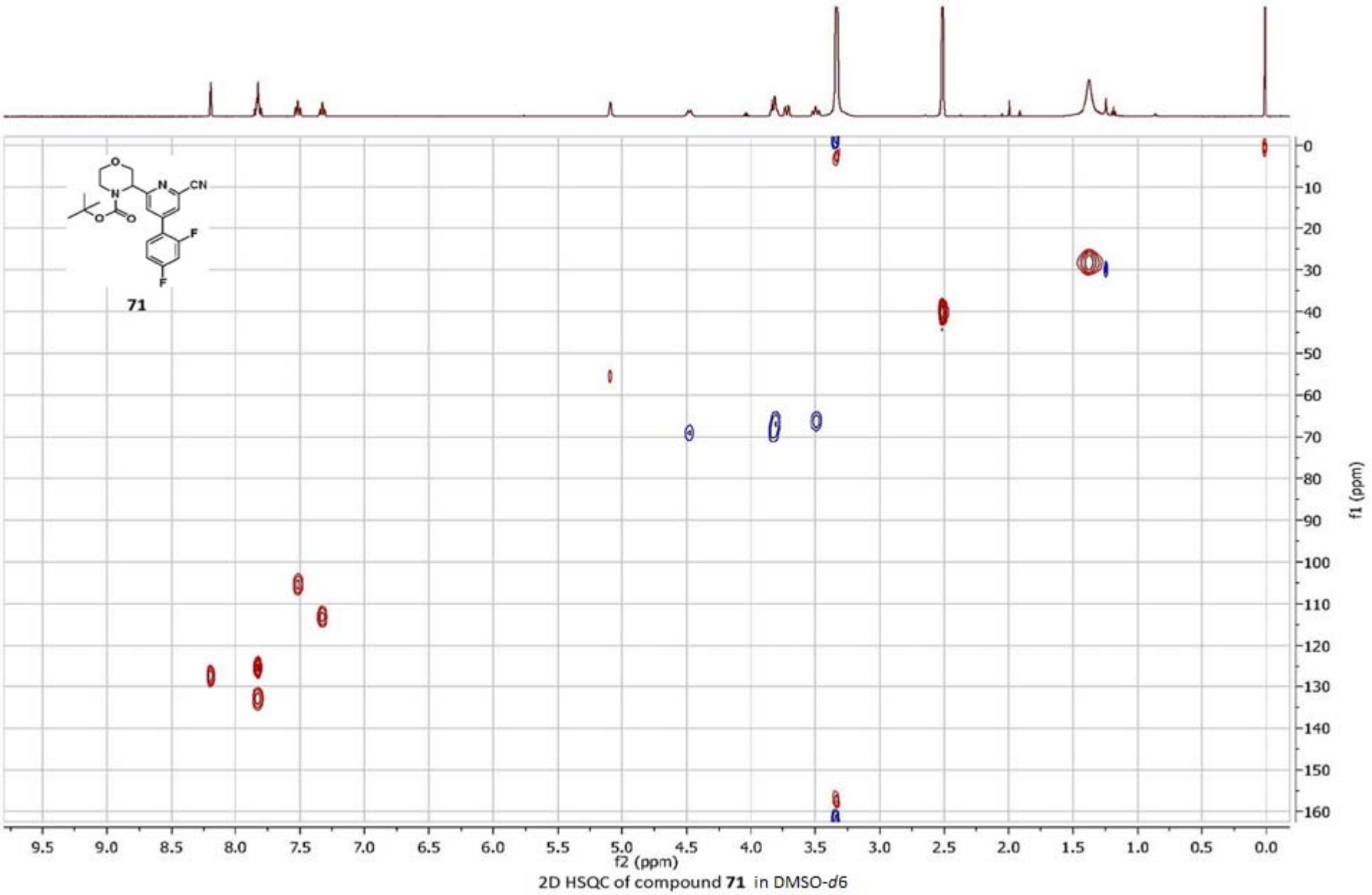


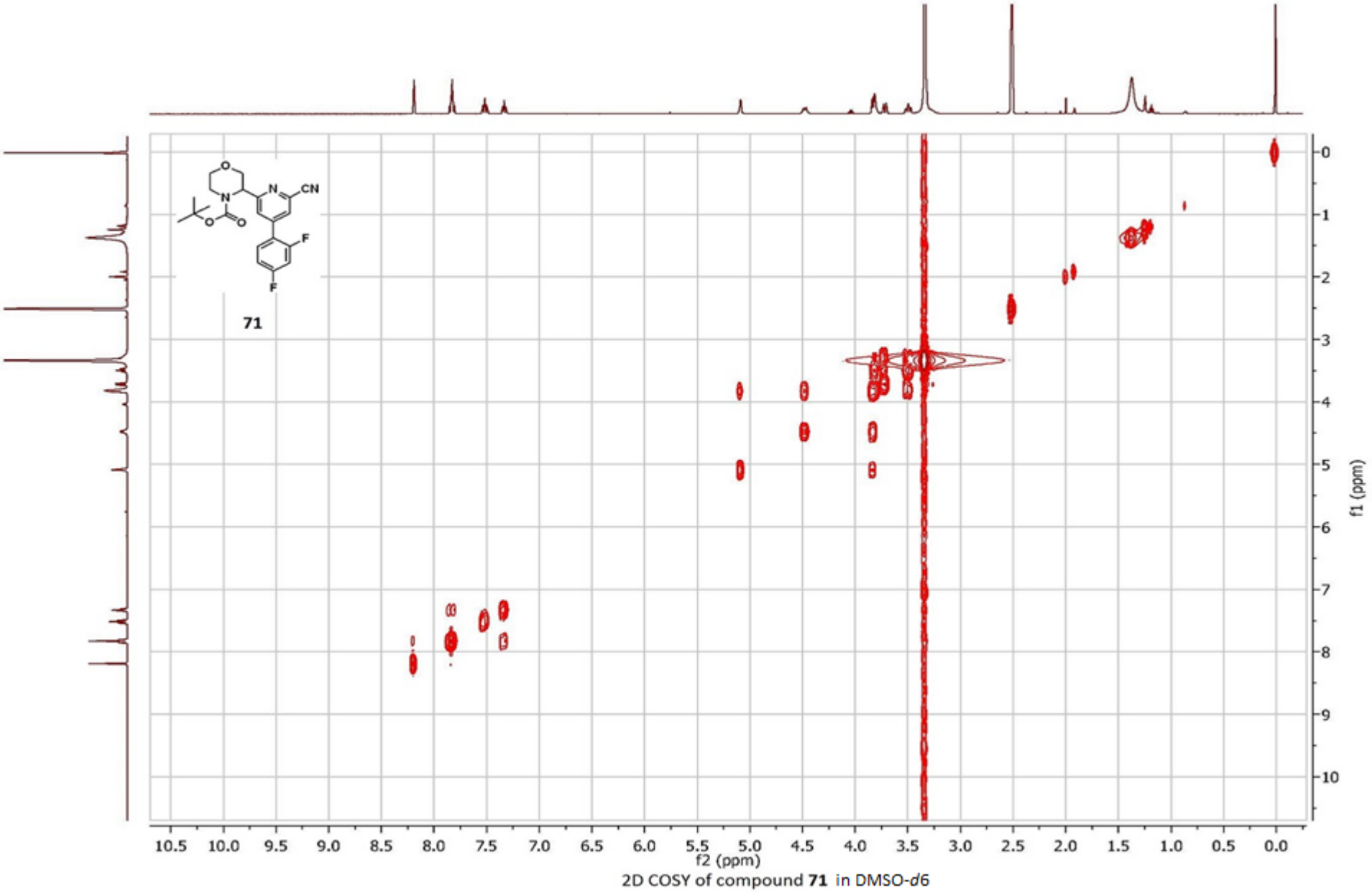
2D HSQC of compound **69** in DMSO-*d*6

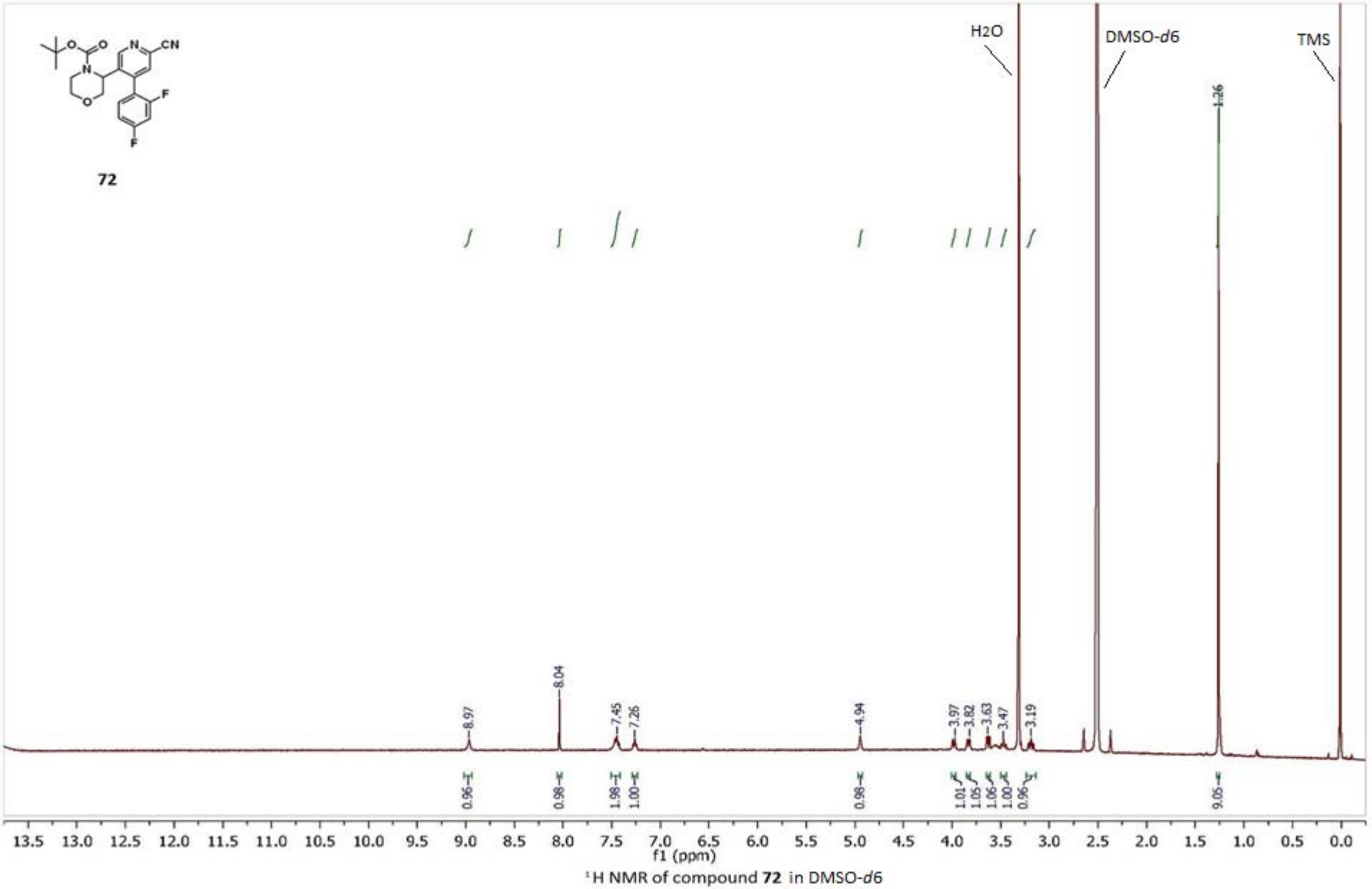

69
f2 (ppm)
f1 (ppm)
2D COSY of compound 69 in DMSO-d6



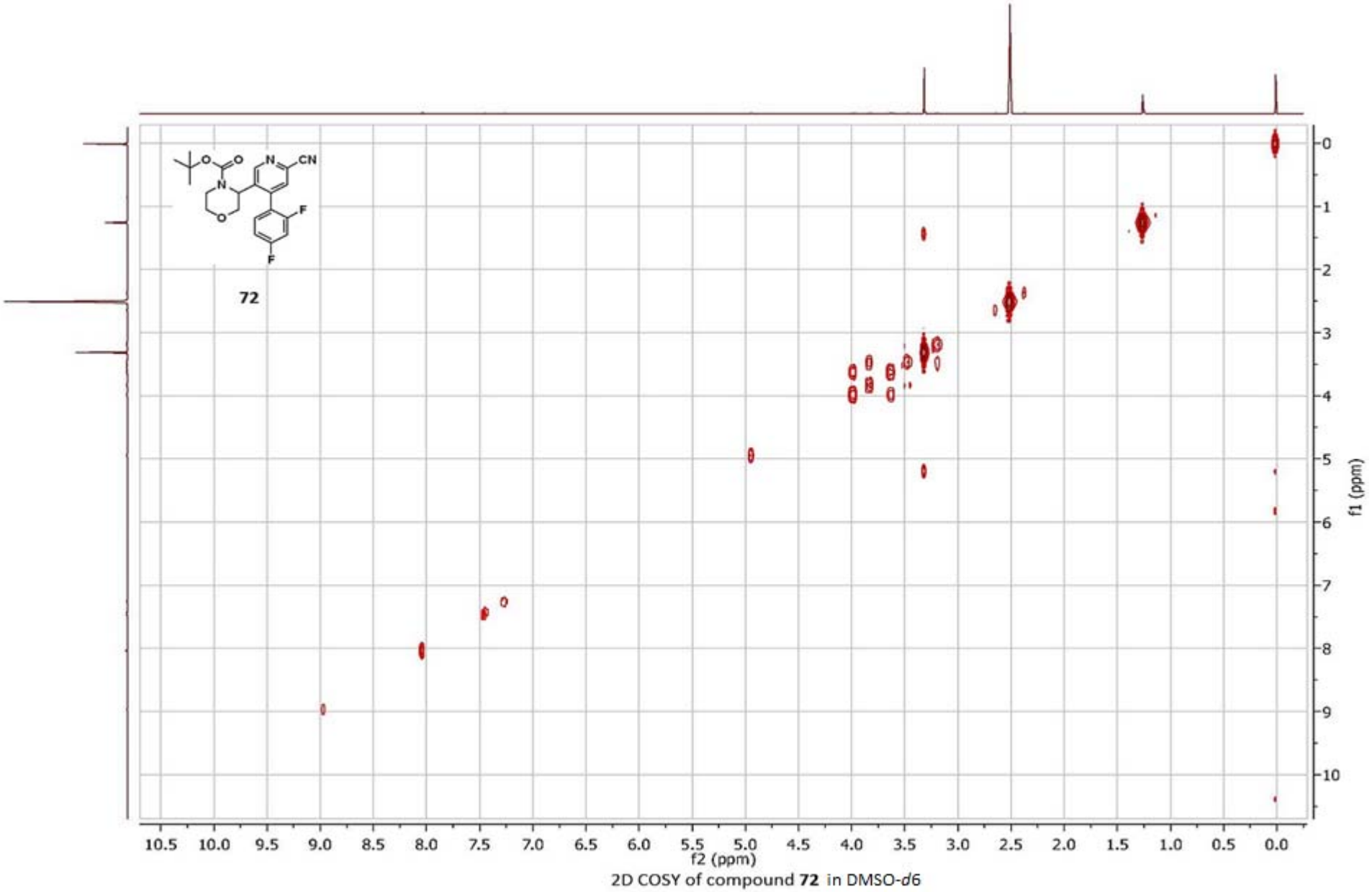
^{1}H NMR of compound **71** in DMSO-*d6*

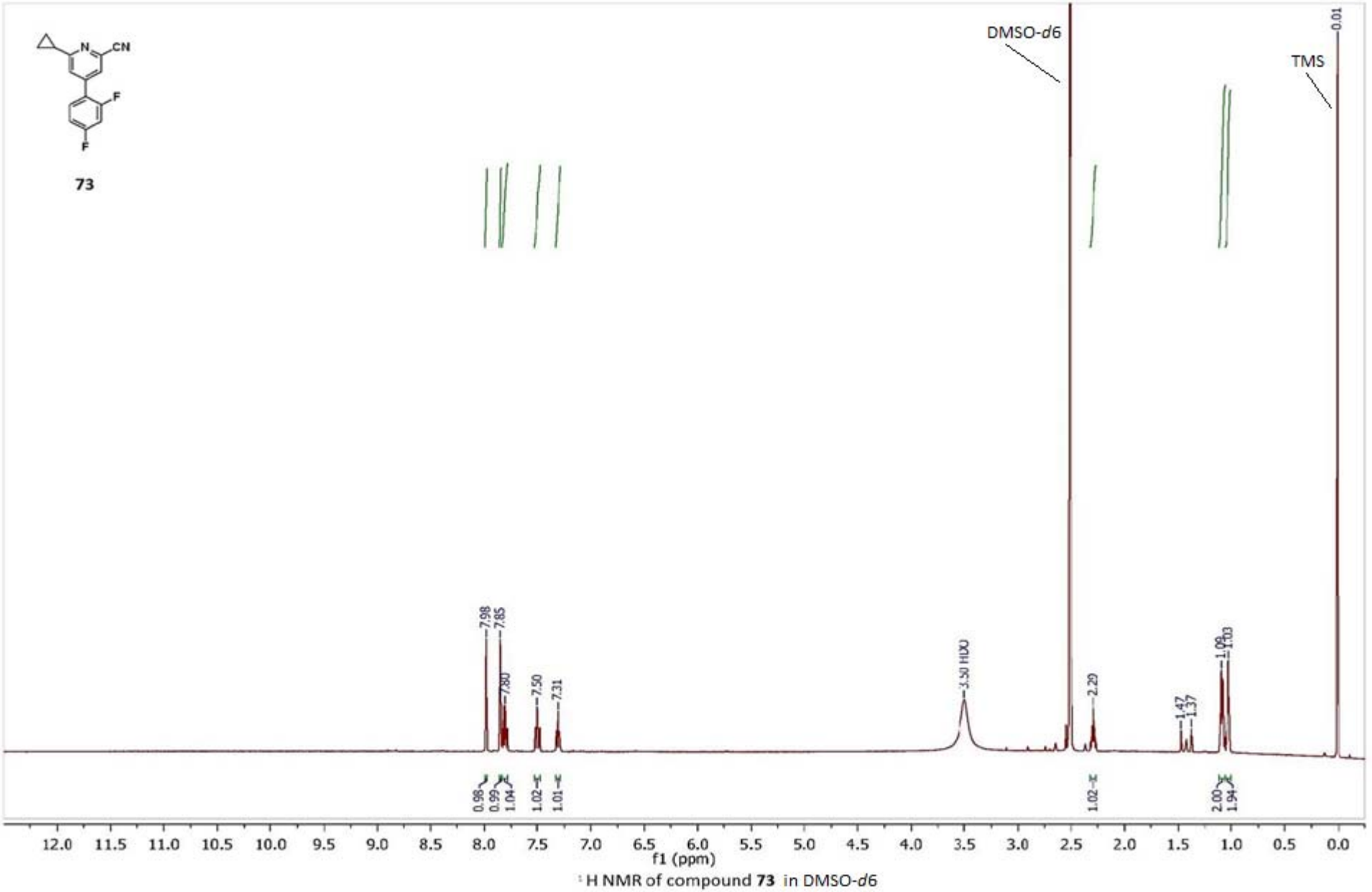

71
f2 (ppm)
f1 (ppm)
2D HSQC of compound 71 in DMSO-d6


71
f2 (ppm)
f1 (ppm)
2D COSY of compound 71 in DMSO-d6

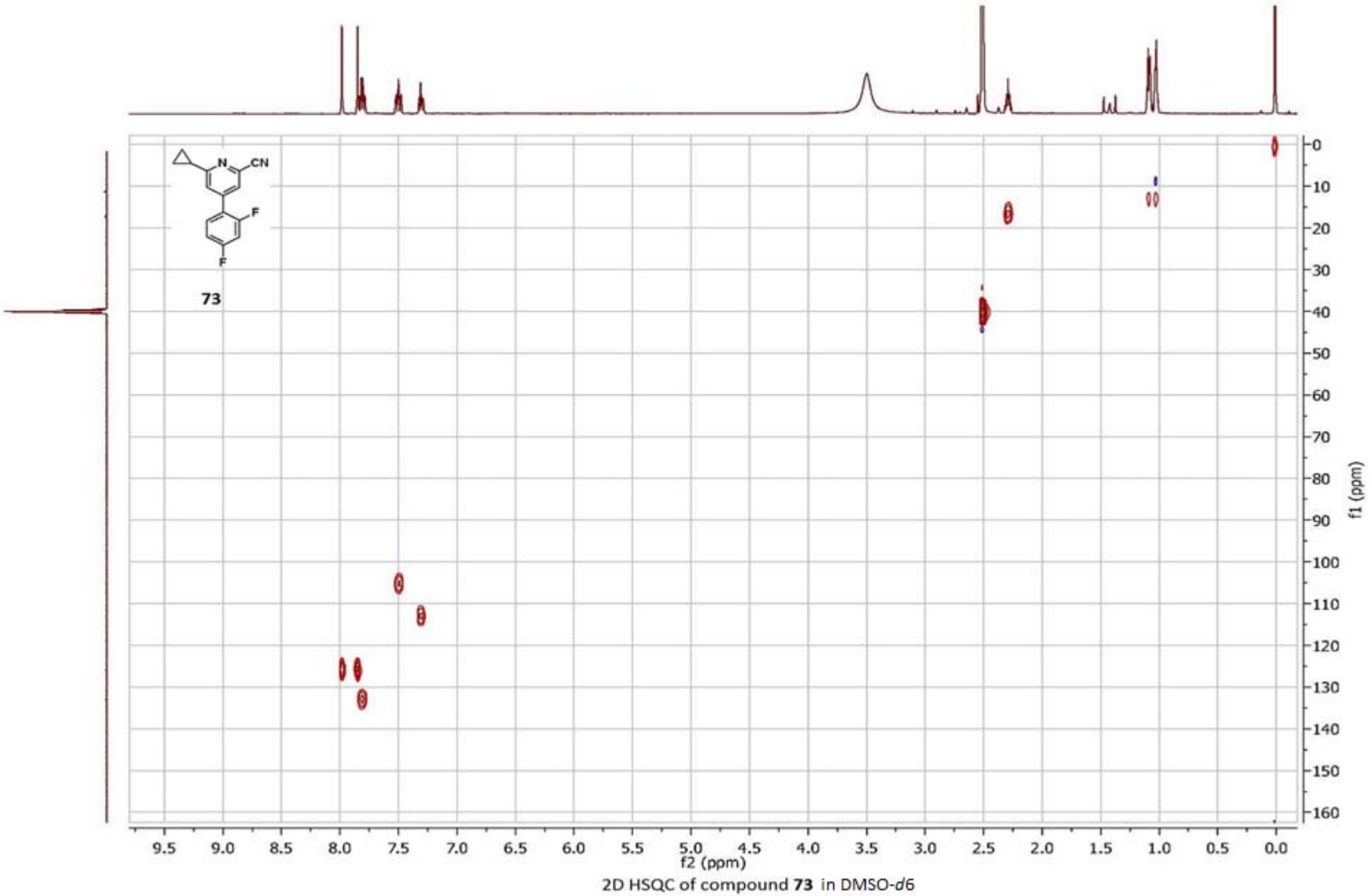


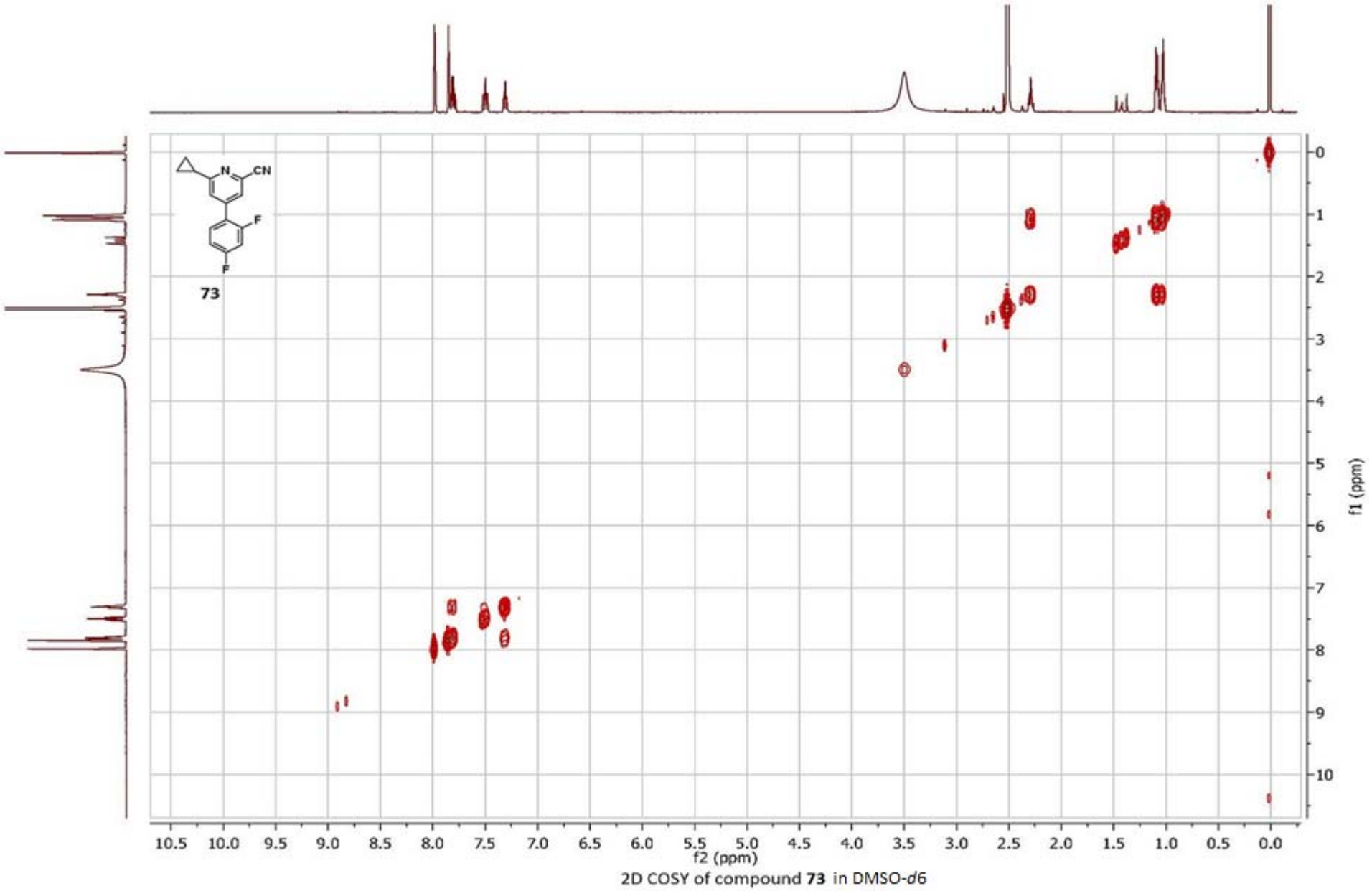
^{1}H NMR of compound **72** in DMSO-*d*6


72
f2 (ppm)
f1 (ppm)
2D COSY of compound 72 in DMSO-d6

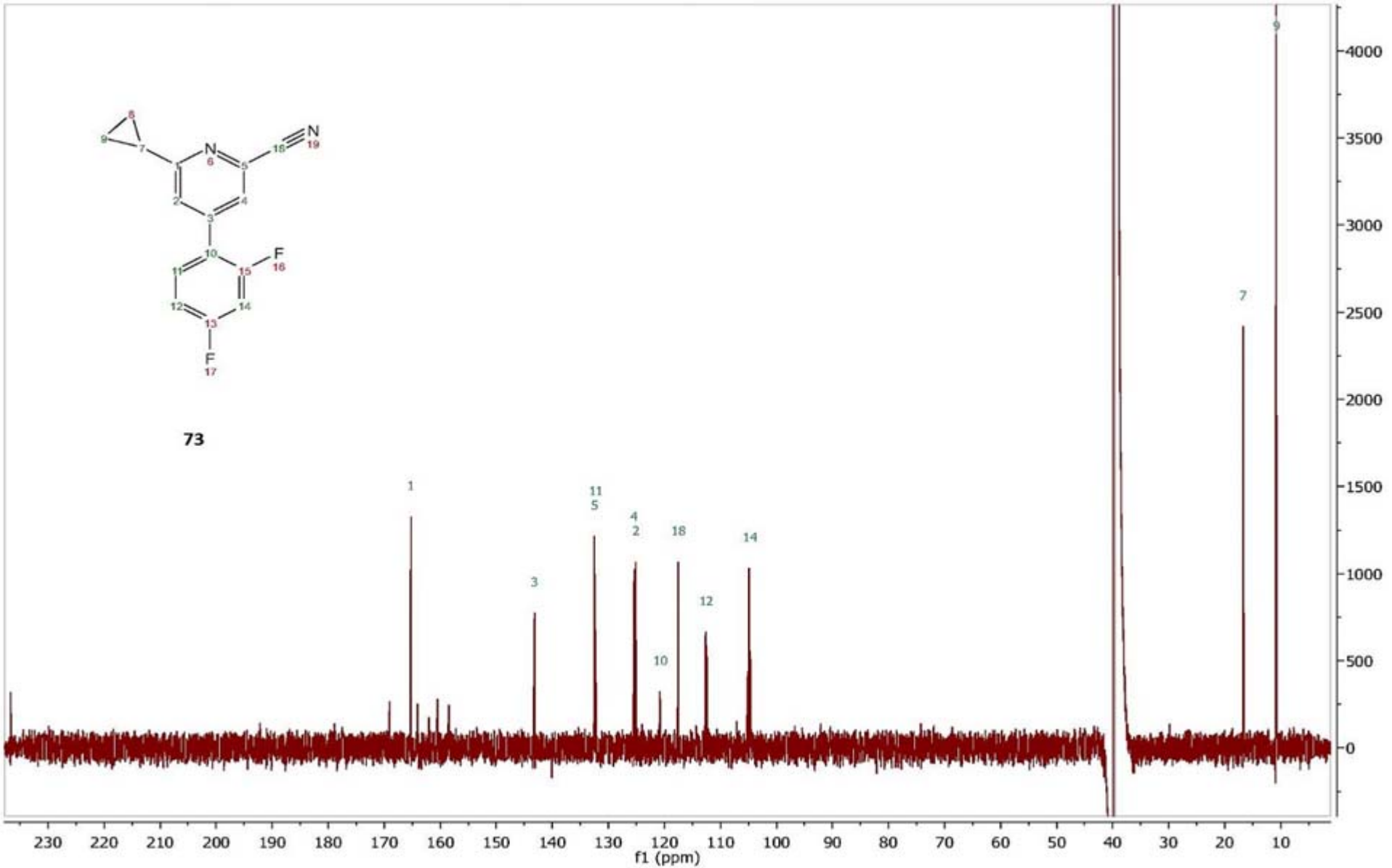


^{1}H NMR of compound **73** in DMSO-*d6*


N
CN
F
F
73
f2 (ppm)
f1 (ppm)
2D HSQC of compound 73 in DMSO-d6



2D COSY of compound **73** in DMSO-*d*6



^{13}C NMR of compound **73** in DMSO-*d*6