Electronic Supplementary Material (ESI) for New Journal of Chemistry.

Supporting Information

for

C_{sp2}-Br Bond Activation of Br-Pyridine by Neophylpalladacycle: Formation of Binuclear Seven-Membered Palladacycle and Bipyridine Species

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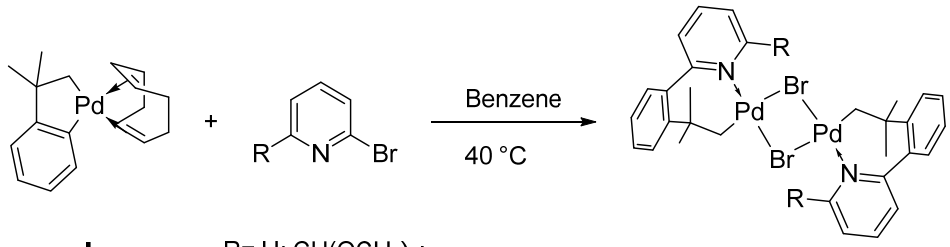
I n d e x

General Information

All reactions were carried out in oven-dried glassware under nitrogen atmosphere unless otherwise noted. Except as otherwise indicated, all reactions were magnetically stirred and monitored by analytical thin layer chromatography (TLC) using Fluka pre-coated silica gel on TLC plates (0.2 mm) with fluorescent indicator 254 nm. The developed chromatography was visualized under UV lamp (254 nm). Flash column chromatography was performed according to the method of Still using silica gel 60 (70-230 mesh) supplied by Aldrich. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Ultra Shield 500 MHz and Advanced 400 MHz spectrometer at ambient temperature. ^{1}H and ^{13}C chemical shifts (δ) are given in parts per million (ppm) relative to TMS. The solvent signal was used as reference and the chemical shifts converted to the TMS scale. The proton spectra are reported as follows δ (position of proton, multiplicity, coupling constant J, number of protons). Multiplicity is indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (quintet), h (septet), m (multiplet) and bs (broad singlet). Complete assignment of each compound were aided using ^{1}H-^{1}H COSY, ^{1}H-^{1}H NOESY, ^{1}H-$^{13}C\{^{1}H\}$ HSQC, and ^{1}H-$^{13}C\{^{1}H\}$ HMBC.

A high resolution, electrospray ionization–quadrupole-time of flight mass spectrometer maXis impact ESI-QTOFMS equipped with Data Analysis 4.1 (Bruker Daltonics) was used with sample introduction by direct infusion (3 µL/min). ESI was operated in a positive mode with ion spray voltage 4500 V, dry gas 4 L/min, drying temperature 180 °C and nebulizing gas pressure 0.4 bar. Spectra were acquired in the m/z range 80–800, using a lock-mass standard m/z 299.2945 (methyl stearate) in the ion source. Before infusion, the samples were diluted with acetonitrile: 0.1% v/v aqueous formic acid (80:20). N,N-dimethylformamide, 1,5-cyclooctadiene, neophyl chloride, triphenylphosphine, magnesium, palladium acetate, sodium hydroxide, K_2CO_3, Cs_2CO_3, Et_2O, toluene, dichloromethane, and all 2-halo-pyridines were purchased from Sigma-Aldrich. Palladium chloride was purchased from Pressure Chemmical Co. Neophyl-Mg-Cl Grignard reagent,[1] palladacycle I,[2] $[PdCl_2(COD)]$,[3] $[PdCl(Me)(COD)]$,[4] $[PdCl(Neophyl)(COD)]$[5] and $[PdCl_2(PPh_3)_2]$,[6] were synthesized according to the procedure described in the literature. All commercial available compounds (Aldrich) were used as received.

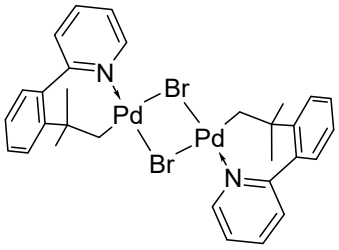
General procedure for the synthesis of seven-membered Pd(II) binuclear complexes.



I R= H; $CH(OCH_2)_2$; COH; CN

1, R= H
2, R= $CH(OCH_2)_2$
3, R= COH
4, R= CN

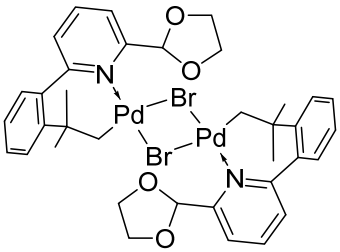
To a solution of 0.1 mmol of palladacycle **1** in 5 mL of benzene, 0.1 mmol of the 2-bromopyridine derivative was added, the reaction mixture was stirred at room temperature for 30 minutes. The corresponding solid was filtered and washed twice with hexanes, and dried under reduced pressure, to get the palladacycle without any further purification.



Compound 1: Prepared following the general procedure to afford a yellow pale solid (22 mg, 56 %).

^{1}H NMR (500 MHz, DMSO-d_6) δ = 8.86 (d, *J*=5.5, 1H), 8.14 (td, *J*=7.7, 1.6, 1H), 7.75 (d, *J*=7.8, 1H), 7.66 – 7.64 (m, 1H), 7.62 (d, *J*=8.4, 1H), 7.51 (td, *J*=7.6, 1.6, 1H), 7.40 (td, *J*=7.4, 1.1, 1H), 7.33 (dd, *J*=7.5, 1.6, 1H), 2.45 (bs, 1H), 2.24 (bs, 1H), 1.44 (s, 3H), 0.61 (s, 3H).

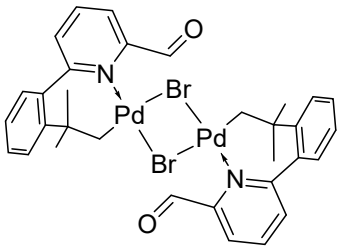
^{13}C NMR (126 MHz, DMSO-d_6) δ = 160.81, 151.89, 139.76, 138.78, 131.38, 129.29, 126.17, 125.46, 125.43, 124.88, 124.11, 52.41, 32.50, 32.22.



Compound 2: Prepared following the general procedure to afford a yellow pale solid (25 mg, 53 %).

^{1}H NMR (500 MHz, DMSO-d_6) δ = 8.23 (t, *J*=7.8, 1H), 7.82 (d, *J*=7.9, 1H), 7.78 (d, *J*=7.3, 1H), 7.62 (d, *J*=7.9, 1H), 7.52 (td, *J*=7.7, 1.6, 1H), 7.41 (td, *J*=7.4, 1.1, 1H), 7.35 (m, 1H), 6.90 (s, 1H), 4.36 – 4.27 (m, 1H), 4.17 – 4.05 (m, 3H), 2.47 (d, *J*=7.5, 1H), 2.41 (d, *J*=7.3, 1H), 1.41 (s, 3H), 0.57 (s, 3H).

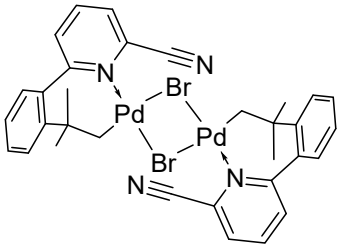
^{13}C NMR (126 MHz, DMSO-d_6) δ = 160.49, 156.78, 146.57, 140.87, 139.18, 131.40, 129.38, 126.24, 125.46, 124.55, 121.95, 103.58, 66.03, 64.89, 45.62, 32.44, 32.35.



Compound 3: Prepared following the general procedure to afford a yellow pale solid (19 mg, 44 %)

^{1}H NMR (500 MHz, DMSO-d_6) δ = 11.17 (s, 1H), 8.40 (t, *J*=7.7, 1H), 8.17 (dd, *J*=7.7, 1.3, 1H), 8.07 (dd, *J*=7.8, 1.3, 1H), 7.67 (d, *J*=7.9, 1H), 7.56 (td, *J*=7.7, 1.7, 1H), 7.45 (t, *J*=7.4, 1H), 7.40 (dd, *J*=7.5, 1.6, 1H), 2.54 (bs, 2H), 1.45 (s, 3H), 0.67 (s, 3H).

^{13}C NMR (126 MHz, DMSO) δ = 190.58, 161.47, 148.97, 146.51, 141.50, 138.77, 131.73, 129.70, 129.34, 126.40, 124.90, 123.39, 46.51, 32.67, 32.35.



Compound 4: Prepared following the general procedure to afford a yellow pale solid (22 mg, 51%).

^{1}H NMR (500 MHz, DMSO-d_6) δ = 8.45 – 8.37 (m, 1H), 8.14 (dd, *J*=6.7, 2.6, 1H), 7.68 (d, *J*=8.0, 1H), 7.57 (td, *J*=7.6, 1.6, 1H), 7.45 (t, *J*=7.4, 1H), 7.44 – 7.38 (m, 1H), 2.47 (d, *J*=8.1, 1H), 2.38 (d, *J*=7.9, 2H), 1.44 (s, 3H), 0.61 (s, 3H).

^{13}C NMR (126 MHz, DMSO-d_6) δ = 162.63, 146.31, 141.39, 137.38, 133.47, 131.45, 130.15, 130.09, 129.01, 126.48, 125.21, 116.07, 46.97, 32.60, 32.49.

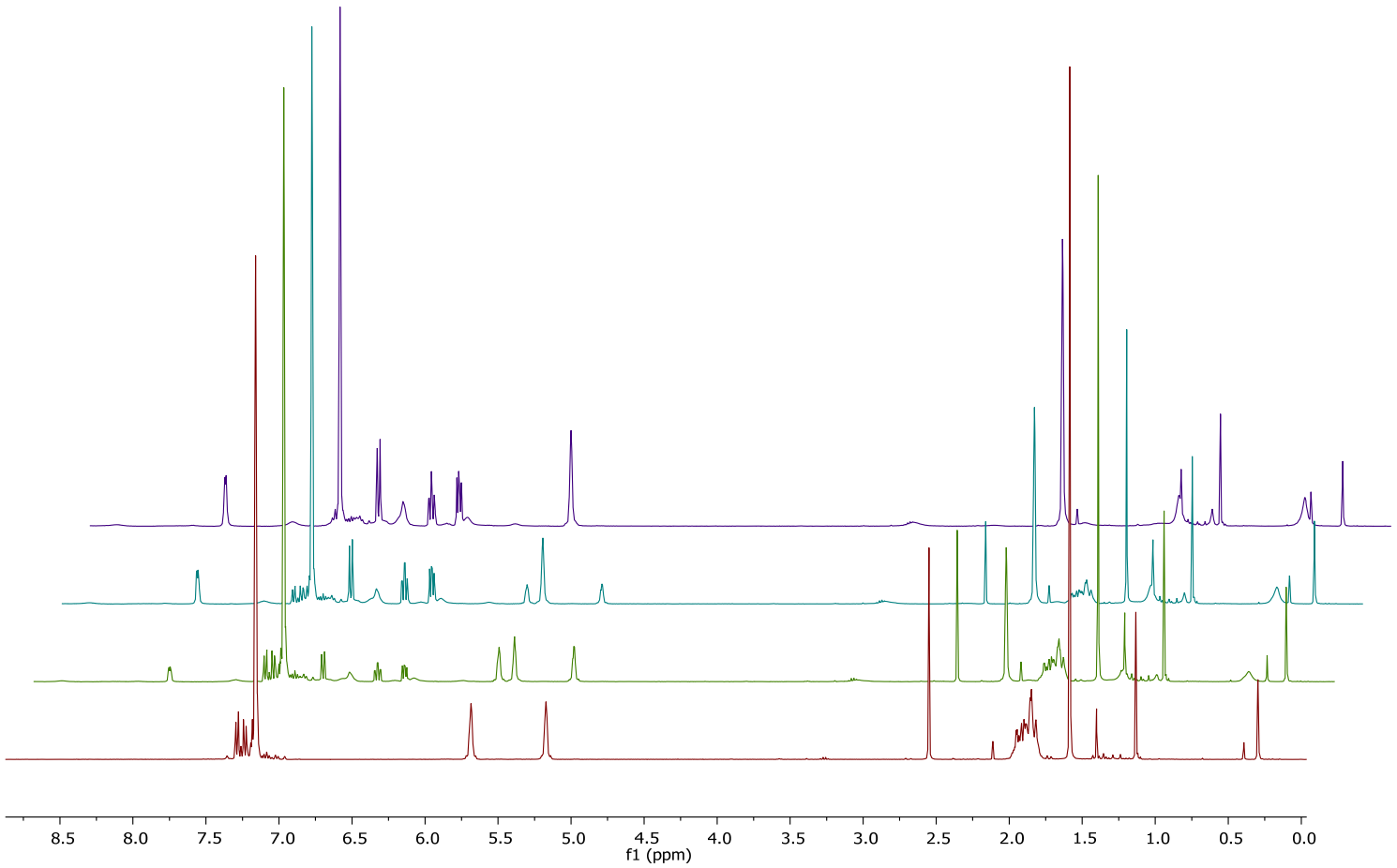


Figure S1. ^{1}H NMR spectra for reaction of **I** and BrPy. From bottom to top, palladacycle **I**, reaction I and BrPy 10 min, 20 min and 30 min at $CDCl_3$ at r.t.

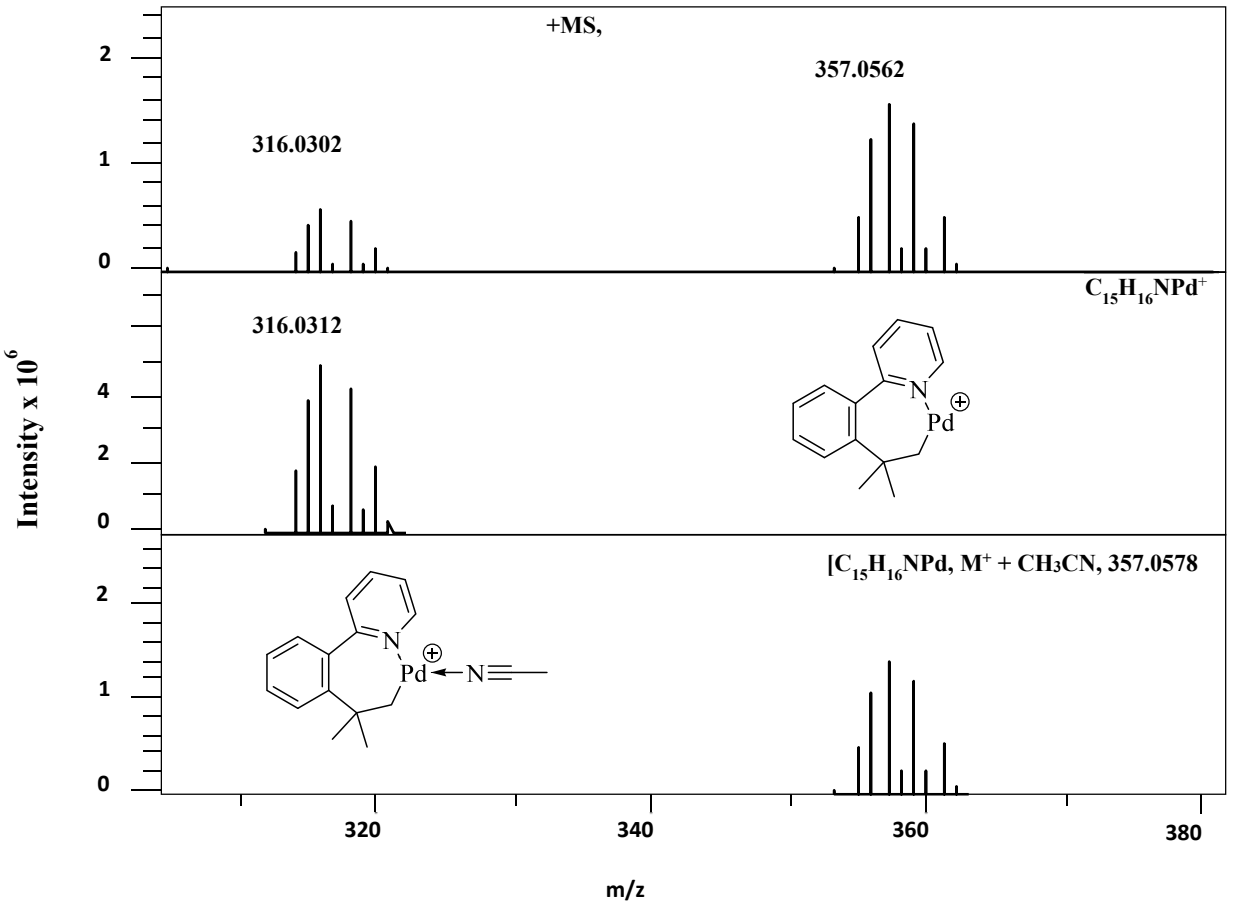


Figure S2. Upper Box: High resolution mass spectrum for compound **1** in CH_3CN solution. Lower boxes: Theoretical isotopic patterns and molecular structures of the two ions detected

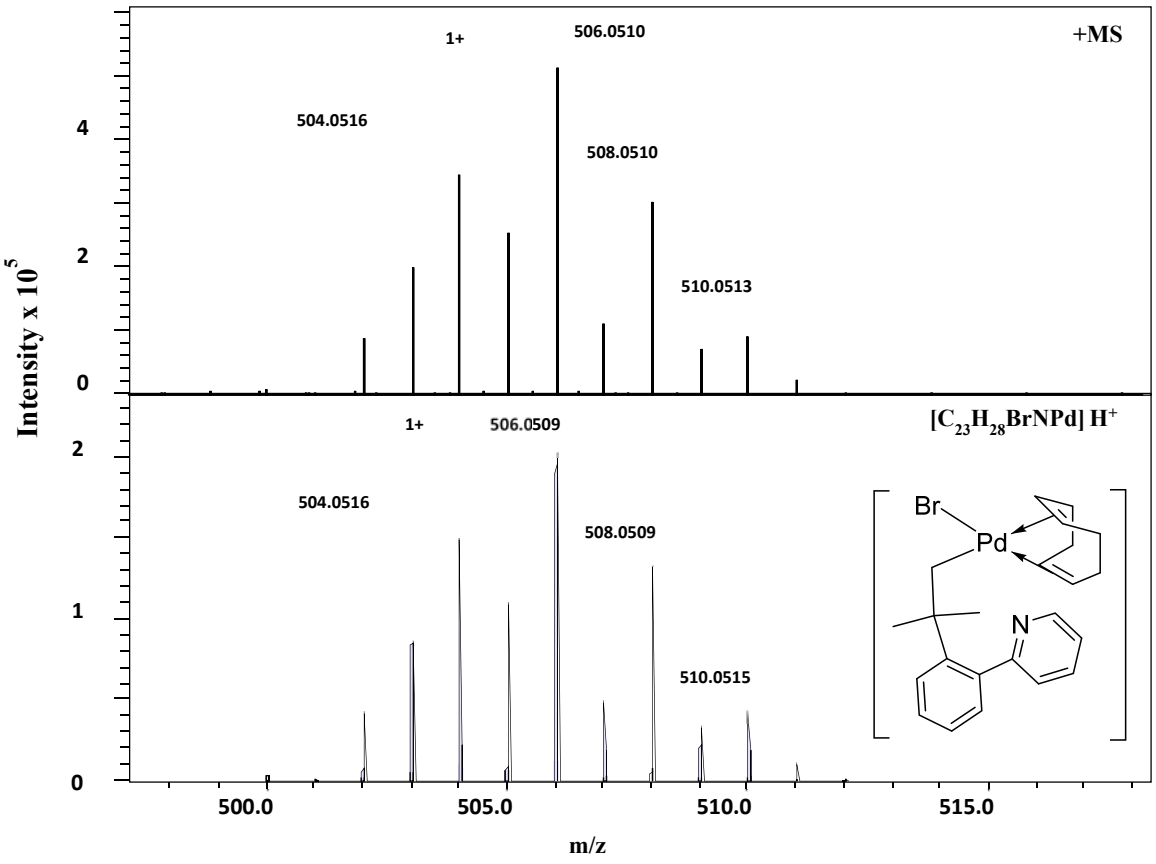


Figure S3. Upper box: Selected region of ESI-HRMS spectrum acquired for the liquor crude solution; Lower box: theoretical isotopic pattern for compound **1a**.

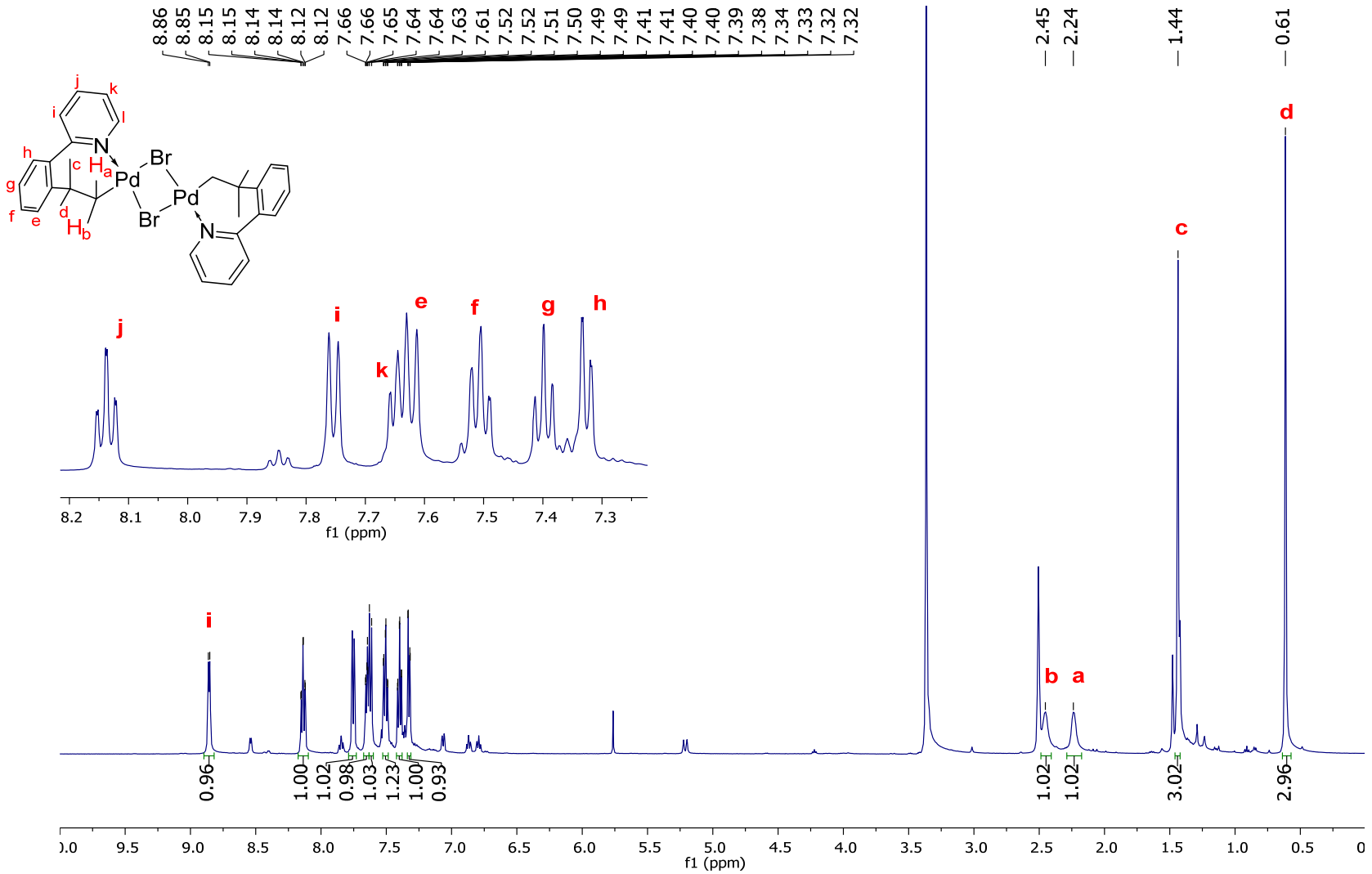


Figure S4. ^{1}H NMR spectrum of **1** in dmso-d_6 at rt.

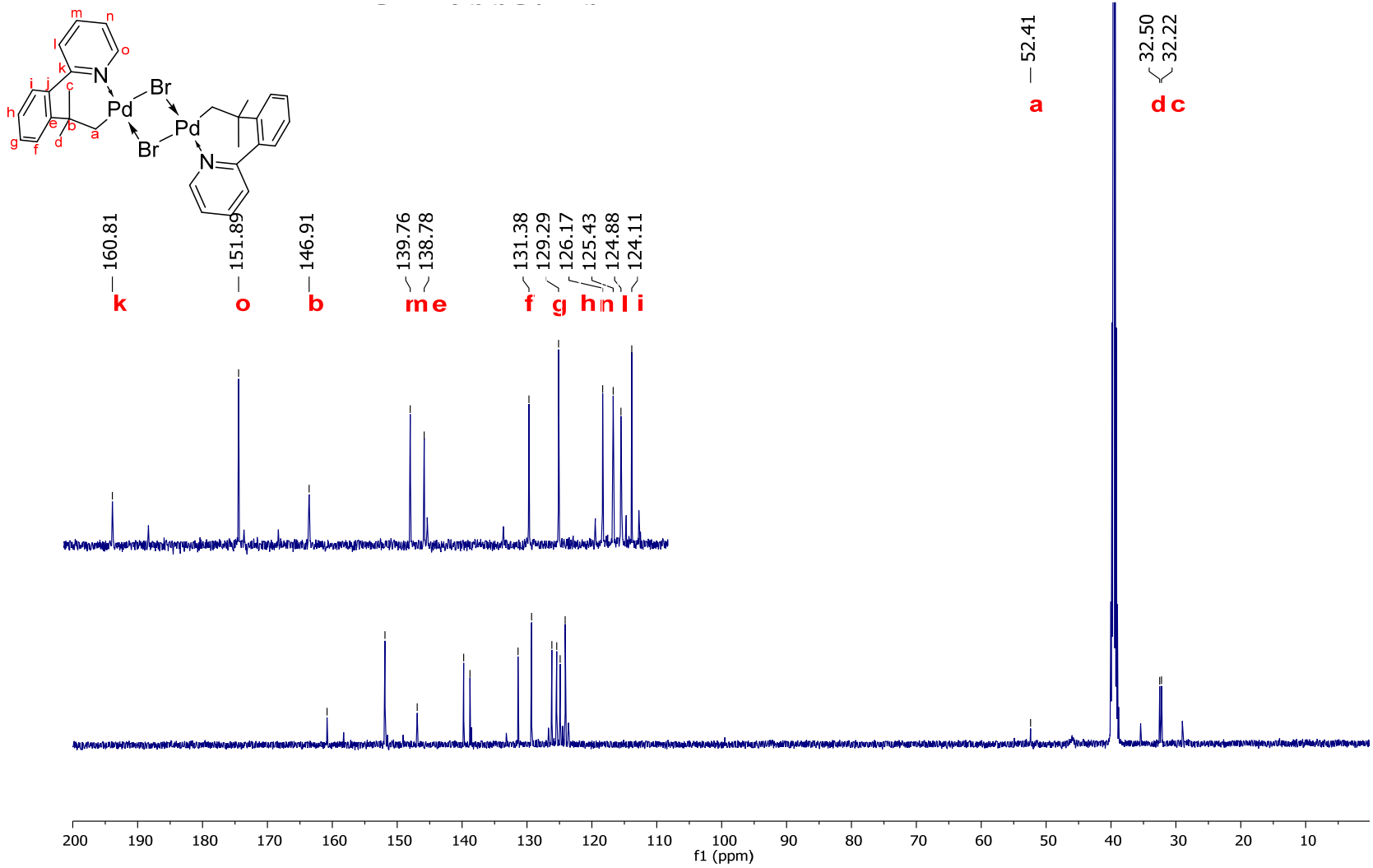


Figure S5. ^{13}C NMR spectrum of **1** in dmso-d_6 at rt.

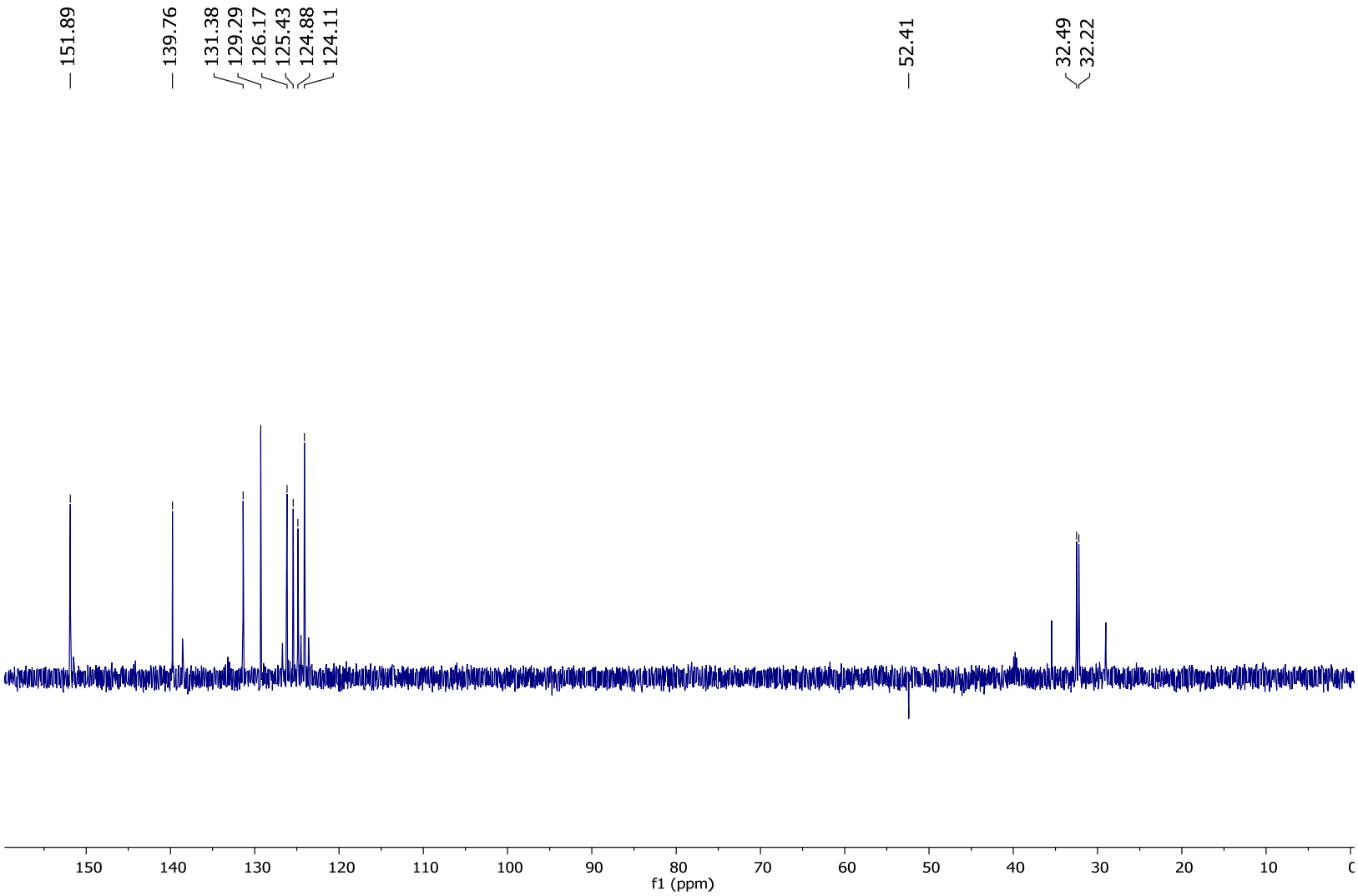


Figure S6. ^{13}C DEPT NMR spectrum of **1** in dmso-d_6 at rt.

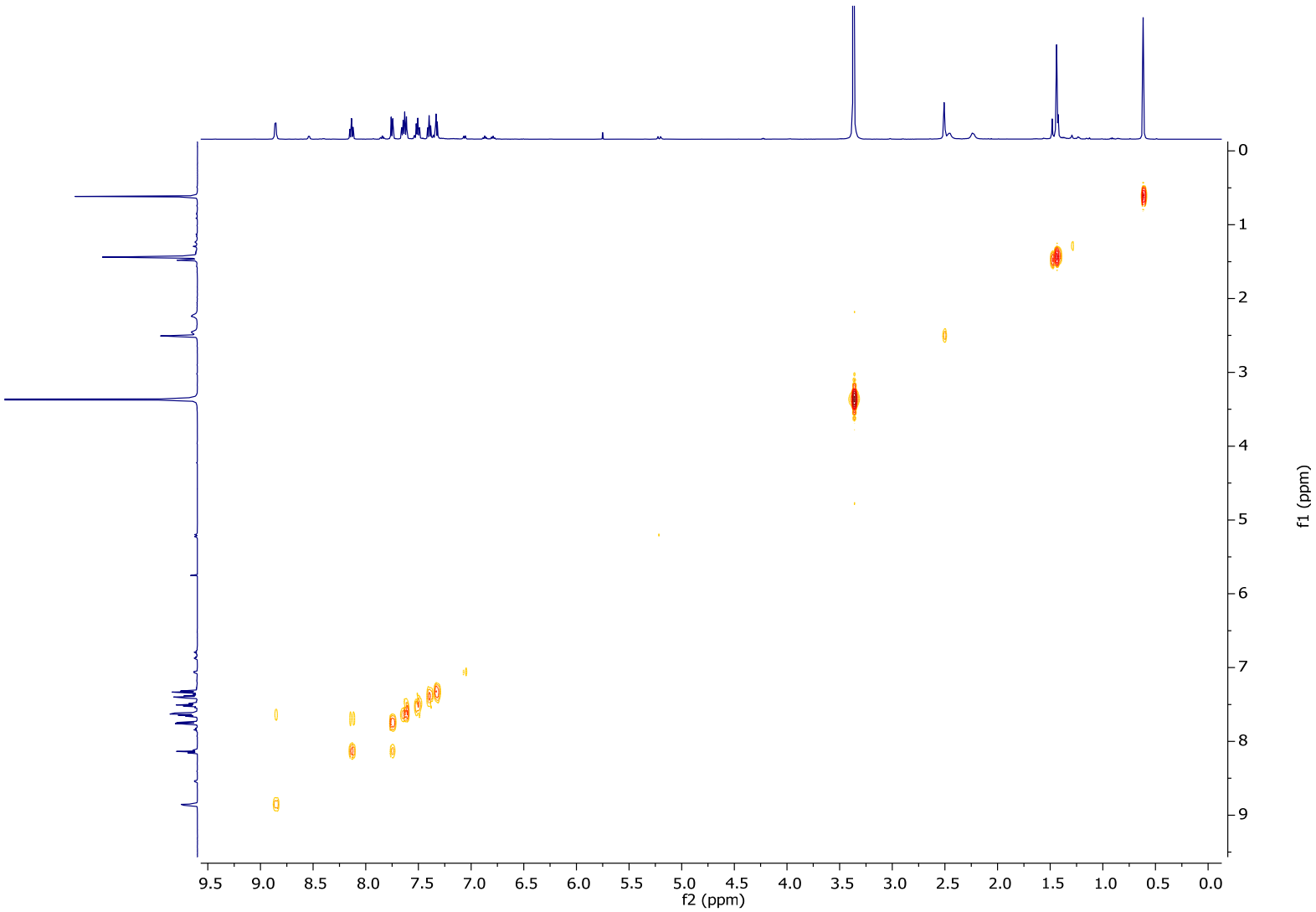


Figure S7. ^{1}H-^{1}H COSY NMR spectrum of **1** in dmso-d_6 at rt.

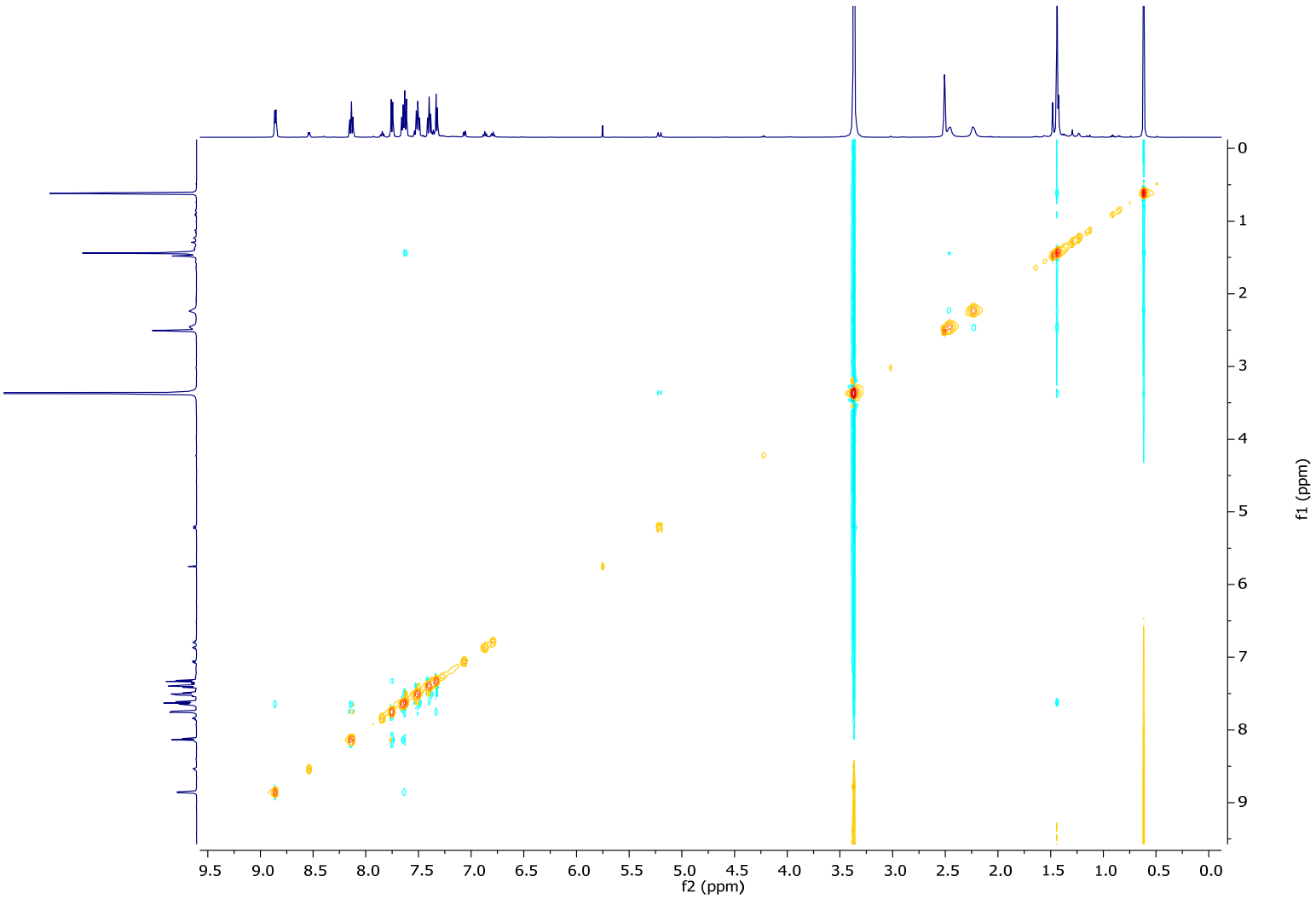


Figure S8. ^{1}H-^{1}H NOESY NMR spectrum of **1** in dmso-d_6 at rt.

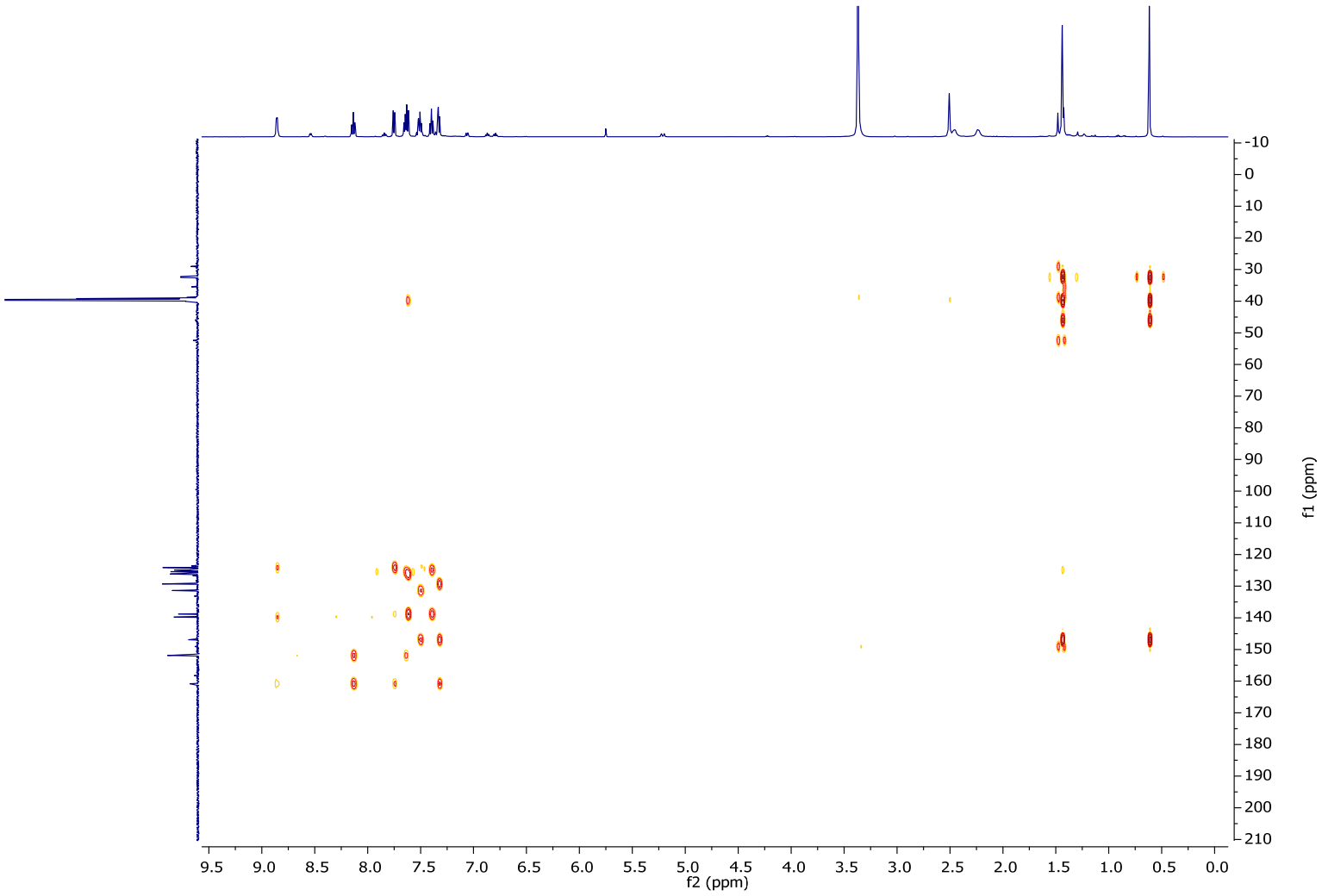


Figure S9. ^{1}H-^{13}C HMQC NMR spectrum of **1** in dmso-d_6 at rt.

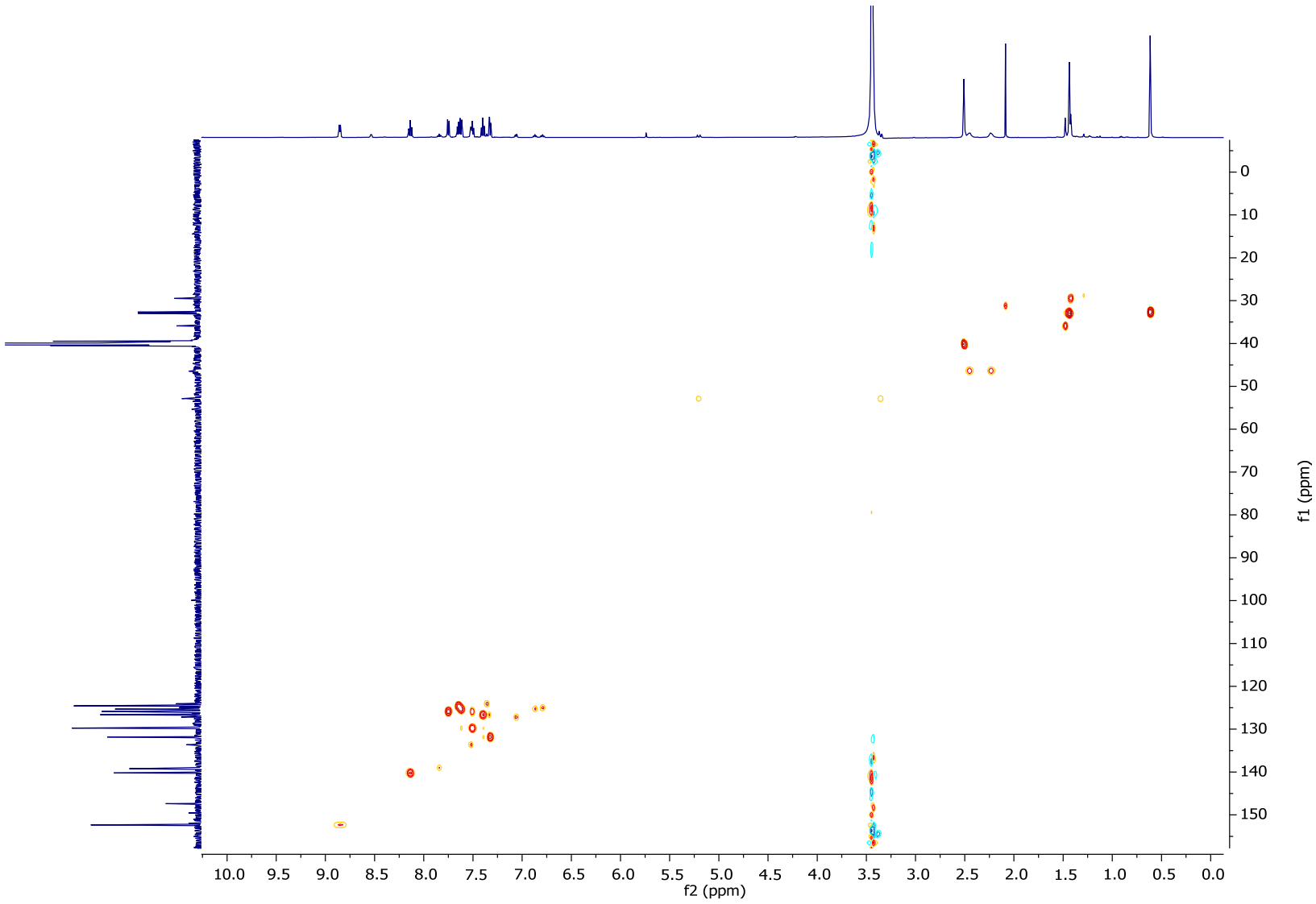


Figure S10. ^{1}H-^{13}C HSQC NMR spectrum of **1** in dmso-d_6 at rt.

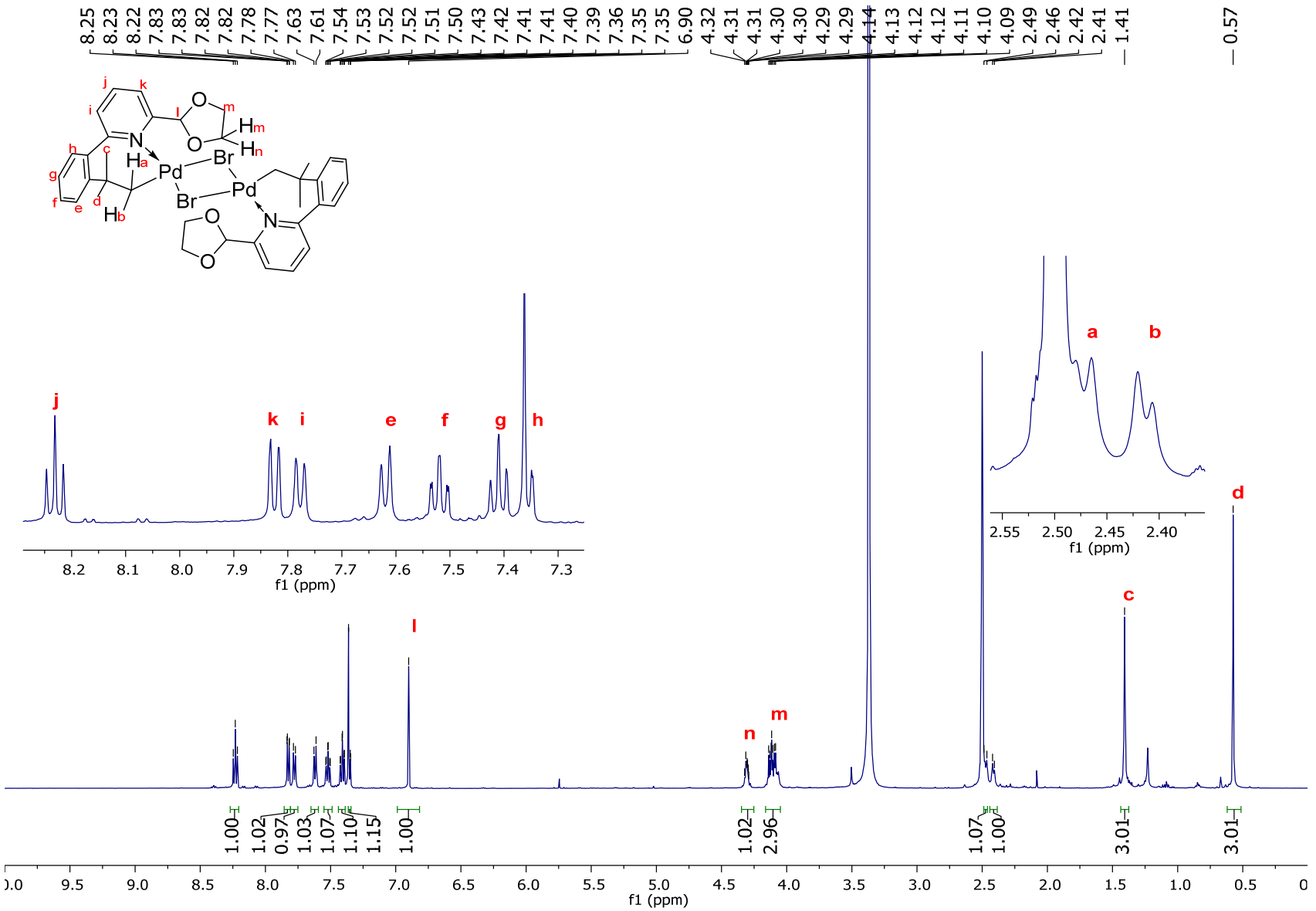


Figure S11. ^{1}H NMR spectrum of **2** in dmso-d_6 at rt.

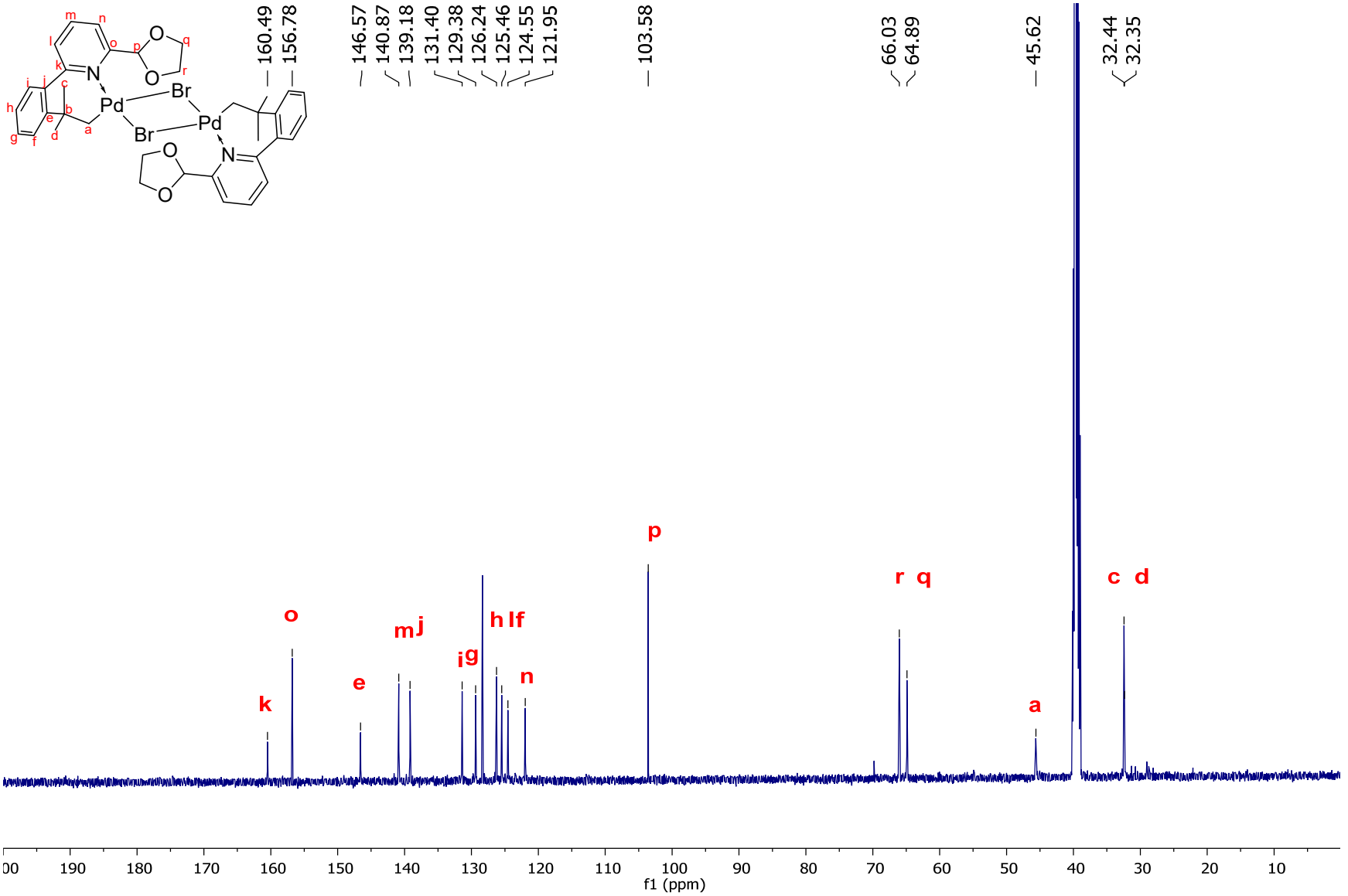


Figure S12. ^{13}C NMR spectrum of **2** in dmso-d_6 at rt.

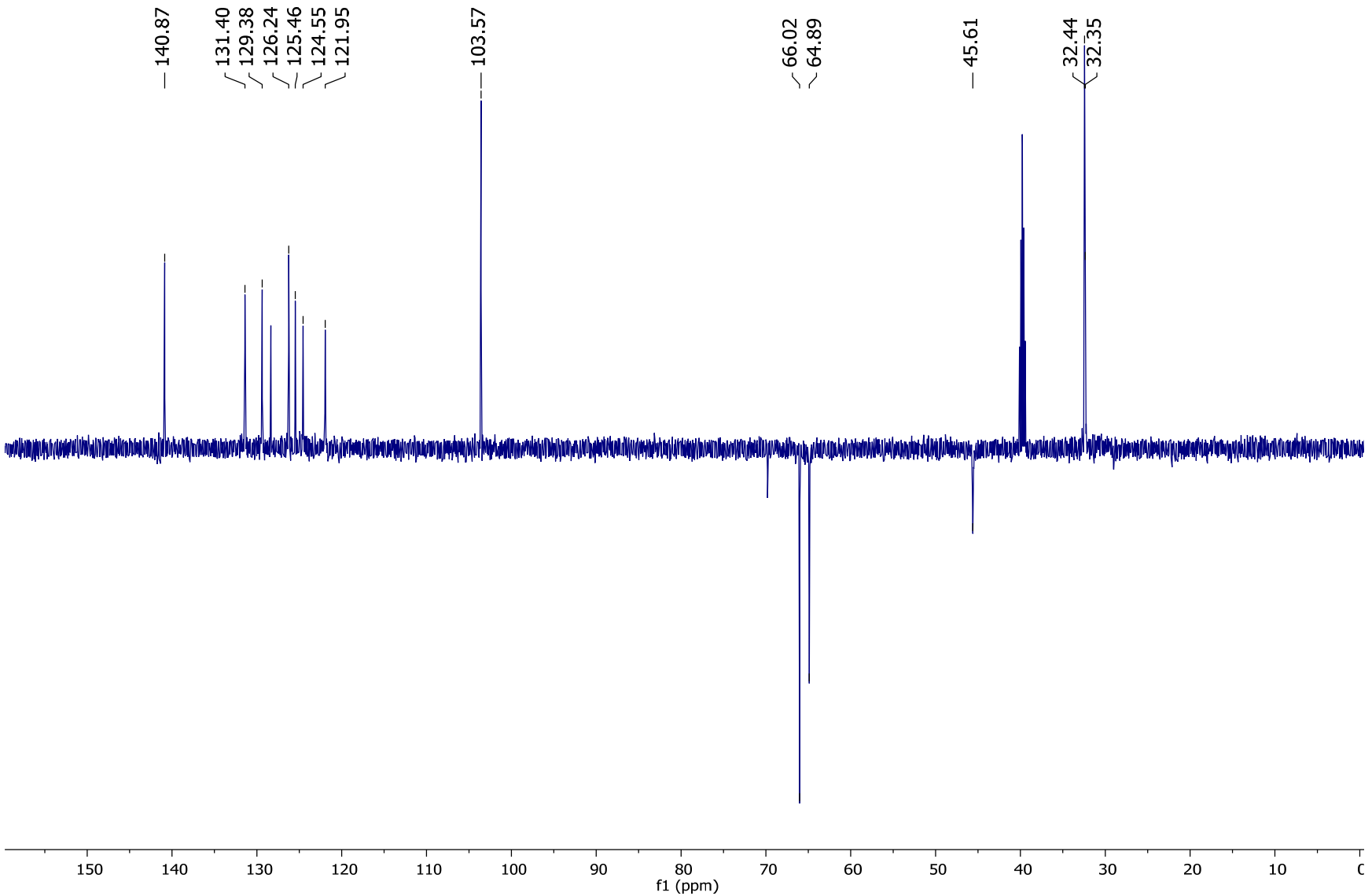


Figure S13. ^{13}C DEPT NMR spectrum of **2** in dmso-d_6 at rt.

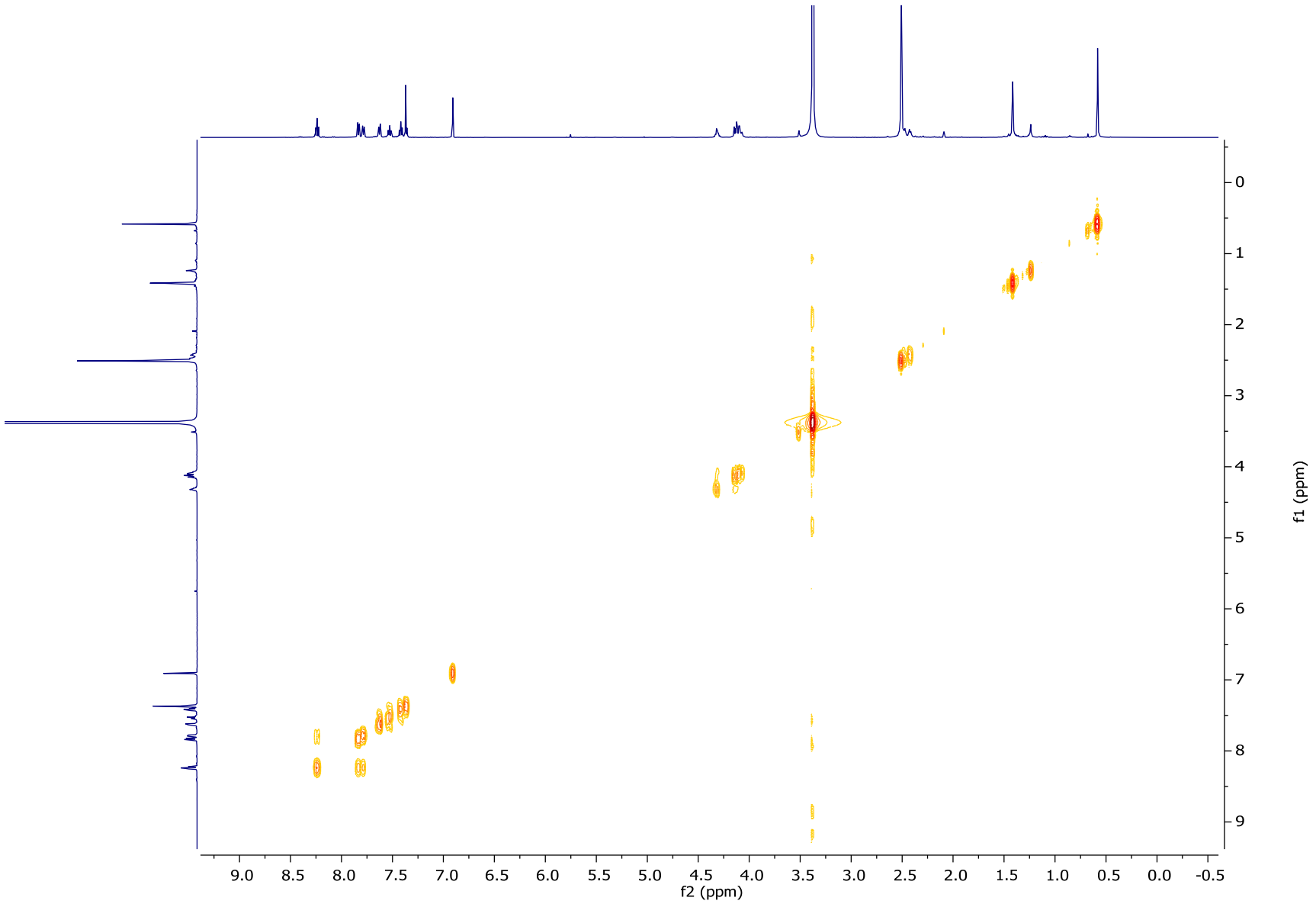


Figure S14. ^{1}H-^{1}H COSY NMR spectrum of **2** in dmso-d_6 at rt.

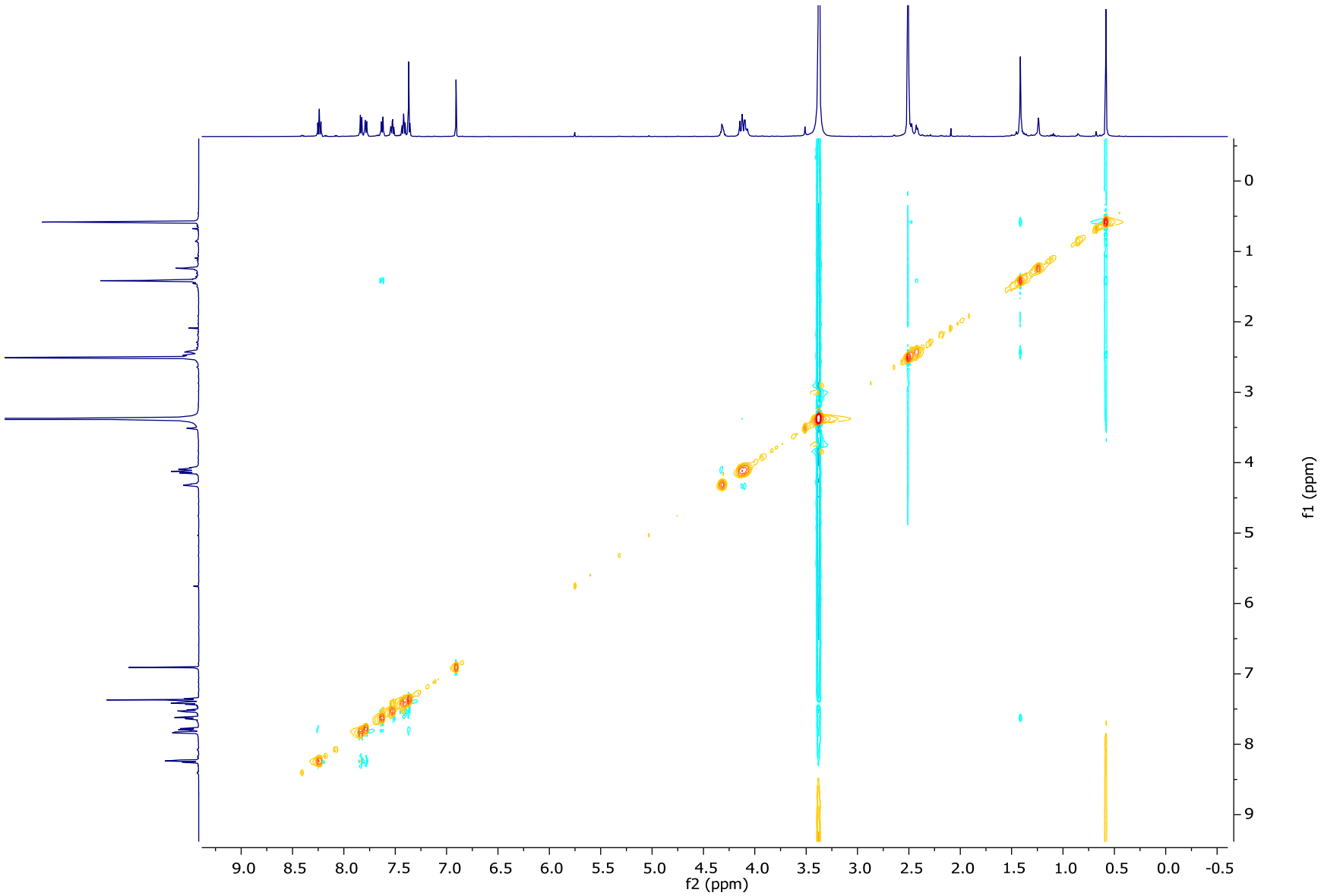


Figure S15. ^{1}H-^{1}H NOESY NMR spectrum of **2** in dmso-d_6 at rt.

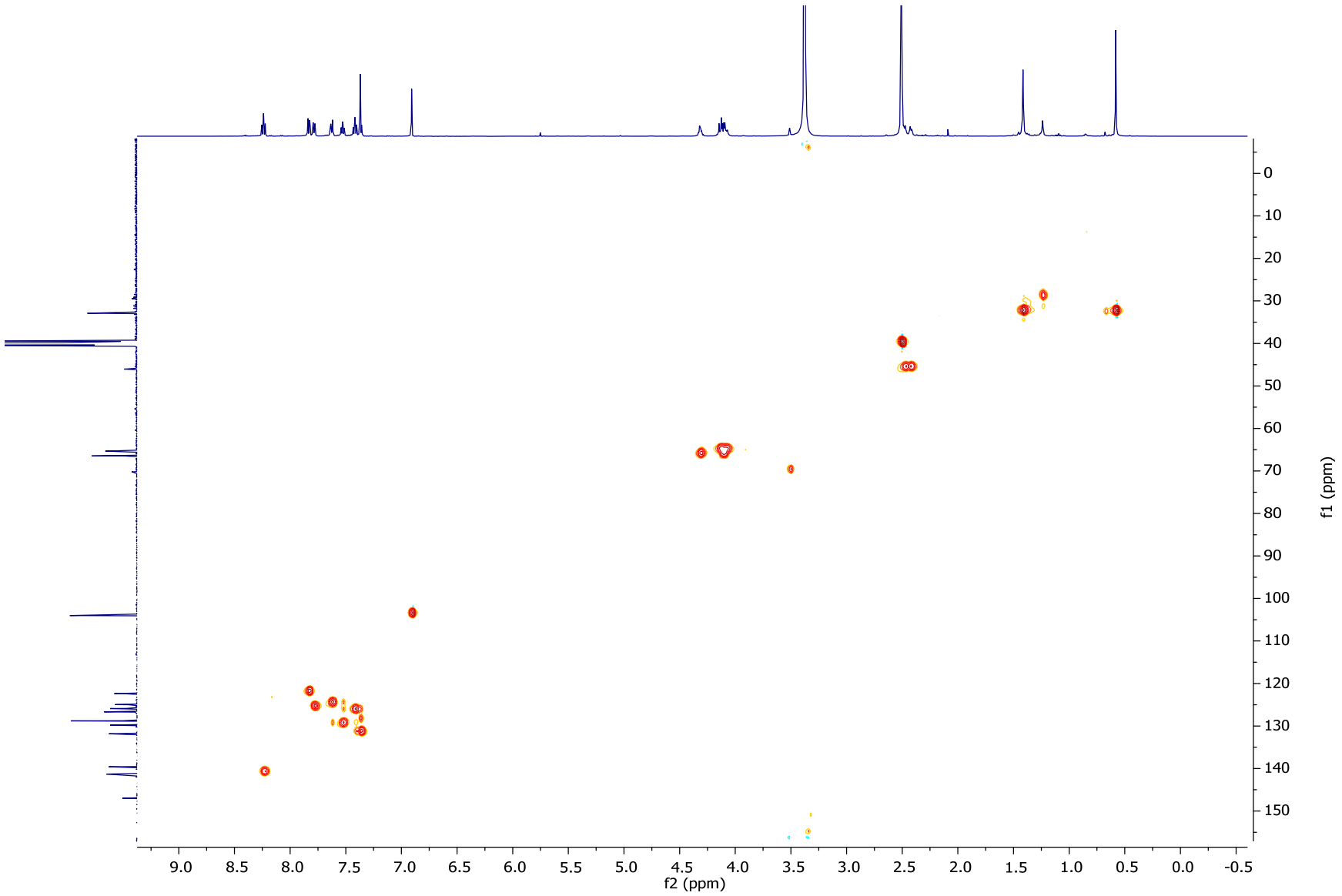


Figure S16. ^{1}H-^{13}C HSQC NMR spectrum of **2** in dmso-d_6 at rt.

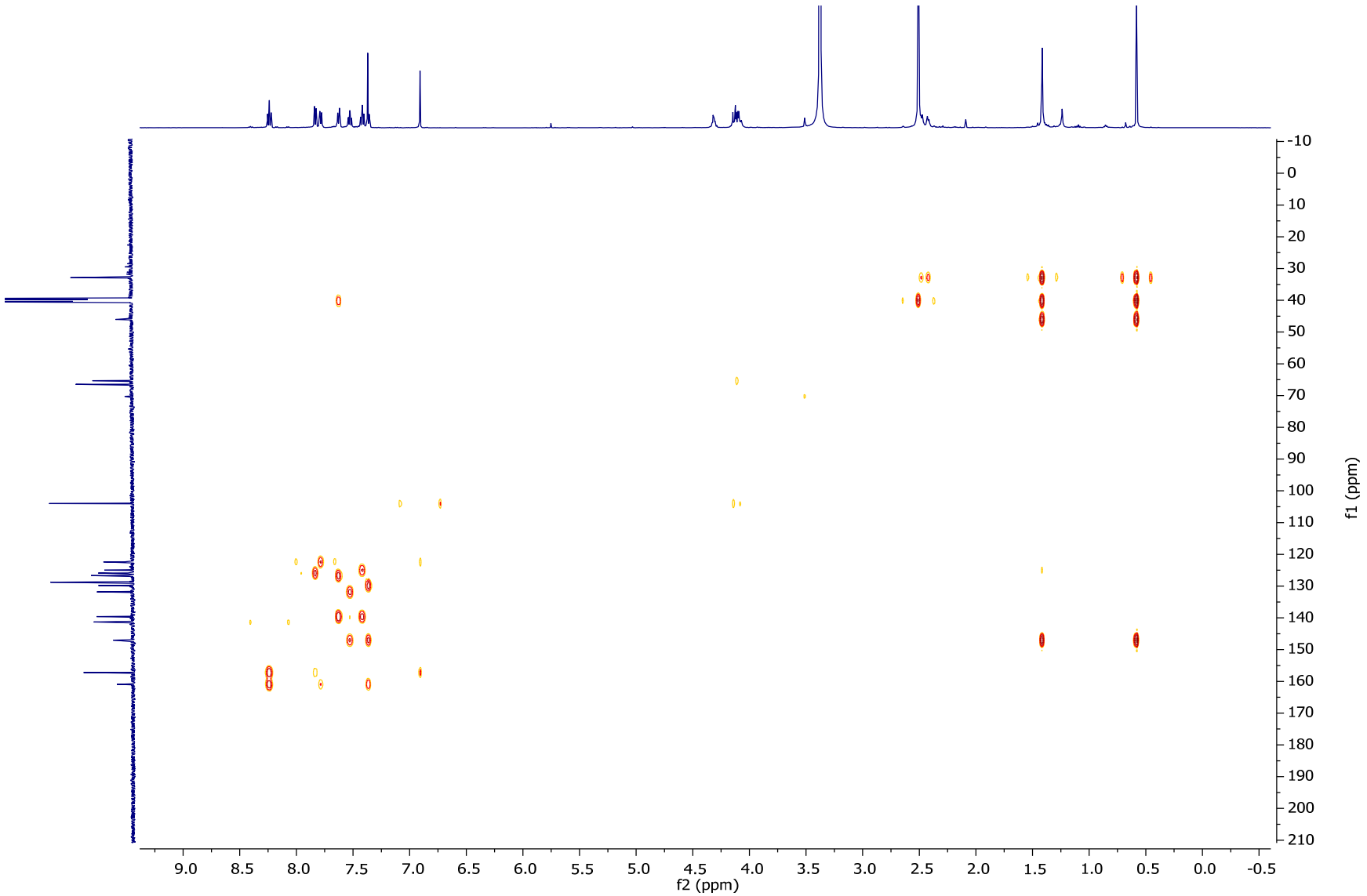


Figure S17. ^{1}H-^{13}C HMQC NMR spectrum of **2** in dmso-d_6 at rt.

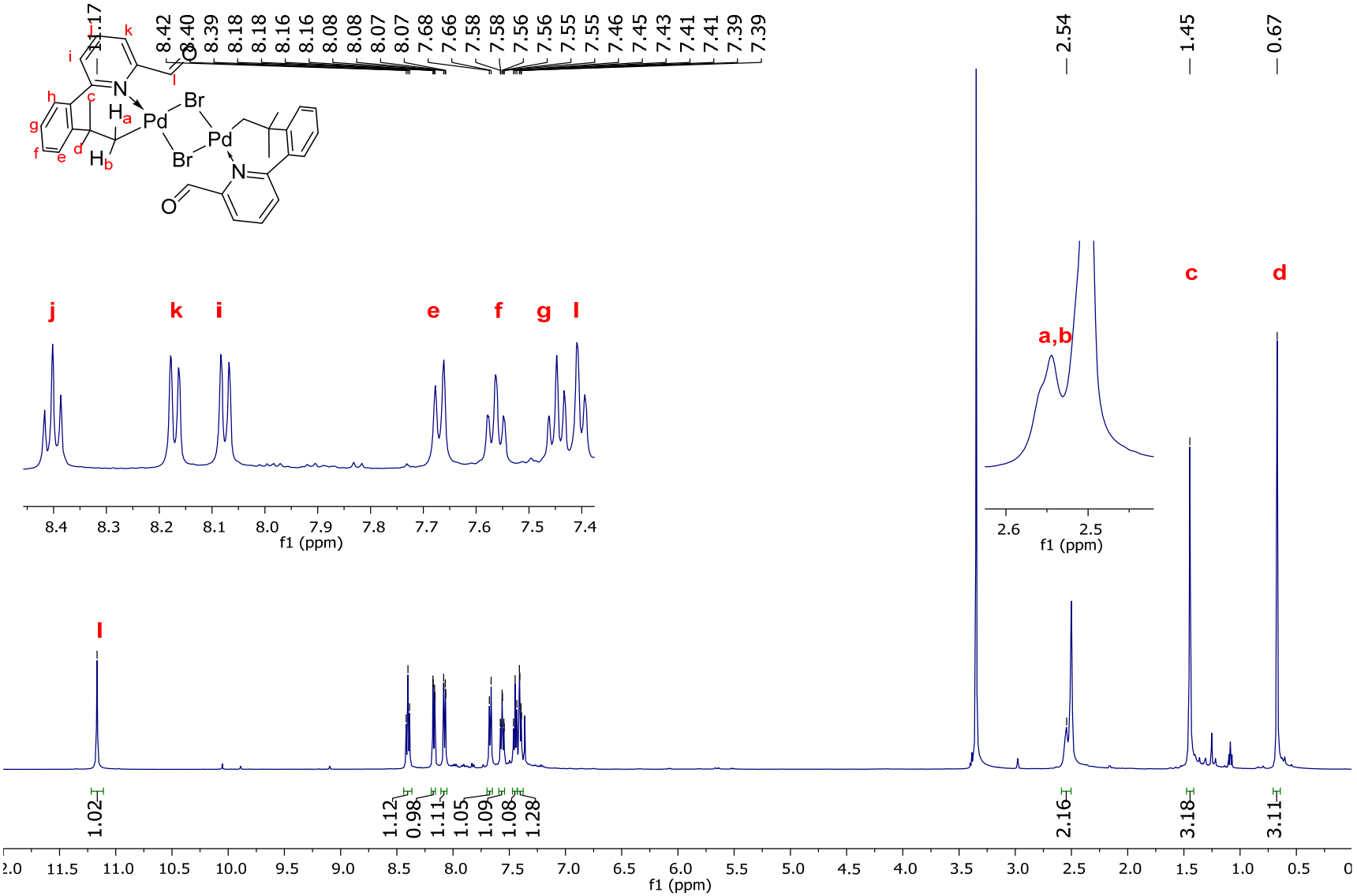


Figure S18. ^{1}H NMR spectrum of **3** in dmso-d_6 at rt.

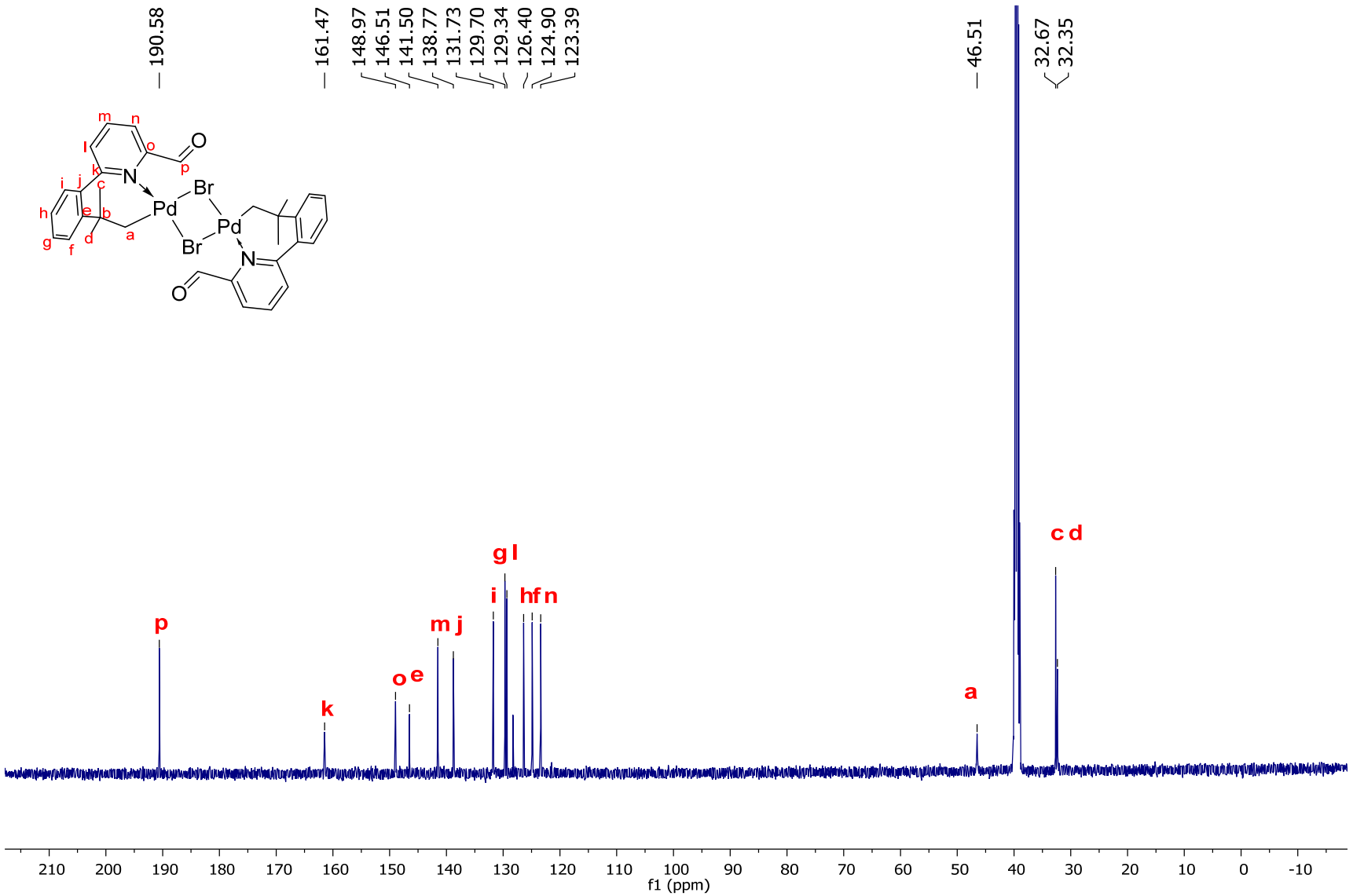


Figure S19. ^{13}C NMR spectrum of **3** in dmso-d_6 at rt.

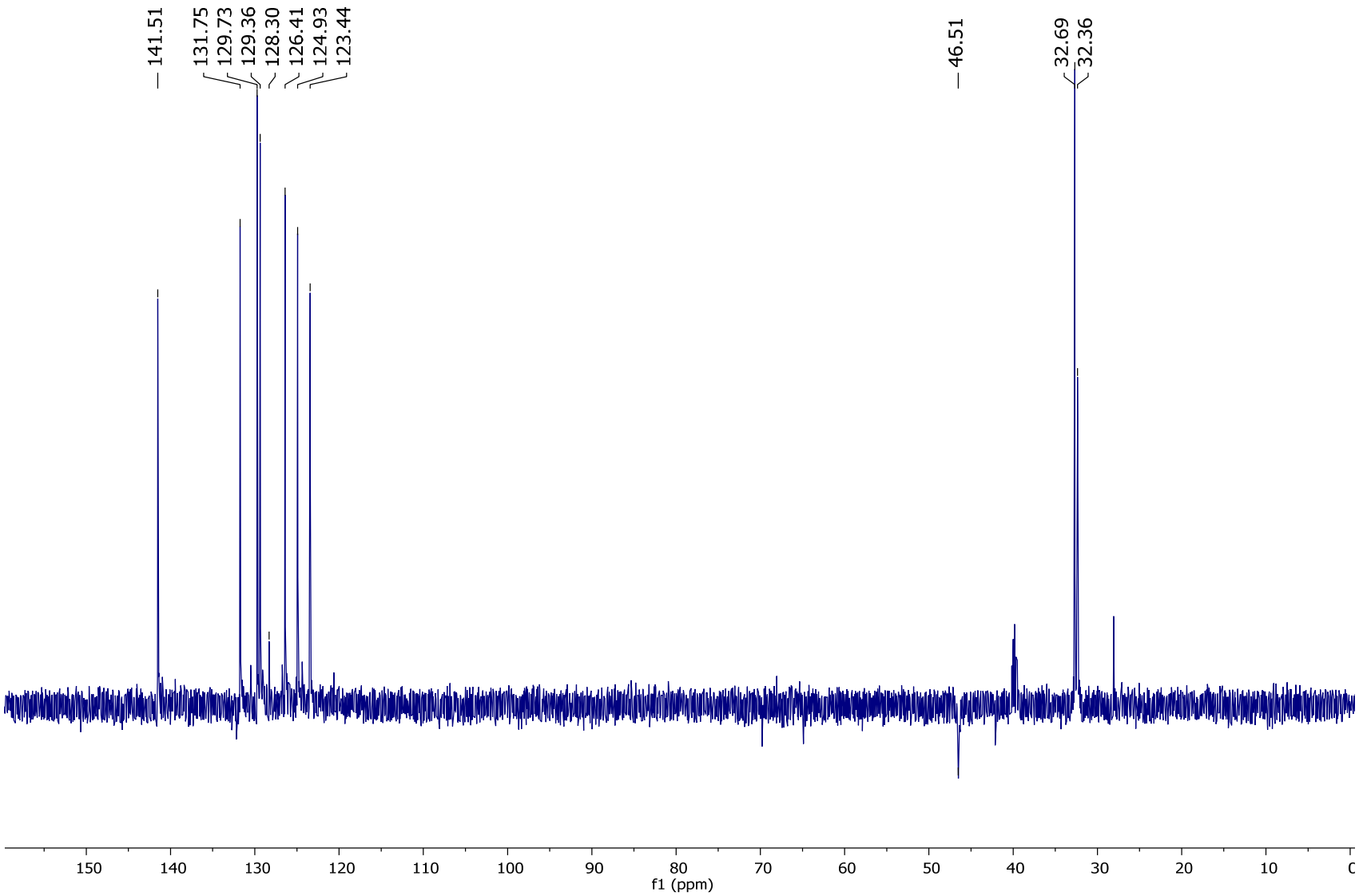


Figure S20. ^{13}C DEPT NMR spectrum of **3** in dmso-d_6 at rt.

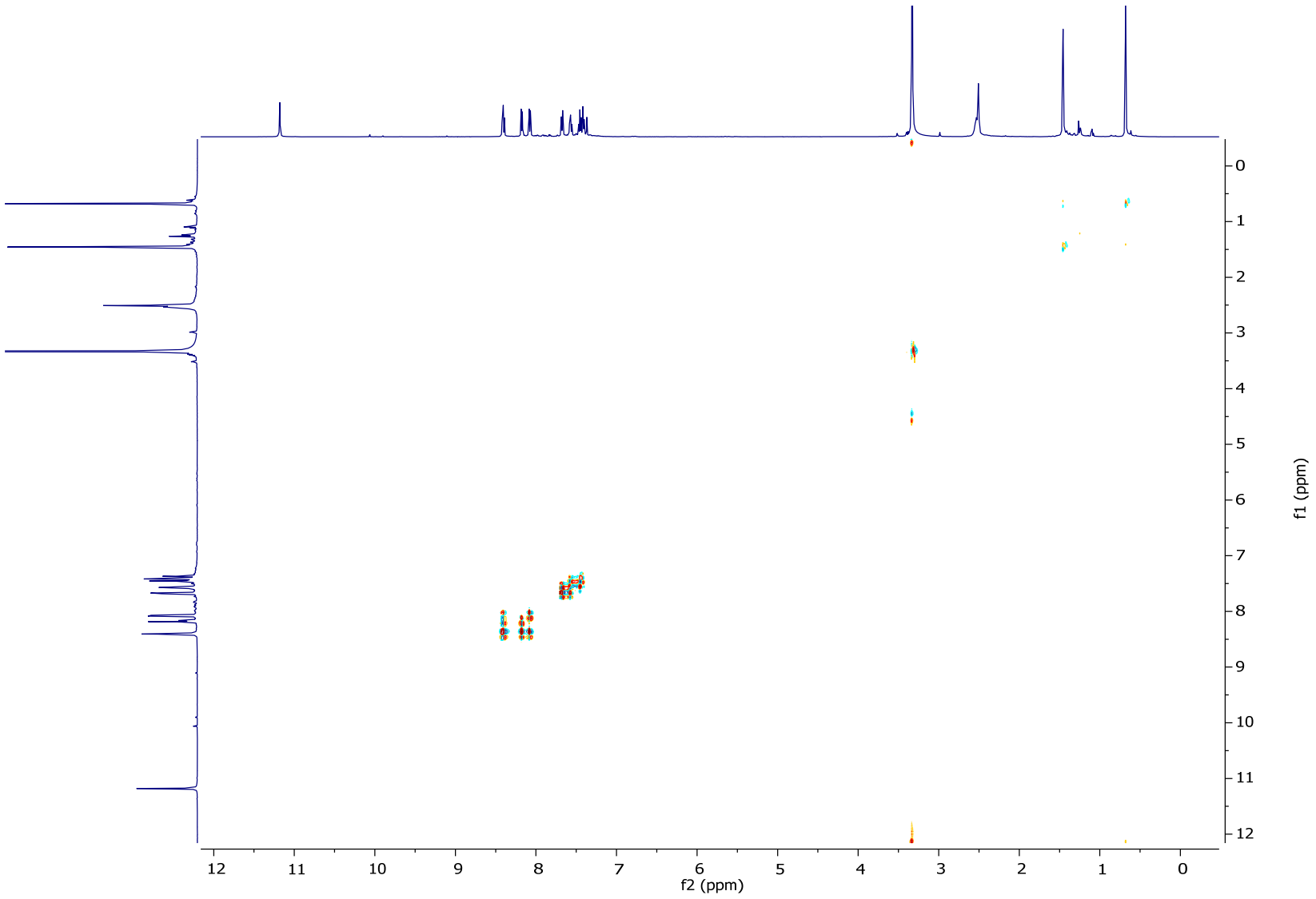


Figure S21. ^{1}H-^{1}H COSY NMR spectrum of **3** in dmso-d_6 at rt.

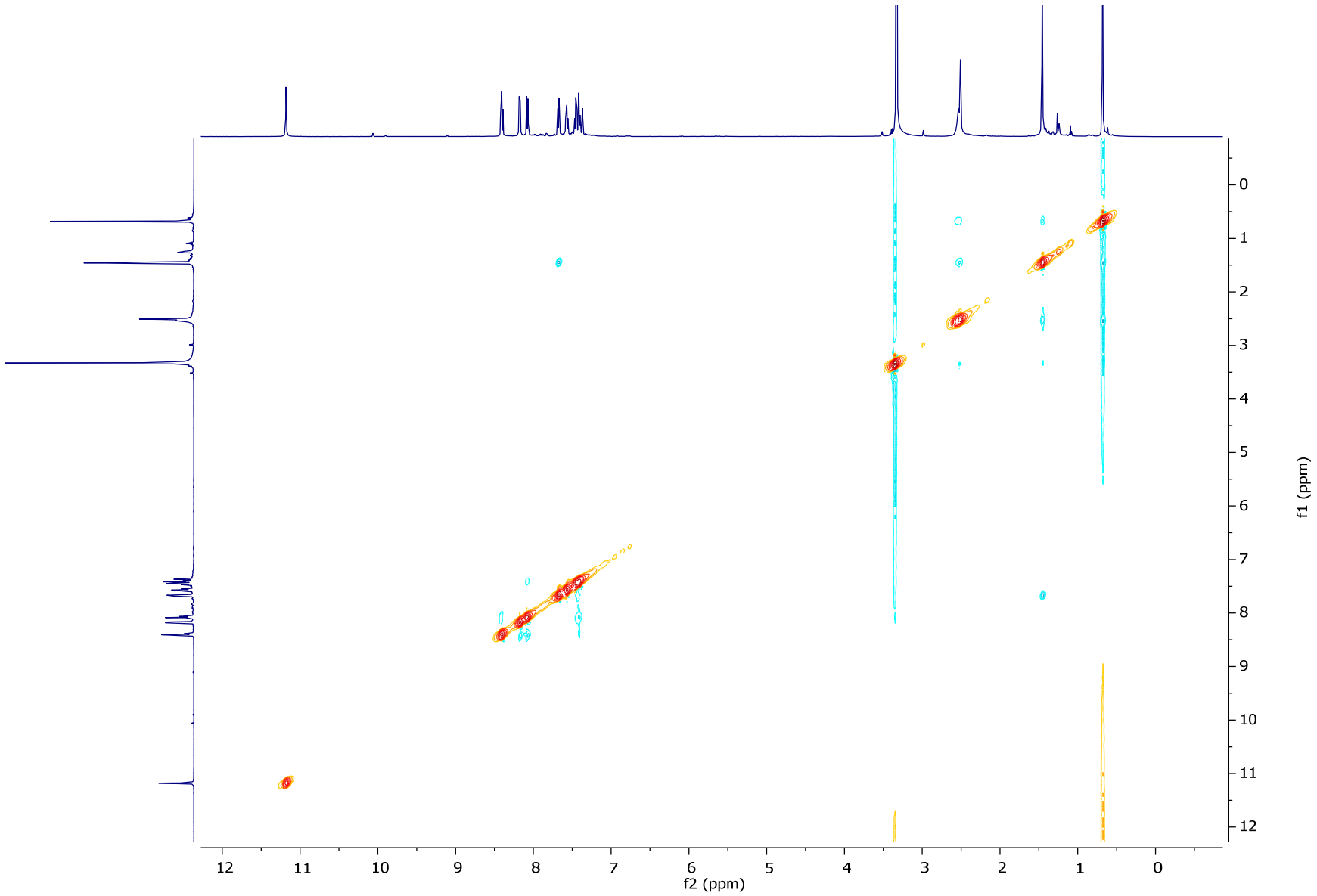


Figure S22. ^{1}H-^{1}H NOESY NMR spectrum of **3** in dmso-d_6 at rt.

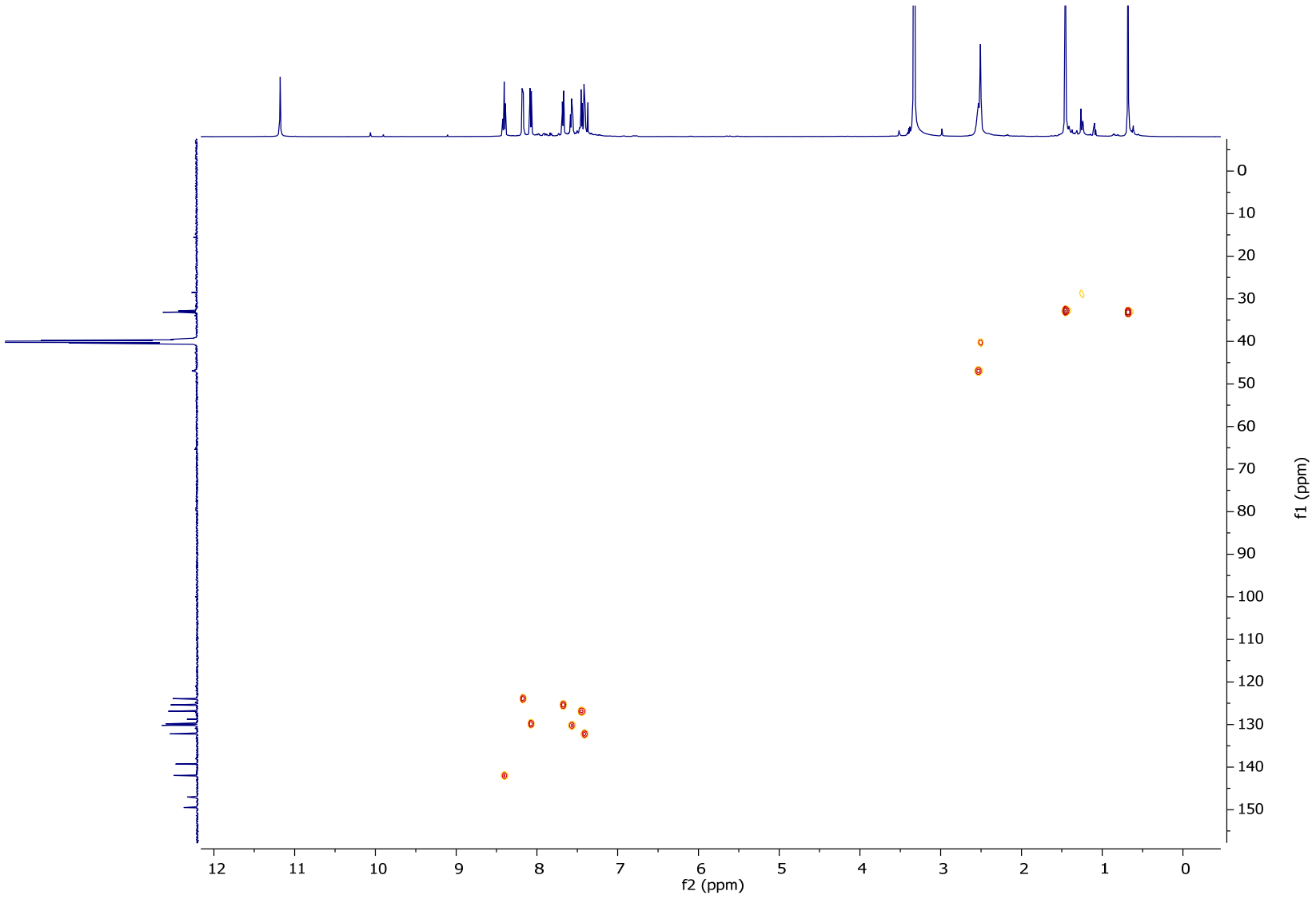


Figure S23. ^{1}H-^{13}C HSQC NMR spectrum of **3** in dmso-d_6 at rt.

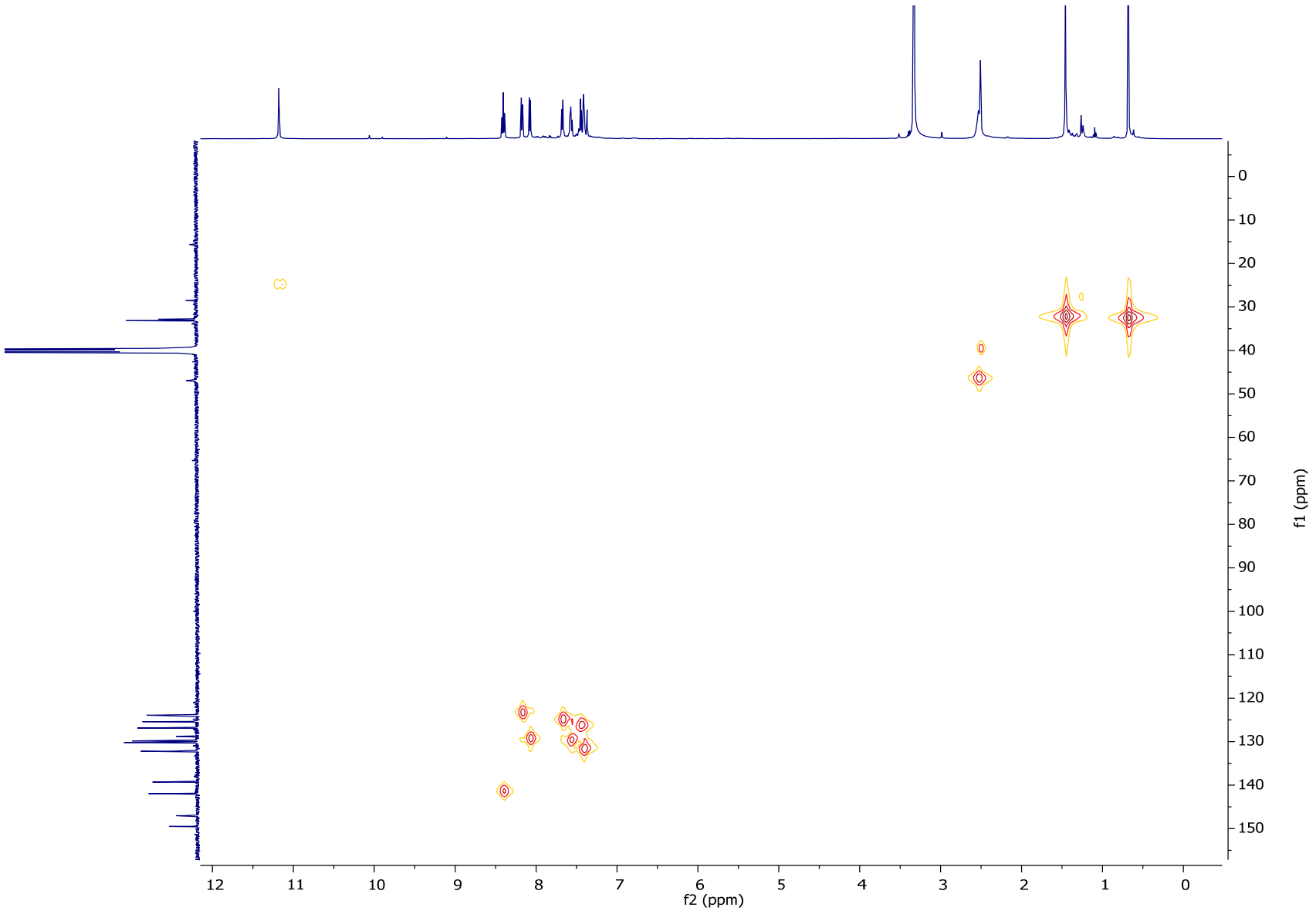


Figure S24. ^{1}H-^{13}C HMQC NMR spectrum of **3** in dmso-d_6 at rt.

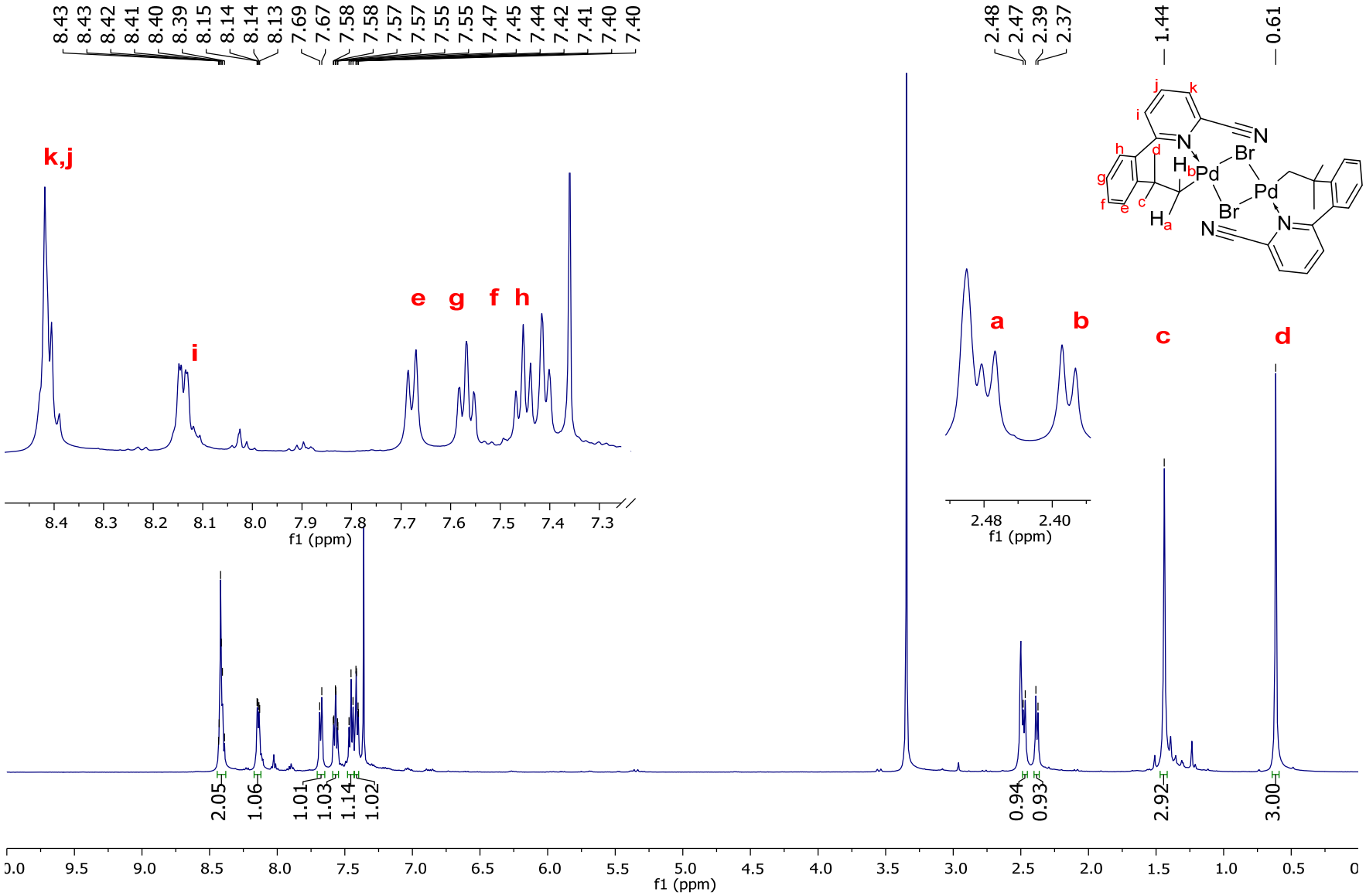


Figure S25. ^{1}H NMR spectrum of **4** in dmso-d_6 at rt.

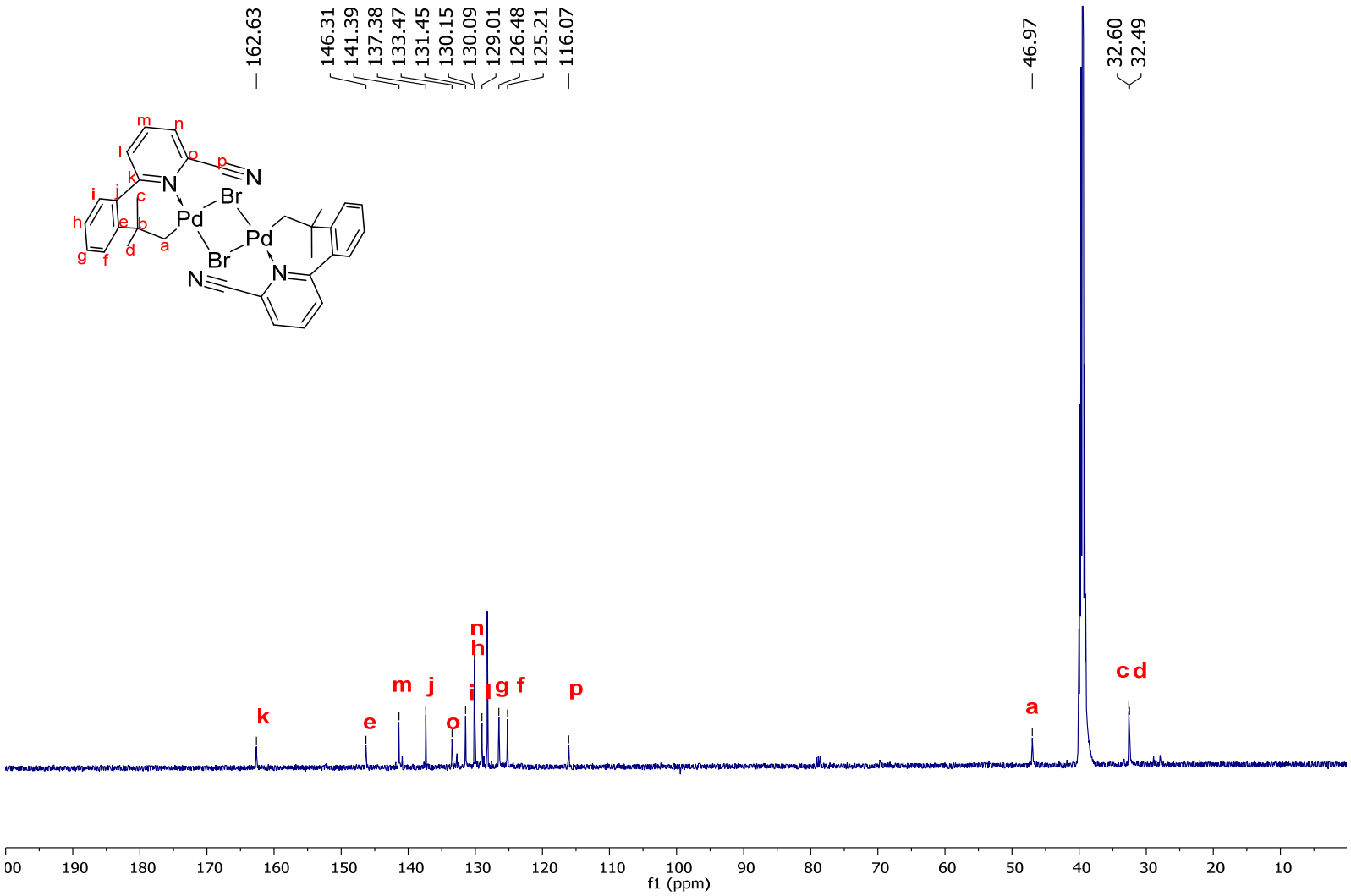


Figure S26. ^{13}C NMR spectrum of **4** in dmso-d_6 at rt.

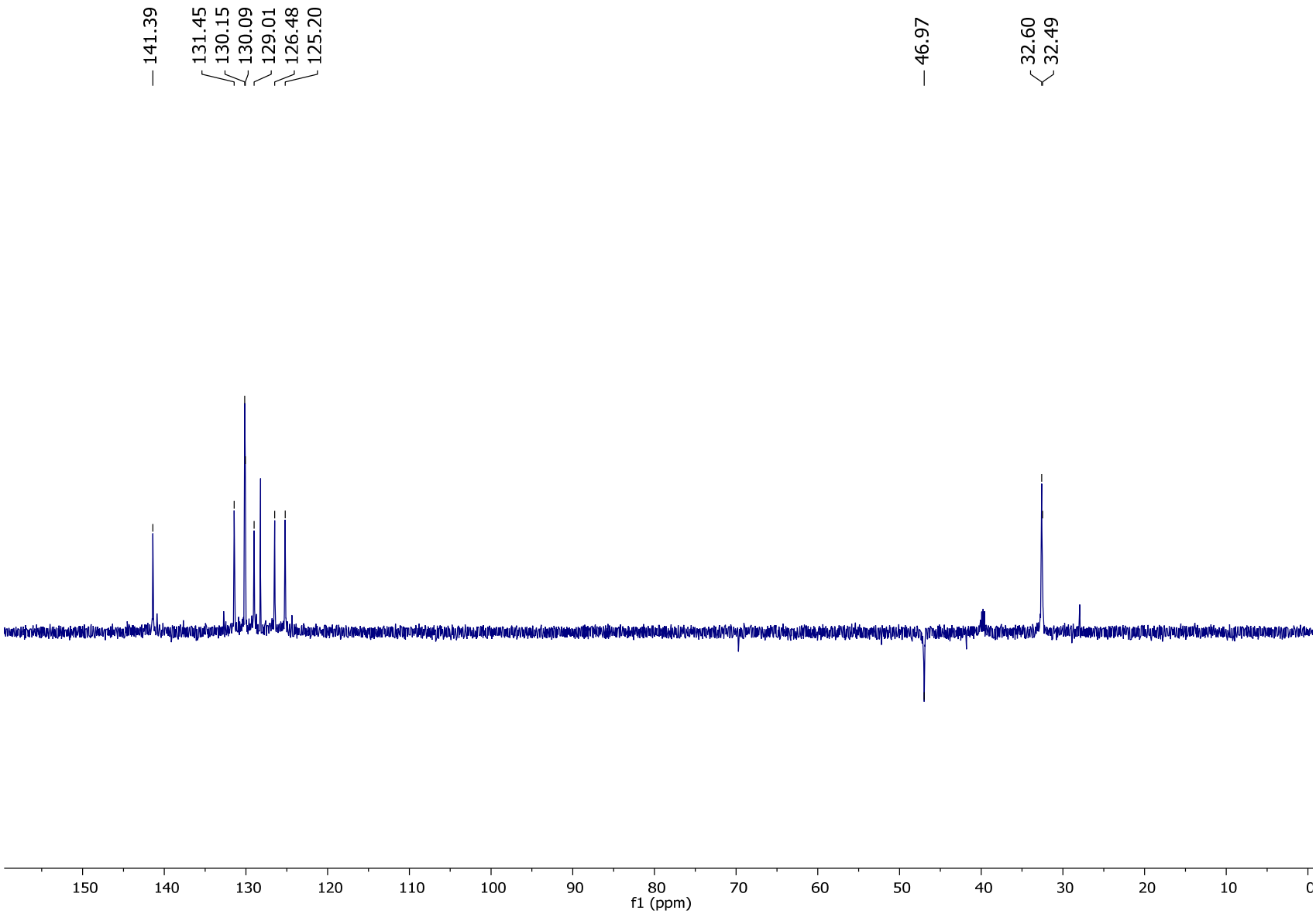


Figure S27. ^{13}C DEPT NMR spectrum of **4** in dmso-d_6 at rt.

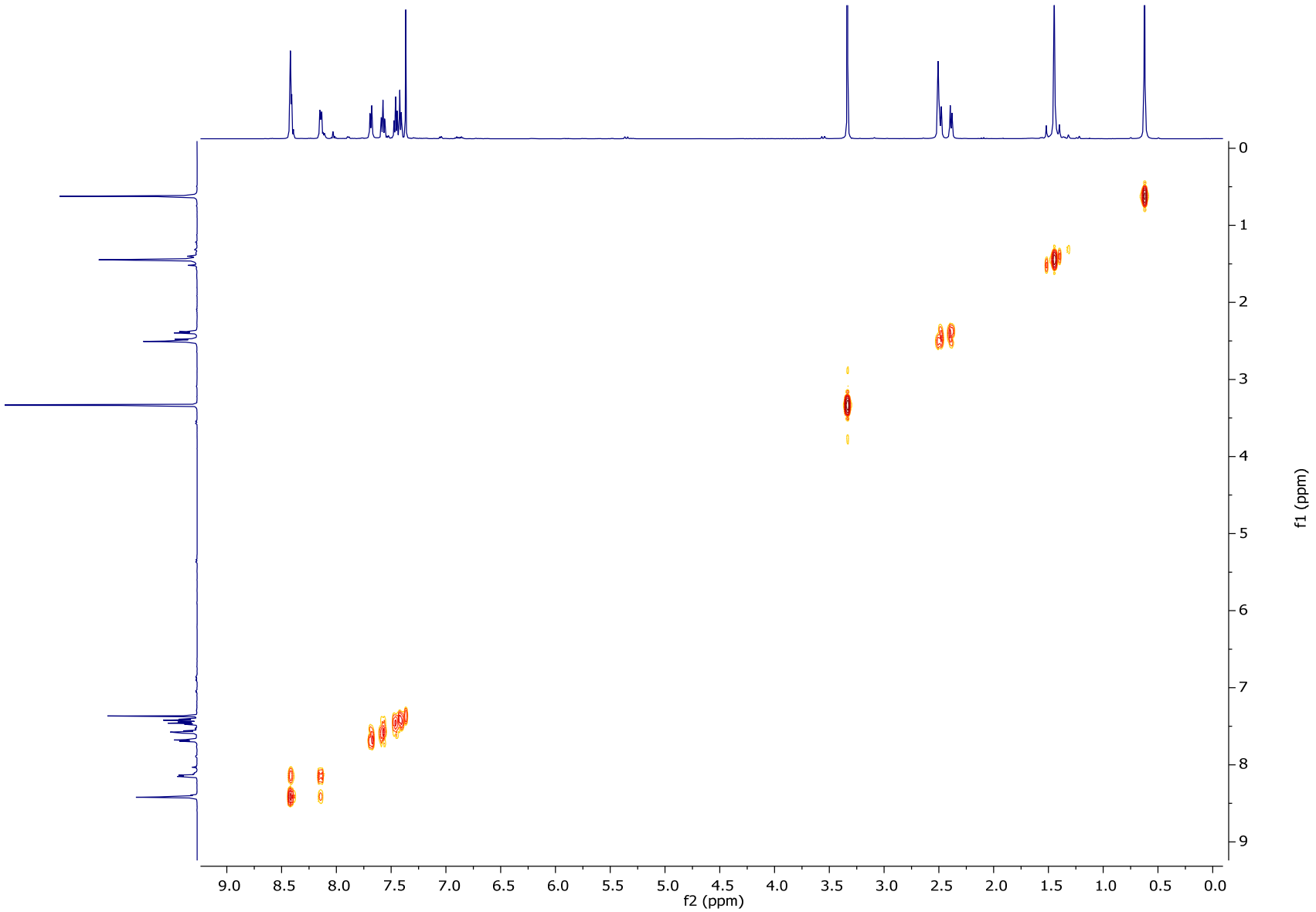


Figure S28. ^{1}H-^{1}H COSY NMR spectrum of **4** in dmso-d_6 at rt.

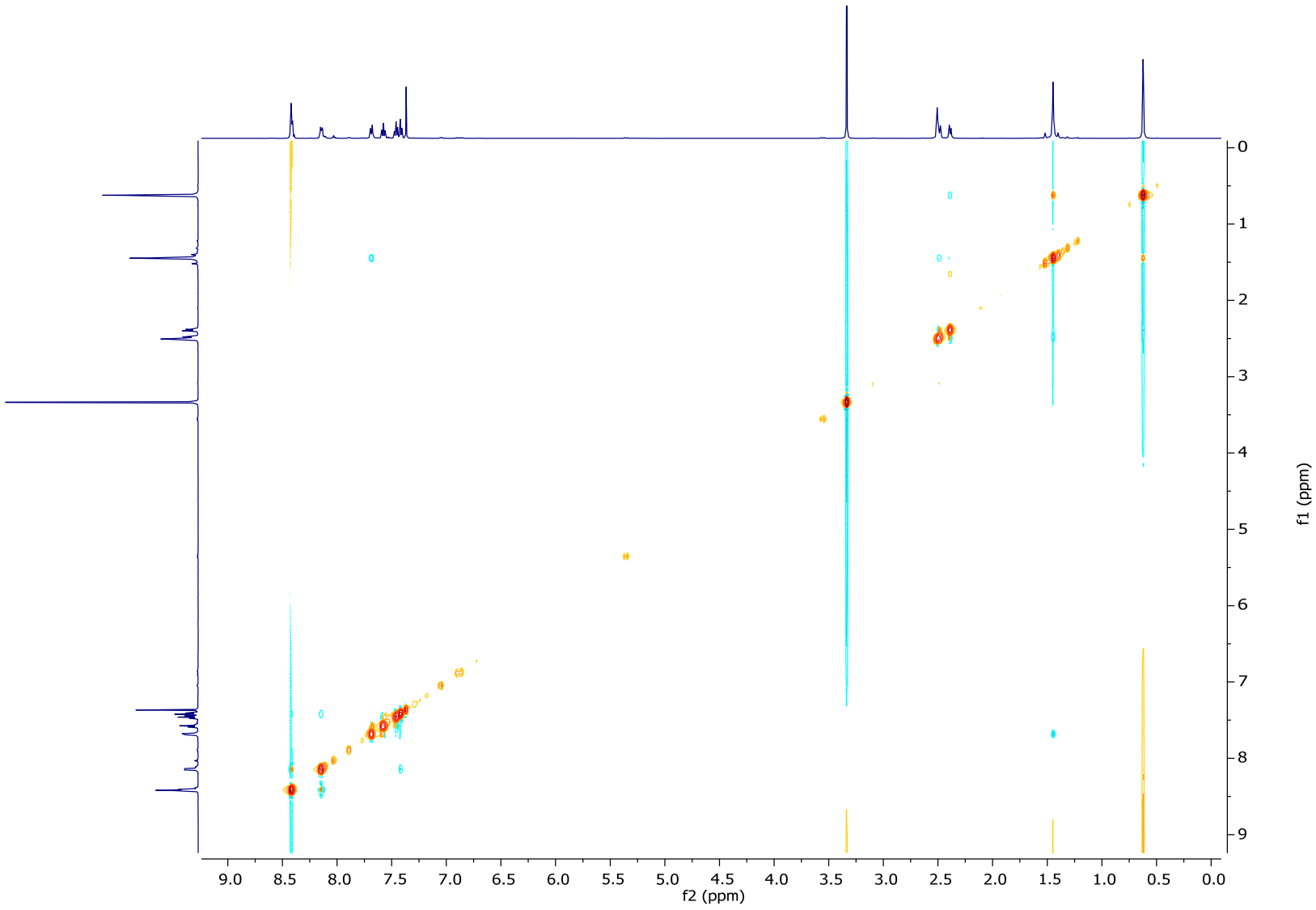


Figure S29. ^{1}H-^{1}H NOESY NMR spectrum of **4** in dmso-d_6 at rt.

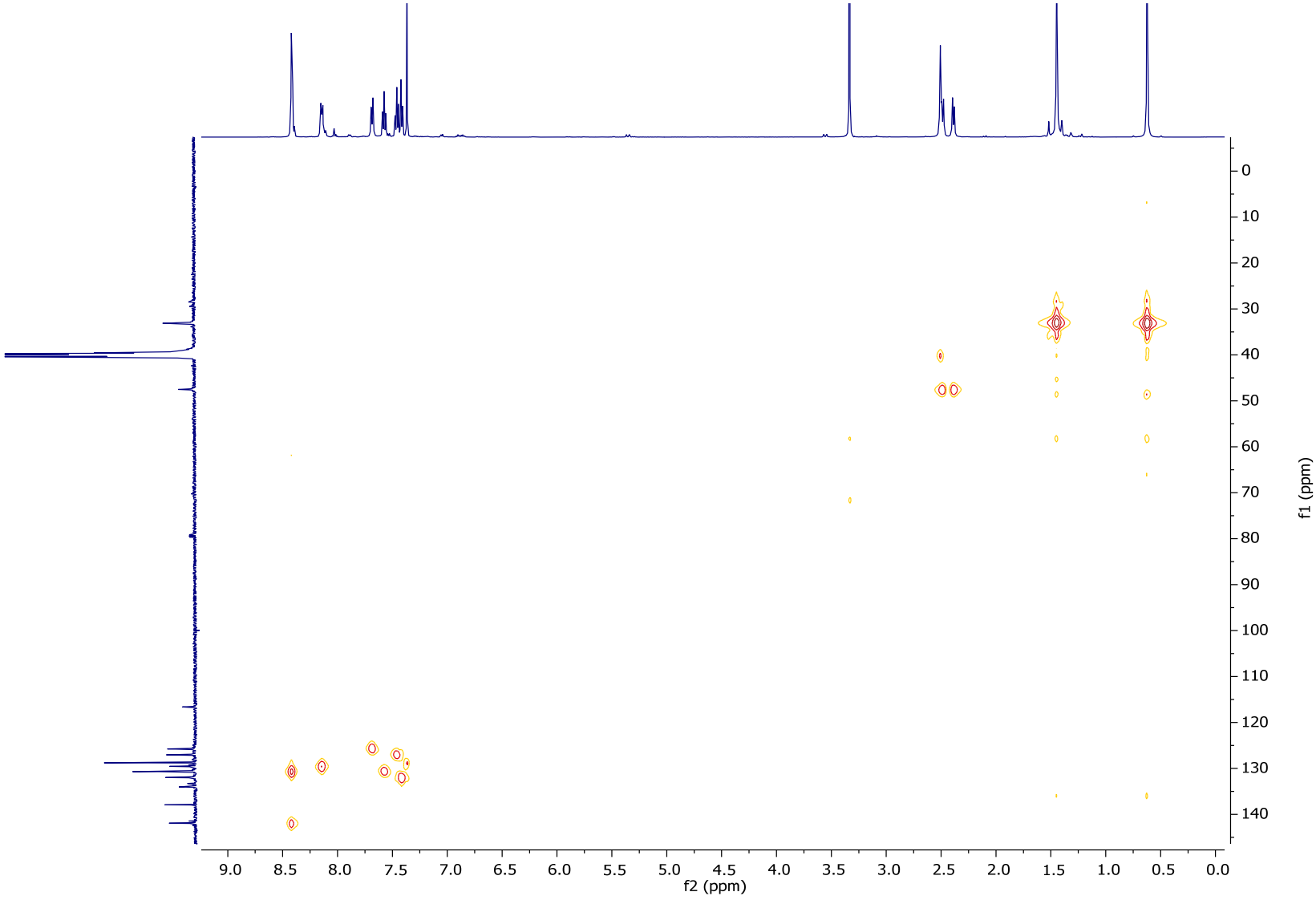


Figure S30. ^{1}H-^{13}C HSQC NMR spectrum of **4** in dmso-d_6 at rt.

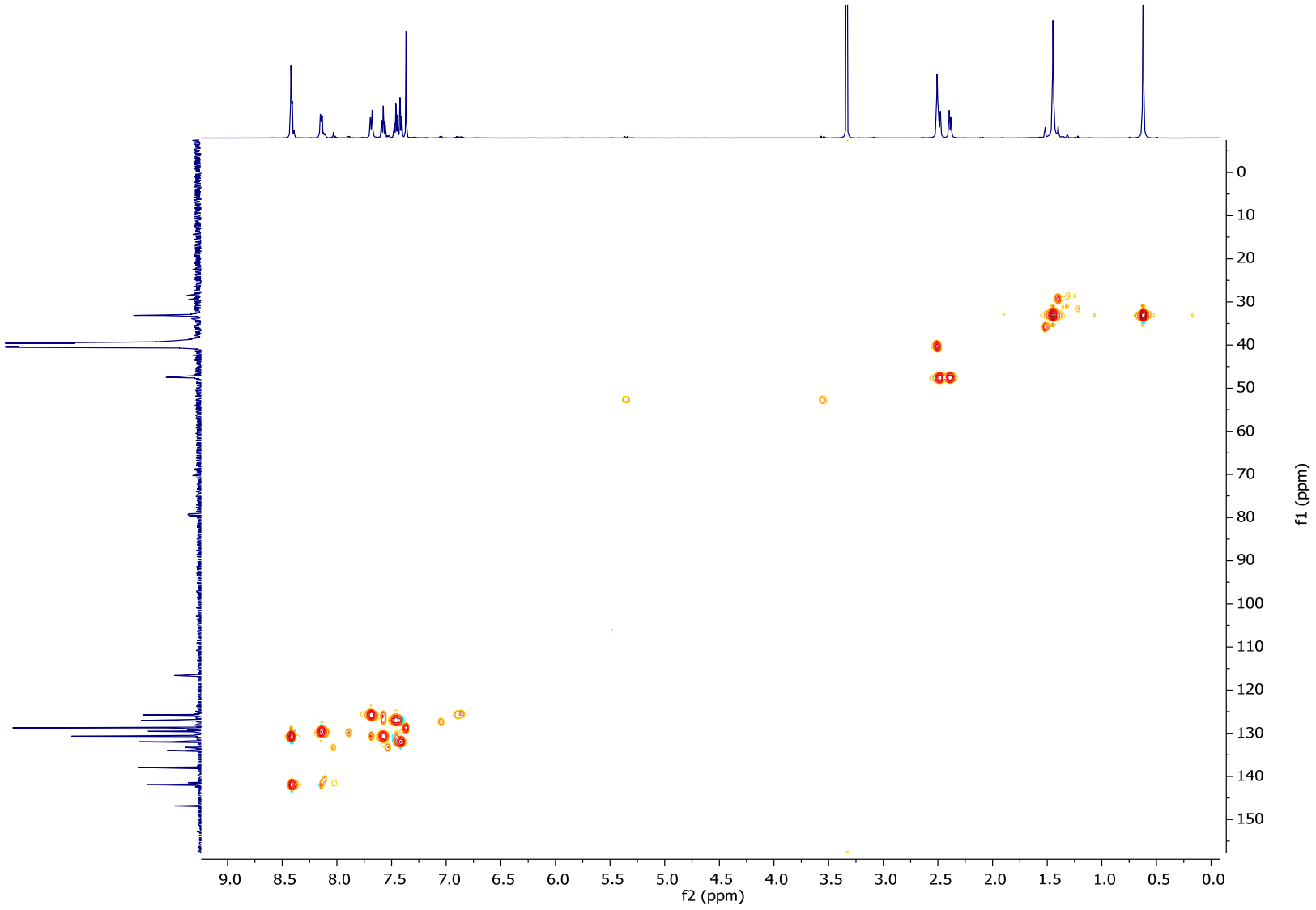


Figure S31. ^{1}H-^{13}C HMQC NMR spectrum of **4** in dmso-d_6 at rt.

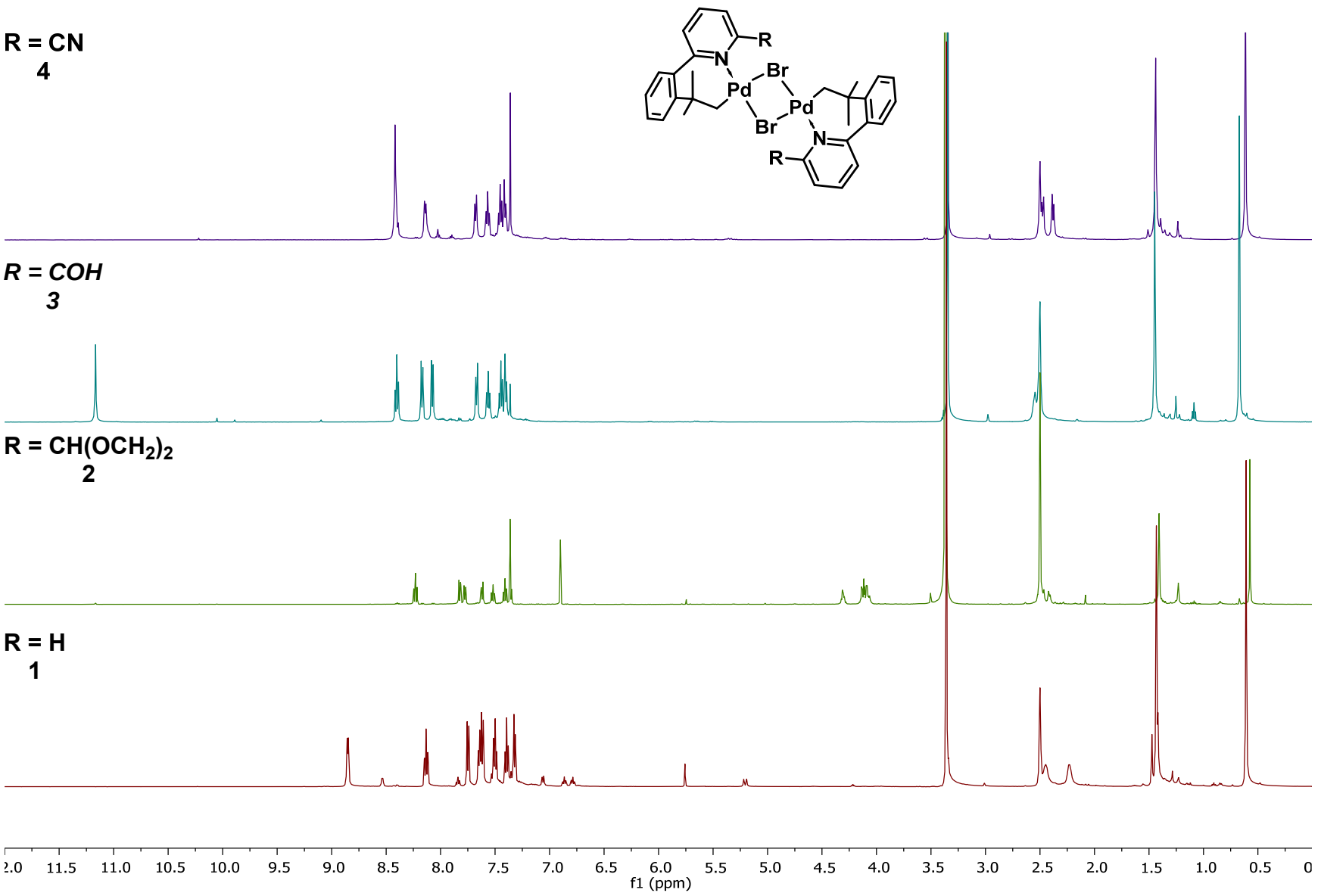


Figure S32. Comparative ^{1}H spectra of compounds **1-4** in dmso-d_6 at rt.

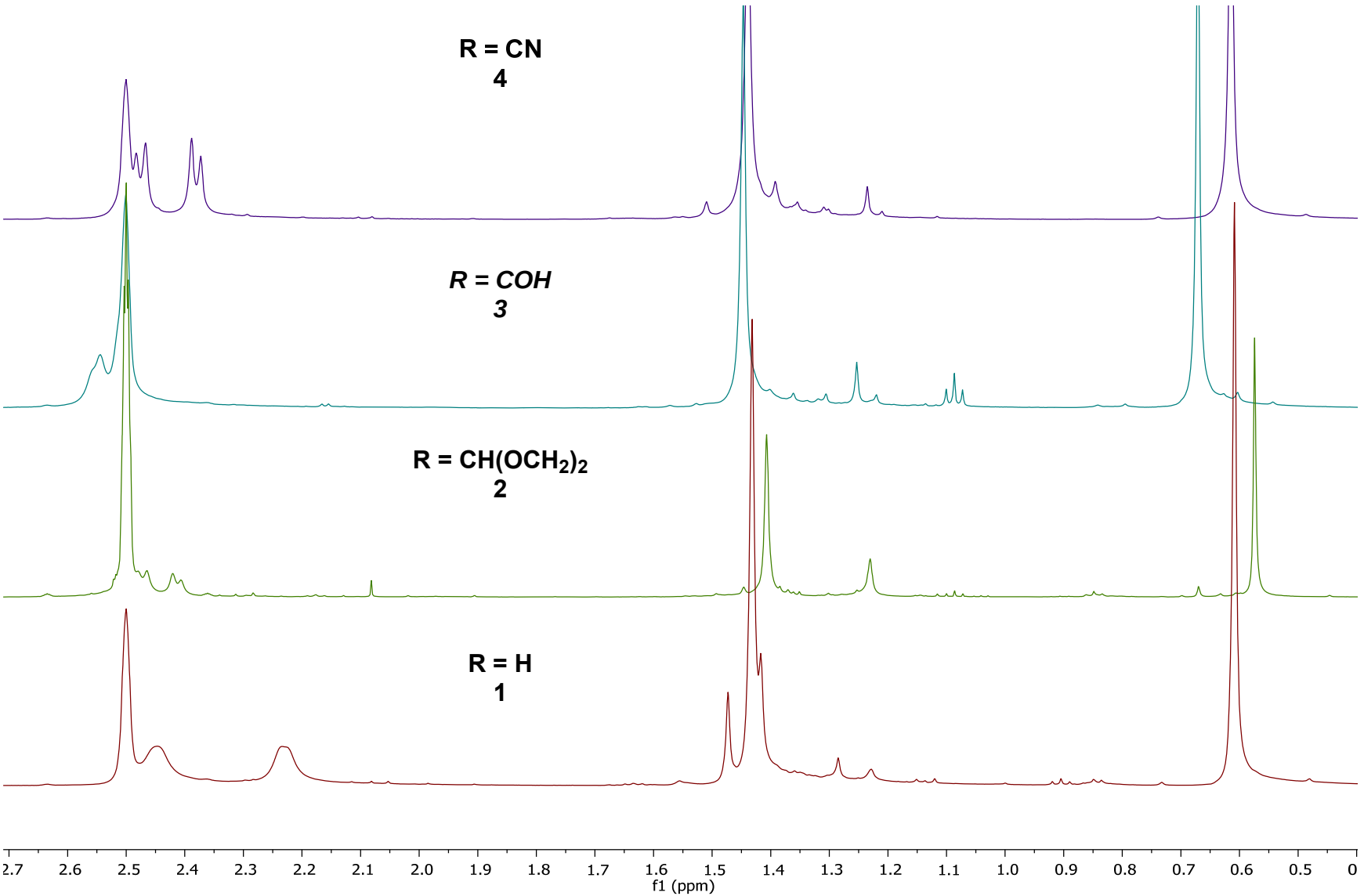
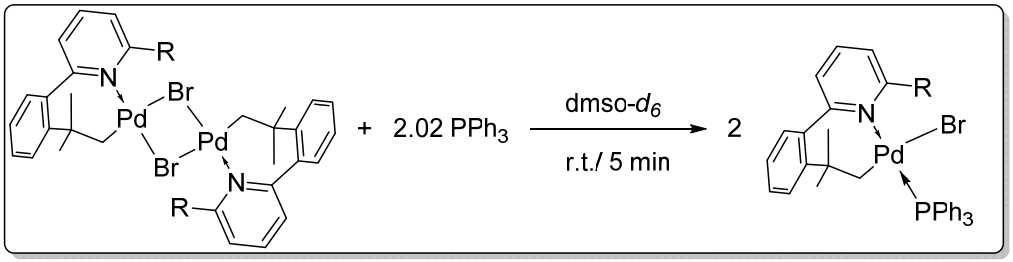


Figure S33. Comparative ^{1}H spectra of compounds **1-4** in dmso-d_6 at rt.

General procedure for the reactivity of seven-membered Pd(II) complexes 1-4 with PPh_3: formation of compound 5-8.



In a NMR tube complexes **1-4** (0.01 mmol) were charged and dissolved in 500 µL. Then a proton NMR spectral was acquired and PPh_3 was added (0.022 mmol), at room temperature. According to the proton NMR spectra a spontaneous reaction take place with the concomitated formation of **5-8**, respectively.

Table S1. *Selected data for:*

Compound	Aromatic	$-CH_2$	$-CH_3$	^{31}P
5	9.00 (d, *J*=5.1, 1H), 8.10 (td, *J*=7.7, 1.7, 1H), 7.69 (d, *J*=7.9, 1H), 7.67 – 7.57 (m, 2H), 7.55 – 7.32 (m, 30H), 7.29 – 7.23 (m, 3H), 7.22 – 7.11 (m, 3H), 6.93 – 6.79 (m, 1H),	1.98 (d, *J*=7.7, 1H) 1.51 (dd, *J*=16.7, 9.1, 1H),	0.71 (s, 3H) 0.46 (s, 3H)	37.62
6	8.20 (t, *J*=7.8, 1H), 7.84 (d, *J*=7.8, 1H), 7.70 (d, *J*=7.7, 1H), 7.67 – 7.58 (m, 3H), 7.57 – 7.43 (m, 10H), 7.43 – 7.29 (m, 17H), 7.25 – 7.12 (m, 6H),	2.32 (dd, *J*=8.5, 4.1, 1H) 1.42 (dd, *J*=17.1, 8.5, 1H)	0.65 (s, 3H) 0.41 (s, 3H)	42.12
7	11.41 (s, 1H), 8.38 (t, *J*=7.9, 1H), 8.19 (d, *J*=7.7, 1H), 8.01 (d, *J*=7.8, 1H), 7.67 – 7.32 (m, 27H), 7.27 (d, *J*=7.8, 2H)	2.35 (dd, *J*=8.7, 4.1, 1H) 1.60 (dd, *J*=16.8, 8.7, 1H)	0.70 (s, 3H) 0.53 (s, 3H).	36.21
8	8.44 – 8.34 (m, 2H), 8.09 (dd, *J*=7.7, 1.6, 1H), 7.65 – 7.53 (m, 6H), 7.53 – 7.36 (m, 35H), 7.34 – 7.29 (m, 4H), 7.27 – 7.16 (m, 11H)	2.08 (dd, *J*=9.0, 3.9, 1H) 1.46 (dd, *J*=15.9, 8.8, 1H)	0.76 (s, 3H), 0.49 (s, 3H)	38.97

Compound	*δ (ppm)*	*Mult. (Hz)*	*# H*	*Compound*	*δ (ppm)*	*Mult. (Hz)*	*# H*
1	$CH_2(H_b)$ 2.45 $CH_2(H_a)$2.24	bs bs	1 1	**5**	1.98 1.51	d (J= 7.7) dd (J= 16.7, 9.1)	1 1
2	$CH_2(H_a)$ 2.47 $CH_2(H_b)$ 2.41	d(J=7.5) d (J=7.3)	1 1	**6**	2.32 1.42	dd (J= 8.5, 4.1) dd (J= 17.0, 8.5)	1 1
3	CH_2 2.54	bs	2	**7**	2.34 1.59	dd (J= 8.7, 4.1) dd (J= 16.8, 8.7)	1 1
4	$CH_2(H_a)$ 2.47 $CH_2(H_b)$ 2.38	d (7.1) d (8.9)	1 1	**8**	2.08 1.45	dd (J= 9.0, 3.9) dd (J= 15.9, 8.8)	1 1

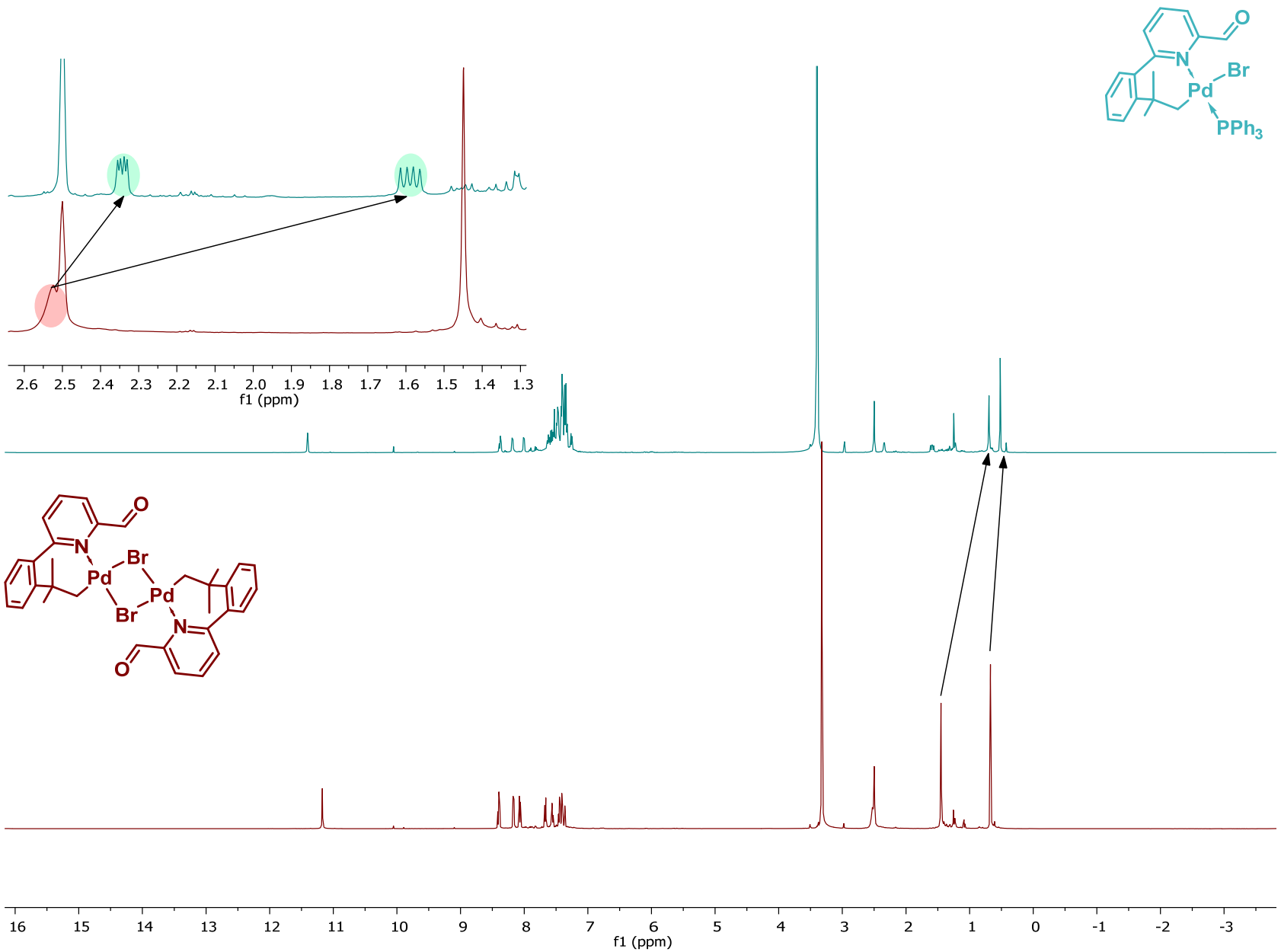


Figure S34. Comparative ^{1}H spectra of compounds **3** and **7** in dmso-d_6 at rt.

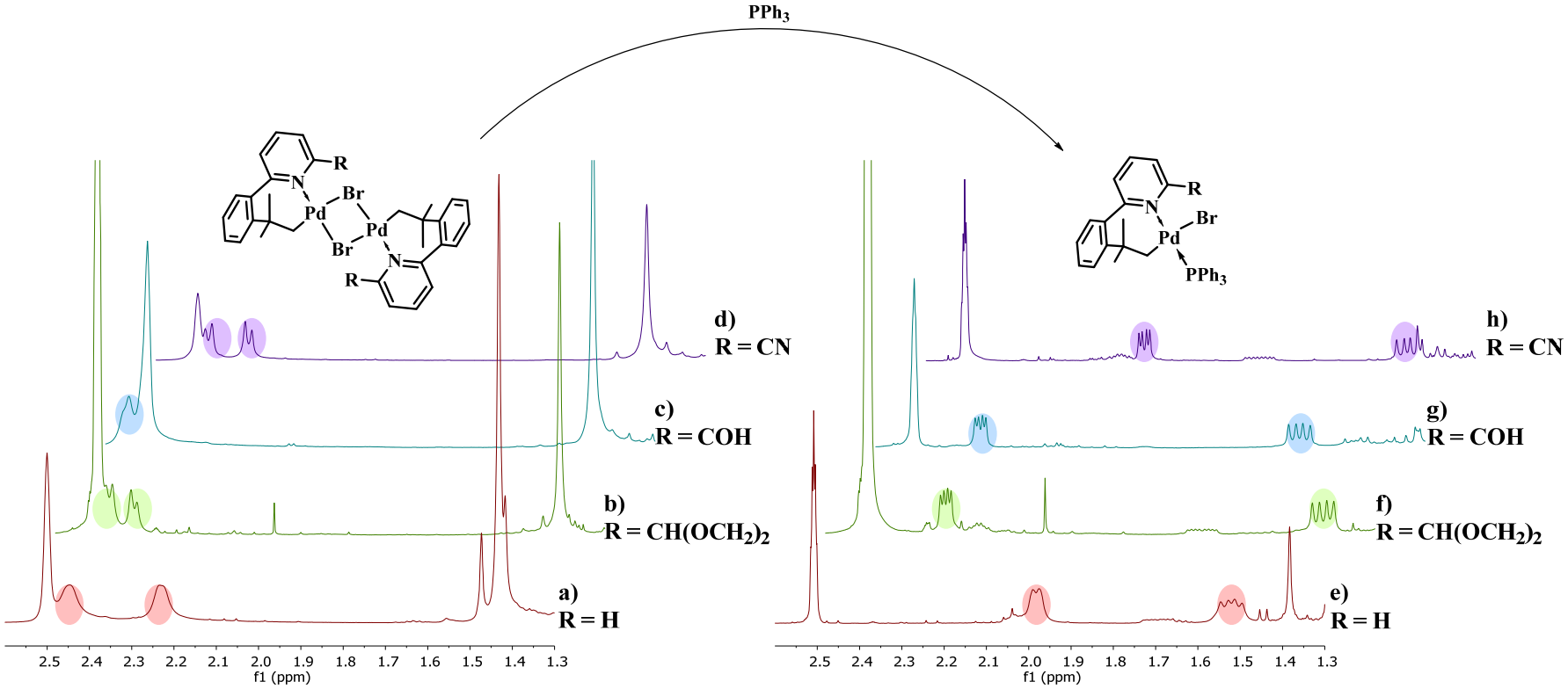


Figure S35. Left side: Comparative ^{1}H NMR spectra of compounds **1-4** on the aliphatic region from *a-d*), respectively (in DMSO-d_6 at r.t.). Right side: Comparative ^{1}H NMR spectra of compounds **5-8** on

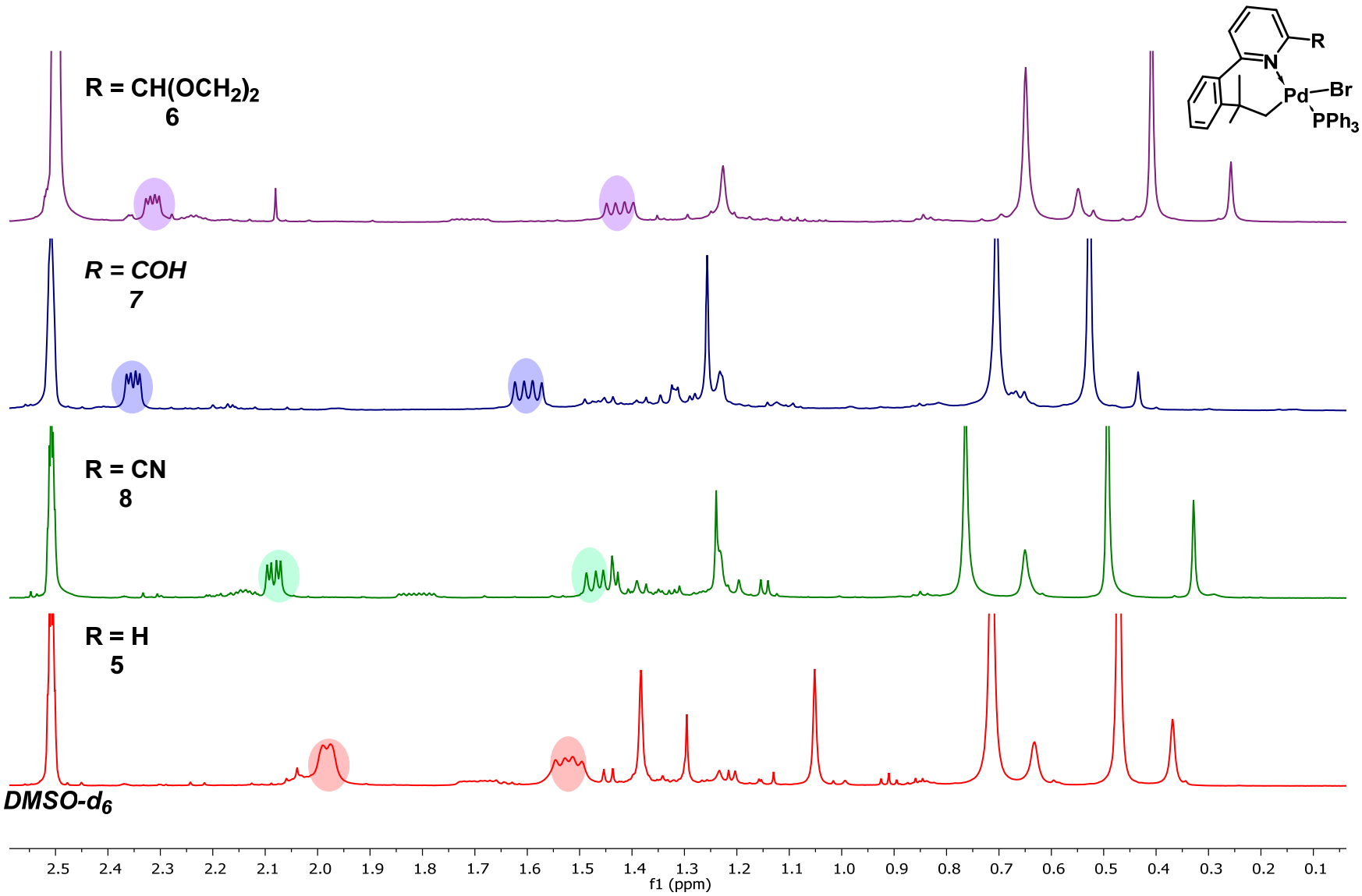


Figure S36. Comparative ^{1}H spectra of compounds **5-8** in dmso-d_6 at rt.

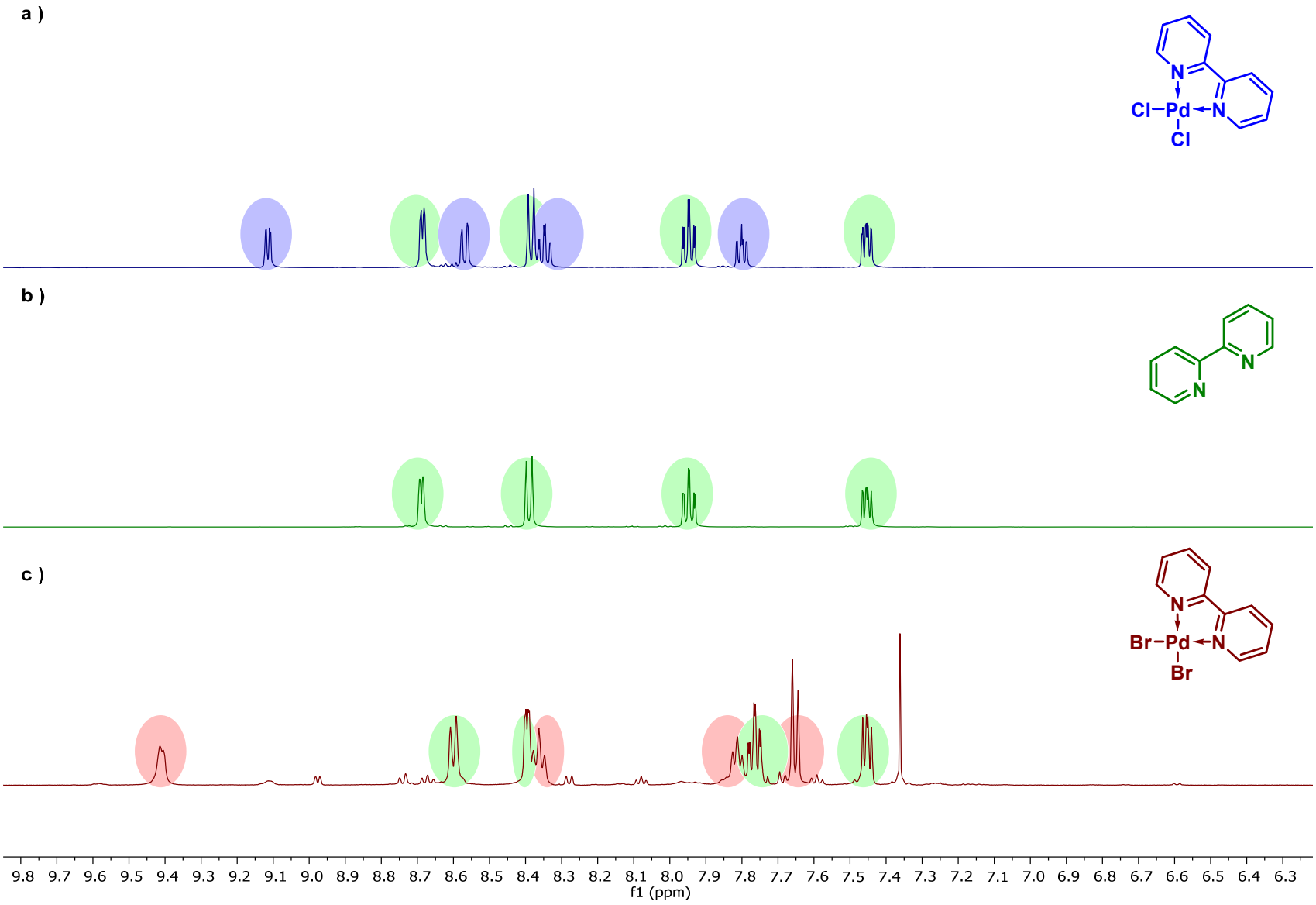


Figure S37. Comparative ^{1}H spectra in dmso-d_6 at rt. a) Compound synthesized in this work b)bipyridine and c) crude reaction.

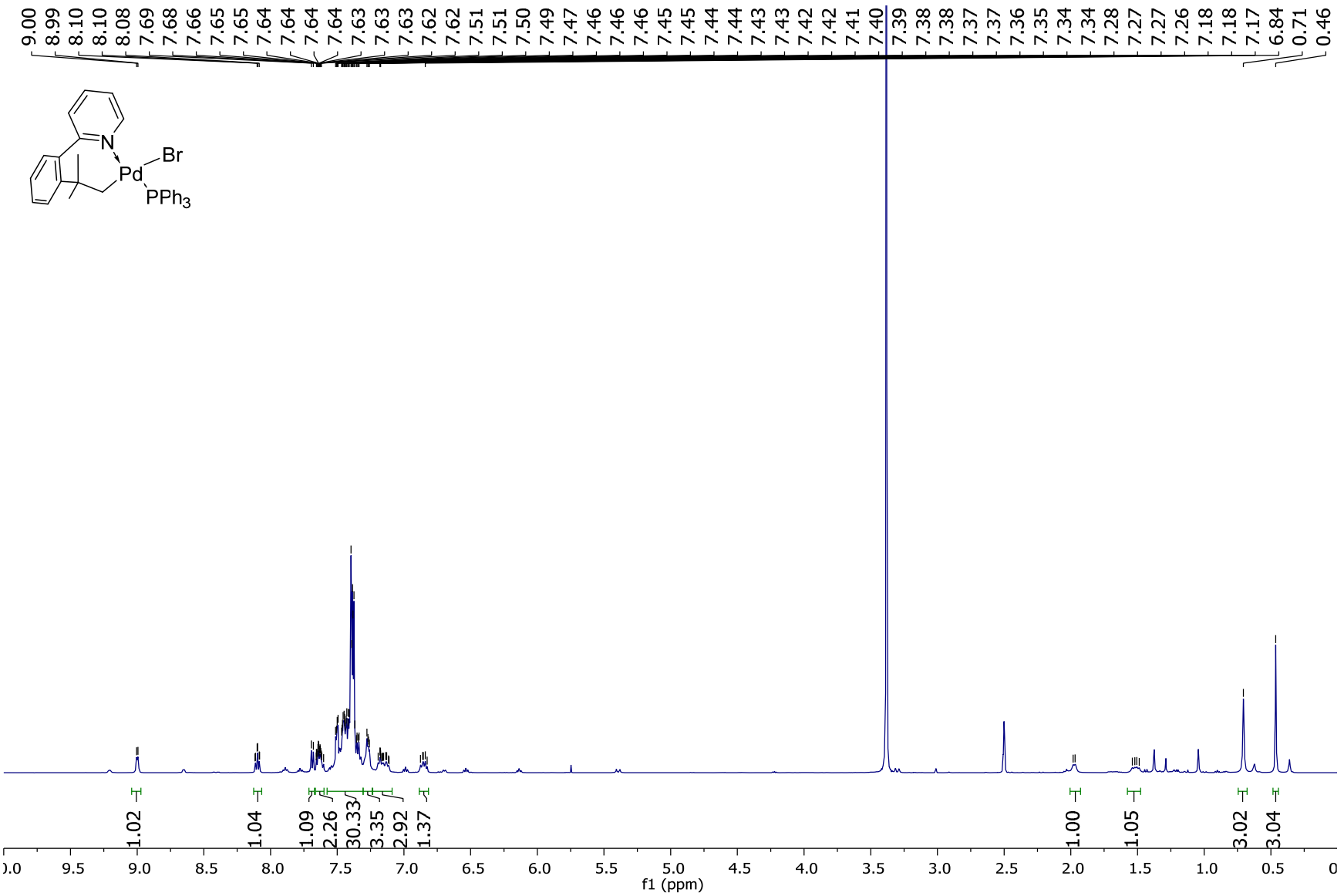


Figure S38. ^{1}H spectrum of **5** in dmso-d_6 at rt.

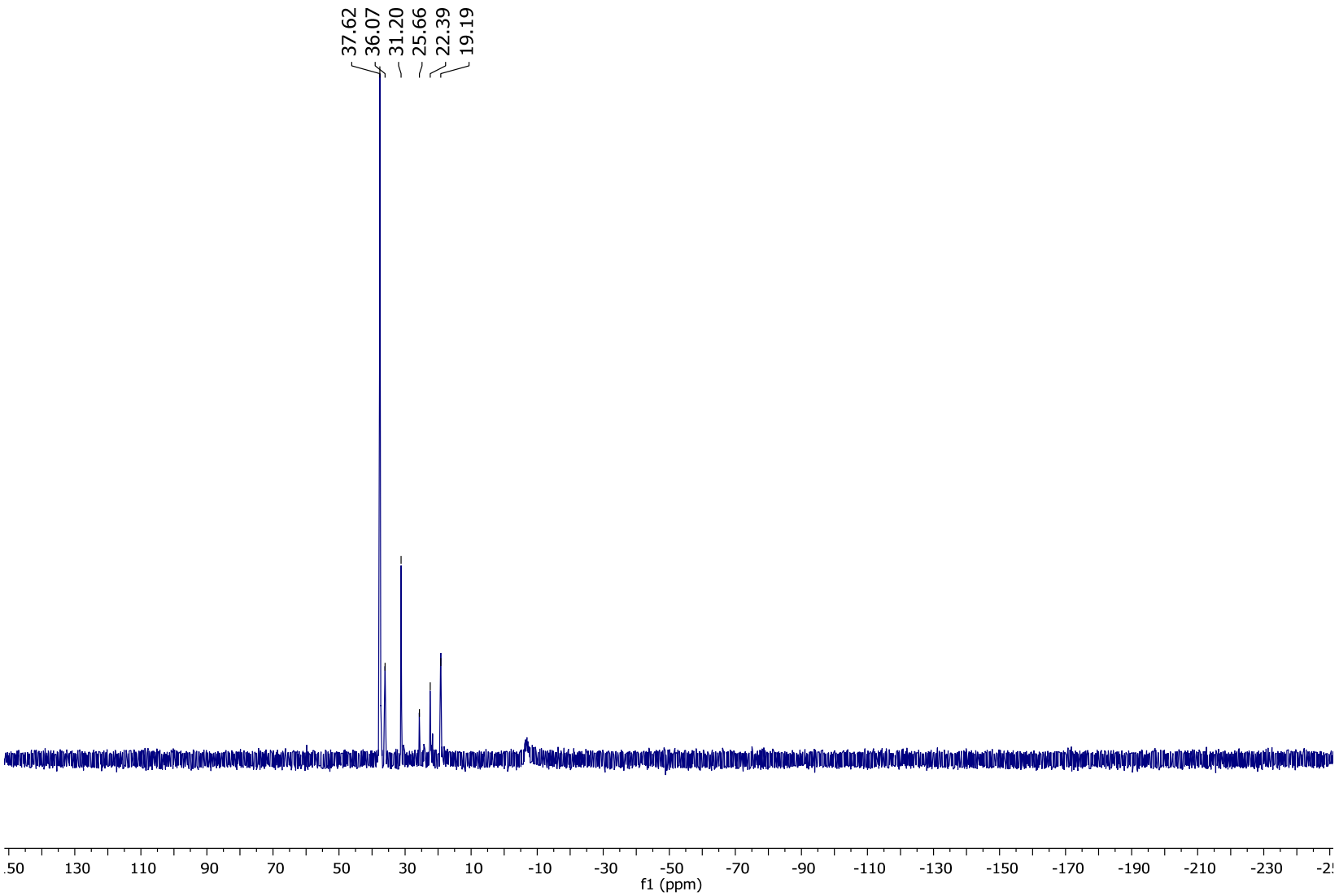


Figure S39. ^{31}P spectrum of **5** in dmso-d_6 at rt

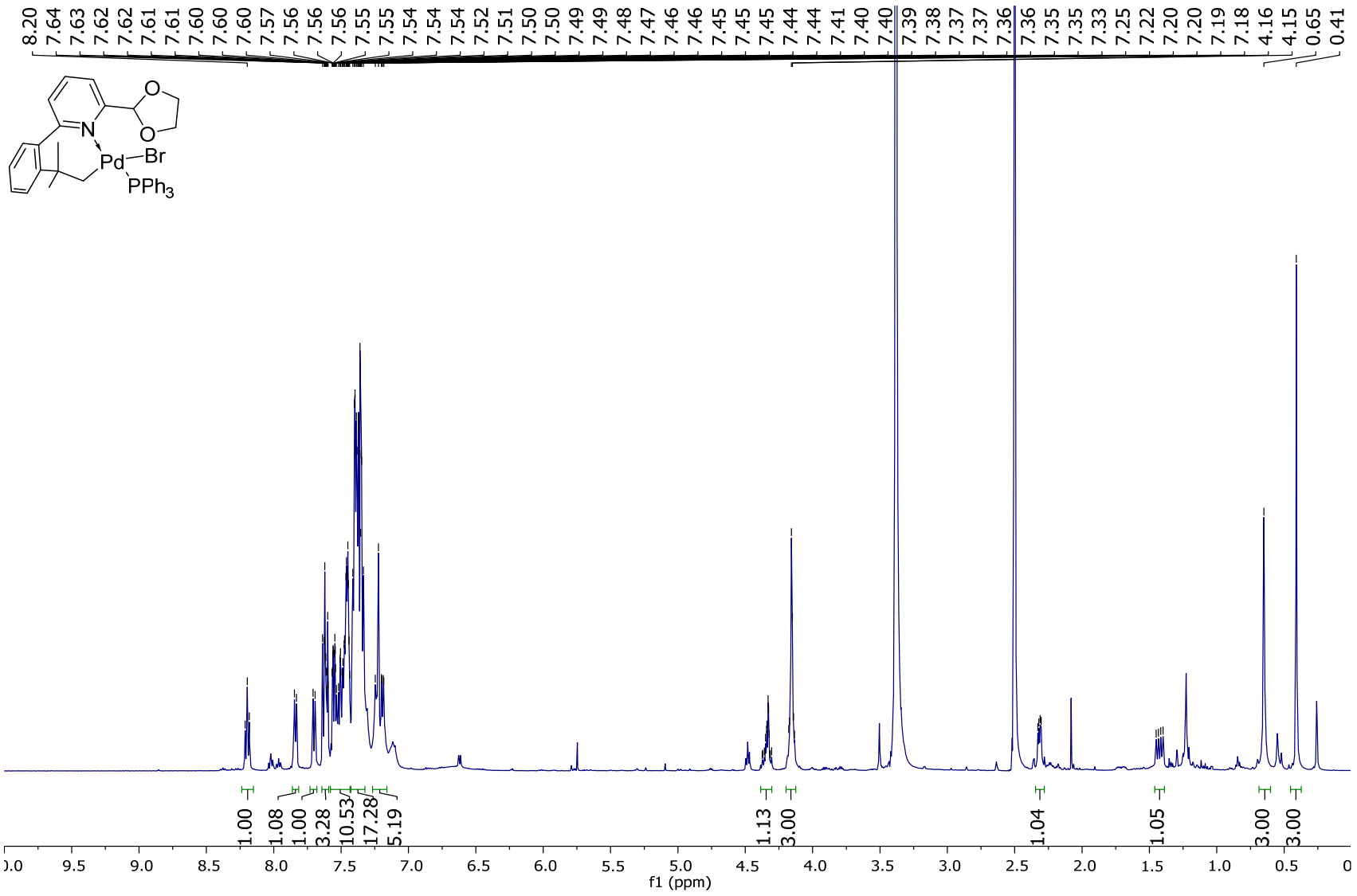


Figure S40. ^{1}H spectrum of **6** in dmso-d_6 at rt.

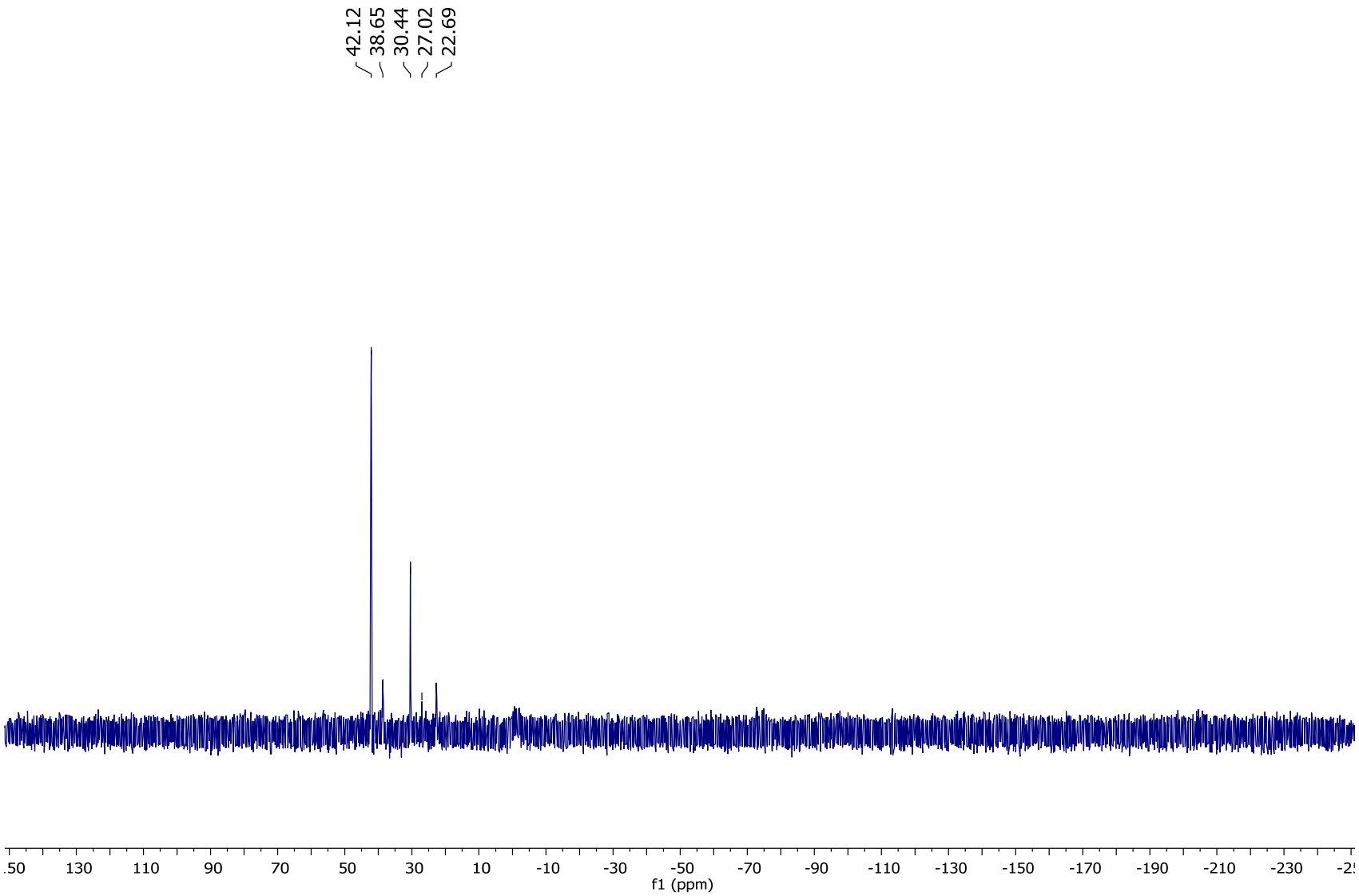


Figure S41. ^{31}P spectrum of **6** in dmso-d_6 at rt.

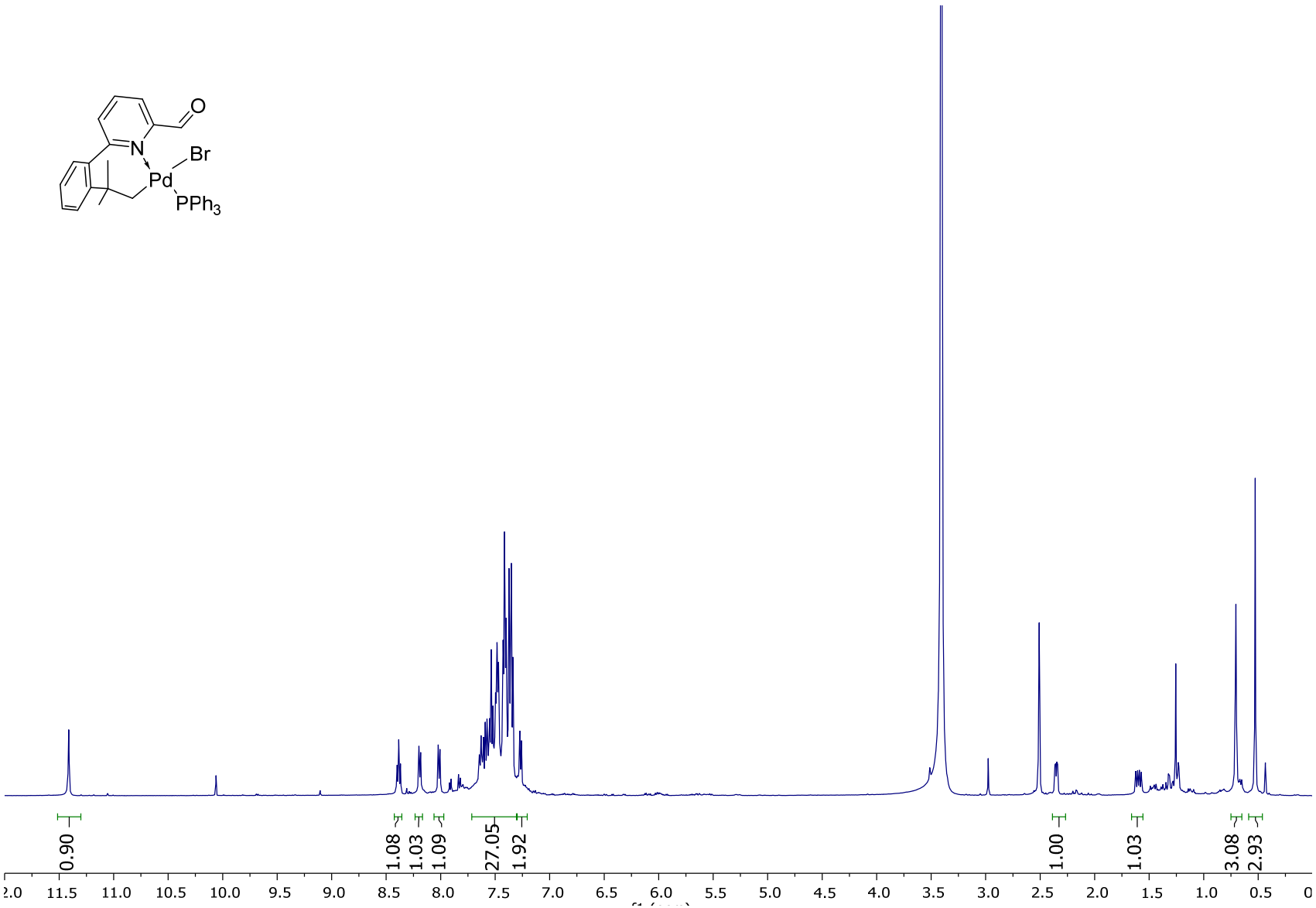


Figure S42. ^{1}H spectrum of **7** in dmso-d_6 at rt.

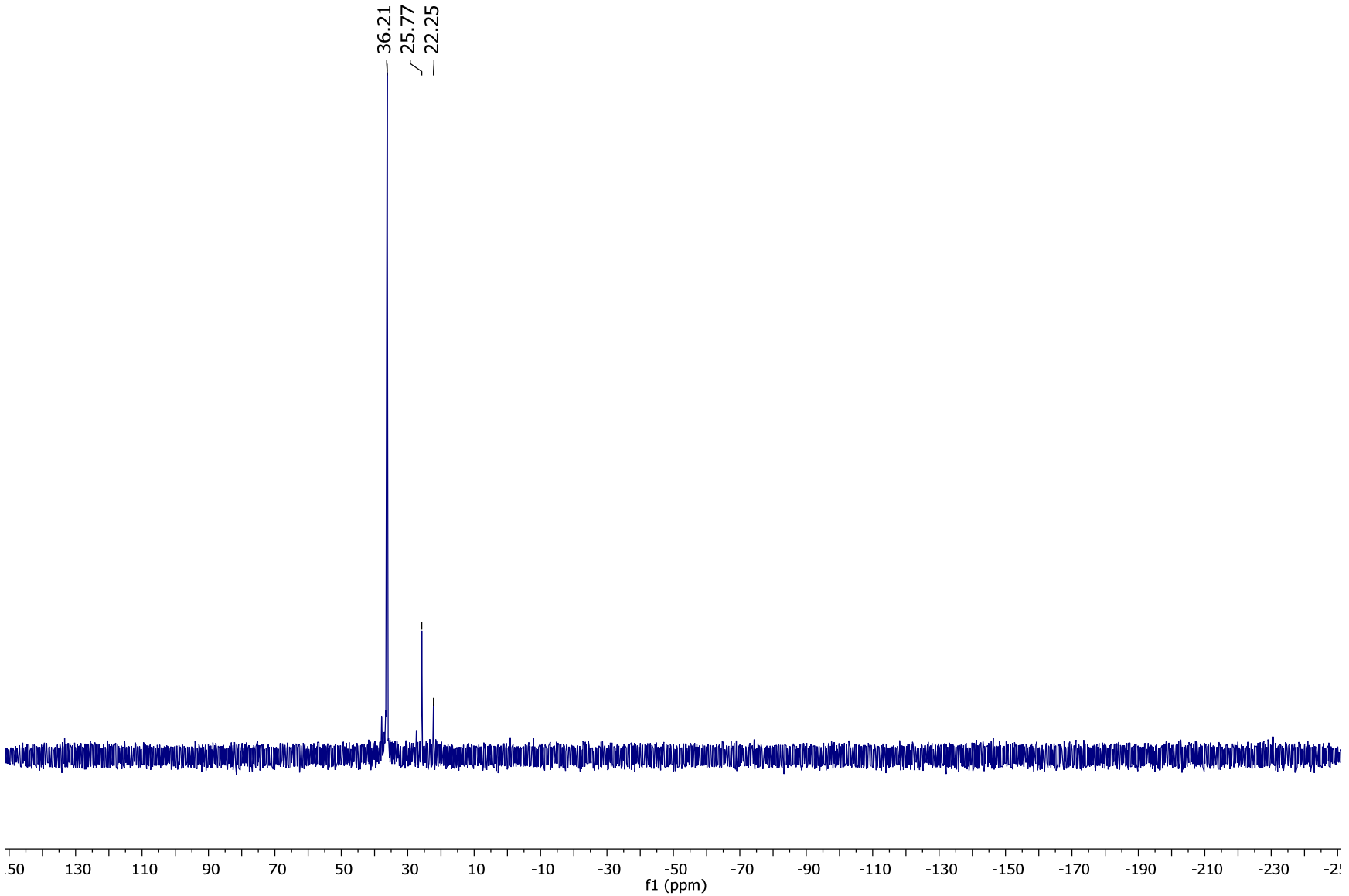


Figure S43 ^{31}P spectrum of **7** in dmso-d_6 at rt.

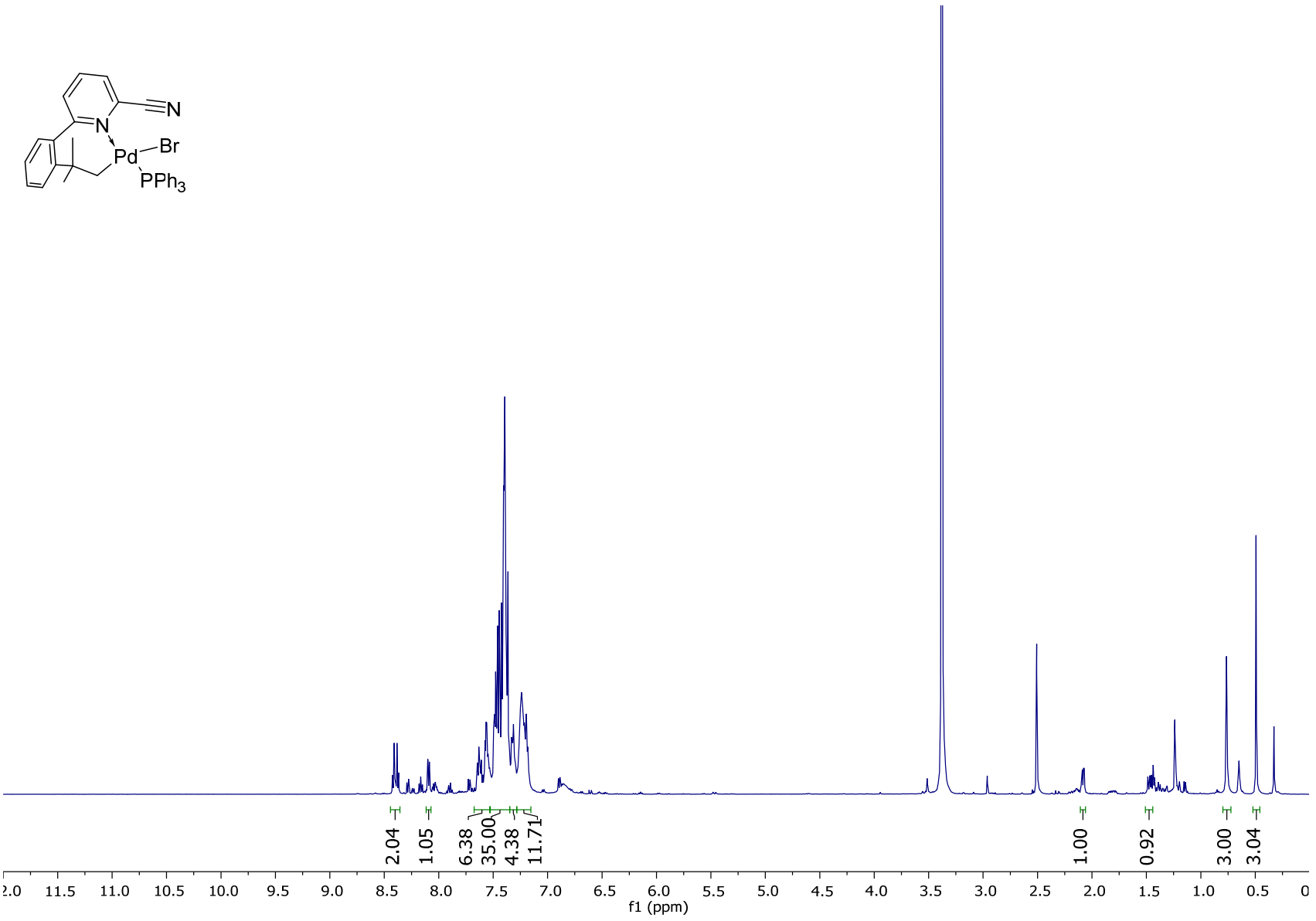


Figure S44. ^{1}H spectrum of **8** in dmso-d_6 at rt.

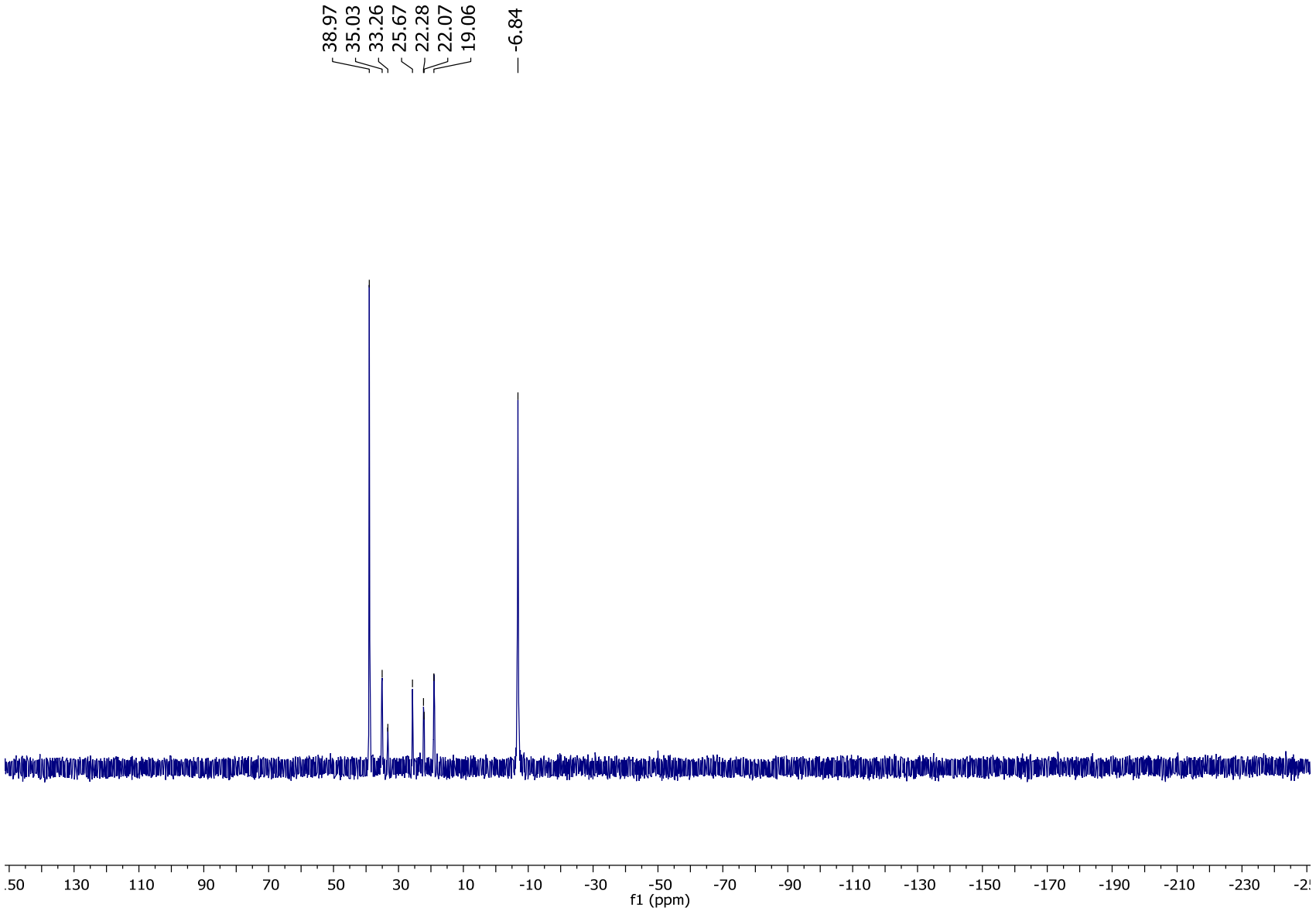


Figure S45. ^{31}P spectrum of **8** in dmso-d_6 at rt.

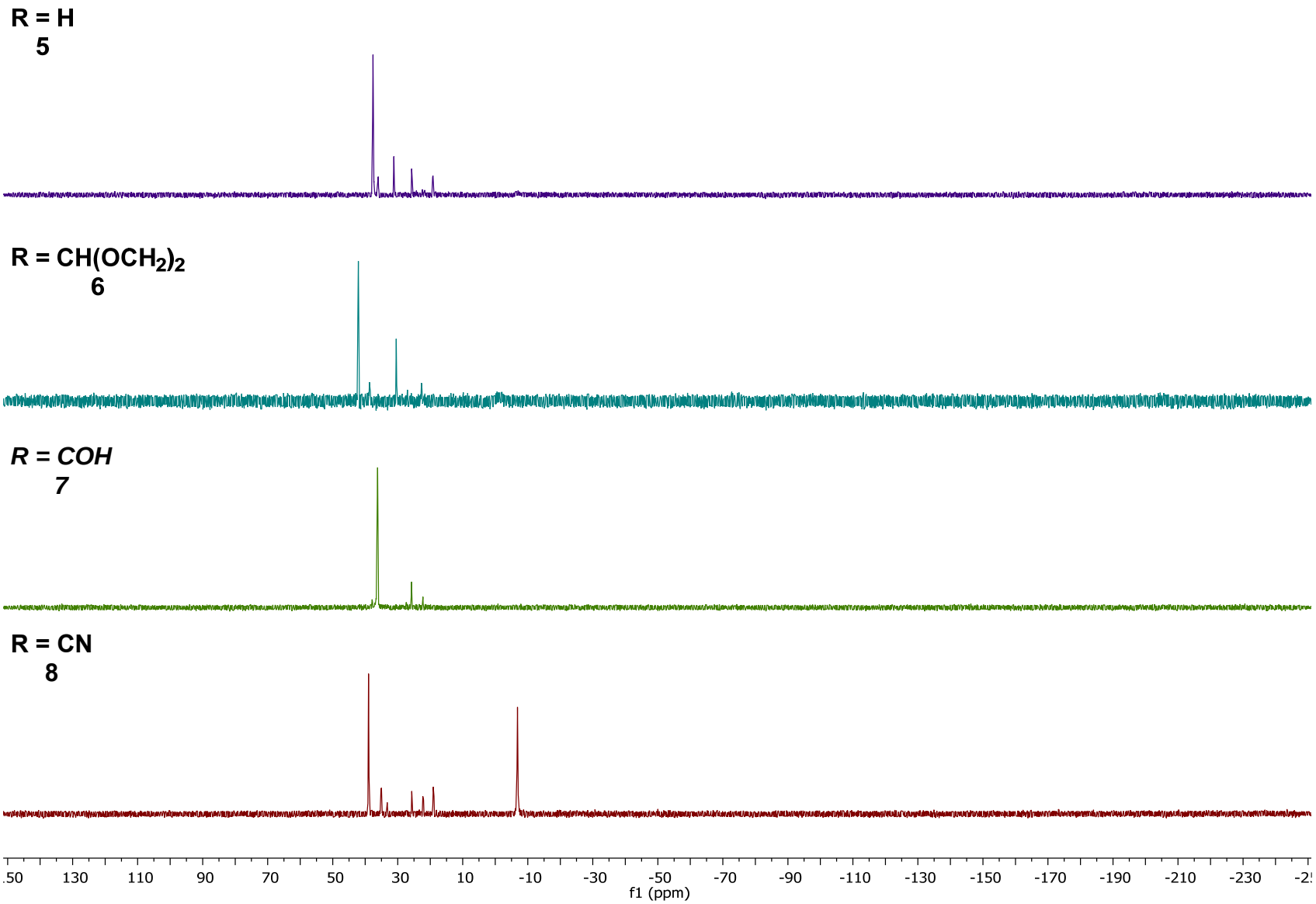


Figure S46. ^{31}P spectra of compounds **5-8** in dmso-d_6 at rt.

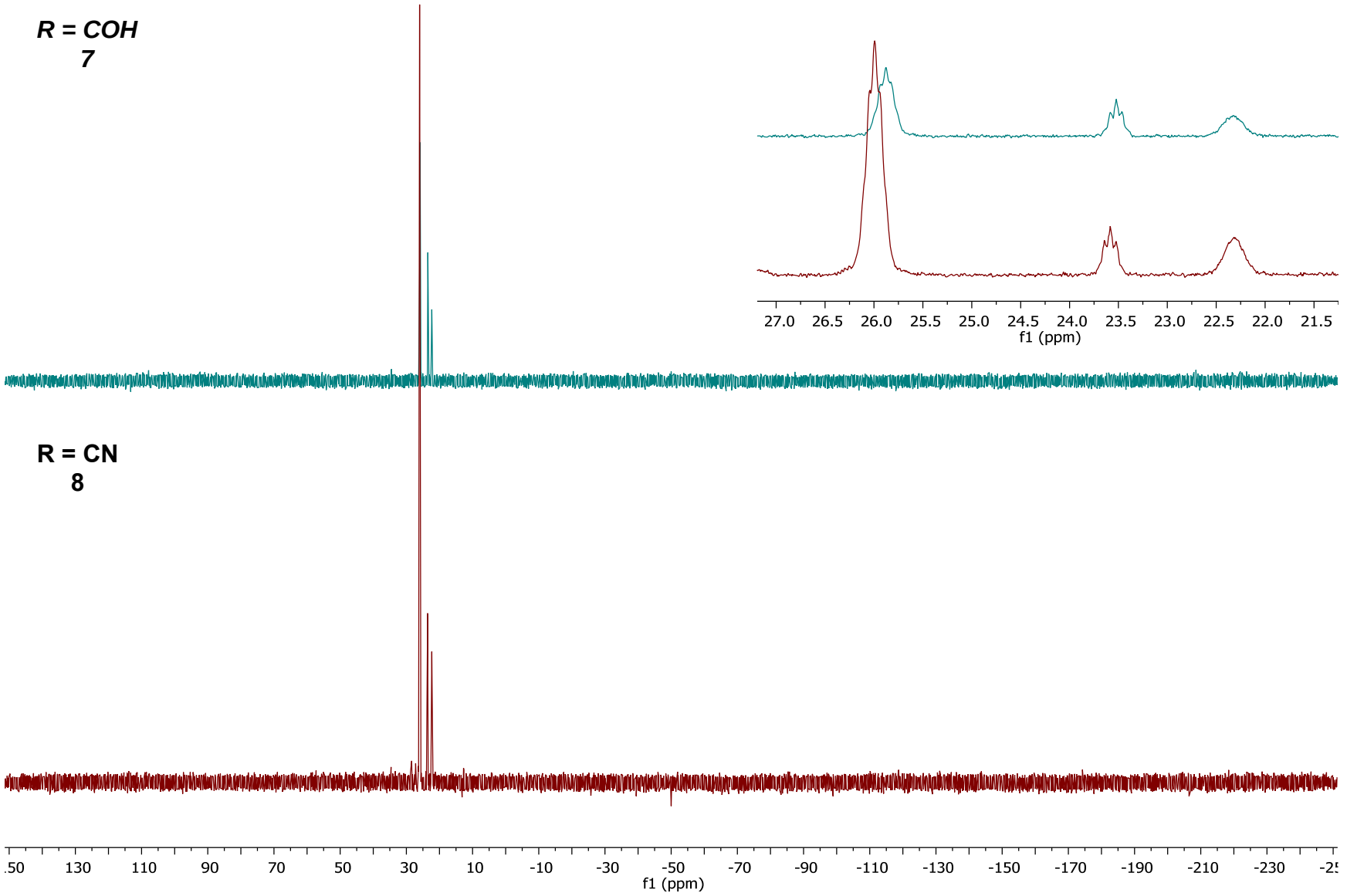


Figure S47. ^{31}P spectra of compounds **7** and **8** in dmso-d_6 at rt.

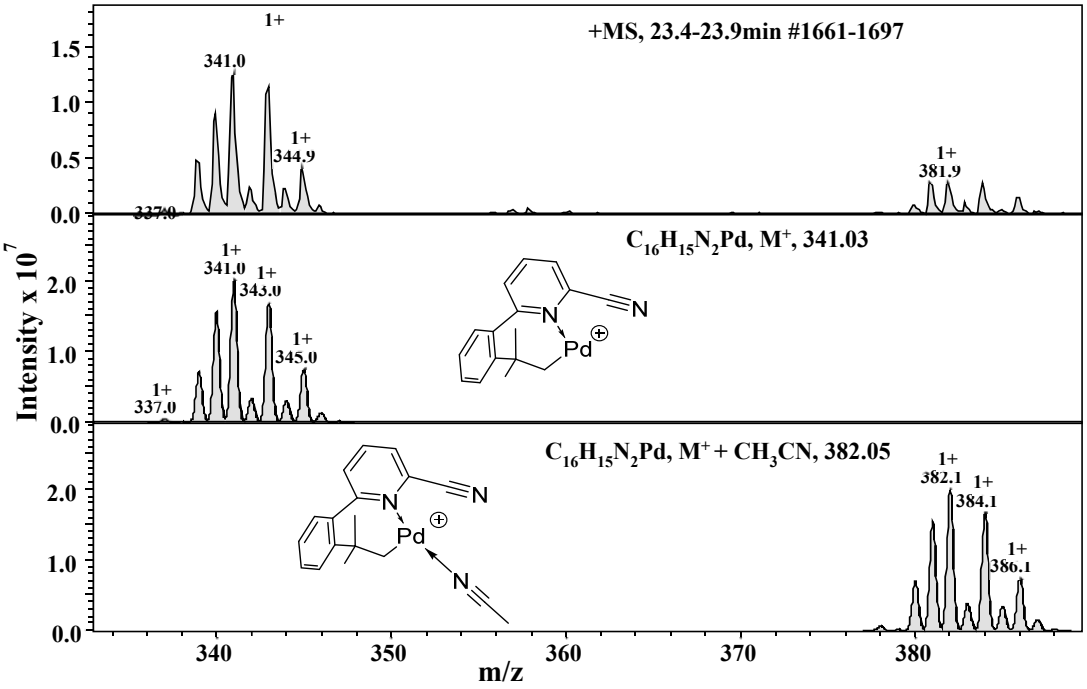


Figure S48. Upper Box: High resolution mass spectrum for compound **1** in CH_3CN solution. Lower boxes: Theoretical isotopic patterns and molecular structures of the two ions detected

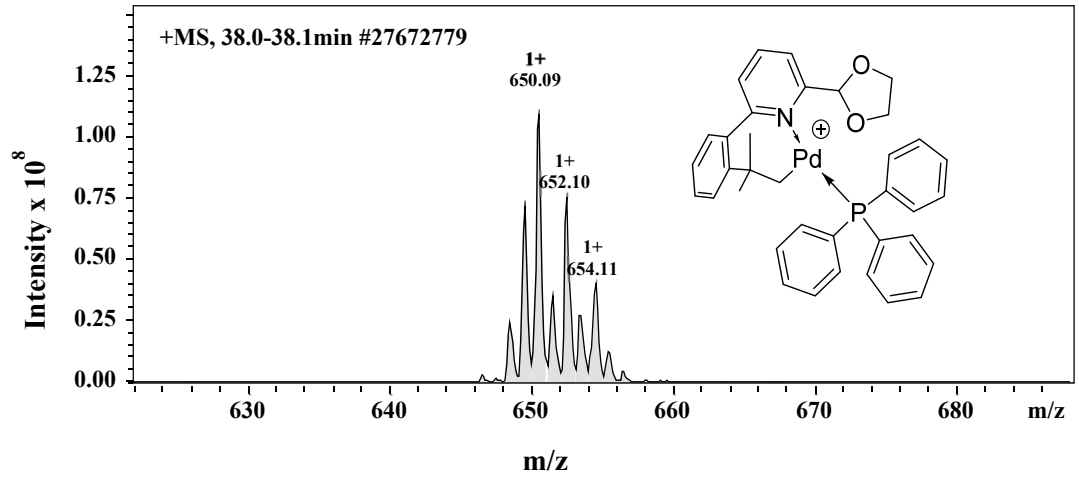
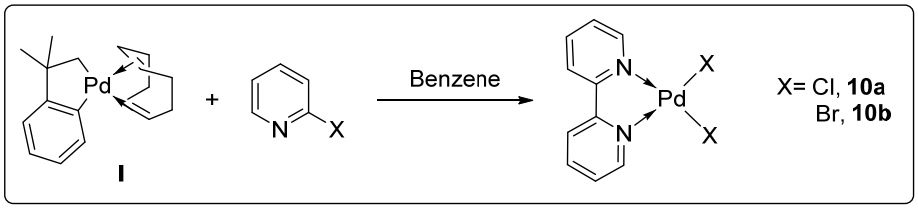


Figure S49. Upper Box: High resolution mass spectrum for compound **6** in CH_3CN solution.

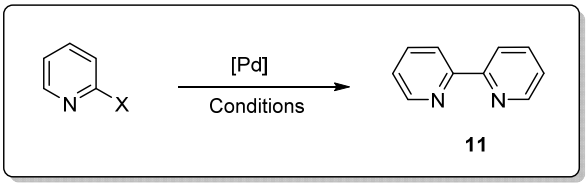
Symmetric and Asymmetric Bipyridine Synthesis through Direct 2-X-Pyridine Coupling (X= Cl or Br) Catalyzed by Palladium in Water.



Thus, palladacycle **I** react easy and cleanly with an excess of X-Py (Ratio 1:3) at room temperature to give the *BiPy* complexes [Pd(*BiPy*)X_2], **10** (Eq. 1). Additionally, complexes **10a**-**b** can be obtained by the reaction of *BiPy* with the appropriate palladium source.[7-8] At this point, we found ourselves into the next question: Could be possible obtain *BiPy* species using **I** as catalytic precursor? To found an answer to this question we carried out the next experiments.

After an initial screen we found that **11** could be isolated in good yield after 24 h of reaction by using *N,N´*-dimethylformamide (DMF) as solvent (Table S2, entries 1-2). However, high temperature must be reached to get this conversion. Below this temperature, only a negligible amount of *BiPy* was detected (Table S2, entries 3-4). Also, the use of different base types like Cs_2CO_3 or K_2CO_3 clearly does not affect the conversion and yield of compound **11**, but without base addition into the reaction mixture compound **11 is not formed** (Table S2, entry 5-6). Finally, the control experiment was carried out without a palladium source and bipyridine specie was not formed (Table S2, entry 7).

Table S2.



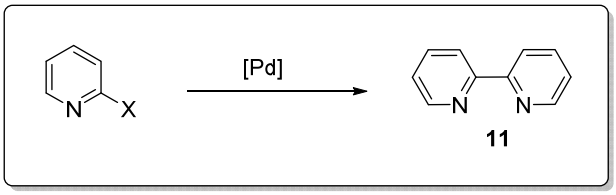
Entry	X	[Pd]	n mol%	Solvent	Base	T(°C)	t(h)	Conversion
1	Br	I	5	DMF	Cs_2CO_3	210	24	100
2	Cl	I	5	DMF	Cs_2CO_3	210	24	100
3	Cl	I	5	DMF	Cs_2CO_3	100	24	n.r.
4	Cl	I	5	DMF	Cs_2CO_3	150	24	n.r.
5	Br	I	1.5	DMF	none	210	24	n.r.
6	Br	I	1.5	DMF	K_2CO_3	210	24	100
7	Br	none		DMF	Cs_2CO_3	210	24	n.r.

n.r. means no reaction

From this knowledge, we decided to test a commercial available coordination palladium complexes ($[PdCl_2(PPh_3)_2]$, $[Pd(OAc)_2]$, $[PdCl_2(COD)]$ and $PdCl_2$), easy handled and cheapest that compounds **I**, as catalytic precursors into the synthesis of **11**. Rewarding, these compounds can convert the 2-X-Py into *BiPy* (Table S3). Additionally, where we found that using toluene as solvent the reaction do not take place, even if water is added as co-solvent into the reaction mixture (Table S3, entries 7-9 and 10-11). Interestingly, addition of DMF into the reaction mixture plays a critical role in the reaction efficiency, and a complete conversion and formation of **11** was observed (Table S3, entries 13-17). These suggest that DMF might act as an auxiliary ligand increasing the solubility and stabilizing the catalytic specie.[9-13] In this regard, the minimum amount of palladium required to catalyzed the complete conversion was found to be 1.5 mol% (Table S3, entries 18-21).

Prompted by these results, we tested the coupling reaction using water as solvent (2 mL) and DMF as additive, observing again completed consumption of 2-halo-pyridines and formation of **10** (Table S3, entry 22). Finally, at this point, we found that the best catalytic conditions to carry out the conversion of 2-halo-pyridine to **11**, is using 1.5 mol % of [$Pd(OAc)_2$], water (2 mL), DMF (500 µL) and K_2CO_3 (Table S3, entry 22). Recently, Duan *et al*. reported homocoupling using Ni as catalyst with a stoichiometric amount of Zn for the classic pre-formation of organozinc-pyridine derivative.[14]

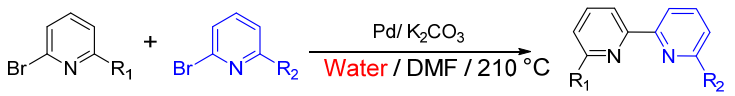
Table S3.

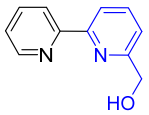
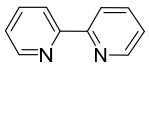
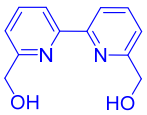
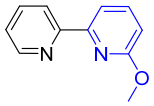
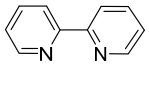
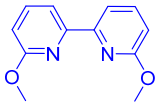
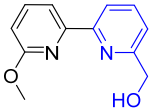
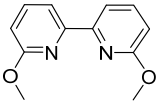
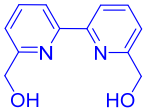
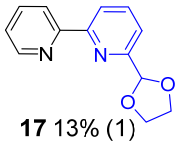
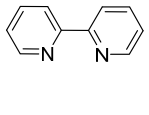
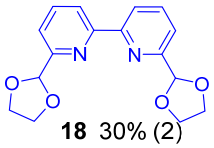
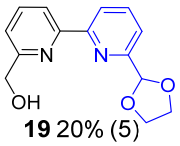
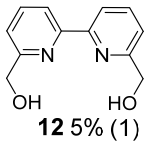
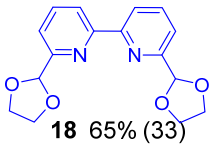


Entry	X	[Pd]	n mol%	Solvent	Base	T(°C)	t(h)	Conversion
1	Br	$PdCl_2(COD)_2$	5	DMF	Cs_2CO_3	210	24	100
2	Br	$PdCl_2(COD)_2$	5	DMF	K_2CO_3	210	24	100
3	Br	$PdCl_2(PPh_3)_2$	5	DMF	K_2CO_3	210	24	100
4	Br	$Pd(OAc)_2$	2.5	DMF	K_2CO_3	210	24	100
5	Br	$Pd(OAc)_2/PPh_3$	2.5	DMF	K_2CO_3	210	24	100
6	Br	$PdCl_2$	2.5	DMF	K_2CO_3	210	24	85
7	Cl	$PdCl_2(COD)_2$	5	Toluene	K_2CO_3	210	24	n.r.
8	Br	$PdCl_2(COD)_2$	5	Toluene	K_2CO_3	210	24	n.r.
9	Br	$PdCl_2(COD)_2$	5	Toluene	Cs_2CO_3	210	24	n.r.
10	Cl	$PdCl_2(COD)_2$	5	Toluene/H_2O (5:1)	K_2CO_3	210	24	n.r.
11	Br	$PdCl_2(COD)_2$	5	Toluene/H_2O (5:1)	K_2CO_3	210	24	n.r.
12	Cl	$PdCl_2(COD)_2$	5	Toluene/H_2O/DMF (10:2:1)	K_2CO_3	210	24	100
13	Br	$PdCl_2(COD)_2$	5	Toluene/H_2O/DMF (10:2:1)	K_2CO_3	210	24	100
14	Br	$PdCl_2(COD)_2$	5	Toluene/DMF (1:0.2)	Cs_2CO_3	210	24	100
15	Br	$Pd(OAc)_2$	1.5	Toluene/H_2O/DMF (10:2:1)	-	210	24	n.r.
16	Br	$Pd(OAc)_2$	1.5	Toluene/H_2O/DMF (10:2:1)	K_2CO_3	210	24	90
17	Br	$Pd(OAc)_2$	1.5	Toluene/H_2O/DMF (10:2:1)	K_2CO_3	210	24	90
18	Br	$Pd(OAc)_2$	0.01	DMF	K_2CO_3	210	72	60
19	Br	$Pd(OAc)_2$	0.5	DMF	K_2CO_3	210	24	45
20	Br	$Pd(OAc)_2$	1.5	DMF	K_2CO_3	210	24	100
21	Cl	$Pd(OAc)_2$	1.5	DMF	K_2CO_3	210	24	87
22	Cl	$Pd(OAc)_2$	1.5	H_2O DMF(additive)	K_2CO_3	210	24	100

n.r. means no reaction

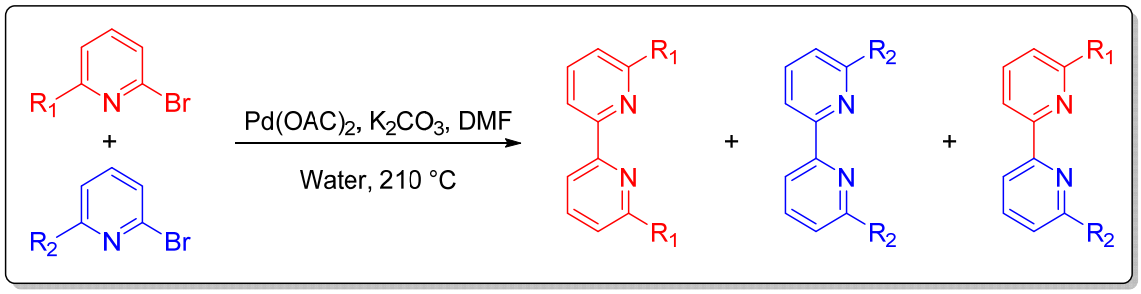
Table S4



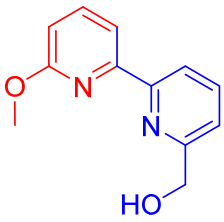
Entry	R_1	R_2	Products[a,b]		
1	H	CHO	 **13** 10% (1)	 **11** 70% (10)	 **12** 20% (3)
2	H	OMe	 **14** 40% (80)	 **11** 2% (1)	 **15** 58% (100)
3	OMe	CHO	 **16** 5% (1)	 **15** 75% (17)	 **12** 15% (3)
4	H	1,3-dioxolan	 **17** 13% (1)	 **11** 45% (3)	 **18** 30% (2)
5	CHO	1,3-dioxolan	 **19** 20% (5)	 **12** 5% (1)	 **18** 65% (33)

[a]Ration determinated by 1H NMR in the reaction crude (In parenthesis).
[b]Yield obtained after purification by column chromatography.

General procedure for the asymmetric coupling reaction.



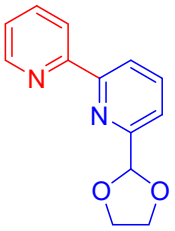
The reactions were conducted under nitrogen atmosphere, in 150 mL *J. Young* glass-tube with *Teflon* stopper. In a typical experiment, 1 mmol of the corresponding 2-halo-pyridine, catalyst, additive, and water were loaded into the tube. The tube was placed in a sand bath preheated to the desired temperature and the stirrer was started. After a suitable reaction time, the reactor was cooled at room temperature. The products were extracted with dichloromethane. Additionally, the *BiPys* **12**-**19**, were fully characterized after purification in chromatographic column on silica.



Compound 16: Prepared following the general procedure.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.32 (d, *J*=7.3, 1H), 8.03 (d, *J*=6.9, 1H), 7.79 (td, *J*=8.0, 2.7, 1H), 7.70 (dt, *J*=9.1, 4.6, 1H), 7.20 (d, *J*=7.1, 1H), 6.78 (d, *J*=7.8, 1H), 4.81 (s, 2H), 4.11 (sb, 1H), 4.04 (s, 3H).

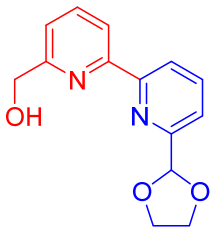
^{13}C NMR (126 MHz, $CDCl_3$) δ = 163.70, 158.16, 154.93, 153.04, 139.46, 137.60, 120.30, 119.71, 113.82, 111.44, 64.04, 53.35.



Compound 17: Prepared following the general procedure.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.61 (d, *J*=5.0, 1H), 8.44 (dd, *J*=8.1, 4.1, 1H), 8.37 (dd, *J*=7.9, 3.3, 1H), 7.80 (dd, *J*=9.1, 6.5, 1H), 7.73 (dddd, *J*=9.7, 7.8, 5.1, 1.9, 1H), 7.55 – 7.48 (m, 1H), 7.22 (ddt, *J*=8.9, 4.8, 1.5, 1H), 6.10 – 5.47 (m, 1H), 4.22 – 4.10 (m, 2H), 4.09 – 3.96 (m, 2H).

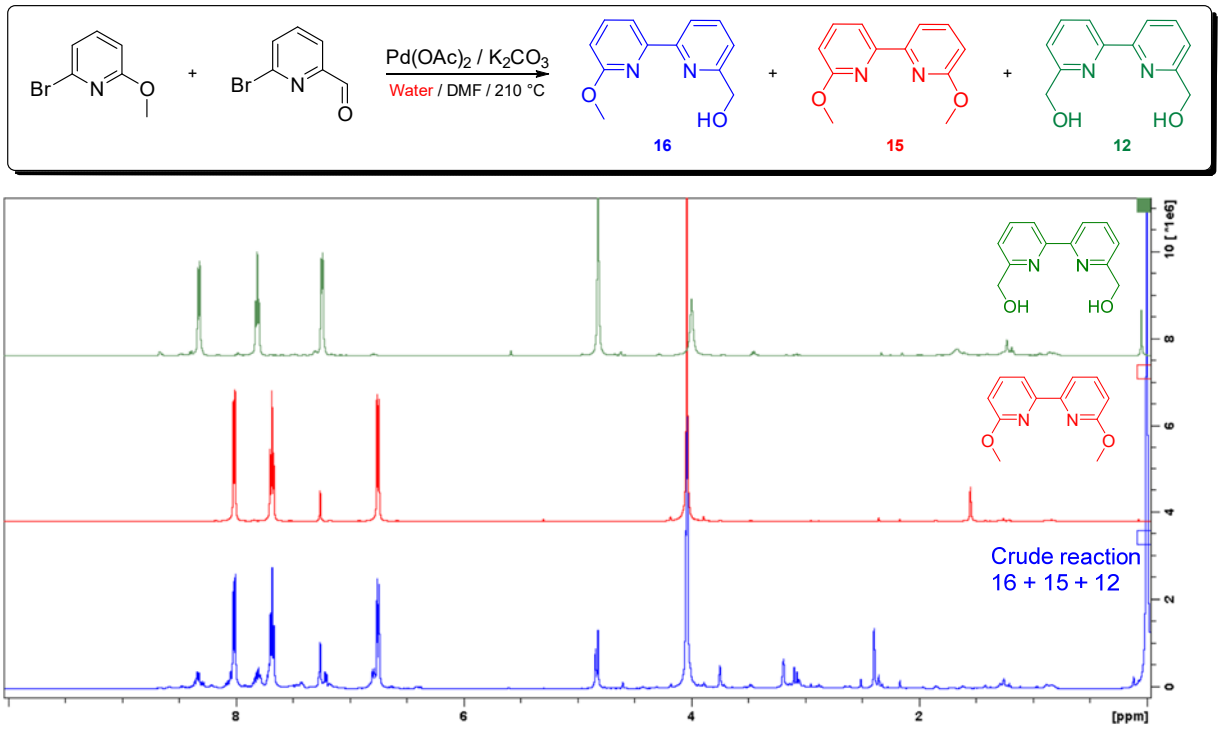
^{13}C NMR (126 MHz, $CDCl_3$) δ = 156.60, 155.69, 155.58, 148.98, 137.62, 136.76, 123.73, 121.31, 121.17, 120.42, 103.94, 65.54.



Compound 19: Prepared following the general procedure.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.46 – 8.34 (m, 2H), 7.86 (t, *J*=7.8, 1H), 7.79 (t, *J*=7.8, 1H), 7.56 (dd, *J*=7.7, 1.1, 1H), 7.23 (d, *J*=7.6, 1H), 5.94 (s, 1H), 4.81 (s, 2H), 4.29 – 4.19 (m, 2H), 4.18 – 4.09 (m, 2H), 4.04 (sb, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 158.26, 156.91, 155.28, 154.68, 137.79, 137.70, 121.28, 120.76, 120.62, 120.19, 104.14, 65.78, 64.11.



^{1}H NMR (500 MHz, $CDCl_3$) for reaction crude.

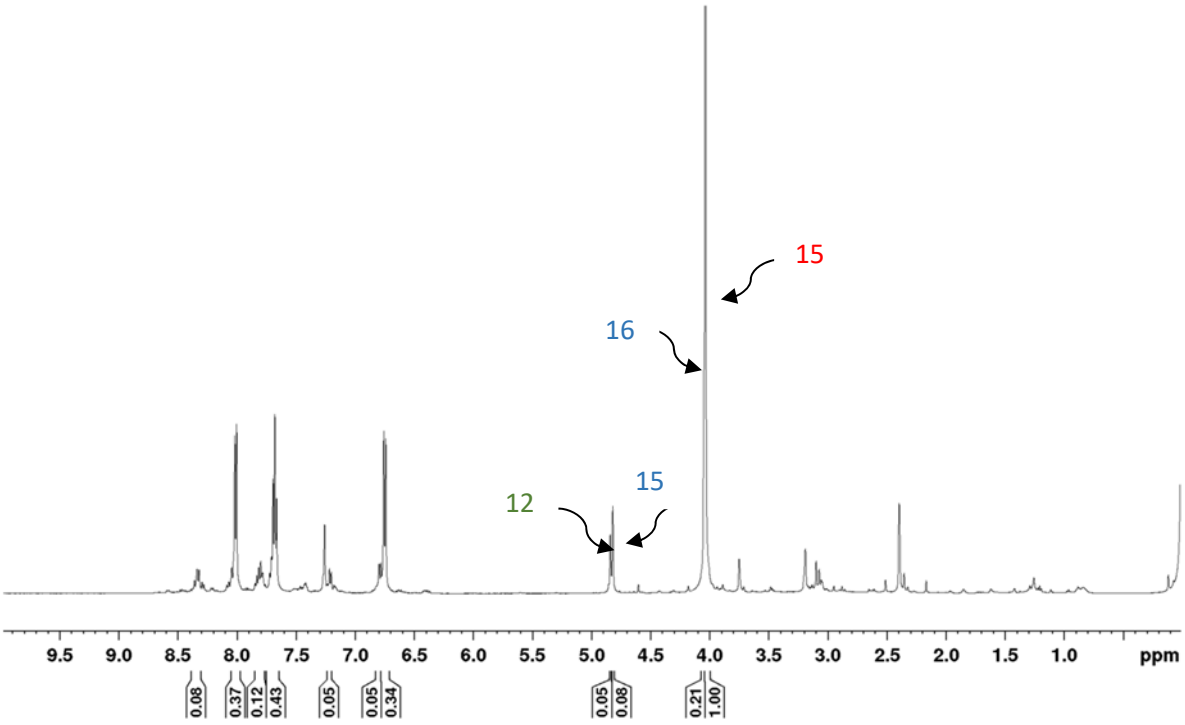
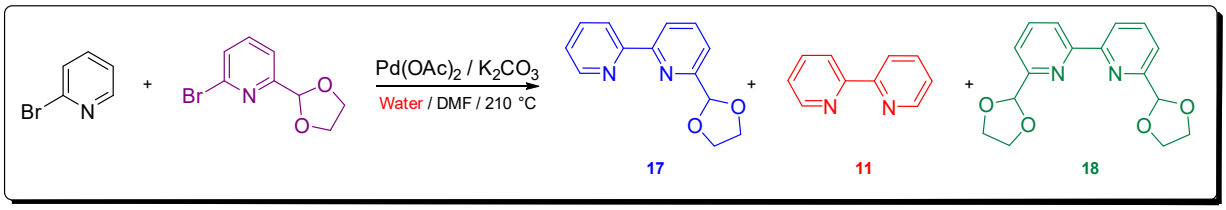
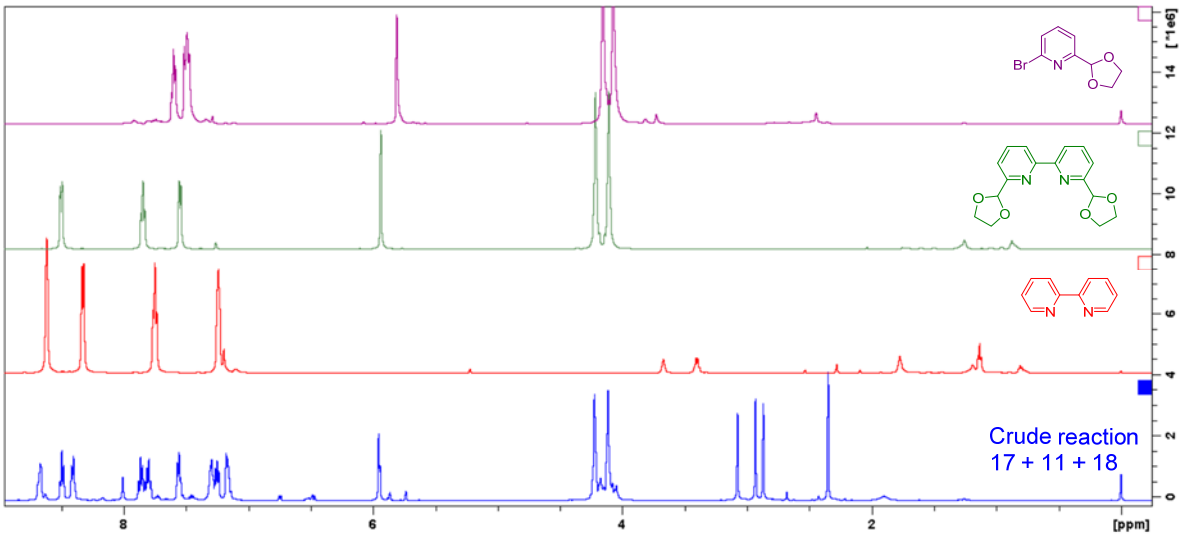


Figure S50. ^{1}H NMR spectrum of reaction crude in $CDCl_3$ at rt.



^{1}H NMR (500 MHz, $CDCl_3$),



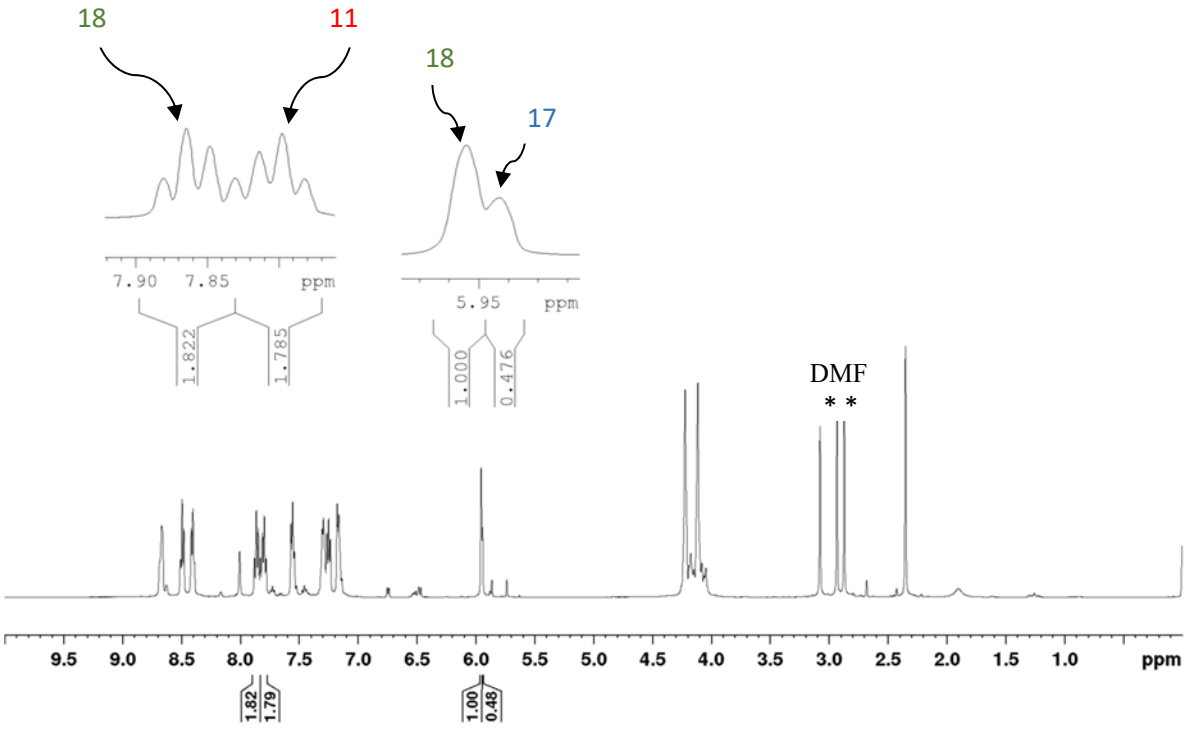
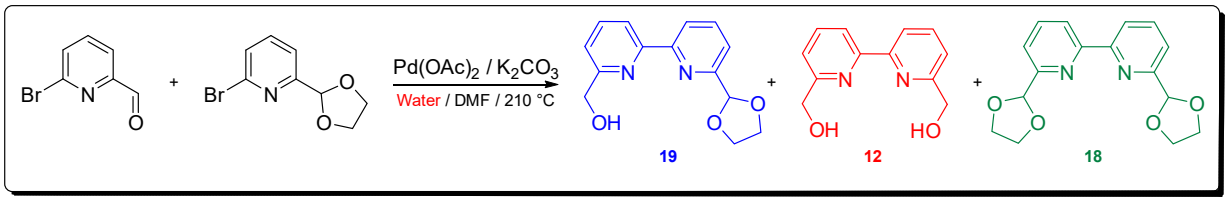
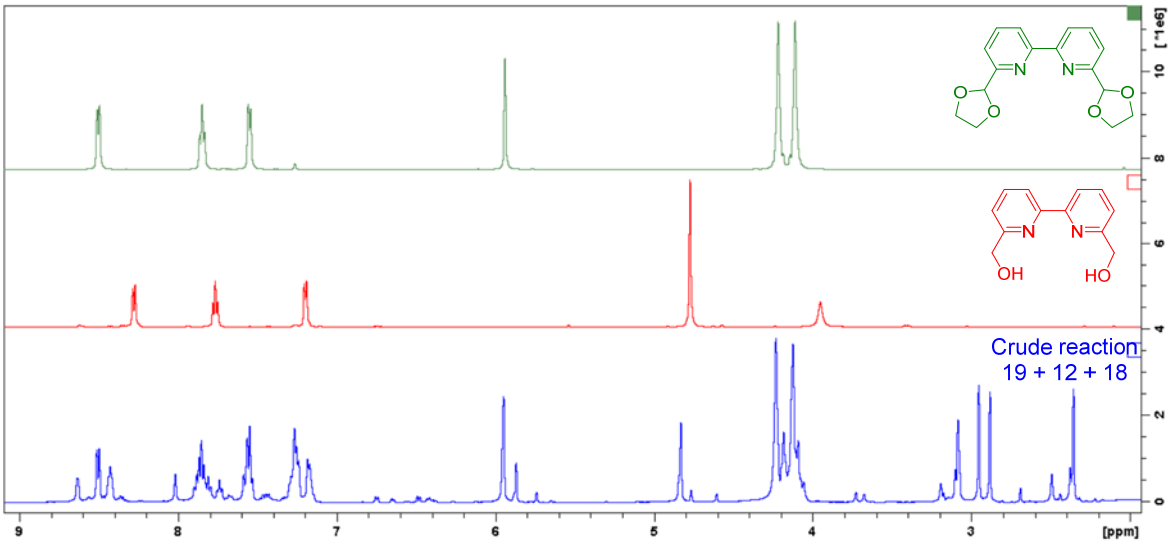


Figure S51. ^{1}H NMR spectrum of reaction crude in $CDCl_3$ at rt.



^{1}H NMR (500 MHz, $CDCl_3$)



^{1}H NMR (500 MHz, $CDCl_3$), reaction crude.

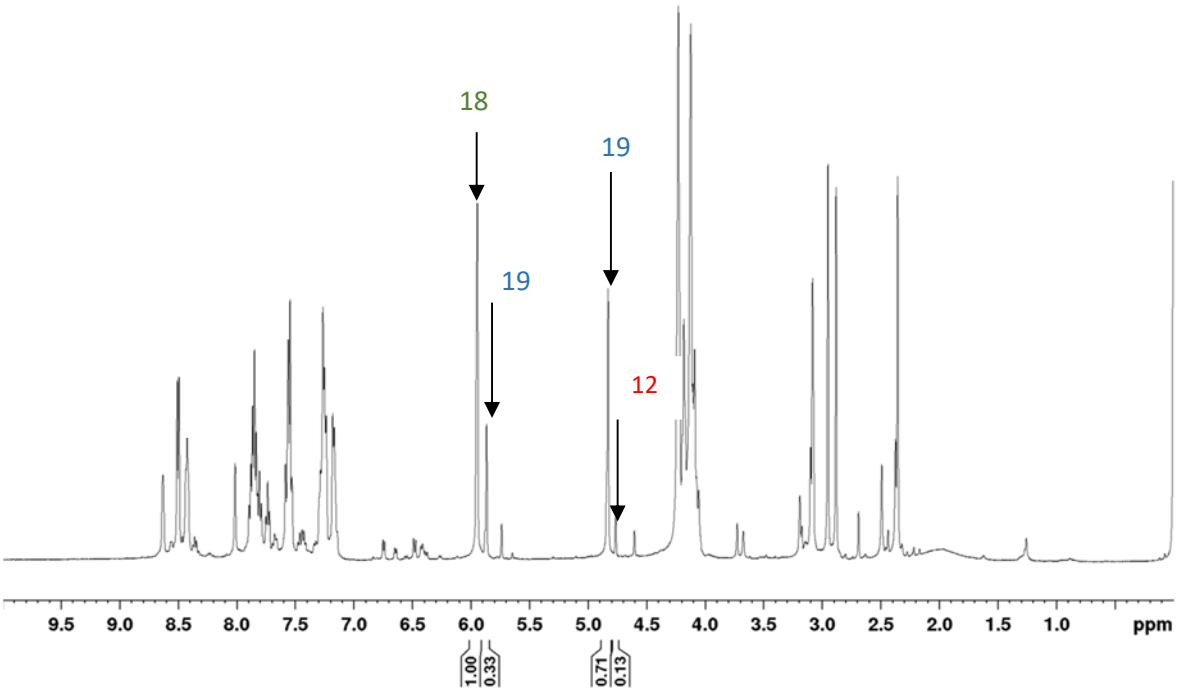


Figure S52. ^{1}H NMR spectrum of reaction crude in $CDCl_3$ at rt.

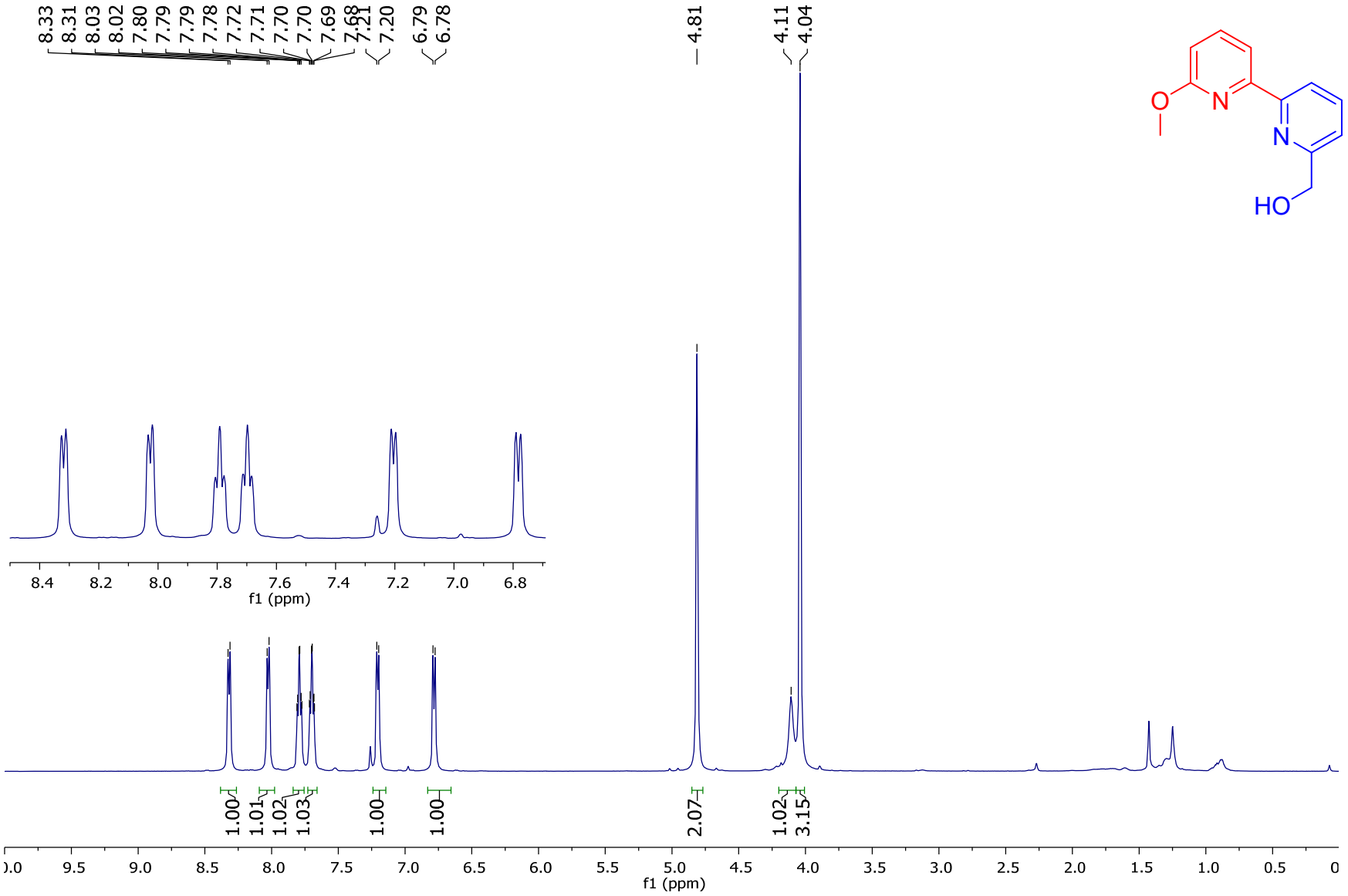


Figure S53. ^{1}H NMR spectrum of **16** in $CDCl_3$ at rt.

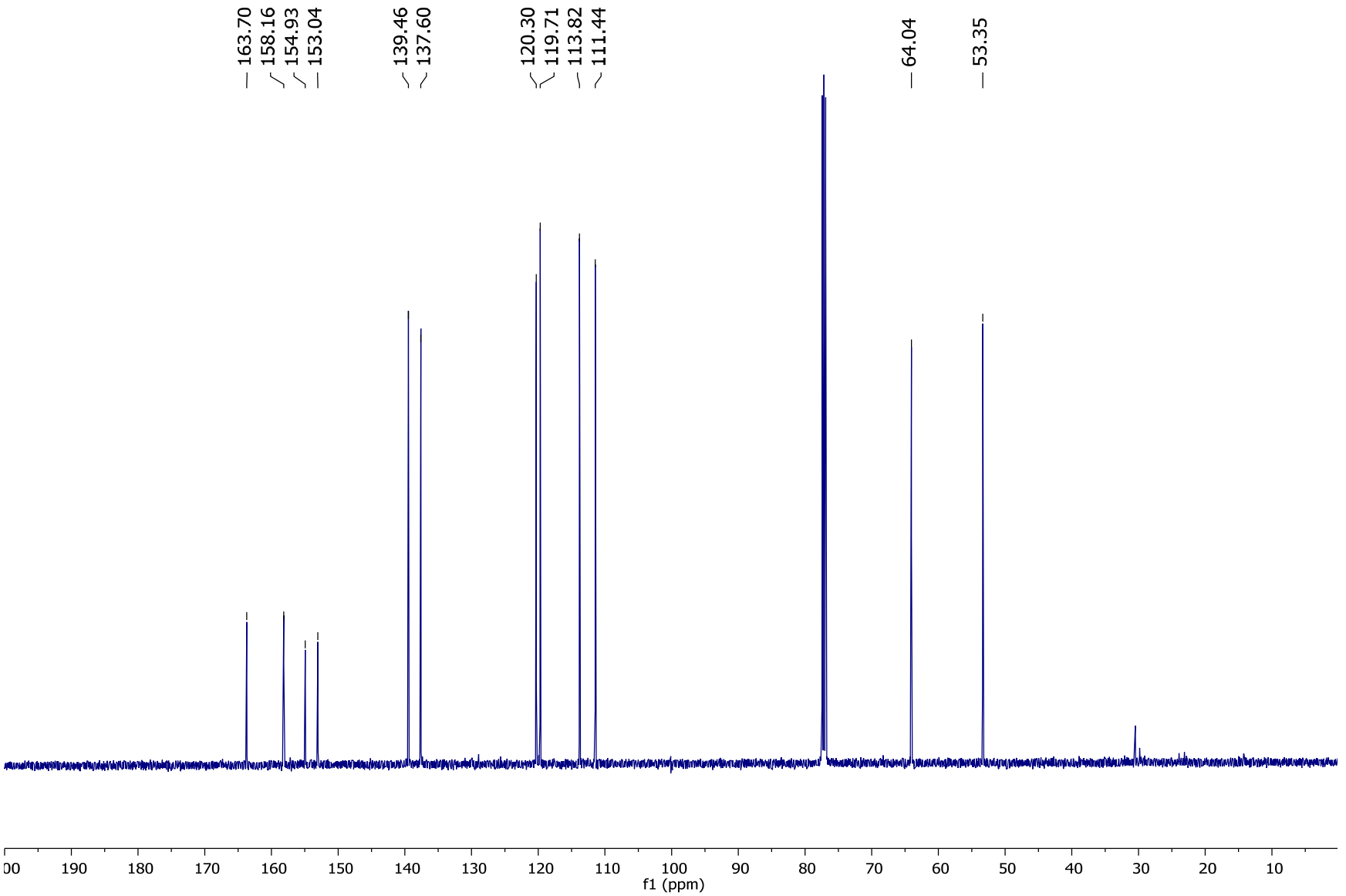


Figure S54. ^{13}C NMR spectrum of **16** in $CDCl_3$ at rt.

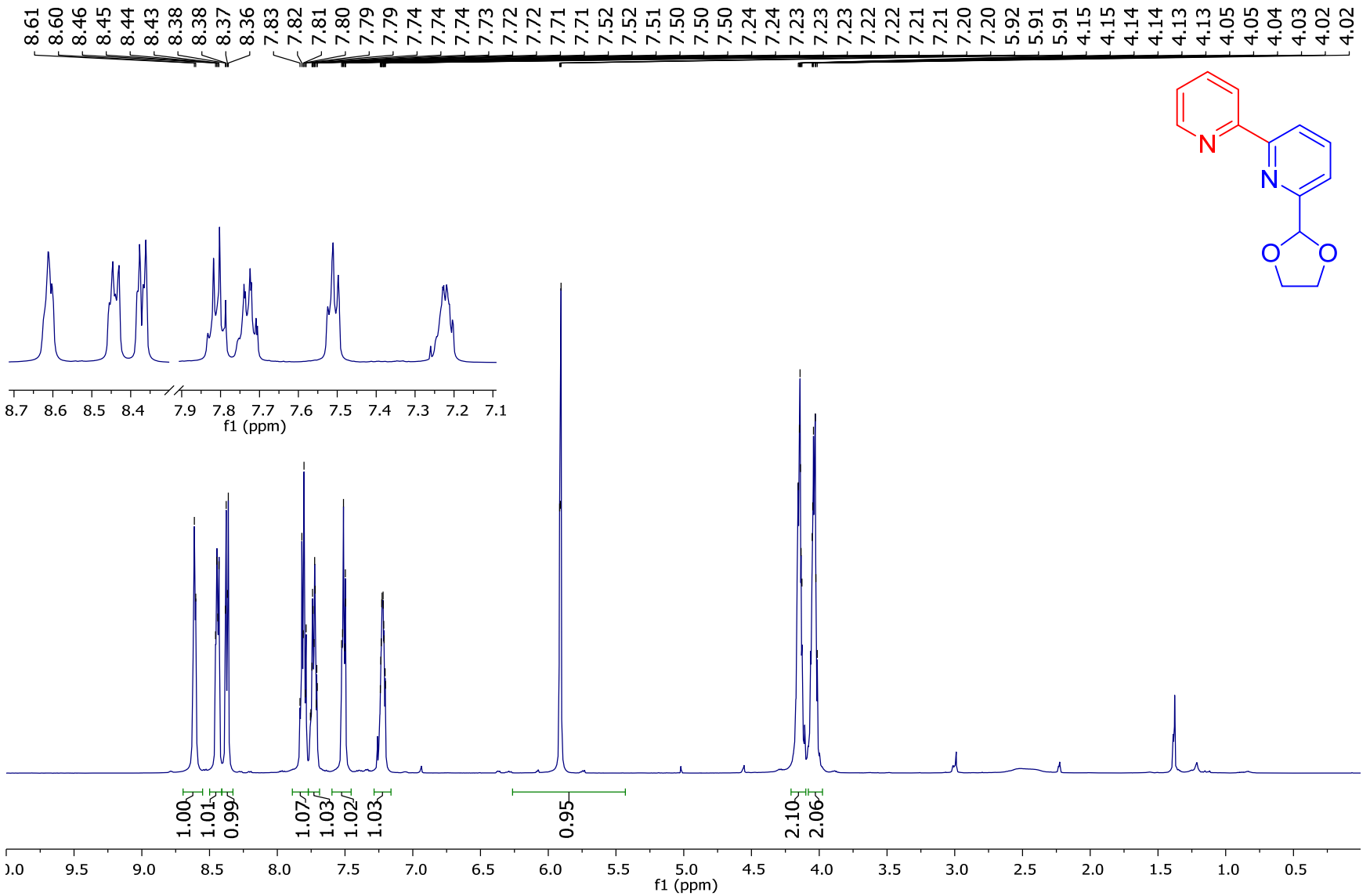


Figure S55. ^{1}H NMR spectrum of **17** in $CDCl_3$ at rt.

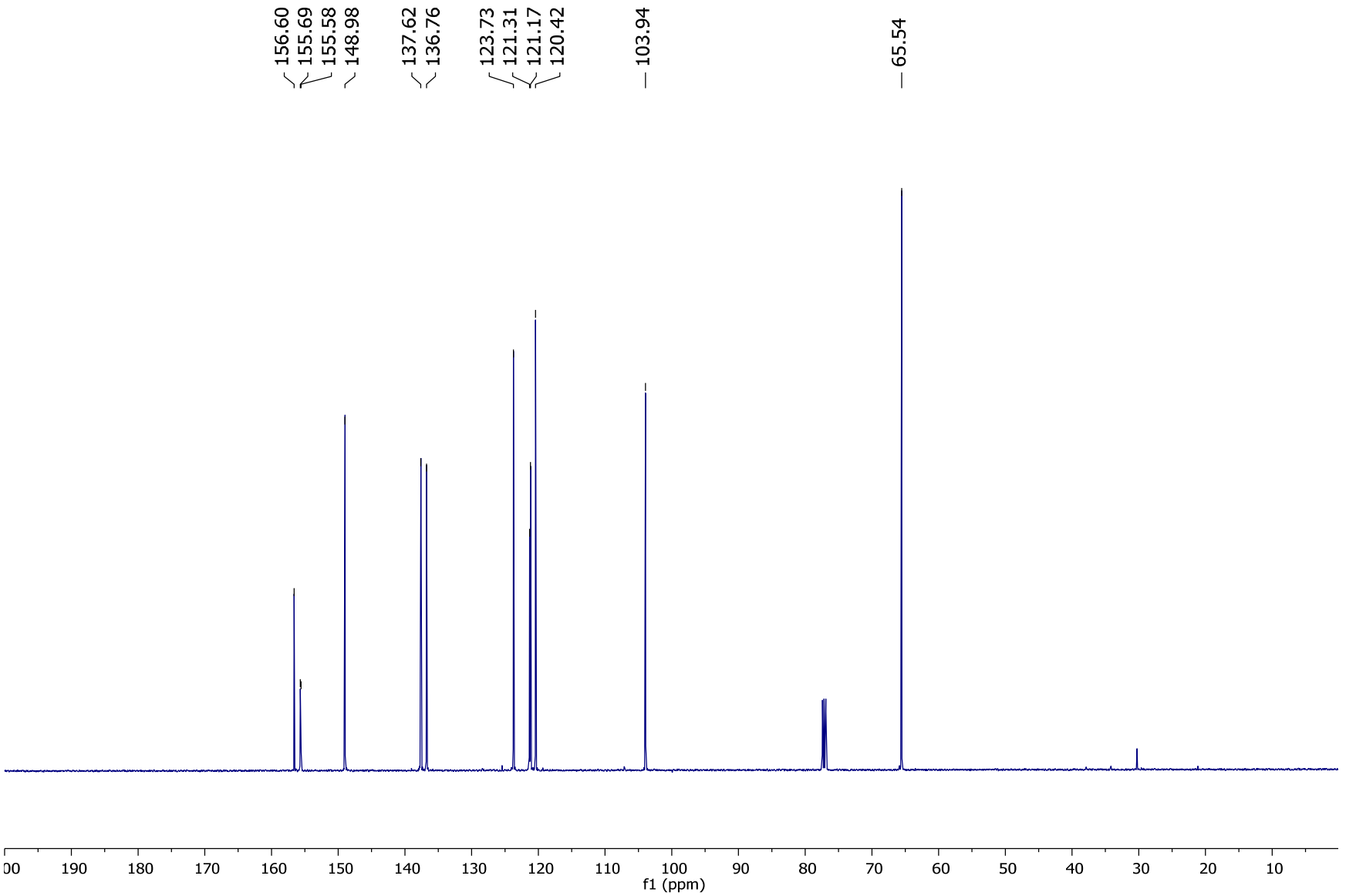


Figure S56. ^{13}C NMR spectrum of **17** in $CDCl_3$ at rt.

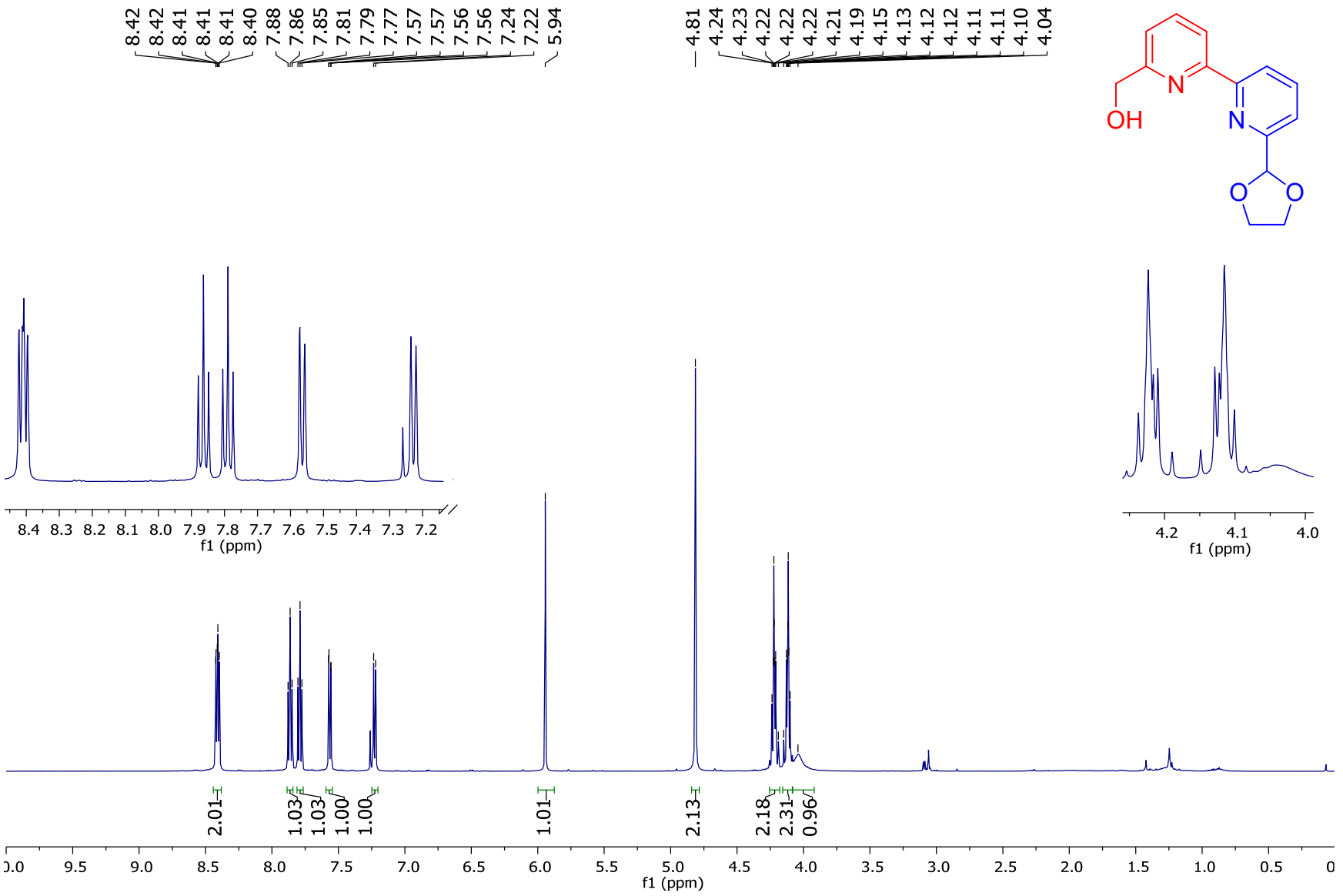


Figure S57. ^{1}H NMR spectrum of **19** in $CDCl_3$ at rt.

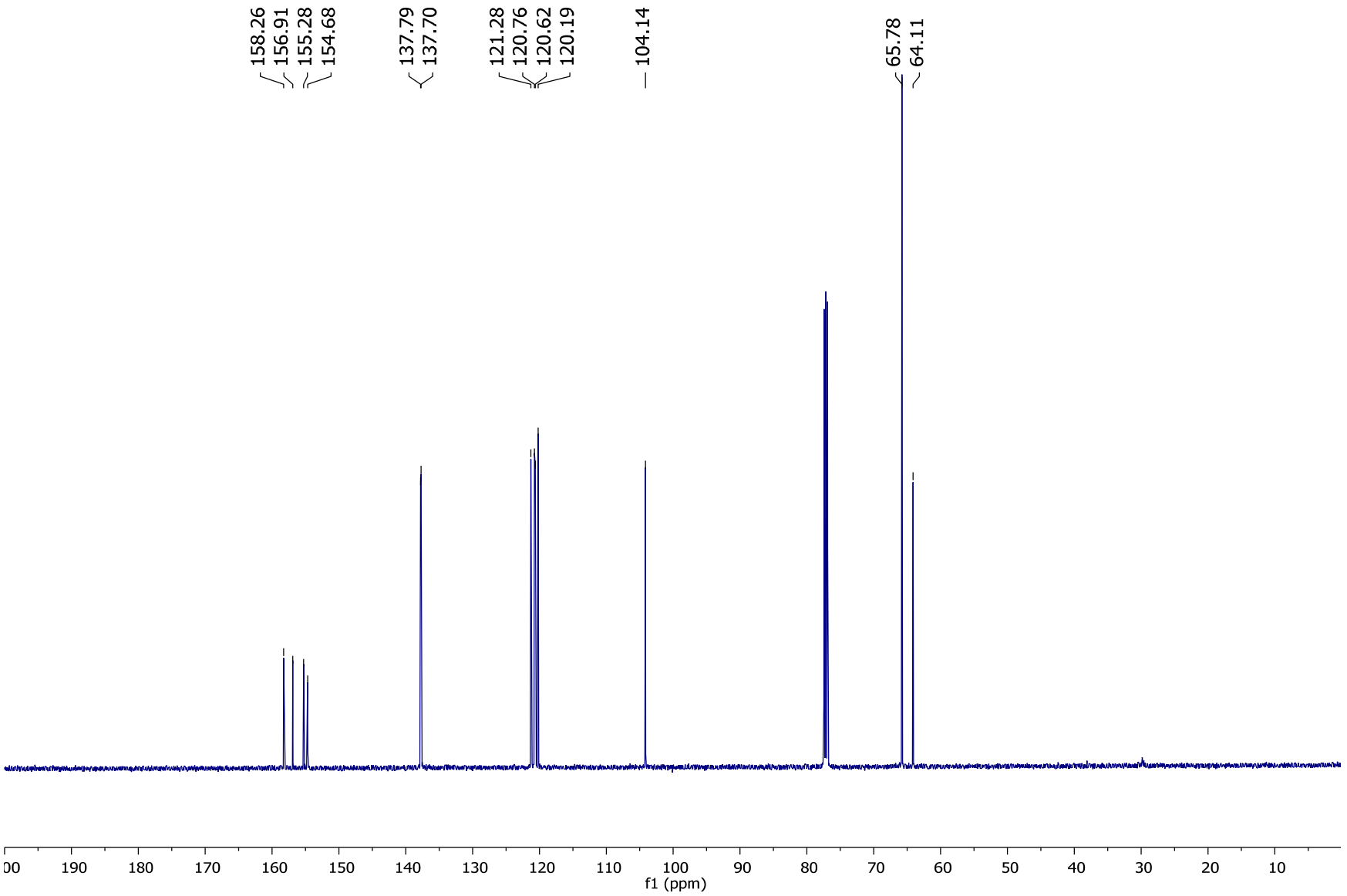


Figure S58. ^{13}C NMR spectrum of **19** in $CDCl_3$ at rt.

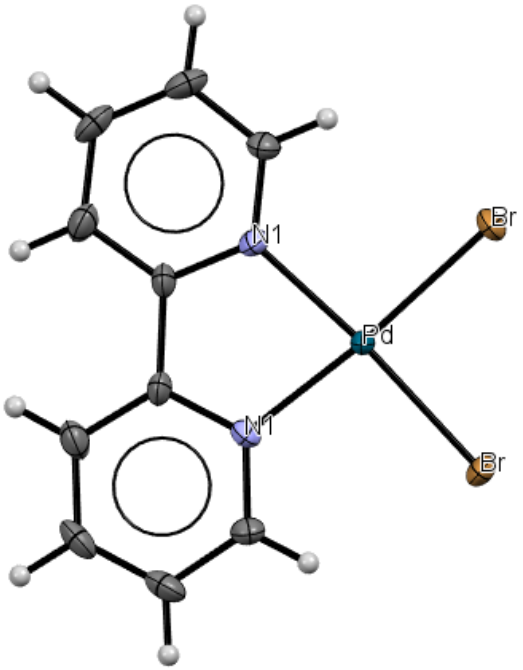


Figure S59. Molecular structure of the compound **10** (thermal ellipsoids are show with a 30 % probability level).

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