Xantphos as a Branch-Selective Ligand for the Acyclic *Sec*-Alkyl Negishi Cross-Coupling of Heteroaryl Halides

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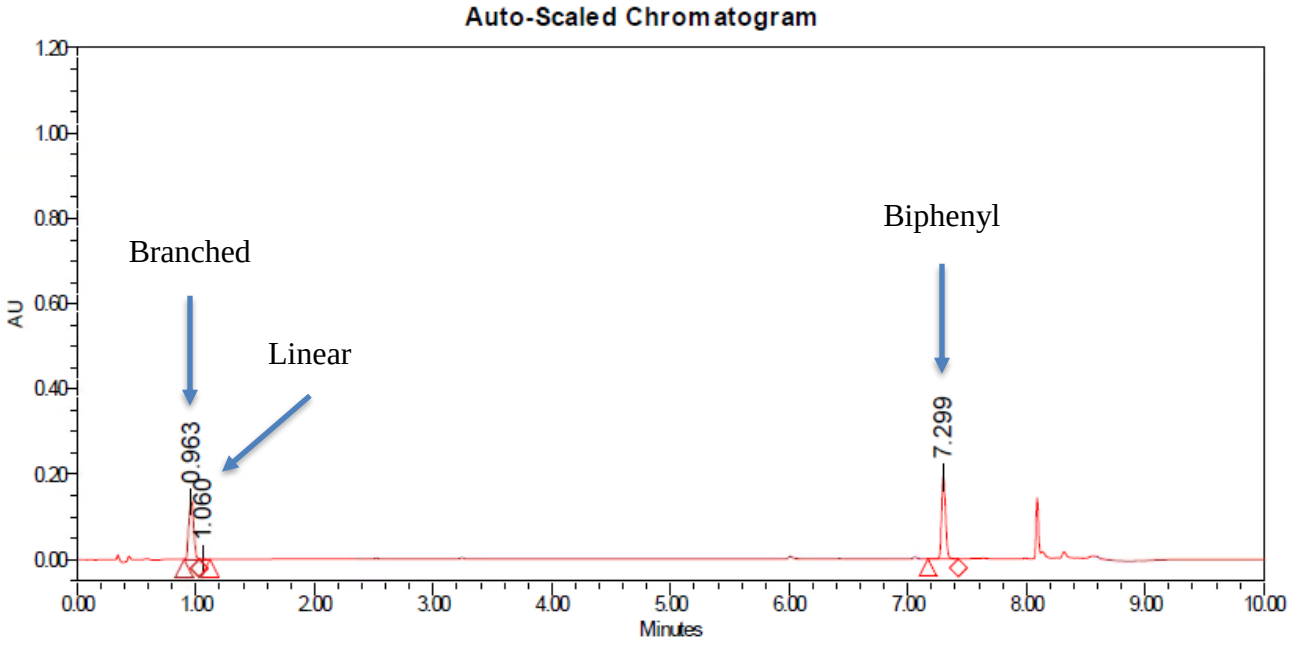
1. Preliminary Catalyst Screening

Table S1: Raw LCAP Results for Preliminary Catalyst Screening

Row	Column	Catalyst	Branched	Linear	Substrate	Biphenyl	*b:l*	Pdt/Std
A	1	BrettPhos Pd G3	25.74	11.83	2.13	55.41	2.2	0.68
A	2	CPhos Pd G3	32.54	14.57	0	52.89	2.2	0.89
A	3	DavePhos Pd G3	41.94	4.8	0	53.26	8.7	0.88
A	4	P(tBu)3 Pd G2	14.74	27.95	0	57.32	0.5	0.74
A	5	J009 Pd G3	9.95	13.17	13.22	63.66	0.8	0.36
A	6	MorDalPhos Pd G3	9.44	18.44	5.27	66.84	0.5	0.42
B	1	BINAP Pd G3	30.63	5.85	6.01	57.51	5.2	0.63
B	2	RuPhos Pd G2	42.07	5.39	0	52.53	7.8	0.90
B	3	SPhos Pd G2	41.35	5.75	0	52.9	7.2	0.89
B	4	tBuXPhos Pd G3	8.33	12.75	14.18	64.73	0.7	0.33
B	5	XantPhos Pd G3	46.45	0.48	0	53.07	96.8	0.88
B	6	XPhos Pd G3	15.07	30.29	0	54.64	0.5	0.83



Peak Results

	Name	RT	RT Ratio	Area	Height	% Area
1		0.963		392172	134731	46.45
2		1.060		4074	1438	0.48
3		7.299		448035	192727	53.07

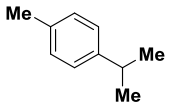
Figure S1: UHPLC Chromatogram for Xantphos Pd G3

2. Preparation of Peak ID's

General Procedure

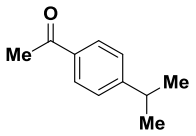
To a vial was added electrophile (0.6 mmol) and either Xantphos Pd G3 or PEPPSI IHept-Cl (0.012 mmol, 0.02 equiv). The vial was transferred to a nitrogen-filled glovebox. To the vial was added 1.7 mL THF followed by 0.9 mL 1.0 M ^{i}PrZnBr in THF (0.9 mmol, 1.5 equiv). The vial was sealed and stirred overnight at 30 °C. The reaction was quenched with 5 mL sat. aq. NH_4Cl (CAUTION: use appropriate venting for gas evolution) and stirred for 10 min. The reaction mixture was extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude material was purified by column chromatography. Work-up and isolation was not optimized to maximize isolated yield.

p-Cymene (Table 2, entry 4)



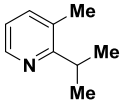
Prepared from 1-bromo-4-methylbenzene (0.6 mmol) and PEPPSI IHept-Cl according to the General Procedure. The crude residue was purified by silica gel chromatography (0 to 10% EtOAc/hept) to yield the desired product (8.2 mg, 10% yield) as a clear oil (product was volatile). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 – 7.10 (m, 4H), 2.89 (spt, *J* = 6.9 Hz, 1H), 2.34 (s, 3H), 1.26 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.9, 135.2, 129.0, 126.3, 33.7, 24.1, 20.9.

1-(4-isopropylphenyl)Ethan-1-one (Table 2, entry 5)



Prepared from 1-(4-bromophenyl)ethan-1-one (0.6 mmol) and PEPPSI IHept-Cl according to the General Procedure. The crude residue was purified by silica gel chromatography (0 to 10% EtOAc/hept) to yield the desired product (80.4 mg, 83% yield) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.5 Hz, 2H), 7.31 (d, *J* = 8.3 Hz, 2H), 2.96 (spt, *J* = 6.9 Hz, 1H), 2.57 (s, 3H), 1.26 (d, *J* = 7.0 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.7, 154.5, 135.0, 128.5, 126.6, 34.2, 26.4, 23.6; HRMS calc'd for $C_{11}H_{14}O$ $[M + H]^+$ 163.1117, found 163.1120.

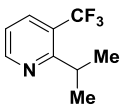
2-Isopropyl-3-methylpyridine (Table 2, entry 6)



Prepared from 2-bromo-3-methylpyridine (0.6 mmol) and PEPPSI IHept-Cl according to the General Procedure. The crude residue was purified by silica gel chromatography (0 to 10% EtOAc/hept) to yield the desired product (18.0 mg, 22% yield) as a clear oil (product was volatile). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, *J* = 3.7 Hz, 1H), 7.39 (d, *J* = 7.7 Hz, 1H), 7.01 (dd, *J* = 4.8, 7.7 Hz, 1H), 3.26 (spt, *J* = 6.8 Hz, 1H), 2.34 (s, 3H), 1.28 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.9, 146.7, 137.7, 129.9, 120.8, 31.3,

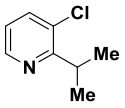
21.6, 18.7; HRMS calc'd for $C_9H_{13}N$ $[M + H]^+$ 136.1121, found 136.1119.

2-isopropyl-3-(trifluoromethyl)pyridine (Table 2, entry 7)



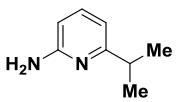
Prepared from 2-bromo-3-(trifluoromethyl)pyridine (0.6 mmol) and PEPPSI IHept-Cl according to the General Procedure, except the quenched reaction mixture was extracted with $CHCl_3$ (3 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to yield the desired product (41.3 mg, 36% yield) as a clear oil (product was volatile). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (d, *J* = 4.1 Hz, 1H), 7.85 (d, *J* = 7.9 Hz, 1H), 7.18 (dd, *J* = 4.8, 7.9 Hz, 1H), 3.40 (spt, *J* = 6.4 Hz, 1H), 1.29 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.9 (q, *J* = 1.7 Hz), 152.2, 133.7 (q, *J* = 6.1 Hz), 124.1 (q, *J* = 272.5 Hz), 123.5 (q, *J* = 31.2 Hz), 120.4, 32.1, 22.4; HRMS calc'd for $C_9H_{10}F_3N$ $[M + H]^+$ 190.0838, found 190.0836.

3-Chloro-2-isopropylpyridine (Table 2, entry 8)



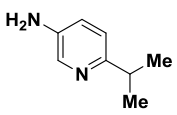
Prepared from 2-bromo-3-chloropyridine (0.6 mmol) and PEPPSI IHept-Cl according to the General Procedure. The crude residue was purified by silica gel chromatography (0 to 10% EtOAc/hept) to yield the desired product (19.9 mg, 21% yield) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (dd, *J* = 1.5, 4.8 Hz, 1H), 7.61 (dd, *J* = 1.7, 8.1 Hz, 1H), 7.06 (dd, *J* = 4.7, 8.0 Hz, 1H), 3.57 (spt, *J* = 6.8 Hz, 1H), 1.29 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.5, 147.2, 136.8, 130.4, 121.9, 31.7, 21.1; HRMS calc'd for $C_8H_{10}ClN$ $[M + H]^+$ 156.0575, found 156.0577.

6-Isopropylpyridin-2-amine (Table 2, entry 9)



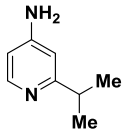
Prepared from 6-bromopyridin-2-amine (0.6 mmol) and PEPPSI IHept-Cl according to the General Procedure. The crude residue was purified by silica gel chromatography (40 to 100% EtOAc/hept) to yield the desired product (27.7 mg, 34% yield) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.33 (m, 1H), 6.52 (d, *J* = 7.5 Hz, 1H), 6.30 (d, *J* = 8.1 Hz, 1H), 4.41 (br s, 2H), 2.84 (spt, *J* = 6.9 Hz, 1H), 1.24 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2, 157.8, 138.1, 110.1, 105.8, 36.1, 22.5; HRMS calc'd for $C_8H_{12}N_2$ $[M + H]^+$ 137.1073, found 137.1072.

6-Isopropylpyridin-3-amine (Table 2, entry 10)



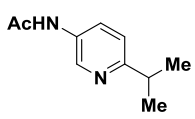
Prepared from 6-bromopyridin-3-amine (0.6 mmol) and Xantphos Pd G3 according to the General Procedure. The crude residue was purified by silica gel chromatography (40 to 100% EtOAc/hept) to yield the desired product (61.9 mg, 76% yield) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 – 7.98 (m, 1H), 6.95 – 6.89 (m, 2H), 3.62 (br s, 2H), 2.94 (spt, *J* = 6.9 Hz, 1H), 1.23 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.4, 140.2, 136.4, 122.6, 120.4, 35.2, 22.7; HRMS calc'd for $C_8H_{12}N_2$ $[M + H]^+$ 137.1073, found 137.1072.

2-Isopropylpyridin-4-amine (Table 2, entry 11)



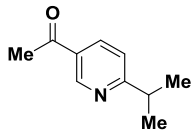
Prepared from 2-bromopyridin-4-amine (0.6 mmol) and Xantphos Pd G3 according to the General Procedure, except the organic layer was removed following aqueous quench. The remaining aqueous layer was adjusted to pH 10 using 5 M NaOH. The aqueous layer was extracted with EtOAc (3 x 5 mL). The combined EtOAc layers were dried over $MgSO_4$, filtered, and concentrated to yield the desired product (62.1 mg, 76% yield) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 5.6 Hz, 1H), 6.38 (d, *J* = 2.3 Hz, 1H), 6.33 (dd, *J* = 2.3, 5.6 Hz, 1H), 4.28 (br s, 2H), 2.88 (spt, *J* = 6.9 Hz, 1H), 1.23 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.8, 153.4, 149.2, 107.4, 106.0, 36.0, 22.4; HRMS calc'd for $C_8H_{12}N_2$ $[M + H]^+$ 137.1073, found 137.1072.

N-(6-isopropylpyridin-3-yl)Acetamide (Table 2, entry 12)



Prepared from N-(6-bromopyridin-3-yl)acetamide (0.6 mmol) and Xantphos Pd G3 according to the General Procedure. The crude residue was purified by silica gel chromatography (0 to 100% EtOAc/hept) to yield the desired product (8.4 mg, 8% yield) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 – 8.40 (m, 1H), 8.11 (br d, *J* = 8.5 Hz, 1H), 7.59 (br s, 1H), 7.16 (d, *J* = 8.7 Hz, 1H), 3.05 (spt, *J* = 6.9 Hz, 1H), 2.19 (s, 3H), 1.28 (d, *J* = 7.0 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.8, 162.9, 140.1, 132.5, 128.6, 120.7, 35.7, 24.3, 22.6; HRMS calc'd for $C_{10}H_{14}N_2O$ $[M + H]^+$ 179.1180, found 179.1180.

1-(6-isopropylpyridin-3-yl)Ethan-1-one (Table 2, entry 14)



Prepared from 1-(6-bromopyridin-3-yl)ethan-1-one (0.6 mmol) and PEPPSI IHept-Cl according to the General Procedure. The crude residue was purified by silica gel chromatography (0 to 30% EtOAc/hept) to yield the desired product (73,5 mg, 75% yield) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.08 (d, *J* = 1.9 Hz, 1H), 8.15 (dd, *J* = 2.3, 8.3 Hz, 1H), 7.28 (d, *J* = 8.1 Hz, 1H), 3.13 (spt, *J* = 6.9 Hz, 1H), 2.61 (s, 3H), 1.32 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.5, 172.0, 149.5, 135.9, 130.1, 120.6, 36.5, 26.5, 22.2; HRMS calc'd for $C_{10}H_{13}NO$ $[M + H]^+$ 164.1070, found 164.1072.

Peak markers for entries 1, 13, and 16 and were not independently isolated. Product identity during substrate screening was determined by LCMS analysis.

3. Substrate Screening

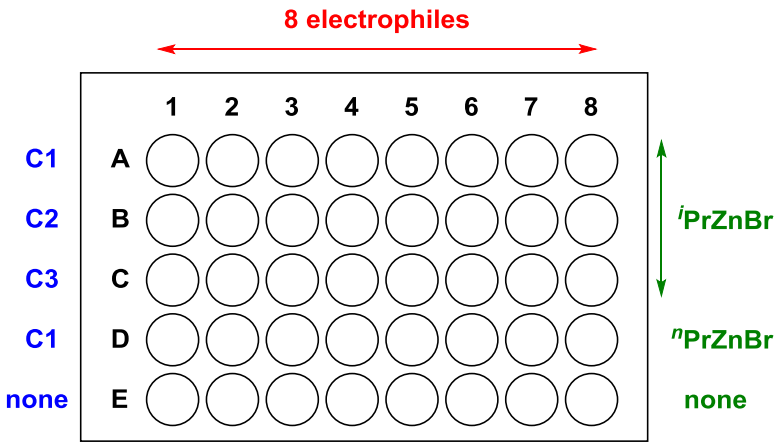
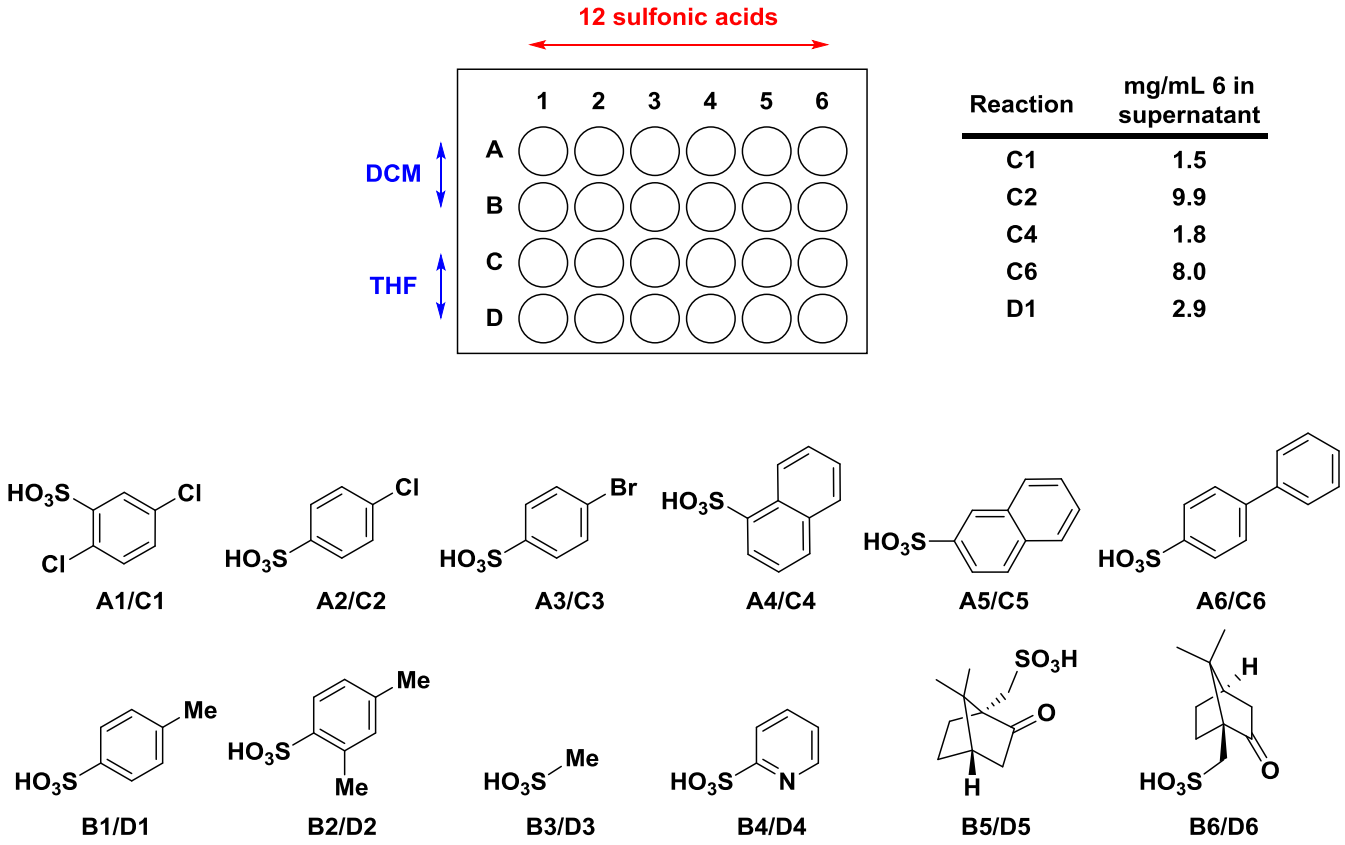


Figure S2: Plate Design for Substrate Screening

4. Salt Formation Screening

To each reaction vial was added 10 µmol sulfonic acid derivative (Figure S3). A 0.1 M stock solution of 2-isopropyl-4-methylpyridin-3-amine (**6**) in DCM or THF was prepared. 0.1 mL aniline **6** (10 µmol, 1 equiv) was added to each reaction. The reactions were sealed and stirred at 50 °C overnight. The reactions were allowed to cool to room temperature. The reactions were visually analyzed for salt precipitation. If precipitation occurred, the reaction was centrifuged and the supernatant was analyzed for remaining aniline concentration.



Reaction	mg/mL 6 in supernatant
C1	1.5
C2	9.9
C4	1.8
C6	8.0
D1	2.9

Figure S3: Plate Design for Salt Formation Screening

5. NMR Spectra

p-Cymene (Table 2, entry 4)

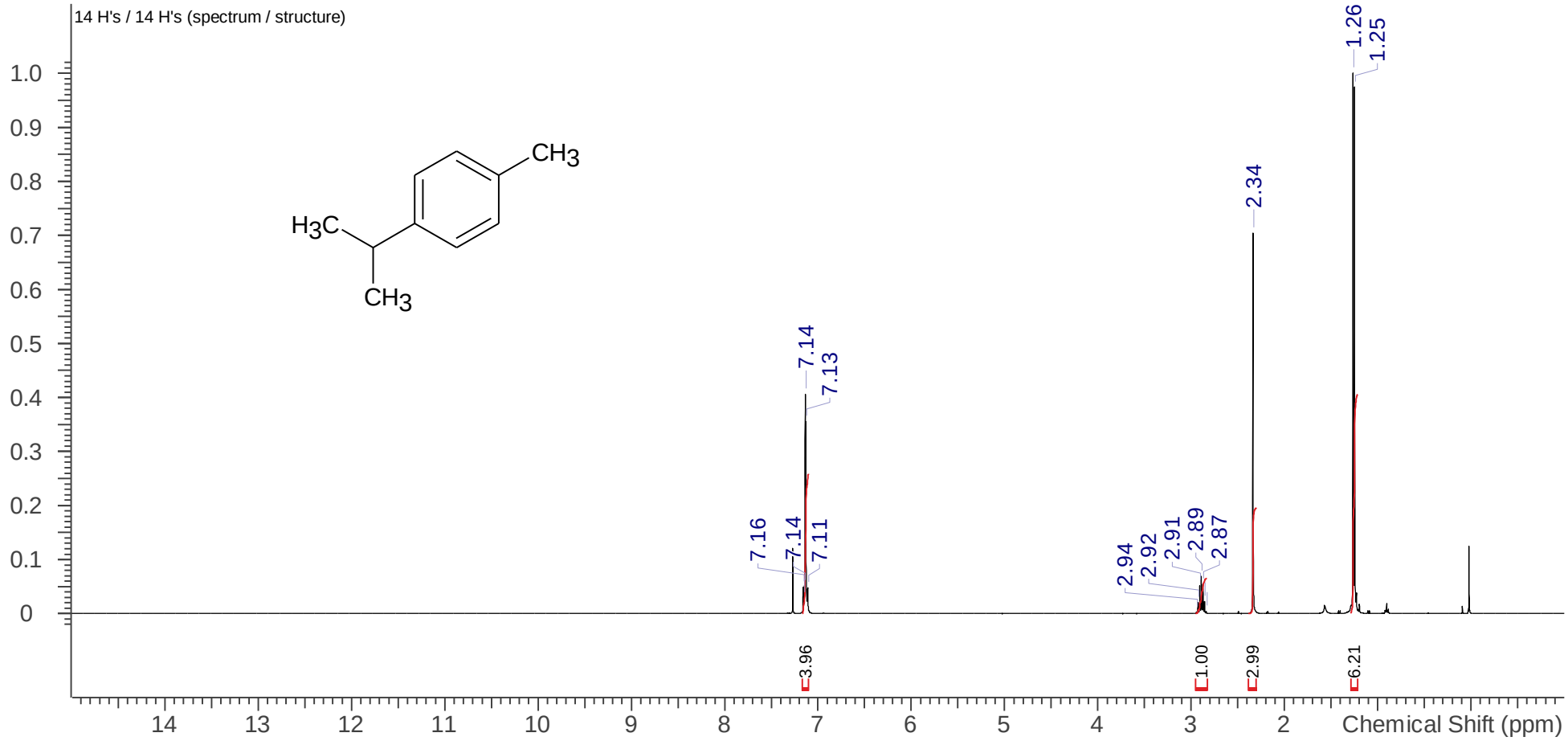


Figure S4: 400 MHz ^{1}H NMR for *p*-Cymene in $CDCl_3$

***p*-Cymene (Table 2, entry 4)**

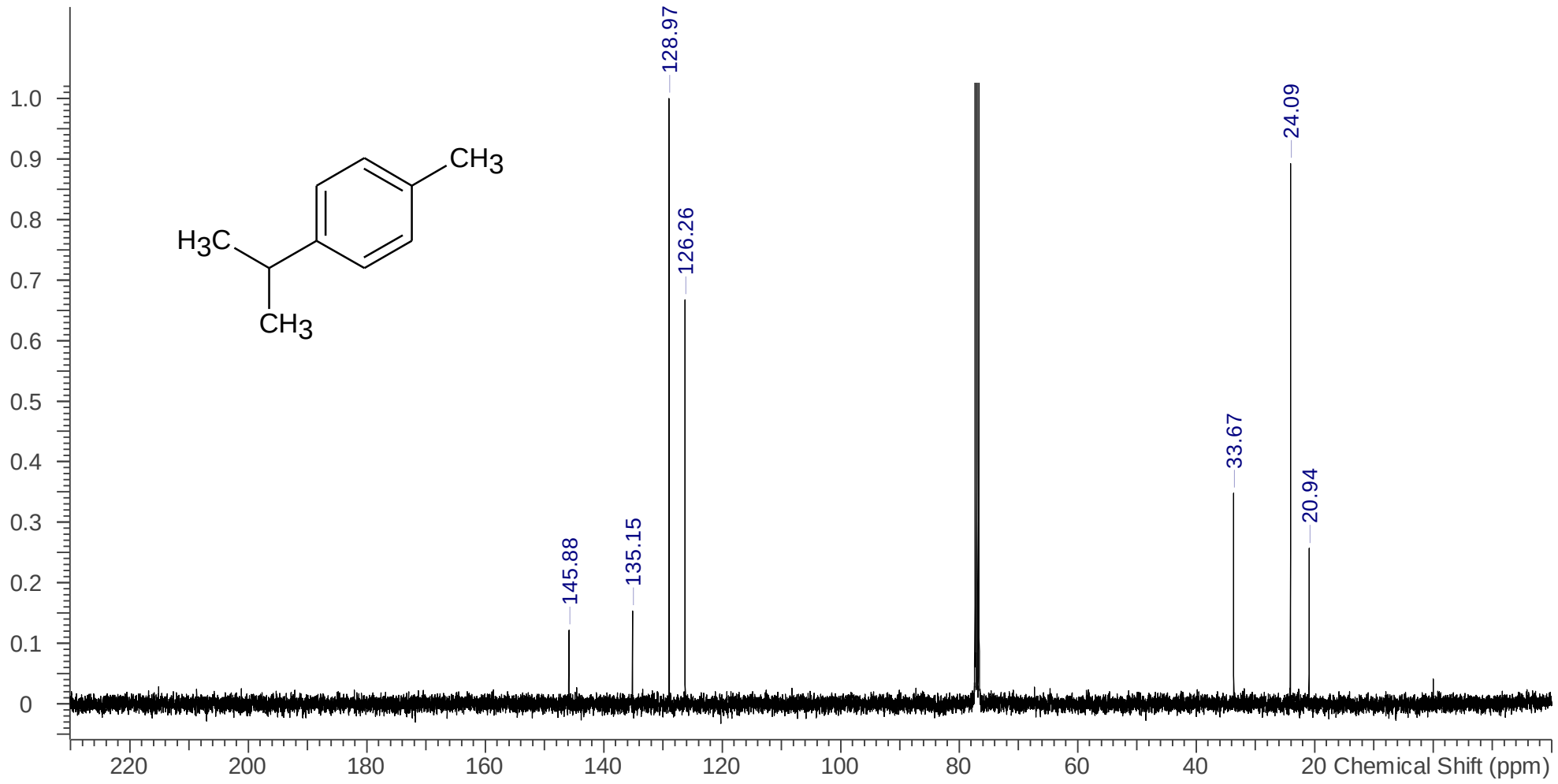


Figure S5: 101 MHz $^{13}C\{^{1}H\}$ NMR for *p*-Cymene in $CDCl_3$

1-(4-isopropylphenyl)Ethan-1-one (Table 2, entry 5)

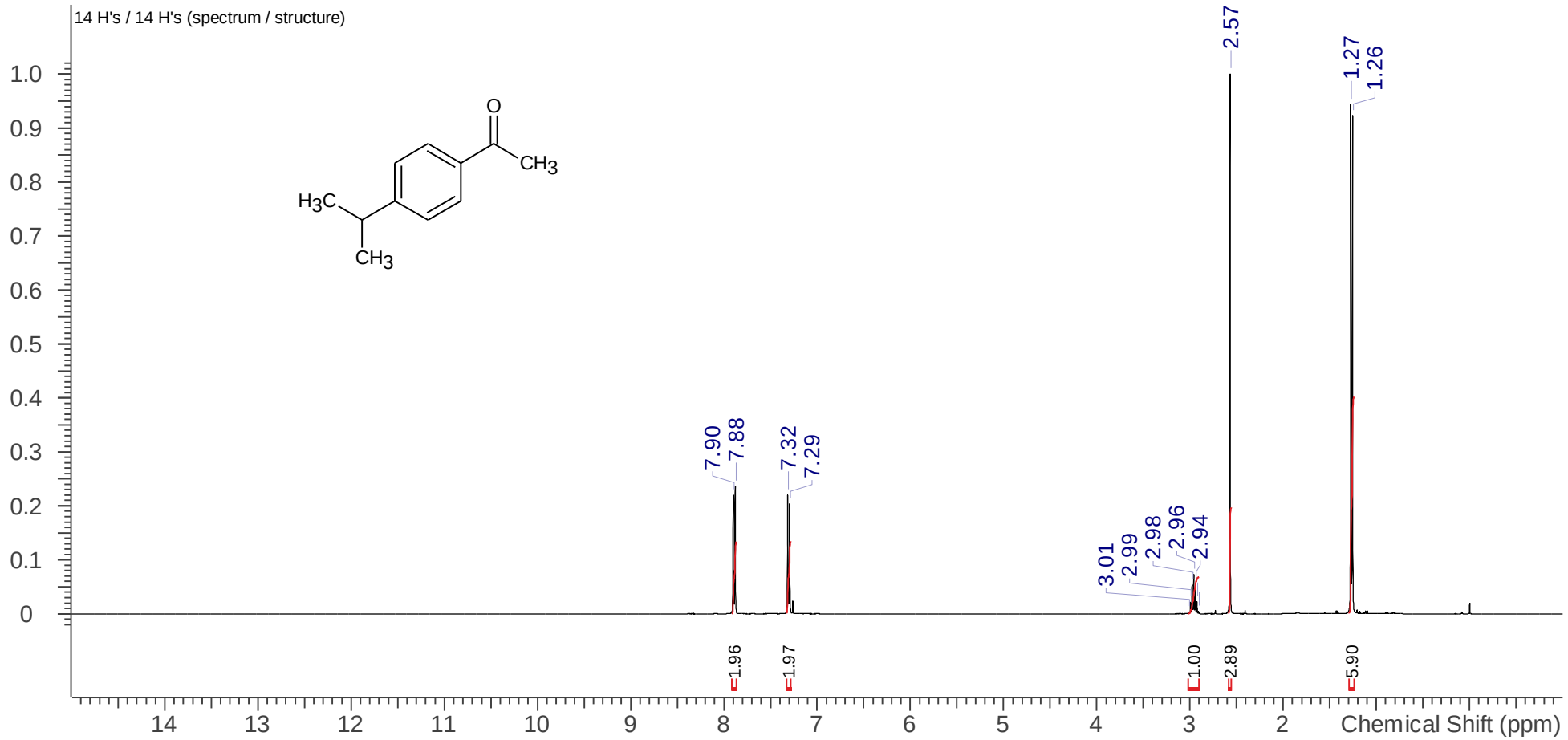


Figure S6: 400 MHz ^{1}H NMR for 1-(4-isopropylphenyl)Ethan-1-one in $CDCl_3$

1-(4-isopropylphenyl)Ethan-1-one (Table 2, entry 5)

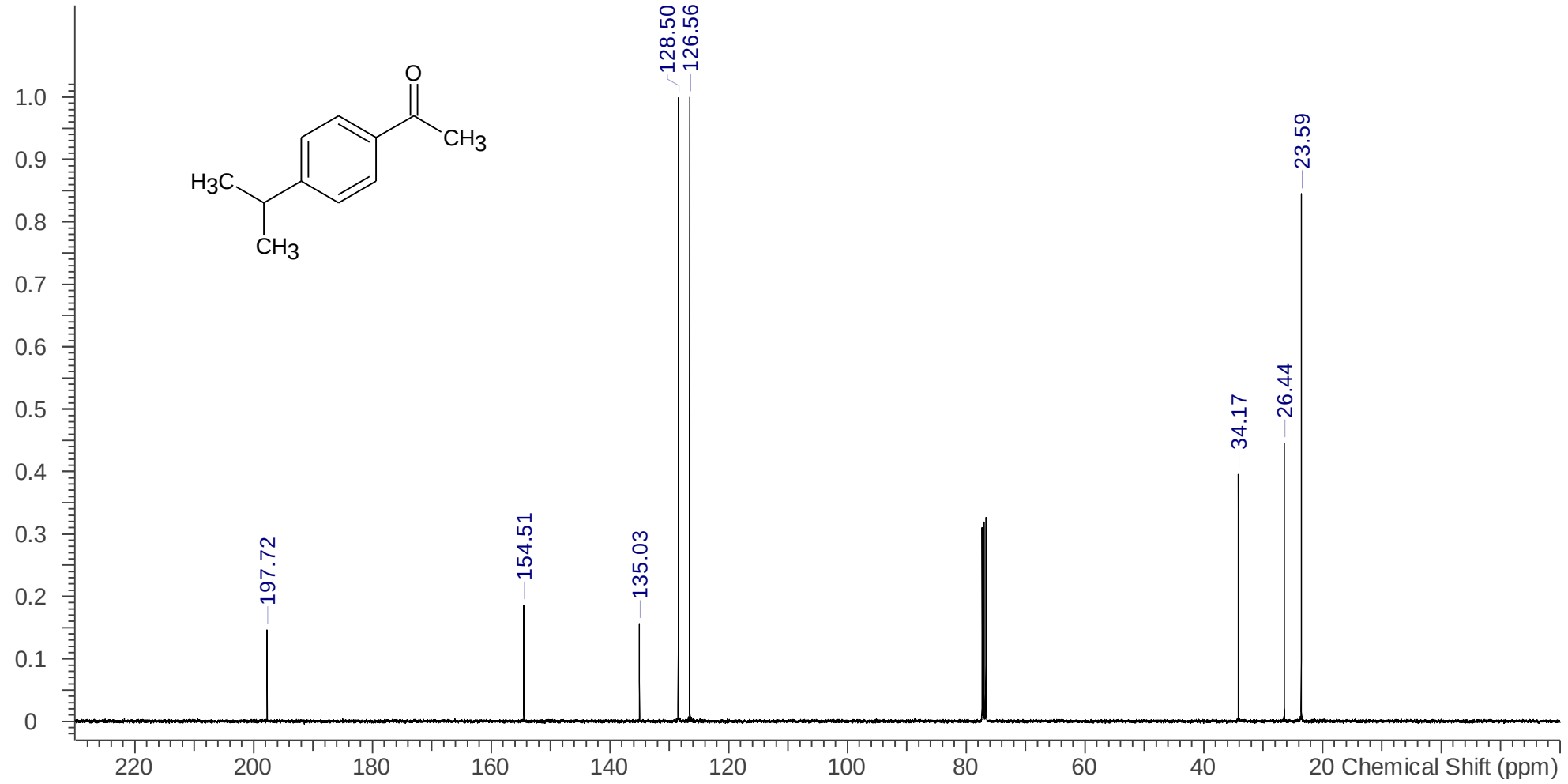


Figure S7: 101 MHz $^{13}C\{^{1}H\}$ NMR for 1-(4-isopropylphenyl)Ethan-1-one in $CDCl_3$

2-Isopropyl-3-methylpyridine (Table 2, entry 6)

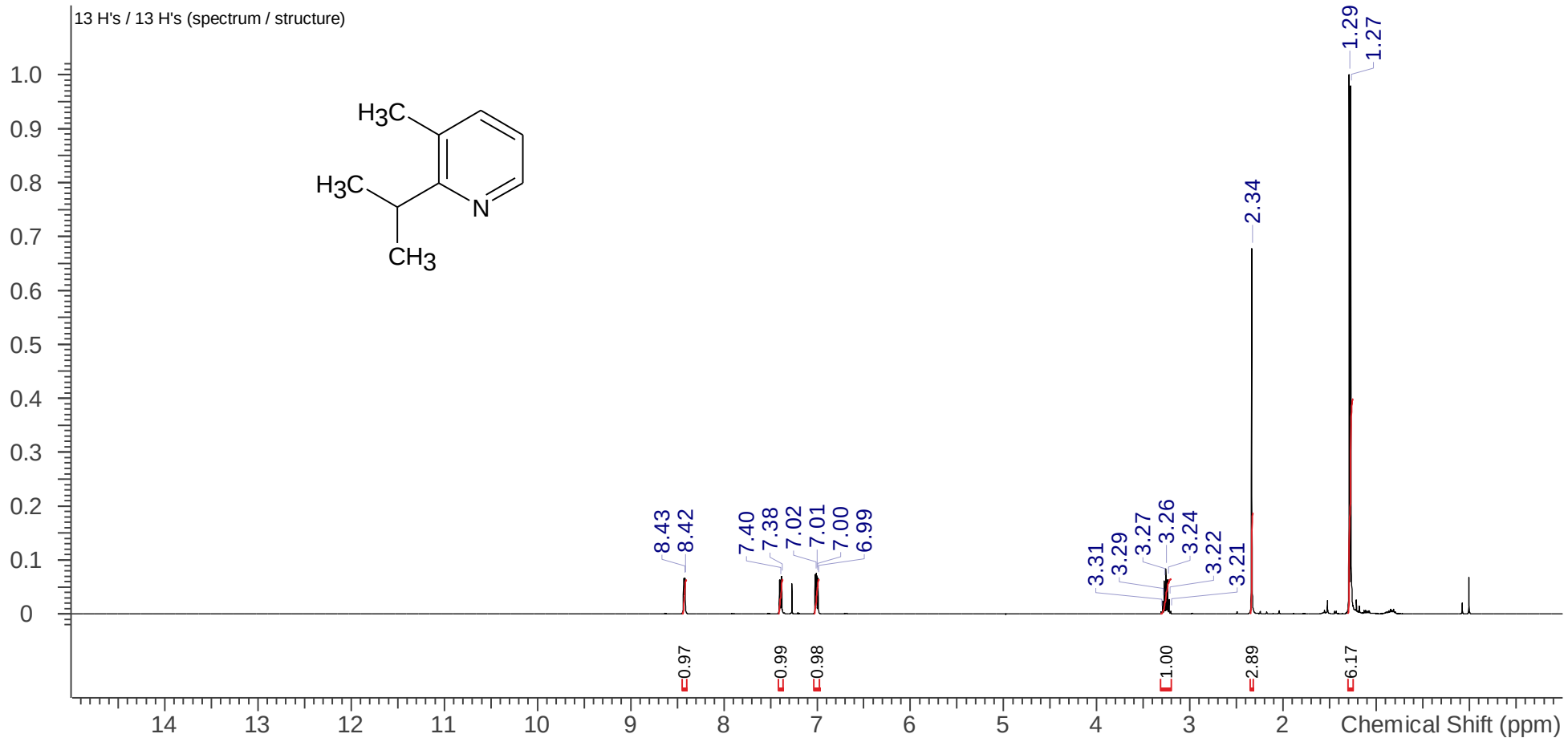


Figure S8: 400 MHz ^{1}H NMR for 2-Isopropyl-3-methylpyridine in $CDCl_3$

2-Isopropyl-3-methylpyridine (Table 2, entry 6)

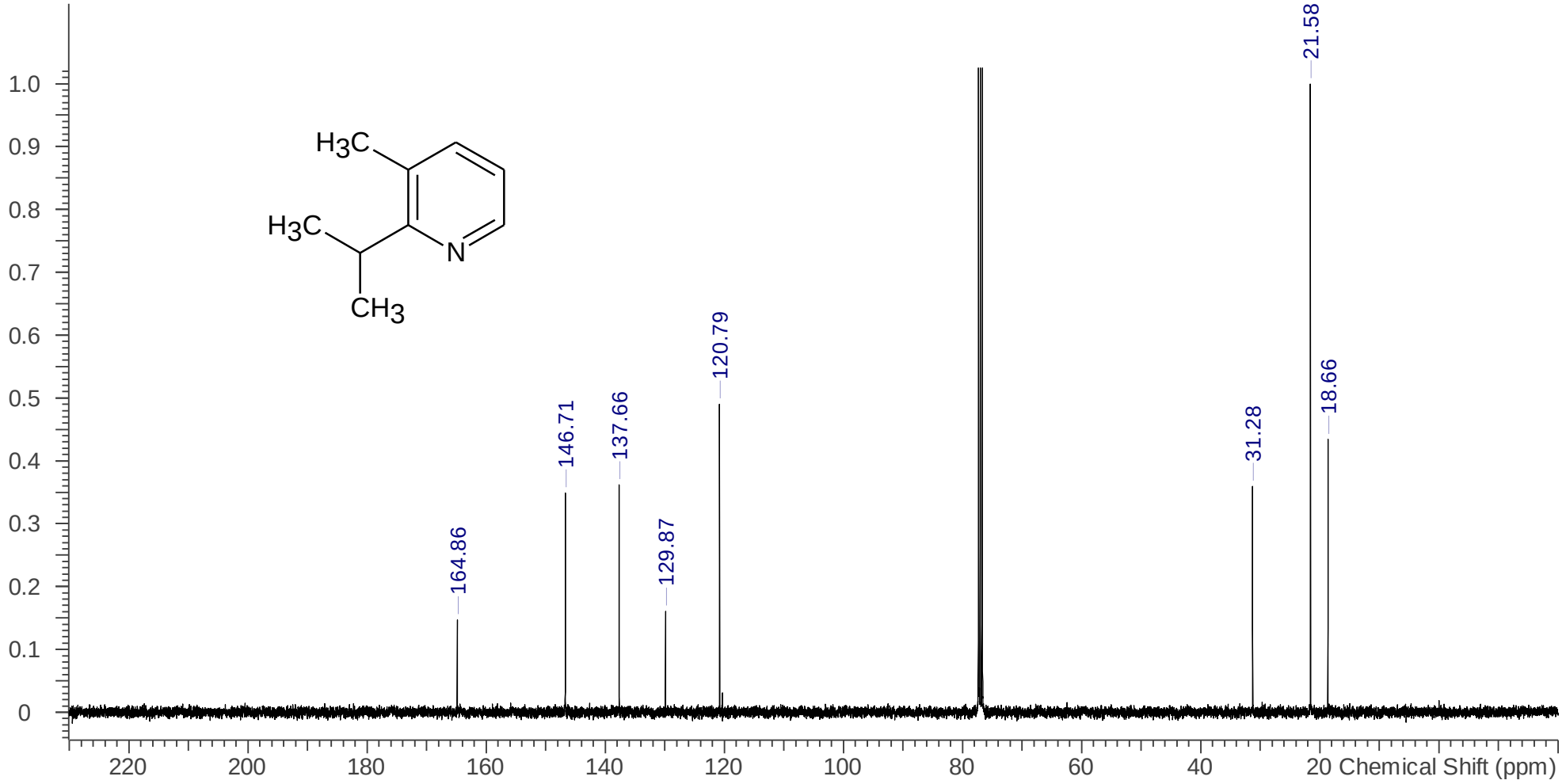


Figure S9: 101 MHz $^{13}C\{^{1}H\}$ NMR for 2-Isopropyl-3-methylpyridine in $CDCl_3$

2-isopropyl-3-(trifluoromethyl)pyridine (Table 2, entry 7)

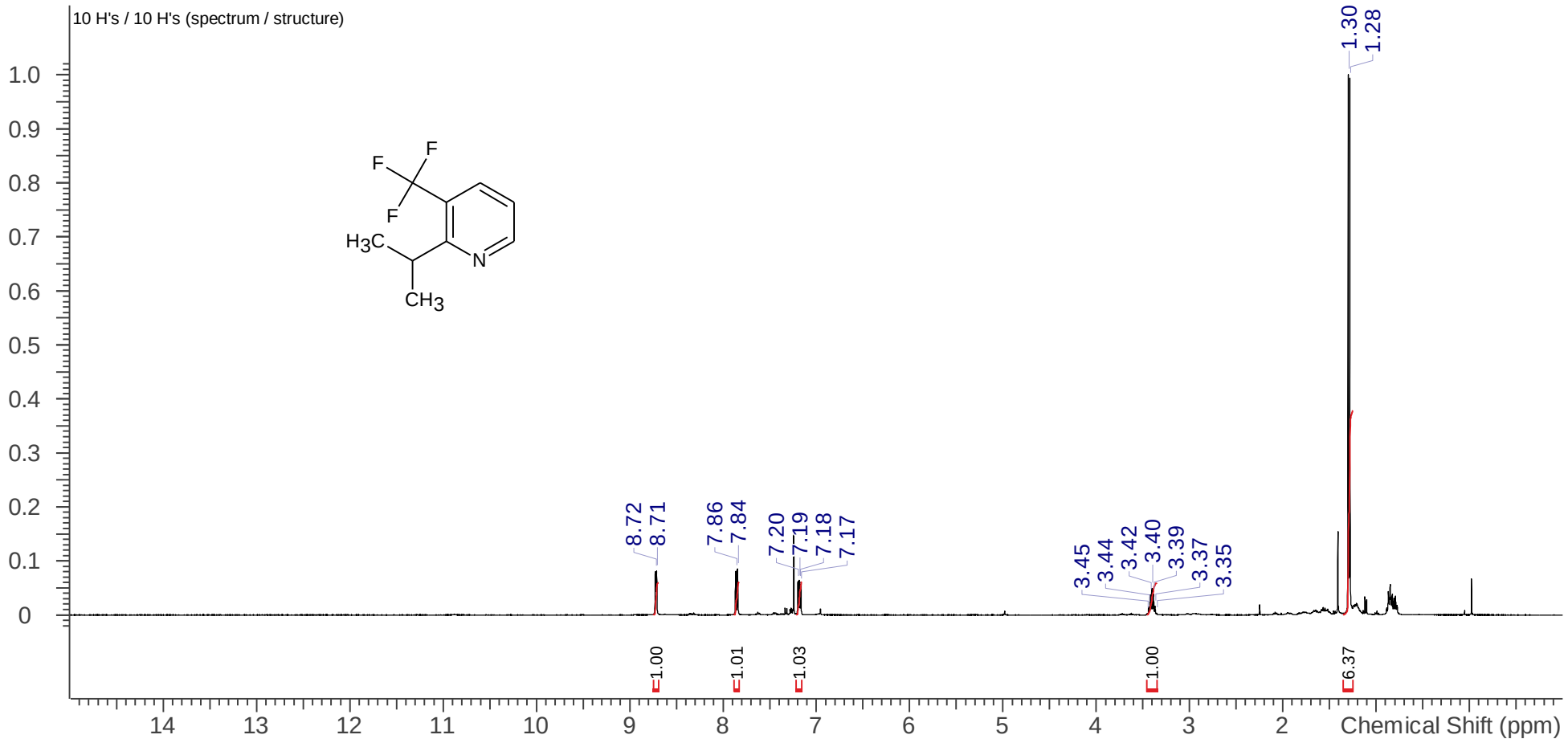


Figure S10: 400 MHz ^{1}H NMR for 2-isopropyl-3-(trifluoromethyl)pyridine in $CDCl_3$

2-isopropyl-3-(trifluoromethyl)pyridine (Table 2, entry 7)

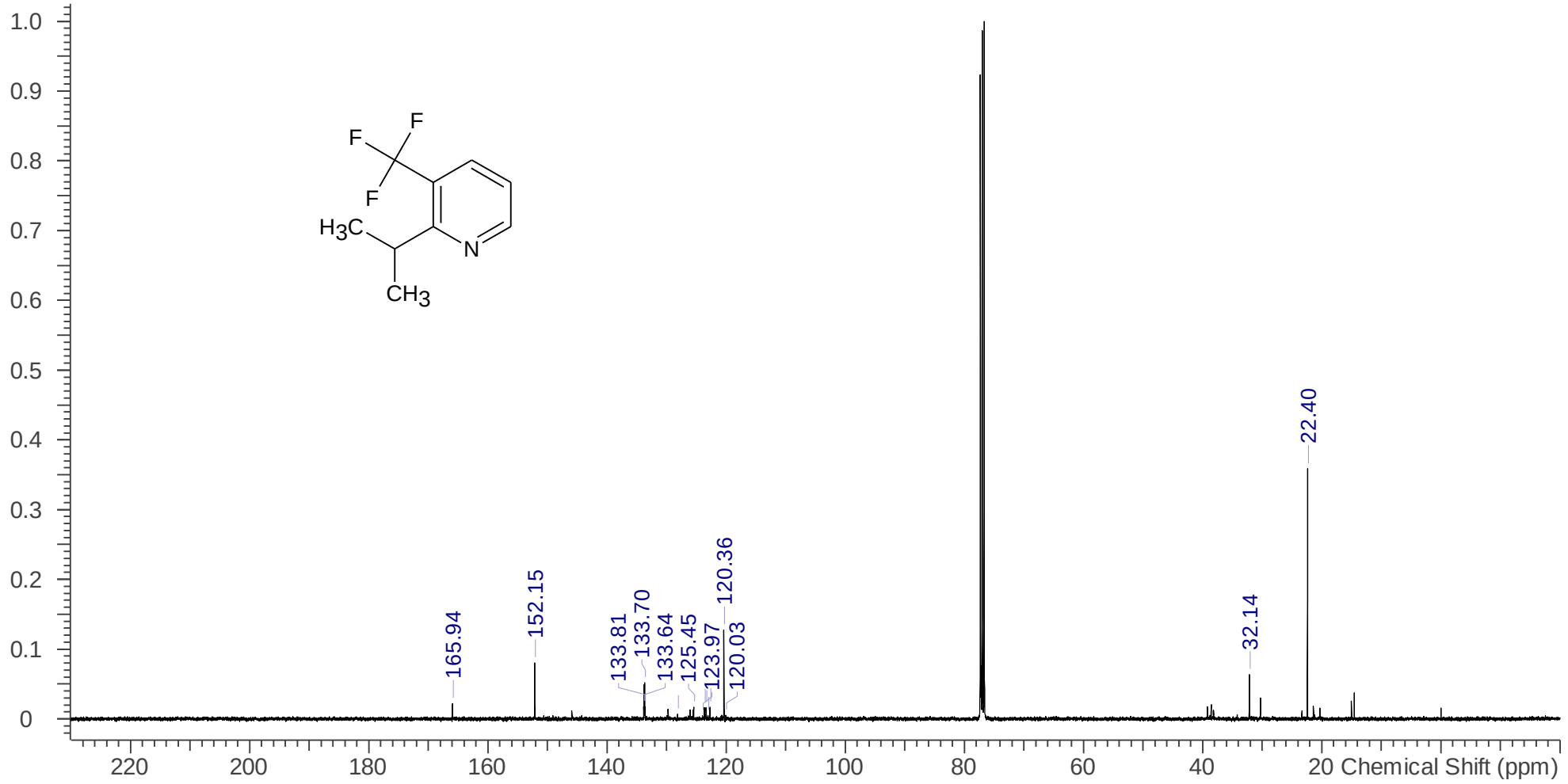


Figure S11: 101 MHz $^{13}C\{^{1}H\}$ NMR for 2-isopropyl-3-(trifluoromethyl)pyridine in $CDCl_3$

3-Chloro-2-isopropylpyridine (Table 2, entry 8)

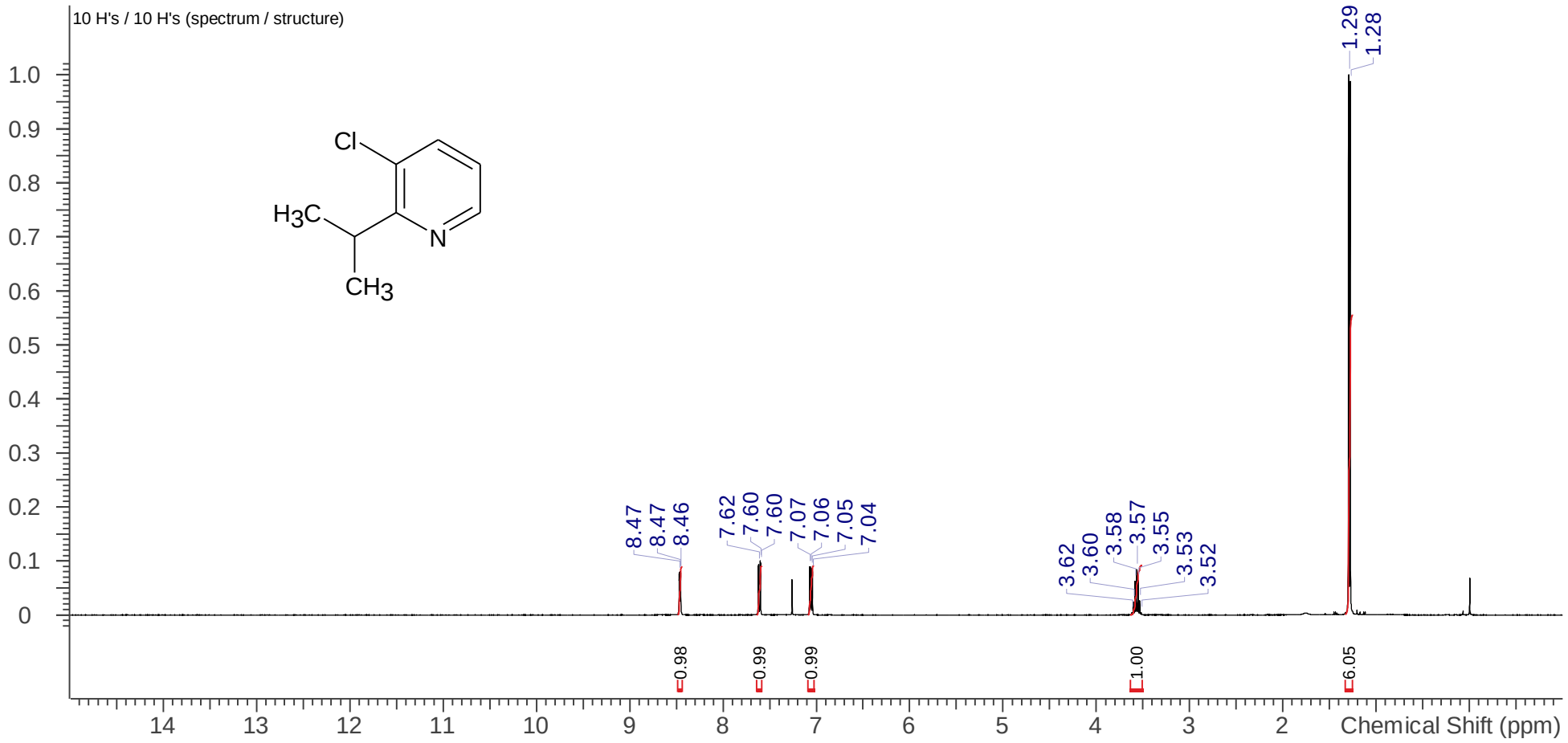


Figure S12: 400 MHz ^{1}H NMR for 3-Chloro-2-isopropylpyridine in $CDCl_3$

3-Chloro-2-isopropylpyridine (Table 2, entry 8)

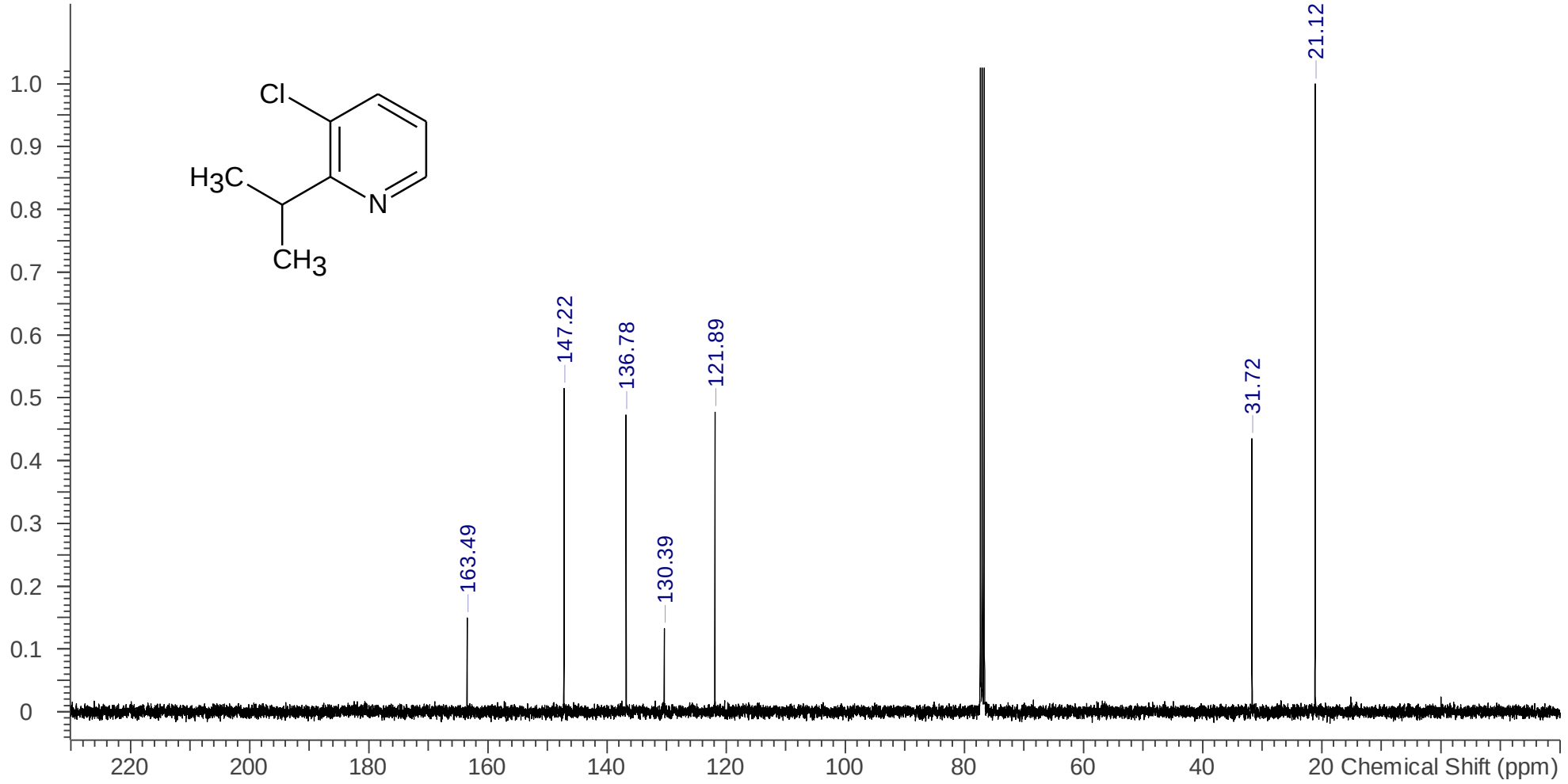


Figure S13: 101 MHz $^{13}C\{^{1}H\}$ NMR for 3-Chloro-2-isopropylpyridine in $CDCl_3$

6-Isopropylpyridin-2-amine (Table 2, entry 9)

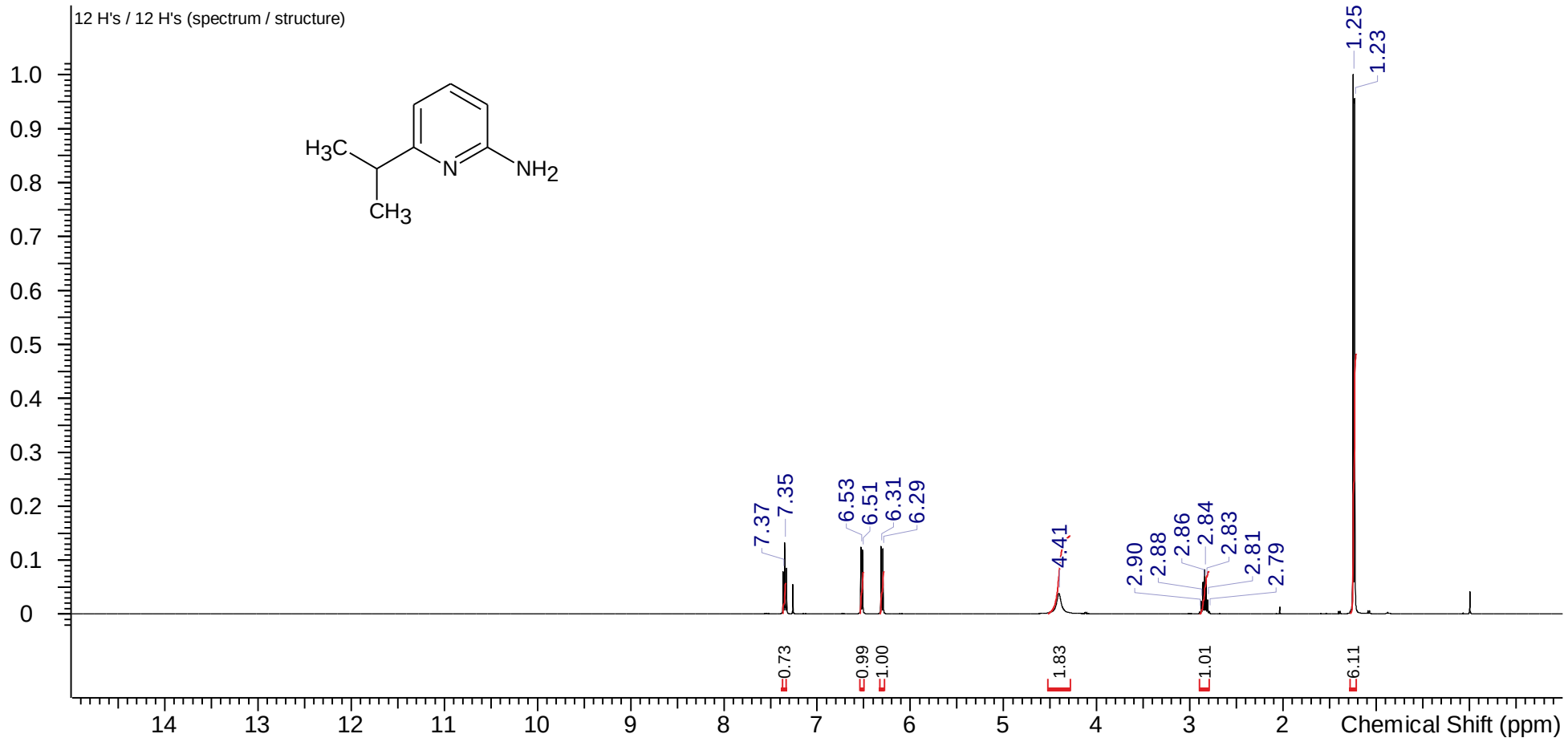


Figure S14: 400 MHz ^{1}H NMR for 6-Isopropylpyridin-2-amine in $CDCl_3$

6-Isopropylpyridin-2-amine (Table 2, entry 9)

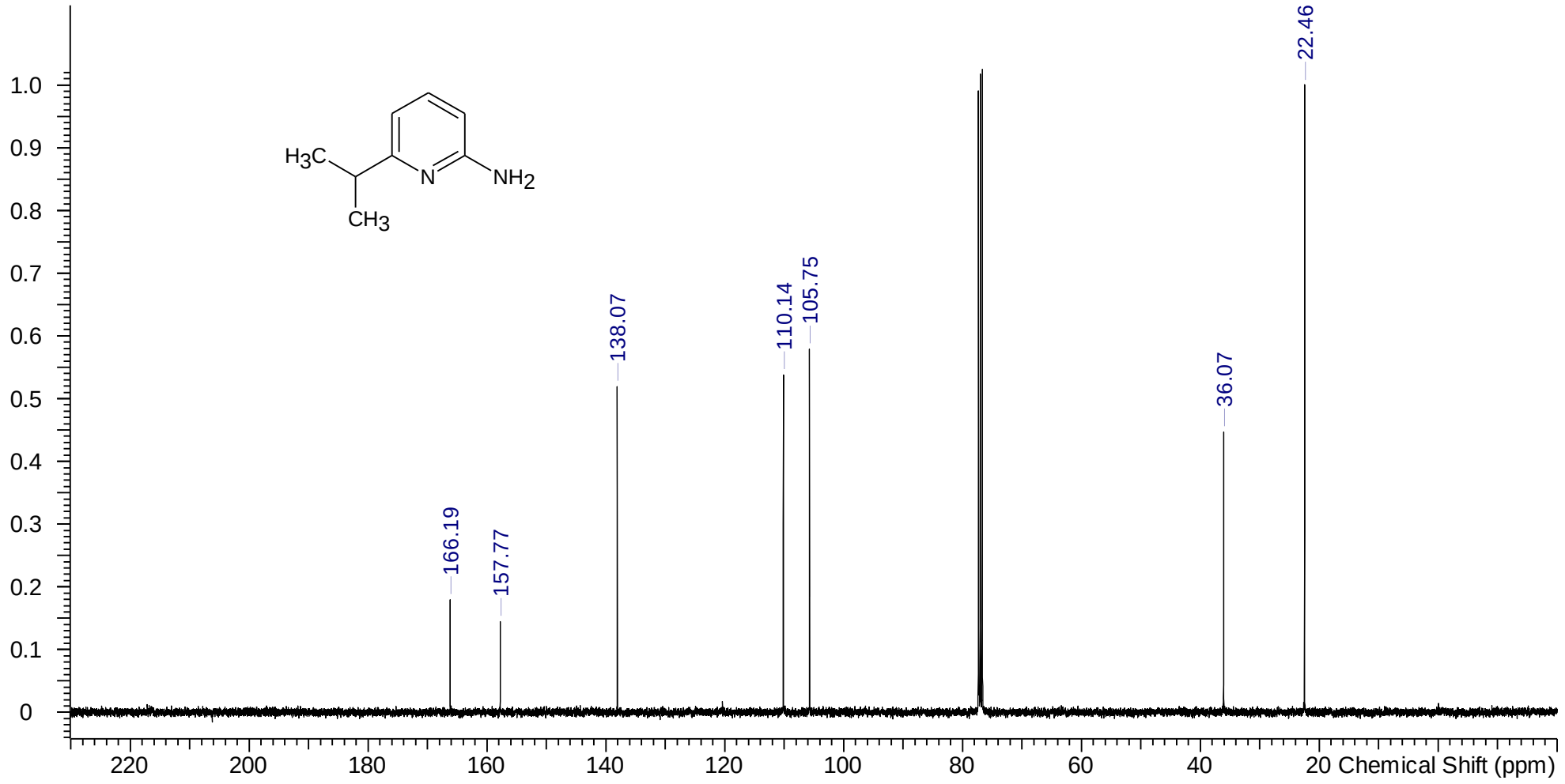


Figure S15: 101 MHz $^{13}C\{^{1}H\}$ NMR for 6-Isopropylpyridin-2-amine in $CDCl_3$

6-Isopropylpyridin-3-amine (Table 2, entry 10)

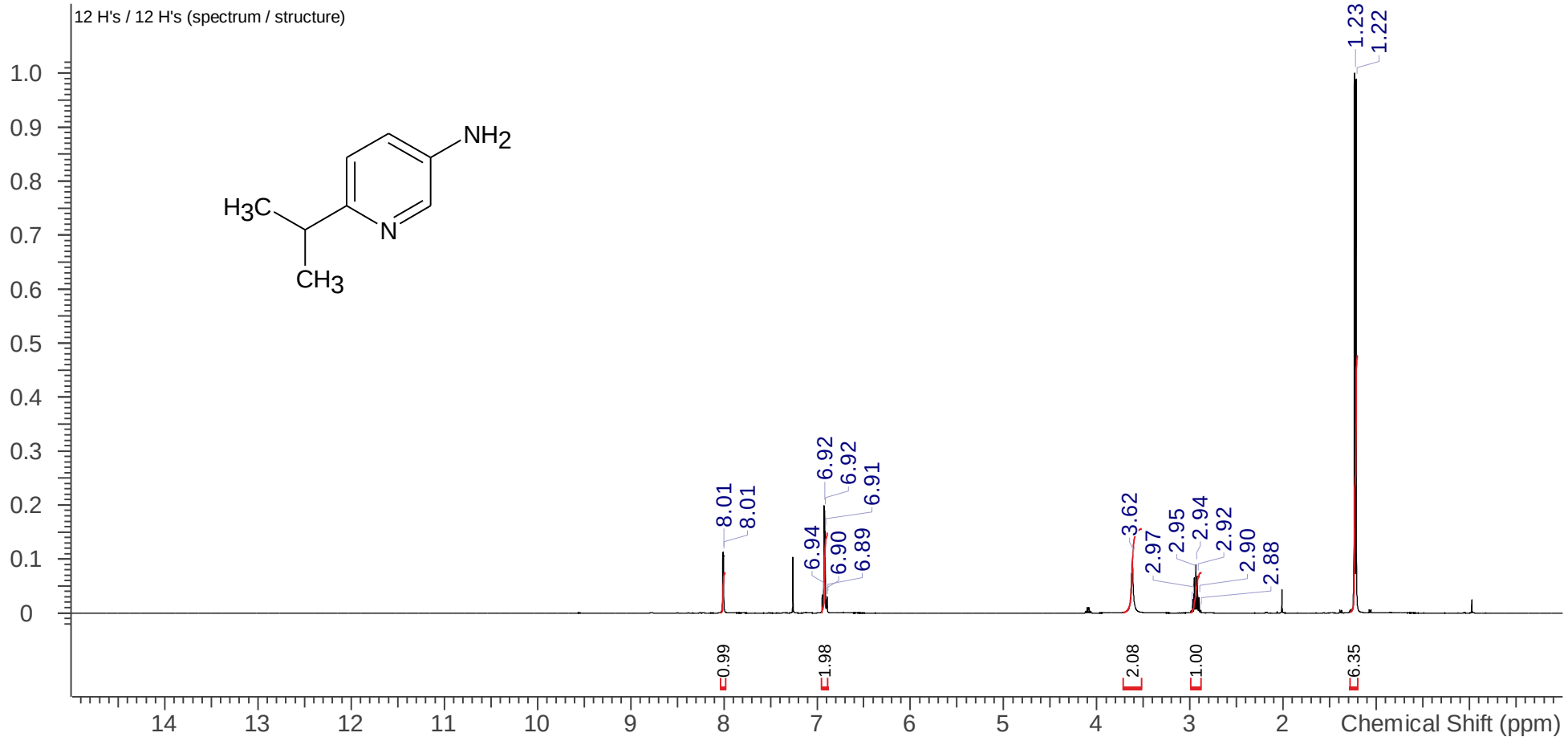


Figure S16: 400 MHz ^{1}H NMR for 6-Isopropylpyridin-3-amine in $CDCl_3$

6-Isopropylpyridin-3-amine (Table 2, entry 10)

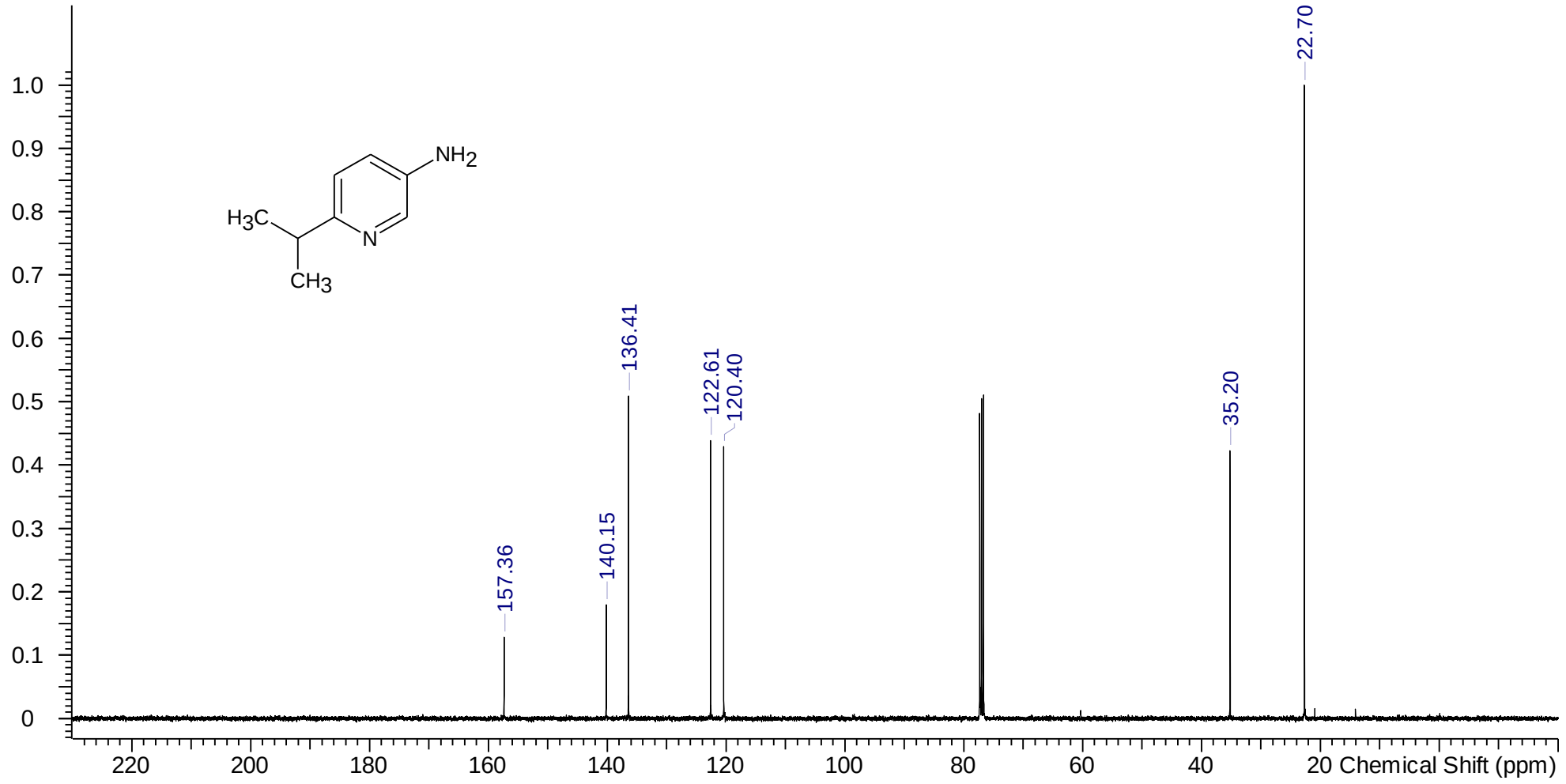


Figure S17: 101 MHz $^{13}C\{^{1}H\}$ NMR for 6-Isopropylpyridin-3-amine in $CDCl_3$

2-Isopropylpyridin-4-amine (Table 2, entry 11)

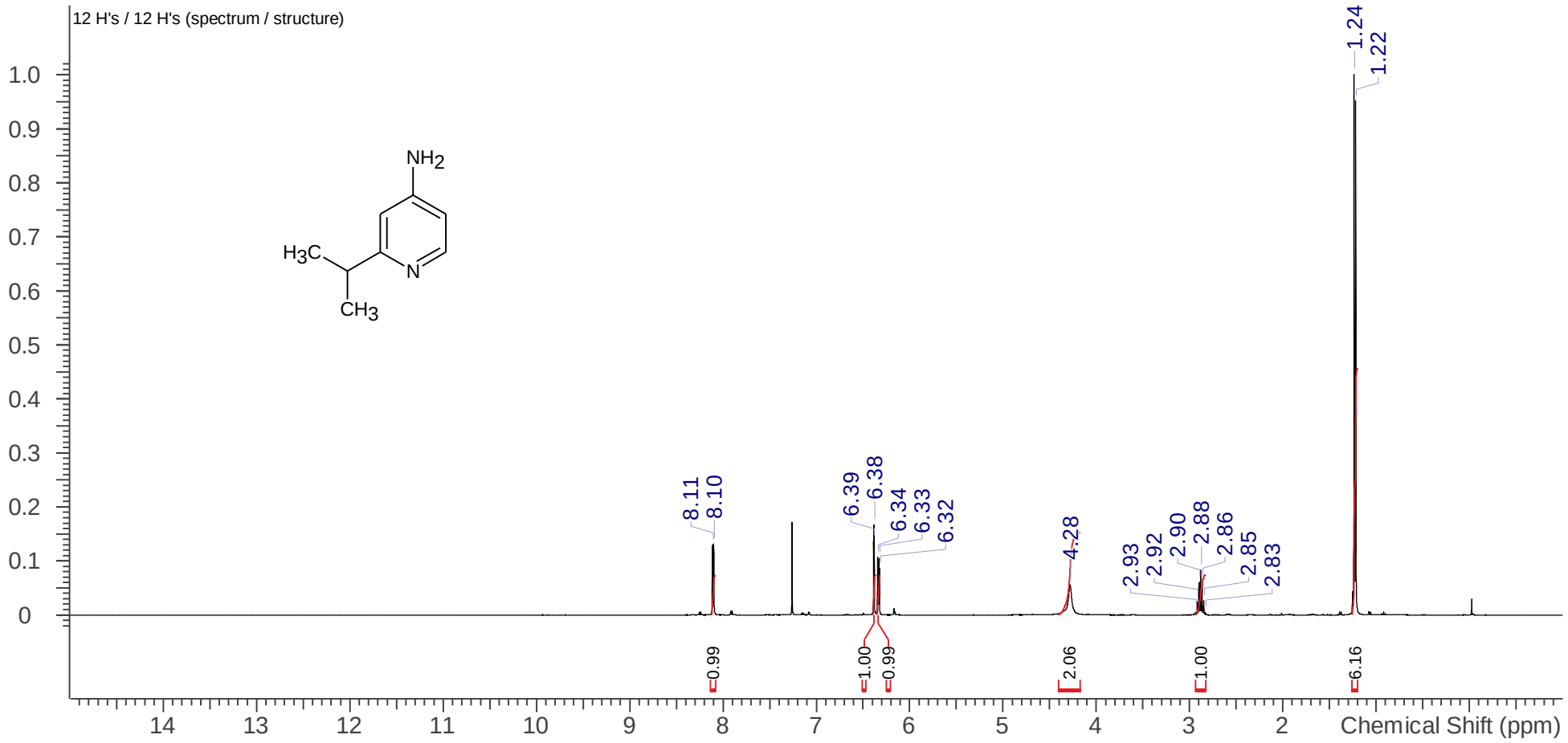


Figure S18: 400 MHz ^{1}H NMR for 2-Isopropylpyridin-4-amine in $CDCl_3$

2-Isopropylpyridin-4-amine (Table 2, entry 11)

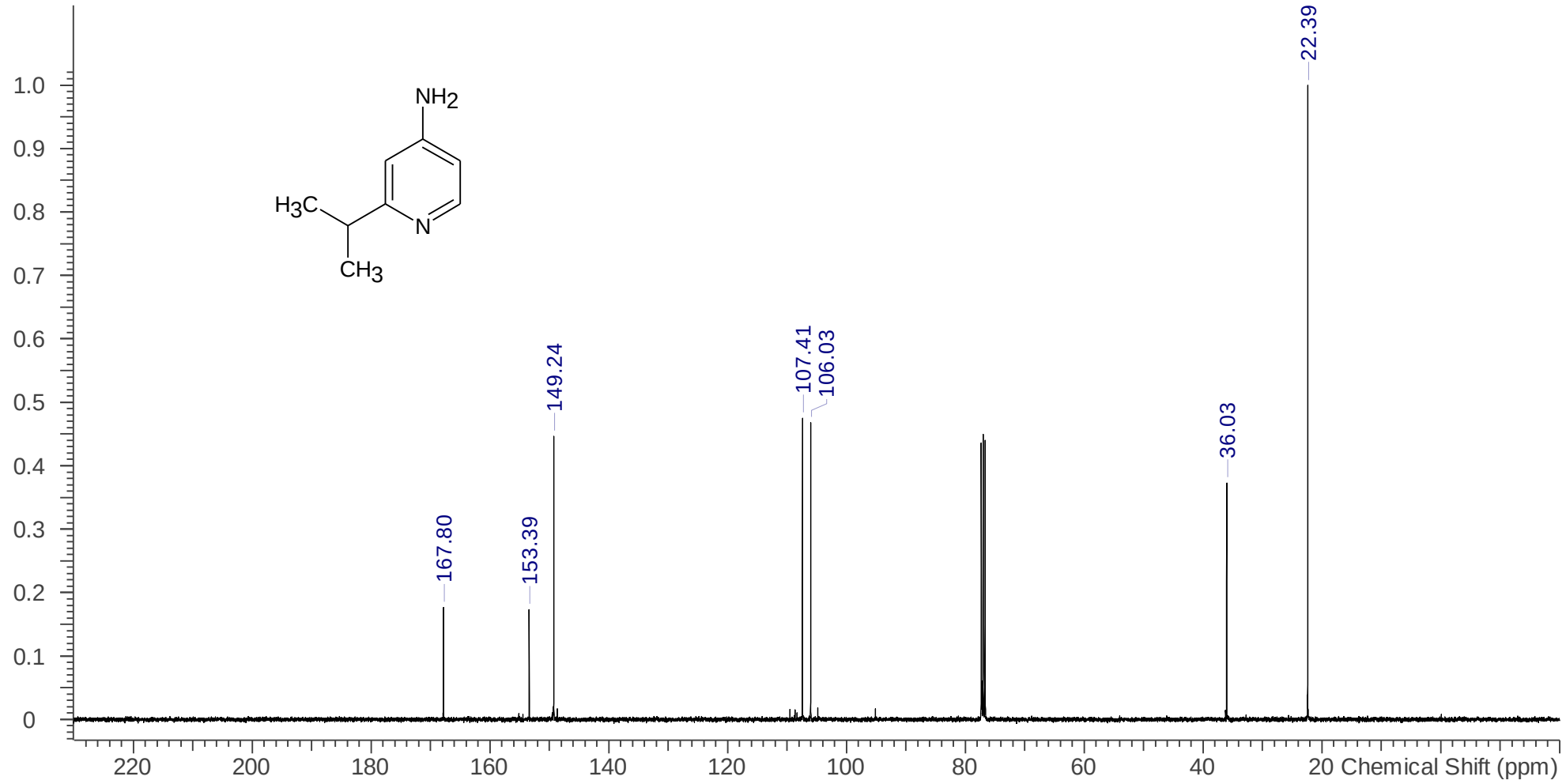


Figure S19: 101 MHz $^{13}C\{^{1}H\}$ NMR for 2-Isopropylpyridin-4-amine in $CDCl_3$

N-(6-isopropylpyridin-3-yl)Acetamide (Table 2, entry 12)

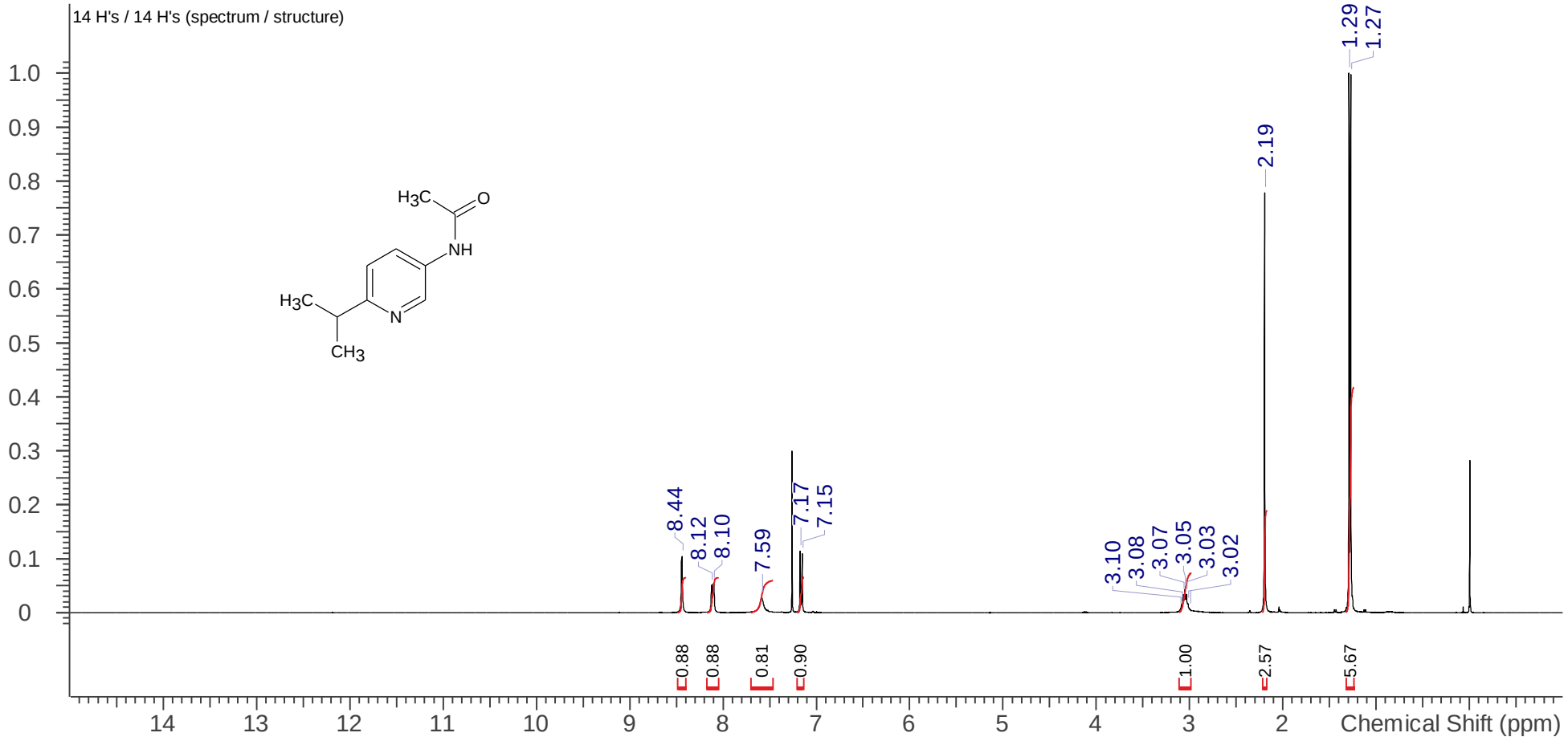


Figure S20: 400 MHz ^{1}H NMR for N-(6-isopropylpyridin-3-yl)Acetamide in $CDCl_3$

N-(6-isopropylpyridin-3-yl)Acetamide (Table 2, entry 12)

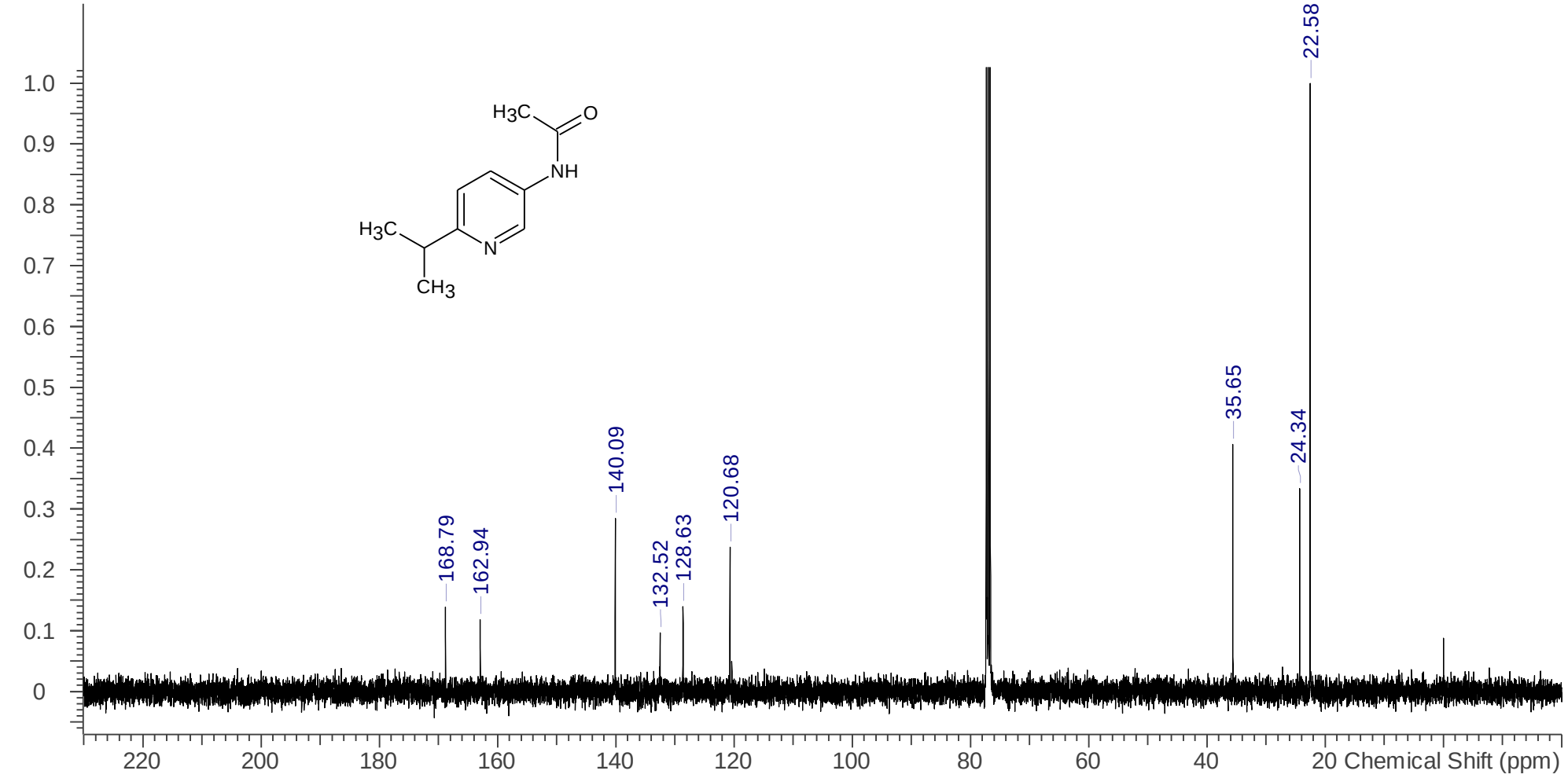


Figure S21: 101 MHz $^{13}C\{^{1}H\}$ NMR for N-(6-isopropylpyridin-3-yl)Acetamide in $CDCl_3$

1-(6-isopropylpyridin-3-yl)Ethan-1-one (Table 2, entry 14)

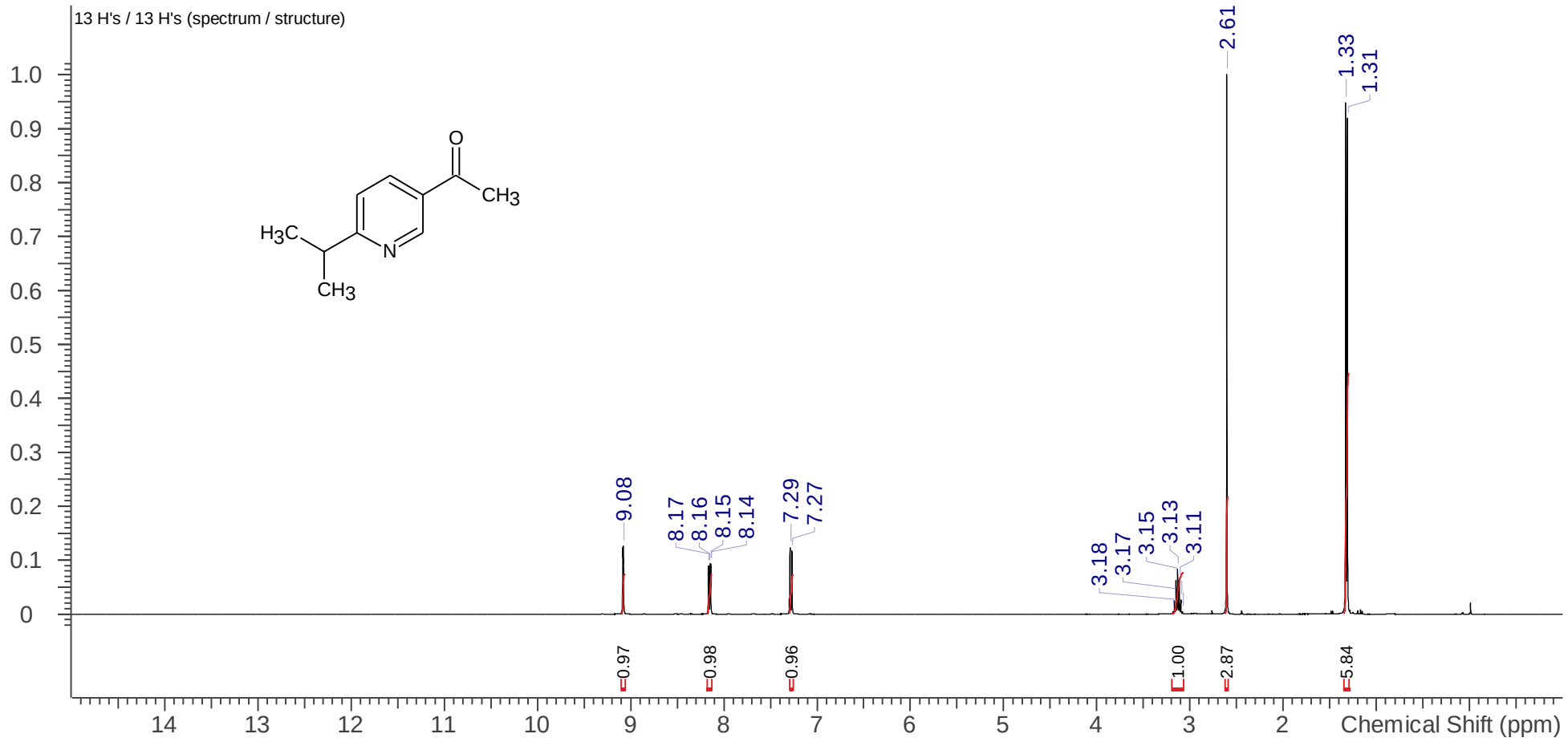


Figure S22: 400 MHz ^{1}H NMR for 1-(6-isopropylpyridin-3-yl)Ethan-1-one in $CDCl_3$

1-(6-isopropylpyridin-3-yl)Ethan-1-one (Table 2, entry 14)

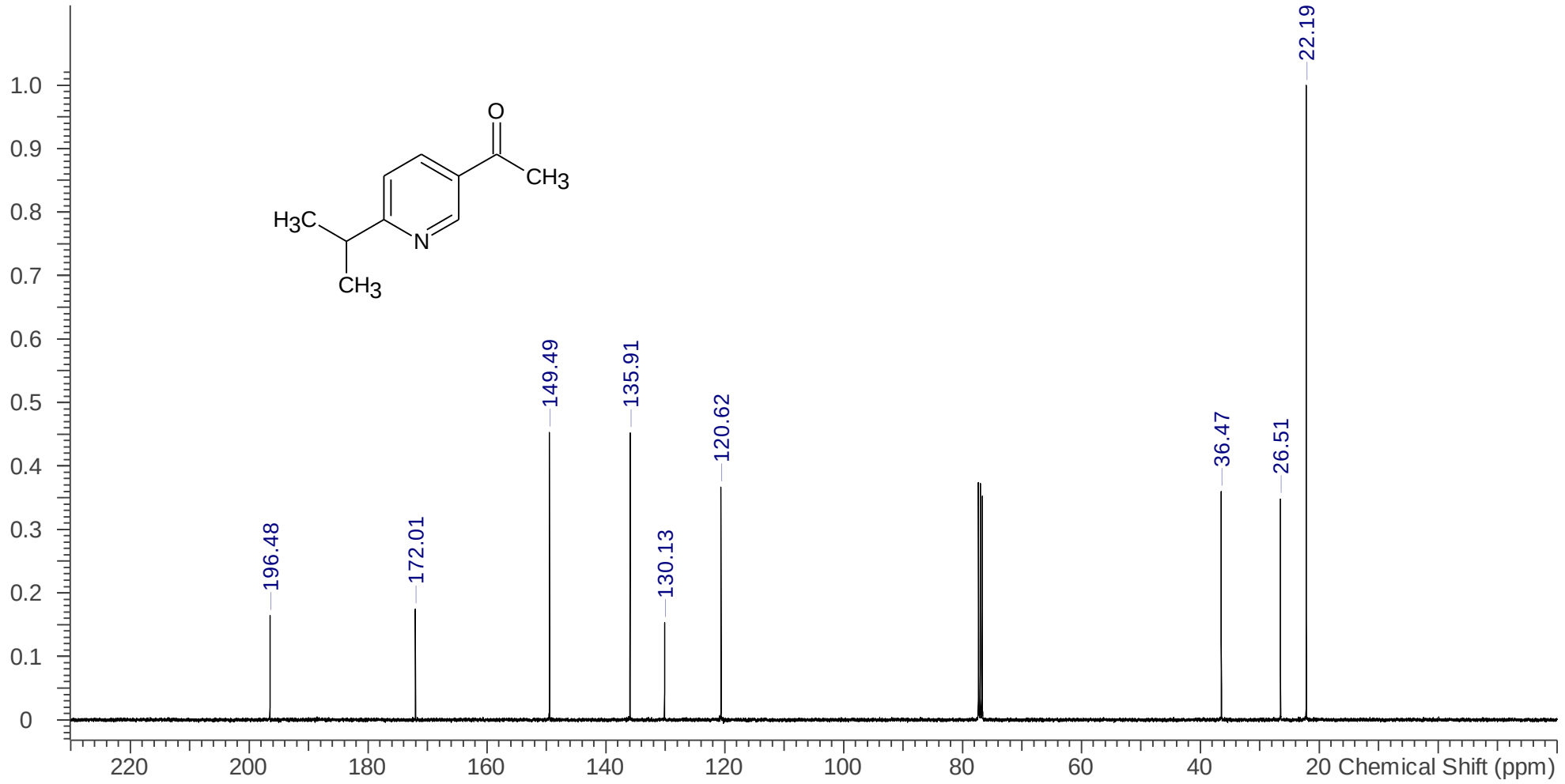


Figure S23: 101 MHz $^{13}C\{^{1}H\}$ NMR for 1-(6-isopropylpyridin-3-yl)Ethan-1-one in $CDCl_3$

2-Isopropyl-4-methylpyridin-3-amine, 4-methylbenzenesulfonate salt (7)

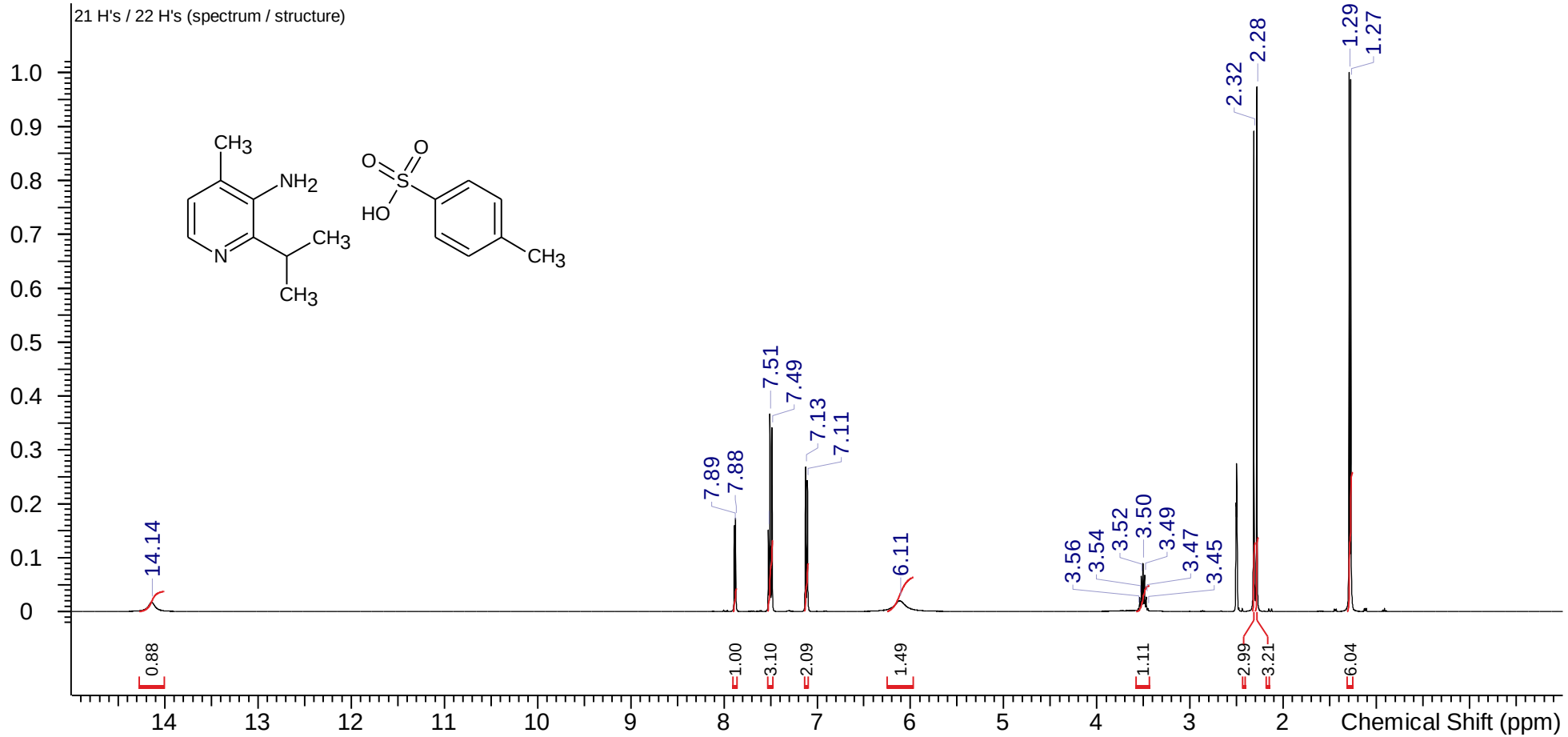


Figure S24: 400 MHz ^{1}H NMR for 2-Isopropyl-4-methylpyridin-3-amine, 4-methylbenzenesulfonate salt in DMSO-*d*$_6$

2-Isopropyl-4-methylpyridin-3-amine, 4-methylbenzenesulfonate salt (7)

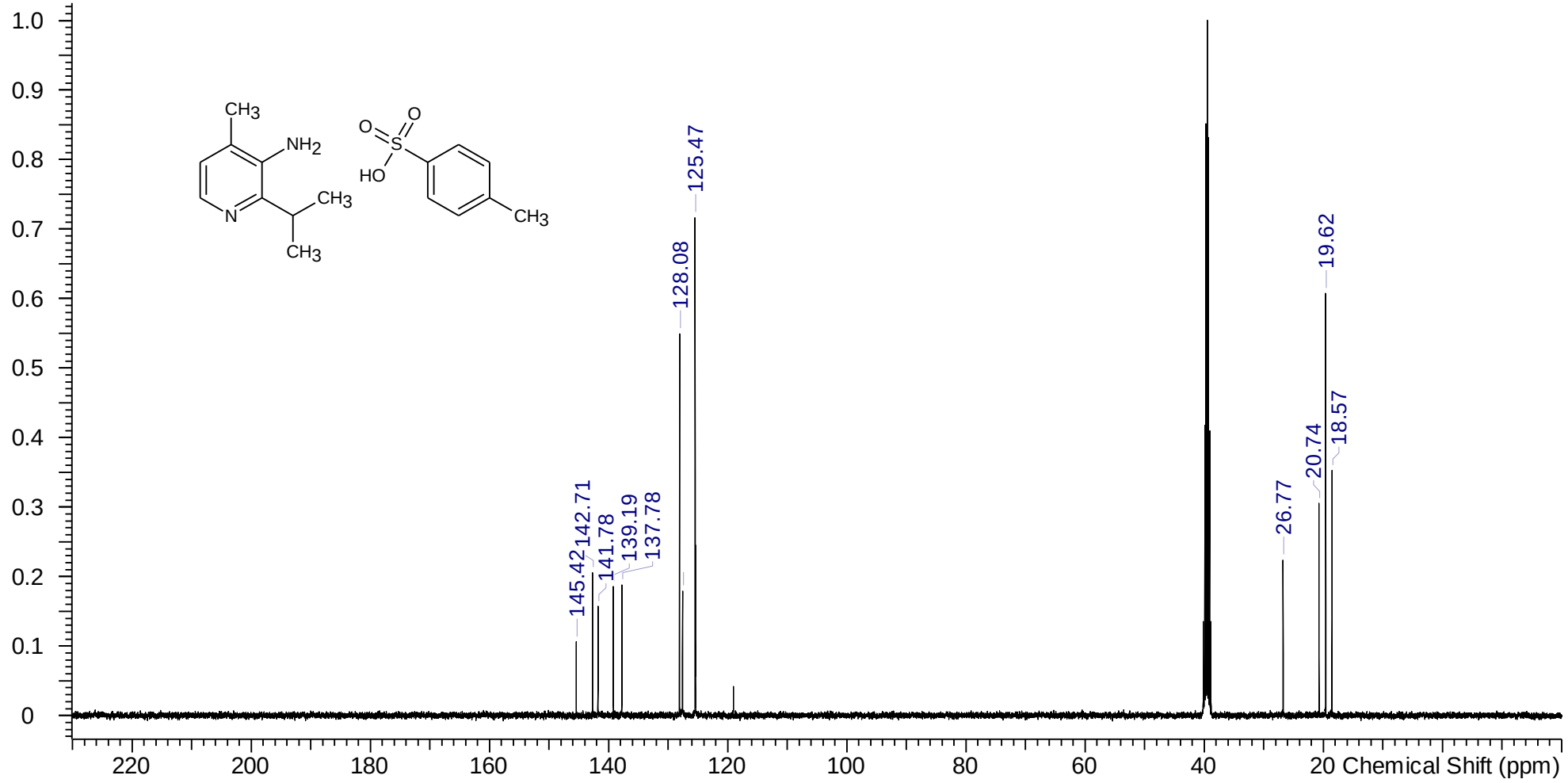


Figure S25: 101 MHz $^{13}C\{^{1}H\}$ NMR for 2-Isopropyl-4-methylpyridin-3-amine, 4-methylbenzenesulfonate salt in DMSO-*d*$_6$