

The Iron-Catalyzed Construction of 2-Aminopyrimidines from Alkynenitriles and Cyanamides

Supporting Information

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General Experimental

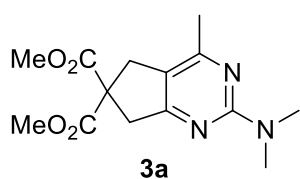
All reactions were conducted under an atmosphere of N₂ using standard Schlenk techniques or in a N₂ filled glove-box unless otherwise noted. Benzene and toluene were dried over neutral alumina under N₂ using a Grubbs type solvent purification system. Iron Chloride (99.95% purity) was purchased from Alfa Aesar. Iron(II) Bromide (98%), Iron(II) Iodide (anhydrous beads, ≥99.99%), and Iron(II) Acetate (≥99.99%) were purchased from Sigma Aldrich. Alkynenitrile **1a** was prepared from the literature procedure and was purified by column chromatography and recrystallization as described below.¹ Alkynenitrile **1c** was prepared according to the literature procedure.⁶ Cyanamides **2a-d** were purchased from Sigma Aldrich and were distilled then degassed using three sequential freeze-pump-thaw cycles. Cyanamide **2e** was prepared from the literature procedure.²

^1H and ^{13}C Nuclear Magnetic Resonance spectra of pure compounds were acquired at 300 and 75 MHz, unless otherwise noted. All spectra are referenced to a singlet at 7.27 ppm for ^1H and to the center line of a triplet at 77.23 ppm for ^{13}C . The abbreviations s, d, dd, dt, dq, td, t, q, quint and sext stand for singlet, doublet, doublet of doublets, doublet of triplets, doublet of quartets, triplet of doublets, triplet, quartet, quintet, and sextet respectively. All ^{13}C NMR spectra were proton decoupled. The infra-red spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer. Gas Chromatography was performed on an Agilent 6890 gas chromatograph with a 30 meter HP-5 column using the following conditions: initial oven temperature: 100 °C; temperature ramp rate 10 °C/min.; final temperature: 300 °C held for 12 minutes; detector temperature: 250 °C.

General Procedure for the Cycloaddition

In a nitrogen filled glove box, 5 mol % Fe_2 beads were added to the reaction vial. The beads were thoroughly crushed into a fine powder to ensure complexation with ligand. 10 mol % *iPr*PDAI and toluene was added to a vial and the mixture was stirred for 1 hour. At this time additional toluene, a toluene solution of alkynenitrile, 30 mol % Zn dust and 3 equivalents of cyanamide were added. The vial was then capped, removed from the glove box and stirred in a 40 °C oil bath. After completion as monitored by GC, the crude mixture was purified by silica gel flash chromatography.

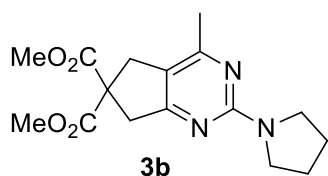
Synthesis of dimethyl 2-(dimethylamino)-4-methyl-5H-cyclopenta[d]pyrimidine-6,6(7H)-dicarboxylate (3a):



Compound **3a** was prepared using the general procedure with Fe_2 (6.9 mg, 2.2×10^{-2} mmol) and *iPr*PDAI (16.6 mg, 4.5×10^{-2} mmol) which were stirred in 1 mL of toluene for 1 hour. 2.5 mL of toluene, alkynenitrile **1a** (100 mg, 4.5×10^{-1} mmol) dissolved in 1 mL of toluene, zinc dust (8.8 mg, 1.3×10^{-1} mmol) and **2a** (100 mg, 1.34 mmol) were added and the reaction was stirred at 40 °C for 12 hours. After the reaction was complete (monitored by GC), the product was isolated using silica gel flash chromatography with

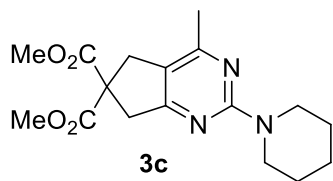
25 % ethyl acetate in hexanes to yield **3a** (119 mg, 90 %) as a white solid. $R_f = 0.38$ (25 % ethyl acetate in hexanes). MP 100.5-102 °C. $^1\text{H NMR}$ (CDCl_3 , 300 MHz) δ 3.75 (s, 6H), 3.47 (s, 2H), 3.39 (s, 2H), 3.15 (s, 6H), 2.25 (s, 3H). $^{13}\text{C NMR}$ (CDCl_3 , 75 MHz) δ 172.1, 169.9, 163.1, 162.3, 116.4, 57.4, 53.3, 42.1, 37.4, 36.2, 22.12. IR (cm^{-1}): 2950, 2852, 1729, 1602, 1440, 1281, 1154, 871. HRMS (ESI) m/z calcd for $\text{C}_{14}\text{H}_{20}\text{N}_3\text{O}_4$ $[\text{M} + \text{H}]^+$ 294.1454, found 294.1455.

Synthesis of dimethyl 4-methyl-2-(pyrrolidin-1-yl)-5H-cyclopenta[d]pyrimidine-6,6(7H)-dicarboxylate (3b):



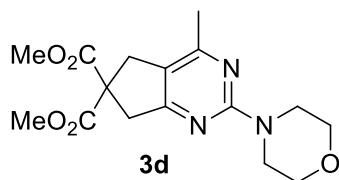
Compound **3b** was prepared using the general procedure with FeI_2 (6.9 mg, 2.2×10^{-2} mmol) and $^{iPr}\text{PDAI}$ (16.6 mg, 4.5×10^{-2} mmol) which were stirred in 1 mL of toluene for 1 hour. 2.5 mL of toluene, alkynenitrile **1a** (100 mg, 4.5×10^{-1} mmol) dissolved in 1 mL of toluene, zinc dust (8.8 mg, 1.3×10^{-1} mmol) and **2b** (129 mg, 1.34 mmol) were added and the reaction was stirred at 40 °C for 72 hours. After the reaction was complete (monitored by GC), the product was isolated using silica gel flash chromatography with 25 % ethyl acetate in hexanes to yield **3b** (57 mg, 40 %) as a white solid. $R_f = 0.14$ (25 % ethyl acetate in hexanes). m.p. 134-135 °C. $^1\text{H NMR}$ (CDCl_3 , 300 MHz) δ 3.75 (s, 6H), 3.54 (t, $J = 6.0$, 4H), 3.49 (s, 2H), 3.40 (s, 2H), 2.26 (s, 3H), 1.94 (t, $J = 6.0$, 4H). $^{13}\text{C NMR}$ (CDCl_3 , 75 MHz) δ 172.1, 169.9, 162.5, 161.3, 116.4, 57.4, 53.3, 47.0, 42.1, 36.3, 25.7, 22.2. IR (cm^{-1}): 2954, 2869, 2360, 1737, 1600, 1515, 1271, 1198, 1165, 883. HRMS (ESI) m/z calcd for $\text{C}_{16}\text{H}_{22}\text{N}_3\text{O}_4$ $[\text{M} + \text{H}]^+$ 320.1610, found 320.1610.

Synthesis of dimethyl 4-methyl-2-(piperidin-1-yl)-5H-cyclopenta[d]pyrimidine-6,6(7H)-dicarboxylate (3c):



Compound **3c** was prepared using the general procedure with FeI_2 (6.9 mg, 2.2×10^{-2} mmol) and *iPr*PDAI (16.6 mg, 4.5×10^{-2} mmol) which were stirred in 1 mL of toluene for 1 hour. 2.5 mL of toluene, alkyne nitrile **1a** (100 mg, 4.5×10^{-1} mmol) dissolved in 1 mL of toluene, zinc dust (8.8 mg, 1.3×10^{-1} mmol) and **2c** (148 mg, 1.34 mmol) were added and the reaction was stirred at 40 °C for 48 hours. After the reaction was complete (monitored by GC), the product was isolated using silica gel flash chromatography with 25 % ethyl acetate in hexanes to yield **3c** (123 mg, 82 %) as a clear oil. $R_f = 0.50$ (25 % ethyl acetate in hexanes). $^1\text{H NMR}$ (CDCl_3 , 300 MHz) δ 3.75 (m, 10H), 3.44 (s, 2H), 3.38 (s, 2H), 2.24 (s, 3H), 1.62 (m, 6H). $^{13}\text{C NMR}$ (CDCl_3 , 75 MHz) δ 172.1, 170.0, 162.6, 162.4, 116.7, 57.4, 53.3, 45.2, 42.1, 36.2, 30.5, 26.03, 25.1, 22.24. $\%$. IR (cm^{-1}): 2932, 2852, 1737, 1600, 1566, 1462, 1443, 1361, 1291, 870. HRMS (ESI) m/z calcd for $\text{C}_{17}\text{H}_{24}\text{N}_3\text{O}_4$ $[\text{M} + \text{H}]^+$ 334.1767, found 334.1772.

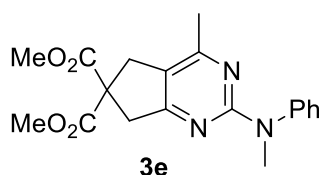
Synthesis of dimethyl 4-methyl-2-morpholino-5H-cyclopenta[d]pyrimidine-6,6(7H)-dicarboxylate (**3d**):



Compound **3d** was prepared using the general procedure with FeI_2 (6.9 mg, 2.2×10^{-2} mmol) and *iPr*PDAI (16.6 mg, 4.5×10^{-2} mmol) which were stirred in 1 mL of toluene for 1 hour. 2.5 mL of toluene, alkyne nitrile **1a** (100 mg, 4.5×10^{-1} mmol) dissolved in 1 mL of toluene, zinc dust (8.8 mg, 1.3×10^{-1} mmol) and **2d** (129 mg, 1.34×10^{-1} mmol) were added and the reaction was stirred at 40 °C for 96 hours. After the reaction was complete (monitored by GC), the product was isolated using silica gel flash chromatography with 25 % ethyl acetate in hexanes to yield **3d** (57 mg, 38 %) as a white solid. $R_f = 0.19$ (25 % ethyl acetate in hexanes). m.p. 104-106 °C. $^1\text{H NMR}$ (CDCl_3 , 300 MHz) δ 3.76 (m, 12H), 3.47 (s, 2H), 3.41 (s, 2H), 2.26 (s, 3H). $^{13}\text{C NMR}$ (CDCl_3 , 75 MHz) δ 175.1, 172.0, 170.2, 162.6,

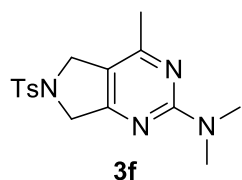
118.1, 67.1, 57.4, 53.4, 44.8, 42.0, 36.2, 22.2. IR (cm⁻¹): 2954, 1792, 1735, 1689, 1559, 1436, 1361, 1203. HRMS (ESI) m/z calcd for C₁₆H₂₂N₃O₅ [M + H]⁺ 336.1559, found 336.1562.

Synthesis of dimethyl 4-methyl-2-(methyl(phenyl)amino)-5H-cyclopenta[d]pyrimidine-6,6(7H)-dicarboxylate (**3e**)



Compound **3e** was prepared using the general procedure with FeI₂ (6.9 mg, 2.2 x 10⁻² mmol) and *i*PrPDAI (16.6 mg, 4.5 x 10⁻² mmol) which were stirred in 1 mL of toluene for 1 hour. 2.5 mL of toluene, alkynenitrile **1a** (100 mg, 4.5 x 10⁻¹ mmol) dissolved in 1 mL of toluene, zinc dust (8.8 mg, 1.3 x 10⁻¹ mmol) and **2e** (178 mg, 1.34 mmol) were added and the reaction was stirred at 40 °C for 96 hours. After the reaction was complete (monitored by GC), the product was isolated using silica gel flash chromatography with 25 % ethyl acetate in hexanes to yield **3e** (64 mg, 40 %) as a yellow oil. R_f = 0.49 (25 % ethyl acetate in hexanes). ¹H NMR (CDCl₃, 300 MHz) δ 7.30-7.38 (m, 3H), 7.13-7.18 (m, 2H) 3.75 (s, 6H), 3.52 (s, 3H), 3.48 (s, 2H), 3.42 (s, 2H), 2.25 (s, 3H). ¹³C NMR (CDCl₃, 75 MHz) δ 172.0, 170.0, 162.4, 146.2, 128.9, 126.3, 125.0, 118.7, 57.4, 53.4, 42.1, 39.0, 36.2, 22.2. IR (cm⁻¹): 2954, 2927, 1736, 1603, 1589, 1388, 1271, 1204, 862. HRMS (ESI) m/z calcd for C₁₉H₂₂N₃O₄ [M + H]⁺ 356.1610, found 356.1613.

Synthesis of N,N,4-trimethyl-6-tosyl-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-2-amine (**3f**)

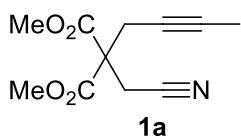


Compound **3f** was prepared using the general procedure with FeI₂ (5.9 mg, 1.9 x 10⁻² mmol) and *i*PrPDAI (17.3 mg, 3.8 x 10⁻² mmol) which were stirred in 1 mL of toluene for 1 hour. 1.8 mL of toluene, alkynenitrile **1b** (100 mg, 3.0 x 10⁻¹ mmol) dissolved in 1 mL of toluene, zinc dust (5.9 mg, 9.0 x 10⁻² mmol) and **2a** (63.1 mg, 9.0 x 10⁻¹ mmol) were added and the reaction was stirred at 40 °C for 96 hours. After the reaction was complete (monitored by GC), the product was isolated using silica gel flash chromatography with 10 % ethyl

acetate in hexanes to yield **3e** (34 mg, 27 %) as a white solid. $R_f = 0.12$ (20 % ethyl acetate in hexanes). MP none, decomposed at 177 °C. ^1H NMR (CDCl_3 , 300 MHz) δ 7.76 (dd, $J_1 = 9.0$, $J_2 = 3.0$, 2H), 7.32 (dd, $J_1 = 9.0$, $J_2 = 3.0$, 2H), 4.46 (s, 2H), 4.40 (s, 2H), 3.13 (s, 6H), 2.41 (s, 2.41), 2.22 (d, $J = 3.0$). ^{13}C NMR (CDCl_3 , 75 MHz) δ 166.1, 161.6, 133.8, 130.1, 127.8, 113.4, 54.0, 50.8, 37.4, 22.3, 21.8. IR (cm^{-1}): 2916.8, 2858.0, 160.7, 1573.4, 1538.3, 1395.6, 1342.3, 1330.7, 1156.7, 1095.3, 1067.6, 820.3, 783.4. HRMS (ESI) m/z calcd for $\text{C}_{16}\text{H}_{20}\text{N}_4\text{NaO}_2\text{S} [\text{M} + \text{Na}]^+$ 355.1205, found 355.1208.

Substrate Synthesis

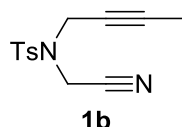
dimethyl 2-(but-2-yn-1-yl)-2-(cyanomethyl)malonate (**1a**)¹



Under nitrogen atmosphere, a round bottom glass with stir bar was charged with NaH (1.32g, 54.9 mmol) and THF (40 mL) at 0°C. A solution of dimethyl 2-(but-2-yn-1-yl)malonate (7.22g, 39.2 mmol) in 20 mL of THF was added slowly added to the NaH solution at 0°C. The reaction was stirred and warmed up to room temperature in 30 min. Then bromoacetonitrile (6.58g, 54.9 mmol) in 20 mL of THF was slowly added to the mixture. The reaction was stirred at room temperature for 1 hour and reflux for another 4 days at 50°C. The reaction was quenched with saturated NH_4Cl , extracted with diethyl ether (3 x 150 mL). The solvent was removed from the extraction by reduced vacuum and purified by flask chromatography (2L 10%, 1L 25% EtOAc/hexanes) to afford the product as a pale yellow oil (8.4g, 96%). The product was further purified by recrystallization. The yellow oil was dissolved in 10 mL of toluene which was layered with pentane. This mixture was stored overnight at -40°C which

afforded a white solid. MP 31.5-32.5 °C. ¹H NMR (CDCl₃, 300 MHz) δ 3.79 (s, 6H), 3.11 (s, 2H), 2.94 (s, 2H), 1.2 (s, 3H).

N-(but-2-yn-1-yl)-N-(cyanomethyl)-4-methylbenzenesulfonamide (**1b**)

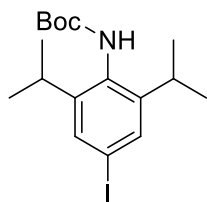


A 50 mL round bottom flask was charged with 561.3 mg (2.14 mmol) of triphenyl phosphine, 456.0 mg (2.04 mmol) of N-(cyanomethyl)-4-methylbenzenesulfonamide,³ approximately 10 mL of anhydrous THF, and 150.0 mg (2.814 mmol) of 2-butyne-1-ol. The reaction was cooled to 0 °C. 432.7 mg (2.14 mmol) of Diisopropyl azodicarboxylate was added dropwise over 15 minutes. The reaction was stirred for 48 hours, concentrated, and isolated by flash column chromatography using 100 mL of each of 5%, 10%, 15%, 20%, 25%, and 30% of ethyl acetate in hexanes. Evaporation of eluent yielded a clear yellow oil which was further purified by recrystallization in layered pentane over toluene to obtain 385 mg (72% yield) of the white solid title compound with melting point 60-61 °C. *R*_f = .23 (20 % ethyl acetate in hexanes). ¹H NMR (500 MHz, CDCl₃) δ = 7.74 (d, *J* = 8.5, 2H), 7.36 (d, *J* = 8.5, 2H), 4.31 (s, 2H), 4.07 (s, 2H), 2.44 (s, 3H), 1.70 (m, 3H) ppm. ¹³C NMR (CDCl₃, 75 MHz) δ = 145.0, 134.1, 130.1, 128.0, 113.8, 84.1, 70.3, 38.2, 35.0, 21.8, 3.6 ppm. IR (cm⁻¹): 3032.96, 2984.53, 2923.11, 2854.27, 2360.66, 2329.90, 2243.38, 1597.68, 1494.33, 1441.26, 1355.44, 1165.82, 1073.74, 909.05, 889.03, 816.30 cm⁻¹. HRMS (EI) calcd. For C₁₃H₁₄N₂O₂S [M + Na]⁺ 285.0674; found 285.0679.

Ligand Synthesis

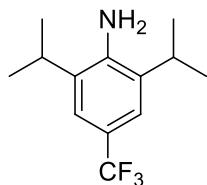
*Me*₂PDAI,⁴ *Mes*₂PDAI,⁴ *p-Ome,Me*₂PDAI,⁵ *Et*₂PDAI,⁴ *iPr*₂PDAI,⁴ and *p-OMe,iPr*₂PDAI⁶ were synthesized according to the literature methods.

Synthesis of *tert*-butyl (4-iodo-2,6-diisopropylphenyl)carbamate



A round bottom flask was charged with 4-iodo-2,6-diisopropylaniline⁶ (1.55 g, 5.10 mmol), di-*tert*-butyl dicarbonate (1.23 g, 5.61 mmol), and stir bar, and dissolved in ethanol (1.5 mL). The reaction was stirred at 30 °C for 3 days. The resulting mixture was stirred with 1M HCl (~1 mL) and extracted with ether (3 x 25 mL). The organic fraction was removed in vacuo to yield ***tert*-butyl (4-iodo-2,6-diisopropylphenyl)carbamate** as orange solid (2g, 97%). MP 120-124 °C. ¹H NMR (CDCl₃, 300 MHz) δ 7.43 (s, 2H), 5.73 (s, 1H) 3.12 (m, 2H), 1.52 (s, 9H), 1.18 (d, 12H). ¹³C (CDCl₃, 75 MHz) δ 149.6, 133.1, 94.6, 85.4, 80.3, 28.8, 28.5, 27.6, 23.6. IR (cm⁻¹): 3229, 3102, 2965, 2931, 2871, 1811, 1699, 1569, 1366, 1119. HRMS (ESI) m/z calcd for C₁₇H₂₆INO₂Na [M + Na]⁺ 426.0906, found 426.0914.

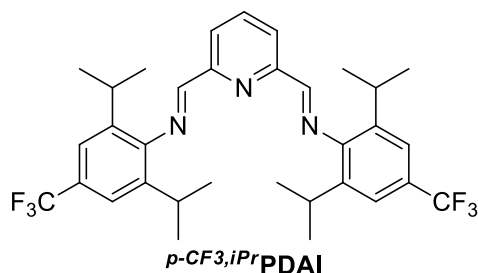
Synthesis of 2,6-diisopropyl-4-(trifluoromethyl)aniline



2,6-diisopropyl-4-(trifluoromethyl)aniline was prepared using a similar literature procedure.⁷ In glove box, a three-neck 250 mL round bottom flask containing stir bar was charged with *tert*-butyl (4-iodo-2,6-diisopropylphenyl)carbamate (0.89 g, 2.20 mmol), copper iodide (2.48 g, 13.01 mmol), [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (0.09g, 0.11 mmol), dissolved in DMF (31 mL). To this mixture, a solution of methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (2.5 g, 13.01 mmol) in DMF (5 mL) was added. The reaction was stirred at 100 °C with a reflux condenser outside the glove box for 2 days under N₂. The reaction was cooled to room temperature and diluted with CH₂Cl₂ (15 mL), filtered through a small plug of celite affording a dark brown solution which was then washed with water (2 x 100 mL), 50% saturated aqueous NaCl (100 mL), and brine (100 mL). The solution was dried over sodium sulfate, filtered through celite, concentrated in vacuo, purified by silica gel flash chromatography (10% EtOAc/hexanes) to afford deprotected **2,6-diisopropyl-4-(trifluoromethyl)aniline** (0.38 g, 50%) as

an orange oil. This product contained unknown impurities but was successfully carried through to the next step (*p*-CF₃,*iPr*PDAI). ¹H NMR (CDCl₃, 300 MHz) δ 7.26 (s, 2H), 2.91 (quint, *J* = 7.5, 2H), 1.29 (d, 12H).

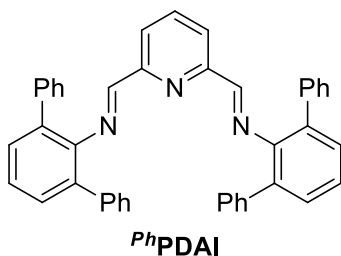
Synthesis of (N,N'E,N,N'E)-N,N'-(pyridine-2,6-diylbis(methanylylidene))bis(2,6-diisopropyl-4-(trifluoromethyl)aniline) (*p*-CF₃,*iPr*PDAI)



p-CF₃,*iPr*PDAI was prepared from the similar literature procedure⁴ with 2,6-diisopropyl-4-(trifluoromethyl)aniline (0.19 g, 0.81 mmol) and 2,6-pyridinedicarboxaldehyde (0.5 g, 0.369 mmol) and ~10 drops of glacial acetic acid in 3 mL 100%

ethanol. The reaction was stirred for 3 days at room temperature. The mixture was then cooled to 0 °C, filtered and rinsed with cold 100% ethanol to yield *p*-CF₃,*iPr*PDAI (1.53 g, 70%) as a yellow solid. MP 185-188 °C. ¹H NMR (CDCl₃, 300 MHz) δ 8.41 (d, *J* = 9.0, 1H), 8.35 (s, 2H), 8.05 (t, *J* = 9.0, 1H), 7.41 (s, 4H), 2.99 (q, *J* = 6.0, 4H), 1.21 (d, 12H). ¹³C NMR (CDCl₃, 75 MHz) δ 163.1, 154.3, 151.0, 138.0, 127.1, 126.6, 123.3, 120.3, 29.9, 28.4, 23.4. IR (cm⁻¹): 2962, 2917, 2869, 2849, 1704, 1646, 1298, 1149, 1116, 845. HRMS (ESI) *m/z* calcd for C₃₃H₃₈N₃F₆ [M + H]⁺ 590.2970, found 590.2972.

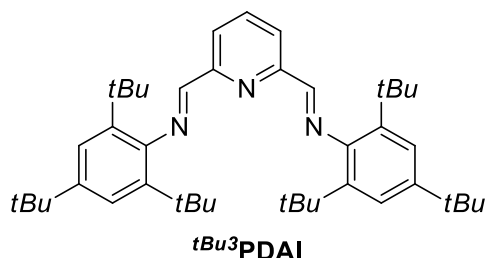
Synthesis of (N',N''E,N',N''E)-N,N''-(pyridine-2,6-diylbis(methanylylidene))bis((1,1':3',1''-terphenyl)-2'-amine) (*Ph*PDAI)



*Ph*PDAI was prepared from the similar literature procedure⁴ with 2,4-diphenyl aniline (250 mg, 1.02 mmol) and 2,6-pyridinedicarboxaldehyde (67.2 mg, 5.0 x 10⁻¹ mmol) and ~5 drops of glacial acetic acid in 5 mL 100% ethanol. The reaction was stirred overnight at room temperature.

The mixture was then cooled to 0 °C, filtered and rinsed with cold 100% ethanol to yield *Ph*PDAI (165 mg, 56 %) as a yellow solid. MP 249 °C. ¹H NMR (CDCl₃, 500 MHz) δ 7.87 (s, 2H), 7.81 (d *J* = 9 Hz, 2H), 7.58 (t, *J* = 9 Hz, 1H), 7.38-7.35 (m, 12H), 7.29-7.15 (m, 14H). ¹³C NMR (CDCl₃, 75 MHz) δ 165.0, 154.1, 147.8, 139.9, 137.0, 133.4, 128.1, 125.2, 122.5. IR (cm⁻¹): 3056, 3027, 2886, 3261, 1598, 1584, 1458, 1441, 1413, 1332, 1265, 1196, 1072, 1028, 992, 967, 917. HRMS (ESI) *m/z* calcd for C₃₃H₃₈N₃F₆ [M + H]⁺ 590.2596, found 590.2592.

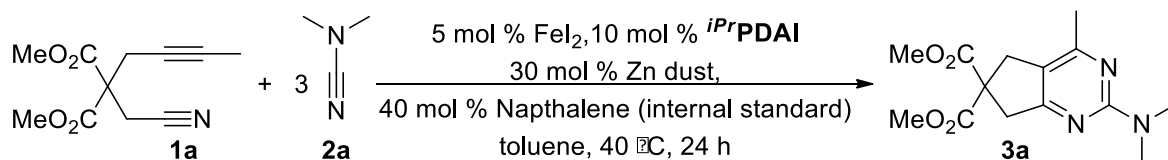
Synthesis of (N,N'E,N,N'E)-N,N'-(pyridine-2,6-diylbis(methanylylidene))bis(2,4,6-tri-*tert*-butylaniline) (*tBu*³PDAI)



*tBu*³PDAI was prepared from the similar literature procedure⁴ with 2,4,6-tri *tert*-butyl aniline (429 mg, 1.65 mmol) and 2,6-pyridinedicarboxaldehyde (109 mg, 8.0 x 10⁻¹ mmol) and ~10 drops of glacial acetic acid in 10 mL 100% ethanol. The

reaction was stirred overnight at room temperature. The mixture was then cooled to 0 °C, filtered and rinsed with cold 100% ethanol to yield *tBu*³PDAI (339 mg, 59 %) as a yellow solid. MP 284-286 °C. ¹H NMR (CDCl₃, 300 MHz) δ 8.41 (d, *J* = 1.5 Hz, 2H), 8.29 (s, 2H), 8.06 (t, *J* = 1.5 Hz, 1H), 7.38 (s, 4H), 1.37 (s, 18H), 1.35 (s, 36H). ¹³C NMR (CDCl₃, 75 MHz) δ 163.1, 154.6, 149.6, 144.7, 138.1, 137.7, 122.9, 122.0, 98.8, 36.1, 35.0, 31.2. IR (cm⁻¹): 2961, 2870, 2360, 1735, 1645, 1567, 1455, 14427, 1392, 1269, 1213, 1118, 878, 812. HRMS (ESI) *m/z* calcd for C₃₃H₃₈N₃F₆ [M + H]⁺ 644.4920, found 644.4918.

Control Reactions



FeI_2	$i\text{PrPDAI}$	Zn dust	% Completion	% Yield (isolated)
present	present	-	0	0
present	-	present	0	0
-	present	present	0	0
present	present	present	100	90

Catalyst/Reagent Screening

Entry	Substrates (equiv)	Conditions	% yield ^a
1	1a (1), 2a (2)	5 mol % $\text{Rh}(\text{cod})_2\text{BF}_4/\text{BINAP}$, CH_2Cl_2 , $40\text{ }^\circ\text{C}$	-
2	1a (1), 2a (5)	15 mol % $\text{CoCp}(\text{CO})_2$, Dioxane, $100\text{ }^\circ\text{C}$	-
3	1a (1), 2a (3)	10 mol % CoCl_2 , 10 mol % dppe , 20 mol % Zn , NMP, $50\text{ }^\circ\text{C}$	-
4	1a (1), 2a (1.5)	10 mol % $\text{Ni}(\text{cod})_2$, 20 mol % SIPr , toluene, rt	-
5	1a (1), 2a (1.5)	10 mol % $\text{Ni}(\text{cod})_2$, 20 mol % IMes , toluene, rt	-
6	1a (1), 2a (1.5)	10 mol % $\text{Ni}(\text{cod})_2$, 10 mol % Xantphos , toluene, rt	-
7	1a (1), 2a (3)	2 mol % $[\text{Ir}(\text{cod})\text{Cl}]_2$, 4 mol % DPPF , benzene, $80\text{ }^\circ\text{C}$	trace
8	1a (1), 2a (1.5)	2 mol % $\text{Cp}^*\text{RuCl}(\text{cod})$ DCE, $60\text{ }^\circ\text{C}$	-
9	1a (1), 2a (3)	1.2 equiv NbCl_5 , toluene, $60\text{ }^\circ\text{C}$	-
10	1a (1), 2a (3)	5 mol % $\text{Ph}_3\text{PAuOPOF}_2$, THF, rt	-
11	1a (1), 2a (3)	5 mol % AuCl_3 , 1.1 equiv MsOH , toluene, rt	-
12	1a (1), 2a (3)	5 mol % AuClPEt_3 , 5 mol % AgSbF_6 (5 mol %), DCE, $85\text{ }^\circ\text{C}$	-
13	1a (1), 2a (3)	10 mol % AgOTf , 10 mol % CuBr , K_3PO_4 , toluene, $60\text{ }^\circ\text{C}$	-
14	1a (1), 2a (3)	10 mol % FeI_2 , 20 mol % dppp , 20 mol % Zn , THF, rt	-
15	1a (1), 2a (3)	10 mol % FeI_2 , 20 mol % dppp , 20 mol % Zn , 20 mol % ZnI_2 , THF, rt	-
16	1a (1), 2a (2)	20 mol % $\text{Fe}(\text{OAc})_2$, 26 mol % $p\text{-OMe}$, $i\text{PrPDAI}$, 40 mol % Zn , DMF, $85\text{ }^\circ\text{C}$	trace
17	1a (1), 2a (2)	10 mol % FeCl_2 , 20 mol % MesPDAI , 20 mol % Zn , benzene, $70\text{ }^\circ\text{C}$	16 ^b

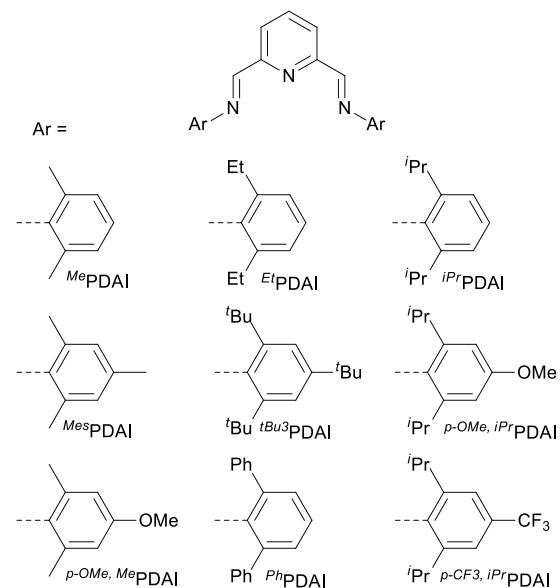
^a Detected by GCMS. ^b NMR yield. ^c BINAP = 2,2'-Bis(diphenylphosphino)-1,1'-binaphthalene. cod = 1,5-cyclooctadiene. Cp = cyclopentadienyl. dppe = 1,2-bis(diphenylphosphino)ethane. SIPr = 1,3-bis(2,6-diisopropylphenyl)imidazolidene. IMes = 1,3-bis(N-Mesityl)imidazole. Xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene. DPPF = 1,1'-bis(diphenylphosphino)ferrocene. Cp^* = pentamethylcyclopentadienyl. MsOH = methanesulfonic acid. OTf = trifluoromethanesulfonate. dppp = 1,3-bis(diphenylphosphino)propane.

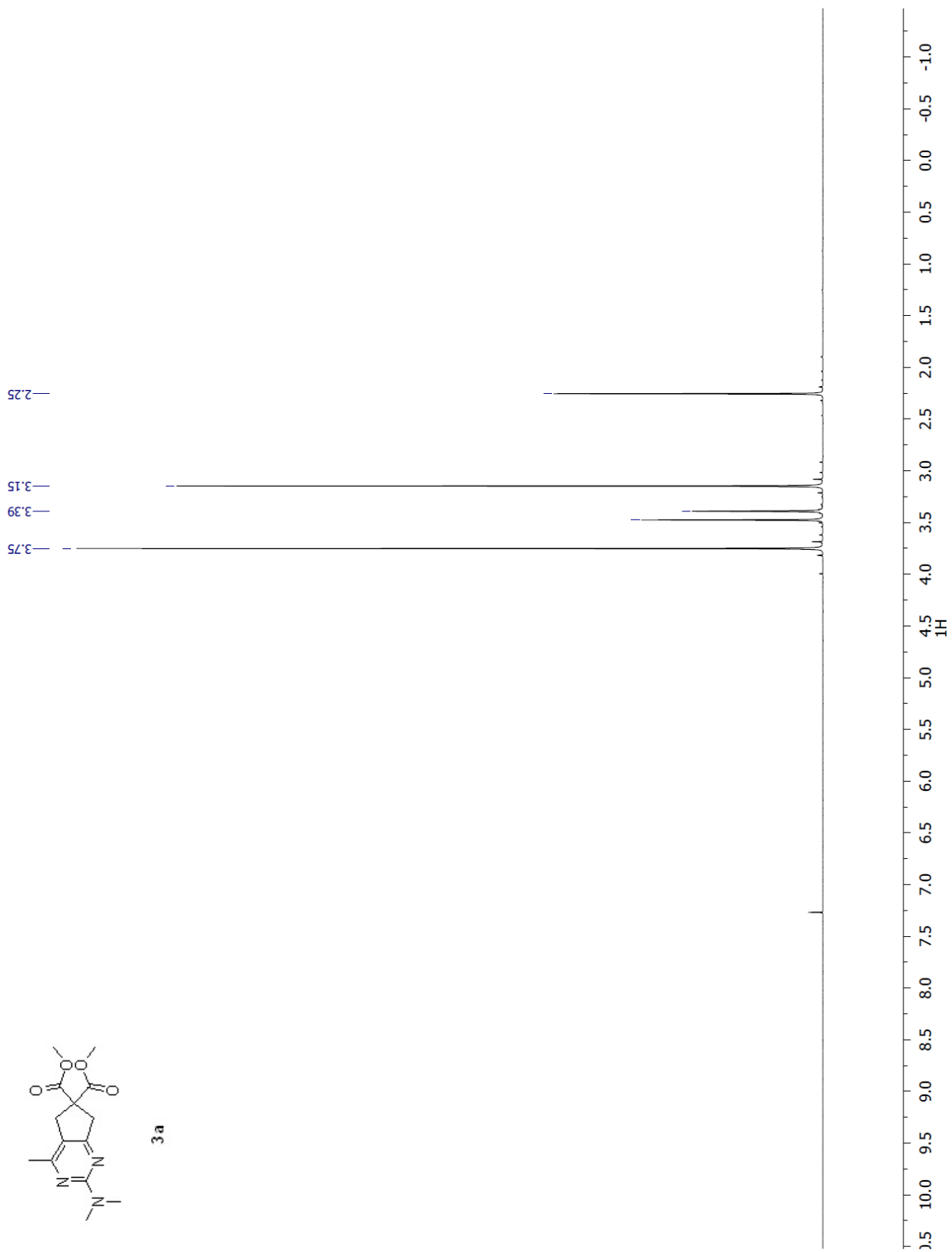
Reaction Optimization

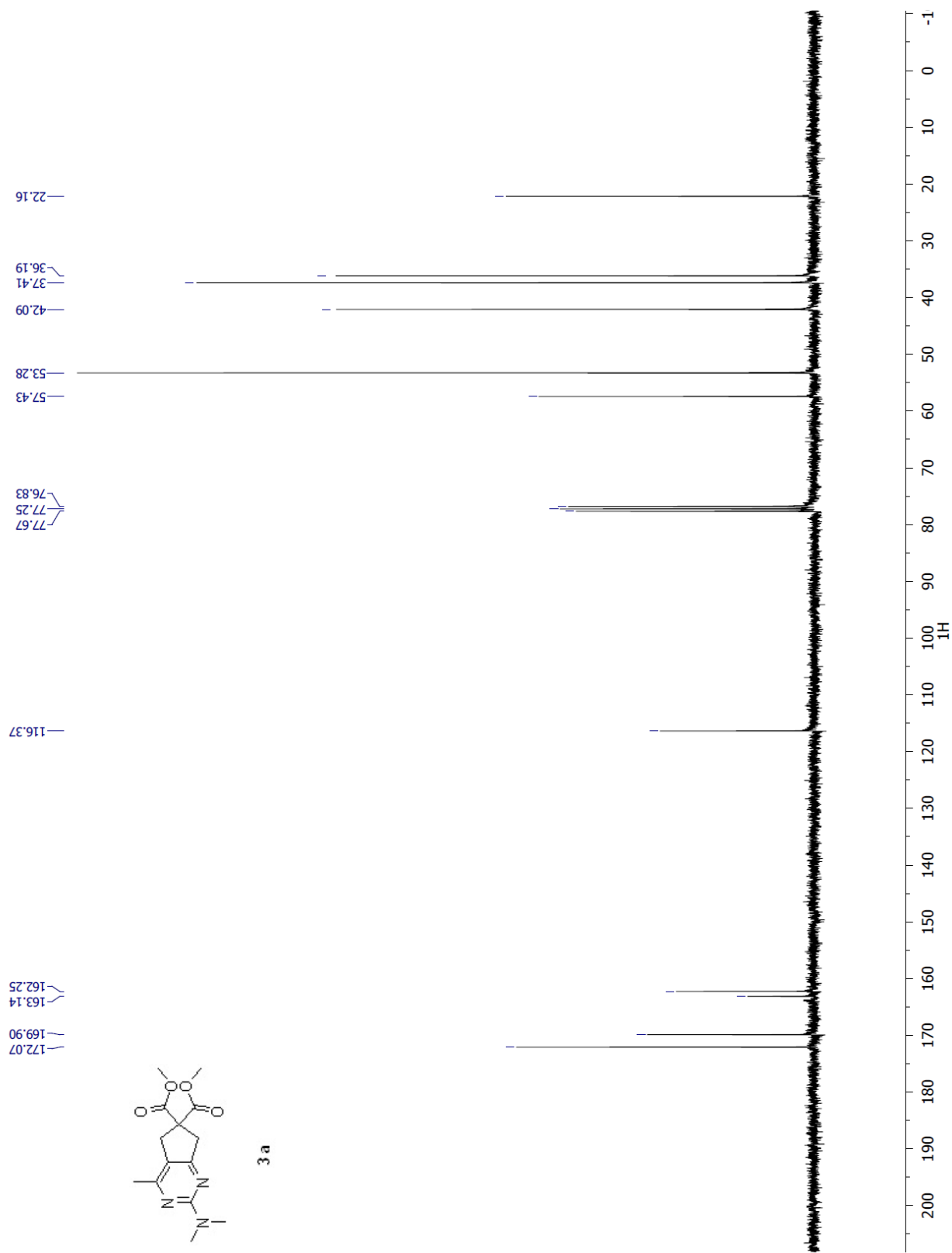
Entry	1a:2a	FeX ₂ (mol %)	Ligand (mol %)	Concentration [1a] (M)	temp (°C)	% yield ^b
1	1:2	FeCl ₂ (10)	<i>Mes</i> PDAI (20)	0.4	70	9
2	1:2	FeBr ₂ (10)	<i>Mes</i> PDAI (20)	0.4	70	10
3	1:2	Fe(OAc) ₂ (10)	<i>Mes</i> PDAI (20)	0.4	70	23
4	1:2	FeI ₂ (10)	<i>Mes</i> PDAI (20)	0.4	70	12
5	1:2	FeI ₂ (10)	<i>Mes</i> PDAI (20)	0.1	70	40
6	1:3	FeI ₂ (10)	<i>iPr</i> PDAI (20)	0.1	70	4
7	1:3	FeI ₂ (10)	<i>Me</i> PDAI (20)	0.1	70	13
8	1:3	FeI ₂ (10)	<i>p-OMe, Me</i> PDAI (20)	0.1	70	n.d. ^c
9	1:3	FeI ₂ (10)	<i>Ph</i> PDAI (20)	0.1	70	n.d.
10	1:3	FeI ₂ (10)	<i>tBu</i> PDAI (20)	0.1	70	n.d.
11	1:3	FeI ₂ (10)	<i>Et</i> PDAI (20)	0.1	70	47
12	1:3	FeI ₂ (10)	<i>p-OMe, iPr</i> PDAI (20)	0.1	70	25
13	1:3	FeI ₂ (10)	<i>p-CF₃, iPr</i> PDAI (20)	0.1	70	70
14	1:3	FeI ₂ (10)	<i>iPr</i> PDAI (20)	0.1	70	72
15	1:3	FeI ₂ (10)	<i>iPr</i> PDAI (20)	0.1	40	>99
16 ^d	1:3	FeI ₂ (5)	<i>iPr</i> PDAI (10)	0.1	40	98

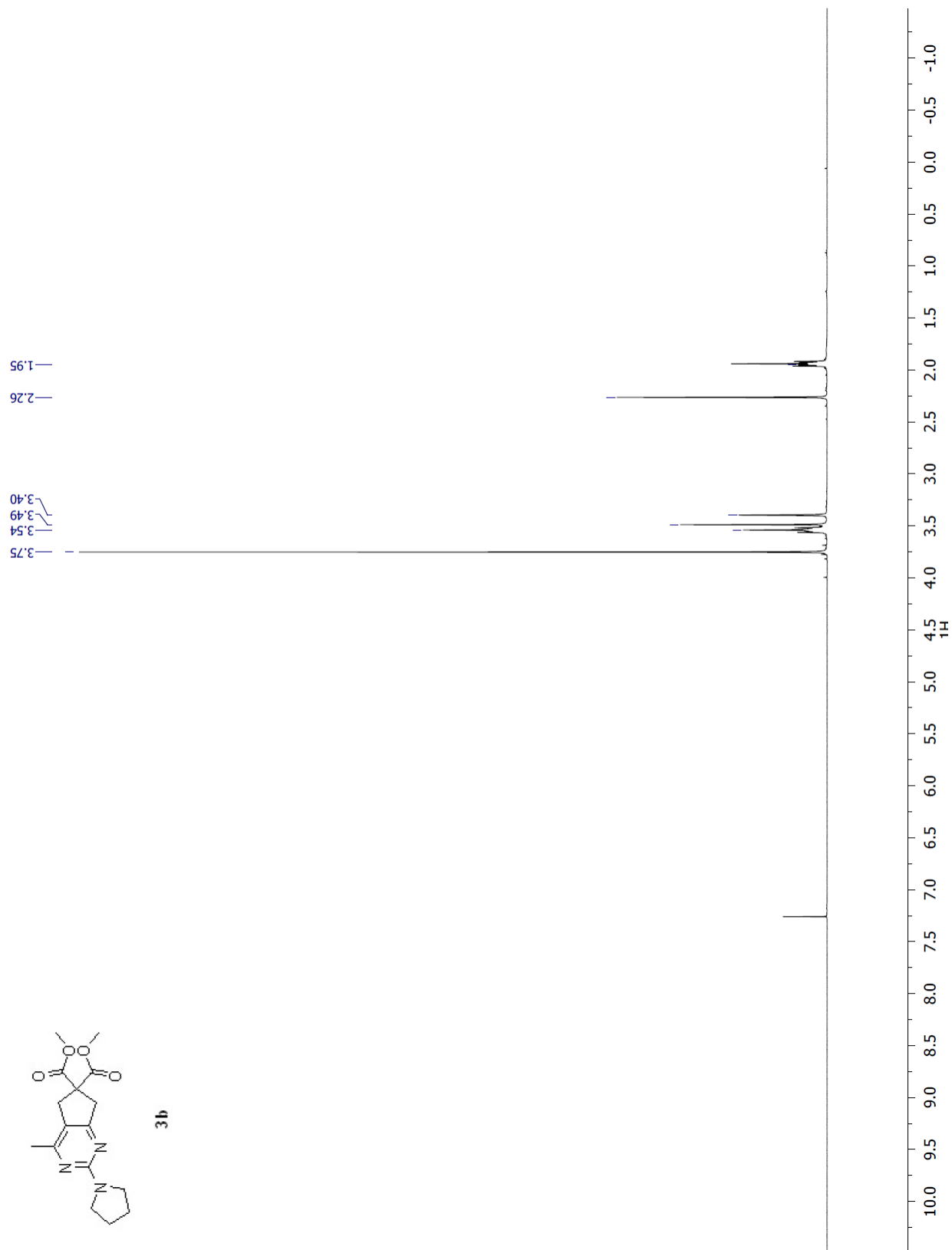
^a 20 mol % Zn dust except where otherwise noted. ^b NMR yield. ^c n.d. = not detected. ^d 30 mol % Zn dust.

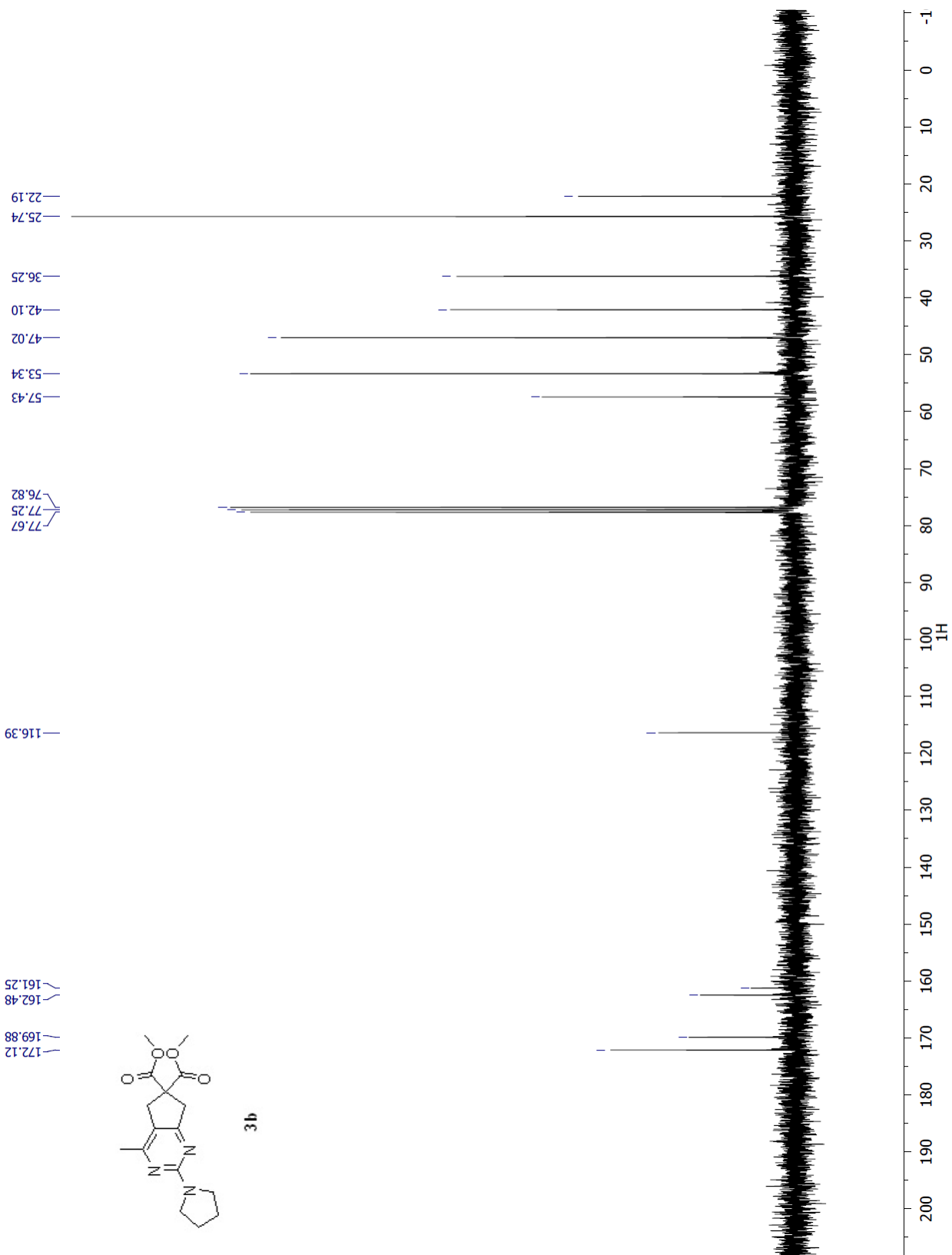
Ligands

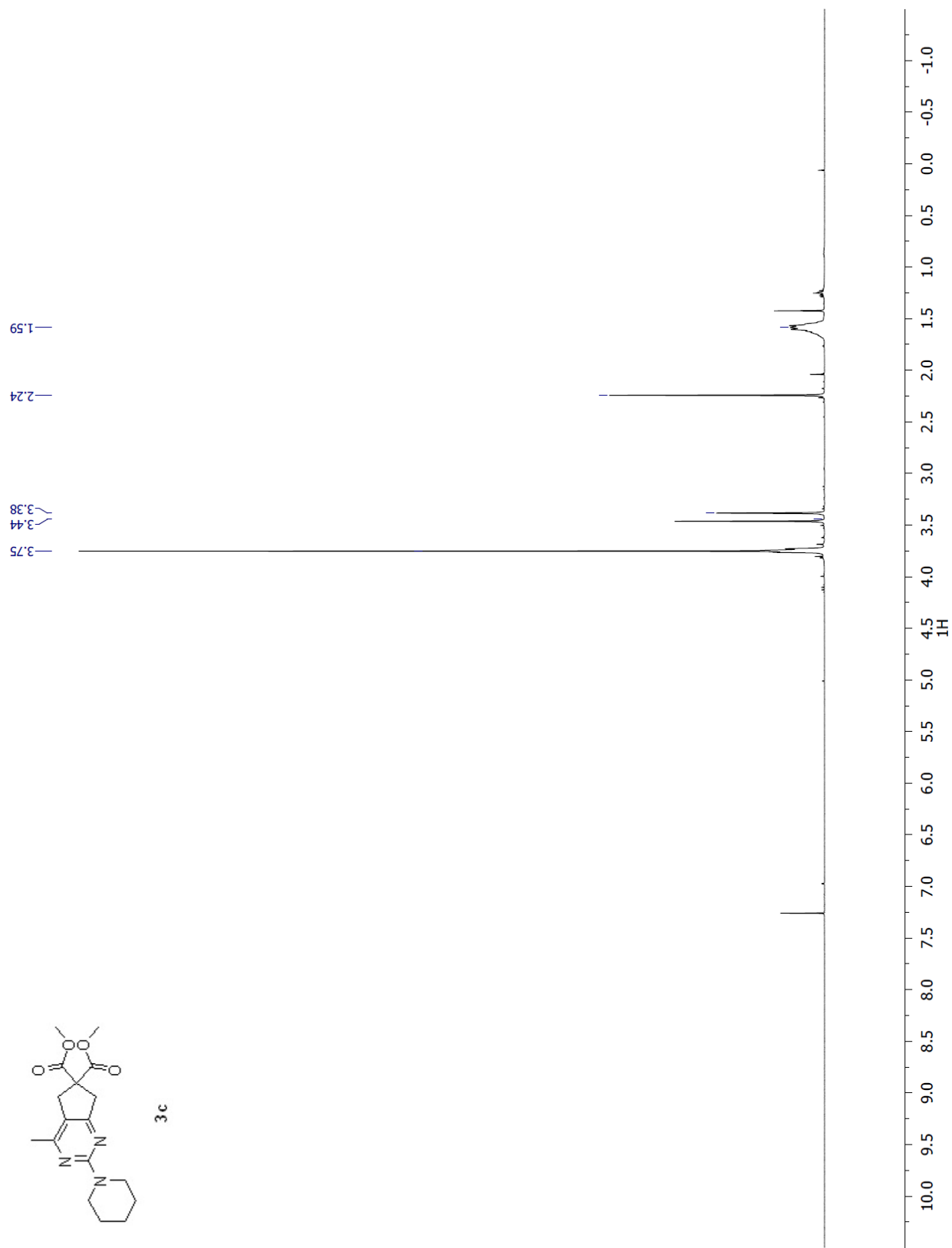


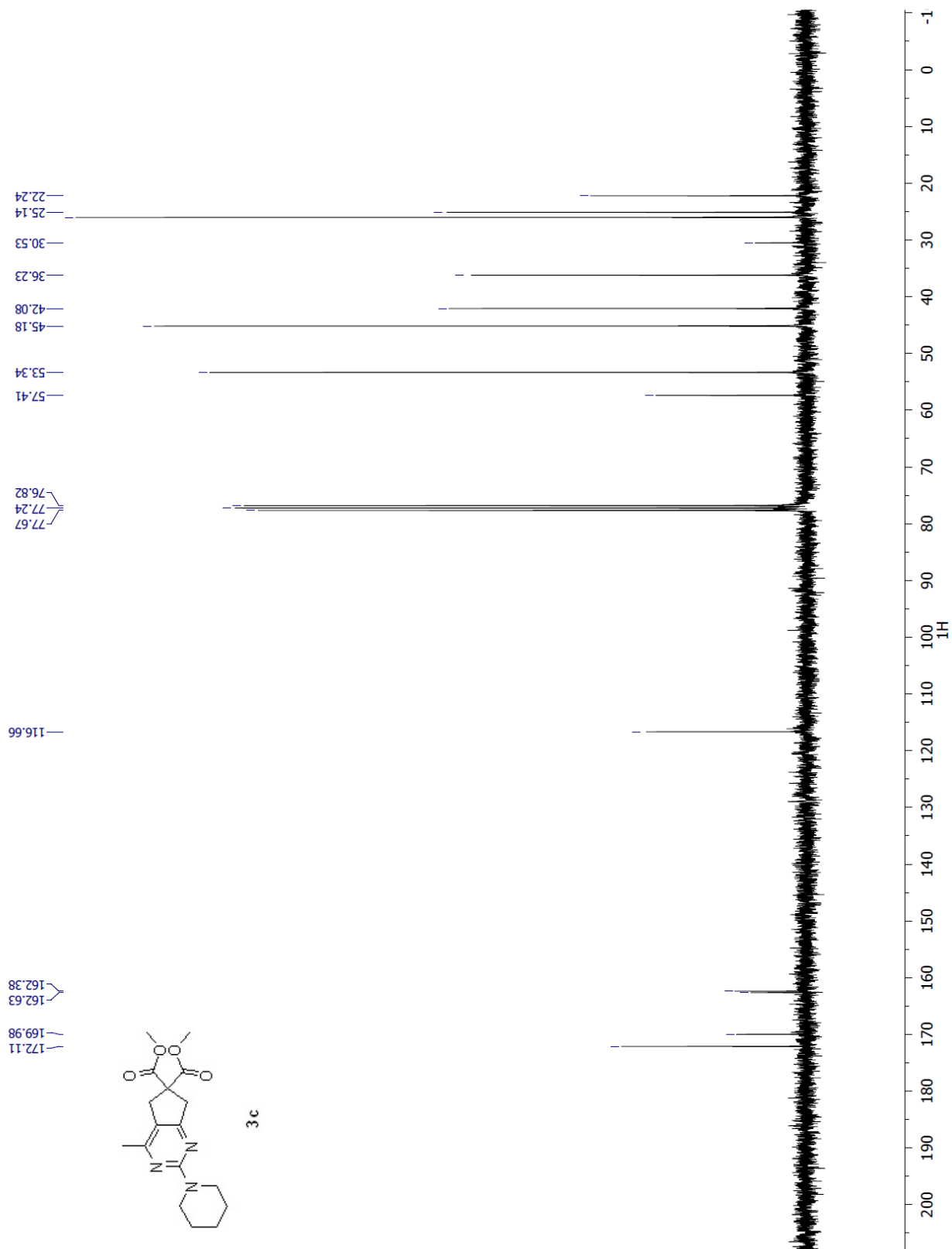


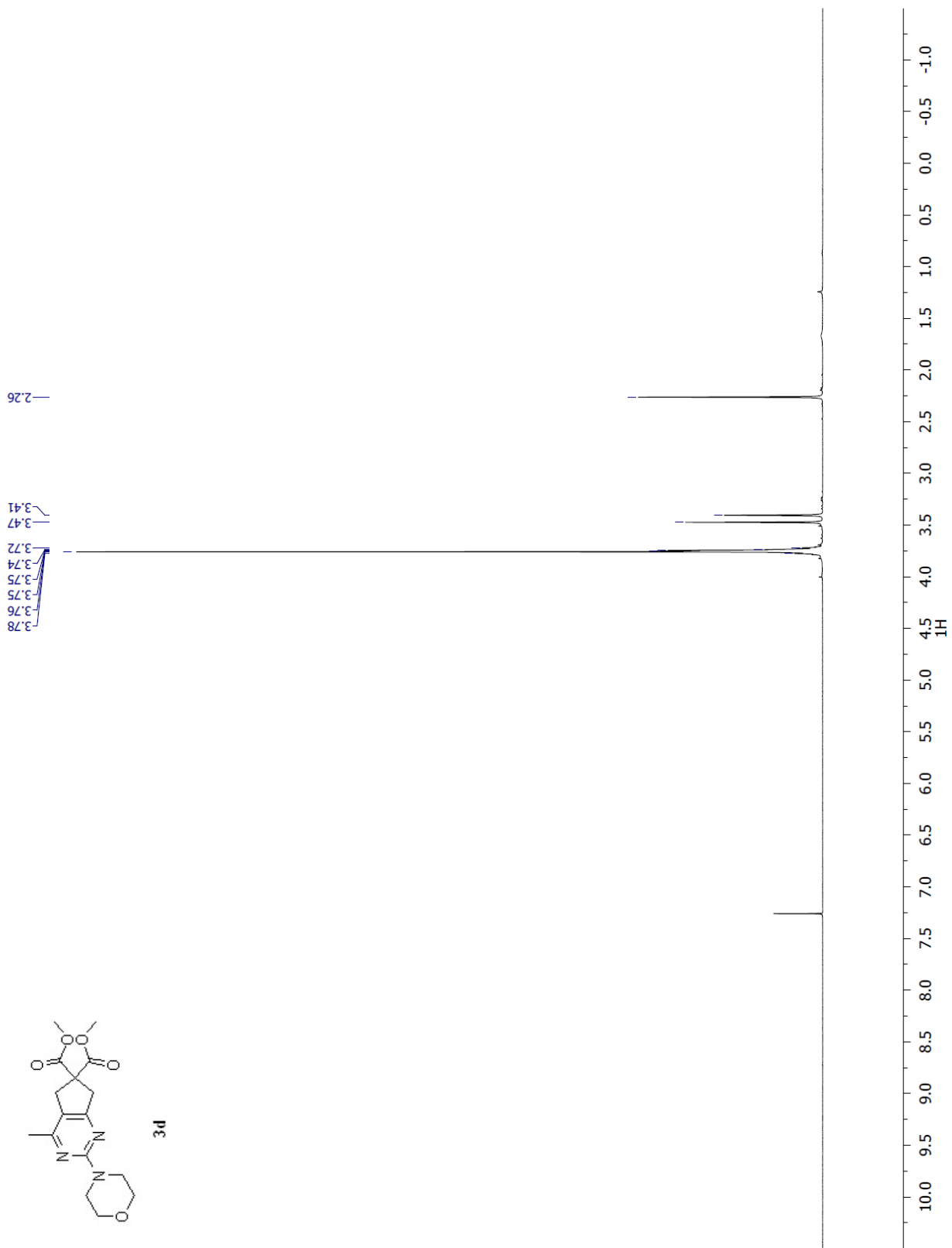


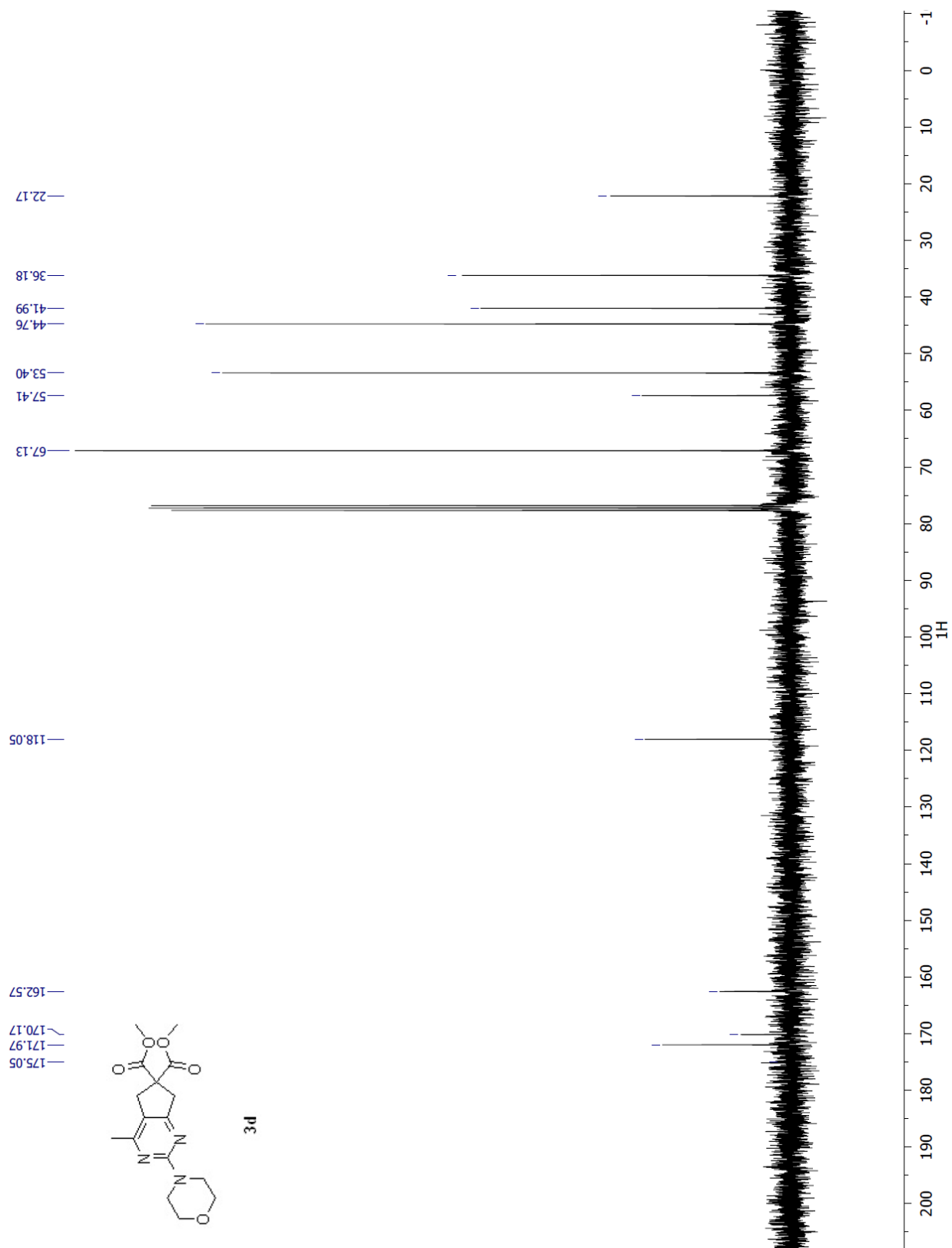


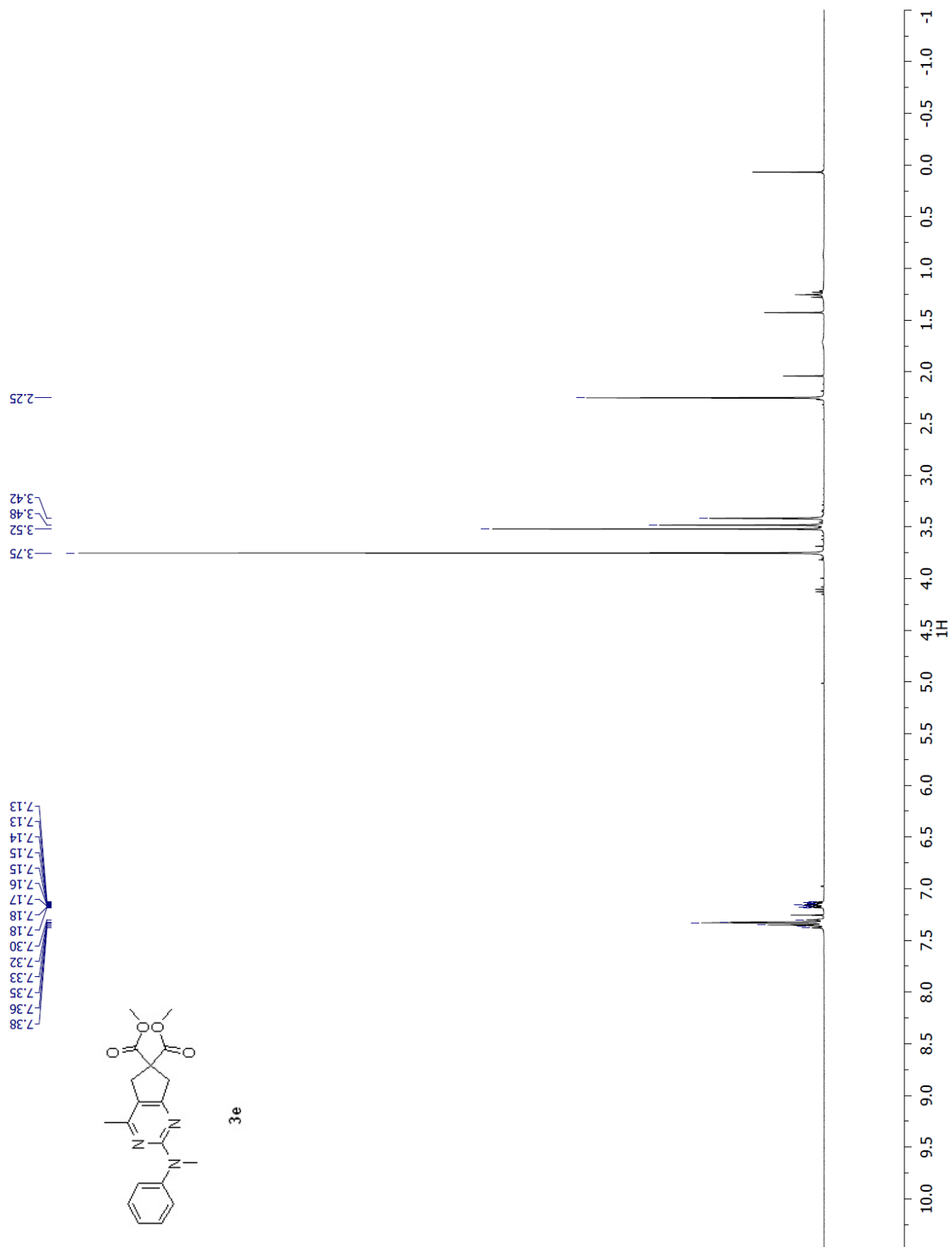


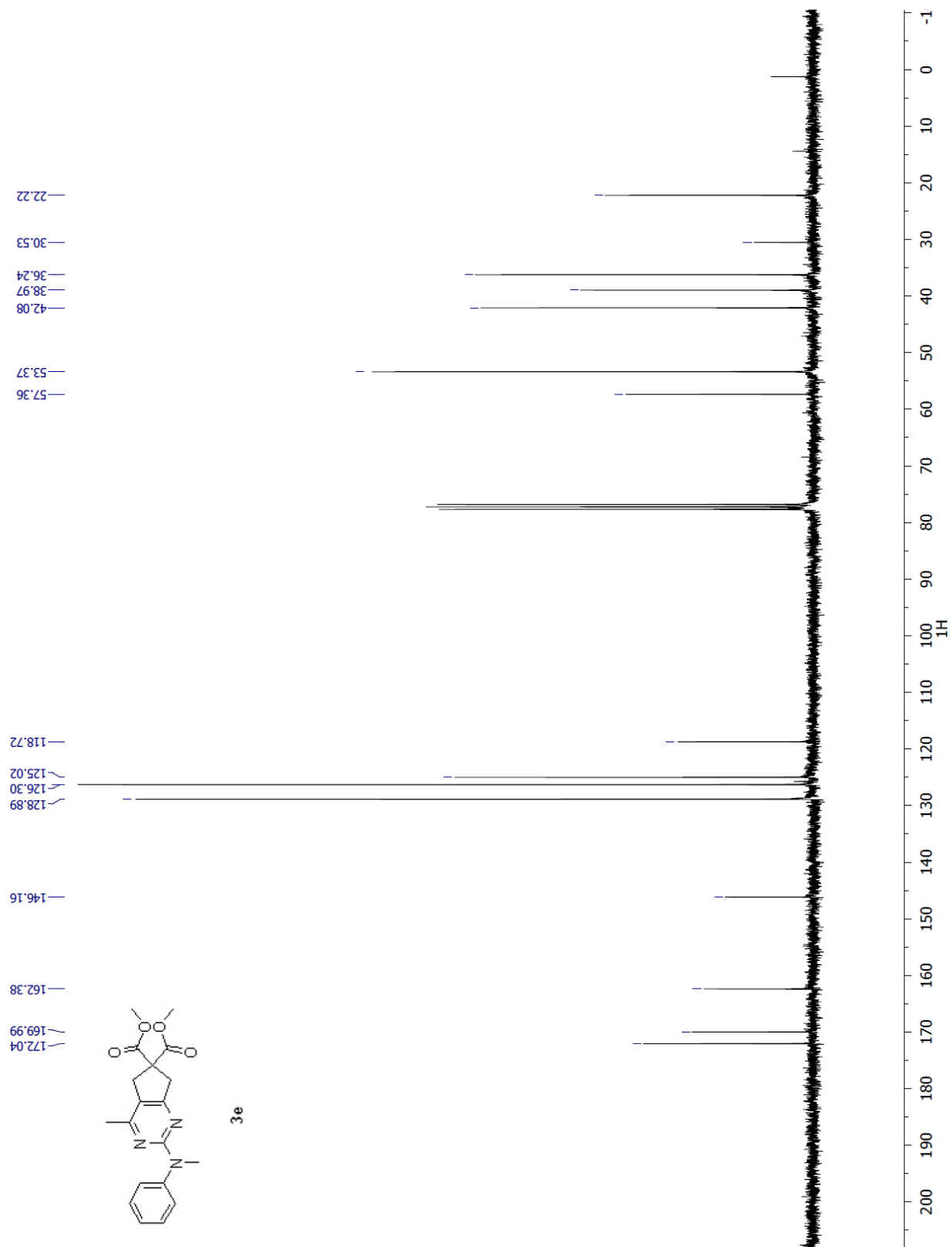


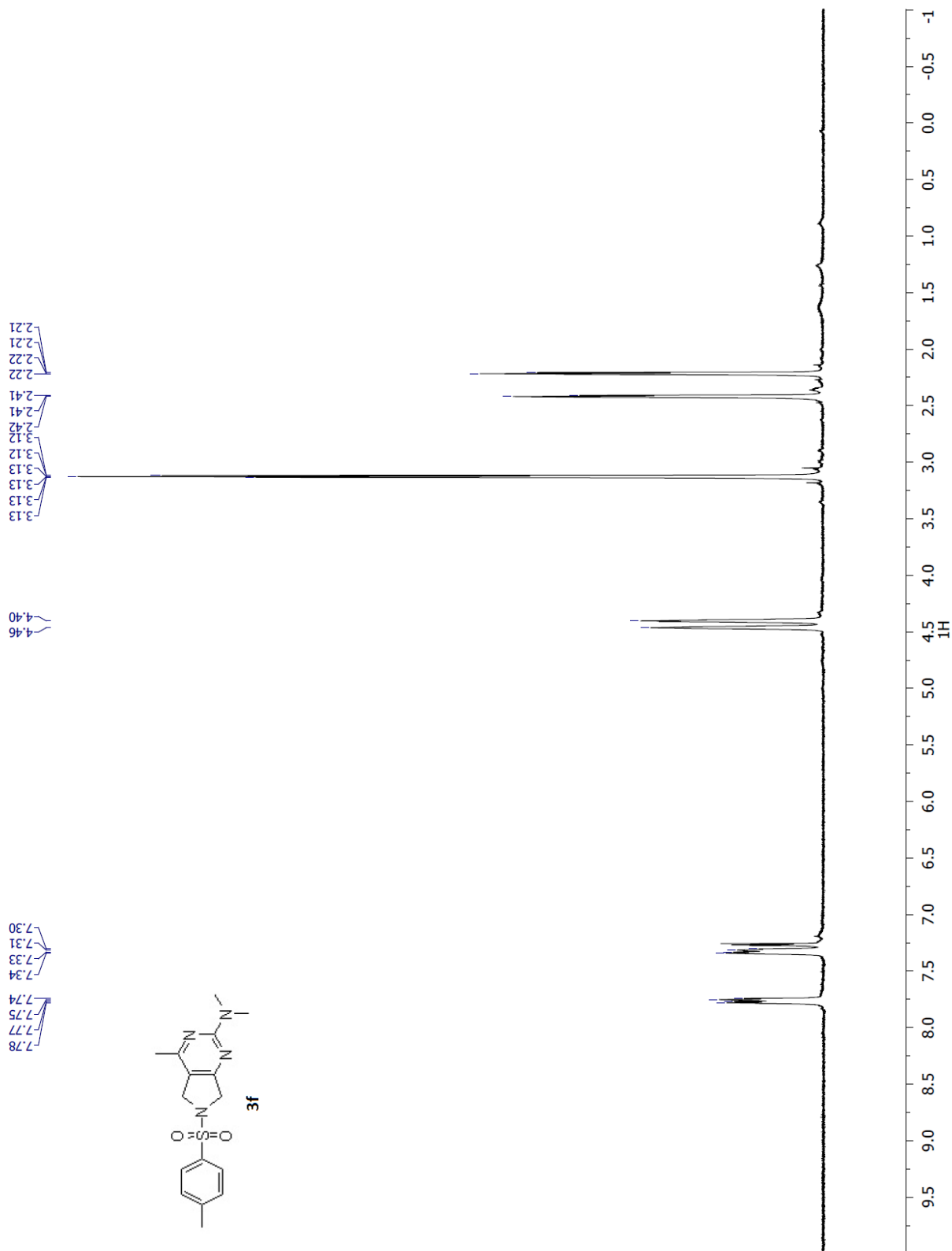


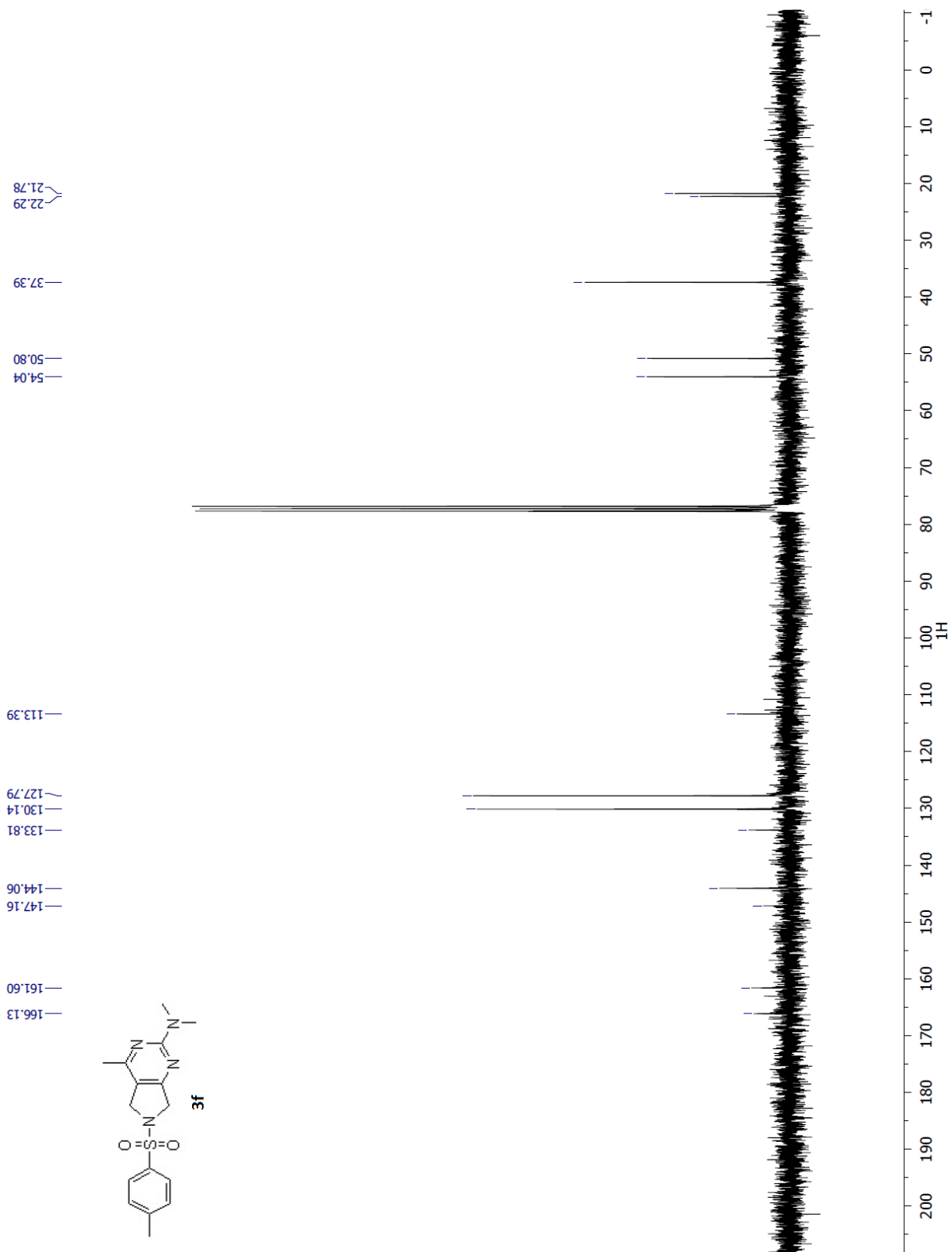


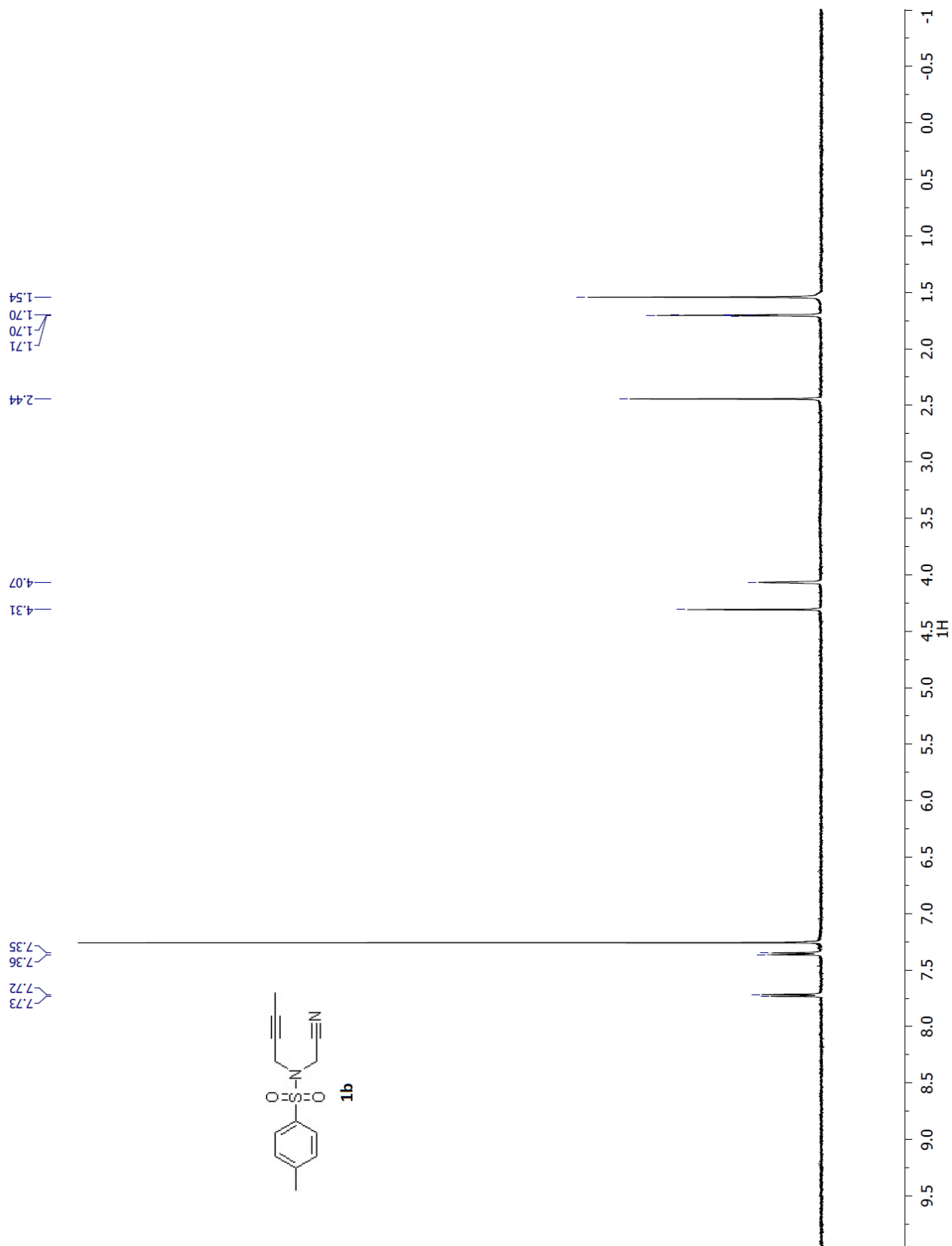


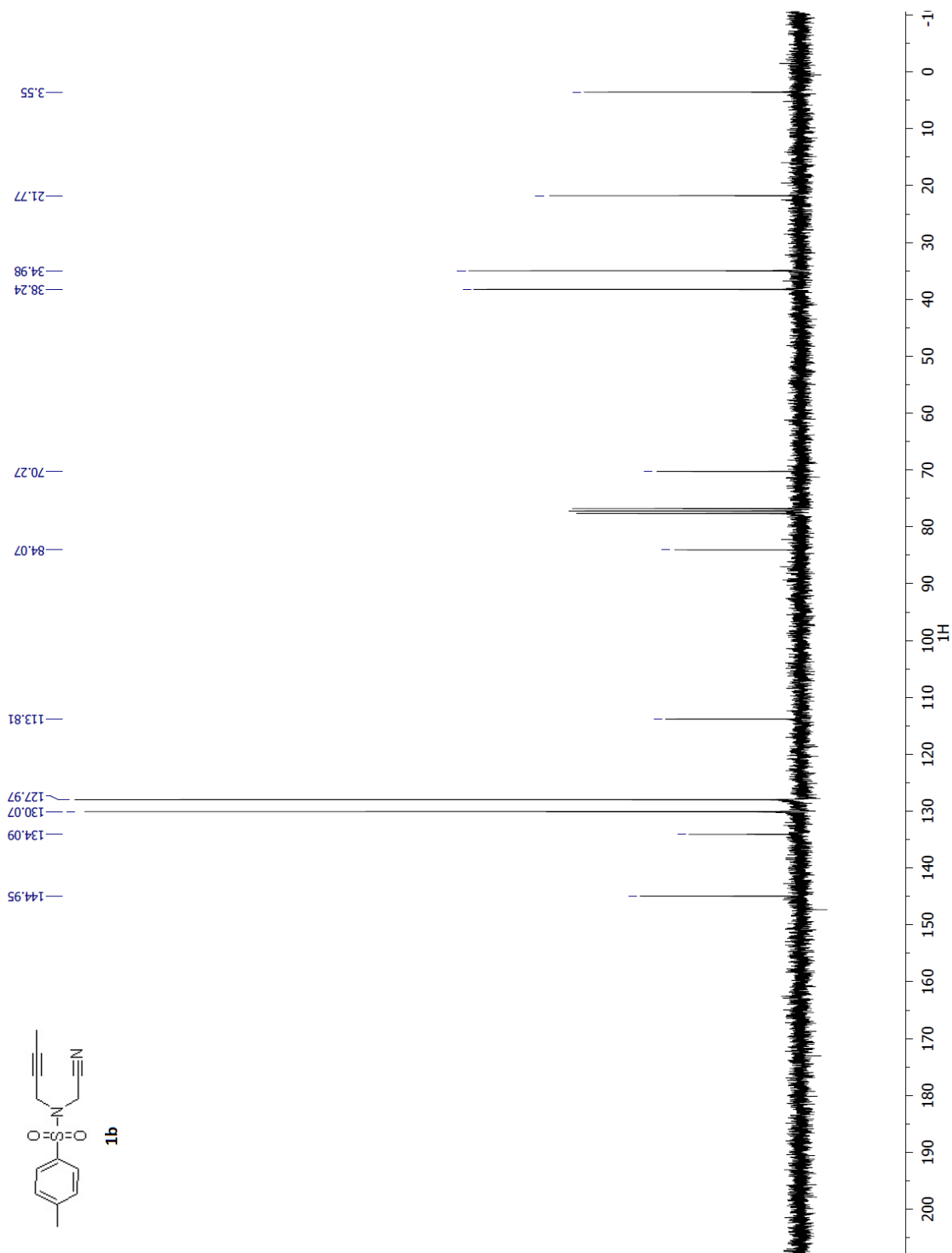


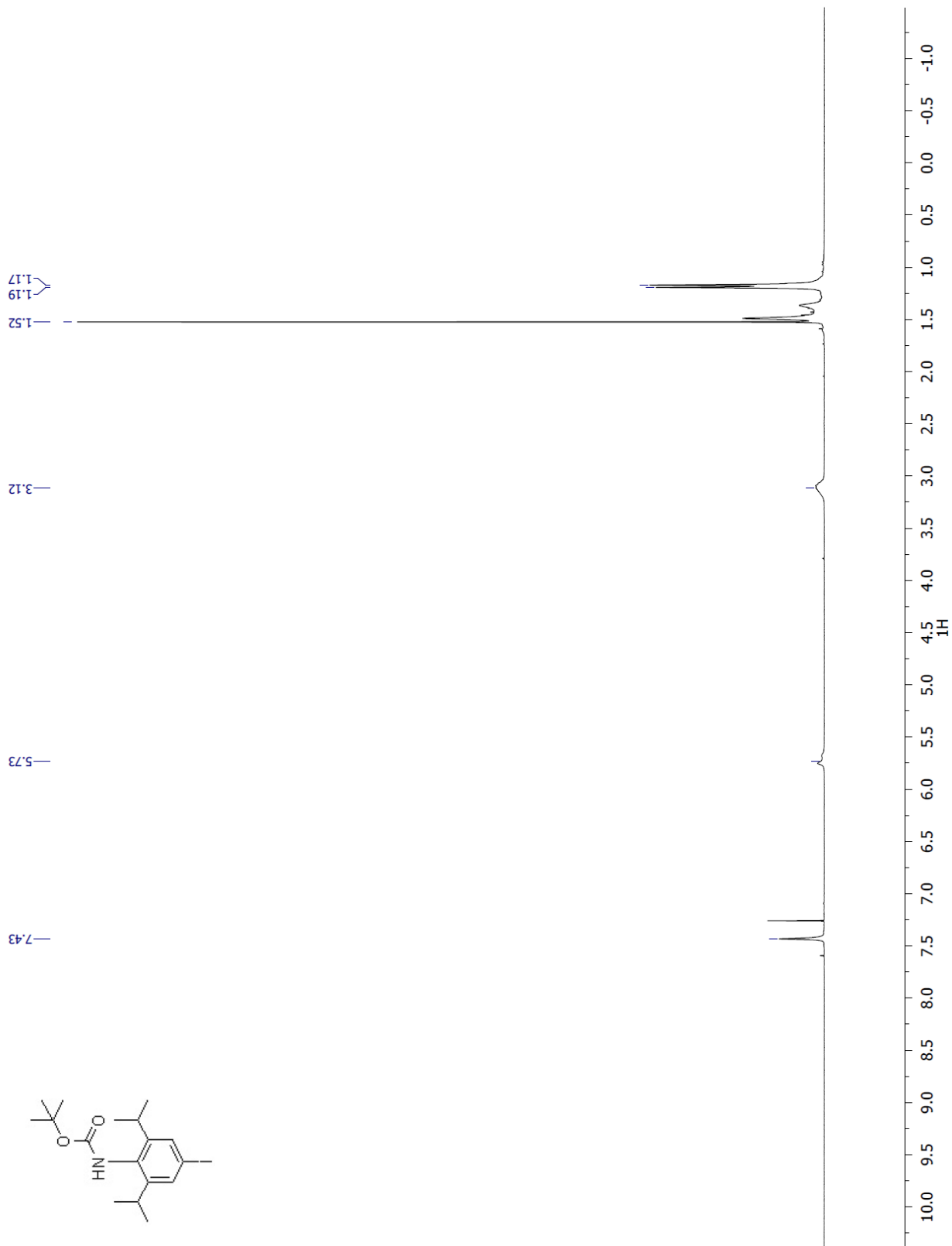


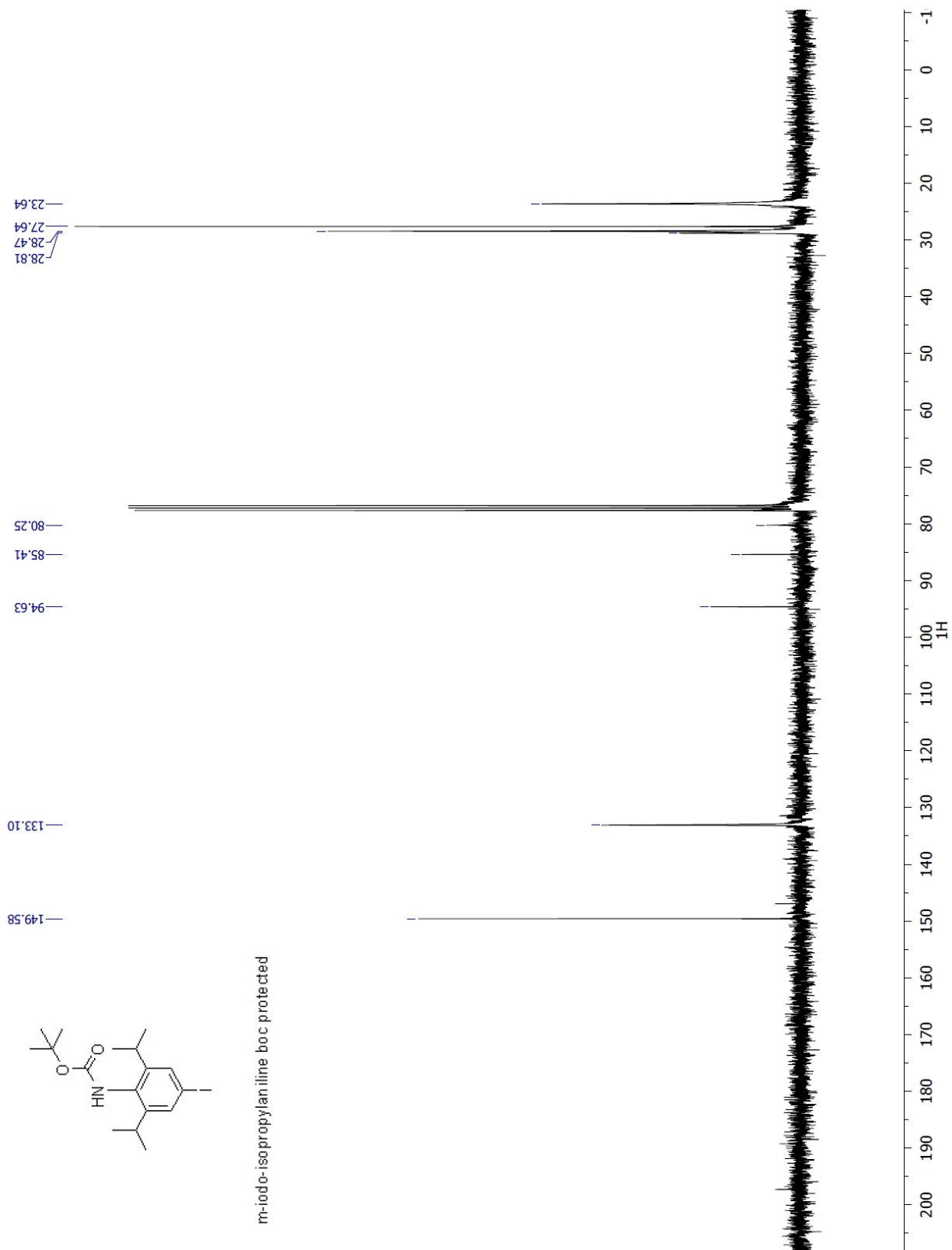


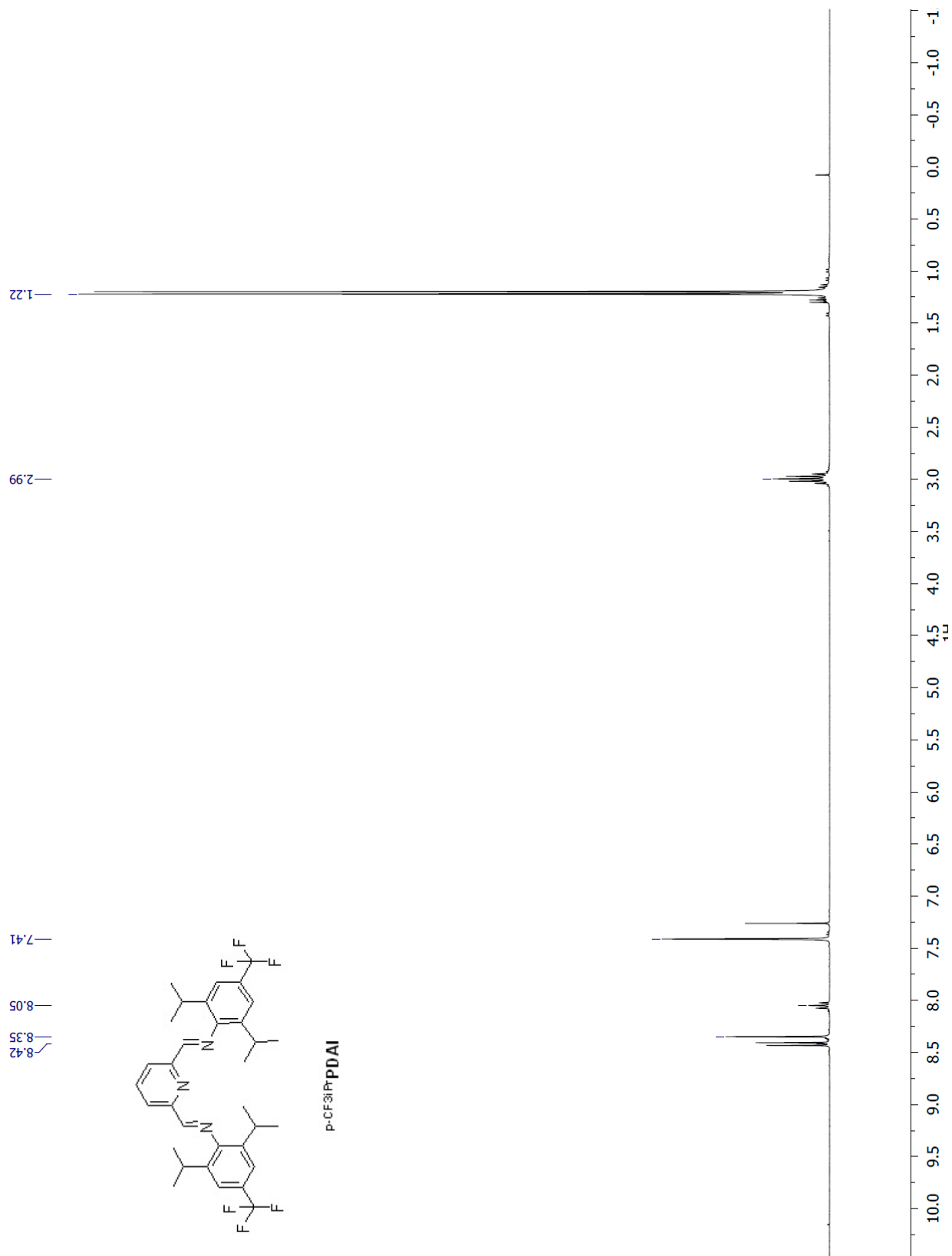


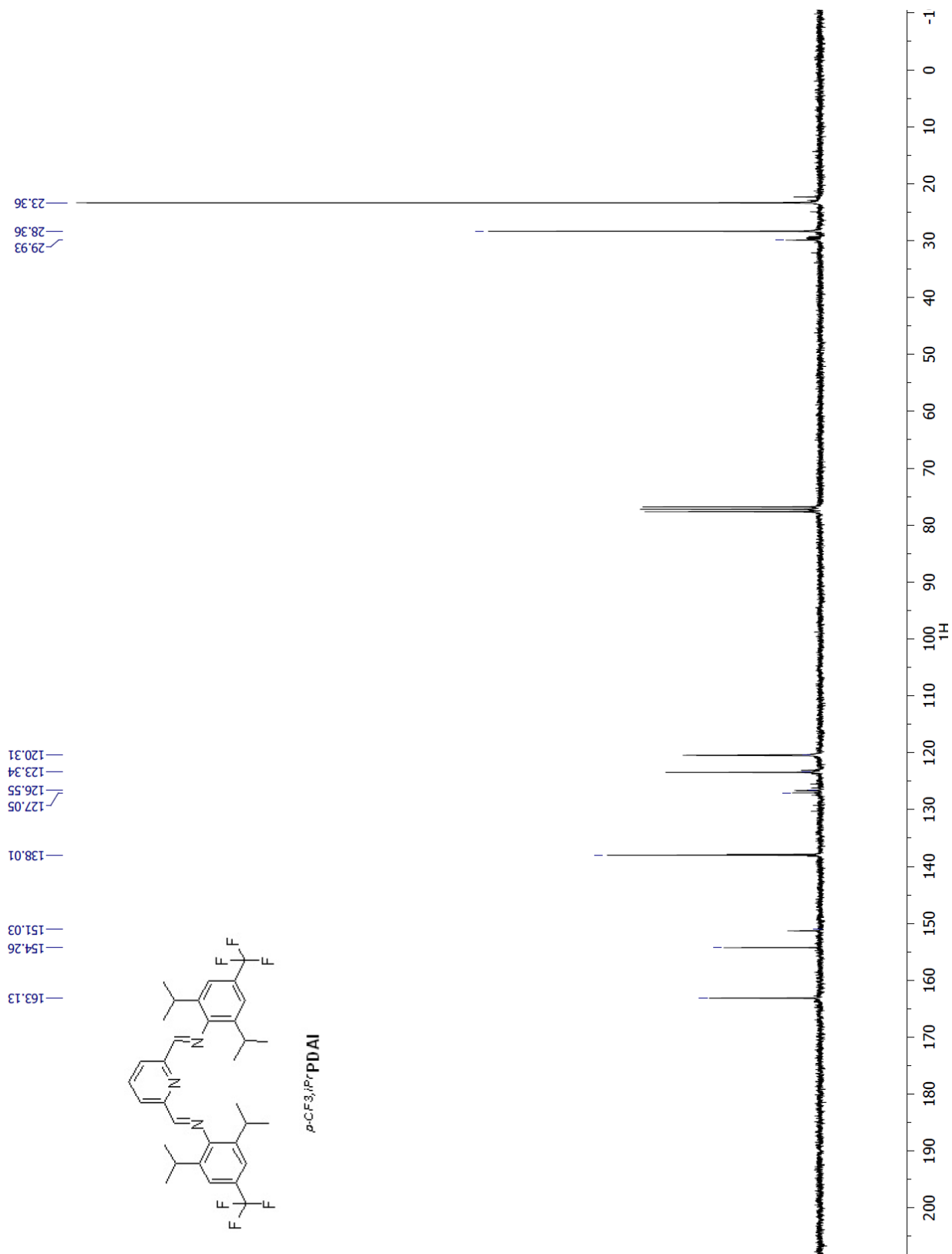


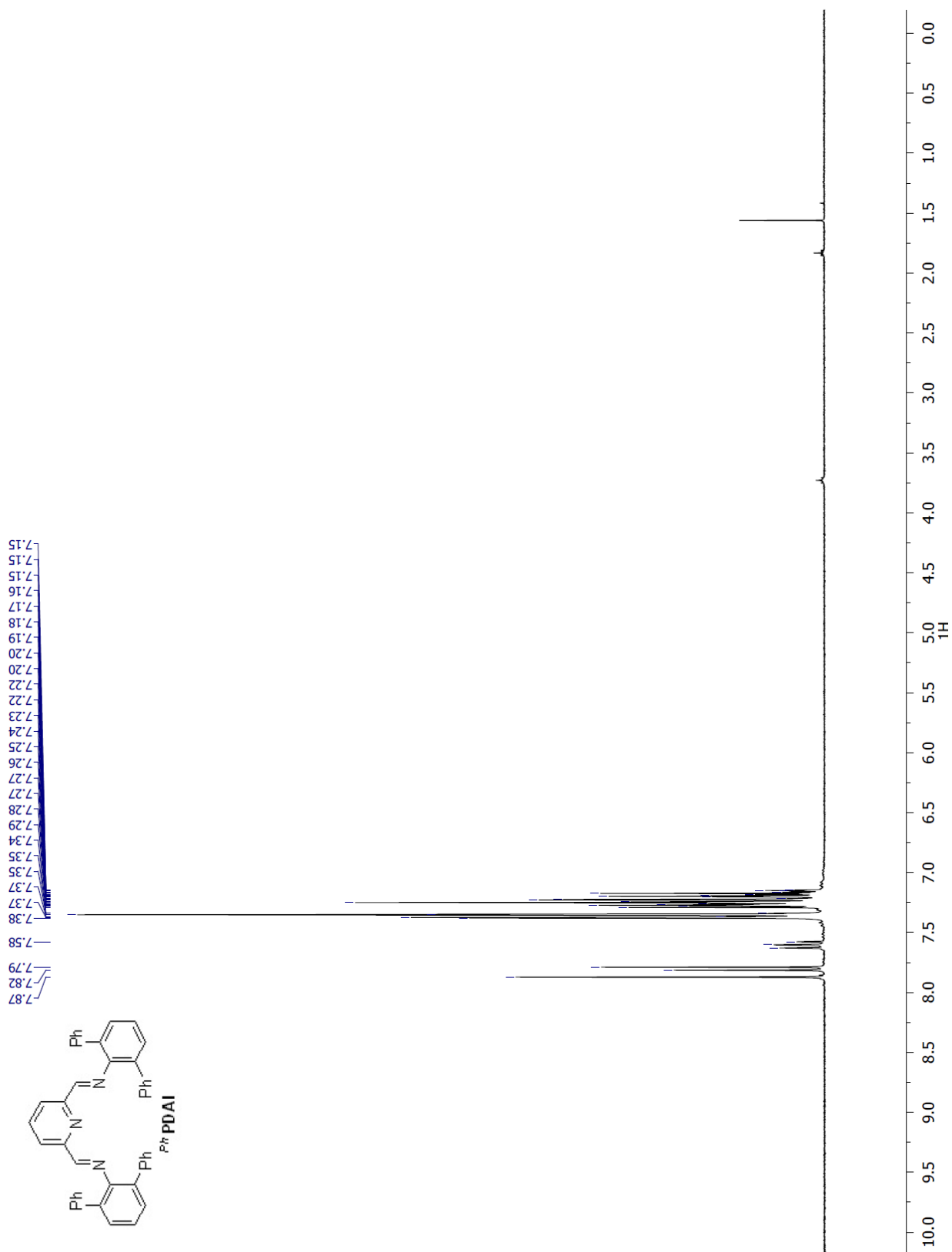


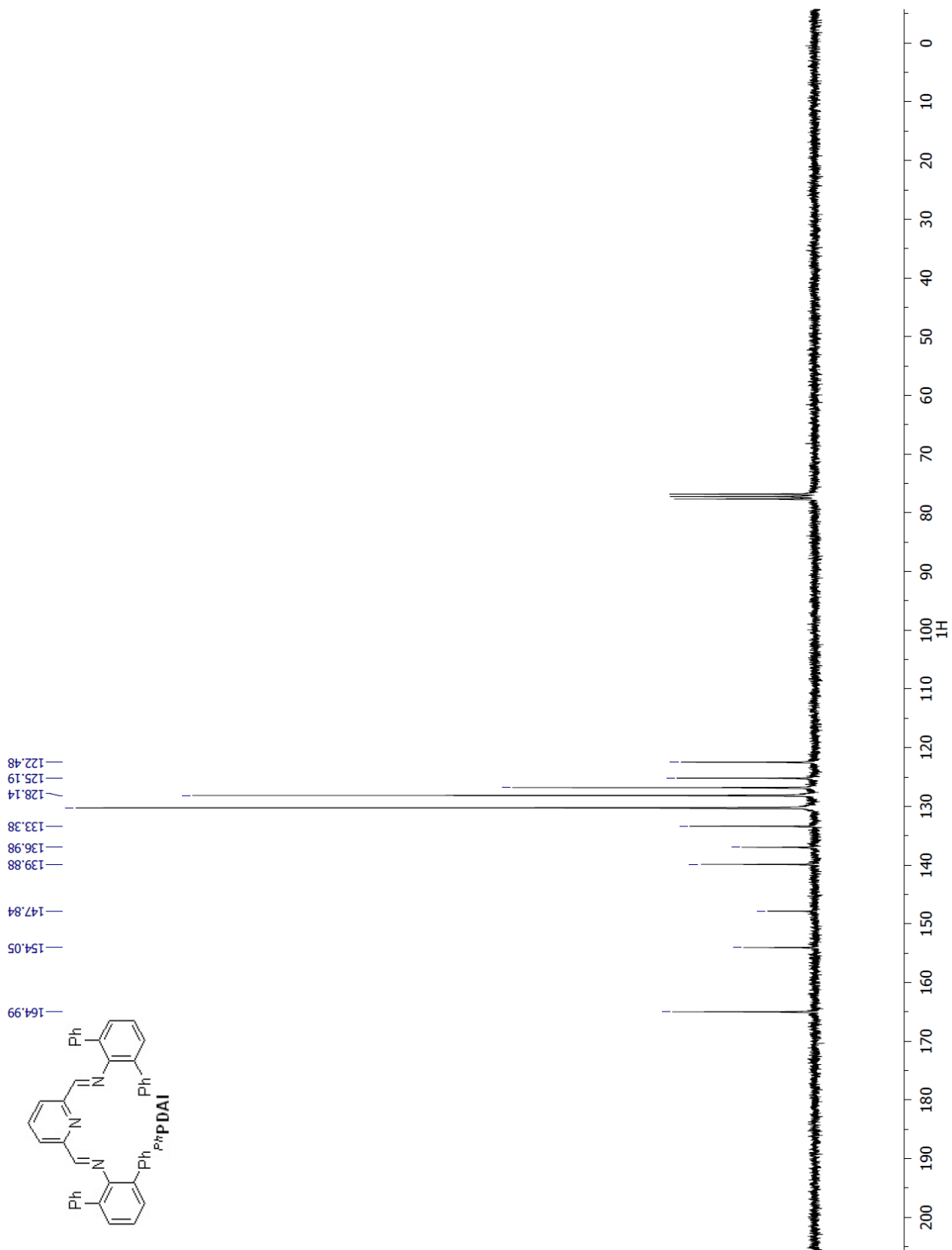


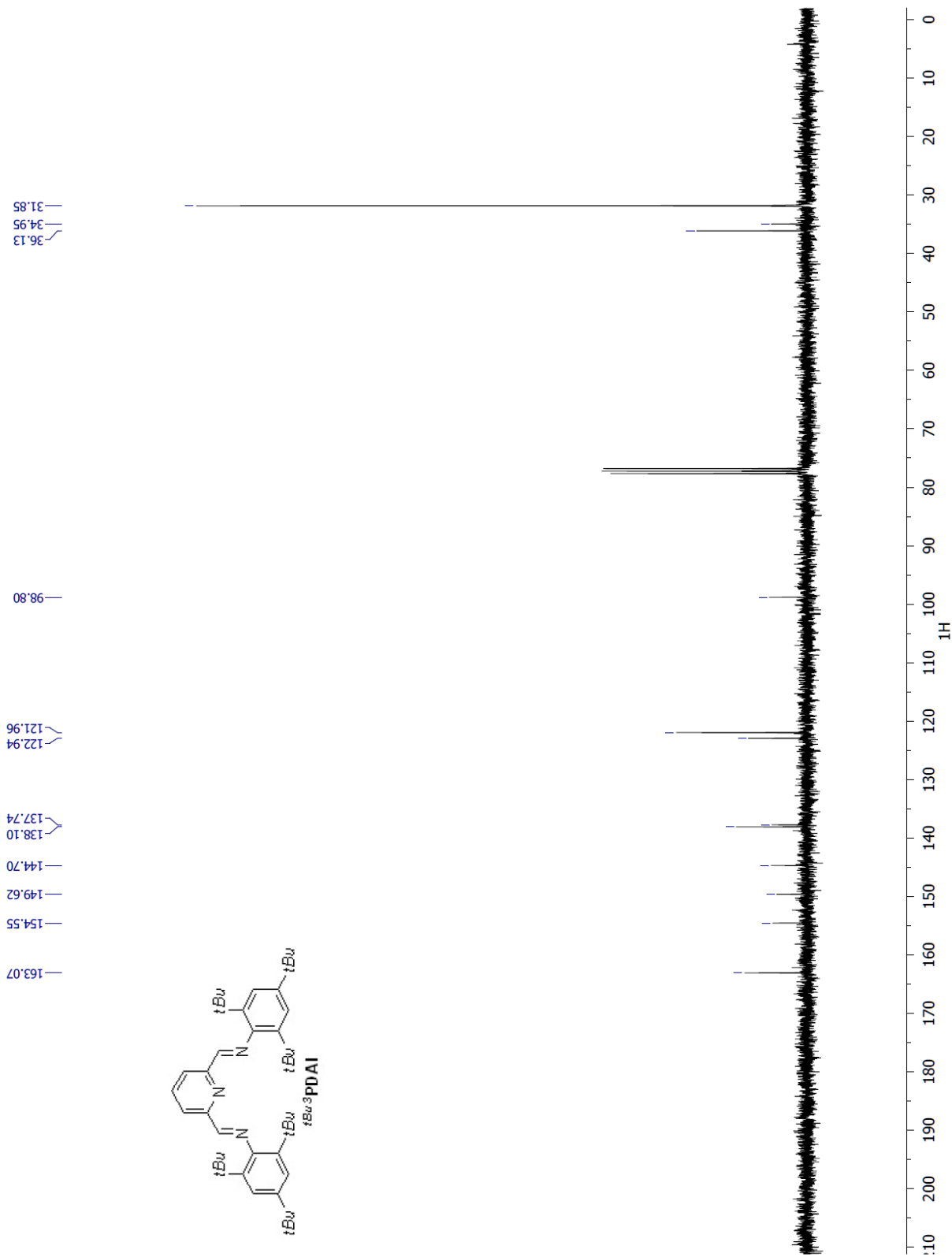


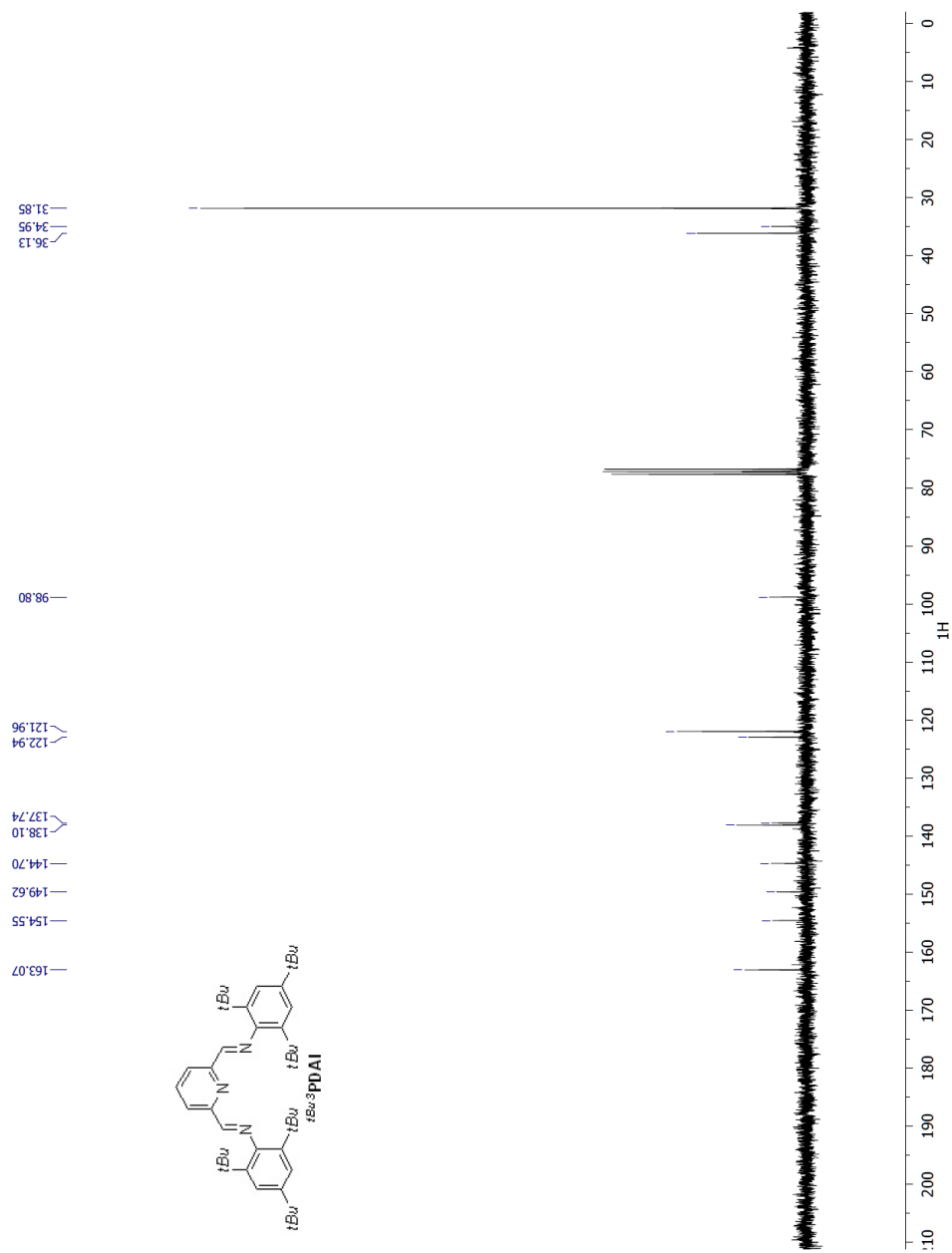












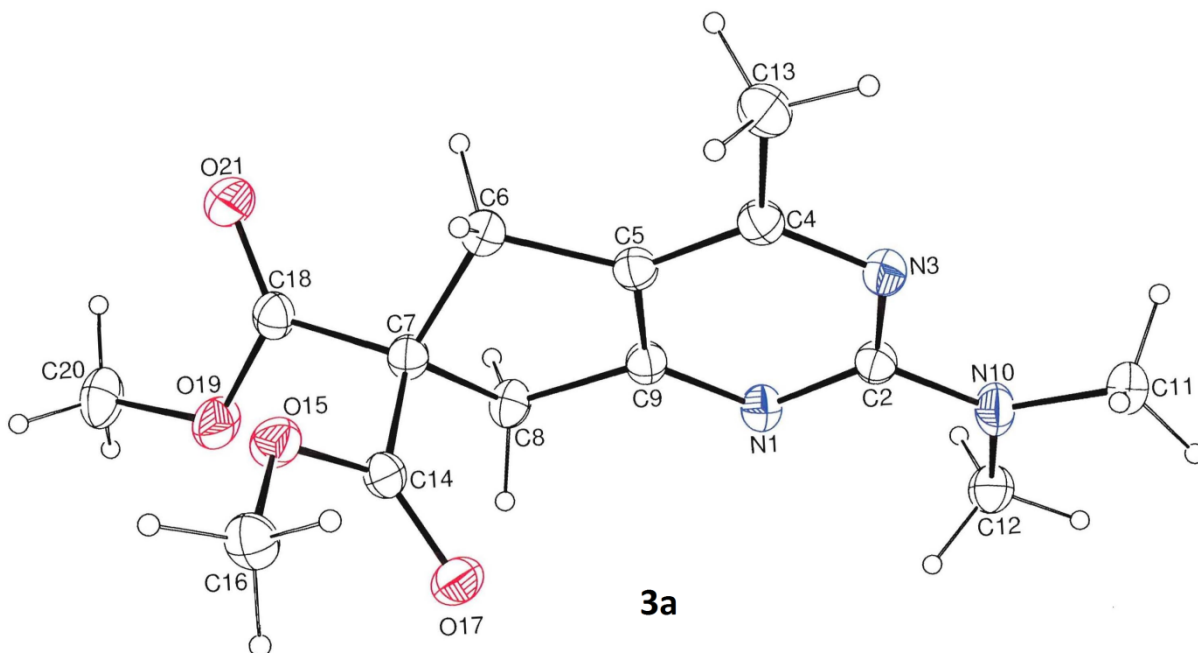


Table 1. Crystal data and structure refinement for **3a**.

Identification code	3a
Empirical formula	C ₁₄ H ₁₉ N ₃ O ₄
Formula weight	293.32
Temperature	150(1) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	<i>P</i> 2₁/c
Unit cell dimensions	a = 7.8233(2) Å a = 90°. b = 20.9085(8) Å b = 113.284(2)°. c = 9.5272(3) Å g = 90°.
Volume	1431.48(8) Å ³
Z	4
Density (calculated)	1.361 Mg/m ³
Absorption coefficient	0.101 mm ⁻¹

F(000)624

Crystal size 0.38 x 0.25 x 0.18 mm³

Theta range for data collection 2.52 to 27.49°.

Index ranges -10<=h<=10, -27<=k<=23, -12<=l<=12

Reflections collected 5098

Independent reflections 3144 [R(int) = 0.0217]

Completeness to theta = 27.49° 95.9 %

Absorption correction Semi-empirical from equivalents

Max. and min. transmission 0.9820 and 0.9626

Refinement method Full-matrix least-squares on F²

Data / restraints / parameters 3144 / 0 / 195

Goodness-of-fit on F² 1.044

Final R indices [I>2sigma(I)] R1 = 0.0513, wR2 = 0.1276

R indices (all data) R1 = 0.0786, wR2 = 0.1456

Largest diff. peak and hole 0.244 and -0.345 e.Å⁻³

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **3a**. $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
O(15)	5295(2)	2122(1)	5456(2)	30(1)
O(17)	4416(2)	1722(1)	3080(2)	32(1)
O(19)	8290(2)	2817(1)	4615(2)	37(1)
O(21)	10059(2)	2323(1)	6796(2)	41(1)
N(1)	7607(2)	435(1)	2167(2)	25(1)
N(3)	7230(2)	-450(1)	3657(2)	26(1)
N(10)	7004(2)	-589(1)	1185(2)	32(1)
C(2)	7299(2)	-189(1)	2384(2)	25(1)
C(4)	7514(2)	-56(1)	4846(2)	25(1)
C(5)	7821(2)	592(1)	4729(2)	24(1)
C(6)	8148(3)	1133(1)	5846(2)	26(1)
C(7)	7682(2)	1731(1)	4784(2)	24(1)
C(8)	8086(3)	1521(1)	3378(2)	26(1)
C(9)	7822(2)	807(1)	3357(2)	23(1)
C(11)	6316(3)	-1235(1)	1187(2)	35(1)
C(12)	7212(3)	-358(1)	-177(2)	32(1)
C(13)	7479(3)	-337(1)	6281(2)	31(1)
C(14)	5611(2)	1864(1)	4301(2)	24(1)
C(16)	3358(3)	2170(1)	5257(2)	31(1)
C(18)	8822(2)	2314(1)	5551(2)	26(1)

C(20) 9373(3) 3399(1) 5105(3) 38(1)

Table 3. Bond lengths [Å] and angles [°] for **3a**.

O(15)-C(14)	1.333(2)
O(15)-C(16)	1.455(2)
O(17)-C(14)	1.206(2)
O(19)-C(18)	1.335(2)
O(19)-C(20)	1.451(2)
O(21)-C(18)	1.198(2)
N(1)-C(9)	1.329(2)
N(1)-C(2)	1.358(2)
N(3)-C(4)	1.346(2)
N(3)-C(2)	1.350(2)
N(10)-C(2)	1.360(2)
N(10)-C(12)	1.453(3)
N(10)-C(11)	1.454(3)
C(4)-C(5)	1.389(3)
C(4)-C(13)	1.498(3)
C(5)-C(9)	1.382(3)
C(5)-C(6)	1.504(3)
C(6)-C(7)	1.559(3)
C(6)-H(6A)	0.9900
C(6)-H(6B)	0.9900
C(7)-C(18)	1.517(3)
C(7)-C(14)	1.525(2)
C(7)-C(8)	1.556(3)

C(8)-C(9)	1.507(3)
C(8)-H(8A)	0.9900
C(8)-H(8B)	0.9900
C(11)-H(11A)	0.9800
C(11)-H(11B)	0.9800
C(11)-H(11C)	0.9800
C(12)-H(12A)	0.9800
C(12)-H(12B)	0.9800
C(12)-H(12C)	0.9800
C(13)-H(13A)	0.9800
C(13)-H(13B)	0.9800
C(13)-H(13C)	0.9800
C(16)-H(16A)	0.9800
C(16)-H(16B)	0.9800
C(16)-H(16C)	0.9800
C(20)-H(20A)	0.9800
C(20)-H(20B)	0.9800
C(20)-H(20C)	0.9800
C(14)-O(15)-C(16)	116.37(14)
C(18)-O(19)-C(20)	117.23(15)
C(9)-N(1)-C(2)	113.77(16)
C(4)-N(3)-C(2)	117.19(16)
C(2)-N(10)-C(12)	120.26(16)
C(2)-N(10)-C(11)	120.66(17)

C(12)-N(10)-C(11) 118.85(16)

N(3)-C(2)-N(1) 126.67(17)

N(3)-C(2)-N(10) 116.90(17)

N(1)-C(2)-N(10) 116.43(17)

N(3)-C(4)-C(5) 120.37(17)

N(3)-C(4)-C(13) 118.11(17)

C(5)-C(4)-C(13) 121.51(17)

C(9)-C(5)-C(4) 117.25(17)

C(9)-C(5)-C(6) 111.20(16)

C(4)-C(5)-C(6) 131.55(17)

C(5)-C(6)-C(7) 102.28(14)

C(5)-C(6)-H(6A) 111.3

C(7)-C(6)-H(6A) 111.3

C(5)-C(6)-H(6B) 111.3

C(7)-C(6)-H(6B) 111.3

H(6A)-C(6)-H(6B) 109.2

C(18)-C(7)-C(14) 110.54(15)

C(18)-C(7)-C(8) 111.14(15)

C(14)-C(7)-C(8) 110.17(15)

C(18)-C(7)-C(6) 112.93(14)

C(14)-C(7)-C(6) 106.90(14)

C(8)-C(7)-C(6) 104.95(14)

C(9)-C(8)-C(7) 102.58(15)

C(9)-C(8)-H(8A) 111.3

C(7)-C(8)-H(8A) 111.3

C(9)-C(8)-H(8B)	111.3
C(7)-C(8)-H(8B)	111.3
H(8A)-C(8)-H(8B)	109.2
N(1)-C(9)-C(5)	124.69(17)
N(1)-C(9)-C(8)	124.18(17)
C(5)-C(9)-C(8)	111.13(16)
N(10)-C(11)-H(11A)	109.5
N(10)-C(11)-H(11B)	109.5
H(11A)-C(11)-H(11B)	109.5
N(10)-C(11)-H(11C)	109.5
H(11A)-C(11)-H(11C)	109.5
H(11B)-C(11)-H(11C)	109.5
N(10)-C(12)-H(12A)	109.5
N(10)-C(12)-H(12B)	109.5
H(12A)-C(12)-H(12B)	109.5
N(10)-C(12)-H(12C)	109.5
H(12A)-C(12)-H(12C)	109.5
H(12B)-C(12)-H(12C)	109.5
C(4)-C(13)-H(13A)	109.5
C(4)-C(13)-H(13B)	109.5
H(13A)-C(13)-H(13B)	109.5
C(4)-C(13)-H(13C)	109.5
H(13A)-C(13)-H(13C)	109.5
H(13B)-C(13)-H(13C)	109.5
O(17)-C(14)-O(15)	124.75(17)

O(17)-C(14)-C(7)	124.85(17)
O(15)-C(14)-C(7)	110.26(15)
O(15)-C(16)-H(16A)	109.5
O(15)-C(16)-H(16B)	109.5
H(16A)-C(16)-H(16B)	109.5
O(15)-C(16)-H(16C)	109.5
H(16A)-C(16)-H(16C)	109.5
H(16B)-C(16)-H(16C)	109.5
O(21)-C(18)-O(19)	124.50(18)
O(21)-C(18)-C(7)	125.46(18)
O(19)-C(18)-C(7)	110.01(15)
O(19)-C(20)-H(20A)	109.5
O(19)-C(20)-H(20B)	109.5
H(20A)-C(20)-H(20B)	109.5
O(19)-C(20)-H(20C)	109.5
H(20A)-C(20)-H(20C)	109.5
H(20B)-C(20)-H(20C)	109.5

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **3a**. The anisotropic displacement factor exponent takes the form: $-2p^2 [h^2 a^2 U_{11} + \dots + 2 h k a^* b^* U_{12}]$

	U11	U22	U33	U23	U13	U12
O(15)	24(1)	36(1)	29(1)	-5(1)	9(1)	1(1)
O(17)	29(1)	35(1)	27(1)	-2(1)	6(1)	-3(1)
O(19)	45(1)	25(1)	33(1)	-1(1)	8(1)	-11(1)
O(21)	37(1)	32(1)	39(1)	-5(1)	-2(1)	-4(1)
N(1)	26(1)	23(1)	28(1)	-3(1)	12(1)	-1(1)
N(3)	26(1)	24(1)	28(1)	-2(1)	8(1)	-1(1)
N(10)	44(1)	22(1)	31(1)	-5(1)	14(1)	-1(1)
C(2)	22(1)	23(1)	27(1)	-2(1)	8(1)	1(1)
C(4)	20(1)	25(1)	28(1)	1(1)	9(1)	0(1)
C(5)	21(1)	24(1)	25(1)	0(1)	8(1)	1(1)
C(6)	27(1)	25(1)	25(1)	-1(1)	9(1)	0(1)
C(7)	25(1)	22(1)	24(1)	-2(1)	10(1)	-1(1)
C(8)	29(1)	24(1)	27(1)	-3(1)	13(1)	-4(1)
C(9)	20(1)	23(1)	26(1)	-2(1)	9(1)	-1(1)
C(11)	41(1)	24(1)	35(1)	-6(1)	8(1)	-1(1)
C(12)	34(1)	32(1)	29(1)	-5(1)	13(1)	3(1)
C(13)	34(1)	29(1)	33(1)	4(1)	15(1)	0(1)
C(14)	27(1)	18(1)	26(1)	1(1)	10(1)	-3(1)
C(16)	26(1)	32(1)	38(1)	-1(1)	15(1)	1(1)
C(18)	25(1)	26(1)	29(1)	-4(1)	12(1)	1(1)

C(20) 50(1) 25(1) 41(1) -7(1) 22(1) -12(1)

Table 5. Hydrogen coordinates (x 104) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$)

for **3a**.

	x	y	z	U(eq)
H(6A)	9456	1142	6597	31
H(6B)	7312	1102	6398	31
H(8A)	7199	1720	2426	32
H(8B)	9371	1633	3514	32
H(11A)	5356	-1230	1605	42
H(11B)	7345	-1511	1818	42
H(11C)	5784	-1400	139	42
H(12A)	6433	21	-565	38
H(12B)	6827	-693	-960	38
H(12C)	8517	-247	76	38
H(13A)	6450	-150	6481	38
H(13B)	8658	-245	7139	38
H(13C)	7307	-801	6161	38
H(16A)	3257	2464	6023	38
H(16B)	2901	1747	5383	38
H(16C)	2612	2333	4232	38
H(20A)	10583	3299	5919	45
H(20B)	8706	3702	5490	45
H(20C)	9563	3590	4238	45

Table 6. Torsion angles [°] for **3a**.

C(4)-N(3)-C(2)-N(1)	-0.8(3)
C(4)-N(3)-C(2)-N(10)	-179.76(15)
C(9)-N(1)-C(2)-N(3)	-1.2(3)
C(9)-N(1)-C(2)-N(10)	177.83(15)
C(12)-N(10)-C(2)-N(3)	-174.70(16)
C(11)-N(10)-C(2)-N(3)	10.9(3)
C(12)-N(10)-C(2)-N(1)	6.2(3)
C(11)-N(10)-C(2)-N(1)	-168.21(17)
C(2)-N(3)-C(4)-C(5)	1.4(2)
C(2)-N(3)-C(4)-C(13)	-178.89(15)
N(3)-C(4)-C(5)-C(9)	-0.1(2)
C(13)-C(4)-C(5)-C(9)	-179.82(16)
N(3)-C(4)-C(5)-C(6)	179.17(16)
C(13)-C(4)-C(5)-C(6)	-0.6(3)
C(9)-C(5)-C(6)-C(7)	18.46(18)
C(4)-C(5)-C(6)-C(7)	-160.83(18)
C(5)-C(6)-C(7)-C(18)	-148.29(15)
C(5)-C(6)-C(7)-C(14)	89.93(16)
C(5)-C(6)-C(7)-C(8)	-27.08(17)
C(18)-C(7)-C(8)-C(9)	148.45(15)
C(14)-C(7)-C(8)-C(9)	-88.67(17)
C(6)-C(7)-C(8)-C(9)	26.07(17)
C(2)-N(1)-C(9)-C(5)	2.6(2)

C(2)-N(1)-C(9)-C(8)	-176.88(16)
C(4)-C(5)-C(9)-N(1)	-2.1(3)
C(6)-C(5)-C(9)-N(1)	178.51(16)
C(4)-C(5)-C(9)-C(8)	177.46(15)
C(6)-C(5)-C(9)-C(8)	-1.9(2)
C(7)-C(8)-C(9)-N(1)	164.03(16)
C(7)-C(8)-C(9)-C(5)	-15.53(19)
C(16)-O(15)-C(14)-O(17)	6.5(3)
C(16)-O(15)-C(14)-C(7)	-169.39(15)
C(18)-C(7)-C(14)-O(17)	135.35(19)
C(8)-C(7)-C(14)-O(17)	12.1(3)
C(6)-C(7)-C(14)-O(17)	-101.4(2)
C(18)-C(7)-C(14)-O(15)	-48.8(2)
C(8)-C(7)-C(14)-O(15)	-172.03(15)
C(6)-C(7)-C(14)-O(15)	74.47(18)
C(20)-O(19)-C(18)-O(21)	4.4(3)
C(20)-O(19)-C(18)-C(7)	-173.58(16)
C(14)-C(7)-C(18)-O(21)	125.1(2)
C(8)-C(7)-C(18)-O(21)	-112.2(2)
C(6)-C(7)-C(18)-O(21)	5.4(3)
C(14)-C(7)-C(18)-O(19)	-57.0(2)
C(8)-C(7)-C(18)-O(19)	65.69(19)
C(6)-C(7)-C(18)-O(19)	-176.68(15)

Symmetry transformations used to generate equivalent atoms:

Crystal Structure Report

Experimental:

A colorless prism shaped crystal 0.38 x 0.25 x 0.18 mm in size was mounted on a glass fiber with traces of viscous oil and then transferred to a Nonius KappaCCD diffractometer equipped with Mo K α radiation ($\lambda = 0.71073 \text{ \AA}$). Ten frames of data were collected at 150(1) K with an oscillation range of 1 deg/frame and an exposure time of 20 sec/frame⁸ Indexing and unit cell refinement based on all observed reflection from those ten frames, indicated a monoclinic *P* lattice. A total of 5098 reflections ($\Theta_{\text{max}} = 27.49^\circ$) were indexed, integrated and corrected for Lorentz, polarization and absorption effects using DENZO-SMN and SCALEPAC.⁹ Post refinement of the unit cell gave $a = 7.8233(2) \text{ \AA}$, $b = 20.9085(8) \text{ \AA}$, $c = 9.5272(3) \text{ \AA}$, $\beta = 113.284(2)$, and $V = 1431.48(8) \text{ \AA}^3$. Axial photographs and systematic absences were consistent with the compound having crystallized in the monoclinic space group *P* 2₁/*c*.

The structure was solved by a combination of direct methods and heavy atom using SIR 97.¹⁰

All of the non-hydrogen atoms were refined with anisotropic displacement coefficients. Hydrogen atoms were assigned isotropic displacement coefficients $U(\text{H}) = 1.2U(\text{C})$ or $1.5U(\text{Cmethyl})$, and their coordinates were allowed to ride on their respective carbons using SHELXL97.¹¹ The weighting scheme employed was $w = 1/[\sigma^2(F_o^2) + (0.0757P)^2 + 0.4926P]$ where $P = (F_o^2 + 2F_c^2)/3$. The refinement converged to $R1 = 0.0513$, $wR2 = 0.1276$, and $S = 1.044$ for 2261 reflections with $1 > 2\sigma(I)$, and $R1 = 0.0786$, $wR2 = 0.1456$, and $S = 1.044$ for 3144 unique reflections and 195 parameters.¹² The maximum Δ/σ in the final cycle of the least-squares was 0, and the residual peaks on the final difference-Fourier map ranged from -0.345 to 0.244 $e/\text{\AA}^3$. Scattering factors were taken from the International Tables for Crystallography, Volume C.^{13, 14, 15, 16}

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