Supporting Information

Synthesis of *N*-benzyl pyridones from *para*-quinone methides (*p*-QMs) at room temperature: Evaluation of *in vitro* blood-stage antiplasmodial activity

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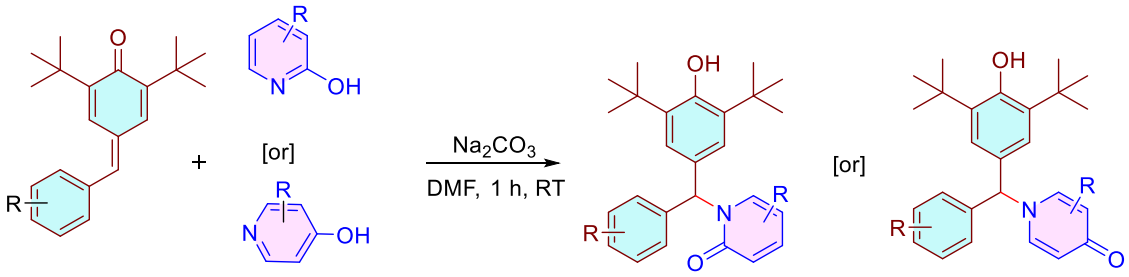
1. Experimental Section: General Information

All chemicals were purchased from commercially available sources and used without further purification. Reactions were performed in the round bottom flask at room temperature. Thin Layer Chromatography was performed using pre-coated plates obtained from E. Merck (TLC silica gel60 F254). TLC plates were visualized by exposure to ultraviolet light (UV) and was further identified with the help of an iodine chamber. Purification of the compounds was performed on silica gel column chromatography (100-200 mesh) using a mixture of ethyl acetate and hexane as an eluent. The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on Bruker spectrometer 300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR respectively with TMS as an internal standard. The HRMS mass spectra were recorded on UHD Q-Tof (ESI-TOF) using a Waters Quattro Micro V 4.1 mass analyzer. p-QMs (**1a–1l**) were prepared using literature procedures.[1]

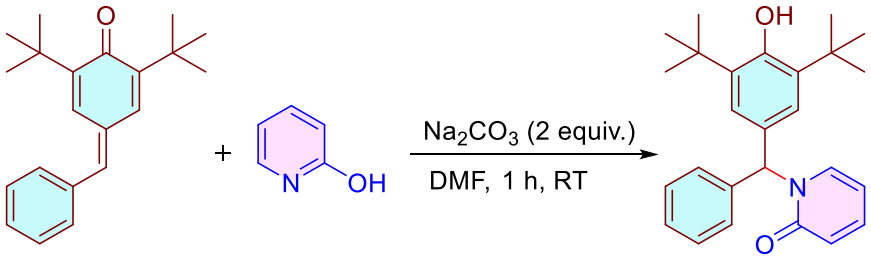
2. Experimental Procedures:

2.2. General procedure for the preparation of *N*-benzyl pyridones:



An oven-dried 25 mL round bottom flask was charged with *p*-QMs (0.34 mmol, 1.0 equiv.), 2-hydroxypyridine or 4-hydroxypyridine (0.51 mmol, 1.5 equiv.) and Na_2CO_3 (0.68 mmol, 2.0 equiv.) in DMSO (3 ml). The resulting solution was stirred at room temperature for 1 h. After completion, the reaction mixture was diluted with water (15 mL) and extracted with ethyl acetate (3x30 mL). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated and purified by silica gel column chromatography (100-200 mesh) using ethyl acetate: hexane.

2.3. Gram scale synthesis of 3a:

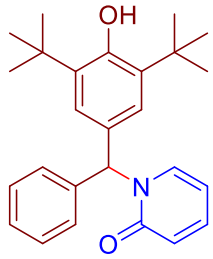


1a	**2a**	**3a; 85%**
1.0 g	0.48 g	1.12g

An oven-dried 100 mL round bottom flask was charged with **1a** (1g, 3.40 mmol, 1.0 equiv.), 2-hydroxypyridine **2a** (5.10 mmol, 1.5 equiv.) and Na_2CO_3 (6.8 mmol, 2.0 equiv.) in DMSO (25 ml). The resulting solution was stirred at room temperature for 1 h. After completion, the reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (3x50 mL). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated and purified by silica gel column chromatography (100-200 mesh) using ethyl acetate: hexane to give **3a** as a colourless foam in 85% (1.12 g) yield.

3. Analytical data for the Products:

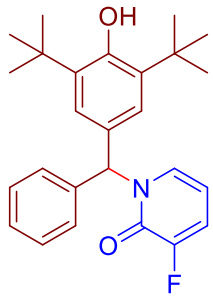
1-((3,5-di-tert-butyl-4-hydroxyphenyl)(phenyl)methyl)pyridin-2(1H)-one (3a):



3a

The title compound was prepared using general procedure 2.2 and then purified by silica column chromatography using 50−70% ethyl acetate in hexane to afford **3a** as a colorless foam (125 mg, 95% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.37 (m, 1H), 7.36 – 7.32 (m, 3H), 7.31 – 7.28 (m, 2H), 7.17 – 7.12 (m, 3H), 6.91 (s, 2H), 6.65 – 6.62 (m, 1H), 6.17 – 6.12 (m, 1H), 5.26 (s, 1H), 1.37 (s, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.7, 153.5, 139.5, 138.9, 136.1, 136.0, 129.0, 128.6, 128.4, 127.6, 125.8, 120.8, 62.1, 34.3, 30.2. HRMS (ESI): m/z [M + H]+ calcd for : $C_{26}H_{32}NO_2$: 390.2433; found: 390.2419

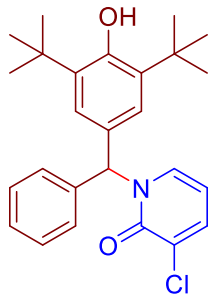
1-((3,5-di-tert-butyl-4-hydroxyphenyl)(phenyl)methyl)-3-fluoropyridin-2(1H)-one (3b):



3b

The title compound was prepared using general procedure 2.2 and then purified by silica column chromatography using 50−70% ethyl acetate in hexane to afford **3b** as a yellow foam (108 mg, 78% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (s, 1H), 7.39 – 7.28 (m, 3H), 7.15 – 7.07 (m, 3H), 7.02 – 6.99 (m, 1H), 6.92 (s, 2H), 6.11 – 6.04 (m, 1H), 5.30 (s, 1H), 1.37 (s, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.3, 156.3, 153.9, 153.6, 150.6, 138.9, 136.2, 131.2 (2), 130.3, 128.6, 128.5, 128.3, 127.8, 125.8, 119.7, 119.5, 103.1, 103.0, 62.7, 34.3, 30.1 HRMS (ESI): m/z [M + H]+ calcd for : $C_{26}H_{31}FNO_2$: 408.2339; found: 408.2274

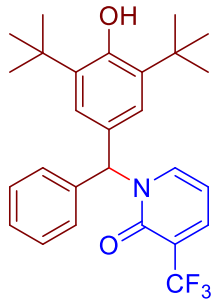
3-chloro-1-((3,5-di-tert-butyl-4-hydroxyphenyl)(phenyl)methyl)pyridin-2(1H)-one (3c):



3c

The title compound was prepared using general procedure 2.2 and then purified by silica column chromatography using 50−70% ethyl acetate in hexane to afford **3c** as a colorless foam (119 mg, 83% yield). ^{1}H NMR (300 MHz, CDCl3) δ 7.54 (d, *J* = 7.2 Hz, 1H), 7.41 (s, 3H), 7.36 – 7.31 (m, 2H), 7.28 – 7.26 (m, 2H), 7.17 – 7.12 (m, 3H), 6.92 – 6.90 (m, 2H), 6.15 – 6.10 (m, 1H), 5.29 (s, 1H), 1.37 (s, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 153.7, 138.9, 137.1, 136.2, 134.6, 128.6, 128.4, 128.3, 127.8, 126.2, 125.8, 104.6, 63.7, 34.3, 30.1. HRMS (ESI): m/z [M + Na]+ calcd for : $C_{26}H_{30}ClNNaO_2$: 446.1863; found: 446.1857

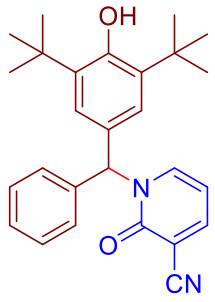
1-((3,5-di-tert-butyl-4-hydroxyphenyl)(phenyl)methyl)-3-(trifluoromethyl)pyridin-2(1H)-one (3d):



3d

The title compound was prepared using general procedure 2.2 and then purified by silica column chromatography using 50−70% ethyl acetate in hexane to afford **3d** as a yellow foam (116 mg, 75% yield). ^{1}H NMR (300 MHz, CDCl3) δ 7.77 (d, *J* = 6.6 Hz, 1H), 7.40 – 7.35 (m, 4H), 7.32 – 7.28 (m, 1H), 7.13 (d, *J* = 6.6 Hz, 2H), 6.91 (s, 2H), 6.25 – 6.20 (m, 1H), 5.32 (s, 1H), 1.37 (s, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.4, 153.8, 140.1, 138.6, 138.4 (2), 136.4, 128.7, 128.2, 128.1, 127.9, 125.8, 124.9, 103.4, 62.9, 34.4, 30.1. HRMS (ESI): m/z [M + H]+ calcd for : $C_{27}H_{30}F_3NNaO_2$: 480.2126; found: 480.2131

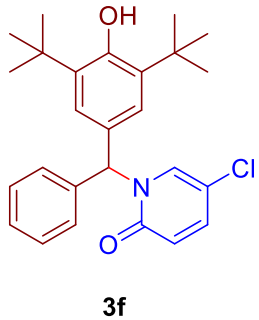
1-((3,5-di-tert-butyl-4-hydroxyphenyl)(phenyl)methyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (3e):



3e

The title compound was prepared using general procedure 2.2 and then purified by silica column chromatography using 50−70% ethyl acetate in hexane to afford **3e** as a yellow foam (108 mg, 77% yield). ^{1}H NMR (300 MHz, CDCl3) δ 7.84 – 7.81 (m, 1H), 7.48 – 7.45 (m, 1H), 7.38 – 7.35 (m, 4H), 7.13 – 7.10 (m, 2H), 6.90 (s, 2H), 6.28 – 6.24 (m, 1H), 5.34 (s, 1H), 1.37 (s, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.7, 154.0, 146.6, 141.3, 138.0, 136.5, 128.9, 128.2, 127.5, 125.8, 115.7, 105.5, 104.8, 63.8, 34.4, 30.1. HRMS (ESI): m/z [M + H]+ calcd for : $C_{27}H_{31}N_2O_2$: 415.2386; found: 415.2345

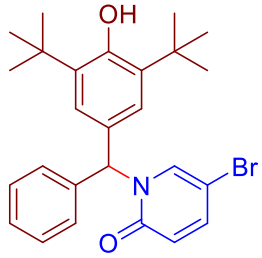
5-chloro-1-((3,5-di-tert-butyl-4-hydroxyphenyl)(phenyl)methyl)pyridin-2(1H)-one (3f):



3f

The title compound was prepared using general procedure 2.2 and then purified by silica column chromatography using 50−70% ethyl acetate in hexane to afford **3f** as a colorless foam (125 mg, 87% yield). ^{1}H NMR (300 MHz, CDCl3) δ 7.37 – 7.35 (m, 3H), 7.32 (s, 1H), 7.28 – 7.27 (m, 1H), 7.19 (s, 1H), 7.13 (d, *J* = 7.2 Hz, 2H), 6.91 (s, 2H), 6.63 – 6.59 (m, 1H), 5.32 (s, 1H), 1.38 (s, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.0, 153.7, 140.0, 138.8, 136.3, 133.5, 128.7, 128.3, 127.9, 125.7, 121.6, 111.9, 62.8, 34.4, 30.1. HRMS (ESI): m/z [M + Na]+ calcd for : $C_{26}H_{30}ClNNaO_2$: 446.1863; found: 446.1864

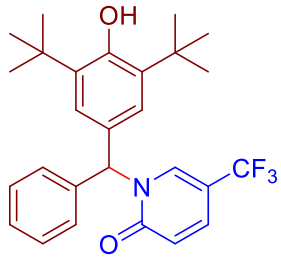
5-bromo-1-((3,5-di-tert-butyl-4-hydroxyphenyl)(phenyl)methyl)pyridin-2(1H)-one (3g):



3g

The title compound was prepared using general procedure 2.2 and then purified by silica column chromatography using 50−70% ethyl acetate in hexane to afford **3g** as a yellow foam (116 mg, 73% yield). ^{1}H NMR (300 MHz, CDCl3) δ 7.39 – 7.35 (m, 5H), 7.28 – 7.27 (m, 2H), 7.13 (d, *J* = 6.3 Hz, 2H), 6.91 – 6.89 (m, 2H), 6.58 – 6.53 (m, 1H), 5.32 – 5.30 (m, 1H), 1.38 (s, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.1, 153.7, 142.1, 138.8, 136.3, 135.9, 128.7, 128.3, 128.2, 127.9, 125.7, 122.0, 97.6, 62.7, 34.4, 30.1. HRMS (ESI): m/z [M + Na]+ calcd for : $C_{26}H_{30}BrNNaO_2$: 490.1358; found: 490.1358

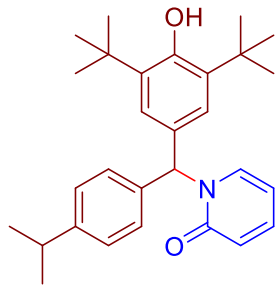
1-((3,5-di-tert-butyl-4-hydroxyphenyl)(phenyl)methyl)-5-(trifluoromethyl)pyridin-2(1H)-one (3h):



3h

The title compound was prepared using general procedure 2.2 and then purified by silica column chromatography using 50−70% ethyl acetate in hexane to afford **3h** as a yellow foam (105 mg, 68% yield). ^{1}H NMR (300 MHz, CDCl3) δ 7.49 – 7.45 (m, 4H), 7.38 – 7.28 (m, 2H), 7.14 – 7.12 (m, 2H), 6.91 (s, 2H), 6.58 – 6.55 (m, 1H), 5.34 – 5.32 (m, 1H), 1.38 (s, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.9, 161.0, 153.9, 153.7, 142.1,138.8, 138.5,136.5,136.3, 135.9, 134.5, 128.8, 128.7, 128.3, 128.2 (2), 128.1, 127.9, 127.8, 125.7 (2), 122.0, 121.3, 97.6, 62.7, 34.4, 30.1 (2). HRMS (ESI): m/z [M + Na]+ calcd for : $C_{27}H_{30}F_3NNaO_2$: 480.2126; found: 480.2131

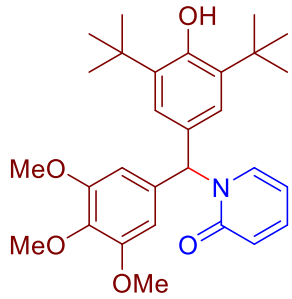
1-((3,5-di-tert-butyl-4-hydroxyphenyl)(4-isopropylphenyl)methyl)pyridin-2(1H)-one (4a):



4a

The title compound was prepared using general procedure 2.2 and then purified by silica column chromatography using 50−70% ethyl acetate in hexane to afford **4a** as a colorless foam (117 mg, 80% yield). ^{1}H NMR (300 MHz, CDCl3) δ 7.39 (s, 1H), 7.36 – 7.28 (m, 1H), 7.21 – 7.16 (m, 3H), 7.06 – 7.03 (m, 2H), 6.91 (s, 2H), 6.65 – 6.62 (m, 1H), 6.16 – 6.11 (m, 1H), 5.28 (s, 1H), 2.95 – 2.86 (m, 1H), 1.37 (s, 18H), 1.25 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.7, 153.4, 148.3, 138.9, 136.8, 136.1, 136.0, 129.1, 128.5, 126.6, 125.6, 120.7, 105.5, 62.0, 34.3, 33.7, 30.2, 23.9. HRMS (ESI): m/z [M + H]+ calcd for : $C_{29}H_{38}NO_2$: 432.2903; found: 432.2901

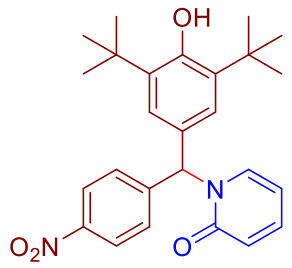
1-((3,5-di-tert-butyl-4-hydroxyphenyl)(3,4,5-trimethoxyphenyl)methyl)pyridin-2(1H)-one (4b):



4b

The title compound was prepared using general procedure 2.2 and then purified by silica column chromatography using 50−70% ethyl acetate in hexane to afford **4b** as a colorless foam (149 mg, 92% yield). ^{1}H NMR (300 MHz, CDCl3) δ 7.38 – 7.32 (m, 2H), 7.16 – 7.13 (m, 1H), 6.92 (s, 2H), 6.65 – 6.62 (m, 1H), 6.33 (s, 2H), 6.18 – 6.13 (m, 1H), 5.29 (s, 1H), 3.84 (s, 3H), 3.74 (s, 6H), 1.37 (s, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.7, 153.5, 153.3, 141.6, 139.1, 137.4, 136.1, 135.9, 135.1, 134.5, 128.6, 125.5, 120.7, 120.5, 106.7, 105.9, 105.6, 67.0, 62.2, 60.8, 60.4, 56.1, 34.3, 30.2. HRMS (ESI): m/z [M + H]+ calcd for : $C_{29}H_{38}NO_5$: 480.2750; found: 480.2710

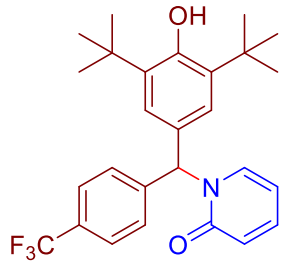
1-((3,5-di-tert-butyl-4-hydroxyphenyl)(4-nitrophenyl)methyl)pyridin-2(1H)-one (4c):



4c

The title compound was prepared using general procedure 2.2 and then purified by silica column chromatography using 50−70% ethyl acetate in hexane to afford **4c** as a yellow foam (117 mg, 80% yield). ^{1}H NMR (300 MHz, CDCl3) δ 8.13 (d, *J* = 8.3 Hz, 2H), 7.32 – 7.21 (m, 1H), 7.21 – 7.19 (m, 4H), 7.03 (d, *J* = 6.9 Hz,1H), 6.80 (s, 2H), 6.67 (d, *J* = 9.0 Hz, 1H), 6.15 – 6.10 (m, 1H), 5.29 (s, 1H), 1.28 (s, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.5, 154.1, 147.2 (2), 139.4, 136.7, 135.3, 128.7, 126.4, 123.8, 120.9, 106.2, 62.3, 34.4, 30.1. HRMS (ESI): m/z [M + H]+ calcd for : $C_{26}H_{31}N_2O_4$: 435.2284; found: 435.2278

1-((3,5-di-tert-butyl-4-hydroxyphenyl)(4-(trifluoromethyl)phenyl)methyl)pyridin-2(1H)-one (4d):

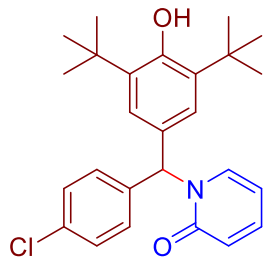


4d

The title compound was prepared using general procedure 2.2 and then purified by silica column chromatography using 50−70% ethyl acetate in hexane to afford **4d** as a yellow foam (124 mg, 80% yield). ^{1}H NMR (300 MHz, CDCl3) δ 7.61 (d, *J* = 8.1 Hz, 2H), 7.42 – 7.35 (m, 2H), 7.28 – 7.23 (m, 2H), 7.13 (d, *J* = 7.2 Hz, 1H), 6.90 (s, 2H), 6.66 (d, *J* = 9.0 Hz, 1H), 6.21 – 6.17 (m, 1H), 5.34 (s, 1H), 1.37 (s, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.6, 153.9, 143.7, 139.2, 136.5, 135.6, 128.4, 128.0, 126.1, 125.5, 125.5, 125.4, 120.9, 105.9, 62.1, 34.4, 30.1. HRMS (ESI):

m/z [M + H]+ calcd for : $C_{27}H_{31}F_3NO_2$: 458.2307; found: 458.2285

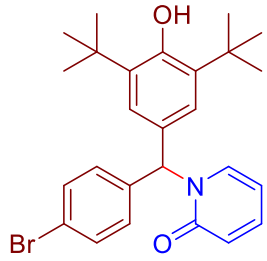
1-((4-chlorophenyl)(3,5-di-tert-butyl-4-hydroxyphenyl)methyl)pyridin-2(1H)-one (4e):



4e

The title compound was prepared using general procedure 2.2 and then purified by silica column chromatography using 50−70% ethyl acetate in hexane to afford **4e** as a colorless foam (121 mg, 84% yield). ^{1}H NMR (300 MHz, CDCl3) δ 7.37 – 7.28 (m, 4H), 7.14 – 7.05 (m, 1H), 6.89 (s, 2H), 6.64 (d, *J* = 9.0 Hz, 1H), 6.18 – 6.14 (m, 1H), 5.32 (s, 1H), 1.37 (s, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.6, 153.7, 139.1, 138.1, 136.3, 135.7, 133.5, 129.6, 128.7, 128.4, 125.8, 120.8, 105.8, 61.7, 34.3, 30.1. HRMS (ESI): m/z [M + H]+ calcd for : $C_{26}H_{31}ClNO_2$: 424.2043; found: 424.2043

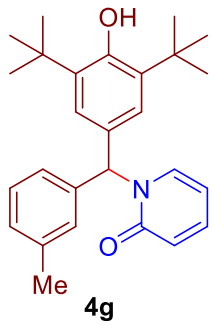
1-((4-bromophenyl)(3,5-di-tert-butyl-4-hydroxyphenyl)methyl)pyridin-2(1H)-one (4f):



4f

The title compound was prepared using general procedure 2.2 and then purified by silica column chromatography using 50−70% ethyl acetate in hexane to afford **4f** as a colorless foam (141 mg, 89% yield). ^{1}H NMR (300 MHz, CDCl3) δ 7.49 – 7.47 (m, 2H), 7.46 – 7.28 (m, 2H), 7.14 – 7.13 (m, 1H), 7.11 – 7.02 (m, 2H), 6.99 (s, 2H), 6.89 – 6.63 (m, 1H), 6.19 – 6.14 (m, 1H), 5.31 (s, 1H), 1.37 (s, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.5, 153.7, 139.1, 138.7, 136.3, 135.7, 131.7, 130.0, 128.3, 125.8, 121.6, 120.8, 105.8, 61.8, 34.3, 30.1. HRMS (ESI): m/z [M + Na]+ calcd for : $C_{26}H_{30}BrNNaO_2$: 490.1358; found: 490.1362

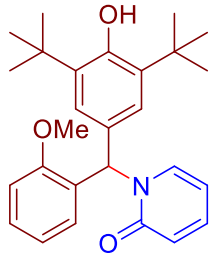
1-((3,5-di-tert-butyl-4-hydroxyphenyl)(m-tolyl)methyl)pyridin-2(1H)-one (4g):



4g

The title compound was prepared using general procedure 2.2 and then purified by silica column chromatography using 50−70% ethyl acetate in hexane to afford **4g** as a colorless foam (120 mg, 88% yield). ^{1}H NMR (300 MHz, CDCl3) δ 7.38 – 7.38 (m, 1H), 7.35 – 7.33 (m, 1H), 7.31 – 7.28 (m, 1H), 7.25 – 7.20 (m, 1H), 7.18 – 7.15 (m, 1H), 7.12 – 6.98 (m, 1H), 6.91 (s, 2H), 6.89 – 6.62 (m, 1H), 6.17 – 6.12 (m, 1H), 5.28 (s, 1H), 2.32 (s, 3H), 1.37 (s, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.7, 153.4, 139.4, 138.9, 138.2, 136.1, 136.0, 129.3, 129.0, 128.4 (2), 125.8, 125.4, 120.7, 105.5, 62.2, 34.3, 30.1. 21.4. HRMS (ESI): m/z [M + H]+ calcd for : C27H34NO2: 404.2590; found: 404.2585

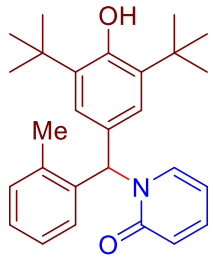
1-((3,5-di-tert-butyl-4-hydroxyphenyl)(2-methoxyphenyl)methyl)pyridin-2(1H)-one (4h):



4h

The title compound was prepared using general procedure 2.2 and then purified by silica column chromatography using 50−70% ethyl acetate in hexane to afford **4h** as a yellow foam (113 mg, 80% yield). ^{1}H NMR (300 MHz, CDCl3) δ 7.51 (s, 1H), 7.36 – 7.28 (m, 1H), 7.12 – 7.10 (m, 1H), 6.93 – 6.92 (m, 1H), 6.91 (s, 2H), 6.89 – 6.82 (m, 3H), 6.64 – 6.61 (m, 1H), 6.12 – 6.07 (m, 1H), 5.20 (s, 1H), 3.76 (s, 3H), 1.36 (s, 18H).^{13}C NMR (75 MHz, $CDCl_3$) δ 162.5, 157.4, 153.1, 138.8, 135.9, 135.8, 129.9, 129.3, 128.4, 128.2, 120.6, 120.2, 110.8, 105.0, 58.0, 55.6, 34.3, 30.2. HRMS (ESI): m/z [M + H]+ calcd for : $C_{27}H_{34}NO_3$: 420.2539; found: 420.2530

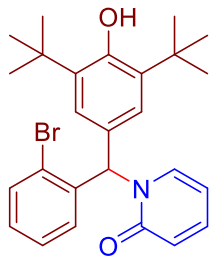
1-((3,5-di-tert-butyl-4-hydroxyphenyl)(o-tolyl)methyl)pyridin-2(1H)-one (4i):



4i

The title compound was prepared using general procedure 2.2 and then purified by silica column chromatography using 50−70% ethyl acetate in hexane to afford **4i** as a colorless foam (120 mg, 88% yield). ^{1}H NMR (300 MHz, CDCl3) δ 7.39 – 7.32 (m, 2H), 7.30 – 7.22 (m, 1H), 7.21 – 7.15 (m, 1H), 7.14 – 7.12 (m, 1H), 7.09 – 7.06 (m, 1H), 6.86 – 6.78 (m, 3H), 6.65 – 6.62 (m, 1H), 6.16 – 6.11 (m, 1H), 5.25 (s, 1H), 2.23 (s, 3H), 1.36 (s, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.5, 153.3, 138.9, 138.1, 137.4, 136.1, 136.0, 130.9, 128.3, 128.2, 127.9, 125.9, 125.2, 120.7, 105.4, 60.3, 34.3, 30.2, 19.3. HRMS (ESI): m/z [M + H]+ calcd for : $C_{27}H_{34}NO_2$: 404.2590; found: 404.2594

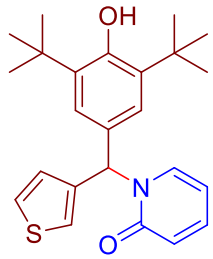
1-((2-bromophenyl)(3,5-di-tert-butyl-4-hydroxyphenyl)methyl)pyridin-2(1H)-one (4j):



4j

The title compound was prepared using general procedure 2.2 and then purified by silica column chromatography using 50−70% ethyl acetate in hexane to afford **4j** as a colorless foam (137 mg, 86% yield). ^{1}H NMR (300 MHz, CDCl3) δ 7.64 – 7.62 (m, 1H), 7.42 – 7.36 (m, 1H), 7.35 – 7.30 (m, 1H), 7.28 – 7.25 (m, 1H), 7.22 – 7.17 (m, 1H), 7.02 – 7.00 (m, 1H), 6.99 – 6.83 (m, 3H), 6.65 – 6.62 (m, 1H), 6.16 – 6.12 (m, 1H), 5.25 (s, 1H), 1.36 (s, 18H).^{13}C NMR (75 MHz, $CDCl_3$) δ 162.4, 153.5, 139.3, 139.0, 136.2, 135.6, 133.6, 130.2, 129.4, 127.4, 127.3, 125.3, 125.2, 121.0, 105.4, 63.0, 34.3, 30.2. HRMS (ESI): m/z [M + H]+ calcd for : $C_{26}H_{31}BrNO_2$: 468.1538; found: 468.1434

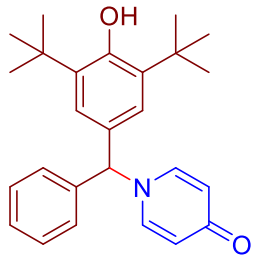
1-((3,5-di-tert-butyl-4-hydroxyphenyl)(thiophen-3-yl)methyl)pyridin-2(1H)-one (4k):



4k

The title compound was prepared using general procedure 2.2 and then purified by silica column chromatography using 50−70% ethyl acetate in hexane to afford **4k** as a yellow foam (111 mg, 83% yield). ^{1}H NMR (300 MHz, CDCl3) δ 7.44 (s, 1H), 7.36 – 7.34 (m, 2H), 7.33 – 7.28 (m, 1H), 7.23 – 7.21 (m, 1H), 6.98 (s, 2H), 6.92 – 6.91 (m, 2H), 6.65 – 6.62 (m, 1H), 6.17 – 6.13 (m, 1H), 5.28 – 5.26 (m, 1H), 1.38 (s, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.4, 153.5, 140.9, 139.0, 136.1 (2), 135.6, 129.1, 127.6, 126.5, 125.1, 124.1, 120.7, 105.7, 58.3, 34.3, 30.2. HRMS (ESI): m/z [M + H]+ calcd for : $C_{24}H_{30}NO_2S$: 396.1997; found: 396.1993

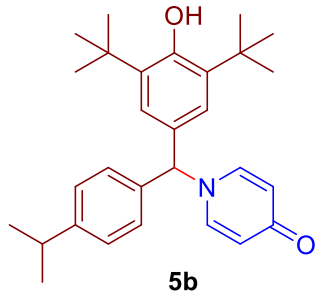
1-((3,5-di-tert-butyl-4-hydroxyphenyl)(phenyl)methyl)pyridin-4(1H)-one (5a):



5a

The title compound was prepared using general procedure 2.2 and then purified by silica column chromatography using 15−30% ethyl acetate in hexane to afford **5a** as a colorless foam (119 mg, 90% yield). ^{1}H NMR (300 MHz, CDCl3) δ 7.40 – 7.38 (m, 3H), 7.32 – 7.28 (m, 2H), 7.0.9 (d, *J* = 6.9 Hz, 2H), 6.86 (s, 2H), 6.40 (d, *J* = 7.2 Hz, 2H), 6.27 (s, 1H), 5.51 – 5.49 (m, 1H), 1.37 (s, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.2, 154.3, 139.6, 138.1, 136.9, 129.0, 128.7, 128.0, 127.4, 125.4, 118.4, 73.1, 34.4, 30.1. HRMS (ESI): m/z [M + H]+ calcd for : $C_{26}H_{32}NO_2$: 390.2433; found: 390.2427

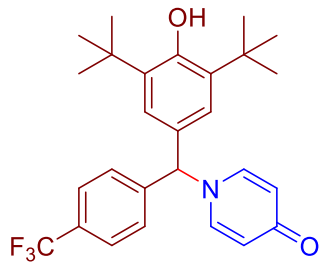
1-((3,5-di-tert-butyl-4-hydroxyphenyl)(4-isopropylphenyl)methyl)pyridin-4(1H)-one (5b):



5b

The title compound was prepared using general procedure 2.2 and then purified by silica column chromatography using 15−30% ethyl acetate in hexane to afford **5b** as a yellow foam (109 mg, 75% yield). ^{1}H NMR (300 MHz, CDCl3) δ 7.35 – 7.24 (m, 5H), 7.02 – 6.99 (m, 2H), 6.85 (s, 2H), 6.43 – 6.41 (m, 1H), 6.24 (s, 1H), 5.26 (s, 1H), 2.98 – 2.91 (m, 1H), 1.37 (s, 18H), 1.26 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.2, 154.2, 149.6, 139.8, 136.7, 135.2, 128.2, 127.7, 127.1, 125.1, 118.2, 73.0, 34.4, 33.8, 30.1, 23.8. HRMS (ESI): m/z [M + H]+ calcd for : $C_{29}H_{38}NO_2$: 432.2903; found: 432.2899

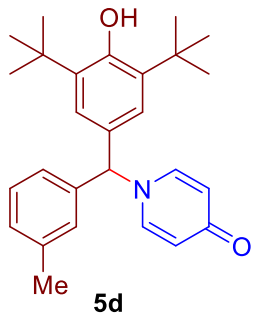
1-((3,5-di-tert-butyl-4-hydroxyphenyl)(4-(trifluoromethyl)phenyl)methyl)pyridin-4(1H)-one (5c):



5c

The title compound was prepared using general procedure 2.2 and then purified by silica column chromatography using 15−30% ethyl acetate in hexane to afford **5c** as a yellow foam (105 mg, 68% yield). ^{1}H NMR (300 MHz, CDCl3) δ 7.70 – 7.67 (m, 3H), 7.33 – 7.28 (m, 2H), 7.24 – 7.22 (m, 2H), 6.86 (s, 2H), 6.47 – 6.44 (m, 2H), 6.17 – 6.33 (s, 1H), 1.38 (s, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.2, 154.6, 142.3, 139.4, 137.1, 128.2, 126.3, 126.1, 126.0, 125.1, 118.6, 72.6, 34.4, 30.0. HRMS (ESI): m/z [M + H]+ calcd for : $C_{27}H_{31}F_3NO_2$: 458.2307; found: 458.2309

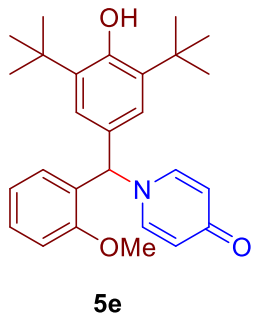
1-((3,5-di-tert-butyl-4-hydroxyphenyl)(m-tolyl)methyl)pyridin-4(1H)-one (5d):



5d

The title compound was prepared using general procedure 2.2 and then purified by silica column chromatography using 15−30% ethyl acetate in hexane to afford **5d** as a yellow foam (96 mg, 70% yield). ^{1}H NMR (300 MHz, CDCl3) δ 7.33 – 7.26 (m, 3H), 7.19 – 7.17 (m, 1H), 6.91 (s, 2H), 6.86 (s, 2H), 6.40 (d, *J* = 7.5 Hz, 2H), 6.23 (s, 1H), 5.50 (s, 1H), 2.35 (s, 3H), 1.37 (s, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.0, 154.2, 139.7, 138.9, 138.0, 136.8, 129.5, 128.9, 128.7, 127.4, 125.3, 125.1, 118.3, 34.3, 30.1, 21.4. HRMS (ESI): m/z [M + H]+ calcd for : $C_{27}H_{34}NO_2$: 404.2590; found: 404.2577

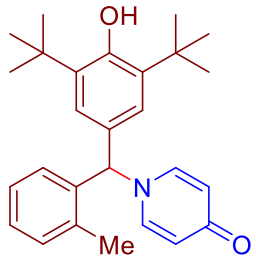
1-((3,5-di-tert-butyl-4-hydroxyphenyl)(2-methoxyphenyl)methyl)pyridin-4(1H)-one (5e):



5e

The title compound was prepared using general procedure 2.2 and then purified by silica column chromatography using 15−30% ethyl acetate in hexane to afford **5e** as a yellow foam (93 mg, 66% yield). ^{1}H NMR (300 MHz, CDCl3) δ 7.42 – 7.36 (m, 1H), 7.32 – 7.28 (m, 2H), 6.98 – 6.93 (m, 2H), 6.84 – 6.82 (m, 3H), 6.53 (s, 1H), 6.39 (d, *J* = 6.9 Hz, 2H), 5.40 (s, 1H), 3.80 (s, 1H), 1.38 (s, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.2, 157.1, 153.8, 139.7, 136.6 (2), 130.5, 129.7, 126.2, 124.3, 120.7, 118.0, 110.9, 67.4, 55.6, 34.4, 30.1. HRMS (ESI): m/z [M + H]+ calcd for : C27H34NO3: 420.2539; found: 420.2530

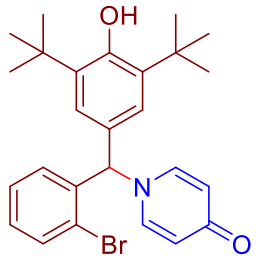
1-((3,5-di-tert-butyl-4-hydroxyphenyl)(o-tolyl)methyl)pyridin-4(1H)-one (5f):



5f

The title compound was prepared using general procedure 2.2 and then purified by silica column chromatography using 15−30% ethyl acetate in hexane to afford **5f** as a colorless foam (89 mg, 65% yield). ^{1}H NMR (300 MHz, CDCl3) δ 7.31 – 7.21 (m, 5H), 6.81 (s, 2H), 6.74 (d, *J* = 7.5 Hz, 1H), 6.42 (d, *J* = 7.5 Hz, 2H), 6.34 (s, 1H), 5.43 (s, 1H), 2.21 (s, 3H), 1.37 (s, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.2, 154.1, 139.7, 136.8, 136.5, 136.3, 131.2, 128.9, 128.0, 127.0, 126.6, 124.8, 118.4, 70.5, 34.4, 30.1, 19.3. HRMS (ESI): m/z [M + H]+ calcd for : $C_{27}H_{34}NO_2$: 404.2590; found: 404.2591

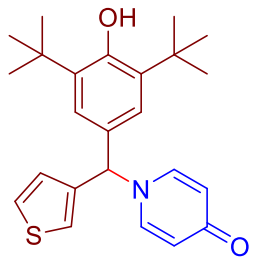
1-((2-bromophenyl)(3,5-di-tert-butyl-4-hydroxyphenyl)methyl)pyridin-4(1H)-one (5g):



5g

The title compound was prepared using general procedure 2.2 and then purified by silica column chromatography using 15−30% ethyl acetate in hexane to afford **5g** as a yellow foam (98 mg, 62% yield). ^{1}H NMR (300 MHz, CDCl3) δ 7.68 (d, *J* = 7.5 Hz, 1H), 7.36 – 7.28 (m, 4H), 6.91 – 6.89 (m, 1H), 6.81 (s, 2H), 6.52 (s, 1H), 6.42 (d, *J* = 6.6 Hz, 1H), 5.44 (s, 1H), 1.38 (s, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.2, 154.2, 139.7, 137.4, 136.9, 133.8, 13-.5, 130.2, 128.0, 126.4, 124.9, 124.8, 118.5, 72.2, 34.4, 30.1. HRMS (ESI): m/z [M + H]+ calcd for : $C_{26}H_{31}BrNO_2$: 468.1538; found: 468.1538

1-((3,5-di-tert-butyl-4-hydroxyphenyl)(thiophen-3-yl)methyl)pyridin-4(1H)-one (5h):



5h

The title compound was prepared using general procedure 2.2 and then purified by silica column chromatography using 15−30% ethyl acetate in hexane to afford **5h** as a yellow foam (80 mg, 60% yield). ^{1}H NMR (300 MHz, CDCl3) δ 7.44 – 7.42 (m, 1H), 7.38 – 7.35 (m, 2H), 6.92 – 6.91 (m, 4H), 6.42 (d, *J* = 7.8 Hz, 2H), 6.24 (s, 1H). 1.37 (s, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.3, 154.3, 139.3, 136.8, 135.3, 128.6, 127.7, 127.6, 127.4, 127.0, 126.8, 125.0, 124.5, 118.4, 69.4, 34.4, 30.1, 29.6, 29.5. HRMS (ESI): m/z [M + H]+ calcd for : C24H30NO2S: 396.1997; found: 396.1997

SUPPORTING DATA FOR ANTIMALARIAL WORK:

Materials

Powdered RPMI 1640 medium, AlbuMAX II are Gibco products from Invitrogen Corporation. Chloroquine, artemisinin, Histopaque-1077, and Giemsa stains were obtained from Sigma-Aldrich. All other chemicals used were of analytical grade.

In vitro culture of P. falciparum 3D7 strain

P. falciparum 3D7, the human malarial parasites, were maintained through continuous passage in human erythrocytes with a hematocrit of 4-5%. The growth medium was composed of RPMI 1640 supplemented with AlbuMAX (5 g/L, a lipid-rich bovine albumin), glucose (6 g/L), hypoxanthine (50 mg/L), sodium bicarbonate (2 g/L), and gentamycin sulphate (10 mg/L). The parasites were incubated at 37 °C in a low-oxygen environment using the candle jar technique [2]. A Histopaque gradient was used to obtain 100% packed RBC. Blood smears were fixed with methanol and stained using Giemsa solution (1:10) to identify parasite stages. The level of parasitemia was determined by manually counting infected and uninfected red blood cells (RBCs) using a cell counter and calculating the percentage

SYBR Green I assay for antiplasmodial activity

A SYBR Green I fluorescence assay was used to assess the impact of the test compound on plasmodial growth, following an established protocol [3]. The compounds were initially solubilized in DMSO at 10 mg/mL and then diluted to 100µg/mL in RPMI medium. A 96-well microdilution plate was used to prepare six 2-fold dilutions ranging from 25 µg/mL to 0.75 µg/mL. The final DMSO concentration in the diluted compounds was maintained below 0.5% to avoid toxicity to parasites. Chloroquine (10 mg/mL) was prepared using sterile distilled water, and artemisinin was dissolved in DMSO. These served as positive controls at 500 µg/mL and 5 µg/mL (complete inhibition), respectively, with a drug-free group acting as the negative control. Asynchronous infected erythrocytes (1% parasitemia, 2% hematocrit) were subjected to the test compounds for 48 hours [4] at 37°C in a candle jar. After incubation, 100 µL of 0.2µL/mL of 10,000 × SYBR Green-I in lysis buffer (20mM Tris-HCl, 5mM EDTA, 0.008% saponin, 0.08% Triton X) was introduced and kept in the dark for 2 h at room temperature. Parasite viability was determined by measuring the fluorescence of DNA-bound SYBR Green-I using a multimode plate reader (Synergy Bioteck) at excitation and emission wavelengths of 485 nm and 528 nm, respectively. Fluorescence readings were plotted against drug concentration to calculate the 50% inhibitory concentration (IC50) values using nonlinear regression analysis in Microsoft Excel. All experiments were conducted in triplicate, and the results are presented as the mean ± SD from at least three independent experiments.

4. References

1. R. Venkatesh, G. Shankar, A. C. Narayanan, G. Modi, S. Sabiah and J. Kandasamy, *J. Org. Chem.*, 2022, **87**, 6730–6741.
2. J. B. Jensen, W. Trager, *J. Parasitol.*, 1977, 883-886.
3. M. Smilkstein, N. Sriwilaijaroen, J. X. Kelly, P. Wilairat and M. Riscoe, *Antimicrob. Agents Chemother.*, 2004, **48**, 1803-1806.
4. L. M. Sanz, B. Crespo, C. De-Cozar, X. C. Ding, J. L. Llergo, J. N. Burrows, J. F. Garcia-Bustos and F. J. Gamo, *PLoS One*, 2012, **7**, e30949.

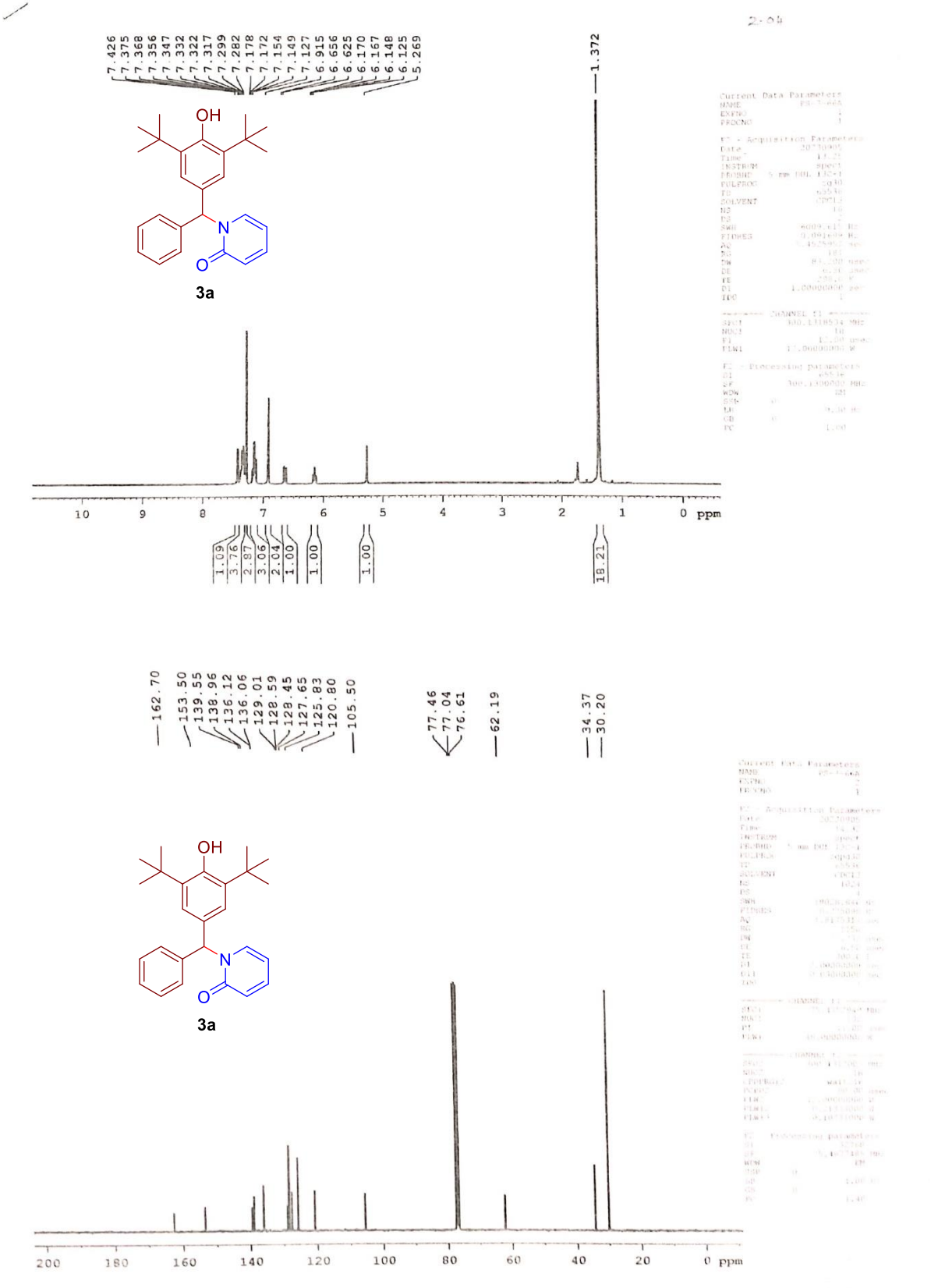


Figure 5.1. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) Spectra of (**3a**) in $CDCl_3$

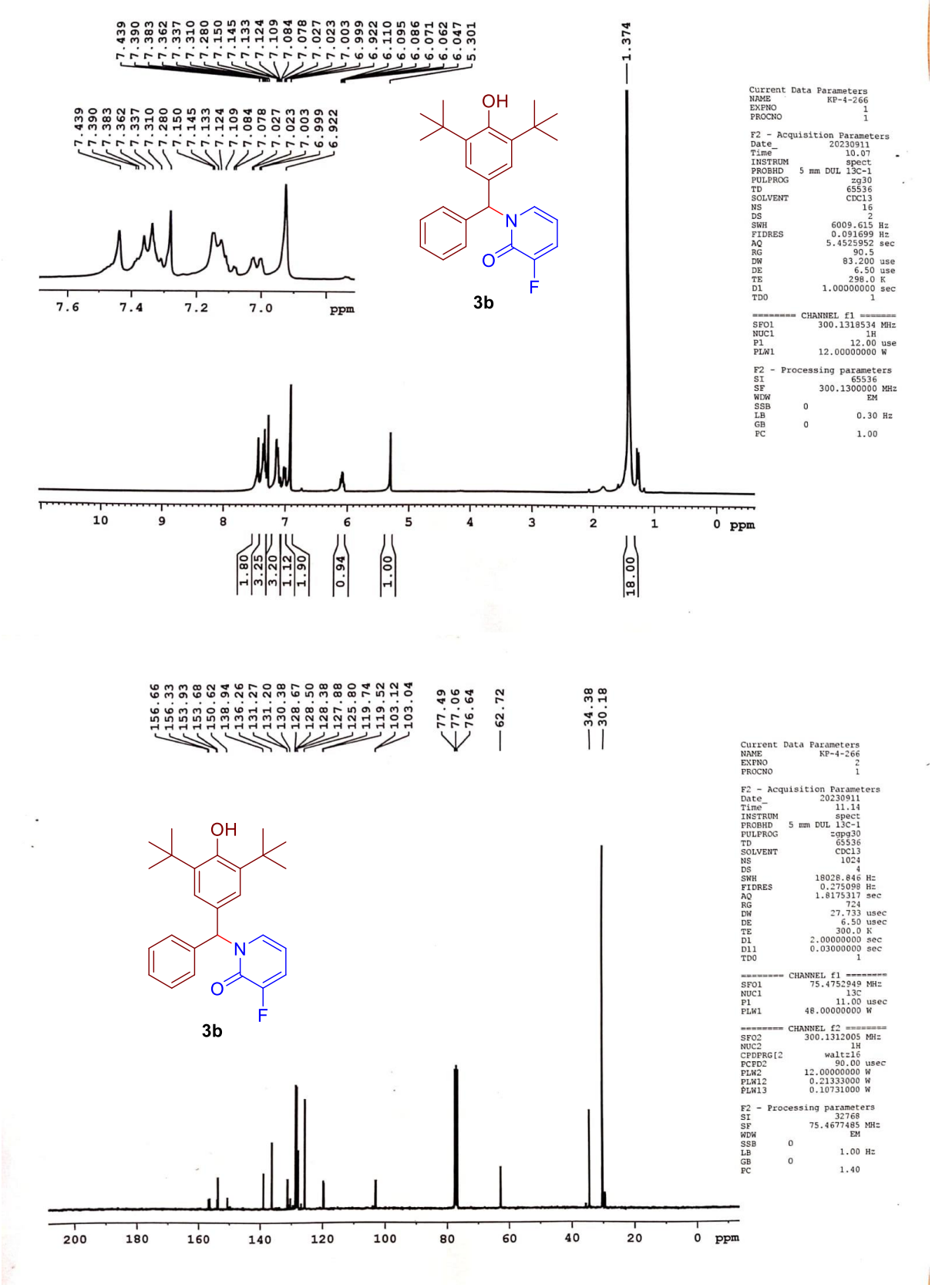


Figure 5.2. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) Spectra of (**3b**) in $CDCl_3$

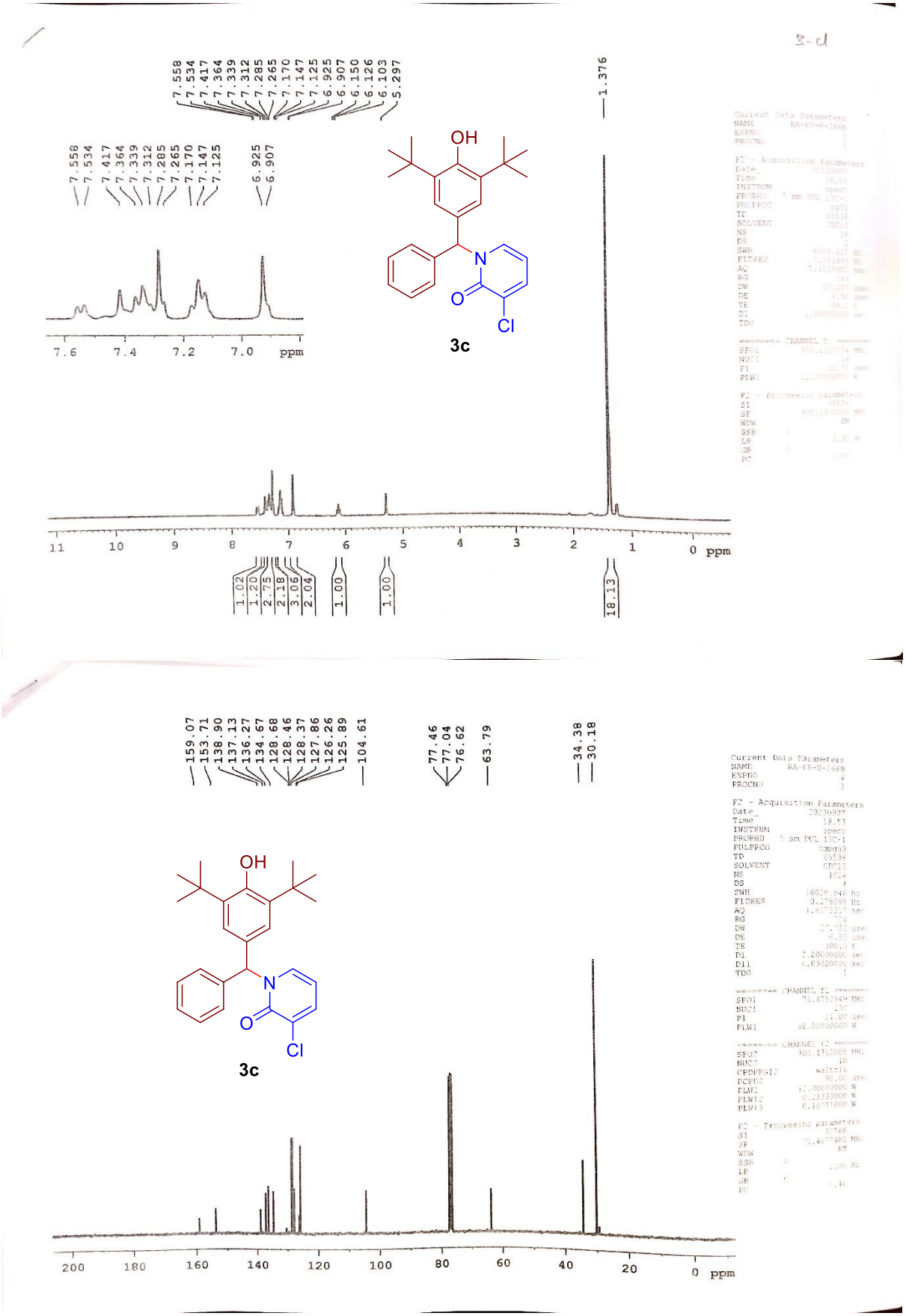


Figure 5.3. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) Spectra of (**3c**) in $CDCl_3$

Figure 5.4. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) Spectra of (**3d**) in $CDCl_3$

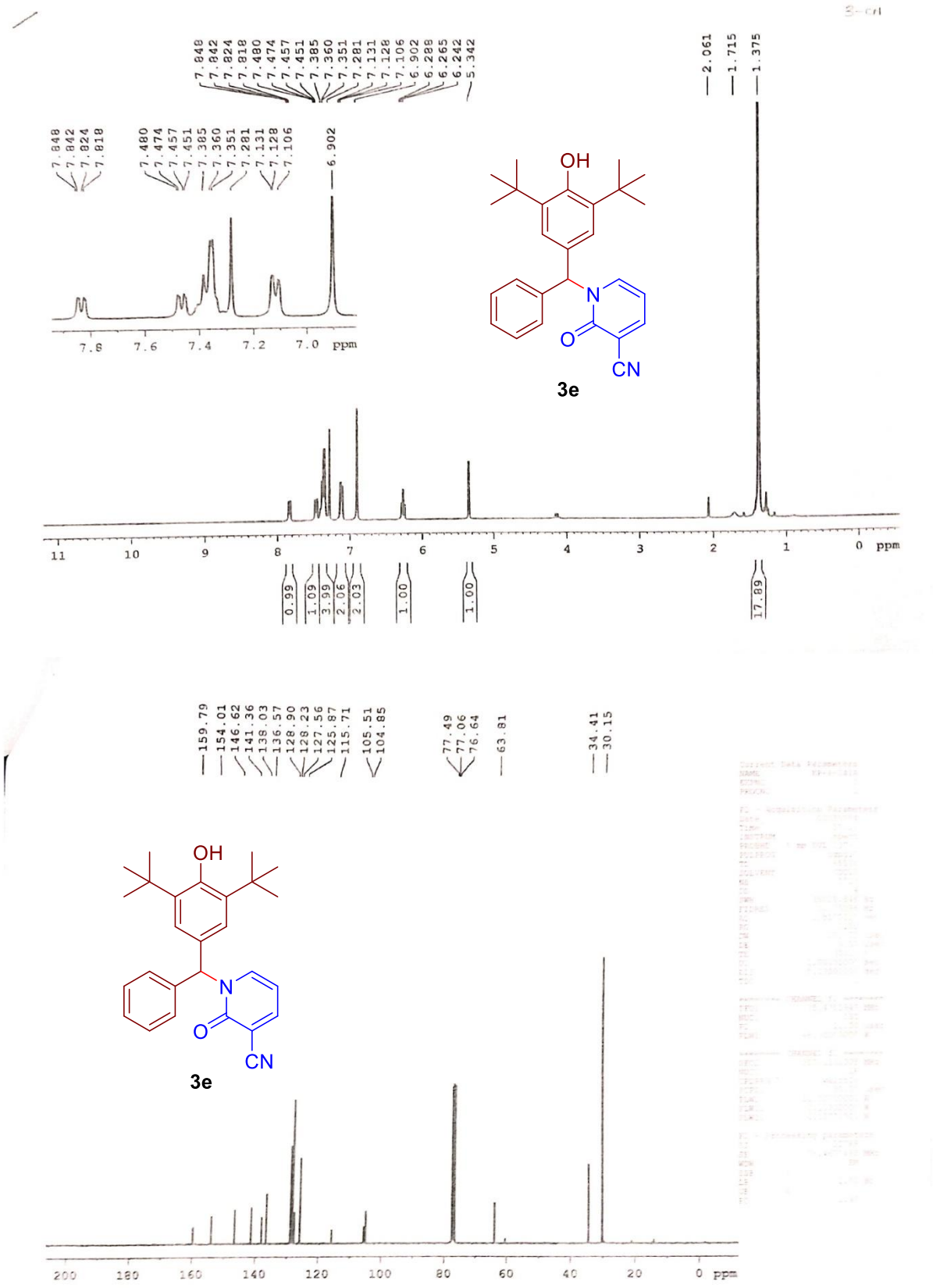


Figure 5.5. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) Spectra of (**3e**) in $CDCl_3$

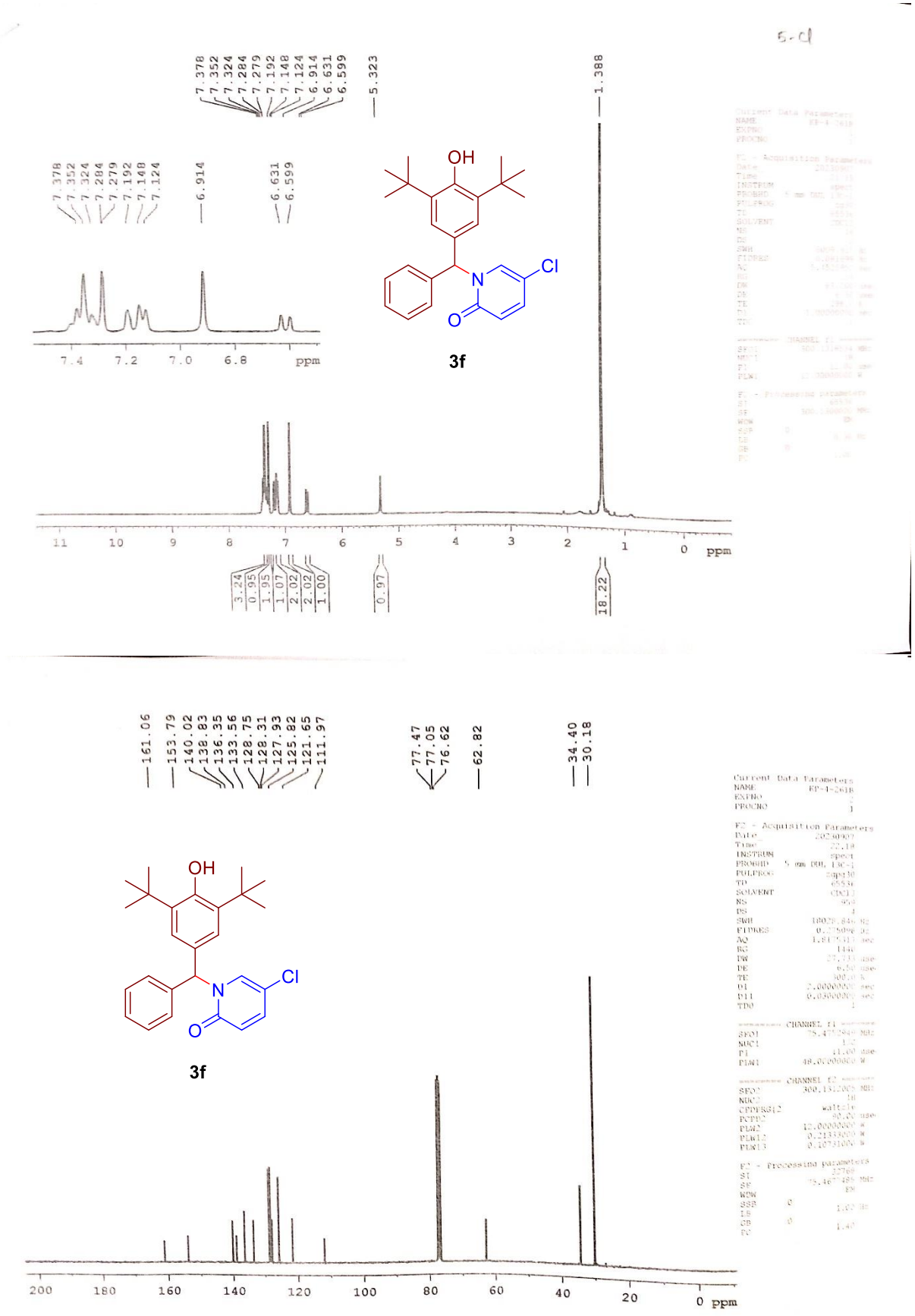


Figure 5.6. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) Spectra of (**3f**) in $CDCl_3$

Figure 5.7. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) Spectra of (**3g**) in $CDCl_3$

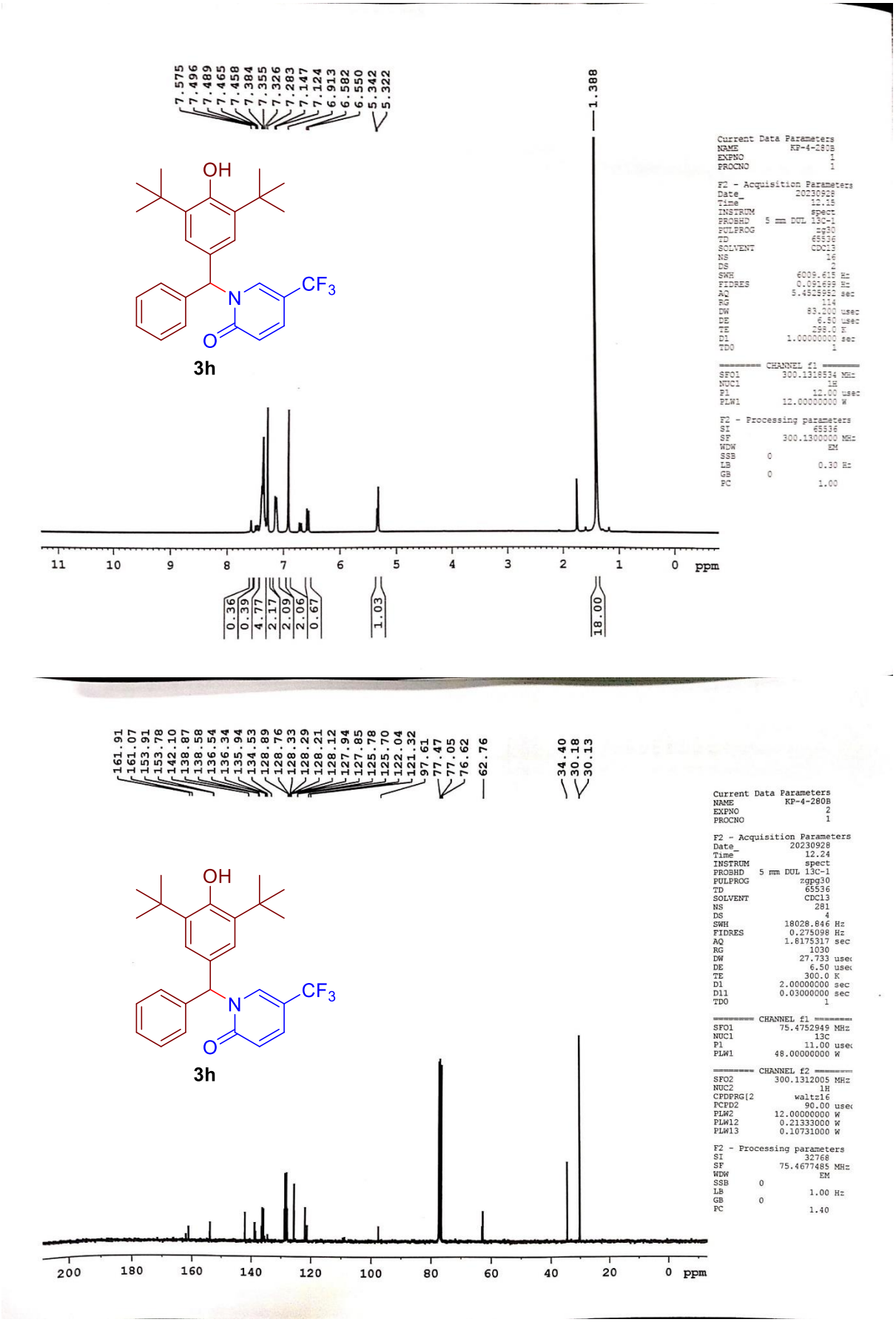


Figure 5.8. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) Spectra of (**3h**) in $CDCl_3$

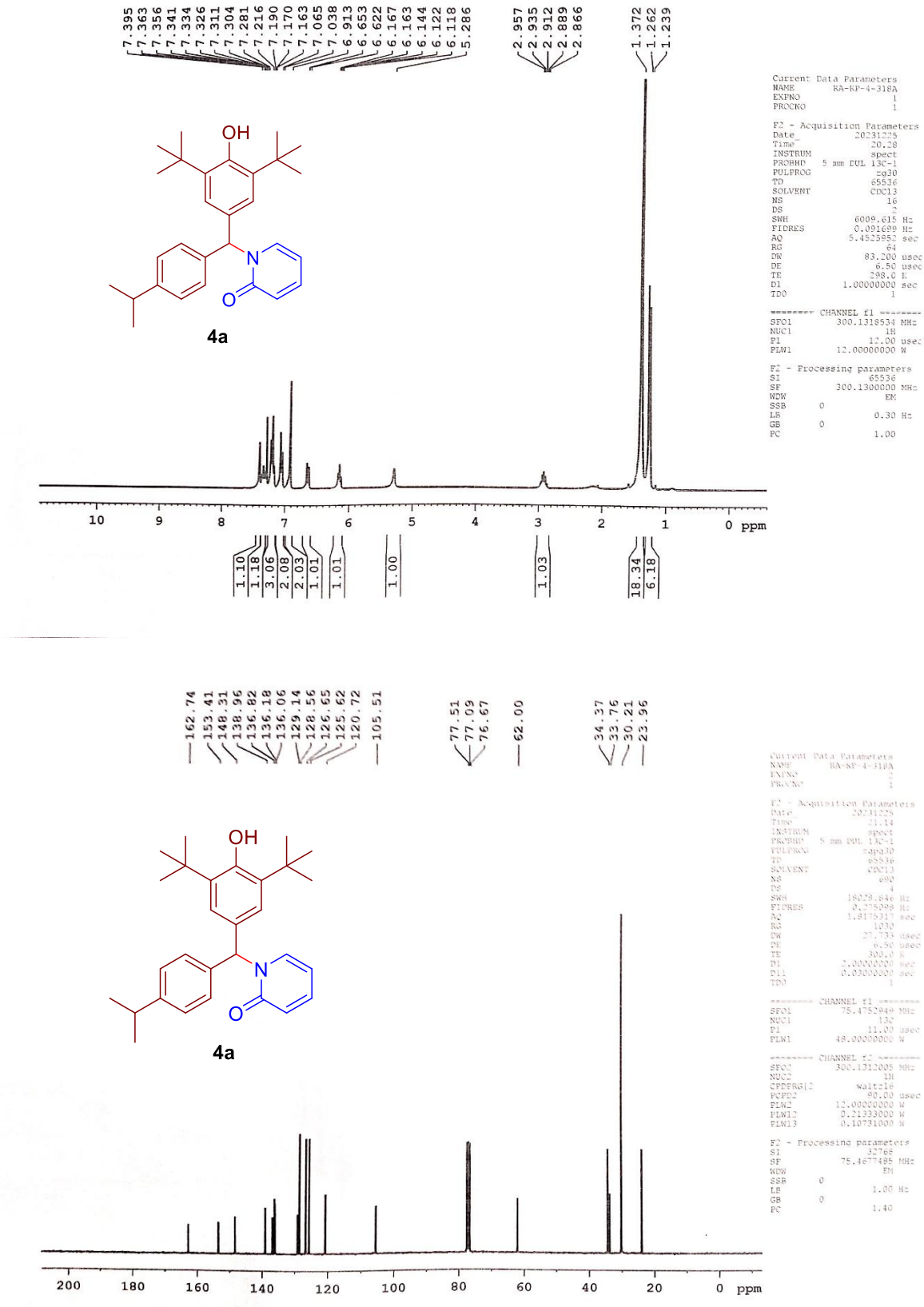


Figure 5.9. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) Spectra of (**4a**) in $CDCl_3$

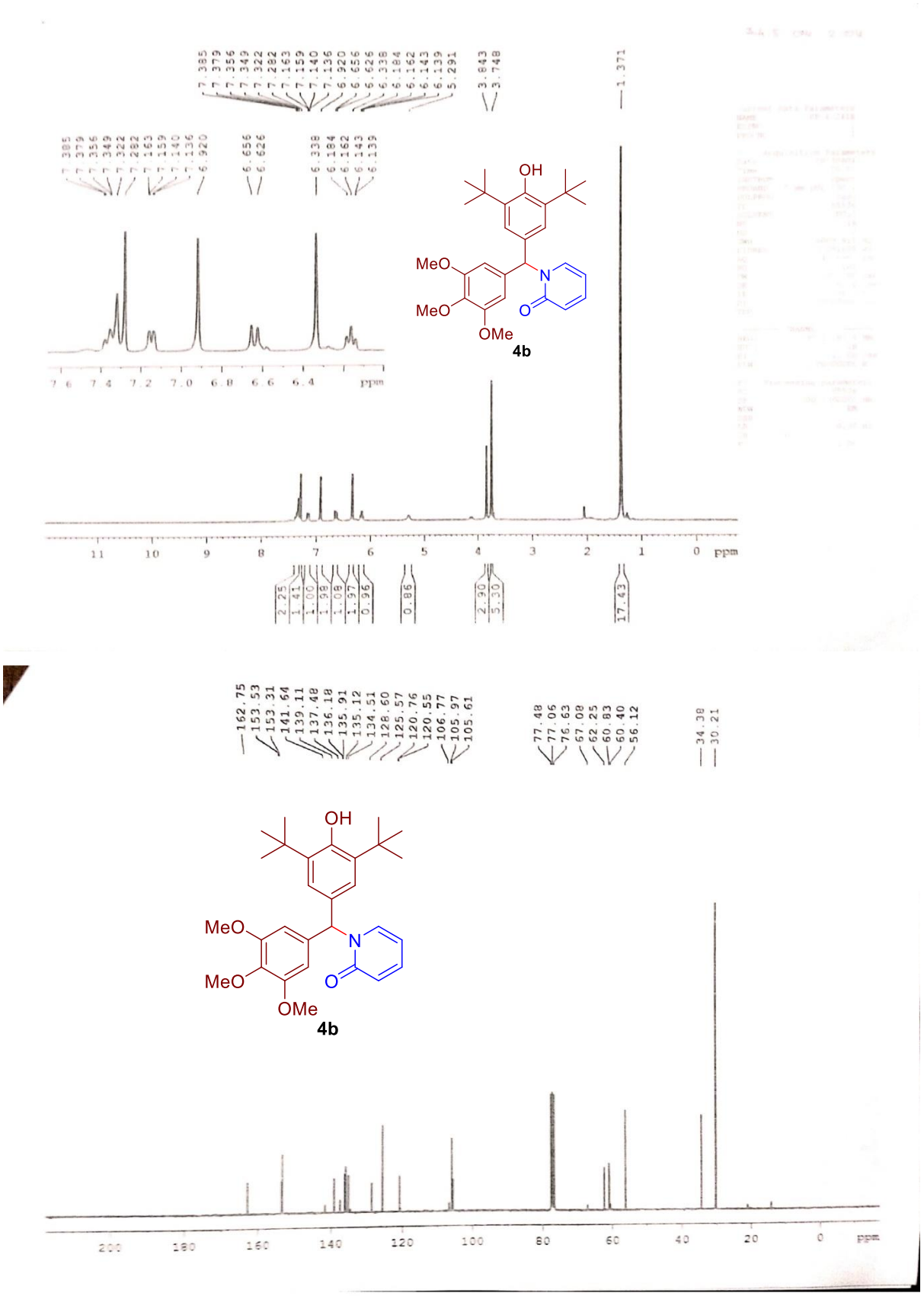


Figure 5.10. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) Spectra of (**4b**) in $CDCl_3$

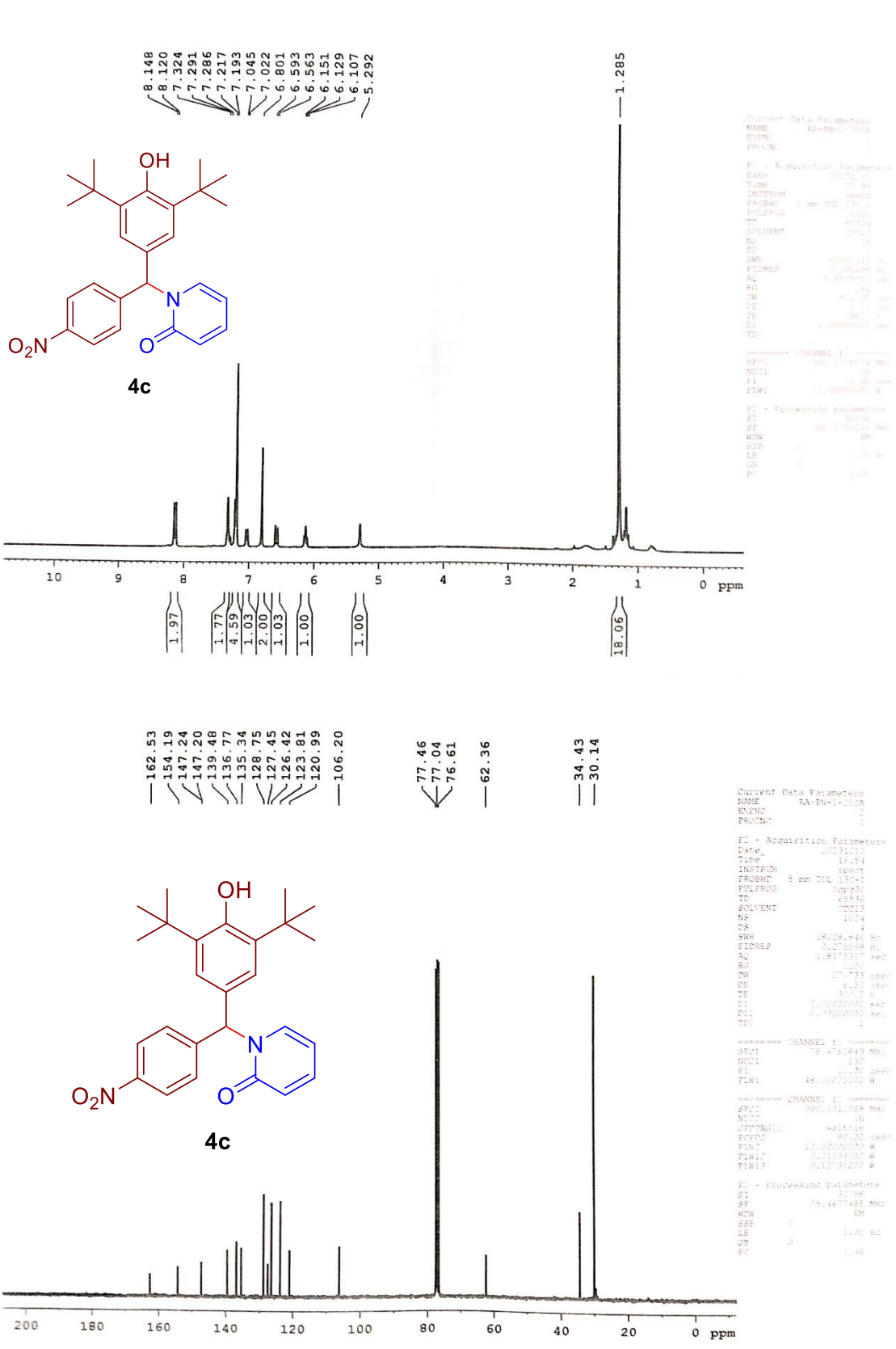


Figure 5.11. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) Spectra of (**4c)** in $CDCl_3$

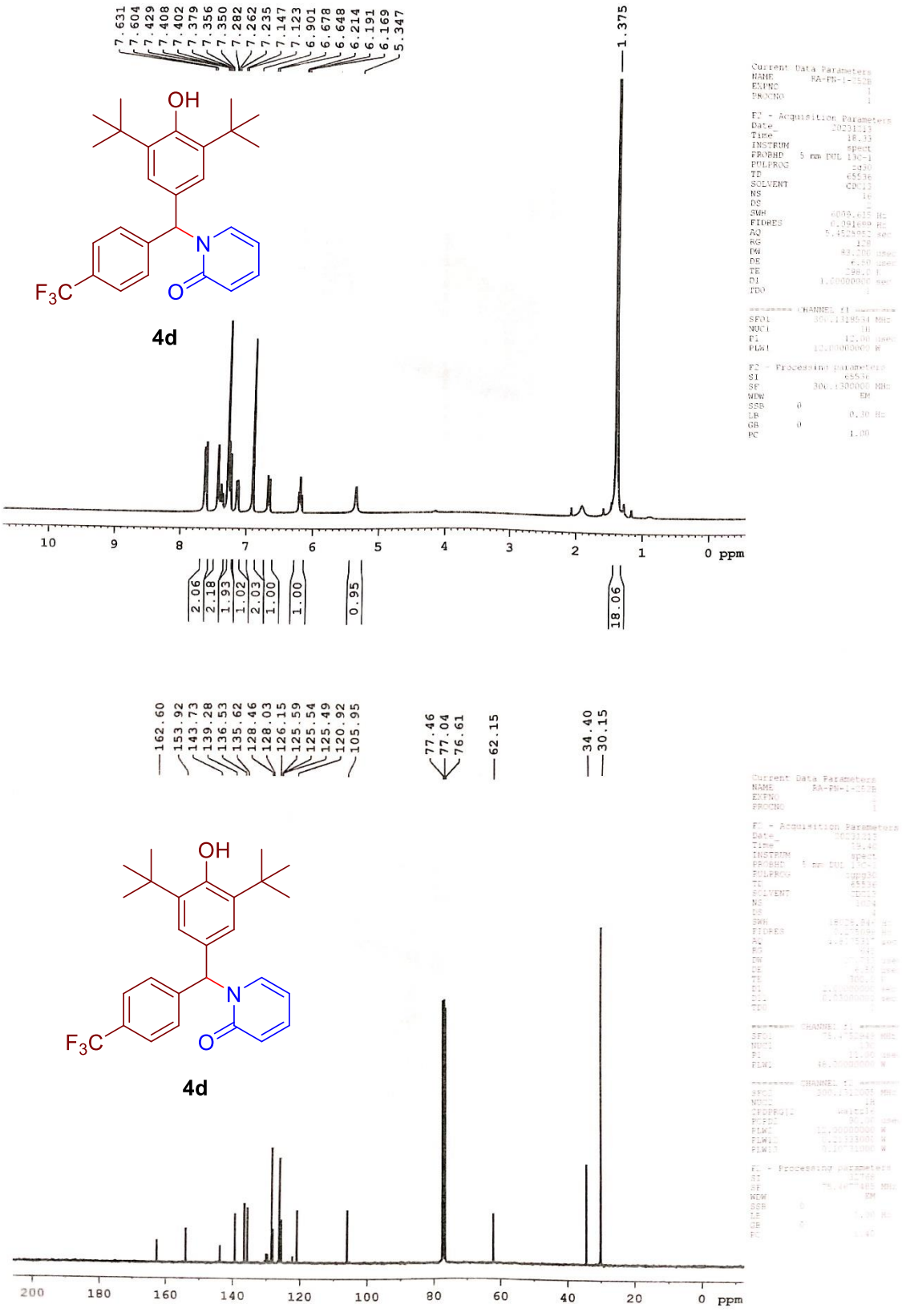


Figure 5.12. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) Spectra of (**4d**) in $CDCl_3$

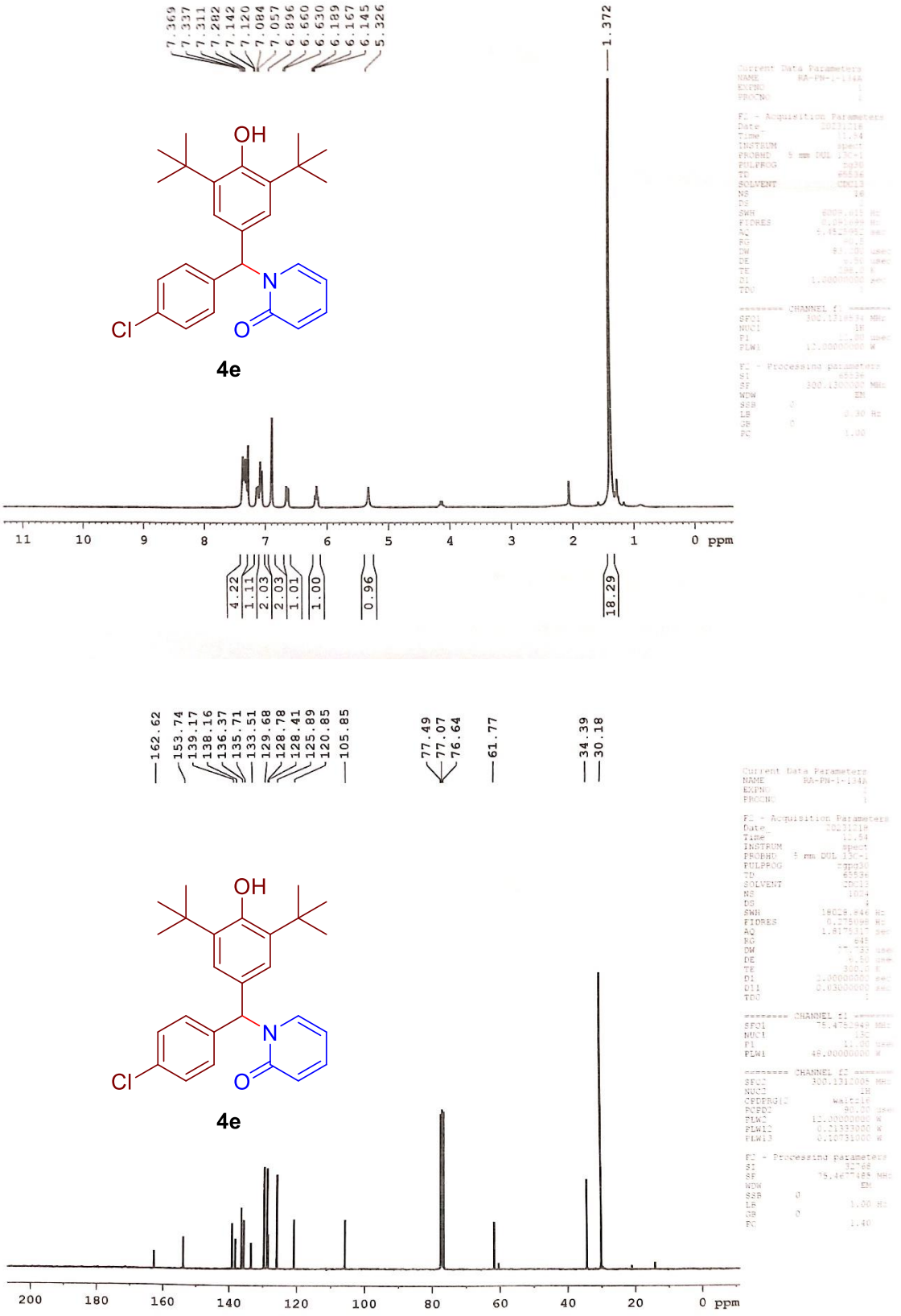


Figure 5.13. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) Spectra of (**4e**) in $CDCl_3$

Figure 5.14. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) Spectra of (**4f**) in $CDCl_3$

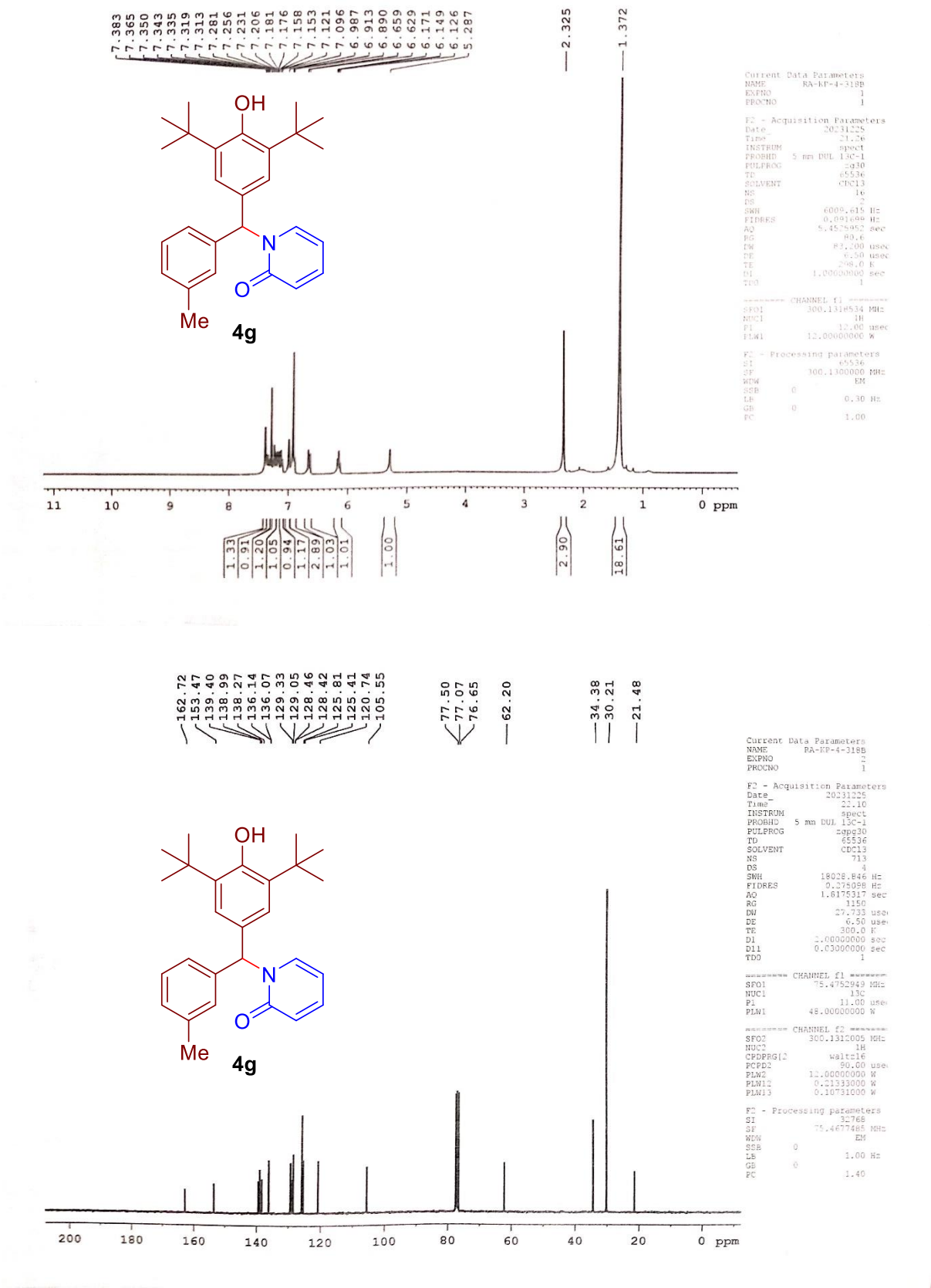


Figure 5.15. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) Spectra of (**4g**) in $CDCl_3$

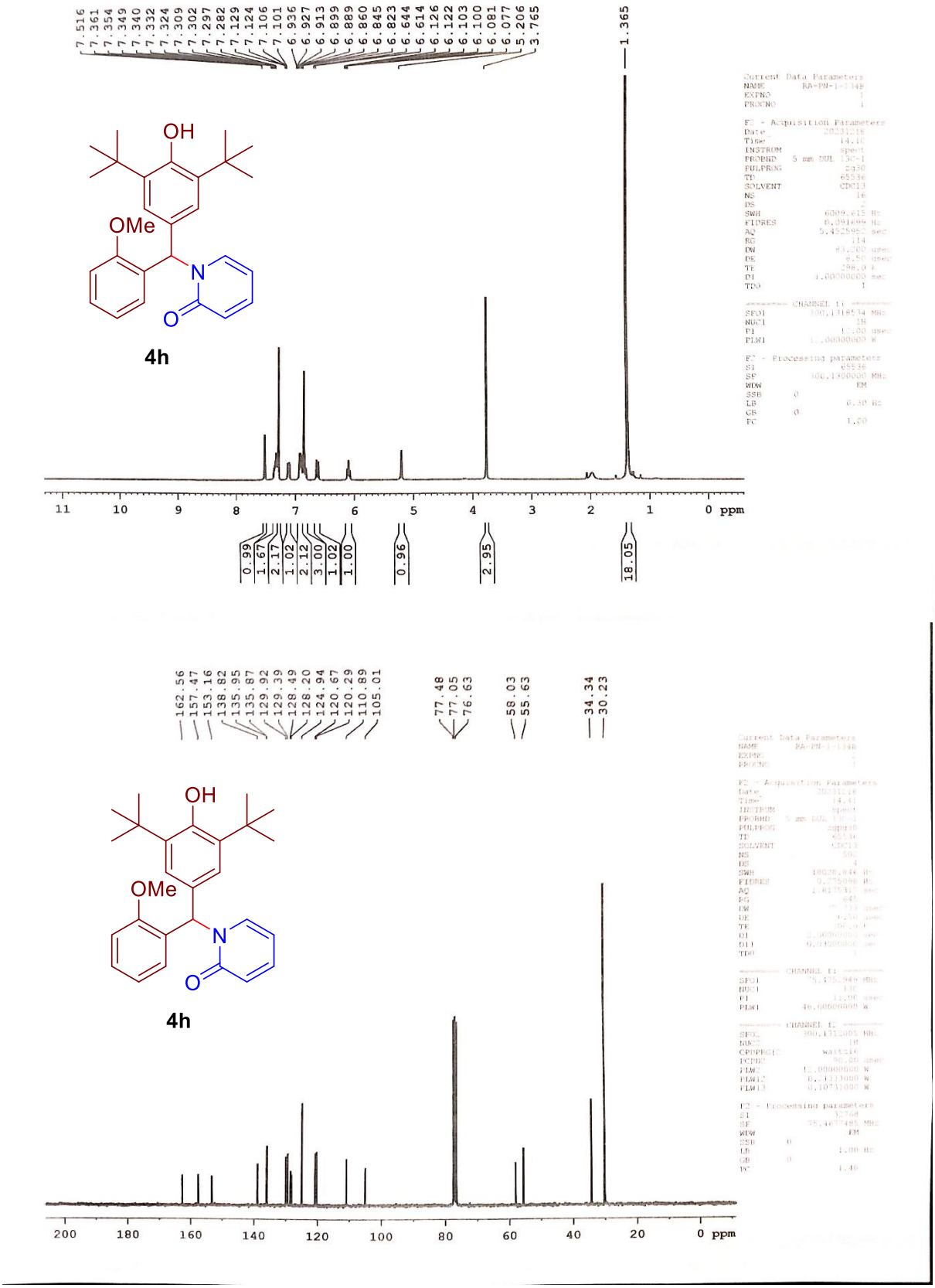


Figure 5.16. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) Spectra of (**4h**) in $CDCl_3$

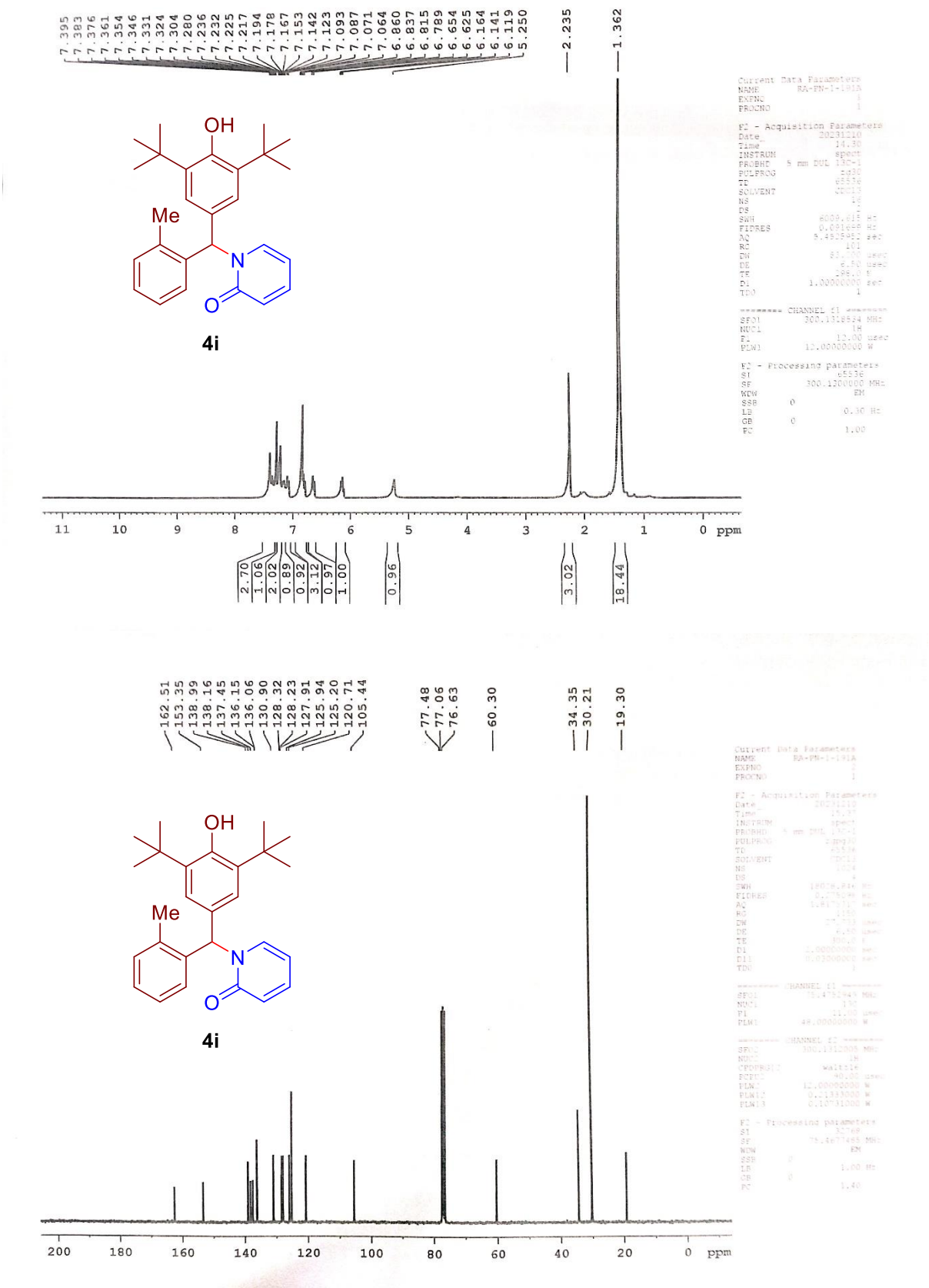


Figure 5.17. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) Spectra of (**4i**) in $CDCl_3$

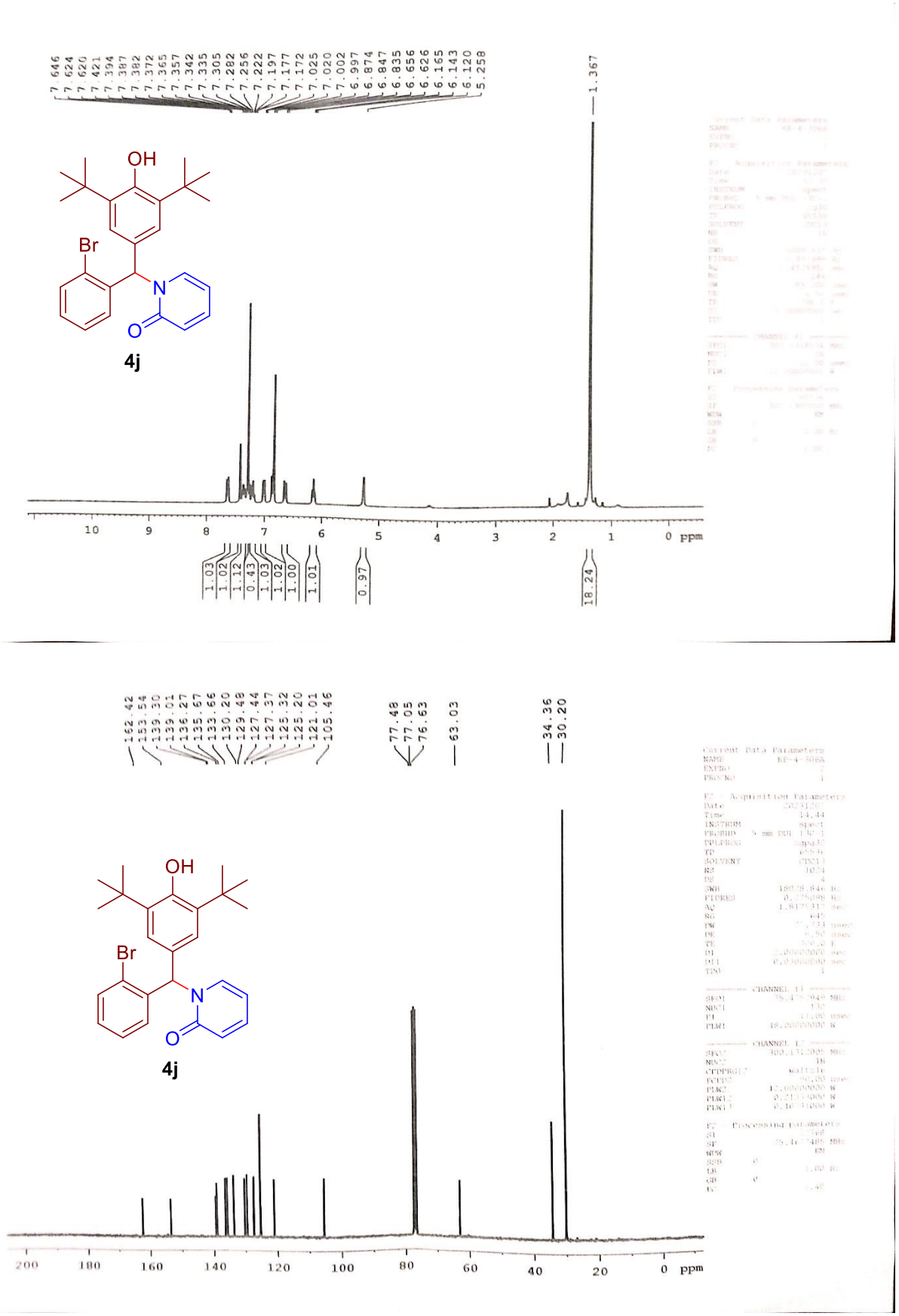


Figure 5.18. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) Spectra of (**4j**) in $CDCl_3$

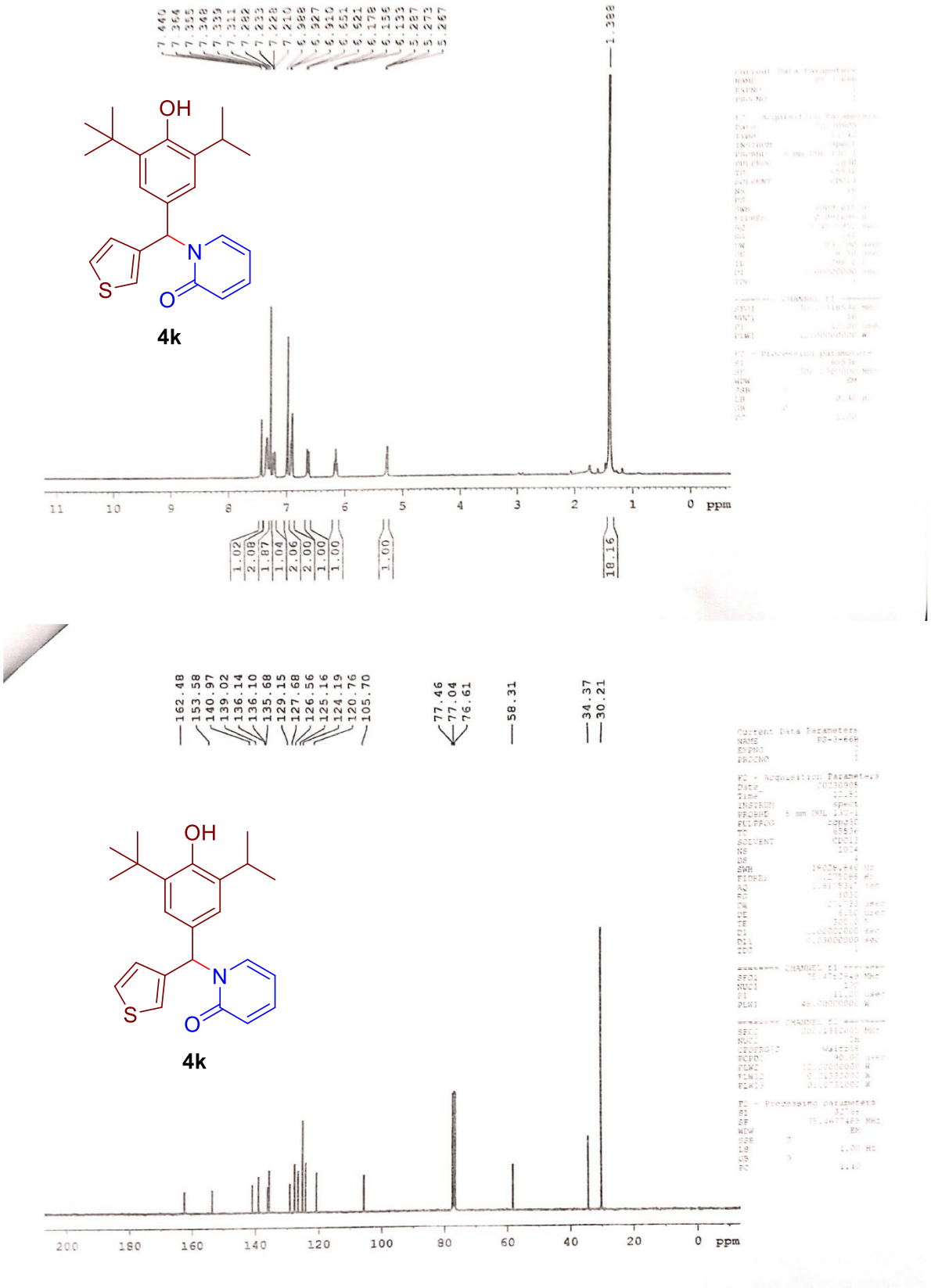


Figure 5.19. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) Spectra of (**4k**) in $CDCl_3$

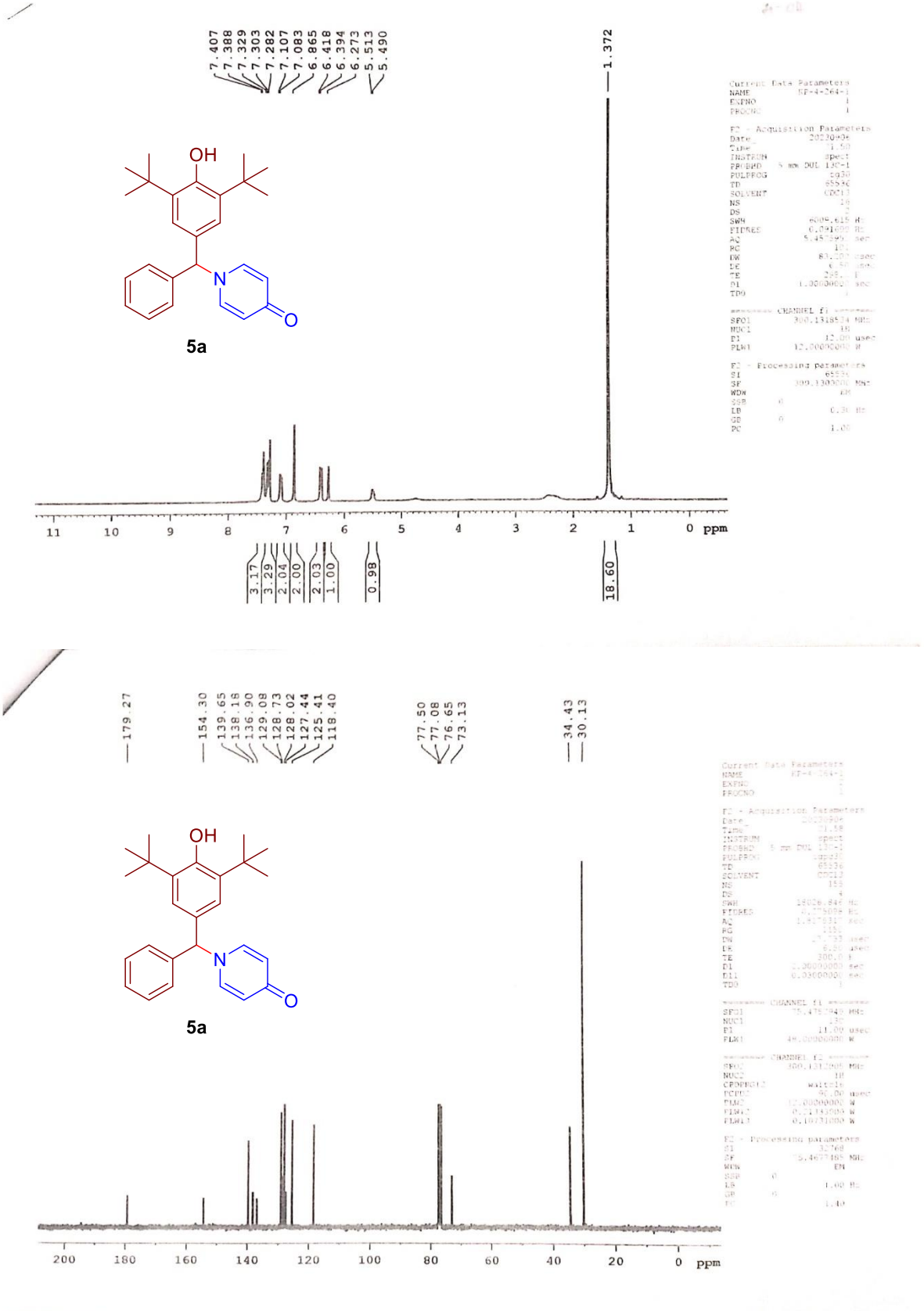


Figure 5.20. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) Spectra of (**5a**) in $CDCl_3$

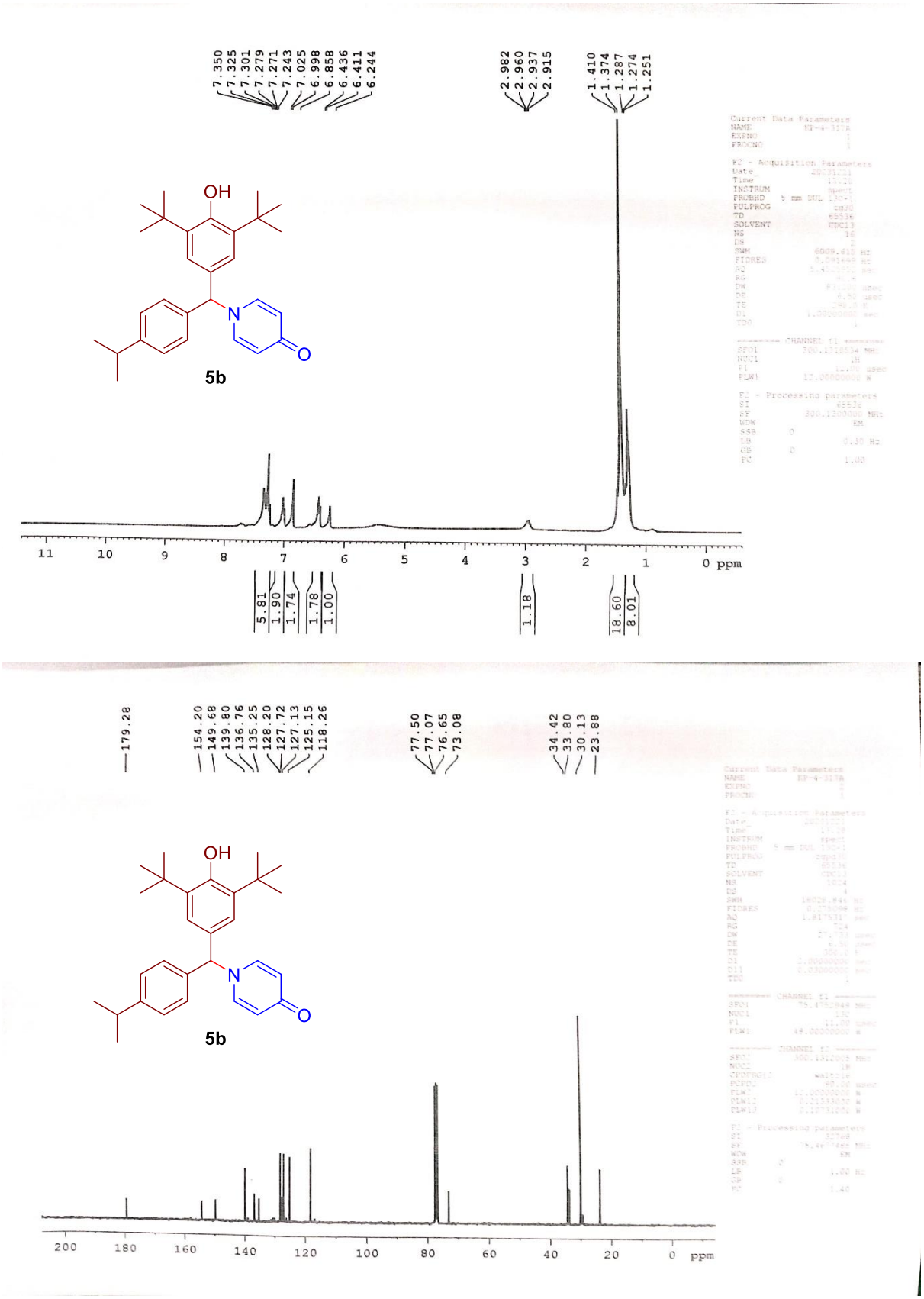


Figure 5.21. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) Spectra of (**5b**) in $CDCl_3$

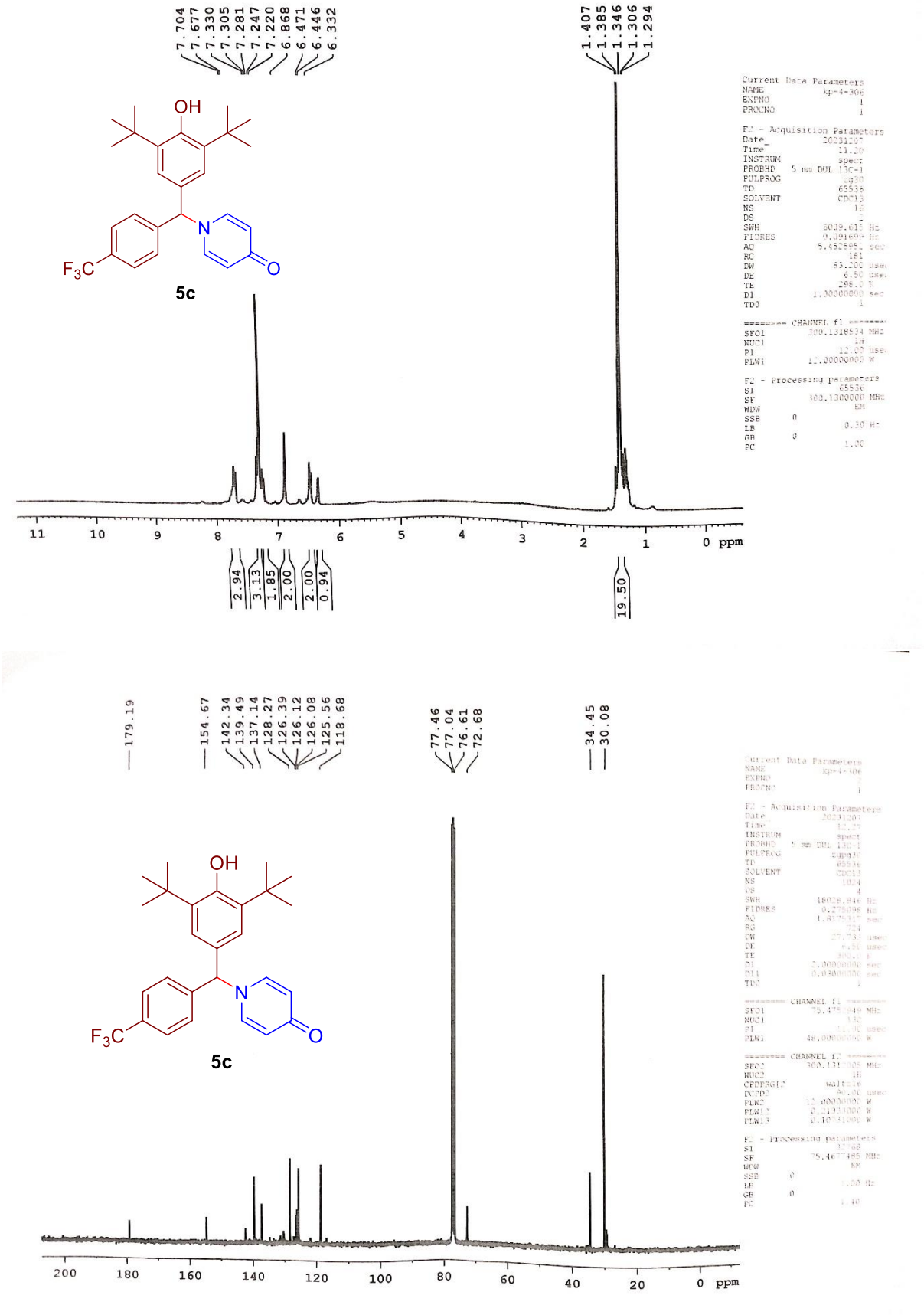


Figure 5.22. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) Spectra of (**5c**) in $CDCl_3$

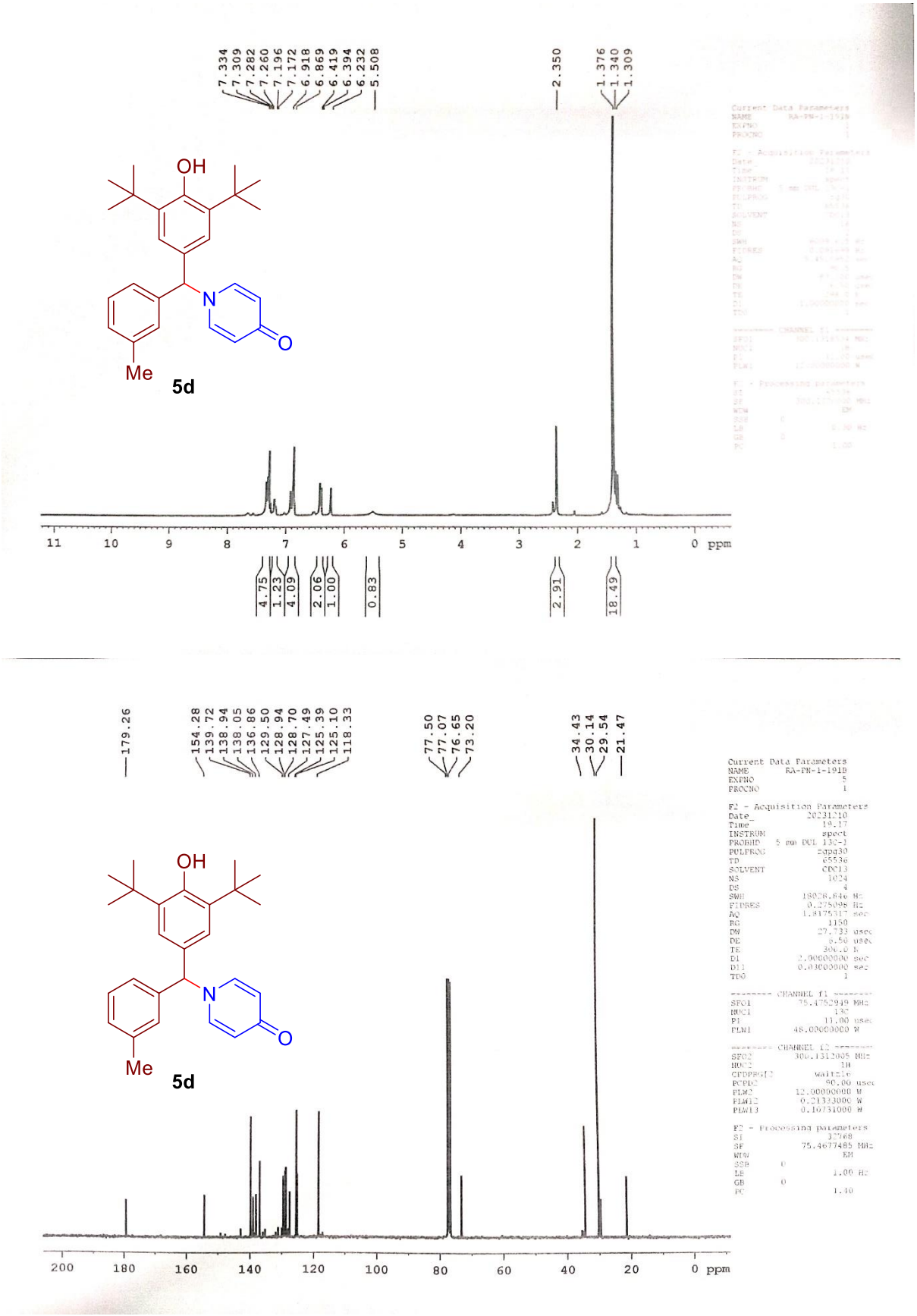


Figure 5.23. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) Spectra of (**5d**) in $CDCl_3$

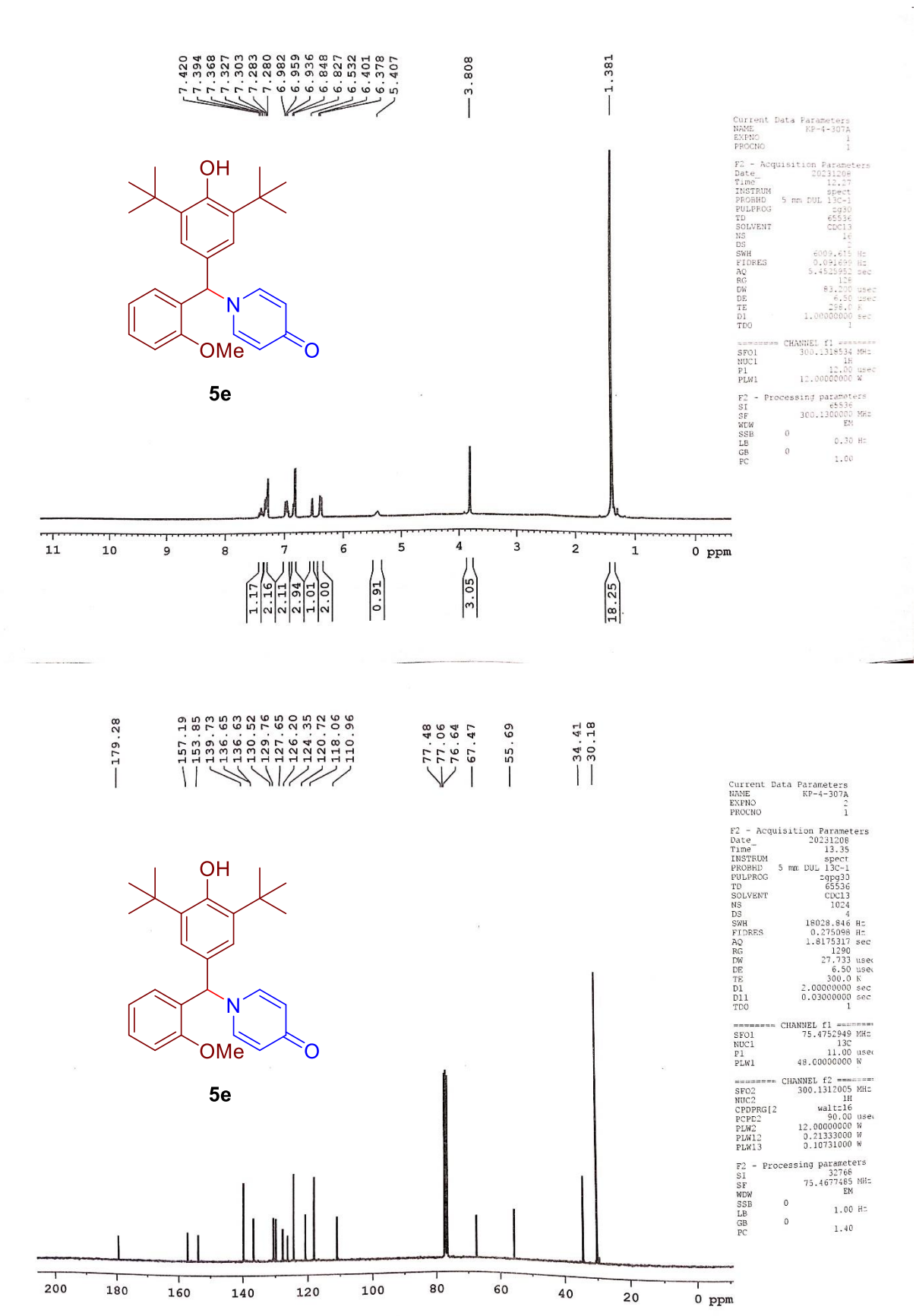


Figure 5.24. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) Spectra of (**5e**) in $CDCl_3$

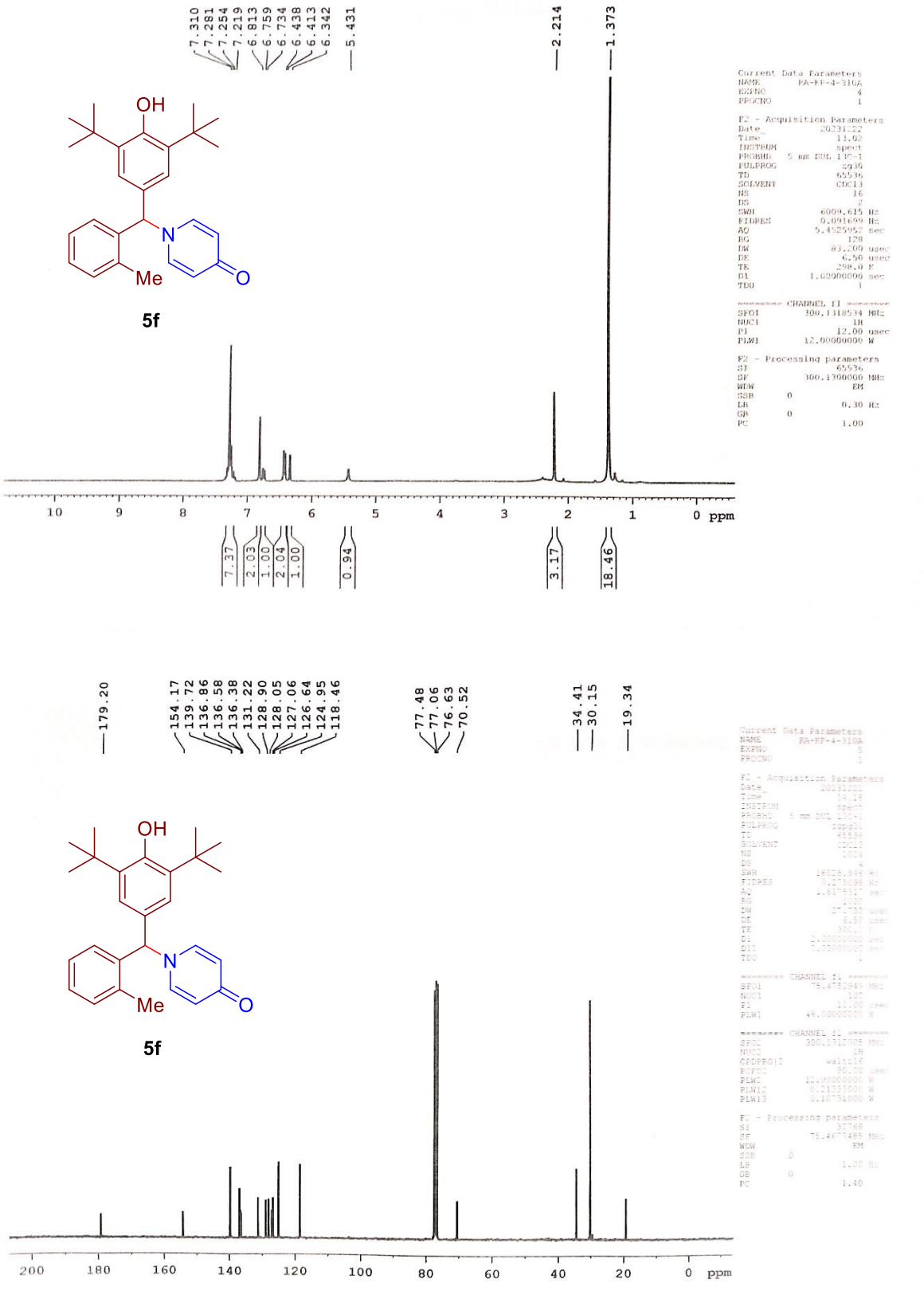


Figure 5.25. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) Spectra of (**5f**) in $CDCl_3$

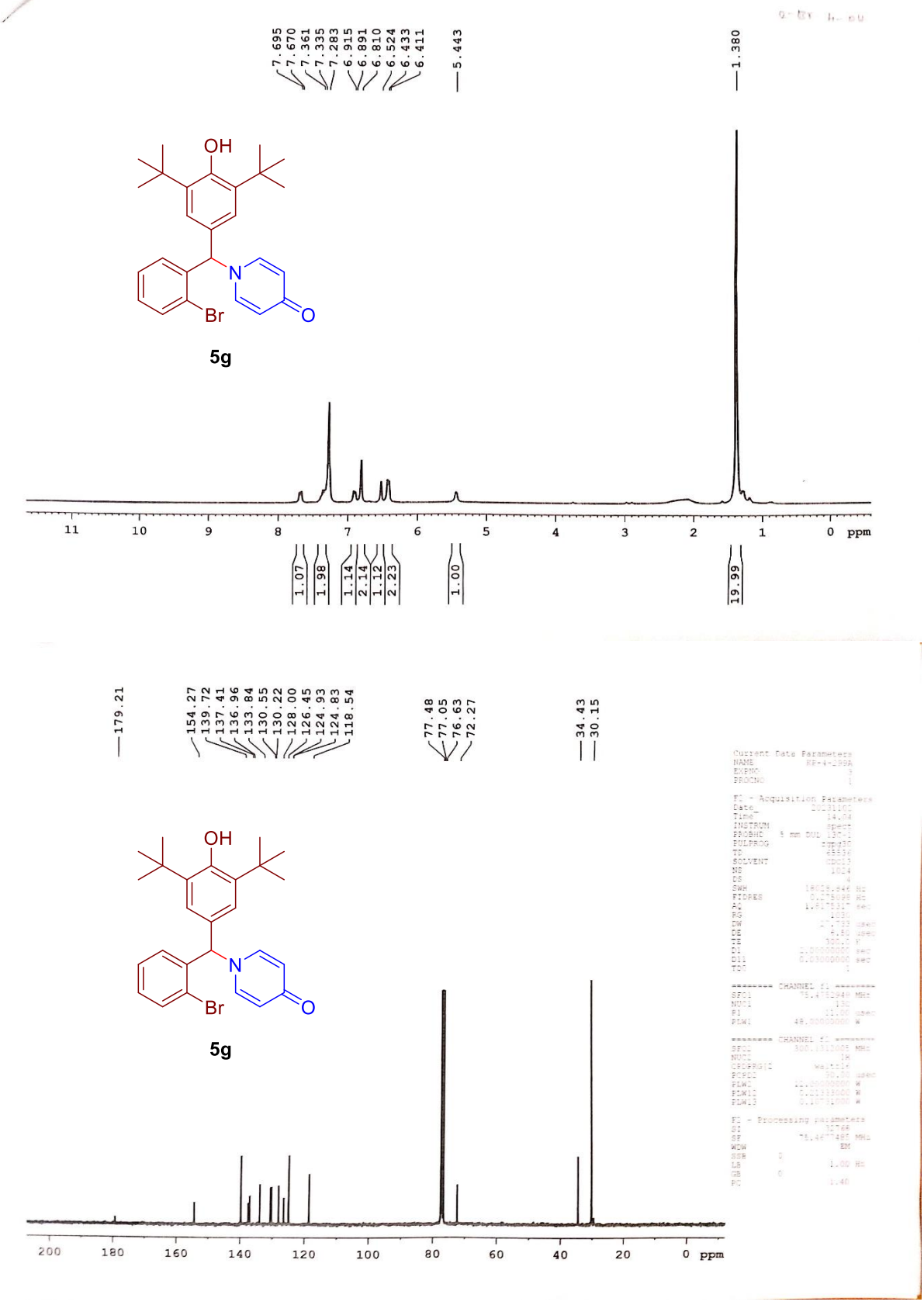


Figure 5.26. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) Spectra of (**5g**) in $CDCl_3$

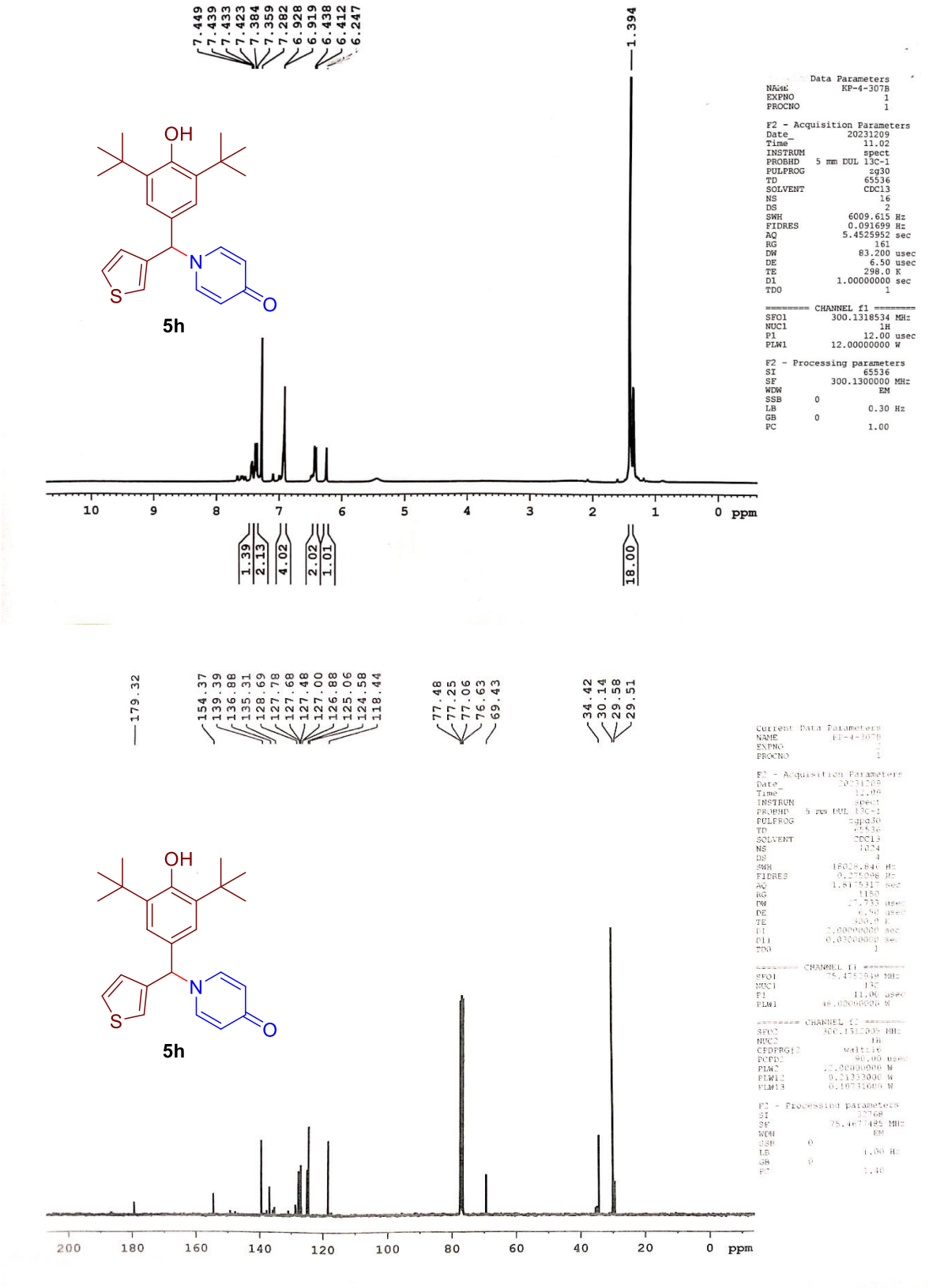


Figure 5.27. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) Spectra of (**5h**) in $CDCl_3$