Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Domino synthesis of fully substituted pyridines by silver-catalyzed chemoselective hetero-dimerization of isocyanides

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1. General Information

All reagents were purchased from commercial sources and used without further purification, unless otherwise indicated. All reactions were carried out without any particular precautions to extrude moisture or oxygen, unless otherwise indicated. All reactions were monitored by TLC, which was performed on precoated aluminum sheets of silica gel 60 (F254). The products were purified by flash column chromatography on silica gel (300−400 mesh). NMR spectra were obtained on a Bruker 400 spectrometer, with $CDCl_3$ or DMSO-d_6 as solvents. All chemical shifts are given in ppm. High-resolution mass spectra (HRMS) were recorded on a Bruker micro TOF IV focus spectrometer.

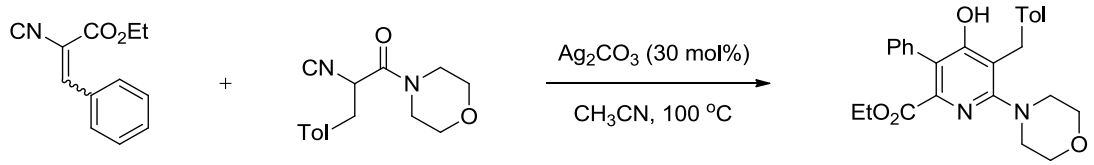
2. Experimental Procedures

2.1 Synthesis of starting materials.

Isocyanides **1** were synthesized according to known literature procedure.[1] α-substituted isocyanoacetamides **2** were synthesized according to known literature procedure.[2]

2.2 Synthesis of products 3,4 and 5.

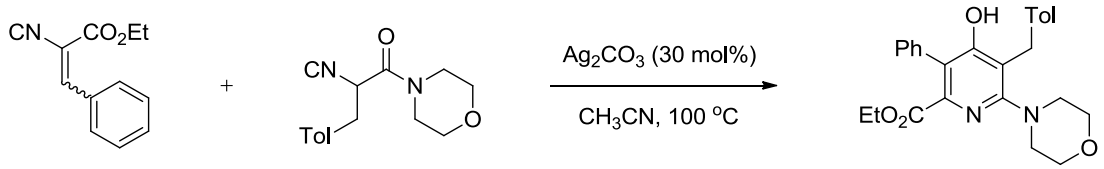
2.2.1 General synthetic procedures of **3** (taking **3a** for example)



1a (0.25 mmol) **2a** (0.25 mmol) **3aa** (70%)

Ag_2CO_3 (20.7 mg, 30 mol%) was added to a solution of isocyanide **1a** (50.3 mg, 0.25 mmol) and isocyanoacetamides **2a** (64.6 mg, 0.25 mmol) in CH_3CN (2 mL). Then the tube was sealed and the reaction mixture was set in a pre-heated (100 ^oC) metal block under stirring for 3 hours. After cooled to room temperature, the reaction mixture was concentrated in vacuo and the residue was purified by flash column chromatography (silica gel; petroleum: ethyl acetate = 10:1) to give pyridin-4-ol product **3aa** (75.3 mg, 70% yield) as a white solid.

2.2.2 Gram-scale synthesis of **3aa**

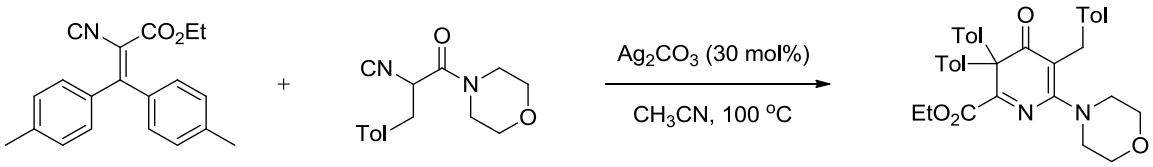


1a (1.066 g, 5.3 mmol) **2a** (1.369 g, 5.3 mmol) **3aa** (1.23 g, 53% yield)

Ag_2CO_3 (0.438 g, 30 mol%) was added to a solution of isocyanide **1a** (1.066 g, 5.3 mmol) and isocyanoacetamides **2a** (1.369 g, 5.3 mmol) in CH_3CN (35 mL) in a sealed tube. Then the reaction mixture

was set in a pre-heated (100 ^{o}C) metal block under stirring for 3 hours. The reaction mixture was cooled to room temperature and the solvent was removed in vacuo. The crude product was purified by flash column chromatography (silica gel; petroleum: ethyl acetate = 10:1) to afford pyridin-4-ol **3aa** (1.23 g, 53% yield) as a white solid.

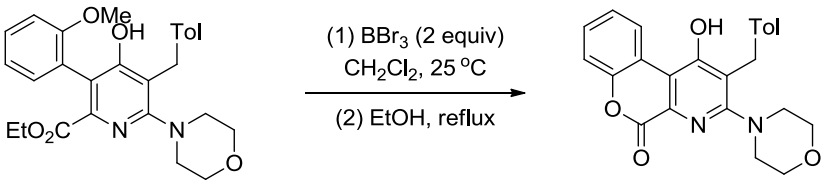
2.2.3 Synthetic procedures of **3qa**



1q (0.3 mmol) **2a** (0.3 mmol) **3qa** (40%)

Ag_2CO_3 (24.8 mg, 30 mol%) was added to a solution of isocyanide **1q** (0.091 g, 0.3 mmol) and isocyanoacetamides **2a** (0.077 g, 0.3 mmol) in CH_3CN (2 mL) in a sealed tube. Then the reaction mixture was set in a pre-heated (100 ^{o}C) metal block under stirring for 3 hours. The reaction mixture was cooled to room temperature and the solvent was removed in vacuo. The crude product was purified by flash column chromatography (silica gel; petroleum: ethyl acetate = 15:1-10:1) to afford **3qa** (64 mg, 40% yield) as a yellow solid.

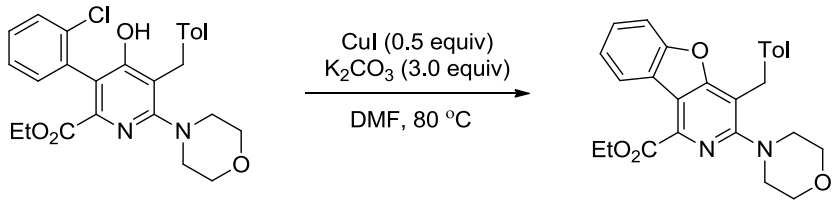
2.2.4 Synthetic procedures of **4a**



3ga (0.2 mmol) **4a** (70%)

Under a nitrogen atmosphere, BBr_3 (378 uL, 0.4 mmol, 0.1 M in CH_2Cl_2) was added to a stirred mixture of **3ga** (92.5 mg, 0.2 mmol) in 2 mL of dry CH_2Cl_2 at 0 ^{o}C. Then, the reaction was stirred at 25 ^{o}C overnight. After quenching the reaction with EtOH (1 mL), the volatiles were removed under reduced pressure, and the residue was dissolved in EtOH (4 mL). The resulting mixture was heated at reflux for 3 h, cooled to ambient temperature, and filtered. The filtrate was evaporated all the volatiles under reduced pressure. The resultant residue was purified by silica gel column chromatography (eluent: petroleum ether (60-90 ^{o}C)/EtOAc/CH_2Cl_2 = 6/1/1, v/v/v) to afford **4a** as a white solid (56.3 mg, 70%).[3]

2.2.5 Synthetic procedures of **5** (taking **5a** for example)



3ha (0.3 mmol) **5a**, 58%

A round bottom flask with a magnetic stirring bar was charged with **3ha** (0.3 mmol, 139.9 mg), K_2CO_3 (3.0 equiv., 124.4 mg), CuI (0.5 equiv., 28.6 mg) in DMF solvent (1 mL). The reaction mixture was heated at 80 ℃ for 48 h. After regular TLC monitoring, the mixture was poured into cold ice water and neutralized carefully using 1N hydrochloric acid which gave the precipitated product. It was filtered and washed with water under vacuum. The product was recrystallised with methanol to get a yellowish solid. Further purification by column chromatography (hexane/ethyl acetate, 10:1) afforded the desired product **5a.**[4]

2.3 References

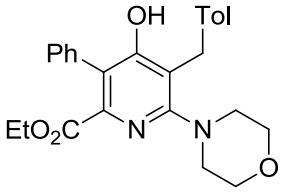
[1] Y. Gao, Z. Hu, J. Dong, J. Liu and X. Xu, *Org. Lett.*, 2017, **19**, 5292.

[2] Z. Hu, J. Dong, Y. Men, Z. Lin, J. Cai and X. Xu, *Angew. Chem., Int. Ed.*, 2017, **56**, 1805.

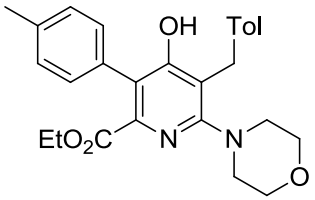
[3] Z. Wang, Z. Liu, J. Lou and Z. Yu, *Org. Lett.*, 2018, **20**, 6007.

[4] P. Iram and A. Naseem, *Tetrahedron Lett.*, 2017, **58**, 2302.

3. Analytical data of compounds 3, 4, 5

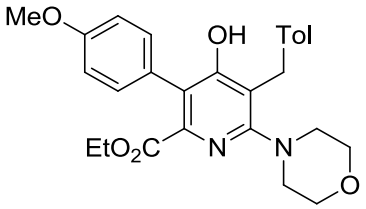


3aa, Ethyl 4-hydroxy-5-(4-methylbenzyl)-6-morpholino-3-phenylpicolinate. White solid in 70% yield, 90.8 mg, m.p. 196-198 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.94 (t, 3H), 2.30 (s, 3H), 3.17 (t, J = 4.6 Hz, 4H), 3.77 (t, J = 4.6 Hz, 4H), 4.04-4.09 (m, 4H), 5.53 (s, 1H), 7.06-7.11 (m, 4H), 7.30-7.32 (m, 2H), 7.40-7.49 (m, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.6, 21.0, 31.1, 50.9, 61.1, 67.0, 115.1, 119.8, 127.8, 128.7, 129.2, 129.3, 129.8, 132.4, 135.7, 136.0, 146.0, 159.7, 162.1, 166.8. **HRMS** (ESI-TOF) m/z calculated for $C_{26}H_{28}N_2NaO_4^+$ ($[M+Na]^+$) 455.1941, found 455.1930.

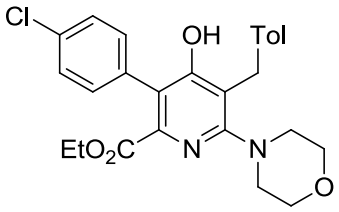


3ba, Ethyl 4-hydroxy-5-(4-methylbenzyl)-6-morpholino-3-(*p*-tolyl)picolinate. White solid in 60% yield, 80.3 mg, m.p. 187-189 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.99 (t, J = 7.2 Hz, 3H), 2.30 (s, 3H), 2.39 (s,

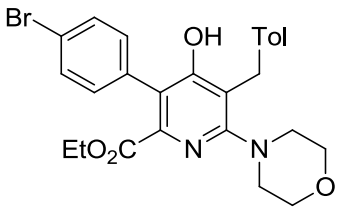
3H), 3.15 (t, *J* = 4.6 Hz, 4H), 3.77 (t, *J* = 4.6 Hz, 4H), 4.06 (s, 2H), 4.09 (q, *J* = 7.1 Hz, 2H), 5.60 (s, 1H), 7.05-7.10 (m, 4H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.6, 21.0, 21.2, 31.1, 50.9, 61.1, 67.0, 115.1, 119.8, 127.8, 129.1, 129.1, 129.7, 130.0, 135.6, 136.1, 138.6, 146.1, 159.8, 161.9, 166.9. **HRMS** (ESI-TOF) m/z calculated for $C_{27}H_{31}N_2O_4^+$ ($[M+H]^+$) 447.2278, found 447.2276.



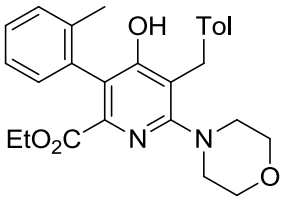
3ca, Ethyl 4-hydroxy-3-(4-methoxyphenyl)-5-(4-methylbenzyl)-6-morpholinopicolinate. White solid in 45% yield, 62.4 mg, m.p. 166-168 ^{o}C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.02 (t, *J* = 7.0 Hz, 3H), 2.30 (s, 3H), 3.15 (t, *J* = 4.6 Hz, 4H), 3.77 (t, *J* = 4.6 Hz, 4H), 3.84 (s, 3H), 4.07 (s, 2H), 4.10 (q, *J* = 7.2 Hz, 2H), 5.59 (s, 1H), 6.99 (d, *J* = 8.8 Hz, 2H), 7.06-7.11 (m, 4H), 7.23 (d, *J* = 8.8 Hz, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.7, 21.0, 31.1, 50.9, 55.3, 61.1, 67.0, 114.7, 115.0, 119.3, 124.0, 127.8, 129.2, 131.1, 135.7, 136.1, 146.3, 159.9, 160.0, 161.9, 166.9. **HRMS** (ESI-TOF) m/z calculated for $C_{27}H_{31}N_2O_5^+$ ($[M+H]^+$) 463.2227, found 463.2237.



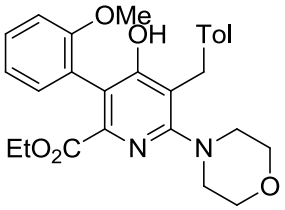
3da, Ethyl-3-(4-chlorophenyl)-4-hydroxy-5-(4-methylbenzyl)-6-morpholinopicolinate. White solid in 50% yield, 70.0 mg, m.p. 184-186 ^{o}C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.02 (t, *J* = 7.2 Hz, 3H), 2.30 (s, 3H), 3.15 (t, *J* = 4.6 Hz, 4H), 3.76 (t, *J* = 4.6 Hz, 4H), 4.06 (s, 2H), 4.10 (q, *J* = 7.2 Hz, 2H), 5.50 (s, 1H), 7.08 (s, 1H), 7.24 (d, *J* = 8.4 Hz, 2H), 7.42 (d, *J* = 8.0 Hz, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.7, 21.0, 31.1, 50.8, 61.2, 67.0, 115.1, 118.8, 127.8, 129.3, 131.1, 131.3, 134.8, 135.6, 136.0, 146.0, 159.8, 162.2, 166.5. **HRMS** (ESI-TOF) m/z calculated for $C_{26}H_{28}ClN_2O_4^+$ ($[M+H]^+$) 467.1732, found 467.1727.



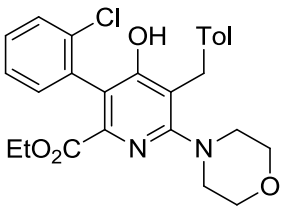
3ea, Ethyl-3-(4-bromophenyl)-4-hydroxy-5-(4-methylbenzyl)-6-morpholinopicolinate. White solid in 60% yield, 92.1 mg, m.p. 197-199 ^{o}C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.03 (t, J = 7.2 Hz, 3H), 2.30 (s, 3H), 3.17 (t, J = 4.6 Hz, 4H), 3.78 (t, J = 4.6 Hz, 4H), 4.07 (s, 2H), 4.11 (q, J = 7.2 Hz, 2H), 5.39 (s, 1H), 7.08 (s, 4H), 7.18 (d, J = 8.0 Hz, 2H), 7.59 (d, J = 8.4 Hz, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.7, 21.0, 31.2, 50.9, 61.3, 67.0, 115.0, 118.8, 122.9, 127.7, 129.4, 131.5, 132.3, 135.5, 136.0, 145.9, 159.7, 162.2, 166.5. **HRMS** (ESI-TOF) m/z calculated for $C_{26}H_{28}BrN_2O_4^+$ ($[M+H]^+$) 511.1227, found 511.1221.



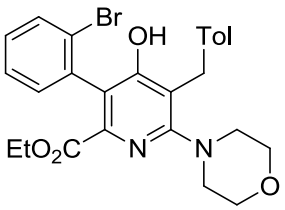
3fa, Ethyl 4-hydroxy-5-(4-methylbenzyl)-6-morpholino-3-(*o*-tolyl)picolinate. White solid in 50% yield, 66.9 mg, m.p. 157-159 ^{o}C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.92 (t, J = 7.0 Hz, 3H), 2.12 (s, 3H), 2.30 (s, 3H), 3.17-3.19 (m, 4H), 3.77-3.79 (m, 4H), 4.05 (q, J = 8.0 Hz, 2H), 4.08 (s, 2H), 5.28 (s, 1H), 7.06 (s, 4H), 7.13 (d, J = 7.2 Hz, 1H), 7.23-7.27 (m, 1H), 7.31-7.33 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.5, 19.7, 20.1, 31.1, 50.9, 61.0, 67.1, 115.1, 119.7, 126.6, 127.7, 129.2, 129.2, 130.4, 130.5, 131.5, 135.7, 136.2, 138.1, 145.4, 159.8, 162.1, 166.3. **HRMS** (ESI-TOF) m/z calculated for $C_{27}H_{30}N_2NaO_4^+$ ($[M+Na]^+$) 469.2098, found 469.2105.



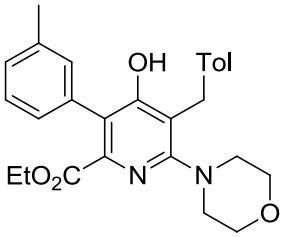
3ga, Ethyl 4-hydroxy-3-(2-methoxyphenyl)-5-(4-methylbenzyl)-6-morpholinopicolinate. White solid in 50% yield, 69.4 mg, m.p. 163-165 ^{o}C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.95 (t, J = 7.0 Hz, 3H), 2.30 (s, 3H), 3.16 (t, J = 4.4 Hz, 4H), 3.76-3.79 (m, 7H), 4.04-4.13 (m, 4H), 5.84 (s, 1H), 6.99-7.10 (m, 6H), 7.19 (dd, J_1 = 7.4 Hz, J_2 = 1.8 Hz, 1H), 7.38-7.43 (m, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.6, 21.0, 31.2, 50.8, 55.8, 61.0, 67.1, 111.4, 115.4, 116.9, 121.5, 121.6, 127.7, 129.1, 130.4, 131.6, 135.5, 136.3, 146.5, 156.8, 160.3, 162.0, 166.9. **HRMS** (ESI-TOF) m/z calculated for $C_{27}H_{31}N_2O_5^+$ ($[M+H]^+$) 463.2227, found 463.2231.



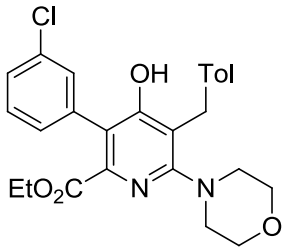
3ha, Ethyl 3-(2-chlorophenyl)-4-hydroxy-5-(4-methylbenzyl)-6-morpholinopicolinate. White solid in 70% yield, 97.9 mg, m.p. 166-168 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 0.82 (t, J = 7.0 Hz, 3H), 2.37 (s, 3H), 2.91-2.94 (m, 4H), 3.65 (t, J = 4.8Hz, 4H), 3.91 (q, J = 7.1 Hz, 2H), 4.00-4.08 (m, 2H), 7.06 (s, 4H), 7.21-7.23 (m, 1H), 7.32-7.41 (m, 2H), 7.50-7.52 (m, 1H), 9.70 (s, 1H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 13.9, 21.1, 30.7, 51.3, 60.9, 66.7, 116.5, 119.1, 127.4, 128.2, 129.4, 129.5, 130.2, 132.6, 133.8, 134.6, 135.3, 137.0, 147.0, 162.0, 162.4, 166.4. **HRMS** (ESI-TOF) m/z calculated for $C_{26}H_{28}ClN_2O_4^+$ ($[M+H]^+$) 467.1732, found 467.1755.



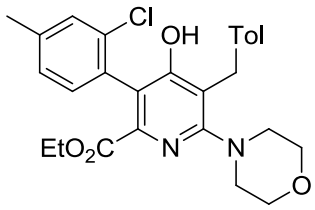
3ia, Ethyl 3-(2-bromophenyl)-4-hydroxy-5-(4-methylbenzyl)-6-morpholinopicolinate. White solid in 50% yield, 76.5 mg, m.p. 169-171 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 0.82 (t, J = 7.0 Hz, 3H), 2.24 (s, 3H), 2.91-2.94 (m, 4H), 3.64-3.67 (m, 4H), 3.91 (q, J = 7.1 Hz, 2H), 4.00-4.09 (m, 2H), 7.06 (s, 4H), 7.22 (d, J = 7.2 Hz, 1H), 7.30 (t, J = 7.4 Hz, 1H), 7.39 (t, J = 7.4 Hz, 1H), 7.67 (d, J = 8.0 Hz, 1H), 9.65 (s, 1H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 13.9, 21.1, 30.7, 51.3, 60.8, 66.7, 116.4, 121.0, 125.5, 127.9, 128.2, 129.4, 130.3, 132.6, 135.2, 135.9, 137.0, 146.7, 161.9, 162.3, 166.3. **HRMS** (ESI-TOF) m/z calculated for $C_{26}H_{28}BrN_2O_4^+$ ($[M+H]^+$) 511.1227, found 511.1238.



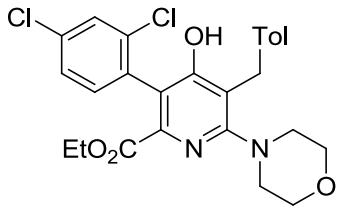
3ja, Ethyl 4-hydroxy-5-(4-methylbenzyl)-6-morpholino-3-(*m*-tolyl)picolinate. White solid in 50% yield, 66.9 mg, m.p. 142-144 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.97 (t, J = 7.2 Hz, 3H), 2.30 (s, 3H), 2.37 (s, 3H), 3.15-3.17 (m, 4H), 3.78 (t, J = 4.6 Hz, 4H), 4.06-4.11 (m, 4H), 5.58 (s, 1H), 7.06-7.12 (m, 6H), 7.23 (d, J = 7.6 Hz, 1H), 7.35 (t, J = 7.6 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.6, 21.0, 21.3, 31.1, 50.9, 61.1, 67.1, 115.1, 119.8, 126.8, 127.8, 129.2, 129.3, 129.5, 130.3, 132.2, 135.7, 136.2, 139.2, 146.0, 159.7, 162.0, 166.9. **HRMS** (ESI-TOF) m/z calculated for $C_{27}H_{30}N_2NaO_4^+$ ($[M+Na]^+$) 469.2098, found 469.2100.



3ka, Ethyl 3-(3-chlorophenyl)-4-hydroxy-5-(4-methylbenzyl)-6-morpholinopicolinate. White solid in 56% yield, 78.3 mg, m.p. 150-152 ^{o}C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.02 (t, J = 7.2 Hz, 3H), 2.31 (s, 3H), 3.17 (t, J = 4.8 Hz, 4H), 3.76 (t, J = 4.8 Hz, 4H), 4.07 (s, 2H), 4.11 (q, J = 7.1 Hz, 2H), 5.59 (s, 1H), 7.08 (s, 4H), 7.18-7.21 (m, 1H), 7.32 (s, 1H), 7.38 (d, J = 4.4 Hz, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.6, 20.9, 31.1, 50.8, 61.2, 66.9, 115.2, 118.6, 127.7, 128.1, 128.6, 129.3, 130.1, 130.2, 134.7, 134.9, 135.6, 135.9, 146.1, 159.8, 162.3, 166.4. **HRMS** (ESI-TOF) m/z calculated for $C_{26}H_{28}ClN_2O_4^+$ ($[M+H]^+$) 467.1732, found 467.1734.

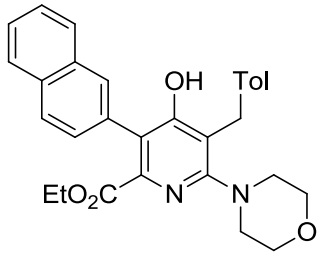


3la, Ethyl 3-(2-chloro-4-methylphenyl)-4-hydroxy-5-(4-methylbenzyl)-6-morpholinopicolinate. White solid in 50% yield, 72.0 mg, m.p. 200-202 ^{o}C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.03 (t, J = 7.0 Hz, 3H), 2.30 (s, 3H), 2.38 (s, 3H), 3.17-3.20 (m, 4H), 3.78 (t, J = 4.4 Hz, 4H), 4.08 (s, 2H), 4.11 (q, J = 7.9 Hz, 2H), 5.22 (s, 1H), 7.07 (s, 4H), 7.15 (t, J = 8.8 Hz, 3H), 7.34 (s, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.7, 21.0, 21.1, 31.2, 50.8, 61.2, 67.0, 115.1, 118.3, 127.7, 128.2, 128.6, 129.3, 130.5, 131.5, 134.5, 135.7, 135.9, 140.7, 145.2, 160.0, 162.2, 166.0. **HRMS** (ESI-TOF) m/z calculated for $C_{27}H_{30}ClN_2O_4^+$ ($[M+H]^+$) 481.1889, found 481.1898.

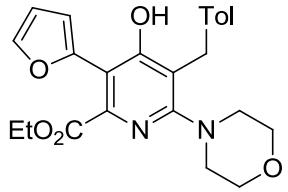


3ma, Ethyl 3-(2,4-dichlorophenyl)-4-hydroxy-5-(4-methylbenzyl)-6-morpholinopicolinate. White solid in 52% yield, 78.0 mg, m.p. 160-162 ^{o}C **.^{1}H NMR** (400 MHz, DMSO-d_6) δ 0.90 (t, J = 6.8 Hz, 3H), 2.23 (s, 3H), 2.94 (s, 4H), 3.65 (s, 4H), 3.94-4.03 (m, 4H), 7.05 (s, 4H), 7.27 (d, J = 8.0 Hz, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.69 (s, 1H), 9.76 (s, 1H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 13.9, 21.0, 30.7, 51.2, 60.9, 66.6,

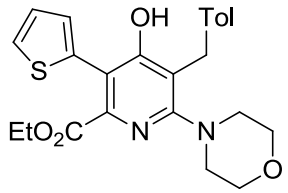
127.5, 128.1, 129.0, 129.3, 133.0, 133.8, 133.8, 135.2, 135.7, 137.0. **HRMS** (ESI-TOF) m/z calculated for $C_{26}H_{26}Cl_2N_2NaO_4^+$ ($[M+Na]^+$) 523.1162, found 523.1158.



3na, Ethyl 4-hydroxy-5-(4-methylbenzyl)-6-morpholino-3-(naphthalen-2-yl)picolinate. White solid in 50% yield, 72.3 mg, m.p. 161-163 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.83 (t, J = 7.2 Hz, 3H), 2.31 (s, 3H), 3.19 (t, J = 4.6 Hz, 3H), 3.79 (t, J = 4.6 Hz, 3H), 4.02 (q, J = 7.1 Hz, 2H), 4.10 (s, 2H), 5.70 (s, 1H), 7.11 (q, J = 7.6 Hz, 4H), 7.40 (dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 1H), 7.80 (s, 1H), 7.82-7.85 (m, 1H), 7.87-7.90 (m, 1H), 7.94 (d, J = 8.4 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.5, 21.0, 31.2, 50.9, 61.1, 67.0, 115.2, 119.7, 126.7, 127.8, 127.5, 127.8, 127.9, 128.8, 129.1, 129.2, 129.9, 133.0, 133.4, 135.7, 136.0, 146.2, 160.0, 162.1, 166.8. **HRMS** (ESI-TOF) m/z calculated for $C_{30}H_{31}N_2O_4^+$ ($[M+H]^+$) 483.2278, found 483.2295.

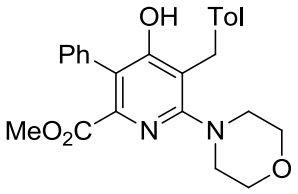


3oa, Ethyl 3-(furan-2-yl)-4-hydroxy-5-(4-methylbenzyl)-6-morpholinopicolinate. White solid in 38% yield, 48.1 mg, m.p. 154-156 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.24 (t, J = 7.2 Hz, 3H), 2.31 (s, 3H), 3.16 (t, J = 4.4 Hz, 4H), 3.76 (t, J = 4.4 Hz, 4H), 4.06 (s, 2H), 4.30 (q, J = 7.1 Hz, 2H), 6.52-6.55 (m, 2H), 6.77 (s, 1H), 7.08 (s, 4H), 7.54 (s, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 14.0, 21.0, 31.1, 50.7, 61.6, 66.9, 108.2, 110.1, 111.7, 114.4, 127.7, 129.3, 135.8, 135.8, 143.0, 146.4, 146.6, 160.0, 162.3, 167.1. **HRMS** (ESI-TOF) m/z calculated for $C_{24}H_{27}N_2O_5^+$ ($[M+H]^+$) 423.1914, found 423.1923.

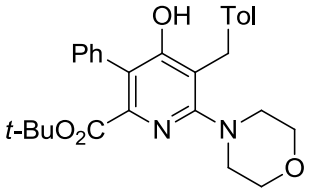


3pa, Ethyl 4-hydroxy-5-(4-methylbenzyl)-6-morpholino-3-(thiophen-2-yl)picolinate. White solid in 50% yield, 65.7 mg, m.p. 177-179 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.08 (t, J = 7.2 Hz, 3H), 2.31 (s, 3H), 3.16-3.18 (m, 4H), 3.76 (t, J = 4.8 Hz, 4H), 4.06 (s, 2H), 4.16 (q, J = 7.2 Hz, 2H), 5.90 (s, 1H), 7.07-7.08 (m, 5H), 7.15 (dd, J_1 = 5.0 Hz, J_2 = 3.4 Hz, 1H), 7.50 (dd, J_1 = 5.2 Hz, J_2 = 1.2 Hz, 1H). **^{13}C NMR** (100

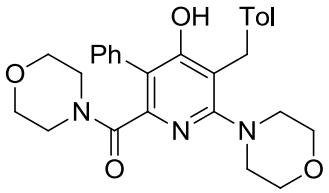
MHz, $CDCl_3$) δ 13.7, 21.0, 31.2, 50.8, 61.4, 67.0, 111.8, 114.4, 127.8, 127.9, 128.4, 129.2, 129.2, 132.2, 135.8, 135.9, 147.4, 160.5, 162.6, 166.6. **HRMS** (ESI-TOF) m/z calculated for $C_{24}H_{27}N_2O_4S^+$ ($[M+H]^+$) 439.1686, found 439.1691.



3qa, Methyl 4-hydroxy-5-(4-methylbenzyl)-6-morpholino-3-phenylpicolinate. White soild in 44% yield, 46.2 mg, m.p. 195-197 ^oC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.30 (s, 3H), 3.16 (t, J = 4.6 Hz, 4H), 3.63 (s, 3H), 3.78 (t, J = 4.6 Hz, 4H), 4.07 (s, 2H), 5.55 (s, 1H), 7.06-7.10 (m, 4H), 7.29-7.31 (m, 2H), 7.40-7.50 (m, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 21.0, 31.2, 50.9, 52.2, 67.1, 115.4, 120.2, 127.8, 128.8, 129.2, 129.4, 129.7, 132.3, 135.8, 136.0, 145.4, 159.8, 162.0, 167.1. **HRMS** (ESI-TOF) m/z calculated for $C_{25}H_{27}N_2O_4^+$ ($[M+H]^+$) 419.1965, found 419.1972.

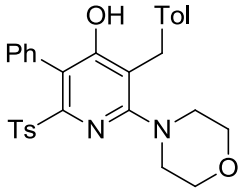


3ra, *tert*-butyl 4-hydroxy-5-(4-methylbenzyl)-6-morpholino-3-phenylpicolinate. White soild in 52% yield, 60.3 mg, m.p. 170-173 ^oC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.19 (s, 9H), 2.30 (s, 3H), 3.17 (t, J = 4.8 Hz, 4H), 3.78 (t, J = 4.6 Hz, 4H), 4.06 (s, 2H), 5.45 (s, 1H), 7.08 (q, J = 6.8 Hz, 4H), 7.29-7.32 (m, 2H), 7.42-7.50 (m, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 21.0, 27.5, 31.1, 50.9, 67.1, 81.9, 114.7, 119.4, 127.8, 128.6, 129.2, 129.3, 130.2, 132.9, 135.7, 136.2, 146.9, 159.7, 162.1, 165.8. **HRMS** (ESI-TOF) m/z calculated for $C_{28}H_{32}N_2NaO_4^+$ ($[M+Na]^+$) 483.2254, found 483.2259.

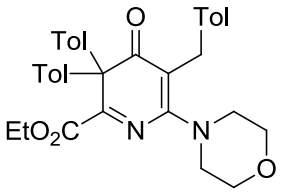


3sa, (4-hydroxy-5-(4-methylbenzyl)-6-morpholino-3-phenylpyridin-2-yl)(morpholino)methanone. White soild in 43% yield, 50.7 mg, m.p. 270-272 ^oC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.30 (s, 3H), 3.12 (t, J = 4.6 Hz, 4H), 3.15 (t, J = 4.6 Hz, 2H), 3.26 (t, J = 4.6 Hz, 2H), 3.46 (t, J = 4.8 Hz, 2H), 3.56 (t, J = 4.8 Hz, 2H), 3.76 (t, J = 4.8 Hz, 4H), 4.06 (s, 2H), 5.63 (s, 1H), 7.09 (q, J = 6.8 Hz, 4H), 7.38-7.44 (m, 3H), 7.46-7.50 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 21.0, 31.1, 41.6, 46.7, 51.0, 66.5, 66.5, 67.0, 113.5,

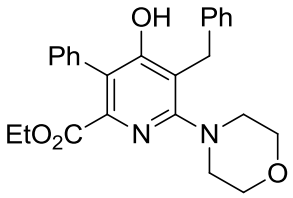
117.5, 127.8, 129.0, 129.3, 129.5, 130.0, 131.4, 135.8, 136.0, 149.5, 159.5, 162.4, 167.1. **HRMS** (ESI-TOF) m/z calculated for $C_{28}H_{32}N_2O_4^+$ ($[M+H]^+$) 474.2387, found 474.2398.



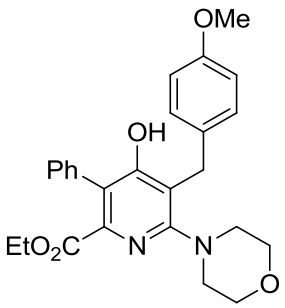
3ta, 3-(4-methylbenzyl)-2-morpholino-5-phenyl-6-tosylpyridin-4-ol. White soild in 34% yield, 42.8 mg, m.p. 214-216 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.29 (s, 3H), 2.43 (s, 3H), 2.90 (t, J = 4.6 Hz, 4H), 3.61 (t, J = 4.6 Hz, 4H), 3.98 (s, 2H), 5.60 (s, 1H), 7.04 (q, J = 7.9 Hz, 4H), 7.28 (d, J = 8.4 Hz, 2H), 7.41-7.43 (m, 2H), 7.48-7.56 (m, 3H), 7.76-7.78 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 21.0, 21.6, 31.3, 50.4, 66.7, 115.2, 118.1, 127.7, 129.0, 129.2, 129.3, 129.4, 129.5, 130.9, 135.5, 135.9, 136.5, 144.0, 152.7, 160.5, 161.1. **HRMS** (ESI-TOF) m/z calculated for $C_{30}H_{31}N_2O_4S^+$ ($[M+H]^+$) 515.1999, found 515.2003.



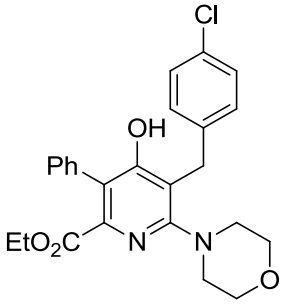
3ua, Ethyl 5-(4-methylbenzyl)-6-morpholino-4-oxo-3,3-diphenyl-3,4-dihydropyridine-2-carboxylate. Orange solid in 40% yield, 64.3 mg, m.p. 166-168 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.91 (t, J = 7.2 Hz, 3H), 2.24 (s, 3H), 2.34 (s, 6H), 3.56 (s, 8H), 3.69 (s, 2H), 3.93 (q, J = 7.1 Hz, 2H), 6.63 (d, J = 7.6 Hz, 2H), 6.87 (d, J = 7.6 Hz, 2H), 7.10 (s, 8H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.5, 20.9, 21.1, 29.7, 48.6, 61.6, 66.2, 67.5, 98.0, 127.4, 128.9, 129.3, 135.0, 135.3, 136.7, 137.4, 158.5, 164.1, 168.4, 194.8. **HRMS** (ESI-TOF) m/z calculated for $C_{32}H_{32}N_2NaO_4^+$ ($[M+Na]^+$) 559.2567, found 559.2540.



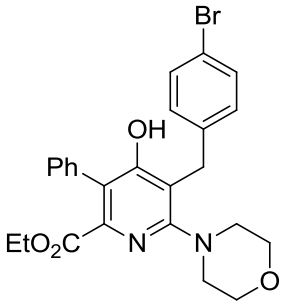
3ab, Ethyl 5-benzyl-4-hydroxy-6-morpholino-3-phenylpicolinate. White solid in 56% yield, 70.2 mg, m.p. 166-168 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.95 (t, J = 7.0 Hz, 3H), 3.16 (t, J = 4.6 Hz, 4H), 3.78 (t, J = 4.6 Hz, 4H), 4.07 (q, J = 7.2 Hz, 2H), 4.12 (s, 2H), 5.52 (s, 1H), 7.17-7.22 (m, 3H), 7.25-7.28 (m, 2H), 7.30-7.33 (m, 2H), 7.41-7.50 (m, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.6, 31.6, 50.9, 61.1, 67.0, 115.1, 119.8, 126.2, 128.0, 128.5, 128.8, 129.4, 129.9, 132.4, 139.3, 146.1, 159.8, 162.2, 166.7. **HRMS** (ESI-TOF) m/z calculated for $C_{26}H_{27}Cl_2N_2O_4^+$ ($[M+H]^+$) 419.1965, found 419.1980.



3ac, Ethyl 4-hydroxy-5-(4-methoxybenzyl)-6-morpholino-3-phenylpicolinate. White solid in 60% yield, 80.7 mg, m.p. 171-173 ^{o}C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.95 (t, J = 7.2 Hz, 3H), 3.17 (t, J = 4.6 Hz, 4H), 3.77-3.80 (m, 7H), 4.04-4.10 (m, 4H), 5.52 (s, 1H), 6.81 (d, J = 8.8 Hz, 2H), 7.12-7.14 (m, 2H), 7.30-7.32 (m, 2H), 7.40-7.49 (m, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.6, 30.7, 50.9, 55.2, 61.1, 67.1, 114.0, 115.4, 119.8, 128.8, 128.9, 129.3, 129.9, 131.1, 132.5, 146.1, 158.1, 159.7, 162.1, 166.7. **HRMS** (ESI-TOF) m/z calculated for $C_{26}H_{28}N_2NaO_5^+$ ($[M+Na]^+$) 471.1890, found 471.1891.

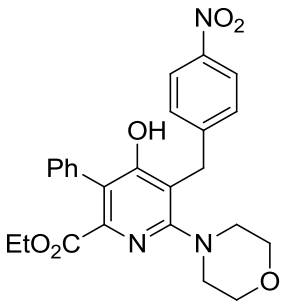


3ad, Ethyl 5-(4-chlorobenzyl)-4-hydroxy-6-morpholino-3-phenylpicolinate. White solid in 40% yield, 54.2 mg, m.p. 174-176 ^{o}C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.94 (t, J = 7.2 Hz, 3H), 3.13 (t, J = 4.6 Hz, 4H), 3.77 (t, J = 4.6 Hz, 4H), 4.04-4.09 (m, 4H), 5.63 (s, 1H), 7.14 (d, J = 8.4 Hz, 2H), 7.22 (d, J = 8.4 Hz, 2H), 7.29-7.31 (m, 2H), 7.41-7.50 (m, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.6, 30.9, 50.9, 61.1, 67.0, 114.8, 119.8, 128.5, 128.9, 129.3, 129.4, 129.8, 131.8, 132.1, 138.0, 146.3, 159.7, 162.1, 166.6. **HRMS** (ESI-TOF) m/z calculated for $C_{25}H_{26}ClN_2O_4^+$ ($[M+H]^+$) 453.1576, found 453.1588.

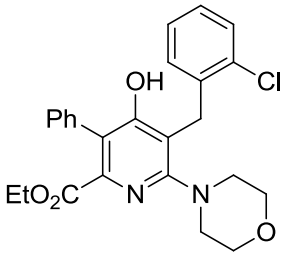


3ae, Ethyl 5-(4-bromobenzyl)-4-hydroxy-6-morpholino-3-phenylpicolinate. White solid in 51% yield, 75.9 mg, m.p. 177-179 ^{o}C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.93 (t, J = 7.0 Hz, 3H), 3.13 (t, J = 4.4 Hz, 4H),

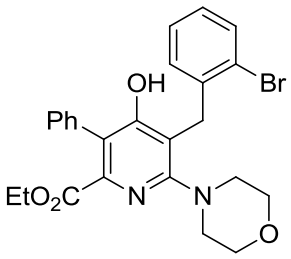
3.76 (t, *J* = 4.4 Hz, 4H), 4.04-4.08 (m, 4H), 5.71 (s, 1H), 7.08 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 7.2 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.43-7.49 (m, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.5, 30.9, 50.9, 61.2, 66.9, 114.6, 119.8, 119.8, 128.9, 129.4, 129.7, 129.8, 131.4, 132.1, 138.5, 146.2, 159.6, 162.0, 166.6. **HRMS** (ESI-TOF) m/z calculated for $C_{25}H_{25}BrN_2NaO_4^+$ ($[M+Na]^+$) 519.0890, found 519.0886.



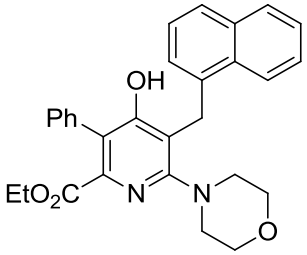
3af, Ethyl 4-hydroxy-6-morpholino-5-(4-nitrobenzyl)-3-phenylpicolinate. Yellow solid in 42% yield, 58.4 mg, m.p. 160-162 ^{o}C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.95 (t, *J* = 7.2 Hz, 3H), 3.14 (t, *J* = 4.6 Hz, 4H), 3.78 (t, *J* = 4.6 Hz, 4H), 4.07 (q, *J* = 7.1 Hz, 2H), 4.19 (s, 2H), 5.61 (s, 1H), 7.29-7.31 (m, 2H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.43-7.51 (m, 3H), 8.12 (d, *J* = 8.4 Hz, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.6, 31.5, 51.0, 61.3, 66.9, 113.9, 119.9, 123.6, 128.8, 129.1, 129.6, 129.7, 131.7, 146.4, 146.6, 147.6, 159.6, 162.1, 166.5. **HRMS** (ESI-TOF) m/z calculated for $C_{25}H_{26}N_3O_6^+$ ($[M+H]^+$) 464.1816, found 463.1812.



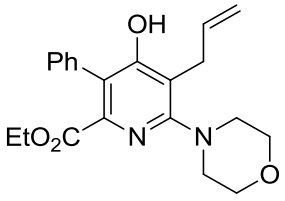
3ag, Ethyl 5-(2-chlorobenzyl)-4-hydroxy-6-morpholino-3-phenylpicolinate. White solid in 65% yield, 88.2 mg, m.p. 158-160 ^{o}C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.95 (t, *J* = 7.0 Hz, 3H), 3.12 (t, *J* = 4.4 Hz, 4H), 3.74 (t, *J* = 4.6 Hz, 4H), 4.08 (q, *J* = 7.1 Hz, 2H), 4.15 (s, 2H), 5.58 (s, 1H), 6.94 (dd, J_1 = 6.8 Hz, J_2 = 2.4 Hz, 1H), 7.11-7.18 (m, 2H), 7.33 (d, *J* = 6.4 Hz, 2H), 7.39 (dd, J_1 = 7.2 Hz, J_2 = 2.4 Hz, 1H), 7.42-7.51 (m, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.6, 29.7, 50.6, 61.2, 66.9, 113.0, 119.3, 126.8, 127.5, 128.3, 128.9, 129.3, 129.5, 129.8, 132.1, 134.2, 136.6, 146.3, 159.9, 162.1, 166.7. **HRMS** (ESI-TOF) m/z calculated for $C_{25}H_{25}ClN_2NaO_4^+$ ($[M+Na]^+$) 475.1395, found 475.1393.



3ah, Ethyl 5-(2-bromobenzyl)-4-hydroxy-6-morpholino-3-phenylpicolinate. White solid in 60% yield, 89.3 mg, m.p. 148-150 ^{o}C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.95 (t, J = 7.0 Hz, 3H), 3.12 (t, J = 4.4 Hz, 4H), 3.75 (t, J = 4.4 Hz, 4H), 4.08 (q, J = 7.1 Hz, 2H), 4.13 (s, 2H), 5.54 (s, 1H), 6.92 (d, J = 4.0 Hz, 1H), 7.08 (t, J = 7.6 Hz, 1H), 7.18 (t, J = 7.6 Hz, 1H), 7.43 (d, J = 3.4 Hz, 2H), 7.42-7.51 (m, 3H), 7.59 (d, J = 4.0 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.6, 32.7, 50.6, 61.2, 67.0, 113.1, 119.2, 124.9, 127.4, 127.8, 128.4, 128.9, 129.5, 129.8, 132.1, 132.7, 138.2, 146.3, 159.8, 162.1, 166.7. **HRMS** (ESI-TOF) m/z calculated for $C_{25}H_{25}BrN_2NaO_4^+$ ($[M+Na]^+$) 519.0890, found 519.0873.

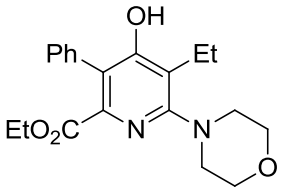


3ai, Ethyl 4-hydroxy-6-morpholino-5-(naphthalen-1-ylmethyl)-3-phenylpicolinate. White solid in 50% yield, 70.2 mg, m.p. 163-165 ^{o}C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.97 (t, J = 7.2 Hz, 3H), 3.18 (t, J = 4.4 Hz, 4H), 3.68 (t, J = 4.4 Hz, 4H), 4.09 (t, J = 7.2 Hz, 2H), 4.51 (s, 2H), 5.58 (s, 1H), 7.13 (d, J = 6.8 Hz, 1H), 7.33-7.37 (m, 3H), 7.40-7.48 (m, 3H), 7.51-7.60 (m, 2H), 7.74 (d, J = 8.0 Hz, 1H), 7.88 (d, J = 8.0 Hz, 1H), 8.24 (d, J = 8.0 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.6, 21.0, 27.8, 31.2, 52.8, 61.1, 115.4, 119.7, 127.7, 128.4, 128.7, 129.1, 129.2, 129.3, 129.8, 132.4, 135.7, 136.0, 145.9, 146.4, 159.7, 162.9, 166.7. **HRMS** (ESI-TOF) m/z calculated for $C_{29}H_{29}N_2O_4^+$ ($[M+H]^+$) 469.2122, found 469.2144.

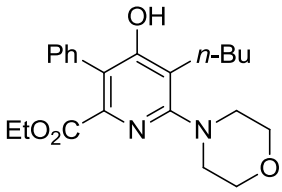


3aj, Ethyl 5-allyl-4-hydroxy-6-morpholino-3-phenylpicolinate. White solid in 48% yield, 53.1 mg, m.p. 137-139 ^{o}C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.93 (t, J = 7.0 Hz, 3H), 3.24 (t, J = 4.4 Hz, 4H), 3.48 (d, J = 5.2 Hz, 2H), 3.84 (t, J = 4.4 Hz, 4H), 4.05 (q, J = 7.2 Hz, 2H), 5.05-5.13 (m, 2H), 5.58 (s, 1H), 6.02-6.12 (m, 1H), 7.31 (d, J = 7.2 Hz, 2H), 7.41-7.50 (m, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.6, 30.4, 50.9, 61.1,

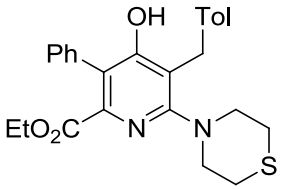
67.1, 113.6, 116.0, 119.7, 128.7, 129.2, 129.8, 132.5, 135.3, 145.9, 159.7, 161.8, 166.8. **HRMS** (ESI-TOF) m/z calculated for $C_{21}H_{24}N_2NaO_4^+$ ([M+Na]$^+$) 391.1628, found 391.1644.



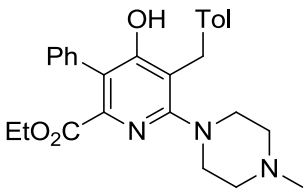
3ak, Ethyl 5-ethyl-4-hydroxy-6-morpholino-3-phenylpicolinate. White solid in 40% yield, 42.7 mg, m.p. 157-159 ^{o}C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.93 (t, J = 7.0 Hz, 3H), 1.24 (t, J = 7.4 Hz, 3H), 2.71 (q, J = 7.5 Hz, 2H), 3.22 (d, J = 4.6 Hz, 4H), 3.86 (t, J = 4.6 Hz, 4H), 4.04 (q, J = 7.1 Hz, 2H), 5.51 (s, 1H), 7.29-7.31 (m, 2H), 7.42-7.51 (m, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 12.8, 13.6, 19.1, 51.2, 61.0, 67.1, 119.0, 119.9, 128.8, 129.4, 129.9, 132.5, 145.0, 159.3, 161.6, 166.7. **HRMS** (ESI-TOF) m/z calculated for $C_{20}H_{24}N_2NaO_4^+$ ([M+Na]$^+$) 379.1628, found 379.1634.



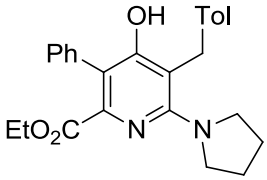
3al, Ethyl 5-butyl-4-hydroxy-6-morpholino-3-phenylpicolinate. White solid in 50% yield, 57.6 mg, m.p. 145-147 ^{o}C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.91-0.97 (m, 6H), 1.35-1.45 (m, 2H), 1.57-1.65 (m, 2H), 2.66 (t, J = 8.0 Hz, 2H), 3.20 (t, J = 4.6 Hz, 4H), 3.85 (d, J = 4.6 Hz, 4H), 4.04 (q, J = 7.2 Hz, 2H), 5.50 (s, 1H), 7.29-7.31 (m, 2H), 7.42-7.51 (m, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.6, 13.8, 23.1, 25.4, 30.4, 51.2, 61.0, 67.1, 118.1, 120.0, 128.7, 129.4, 129.9, 132.6, 144.9, 159.3, 161.8, 166.7. **HRMS** (ESI-TOF) m/z calculated for $C_{22}H_{29}N_2O_4^+$ ([M+H]$^+$) 385.2122, found 385.2140.



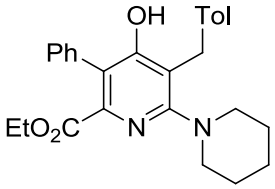
3am, Ethyl 4-hydroxy-5-(4-methylbenzyl)-3-phenyl-6-thiomorpholinopicolinate. White solid in 60% yield, 80.7 mg, m.p. 155-157 ^{o}C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.95 (t, J = 7.2 Hz, 3H), 2.30 (s, 3H), 2.73 (t, J = 5.2 Hz, 4H), 3.42 (t, J = 5.2 Hz, 4H), 4.03 (s, 2H), 4.06 (q, J = 7.1 Hz, 2H), 5.58 (s, 1H), 7.06-7.11 (m, 4H), 7.30-7.32 (m, 2H), 7.40-7.50 (m, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.6, 21.0, 27.8, 31.2, 52.8, 61.1, 115.5, 119.7, 127.8, 128.7, 129.2, 129.3, 129.9, 132.4, 135.7, 136.1, 146.0, 159.8, 162.9, 166.7. **HRMS** (ESI-TOF) m/z calculated for $C_{26}H_{29}N_2O_3S^+$ ([M+H]$^+$) 449.1893, found 449.1904.



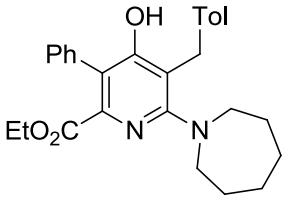
3an, Ethyl 4-hydroxy-5-(4-methylbenzyl)-6-(4-methylpiperazin-1-yl)-3-phenylpicolinate. White oil in 40% yield, 53.4 mg. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.95 (t, J = 7.2 Hz, 3H), 2.30 (s, 3H), 2.86 (s, 6H), 4.04-4.10 (m, 4H), 5.46 (s, 1H), 7.06-7.11 (m, 4H), 7.31 (d, J = 6.8 Hz, 2H), 7.40-7.48 (m, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.6, 21.0, 31.4, 42.5, 42.9, 61.0, 113.0, 118.4, 127.8, 128.3, 128.5, 129.0, 129.1, 129.2, 130.0, 130.5, 132.8, 135.5, 136.4, 159.7. **HRMS** (ESI-TOF) m/z calculated for $C_{27}H_{32}N_3O_3^+$ ($[M+H]^+$) 446.2438, found 446.2445.



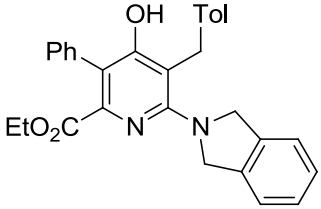
3ao, Ethyl 4-hydroxy-5-(4-methylbenzyl)-3-phenyl-6-(pyrrolidin-1-yl)picolinate. Yellow oil in 43% yield, 53.7 mg. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.95 (t, J = 7.0 Hz, 3H), 1.81-1.84 (m, 4H), 2.31 (s, 3H), 3.53 (t, J = 6.4 Hz, 4H), 4.07 (q, J = 7.2 Hz, 2H), 4.13 (s, 2H), 5.42 (s, 1H), 7.08 (s, 4H), 7.31 (d, J = 7.2 Hz, 2H), 7.37-7.46 (m, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.6, 20.1, 25.6, 30.8, 50.2, 60.9, 108.0, 115.7, 127.6, 128.3, 129.0, 129.2, 130.1, 133.1, 135.3, 137.2, 145.3, 159.5, 167.2. **HRMS** (ESI-TOF) m/z calculated for $C_{26}H_{29}N_2O_3^+$ ($[M+H]^+$) 417.2173, found 417.2181.



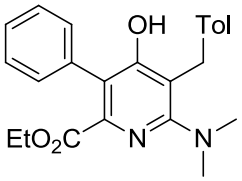
3ap, Ethyl 4-hydroxy-5-(4-methylbenzyl)-3-phenyl-6-(piperidin-1-yl)picolinate. Yellow solid in 35% yield, 45.2 mg, m.p. 149-151 ^{o}C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.93 (t, J = 7.2 Hz, 3H), 1.55-1.60 (m, 2H), 1.63-1.67 (m, 4H), 2.30 (s, 3H), 3.12 (t, J = 5.4 Hz, 4H), 4.03-4.08 (m, 4H), 5.43 (s, 1H), 7.06 (d, J = 8.0 Hz, 2H), 7.13 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 7.2 Hz, 2H), 7.38-7.49 (m, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.5, 20.9, 24.5, 26.1, 31.2, 51.7, 60.9, 115.4, 119.3, 127.9, 128.5, 129.0, 129.1, 129.9, 132.8, 135.5, 136.5, 145.8, 159.4, 163.4, 166.9. **HRMS** (ESI-TOF) m/z calculated for $C_{27}H_{31}N_2O_3^+$ ($[M+H]^+$) 431.2329, found 431.2337.



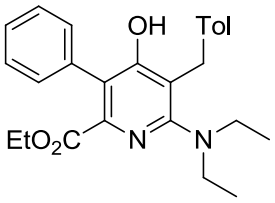
3aq, Ethyl 6-(azepan-1-yl)-4-hydroxy-5-(4-methylbenzyl)-3-phenylpicolinate. White solid in 51% yield, 68.0 mg, m.p. 100-102 ^{o}C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 0.82 (t, J = 7.2 Hz, 3H), 1.57 (s, 8H), 2.24 (s, 3H), 3.21 (t, J = 4.8 Hz, 4H), 3.91 (q, J = 7.1 Hz, 2H), 3.99 (s, 2H), 7.23 (d, J = 7.2 Hz, 2H), 7.32-7.41 (m, 3H), 9.26 (s, 1H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 13.6, 21.0, 27.2, 29.2, 31.4, 52.7, 60.9, 112.1, 117.5, 127.6, 128.4, 129.0, 129.2, 129.9, 132.9, 135.4, 136.4, 145.1, 159.7, 163.3, 167.0. **HRMS** (ESI-TOF) m/z calculated for $C_{28}H_{33}N_2O_3^+$ ([M+H]$^+$) 445.2486, found 445.2498.



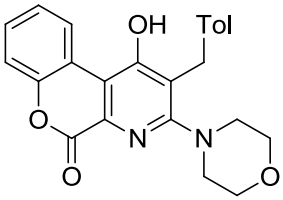
3ar, Ethyl 4-hydroxy-6-(isoindolin-2-yl)-5-(4-methylbenzyl)-3-phenylpicolinate. Yellow solid in 45% yield, 62.7 mg, m.p. 112-114 ^{o}C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.97 (t, J = 7.2 Hz, 3H), 2.31 (s, 3H), 4.09 (q, J = 7.1 Hz, 2H), 4.28 (s, 2H), 5.00 (s, 4H), 5.48 (s, 1H), 7.08-7.12 (m, 4H), 7.21 (s, 4H), 7.33 (d, J = 6.8 Hz, 2H), 7.39-7.48 (m, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.6, 21.0, 29.7, 30.6, 55.7, 61.0, 108.2, 116.0, 122.3, 126.9, 127.6, 128.5, 129.2, 129.3, 130.2, 133.0, 135.5, 137.1, 137.9, 159.9, 167.1. **HRMS** (ESI-TOF) m/z calculated for $C_{36}H_{29}N_2O_3^+$ ([M+H]$^+$) 465.2173, found 465.2174.



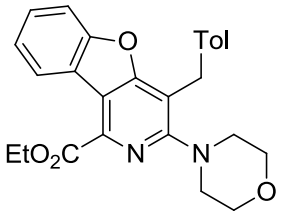
3as, ethyl 6-(dimethylamino)-4-hydroxy-5-(4-methylbenzyl)-3-phenylpicolinate. Yellow oil in 17% yield, 16.6 mg. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.94 (t, J = 7.2 Hz, 3H), 2.30 (s, 3H), 2.86 (s, 6H), 4.04-4.09 (m, 4H), 5.46 (s, 1H), 7.06-7.11 (m, 4H), 7.30 (d, J = 6.8 Hz, 2H), 7.37-7.47 (m, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.6, 21.0, 31.4, 42.5, 61.0, 113.0, 118.4, 127.8, 128.5, 129.1, 129.2, 129.9, 132.8, 135.5, 136.3, 145.4, 159.6, 163.1, 167.0. **HRMS** (ESI-TOF) m/z calculated for $C_{24}H_{26}N_2O_3Na^+$ ([M+Na]$^+$) 413.1836, found 413.1841.



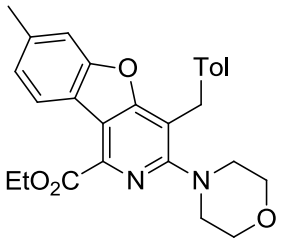
3at, ethyl 6-(diethylamino)-4-hydroxy-5-(4-methylbenzyl)-3-phenylpicolinate. Yellow oil in 26% yield, 26.6 mg. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.95 (t, J = 7.2 Hz, 3H), 1.10 (t, J = 7.0 Hz, 6H), 2.30 (s, 3H), 3.20 (q, J = 6.9 Hz, 4H), 4.04-4.09 (m, 4H), 5.46 (s, 1H), 7.08 (q, J = 8.0 Hz, 4H), 7.32 (d, J = 7.2 Hz, 2H), 7.40-7.47 (m, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.3, 13.6, 21.0, 31.2, 45.5, 60.9, 115.2, 118.5, 127.7, 128.5, 129.0, 129.2, 129.9, 132.8, 135.4, 136.5, 145.4, 159.5, 162.2, 167.0. **HRMS** (ESI-TOF) m/z calculated for $C_{26}H_{30}N_2O_3Na^+$ ($[M+Na]^+$) 441.2149, found 441.2148.



4a, 1-hydroxy-2-(4-methylbenzyl)-3-morpholino-5*H*-chromeno[3,4-*b*]pyridin-5-one. White solid in 70% yield, 56.0 mg, m.p. 195-197 ^{o}C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.26 (s, 3H), 3.13 (t, J = 4.4 Hz, 4H), 3.79 (t, J = 4.2 Hz, 4H), 4.01 (s, 2H), 7.02 (d, J = 8.0 Hz, 2H), 7.11 (d, J = 8.0 Hz, 2H), 7.32-7.38 (m, 2H), 7.45-7.49 (m, 1H), 8.97 (s, 1H), 9.67 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 15.2, 20.9, 30.5, 49.8, 66.5, 116.2, 117.2, 121.3, 122.1, 125.2, 125.6, 127.7, 127.9, 129.1, 129.7, 135.4, 136.5, 149.1, 151.6, 158.3, 178.0. **HRMS** (ESI-TOF) m/z calculated for $C_{24}H_{23}N_2O_4^+$ ($[M+H]^+$) 403.1652, found 403.1661.



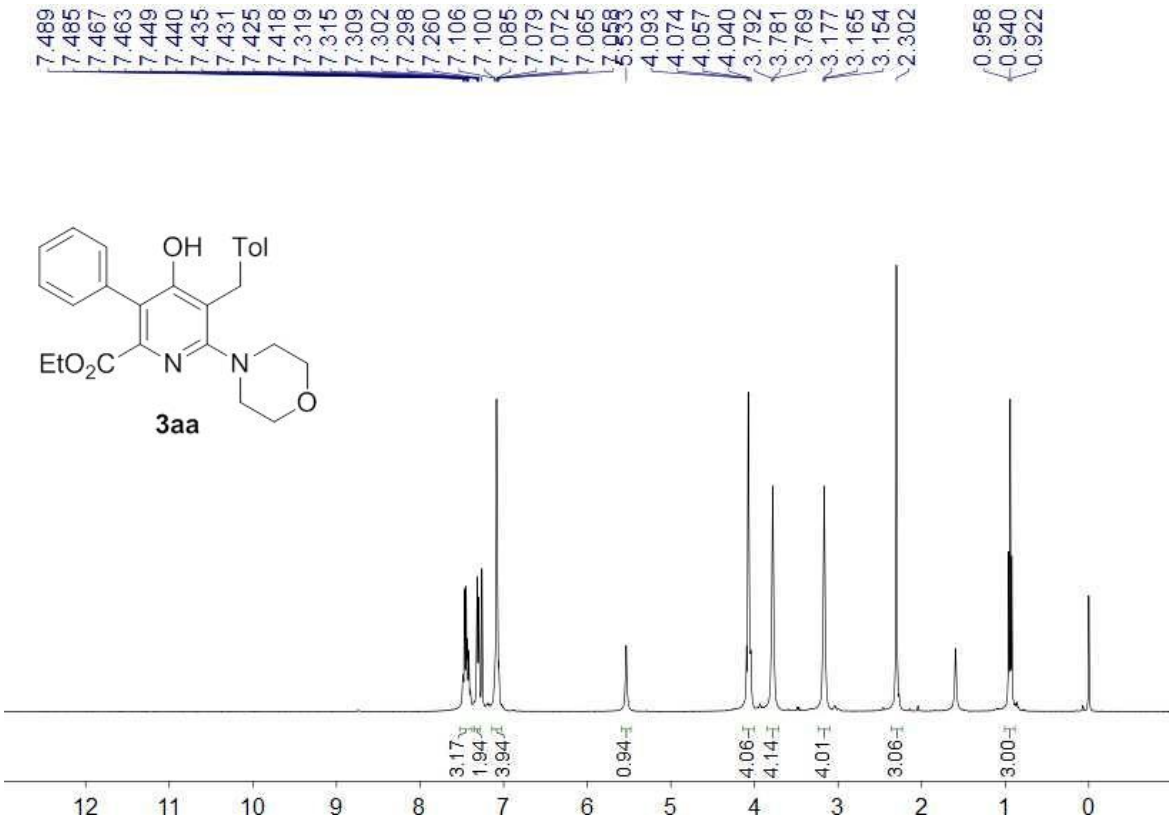
5a, Ethyl 4-(4-methylbenzyl)-3-morpholinobenzofuro[3,2-*c*]pyridine-1-carboxylate. White solid in 58% yield, 74.9 mg. m.p. 112-114 ^{o}C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.52 (t, J = 7.2 Hz, 3H), 2.29 (s, 3H), 3.23 (t, J = 4.6 Hz, 4H), 3.81 (t, J = 4.6 Hz, 4H), 4.36 (s, 2H), 4.58 (q, J = 7.2 Hz, 2H), 7.05 (d, J = 7.6 Hz, 2H), 7.11 (d, J = 8.0 Hz, 2H), 7.37-7.41 (m, 1H), 7.47-7.53 (m, 2H), 8.70 (d, J = 7.6 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 14.4, 21.0, 31.1, 51.1, 61.7, 67.1, 111.3, 114.4, 118.5, 121.7, 123.7, 126.0, 128.0, 128.4, 129.2, 135.6, 135.9, 138.8, 157.1, 159.0, 163.4, 166.0. **HRMS** (ESI-TOF) m/z calculated for $C_{26}H_{27}N_2O_4^+$ ($[M+H]^+$) 431.1965, found 431.1973.



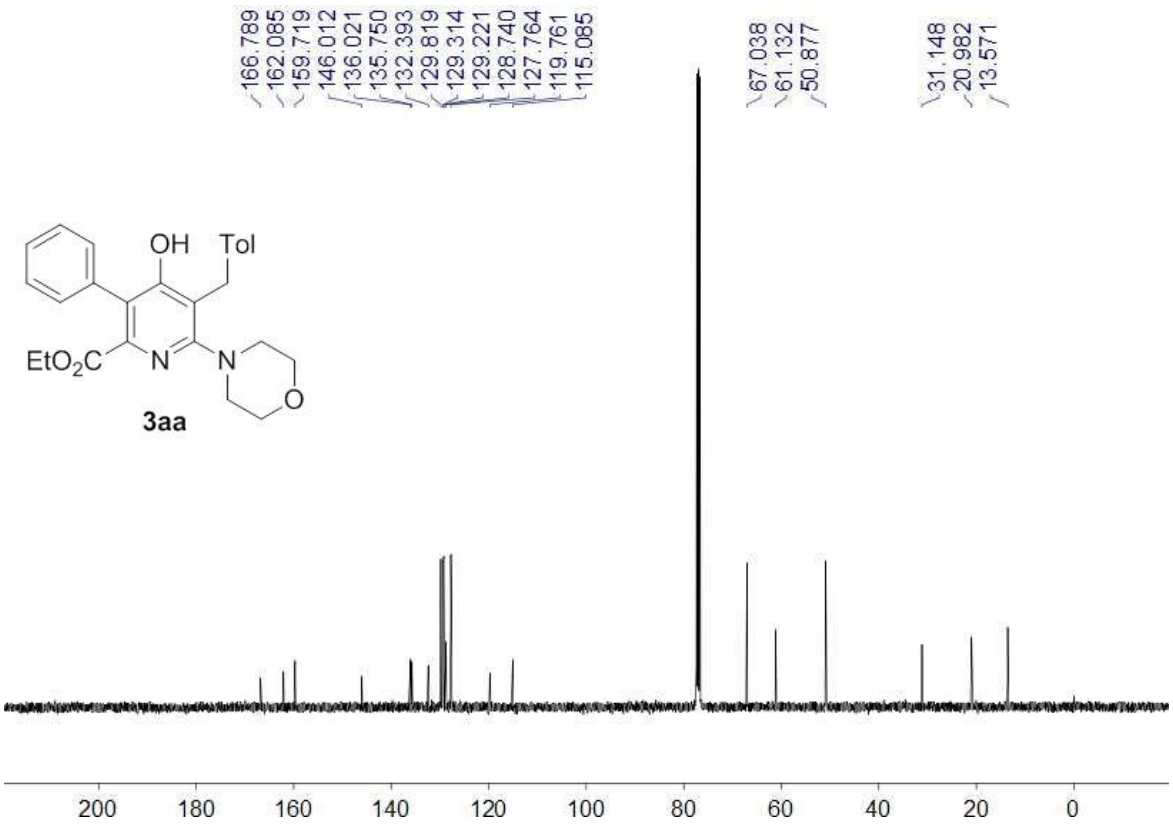
5b, Ethyl 7-methyl-4-(4-methylbenzyl)-3-morpholinobenzofuro[3,2-*c*]pyridine-1-carboxylate. White solid in 70% yield, 93.3 mg. m.p. 107-109 ^{o}C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.52 (t, J = 7.2 Hz, 3H), 2.29 (s, 3H), 2.51 (s, 3H), 3.22 (t, J = 4.6 Hz, 4H), 3.82 (t, J = 4.8 Hz, 4H), 4.35 (s, 2H), 4.57 (q, J = 7.1 Hz, 2H), 7.05 (d, J = 8.0 Hz, 2H), 7.11 (d, J = 8.0 Hz, 2H), 7.20 (d, J = 8.4 Hz, 1H), 7.32 (s, 1H), 8.56 (d, J = 8.0 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 14.3, 20.9, 21.8, 31.1, 51.1, 61.6, 67.1, 111.6, 114.6, 118.8, 119.0, 124.9, 125.5, 128.0, 129.2, 135.7, 135.8, 138.2, 139.2, 157.5, 158.7, 163.4, 166.0. **HRMS** (ESI-TOF) m/z calculated for $C_{27}H_{29}N_2O_4^+$ ($[M+H]^+$) 445.2122, found 445.2137.

4. Copies of ^{1}H NMR and ^{13}C NMR spectra of compounds 3, 4 and 5

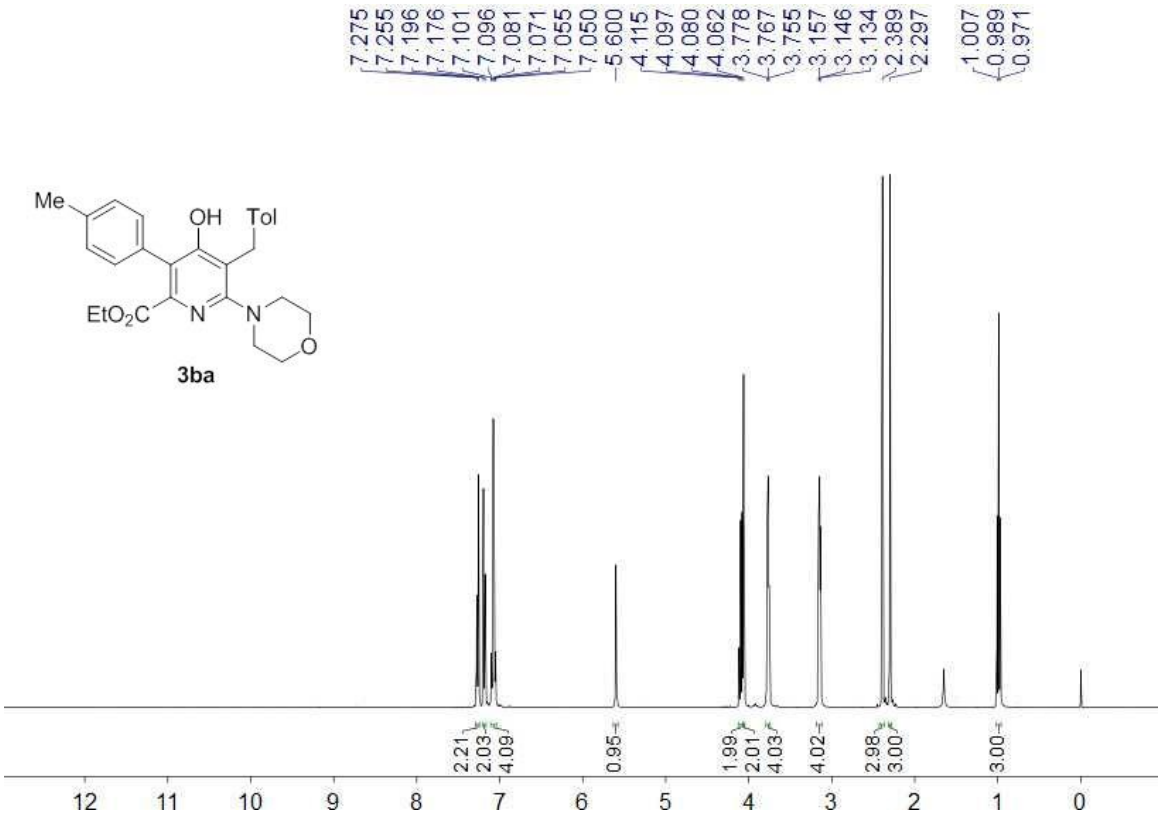
^{1}H NMR spectrum of the compound **3aa** (400 MHz, $CDCl_3$)



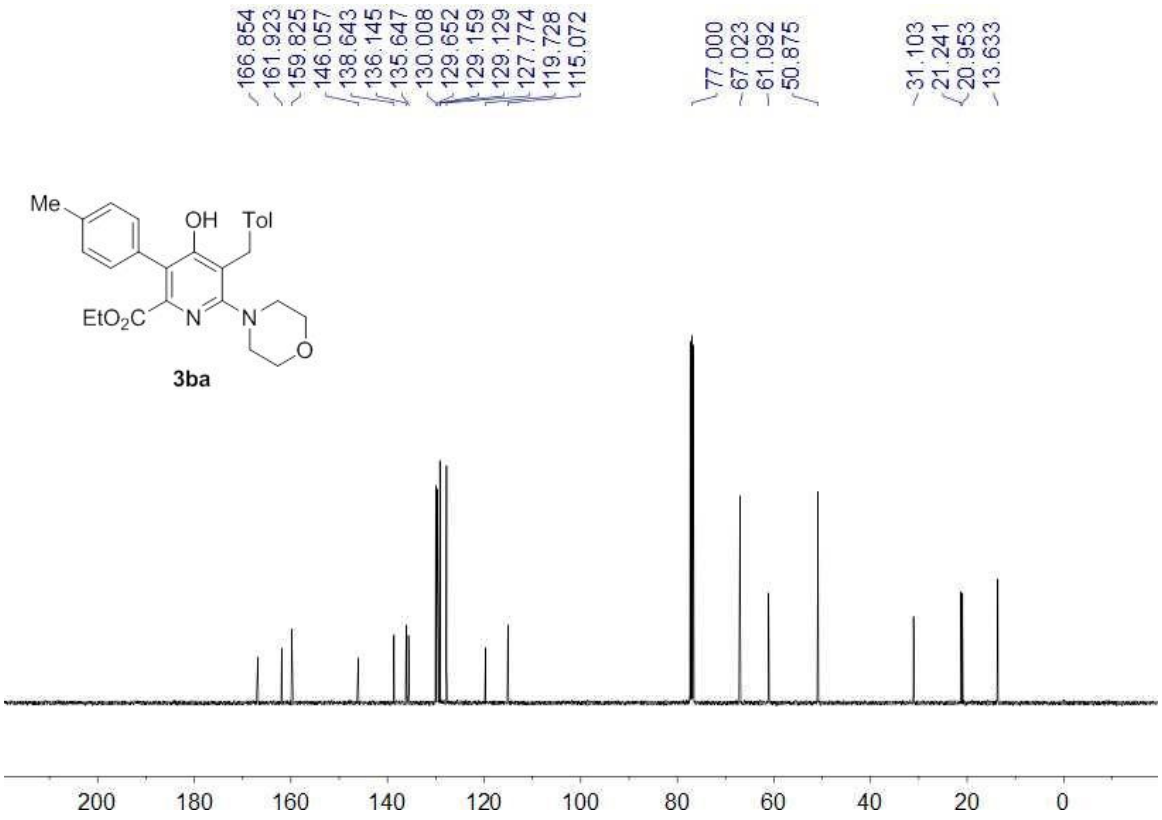
^{13}C NMR spectrum of the compound **3aa** (100 MHz, $CDCl_3$)



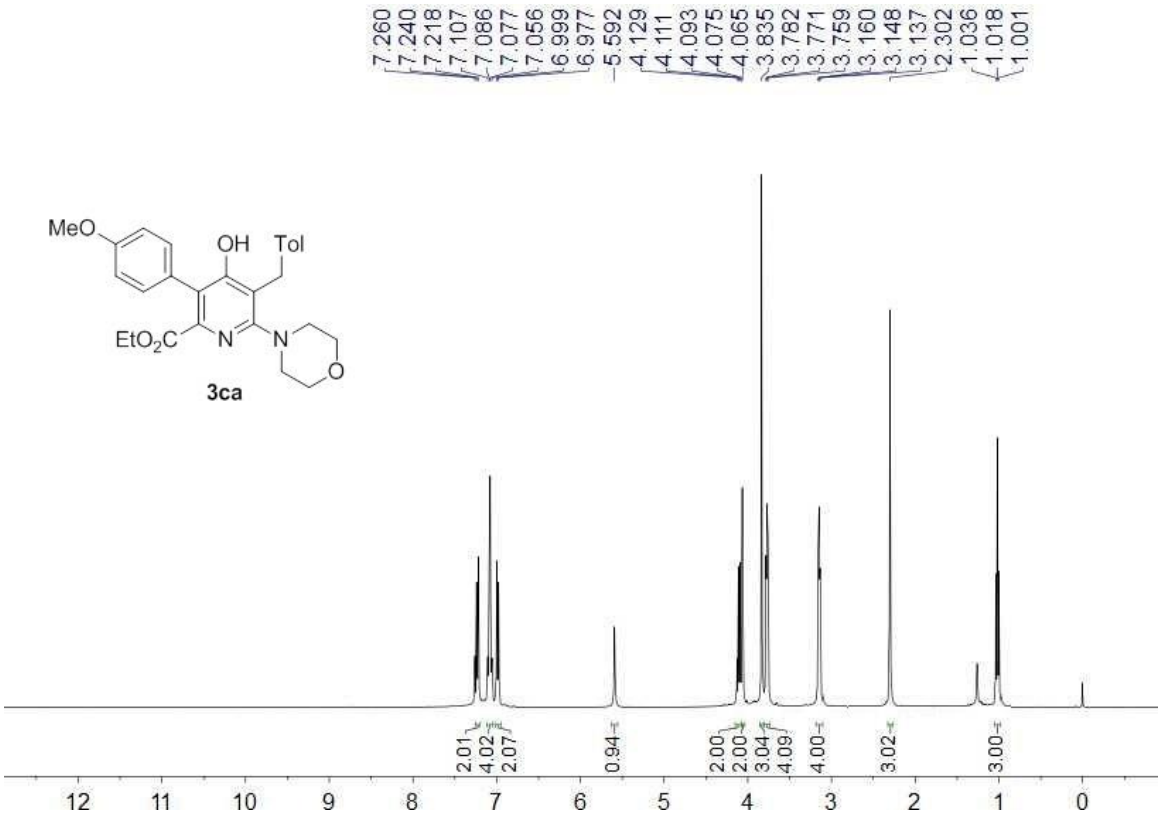
^{1}H NMR spectrum of the compound **3ba** (400 MHz, $CDCl_3$)



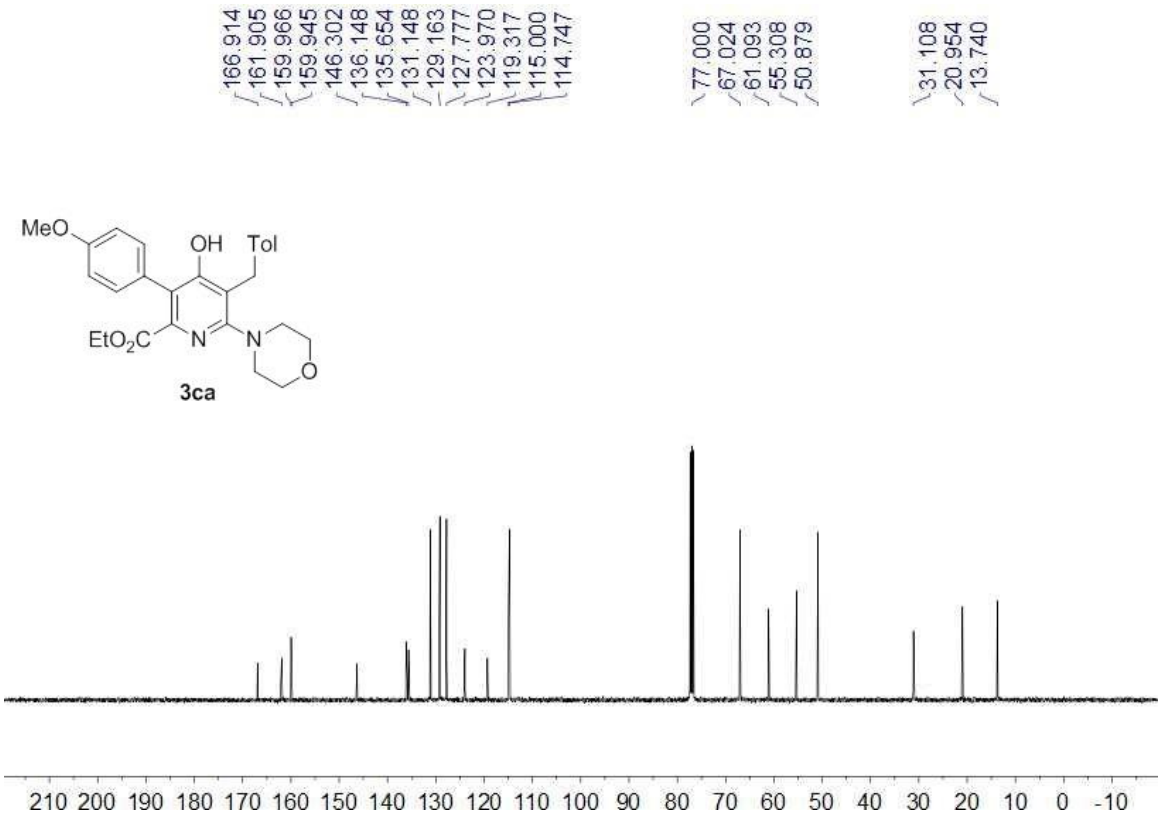
^{13}C NMR spectrum of the compound **3ba** (100 MHz, $CDCl_3$)



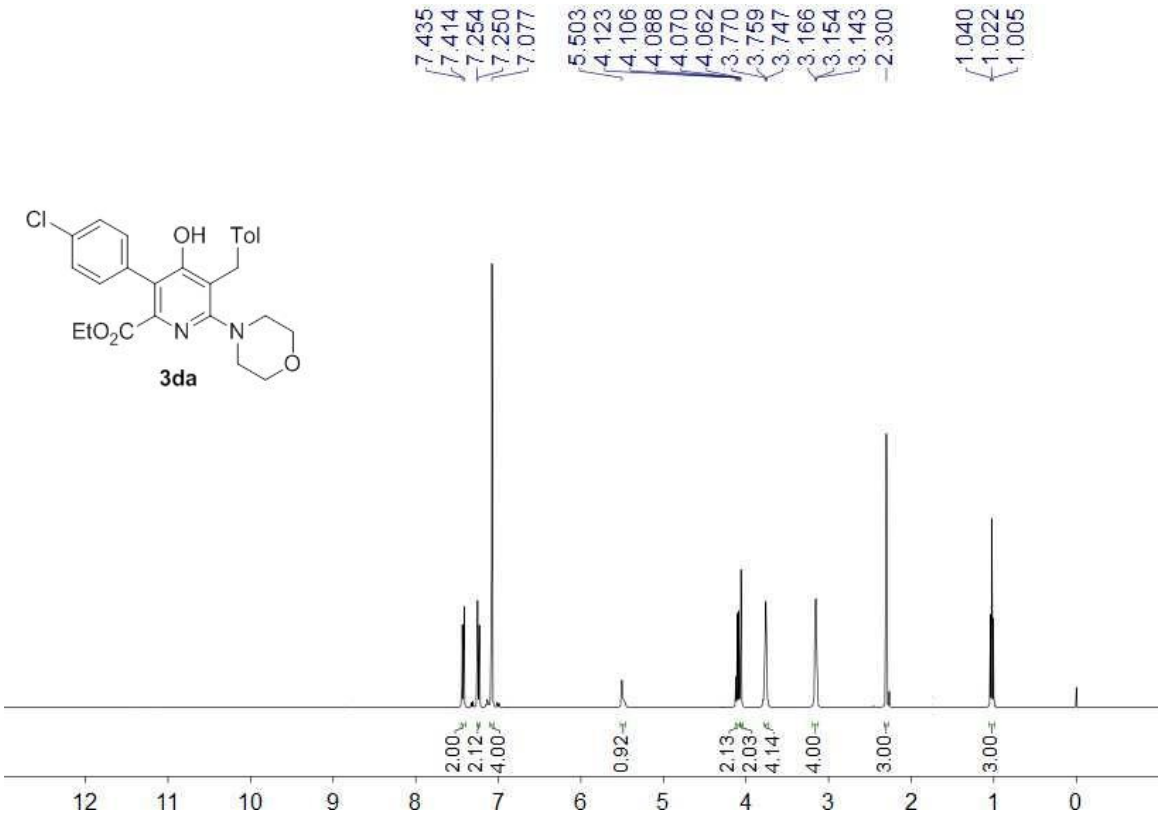
^{1}H NMR spectrum of the compound **3ca** (400 MHz, $CDCl_3$)



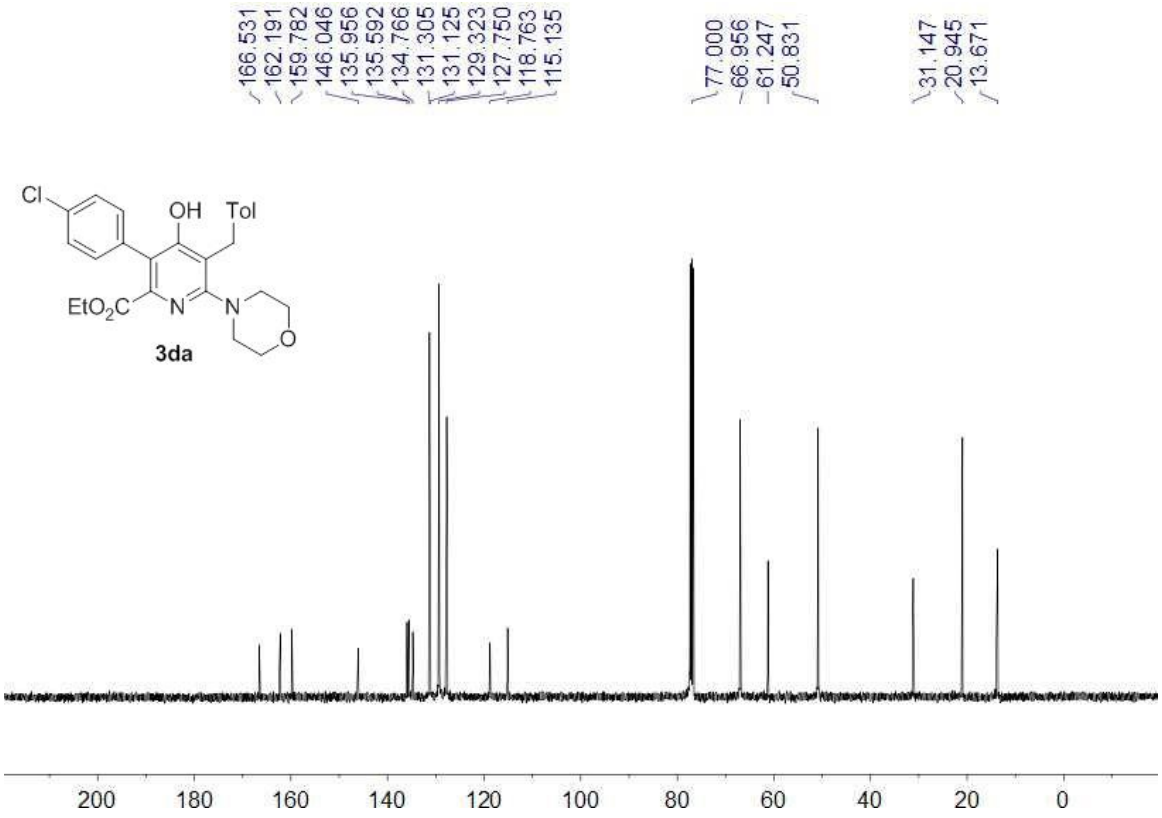
^{13}C NMR spectrum of the compound **3ca** (100 MHz, $CDCl_3$)



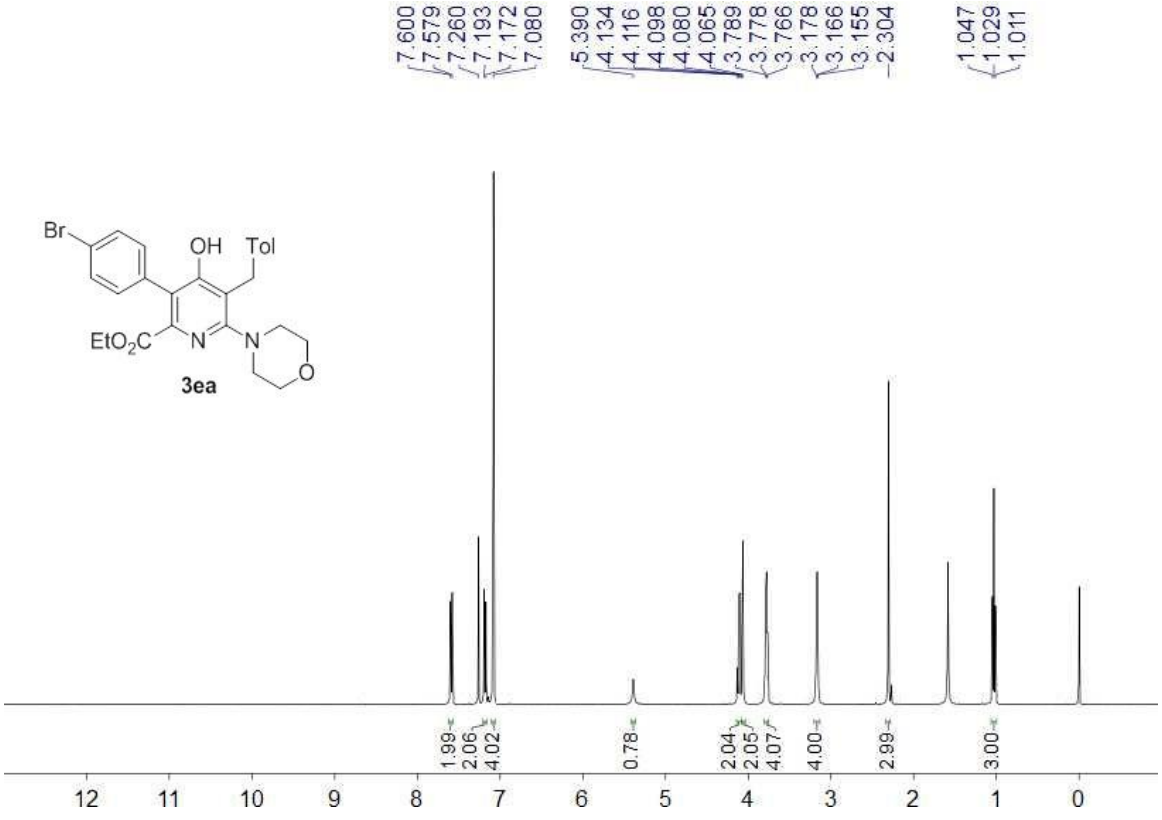
^{1}H NMR spectrum of the compound **3da** (400 MHz, $CDCl_3$)



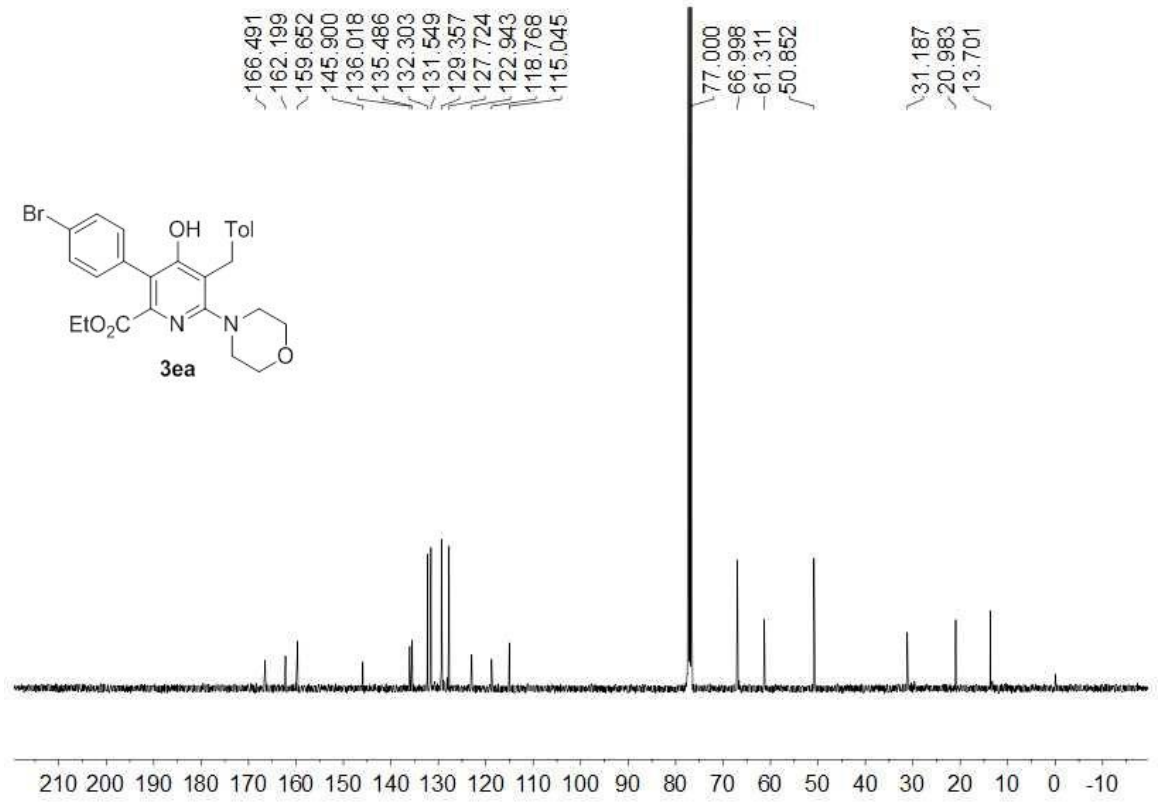
^{13}C NMR spectrum of the compound **3da** (100 MHz, $CDCl_3$)



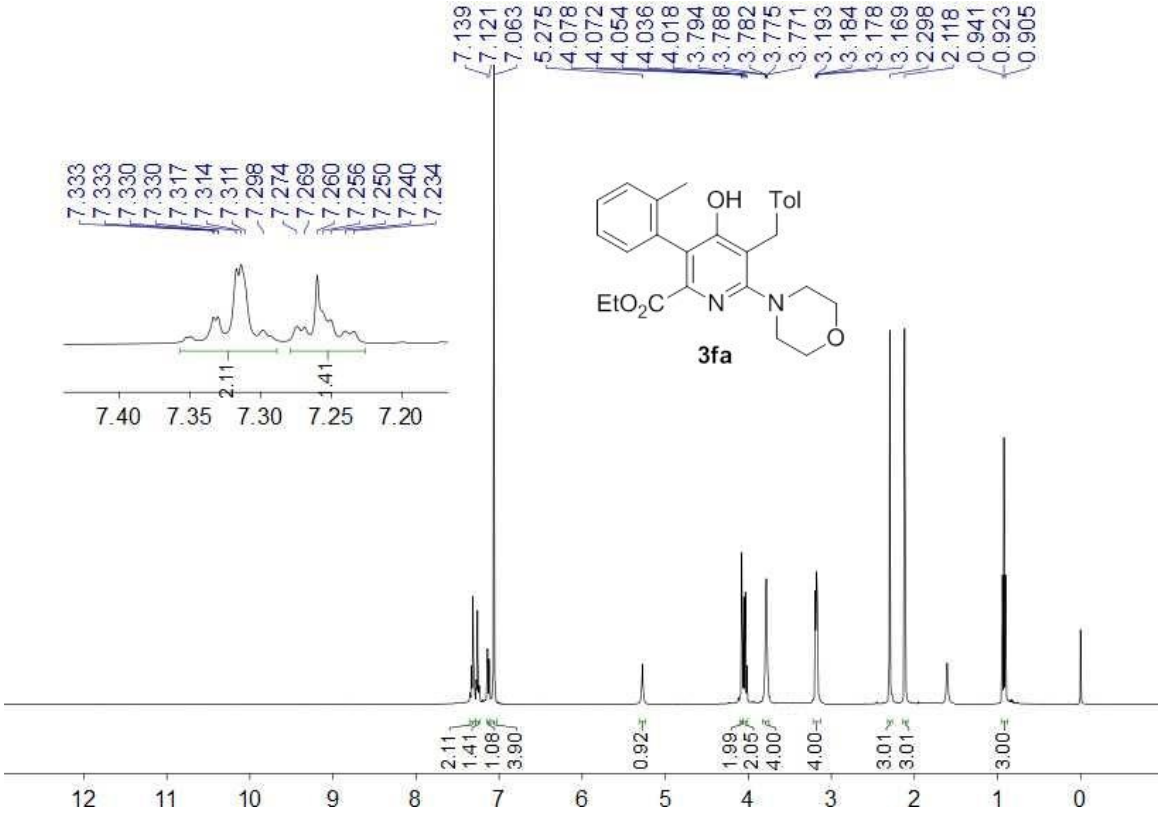
^{1}H NMR spectrum of the compound **3ea** (400 MHz, $CDCl_3$)



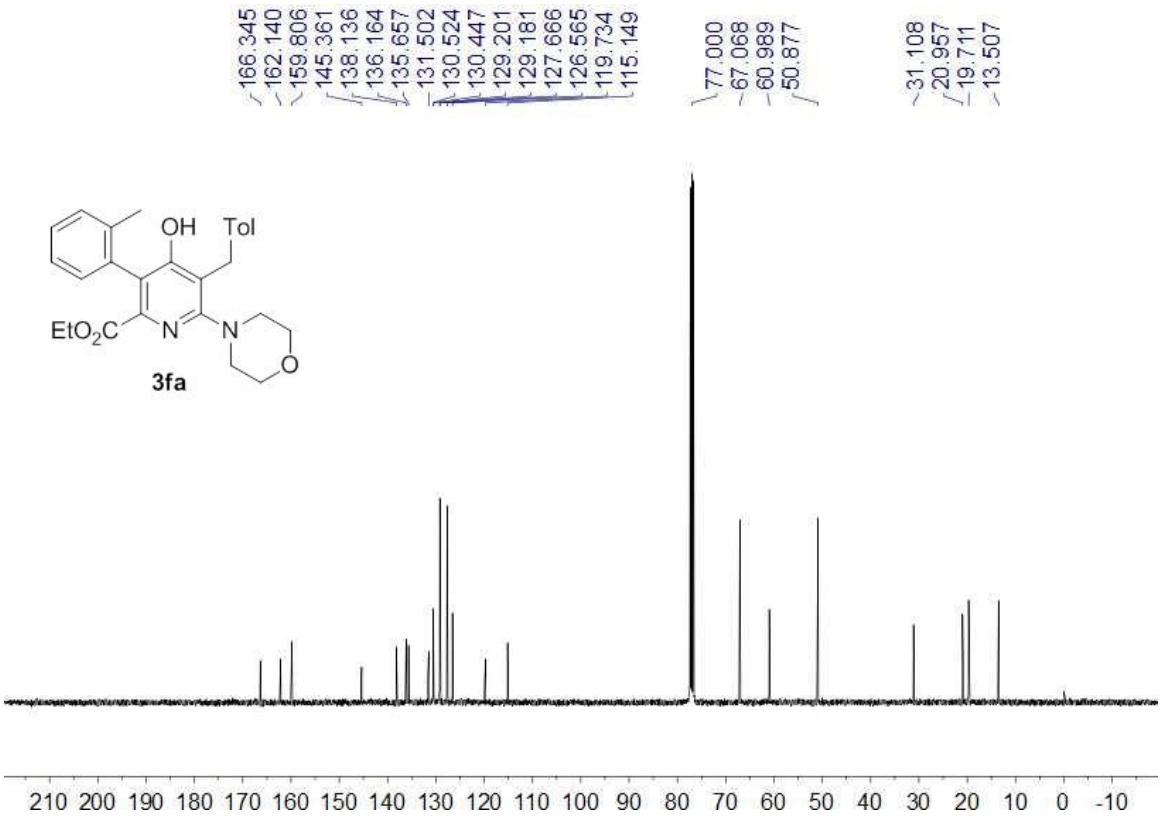
^{13}C NMR spectrum of the compound **3ea** (100 MHz, $CDCl_3$)



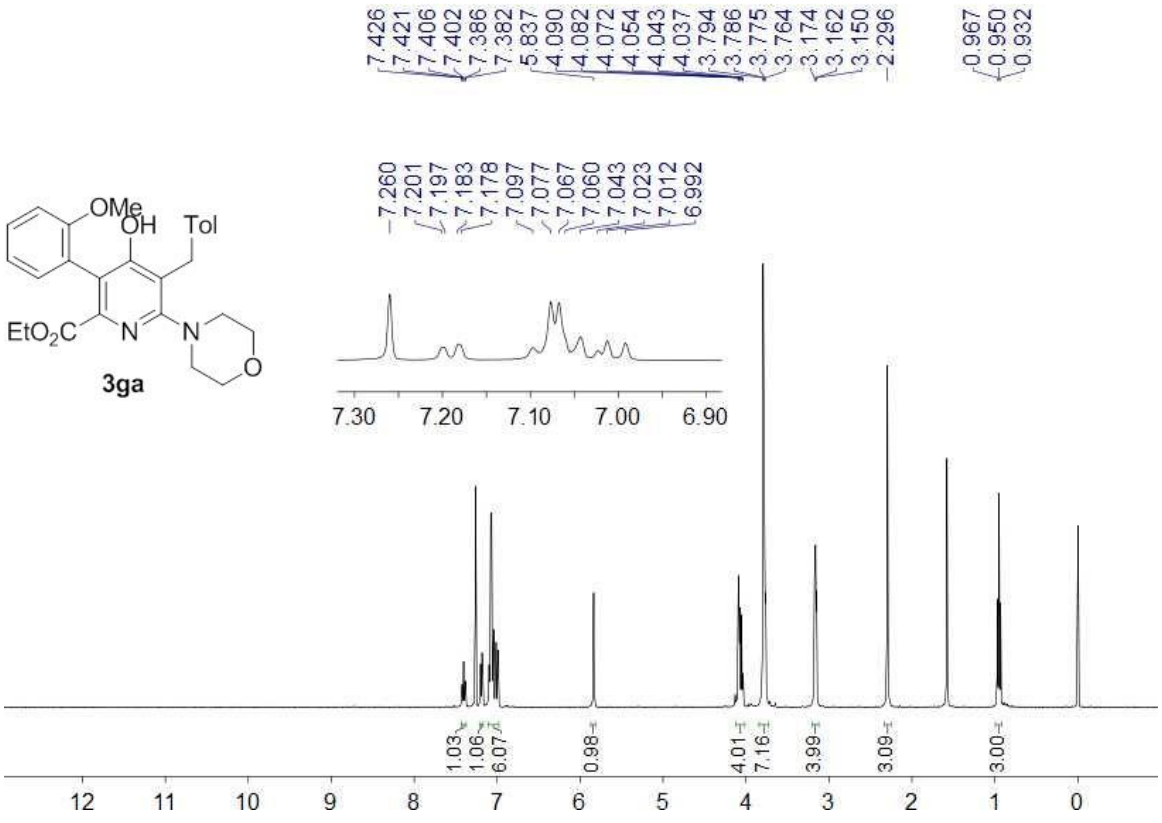
^{1}H NMR spectrum of the compound **3fa** (400 MHz, $CDCl_3$)



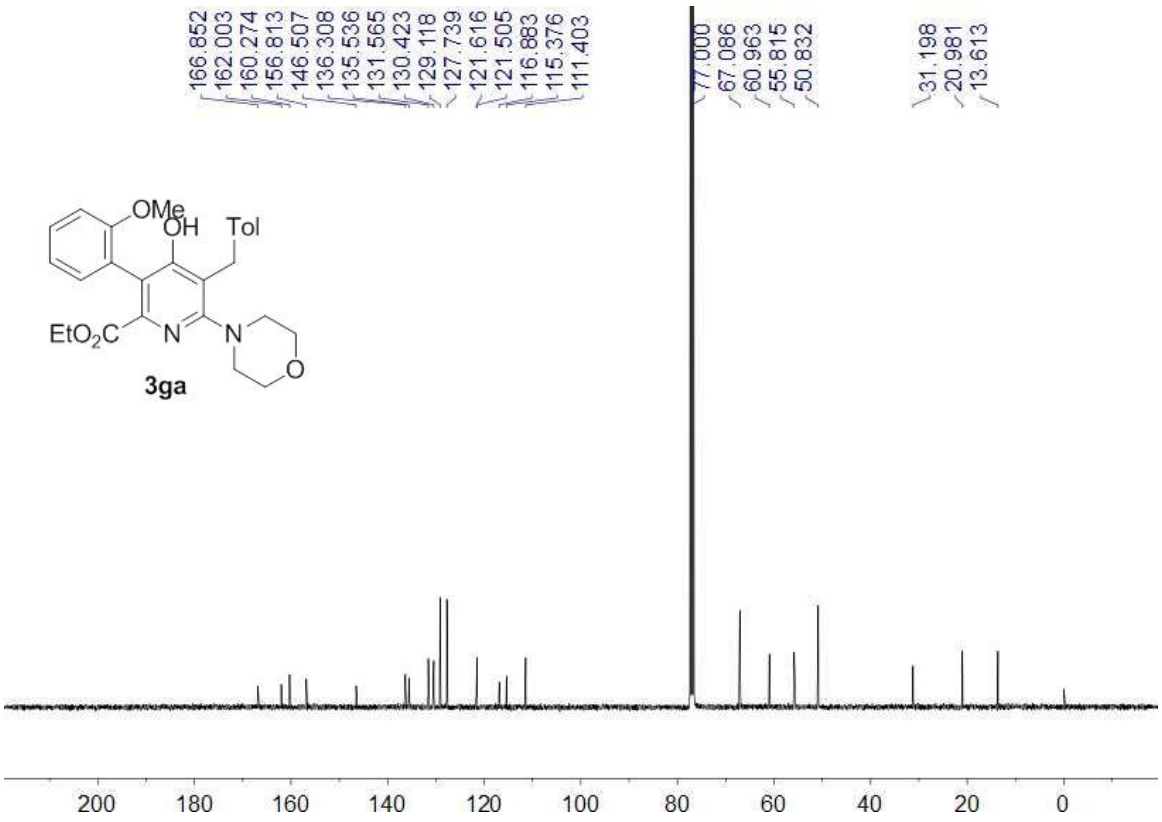
^{13}C NMR spectrum of the compound **3fa** (100 MHz, $CDCl_3$)



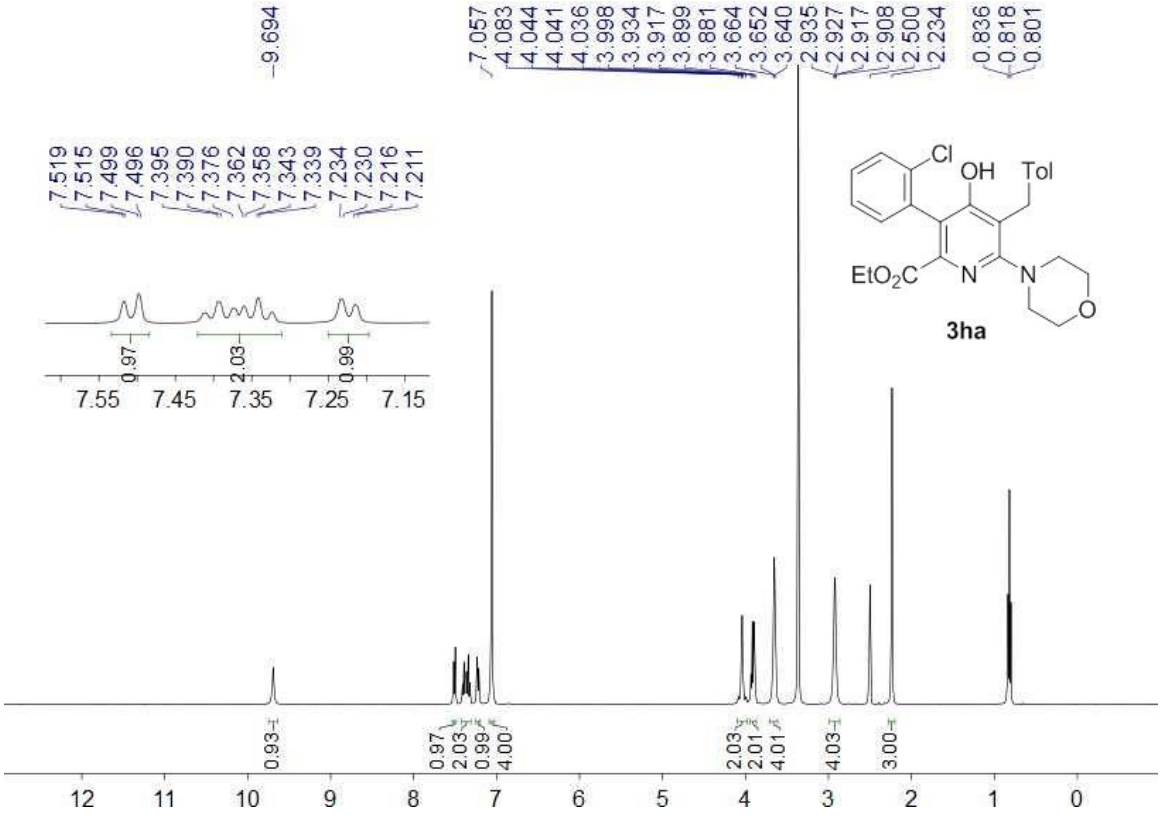
^{1}H NMR spectrum of the compound **3ga** (400 MHz, $CDCl_3$)



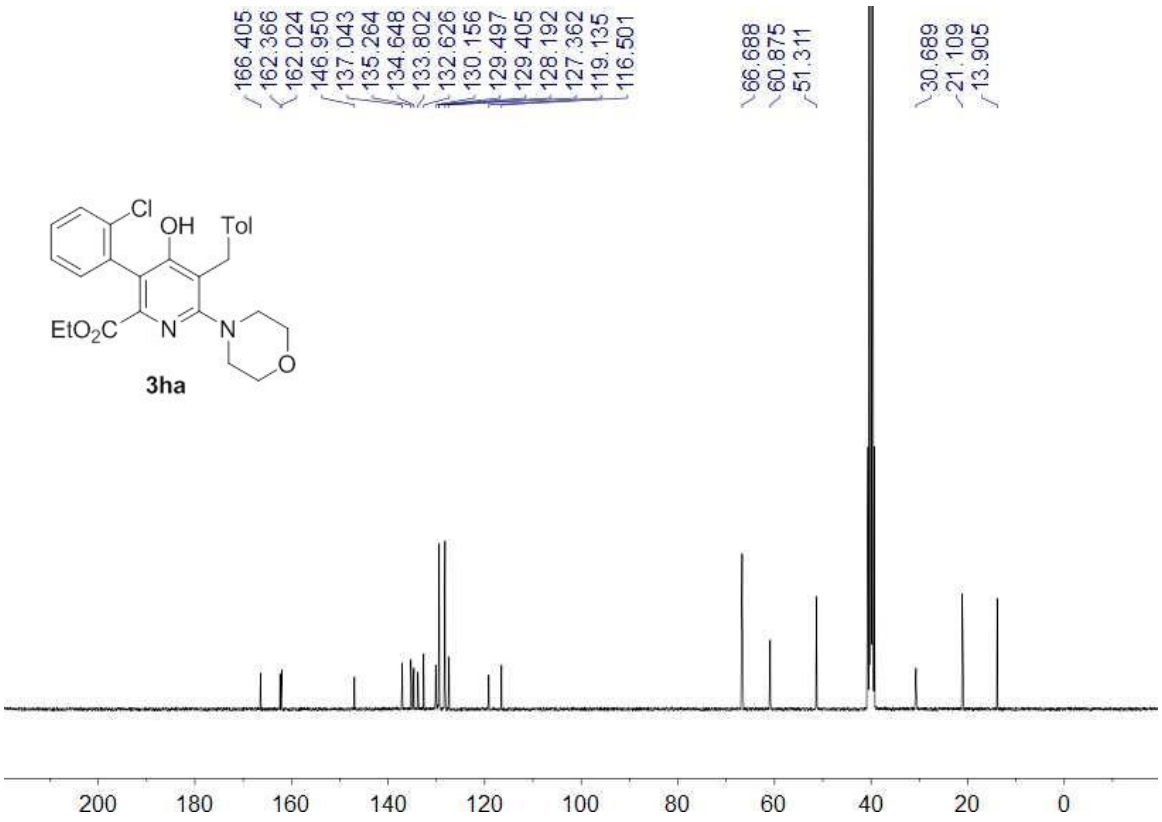
^{13}C NMR spectrum of the compound **3ga** (100 MHz, $CDCl_3$)



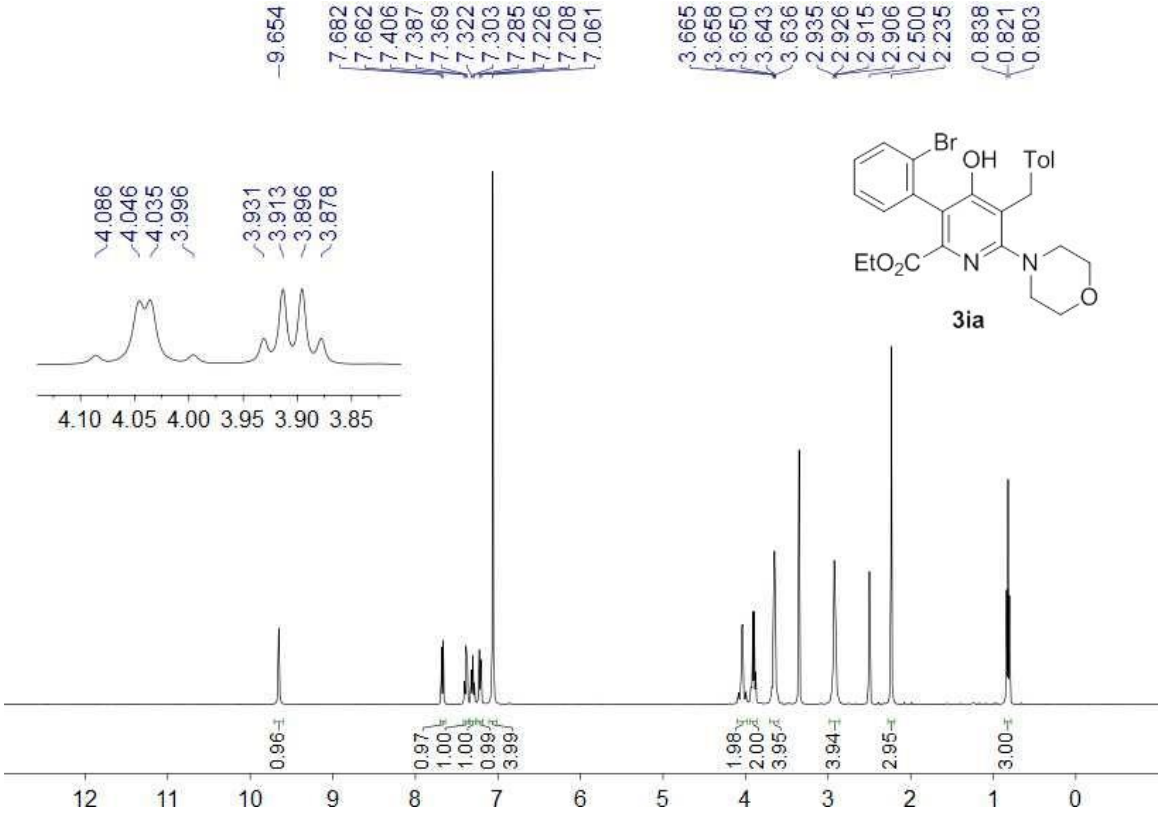
[1]H NMR spectrum of the compound **3ha** (400 MHz, DMSO-d_6)



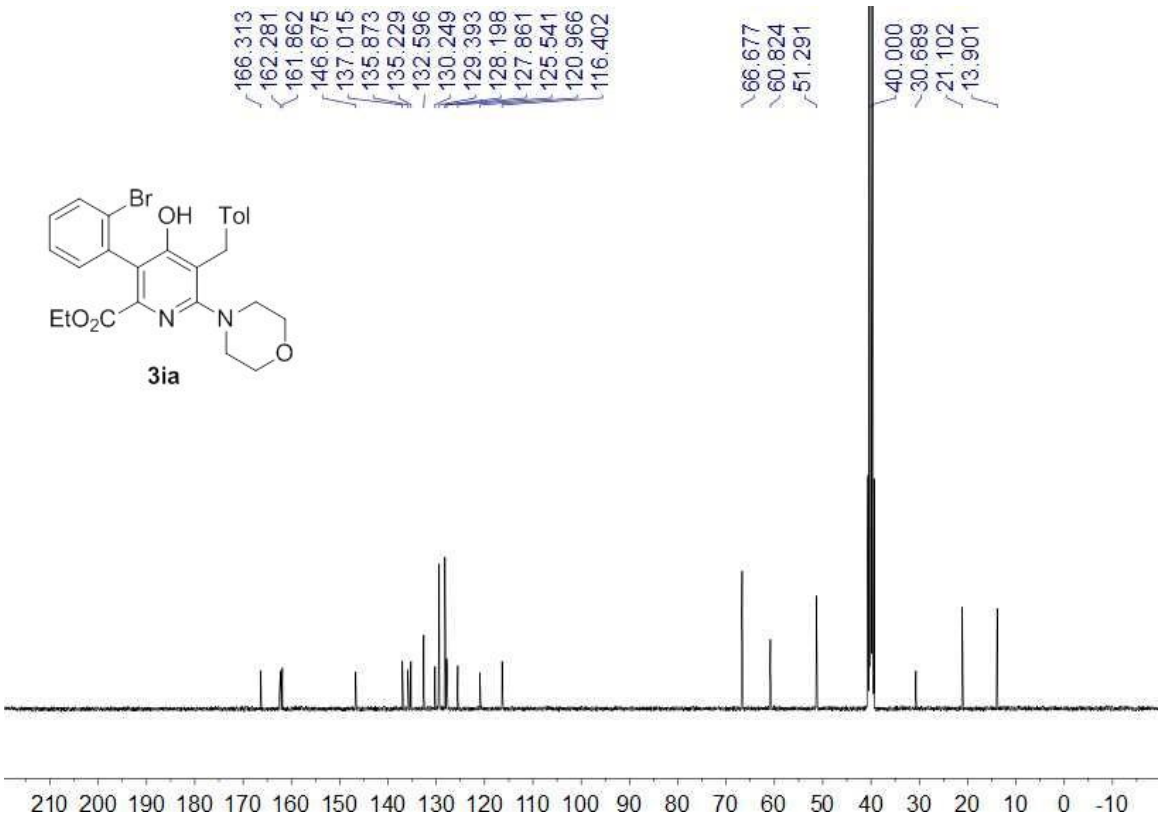
[13]C NMR spectrum of the compound **3ha** (100 MHz, DMSO-d_6)



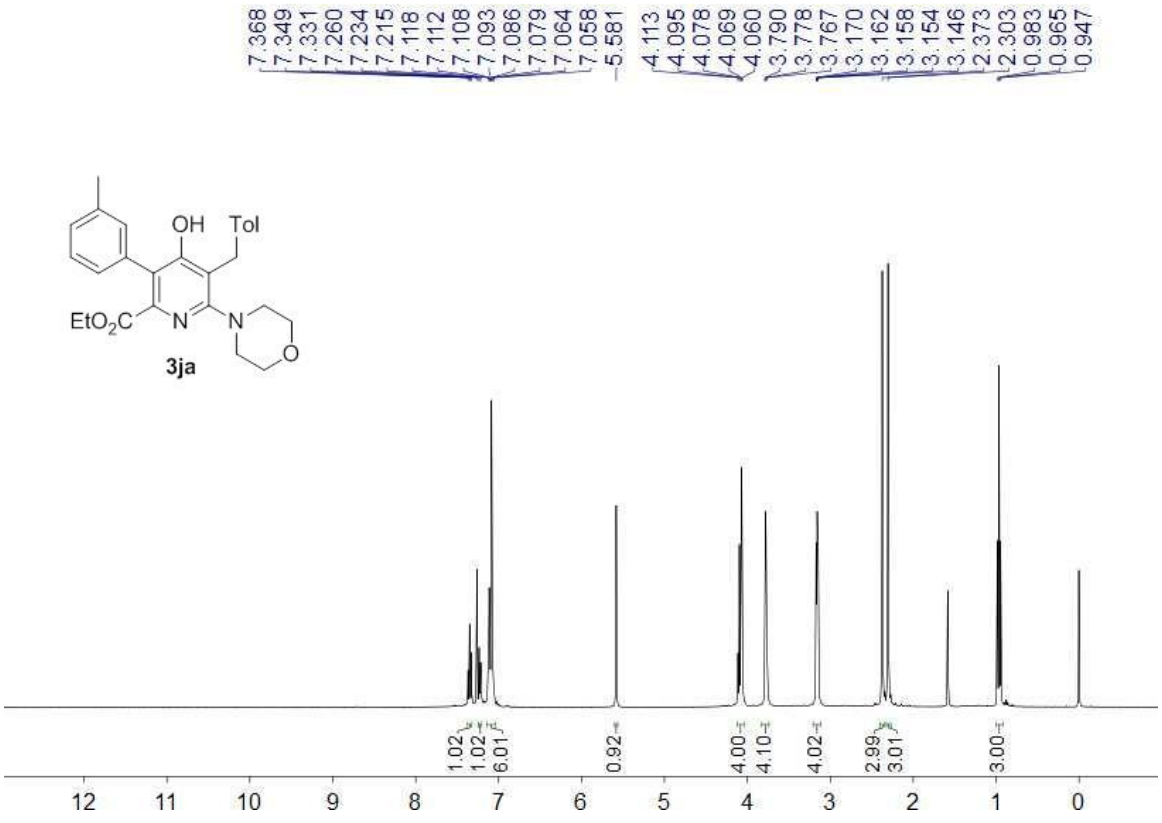
[1]H NMR spectrum of the compound **3ia** (400 MHz, DMSO-d_6)



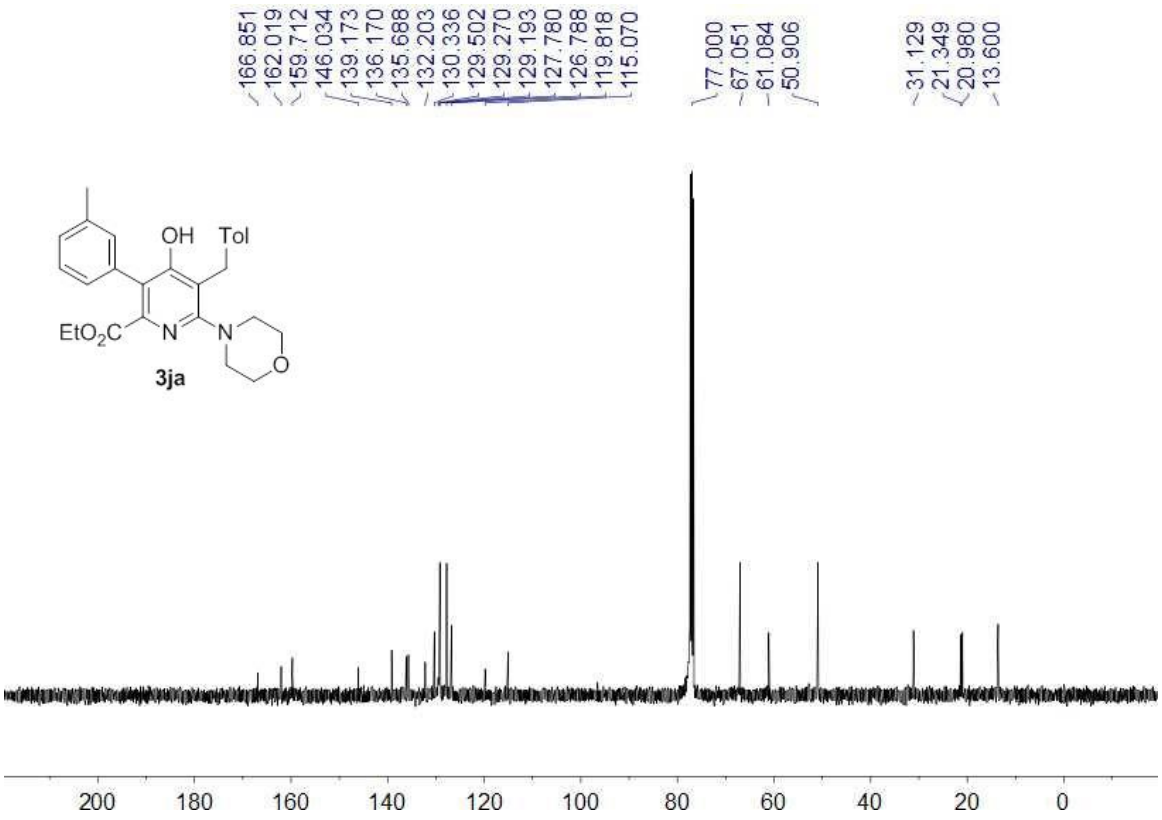
[13]C NMR spectrum of the compound **3ia** (100 MHz, DMSO-d_6)



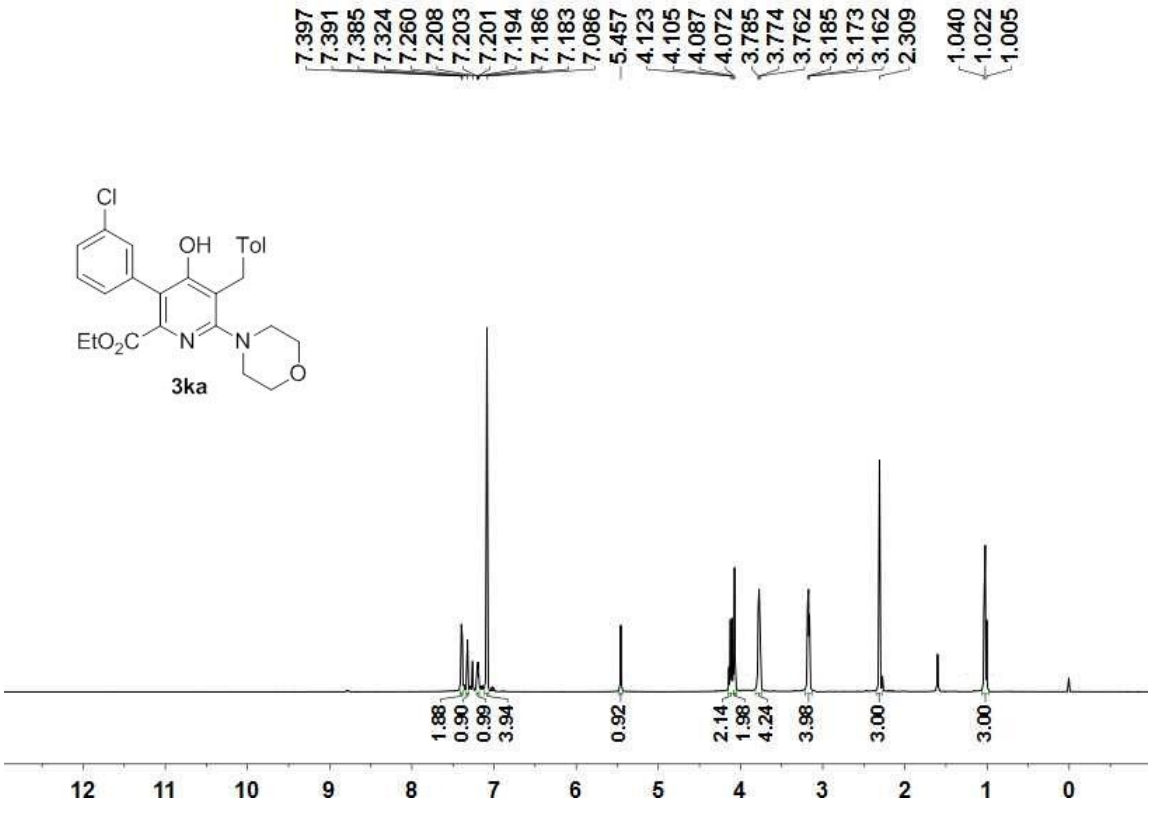
^{1}H NMR spectrum of the compound **3ja** (400 MHz, $CDCl_3$)



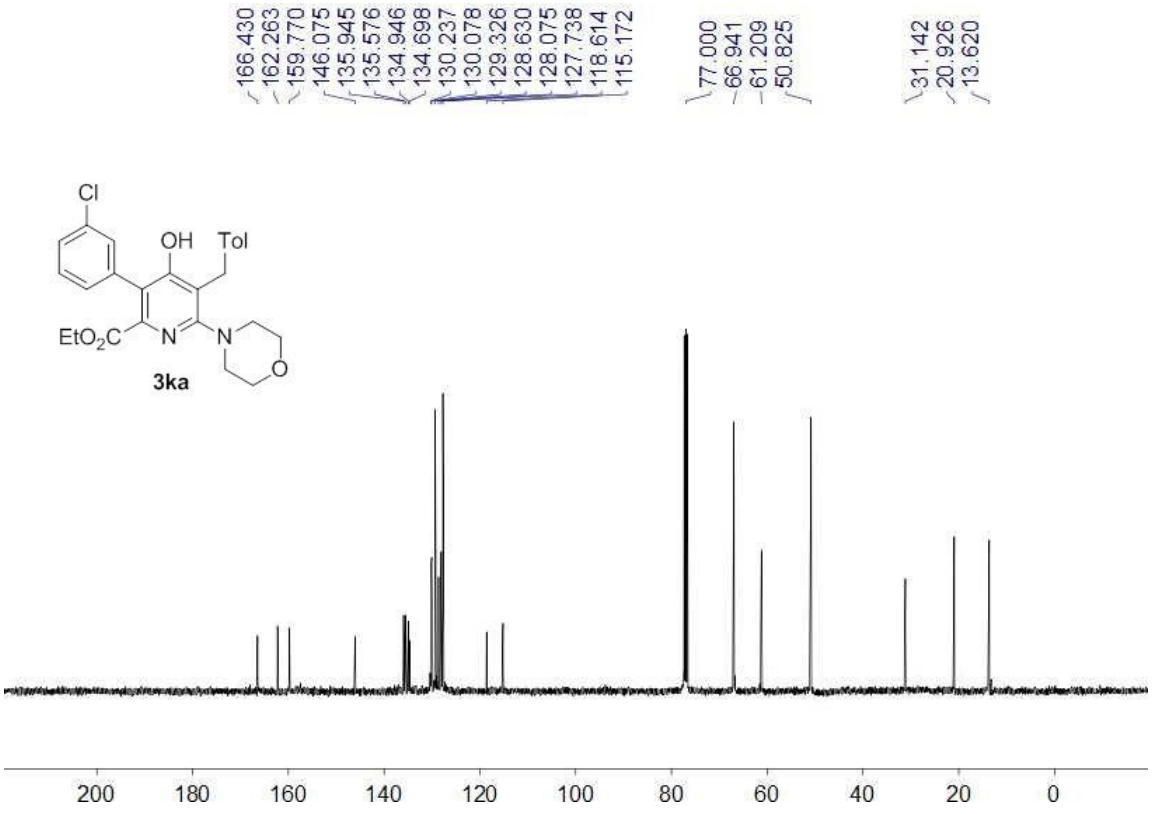
^{13}C NMR spectrum of the compound **3ja** (100 MHz, $CDCl_3$)



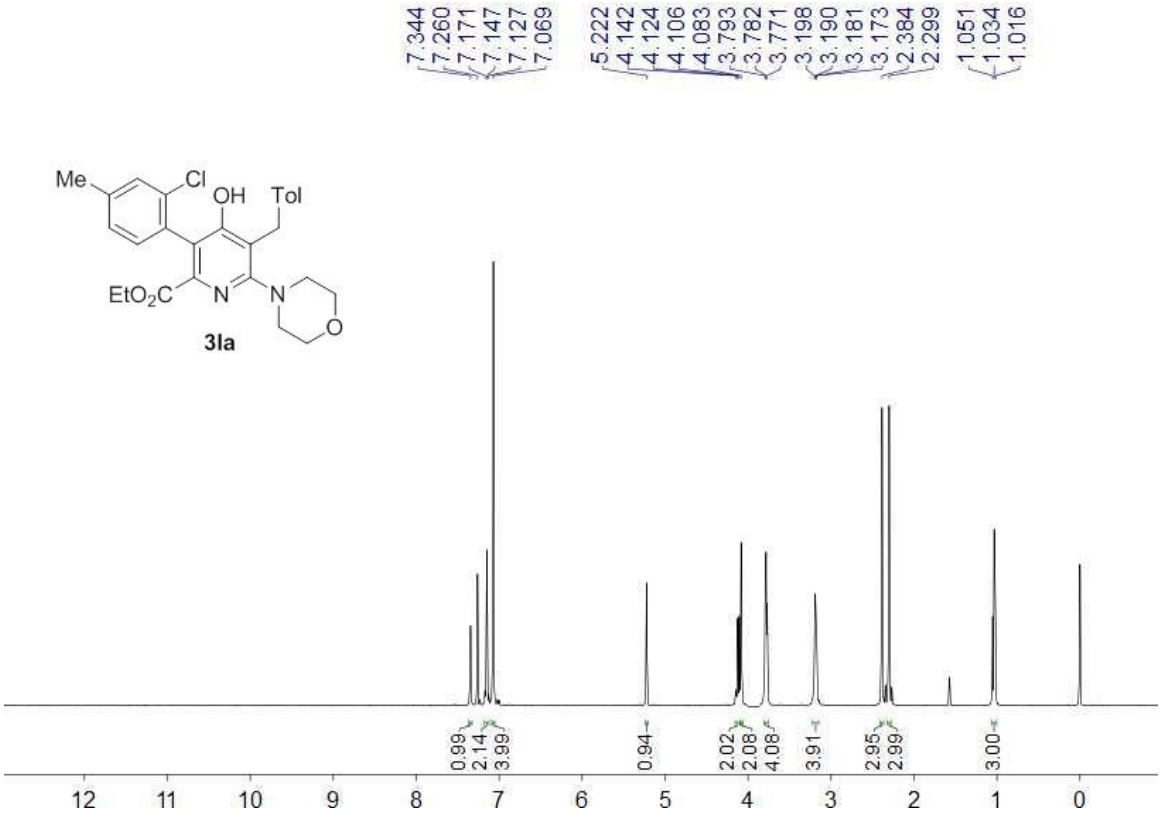
^{1}H NMR spectrum of the compound **3ka** (400 MHz, $CDCl_3$)



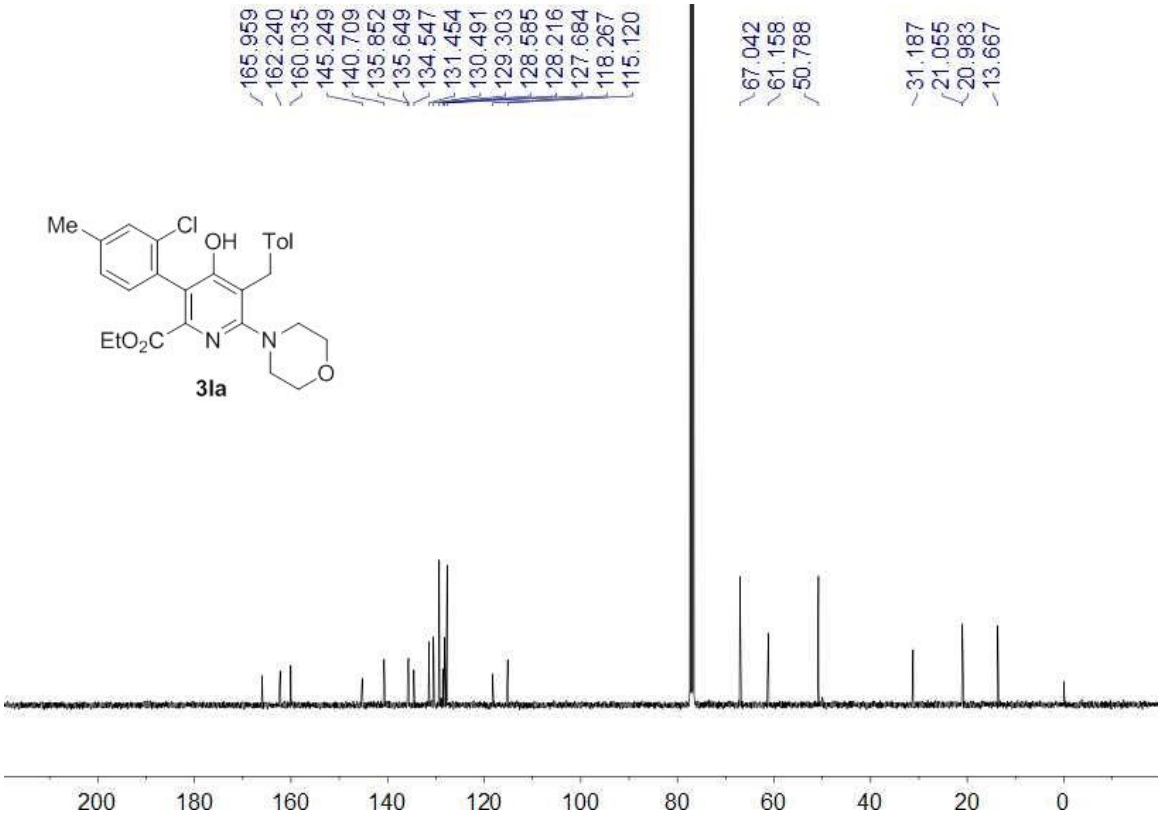
^{13}C NMR spectrum of the compound **3ka** (100 MHz, $CDCl_3$)



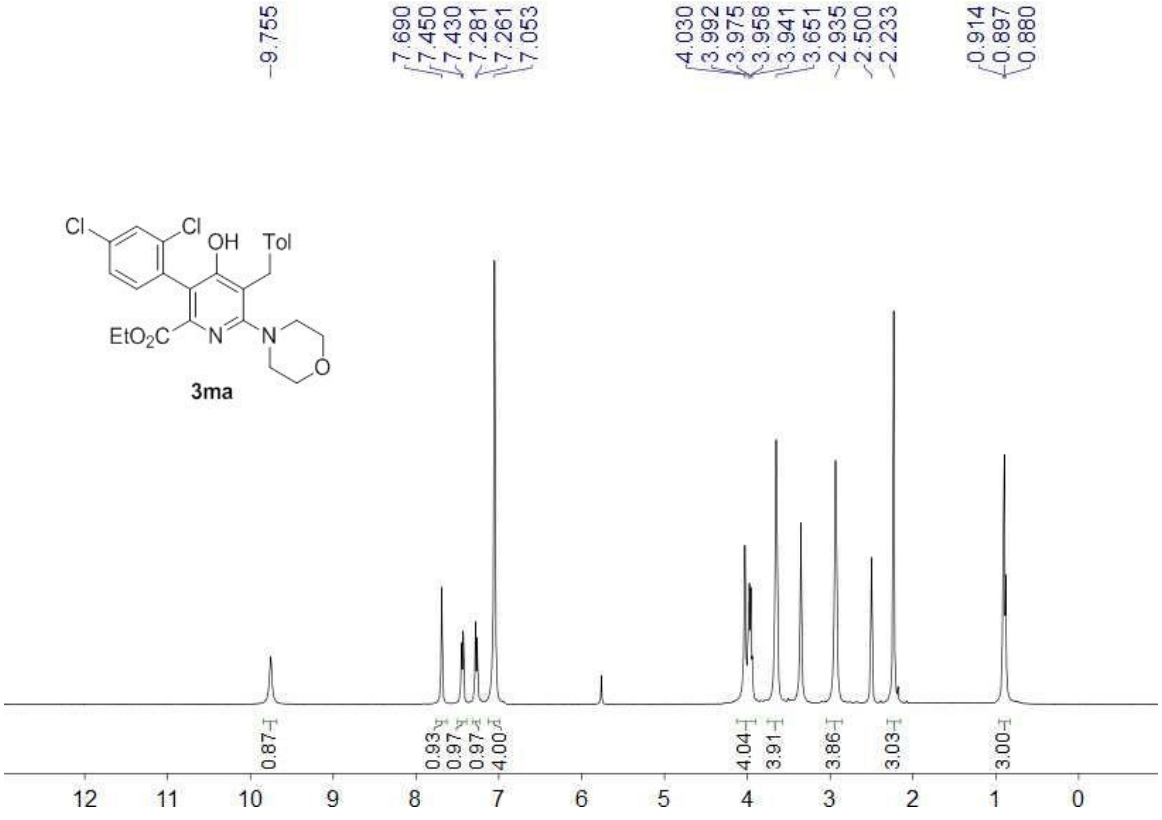
^{1}H NMR spectrum of the compound **3la** (400 MHz, $CDCl_3$)



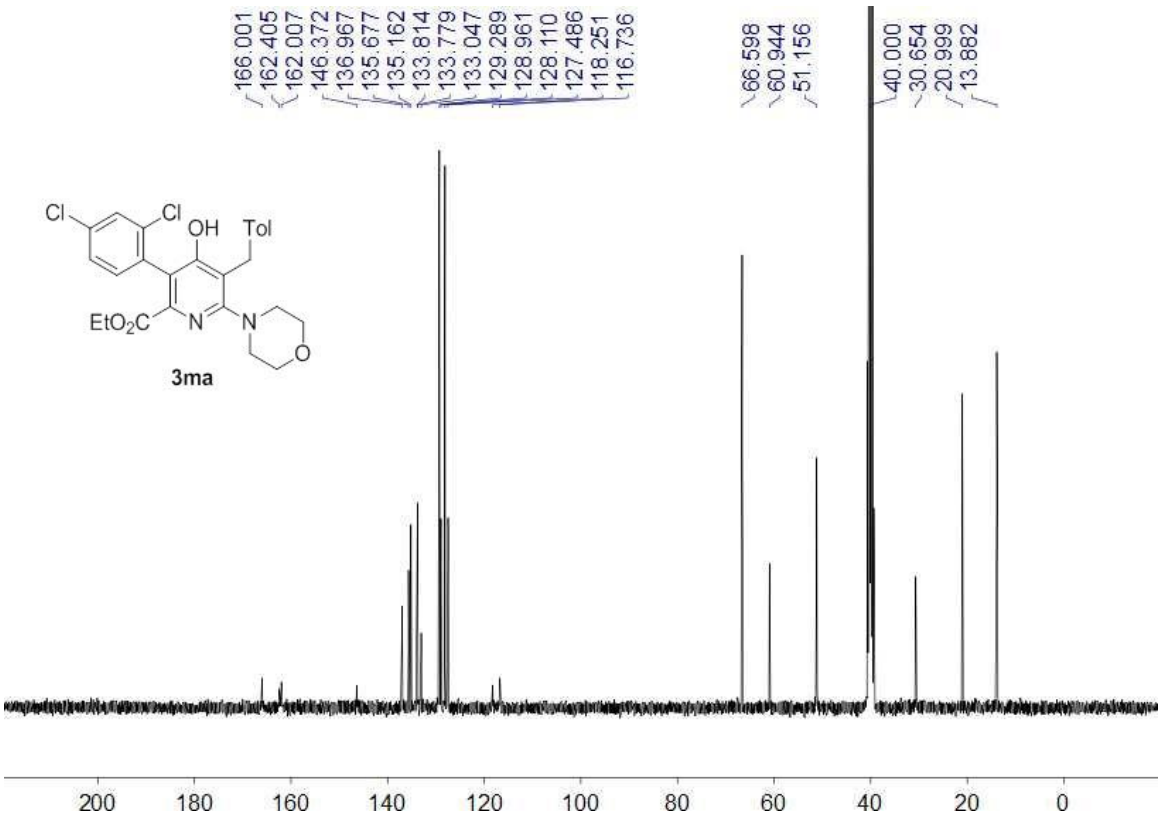
^{13}C NMR spectrum of the compound **3la** (100 MHz, $CDCl_3$)



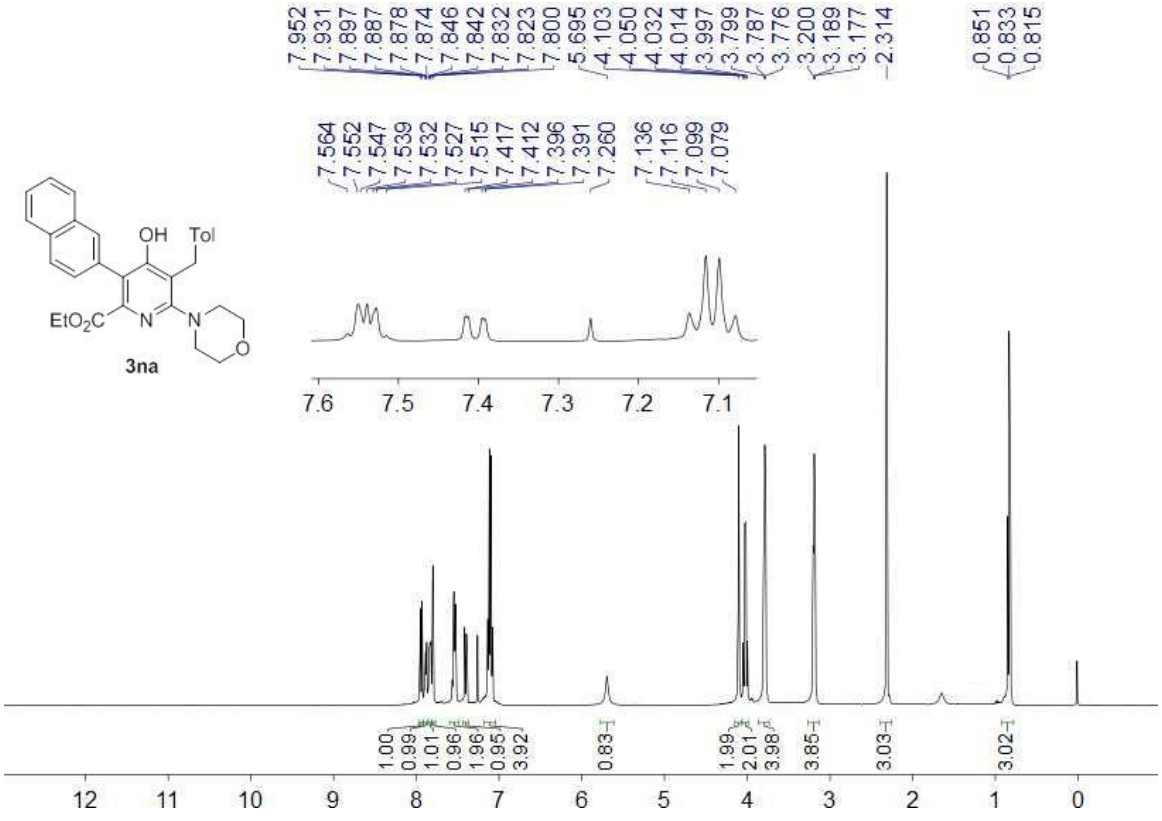
[1]H NMR spectrum of the compound **3ma** (400 MHz, DMSO-d_6)



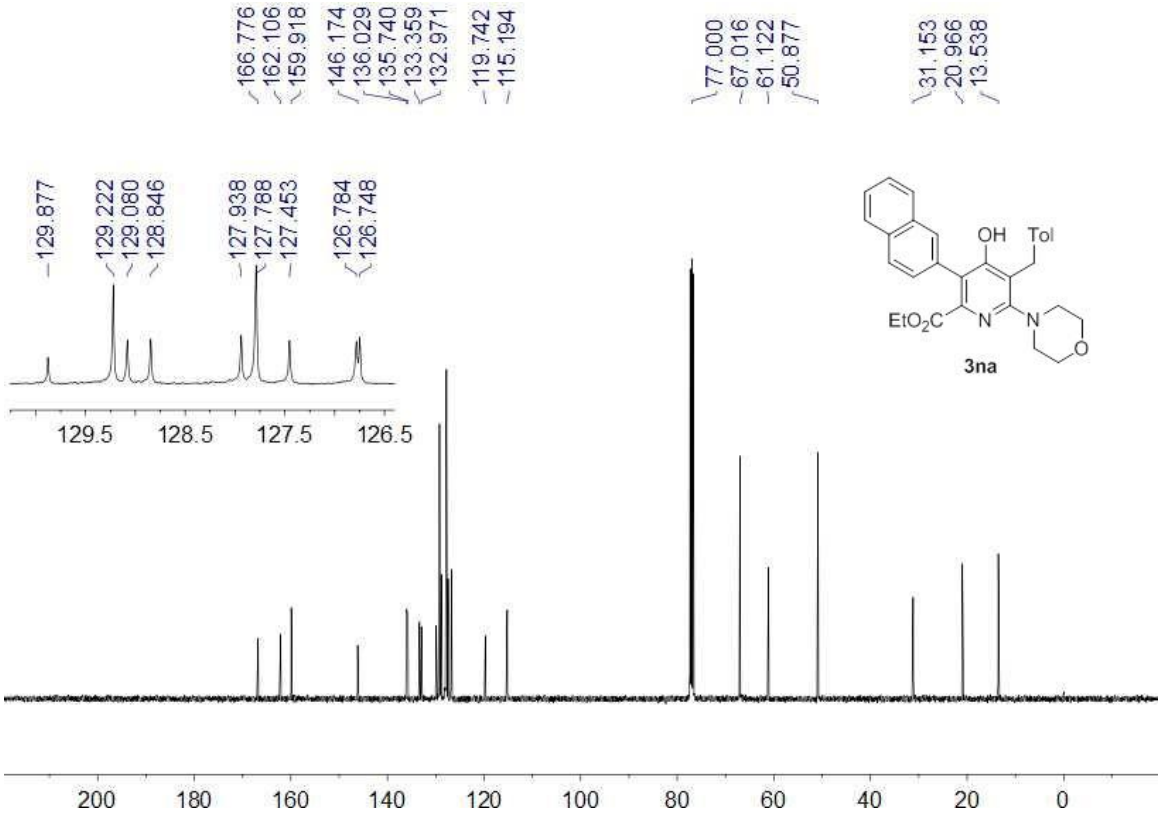
[13]C NMR spectrum of the compound **3ma** (100 MHz, DMSO-d_6)



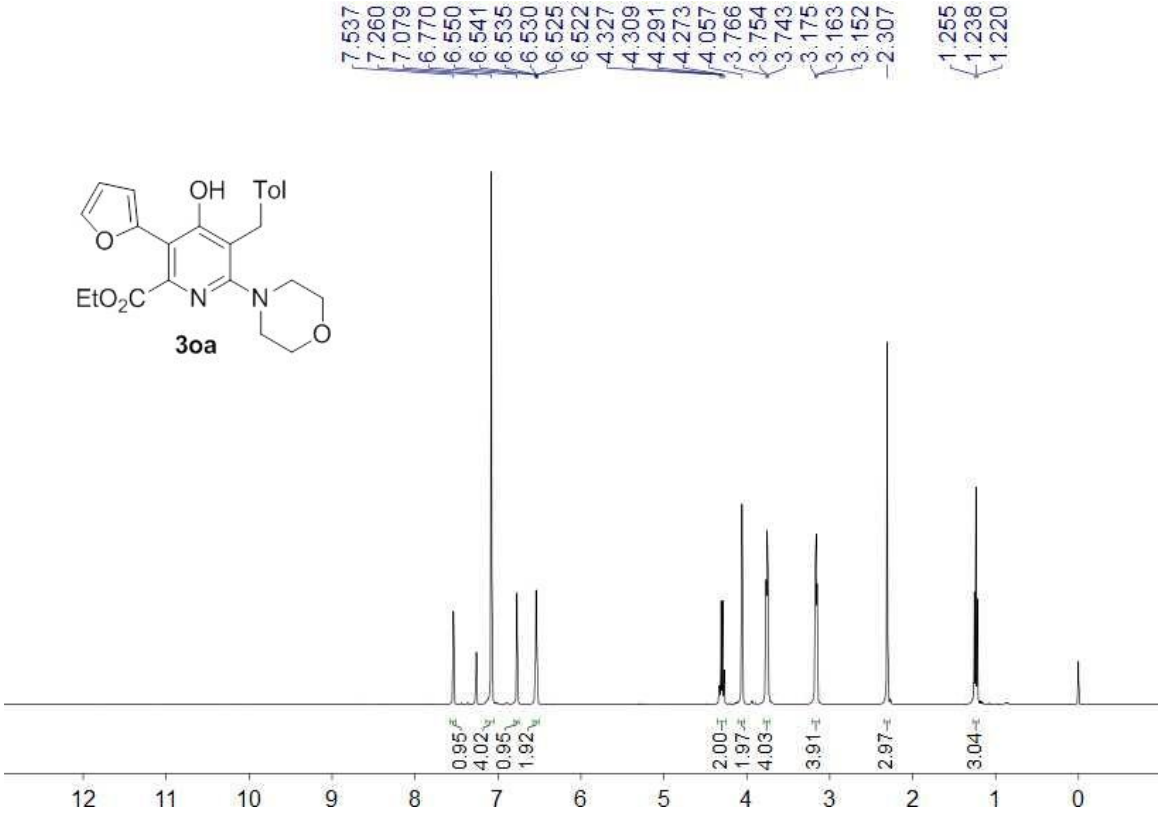
^{1}H NMR spectrum of the compound **3na** (400 MHz, $CDCl_3$)



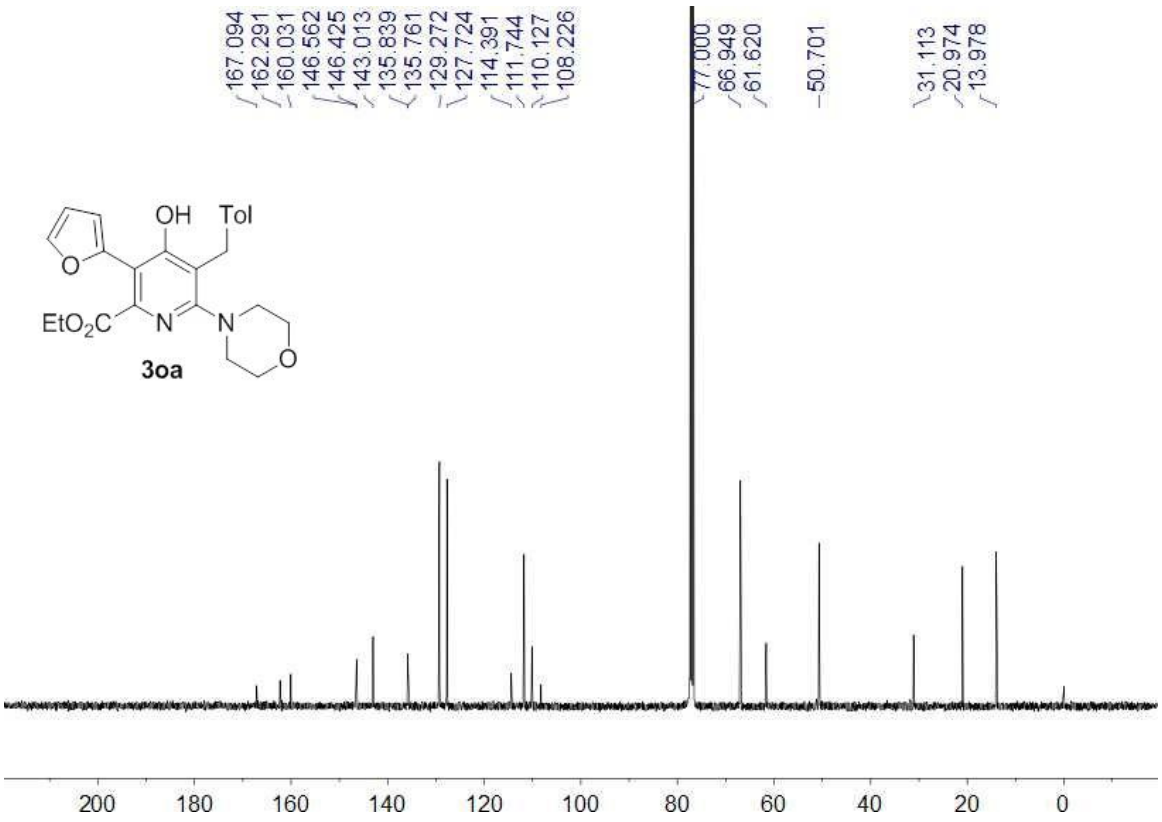
^{13}C NMR spectrum of the compound **3na** (100 MHz, $CDCl_3$)



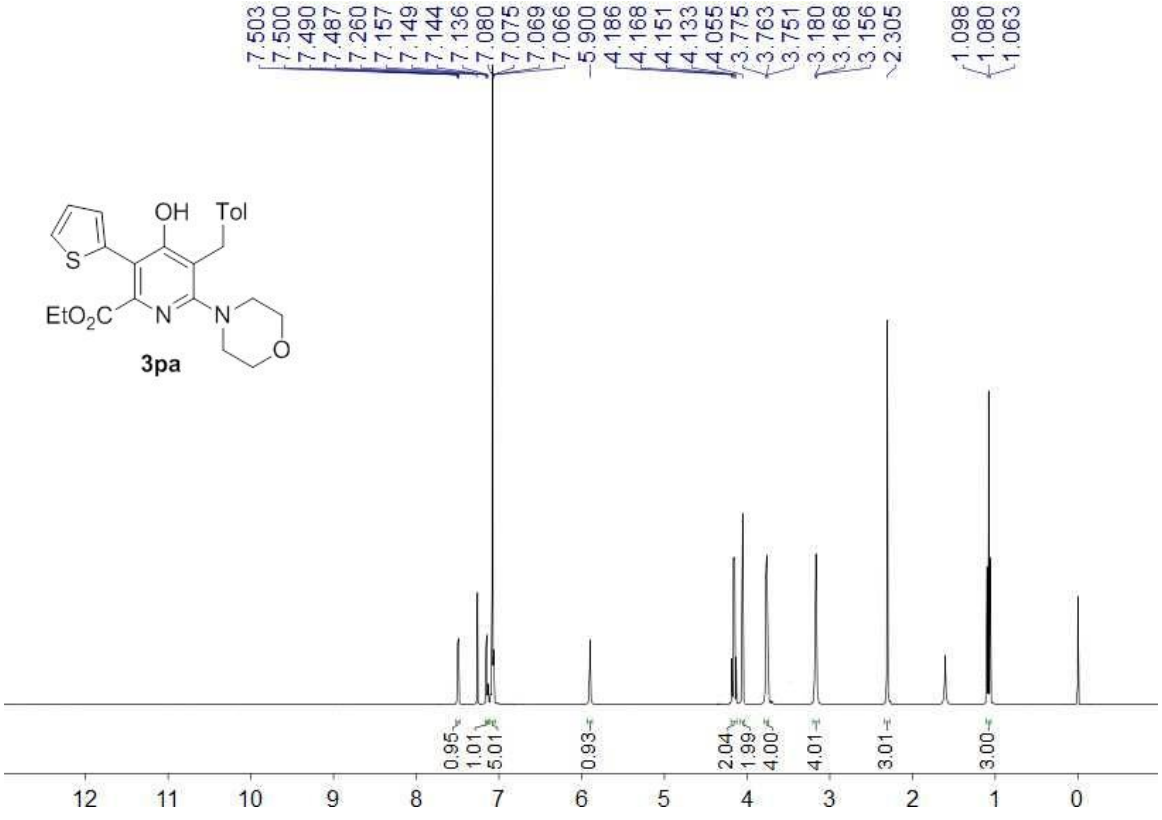
^{1}H NMR spectrum of the compound **3oa** (400 MHz, $CDCl_3$)



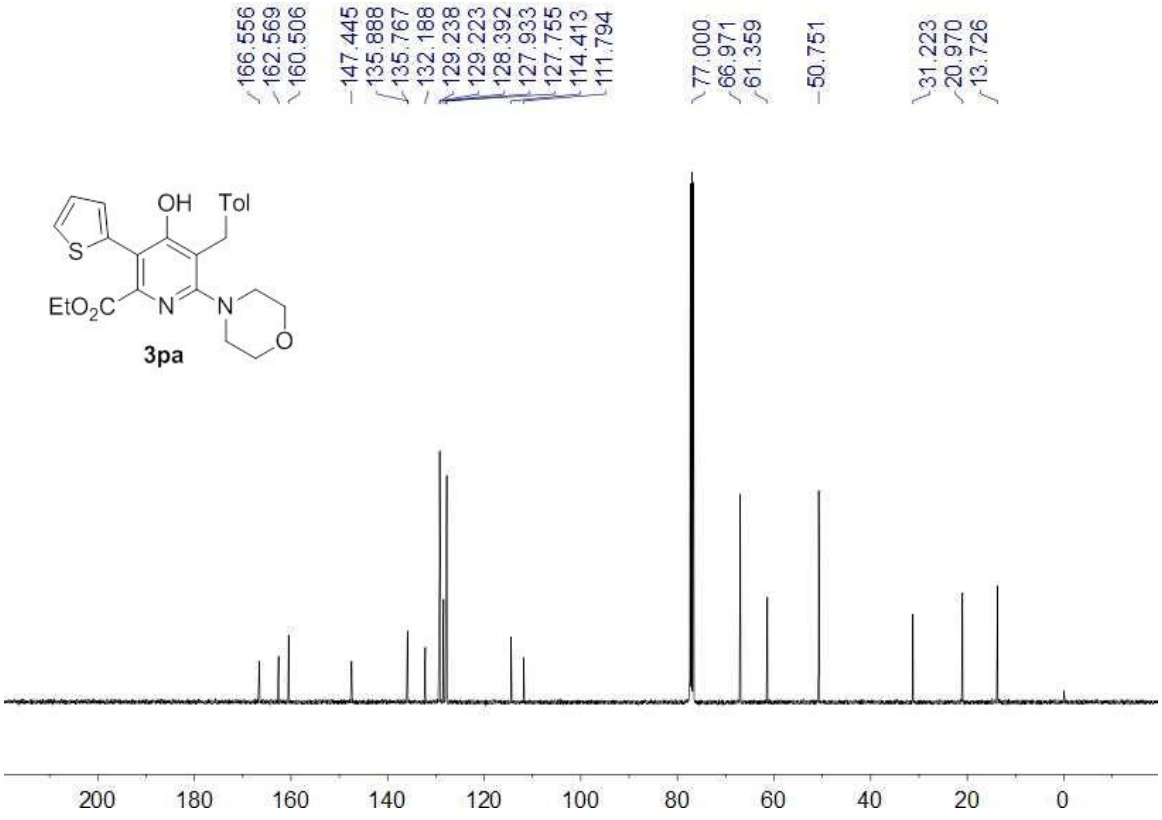
^{13}C NMR spectrum of the compound **3oa** (100 MHz, $CDCl_3$)



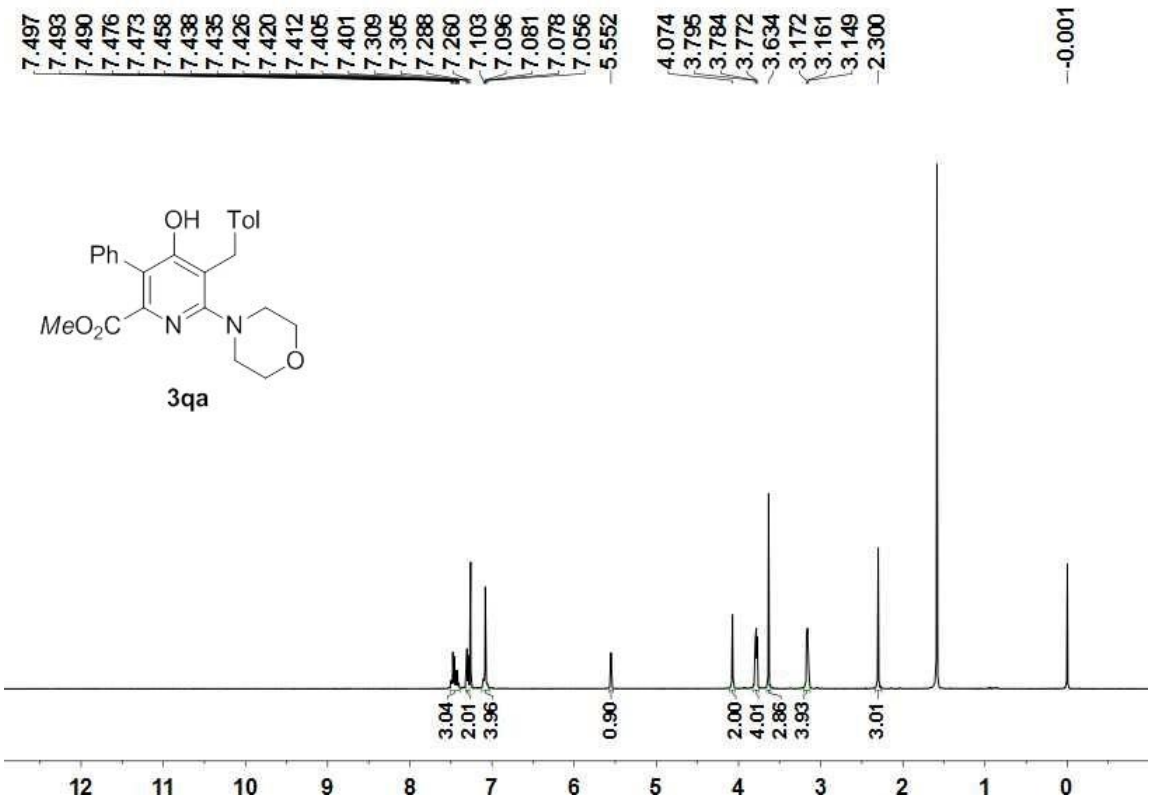
[1]H NMR spectrum of the compound **3pa** (400 MHz, $CDCl_3$)



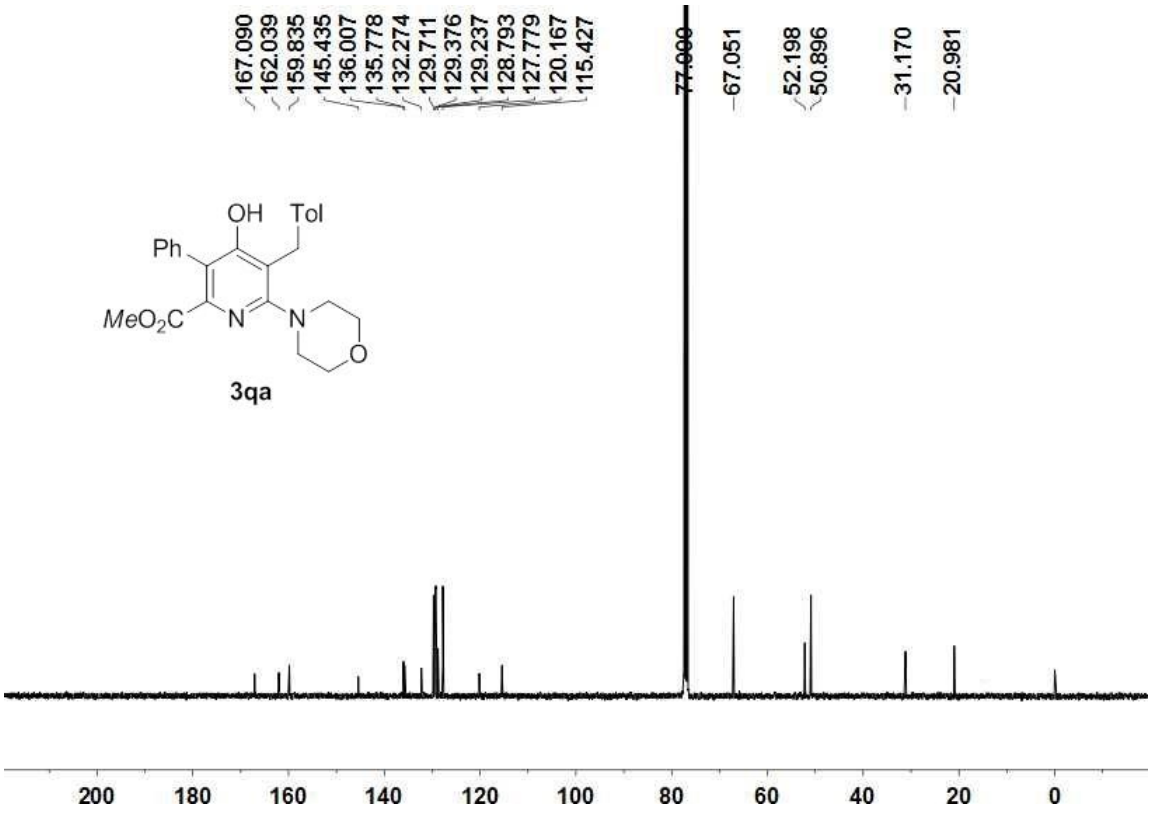
[13]C NMR spectrum of the compound **3pa** (100 MHz, $CDCl_3$)



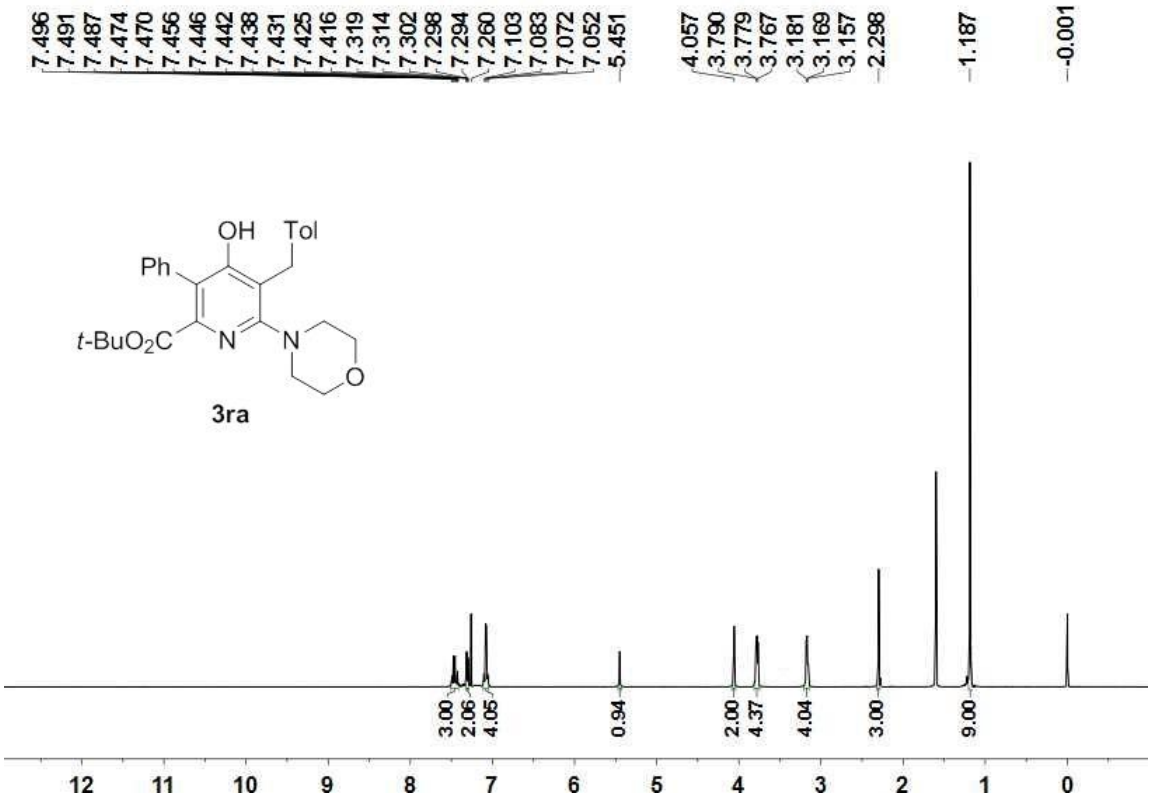
^{1}H NMR spectrum of the compound **3qa** (400 MHz, $CDCl_3$)



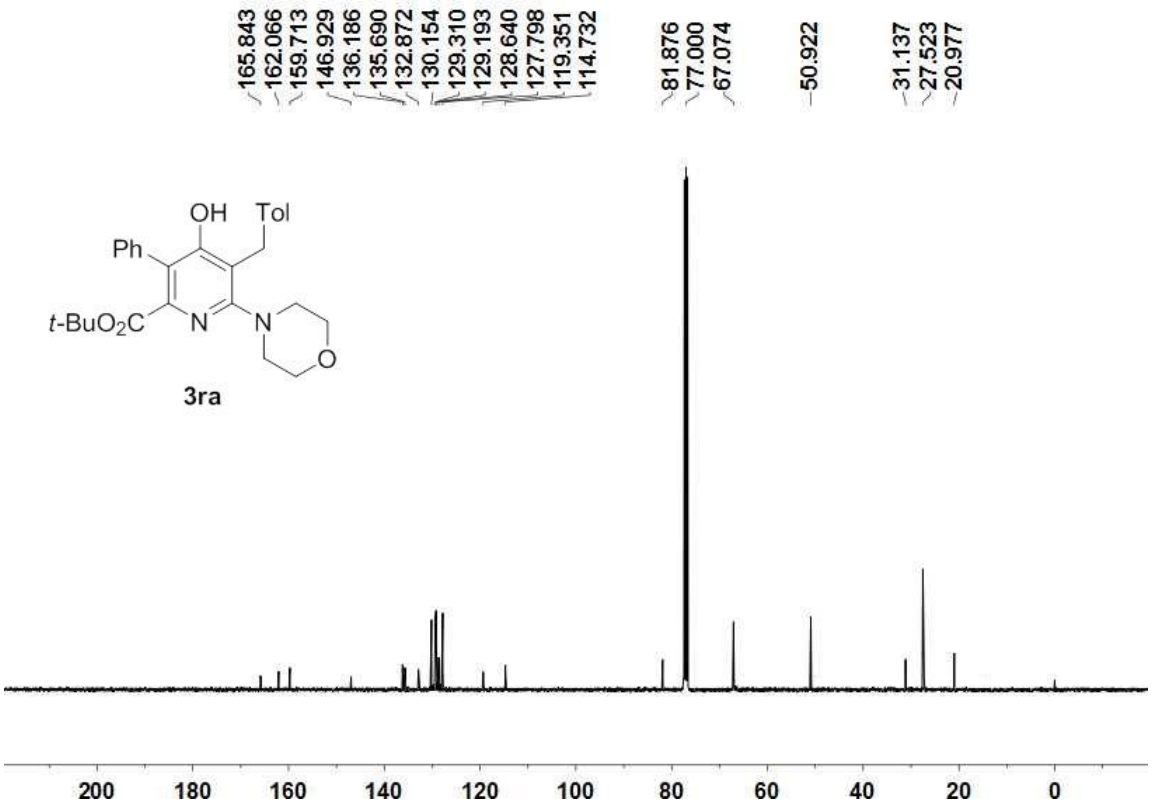
^{13}C NMR spectrum of the compound **3qa** (100 MHz, $CDCl_3$)



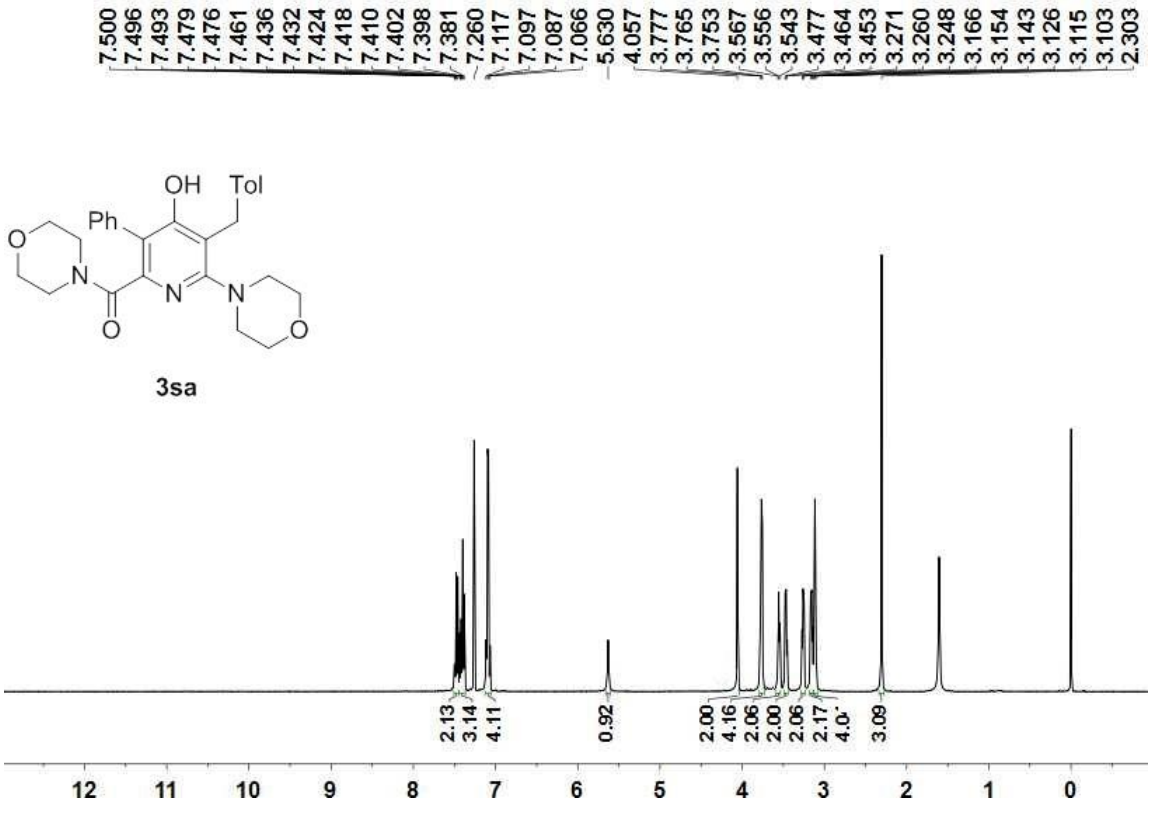
^{1}H NMR spectrum of the compound **3ra** (400 MHz, $CDCl_3$)



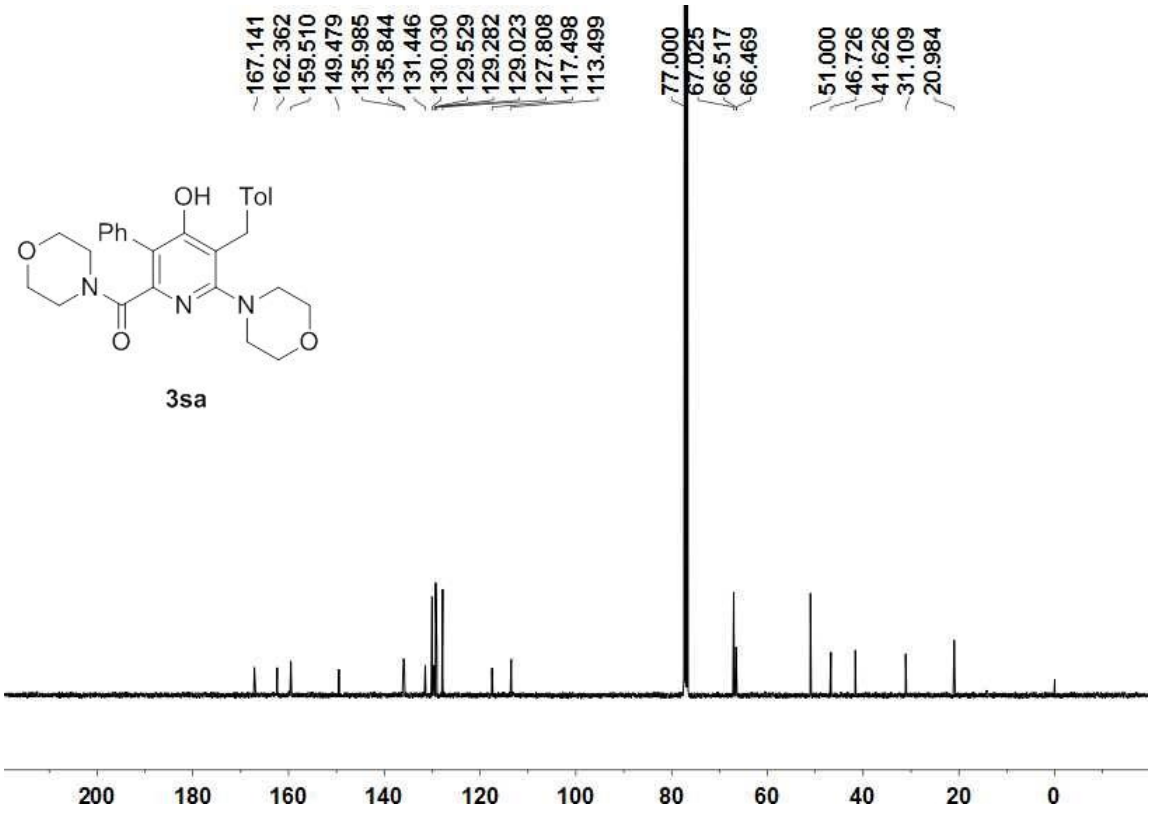
^{13}C NMR spectrum of the compound **3ra** (100 MHz, $CDCl_3$)



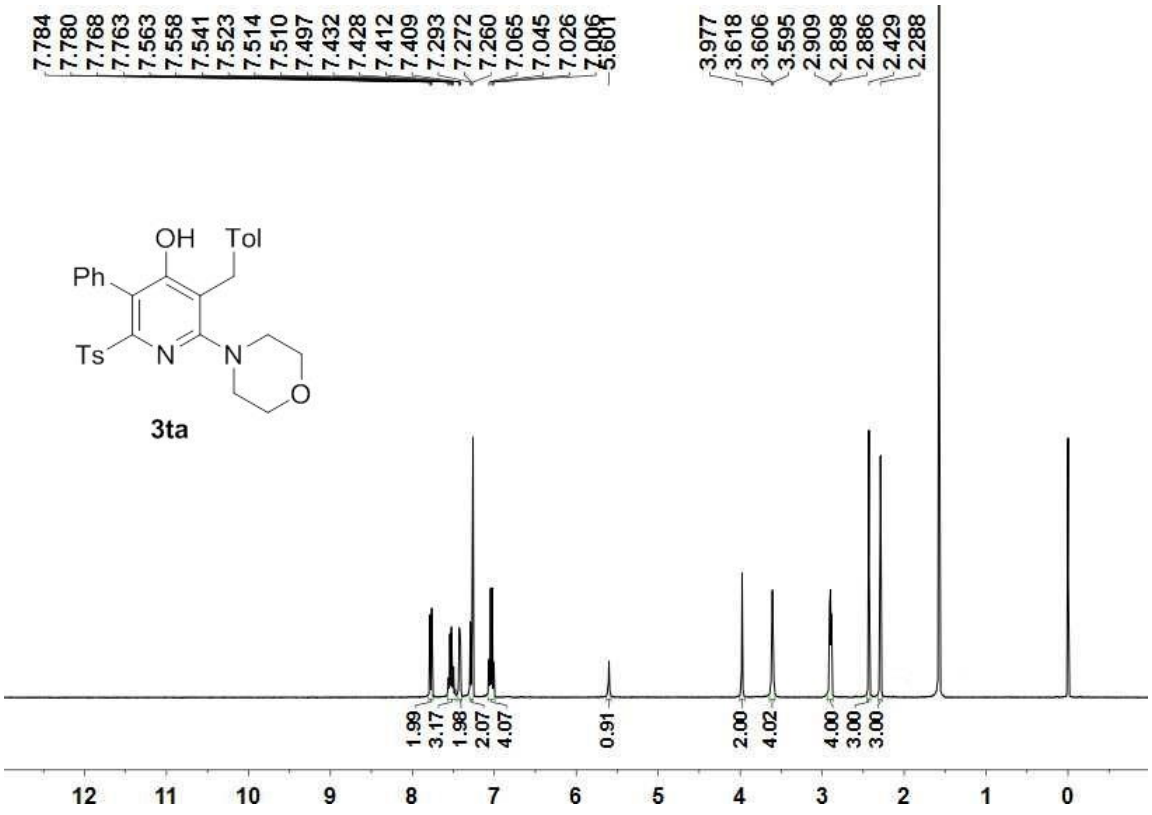
^{1}H NMR spectrum of the compound **3sa** (400 MHz, $CDCl_3$)



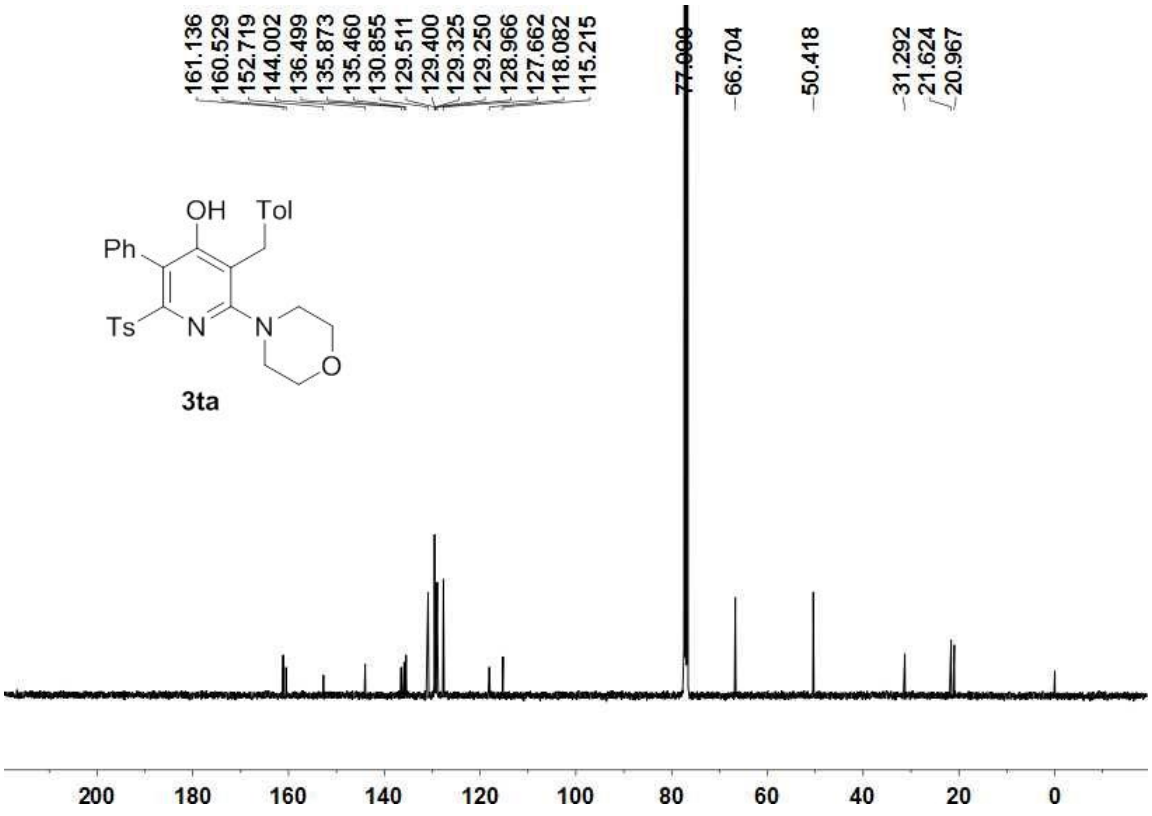
^{13}C NMR spectrum of the compound **3sa** (100 MHz, $CDCl_3$)



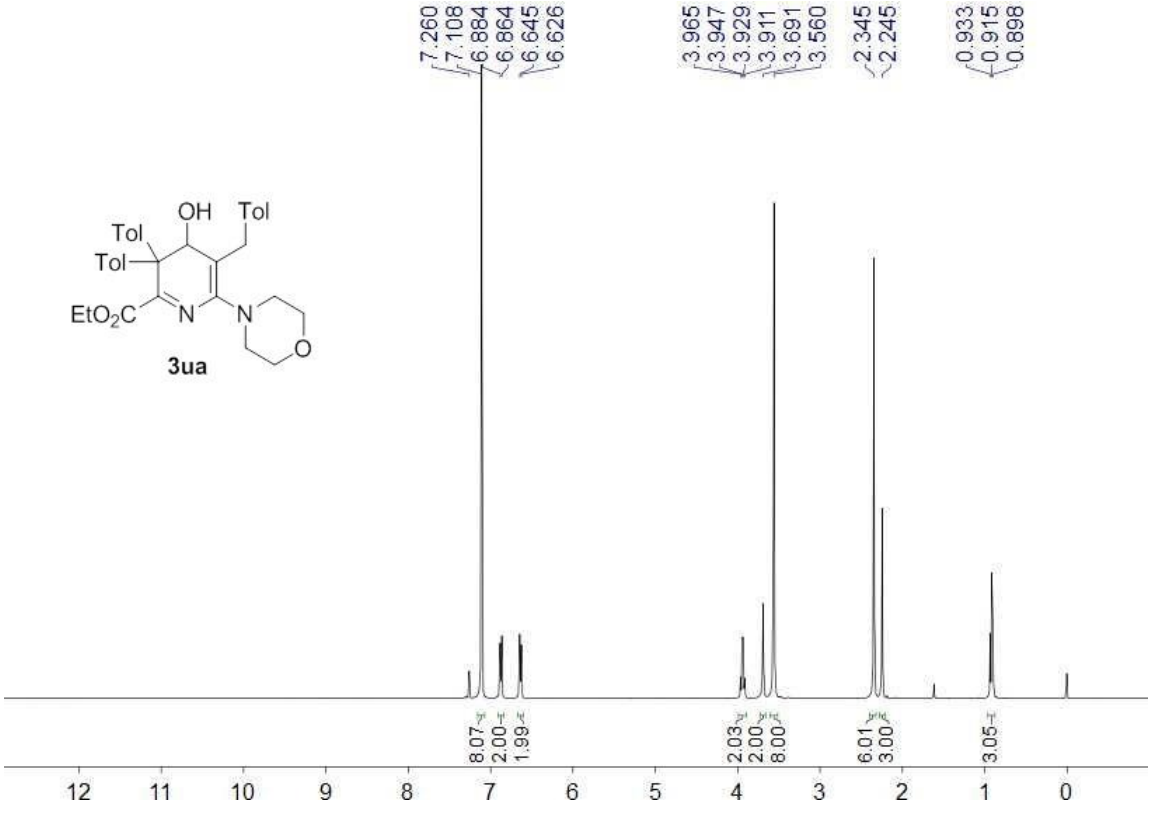
^{1}H NMR spectrum of the compound **3ta** (400 MHz, $CDCl_3$)



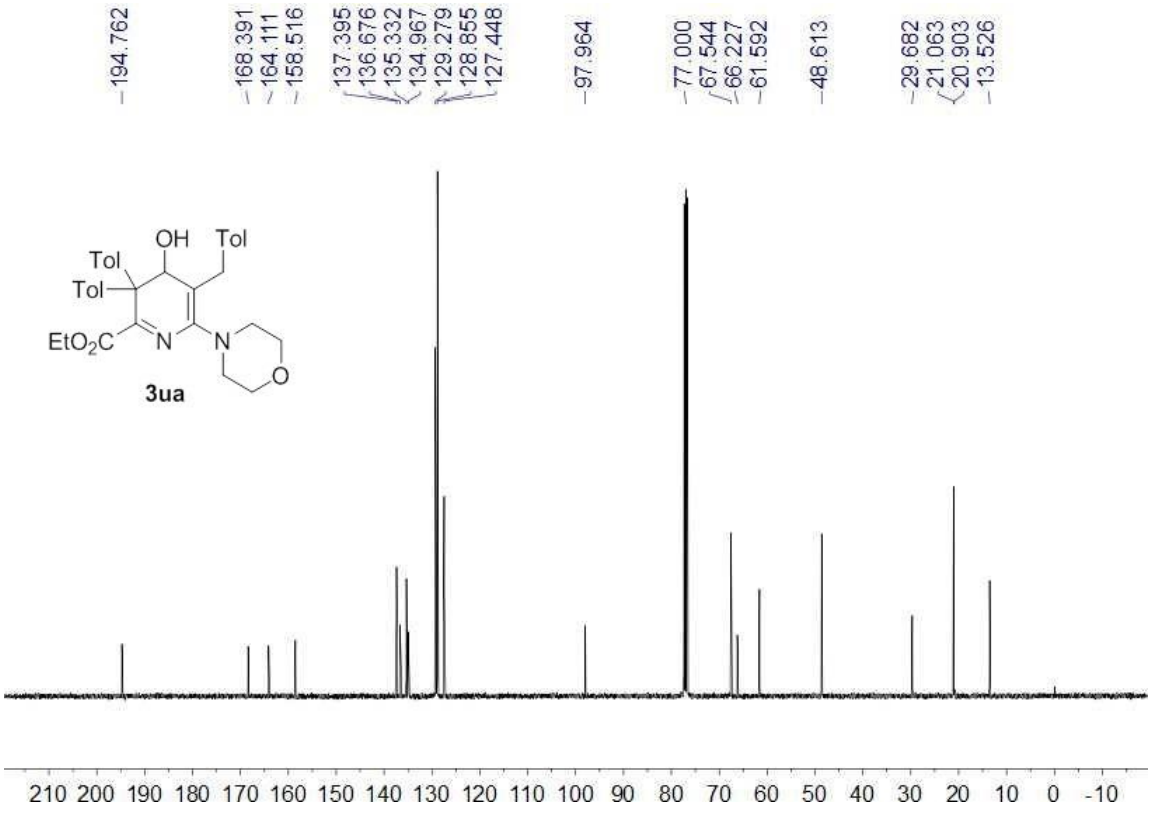
^{13}C NMR spectrum of the compound **3ta** (100 MHz, $CDCl_3$)



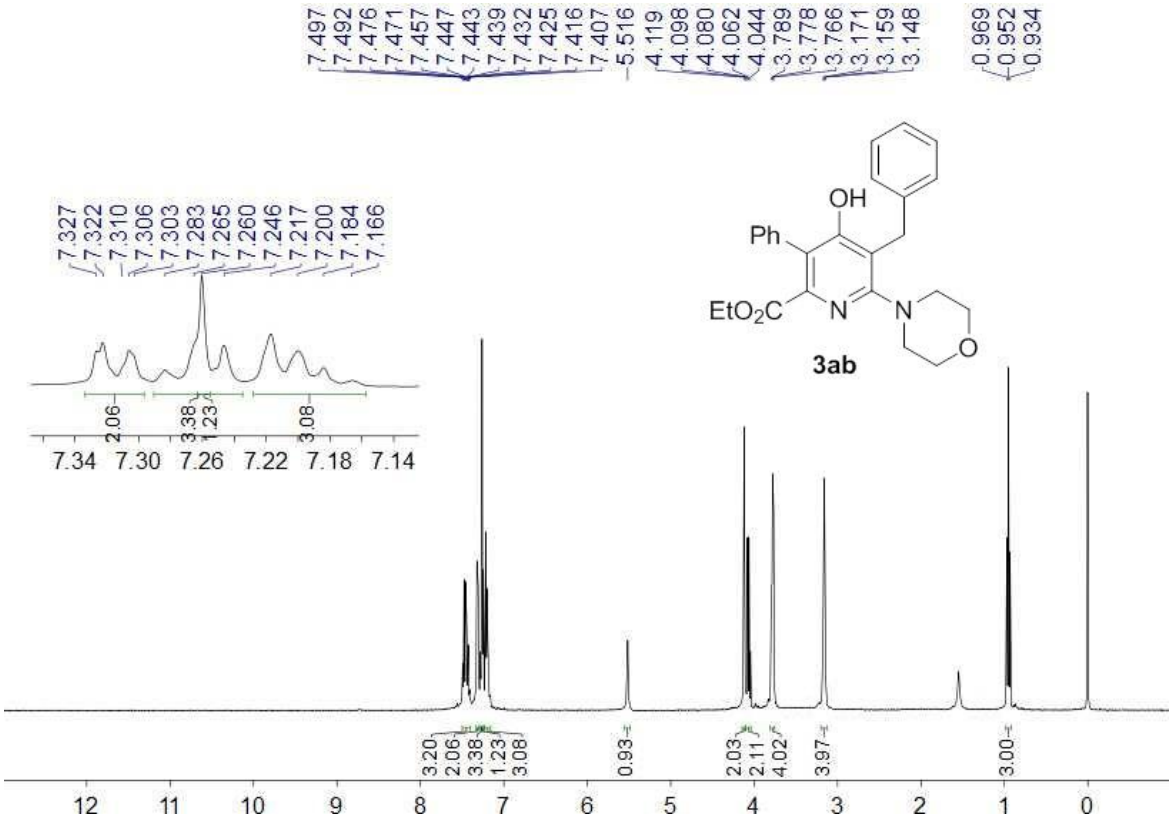
^{1}H NMR spectrum of the compound **3ua** (400 MHz, $CDCl_3$)



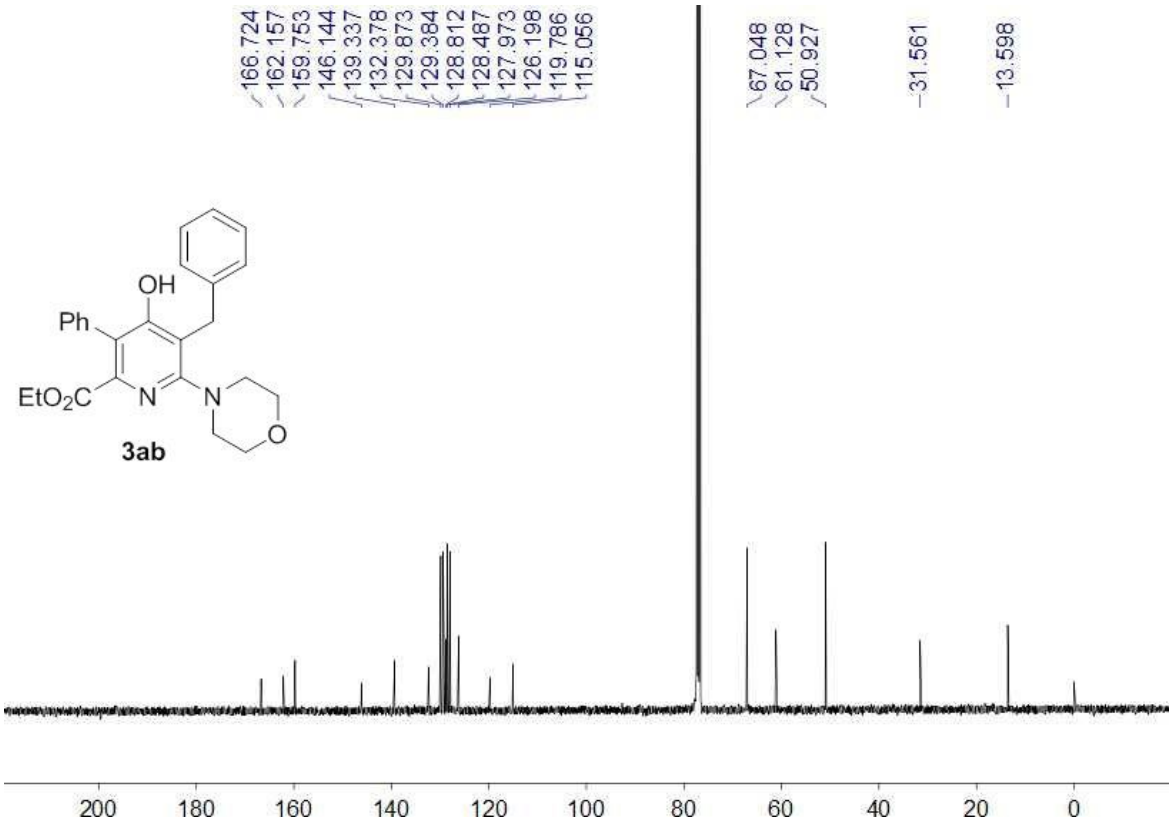
^{13}C NMR spectrum of the compound **3ua** (100 MHz, $CDCl_3$)



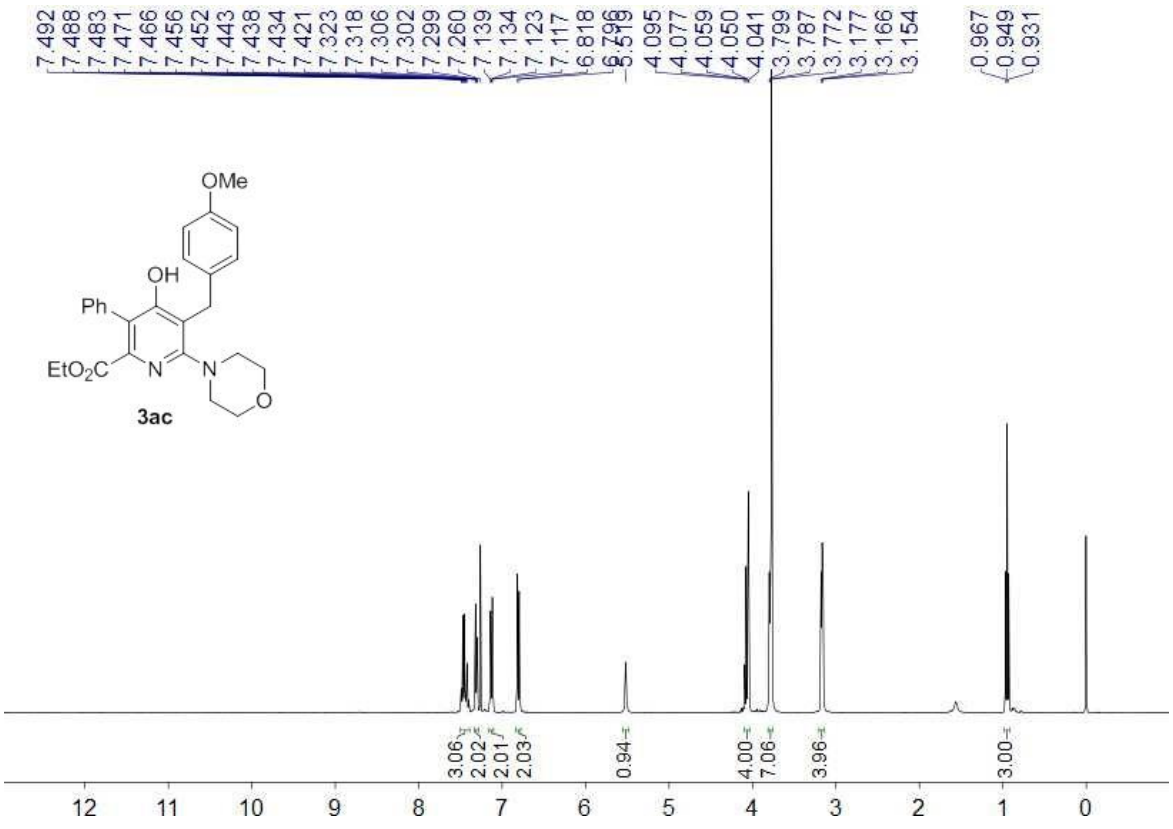
[1]H NMR spectrum of the compound **3ab** (400 MHz, $CDCl_3$)



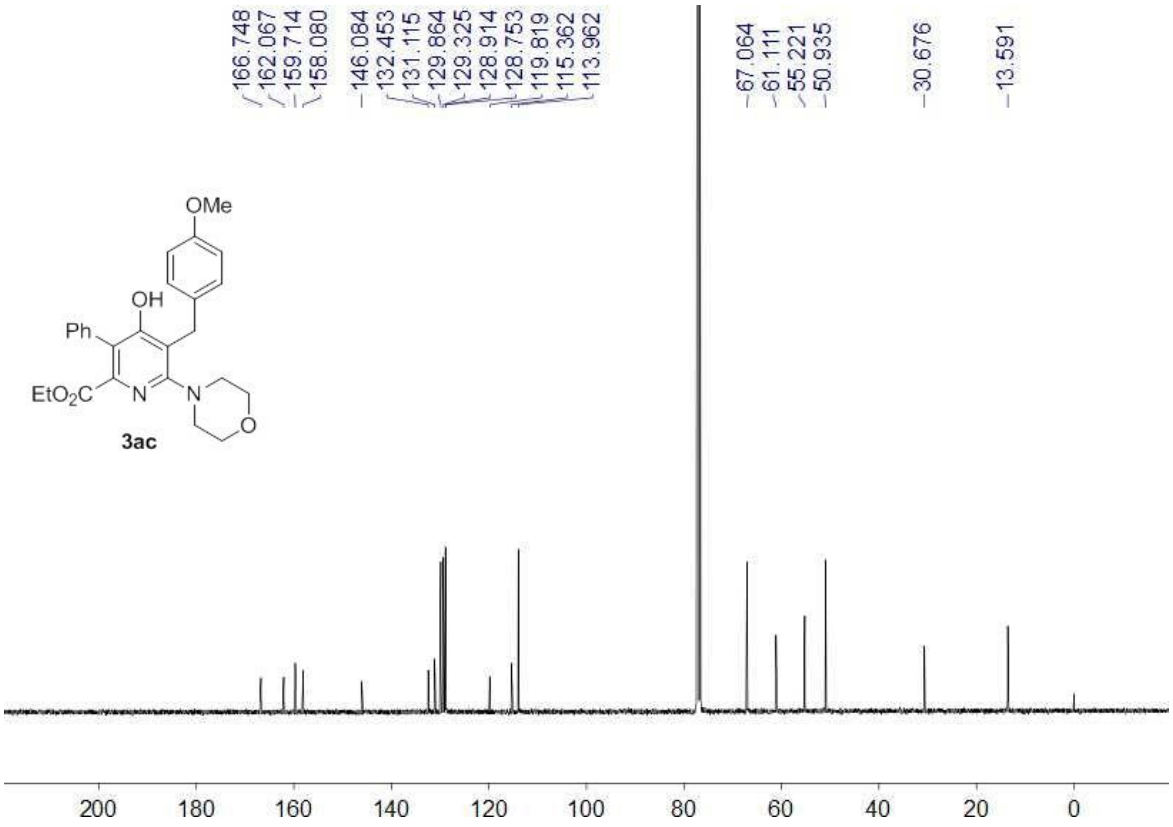
[13]C NMR spectrum of the compound **3ab** (100 MHz, $CDCl_3$)



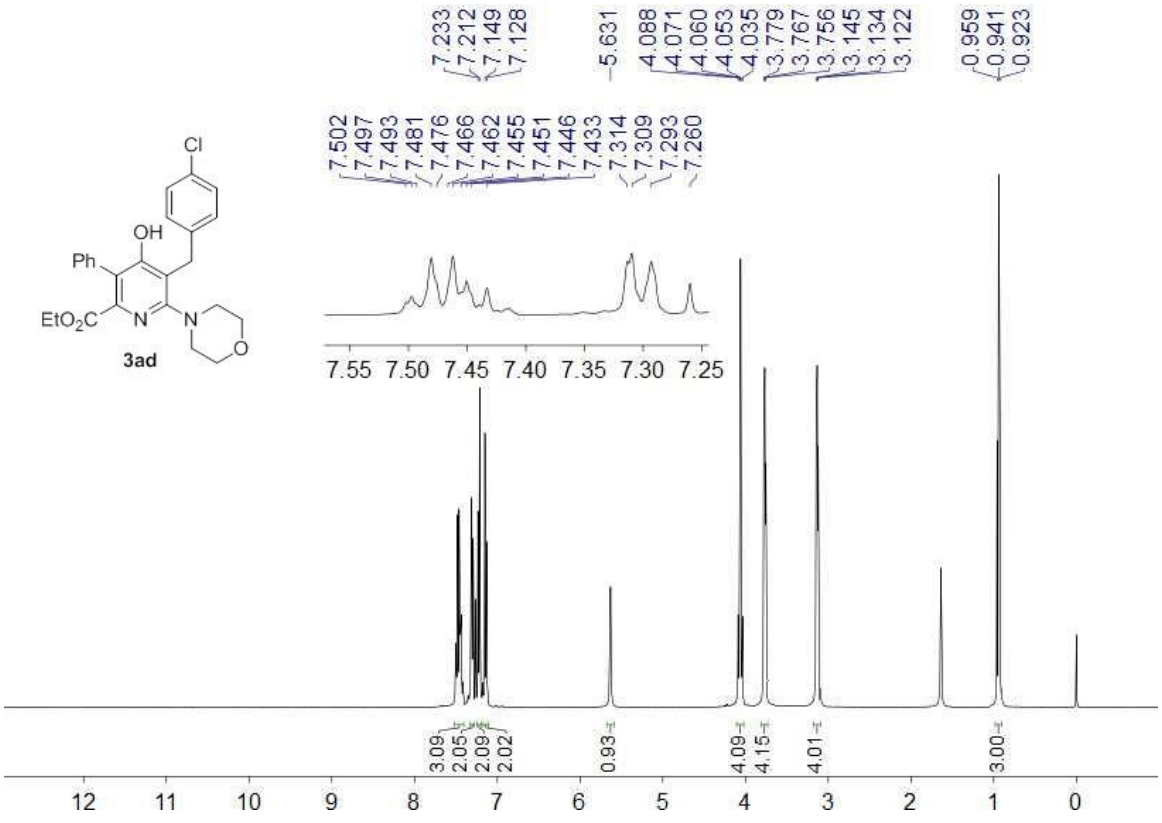
^{1}H NMR spectrum of the compound **3ac** (400 MHz, $CDCl_3$)



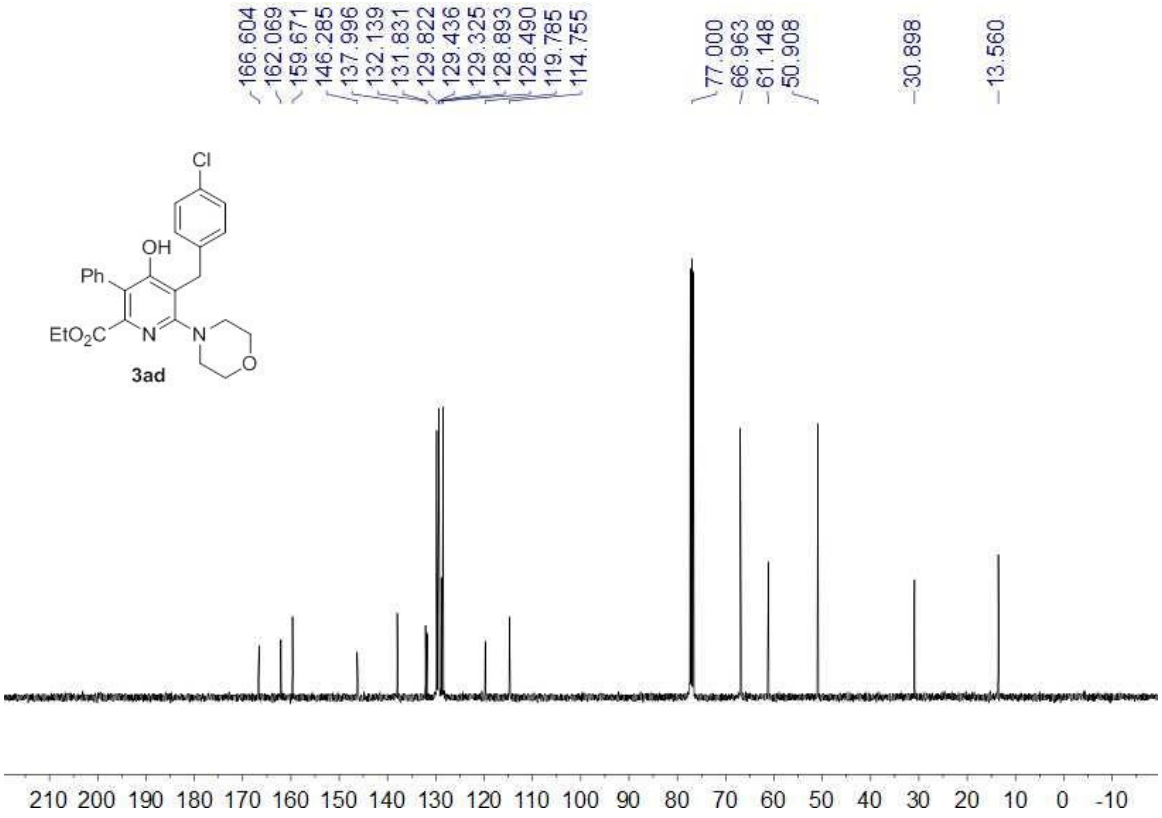
^{13}C NMR spectrum of the compound **3ac** (100 MHz, $CDCl_3$)



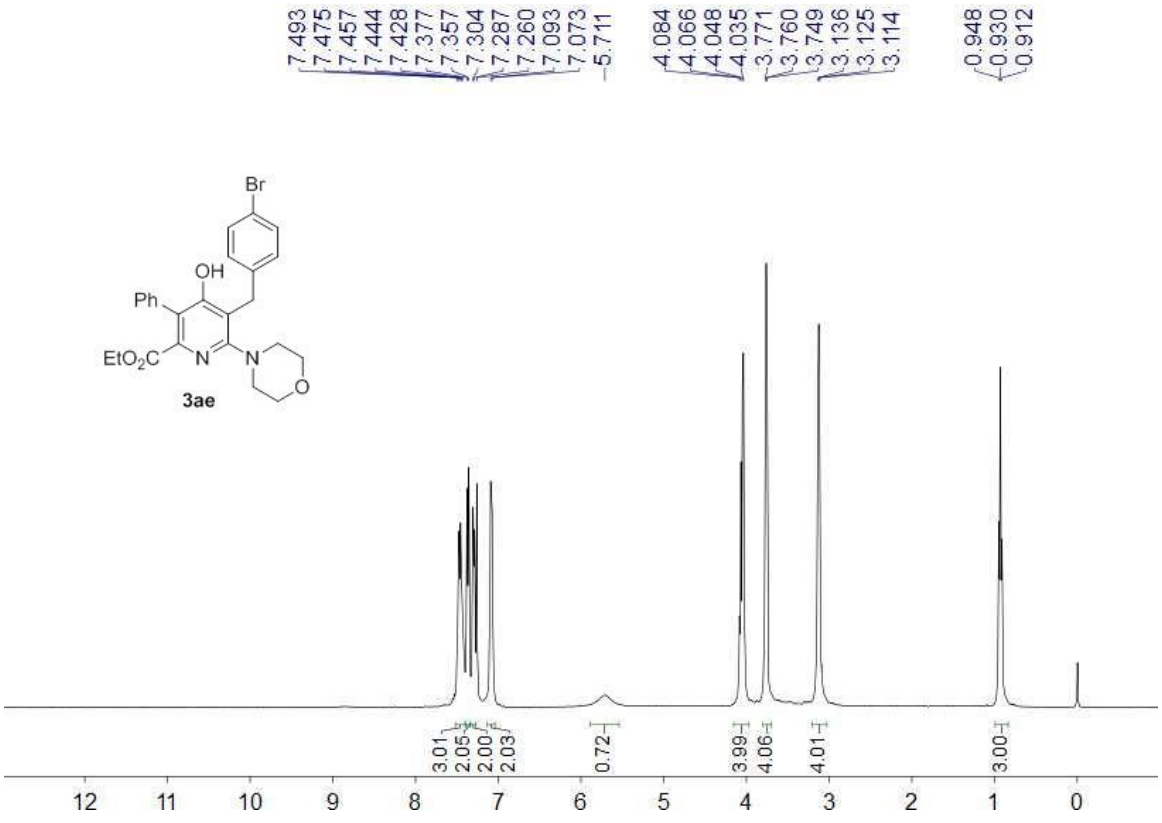
^{1}H NMR spectrum of the compound **3ad** (400 MHz, $CDCl_3$)



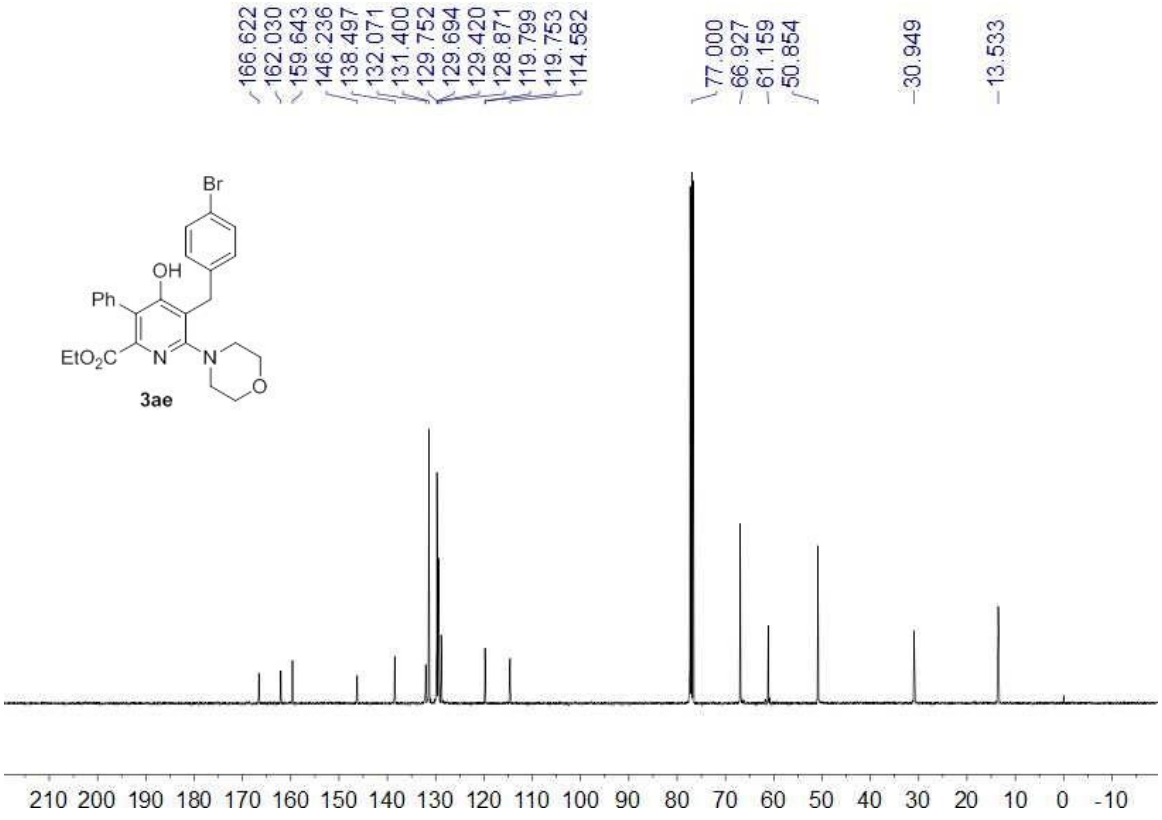
^{13}C NMR spectrum of the compound **3ad** (100 MHz, $CDCl_3$)



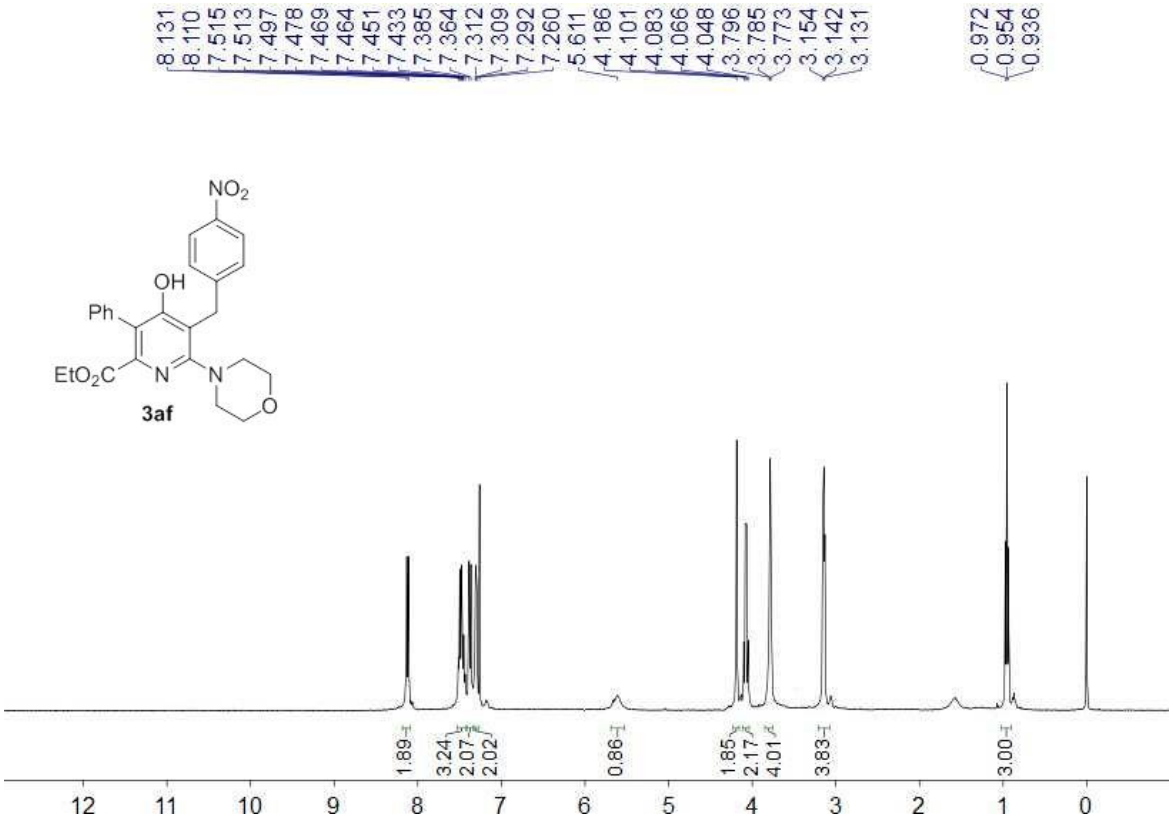
^{1}H NMR spectrum of the compound **3ae** (400 MHz, $CDCl_3$)



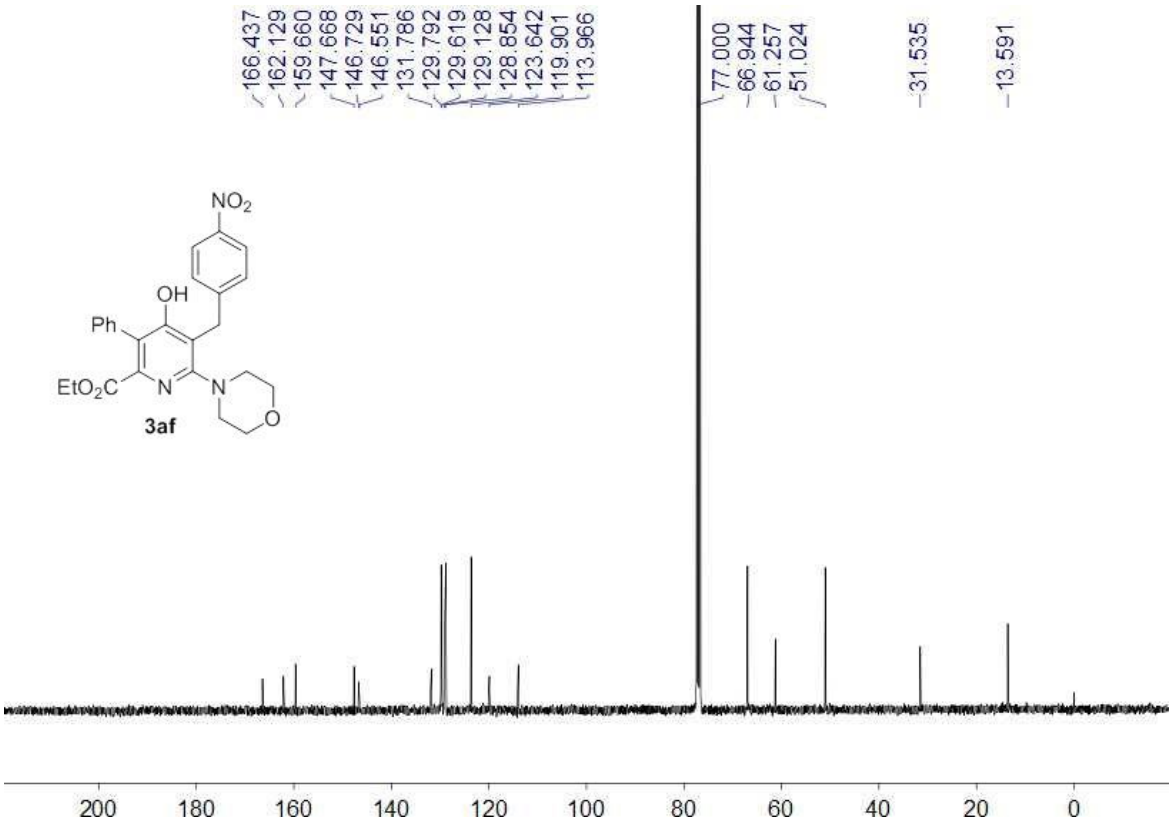
^{13}C NMR spectrum of the compound **3ae** (100 MHz, $CDCl_3$)



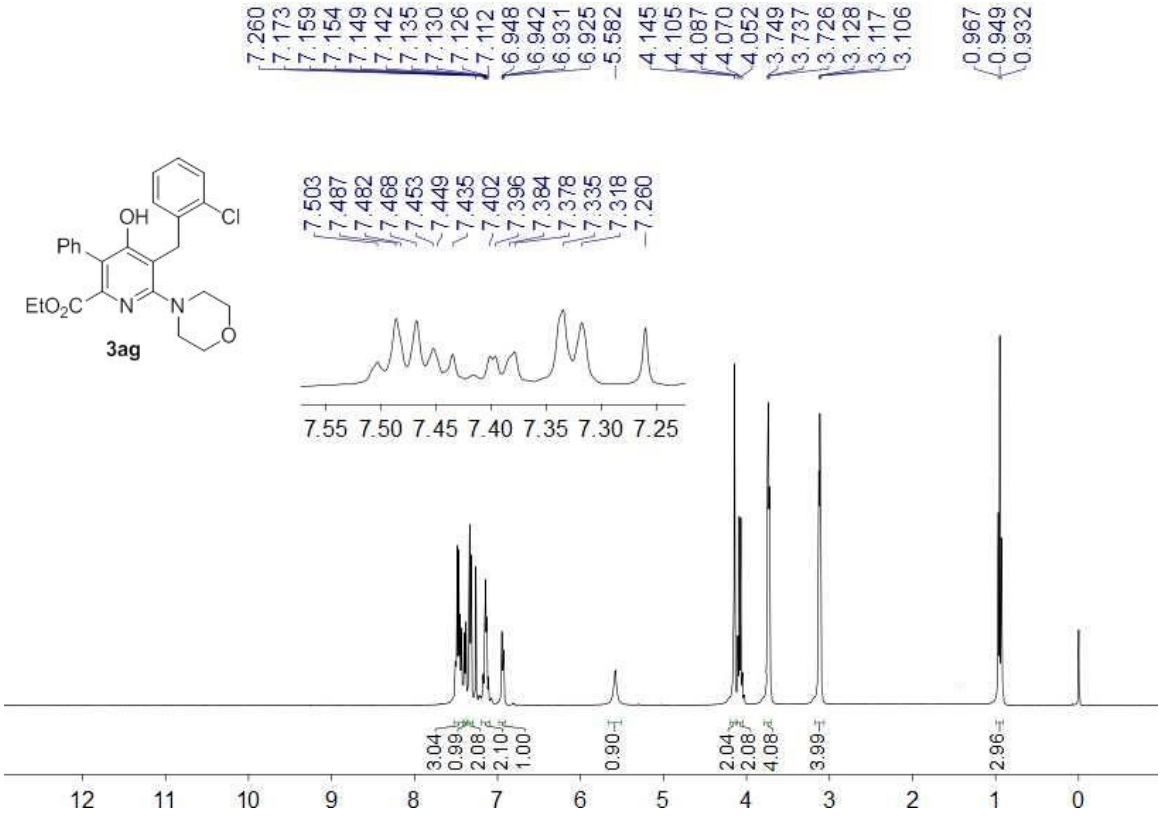
^{1}H NMR spectrum of the compound **3af** (400 MHz, $CDCl_3$)



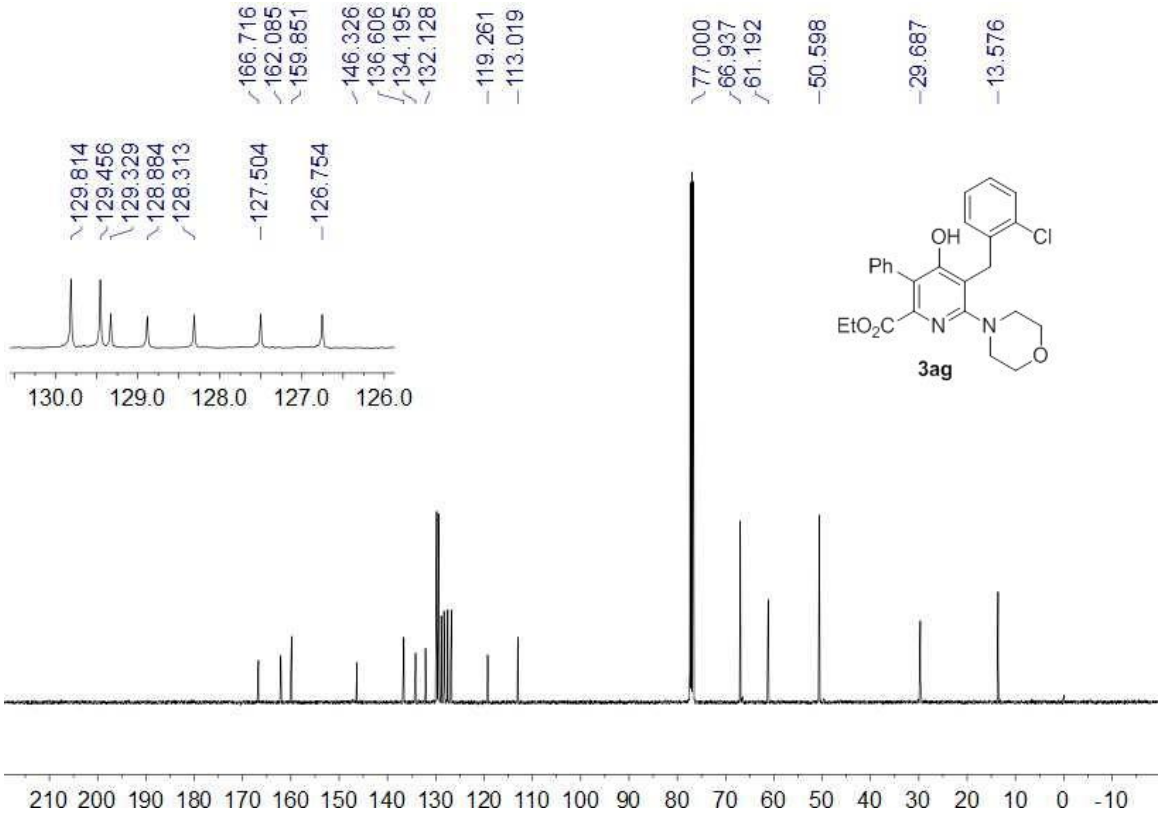
^{13}C NMR spectrum of the compound **3af** (100 MHz, $CDCl_3$)



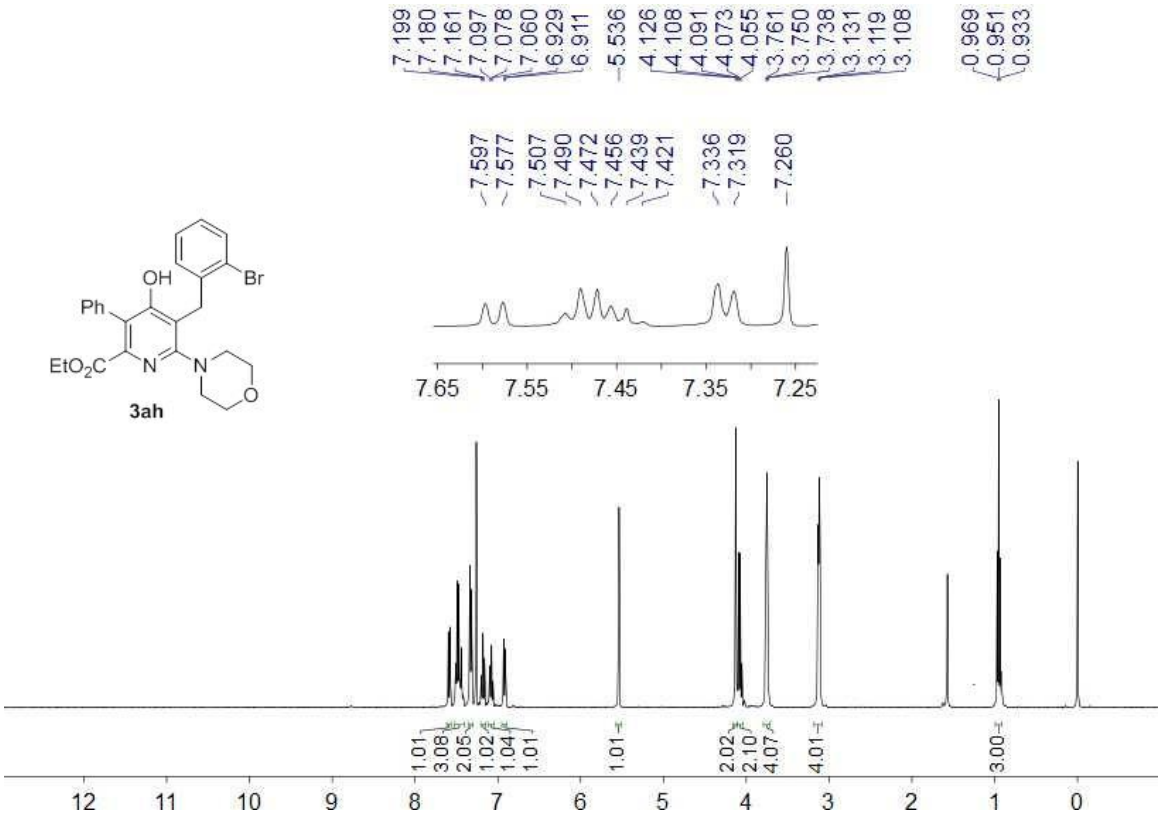
^{1}H NMR spectrum of the compound **3ag** (400 MHz, $CDCl_3$)



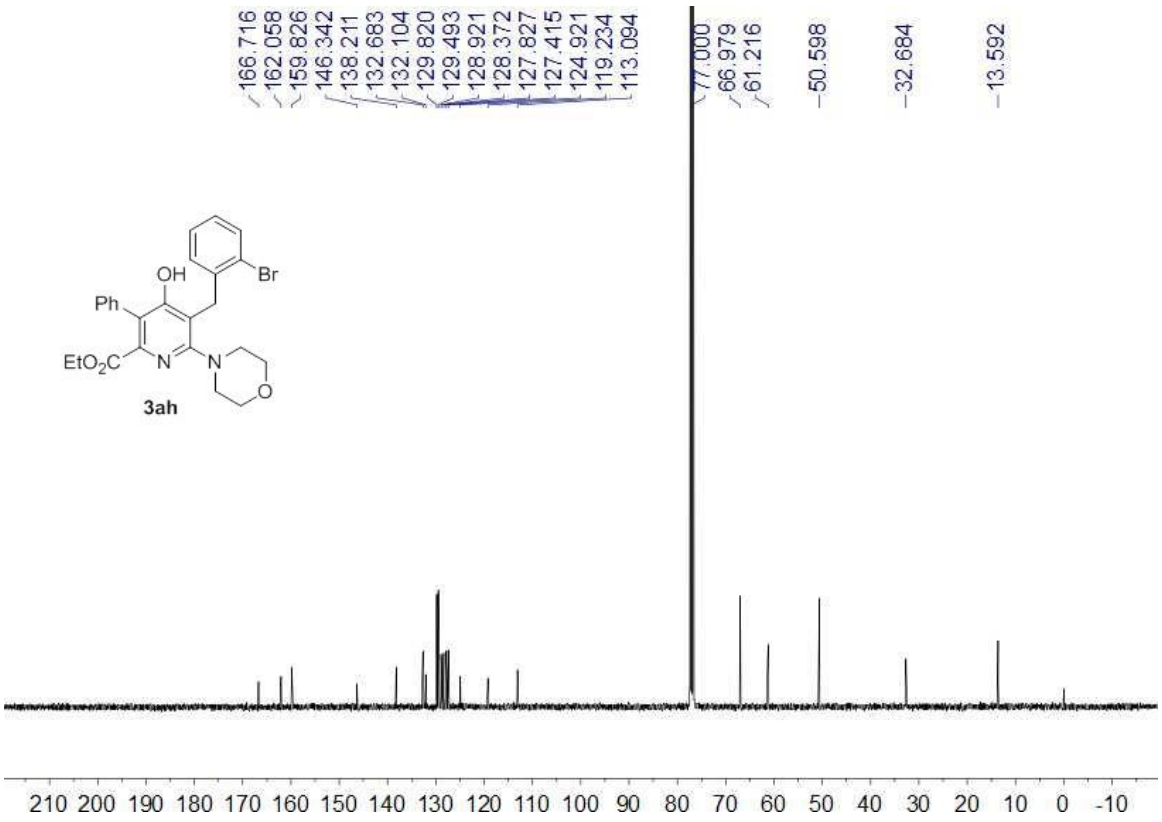
^{13}C NMR spectrum of the compound **3ag** (100 MHz, $CDCl_3$)



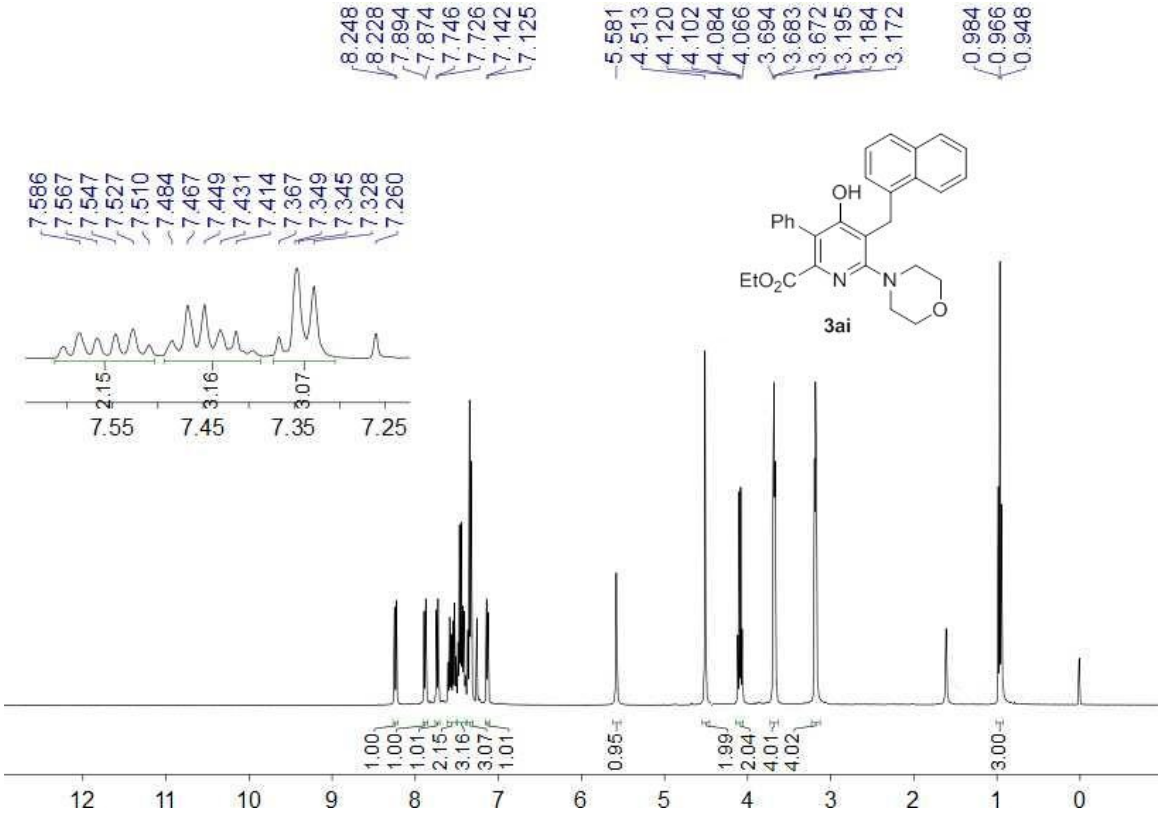
^{1}H NMR spectrum of the compound **3ah** (400 MHz, $CDCl_3$)



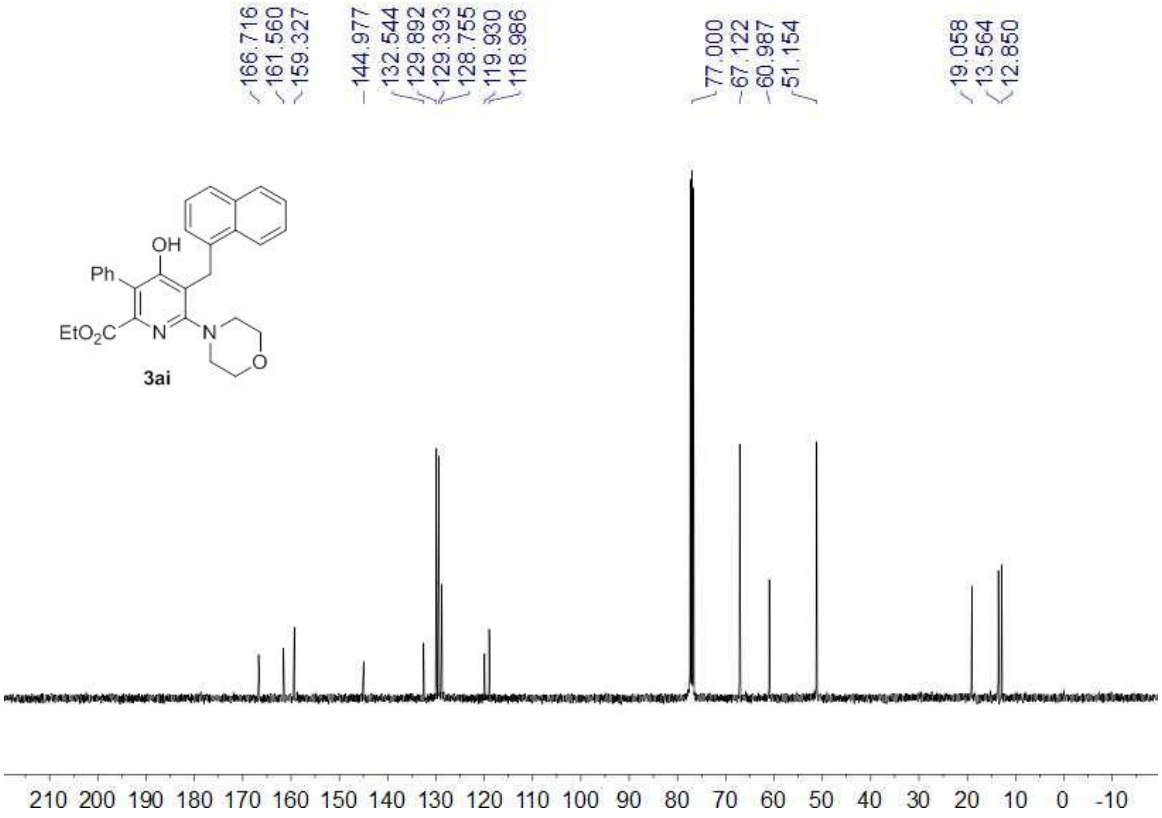
^{13}C NMR spectrum of the compound **3ah** (100 MHz, $CDCl_3$)



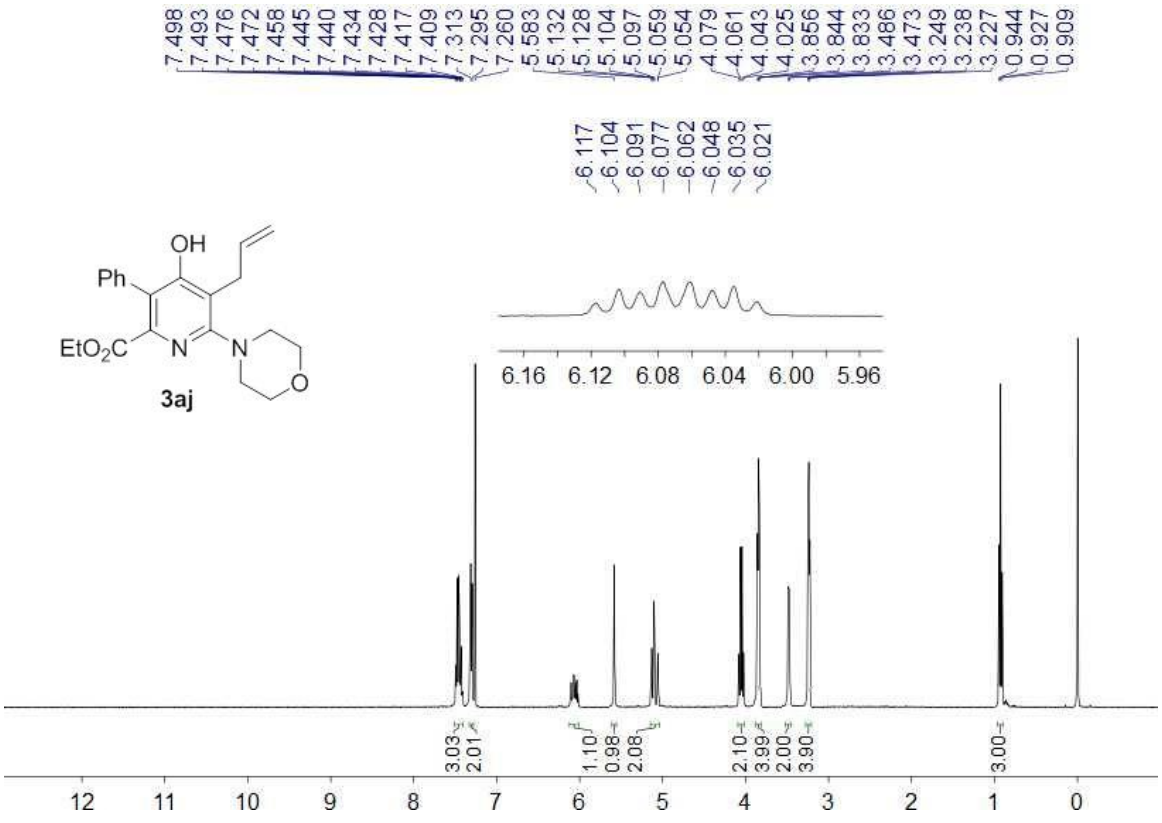
[1]H NMR spectrum of the compound **3ai** (400 MHz, $CDCl_3$)



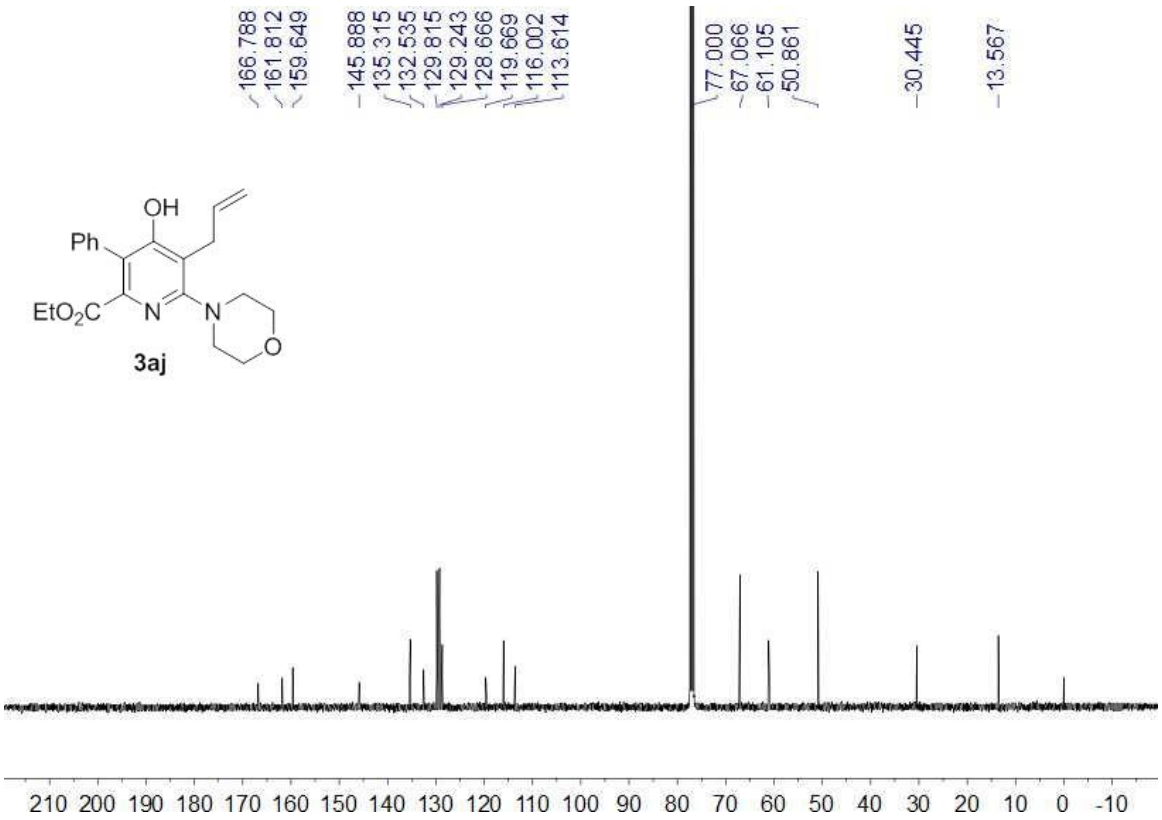
[13]C NMR spectrum of the compound **3ai** (100 MHz, $CDCl_3$)



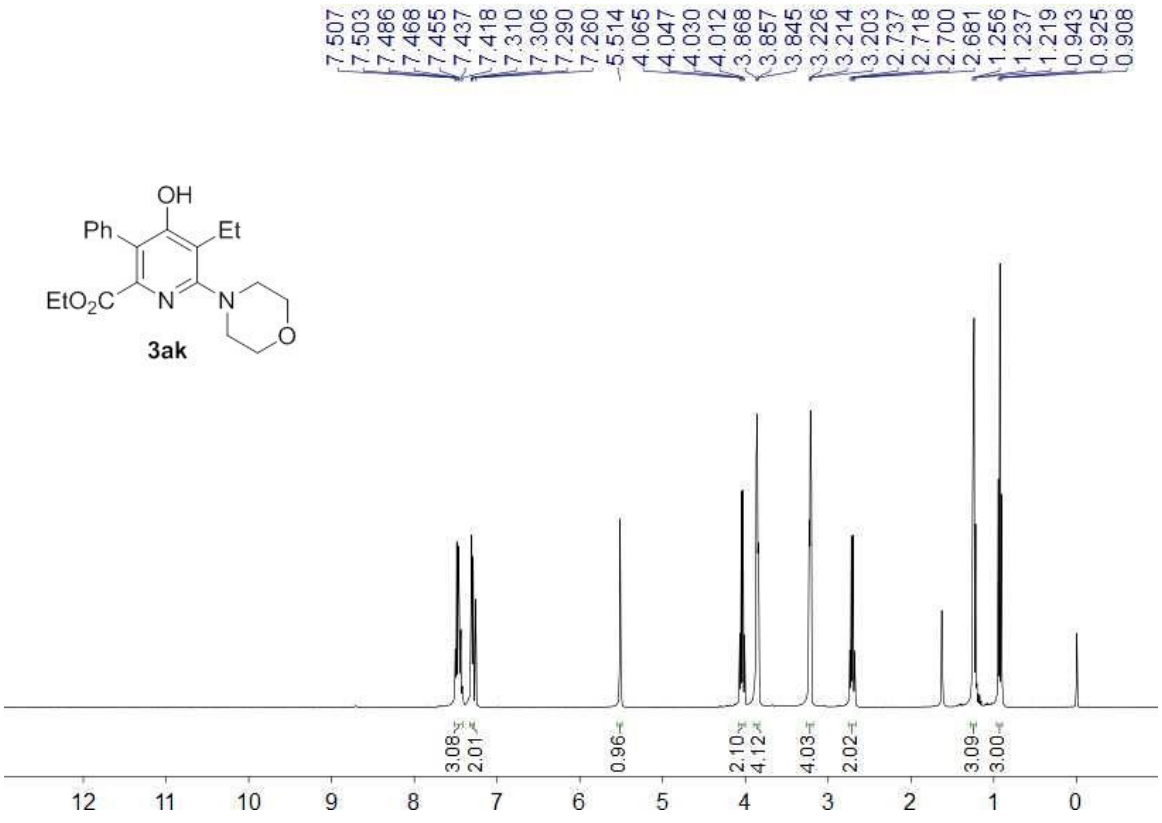
^{1}H NMR spectrum of the compound **3aj** (400 MHz, $CDCl_3$)



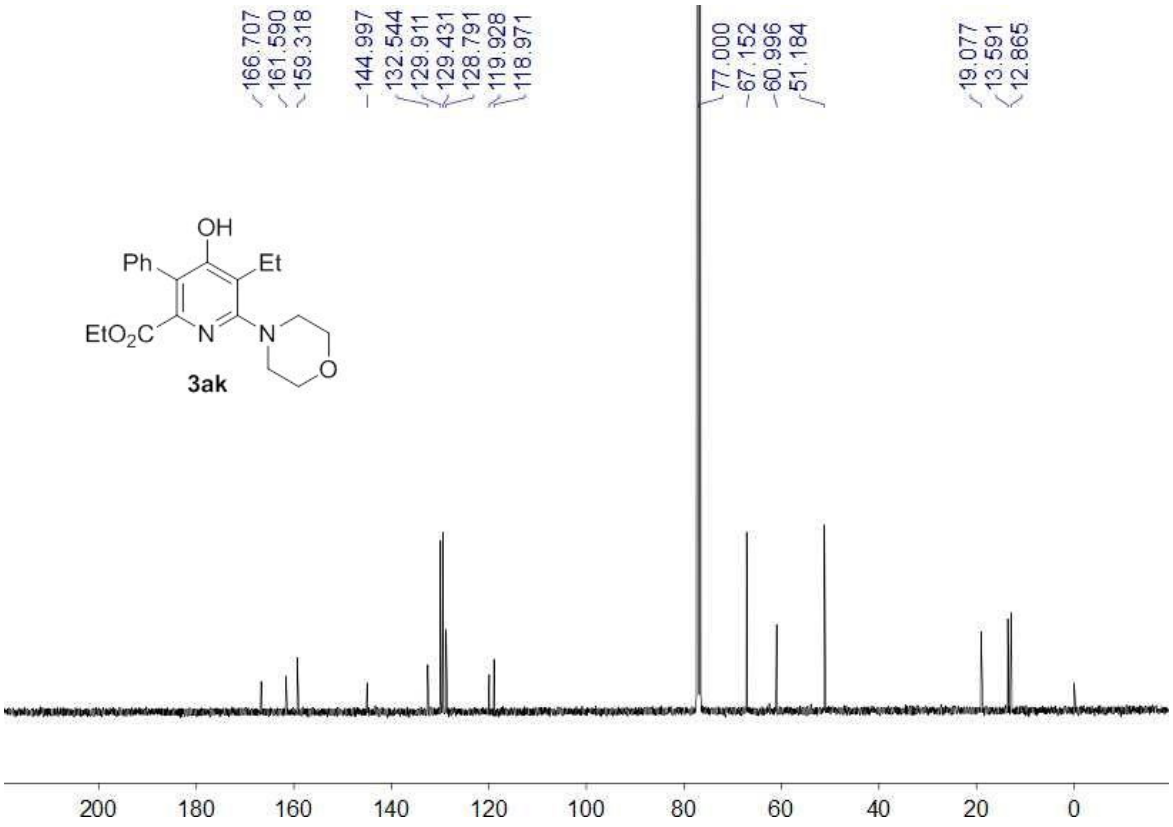
^{13}C NMR spectrum of the compound **3aj** (100 MHz, $CDCl_3$)



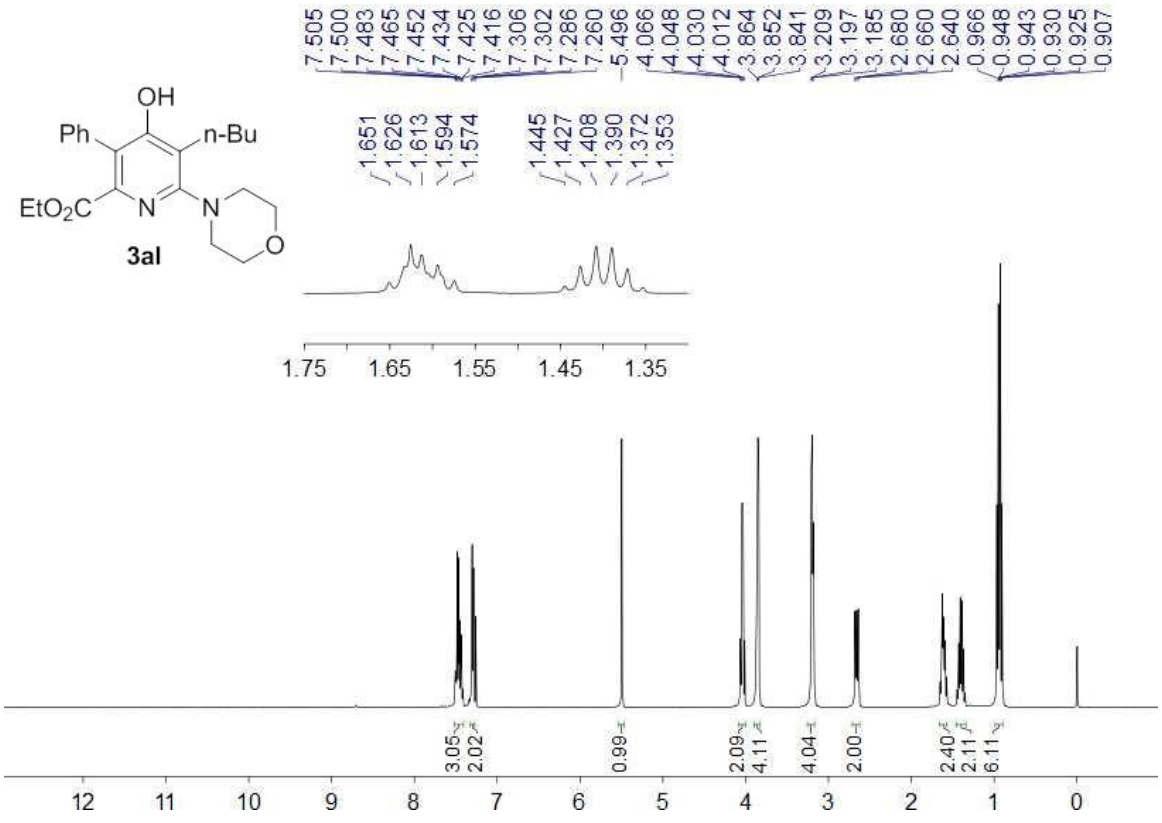
^{1}H NMR spectrum of the compound **3ak** (400 MHz, $CDCl_3$)



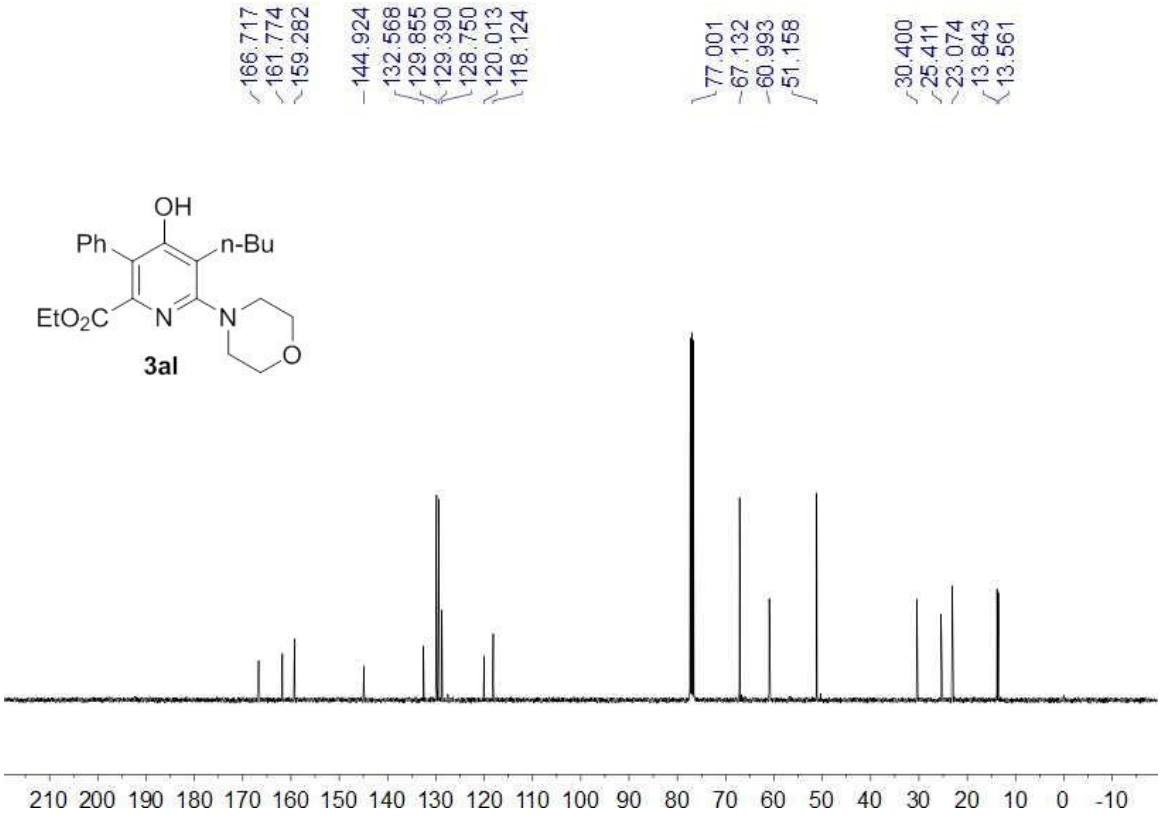
^{13}C NMR spectrum of the compound **3ak** (100 MHz, $CDCl_3$)



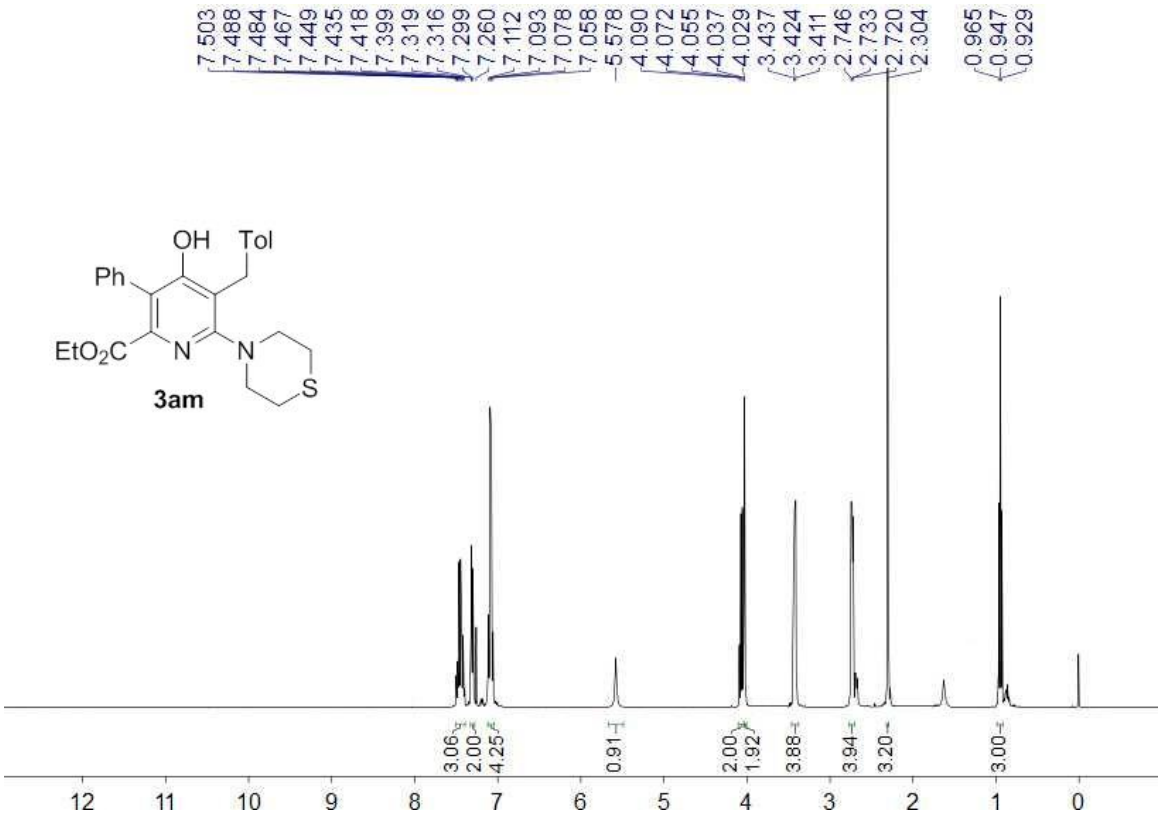
^{1}H NMR spectrum of the compound **3al** (400 MHz, $CDCl_3$)



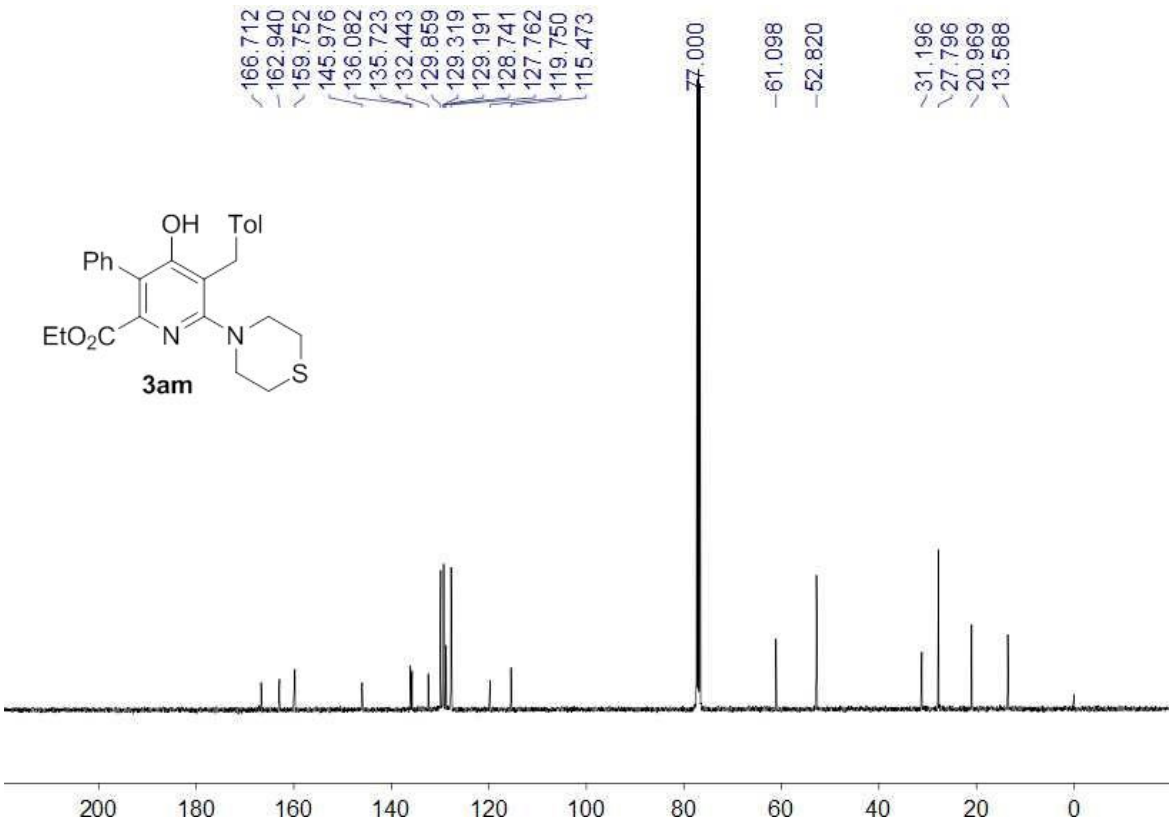
^{13}C NMR spectrum of the compound **3al** (100 MHz, $CDCl_3$)



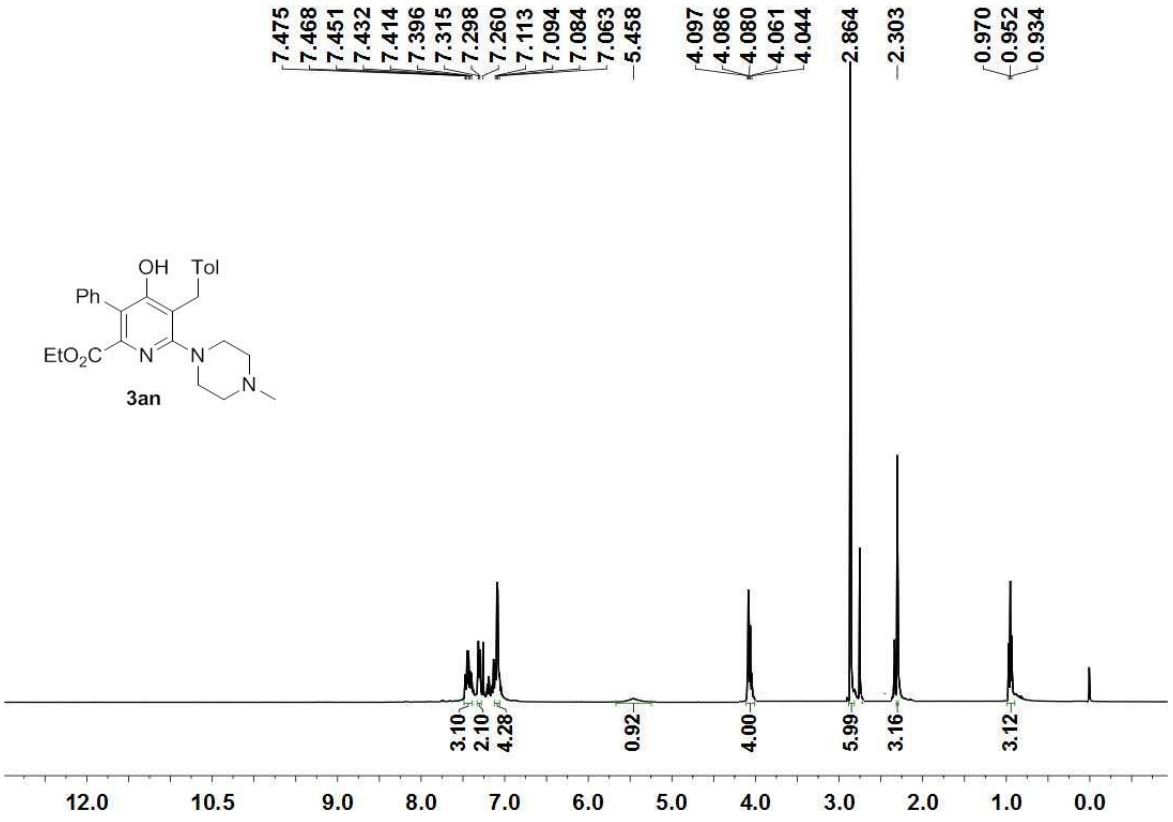
^{1}H NMR spectrum of the compound **3am** (400 MHz, $CDCl_3$)



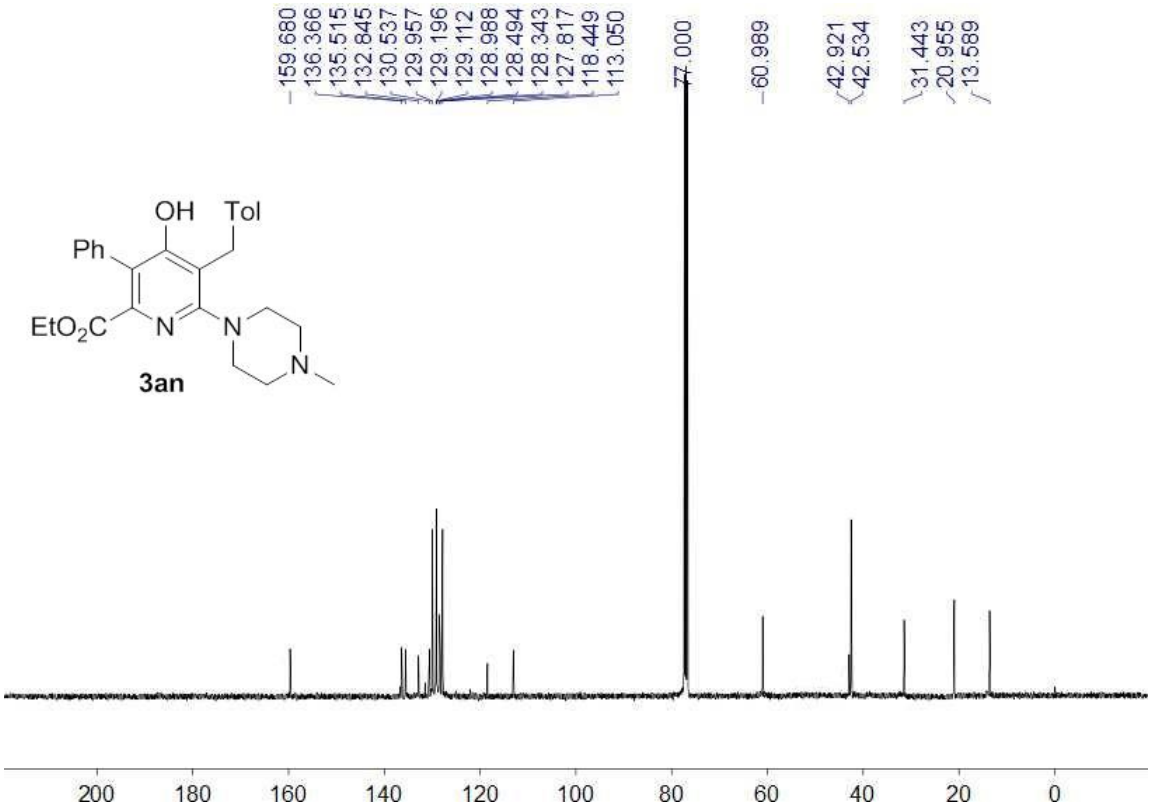
^{13}C NMR spectrum of the compound **3am** (100 MHz, $CDCl_3$)



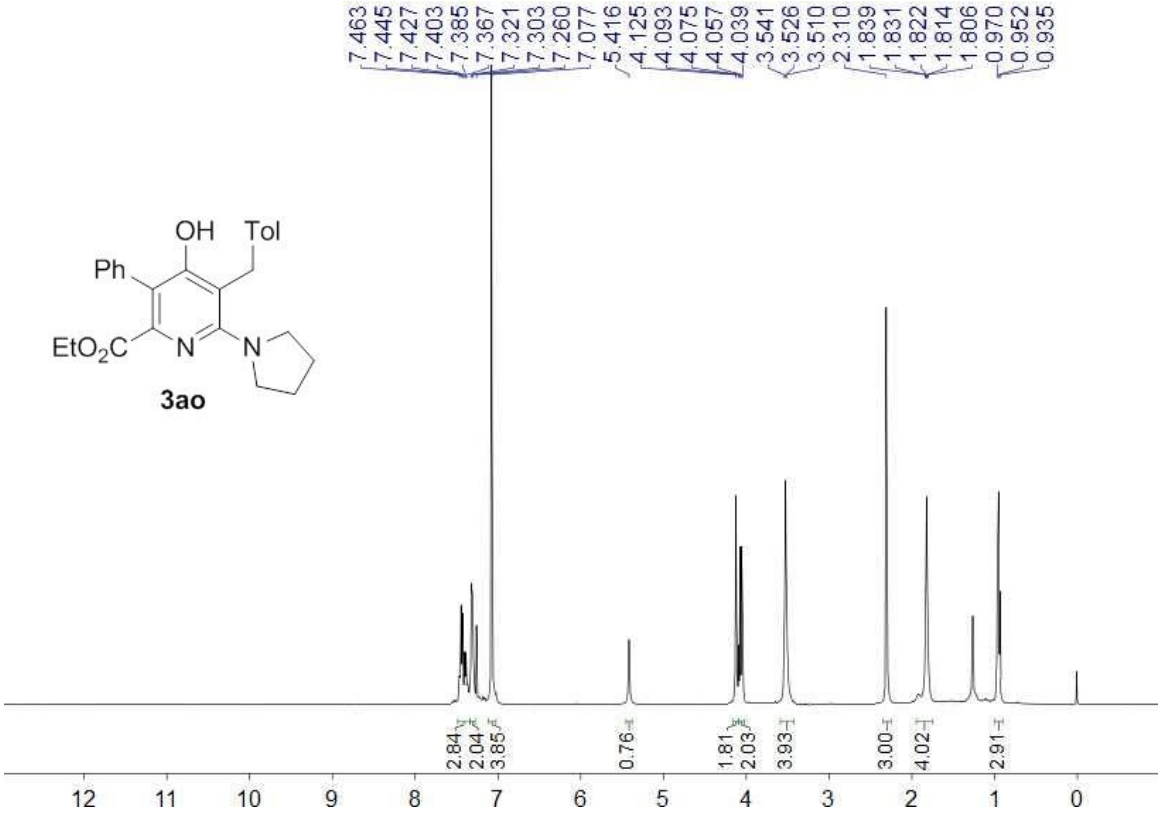
^{1}H NMR spectrum of the compound **3an** (400 MHz, $CDCl_3$)



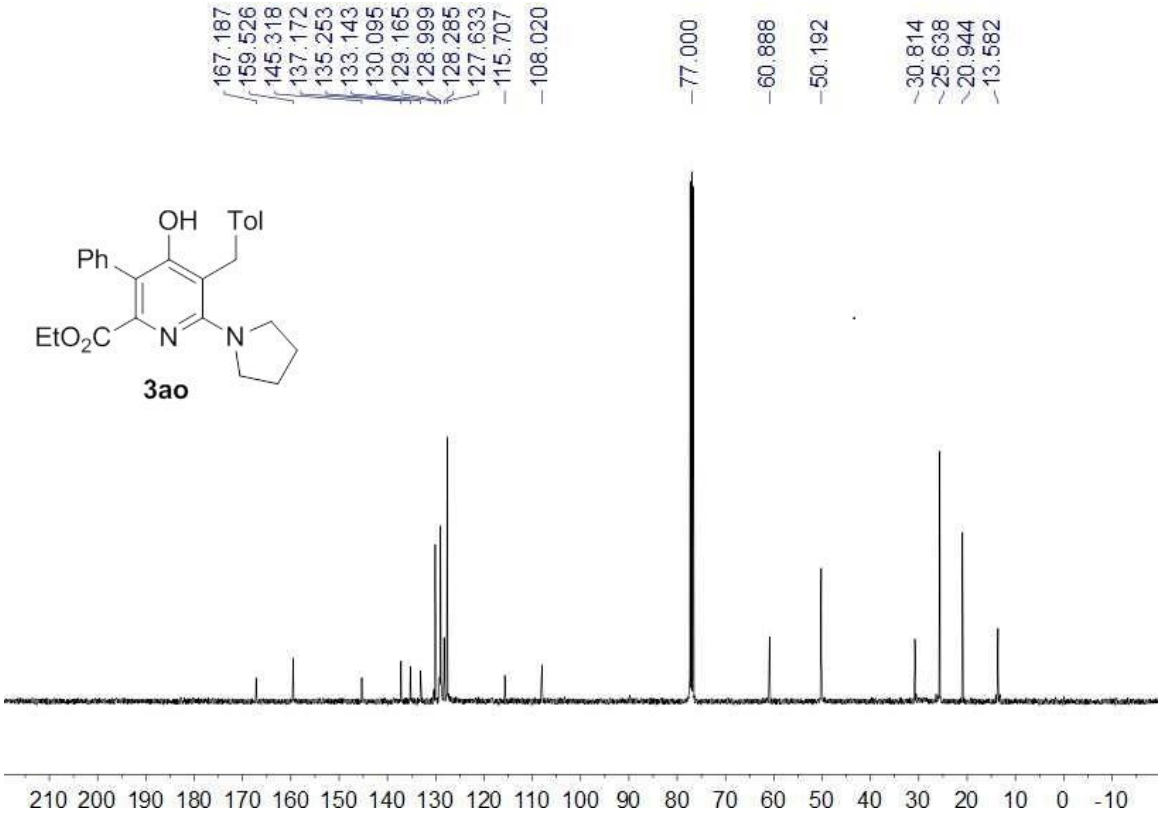
^{13}C NMR spectrum of the compound **3an** (100 MHz, $CDCl_3$)



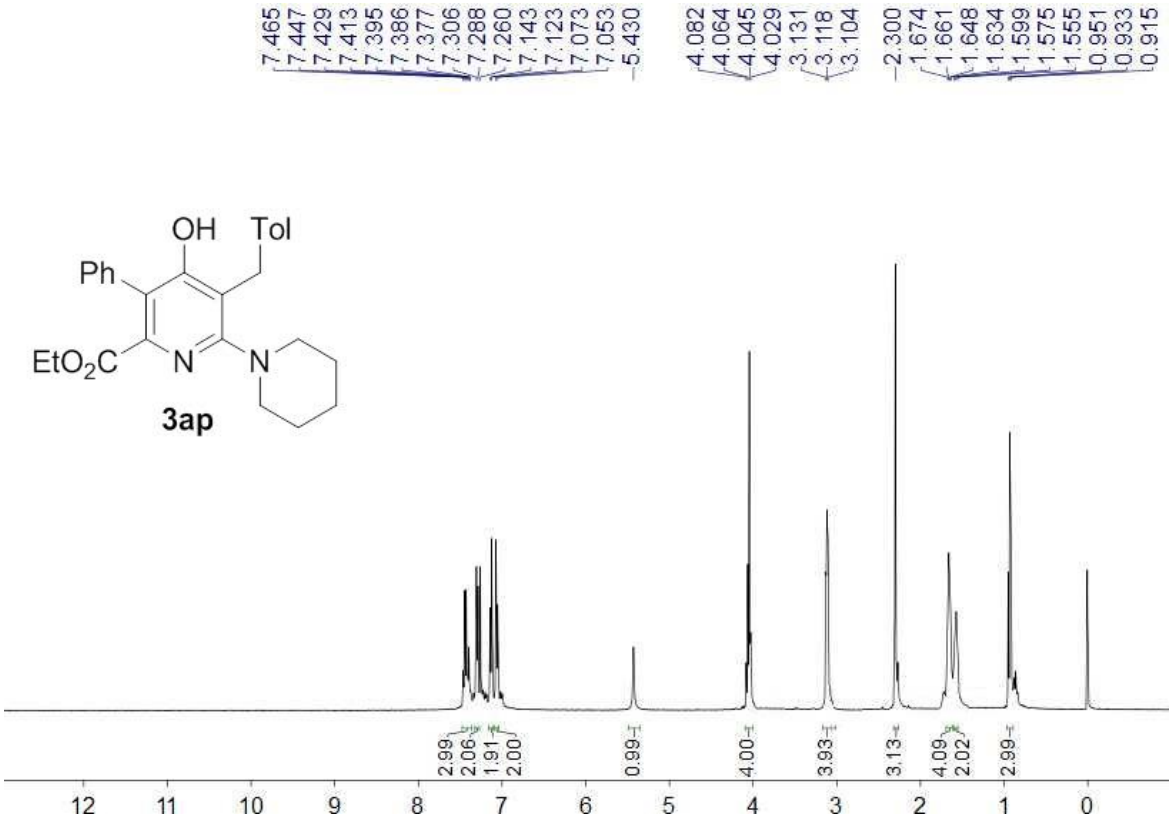
^{1}H NMR spectrum of the compound **3ao** (400 MHz, $CDCl_3$)



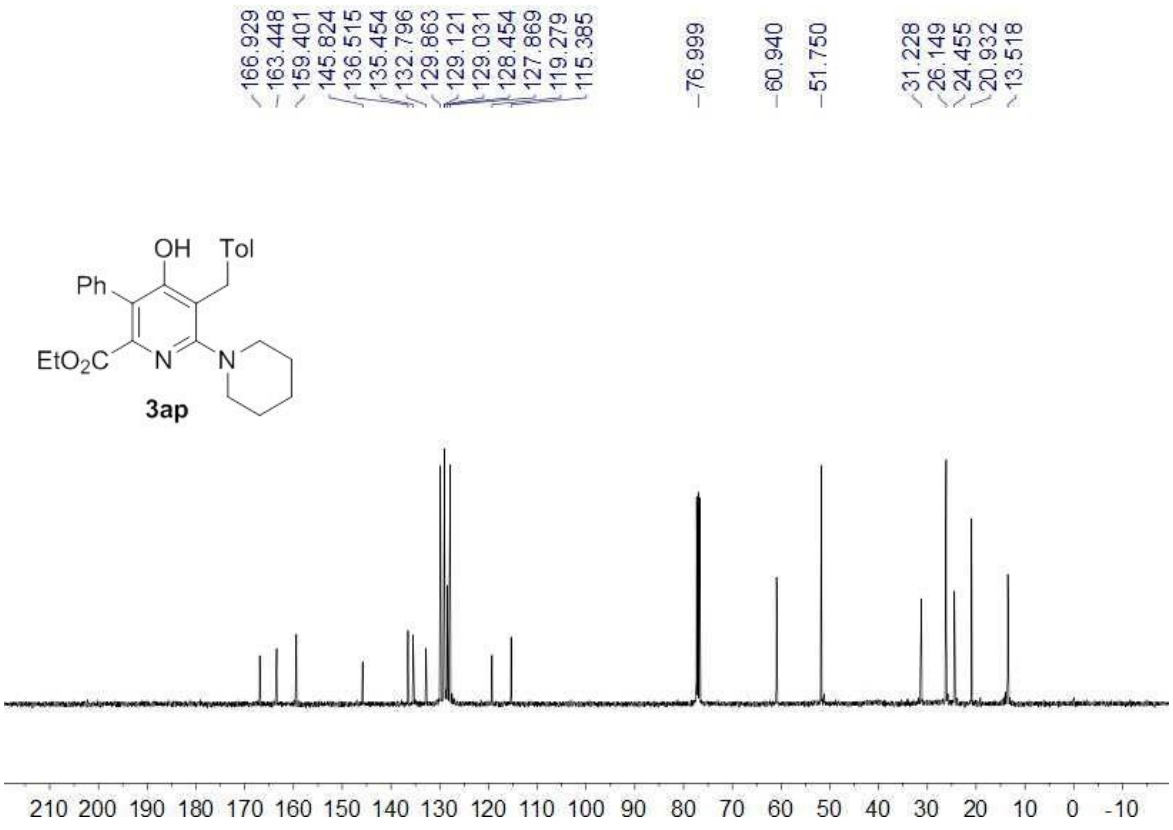
^{13}C NMR spectrum of the compound **3ao** (100 MHz, $CDCl_3$)



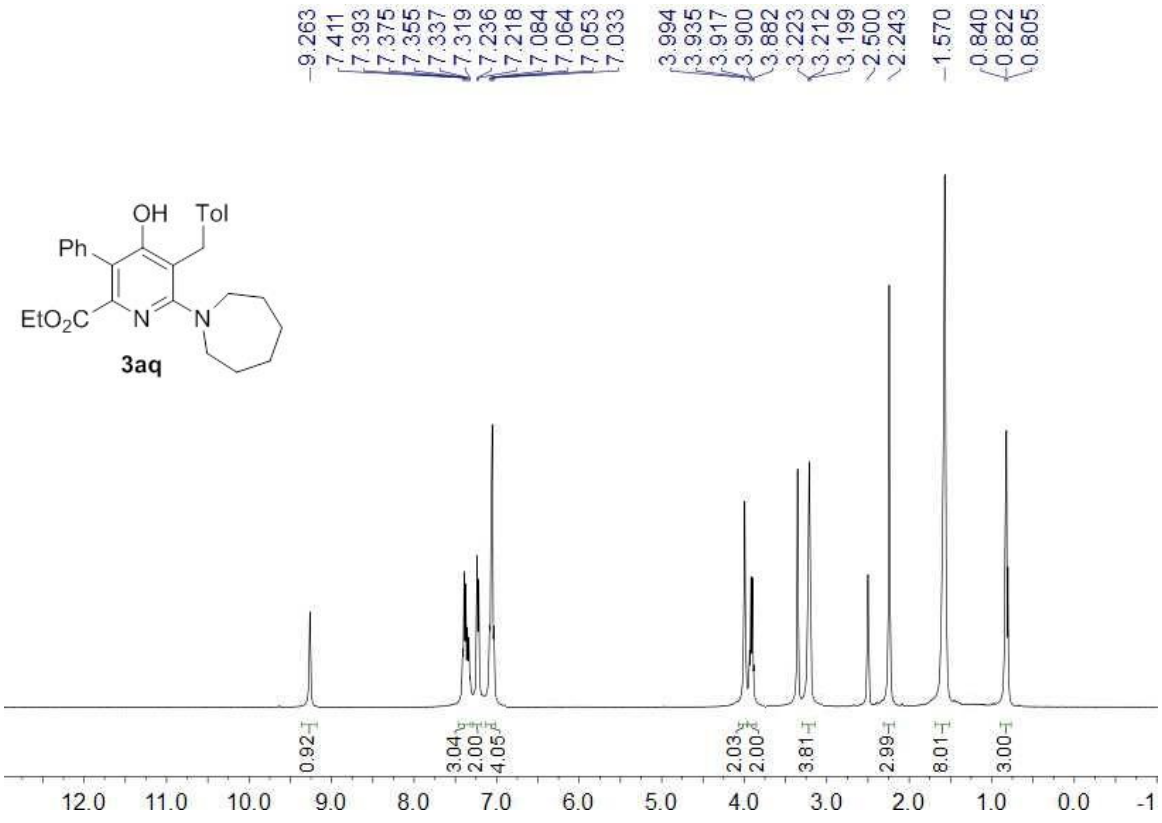
[1]H NMR spectrum of the compound **3ap** (400 MHz, $CDCl_3$)



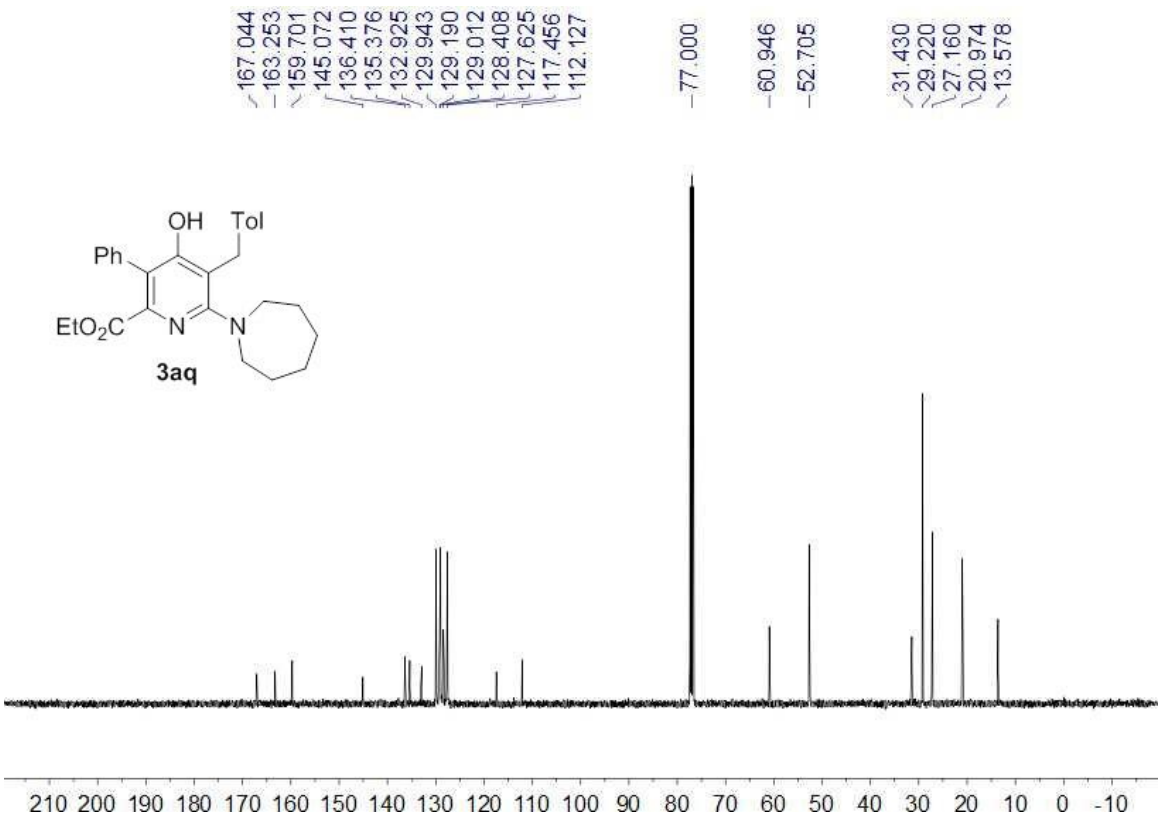
[13]C NMR spectrum of the compound **3ap** (100 MHz, $CDCl_3$)



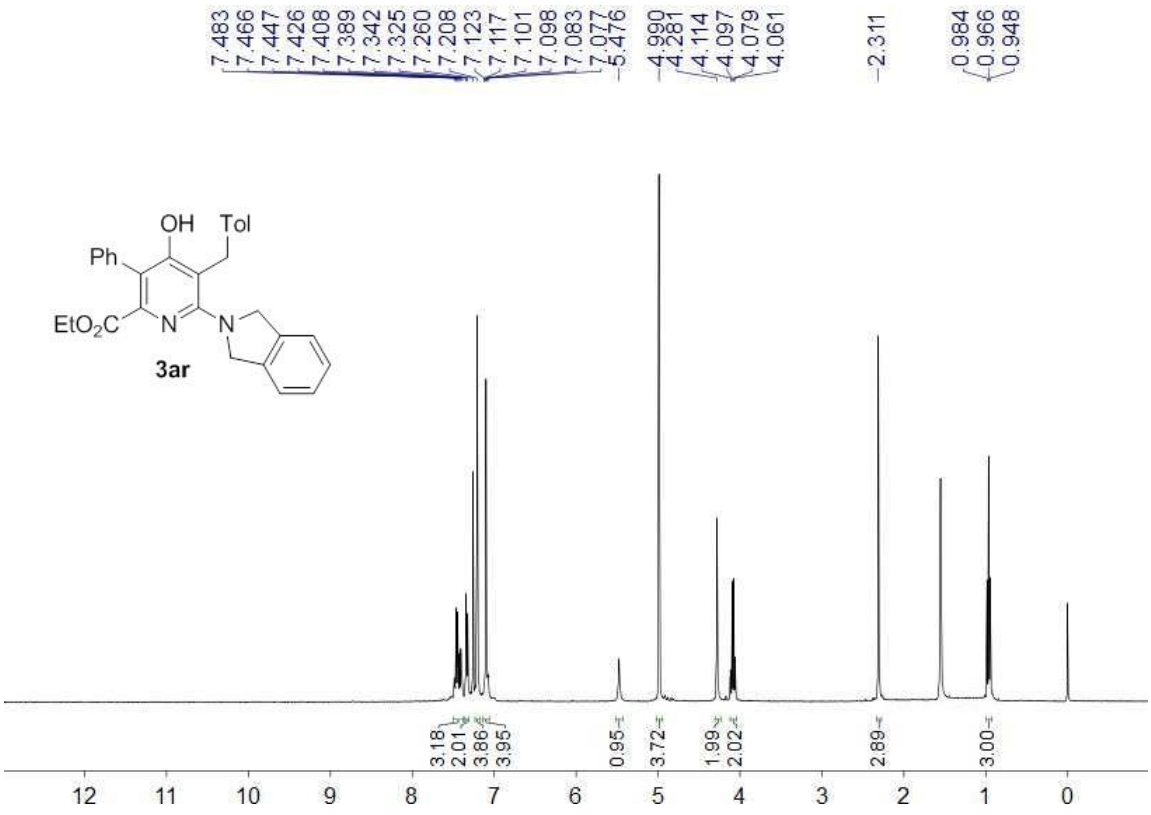
[1]H NMR spectrum of the compound **3aq** (400 MHz, DMSO-d_6)



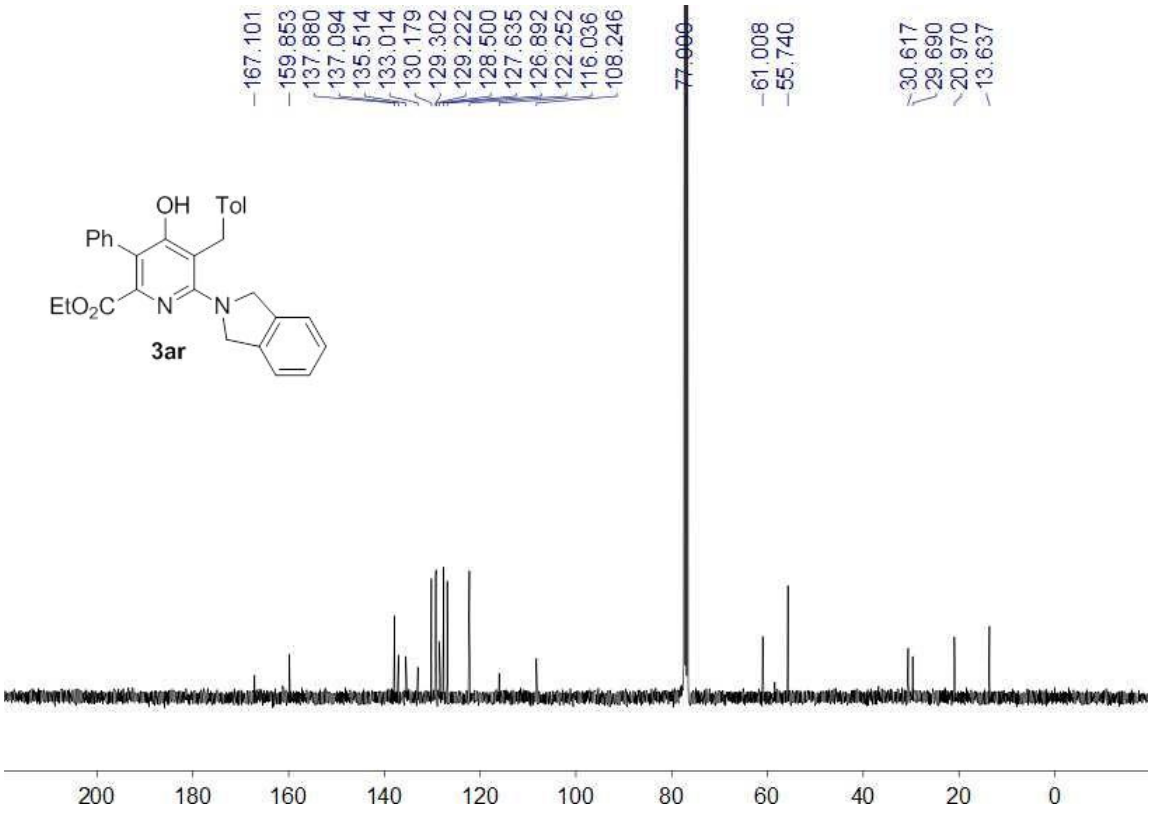
[13]C NMR spectrum of the compound **3aq** (100 MHz, $CDCl_3$)



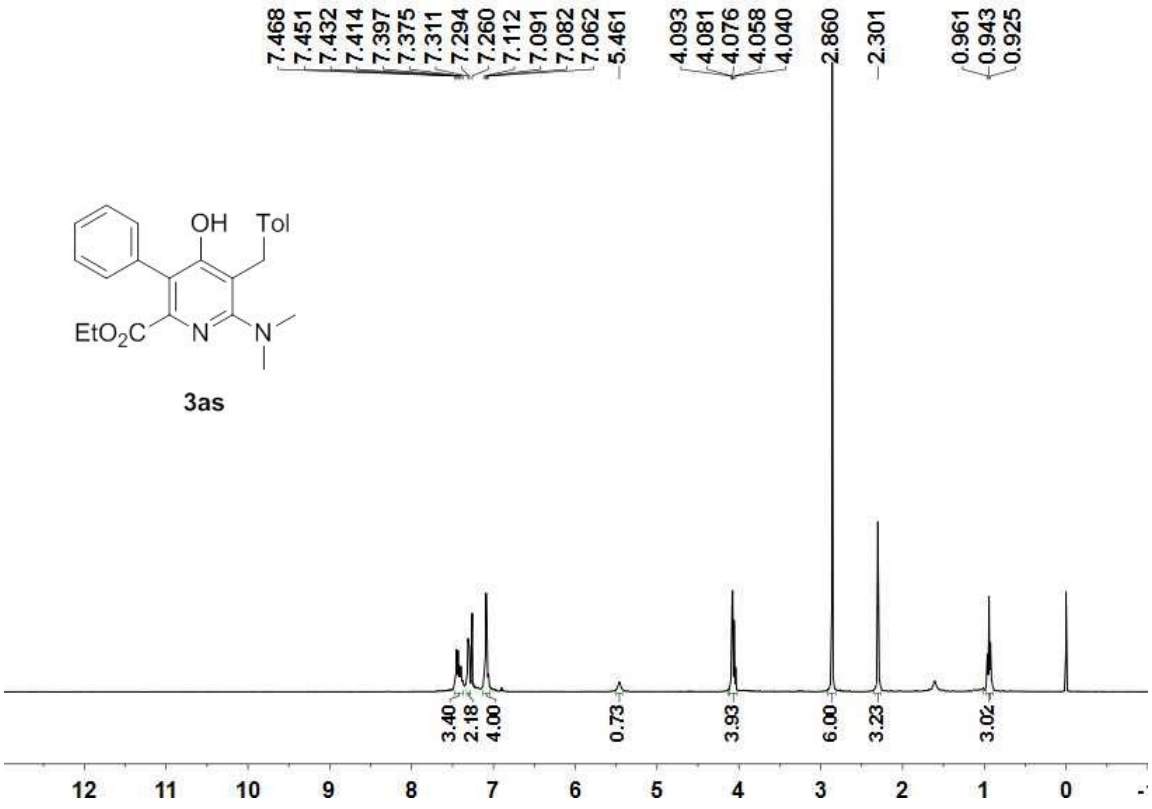
^{1}H NMR spectrum of the compound **3ar** (400 MHz, $CDCl_3$)



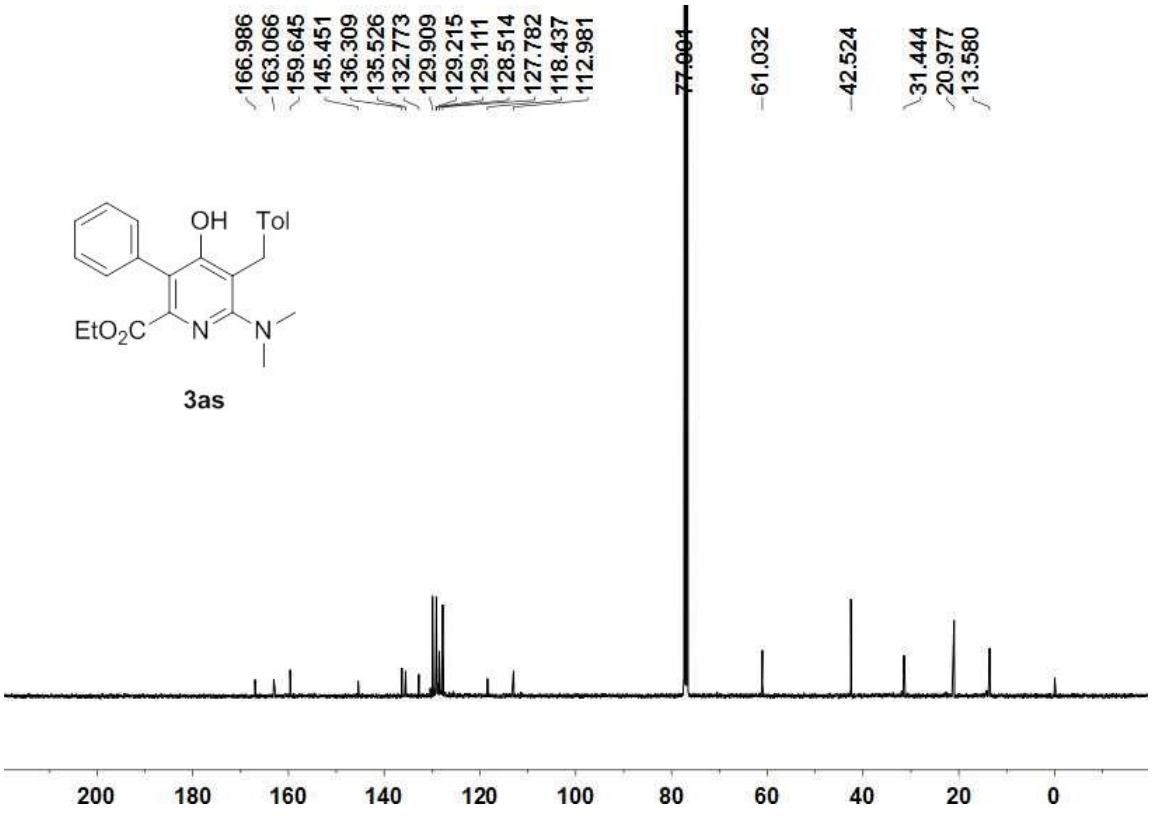
^{13}C NMR spectrum of the compound **3ar** (100 MHz, $CDCl_3$)



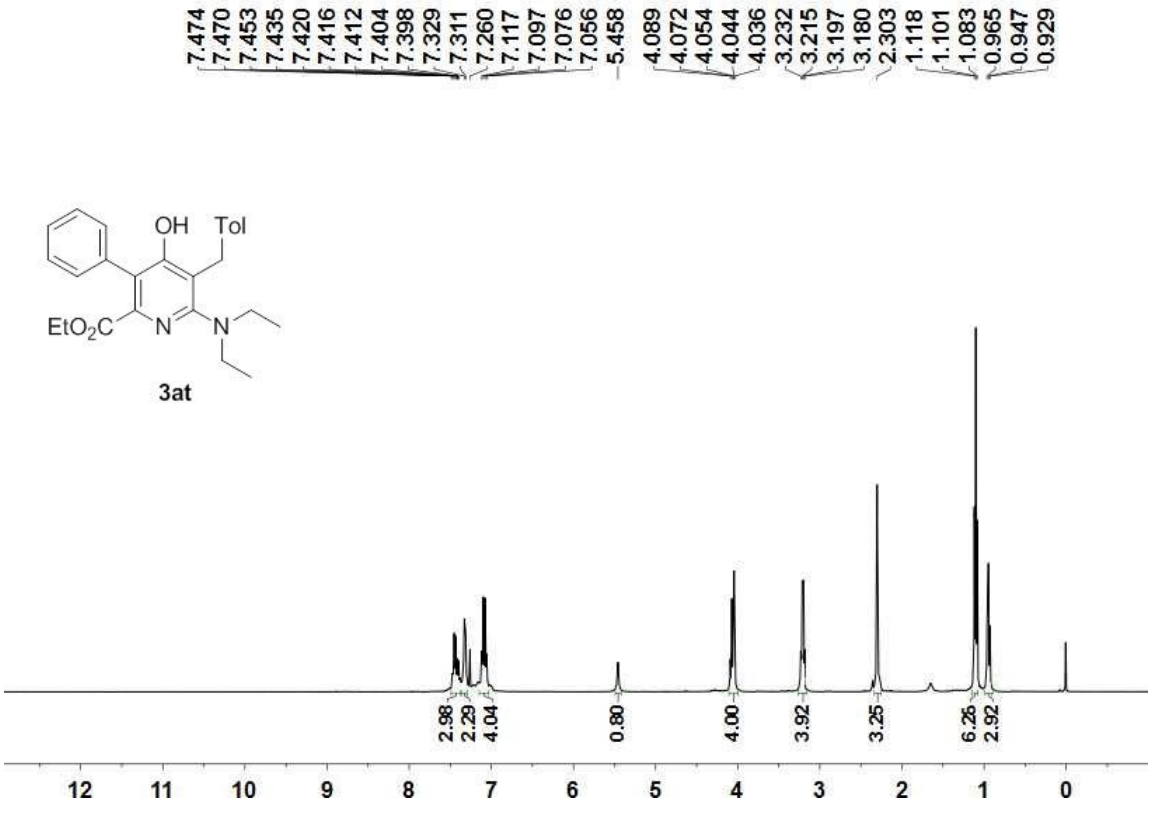
^{1}H NMR spectrum of the compound **3as** (400 MHz, $CDCl_3$)



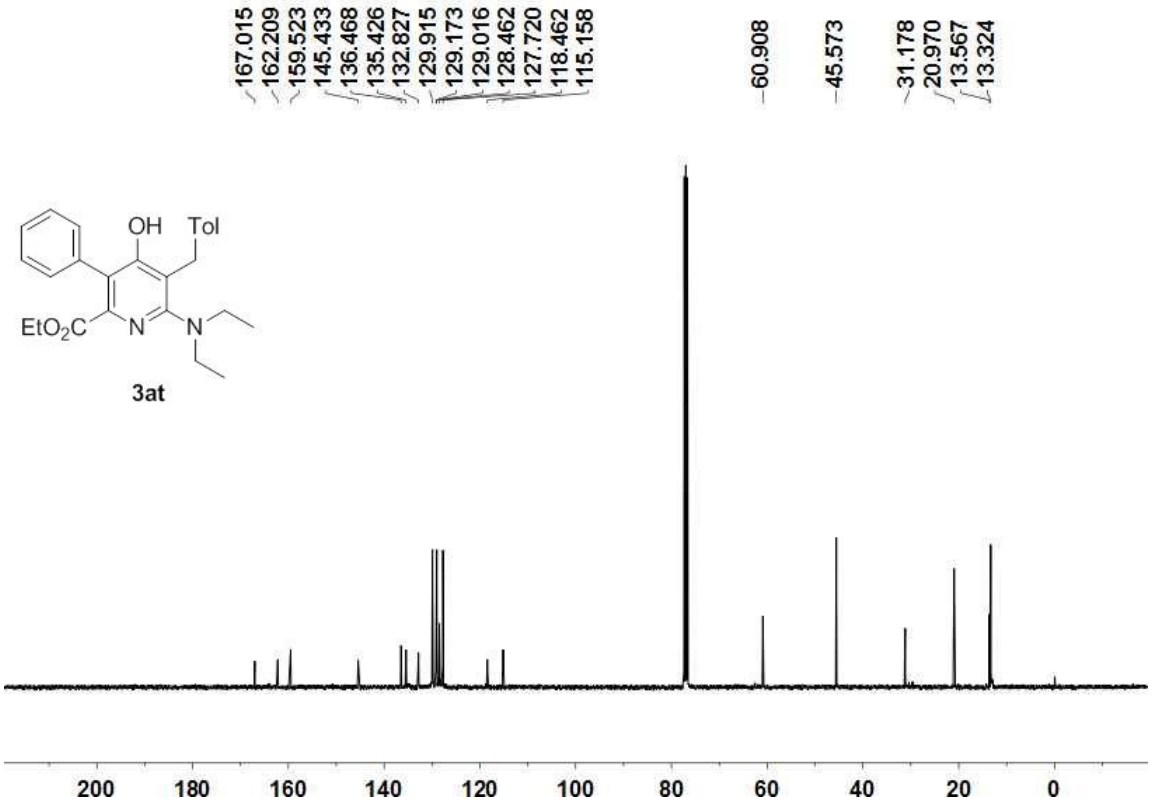
^{13}C NMR spectrum of the compound **3ar** (100 MHz, $CDCl_3$)



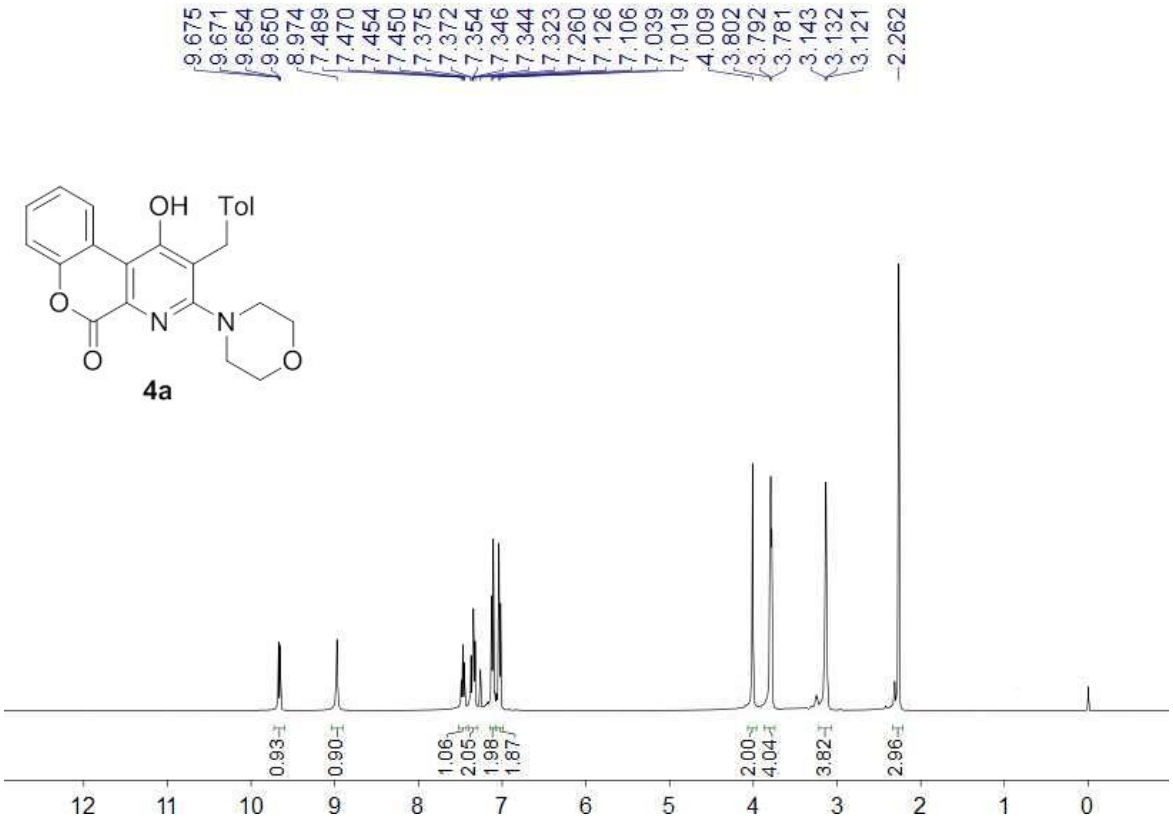
^{1}H NMR spectrum of the compound **3at** (400 MHz, $CDCl_3$)



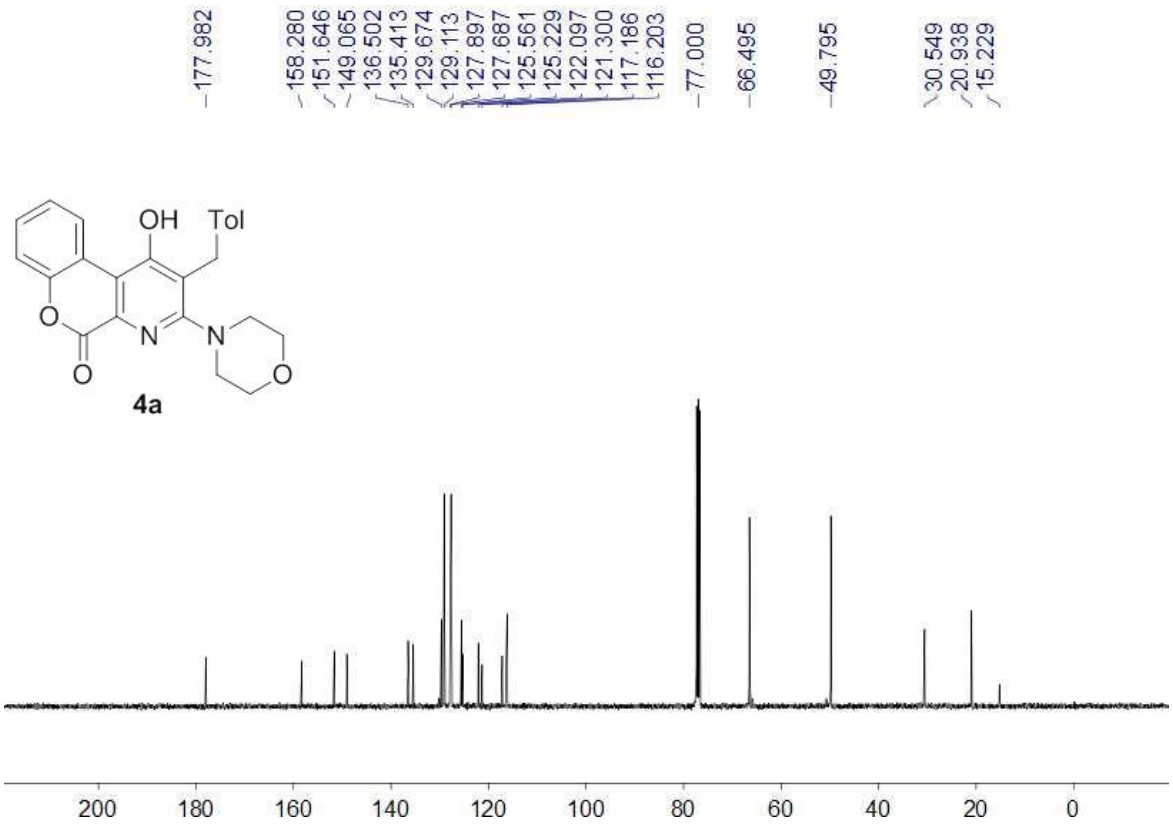
^{13}C NMR spectrum of the compound **3ar** (100 MHz, $CDCl_3$)



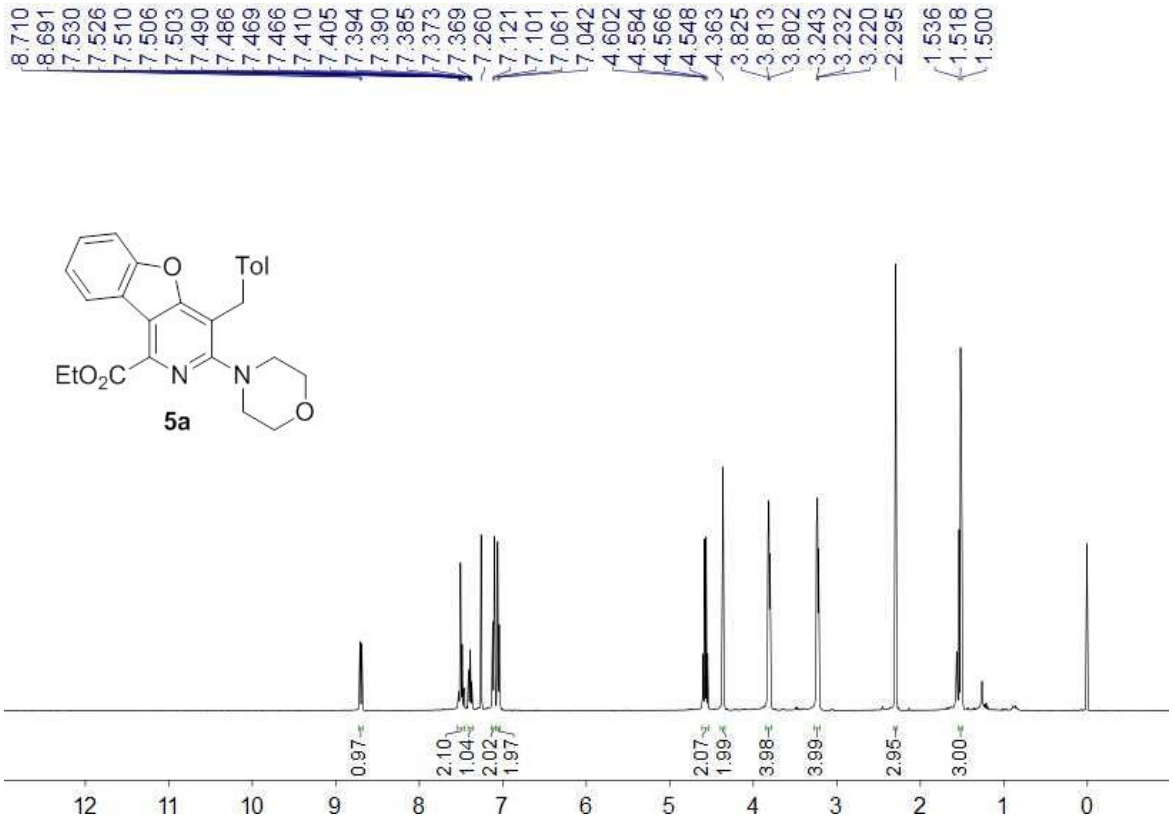
[1]H NMR spectrum of the compound **4a** (400 MHz, $CDCl_3$)



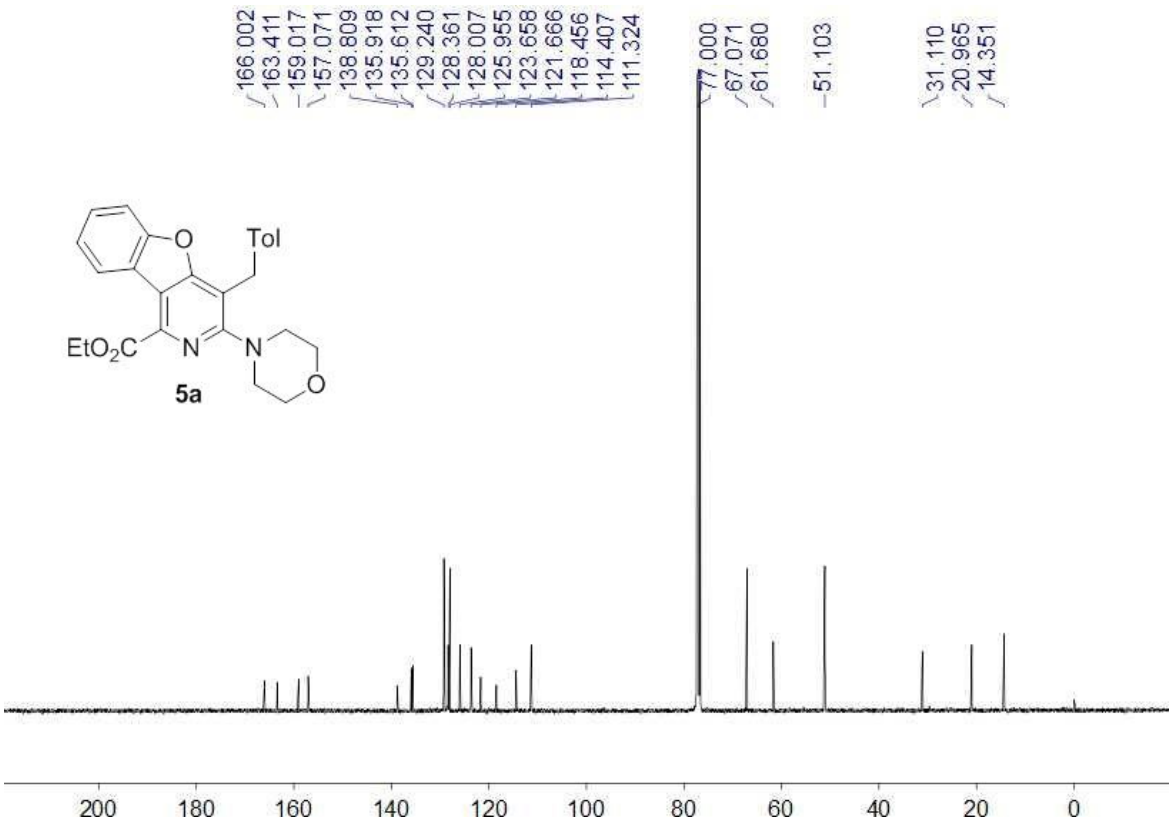
[13]C NMR spectrum of the compound **4a** (100 MHz, $CDCl_3$)



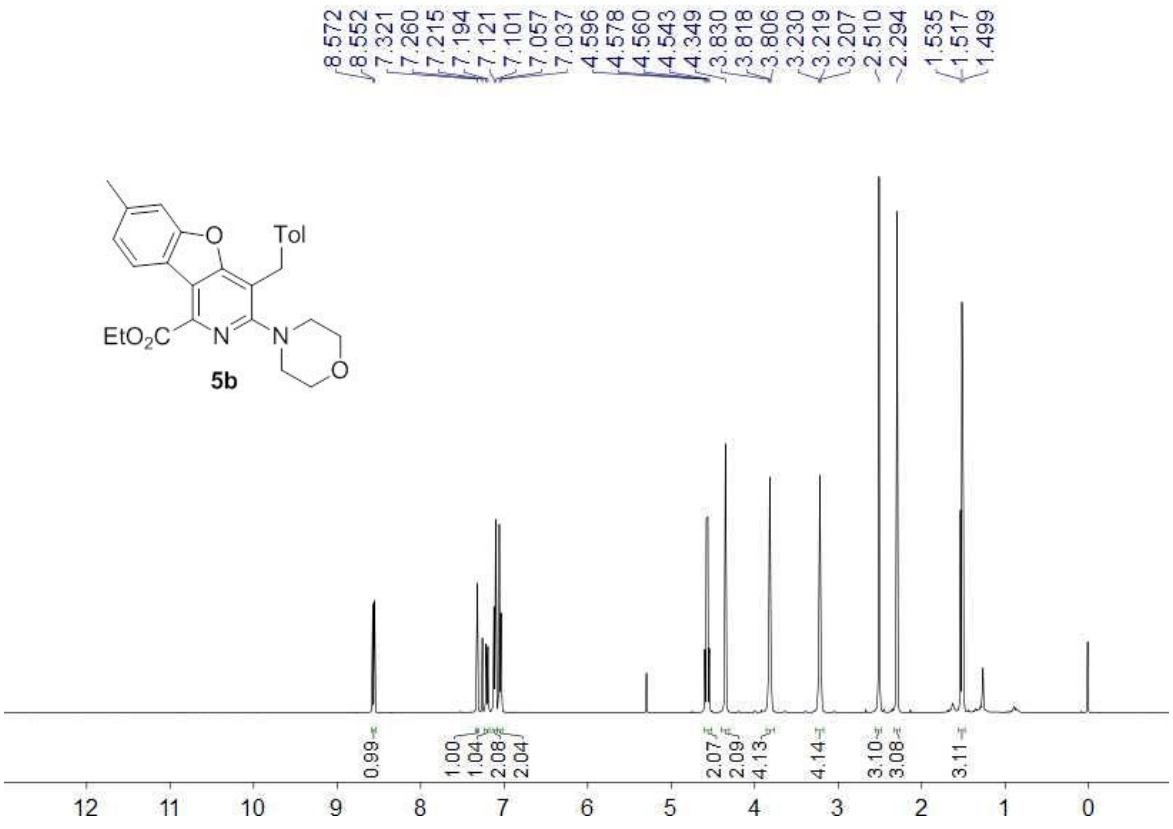
^{1}H NMR spectrum of the compound **5a** (400 MHz, $CDCl_3$)



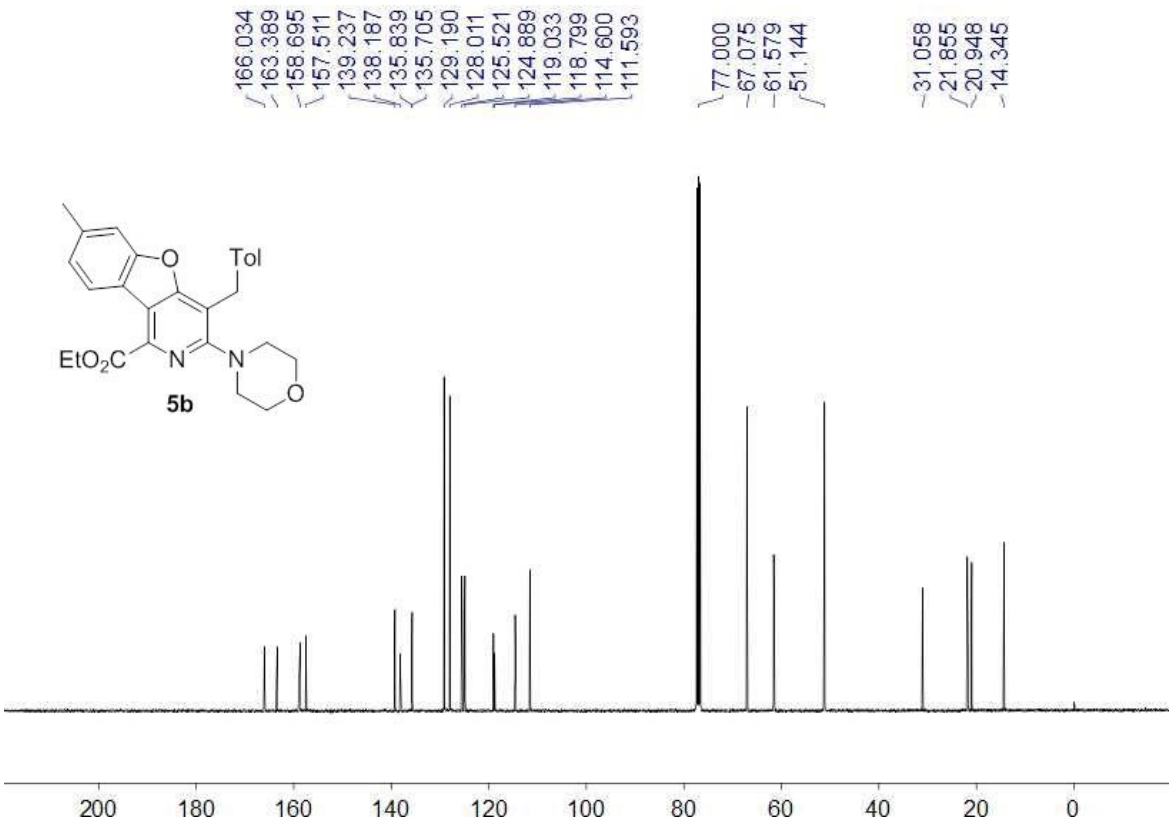
^{13}C NMR spectrum of the compound **5a** (100 MHz, $CDCl_3$)



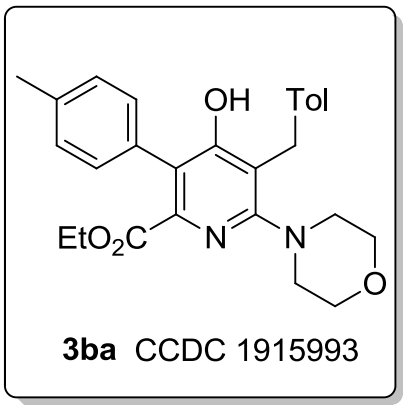
^{1}H NMR spectrum of the compound **5b** (400 MHz, $CDCl_3$)

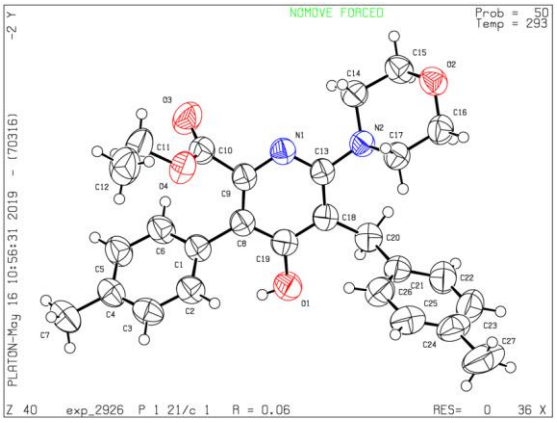


^{13}C NMR spectrum of the compound **5b** (100 MHz, $CDCl_3$)



5. X-ray Crystallographic Data of compound 3ba and 3ua

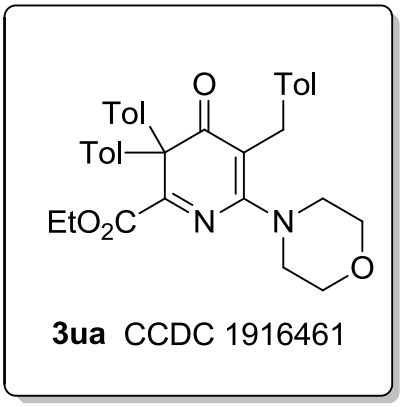


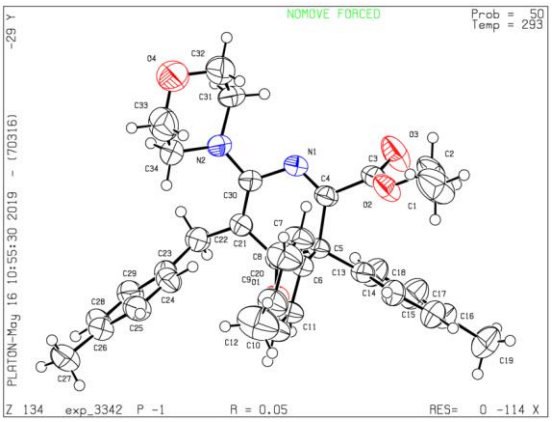


Crystal data:

Empirical formula	$C_{27}H_{30}N_2O_4$
Formula weight	446.53
Temperature/K	293(2)
Crystal system	monoclinic
Space group	P 1 21/c 1
a/Å	22.1582(15)
b/Å	6.7307(3)
c/Å	16.2742(8)
α/°	90.00
β/°	93.660(5)
γ/°	90.00
Volume/Å^3	2422.2(2)
Z	4
Mu (mm-1)	0.662
ρ_{calc}g/cm^3	1.224
F(000)	952.0
Crystal size/mm^3	0.26 × 0.20 × 0.10
Radiation	CuK\a
Index ranges	-26 ≤ h ≤ 25, -8 ≤ k ≤ 7, -19 ≤ l ≤ 12
Reflections collected	8845
Independent reflections	4302 [R_{int} = 0.0228]
Data/restraints/parameters	2926/0/302

Goodness-of-fit on F^2	1.043
Final R indexes [$I>=2\sigma\ (I)$]	R_1 = 0.0569, wR_2 = 0.1418
Final R indexes [all data]	R_1 = 0.0883, wR_2 = 0.1685





Crystal data:

Empirical formula	$C_{34}H_{36}N_2O_4$
Formula weight	536.65
Temperature/K	293(2)
Crystal system	triclinic
Space group	P -1
a/Å	9.9182(5)
b/Å	12.2130(7)
c/Å	13.3822(7)
α/°	109.450(5)
β/°	91.850(4)
γ/°	102.819(5)
Volume/$Å^3$	1480.43(14)
Z	2
Mu (mm-1)	0.627
$\rho_{calc}g/cm^3$	1.204
F(000)	572
Crystal size/mm^3	0.23 ×0.15 ×0.07
Radiation	CuK\a

Index ranges	$-11 \leq h \leq 11$, $-14 \leq k \leq 14$, $-15 \leq l \leq 12$
Reflections collected	8991
Independent reflections	5129 [$R_{int} = 0.0181$]
Data/restraints/parameters	3342 /0/366
Goodness-of-fit on F^2	1.092
Final R indexes [$I>=2\sigma\ (I)$]	$R_1 = 0.0473$, $wR_2 = 0.1316$
Final R indexes [all data]	$R_1 = 0.0590$, $wR_2 = 0.1548$