Electronic supplementary materials *Mendeleev Commun.*, 2024, **34**, 129–130

New synthesis of 6,8-diamino-substituted pyrano[3,4-*c*]pyridines from related pyrano[3,4-*c*]pyridin-6-one

Ervand G. Paronikyan, Armen G. Ayvazyan, Suren S. Mamyan and Shushanik Sh. Dashyan

^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6/CCl_4, 1/3 solution on a Varian Mercury 300VX 300 MHz spectrometer. Chemical shifts are reported as δ (parts per million) relative to TMS (tetramethylsilane) as the internal standard. IR spectra were recorded on Nicolet Avatar 330-FT-IR spectrophotometer and the reported wave numbers are given in cm^{-1}. All melting points were determined in an open capillary and are uncorrected. Elemental analyses were performed on a Carlo Erba 1108 machine. Quoted values are in the range ±0.4% of the theoretical ones.

Synthesis of 5-cyano-3,3-dimethyl-8-morpholin-4-yl-3,4-dihydro-1H-pyrano[3,4-c]pyridin-6-yl 4-methylbenzenesulfonate ***2***. Compound **1** (1.45 g, 5 mmol), TsCl (1.0 g, 5.3 mmol) trimethylamine (1 ml) and 1,4-dioxane (14 ml) was refluxed for 12 h. Dioxane was distilled off, and water (20 ml) was added. The precipitate formed was filtered off and recrystallized from ethanol to afford a white solid; yield 83 %; mp 201–202ºC; IR *ν*/cm^{-1}: 2221 (CN), 1606 (C=C_{Ar}). ^{1}H NMR (300 MHz, DMSO-d_6/CCl_4, 1/3) δ 1.30 (s, 6H, $C(CH_3)_2$), 2.50 (s, 3H, CH_3), 2.75 (s, 2H, 4-CH_2), 3.11-3.17 (m, 4H, $N(CH_2)_2$), 3.56-3.62 (m, 4H, $O(CH_2)_2$), 4.48 (s, 2H, 1-CH_2),7.42-7.48 (m, 2H, 2CH_{Ar}), 7.86-7.92 (m, 2H, 2CH_{Ar}). ^{13}C NMR (300 MHz, DMSO-d_6/CCl4, 1/3) δ 21.0 (CH_3), 26.3 (2CH_3), 38.2 (4-CH_2), 48.5 ($N(CH_2)_2$), 58.9 (1-CH_2), 65.7 ($O(CH_2)_2$), 69.3 (C^3), 90.7 (C^5), 112.5 (C), 117.4 (CN), 127.8 (2CH_{Ar}), 129.3 (2CH_{Ar}), 133.9 (C_{Ar}), 144.6 (C_{Ar}), 150.0 (C), 154.4 (C), 156.9 (C_{Ar}). Anal. Calcd for $C_{22}H_{25}N_3O_5S$: C 59.58; H 5.68; N 9.47; S 7.23 %. Found: C 59.65; H 5.63; N 9.54; S 7.17%.

Compounds ***3a-j*** *(General procedure).* A mixture of compound **2** (0.9 g, 2.0 mmol) and appropriate amine (5 mmol) was refluxed in 1,4-dioxane (20 ml) for 5 h. Dioxane was evaporated in vacuum and residue was triturated with water. The precipitate, which was formed, was filtered off and recrystallized from ethanol.

3,3-Dimethyl-6,8-di(morpholin-4-yl)-3,4-dihydro-1H-pyrano[3,4-c]pyridine-5-carbonitrile ***3a***. A white solid; yield 76 %; mp 170–171ºC; IR *ν*/cm^{-1}: 2202 (CN), 1575 (C=C_{Ar}). ^{1}H NMR (300 MHz, DMSO-d_6/CCl_4, 1/3) δ 1.29 (s, 6H, $C(CH_3)_2$), 2.66 (s, 2H, 4-CH_2), 3.18-3.24 (m, 4H, $N(CH_2)_2$), 3.53-3.59 (m, 4H, $N(CH_2)_2$), 3.68-3.76 (m, 8H, 2[$O(CH_2)_2$]), 4.45 (s, 2H, 1-CH_2). ^{13}C NMR (300 MHz, DMSO-d_6/CCl_4, 1/3) δ 26.3 (2CH_3), 38.3 (4-CH_2), 48.0 ($N(CH_2)_2$), 48.9 ($N(CH_2)_2$), 58.7 (1-CH_2), 65.8 (2[$O(CH_2)_2$]), 69.3 (C^3), 86.8 (C^5), 111.2 (C), 116.4 (CN), 149.3 (C), 157.5 (C), 158.9 (C). Anal. Calcd for $C_{19}H_{26}N_4O_3$: C 63.67; H 7.31; N 15.63 %. Found: C 63.72; H 7.26; N 15.69%.

3,3-Dimethyl-8-(morpholin-4-yl)-6-pyrrolidin-1-yl-3,4-dihydro-1H-pyrano[3,4-c]pyridine-5-carbonitrile ***3b***. A white solid; yield 73.5 %; mp 144–145°C; IR ν/cm^{-1}: 2205 (CN), 1575 (C=C$_{Ar}$). ^{1}H NMR (300 MHz, DMSO-d$_6$/CCl$_4$, 1/3) δ 1.28 (s, 6H, C(CH$_3$)$_2$), 1.94-2.02 (m, 4H, (CH$_2$)$_2$), 2.62 (s, 2H, 4-CH$_2$), 3.13-3.21 (m, 4H, N(CH$_2$)$_2$), 3.65-3.75 (m, 8H, O(CH$_2$)$_2$,N(CH$_2$)$_2$), 4.41 (s, 2H, 1-CH$_2$). ^{13}C NMR (300 MHz, DMSO-d$_6$/CCl$_4$, 1/3) δ 24.9 (2CH$_2$), 26.4 (2CH$_3$), 38.4 (4-CH$_2$), 47.9 (N(CH$_2$)$_2$), 48.9 (N(CH$_2$)$_2$), 58.7 (1-CH$_2$), 65.8 (O(CH$_2$)$_2$), 69.3 (C^3), 82.0 (C^5), 108.2 (C), 117.6 (CN), 149.1 (C), 155.0 (C), 157.9 (C). Anal. Calcd for $C_{19}H_{26}N_4O_2$: C 66.64; H 7.65; N 16.36%. Found: C 66.70; H 7.61; N 16.45%.

3,3-Dimethyl-8-(morpholin-4-yl)-6-piperidin-1-yl-3,4-dihydro-1H-pyrano[3,4-c]pyridine-5-carbonitrile ***3c***. A white solid; yield 71.4 %; mp 113–114°C; IR ν/cm^{-1}:2205 (CN), 1575 (C=C$_{Ar}$). ^{1}H NMR (300 MHz, DMSO-d$_6$/CCl$_4$, 1/3) δ 1.29 (s, 6H, C(CH$_3$)$_2$), 1.64-1.72 (m, 6H, (CH$_2$)$_3$), 2.64 (s, 2H, 4-CH$_2$), 3.14-3.22 (m, 4H, N(CH$_2$)$_2$), 3.53-3.61 (m, 4H, N(CH$_2$)$_2$), 3.67-3.75 (m, 4H, O(CH$_2$)$_2$), 4.43 (s, 2H, 1-CH$_2$). ^{13}C NMR (300 MHz, DMSO-d$_6$/CCl$_4$, 1/3) δ 24.0 (CH$_2$), 25.3 (2CH$_2$), 26.4 (2CH$_3$), 38.4 (4-CH$_2$), 48.7 (N(CH$_2$)$_2$), 48.9 (N(CH$_2$)$_2$), 58.7 (1-CH$_2$), 65.8 (O(CH$_2$)$_2$), 69.3 (C^3), 86.3 (C^5), 110.3 (C), 116.6 (CN), 149.2 (C), 157.6 (C), 159.1 (C). Anal. Calcd for $C_{20}H_{28}N_4O_2$: C 67.39; H 7.92; N 15.72%. Found: C 67.33; H 7.96; N 15.78%.

3,3-Dimethyl-8-(morpholin-4-yl)-6-piperazin-1-yl-3,4-dihydro-1H-pyrano[3,4-c]pyridine-5-carbonitrile ***3d***. A white solid; yield 70 %; mp 152–153°C; IR ν/cm^{-1}:3258-3320 (NH), 2203 (CN), 1578 (C=C$_{Ar}$). ^{1}H NMR (300 MHz, DMSO-d$_6$/CCl$_4$, 1/3) δ 1.28 (s, 6H, C(CH$_3$)$_2$), 2.64 (s, 2H, 4-CH$_2$), 2.72-2.96 (m, 5H,NH(CH$_2$)$_2$), 3.15-3.23 (m, 4H, N(CH$_2$)$_2$), 3.49-3.59 (m, 4H, N(CH$_2$)$_2$), 3.66-3.74 (m, 4H, O(CH$_2$)$_2$), 4.43 (s, 2H, 1-CH$_2$). ^{13}C NMR (300 MHz, DMSO-d$_6$/CCl$_4$, 1/3) δ 26.4 (2CH$_3$), 38.4 (4-CH$_2$), 44.8 (NH(CH$_2$)$_2$), 48.2 (N(CH$_2$)$_2$), 48.9 (N(CH$_2$)$_2$), 58.8 (1-CH$_2$), 65.9 (O(CH$_2$)$_2$), 69.3 (C^3), 86.4 (C^5), 110.7 (C), 116.6 (CN), 149.3 (C), 157.6 (C), 159.0 (C). Anal. Calcd for $C_{19}H_{27}N_5O_2$: C 63.84; H 7.61; N 19.59%. Found: C 63.89; H 7.58; N 19.51%.

3,3-Dimethyl-6-(4-methylpiperazin-1-yl)-8-(morpholin-4-yl)-3,4-dihydro-1H-pyrano[3,4-c]-pyridine-5-carbonitrile ***3e***. A white solid; yield 81 %; mp 135–136°C; IR ν/cm^{-1}:2211 (CN), 1573 (C=C$_{Ar}$). ^{1}H NMR (300 MHz, DMSO-d$_6$/CCl$_4$, 1/3) δ 1.29 (s, 6H, C(CH$_3$)$_2$), 2.26 (s, 3H, NCH$_3$), 2.42-2.48 (m, 4H, N(CH$_2$)$_2$), 2.65 (s, 2H, 4-CH$_2$), 3.17-3.23 (m, 4H, N(CH$_2$)$_2$), 3.56-3.62 (m, 4H, N(CH$_2$)$_2$), 3.67-3.73 (m, 4H, O(CH$_2$)$_2$), 4.44 (s, 2H, 1-CH$_2$). ^{13}C NMR (300 MHz, DMSO-d$_6$/CCl$_4$, 1/3) δ 26.4 (2CH$_3$), 38.4 (4-CH$_2$), 45.5 (NCH$_3$), 47.2 (N(CH$_2$)$_2$), 48.9 (N(CH$_2$)$_2$), 54.2 (N(CH$_2$)$_2$), 58.7 (1-CH$_2$), 65.8 (O(CH$_2$)$_2$), 69.3 (C^3), 86.4 (C^5), 110.7 (C), 116.5 (CN), 149.3 (C), 157.5 (C), 159.0 (C). Anal. Calcd for $C_{20}H_{29}N_5O_2$: C 64.66; H 7.87; N 18.85%. Found: C 64.59; H 7.92; N 18.78%.

6-(4-Ethylpiperazin-1-yl)-3,3-dimethyl-8-(morpholin-4-yl)-3,4-dihydro-1H-pyrano[3,4-c]-pyridine-5-carbonitrile ***3f***. A white solid; yield 78 %; mp 142–144°C; IR ν/cm^{-1}:2200 (CN), 1575 (C=C$_{Ar}$). ^{1}H NMR (300 MHz, DMSO-d$_6$/CCl$_4$, 1/3) δ 1.08 (t, *J*= 7.2 Hz, 3H, CH$_2$<u>CH$_3$</u>), 1.29 (s, 6H, C(CH$_3$)$_2$), 2.40 (q, *J*= 7.2 Hz, 2H, N<u>CH$_2$</u>CH$_3$), 2.48-2.54 (m, 4H, N(CH$_2$)$_2$), 2.65 (s, 2H, 4-CH$_2$), 3.17-3.23 (m, 4H, N(CH$_2$)$_2$), 3.57-3.63 (m, 4H, N(CH$_2$)$_2$), 3.68-3.74 (m, 4H, O(CH$_2$)$_2$), 4.44 (s, 2H, 1-CH$_2$). ^{13}C NMR (300 MHz, DMSO-d$_6$/CCl$_4$, 1/3) δ 11.5 (CH$_2$<u>C</u>H$_3$), 26.4 (2CH$_3$), 38.3 (4-CH$_2$), 47.3 (<u>C</u>H$_2$CH$_3$), 48.9 (N(CH$_2$)$_2$), 51.5 (N(CH$_2$)$_2$), 52.0 (N(CH$_2$)$_2$), 58.7 (1-CH$_2$), 65.8 (O(CH$_2$)$_2$), 69.3 (C^3), 86.3 (C^5), 110.7 (C), 116.5 (CN), 149.3 (C), 157.5 (C), 158.7 (C). Anal. Calcd for $C_{21}H_{31}N_5O_2$: C 65.43; H 8.11; N 18.17%. Found: C 65.48; H 8.13; N 18.11%.

6-(4-Benzylpiperazin-1-yl)-3,3-dimethyl-8-(morpholin-4-yl)-3,4-dihydro-1H-pyrano[3,4-c]-pyridine-5-carbonitrile ***3g***. A white solid; yield 86 %; mp 147–148ºC; IR ν/cm^{-1}: 2207 (CN), 1575 (C=C$_{Ar}$). ^{1}H NMR (300 MHz, DMSO-d$_6$/CCl$_4$, 1/3) δ 1.29 (s, 6H, C(CH$_3$)$_2$), 2.50-2.56 (m, 4H, N(CH$_2$)$_2$), 2.64 (s, 2H, 4-CH$_2$), 3.15-3.21 (m, 4H, N(CH$_2$)$_2$), 3.52 (s, 2H, NCH$_2$), 3.57-3.63 (m, 4H, N(CH$_2$)$_2$), 3.66-3.72 (m, 4H, O(CH$_2$)$_2$), 4.43 (s, 2H, 1-CH$_2$), 7.15-7.33 (m, 5H, 5CH$_{Ar}$). ^{13}C NMR (300 MHz, DMSO-d$_6$/CCl$_4$, 1/3) δ 26.4 (2CH$_3$), 38.3 (4-CH$_2$), 47.4 (N(CH$_2$)$_2$), 48.8 (N(CH$_2$)$_2$), 52.3 (N(CH$_2$)$_2$), 58.7 (1-CH$_2$), 62.2 (NCH$_2$), 65.8 (O(CH$_2$)$_2$), 69.3 (C^3), 86.4 (C^5), 110.7 (C), 116.5 (CN), 126.4 (CH$_{Ar}$), 127.5 (2CH$_{Ar}$), 128.3 (2CH$_{Ar}$), 137.5 (C$_{Ar}$), 149.3 (C), 157.5 (C), 158.7 (C). Anal. Calcd for C$_{26}$H$_{33}$N$_5$O$_2$: C 69.77; H 7.43; N 15.65%. Found: C 69.83; H 7.46; N 15.59%.

6-[4-(Diphenylmethyl)piperazin-1-yl]-3,3-dimethyl-8-(morpholin-4-yl)-3,4-dihydro-1H-pyrano[3,4-c]pyridine-5-carbonitrile ***3h***. A white solid; yield 68.6 %; mp 251–253ºC; IR ν/cm^{-1}: 2208 (CN), 1575 (C=C$_{Ar}$). ^{1}H NMR (300 MHz, DMSO-d$_6$/CCl$_4$, 1/3) δ 1.28 (s, 6H, C(CH$_3$)$_2$), 2.47-2.55 (m, 4H, N(CH$_2$)$_2$), 2.63 (s, 2H, 4-CH$_2$), 3.15-3.21 (m, 4H, N(CH$_2$)$_2$), 3.59-3.71 (m, 8H, N(CH$_2$)$_2$, O(CH$_2$)$_2$), 4.26 (s, 1H, CH),4.43 (s, 2H, 1-CH$_2$), 7.10-7.19 (m, 2H, 2CH$_{Ar}$), 7.20-7.30 (m, 4H, 4CH$_{Ar}$), 7.39-7.45 (m, 4H, 4CH$_{Ar}$). ^{13}C NMR (300 MHz, DMSO-d$_6$/CCl$_4$, 1/3) δ 26.3 (2CH$_3$), 38.3 (4-CH$_2$), 47.5 (N(CH$_2$)$_2$), 48.9 (N(CH$_2$)$_2$), 51.2 (N(CH$_2$)$_2$), 58.7 (1-CH$_2$), 65.8 (O(CH$_2$)$_2$), 69.3 (C^3),75.4 (CH), 86.3 (C^5), 110.7 (C), 116.5 (CN), 126.4 (2CH$_{Ar}$), 127.2 (4CH$_{Ar}$), 127.9 (4CH$_{Ar}$), 142.1 (2C$_{Ar}$), 149.3 (C), 157.5 (C), 158.6 (C). Anal. Calcd for C$_{32}$H$_{37}$N$_5$O$_2$: C 73.39; H 7.12; N 13.37%. Found: C 73.34; H 7.16; N 13.31%.

6-Diethylamino-3,3-dimethyl-8-(morpholin-4-yl)-3,4-dihydro-1H-pyrano[3,4-c]pyridine-5-carbonitrile ***3i***. A white solid; yield 68 %; mp 101–102ºC; IR ν/cm^{-1}: 2201 (CN), 1581 (C=C$_{Ar}$). ^{1}H NMR (300 MHz, DMSO-d$_6$/CCl$_4$, 1/3) δ 1.24 (t, *J*= 6.9 Hz, 6H, (CH$_2$<u>CH$_3$</u>)$_2$), 1.28 (s, 6H, C(CH$_3$)$_2$), 2.62 (s, 2H, 4-CH$_2$),3.12-3.18 (m, 4H, N(CH$_2$)$_2$),1.24 (q, *J*= 6.9 Hz, 4H, (<u>CH$_2$</u>CH$_3$)$_2$), 3.68-3.74 (m, 4H, O(CH$_2$)$_2$), 4.42 (s, 2H, 1-CH$_2$). ^{13}C NMR (300 MHz, DMSO-d$_6$/CCl$_4$, 1/3) δ 13.3 (2CH$_2$<u>C</u>H$_3$), 26.4 (2CH$_3$), 38.6 (4-CH$_2$), 43.3 (2<u>C</u>H$_2$CH$_3$), 48.9 (N(CH$_2$)$_2$), 58.7 (1-CH$_2$), 65.8 (O(CH$_2$)$_2$), 69.3 (C^3), 82.1 (C^5), 108.7 (C), 117.4 (CN), 149.6 (C), 155.8 (C), 157.7 (C). Anal. Calcd for C$_{19}$H$_{28}$N$_4$O$_2$: C 66.25; H 8.19; N 16.27%. Found: C 66.19; H 8.25; N 16.22%.

6-[4-(2-Hydroxyethyl)piperazin-1-yl]-3,3-dimethyl-8-(morpholin-4-yl)-3,4-dihydro-1H-pyrano[3,4-c]pyridine-5-carbonitrile ***3j***. A yellow solid; yield 70.1 %; mp 161–162ºC; IR ν/cm^{-1}: 3370 (OH), 2204 (CN), 1573 (C=C$_{Ar}$). ^{1}H NMR (300 MHz, DMSO-d$_6$/CCl$_4$, 1/3) δ 1.28 (s, 6H, C(CH$_3$)$_2$), 2.46 (t, *J*= 6.0 Hz, 2H, <u>CH$_2$</u>CH$_2$OH), 2.54-2.60 (m, 4H, N(CH$_2$)$_2$), 2.64 (s, 2H, 4-CH$_2$), 3.16-3.22 (m, 4H, N(CH$_2$)$_2$), 3.53 (t, *J*= 6.0 Hz, 2H, CH$_2$<u>CH$_2$</u>OH), 3.57-3.63 (m, 4H, N(CH$_2$)$_2$), 3.67-3.73 (m, 4H, O(CH$_2$)$_2$), 3.86-3.96 (br. s, 1H, OH), 4.43 (s, 2H, 1-CH$_2$). ^{13}C NMR (300 MHz, DMSO-d$_6$/CCl$_4$, 1/3) δ 26.4 (2CH$_3$), 38.4 (4-CH$_2$), 47.5 (N(CH$_2$)$_2$), 48.9 (N(CH$_2$)$_2$), 52.7 (N(CH$_2$)$_2$), 58.2 (CH$_2$), 58.8 (1-CH$_2$), 59.9 (CH$_2$), 65.9 (O(CH$_2$)$_2$), 69.3 (C^3),86.3 (C^5),110.7 (C), 116.6 (CN), 149.3 (C), 157.6 (C), 158.8 (C). Anal. Calcd for C$_{21}$H$_{31}$N$_5$O$_3$: C 62.82; H 7.78; N 17.44%. Found: C 62.88; H 7.75; N 17.51%.

*Compounds **4a-c** (General procedure).* A mixture of compound **2** (0.9 g, 2.0 mmol) and appropriate amine (5 mmol) and DIPEA (0.65 g, 5 mmol) was refluxed in 1,4-dioxane (20 ml) for 8 h. Dioxane was evaporated in vacuum, and the residue was triturated with water. The precipitate formed was filtered off and recrystallized from ethanol.

*6-(Benzylamino)-3,3-dimethyl-8-(morpholin-4-yl)-3,4-dihydro-1H-pyrano[3,4-c]pyridine-5-carbonitrile **4a**.* A white solid; yield 71.1 %; mp 183–184°C; IR *ν*/cm^{-1}: 3354 (NH), 2207 (CN), 1579 (C=C$_{Ar}$). ^{1}H NMR (300 MHz, DMSO-d$_6$/CCl$_4$, 1/3) δ 1.27 (s, 6H, C(CH$_3$)$_2$), 2.60 (s, 2H, 4-CH$_2$), 3.04-3.09 (m, 4H, N(CH$_2$)$_2$), 3.56-3.64 (m, 4H, O(CH$_2$)$_2$), 4.37 (s, 2H, 1-CH$_2$), 4.54 (d, *J*= 5.8 Hz,2H, NHCH$_2$), 7.05 (s, 1H, NH), 7.11-7.31 (m, 5H, 5CH$_{Ar}$).^{13}C NMR (300 MHz, DMSO-d$_6$/CCl$_4$, 1/3) δ 26.4 (2CH$_3$), 38.2 (4-CH$_2$), 44.1 (NHCH$_2$), 48.9 (N(CH$_2$)$_2$), 58.8 (1-CH$_2$), 65.8 (O(CH$_2$)$_2$), 69.2 (C^3), 82.1 (C^5),107.7 (C),116.2 (CN), 125.8 (CH$_{Ar}$), 126.7 (2CH$_{Ar}$), 127.4 (2CH$_{Ar}$), 140.3 (C), 148.0 (C), 156.5 (C), 158.5 (C). Anal. Calcd for C$_{22}$H$_{26}$N$_4$O$_2$: C 69.82; H 6.92; N 14.80%. Found: C 69.87; H 6.95; N 14.76%.*3,3-Dimethyl-8-(morpholin-4-yl)-6-[(2-phenylethyl)amino]-3,4-dihydro-1H-pyrano[3,4-c]-pyridine-5-carbonitrile **4b**.* A white solid; yield 68.5 %; mp 142–143°C; IR *ν*/cm^{-1}: 3425 (NH), 2201 (CN), 1577 (C=C$_{Ar}$). ^{1}H NMR (300 MHz, DMSO-d$_6$/CCl$_4$, 1/3) δ 1.28 (s, 6H, C(CH$_3$)$_2$), 2.60 (s, 2H, 4-CH$_2$), 2.87 (t, *J*= 7.7 Hz, 2H, NHCH$_2$CH$_2$), 3.18-3.23 (m, 4H, N(CH$_2$)$_2$), 3.58 (td, *J*= 7.7 Hz, 2H, NHCH$_2$), 3.69-3.74 (m, 4H, O(CH$_2$)$_2$), 4.41 (s, 2H, 1-CH$_2$), 6.45 (t, *J*= 5.7 Hz , NH), 7.11-7.28 (m, 5H, 5CH$_{Ar}$). ^{13}C NMR (300 MHz, DMSO-d$_6$/CCl$_4$, 1/3) δ 26.4 (2CH$_3$), 35.5 (CH$_2$), 38.2 (4-CH$_2$), 42.2 (NHCH$_2$),49.0 (N(CH$_2$)$_2$), 58.8 (1-CH$_2$), 65.9 (O(CH$_2$)$_2$), 69.2 (C^3), 82.3 (C^5), 107.6 (C),116.1 (CN), 125.4 (CH$_{Ar}$), 127.7 (2CH$_{Ar}$) 128.2 (2CH$_{Ar}$), 139.3 (C), 148.0 (C), 156.7 (C), 158.7 (C). Anal. Calcd for C$_{21}$H$_{31}$N$_5$O$_3$: C 70.38.; H 7.19; N 14.27%. Found: C 70.46.88; H 7.14; N 14.33%.

*6-[(2-Furylmethyl)amino]-3,3-dimethyl-8-(morpholin-4-yl)-3,4-dihydro-1H-pyrano[3,4-c]-pyridine-5-carbonitrile **4c**.* A yellow solid; yield 66.1 %; mp 152–153°C; IR *ν*/cm^{-1}: 3365 (NH), 2209 (CN), 1581 (C=C$_{Ar}$). ^{1}H NMR (300 MHz, DMSO-d$_6$/CCl$_4$, 1/3) δ 1.27 (s, 6H, C(CH$_3$)$_2$), 2.60 (s, 2H, 4-CH$_2$), 3.14-3.20 (m, 4H, N(CH$_2$)$_2$), 3.64-3.70 (m, 4H, O(CH$_2$)$_2$), 4.40 (s, 2H, 1-CH$_2$), 4.54 (d, *J*= 5.7 Hz, 2H, NHCH$_2$), 6.13 (dd, *J*= 0.7, 3.1 Hz, 1H, CH^3$_{furyl}$), 6.26 (dd, *J*= 1.9, 3.1 Hz, 1H, CH^4$_{furyl}$), 6.86 (t, *J*= 5.7 Hz, 1H, NH), 7.33 (dd, *J*= 0.7, 1.9 Hz, 1H, CH^5$_{furyl}$). ^{13}C NMR (300 MHz, DMSO-d$_6$/CCl$_4$, 1/3) δ 26.4 (2CH$_3$), 37.3 (NHCH$_2$), 38.2 (4-CH$_2$), 48.9 (N(CH$_2$)$_2$), 58.8 (1-CH$_2$), 65.8 (O(CH$_2$)$_2$), 69.2 (C^3), 82.3 (C^5), 105.7, (C^{3}H$_{furyl}$), 108.0 (C), 109.7 (C^{4}H$_{furyl}$), 116.0 (CN), 140.4 (C^{5}H$_{furyl}$), 148.0 (C), 153.3 (C), 156.3 (C), 158.5 (C). Anal. Calcd for C$_{20}$H$_{24}$N$_4$O$_3$: C 65.20; H 6.57; N 15.21%. Found: C 62.16; H 6.53; N 15.25%.

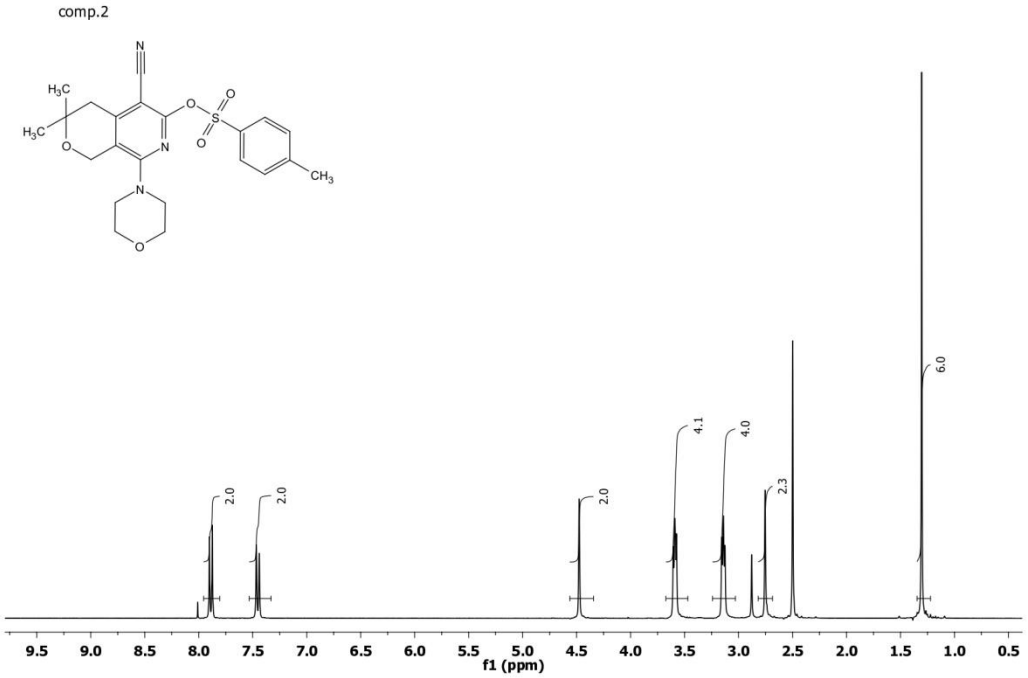
X-ray structural analysis of compound **2.**

All diffraction measurements were carried out at room temperature on the Enraf-Nonius Cad-4 automated diffractometer (graphite monochromator, Mo-Kα radiation, θ/2θ-scan). The monoclinic unit cell parameters measured and refined using the diffraction angles of 24 reflections (12.05<θ<13.85). The absorption correction carried by psi-scan method [Sheldrick, G. M. (2015). Crystal structure refinement with SHELXL. *Acta Crystallographica Section C: Structural Chemistry*, **71(1)**, 3-8.]. The structure were solved by direct method and refined using the software package SHELXTL [North, A. C. T., Phillips, D. T., Mathews, F. S. (1968). A semi-empirical method of absorption correction. *Acta Crystallographica Section A: Crystal Physics, Diffraction, Theoretical and General Crystallography*, **24(3)**, 351-359]. All non-hydrogen atoms were refined anisotropically by full-matrix least squares method. All hydrogen atoms were positioned geometrically and refined using riding model, with C-H=0.93÷0.97Å, $U_{iso}(H)=1.2\div1.5U_{eq}(C)$. Crystallographic and experimental data are listed in table 1. The full crystallographic data in CIF format available free of charge via internet at: http://www.ccdc.cam.ac.uk/products/csd/request/, deposition number: CCDC 2283397.

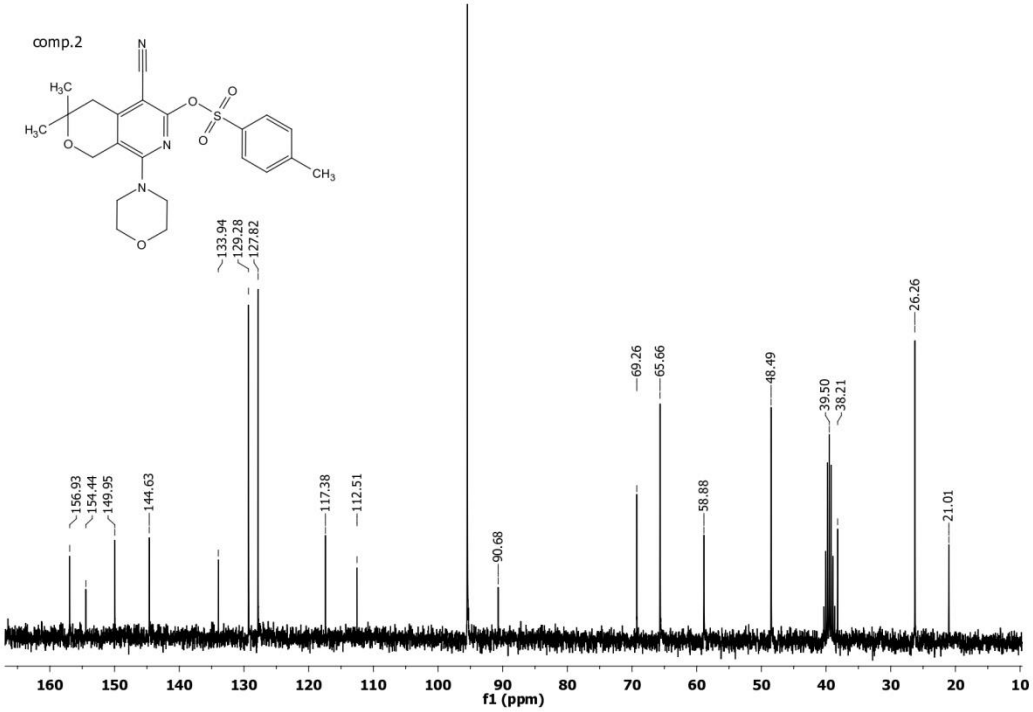
Table S1. Crystallographic and experimental data

Crystal Data	
Formula	$C_{22}H_{25}N_3O_5S$
Formula Weight	443.51
Crystal System	triclinic
Space group	P-1
a, b, c [Å]	9.4737(19), 10.641(2), 11.724(2)
α, β, γ [deg.]	76.33(3), 67.06(3), 82.52(3)
V [$Å^3$]	1056.6(4)
Z	2
D(calc) [g/cm^3]	1.394
μ(MoKα) [mm^{-1}], T_{min}, T_{max}	0.193, 0.78635, 0.88529
F(000)	468
Crystal Size [mm]	0.40x0.30x0.26
Data Collection	
Temperature (K)	295
Radiation [Å]	MoKα 0.71073
$\theta_{min},\theta_{max}$ [Deg]	1.9, 30.0
Dataset	$0\leq h\leq 13$; $-14\leq k\leq 14$; $-15\leq l\leq 16$
Tot., Uniq. Data, R(int)	6488, 6144, 0.021
Observed data [I > 2.0 σ(I)]	3797
Refinement	
Nref, Npar	6144, 283
R, wR2, S	0.0674, 0.1989, 1.02

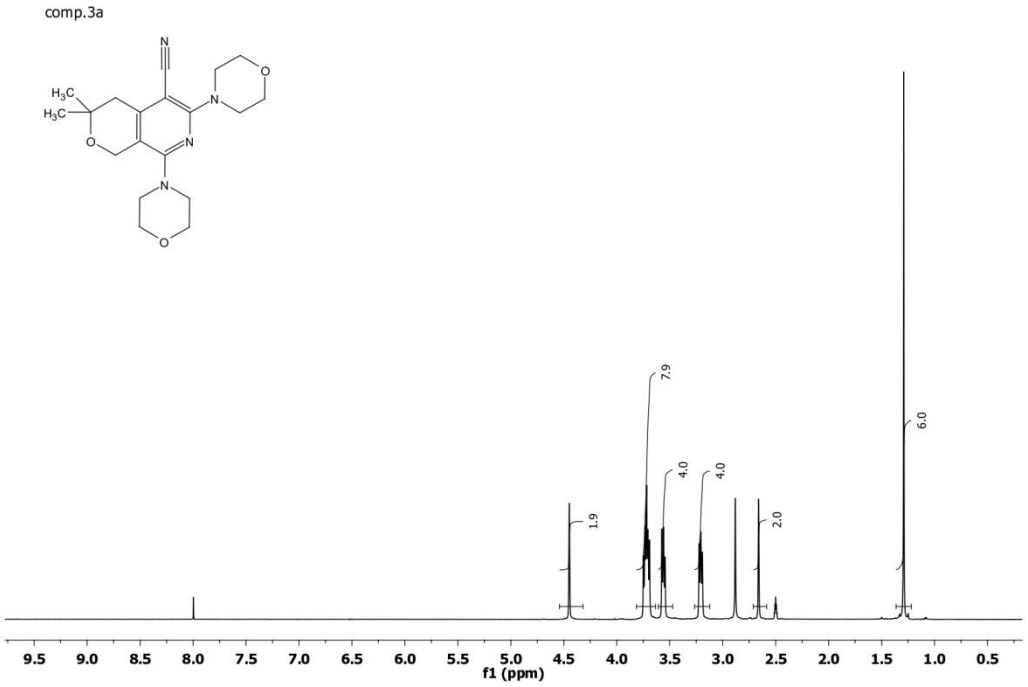
^{1}H NMR spectrum of compound **2**



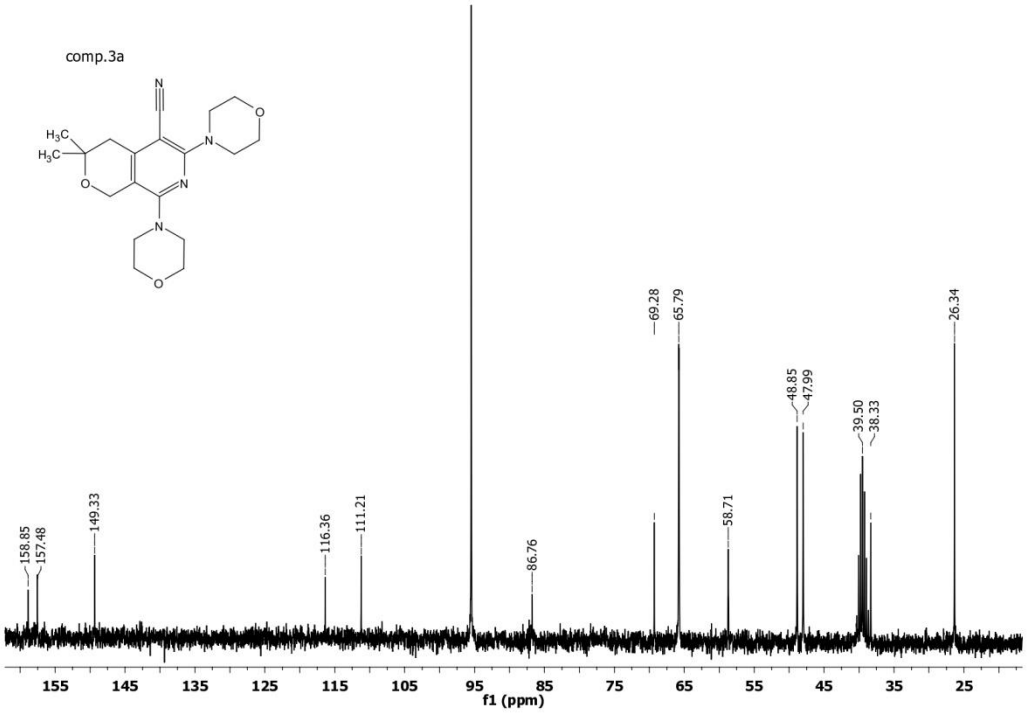
^{13}C NMR spectrum of compound **2**



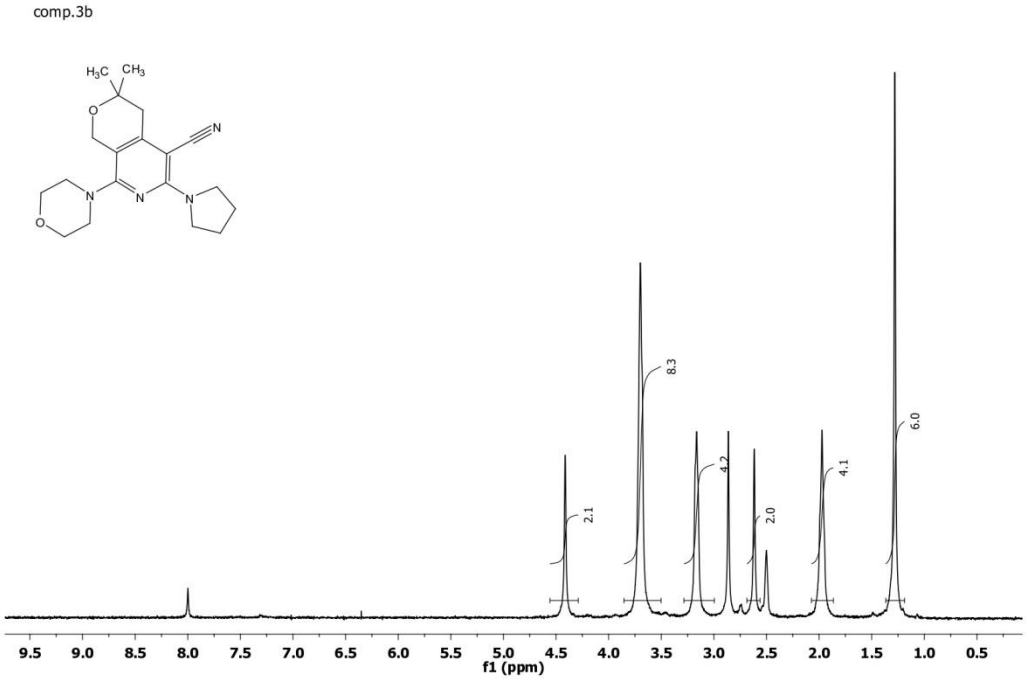
^{1}H NMR spectrum of compound **3a**



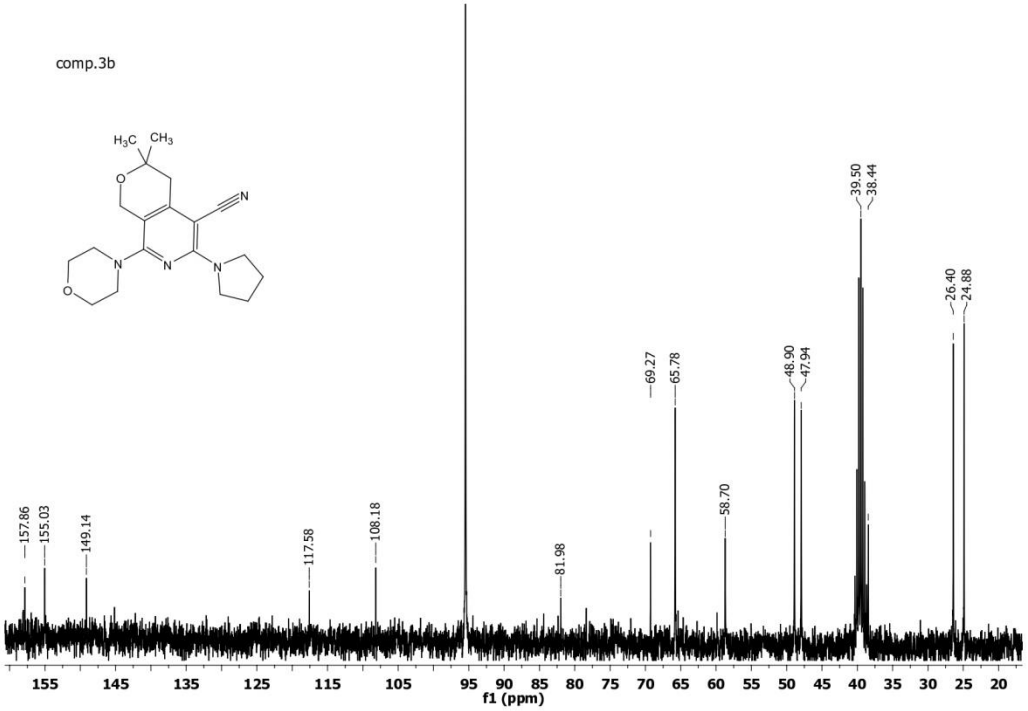
^{13}C NMR spectrum of compound **3a**



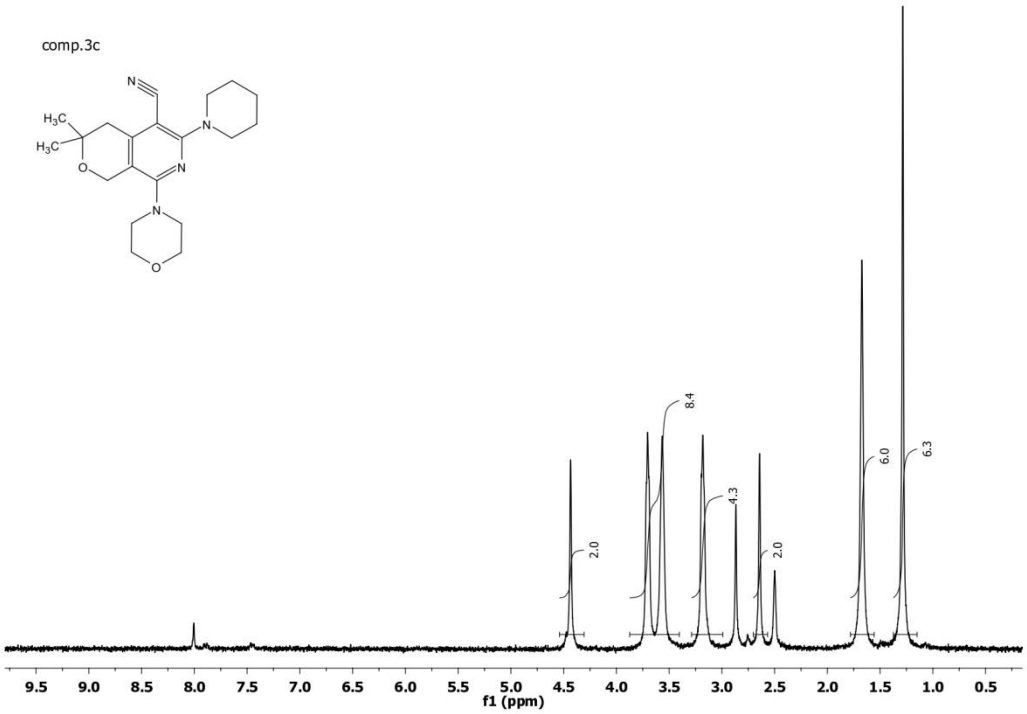
^{1}H NMR spectrum of compound **3b**



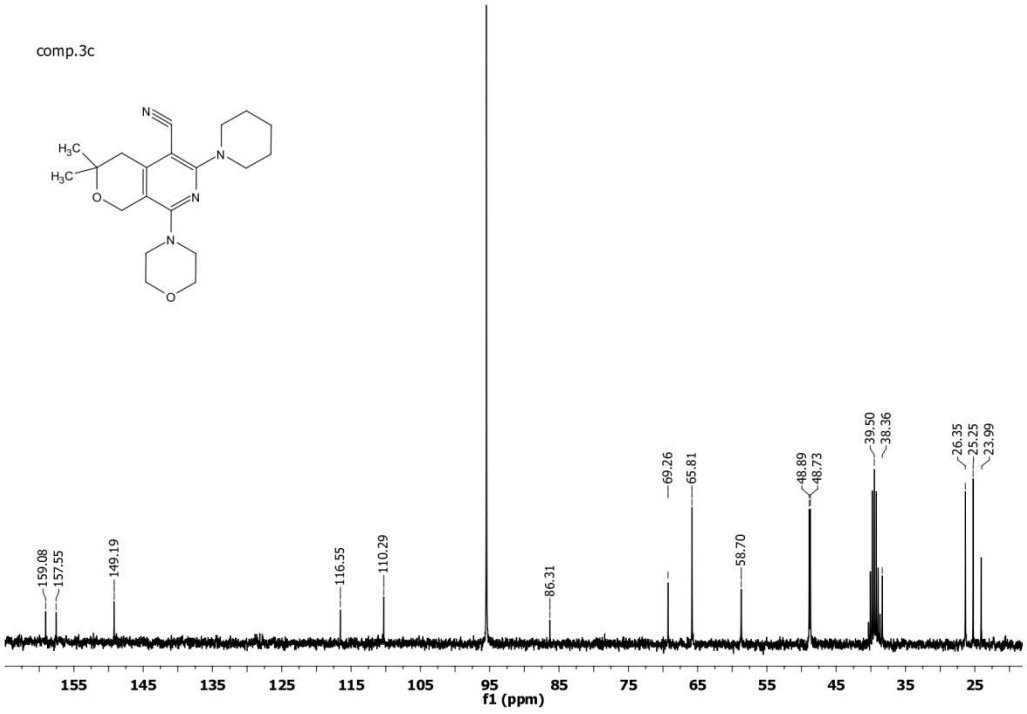
^{13}C NMR spectrum of compound **3b**



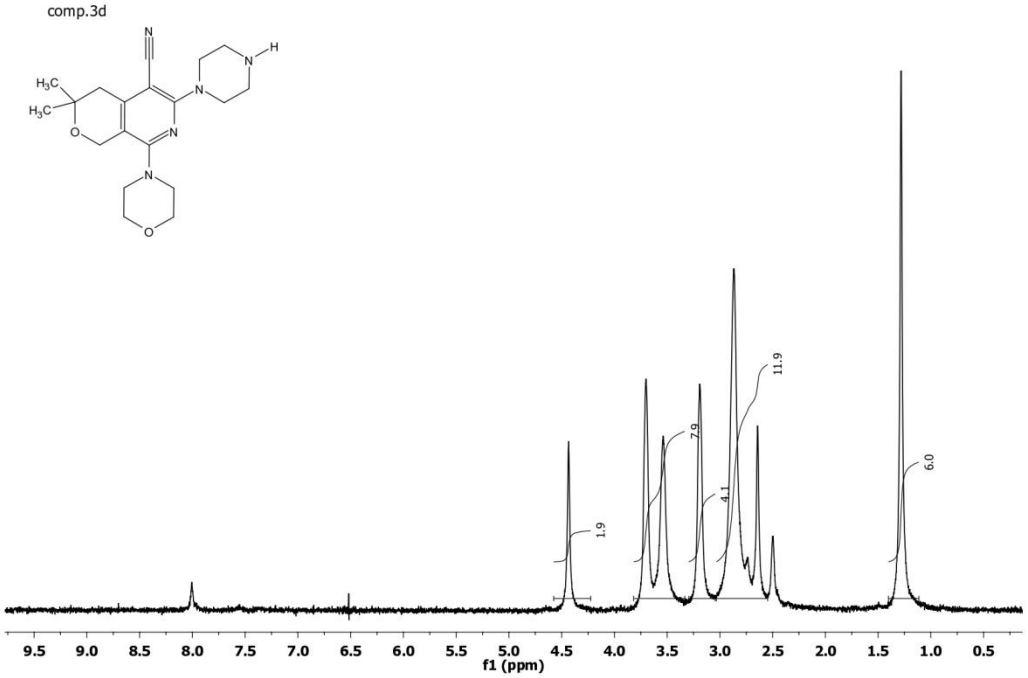
^{1}H NMR spectrum of compound **3c**



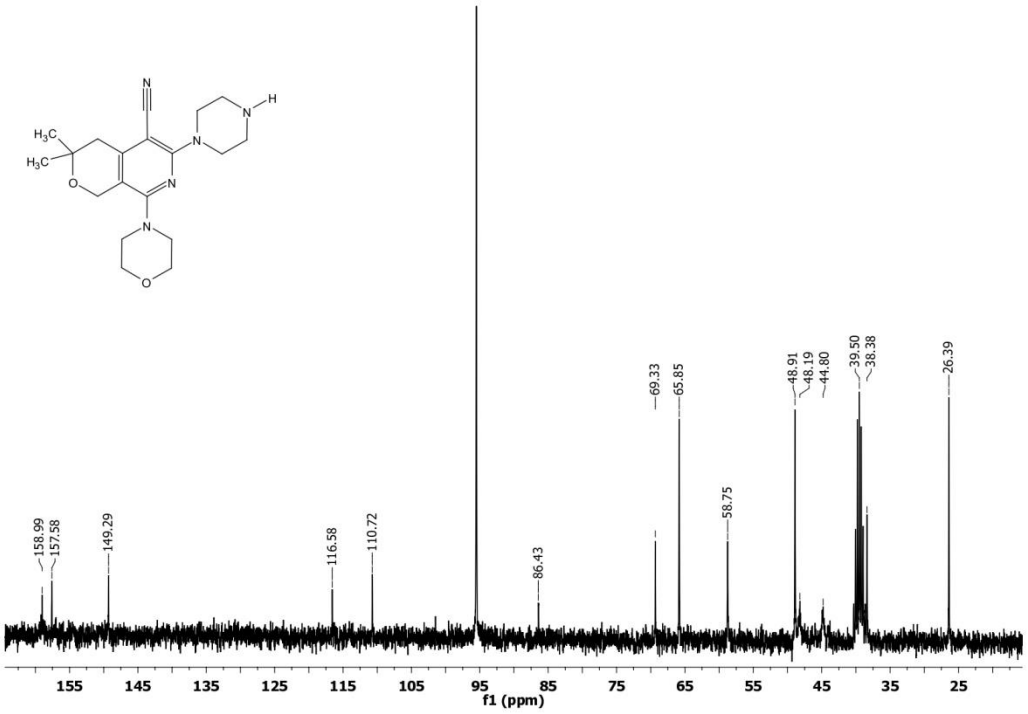
^{13}C NMR spectrum of compound **3c**



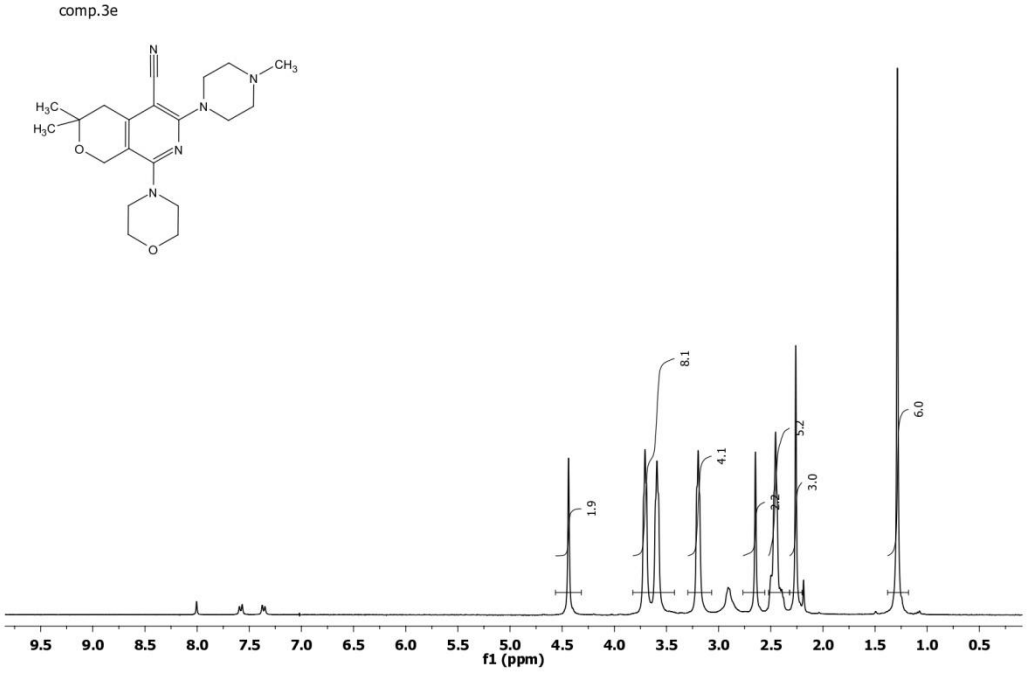
^{1}H NMR spectrum of compound **3d**



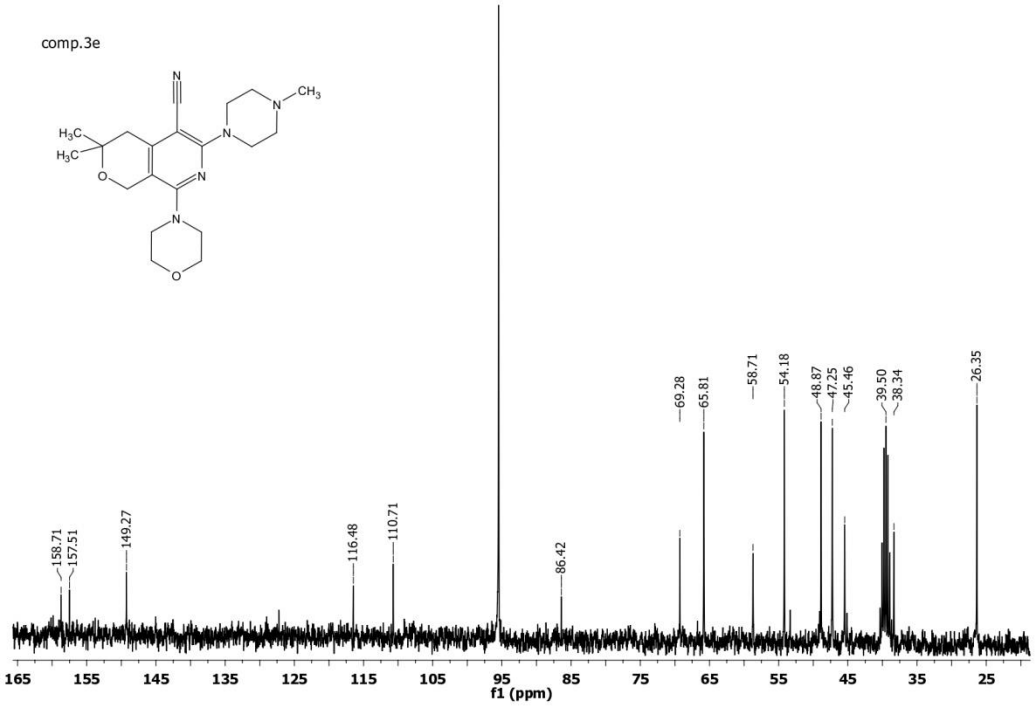
^{13}C NMR spectrum of compound **3d**



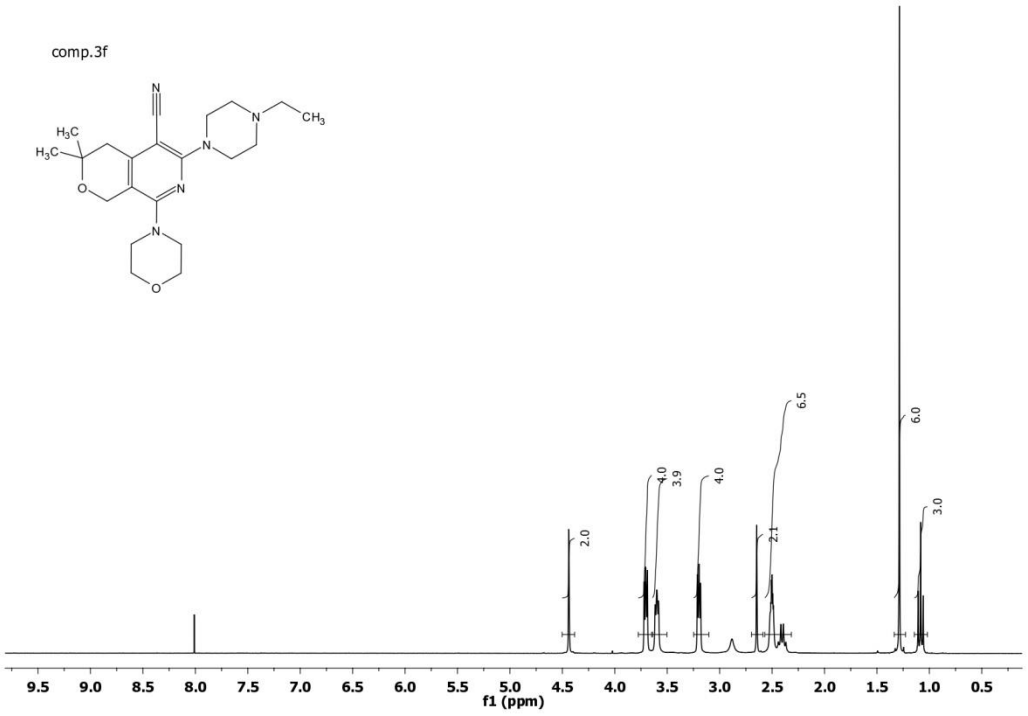
^{1}H NMR spectrum of compound **3e**



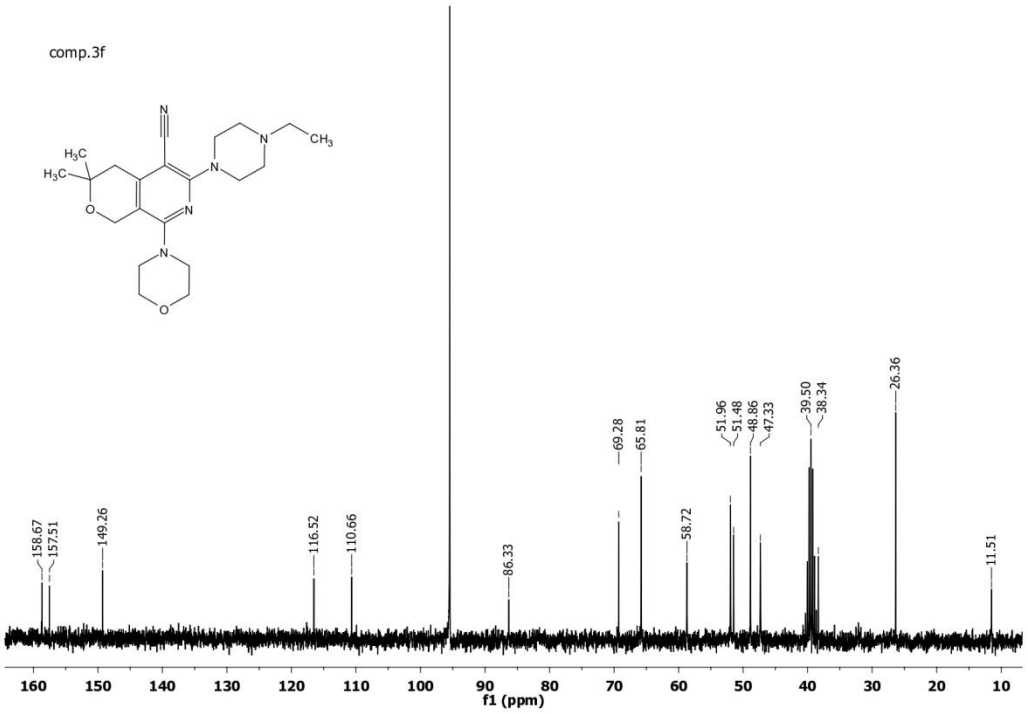
^{13}C NMR spectrum of compound **3e**



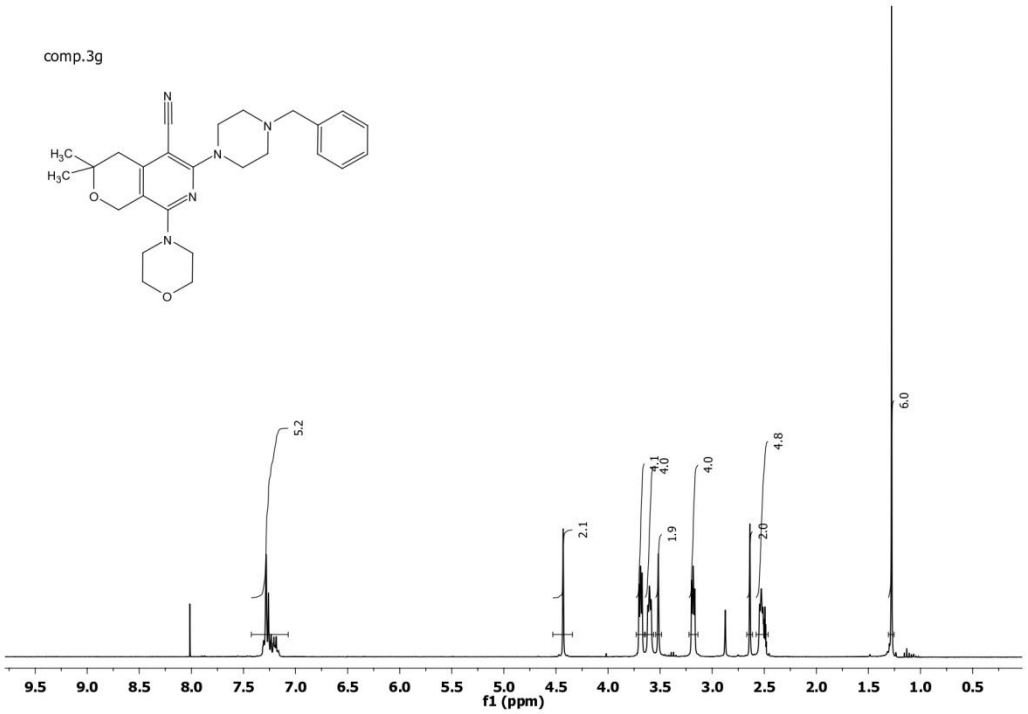
^{1}H NMR spectrum of compound **3f**



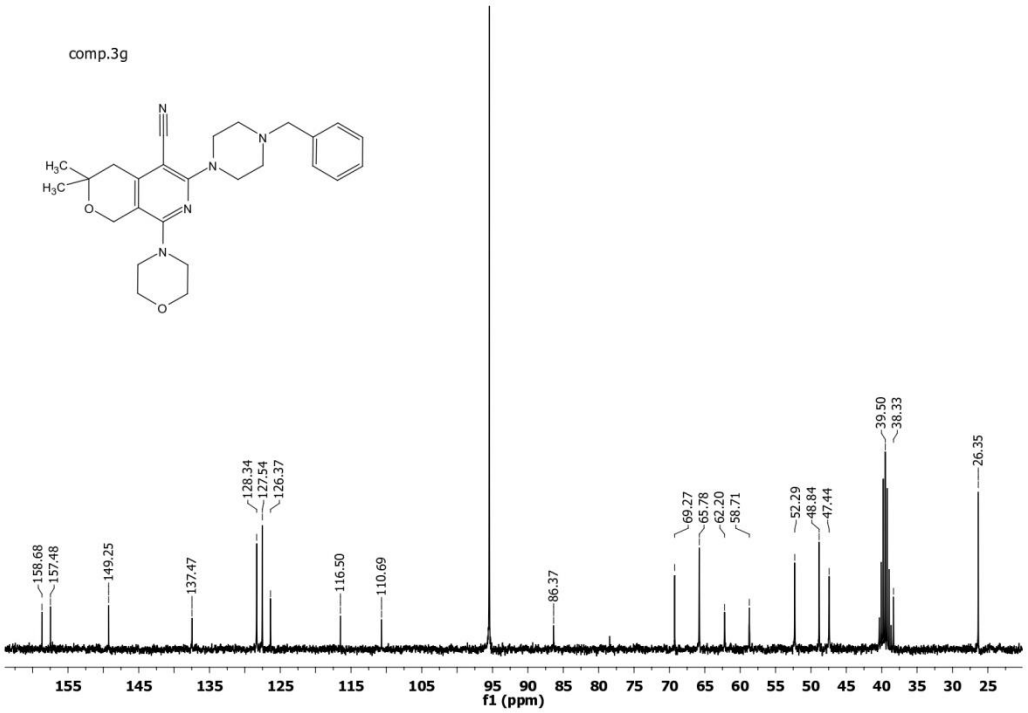
^{13}C NMR spectrum of compound **3f**



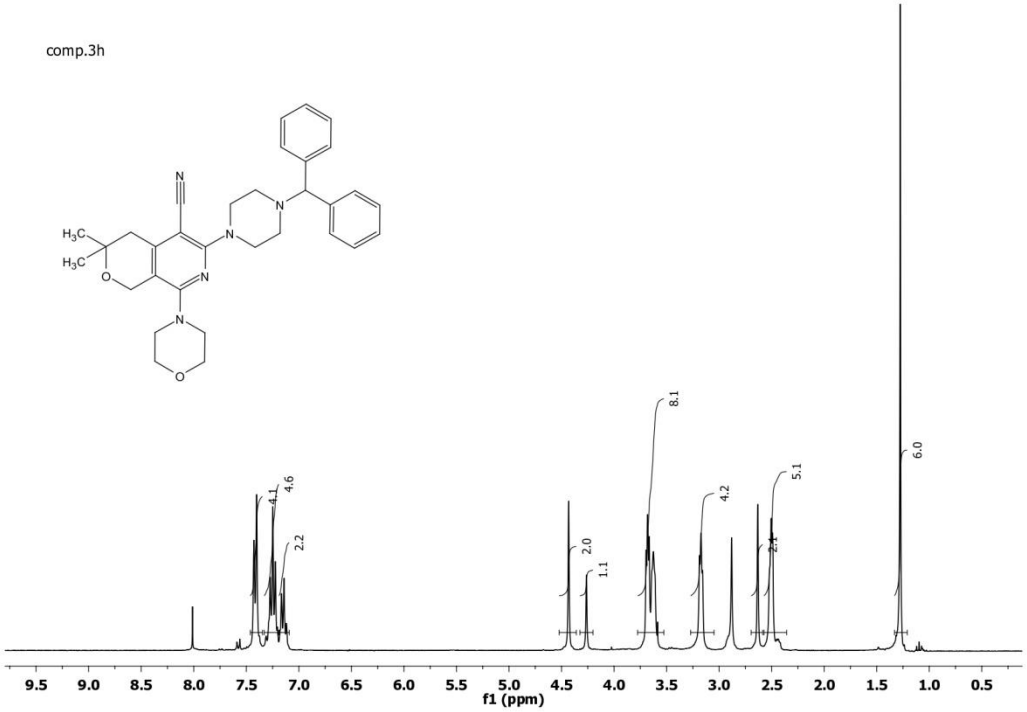
^{1}H NMR spectrum of compound **3g**



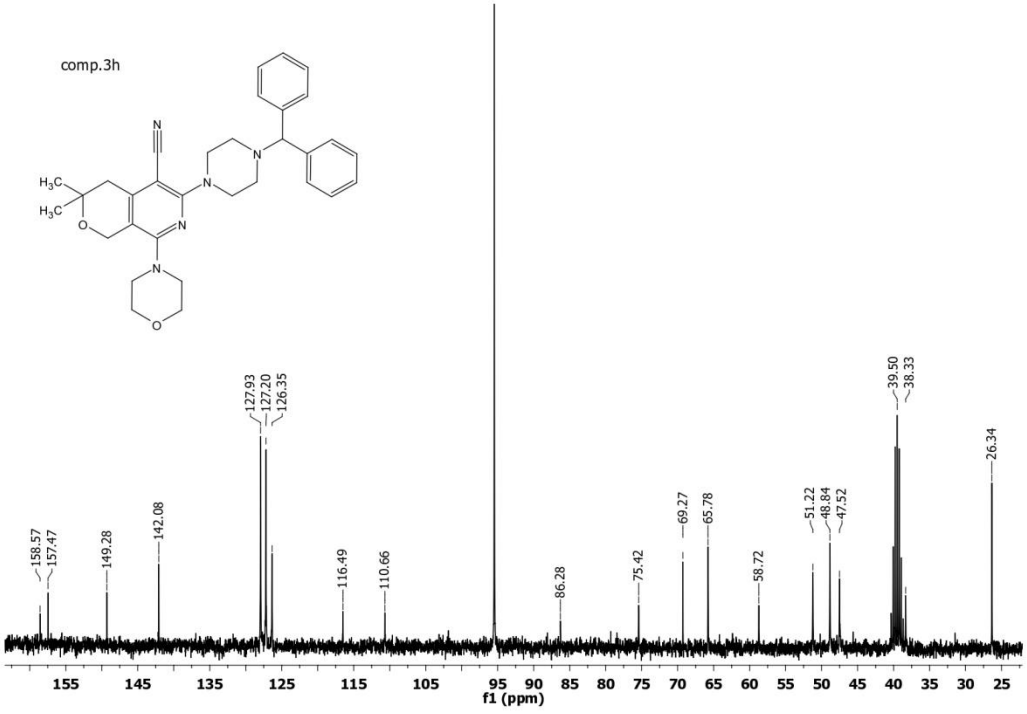
^{13}C NMR spectrum of compound **3g**



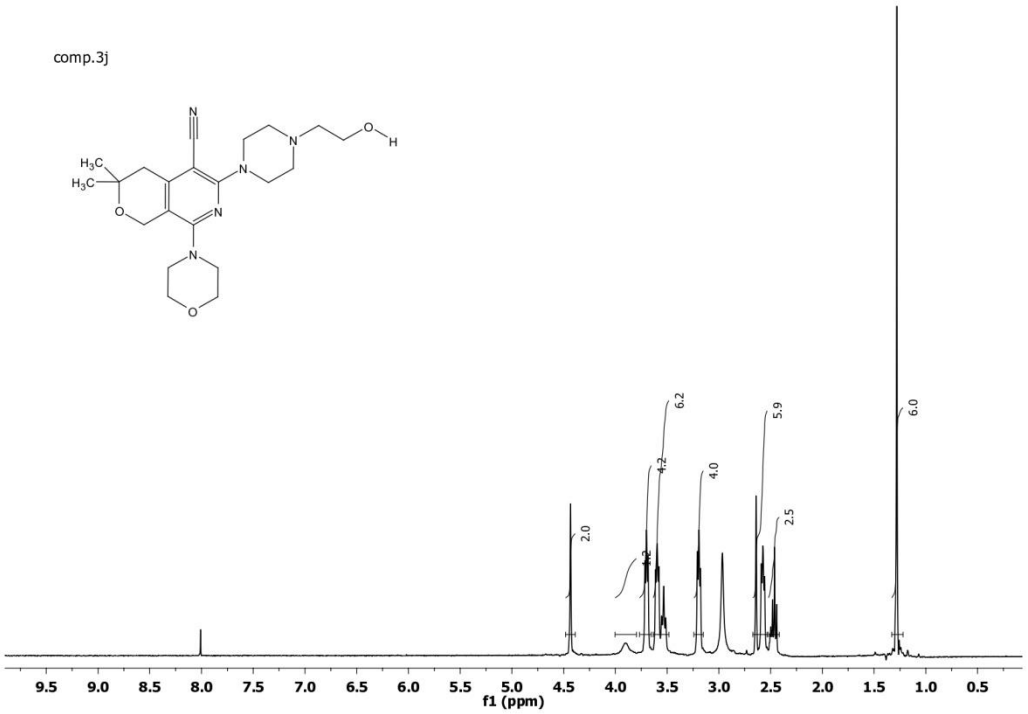
^{1}H NMR spectrum of compound **3h**



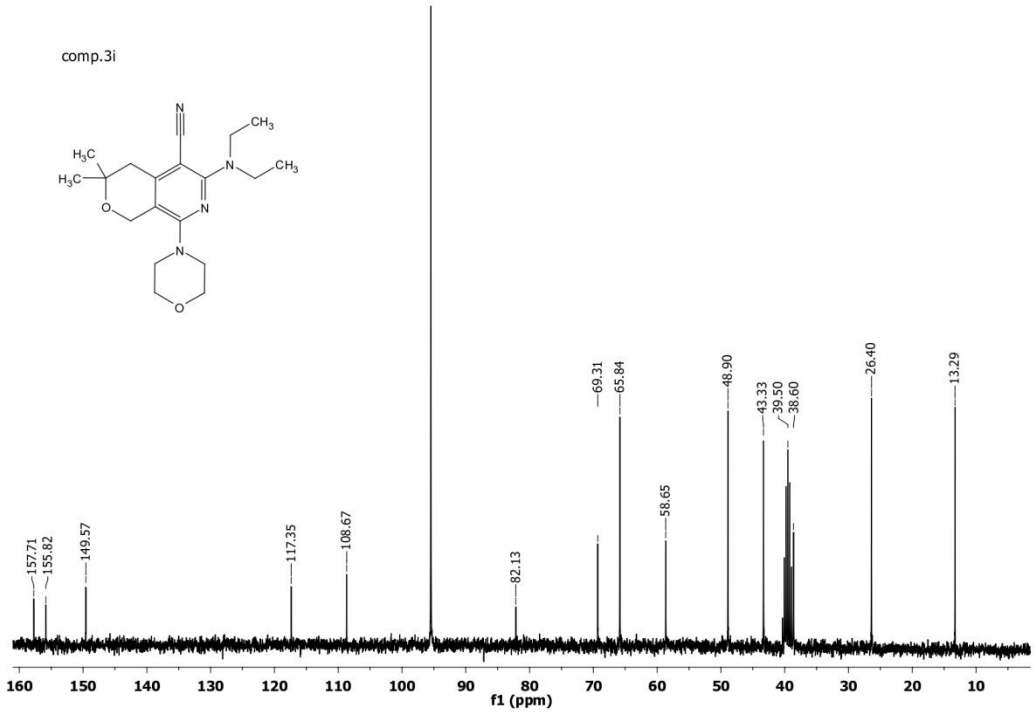
^{13}C NMR spectrum of compound **3h**



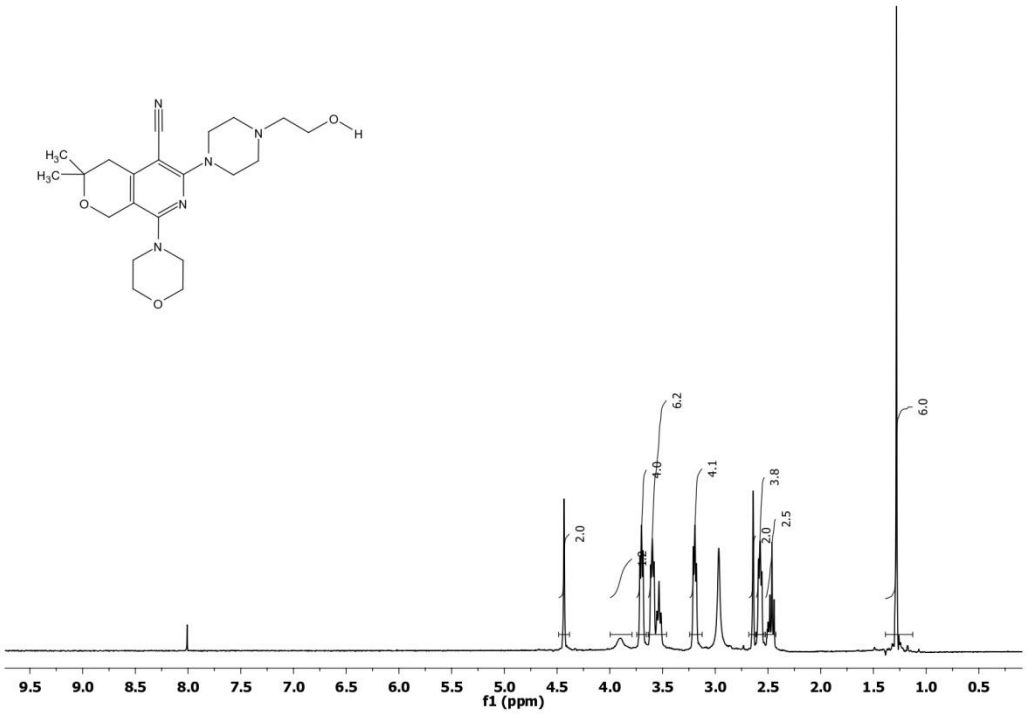
^{1}H NMR spectrum of compound **3i**



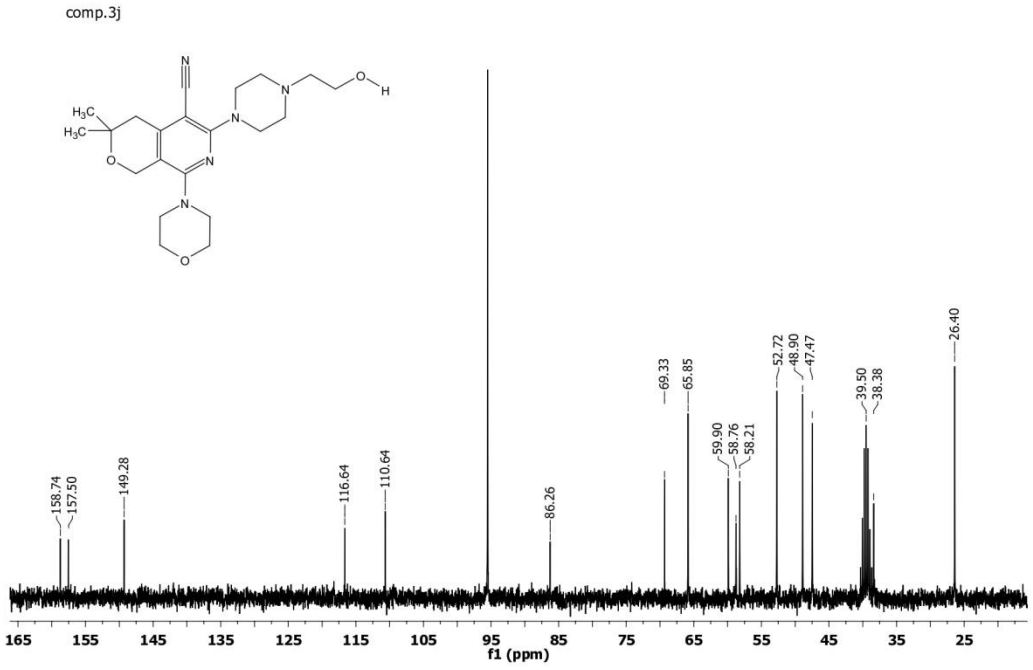
^{13}C NMR spectrum of compound **3i**



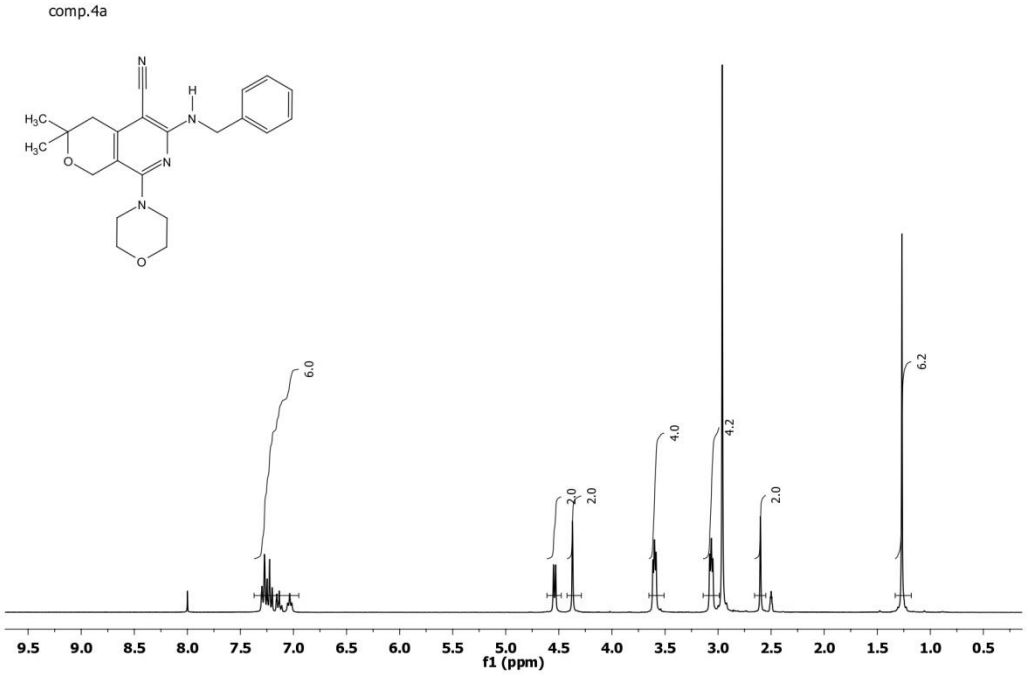
^{1}H NMR spectrum of compound **3j**



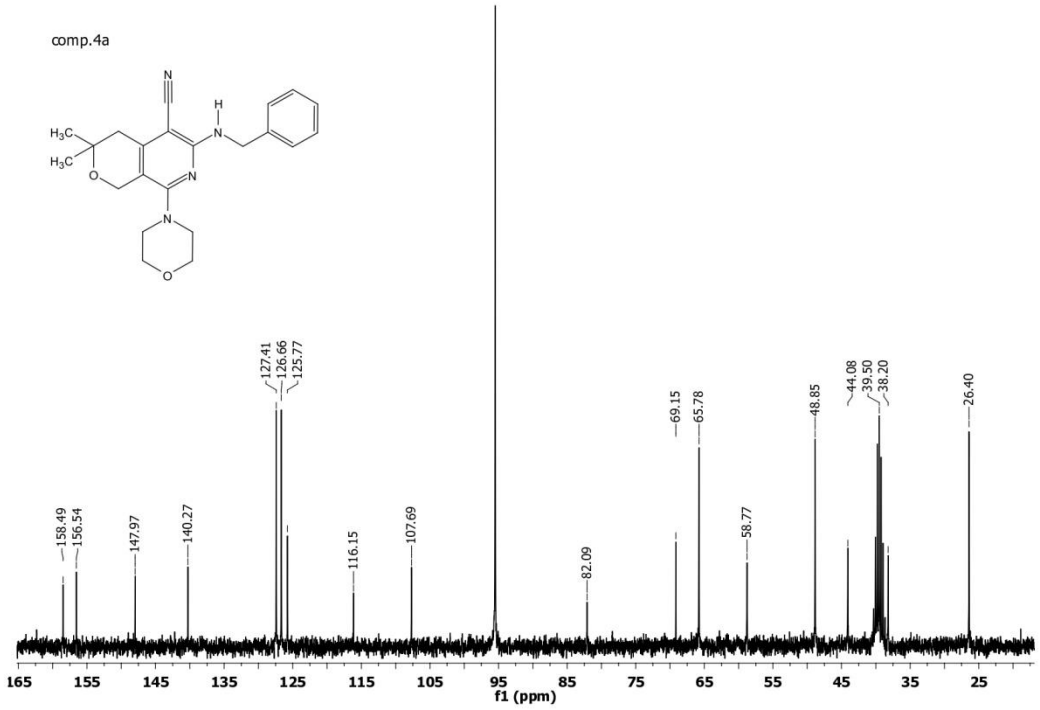
^{13}C NMR spectrum of compound **3j**



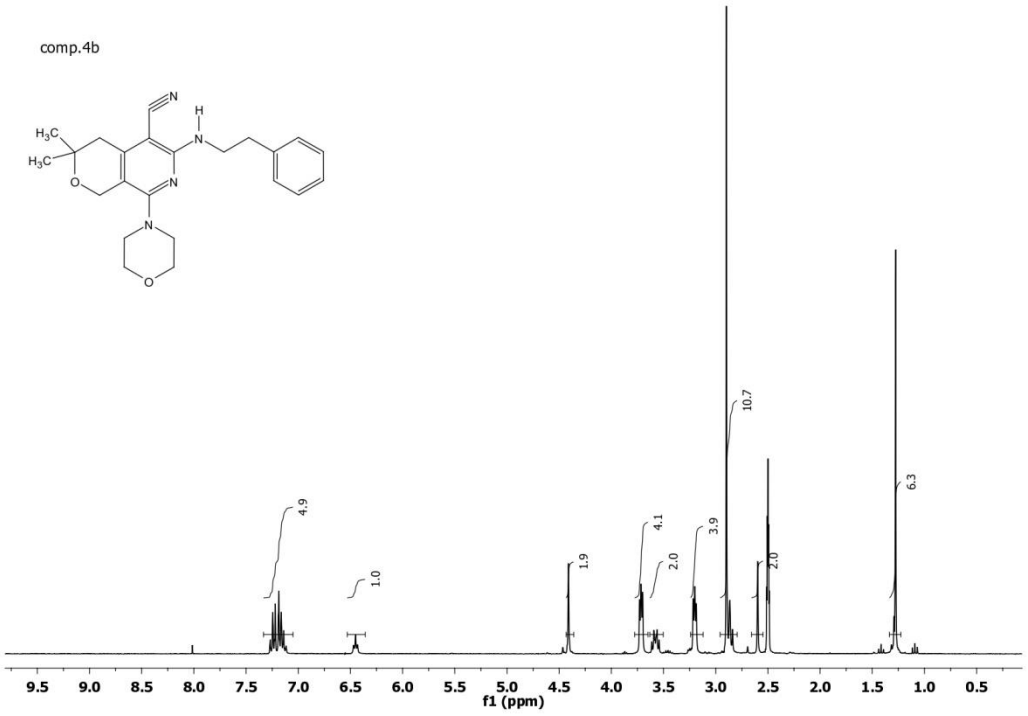
^{1}H NMR spectrum of compound **4a**



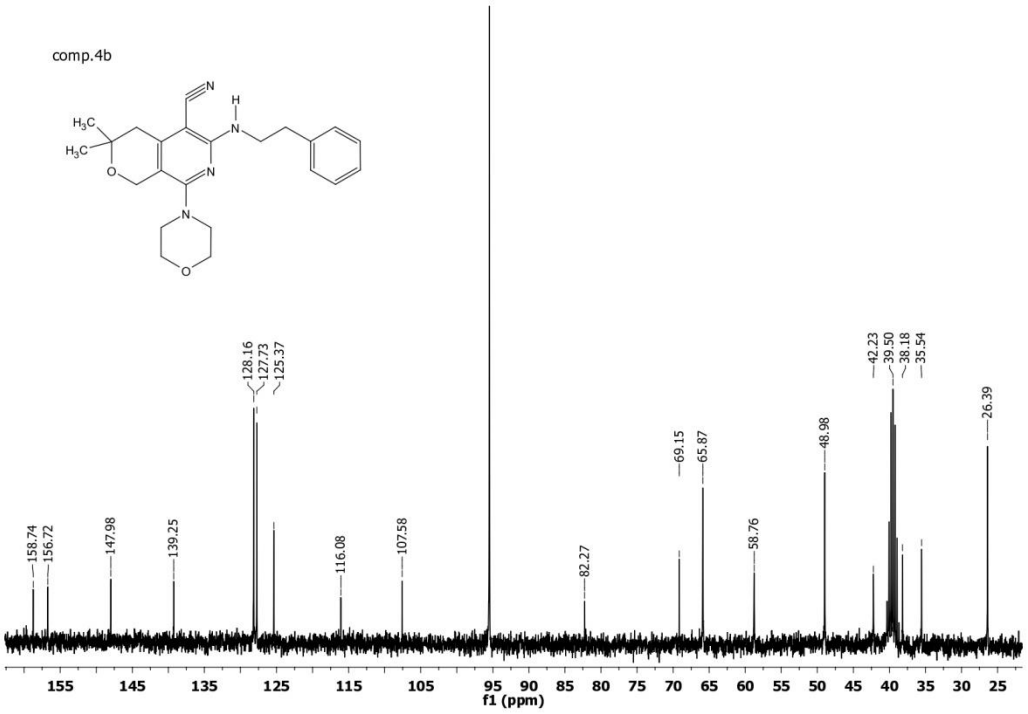
^{13}C NMR spectrum of compound **4a**



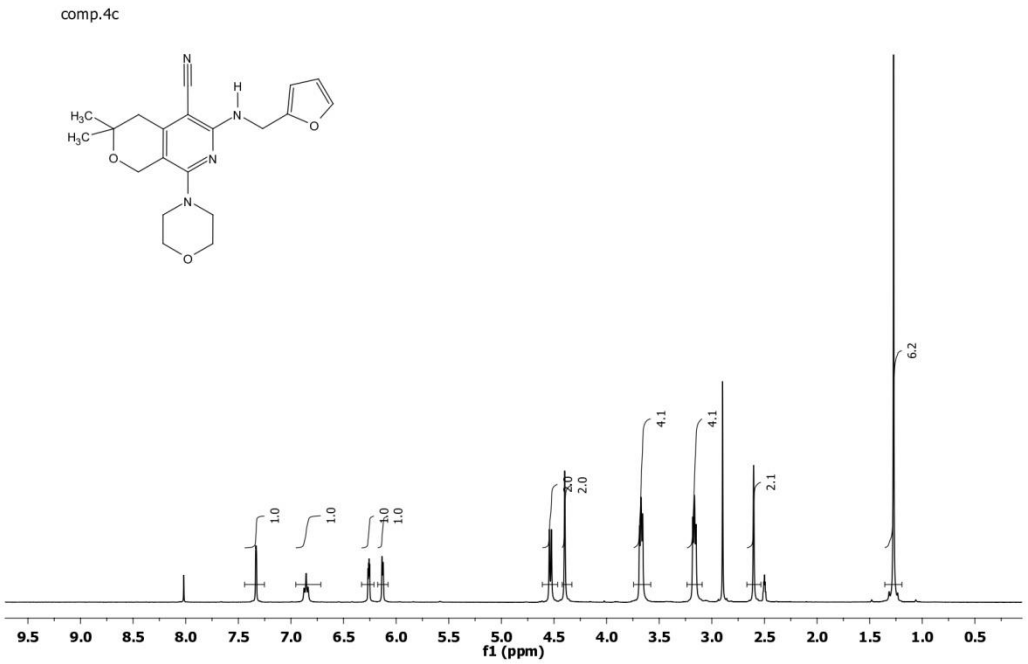
^{1}H NMR spectrum of compound **4b**



^{13}C NMR spectrum of compound **4b**



^{1}H NMR spectrum of compound **4c**



^{13}C NMR spectrum of compound **4c**