SUPPORTING INFORMATION I FOR:

ANRORC type rearrangement/intermolecular cyclocondensation cascade of 5,6-dicyano-3-(2-oxo-2-ethyl)pyrazin-2(1*H*)-ones with hydrazine hydrate for the synthesis of 2-(pyrazol-3-yl)imidazo[4,5-*d*]pyridazines

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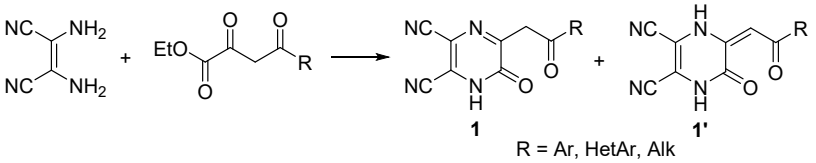
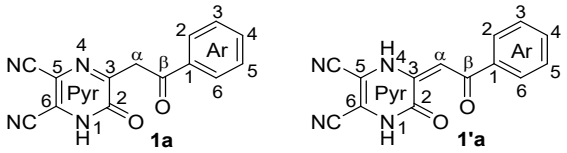
EXPERIMENTAL SECTION

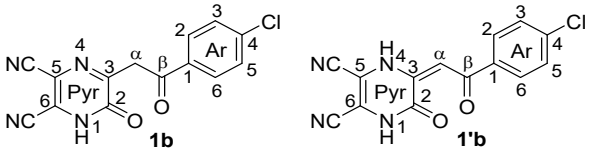
General. Melting points were determined on a Boetius melting point apparatus. IR spectra were recorded on a Tensor 27 (Bruker) FT-IR spectrometer with KBr pellets. The elemental analysis was carried out on a CHNS analyzer EuroEA3028-HT-OM (Eurovector SpA, Italy). The samples were weighed on Sartorius CP2P (Germany) microbalances in tin capsules. Callidus 4.1 software was used to perform quantitative measurements and evaluate the data received. NMR experiments were carried out with Bruker spectrometers AVANCE*III*-500 (500 MHz for ^{1}H, 126 MHz for ^{13}C, and 51 MHz for ^{15}N, respectively) equipped with a pulsed gradient unit capable of producing magnetic field pulse gradients in the z-direction of 53.5 G cm^{-1}. All the spectra were obtained in a 5-mm gradient inverse broad band probehead. Chemical shifts are reported on the δ (ppm) scale and are relative to the residual ^{1}H and ^{13}C signal of DMSO-d_6 (δ 2.50 ppm for ^{1}H and 39.5 ppm for ^{13}C). ^{15}N chemical shifts were referred to the ^{15}N signal of MeCN (δ 235.50 ppm). The pulse programs for all NMR experiments were taken from the Bruker software library. The relative error in determining the exact mass values was no more than 3 ppm. Silica gel "Kieselgel, 0.060-0.200 mm, 40 A" (Acros) was used for column chromatography. All solvents were of regent grade and were dried and distilled before use.

General Procedure for the Preparation of Pyrazin-2(1*H*)-one-5,6-dicarbonitriles 1. Pyrazin-2(1*H*)-one-5,6-dicarbonitriles **1** were synthesized according to the published procedure.[1]To a stirred solution of diaminomaleonitrile (9.08 mmol, 1.0 equiv) in glacial acetic acid (10 mL) was added corresponding ethyl 2,4-dioxo-4-aryl(ethyl)lbutanoate (9.08 mmol, 1.0 equiv) at room temperature and the mixture was stirred at rt for 3 days. Precipitate produced during the reaction was filtered, washed by chloroform (3×5 mL) and was dried in air to give product as a tautomeric mixture **1⇄1′**.

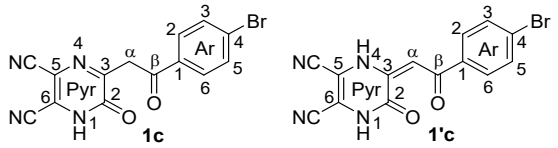




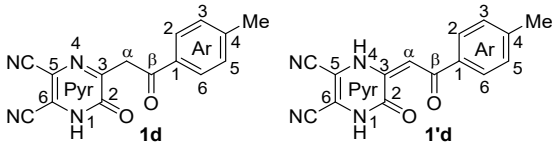
3-(2-(Phenyl)-2-oxoethyl)pyrazin-2(1*H*)-one-5,6-dicarbonitrile (1a) and (*E*)-3-(2-(phenyl)-2-oxoethylidene)-3,4-dihydropyrazin-2(1*H*)-one-5,6-dicarbonitrile (1′a). The compound was obtained by the same procedure starting from diaminomaleonitrile (0.98 g, 9.08 mmol, 1.0 equiv) and ethyl 2,4-dioxo-4-phenylbutanoate (2.0 g, 9.08 mmol, 1.0 equiv) in glacial acetic acid (10 mL) following the general procedure. Data for **1b** and **1′b**: yield 2.23 g, 93%; brown solid; mp 265−266 °C (compare with lit. 242−244 °C[1], 243 °C[2], >300 °C[3]). Spectroscopic data for the title compound were consistent with those reported in the literature.[1-3]



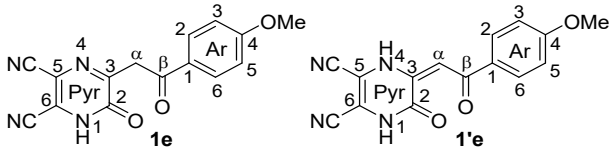
3-(2-(2-Chlorophenyl)-2-oxoethyl)pyrazin-2(1*H*)-one-5,6-dicarbonitrile (1b) and (*E*)-3-(2-(2-chlorophenyl)-2-oxoethylidene)-3,4-dihydropyrazin-2(1*H*)-one-5,6-dicarbonitrile (1′b). The compound was obtained by the same procedure starting from diaminomaleonitrile (0.98 g, 9.08 mmol, 1.0 equiv) and ethyl 4-(4-chlorophenyl)-2,4-dioxobutanoate (2.31 g, 9.08 mmol, 1.0 equiv) in glacial acetic acid (10 mL) following the general procedure. Data for **1b** and **1′b**: yield 2.44 g, 90%; brown solid; mp 283−284 °C (compare with lit. 262−264 °C[1], 271−272 °C[3]). Spectroscopic data for the title compound were consistent with those reported in the literature.[1, 3]



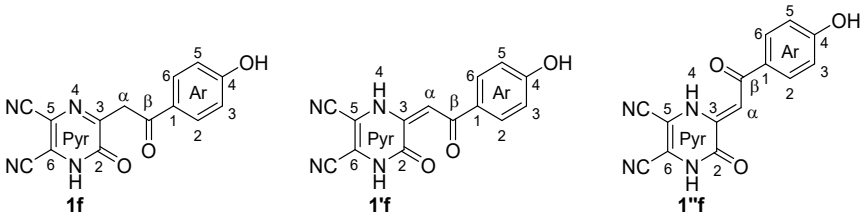
3-(2-(2-Bromophenyl)-2-oxoethyl)pyrazin-2(1*H*)-one-5,6-dicarbonitrile (1c) and (*E*)-3-(2-(2-bromophenyl)-2-oxoethylidene)-3,4-dihydropyrazin-2(1*H*)-one-5,6-dicarbonitrile (1′c). The compound was obtained by the same procedure starting from diaminomaleonitrile (0.97 g, 9.08 mmol, 1.0 equiv) and ethyl 4-(4-bromophenyl)-2,4-dioxobutanoate (2.72 g, 9.08 mmol, 1.0 equiv) in glacial acetic acid (10 mL) following the general procedure. Data for **1c** and **1′c**: yield 2.78 g, 89%; yellow solid; mp 278−279 °C (compare with lit. 270−272 °C[1]). Spectroscopic data for the title compound were consistent with those reported in the literature.[1]



3-(2-(*P*-tolyl)-2-oxoethyl)pyrazin-2(1*H*)-one-5,6-dicarbonitrile (1d) and (*E*)-3-(2-(*p*-tolyl)-2-oxoethylidene)-3,4-dihydropyrazin-2(1*H*)-one-5,6-dicarbonitrile (1′d). The compound was obtained by the same procedure starting from diaminomaleonitrile (0.97 g, 9.08 mmol, 1.0 equiv) and ethyl 2,4-dioxo-4-(*p*-tolyl)butanoate (2.13 g, 9.08 mmol, 1.0 equiv) in glacial acetic acid (10 mL) following the general procedure. Data for **1d** and **1′d**: yield 2.90 g, 93%; brown solid; mp 279−280 °C (compare with lit. 267 °C[2], 264−266 °C[3]). Spectroscopic data for the title compound were consistent with those reported in the literature.[2, 3]

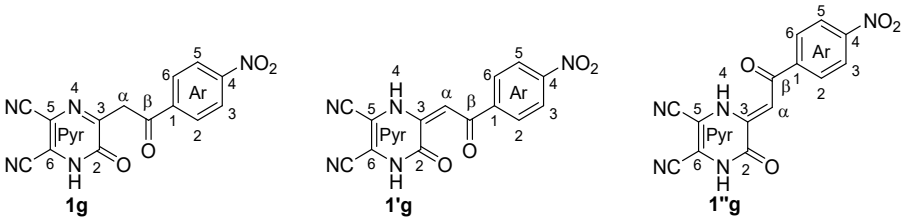


3-(2-(4-Methoxyphenyl)-2-oxoethyl)pyrazin-2(1*H*)-one-5,6-dicarbonitrile (1e) and (*E*)-3-(2-(4-methoxyphenyl)-2-oxoethylidene)-3,4-dihydropyrazin-2(1*H*)-one-5,6-dicarbonitrile (1′e). The compound was obtained by the same procedure starting from diaminomaleonitrile (0.97 g, 9.08 mmol, 1.0 equiv) and ethyl 4-(4-methoxyphenyl)-2,4-dioxobutanoate (2.27 g, 9.08 mmol, 1.0 equiv) in glacial acetic acid (10 mL) following the general procedure. Data for **1e** and **1′e**: yield 2.46 g, 92%; brown solid; mp 266−267 °C (compare with lit. 266 °C[2]). Spectroscopic data for the title compound were consistent with those reported in the literature.[2]

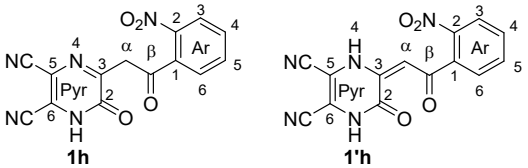


3-(2-(4-Hydroxyphenyl)-2-oxoethyl)pyrazin-2(1*H*)-one-5,6-dicarbonitrile (1f), (*E*)-3-(2-(4-hydroxyphenyl)-2-oxoethylidene)-3,4-dihydropyrazin-2(1*H*)-one-5,6-dicarbonitrile (1′f) and **(*Z*)-3-(2-(4-hydroxyphenyl)-2-oxoethylidene)-3,4-dihydropyrazin-2(1*H*)-one-5,6-dicarbonitrile (1′′f)** were obtained and characterized as the mixture of tautomers in percentage ratio 45:32:23, respectively. The compound was obtained by the same procedure starting from diaminomaleonitrile (0.97 g, 9.08 mmol, 1.0 equiv) and ethyl 4-(4-hydroxyphenyl)-2,4-dioxobutanoate (2.14 g, 9.08 mmol, 1.0 equiv) in glacial acetic acid (10 mL) following the general procedure. Yield 2.21 g, (87%); brown powder; mp 240−241 °C. IR (KBr, cm^{-1}): ν_{max} 3439, 3347, 3066, 2896, 2230, 1698, 1629, 1590, 1543, 1519, 1478, 1458, 1355, 1247, 1207, 1178, 1157, 1118, 1057, 852, 809, 648, 513. Anal. Calcd. for $C_{14}H_8N_4O_3$: C, 60.00; H, 2.88; N, 19.99. Found: C, 60.04; H, 2.85; N, 19.95%. NMR data for **1f**: ^{1}H NMR (500.1 MHz, DMSO-d_6): δ 7.88 (d, J = 8.8 Hz, 2H, H2/H6-Ar), 6.87 (d, J = 8.8 Hz, 2H, H3/H5-Ar), 4.41 (s, 2H, Hα). ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-d_6): δ 193.4 (Cβ), 162.5 (C4-Ar), 160.5 (C2-Pyr), 152.2 (C3-Pyr), 130.9 (C2/C6-Ar), 129.9 (C6-

Pyr), 127.8 (C1-Ar), 115.7 (CN6-Pyr), 115.4 (C3/C5-Ar), 114.9 (C5-Pyr), 113.7 (CN5-Pyr), 43.1 (Cα). NMR data for **1′f** (*trans*-(N4Pyr-C5Pyr-Cα-Cβ)): ^{1}H NMR (500.1 MHz, DMSO-d_6): δ 10.45 (s, 1H, N(4)H), 7.81 (d, J = 8.8 Hz, 2H, H2/H6-Ar), 6.87 (d, J = 8.8 Hz, 2H, H3/H5-Ar), 6.61 (s, 1H, Hα). ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-d_6): δ 176.9 (Cβ), 162.0 (C4-Ar), 158.6 (C2-Pyr), 154.6 (C3-Pyr), 129.3 (C6-Pyr), 129.1 (C2/C6-Ar), 127.8 (C1-Ar), 115.7 (C3/C5-Ar), 115.1 (CN5-Pyr), 113.9 (C5-Pyr), 113.7 (CN6-Pyr), 90.9 (Cα). NMR data for **1′′f** (*cis*-(N4Pyr-C5Pyr-Cα-Cβ)): ^{1}H NMR (500.1 MHz, DMSO-d_6): δ 7.81 (d, J = 8.8 Hz, 2H, H2/H6-Ar), 6.88 (d, J = 8.8 Hz, 2H, H3/H5-Ar), 6.01 (s, 1H, Hα). ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-d_6): in this case the signals cannot be accurately assigned.

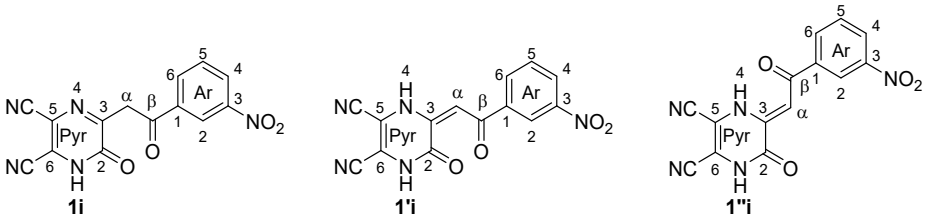


3-(2-(4-Nitrophenyl)-2-oxoethyl)pyrazin-2(1*H*)-one-5,6-dicarbonitrile (1g), (*E*)-3-(2-(4-nitrophenyl)-2-oxoethylidene)-3,4-dihydropyrazin-2(1*H*)-one-5,6-dicarbonitrile (1′g) and **(*Z*)-3-(2-(4-nitrophenyl)-2-oxoethylidene)-3,4-dihydropyrazin-2(1*H*)-one-5,6-dicarbonitrile (1′′g)** were obtained and characterized as the mixture of tautomers in percentage ratio 28:56:16, respectively. The compound was obtained by the same procedure starting from diaminomaleonitrile (0.97 g, 9.08 mmol, 1.0 equiv) and ethyl 4-(4-nitrophenyl)-2,4-dioxobutanoate (2.41 g, 9.08 mmol, 1.0 equiv) in glacial acetic acid (10 mL) following the general procedure. Yield 2.56 g, (91%); orange solid; mp 253−254 °C. IR (KBr, cm^{-1}): ν_{max} 3439, 3080, 2925, 2231, 1705, 1628, 1604, 1560, 1522, 1485, 1459, 1343, 1247, 1212, 1063, 816, 710, 643. Anal. Calcd. for $C_{14}H_7N_5O_4$: C, 54.38; H, 2.28; N, 22.65. Found: C, 54.35; H, 2.30; N, 22.69%. NMR data for **1g**: ^{1}H NMR (500.1 MHz, DMSO-d_6): δ 8.36 (d, J = 8.8 Hz, 2H, H3/H5-Ar), 7.71 (d, J = 8.8 Hz, 2H, H2/H6-Ar), 4.69 (s, 2H, Hα). ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-d_6): δ 155.2 (Cβ), 153.2 (C2-Pyr), 151.1 (C3-Pyr), 148.5 (C4-Ar), 141.8 (C1-Ar), 129.0 (C2/C6-Ar), 124.0(C3/C5-Ar), 120.1 (C6-Pyr), 114.7 (CN6-Pyr), 113.6 (CN5-Pyr), 112.6 (C5-Pyr), 44.0 (Cα). ^{15}N NMR (50.7 MHz, DMSO-d_6): δ 331.2 ($NO_2$4-Ar). The signals of (N1-Pyr), (N4-Pyr), (C<u>N</u>5-Pyr), (C<u>N</u>6-Pyr) have not been observed. NMR data for **1′g** (*trans*-(N4Pyr-C5Pyr-Cα-Cβ)):^{1}H NMR (500.1 MHz, DMSO-d_6): δ 8.28 (d, J = 9.0 Hz, 2H, H3/H5-Ar), 8.13 (d, J = 9.0 Hz, 2H, H2/H6-Ar), 6.65 (s, 1H, Hα). ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-d_6): δ 168.9 (Cβ), 157.7 (C2-Pyr), 155.2 (C3-Pyr), 148.7 (C4-Ar), 141.0 (C1-Ar), 127.6 (C2/C6-Ar), 123.9 (C3/C5-Ar), 114.7 (CN5-Pyr), 114.2 (C6-Pyr), 113.6 (CN6-Pyr), 113.0 (C5-Pyr), 94.9 (Cα). ^{15}N NMR (50.7 MHz, DMSO-d_6): the signals of ($NO_2$4-Ar), (N4-Pyr), (N1-Pyr), (C<u>N</u>5-Pyr) and (C<u>N</u>6-Pyr) have not been observed. NMR data for **1′′g** (*cis*-(N4Pyr-C5Pyr-Cα-Cβ)): ^{1}H NMR (500.1 MHz, DMSO-d_6): δ 10.22 (s, 1H, N4H) (hydrogen bounded and therefore is not lost), 8.36 (d, J = 9.0 Hz, 2H, H3/H5-Ar), 8.24 (d, J = 9.0 Hz, 2H, H2/H6-Ar), 6.04 (s, 1H, Hα). ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-d_6): δ 197.2 (Cβ), 155.2 (C2-Pyr), 153.2 (C3-Pyr), 150.3 (C4-Ar), 141.8 (C1-Ar), 129.6 (C2/C6-Ar), 124.1 (C3/C5-Ar), 116.5 (C5-Pyr),), 114.7 (CN5-Pyr), 113.6 (CN6-Pyr), 113.0 (C6-Pyr), 95.6 (Cα). ^{15}N NMR (50.7 MHz, DMSO-d_6): δ 101.1 (N4-Pyr), 284.3 (N1-Pyr). The signals of ($NO_2$4-Ar), (C<u>N</u>5-Pyr), (C<u>N</u>6-Pyr) have not been observed.

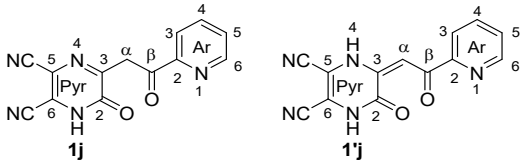


3-(2-(2-Nitrophenyl)-2-oxoethyl)pyrazin-2(1*H*)-one-5,6-dicarbonitrile (1h) and **(*E*)-3-(2-(2-nitrophenyl)-2-oxoethylidene)-3,4-dihydropyrazin-2(1*H*)-one-5,6-dicarbonitrile (1′h)** were obtained and characterized as the mixture of tautomers in percentage ratio 40:60, respectively. The compound was obtained by the same procedure starting from diaminomaleonitrile (0.97 g, 9.08 mmol, 1.0 equiv) and ethyl 4-(2-nitrophenyl)-2,4-dioxobutanoate (2.41 g, 9.08 mmol, 1.0 equiv) in glacial acetic acid (10 mL) following the general procedure. Yield 2.50 g, (89%); orange solid; mp 197−198 °C. IR (KBr, cm^{-1}): ν_{max} 3437, 3206, 3126, 3100, 2927, 2236, 1710, 1630, 1616, 1601, 1588, 1568, 1532, 1483, 1368, 1341, 1247, 1212, 1042, 777, 739, 636. Anal. Calcd. for $C_{14}H_7N_5O_4$: C, 54.38; H, 2.28; N, 22.65. Found: C, 54.33; H, 2.31; N, 22.61%. NMR data for **1h**: ^{1}H NMR (500.1 MHz, DMSO-d_6): δ 8.11 (dd, J = 8.3, J = 1.0, Hz, 1H,

H6-Ar), 7.91-7.92 (m, 1H, H3-Ar), 7.89-7.90 (m, 1H, H4-Ar), 7.71-7.73 (m, 1H, H5-Ar), 4.55 (s, 2H, Hα). $^{13}C\{^{1}H\}$ NMR (125.8 MHz, DMSO-d_6): δ 196.2 (Cβ), 159.4 (C2-Pyr), 149.5 (C3-Pyr), 146.2 (C2-Ar), 134.2 (C4-Ar), 132.4 (C5-Ar), 129.1 (C1-Ar), 128.7 (C3-Ar), 124.3 (C6-Ar), 119.8 (C6-Pyr), 114.6 (CN6-Pyr), 114.0 (C5-Pyr), 113.3 (CN5-Pyr), 46.0 (Cα). ^{15}N NMR (50.7 MHz, DMSO-d_6,): δ 371.7 ($NO_2$2-Ar), 334.2 (N4-Pyr). The signals of (N1-Pyr), (CN5-Pyr) and (CN6-Pyr) have not been observed. NMR data for **1′h**:^{1}H NMR (500.1 MHz, DMSO-d_6): δ 7.97 (brd, J = 7.8 Hz, 1H, H6-Ar), 7.81-7.83 (m, 1H, H4-Ar), 7.79-7-82 (m, 1H, H3-Ar), 7.73-7.75 (m, 1H, H5-Ar), 6.34 (s, 1H, Hα). $^{13}C\{^{1}H\}$ NMR (125.8 MHz, DMSO-d_6): δ 179.1 (Cβ), 156.2 (C2-Pyr), 147.9 (C2-Ar), 147.3 (C3-Pyr), 134.1 (C3-Ar), 133.2 (C4-Ar), 132.8 (C1-Ar), 131.7 (C5-Ar), 129.3 (C6-Pyr), 124.3 (C6-Ar), 112.8 (CN6-Pyr), 112.3 (CN5-Pyr), 109.8 (C5-Ar), 95.5 (Cα). ^{15}N NMR (50.7 MHz, DMSO-d_6): δ 375.3 ($NO_2$2-Ar), 192.1 (N4-Pyr). The signals of (N1-Pyr), (CN5-Pyr) and (CN6-Pyr) have not been observed.

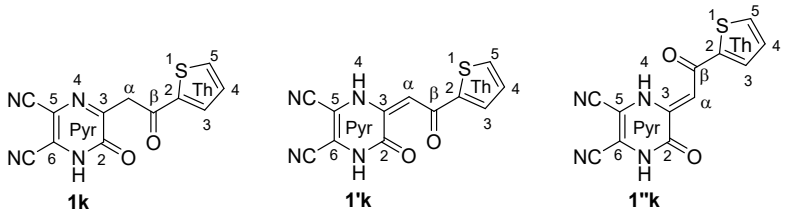


3-(2-(3-Nitrophenyl)-2-oxoethyl)pyrazin-2(1*H*)-one-5,6-dicarbonitrile (1i), (*E*)-3-(2-(3-nitrophenyl)-2-oxoethylidene)-3,4-dihydropyrazin-2(1*H*)-one-5,6-dicarbonitrile (1′i) and **(*Z*)-3-(2-(3-nitrophenyl)-2-oxoethylidene)-3,4-dihydropyrazin-2(1*H*)-one-5,6-dicarbonitrile (1′′i)** were obtained and characterized as the mixture of tautomers in percentage ratio 30:60:10, respectively. The compound was obtained by the same procedure starting from diaminomaleonitrile (0.97 g, 9.08 mmol, 1.0 equiv) and ethyl 4-(3-nitrophenyl)-2,4-dioxobutanoate (2.41 g, 9.08 mmol, 1.0 equiv) in glacial acetic acid (10 mL) following the general procedure. Yield 2.44 g, (87%); orange solid; mp 215−216 °C. IR (KBr, cm^{-1}): ν_{max} 3442, 3087, 2921, 2227, 1703, 1627, 1613, 1584, 1554, 1531, 1480, 1453, 1349, 1267, 1248, 1205, 1163, 1112, 1055, 807, 742, 712, 690, 653, 638. Anal. Calcd. for $C_{14}H_7N_5O_4$: C, 54.38; H, 2.28; N, 22.65. Found: C, 54.35; H, 2.31; N, 22.69%. NMR data for **1i**: ^{1}H NMR (500.1 MHz, DMSO-d_6): δ 8.70 (dd, J = 2.0 Hz, J = 2.2 Hz, 1H, H2-Ar), 8.51 (ddd, J = 8.0 Hz, J = 2.2 Hz, J = 1.0 Hz, 1H, H4-Ar), 8.46 (d, J = 8.0 Hz, 1H, H6-Ar), 7.89 (dd, J = 8.0 Hz, J = 8.0 Hz, 1H, H5-Ar), 4.72 (s, 2H, Hα). $^{13}C\{^{1}H\}$ NMR (125.8 MHz, DMSO-d_6): δ 193.8 (Cβ), 159.4 (C2-Pyr), 150.6 (C3-Pyr), 148.2 (C3-Ar), 137.1 (C1-Ar), 134.5 (C6-Ar), 130.7 (C5-Ar), 127.3 (C4-Ar), 122.6 (C2-Ar), 119.1 (C6-Pyr), 116.6 (CN6-Pyr), 113.6 (C5-Pyr), 112.6 (CN5-Pyr), 43.7 (Cα). ^{15}N NMR (50.7 MHz, DMSO-d_6): δ 331.4 ($NO_2$3-Ar). The signals of (N1-Pyr), (N4-Pyr), (CN5-Pyr) and (CN6-Pyr) have not been observed. NMR data for **1′i** (*trans*-(N4Pyr-C5Pyr-Cα-Cβ)): ^{1}H NMR (500.1 MHz, DMSO-d_6): δ 8.58 (dd, J = 2.0 Hz, J = 2.3 Hz, 1H, H2-Ar), 8.35-8.36 (m, 1H, H6-Ar), 8.34-8.35 (m, 1H, H4-Ar), 7.78 (dd, J = 7.8 Hz, J = 7.8 Hz,1H, H5-Ar), 6.66 (s, 1H, Hα). $^{13}C\{^{1}H\}$ NMR (125.8 MHz, DMSO-d_6): δ 170.3 (Cβ), 157.7 (C2-Pyr), 148.1 (C3-Pyr), 147.8 (C3-Ar), 137.2 (C1-Ar), 132.6 (C6-Ar), 130.5 (C5-Ar), 125.6 (C4-Ar), 120.7 (C2-Ar), 114.8 (CN6-Pyr), 113.3 (CN5-Pyr), 112.3 (C5-Pyr), 106.1 (C6-Pyr), 94.1 (Cα). ^{15}N NMR (50.7 MHz, DMSO-d_6): the signals of ($NO_2$3-Ar), (N1-Pyr), (N4-Pyr), (CN5-Pyr) and (CN6-Pyr) have not been observed. NMR data for **1′′i** (*cis*-(N4Pyr-C5Pyr-Cα-Cβ)): ^{1}H NMR (500.1 MHz, DMSO-d_6): δ 10.15 (s, 1H, N4H) (hydrogen bounded and therefore is not lost), 8.39 (ddd, J = 8.0 Hz, J = 2.2 Hz, J = 1.0 Hz, 1H, H4-Ar), 8.23 (dd, J = 2.0 Hz, J = 2.3 Hz, 1H, H2-Ar), 7.90-7.92 (m, 1H, H6-Ar), 7.84 (dd, J = 7.8 Hz, J = 7.8 Hz, 1H, H5-Ar), 6.06 (s, 1H, Hα). $^{13}C\{^{1}H\}$ NMR (125.8 MHz, DMSO-d_6): δ 170.3 (Cβ), 157.4 (C2-Pyr), 137.7 (C3-Pyr), 148.0 (C3-Ar), 137.0 (C1-Ar), 133.8 (C6-Ar), 130.8 (C5-Ar), 125.2 (C4-Ar), 122.0 (C2-Ar), 114.8 (CN6-Pyr), 113.3 (CN5-Pyr), 112.3 (C5-Pyr), 106.1 (C6-Pyr), 95.3 (Cα). ^{15}N NMR (50.7 MHz, DMSO-d_6): δ 101.7 (N4-Pyr), 285.2 (N1-Pyr). The signals of ($NO_2$3-Ar), (CN5-Pyr) and (CN6-Pyr) have not been observed.

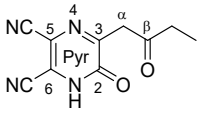


3-(2-Oxo-2-(pyridin-2-yl)ethyl)pyrazin-2(1*H*)-one-5,6-dicarbonitrile (1j) and **(*E*)-3-(2-oxo-2-(pyridin-2-yl)ethylidene)-3,4-dihydropyrazin-2(1*H*)-one-5,6-dicarbonitrile (1′j)** were obtained and

characterized as the mixture of tautomers in percentage ratio 25:75, respectively. The compound was obtained by the same procedure starting from diaminomaleonitrile (0.97 g, 9.08 mmol, 1.0 equiv) and ethyl 2,4-dioxo-4-(pyridin-2-yl)butanoate (2.01 g, 9.08 mmol, 1.0 equiv) in glacial acetic acid (10 mL) following the general procedure. Yield 1.76 g, (73%); black powder; mp 257−259 °C. IR (KBr, cm^{-1}): ν_{max} 3434, 3108, 2222, 1602, 1552, 1525, 1468, 1388, 1289, 1240, 1073, 952, 784, 667, 651, 603, 460. Anal. Calcd. for $C_{13}H_7N_5O_2$: C, 58.87; H, 2.66; N, 26.41. Found: C, 58.90; H, 2.64; N, 26.45%. NMR data for **1j**: ^{1}H NMR (500.1 MHz, DMSO-d_6): δ 8.73 (ddd, J = 4.7 Hz, J = 1.6 Hz, J = 1.0 Hz, 1H, H3-Ar), 8.04 (ddd, J = 7.7 Hz, J = 1.6 Hz, J = 1.6 Hz, 1H, H5-Ar), 8.00 (d, J = 7.7 Hz, 1H, H6-Ar), 7.70 (ddd, J = 7.4 Hz, J = 4.7 Hz, J = 1.4 Hz, 1H, H4-Ar), 4.70 (s, 2H, Hα). ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-d_6): δ 196.1 (Cβ), 158.9 (C2-Pyr), 152.2 (C3-Pyr), 151.6 (C1-Ar), 149.2 (C3-Ar), 137.8 (C5-Ar), 128.2 (C4-Ar), 121.6 (C6-Ar), 119.7 (C6-Pyr), 114.0 (CN6-Pyr), 113.2 (CN5-Pyr), 112.6 (C5-Pyr), 42.5 (Cα). ^{15}N NMR (50.7 MHz, DMSO-d_6): δ 331.9 (N2-Py). The signals of (N1-Pyr), (N4-Pyr), (C<u>N</u>5-Pyr) and (C<u>N</u>6-Pyr) have not been observed. NMR data for **1'j**: ^{1}H NMR (500.1 MHz, DMSO-d_6): δ 8.71 (ddd, J = 4.7 Hz, J = 1.6 Hz, J = 0.9 Hz, 1H, H3-Ar), 8.06-8.08 (m, 1H, H6-Ar), 8.04-8.06 (m, 1H, H5-Ar), 7.62 (ddd, J = 7.4 Hz, J = 4.7 Hz, J = 0.9 Hz, 1H, H4-Ar), 7.19 (s, 1H, Hα). ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-d_6): δ 171.9 (Cβ), 157.1 (C2-Pyr), 150.9 (C1-Ar), 150.3 (C3-Pyr), 148.4 (C3-Ar), 138.8 (C5-Ar), 126.3 (C4-Ar), 121.5 (C6-Ar), 116.3 (CN6-Pyr), 114.5 (CN5-Pyr), 113.7 (C6-Pyr), 112.7 (C5-Pyr), 94.2 (Cα). ^{15}N NMR (50.7 MHz, DMSO-d_6): the signals of (N2-Py), (N1-Pyr), (N4-Pyr), (C<u>N</u>5-Pyr) and (C<u>N</u>6-Pyr) have not been observed.



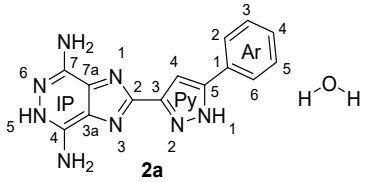
3-(2-(Thien-2-yl)-2-oxoethyl)pyrazin-2(1*H*)-one-5,6-dicarbonitrile (1k), (*E*)-3-(2-(thien-2-yl)-2-oxoethylidene)-3,4-dihydropyrazin-2(1*H*)-one-5,6-dicarbonitrile (1′k) and **(*Z*)-3-(2-(thien-2-yl)-2-oxoethylidene)-3,4-dihydropyrazin-2(1*H*)-one-5,6-dicarbonitrile (1′′k)** were obtained and characterized as the mixture of tautomers in percentage ratio 45:32:23, respectively. The compound was obtained by the same procedure starting from diaminomaleonitrile (0.97 g, 9.08 mmol, 1.0 equiv) and ethyl 2,4-dioxohexanoate (2.05 g, 9.08 mmol, 1.0 equiv) in glacial acetic acid (10 mL) following the general procedure. Yield 2.38 g, (97%); brown solid; mp 230−231 °C. IR (KBr, cm^{-1}): ν_{max} 3426, 3332, 3212, 2997, 2209, 1663, 1636, 1576, 1525, 1500, 1437, 1331, 1260, 1139, 1022, 733, 652, 556. Anal. Calcd. for $C_{12}H_6N_4O_2S$: C, 53.33; H, 2.24; N, 20.73; S, 11.86. Found: C, 53.37; H, 2.29; N, 20.75; S, 11.82%. NMR data for **1k**: ^{1}H NMR (500.1 MHz, DMSO-d_6): δ 8.11 (d, J = 4.0 Hz, 1H, H3-Th), 8.06 (d, J = 4.8 Hz, 1H, H5-Th), 7.30 (dd, J = 4.8 Hz, J = 4.0 Hz, 1H, H4-Th), 4.58 (s, 2H, Hα-Sp). The signals of (N(4)H) and (N(1)H) have not been observed. ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-d_6): δ 187.7 (Cβ-Sp), 159.2 (C2-Pyr), 150.8 (C3-Pyr), 142.9 (C2-Th), 135.8 (C5-Th), 134.7 (C3-Th), 128.9 (C4-Th), 119.9 (C6-Pyr), 114.6 (C6a-Pyr), 113.3 (C5-Pyr), 111.9 (C5a-Pyr), 43.7(Cα-Sp). NMR data for **1′k** (*trans*-(N4Pyr-C5Pyr-Cα-Cβ)): ^{1}H NMR (500.1 MHz, DMSO-d_6): δ 7.96 (d, J = 4.5 Hz, 1H, H5-Th), 7.73 (d, J = 4.0 Hz, 1H, H3-Th), 7.22 (dd, J = 4.5 Hz, J = 4.0 Hz, 1H, H4-Th), 6.70 (s, 1H, Hα-Sp). The signals of (N(4)H) and (N(1)H) have not been observed. ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-d_6): δ 177.0 (Cβ-Sp, based on ^{1}H-^{13}C HMBC spectrum), 162.9 (C2-Pyr), 155.2 (C3-Pyr), 142.7 (C2-Th), 133.9 (C5-Th), 131.1 (C3-Th), 129.1 (C4-Th), 113.9 (C5-Pyr), 113.6 (C6-Pyr), 113.1 (C6a-Pyr), 108.6 (C5a-Pyr), 92.4 (Cα-Sp). NMR data for **1′′k** (*cis*-(N4Pyr-C5Pyr-Cα-Cβ)): ^{1}H NMR (500.1 MHz, DMSO-d_6): δ 7.96 (dd, J = 3.5 Hz, J = 1.1 Hz, 1H, H5-Th), 7.87 (dd, J = 4.9 Hz, J = 1.1 Hz, 1H, H3-Th), 7.18 (dd, J = 4.9 Hz, J = 3.5 Hz, 1H, H4-Th), 5.95 (s, 1H, Hα-Sp). The signals of (N(4)H) and (N(1)H) have not been observed. ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-d_6): δ 177.8 (Cβ-Sp, based on ^{1}H-^{13}C HMBC spectrum), n/o (C2-Pyr), n/o (C3-Pyr), 142.7 (C2-Th), 133.6 (C5-Th), 133.2 (C3-Th), 128.2 (C4-Th). The signals of (C2-Pyr), (C3-Pyr), (C6-Pyr), (C6a-Pyr), (C5-Pyr), (C5a-Pyr) and (Cα-Sp) have not benn observed. In the 1D spectra of ^{13}C, due to the broadening caused by exchange processes between different tautomeric forms, signals of some carbon nuclei are not observed. However, in some cases it was possible to determine their values from cross peaks in the ^{1}H-^{13}C HMBC spectra.



1l

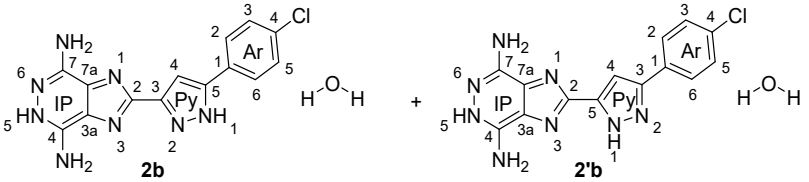
3-(2-Oxobutyl)pyrazin-2(1*H*)-one-5,6-dicarbonitrile (1l). The compound was obtained by the same procedure starting from diaminomaleonitrile (0.97 g, 9.08 mmol, 1.0 equiv) and ethyl 2,4-dioxohexanoate (1.56 g, 9.08 mmol, 1.0 equiv) in glacial acetic acid (10 mL) following the general procedure. Yield 1.67 g, (85%); orange solid; mp 211−212 °C. IR (KBr, cm^{-1}): ν_{max} 3424, 3328, 2218, 1699, 1668, 1634, 1574, 1500, 1436, 1333, 1258, 649. Anal. Calcd. for $C_{10}H_8N_4O_2$: C, 55.56; H, 3.73; N, 25.91. Found: C, 55.52; H, 3.75; N, 25.89%. NMR data for **1l**: ^{1}H NMR (500.1 MHz, DMSO-d_6): δ 7.80 (s, 1H, N(1)H), 3.95 (s, 2H, Hα-Sp), 2.58 (q, J = 7.5 Hz, 2H, $CH_3\underline{CH_2}$-Pyr), 0.94 (t, J = 7.5 Hz, 3H, $\underline{CH_3}CH_2$-Pyr). ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-d_6): δ 206.0 (Cβ-Sp), 159.9 (C2-Pyr), 151.3 (C3-Pyr), 118.3 (C5a-Pyr), 115.1 (C6-Pyr), 113.7 (C6a-Pyr), 113.6 (C5-Pyr), 46.7(Cα-Sp), 35.6 (C2a-Pyr), 7.5 (C2b-Pyr). This compound in the solution (DMSO-d_6) investigated exists almost exclusively in ketone form **1l** (95%). **1′l** Not determined but present.

General Procedure for the Preparation of 2-(5-Aryl(ethyl)-1*H*-pyrazol-3-yl)-5*H*-imidazo[4,5-*d*]pyridazine-4,7-diamine hydrate 2. *Method a*. To a stirred suspension of pyrazin-2(1*H*)-one-5,6-dicarbonitriles **1** (1.89 mmol, 1.0 equiv) and 64% solution of hydrazine hydrate (5.67 mmol, 3.0 equiv) in *n*-BuOH (10 mL) was added 0.055 g (5.61 mmol) of concentrated H_2SO_4 at rt. The reaction mixture was stirred with heating at reflux for 6 h. The reaction mixture was allowed to cool to room temperature and precipitate produced was filtered, washed with washed with 5% $NaHCO_3$ solution, dried in air to give pure product **2**. The filtrate was evaporated to dryness and the resulting residue was washed with washed with 5% $NaHCO_3$ solution, to afford an additional portion of the product **2**. *Method b*. To a stirred suspension of spiro[pyrazino[2,3-*d*]pyridazine-2,3′-pyrazol]-3(4*H*)-ones **3** (1.61 mmol) (As to the synthesis of spiro[pyrazino[2,3-*d*]pyridazine-2,3′-pyrazol]-3(4*H*)-ones see below) in *n*-BuOH (10 mL) was added 0.023 g (2.81 mmol) of concentrated H_2SO_4 at rt. The reaction mixture was stirred with heating at reflux for 6 h. The reaction mixture was allowed to cool to room temperature and precipitate produced was filtered, washed with washed with 5% $NaHCO_3$ solution, dried in air to give pure product **2**. The filtrate was evaporated to dryness and the resulting residue was washed with washed with 5% $NaHCO_3$ solution, to afford an additional portion of the product **2**.

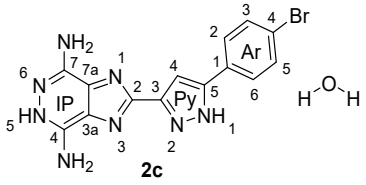


2a

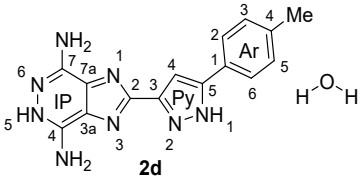
2-(5-Phenyl-1*H*-pyrazol-3-yl)-5*H*-imidazo[4,5-*d*]pyridazine-4,7-diamine (2a). *Method a*. The compound was obtained by the same procedure starting from pyrazin-2(1*H*)-one-5,6-dicarbonitrile **1a** (0.5 g, 1.89 mmol, 1.0 equiv) and hydrazine hydrate (0.28 g, 0.27 mL, 5.67 mmol, 3.0 equiv) in *n*-BuOH (10 mL)/H_2SO_4 (0.055 g, 5.61 mmol) following the general procedure. *Method b*. The compound was obtained by the same procedure starting from spiro[pyrazino[2,3-*d*]pyridazine-2,3′-pyrazol]-3(4*H*)-one **3a** (0.5 g, 1.61 mmol) in *n*-BuOH (10 mL)/H_2SO_4 (0.023 g, 2.81 mmol) following the general procedure. Yield 0.53 g, (97%) (*Method a*); 0.46 g, (99%) (*Method b*); brown solid; mp 222−223 °C. IR (KBr, cm^{-1}): ν_{max} 3425, 3338, 3292, 3204, 1644, 1522, 1451, 1348, 1299, 1275, 1245, 1194, 1157, 1130, 1101, 1075, 1029, 1000, 961, 871, 826, 761, 692, 615, 557, 508, 453. Anal. Calcd. for $C_{14}H_{12}N_8 \cdot H_2O$: C, 54.19; H, 4.55; N, 36.11. Found: C, 54.23; H, 4.57; N, 36.17%. NMR data for **2a**: ^{1}H NMR (500.1 MHz, DMSO-d_6): δ 13.73 (very broad singlet, 1H, NH(6)-IP), 9.32 (brs, 1H, H1-Py), 7.84 (d, J = 7.2 Hz, 2H, H2/H6-Ar), 7.47 (dd, J = 7.2 Hz, J = 7.2 Hz, 2H, H3/H5-Ar), 7.36 (dd, J = 7.2 Hz, J = 7.1 Hz, 2H, H4-Ar), 7.31 (s, 1H, H4-Py), 5.74 (brs, 2H, H_2O), 5.39 (brs, 2H, $NH_2$4-IP), 5.23 (brs, 2H, $NH_2$7-IP). ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-d_6): δ 159.5 (C4-IP), 152.5 (C7-IP), 147.1 (C7a-IP), 146.6 (C3-Py), 143.7 (C5-Py), 133.8 (C3a-IP), 130.7 (C1-Ar), 129.0 (C3/C5-Ar), 128.2 (C4-Ar), 125.3 (C2/C6-Ar), 105.3 (C2-IP), 103.4 (C4-Py). ^{15}N NMR (50.7 MHz, DMSO-d_6): δ 263.3 (N1-Py), 244.9 (N2-Py), 61.3 (N1-IP), 57.7 ($NH_2$7-IP), 57.2 ($NH_2$4-IP). The signals of (N5-IP), (N6-IP), (N1-IP) and (N3-IP) have not been observed.



2-(5-(4-Chlorophenyl)-1*H*-pyrazol-3-yl)-5*H*-imidazo[4,5-*d*]pyridazine-4,7-diamine hydrate (2b) and 2-(3-(4-chlorophenyl)-1*H*-pyrazol-5-yl)-5*H*-imidazo[4,5-*d*]pyridazine-4,7-diamine monohydrate (2′b) were obtained and characterized as the mixture of regioisomers in percentage ratio 70:30, respectively. *Method a*. The compound was obtained by the same procedure starting from pyrazin-2(1*H*)-one-5,6-dicarbonitrile **1b** (0.56 g, 1.89 mmol, 1.0 equiv) and hydrazine hydrate (0.28 g, 0.27 mL, 5.67 mmol, 3.0 equiv) in *n*-BuOH (10 mL)/H_2SO_4 (0.055 g, 5.61 mmol) following the general procedure. *Method b*. The compound was obtained by the same procedure starting from spiro[pyrazino[2,3-*d*]pyridazine-2,3′-pyrazol]-3(4*H*)-one **3b** (0.56 g, 1.61 mmol) in *n*-BuOH (10 mL)/H_2SO_4 (0.023 g, 2.81 mmol) following the general procedure. Yield 0.51 g, (82%) (*Method a*); 0.49 g, (93%) (*Method b*); beige solid; mp 321−322 °C. IR (KBr, cm^{-1}): ν_{max} 3418, 3296, 3181, 3158, 2962, 2875, 1663, 1606, 1578, 1560, 1492, 1445, 1425, 1390, 1369, 1234, 1097, 1047, 1015, 965, 826, 813, 739, 579, 504. Anal. Calcd. for $C_{14}H_{11}ClN_8 \cdot H_2O$: C, 48.77; H, 3.80; N, 32.50. Found: C, 48.79; H, 3.85; N, 32.55%. NMR data for **2b** and **2′b**: the NMR spectra of this compound consist of two sets of signals, *seemed to* pyrazole tautomerism. Signals from the minor tautomer are shown in square brackets. ^{1}H NMR (500.1 MHz, DMSO-d_6): δ 13.6 (very broad singlet, 2H, NH(1)-Py + NH(6)-IP), 7.90 [7.88] (d, J = 8.6 Hz, 2H, H3/H5-Ar), 7.53 [7.50] (d, J = 8.6 Hz, 2H, H2/H6-Ar), 7.29 [7.13] (s, 1H, H4-Py), 6.79 (brs, 2H, H_2O), 6.69 (brs, 2H, $NH_2$4-IP), 5.89 (brs, 2H, $NH_2$7-IP). ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-d_6): δ 159.6 (C4-IP), 152.9 (C7-IP), 147.5 (C7a-IP), 146.2 (C5-Py br), 144.1 (C3-Py br), 134.1 (C3a-IP), 132.6 (C4-Ar), 131.6 (C1-Ar), 129.9 [128.8] (C2/C6-Ar), 127.0 [126.9] (C3/C5-Ar), 104.6 (C2-IP), 102.3 [100.9] (C4-Py).

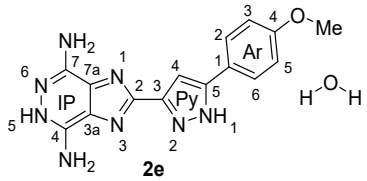


2-(5-(4-Bromophenyl)-1*H*-pyrazol-3-yl)-5*H*-imidazo[4,5-*d*]pyridazine-4,7-diamine hydrate (2c). *Method a*. The compound was obtained by the same procedure starting from pyrazin-2(1*H*)-one-5,6-dicarbonitrile **1c** (0.65 g, 1.89 mmol, 1.0 equiv) and 64% hydrazine hydrate (0.28 g, 0.27 mL, 5.67 mmol, 3.0 equiv) in *n*-BuOH (10 mL)/H_2SO_4 0.055 g, 5.61 mmol) following the general procedure. *Method b*. The compound was obtained by the same procedure starting from spiro[pyrazino[2,3-*d*]pyridazine-2,3′-pyrazol]-3(4*H*)-one **3c** (0.63 g, 1.61 mmol) in *n*-BuOH (10 mL)/H_2SO_4 (0.023 g, 2.81 mmol) following the general procedure. Yield 0.56 g, (80%) (*Method a*); 0.54 g, (90%) (*Method b*); brown solid; mp 271−272 °C. IR (KBr, cm^{-1}): ν_{max} 3448, 3338, 3234, 3191, 1665, 1635, 1524, 1484, 1441, 1309, 1292, 1265, 1239, 1192, 1074, 1010, 999, 961, 887, 871, 816, 769, 697, 559, 506. Anal. Calcd. for $C_{14}H_{11}BrN_8 \cdot H_2O$: C, 43.20; H, 3.37; N, 28.79. Found: C, 43.25; H, 3.35; N, 28.81%. NMR data for **2c**: ^{1}H NMR (500.1 MHz, DMSO-d_6): δ 13.66 (very broad singlet, 1H, NH(6)-IP), 9.32 (brs, 1H, NH(1)-Py), 7.77 (d, J = 8.6 Hz, 2H, H2/H6-Ar), 7.67 (d, J = 8.6 Hz, 2H, H3/H5-Ar), 7.34 (s, 1H, H4-Py), 5.58 (brs, 2H, H_2O), 5.25 (brs, 2H, $NH_2$4-IP), 4.95 (brs, 2H, $NH_2$7-IP). ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-d_6): δ 158.9 (C4-IP), 152.5 (C7-IP), 147.1 (C7a-IP), 146.2 (C5-Py br), 143.1 (C3-Py br), 133.1 (C3a-IP), 131.9 (C3/C5-Ar), 130.4 (C1-Ar), 127.1 (C2/C6-Ar), 121.1 (C4-Ar), 105.1 (C2-IP), 103.6 (C4-Py). ^{15}N NMR (50.7 MHz, DMSO-d_6): δ 60.3 (N1-IP), 56.5 ($NH_2$4-IP), 55.5 ($NH_2$7-IP). The signals of (N1-Py), (N2-Py), (N5-IP), (N6-IP), (N1-IP) and (N3-IP) have not been observed.



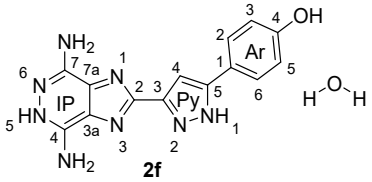
2d

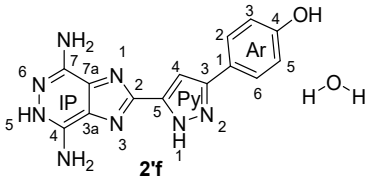
2-(5-(*p*-Tolyl)-1*H*-pyrazol-3-yl)-5*H*-imidazo[4,5-*d*]pyridazine-4,7-diamine hydrate (2d). *Method a*. The compound was obtained by the same procedure starting from pyrazin-2(1*H*)-one-5,6-dicarbonitrile **1d** (0.53 g, 1.89 mmol, 1.0 equiv) and hydrazine hydrate (0.28 g, 0.27 mL, 5.67 mmol, 3.0 equiv) in *n*-BuOH (10 mL)/H_2SO_4 (0.055 g, 5.61 mmol) following the general procedure. *Method b*. The compound was obtained by the same procedure starting from spiro[pyrazino[2,3-*d*]pyridazine-2,3′-pyrazol]-3(4*H*)-one **3d** (0.52 g, 1.61 mmol) in *n*-BuOH (10 mL)/H_2SO_4 (0.023 g, 2.81 mmol) following the general procedure. Yield 0.52 g, (89%) (*Method a*); 0.48 g, (97%) (*Method b*); brown solid; mp > 400 °C. IR (KBr, cm^{-1}): ν_{max} 3346, 3346, 3269, 3206, 2956, 2924, 1676, 1638, 1515, 1508, 1449, 1317, 1300, 1244, 1191, 1130, 1045, 1019, 999, 963, 871, 810, 770, 700, 670, 618, 587, 551, 510. Anal. Calcd. for $C_{15}H_{14}N_8 \cdot H_2O$: C, 55.55; H, 4.97; N, 34.55. Found: C, 55.52; H, 4.99; N, 34.57%. NMR data for **2d**: ^{1}H NMR (500.1 MHz, DMSO-d_6): δ 13.67 (very broad singlet, 1H, NH(6)-IP), 9.28 (brs, 1H, NH(1)-Py), 7.71 (d, J = 8.0 Hz, 2H, H2/H6-Ar), 7.28 (d, J = 8.0 Hz, 2H, H3/H5-Ar), 7.22 (s, 1H, H4-Py), 5.76 (brs, 2H, H_2O), 5.39 (brs, 2H, $NH_2$4-IP), 5.20 (brs, 2H, $NH_2$7-IP), 2.34 (s, 3H, H4a-Ar). ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-d_6): δ 159.6 (C4-IP), 152.2 (C7-IP), 147.0 (C7a-IP), 146.2 (C5-Py br), 144.0 (C3-Py br), 137.6 (C4-Ar), 134.0 (C3a-IP), 129.5 (C3/C5-Ar), 127.7 (C1-Ar), 125.2 (C2/C6-Ar), 104.9 (C2-IP), 103.0 (C4-Py), 20.8 (C4b-Ar). ^{15}N NMR (50.7 MHz, DMSO-d_6): δ 62.7 (N1-IP), 57.9 ($NH_2$7-IP), 57.7 ($NH_2$4-IP). The signals of (N1-Py), (N2-Py), (N5-IP), (N6-IP), (N1-IP) and (N3-IP) have not been observed.



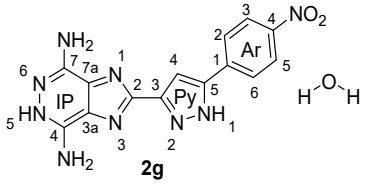
2e

2-(5-(4-Methoxyphenyl)-1*H*-pyrazol-3-yl)-5*H*-imidazo[4,5-*d*]pyridazine-4,7-diamine hydrate (2e). *Method a*. The compound was obtained by the same procedure starting from pyrazin-2(1*H*)-one-5,6-dicarbonitrile **1e** (0.56 g, 1.89 mmol, 1.0 equiv) and hydrazine hydrate (0.28 g, 0.27 mL, 5.67 mmol, 3.0 equiv) in *n*-BuOH (10 mL)/H_2SO_4 (0.055 g, 5.61 mmol) following the general procedure. *Method b*. The compound was obtained by the same procedure starting from spiro[pyrazino[2,3-*d*]pyridazine-2,3′-pyrazol]-3(4*H*)-one **3e** (0.55 g, 1.61 mmol) in *n*-BuOH (10 mL)/H_2SO_4 (0.023 g, 2.81 mmol) following the general procedure. Yield 0.57 g, (94%) (*Method a*); 0.52 g, (100%) (*Method b*); brown solid; mp 230−231 °C. IR (KBr, cm^{-1}): ν_{max} 3444, 3333, 3212, 3212, 2957,1676, 1641, 1618, 1508, 1449, 1411, 1308, 1254, 1180, 1129, 1113, 1058, 1029, 999, 962, 872, 813, 796, 770, 702, 677, 617, 582, 553, 529, 518. Anal. Calcd. for $C_{15}H_{14}N_8O \cdot H_2O$: C, 52.94; H, 4.74; N, 32.92. Found: C, 52.97; H, 4.77; N, 32.87%. NMR data for **2e**: ^{1}H NMR (500.1 MHz, DMSO-d_6): δ 13.64 (very broad singlet, 1H, NH(6)-IP), 9.36 (brs, 1H, NH(1)-Py), 7.75 (d, J = 8.8 Hz, 2H, H2/H6-Ar), 7.17 (s, 1H, H4-Py), 7.03 (d, J = 8.8 Hz, 2H, H3/H5-Ar), 6.55 (brs, 2H, H_2O), 6.35 (brs, 2H, $NH_2$4-IP), 5.92 (brs, 2H, $NH_2$7-IP), 3.80 (s, 3H, CH_3O-Ar). ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-d_6): δ 160.0 (C4-IP), 159.3 (C4-Ar), 150.9 (C7-IP), 147.8 (C5-Py br), 146.1 (C7a-IP), 145.4 (C3-Py br), 137.6 (C3a-IP), 126.6 (C2/C6-Ar), 123.0 (C1-Ar), 114.4 (C3/C5-Ar), 103.3 (C2-IP), 102.8 (C4-Py), 55.2 (CH_3O-Ar).

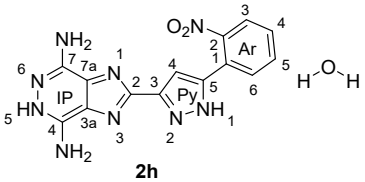




2-(5-(4-Hydroxyphenyl)-1*H*-pyrazol-3-yl)-5*H*-imidazo[4,5-d]pyridazine-4,7-diamine hydrate (2f) and 2-(3-(4-hydroxyphenyl)-1*H*-pyrazol-5-yl)-5*H*-imidazo[4,5-d]pyridazine-4,7-diamine hydrate (2′f) were obtained and characterized as the mixture of regioisomers in percentage ratio 70:30, respectively. *Method a*. The compound was obtained by the same procedure starting from pyrazin-2(1*H*)-one-5,6-dicarbonitrile **1f** (0.53 g, 1.89 mmol, 1.0 equiv) and hydrazine hydrate (0.28 g, 0.27 mL, 5.67 mmol, 3.0 equiv) in *n*-BuOH (10 mL)/H_2SO_4 (0.055 g, 5.61 mmol) following the general procedure. *Method b*. The compound was obtained by the same procedure starting from spiro[pyrazino[2,3-*d*]pyridazine-2,3′-pyrazol]-3(4*H*)-one **3f** (0.53 g, 1.61 mmol) in *n*-BuOH (10 mL)/H_2SO_4 (0.023 g, 2.81 mmol) following the general procedure. Yield 0.50 g, (87%) (*Method a*); 0.46 g, (91%) (*Method b*); brown solid; mp 248−250 °C. IR (KBr, cm^{-1}): ν_{max} 3444, 3325, 3325, 3290, 3205, 1617, 1384, 1251, 1021, 576. Anal. Calcd. for $C_{14}H_{12}N_8O \cdot H_2O$: C, 51.53; H, 4.32; N, 34.34. Found: C, 51.55; H, 4.29; N, 34.37%. NMR data for **2f** and **2′f**: signals from the minor tautomer are shown in square brackets. ^{1}H NMR (500.1 MHz, DMSO-d_6): δ 7.66 [7.65] (d, J = 8.0 Hz, 2H, H2/H6-Ar), 7.06 [6.92] (s, 1H, H4-Py), 6.85 [6.82] (d, J = 8.6 Hz, 2H, H3/H5-Ar), 6.43 (brs, 2H, $NH_2$7-IP), 6.17 (brs, 2H, $NH_2$4-IP), 5.39 (s, 2H H_2O). The signals of (H1-Py) and (NH(6)-IP) have not been observed. ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-d_6): δ 158.5 (C4-IP), 157.5 (C1-Ar), 151.7 (C7-IP), 148.7 [152.5] (C5-Py, br), 148.1 (C7a-IP), 142.3 [142.9] (C3-Py, br), 134.6 (C4a-IP), 126.7 [126.4] (C2/C6-Ar), 121.9 [123.5] (C4-Ar), 115.6 (C3/C5-Ar), 104.3 (C2-IP), 100.6 [99.7] (C4-Py).

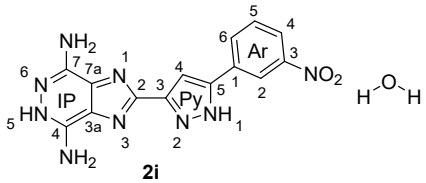


2-(5-(4-Nitrophenyl)-1*H*-pyrazol-3-yl)-5*H*-imidazo[4,5-*d*]pyridazine-4,7-diamine hydrate (2g). *Method a*. The compound was obtained by the same procedure starting from pyrazin-2(1*H*)-one-5,6-dicarbonitrile **1g** (0.58 g, 1.89 mmol, 1.0 equiv) and hydrazine hydrate (0.28 g, 0.27 mL, 5.67 mmol, 3.0 equiv) in *n*-BuOH (10 mL)/H_2SO_4 (0.055 g, 5.61 mmol) following the general procedure. *Method b*. The compound was obtained by the same procedure starting from spiro[pyrazino[2,3-*d*]pyridazine-2,3′-pyrazol]-3(4*H*)-one **3g** (0.57 g, 1.61 mmol) in *n*-BuOH (10 mL)/H_2SO_4 (0.023 g, 2.81 mmol) following the general procedure. Yield 0.52 g, (74%) (*Method a*); 0.45 g, (79%) (*Method b*); brown solid; mp 204−205 °C. IR (KBr, cm^{-1}): ν_{max} 3430, 3330, 3304, 3204, 1656, 1612, 1515, 1450, 1342, 1249, 1181, 1109, 854, 752, 694. Anal. Calcd. for $C_{14}H_{11}N_9O_2 \cdot H_2O$: C, 47.32; H, 3.69; N, 35.48. Found: C, 47.35; H, 3.71; N, 35.45%. NMR data for **2g**: ^{1}H NMR (500.1 MHz, DMSO-d_6): δ 9.60 (brs, 1H, NH(1)-Py), 8.33 (d, J = 8.9 Hz, 2H, H3/H5-Ar), 8.09 (d, J = 8.9 Hz, 2H, H2/H6-Ar), 7.54 (s, 1H, H4-Py), 6.11 (brs, 2H, H_2O), 5.67 (brs, 2H, $NH_2$7-IP), 5.58 (brs, 2H, $NH_2$4-IP). The signal of (NH(6)-IP) has not been observed. ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-d_6): δ 158.5 (C4-IP), 151.7 (C7-IP), 146.6 (C7a-IP), 146.6 (C4-Ar), 146.2 (C5-Py, br), 142.3 (C3-Py, br), 138.1 (C1-Ar), 135.1 (C4a-IP), 125.9 (C2/C6-Ar), 124.4 (C3/C5-Ar), 105.0 (C4-Py), 104.4 (C2-IP).



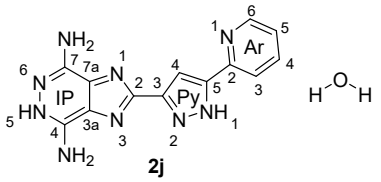
2h

2-(5-(2-Nitrophenyl)-1*H*-pyrazol-3-yl)-5*H*-imidazo[4,5-*d*]pyridazine-4,7-diamine hydrate (2h). *Method a*. The compound was obtained by the same procedure starting from pyrazin-2(1*H*)-one-5,6-dicarbonitrile **1h** (0.58 g, 1.89 mmol, 1.0 equiv) and hydrazine hydrate (0.28 g, 0.27 mL, 5.67 mmol, 3.0 equiv) in *n*-BuOH (10 mL)/H_2SO_4 (0.055 g, 5.61 mmol) following the general procedure. *Method b*. The compound was obtained by the same procedure starting from spiro[pyrazino[2,3-*d*]pyridazine-2,3′-pyrazol]-3(4*H*)-one **3h** (0.57 g, 1.61 mmol) in *n*-BuOH (10 mL)/H_2SO_4 (0.023 g, 2.81 mmol) following the general procedure. Yield 0.47 g, (70%) (*Method a*); 0.5 g, (87%) (*Method b*); brown solid; mp 241−242 °C. IR (KBr, cm^{-1}): ν_{max} 3435, 3309, 3180, 2960, 2873, 1720, 1632, 1568, 1533, 1463, 1314, 1240, 1198, 1044, 949, 784, 587. Anal. Calcd. for $C_{14}H_{11}N_9O_2 \cdot H_2O$: C, 47.32; H, 3.69; N, 35.48. Found: C, 47.37; H, 3.65; N, 35.51%. NMR data for **2h**: ^{1}H NMR (500.1 MHz, DMSO-d_6): δ 12.64 (brs, 1H, NH(1)-Py), 12.52 (very broad singlet, 1H, NH(6)-IP), 8.08 (d, J = 8.0 Hz, 1H, H3-Ar), 7.84 (dd, J = 8.0 Hz, J = 8.0 Hz, 1H, H5-Ar), 7.84 (d, J = 8.0 Hz, 1H, H6-Ar), 7.79 (dd, J = 8.0 Hz, J = 8.0 Hz, 1H, H4-Ar), 6.63 (s, 1H, H4-Py). The signals of ($NH_2$7-IP) and ($NH_2$4-IP) have not been observed. ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-d_6): δ 155.8 (C5-Py), 147.6 (C2-Ar), 144.9 (C7-IP), 144.0 (C4-IP), 134.1 (C3a-IP), 133.8 (C1-Ar), 133.6 (C5-Ar), 132.1 (C4-Ar), 129.2 (C6-Ar), 127.2 (C3-Py br), 124.4 (C3-Ar), 124.3 (C7a-IP), 117.0 (C2-IP), 95.8 (C4-Py).

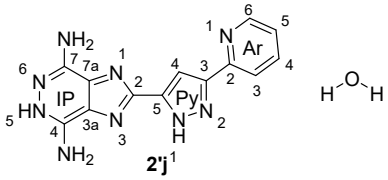


2i

2-(5-(3-Nitrophenyl)-1*H*-pyrazol-3-yl)-5*H*-imidazo[4,5-*d*]pyridazine-4,7-diamine hydrate (2i). *Method a*. The compound was obtained by the same procedure starting from pyrazin-2(1*H*)-one-5,6-dicarbonitrile **1i** (0.58 g, 1.89 mmol, 1.0 equiv) and hydrazine hydrate (0.28 g, 0.27 mL, 5.67 mmol, 3.0 equiv) in *n*-BuOH (10 mL)/H_2SO_4 (0.055 g, 5.61 mmol) following the general procedure. *Method b*. The compound was obtained by the same procedure starting from spiro[pyrazino[2,3-*d*]pyridazine-2,3′-pyrazol]-3(4*H*)-one **3i** (0.57 g, 1.61 mmol) in *n*-BuOH (10 mL)/H_2SO_4 (0.023 g, 2.81 mmol) following the general procedure. Yield 0.53 g, (79%) (Method a); 0.43 g, (76%) (Method b); brown solid; mp 250−251 °C. IR (KBr, cm^{-1}): ν_{max} 3425, 3356, 3204, 2932, 2857, 1675, 1646, 1626, 1526, 1451, 1349, 1312, 1277, 1243, 1199, 1171, 1105, 1071, 1032, 999, 975, 875, 864, 805, 770, 739, 678, 616, 593, 557, 522, 508. Anal. Calcd. for $C_{14}H_{11}N_9O_2 \cdot H_2O$: C, 47.32; H, 3.69; N, 35.48. Found: C, 47.36; H, 3.65; N, 35.52%. NMR data for **2i**: ^{1}H NMR (500.1 MHz, DMSO-d_6): δ 13.74 (very broad singlet, 1H, NH(6)-IP), 9.45 (brs, 1H, NH(1)-Py), 8.63 (s, 1H, H2-Ar), 8.25 (dd, J = 8.0 Hz, J = 1.4 Hz, 1H, H6-Ar), 8.20 (dd, J = 8.0 Hz, J = 1.6 Hz, 1H, H4-Ar), 7.77 (dd, J = 8.0 Hz, J = 8.0 Hz, 1H, H5-Ar), 7.54 (s, 1H, H4-Py), 5.85 (brs, 2H, H_2O), 5.41 (brs, 2H, $NH_2$4-IP), 5.32 (brs, 2H, $NH_2$7-IP). ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-d_6): δ 158.5 (C4-IP), 152.1 (C7-IP), 148.4 (C3-Ar), 146.8 (C7a-IP), 146.2 (C5-Py br), 141.8 (C3-Py br), 134.1 (C3a-IP), 133.4 (C1-Ar), 131.3 (C6-Ar), 130.7 (C5-Ar), 122.4 (C4-Ar), 119.2 (C2-Ar), 105.3 (C2-IP), 104.2 (C4-Py).

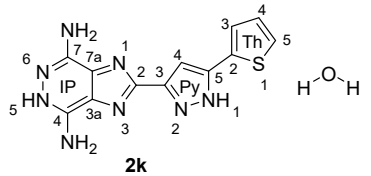


2j

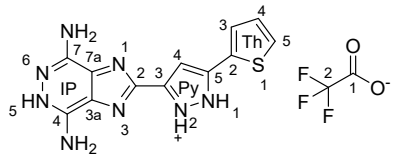


2'j[1]

2-(5-(Pyridin-2-yl)-1*H*-pyrazol-3-yl)-5*H*-imidazo[4,5-*d*]pyridazine-4,7-diamine hydrate (2j) and **2-(3-(pyridin-2-yl)-1*H*-pyrazol-5-yl)-5*H*-imidazo[4,5-*d*]pyridazine-4,7-diamine hydrate (2′j)** were obtained and characterized as the mixture of regioisomers in percentage ratio 50:50, respectively. *Method a*. The compound was obtained by the same procedure starting from pyrazin-2(1*H*)-one-5,6-dicarbonitrile **1j** (0.50 g, 1.89 mmol, 1.0 equiv) and hydrazine hydrate (0.28 g, 0.27 mL, 5.67 mmol, 3.0 equiv) in *n*-BuOH (10 mL)/H_2SO_4 (0.055 g, 5.61 mmol) following the general procedure. *Method b*. The compound was obtained by the same procedure starting from spiro[pyrazino[2,3-*d*]pyridazine-2,3′-pyrazol]-3(4*H*)-one **3j** (0.50 g, 1.61 mmol) in *n*-BuOH (10 mL)/H_2SO_4 (0.023 g, 2.81 mmol) following the general procedure. Yield 0.44 g, (80%) (*Method a*); 0.39 g, (83%) (*Method b*); black solid; mp 313−314 °C. IR (KBr, cm^{-1}): ν_{max} 3440, 3364, 3176, 3330, 3090, 2989, 1655, 1640, 1599, 1568, 1508, 1460, 1440, 1422, 1372, 1341, 1310, 1286, 1192, 1151, 1093, 1073, 1000, 968, 785,745, 726, 687, 625, 576, 497. Anal. Calcd. for $C_{13}H_{11}N_9 \cdot H_2O$: C, 50.16; H, 4.21; N, 40.49. Found: C, 50.20; H, 4.19; N, 40.51%. NMR data for **2j** and **2′j**: signals from the second tautomer are shown in square brackets. ^{1}H NMR (500.1 MHz, DMSO-d_6): δ 13.4 [13.4] (very broad singlet, H, (H1-Py) and (NH(6)-IP)), 8.61 (dd, J = 4.4 Hz, J = 1.5 Hz, 1H, H3-Pyr), 7.98 [7.99] (d, J = 7.2 Hz, 1H, H6-Pyr), 7.83 (dd, J = 7.8 Hz, J = 1.9 Hz, 1H, H5-Pyr), [7.89 (d, J = 7.8 Hz, 1H, H5-Pyr)], 7.30 [7.35] (dd, J = 5.2 Hz, J = 5.2 Hz, 1H, H4-Pyr), 7.24 [7.40, br] (s, 1H, H4-Py), 6.50 (brs, 2H, $NH_2$4-IP), 6.50 (brs, 2H, $NH_2$7-IP), 5.49 (brs, 2H H_2O). ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-d_6): δ 156.6 (C4-IP), 156.1 (C7-IP), 151.5 (C1-Pyr), 149.4 (C3-Pyr), 148.0 (C7a-IP), 146.6 (C3-Py br), 143.7 (C5-Py br), 137.1 (C5-Pyr), 133.8 (C3a-IP), 122.9 (C4-Pyr), 119.9 (C6-Ar), 105.3 (C2-IP), 101.9 (C4-Py).



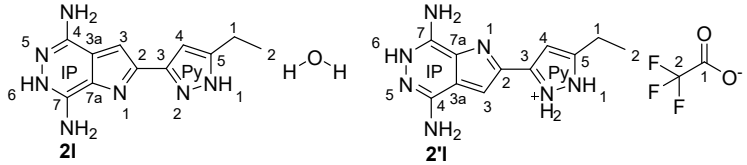
2k



2'k

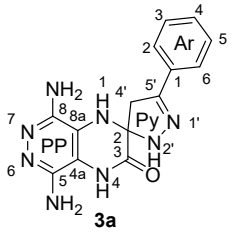
2-(5-(Thien-2-yl)-1*H*-pyrazol-3-yl)-5*H*-imidazo[4,5-*d*]pyridazine-4,7-diamine hydrate (2k) and **3-(4,7-diamino-5*H*-imidazo[4,5-*d*]pyridazin-2-yl)-5-(thiophen-2-yl)-1*H*-pyrazol-2-ium trifluoroacetate (2′k).** *Method a*. The compound was obtained by the same procedure starting from pyrazin-2(1*H*)-one-5,6-dicarbonitrile **1k** (0.51 g, 1.89 mmol, 1.0 equiv) and hydrazine hydrate (0.28 g, 0.27 mL, 5.67 mmol, 3.0 equiv) in *n*-BuOH (10 mL)/H_2SO_4 (0.055 g, 5.61 mmol) following the general procedure. *Method b*. The compound was obtained by the same procedure starting from spiro[pyrazino[2,3-*d*]pyridazine-2,3′-pyrazol]-3(4*H*)-one **3k** (0.51 g, 1.61 mmol) in *n*-BuOH (10 mL)/H_2SO_4 (0.023 g, 2.81 mmol) following the general procedure. Yield 0.55 g, (99%) (*Method a*); 0.35 g, (73%) (*Method b*); brown solid; mp 277−278 °C. IR (KBr, cm^{-1}): ν_{max} 3445, 3312, 3173, 2980, 1617, 1504, 1456, 1408, 1063, 713, 619, 511. Anal. Calcd. for $C_{12}H_{10}N_8S \cdot H_2O$: C, 45.56; H, 3.82; N, 35.42; S, 10.13. Found: C, 45.53; H, 3.87; N, 35.39; S, 10.17%. NMR data for **2k** and **2′k**: in this case, for a clear assignment of signals to the NMR ampoule with the sample three drops of CF_3CO_2H was added. As a result, two sets of signals from the free and N2-Py protonated target compounds appear in the ^{1}H and ^{13}C NMR spectra in a percentage ratio of 50:50, respectively. Data for unprotonated form **2k**: ^{1}H NMR (500.1 MHz, DMSO-d_6): δ 7.87 (d, J = 3.8 Hz, 1H, H3-Th), 7.40 (d, J = 4.9 Hz, 1H, H5-Th), 7.07 (dd, J = 4.9 Hz, J = 3,8 Hz, 1H, H4-Th), 6.91 (s, 1H, H4-Py). The signals of ($NH_2$4-IP), ($NH_2$7-IP), (NH(6)-IP), (H1-Py) and (H_2O) have not been observed. ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-d_6): δ 181.8 (C5-Py), 155.9 (C3-Py), 149.8 (C7-IP), 145.5 (C4-IP), 144.6 (C2-Th), 140.1 (C3a-IP), 134.3 (C5-Th), 131.5 (C3-Th), 128.8 (C4-Th), 117.2 (C2-IP), 115.6 (C7a-IP), 94.0 (C4-Py). Data for protonated form **2′k**: ^{1}H NMR (500.1 MHz, DMSO-d_6): δ 7.97 (d, J = 5.1 Hz, 1H, H3-

Th), 7.42 (d, J = 3.7 Hz, 1H, H5-Th), 7.19 (dd, J = 5.1 Hz, J = 3.7 Hz, 1H, H4-Th), 7.15 (s, 1H, H4-Py). The signals of ($NH_2$4-IP), ($NH_2$7-IP), (NH(6)-IP) and (H1-Py) have not been observed. $^{13}C\{^1H\}$ NMR (125.8 MHz, DMSO-d_6): δ 148.9 (C7-IP), 145.2 (C4-IP), 145.0 (C3-Py), 142.7 (C2-Th), 141.7 (C2-IP), 133.9 (C5-Py), 127.6 (C4-Th), 126.1 (C3a-IP), 125.2 (C3-Th), 124.0 (C5-Th), 115.6 (C7a-IP), 103.6 (C4-Py).

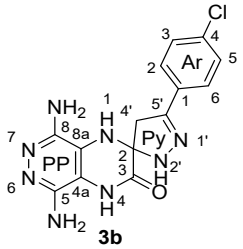


2-(5-Ethyl-1*H*-pyrazol-3-yl)-6*H*-pyrrolo[2,3-*d*]pyridazine-4,7-diamine hydrate (2l) and 3-(4,7-diamino-6*H*-pyrrolo[2,3-*d*]pyridazin-2-yl)-5-ethyl-1*H*-pyrazol-2-ium trifluoroacetate (2′l). *Method a*. The compound was obtained by the same procedure starting from pyrazin-2(1*H*)-one-5,6-dicarbonitrile **1l** (0.41 g, 1.89 mmol, 1.0 equiv) and hydrazine hydrate (0.28 g, 0.27 mL, 5.67 mmol, 3.0 equiv) in *n*-BuOH (10 mL)/H_2SO_4 (0.055 g, 5.61 mmol) following the general procedure. *Method b*. The compound was obtained by the same procedure starting from spiro[pyrazino[2,3-*d*]pyridazine-2,3′-pyrazol]-3(4*H*)-one **3l** (0.42 g, 1.61 mmol) in *n*-BuOH (10 mL)/H_2SO_4 (0.023 g, 2.81 mmol) following the general procedure. Yield 0.31 g, (68%) (*Method a*); 0.37 g, (81%) (*Method b*); brown solid; mp 277−278 °C. IR (KBr, cm^{-1}): ν_{max} 3440, 3369, 3348, 3205, 2974, 1644, 1620, 1516, 1451, 1365, 1246, 1165, 773, 723, 623, 522, 467. Anal. Calcd. for $C_{11}H_{13}N_7 \cdot H_2O$: C, 50.57; H, 5.79; N, 37.53. Found: C, 50.53; H, 5.81; N, 37.57%. NMR data for **2l** and **2′l**: in this case, for a clear assignment of signals to the NMR ampoule with the sample three drops of CF_3CO_2H was added. As a result, two sets of signals from the free and N2-Py protonated target compounds appear in the ^1H and ^{13}C NMR spectra in a percentage ratio of 60:40, respectively. Data for unprotonated form **2l**:^1H NMR (500.1 MHz, DMSO-d_6): δ 6.53 (s, 1H, H4-Py), 2.57 (q, J = 7.5 Hz, 2H, $CH_3\underline{CH_2}$-Py), 1.12 (t, J = 7.7 Hz, 3H, $\underline{CH_3}CH_2$-Py). The signals of ($N(4)H_2$-IP), ($N(7)H_2$-IP), (1H, H1-Py and (H_2O) have not been observed. $^{13}C\{^1H\}$ NMR (125.8 MHz, DMSO-d_6): δ 162.2 (C2-IP), 161.2 (C4-IP), 159.9 (C7-IP), 149.5 (C5-Py), 145.4 (C3-Py), 128.3 (C7a-IP), 105.1 (C4-Py), 91.0 (C3a-IP), 19.7 ($CH_3\underline{CH_2}$-Py), 14.1 ($\underline{C}H_3CH_2$-Py). Data for protonated form **2′l**: ^1H NMR (500.1 MHz, DMSO-d_6): δ 6.49 (s, 1H, H4-Py), 2.56 (q, J = 7.5 Hz, 2H, $CH_3\underline{CH_2}$-Py), 1.11 (t, J = 7.7 Hz, 3H, $\underline{CH_3}CH_2$-Py). The signals of ($N(4)H_2$-IP), ($N(7)H_2$-IP) and (1H, H1-Py) have not been observed. $^{13}C\{^1H\}$ NMR (125.8 MHz, DMSO-d_6): δ 162.2 (C2-IP), 161.2 (C4-IP), 159.9 (C7-IP), 150.2 (C5-Py), 142.0 (C3-Py), 128.3 (C7a-IP), 107.0 (C4-Py), 91.0 (C3a-IP), 19.9 ($CH_3\underline{CH_2}$-Py), 13.9 ($\underline{C}H_3CH_2$-Py).

General Procedure for the Preparation of 5,8-Diamino-5′-aryl(ethyl)-1,4′-dihydrospiro[pyrazino[2,3-*d*]pyridazine-2,3′-pyrazol]-3(4*H*)-ones 3. To a stirred suspension of pyrazin-2(1*H*)-one-5,6-dicarbonitrile **1** (1.89 mmol, 1.0 equiv) in *n*-BuOH (20 mL) a 64% solution of hydrazine hydrate (5.62 mmol, 3.0 equiv) was added at rt. The reaction mixture was stirred for 2 h with heating at reflux. The reaction mixture was allowed to cool to room temperature and precipitate produced was filtered, washed with water (3×5mL), dried in air to give pure product **3a-e**. The filtrate was evaporated to dryness and the resulting residue was crystallized from DMF (5 mL) to afford an additional portion of the product **3a-e**. In the cases of synthesis **3f-l** the reaction mixture was stirred for 12 h. Precipitate produced during the rection was filtered, washed with water (3×5mL), dried in air to give pure product **3f-l**. The filtrate was evaporated to dryness and the resulting residue was crystallized from DMF (5 mL) to afford an additional portion of the product **3f-l**.

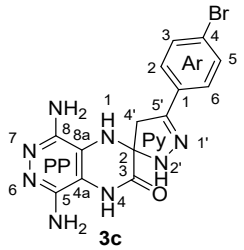


5,8-Diamino-5′-phenyl-1,2′,4,4′-tetrahydro-3*H*-spiro[pyrazino[2,3-*d*]pyridazine-2,3′-pyrazol]-3-one (3a). The compound was obtained by the same procedure starting from pyrazin-2(1*H*)-one-5,6-dicarbonitrile **1a** (0.50 g, 1.89 mmol, 1.0 equiv) and hydrazine hydrate (0.28 g, 0.27 mL, 5.67 mmol, 3.0 equiv) in *n*-BuOH (20 mL) following the general procedure. Yield 0.57 g, (97%); yellow solid; mp 195−196 °C. IR (KBr, cm^{-1}): ν_{max} 3411, 3244, 3160, 3088, 2958, 2928, 2858, 1696, 1666, 1651, 1578, 1522, 1497, 1456, 1384, 1369, 1354, 1312, 1254, 1095, 1045, 989, 865, 790, 768, 727, 695, 661, 586, 471. Anal. Calcd. for $C_{14}H_{14}N_8O$: C, 54.19; H, 4.55; N, 36.11. Found: C, 54.22; H, 4.52; N, 36.09%. NMR data for **3a:** ^{1}H NMR (500.1 MHz, DMSO-d_6): δ 10.41 (s, 1H, NH(4)-PP), 8.25 (s, 1H, NH(2)-Py), 7.68 (dd, J = 7.4 Hz, J = 1.5 Hz,2H, H2/H6-Ar), 7.42 (dd, J = 7.4 Hz, J = 7.4 Hz, 2H, H3/H5-Ar), 7.35 (ddd, J = 7.4 Hz, J = 7.2 Hz, J = 1.2 Hz, 1H, H4-Ar), 7.22 (s, 1H, NH(1)-PP), 5.43 (brs, 2H, $NH_2$5-PP), 5.30 (brs, 2H, $NH_2$8-PP), 4.00 and 3.12 (both d, J = 17.4 Hz, 2H, $CH_2$4-Py). ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-d_6): δ 163.0 (C3-PP), 147.1 (C5-Py), 145.7 (C8-PP), 144.6 (C5-PP), 132.7 (C1-Ar), 128.5 (C3/C5-Ar), 128.3 (C4-Ar), 125.4 (C2/C6-Ar), 117.9 (C8a-PP), 109.7 (C4a-PP), 77.6 (C3-Py), 41.7 (C4-Py). ^{15}N NMR (50.7 MHz, DMSO-d_6): δ 330.0 (N1-Py), 304.2 (N7-PP), 297.6 (N6-PP), 157.7 (N2-Py), 80.9 (N1-PP), 57.4 ($NH_2$8-PP), 55.2 ($NH_2$5-PP). The signal of (N4-PP) has not been observed.



3b

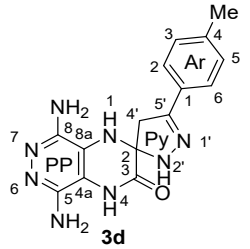
5,8-Diamino-5′-(4-chlorophenyl)-1,4′-dihydrospiro[pyrazino[2,3-*d*]pyridazine-2,3′-pyrazol]-3(4*H*)-one (3b). The compound was obtained by the same procedure starting from pyrazin-2(1*H*)-one-5,6-dicarbonitrile **1b** (0.56 g, 1.89 mmol, 1.0 equiv) and hydrazine hydrate (0.28 g, 0.27 mL, 5.67 mmol, 3.0 equiv) in *n*-BuOH (20 mL) following the general procedure. Yield 0.53 g, (82%); beige solid; mp 238−239 °C. IR (KBr, cm^{-1}): ν_{max} 3317, 3168, 2963, 2872, 1690, 1647, 1619, 1600, 1519, 1498, 1449, 1409, 1377, 1319, 1250, 1095, 1038, 1012, 986, 920, 869, 824, 730, 686, 653, 589, 532, 507. Anal. Calcd. for $C_{14}H_{13}ClN_8O$: C, 48.77; H, 3.80; N, 32.50. Found: C, 48.72; H, 3.75; N, 32.47%. NMR data for **3b**: ^{1}H NMR (500.1 MHz, DMSO-d_6): δ 10.21 (s, 1H, NH(4)-PP), 8.37 (s, 1H, NH(2)-Py), 7.68 (d, J = 8.6 Hz, 2H, H2/H6-Ar), 7.47 (d, J = 8.6 Hz, 2H, H3/H5-Ar), 7.17 (s, 1H, NH(1)-PP), 5.34 (brs, 2H, $NH_2$5-PP), 5.22 (brs, 2H, $NH_2$8-PP), 3.99 and 3.10 (both d, J = 17.6 Hz, 2H, $CH_2$4-Py). ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-d_6): δ 162.9 (C3-PP), 146.0 (C5-PP), 145.7 (C5-Py), 144.7 (C8-PP), 132.6 (C4-Ar), 131.6 (C1-Ar), 128.6 (C3/C5-Ar), 127.0 (C2/C6-Ar), 117.5 (C8a-PP), 109.7 (C4a-PP), 77.8 (C3-Py), 41.6 (C4-Py). ^{15}N NMR (50.7 MHz, DMSO-d_6): δ 330.7 (N1-Py), 308.6 (N7-PP), 297.6 (N6-PP), 160.0 (N2-Py), 81.9 (N1-PP), 56.4 ($NH_2$8-PP), 55.3 ($NH_2$5-PP). The signal of (N4-PP) has not been observed.



3c

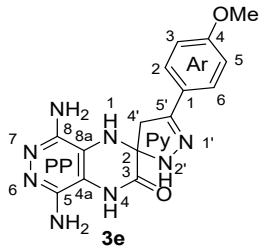
5,8-Diamino-5′-(4-bromophenyl)-1,4′-dihydrospiro[pyrazino[2,3-*d*]pyridazine-2,3′-pyrazol]-3(4*H*)-one (3c). The compound was obtained by the same procedure starting from pyrazin-2(1*H*)-one-5,6-dicarbonitrile **1c** (0.65 g, 1.89 mmol, 1.0 equiv) and hydrazine hydrate (0.28 g, 0.27 mL, 5.67 mmol, 3.0 equiv) in *n*-BuOH (20 mL) following the general procedure. Yield 0.59 g, (80%); beige solid; mp 215−216 °C. IR (KBr, cm^{-1}): ν_{max} 3318, 3169, 2962, 2930, 2868, 1686, 1647, 1618, 1518, 1492, 1447, 1398, 1375, 1317, 1249, 1074, 1008, 986, 920, 867, 820, 728, 670, 587, 530. Anal. Calcd. for $C_{14}H_{13}BrN_8O$: C, 43.20; H, 3.37; N, 28.79. Found: C, 43.25; H, 3.33; N, 28.75%. NMR data for **3c**: ^{1}H NMR (500.1 MHz, DMSO-d_6): δ 10.47 (s, 1H, NH(4)-PP), 8.39 (s, 1H, NH(2)-Py), 7.62 (d, J = 8.4 Hz, 2H, H3/H5-Ar), 7.60 (d, J = 8.6 Hz, 2H, H2/H6-Ar), 7.31 (s, 1H, NH(1)-PP), 5.55 (brs, 2H, $NH_2$5-PP), 5.39 (brs, 2H, $NH_2$8-PP), 3.99 and 3.11 (both d, J = 17.6 Hz, 2H, $CH_2$4-Py). ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-d_6): δ 162.7 (C3-PP),

146.1 (C5-Py), 145.6 (C8-PP), 144.5 (C5-PP), 131.9 (C1-Ar), 131.5 (C3/C5-Ar), 127.3 (C2/C6-Ar), 121.3 (C1-Ar), 118.1 (C8a-PP), 109.8 (C4a-PP), 77.7 (C3-Py), 41.5 (C4-Py). ^{15}N NMR (50.7 MHz, DMSO-d_6): δ 331.4 (N1-Py), 308.6 (N7-PP), 297.6 (N6-PP), 162.6 (N2-Py), 81.4 (N1-PP), 56.2 (N8-PP), 55.6 (N5-PP). The signal of (N4-PP) has not been observed.



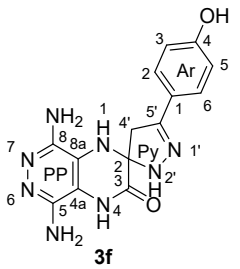
3d

5,8-Diamino-5′-(*p*-tolyl)-1,4′-dihydrospiro[pyrazino[2,3-*d*]pyridazine-2,3′-pyrazol]-3(4*H*)-one (3d). The compound was obtained by the same procedure starting from pyrazin-2(1*H*)-one-5,6-dicarbonitrile **1d** (0.53 g, 1.89 mmol, 1.0 equiv) and hydrazine hydrate (0.28 g, 0.27 mL, 5.67 mmol, 3.0 equiv) in *n*-BuOH (20 mL) following the general procedure. Yield 0.54 g, (89%); gray solid; mp 239−240 °C. IR (KBr, cm^{-1}): ν_{max} 3319, 3166, 2966, 2923, 2871, 1691, 1647, 1619, 1518, 1482, 1449, 1377, 1319, 1250, 1201, 1188, 1092, 987, 920, 871, 816, 729, 686, 674, 583, 534. Anal. Calcd. for $C_{15}H_{16}N_8O$: C, 55.55; H, 4.97; N, 34.55. Found: C, 55.52; H, 4.95; N, 34.52%. NMR data for **3d**: ^{1}H NMR (500.1 MHz, DMSO-d_6): δ 10.21 (s, 1H, NH(4)-PP), 8.13 (s, 1H, NH(2)-Py), 7.57 (d, J = 8.0 Hz, 2H, H2/H6-Ar), 7.22 (d, J = 8.0 Hz, 2H, H3/H5-Ar), 7.14 (s, 1H, NH(1)-PP), 5.33 (brs, 2H, $NH_2$5-PP), 5.22 (brs, 2H, $NH_2$8-PP), 3.97 and 3.08 (both d, J = 17.4 Hz, 2H, $CH_2$4-Py), 2.33 (s, 3H, H4a-Ar). ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-d_6): δ 163.1 (C3-PP), 147.3 (C5-Py), 145.7 (C8-PP), 144.7 (C5-PP), 137.8 (C4-Ar), 130.0 (C1-Ar), 129.1 (C3/C5-Ar), 125.4 (C2/C6-Ar), 117.7 (C8a-PP), 109.7 (C4a-PP), 77.5 (C3-Py), 41.9 (C4-Py), 20.9 (C4a-Ar). ^{15}N NMR (50.7 MHz, DMSO-d_6): δ 326.6 (N1-Py), 308.7 (N7-PP), 297.8 (N6-PP), 158.6 (N2-Py), 81.1 (N1-PP), 56.1 (N8-PP), 56.0 (N5-PP). The signal of (N4-PP) has not been observed.



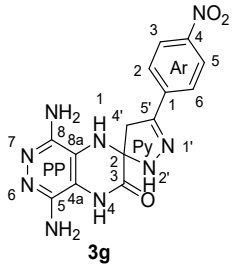
3e

5,8-Diamino-5′-(4-methoxyphenyl)-1,4′-dihydrospiro[pyrazino[2,3-*d*]pyridazine-2,3′-pyrazol]-3(4*H*)-one (3e). The compound was obtained by the same procedure starting from pyrazin-2(1*H*)-one-5,6-dicarbonitrile **1e** (0.56 g, 1.89 mmol, 1.0 equiv) and hydrazine hydrate (0.28 g, 0.27 mL, 5.67 mmol, 3.0 equiv) in *n*-BuOH (20 mL) following the general procedure. Yield 0.60 g, (94%); yellow solid; mp 232−233 °C. IR (KBr, cm^{-1}): ν_{max} 3318, 3170, 2962, 2936, 2838, 1690, 1648, 1611, 1518, 1482, 1450, 1422, 1373, 1354, 1318, 1255, 1177, 1092, 1043, 1021, 986, 918, 871, 828, 747, 686, 674, 584, 540. Anal. Calcd. for $C_{15}H_{16}N_8O_2$: C, 52.94; H, 4.74; N, 32.92. Found: C, 52.92; H, 4.75; N, 32.89%. NMR data for **3e**: ^{1}H NMR (500.1 MHz, DMSO-d_6): δ 10.30 (s, 1H, NH(1)-PP), 8.01 (s, 1H, NH(2)-Py), 7.62 (d, J = 9.9 Hz, 2H, H2/H6-Ar), 7.19 (s, 1H, NH(4)-PP), 6.93 (d, J = 9.9 Hz, 2H, H3/H5-Ar), 5.42 (brs, 2H, $NH_2$5-PP), 5.29 (brs, 2H, $NH_2$8-PP), 3.79 (s, 3H, CH_3-Ar), 3.97 and 3.08 (both d, J = 17.4 Hz, 2H, $CH_2$4-Py). ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-d_6): δ 163.1 (C3-PP), 159.5 (C4-Ar), 147.3 (C5-Py), 145.7 (C5-PP), 144.6 (C8-PP), 126.9 (C2/C6-Ar), 125.3 (C1-Ar), 117.9 (C8a-PP), 114.0 (C3/C5-Ar), 109.8 (C4a-PP), 77.4 (C3-Py), 55.2 (CH3-Ar), 42.0 (C4-Py). ^{15}N NMR (50.7 MHz, DMSO-d_6): δ 324.9 (N1-Py), 305.4 (N7-PP), 157.6 (N2-Py), 80.5 (N4-PP), 56.3 (N8-PP), 48.1 (N5-PP). The signals of (N1-PP) and (N6-PP) have not been observed.



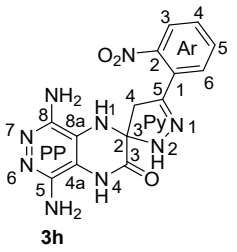
3f

5,8-Diamino-5′-(4-hydroxyphenyl)-1,4′-dihydrospiro[pyrazino[2,3-*d*]pyridazine-2,3′-pyrazol]-3(4*H*)-one (3f). The compound was obtained by the same procedure starting from pyrazin-2(1*H*)-one-5,6-dicarbonitrile **1f** (0.53 g, 1.89 mmol, 1.0 equiv) and hydrazine hydrate (0.28 g, 0.27 mL, 5.67 mmol, 3.0 equiv) in *n*-BuOH (20 mL) following the general procedure. Yield 0.42 g, 67%; brown solid; mp 237-238 °C. IR (KBr, cm^{-1}): ν_{max} 3438, 3411, 3202, 2928, 2882, 2810, 1696, 1652, 1611, 1578, 1520, 1495, 1457, 1411, 1389, 1357, 1311, 1299, 1275, 1255, 1211, 1176, 1096, 1044, 996, 917, 877, 836, 795, 737, 661, 624, 540. Anal. Calcd. for $C_{14}H_{14}N_8O_2$: C, 51.53; H, 4.32; N, 34.34. Found: C, 51.55; H, 4.35; N, 34.31. NMR data for **3f**:^{1}H NMR (500.1 MHz, DMSO-d_6): δ 7.89 (s, 1H, NH(2)-Py), 7.51 (d, J = 8.7 Hz, 2H, H2/H6-Ar), 7.13 (s, 1H, NH(1) PP), 6.80 (d, J = 8.7 Hz, 2H, H3/H5-Ar), 5.33 (brs, 2H, $NH_2$5-PP), 5.24 (brs, 2H, $NH_2$8-PP), 3.93 and 3.04 (both d, J = 17.4 Hz, 2H, $CH_2$4-Py). The signals of (HO-Ar) and (NH(4) PP) have not been observed. ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-d_6): δ 163.2 (C3-PP), 157.9 (C4-Ar), 147.8 (C5-Py), 145.8 (C5-PP), 144.8 (C8-PP), 127.1 (C2/C6-Ar), 123.8 (C1-Ar), 117.8 (C8a-PP), 115.4 (C3/C5-Ar), 109.8 (C4a-PP), 77.4 (C3-Py), 42.1 (C4-Py).



3g

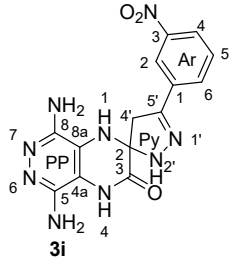
5,8-Diamino-5′-(4-nitrophenyl)-1,4′-dihydrospiro[pyrazino[2,3-*d*]pyridazine-2,3′-pyrazol]-3(4*H*)-one (3g). The compound was obtained by the same procedure starting from pyrazin-2(1*H*)-one-5,6-dicarbonitrile **1g** (0.58 g, 1.89 mmol, 1.0 equiv) and hydrazine hydrate (0.28 g, 0.27 mL, 5.67 mmol, 3.0 equiv) in *n*-BuOH (20 mL) following the general procedure. Yield 0.50 g, (74%); orange solid; mp 223−224 °C. IR (KBr, cm^{-1}): ν_{max} 3334, 1612, 1518, 1452, 1377, 1342, 848, 537. Anal. Calcd. for $C_{14}H_{13}N_9O_3$: C, 47.32; H, 3.69; N, 35.48. Found: C, 47.31; H, 3.72; N, 35.46%. Data for **3g**: ^{1}H NMR (500.1 MHz, DMSO-d_6): δ 8.24 (d, J = 9.0 Hz, 2H, H3/H5-Ar), 7.88 (d, J = 9.0 Hz, 2H, H2/H6-Ar), 6.11 (s, 1H, N(2)H-Py), 5.48 (s, 1H, NH(4) PP), 5.40 (brs, 2H, $NH_2$5-PP), 5.27 (brs, 2H, $NH_2$8-PP), 4.05 and 3.17 (both d, J = 17.6, 2H, $CH_2$4-Py). The signal of (NH(1) PP) has not been observed. ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-d_6): δ 163.3 (C3-PP), 146.4 (C4-Ar), 145.7 (C8-PP), 144.7 (C5-PP), 144.5 (C5-Py), 139.2 (C1-Ar), 125.9 (C2/C6-Ar), 123.9 (C3/C5-Ar), 117.5 (C8a-PP), 109.8 (C4a-PP), 78.2 (C3-Py), 41.1 (C4-Py).



3h

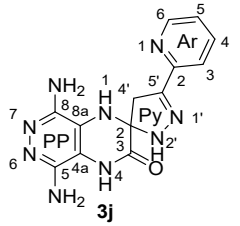
5,8-Diamino-5′-(2-nitrophenyl)-1,4′-dihydrospiro[pyrazino[2,3-*d*]pyridazine-2,3′-pyrazol]-3(4*H*)-one (3h). The compound was obtained by the same procedure starting from pyrazin-2(1*H*)-one-5,6-dicarbonitrile **1h** (0.58 g, 1.89 mmol, 1.0 equiv) and hydrazine hydrate (0.28 g, 0.27 mL, 5.67 mmol, 3.0 equiv) in *n*-BuOH (20 mL) following the general procedure. Yield 0.46 g, (68%); yellow solid; mp 215−25816 °C. IR (KBr, cm^{-1}): ν_{max} 3322, 3174, 1613, 1525, 1392, 1350, 1291, 855, 753, 514. Anal. Calcd. for $C_{14}H_{13}N_9O_3$: C, 47.32; H, 3.69; N, 35.48. Found: C, 47.37; H, 3.65; N, 35.51%. NMR data for **3h**: ^{1}H NMR (500.1 MHz, DMSO-d_6): δ 8.72 (s, 1H, N(2)H-Py), 7.87 (dd, J = 7.9 Hz, J = 1.1 Hz, 1H, H3-Ar),

7.74 (dd, J = 7.9 Hz, J = 1.1 Hz, 1H, H6-Ar), 7.72 (dd, J = 7.9 Hz, J = 7.8 Hz, 1H, H5-Ar), 7.63 (dd, J = 7.9 Hz, J = 1.1 Hz, 1H, H4-Ar), 6.95 (brs, 2H, $NH_2$5-PP), 6.75 (brs, 2H, $NH_2$8-PP), 4.02 and 3.16 (both d, J = 17.6, 2H, $CH_2$4-Py). The signals of (NH(4) PP) and (NH(6) PP) have not been observed. $^{13}C\{^1H\}$ NMR (125.8 MHz, DMSO-d_6): δ164.9 (C3-PP), 153.5 (C8-PP), 150.03 (C5-PP), 149.1 (C8a-PP), 148.5 (C2-Ar), 142.2 (C5-Py), 134.6 (C1-Ar), 132.6 (C5-Ar), 130.3 (C4-Ar), 129.2 (C6-Ar), 124.0 (C6-Ar), 100.3 (C4a-PP), 77.5 (C3-Py), 41.9 (C4-Py).



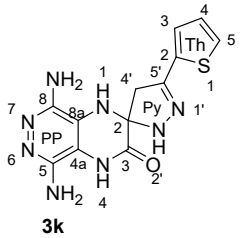
3i

5,8-Diamino-5′-(3-nitrophenyl)-1,4′-dihydrospiro[pyrazino[2,3-*d*]pyridazine-2,3′-pyrazol]-3(4*H*)-one (3i). The compound was obtained by the same procedure starting from pyrazin-2(1*H*)-one-5,6-dicarbonitrile **1i** (0.58 g, 1.89 mmol, 1.0 equiv) and hydrazine hydrate (0.28 g, 0.27 mL, 5.67 mmol, 3.0 equiv) in *n*-BuOH (20 mL) following the general procedure. Yield 0.48 g, (71%); yellow solid; mp 257−258 °C. IR (KBr, cm^{-1}): ν_{max} 3325, 1616, 1526, 1349, 1092, 1061, 808, 738, 679. Anal. Calcd. for $C_{14}H_{13}N_9O_3$: C, 47.32; H, 3.69; N, 35.48. Found: C, 47.30; H, 3.71; N, 35.45%. NMR data for **3i**: ^1H NMR (500.1 MHz, DMSO-d_6): δ8.68 (s, 1H, N(2)H-Py), 8.42 (d, J = 1.7 Hz, 1H, H2-Ar), 8.19 (dd, J = 8.0, J = 1.7 Hz, 1H, H4-Ar), 8.08 (d, J = 8.0 Hz, 1H, H6-Ar), 7.72 (dd, J = 8.0 Hz, J = 8.0 Hz, 1H, H5-Ar), 6.43 (brs, 2H, $NH_2$5-PP), 6.15 (brs, 2H, $NH_2$8-PP), 4.07 and 3.22 (both d, J = 17.7, 2H, $CH_2$4-Py). The signals of (NH(4) PP, and NH(1) PP) havt not been observed. $^{13}C\{^1H\}$ NMR (125.8 MHz, DMSO-d_6): δ161.9 (C3-PP), 148.1 (C3-Ar), 145.5 (C5-Py), 145.2 (C5-PP), 143.6 (C8-PP), 134.2 (C1-Ar), 131.6 (C6-Ar), 130.3 (C5-Ar), 122.7 (C4-Ar), 120.3 (C8a-PP), 119.4 (C2-Ar), 110.0 (C4a-PP), 77.8 (C3-Py), 41.1 (C4-Py).

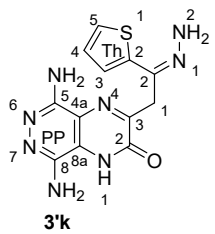


3j

5,8-Diamino-5′-(pyridin-2-yl)-1,4′-dihydrospiro[pyrazino[2,3-*d*]pyridazine-2,3′-pyrazol]-3(4*H*)-one (3j). The compound was obtained by the same procedure starting from pyrazin-2(1*H*)-one-5,6-dicarbonitrile **1j** (0.50 g, 1.89 mmol, 1.0 equiv) and hydrazine hydrate (0.28 g, 0.27 mL, 5.67 mmol, 3.0 equiv) in *n*-BuOH (20 mL) following the general procedure. Yield 0.53 g, (89%); brown solid solid; mp > 400 °C. IR (KBr, cm^{-1}): ν_{max} 3324, 3210, 1615, 1510, 1478, 1454, 1389, 1360, 1323, 1256, 1196, 1152, 1073, 1052, 1032, 997, 917, 872, 781, 743, 669, 623, 592, 544. Anal. Calcd. for $C_{13}H_{13}N_9O$: C, 50.16; H, 4.21; N, 40.49. Found: C, 50.19; H, 4.19; N, 40.45%. NMR data for **3j**: ^1H NMR (500.1 MHz, DMSO-d_6): δ8.61 (s, 1H, NH(2)-Py), 8.58 (d, J = 5.0 Hz, 1H, H3-Ar), 7.89 (d, J = 7.7 Hz, 1H, H6-Ar), 7.80 (ddd, J = 7.4 Hz, J = 7.7 Hz, J = 1.1 Hz, 1H, H5-Ar), 7.33 (ddd, J = 7.4 Hz, J = 5.0 Hz, J = 1.1 Hz, 1H, H4-Ar), 5.35 (brs, 2H, $NH_2$5-PP), 5.22 (brs, 2H, $NH_2$8-PP), 4.03 and 3.21 (both d, J = 18.0 Hz, 2H, $CH_2$4-Py). $^{13}C\{^1H\}$ NMR (125.8 MHz, DMSO-d_6): δ162.9 (C3-PP), 151.8 (C1-Ar), 149.0 (C3-Ar), 148.1 (C5-Py), 145.7 (C5-PP), 144.8 (C8-PP), 136.3 (C5-Ar), 122.9 (C4-Ar), 119.5 (C6-Ar), 117.4 (C8a-PP), 109.8 (C4a-PP), 77.5 (C3-Py), 41.3 (C4-Py).

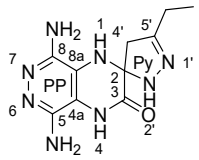


3k



3'k

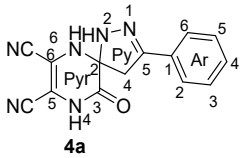
5,8-Diamino-5′-thienyl-1,4′-dihydrospiro[pyrazino[2,3-*d*]pyridazine-2,3′-pyrazol]-3(4*H*)-one (3k) and (*Z*)-5,8-diamino-3-(2-hydrazineylidene-2-(thiophen-2-yl)ethyl)pyrazino[2,3-*d*]pyridazin-2(1*H*)-one (3′k) were obtained and characterized as the mixture of tautomers in percentage ratio 64:36, respectively. The compound was obtained by the same procedure starting from pyrazin-2(1*H*)-one-5,6-dicarbonitrile **1k** (0.51 g, 1.89 mmol, 1.0 equiv) and hydrazine hydrate (0.28 g, 0.27 mL, 5.67 mmol, 3.0 equiv) in *n*-BuOH (20 mL) following the general procedure. Yield 0.52 g, (87%); orange solid solid; mp 275−276 °C. IR (KBr, cm^{-1}): ν_{max} 3314, 3158, 1609, 1507, 1455, 1407, 1353, 1329, 1284, 1062, 709, 515. Anal. Calcd. for $C_{12}H_{12}N_8OS$: C, 45.56; H, 3.82; N, 35.42; S, 10.13. Found: C, 45.59; H, 3.87; N, 35.39; S, 10.17%. NMR data for **3k**: ^{1}H NMR (500.1 MHz, DMSO-d_6): δ 11.0 (s, 1H, NH(1) PP), 10.21 (brs, 1H, NH(4)-PP), 8.23 (s, 1H, NH(2)-Py), 7.72 (d, J = 4.6 Hz, 1H, H5-Th), 7.64 (brs, 1H, H3-Th), 7.16 (dd, J = 4.9 Hz, J = 3,8 Hz, 1H, H4-Th), 6.62 (brs, 2H, $NH_2$5-PP), 6.24 (brs, 2H, $NH_2$8-PP), 4.02 and 3.16 (both d, J = 17.5 Hz, 2H, $CH_2$4-Py). ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-d_6): δ 162.2 (C3-PP), 143.9 (C5-PP), 143.9 (C8-PP), 143.6 (C5-Py), 143.4 (C2-Th), 132.7 (C5-Th), 128.5 (C4-Th), 128.4 (C8a-PP), 127.7 (C3-Th), 110.1 (C4a-PP), 77.5 (C3-Py), 42.5 (C4-Py). NMR data for **3′k**: ^{1}H NMR (500.1 MHz, DMSO-d_6): δ 8.07 (dd, J = 3.8 Hz, J = 1.1 Hz, 1H, H3-Th), 7.99 (dd, J = 4.9 Hz, J = 1.1 Hz, 1H, H5-Th), 7.25 (dd, J = 4.9 Hz, J = 3.8 Hz, 1H, H4-Th), 6.42 (s, 1H, (N(1)H)), 5.95 (brs, 2H, NH_2), 4.35 (s, 2H, Hα-Sp). ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-d_6): δ 189.1 (Cα-Sp), 166.3 (C2-PP), 156.2 (C3-PP), 145.2 (C2-Th), 134.7 (C5-Th), 133.7 (C3-Th), 128.7 (C4-Th), 121.4 (C5-PP), 120.1 (C6-PP), 116.1 (C5-PP), 115.5 (C8-PP), 44.9 (Cα-Sp).



3l

5,8-Diamino-5′-(ethyl)-1,4′-dihydrospiro[pyrazino[2,3-*d*]pyridazine-2,3′-pyrazol]-3(4*H*)-one (3l). The compound was obtained by the same procedure starting from pyrazin-2(1*H*)-one-5,6-dicarbonitrile **1l** (0.41 g, 1.89 mmol, 1.0 equiv) and hydrazine hydrate (0.28 g, 0.27 mL, 5.67 mmol, 3.0 equiv) in *n*-BuOH (20 mL) following the general procedure. Yield 0.46 g, 91%; light-brown solid; mp 231-232 °C. IR (KBr, cm^{-1}): ν_{max} 3314, 3203, 2972, 2937, 2878, 1699, 1618, 1509, 1458, 1378, 1326, 1259, 1201, 1154, 1106, 1063, 1049, 988, 914, 870, 816, 729, 680, 658, 602, 572, 561, 514. Anal. Calcd. for $C_{10}H_{14}N_8O$: C, 45.80; H, 5.38; N, 42.72. Found: C, 45.83; H, 5.33; N, 42.78. NMR data for **3l**: ^{1}H NMR (500.1 MHz, DMSO-d_6): δ 8.09 (s, 1H, H N(4) PP), 7.46 (s, 1H, NH(2)-Py), 6.61 (brs, 2H, $NH_2$5-PP), 6.40 (brs, 2H, $NH_2$8-PP), 3.62 and 2.73 (both d, J = 17.7 Hz, 2H, $CH_2$4-Py), 2.30 (q, J = 7.5 Hz, 2H, $CH_3\underline{CH_2}$-Py), 1.10 (t, J = 7.5 Hz, 3H, $\underline{CH_3}CH_2$-Py). The signal of (HN(1)PP) has not been observrd. ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-d_6): δ 162.4 (C3-PP), 153.1 (C5-Py), 145.1 (C5-PP), 143.1 (C8-PP), 121.4 (C8a-PP), 110.0 (C4a-PP), 76.8 (C3-Py), 43.8 (C4-Py), 22.7 (C5a-Py), 10.7 (C5b-Py).

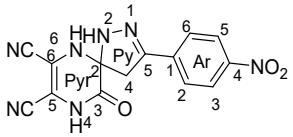
General Procedure for the Preparation of 5′-Aryl-1,4′-dihydrospiro[pyrazine-2,3′-pyrazol]-3(4*H*)-one-5,6-dicarbonitrile. To a stirred suspension of pyrazin-2(1*H*)-one-5,6-dicarbonitriles **1** (1.89 mmol, 1.0 equiv) in *n*-BuOH (20 mL) a 64% solution of hydrazine hydrate (1.9 mmol, 1.0 equiv) was added at rt. The reaction mixture was stirred for 12 h. Precipitate produced during the rection was filtered, washed with water (3×5mL), dried in air to give pure product **4**. The filtrate was evaporated to dryness to afford an additional portion of the product **4**. In the case of the synthesis **4c** EtOH was used as solvent instead of *n*-BuOH.



4a

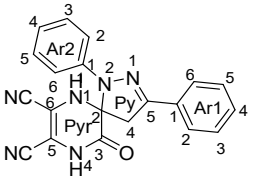
5′-Phenyl-1,4′-dihydrospiro[pyrazine-2,3′-pyrazol]-3(4*H*)-one-5,6-dicarbonitrile (4a). The compound was obtained by the same procedure starting from pyrazin-2(1*H*)-one-5,6-dicarbonitrile **1a** (0.5 g, 1.89 mmol, 1.0 equiv) in *n*-BuOH (20 mL) a 64% solution of hydrazine hydrate (0.09 g, 0.08 mL, 1.89 mmol, 1.0 equiv) following the general procedure. Yield 0.48 g, 90%; light-brown solid; mp 218−219 °C.

IR (KBr, cm^{-1}): ν_{max} 3325, 3185, 3081, 2914, 2776, 2225, 1698, 1636, 1599,1572, 1528, 1492, 1446, 1411, 1378, 1355, 1297, 1249, 1198, 1002, 875, 865, 828, 785, 754, 741, 691, 665, 632, 594, 544, 483. Anal. Calcd. for $C_{14}H_{10}N_6O$: C, 60.43; H, 3.62; N, 30.20. Found: C, 60.39; H, 3.65; N, 30.23. NMR data for **4a**: ^{1}H NMR (500.1 MHz, DMSO-d_6): δ 11.30 (s, 1H, N(4)H-Pyr), 9.52 (brs, 1H, N(2)H-Py), 8.98 (s, 1H, H1-Pyr), 7.65 (dd, J = 8.0 Hz, J = 1.3 Hz, 2H, H2/H6-Ar), 7.41 (dd, J = 8.0 Hz, J = 8.0 Hz, 2H, H3/H5-Ar), 7.36 (dd, J = 8.0 Hz, J = 7.9 Hz, 1H, H4-Ar), 3.87 and 3.05 (both d, J = 17.6 Hz, 2H, $CH_2$4-Py). ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-d_6): δ 160.1 (C3-Pyr), 148.0 (C5-Py), 132.2 (C1-Ar), 128.6 (C4-Ar), 128.5 (C3/C5-Ar), 125.6 (C2/C6-Ar), 113.1 (C5a-Pyr), 112.6 (C6a-Pyr), 110.6 (C6-Pyr), 98.3 (C5-Pyr), 77.0 (C2-Pyr/C3-Py), 40.8 (C4-Py). ^{15}N NMR (50.7 MHz, DMSO-d_6): δ 328.2 (N1-Py), 129.4 (N4-Pyr), 107.6 (N2-Py), 96.6 (N1-Pyr). The signals of (CN5-Pyr), (CN6-Pyr) have not been observed.



4b

5′-Nitrophenyl-1,4′-dihydrospiro[pyrazine-2,3′-pyrazol]-3(4*H*)-one-5,6-dicarbonitrile (4b). The compound was obtained by the same procedure starting from pyrazin-2(1*H*)-one-5,6-dicarbonitrile **1g** (0.58 g, 1.89 mmol, 1.0 equiv) in *n*-BuOH (20 mL) a 64% solution of hydrazine hydrate (0.09 g, 0.08 mL, 1.89 mmol, 1.0 equiv) following the general procedure. Yield 0.57 g, 94%; red solid; mp 271−272 °C. IR (KBr, cm^{-1}): ν_{max} 3424, 3063, 2907, 2227, 1694, 1619, 1585, 1541, 1528, 1483, 1458, 1447, 1351, 1250, 1208, 1156, 1051, 816, 780, 691, 659, 631. Anal. Calcd. for $C_{14}H_9N_7O_3$: C, 52.02; H, 2.81; N, 30.33. Found: C, 51.91; H, 2.83; N, 30.39. NMR data for **4b**: ^{1}H NMR (500.1 MHz, DMSO-d_6): δ 14.18 (s, 1H, N(2)H-Py), 11.39 (s, 1H, H1-Pyr), 9.02 (s, 1H, H1-Pyr), 8.25 (d, J = 9.0 Hz, *2*H, H3/H5-Ar), 7.87 (d, J = 9.0 Hz, *2*H, H2/H6-Ar), 3.93 and 3.11 (both d, J = 17.8 Hz, 2H, $CH_2$4-Py). ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-d_6): δ 159.8 (C3-Pyr), 146.7 (C4-Ar), 145.7 (C5-Py), 138.7 (C1-Ar), 126.3 (C2/C6-Ar), 124.4 (C3/C5-Ar), 113.0 (CN5-Pyr), 112.6 (CN6-Pyr), 110.4 (C6-Pyr), 98.5 (C5-Pyr), 77.5 (C2-Pyr/C3-Py), 40.3 (C4-Py).

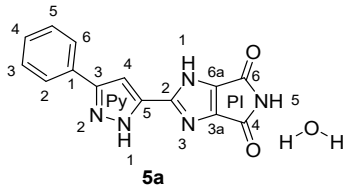


4c

2′,5′-Diphenyl-1,4′-dihydrospiro[pyrazine-2,3′-pyrazol]-3(4*H*)-one-5,6-dicarbonitrile 4c. To a stirred suspension of pyrazin-2(1*H*)-one-5,6-dicarbonitrile **1a** (0.5 g, 1.89 mmol, 1.0 equiv) in EtOH (20 mL) a phenyl hydrazine (0.20 g, 0.18 mL, 1.89 mmol, 1.0 equiv) was added at rt. The reaction mixture was stirred for 12 h. The reaction mixture filtrate was evaporated to dryness to afford pure product **4c**. Yield 0.66 g, 98%; red solid; mp 255−256 °C. IR (KBr, cm^{-1}): ν_{max} 3426, 3066, 2901, 2230, 1698, 1623, 1596, 1584, 1543, 1509, 1481, 1458, 1439, 1352, 1253, 1205, 1159, 1055, 816, 782, 698, 662, 638. Anal. Calcd. for $C_{20}H_{14}N_6O$: C, 67.79; H, 3.98; N, 23.72. Found: C, 67.81; H, 3.95; N, 23.69. NMR data for **4c**: ^{1}H NMR (500.1 MHz, DMSO-d_6): δ 11.50 (s, 1H, H4-P), 9.10 (s, 1H, H1-P), 7.74 (dd, J = 8.0 Hz, J = 1.3 Hz, 2H, H2/H6-Ar), 7.47 (dd, J = 8.0 Hz, J = 8.0 Hz, 2H, H3/H5-Ar), 7.43 (dd, J = 8.0 Hz, J = 8.0 Hz, 1H, H4-Ar), 7.36 (dd, J = 8.0 Hz, J = 8.0 Hz, 2H, H3/H5-Ar2), 7.16 (dd, J = 8.0 Hz, J = 8.0 Hz, 1H, H4-Ar2), 7.14 (dd, J = 8.0 Hz, J = 1.3 Hz, 2H, H2/H6-Ar2), 4.08 and 3.54 (both d, J = 17.9 Hz, 2H, $CH_2$4-Py). ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-d_6): δ 160.8 (C3-P), 147.7 (C5-Py), 142.4 (C1-Ar2), 131.5 (C1-Ar), 129.3 (C4-Ar), 129.0 (C3/C5-Ar2), 128.7 (C3/C5-Ar), 125.8 (C2/C6-Ar), 123.6 (C4-Ar2), 119.3 (C2/C6-Ar2), 112.5 (C5a-P), 111.7 (C6a-P), 110.5 (C6-P), 96.5 (C5-P), 80.7 (C2-P/C3-Py), 46.6 (C4-Py). ^{15}N NMR (50.7 MHz, DMSO-d_6): δ 327.1 (N1-Py), 170.7 (N2-Py), 131.1 (N4-P), 92.9 (N1-P). The signals of (CN5-Pyr), (CN6-Pyr) have not been observed.

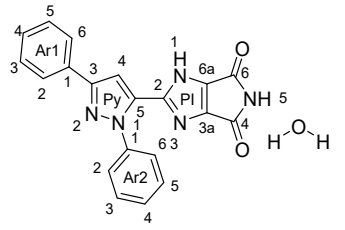
General Procedure for the Preparation of 2-(3-Phenyl(and 1,3-diphenyl)-1*H*-pyrazol-5-yl)pyrrolo[3,4-*d*]imidazol-4,6(1*H*,5*H*)-dione hydrates 5a,b. To a stirred suspension of pyrazin-

2(1*H*)-one-5,6-dicarbonitriles **4** (1.8 mmol) in *n*-BuOH (5 mL) was added 0.055 g (5.61 mmol) of concentrated H_2SO_4 at rt. The reaction mixture was stirred with heating at reflux for 6 h. The reaction mixture was allowed to cool to room temperature and precipitate produced was filtered, washed with washed with 5% $NaHCO_3$ solution, dried in air to give pure product **5**. The filtrate was evaporated to dryness and the resulting residue was washed with washed with 5% $NaHCO_3$ solution, to afford an additional portion of the product **5**.



5a

2-(3-Phenyl-1*H*-pyrazol-5-yl)pyrrolo[3,4-*d*]imidazol-4,6(1*H*,5*H*)-dione hydrate (5a). The compound was obtained by the same procedure starting from 5′-phenyl-1,4′-dihydrospiro[pyrazine-2,3′-pyrazol]-3(4*H*)-one-5,6-dicarbonitrile **4a** (0.5 g, 1.8 mmol) in *n*-BuOH (10 mL)/H_2SO_4 (0.055 g, 5.61 mmol) following the general procedure. Yield 0.50 g, 100%; brown solid; mp 273-275 °C. IR (KBr): ν_{max} 3451, 3356, 3339, 3263, 1787, 1677, 1652, 1559, 1544, 1485, 1466, 1374, 1360, 1265, 1196, 992, 962, 851, 820, 770, 748, 692, 671, 651, 634, 453, 424. Anal. Calcd. for $C_{14}H_9N_5O_2$: C, 60.21; H, 3.25; N, 25.08. Found: C, 60.19; H, 3.28; N, 25.15. NMR data for **5a**: ^{1}H NMR (500.1 MHz, DMSO-d_6): δ 13.83 (brs, 1H, NH(5)-PI), 10.30 (s, 1H, NH(1)-PI), 7.81 (d, J = 7.4 Hz, 2H, H2/H6-Ar1), 7.47 (dd, J = 7.4 Hz, J = 7.4 Hz, 2H, H3/H5-Ar), 7.38 (dd, J = 7.4 Hz, J = 7.4 Hz, 1H, H4-Ar1), 7.20 (brs, 1H, H4-Py), 6.60(brs, 2H, H_2O). ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-d_6): δ 169.8 (C6-PI), 168.0 (C4-PI), 156.6 (C6a-PI), 146.6 (C3-Py), 144.1 (C5-Py), 136.1 (C3a-PI), 133.1 (C1-Ar1), 129.0 (C3/C5-Ar1), 128.5 (C4-Ar1), 125.3 (C2/C6-Ar1), 103.0 (C4-Py), 99.6 (C2-PI).



5b

2-(1,3-Diphenyl-1*H*-pyrazol-5-yl)pyrrolo[3,4-*d*]imidazol-4,6(1*H*,5*H*)-dione hydrate (5b). The compound was obtained from 2′,5′-diphenyl-1,4′-dihydrospiro[pyrazine-2,3′-pyrazol]-3(4*H*)-one-5,6-dicarbonitrile **4c** (0.64 g, 1.8 mmol) in *n*-BuOH (10 mL)/H_2SO_4 (0.055 g, 5.61 mmol) following the general procedure. Yield 0.53 g, 83%; yellow solid; mp 229-230 °C. IR (KBr, cm^{-1}): ν_{max} 3318, 1775, 1723, 1659, 1563, 1540, 1524, 1497, 1459, 1366, 1287, 1257, 850, 769, 743, 693. Anal. Calcd. for $C_{20}H_{13}N_5O_2$: C, 67.60; H, 3.69; N, 19.71. Found: C, 67.53; H, 3.72; N, 19.76%. NMR data for **5b**:^{1}H NMR (500.1 MHz, DMSO-d_6): δ 10.28 (s, 1H, NH(5)-PI), 9.81 (s, 1H, NH(1)-PI), 7.86 (d, J = 7.4 Hz, 2H, H2/H6-Ar1), 7.56 (s, 1H, H4-Py), 7.55 (d, J = 7.8 Hz, 2H, H2/H6-Ar2), 7.48 (dd, J = 8.0 Hz, J = 7.4 Hz, 4H, H3/H5-Ar1 and H3/H5-Ar2), 7.42 (dd, J = 7.8 Hz, J = 7.8 Hz, 1H, H4-Ar2), 7.39 (dd, J = 7.4 Hz, J = 7.4 Hz, 1H, H4-Ar1), 6.66 (brs, 2H, H_2O). ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-d_6): δ 169.6 (C6-Pi), 167.6 (C4-Pi), 157.3 (C6a-PI), 150.2 (C3-Py), 140.1 (C1-Ar2), 139.4 (C3a-Pi), 137.5 (C5-Py), 132.1 (C1-Ar1), 128.9 (C3/C5-Ar2), 128.6 (C3/C5-Ar1), 128.3 (C4-Ar2), 127.8 (C4-Ar1), 125.2 (C2/C6-Ar2), 124.8 (C2/C6-Ar1), 107.1 (C4-Py), 98.2 (C2-Pi). ^{15}N NMR (50.7 MHz, DMSO-d_6): δ 311.0 (N1-Py), 219.4 (N2-Py), 139.1 (N5-Pi), 113.3 (N1-Pi), 73.5 (N3-Pi).

General Procedure for the Preparation of 2-(5-Aryl)-1*H*-pyrazol-3-yl)-5*H*-imidazo[4,5-*d*]pyridazine-4,7-diamine hydrates 2a,g from Spiro[pyrazino[2,3-*d*]pyridazine-2,3′-pyrazol]-3(4*H*)-ones 4a,b. To a stirred suspension of pyrazin-2(1*H*)-one-5,6-dicarbonitrile **4a,b** (1.8 mmol, 1.0 equiv) and 64% solution of hydrazine hydrate (0.28 g, 0.27 mL, 5.67 mmol, 3.0 equiv) in *n*-BuOH (10 mL) was added 0.055 g (5.61 mmol) of concentrated H_2SO_4 at rt. The reaction mixture was stirred with heating at reflux for 6 h. The reaction mixture was allowed to cool to room temperature and precipitate produced was filtered, washed with washed with 5% $NaHCO_3$ solution, dried in air to give pure product **2a,g**. The filtrate was evaporated to dryness and the resulting residue was washed with washed with 5% $NaHCO_3$ solution, to afford an additional portion of the product **2a,g**.

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2) Ş. H. Üngören, E. Dilekoğlu, İ. Koca, Synthesis of Pyrazine-2,3-dicarbonitrile and 1,2,4-triazine-5(4*H*)-one derivatives from furan-2,3-diones, *Chinese Chemical Letters*, 2013, **24**, 1130–1133.

3) D. D. Nekrasov, S. V. Koltsova, Yu. S. Andreichikov, Vzaimodeistvie Reacting 5-aryl-2,3-dihydrofuran-2,3-diones and N- and C-substituted nitrilamins, *Russ. Jour. Org.Chem.*, 1995, **31**, 591–594.

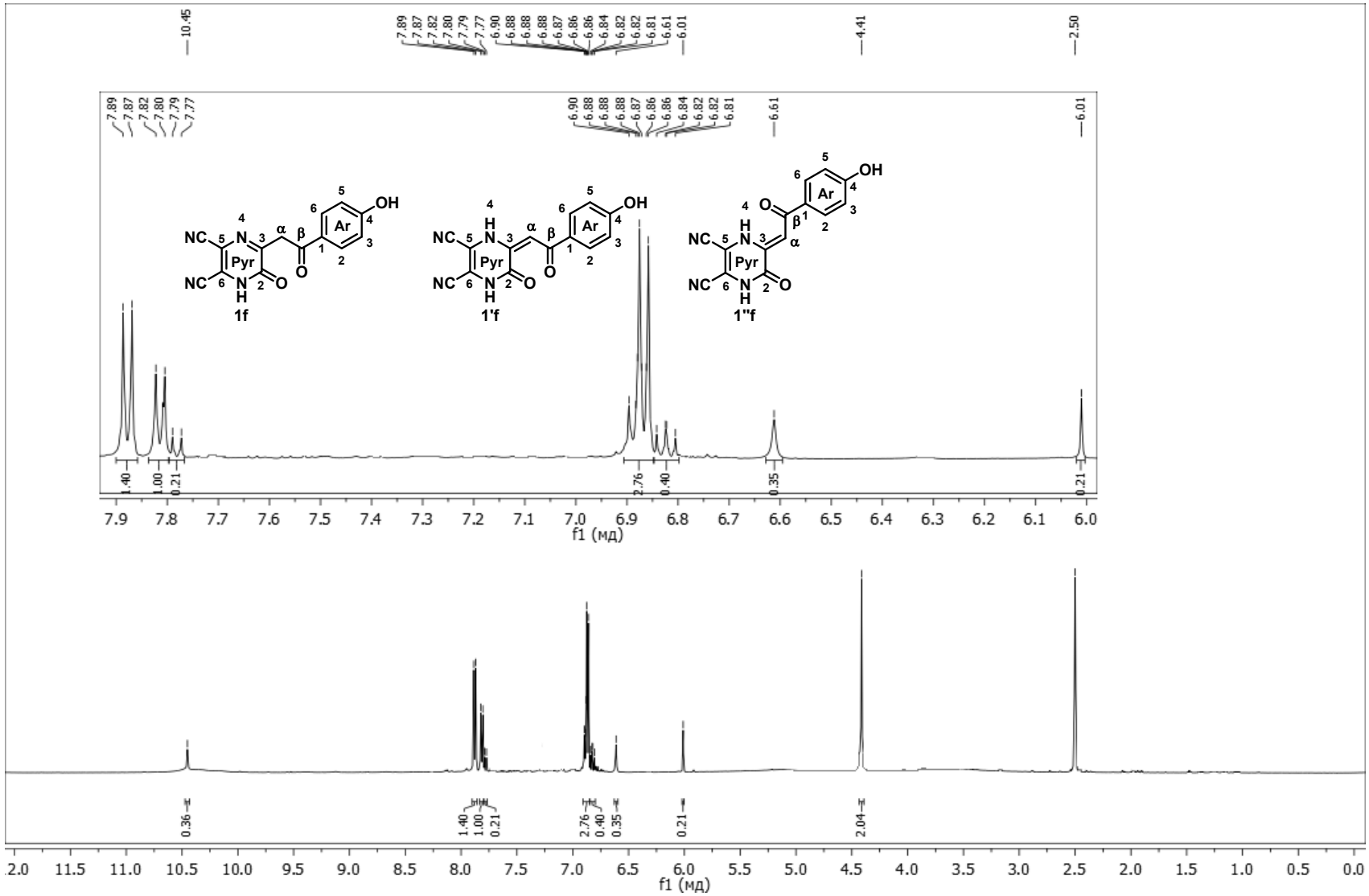

Figure S1. 1D ^{1}H NMR spectrum of **1f**, **1′f** and **1′′f** in DMSO-d_6 at T = 303 K. Chemical shifts are given in ppm (Bruker spectrometer at 500.1 MHz).

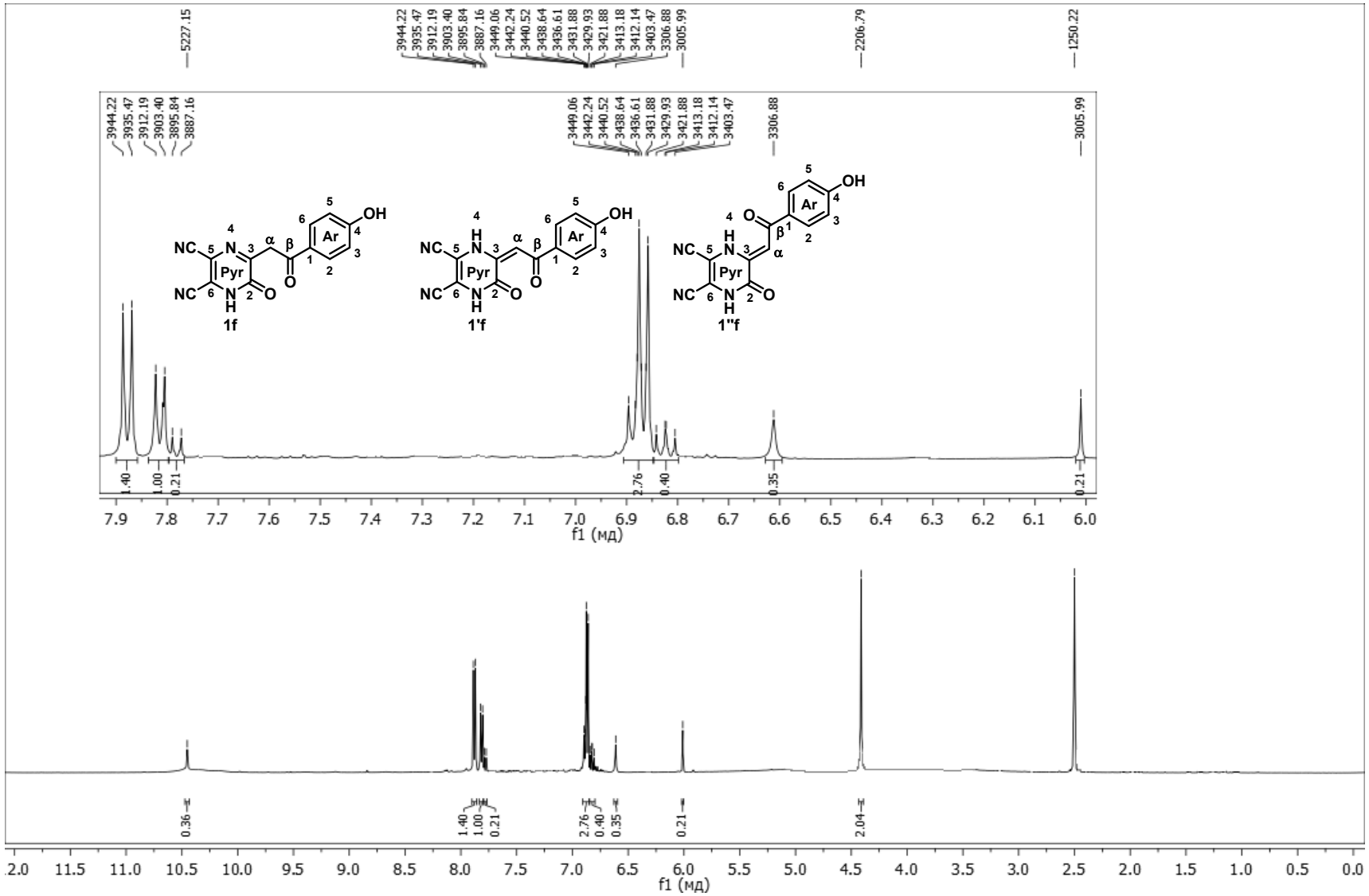

Figure S2. 1D ^{1}H NMR spectrum of **1f**, **1′f** and **1′′f** in DMSO-d_6 at T = 303 K. Chemical shifts are given in Hz (Bruker spectrometer at 500.1 MHz).

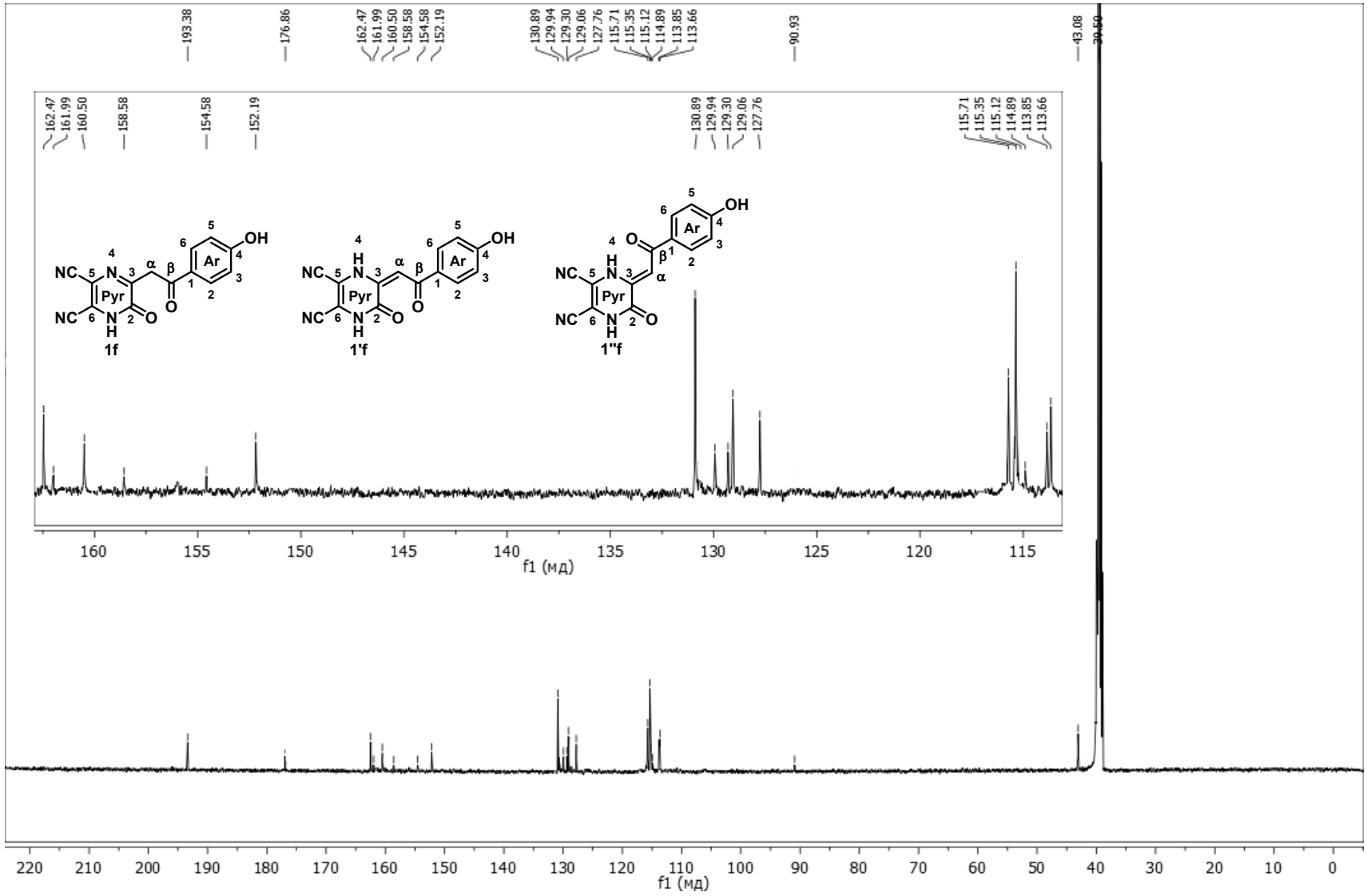

Figure S3. $^{13}C\{^{1}H\}$ NMR spectrum of **1f**, **1′f** and **1′′f** in DMSO-d_6 at T = 303 K (Bruker spectrometer at 125.7 MHz).

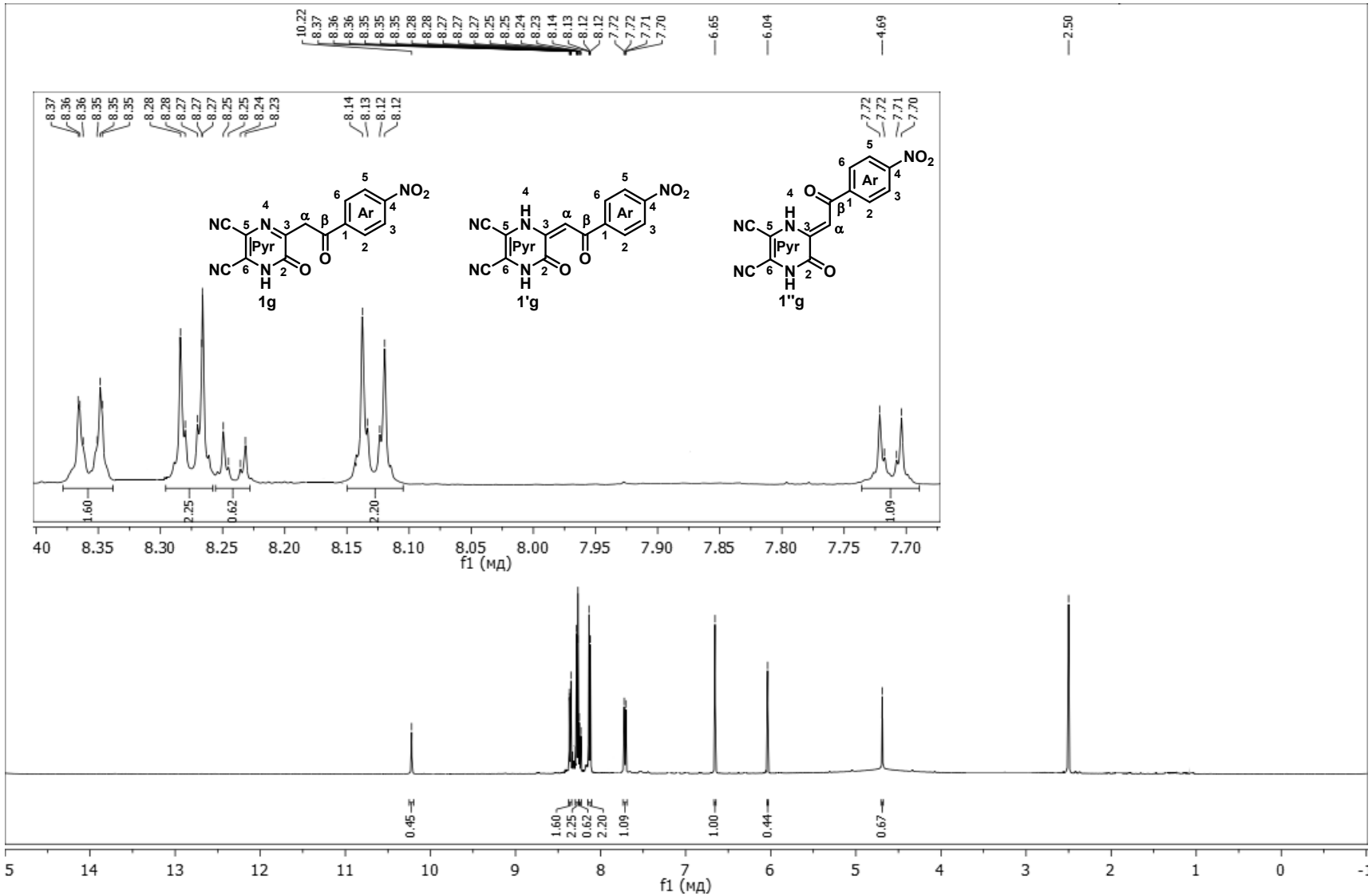

Figure S4. 1D ^{1}H NMR spectrum of **1g**, **1′g** and **1′′g** in DMSO-d_6 at T = 303 K. Chemical shifts are given in ppm (Bruker spectrometer at 500.1 MHz).

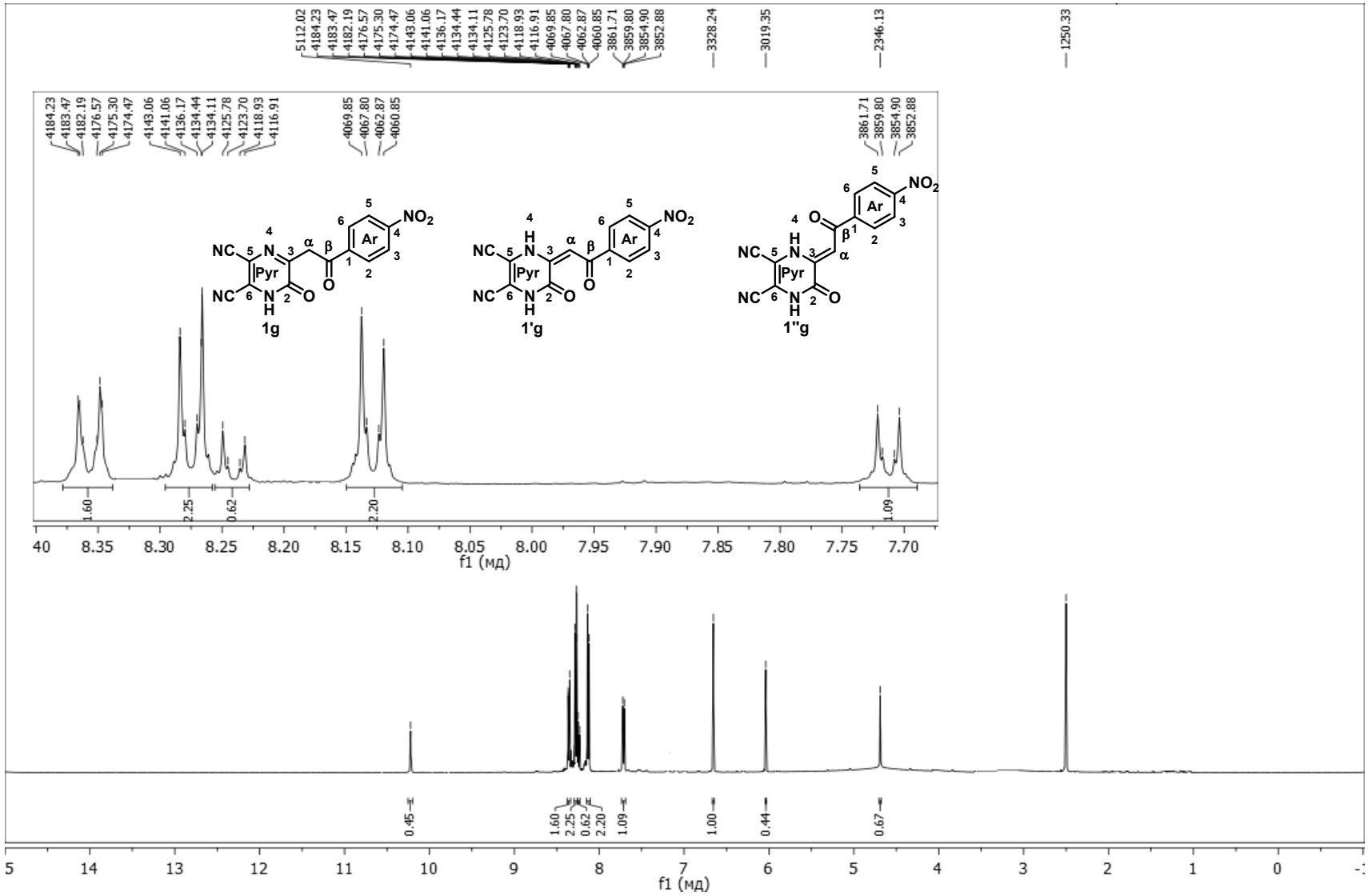

Figure S5. 1D ^{1}H NMR spectrum of **1g**, **1′g** and **1′′g** in DMSO-d_6 at T = 303 K. Chemical shifts are given in Hz (Bruker spectrometer at 500.1 MHz).

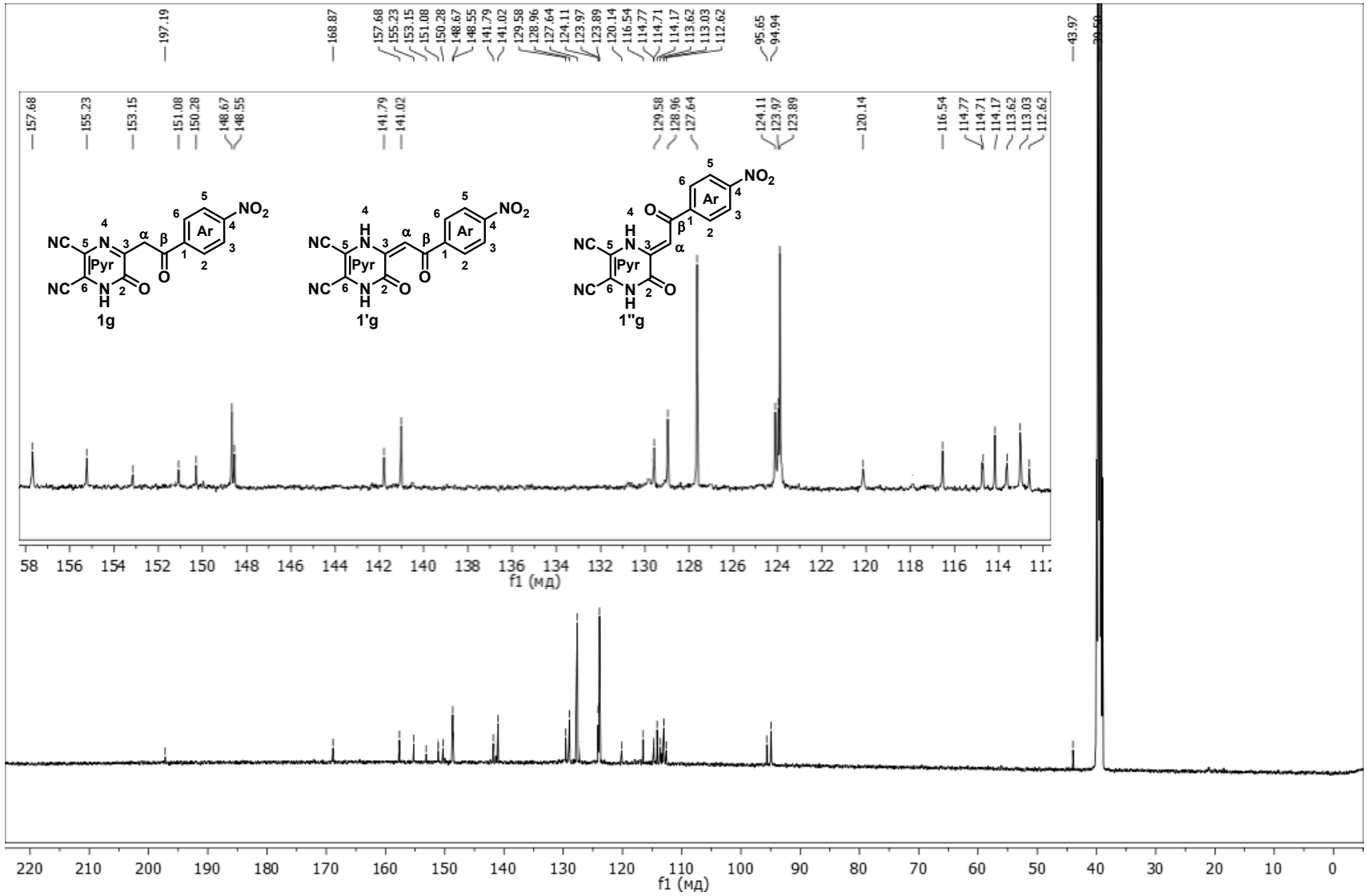

Figure S6. $^{13}C\{^{1}H\}$ NMR spectrum of **1g**, **1′g** and **1′′g** in DMSO-d_6 at T = 303 K (Bruker spectrometer at 125.7 MHz).

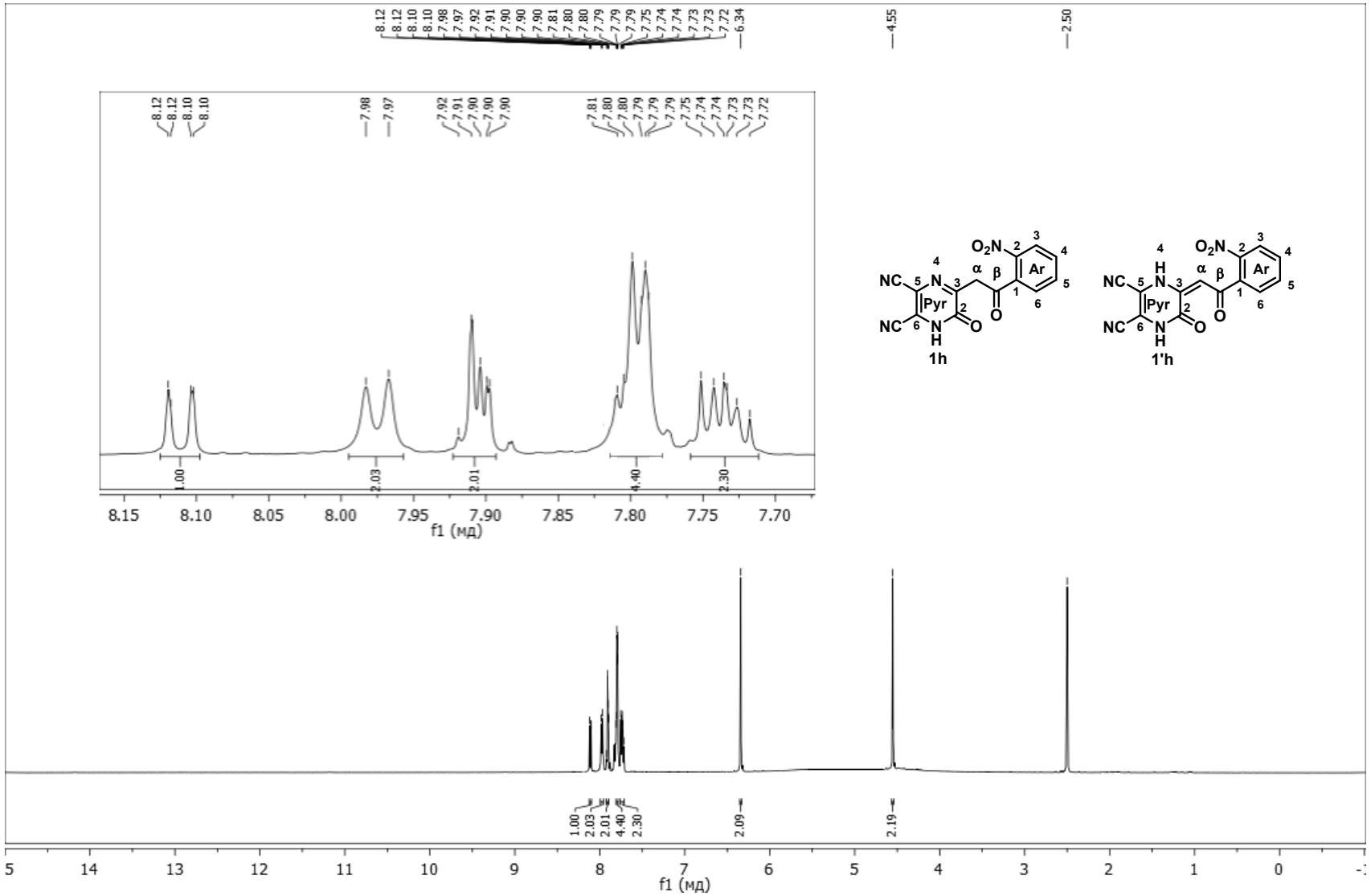

Figure S7. 1D ^{1}H NMR spectrum of of **1h** and **1′h** in DMSO-d_6 at T = 303 K. Chemical shifts are given in ppm (Bruker spectrometer at 500.1 MHz).

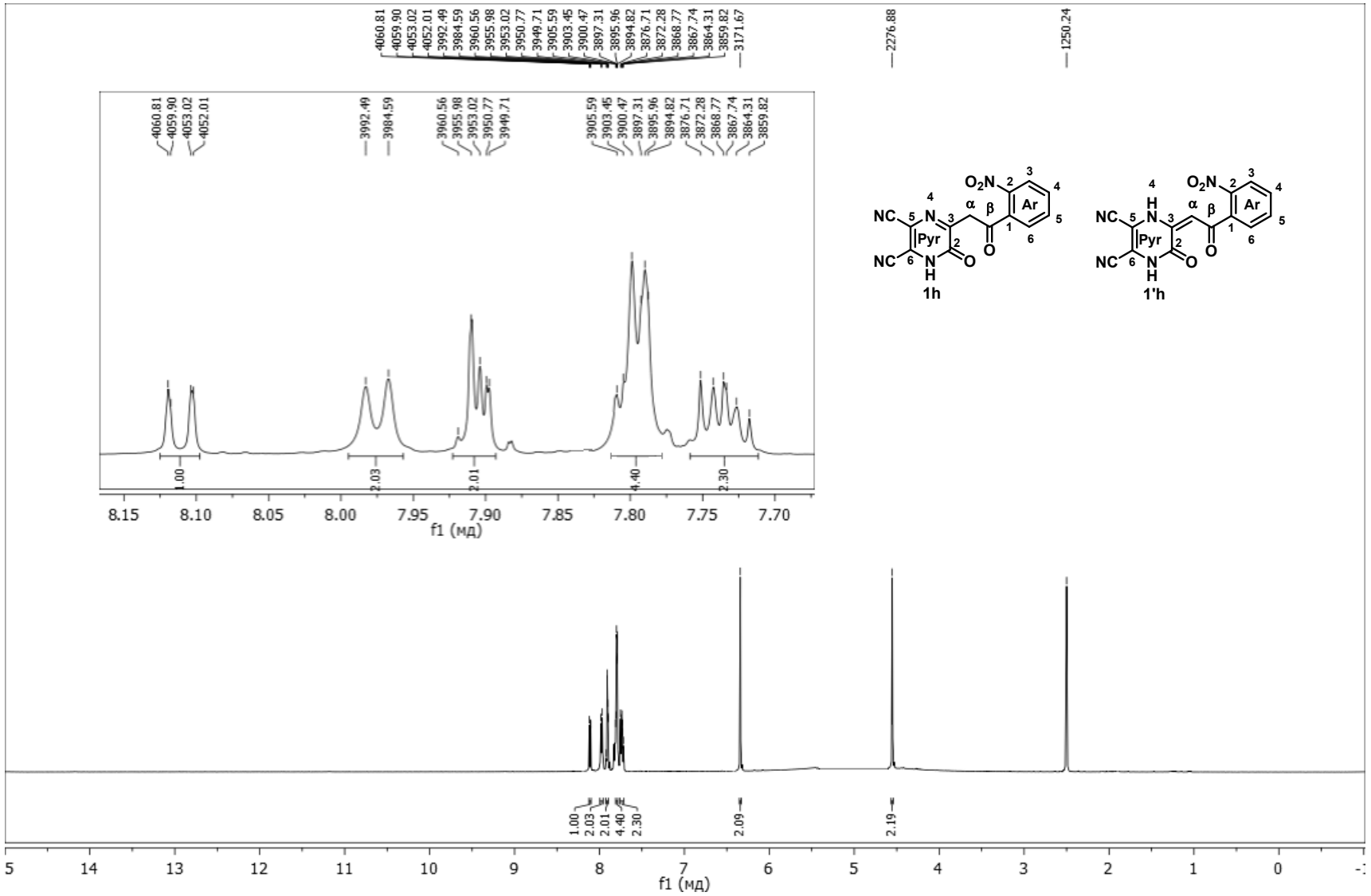

Figure S8. 1D ^{1}H NMR spectrum of **1h** and **1′h** in DMSO-d_6 at T = 303 K. Chemical shifts are given in Hz (Bruker spectrometer at 500.1 MHz).

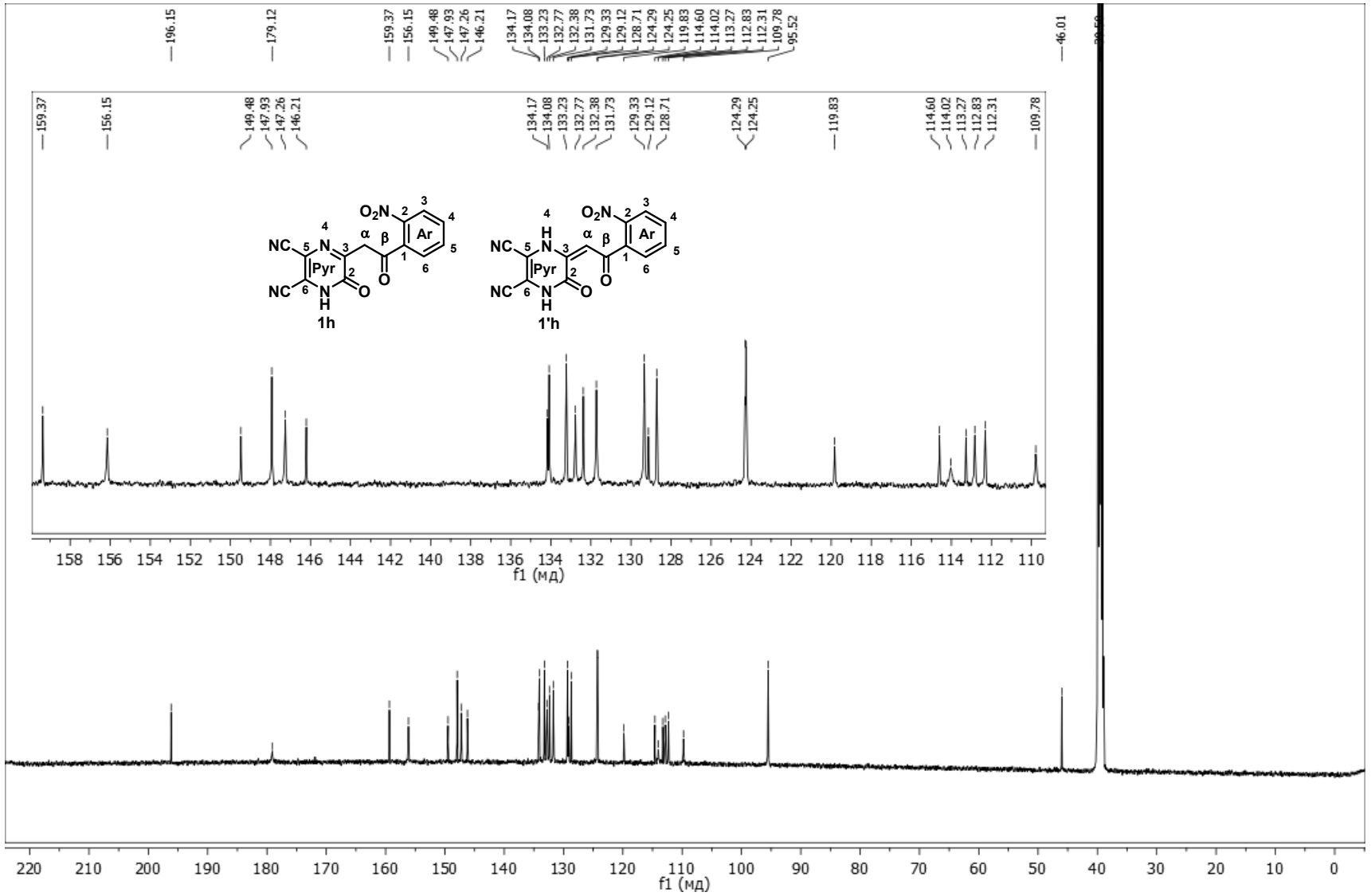

Figure S9. $^{13}C\{^{1}H\}$ NMR spectrum of of **1h** and **1′h** in DMSO-d_6 at T = 303 K (Bruker spectrometer at 125.7 MHz).

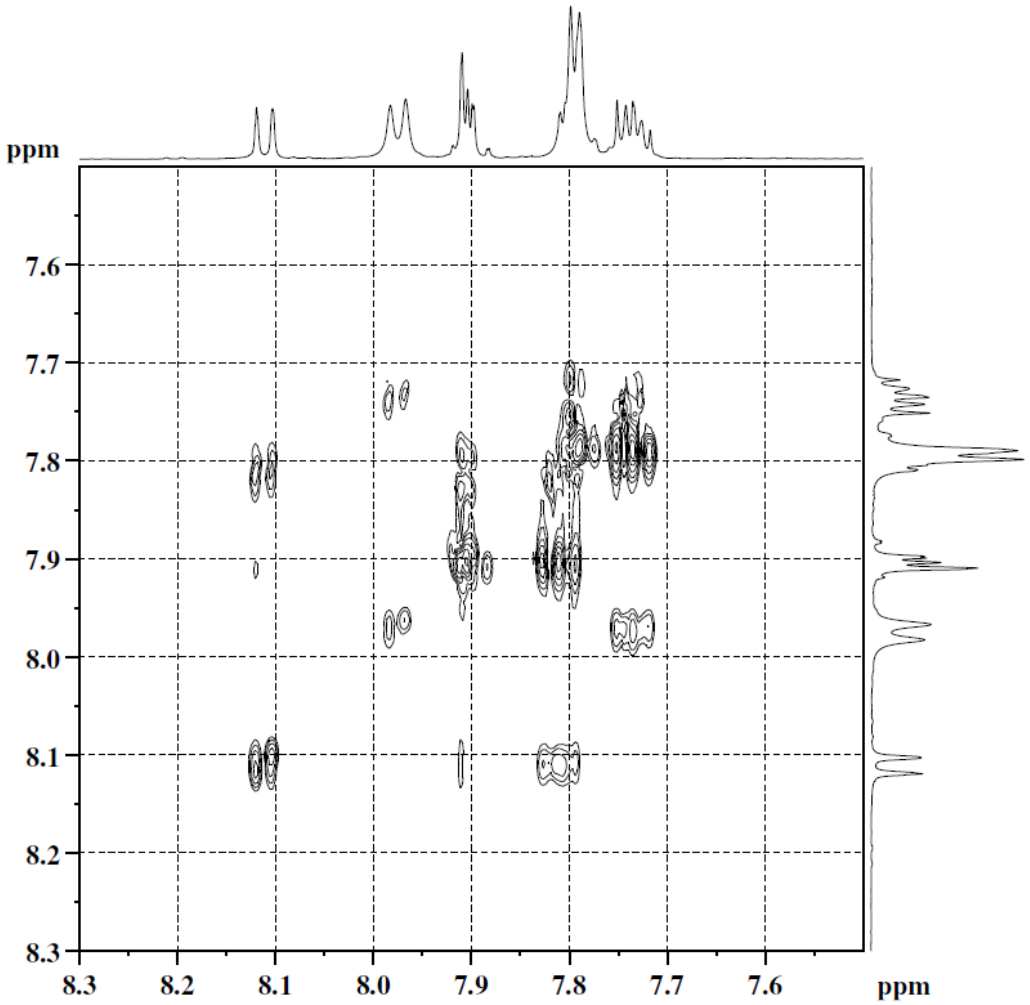

Figure S10. 2D ^{1}H-^{1}H COSY NMR spectrum of of **1h** and **1′h** in DMSO-d_6 at T = 303 K.

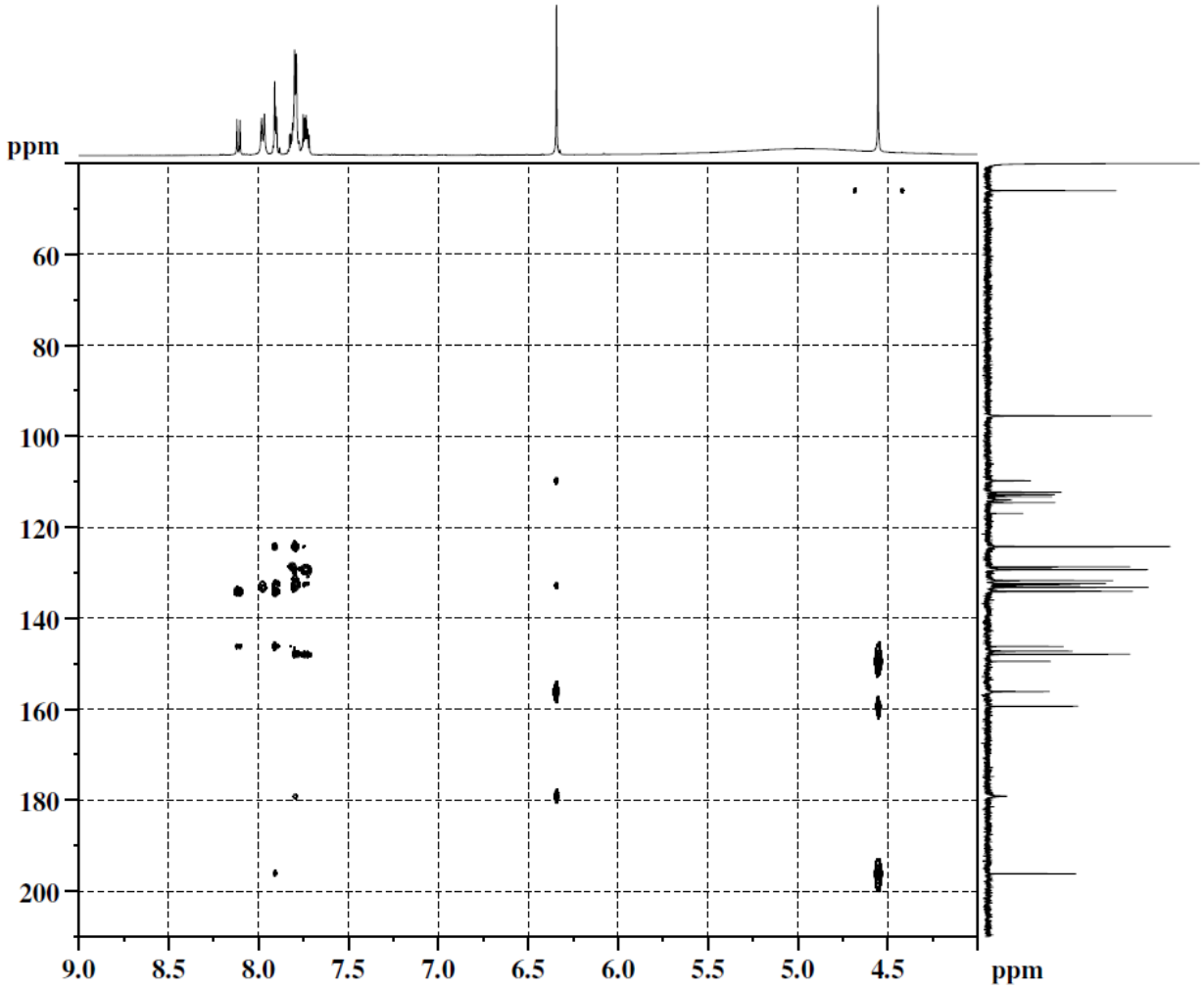

Figure S11. 2D ^{1}H-^{13}C HMBC NMR spectrum of of **1h** and **1′h** in DMSO-d_6 at T = 303 K.

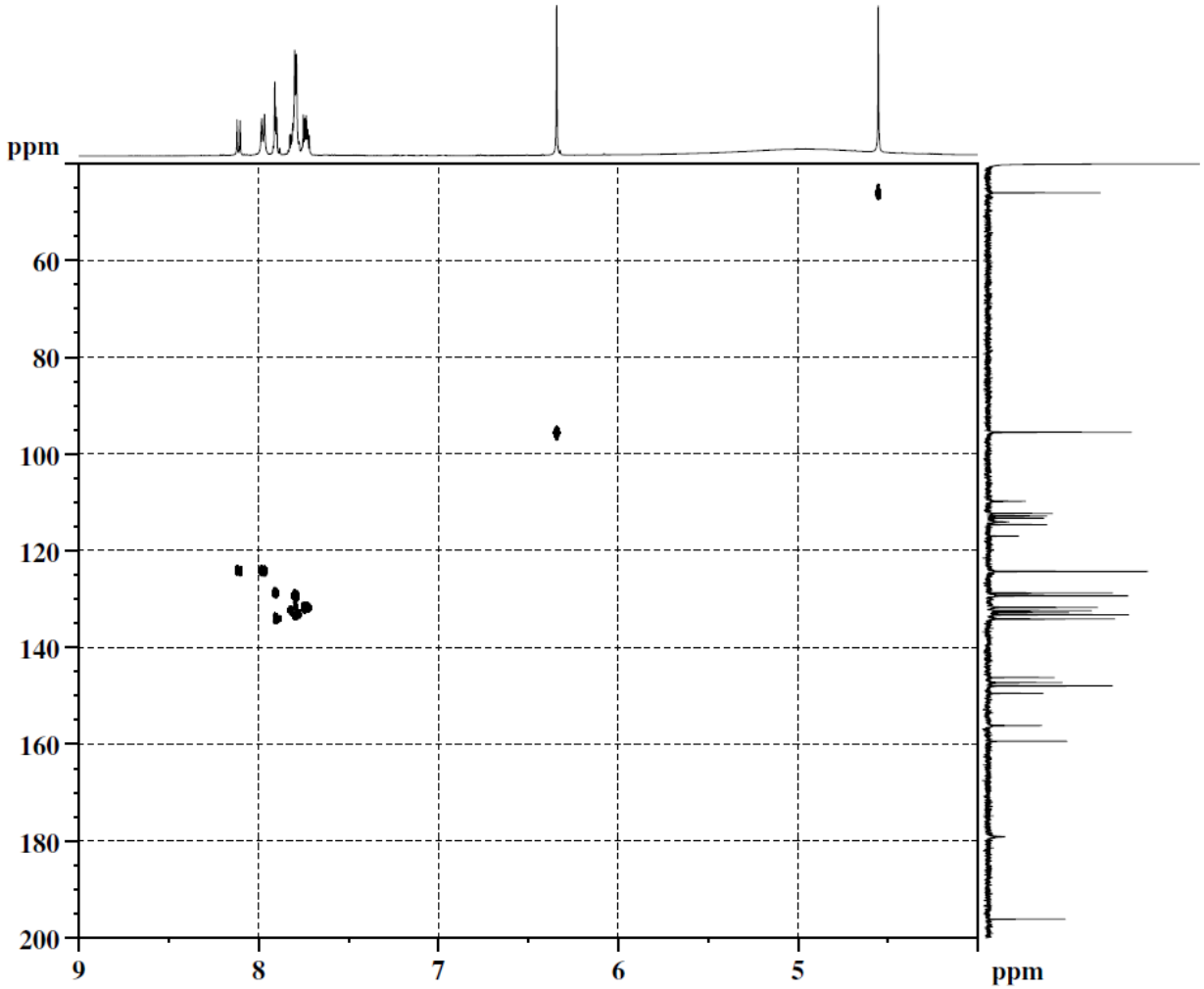

Figure S12. 2D 1H-^{13}C HSQC NMR spectrum of of **1h** and **1′h** in DMSO-d_6 at T = 303 K.

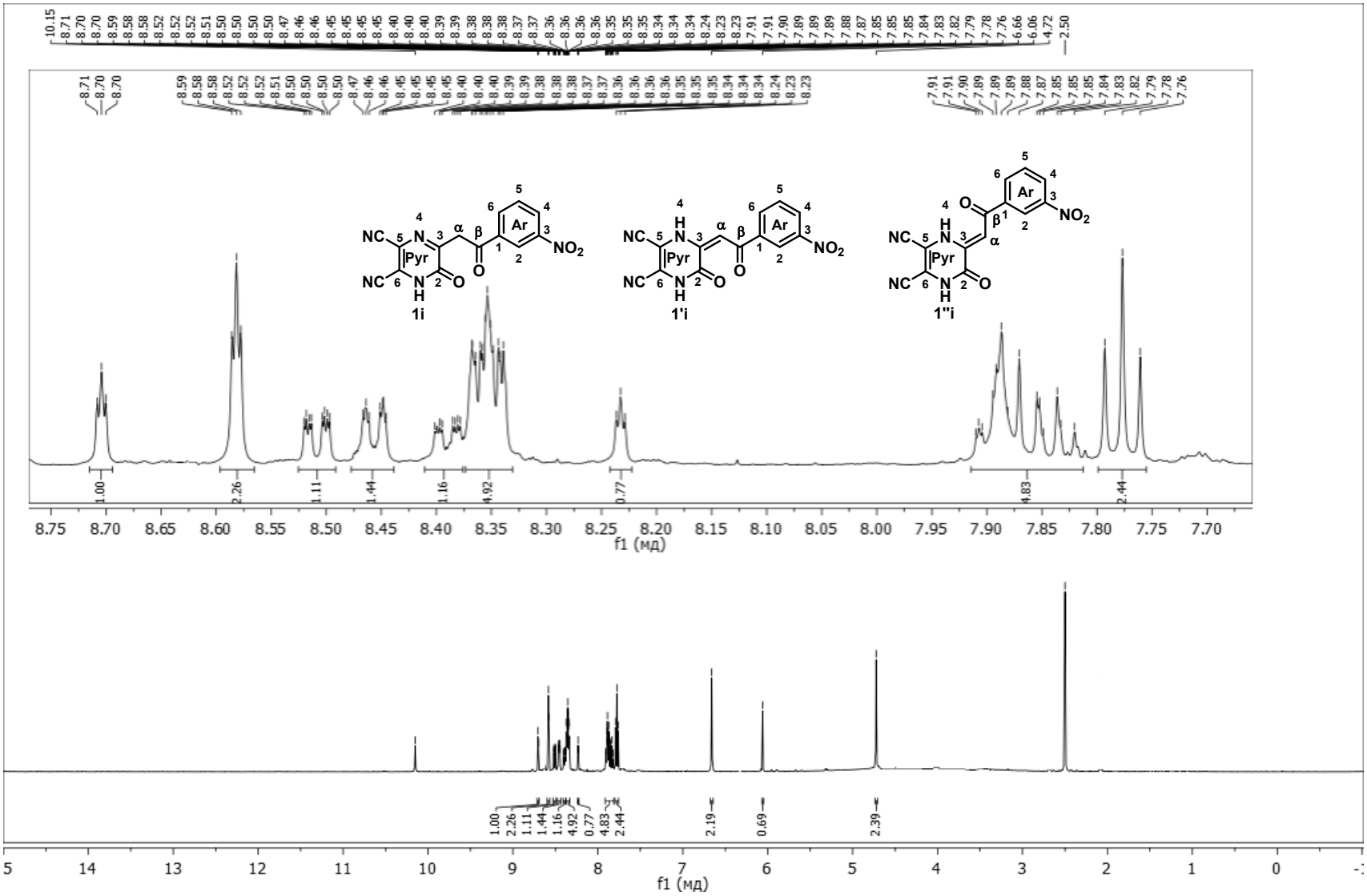

Figure S13. 1D ^{1}H NMR spectrum of **1i**, **1′i** and **1′′i** in DMSO-d_6 at T = 303 K. Chemical shifts are given in ppm (Bruker spectrometer at 500.1 MHz).

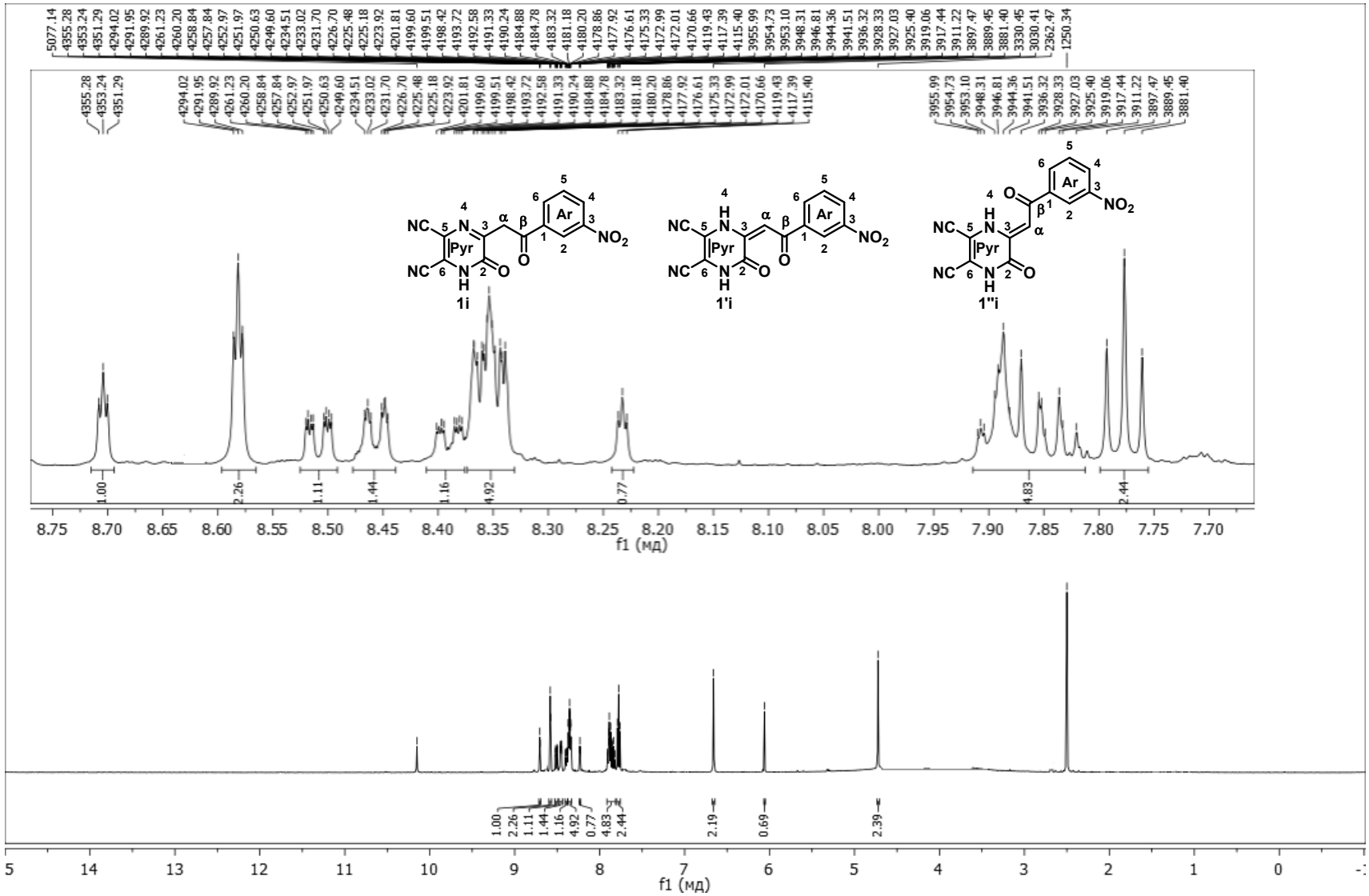

Figure S14. 1D ^{1}H NMR spectrum of **1i**, **1′i** and **1′′i** in DMSO-d_6 at T = 303 K. Chemical shifts are given in Hz (Bruker spectrometer at 500.1 MHz).

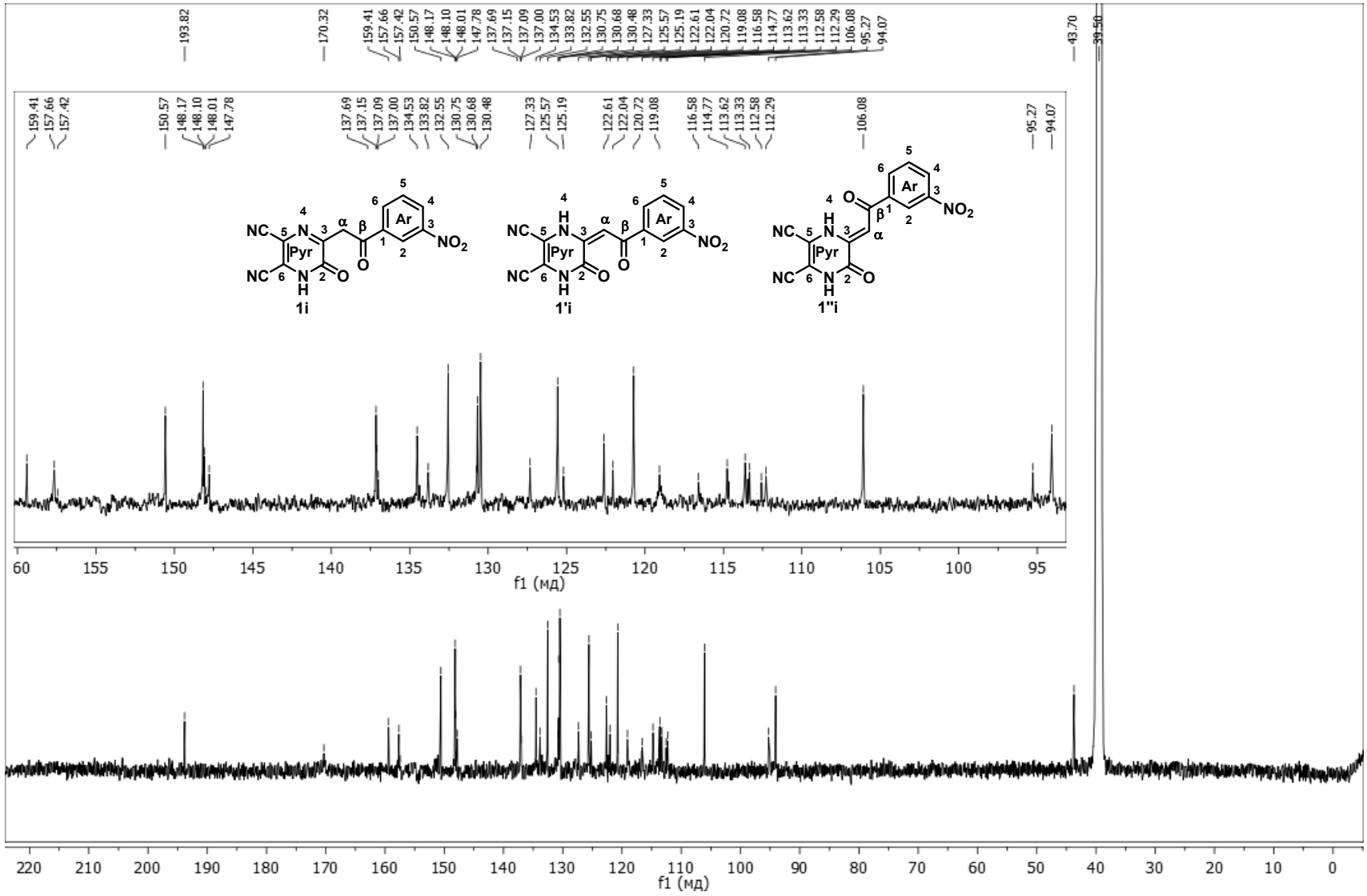

Figure S15. $^{13}C\{^{1}H\}$ NMR spectrum of **1i**, **1′i** and **1′′i** in DMSO-d_6 at T = 303 K (Bruker spectrometer at 125.7 MHz).

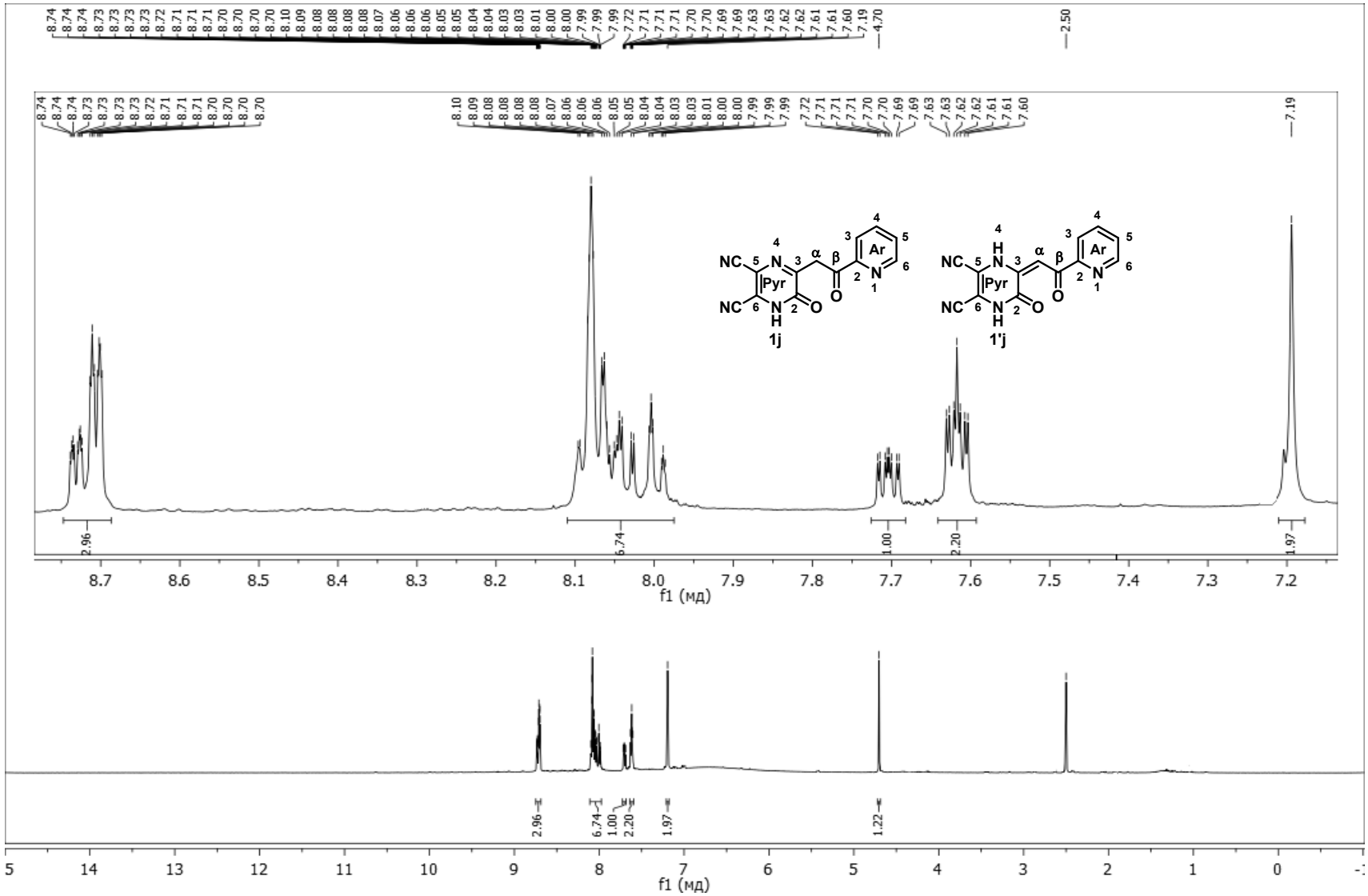

Figure S16. 1D ^{1}H NMR spectrum of **1j** and **1′j** in DMSO-d_6 at T = 303 K. Chemical shifts are given in ppm (Bruker spectrometer at 500.1 MHz).

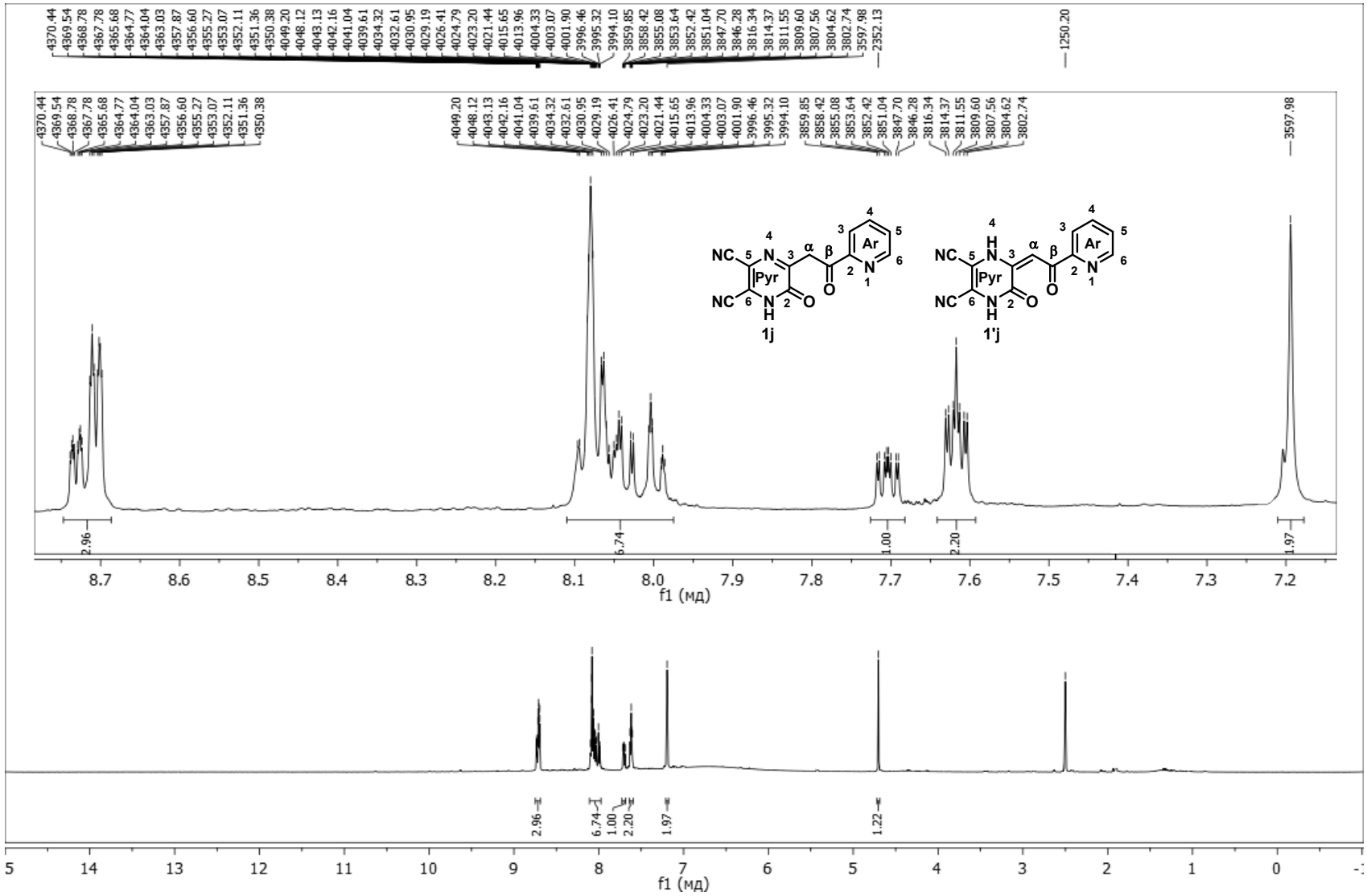

Figure S17. 1D ^{1}H NMR spectrum of **1j** and **1′j** in DMSO-d_6 at T = 303 K. Chemical shifts are given in Hz (Bruker spectrometer at 500.1 MHz).

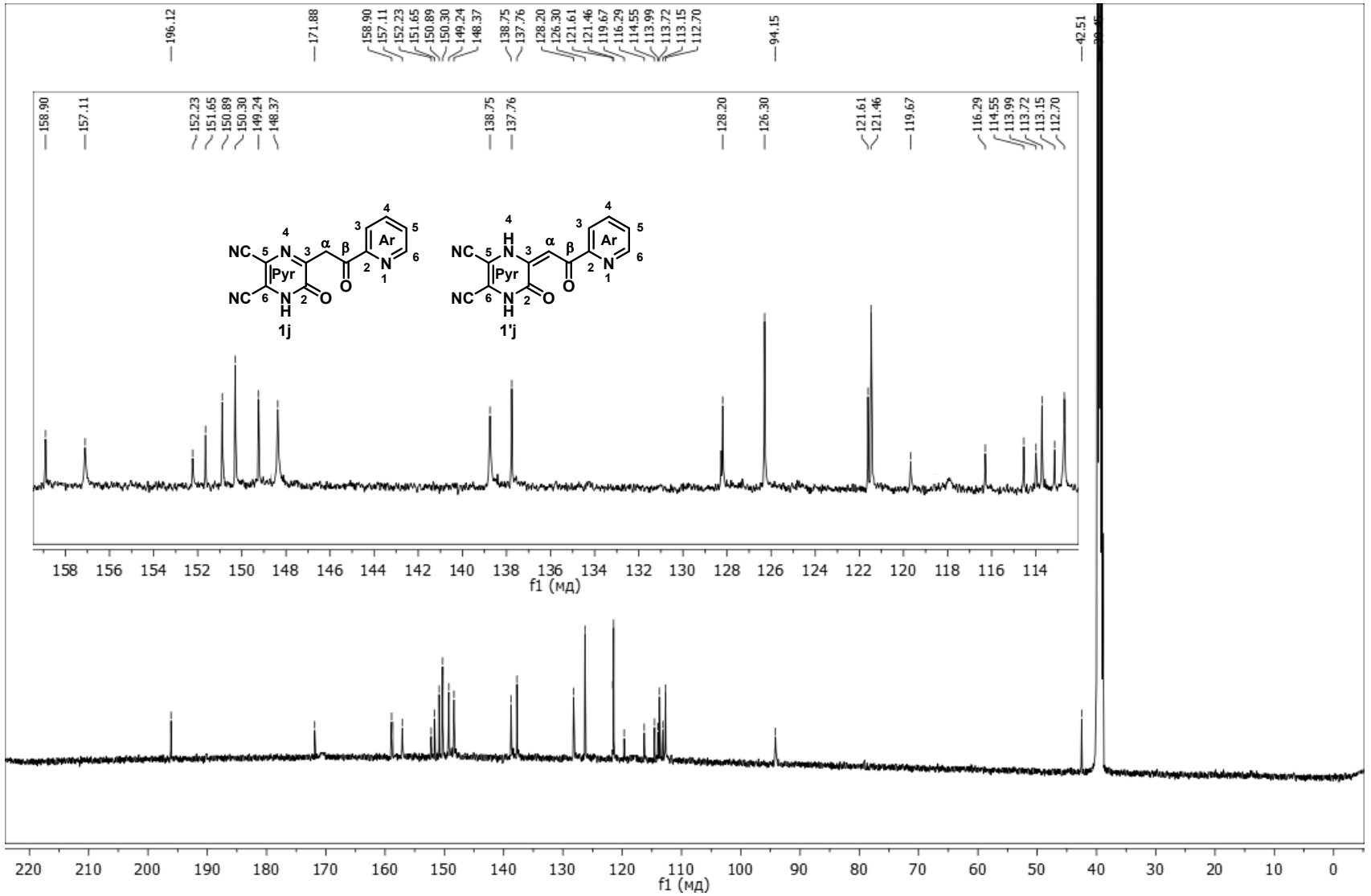

Figure S18. $^{13}C\{^{1}H\}$ NMR spectrum of **1j** and **1′j** in DMSO-d_6 at T = 303 K (Bruker spectrometer at 125.7 MHz).

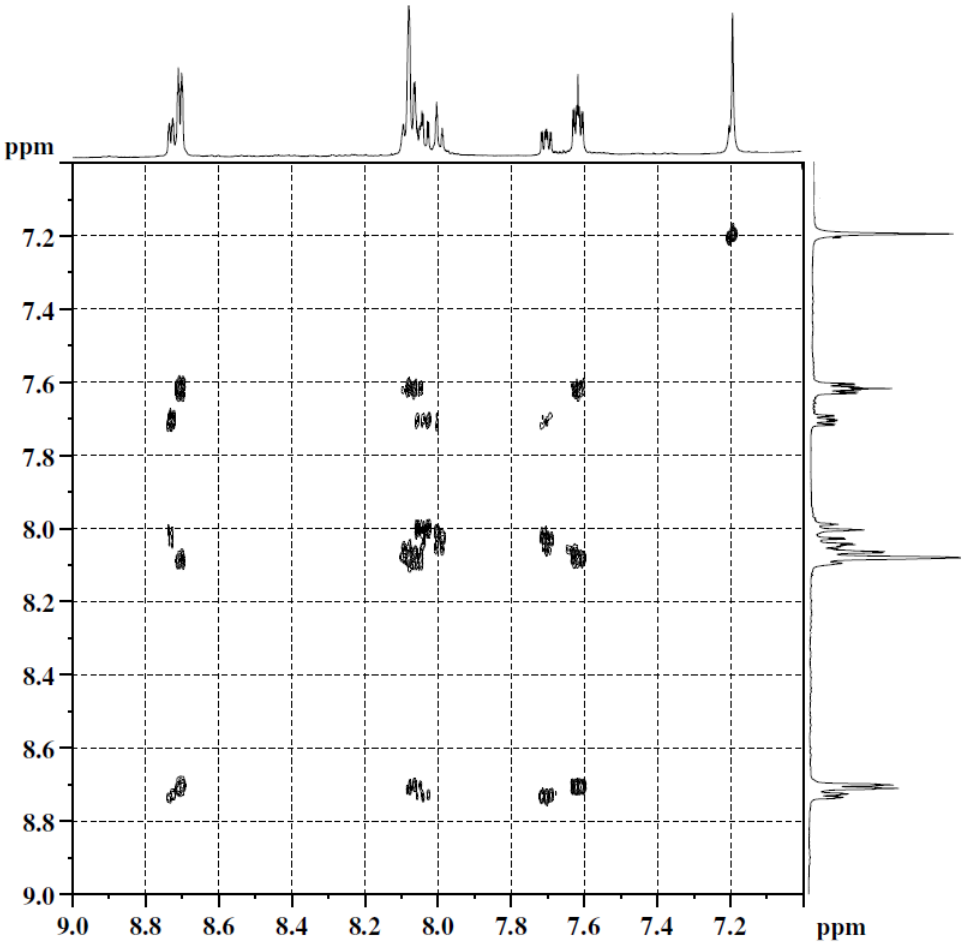

Figure S19. 2D ^{1}H-^{1}H COSY NMR spectrum of **1j** and **1′j** in DMSO-d_6 at T = 303 K.

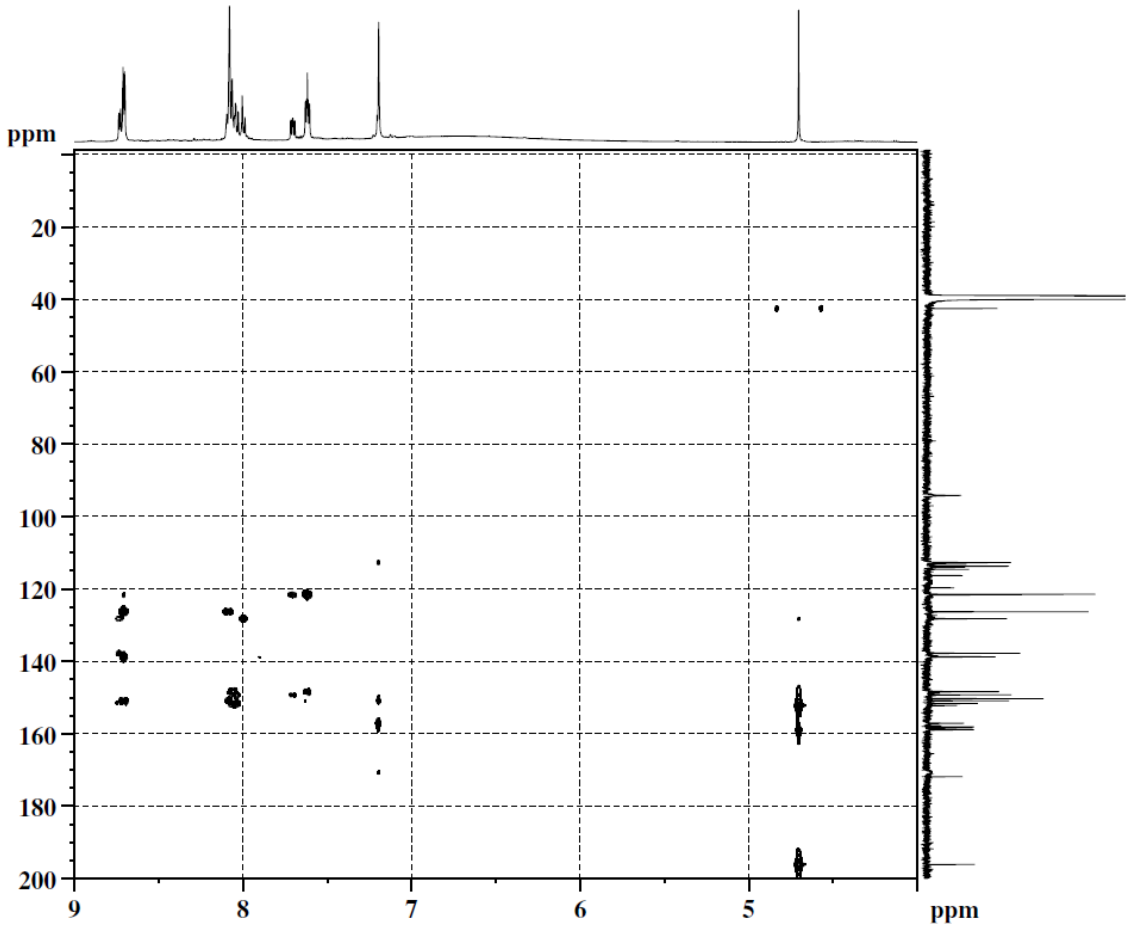

Figure S20. 2D ^{1}H-^{13}C HMBC NMR spectrum of **1j** and **1′j** in DMSO-d_6 at T = 303 K.

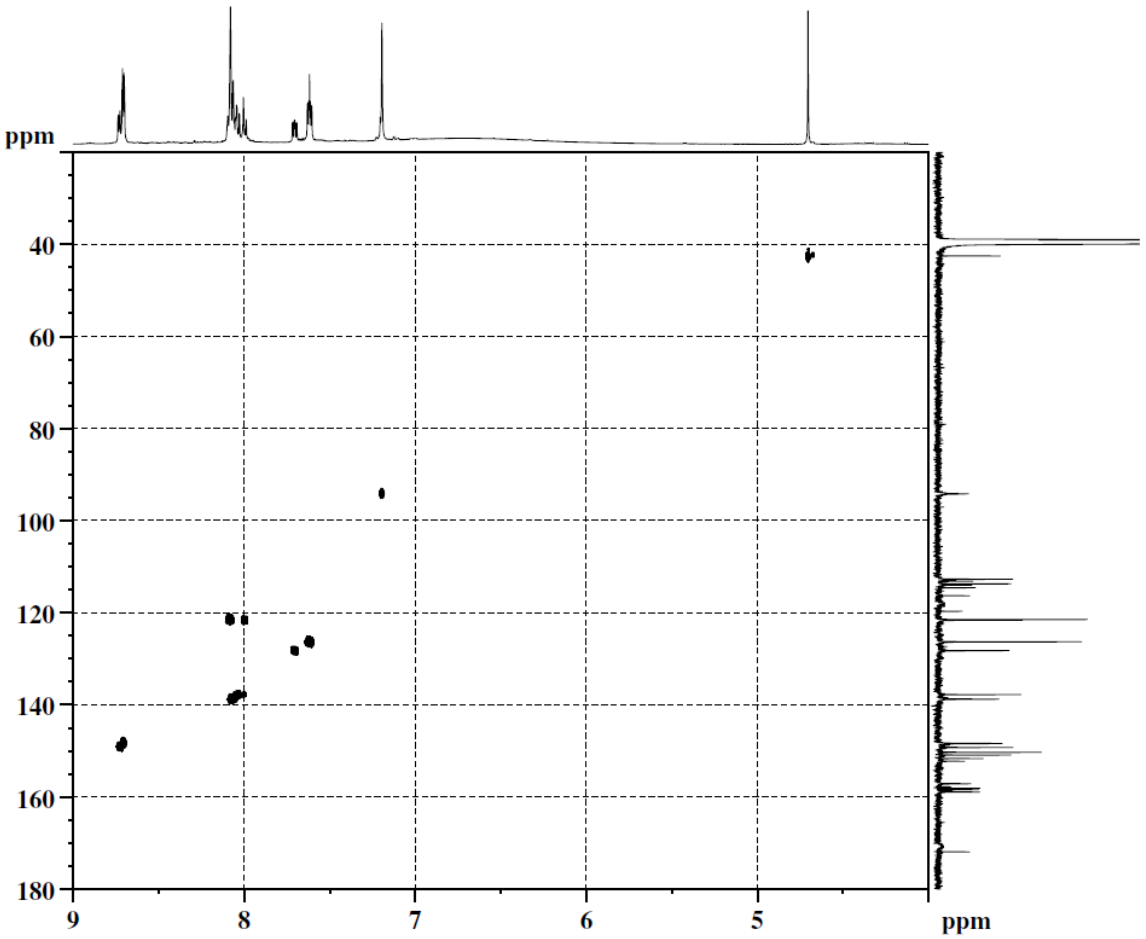

Figure S21. 2D 1H-^{13}C HSQC NMR spectrum of **1j** and **1′j** in DMSO-d_6 at T = 303 K.

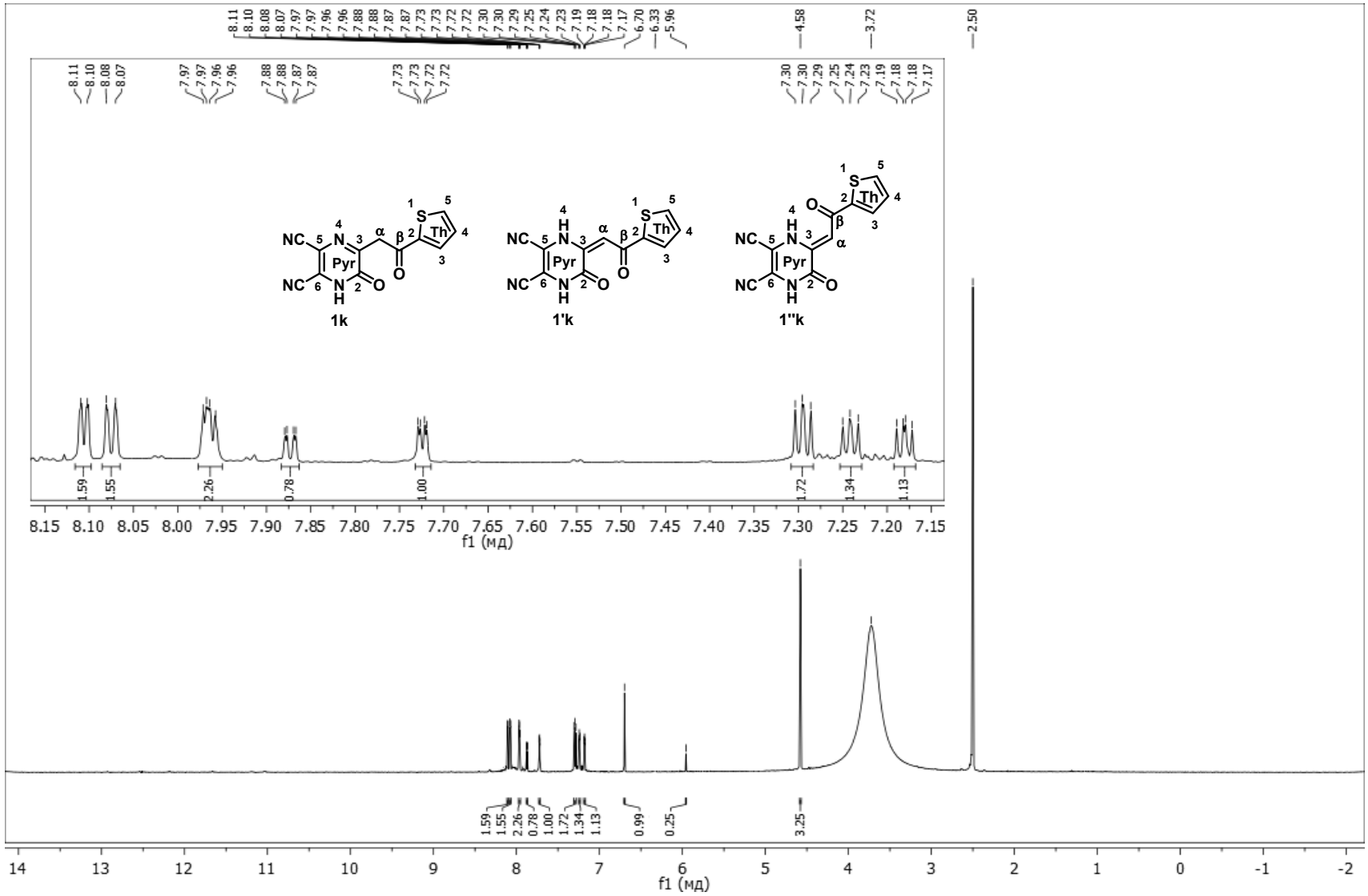

Figure S22. 1D ^{1}H NMR spectrum of **1k**, **1′k** and **1′′k** in DMSO-d_6 at T = 303 K. Chemical shifts are given in ppm (Bruker spectrometer at 500.1 MHz).

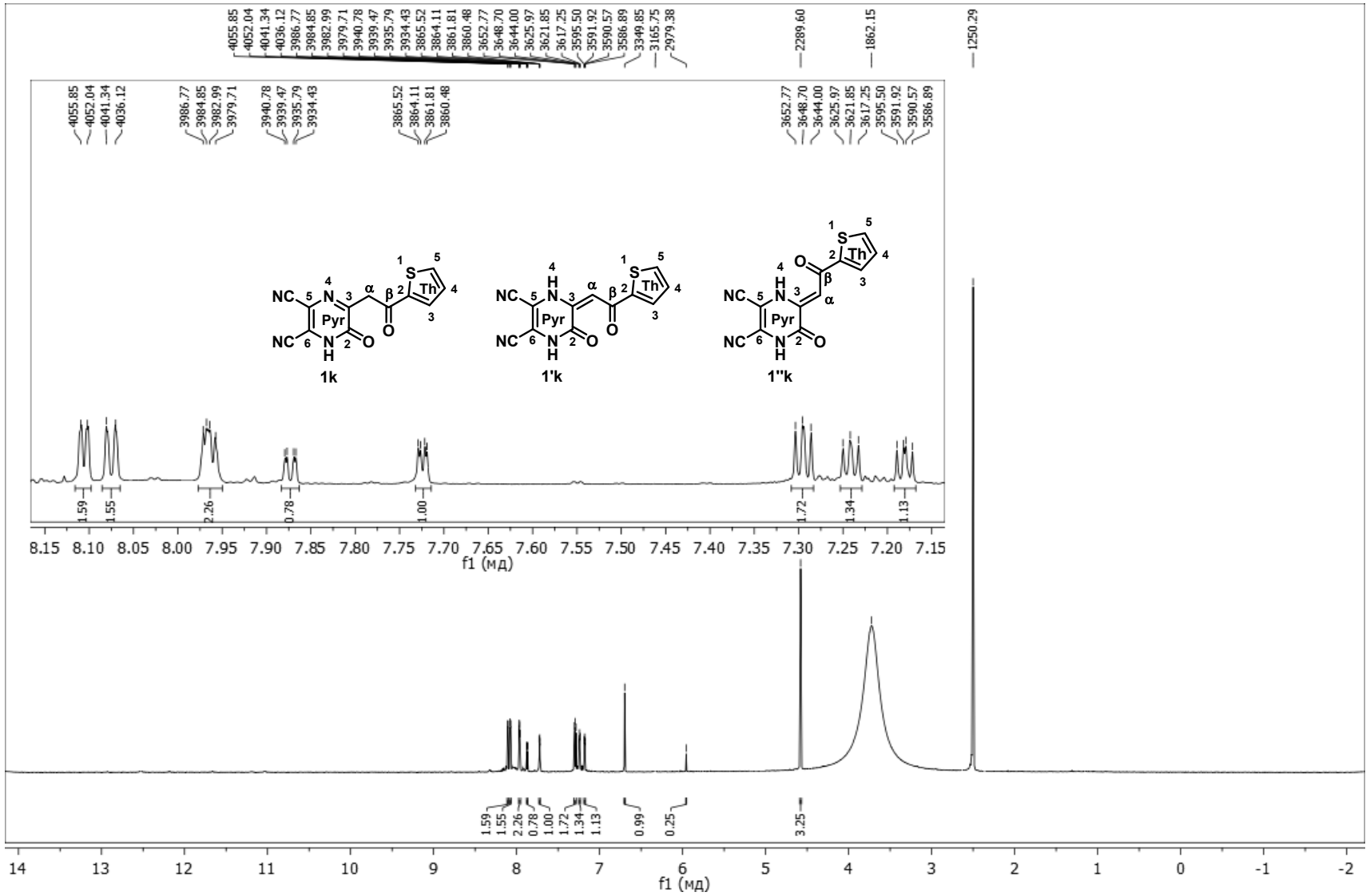

Figure S23. 1D ^{1}H NMR spectrum of **1k**, **1′k** and **1′′k** in DMSO-d_6 at T = 303 K. Chemical shifts are given in Hz (Bruker spectrometer at 500.1 MHz).

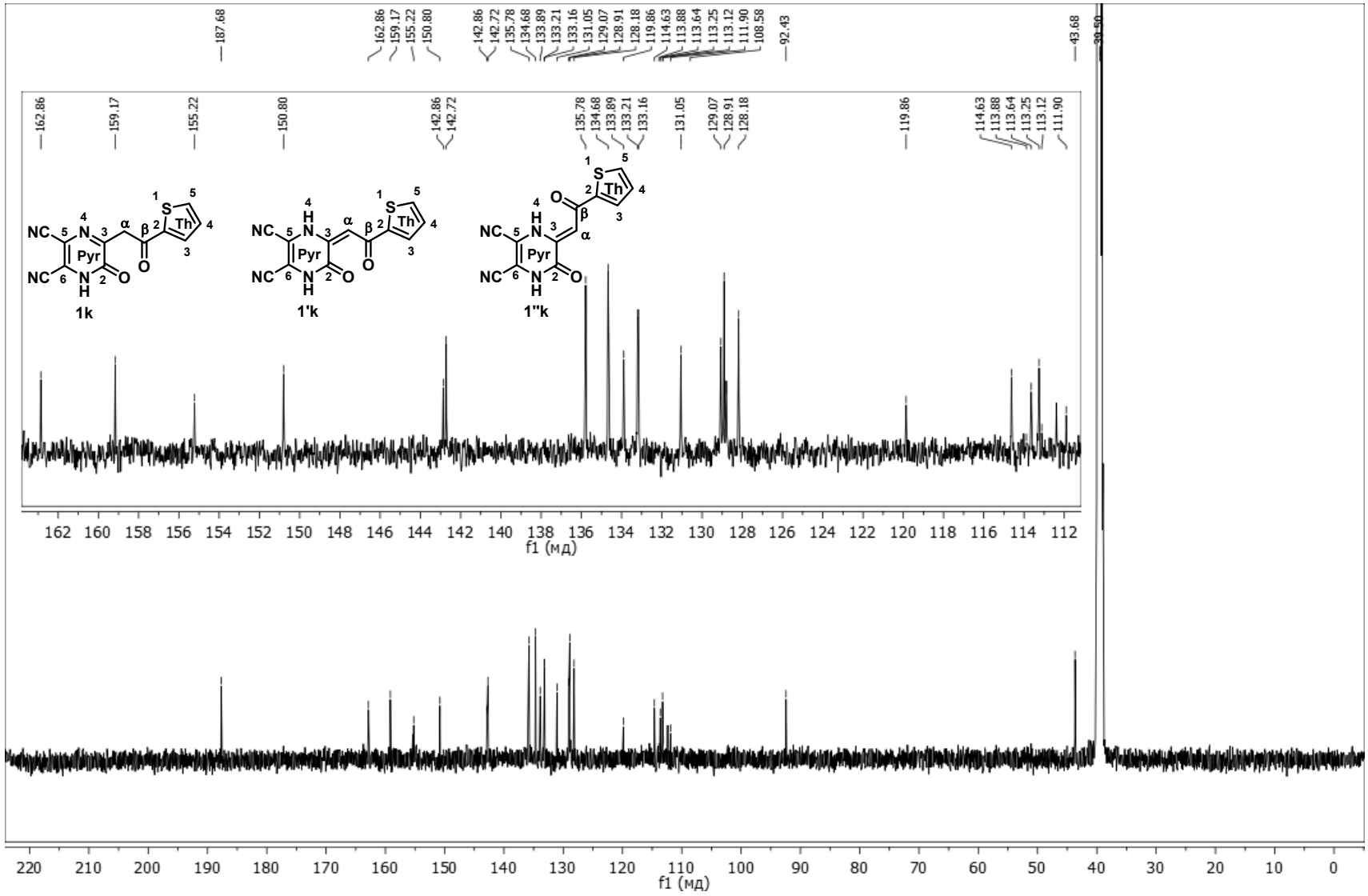

Figure S24. $^{13}C\{^{1}H\}$ NMR spectrum of **1k**, **1′k** and **1′′k** in DMSO-d_6 at T = 303 K (Bruker spectrometer at 125.7 MHz).

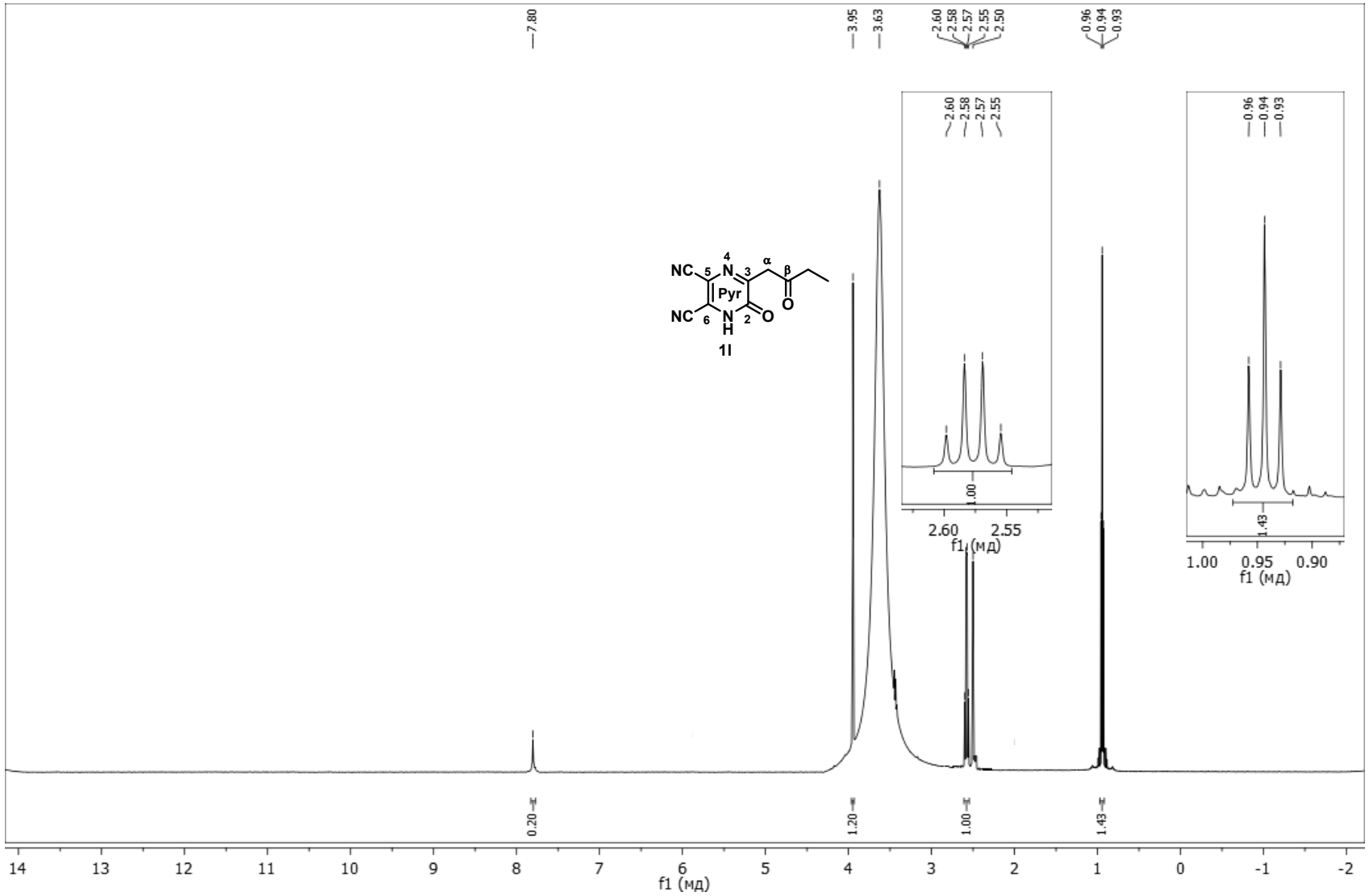

Figure S25. 1D ^{1}H NMR spectrum of **1l** in DMSO-d_6 at T = 303 K. Chemical shifts are given in ppm (Bruker spectrometer at 500.1 MHz).

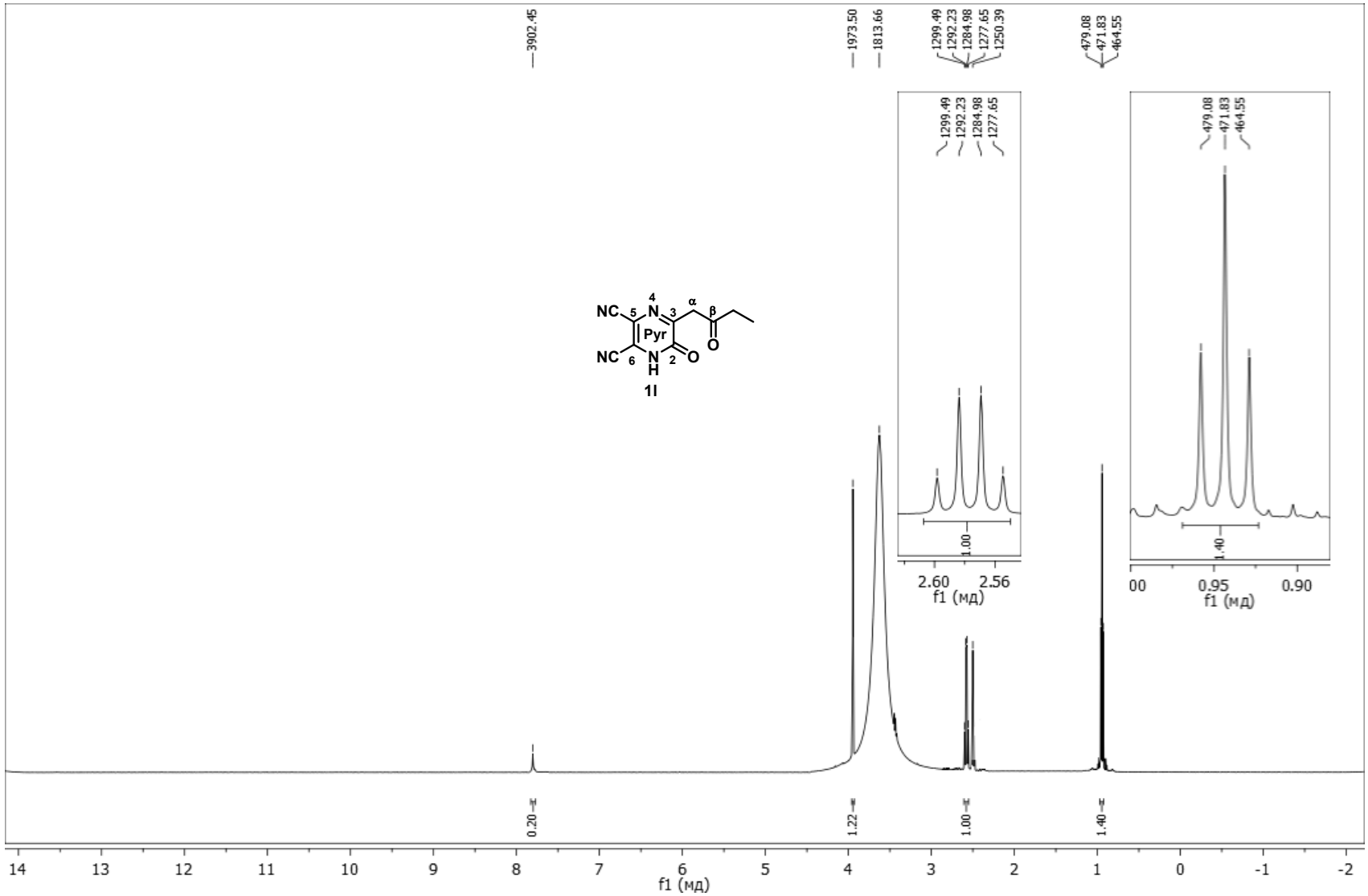

Figure S26. 1D ^{1}H NMR spectrum of **1l** in DMSO-d_6 at T = 303 K. Chemical shifts are given in Hz (Bruker spectrometer at 500.1 MHz).

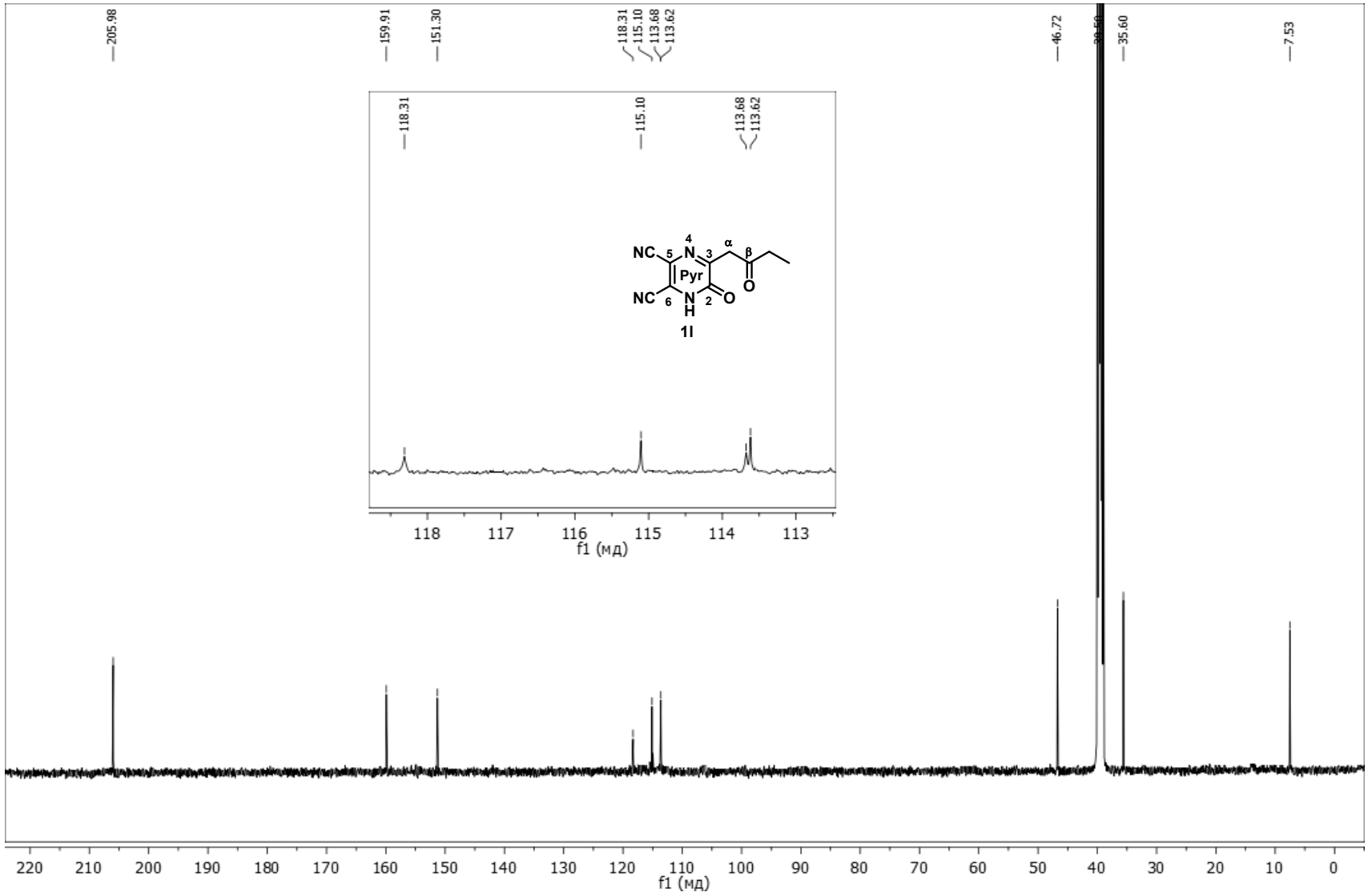

Figure S27. $^{13}C\{^{1}H\}$ NMR spectrum of **1l** in DMSO-d_6 at T = 303 K (Bruker spectrometer at 125.7 MHz).

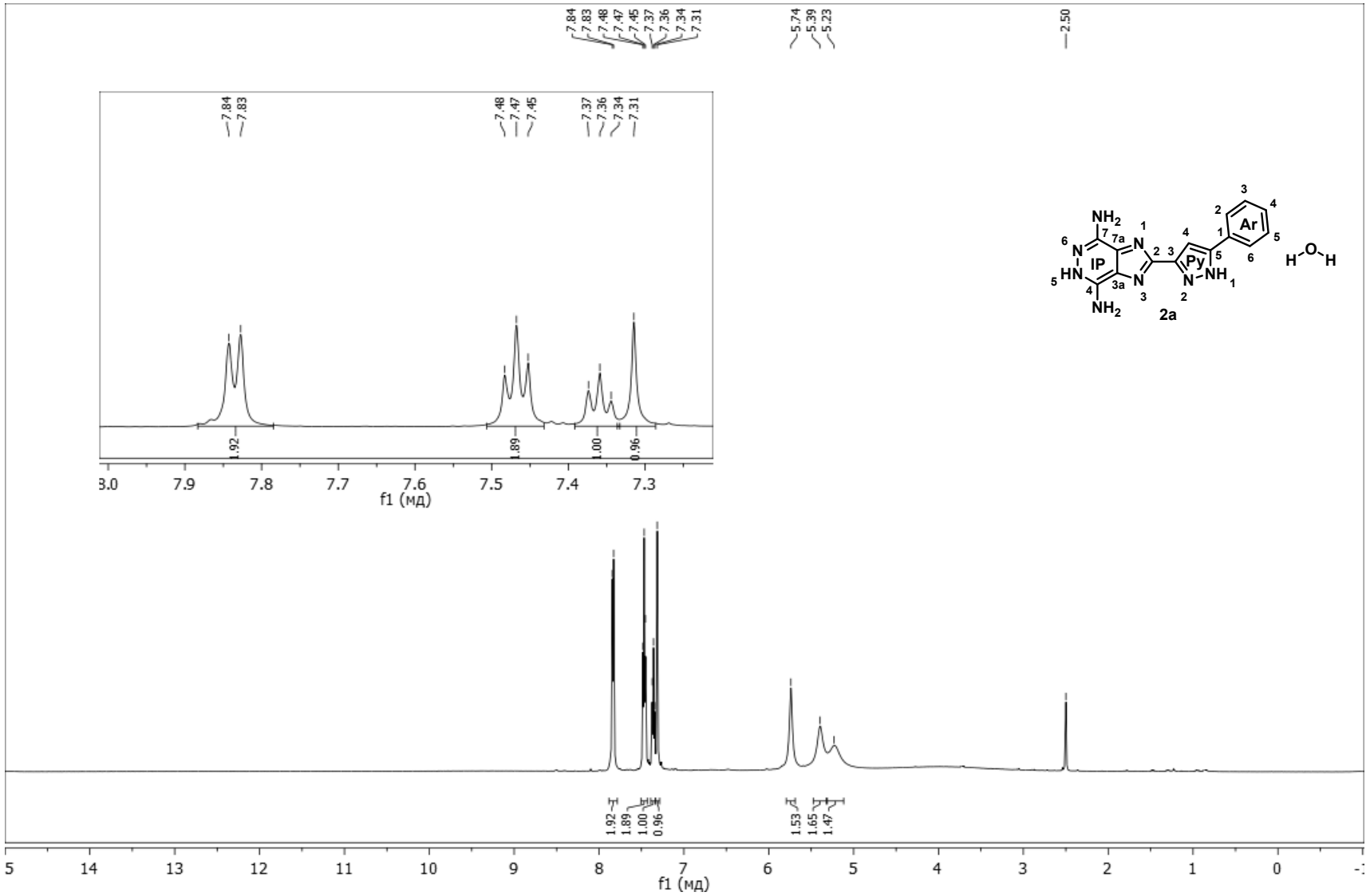

Figure S28. 1D ^{1}H NMR spectrum of **2a** in DMSO-d_6 at T = 303 K. Chemical shifts are given in ppm (Bruker spectrometer at 500.1 MHz).

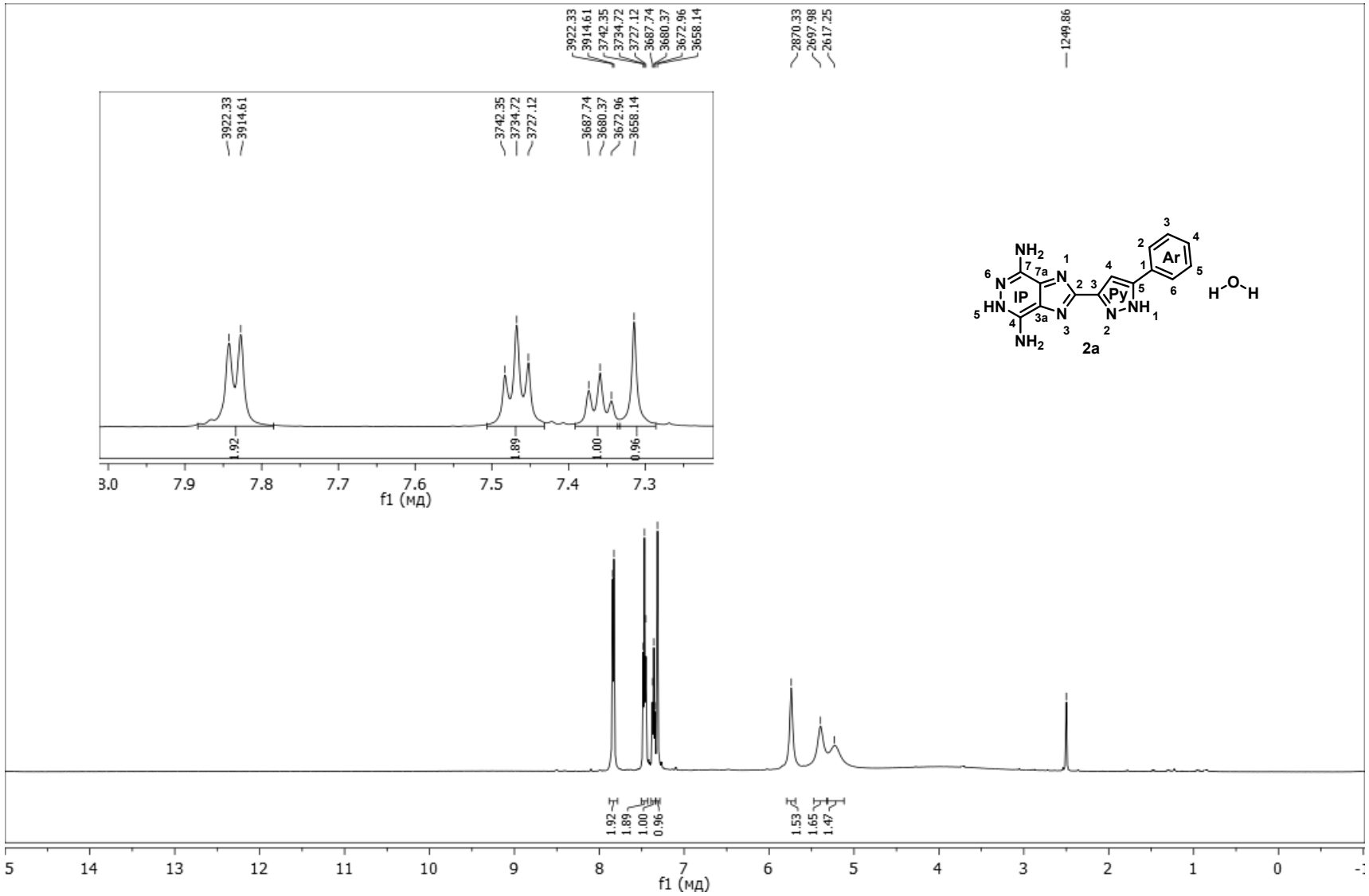

Figure S29. 1D ^{1}H NMR spectrum of **2a** in DMSO-d_6 at T = 303 K. Chemical shifts are given in Hz (Bruker spectrometer at 500.1 MHz).

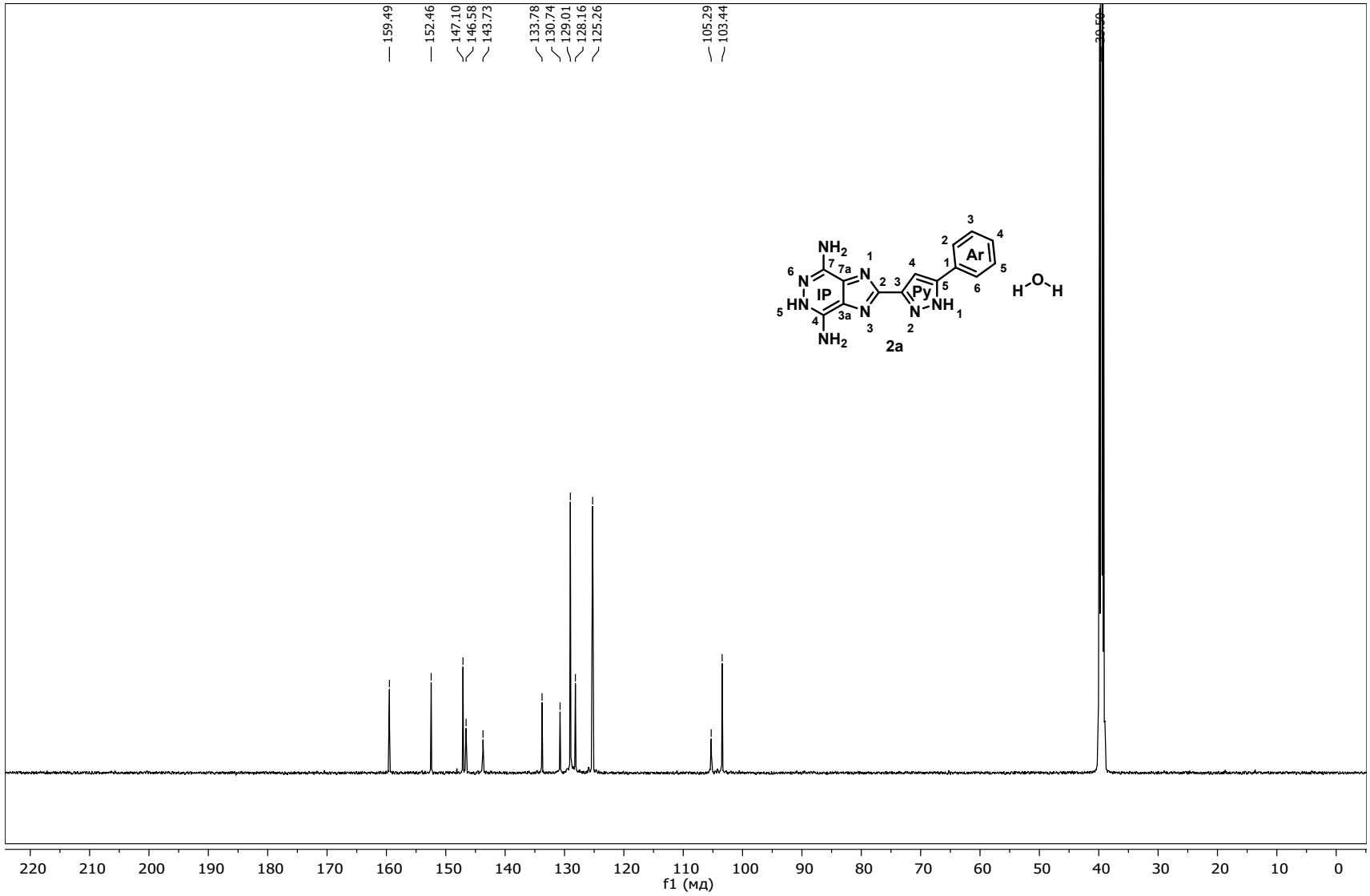

Figure S30. $^{13}C\{^{1}H\}$ NMR spectrum of **2a** in DMSO-d_6 at T = 303 K (Bruker spectrometer at 125.7 MHz).

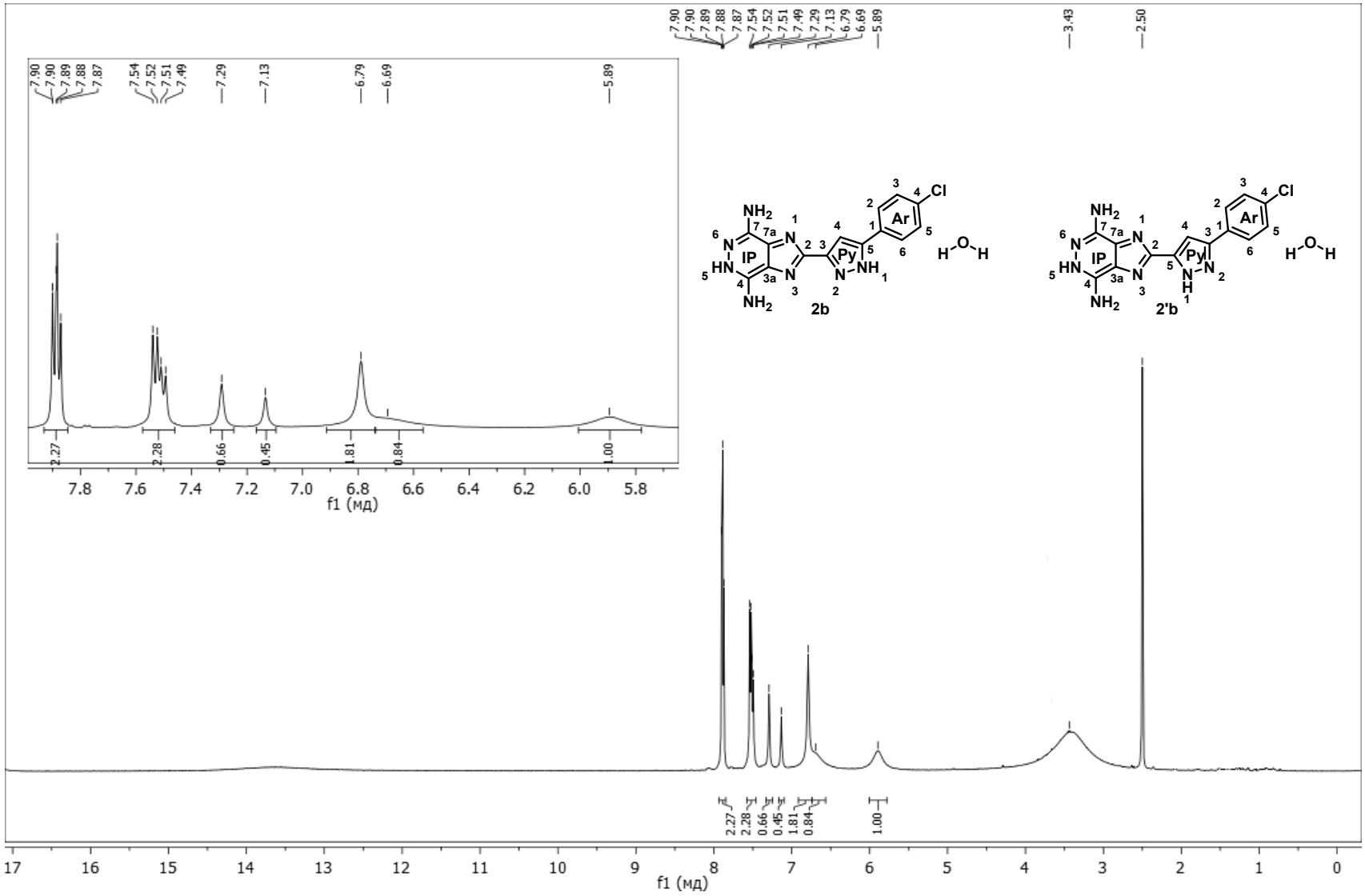

Figure S31. 1D ^{1}H NMR spectrum of **2b** and **2′b** in DMSO-d_6 at T = 303 K. Chemical shifts are given in ppm (Bruker spectrometer at 500.1 MHz).

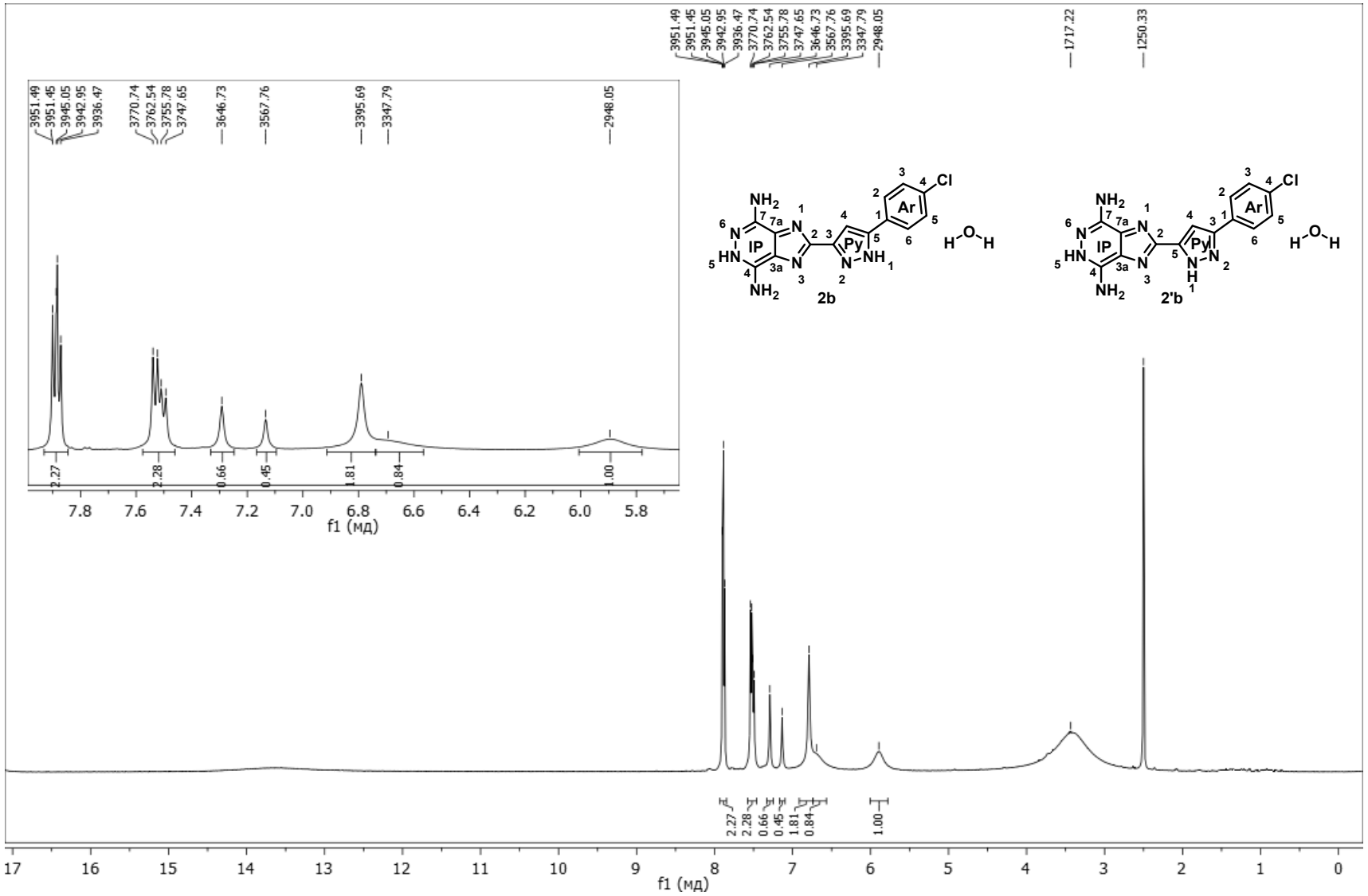

Figure S32. 1D ^{1}H NMR spectrum of **2b** and **2′b** in DMSO-d_6 at T = 303 K. Chemical shifts are given in Hz (Bruker spectrometer at 500.1 MHz).

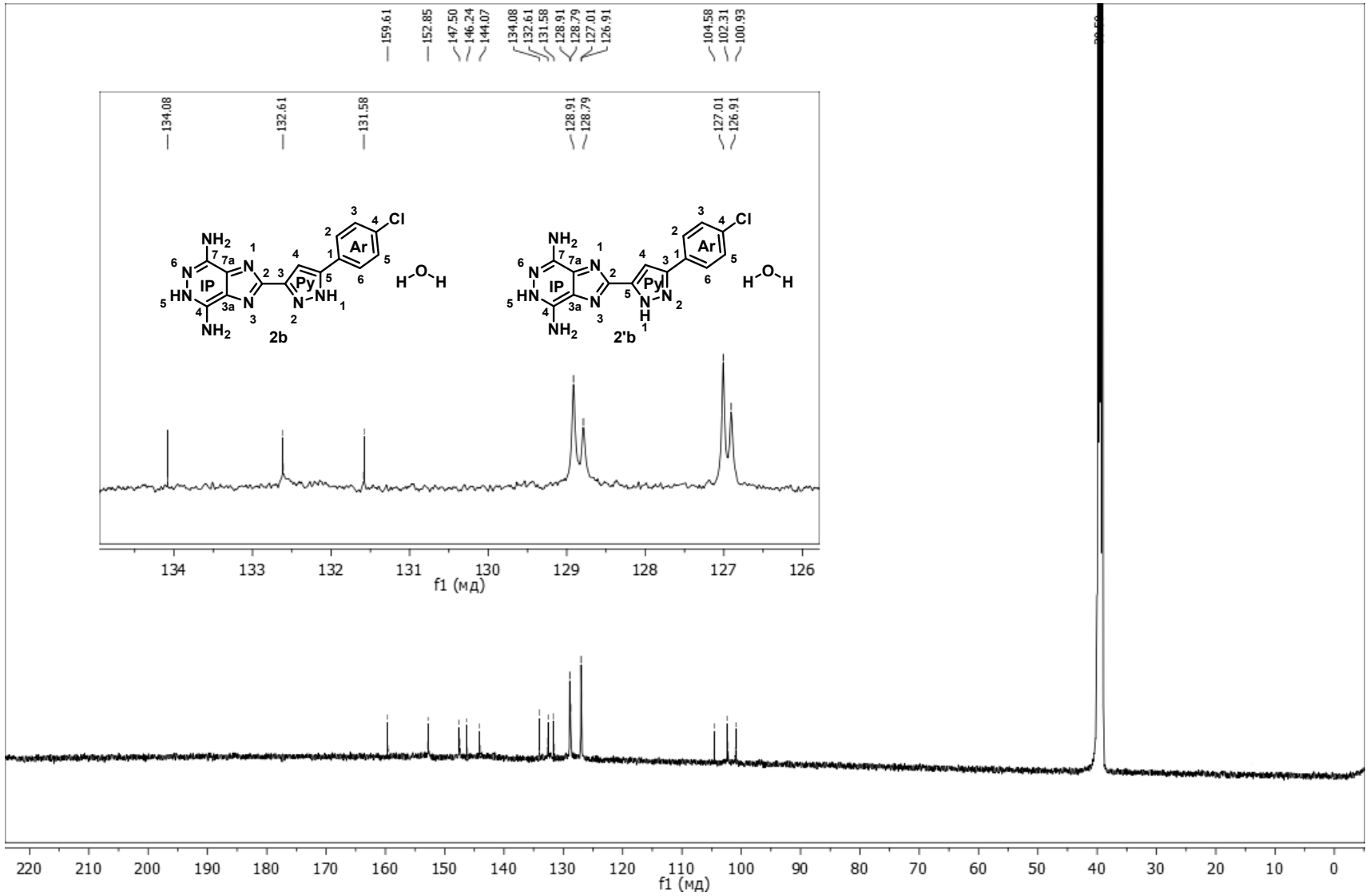

Figure S33. $^{13}C\{^{1}H\}$ NMR spectrum of **2b** and **2′b** in DMSO-d_6 at T = 303 K (Bruker spectrometer at 125.7 MHz).

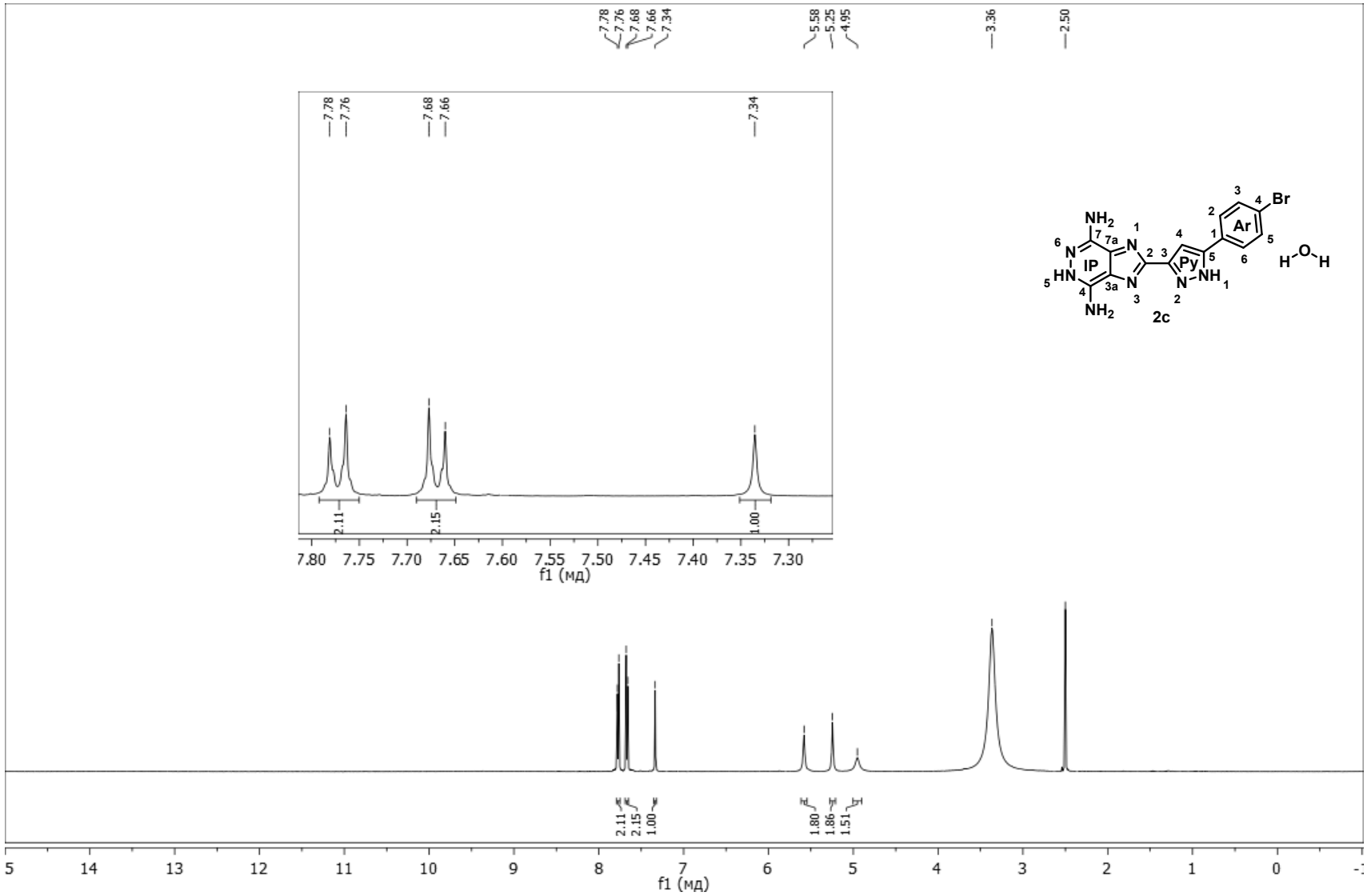

Figure S34. 1D ^{1}H NMR spectrum of **2c** in DMSO-d_6 at T = 303 K. Chemical shifts are given in ppm (Bruker spectrometer at 500.1 MHz).

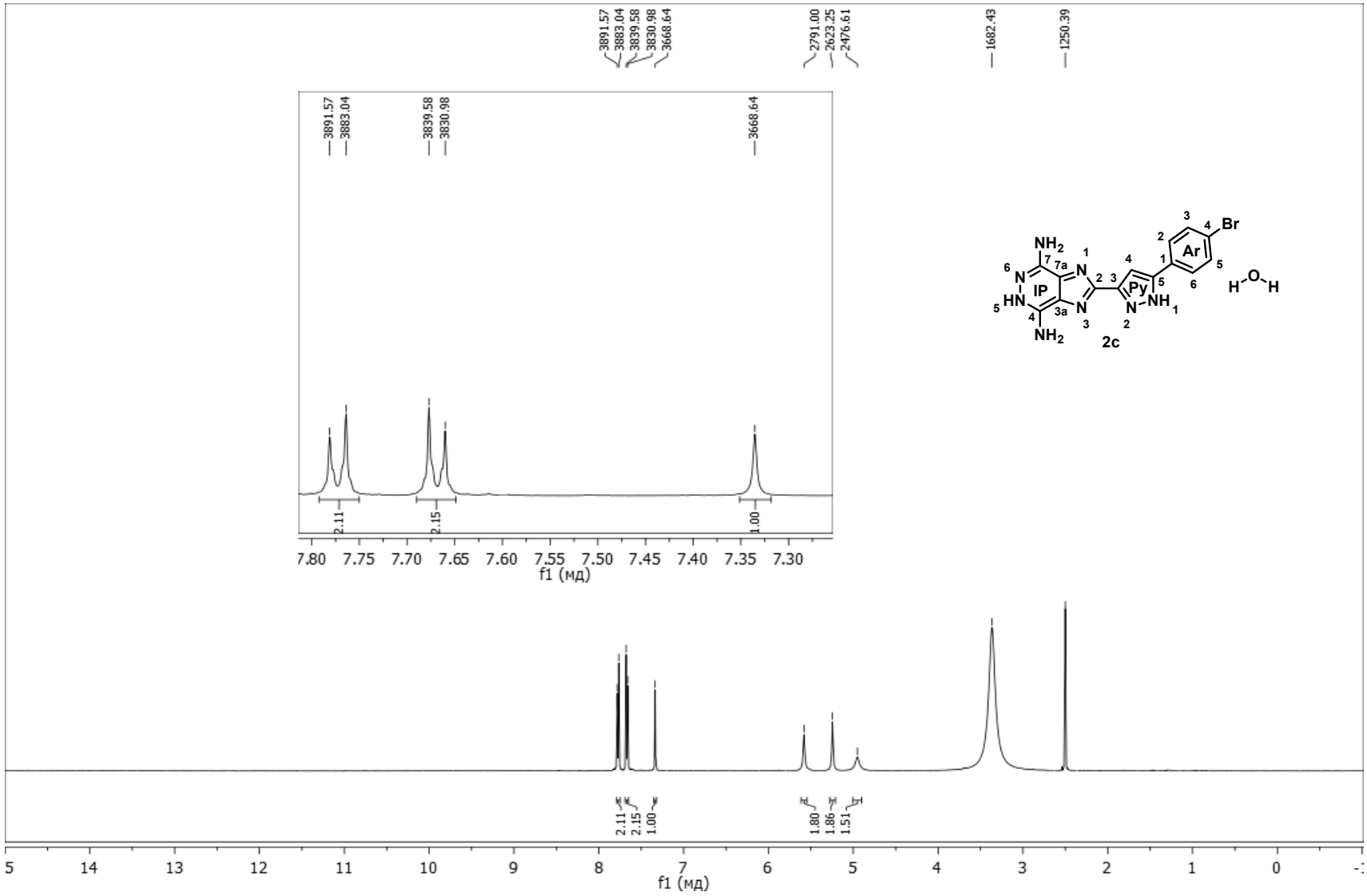

Figure S35. 1D ^{1}H NMR spectrum of **2c** in DMSO-d_6 at T = 303 K. Chemical shifts are given in Hz (Bruker spectrometer at 500.1 MHz).

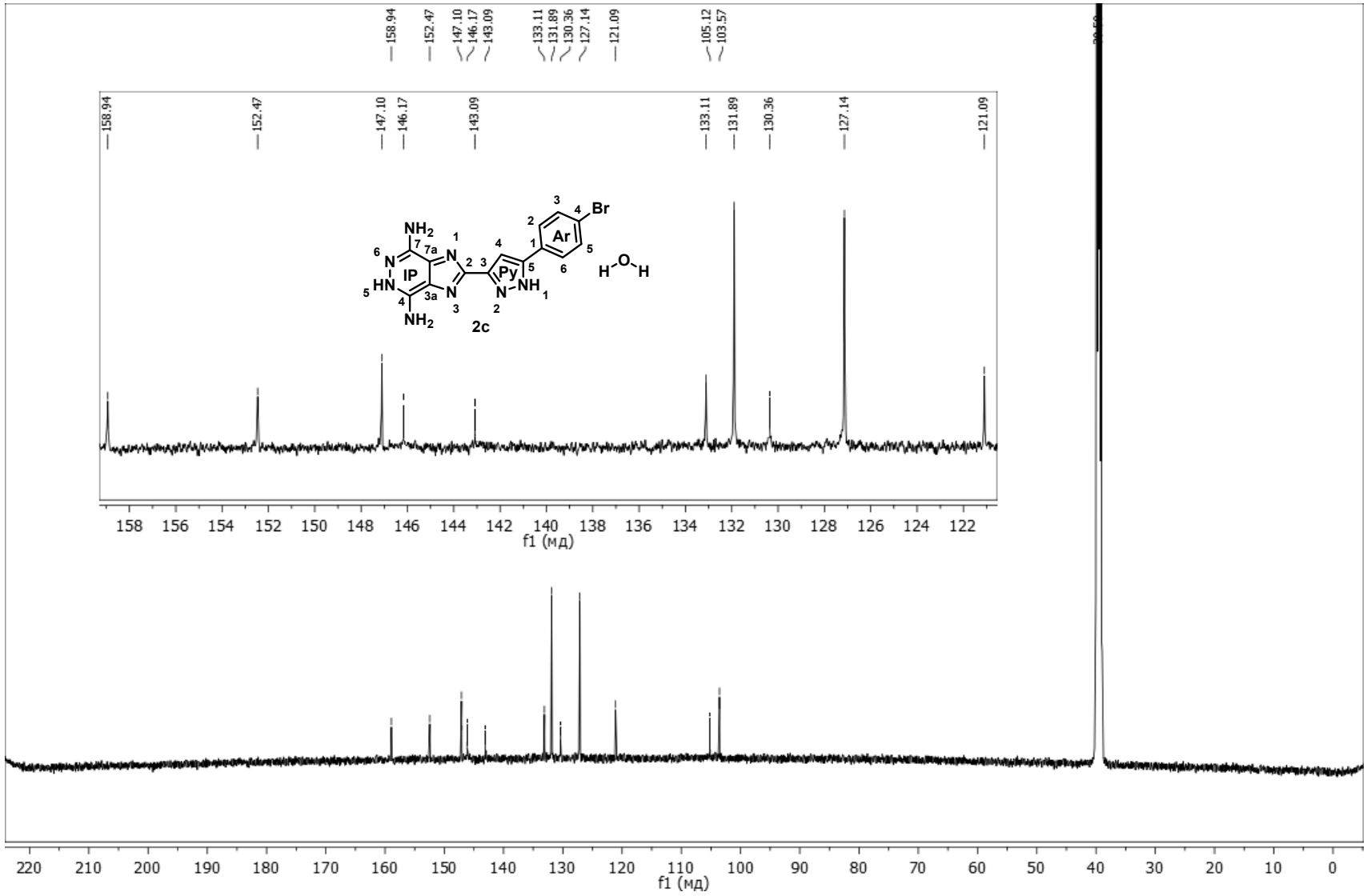

Figure S36. $^{13}C\{^{1}H\}$ NMR spectrum of **2c** in DMSO-d_6 at T = 303 K (Bruker spectrometer at 125.7 MHz).

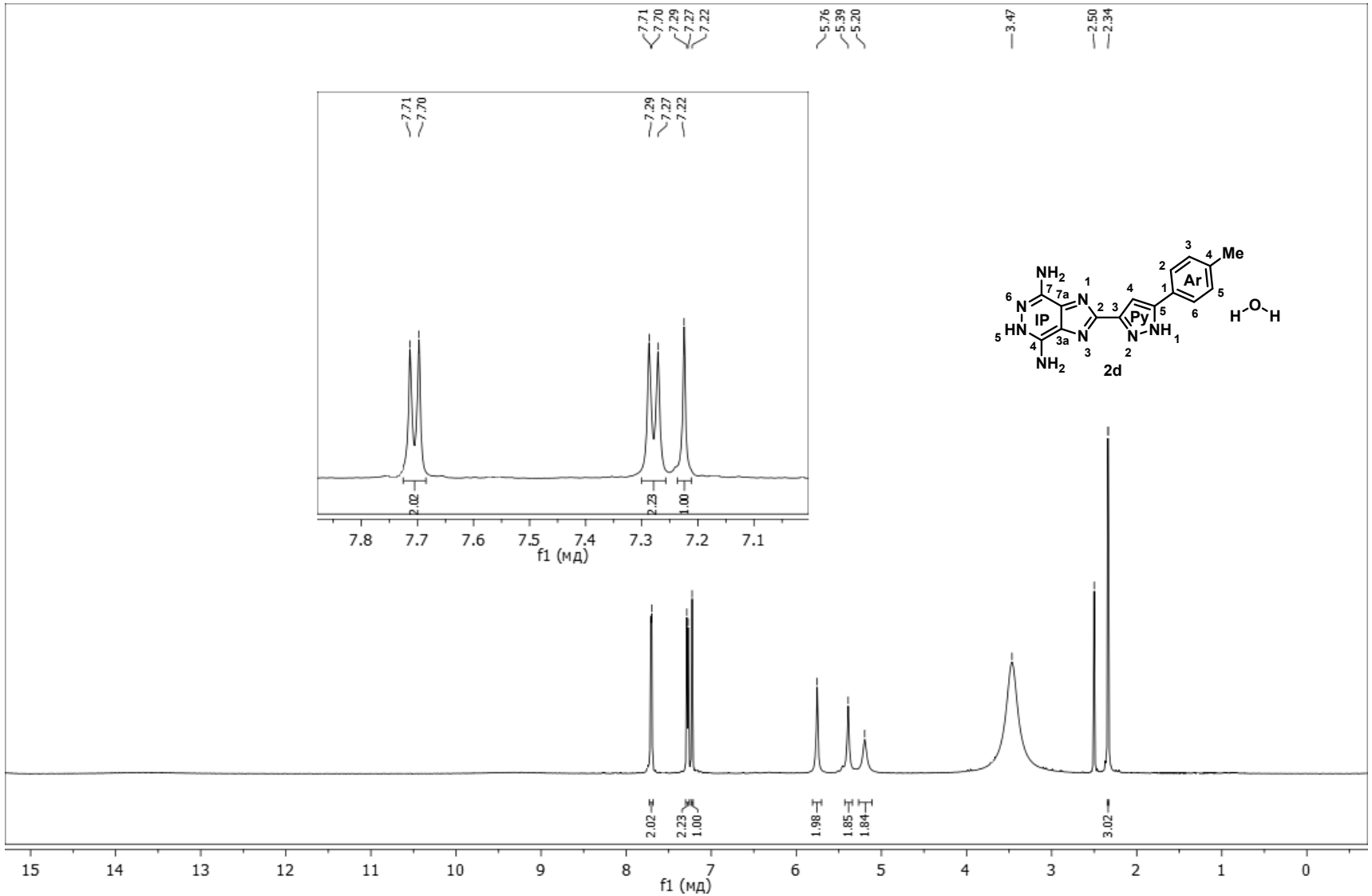

Figure S37. 1D ^{1}H NMR spectrum of **2d** in DMSO-d_6 at T = 303 K. Chemical shifts are given in ppm (Bruker spectrometer at 500.1 MHz).

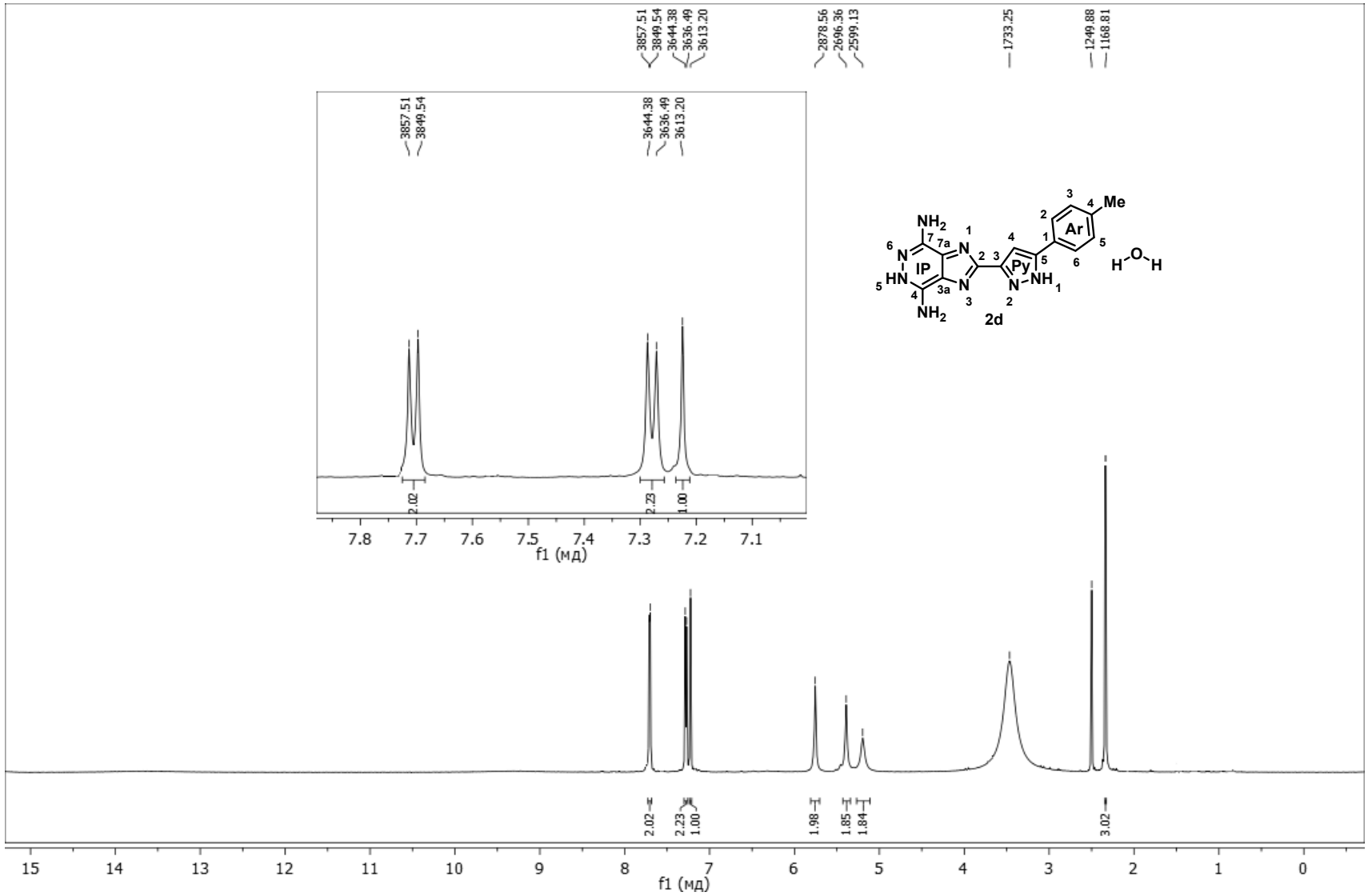

Figure S38. 1D ^{1}H NMR spectrum of **2d** in DMSO-d_6 at T = 303 K. Chemical shifts are given in Hz (Bruker spectrometer at 500.1 MHz).

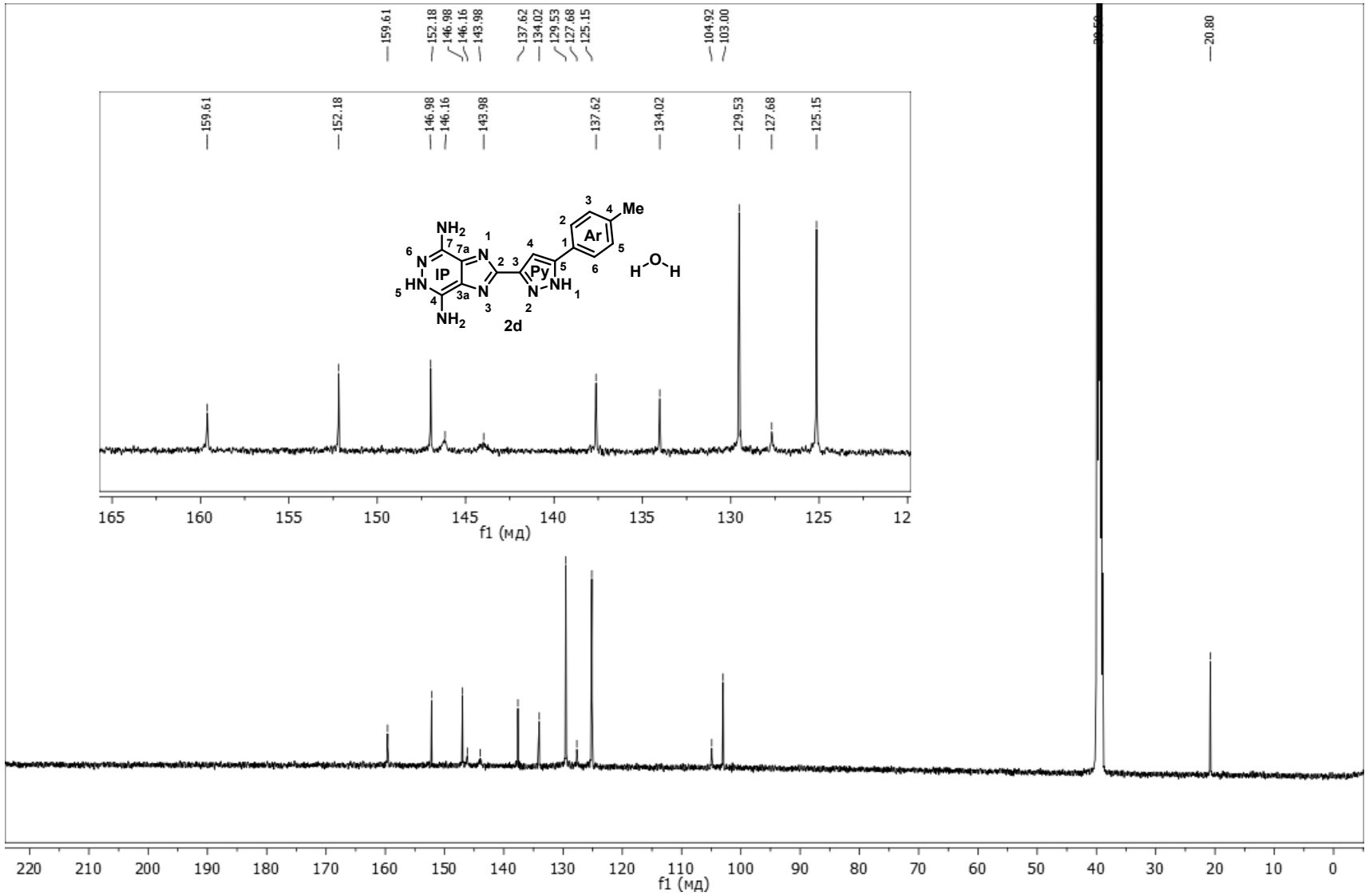

Figure S39. $^{13}C\{^{1}H\}$ NMR spectrum of **2d** in DMSO-d_6 at T = 303 K (Bruker spectrometer at 125.7 MHz).

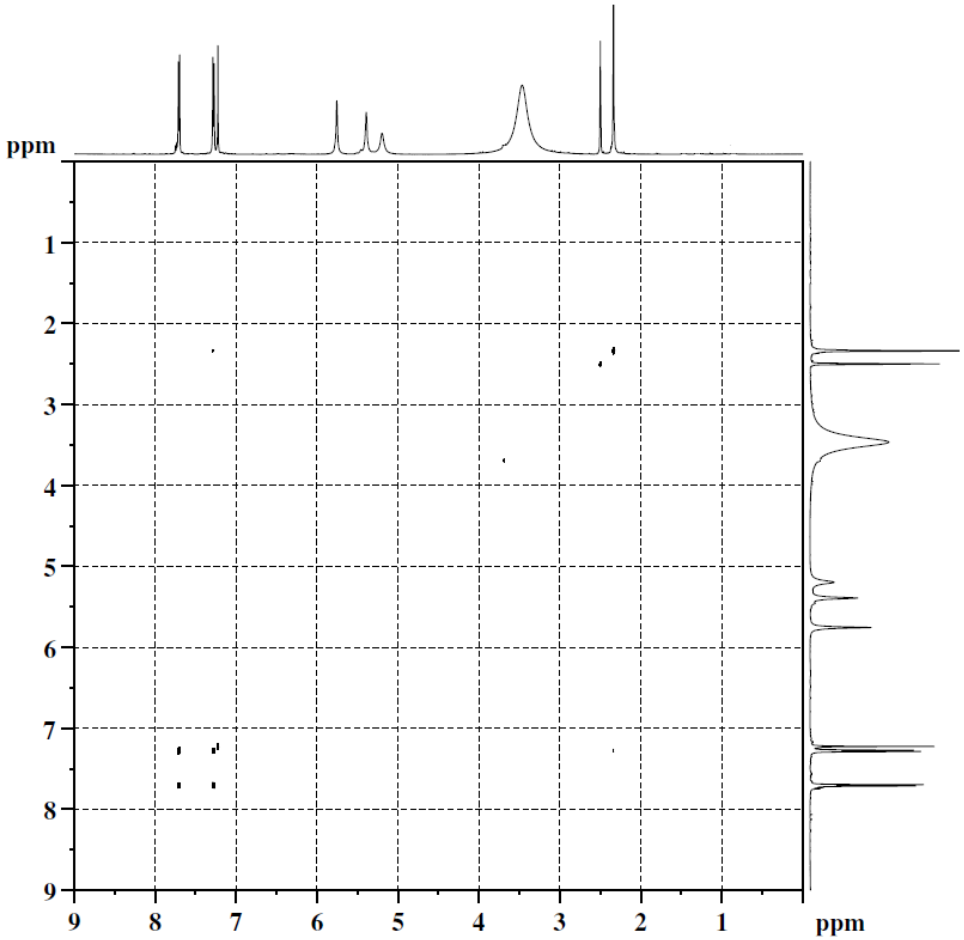

Figure S40. 2D ^{1}H-^{1}H COSY NMR spectrum of **2d** in DMSO-d_6 at T = 303 K.

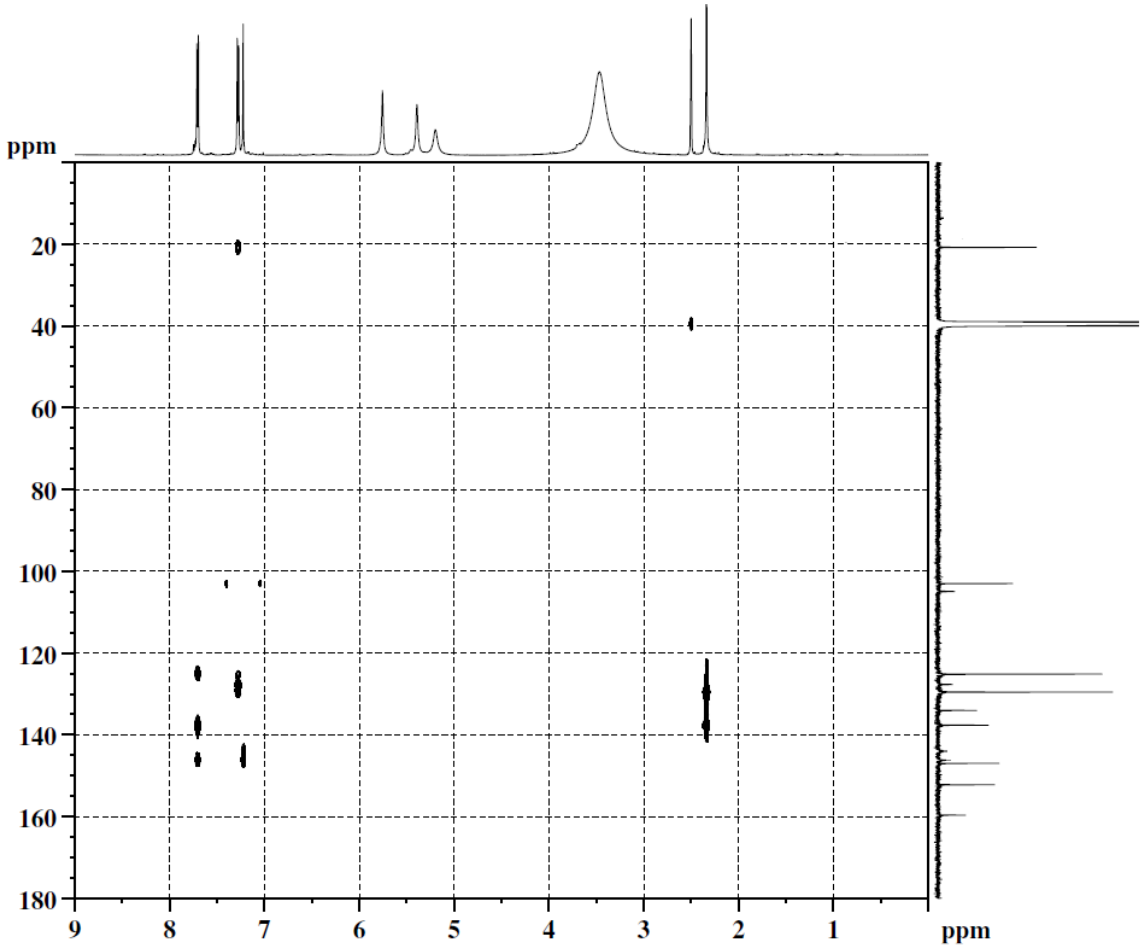

Figure S41. 2D ^{1}H-^{13}C HMBC NMR spectrum of **2d** in DMSO-d_6 at T = 303 K.

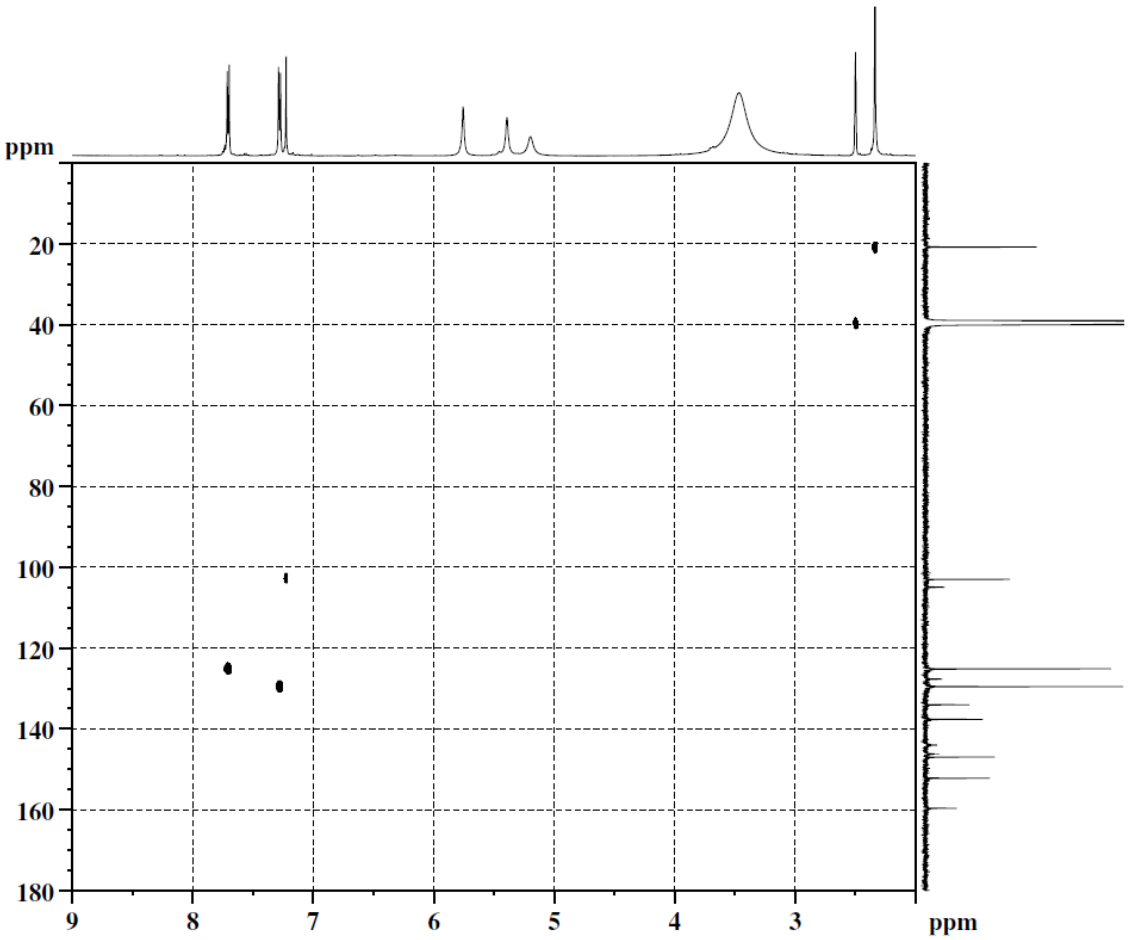

Figure S42. 2D 1H-^{13}C HSQC NMR spectrum of **2d** in DMSO-d_6 at T = 303 K.

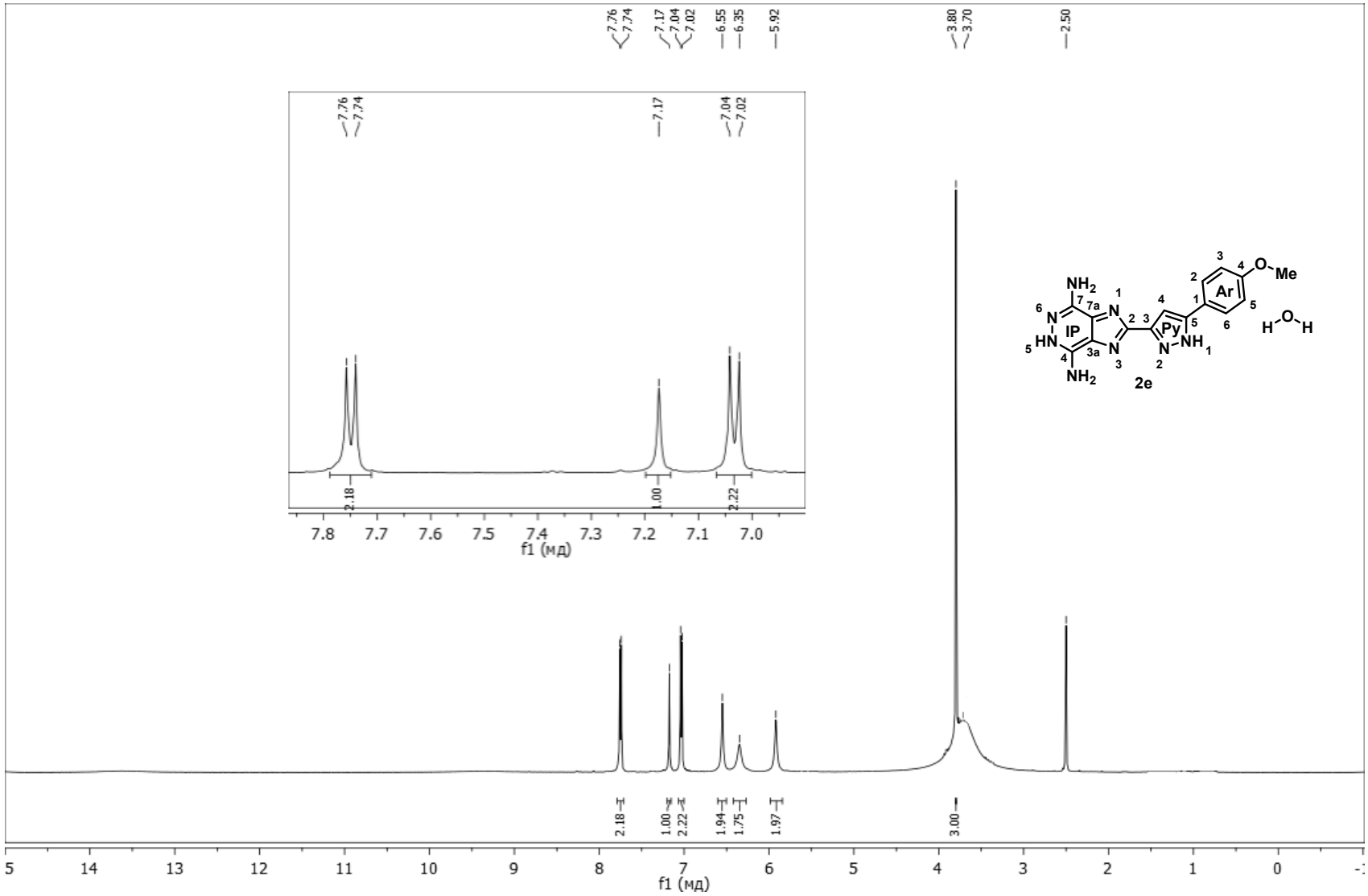

Figure S43. 1D ^{1}H NMR spectrum of **2e** in DMSO-d_6 at T = 303 K. Chemical shifts are given in ppm (Bruker spectrometer at 500.1 MHz).

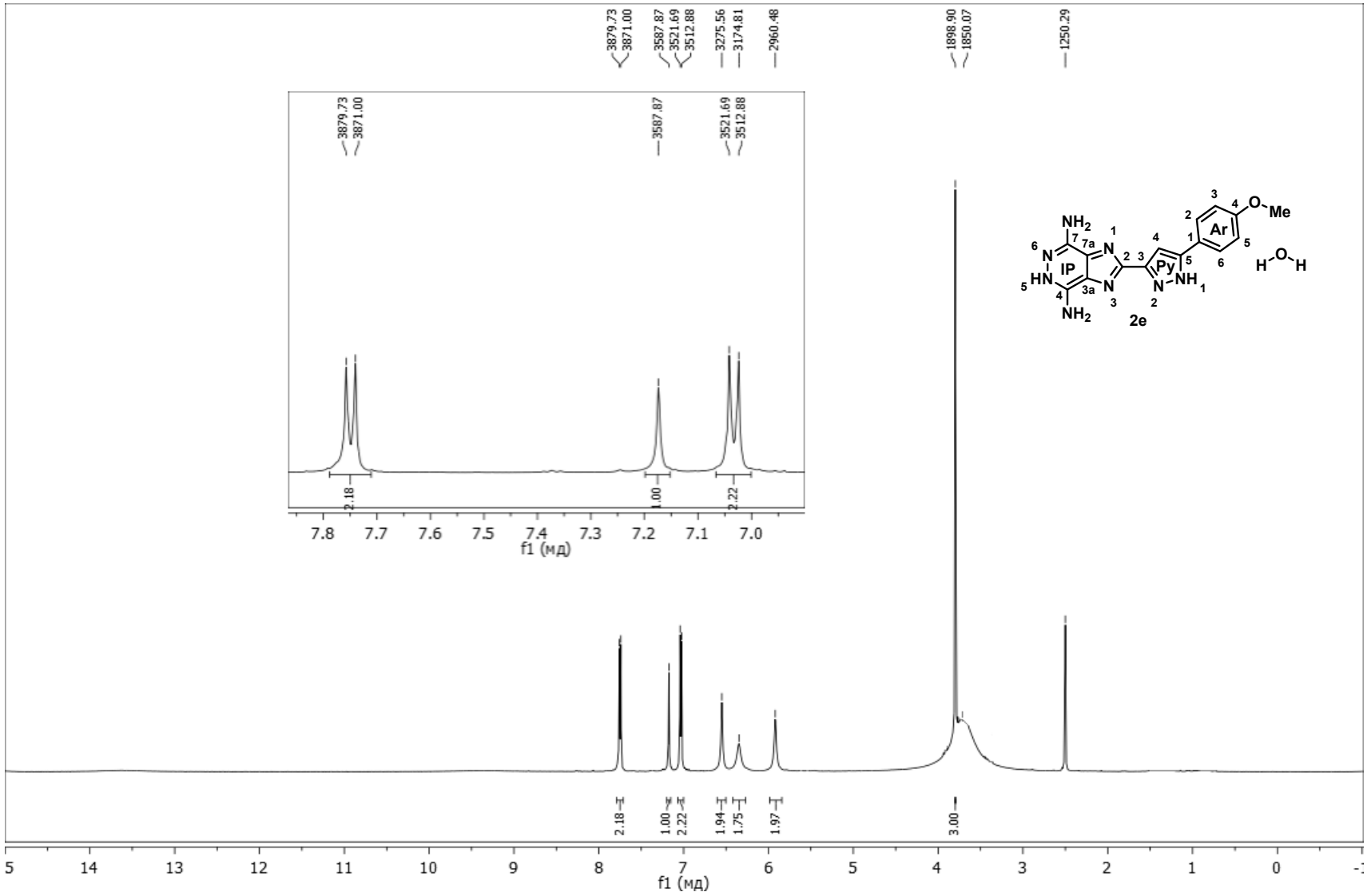

Figure S44. 1D ^{1}H NMR spectrum of **2e** in DMSO-d_6 at T = 303 K. Chemical shifts are given in Hz (Bruker spectrometer at 500.1 MHz).

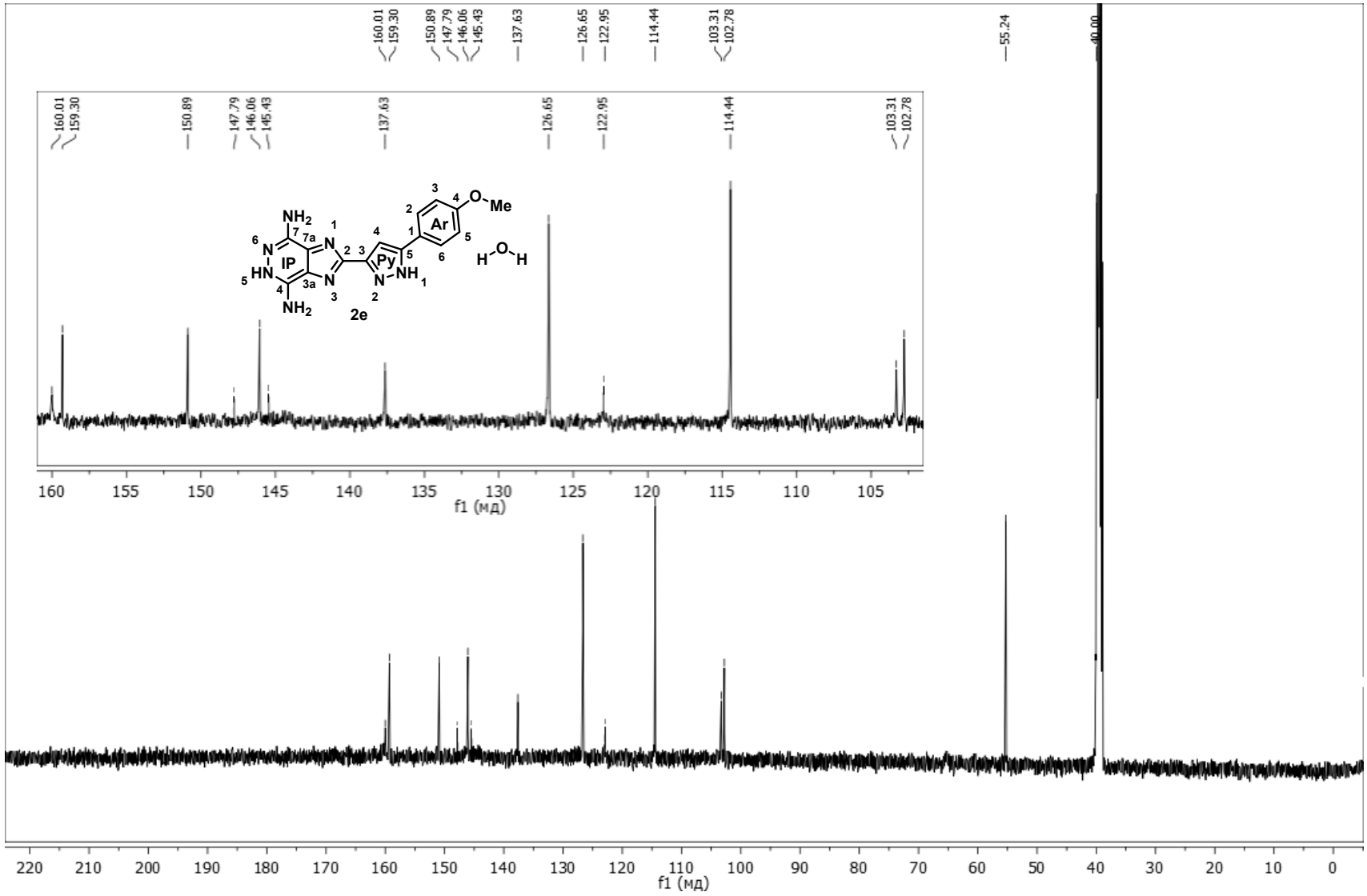

Figure S45. $^{13}C\{^{1}H\}$ NMR spectrum of **2e** in DMSO-d_6 at T = 303 K (Bruker spectrometer at 125.7 MHz).

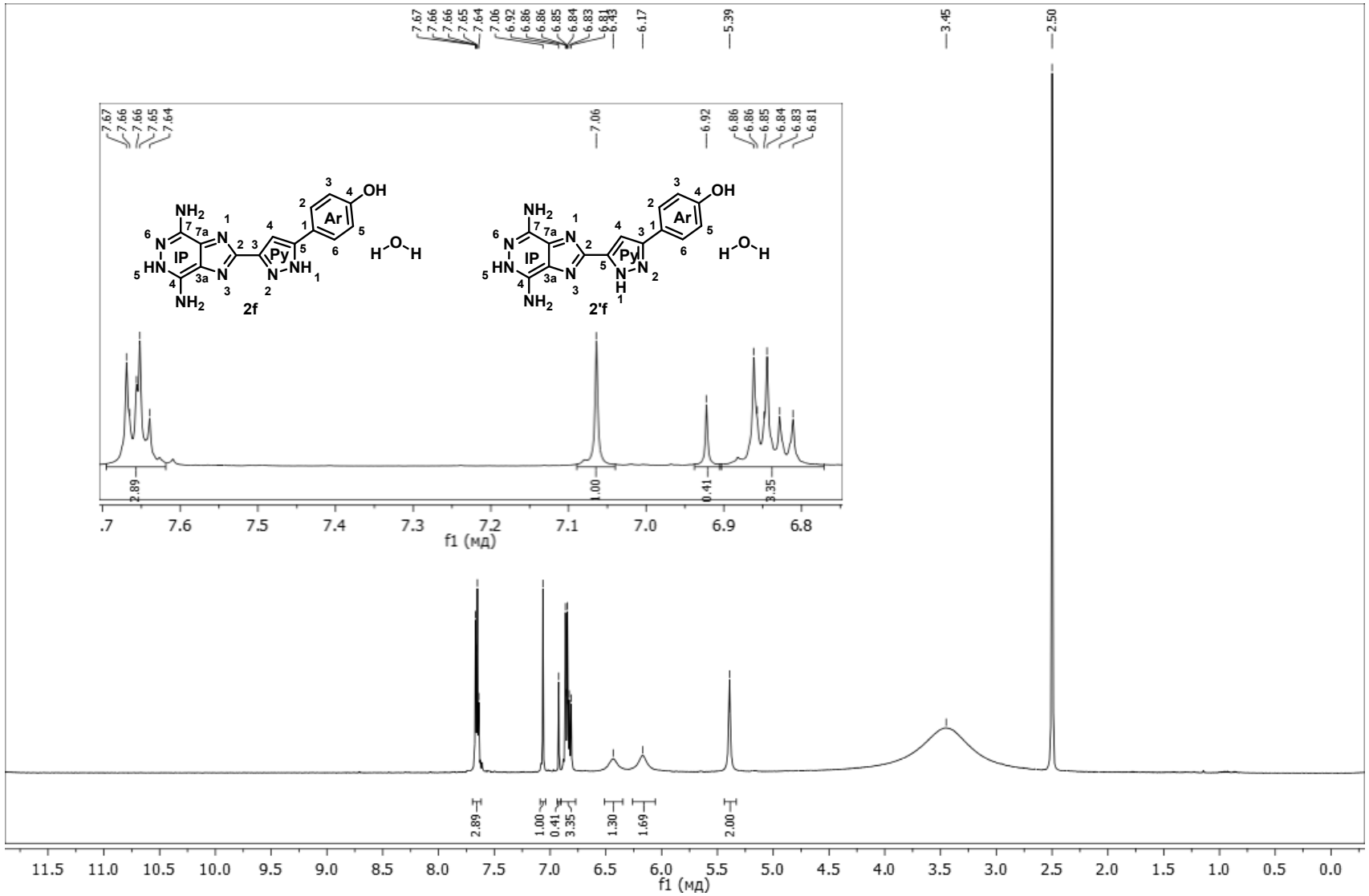

Figure S46. 1D ^{1}H NMR spectrum of **2f** and **2′f** in DMSO-d_6 at T = 303 K. Chemical shifts are given in ppm (Bruker spectrometer at 500.1 MHz).

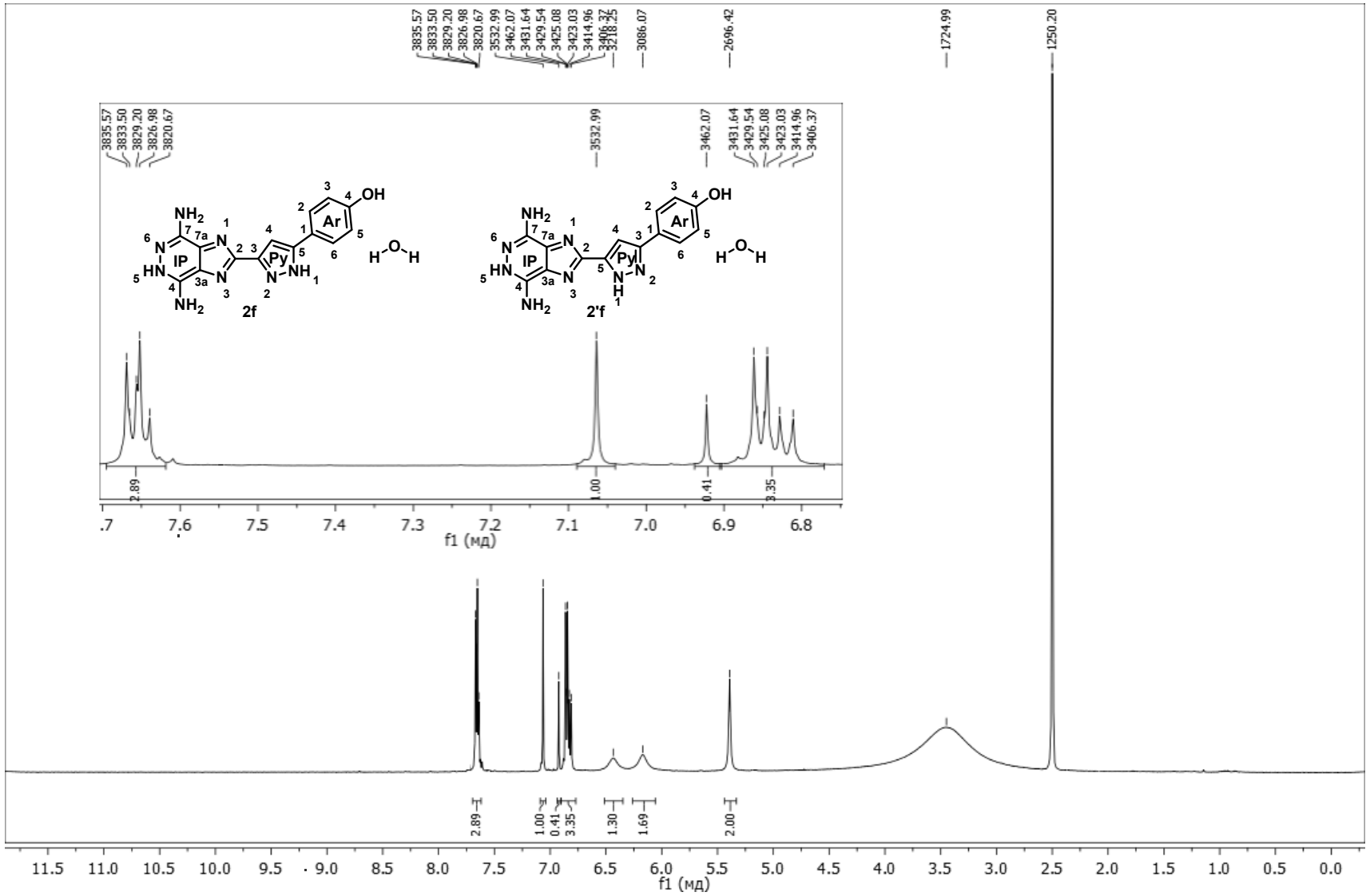

Figure S47. 1D ^{1}H NMR spectrum of **2f** and **2′f** in DMSO-d_6 at T = 303 K. Chemical shifts are given in Hz (Bruker spectrometer at 500.1 MHz).

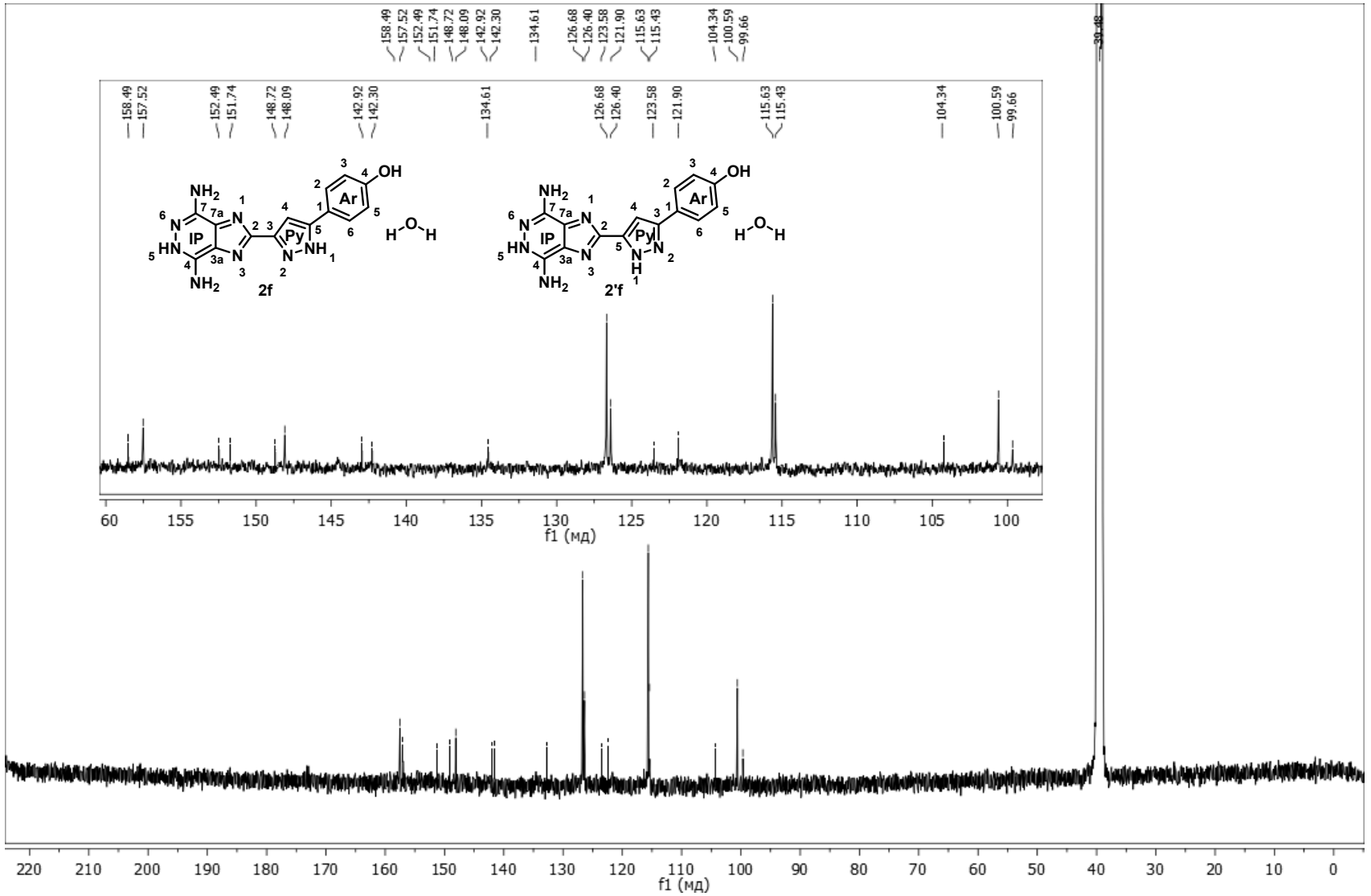

Figure S48. $^{13}C\{^{1}H\}$ NMR spectrum of **2f** and **2′f** in DMSO-d_6 at T = 303 K (Bruker spectrometer at 125.7 MHz).

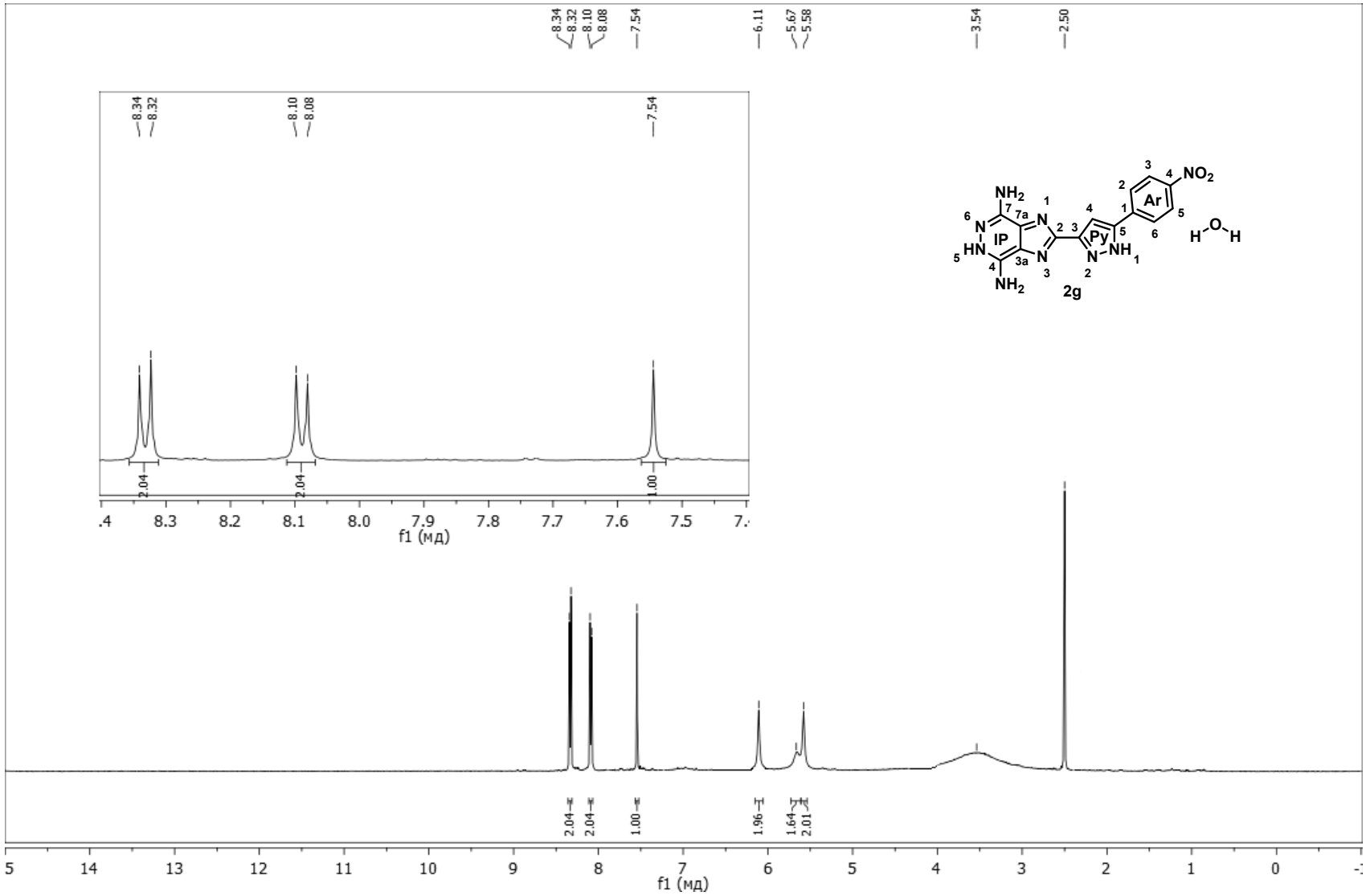

Figure S49. 1D ^{1}H NMR spectrum of **2g** in DMSO-d_6 at T = 303 K. Chemical shifts are given in ppm (Bruker spectrometer at 500.1 MHz).

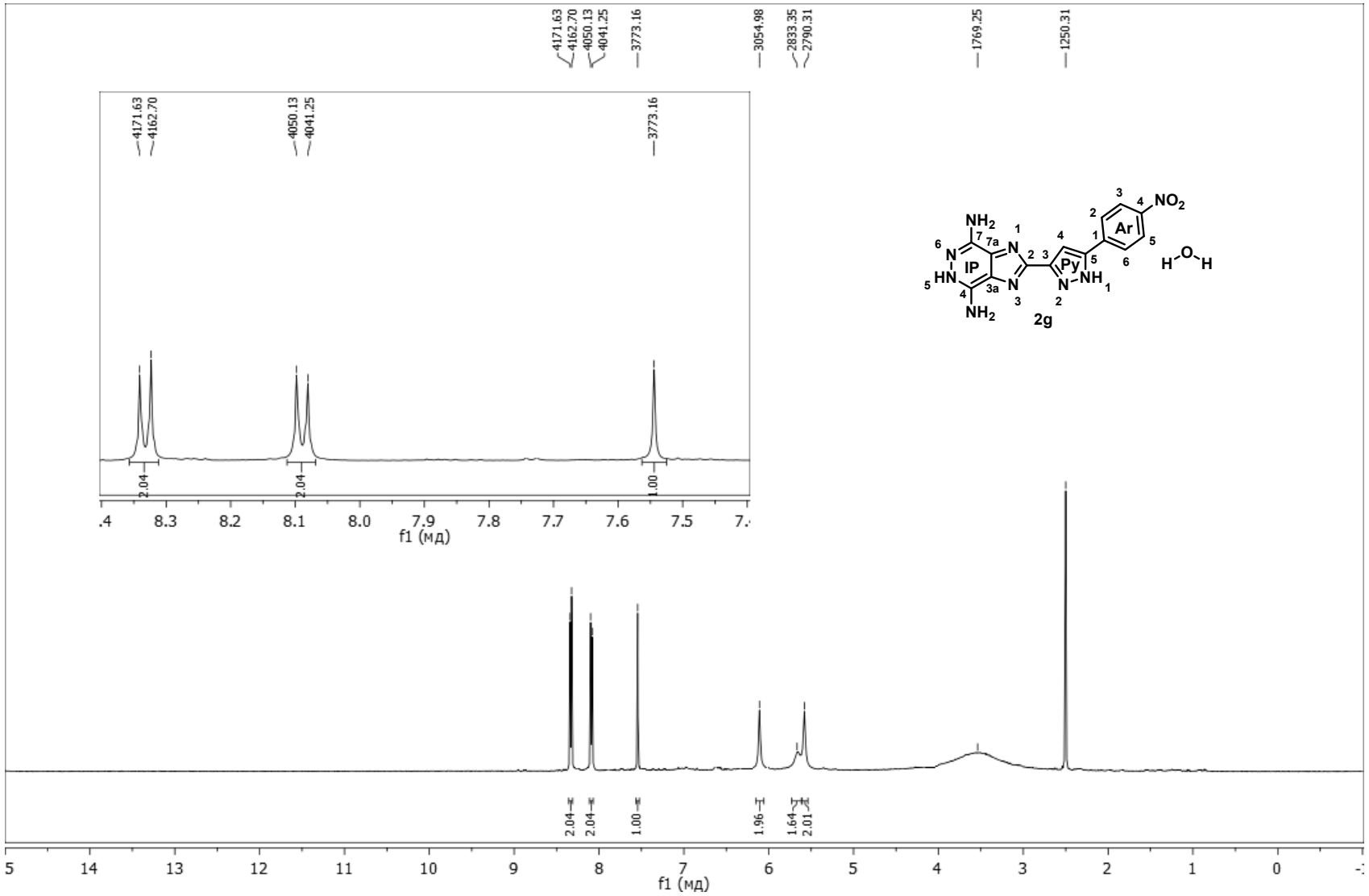

Figure S50. 1D ^{1}H NMR spectrum of **2g** in DMSO-d_6 at T = 303 K. Chemical shifts are given in Hz (Bruker spectrometer at 500.1 MHz).

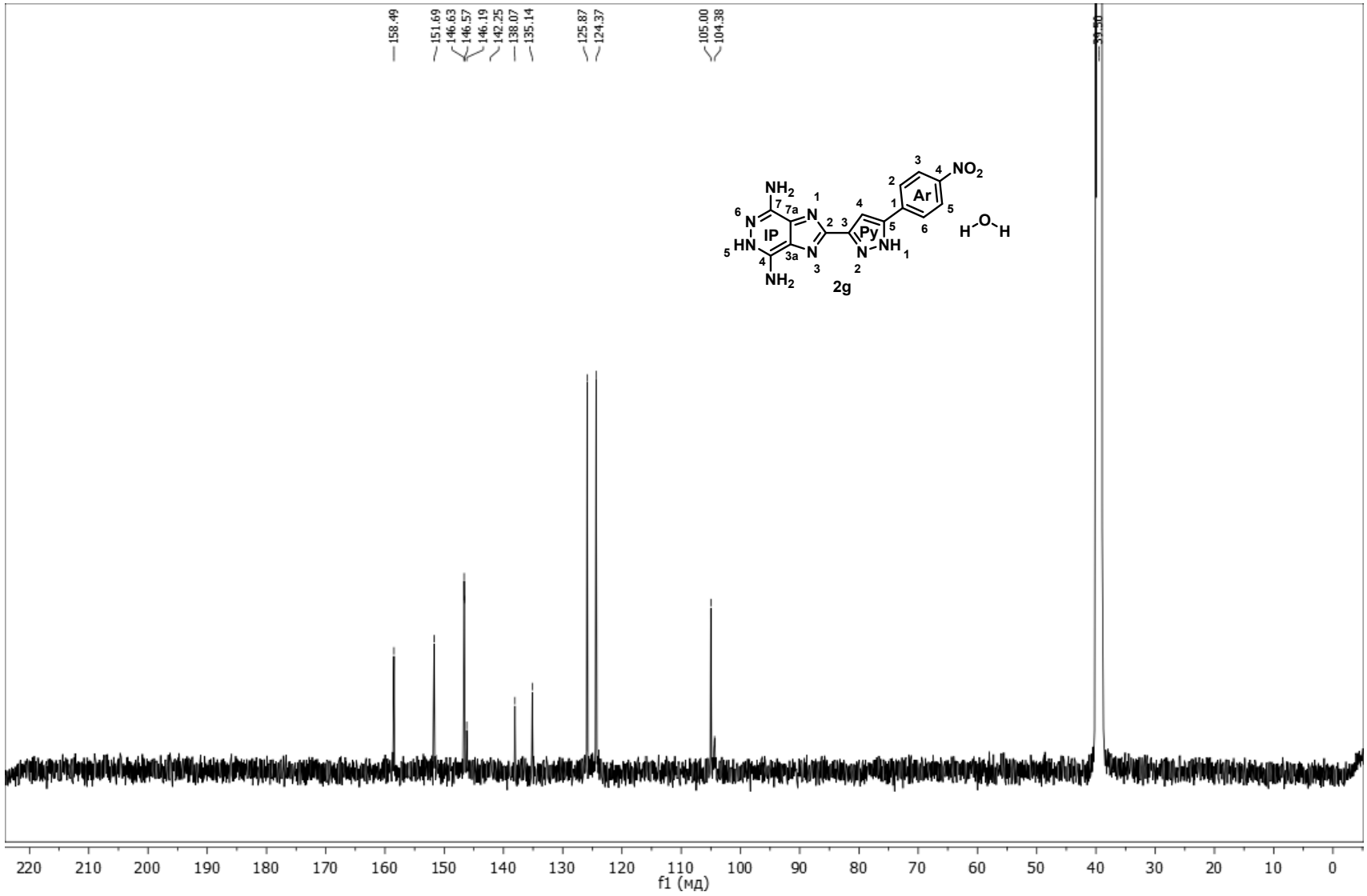

Figure S51. $^{13}C\{^{1}H\}$ NMR spectrum of **2g** in DMSO-d_6 at T = 303 K (Bruker spectrometer at 125.7 MHz).

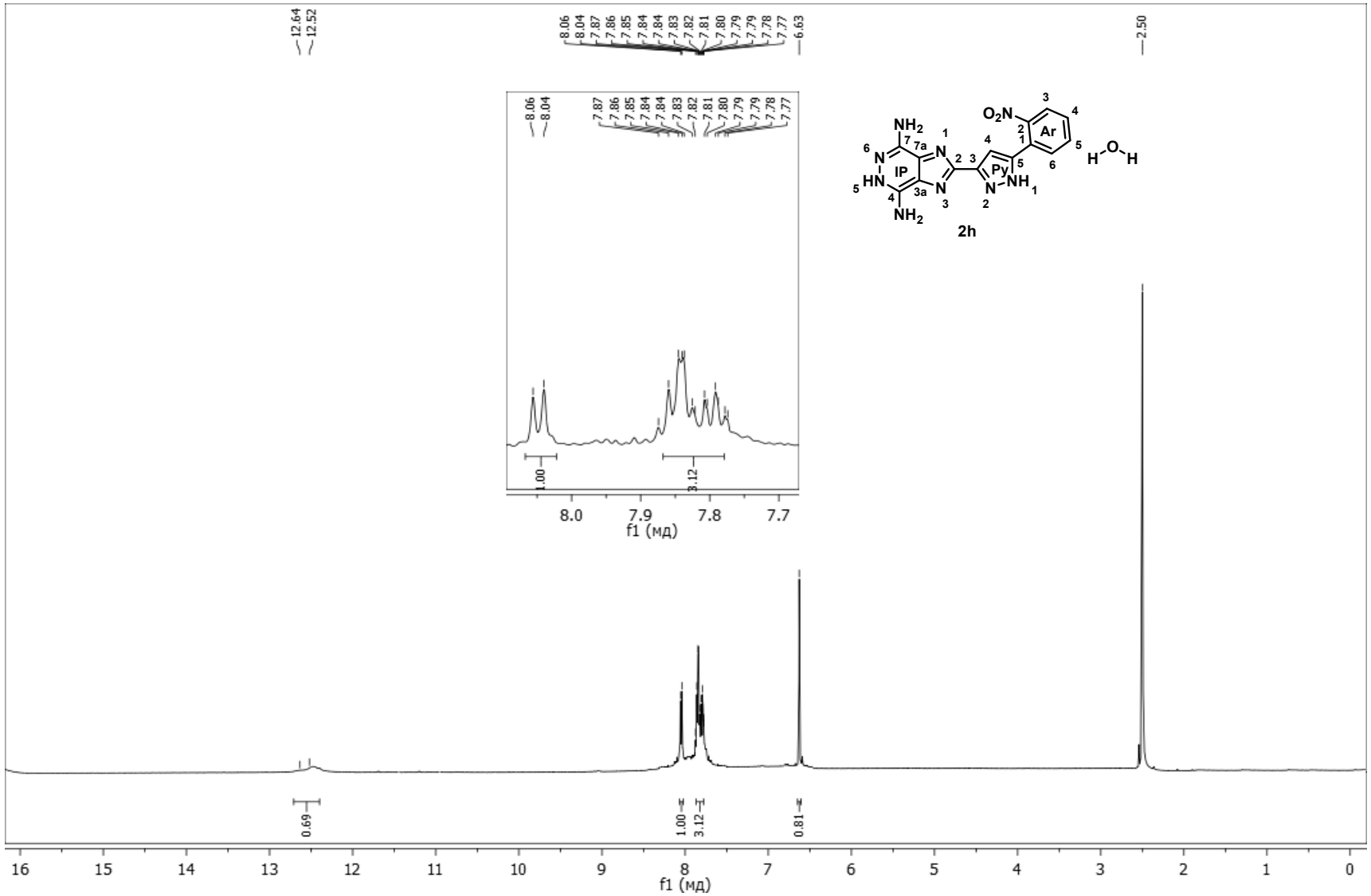

Figure S52. 1D ^{1}H NMR spectrum of **2h** in DMSO-d_6 at T = 303 K. Chemical shifts are given in ppm (Bruker spectrometer at 500.1 MHz).

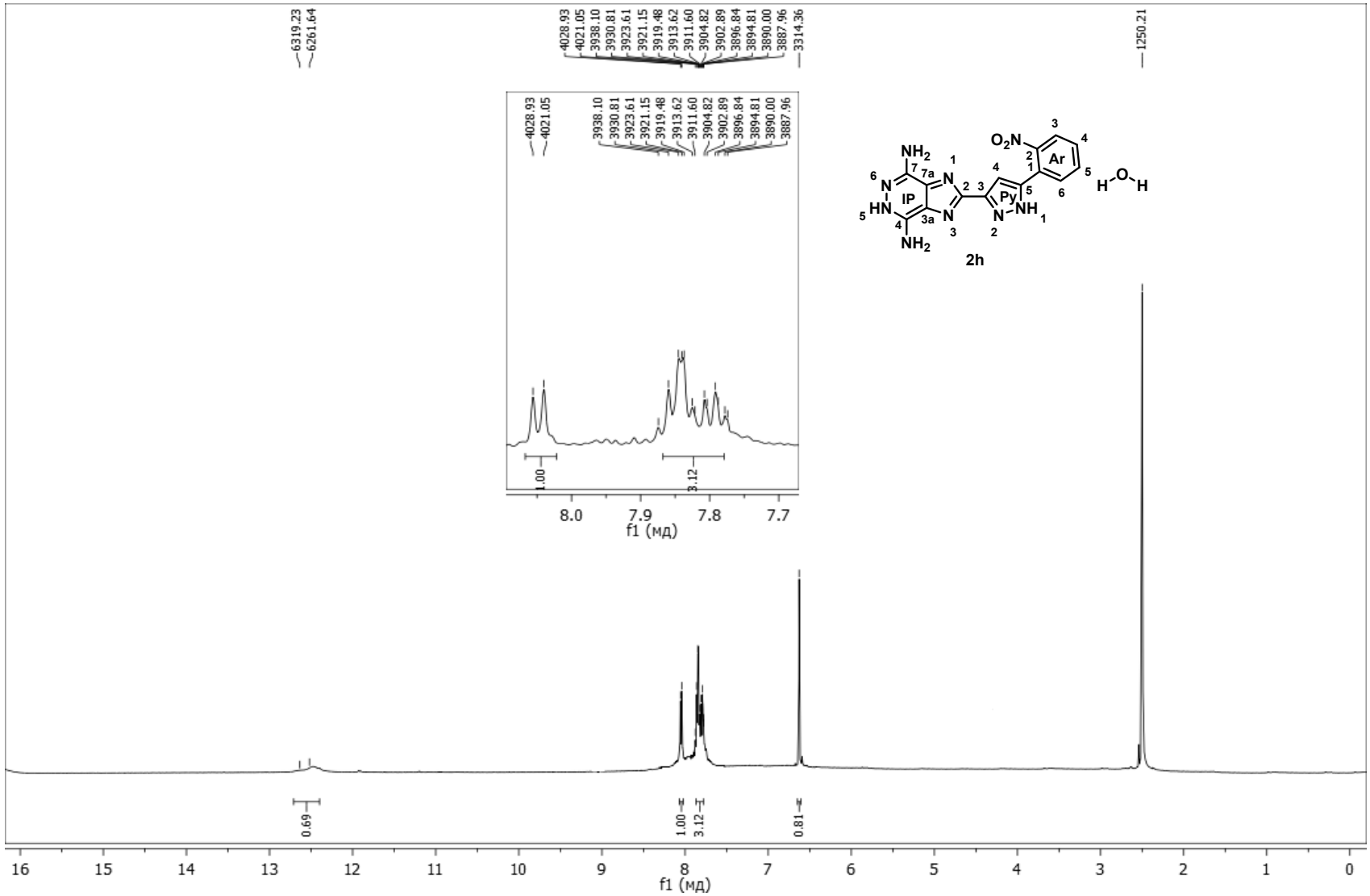

Figure S53. 1D ^{1}H NMR spectrum of **2h** in DMSO-d_6 at T = 303 K. Chemical shifts are given in Hz (Bruker spectrometer at 500.1 MHz).

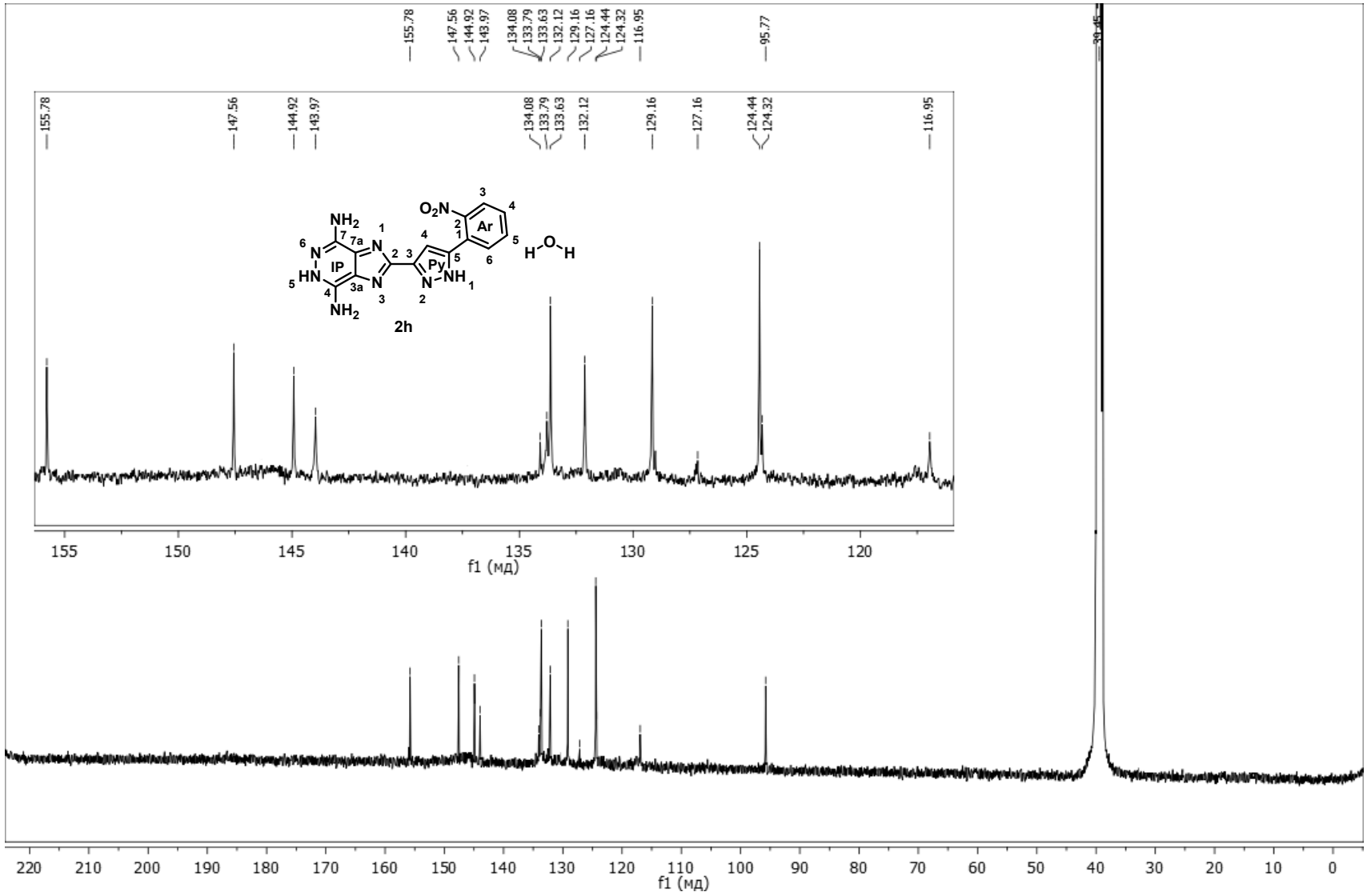

Figure S54. $^{13}C\{^{1}H\}$ NMR spectrum of **2h** in DMSO-d_6 at T = 303 K (Bruker spectrometer at 125.7 MHz).

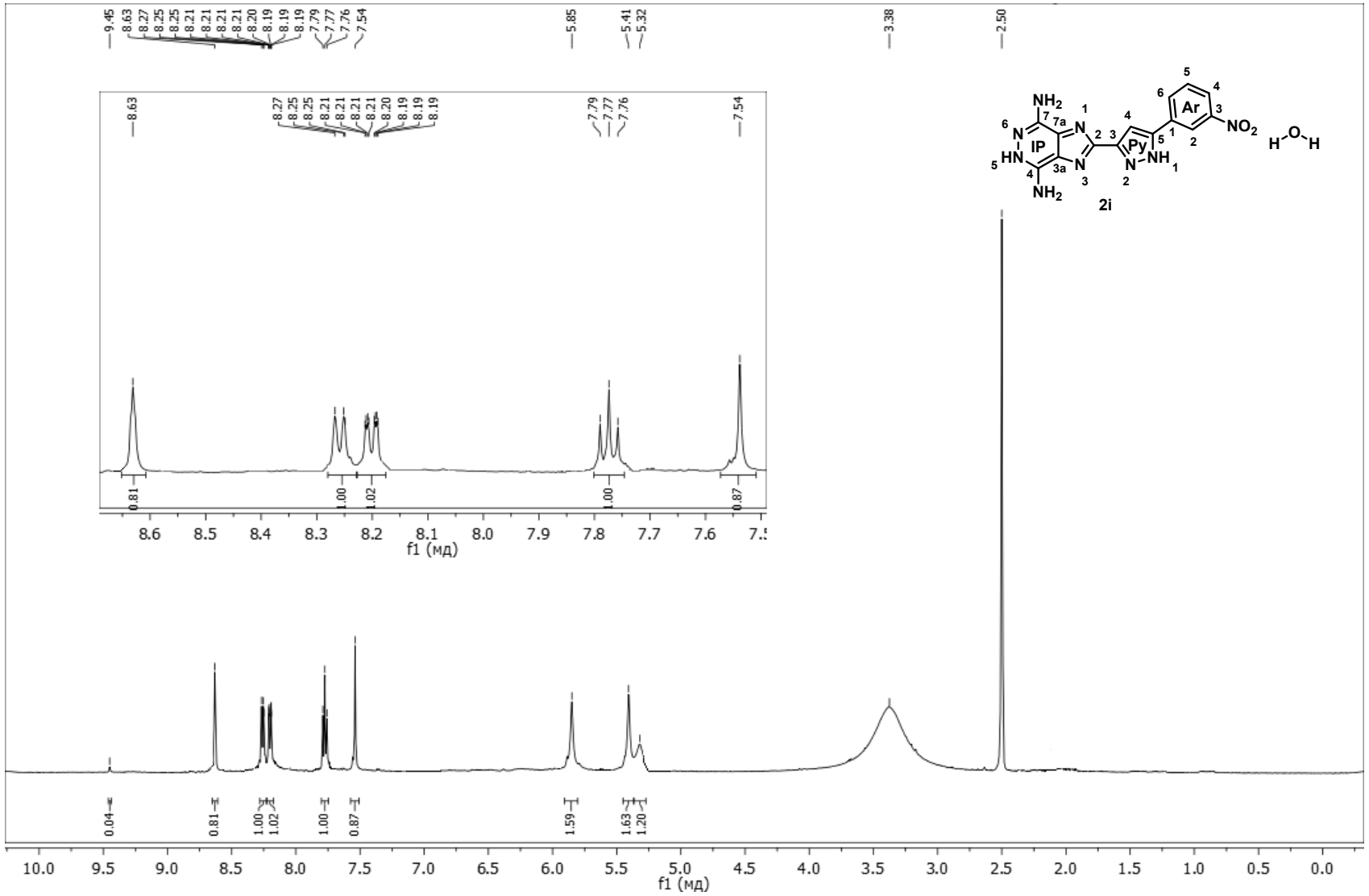

Figure S55. 1D ^{1}H NMR spectrum of **2i** in DMSO-d_6 at T = 303 K. Chemical shifts are given in ppm (Bruker spectrometer at 500.1 MHz).

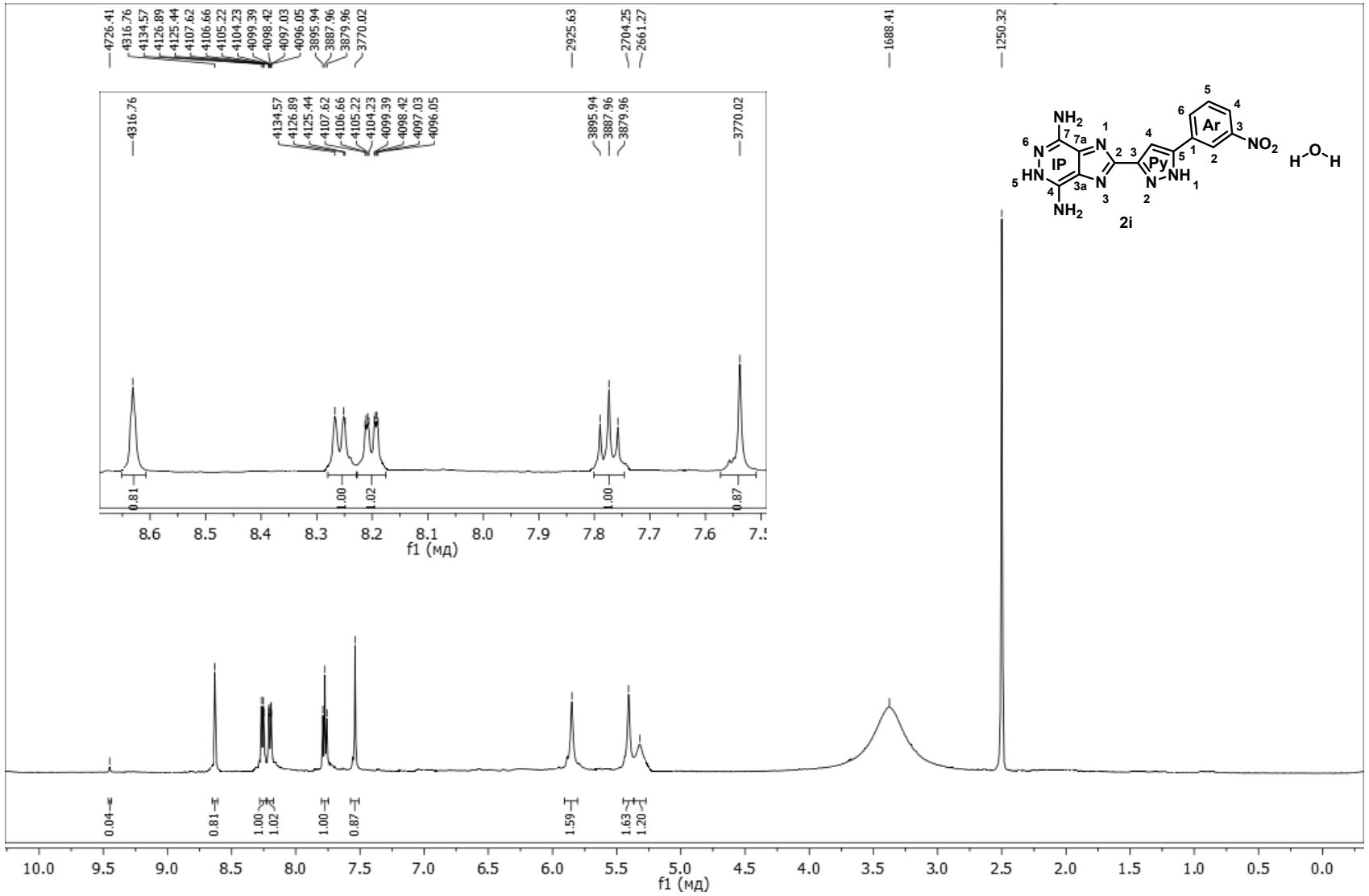

Figure S56. 1D ^{1}H NMR spectrum of **2i** in DMSO-d_6 at T = 303 K. Chemical shifts are given in Hz (Bruker spectrometer at 500.1 MHz).

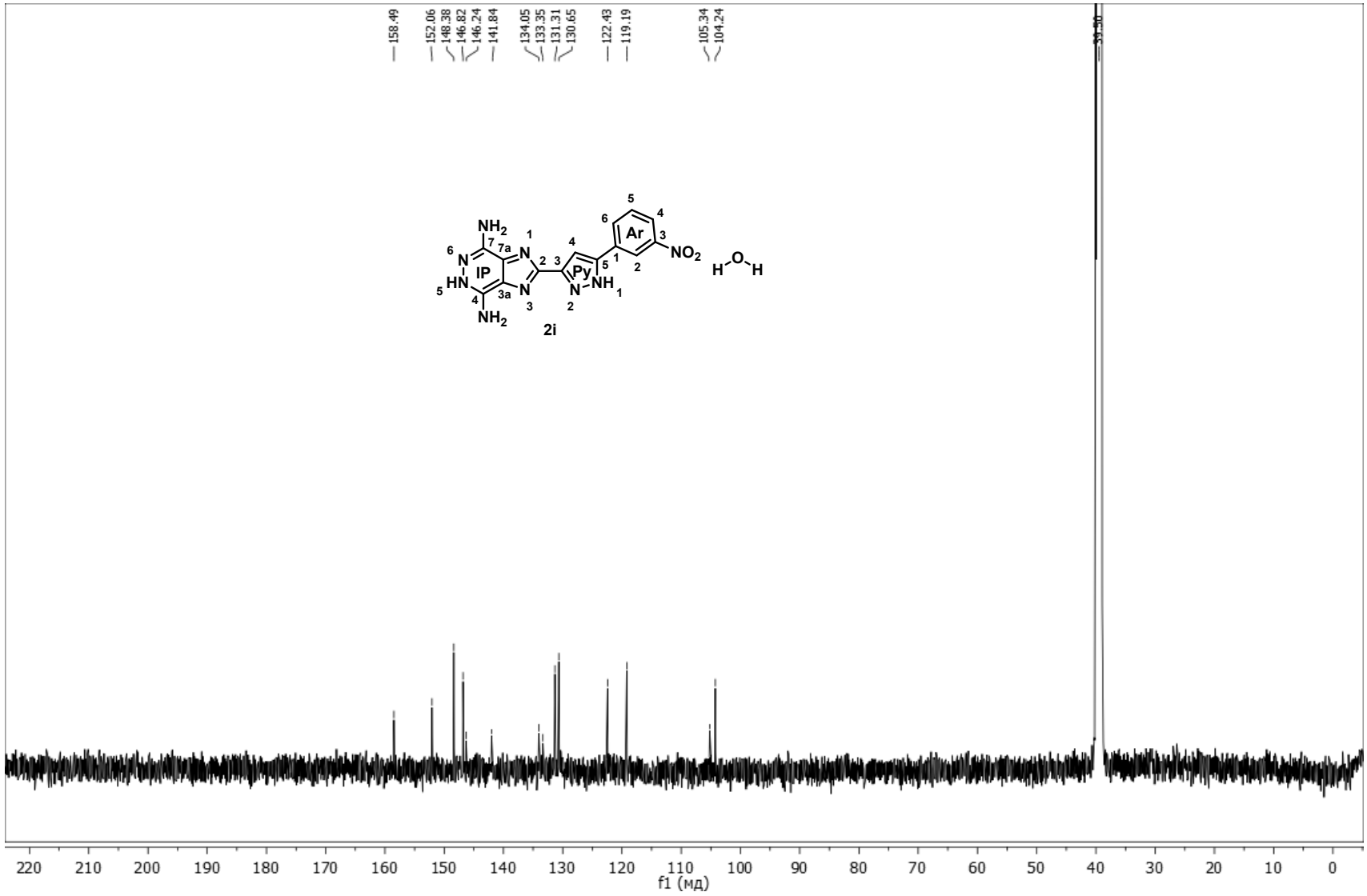

Figure S57. $^{13}C\{^{1}H\}$ NMR spectrum of **2i** in DMSO-d_6 at T = 303 K (Bruker spectrometer at 125.7 MHz).

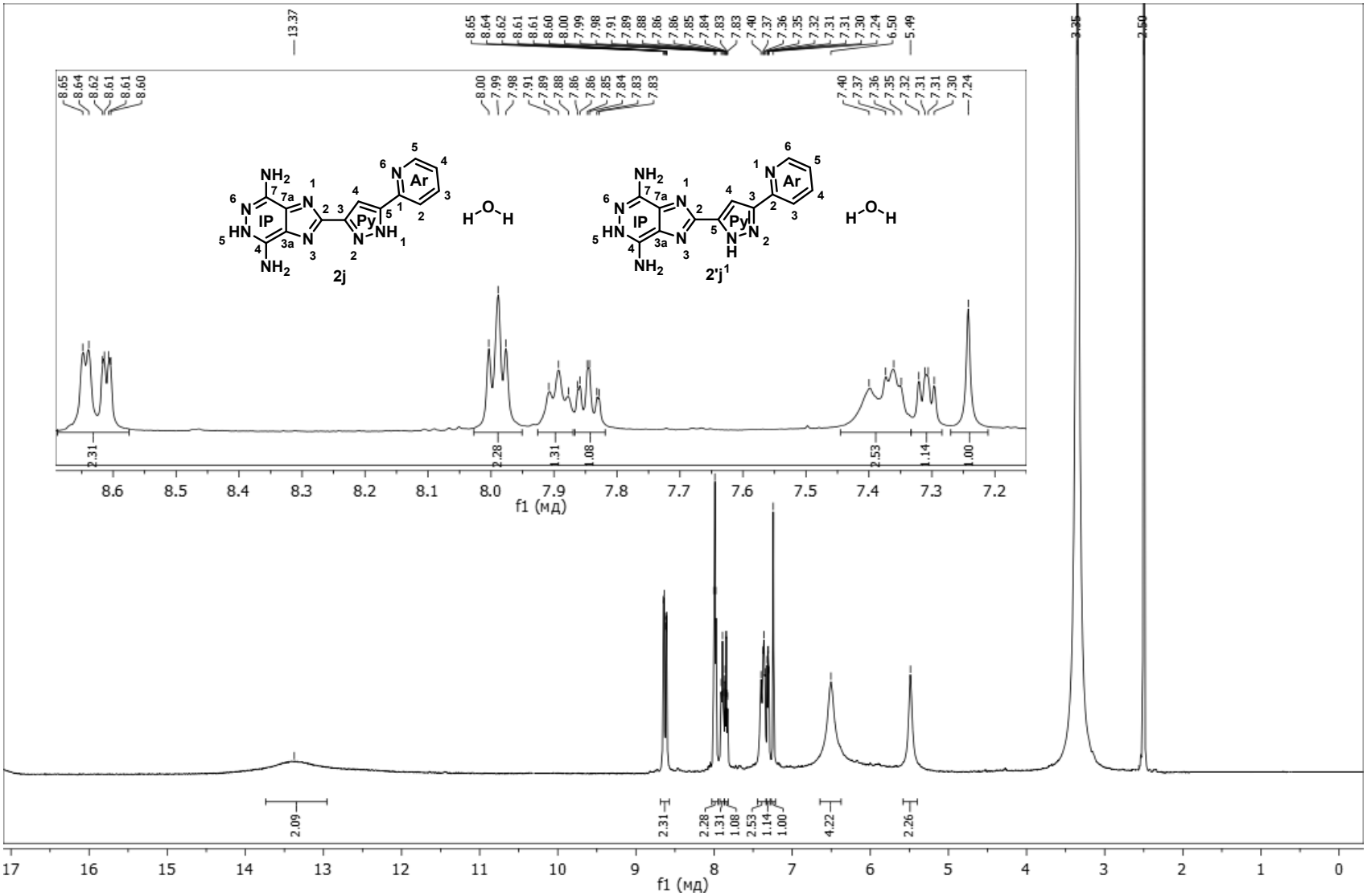

Figure S58. 1D ^{1}H NMR spectrum of **2j** and **2′j** in DMSO-d_6 at T = 303 K. Chemical shifts are given in ppm (Bruker spectrometer at 500.1 MHz).

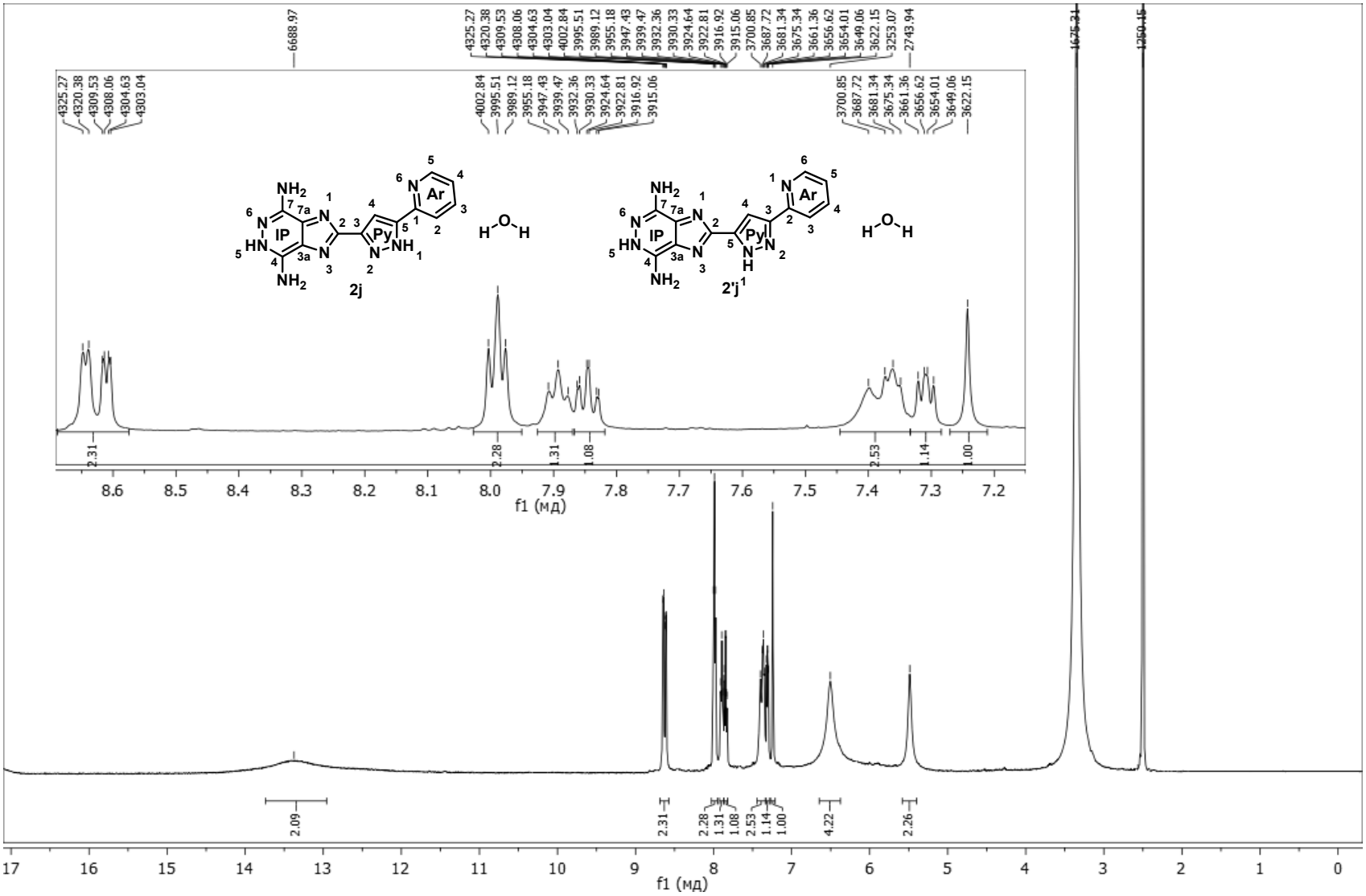

Figure S59. 1D ^{1}H NMR spectrum of **2j** and **2′j** in DMSO-d_6 at T = 303 K. Chemical shifts are given in Hz (Bruker spectrometer at 500.1 MHz).

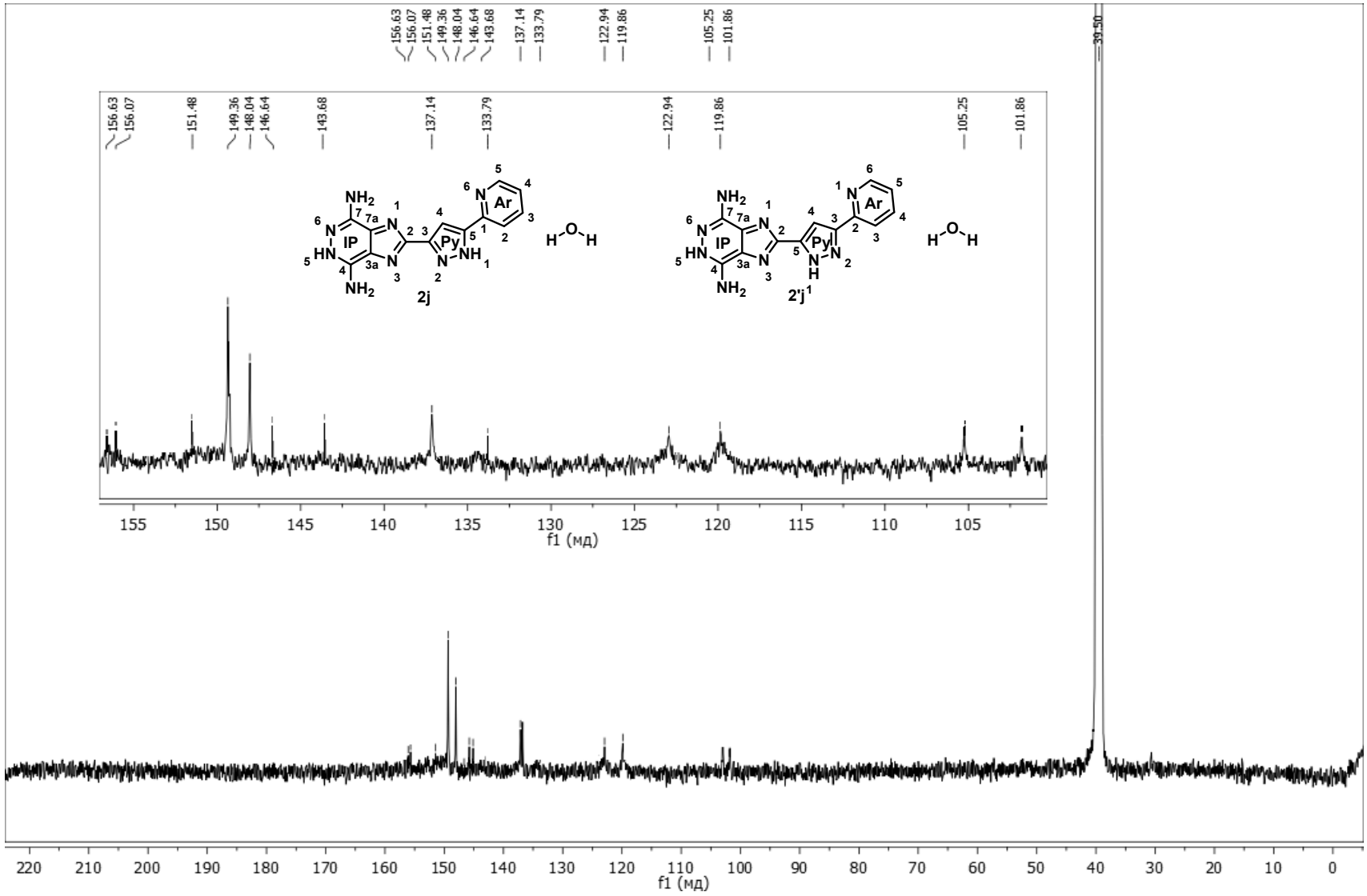

Figure S60. $^{13}C\{^{1}H\}$ NMR spectrum of **2j** and **2′j** in DMSO-d_6 at T = 303 K (Bruker spectrometer at 125.7 MHz).

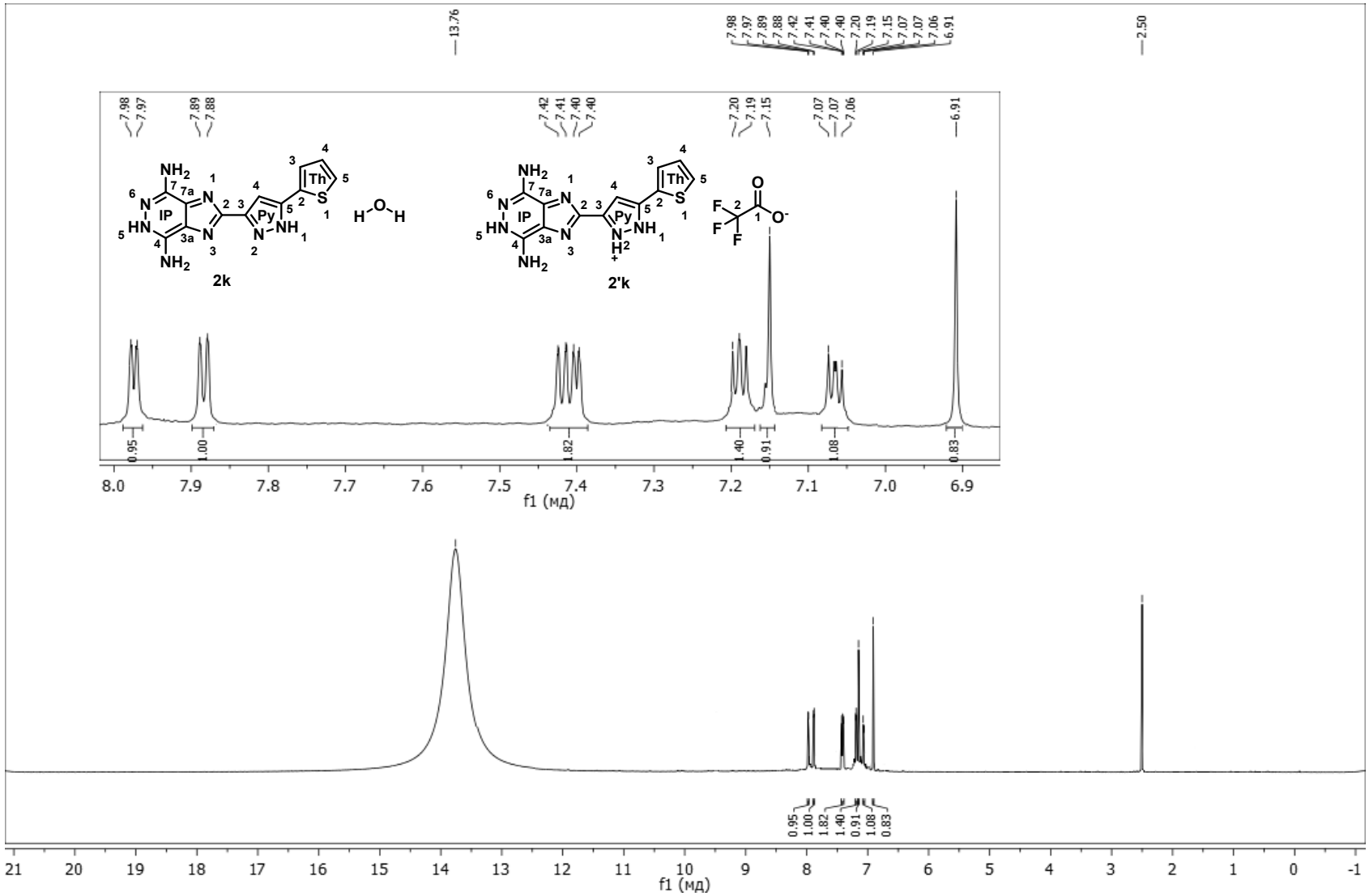

Figure S61. 1D ^{1}H NMR spectrum of **2k** and **2′k** in DMSO-d_6 at T = 303 K. Chemical shifts are given in ppm (Bruker spectrometer at 500.1 MHz).

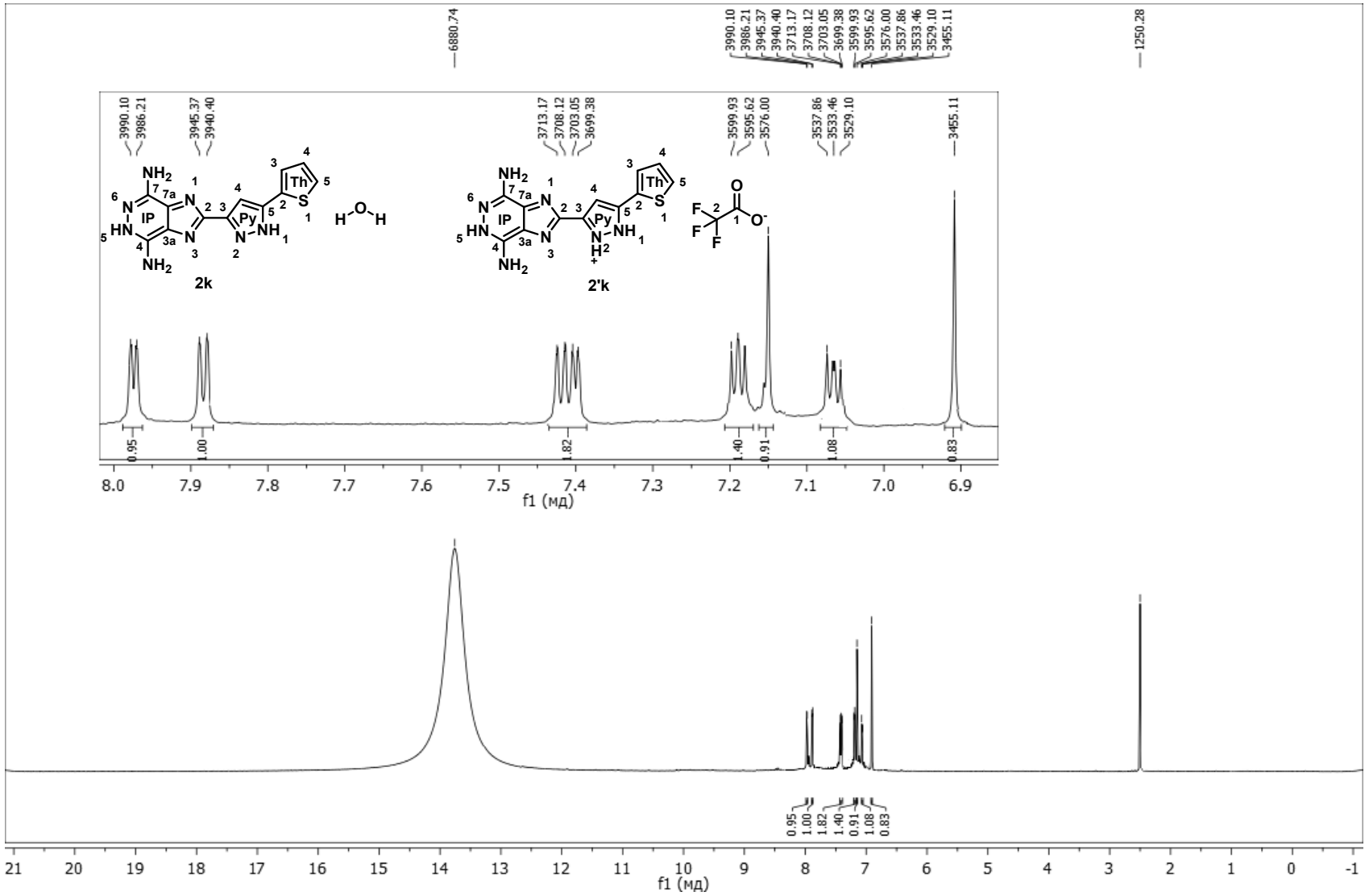

Figure S62. 1D ^{1}H NMR spectrum of **2k** and **2′k** in DMSO-d_6 at T = 303 K. Chemical shifts are given in Hz (Bruker spectrometer at 500.1 MHz).

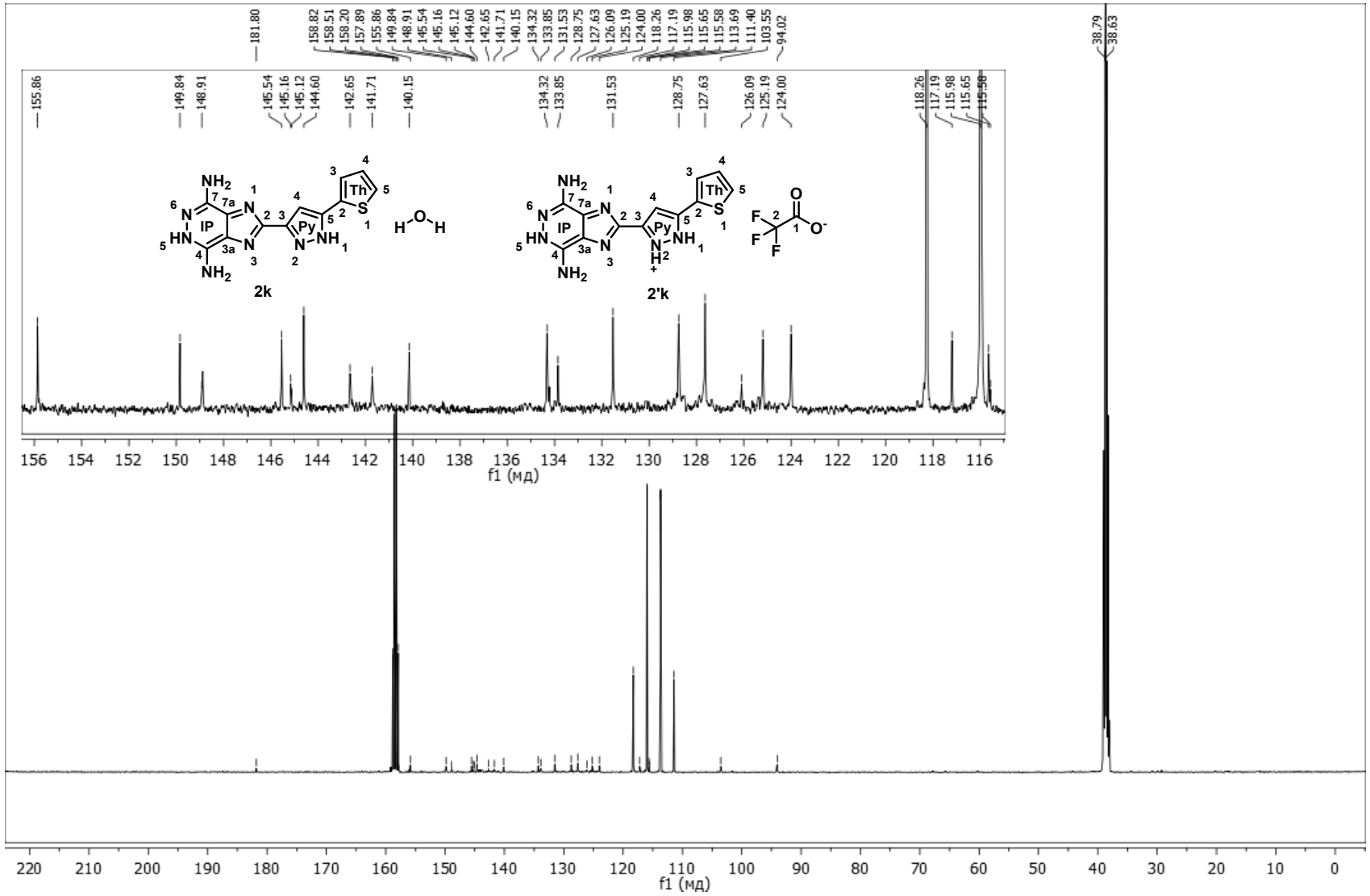

Figure S63. $^{13}C\{^{1}H\}$ NMR spectrum of **2k** and **2′k** in DMSO-d_6 at T = 303 K (Bruker spectrometer at 125.7 MHz).

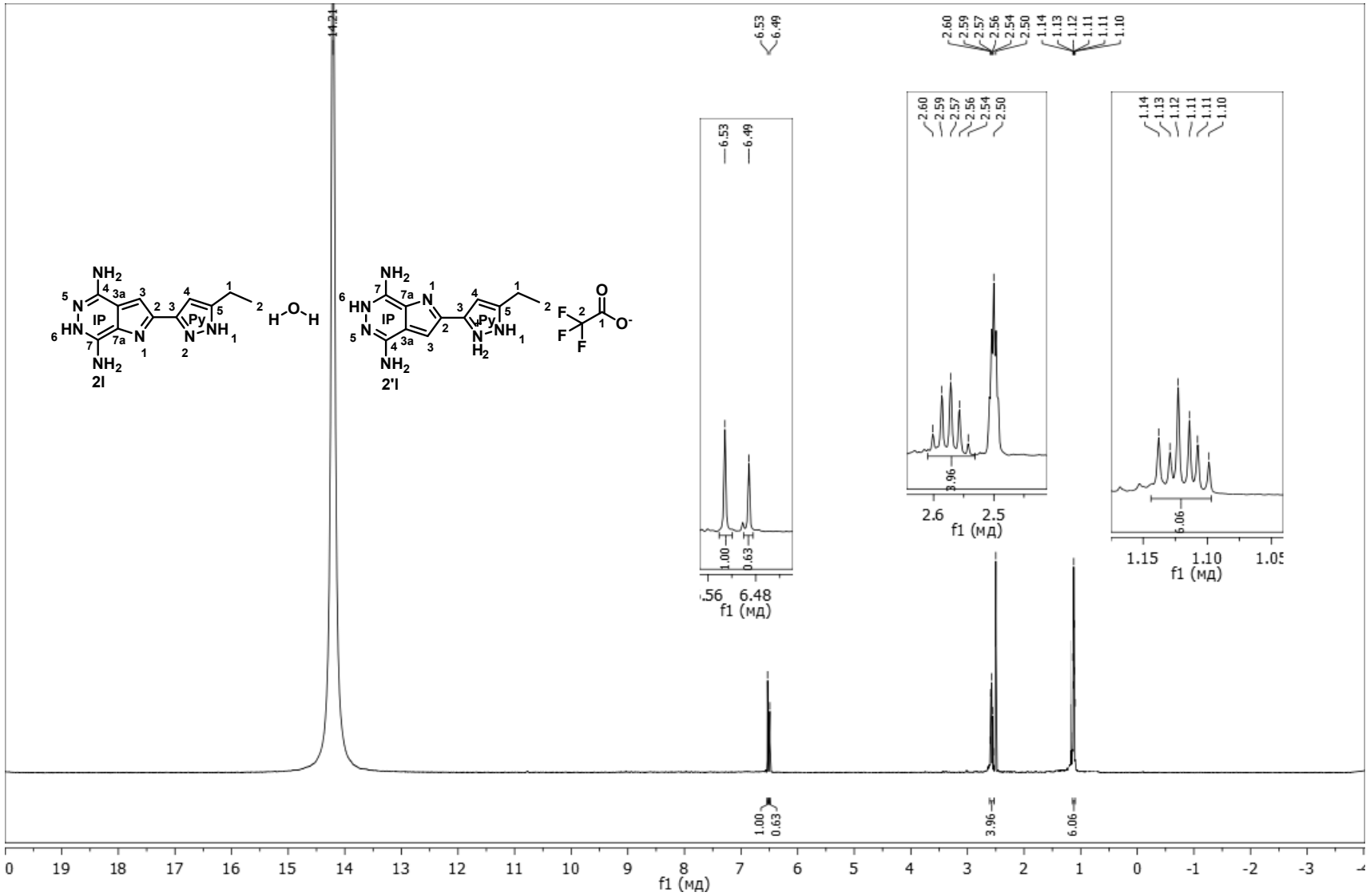

Figure S64. 1D ^{1}H NMR spectrum of **2l** and **2′l** in DMSO-d_6 at T = 303 K. Chemical shifts are given in ppm (Bruker spectrometer at 500.1 MHz).

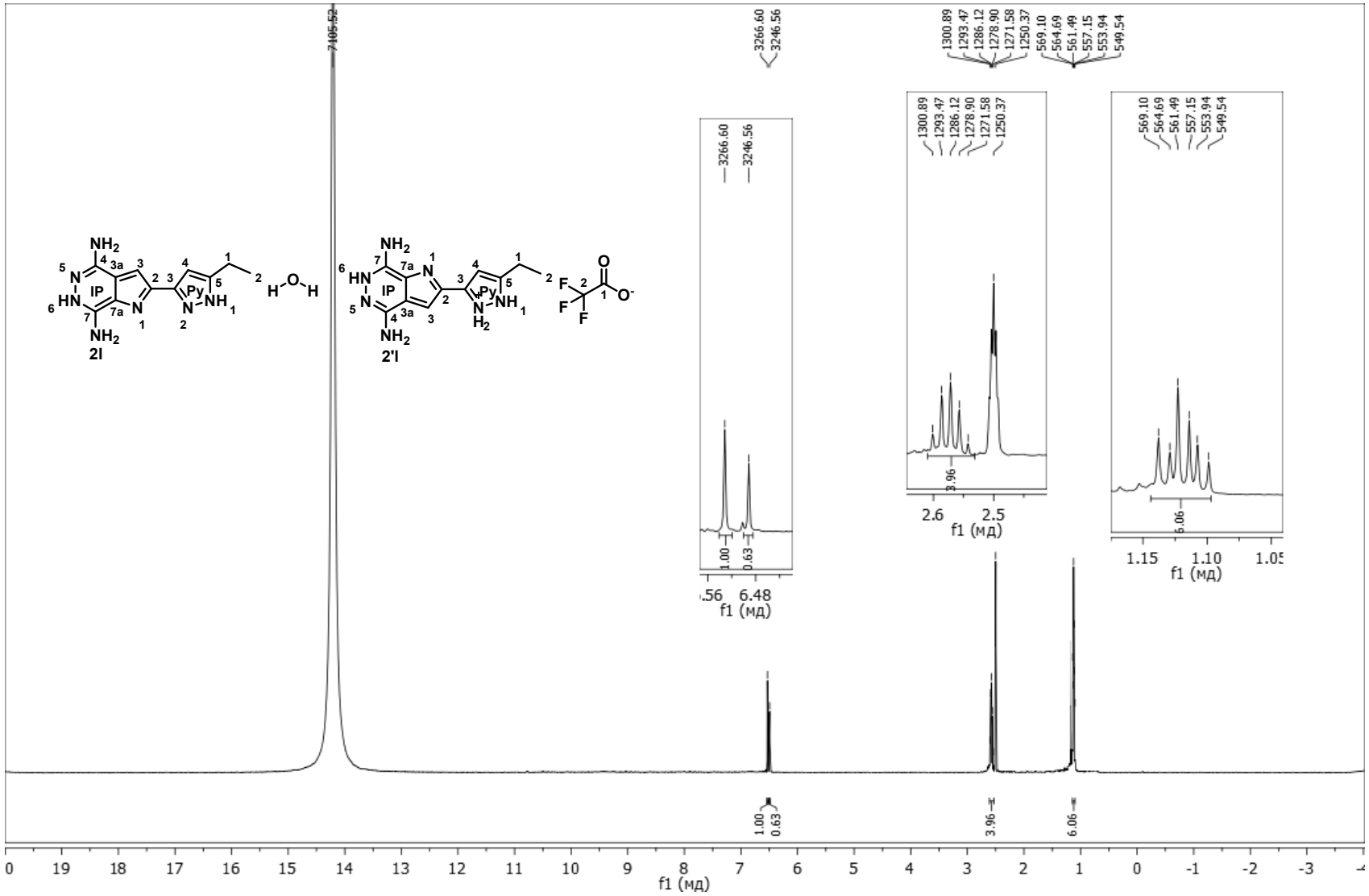

Figure S65. 1D ^{1}H NMR spectrum of **2l** and **2′l** in DMSO-d_6 at T = 303 K. Chemical shifts are given in Hz (Bruker spectrometer at 500.1 MHz).

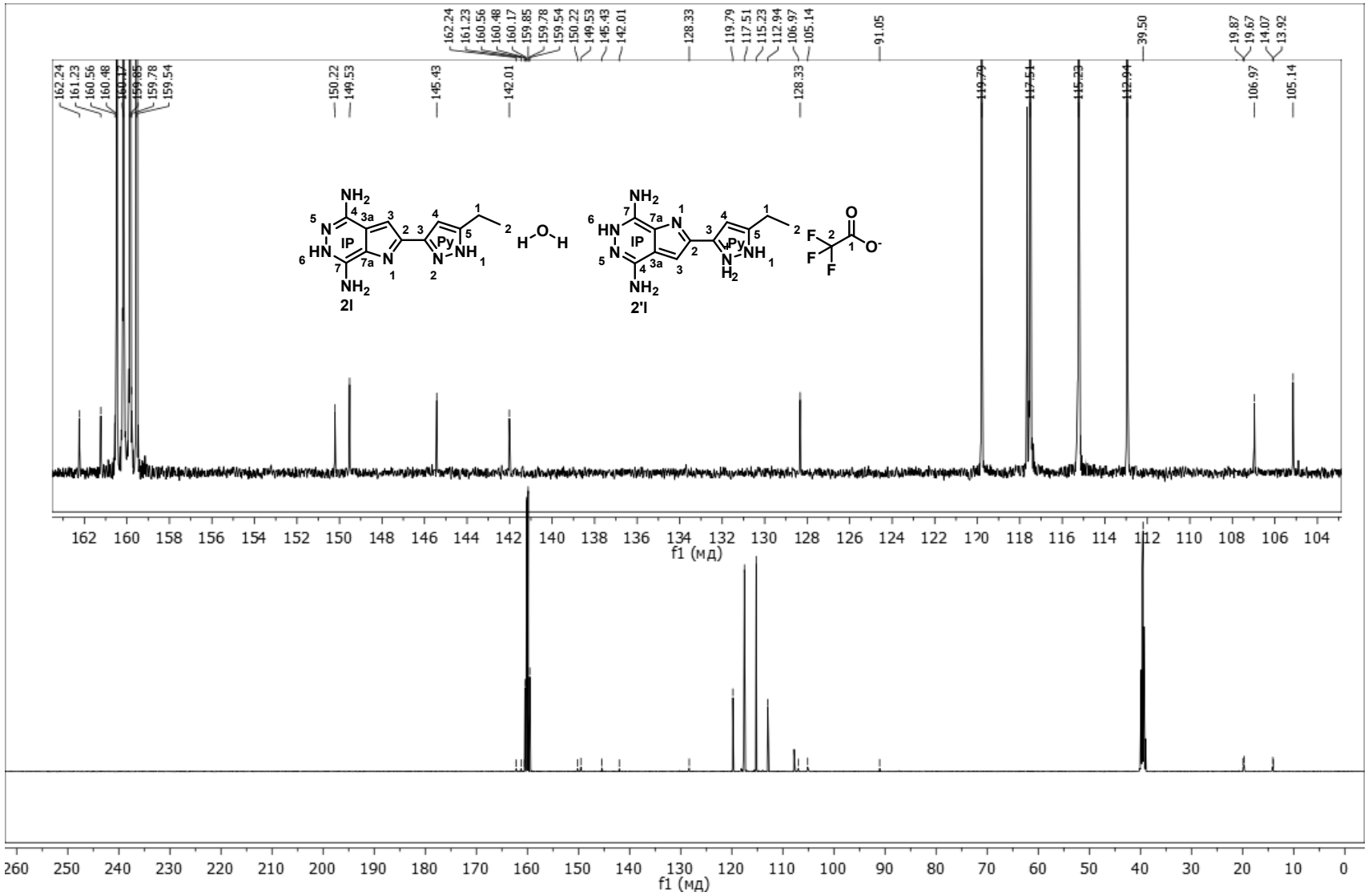

Figure S66. $^{13}C\{^{1}H\}$ NMR spectrum of **2l** and **2′l** in DMSO-d_6 at T = 303 K (Bruker spectrometer at 125.7 MHz).

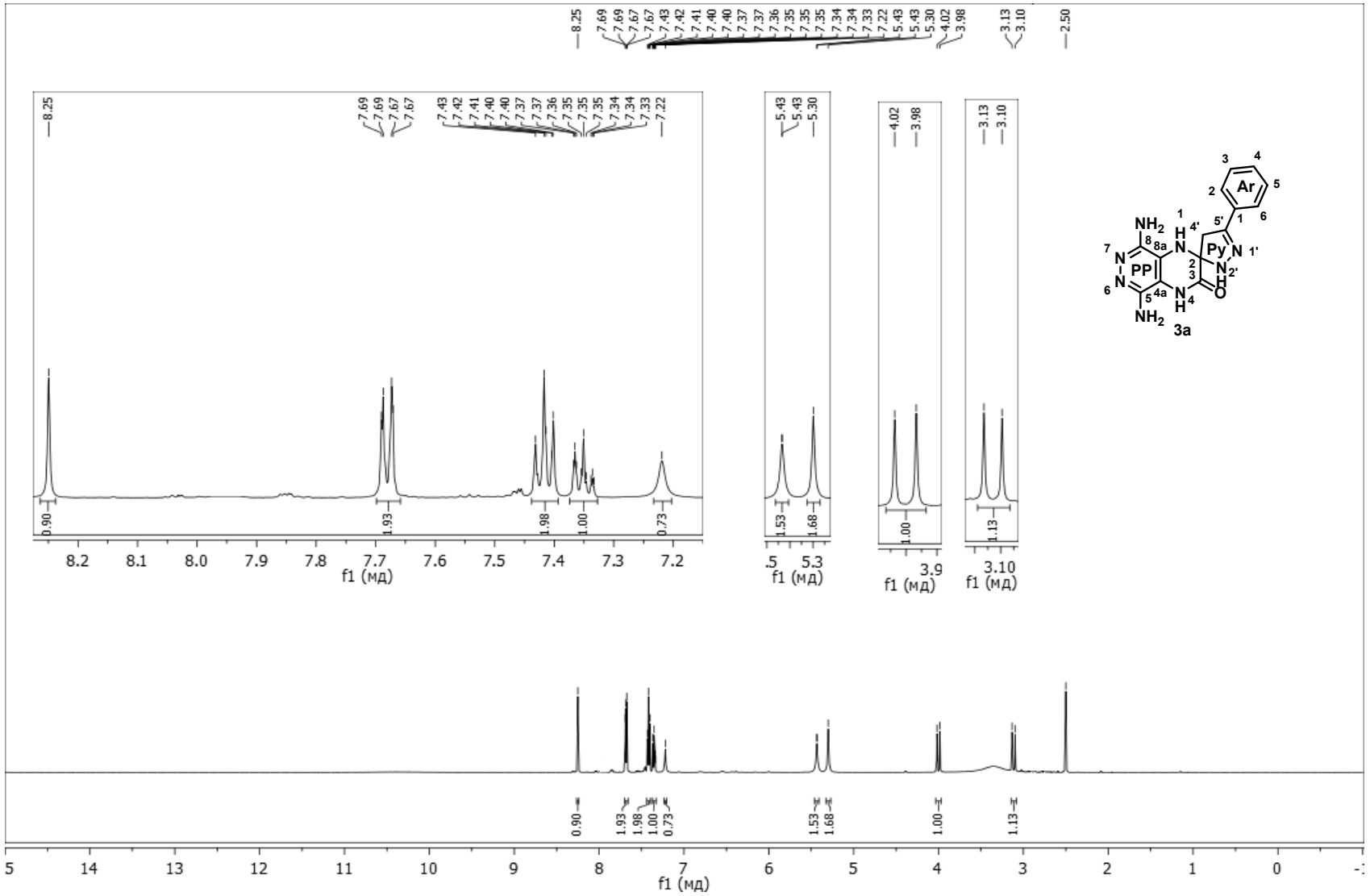

Figure S67. 1D ^{1}H NMR spectrum of **3a** in DMSO-d_6 at T = 303 K. Chemical shifts are given in ppm (Bruker spectrometer at 500.1 MHz).

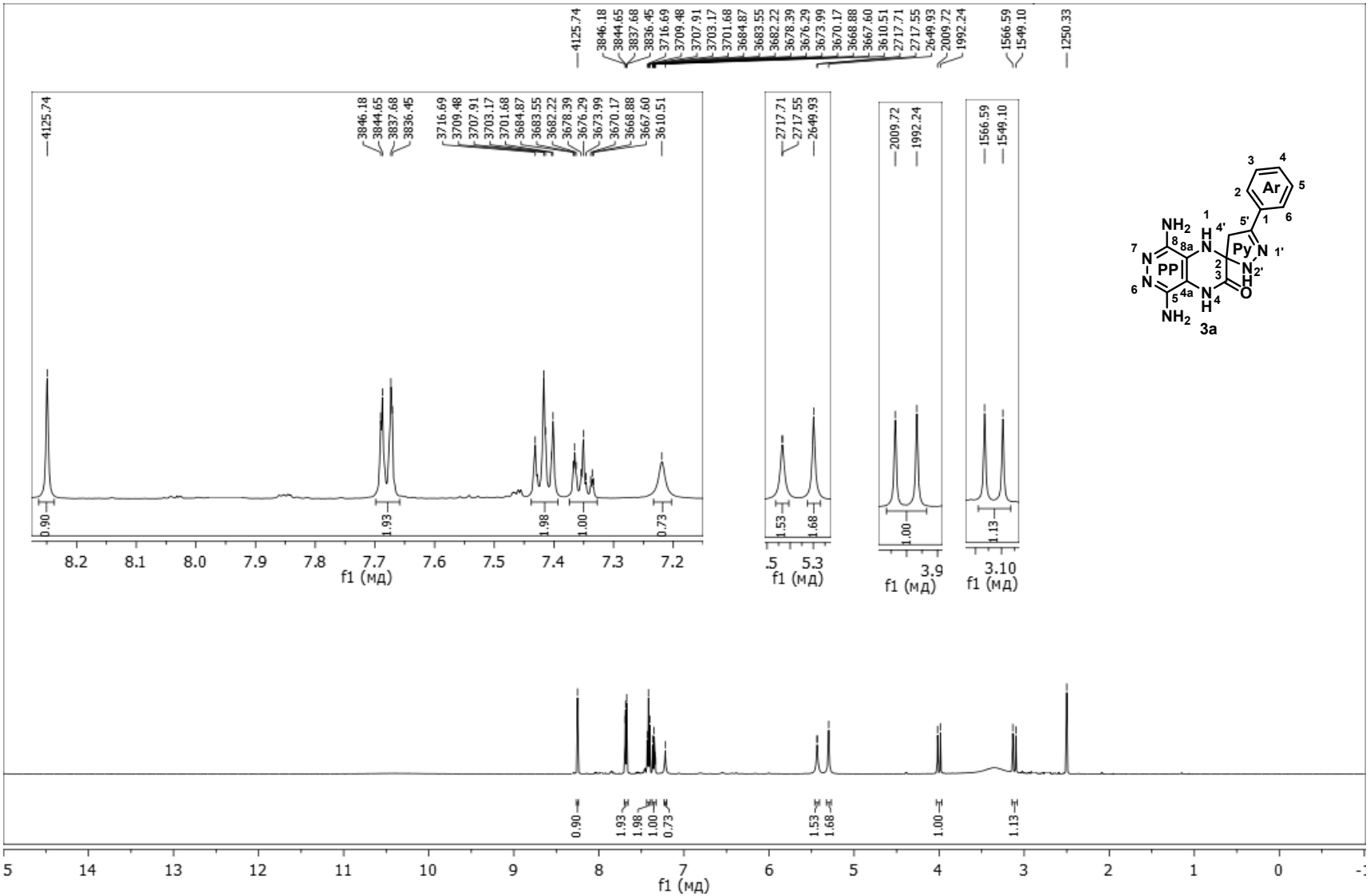

Figure S68. 1D ^{1}H NMR spectrum of **3a** in DMSO-d_6 at T = 303 K. Chemical shifts are given in Hz (Bruker spectrometer at 500.1 MHz).

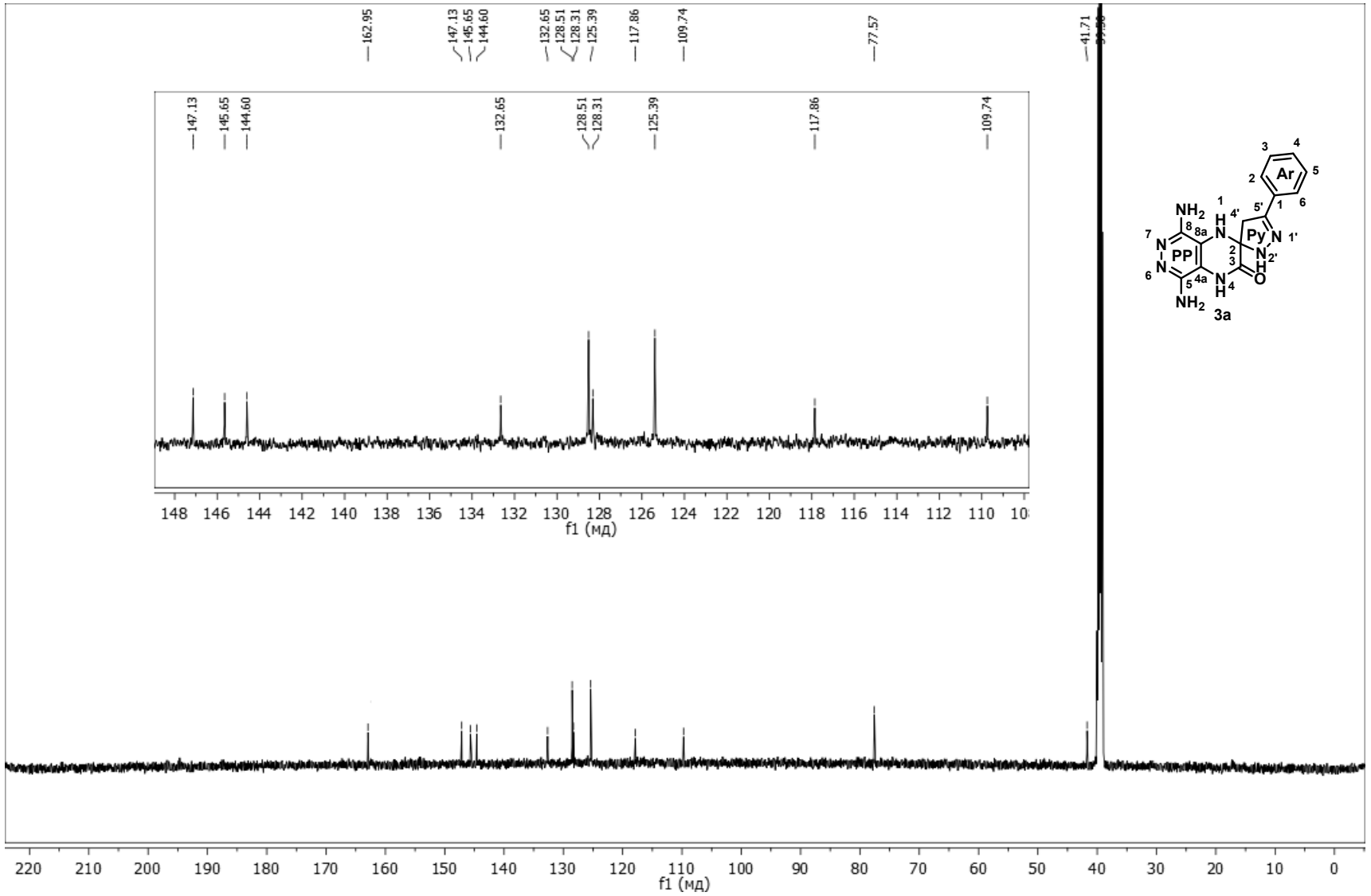

Figure S69. $^{13}C\{^{1}H\}$ NMR spectrum of **3a** in DMSO-d_6 at T = 303 K (Bruker spectrometer at 125.7 MHz).

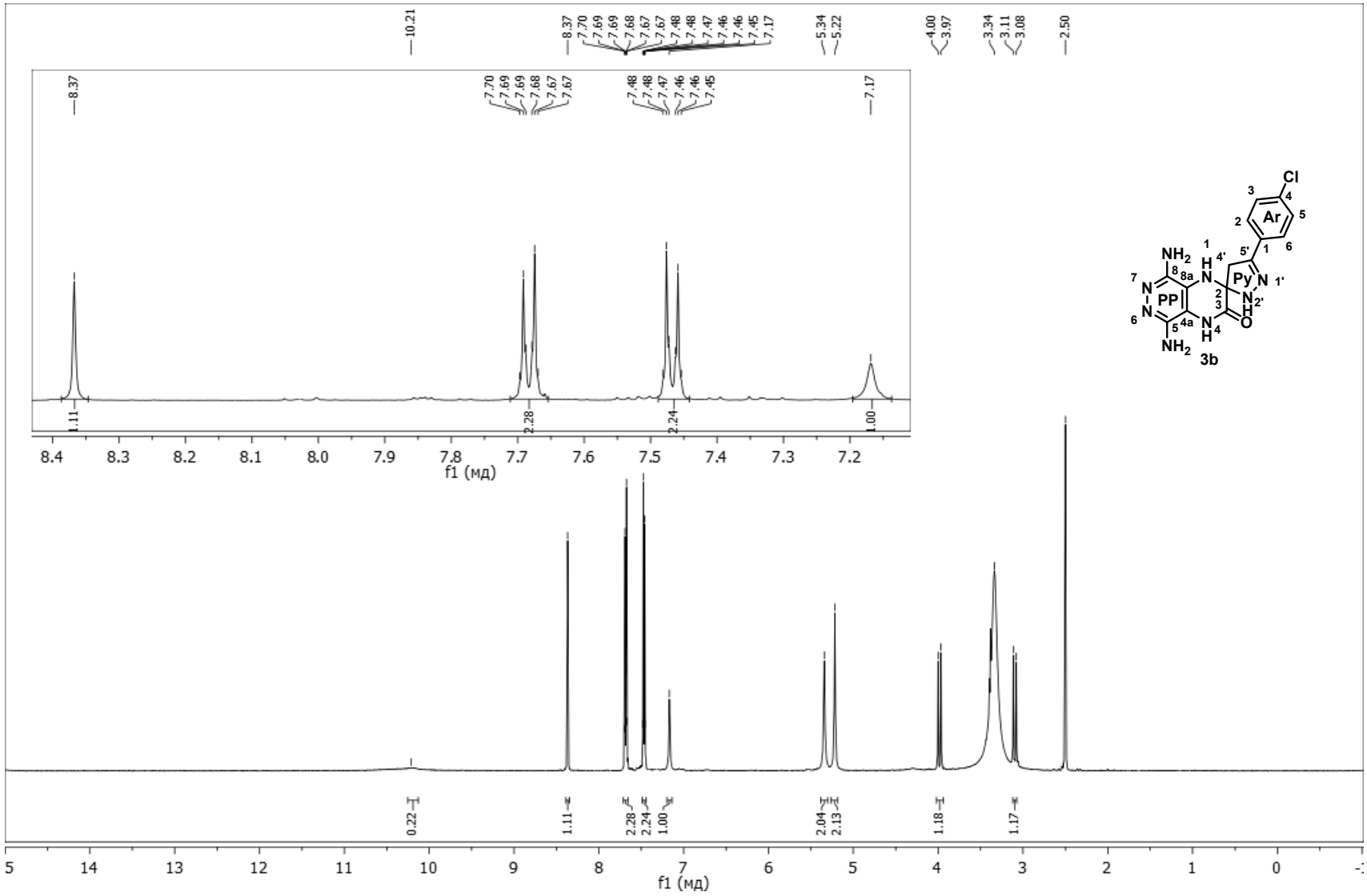

Figure S70. 1D ^{1}H NMR spectrum of **3b** in DMSO-d_6 at T = 303 K. Chemical shifts are given in ppm (Bruker spectrometer at 500.1 MHz).

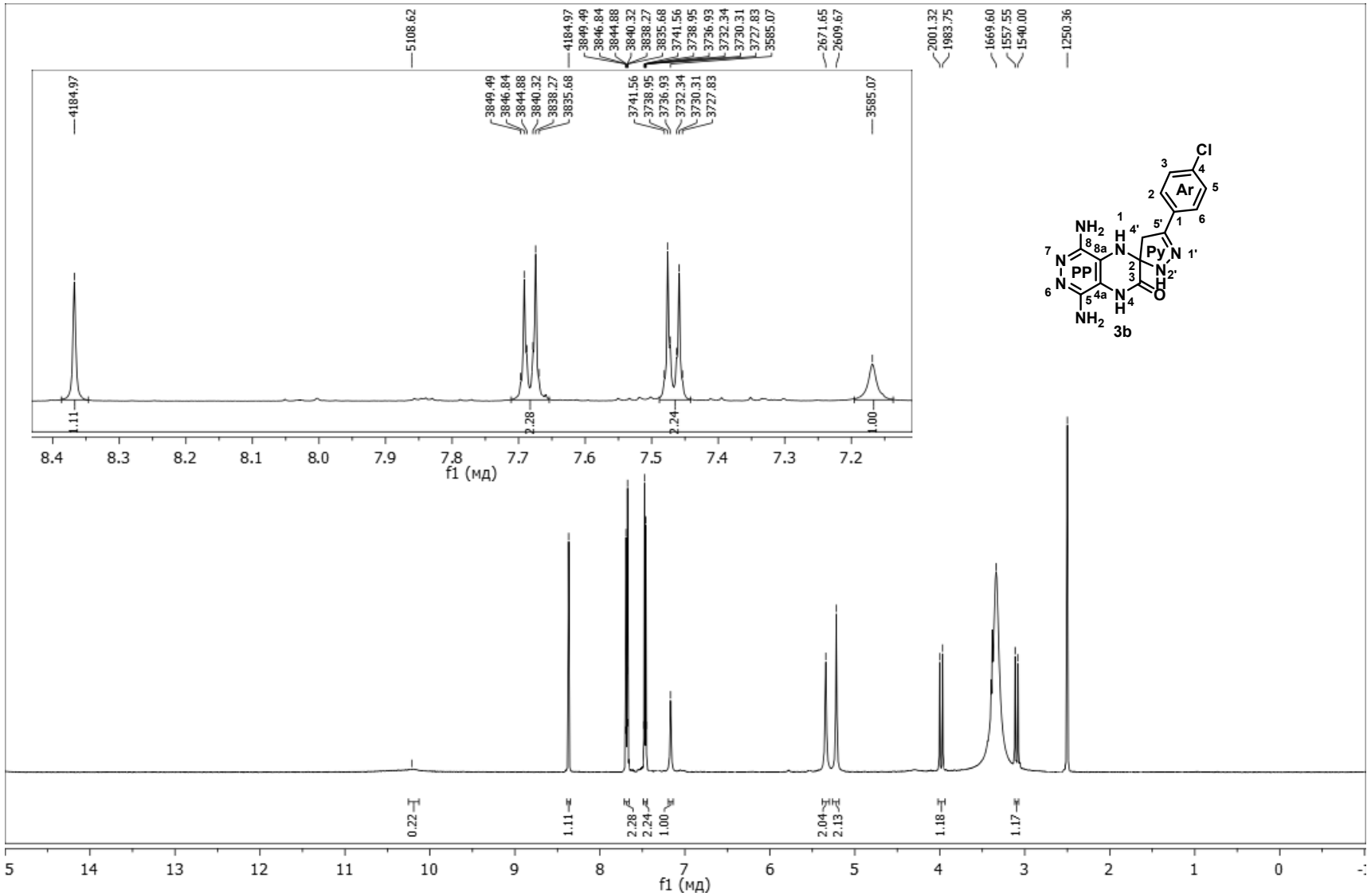

Figure S71. 1D ^{1}H NMR spectrum of **3b** in DMSO-d_6 at T = 303 K. Chemical shifts are given in Hz (Bruker spectrometer at 500.1 MHz).

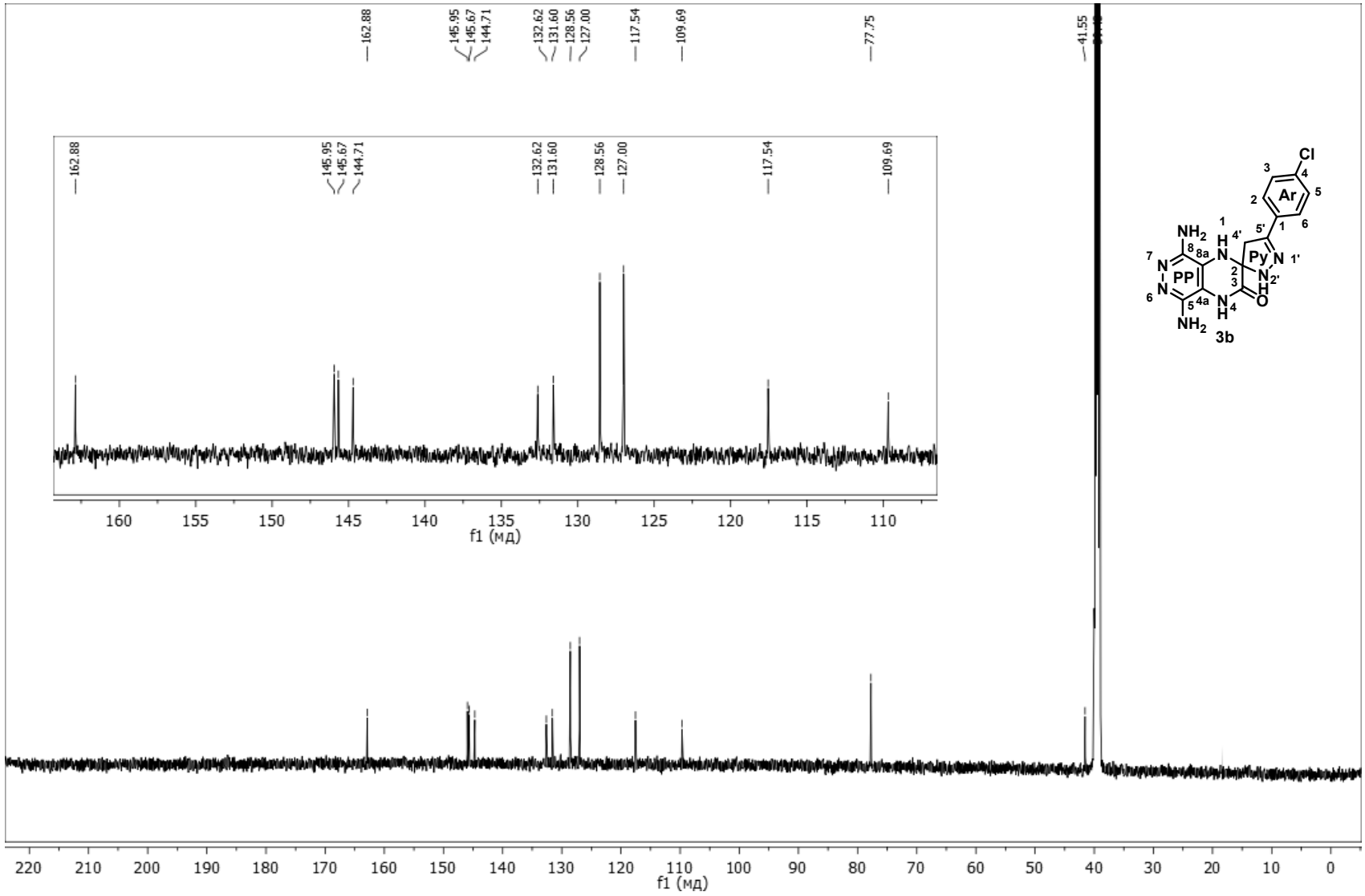

Figure S72. $^{13}C\{^{1}H\}$ NMR spectrum of **3b** in DMSO-d_6 at T = 303 K (Bruker spectrometer at 125.7 MHz).

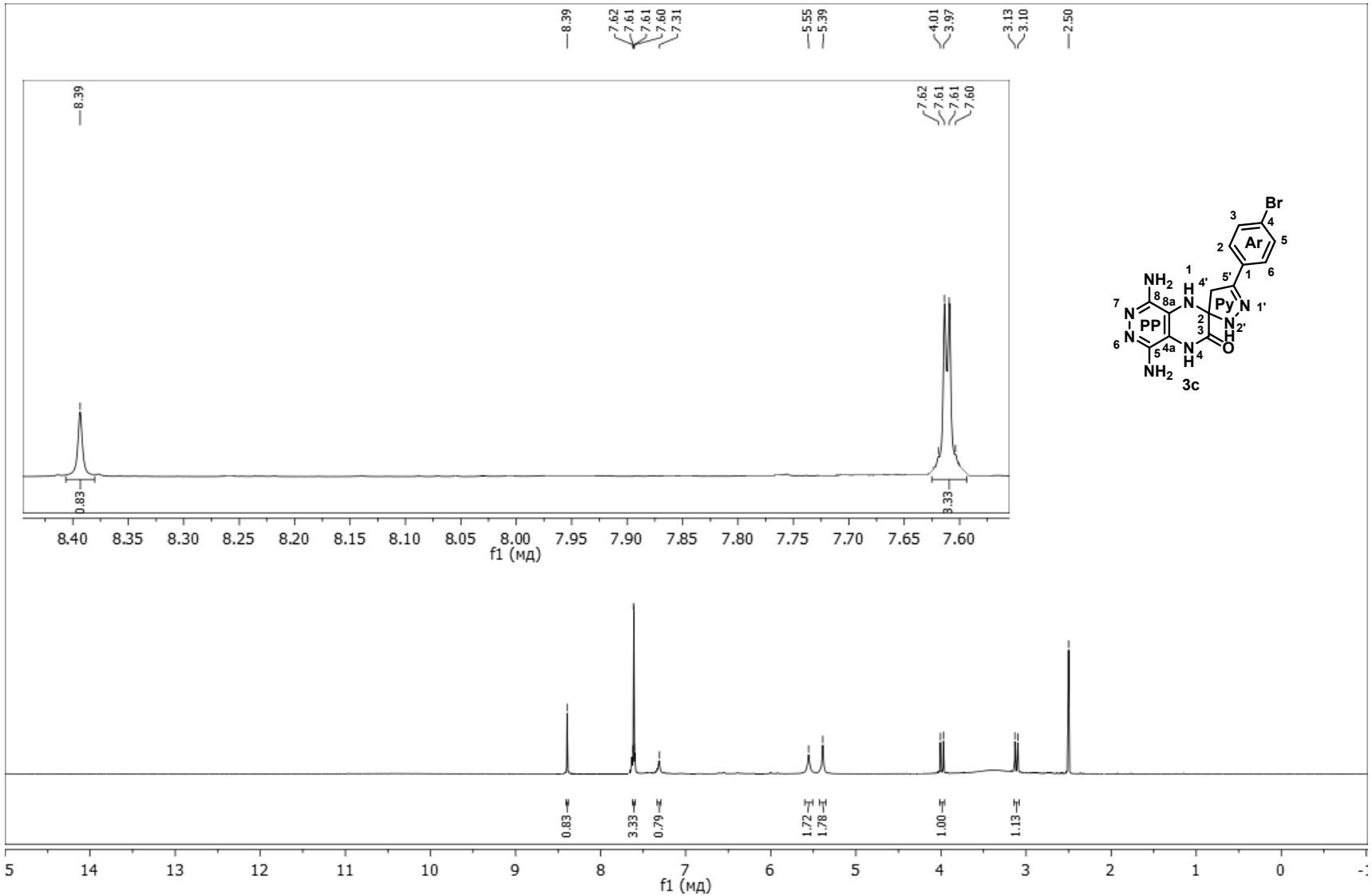

Figure S73. 1D ^{1}H NMR spectrum of **3c** in DMSO-d_6 at T = 303 K. Chemical shifts are given in ppm (Bruker spectrometer at 500.1 MHz).

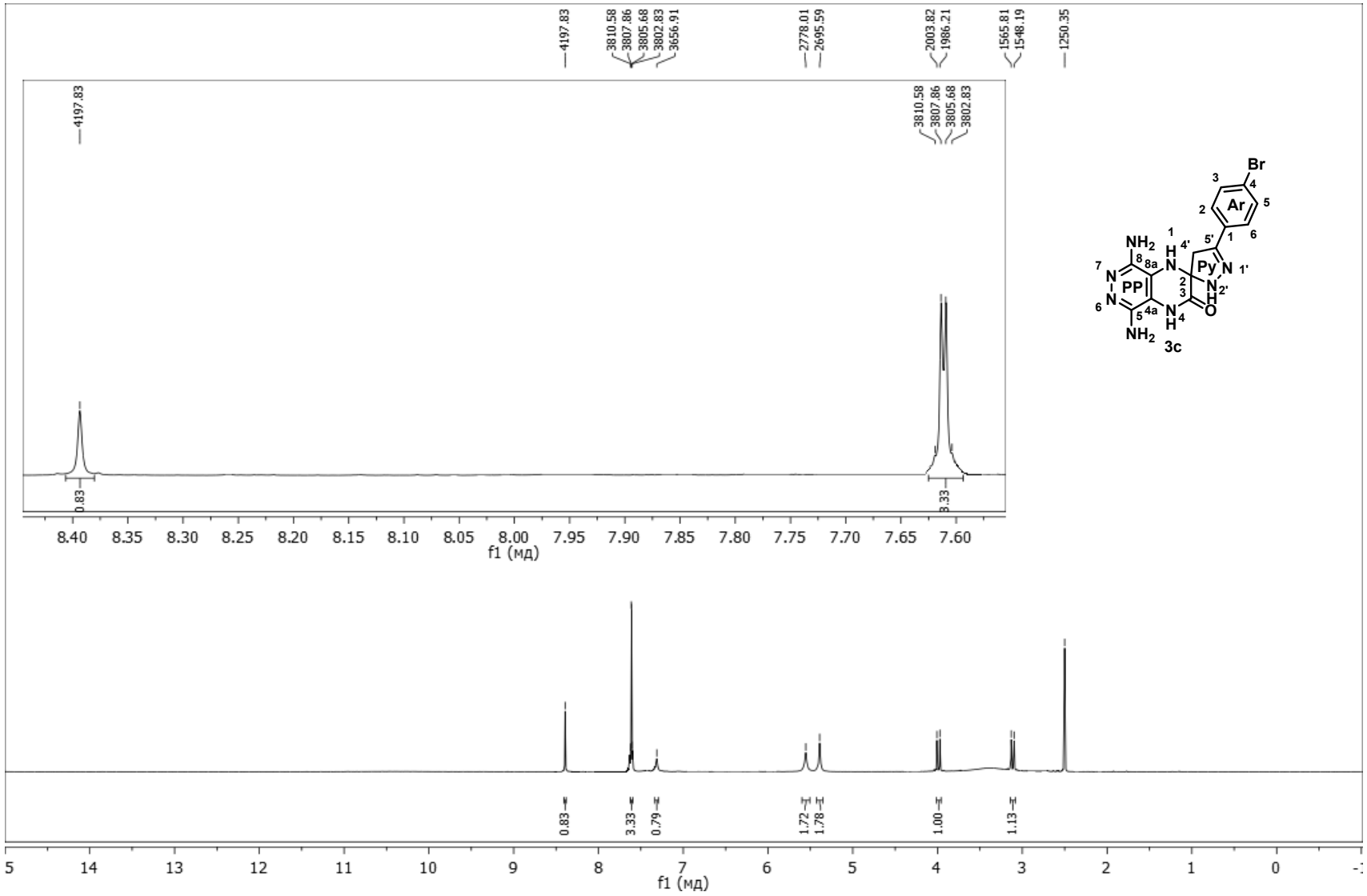

Figure S74. 1D ^{1}H NMR spectrum of **3c** in DMSO-d_6 at T = 303 K. Chemical shifts are given in Hz (Bruker spectrometer at 500.1 MHz).

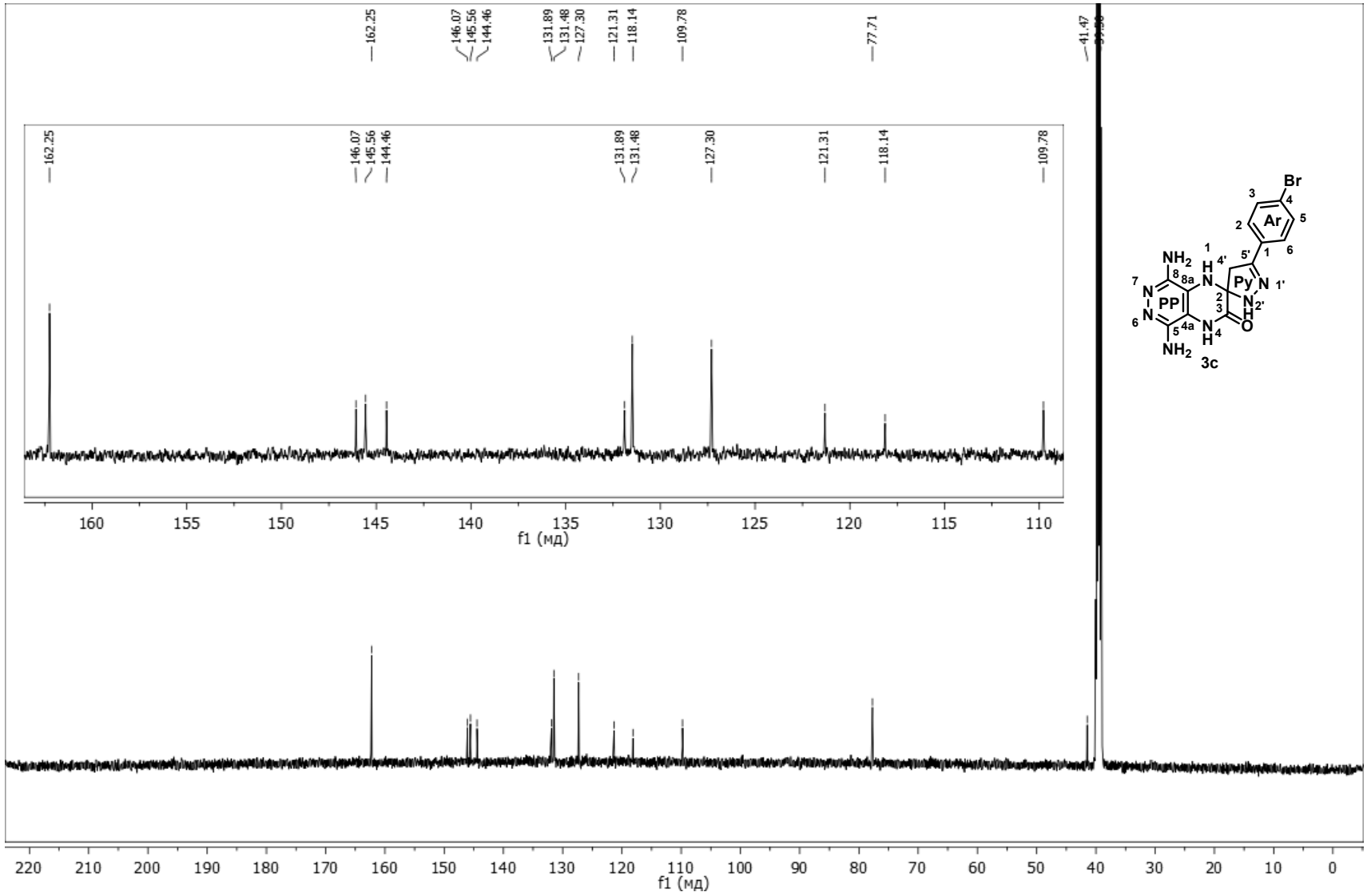

Figure S75. $^{13}C\{^{1}H\}$ NMR spectrum of **3c** in DMSO-d_6 at T = 303 K (Bruker spectrometer at 125.7 MHz).

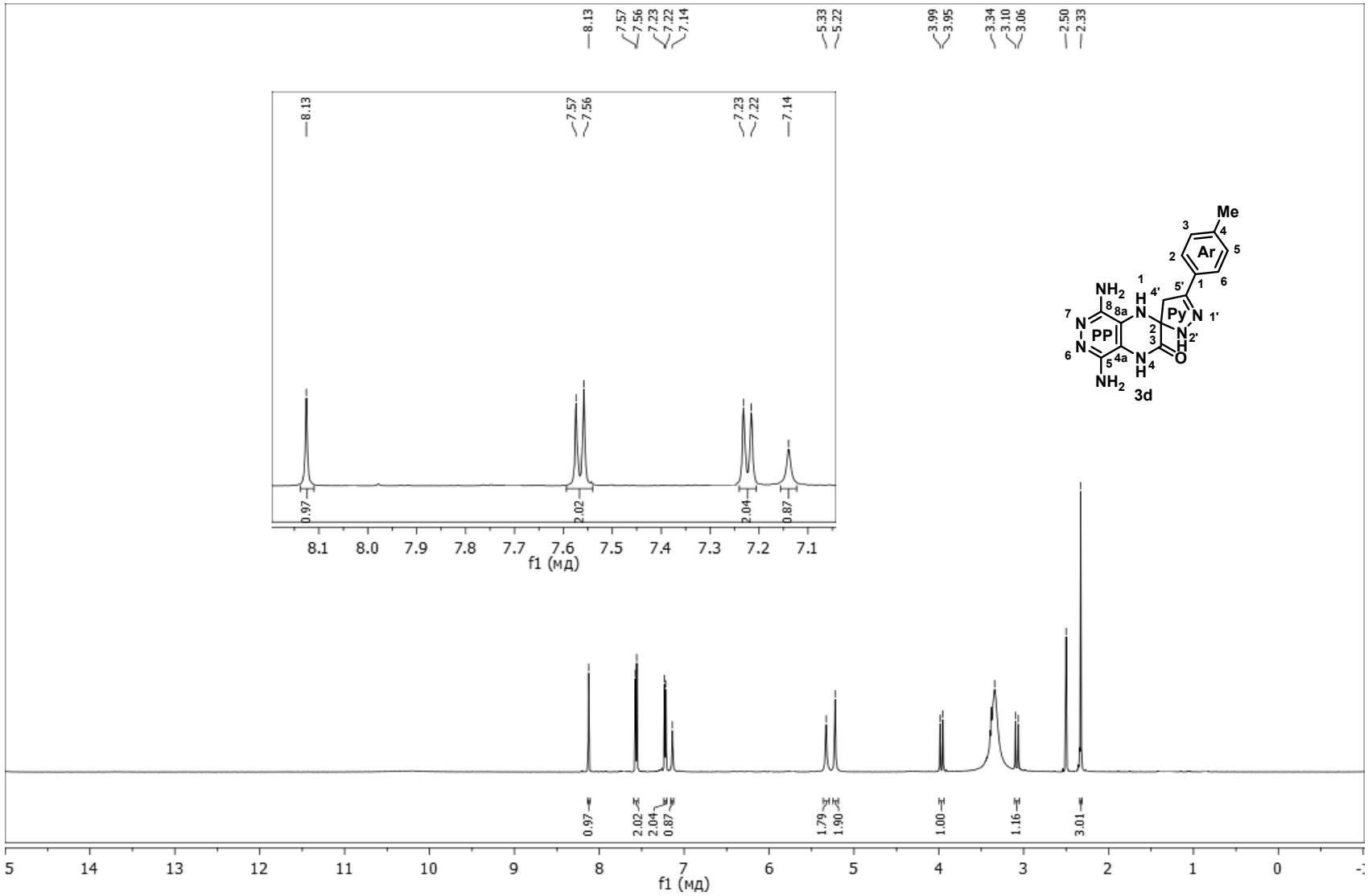

Figure S76. 1D ^{1}H NMR spectrum of **3d** in DMSO-d_6 at T = 303 K. Chemical shifts are given in ppm (Bruker spectrometer at 500.1 MHz).

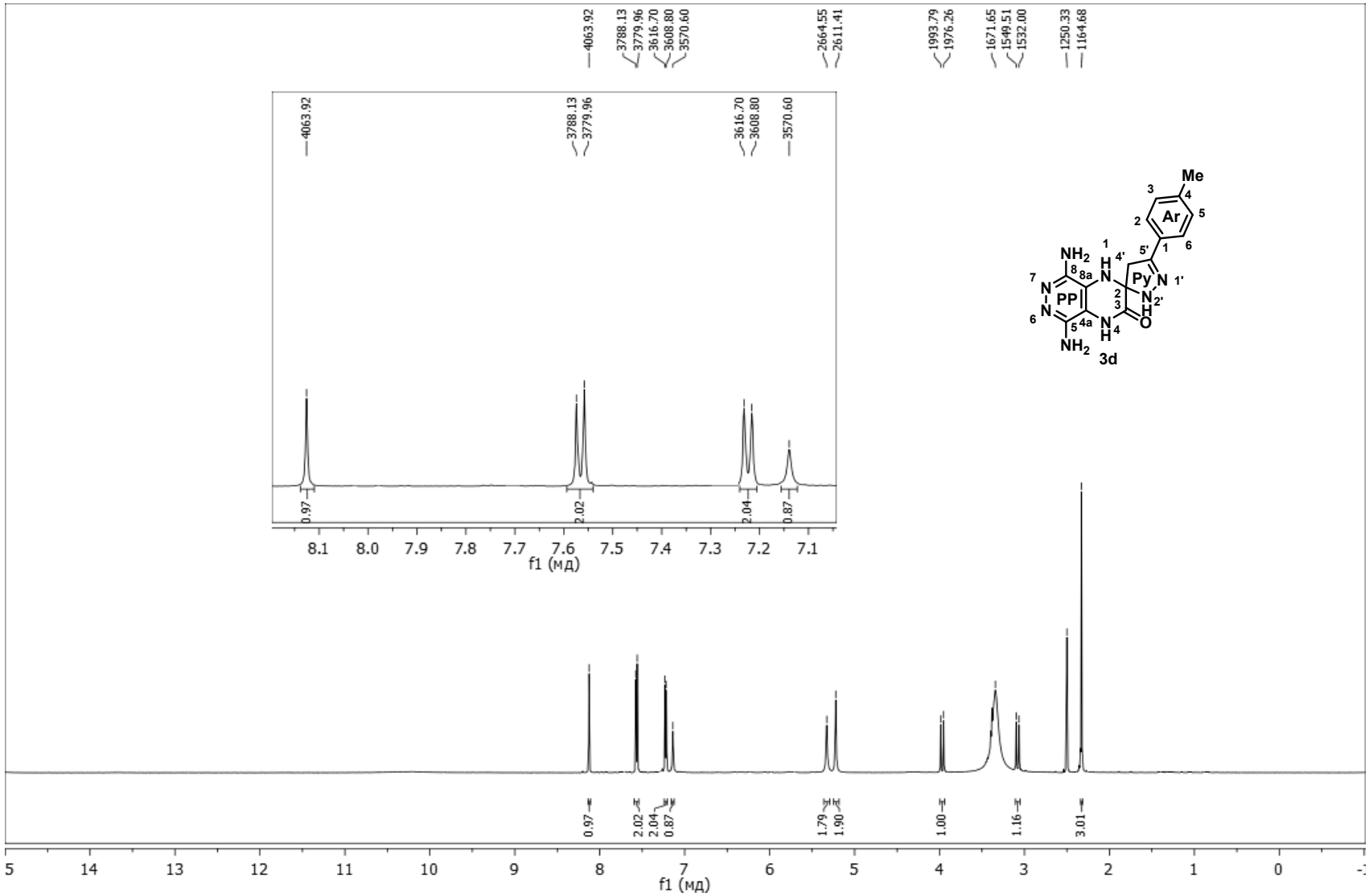

Figure S77. 1D ^{1}H NMR spectrum of **3d** in DMSO-d_6 at T = 303 K. Chemical shifts are given in Hz (Bruker spectrometer at 500.1 MHz).

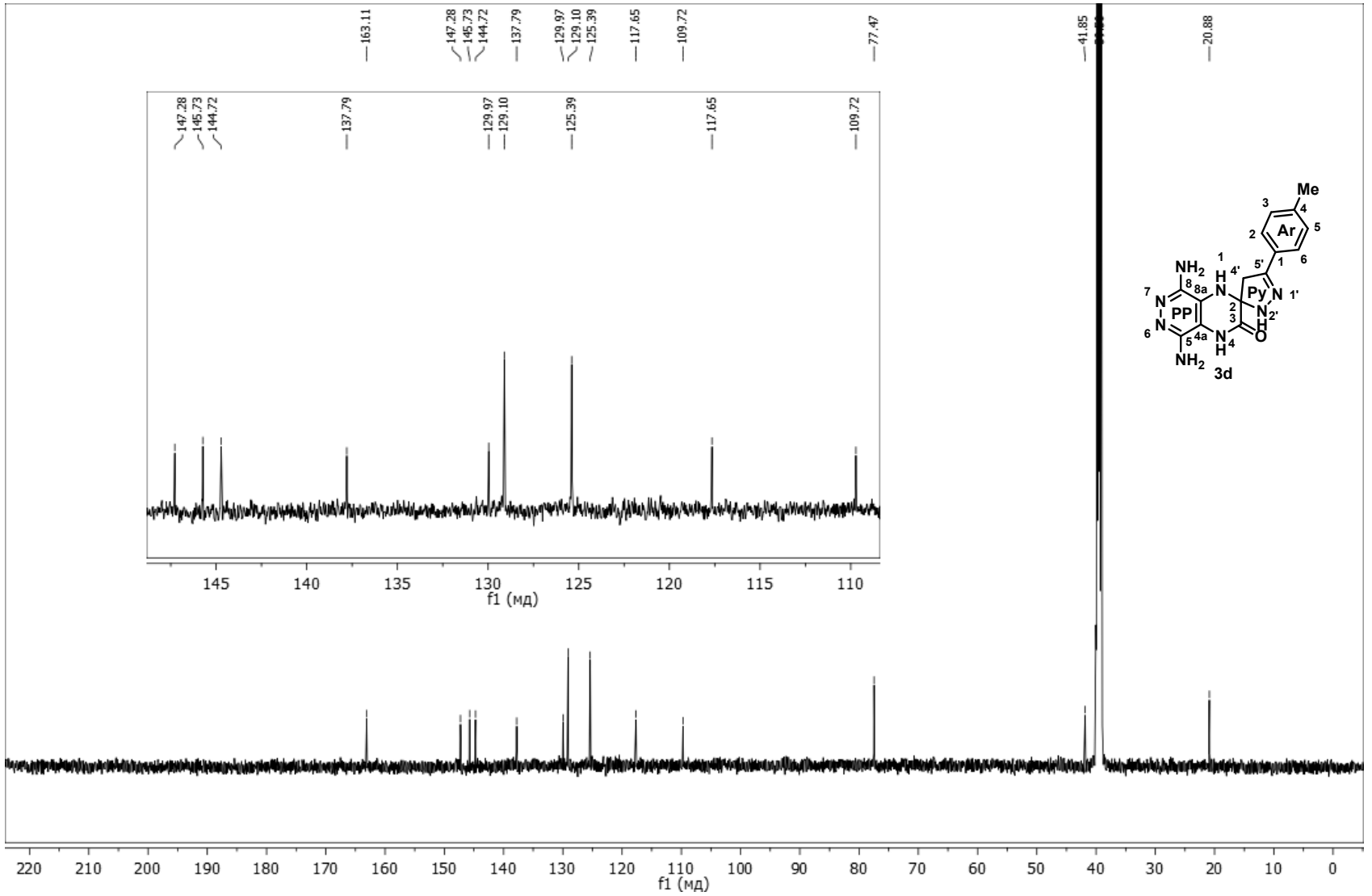

Figure S78. $^{13}C\{^{1}H\}$ NMR spectrum of **3d** in DMSO-d_6 at T = 303 K (Bruker spectrometer at 125.7 MHz).

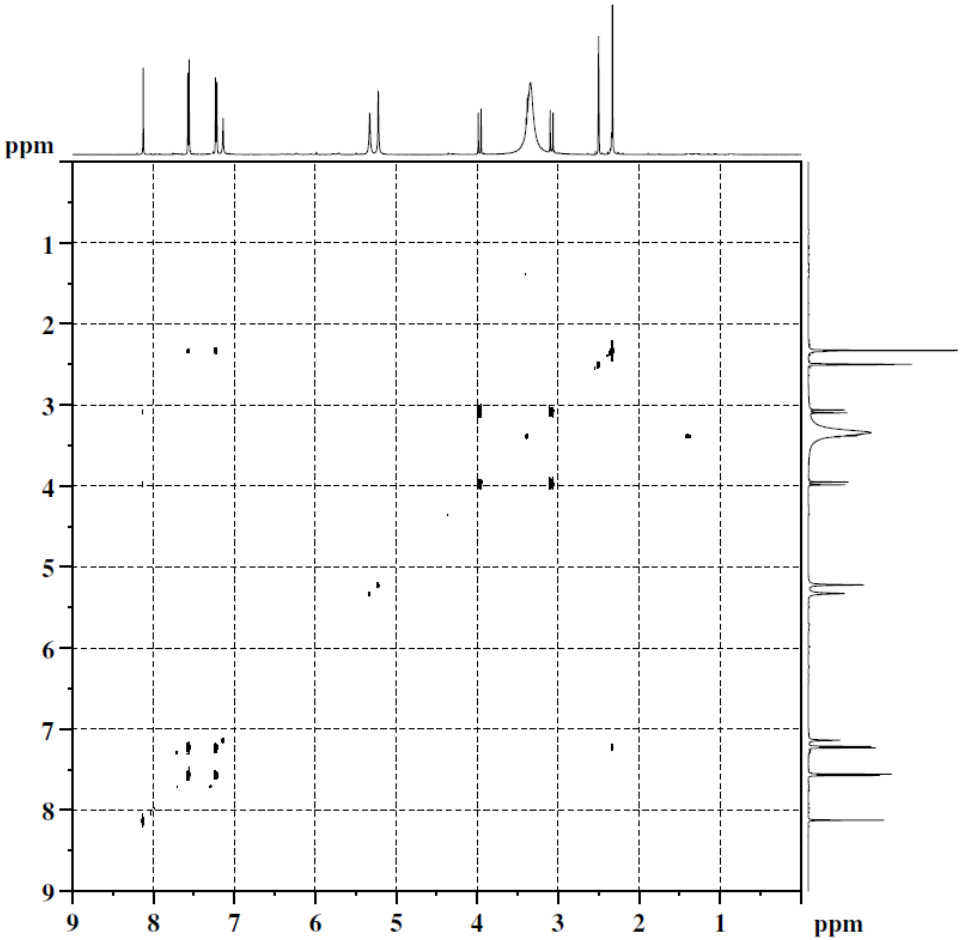

Figure S79. 2D ^{1}H-^{1}H COSY NMR spectrum of **3d** in DMSO-d_6 at T = 303 K.

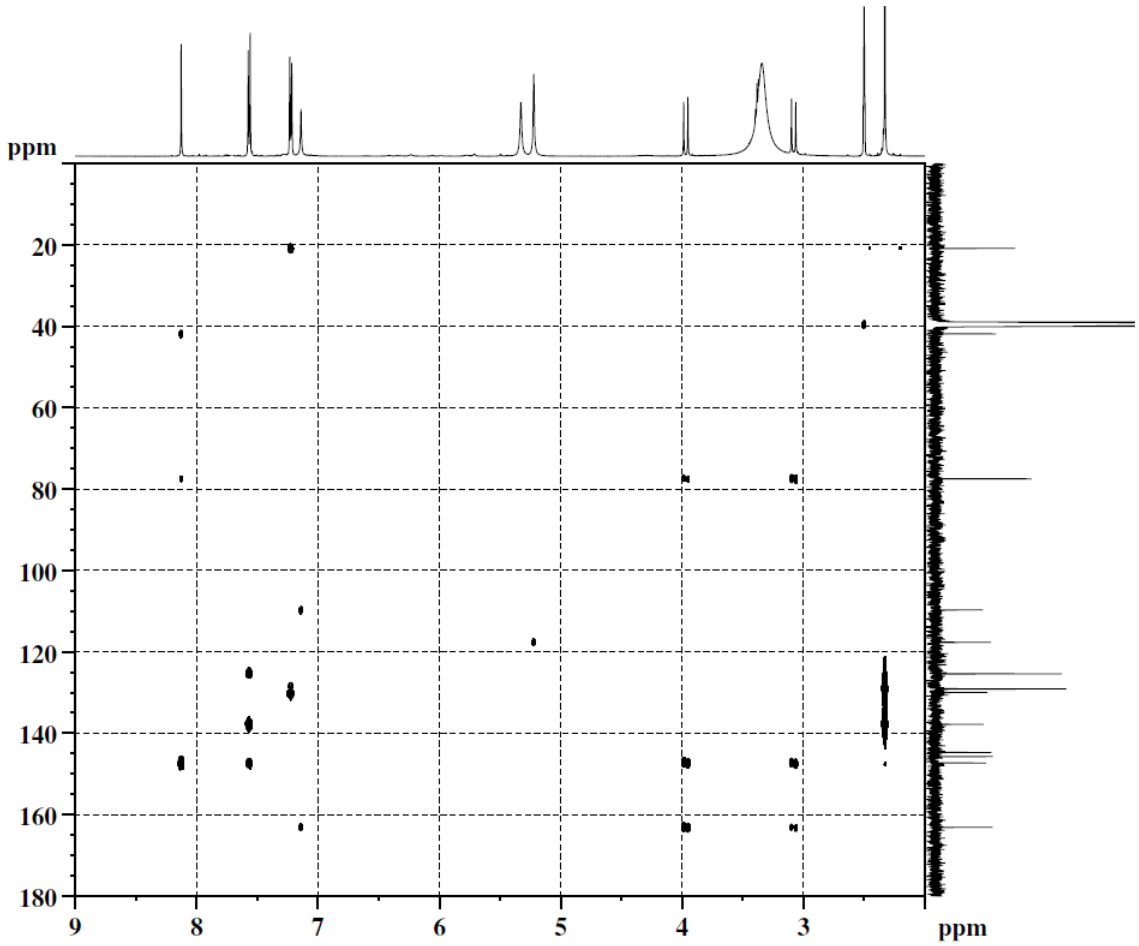

Figure S80. 2D ^{1}H-^{13}C HMBC NMR spectrum of **3d** in DMSO-d_6 at T = 303 K.

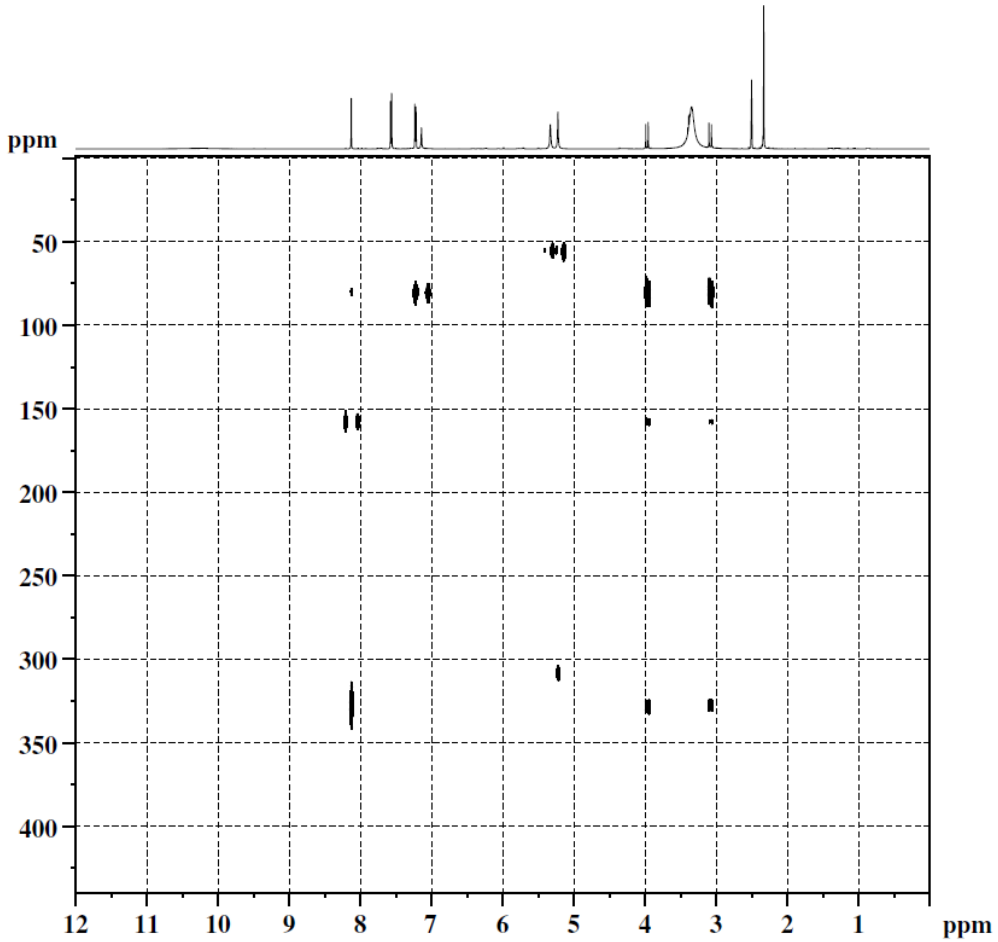

Figure S81. 2D ^{1}H-^{15}N HMBC NMR spectrum of **3d** in DMSO-d_6 at T = 303 K.

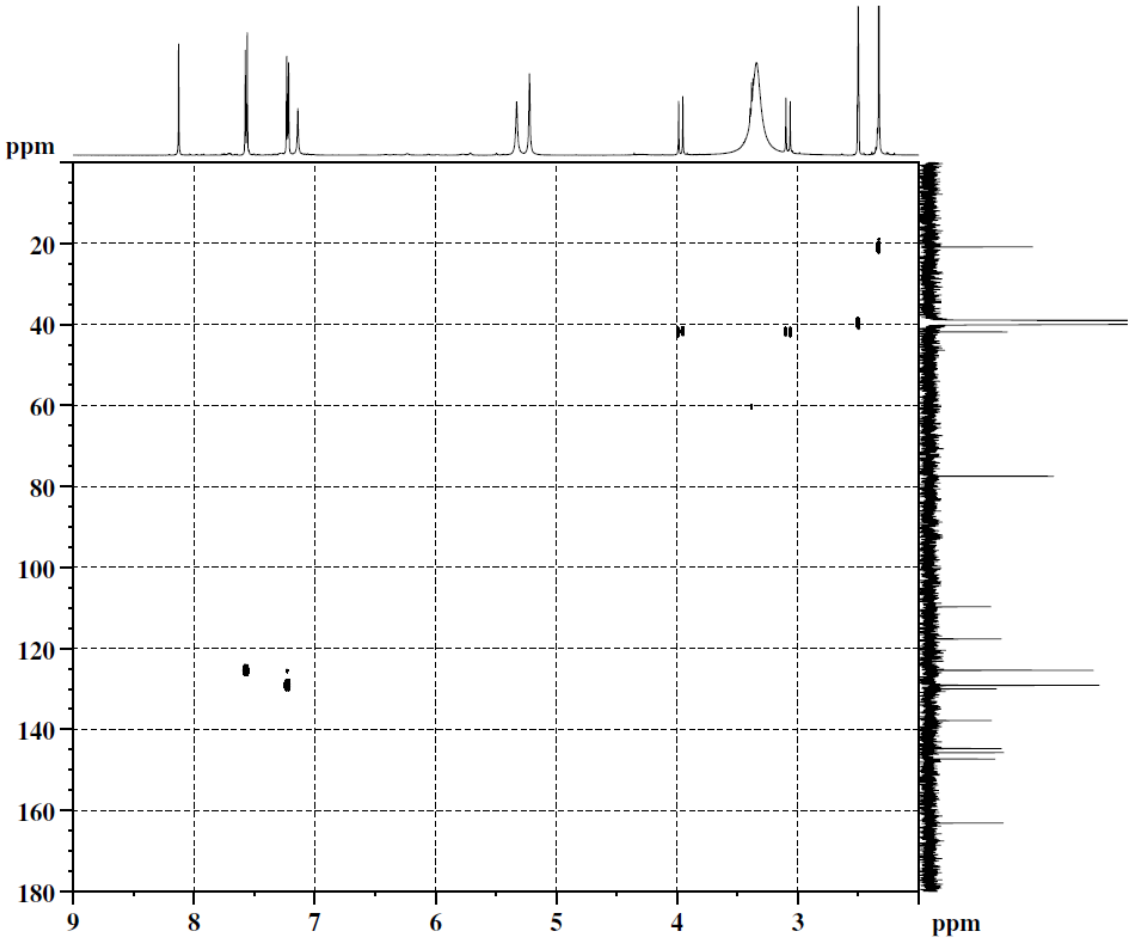

Figure S82. 2D 1H-^{13}C HSQC NMR spectrum of **3d** in DMSO-d_6 at T = 303 K.

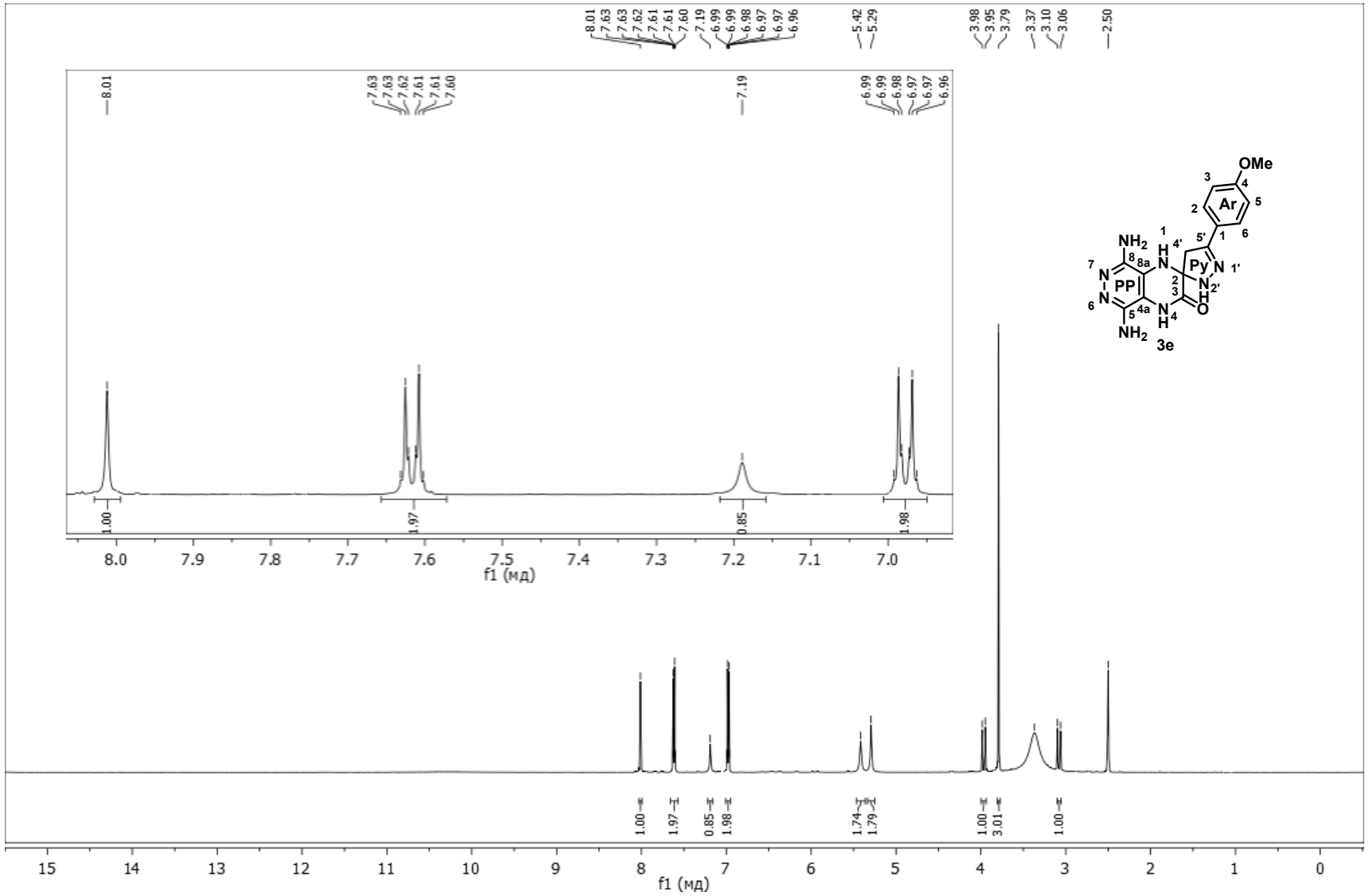

Figure S83. 1D ^{1}H NMR spectrum of **3e** in DMSO-d_6 at T = 303 K. Chemical shifts are given in ppm (Bruker spectrometer at 500.1 MHz).

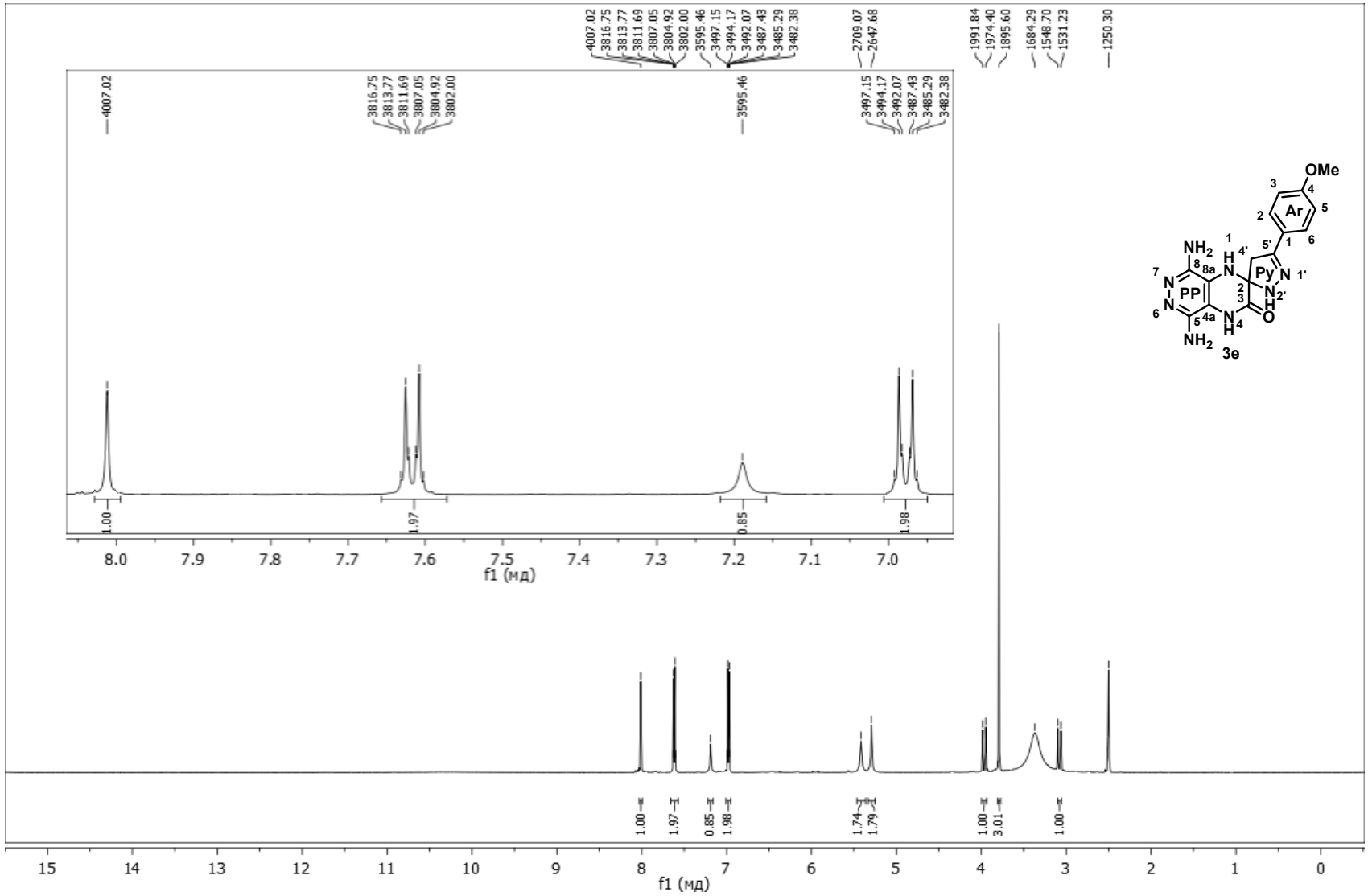

Figure S84. 1D ^{1}H NMR spectrum of **3e** in DMSO-d_6 at T = 303 K. Chemical shifts are given in Hz (Bruker spectrometer at 500.1 MHz).

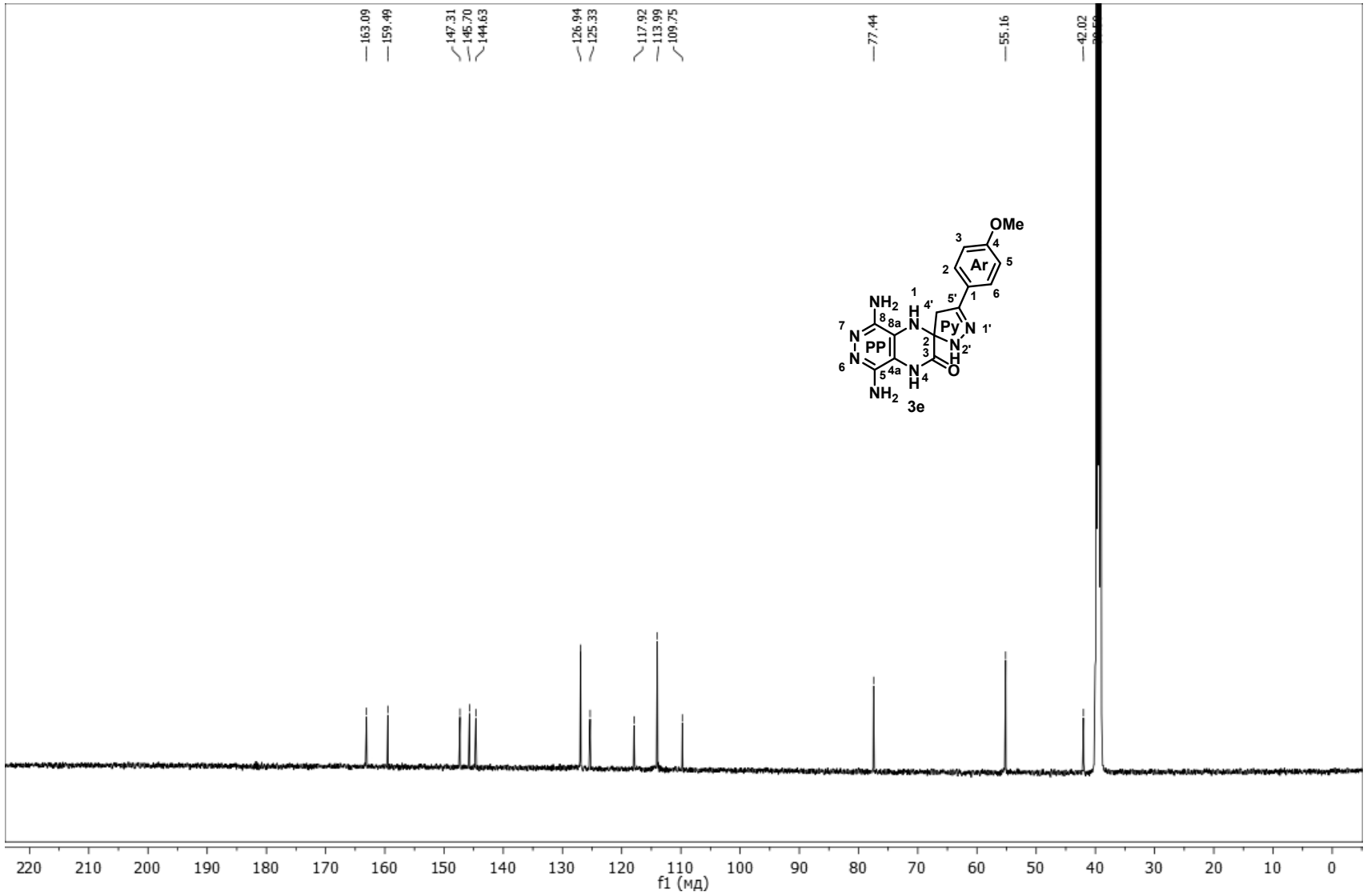

Figure S85. $^{13}C\{^{1}H\}$ NMR spectrum of **3e** in DMSO-d_6 at T = 303 K (Bruker spectrometer at 125.7 MHz).

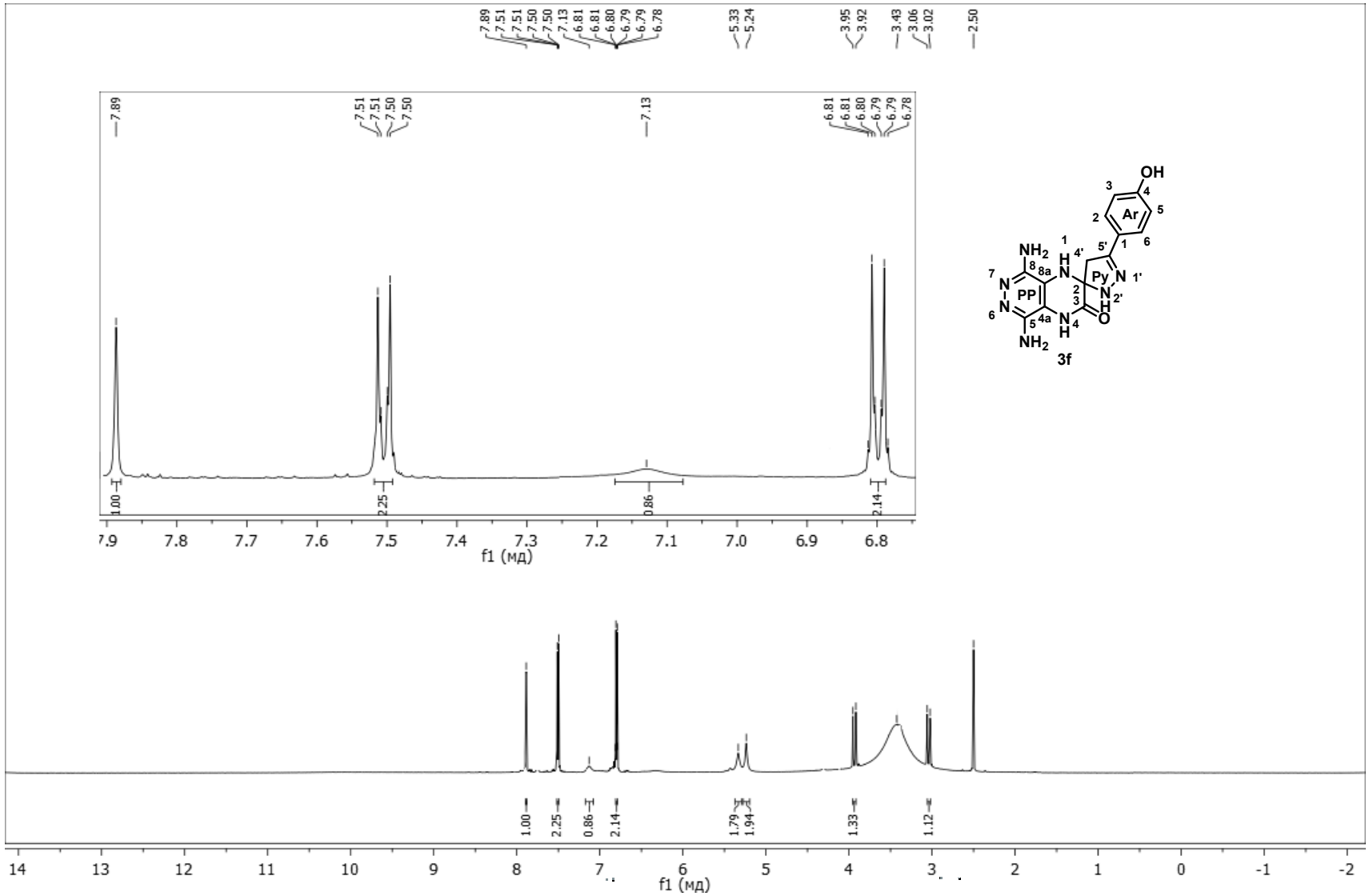

Figure S86. 1D ^{1}H NMR spectrum of **3f** in DMSO-d_6 at T = 303 K. Chemical shifts are given in ppm (Bruker spectrometer at 500.1 MHz).

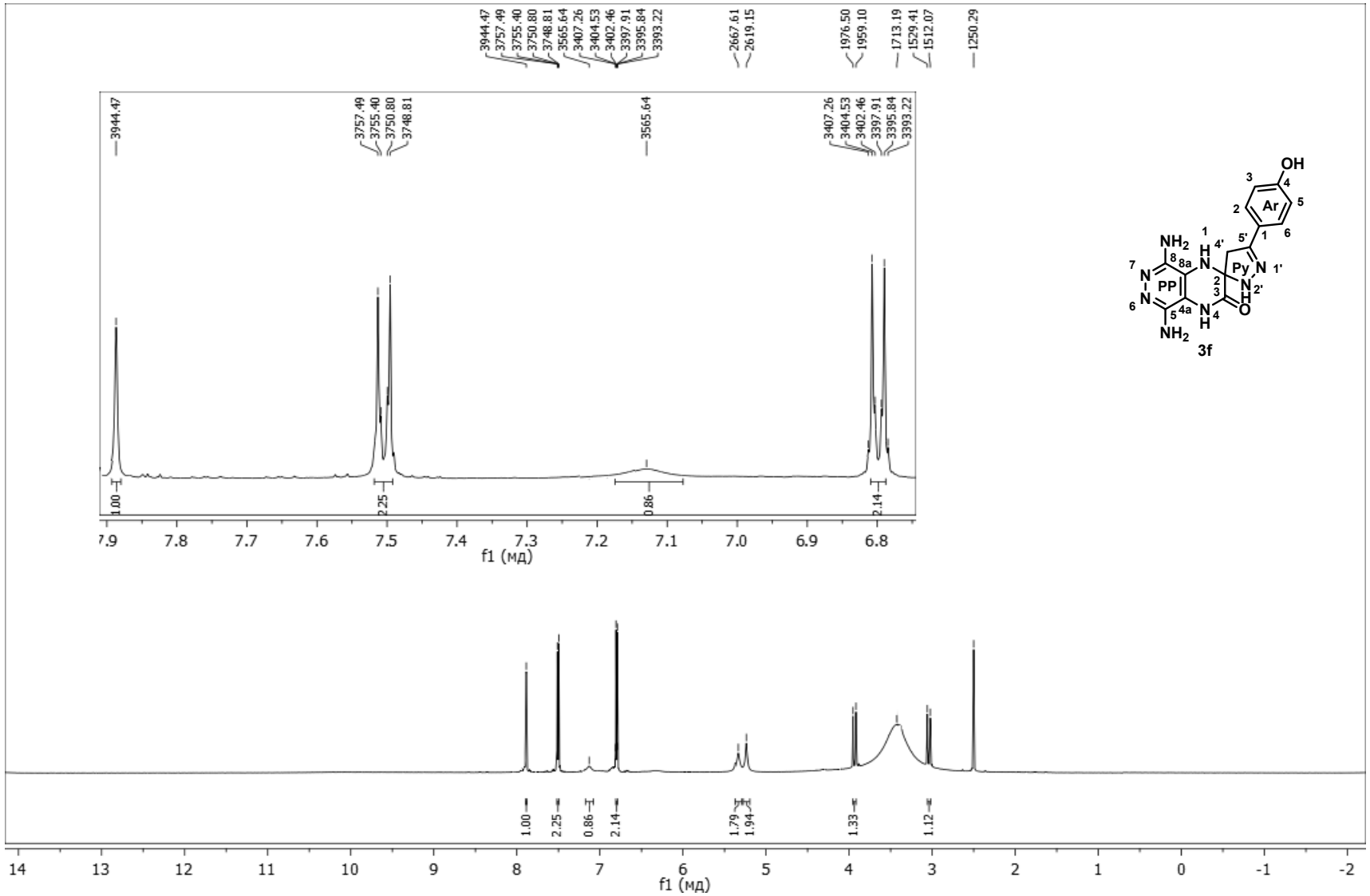

Figure S87. 1D ^{1}H NMR spectrum of **3f** in DMSO-d_6 at T = 303 K. Chemical shifts are given in Hz (Bruker spectrometer at 500.1 MHz).

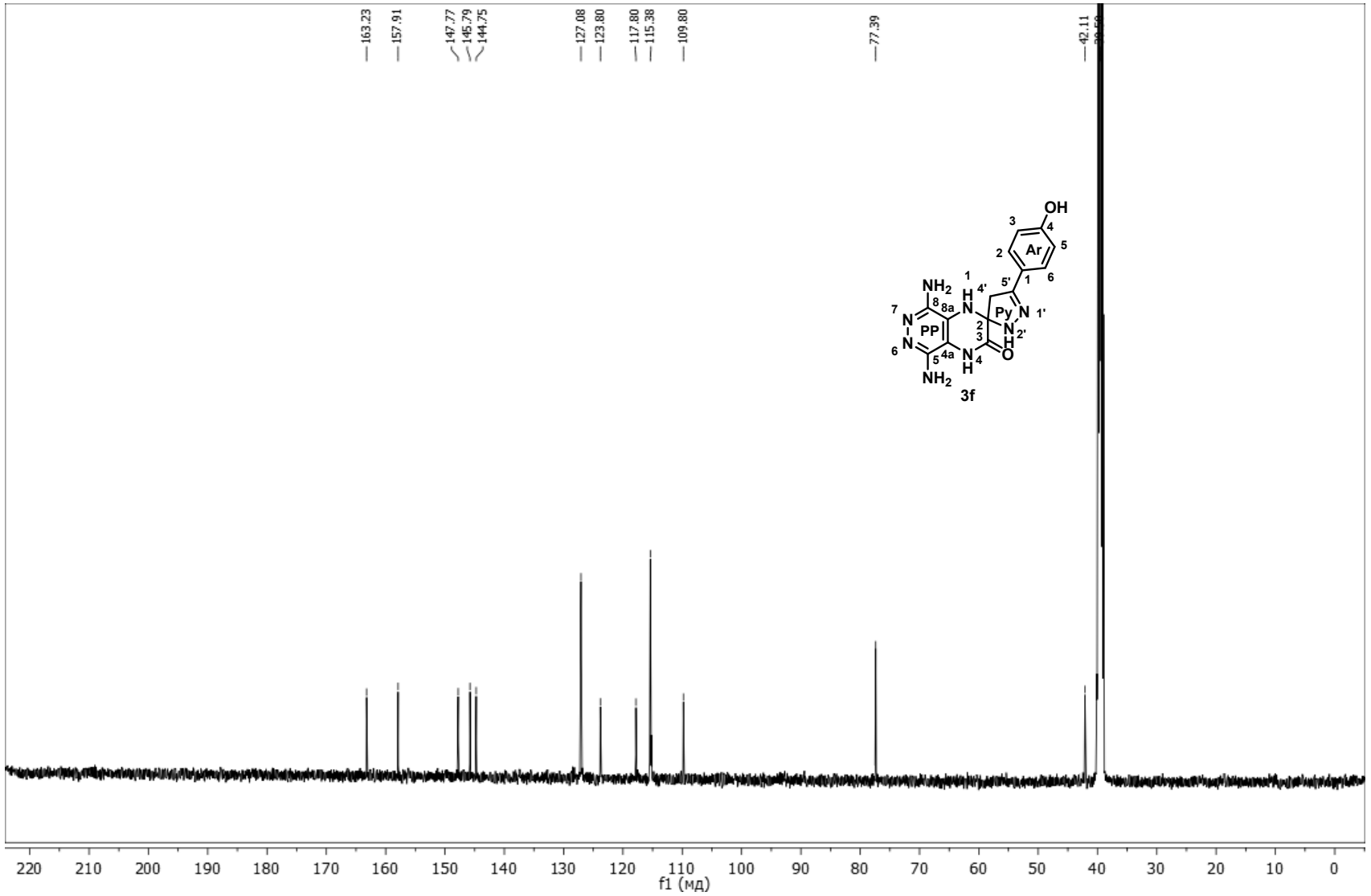

Figure S88. $^{13}C\{^{1}H\}$ NMR spectrum of **3f** in DMSO-d_6 at T = 303 K (Bruker spectrometer at 125.7 MHz).

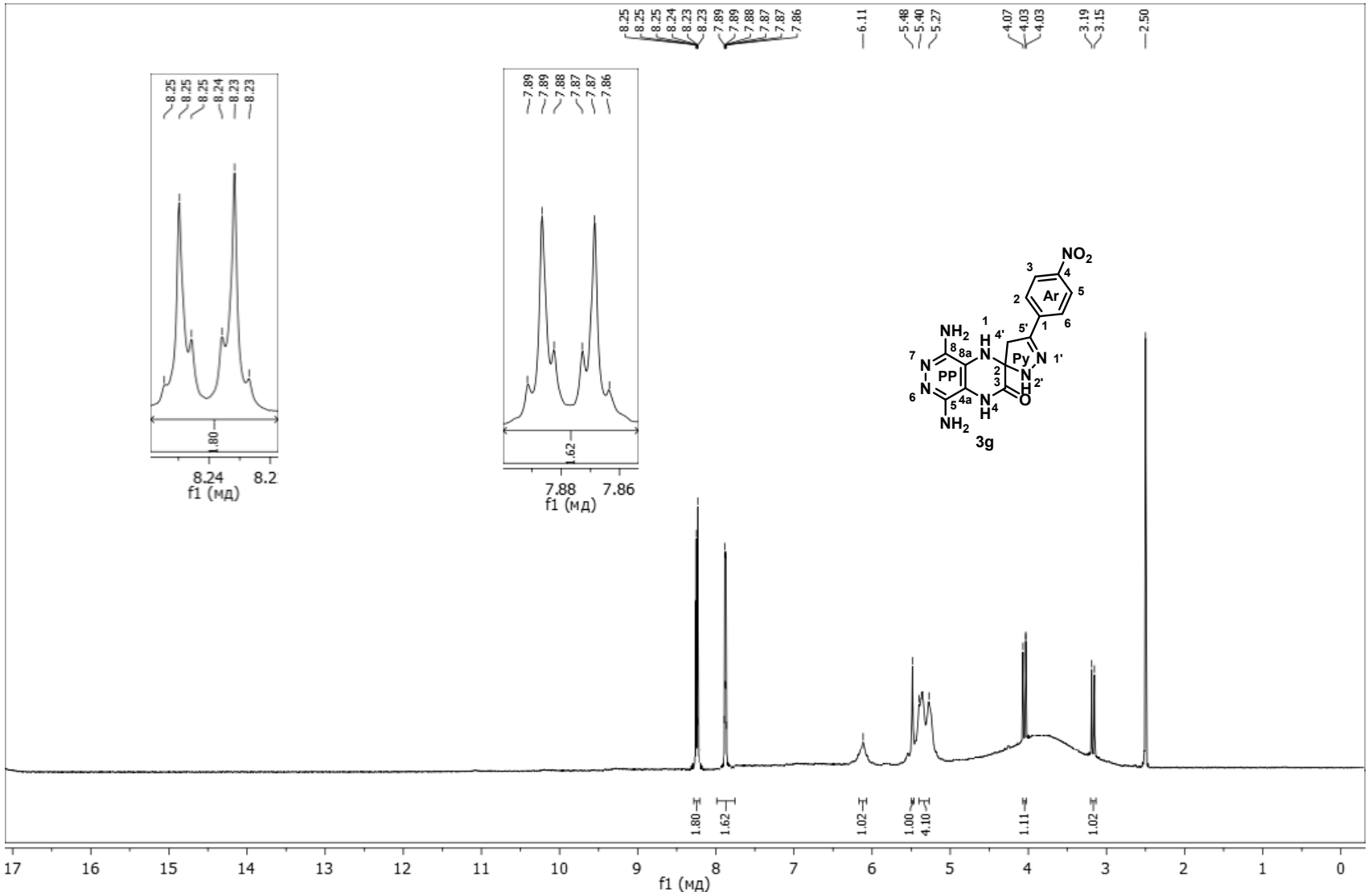

Figure S89. 1D ^{1}H NMR spectrum of **3g** in DMSO-d_6 at T = 303 K. Chemical shifts are given in ppm (Bruker spectrometer at 500.1 MHz).

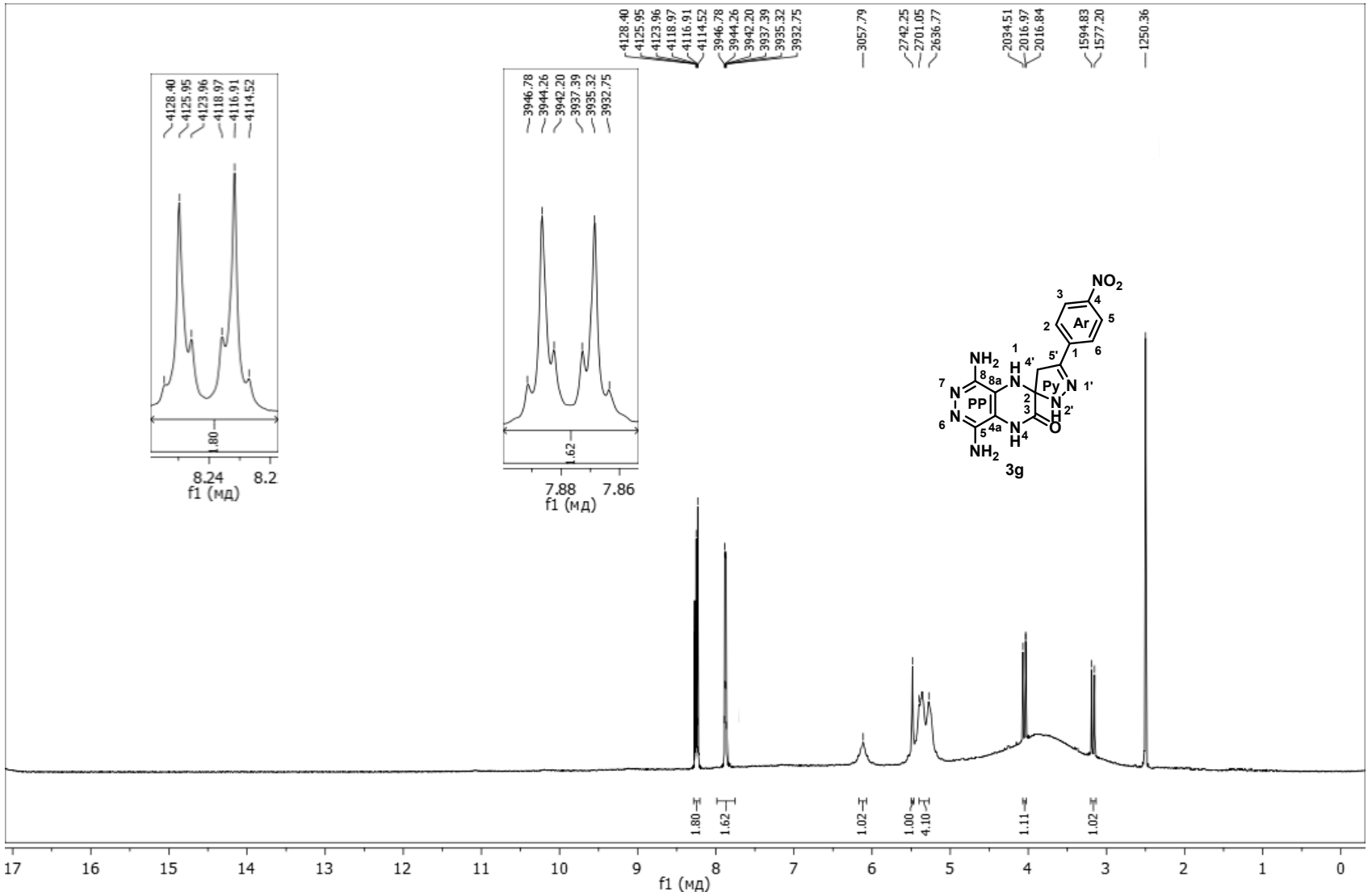

Figure S90. 1D ^{1}H NMR spectrum of **3g** in DMSO-d_6 at T = 303 K. Chemical shifts are given in Hz (Bruker spectrometer at 500.1 MHz).

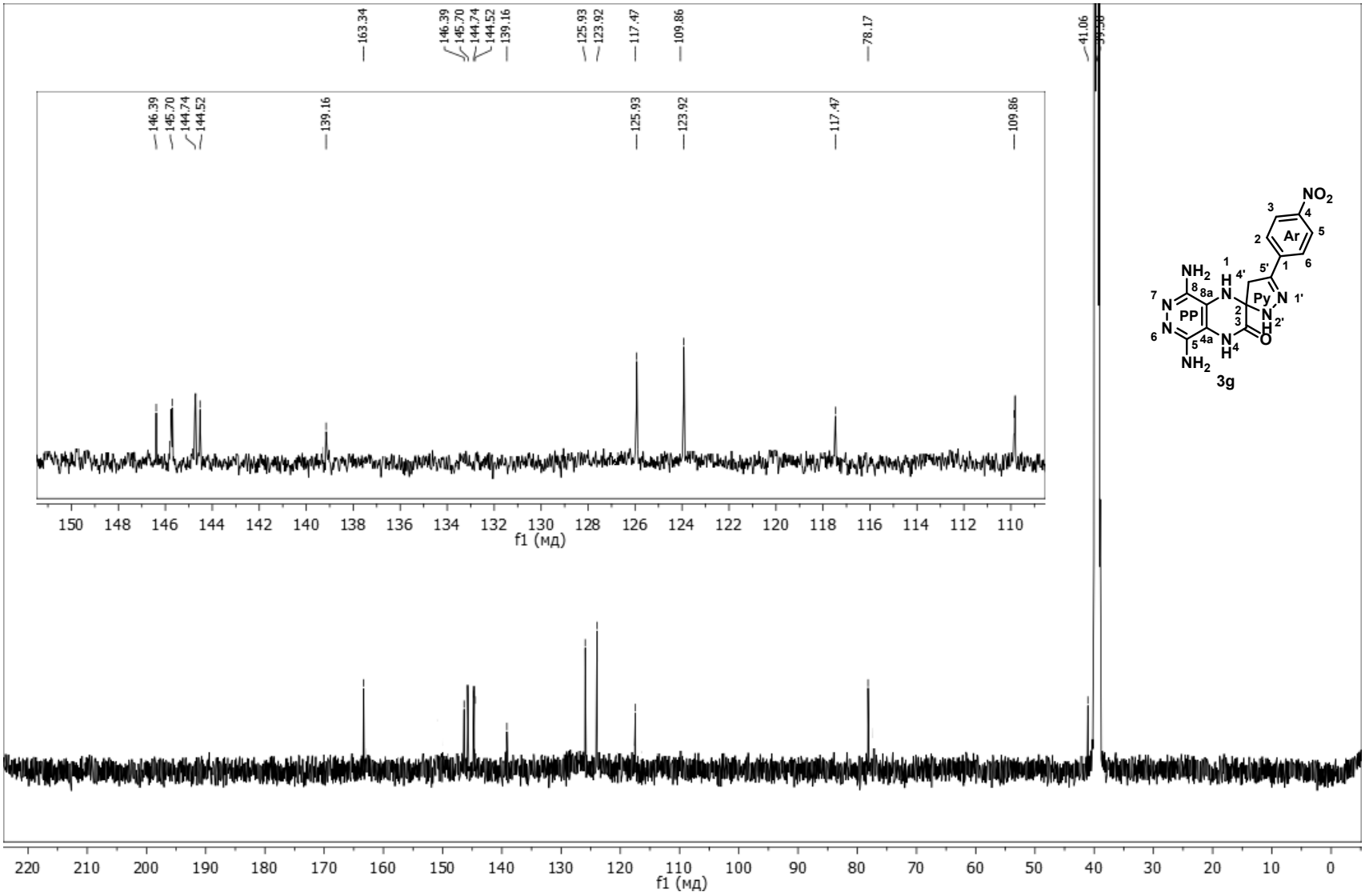

Figure S91. $^{13}C\{^{1}H\}$ NMR spectrum of **3g** in DMSO-d_6 at T = 303 K (Bruker spectrometer at 125.7 MHz).

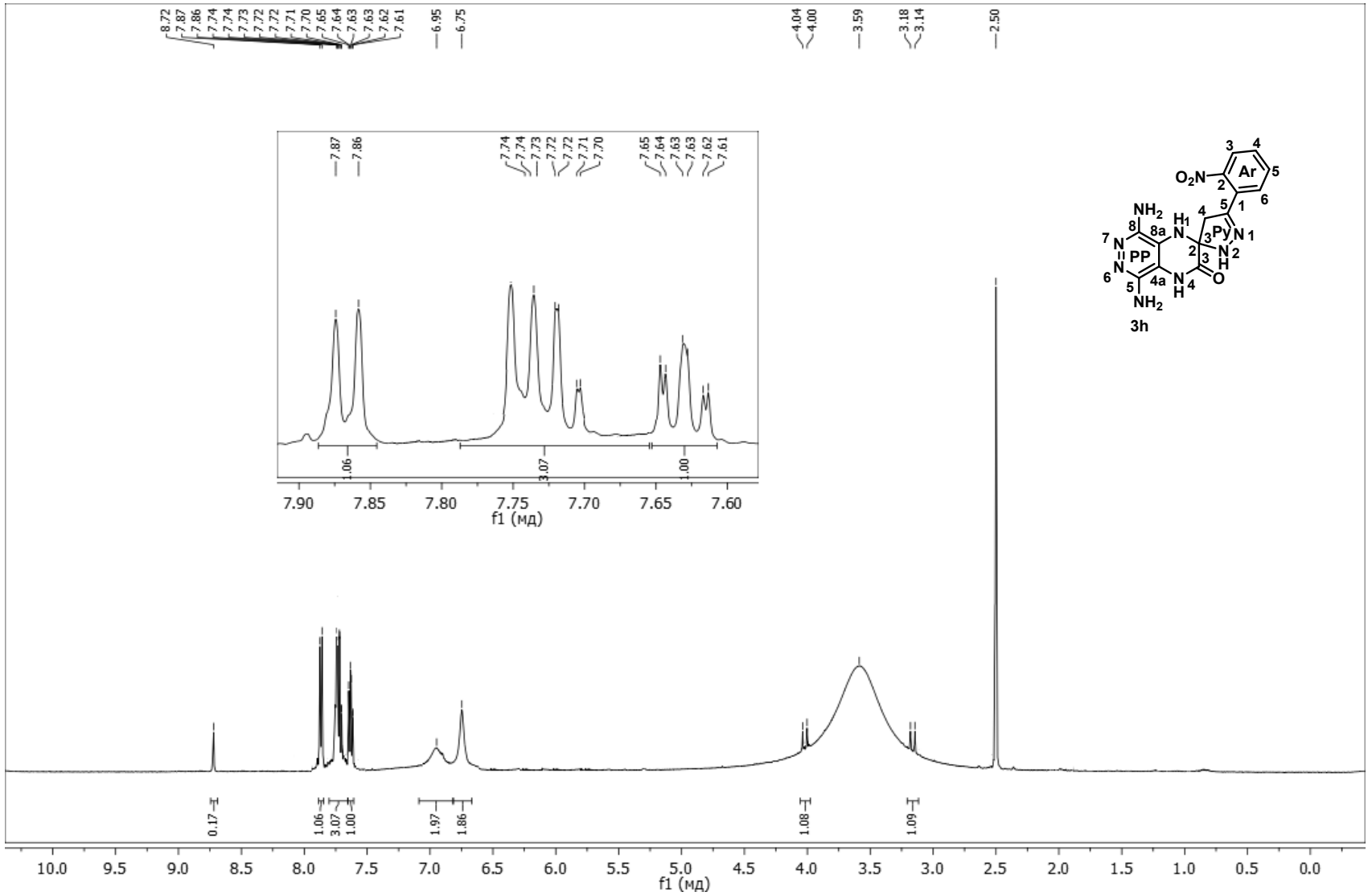

Figure S92. 1D ^{1}H NMR spectrum of **3h** in DMSO-d_6 at T = 303 K. Chemical shifts are given in ppm (Bruker spectrometer at 500.1 MHz).

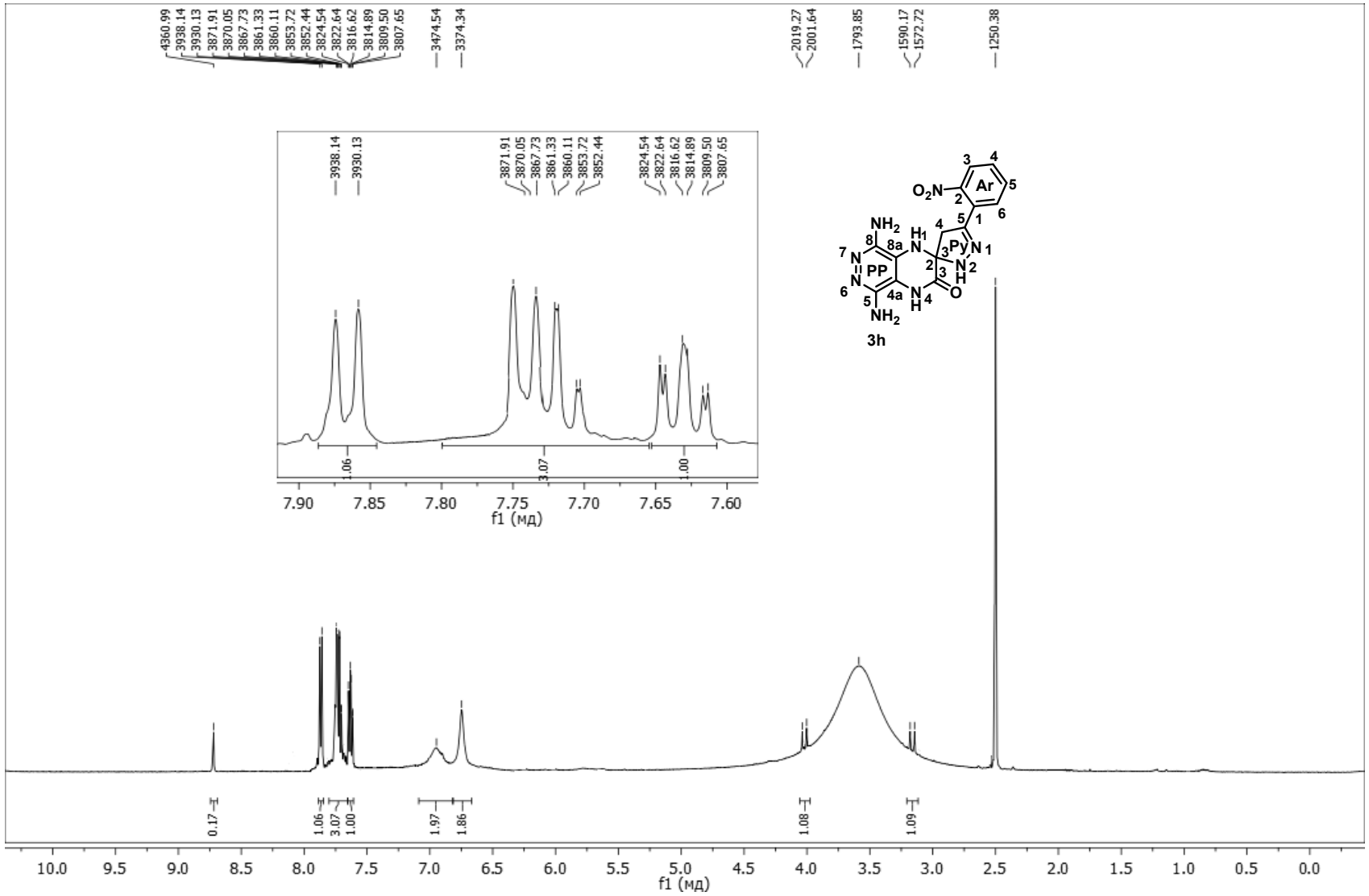

Figure S93. 1D ^{1}H NMR spectrum of **3h** in DMSO-d_6 at T = 303 K. Chemical shifts are given in Hz (Bruker spectrometer at 500.1 MHz).

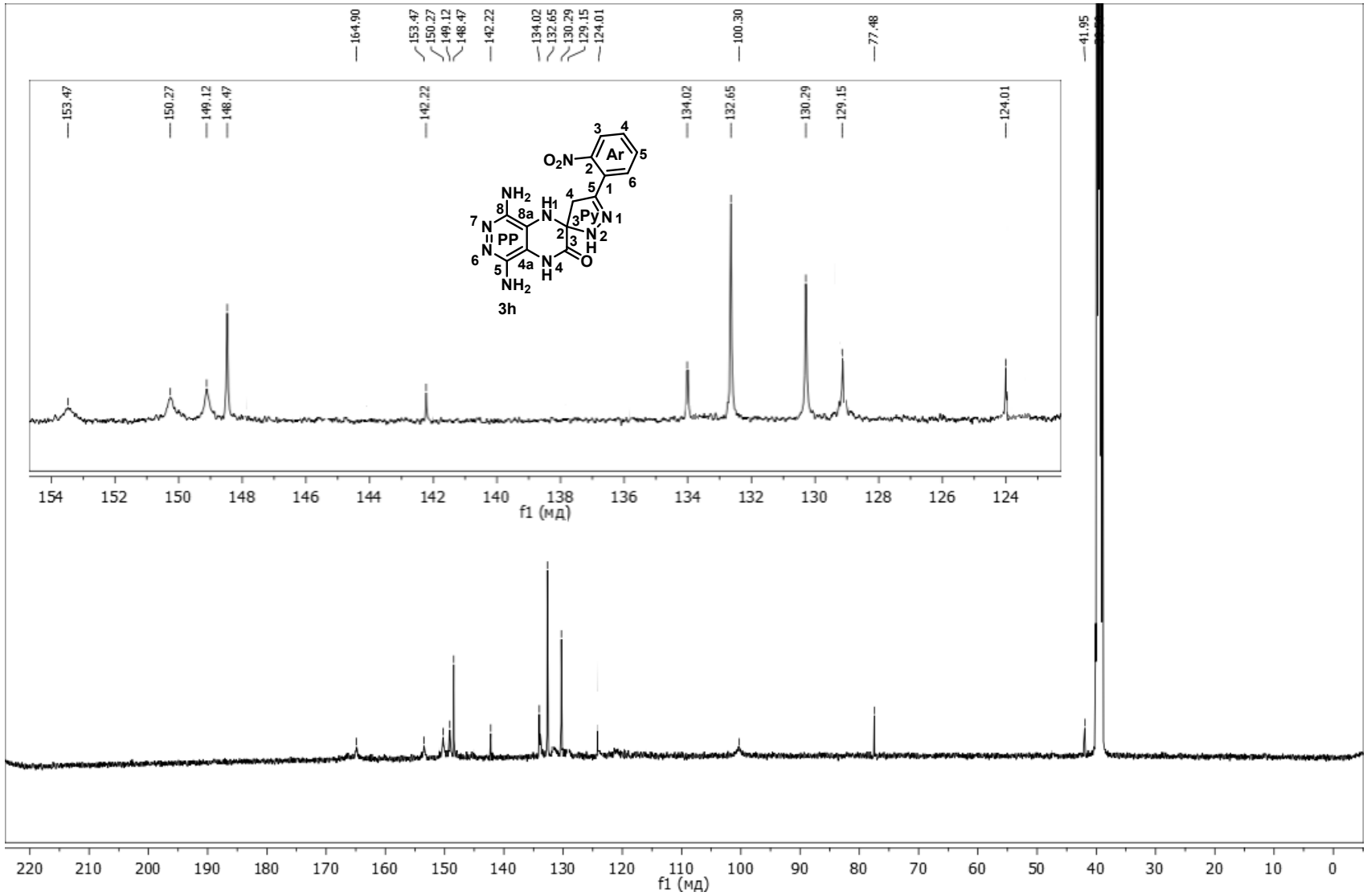

Figure S94. $^{13}C\{^{1}H\}$ NMR spectrum of **3h** in DMSO-d_6 at T = 303 K (Bruker spectrometer at 125.7 MHz).

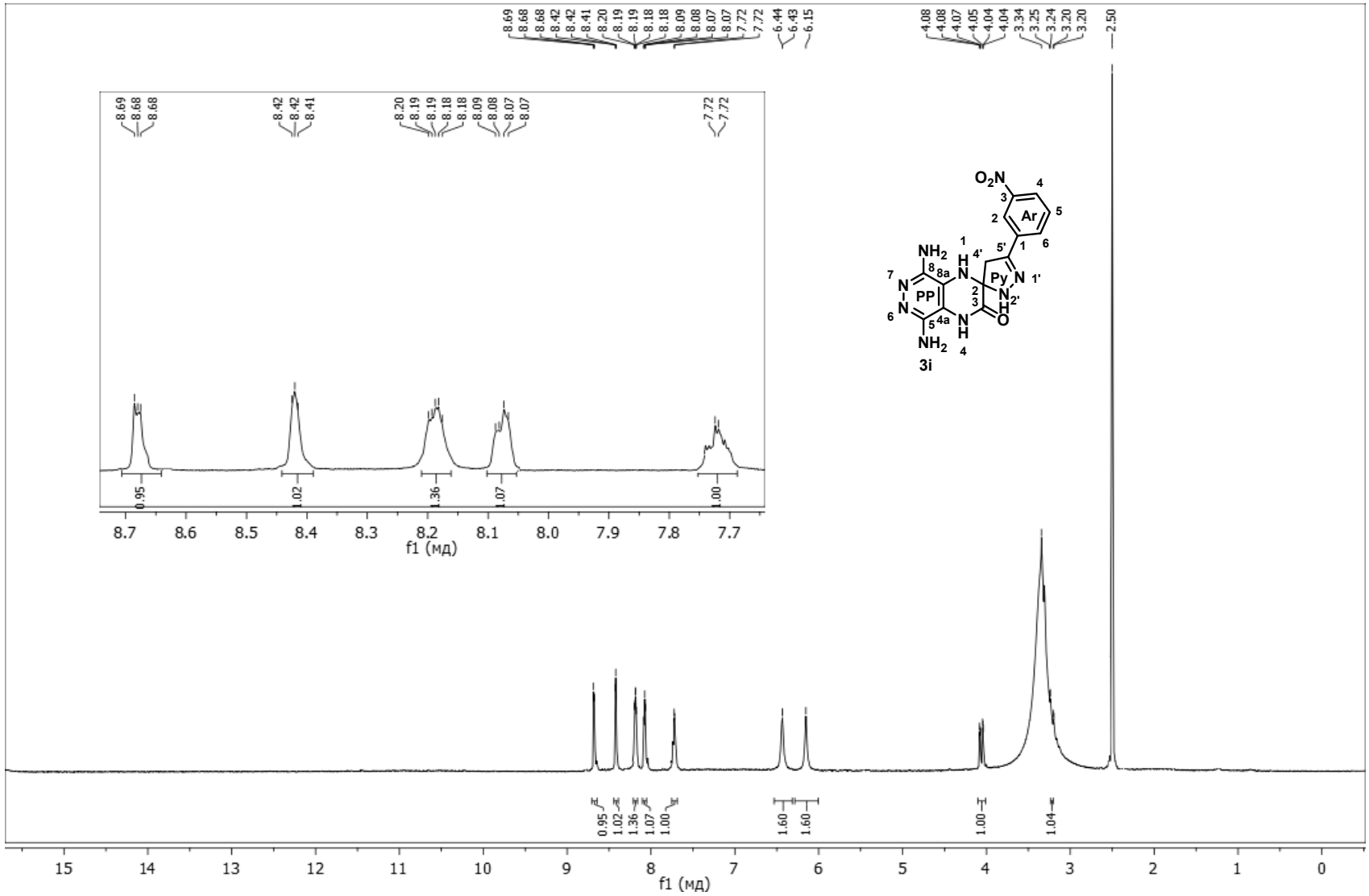

Figure S95. 1D ^{1}H NMR spectrum of **3i** in DMSO-d_6 at T = 303 K. Chemical shifts are given in ppm (Bruker spectrometer at 500.1 MHz).

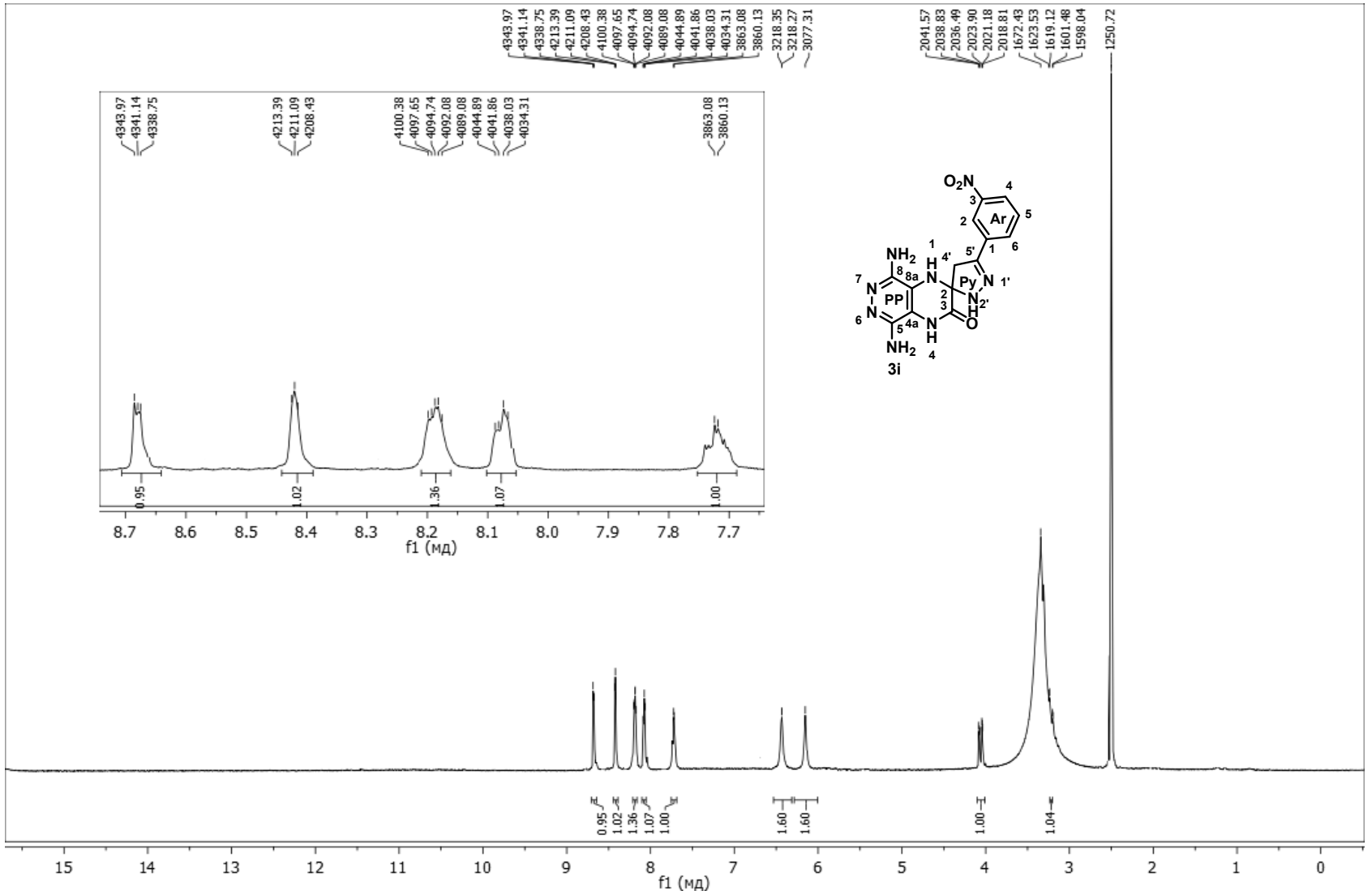

Figure S96. 1D ^{1}H NMR spectrum of **3i** in DMSO-d_6 at T = 303 K. Chemical shifts are given in Hz (Bruker spectrometer at 500.1 MHz).

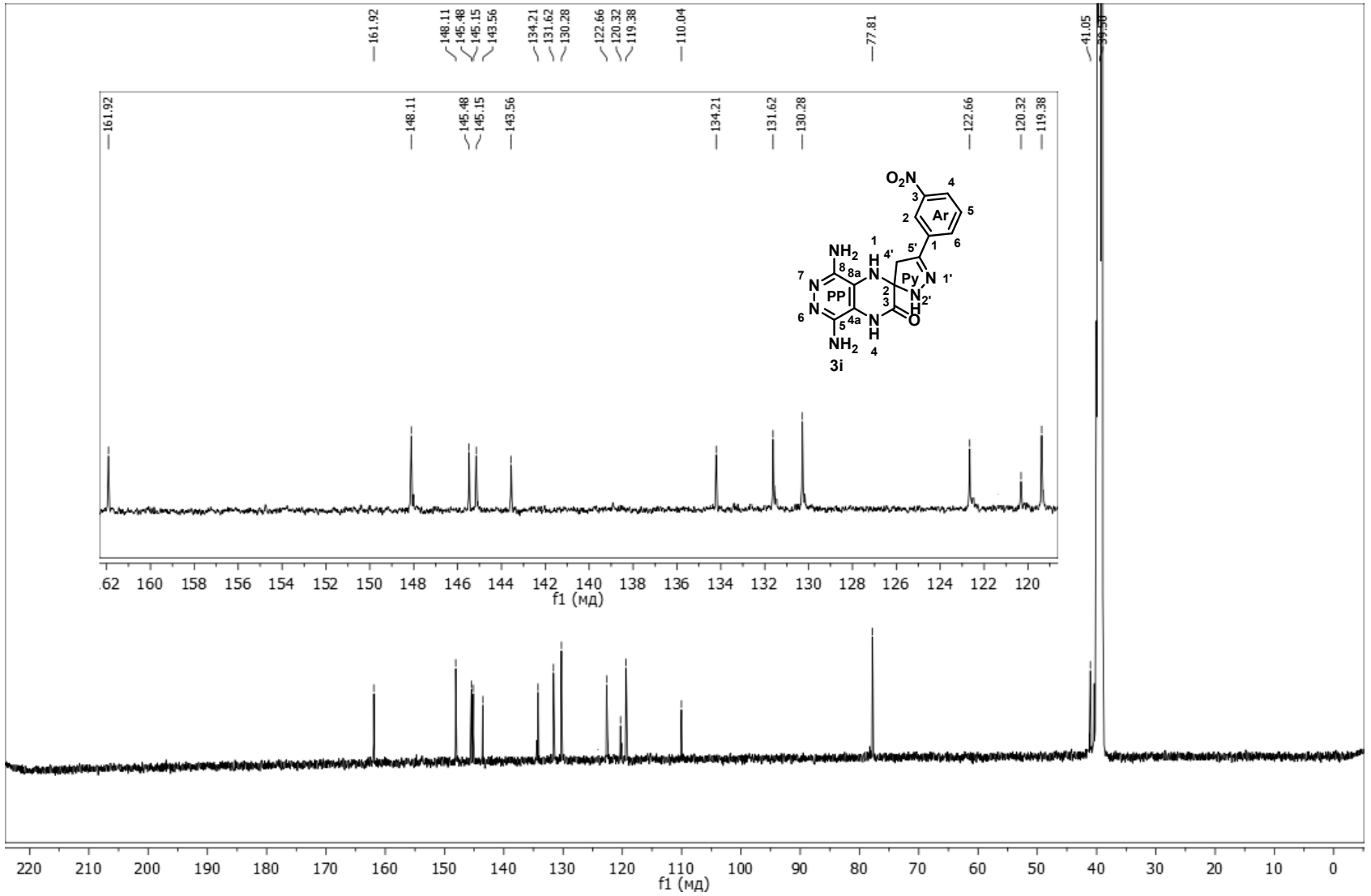

Figure S97. $^{13}C\{^{1}H\}$ NMR spectrum of **3i** in DMSO-d_6 at T = 303 K (Bruker spectrometer at 125.7 MHz).

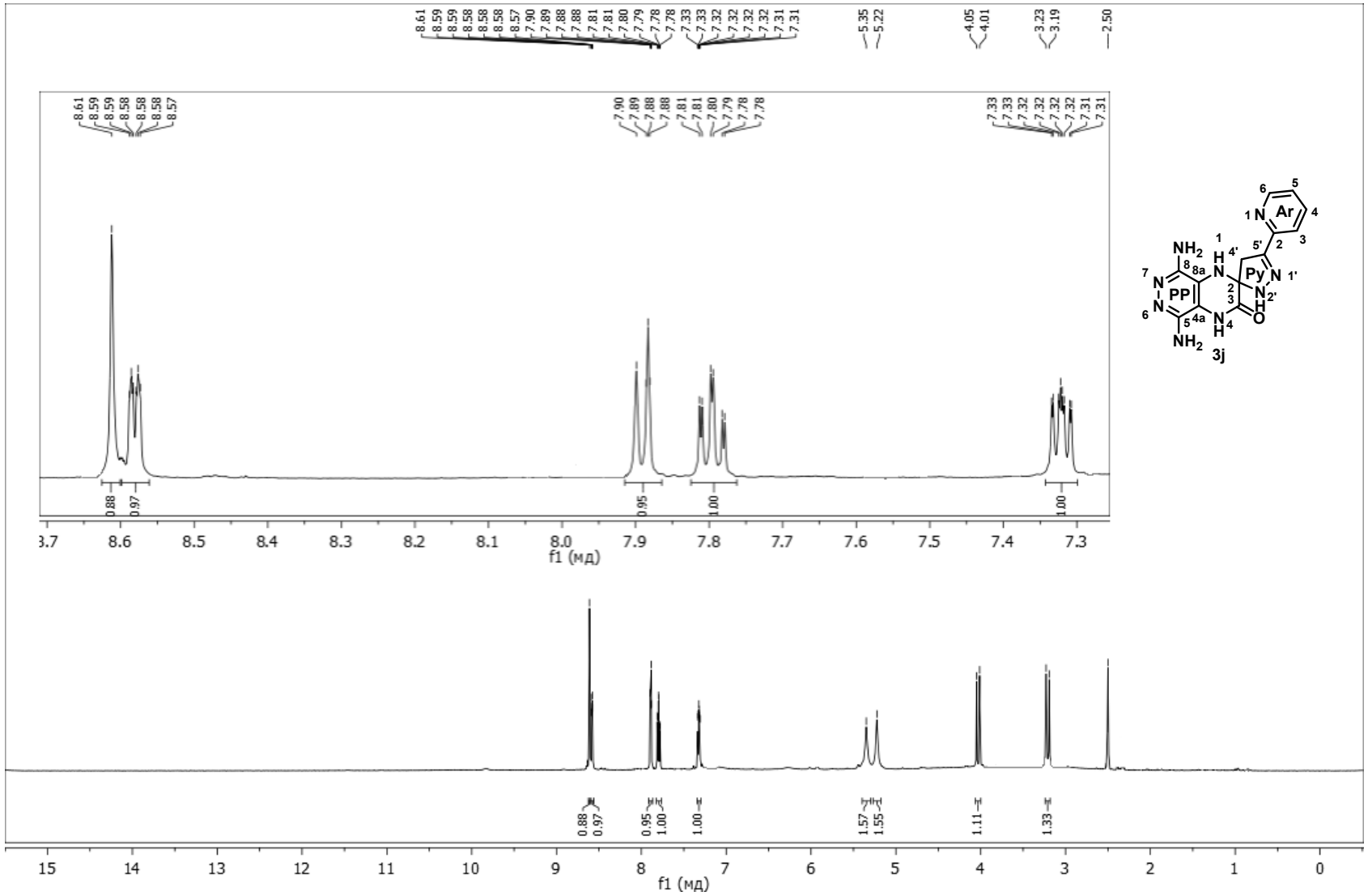

Figure S98. 1D ^{1}H NMR spectrum of **3j** in DMSO-d_6 at T = 303 K. Chemical shifts are given in ppm (Bruker spectrometer at 500.1 MHz).

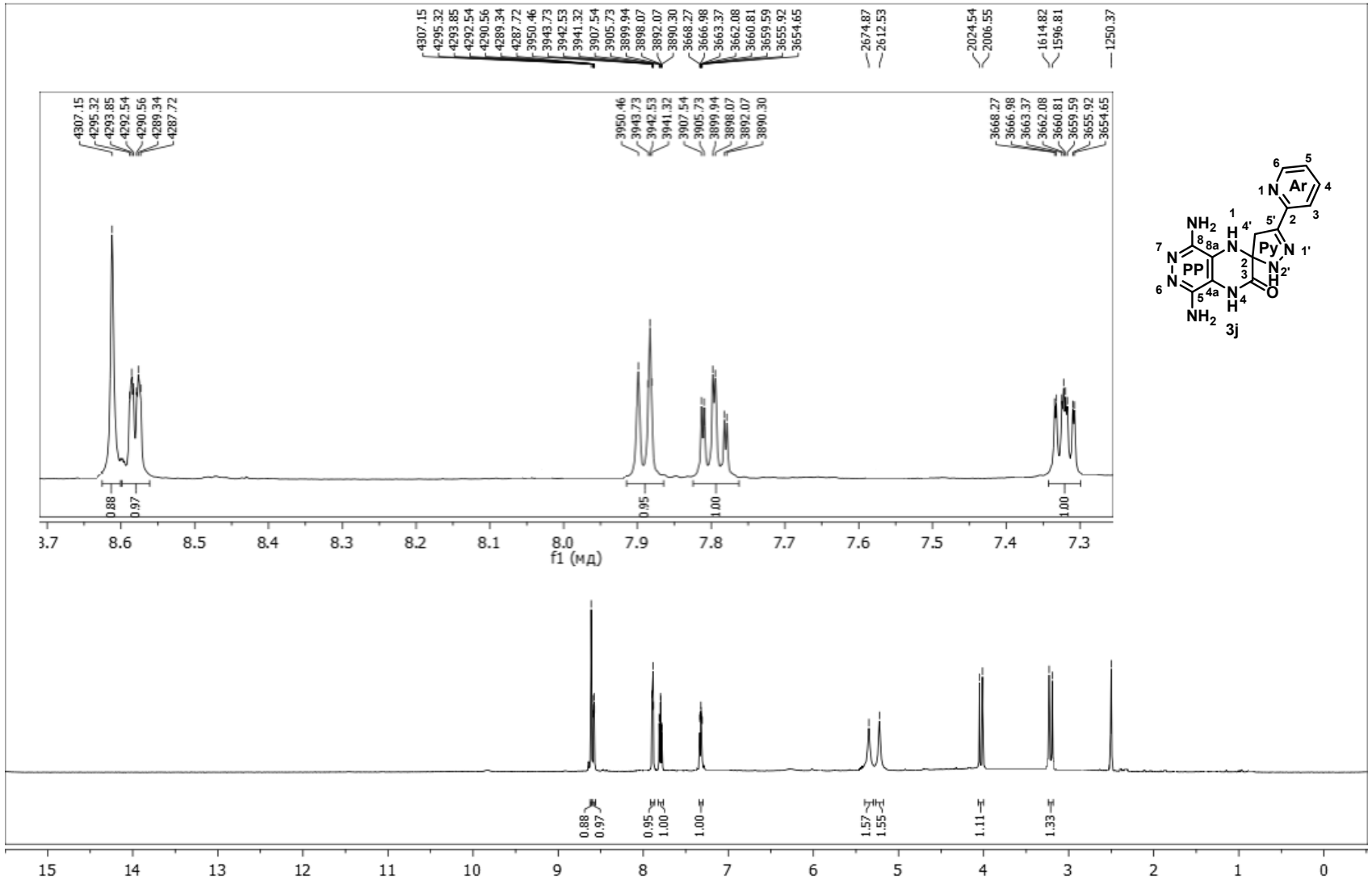

Figure S99. 1D ^{1}H NMR spectrum of **3j** in DMSO-d_6 at T = 303 K. Chemical shifts are given in Hz (Bruker spectrometer at 500.1 MHz).

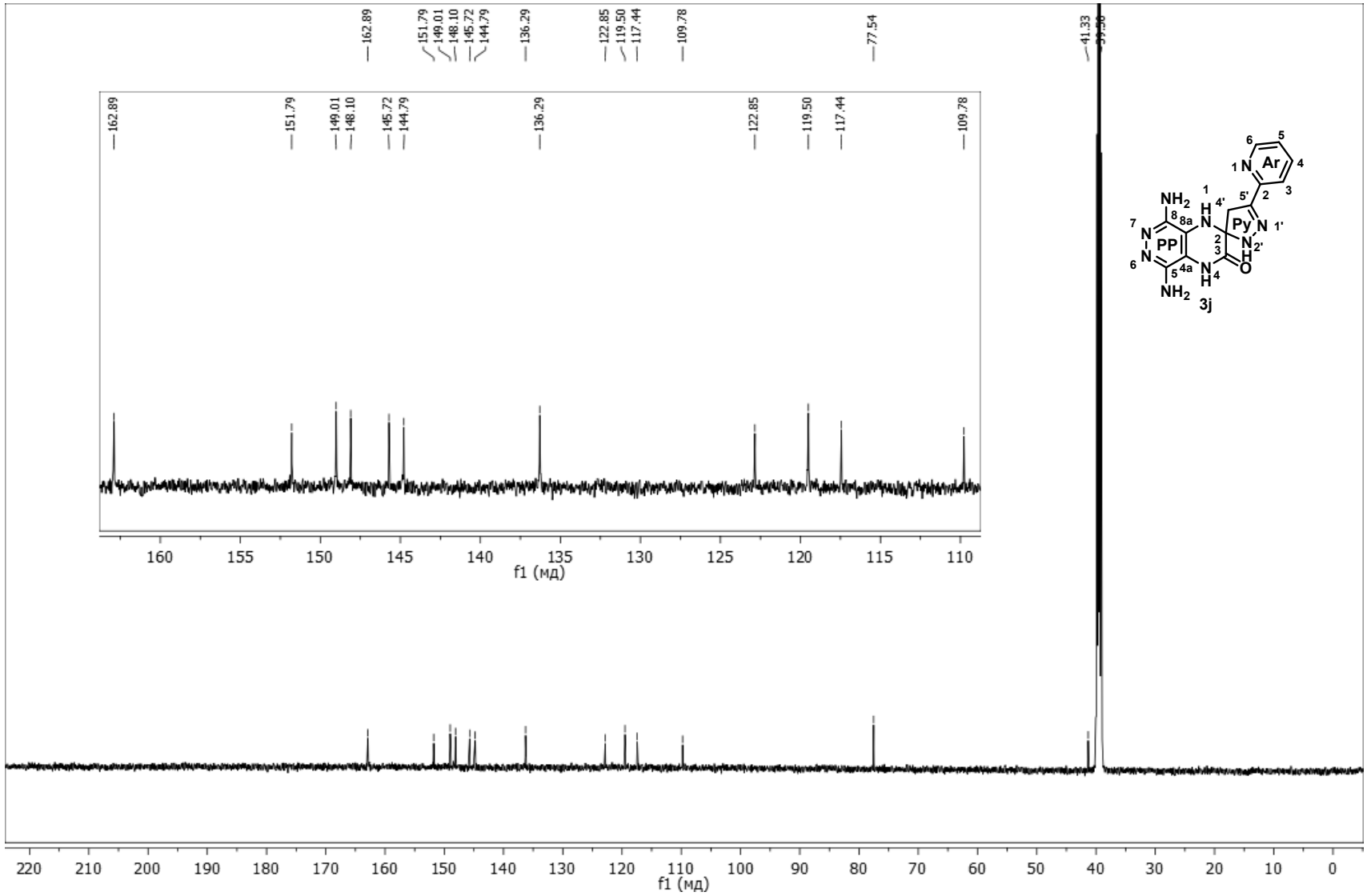

Figure S100. $^{13}C\{^{1}H\}$ NMR spectrum of **3j** in DMSO-d_6 at T = 303 K (Bruker spectrometer at 125.7 MHz).

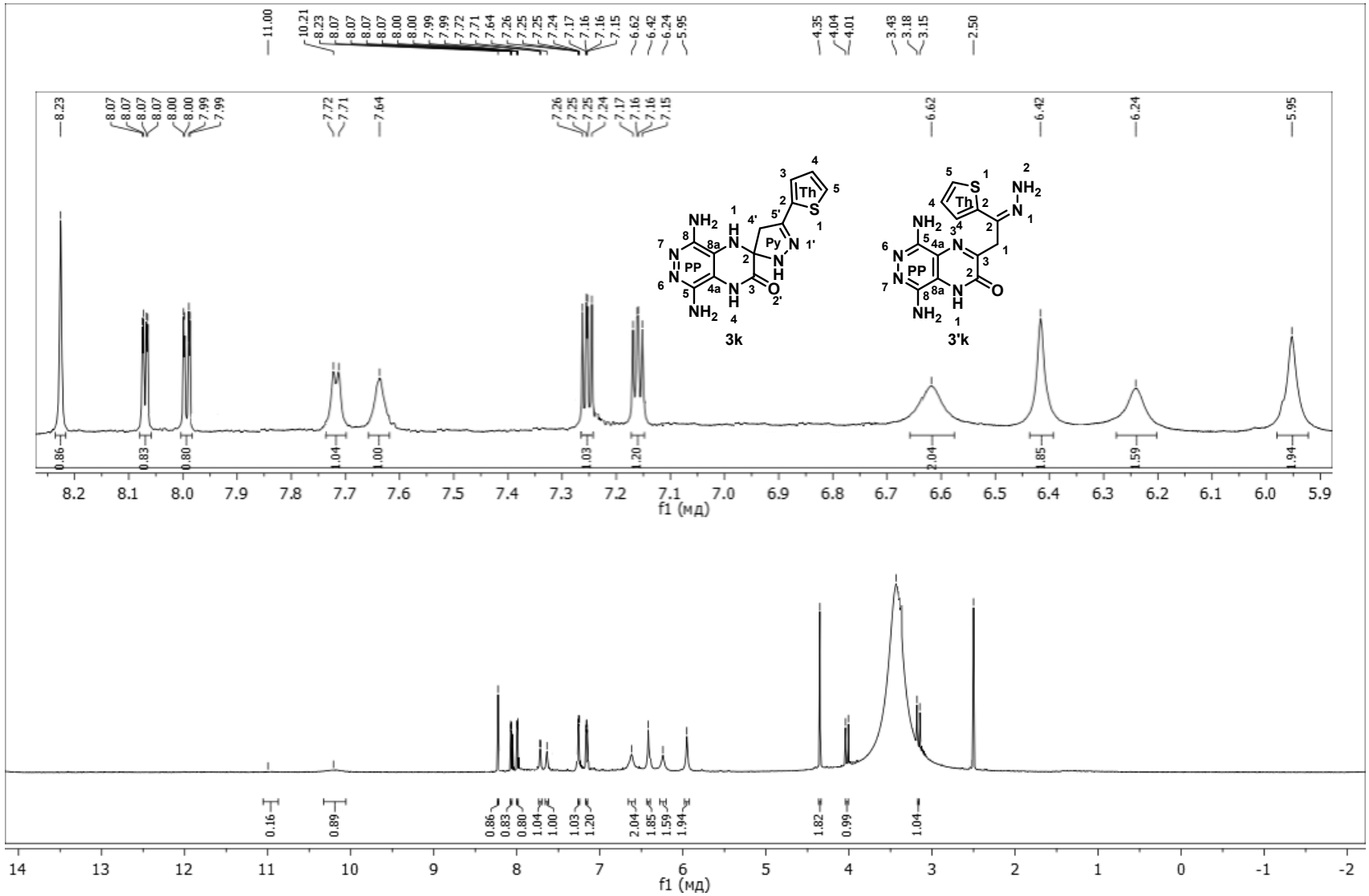

Figure S101. 1D ^{1}H NMR spectrum of **3k** and **3′k** in DMSO-d_6 at T = 303 K. Chemical shifts are given in ppm (Bruker spectrometer at 500.1 MHz).

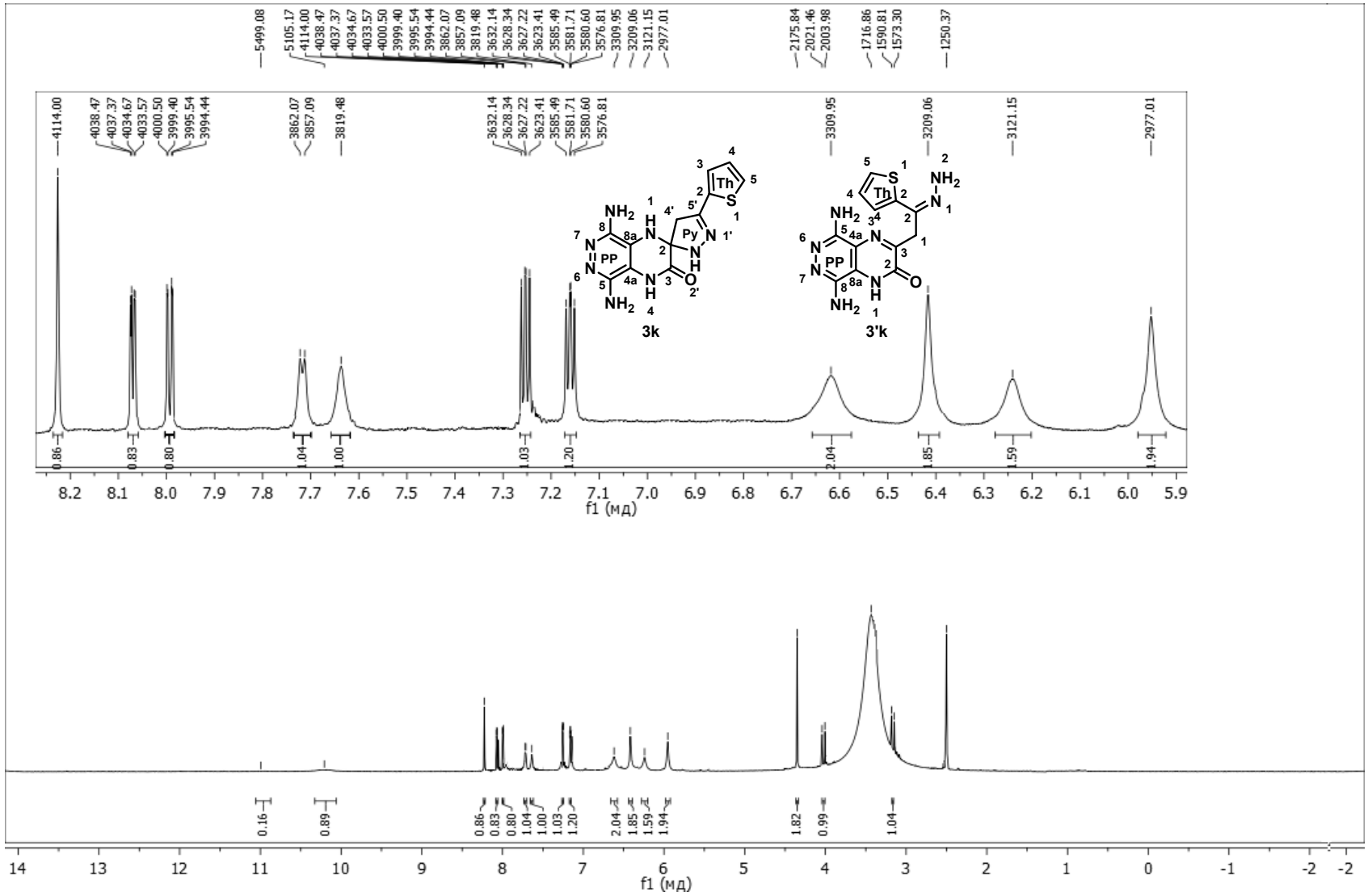

Figure S102. 1D ^{1}H NMR spectrum of **3k** and **3′k** in DMSO-d_6 at T = 303 K. Chemical shifts are given in Hz (Bruker spectrometer at 500.1 MHz).

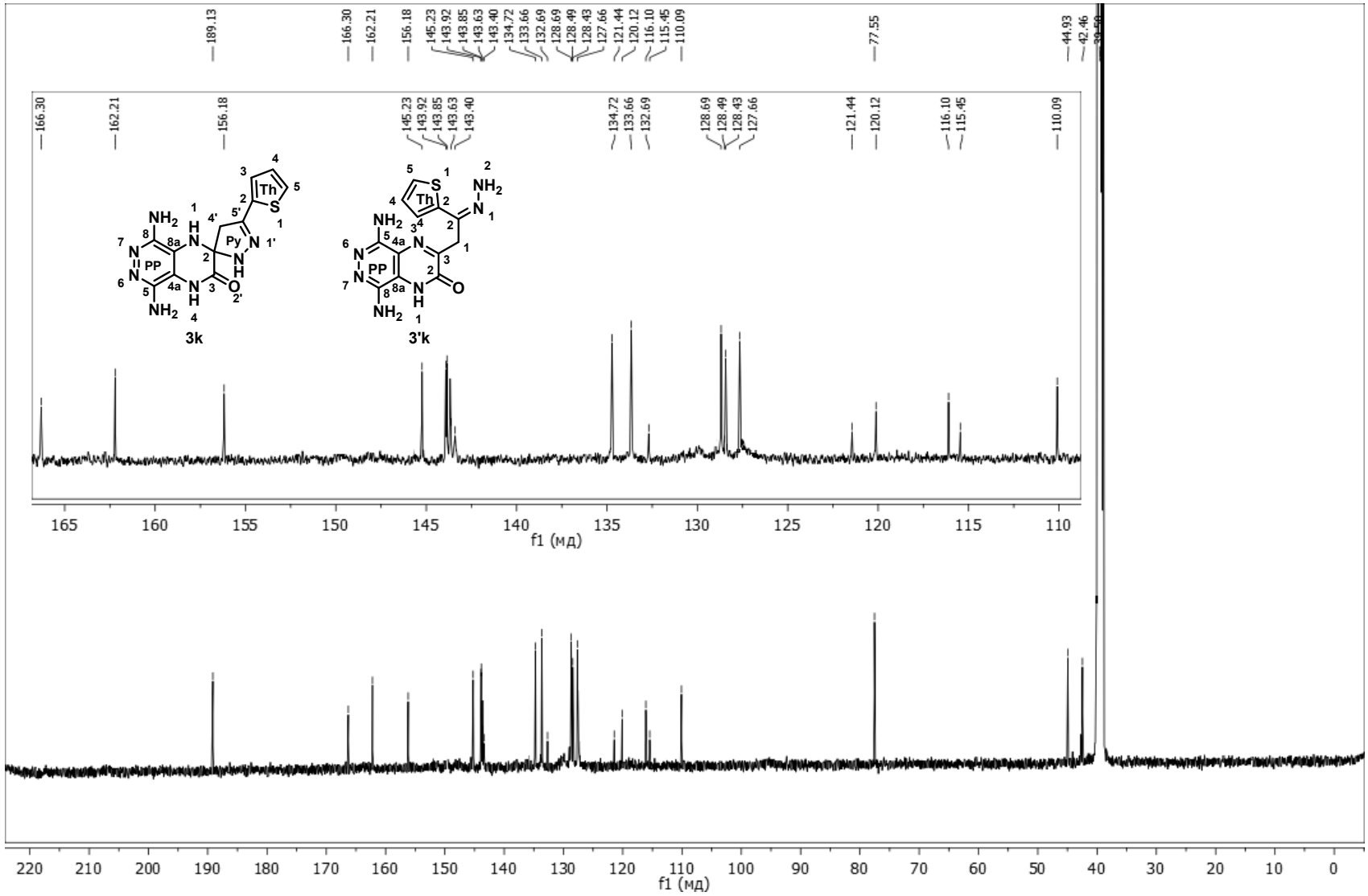

Figure S103. $^{13}C\{^{1}H\}$ NMR spectrum of **3k** and **3′k** in DMSO-d_6 at T = 303 K (Bruker spectrometer at 125.7 MHz).

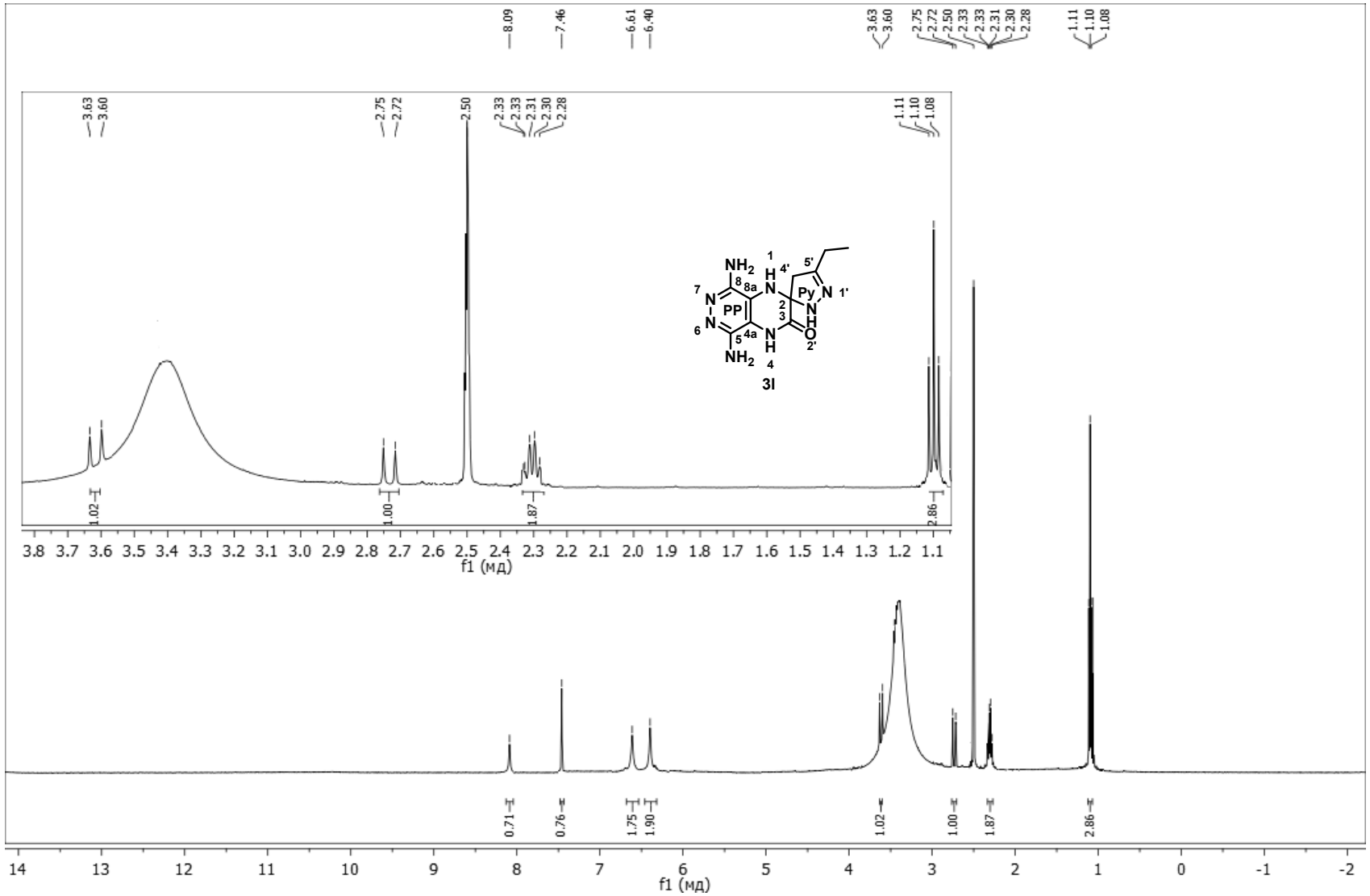

Figure S104. 1D ^{1}H NMR spectrum of **3l** in DMSO-d_6 at T = 303 K. Chemical shifts are given in ppm (Bruker spectrometer at 500.1 MHz).

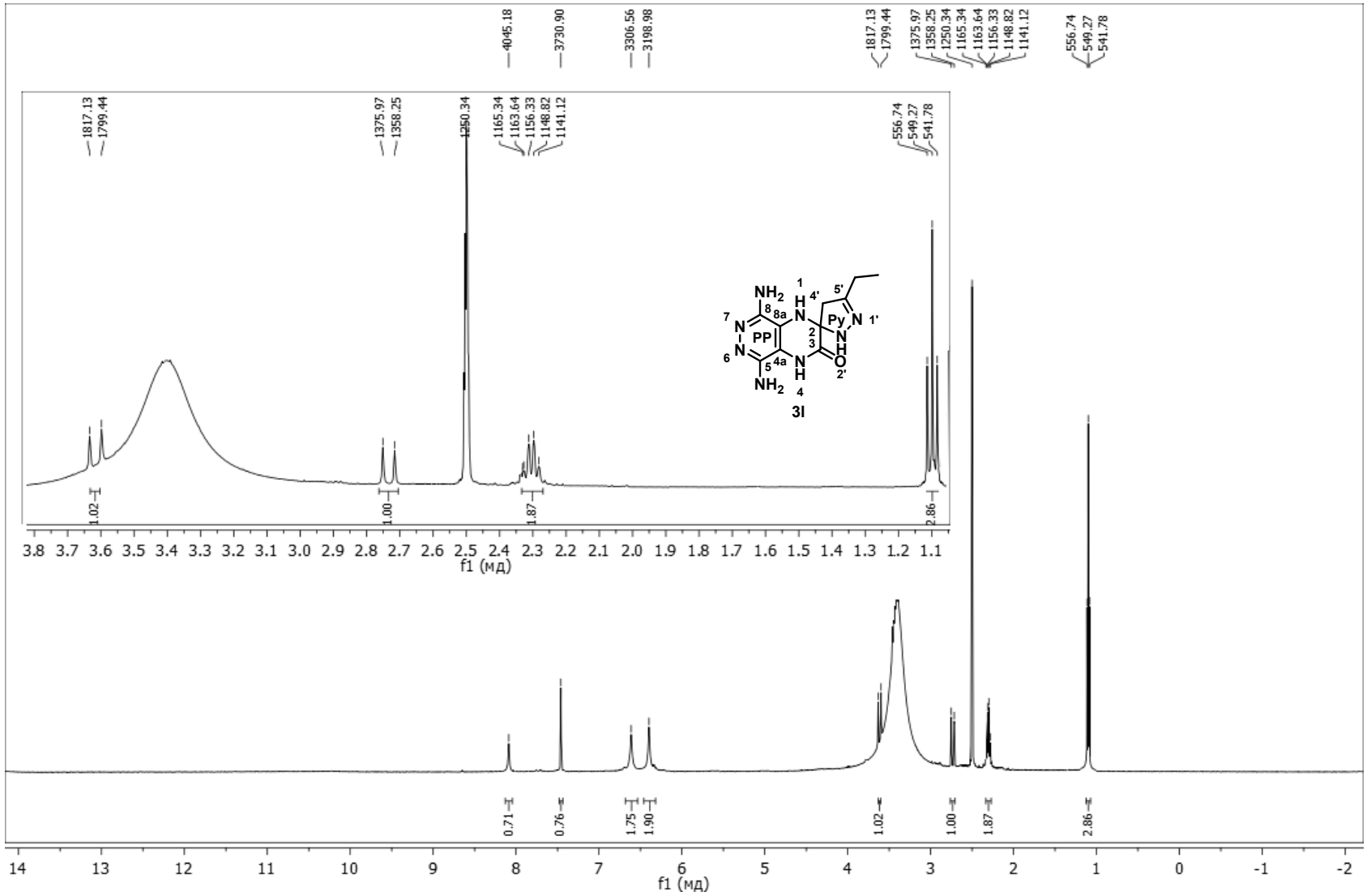

Figure S105. 1D ^{1}H NMR spectrum of **3l** in DMSO-d_6 at T = 303 K. Chemical shifts are given in Hz (Bruker spectrometer at 500.1 MHz).

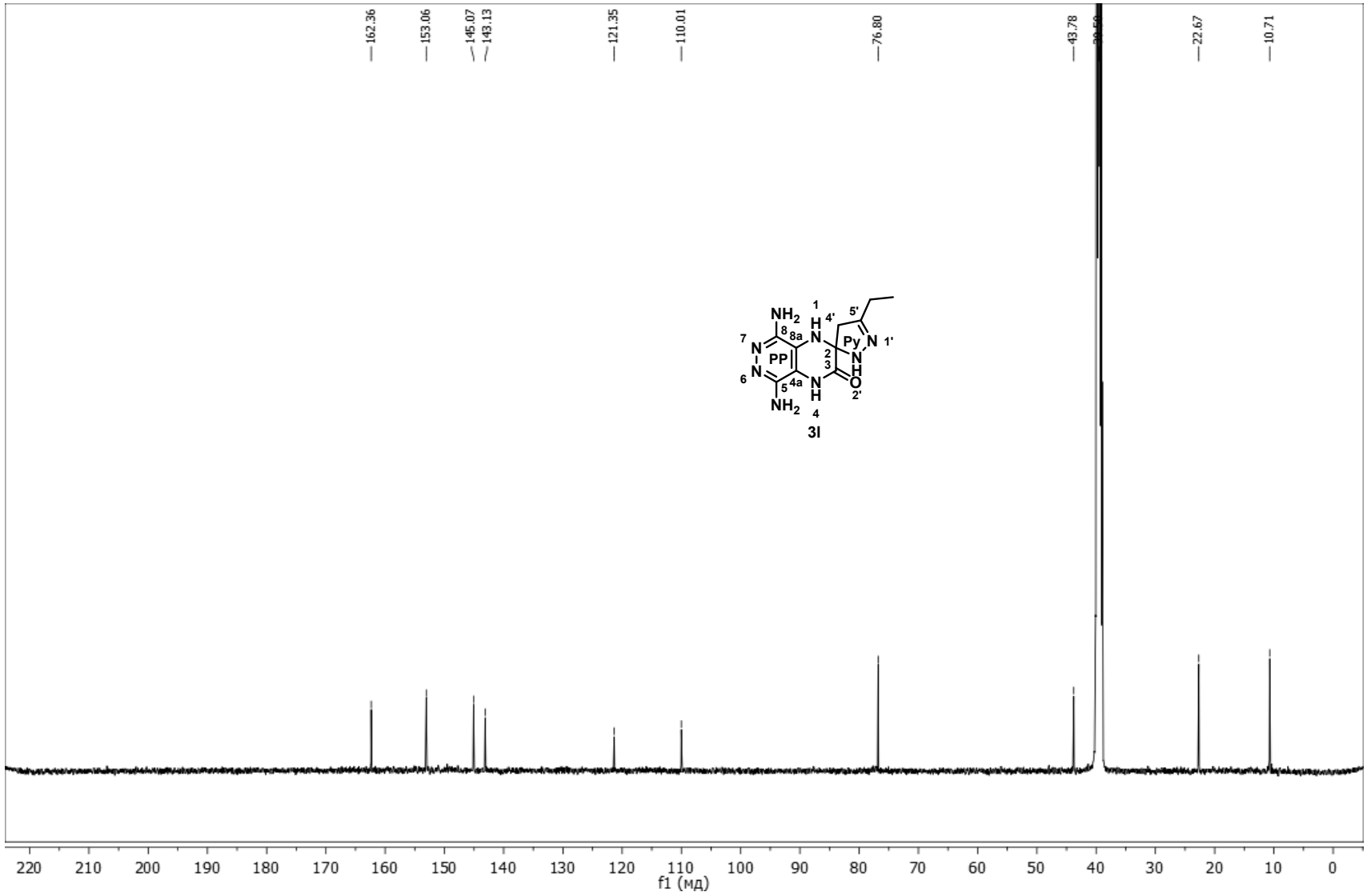

Figure S106. $^{13}C\{^{1}H\}$ NMR spectrum of **3l** in DMSO-d_6 at T = 303 K (Bruker spectrometer at 125.7 MHz).

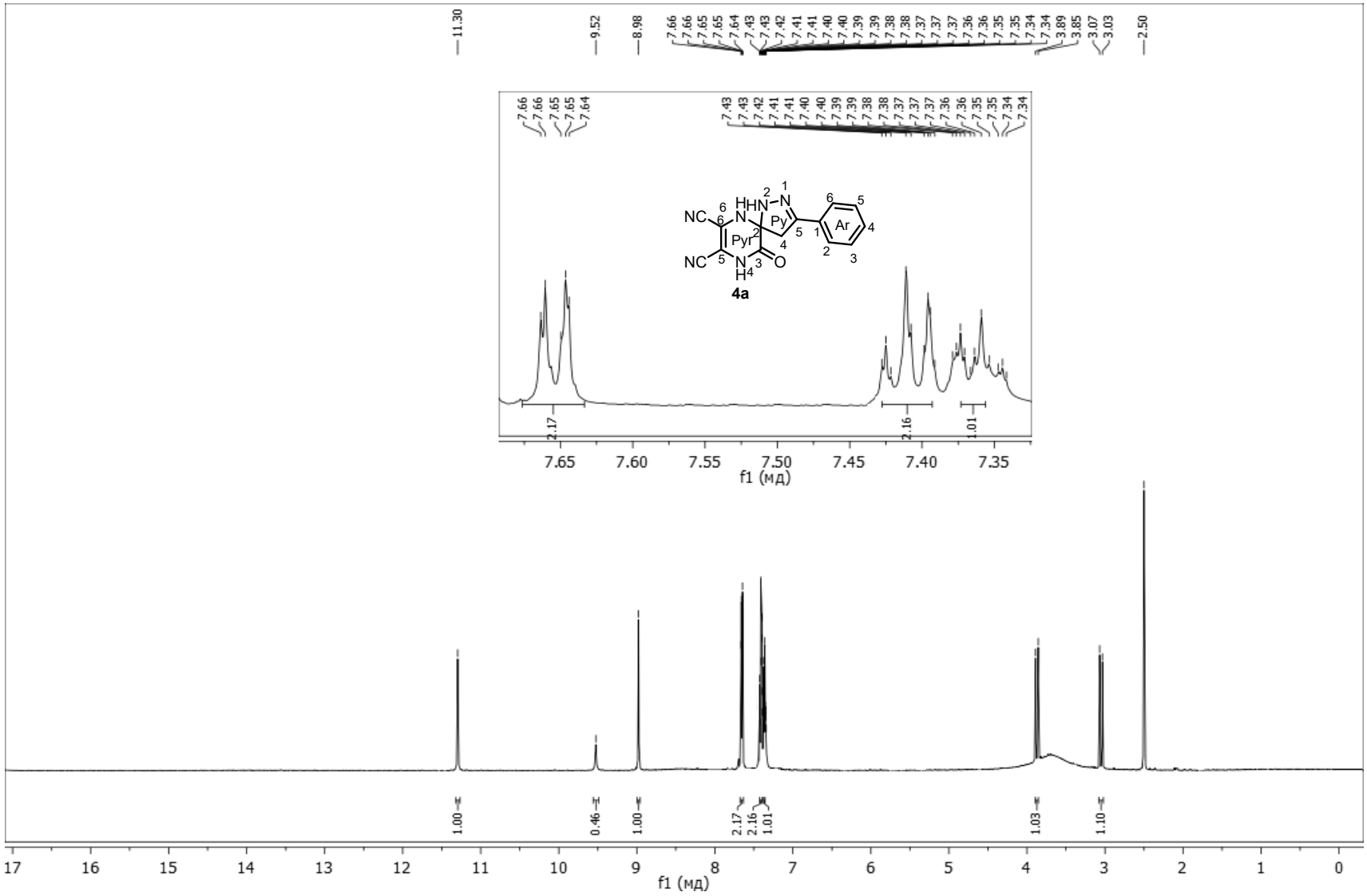

Figure S107. 1D ^{1}H NMR spectrum of **4a** in DMSO-d_6 at T = 303 K. Chemical shifts are given in ppm (Bruker spectrometer at 500.1 MHz).

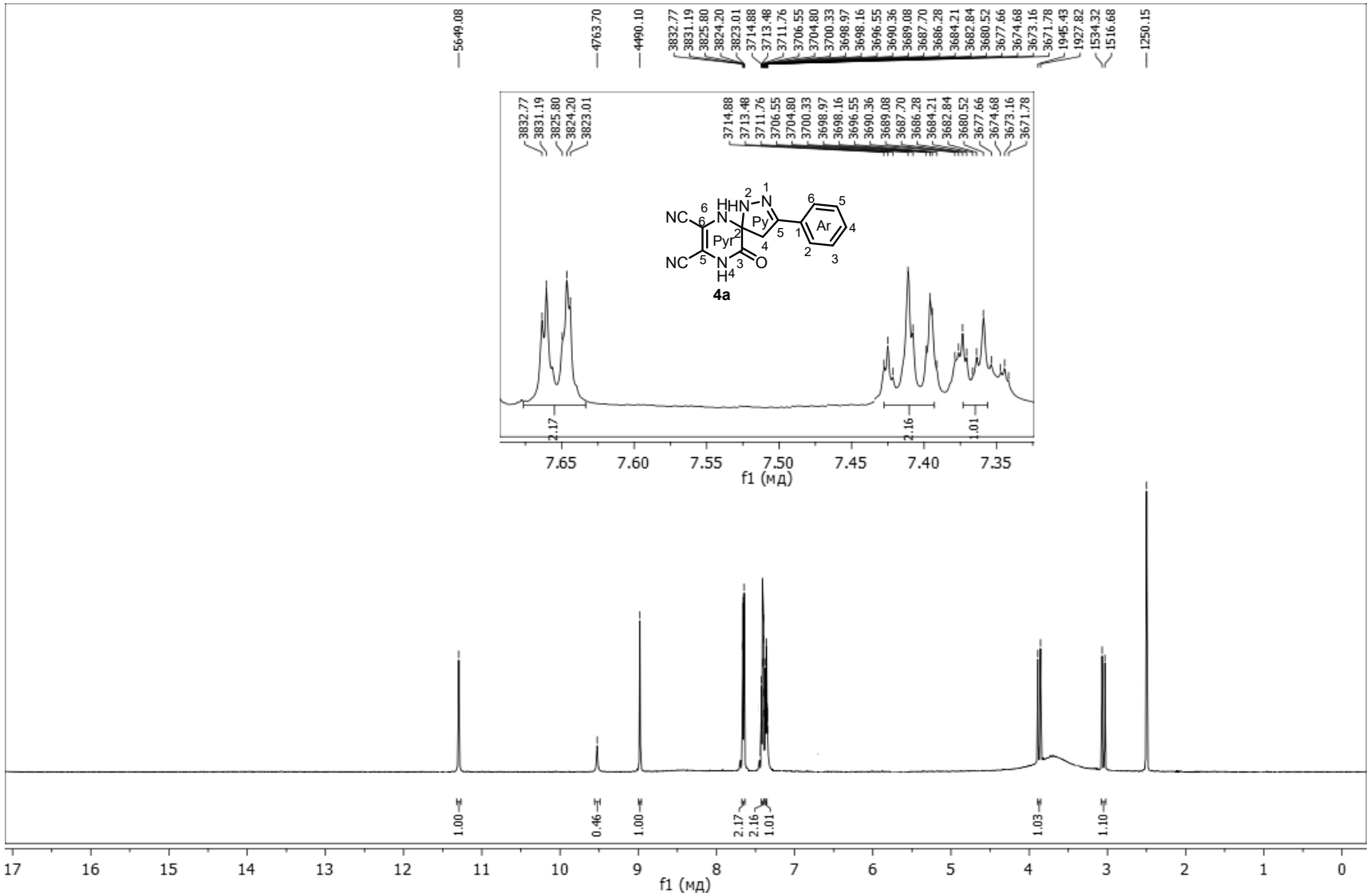

Figure S108. 1D ^{1}H NMR spectrum of **4a** in DMSO-d_6 at T = 303 K. Chemical shifts are given in Hz (Bruker spectrometer at 500.1 MHz).

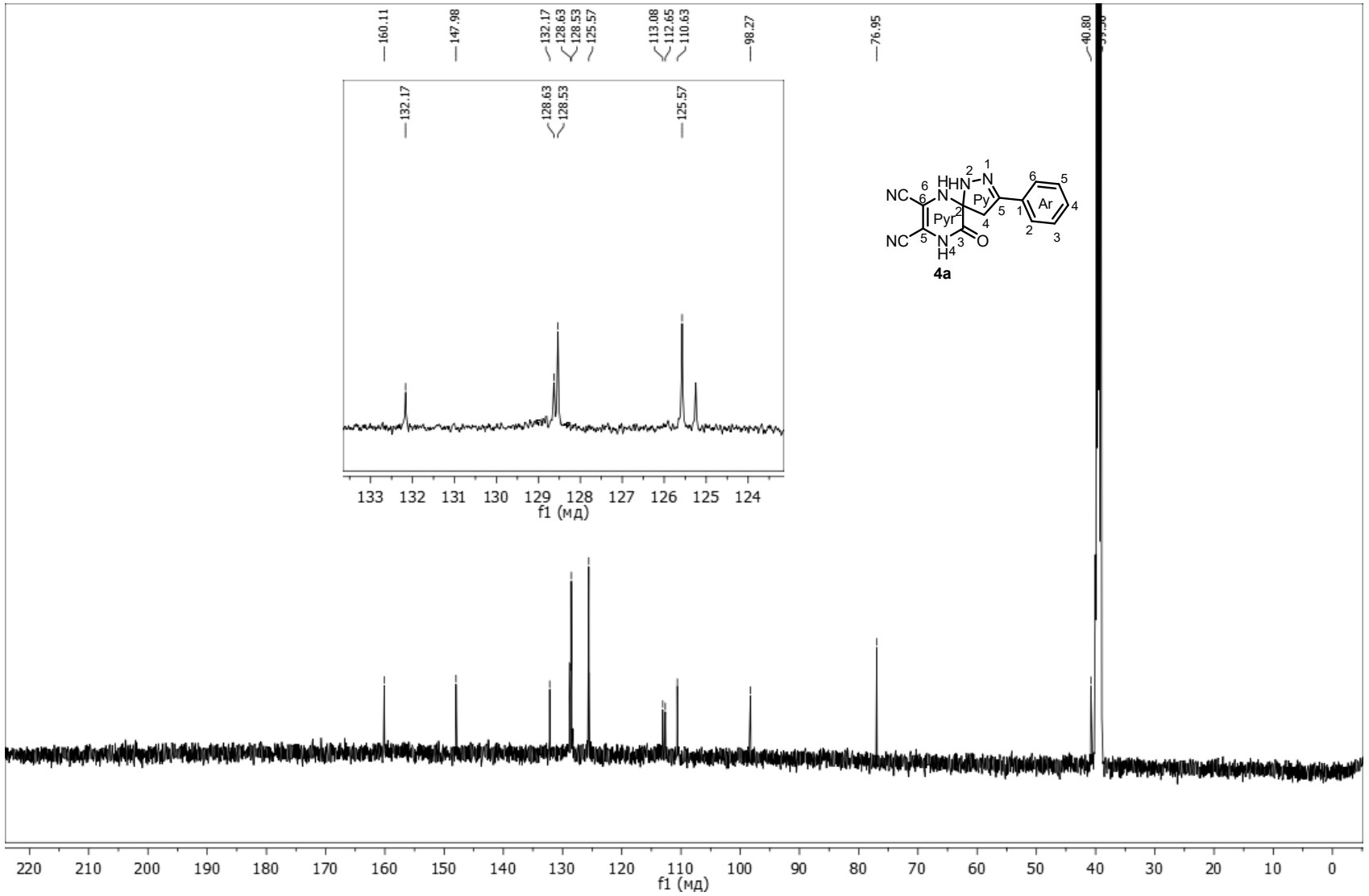

Figure S109. $^{13}C\{^{1}H\}$ NMR spectrum of **4a** in DMSO-d_6 at T = 303 K (Bruker spectrometer at 125.7 MHz).

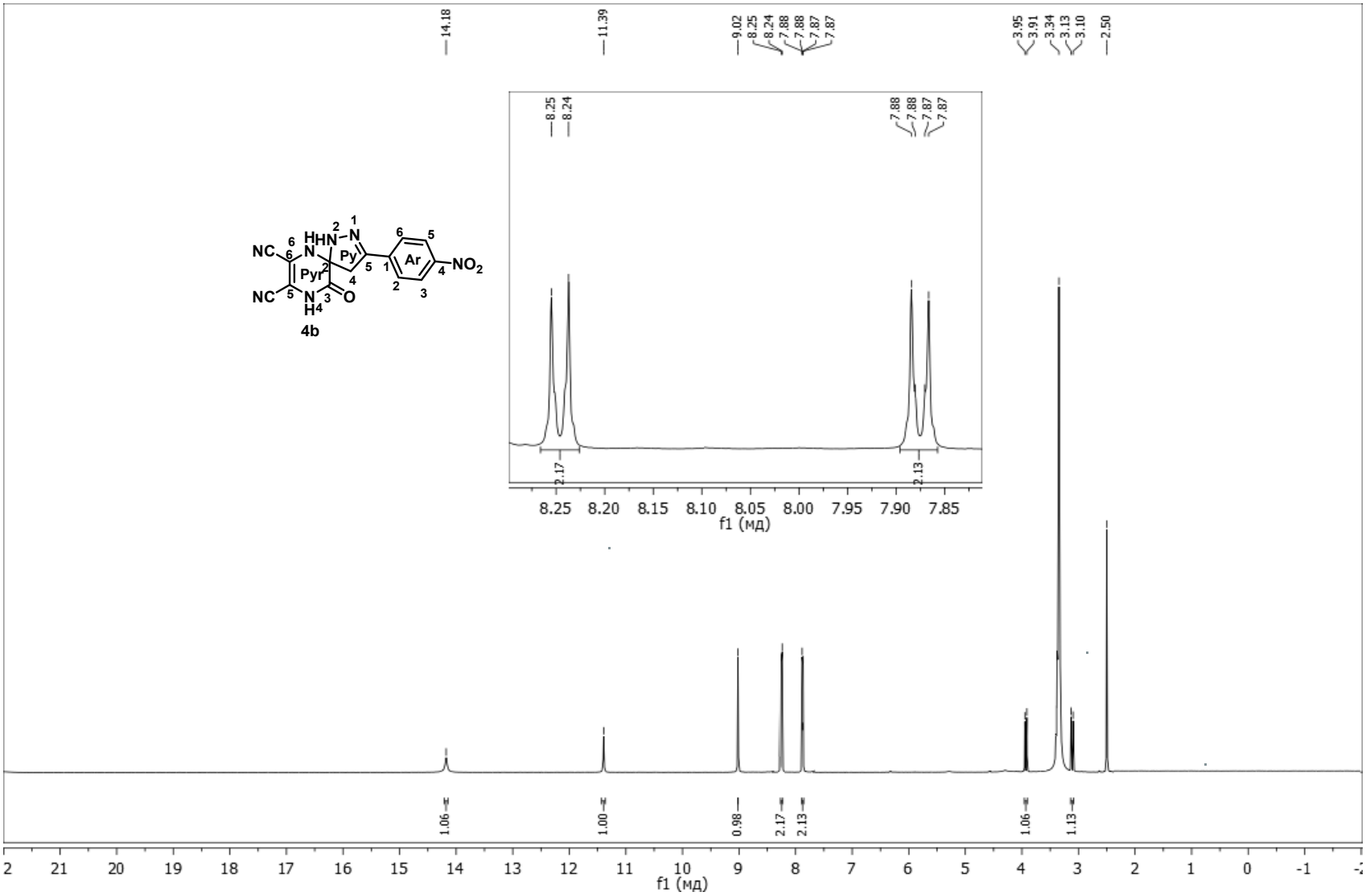

Figure S110. 1D ^{1}H NMR spectrum of **4b** in DMSO-d_6 at T = 303 K. Chemical shifts are given in ppm (Bruker spectrometer at 500.1 MHz).

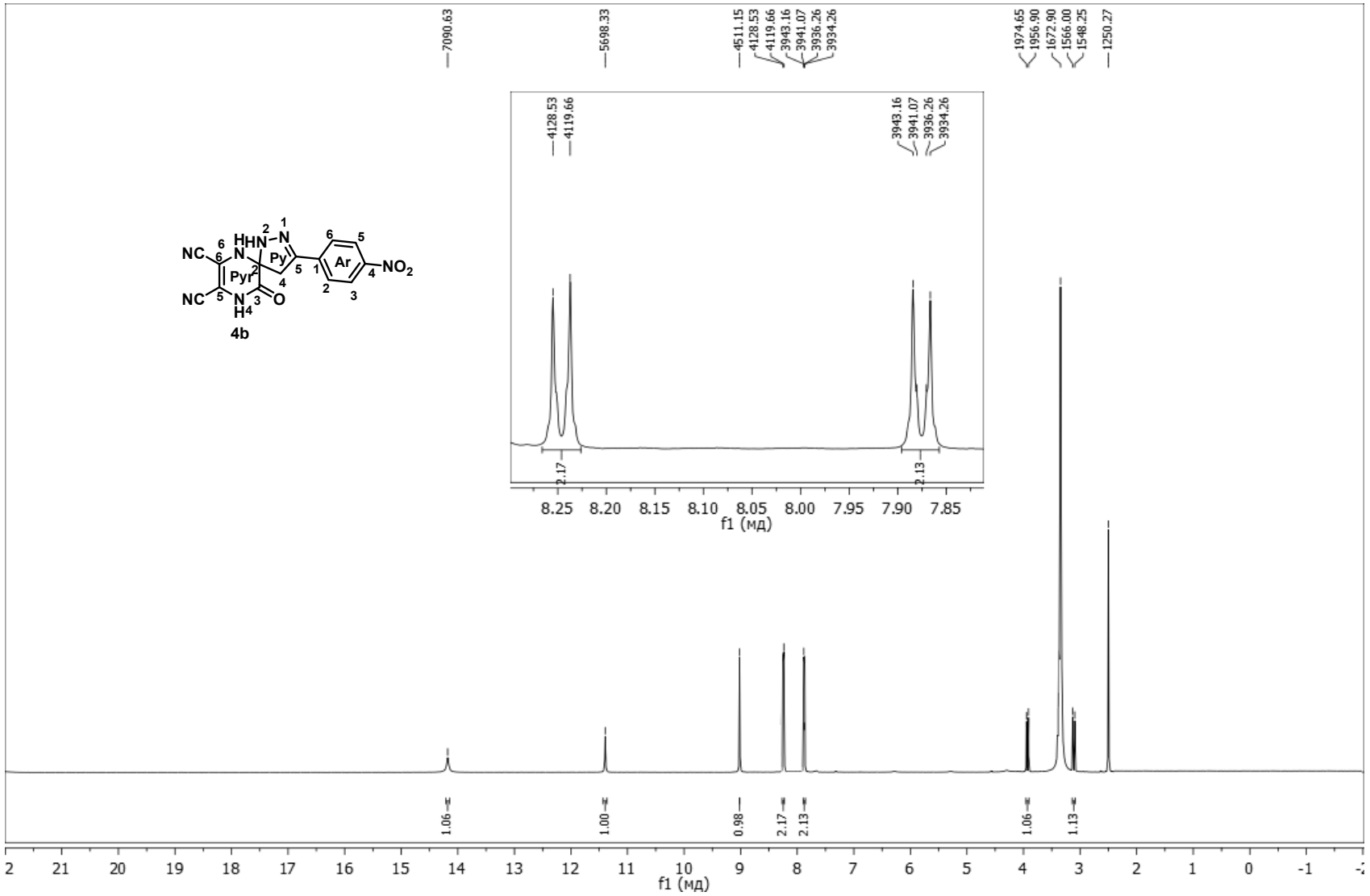

Figure S111. 1D ^{1}H NMR spectrum of **4b** in DMSO-d_6 at T = 303 K. Chemical shifts are given in Hz (Bruker spectrometer at 500.1 MHz).

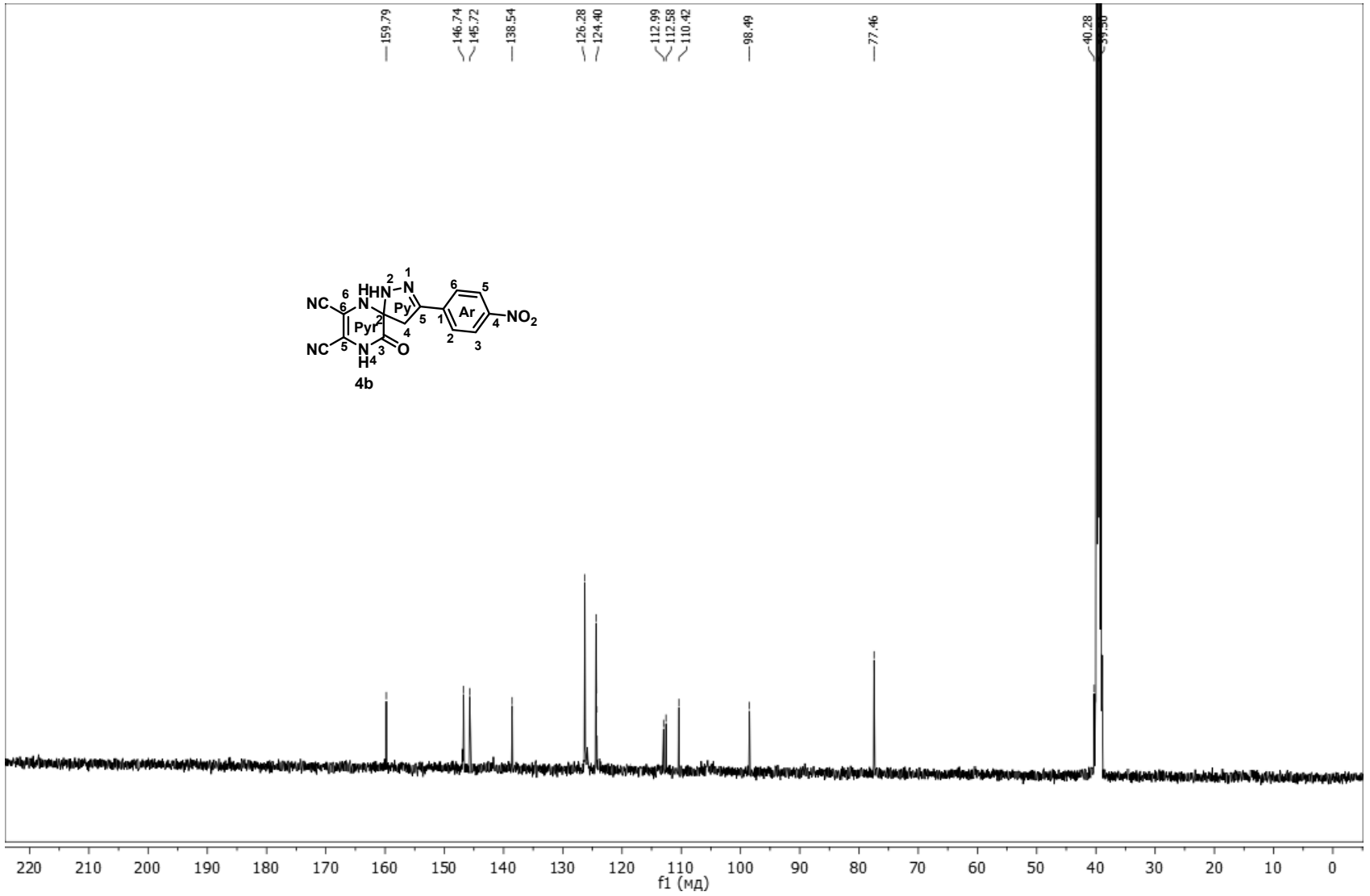

Figure S112. $^{13}C\{^{1}H\}$ NMR spectrum of **4b** in DMSO-d_6 at T = 303 K (Bruker spectrometer at 125.7 MHz).

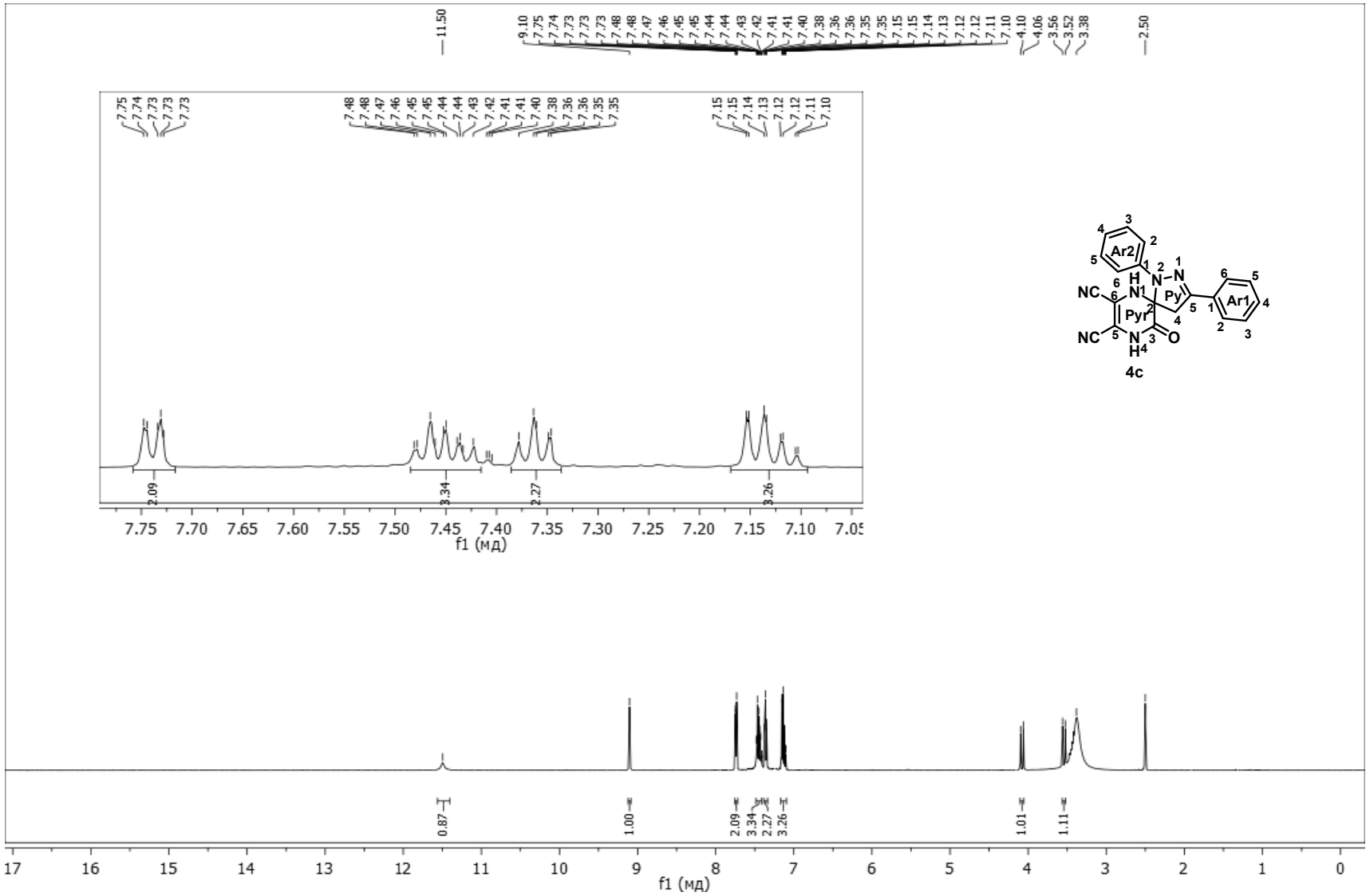

Figure S113. 1D ^{1}H NMR spectrum of **4c** in DMSO-d_6 at T = 303 K. Chemical shifts are given in ppm (Bruker spectrometer at 500.1 MHz).

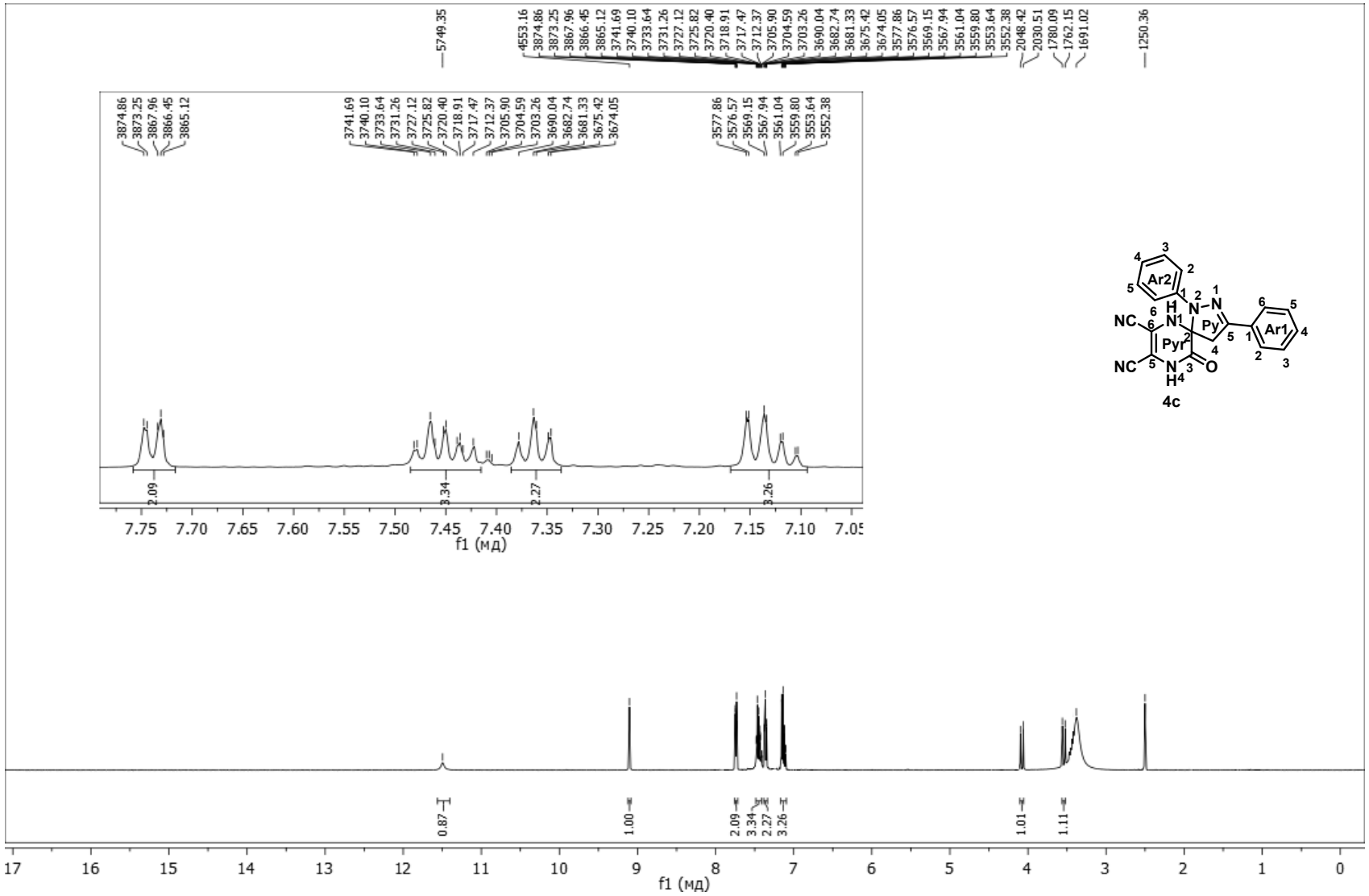

Figure S114. 1D ^{1}H NMR spectrum of **4c** in DMSO-d_6 at T = 303 K. Chemical shifts are given in Hz (Bruker spectrometer at 500.1 MHz).

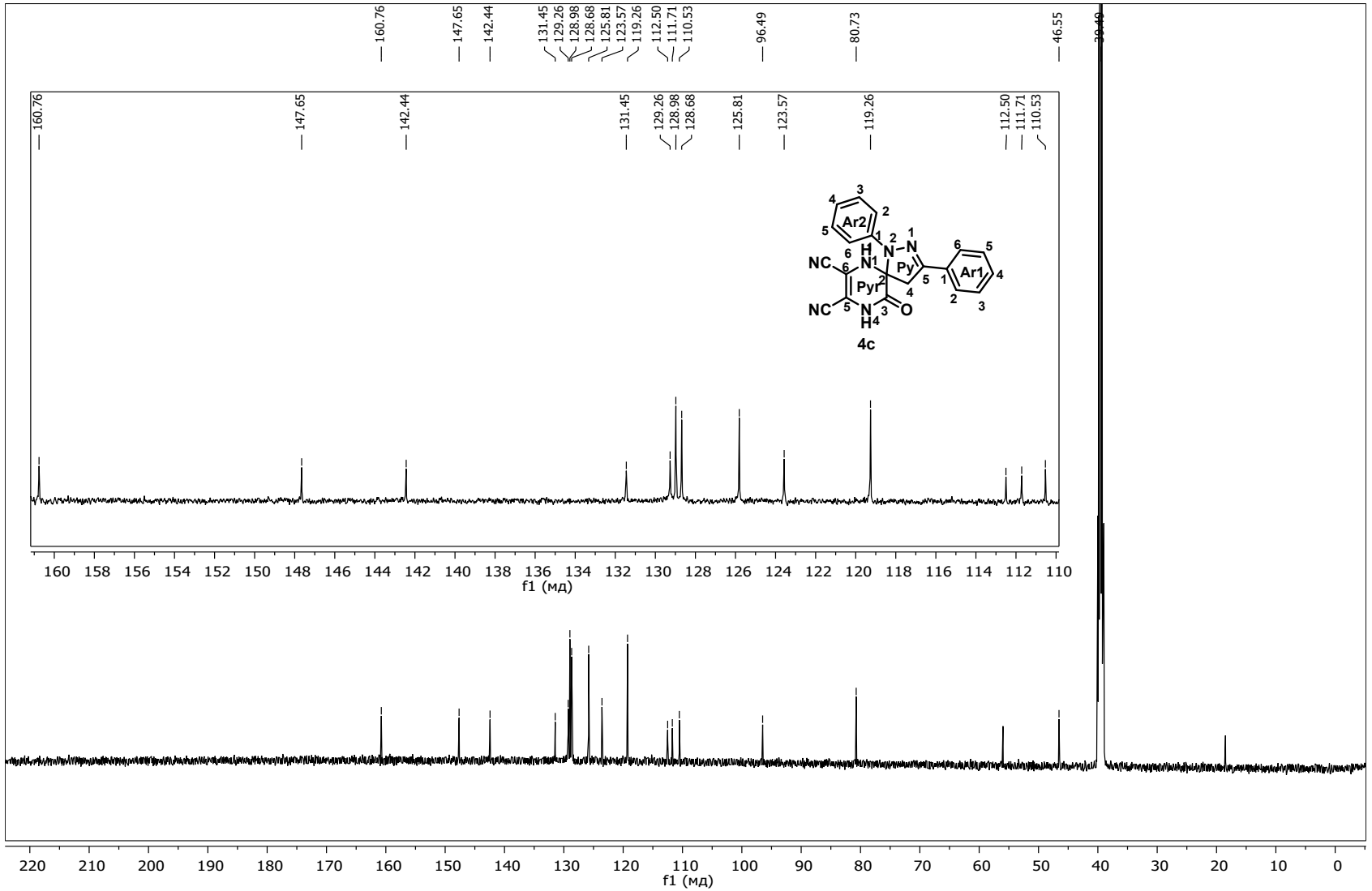

Figure S115. $^{13}C\{^{1}H\}$ NMR spectrum of **4c** in DMSO-d_6 at T = 303 K (Bruker spectrometer at 125.7 MHz).

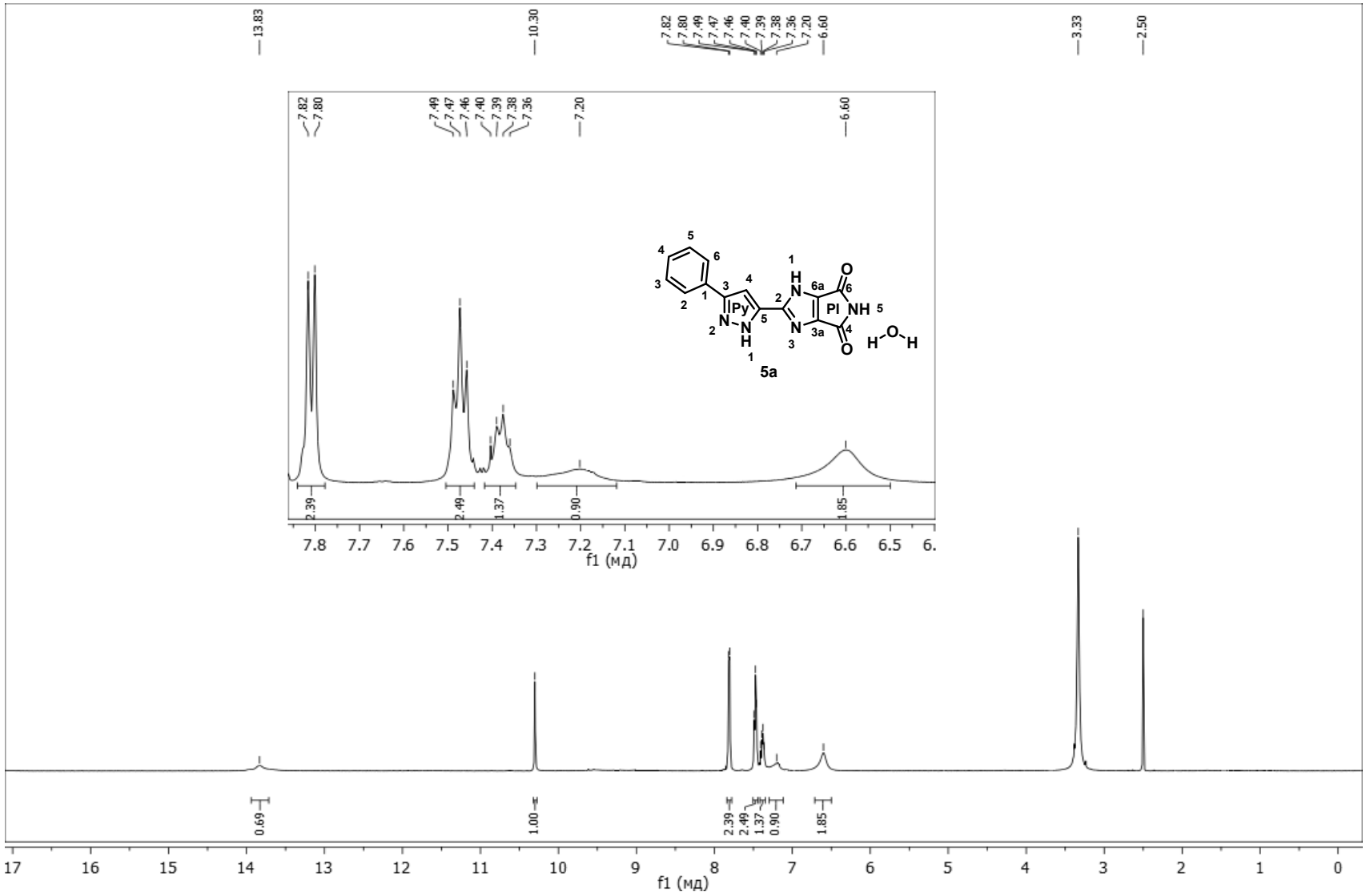

Figure S116. 1D ^{1}H NMR spectrum of **5a** in DMSO-d_6 at T = 303 K. Chemical shifts are given in ppm (Bruker spectrometer at 500.1 MHz).

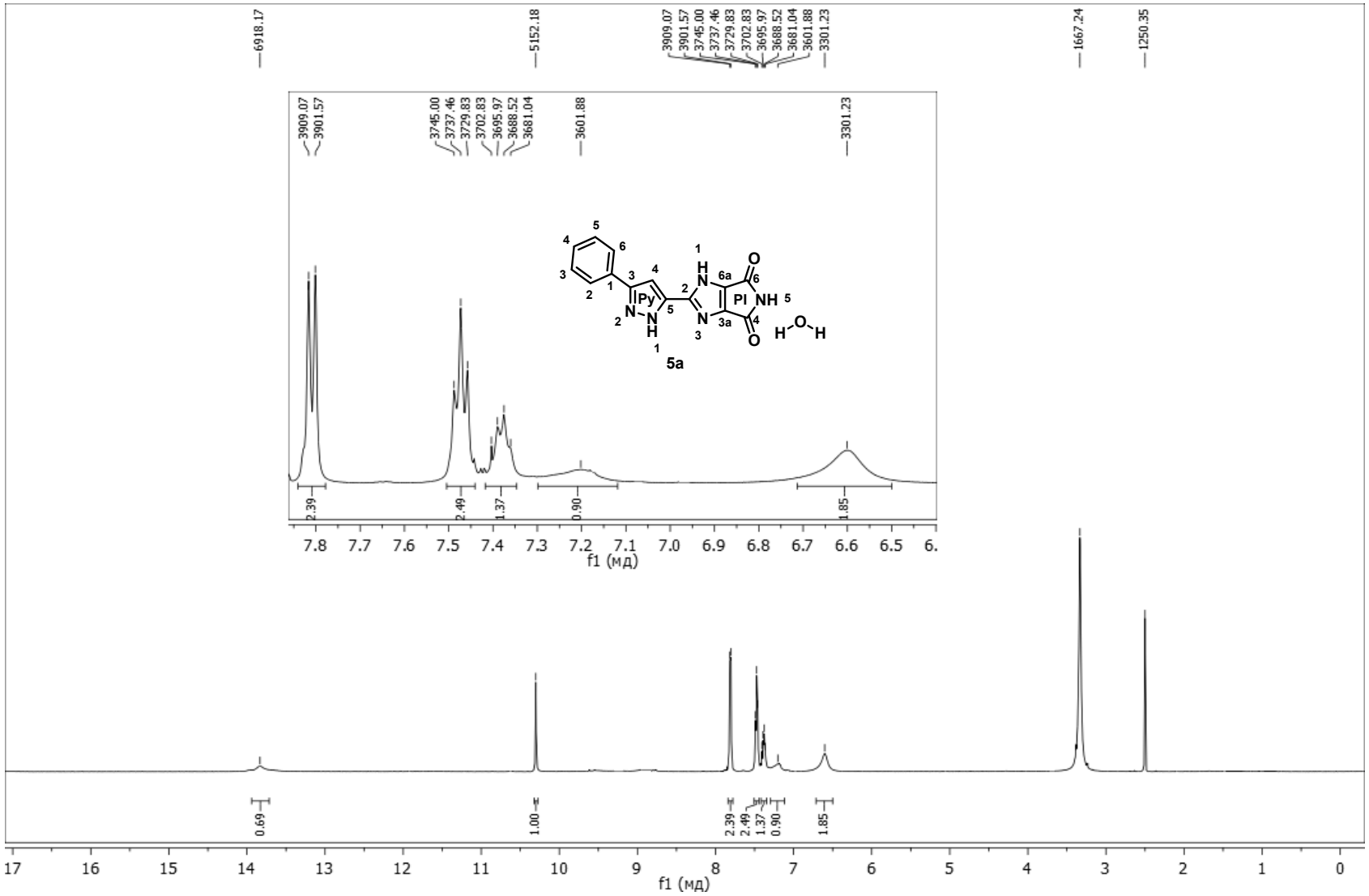

Figure S117. 1D ^{1}H NMR spectrum of **5a** in DMSO-d_6 at T = 303 K. Chemical shifts are given in Hz (Bruker spectrometer at 500.1 MHz).

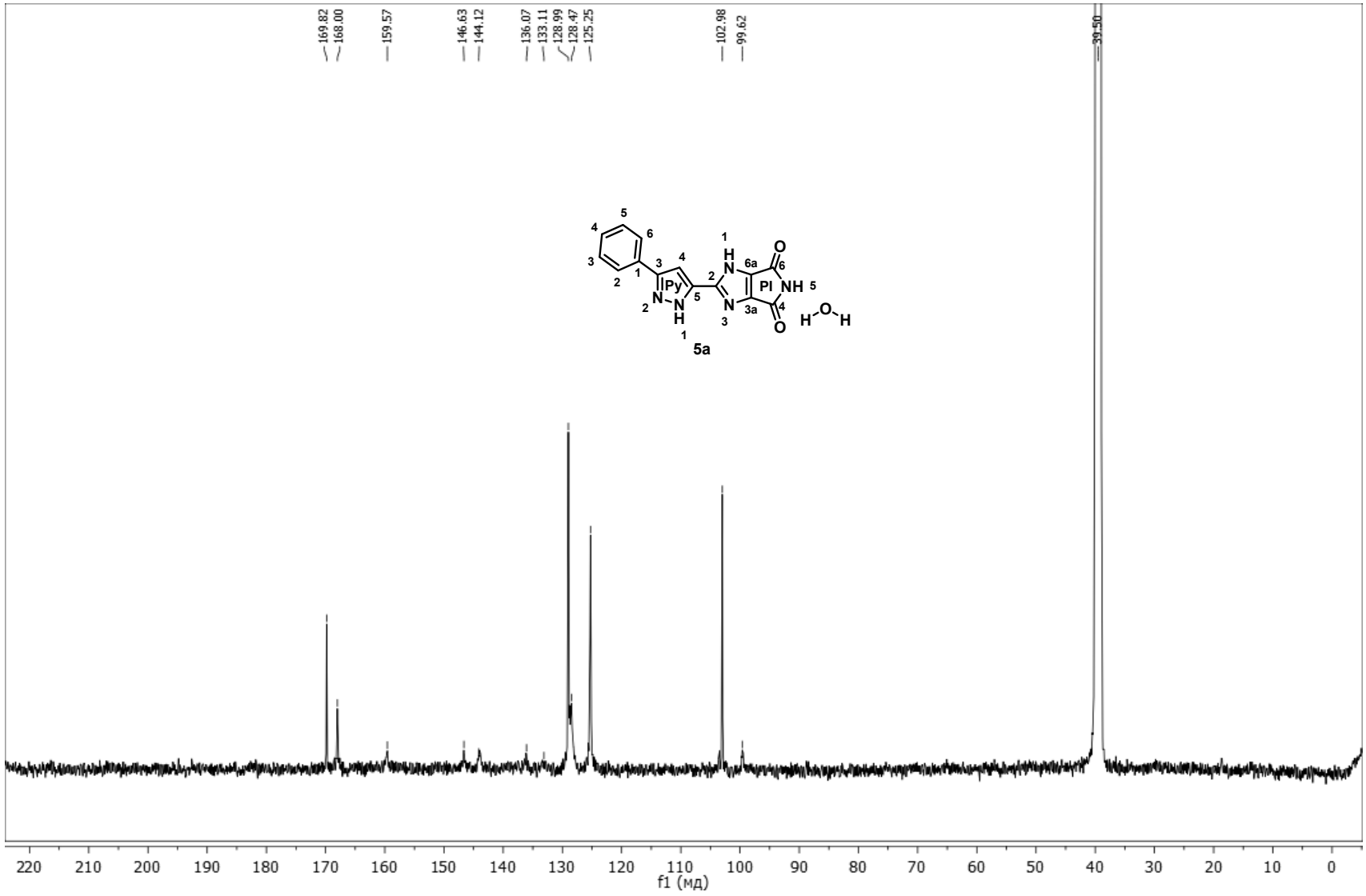

Figure S118. $^{13}C\{^{1}H\}$ NMR spectrum of **5a** in DMSO-d_6 at T = 303 K (Bruker spectrometer at 125.7 MHz).

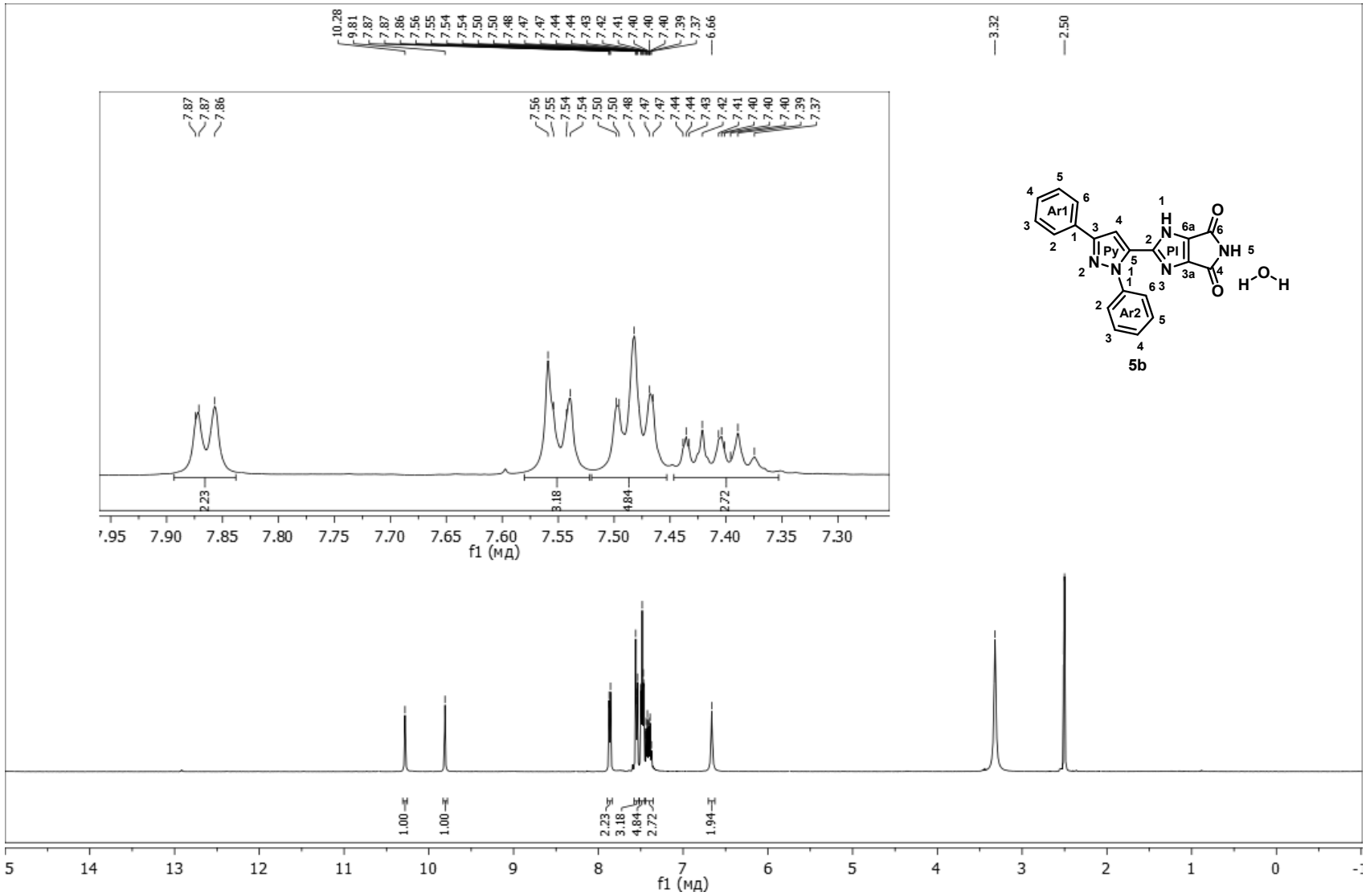

Figure S119. 1D ^{1}H NMR spectrum of **5b** in DMSO-d_6 at T = 303 K. Chemical shifts are given in ppm (Bruker spectrometer at 500.1 MHz).

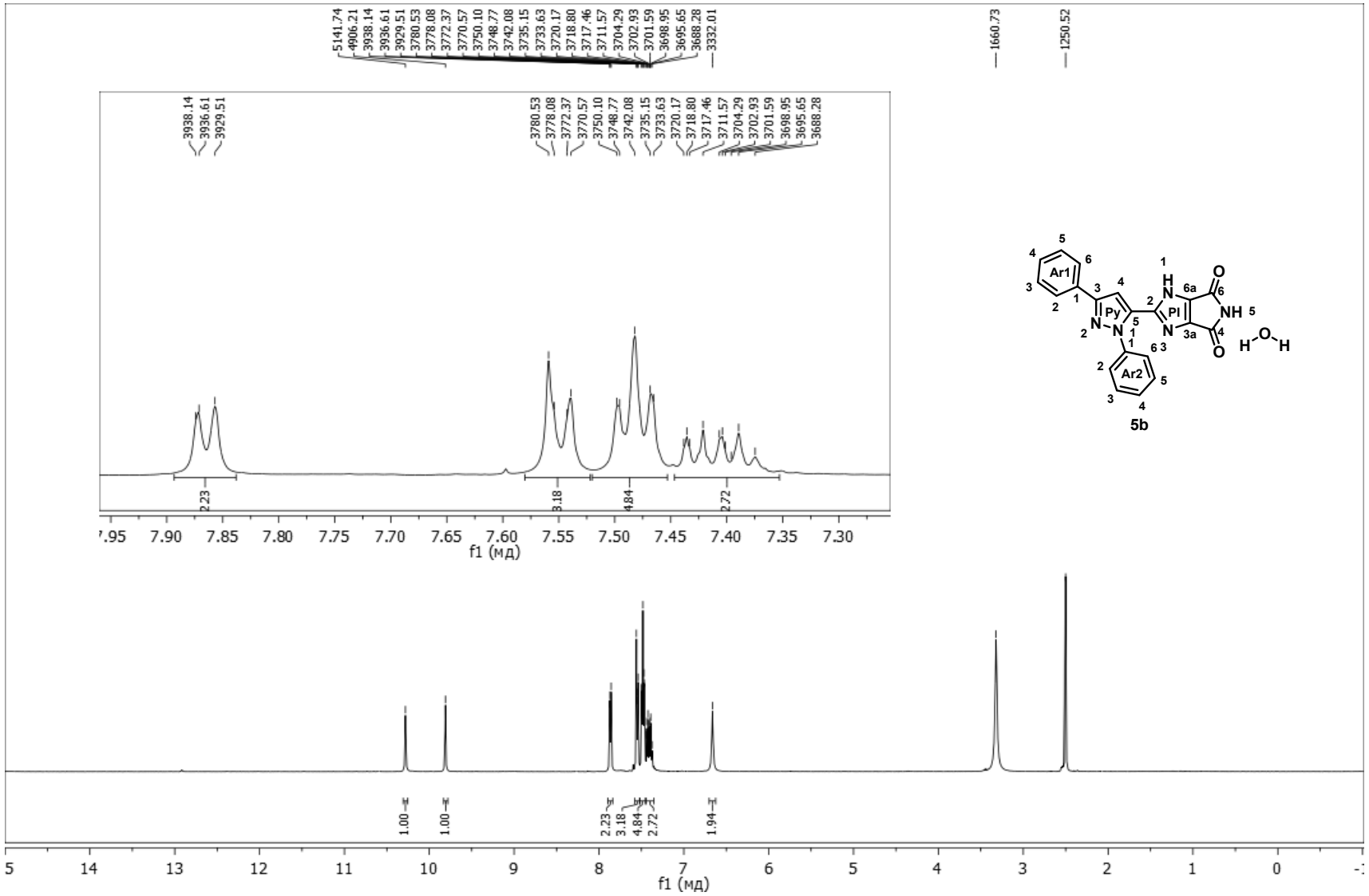

Figure S120. 1D ^{1}H NMR spectrum of **5b** in DMSO-d_6 at T = 303 K. Chemical shifts are given in Hz (Bruker spectrometer at 500.1 MHz).

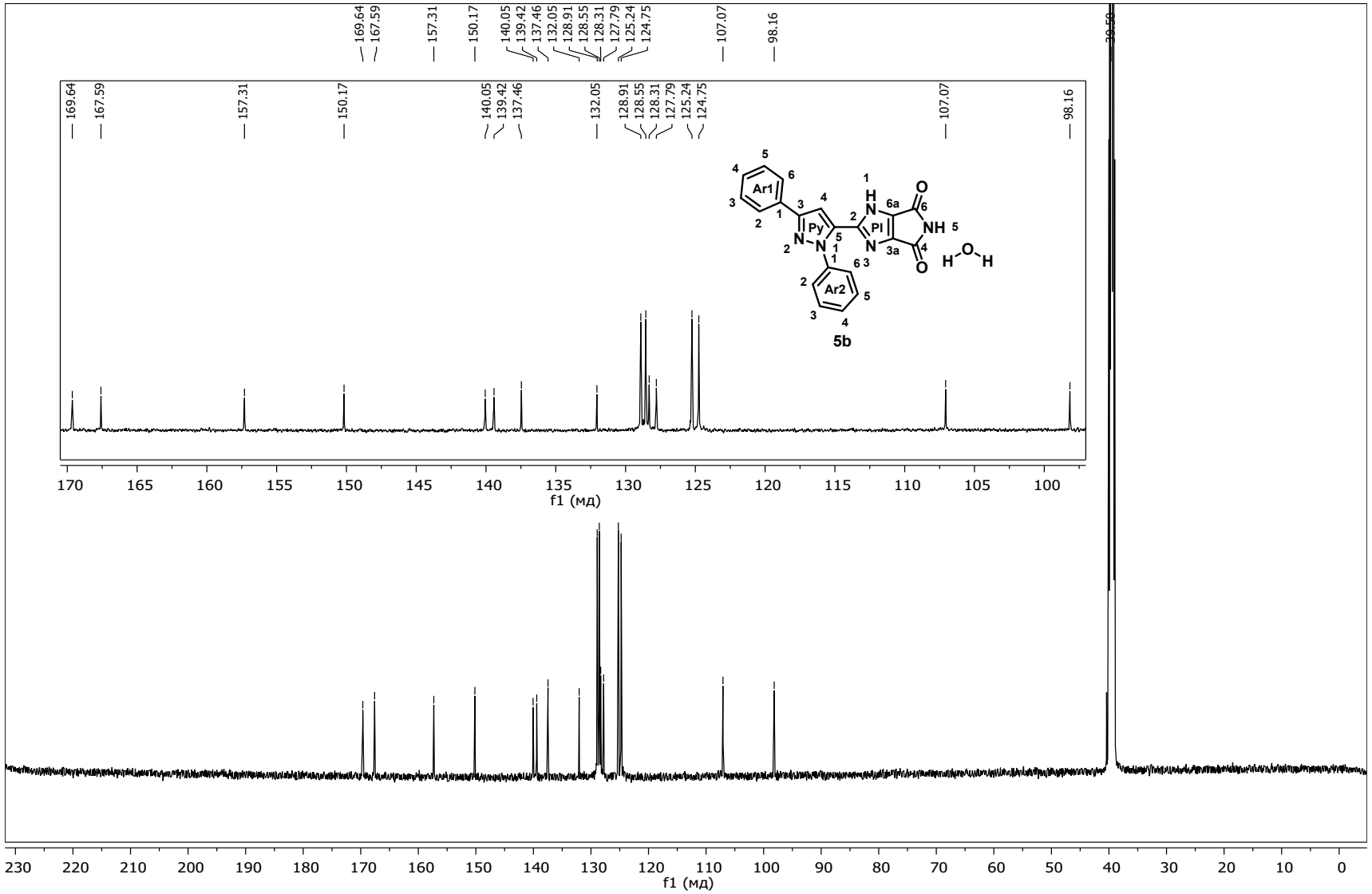

Figure S121. $^{13}C\{^{1}H\}$ NMR spectrum of **5b** in DMSO-d_6 at T = 303 K (Bruker spectrometer at 125.7 MHz).