Electronic supplementary materials *Mendeleev Commun*., 2013, **23**, 142−144

A rational protocol for the synthesis of 1-(2-pyridyl)isoquinolines

Dmitry S. Kopchuk, Igor S. Kovalev, Albert F. Khasanov, Grigory V. Zyryanov, Pavel A. Slepukhin, Vladimir L. Rusinov and Oleg N. Chupakhin

General. Unless otherwise indicated all common reagents and solvents were used from commercial suppliers without further purification. Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were acquired on a Bruker Avance-400 spectrometer, 298 K, digital resolution ± 0.01 ppm, using TMS as internal reference. Mass-spectra were recorded on MicrOTOF-Q II (Bruker Daltonics), electrospray as a method of ionization. Microanalyses (C, H, N) were performed using a Perkin–Elmer 2400 elemental analyzer. The structure of compounds **2c,e** was determined on a single-crystal X-ray diffractometer "Xcalibur 3" with CCD detector at the standard procedure (MoK_α radiation, T= 295(2) K, ω-scanning, scanning step 1º).

Synthesis

Triazines **3a-c** [1], **3d** [2]**, 3e** [3] were prepared by literature methods.

2-(2-Pyridyl)-5-(*p*-tolyl)cyclohexeno[*c*]pyridine (2a). Yield 40 %. Mp 104-106 °C. **^{1}H NMR** ($CDCl_3$, δ, ppm): 1.74 (m, 4H, $ArCH_2C\underline{H_2}C\underline{H_2}$), 2.42 (s, 3H, Me), 2.68 (m, 2H, $C\underline{H_2}C3$), 2.93 (m, 2H, $C\underline{H_2}C4$), 7.20-7.33 (m, 5H, C-H_{arom}, H-5'), 7.70 (dd, 1H, ^{3}J 7.8 Hz, ^{4}J 0.8 Hz, H-3'), 7.82 (ddd, 1H, ^{3}J 7.8, 7.8 Hz, ^{4}J 2.0 Hz, H-4'), 8.31 (s, 1H, H-6), 8.67 (dd, 1H, ^{3}J = 4.8 Hz, ^{4}J = 2.0 Hz, H-6'). **^{13}C NMR** ($CDCl_3$, δ, ppm): 21.2, 22.2, 22.6, 27.1, 28.2, 122.5, 124.3, 129.1, 129.3, 131.4, 135.2, 136.6, 137.0, 137.3, 145.1, 146.3, 148.6, 155.6, 159.4. **ESI-MS**, *m/z*: found 301.17, calculated 301.17 $(M+H)^+$. Found, %: C 83.72, H 6.49, N 9.21. **$C_{21}H_{20}N_2$**. Calculated, %: C 83.96, H 6.71, N 9.33.

5-(4-Chlorophenyl)-2-(2-pyridyl)cyclohexeno[*c*]pyridine (2b). Yield 44%. Mp 132-134 °C. **^{1}H NMR** ($CDCl_3$, δ, ppm): 1.75 (m, 4H, $ArCH_2C\underline{H_2}C\underline{H_2}$), 2.64 (m, 2H, $C\underline{H_2}C3$), 2.93 (m, 2H, $C\underline{H_2}C4$), 7.27 (m, 2H, C-H_{arom}), 7.31 (ddd, 1H, ^{3}J 4.8, 7.7 Hz, ^{4}J 1.0 Hz, H-5'), 7.43 (m, 2H, C-H_{arom}), 7.70 (dd, 1H, ^{3}J 7.7 Hz, ^{4}J 1.0 Hz, H-3'), 7.83 (ddd, 1H, ^{3}J 7.7, 7.7 Hz, ^{4}J 2.0 Hz, H-4'), 8.28 (s, 1H, H-6), 8.69 (dd, 1H, ^{3}J = 4.8 Hz, ^{4}J = 2.0 Hz, H-6'). **ESI-MS**, *m/z*: found

321.11, calculated 321.11 $(M+H)^+$. Found, %: C 74.59, H 5.22, N 8.51. **$C_{20}H_{17}N_2Cl$**. Calculated, %: C 74.88, H 5.34, N 8.73.

5-(4-Bromophenyl)-2-(2-pyridyl)cyclohexeno[*c*]pyridine (2c). Yield 38%. Mp 145-147 °C. **^{1}H NMR** ($CDCl_3$, δ, ppm): 1.75 (m, 4H, $ArCH_2C\underline{H_2}C\underline{H_2}$), 2.64 (m, 2H, $C\underline{H_2}C3$), 2.94 (m, 2H, $C\underline{H_2}C4$), 7.21 (m, 2H, C-H_{arom}), 7.31 (ddd, 1H, ^3J 4.8, 7.7 Hz, ^4J 1.0 Hz, H-5'), 7.59 (m, 2H, C-H_{arom}), 7.70 (dd, 1H, ^3J 7.7 Hz, ^4J 1.0 Hz, H-3'), 7.83 (ddd, 1H, ^3J 7.7, 7.7 Hz, ^4J 2.0 Hz, H-4'), 8.28 (s, 1H, H-6), 8.69 (dd, 1H, ^3J = 4.8 Hz, ^4J = 2.0 Hz, H-6'). **^{13}C NMR** ($CDCl_3$, δ, ppm): 22.1, 22.5, 27.1, 28.1, 121.9, 122.6, 124.3, 131.0, 131.6, 131.7, 135.9, 136.6, 137.1, 145.0, 145.9, 148.6, 156.1, 159.2. **ESI-MS**, *m/z*: found 367.06, calculated 367.06 $(M+H)^+$. Found, %: C 65.48, H 4.60, N 7.43. **$C_{20}H_{17}N_2Br$**. Calculated, %: C 65.76, H 4.69, N 7.67.

6-Phenyl-2-(2-pyridyl)cyclohexeno[*c*]pyridine (2d). Yield 37%. Yellow oil. **^{1}H NMR** ($CDCl_3$, δ, ppm): 1.72-1.92 (m, 4H, $ArCH_2C\underline{H_2}C\underline{H_2}$), 2.87-2.97 (m, 4H, $ArC\underline{H_2}CH_2$), 7.30 (ddd, 1H, ^3J 4.8, 7.7 Hz, ^4J 1.0 Hz, H-5'), 7.37 (m, 1H, Ph), 7.44 (m, 2H, Ph), 7.48 (s, 1H, H-5), 7.84 (m, 2H, Ph), 8.02 (m, 2H, H-3',4'), 8.67 (dd, 1H, ^3J = 4.8 Hz, ^4J = 2.0 Hz, H-6'). **ESI-MS**, *m/z*: found 287.16, calculated 287.15 $(M+H)^+$.

5,6-Diphenyl-2-(2-pyridyl)cyclohexeno[*c*]pyridine (2e). Yield 54%. Mp 201-203 °C. **^{1}H NMR** ($CDCl_3$, δ, ppm): 1.74 (m, 4H, $ArCH_2C\underline{H_2}C\underline{H_2}$), 2.53 (m, 2H, $ArC\underline{H_2}C3$), 2.98 (m, 2H, $C\underline{H_2}C4$), 7.07-7.18 (m, 5H), 7.23-7.37 (m, 6H), 7.82 (m, 2H), 8.68 (dd, 1H, ^3J = 4.8 Hz, ^4J = 1.8 Hz, H-6'). **^{13}C NMR** ($CDCl_3$, δ, ppm): 22.4, 22.5, 27.2, 28.9, 122.5, 124.6, 126.9, 127.4, 128.2, 129.9, 130.3, 130.4, 135.4, 136.7, 138.6, 140.9, 146.4, 148.3, 153.7, 155.4, 159.6. **ESI-MS**, *m/z*: found 363.19, calculated 363.19 $(M+H)^+$. Found, %: C 85.92, H 5.94, N 7.65. **$C_{26}H_{22}N_2$**. Calculated, %: C 86.15, H 6.12, N 7.73.

1-(2-Pyridyl)-4-(*p*-tolyl)isoquinoline (1a). Yield 63%. Mp 110-112 °C. **^{1}H NMR** ($CDCl_3$, δ, ppm): 2.48 (s, 3H, Me), 7.36 (m, 2H, C-H_{arom}), 7.39-7.48 (m, 3H, C-H_{arom}, H-5'), 7.56-7.69 (m, 2H, isoquin.), 7.93 (ddd, 1H, ^3J 7.8, 7.8 Hz, ^4J 1.8 Hz, H-4'), 7.96-8.05 (m, 2H, isoquin.), 8.58 (s, 1H, H-3), 8.64 (dd, 1H, ^3J 7.8 Hz, ^4J 1.6 Hz, H-3'), 8.82 (dd, 1H, ^3J 4.8 Hz, ^4J 1.6 Hz, H-6'). **^{13}C NMR** ($CDCl_3$, δ, ppm): 21.3, 123.8, 125.5, 125.7, 126.4, 128.0, 128.4, 129.2, 129.5, 130.1, 131.1, 133.5, 134.7, 136.2, 137.3, 138.3, 139.8, 145.0, 155.8. **ESI-MS**, *m/z*: found 297.15, calculated 297.14 $(M+H)^+$. Found, %: C 84.79, H 5.21, N 9.22. **$C_{21}H_{16}N_2$**. Calculated, %: C 85.11, H 5.44, N 9.45.

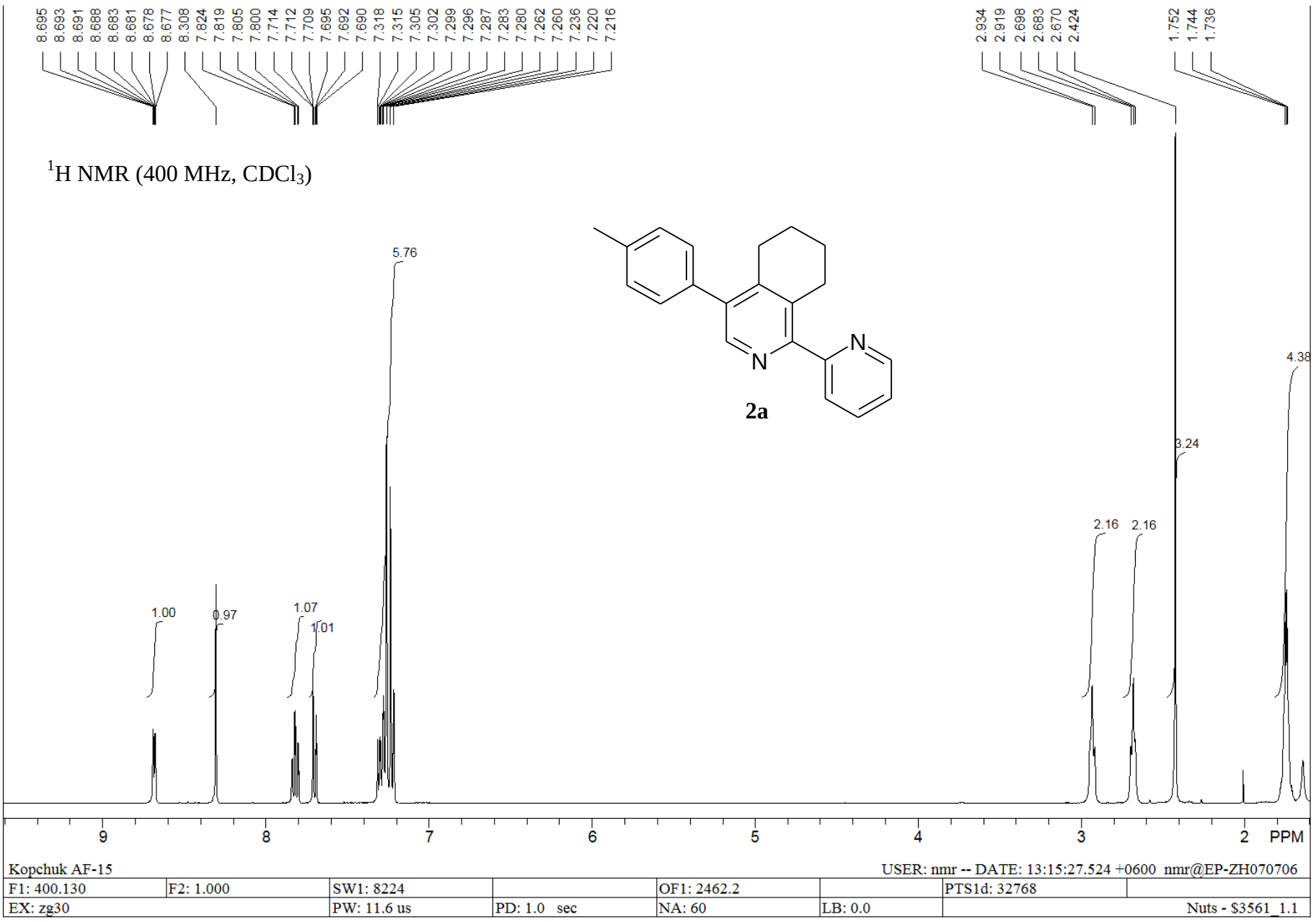
4-(4-Chlorophenyl)-1-(2-pyridyl)isoquinoline (1b). Yield 67%. Mp 141-143 °C. **^{1}H NMR** ($CDCl_3$, δ, ppm): 7.44 (ddd, 1H, ^3J 4.8, 8.4 Hz, ^4J 1.6 Hz, H-5'), 7.47-7.57 (m, 4H, C-H_{arom}), 7.62 (m, 1H, isoquin.), 7.69 (m, 1H, isoquin.), 7.88-7.97 (m, 2H, isoquin., H-4'), 8.02 (м, 1H, isoquin.), 8.55 (s, 1H, H-3), 8.65 (dd, 1H, ^3J 8.4 Hz, ^4J 1.6 Hz, H-3'), 8.82 (dd, 1H, ^3J 4.8

Hz, ^4J 1.6 Hz, H-6'). **^{13}C NMR** ($CDCl_3$, δ, ppm): 123.5, 125.0, 125.4, 126.5, 127.8, 128.2, 129.0, 130.6, 131.6, 132.8, 134.4, 135.5, 135.7, 137.2, 141.7, 148.9, 157.5, 158.3. **ESI-MS**, *m/z*: found 317.08, required 317.08 $(M+H)^+$. Found, %: C 75.68, H 3.99, N 8.71. **$C_{20}H_{13}N_2Cl$**. Required, %: C 75.83, H 4.14, N 8.84.

4-(4-Bromophenyl)-1-(2-pyridyl)isoquinoline (1c). Yield 59%. Mp 152-154 °C. **^{1}H NMR** ($CDCl_3$, δ, ppm): 7.36 (m, 3H, H-5', C-H_{arom}), 7.51-7.65 (m, 4H, C-H_{arom}, H-5'), 7.56-7.69 (m, 4H, C-H_{arom}, isoquin.), 7.80-7.89 (m, 2H, H-4', isoquin.), 7.95 (m, 1H, isoquin.), 8.48 (s, 1H, H-3), 8.58 (dd, 1H, ^3J 7.8 Hz, ^4J 1.6 Hz, H-3'), 8.74 (dd, 1H, ^3J 4.8 Hz, ^4J 1.6 Hz, H-6'). **^{13}C NMR** ($CDCl_3$, δ, ppm): 122.4, 123.3, 124.8, 125.3, 126.4, 127.6, 128.1, 130.1, 130.4, 131.9, 132.6, 135.3, 136.1, 137.0, 141.7, 148.8, 157.5, 158.3. **ESI-MS**, *m/z*: found 363.04, required 363.04 $(M+H)^+$. Found, %: C 66.34, H 3.44, N 7.56. **$C_{20}H_{13}N_2Br$**. Required, %: C 66.50, H 3.63, N 7.75.

3-Phenyl-1-(2-pyridyl)isoquinoline (1d). Yield 51%. Mp 107-109 °C. **^{1}H NMR** ($CDCl_3$, δ, ppm): 7.43 (m, 3H, Ph), 7.52 (m, 2H, isoquin.), 7.58 (м, 1H, isoquin.), 7.69 (m, 1H, isoquin.), 7.94 (m, 2H, Ph), 8.15 (s, 1H, H-4), 8.22 (m, 2H, py), 8.75 (d, 1H, ^3J = 8.4 Hz, py), 8.81 (d, 1H, ^3J = 4.8 Hz, H-6'). **^{13}C NMR** ($CDCl_3$, δ, ppm): 117.0, 123.2, 125.6, 127.0, 127.4, 127.5, 128.0, 128.5, 128.6, 128.8, 130.1, 137.0, 138.2, 139.5, 148.3, 149.8, 157.0, 158.8. **ESI-MS**, *m/z*: found 283.12, required 283.12 $(M+H)^+$. Found, %: C 84.81, H 4.80, N 9.61. **$C_{20}H_{14}N_2$**. Required, %: C 85.08, H 5.00, N 9.92.

3,4-Diphenyl-1-(2-pyridyl)isoquinoline (1e). Yield 68%. Mp 182-184 °C. **^{1}H NMR** ($CDCl_3$, δ, ppm): 7.07-7.24 (m, 3H), 7.26-7.34 (m, 2H), 7.35-7.51 (m, 6H), 7.59 (m, 2H), 7.71 (m, 1H), 7.91 (ddd, 1H, ^3J 7.8, 7.8 Hz, ^4J 1.8 Hz, H-4'), 8.16 (d, 1H, ^3J 7.8 Hz), 8.72 (m, 1H), 8.81 (dd, 1H, ^3J 4.8 Hz, ^4J 1.6 Hz, H-6'). **^{13}C NMR** ($CDCl_3$, δ, ppm): 123.2, 125.4, 125.6, 126.0, 127.1, 127.4, 127.5, 127.6, 127.7, 128.3, 130.1, 130.5, 131.1, 131.3, 137.0, 137.3, 137.5, 140.9, 148.5, 149.4, 156.7, 158.7. **ESI-MS**, *m/z*: found 359.15, required 359.15 $(M+H)^+$. Found, %: C 86.92, H 4.88, N 7.51. **$C_{26}H_{18}N_2$**. Required, %: C 87.12, H 5.06, N 7.82.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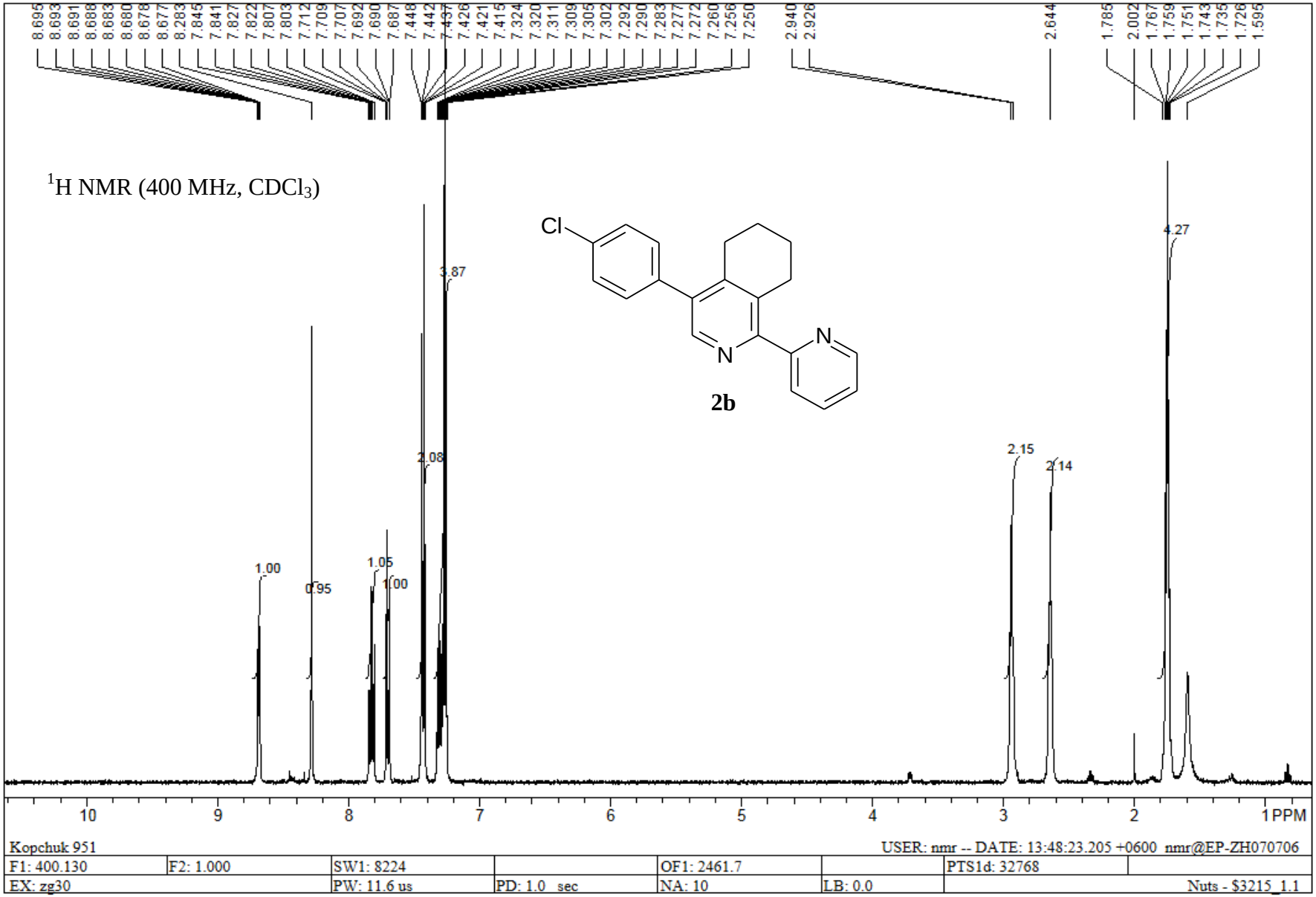
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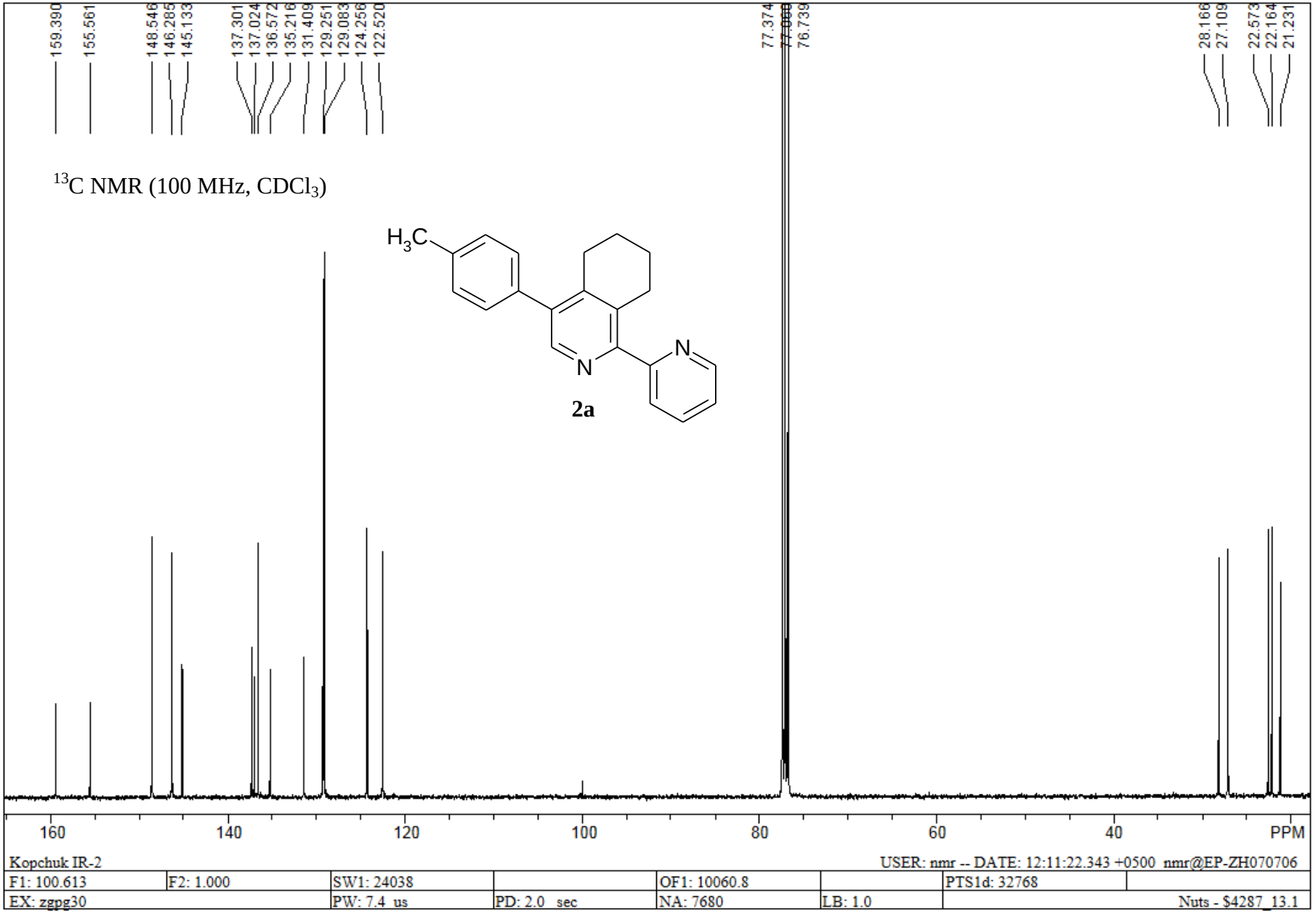
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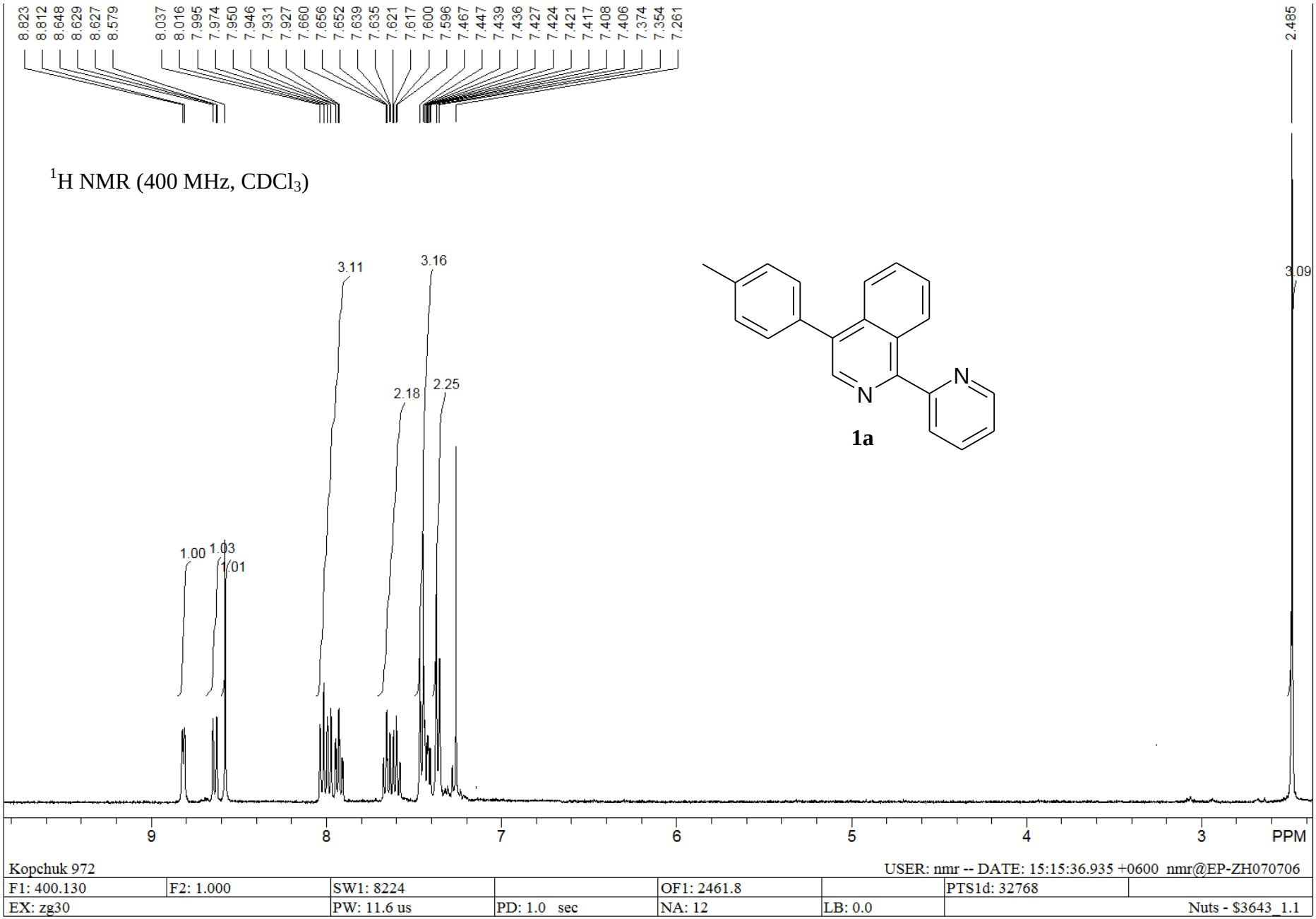
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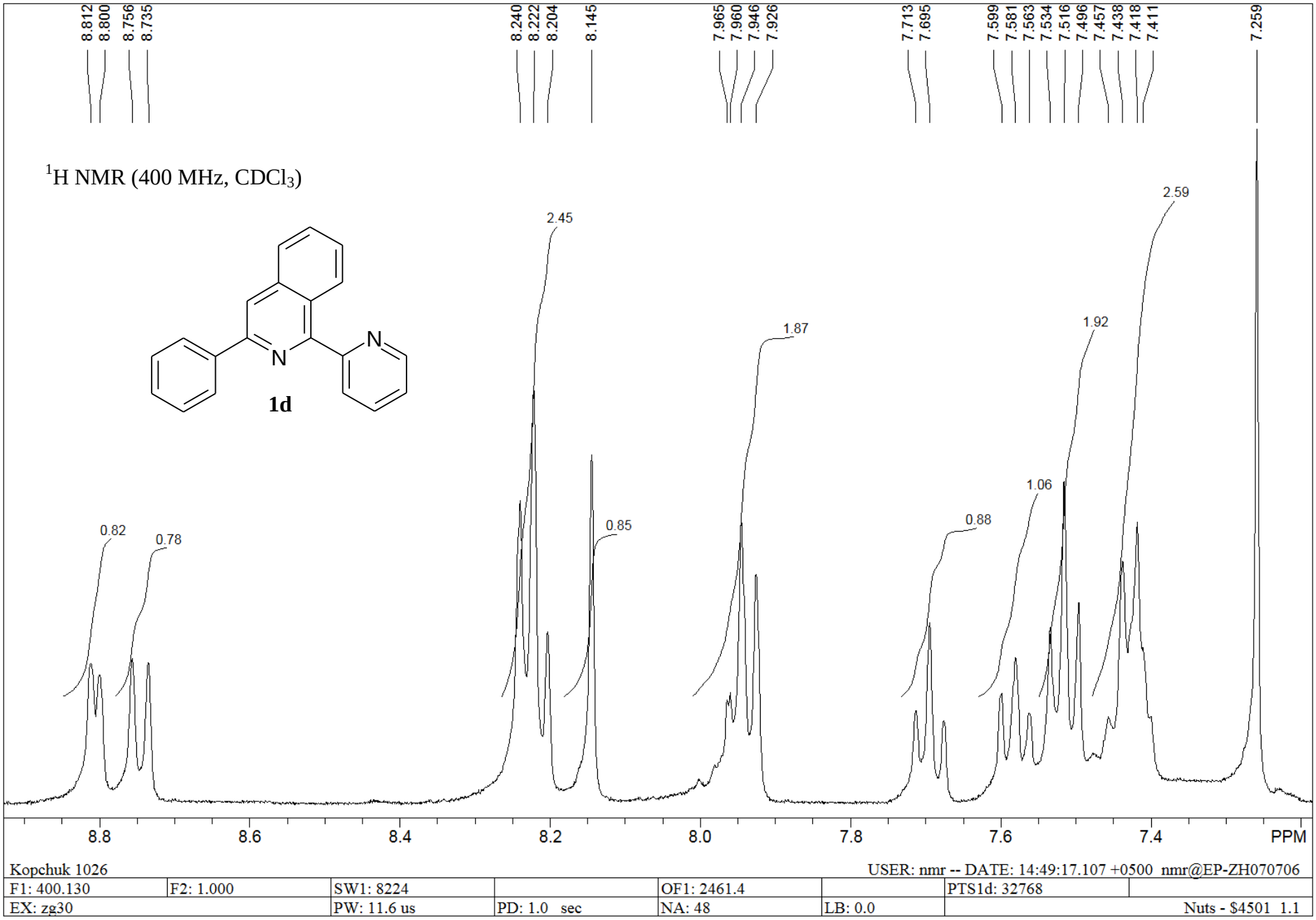
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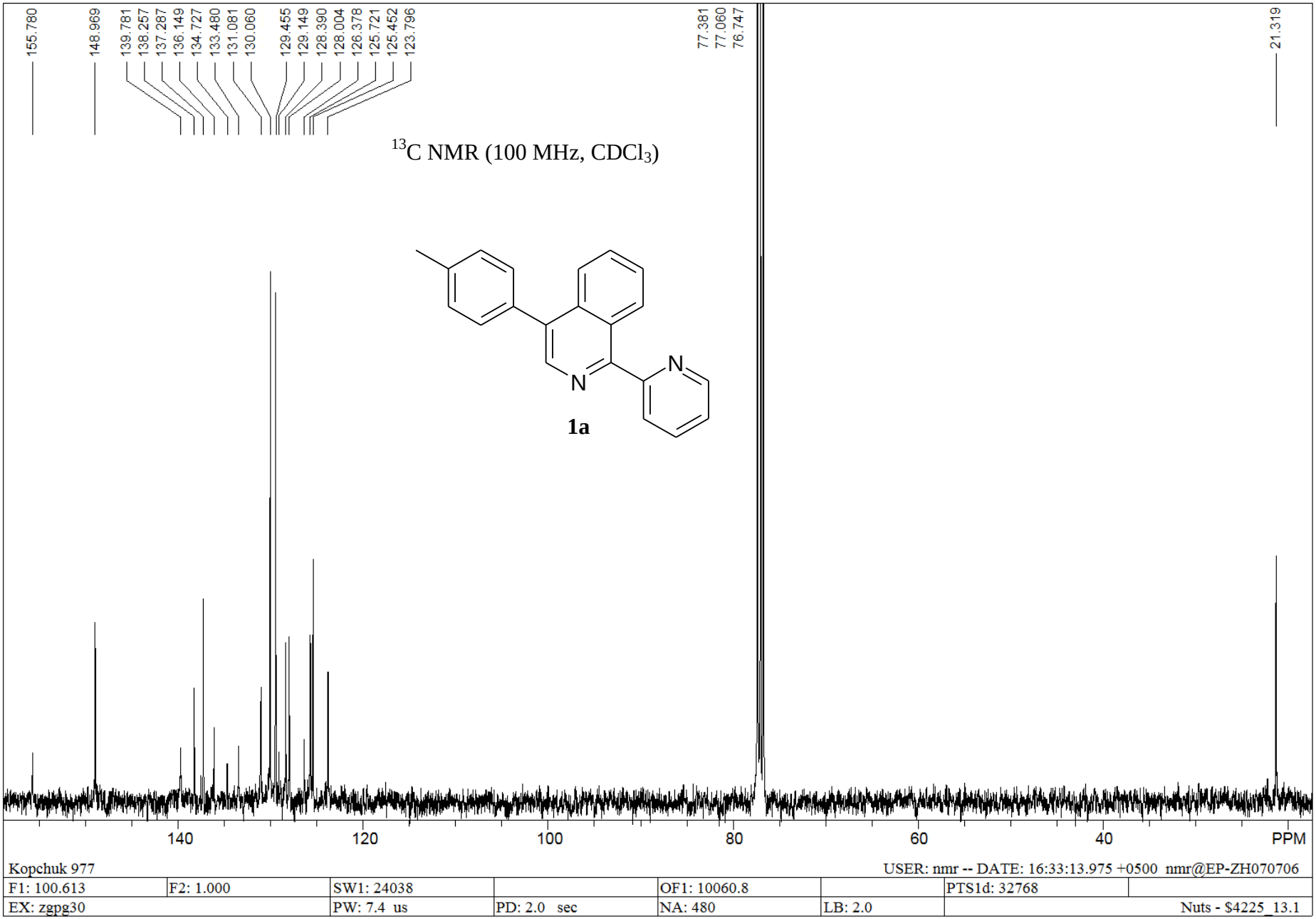
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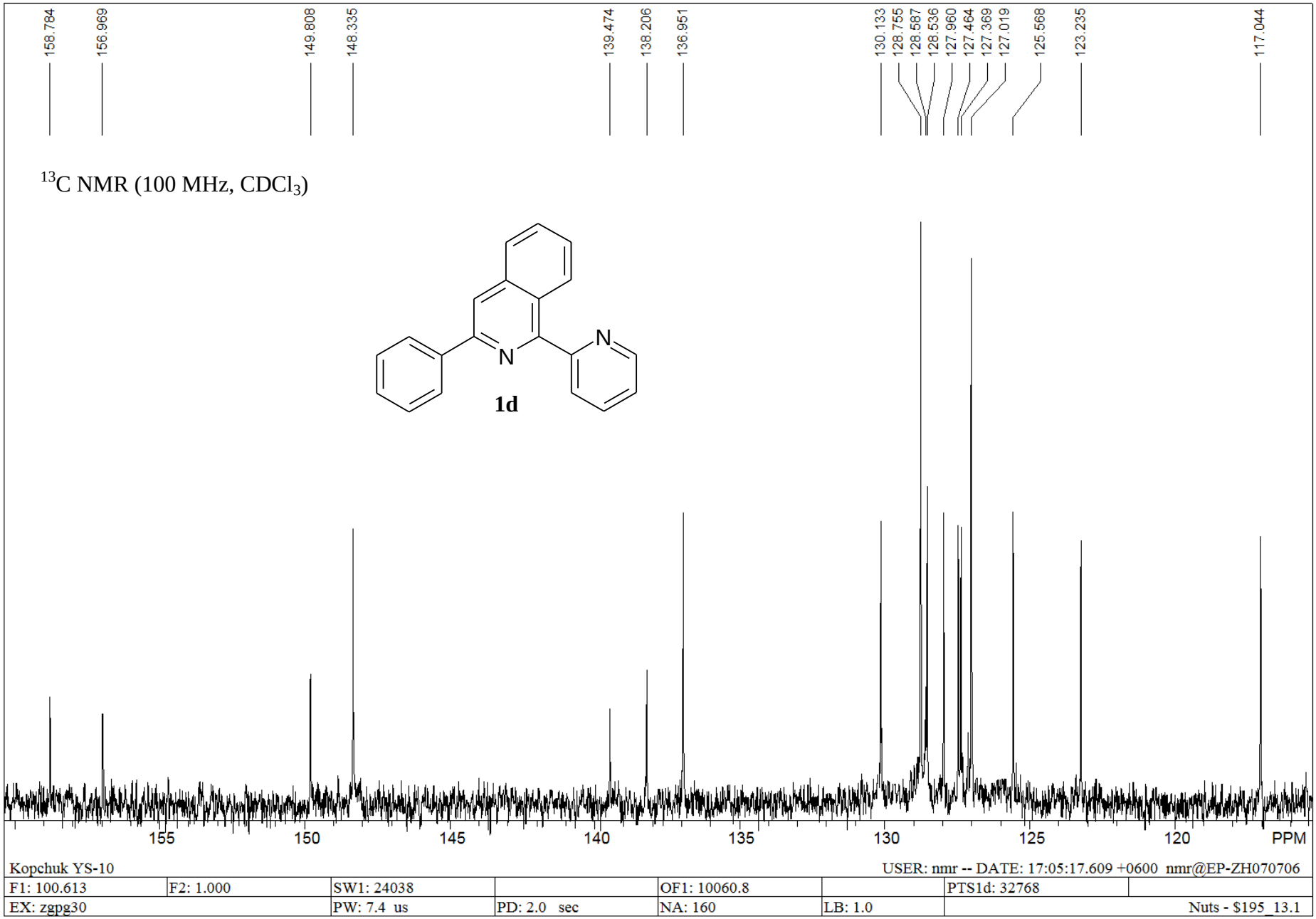
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References

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2. M. O'Rourke, S. A. Lang Jr. and E. Cohen, *J. Med. Chem.*, 1977, **20**, 723.

3. F. H. Case, *J. Org. Chem.*, 1965, **30**, 931.