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2-Aminooxazoles as novel dienophiles in the inverse demand Diels–Alder reaction with 1,2,4-triazines

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General. All reagents were purchased from commercial sources and used without further purification. Silica gel 60 (Kieselgel 60, 230-400 mesh) was used for the column chromatography. TLC was done on silica gel coated glass slide (Merck, Silica gel G for TLC). NMR spectra were recorded on a Bruker Avance-400 spectrometer, 298 K, digital resolution ± 0.01 ppm, using TMS as internal standard. Mass spectrometric studies were performed on an Agilent 6545 Q-TOF LC/MS (Agilent Technologies, USA) quadrupole time-of-flight mass spectrometer with an electrospray ionization source in the positive (negative) ion mode. An Agilent 1290 Infinity II chromatographic system was used to inject the sample. Elemental analysis was performed on a PE 2400 II CHN-analyzer (Perkin Elmer).

Starting compounds **1**[S1] and **3**[S2] were synthesized as described in literature.

The XRD analysis of the single crystals of $C_{24}H_{16}ClN_3O$ was performed on a Xcalibur 3 diffractometer on standard procedure (MoK-irradiation, graphite monochromator, ω-scans with 1° step at T=295(2) K). The structure was solved with the ShelXS[S3] structure solution program using Direct Methods and refined with the ShelXL[S3] refinement package using Least Squares minimization in anisotropic approximation for non-hydrogen atoms. The H-atoms at C-H bonds were placed in the calculated positions and refined in the riding model in isotropic approximation. The H-atom of the OH-group was solved by direct method and refined independently in isotropic approximation.

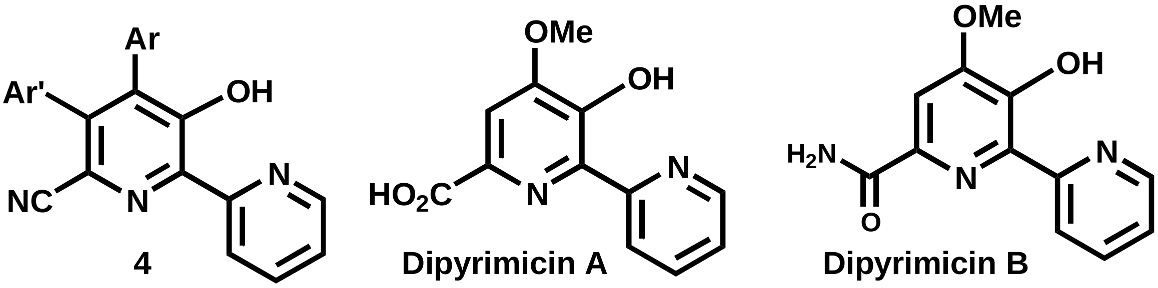
Quantum chemical calculations was performed using ‘Uran’ supercomputer of IMM UB RAS using the software package Orca 4.0.1, B3LYP, 6-311G*.

General method for the synthesis of compounds **4a-c**. A mixture of the corresponding 1,2,4-triazine-5-carbonitrile **1** (0.40 mmol) and corresponding 4-aryloxazol-2-amine **3** (0.44 mmol) was stirred at 150 ºC for 8 h under argon atmosphere. The reaction mixture was cooled to room temperature. The products were separated by column chromatography (CH_2Cl_2 – ethyl acetate, 9:1) as eluent, R_f = 0.7). Analytical samples were obtained by recrystallization from ethanol.

4-(4-Chlorophenyl)-3-hydroxy-5-(*p*-tolyl)-[2,2'-bipyridine]-6-carbonitrile (4a). Yield 83 mg (0.21 mmol, 52%). M.p. > 250 °C. **^{1}H NMR** ($CDCl_3$, *δ*, ppm): 2.36 (s, 3H, CH_3), 7.07-7.09 (m, 2H, $C_6\underline{H}_4Me$), 7.10-7.12 (m, 2H, C_6H_4Cl), 7.12-7.14 (m, 2H, $C_6\underline{H}_4Me$), 7.26-7.28 (m, 2H, C_6H_4Cl), 7.47-7.50 (m, 1H, H-5′), 8.05 (ddd, 1H, ^3J 7.6 Hz, 7.6 Hz, ^4J 1.6 Hz, H-4′), 8.52 (d, 1H, ^3J 4.8 Hz, H-6′), 8.75 (d, 1H, ^3J 8.0 Hz, H-3′), 15.77 (s, 1H, OH). **^{13}C NMR** ($CDCl_3$, δ, ppm): 21.3, 117.6, 121.9, 123.5, 124.2, 128.3, 129.2, 129.9, 131.2, 131.6, 131.7, 133.9, 136.8, 137.2, 138.7, 138.7, 143.1, 144.9, 156.5, 156.9. **ESI-MS**, *m/z*: found 398.11, calculated 398.11 $(M+H)^+$. Found, %: C 72.32, H 4.18, N 10.79. **$C_{24}H_{16}ClN_3O$**. Calculated, %: C 72.45, H 4.05, N 10.56.

4-(4-Chlorophenyl)-3-hydroxy-5-phenyl-[2,2'-bipyridine]-6-carbonitrile (4b). Yield 84 mg (0.22 mmol, 55%). M.p. 235-237 °C. **^{1}H NMR** ($CDCl_3$, δ, ppm): 7.08-7.13 (m, 2H, C_6H_4Cl), 7.18-7.23 (m, 2H, Ph), 7.24-7.28 (m, 2H, C_6H_4Cl), 7.32-7.37 (m, 3H, Ph), 7.47-7.52 (m, 1H, H-5′), 8.06 (ddd, 1H, ^3J 7.6 Hz, 7.6 Hz, ^4J 1.6 Hz, H-4′), 8.53 (d, 1H, ^3J 4.8 Hz, H-6′), 8.77 (d, 1H, ^3J 8.0 Hz, H-3′), 15.79 (s, 1H, OH). **^{13}C NMR** ($CDCl_3$, δ, ppm): 117.5, 121.7, 123.3, 124.4, 128.2, 128.4, 128.8, 130.0, 131.4, 131.8, 134.0, 134.3, 136.9, 137.4, 138.7, 143.0, 145.0. **ESI-MS**, *m/z*: found 384.09, calculated 384.09 $(M+H)^+$. Found, %: C 72.06, H 3.53, N 10.81. **$C_{23}H_{14}ClN_3O$**. Calculated, %: C 71.97, H 3.68, N 10.95.

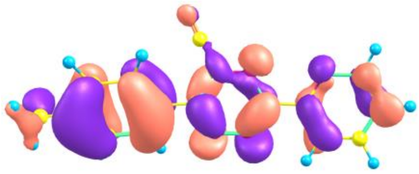
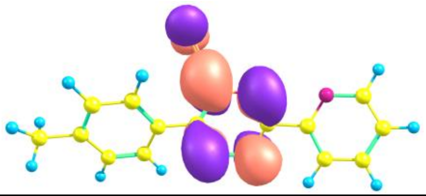
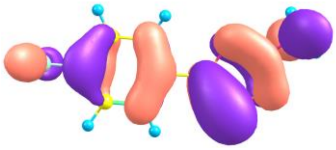
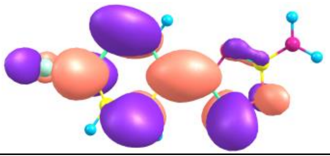
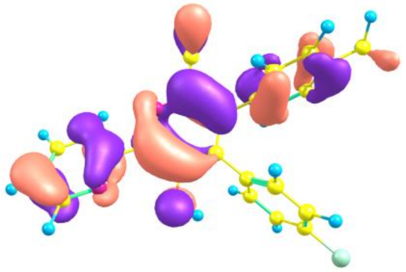
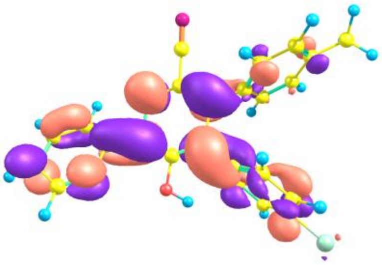
3-Hydroxy-4-(naphthalen-2-yl)-5-(*p*-tolyl)-[2,2'-bipyridine]-6-carbonitrile (4c). Yield 95 mg (0.23 mmol, 57%). M.p. > 250 °C. **^{1}H NMR** ($CDCl_3$, δ, ppm): 2.28 (s, 3H, CH_3), 7.06-7.09 (m, 2H, $C_6\underline{H}_4Me$), 7.11-7.14 (m, 2H, $C_6\underline{H}_4Me$), 7.18 (dd, 1H, ^3J 8.0 Hz, ^4J 1.2 Hz, H-3 (napth)), 7.44-7.51 (m, 2H, H-6,7 (napth)), 7.65-7.68 (m, 1H, H-5′), 7.70 (s, 1H, H-1 (napth)), 7.71-7.76 (m, 2H, H-5,8 (napth)), 7.82 (d, 1H, ^3J 8.0 Hz, H-4 (napth)), 8.22 (ddd, 1H, ^3J 8.0 Hz, 8.0 Hz, ^4J 1.6 Hz, H-4′), 8.67 (d, 1H, ^3J 4.8 Hz, H-6′), 8.70 (d, 1H, ^3J 8.0 Hz, H-3′), 15.76 (s, 1H, OH). **^{13}C NMR** ($CDCl_3$, δ, ppm): 21.2, 117.6, 122.5, 124.0, 124.7, 126.1, 126.5, 127.6, 127.9, 128.2, 128.6, 128.8, 129.1, 129.9, 130.0, 130.1, 130.9, 131.2, 132.6, 132.8, 136.7, 138.4, 138.5, 140.2, 143.7, 144.3, 154.6, 156.5. **ESI-MS**, *m/z*: found 414.16, calculated 414.16 $(M+H)^+$. Found, %: C 81.47, H 4.51, N 10.31. **$C_{28}H_{19}N_3O$**. Calculated, %: C 81.34, H 4.63, N 10.16.



4 Dipyrimicin A Dipyrimicin B

Figure S1 Bipyridines **4** and dipyrimicins A and B.

Table S1 HOMO and LUMO orbitals for compounds **1a**, **3a** and **4a**.

Substance	HOMO	LUMO	$E_{0\text{-}0}$
1a	-6.7702 	-2.8812 	3.8890
3a	-5.6574 	-1.0310 	4.6264
4a	-6.4666 	-1.8853 	4.5813

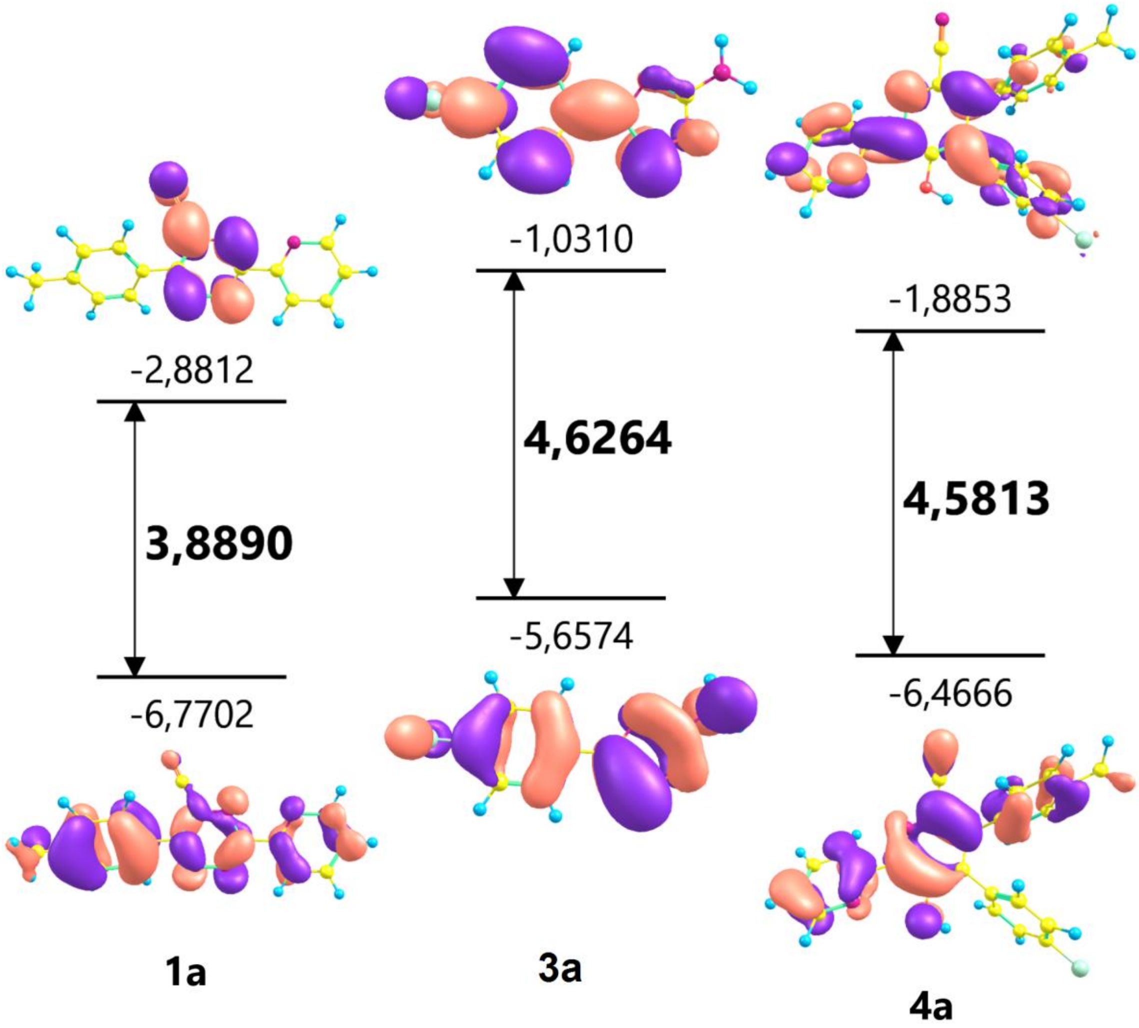


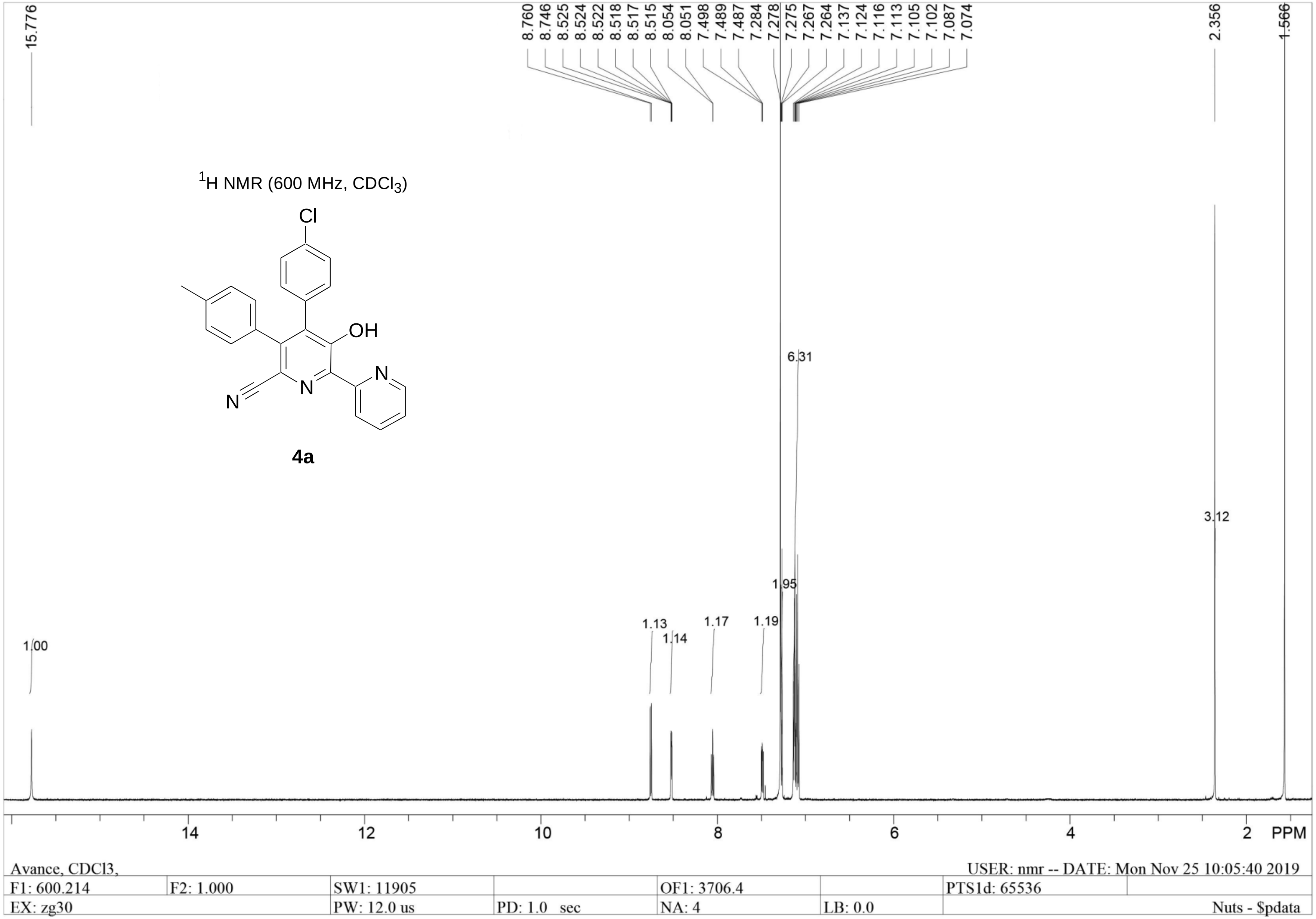
Figure S2 Calculated energies and localizations of frontier molecular orbitals of the compounds **1a**, **3a** and **4a**.

References

S1 V. N. Kozhevnikov, D. N. Kozhevnikov, T. V. Nikitina, V. L. Rusinov, O. N. Chupakhin, M. Zabel and B. König, *J. Org. Chem*., 2003, **68**, 2882.

S2 W. W. Turner, L. D. Arnold, H. Maag and A. Zlotnick, Patent WO 2015/138895 A1, 2015.

S3 G. M. Sheldrick, *Acta Crystallogr*., 2008, **A64**, 112.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8.746
8.525
8.524
8.522
8.518
8.517
8.515
8.054
8.051
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7.487
7.284
7.278
7.275
7.267
7.264
7.137
7.124
7.116
7.113
7.105
7.102
7.087
7.074
2.356
1.566
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OH
N
N
N
4a
1.00
1.13
1.14
1.17
1.19
1.95
6.31
3.12
14
12
10
8
6
4
2
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Avance, CDCl3,
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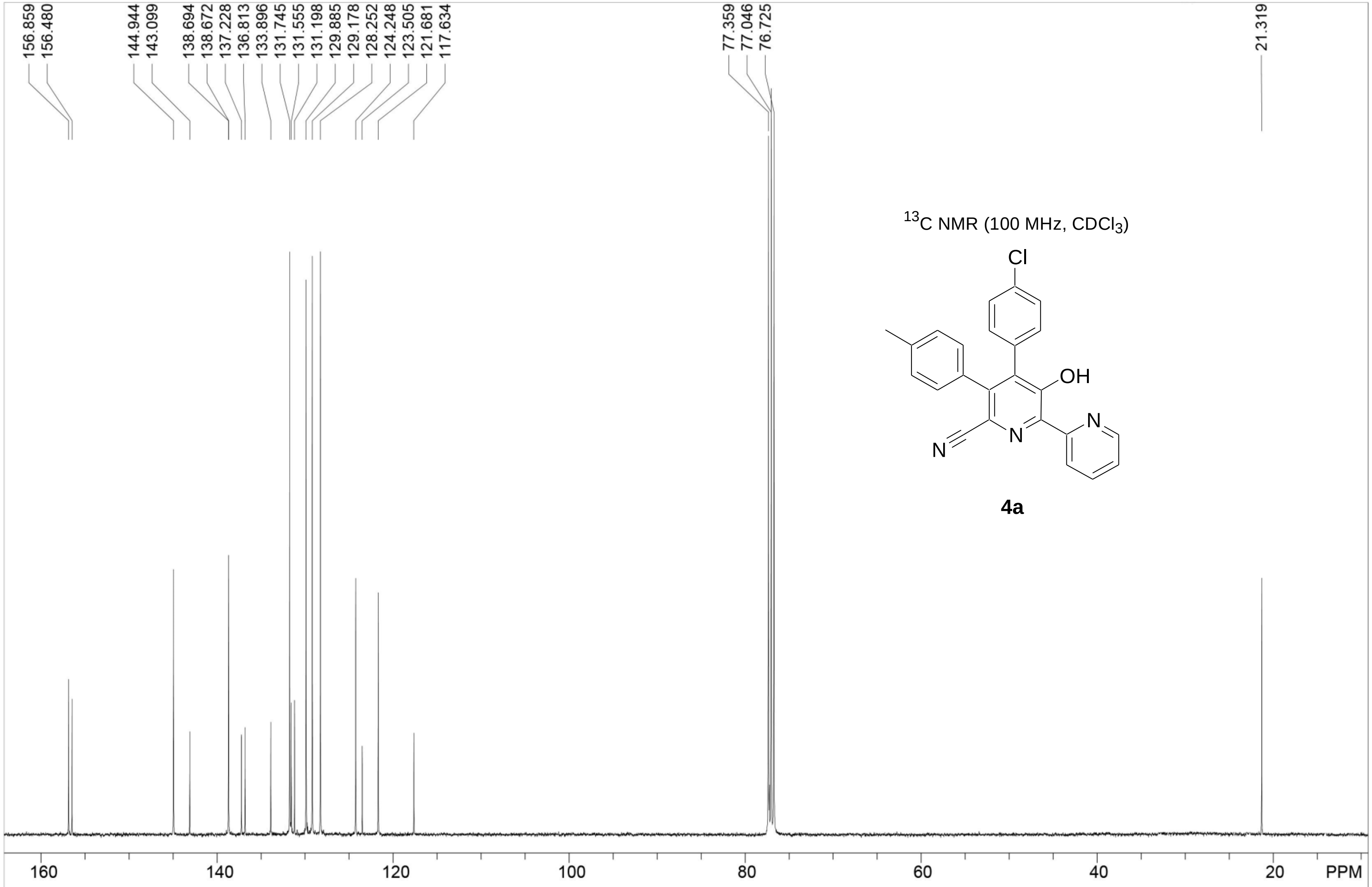

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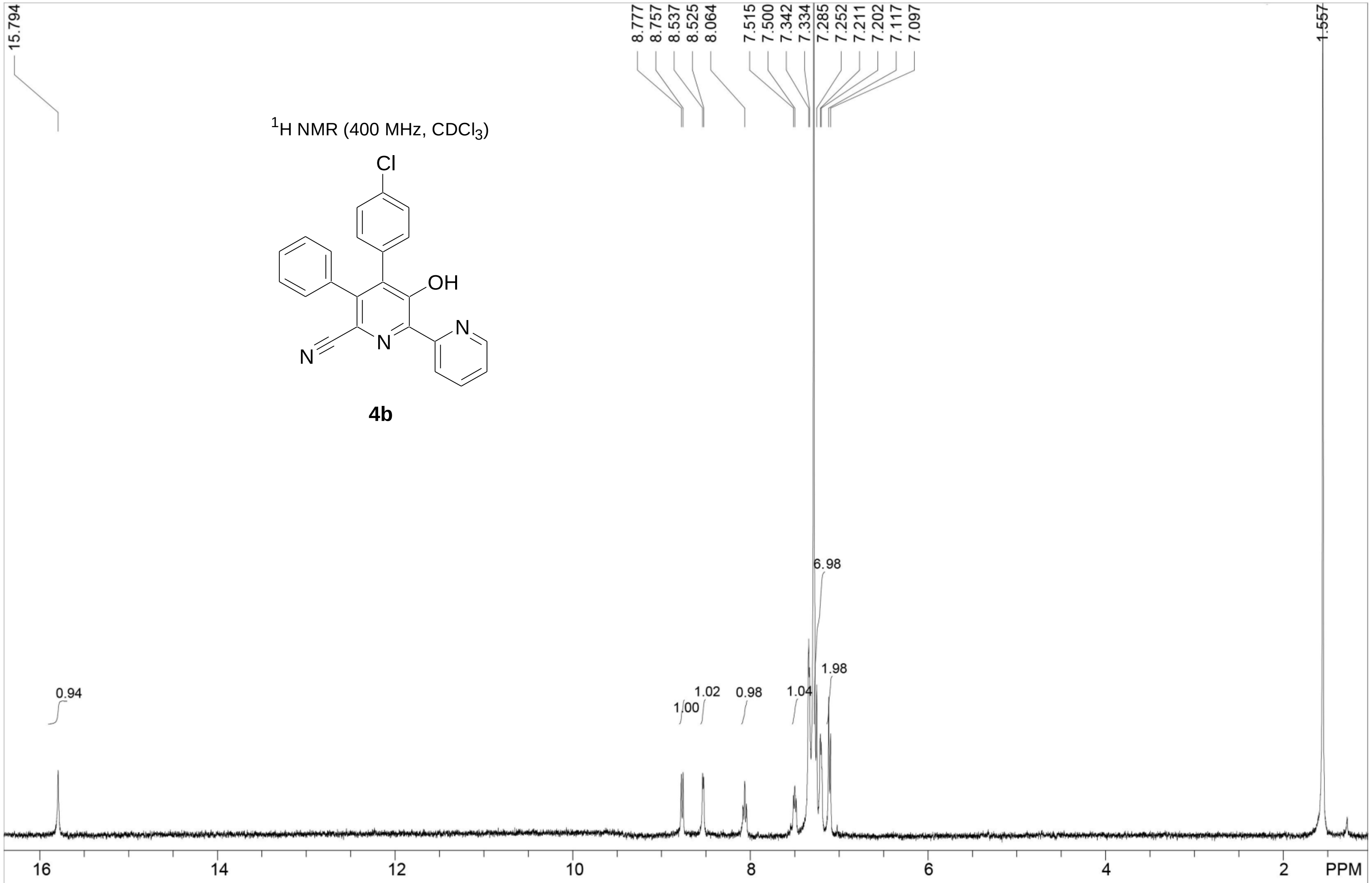

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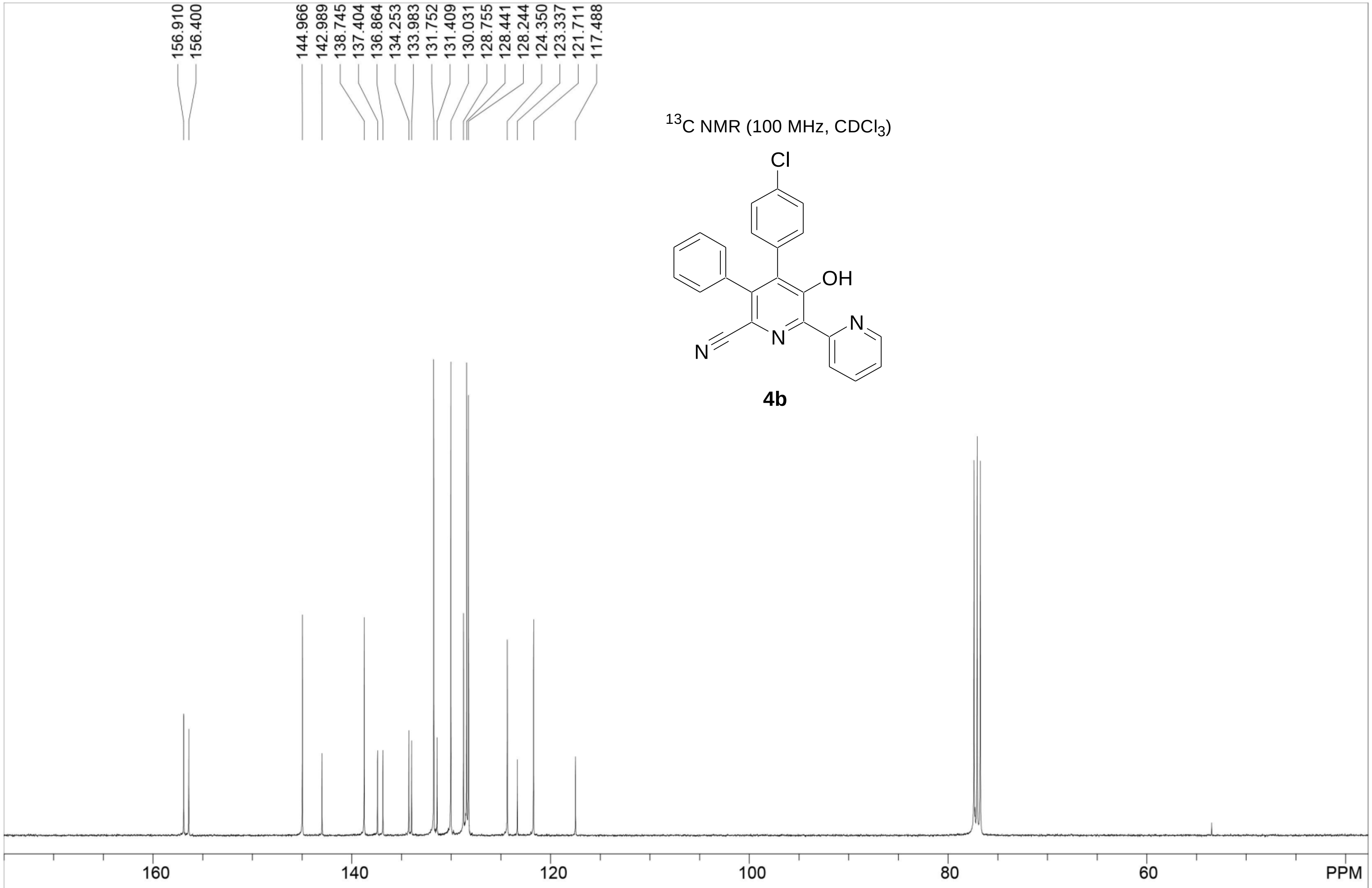

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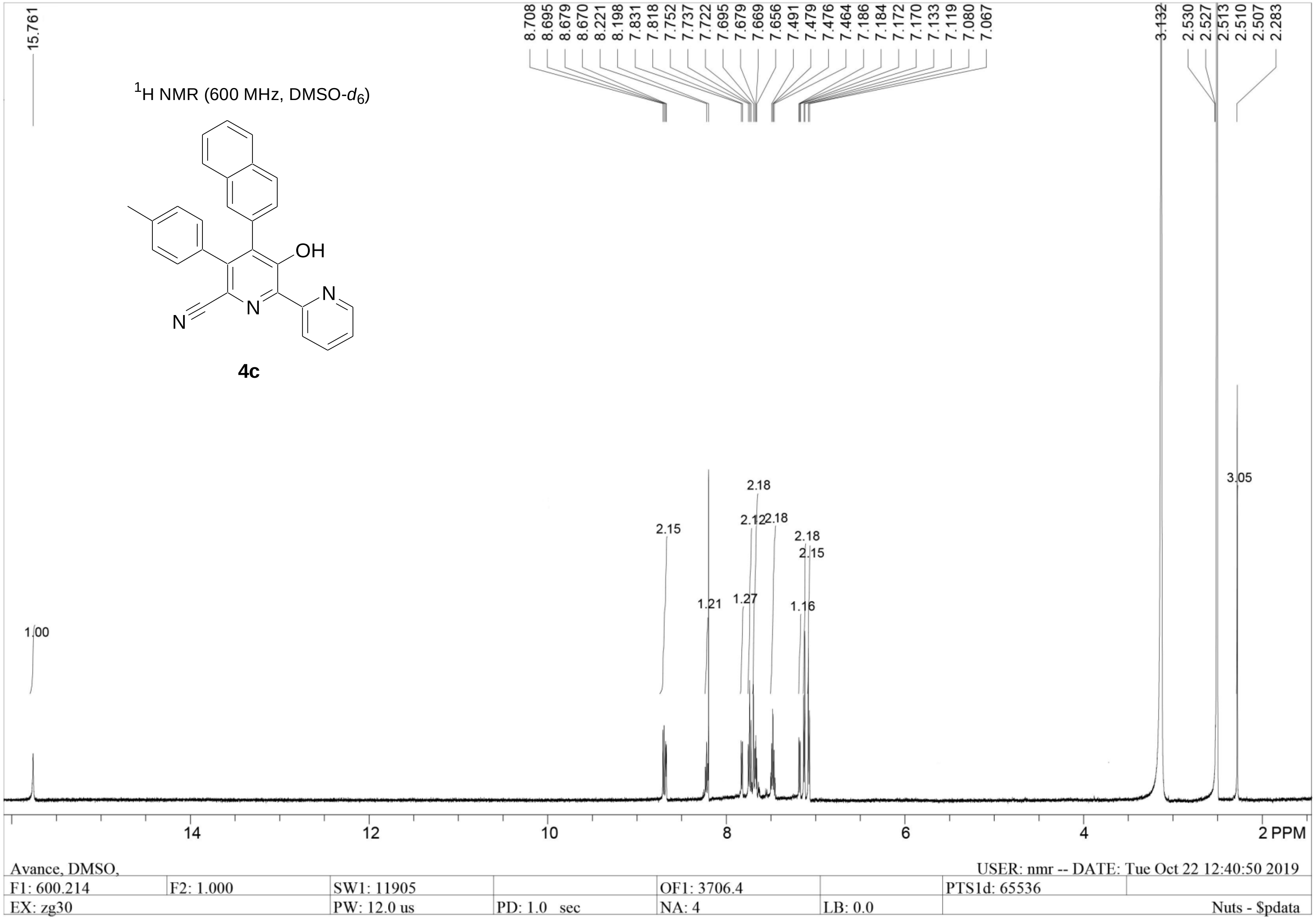
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4c
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N
N
N
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8.708
8.695
8.679
8.670
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8.198
7.831
7.818
7.752
7.737
7.722
7.695
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7.669
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7.491
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7.464
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7.184
7.172
7.170
7.133
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7.080
7.067
3.132
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2.513
2.510
2.507
2.283
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1.21
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2.12
2.18
2.18
2.18
2.15
1.16
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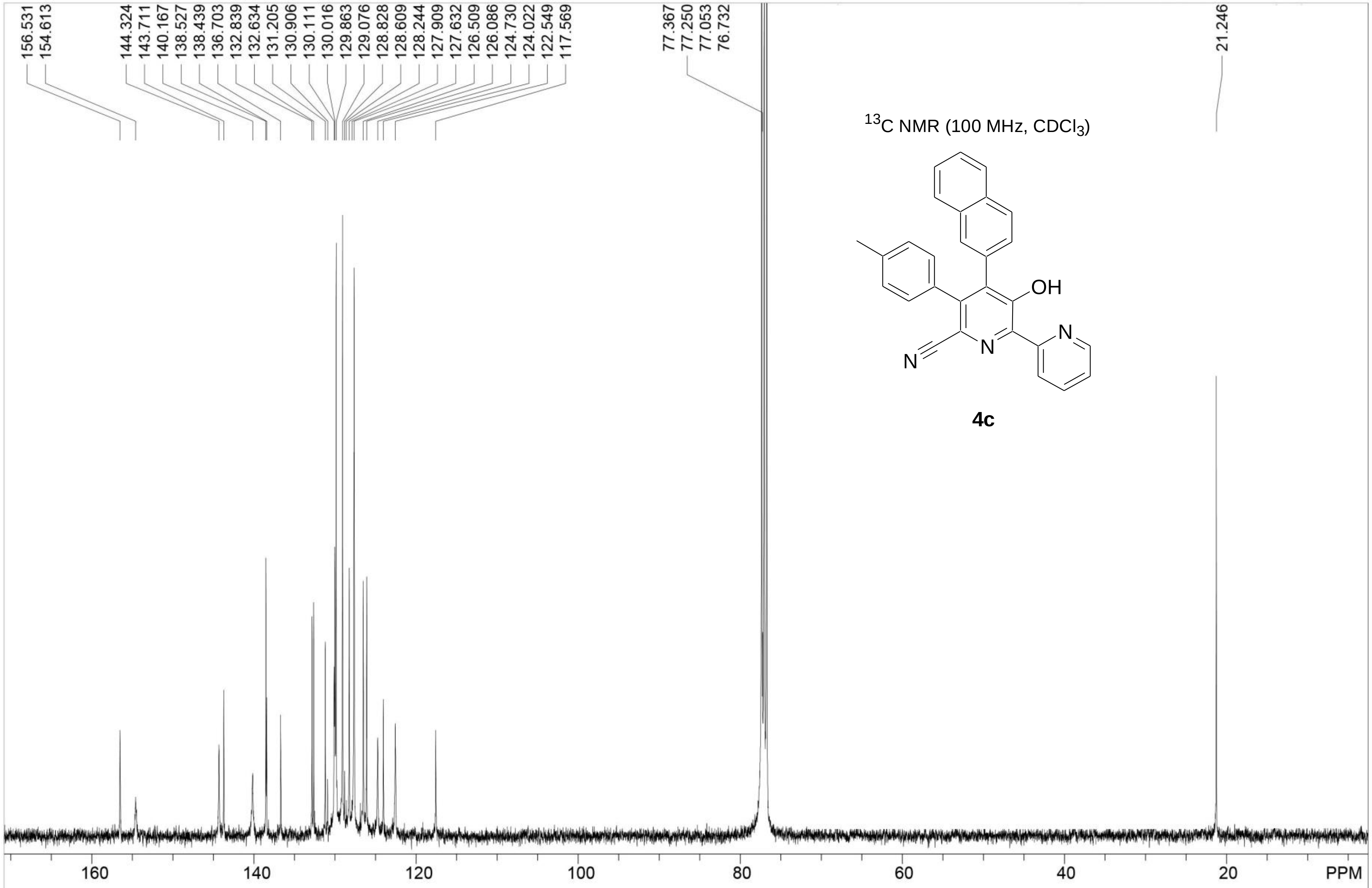

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