Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Supporting Information

Autocatalytic Photoinduced Oxidative Dehydrogenation of Pyrido[2,3-*d*]pyrimidine-7(8*H*)-ones: Synthesis of C5-C6 Unsaturated Systems with Concomitant Formation of a Long-lived Radical

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General information

All solvents and chemicals were reagent grade. Unless otherwise mentioned, all solvents and chemicals were purchased from commercial vendors (Sigma Aldrich, ABCR, Fluorochem, Apollo scientific, Activate scientific, Alfa Aesar and ACROS Organics) and used without further purification.

^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a Varian 400-MR spectrometer (^{1}H NMR at 400 MHz, ^{13}C NMR at 100.5 MHz and ^{19}F NMR at 376 MHz). Chemical shifts were reported in parts per million (δ) and are referenced to the residual signal of the solvent DMSO-d_6 2.50 ppm or tetramethylsilane (TMS) 0 ppm in ^{1}H NMR spectra and to the residual signal of the solvent DMSO-d_6 39.5 ppm in ^{13}C NMR. Coupling constants are reported in Hertz (Hz). Standard and peak multiplicities are designed as follows: s, singlet; d, doublet; dd, doublet of doublets; ddd, doublet of doublets of doublets; t, triplet; tt, triplet of triplets; qd, quintet of doublets, br, broad signal. "*" means interchangeable assignment.

IR spectra were recorded in a Thermo Scientific Nicolet iS10 FTIR spectrophotometer with Smart iTr. Wavenumbers (ν) are reported in cm^{-1}.

MS data (m/z (%), EI, 70 eV) were acquired on an Agilent Technologies 5975. HRMS data were acquired on a Bruker micrOTOF (APCI-FIA-TOF) or on a X500B SCIEX QTOF high-resolution mass spectrometer (ESI mode).

Elemental microanalyses were obtained on a EuroVector Instruments Euro EA 3000 elemental analyser.

The melting points were determined on a Stuart Scientific SMP20 apparatus with 0.1 °C resolution in open capillary tubes and are uncorrected.

All microwave irradiation experiments were carried out in a dedicated *Biotage-Initiator* microwave apparatus, operating at a frequency of 2.45 GHz with continuous irradiation power from 0 to 400 W with utilization of the standard absorbance level of 400 W maximum power. Reactions were carried out in glass tubes, sealed with aluminium/Teflon crimp tops, which can be exposed up to 250 °C and 20 bar internal pressure. Temperature was measured with an IR sensor on the outer surface of the process vial. After the irradiation period, the reaction vessel was cooled rapidly (60–120s) to ambient temperature by air jet cooling.

Automated flash column chromatography was performed by a Teledyne ISCO CombiFlash Rf200 system through pre-packed RediSep Rf silica gel columns. The wavelength of the UV-detector was calibrated at 254 and 365 nm.

EPR spectra were obtained with an X-Band (9.7 GHz) Bruker ELEXSYS E500 spectrometer equipped with a ST8911 microwave cavity, a Bruker variable temperature unit, a field frequency lock system Bruker ER 033 M and an NMR Gaussmeter Bruker ER 035 M. The modulation amplitude was kept well below the line width, and the microwave power was well below saturation. Samples were previously degassed with Ar. The EPR spectra were simulated with Bruker WIN-EPR SimFonia software version 901201.

Photoreactions were carried out in a Penn PhD Photoreactor M2 from Merck. AC/DC input 100-240 V AC, 50/60 Hz. The experiments were carried out in a glass vial in the 8/40 mL reflector irradiated with the 450/365 nm LED Module.

Agilent technologies 1200 series LC / LC MSD iQ. The column used was XBridge® C18 (100 mm x 4.6 mm x 3.5 µm). Mobile phases used were water Milli-Q® (+ 0.1% formic acid Optima LC-MS Fisher Chemical) and acetonitrile for HPLC – SUPER GRADIENT VWR (+ 0.1 % formic acid LC-MS LiChropur™) with the follow gradient:

HPLC method:

Time (min)	Flow (mL/min)	% Water	% ACN
0	0.5	60	40
5	0.5	60	40
15	0.5	0	100
20	0.5	0	100
30	0.5	60	40
35	0.5	60	40

Injection volume is set to 10.0 µL.

Temperature: column at 40 °C and sample at 25 °C

Detector DAD: 254, 360, 265 nm

- Mass method:

Ionization method: ESI+

Cone: 110 V.

Time: 11 min

Scan time: 0.02 min

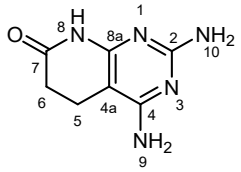
MS Scan (m/z) positive and negative: 100 – 1000.

Synthesis of 5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-ones

General method for the synthesis of 2-amino-4,5,6-trisubstituted-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-ones

A mixture of guanidine carbonate, the active malononitrile (or methyl cyanoacetate) and the corresponding methyl acrylate are dissolved with anhydrous methanol. The mixture is sealed in a microwave vial and heated at 140 °C under microwave irradiation for 10 min. Compound can be isolated by filtration, washed with water, ethanol, and diethyl ether to afford spectroscopically pure the desired product.

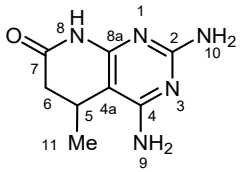
2,4-diamino-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (11a)



11a

Following the general procedure described above using 1.2 mL (13.3 mmol) of methyl acrylate, 1.2 g (6.64 mmol) of guanidine carbonate and 440 mg (6.64 mmol) of malononitrile to give 823 mg of an off-white powder (4.59 mmol, 69%) of spectroscopically pure **11a**. **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm): 10.25 (s, 1H, H-N8), 6.17 (s, 2H, NH_2), 5.86 (s, 2H, NH_2), 2.52 – 2.45 (m, 4H, H-C5, H-C6). Spectroscopic data are consistent with those reported in the literature.[1]

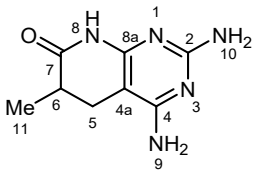
2,4-diamino-5-methyl-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (11b)



11b

Following the general procedure previously described using 1.0 g (10.0 mmol) of methyl crotonate, 1.8 g (9.8 mmol) of guanidine carbonate and 792 mg (12.0 mmol) of malononitrile to give 910 mg of an off-white powder (4.71mmol, 47%) of spectroscopically pure **11b**. **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm): 9.19 (br s, 1H, H-N8), 6.20 (s, 2H, H-N9), 5.83 (s, 2H, H-N10), 2.97 (pd, J = 6.9, 1.6 Hz, 1H, H-C5), 2.67 (dd, J = 16.0, 6.9 Hz, 1H, Hb-C6), 2.20 (dd, J = 16.0, 1.5 Hz, 1H, Ha-C6), 0.94 (d, J = 6.8 Hz, 3H, H-C11). Spectroscopic data are consistent with those reported in the literature.[1]

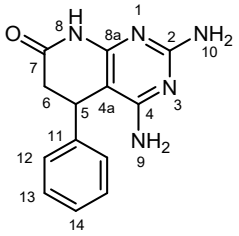
2,4-diamino-6-methyl-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (11c)



11c

Following the general procedure previously described using 1.0 g (10.0 mmol) of methyl methacrylate, 1.8 g (9.8 mmol) of guanidine carbonate and 792 mg (12.0 mmol) of malononitrile to give 670 mg of an off-white powder (3.47 mmol, 36%) of spectroscopically pure **11c**. **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm): 10.06 (s, 1H, H-N8), 6.12 (s, 2H, H-N9), 5.78 (s, 2H, H-N10), 2.70 (dd, J = 15.4, 6.8 Hz, 1H, Ha-C5), 2.53 – 2.47 (m, 1H, H-C6), 2.15 (dd, J = 15.4, 11.3 Hz, 1H, Hb-C5), 1.11 (d, J = 6.8 Hz, 3H, H-C11). Spectroscopic data are consistent with those reported in the literature.[1]

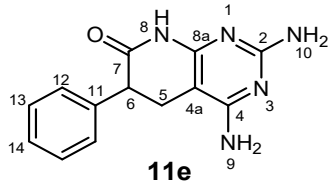
2,4-diamino-5-phenyl-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (11d)



11d

Following the general procedure previously described using 1.0 g (6.17 mmol) of methyl cinnamate, 1.1 g (6.1 mmol) of guanidine carbonate and 489 mg (7.4 mmol) of malononitrile to give 501 mg of an off-white powder (1.96 mmol, 32%) of spectroscopically pure **11d**. **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm): 10.13 (br s, 1H, H-N8), 7.30 – 7.24 (m, 2H, H-C13), 7.22 – 7.16 (m, 1H, H-C14), 7.15 – 7.10 (m, 2H, H-C12), 6.10 (s, 2H, NH_2), 5.87 (s, 2H, NH_2), 4.18 (dd, J = 7.5, 1.6 Hz, 1H, H-C5), 3.00 (dd, J = 16.1, 7.5 Hz, 1H, Hb-C6), 2.52 – 2.48 (dd, J = 16.1, 1.7 Hz, 1H, Ha-C6). Spectroscopic data are consistent with those reported in the literature.[1]

2,4-diamino-6-phenyl-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (11e)



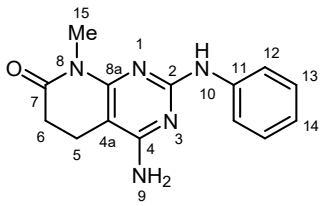
11e

A mixture of methyl-2-phenylacetate (3.32 g, 22.1 mmol), paraformaldehyde 95% (908 mg, 28.7 mmol) and potassium carbonate (3.06 g, 22.1 mmol) with 90 mL of anhydrous DMF is heated at 100 °C for 2.5 h. Then the mixture is cooled, and 100 mL of water are added. To isolate the product 4x30 mL of diethyl ether extractions are required, and the organic phase is washed with 3x30 mL of a saturated LiCl solution. The solvent is eliminated under vacuum to afford 1.72 g

(10.6 mmol, 48%) of spectroscopically pure methyl-2-phenylacrylate as a yellow liquid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm): 7.50 – 7.30 (m, 5H, H-C1+H-C2+H-C3), 6.25 (d, J = 0.9 Hz, 1H, Hb-C6), 6.02 (d, J = 0.9 Hz, 1H, Ha-C6), 3.76 (s, 3H, H-C8).

Following the general procedure previously described using 1.0 g (6.17 mmol) of methyl 2-phenylacrylate, 1.1 g (6.1 mmol) of guanidine carbonate and 489 mg (7.4 mmol) of malononitrile to give 958 mg of an off-white powder (3.80 mmol, 61%) of spectroscopically pure **11c**. **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm): 10.30 (s, 1H, H-N8), 7.41 – 7.11 (m, 5H, H-C12, H-C13, H-C14), 6.16 (s, 2H, H-N9/10), 5.80 (s, 2H, H-N9/10), 3.81 (dd, J = 9.4, 6.8 Hz, 1H, H-C6), 2.87 (dd, J = 15.7, 7.0 Hz, 1H, Ha-C5), 2.73 (dd, J = 15.7, 9.5 Hz, 1H, Hb-C5). Spectroscopic data are consistent with those reported in the literature.[2]

4-amino-8-methyl-2-(phenylamino)-5,8-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (13).



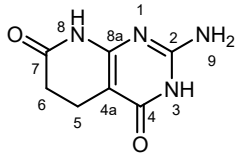
13

A mixture of *N*-phenylguanidine carbonate (having a $C_7H_9N_3 \cdot (H_2CO_3)_{0.69}$ stoichiometry) (1184 mg, guanidine 6.64 mmol, carbonate 4.56 mmol), malononitrile (440 mg, 6.64 mmol), methyl acrylate (1144 mg, 13.28 mmol) and anhydrous methanol (20 mL) is sealed in a 20 mL microwave vial and heated at 160 °C under microwave irradiation for 5 min. 4-amino-2-(phenylamino)-5,8-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one is obtained as a white solid that can be isolated by filtration, washed with water and diethyl ether to afford 316.6 mg (1.24 mmol, 37%) of spectroscopically pure intermediate. **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm): 10.05 (br s, 1H, H-N8), 8.70 (br s, 1H, H-N10), 7.83 – 7.81 (m, 2H, H-C12), 7.19 – 7.18 (m, 2H, H-C13), 6.84 – 6.82 (m, 1H, H-C14), 6.36 (br s, 2H, H-N9), 2.60-2.48 (m, 4H, H-C5 and H-C6). **^{13}C NMR** (100.5 MHz, DMSO-d_6) δ (ppm): 171.7 (C7), 161.4 (C4), 158.1 (C2), 156.3 (C8a), 141.5 (C10), 128.2 (C12), 120.2 (C13), 118.3 (C11), 85.8 (C4a), 30.5 (C6), 17.2 (C5). Spectroscopic data are consistent with those reported in the literature[1].

4-amino-2-(phenylamino)-5,8-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (2.50 g, 9.80 mmol) and sodium hydride (60% in mineral oil) (392 mg, 9.80 mmol) in anhydrous DMSO (100 mL) are added in a 100 mL round bottom flask and the mixture is stirred for 1 hour at room temperature. Then, methyl iodide (0.610 mL, 9.80 mmol) is added, and the mixture is stirred overnight at room temperature. After addition of water (1 L), the solid appeared can be isolated by filtration, washed with water and dried under vacuum to afford 2.43 g (9.02 mmol, 92%) of **13** as a light beige powder, mp (°C): 216-218. **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm): 8.82 (s, 1H, H-N10), 7.80 – 7.73 (m, 2H, H-C12), 7.25 – 7.17 (m, 2H, H-C13), 6.85 (tt, J = 7.5, 1.1 Hz, 1H, H-C14), 6.40 (s, 2H, H-N9), 3.26 (s, 3H, H-C15), 2.57 – 2.55 (m, 4H, H-C6 and H-C5). **^{13}C NMR** (100.5 MHz, DMSO-d_6) δ (ppm): 170.4 (C7), 161.5 (C4), 157.8 (C2), 157.1 (C8a), 141.4 (C11), 128.3 (C13), 120.3 (C14), 118.4 (C12), 87.6 (C4a), 30.7 (C6), 27.4 (C15), 16.5 (C5). **IR** (KBr) ν_{max} (cm^{-1}): 3462, 3388, 3338, 3062, 2927, 1673, 1657, 1621, 1581, 1539, 1456, 1436, 1371, 1130, 751, 699. **Elemental analysis**

calcd (%) for $C_{14}H_{15}N_5O$: C 62.44, H 5.61, N 26.01; found: C 62.18, H 5.36, N 25.62. **MS** (70 eV, EI): m/z (%): 269.1 (74) $[M]^+$, 241.1 (52) $[M\text{-}CO]^+$, 240.2 (100) $[M\text{-}NMe]^+$. Spectroscopic data are consistent with those reported in the literature[3].

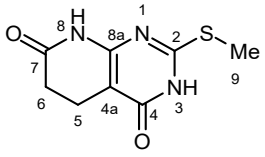
2-amino-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (16)



16

Following the general procedure previously described using 1.2 mL (13.3 mmol) of methyl acrylate, 1.2 g (6.64 mmol) of guanidine carbonate and 658 mg (6.64 mmol) of methyl cyanoacetate to give 122 mg of an off-white powder (0.678 mmol, 10%) of spectroscopically pure **16**. **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm): 10.58 (s, 1H, H-N3), 9.92 (s, 1H, H-N8), 6.46 (s, 2H, H-N9), 2.47 – 2.41 (m, 2H, H-C5), 2.41 – 2.35 (m, 2H, H-C6). **^{13}C NMR** (100.5 MHz, DMSO-d_6) δ (ppm): 171.9 (C4*), 161.6 (C7*), 156.4 (C8a*), 154.8 (C2), 88.3 (C4a), 30.6 (C6), 16.4 (C5). Spectroscopic data are consistent with those reported in the literature.[1]

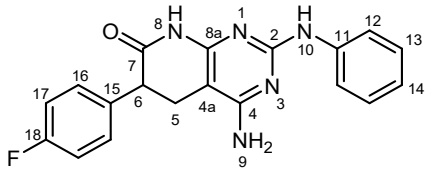
2-(methylthio)-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (17)



17

A mixture of methyl acrylate (0.40 g, 4.65 mmol), 6-amino-2-(methylthio)pyrimidin-4(3*H*)-one (876 mg, 5.58 mmol) and potassium carbonate (642 mg, 4.65 mmol) is dissolved with anhydrous isopropanol (20 mL) is sealed in a 20 mL microwave vial and heated at 170 °C under microwave irradiation for 3h. The solvent is removed under vacuum in a rotavapor, a minimum quantity of water is added to dissolve the crude and is neutralized with a HCl 2M solution. The product is obtained as a whitish solid that can be isolated by filtration, washed with water, ethanol, and diethyl ether to afford 247mg (1.17 mmol, 25%) of spectroscopically pure **17**, mp (°C): >300. **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm): 12.42 (br s, 1H, H-N3), 10.32 (s, 1H, H-N8), 2.57 – 2.53 (m, 2H, H-C5*), 2,47 – 2.42 (m, 5H, H-C9, H-C6*). **^{13}C NMR** (100.5 MHz, DMSO-d_6) δ (ppm): 171.2 (C7), 162.0 (C8a*), 161.1 (C2), 154.8 (C4*), 95.2 (C4a), 29.9 (C6*), 16.4 (C5*), 12.7 (C9). **IR** (ATR) ν_{max} (cm^{-1}): 1631, 1559, 1504, 1459, 1300, 1238, 1201, 825, 767, 719. **HRMS** (APCI-FIA-QTOF) (m/z): calculated for $C_8H_{10}N_3O_2S$ $[M+H]^+$: 212.0494; found: 212.0491.

4-amino-6-(4-fluorophenyl)-2-(phenylamino)-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (18)



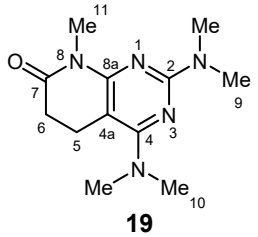
18

A mixture of *N*-phenylguanidine carbonate (having a $C_7H_9N_3 \cdot (H_2CO_3)_{0.7}$ stoichiometry) (218 mg, 1.2 mmol, 3.0 equiv.), sodium methoxide (92.1 mg, 1.71 mmol, 4.2 equiv.) are dissolved with 1,4-dioxane (15 mL) in a 20 mL microwave vial. Heat the mixture at 65 °C under microwave irradiation for 15 minutes to obtain a clear solution with a white precipitate. Remove the solid by filtration. Transfer the mother liquor to a 20 mL microwave vial together with 5-(4-fluorophenyl)-2-methoxy-6-oxo-4,5-dihydropyridine-3-carbonitrile (100 mg, 0.406 mmol)[3]. Seal the vial and heat at 140 °C under microwave irradiation for 40 minutes. The solid appeared is filtered, washed with acetone and dried under vacuum to afford 69.6 mg (0.200 mmol, 49%) spectroscopically pure of 2-amino-6-(4-fluorophenyl)-4-imino-3-phenyl-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one as a white powder, mp (°C): 249 – 252. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 9.93 (br s, 1H, H-N8), 7.57 (m, 2H, H-C13), 7.52 (m, 1H, H-C14), 7.35 – 7.28 (m, 2H, H-C16), 7.28 – 7.23 (m, 2H, H-C12), 7.20 – 7.10 (m, 2H, H-C17), 6.10 (s, 2H, H-N10), 4.93 (br s, 1H, H-N9), 3.83 (t, *J* = 8.8 Hz, 1H, H-C6), 2.83 (dd, *J* = 15.1, 7.0 Hz, 1H, H-C5), 2.69 – 2.63 (m, 1H, H-C5). **^{13}C NMR** (100.5 MHz, $CDCl_3$) δ (ppm): 172.1 (C7*), 161.1 (d, *J* = 242.4 Hz, C18), 156.6 (C2*), 153.8 (C8a*), 149.3 (C4*), 135.9 (d, *J* = 3.1 Hz, C15), 135.5 (C11), 130.5 (C13), 130.2 (d, *J* = 8.1 Hz, C16), 129.4 (C14), 129.1 (C12), 114.9 (d, *J* = 21.1 Hz, C17), 86.6 (C4a), 45.4 (C6), 26.5 (C5). **^{19}F NMR** (376 MHz, DMSO-d_6) δ (ppm): -116.30 (br s, 1F). **IR** (ATR) ν_{max} (cm^{-1}): 3188, 1632, 1603, 1509, 1489, 1379, 1313, 1263, 1225, 1157, 767, 698. **HRMS** (APCI-FIA-QTOF) (m/z): calcd for $C_{19}H_{17}FN_5O$ $[M+H]^+$: 350.1417; found: 350.1411.

A mixture of 2-amino-6-(4-fluorophenyl)-4-imino-3-phenyl-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (50 mg, 0.143 mmol) and sodium methoxide (7.8 mg, 0.143 mmol) is dissolved with methanol anhydrous (3 mL) in a 5 mL microwave vial. Heat the mixture at 140 °C under microwave irradiation for 40 minutes to obtain a clear solution with a white precipitate. The solid appeared is filtered, washed with water, ethanol and diethyl ether and dried under vacuum to afford 37.5 mg (0.106 mmol, 74%) spectroscopically pure **18** as a white powder mp (°C): > 300 **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 10.27 (s, 1H, H-N8), 8.71 (s, 1H, H-N10), 7.86 – 7.76 (m, 2H, H-C12), 7.32 (m, 2H, H-C16), 7.22 – 7.10 (m, 4H, H-C13, H-C17), 6.83 (m, 1H, H-C14), 6.38 (s, 2H, H-N9), 3.91 (dd, *J* = 10.3, 6.8 Hz, 1H, H-C6), 2.94 (dd, *J* = 15.8, 6.9 Hz, 1H, H-C5), 2.79 (dd, *J* = 15.8, 10.3 Hz, 1H, H-C5). **^{13}C NMR** (100.5 MHz, $CDCl_3$) δ (ppm): 171.9 (C7*), 161.3 (C8a*), 161.2 (d, *J* = 242.5 Hz, C18), 158.2 (C2), 156.2 (C4*), 141.5 (C11), 135.7 (d, *J* = 3.0 Hz, C15), 130.2 (d, *J* = 8.0 Hz, C16), 128.2 (C13), 120.2 (C14), 118.4 (C12), 115.0 (d, *J* = 21.2 Hz, C17), 85.8 (C4a), 45.4 (C6), 25.7 (C5).**^{19}F NMR** (376 MHz, DMSO-d_6) δ (ppm): -116.08 – -116.15 (m, 1F). **IR** (ATR) ν_{max} (cm^{-1}): 3468, 3261, 3116, 1694, 1639, 1572, 1541, 1487, 1451, 1434, 1252, 1222, 836, 819,

781, 709. **HRMS** (APCI-FIA-QTOF) (m/z): calcd for $C_{19}H_{17}FN_5O$ $[M+H]^+$: 350.1417; found: 350.1311.

2,4-bis(dimethylamino)-8-methyl-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (19)

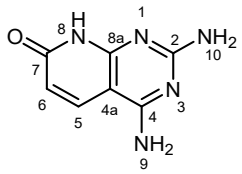


19

2,4-diamino-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**11a**) (200 mg, 1.12 mmol) and sodium hydride (60% in mineral oil) (446 mg, 11.2 mmol) in anhydrous DMSO (10 mL) are added in a 50 mL flask and the mixture is stirred for 1 hour at room temperature. Then, methyl iodide (0.74 mL, 11.2 mmol) is added and the mixture is stirred overnight at room temperature. To isolate the product 3x30 mL of dichloromethane extractions are required, and the organic phase is washed with 3x30 mL of water. The solvent is eliminated under vacuum using a rotavapor. 251 mg (1.01 mmol, 91%) of a semi-solid spectroscopically pure **19** is obtained after an automatic flash chromatography (silica, from 100:0 to 80:20 of AcOEt/Cy as eluent in 35 min.; retention time of: 17 - 25 min.). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 3.37 (s, 3H, H-C11), 3.13 (s, 6H, H-C9), 2.93 (s, 6H, H-C10), 2.75 – 2.67 (m, 2H, H-C5), 2.58 – 2.50 (m, 2H, H-C6). **^{13}C NMR** (100.5 MHz, $CDCl_3$) δ (ppm): 171.6 (C7), 165.8 (C4), 160.0 (C2), 159.6 (C8a), 90.2 (C4a), 40.7 (C10), 36.8 (C9), 32.2 (C6), 28.1 (C11), 20.4 (C5). **IR** (ATR) ν_{max} (cm^{-1}): 2955, 2922, 2852, 1696, 1590, 1550, 1460, 1387, 1140, 1115, 1030, 723. **HRMS** (APCI-FIA-QTOF) (m/z): calculated for $C_{12}H_{20}N_5O$ $[M+H]^+$:250.1668; found: 250.1646.

Photodehydrogenation of 5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-ones

2,4-diaminopyrido[2,3-*d*]pyrimidin-7(8*H*)-one (12a)

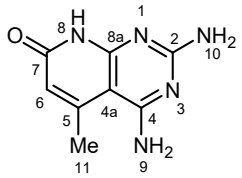


12a

2,4-diamino-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**11a**) (1.0 g, 5.6 mmol) is dissolved in 40 mL of DMSO in a 50 mL round bottom flask. The mixture is bubbled with dry air and irradiated at 365 nm for 43 h with a Penn PhD Photoreactor M2. % LED: 100, stirrer: 400 rpm. After addition of acetone (500 mL) the solid appeared can be isolated by filtration, washed with acetone and water and dried to afford 751 mg (4.24mmol, 76%) of spectroscopically pure **12a** as a beige solid, mp (°C): > 300. **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm): 11.90 (br s, 1H, H-N8), 7.94 (d, J = 9.4 Hz, 1H, H-C5), 7.21 (br s, 2H, H-N9), 6.75 (br s, 2H, H-N10), 5.95 (d, J = 9.4 Hz, 1H, H-C6). **^{13}C NMR** (100.5 MHz, DMSO-d_6) δ (ppm): 164.6 (C8a), 162.7 (C2), 161.5 (C7), 156.6 (C4), 136.0 (C5), 112.3 (C6), 90.9 (C4a). **IR** (KBr) ν_{max} (cm^{-1}): 3414, 3349, 3138, 1640, 1544, 1468, 1322. **MS** (EI, 70 eV) *m/z*

(%): 177.1 (43) $[M]^+$, 149.1 (55) $[M\text{-}CO]^+$. **HRMS** (APCI-FIA-QTOF) (m/z): calculated for $C_7H_8N_5O$ $[M+H]^+$: 178.0729; found: 178.0726. Spectroscopic data are consistent with those reported in the literature.[3]

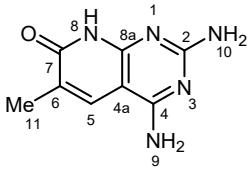
2,4-diamino-5-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (12b)



12b

2,4-diamino-5-methyl-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**11b**) (50 mg, 0,259 mmol) is dissolved in 2 mL of DMSO in a glass vial. The vial is bubbled with dry air and irradiated at 365 nm for 2 h with a Penn PhD Photoreactor M2. % LED: 100; stirrer 400 rpm; distance led – vial: 2 cm. After addition of acetone (50 mL) the yellow solid appeared can be isolated by filtration, washed with water and dried under vacuum to afford 22.5 mg (0.118 mmol, 45%) of **12b**. **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm): 11.50 (s, 1H, H-N8), 6.55 (s, 4H, H-N9, H-N10), 5.77 (s, 1H, H-C6), 2.46 (s, 3H, H-C11). **^{13}C NMR** (100.5 MHz, DMSO-d_6) δ (ppm): 163.2 (C8a), 162.1 (C7), 161.8 (C2), 157.4 (C4), 148.9 (C5), 113.8 (C6), 92.0 (C4a), 22.9 (C11). Spectroscopic data are consistent with those reported in the literature[4].

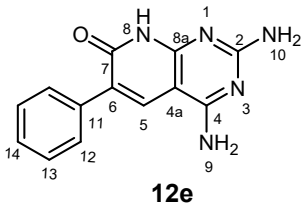
2,4-diamino-6-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (12c)



12c

2,4-diamino-6-methyl-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**11c**) (50 mg, 0,259 mmol) is dissolved in 2 mL of DMSO in a glass vial. The vial is bubbled with dry air and irradiated at 365 nm for 2 h with a Penn PhD Photoreactor M2. % LED: 100; stirrer: 400 rpm; distance led – vial: 2 cm. After addition of acetone (50 mL) the yellow solid appeared can be isolated by filtration, washed with water and dried under vacuum to afford 33.1 mg (0.173 mmol, 67%) of **12c**. **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm) 12.35 (br s, 1H, H-N8), 7.86 (s, 1H, H-C5), 7.10 (s, 2H, H-N9), 6.82 (s, 2H, H-N10), 1.97 (s, 3H, H-C11). **^{13}C NMR** (100.5 MHz, DMSO-d_6) δ (ppm) 164.9 (C7), 161.9 (C2), 160.8 (C8a), 155.3 (C4), 132.7 (C5), 120.4 (C6), 90.5 (C4a), 16.1 (C11). Spectroscopic data are consistent with those reported in the literature[4].

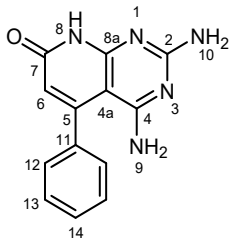
2,4-diamino-6-phenylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (12e)



12e

2,4-diamino-6-phenyl-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**11e**) (50 mg, 0,196 mmol) is dissolved in 2 mL of DMSO in a glass vial. The vial is bubbled with dry air and irradiated at 365 nm for 7 h with a Penn PhD Photoreactor M2. % LED: 100; stirrer 400 rpm; distance led – vial: 2 cm. After addition of brine (50 mL) the yellow solid appeared can be isolated by filtration, washed with water and dried under vacuum to afford 28.1 mg (0.111 mmol, 57%) of **12e**. **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm) 12.10 (s, 1H, H-N8), 8.24 (s, 1H, H-C5), 7.85 – 7.63 (m, 2H, H-C12), 7.50 – 7.35 (m, 2H, H-C13), 7.32 – 7.24 (m, 3H, H-C14, H-N9), 6.80 (br s, 2H, H-N10). **^{13}C NMR** (100.5 MHz, DMSO-d_6) δ (ppm) 163.4 (C7), 162.9 (C2), 161.7 (C8a), 155.8 (C4), 136.6 (C11), 134.0 (C5), 128.4 (C12), 128.0 (C13), 126.9 (C14), 122.4 (C6), 91.4 (C4a). Spectroscopic data are consistent with those reported in the literature.[2]

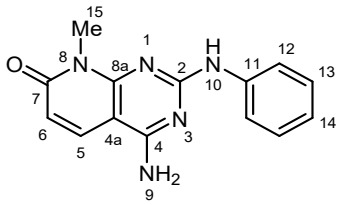
2,4-diamino-5-phenylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (12d)



12d

2,4-diamino-5-phenyl-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**11d**) (50 mg, 0.196 mmol) is dissolved in 2 mL of DMSO in a glass vial. The vial is bubbled with dry air and irradiated at 365 nm for 10 h with a Penn PhD Photoreactor M2. % LED: 100; stirrer 400 rpm; distance led – vial: 2 cm. After addition of brine (50 mL) the yellow solid appeared can be isolated by filtration, washed with water and dried under vacuum to afford 12.0 mg (0.047 mmol, 24%) of **12d**. **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm): 11.82 (s, 1H, H-N8), 7.55 – 7.51 (m, 4H, H-C12, H-N9), 7.42 – 7.40 (m, 3H, H-C13, H-C14), 6.70 (s, 2H, H-N10), 5.69 (s, 1H, H-C6). **^{13}C NMR** (100.5 MHz, DMSO-d_6) δ (ppm): 162.5 (C8a), 162.2 (C7), 160.9 (C2), 157.3 (C4), 150.6 (C5), 138.6 (C11), 129.1 (C12), 129.0 (C14), 127.6 (C13), 114.5 (C6), 89.4 (C4a). Spectroscopic data are consistent with those reported in the literature[4].

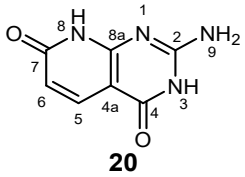
4-amino-8-methyl-2-(phenylamino)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (14)



14

4-amino-8-methyl-2-(phenylamino)-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**13**) (50 mg, 0.186 mmol) is dissolved in 2 mL of DMSO in a glass vial. The vial is bubbled with dry air and irradiated at 365 nm for 2 h with a Penn PhD Photoreactor M2. % LED: 100; stirrer 400 rpm; distance led – vial: 2 cm. Then, about 50 mL of brine is added and the solid is filtered, washed with water and dried to afford 40.4 mg (0.152 mmol, 82%) of spectroscopically pure of **14** as a yellow powder, mp (°C): 184 – 187 (decomp.). **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm): 9.30 (s, 1H, H-N10), 8.01 (d, J = 9.5 Hz, 1H, H-C5), 7.86 – 7.77 (m, 2H, H-C12), 7.42 – 7.24 (m, 4H, H-N9, H-C13), 6.97 – 6.92 (m, 1H, H-C14), 6.16 (d, J = 9.5 Hz, 1H, H-C6), 3.53 (s, 3H, H-C15). **^{13}C NMR** (100.5 MHz, DMSO-d_6) δ (ppm): 162.8 (C7), 161.5 (C4), 158.9 (C2), 156.1 (C8a), 140.5 (C11), 133.4 (C5), 128.4 (C13), 121.5 (C14), 119.4 (C12), 112.6 (C6), 91.9 (C4a), 27.8 (C15). **IR** (ATR) ν_{max} (cm^{-1}): 3196, 1631, 1607, 1516, 1444, 1358, 1140, 795, 745, 688. **HRMS** (APCI-FIA-QTOF) (m/z): calculated for $C_{14}H_{14}N_5O$ $[M+H]^+$: 268.1198; found: 268.1195.

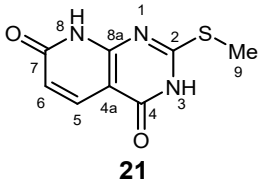
2-aminopyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (20)



20

2-amino-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (**16**) (25 mg, 0.139 mmol) is dissolved in 2 mL of DMSO in a glass vial. The vial is bubbled with dry air and irradiated at 365 nm for 1.5 h with a Penn PhD Photoreactor M2. % LED: 100; stirrer 400 rpm; distance led – vial: 2 cm. After addition of brine (50 mL) the yellow solid appeared can be isolated by filtration, washed with water and dried under vacuum to afford 10.2 mg (0.057 mmol, 41%) of spectroscopically pure **20** as a yellow powder. **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm): 11.64 (s, 1H, H-N3*), 10.90 (s, 1H, H-N8*), 7.68 (d, J = 9.3 Hz, 1H, H-C5), 6.96 (s, 2H, H-N9), 5.93 (d, J = 9.3 Hz, 1H, H-C6). **^{13}C NMR** (100.5 MHz, DMSO-d_6) δ (ppm): 164.0 (C4), 160.0 (C7), 157.0 (C8a), 155.4 (C2), 136.6 (C5), 113.0 (C6), 95.3 (C4a). Spectroscopic data are consistent with those reported in the literature.[5]

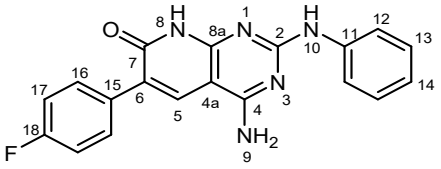
2-(methylthio)pyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (21)



21

2-(methylthio)-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (**17**) (25 mg, 0.118 mmol) is dissolved in 2 mL of DMSO in a glass vial. The vial is bubbled with dry air and irradiated at 365 nm for 5 h with a Penn PhD Photoreactor M2. % LED: 100; stirrer 400 rpm; distance led – vial: 2 cm. Then, about 25 mL of brine is added and the solid is filtered, washed with water and dried to afford 14.2 mg (0.068 mmol, 57%) of spectroscopically pure **21** as a yellow powder, mp (°C): >300. **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm): 12.83 (s, 1H, H-N3), 12.16 (s, 1H, H-N8), 7.79 (d, J = 9.5 Hz, 1H, H-C5), 6.24 (d, J = 9.4 Hz, 1H, H-C6), 2.55 (s, 3H, H-C9). **^{13}C NMR** (100.5 MHz, DMSO-d_6) δ (ppm): 163.3 (C2), 159.5 (C7 and C4), 153.7 (C8a), 136.1 (C5), 118.0 (C6), 99.2 (C4a), 12.9 (C9). **IR** (ATR) ν_{max} (cm^{-1}): 1624, 1521, 1410, 1357, 1264, 1181, 1103, 935, 791. **HRMS** (APCI-FIA-QTOF) (m/z): calculated for $C_8H_8N_3O_2S$ $[M+H]^+$:210.0337; found: 210.0328.

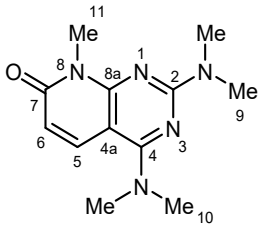
4-amino-6-(4-fluorophenyl)-2-(phenylamino)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (22)



22

4-amino-6-(4-fluorophenyl)-2-(phenylamino)-5,6-dihydropyrido[2,3-d]pyrimidin-7(8*H*)-one (**18**) (25 mg, 0.072 mmol) is dissolved in 2 mL of DMSO in a glass vial. The vial is bubbled with dry air and irradiated at 365 nm for 10 h with a Penn PhD Photoreactor M2. % LED: 100; stirrer 400; distance led – vial: 2 cm. Then, about 25 mL of brine is added, the solid is filtered and washed with water to afford 13.1 mg (0.038 mmol, 53%) of spectroscopically pure of **22** as a yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 11.76 (s, 1H, H-N8), 9.20 (s, 1H, H-N10), 8.29 (s, 1H, H-C5), 7.94 – 7.87 (m, 2H, H-C12), 7.85 – 7.75 (m, 2H, H-C16), 7.35 (br s, 2H, H-N9), 7.26 – 7.21 (m, 2H, H-C13), 7.20 – 7.10 (m, 4H, H-C17), 6.94 – 6.91 (m, 1H, H-C14).**^{13}C NMR** (100.5 MHz, $CDCl_3$) δ (ppm): 162.6 (C7), 161.1 (C4), 161.0 (d, J = 243.2 Hz, H-C18), 159.3 (C2), 155.3 (C8a), 140.7 (C11), 133.0 (d, J = 18.1 Hz, C15), 130.3 (d, J = 7.8 Hz, H-C16), 128.4 (C13), 123.0 (C6), 121.3 (C14), 119.4 (C12), 114.6 (d, J = 21.1 Hz, H-C17), 92.0 (C4a). **^{19}F NMR** (376 MHz, DMSO-d_6) δ (ppm): -115.24 – -115.32 (m, 1F). **IR** (ATR) ν_{max} (cm^{-1}): 3058, 1632, 1563, 1531, 1499, 1440, 1313, 1224, 1158, 1024, 1003, 838, 754, 691. **HRMS** (APCI-FIA-QTOF) (m/z): calculated for $C_{19}H_{15}FN_5O$ $[M+H]^+$: 348.1261; found: 348.1203.

2,4-bis(dimethylamino)-8-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (23)



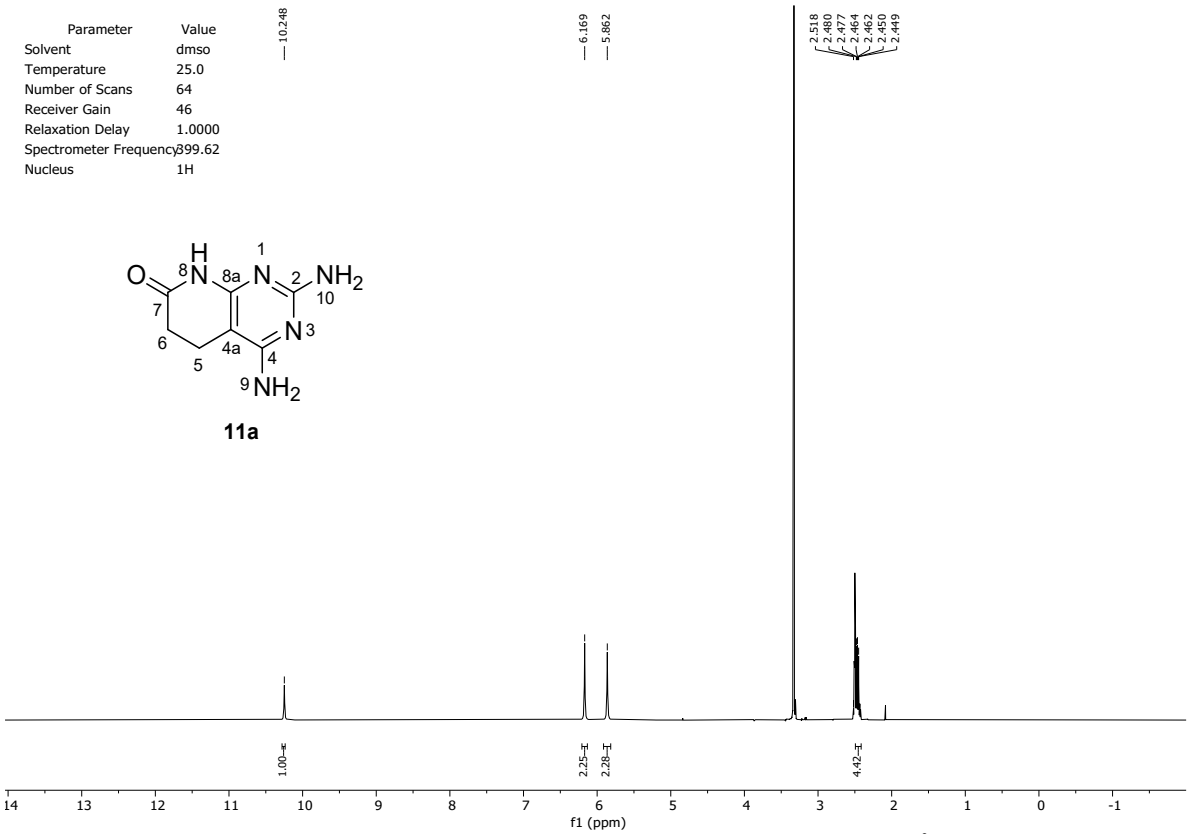
23

4-amino-8-methyl-2-(phenylamino)-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**19**) (25 mg, 0.100 mmol) is dissolved in 2 mL of DMSO in a glass vial. The vial is bubbled with dry air and

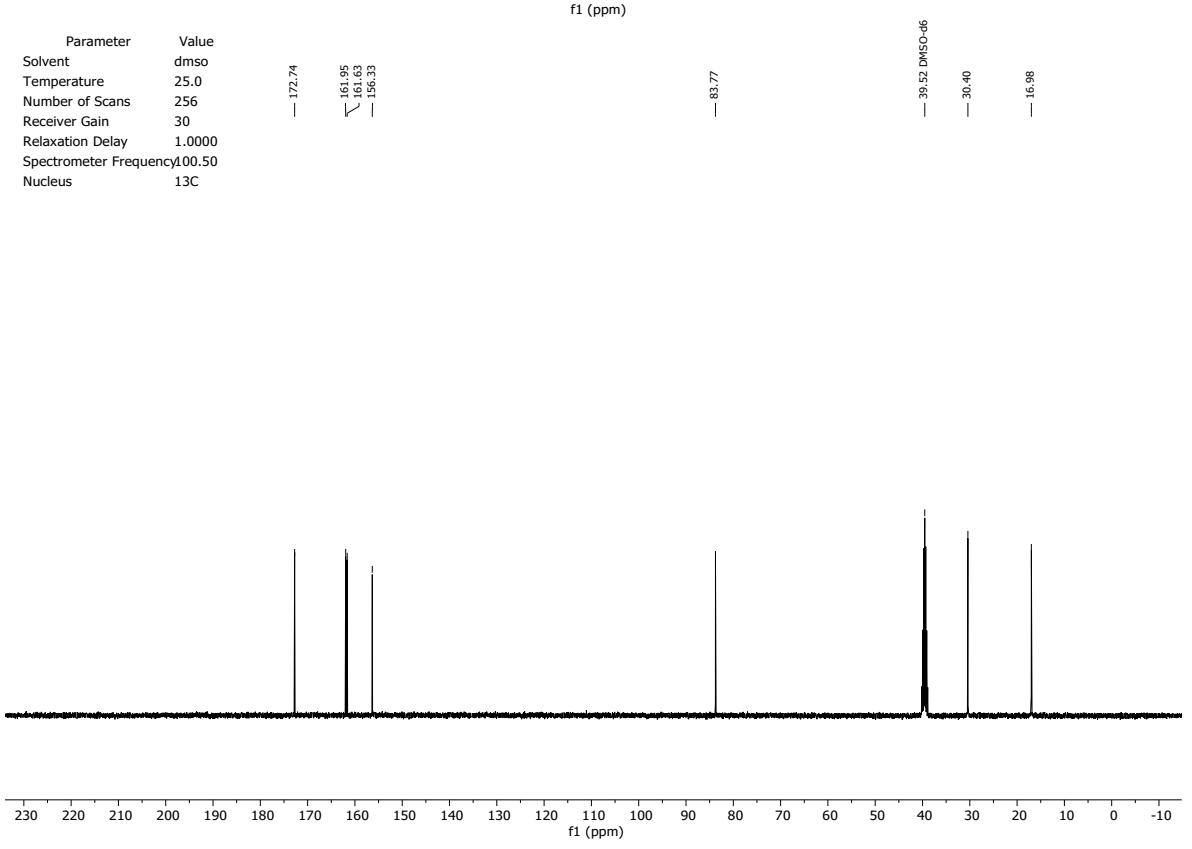
irradiated at 365 nm for 1 h with a Penn PhD Photoreactor M2. % LED: 100; stirrer 400 rpm; distance led – vial: 2 cm. Then, 25 mL of brine is added, and the product is extract with dichloromethane (20 mL x3) and washed with water (20 mL x3). The solvent is eliminated under vacuum to afford 13.2 mg (0.053 mmol, 53%) of spectroscopically pure **23** as a yellow powder. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 7.69 (d, *J* = 9.6 Hz, 1H, H-C5), 6.17 (d, *J* = 9.6 Hz, 1H, H-C6), 3.66 (s, 3H, H-C11), 3.20 (s, 6H, H-C9), 3.18 (s, 6H, H-C10). **^{13}C NMR** (100.5 MHz, $CDCl_3$) δ (ppm): 164.2 (C7), 164.0 (C4), 160.0 (C2), 158.2 (C8a), 135.4 (C5), 111.2 (C6), 92.8 (C4a), 41.7 (C10), 36.9 (C9), 28.4 (C11). **IR** (ATR) ν_{max} (cm^{-1}): 2932, 1644, 1512, 1390, 1152, 1036, 1015, 920, 794, 727. **HRMS** (APCI-FIA-QTOF) (m/z): calculated for $C_{12}H_{18}N_5O$ $[M+H]^+$:248.1511; found: 248.1498.

NMR Spectra

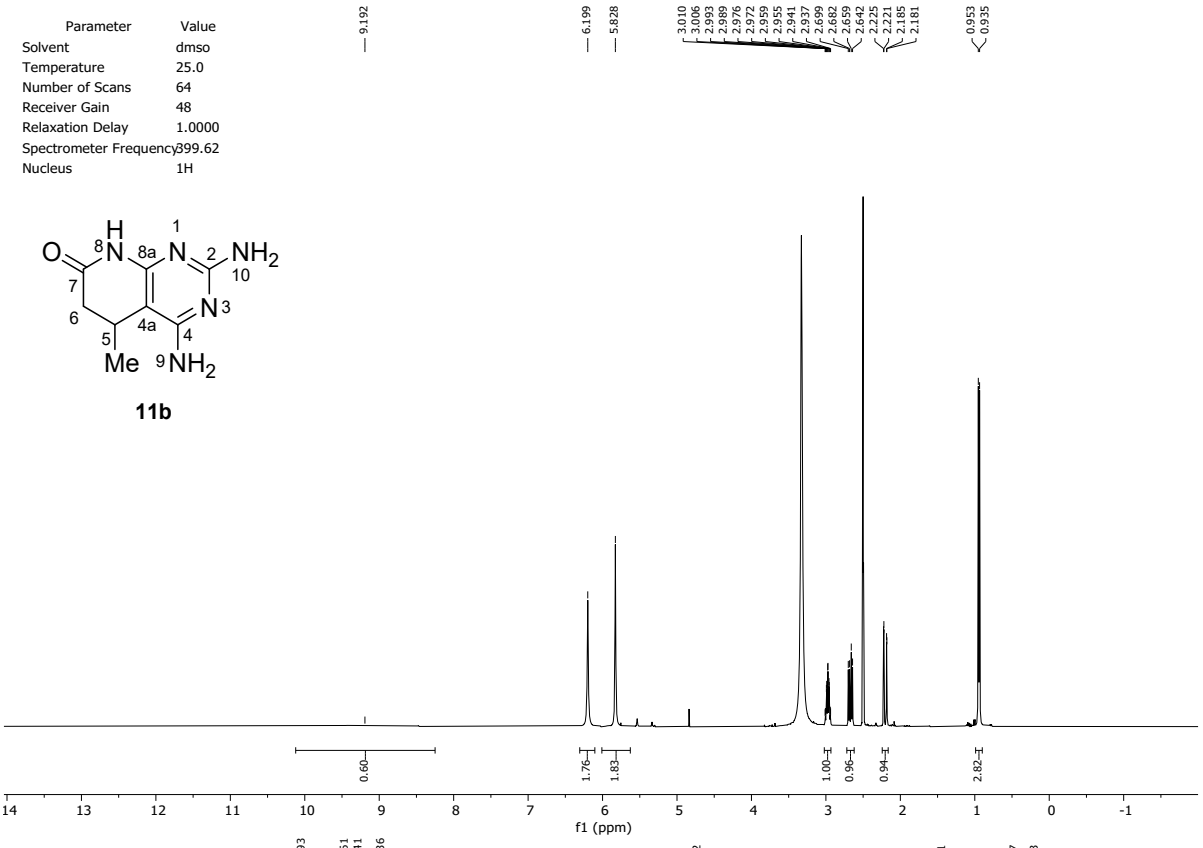
2,4-diamino-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**11a**)



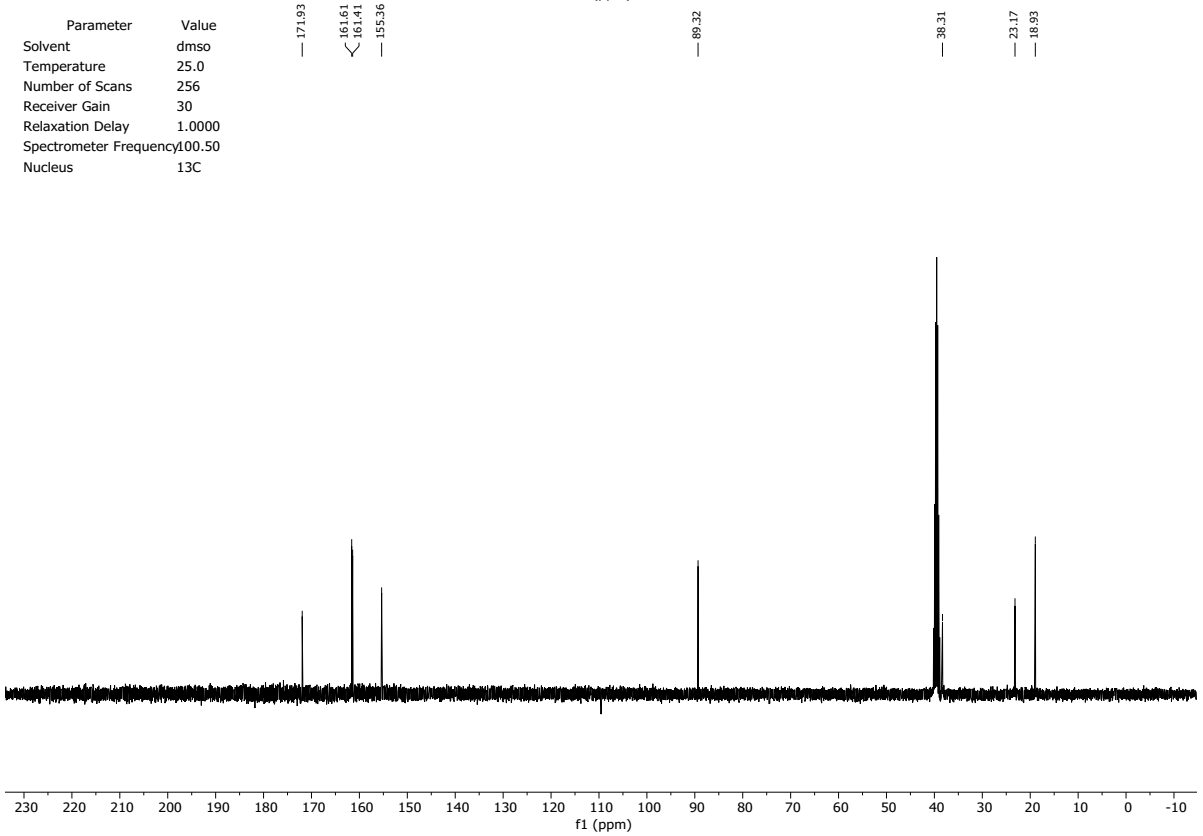
11a



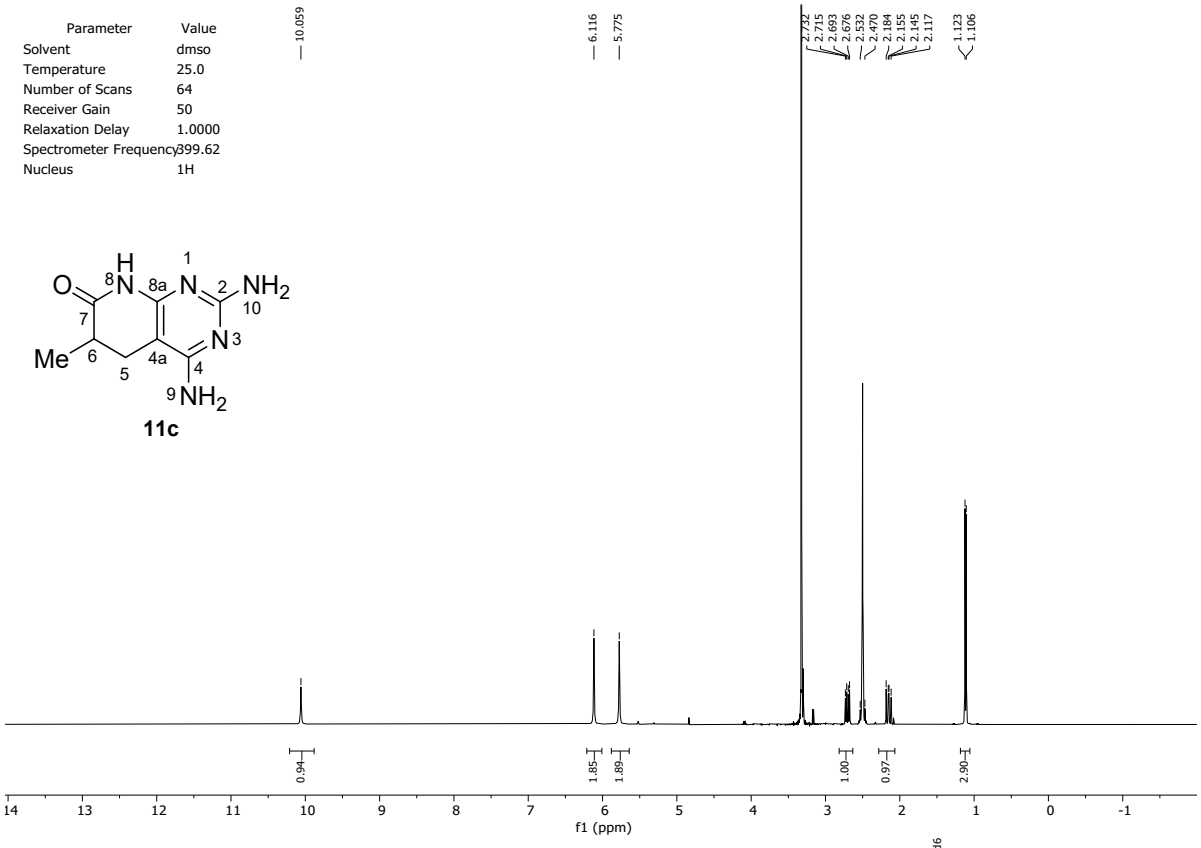
2,4-diamino-5-methyl-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**11b**)



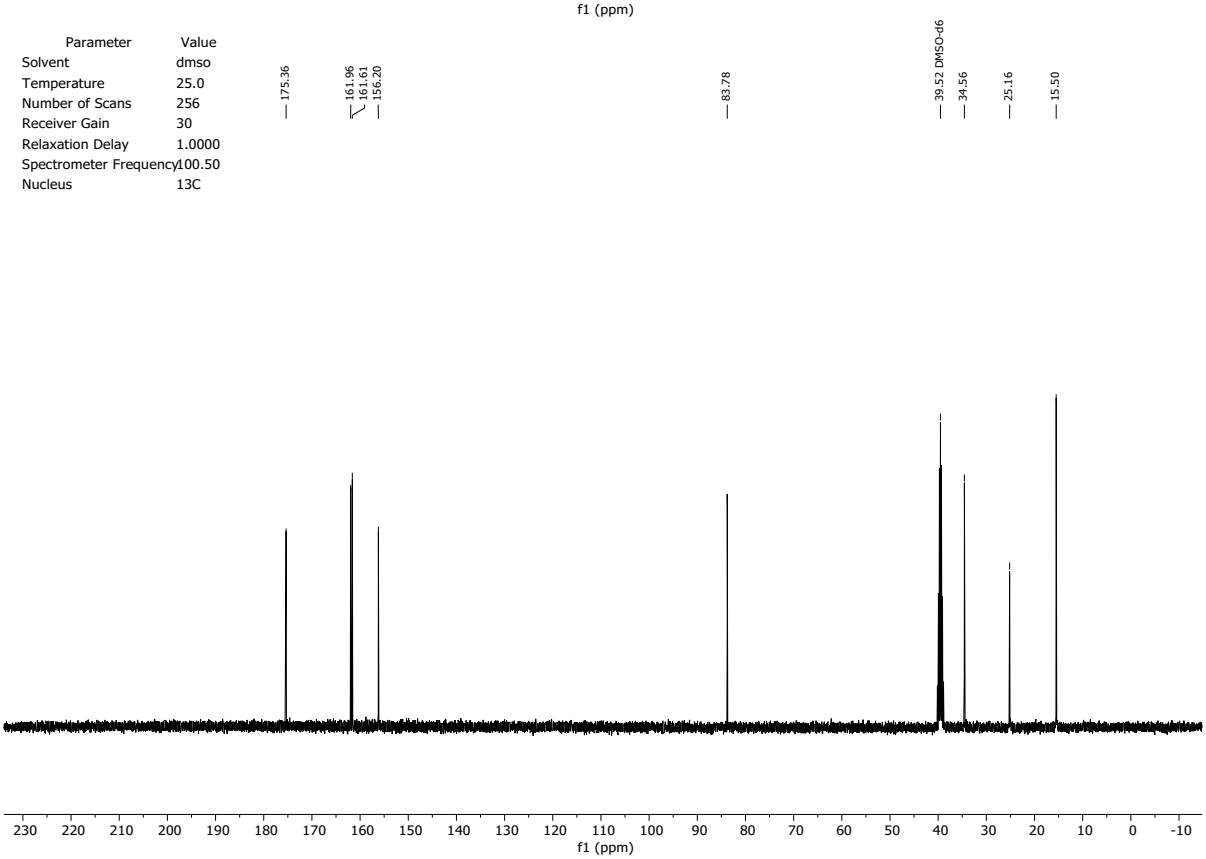
11b



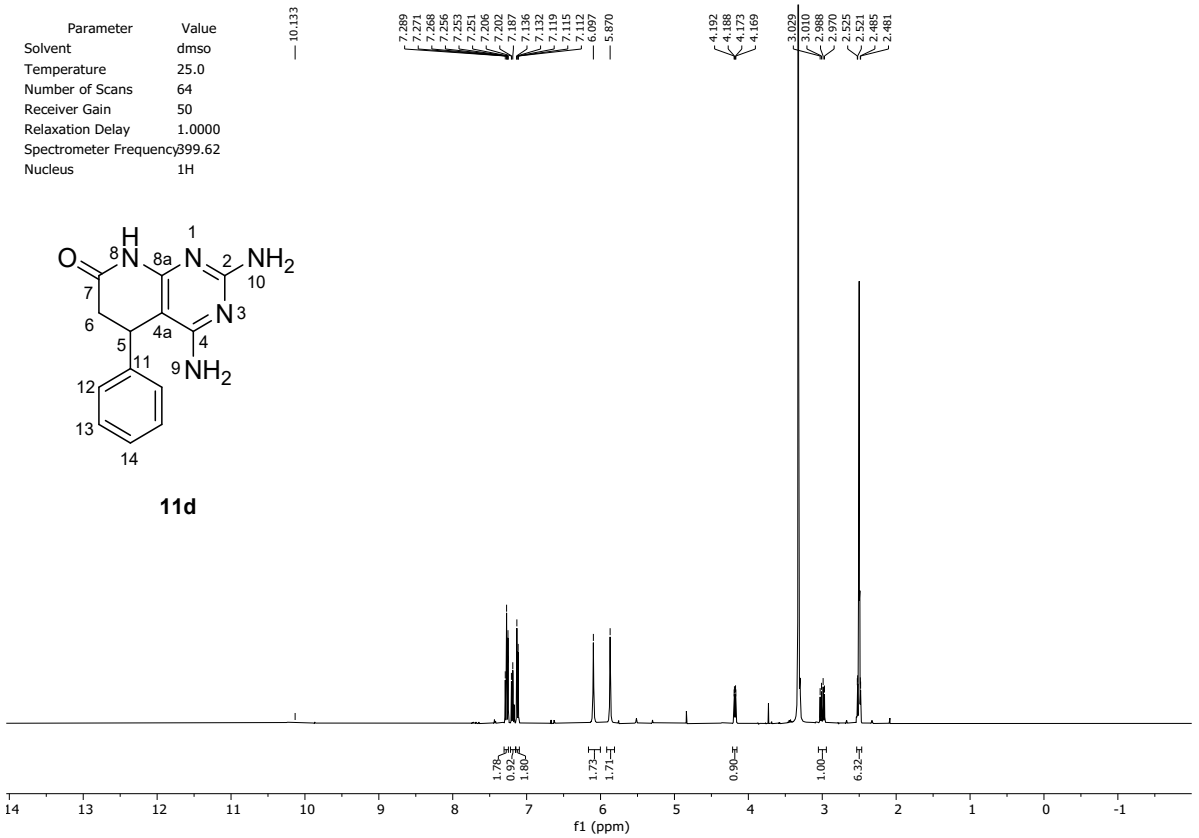
2,4-diamino-6-methyl-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**11c**)



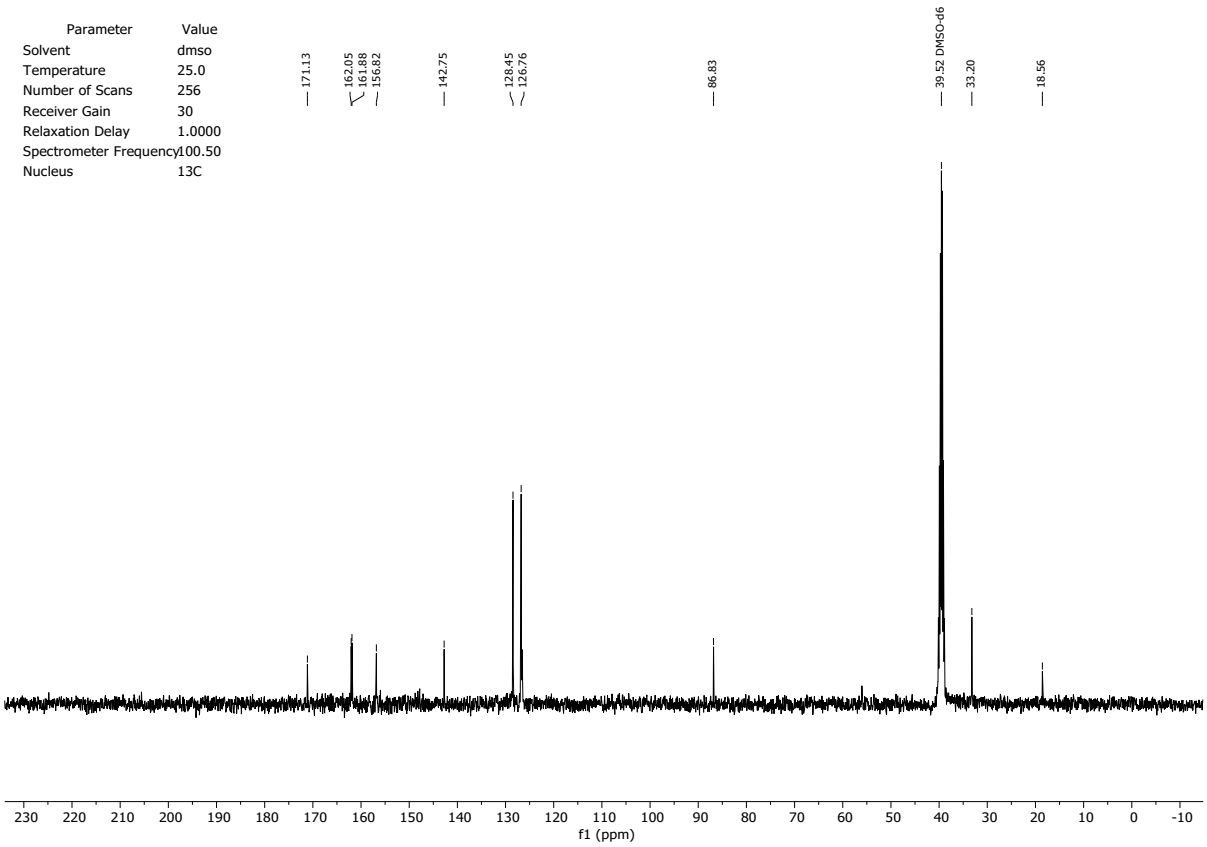
11c



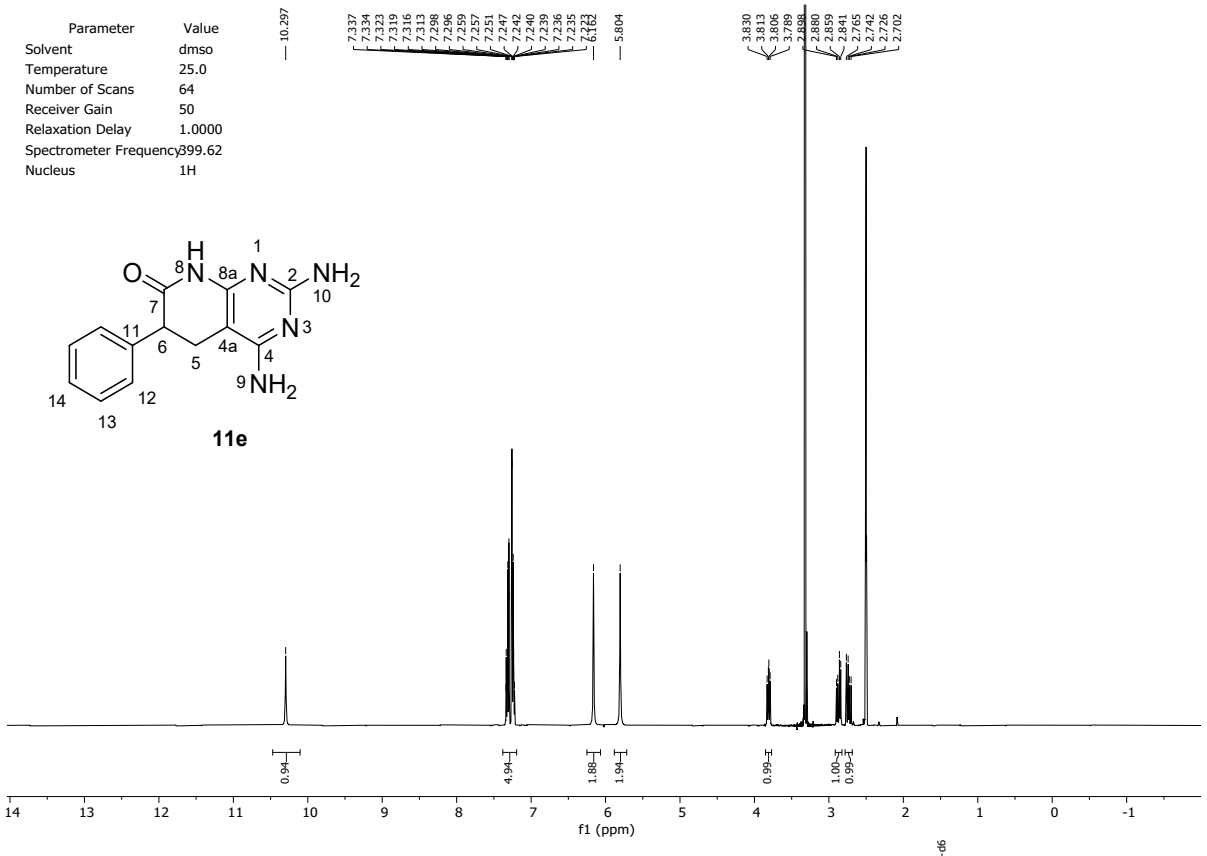
2,4-diamino-5-phenyl-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**11d**)



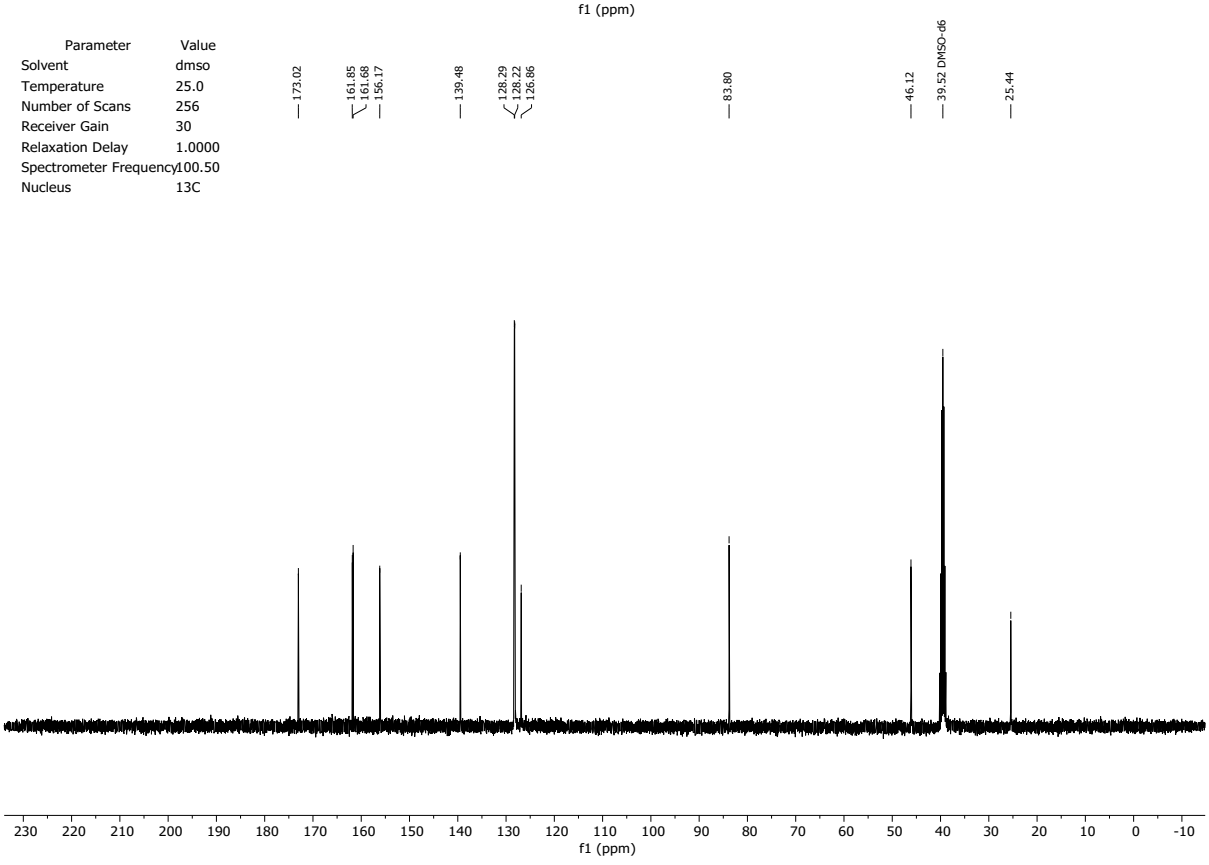
11d



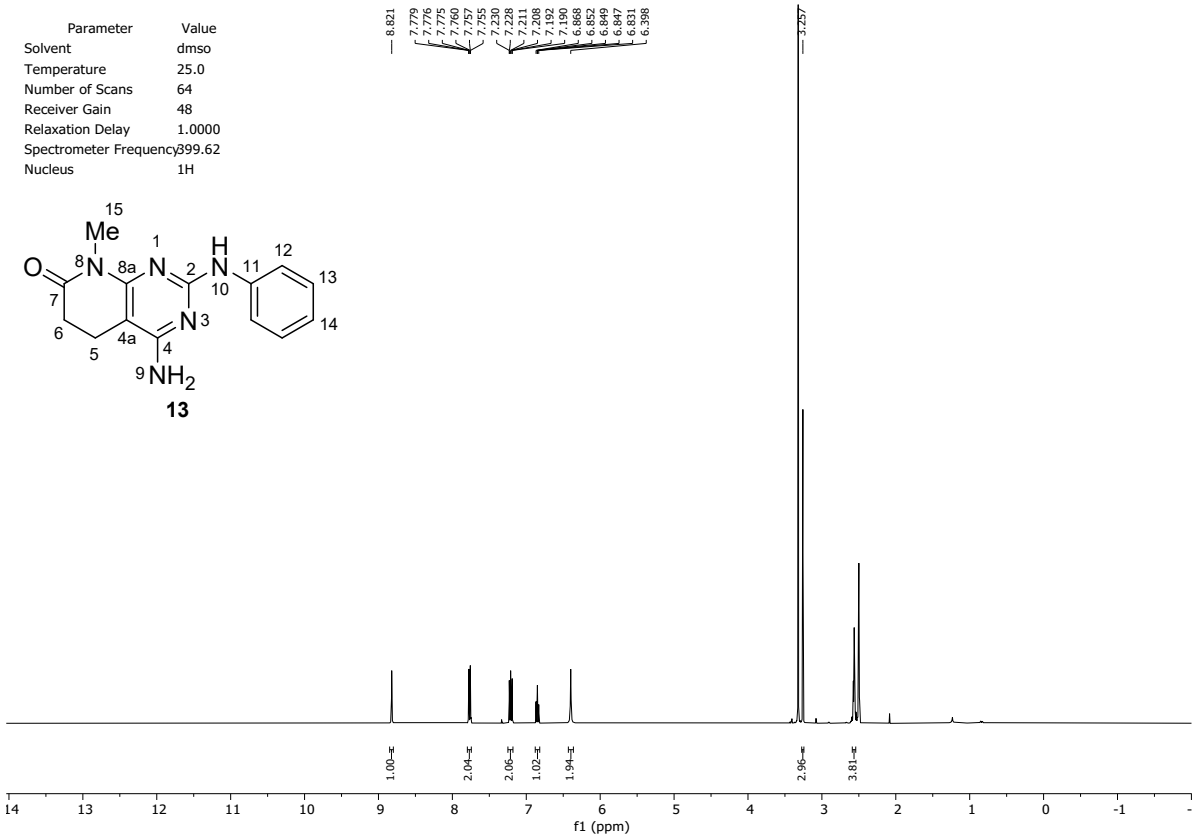
2,4-diamino-6-phenyl-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**11e**)

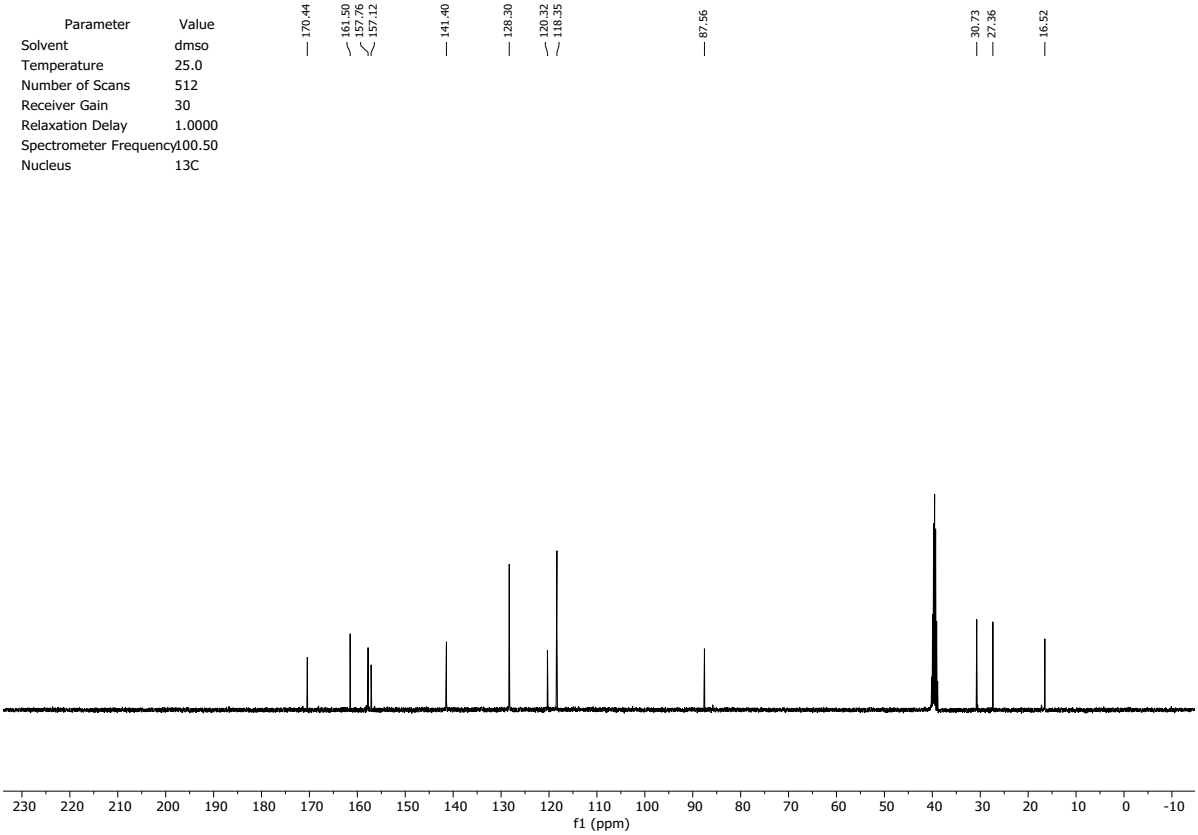


11e

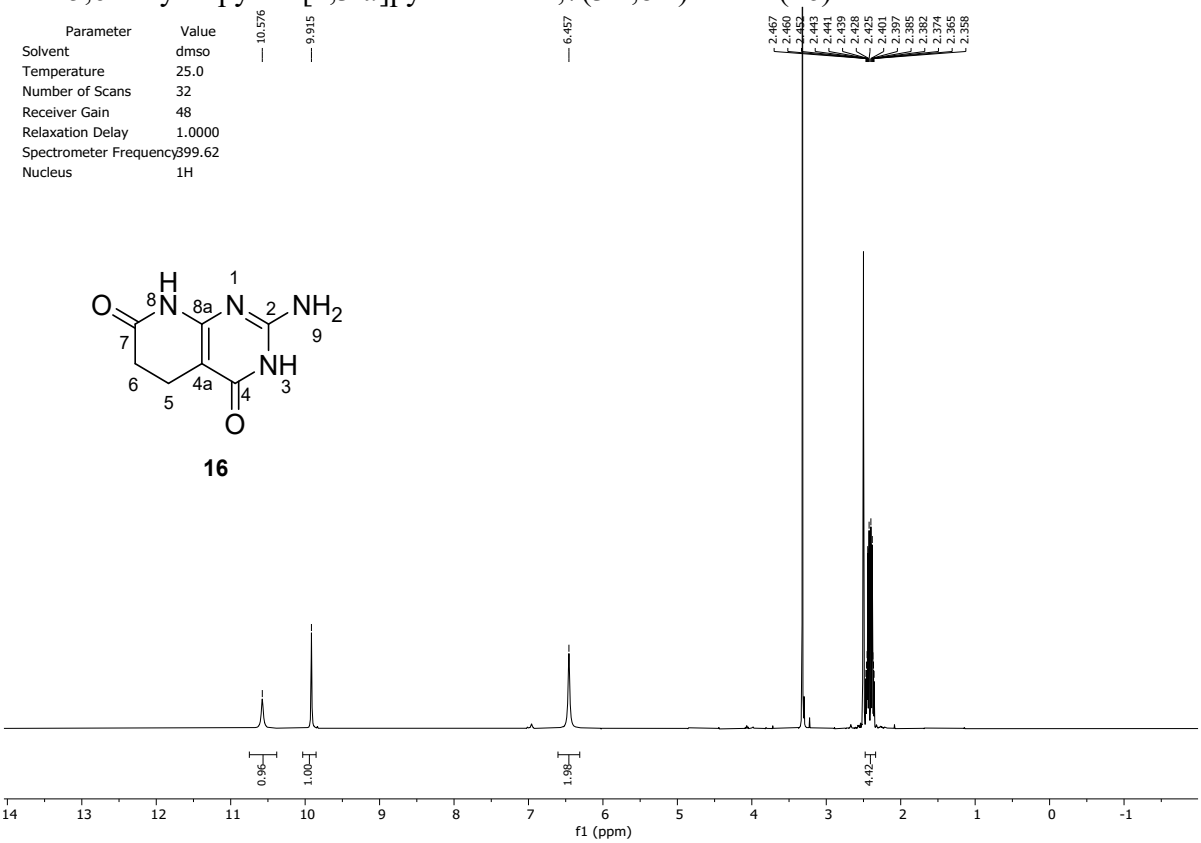


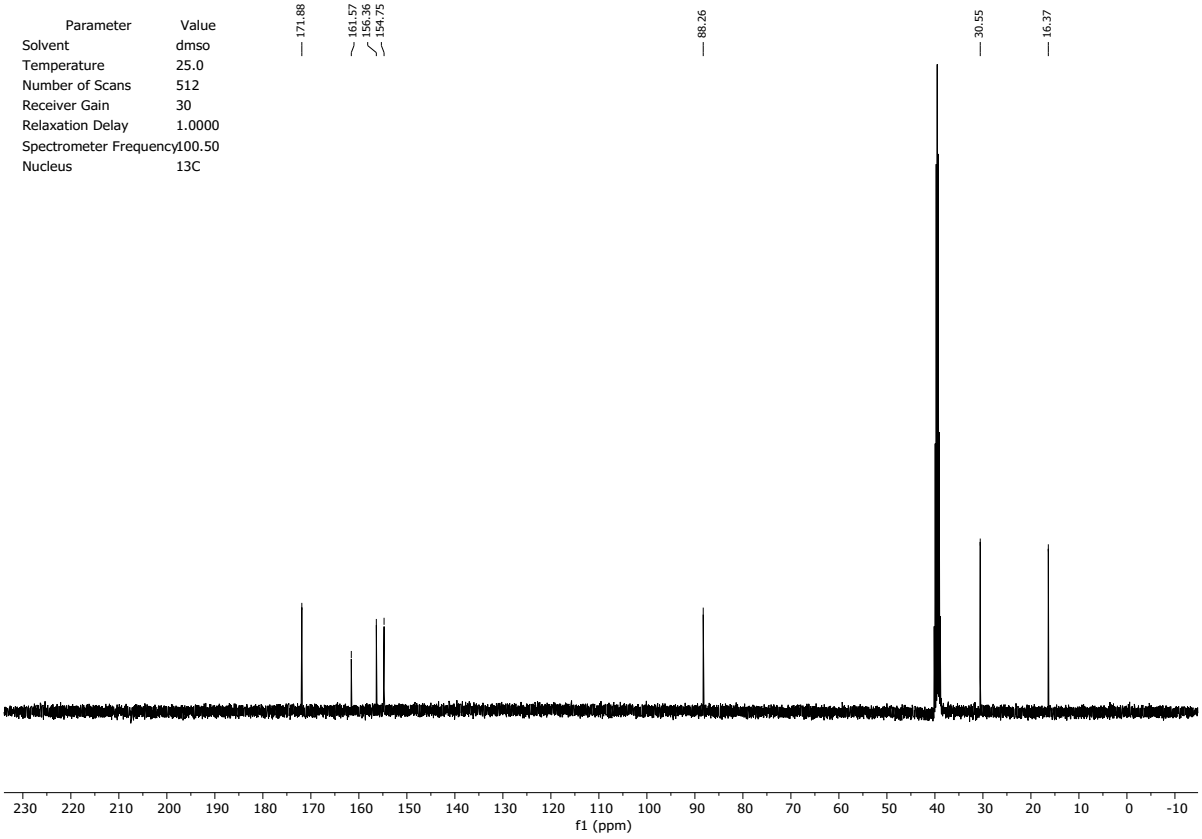
4-amino-8-methyl-2-(phenylamino)-5,8-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**13**)





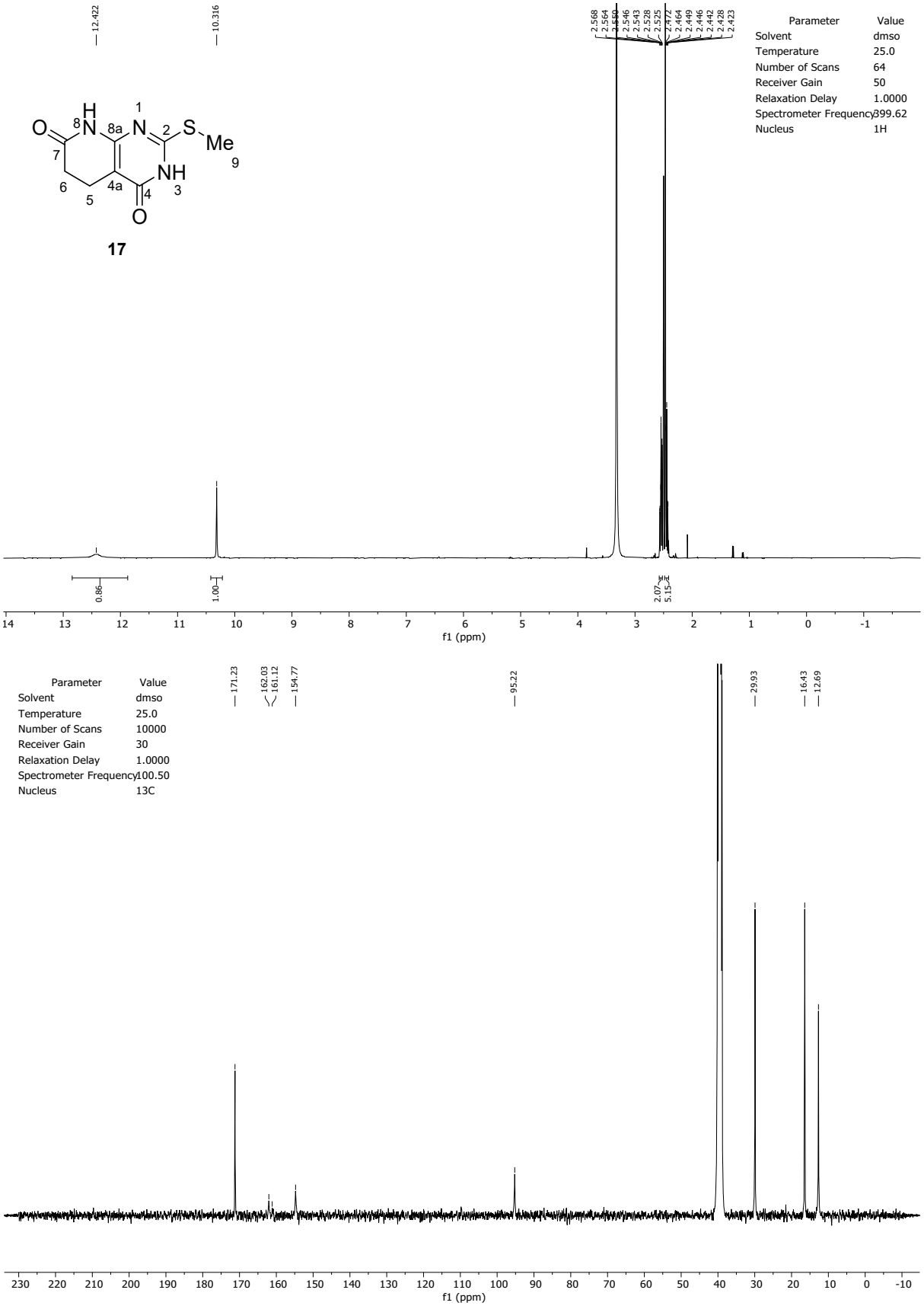
2-amino-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (**16**)





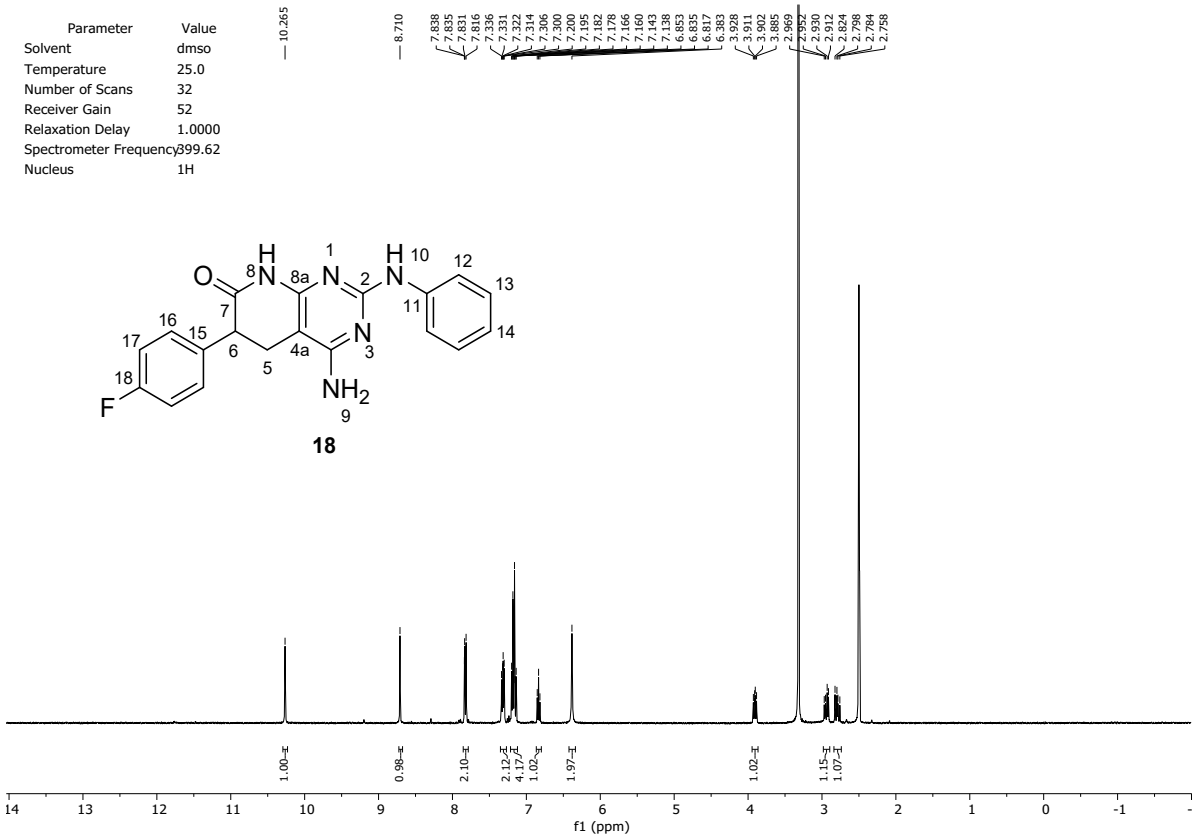
16

2-(methylthio)-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (**17**)



17

4-amino-6-(4-fluorophenyl)-2-(phenylamino)-5,6-dihydropyrido[2,3-d]pyrimidin-7(8*H*)-one (**18**)



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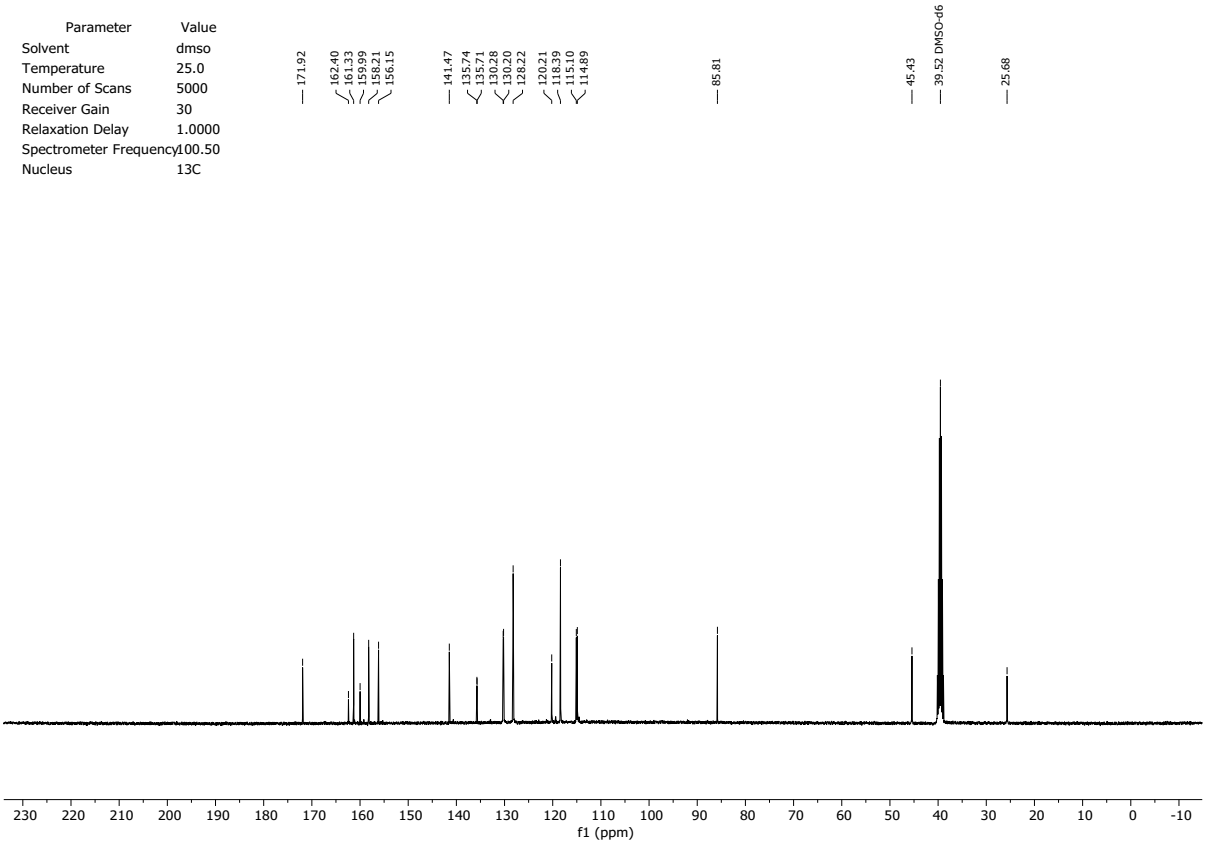
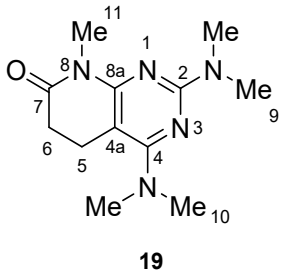


2,4-bis(dimethylamino)-8-methyl-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**19**)

Parameter	Value
Solvent	cdcl3
Temperature	25.0
Number of Scans	32
Receiver Gain	50
Relaxation Delay	1.0000
Spectrometer Frequency	399.62
Nucleus	1H



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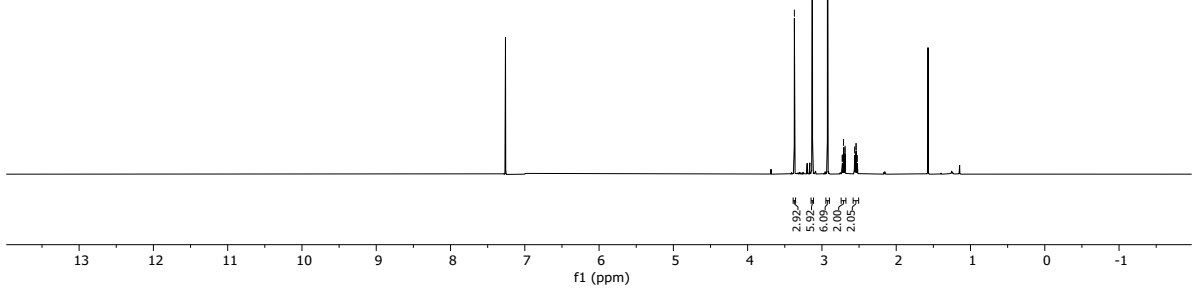
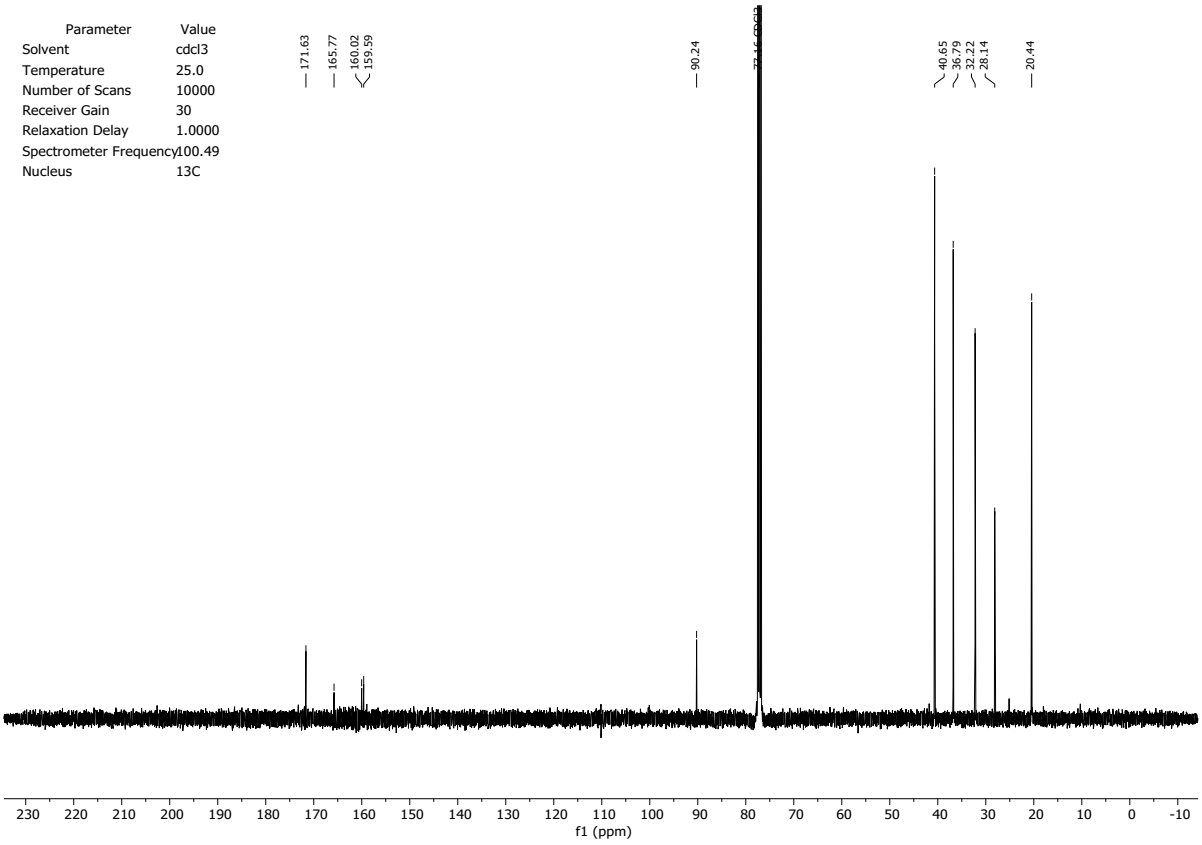
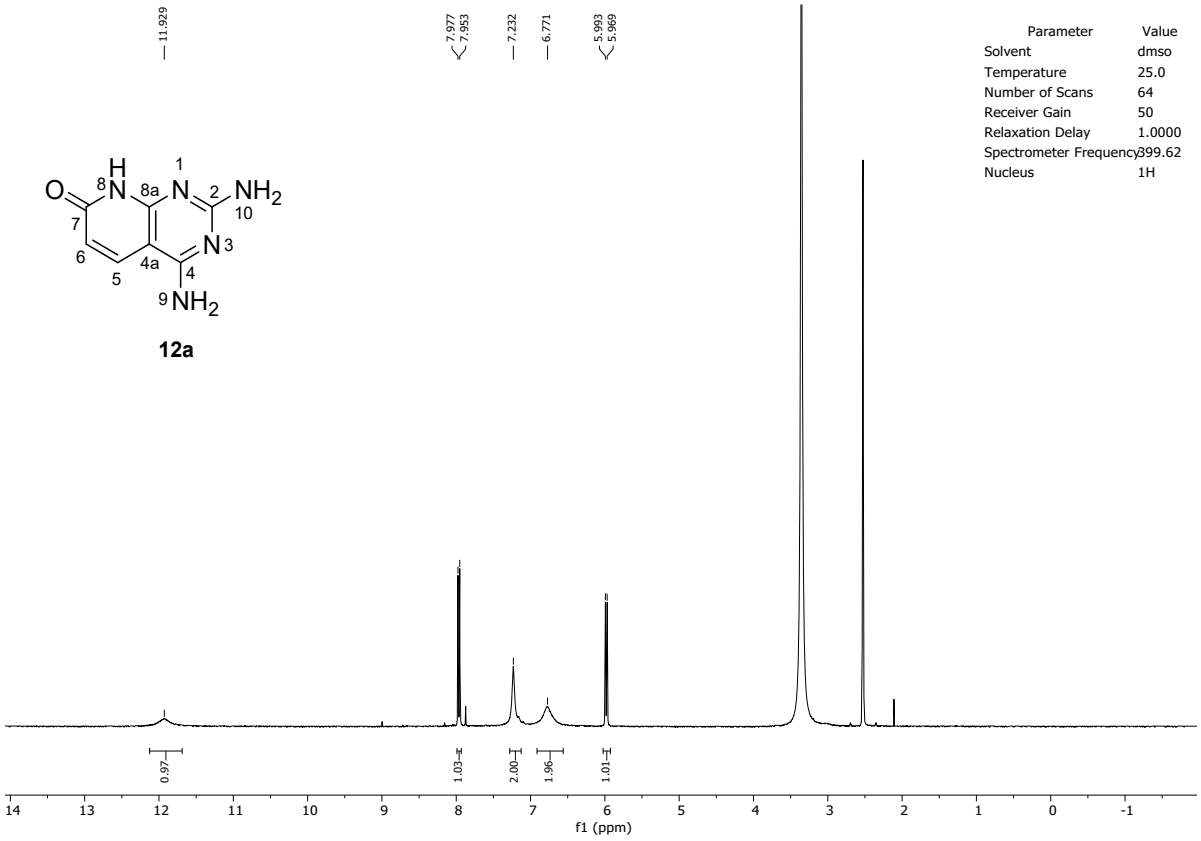


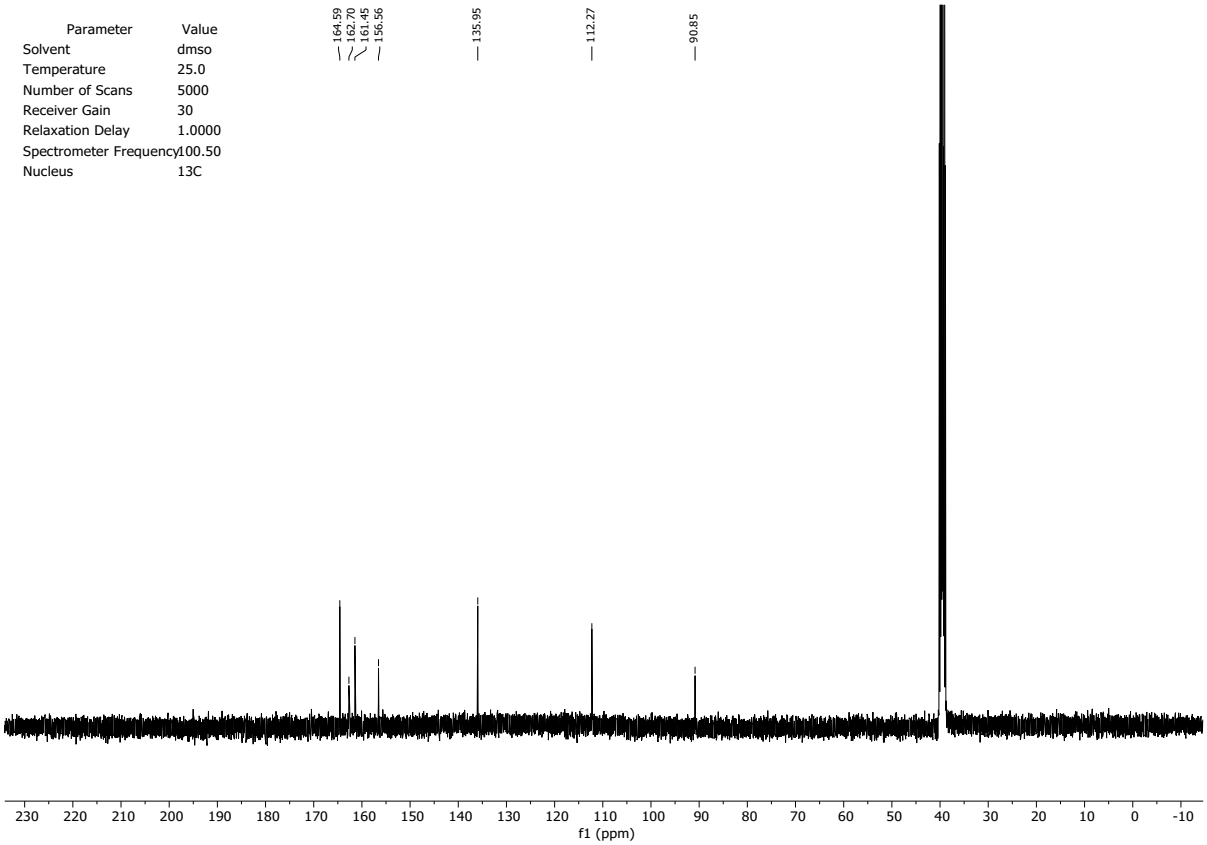
Parameter	Value
Solvent	cdcl3
Temperature	25.0
Number of Scans	10000
Receiver Gain	30
Relaxation Delay	1.0000
Spectrometer Frequency	100.49
Nucleus	13C



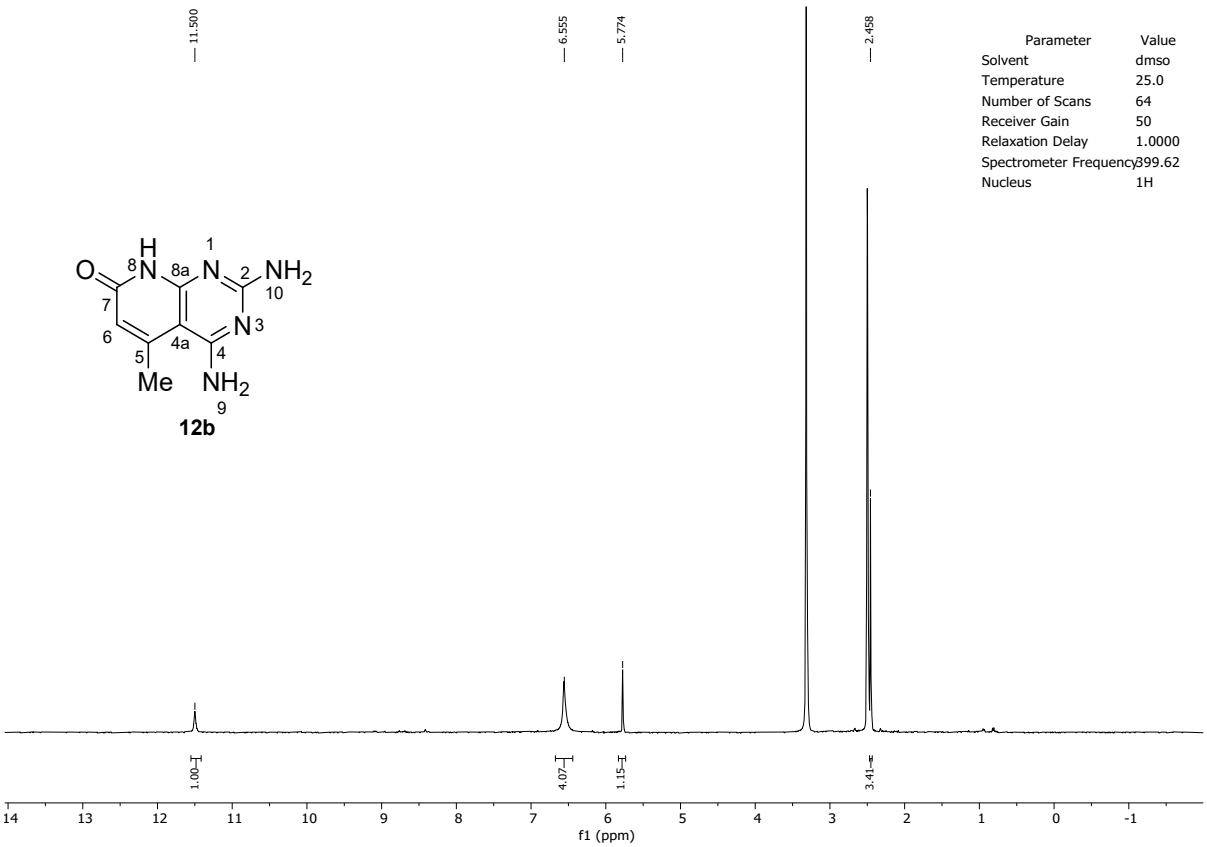
2,4-diaminopyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**12a**)

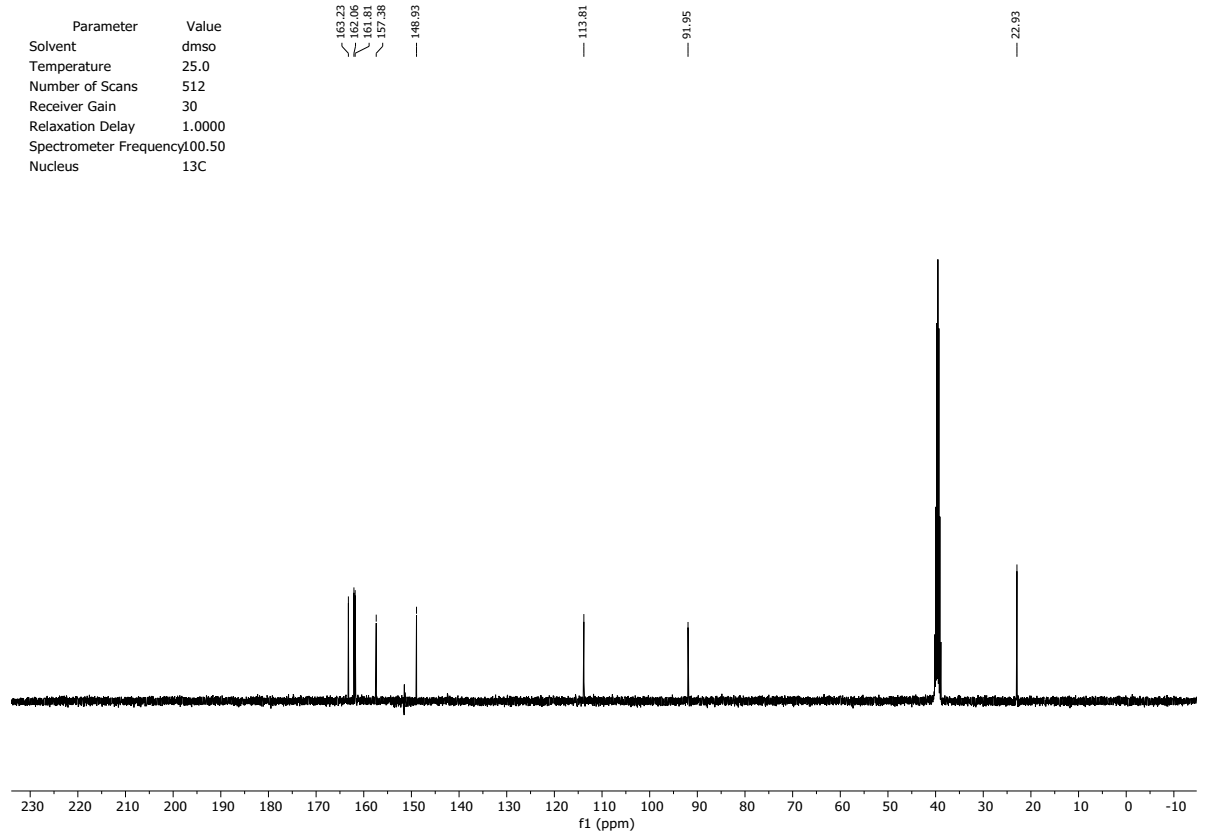


12a

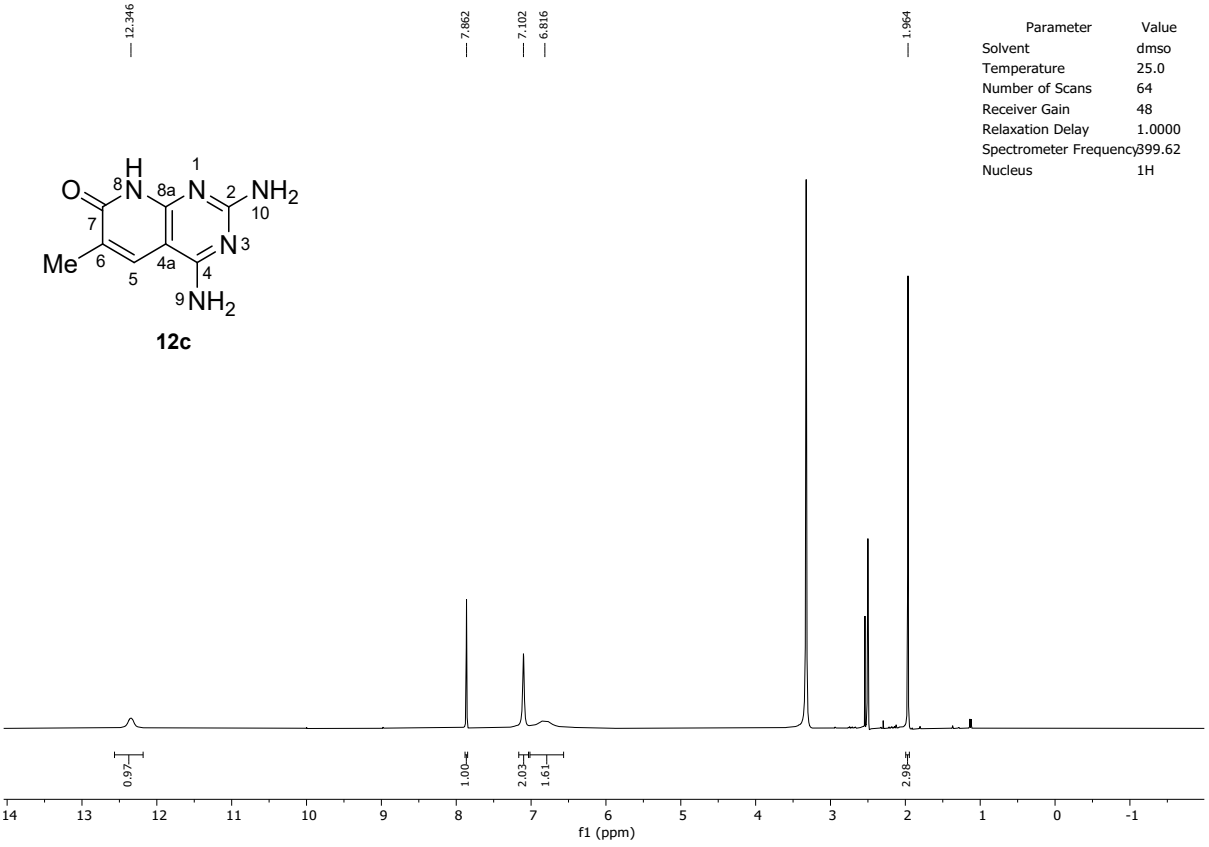


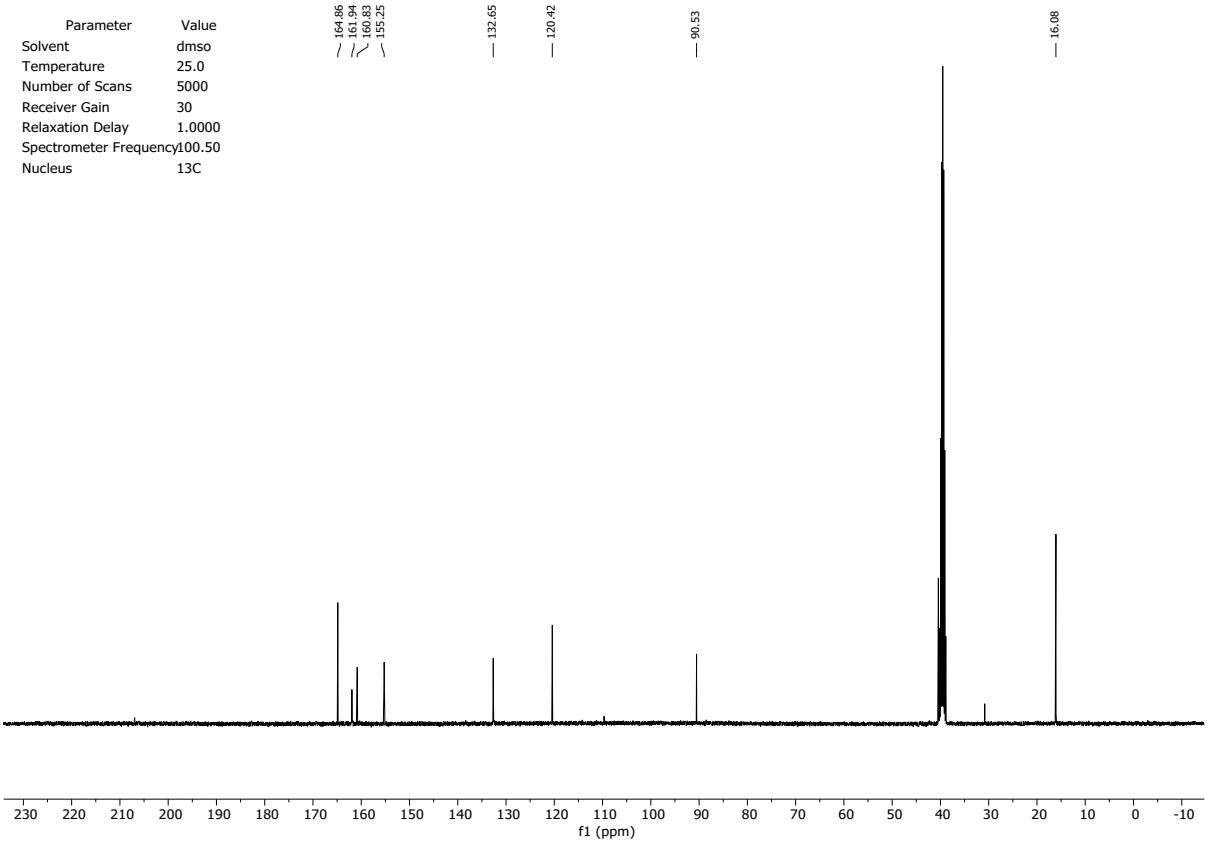
2,4-diamino-5-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**12b**)



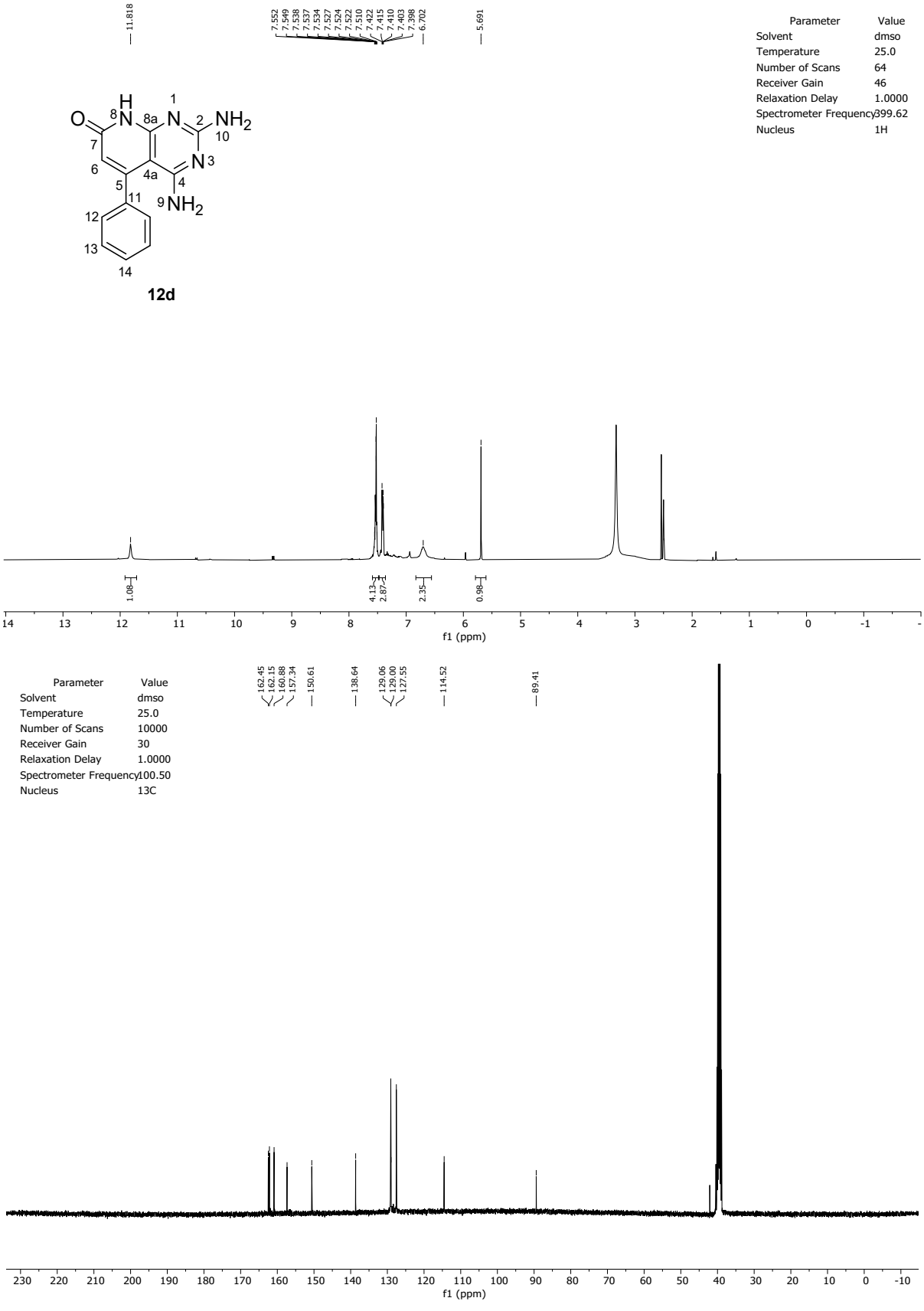


2,4-diamino-6-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**12c**)

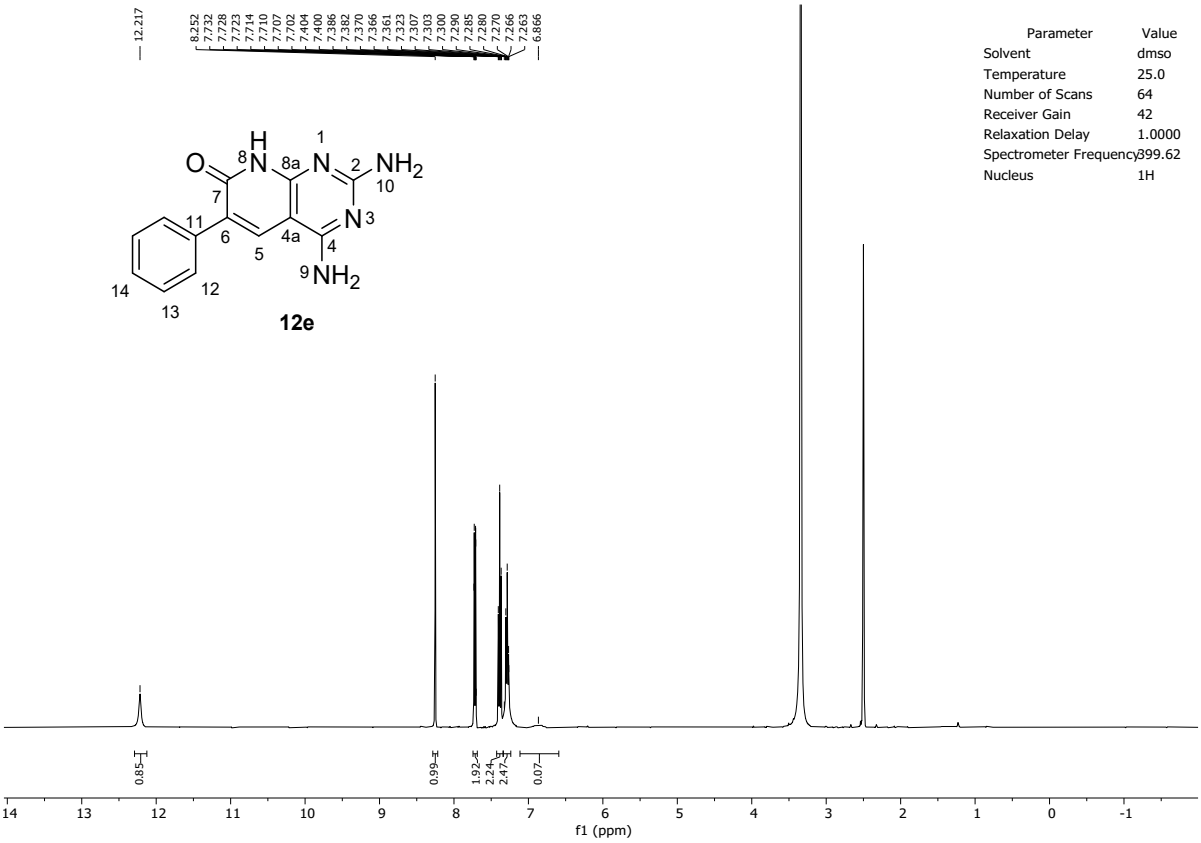


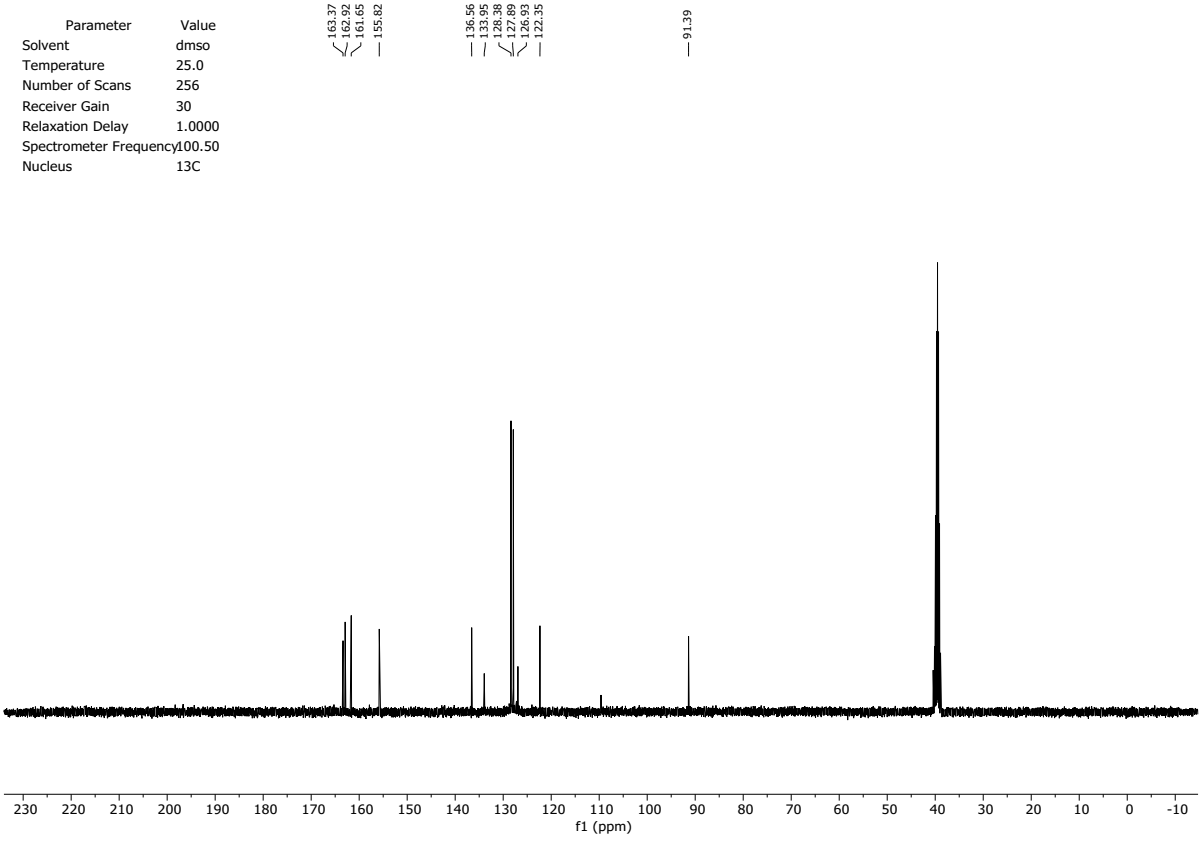


2,4-diamino-5-phenylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**12d**)

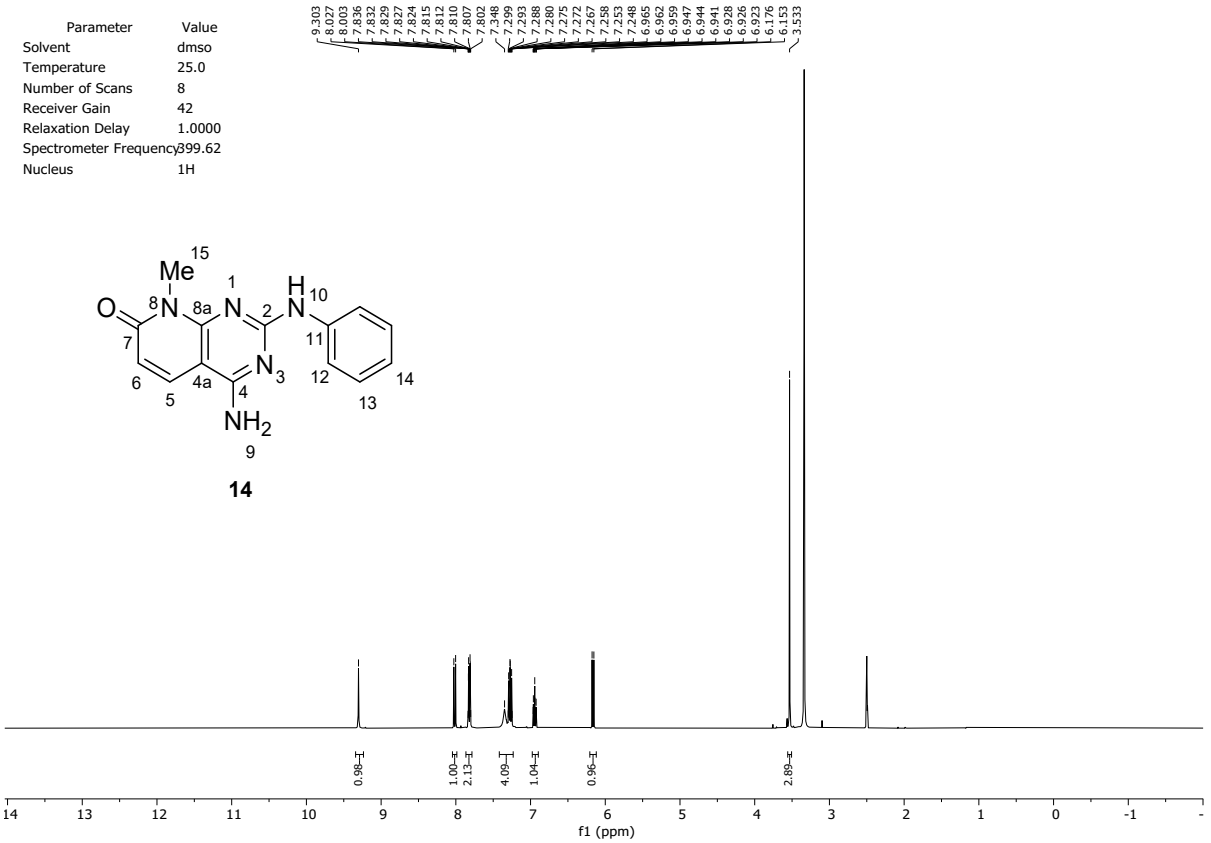


2,4-diamino-6-phenylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**12e**)

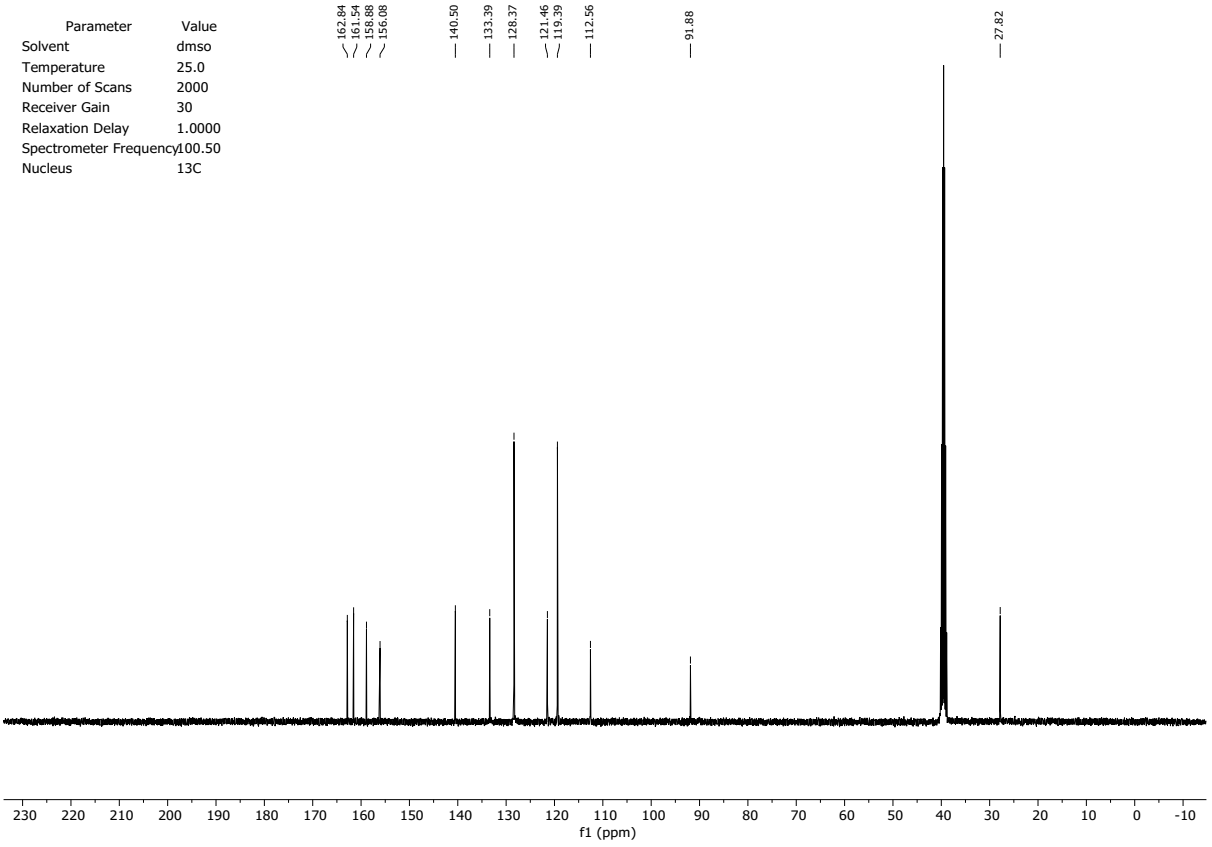




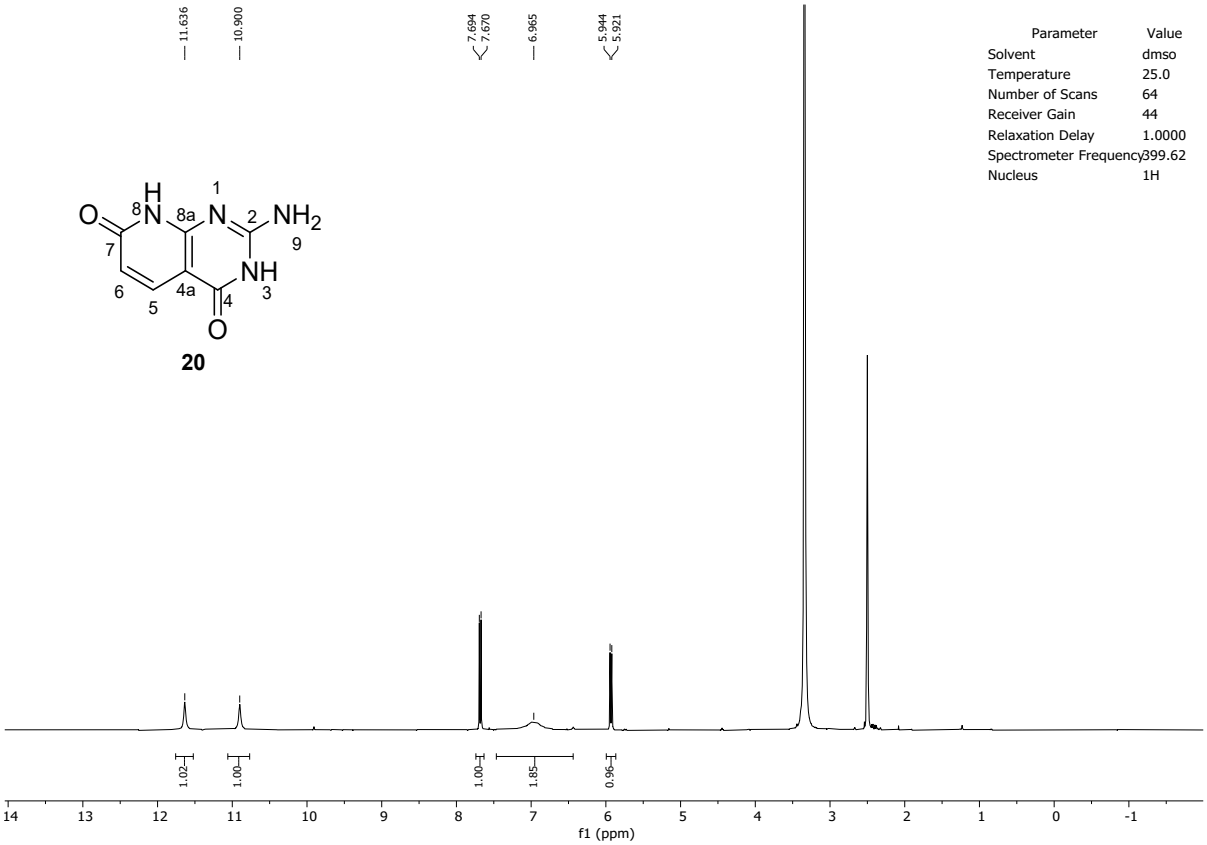
4-amino-8-methyl-2-(phenylamino)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**14**)



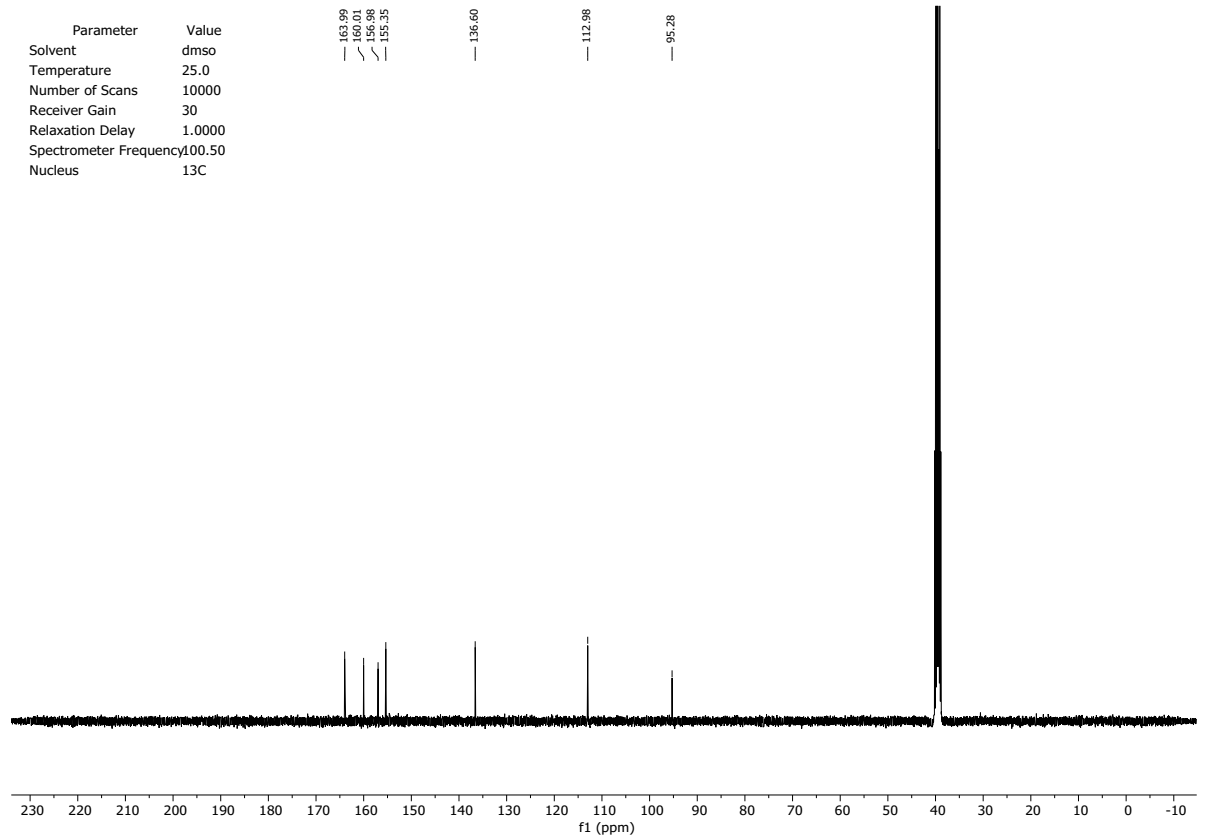
14



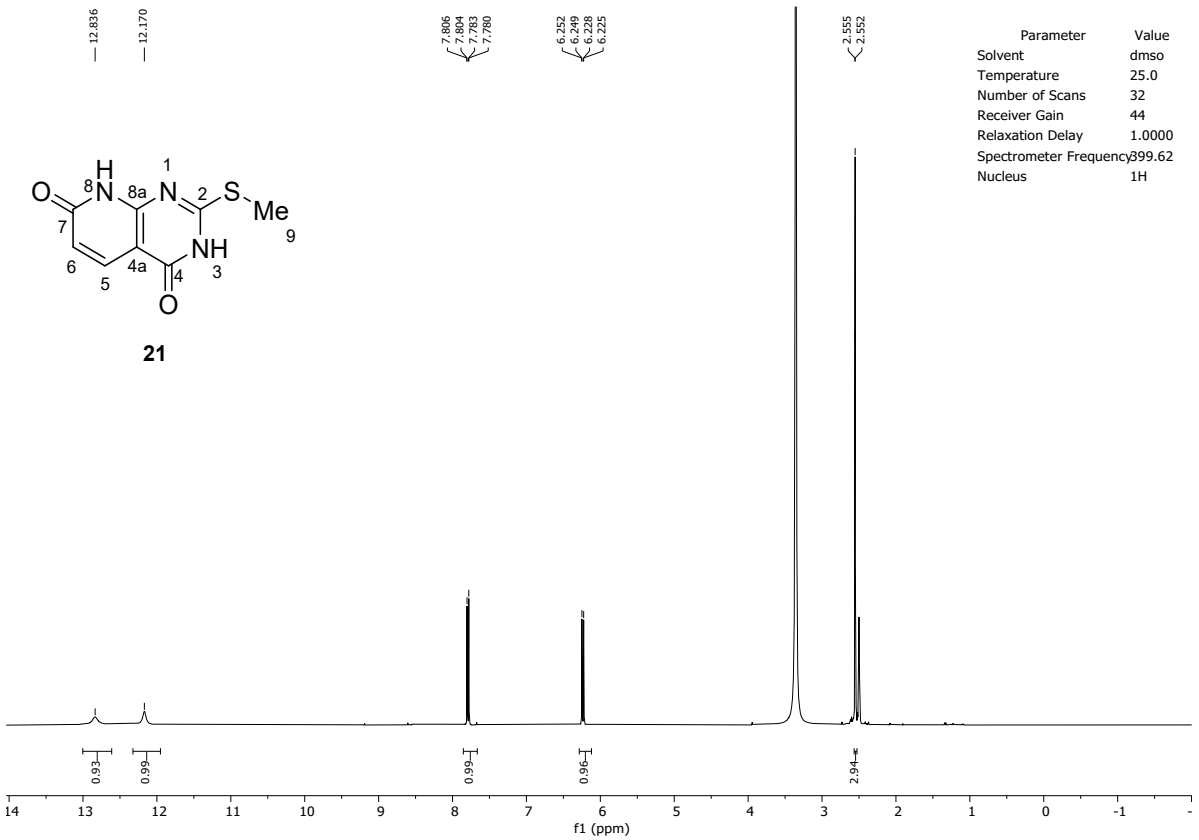
2-aminopyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (**20**)



20



2-(methylthio)pyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (**21**)



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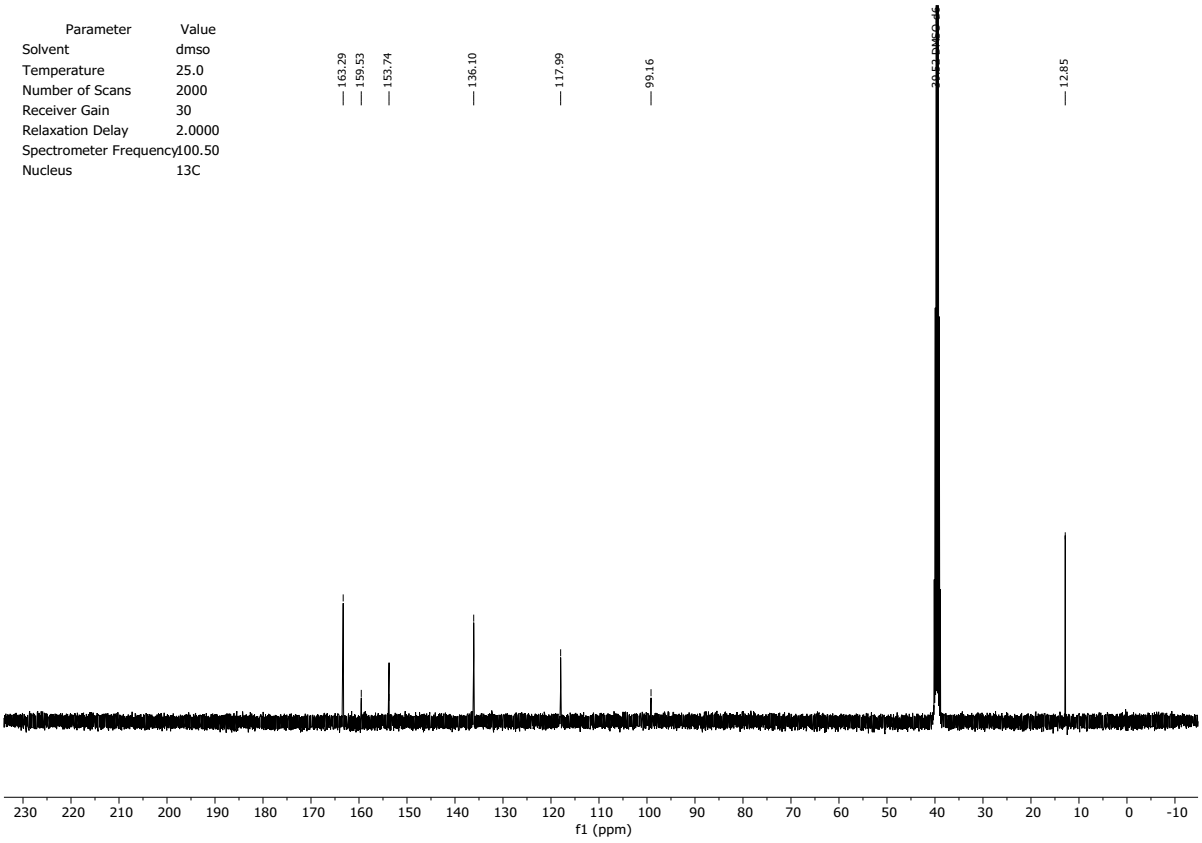
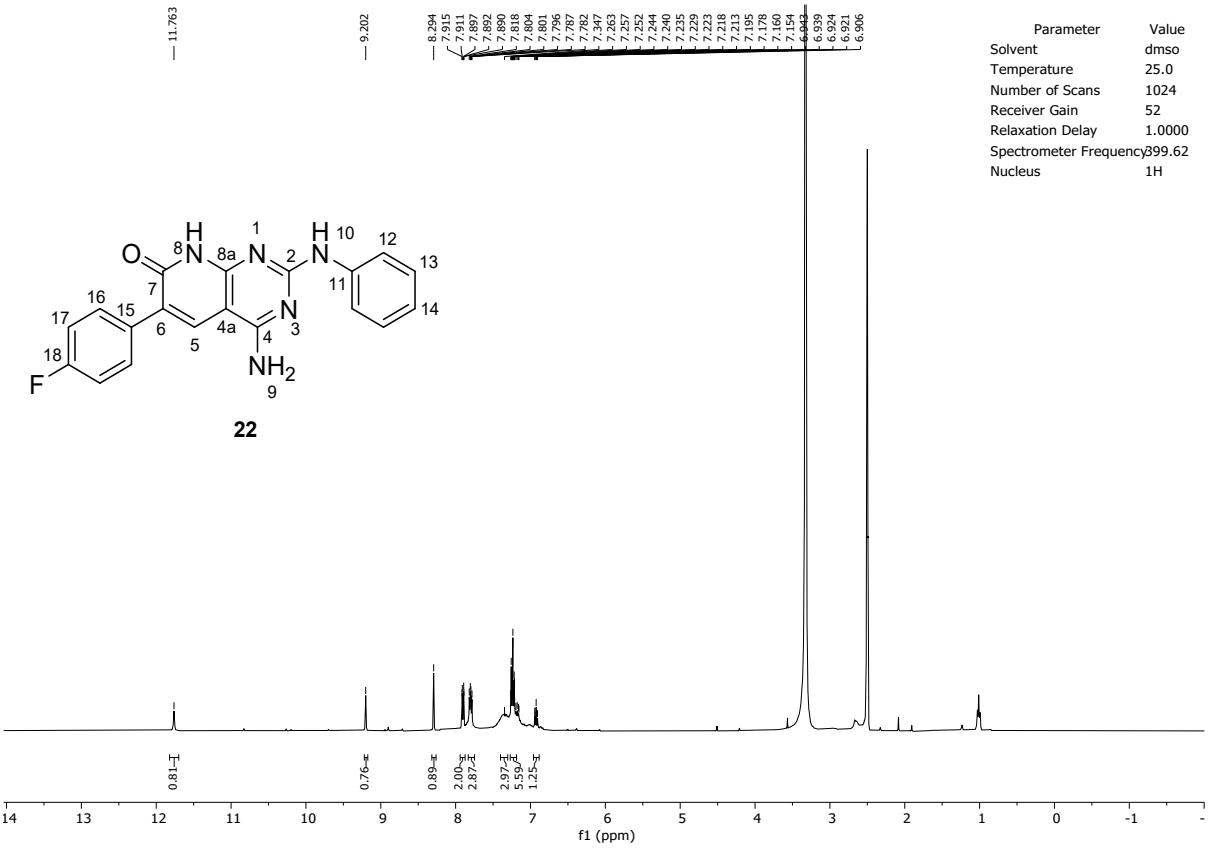


4-amino-6-(4-fluorophenyl)-2-(phenylamino)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**22**)



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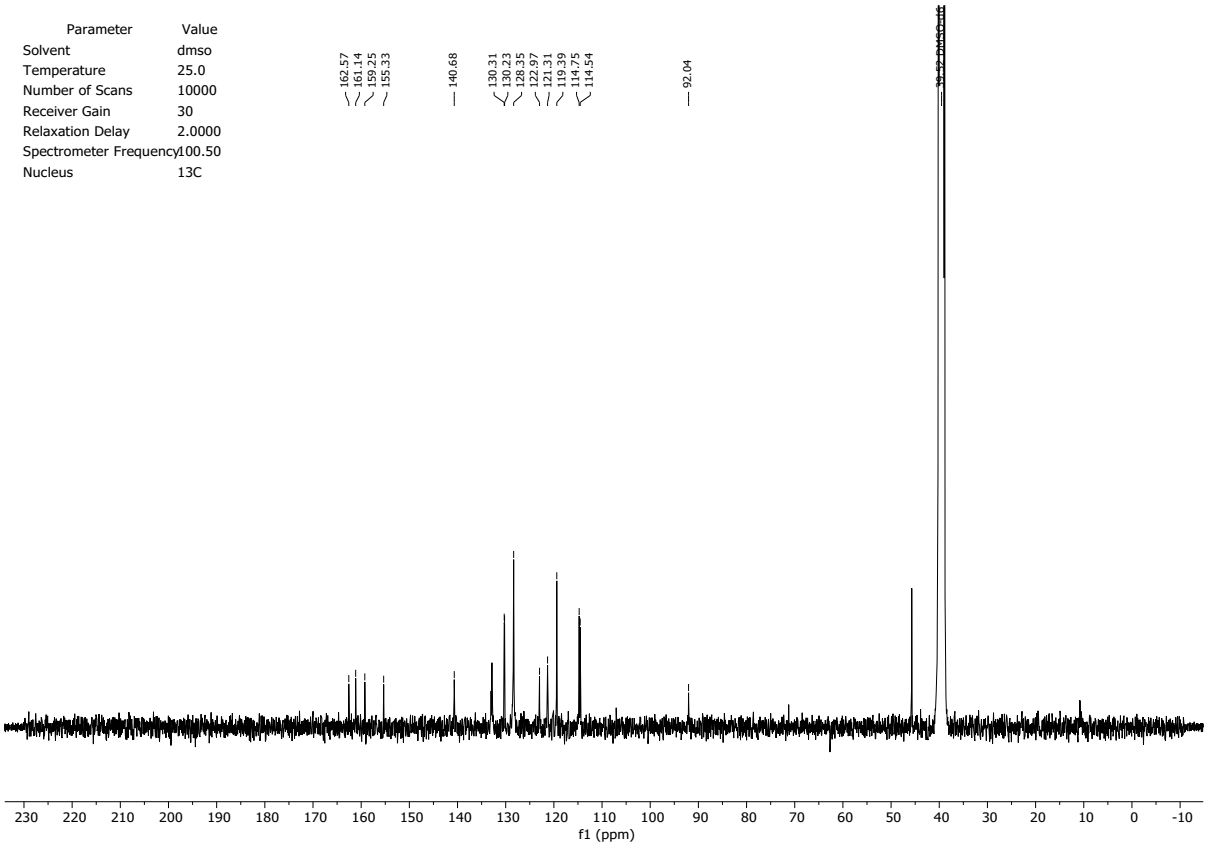
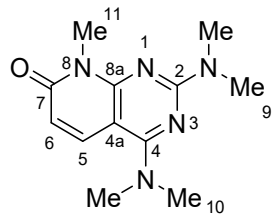


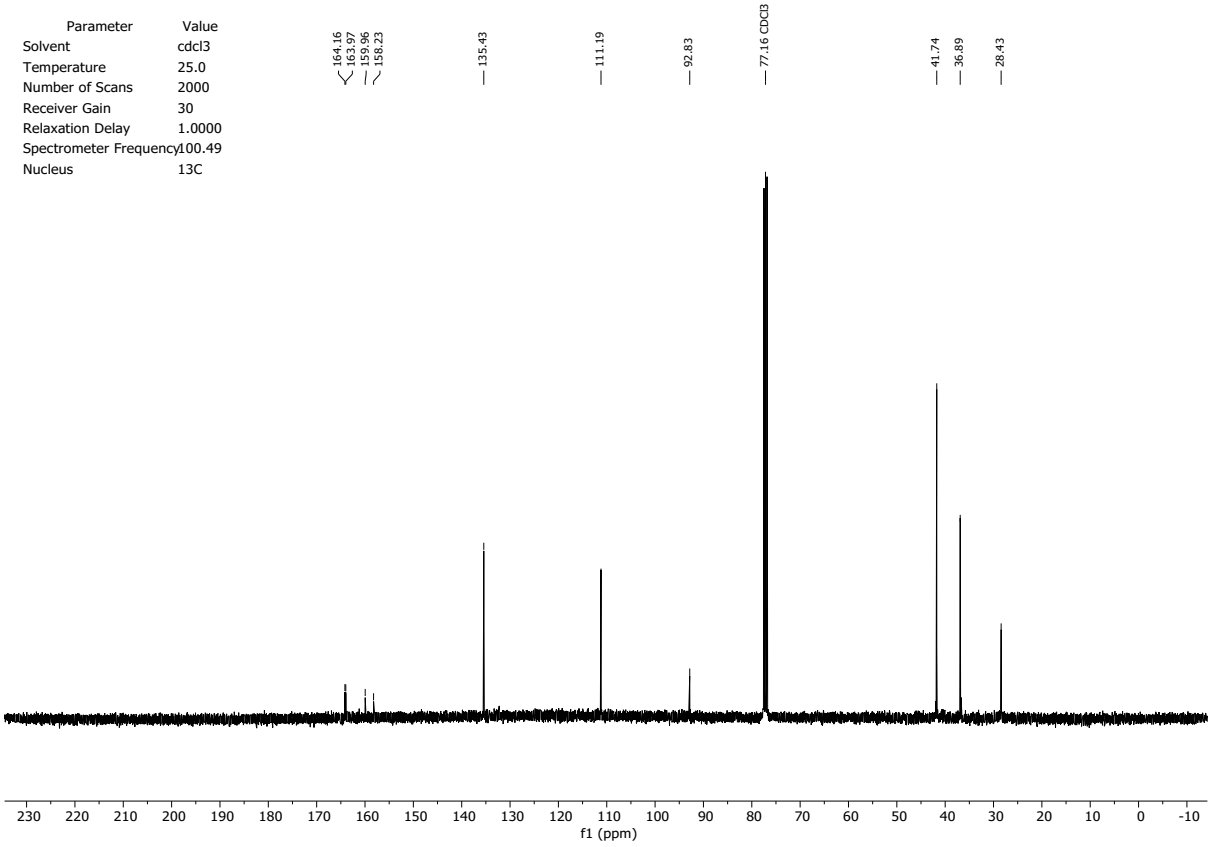
2,4-bis(dimethylamino)-8-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**23**)

Parameter	Value
Solvent	cdcl3
Temperature	25.0
Number of Scans	8
Receiver Gain	44
Relaxation Delay	1.0000
Spectrometer Frequency	399.62
Nucleus	1H



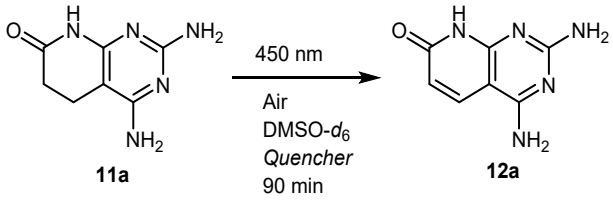
23

Parameter	Value
Solvent	cdcl3
Temperature	25.0
Number of Scans	2000
Receiver Gain	30
Relaxation Delay	1.0000
Spectrometer Frequency	100.49
Nucleus	13C



Methodologies using radical quenchers

General methodology for the quenching of the radical formed from 2,4-diamino-5,8-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (11a)

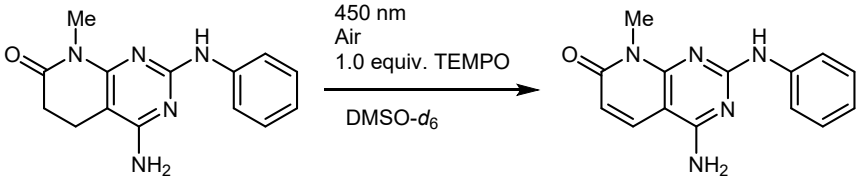


11a **12a**

2,4-diamino-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**11a**) (25.0 mg, 0.14 mmol) and the corresponding quencher are dissolved in 1 mL of DMSO-d_6 in a glass vial. The vial is bubbled with dry air and irradiated at 450 nm for 90 min in a Penn PhD Photoreactor M2. % LED: 100; rpm FAN: 6800; distance led – vial: 2 cm.

Quencher	mg (mmol)	Conversion (^{1}H-RMN %)	Type
BHT	30.9 (0.14)	7	Radical
NaN_3	91.0 (1.4)	100	Singlet oxygen
Benzoquinone	15.1 (0.14)	4	Superoxide anion radical
t-BuOH	10.4 (0.14)	100	Hydroxyl radical
$CuCl_2$	18.8 (0.14)	20	Electronic

Methodology with TEMPO and analysis by HPLC-MS



13 **14**

4-amino-8-methyl-2-(phenylamino)-5,8-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**13**) (10.0 mg, 0.04 mmol) and TEMPO (5,8 mg, 0.04 mmol) is dissolved in 1.0 mL of DMSO-d_6 in a glass vial. The vial is bubbled with dry air and irradiated at 450 nm for 30 and 60 min in a Penn PhD Photoreactor M2. % LED: 100; rpm FAN: 6800; distance led – vial: 2 cm. Both samples were diluted with ACN (DMSO-d_6 < 5%) and analysed by HPLC-MS.

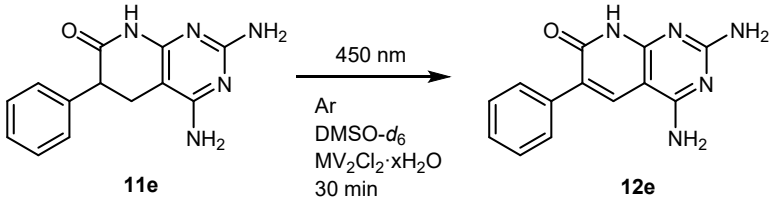
Retention time of **13**: 2.99 min

Retention time of **14**: 3.70 min

Retention time of TEMPO: 14.96 min

Exp.	% 13	% 14
without TEMPO at 30 min (Blank)	60	40
without TEMPO at 60 min (Blank)	27	73
with TEMPO at 30 min	96	4
with TEMPO at 60 min	94	6

Methodology with methyl viologen dichloride hydrate



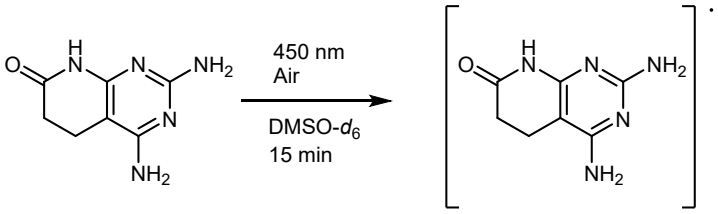
11e **12e**

2,4-diamino-6-phenyl-5,8-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**11e**) (25.0 mg, 0.10 mmol) and methyl viologen dichloride hydrate (25.2 mg, 0.10 mmol) are dissolved in 1 mL of DMSO-d_6 in a glass vial. The vial is bubbled with argon for 10 min, sealed and irradiated at 450 nm for 30 min with a Penn PhD Photoreactor M2. % LED: 100; rpm FAN: 6800; distance led – vial: 2 cm. The crude colour becomes blue.

EPR methodologies and spectra

Characterization of radical products

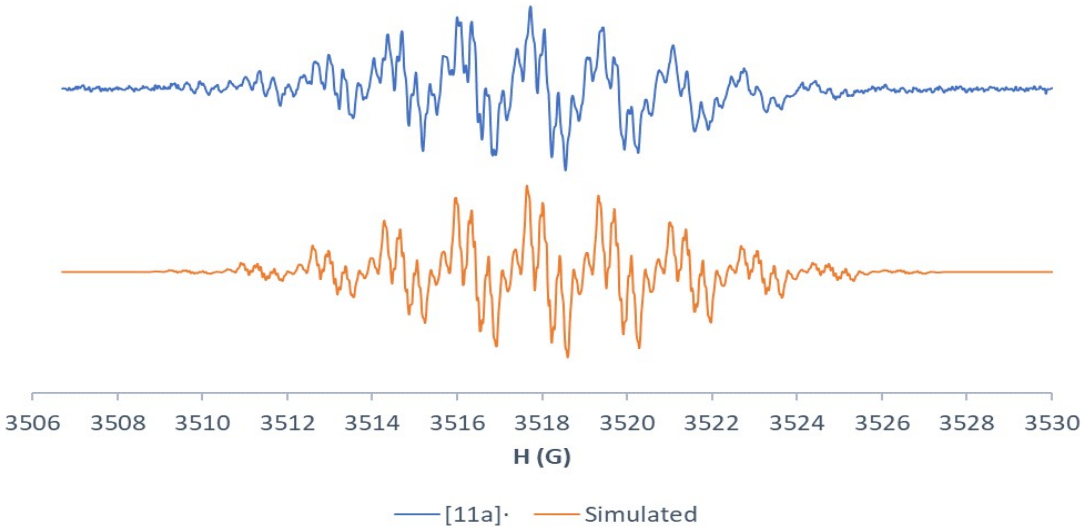
Radical of 2,4-diamino-5,8-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (11a)



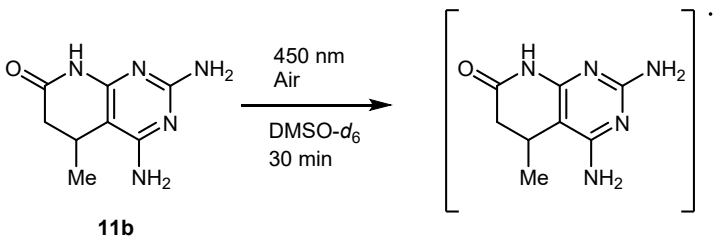
11a

2,4-diamino-5,8-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**11a**) (25.0 mg, 0.14 mmol) is dissolved in 2 mL of DMSO-d_6 in a glass vial. The vial is bubbled with dry air and irradiated at 450 nm for 15 min with a Penn PhD Photoreactor M2. % LED: 100; rpm FAN: 6800; distance led – vial: 2 cm. Then, an aliquot is introduced in a EPR tube and bubbled with argon for 20 seconds. The spectrum was recorded on a Bruker ELEXSYS E500 X-band EPR spectrometer.

The EPR spectrum at 300 K in DMSO-d6 appeared to be quite symmetrical with a *g*-factor of 2.0045, and linewidth of 0.1 G. It showed 11 main groups of lines derived from the coupling of the unpaired electron with 5 quasi-equivalent N atoms (a group of 3 nitrogens with a coupling constant a_N = 1.67 G and 2 nitrogens with a_N = 1.69 G). Each group presents mainly 5 lines, that matches with a coupling of the electron with 4 hydrogens with a_H = 0.32 G and 1 hydrogen with a_H = 0.15 G.



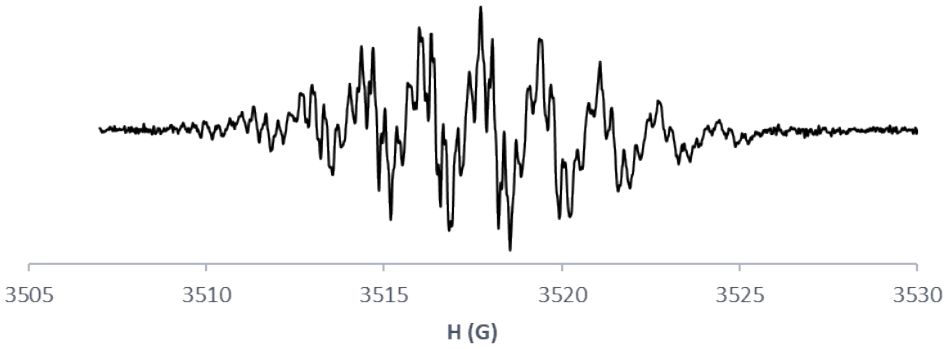
Radical of 2,4-diamino-5-methyl-5,8-dihydropyrido[2,3-*d*]pyrimidin-7(6*H*)-one (11b)



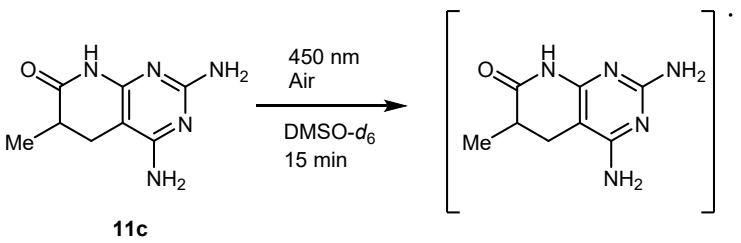
11b

2,4-diamino-5-methyl-5,8-dihydropyrido[2,3-*d*]pyrimidin-7(6*H*)-one (**11b**) (25.0 mg, 0.13 mmol) is dissolved in 2 mL of DMSO-d_6 in a glass vial. The vial is bubbled with dry air and irradiated at 450 nm for 30 min with a Penn PhD Photoreactor M2. % LED: 100; rpm FAN: 6800; distance led – vial: 2 cm. Then, an aliquot is introduced in a EPR tube and bubbled with argon for 20 seconds. The spectrum was recorded on a Bruker ELEXSYS E500 X-band EPR spectrometer.

The EPR spectrum at 300 K in DMSO-d_6 appeared to be exactly the same than in the case of **11a** (a_N (3N) = 1.67 G, a_N (2N) = 1.69 G, a_H (4H) = 0.32 G and a_H (1H) = 0.15 G) with a *g*-factor of 2.0043, and linewidth of 0.1 G.



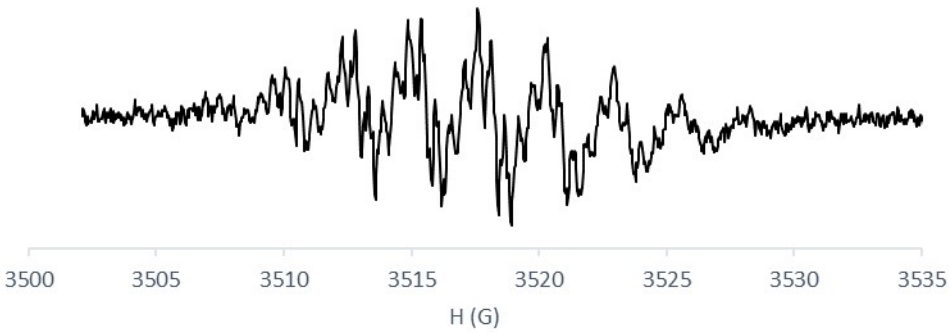
Radical of 2,4-diamino-6-methyl-5,8-dihydropyrido[2,3-d]pyrimidin-7(6H)-one (11c)



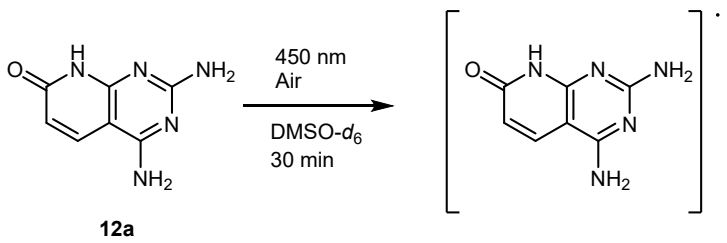
11c

2,4-diamino-6-methyl-5,8-dihydropyrido[2,3-d]pyrimidin-7(6H)-one (**11c**) (25.0 mg, 0.13 mmol) is dissolved in 2 mL of DMSO-d_6 in a glass vial. The vial is bubbled with dry air and irradiated at 450 nm for 15 min with a Penn PhD Photoreactor M2. % LED: 100; rpm FAN: 6800; distance led – vial: 2 cm. Then, an aliquot is introduced in a EPR tube and bubbled with argon for 20 seconds. The spectrum was recorded on a Bruker ELEXSYS E500 X-band EPR spectrometer.

The EPR spectrum at 300 K in DMSO-d_6 appeared to be exactly the same than in the case of **11a** and **11b** (a_N (3N) = 1.67 G, a_N (2N) = 1.69 G, a_H (4H) = 0.32 G and a_H (1H) = 0.15 G) with a *g*-factor of 2.0043, and linewidth of 0.1 G.



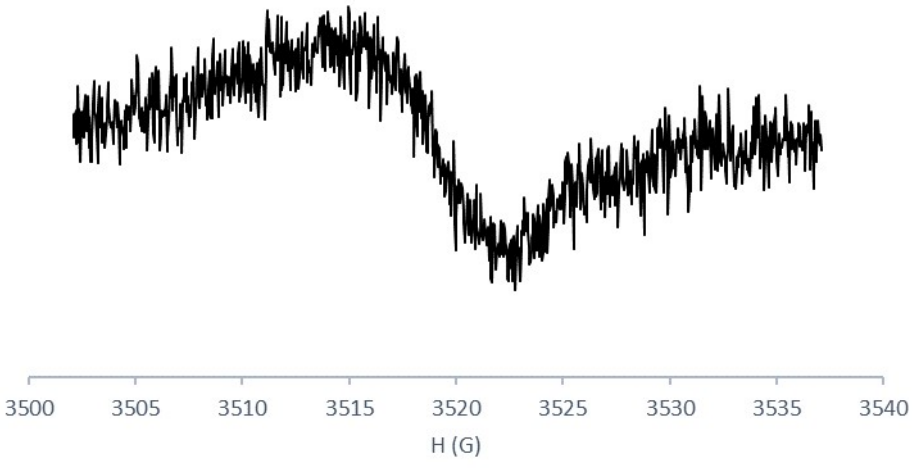
Radical of 2,4-diaminopyrido[2,3-*d*]pyrimidin-7(8*H*)-one (12a)



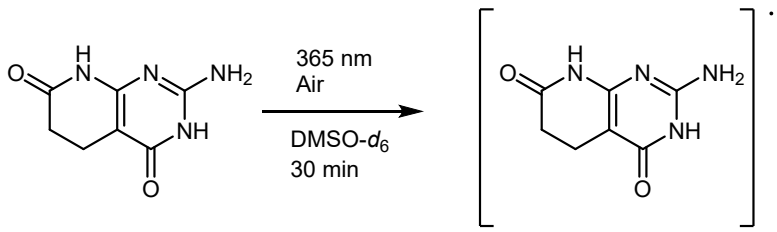
12a

2,4-diaminopyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**12a**) (25.0 mg, 0.14 mmol) is dissolved in 2 mL of DMSO-d_6 in a glass vial. The vial is bubbled with dry air and irradiated at 450 nm for 30 min with a Penn PhD Photoreactor M2. % LED: 100; rpm FAN: 6800; distance led – vial: 2 cm. Then, an aliquot is introduced in a EPR tube and bubbled with argon for 20 seconds. The spectrum was recorded on a Bruker ELEXSYS E500 X-band EPR spectrometer.

The EPR spectrum showed one unresolved broad line, due to problems of solubility of such an irradiated sample. It is important to highlight that, even the lack of resolution, the corresponding *g*-factor (2.0039) and the total width of the spectrum obtained (Δtotal ≈ 20 G) were very similar to the ones obtained in compounds **11a**, **11b** and **11c**, suggesting that a similar radical was also obtained in the case of **12a**.



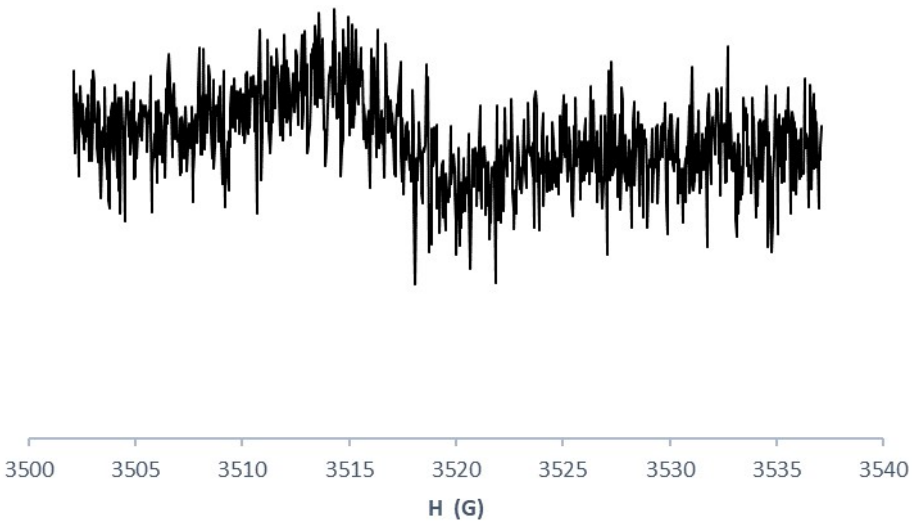
Radical of 2-amino-5,8-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (16)



16

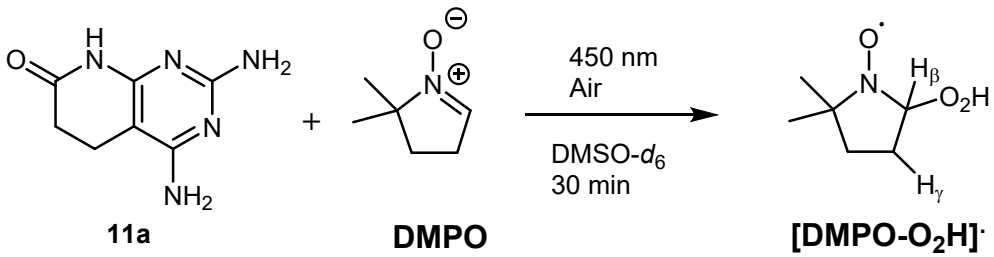
2-amino-5,8-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (**16**) (25.0 mg, 0.14 mmol) is dissolved in 2 mL of DMSO-d_6 in a glass vial. The vial is bubbled with dry air and irradiated at 365 nm for 30 min with a Penn PhD Photoreactor M2. % LED: 100; rpm FAN: 6800; distance led – vial: 2 cm. Then, an aliquot is introduced in a EPR tube and bubbled with argon for 20 seconds. The spectrum was recorded on a Bruker ELEXSYS E500 X-band EPR spectrometer.

The EPR spectrum showed one unresolved broad line, due to problems of solubility of such an irradiated sample. It is important to highlight that, even the lack of resolution, the corresponding *g*-factor (2.0046) and the total width of the spectrum obtained (Δtotal ≈ 20 G) were very similar to the ones obtained in compounds **11a**, **11b** and **11c**, suggesting that a similar radical was also obtained in the case of **16**.



Characterization of spin trapping adducts

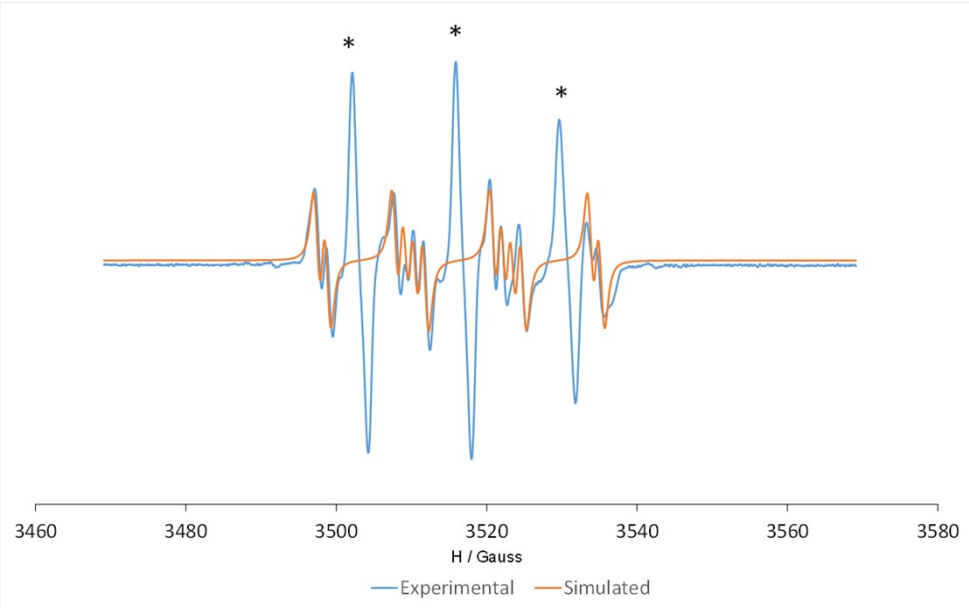
Radical superoxide anion–DMPO adduct [DMPO-O_2H]$^{\cdot}$



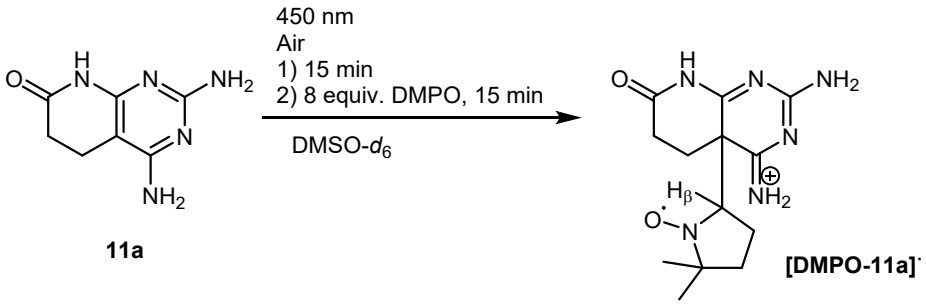
11a **DMPO** **[DMPO-O_2H]$^{\cdot}$**

2,4-diamino-5,8-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**11a**) (25.0 mg, 0.14 mmol) and DMPO (75 mg, 8 equiv.) are dissolved in 2 mL of DMSO-d_6 in a glass vial. The vial is bubbled with dry air and irradiated at 450 nm for 15 min with a Penn PhD Photoreactor M2 (% LED: 100; rpm FAN: 6800; distance led – vial: 2 cm). Then, an aliquot is introduced in a EPR tube and bubbled with argon for 20 seconds. The spectrum was recorded on a Bruker ELEXSYS E500 X-band EPR spectrometer.

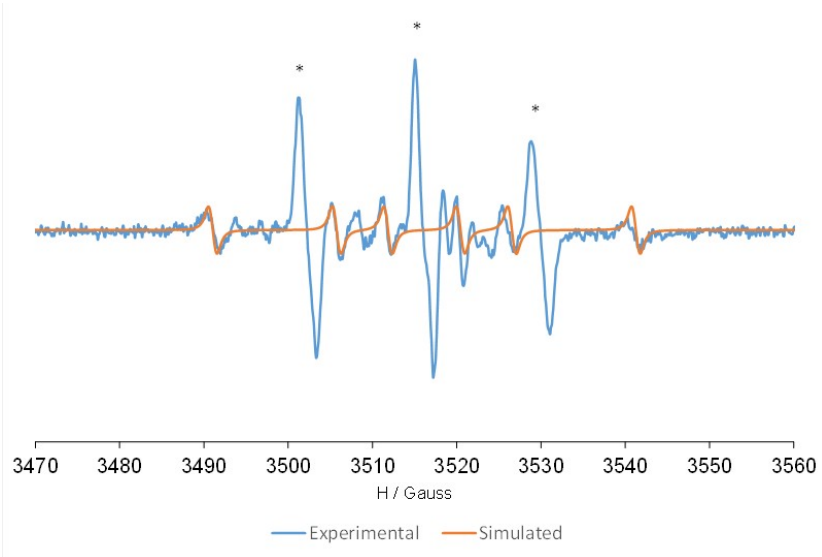
The EPR spectrum showed 2 groups of lines. A group of 3 main lines (marked with asterisks in Figure below) which correspond to a DMPO impurity that is already present in the blank spectrum of the DMPO used. The second group is composed of 4 groups of 2-4-4-2 lines (simulated orange spectrum of Figure below) which appeared to be quite symmetrical. Their corresponding coupling constants obtained from the simulation are a_N = 13 G, $a_{H\beta}$ = 10.4 G and $a_{H\gamma}$ = 1.35 G with a linewidth of 0.7 G and a *g*-factor of 2.0056 at 300 K in DMSO-d_6. This DMPO radical adduct spectral pattern is compatible with the trapping of superoxide radical anion.



Radical 2,4-diamino-5,8-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one–DMPO adduct ([DMPO-11a]$^{\cdot}$)



2,4-diamino-5,8-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**11a**) (12.5 mg, 0.07 mmol) is dissolved in 0.5 mL of DMSO-d_6 in a glass vial. The vial is bubbled with dry air and irradiated at 450 nm for 15 min with a Penn PhD Photoreactor M2 (% LED: 100; rpm FAN: 6800; distance led – vial: 2 cm). Then, DMPO (75 mg, 8 equiv.) is added. An aliquot is introduced in a EPR tube and bubbled with argon for 20 seconds. The spectrum was recorded on a Bruker ELEXSYS E500 X-band EPR spectrometer. The EPR spectrum showed mainly 2 groups of lines. A group of 3 main lines (marked with asterisks, Figure below) which correspond to a DMPO impurity that is already present in the blank spectrum of the DMPO used and a second group composed of 6 lines (simulated orange spectrum of Figure below) which appeared to be quite symmetrical. The corresponding coupling constants of such DMPO radical adduct spectrum obtained from the simulation are a_N = 14.7 G and $a_{H\beta}$ = 20.8 G with a linewidth of 0.7 G and a *g*-factor of 2.0056 at 300 K in DMSO-d_6. This DMPO radical adduct spectral pattern is compatible with the trapping of a C centred radical. We can also observe in the spectrum the EPR lines corresponding to the not trapped radical compound of **11a** centred at around 3520 G.



Computational results

2,4-diamino-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (11a)

Optimized coordinates:

```
C  -0.13124677   -0.64103941   -0.07409325
C  -0.00901639    0.74299863   -0.06606718
C   1.31906799    1.21141951   -0.01751877
N   2.37146408    0.37593102    0.04768550
C   2.10634626   -0.93546114    0.04395612
N   0.89061389   -1.50184098   -0.02405910
N  -1.39985993   -1.22083482   -0.16461574
C  -2.58966262   -0.56003894    0.01923306
C  -2.46666208    0.89951610    0.40701168
C  -1.24011163    1.60436060   -0.19137834
O  -3.66002965   -1.14701563   -0.07399151
N   3.17513561   -1.78515954    0.15688720
N   1.60861951    2.54528542   -0.00396046
H  -1.43036714    1.84141269   -1.24624593
H   0.92029181    3.21090978   -0.31595624
H  -3.39434282    1.40051648    0.13106516
H   3.02206704   -2.74625468   -0.10725242
H  -2.40425887    0.91311356    1.50223386
H  -1.10766929    2.55919760    0.32316714
H   2.57260071    2.80067641   -0.15672370
H   4.08423532   -1.40280696   -0.05336280
H  -1.43642028   -2.22483979   -0.29541475

1 2 1.0 6 2.0 7 1.0
2 3 2.0 10 1.0
3 4 1.0 13 1.0
4 5 2.0
5 6 1.0 12 1.0
6
7 8 1.0 22 1.0
8 9 1.0 11 2.0
9 10 1.0 16 1.0 18 1.0
10 14 1.0 19 1.0
11
12 17 1.0 21 1.0
13 15 1.0 20 1.0
14
15
16
17
18
19
20
21
22
```

Excited State of 2,4-diamino-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one ([11a]*)

Optimized coordinates:

```
C   -0.13124700   -0.64103900   -0.07409300
C   -0.00901600    0.74299900   -0.06606700
C    1.31906800    1.21141900   -0.01751900
N    2.37146400    0.37593100    0.04768600
C    2.10634600   -0.93546100    0.04395600
N    0.89061400   -1.50184100   -0.02405900
N   -1.39986000   -1.22083500   -0.16461600
C   -2.58966200   -0.56003900    0.01923300
C   -2.46666200    0.89951600    0.40701200
C   -1.24011200    1.60436000   -0.19137800
O   -3.66002900   -1.14701600   -0.07399200
N    3.17513500   -1.78515900    0.15688700
N    1.60861900    2.54528500   -0.00396000
H   -1.43036700    1.84141300   -1.24624600
H    0.92029200    3.21091000   -0.31595600
H   -3.39434300    1.40051600    0.13106500
H    3.02206700   -2.74625400   -0.10725200
H   -2.40425900    0.91311300    1.50223400
H   -1.10766900    2.55919700    0.32316700
H    2.57260100    2.80067600   -0.15672400
H    4.08423500   -1.40280700   -0.05336300
H   -1.43642000   -2.22484000   -0.29541500

1 2 1.5 6 1.5 7 1.0
2 3 1.5 10 1.0
3 4 1.5 13 1.5
4 5 1.5
5 6 1.5 12 1.5
6
7 8 1.5 22 1.0
8 9 1.0 11 2.0
9 10 1.0 16 1.0 18 1.0
10 14 1.0 19 1.0
11
12 17 1.0 21 1.0
13 15 1.0 20 1.0
14
15
16
17
18
19
20
21
22
```

Excitation energies and oscillator strengths:

```
Excited State   1:  3.000-A      3.6251 eV  342.01 nm  f=0.0000  <S**2>=2.000
```

Cation-radical of 2,4-diamino-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one ([11a]$^{\cdot+}$)

Optimized coordinates:

```
C    -0.14507900   -0.69185800   -0.04614300
C    -0.00563200    0.73964300   -0.05408400
C     1.36582300    1.21664600   -0.01097000
N     2.39316300    0.37645400    0.03673800
C     2.11100000   -0.93549100    0.02937200
N     0.87335800   -1.51514500   -0.01232500
N    -1.40432500   -1.22820900   -0.11278600
C    -2.60646600   -0.53367000    0.02271600
C    -2.47681200    0.93274800    0.35553500
C    -1.21004900    1.59655900   -0.20500300
O    -3.66127500   -1.12438900   -0.07391400
N     3.13459000   -1.78301100    0.07046100
N     1.61773100    2.52525200   -0.02392000
H    -1.33851700    1.79457700   -1.28083900
H     0.89327700    3.22460600   -0.06122000
H    -3.37155600    1.44202700    0.00157500
H     2.96709600   -2.77867900    0.06799900
H    -2.47627200    0.99902000    1.44924000
H    -1.07449200    2.57110200    0.26643100
H     2.57865900    2.83775100    0.00067200
H     4.08142700   -1.43364400    0.10731600
H    -1.46775300   -2.23649500   -0.21558000

1 2 1.5 6 2.0 7 1.5
2 3 1.0 10 1.0
3 4 1.5 13 1.5
4 5 1.5
5 6 1.5 12 1.5
6
7 8 1.0 22 1.0
8 9 1.0 11 2.0
9 10 1.0 16 1.0 18 1.0
10 14 1.0 19 1.0
11
12 17 1.0 21 1.0
13 15 1.0 20 1.0
14
15
16
17
18
19
20
21
22
```

Intermediate tautomer 15a

Optimized coordinates:

```
C     0.18038300   -0.67777400   -0.00948900
C     0.02145600    0.77489100    0.00423800
C    -1.38164500    1.22522900   -0.01039100
N    -2.37829500    0.35404700   -0.00037100
C    -2.06864200   -0.95501900    0.00649700
N    -0.81721500   -1.51302000   -0.00860300
N     1.44359400   -1.19550300   -0.02011800
C     2.63190300   -0.47522200   -0.00641500
C     2.49482400    1.02915100    0.03980500
C     1.11175900    1.56604900    0.03727100
O     3.70105100   -1.04517700   -0.02598600
N    -3.07545500   -1.81716500    0.02561300
N    -1.68690100    2.51667100   -0.03545600
H    -0.99908500    3.25169200   -0.06394100
H     3.02767900    1.39270600    0.92764800
H     1.52190100   -2.20827100   -0.03609400
H    -4.02812700   -1.48389800    0.03653700
H    -2.89149700   -2.80937800    0.02919100
H     3.05280000    1.45048800   -0.80570200
H    -2.66169900    2.78269300   -0.04344900
H     1.02929500    2.64633300    0.06714000

1 2 1.0 6 2.0 7 1.5
2 3 1.0 10 2.0
3 4 1.5 13 1.5
4 5 1.5
5 6 1.5 12 1.5
6
7 8 1.0 16 1.0
8 9 1.0 11 2.0
9 10 1.0 15 1.0 19 1.0
10 21 1.0
11
12 17 1.0 18 1.0
13 14 1.0 20 1.0
14
15
16
17
18
19
20
21
```

2,4-diaminopyrido[2,3-*d*]pyrimidin-7(8*H*)-one (12a)

Optimized coordinates:

```
C   -0.19079900   -0.64121700   -0.00367200
C   -0.05071900    0.76127700   -0.00042800
C    1.30220300    1.22515500   -0.00108000
N    2.32975900    0.37213900   -0.00095600
C    2.04668100   -0.94434400   -0.00164700
N    0.82654400   -1.50558300   -0.00313400
N   -1.45729600   -1.16540400   -0.00468400
C   -2.64707900   -0.43702300   -0.00053600
C   -2.47313700    0.99943200    0.00811400
C   -1.23079500    1.55857000    0.00871200
O   -3.73045600   -1.03094500   -0.00295600
N    3.10745500   -1.78864500   -0.03061500
N    1.60766900    2.54092300    0.02043500
H    0.91298500    3.25641000   -0.10877500
H   -1.53953200   -2.17597200   -0.00801500
H    4.02937200   -1.41586800    0.12835500
H    2.95116700   -2.77153300    0.12391100
H   -3.37030400    1.60321700    0.01575000
H    2.57589300    2.80611000   -0.07191500
H   -1.15298900    2.64009500    0.02024700

1 2 1.5 6 1.5 7 1.5
2 3 1.5 10 1.5
3 4 1.5 13 1.5
4 5 1.5
5 6 1.5 12 1.5
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7 8 1.0 15 1.0
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19
20
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References

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