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SUPPLEMENTARY INFORMATION

A captured room temperature stable Wheland intermediate as key structure for the orthogonal decoration of 4-amino-pyrido[2,3-*d*]pyrimidin-7(8*H*)-ones

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Experimental Procedures

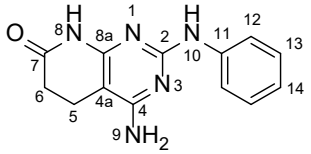
General considerations

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; 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 obtained by using an Agilent Technologies 5975. HRMS data were obtained by using a VG AutoSpec (Micromass Instruments) Trisector EBE high resolution spectrometer (EI or FAB mode) or a Bruker micrOTOF (ESI-FIA-TOF or APCI-FIA-TOF). Elemental microanalyses were obtained on a EuroVector Instruments Euro EA 3000 elemental analyzer. Single-crystal X-ray diffraction data were generated from measurements with a Bruker D8 Venture diffractometer. Crystal structure of compound **12** was solved from synchrotron X-ray powder diffraction data collected in the MSPD-BL04 beamline at ALBA Synchrotron (https://www.albasynchrotron.es/en) and data were collected with the microstrip Mythen-II detector. The melting points were determined with a Büchi-Tottoli 530 capillary apparatus 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 (60–120 s) 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.

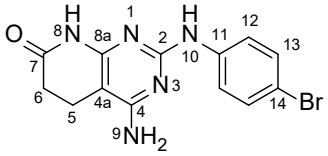
Synthesis and characterization of 4-amino-2-(phenylamino)-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**7**)



7

A mixture of 148 mg of *N*-phenylguanidine carbonate **10** (having a $C_7H_9N_3{\cdot}(H_2CO_3)_{0.69}$ stoichiometry which corresponds to 0.83 mmol of guanidine and 0.57 mmol of H_2CO_3), 55 mg (0.83 mmol) of malononitrile **9**, 143 mg (1.66 mmol) of methyl acrylate **8** and methanol (5 mL) is sealed in a 5 mL microwave vial and heated at 140 ºC under microwave irradiation for 10 min. Compound **7** is obtained as a white solid that can be isolated by filtration, washed with water, ethanol and diethyl ether to afford 107 mg (51%) of spectroscopically pure 4-amino-2-(phenylamino)-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**7**), m.p. >250 ºC. **^{1}H NMR** (400 MHz, DMSO-*d*$_6$) δ (ppm): 10.04 (br s, 1H, H-N8), 8.69 (br s, 1H, H-N10), 7.85 – 7.78 (m, 2H, H-C12), 7.21 – 7.14 (m, 2H, H-C13), 6.83 (tt, *J* = 7.5 Hz, *J* = 1.2 Hz, 1H, H-C14), 6.36 (s, 2H, H-N9), 2.59-2.47 (m, 4H, H-C5 and H-C6); **^{13}C NMR** (100.5 MHz, DMSO-*d*$_6$) δ (ppm): 171.9 (C7), 161.4 (C4), 158.1 (C2), 156.3 (C8a), 141.4 (C11), 128.2 (C13), 120.2 (C14), 118.3 (C12), 85.8 (C4a), 30.4 (C6), 17.2 (C5); **IR** (KBr) ν_{max} (cm^{-1}): 3467, 3198, 1679, 1641, 1593, 1575, 1543, 1438, 1375, 1226, 781, 750, 701; **MS** (EI, 70 eV) *m/z* (%): 254.1 (100) [M-H]$^+$; **HRMS** (EI) *m/z* calcd. for $C_{13}H_{13}N_5O$ [M]$^+$: 255.1120; found: 255.1123; **elemental analysis** calcd (%) for $C_{13}H_{13}N_5O$: C 61.17, H 5.13, N 27.43; found: C 61.22, H 5.42, N 27.65.

Synthesis and characterization of 4-amino-2-(4-bromophenylamino)-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**11**)

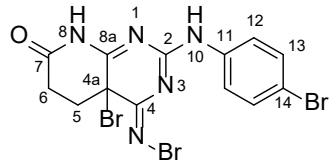


11

A suspension of 651 mg of 4-amino-2-(phenylamino)-5,8-dihydropyrido[2,3-*d*]pyrimidin-7(6*H*)-one (**7**) (2.55 mmol) in acetic acid (35 mL) is treated with 1.3 mL (2.6 mmol) of a 2 M solution of bromine in acetic acid for 3 h at room temperature. Then, water is added, and the white solid appeared can be isolated by filtration, washed with water and dried under vacuum to afford 826 mg (2.47 mmol, 97%) of spectroscopically pure of 4-amino-2-((4-bromophenyl)amino)-8-methyl-5,8-dihydropyrido[2,3-*d*]pyrimidin-7(6H)-one (**11**).

Or alternatively, 4-amino-2-(phenylamino)-5,8-dihydropyrido[2,3-*d*]pyrimidin-7(6*H*)-one (**7**) (100.0 mg, 0.372 mmol, 1.0 equiv.) and NBS (66.1 mg, 0.372 mmol, 1.0 equiv.) are added in a vial with 1.0 mL of anhydrous DMSO and heated for 1h at 60 ºC and 100 mbar, protected from light. Then, water (20 mL) is added, and the white solid appeared can be isolated by filtration, washed with water and dried under vacuum to afford 88.4 mg (0.265 mmol, 68%) of 4-amino-2-((4-bromophenyl)amino)-8-methyl-5,8-dihydropyrido[2,3-*d*]pyrimidin-7(6H)-one (**11**). m.p. >250 ºC. **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm): 10.04 (s, 1H, H-N8), 8.89 (s, 1H, H-N10), 7.85 – 7.80 (m, 2H, H-C12), 7.33 – 7.29 (m, 2H, H-C13), 6.40 (s, 2H, H-N9), 2.57 – 2.46 (m, 4H, H-C5 and H-C6); **^{13}C NMR** (100.5 MHz, DMSO-d_6) δ (ppm): 171.7 (C7), 161.4 (C4), 157.8 (C2), 157.8 (C8a), 140.9 (C11), 130.9 (C13), 120.2 (C12), 111.4 (C14), 86.1 (C4a), 30.4 (C6), 17.2 (C5). **IR** (KBr) ν_{max} (cm^{-1}): 3503, 3393, 3200, 3136, 1672, 1636, 1613, 1574, 1544, 1491, 1433, 1377, 1243, 823, 745; **MS** (EI, 70 eV) *m/z* (%): 333.0 (100) [M]$^+$, 253.9 (35) [M-Br]$^+$; **elemental analysis** calcd (%) for $C_{13}H_{12}BrN_5O$: C 46.72, H 3.62, N 20.96; found: C 46.67, H 3.62, N 20.58.

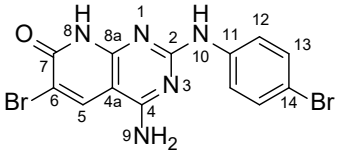
Synthesis and characterization of (*Z*)-4a-bromo-4-(bromoimino)-2-((4-bromophenyl)amino)-4,5,6,8-tetrahydropyrido[2,3-*d*]pyrimidin-7(4a*H*)-one (**12**)



12

A dispersion of 4-amino-2-(phenylamino)-5,8-dihydropyrido[2,3-*d*]pyrimidin-7(6*H*)-one (**7**) (199.0 mg, 0.78 mmol) in acetic acid (10 mL) is treated with 0.123 mL of bromine (382.5 mg, 2.34 mmol) for 3 h at room temperature. The orange cake obtained is diluted with water (90 mL), filtered and washed with water, ethanol and diethyl ether to afford 374.5 mg (0.77 mmol, 98%) of spectroscopically pure (*Z*)-4a-Bromo-4-(bromoimino)-2-((4-bromophenyl)amino)-4,5,6,8-tetrahydropyrido[2,3-*d*]pyrimidin-7(4a*H*)-one (**12**). m.p. 166 °C (decomposition); **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm): 11.82 (s, 1H, H-N8), 10.53 (s, 1H, H-N10), 8.24 – 8.13 (m, 2H, H-C12), 7.61 – 7.53 (m, 2H, H-C13), 2.96 – 2.85 (m, 1H, H-C6), 2.80 – 2.69 (m, 2H, H-C5, H-C6), 2.66 – 2.57 (m, 1H, H-C5); **^{13}C NMR** (100.5 MHz, DMSO-d_6) δ (ppm): 170.5 (C7), 167.8 (C4), 166.7 (C2), 156.0 (C8a), 137.9 (C11), 131.5 (C13), 122.9 (C12), 116.2 (C14), 43.7 (C4a), 30.1 (C6), 28.2 (C5); **IR** (KBr) ν_{max} (cm^{-1}): 3399, 3119, 2914, 1710, 1654, 1608, 1544, 1519, 1489, 1209, 1078, 1006, 832, 510; **HRMS** (ESI-TOF) *m/z* calcd for $C_{13}H_{11}{}^{79}Br_3N_5O$ [M+H]$^+$: 489.8514; found: 489.8497; **elemental analysis** calcd (%) for $C_{13}H_{10}Br_3N_5O$: C 31.74, H 2.05, N 14.24; found: C 31.86, H 2.07, N 14.10.

Synthesis and characterization of 4-amino-6-bromo-2-((4-bromophenyl)amino)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**13**)



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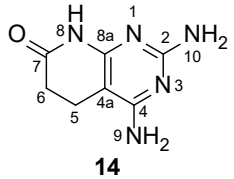
A solution of (*Z*)-4a-Bromo-4-(bromoimino)-2-((4-bromophenyl)amino)-4,5,6,8-tetrahydropyrido[2,3-*d*]pyrimidin-7(4a*H*)-one (**12**) (102.0 mg, 0.21 mmol) in DMSO (5 mL) is heated at 80 ºC for 3 h in a conventional vacuum distillation system at 50 mbar. The resulting white or slightly pale-yellow solid is isolated by filtration and washed with water, ethanol and diethyl ether to afford 68.0 mg (0,17 mmol, 79%) of spectroscopically pure 4-amino-6-bromo-2-((4-bromophenyl)amino)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**13**).

Or alternatively, 4-amino-2-((4-bromophenyl)amino)-8-methyl-5,8-dihydropyrido[2,3-*d*]pyrimidin-7(6*H*)-one (**11**) (50.0 mg, 0.15 mmol, 1.0 equiv.) and NBS (53.3 mg, 0.30 mmol, 1.0 equiv.) are added in a vial with 0.5 mL of anhydrous DMSO and heated for 3h at 80 ºC and 100 mbar, protected from light. Then, water (10 mL) is added, and the yellowish solid appeared can be isolated by filtration, washed with water and dried under vacuum to afford 48.8 mg (0.119 mmol, 79%) of 4-amino-6-bromo-2-((4-bromophenyl)amino)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**13**). Crystals suitable for single-crystal X-ray diffraction analysis were obtained by slow evaporation of an acetone solution. m.p. >300 ºC. **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm): 12.14 (s, 1H, H-N8), 9.43 (s, 1H, H-N10), 8.56 (s, 1H, H-C5), 7.93 – 7.84 (m, 2H, 12), 7,43 (br s, 2H, H-N9), 7.40 – 7.34 (m, 2H, 13). **^{13}C NMR** (100.5 MHz, DMSO-d_6) δ (ppm): 160.3 (C8a*), 159.4 (C7), 159.1 (C2), 155.4 (C4*), 140.0 (C11), 136.7 (C5), 131.0 (C13), 121.3 (C12), 112.8 (C14), 107.8 (C6), 92.3 (C4a). **IR** (KBr) ν_{max} (cm^{-1}): 3456, 3330, 1633, 1603, 1555, 1508, 1438, 1310, 1290, 1268, 1072, 1039, 1008, 808, 792, 608; **HRMS**

(FAB) *m/z* calcd. for $C_{13}H_{10}{}^{79}Br^{81}BrN_5O$ $[M+H]^+$: 411.9232; found: 411.9240; **elemental analysis** calcd (%) for $C_{13}H_9Br_2N_5O$: C 37.99, H 2.21, N 17.04; found: C 37.96, H 2.26, N 16.81.

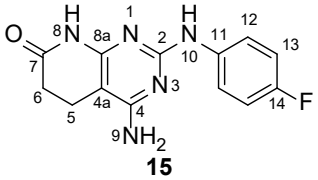
Synthesis and characterization of 2,4-diamino-7-oxo-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidine (**14**)[1]



14

Guanidine carbonate (0.82 g, 6.64 mmol), malononitrile (0.44 g, 6.64 mmol) and methyl acrylate (1.2 mL, 13.28 mmol) were dissolved in 20 mL of anhydrous methanol. The resulting mixture was heated by microwave irradiation for 10 minutes at 140 °C. After cooling to room temperature, water was added, and the formed precipitate was collected by filtration and washed thoroughly with water, ethanol and diethyl ether. The product was oven dried providing 2,4-diamino-7-oxo-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidine (**14**) as a white solid (1.16 g, 76%). m.p. > 300 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm): 10.30 (s, H-N8), 6.17 (s, 2H, NH_2), 5.88 (s, 2H, NH_2), 2.63 – 2.29 (m, 4H, H-C5, H-C6). **^{13}C NMR** (100.5 MHz, DMSO-d_6) δ(ppm): 172.2 (C7), 161.8 (C2), 161.6 (C8a), 156.5 (C4), 83.8 (C4a), 30.5 (C6), 17.0 (C5); **IR** (KBr) ν_{max} (cm^{-1}): 3416, 3337, 3185, 1624, 1575, 1442, 1378, 1322, 1289, 1216, 835, 783; **MS** (EI) m/z (%): 179.1 (100) $[M]^+$; **elemental analysis** calcd (%) for $C_7H_9N_5O$: C 46.92, H 5.06, N 39.09; found: C 46.81, H 4.99, N 39.29.

Synthesis and characterization of 4-amino-2-((4-fluorophenyl)amino)-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**15**)



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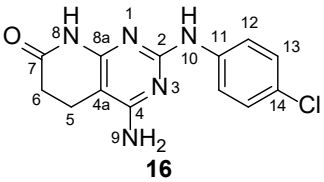
A mixture of *p*-fluorophenylguanidine nitrate (1.442 g, 6.67 mmol), malononitrile (**9**) (440 mg, 6.64 mmol), methyl acrylate (**8**) (1.144 g, 1.2 mL, 13.30 mmol), potassium carbonate (917.7 mg, 6.64 mmol) and anhydrous MeOH (20 mL) is sealed in a 20 mL microwave vial and heated at 140 °C under microwave irradiation for 10 min. The white solid formed is filtered, washed with water and diethyl ether to afford 670 mg (2.50 mmol, 37%) of spectroscopically pure 4-amino-2-((4-fluorophenyl)amino)-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**15**), m.p. >250 ºC; **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm): 10.16 (s, 1H, H-N8), 8.83 (s, 1H, H-N8), 7.89 – 7.77 (m, 2H, H-C12), 7.07 – 6.95 (m, 2H, H-C13), 6.40 (s, 2H, H-N10), 2.60 – 2.50 (m, 4H, H-C5, H-C6). **^{13}C NMR** (100.5 MHz, DMSO-d_6) δ (ppm): 171.6 (C7), 161.4 (C4*), 158.0 (C2), 156.4 (d, $J_{C\text{-}F}$ = 236.5 Hz, C14), 156.3 (C8a*), 137.9 (d, $J_{C\text{-}F}$= 2.2 Hz, C11), 119.7 (d, $J_{C\text{-}F}$ = 7.2 Hz, C12), 114.6 (d, $J_{C\text{-}F}$= 21.6 Hz, C13), 85.8 (C4a), 30.5 (C6), 17.2 (C5); **^{19}F NMR** (376 MHz, DMSO-d_6) δ (ppm): -123.7 to -123.8 (m, 1F); **IR** (KBr) ν_{max} (cm^{-1}): 3477, 3175, 2933, 1690, 1639, 1574, 1545, 1509, 1484, 1436, 1371, 1322, 1209, 848, 815, 776; **MS** (70 eV, EI): *m/z* (%) = 273.1 (100) $[M]^+$, 230.1 (11) $[M\text{-}CHNO]^+$; **elemental analysis** calcd (%) for $C_{13}H_{12}FN_5O$: C 57.14, H 4.43, N 25.63; found: C 57.06, H 4.49, N 25.57.

Synthesis and characterization of 4-amino-2-((4-chlorophenyl)amino)-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**16**)[2]



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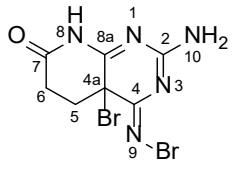
A mixture of *p*-chlorophenylguanidine carbonate (666.1 mg, 1.66 mmol, 3.32 mmol of *p*-chlorophenylguanidine), malononitrile (**9**) (219 mg, 3.32 mmol), methyl acrylate (**8**) (571,5 mg, 0.6 mL, 6.64 mmol), potassium carbonate (458.9 mg, 3.32 mmol) and anhydrous MeOH (10 mL) is sealed in a 20 mL microwave vial and heated at 140 °C under microwave irradiation for 10 min. The white solid formed is filtered, washed with water and diethyl ether to afford 287.0 mg (0.99 mmol, 30%) of spectroscopically pure 4-amino-2-((4-chlorophenyl)amino)-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**16**), m.p. >250 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm): 10.04 (s, 1H, H-N8), 8.89 (s, 1H, H-N10), 7.91 – 7.83 (m, 2H, H-C12), 7.22 – 7.15 (m, 2H, H-C13), 6.39 (s, 2H, H-N9), 2.61 – 2.54 (m, 2H, H-C5), 2.50 – 2.45 (m, 2H, H-C6); **^{13}C NMR** (100.5 MHz, DMSO-d_6) δ (ppm): 171.7 (C7), 161.4 (C4*), 157.8 (C2), 156.3 (C8a*), 140.5 (C11), 128.0 (C13), 123.5 (C14), 119.7 (C12), 86.1 (C4a), 30.4 (C6), 17.2 (C5); **IR** (KBr) ν_{max} (cm^{-1}): 3509, 3400, 3202, 1676, 1638,

1613, 1593, 1575, 1545, 1494, 1433, 1375, 1243, 824. **MS** (FAB) m/z (%): 290.0 (25) [$C_{13}H_{13}{}^{35}ClN_5O$, M+H]$^+$; **HRMS** (FAB) m/z calcd for $C_{13}H_{13}{}^{35}ClN_5O$ [M+H]$^+$: 290.0809; found: 290.0816.

Synthesis and characterization of 2-amino-4a-bromo-4-(bromoimino)-4,5,6,8-tetrahydropyrido[2,3-*d*]pyrimidin-7(4a*H*)-one (**17**)



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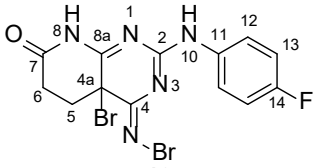
Bromine (610 µL, 11.2 mmol) was added to a suspension of 2,4-diamino-7-oxo-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidine (**14**) (1.00 g, 5.6 mmol) in 100 mL of acetic acid. The resulting mixture was stirred 3 h at room temperature protected from light. Then, water was added, and the formed precipitate was collected by filtration and washed thoroughly with water, ethanol and diethyl ether. The product was oven dried providing 2-amino-4a-bromo-4-(bromoimino)-4,5,6,8-tetrahydropyrido[2,3-*d*]pyrimidin-7(4a*H*)-one (**17**) as a yellow solid (1.52 g, 4.5 mmol, 81%). m.p. 175 °C (decomposition); **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm): 11.65 (s, 1H), 8.32 (s, 1H, NH_2), 7.92 (s, 1H, NH_2), 2.93 – 2.77 (m, 1H, H-C6), 2.74 – 2.62 (m, 2H, H-C5, H-C6), 2.56 – 2.42 (m, 1H, H-C5); **^{13}C NMR** (100.5 MHz, DMSO-d_6) δ (ppm): 170.4 (C7), 168.0 (C4*), 167.0 (C8a*), 160.5 (C2*), 43.1 (C4a), 30.1 (C6), 28.5 (C5); **IR** (KBr) ν_{max} (cm^{-1}): 3311, 3190, 1703, 1644, 1521, 1392, 1348, 1295, 1268, 1220, 1045, 993, 899, 844, 748, 710. **MS** (ESI-FIA-TOF) m/z (%): 339.9 (7) [$C_7H_8{}^{81}Br_2N_5O$, M+H]$^+$, 338.0 (16) [$C_7H_8{}^{81}Br^{79}BrN_5O$, M+H]$^+$, 335.9 (9) [$C_7H_8{}^{79}Br_2N_5O$, M+H]$^+$, 259.0 (7) [$C_7H_8{}^{81}BrN_5O$, M+H-Br]$^+$, 257.0 (13) [$C_7H_8{}^{79}BrN_5O$, M+H-Br]$^+$; **HRMS** (ESI-FIA-TOF) m/z: calcd for $C_7H_8{}^{79}Br_2N_5O$: 335.9090 [M+H]$^+$; found: 335.9091; **elemental analysis** calcd (%) for $C_7H_7N_5OBr_2$: C 24.95, H 2.09, N 20.78; found: C 25.28, H 2.09, N 20.72.

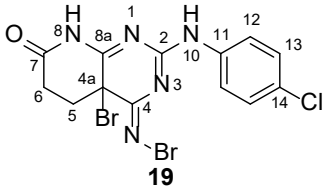
Synthesis and characterization of (*Z*)-4a-bromo-4-(bromoimino)-2-((4-fluorophenyl)amino)-4,5,6,8-tetrahydropyrido[2,3-*d*]pyrimidin-7(4a*H*)-one (**18**)



18

Bromine (83.1 µL, 1.62 mmol) was added to a suspension of 4-amino-2-((4-fluorophenyl)amino)-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**15**) (222.0 mg, 0.81 mmol) in 10.8 mL of acetic acid. The resulting mixture was stirred 3 h at room temperature protected from light. Then, water was added, and the formed precipitate was collected by filtration and washed thoroughly with water, ethanol and diethyl ether. The product was dried under vacuum providing (*Z*)-4a-bromo-4-(bromoimino)-2-((4-fluorophenyl)amino)-4,5,6,8-tetrahydropyrido[2,3-*d*]pyrimidin-7(4a*H*)-one (**18**) as a yellowish solid (346.2 g, 0.80 mmol, 99%). m.p. 202 °C (decomposition); **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm): 11.80 (s, 1H, H-N8), 10.49 (s, 1H, H-N10), 8.33 – 8.18 (m, 2H, H-C12), 7.26 – 7.17 (m, 2H, H-C13), 2.91 (ddd, J = 18.2, 12.8, 5.6 Hz, 1H, H-C6), 2.82 – 2.67 (m, 2H, H-C6, H-C5), 2.60 (ddd, J = 15.4, 12.8, 5.1 Hz, 1H, H-C5); **^{13}C NMR** (100.5 MHz, DMSO-d_6) δ (ppm): 170.5 (C7), 167.6 (C4), 166.7 (C2), 158.7 (d, $J_{C\text{-}F}$ = 241.9 Hz, C14), 155.9 (C8a), 134.9 (d, $J_{C\text{-}F}$ = 2.5 Hz, C11), 122.7 (d, $J_{C\text{-}F}$ = 7.9 Hz, C12), 115.4 (C), 115.3 (d, $J_{C\text{-}F}$ = 22.2 Hz, C13), 43.7 (C4a), 30.1 (C6), 28.3 (C5); **^{19}F NMR** (376 MHz, DMSO-d_6) δ (ppm): -117.9 (tt, J = 8.8, 4.9 Hz, 1F); **IR** (KBr) ν_{max} (cm^{-1}): 3216, 3156, 3102, 2920, 1707, 1654, 1618, 1563, 1506, 1409, 1389, 1337, 1293, 1266, 1214, 1161, 1080, 837, 727, 667, 585; **MS** (ESI-FIA-TOF) m/z (%): 433.9 (9) [$C_{13}H_{11}{}^{81}Br_2FN_5O$, M+H]$^+$, 431.9 (22) [$C_{13}H_{11}{}^{81}Br^{79}BrFN_5O$, M+H]$^+$, 429.9 (12) [$C_{13}H_{11}{}^{79}Br_2FN_5O$, M+H]$^+$, 354.0 (55) [$C_{13}H_{12}{}^{81}BrFN_5O$, M+2H-Br]$^+$, 352.0 (60) [$C_{13}H_{12}{}^{79}BrFN_5O$, M+2H-Br]$^+$, 274.1 (63) [$C_{13}H_{13}FN_5O$, M+3H-2Br]$^+$; **HRMS** (ESI-FIA-TOF) m/z: calcd for $C_{13}H_{11}{}^{79}Br_2FN_5O$: 429.9309 [M+H]$^+$; found: 429.9301; **elemental analysis** calcd (%) for $C_{13}H_{10}NBr_2FN_5O$: C 36.22, H 2.34, N 16.25; found: C 35.84, H 2.13, N 15.81.

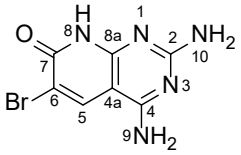
Synthesis and characterization of (*Z*)-4a-bromo-4-(bromoimino)-2-((4-chlorophenyl)amino)-4,5,6,8-tetrahydropyrido[2,3-*d*]pyrimidin-7(4a*H*)-one (**19**)



19

Bromine (83.1 µL, 1.62 mmol) was added to a suspension of 4-amino-2-((4-chlorophenyl)amino)-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**16**) (234.7 mg, 0.81 mmol) in 10.8 mL of acetic acid. The resulting mixture was stirred 3 h at room temperature protected from light. Then, water was added, and the formed precipitate was collected by filtration and washed thoroughly with water, ethanol and diethyl ether. The product was dried under vacuum providing (*Z*)-4a-bromo-4-(bromoimino)-2-((4-chlorophenyl)amino)-4,5,6,8-tetrahydropyrido[2,3-*d*]pyrimidin-7(4a*H*)-one (**19**) as a yellow solid (357.0 g, 0.80 mmol, 99%). m.p. 218 °C (decomposition); **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm): 11.82 (s, 1H, H-N8), 10.54 (s, 1H, H-N10), 8.29 – 8.20 (m, 2H, H-C12), 7.48 – 7.40 (m, 2H, H-C13), 2.91 (ddd, *J* = 18.2, 12.8, 5.6 Hz, 1H, H-C6), 2.81 – 2.69 (m, 2H, H-C5, H-C6), 2.61 (ddd, *J* = 15.5, 12.8, 5.1 Hz, 1H, H-C5); **^{13}C NMR** (100.5 MHz, DMSO-d_6) δ (ppm): 170.5 (C7), 167.8 (C4), 166.7 (C2), 156.0 (C8a), 137.5 (C11), 128.6 (C13), 128.0 (C14), 122.5 (C12), 43.7 (C4a), 30.1 (C6), 28.3 (C5); **IR** (KBr) ν_{max} (cm^{-1}): 3402, 3196, 3122, 2913, 1713, 1654, 1612, 1548, 1517, 1493, 1403, 1335, 1289, 1267, 1211, 1095, 1080, 835, 661, 520; **elemental analysis** calcd (%) for $C_{13}H_{10}Br_2ClN_5O$: C 34,89, H 2,25, N 15,65; found: C 35.06, H 2.25, N 15.44.

Synthesis and characterization of 2,4-diamino-6-bromopyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**20**)

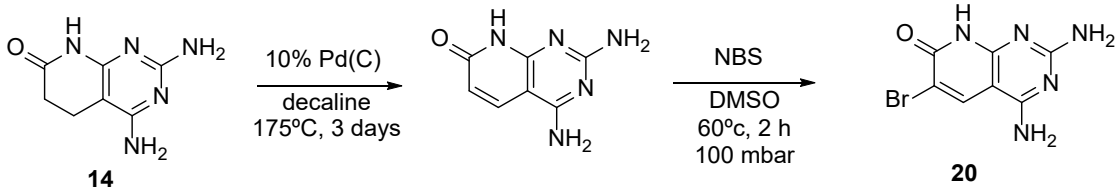


20

A solution of 2-amino-4a-bromo-4-(bromoimino)-4,5,6,8-tetrahydropyrido[2,3-*d*]pyrimidin-7(4a*H*)-one (**17**) (1.52 g, 4.51 mmol) in DMSO was heated *in vacuo* for 3 h at 80 °C. Then, water was added, and the formed precipitate was collected by filtration and washed thoroughly with water, ethanol and diethyl ether. The product was oven dried providing 2,4-diamino-6-bromopyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**20**) as a brownish solid (992.4 mg, 86%).

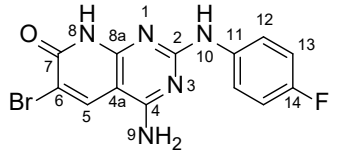
Alternatively, a solution of compound 2,4-diamino-7-oxo-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidine (**14**) (45.0 mg, 0.25 mmol) and *N*-bromosuccinimide (94 mg, 0,52 mmol, 2.1 eq) in DMSO (0,5 mL) was heated *in vacuo* for 6 h at 60 °C. Then, water was added, and the formed precipitate was collected by filtration and washed thoroughly with water, ethanol and diethyl ether. The product was oven dried providing 2,4-diamino-6-bromopyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**20**) (48.8 mg, 0.19 mmol, 76%) as a yellowish solid. m.p. > 300 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm): 12.21 (s, 1H, H-N8), 8.47 (s, 1H, H-C5), 7.25 (s, 2H, NH_2), 6.75 (s, 2H, NH_2); **^{13}C NMR** (100.5 MHz, DMSO-d_6) δ (ppm): 162.9 (C2), 160.8 (C8a*), 159.7 (C7*), 156.1 (C4*), 137.1 (C5), 105.3 (C6), 91.3 (C4a); **IR** (KBr) ν_{max} (cm^{-1}): 3344, 3184, 2844, 1649, 1589, 1534, 1466, 1274, 1020, 790, 554; **MS** (EI) m/z (%): 255.0 (100) [M]$^+$, 176.1 (16) [M-Br]$^+$; **HRMS** (ESI) m/z (%): calcd for $C_7H_7{}^{79}BrN_5O$ [M+H]$^+$: 255.9898; found: 255.9898.

From 2,4-diaminopyrido[2,3-*d*]pyrimidin-7(8*H*)-one: A mixture of 2,4-diamino-7-oxo-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidine (**14**) (125 mg, 0.7 mmol), 10% Pd(C) (130 mg, 20% mol.) and decaline (2mL) were heated at 175 ºC for 3 days. Once cooled, DMSO is added and the resulting mixture is filtered through a celite pad to remove the catalyst. Finally, the solvent is removed under reduced pressure to afford a mixture of **14** and the desired 2,4-diaminopyrido[2,3-*d*]pyrimidin-7(8*H*)-one (the observed conversion assessed via ^{1}H NMR was 58% and the total mass recuperation was 73%). 2,4-diaminopyrido[2,3-*d*]pyrimidin-7(8*H*)-one was purified by column chromatograpphy to afford 49.6 mg (0.28 mmol, 40%) which was used without further purification. **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm): 11.90 (br s, 1H, N8-H), 7.94 (*d*, *J* = 9.4 Hz, 1H, C5-H), 7.21 (br s, 2H, NH_2), 6.75 (br s, 2H, NH_2), 5.95 (d, *J* = 9.4 Hz, 1H, C6-H). 2,4-diaminopyrido[2,3-*d*]pyrimidin-7(8*H*)-one (20.0 mg, 0.113 mmol, 1.0 eq.) and NBS (20.1 mg, 0.113 mmol, 1.0 eq.) were dissolved in a vial with 0.5 mL of anhydrous DMSO and heated for 2h at 60ºC at 100 mbar protected from light. Then, acetone (20 mL) was added and the yellow solid appeared can be isolated by filtration, washed with water and dried under vacuum to afford 20.3 mg (0.062 mmol, 70%) of 2,4-diamino-6-bromopyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**20**) as a yellowish solid.



14 **20**

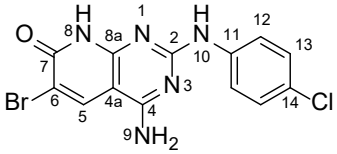
Synthesis and characterization of 4-amino-6-bromo-2-((4-fluorophenyl)amino)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**21**)



21

A dispersion of (*Z*)-4a-bromo-4-(bromoimino)-2-((4-fluorophenyl)amino)-4,5,6,8-tetrahydropyrido[2,3-*d*]pyrimidin-7(4a*H*)-one (**18**) (346.2 mg, 0.80 mmol) in DMSO (11.5 mL) is heated at 80 °C for 3 h in a conventional vacuum distillation system (50 mbar). The resulting ochre solid is obtained by addition of water (25 mL) and is isolated by filtration and washed with water and diethyl ether to afford 222.6 mg (0.64 mmol, 79%) of spectroscopically pure 4-amino-6-bromo-2-(4-fluorophenylamino)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**21**). mp: >250 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm): 12.08 (s, 1H, H-N8), 9.31 (s, 1H, H-N9), 8.54 (s, 1H, H-C5), 7.93 – 7.82 (m, 2H, H-C12), 7.39 (s, 2H, NH_2), 7.11 – 7.01 (m, 2H, H-C13); **^{13}C NMR** (100.5 MHz, DMSO-d_6) δ (ppm): 160.4 (C8a*), 159.4 (C4*), 159.3 (C2), 157.2 (d, $J_{C\text{-}F}$ = 238.0 Hz, C14), 155.5 (C7*), 136.9 (d, $J_{C\text{-}F}$ = 13.1 Hz, C12), 136.7 (C5), 121.0 (d, $J_{C\text{-}F}$ = 7.5 Hz, C11), 114.7 (d, $J_{C\text{-}F}$ = 21.8 Hz, C13), 107.4 (C6), 92.2 (C4a); **^{19}F NMR** (376 MHz, DMSO-d_6) δ (ppm): -122.0 (tt, J = 9.0, 5.1 Hz, 1F); **IR** (KBr) ν_{max} (cm^{-1}): 3478, 3409, 3074, 1640, 1614, 1576, 1506, 1444, 1310, 1270, 1208, 1156, 1037, 830, 790, 734, 647. **MS** (70 eV, EI): m/z (%) = 351.0 (45) [$C_{13}H_9{}^{81}BrFN_5O$, M]$^+$, 349.0 (43) [$C_{13}H_9{}^{79}BrFN_5O$, M]$^+$. **HRMS** (APCI-FIA-TOF) m/z (%): calcd for $C_{13}H_{10}{}^{79}BrFN_5O$ [M+H]$^+$: 350.0047; found: 350.0047.

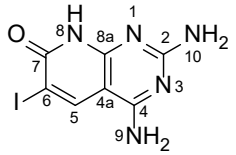
Synthesis and characterization of 4-amino-6-bromo-2-((4-chlorophenyl)amino)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**22**)



22

A dispersion of (*Z*)-4a-bromo-4-(bromoimino)-2-((4-chlorophenyl)amino)-4,5,6,8-tetrahydropyrido[2,3-*d*]pyrimidin-7(4a*H*)-one (**19**) (342.5 mg, 0.97 mmol) in DMSO (8.6 mL) is heated at 80 °C for 3 h in a conventional vacuum distillation system (50 mbar). The resulting ochre solid is obtained by addition of water (20 mL) and is isolated by filtration and washed with water and diethyl ether to afford 333.4 mg (0.91 mmol, 94%) of spectroscopically pure 4-amino-6-bromo-2-(4-chlorophenylamino)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**22**). mp: >300 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm): 12.13 (s, 1H, H-N8), 9.42 (s, 1H, H-N10), 8.55 (s, 1H, H-C5), 7.96 – 7.91 (m, 2H, H-C12), 7.42 (s, 2H, NH_2), 7.28 – 7.23 (m, 2H, H-C13). **^{13}C NMR** (100.5 MHz, DMSO-d_6) δ (ppm): 160.4 (C8a*), 159.4 (C7), 159.1 (C2), 155.4 (C4*), 139.5 (C11), 136.7 (C5), 128.1 (C13), 124.9 (C14), 120.9 (C12), 107.8 (C6), 92.3 (C4a); **IR** (KBr) ν_{max} (cm^{-1}): 3456, 3096, 2921, 1639,1613, 1560, 1495, 1445, 1311, 1293, 1268, 1236, 1090, 1039, 828, 790, 568. **MS** (ESI-FIA-TOF): m/z (%) 370.0 (7) [$C_{13}H_{10}{}^{81}Br^{37}ClN_5O$, M+H]$^+$, 368.0 (35) [$C_{13}H_{10}{}^{81}Br^{35}ClN_5O$ and $C_{13}H_{10}{}^{79}Br^{37}ClN_5O$, M+H]$^+$, 366.0 (24) [$C_{13}H_{10}{}^{79}Br^{35}ClN_5O$, M+H]$^+$; **HRMS** (ESI-FIA-TOF) m/z (%): calcd for $C_{13}H_{10}{}^{79}Br^{35}ClN_5O$ [M+H]$^+$: 365.9752; found: 365.9753.

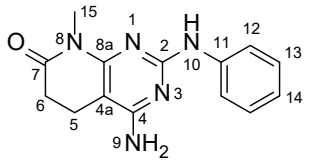
Synthesis and characterization of 2,4-diamino-6-iodopyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**23**)



23

A solution of compound 2,4-diamino-7-oxo-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidine (**14**) (177 mg, 1.0 mmol) and *N*-iodosuccinimide (467 mg, 2.1 mmol) in DMSO (5 mL) was heated *in vacuo* for 6 h at 60 °C. Then, water was added, and the formed precipitate was collected by filtration and washed thoroughly with water, ethanol and diethyl ether. The product was oven dried providing 2,4-diamino-6-iodopyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**23**) (249 mg, 0.8 mmol, 83% yield) as a yellow solid. m.p. 286 °C (decomposition); **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm) 12.07 (s, 1H, H-N8), 8.62 (s, 1H, H-C5), 7.26 (s, 2H, NH_2), 6.76 (s, 2H, NH_2); **^{13}C NMR** (100.5 MHz, DMSO-d_6) δ (ppm): 163.0 (C2), 160.7 (C7*), 160.4 (C4a*), 156.9 (C4), 143.6 (C5), 92.8 (C4a), 81.2 (C6); **IR** (KBr) ν_{max} (cm^{-1}): 3355, 3185, 1625, 1583, 1529, 1460, 1276, 788, 550; **MS** (ESI-FIA-TOF) m/z (%): 303.97 (100) [M+H]$^+$; **HRMS** (ESI-FIA-TOF) m/z (%): calcd for $C_7H_7IN_5O$ [M+H]$^+$: 303.9690; found: 303.9692.

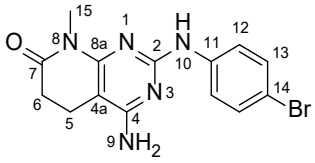
Synthesis and characterization of 4-amino-8-methyl-2-(phenylamino)-5,8-dihydropyrido[2,3-*d*]pyrimidin-7(6*H*)-one (**24**)



24

4-amino-2-(phenylamino)-5,8-dihydropyrido[2,3-*d*]pyrimidin-7(6*H*)-one (**7**) (658.0 mg, 2.58 mmol, 1.0 equiv.) and sodium hydride (60% in mineral oil) (103.1 mg, 2.58 mmol, 1.0 equiv.) in DMSO anhydrous (40 mL) are added in a 100 mL flask and the mixture is stirred for 1 h at room temperature. Then, methyl iodide (0.16 ml, 2.58 mmol, 1.0 equiv.) is added and the mixture is stirred overnight at room temperature. After addition of water (400 mL), the solid appeared can be isolated by filtration, washed with water and dried under vacuum to afford 660.0 mg (2.45 mmol, 95%) of 4-amino-8-methyl-2-(phenylamino)-5,8-dihydropyrido[2,3-*d*]pyrimidin-7(6*H*)-one (**24**) as a light beige powder. m.p. 216-218 °C; **^{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, 3125, 1673, 1657, 1621, 1581, 1539, 1436, 1371, 1130, 751, 699; **MS** (70 eV, EI): m/z (%): 269.1 (74) [M]$^+$, 241.1 (52) [M-CO]$^+$, 240.2 (100) [M-NMe]$^+$; **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.

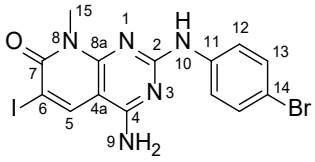
Synthesis and characterization of 4-amino-2-((4-bromophenyl)amino)-8-methyl-5,8-dihydropyrido[2,3-*d*]pyrimidin-7(6*H*)-one (**25**)



25

4-amino-8-methyl-2-(phenylamino)-5,8-dihydropyrido[2,3-*d*]pyrimidin-7(6*H*)-one (**24**) (200.0 mg, 0.743 mmol, 1.0 equiv.) and NBS (132.2 mg, 0.743 mmol, 1.0 equiv.) are dissolved in a vial with 0.5 mL of anhydrous DMSO and heated for 1 h at 60 ºC at 100 mbar protected from light. Then, water (20 mL) is added and the white solid appeared can be isolated by filtration, washed with water and dried under vacuum to afford 223.7 mg (0.642 mmol, 87%) of 4-amino-2-((4-bromophenyl)amino)-8-methyl-5,8-dihydropyrido[2,3-*d*]pyrimidin-7(6*H*)-one (**25**) as a whitish solid. m.p. 267-270 °C (decomposition); **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm): 9.02 (s, 1H, H-N10), 7.80 – 7.71 (m, 2H, H-C12), 7.40 – 7.33 (m, 2H, H-C13), 6.45 (s, 2H, H-N9), 3.25 (s, 3H, H-C15), 2.57 – 2.55 (m, 4H, H-C5 and H-C6); **^{13}C NMR** (100.5 MHz, DMSO-d_6) δ (ppm): 170.5 (C7), 161.5 (C4), 157.5 (C2), 157.2 (C8a), 140.9 (C11), 131.0 (C13), 120.3 (C12), 111.6 (C14), 88.0 (C4a), 30.7 (C6), 27.5 (C15), 16.5 (C5); **IR** (KBr) ν_{max} (cm^{-1}): 3494, 3396, 3288, 3197, 1665, 1623, 1577, 1532, 1491, 1444, 1396, 1369, 1326, 1240, 1221, 1130, 823; **MS** (70 eV, EI) m/z (%): 347.0 (100) [M]$^+$, 319.0 (93) [M-CO]$^+$, 268.1 (90) [M-Br]$^+$; **elemental analysis** calcd (%) for $C_{14}H_{14}BrN_5O$: C 48.29, H 4.05, N 20.11; found: C 48.32, H 3.97, N 19.78.

Synthesis and characterization of 4-amino-2-((4-bromophenyl)amino)-6-iodo-8-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**26**)

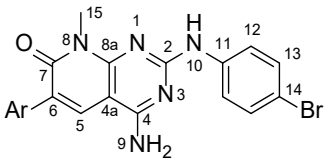


26

4-amino-2-((4-bromophenyl)amino)-8-methyl-5,8-dihydropyrido[2,3-*d*]pyrimidin-7(6*H*)-one (**25**) (1.44 g, 4.13 mmol, 1.0 equiv.) and NIS (1.86 g, 8.27 mmol, 2.0 equiv.) are dissolved in a round-bottom flask with 15 mL anhydrous DMSO and heated for 1 h, at 60 °C at 100 mbar protected from light. Then, water (150 mL) is added and the brown-yellow solid appeared can be isolated by filtration and washed with water. To purify the product, a digestion with ethanol (50 mL) is performed for 4h. The resultant brownish solid is filtrated and dried under vacuum to afford 1.62 g (3.43 mmol, 83%) of 4-amino-2-((4-bromophenyl)amino)-6-iodo-8-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**26**) as a light beige powder. m.p. 250-253 °C (decomposition); **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm): 9.57 (s, 1H, H-N10), 8.75 (s, 1H, H-C5), 7.82 – 7.76 (m, 2H, H-C12), 7.45 (br s, 2H, H-N9), 7.47 – 7.41 (m, 2H, H-C13), 3.60 (s, 3H, H-C15). **^{13}C NMR** (100.5 MHz, DMSO-d_6) δ (ppm): 160.6 (C4), 159.8 (C7*), 158.7 (C2), 156.1 (C8b*), 141.8 (C5), 139.8 (C11), 131.2 (C13),

121.5 (C12), 113.2 (C14), 94.3 (C4a), 82.7 (C6), 29.7 (C15); **IR** (KBr) ν_{max} (cm^{-1}): 3404, 3188, 1626, 1596, 1572, 1526, 1488, 1413, 1330, 1201, 793, 563, 501; **MS** (70 eV, EI) m/z (%): 470.9 (100) $[M]^+$, 392.0 (17) $[M\text{-}Br]^+$, 344.0 (92) $[M\text{-}I]^+$; **elemental analysis** calcd (%) for $C_{14}H_{11}BrIN_5O$: C 35.62, H 2.35, N 14.84; found: C 35.54, H 2.55, N 14.43.

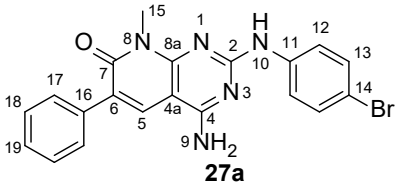
General synthesis methodology of 4-amino-2-((4-bromophenyl)amino)-8-methyl-6-substitutedpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**27**)



27

4-amino-2-((4-bromophenyl)amino)-6-iodo-8-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**26**) (1.0 equiv.), boronic acid (1.4 equiv.) and cesium carbonate (2.5 equiv. with regarding to boronic acid) are dissolved with a deoxygenated mixture of 1,4-dioxane/water (10:1) in a sealed microwave vial. Tetrakis(triphenylphosphine)palladium(0) is then added, the vial is sealed and the reaction is heated in an oil bath at 90 °C for 2 h. After addition of water (solvent volume x10 mL), the solid appeared can be isolated by filtration and washed with water. Purification by silica gel flash chromatography is carried out with automatic equipment Isco Teledyne CombiFlash®Rf column pack (Silica, cyclohexane/AcOEt as eluent).

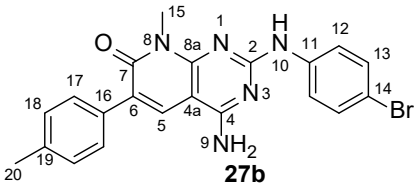
Synthesis and characterization of 4-amino-2-((4-bromophenyl)amino)-8-methyl-6-phenylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**27a**)



27a

4-amino-2-((4-bromophenyl)amino)-6-iodo-8-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**26**) (80.0 mg, 0.169 mmol), phenylboronic acid (28.9 mg, 0.237 mmol), cesium carbonate (193.9 mg, 0.593 mmol) and tetrakis(triphenylphosphine)palladium(0) (3.9 mg, 0.0034 mmol, 2 mol%) with deoxygenated 1,4-dioxane/water (8 mL) mixture. 54.0 mg (0.128 mmol, 75%) of a pale yellow solid spectroscopically pure 4-amino-2-((4-bromophenyl)amino)-8-methyl-6-phenylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**27a**) were obtained after an automatic flash chromatography (silica, from 100:0 to 50:50 of cyclohexane/AcOEt as eluent in 40 min.; retention time of **27a**: 26-33 min.). m.p. 287-290 °C (decomposition); **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm): 9.52 (s, 1H, H-N10), 8.30 (s, 1H, H-C5), 7.86 – 7.80 (m, 2H, H-C12), 7.75 – 7.69 (m, 2H, H-C17), 7.46 (br s, 2H, H-N9), 7.47 – 7.43 (m, 2H, H-C13), 7.43 – 7.38 (m, 2H, H-C18), 7.32 (tt, *J* = 7.4 Hz, 1.3 Hz, 1H, H-C19), 3.62 (s, 3H, H-C15); **^{13}C NMR** (100.5 MHz, DMSO-d_6) δ (ppm): 161.8 (C7*), 161.7 (C4), 158.5 (C2), 155.2 (C8a*), 140.0 (C11), 137.0 (C16), 131.4 (C5), 131.1 (C13), 128.6 (C17), 127.8 (C18), 127.0 (C19), 123.3 (C6), 121.2 (C12), 112.8 (C14), 92.4 (C4a), 28.5 (C15); **IR** (KBr) ν_{max} (cm^{-1}): 3383, 3179, 2925, 1677, 1630, 1563, 1515, 1412, 1346, 1203, 798, 755, 551; **MS** (70 eV, EI) m/z (%): 423.1 (94) $[C_{20}H_{16}{}^{81}BrN_5O, M]^+$, 421.1 (100) $[C_{20}H_{16}{}^{79}BrN_5O, M]^+$, 394.1 (18) $[C_{19}H_{13}{}^{81}BrN_4O, M\text{-}NMe]^+$, 392.1 (18) $[C_{19}H_{13}{}^{79}BrN_4O, M\text{-}NMe]^+$, 342.2 (9) $[M\text{-}Br]^+$; **HRMS** (APCI-FIA-TOF) (m/z) calcd for $C_{20}H_{17}{}^{79}BrN_5O$ $[M+H]^+$: 422.0611; found: 422.0608.

Synthesis and characterization of 4-amino-2-((4-bromophenyl)amino)-8-methyl-6-(*p*-tolyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**27b**)

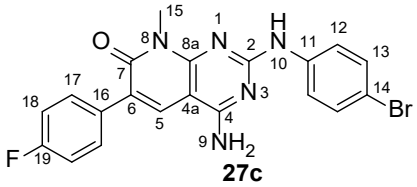


27b

4-amino-2-((4-bromophenyl)amino)-6-iodo-8-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**26**) (66.0 mg, 0.140 mmol), *p*-tolyl boronic acid (26.6 mg, 0.196 mmol), cesium carbonate (159.5 mg, 0.490 mmol) and tetrakis(triphenylphosphine)palladium(0) (24.3 mg, 0.021 mmol, 15 mol%) with deoxygenated 1,4-dioxane/water (6 mL) mixture. 21.7 mg (0.0497 mmol, 36%) of a pale yellow solid

spectroscopically pure 4-amino-2-((4-bromophenyl)amino)-8-methyl-6-(p-tolyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**27b**) were obtained after an automatic flash chromatography (silica, from 100:0 to 50:50 of cyclohexane/AcOEt as eluent in 40 min.; retention time of **27b**: 23-28 min.). m.p. 295-297 °C (decomposition); **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm): 9.50 (s, 1H, H-N10), 8.27 (s, 1H, H-C5), 7.85 – 7.80 (m, 2H, H-C12), 7.66 – 7.61 (m, 2H, H-C17), 7.54 – 7.37 (m, 4H, H-N9 and H-C13), 7.23 – 7.19 (m, 2H, H-C18), 3.62 (s, 3H, H-C15), 2.34 (s, 3H, H-C20); **^{13}C NMR** (100.5 MHz, DMSO-d_6) δ (ppm): 161.8 (C7*), 161.6 (C4), 158.4 (C2), 155.1 (C8a*), 140.0 (C11), 136.2 (C19), 134.1 (C16), 131.1 (C13), 130.8 (C5), 128.4 (C17 and C18), 123.3 (C6), 121.2 (C12), 112.8 (C14), 92.4 (C4a), 28.5 (C15), 20.8 (C20); **IR** (KBr) ν_{max} (cm^{-1}): 3405, 3175, 2923, 1678, 1631, 1613, 1566, 1517, 1403, 1345, 1206, 822, 798, 533; **MS** (70 eV, EI) m/z (%): 437.2 (93) [$C_{21}H_{18}{}^{81}BrN_5O$, M]$^+$,435.2 (100) [$C_{21}H_{18}{}^{79}BrN_5O$, M]$^+$, 408.2 (17) [$C_{20}H_{15}{}^{81}BrN_4O$, M-NMe]$^+$, 406.2 (17) [$C_{20}H_{15}{}^{79}BrN_4O$, M-NMe]$^+$, 356.2 (9) [M-Br]$^+$; **HRMS** (APCI-FIA-TOF) (m/z): calcd for $C_{21}H_{19}{}^{79}BrN_5O$ [M+H]$^+$: 436.0767; found: 436.0765.

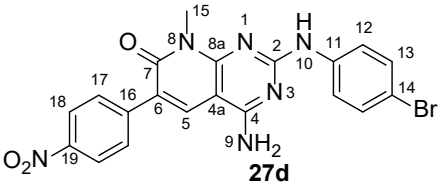
Synthesis and characterization of 4-amino-2-((4-bromophenyl)amino)-6-(4-fluorophenyl)-8-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**27c**)



27c

4-amino-2-((4-bromophenyl)amino)-6-iodo-8-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**26**) (150 mg, 0.318 mmol), *p*-fluorophenyl boronic acid (62.2 mg, 0.445 mmol), cesium carbonate (0.362 g, 1.11 mmol) and tetrakis(triphenylphosphine)palladium(0) (7.4 mg, 0.0064 mmol, 2 mol%) with deoxygenated 1,4-dioxane/water (15 mL) mixture. 88.2 mg (0.200 mmol, 63%) of a white solid spectroscopically pure 4-amino-2-((4-bromophenyl)amino)-8-methyl-6-(4-fluorophenyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**27c**) were obtained after an automatic flash chromatography (silica, from 100:0 to 50:50 of cyclohexane/AcOEt as eluent in 40 min.; retention time of **27c**: 25-31 min.). m.p. 295-297 °C (decomposition); **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm): 9.53 (s, 1H, H-N10), 8.31 (s, 1H, H-C5), 7.86 – 7.79 (m, 2H, H-C12), 7.79 – 7.73 (m, 2H, H-C17), 7.51 (s, 2H, H-N9), 7.47 – 7.41 (m, 2H, H-C13), 7.28 – 7.21 (m, 2H, H-C18), 3.62 (s, 3H, H-C15); **^{13}C NMR** (100.5 MHz, DMSO-d_6) δ (ppm): 161.8 (C4), 161.7 (C7*), 161.4 (d, *J* = 244.1 Hz, C19), 158.5 (C2), 155.3 (C8a*), 140.0 (C11), 133.4 (d, *J* = 3.2 Hz, C16), 131.4 (C5), 131.2 (C13), 130.5 (d, *J* = 7.9 Hz, C17), 122.2 (C6), 121.3 (C12), 114.7 (d, *J* = 21.0 Hz, C18), 113.0 (C14), 92.4 (C4a), 28.6 (C15); **^{19}F NMR** (376 MHz, DMSO-d_6) δ (ppm): -115.2 (tt, *J* = 8.9, 5.6 Hz, 1F); **IR** (KBr) ν_{max} (cm^{-1}): 3529, 3420, 3319, 2924, 1646, 1618, 1567, 1516, 1451, 1404, 1303, 1211, 1158, 1007, 832, 795, 541; **MS** (70 eV, EI) m/z (%): 441.1 (95) [$C_{20}H_{15}{}^{81}BrFN_5O$, M]$^+$, 439.2 (100) [$C_{20}H_{15}{}^{79}BrFN_5O$, M]$^+$, 412.1 (20) [$C_{19}H_{12}{}^{81}BrFN_4O$, M-NMe]$^+$, 410.1 (20) [$C_{19}H_{12}{}^{79}BrFN_4O$, M-NMe]$^+$, 360.2 (16) [M-Br]$^+$; **HRMS** (APCI-FIA-TOF) (m/z): calcd for $C_{20}H_{16}{}^{79}BrFN_5O$ [M+H]$^+$: 440.0517; found: 440.0514.

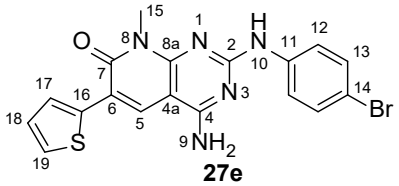
Synthesis and characterization of 4-amino-2-((4-bromophenyl)amino)-8-methyl-6-(4-nitrophenyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**27d**)



27d

4-amino-2-((4-bromophenyl)amino)-6-iodo-8-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**26**) (150 mg, 0.318 mmol), *p*-nitrophenyl boronic acid (74.3 mg, 0.445 mmol), cesium carbonate (0.362 g, 1.11 mmol) and tetrakis(triphenylphosphine)palladium(0) (7.35 mg, 0.0064 mmol, 2 mol%) with deoxygenated 1,4-dioxane/water (15 mL) mixture. 90.4 mg (0.193 mmol, 61%) of a orange solid spectroscopically pure 4-amino-2-((4-bromophenyl)amino)-8-methyl-6-(4-nitrophenyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**27d**) were obtained after an automatic flash chromatography (silica, from 100:0 to 10:90 of cyclohexane/AcOEt as eluent in 70 min.; retention time of **27d**: 22-55 min.). m.p. > 300 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm): 9.64 (s, 1H, H-N10), 8.54 (s, 1H, H-C5), 8.30 – 8.24 (m, 2H, H-C18), 8.11 – 8.05 (m, 2H, H-C17), 7.85 – 7.80 (m, 2H, H-C12), 7.65 (br s, 2H, H-N9), 7.48 – 7.43 (m, 2H, H-C13), 3.63 (s, 3H, H-C15); **^{13}C NMR** (100.5 MHz, DMSO-d_6) δ (ppm): 162.0 (C4), 161.5 (C7*), 159.0 (C2), 155.8 (C8a*), 145.9 (C19), 144.0 (C16), 139.8 (C11), 133.3 (C5), 131.2 (C13), 129.2 (C17), 123.1 (C18), 121.6 (C12), 120.2 (C6), 113.3 (C14), 92.8 (C4a), 28.6 (C15); **IR** (KBr) ν_{max} (cm^{-1}): 3500, 3385, 3339, 1629, 1586, 1531, 1506, 1489, 1452, 1423, 1403, 1338, 1195, 857, 828, 795, 714; **MS** (70 eV, EI) m/z (%): 468.1 (100) [$C_{20}H_{15}{}^{81}BrN_6O_3$, M]$^+$, 466.1 (100) [$C_{20}H_{15}{}^{79}BrN_6O_3$, M]$^+$, 439.1 (14) [$C_{19}H_{12}{}^{81}BrN_5O_3$, M-NMe]$^+$, 437.1 (14) [$C_{19}H_{12}{}^{79}BrN_5O_3$, M-NMe]$^+$, 422.1 (9) [$C_{20}H_{15}{}^{81}BrN_5O$, M-$NO_2$]$^+$, 437.1 (14) [$C_{20}H_{15}{}^{79}BrN_5O$, M-$NO_2$]$^+$, 387.2 (11) [M-Br]$^+$; **HRMS** (APCI-FIA-TOF) (m/z): calcd for $C_{20}H_{16}{}^{79}BrN_6O_3$ [M+H]$^+$: 467.0462; found: 467.0459.

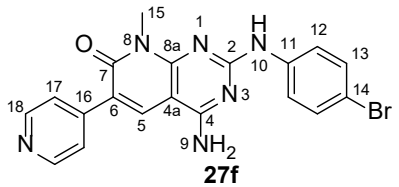
Synthesis and characterization of 4-amino-2-((4-bromophenyl)amino)-8-methyl-6-(thiophen-2-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**27e**)



27e

4-amino-2-((4-bromophenyl)amino)-6-iodo-8-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**26**) (200 mg, 0.424 mmol), thiophen-2-ylboronic acid (75.9 mg, 0.593 mmol), cesium carbonate (0.483 g, 1.48 mmol) and tetrakis(triphenylphosphine)palladium(0) (9.80 mg, 0.0085 mmol, 2 mol%) with deoxygenated 1,4-dioxane/water (20 mL) mixture. 132.0 mg (0.30 mmol, 73%) of a brownish solid spectroscopically pure 4-amino-2-((4-bromophenyl)amino)-8-methyl-6-(thiophen-2-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**27e**) were obtained after an automatic flash chromatography (silica, from 100:0 to 50:50 of cyclohexane/AcOEt as eluent in 40 min.; retention time of **27e**: 27-35 min.). m.p. 252-254 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm): 9.56 (s, 1H, H-N10), 8.70 (s, 1H, H-C5), 7.86 – 7.79 (m, 2H, H-C12), 7.74 (dd, J = 3.8, 1.2 Hz, 1H, H-C17), 7.60 (br s, 2H, H-N9), 7.49 (dd, J = 5.1, 1.2 Hz, 1H, H-C19), 7.47 – 7.42 (m, 2H, H-C13), 7.13 (dd, J = 5.1, 3.7 Hz, 1H, H-C18), 3.65 (s, 3H, H-C15); **^{13}C NMR** (100.5 MHz, DMSO-d_6) δ (ppm): 161.6 (C4), 160.8 (C7*), 158.4 (C2), 154.4 (C8a*), 139.9 (C11), 137.6 (C16), 131.2 (C13), 127.2 (C5), 126.5 (C19), 126.3 (C18), 123.2 (C17), 121.4 (C12), 117.1 (C6), 113.0 (C14), 92.5 (C4a), 28.7 (C15); **IR** (KBr) ν_{max} (cm^{-1}): 3408, 3183, 1677, 1630, 1603, 1564, 1537, 1462, 1415, 1332, 1073, 1005, 792, 759, 689; **MS** (70 eV, EI) m/z (%): 429.1 (100) [$C_{18}H_{14}{}^{81}BrN_5OS$, M]$^+$, 427.1 (100) [$C_{18}H_{14}{}^{79}BrN_5OS$, M]$^+$, 349.1 (35) [M-Br]$^+$; **HRMS** (APCI-FIA-TOF) (m/z): calcd for $C_{18}H_{15}{}^{79}BrN_5OS$ [M+H]$^+$: 428.0175; found: 428.0173.

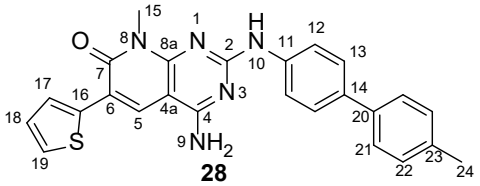
Synthesis and characterization of 4-amino-2-((4-bromophenyl)amino)-8-methyl-6-(pyridin-4-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**27f**)



27f

4-amino-2-((4-bromophenyl)amino)-6-iodo-8-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**26**) (80.0 mg, 0.169 mmol), 4-pyridinylboronic acid (29.2 mg, 0.237 mmol), cesium carbonate (0.194 g, 0.593 mmol) and tetrakis(triphenylphosphine)palladium(0) (3.92 mg, 0.0034 mmol, 2 mol%) with deoxygenated 1,4-dioxane/water (8 mL) mixture. 37.3 mg (0.0881 mmol, 52%) of a yellowish solid spectroscopically pure 4-amino-2-((4-bromophenyl)amino)-8-methyl-6-(pyridin-4-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**27f**) were obtained after an automatic flash chromatography (silica, from 100:0 to 0:100 of cyclohexane/AcOEt as eluent in 110 min.; retention time of **27f**: 59-100 min.). m.p. > 300 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm): 9.62 (s, 1H, H-N10), 8.62 – 8.56 (m, 2H, H-C18), 8.55 (s, 1H, H-C5), 7.86 – 7.80 (m, 4H, H-C17 and H-C12), 7.64 (br s, 2H, H-N9), 7.49 – 7.43 (m, 2H, H-C13), 3.62 (s, 3H, H-C15). **^{13}C NMR** (100.5 MHz, DMSO-d_6) δ (ppm): 161.9 (C7*), 161.4 (C4), 159.0 (C2), 155.8 (C8a*), 149.3 (C18), 144.3 (C16), 139.8 (C11), 132.9 (C5), 131.2 (C13), 122.6 (C17), 121.5 (C12), 119.4 (C6), 113.2 (C14), 92.6 (C4a), 28.5 (C15); **IR** (KBr) ν_{max} (cm^{-1}): 3423, 3382, 3197, 2922, 1645, 1572, 1513, 1489, 1448, 1410, 1340, 1202, 1072, 996, 826, 798; **MS** (70 eV, EI) m/z (%): 424.2 (91) [$C_{19}H_{15}{}^{81}BrN_6O$, M]$^+$, 422.2 (100) [$C_{19}H_{15}{}^{79}BrN_6O$, M]$^+$, 395.1 (21) [$C_{18}H_{12}{}^{81}BrN_5O$, M-NMe]$^+$, 393.1 (21) [$C_{18}H_{12}{}^{79}BrN_5O$, M-NMe]$^+$, 343.2 (10) [M-Br]$^+$; **HRMS** (APCI-FIA-TOF) (m/z): calcd for $C_{19}H_{16}{}^{79}BrN_6O$ [M+H]$^+$: 423.0563; found: 423.0560.

Synthesis and characterization of 4-amino-8-methyl-2-((4'-methyl-[1,1'-biphenyl]-4-yl)amino)-6-(thiophen-2-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**28**)



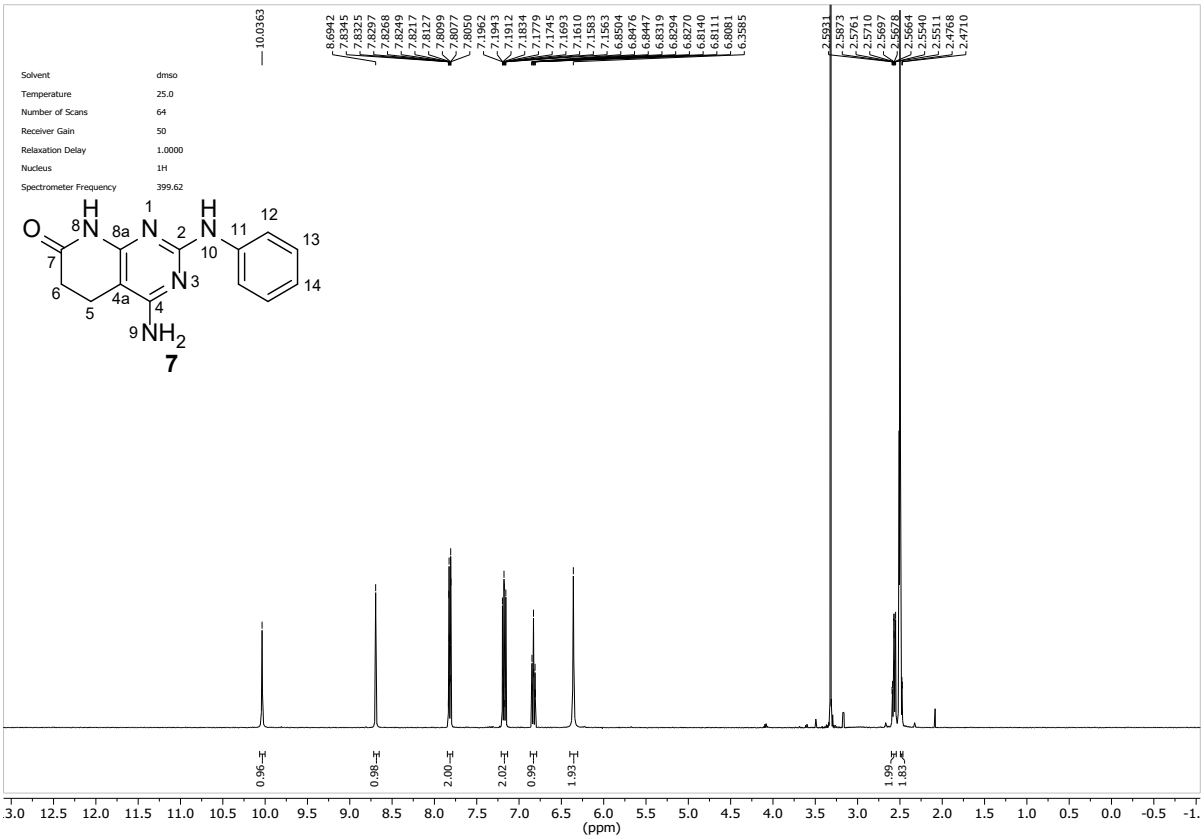
28

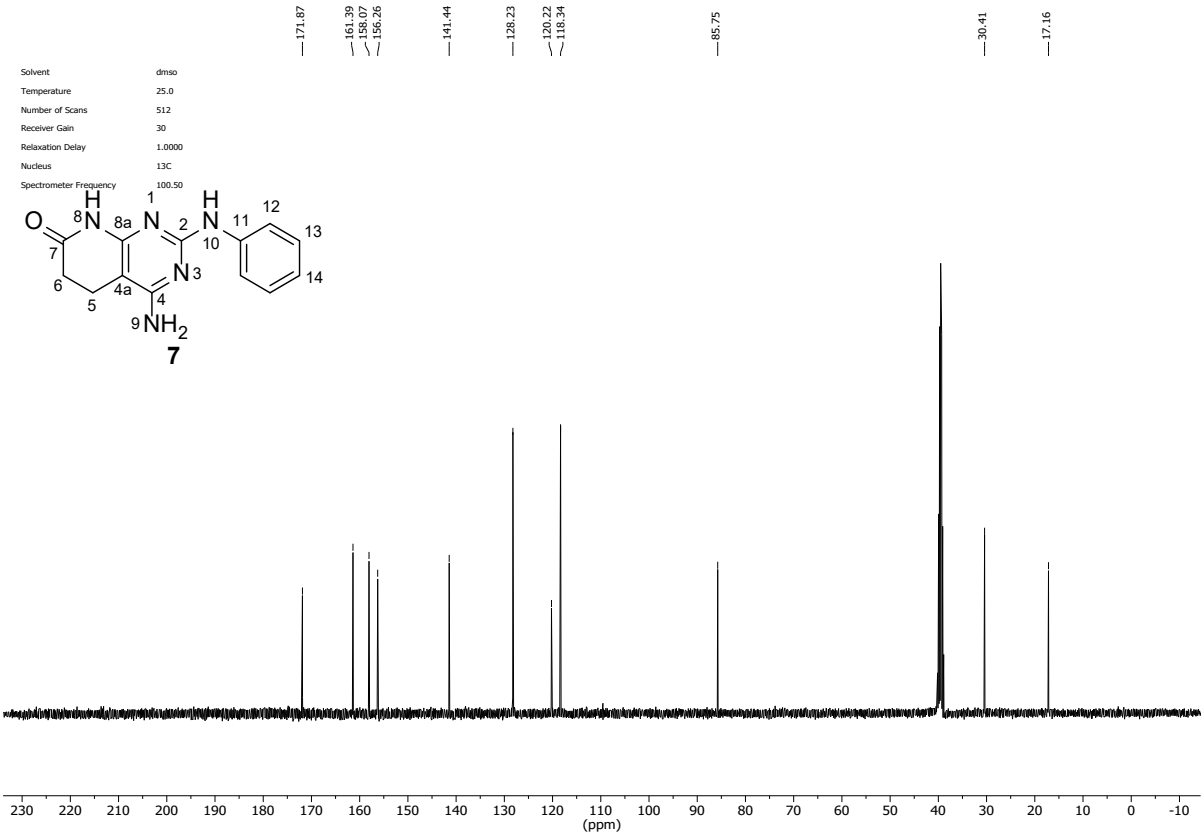
4-amino-2-((4-bromophenyl)amino)-8-methyl-6-(thiophen-2-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**27e**) (50.0 mg, 0.117 mmol), *p*-tolyl boronic acid (22.2 mg, 0.163 mmol, 1.4 equiv.) and cesium carbonate (0.133 g, 0.407 mmol, 2.5 equiv. with regarding to boronic acid) are dissolved with 1,4-dioxane/water (5 mL, 10:1) deoxygenated mixture in a microwave vial. Tetrakis(triphenylphosphine)palladium(0) (20.2 mg, 0.017 mmol, 15 mol%) is added, the vial is sealed and the reaction is heated in an

oil bath at 90 °C for 2 h. After addition of water (solvent volume x 10 mL), the solid appeared can be isolated by filtration and washed with water. 11.6 mg (0.0264 mmol, 23%) of a brownish solid spectroscopically pure 4-amino-8-methyl-2-((4'-methyl-[1,1'-biphenyl]-4-yl)amino)-6-(thiophen-2-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**28**) were obtained after an automatic flash chromatography (silica, from 100:0 to 50:50 of cyclohexane/AcOEt as eluent in 45 min.; retention time of **28**: 25-33 min.). m.p. 265-268 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm): 9.53 (s, 1H, H-N10), 8.72 (s, 1H, H-C5), 7.96 – 7.90 (m, 2H, H-C12), 7.75 (dd, *J* = 3.8, 1.2 Hz, 1H, H-C17), 7.60 – 7.54 (m, 6H, H-C13, H-N9, H-C21), 7.48 (dd, *J* = 5.1, 1.1 Hz, 1H, H-C19), 7.27 – 7.23 (m, 2H, H-C22), 7.14 (dd, *J* = 5.1, 3.7 Hz, 1H, H-C18), 3.69 (s, 3H, H-C15), 2.33 (s, 3H, H-C24); **^{13}C NMR** (100.5 MHz, DMSO-d_6) δ (ppm): 161.6 (C4), 160.8 (C7*), 158.6 (C2), 154.5 (C8a*), 139.7 (C11), 137.7 (C16), 137.1 (C20), 135.9 (C23), 133.2 (C14), 129.5 (C22), 127.3 (C5), 126.43 (C19), 126.35 (C13), 126.2 (C18), 125.9 (C21), 123.1 (C17), 119.8 (C12), 116.8 (C6), 92.4 (C4a), 28.7 (C15), 20.7 (C24); **IR** (KBr) ν_{max} (cm^{-1}): 3625, 3431, 3351, 3173, 2922, 1674, 1627, 1602, 1578, 1540, 1499, 1462, 1422, 1336, 1198, 1005, 814, 793, 696, 552; **MS** (70 eV, EI) m/z (%): 440.2 (14) $[C_{25}H_{21}N_5OS, M]^+$, 439.2 (45) $[C_{25}H_{21}N_5OS, M]^+$.

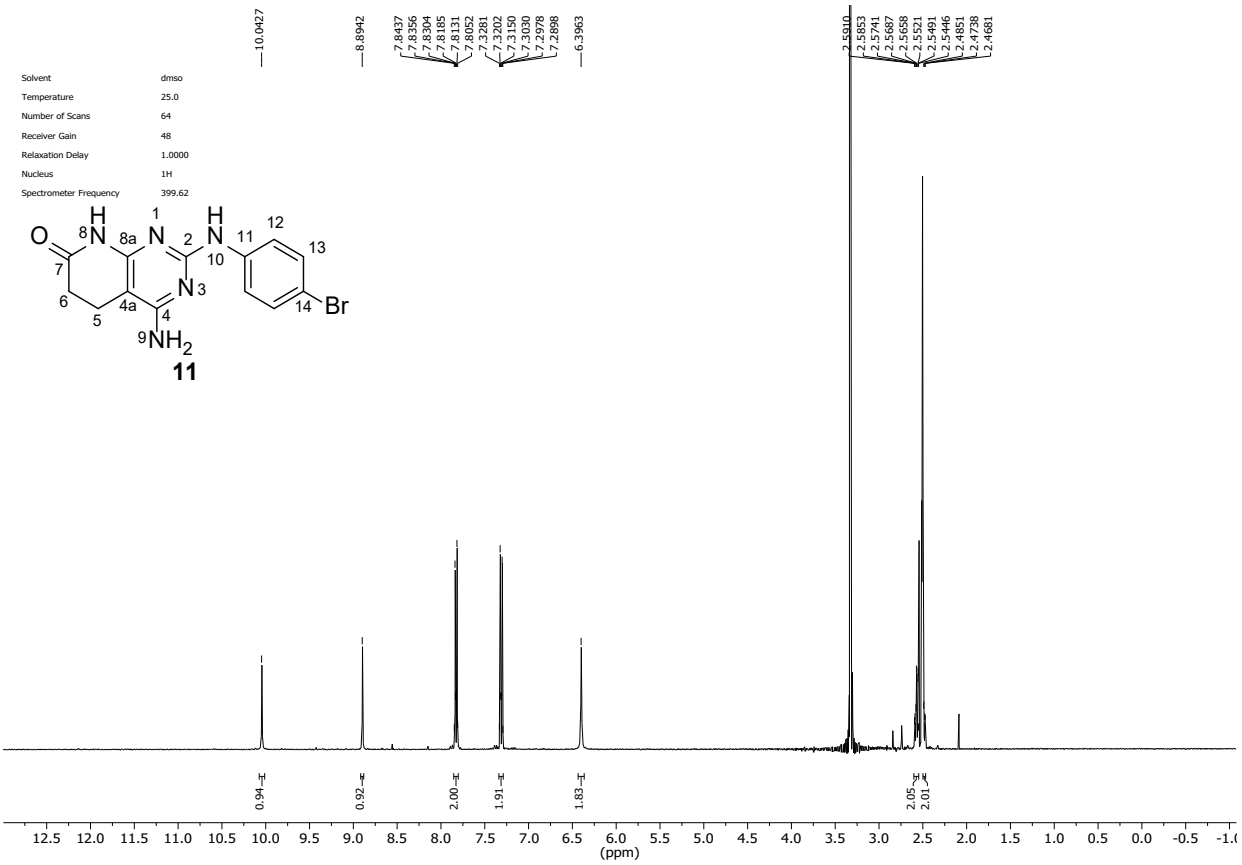
NMR Spectra

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

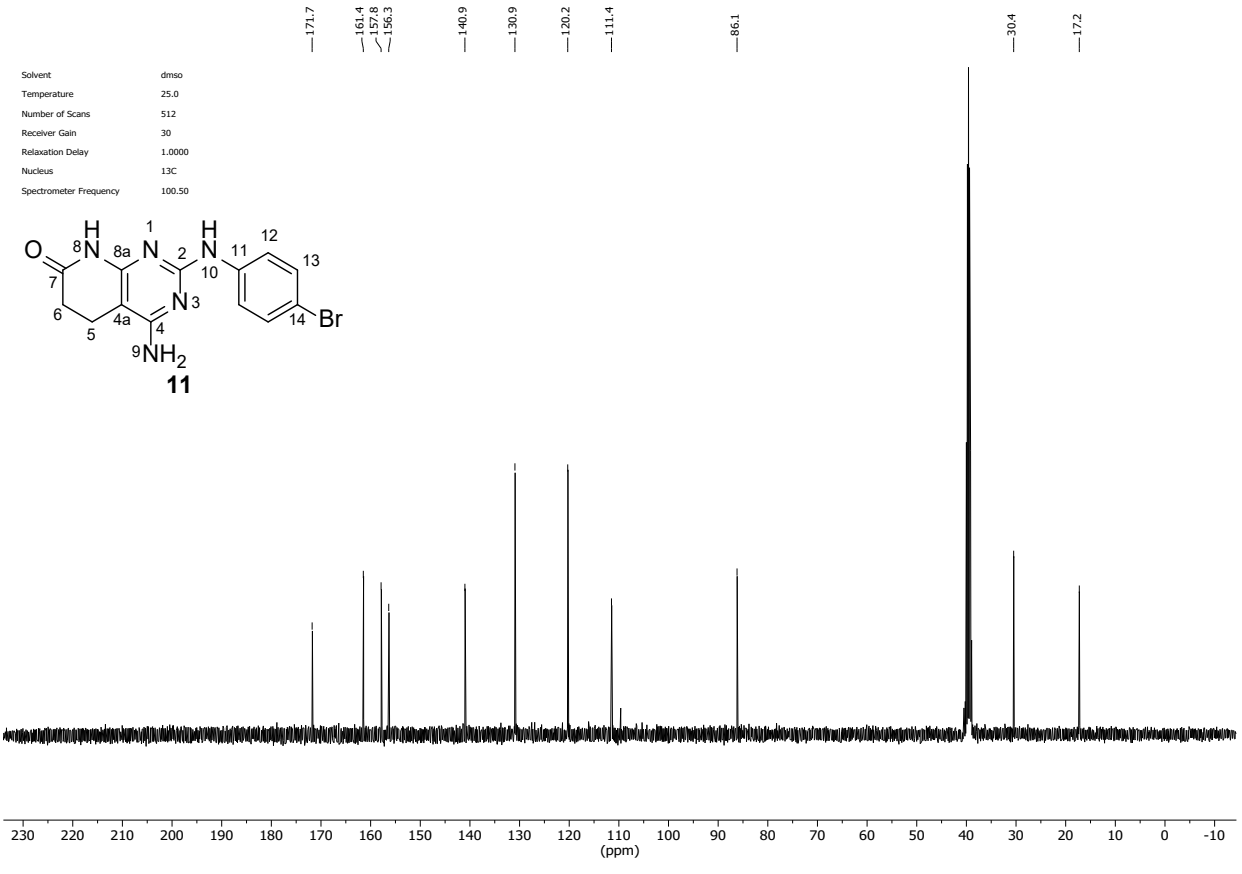




4-Amino-2-(4-bromophenylamino)-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (11)

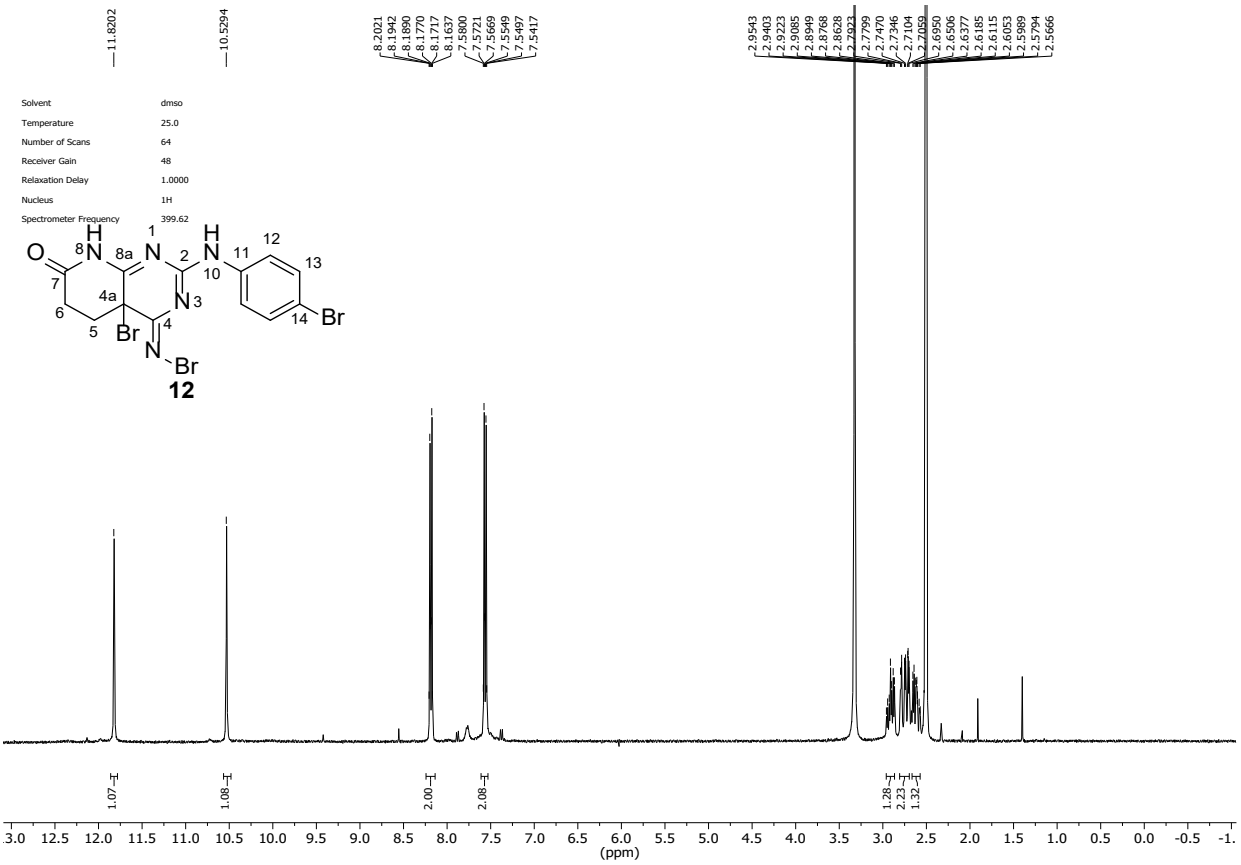


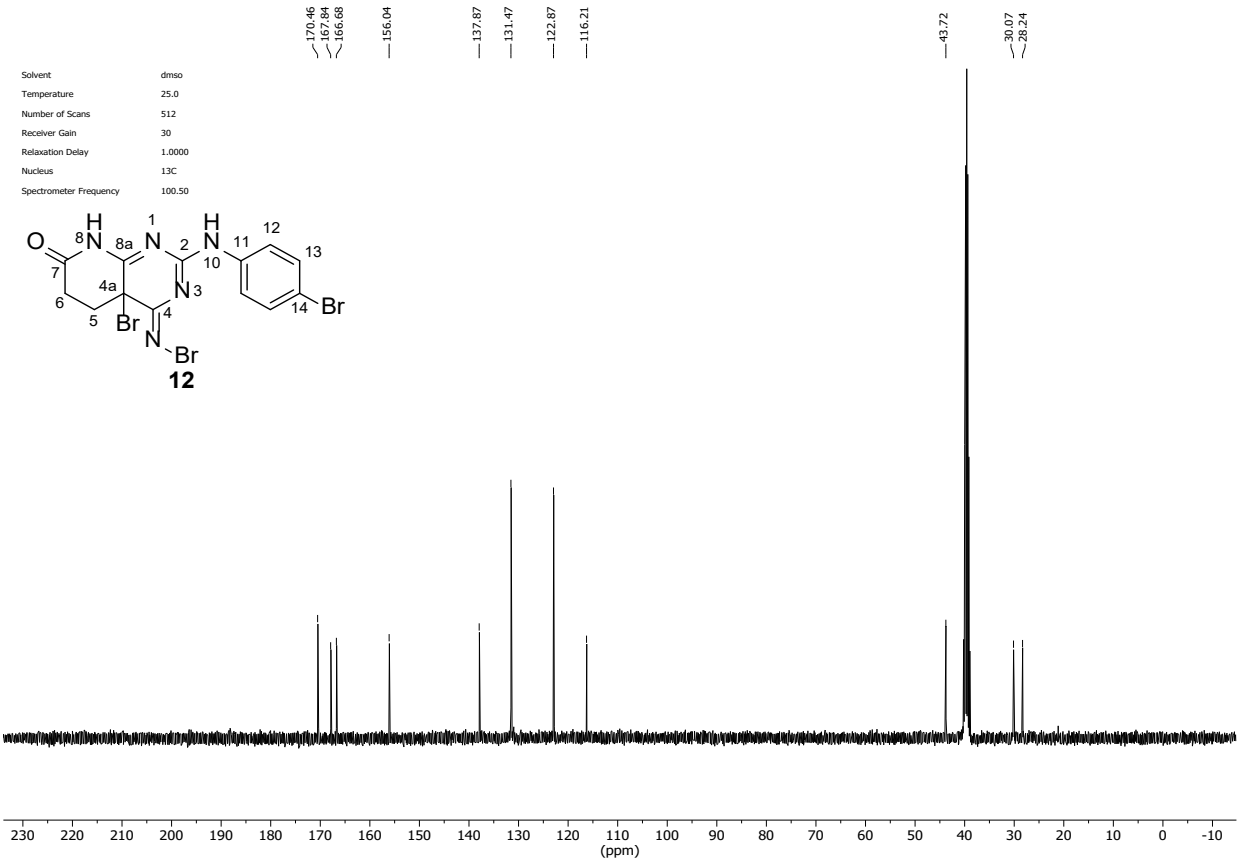
11



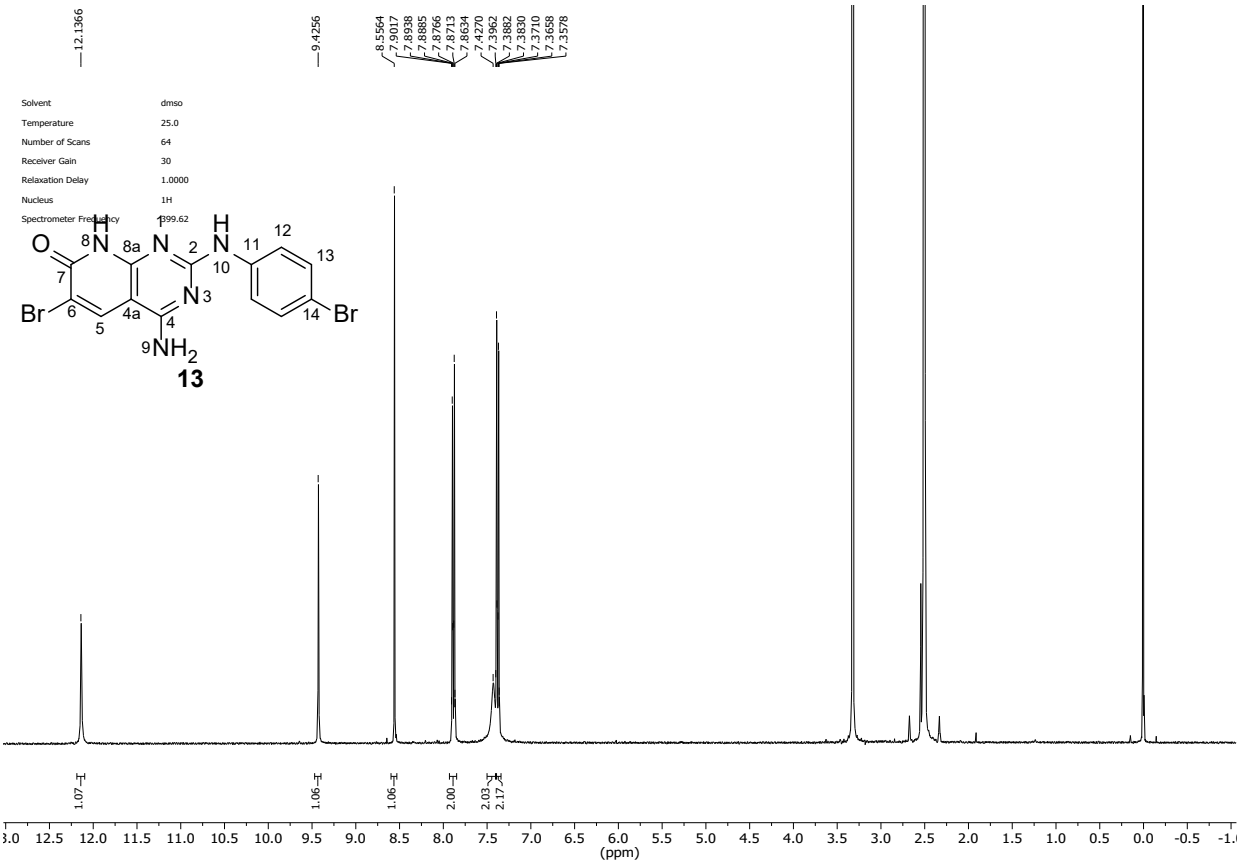
11

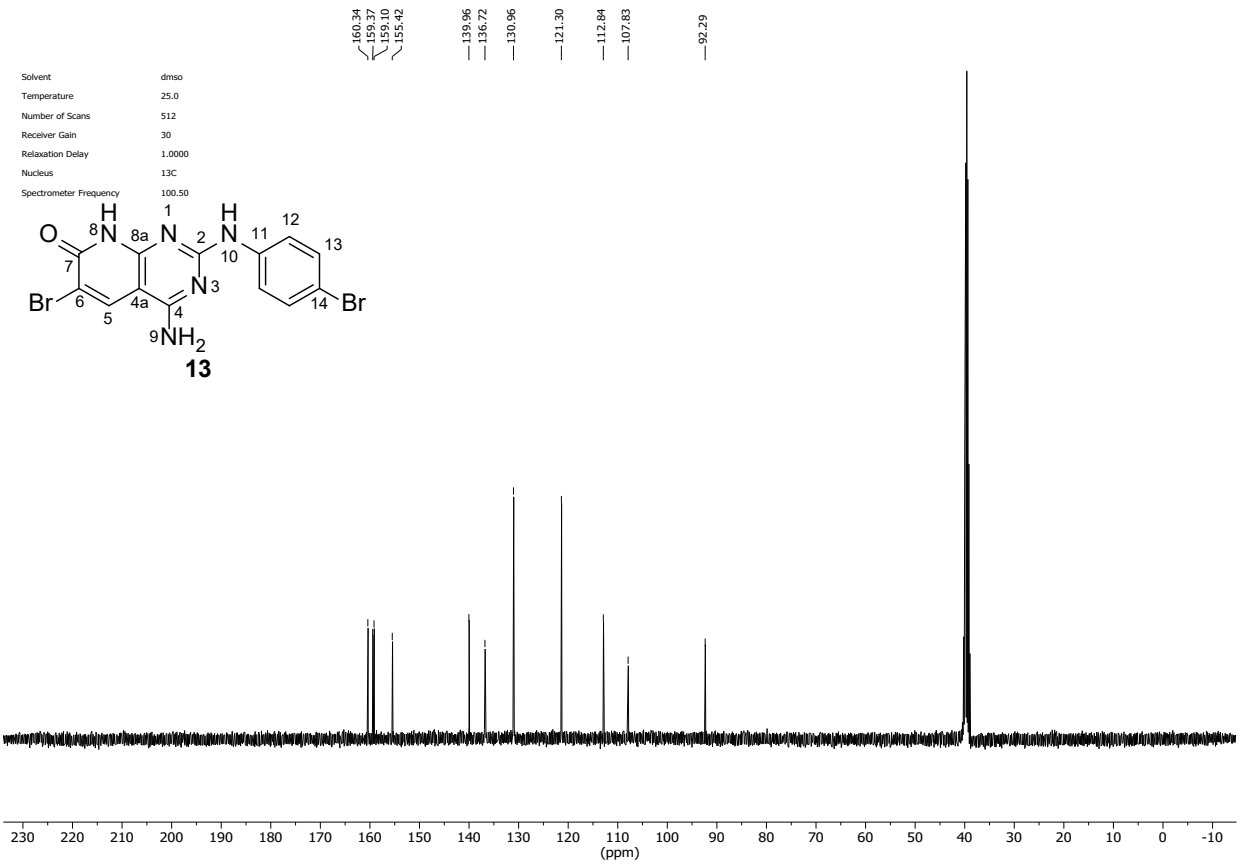
(*Z*)-4a-Bromo-4-(bromoimino)-2-((4-bromophenyl)amino)-4,5,6,8-tetrahydropyrido[2,3-*d*]pyrimidin-7(4a*H*)-one (12)



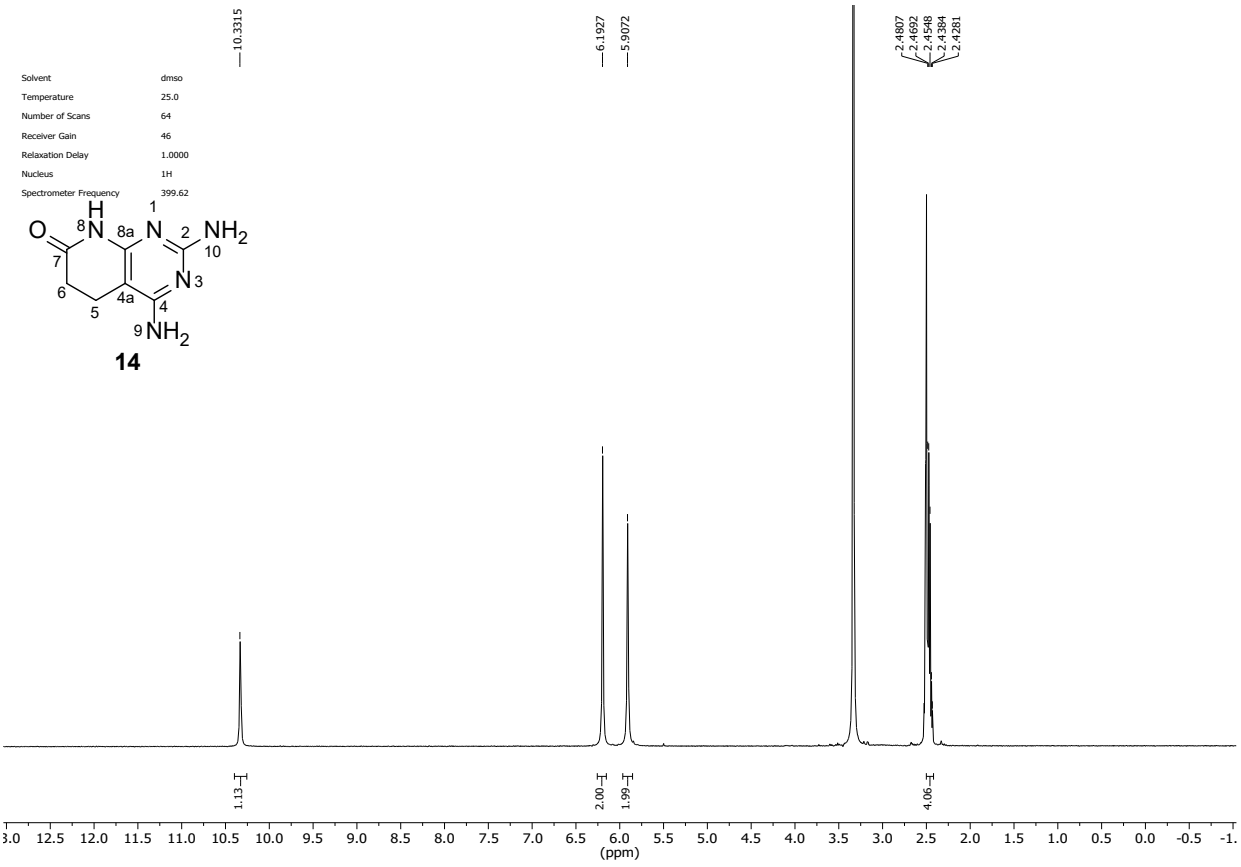


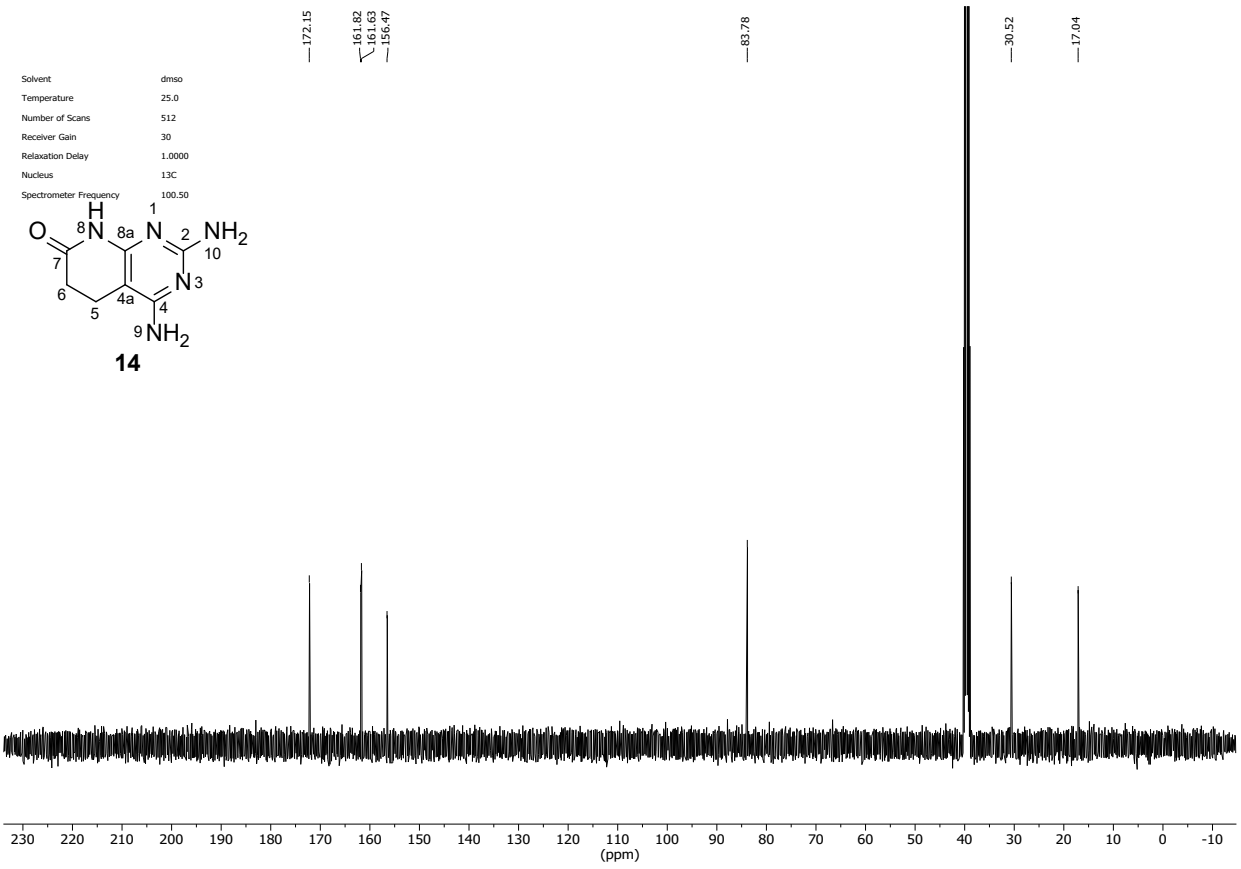
4-Amino-6-bromo-2-((4-bromophenyl)amino)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (13)



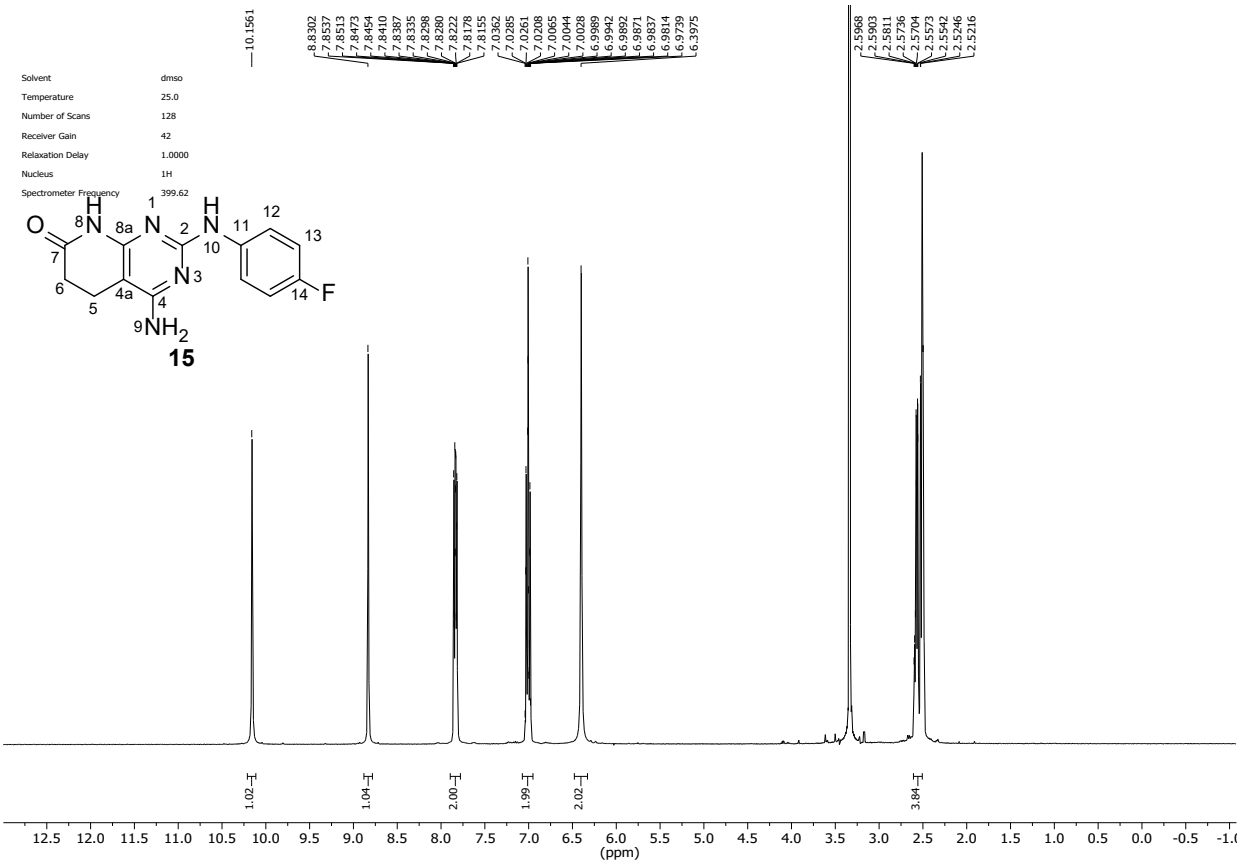


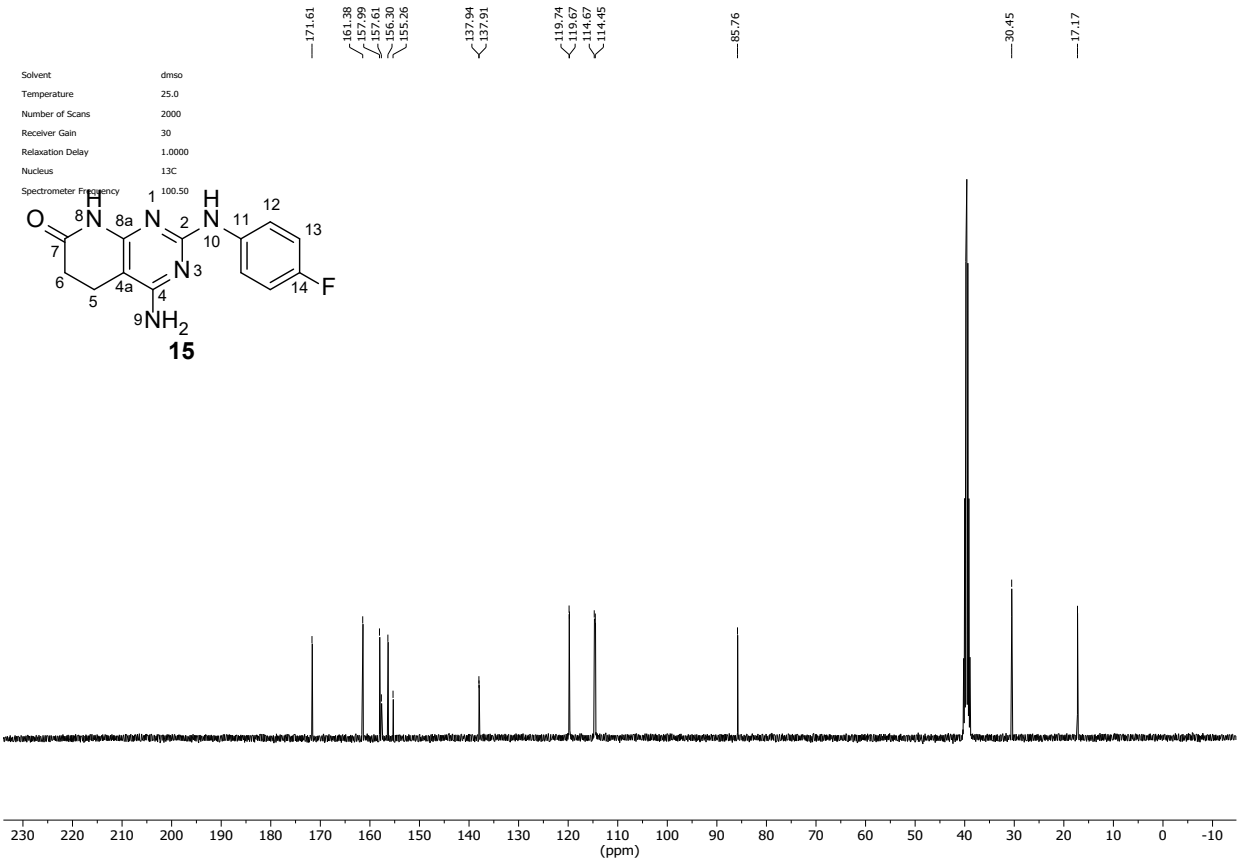
2,4-diamino-7-oxo-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidine (14)

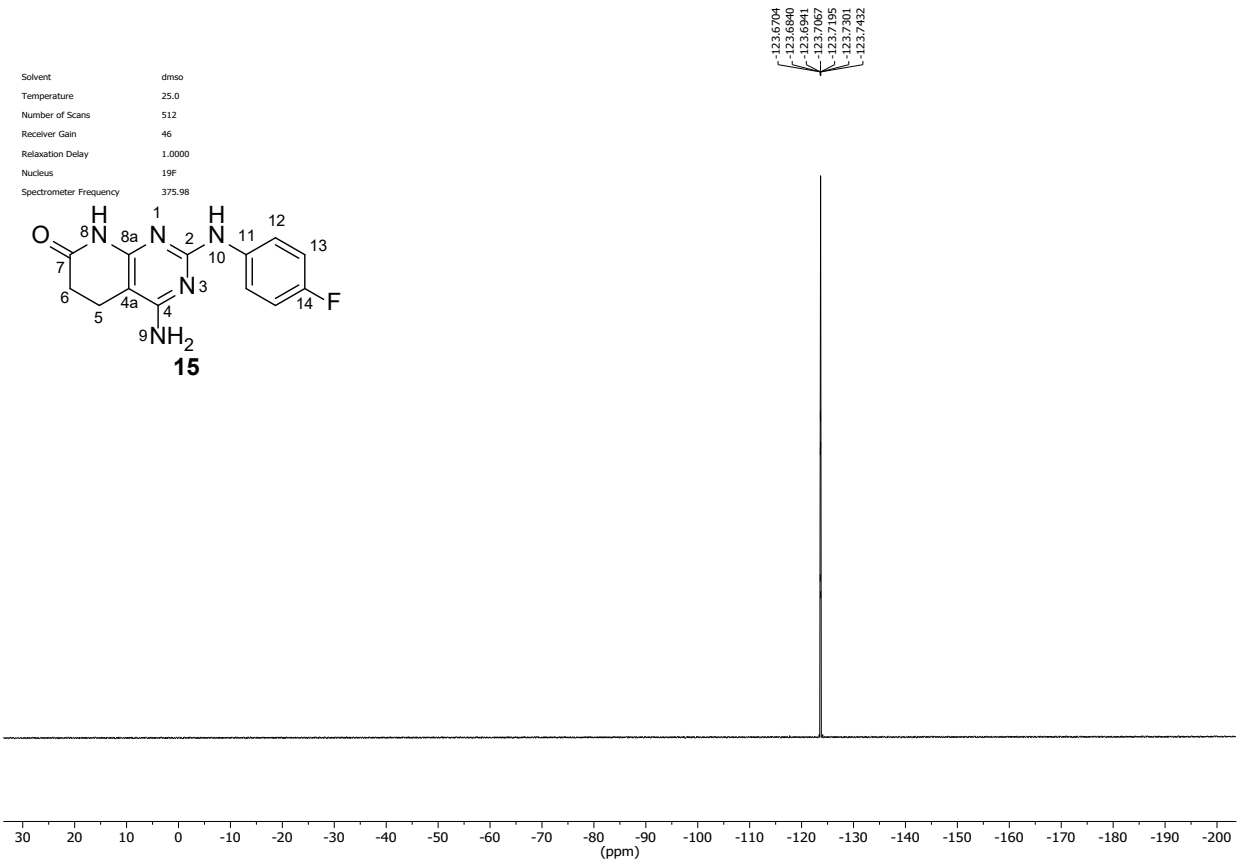




4-Amino-2-((4-fluorophenyl)amino)-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (15)



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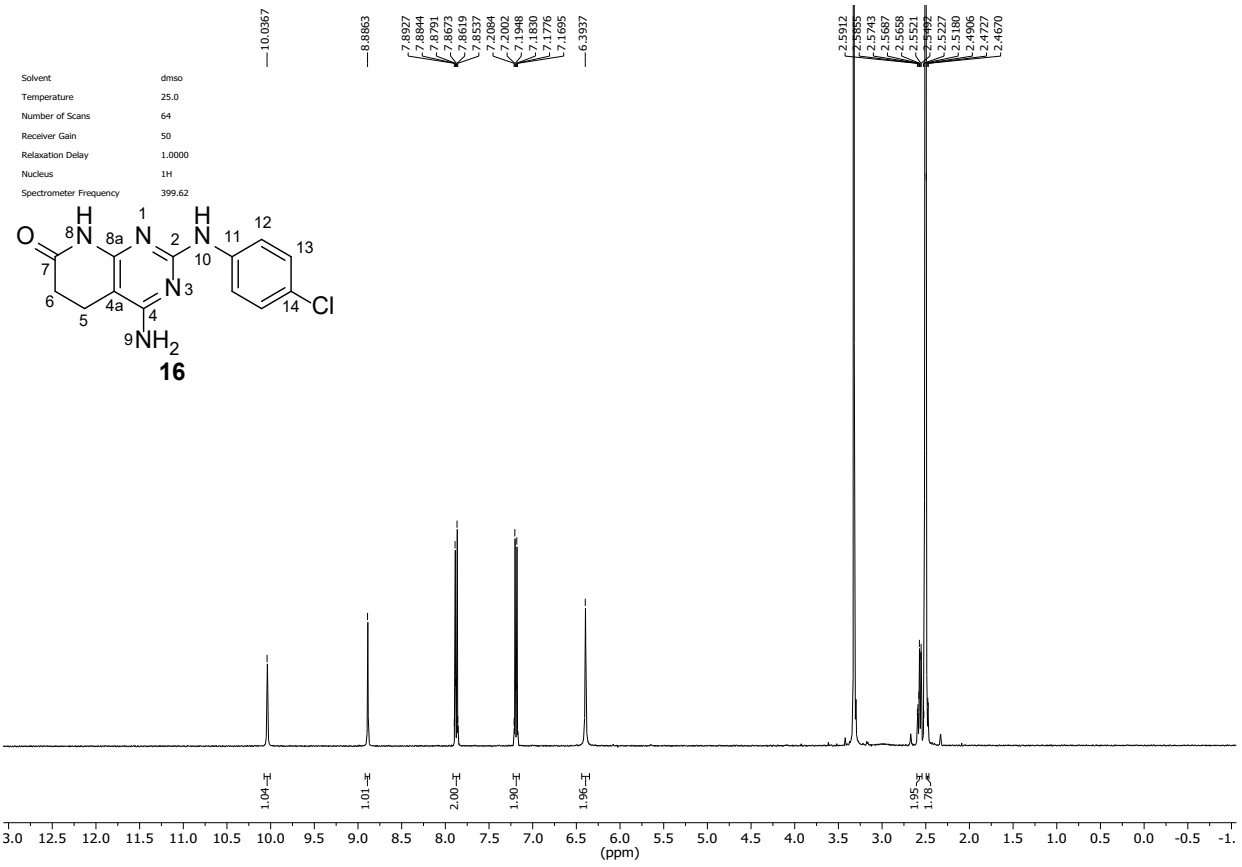
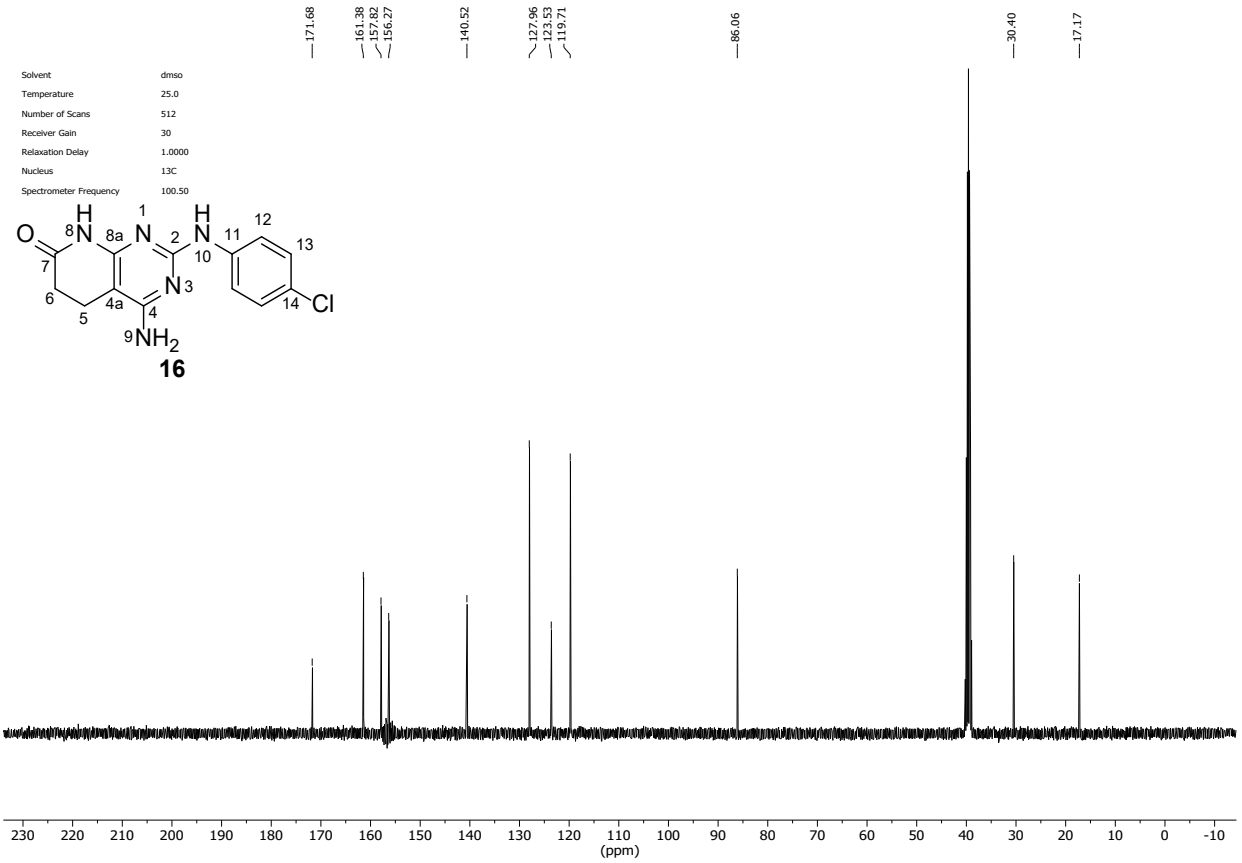
-123.7067
-123.7195
-123.7301
-123.7432
Solvent dmso
Temperature 25.0
Number of Scans 512
Receiver Gain 46
Relaxation Delay 1.0000
Nucleus 19F
Spectrometer Frequency 375.98
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
(ppm)

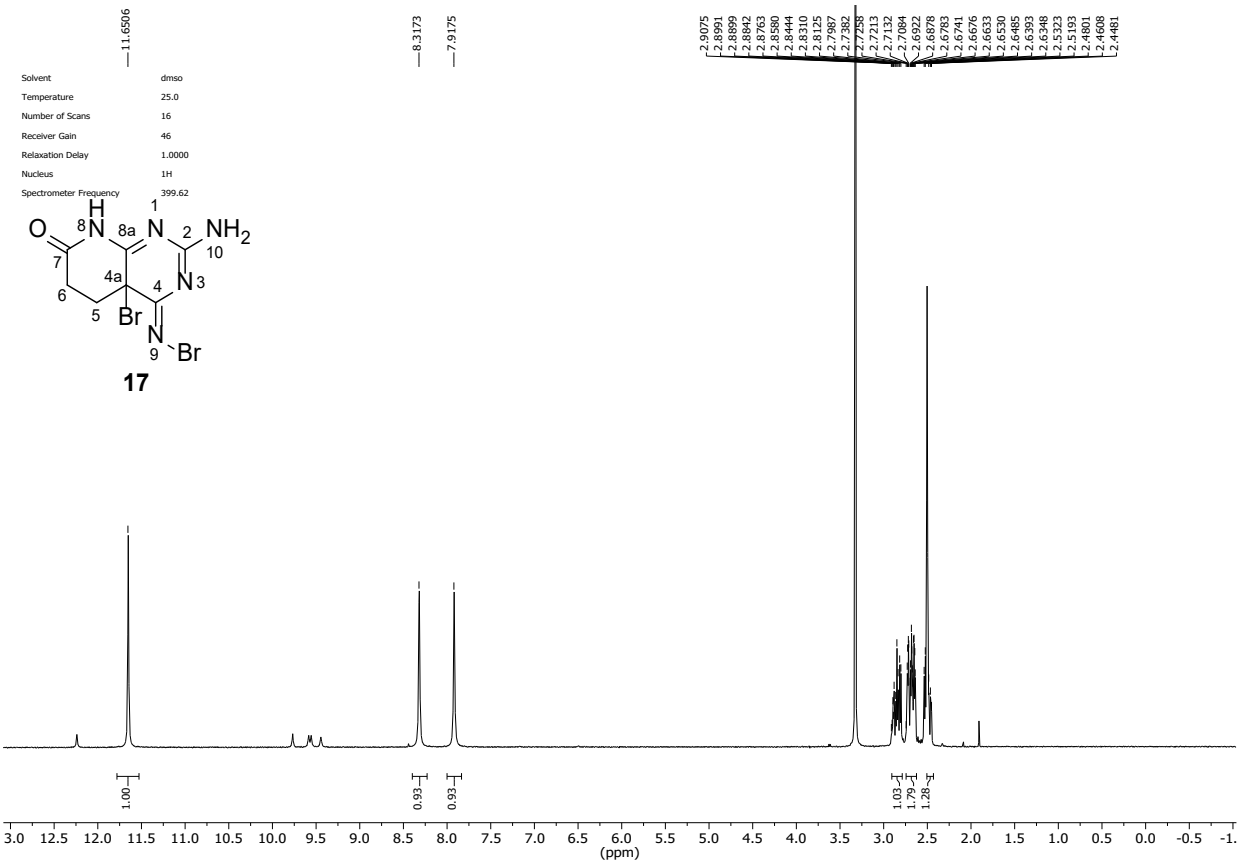
15

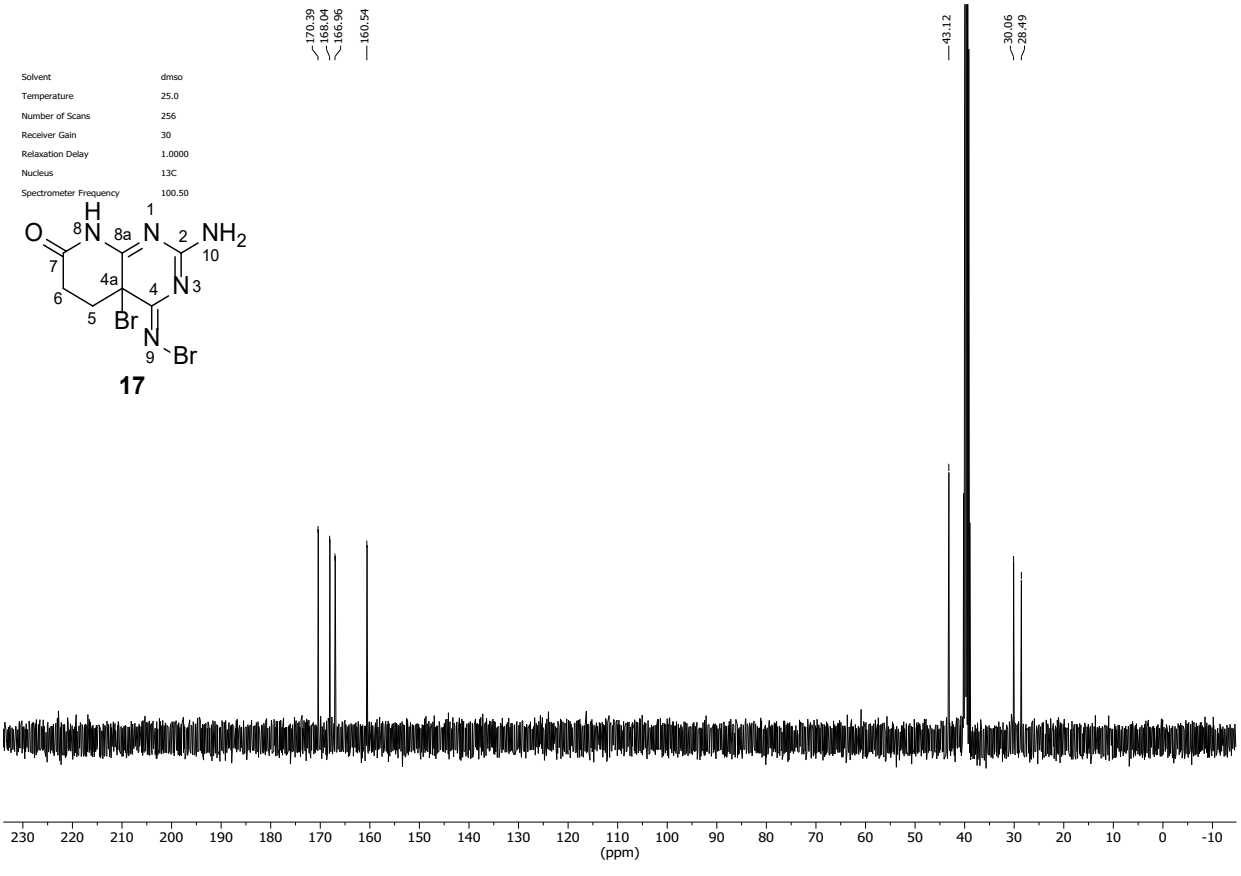
4-Amino-2-((4-chlorophenyl)amino)-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (16)



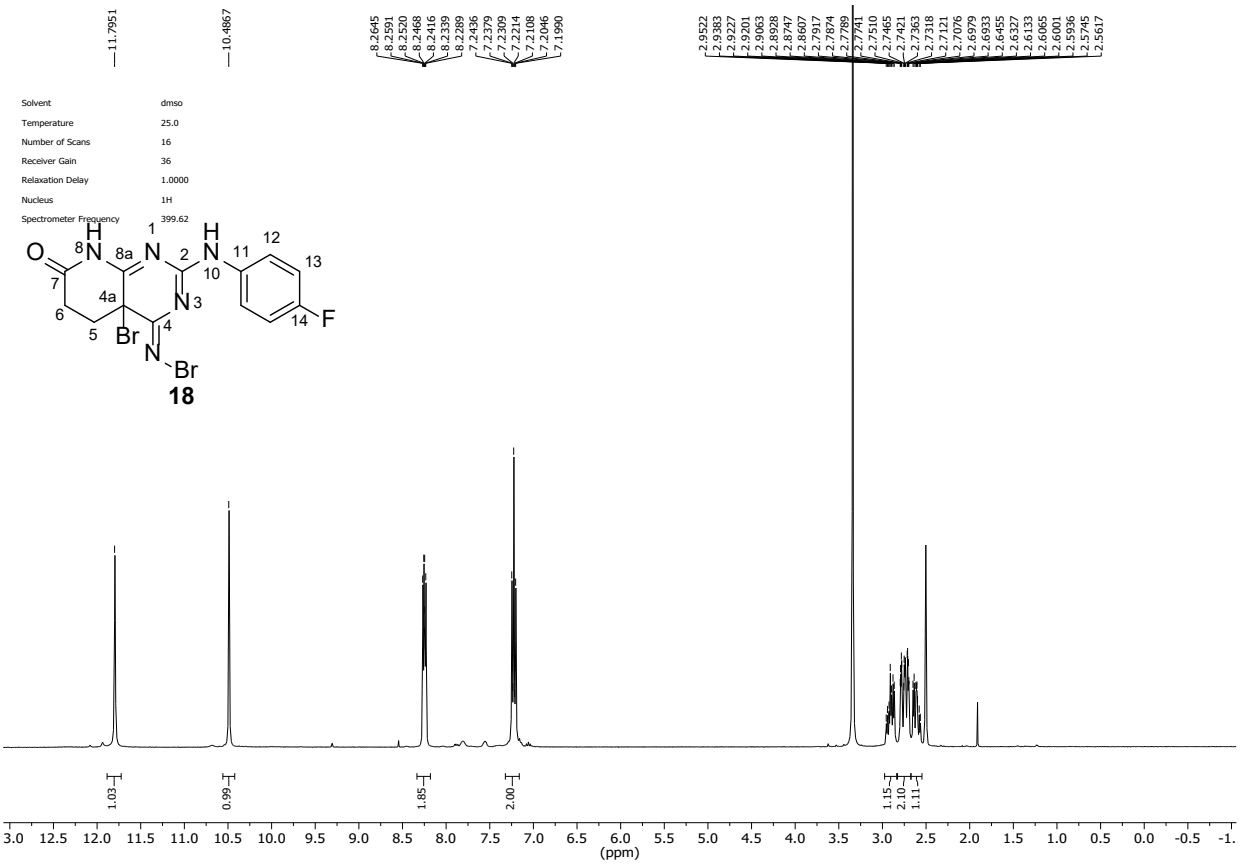


2-amino-4a-bromo-4-(bromoimino)-4,5,6,8-tetrahydropyrido[2,3-*d*]pyrimidin-7(4*aH*)-one (17)

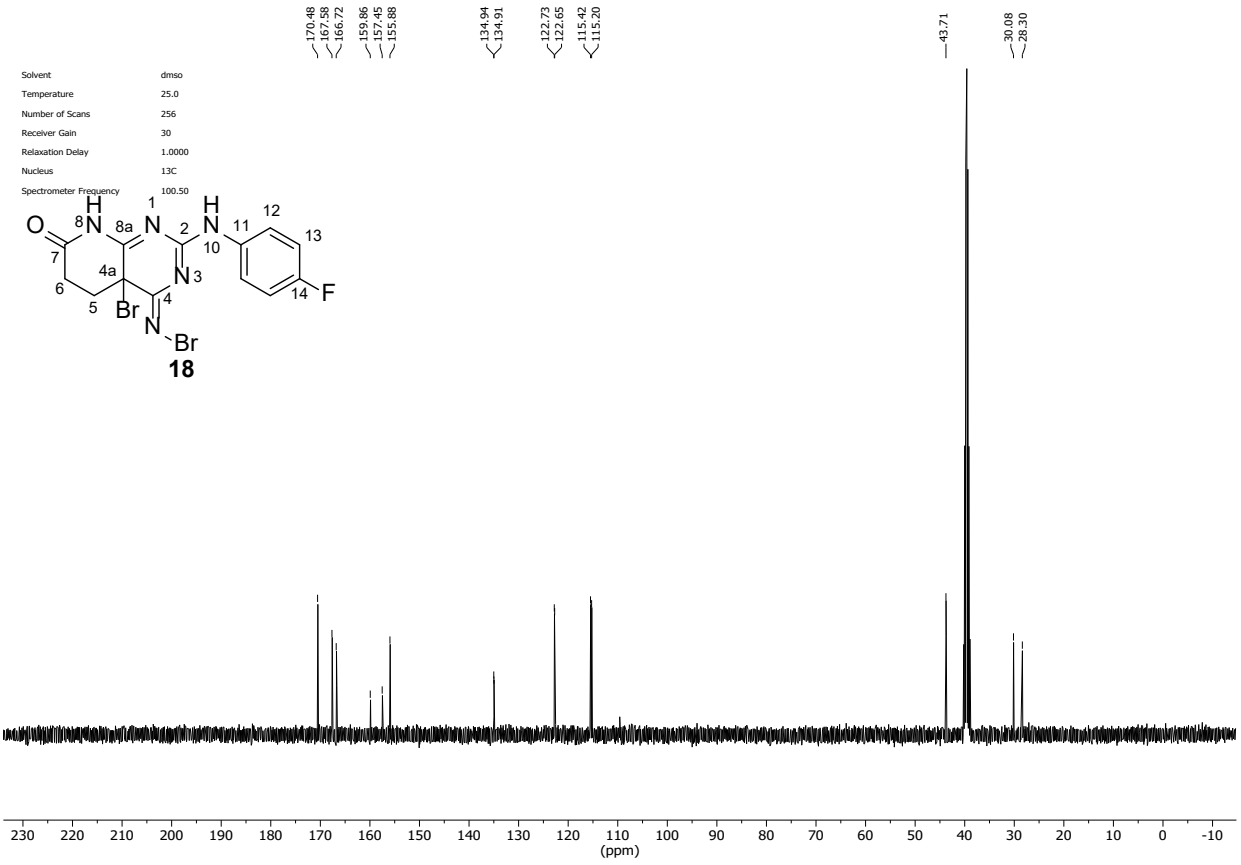




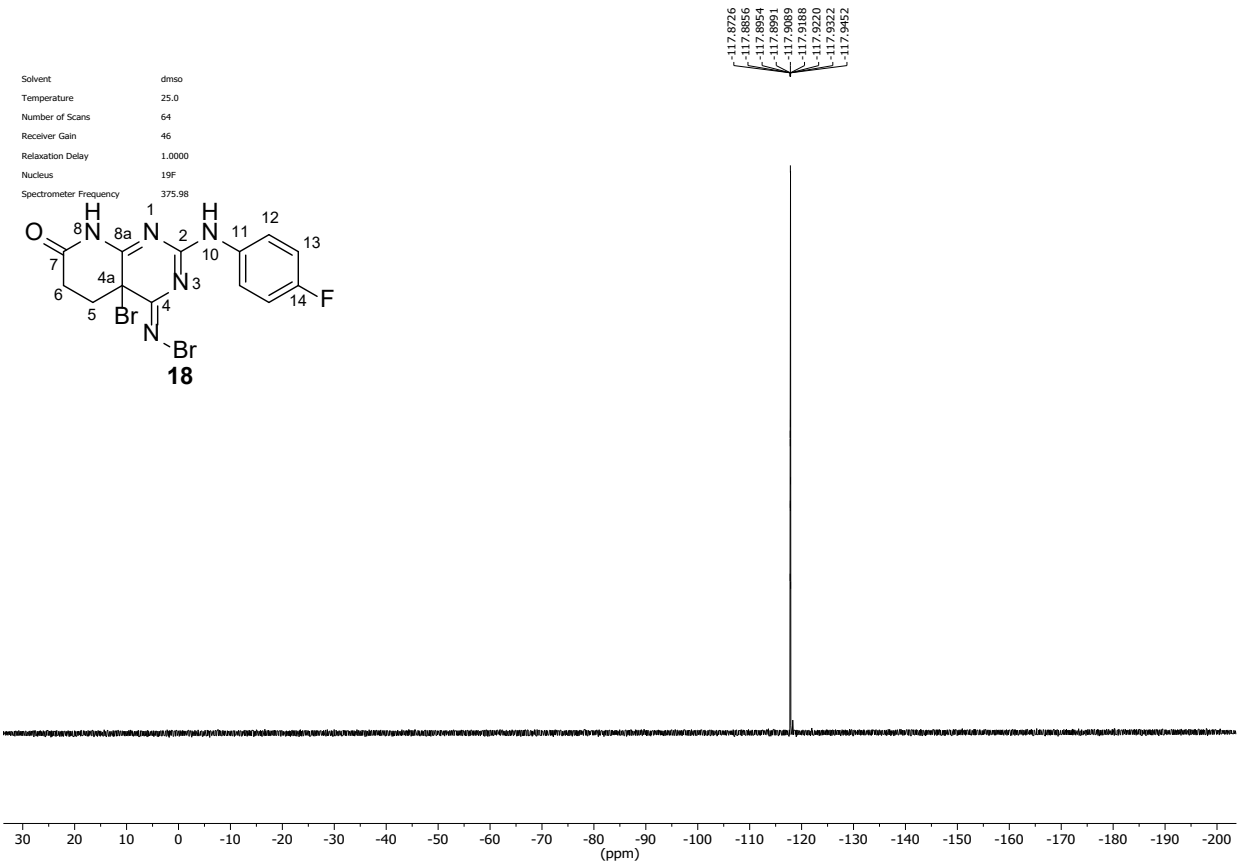
(*Z*)-4a-bromo-4-(bromoimino)-2-((4-fluorophenyl)amino)-4,5,6,8-tetrahydropyrido[2,3-*d*]pyrimidin-7(4a*H*)-one (18)



18



18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-117.8856
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-117.8991
-117.9089
-117.9188
-117.9220
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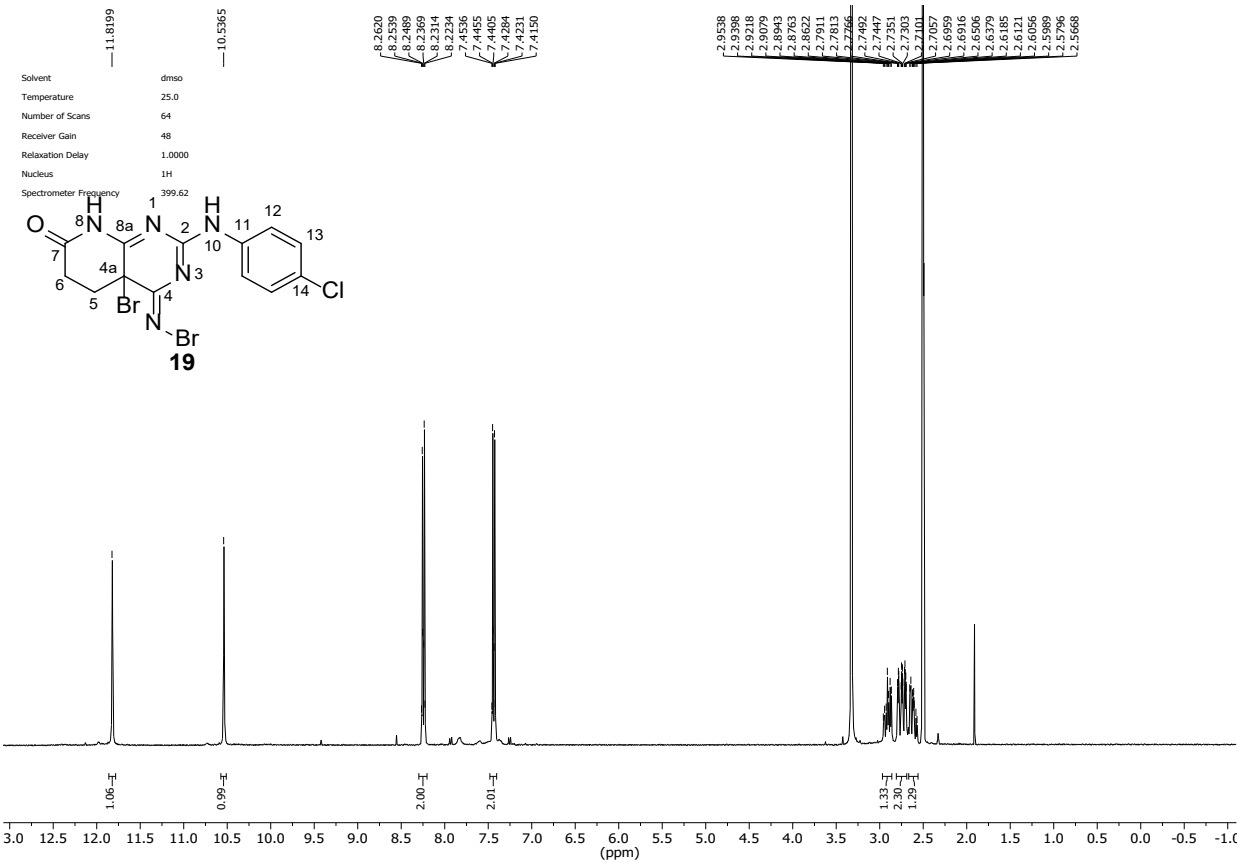
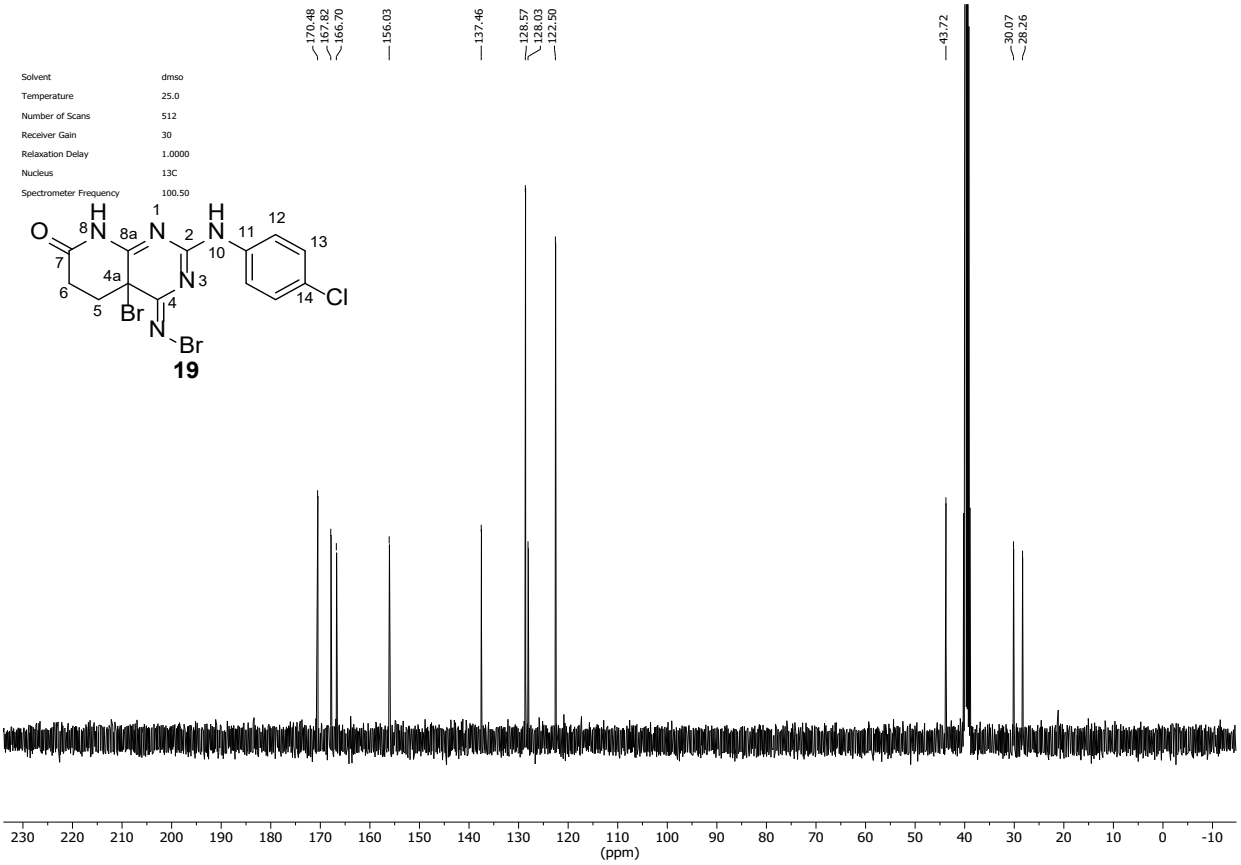
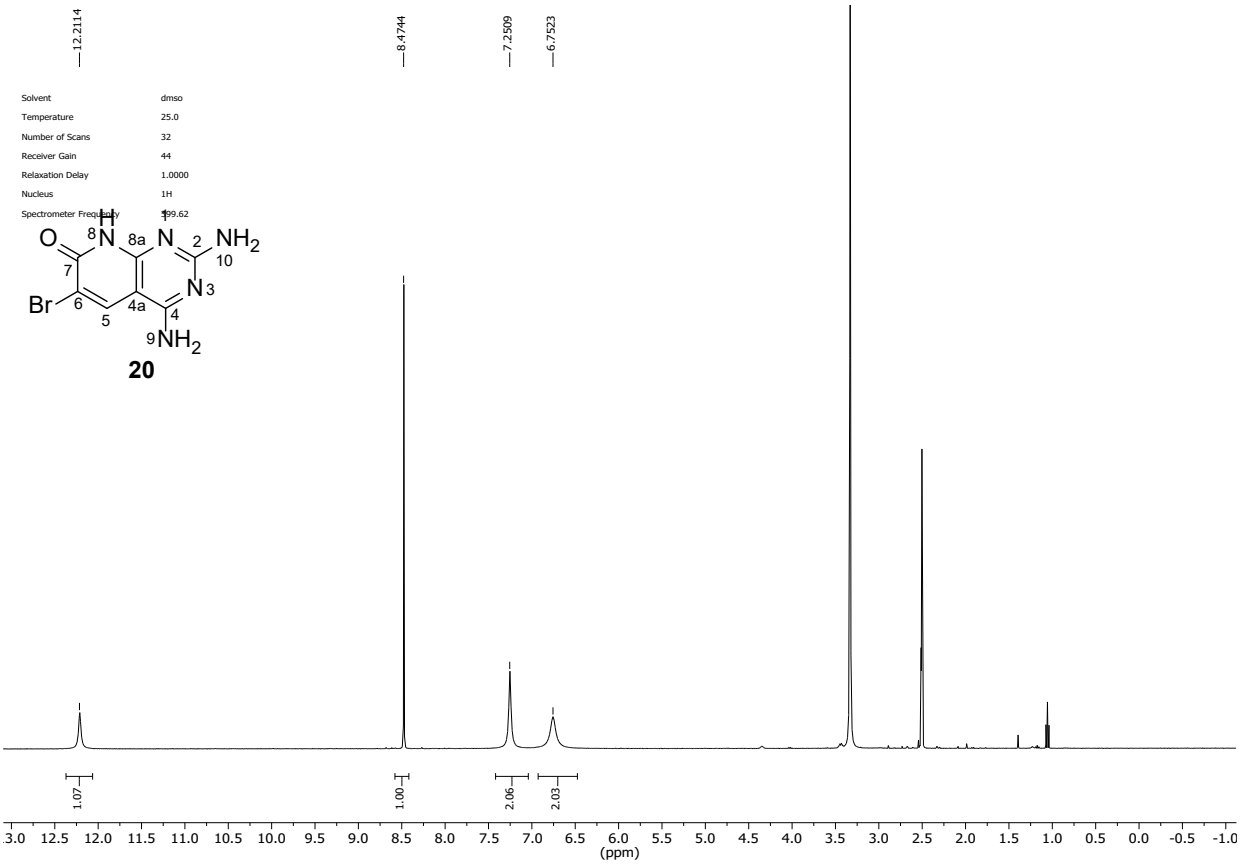
-117.9452
Solvent dmso
Temperature 25.0
Number of Scans 64
Receiver Gain 46
Relaxation Delay 1.0000
Nucleus 19F
Spectrometer Frequency 375.98
18
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
(ppm)

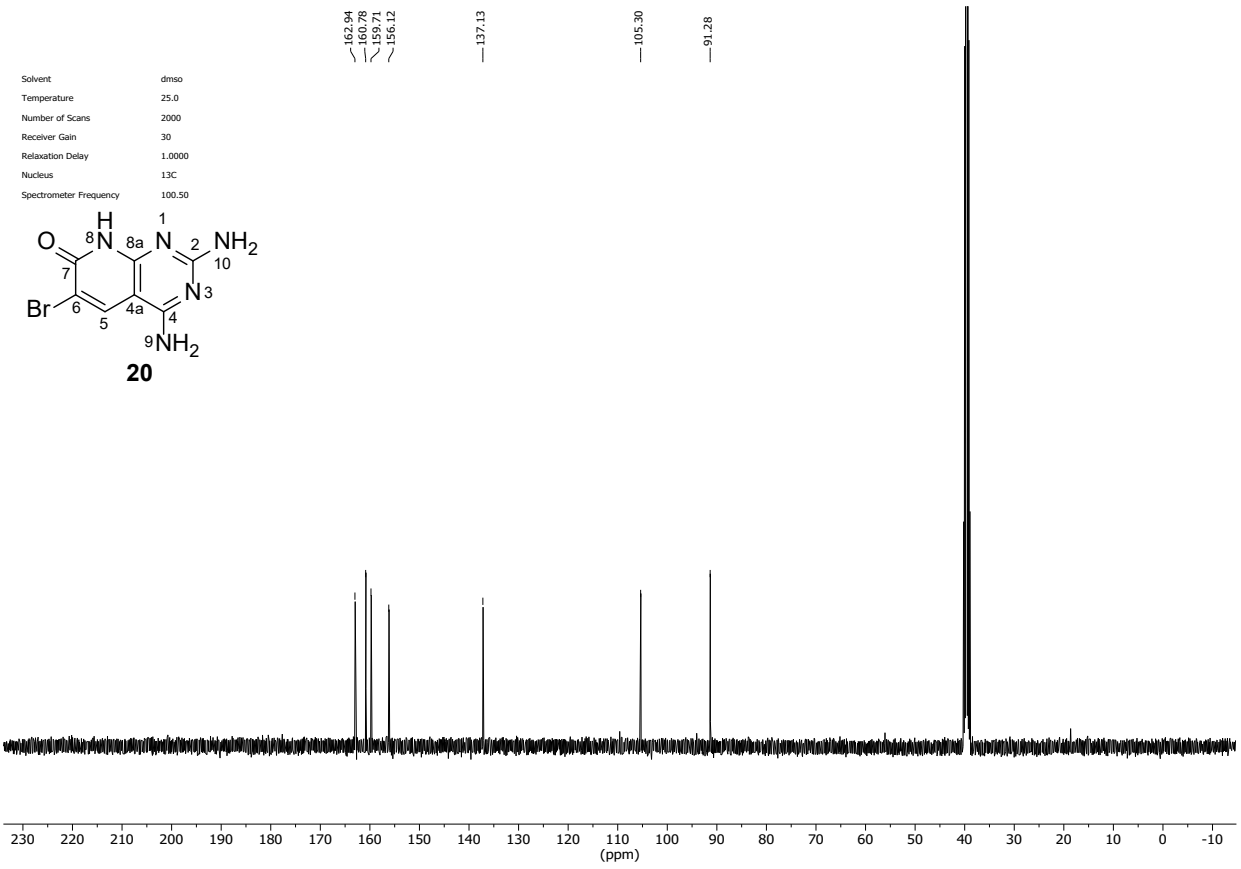
(*Z*)-4a-bromo-4-(bromoimino)-2-((4-chlorophenyl)amino)-4,5,6,8-tetrahydropyrido[2,3-*d*]pyrimidin-7(4a*H*)-one (19)



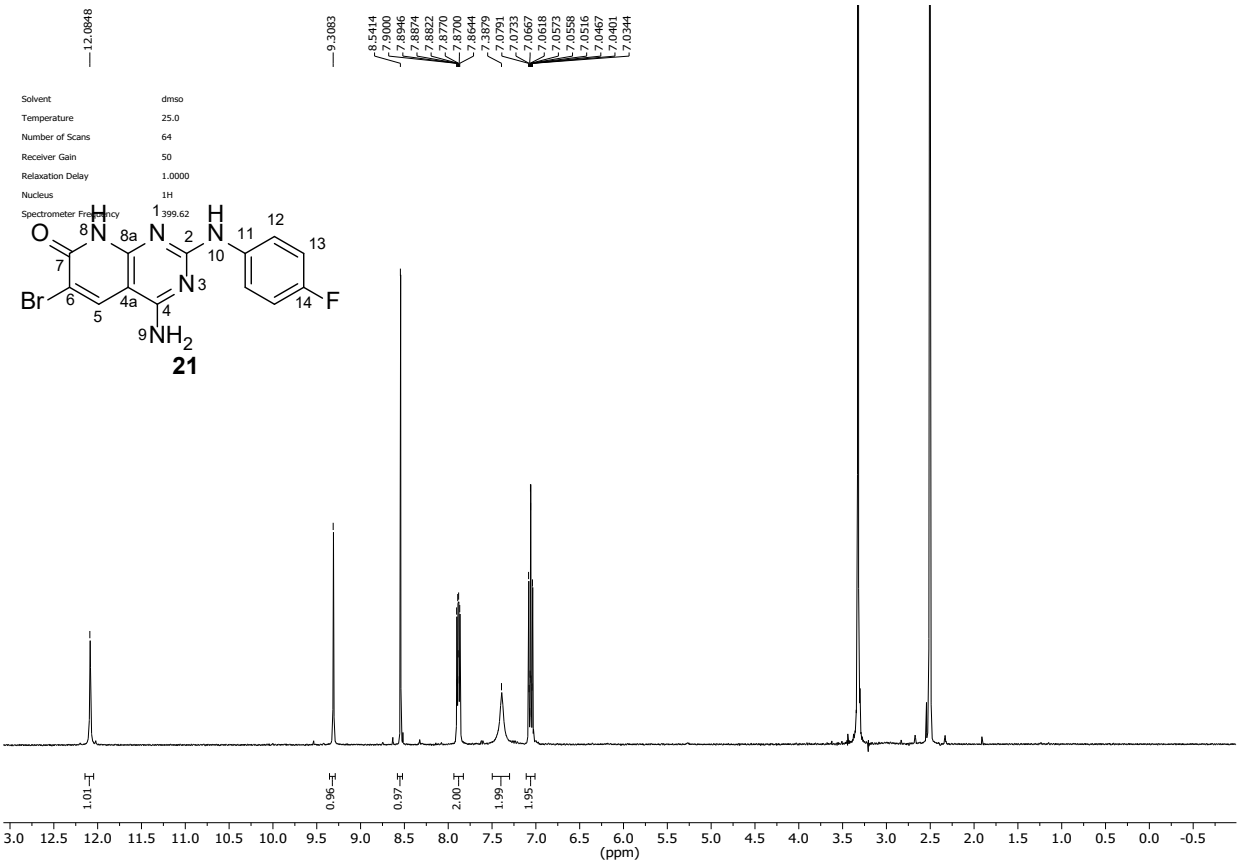


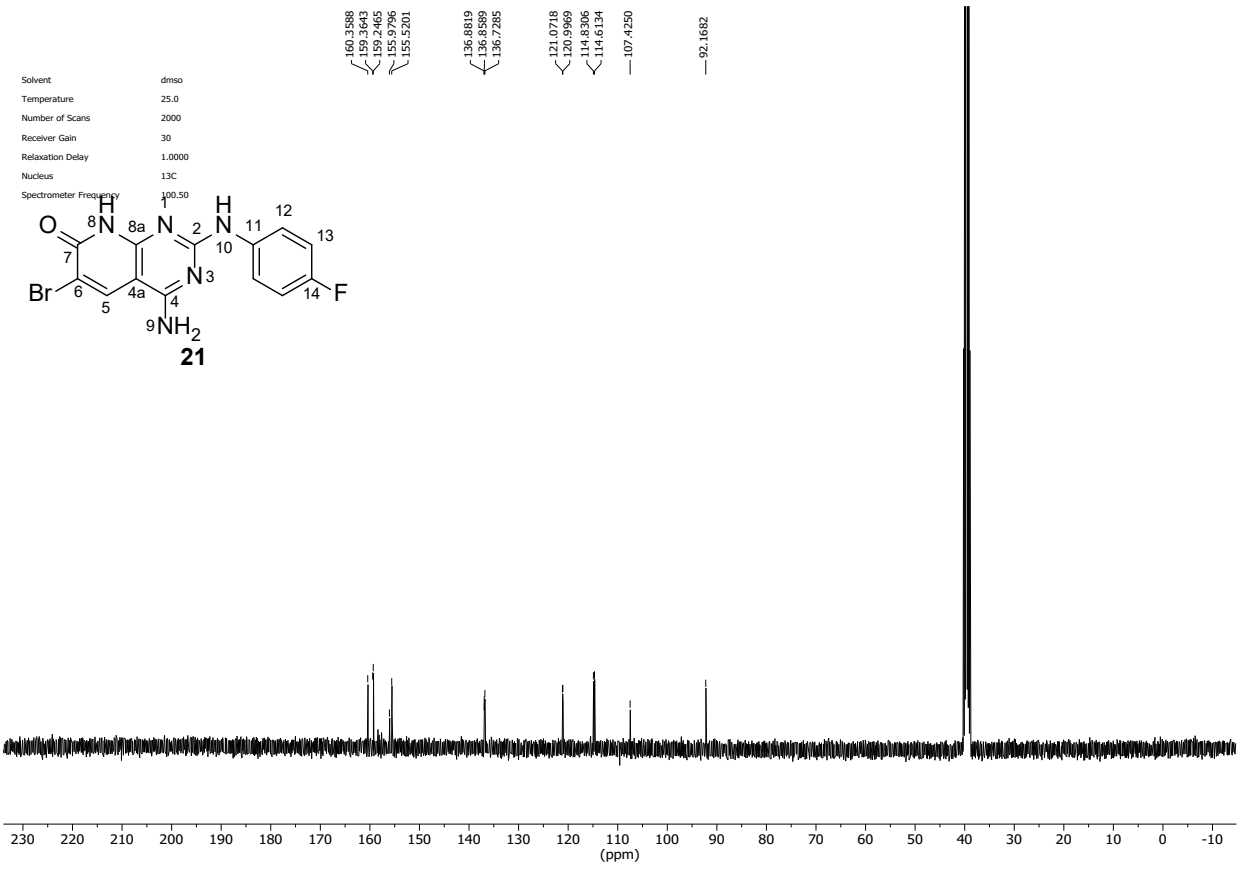
2,4-diamino-6-bromopyrido[2,3-*d*]pyrimidin-7(8*H*)-one (20)

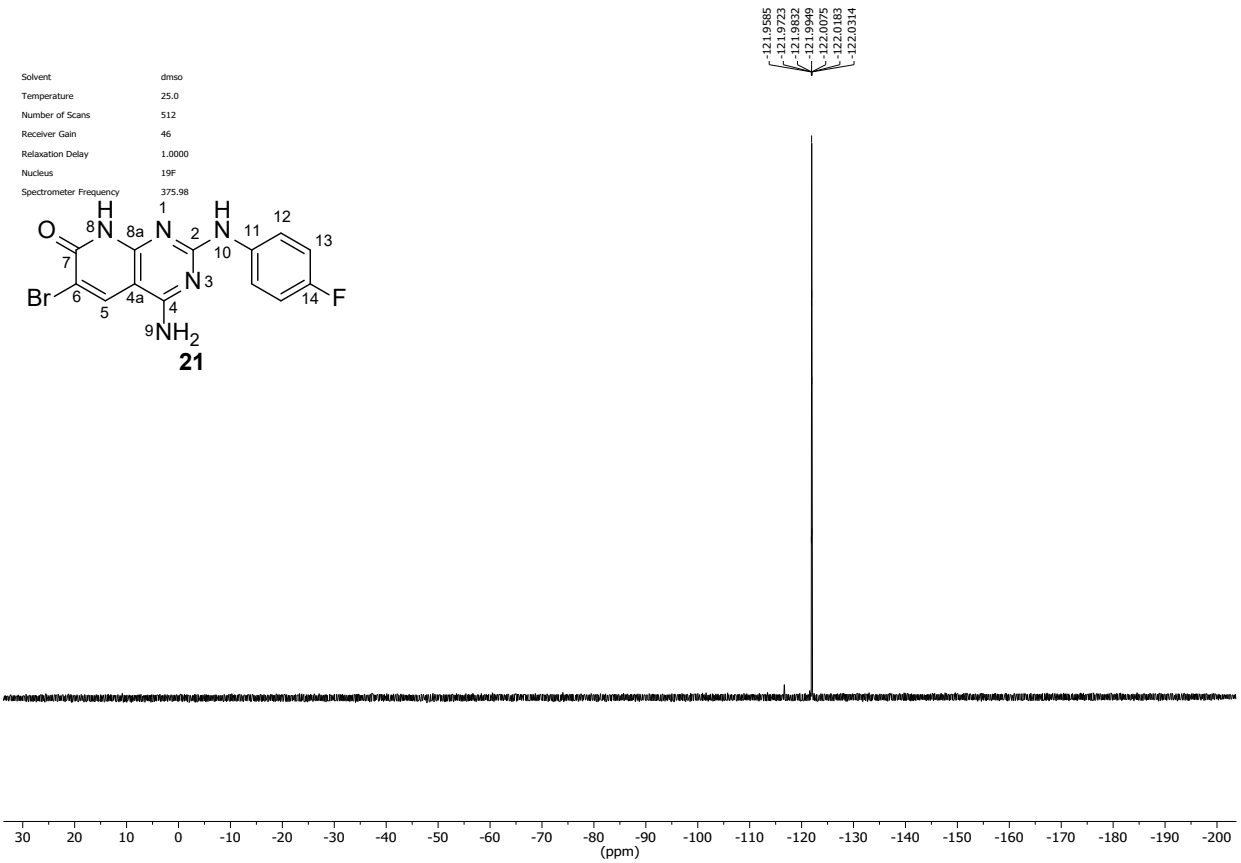




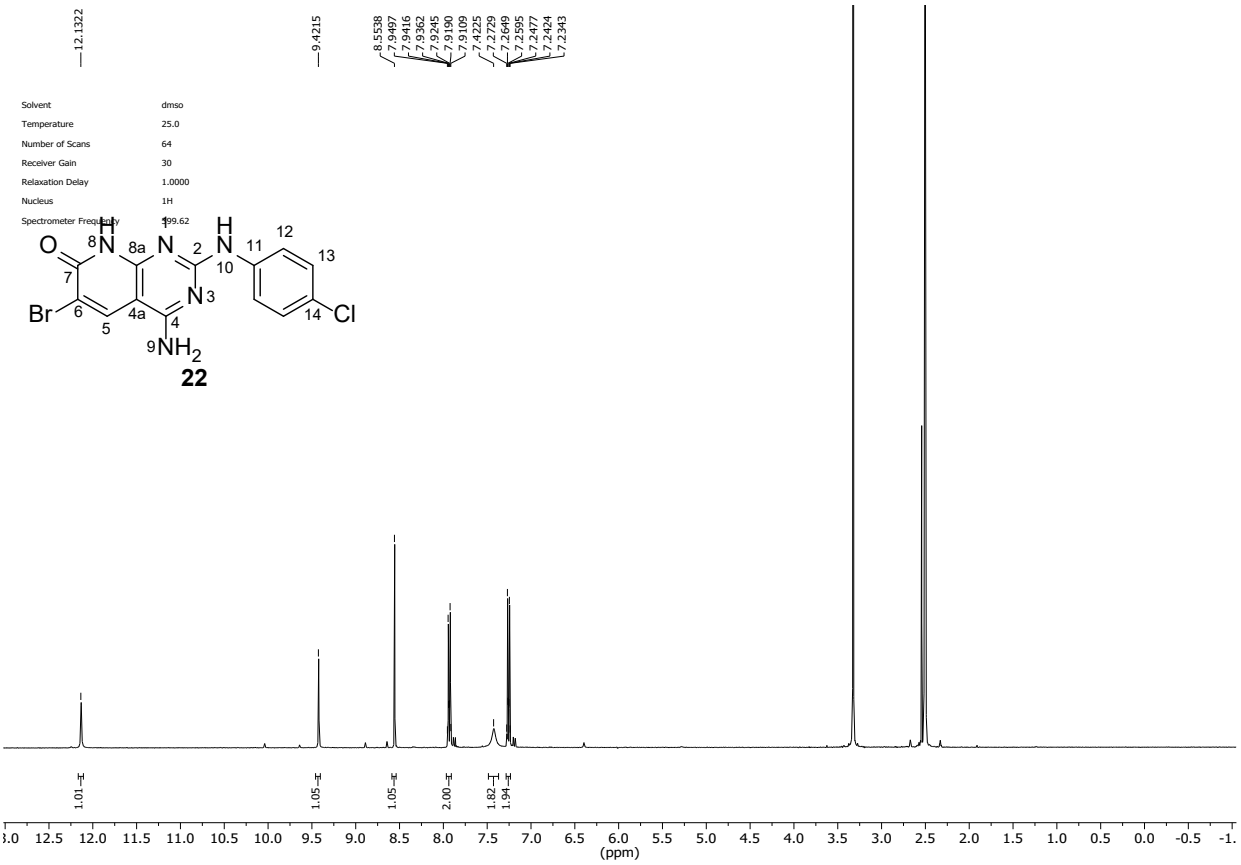
4-Amino-6-bromo-2-((4-fluorophenyl)amino)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (21)

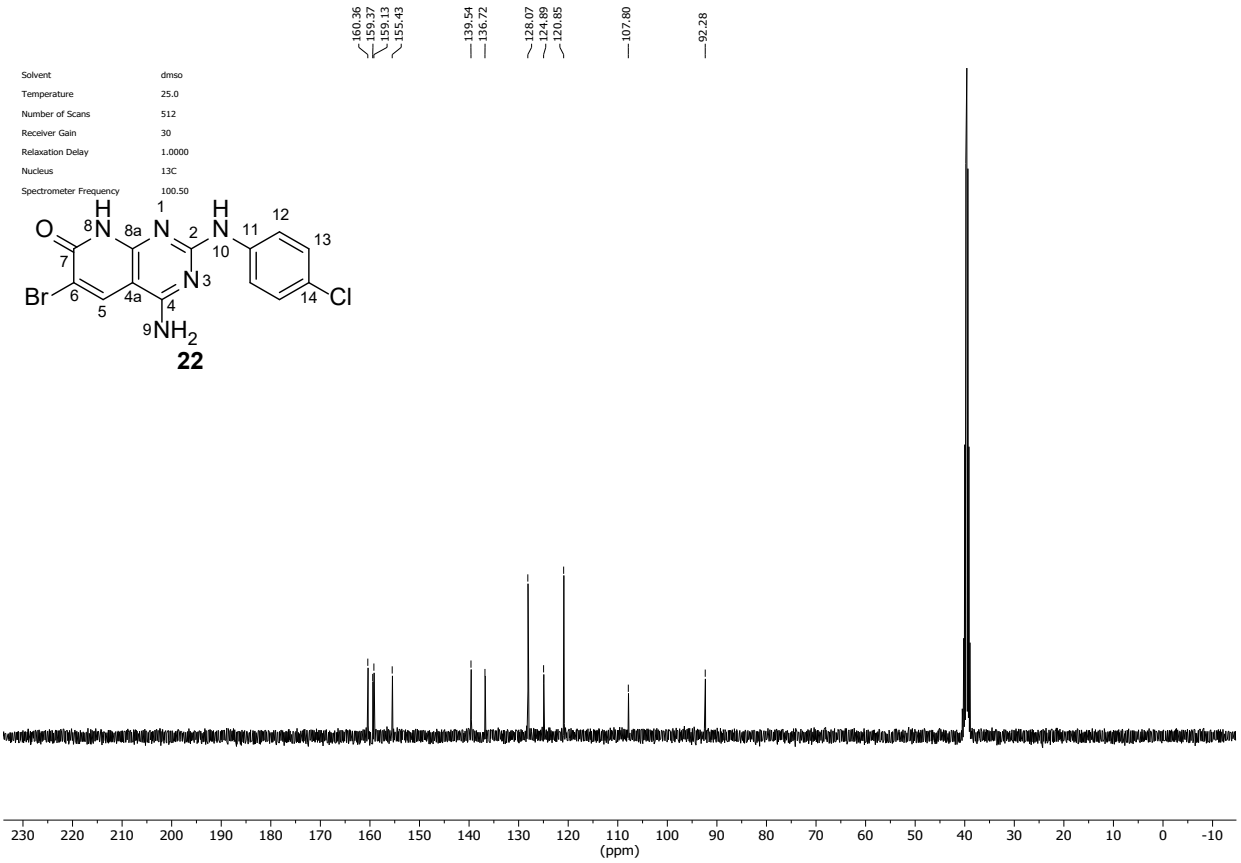




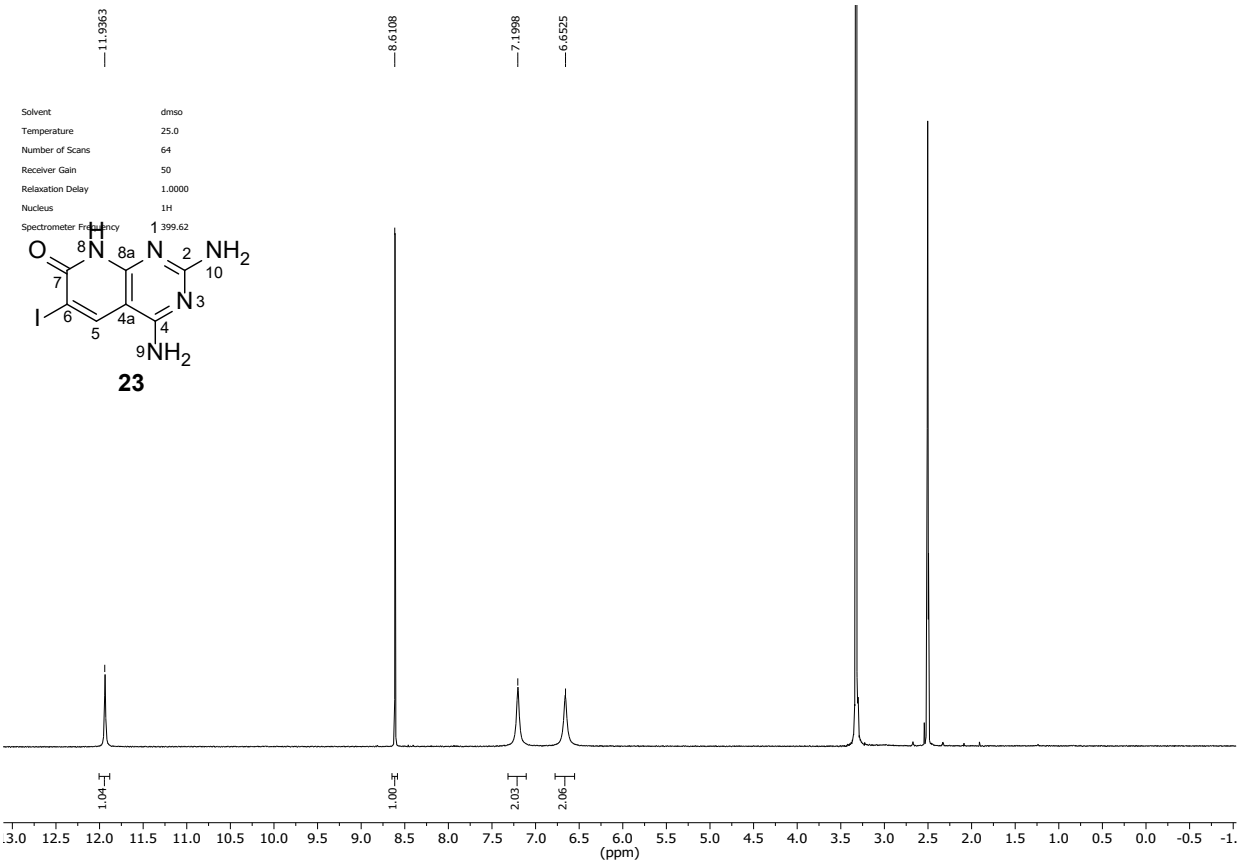

-121.9585
-121.9723
-121.9832
-121.9949
-122.0075
-122.0183
-122.0314
Solvent dmso
Temperature 25.0
Number of Scans 512
Receiver Gain 46
Relaxation Delay 1.0000
Nucleus 19F
Spectrometer Frequency 375.98
O
H
N
8
1
8a
N
2
H
N
10
11
12
13
7
N
3
Br
6
5
4a
4
9NH2
14
F
21
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
(ppm)

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





2,4-diamino-6-iodopyrido[2,3-*d*]pyrimidin-7(8*H*)-one (23)



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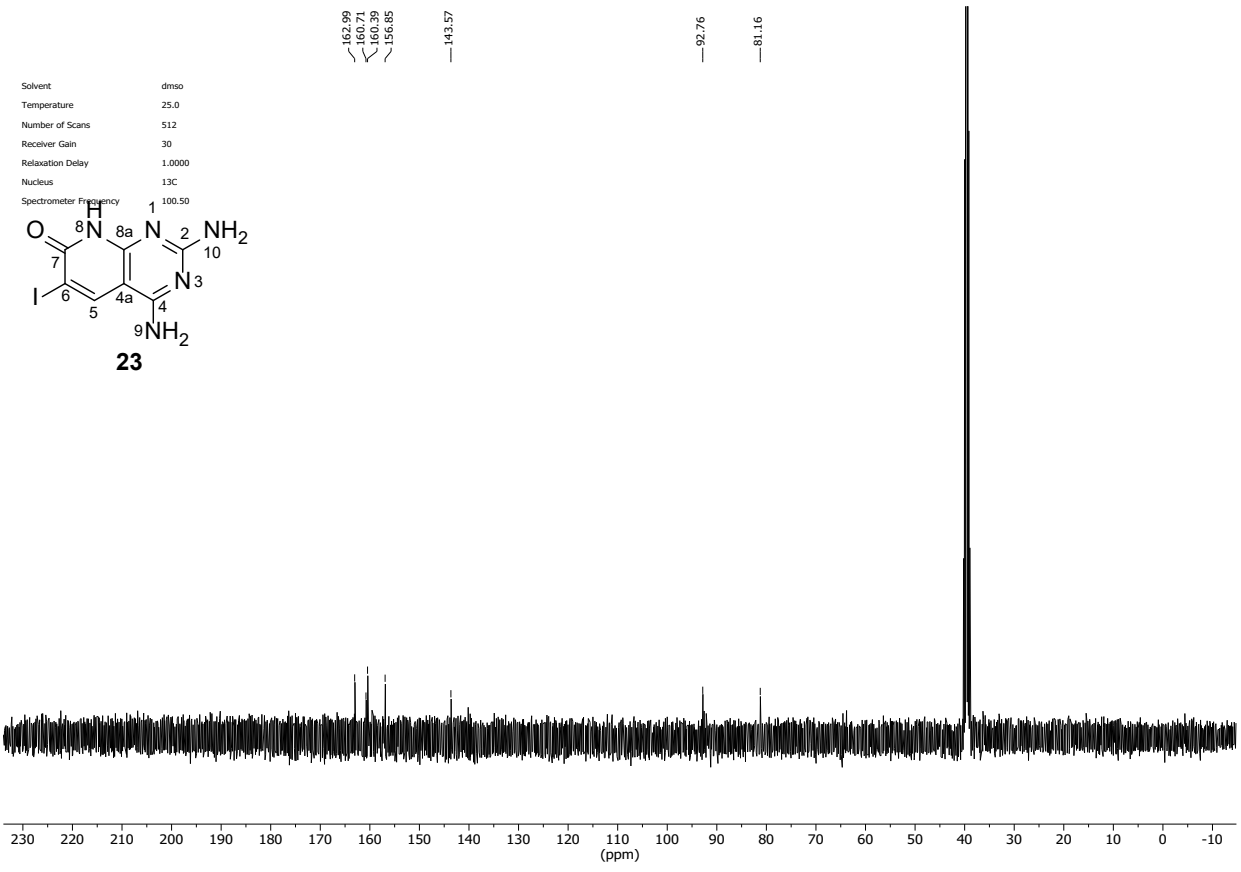
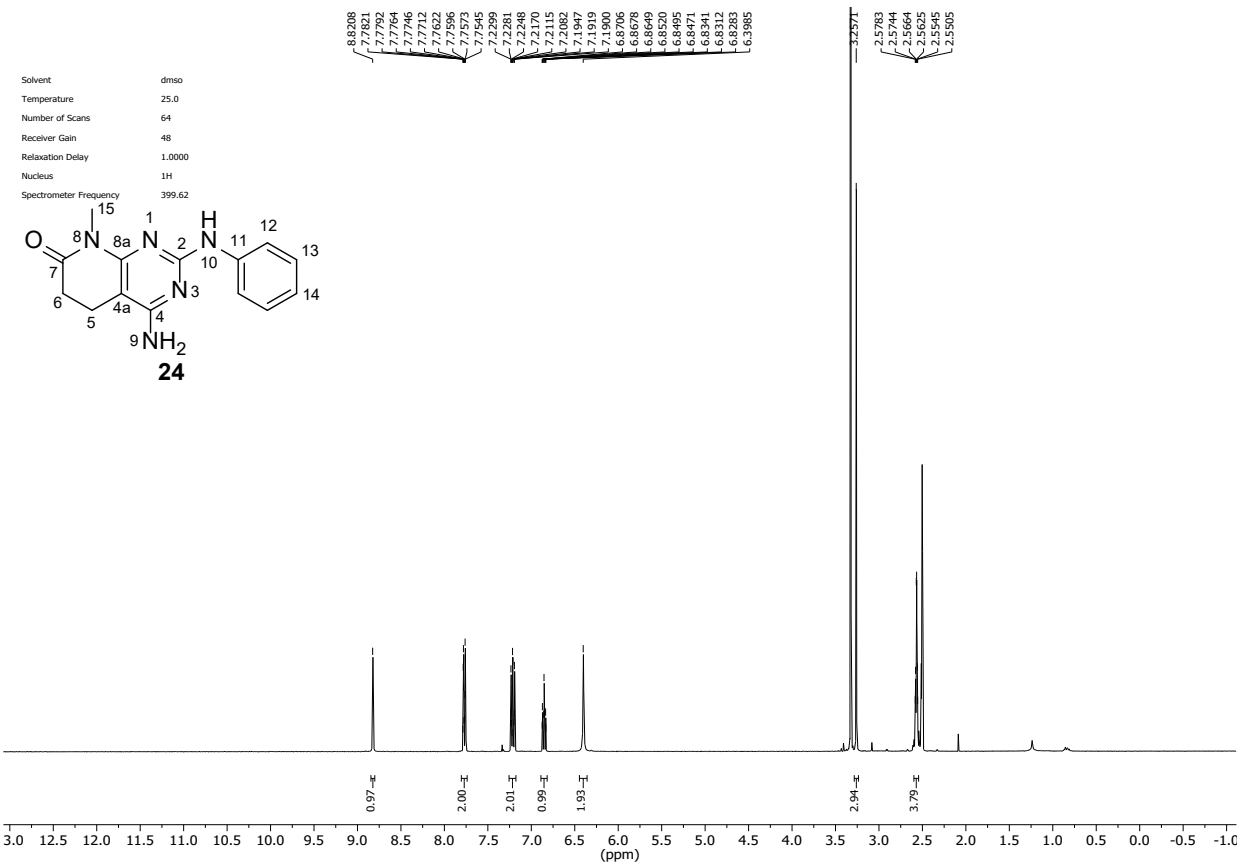
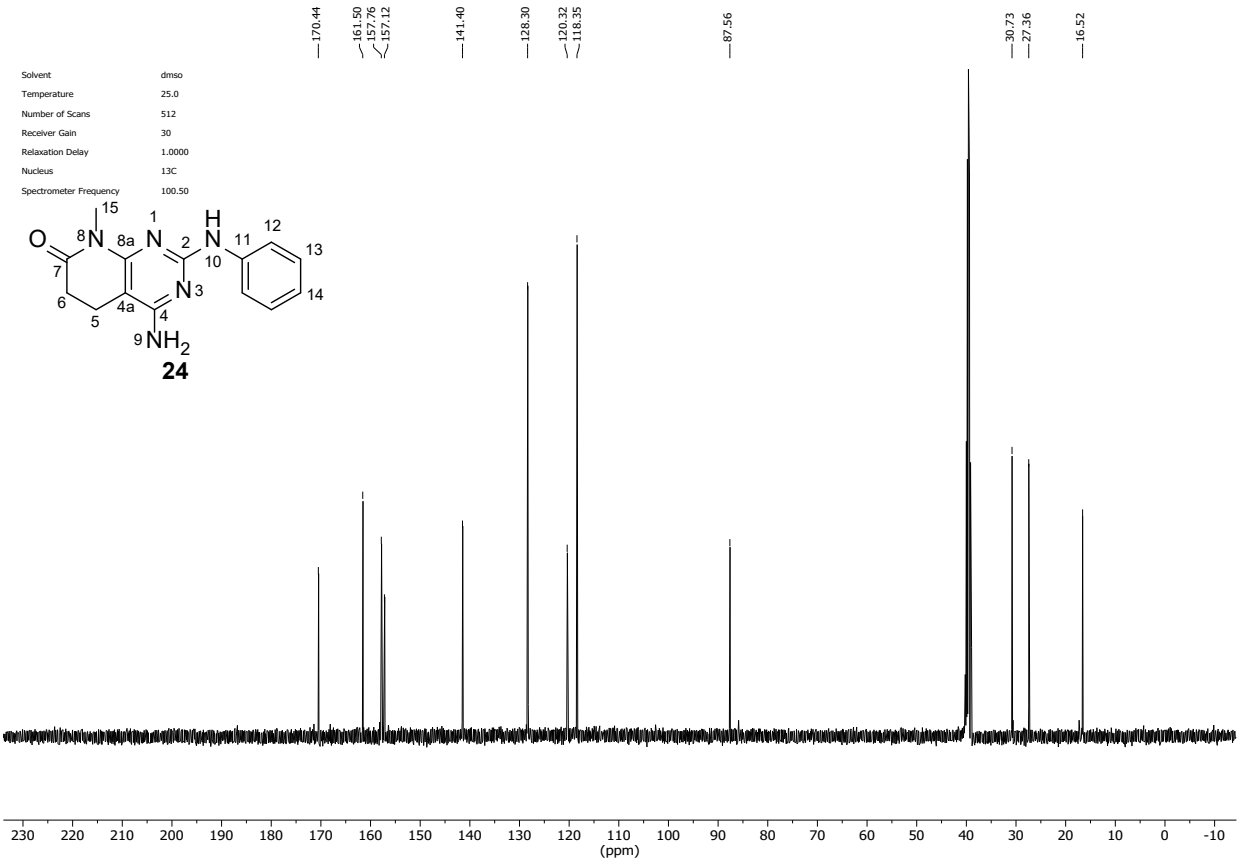


23

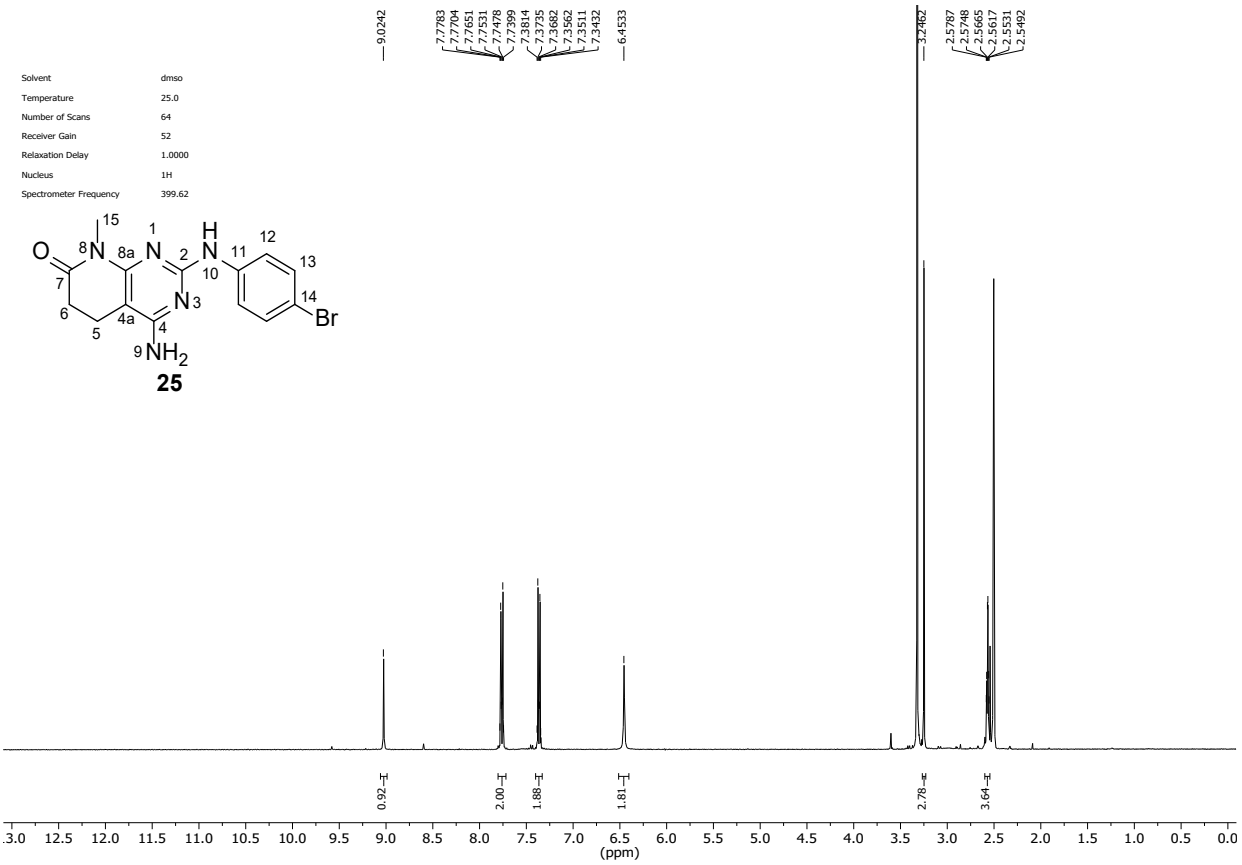
4-amino-8-methyl-2-(phenylamino)-5,8-dihydropyrido[2,3-*d*]pyrimidin-7(6*H*)-one (24)



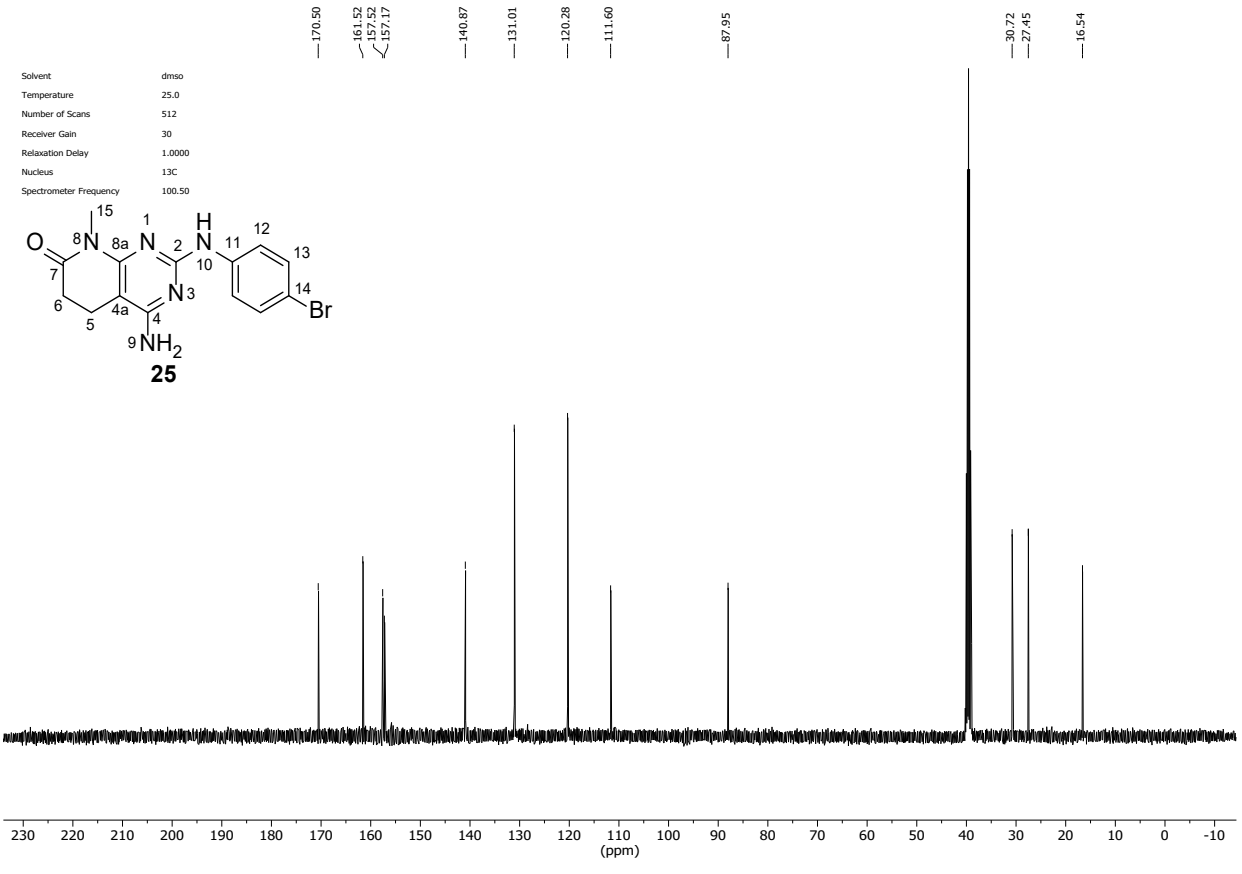


24

4-amino-2-((4-bromophenyl)amino)-8-methyl-5,8-dihydropyrido[2,3-*d*]pyrimidin-7(6*H*)-one (25)

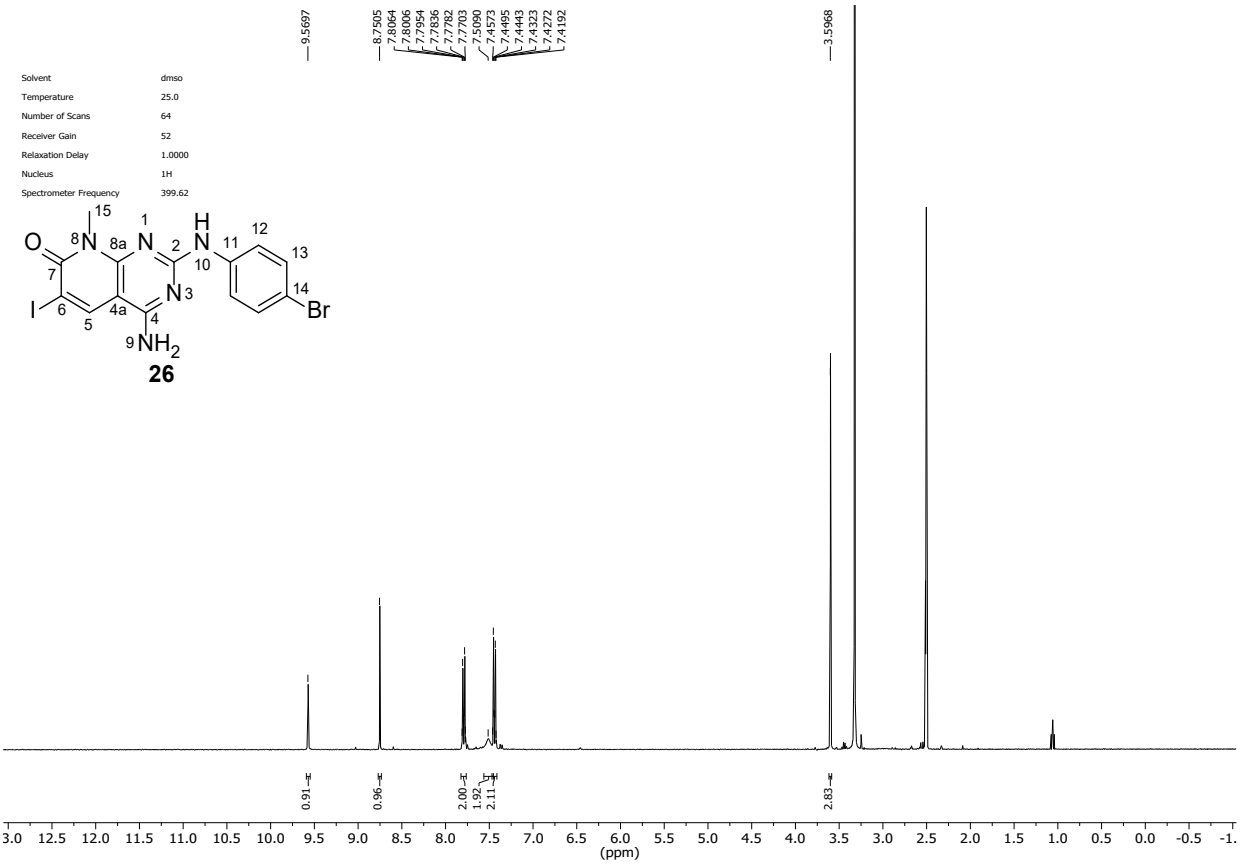


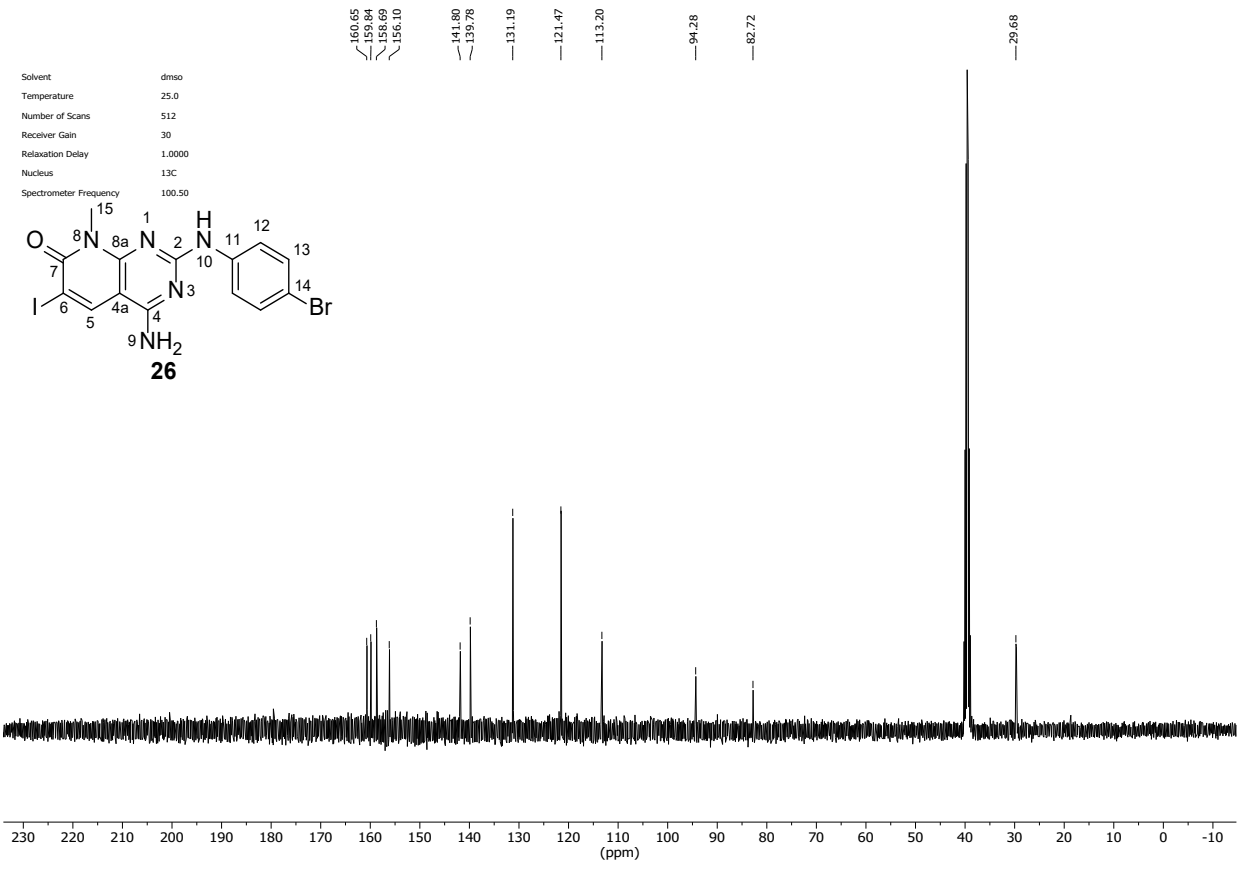
25



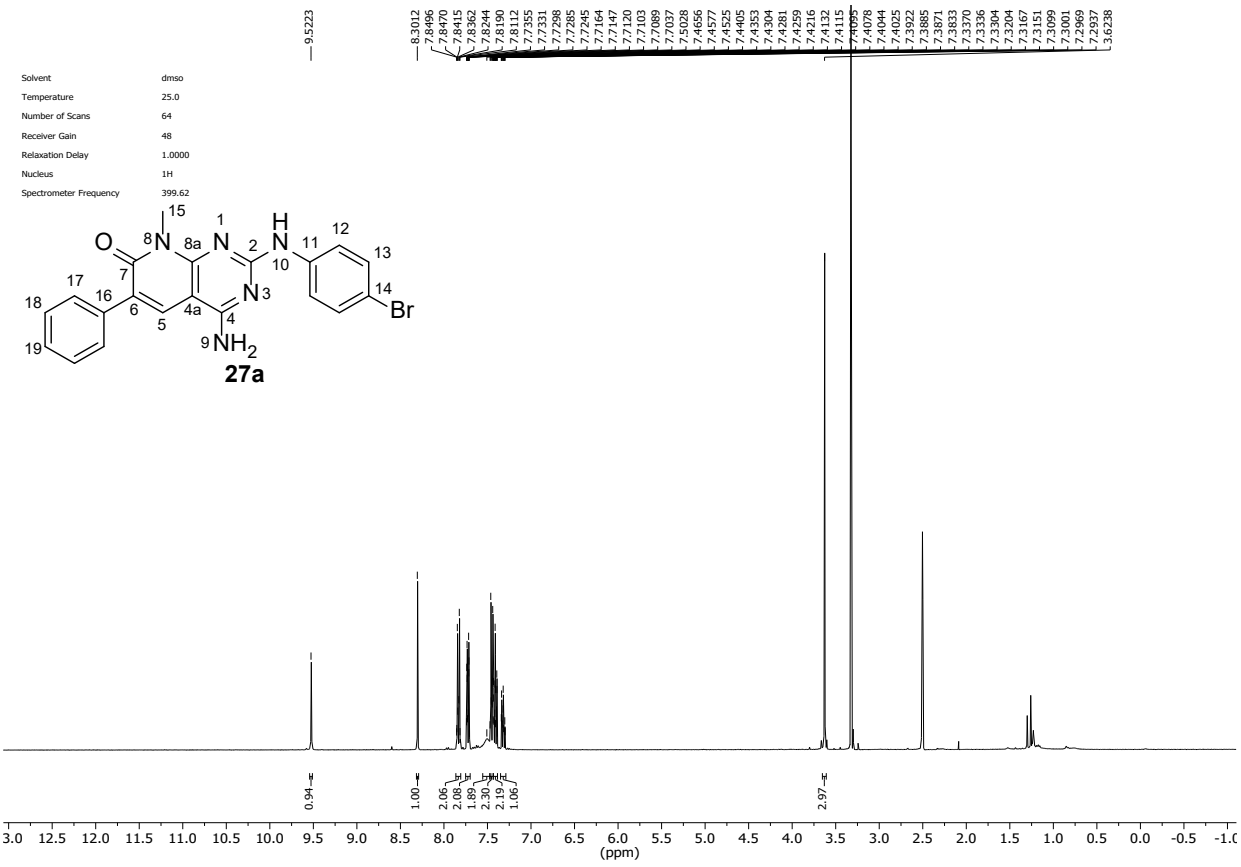
25

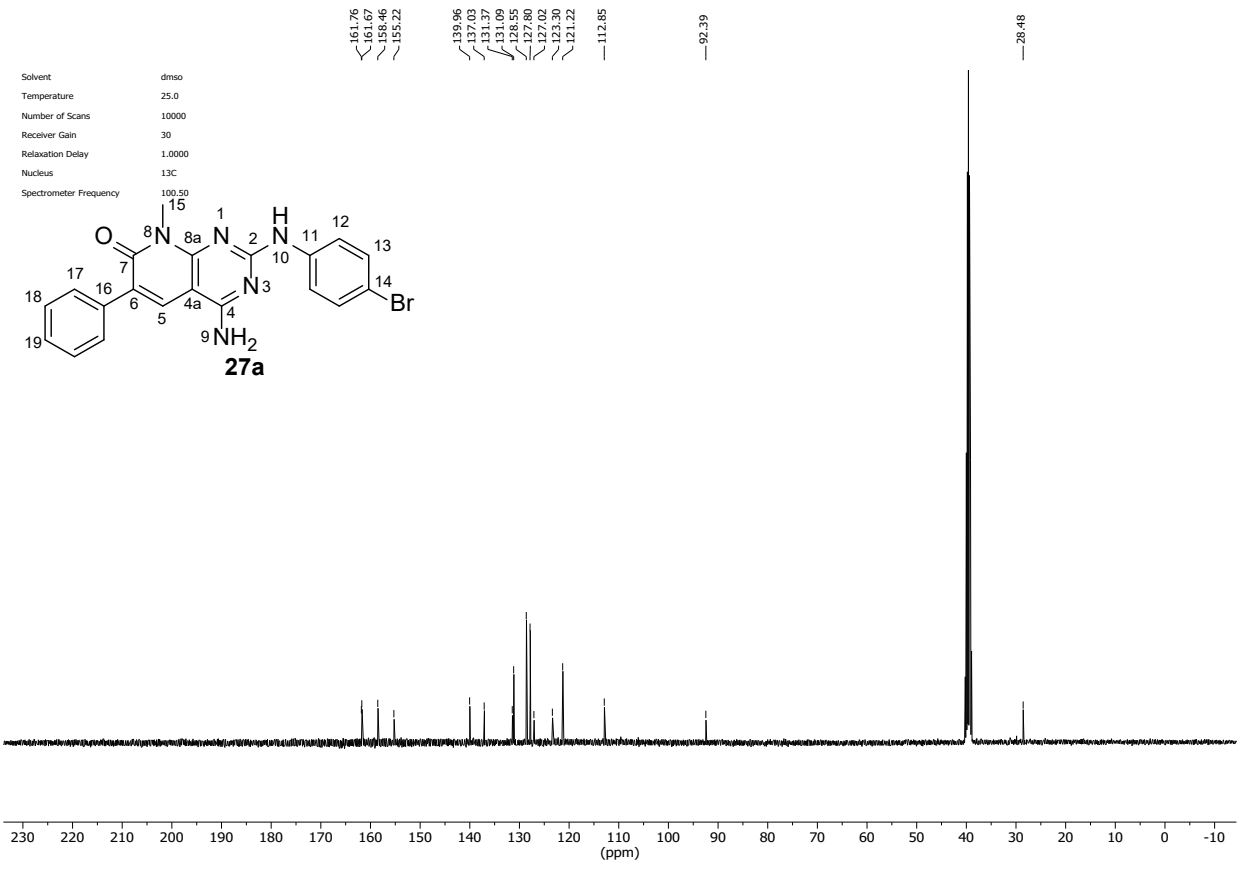
4-amino-2-((4-bromophenyl)amino)-6-iodo-8-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (26)



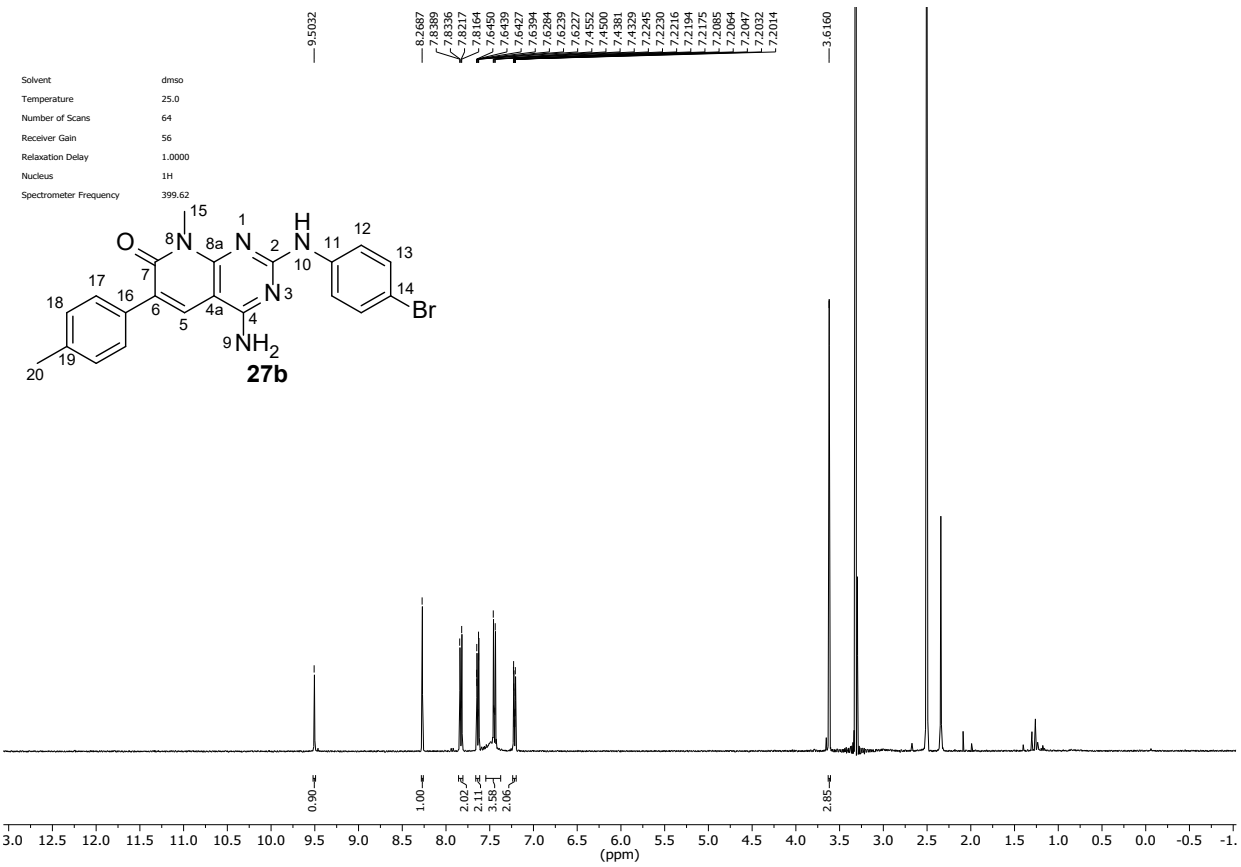


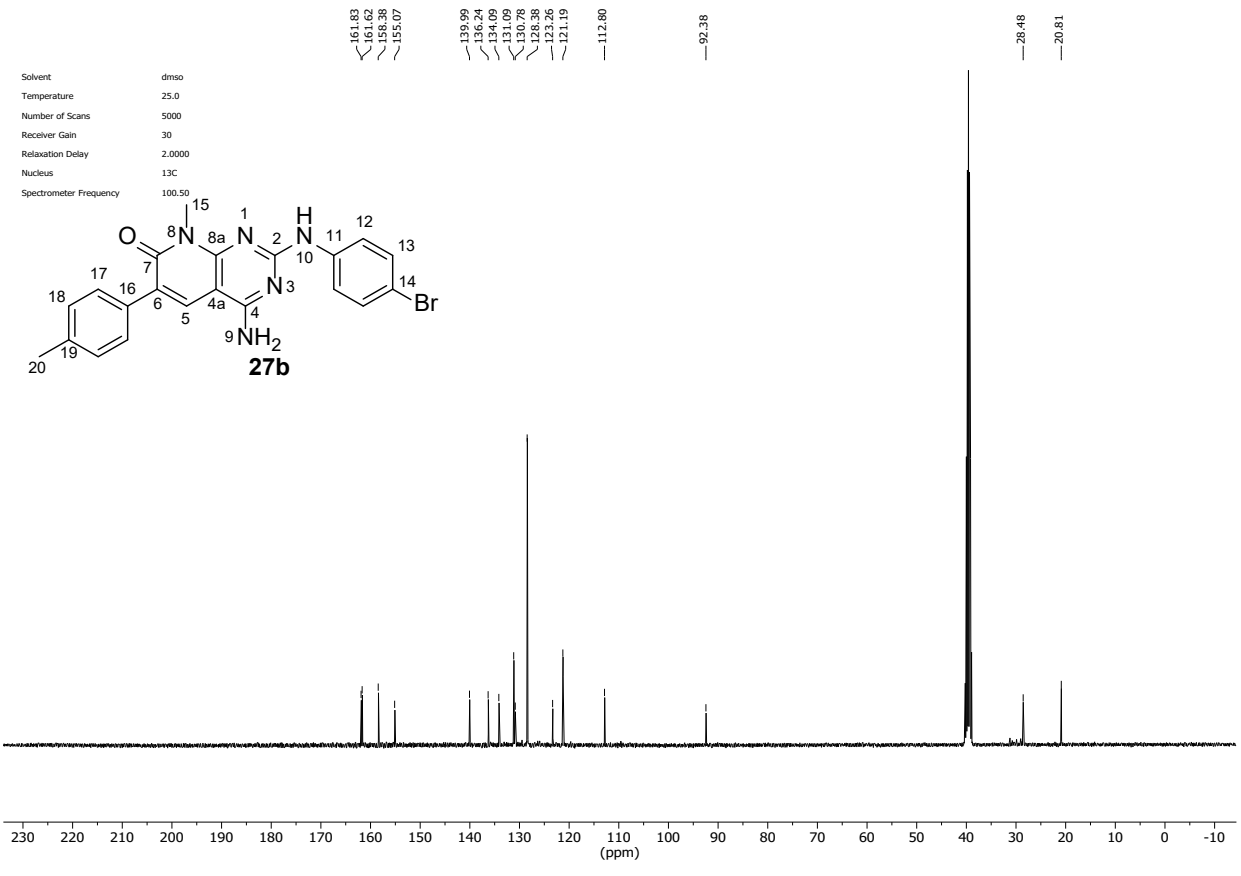
4-amino-2-((4-bromophenyl)amino)-8-methyl-6-phenylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (27a)



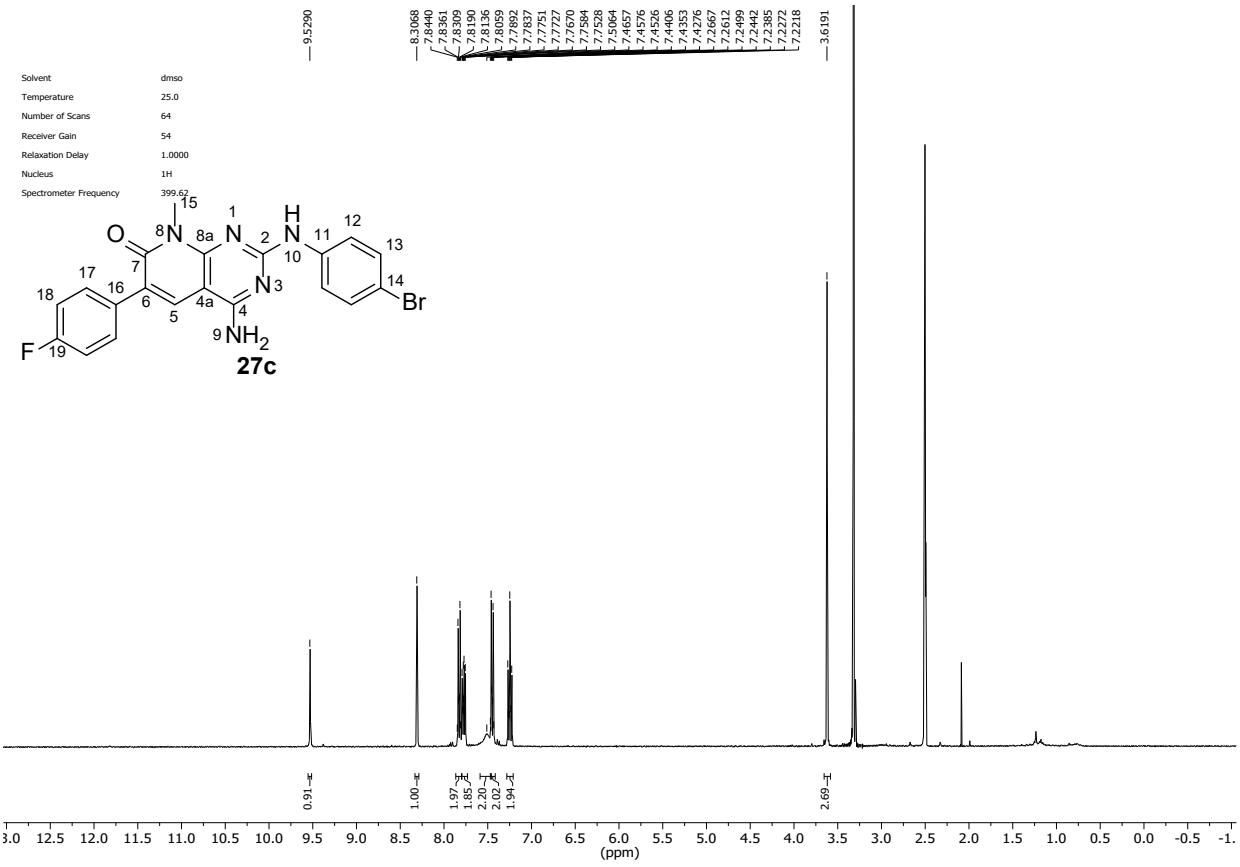


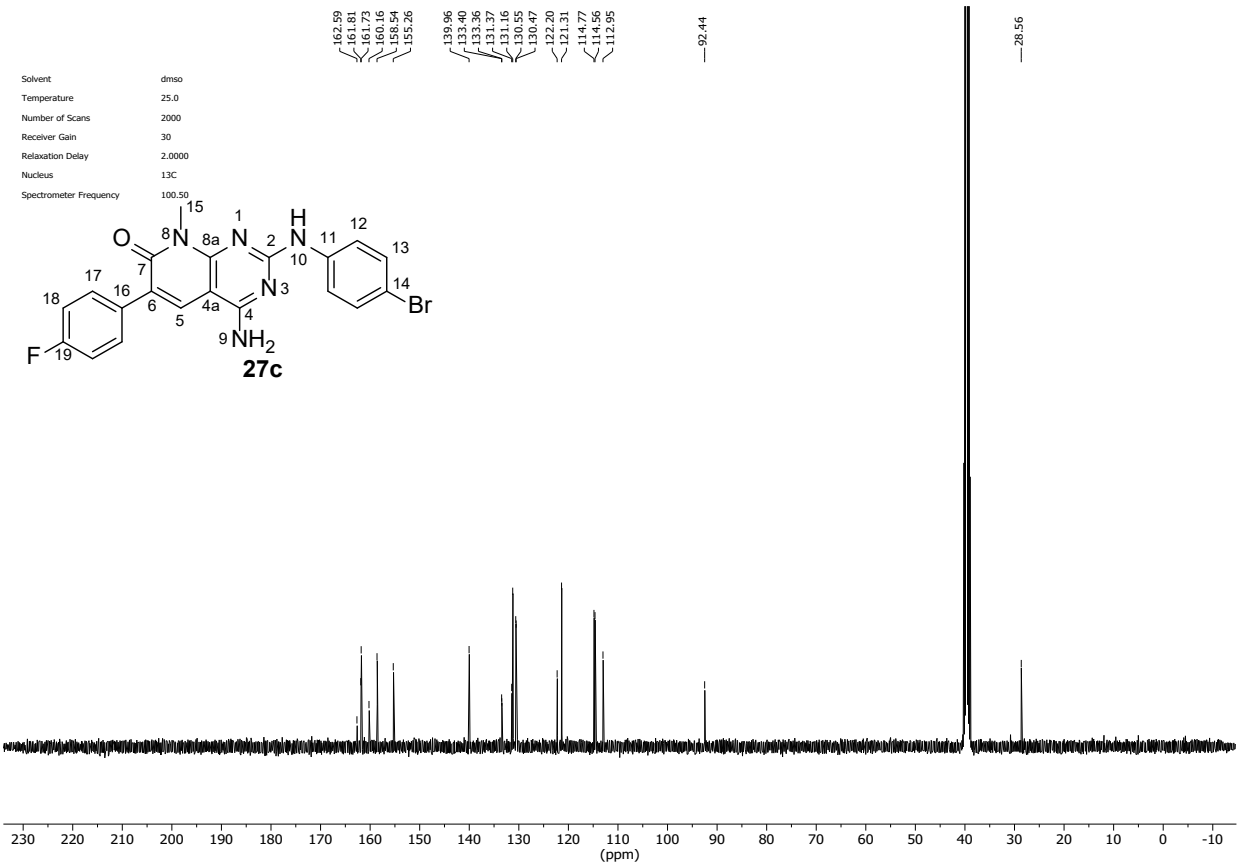
4-amino-2-((4-bromophenyl)amino)-8-methyl-6-(*p*-tolyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (27b)



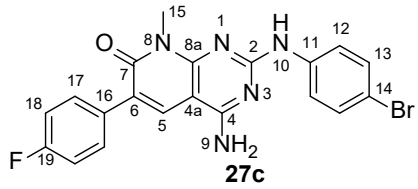


4-amino-2-((4-bromophenyl)amino)-6-(4-fluorophenyl)-8-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (27c)



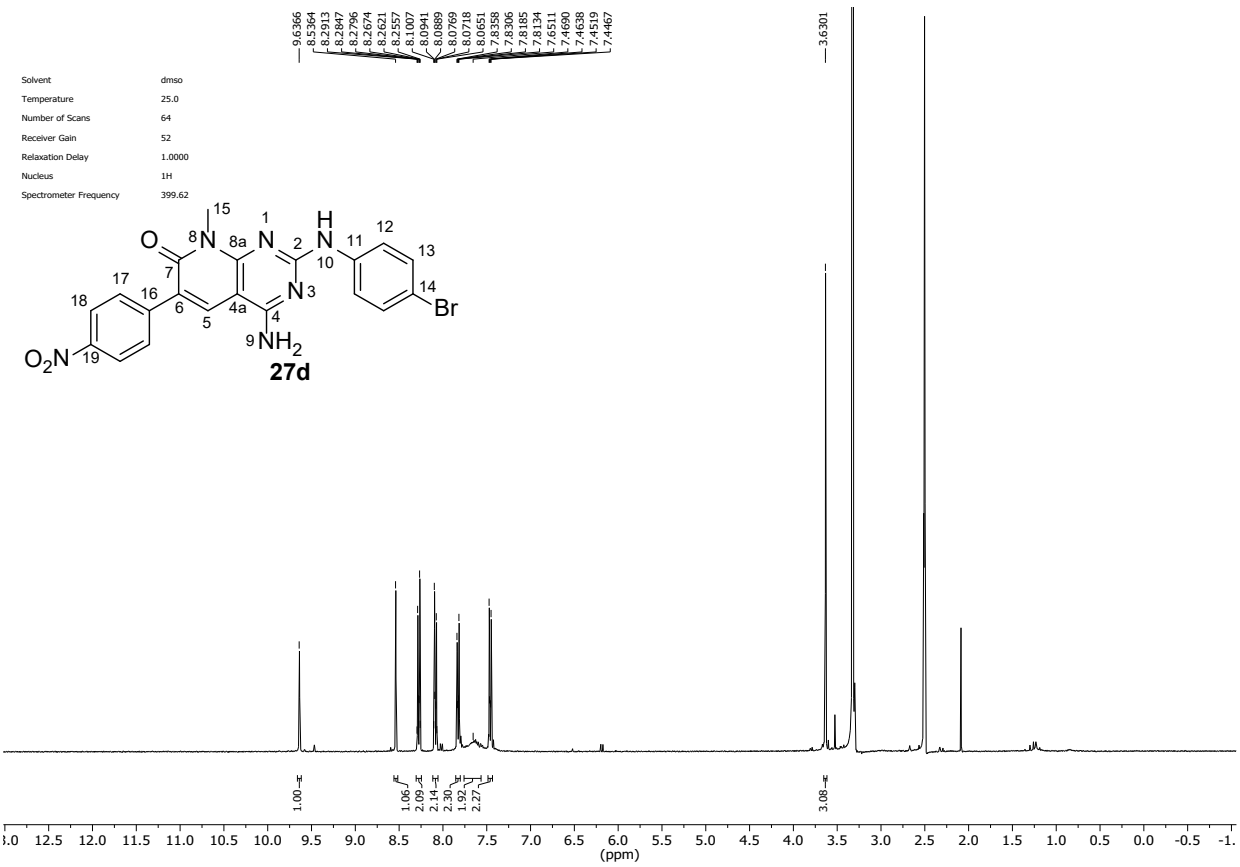


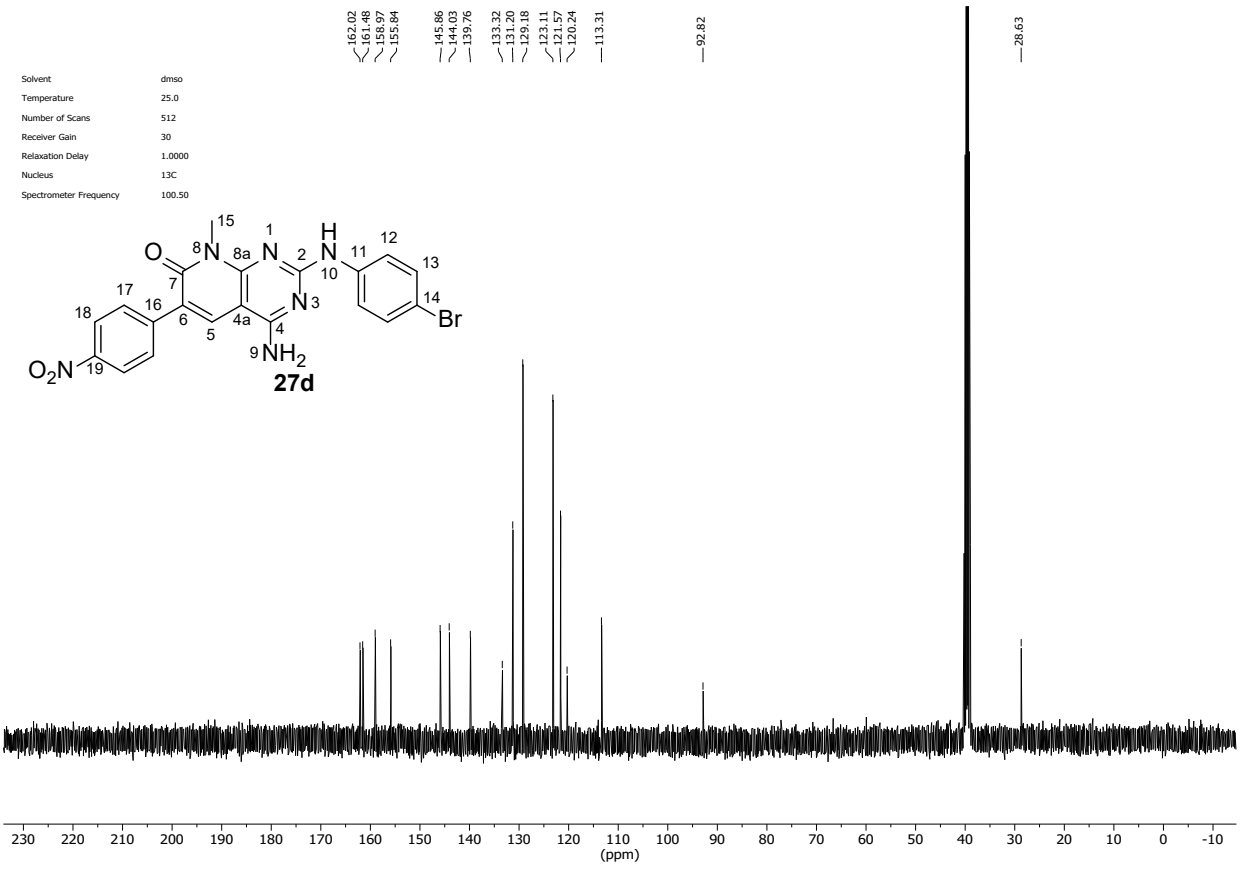
Solvent	dmso
Temperature	25.0
Number of Scans	128
Receiver Gain	46
Relaxation Delay	1.0000
Nucleus	19F
Spectrometer Frequency	375.98



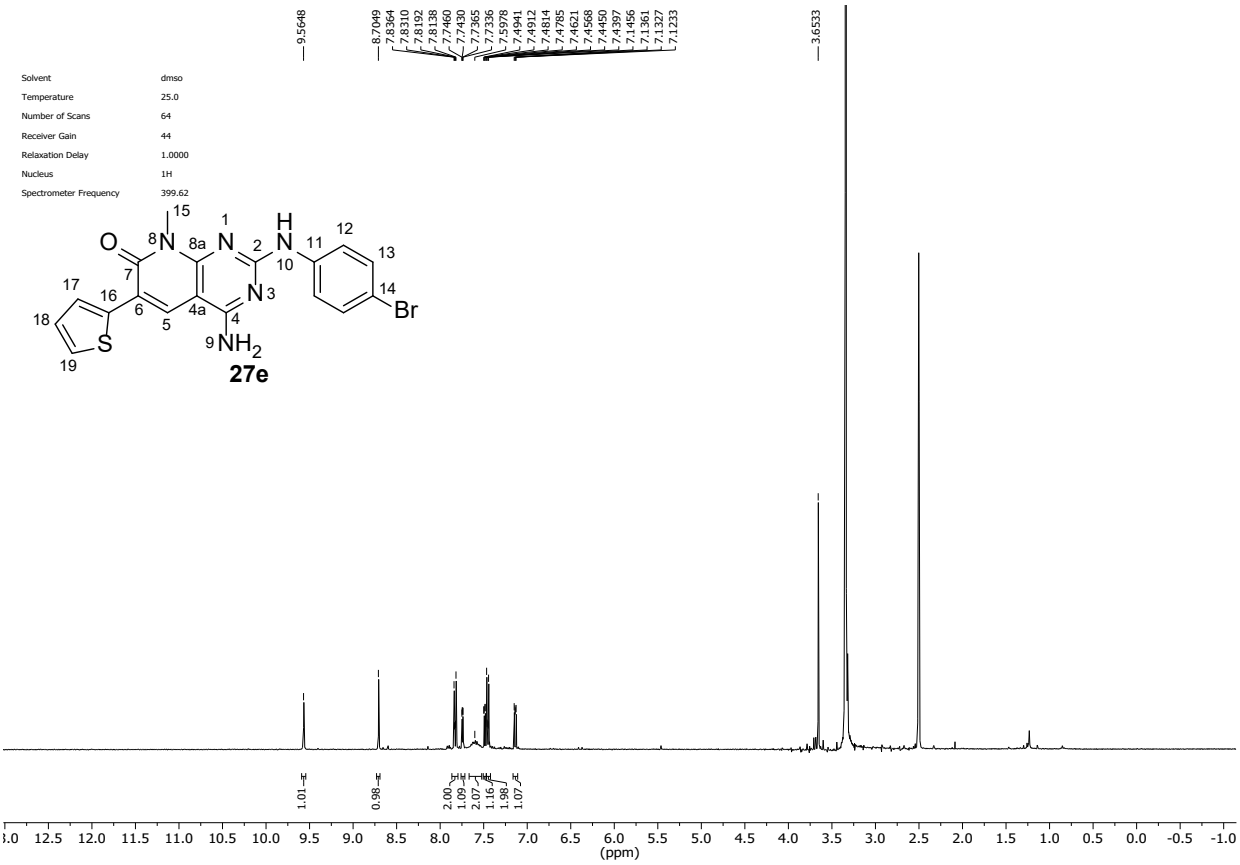
27c

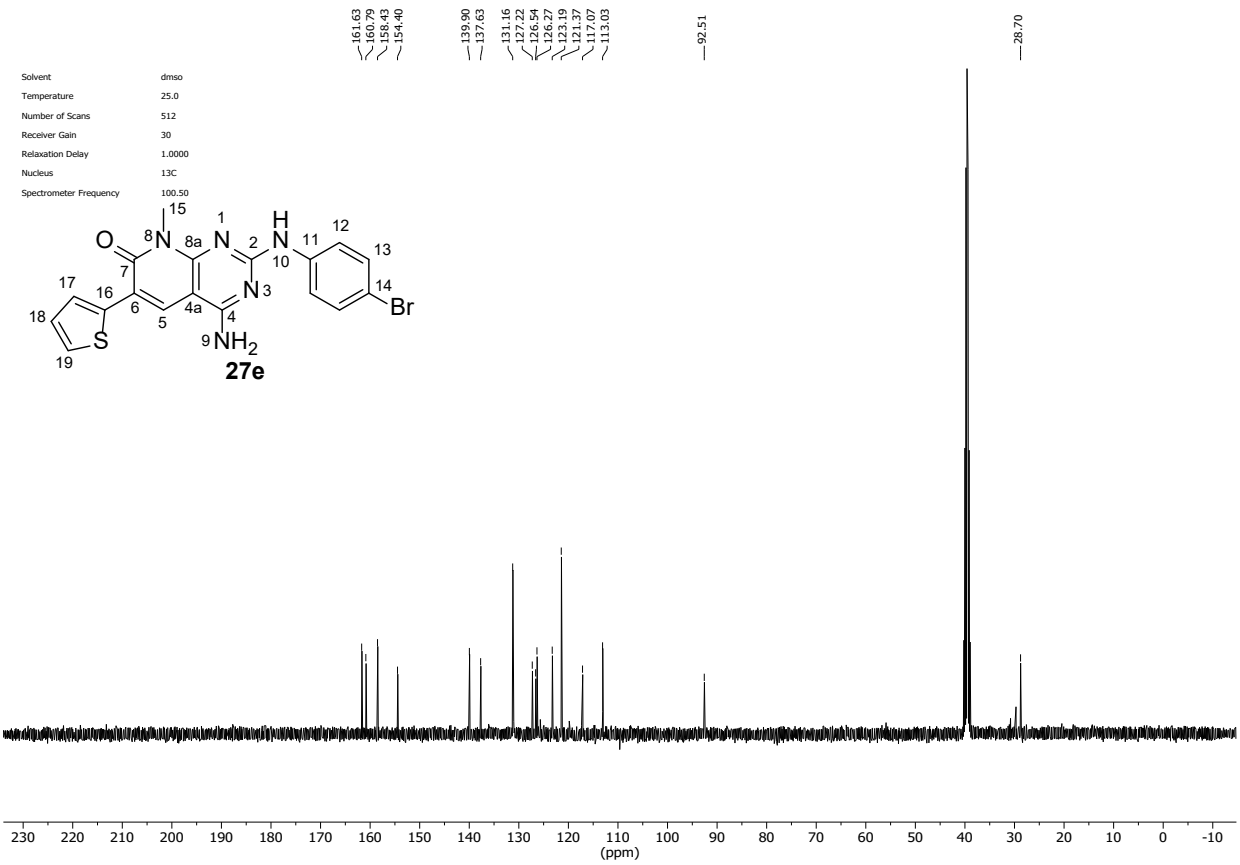
4-amino-2-((4-bromophenyl)amino)-8-methyl-6-(4-nitrophenyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (27d)



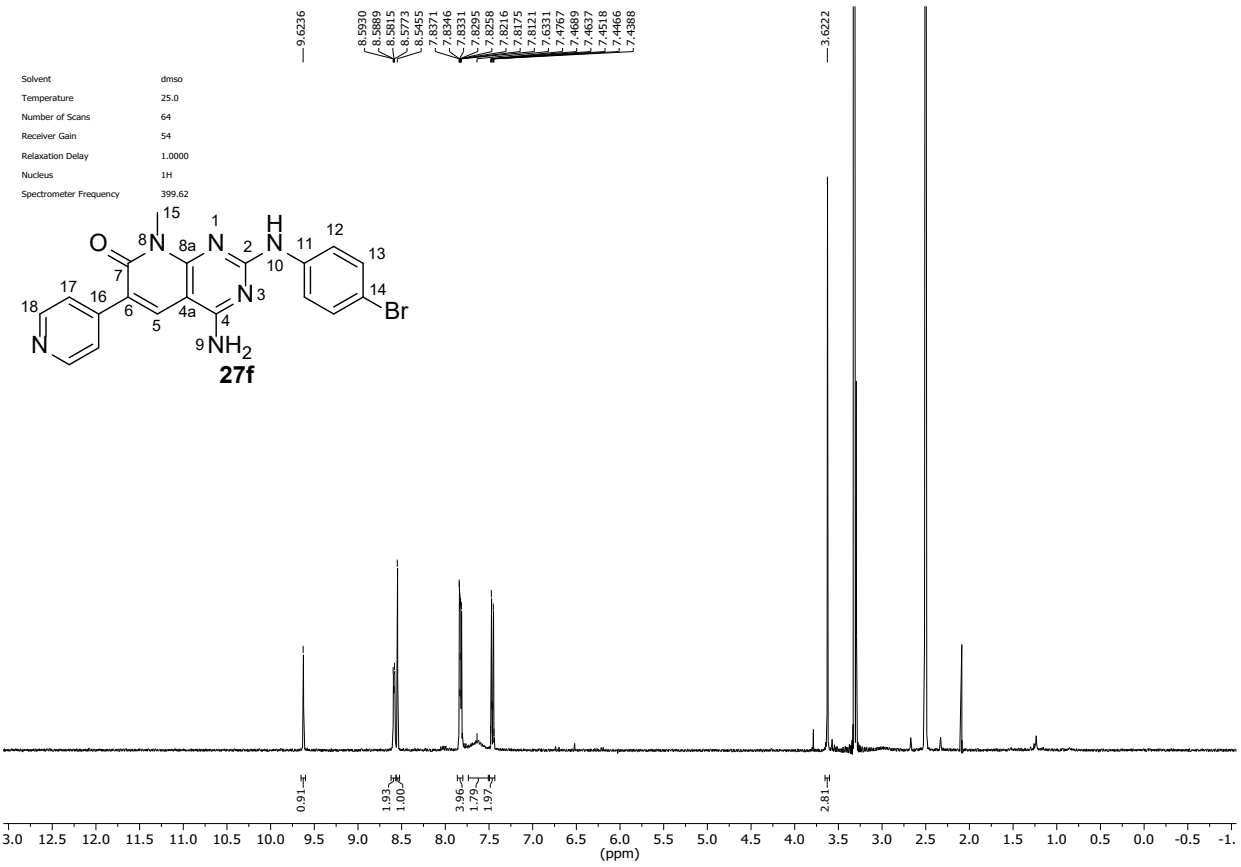


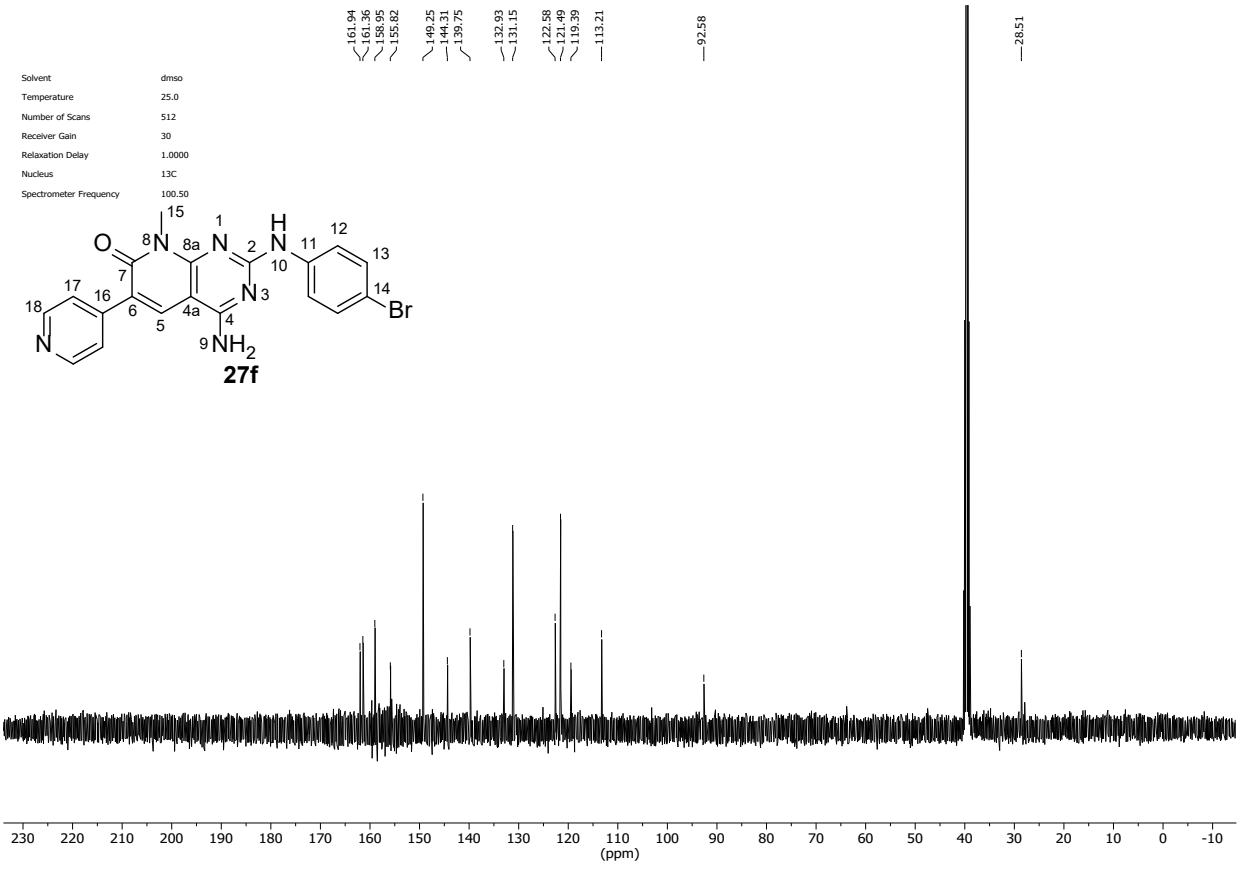
4-amino-2-((4-bromophenyl)amino)-8-methyl-6-(thiophen-2-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (27e)



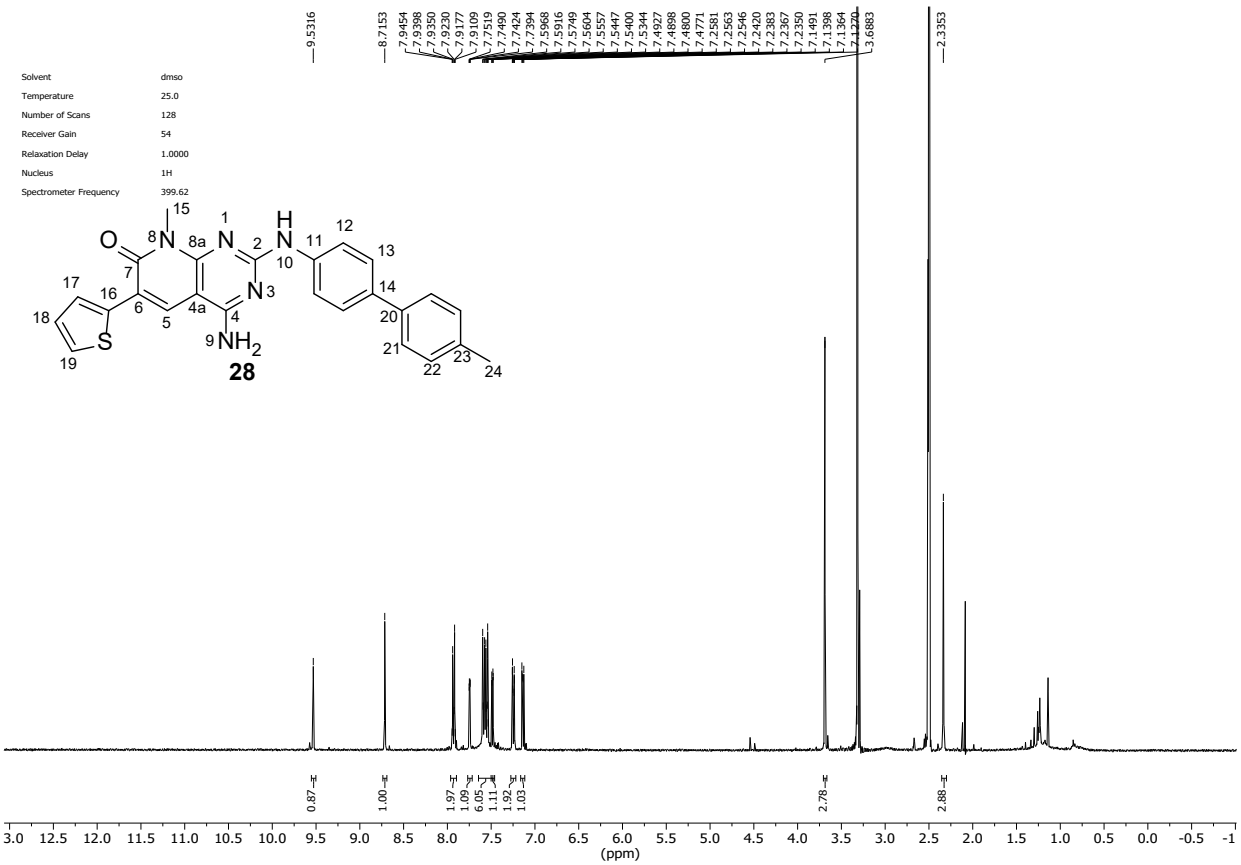


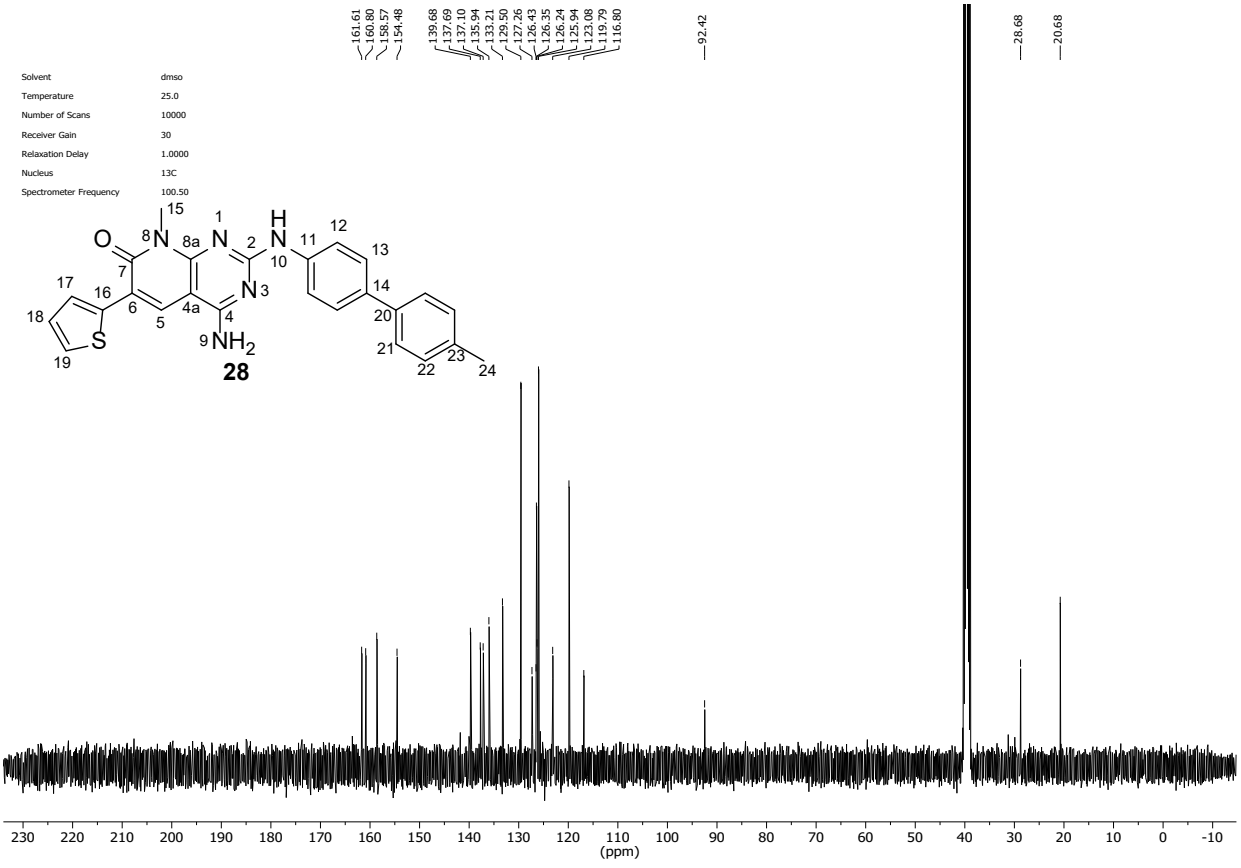
4-amino-2-((4-bromophenyl)amino)-8-methyl-6-(pyridin-4-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**27f**)





4-amino-8-methyl-2-((4'-methyl-[1,1'-biphenyl]-4-yl)amino)-6-(thiophen-2-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**28**)





X-ray Structure Determinations

Crystal Structure Report for 13

A yellow prism-like specimen of $C_{13}H_9Br_2N_5O \cdot$ acetone, approximate dimensions 0.066 mm x 0.141 mm x 0.362 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured on a D8 Venture system equipped with a multilayer monochromator.

The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm. The integration of the data using a monoclinic unit cell yielded a total of 41291 reflections to a maximum θ angle of 30.62° (0.70 Å resolution), of which 5210 were independent (average redundancy 7.925, completeness = 99.5%, R_{int} = 4.29%, R_{sig} = 2.56%) and 4434 (85.11%) were greater than $2\sigma(F^2)$. The final cell constants of a = 18.4913(6) Å, b = 4.76720(10) Å, c = 19.3160(7) Å, β = 94.258(2)°, volume = 1698.04(9) $Å^3$, are based upon the refinement of the XYZ-centroids of reflections above 20 σ(I). Data were corrected for absorption effects using the multi-scan method (SADABS). The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.5514 and 0.7461.

The structure was solved and refined using the Bruker SHELXTL Software Package[3] using the space group P 1 21/n 1, with Z = 4 for the formula unit, $C_{13}H_9Br_2N_5O \cdot$ acetone. The final anisotropic full-matrix least-squares refinement on F^2 with 210 variables converged at R1 = 5.61%, for the observed data and wR2 = 17.29% for all data. The goodness-of-fit was 1.074. The largest peak in the final difference electron density synthesis was 1.780 $e^-/Å^3$ and the largest hole was -2.479 $e^-/Å^3$ with an RMS deviation of 0.191 $e^-/Å^3$. On the basis of the final model, the calculated density was 1.835 g/cm^3 and F(000), 928 e^-.

Table S1. Crystal data and structure refinement for **13**.

Identification code	mo_023VB5A_0m_a	
Empirical formula	$C_{13}H_9Br_2N_5O \cdot C_3H_6O$	
Formula weight	469.15	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21/n	
Unit cell dimensions	a = 18.4913(6) Å	α = 90°.
	b = 4.76720(10) Å	β = 94.258(2)°.
	c = 19.3160(7) Å	γ = 90°.
Volume	1698.04(9) $Å^3$	
Z	4	
Density (calculated)	1.835 Mg/m^3	
Absorption coefficient	4.795 mm^{-1}	
F(000)	928	
Crystal size	0.326 x 0.141 x 0.066 mm^3	
Theta range for data collection	2.209 to 30.623°.	
Index ranges	-26 ≤ h ≤ 26, -6 ≤ k ≤ 6, -27 ≤ l ≤ 27	
Reflections collected	41290	
Independent reflections	5209 [R(int) = 0.0429]	
Completeness to theta = 25.242°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7461 and 0.5514	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5209 / 0 / 210	
Goodness-of-fit on F^2	1.074	
Final R indices [I>2sigma(I)]	R1 = 0.0561, wR2 = 0.1550	
R indices (all data)	R1 = 0.0679, wR2 = 0.1626	
Extinction coefficient	n/a	
Largest diff. peak and hole	1.780 and -2.479 $e.Å^{-3}$	
CCDC	1841265	

Table S2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **13**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y]	z]	U(eq)
Br(1)	3128(1)	14071(1)	7183(1)	28(1)
Br(1)	8530(1)	-4626(1)	6429(1)	21(1)
O(1)	3592(2)	14377(7)	5685(2)	16(1)
N(1)	4443(2)	10928(7)	5742(2)	11(1)
N(2)	5314(2)	7463(7)	5719(2)	11(1)
N(3)	6166(2)	4005(7)	5704(2)	12(1)
N(4)	5214(2)	5786(8)	7803(2)	19(1)
N(5)	5681(2)	4884(7)	6761(2)	14(1)
C(1)	3925(2)	12538(8)	6024(2)	14(1)
C(2)	3824(3)	11940(10)	6752(2)	22(1)
C(3)	4236(2)	10041(9)	7126(2)	16(1)
C(4)	4763(2)	8441(8)	6790(2)	13(1)
C(5)	4852(2)	8884(8)	6089(2)	11(1)
C(6)	5220(2)	6365(9)	7117(2)	13(1)
C(7)	5709(2)	5493(8)	6085(2)	11(1)
C(8)	6680(2)	1944(8)	5910(2)	12(1)
C(9)	6794(2)	824(9)	6579(2)	15(1)
C(10)	7332(2)	-1177(9)	6729(2)	18(1)
C(11)	7763(2)	-2026(9)	6208(2)	17(1)
C(12)	7648(2)	-1014(9)	5536(2)	19(1)
C(13)	7108(2)	964(9)	5389(2)	16(1)
O(1W)	4330(5)	8790(20)	8816(4)	104(2)
C(3W)	4584(7)	12640(30)	9545(5)	104(2)
C(1W)	3349(7)	11350(30)	9171(5)	104(2)
C(2W)	4086(8)	10670(30)	9122(6)	104(2)

Table S3. Bond lengths [Å] and angles [°] for **13**.

Br(1)-C(2)	1.881(4)
Br(2)-C(11)	1.908(4)
O(1)-C(1)	1.232(5)
N(1)-C(1)	1.372(5)
N(1)-C(5)	1.377(5)
N(1)-H(1)	0.8800
N(2)-C(5)	1.338(5)
N(2)-C(7)	1.355(5)
N(3)-C(7)	1.361(5)
N(3)-C(8)	1.404(5)
N(3)-H(3)	0.8800
N(4)-C(6)	1.355(5)
N(4)-H(4A)	0.8800
N(4)-H(4B)	0.8800
N(5)-C(6)	1.335(5)
N(5)-C(7)	1.343(5)
C(1)-C(2)	1.460(6)
C(2)-C(3)	1.356(6)
C(3)-C(4)	1.430(6)
C(3)-H(3A)	0.9500
C(4)-C(5)	1.391(5)
C(4)-C(6)	1.419(5)
C(8)-C(9)	1.399(5)
C(8)-C(13)	1.406(6)
C(9)-C(10)	1.393(6)
C(9)-H(9)	0.9500
C(10)-C(11)	1.388(6)
C(10)-H(10)	0.9500
C(11)-C(12)	1.387(6)
C(12)-C(13)	1.388(6)
C(12)-H(12)	0.9500
C(13)-H(13)	0.9500
O(1W)-C(2W)	1.184(14)
C(3W)-C(2W)	1.51(2)
C(3W)-H(3WA)	0.9800
C(3W)-H(3WB)	0.9800
C(3W)-H(3WC)	0.9800

C(1W)-C(2W)	1.411(16)
C(1W)-H(1WA)	0.9800
C(1W)-H(1WB)	0.9800
C(1W)-H(1WC)	0.9800
C(1)-N(1)-C(5)	125.2(3)
C(1)-N(1)-H(1)	117.4
C(5)-N(1)-H(1)	117.4
C(5)-N(2)-C(7)	114.4(3)
C(7)-N(3)-C(8)	130.2(3)
C(7)-N(3)-H(3)	114.9
C(8)-N(3)-H(3)	114.9
C(6)-N(4)-H(4A)	120.0
C(6)-N(4)-H(4B)	120.0
H(4A)-N(4)-H(4B)	120.0
C(6)-N(5)-C(7)	117.2(3)
O(1)-C(1)-N(1)	121.6(4)
O(1)-C(1)-C(2)	123.8(4)
N(1)-C(1)-C(2)	114.6(4)
C(3)-C(2)-C(1)	122.4(4)
C(3)-C(2)-Br(1)	120.0(3)
C(1)-C(2)-Br(1)	117.4(3)
C(2)-C(3)-C(4)	119.3(4)
C(2)-C(3)-H(3A)	120.4
C(4)-C(3)-H(3A)	120.4
C(5)-C(4)-C(6)	115.4(4)
C(5)-C(4)-C(3)	119.6(4)
C(6)-C(4)-C(3)	125.0(4)
N(2)-C(5)-N(1)	116.6(3)
N(2)-C(5)-C(4)	124.7(4)
N(1)-C(5)-C(4)	118.7(4)
N(5)-C(6)-N(4)	116.5(4)
N(5)-C(6)-C(4)	121.5(4)
N(4)-C(6)-C(4)	122.0(4)
N(5)-C(7)-N(2)	126.8(4)
N(5)-C(7)-N(3)	118.9(3)
N(2)-C(7)-N(3)	114.3(3)
C(9)-C(8)-N(3)	125.6(4)
C(9)-C(8)-C(13)	118.6(4)
N(3)-C(8)-C(13)	115.8(3)

C(10)-C(9)-C(8)	120.7(4)
C(10)-C(9)-H(9)	119.6
C(8)-C(9)-H(9)	119.6
C(11)-C(10)-C(9)	119.2(4)
C(11)-C(10)-H(10)	120.4
C(9)-C(10)-H(10)	120.4
C(12)-C(11)-C(10)	121.4(4)
C(12)-C(11)-Br(2)	119.7(3)
C(10)-C(11)-Br(2)	119.0(3)
C(11)-C(12)-C(13)	119.1(4)
C(11)-C(12)-H(12)	120.5
C(13)-C(12)-H(12)	120.5
C(12)-C(13)-C(8)	121.0(4)
C(12)-C(13)-H(13)	119.5
C(8)-C(13)-H(13)	119.5
C(2W)-C(3W)-H(3WA)	109.5
C(2W)-C(3W)-H(3WB)	109.5
H(3WA)-C(3W)-H(3WB)	109.5
C(2W)-C(3W)-H(3WC)	109.5
H(3WA)-C(3W)-H(3WC)	109.5
H(3WB)-C(3W)-H(3WC)	109.5
C(2W)-C(1W)-H(1WA)	109.5
C(2W)-C(1W)-H(1WB)	109.5
H(1WA)-C(1W)-H(1WB)	109.5
C(2W)-C(1W)-H(1WC)	109.5
H(1WA)-C(1W)-H(1WC)	109.5
H(1WB)-C(1W)-H(1WC)	109.5
O(1W)-C(2W)-C(1W)	127.7(17)
O(1W)-C(2W)-C(3W)	120.2(13)
C(1W)-C(2W)-C(3W)	112.0(12)

Symmetry transformations used to generate equivalent atoms:

Table S4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **13**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}]$.

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Br(1)	30(1)	27(1)	31(1)	3(1)	13(1)	6(1)
Br(2)	17(1)	15(1)	31(1)	-5(1)	-10(1)	5(1)
O(1)	16(1)	17(1)	16(1)	2(1)	2(1)	5(1)
N(1)	11(1)	10(1)	11(1)	3(1)	2(1)	1(1)
N(2)	11(1)	10(1)	11(1)	0(1)	-1(1)	-1(1)
N(3)	13(1)	11(2)	12(1)	1(1)	-2(1)	1(1)
N(4)	24(2)	21(2)	11(2)	4(1)	-1(1)	5(1)
N(5)	14(2)	13(2)	14(2)	2(1)	-1(1)	1(1)
C(1)	14(2)	12(2)	15(2)	1(1)	2(1)	1(1)
C(2)	27(2)	21(2)	19(2)	2(2)	11(2)	9(2)
C(3)	17(2)	15(2)	16(2)	2(2)	2(1)	-2(2)
C(4)	14(2)	11(2)	13(2)	0(1)	0(1)	0(1)
C(5)	10(2)	9(2)	13(2)	1(1)	-3(1)	-3(1)
C(6)	15(2)	12(2)	12(2)	2(1)	-2(1)	-2(1)
C(7)	9(2)	9(2)	14(2)	0(1)	-2(1)	-2(1)
C(8)	12(2)	9(2)	16(2)	0(1)	-4(1)	0(1)
C(9)	15(2)	13(2)	17(2)	1(1)	-2(1)	2(1)
C(10)	16(2)	15(2)	21(2)	2(2)	-5(2)	2(1)
C(11)	12(2)	11(2)	25(2)	-2(2)	-8(1)	2(1)
C(12)	17(2)	16(2)	24(2)	-3(2)	-1(2)	3(2)
C(13)	16(2)	15(2)	18(2)	2(2)	-2(1)	2(1)
O(1W)	128(5)	135(5)	51(2)	6(3)	26(3)	65(4)
C(3W)	128(5)	135(5)	51(2)	6(3)	26(3)	65(4)
C(1W)	128(5)	135(5)	51(2)	6(3)	26(3)	65(4)
C(2W)	128(5)	135(5)	51(2)	6(3)	26(3)	65(4)

Table S5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **13**.

	x	y[]	z	U(eq)
H(1)	4520	11224	5304	13
H(3)	6134	4396	5257	15
H(4A)	5505	4491	7992	23
H(4B)	4920	6705	8059	23
H(3A)	4175	9776	7606	19
H(9)	6502	1434	6934	18
H(10)	7404	-1952	7182	21
H(12)	7936	-1667	5181	23
H(13)	7027	1667	4929	20
H(3WA)	5088	12048	9518	156
H(3WB)	4463	12609	10031	156
H(3WC)	4524	14554	9362	156
H(1WA)	3252	13227	8980	156
H(1WB)	3236	11307	9658	156
H(1WC)	3045	9976	8906	156

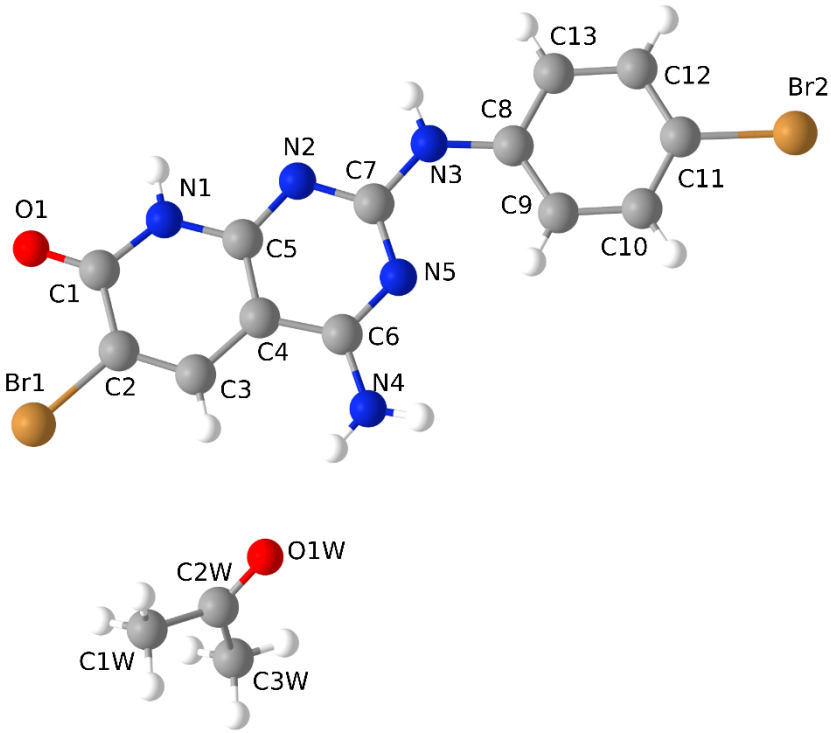


Figure S1. Crystal structure of **13 · acetone** showing the atom labels.

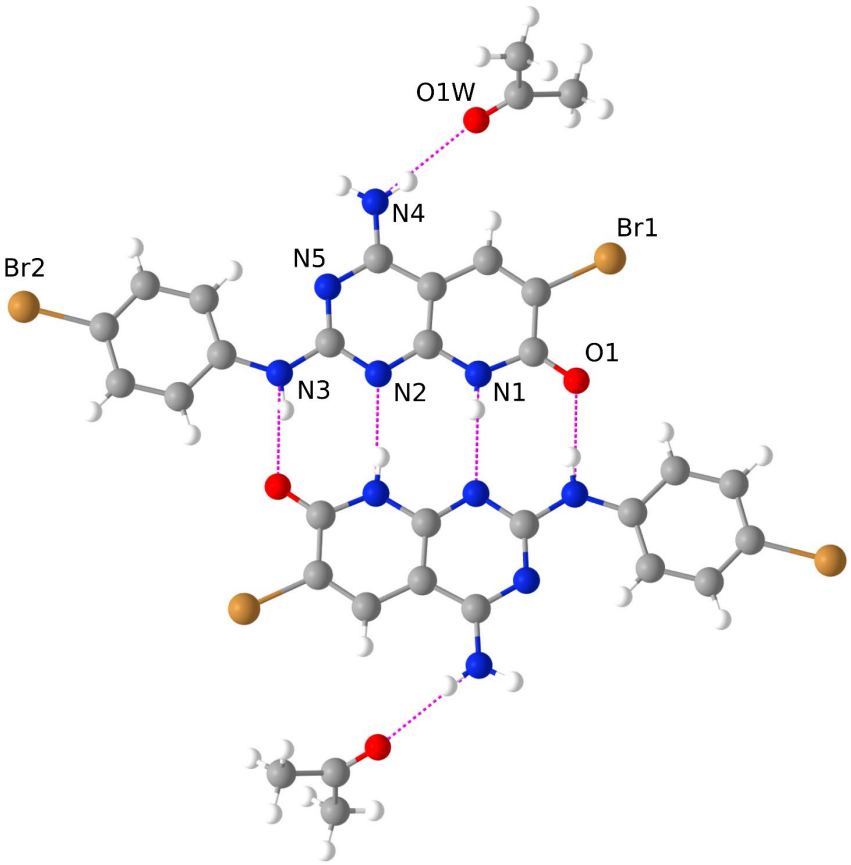


Figure S2. Crystal structure of **13** cocrystallized with acetone, showing the self-complementarity through quadruple hydrogen bonding..

Crystal Structure Determination for 12

Crystal structure of compound **12** was solved from synchrotron X-ray powder diffraction data collected in the MSPD-BL04 beamline[4] at ALBA Synchrotron. Data were collected with the microstrip Mythen-II detector (six modules, 1280 channels/module, 50 μm/channel, sample-to-detector distance 550 mm) at an energy of 13keV (0.95250Å wavelength, determined with Si NIST-640d reference) in transmission mode with the sample inserted in a 0.7mm glass capillary.

The powder diffraction pattern was indexed using DICVOL06[5] obtaining a triclinic cell [a = 10.44(1), b = 10.14(2), c = 8.74(3) Å, α = 102.6(1), β = 85.1(2), γ = 123.9(1)º] with figures of merit M_{20} = 12.7 and F_{20} = 39.0 (0.0097, 53). The extraction of the intensities and refinement of the reduced cell parameters [a = 8.757(1), b = 9.668(2), c = 10.106(1) Å, α = 63.6(4), β = 77.3(7), γ = 82.0(7)º] was performed with DAjust software[6]. The crystal structure was solved with the direct-space strategy TALP[7]. The candidate solution was refined with the restrained Rietveld refinement program RIBOLS, using distance restraints taken from MOGUL[8] except for the free Br position which was refined without restraints. H-atoms were placed to calculated positions after the final refinement. Crystallographic data and refinement details can be found in table S6.

Table S6. Crystallographic data and refinement details for compound **12**.

Molecular formula	$C_{13}H_{10}Br_3N_5O$
Formula weight	491.97
Crystal System	Triclinic
Space group	P -1
a (Å)	8.759(1)
b (Å)	9.671(2)
c (Å)	10.109(1)
α (º)	63.5(4)
β (º)	77.3(7)
γ (º)	82.0(7)
Z	2
Calculated density (g/cm^3)	2.187
Measurement temperature (K)	298
Wavelength (Å)	0.95250
Measured 2*θ* range, stepsize (º)	1.026 to 43.494, 0.006
Rietveld Refinement Details:	
Profile function	Pseudo-Voigt
2θ range used (º)	3.506 to 36.000
Num. of reflections	433
Data points	5416
Parameters[a]	79
Restraints[b]	79
Rwp	0.036
X	7.738
CCDC	1841815

[a] Parameters: 22 atomic coordinates, $B_{C,N,O}$, B_{Br}, scale factor, zero shift, 3 profile parameters, 6 cell parameters. [b] Restraints: 24 bond, 32 angleº and 23 to define atomic planes.

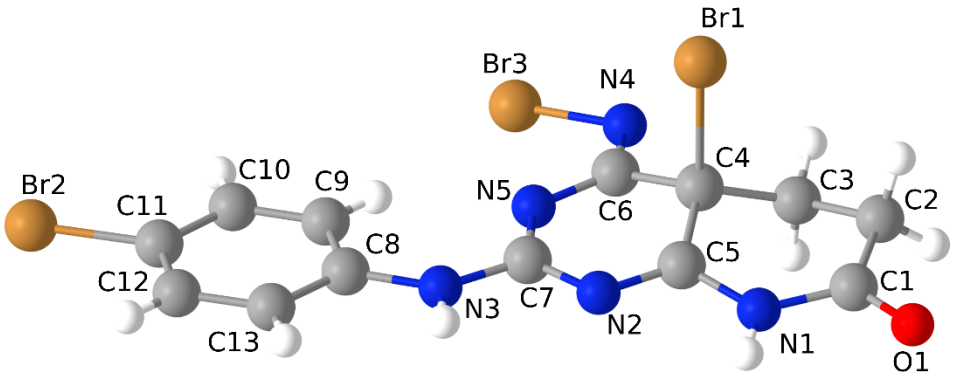


Figure S3. Crystal structure of **12** showing the atom labels.

Table S7. Most important intermolecular interactions in compound **12** (Cg = centroid).

Potential H bonds (D-H···A)	Length D-A (Å)	Angle (º)
N1–H1N ··· N2	3.017(14)	159
N3–H3N ··· O1	2.704(15)	163
Potential *π*- *π* interactions	Distance Cg-Cg (Å)	Angle[a] (º)
[C8…C13] ··· [C8…C13]	3.741(7)	22

[a] Angle between vector Cg-Cg and vector normal to the ring plane

Table S8. Most important intermolecular interactions in compound **13** (Cg = centroid).

Potential H bonds (D-H···A)	Length D-A (Å)	Angle (º)
N1–H1 ··· N2	2.991(5)	172
N3–H3 ··· O1	2.858(5)	161
N4–H4 ··· O1W	3.005(9)	171
Potential *π*- *π* interactions	Distance Cg-Cg (Å)	Angle[a] (º)
[C1…C5,N1] ··· [C4…C7,N2,N5]	3.514(2)	21.1
[C8…C13] ··· [C4…C7,N2,N5]	4.016(2)	36.2

[a] Angle between vector Cg-Cg and vector normal to the ring plane

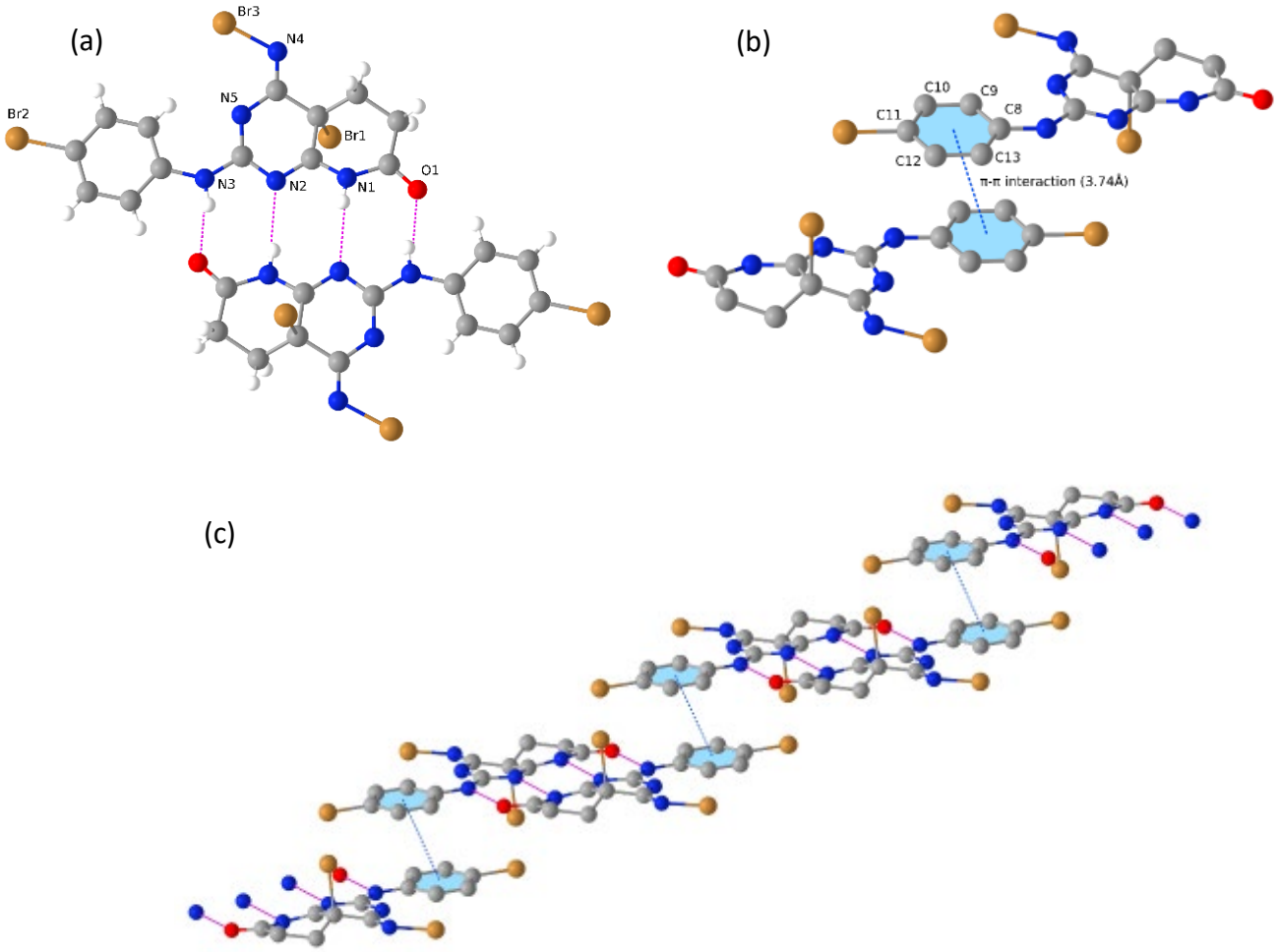


Figure S4. (a) The two enantiomers of **12** associated in a self-complementary ADAD-DADA quadruple hydrogen-bonding centrosymmetric motif. (b) Potential π-π interaction in the crystal structure of **12**. (c) Propagation of the structure dimer (H-bonds) in one dimension as a result of the π-π interaction.

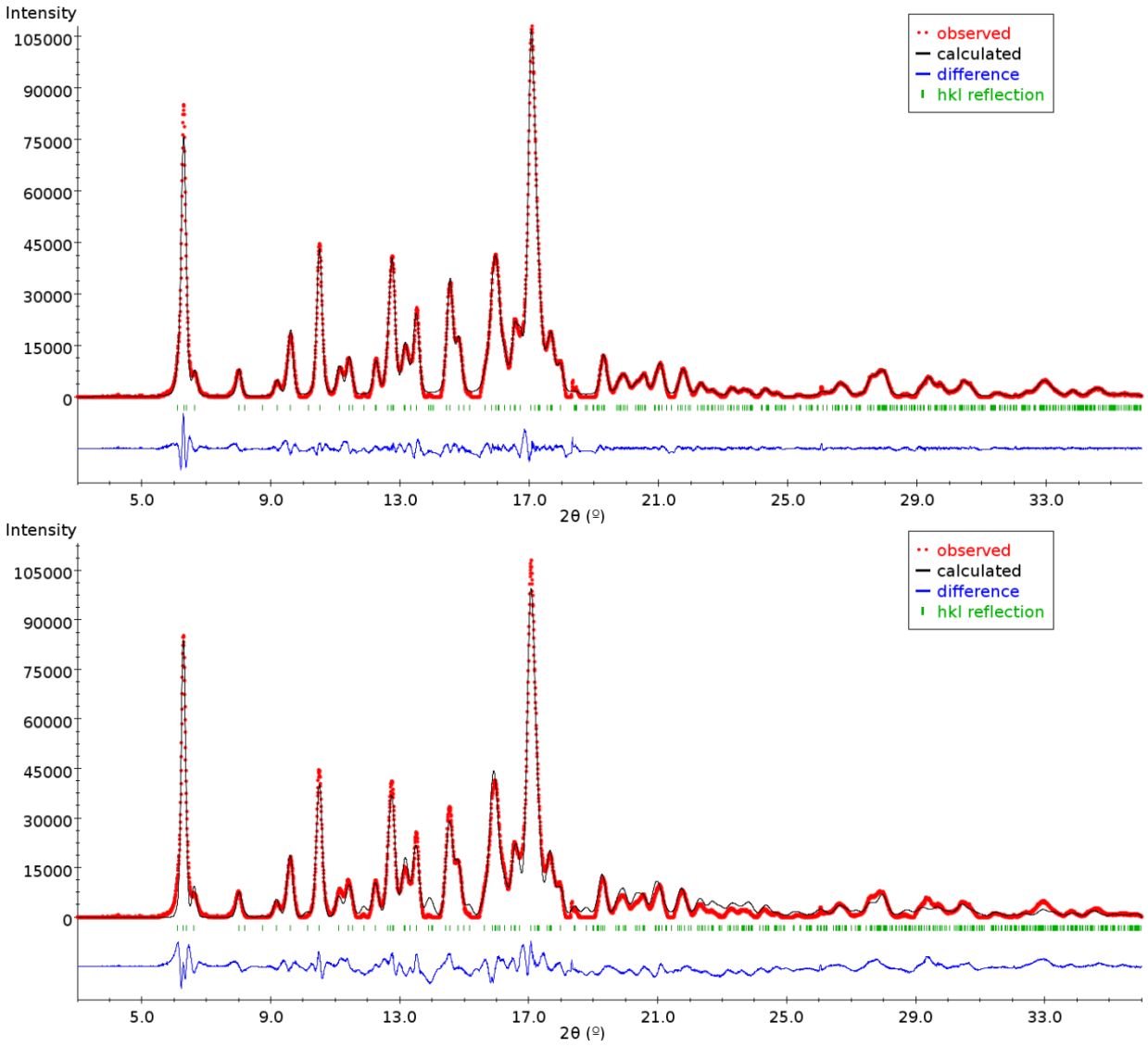


Figure S5. Pattern matching (top) and Rietveld refinement (bottom) plots of observed (red points) and calculated (black line) patterns, with the difference profile (bottom blue line) and *hkl* reflections (green vertical lines). Wavelength 0.95250Å.

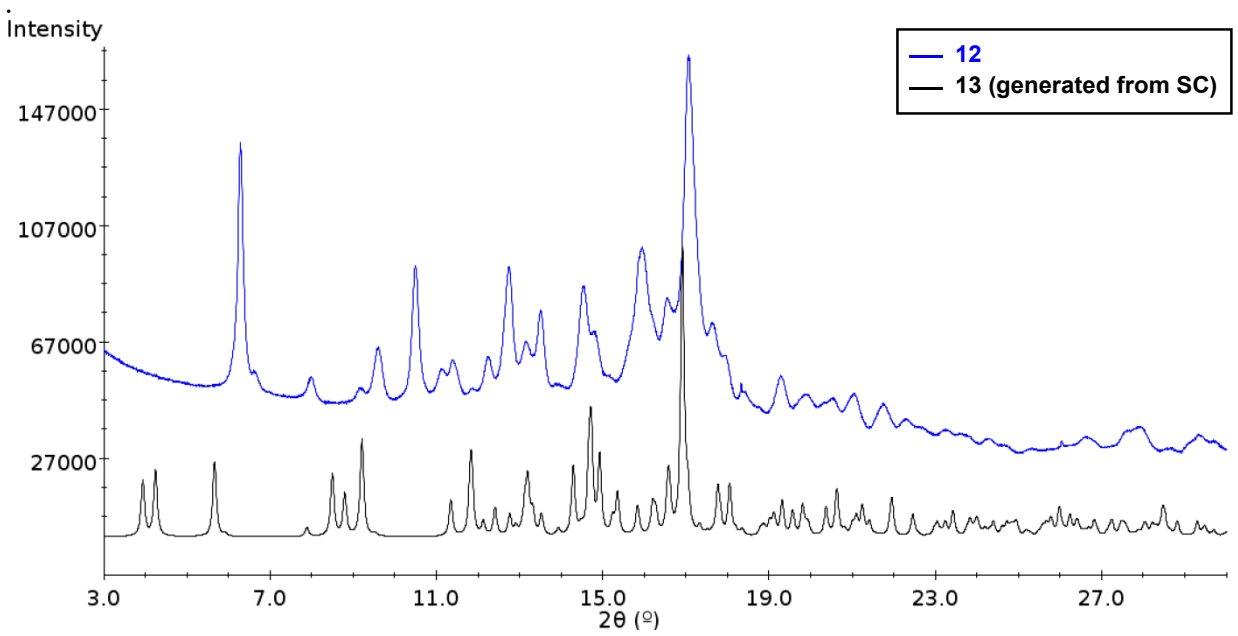


Figure S6. Measured powder diffraction pattern of **12** (top, in blue) compared with the simulated powder pattern generated from the single-crystal structure of **13** (bottom, in black). Wavelength 0.95250Å.

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