2. EXPERIMENTAL PART

2.1. Instrumentation

Infrared Spectra (IR) was recorded in a Nicolet iS10 FTIR spectrometer with Smart iTr of the Organic Chemistry department at IQS, by Mrs. Núria Ruiz, under the leadership of Dr. Xavier Batllori. Values are reported in wave numbers (cm^{-1}). The notation used is: KBr (potassium bromide plates), film (evaporated film from chloroform), t (tension), δ (deformation vibration), γ (skeletal vibration), ip (in plan), oop (out of plan), sim (symmetrical), as (antisymmetrical).

Nuclear Magnetic Resonance spectra (^{1}H-NMR and ^{13}C-NMR) were recorded on a Varian 400-NMR spectrometer with a 400 MHz frequency generators for ranges 1H-19F and 15N-31P, temperature control system, automatic tuning probe and sample introduction robot 50 positions (^{1}H-NMR at 400 MHz and ^{13}C-NMR at 100.6 MHz) by myself in the Organic Chemistry department at IQS under leadership of Dr. X. Batllori Chemical shifts are reported in part per million (ppm) on the δ scale, and are referenced to tetramethylsilane (TMS) or 3-(trimethylsilyl)propionic acid-d_4 sodium salt (TSPNa) in ^{1}H-NMR spectra and to residual signal of the solvent $CDCl_3$ (77.0), DMSO-d_6 (39.5), TFA-d (116.6), methanol-d_4 (49.0), acetone-d_6 (29.8) in ^{13}C-NMR spectra. Coupling constants are reported in Hertz (Hz). Spectral splitting patterns are designed as a: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), ddd (doublet of doublet of doublets), m (complex multiplet).

Mass Spectrometry (MS) was conducted on a Agilent Technologies 5975 mass spectrometer operating in electron ionisation (EI) mode at 70 eV and at 4kV accelerating potential or on a VG AutoSpec (Micromass Instruments) Triosector EBE spectrometer operating in Fast Atom Bombardment (FAB) mode or on a Biotoff II (Bruker) in Electrospray ionization (ESI) mode with a Time Of Flight (TOF) detector at Unidade de Espectrometria de Masas (Universidad de Santiago de Compostela) under the leadership of Dr. Esteban Gutián and on an Agilent Technologies 5975 spectrometer at Organic Chemistry department at IQS under the leadership of Dr. Xavier Batllori by Mrs. Núria Ruiz.

High Resolution Mass Spectrometry (HRMS) was conducted on a VG AutoSpec (Micromass Instruments) Trisector EBE of high resolution spectrometer operating in FAB or EI mode and on Biotoff II (Bruker) apparatus in ESI-TOF mode at Servicio de Espectroscopía de Masas (Universidade de Santiago de Compostela) under the leadership of Dr. Esteban Gutián.

Elemental microanalyses were obtained in a EuroVector Instruments Euro EA elemental analyzer for determination of elemental microanalyses at Organic Chemistry department at IQS by Mrs. N. Ruiz under the leadership of Dr. X. Batllori.

The **melting point (mp)** and **decomposition point (dp)** were determined with a Büchi-Tottoli 530 capillary apparatus and are uncorrected.

Microwave irradiation experiments were carried out in an Initiator™ (Biotage) microwave apparatus, operating at a frequency of 2.45 GHz with continuous irradiation power from 0 to 400 W. Reactions were carried out in 0.5, 2.5, 5, 20 mL glass tubes, sealed with aluminium/Teflon crimp tops, which can be exposed up to 250 ºC 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 to 50 ºC by air jet cooling.

Automatic flash chromatography was done in an Isco Combiflash medium pressure liquid chromatograph with Redi*Sep*® silica gel columns (35-70 μm) or basic alumina columns (50-200 μm).

Thank to all of them for all their work.

2.2. Synthesis of starting materials

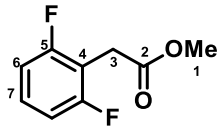
2.2.1. General procedure for alkyl 2-arylacetates

The corresponding substituted phenylacetic acid (5.81 mmol) was dissolved in a solution of HCl/MeOH 1.25M (9.3mL, 11.63 mmol). Na_2SO_4 (1.650 g) was added and the mixture was stirred overnight at room temperature. The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure to afford the corresponding methyl 2-acetate, as a colorless liquid.

Methyl 2-(2,6-difluorophenyl)acetate (29{*4*})

Starting from 2-(2,6-difluorophenyl)acetic acid. 65% yield, colourless liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 – 7.20 (m, 1H, C7-CH), 6.94 - 6.86 (m, 2H, C6-CHx2), 3.72 (s, 5H, C1-CH_3, C3-CH_2).



^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.3, 161.7 (d, *J* = 248.6 Hz, C5), 161.6 (d, *J* = 248.6 Hz, C5), 129.1 (t, *J* = 129.1 Hz, C7), 111.2 (dd, *J* = 19.0, 6.5 Hz. C6), 110.7 (d, *J* = 20.0 Hz, C4), 52.5 (C1), 27.9 (t, *J* = 3.2 Hz, C3).

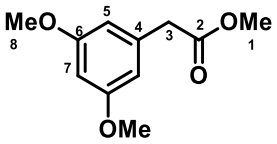
Anal. Calcd. (%) for $C_9H_8F_2O_2$: C, 58.07; H, 4.33. Found: C, 57.85; H, 4.53.

IR (film), ν_{max} (cm $^{-1}$): 3004, 2956, 2847, 1746, 1629, 1595, 1471, 1271, 1217, 1169, 1021, 786

Methyl 2-(3,5-dimethoxyphenyl)acetate (29{*10*})

Starting from 2-(3,5-dimethoxyphenyl)acetic acid. Quantitative yield, colourless liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.43 (d, *J* = 2.3 Hz, 2H, C5-CHx2), 6.37 (t, *J* = 2.3 Hz, 1H, C7-CH), 3.78 (s, 6H, C8-OCH_3x2), 3.69 (s, 3H, C1-OCH_3), 3.56 (s, 2H, C3-CH_2).



^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.9, 161.0, 136.1, 107.4 (C5), 99.3 (C7), 55.4 (C6), 52.2 (C1), 41.6 (C3).

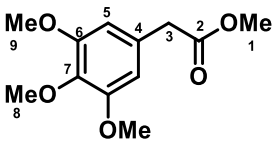
Anal. Calcd. (%) for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71. Found: C, 63.25; H, 7.05.

IR (film), ν_{max} (cm $^{-1}$): 3001, 2953, 2840, 1739, 1598, 1463, 1432, 1206, 1153, 1066

Methyl 2-(3,4,5-trimethoxyphenyl)acetate (29{*11*})

Starting from 2-(3,4,5-trimethoxyphenyl)acetic acid. 84% yield, colourless liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.50 (s, 2H, C5-CHx2), 3.86 (s, 6H, C9-OCH_3x2), 3.83 (s, 3H, C8-OCH_3), 3.71 (s, 3H, C1-CH_3), 3.56 (s, 2H, C3-CH_2).



^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.0, 153.2, 137.1, 129.5, 106.3 (C5), 60.8 (C8), 56.1 (C9), 52.1 (C1), 41.4 (C3).

IR (film), ν_{max} (cm^{-1}): 2994, 2947, 2840, 1738, 1591, 1508, 1461, 1424, 1320, 1242, 1127, 1009.

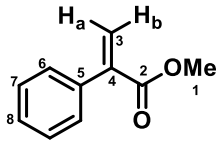
2.2.2. General procedure for alkyl 2-arylacrylates (1{*x*})

The corresponding alkyl 2-arylacetate (**29**{*x*}) (29.7 mmol) is dissolved in DMF (120 mL), paraformaldehyde (3.480 g, 38.63 mmol) was added and lastly potassium carbonate (4.110 g, 29.74 mmol) was added. The reaction temperature is kept at 100 ºC during 3 hours. The reaction mixture is quenched with water and extracted with diethyl ether. The organic layer was washed with an aqueous solution of lithium chloride and the solvent was dried ($MgSO_4$) and removed under reduced pressure to afford the corresponding alkyl 2-arylcrylate.

Methyl 2-phenylacrylate (1{*2*})

Starting from methyl 2-phenylacetate (**29**{*2*}). 68% yield, colourless liquid.

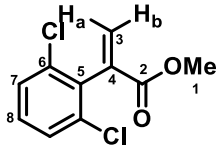
Spectral data are consistent to those previously described[1].



Methyl 2-(2,6-dichlorophenyl)acrylate (1{*3*})

Starting from methyl 2-(2,6-dichlorophenyl)acetate (**29**{*3*}). 94% yield, colourless liquid.

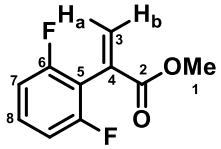
Spectral data are consistent to those previously described[2].



Methyl 2-(2,6-difluorophenyl)acrylate (1{*4*})

Starting from methyl 2-(2,6-difluorophenyl)acetate (**29**{*4*}). 65% yield, colourless liquid

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 - 7.25 (m, 1H, C8), 6.96 - 6.88 (m, 2H, C17-CHx2), 6.74 (m, 1H, C3-CH_a), 5.96 (m, 1H, C3-CH_b), 3.79 (s, 3H, C1-CH_3).



^{13}C NMR (100.6 MHz, $CDCl_3$) δ 165.9, 160.5 (d, *J* = 249.6 Hz, C6), 160.4 (d, *J* = 249.6 Hz, C6), 132.6 (t, *J* = 1.4 Hz, C3), 129.9 (t, *J* = 10.3 Hz, C8), 129.5 (C4), 114.6 (t, *J* = 19.6 Hz, C5), 111.4 (dd, *J* = 6.6, 19.6 Hz, C7), 52.6 (C1).

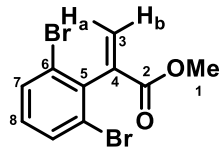
HRMS (70 eV, EI): m/z calculated for $C_{10}H_8F_2O_2$: 198.0492, $[M]^+$, found: 198.0490.

IR (film), ν_{max} (cm^{-1}): 3004, 2957, 2848, 1747, 1629, 1595, 1472, 1437, 1345, 1272, 1239, 1213, 1169, 1021, 786.

Methyl 2-(2,6-dibromohenyl)acrylate (1{*5*})

Starting from methyl 2-(2,6-dibromophenyl)acetate (**29**{*5*}). quantitative yield, colourless liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, *J* = 8.1 Hz, 2H, C7-CHx2), 7.09–7.03 (m, 1H, C8-CH), 6.75 (d, *J* = 0.9 Hz, 1H), 5.79 (d, *J* = 0.9 Hz, 1H), 3.78 (s, 3H, CH_3).



^{13}C NMR (100.6 MHz, $CDCl_3$) δ 165.1, 140.2, 138.7, 131.7, 131.6, 130.2, 124.3, 52.5.

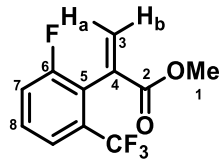
Anal. Calcd. (%) for $C_{10}H_8Br_2O_2$: C, 37.54; H, 2.52. Found: C, 37.91; H, 2.60.

IR (film), ν_{max} (cm $^{-1}$): 2997, 2951, 1728, 1629, 1548, 1425, 1301, 1211, 1115, 993, 962, 775, 735

Methyl 2-(2-fluoro-6-(trifluoromethyl)phenyl)acrylate (1{*6*})

Starting from methyl 2-(2-fluoro-6-(trifluoromethyl)phenyl)acetate (**29**{*6*}). 95% yield, colourless liquid

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52–7.42 (m, 2H, C7-CHx2), 7.32–7.26 (m,1H, C8-CH), 6.78 (d, *J* = 0.9 Hz, 1H), 5.85 (d, *J* = 0.9 Hz, 1H), 3.76 (s, 3H, CH_3).



^{13}C NMR (100.6 MHz, $CDCl_3$) δ 165.3, 160.2 (d, *J* = 247.6 Hz), 132.1 (d, *J* = 1.1 Hz), 132.0, 130.9 (qd, *J* = 30.7*,* 3.1Hz), 129.8 (q, *J* = 8.8Hz), 124.1 (dq, *J* = 20.4*,* 1.9 Hz), 123.2 (qd, *J* = 274.1*,* 3.5 Hz), 121.6 (m), 118.9 (dd, *J* = 22.8*,* 0.9Hz), 52.4.

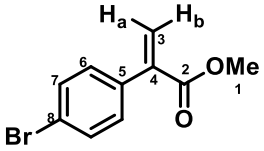
Anal. Calcd. (%) for $C_{11}H_8F_4O_2$: C, 53.24; H, 3.25. Found: C, 52.88; H, 3.00.

IR (film), ν_{max} (cm $^{-1}$): 3004, 2957, 2846, 1731, 1635, 1582, 1469, 1440, 1321, 1254, 1212, 1169, 1127, 993, 970, 909, 807, 755, 734.

Methyl 2-(4-bromophenyl)acrylate (1{*8*})

Starting from methyl 2-(4-bromophenyl)acetate (**29**{*8*}). 36% yield, colourless liquid.

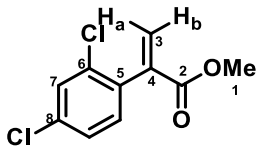
Spectral data are consistent to those previously described[3].



Methyl 2-(2,4-difluorophenyl)acrylate (1{*9*})

Starting from methyl 2-(2,4-difluorophenyl)acetate (**29**{*9*}). 90% yield, colourless liquid

^{1}H NMR (400 MHz, $CDCl_3$): δ 7,41 (d, *J* = 2 Hz, 1H, C7-CH), 7,26(dd, *J* = 8,4, 2,0 Hz), 7,19 (d, *J* = 8,4 Hz, 1H), 6,55 (d, *J* = 1,2 Hz, 1H; C3-CH_b), 5,79 (d, *J* = 1,2 Hz, 1H, C3-CH_a), 3,78(s, 3H, CH_3).



^{13}C NMR (100.6 MHz, $CDCl_3$) δ 166.2, 139.3(C6), 135.2(C8), 134.9(C5), 134.3, 131.8, 129.9, 129.4 (C7), 127.2, 52.6 (CH_3).

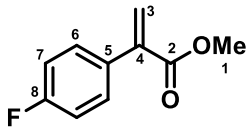
Anal. Calcd. (%) for $C_{10}H_6Cl_2O_2$: C, 51.98; H, 3.49. Found: C, 52.04; H, 3.36.

IR (film), ν_{max} (cm $^{-1}$): 3091, 2998, 2951, 1729, 1630, 1587, 1473,1437, 1314, 1210, 1102, 1044, 994, 960.

Methyl 2-(4-fluorophenyl)acrylate (1{*7*})

Starting from methyl 2-(*p*-fluorophenyl)acetate (**29**{*7*}). 52% yield, colourless liquid

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (dd, *J* = 8.9, 5.4 Hz, 2H, C6-2xCH), 7.04 (t, *J* = 8.8 Hz, 2H, C7-2xCH), 6.36 (d, *J* = 1.1 Hz, 1H, C3-CH), 5.87 (d, *J* = 1.1 Hz, 1H, C3-CH), 3.82 (s, 3H, CH_3).



^{13}C NMR (100.6 MHz, $CDCl_3$) δ 167.0 (CO), 162.7 (d, *J* = 246 Hz, C8), 140.2 (C4), 132.7 (d, *J* = 3.1 Hz, C5), 130.1 (d, *J* = 8.2 Hz, C6), 126.9 (d, *J* = 1.0 Hz, C3), 115.5 (d, *J* = 21.3 Hz C7), 52.2 (C1).

MS (70 eV, EI): m/z (%): 179.8 (32) $[M]^+$, 160.8 (12) $[M\text{-}F]^+$, 145.8 (70) $[M\text{-}C_1H_3F_1]^+$, 132.8 (17) $[M\text{-}C_2H_4F_1]^+$, 120.8 (19) $[M\text{-}C_2H_3O_2]^+$.

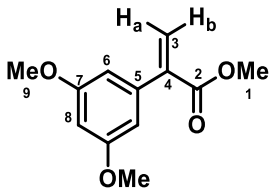
HRMS (70 eV, EI): m/z calculated for $C_{10}H_9FO_2$: 180.0587, $[M]^+$, found: 180.0587.

IR (dry film) vmax: 1725, 1603, 1511, 1224, 1163, 1087 cm^{-1}.

Methyl 2-(3,5-dimethoxyphenyl)acrylate (1{*10*})

Starting from methyl 2-(3,5-dimethoxyphenyl)acetate (**29**{*10*}). 55% yield, colourless liquid

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.56 (d, *J* = 2.4 Hz, 2H, C6-CHx2), 6.46 (t, *J* = 2.2 Hz, 1H, C8-CH), 6.34 (d, *J* = 1.2 Hz, 1H, C3-CH_b), 5.89 (d, *J* = 1.3 Hz, 1H, C3-CH_a), 3.82 (s, 3H, $COOCH_3$), 3.80 (s, 6H, OCH_3x2).



^{13}C NMR (100.6 MHz, $CDCl_3$) δ 167.1, 160.4, 141.2, 138.6, 127.1 (C3), 106.6 (C6), 100.3 (C8), 55.4 (9), 52.3 (C1).

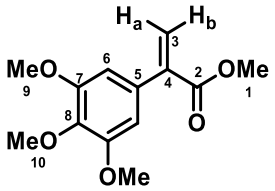
Anal. Calcd. (%) for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.51; H, 6.41.

IR (film), ν_{max} (cm $^{-1}$): 3528, 3000, 2951, 2839, 1724, 1593, 1457, 1424, 1280, 1205, 1157, 1051, 837.

Methyl 2-(3,4,5-trimethoxyphenyl)acrylate (1{*11*})

Starting from methyl 2-(3,4,5-trimethoxyphenyl)acetate (**29**{*11*}). 40% yield, colourless liquid

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.65 (s, 2H, C6-CHx2), 6.33 (d, *J* = 1.2 Hz, 1H, C3-H_a), 5.89 (d, *J* = 1.2 Hz, 1H, C3-H_b), 3.87 (s, 6H, C9-OCH_3x2), 3.86 (s, 3H, C10- OCH_3), 3.84 (s, 3H, C1-CH_3).



^{13}C NMR (100.6 MHz, $CDCl_3$) δ 167.3, 153.0, 141.2, 138.4, 132.3, 126.6 (C3), 105.9 (C6), 61.0 (C10), 56.3 (C9), 52.4 (C1).

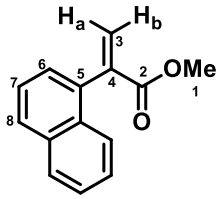
Anal. Calcd. (%) for $C_{13}H_{16}O_5$: C, 61.90; H, 6.39. Found: C, 61.88; H, 6.26.

IR (film), ν_{max} (cm $^{-1}$): 3531, 2997, 2949, 2838, 1723, 1582, 1508, 1414, 1290, 1242, 1158, 1128, 1007.

Methyl 2-(naphthalen-1-yl)acrylate (1{*12*})

Starting from methyl 2-(naphthalen-1-yl)acetate (**29**{*12*}). 88% yield, pale solid.

Spectral data are consistent to those previously described[3].



2.3. Synthesis of 4-oxopyrido[2,3-*d*]pyrimidines

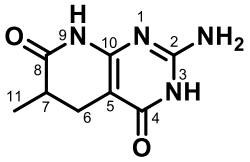
2.3.1. General procedure for 2-amino-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-diones (7{*x*})

The corresponding Alkyl 2-acrylate (**1**{*x*}) (4.00 mmol) was dissolved in anhydrous ethylene glycol (20 mL), 2,6-diaminopyrimidin-4(3*H*)-one (**24**) (5.60 mmol) and sodium methoxide (4.00 mmol) were added into the solution. The mixture was heated under microwave irradiation at 180ºC for 3 hours. Water was added and the reaction crude was neutralized with a 2M solution of HCl. The solid was collected by filtration and washed with water, MeOH and Et_2O.

2-amino-6-methyl-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (7{*1*})

Starting from methyl methacrylate (**1**{*1*}). 49% yield, white solid.

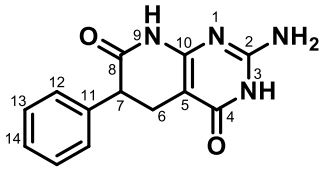
Spectral data are consistent to those previously described[4].



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

Starting from methyl 2-(phenyl)acrylate (**1**{*2*}). 68% yield, white solid.

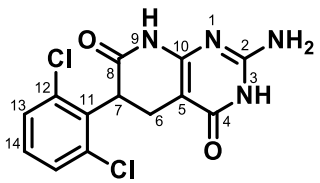
Spectral data are consistent to those previously described[5].



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

Starting from methyl 2-(2,6-dichlorophenyl)acrylate (**1**{*3*}). 89% yield, white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.65 (s, 1H, NH), 10.23 (s, 1H, NH), 7.51 (ddd, *J* = 16.6, 8.1, 1.3 Hz, 2H, C13-CHx2), 7.36 (t, *J* = 8.0, 1H, C14-CH), 6.53 (s, 2H, NH_2), 4.53 (dd, *J* = 13.4, 8.9 Hz, 1H, C7-CH), 2.87 – 2.59 (m, 2H, C6-CH_2).



^{13}C NMR (100.6 MHz, DMSO-d_6): δ 170.2, 161.5, 155.8, 155.0, 135.4, 135.2, 134.7, 129.8, 129.7, 128.3, 86.9 (C5), 43.3 (C7), 22.4 (C6).

Anal. Calcd. (%) for $C_{13}H_{10}Cl_2N_4O_2$: C, 48.02; H, 3.10; N, 17.23. Found: C, 48.01; H, 3.29; N, 16.97. MS (70 eV, EI): m/z (%) = 324.0 (70) $[M]^+$, 289.0 (100) $[M\text{-}Cl]^+$, 185.8 (30) $[M\text{-}C_8H_4Cl_2O]^+$, 138.9 (90) $[M\text{-}C_5H_6N_4O]^+$.

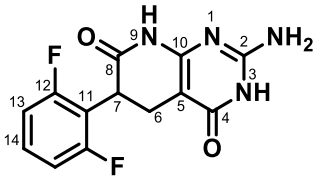
HRMS (70 eV, EI): m/z calculated for $C_{13}H_{10}N_4O_2Cl_2$: 324.0183, $[M]^+$, found: 324.0181.

IR (KBr), ν_{max} (cm^{-1}): 2282, 3193, 2904, 1649, 1597, 1537, 1375, 1283, 770.

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

Starting from methyl 2-(2,6-difluorophenyl)acrylate (**1**{*4*}). 88% yield, white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.61 (s, 1H, NH), 10.25 (s, 1H, NH), 7.40 (m, 1H, C14-CH), 7.11 (t, *J* = 8.6 Hz, 2H, C13-CHx2), 6.51 (s, 2H, NH_2), 4.10 (dd, *J* = 14.1, 7.6 Hz, 1H, C7-CH), 2.82 (dd, *J* = 15.4, 7.7 Hz, 1H, C6-CH), 2.55 – 2.48 (m, 1H, C6-CH).



^{13}C NMR (100.6 MHz, DMSO-d_6): δ 170.2, 161.2, 160.8 (d, *J* = 246.6 Hz, C12), 160.7 (d, *J* = 246.6 Hz, C12), 156.2, 154.9, 129.5 (t, *J* = 11.0 Hz, C14), 115.3 (t, *J* = 18.7 Hz, C11), 111.7 (dd, *J* = 22.4, 3.2 Hz, C13), 87.7 (C5), 36.6 (C7), 23.3 (C6).

Anal. Calcd. (%) for $C_{13}H_{10}F_2N_4O_2$: C, 53.43; H, 3.45; N, 19.17. Found: C, 53.03; H, 3.26; N, 19.30.

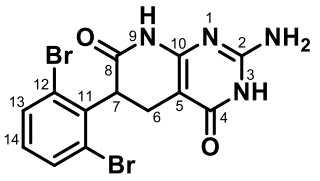
HRMS (70 eV, EI): m/z calculated for $C_{13}H_{10}N_4O_2F_2$: 292.0772, $[M]^+$, found: 292.0772.

IR (KBr), ν_{max} (cm^{-1}): 3469, 3166, 2859, 2740, 1695, 1653, 1596, 1470, 1272, 1207, 1008, 782.

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

Starting from methyl 2-(2,6-dibromophenyl)acrylate (**1**{*5*}). 75% yield, white solid.

^{1}H NMR (400MHz, DMSO-d_6): δ 10.66 (s, 1H, NH), 10.23 (s, 1H, NH), 7.73–7.67 (m, 2H, C13-CHx2), 7.18 (t, *J* = 8.0Hz, 1H, C14-CH), 6.54 (s, 2H, NH_2), 4.55 (dd, *J* = 13.5, 9.0Hz, 1H, C7-CH), 2.84–2.69(m, 2H, C6-CH_2).



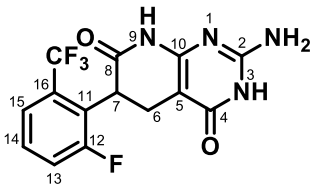
^{13}C NMR (100.6MHz, DMSO-d_6): δ 169.8, 161.5, 155.8, 154.9, 138.0, 133.9 (C13), 132.2 (C13), 130.5 (C14), 126.3, 124.2, 86.6 (C5), 48.0 (C7), 22.7 (C6)

HRMS (70 eV, EI): *m/z* calculated for $C_{13}H_{10}N_4O_2Br_2$: 411.9170, [M]+. Found: 411.9184

IR (KBr), ν_{max} (cm^{-1}): 3338, 3169, 2914, 1622, 1550, 1536, 1372, 1285, 823, 772.

2-amino-6-(2-fluoro-6-(trifluoromethyl)phenyl)-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (7{*6*})

Starting from methyl 2-(2-fluoro-6-(trifluoromethyl)phenyl)acrylate (**1**{*6*}). 81% yield, white solid.



^{1}H NMR (400MHz, DMSO-d_6): δ 10.68 (s, 1H, NH), 10.35 (s, 1H, NH), 7.63–7.56 (m, 3H, C14-CH, C13-CHx2), 6.55 (s, 2H, NH_2), 3.94 (dd, *J* = 13.8, 7.6Hz, 1H, C7-CH), 2.86 (dd, *J* = 16.5, 7.8Hz, 1H, C6-CH), 2.58–2.52 (m, 1H, C6-CH)

^{13}C NMR (100.6MHz, DMSO-d_6): δ 170.0, 161.3, 161.1 (d, *J* = 245.9Hz, C12), 156.1, 155.0, 129.9 (d, *J* = 9.7Hz, C14), 129.6 (qd, *J* = 29.6, 5.6Hz, C16), 126.1 (d, *J* = 15.7Hz, C15), 123.7 (qd, *J* = 274.0, 1.26 Hz, CF_3), 121.8 (m, C11), 120.6 (d, *J* = 22.9Hz, C13), 87.5 (C5), 40.9 (C7), 23.9 (C6).

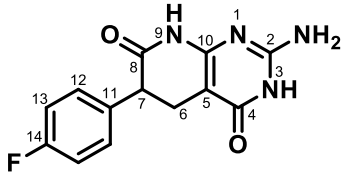
Anal. Calcd. (%) for $C_{13}H_{10}N_4O_2F_4$: C, 48.84; H, 3.51; N, 16.24. Found: C, 49.02; H, 3.09; N, 16.14

HRMS(70 eV, EI):*m*/*z* calculated for$C_{13}H_{10}N_4O_2F_4$: 342.0733, [M]+. Found: 342.0740

IR (KBr), ν_{max} (cm $^{-1}$): 3478, 3322, 3171, 2907, 2748, 1651, 1596, 1538, 1469, 1321, 1123, 796.

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

Starting from methyl 2-(4-fluorophenyl)acrylate (**1**{*7*}). 83% yield, white solid.



^{1}H NMR (400 MHz, DMSO-d_6): δ 10.72 (s, 1H, NH), 10.19 (s, 1H, NH), 7.29 – 7.23 (m, 2H, C12-2xCH), 7.17 – 7.11 (m, 2H, C13-2xCH), 6.54 (s, 2H, NH_2), 3.78 (dd, *J* = 9.6, 7.0 Hz, 1H, C7-CH), 2.78 (dd, *J* = 15.8, 7.0 Hz, 1H, C6-CH), 2.65 (dd, *J* = 15.8, 9.7 Hz, 1H, C6-CH).

^{13}C NMR (100.6 MHz, DMSO-d_6) δ 172.6 (CO), 162.8, 161.9, 160.4, 155.5 (d, *J* = 138.4 Hz, C14), 135.5 (d, *J* = 3.0 Hz, C11), 130.0 (d, *J* = 8.0 Hz, C12), 115.0 (d, *J* = 21.0 Hz, C13), 88.4 (C5), 45.7 (C7), 25.0 (C6).

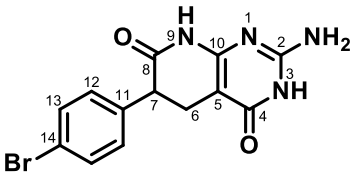
HRMS (ESI–TOF): m/z calculated for $C_{13}H_{11}FN_4O_2$: 275.0934, $[M+H]^+$, found: 275.0939.

IR (KBr), ν_{max} (cm $^{-1}$): 3324, 3186, 2904, 1637, 1595, 1514, 1384, 1231, 837.

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

Starting from methyl 2-(4-bromophenyl)acrylate (**1**{*8*}). 71% yield, white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.59 (s, 1H, NH), 10.19 (s, 1H, NH), 7.51 (d, *J* = 8.4 Hz, 2H, C13-CHx2), 7.19 (d, *J* = 8.4 Hz, 2H, C12-CHx2), 6.48 (s, 2H, NH_2), 3.77 (dd, *J* = 9.8, 6.9 Hz, 1H, C7-CH), 2.78 (dd, *J* = 15.8, 7.0 Hz, 1H, C6-CH), 2.69 – 2.61 (m, 1H, C6-CH).



^{13}C NMR (100.6 MHz, DMSO-d_6) δ 171.9, 161.4, 156.2, 154.8, 138.8, 131.2 (C13), 130.4 (C12), 120.0, 88.0 (C5), 45.5 (C7), 24.4 (C6).

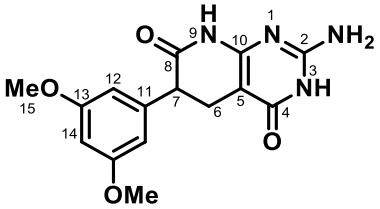
HRMS (70 eV, EI): m/z calculated for $C_{13}H_{11}BrN_4O_2$: 334.0065, $[M]^+$, found: 334.0063.

IR (KBr), *ν*max*(*cm−1*)*: 3469, 3184, 2904, 1647, 1592, 1488, 826.

2-amino-6-(3,5-dimethoxyphenyl)-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (7{*10*})

Starting from methyl 2-(3,5-dimethoxyphenyl)acrylate (**1**{*10*}). 75% yield, white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.57 (s, 1H, NH), 10.15 (s, 1H, NH), 6.47 (s, 2H, NH_2), 6.38 (s, 3H, C12-CHx2, C14-CH), 3.70 (s, 6H, C15-OCH_3), 3.67 (dd, *J* = 8.4, 7.1 Hz, 1H, C7-CH), 2.80 - 2.65 (m, 2H, C6-CH).



^{13}C NMR (100.6 MHz, DMSO-d_6): δ 172.2, 161.5, 160.3, 156.0, 154.8, 141.4, 106.3 (C12), 98.3 (C14), 88.0 (C5), 55.1 (C15), 46.0 (C7), 24.2 (C6).

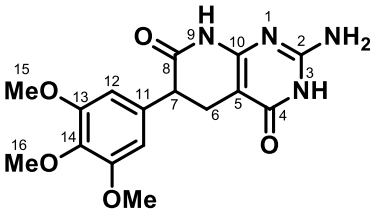
HRMS (70 eV, EI): m/z calculated for $C_{15}H_{16}N_4O_4$: 316.1172, $[M]^+$, found: 316.1171.

IR (KBr), ν_{max} (cm^{-1}*)*: 3331, 3164, 2902, 1596, 1463, 1206, 1155, 1062.

2-amino-6-(3,4,5-trimethoxyphenyl)-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (7{*11*})

Starting from methyl 2-(3,4,5-trimethoxyphenyl)acrylate (**1**{*11*}). 71% yield, white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.61 (s, 1H, NH), 10.19 (s, 1H, NH), 6.55 (s, 2H, C12-CHx2), 6.51 (s, 2H, NH_2), 3.72 (s, 6H, C15-OCH_3x2), 3.68 (dd, *J* = 9.3, 7.4 Hz, 1H, C7-CH), 3.64 (s, 3H, C16-OCH_3), 2.82 - 2.67 (m, 2H, C6-CH_2).



^{13}C NMR (100.6 MHz, DMSO-d_6): δ 172.3, 161.4, 156.1, 154.8, 152.6, 136.4, 134.8, 105.6 (C12), 88.2 (C5), 59.9 (C16), 55.8 (C15), 46.2 (C7), 24.4 (C6).

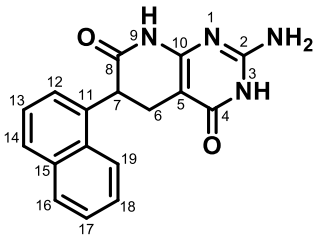
HRMS (70 eV, EI): m/z calculated for $C_{16}H_{18}N_4O_5$: 346.1277, $[M]^+$, found: 346.1273.

IR (KBr), ν_{max} (cm^{-1}): 3579, 3340, 3176, 2939, 1638, 1593, 1512, 1337, 1241, 1127.

2-amino-6-(naphthalen-1-yl)-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (7{*12*})

Starting from methyl 2-(naphthalen-1-yl)acrylate (**1**{*12*}). 93% yield, white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.57 (s, 1H, NH), 10.30 (s, 1H, NH), 8.07 (d, *J* = 7.8 Hz, 1H, C19-CH), 7.94 (d, *J* = 7.4, 1H, C16-CH), 7.84 (d, *J* = 8.4 Hz, 1H, C12-CH), 7.58 - 7.49 (m, 2H, C18-CH, C17-CH), 7.45 (t, *J* = 7.5 Hz, 1H, C13-CH), 7.33 (d, *J* = 7.1 Hz, 1H, C14-CH), 6.49 (s, 2H, NH_2), 4.56 (t, *J* = 8.5 Hz, 1H, C7-CH), 2.96 - 2.71 (m, 2H, C6-CH_2).



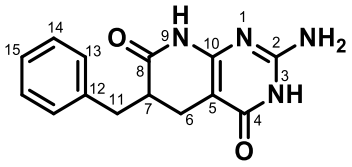
^{13}C NMR (100.6 MHz, DMSO-d_6): δ 172.4, 161.6, 156.2, 154.8, 135.9, 133.7, 131.0, 128.8 (C16), 127.5 (C12), 126.1 (C17), 125.6 (C18), 125.44 (C13), 125.1 (C14), 124.0 (C19), 88.04 (C5), 42.8 (C7), 24.8 (C6).

HRMS (70 eV, EI): m/z calculated for $C_{17}H_{14}N_4O_2$: 306.1117, $[M]^+$, found: 306.1116.

IR (KBr), ν_{max}(cm^{-1}): 3465, 3190, 2851, 2740, 1696, 1651, 1594, 1537, 1403, 1207, 755.

2-amino-6-benzyl-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (7{*13*})

Starting from methyl 2-benzylacrylate (**1**{*13*}). 78% yield, white solid.



^{1}H NMR (400 MHz, DMSO-d_6): δ 10.51 (s, 1H, NH), 10.01 (s, 1H, NH), 7.33 - 7.26 (m, 2H, C14-CHx2), 7.24 7.18 (m, 3H, C15-CH, C13-CHx2), 6.44 (s, 2H, NH_2), 3.19 (dd, *J* = 13.3, 4.0 Hz, 1H, C11-CH_2), 2.69 - 2.58 (m, 1H, C7-CH), 2.54 – 2.48 (m, 1H, C11-CH_2), 2.39 (dd, *J* = 15.8, 6.7 Hz, 1H, C6-CH_2), 2.04 (dd, *J* = 15.8, 11.2 Hz, 1H, C6-CH_2).

^{13}C NMR (100.6 MHz, DMSO-d_6): δ 173.5, 161.5, 156.1, 154.7, 139.3, 129.1 (C14), 128.3 (C13), 126.1 (C15), 87.9 (C5), 41.2 (C7), 35.1 (C11), 21.1 (C6).

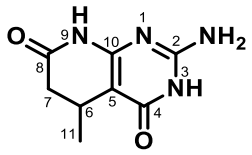
HRMS (70 eV, EI): m/z calculated for $C_{14}H_{14}N_4O_2$: 270.1117, $[M]^+$, found: 270.1118.

IR (KBr), ν_{max} (cm^{-1}): 3322, 3167, 2904, 1651, 1536, 1485, 1376, 1290, 1212, 700.

2-amino-5-methyl-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (7{*14*})

Starting from methyl crotonate (**1**{*14*}). 30% yield, white solid.

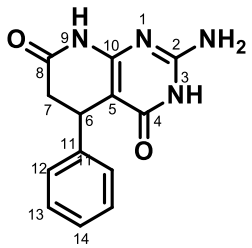
Spectral data are consistent to those previously described[4].



2-amino-5-phenyl-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (7{*15*})

Starting from methyl cinnamate (**1**{*15*}). 32% yield, white solid.

Spectral data are consistent to those previously described[6].



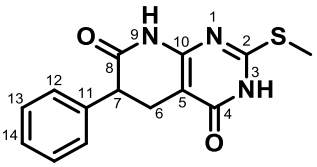
2.3.2. General procedure for 2-(methylthio)-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-diones

The corresponding alkyl 2-acrylate (**1**{*x*}) (4.00 mmol) was dissolved in 2-propanol (20 mL), 6-amino-2-(methylthio)pyrimidin-4(3*H*)-one (**52**) (5.60 mmol) and potassium carbonate (4.00 mmol) were added into the solution. The mixture was heated under microwave irradiation at 170ºC for 3 hours. Then, the solvent was removed under reduced pressure, water was added to the crude and this was neutralized with a 2M solution of HCl. The solid was collected by filtration and washed with water, and Et_2O.

2-(methylthio)-6-phenyl-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (51{*2*})

Starting from methyl 2-phenylacrylate (**1**{*2*}). 56% yield, white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ 12.54 (s, 1H, NH), 10.61 (s, 1H, NH), 7.32 (t, *J* = 6.9 Hz, 2H, C13-CHx2), 7.27 – 7.20 (m, 3H, C14-CH, C12-CHx2), 3.84 (dd, *J* = 8.8, 7.2 Hz, 1H, C7-CH), 2.93 – 2.76 (m, 2H, C6-CH_2), 2.43 (s, 3H, SCH_3).



^{13}C NMR (100.6 MHz, DMSO-d_6): δ 171.8, 163.8, 161.1, 157.9, 139.0, 128.4, 127.9, 127.0, 91.8 (C5), 45.4 (C7), 24.4 (C6), 12.5 (SCH_3).

MS (70 eV, EI): m/z (%) = 287.2 (100) $[M]^+$, 209.9 (33.0) $[M\text{-}C_6H_5]^+$, 195.8 (20.0) $[M\text{-}C_7H_8]^+$, 169.8 (64.2) $[C_6H_7N_3OS]^+$, 117.8 (70.2) $[C_8H_6O]^+$.

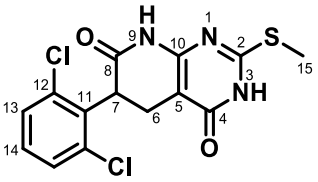
HRMS (70 eV, EI): m/z calculated for $C_{14}H_{13}N_3O_2S$: 287.0730, $[M]^+$, found: 287.0728.

IR (KBr): ν (cm^{-1}): 3478, 3145, 3032, 2925, 1634, 1562, 1505, 1444, 1247, 968, 698, 554.

6-(2,6-dichlorophenyl)-2-(methylthio)-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (51{*3*})

Starting from methyl 2-(2,6-dichlorophenyl)acrylate (**1**{*3*}). 88% yield, white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ 12.55 (s, 1H, NH), 10.64 (s, 1H, NH), 7.52 (dd, *J* = 14.6, 8.1 Hz, 2H, C13-CHx2), 7.37 (t, *J* = 8.0 Hz, 1H, C14-CH), 4.65 (dd, *J* = 13.4, 9.1 Hz, 1H, C7-CH), 2.94 – 2.71 (m, 2H, C6-CH_2), 2.50 (s, 3H, CH_3).



^{13}C NMR (100.6 MHz, DMSO-d_6): δ 169.3, 161.9, 153.9, 135.1, 135.1, 134.6, 129.7 (C14), 129.6 (C13), 128.2 (C13), 93.8 (C5), 42.7 (C7), 22.4 (C6), 12.6 (CH_3).

Anal. Calcd. (%) for $C_{14}H_{11}Cl_2N_3O_2S$: C, 47.20; H, 3.11; N, 11.80; S, 9.00. Found: C, 47.44; H, 3.21; N, 11.54; S, 8.89.

MS (70 eV, EI): m/z (%) = 355.0 (61.4), $[M]^+$, 320.0 (100) $[M-Cl]^+$, 209.8 (18.5) $[M-C_6H_4Cl_2]^+$, 195.7 (12.0) $[M-C_7H_7Cl_2]^+$, 169.7 (70.5) $[C_6H_7N_3OS]^+$.

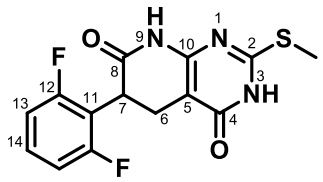
HRMS (70 eV, EI): m/z calculated for $C_{14}H_{11}N_3O_2Cl_2S$: 354.9955, $[M]^+$, found: 354.9949.

IR (KBr): ν (cm^{-1}): 3389, 2875, 1630, 1592, 1468, 1437, 1315, 1277, 1232, 1197, 770.

6-(2,6-difluorophenyl)-2-(methylthio)-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (51{*4*})

Starting from methyl 2-(2,6-difluorophenyl)acrylate (**1**{*4*}). 80% yield, white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ 12.58 (s, 1H, NH), 10.70 (s, 1H, NH), 7.42 (m, 1H, C14-CH), 7.12 (t, *J* = 8.6 Hz, 2H, C13-CHx2), 4.24 (dd, *J* = 14.1, 7.7 Hz, 1H, C7-CH), 2.92 (dd, *J* = 16.1, 7.8 Hz, 1H, C6-CH), 2.68 - 2.56 (m, 1H, C6-CH), 2.50 (s, 3H, CH_3).



^{13}C NMR (100.6 MHz, DMSO-d_6): δ 169.8, 161.5, 160.8 (d, *J* = 246.7 Hz, C12), 160.7 (d, *J* = 246.9 Hz, C5), 156.4, 154.5, 129.7 (t, *J* = 10.5 Hz, C14), 115.0 (t, *J* = 18.6 Hz, C11), 111.7 (dd, *J* = 3.2, 22.4 Hz, C13), 94.8 (C5), 35.9 (C7), 23.2 (C6), 12.7 (SCH_3).

Anal. Calcd. (%) for $C_{14}H_{11}F_2N_3O_2S$: C, 52.01; H, 3.43; N, 13.00; S, 9.92. Found: C, 51.97; H, 3.50; N, 12.99; S, 9.69.

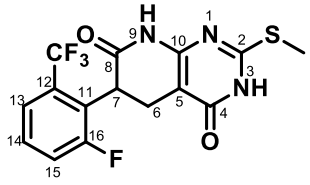
HRMS (70 eV, EI): m/z calculated for $C_{14}H_{11}N_3O_2F_2S$: 323.0540, $[M]^+$, found: 323.0541.

IR (KBr): ν (cm^{-1}): 3406, 3046, 2934, 1697, 1640, 1607, 1562, 1508, 1470, 1272, 1237, 1010, 780

6-(2-fluoro-6-(trifluoromethyl)phenyl)-2-(methylthio)-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (51{*6*})

Starting from methyl 2-(2-fluoro-6-(trifluoromethyl)phenyl)acrylate (**1**{*6*}). 62% yield, white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ 12.63 (s, 1H, NH), 10.75 (s, 1H, NH), 7.65 – 7.58 (m, 3H, Ar-CHx3), 4.08 (dd, *J* = 14.0, 8.0 Hz, 1H, C7-CH), 2.93 (m, C7-CH_2), 2.51 (s, SCH_3).



^{13}C NMR (100.6 MHz, DMSO-d_6): δ 169.5, 161.4, 161.1 (d, *J* = 246.3 Hz, C16), 154.2, 130.1 (d, *J* = 9,5 Hz, C14), 129.6 (qd, *J* = 29.7, 4.15 Hz, C12), 125.8 (d, *J* = 16.0 Hz, C13), 123.6 (q, *J* = 272 Hz, CF_3), 121.8 (C11), 120.7 (d, *J* = 22.1 Hz, C15), 94.5 (C5), 40.0 (C7), 23.9 (C6), 12.7 (SCH_3).

Anal. Calcd. (%) for $C_{15}H_{11}F_4N_3O_2S$: C, 48.26; H, 2.97; N, 11.26; S, 8.59. Found: C, 48.65; H, 2.65; N, 11.46; S, 8.21.

MS (70 eV, EI): m/z (%) = 373.0 (100) $[M]^+$, 209.8 (31.6) $[C_8H_8N_3O_2S]^+$, 203.8 (40.2) $[C_9H_4F_4O]^+$, 195.7 (16.0)) $[C_7H_5N_3O_2S]^+$,169.7 (47.9) $[C_6H_7N_3OS]^+$.

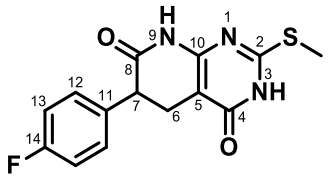
HRMS (70 eV, EI): m/z calculated for $C_{15}H_{11}N_3O_2F_4S$: 373.0504, $[M]^+$, found: 373.0508.

IR (KBr): ν (cm^{-1}): 3406, 3276, 2937, 2863, 1710, 1637, 1550, 1468, 1320, 1268, 1227, 1165, 1118.

6-(4-fluorophenyl)-2-(methylthio)-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (51{*7*})

Starting from methyl 2-(4-fluorophenyl)acrylate (**1**{*7*}). 63% yield, white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ 12.42 (s, 1H, NH), 10.62 (s, 1H, NH), 7.27 (dd, *J* = 8.8, 5.6 Hz, 2H, C12-CHx2), 7.15 (t, *J* = 8.8 Hz, 2H, C13-CHx2), 3.87 (dd, *J* = 9.7, 7.1 Hz, 1H, C7-CH), 2.94 – 2.72 (m, 2H, C6-CH_2), 2.49 (s, 3H, SCH_3).



^{13}C NMR (100.6 MHz, DMSO-d_6): δ 171.7, 163.7, 161.2 (d, *J* = 241.5 Hz, C14), 161.1, 157.9, (d, *J* = 3.1 Hz, C11), 130.0 (d, *J* = 7.92 Hz, C12),115.1 (d, *J* = 21.2 Hz, C13), 91.8 (C5), 44.6 (C7), 24.5 (C6), 12.7 (SCH_3)

MS (70 eV, EI): m/z (%) = 305.1 (18) $[M]^+$, 135.7 (15) $[C_8H_5FO]^+$, 69.0 (100) $[C_2HN_2O]^+$.

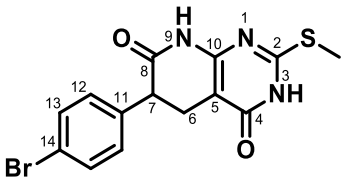
HRMS (70 eV, EI): m/z calculated for $C_{14}H_{12}N_3O_2FS$: 305.0635, $[M]^+$, found: 305.0634.

IR (KBr): ν (cm^{-1}): 3476, 3145, 3038, 2926, 1633, 1555, 1512, 1235.

6-(4-bromophenyl)-2-(methylthio)-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (51{*8*})

Starting from methyl 2-(4-bromophenyl)acrylate (**1**{*8*}). 74% yield, white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ 12.49 (s, 1H, NH), 10.65 (s, 1H, NH), 7.52 (d, *J* = 8.4 Hz, 2H, C13-CHx2), 7.20 (d, *J* = 8.5 Hz, 2H, C12-CHx2), 3.86 (dd, *J* = 10.0, 7.1 Hz, 1H, C7-CH), 2.91 - 2.73 (m, 2H, C6-CH_2), 2.49 (s, 3H, SCH_3).



^{13}C NMR (100.6 MHz, DMSO-d_6): δ 171.4, 163.7, 161.7, 154.4, 138.4, 131.2 (C13), 130.4 (C12), 120.2, 94.9 (C5), 44.9 (C7), 24.3 (C6), 12.7 (SCH_3).

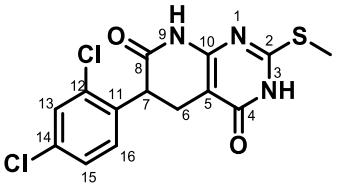
HRMS (70 eV, EI): m/z calculated for $C_{14}H_{12}N_3O_2SBr$: 364.9834, $[M]^+$, found: 364.9835.

IR (KBr): ν (cm^{-1}): 3476, 3342, 3144, 3031, 2925, 1634, 1557, 1490, 1444, 1245

6-(2,4-dichlorophenyl)-2-(methylthio)-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (51{*9*})

Starting from methyl 2-(2,4-dichlorophenyl)acrylate (**1**{*9*}). 80% yield, white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.73 (s, 1H), 7.63 (d, *J* = 1.9 Hz, 1H), 7.43 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.40 (d, *J* = 8.3 Hz, 1H), 4.19 (dd, J = 12.8, 7.7 Hz, 1H, C7-CH), 2.89 (dd, J = 16.2, 7.7 Hz, 1H, C6-CH_2), 2.75 (dd, J = 16.1, 12.8 Hz, 1H, C6-CH_2), 2.50 (s, 3H, SCH_3)



^{13}C NMR (100.6 MHz, DMSO-d_6): δ 170.25, 161.8, 154.4, 135.9 (C12), 134.3 (C14), 132.6(C16), 132.0 (C12), 129.0 (C13), 127.6 (C15), 95.0 (C5), 43.3 (C7), 23.7 (C6), 12.8 (SCH_3)

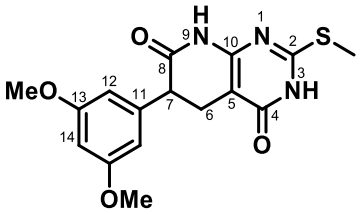
Anal. Calcd. (%) for $C_{14}H_{11}Cl_2N_3O_2S$: C, 47.20; H, 3.11; N, 11.80; S, 9.00. Found: C, 47.07; H, 2.97; N, 11.96; S, 9.01.

IR (KBr): ν (cm^{-1}): 3404, 3131, 2868, 1694, 1633, 1557, 1505, 1479, 1459, 1374, 1285, 1241, 1151, 1103, 964, 823, 576.

6-(3,5-dimethoxyphenyl)-2-(methylthio)-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (51{*10*})

Starting from methyl 2-(3,5-dimethoxyphenyl)acrylate (**1**{*10*}). 76% yield, white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ 12.54 (s, 1H, NH), 10.59 (s, 1H, NH), 6.41 - 6.38 (m, 3H, C12-CHx2, C14-CH), 3.79 - 3.73 (m, 1H, C7-CH), 3.71 (s, 6H, OCH_3x2), 2.91 - 2.77 (m, 2H, C6-CH_2), 2.49 (s, 3H, SCH_3).



^{13}C NMR (100.6 MHz, DMSO-d_6): δ 171.5, 163.9, 161.8, 160.4, 154.6, 141.0, 106.2 (C12), 98.4 (C14), 95.0 (C5), 55.1 (C15), 45.4 (C7), 24.1 (C6), 12.7 (SCH_3).

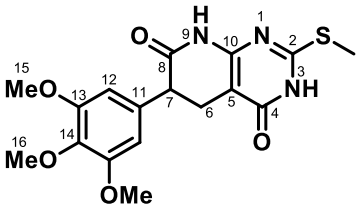
HRMS (70 eV, EI): m/z calculated for $C_{16}H_{17}N_3O_4S$: 347.0940, $[M]^+$, found: 347.0943.

IR (KBr): ν (cm^{-1}): 3406, 3036, 2932, 2836, 1635, 1599, 1500, 1459, 1430, 1154.

2-(methylthio)-6-(3,4,5-trimethoxyphenyl)-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (51{*11*})

Starting from methyl 2-(3,4,5-trimethoxyphenyl)acrylate (**1**{*11*}). 48% yield, white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ 12.54 (s, 1H, NH), 10.57 (s, 1H, NH), 6.56 (s, 2H, C12-CHx2), 3.78 (m, 1H, C7-CH), 3.72 (s, 6H, C15-OCH_3x2), 3.64 (s, 3H, C16-OCH_3), 2.86 (d, *J* = 8.7 Hz, 2H, C6-CH_2), 2.49 (s, 3H, SCH_3).



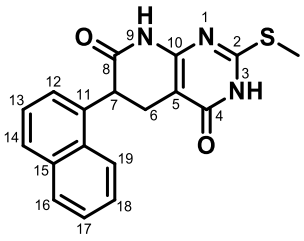
^{13}C NMR (100.6 MHz, DMSO-d_6): δ 171.7, 161.4, 154.1, 152.7, 149.8, 136.4, 134.3, 105.6, 95.3 (C5), 59.9 (C16), 55.8 (C15), 45.6 (C6), 24.3 (C7), 12.7 (SCH_3).

HRMS (70 eV, EI): m/z calculated for $C_{17}H_{19}N_3O_5S$: 377.1045, $[M]^+$, found: 377.1046.

IR (KBr): ν (cm^{-1}): 3409, 3046, 2929, 1696, 1633, 1551, 1500, 1457, 1232, 770.

2-(methylthio)-6-(naphthalen-1-yl)-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (51{*12*})

Starting from methyl 2-(naphthalen-1-yl)acrylate (**1**{*12*}). 83% yield, white solid.



^{1}H NMR (400 MHz, DMSO-d_6): δ 12.55 (s, 1H, NH), 10.76 (s, 1H, NH), 8.08 (m, 1H, C19-CH), 7.95 (m, 1H, C16-CH), 7.85 (d, *J* = 8.1 Hz, 1H, C12-CH), 7.58 - 7.50 (m, 2H, C17-CH, C18-CH), 7.49 – 7.43 (t, 1H, C13-CH), 7.35 (d, *J* = 6.3 Hz, 1H, C14-CH), 4.67 (dd, *J* = 9.5, 7.7 Hz, 1H, C7-CH), 3.02 (dd, *J* = 16.5, 7.7 Hz, 1H, C6-CH), 2.94 - 2.85 (m, 1H, C6-CH), 2.53 (s, 3H, SCH_3).

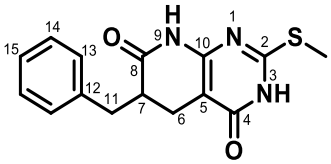
^{13}C NMR (100.6 MHz, DMSO-d_6): δ 172.3, 168.2, 162.4, 154.9, 136.0, 134.1, 131.4, 129.3 (C16), 128.1 (C12), 126.6 (C17), 126.1 (C18), 125.9 (C13), 125.5 (C14), 124.3 (C19), 95.6 (C5), 42.6 (C7), 25.2 (C6), 13.2 (SCH_3).

HRMS (70 eV, EI): m/z calculated for $C_{18}H_{15}N_3O_2S$: 337.0885, $[M]^+$, found: 337.0887.

IR (KBr): ν (cm^{-1}): 3411, 3045, 2859, 1696, 1632, 1553, 1500, 1455, 1228, 769.

6-benzyl-2-(methylthio)-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (51{*13*})

Starting from methyl 2-benzylacrylate (**1**{*1*}3). 20% yield, white solid.



^{1}H NMR (400 MHz, DMSO-d_6): δ 12.45 (s, 1H, NH), 10.44 (s, 1H, NH), 7.33 - 7.27 (m, 2H, C14-CHx2), 7.25 - 7.19 (m, 3H, C15-CH, C13-CHx2), 3.19 (dd, *J* = 13.5, 4.3 Hz, 1H, C11-CH), 2.77 - 2.64 (m, 1H, C7-CH), 2.59 - 2.52 (m, 1H, C11-CH), 2.47 (s, 3H, SCH_3), 2.47 – 2.40 (m, 1H, C6-CH), 2.17 (dd, *J* = 16.3, 11.2 Hz, 1H, C6-CH).

^{13}C NMR (100.6 MHz, DMSO-d_6): δ 172.9, 161.7, 156.3, 154.6, 139.1, 129.1 (C13), 128.3 (C14), 126.2 (C15), 81.2 (C5), 40.6 (C7), 35.1 (C11), 21.1 (C6), 12.7 (SCH_3).

Anal. Calcd. (%) for $C_{15}H_{15}N_3O_2S$: C, 59.78; H, 5.06; N, 13.94; S, 10.64. Found: C, 59.59; H, 5.08; N, 14.07; S, 10.17.

HRMS (70 eV, EI): m/z calculated for $C_{15}H_{15}N_3O_2S$: 301.0885, $[M]^+$, found: 301.0885.

IR (KBr): ν (cm^{-1}): 3414, 3025, 2925, 1691, 1634, 1562, 1506, 1460, 1302, 1290, 1232

2.4. Synthesis of C4 substituted pyrido[2,3-*d*]pyrimidines (14{*x*,*y*} and 15{*x*,*y*})

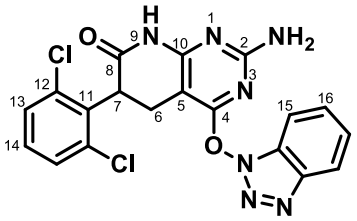
2.4.1. Synthesis of intermediates for 4-substituted pyrido[2,3-*d*]pyrimidines (18{*x*})

0.4 mmol of the corresponding 4-oxopyrido[2,3-*d*]pyrimidine (**7**{*x*}) was suspended in ACN (19 mL), then BOP (265 mg, 0.6 mmol) and DBU (152 mg, 1 mmol) were added to the solution. The mixture was stirred at room temperature for two days. Then, water was added to the reaction mixture and the solid was collected by filtration and washed with water and EtOEt.

4-((1H-benzo[*d*][1,2,3]triazol-1-yl)oxy)-2-amino-6-(2,6-dichlorophenyl)-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (18{*3*})

Starting from compound **7**{*3*}. 78% yield, white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ 11.00 (s, 1H, NH), 8.13 (dt, *J* = 8.4, 0.9 Hz, 1H), 7.81 (dt, *J* = 8.4, 1.0 Hz, 1H), 7.68 – 7.61 (m, 1H), 7.60 – 7.46 (m, 3H, C13-CHx2, CH), 7.39 (t, *J* = 8.1 Hz, 1H, C14-CH), 6.63 (s, 2H, NH_2), 4.91 (dd, *J* = 12.6, 9.3 Hz, 1H, C7-CH), 3.31 – 3.16 (m, 2H, C6-CH_2).



^{13}C NMR (100.6 MHz, DMSO-d_6): 170.1, 166.2, 161.8, 160.5, 143.2, 135.8, 135.4, 135.2, 130.4 (C14), 130.2 (C13), 129.4 (C16), 128.9, 128.9 (C14), 125.6 (16), 120.2 (C15), 110.1 (C15), 84.6 (5), 43.2 (7), 22.0 (6).

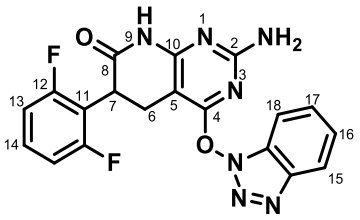
HRMS (70 eV, EI): m/z calculated for $C_{19}H_{13}N_7O_2Cl_2$: 441.0508, $[M]^+$, found: 441.0507.

IR (KBr): ν (cm^{-1}): 3382, 3324, 3215, 2898, 1670, 1648, 1571, 1367, 1241, 1089, 1037, 774, 734.

4-((1H-benzo[*d*][1,2,3]triazol-1-yl)oxy)-2-amino-6-(2,6-difluorophenyl)-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (18{*4*})

Starting from compound **7**{*4*}. 93% yield, white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ 11.03 (s, 1H, NH), 8.13 (dt, *J* = 8.4, 0.9 Hz, 1H, C15-CH), 7.80 (dt, *J* = 8.3, 0.9 Hz, 1H, C18-CH), 7.64 (ddd, *J* = 8.3, 6.9, 0.9 Hz, 1H, C16-CH), 7.51 (ddd, *J* = 8.4, 6.9, 1.0 Hz, 1H, C17-CH), 7.49 - 7.42 (m, 1H, C14-CH), 7.16 (t, *J* = 8.7 Hz, 2H, C13-CHx2), 6.63 (s, 2H, NH_2), 4.51 (dd, *J* = 13.9, 7.5 Hz, 1H, C7-CH), 3.31 – 3.25 (m, 1H, C6-CH), 3.10 - 3.03 (m, 1H, C6-CH).



^{13}C NMR (100.6 MHz, DMSO-d_6): δ 170.0, 165.5, 161.4, 160.9 (d, *J* = 247.2 Hz, C12), 160.8 (d, *J* = 246.8 Hz, C12), 160.4, 142.7, 129.9 (t, *J* = 10.6 Hz, C14), 128.9 (C16), 128.5, 125.1 (C17), 119.8

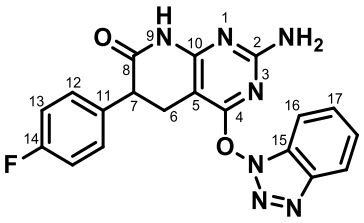
(C15), 114.7 (t, *J* = 18.5 Hz, C11), 111.8 (dd, *J* = 22.3, 2.5 Hz, C13), 109.6 (C18), 85.1 (C5), 36.1 (C7), 22.4 (C6).

Anal. Calcd. (%) for $C_{19}H_{13}F_2N_7O_2$: C, 55.75; H, 3.20; N, 23.95. Found: C, 56.06; H, 3.22; N, 23.78.

IR (film), ν_{max} (cm^{-1}): 3374, 3207, 2895, 1698, 1651, 1571, 1470, 1371, 1273, 1247, 1008, 785.

4-((1H-benzo[*d*][1,2,3]triazol-1-yl)oxy)-2-amino-6-(4-fluorophenyl)-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (18{*7*})

Starting from compound **7**{*7*}. 74% yield, white solid.



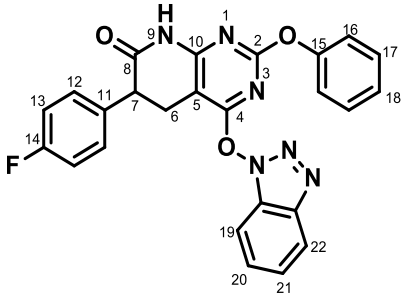
^{1}H NMR (400 MHz, DMSO-d_6): δ 10.95 (s, 1H, NH), 8.13 (dt, *J* = 8.4, 0.9 Hz, 1H, C19-CH), 7.70 – 7.61 (m, 2H, C16, C17-CHx2), 7.51 (ddd, *J* = 8.1, 6.4, 1.6 Hz, 1H, C18-CH), 7.39 (dd, *J* = 8.7, 5.6 Hz, 2H, C12-CHx2), 7.21 (t, *J* = 8.9 Hz, 1H, C13-CHx2), 6.59 (s, 2H, NH_2), 4.11 (dd, *J* = 10.7, 6.9 Hz, 1H, C7-CH), 3.29 – 3.12 (m, 2H, C6-CH_2).

^{13}C NMR (100.6 MHz, DMSO-d_6): δ 172.4, 166.0, 161.8, 161.0, 143.2, 135.4, 130.8 (d, *J* = 7.9 Hz, C12), 129.5 (C17), 128.9, 125.6 (C18), 120.3 (C19), 115.6 (d, *J* = 21.1 Hz, C13), 110.0, 109.8 (C16), 86.0 (C5), 45.4 (C7), 24.5 (C6).

IR (film), ν_{max} (cm^{-1}): 3425, 3337, 3223, 1637, 1575, 1510, 1356, 1237, 1160, 1088, 847, 738.

4-((1H-benzo[*d*][1,2,3]triazol-1-yl)oxy)-6-(4-fluorophenyl)-2-phenoxy-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (57)

Starting from compound **53**{*7,5*}. 72% yield, white solid.



^{1}H NMR (400 MHz, DMSO-d_6): δ 11.50 (s, 1H, NH), 8.07 (dt, *J* = 8.4, 0.9 Hz, 1H, C22), 7.70 – 7.60 (m, 2H, C19-CH, C20-CH), 7.53 – 7.49 (m, 1H, C21-CH), 7.41 (dd, *J* = 8.7, 5.5 Hz, 2H, C12-CHx2), 7.22 (t, *J* = 8.9 Hz, 2H, C13-CHx2), 7.11 - 7.00 (m, 3H, C18-CH, C17-CHx2), 6.84 - 6.78 (m, 2H, C16-CHx2), 4.20 (dd, *J* = 11.5, 7.1 Hz, 1H, C7-CH), 3.44 - 3.34 (m, 2H, C6-CH_2).

^{13}C NMR (100.6 MHz, DMSO-d_6): δ 171.5, 165.9, 162.2, 162.1, 161.4 (d, *J* = 243.5 Hz, C14), 151.6, 142.5, 134.3 (d, *J* = 3.1 Hz, C11), 130.5 (d, *J* = 8.2 Hz, C12), 129.1 (C20), 129.1 (C17), 128.3, 125.1 (C21), 125.0 (C18), 120.8 (C16), 119.9 (C22), 115.2 (d, *J* = 21.3 Hz, C13), 109.2 (C19), 92.9 (C5), 44.3 (C7), 24.0 (C6).

HRMS (70 eV, EI): m/z calculated for $C_{25}H_{17}N_6O_3F$: 468.1346, $[M]^+$, found: 468.1337.

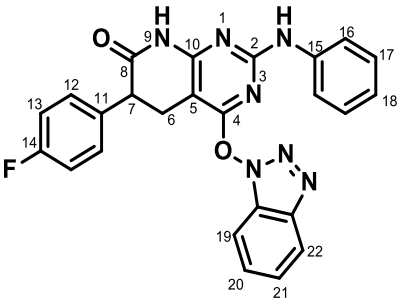
Anal. Calcd. (%) for $C_{25}H_{17}FN_6O_3$: C, 64.10; H, 3.66; N, 17.94. Found: C, 64.06; H, 3.62; N, 18.04.

IR (film), ν_{max} (cm^{-1}): 3061, 2977, 2863, 1714, 1635, 1581, 1512, 1412, 1364, 1219, 1099, 746.

4-((1H-benzo[*d*][1,2,3]triazol-1-yl)oxy)-6-(4-fluorophenyl)-2-(phenylamino)-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (18{*7,9*})

Starting from compound **7**{*7,9*}. 88% yield, white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ 11.19 (s, 1H, NH), 9.46 (s, 1H, NH), 8.23 (d, *J* = 8.5 Hz, 1H), 7.76 (dt, *J* = 8.4, 0.9 Hz, 1H), 7.69 – 7.64 (m, 1H), 7.56 (ddd, *J* = 8.2, 6.9, 1.1 Hz, 1H), 7.43 (dd, *J* = 8.7, 5.5 Hz, 2H, C12-CHx2), 7.23 (t, *J* = 8.9 Hz, 2H, C13-CHx2), 6.95 - 6.90 (m, 2H), 6.85 - 6.79 (m, 2H), 6.75 – 6.77 (m, 1H, C18-CH), 4.19 (dd, *J* = 11.0, 7.0 Hz, 1H, C7-CH), 3.41 – 3.29 (m, 2H, C6-CH_2).

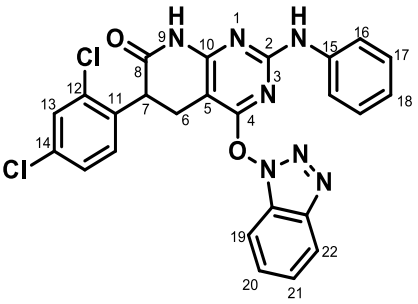


HRMS (70 eV, EI): m/z calculated for $C_{25}H_{18}N_7O_2F$: 467.1506, $[M]^+$, found: 467.1508.

4-((1H-benzo[*d*][1,2,3]triazol-1-yl)oxy)-6-(2,4-dichlorophenyl)-2-(phenylamino)-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (18{*9,9*})

Starting from compound **7**{*9,9*}. 66% yield, white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ 11.27 (s, 1H,), 9.48 (s, 1H), 8.22 (d, *J* = 8.4 Hz, 1H), 7.81 (dt, *J* = 8.4, 0.9 Hz, 1H), 7.70 (d, *J* = 2.2 Hz, 1H, C13-CH), 7.66 (ddd, *J* = 8.3, 6.9, 0.9 Hz, 1H), 7.58 (d, *J* = 8.4 Hz, 1H), 7.56 (ddd, *J* = 8.1, 6.9, 1.0 Hz, 1H), 7.51 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.03 – 6.78 (m, 4H), 6.78 – 6.72 (m, 1H, C18-CH), 4.55 (dd, *J* = 11.6, 9.0 Hz, 1H, C7-CH), 3.35 (d, *J* = 8.9 Hz, 2H, C6-CH_2).



^{13}C NMR (100.6 MHz, DMSO-d_6): δ δ 170.4, 165.0, 160.3, 157.2, 142.9, 139.3, 135.4, 134.6, 132.8, 132.2, 129.2, 129.0, 128.6, 127.9, 127.6, 125.2, 121.6, 119.9, 118.5, 109.5, 87.9, 43.3.

IR (KBr): ν (cm^{-1}): 3418, 3274, 3143, 2983, 1687, 1652, 1581, 1555, 1461, 1327, 1252, 1088, 1064, 1043, 901, 814, 741, 603, 507.

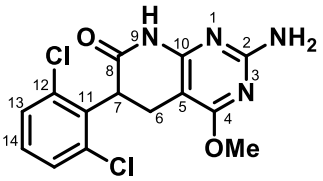
2.4.2. General procedure for C4 alkoxy substituted 6-aryl-3,4,5,6-tetrahydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (15{*x,y*})

1 mmol of the corresponding intermediate **18**{*x*} was suspended in the corresponding alcohol (**37**{*x*}) (22 ml) and Cs_2CO_3 (391 mg, 1.2 mmol) was added to the suspension and the mixture was heated at reflux temperature for two days. Then, the solvent was removed under vacuum pressure and water was added to the residue. The solid was collected by filtration and washed with water and EtOEt.

2-amino-6-(2,6-dichlorophenyl)-4-methoxy-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (15{*3,1*})

Starting from compound **18**{*3*} and methanol (**37**{*1*}). 96% yield, white solid.

^{1}H NMR (400 MHz, d-TFA): δ 7.37 (dd, *J* = 15.0, 8.1 Hz, 2H, C13-CHx2), 7.24 (t, *J* = 8.2 Hz, 1H, C13-CH), 5.08 (dd, *J* = 13.3, 9.4 Hz, 1H, C7-CH), 4.11 (s, 3H, OCH_3), 3.30 – 3.08 (m, 2H, C6-CH_2).



^{13}C NMR (100.6 MHz, d-TFA): δ 173.9, 170.8, 154.3, 146.6, 136.0, 134.7, 131.7, 130.2 (C13), 129.4 (C12), 128.4 (C12), 90.0 (C5), 55.7 (OCH_3), 42.6 (C7), 21.0 (C6).

MS (70 eV, EI): m/z (%) = 338.1 (60) $[M]^+$, 303.1 (100) $[M\text{-}Cl]^+$, 153.0 (67) $[M\text{-}C_6H_9N_4O]^+$.

HRMS (70 eV, EI): m/z calculated for $C_{14}H_{12}N_4O_2Cl_2$: 338.0340, $[M]^+$, found: 338.0337.

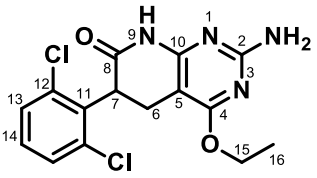
Anal. Calcd. (%) for $C_{14}H_{12}Cl_2N_4O_2$: C, 49.58; H, 3.57; N, 16.52. Found: C, 49.41; H, 3.76; N, 16.89.

IR (film), ν_{max} (cm^{-1}): 3438, 3330, 3222, 2951, 2891, 1688, 1634, 1577, 1488, 1466, 1371, 1257, 1196, 774.

2-amino-6-(2,6-dichlorophenyl)-4-ethoxy-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (15{*3,2*})

Starting from compound **18**{*3*} and ethanol (**37**{*2*}). 31% yield, white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.47 (s, 1H, NH), 7.54 – 7.48 (m, 2H, C13-CHx2), 7.36 (t, *J* = 8.1 Hz, 1H, C13-CH), 6.38 (s, 2H, NH_2), 4.62 (dd, *J* = 12.8, 9.3 Hz, 1H, C7-CH), 4.26 (qd, *J* = 7.1, 2.1 Hz, 2H, C15-CH_2), 2.88 – 2.79 (m, 2H, C6-CH_2), 1.25 (t, *J* = 7.0 Hz, 3H, C16-CH_3).



^{13}C NMR (100.6 MHz, DMSO-d_6): δ 169.5, 166.4, 161.83 157.9, 135.3, 134.7, 129.7, 128.3, 85.1 (C5), 61.4 (C15), 43.1 (C7), 22.2 (C6), 14.5 (C16).

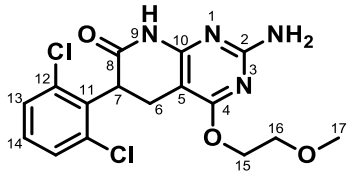
HRMS (70 eV, EI): m/z calculated for $C_{15}H_{14}N_4O_2Cl_2$: 352.0494, $[M]^+$, found: 352.0494.

IR (film), ν_{max} (cm $^{-1}$): 3409, 3329, 3220, 1686, 1633, 1577, 1435, 1373, 778.

2-amino-6-(2,6-dichlorophenyl)-4-(2-methoxyethoxy)-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (15{*3,4*})

Starting from compound **18**{*3*} and alcohol **37**{*4*}. 76% yield, white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.54 (s, 1H, NH), 7.55 – 7.48 (m, 2H, C-13-CHx2), 7.37 (t, *J* = 8.1 Hz, 1H, C14-CH), 6.44 (s, 2H, NH_2), 4.64 (dd, *J* = 12.8, 9.4 Hz, 1H, C7-CH), 4.37 – 4.32 (m, 2H, C15-CH_2), 3.60 (t, *J* = 4.8 Hz, 2H, C16-CH_2), 3.26 (s, 3H, OCH_3), 2.93 – 2.79 (m, 2H, C6-CH_2).



^{13}C NMR (100.6 MHz, DMSO-d_6): δ 169.8, 166.4, 161.6, 157.9, 135.3, 135.2, 134.7, 129.8 (C14), 129.7 (C13), 128.3 (C13), 85.2 (C5), 70.1 (C16), 64.8 (C15), 58.2 (OCH_3), 43.1 (C7), 22.2 (C6).

MS (70 eV, EI): m/z (%) = 382.0 (15) $[M]^+$, 351.0 (23) $[M\text{-}CH_3O]^+$, 322.9 (33) $[M\text{-}C_3H_6O]^+$, 289.0 (100) $[M\text{-}C_3H_6OCl]^+$, 205.9 (26) $[C_9H_{10}N_4O_2]^+$.

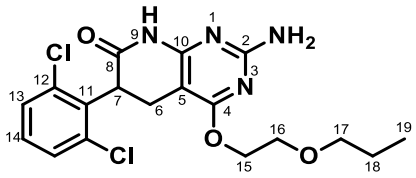
HRMS (70 eV, EI): m/z calculated for $C_{16}H_{16}N_4O_3F_4Cl_2$: 382.0598, $[M]^+$, found: 382.0599.

IR (film), ν_{max} (cm $^{-1}$): 3404, 3218, 2894, 1688, 1633, 1576, 1434, 1372, 775.

2-amino-6-(2,6-dichlorophenyl)-4-(2-propoxyethoxy)-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (15{*3,6*})

Starting from compound **18**{*3*} and alcohol **37**{*6*}. 38% yield, white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.51 (s, 1H, NH), 7.58 – 7.47 (m, 2H, C13-CH), 7.37 (t, *J* = 8.1 Hz, 1H, C14-CH), 6.42 (s, 2H, NH_2), 4.63 (dd, *J* = 12.9, 9.2 Hz, 1H, C7-CH), 4.35 – 4.32 (m, 2H, C15-CH_2), 3.63 (t, *J* = 4.9 Hz, 2H, C16-CH_2), 3.35 (t, *J* = 6.6 Hz, 2H, C17-CH_2), 2.93 – 2.79 (m, 2H, C6-CH_2), 1.46 (h, *J* = 7.3 Hz, 2H, C18-CH_2), 0.80 (t, *J* = 7.4 Hz, 3H, CH_3).



^{13}C NMR (100.6 MHz, DMSO-d_6): δ 169.6, 166.4, 161.8, 158.0, 135.3, 135.1, 129.8, 128.3, 85.2 (C5), 71.9 (C17), 68.2 (C16), 65.0 (C15), 43.1 (C7), 22.4 (C18), 22.2 (C16), 10.4 (C19).

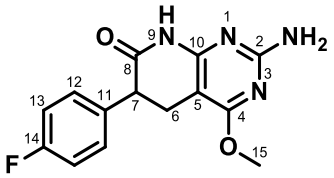
Anal. Calcd. (%) for $C_{18}H_{20}Cl_2N_4O_2$: C, 52.57; H, 4.90; N, 13.62. Found: C, 52.76; H, 5.12; N, 13.98.

IR (film), ν_{max} (cm^{-1}): 3479, 3332, 3220, 2773, 1692, 1631, 1575, 1458, 1435, 1373, 777.

2-amino-6-(4-fluorophenyl)-4-methoxy-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (15{*7,1*})

Starting from compound **18**{*7*} and methanol (**37**{*1*}). 39% yield, white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.49 (s, 1H, NH), 7.26 (dd, *J* = 8.7, 5.7 Hz, 2H, C12-CHx2), 7.14 (t, *J* = 8.9 Hz, 2H, C13-CHx2), 6.40 (s, 2H, NH_2), 3.86 (dd, *J* = 9.9, 6.9 Hz, 1H, C7-CH), 3.80 (s, 3H; OCH_3), 2.93 – 2.72 (m, 2H, C6-CH_2).



^{13}C NMR (100.6 MHz, DMSO-d_6): δ 172.0, 166.7, 161.7, 158.3, 153.0, 135.4 (d, *J* = 2.9 Hz, C11), 130.1 (d, *J* = 8.1 Hz, C12), 115.0 (d, *J* = 21.3 Hz, C13) , 86.5 (C5), 53.2 (OCH_3), 45.3 (7), 24.6 (6).

MS (70 eV, EI): m/z (%) = 288.2 (100) $[M]^+$, 193.0 (25) $[M\text{-}C_6H_4F]^+$.

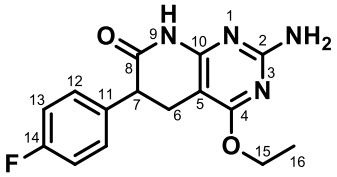
HRMS (70 eV, EI): m/z calculated for $C_{14}H_{13}N_4O_2F$: 288.1028, $[M]^+$, found: 288.1023.

IR (film), ν_{max} (cm^{-1}): 3381, 3227, 1686, 1658, 1633, 1575, 1511, 1464, 1384, 1247.

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

Starting from compound **18**{*7*} and ethanol (**37**{*2*}). 20% yield, white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.45 (s, 1H, NH), 7.27 (dd, J = 8.8, 5.6 Hz, 2H, C12-CHx2), 7.14 (t, J = 8.8 Hz, 2H, C13-CHx2), 6.35 (s, 2H, NH_2), 4.26 (qd, J = 7.2, 1.3 Hz, 2H, C15-CH_2), 3.86 (dd, J = 10.4, 7.2 Hz, 1H, C7-CH), 2.93 – 2.71 (m, 2H, C6-CH_2), 1.25 (t, J = 7.0 Hz, 3H, C16-CH_3).



^{13}C NMR (100.6 MHz, DMSO-d_6): δ 172.1, 166.4, 162.4, 161.8, 160.0, 158.4, 135.5 (C11), 130.2 (d, *J* = 8,5 Hz, C12), 115.1 (d, *J* = 21.0 Hz, C12), 86.7 (C5), 61.5 (C15), 45.4 (C7), 24.8 (C6), 14.6 (C16).

MS (70 eV, EI): m/z (%) = 302.1 (100) $[M]^+$, 287.1 (25) $[M\text{-}CH_3]^+$, 273.1 (42) $[M\text{-}C_2H_5]^+$, 258.1 (19) $[M\text{-}OC_2H_5]^+$.

HRMS (70 eV, EI): m/z calculated for $C_{15}H_{15}N_4O_2F$: 302.1183, $[M]^+$, found: 302.1179.

IR (film), ν_{max} (cm^{-1}): 3408, 3338, 3220, 1686, 1632, 1575, 1511, 1434, 1227.

2.4.3. General procedure for C4 amino substituted 6-aryl-3,4,5,6-tetrahydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (14{*x,y*})

Procedure A:

4.88 mmol of the corresponding 4-oxopyrido[2,3-*d*]pyrimidine (**7**{*x*}) was suspended in ACN (350 mL), then BOP (2.805 g, 6.34 mmol) and DBU (1.1 ml, 7.32 mmol) were added to the solution. The mixture was stirred at room temperature for 2 hours. The corresponding amine (**35**{*y*}) (14.6 mmol) was added and the mixture was heated at 90ºC for 2 days. The solvent was concentrated by removing it under reduced pressure and water was added to the residue. The solid was collected by filtration and washed with water and EtOEt.

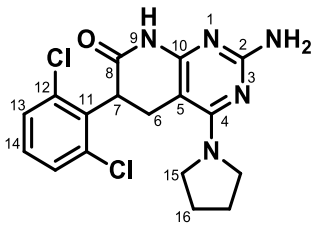
Procedure B:

0.419 mmol of the corresponding intermediate **18**{*x*} was suspended in ACN (20 ml) and 3 equivalents of the corresponding amine (**35**{*y*}) (1.257 mmol) was added to the suspension and the mixture was heated at 140 ºC by microwave irradiation for 5 hours. Then, water was added to the residue and the solid was collected by filtration and washed with water and EtOEt.

2-amino-6-(2,6-dichlorophenyl)-4-(pyrrolidin-1-yl)-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (14{*3,5*})

Starting from compound **7**{*3*} and amine **35**{*5*} and following procedure A. 78% yield, white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.11 (s, 1H, NH), 7.50 (dd, *J* = 15.6, 8.4 Hz, 4H, C13-CHx2), 7.36 (t, *J* = 8.0 Hz, 1H, C14-CH), 5.85 (s, 2H, NH_2), 4.48 (dd, *J* = 13.6, 8.0 Hz, 1H, C7-CH), 3.46 (m, 4H, C15-CH_2x2), 2.85 – 2.65 (m, 2H, C6-CH_2), 1.76 (m, 4H, C16-CH_2x2).



^{13}C NMR (100.6 MHz, TFA-*d*): δ 173.7, 151.8, 151.6, 134.8, 130.7, 130.6, 129.6, 128.5, 86.8 (C5), 51.9 (C15), 42.5 (C7), 24.4 (C16, C7).

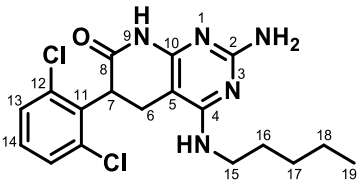
MS (70 eV, EI): m/z (%) = 377.1 (100) $[M]^+$, 232.1 (73) $[M\text{-}C_6H_3Cl_2]^+$, 218.0 (42) $[M\text{-}C_7H_5Cl_2]^+$, 204.0 (59) $[M\text{-}C_8H_7Cl_2]^+$, 176 (13) $[M\text{-}C_{10}H_{11}Cl_2]^+$.

HRMS (70 eV, EI): m/z calculated for $C_{17}H_{17}N_5OCl_2$: 377.0801, $[M]^+$, found: 377.0810.

IR (film), ν_{max} (cm $^{-1}$): 3468, 3309, 3203, 2971, 2874, 1686, 1614, 1540, 1457, 1441, 1386, 1340, 1286, 772.

2-amino-6-(2,6-dichlorophenyl)-4-(pentylamino)-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (14{3,*6*})

Starting from compound **7**{*3*} and amine **35**{*6*} and following procedure A. 62% yield, white solid.



^{1}H NMR (400 MHz, DMSO-d_6): δ 10.57 (s, 1H, CONH), 7.53 (m, 2H, C12-CHx2), 7.37 (t, *J* = 8.1 Hz, 1H, C13-CH), 6.30 (s, 1H, NH), 6.06 (s, 2H, NH_2), 4.64 (dd, *J* = 13.1, 8.9 Hz, 1H, C7-CH), 3.31 – 3.20 (m, 2H, C14-CH_2), 2.94 – 2.65 (m, 2H, CH_2), 1.49 (p, *J* = 7.1 Hz, 2H, C15-CH_2), 1.27 (m, 4H, C15,C16-CH_2x2), 0.85 (t, *J* = 6.9 Hz, 3H, CH_3).

^{13}C NMR (100.6 MHz, DMSO-d_6): δ 169.8, 161.8, 160.5, 154.9, 135.7, 135.2, 134.8, 129.7, 128.3, 82.5 (C5), 43.1 (C7), 40.3 (C14) 28.8 (C15), 28.7 (C16), 23.2 (C6), 22.0 (C17), 14.0 (C18).

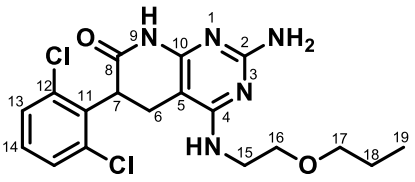
MS (70 eV, EI): m/z (%) = 393.1 (69) $[M]^+$,351.0 (78) $[M\text{-}C_3H_7]^+$,336.0 (91) $[M\text{-}C_4H_9]^+$,322.9 (54) $[M\text{-}C_5H_{11}]^+$, 248.1 (43) $[M\text{-}C_6H_3Cl_2]^+$, 206.1 (83) $[C_9H_{12}N_5O]^+$, 192.0 (69) $[C_8H_8N_5O]^+$.

HRMS (70 eV, EI): m/z calculated for $C_{18}H_{21}N_5OCl_2$: 393.1123, $[M]^+$, found: 393.1122.

IR (film), ν_{max} (cm $^{-1}$): 3505, 3392, 3323, 3206, 2929, 2870, 1675, 1629, 1577, 1472, 1436, 1385, 1287, 776.

2-amino-6-(2,6-dichlorophenyl)-4-((2-propoxyethyl)amino)-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (14{3,*7*})

Starting from compound **7**{*3*} and amine **35**{*7*} and following procedure A. 70% yield, white solid.



^{1}H NMR (400 MHz, DMSO-d_6): δ 10.28 (s, 1H, CONH), 7.53 (ddd, *J* = 14.8, 8.3, 1.3 Hz, 2H, C13-2xCH), 7.37 (t, *J* = 8.1 Hz, 1H, C14-CH), 6.33 (s, 1H, NH), 5.95 (s, 2H, NH_2), 4.60 (dd, *J* = 13.1, 8.9 Hz, 1H, C7-CH), 3.44 (m, 4H, C15-CH_2, C16- CH_2), 3.31 – 3.34 (m, 2H, C17-CH_2) 2.92 – 2.64 (m, 2H, C6-CH_2), 1.48 (h, *J* = 7.2 Hz, 2H, C18-CH_2), 0.84 (t, *J* = 7.4 Hz, 3H, C19-CH_3).

^{13}C NMR (100.6 MHz, DMSO-d_6): δ 169.5, 161.9, 155.1, 135.6, 135.1, 134.8, 129.7, 128.3, 82.62 (C5), 71.7 (C17), 68.6 (C16), 43.2 (C7), 39.5 (C15) 23.2 (C6), 22.5 (C18), 10.5 (C19).

Anal. Calcd. (%) for $C_{18}H_{21}Cl_2N_5O_2$: C, 52.69; H, 5.16; N, 17.07. Found: C, 52.60; H, 65.36; N, 17.24.

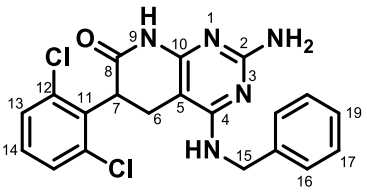
HRMS (70 eV, EI): m/z calculated for $C_{18}H_{21}N_5O_2Cl_2$: 409.1077, $[M]^+$, found: 409.1072.

IR (film), ν_{max} (cm $^{-1}$): 3440, 3333, 3217, 2928, 2869, 1631, 1576, 1478, 776.

2-amino-4-(benzylamino)-6-(2,6-dichlorophenyl)-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (14{3,*8*})

Starting from compound **18**{*3*} and amine **35**{*8*} and following procedure B. 60% yield, white solid

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.18 (s, 1H, NH), 7.56 – 7.47 (m, 3H), 7.39 – 7.34 (m, 2H), 7.30 – 7.28 (m, 2H), 7.22 -7.17 (m, 1H), 6.88 (t, *J* = 6.0 Hz, 1H, NH), 5.90 (s, 2H, NH_2), 4.62 (dd, *J* = 13.1, 8.9 Hz, 1H, C7-CH), 4.52 (td, *J* = 9.2, 3.5 Hz, 2H, C15-CH_2), 2.97 – 2.66 (m, 2H, C6-CH_2).

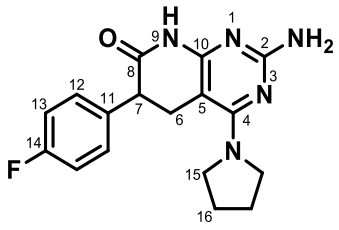


HRMS (70 eV, EI): m/z calculated for $C_{20}H_{17}N_5OCl_2$: 413.0810, $[M]^+$, found: 413.0809.

2-amino-6-(4-fluorophenyl)-4-(pyrrolidin-1-yl)-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (14{7,*5*})

Starting from compound **7**{*7*} and amine **35**{*5*} and following procedure A. 44% yield, white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.31 (s, 1H, NH), 7.30 – 7.24 (m, 2H, C12-2xCH), 7.14 (t, *J* = 8.9 Hz, 2H, C13-2xCH), 5.89 (s, 2H, NH_2), 3.78 (dd, *J* = 10.4, 6.6 Hz, 1H, C7-CH), 3.50 - 3.41 (m, 4H, 2xCH_2), 3.16 – 3.02 (m,2H, C6-CH_2 1.85 – 1.67 (m, 4H, 2xCH_2).



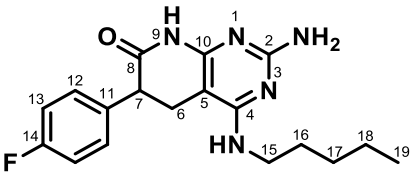
^{13}C NMR (100.6 MHz, DMSO-d_6): δ 171.6 (CO), 161.2, 161.1 (d, *J* = 241.2 Hz, C14) 160.7, 157.5, 135.5 (d, *J* = 3.0 Hz, C11), 130.3 (d, *J* = 8.1 Hz, C12), 114.9 (d, *J* = 21.0 Hz, C13), 86.3 (C5), 48.9 (C15), 45.9 (C7), 28.5 (C6), 25.0 (C16).

HRMS (70 eV, EI): m/z calculated for $C_{17}H_{18}N_5OF$: 327.1495, $[M]^+$, found: 327.1496.

IR (film), ν_{max} (cm $^{-1}$): 3441, 3329, 3227, 2963, 2873, 1695, 1639, 1608, 1540, 1510, 1448, 1340, 1232, 840.

2-amino-6-(4-fluorophenyl)-4-(pentylamino)-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (14{*7*,*6*})

Starting from compound **7**{*7*} and amine **35**{*6*} and following procedure A. 40% yield, white solid.



^{1}H NMR (400 MHz, acetone): δ 7.38 (m, 2H, 2xCH), 7.11 (t, *J* = 8.8 Hz, 2H, 2xCH), 3.94 (dd, *J* = 10.3, 7.2 Hz, 1H, CH-C7), 3.42 (dd, *J* = 12.9, 6.6 Hz, 2H, CH_2-C15), 2.87 (m, 2H, CH_2-C6), 1.67 – 1.51 (m, 2H, CH_2-C16), 1.41 – 1.25 (m, 4H, 2xCH_2-C17, C18), 0.88 (t, *J* = 6.8 Hz, 3H, CH_3).

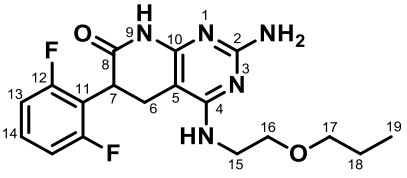
^{13}C NMR (100.6 MHz, acetone) δ 174.4 (CO), 163.3, 162.9 (d, *J* = 69.1 Hz, C14), 161.6, 156.6 (C10), 136.6 (d, *J* = 3.3 Hz, C11), 131.2 (d, *J* = 8.1 Hz, C12), 115.8 (d, *J* = 21.3 Hz, C31), 85.1 (C5), 46.7 (C7), 41.5 (C15), 29.2 (C16), 29.0 (C17), 26.6 (C6), 23.2 (C18), 14.4 (C19).

MS (70 eV, EI): m/z (%) = 343.3 $[M]^+$, 314.2 $[M\text{-}C_2H_5]^+$, 300.1 $[M\text{-}C_3H_9]^+$, 286.1 $[M\text{-}C_4H_9]^+$, 272.1 $[M\text{-}C_5H_{11}]^+$.

IR (film), ν_{max} (cm $^{-1}$): 3395, 3333, 3219, 2930, 2869, 1694, 1630, 1578, 1510, 1469, 1376, 1214, 841.

2-amino-6-(2,6-difluorophenyl)-4-((2-propoxyethyl)amino)-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (14{*4*,*7*})

Starting from compound **18**{*4*} and amine **35**{*7*} and following procedure B. 60% yield, white solid.



^{1}H NMR (400 MHz, DMSO-d_6): δ 10.25 (s, 1H, NH), 7.46 - 7.37 (m, 1H, C14-CH), 7.13 (t, *J* = 8.8 Hz, 2H, C13-CHx2), 6.34 (s, 1H, NH), 5.91 (s, 2H, NH_2), 4.16 (dd, *J* = 14.0, 7.6 Hz, 1H, C7-CH), 3.44 – 3.43 (m, 4H, C15-CH_2, C16-CH_2), 3.34 – 3.31 (m, 2H, C17-CH_2), 2.97 - 2.78 (m, 2H, C6-CH_2), 1.48 (h, *J* = 7.4 Hz, 2H, C18-CH_2), 0.83 (t, *J* = 7.4 Hz, 3H, C19-CH_3).

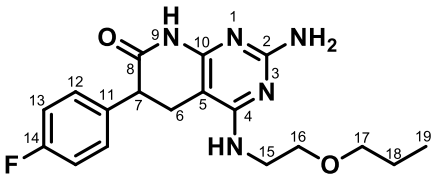
^{13}C NMR (100.6 MHz, DMSO-d_6): δ 170.3, 160.8 (d, *J* = 246.8 Hz, C12), 160.7 (d, *J* = 246.6 Hz, C12), 161.8, 160.2, 155.6, 129.7 (t, *J* = 10.2 Hz, C14), 115.4 (t. *J* = 18.7 Hz, C11), 111.7 (dd, *J* = 1.9, 22.3 Hz, C13), 83.6 (C5), 71.7 (C17), 68.7 (C16), 40.0 (C15), 36.4 (C7), 24.0 (C6), 22.5 (C18), 10.5 (C19).

Anal. Calcd. (%) for $C_{18}H_{21}F_2N_5O_2$: C, 57.29; H, 5.61; N, 18.56. Found: C, 57.25; H, 3.41; N, 18.74.

IR (film), ν_{max} (cm $^{-1}$): 3416, 3332, 3212, 2929, 2871, 1630, 1577, 1470, 1388, 1007, 783.

2-amino-6-(4-fluorophenyl)-4-((2-propoxyethyl)amino)-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (14{7,*7*})

Starting from compound **7**{*7*} and amine **35**{*7*} and following procedure A. 63% yield, white solid.



^{1}H NMR (400 MHz, $CDCl_3$): δ 11.99 (s, 1H, NH), 7.26 – 7.20 (m, 2H, C12-CHx2), 7.04 (t, *J* = 8.7 Hz, 2H, C13-CHx2), 4.81 – 4.75 (m, 1H, NH), 3.84 (dd, *J* = 10.2, 7.3 Hz, 1H, C7-CH), 3.64 - 3.61 (m, 2H, C15-CH_2), 3.58 – 3.52 (m, 2H, C16-CH_2), 3.39 (t, *J* = 6.7 Hz, 2H, C17-CH_2), 2.85 – 2.67 (m, 2H, C16-CH_2), 1.63 – 1.51 (m, 2H, C18-CH_2), 0.88 (t, *J* = 7.4 Hz, 3H, CH_3).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ 173.8 (CO), 161.5 (d, *J* = 161.0 Hz, C14), 161.1, 155.9, 134.4 (d, *J* = 3.4 Hz, C11), 129.9 (d, *J* = 8.1 Hz, C12), 115.9 (d, *J* = 21.2 Hz, C13), 84.5 (C5), 72.9 (C17), 69.3 (C16), 46.2 (C7), 40.8 (C15), 26.3 (C6), 22.9 (C18), 10.7 (C19).

Anal. Calcd. (%) for $C_{18}H_{22}FN_5O_2$: C, 60.15; H, 6.17; F, 5.29; N, 19.49; O, 8.90. Found: C, 59.80; H, 6.04; N, 19.82.

MS (70 eV, EI): m/z (%) = 359.1 (24) $[M]^+$, 316.1 (11) $[M\text{-}C_3H_5]^+$, 301.1 (17) $[M\text{-}C_3H_8O]^+$, 286.1 (100) $[M\text{-}C_4H_9O]^+$, 273.1 (80) $[M\text{-}C_5H_{12}O]^+$.

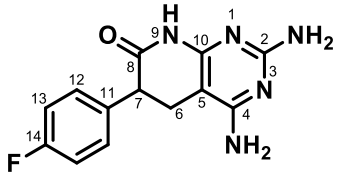
HRMS (70 eV, EI): m/z calculated for $C_{18}H_{22}N_5O_2F$: 359.1758, $[M]^+$, found: 359.1742.

IR (film), ν_{max} (cm^{-1}): 3391, 3226, 2932, 2874, 1689, 1629, 1575, 1511, 1477, 1226.

2.4.4. 2,4-diamino-6-(4-fluorophenyl)-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (6{7})

Alkyl 2-(4-fluorophenyl)acrylate (**1**{*7*}) (4.00 mmol) was dissolved in anhydrous ethylene glycol (20 mL), 2,6-diaminopyrimidin-4(3*H*)-one (**42**) (4.00 mmol) and sodium methoxide (4.00 mmol) were added into the solution. The mixture was heated under microwave irradiation at 180ºC for 3 hours. Water was added and the reaction crude was neutralized with a 2M solution of HCl. The solid was collected by filtration and washed with water, MeOH and Et_2O. White solid, 26% yield.

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.72 (s, 1H, NH), 7.31 (dd, *J* = 8.8, 5.6 Hz, 2H, C12-CHx2), 7.15 (t, *J* = 8.9 Hz, 2H, C13-CHx2), 6.26 (s, 2H, C2-NH_2), 6.01 (s, 2H, C4-NH_2), 3.88 (dd, *J* = 10.4, 6.9 Hz, 1H, C7-CH), 2.90 – 2.69 (m, 2H, C6-CH_2).



^{13}C NMR (100.6 MHz, DMSO-d_6): δ 172.6 (CO), 161.8, 161.7, 161.2 (d, J = 241 Hz, C14) 156.3, 135.7 (d, *J* = 3.1 Hz, C11), 130.2 (d, *J* = 7.9 Hz, C12), 115.0 (d, *J* = 20.9 Hz, C13), 83.9 (C5), 45.5 (C7), 25.6 (C6).

MS (70 eV, EI): m/z (%) = 273.1 (100) $[M]^+$.

HRMS (70 eV, EI): m/z calculated for $C_{13}H_{12}N_5OF$: 273.1026, $[M]^+$, found: 273.1026.

IR (film), ν_{max} (cm^{-1}): 3495, 3334, 3219, 3104, 2888, 1698, 1659, 1638, 1570, 1510, 1460, 1210, 837.

2.5. Synthesis of C2 substituted pyrido[2,3-*d*]pyrimidines

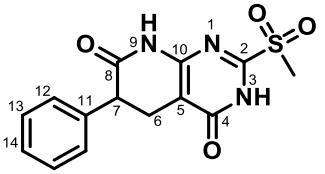
2.5.1. General procedure for oxidation of 2-(methylthio)-5,6-dihydropyridi[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-diones

m-CPBA (18 mmol) was suspended in 20 mL of DMF and was added dropwise into a solution of the 2-methylthio-substituted pyridopyrimidine (**51**{*x*}) (6 mmol) in 20 mL of DMF a 0 ºC. The mixture was stirred overnight at room temperature. Then the solvent was removed under reduced pressure and the residue was suspended in EtOEt and the solid was collected by filtration and washed with water, and EtOEt to afford the corresponding 2-methylsulphonyl-substituted pyrido[2,3-*d*]pyrimidine (**54**{*x*}).

2-(methylsulfonyl)-6-phenyl-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (54{*2*})

Starting from **51**{2}. 74% yield, white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ 13.29 (s, 1H, NH), 11.32 (s, 1H, NH), 7.36 – 7.31 (m, 2H, C13-CHx2), 7.30 – 7.22 (m, 3H, C12-CHx2, C14-CH), 4.00 (dd, *J* = 9.4, 7.3 Hz, 1H, C7-CH), 3.31 (s, 3H, SCH_3), 3.14 – 3.00 (m, 2H, C6-CH_2).



^{13}C NMR (100.6 MHz, DMSO-d_6): δ 171.4, 167.1, 162.6, 158.6, 138.4, 128.5, 128.0, 127.1 (C12), 100.4 (C5), 44.8 (C7), 39.1 (SCH_3), 24.7 (C6).

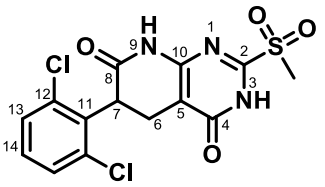
Anal. Calcd. (%) for $C_{14}H_{13}N_3O_4S$: C, 52.66; H, 4.10; N, 13.16; S, 10.04. Found: C, 52.32; H, 4.16 N, 13.02; S, 10.34.

IR (KBr), ν_{max}(cm^{-1}): 3429, 3200, 3136, 3022, 2919, 2866, 1691, 1643, 1612, 1486, 1341, 1235, 1165, 1134, 699.

6-(2,6-dichlorophenyl)-2-(methylsulfonyl)-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (54{*3*})

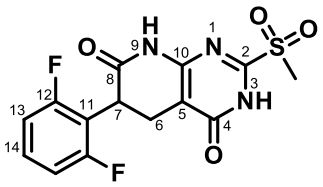
Starting from **51**{3}. 98% yield, white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ 11.35 (s, 1H, NH), 7.53 (dd, *J* = 12.3, 8.1 Hz, 2H, C13-CHx2), 7.39 (t, *J* = 8.1 Hz, 1H, C14-CH), 4.87 (dd, *J* = 12.9, 9.2 Hz, 1H, C7-CH), 3.31 (s, 3H, SCH_3), 3.06 (dd, J = 17.1, 9.4 Hz, 1H, C6-CH_2), 2.99 (dd, J = 17.0, 13.5 Hz, 1H, C6-CH_2).



6-(2,6-difluorophenyl)-2-(methylsulfonyl)-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (54{*4*})

Starting from **51**{4}. 60% yield, white solid.



^{1}H NMR (400 MHz, DMSO-d_6): δ 13.33 (s, 1H), 11.41 (s, 1H), 7.44 (tt, *J* = 8.4, 6.6 Hz, 1H, C14-CH), 7.14 (t, *J* = 8.8 Hz, 2H, C13-CHx2), 4.46 (dd, *J* = 14.0, 7.6 Hz, 1H, C7-CH), 3.31 (s, 3H, SCH_3), 3.10 (dd, *J* = 16.5, 7.7 Hz, 1H, C6-CH_2), 2.94 – 2.82 (m, 1H, C6-CH_2).

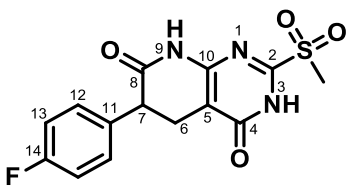
^{13}C NMR (100.6 MHz, DMSO-d_6): δ 169.6, 167.0, 162.7, 162.0 (d, *J* = 8.3 Hz, C12), 159.6 (d, *J* = 8.2 Hz, C12), 158.7, 130.0 (t, *J* = 10.6 Hz, C11), 114.5 (t, *J* = 18.6 Hz, C14), 111.8 (dd, *J* = 22.3, 3.1 Hz, C13), 100.0 (C5), 39.2 (SCH_3), 35.3 (C7), 23.4 (C6).

Anal. Calcd. (%) for $C_{14}H_{11}F_2N_3O_4S$: C, 47.32; H, 3.12; N, 11.83; S, 9.02. Found: C, 47.14; H, 3.19 N, 11.72; S, 9.28.

IR (KBr): ν (cm^{-1}): 3432, 3219, 3027, 2923, 1704, 1649, 1612, 1474, 1459, 1339, 1235, 1164, 1134, 1010, 783, 542.

6-(4-fluorophenyl)-2-(methylsulfonyl)-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (54{*7*})

Starting from **51**{7}. 60% yield, white solid.



^{1}H NMR (400 MHz, DMSO-d_6): δ 13.28 (s, 1H, NH), 11.33 (s, 1H, NH), 7.30 (dd, *J* = 8.7, 5.8 Hz, 2H, C12-CHx2), 7.17 (t, *J* = 8.9 Hz, 2H, C13-CHx2), 4.03 (dd, *J* = 10.2, 7.4 Hz, 1H, C7-CH), 3.31 (s, 3H, SCH_3), 3.14 - 2.94 (m, 2H, C6-CH_2).

^{13}C NMR (100.6 MHz, DMSO-d_6): δ 171.4, 167.0, 162.7, 161.3 (d, J = 243.2 Hz, C14), 158.7, 134.6 (d, *J* = 3.1 Hz, C11), 130.2 (d, *J* = 8.1 Hz, C12), 115.2 (d, *J* = 21.3 Hz, C13), 100.4 (C5), 44.1 (C7), 29.5 (SCH_3), 24.8 (C6).

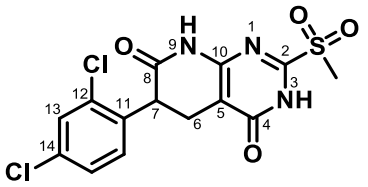
Anal. Calcd. (%) for $C_{14}H_{12}FN_3O_4S$: C, 49.85; H, 3.59; N, 12.46; S, 9.51. Found: C, 49.68; H, 3.84; N, 12.70; S, 9.18.

HRMS (70 eV, EI): m/z calculated for $C_{14}H_{12}N_3O_4FS$: 337.0533, $[M]^+$, found: 337.0533.

IR (KBr): ν (cm^{-1}): 3393, 3036, 2867, 1635, 1607, 1513, 1490, 1337, 1233, 1160, 839, 767, 541.

6-(2,4-dichlorophenyl)-2-(methylsulfonyl)-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (54{*9*})

Starting from **51**{9}. 70% yield, white solid.



^{1}H NMR (400 MHz, DMSO-d_6): δ 13.34 (s, 1H, NH), 11.42 (s, 1H, NH), 7.65 (dd, *J* = 1.5, 0.9 Hz, 1H), 7.46 (s, 1H, C13-CH), 7.46 (d, *J* = 0.9 Hz, 1H), 4.38 (dd, *J* = 11.6, 9.3 Hz, 1H, C7-CH), 3.31 (s, 3H, SCH_3), 3.07 – 2.81 (s, 2H, C6-CH_2).

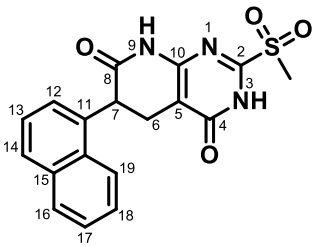
^{13}C NMR (100.6 MHz, DMSO-d_6): δ 169.9, 167.0, 162.7, 158.6, 135.3, 134.4, 132.7, 132.1, 129.0 (C13), 127.6, 100.2 (C5), 42.6 (C7), 28.5 (SCH_3), 23.8 (C6).

Anal. Calcd. (%) for $C_{14}H_{11}Cl_2N_3O_4S$: C, 43.31; H, 2.86; N, 10.82; S, 8.26. Found: C, 43.48; H, 2.66; N, 10.91; S, 8.11.

IR (KBr), ν_{max}(cm^{-1}): 3432, 3279, 3040, 2925, 2868, 1651, 1492, 1329, 1276, 1231, 1156, 1132, 944, 766, 572, 529.

2-(methylsulfonyl)-6-(naphthalen-1-yl)-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (54{*12*})

Starting from **51**{12}. 68% yield, white solid.



^{1}H NMR (400 MHz, DMSO-d_6): δ 13.24 (s, 1H, NH), 11.44 (s, 1H, NH), 8.13 – 8.07 (m, 1H, C19-CH), 8.00 – 7.94 (m, 1H, C16-CH), 7.87 (d, *J* = 8.2 Hz, 1H, C12-CH), 7.58 – 7.51 (m, 2H, C17-CH, C18-CH), 7.48 (t, *J* = 7.2 Hz, 1H, C13-CH), 7.40 (dd, *J* = 7.2, 1.2 Hz, 1H, C14-CH), 4.85 (dd, *J* = 10.2, 7.9 Hz, 1H, C7-H), 3.33 (s, 3H, SCH_3), 3.23 – 3.13 (m, 2H, C6-CH_2).

^{13}C NMR (100.6 MHz, DMSO-d_6): δ 171.5, 167.1, 162.7, 158.8, 135.0, 133.6, 131.1, 129.0 (C16), 127.8 (C12), 126.2 (C17), 125.7 (C18), 125.5 (C14, C13), 124.0 (C19), 100.6 (C5), 41.5 (C7), 39.1 (SCH_3), 25.0 (C6).

Anal. Calcd. (%) for $C_{18}H_{15}N_3O_4S$: C, 58.53; H, 4.09; N, 11.38; S, 8.68. Found: C, 58.47; H, 4.18 N, 11.57; S, 8.69.

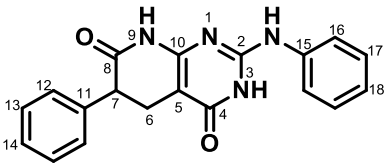
IR (KBr), ν_{max}(cm^{-1}): 3432, 3211, 3022, 1690, 1641, 1614, 1487, 1345, 1225, 1167, 1136, 775.

2.5.2 General procedure for synthesis of 2-(arylamino)-5,6-dihydropyridi[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-diones

The corresponding amine (**35**{*y*}) (10 mmol) was added into the solution of 2-methylsulphonyl-substituted pyridopyrimidine (**54**{*x*}) (2 mmol) in 14 mL IPA and the mixture was heated under microwave irradiation at 170 ºC for 5 hours. Cyclohexane was added to the solution and the solid was collected by filtration and washed with cyclohexane, and Et_2O to afford the corresponding 2-substituted pyrido[2,3-*d*]pyrimidine (**7**{*x,y*}) as a white solid.

6-phenyl-2-(phenylamino)-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (7{*2,9*})

Starting from pyridopyrimidine **54**{*2*} and amine **35**{*9*}. 82% yield, white solid.



^{1}H NMR (400 MHz, DMSO-d_6): δ 10.48 (s, 2H, NHx2), 8.80 (s, 1H, NH), 7.73 – 7.66 (m, 2H, C16-CHx2), 7.34 – 7.22 (m, 7H, C17-CHx2, C12-CHx2, C13-CHx2, C14-CH), 7.02 (tt, *J* = 7.3, 1.2 Hz, 1H, C8-CH), 3.82 (dd, *J* = 8.5, 7.1 Hz, 1H, C7-CH), 2.92 – 2.72 (m, 2H, C6-CH_2).

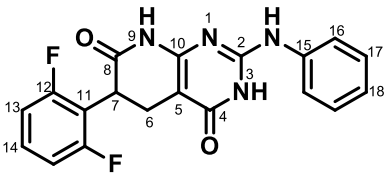
^{13}C NMR (100.6 MHz, DMSO-d_6): δ 172.4, 139.7, 139.1, 129.2, 128.8, 128.8, 128.5, 128.4, 127.3, 123.0 (C18), 119.8 (C16), 114.3, 90.7 (C5), 46.2 (C7), 25.0 (C6.)

HRMS (70 eV, EI): m/z calculated for $C_{19}H_{16}N_4O_2$: 332.1273, $[M]^+$, found: 332.1275.

IR (KBr), ν_{max}(cm^{-1}): 3401, 3058, 1615, 1654, 1462, 750, 395.

6-(2,6-difluorophenyl)-2-(phenylamino)-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (7{*4,9*})

Starting from pyridopyrimidine **54**{*4*} and amine **35**{*9*}. 83% yield, white solid.



^{1}H NMR (400 MHz, DMSO-d_6): δ 10.58 (s, 2H, 2xNH), 8.83 (s, 1H, NH), 7.74 – 7.68 (m, 2H, C15-CHx2), 7.46 - 7.40 (m, 1H, C14-CH), 7.34 – 7.27 (m, 2H, C16-CHx2), 7.13 (t, *J* = 8.8 Hz, 2H, C13-CHx2), 7.03 (t, *J* = 7.4 Hz, 1H, C17-CH), 4.19 (dd, *J* = 14.1, 7.7 Hz, 1H, C7-CH), 2.90 (dd, *J* = 15.7, 7.8 Hz, 1H, C6-CH_2), 2.53 – 2.55 (m, 1H, C6-CH_2).

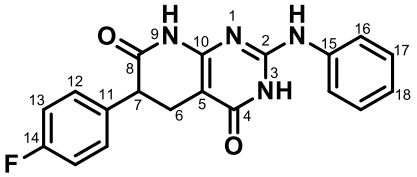
^{13}C NMR (100.6 MHz, DMSO-d_6): δ 170.0, 162.6, 160.8 (d, *J* = 246.7 Hz, C12), 160.7 (d, *J* = 246.8 Hz, C12), 155.5, 138.6, 129.7 (t, *J* = 10.3 Hz, C14), 128.8 (C15), 122.7 (C17), 119.4 (C16), 115.2 (t, *J* = 18.6 Hz, C11), 113.9, 111.7 (d, *J* = 22.4, 3.2 Hz, C13), 90.1 (C5), 36.4 (C7), 23.3 (C6).

HRMS (70 eV, EI): m/z calculated for $C_{19}H_{14}N_4O_2F_2$: 368.1085, $[M]^+$, found: 368.1087.

IR (KBr), ν_{max}(cm^{-1}): 3423, 3231, 3060, 2931, 1701, 1643, 1627, 1593, 1469, 1235, 1009, 786.

6-(4-fluorophenyl)-2-(phenylamino)-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (7{*7,9*})

Starting from pyridopyrimidine **54**{*7*} and amine **35**{*9*}. 94% yield, white solid.



^{1}H NMR (400 MHz, DMSO-d_6): δ 10.47 (s, 2H, 2xNH), 9.25 (s, 1H, NH-Ph), 7.79 -7.67 (m, 2H, 2xCH_{Ph}), 7.33 - 7.24 (m, 4H, 2xCH_{Ph} + C12-CHx2), 7.15 (t, *J* = 8.9 Hz, 2H, C13-CHx2), 7.04 - 6.98 (m, 1H), 3.85 (dd, *J* = 9.6, 7.0 Hz, 1H), 2.92 - 2.70 (m, 2H, C6-CH_2).

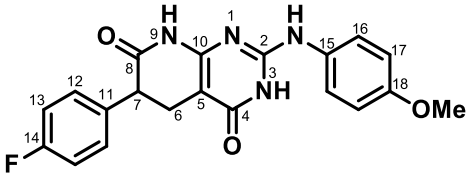
^{13}C NMR (100.6 MHz, DMSO-d_6): δ 172.0, 161.8, 161.3 (d, *J* = 242.8 Hz, C14), 155.6, 151.1, 138.8, 135.5 (d, *J* = 3.1 Hz, C11), 130.1 (d, *J* = 8.1 Hz, C12), 128.8, 122.6, 119.5, 115.2 (d, *J* = 21.1 Hz, C13) 90.4 (C5), 45.1 (C7), 24.7 (C6).

HRMS (70 eV, EI): m/z calculated for $C_{19}H_{15}N_4O_2F$: 350.1179, $[M]^+$, found: 350.1179.

IR (film), ν_{max} (cm^{-1}): 3400, 3186, 3049, 1655, 1614, 1511, 1461, 1232.

6-(4-fluorophenyl)-2-((4-methoxyphenyl)amino)-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (7{*7,11*})

Starting from pyridopyrimidine **54**{*7*} and 1.2 equivalents of amine **35**{*11*}. 79% yield, white solid.



^{1}H NMR (400 MHz, DMSO-d_6): δ 10.40 (s, 1H, NH), 8.62 (s, 1H, NH), 7.56 (d, *J* = 9.0 Hz, 2H, C17-CHx2), 7.28 (dd, *J* = 8.7, 5.6 Hz, 2H, C12-CHx2), 7.15 (t, *J* = 8.9 Hz, 2H, C13-CHx2), 6.87 (d, *J* = 9.0 Hz, 2H, C16-CHx2), 3.83 (dd, *J* = 9.5, 7.0 Hz, 1H, C7-CH), 3.73 (s, 3H, OCH_3), 2.89 - 2.69 (m, 2H, C6-CH_2).

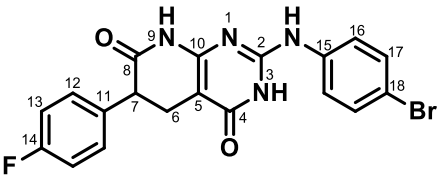
^{13}C NMR (100.6 MHz, DMSO-d_6): δ 171.9, 161.4, 161.1 (d, *J* = 242.8 Hz, C14), 156.2, 155.1, 154.8, 135.4 (d, *J* = 3.1 Hz, C11), 131.55, 130.0 (d, *J* = 8.1 Hz, C12), 121.5 (C17), 115.0 (d, *J* = 21.3 Hz, C13), 113.9 (C16), 89.8 (C5) 55.2 (OMe), 45.1 (C7), 24.6 (C6).

HRMS (70 eV, EI): m/z calculated for $C_{20}H_{17}N_4O_3F$: 380.1285, $[M]^+$, found: 380.1286.

IR (film), ν_{max} (cm^{-1}): 3404, 3148, 2813, 1656, 1615, 1509, 1457, 1228, 844.

2-((4-bromophenyl)amino)-6-(4-fluorophenyl)-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (7{*7,12*})

Starting from pyridopyrimidine **54**{*7*} and amine **35**{*12*}. 74% yield, white solid.



^{1}H NMR (400 MHz, DMSO-d_6): δ 10.53 (s, 1H, NHx2), 8.93 (s, 1H, NH), 7.69 (d, *J* = 8.9 Hz, 2H, C17-CHx2), 7.43 (d, *J* = 8.8 Hz, 2H, C16-CHx2), 7.28 (dd, *J* = 8.7, 5.6 Hz, 2H, C12-CHx2), 7.15 (t, *J* = 8.9 Hz, 2H, C13-CHx2), 3.85 (dd, *J* = 9.6, 7.1 Hz, 1H, C7-CH), 2.91 – 2.69 (m, 2H, C6-CH_2).

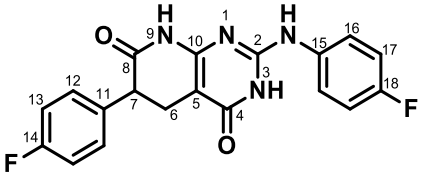
^{13}C NMR (100.6 MHz, DMSO-d_6): δ 171.9, 161.2 (d, *J* = 242.8 Hz, C14), 158.5, 158.2, 155.4, 138.2 (C15), 135.4 (d, *J* = 3.1 Hz, C11), 131.4 (C17), 130.0 (d, *J* = 8.1 Hz, C12), 121.4 (C16), 115.1 (d, *J* = 21.3 Hz, C13), 114.0 (C18), 90.6 (C5), 45.0 (C7), 24.6 (C6).

HRMS (70 eV, EI): m/z calculated for $C_{19}H_{14}N_4O_2FBr$: 428.0284, $[M]^+$, found: 428.0287.

IR (film), ν_{max} (cm $^{-1}$): 3400, 3163, 2963, 1643, 1600, 1511, 1488, 1236, 835, 795, 771.

6-(4-fluorophenyl)-2-((4-fluorophenyl)amino)-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (7{*7,13*})

Starting from pyridopyrimidine **54**{*7*} and amine **35**{*13*}. 67% yield, white solid.



^{1}H NMR (400 MHz, DMSO-d_6): δ 10.58 (s, 1H, NH), 10.48 (s, 1H, NH), 8.88 (s, 1H, NH), 7.71 (dd, *J* = 9.1, 4.9 Hz, 2H, C16-CHx2), 7.28 (dd, *J* = 8.7, 5.6 Hz, 2H, C12-CHx2), 7.13 (m, 4H, C13-CHx2, C17-CHx2), 3.84 (dd, *J* = 9.5, 7.1 Hz, 1H, C7-CH), 2.86 (dd, *J* = 16.0, 7.1 Hz, 1H, C6-CH), 2.73 (dd, *J* = 16.0, 9.6 Hz, 1H, C6-CH).

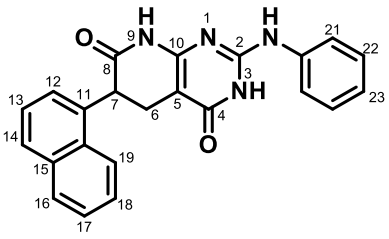
^{13}C NMR (100.6 MHz, DMSO-d_6): δ 171.9, 161.2 (d, *J* = 242.6 Hz, C14), 157.8 (d, *J* = 239.4 Hz, C18), 156.2, 155.4, 154.8, 135.4 (d, *J* = 3.1 Hz, C11), 135.0 (C15), 130.0 (d, *J* = 8.1 Hz, C12), 121.3 (d, *J* = 7.6 Hz, C16), 115.2 (d, *J* = 17.7 Hz, C13), 115.0 (d, *J* = 16.7 Hz, C17), 90.3 (C5), 45.0 (C7), 24.6 (C6).

HRMS (70 eV, EI): m/z calculated for $C_{19}H_{14}N_4O_2F_2$: 368.1085, $[M]^+$, found: 368.1081.

IR (film), ν_{max} (cm $^{-1}$): 3409, 3171, 2958, 1645, 1603, 1512, 1242, 836

6-(naphthalen-1-yl)-2-(phenylamino)-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (7{*12,9*})

Starting from pyridopyrimidine **54**{*12*} and amine **35**{*9*}. 67% yield, white solid.



^{1}H NMR (400 MHz, DMSO-d_6): δ 10.64 (s, 1H, NH), 8.86 (s, 1H, NH), 8.09 (d, *J* = 7.7 Hz, 1H, C19-CH), 7.98 – 7.93 (m, 1H, C16-CH), 7.85 (d, *J* = 8.1 Hz, 1H, C14-CH), 7.74 (d, *J* = 7.7 Hz, 2H, C21-CHx2), 7.60 – 7.50 (m, 3H, C17-CH, C18-CH), 7.46 (dd, *J* = 8.2, 7.1 Hz, 1H, C13-CH), 7.41 – 7.29 (m, 3H, C12-CH, C22-CHx2), 7.04 (t, *J* = 7.3 Hz, 1H, C23-CH), 4.64 (dd, *J* = 9.1, 7.6 Hz, 1H, C7-CH), 3.00 (dd, *J* = 16.1, 7.7 Hz, 1H, C6-CH_2), 2.85 (dd, *J* = 16.1, 9.1 Hz, 1H, C6-CH_2).

^{13}C NMR (100.6 MHz, DMSO-d_6): δ 172.0, 171.0, 162.9, 155.4, 138.7, 135.9, 133.7, 131.0, 128.8 (C22,C16), 127.5 (C14), 126.1, 125.6, 125.4 (C13), 125.1 (C12), 123.9 (C19), 122.6 (C23), 119.4 (C21), 90.3 (C5), 42.5 (C7), 24.8 (C6).

HRMS (70 eV, EI): m/z calculated for $C_{23}H_{18}N_4O_2$: 382.1430, $[M]^+$, found: 382.1429.

IR (KBr), ν_{max}(cm^{-1}): 3430, 3167, 3054, 1644, 1595, 1579, 1540, 1495, 1235, 777.

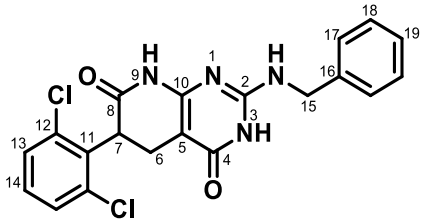
2.5.3 General procedure for synthesis of 2-(benzylamino)-5,6-dihydropyridi[2,3-d]pyrimidine-4,7(3*H*,8*H*)-diones

The corresponding amine (**35**{*y*}) (20 mmol) was added to the solution of 2-methylthio-substituted pyridopyrimidine (**51**{*x*}) (2 mmol) in 14 mL IPA and the mixture was heated under microwave irradiation at 170 ºC for 5 hours. Cyclohexane was added to the solution and the solid was collected by filtration and washed with cyclohexane, and Et_2O to afford the corresponding 2-substituted pyrido[2,3-*d*]pyrimidine (**7**{*x,y*}) as a white solid.

2-(benzylamino)-6-(2,6-dichlorophenyl)-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (7{*3,8*})

Starting from pyridopyrimidine **51**{*3*} and amine **35**{*8*}. 36% yield, white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.57 (s, 1H, NH), 10.27 (s, 1H, NH), 7.50 (ddd, *J* = 16.6, 8.1, 1.3 Hz, 2H, CH-C13x2), 7.40 – 7.31 (m, 5H, CH-Ar), 7.27 (d, *J* = 7.0 Hz, 1H, CH-Ar), 6.99 (s, 1H, NH-Bz), 4.53 (dd, *J* = 13.4, 8.9 Hz, 1H, CH-C7), 4.47 (d, *J* = 6.1 Hz, 2H), 2.84 – 2.64 (m, 2H, CH_2-C6).



^{13}C NMR (100.6 MHz, DMSO-d_6): δ 169.7, 161.6, 155.5, 153.7, 139.1, 135.4, 135.2, 134.7, 129.7, 129.7, 128.3, 128.3, 127.6, 127.0, 87.1 (C5), 43.4 (C15), 43.4 (C7), 22.4 (C6).

Anal. Calcd. (%) for $C_{20}H_{16}Cl_2N_4O_2$: C, 57.84; H, 3.88; N, 13.49. Found: C, 57.71; H, 3.78; N, 13.47.

MS (70 eV, EI): m/z (%) = 414.0 (100), $[M]^+$, 379.1 $[M\text{-}Cl]^+$, 228.9 (34.0) $[C_{12}H_{12}N_4O]^+$, 105.8 (62.6) $[C_7H_8N]^+$, 90.9 (100) $[C_7H_7]^+$.

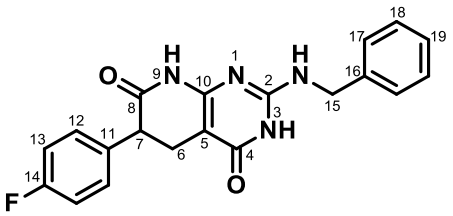
HRMS (70 eV, EI): m/z calculated for $C_{20}H_{16}N_4O_2Cl_2$: 414.0650, $[M]^+$, found: 414.0650.

IR (film), ν_{max} (cm $^{-1}$): 3263, 3181, 3066, 2934, 1686, 1639, 1613, 1597, 1545, 1520, 1374, 1289, 770.

2-(benzylamino)-6-(4-fluorophenyl)-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (7{*7,8*})

Starting from pyridopyrimidine **51**{*7*} and amine **35**{*8*}. 53% yield, white solid.

^{1}H NMR (400 MHz, TFA-*d*): δ 7.42 - 7.30 (m, 5H, CH_{Ar}x5), 7.22 (dd, *J* = 7.8, 5.2 Hz, 2H, CH-C12x2), 7.05 (t, *J* = 8.5 Hz, 2H, CH-C13x2), 4.75 (s, 2H, CH_2-C15), 4.05 (dd, *J* = 11.3, 7.3 Hz, 1H, CH-C7), 3.24 (dd, *J* = 16.8, 7.4 Hz, 1H, C6-CH_2), 3.03 (dd, *J* = 16.8, 11.4 Hz, 1H, C6-CH_2).



^{13}C NMR (100.6 MHz, TFA-*d*): δ 179.9, 168.9, 166.5 (d, *J* = 235.5 Hz, C14) 153.9, 150.6, 136.2, 134.7 (d, *J* = 3.4 Hz, C11), 134.0 (d, *J* = 8.5 Hz, C12) 133.7 (C_{Ar}), 133.7 (C_{Ar}), 131.6 (C_{Ar}), 120.3 (d, *J* = 22.7 Hz, C13) 96.2 (C5), 50.7 (C15), 49.7 (C7), 27.8 (C6).

Anal. Calcd. (%) for $C_{20}H_{17}FN_4O_2$: C, 65.93; H, 4.70; N, 15.38. Found: C, 65.53; H, 4.47; N, 15.49.

IR (KBr): ν (cm^{-1}): 3423, 3180, 3069, 2958, 1689, 1644, 1612, 1513, 1229, 1209, 836, 582.

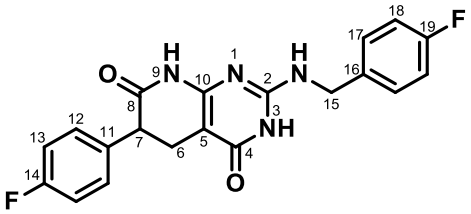
HRMS (70 eV, EI): m/z calculated for $C_{20}H_{17}N_4O_2F$: 324.0183, $[M]^+$, found: 324.0181.

IR (film), ν_{max} (cm^{-1}): 3423, 3180, 3068, 2958, 1689, 1644, 1612, 1513, 1229, 836, 582.

2-((4-fluorobenzyl)amino)-6-(4-fluorophenyl)-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (7{*7,10*})

Starting from pyridopyrimidine **51**{*7*} and amine **35**{*10*}. 40% yield, white solid.

^{1}H NMR (400 MHz, TFA-*d*): δ 7.31 (dd, *J* = 8.6, 5.0 Hz, 2H, C17-CHx2), 7.19 (dd, *J* = 8.7, 5.0 Hz, 2H, C12-CHx2), 7.06 – 7.00 (m, 4H, C18-CHx2, C13-CHx2), 4.70 (s, 2H, C15-CH_2), 4.02 (dd, *J* = 11.2, 7.2 Hz, 1H, C7-CH), 3.22 (dd, *J* = 16.8, 7.4 Hz, 1H, C6-CH_2), 3.00 (dd, *J* = 16.8, 11.4 Hz, 1H, C6-CH_2).



^{13}C NMR (100.6 MHz, DMSO-d_6): δ 179.9, 168.0 (d, *J* = 248.8 Hz, C14), 167.6 (d, *J* = 247.7 Hz), 165.3, 154.0, 150.7, 134.7 (d, J = 3.5Hz, C11), 134.0 (d, *J* = 8.5 Hz, C12), 133.7 (C17), 132.2 (C16), 120.5 (d, *J* =24.5 Hz), 120.4 (d, *J* = 22.3 Hz), 96.1 (C5), 50.0 (C15), 49.7 (C7), 27.8 (C6).

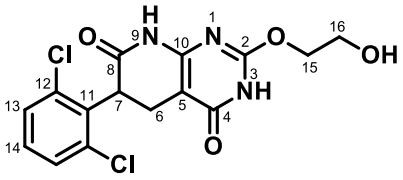
HRMS (70 eV, EI): m/z calculated for $C_{20}H_{16}N_4O_2F_2$: 382.1241, $[M]^+$, found: 382.1241.

IR (film), ν_{max} (cm^{-1}): 3424, 3248, 3181, 2931, 1637, 1611, 1513, 1230, 834.

2.5.4 6-(2,6-dichlorophenyl)-2-(2-hydroxyethoxy)-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (7{*3,7*})

Methyl 2-(2,6-dichlorophenyl)acrylate (**1**{*3*}) (4.00 mmol) was dissolved in ethyleneglycol (20 mL), 6-amino-2-(methylthio)pyrimidin-4(3*H*)-one (**52**) (4.00 mmol) and sodium methoxyde (4.00 mmol) were added into the solution. The mixture was heated under microwave irradiation at 140ºC for 3 hours. Then water was added to the crude and this was neutralized with a 2M solution of HCl. The solid was collected by filtration and washed with water, and Et_2O to afford the product **7**{*3,7*} in 40% as a white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ 12.20 (s, 1H, NH), 10.56 (s, 1H, NH), 7.52 (ddd, *J* = 15.5, 8.1, 1.3 Hz, 2H, C13-CHx2), 7.37 (t, *J* = 8.1 Hz, 1H, C14-CH), 4.89 (s, 1H, OH), 4.61 (dd, *J* = 13.5, 9.0 Hz, 1H, C7-CH), 4.32 (t, *J* = 4.8 Hz, 2H, C15- CH_2), 3.69 (t, *J* = 4.4 Hz, 2H, C16- CH_2), 2.89 – 2.68 (m, 2H, C6-CH_2).



^{13}C NMR (100.6 MHz, DMSO-d_6): δ 169.6, 162.2, 157.0, 154.3, 135.3, 135.2, 134.7, 129.8 (C14), 129.8 (C13), 128.3 (C13), 91.6 (C5), 69.3 (C15), 58.8 (C16), 43.0 (C7), 22.5 (C6).

MS (70 eV, EI): m/z (%) = 369.0 (39.8) $[M]^+$, 334.1 (48.2) $[M\text{-}Cl]^+$, 185.7 (100) $[C_8H_4Cl_2O]^+$.

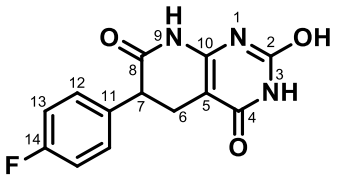
HRMS (70 eV, EI): m/z calculated for $C_{15}H_{13}N_3O_4Cl_2$: 369.0286, $[M]^+$, found: 369.0283.

IR (film), ν_{max} (cm^{-1}): 3389, 2875, 1630, 1592, 1468, 1437, 1315, 770.

2.5.5 6-(4-fluorophenyl)-2-hydroxy-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (56)

Phenol (4 mmol) was added into the solution of 2-methylsulphonyl-substituted pyridopyrimidine (**54**{*7*}) (2 mmol) in 14 mL IPA and the mixture was heated under microwave irradiation at 170 ºC for 12 hours. Cyclohexane was added to the solution and the solid was collected by filtration and washed with cyclohexane, and Et_2O to afford the pyrido[2,3-*d*]pyrimidine **56** in 82% as a white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.92 (s, 1H, NH), 10.18 (s, 1H), 9.69 (s, 1H), 7.29 (dd, *J* = 8.6, 5.6 Hz, 2H, C12-CHx2), 7.16 (t, *J* = 8.8 Hz, 2H, C13-CHx2), 3.93 (dd, *J* = 10.8, 7.2 Hz, 1H, C7-CH), 2.78 (dd, *J* = 15.8, 7.2 Hz, 1H, C6-CH), 2.65 (dd, *J* = 15.8, 10.8 Hz, 1H, C6-CH).



^{13}C NMR (100.6 MHz, DMSO-d_6): δ 170.9, 162.7, 161.3 (d, *J* = 243.0 Hz, C14), 150.0, 145.3, 134.6 (d, *J* = 3.1 Hz, C11), 130.3 (d, *J* = 8.1 Hz, C12), 115.1 (d, *J* = 21.2 Hz, C13), 86.2 (C5), 45.0 (C7), 24.3 (C6).

Anal. Calcd. (%) for $C_{13}H_{10}FN_3O_3$: C, 56.73; H, 3.66; N, 15.27. Found: C, 56.45; H, 3.45; N, 15.15.

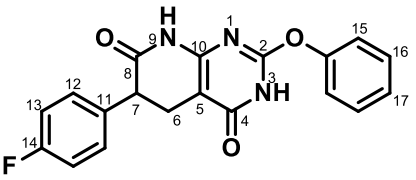
HRMS (70 eV, EI): m/z calculated for $C_{13}H_{10}N_3O_3F$: 275.0706, $[M]^+$, found: 275.0708.

IR (film), ν_{max} (cm^{-1}): 3181, 1763, 1721, 1650, 1560, 1515, 1393, 1189, 835.

2.5.6 6-(4-fluorophenyl)-2-phenoxy-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (53{*7,5*})

Phenol (4 mmol) was heated at 60ºC in a mixture of sodium methoxyde (4 mmol) in IPA (20 mL) for 20 minutes. 2-methylsulphonyl-substituted pyridopyrimidine (**54**{*7*}) (2 mmol) was added to the mixture and it was heated under microwave irradiation at 170 ºC for 3 hours. The solvent was eliminated under reduced pressure, water was added to the residue and the mixture was neutralized with HCl 2M. The solid was collected by filtration, washed with cyclohexane and Et_2O to afford the pyrido[2,3-*d*]pyrimidine **53**{*7,5*} in 72% as a white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ 12.58 (s, 1H, NH), 10.48 (s, 1H, NH), 7.44 (dd, *J* = 8.6, 7.3 Hz, 2H, C12-CHx2), 7.28 – 7.25 (m, 5H, C15-CHx2, C16-CHx2, C17-CH), 7.15 (t, *J* = 8.9 Hz, 2H, C13-CHx2), 3.84 (dd, *J* = 10.0, 7.1 Hz, 1H, C7), 2.88 (dd, *J* = 16.2, 7.1 Hz, 1H, C6-CH), 2.76 (dd, *J* = 16.2, 10.2 Hz, 1H, C6-CH).



^{13}C NMR (100.6 MHz, DMSO-d_6): δ 171.5, 163.2, 161.2 (d, *J* = 242.7 Hz, C14), 157.6, 155.6, 151.6, 135.1 (d, *J* = 3.1 Hz, C11), 130.1 (d, *J* = 8.9 Hz, C12), 129.8 (C16), 125.8 (C17), 121.6 (C15), 115.1 (d, *J* = 21.3 Hz, C13), 93.7 (C5), 44.7 (C7), 24.5 (C6).

HRMS (70 eV, EI): m/z calculated for $C_{19}H_{14}N_3O_3F$: 351.1019, $[M]^+$, found: 351.1033.

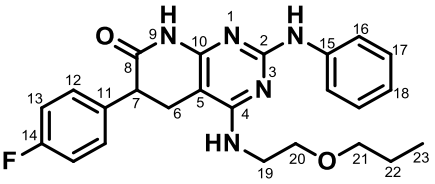
IR (film), ν_{max} (cm $^{-1}$): 3408, 3129, 2902, 1692, 1632, 1577, 1513, 1469, 1337, 1220.

2.6. Pyrido[2,3-*d*]pyrimidines substituted in C2 and C4 position

0.419 mmol of the corresponding disubstituted intermediate (**18**{*x,y*} or **57**) were suspended in ACN (20 ml) and 3 equivalents of the corresponding amine (**35**{*y*}) (1.257 mmol) were added into the suspension and the mixture was heated at 140 ºC by microwave irradiation for 5 hours. Then, water was added to the residue and the solid was collected by filtration and washed with water and EtOEt.

6-(4-fluorophenyl)-2-(phenylamino)-4-((2-propoxyethyl)amino)-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (14{*7,7,9*})

Starting from **18**{7,9} and amine **35**{*9*}. 64% yield, white solid.



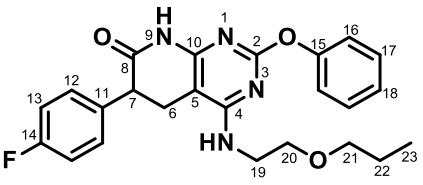
^{1}H NMR (400 MHz, DMSO-d_6): δ 10.28 (s, 1H, CONH), 8.82 (s, 1H, NH_{Ph}), 7.81 (d, *J* = 7.7 Hz, 2H, C16-CHx2), 7.32 (dd, *J* = 8.7, 5.6 Hz, 2H, C12-CHx2), 7.22 - 7.12 (m, 4H, C17-CHx2, C13-CHx2), 6.85 (t, *J* = 7.3 Hz, 1H, C18-CH), 6.70 (s, 1H, C4-NH), 3.92 (dd, *J* = 10.5, 6.9 Hz, 1H, C7-CH), 3.54 - 3.51 (m, 4H, C19-CH_2, C20-CH_2), 3.37 - 3.29 (m, 2H, C21-CH_2), 2.99 - 2.71 (m, 2H, C6-CH_2), 1.48 (p, *J* = 7.0 Hz, 2H, C22-CH_2), 0.84 (t, *J* = 7.4 Hz, 3H, CH_3).

^{13}C NMR (100.6 MHz, DMSO-d_6): δ 171.7, 161.2 (d, *J* = 242.8 Hz, C14), 160.0, 158.0, 155.5, 141.4, 135.7 (d, J = 3.1 Hz, C11), 130.3 (d, J = 7.9 Hz, C12), 128.2 (C17), 120.3 (C18), 118.4 (C16), 115.0 (d, J = 21.3 Hz, C13), 86.1 (C5), 71.8 (C21), 68.7 (C20), 45.3 (C7), 41.4 (19), 25.6 (C6), 22.5 (C22), 10.5(C23).

HRMS (70 eV, EI): m/z calculated for $C_{24}H_{26}N_5O_2F$: 435.2071, $[M]^+$, found: 435.2070.

6-(4-fluorophenyl)-2-phenoxy-4-((2-propoxyethyl)amino)-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (44)

Starting from **57** and amine **35**{*9*}. 54% yield, white solid.



^{1}H NMR (400 MHz, DMSO-d_6): δ 8.01 (s, 1H, NH), 7.35 (t, *J* = 7.7 Hz, 2H, C12-CHx2), 7.23 - 7.12 (m, 5H, C16-CHx2, C17-CHx2, C18-CH), 7.01 (t, *J* = 8.6 Hz, 2H, C13-CHx2), 5.14 (s, 1H, NH), 3.83 (dd, *J* = 9.7, 7.2 Hz, 1H, C7-CH), 3.61 - 3.44 (m, 4H, C19-CH_2, C20-CH_2), 3.35 (t, *J* = 6.7 Hz, 2H, C21-CH_2), 2.94 - 2.68 (m, 2H, C6-CH_2), 1.54 (h, *J* = 7.1 Hz, 2H, C22-CH_2), 0.87 (t, *J* = 7.4 Hz, 3H, C23-CH_2).

^{13}C NMR (100.6 MHz, DMSO-d_6): δ 170.8, 163.9, 162.3 (d, *J* = 246.6 Hz, C14), 161.4, 156.2, 153.1, 133.8 (d, *J* = 3.3 Hz, C11), 129.8 (d, *J* = 8.1 Hz, C12) 129.2 (C17), 125.0 (C18), 122.0 (C16), 115.9 (d, *J* = 21.5 Hz, C13), 88.8 (C5), 72.8 (C21) , 68.9 (C20), 45.9 (C7), 41.1 (C19), 26.0 (C6), 22.8 (C22), 10.6 (C23).

HRMS (70 eV, EI): m/z calculated for $C_{24}H_{25}N_4O_3F$: 436.1911, $[M]^+$, found: 436.1913.

Anal. Calcd. (%) for $C_{24}H_{25}N_4O_3F$: C, 66.04; H, 5.77; N, 12.84. Found: C, 66.09; H, 6.08; N, 12.56.

IR (film), ν_{max} (cm $^{-1}$): 3466, 3412, 2961, 2333, 2856, 1700, 1623, 1587, 1510, 1407, 1348, 1214.

2.7. General procedure for aromatization of pyrido[2,3-*d*]pyrimidines

Procedure A:

A mixture of 0.5 mmol of pyrido[2,3-*d*]pyrimidine and 60.0 mg (1.5 mmol) of sodium hydride (60% dispersion in mineral oil) in 5 mL of anhydrous DMSO was heated for 4 hours at 100ºC protected from moisture. The resulting solution was cooled down, water (300 mL) was added and it was neutralized with AcOH. The resulting precipitate was filtered, washed with MeOH and EtOEt and dried in vacuo over phosphorus pentoxide to afford the corresponding pyrido[2,3-*d*]pyrimidine as a brownish solid.

Procedure B:

A mixture of 2.7 mmol of pyrido[2,3-*d*]pyrimidine and 3.5 mmol of DDQ in 30 mL of 1,2-DCE was heated at 100 ºC overnight protected from moisture. The resulting solution was cooled down, water (300 mL) was added and the resulting precipitate was filtered, washed with EtOH and EtOEt and dried in vacuo over phosphorus pentoxide to afford the corresponding pyrido[2,3-*d*]pyrimidine as a brownish solid.

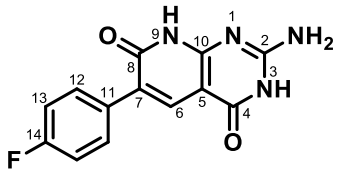
Procedure C:

A mixture of 0.5 mmol of pyrido[2,3-*d*]pyrimidine and 114 mg (1.0 mmol) of activated MnO_2 in 8.5 mL of acetic acid was refluxed for 3 hours. The resulting hot suspension was filtered and the solvent was removed *in vacuo*. The resulting solid was refluxed with water in order to eliminate MnO_2 traces, then filtrated and dried in vacuo over phosphorus pentoxide to afford the corresponding pyrido[2,3-d]pyrimidine as a brownish solid.

2-amino-6-(4-fluorophenyl)pyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (38{*7*})

Starting from **7**{*7*} and following procedure B. 90% yield, yellow solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ 11.92 (s, 1H, NH-CO), 7.84 (s, 1H, C6-CH), 7.71 (dd, J = 8.9, 5.6 Hz, 2H, C12-2xCH), 7.19 (t, J = 9.0 Hz, 2H, C13-2xCH), 6.08 (s, 2H, NH_2).



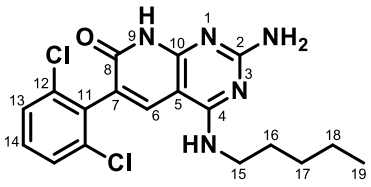
^{13}C NMR (100.6 MHz, DMSO-d_6) δ 162.7 (CO), 162.4, 160.0, 156.2, 155.7, 134.0 (C7), 132.8 (d, *J* = 3.0 Hz), 130.0 (d, *J* = 31.8 Hz, C12), 121.9 (C6) 114.7 (d, *J* = 84.1 Hz C13), 95.9 (C5).

HRMS (ESI–TOF): m/z calculated for $C_{13}H_9FN_4O_2$: 273.0775, $[M+H]^+$, found: 273.0782.

IR (film), ν_{max} (cm $^{-1}$): 3323, 3096, 2922, 1633, 1505, 1393, 1231, 1159, 582.

2-amino-6-(2,6-dichlorophenyl)-4-(pentylamino)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (16{*3,6*})

Starting from **14**{*3,6*} and following procedure B. 51% yield, white solid.



^{1}H NMR (400 MHz, DMSO-d_6): δ 10.27 (s, 1H, NH), 8.89 (s, 1H, NH), 8.36 (s, 1H, C6-CH), 7.98 (s, 2H, NH_2), 7.60 (d, *J* = 7.8 Hz, 2H, C13-CHx2), 7.47 (dd, *J* = 8.8, 7.4 Hz, 1H, C14-CH), 3.49 (q, *J* = 6.8 Hz, 2H, C15-CH_2), 1.60 (m, 2H, C16-CH_2), 1.37 – 1.25 (m, 4H, C17-CH_2, C18-CH_2), 0.91 – 0.83 (m, 3H, C19-CH_3).

^{13}C NMR (100.6 MHz, DMSO-d_6): δ 169.9, 161.3, 155.7, 154.9, 135.4 (C6), 135.0, 134.7, 133.9, 130.7 (C14), 129.7, 128.1 (C13), 86.8 (C5), 43.4 (C15), 28.5 (C17), 27.9 (C16), 21.8 (C18), 13.9 (C19).

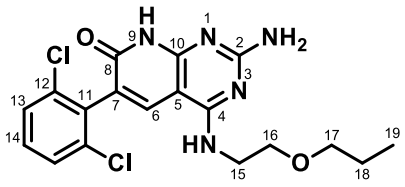
MS (70 eV, EI): m/z (%) = 391.2 (20.6) $[M]^+$, 356.3 (100) $[M-Cl]^+$, 326.1 (19.0) $[M-C_2H_5Cl]^+$, 300.1 (7.5) $[M-C_4H_9Cl]^+$.

HRMS (70 eV, EI): m/z calculated for $C_{18}H_{19}N_5OCl_2$: 391.0967, $[M]^+$, found: 391.0967.

IR (film), ν_{max} (cm $^{-1}$): 3126, 1856, 1640, 1465, 1430, 169, 780.

2-amino-6-(2,6-dichlorophenyl)-4-((2-propoxyethyl)amino)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (16{*3,7*})

Starting from **14**{*3,7*} and following procedure B. 52% yield, light brown solid.



^{1}H NMR (400 MHz, DMSO-d_6): δ 8.94 (s, 1H, NH), 8.36 (s, 1H, C6-CH), 7.62 – 7.55 (m, 2H, C13-CHx2), 7.47 (t, *J* = 8.7 Hz, 1H, C14-CH), 3.66 (t, *J* = 4.8 Hz, 2H, C15-CH_2), 3.58 (t, *J* = 5.3 Hz, 2H, C16-CH_2), 3.36 (t, *J* = 6.6 Hz, 2H, C17-CH_2), 1.48 (h, *J* = 7.4, 6.4 Hz, 2H, C18-CH_2), 0.82 (t, *J* = 7.4 Hz, 3H, C19-CH_3).

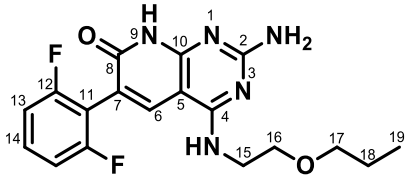
^{13}C NMR (100.6 MHz, DMSO-d_6): δ 156.42, 155.79, 150.86, 135.99 (C6), 135.00 (C-Cl), 133.81, 130.83 (C14), 129.23, 128.15 (C13), 113.74, 101.71 (C5), 71.80 (C17), 67.68 (C16), 41.25 (C15), 22.38 (C18), 10.46 (C19).

HRMS (70 eV, EI): m/z calculated for $C_{18}H_{19}N_5O_2Cl_2$: 407.0916, $[M]^+$, found: 407.0911.

IR (film), ν_{max} (cm^{-1}): 3128, 2870, 1640, 1453, 1430, 1284, 796.

2-amino-6-(2,6-difluorophenyl)-4-((2-propoxyethyl)amino)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (16{*4,7*})

Starting from **14**{*4,7*} and following procedure A. 60% yield, light brown solid.



^{1}H NMR (400 MHz, DMSO-d_6): δ 11.93 (s, 1H, NH), 8.16 (s, 1H, C6-CH), 7.70 (s, 1H, NH), 7.49 – 7.41 (m, 1H, C14-CH), 7.20 - 7.12 (m, 2H, C13-CHx2), 6.81 (s, 2H, NH_2), 3.50 – 3.57 (m, 4H, C15-CH_2, C16-CH_2), 3.35 – 3.40 (m, 2H, C17-CH_2), 1.49 (h, *J* = 7.4 Hz, 2H, C18-CH_2), 0.84 (t, *J* = 7.4 Hz, 3H, C19-CH_3).

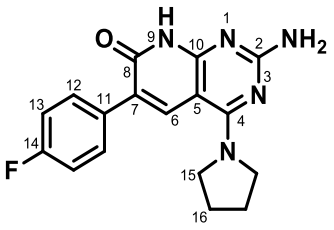
^{13}C NMR (100.6 MHz, DMSO-d_6): δ 163.0, 161.9, 160.4 (d, *J* = 246.6 Hz, C12), 160.3 (d, *J* = 246.7 Hz, C12), 159.6, 156.4, 136.7, 129.9 (t, *J* = 10.3 Hz, C14), 113.8 (t, *J* = 20.1 Hz, C11), 111.6 – 111.3 (m, C13), 111.2, 91.0 (C5), 71.8 (C17), 68.3 (C16), 40.2 (C15), 22.4 (C18), 10.5 (C19).

HRMS (70 eV, EI): m/z calculated for $C_{18}H_{19}N_5O_2F_2$: 375.1507, $[M]^+$, found: 375.1509.

IR (film), ν_{max} (cm^{-1}): 3387, 3188, 2931, 2858, 1627, 1568, 1466, 1004, 788.

2-amino-6-(4-fluorophenyl)-4-(pyrrolidin-1-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (16{*7,5*})

Starting from **14**{*7,5*} and following procedure C. 82% yield, light brown solid.

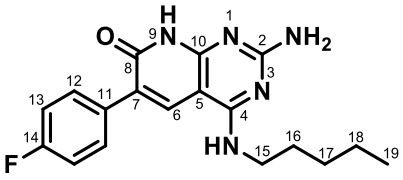


^{1}H NMR (400 MHz, DMSO-d_6): δ 11.77 (s, 1H, NH), 8.10 (s, 1H, C6-CH), 7.73 (m, 2H, C12-CHx2), 7.19 (t, *J* = 9.0 Hz, 2H, C13-CHx2), 6.65 (s, 2H, NH_2), 3.76 (t, J = 6.4 Hz, 4H, C15-CH_2x2), 1.91 (t, *J* = 6.5 Hz, 4H, C16-CH_2x2).

IR (film), ν_{max} (cm^{-1}):3459, 3311, 3181, 2970, 2874, 1635, 1606, 1530, 1511, 1452, 1452, 1224, 839.

2-amino-6-(4-fluorophenyl)-4-(pentylamino)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (16{*7,6*})

Starting from **14**{*7,6*} and following procedure C. 73% yield, white solid.



^{1}H NMR (400 MHz, DMSO-d_6): δ 12.11 (s, 1H, NHCO), 8.27 (s, 1H, C6-CH), 7.76 (m, 2H, C12-CHx2), 7.24 (m, 2H, C13-CHx2), 3.47-3.30 (m, 2H, C15-CH_2) 1.65 – 1.54 (m, 2H, C16-CH_2), 1.37 – 1.29 (m, 4H, C17-CH_2, C18-CH_2), 0.89 (t, *J* = 6.8 Hz, 3H, CH_3).

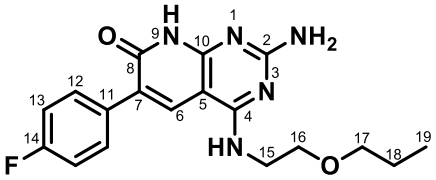
^{13}C NMR (100.6 MHz, DMSO-d_6): δ 162.8, 162.5, 160.0, 159.6, 155.5, 130.6, 133.1 (d, *J* = 6.6 Hz, C11), 130.3 (d, *J* = 7.7 Hz, C12), 121.0 (C7), 114.7 (d, *J* = 21.0 Hz, C13), 91.7 (C5), 40.4 (C15), 28.8 (C17), 28.6 (C16), 22.1 (C18), 14.0 (C19).

HRMS (70 eV, EI): m/z calculated for $C_{18}H_{20}N_5OF$: 341.1653, $[M]^+$, found: 341.1652.

IR (film), ν_{max} (cm $^{-1}$): 3380, 3171, 2930, 2859, 1619, 1564, 1509, 1475, 1227, 837, 796.

2-amino-6-(4-fluorophenyl)-4-((2-propoxyethyl)amino)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (16{*7,7*})

Starting from **14**{*7,7*} and following procedure C. 72% yield, white solid.



^{1}H NMR (400 MHz, DMSO-d_6): δ 12.26 (s, 1H, NH), 8.30 (s, 1H, C6-CH), 7.90 (s, 1H, NH), 7.83 – 7.73 (m, 2H, C12-CH_2), 7.23 (t, *J* = 8.7 Hz, 3H, C13-CH_2), 6.98 (s, 2H, NH_2), 3.60 – 3.55 (m, 4H, C15-CH_2, C16-CH_2), 3.40 – 3.35 (m, 2H, C17-CH_2), 1.57 - 1.45 (m, 2H, C18-CH_2), 0.85 (t, J = 7.4 Hz, 3H, C19-CH_3).

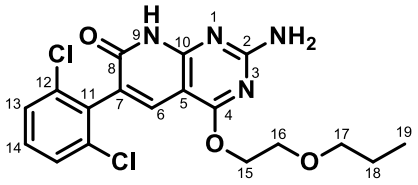
^{13}C NMR (100.6 MHz, DMSO-d_6): δ 162.6, 161.1 (d, *J* = 245.0 Hz, C14), 159.6, 155.6, 133.1 (d, *J* = 1.9 Hz, C11), 132.8, 130.1 (d, *J* = 7.9 Hz, C12), 121.1, 121.0, 114.5 (d, *J* = 21.1 Hz, C13), 91.5 (C5), 71.8 (C17), 68.5 (C16), 39.5 (C15), 22.4 (C18), 10.5 (C19).

HRMS (ESI–TOF): m/z calculated for $C_{18}H_{21}FN_5O_2$, 358.1678, $[M-H]^+$, found: 358.1674.

IR (film), ν_{max} (cm $^{-1}$): 3380, 2177, 2961, 2873, 1621, 1566, 1509, 1481, 1228, 838,796.

2-amino-6-(2,6-dichlorophenyl)-4-(2-propoxyethoxy)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (17{*3,6*})

Starting from **15**{*3,6*} and following procedure B. 82% yield, white solid.



^{1}H NMR (400 MHz, DMSO-d_6): δ 12.00 (s, 1H, NH), 7.58 – 7.51 (m, 3H, C13-CHx2, C7-CH), 7.42 (dd, *J* = 8.7, 7.4 Hz, 1H, C14-CH), 7.21 (s, 2H, NH_2), 4.51 – 4.45 (m, 2H, C15-CH_2), 3.74 – 3.68 (m, 2H, C16-CH_2), 3.38 (t, *J* = 6.6 Hz, 2H, C17-CH_2), 1.47 (h, *J* = 7.3 Hz, 2H, C18-CH_2), 0.80 (t, *J* = 7.4 Hz, 3H, CH_3).

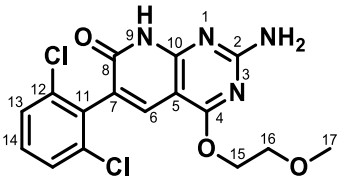
^{13}C NMR (100.6 MHz, DMSO-d_6): δ 166.1, 162.7, 161.4, 157.4, 150.8, 135.2, 134.5, 134.2 (C6), 130.3 (C14), 129.2, 128.0 (C13), 122.1, 91.6 (C5), 71.9 (C17), 67.9 (C16), 65.7 (C15), 22.4 (C18), 10.4 (C19).

HRMS (70 eV, EI): m/z calculated for $C_{18}H_{18}N_4O_3Cl_2$: 408.0750, $[M]^+$, found: 408.0756.

IR (film), ν_{max} (cm $^{-1}$): 3392, 3183, 2962, 2868, 1626, 1553, 1509, 1432, 1336, 1252, 802.

2-amino-6-(2,6-dichlorophenyl**)-4-(2-methoxyethoxy)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (17{*3,4*})**

Starting from **15**{*3,4*} and following procedure B. 50% yield, white solid.



^{1}H NMR (400 MHz, DMSO-d_6): δ 12.01 (s, 1H, NH), 7.57 (s, 1H, C6-CH), 7.56 – 7.51 (m, 2H, C13-CHx2), 7.42 (dd, *J* = 8.8, 7.4 Hz, 1H, C14-CH), 7.22 (s, 2H, NH_2), 4.51 – 4.44 (m, 2H, C16-CH_2), 3.71 – 3.65 (m, 2H, C15-CH_2), 3.28 (s, 3H, C17-CH_3).

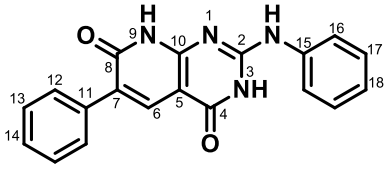
Anal. Calcd. (%) for $C_{16}H_{14}Cl_2N_4O_3$: C, 50.41; H, 3.70; N, 14.70. Found: C, 50.27; H, 3.54; N, 14.87.

HRMS (70 eV, EI): m/z calculated for $C_{16}H_{14}N_4O_3Cl_2$:380.0443, $[M]^+$, found: 380.0443.

IR (film), ν_{max} (cm $^{-1}$):3380, 3181, 2930, 1627, 1555, 1507, 1430, 1337, 1252, 801, 778.

6-phenyl-2-(phenylamino)pyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (38{*2,9*})

Starting from **7**{*2,9*} and following procedure A. 30% yield, white solid.



^{1}H NMR (400 MHz, DMSO-d_6): 12.15 (s, 1H, NH), 10.82 (s, 1H), 9.14 (s, 1H, NH), 7.89 (s, 1H, C6-CH), 7.77 (dd, *J* = 8.6, 1.2 Hz, 2H, C16-CHx2), 7.69 (dd, *J* = 8.3, 1.3 Hz, 2H, C17-CHx2), 7.42 – 7.29 (m, 5H, C13-CHx2, C12-CHx2, C14-CH), 7.10 (t, *J* = 7.4 Hz, 1H, C18-CH).

^{13}C NMR (100.6 MHz, DMSO-d_6): δ 162.5, 159.9, 155.1, 151.1, 138.0, 136.3, 133.6 (C6), 129.0, 128.2, 128.0, 127.2 (C17), 124.9 (C14), 123.5, 120.2 (C18), 97.2 (C5).

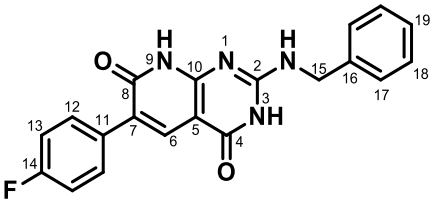
HRMS (70 eV, EI): m/z calculated for $C_{19}H_{14}N_4O_2$: 330.1117, $[M]^+$, found: 330.1114.

IR (KBr): ν (cm^{-1}):3433, 2936, 1634, 1594, 1466, 1358, 691.

2-(benzylamino)-6-(4-fluorophenyl)pyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (38{*7,8*})

Starting from **7**{*7,8*} and following procedure A. 55% yield, white solid.

^{1}H NMR (400 MHz, DMSO-d_6): 11.91 (s, 1H, NH), 11.02 (s, 1H, NH), 10.35 (s, 1H, NH), 7.83 (s, 1H, C6), 7.71 (dd, *J* = 9.0, 5.7 Hz, 2H, C12-CHx2), 7.43 – 7.27 (m, 10H), 7.19 (t, *J* = 9.0 Hz, 3H, C13-CHx2), 4.56 (d, *J* = 5.9 Hz, 2H, C15-CH_2).



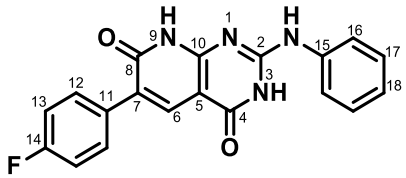
HRMS (70 eV, EI): m/z calculated for $C_{20}H_{15}N_4O_2F$: 362.1179, $[M]^+$, found: 362.1176.

IR (film), ν_{max} (cm^{-1}): 3391, 2925, 1632, 1602, 1501, 1454, 1296, 1232, 1160, 837, 584.

6-(4-fluorophenyl)-2-(phenylamino)pyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (38{*7,9*})

Starting from **7**{7,9} and following procedure A. 78% yield, white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ 12.18 (s, 1H, NH), 10.81 (s, 1H, NH), 9.12 (s, 1H, NH), 7.89 (s, 1H, C6-CH), 7.78 - 7.72 (m, 4H, C12-CHx2, C16-CHx2), 7.35 (dd, *J* = 8.6, 7.3 Hz, 2H, C17-CHx2), 7.21 (t, *J* = 8.9 Hz, 2H, C13-CHx2), 7.14 - 7.08 (m, 1H, C18-CH).



^{13}C NMR (100.6 MHz, DMSO-d_6): δ 162.4, 161.4 (d, *J* = 244.6 Hz, C14), 159.7, 155.1, 151.0, 137.9, 133.5 (C7), 132.6 (d, *J* = 3.1 Hz, C11), 130.1 (d, *J* = 8.1 Hz, C12), 128.9 (C17), 123.7 (C18), 123.5, 120.1 (C16), 114.8 (d, *J* = 21.2 Hz, C13), 97.2 (C5).

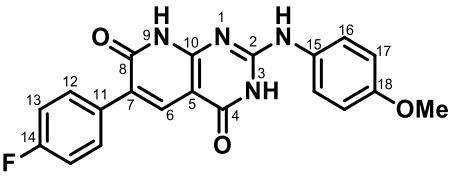
HRMS (70 eV, EI): m/z calculated for $C_{19}H_{13}N_4O_2F$: 348.1023, $[M]^+$, found: 348.1022.

IR (film), ν_{max} (cm^{-1}): 3391, 2924, 2850, 1611, 1554, 1497, 1442, 1226.

6-(4-fluorophenyl)-2-((4-methoxyphenyl)amino)pyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (38{*7,11*})

Starting from **7**{7,11} and following procedure A. 70% yield, white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ 12.07 (s, 1H, NH), 10.74 (s, 1H, NH), 8.96 (s, 1H, NH), 7.87 (s, 1H, C6-CH), 7.74 (dd, *J* = 8.9, 5.6 Hz, 2H, C12-CHx2), 7.62 (d, *J* = 9.0 Hz, 2H, C16-CHx2), 7.20 (t, *J* = 8.9 Hz, 2H, C13-CHx2), 6.92 (d, *J* = 9.0 Hz, 2H, C15-CHx2), 3.76 (s, 3H, OCH_3).

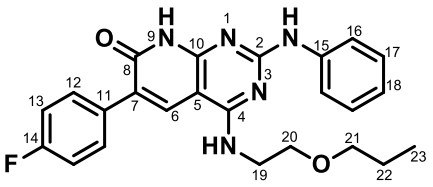


^{13}C NMR (100.6 MHz, DMSO-d_6): δ 162.5, 160.1, 159.8, 155.8, 155.3, 151.3, 133.9, 133.6 (C6), 132.7 (d, *J* = 2.9 Hz, C11), 130.7, 130.1 (d, *J* = 8.0 Hz, C12), 123.3, 122.4 (C16), 114.8 (d, *J* = 21.2 Hz, C13), 114.1 (C17), 97.0 (C5), 55.3 (C6).

6-(4-fluorophenyl)-2-(phenylamino)-4-((2-propoxyethyl)amino)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (16{*7,7,9*})

Starting from **14**{*7,7,9*} and following procedure A. 78% yield, white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ 11.80 (s, 1H, NH), 9.31 (s, 1H, NH), 8.32 (s, 1H, C6), 7.90 - 7.85 (m, 2H, C16-CHx2), 7.80 (dd, *J* = 8.8, 5.7 Hz, 2H, C12-CHx2), 7.27 -7.22 (m, 4H, C13-CHx2, C17-CHx2), 6.96 - 6.91 (m, 1H, C18), 3.67 - 3.57 (m, 4H, C19-CH_2, C20-CH_2), 3.38 (t, *J* = 6.7 Hz, 2H, C21-CH_2), 1.51 (h, *J* = 7.2 Hz, 2H, C22-CH_2), 0.84 (t, *J* = 7.4 Hz, 3H, C23-CH_3).



^{13}C NMR (100.6 MHz, DMSO-d_6): δ 162.4, 161.3 (d, *J* = 244.6 Hz, C14), 158.9, 157.5, 155.0, 140.6 (C15), 133.0 (d, *J* = 7.9 Hz, C11), 132.2 (C6), 130.2 (d, *J* = 7.7 Hx, C12), 128.3 (C17), 122.8 (C7), 121.4 (C18), 119.4 (C16), 114.6 (d, *J* = 21.4 Hz, C13), 92.4 (C5), 71.9 (C21), 68.4 (C20), 41.4 (C19), 22.4 (C22), 10.5 (C23).

HRMS (70 eV, EI): m/z calculated for $C_{24}H_{24}N_5O_2F$: 433.1914, $[M]^+$, found: 433.1927.

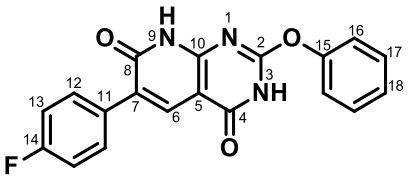
Anal. Calcd. (%) for $C_{24}H_{24}FN_5O_2$: C, 66.50; H, 5.58; N, 16.16. Found: C, 66.53; H, 5.86; N, 16.25.

IR (film), ν_{max} (cm^{-1}): 3445, 3059, 2928, 1636, 1603, 1570, 1499, 1451, 1310, 1228.

6-(4-fluorophenyl)-2-phenoxypyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (43)

Starting from **53**{*7,5*} and following procedure A. 67% yield, white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ 12.96 (s, 1H, NH), 12.24 (s, 1H, NH), 7.93 (s, 1H, C6-CH), 7.73 (dd, *J* = 8.7, 5.8 Hz, 2H, C12-CHx2), 7.48 (t, *J* = 7.9 Hz, 2H, C17-CHx2), 7.40 - 7.29 (m, 3H, C16-CH, C18-CHx2), 7.21 (t, *J* = 8.9 Hz, 2H, C13-CHx2).



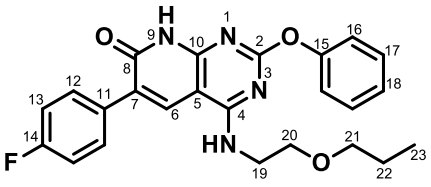
^{13}C NMR (100.6 MHz, DMSO-d_6): δ 162.0, 161.6 (d, *J* = 244.9 Hz, C14), 160.7, 157.3, 154.1, 151.1 (C15), 133.1 (C6) , 132.2 (d, *J* = 3.1 Hz, C11), 130.3 (d, *J* = 8.1 Hz, C12), 129.8 (C17), 126.3 (C18), 126.0 (C7), 121.7 (C16), 114.8 (d, *J* = 21.2 Hz, C13), 98.9 (C5).

HRMS (70 eV, EI): m/z calculated for $C_{19}H_{12}N_3O_3F$: 349.0863, $[M]^+$, found: 349.0860.
IR (film), ν_{max} (cm $^{-1}$): 3397, 2924, 2854, 1638, 1605, 1565, 1518, 1489, 1324, 1236, 1196, 600, 549, 512.

6-(4-fluorophenyl)-2-phenoxy-4-((2-propoxyethyl)amino)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (58)

Starting from **44** and following procedure A. 75% yield, white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.08 (s, 1H, NH), 7.64 - 7.58 (m, 3H, C12-CHx2, C6-CH), 7.43 - 7.37 (m, 2H, C17-CHx2), 7.25 - 7.17 (m, 3H, C18-CHx2, C16-CH), 7.07 (t, *J* = 8.7 Hz, 2H, C13-CHx2), 6.08 (s, 1H, NH), 3.69 (q, *J* = 5.1 Hz, 2H, C19-CH_2), 3.58 (t, *J* = 5.0 Hz, 2H, C20-CH_2), 3.42 (t, *J* = 6.7 Hz, 2H, C21-CH_2), 1.64 - 1.58 (m, 2H, C22.CH_2), 0.93 (t, *J* = 7.4 Hz, 3H, C23-CH_3).



^{13}C NMR (100.6 MHz, DMSO-d_6): δ 164.8, 162.7 (d, *J* = 248.1 Hz, C14), 162.4, 160.7, 155.2, 152.8, 131.7 (d, *J* = 3.3 Hz, C11), 130.6, 130.4 (d, *J* = 8.1 Hz, C12), 129.3 (C17), 127.9, 125.4 (C18), 122.1 (C16), 115.3 (d, *J* = 21.4 Hz, C13), 94.5 (C5), 72.9 (C21), 68.7 (C20), 41.3 (C19), 22.7 (C22), 10.6 (C23).

HRMS (70 eV, EI): m/z calculated for $C_{24}H_{23}N_4O_3F$: 434.1754, $[M]^+$, found: 434.1758.

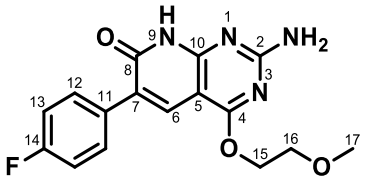
Anal. Calcd. (%) for $C_{24}H_{23}N_4O_3F$: C, 66.35; H, 5.34; N, 12.90. Found: C, 66.57; H, 5.31; N, 12.51.

IR (film), ν_{max} (cm $^{-1}$): 3313, 2933, 2873, 1648, 1612, 1591, 1571, 1510, 1419, 1401, 1264, 1207.

2-amino-6-(4-fluorophenyl)-4-(2-methoxyethoxy)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (17{*7,4*})

Starting from **18**{*7*} and following procedure A. 42% yield, white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ 11.93 (s, 1H, NH), 7.74 (s, 1H, C7-CH), 7.67 (dd, *J* = 8.8, 5.8 Hz, 2H, C12-CHx2), 7.21 (t, *J* = 9.0 Hz, 2H, C13-CHx2), 7.13 (s, 2H, NH_2), 4.55 – 4.48 (m, 2H, C15-CH), 3.73 – 3.67 (m, 2H, C16-CH), 3.31 (s, 3H, OCH_3).



^{13}C NMR (100.6 MHz, DMSO-d_6): δ 165.97, 162.68, 162.62, 162.30, 156.73, 132.70, 131.37 (C6), 130.33 (d, *J* = 7.9 Hz C12-CHx2), 123.85, 114.76 (d, *J* = 21.6 Hz C13-CHx2), 92.28 (C15), 69.89 (C15), 65.36 (C16), 58.22 (C17).

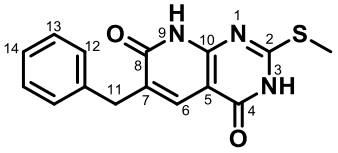
HRMS (70 eV, EI): m/z calculated for $C_{16}H_{15}N_4O_3F$, 330.1131, $[M]^+$, found: 330.1128.

IR (film), ν_{max} (cm^{-1}): 3404, 3218, 2894, 1688, 1633, 1576, 1434, 1372, 775.

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

Starting from **51**{*13*} and following the procedure described in reference [7]. 54% yield, white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ 12.77 (s, 1H, NH), 12.22 (s, 1H, NH), 7.49 (s, 1H, C6-CH), 7.49 – 7.21 (m, 5H, C_{Ar}), 3.74 (s, 2H, C11-CH_2), 2.55 (s, 3H, SCH_3).



^{13}C NMR (100.6 MHz, DMSO-d_6): δ 163.0, 159.5, 152.4, 139.5, 132.3, 130.1, 129.0, 128.8, 128.4, 126.1, 99.0 (C5), 35.0 (C11), 12.8 (SCH_3).

IR (film), ν_{max} (cm^{-1}): 3435, 3024, 2808, 1627, 1552, 1494, 1451, 1367, 1266, 1151, 696, 569.

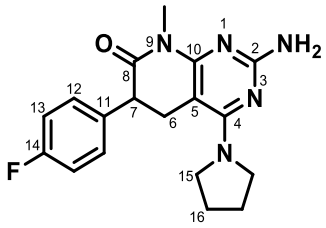
2.8. General procedure for derivatization in N8 of pyridp[2,3-*d*]pyrimidines

To a solution of 0.7 mmol of the corresponding pyrido[2,3-*d*]pyrimidine, 28.0 mg (0.7 mmol) of sodium hydride (60% dispersion in mineral oil) were added and the mixture was stirred for 1 hour at room temperature under nitrogen atmosphere. After this period, 0.7 mmol of methyl iodide were added dropwise and then stirred overnight at room temperature. The reaction was quenched by addition of 300 mL of water and the resulting precipitate was filtered, washed with water and dried in vacuo over phosphorus pentoxide to afford the corresponding pyrido[2,3-*d*]pyrimidine as a brownish solid.

2-amino-6-(4-fluorophenyl)-8-methyl-4-(pyrrolidin-1-yl)-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one 48{*7,5,1*}

Starting from **14**{*7,5*}. 25% yield, white solid.

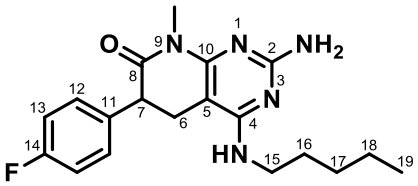
^{1}H NMR (400 MHz, DMSO-d_6): δ 10.15 (s, 1H, NH), 7.27 (dd, *J* = 8.7, 5.7 Hz, 2H, C12-CHx3), 7.14 (t, *J* = 8.9 Hz, 2H, C13-CHx3), 5.82 (s, 2H, NH_2), 3.77 (dd, *J* = 10.3, 6.6 Hz, 1H, C7-CH), 3.55 – 3.37 (m, 4H, C15-CH_2x2), 3.30 (s, 3H, NCH_3), 3.18 – 2.96 (m, 2H, C6-CH_2), 1.76 (dt, *J* = 13.3, 6.3 Hz, 4H, C15-CH_2x2).



2-amino-6-(4-fluorophenyl)-8-methyl-4-(pentylamino)-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (48{*7,6,1*})

Starting from **14**{*7,6*}. 74% yield, white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16 (dd, *J* = 8.7, 5.4 Hz, 2H, C12-CHx2), 6.98 (t, *J* = 8.7 Hz, 2H, C13-CHx2), 4.76 (s, 2H, NH_2), 3.85 – 3.77 (m, 1H, C7-CH) 3.42 – 3.39 (m, 2H,C15-CH_2), 3.35 (s, 3H, NCH_3), 2.77 – 2.59 (m, 2H, C6-CH_2), 1.57-1.53 (m, 2H, C16-CH_2), 1.38 – 1.26 (m, 4H, C17-CH_2, C18-CH_2), 0.89 (t, *J* = 6.8 Hz, 3H, C19-CH_3).



^{13}C NMR (100.6 MHz, $CDCl_3$): δ 171.13, 163.23, 161.06 (d, *J* = 64,6 Hz, C14), 160.78, 157.02, 134.60 (d, *J* = 3.2 Hz, C11), 129.53 (d, *J* = 8.0 Hz, C12), 115.49 (d, *J* = 21.3 Hz, C13), 86.34 (C5), 46.10 (C7), 41.20 (C15), 29.48 (C16), 29.09 (C17), 28.18 (N-CH_3), 25.25 (C6), 22.41 (C18), 13.99 (C19).

Anal. Calcd. (%) for $C_{19}H_{24}FN_5O$: C, 63.85; H, 6.77; F, 5.32; N, 19.59; O, 4.48. Found: C, 63.54; H, 6.63; N, 19.25.

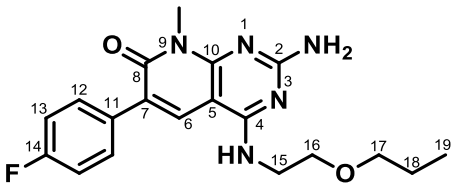
MS (70 eV, EI): m/z (%) = 257.2 (100) $[M]^+$, 342.2 (5) $[M\text{-}CH_3]^+$, 328.1 (11) $[M\text{-}C_2H_5]^+$, 314.1 (73) $[M\text{-}C_3H_7]^+$, 300.1 (75) $[M\text{-}C_4H_9]^+$, 286.1 (36) $[M\text{-}C_5H_{11}]^+$, 262.1 (25) $[M\text{-}C_6H_4F]^+$.

HRMS (70 eV, EI): m/z calculated for $C_{19}H_{24}N_5OF$: 375.1965, $[M]^+$, found: 375.1967.

IR (film), ν_{max} (cm^{-1}): 3388, 2956, 2930, 2958, 1674, 1608, 1580, 1511, 1463, 1120.

2-amino-6-(4-fluorophenyl)-8-methyl-4-((2-propoxyethyl)amino)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (49{*7,7,1*})

Starting from **16**{*7,7*}. 87% yield, white solid.



^1H NMR (400 MHz, $CDCl_3$): δ 7.58 (dd, *J* = 8.7, 5.6 Hz, 2H, C12-CHx2), 7.47 (s, 1H, C6-CH), 7.05 (t, *J* = 8.8 Hz, 2H, C13-CHx2), 5.81 (s, 1H, NH), 5.03 (s, 2H, NH_2), 3.72 (q, *J* = 5.1 Hz, 2H, C15-CH_2), 3.68 (s, 3H, NCH_3), 3.63 (t, *J* = 5.0 Hz, 2H, C16-CH_2), 3.44 (t, *J* = 6.7 Hz, 2H, C17-CH_2), 1.61 (dq, *J* = 14.2, 7.2 Hz, 2H, C18-CH_2), 0.93 (t, *J* = 7.4 Hz, 3H, C19-CH_3).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ 163.59, 162.00 (d, *J* = 162.0 Hz), 160.32, 155.98, 155.52, 133.21, 130.50 (d, *J* = 7.9 Hz, C12), 128.97 (C6), 124.01, 115.11 (d, *J* = 21.0 Hz, C13), 92.73 (C5), 73.04 (C17), 69.05 (C16), 41.06 (C15), 28.81 (NCH_3), 22.91 (C18), 10.71 (C19).

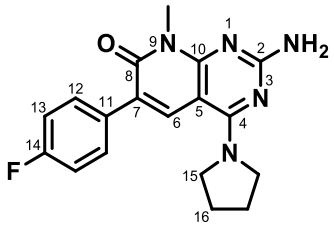
MS (70 eV, EI): m/z (%) = 371.2 (73) $[M]^+$, 312.1 (15) $[M-C_3H_7O]^+$, 298.1 (86) $[M-C_4H_9O]^+$, 285.1 (100) $[M-C_5H_{12}O]^+$, 158.0 (44) $[M-C_{12}H_{20}NFO]^+$.

HRMS (70 eV, EI): m/z calculated for $C_{19}H_{22}N_5O_2F$: 371.1758, $[M]^+$, found: 371.1755.

IR (film), ν_{max} (cm^{-1}): 3341, 3199, 2932, 2872, 1603, 1570, 1509, 1468, 1227, 1160, 837, 799.

2-amino-6-(4-fluorophenyl)-8-methyl-4-(pyrrolidin-1-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (49{*7,5,1*})

Starting from **16**{*7,5*}. 59% yield, white solid.



^1H NMR (400 MHz, $CDCl_3$): δ 8.01 (s, 1H, C7-CH), 7.61 (dd, *J* = 8.8, 5.4 Hz, 2H, C12-CHx2), 7.08 (t, *J* = 8.8 Hz, 2H, C13-CHx2), 4.89 (s, 2H, NH_2), 3.82 – 3.75 (m, 4H, C15-CH_2), 2.03 – 1.96 (m, 4H, C16-CH_2).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ 162.4, 162.1 (d, *J* =265.8 Hz, C14), 161.0, 160.9, 157.8, 133.8 (C11), 133.3 (C6), 130.4 (d, *J* = 7.8 Hz, C12), 122.2 (C7), 115.1 (d, *J* = 21.2 Hz, C13), 94.6 (C5), 51.0 (C15), 29.2 (CH_3), 25.8 (C16).

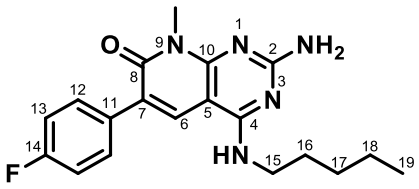
HRMS (70 eV, EI): m/z calculated for $C_{18}H_{18}N_5OF$: 339.1493, $[M]^+$, found: 339.1495.

IR (film), ν_{max} (cm^{-1}): 3508, 3345, 3233, 2964, 2868, 1638, 1590, 1564, 1524, 1504, 1443, 833, 795.

2-amino-6-(4-fluorophenyl)-8-methyl-4-(pentylamino)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (49{*7,6,1*})

Starting from **16**{*7,6*}. 89% yield, white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (s, 1H, C6-CH), 7.52 – 7.46 (m, 2H, C12-CHx2), 6.94 (t, *J* = 8.4 Hz, 2H, C13-CHx2), 5.64 (t, *J* = 5.4 Hz, 1H, NH), 5.09 (s, 2H, NH_2), 3.63 (s, 3H, CH_3), 3.53 – 3.41 (m, 2H, C15-CH_2), 1.65 – 1.58 (m, 2H, C16-CH_2), 1.40 – 1.29 (m, 4H, C17-CH_2, C18-CH_2), 0.90 (t, *J* = 7.2 Hz, 3H, CH_3).



^{13}C NMR (100.6 MHz, $CDCl_3$): δ 163.4, 162.9, 161.3 (d, *J* = 166.4 Hz, C14), 161.0, 155.8, 133.2 (d, *J* = 3.2 Hz, C11), 130.4 (d, *J* = 7.8 Hz, C12), 129.4 (C6), 123.4 (C7), 114.9 (d, *J* = 21.3 Hz, C13), 92.8 (C5), 41.4 (C15), 29.3, 29.3, 28.78 (N-CH_3), 22.5 (C18), 14.1 (C19).

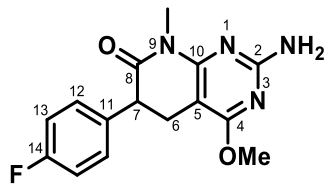
MS (70 eV, EI): m/z (%) = 355.2 (100) $[M]^+$, 312.1 (42) $[M\text{-}C_3H_7]^+$, 298.1 (61) $[M\text{-}C_4H_9]^+$, 285.1 (62) $[M\text{-}C_5H_{12}]^+$, 158.0 (40) $[M\text{-}C_{12}H_{20}FN]^+$.

IR (film), ν_{max} (cm^{-1}): 3345, 2930, 2858, 1603, 1567, 1508, 1466, 835, 799.

2-amino-6-(4-fluorophenyl)-4-methoxy-8-methyl-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (45{*7,1,1*})

Starting from **15**{*7,1*}. 50% yield, white solid.

^{1}H NMR (400 MHz, CD_3OD-d_4): δ 7.20 (dd, *J* = 8.7, 5.3 Hz, 2H, C12-2xCH), 7.02 (t, *J* = 8.8 Hz, 2H, C13-2xCH), 3.88 (s, 3H, NCH_3), 3.36 (s, 4H, C7-CH; OCH_3), 2.82 – 3.00 (m, 2H, C6-CH_2).



^{13}C NMR (100.6 MHz, CD_3OD-d_4): δ 174.1, 169.0, 164.6, 162.8, 160.3, 136.3 (d, *J* = 8.0 Hz, 2H, C12-CHx2), 130.8 (d, *J* = 8.0 Hz, 2H, C12-CHx2),116.2 (d, *J* = 21.5 Hz, 2H, C13-CHx2), 90.3 (C5), 54.2 (OCH_3), 47.4 (C7), 28.7 (NCH_3), 24.9 (C6).

MS (70 eV, EI): m/z (%) = 302.1 (100) $[M]^+$, 287.1 (11) $[M\text{-}CH_3]^+$, 207.1 (24) $[M\text{-}C_6H_4F]^+$, 179.1 (13) $[M\text{-}C_{10}H_{10}FNO]^+$.

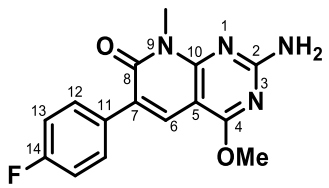
HRMS (70 eV, EI): m/z calculated for $C_{15}H_{15}N_4O_2F$:302.1174, $[M]^+$, found: 302.1179.

IR (film), ν_{max} (cm^{-1}): 3349, 2924, 1690, 1614, 1576, 1511, 1460, 1388, 1108.

2-amino-6-(4-fluorophenyl)-4-methoxy-8-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (50{*7,1,1*})

Starting from **16**{*7,1*}. 71% yield, white solid.

^1H NMR (400 MHz, $CDCl_3$): δ 7.88 (s, 1H, C7-CH), 7.65 (dd, *J* = 8.9, 5.5 Hz, 2H, C12-CHx2), 7.08 (t, *J* = 8.8 Hz, 2H, C13-CHx2), 4.03 (s, 3H, OCH_3), 3.71 (s, 3H, NCH_3).



^{13}C NMR (100.6 MHz, CDCl3) δ 167.85, 163.72, 163.13, 161.27, 156.81, 132.95 (C7), 130.61 (d, *J* = 7.9 Hz,C12-CHx2), 130.45 (C6), 125.64 (C11), 115.12 (d, *J* = 21.3 Hz,C13-CHx2), 94.75 (C5), 54.42 (OCH_3), 28.89 (NCH_3).

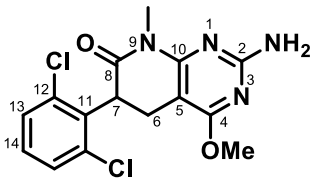
HRMS (70 eV, EI): m/z calculated for $C_{15}H_{13}N_4O_2F$: 300.1025, $[M]^+$, found: 300.1023.

IR (film), ν_{max} (cm^{-1}): 3494, 3338, 2926, 1608, 1587, 1510, 1468, 1390, 834, 796.

2-amino-6-(2,6-dichlorophenyl)-4-methoxy-8-methyl-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (45{*3,1,1*})

Starting from **15**{*3,1*}. 71% yield, white solid.

^1H NMR (400 MHz, DMSO-d_6): δ 7.51 (dd, *J* = 17.4, 8.1 Hz, 2H, C13-CHx2), 7.36 (t, *J* = 8.1, 1H, C14-CH), 6.58 (s, 2H, NH_2), 4.67 (t, *J* = 11.1 Hz, 1H, C7-CH), 3.83 (s, 3H, OCH_3), 3.27 (s, 3H, NCH_3), 2.89 – 2.82 (m, 2H, C6-CH_2).



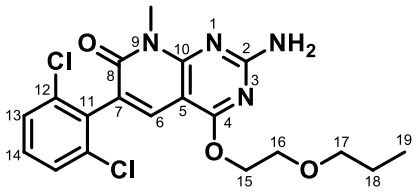
^{13}C NMR (100.6 MHz, DMSO-d_6): δ 169.00, 166.89, 161.51, 158.28, 135.55, 135.00, 134.69, 129.77, 129.74, 128.34, 86.50, 53.44, 43.31, 27.84 (NCH_3), 21.11 (C6).

HRMS (70 eV, EI): m/z calculated for $C_{15}H_{14}N_4O_2Cl_2$: 352.0494, $[M]^+$, found: 352.0493.

IR (film), ν_{max} (cm^{-1}): 3387, 3348, 2117, 1690, 1655, 1607, 1576, 1466, 1432, 1389, 1354, 1316, 1114, 1064, 1012, 776.

2-amino-6-(2,6-dichlorophenyl)-8-methyl-4-(2-propoxyethoxy)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (50{*3,6,1*})

Starting from **16**{*3,6*}. 26% yield, white solid.



^{1}H NMR (400 MHz, DMSO-d_6): δ 7.62 (s, 1H, C6-CH), 7.54 (d, *J* = 8.0 Hz, 2H, CH-C13x2), 7.42 (dd, *J* = 8.8, 7.3 Hz, 1H, CH-C14), 7.38 (s, 2H, NH_2), 4.53 – 4.45 (m, 2H, C15-CH_2), 3.77 – 3.68 (m, 2H, C16-CH_2), 3.59 (m, 2H, C17- CH_2), 3.55 (s, 3H, NCH_3), 1.46 (h, *J* = 7.1 Hz, 2H, C18-CH_2), 0.79 (t, *J* = 7.4 Hz, 3H, C19-CH_3).

^{13}C NMR (100.6 MHz, DMSO-d_6): δ 166.6, 162.4, 160.6, 157.2, 135.2, 134.8, 132.8 (C6), 130.4 (C14), 128.0 (C13), 120.6, 109.6, 92.0 (C5), 71.9 (C17), 67.9 (C16), 65.9 (C15), 28.2 (NCH_3), 22.4 (C18), 10.4 (C19).

Anal. Calcd. (%) for $C_{19}H_{20}Cl_2N_4O_3$: C, 53.91; H, 4.76; N, 13.24. Found: C, 53.97; H, 4.94; N, 12.93.

HRMS (ESI–TOF): m/z calculated for $C_{19}H_{21}Cl_2N_4O_3$: 223.0983, $[M+H]^+$, found: 423.0985.

IR (film), ν_{max} (cm $^{-1}$): 3336, 2960, 2872, 1658, 1585, 1464, 1429, 1338, 801.

2.9. Bibliography

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CONCLUSIONS

3.0 CONCLUSIONS

1. S'ha desenvolupat una estratègia sintètica per a la síntesi de 2-amino-6-aril-5,6-dihidropirido[2,3-*d*]pirimidin-4,7(3*H*,8*H*)-diones per reacció entre un ester α,β–insaturat amb la 2,6-diaminopirimidin-4(3*H*)-ona en metòxid sòdic en etilenglicol amb calefacció de microones amb rendiments elevats que permet la introducció de substituents arílics en la posició C6 de la piridopirimidina formada.

2. S'ha desenvolupat una estratègia sintètica per a la síntesi de 6-aril-2-metiltio-5,6-dihidropirido[2,3-*d*]pirimidina-4,7(3*H*,8*H*)-diona per reacció entre un ester α,β–insaturat amb la 6-amino-2-(metiltio)pirimidin-4(3*H*)-ona en carbonat potàssic en isopropanol amb calefacció de microones amb bons rendiments.

3. L'oxidació del grup metiltio a metilsulfonil amb àcid *m*-cloroperbenzoic permet la introducció de grups arilamino (o alquilamino) o alcoxi en la posició C2 de sistemes piridopirimidínics per substitució amb amines o alcohols. La transformació del grup 4-oxo en un grup benzotriazolil per reacció amb BOP ((Benzotriazol-1-iloxi)tris(dimetilamino)fosfoni hexafluorofosfat) permet la introducció de grups amino o alcoxi en la posició C4. D'aquesta forma es pot accedir, per primera vegada en 7-oxopirido[2,3-d]pirimidines, a sistemes disubstituïts en C2 i C4.

4. La deshidrogenació d'aquests sistemes en l'enllaç entre les posicions C5-C6 combinada amb la metilació del nitrogen lactàmic N8 permet la obtenció de pirido[2,3-*d*]pirimidines amb fins a quatre punts de diversitat, la qual cosa s'ha emprat per accedir a una quimioteca amplia d'aquests tipus de sistemes.

5. L'avaluació de l'activitat biològica dels compostos sintetitzats front el virus de l'Hepatitis C ha permès identificar una família de sistemes pirido[2,3-*d*]pirimidínics amb elevada activitat antiviral, d'entre els quals destaca la 2-(fenilamino)-6-(4-fluorofenil)pirido[2,3-*d*]pirimidin-4,7(3*H*,8*H*)-diona amb una EC_{50} = 23 nM i un índex de selectivitat de 389.

6. Aquests resultats permeten concloure que les pirido[2,3-*d*]pirimidines són un esquelet adequat per a l'obtenció d'activitat anti-VHC.

ANNEX

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FULL-LENGTH PAPER

A new and practical method for the synthesis of 6-aryl-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-diones

Marta Camarasa · Christian Barnils · Raimon Puig de la Bellacasa · Jordi Teixidó · José I. Borrell

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Abstract A one step general synthetic methodology for the synthesis of 6-aryl-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-diones (**17**{*x*} (G = NH_2) and **20**{*x*} (G=SMe)) is described. This methodology is based on reacting a 2-aryl-substituted acrylate (**16**{*x*}) with the corresponding 6-aminopyrimidin-4(3*H*)-one (**13** (G=NH_2); **19** (G=SMe)) in presence of a base under microwave irradiation. The resulting pyrido[2,3-*d*]pyrimidines present an aryl substituent at position C6, precisely the one directly related to the biological activity of such heterocycles. These protocols have been extended to other 2-alkyl-substituted and 3-alkyl (or aryl)-substituted acrylates but with lower yields.

Keywords Pyrido[2,3-*d*]pyrimidines · 2-Aryl acrylates · Michael addition · 4-Oxopyrido[2,3-*d*]pyrimidines · 6-Aminopyrimidine-4(3*H*)-ones

Introduction

Functionalized pyrido[2,3-*d*]pyrimidine derivatives comprise a privileged scaffold for pharmacologically active compounds with well-known activity as tyrosine kinase inhibitors [26]. The range of therapeutic applications of pyrido[2,3-*d*]pyrimidines continues to expand. In addition to being used as antitumor agents, pyrido[2,3-*d*]pyrimidines have been proposed for the treatment of bone disorders, autism, HCV replication, prevention of sudden cardiac death, etc. [4,6,14,22,24]. Despite continued interest in pyrido[2,3-*d*]pyrimidines as promising drug candidates, the methods for their preparation have several limitations.

Usually these kind of compounds are obtained through a multistep strategy in which the pyridine ring is constructed by condensation of a nitrile **2** (bearing the desired substituent R^1) onto a preformed pyrimidine aldehyde **3** bearing substituent R^5 and a methylthio group which can later be substituted by NH_2R^4 substituent using an amine **4** (Fig. 1).

In this context, our group has a broad experience in the synthesis of 5,6-dihydropyrido[2,3-*d*]pyrimidin-7-(8*H*)-ones (**10**; $R^3 = NH_2$) and (**11**; $R^3 = OH$) from α, β -unsaturated esters (**5**). Thus, in the so called *cyclic strategy* 2-methoxy-6-oxo-1,4,5,6-tetrahydropyridin-3-carbonitriles (**7**) are obtained by reaction of an α, β-unsaturated ester (**5**) and malononitrile (**6,** G = CN) in NaOMe/MeOH. Treatment of pyridones **7** with guanidine systems (**9**, R^4 = H, alkyl, aryl, heteroaryl) affords 4-amino-pyrido[2,3-*d*]pyrimidines (**10**, $R^3 = NH_2$). On the other hand, we described an *acyclic* variation of the above protocol for the synthesis of pyridopyrimidines (**10**, $R^3 = NH_2$) based on the isolation of the corresponding Michael adduct (**8**, G = CN) and later cyclization with a guanidine **9**. This approach also allowed us to obtain 4-oxopyrido[2,3-*d*]pyrimidines by treatment of intermediates (**8**, G = COOMe), synthesized by Michael addition of α, β-unsaturated esters (**5**) and methyl cyanoacetate (**6**, G = COOMe), with guanidine **9**. We have also described a multicomponent microwave-assisted cyclocondensation affording systems **10** and **11** via acyclic intermediates **8** (Scheme 1) [15,16,19].

These synthetic routes allow to obtain pyrido[2,3-*d*]pyrimidines quickly and effectively, but unfortunately they afford 4-oxo derivatives with low yields and several limitations regarding R^1, R^2, and R^4 substituents. 4-Oxo

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M. Camarasa · C. Barnils · R. Puig de la Bellacasa · J. Teixidó · J. I. Borrell (✉)
Grup d'Enginyeria Molecular, Institut Químic de Sarrià, Universitat Ramon Llull, Via Augusta, 390, 08017 Barcelona, Spain
e-mail: j.i.borrell@iqs.url.edu

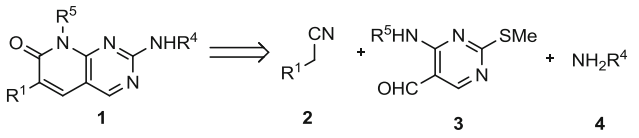


Fig. 1 Classical approach to pyrido[2,3-*d*]pyrimidines

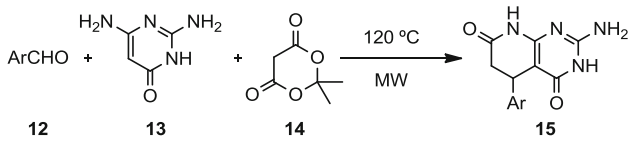


Fig. 2 Synthesis of 2-amino-5-aryl-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-diones (**15**) from Meldrum's acid (**14**)

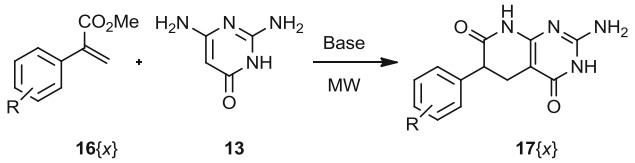


Fig. 3 Method for the synthesis of 2-amino-6-aryl-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-diones **17**{*x*} from 2-aryl acrylates **16**{*x*} and 2,6-diaminopyrimidin-4(3*H*)-one (**13**)

compounds are key intermediates in order to obtain more complex structures with a derivatized amino or alkoxy group in R^3. Such derivatization can be accomplished by nucleophilic substitution of a 4-chloro derivative, formed upon treatment with $POCl_3$ or $SOCl_2$ [17], or by formation of an activated intermediate using BOP or PyBOP [1,7,8,13,25].

In 2006, Tu et al. [23] described a multicomponent method for the preparation of 4-oxopyridopyrimidines (**15**) by coupling of an aromatic aldehyde (**12**), 2,6-diaminopyrimidine-4(3*H*)-one (**13**), and Meldrum's acid (**14**) at 120 °C under microwave irradiation (Fig. 2). More recently, Shi et al. [21] described a modification of such method in the presence of TEBAC in water at 90 °C for a few hours (Fig. 2).

This methodology allows to obtain the 2-amino-5-aryl-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-diones (**15**) in high yields but presents an important limitation: it is not possible to introduce a substituent at position C6 of the pyridine ring. As it is well known, most of the pyrido[2,3-*d*]pyrimidines described as kinase inhibitors present an aryl substituent at C6. Consequently, the development of a methodology for the synthesis of 2-amino-6-aryl-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-diones (**17**{*x*}) based on using a 2-aryl-substituted acrylates (**16**{*x*}) and the 2,6-diaminopyrimidin-4(3*H*)-one (**13**) acting as a Michael donor in presence of a base under microwave irradiation would be highly desirable (Fig. 3). The present paper deals with the results obtained in such study.

Results and discussion

As in the method of Shi et al., our approach to compounds **17**{*x*} (Fig. 3) starts from the commercially available 2,6-diaminopyrimidin-4(3*H*)-one (**13**). The 2-aryl acrylates (**16**{*x*}) were synthesized from the corresponding aryl acetate by condensation with paraformaldehyde in the presence of K_2CO_3 in DMF [9].

In an initial screening to find the optimal reaction conditions, we selected ethyl atropate (**16**{*1*}) as α, β-unsaturated ester. After some trials varying the solvent, temperature, reaction time, molar ratios, and different bases, we found that the treatment of a 1:1 mixture of **16**{*1*} and **13** with 1 equivalent of sodium methoxide in ethylene glycol at 180 °C for 3 h under microwave irradiation yielded the desired product **17**{*1*}, in 68 % yield. Consequently, we decided to extend such reaction conditions to the rest of 2-aryl acrylates (**16**{*1-10*}). As it is shown in Table 1, the reaction proceeded in all cases, the yields being in the range of 68–94 % and being favored by the presence of a substituent in the phenyl ring.

However, the methodology developed is limited to the presence of an amino group at position C2. In order to increase the diversity of substituents in such position, we considered the presence of a methylthio group as a leaving group to be substituted in further synthetic steps. In fact this is the strategy followed by other authors in the past [12].

For this purpose, we selected 4-amino-6-hydroxy-2-mercaptopyrimidine (**18**) and converted it to the methylthio derivative **19** upon treatment with methyl iodide in the presence of aqueous NaOH as base (Fig. 4) [5].

Scheme 1 Synthesis of pyrido[2,3-*d*]pyrimidines from α, β-unsaturated esters (**5**)

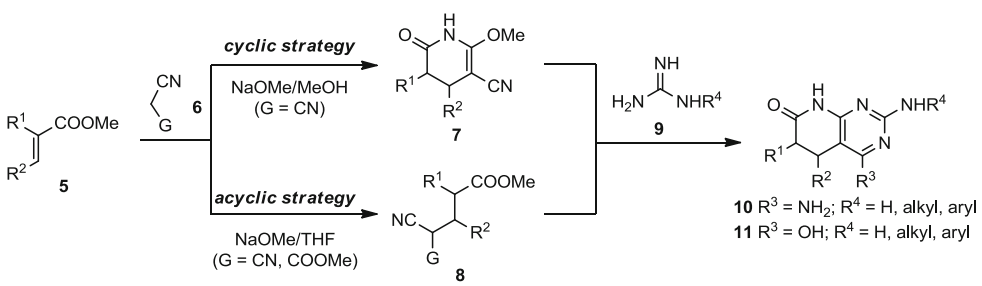
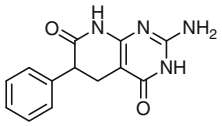
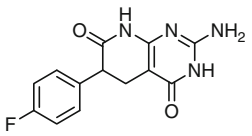
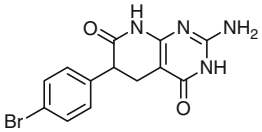
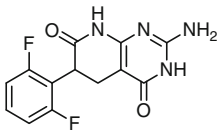
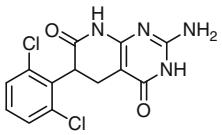
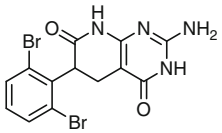
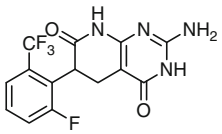
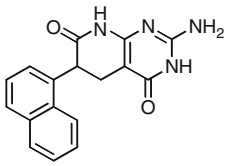
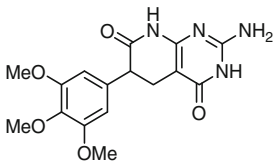
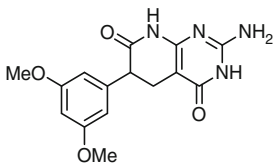


Table 1 Yields of pyrido[2,3-*d*]pyrimidines **17**{*x*}

Reagent	Compound **17**{*x*}	Yield (%)[a]
16{*1*}		**68**
16{*2*}		**75**(83[b])
16{*3*}		**71**
16{*4*}		**88**[b]
16{*5*}		**89**(94)[b]
16{*6*}		**75**
16{*7*}		**81**
16{*8*}		**93**[b]
16{*9*}		**71**[b]
16{*10*}		**75**[b]

[a] Reaction conditions: 1:1:1 ratio of **16**{*x*}:**13**:NaOMe in ethylene glycol at 180 °C for 3 h under microwave irradiation

[b] When we used 1.4 equivalent of compound **13** the yield was increased

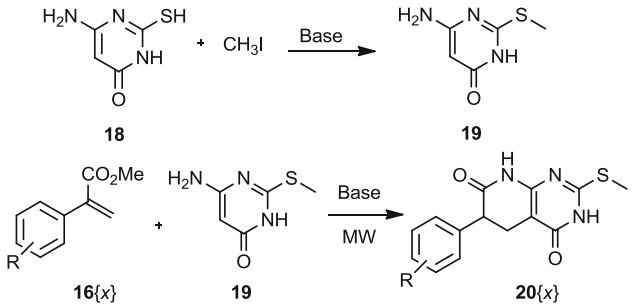


Fig. 4 Synthesis of 2-(methylthio)-6-aryl-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-diones (**20**{*x*}) from 6-amino-2-(methylthio)pyrimidin-4(3*H*)-one (**19**)

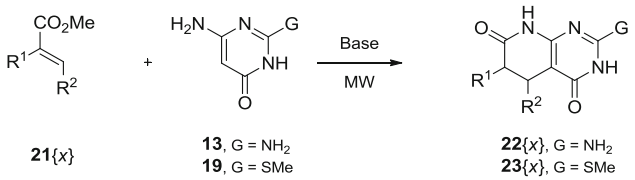


Fig. 5 Synthesis of 5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-diones (**22**{*x*} and **23**{*x*})

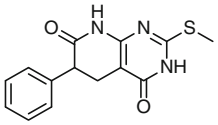
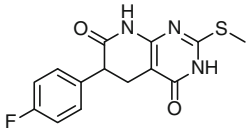
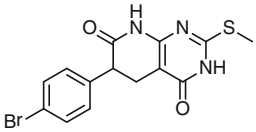
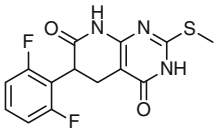
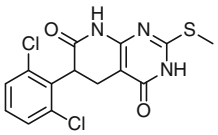
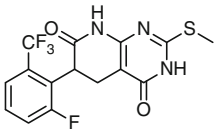
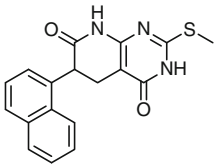
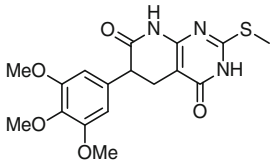
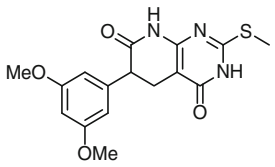
The subsequent treatment of **19** with the corresponding 2-aryl acrylate (**16**{*x*}) using K_2CO_3 as base in 2-propanol at 170 °C for 3 h under microwave irradiation allowed to obtain 2-methylthio-5-aryl-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-diones(**20**{*x*}) in 56–88 % yield (Table 2).

As it can be seen in Tables 1 and 2, we have developed a methodology capable of synthesizing 6-aryl-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-diones (**17**{*x*} and **20**{*x*}) in only one step from different 2-aryl-substituted acrylates (**16**{*x*}), which can present acceptor or donor groups in the aryl ring. Such methodology allows to introduce aryl substituents in position C6 of the resulting pyridopyrimidines, precisely the kind of substituents more relevant for biological activities of the resulting compounds.

Once accomplished our initial objective, we decided to extend this methodology to 2-alkyl-substituted acrylates (**21**{*x*}, R^1 = alkyl, R^2 = H) and 3-alkyl (or aryl)-substituted acrylates (**21**{*x*}, R^1 = H, R^2 = alkyl or aryl). So we selected methyl methacrylate (**21**{*1*}), methyl 2-benzylacrylate (**21**{*2*}), methyl crotonate (**21**{*3*}), and methyl cinnamate (**21**{*4*}) as model compounds and we tested the same reactions conditions used for the 2-aryl-substituted acrylates. The results obtained are summarized in Table 3 (Fig. 5).

As it can be seen in Table 3, when the reaction was carried out using 2-alkyl or 3-alkyl (or aryl)-substituted acrylates **21**{*x*}, the corresponding 2-amino-4-oxopyridopyrimidines (**22**{*x*}) were obtained in all cases although the yields were in general lower than those obtained from 2-aryl-substituted acrylates **16**{*x*}. On the other hand, the synthesis of

Table 2 Yields of 2-methylthio-substituted pyrido[2,3-*d*]pyrimidines **20**{*x*}

Reagent	Compound **20**{*x*}	Yield (%)[a]
16{*1*}		**56**
16{*2*}		**63**
16{*3*}		**74**[b]
16{*4*}		**80**[b]
16{*5*}		**88**
16{*7*}		**62**
16{*8*}		**83**[b]
16{*9*}		**48**[b]
16{*10*}		**76**[b]

[a] Reaction conditions: 1:1:1 ratio of **16**{*x*}:**19**:K_2CO_3 in 2-propanol at 170 °C for 3 h under microwave irradiation

[b] When we used 1.4 equivalent of compound **19** the yield was increased

2-methylthio-4-oxo-substituted derivatives **23**{*x*}, was only achieved in the case of methyl 2-benzylacrylate (**21**{*2*}). Consequently, the protocol developed allows the synthesis of 6-aryl-substituted pyridopyrimidines **17**{*x*} and **20**{*x*} in good yields but is only partially useful for the synthesis of 6-alkyl and 5-alkyl (or aryl)-substituted pyridopyrimidines **22**{*x*} and **23**{*x*} (Fig. 5).

Conclusions

In summary, we have developed a protocol for the synthesis of 6-aryl-substituted 5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*, 8*H*)-diones (**17**{*x*} (G = NH_2) and **20**{*x*} (G = SMe)) with up to three diversity centers (C2, C4, N8) easily amenable to combinatorialization. Such protocol reduces the number of steps usually necessary for the construction of the pyrido[2,3-*d*]pyrimidine skeleton with respect to the classical approaches (6 steps) with a higher overall yield. To the best of our knowledge, this is the first example of a Michael addition between 6-aminopyrimidine-4(3*H*)-ones and α, β-unsaturated esters.

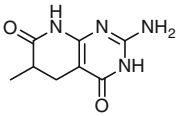
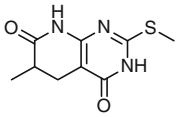
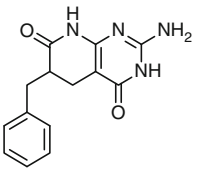
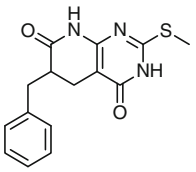
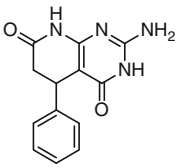
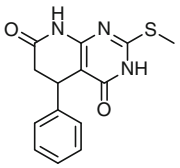
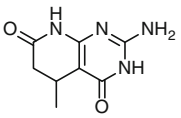
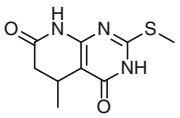
An application of such methodology to the production of pyrido[2,3-*d*]pyrimidine libraries is currently underway.

Experimental

General

The ^{1}H and ^{13}C NMR spectra were recorded on a Varian 400-MR spectrometer (^{1}HNMR at 400 MHz and ^{13}C NMR at 100.6 MHz). All ^{1}HNMR and ^{13}CNMR spectra were measured in $CDCl_3$ or DMSO-d_6 with the solvent resonance as the internal standard (7.26 and 77.16 for $CDCl_3$; 2.50 and 39.52 for DMSO-d_6). Chemical shifts are expressed in part per million (ppm) on the δ scale and coupling constants (J) are reported in Hertz (Hz). Spectral splitting patterns are designed as a: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), ddd (doublet of doublet of doublets), and m (complex multiplet). Infrared spectra (IR) were recorded in a Nicolet iS10 spectrophotometer, values are reported in wave numbers (cm^{-1}). The notation used is KBr (potassium bromide plates) and film (evaporated film from chloroform or DMSO). High resolution mass spectrometry (HRMS) was conducted on a VG AutoSpec (Micromass Instruments) Trisector EBE of high resolution spectrometer operating in FAB or EI mode and on Biotoff II (Bruker) apparatus in ESI–TOF mode. Melting points (mp) were recorded on a Büchi-Tottoli 530 capillary apparatus. Elemental Microanalyses were obtained in a Eurovector EA3011. All microwave irradiation experiments were carried out in an Initiator^{TM} (Biotage) microwave apparatus, operating at a frequency of 2.45 GHz with continuous irradiation power from 0 to 400 W. Reactions were carried out in 2.5 or 20 mL glass tubes, always are sealed

Table 3 Yields of C5, C6-substituted pyrido[2,3-*d*]pyrimidines **22**{*x*} and **23**{*x*}

Reagent	Compound **22**{*x*}	Yield (%)[a]	Compound **23**{*x*}	Yield (%)[b]
21{*1*}		**49**[c]		**0**
21{*2*}		**78**[c]		**20**[c]
21{*3*}		**22**[c]		**0**
21{*4*}		**30**[c]		**0**

[a] Reaction conditions: 1:1:1 ratio of **16**{*x*}:**13**:NaOMe in ethylene glycol at 180 °C for 3 h under microwave

[b] Reaction conditions: 1:1:1 ratio of **16**{*x*}:**19**:K_2CO_3 in 2-propanol at 170 °C for 3 h under microwave irradiation

[c] When we used 1.4 equivalent of compound **13** or **19** the yield was increased

with aluminum/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 to 50 °C by air jet cooling. Solvent and general reagents for organic synthesis were reagent-grade and were used without further purification (Sigma-Aldrich). 2,6-Diaminopyrimidin-4(3*H*)-one (**13**), 4-amino-6-hydroxy-2-mercaptopyrimidine (**18**), methyl 2-phenylacetate, methyl 2-(4-fluorophenyl)acetate, and methyl 2-(2,6-chlorophenyl) acetate are also commercially available (Sigma-Aldrich, Acros Organics). Unless otherwise noted, materials obtained from commercial suppliers were used without further purification.

General procedure for the synthesis of 2-aryl acrylates (**16**{*x*})

*General procedure for the synthesis of alkyl 2-arylacrylates (**16**{x}) starting from alkyl 2-arylacetates*

The corresponding alkyl 2-arylacetate (29.70 mmol) is dissolved in DMF (120 mL) and paraformaldehyde (3.480 g, 38.63 mmol) and potassium carbonate (4.110 g, 29.74 mmol) were added. The reaction temperature is kept at 100 °C during 3 h. The reaction mixture is quenched with water and extracted with diethyl ether (3 × 60 mL). The combined extracts were washed with a solution of lithium chloride (3 × 60 mL) and the solvent was dried over anhydrous $MgSO_4$, filtered and removed under reduced pressure to afford the corresponding alkyl 2-arylacrylate **16**{*x*} which was used without further purification.

*Ethyl 2-phenylacrylate (**16**{1})* As above using methyl phenylacetate as starting material. Colorless liquid (69 % yield). Spectral data are consistent to those previously described [9,10].

*Methyl 2-(4-fluorophenyl)acrylate (**16**{2})* As above using methyl 2-(4-fluorophenyl)acetate as starting material. Colorless liquid (52 % yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39(dd, J = 8.9, 5.4 Hz, 2H), 7.04 (t, J = 8.8 Hz, 2H), 6.36 (d, J = 1.1 Hz, 1H), 5.87 (d, J = 1.1 Hz, 1H), 3.82 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 167.0, 162.7 (d, J = 246 Hz), 140.2, 132.7 (d, J = 3.1 Hz), 130.1 (d, J = 8.2 Hz), 126.9, 115.5 (d, J = 21.3 Hz), 52.2; HRMS (70 eV, EI): *m/z* calculated for $C_{10}H_9FO_2$: 180.0587, $[M]^+$. Found: 180.0587; IR (dry film), ν_{max}(cm^{-1}): 1725, 1603, 1511, 1224, 1163, 1087.

*Methyl 2-(4-dibromophenyl)acrylate (**16**{3})* As above using methyl 2-(*4-dibromophenyl*)acetate as starting material. Colorless liquid (36 % yield). Spectral data are consistent to those previously described [18].

*Methyl 2-(2,6-difluorophenyl)acrylate (**16**{4})* 2-(2,6-Difluorophenyl)acetic acid (1.000 g, 5.81 mmol) was dissolved in a solution of HCl/MeOH 1.25 M (9.3 mL, 11.63 mmol). Na_2SO_4 (1.650 g) was added and the mixture was stirred overnight at room temperature. The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure to afford the corresponding methyl 2-(2,6-

difluorophenyl)acetate (842 mg, 4.53 mmol) as a colorless liquid (77 % yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28–7.20 (m, 1H), 6.94–6.86 (m, 2H), 3.72 (s, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 170.3, 161.7 (d, $J = 248.6$ Hz), 161.6 (d, $J = 248.6$ Hz), 129.1 (t, $J = 129.1$ Hz), 111.2 (dd, $J = 19.0, 6.5$ Hz), 110.7 (d, $J = 20.0$ Hz), 52.5, 27.9 (t, $J = 3.2$ Hz); Anal. Calcd. (%) for $C_9H_8F_2O_2$: C, 58.07; H, 4.33. Found: C, 57.85; H, 4.53; IR (film), ν_{max} (cm $^{-1}$): 3004, 2956, 2847, 1746, 1629, 1595, 1471, 1271, 1217, 1169, 1021, 786. Methyl 2-(2,6-difluorophenyl)acrylate (**16**{*4*}) was synthesized starting from 2-(2,6-difluorophenyl)acetate as described above. Colorless liquid (57 % yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33–7.25 (m, 1H), 6.96–6.88 (m, 2H), 6.74 (m, 1H), 5.96 (m, 1H), 3.79 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): 165.9, 160.5 (d, $J = 249.6$ Hz), 160.4 (d, $J = 249.6$ Hz), 132.6 (t, $J = 1.4$ Hz), 129.9 (t, $J = 10.3$ Hz), 129.5, 114.6 (t, $J = 19.6$ Hz), 111.4 (dd, $J = 6.6, 19.6$ Hz), 52.6; HRMS (70 eV, EI): *m/z* calculated for $C_{10}H_8F_2O_2$: 198.0492, $[M]^+$. Found: 198.0490; IR (film), ν_{max} (cm $^{-1}$): 3002, 2955, 1730, 1637, 1588, 1467, 1235, 1209, 1004, 790.

*Methyl 2-(2,6-dichlorophenyl)acrylate (***16***{5})* As above using methyl 2-(2,6-dichlorophenyl)acetate as starting material. Colorless liquid (94 % yield). Spectral data are consistent to those previously described [3].

*Methyl 2-(2,6-dibromophenyl)acrylate (***16***{6})* Concd. sulfuric acid (6.8 mL, 127.96 mmol) was added dropwise to a stirred solution of 2,6-dibromophenylacetonitrile [11] (3.113 g, 11.32 mmol) in anhydrous MeOH (19 mL) at 0 °C. The mixture was then refluxed for 2 h. After cooling, water (100 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined extracts were washed with brine (2 × 60 mL), dried ($MgSO_4$) and the solvent removed under reduced pressure to afford the corresponding methyl 2,6-dibromophenylacetate (3.444 g, 11.18 mmol) as a colorless liquid (99 % yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, $J = 8.0$ Hz, 2H), 7.01 (t, $J = 8.0$ Hz, 2H), 4.12 (s, 2H), 3.73 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ. 169.8, 134.2, 132.1, 129.8, 126.1, 52.3, 42.3; Anal. Calcd. (%) for $C_9H_8Br_2O_2$: C, 35.10; H, 2.62. Found: C, 35.45; H, 2.62; LRMS (70 eV, EI): *m/z* 307.7 $[M]^+$, 290.7, 276.7, 246.7, 229.1, 183.8, 167.8, 147.9, 132.9, 116.8, 89.1; IR (film), ν_{max}(cm^{-1}): 2998, 2951, 2844, 1743, 1579, 1555, 1433, 1337, 1215, 1169, 927, 773, 713. Methyl 2-(2,6-dibromophenyl)acrylate (**16**{*6*}) was synthesized starting from 2-(2,6-dibromophenyl)acetate as described above. Colorless liquid quantitative yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, $J = 8.1$ Hz, 2H), 7.09–7.03 (m, 1H), 6.75 (d, $J = 0.9$ Hz, 1H), 5.79 (d, $J = 0.9$ Hz, 1H), 3.78 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 165.1, 140.2, 138.7, 131.7, 131.6, 130.2, 124.3, 52.5; Anal. Calcd. (%) for $C_{10}H_8Br_2O_2$: C, 37.54; H, 2.52. Found: C, 37.91; H, 2.60; LRMS (70 eV, EI): *m/z* 318.8 $[M+H]^+$, 260.8, 238.8, 129.0; IR (film), ν_{max} (cm^{-1}): 2997, 2951, 1728, 1629, 1548, 1425, 1301, 1211, 1115, 993, 962, 775, 735.

*Methyl 2-(2-fluoro-6-(trifluoromethyl)phenyl)acrylate (***16***{7})* 2-(2-Fluoro-6-(trifluoromethyl)phenyl)acetic acid (5.000 g, 22.06 mmol) was dissolved in a solution of HCl/MeOH 1.25 M (38.5 mL, 44.12 mmol). 6.3 g of Na_2SO_4 (44.12 mmol) were added and the mixture was stirred overnight at room temperature. The reaction crude was neutralized with NaOH/H_2O 1 M and extracted with dichlorome thane (3 × 100 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure to afford the corresponding methyl 2-(2-fluoro-6-(trifluoromethyl)phenyl)acetate (4.833 g, 20.47 mmol) as a colorless liquid (93 % yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (s, $J = 7.8$ Hz, 1H), 7.44–7.36 (m, 1H), 7.29 (t, $J = 8.8$ Hz, 1H), 3.88 (s, 2H), 3.72 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 170.0, 161.8 (d, $J = 248.1$ Hz), 130.9 (m), 129.1 (m), 123.5 (m), 121.7 (m), 120.6 (dd, $J = 18.6, 1.6$ Hz), 119.1 (dd, $J = 23.1, 1.1$ Hz), 52.3, 30.8 (m); HRMS (70 eV, EI): *m/z* calculated for $C_{10}H_8F_4O_2$: 236.0460, $[M]^+$. Found: 236.0461; IR (film), ν_{max} (cm $^{-1}$): 3005, 2958, 2845, 1749, 1591, 1471, 1438, 1322, 1255, 1217, 1171, 1125, 960, 802, 730. Methyl 2-(2-fluoro-6-(trifluoromethyl)phenyl)acrylate (**16**{*7*}) was synthesized starting from 2-(2-fluoro-6-(trifluoromethyl)acetate as described above. Colorless liquid (95 % yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52–7.42 (m, 2H), 7.32–7.26 (m, 1H), 6.78 (d, $J = 0.9$ Hz, 1H), 5.85 (d, $J = 0.9$ Hz, 1H), 3.76 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 165.3, 160.2 (d, $J = 247.6$ Hz), 132.1 (d, $J = 1.1$ Hz), 132.0, 130.9 (qd, $J = 30.7, 3.1$ Hz), 129.8 (q, $J = 8.8$ Hz), 124.1 (dq, $J = 20.4, 1.9$ Hz), 123.2 (qd, $J = 274.1, 3.5$ Hz), 121.6 (m), 118.9 (dd, $J = 22.8, 0.9$ Hz), 52.4; Anal. Calcd. (%) for $C_{11}H_8F_4O_2$: C, 53.24; H, 3.25. Found: C, 52.88; H, 3.00; IR (film), ν_{max}(cm^{-1}): 3004, 2957, 2846, 1731, 1635, 1582, 1469, 1440, 1321, 1254, 1212, 1169, 1127, 993, 970, 909, 807, 755, 734.

*Methyl 2-(naphthalen-1-yl)acrylate (***16***{8})* As above using methyl 2-(naphthalen-1-yl)acetate as starting material. Colorless liquid (88 % yield). Spectral data are consistent to those previously described [18].

*Methyl 2-(3,4,5-trimethoxyphenyl)acrylate (***16***{9})* 2-(3,4,5-Trimethoxyphenyl)acetic acid (1.000 g, 4.42 mmol) was dissolved in a solution of HCl/MeOH 1.25 M (7.1 mL, 8.84 mmol). Na_2SO_4 (1.256 g) was added and the mixture was stirred overnight at room temperature. The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure to afford the corresponding methyl

2-(3,4,5-trimethoxyphenyl acetate (902 mg, 3.75 mmol) as a colorless liquid (84 % yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.50 (s, 2H), 3.86 (s, 6H), 3.83 (s, 3H), 3.71 (s, 3H), 3.56 (s, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 172.0, 153.2, 137.1, 129.5, 106.3, 60.8, 56.1, 52.1, 41.4; IR (film), ν_{max} (cm^{-1}): 2994, 2947, 2840, 1738, 1591, 1508, 1461, 1424, 1320, 1242, 1127, 1009. Methyl 2-(3,4,5-trimethoxyphenyl)acrylate (**16**{*9*}) was synthesized starting from 2-(3,4,5-trimethoxyphenyl)acetate as described above. Colorless liquid (40 % yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.65 (s, 2H), 6.33 (d, J = 1.2 Hz, 1H), 5.89 (d, J = 1.2 Hz, 1H), 3.87 (s, 6H), 3.86 (s, 3H), 3.84 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): 167.3, 153.0, 141.2, 138.4, 132.3, 126.6, 105.9, 61.0, 56.3, 52.4; Anal. Calcd. (%) for $C_{13}H_{16}O_5$: C, 61.90; H, 6.39. Found: C, 61.88; H, 6.26; IR (film), ν_{max} (cm^{-1}): 3531, 2997, 2949, 2838, 1723, 1582, 1508, 1414, 1290, 1242, 1158, 1128, 1007.

*Methyl 2-(3,5-dimethoxyphenyl)acrylate (***16***{10})* 2-(*3,5-Dimethoxyphenyl*)acetic acid (2.000 g, 10.19 mmol) was dissolved in a solution of HCl/MeOH 1.25 M (16.3 mL, 20.39 mmol). Na_2SO_4 (2.897 g) was added and the mixture was stirred overnight at room temperature. The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure to afford the corresponding methyl 2-(3,5-dimethoxyphenyl) acetate (2.142 mg, 10.18 mmol) as a colorless liquid (quantitative yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.43 (d, J = 2.3 Hz, 2H), 6.37 (t, J = 2.3 Hz, 1H), 3.78 (s, 6H), 3.69 (s, 3H), 3.56 (s, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 171.9, 161.0, 136.1, 107.4, 99.3, 55.4, 52.2, 41.6; Anal. Calcd. (%) for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71. Found: C, 63.25; H, 7.05; IR (film), ν_{max} (cm^{-1}): 3001, 2953, 2840, 1739, 1598, 1463, 1432, 1206, 1153, 1066. Methyl 2-(3,5-dimethoxyphenyl)acrylate (**16**{*10*}) was synthesized starting from 2-(3,5-dimethoxyphenyl)acetate as described above. Colorless liquid (55 % yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.56 (d, J = 2.4 Hz, 2H), 6.46 (t, J = 2.2 Hz, 1H), 6.34 (d, J = 1.2Hz, 1H), 5.89 (d, J = 1.3 Hz, 1H), 3.82 (s, 3H), 3.80 (s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 167.11, 160.41, 141.24, 138.59, 127.05, 106.61, 100.32, 55.39, 52.24; Anal. Calcd. (%) for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.51; H, 6.41; IR (film), ν_{max} (cm^{-1}): 3527, 302, 2839, 1724, 1593, 1457, 1425, 1280, 1205, 1157, 1051, 838.

Synthesis of 2-amino-6-aryl-5,6-dihydropyirdo[2,3-*d*]pyrimidine-4,7(3*H*, 8*H*)-diones (**17**{*x*})

General procedure for the synthesis of pyridopyrimidines **17***{x}*

The corresponding 2-aryl acrylate **16**{*x*} was dissolved in anhydrous ethylene glycol (20 mL), 2,6-diaminopyrimidin-4(3*H*)-one (**13**) (757 mg, 6.00 mmol) and sodium methoxide (320 mg, 6.00 mmol) were added into the solution. The mixture was heated under microwave irradiation at 180 °C for 3 h. Water was added and the reaction crude was neutralized with a 2 M HCl. The solid was collected by filtration and washed with water, MeOH, and Et_2O to afford the corresponding pyridio[2,3-*d*]pyrimidine **17**{*x*}.

*2-Amino-6-phenyl-5,6-dihydropyrido[2,3-d]pyrimidine-4,7 (3H,8H)-dione (***17***{1})*. As above using ethyl 2-phenylacrylate (**16**{*1*}) and 2,6-diaminopyrimidin-4(3*H*)-one (**13**) as starting materials. White solid (68 % yield). Spectral data are consistent to those previously described [2].

*2-Amino-6-(4-fluorophenyl)-5,6-dihydropyrido[2,3-d]pyrimidine-4,7(3H,8H)-dione (***17***{2})* As above using methyl 2-(4-fluorophenyl)acrylate (**16**{*2*}) and 2,6-diaminopyrimidin-4(3*H*)-one (**13**) as starting materials. White solid (83 % yield); mp >280 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.72 (s, 1H), 10.19 (s, 1H), 7.29–7.23 (m, 2H), 7.17–7.11 (m, 2H), 6.54 (s, 2H), 3.78 (dd, J = 9.6, 7.0 Hz, 1H), 2.78 (dd, J = 15.8, 7.0 Hz, 1H), 2.65 (dd, J = 15.8, 9.7 Hz, 1H); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ172.6, 162.8, 161.9, 160.4, 155.5 (d, J = 138.4 Hz), 135.5 (d, J = 3.0 Hz), 130.0 (d, J = 8.0 Hz), 115.0 (d, J = 21.0 Hz), 88.4, 45.7, 25.0; HRMS (ESI–TOF): *m/z* calculated for $C_{13}H_{11}FN_4O_2$: 275.0934, $[M+H]^+$. Found: 275.0939; IR (KBr), ν_{max} (cm^{-1}): 3324, 3186, 2904, 1637, 1595, 1514, 1384, 1231, 837.

*2-Amino-6-(4-bromophenyl)-5,6-dihydropyrido[2,3-d] pyrimidine-4,7(3H,8H)-dione (***17***{3})* As above using methyl 2-(4-bromophenyl)acrylate (**16**{*3*}) and 2,6-diaminopyrimidin-4(3*H*)-one (**13**) as starting materials. White solid (71 % yield); mp >280 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.59 (s, 1H), 10.19 (s, 1H), 7.51 (d, J = 8.4 Hz, 2H), 7.19 (d, J = 8.4 Hz, 2H), 6.48 (s, 2H), 3.77 (dd, J = 9.8, 6.9 Hz, 1H), 2.78 (dd, J = 15.8, 7.0 Hz, 1H), 2.69–2.61 (m, 1H); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 171.9, 161.4, 156.2, 154.8, 138.8, 131.2, 130.4, 120.0, 88.0, 45.5, 24.4; HRMS (70 eV, EI): *m/z* calculated for $C_{13}H_{11}BrN_4O_2$: 334.0065, $[M]^+$. Found: 334.0063; IR (KBr), ν_{max} (cm^{-1}): 3469, 3184, 2904, 1647, 1592, 1488, 826.

*2-Amino-6-(2,6-difluorophenyl)-5,6-dihydropyrido[2,3-d]pyrimidine-4,7(3H,8H)-dione (***17***{4})* As above using methyl 2-(2,6-difluorophenyl)acrylate (**16**{*4*}) and 2,6-diaminopyrimidin-4(3*H*)-one (**13**) as starting materials. White solid (88 % yield); mp >280 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.61 (s, 1H), 10.25 (s, 1H), 7.40 (m, 1H), 7.11 (t, J = 8.6 Hz, 2H), 6.51 (s, 2H), 4.10 (dd, J = 14.1, 7.6 Hz, 1H), 2.82 (dd, J = 15.4, 7.7 Hz, 1H), 2.55–2.48 (m, 1H); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 170.2, 161.2, 160.8 (d, J = 246.6 Hz), 160.7 (d, J = 246.6 Hz), 156.2, 154.9,

129.5 (t, J = 11.0 Hz), 115.3 (t, J = 18.7 Hz), 111.7 (dd, J = 22.4, 3.2 Hz), 87.7, 36.6, 23.3; Anal. Calcd. (%) for $C_{13}H_{10}F_2N_4O_2$: C, 53.43; H, 3.45; N, 19.17. Found: C, 53.03; H, 3.26; N, 19.30; HRMS (70 eV, EI): *m/z* calculated for $C_{13}H_{10}N_4O_2F_2$: 292.0772, $[M]^+$. Found: 292.0772; IR (KBr), $\nu_{max}(cm^{-1})$: 3469, 3166, 2859, 2740, 1695, 1653, 1596, 1470, 1272, 1207, 1008, 782.

*2-Amino-6-(2,6-dichlorophenyl)-5,6-dihydropyrido[2,3-d]pyrimidine-4,7(3H,8H)-dione (***17***{5})* As above using methyl 2-(2,6-dichlorophenyl)acrylate (**16**{*5*}) and 2,6-diaminopyrimidin-4(3*H*)-one (**13**) as starting materials. White solid (94 % yield); mp >280 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.65 (s, 1H), 10.23 (s, 1H), 7.51 (ddd, J = 16.6, 8.1, 1.3 Hz, 2H), 7.36 (t, J = 8.0, 1H), 6.53 (s, 2H), 4.53 (dd, J = 13.4, 8.9 Hz, 1H), 2.87–2.59 (m, 2H); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 170.2, 161.5, 155.8, 155.0, 135.4, 135.2, 134.7, 129.8, 129.7, 128.3, 86.9, 43.3, 22.4; Anal. Calcd. (%) for $C_{13}H_{10}Cl_2N_4O_2$: C, 48.02; H, 3.10; N, 17.23. Found: C, 48.01; H, 3.29; N, 16.97; HRMS (70 eV, EI): *m/z* calculated for $C_{13}H_{10}N_4O_2Cl_2$: 324.0183, $[M]^+$. Found: 324.0181; IR (KBr), $\nu_{max}(cm^{-1})$: 3282, 3193, 2904, 1649, 1597, 1537, 1375, 1283, 770.

*2-Amino-6-(2, 6-dibromophenyl)-5, 6-dihydropyrido[2, 3-d]pyrimidine-4,7(3H,8H)-dione (***17***{6})* As above using methyl 2-(2,6-dibromophenyl)acrylate (**16**{*6*}) and 2,6-diaminopyrimidin-4(3*H*)-one (**13**) as starting materials. White solid (75 % yield); ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.66 (s, 1H), 10.23 (s, 1H), 7.73–7.67 (m, 2H), 7.18 (t, J = 8.0 Hz, 1H), 6.54 (s, 2H), 4.55 (dd, J = 13.5, 9.0 Hz, 1H), 2.84–2.69(m, 2H); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 169.8, 161.5, 155.8, 154.9, 138.0, 133.9, 132.2, 130.5, 126.3, 124.2, 86.6, 48.0, 22.7; HRMS (70 eV, EI): *m/z* calculated for $C_{13}H_{10}N_4O_2Br_2$: 411.9170, $[M]^+$. Found: 411.9184; IR (KBr), $\nu_{max}(cm^{-1})$: 3338, 3169,2914, 1622, 1550, 1536, 1372, 1285, 823, 772.

*2-Amino-6-(2-fluoro-6-(trifluoromethyl)phenyl)-5,6-dihydropyrido[2,3-d]pyrimidine-4,7(3H,8H)-dione (***17***{7})* As above using methyl 2-(2-fluoro-6-(trifluoromethyl)phenyl) acrylate (**16**{*7*}) and 2,6-diaminopyrimidin-4(3*H*)-one (**13**) as starting materials. White solid (81 % yield); mp >280 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.68 (s, 1H), 10.35 (s, 1H), 7.63–7.56 (m, 3H), 6.55 (s, 2H), 3.94 (dd, J = 13.8, 7.6 Hz, 1H), 2.86 (dd, J = 16.5, 7.8 Hz, 1H), 2.58–2.52 (m, 1H); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 170.0, 161.3, 161.1 (d, J = 245.9 Hz), 156.1, 155.0, 129.9 (d, J = 9.7 Hz), 129.6 (qd, J = 29.6, 5.6 Hz), 126.1 (d, J = 15.7 Hz), 123.7 (qd, J = 274.0, 1.26 Hz), 121.8 (m), 120.6 (d, J = 22.9 Hz) 87.5, 40.9, 23.9; Anal. Calcd. (%) for $C_{14}H_{10}F_4N_4O_2$: C, 48.84; H, 3.51; N, 16.24. Found: C, 49.02; H, 3.09; N, 16.14; HRMS (70 eV, EI): *m/z* calculated for $C_{13}H_{10}N_4O_2F_4$: 342.0733, $[M]^+$. Found: 342.0740; IR (KBr), $\nu_{max}(cm^{-1})$: 3478, 3322, 3171, 2907, 2748, 1651, 1596, 1538, 1469, 1321, 1123, 796.

*2-Amino-6-(naphthalen-1-yl)-5,6-dihydropyrido[2,3-d]pyrimidine-4,7(3H,8H)-dione (***17***{8})* As above using methyl 2-(naphthalene-1-yl)acrylate (**16**{*8*}) and 2,6-diaminopyrimidin-4(3*H*)-one (**13**) as starting materials. White solid (93 % yield); mp >280 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.57 (s, 1H), 10.30 (s, 1H), 8.07 (d, J = 7.8 Hz, 1H), 7.94 (d, J = 7.4, 1H), 7.84 (d, J = 8.4 Hz, 1H), 7.58–7.49 (m, 2H), 7.45 (t, J = 7.5 Hz, 1H), 7.33 (d, J = 7.1 Hz, 1H), 6.49 (s, 2H), 4.56 (t, J = 8.5 Hz, 1H), 2.96–2.71 (m, 2H); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 172.37, 161.55, 156.19, 154.82, 135.93, 133.66, 131.01, 128.8, 127.5, 126.1, 125.6, 125.44, 125.1, 124.0, 88.04, 42.78, 24.78; HRMS (70 eV, EI): *m/z* calculated for $C_{17}H_{14}N_4O_2$: 306.1117, $[M]^+$. Found: 306.1116; IR (KBr), $\nu_{max}(cm^{-1})$: 3465, 3190, 2851, 2740, 1696, 1651, 1594, 1537, 1403, 1207, 755.

*2-Amino-6-(3,4,5-trimethoxyphenyl)-5,6-dihydropyrido[2,3-d]pyrimidine-4,7(3H,8H)-dione (***17***{9})* As above using methyl 2-(*3,4,5-trimethoxyphenyl*)acrylate (**16**{*9*}) and 2,6-diaminopyrimidin-4(3*H*)-one (**13**) as starting materials. White solid (71 % yield); mp >280 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.61 (s, 1H), 10.19 (s, 1H), 6.55 (s, 2H), 6.51 (s, 2H), 3.72 (s, 6H), 3.68 (dd, J = 9.3, 7.4 Hz, 1H), 3.64 (s, 3H), 2.82–2.67 (m, 2H); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 172.3, 161.4, 156.1, 154.8, 152.6, 136.4, 134.8, 105.6, 88.2, 59.9, 55.8, 46.2, 24.4; HRMS (70 eV, EI): *m/z* calculated for $C_{16}H_{18}N_4O_5$: 346.1277, $[M]^+$. Found: 346.1273; IR (KBr), $\nu_{max}(cm^{-1})$: 3579, 3340, 3176, 2939, 1638, 1593, 1512, 1337, 1241, 1127.

*2-Amino-6-(3, 5-dimethoxyphenyl)-5, 6-dihydropyrido[2, 3-d]pyrimidine-4,7(3H,8H)-dione (***17***{10})* As above using methyl 2-(*3,5-dimethoxyphenyl*)acrylate (**16**{*10*}) and 2,6-diaminopyrimidin-4(3*H*)-one (**13**) as starting materials. White solid (75 % yield); mp >280 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.57 (s, 1H), 10.15 (s, 1H), 6.47 (s, 2H), 6.38 (s, 3H), 3.70 (s, 6H), 3.67 (dd, J = 8.4, 7.1 Hz, 1H), 2.80–2.65 (m, 2H); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 172.2, 161.5, 160.3, 156.0, 154.8, 141.4, 106.3, 98.3, 88.0, 55.1, 46.0, 24.2; HRMS (70 eV, EI): *m/z* calculated for $C_{15}H_{16}N_4O_4$: 316.1172, $[M]^+$. Found: 316.1171; IR (KBr), $\nu_{max}(cm^{-1})$: 3331, 3164, 2902, 1596, 1463, 1206, 1155, 1062.

Synthesis of 2-(methylthio)-6-aryl-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-diones (**20**{*x*})

*Synthesis of 6-amino-2-(methylthio)pyrimidin-4(3H)-one (**19**)*

Iodomethane (2.78 mL, 44.66 mmol) was added dropwise into a solution of 4-amino-6-hydroxy-2-mercaptopyrimidine monohydrate (6.00 g, 37.22 mmol) in 1 M NaOH (67 mL). The reaction mixture was kept under stirring at 50 °C for 4 h and then was left overnight at room temperature. Next, the mixture was neutralized with acetic acid, obtaining a solid that was collected by filtration, washed with diethyl ether and dried to afford the desired compound **19** with in a 88 % yield as a white solid. Spectral data are consistent to those previously described [5].

*General procedure for the synthesis of pyridopyrimidines **20**{x} from 6-amino-2-(methylthio)pyrimidin-4(3H)-one (**19**)*

The corresponding 2-aryl acrylate **16**{*x*} was dissolved in 2-propanol (2 mL), 6-amino-2-(methylthio)pyrimidin-4(3*H*)-one (**19**) (63.0 mg, 0.40 mmol), and potassium carbonate (55.4 mg, 0.40 mmol) were added into the solution. The mixture was heated under microwave irradiation at 170 °C for 3 h. Then, the solvent was removed under reduced pressure, water was added and the crude was neutralized with a 2 M HCl. The solid was collected by filtration and washed with water, and Et_2O to afford the corresponding pyrido[2,3-*d*]pyrimidine **20**{*x*} as a white solid.

*2-(Methylthio)-6-phenyl-5,6-dihydropyrido[2,3-d]pyrimidine-4,7(3H,8H)-dione (**20**{1})* As above using ethyl 2-phenylacrylate (**16**{*1*}) and 6-amino-2-(methylthio)pyrimidin-4-(3*H*)-one (**19**) as starting materials. White solid (56 % yield); mp >280 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.54 (s, 1H), 10.61 (s, 1H, NH), 7.32 (t, J = 6.9 Hz, 2H), 7.27–7.20 (m, 3H), 3.84 (dd, J = 8.8, 7.2 Hz, 1H), 2.93–2.76 (m, 2H), 2.43 (s, 3H); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 171.7, 162.8, 161.8, 154.4, 139.1, 128.4, 127.9, 126.9, 94.8, 45.4, 24.5, 12.7; HRMS (70 eV, EI): *m/z* calculated for $C_{14}H_{13}N_3O_2S$: 287.0730, $[M]^+$. Found: 287.0728; IR (KBr), ν_{max}(cm^{-1}): 3478, 3145, 3032, 2925, 1634, 1562, 1505, 1444, 1247, 968, 698, 554.

*6-(4-Fluorophenyl)-2-(methylthio)-5,6-dihydropyrido[2,3-d]pyrimidine-4,7(3H,8H)-dione (**20**{2})* As above using methyl 2-(4-fluorophenyl)acrylate (**16**{*2*}) and 6-amino-2-(methylthio)pyrimidin-4(3*H*)-one (**19**) as starting materials. White solid (63 % yield); mp >280 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.42 (s, 1H), 10.62 (s, 1H), 7.27 (dd, J = 8.8, 5.6 Hz, 2H), 7.15 (t, J = 8.8 Hz, 2H), 3.87 (dd, J = 9.7, 7.1 Hz, 1H), 2.94–2.72 (m, 2H), 2.49 (s, 3H); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 171.7, 161.9, 161.8, 161.2 (d, J = 243.0 Hz), 154.2, 135.1 (d, J = 3.1 Hz), 130.0 (d, J = 8.1 Hz), 115.1 (d, J = 21.3), 95.1, 44.7, 24.5, 12.7; HRMS (70 eV, EI): *m/z* calculated for $C_{14}H_{12}N_3O_2FS$: 305.0635, $[M]^+$. Found: 305.0634; IR (KBr), ν_{max}(cm^{-1}): 3476, 3145, 3038, 2926, 1633, 1555, 1512, 1235.

*6-(4-Bromophenyl)-2-(methylthio)-5,6-dihydropyrido[2,3-d]pyrimidine-4,7(3H,8H)-dione (**20**{3})* As above using methyl 2-phenylacrylate (**16**{*3*}) and 6-amino-2-(methylthiopyrimidin-4(3*H*)-one (**19**) as starting materials. White solid (74 % yield); mp >280 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.49 (s, 1H), 10.65 (s, 1H), 7.52 (d, J = 8.4 Hz, 2H), 7.20 (d, J = 8.5 Hz, 2H), 3.86 (dd, J = 10.0, 7.1 Hz, 1H), 2.91–2.73 (m, 2H), 2.49 (s, 3H); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 171.4, 163.7, 161.7, 154.4, 138.4, 131.2, 130.4, 120.2, 94.9, 44.9, 24.3, 12.7; HRMS (70 eV, EI): *m/z* calculated for $C_{14}H_{12}N_3O_2SBr$: 364.9834, $[M]^+$. Found: 364.9835; IR (KBr), ν_{max}(cm^{-1}): 3476, 3342, 3144, 3031, 2925, 1634, 1557, 1490, 1444, 1245.

*6-(2,6-Difluorophenyl)-2-(methylthio)-5,6-dihydropyrido[2,3-d]pyrimidine-4,7(3H,8H)-dione (**20**{4})* As above using methyl 2-(2,6-difluorophenyl)acrylate (**16**{*4*}) and 6-amino-2-(methylthio)pyrimidin-4(3*H*)-one (**19**) as starting materials. White solid (80 % yield); mp >280 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.58 (s, 1H), 10.70 (s, 1H), 7.42 (m, 1H), 7.12 (t, J = 8.6 Hz, 2H), 4.24 (dd, J = 14.1, 7.7 Hz, 1H), 2.92 (dd, J = 16.1, 7.8 Hz, 1H), 2.68–2.56 (m, 1H), 2.50 (s, 3H); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 169.8, 161.5, 160.8 (d, J = 246.7 Hz), 160.7 (d, J = 246.9 Hz), 156.4, 154.5, 129.7 (t, J = 10.5 Hz), 115.0 (t, J = 18.6 Hz), 111.7 (dd, J = 3.2, 22.4 Hz), 94.8, 35.9, 23.2, 12.7; Anal. Calcd. (%) for $C_{14}H_{11}F_2N_3O_2S$: C, 52.01; H, 3.43; N, 13.00; S, 9.92. Found: C, 51.97; H, 3.50; N, 12.99; S, 9.69; HRMS (70 eV, EI): *m/z* calculated for $C_{14}H_{11}N_3O_2F_2S$: 323.0540, $[M]^+$. Found: 323.0541; IR (KBr), ν_{max}(cm^{-1}): 3406, 3046, 2934, 1697, 1640, 1607, 1562, 1508, 1470, 1272, 1237, 1010, 780.

*6-(2,6-Dichlorophenyl)-2-(methylthio)-5,6-dihydropyrido[2,3-d]pyrimidine-4,7(3H,8H)-dione (**20**{5})* As above using methyl 2-(2,6-dichlorophenyl)acrylate (**16**{*5*}) and 6-amino-2-(methylthio)pyrimidin-4(3*H*)-one (**19**) as starting materials. White solid (88 % yield); mp >280 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.55 (s, 1H), 10.64 (s, 1H), 7.52 (dd, J = 14.6, 8.1 Hz, 2H), 7.37 (t, J = 8.0 Hz, 1H), 4.65 (dd, J = 13.4, 9.1 Hz, 1H), 2.94–2.71 (m, 2H), 2.50 (s, 3H); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 169.4, 161.9, 153.9, 135.1, 135.1, 134.6, 129.7, 129.6, 128.2, 93.8, 42.7, 22.4, 12.6. Anal. Calcd. (%) for $C_{14}H_{11}Cl_2N_3O_2S$: C, 47.20; H, 3.11; N, 11.80; S, 9.00. Found: C, 47.44; H,

3.21; N, 11.54; S, 8.89. HRMS (70 eV, EI): *m/z* calculated for $C_{14}H_{11}N_3O_2Cl_2S$: 354.9955, $[M]^+$. Found: 354.9949. IR (KBr): $\nu(cm^{-1})$: 3389, 2875, 1630, 1592, 1468, 1437, 1315, 1277, 1232, 1197, 770.

*6-(2-Fluoro-6-(trifluoromethyl)phenyl)-2-(methylthio)-5,6-dihydropyrido[2,3-d]pyrimidine-4,7 (3H,8H)-dione (***20***{7})* As above using methyl 2-(2-fluoro-6-(trifluoromethyl) phenyl)acrylate (**16**{*7*}) and 6-amino-2-(methylthio)pyr imidin-4(3*H*)-one (**19**) as starting materials. White solid (62 % yield); mp >280 °C (decomp.); ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.63 (s, 1H), 10.75 (s, 1H), 7.65–7.58 (m, 3H), 4.08 (dd, J = 14.0, 8.0 Hz, 1H), 2.93 (m, 2H), 2.51 (s, 3H); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 169.5, 161.4, 161.1 (d, J = 246.3 Hz), 154.2, 130.1 (d, J = 9, 5 Hz), 129.6 (qd, J = 29.7, 4.15 Hz), 125.8 (d, J = 16.0 Hz), 123.6 (q, J = 272 Hz), 121.8, 120.7 (d, J = 22.1 Hz), 94.5, 40.0, 23.9, 12.8; Anal. Calcd. (%) for $C_{15}H_{11}F_4N_3O_2S$: C, 48.26; H, 2.97; N, 11.26; S, 8.59. Found: C, 48.65; H, 2.65; N, 11.46; S, 8.21; HRMS (70 eV, EI): *m/z* calculated for $C_{15}H_{11}N_3O_2F_4S$: 373.0504, $[M]^+$. Found: 373.0508; IR (KBr), $\nu_{max}(cm^{-1})$: 3406, 3276, 2937, 2863, 1710, 1637, 1550, 1468, 1320, 1268, 1227, 1165, 1118.

*2-(Methylthio)-6-(naphthalen-1-yl)-5,6-dihydropyrido[2,3-d]pyrimidine-4,7 (3H,8H)-dione (***20***{8})* As above using methyl 2-(*naphthalen-1-yl*)acrylate (**16**{*8*}) and 6-amino-2-(methylthio)pyrimidin-4(3*H*)-one (**19**) as starting materials. White solid (83 % yield); mp >280 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.55 (s, 1H), 10.76 (s, 1H), 8.08 (m, 1H), 7.95 (m, 1H), 7.85 (d, J = 8.1 Hz, 1H), 7.58–7.50 (m, 2H), 7.49–7.43 (t, 1H), 7.35 (d, J = 6.3 Hz, 1H), 4.67 (dd, J = 9.5, 7.7 Hz, 1H), 3.02 (dd, J = 16.5, 7.7 Hz, 1H), 2.94–2.85 (m, 1H), 2.53 (s, 3H); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 172.3, 168.2, 162.4, 154.9, 136.0, 134.1, 131.4, 129.3, 128.1, 126.6, 126.1, 125.9, 125.5, 124.3, 95.6, 42.6, 25.2, 13.2; HRMS (70 eV, EI): *m/z* calculated for $C_{18}H_{15}N_3O_2S$: 337.0885, $[M]^+$. Found: 337.0887; IR (KBr), $\nu_{max}(cm^{-1})$: 3411, 3045, 2859, 1696, 1632, 1553, 1500, 1455, 1228, 769.

*2-(Methylthio)-6-(3,4,5-trimethoxyphenyl)-5,6-dihydropyrido[2,3-d]pyrimidine-4,7 (3H,8H)-dione (***20***{9})* As above using methyl 2-(3,4,5-trimethoxyphenyl)acrylate (**16**{9}) and 6-amino-2-(methylthio)pyrimidin-4(3*H*)-one (**19**) as starting materials. White solid (48 % yield); mp >280 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.54 (s, 1H), 10.57 (s, 1H), 6.56 (s, 2H), 3.78 (m, 1H), 3.72 (s, 6H), 3.64 (s, 3H), 2.86 (d, J = 8.7 Hz, 2H), 2.49 (s, 3H); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 171.7, 161.4, 154.1, 152.7, 149.8, 136.4, 134.3, 105.6, 95.3, 59.9, 55.8, 45.6, 24.3, 12.7; HRMS (70 eV, EI): *m/z* calculated for $C_{17}H_{19}N_3O_5S$: 377.1045, $[M]^+$. Found: 377.1046; IR (KBr), $\nu_{max}(cm^{-1})$: 3409, 3046, 2929, 1696, 1633, 1551, 1500, 1457, 1232, 770.

*2-(Methylthio)-6-(3,5-dimethoxyphenyl)-5,6-dihydropyrido[2,3-d]pyrimidine-4,7 (3H,8H)-dione (***20***{10})* As above using methyl 2-(3,5-dimethoxyphenyl)acrylate (**16**{10}) and 6-amino-2-(methylthio)pyrimidin-4(3*H*)-one (**19**) as starting materials. White solid (76 % yield); mp >280 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.54 (s, 1H), 10.59 (s, 1H), 6.41–6.38 (m, 3H), 3.79–3.73 (m, 1H), 3.71 (s, 6H), 2.91–2.77 (m, 2H), 2.49 (s, 3H); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 171.5, 163.9, 161.8, 160.4, 154.6, 141.0, 106.2, 98.4, 95.0, 55.1, 45.4, 24.1, 12.7; HRMS (70 eV, EI): *m/z* calculated for $C_{16}H_{17}N_3O_4S$: 347.0940, $[M]^+$. Found: 347.0943; IR (KBr), $\nu_{max}(cm^{-1})$: 3406, 3036, 2932, 2836, 1635, 1599, 1500, 1459, 1430, 1154.

Synthesis of 2-amino-5,6-dihydropyirdo[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-diones (**22**{*x*})

General procedure for the synthesis of pyridopyrimidines **22***{x}*

*2-Amino-6-methyl-5,6-dihydropyrido[2,3-d]pyrimidine-4,7 (3H,8H)-dione (***22***{1})* As above using methyl methacrylate (**21**{*1*}) and 2,6-diaminopyrimidin-4(3*H*)-one (**13**) as starting materials. White solid (49 % yield). Spectral data are consistent to those previously described [15].

*2-Amino-6-benzyl-5,6-dihydropyrido[2,3-d]pyrimidine-4,7 (3H,8H)-dione (***22***{2})* Methyl 2-benzylacrylate (**21**{*2*}) was synthetized starting from 2-benzylacrylic acid as starting material. Colorless liquid (93 % yield). Spectral data are consistent to those previously described [20]. As above using methyl 2-benzylacrylate (**21**{*2*}) and 2,6-diaminopyrimidin-4(3*H*)-one (**13**) as starting materials. White solid (78 % yield); mp >280 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.51 (s, 1H), 10.01 (s, 1H), 7.33–7.26 (m, 2H), 7.24–7.18 (m, 3H), 6.44 (s, 2H), 3.19 (dd, J = 13.3, 4.0 Hz, 1H), 2.69–2.58 (m, 1H), 2.54–2.48 (m, 1H), 2.39 (dd, J = 15.8, 6.7 Hz, 1H), 2.04 (dd, J = 15.8, 11.2 Hz, 1H); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 173.5, 161.5, 156.1, 154.7, 139.3, 129.1, 128.28, 126.1, 87.9, 41.2, 35.1, 21.1; HRMS (70 eV, EI): *m/z* calculated for $C_{14}H_{14}N_4O_2$: 270.1117, $[M]^+$. Found: 270.1118; IR (KBr), $\nu_{max}(cm^{-1})$: 3322, 3167, 2904, 1651, 1536, 1485, 1376, 1290, 1212, 700.

*2-Amino-5-phenyl-5,6-dihydropyrido[2,3-d]pyrimidine-4,7 (3H,8H)-dione (***22***{3})* As above using methyl 3-phenyl acrylate (**21**{*3*}) and 2,6-diaminopyrimidin-4(3*H*)-one (**13**) as starting materials. White solid (22 % yield). Spectral data are consistent to those previously described [23].

*2-Amino-5-methyl-5,6-dihydropyrido[2,3-d]pyrimidine-4,7(3H,8H)-dione (**22**{4})* As above using methyl crotonate (**21**{*4*}) and 2,6-diaminopyrimidin-4(3*H*)-one (**13**) as starting materials. White solid (30 % yield). Spectral data are consistent to those previously described [15].

Synthesis of 2-(methylthio)-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-diones (**23**{*x*})

*6-Benzyl-2-(methylthio)-5,6-dihydropyrido[2,3-d]pyrimidine-4,7(3H,8H)-dione (**23**{2})*

As above using methyl 2-benzylacrylate (**21**{*2*}) and 6-amino-2-(methylthio)pyrimidin-4(3*H*)-one (**19**) as starting materials. White solid (20 % yield); mp >280 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.45 (s, 1H), 10.44 (s, 1H), 7.33–7.27 (m, 2H), 7.25–7.19 (m, 3H), 3.19 (dd, J = 13.5, 4.3 Hz, 1H), 2.77–2.64 (m, 1H), 2.59–2.52 (m, 1H), 2.47 (s, 3H), 2.47–2.40 (m, 1H), 2.17 (dd, J = 16.3, 11.2 Hz, 1H); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 172.9, 161.7, 156.3, 154.6, 139.1, 129.1, 128.3, 126.2, 81.2, 40.6, 35.1, 21.1, 12.7; Anal. Calcd. (%) for $C_{15}H_{15}N_3O_2S$: C, 59.78; H, 5.06; N, 13.94; S, 10.64. Found: C, 59.59; H, 5.08; N, 14.07; S, 10.17; HRMS (70 eV, EI): *m/z* calculated for $C_{15}H_{15}N_3O_2S$: 301.0885, $[M]^+$. Found: 301.0885; IR (KBr), ν_{max} (cm^{-1}): 3414, 3025, 2925, 1691, 1634, 1562, 1506, 1460, 1302, 1290, 1232.

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