Supplementary Information

Structure based design and synthesis of antiparasitic pyrrolopyrimidines targeting pteridine reductase 1


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Synthetic Chemistry

General

$^1$H and $^{13}$C NMR spectra were measured on a Bruker DPX- 400 MHz spectrometer with chemical shifts given in ppm ($\delta$ values), relative to proton and carbon traces in solvent. Coupling constants are reported in Hz. IR spectra were recorded on Shimadzu, IRAffinity-1 spectrometer. Elemental analysis was carried out on a Perkin Elmer 2400, analyser series 2. Accurate mass was measured using Thermo Exactive MS and a Thermo U3000 HPLC system. Ionisation is carried out by an ESI source (not heated). Anhydrous solvents were obtained from a Puresolv purification system, from Innovative Technologies, or purchased as such from Aldrich. Melting points were recorded on a Reichert hot-stage microscope, and are uncorrected. Chromatography was carried out using 200–400 mesh silica gels, or using reverse-phase HPLC on a Waters system using a C18 Luna column.

Declaration of Purity: All final compounds were equal or more than 95% pure by HPLC

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2-Amino-6-bromo-4-oxo-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (0.108 g, 0.43 mmol), 3-(methylsulfonylaminobenzene)boronic acid (0.140 g, 0.65 mmol), Pd(PPh_3)_4 (0.049 g, 0.042 mmol) in isopropanol:H_2O (3:1.5 mL) was degassed under nitrogen. t-Butylamine (0.18 mL, 1.71 mmol) was added and the reaction mixture was irradiated with microwaves at 160°C for 40 minutes. The resulting solution was washed with ethyl acetate, water and brine. Organics were filtered through a pad of Celite and concentrated under reduced
pressure. The resulting solid was triturated with hot methanol, acetone and ether to afford the title compound as a brown solid (15 mg, 10%). $^1$H NMR (DMSO-d$_6$): 3.10 (3H, s), 6.49 (2H, br, s), 7.23 (1H, m), 7.48 (2H, m), 7.63 (1H, s), 10.05 (1H, br, s), 10.84 (1H, br, s), 12.57 (1H, br, s). IR: 1316, 1422, 1563, 1581, 1624, 1756, 2220, 3177, 3322, 3338 cm$^{-1}$ HRESIMS: Found: 343.0621 Calculated for C$_{14}$H$_{10}$O$_3$N$_6$S 343.0619.

2-Amino-6-[3-(methylsulfonyl)phenyl]-4-oxo-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile 3b

2-Amino-6-bromo-4-oxo-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (0.105 g, 0.42 mmol), 3-(methylsulfonylbenzene)boronic acid (0.129 g, 0.64 mmol), Pd(PPh$_3$)$_4$ (0.041 g, 0.035 mmol) in isopropanol:H$_2$O (3:1.5 mL) was degassed under nitrogen. $t$-Butylamine (0.18 mL, 1.71 mmol) was added and the reaction mixture was irradiated with microwaves at 160 °C for 40 minutes. The resulting solution was washed with ethyl acetate, water and brine. Organics were filtered through a pad of Celite and concentrated under reduced pressure. The resulting solid was triturated with hot methanol, acetone and diethyl ether to afford the title compound as an off-white solid (74 mg, 55%) with no distinct melting point. $^1$H NMR (DMSO-d$_6$): 3.27 (3H, s), 6.76 (2H, br, s), 7.78 (1H, t, J = 7.4 Hz), 7.91 (1H, d, J = 7.5 Hz), 8.17 (1H, d), 8.37 (1H, s), 10.84 (2H, br, s). IR: 1316, 1422, 1563, 1581, 1624, 1756, 2220, 3177 cm$^{-1}$ HRESIMS: Found: 328.0513 Calculated for C$_{14}$H$_{10}$O$_3$N$_5$S 328.0509.

2-Amino-4-oxo-6-[(E)-2-phenylethenyl]-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile 3c

(E)-2-Phenylethenylboronic acid (93 mg, 0.630 mmol), 2-amino-6-bromo-4-oxo-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (80 mg, 0.315 mmol) and cesium carbonate (513 mg, 1.575 mmol) were suspended in isopropanol:water (2:1) (6 mL) to which (1,1'-bis(diphenylphosphino)ferrocene)-dichloropalladium(II) [Pd(dpdpf)Cl$_2$] (29 mg, 0.0395 mmol) was added. The reaction mixture was purged with nitrogen for 20 min then heated overnight at 100 °C [oil bath temperature] in a sealed tube. Silica gel was added to the reaction mixture and the solvents were removed under reduced pressure. The residue was partitioned between ethyl acetate and water and then the organic layer was collected and the solvent removed. The crude material was purified by HPLC. Fractions containing the required material were collected and freeze-dried to give the desired product as a yellow solid (20 mg, 23%), mp > 230 °C. $^1$H NMR (DMSO-d$_6$): 12.28 (1H, s), 10.73 (1H, s), 7.55 (2H, d, J = 7.4 Hz), 7.42-7.30 (4H, m), 6.99 (1H, d, J = 16.4 Hz), 6.50 (2H, br). IR (KBr): 2209, 1701, 1609, 1580, 1488, 1419, 1273, 1037, 954, 791, 753, 695 cm$^{-1}$ HRESIMS: Found: 278.1039 calculated for C$_{14}$H$_{11}$O$_3$N$_5$ 278.1036.

2,4-Diamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile 4

(a) 2-Chloro-3-oxopropanenitrile$^1$

While the temperature was maintained between 0 and 5 °C, methyl formate (4.45 mL, 4.317 g; 71.9 mmol) was added to a stirred mixture of sodium methoxide (3.600 g, 66.6 mmol) in toluene (100 mL, dry). This was followed by dropwise addition of chloroacetonitrile (4.2 mL, 5.011 g; 66.6 mmol) over a period of 1 h. The mixture was left stirring for an additional 3 h. Water (100 mL) was added, and the mixture was extracted with ethyl acetate (100 mL). The aqueous layer was cooled to 0 °C and acidified to pH 4 using concentrated hydrochloric acid. This was extracted with ethyl acetate (3 x 100 mL), and the combined organic layers was dried (Na$_2$SO$_4$)
and the solvent was removed under reduced pressure to give the crude product (2.620 g, 38%) as brown oil, which was used in the next step without further purification.

(b) **2,4-Diamino-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (4)**

Sodium acetate (3.10 g, 37.8 mmol, 3.3 eq.) was dissolved in water (40 mL) to which pyrimidine-2,4,6-triamine (1.427 g, 11.40 mmol) was added. The reaction mixture was heated to 100 °C for a few minutes. The solution became homogeneous. 2-Chloro-3-oxopropanenitrile (1.18 g, 14.2 mmol, 1.2 eq.) was dissolved in water (20 mL) then the aqueous solution was added to the reaction mixture. The reaction mixture was heated to 100 °C with stirring for 17 h. The reaction mixture was cooled to 0 °C and the brown precipitate was filtered, washed with water and acetone and dried to give (0.640 g, 32%) as dark brown solid. When the filtrate was left at room temperature overnight an additional amount (77 mg) was obtained as light brown solid (0.717 g, 36%) mp > 230 °C. ^1H NMR (DMSO-d_6): 11.79 (1H, br, NH, exchangeable), 7.69 (1H, s), 6.14 (2H, br, NH_2, exchangeable), 5.86 (2H, NH_2, exchangeable). IR (KBr): 2217, 1629, 1582, 1529, 1480, 1410, 1187, 1100, 831, 807, 790 cm.^{-1} HRESIMS: Found: 275.1040 calculated for C_{15}N_6H_9Cl.

**2,4-Diamino-6-(3-formylphenyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile 6a**

3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (172 mg, 0.74 mmol), 2,4-diamino-6-bromo-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile and cesium carbonate (619 mg, 1.9 mmol) were suspended in isopropanol:water (2:1) (6 mL) to which (1,1’-bis(diphenylphosphino)ferrocene)-dichloropalladium(II) [Pd(dppf)Cl_2] (27 mg, 0.037 mmol) was added. The reaction mixture was purged with nitrogen for 20 min then heated overnight at 100 °C [oil bath temperature] in a sealed tube. Solvents were removed under reduced pressure and the residue was applied to a silica gel column chromatography and eluted with [1] n-hexane [2] ethyl acetate [3] methanol:ethyl acetate [10%. The required product was obtained as a yellow solid (41 mg, 20%) with no distinct melting point. ^1H NMR (DMSO-d_6): 12.45 (1H, br), 10.09 (1H, s), 8.39 (1H, t, J = 1.6 Hz), 8.18 (1H, d, J = 7.7 Hz), 7.99 (1H, d, J = 7.7 Hz), 7.81 (1H, t, J = 7.7 Hz), 6.30 (2H, br), 6.07 (2H, br). IR (KBr): 3435, 2212, 1691, 1622, 1579 cm.

**2,4-Diamino-6-(phenylethynyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile 6c**

4,4,5,5-Tetramethyl-2-(phenylethynyl)-1,3,2-dioxaborolane [alternative name: 2-phenyl-1-ethynylboronic acid pinacol ester] (180 mg, 0.790 mmol, 2 mol eq), 2,4-diamino-6-bromo-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (100 mg, 0.395 mmol) and t-butylamine [145 mg, 1.975 mmol, 5 mol eq] Pd(dppf)Cl_2 (29 mg, 0.0395 mmol, 10% mol eq) in isopropanol:water (6 mL, 4:2). The reaction mixture was purged with N_2 for 20 min then heated overnight at 100 °C [oil bath temperature] in a sealed tube. The reaction mixture was filtered over cotton and the solvents were removed under reduced pressure. This material was purified by HPLC. Fractions containing the desired material were collected and freeze-dried to give required product as a pale yellow solid with no distinct melting point (20 mg, 22%). ^1H NMR (DMSO-d_6): 12.89 (1H, br), 7.60-6.89 (9H, m). IR: 2210, 1630, 1602, 1541, 1487, 1378, 1178, 1112, 1013, 786, 754 cm.^{-1} HRESIMS: Found: 275.1044 Calculated for: C_{17}H_{11}N_6.

**2,4-Diamino-6-[(E)-2-(4-methylphenyl)ethenyl]-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile 6d**

(E)-2-(4-Methylphenyl)ethenylboronic acid (130 mg, 0.790 mmol, 2 mol eq), 2,4-diamino-6-bromo-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (100 mg, 0.395 mmol) and t-butylamine [208
mg, 2.00 mmol, 5 mol eq.) Pd(dpdpf)Cl₂ (29 mg, 0.0395 mmol, 10% mol eq) in isopropanol:water (6 mL, 4:2). The reaction mixture was purged with N₂ for 20 min then heated in a microwave oven at 140 °C for 40 min. The reaction mixture was filtered over cotton and the solvents were removed under reduced pressure. The crude product was applied to a silica gel column chromatography using methanol:ethyl acetate 1:10 [Rᶠ = 0.5]. The required product was obtained as light brown solid (17 mg, 15%) with no distinct melting point. ¹H-NMR (DMSO-d₆): 12.08 (1H, s), 7.46 (2H, d, J = 8.1 Hz), 7.37 (1H, d, J = 16.4 Hz), 7.23 (2H, d, J = 8.1 Hz), 6.99 (1H, d, J = 16.4 Hz), 6.19 (2H, s, br), 5.99 (2H, s, br), 2.32 (3H, s). IR (KBr): 2209, 1705, 1610, 1582, 1490, 1416, 1273, 1040, 955, 793, 755, 693 cm⁻¹. HRESIMS: Found: 291.1349 Calculated for C₁₆H₁₅N₆ 279.1353.

2,4-Diamino-6-(2-phenylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-carbonitrile 6e

2,4-Diamino-6-[(E)-2-phenylethenyl]-7H-pyrrolo[2,3-d]pyrimidin-5-carbonitrile (24 mg, 86.9 mmol) was dissolved in methanol (25 mL), cooled to 0 °C. Pd:C-10% (20 mg) was added under N₂ with stirring. The reaction mixture was hydrogenated for 3 h at room temperature and atmospheric pressure. The catalyst was removed over Kieselguhr and the solvent was removed under reduced pressure. The crude material obtained was purified by HPLC. Fractions containing the required product were collected and freeze-dried to give the pure product as a white solid (9 mg, 26%) with no distinct melting point. ¹H-NMR (DMSO-d₆): 12.45 (1H, br, s), 7.43-7.29 (2H, br), 7.28-7.18 (5H, m), 7.17-6.98 (2H, br), 3.02-2.98 (4H, m). IR (KBr): 2209, 1700, 1610, 1582, 1493, 1416, 1270, 1040, 955, 793, 754, 696 cm⁻¹. HRESIMS: Found: 279.1349 Calculated for C₁₅H₁₅N₆ 279.1353.

4-(4-Thiomorpholinyl)-7H-pyrrolo[2,3-d]pyrimidin-2-amine 8b

A mixture of 4-chloro-7H-pyrrolo[2,3-d]pyrimidin-2-amine (100 mg, 0.593 mmol), thiomorpholine (109 mg, 1.06 mmol, 100 µL, d1.088) and triethylamine (63 mg, d0.726, 87 µL, 0.720 mmol) were dissolved in 1,4-dioxane (2 mL, dry). The reaction mixture was heated in a microwave reactor for 1 h at 200 °C. The reaction mixture was diluted with methanol then silica gel was added. Solvents and excess reagents were removed under reduced pressure. The residue was applied to a silica gel column and eluted with methanol:ethyl acetate (1:9), Rᶠ = 0.1. The required product was obtained as light brown solid (60 mg, 43%), mp > 230 °C. ¹H NMR (DMSO-d₆): 10.84 (1H, s), 6.75 (1H, q, J = 2.3 Hz), 6.28 (1H, q, J = 1.8 Hz), 5.51 (2H, s), 4.07 (4H, qt, J = 2.8 Hz), 2.64 (4H, qt, J = 2.8 Hz). IR (KBr): 1598, 1562, 1493, 1475, 1436, 1357, 1311, 1071, 952, 814, 787 cm⁻¹. HRESIMS: Found: 236.0964 Calculated for C₁₀H₁₄N₅S 236.0964.

N-(4-Chloro-5-cyano-7H-pyrrolo[2,3-d]pyrimidin-2-yl)pivalamide 9

Dimethylaniline (3.3 ml, 26.03 mmol), TEBACl (0.731 g, 3.2 mmol), and POCl₃ (5.5 ml, 60 mmol) were added to a stirred suspension of 2-amino-4-oxo-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (1.570 g, 6.09 mmol) at room temperature under nitrogen. The resultant suspension was heated to 90 °C for 1 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure to give brown oil. Ice was added to the resultant oil and the pH adjusted to 4 using 7N ammonia in methanol resulting in the precipitation of a brown solid. The resultant solid was filtered and washed with water and ether to give the required product as a brown solid (0.700 g, 41%), mp > 300 °C. ¹H NMR (DMSO-d₆): 1.24 (9H, s), 7.93 (1H, d, J = 2.5 Hz), 10.97 (1H, s), 12.57 (1H, s). IR: 1280, 1560, 1657,
N-(5-Cyano-4-methoxy-7H-pyrrolo[2,3-d]pyrimidin-2-yl)pivalamide 12a

(a) Sodium methoxide (95 mg, 3.6 mmol) was added to a stirred suspension of N-(4-chloro-5-cyano-7H-pyrrolo[2,3-d]pyrimidin-2-yl)pivalamide (0.100 g, 0.361 mmol) in methanol (10 mL, dry). The resultant solution was stirred at 80 °C for 48 h after which time the resultant off white solid was triturated with dilute HCl and filtered under reduced pressure and dried to give the required product as an off white solid (17 mg, 25%). IR (KBr): 1574, 1555, 1532, 1495, 1427, 1408, 1366, 1346, 1238, 1097, 961, 889, 793 cm⁻¹. HRESIMS: Found: 190.0723 Calculated for C₇H₁₅N₄O 189.0710.

(b) Potassium hydroxide (0.295 g, 5.25 mmol) was added to a stirred suspension of N-(4-chloro-5-cyano-7H-pyrrolo[2,3-d]pyrimidin-2-yl)pivalamide (0.100 g, 0.36 mmol) in methanol (5 ml, dry). The suspension was heated at 80 °C for 96 h after which time the resultant solid was triturated with HCl, filtered under reduced pressure and dried to give the required product as an off white solid (30 mg, 44%).

2-Amino-4-isopropoxy-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile 12b

Sodium (83 mg, 3.6 mmol) was added to a solution of isopropanol (7 mL, anhydrous) and stirred at room temperature under nitrogen for 2 h. The solution was heated until the solid and Na metal dissolved and N-(4-chloro-5-cyano-7H-pyrrolo[2,3-d]pyrimidin-2-yl)pivalamide (0.100 g, 0.36 mmol) was added. The reaction mixture was heated to 90 °C for 24 h and concentrated under reduced pressure to give a brown solid. The resultant solid was dry loaded onto silica and purified by flash column chromatography using 100% ethyl acetate to give the required product as a white solid (70 mg, 90%), mp > 300 °C. H NMR (DMSO-d₆): 1.34 (6H, d, J = 6.2 Hz), 5.39-5.45 (1H, m), 6.36 (2H, s), 7.78 (1H, s), 12.01 (1H, s). C NMR (DMSO-d₆): 22.3, 68.64, 83.05, 96.11, 116.40, 130.49, 155.36, 161.23, 162.55 IR: 1314, 1420, 1562, 1580, 1625, 1759, 2220, 3176, 3320, 3336 cm⁻¹. HRESIMS: Found: 218.1035 Calculated for C₁₀H₁₁N₅O 217.1010.

2-Amino-4-(cyclopentyloxy)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile 12c
To a solution of cyclopentanol (7 mL, anhydrous), was added sodium metal (83 mg, 0.36 mmol). The solution was heated to 30 °C under nitrogen until the solid had dissolved, N-(4-chloro-5-cyano-7H-pyrrolo[2,3-d]pyrimidin-2-yl)pivalamide (0.100 g, 0.36 mmol) was then added. The solution heated to 150 °C for 24 h and the solvent evaporated under reduced pressure to give an off white solid. The solid was dry loaded onto silica and purified by column chromatography using 0-10% methanol-ethyl acetate to give the required product as a white solid (53 mg, 59 %), mp > 300 °C. 1H NMR (DMSO-d6): 1.61-1.98 (9H, m), 5.55 (1H, m), 6.35 (2H, s), 7.75 (1H, s), 11.9 (1H, s). 13C NMR (DMSO-d6): 23.15, 32.36, 71.58, 77.54, 95.94, 115.81, 129.83, 154.78, 160.74, 162.10. IR: 1146, 1302, 1398, 1575, 1603, 2220, 3398, 3517 cm⁻¹ HRESIMS: Found 244.1101 Calculated for C6H13N3O 244.1100.

N4,N4-Dimethyl-2,4,6-pyrimidinetriamine 25

6-Chloro-2,4-pyrimidinediamine (2.000 g, 13.83 mmol) was dissolved in DMF (6 mL, dry). The reaction mixture was heated at 185 °C for 18 h. The excess of DMF was removed in vacuo and the residue was dissolved in hydrochloric acid (2N, 10 mL) then made alkaline with 5% aqueous ammonia. The solution was extracted with chloroform. The organic layer was collected, dried (Na2SO4) and the solvent removed under reduced pressure. Trituration with ethyl acetate gave the required product (1.020 g, 48%) as pale yellow solid, mp 190-194 °C. 1H NMR (DMSO-d6): 5.67 (2H, s), 5.50 (2H, s), 4.93 (1H, s), 2.88 (6H, s). IR (KBr): 1676, 1631, 1589, 1483, 1553, 1437, 1372, 840, 790, 695 cm⁻¹. C for 24 h. The excess of DMF was removed in vacuo. The solution was filtered, washed with small amount of ethyl acetate and dried to give the required product as light pink microcrystalline solid (2.50 g, 96%), mp 188-190 °C. 1H NMR (DMSO-d6): 9.72 (1H, s), 7.38 (2H, d, J = 8.1 Hz), 7.06 (2H, d, J = 8.1 Hz), 5.97 (2H, s), 5.85 (2H, s), 5.42 (1H, dd, J = 8.0 Hz & J = 12.7 Hz), 5.27 (1H, dd, J = 8.0 Hz & J = 12.7 Hz), 4.54 (1H, t, J = 7.6 Hz), 2.25 (3H, s). IR (KBr): 1676, 1631, 1589, 1483, 1533, 1437, 1372, 840, 790, 695 cm⁻¹. HRESIMS: Found: 154.1087 Calculated for C6H12N5 154.1087.

2,6-Diamino-5-[1-(4-methylphenyl)-2-nitroethyl]-4(3H)-pyrimidinone 26a

2,6-Diamino-3H-pyrimidin-4-one (1.16 g, 9.20 mmol) and 1-methyl-4-[(E)-2-nitroethenyl]benzene (1.71 g, 10.5 mmol) were suspended in a mixture of (20 mL) of water and (20 mL) of ethyl acetate at room temperature. The resulting mixture was heated for 18 h at 50 °C. The reaction mixture was left to cool to room temperature and solid material was formed; this was filtered, washed with small amount of ethyl acetate and dried to give the required product as light pink microcrystalline solid (2.50 g, 96%), mp 188-190 °C. 1H NMR (DMSO-d6): 9.72 (1H, s), 7.38 (2H, d, J = 8.1 Hz), 7.06 (2H, d, J = 8.1 Hz), 5.97 (2H, s), 5.85 (2H, s), 5.42 (1H, dd, J = 8.0 Hz & J = 12.7 Hz), 5.27 (1H, dd, J = 8.0 Hz & J = 12.7 Hz), 4.54 (1H, t, J = 7.6 Hz), 2.25 (3H, s). IR (KBr): 1676, 1631, 1589, 1483, 1533, 1437, 1372, 840, 790, 695 cm⁻¹. HRESIMS: Found: 290.1243 calculated for C13H18O3N5 290.1248.

2,6-Diamino-5-[1-(4-fluorophenyl)-2-nitroethyl]-4(3H)-pyrimidinone 26b

2,6-Diamino-3H-pyrimidin-4-one (1.16 g, 9.20 mmol) and 1-fluoro-4-[(E)-2-nitroethenyl]benzene (1.75 g, 10.5 mmol) were suspended in a mixture of water (20 mL) and ethyl acetate (20 mL) at room temperature. The resulting mixture was heated for 18 h at 5 °C. The reaction mixture was left to cool to room temperature but no solid material was formed; the mixture was extracted with ethyl acetate, dried (Na2SO4), filtered and the solvent removed under reduced pressure to give a crude product (3.0 g, 100%) of product as light pink solid. Purification by column chromatography [1:9 methanol:ethyl acetate] afforded the pure material as white microcrystalline solid (2.22g, 82%), mp 110-115 °C. 1H NMR (DMSO-d6): 9.82 (1H, s), 7.57-7.54 (2H, m), 7.09 (2H, d, J = 6.7 Hz & J = 9.0 Hz), 6.14 (2H, s), 5.07 (2H, s), 5.45 (1H, dd, J = 8.0 Hz & J = 12.7 Hz), 5.27 (1H, dd, J = 8.0 Hz & J = 12.7 Hz), 4.54 (1H, t, J = 7.6 Hz). IR
(KBr): 1622, 1547, 1436, 1375, 1342, 1226, 1161, 832, 787 cm.\textsuperscript{1} HRESIMS: Found: 294.0992 calculated for C\textsubscript{12}H\textsubscript{13}O\textsubscript{3}N\textsubscript{3}F 294.0997.

**2,6-Diamino-5-(2-nitro-1-phenylethyl)-4(3H)-pyrimidinone 26c**

2,6-Diamino-3H-pyrimidin-4-one (1.16g, 9.20 mmol) and [(E)-2-nitroethenyl]benzene (1.56g, 10.5 mmol) were suspended in a mixture of water (20 mL) and ethyl acetate (20 mL) at room temperature. The resulting mixture was heated in a sealed tube at 50 °C overnight. The resulting mixture was stirred for 2 h, then poured into water (20 mL) and extracted with dichloromethane (25 mL). The organic layer was separated, dried (Na\textsubscript{2}SO\textsubscript{4}), filtered and the solvent removed under reduced pressure to give the required product as a yellow oil (1.250 g, 94%). TLC: R\textsubscript{f} = 0.5 (9:1 ethyl acetate:n-hexane). \textsuperscript{1}H NMR (CDCl\textsubscript{3}): 7.34-7.23 (m, 5H), 7.18 (1H, d, J = 7.7 Hz), 6.96 (1H, d, J = 13.3 Hz), 2.84 (2H, t, J = 7.4 Hz), 2.60 (2H, dd, J = 7.5 & 14.7 Hz). IR: 1648, 1555, 1524, 1484, 1437, 1373, 832, 787 cm.\textsuperscript{1} HRESIMS: Found: 276.1086 calculated for C\textsubscript{12}H\textsubscript{14}O\textsubscript{3}N\textsubscript{5} 276.1091.

**[(3E)-4-Nitro-3-butenyl]benzene – intermediate for (26d) and 28d**

To a solution of 1-nitro-4-phenyl-2-butanol (1.462 g, 7.50 mmol) in dichloromethane (20 mL, dry) at 0°C was added methanesulfonyl chloride (1.719 g, 15.0 mmol) followed by addition of triethylamine (3.036 g, 30.0 mmol, dry). The mixture was warmed up to room temperature, stirred for 20 min, then poured into water (20 mL) and extracted with dichloromethane (25 mL). The organic layer was separated, dried (Na\textsubscript{2}SO\textsubscript{4}), filtered and the solvent removed under reduced pressure to give the required product as a pale yellow solid (0.620 g, 3.50 mmol) and then was slowly added to an aqueous solution of 1.37 g (14.5 mmol) of one (1.16g, 9.20 mmol) in 5 mL of water at 0°C [the sequence of the addition is important]. The resulting mixture was stirred for 0 °C for 1 h and at room temperature overnight. The solid material was filtered, washed with water and dried. The crude material was purified by HPLC.
fractions containing the required product were collected and freeze dried to give lilac colored solid (60 mg, 16%), mp > 230 °C. 1H NMR (DMSO-d6): 11.16 (1H, s), 10.31 (1H, s), 7.84 (2H, d, J = 8.0 Hz), 7.10 (2H, d, J = 8.0 Hz), 6.96 (1H, d, J = 2.4 Hz), 6.13 (2H, br), 2.29 (3H, s). IR (KBr): 1718, 1684, 1658, 1213, 1177, 1141, 833, 723, 707, 686 cm⁻¹. HRESIMS: Found: 241.1083 calculated for C13H13ON4 241.1084.

2-Amino-5-(4-fluorophenyl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one 27b
To a solution of NaOH (0.330 g, 8.25 mmol) in water (5 mL) was added (0.450 g, 1.53 mmol) of 2,6-diamino-5-[1-(4-methylphenyl)-2-nitroethyl]-4(3H)-pyrimidinone at room temperature. The mixture was stirred for 2 h, and then was slowly added to an aqueous solution of 1.37 g (14 mmol) of sulfuric acid (98%) in 5 mL of water at 0 °C [the sequence of the addition is important]. The resulting mixture was stirred at 0 °C for 1 h and at room temperature overnight. The solid material was filtered, washed with water and dried. The crude material was purified by HPLC, fractions containing the required product were collected and freeze dried to give lilac colored solid (70 mg, 19%), mp > 230 °C. 1H NMR (DMSO-d6): 11.25 (1H, s), 10.42 (1H, s), 8.01 (2H, dd, J = 5.6 Hz & J = 8.9 Hz), 7.13 (2H, t, J = 9.0 Hz), 7.03 (1H, d, J = 2.4 Hz), 6.21 (2H, br). IR (KBr): 1719, 1682, 1655, 1505, 1186, 1137, 845, 724 cm⁻¹. HRESIMS: Found: 245.0830 Calculated for C13H10ON4F 245.0833.

2-Amino-5-(phenylethyl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one 27c
To a solution of NaOH (0.330 g, 8.25 mmol) in of water (5 mL) was added (0.398 g, 1.53 mmol) of 2,6-diamino-5-(2-nitro-1-phenylethyl)-4(3H)-pyrimidinone at room temperature. The mixture was stirred for 2 h, and then was slowly added to an aqueous solution of 1.37 g (14 mmol) of sulfuric acid (98%) in 5 mL of water at 0 °C [the sequence of the addition is important]. The resulting mixture was stirred at 0 °C for 1 h and at room temperature overnight. The solid material was filtered, washed with water and dried. The crude material was purified by HPLC, fractions containing the required product were collected and freeze dried to give lilac colored solid (50 mg, 15%), mp > 230 °C. 1H NMR (DMSO-d6): 11.26 (1H, s), 10.43 (1H, s), 7.95 (2H, dd, J = 1.4 Hz & J = 8.4 Hz), 7.31 (2H, t, J = 7.5 Hz), 7.16 (1H, t, 7.3 Hz), 7.03 (1H, d, J = 2.4 Hz), 6.25 (2H, br). IR (KBr): 1719, 1684, 1657, 1210, 1181, 1146, 763, 723, 705 cm⁻¹. HRESIMS: Found: 227.0925 Calculated for C12H10ON4 227.0927.

2-Amino-5-(2-phenylethyl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one 27d
To a solution of NaOH (0.500 g, 12.5 mmol) in water (5 mL) was added (0.444 g, 1.469 mmol) of 2,6-diamino-5-[1-(nitromethyl)-3-phenylpropyl]-4(3H)-pyrimidinone at room temperature. The mixture was stirred for 2 h, and then was slowly added to an aqueous solution of 1.37 g (14 mmol) of sulfuric acid (98%) in 5 mL of water at 0 °C [the sequence of the addition is important]. The resulting mixture was stirred at 0 °C for 1 h and at room temperature overnight. The solid material was filtered, washed with water and dried. The crude material was purified by HPLC, fractions containing the required product were collected and freeze dried to give lilac colored solid (72 mg, 20%) with no distinct melting point. 1H NMR (DMSO-d6): 10.78 (1H, s), 10.47 (1H, s), 7.28-7.09 (6H, m), 6.38 (2H, d, J = 2.0 Hz), 2.92-2.81 (4H, m). IR (KBr): 1720, 1684, 1656, 1504, 1210, 1188, 1135, 844, 725 cm⁻¹. HRESIMS: Found: 255.1244 Calculated for C14H13N4O 255.1240.

2-Amino-4-oxo-5-methylpyrrolo[2,3-d]pyrimidine 27e

To a solution of 2,4-diamino-6-oxopyrimidine (5 g, 39 mmol) in DMSO (30 mL) was added 2-bromopropanal (5 mL, 48 mmol) and 10 mL of triethylamine (10 mL). The reaction mixture was stirred vigorously at room temperature for 1 h and then loaded on to a dry silica gel column. The column was eluted with chloroform (1.5 L) and then with chloroform:methanol (1.5L, 10:1). The fractions containing the product (TLC) were pooled and the solvent was evaporated to afford the required product (4.60 g, 71%), mp > 230 °C. TLC: Rf = 0.45 (CHCl3:CH3OH 5:1). 1H NMR (DMSO-d6): 10.59 (1H, s), 10.13 (1H, s), 6.33 (1H, q, J = 1.2 Hz), 5.99 (2H, br), 2.17 (3H, d, J = 1.1 Hz). IR (KBr): 1720, 1649, 1604, 1436, 1370, 1212, 1177, 1138, 757, 728, 699 cm.\(^{-1}\) HRESIMS: Found: 165.0770 calculated for C7H6N2O 165.0771.

5-[1-(4-Methylphenyl)-2-nitroethyl]-2,4,6-pyrimidinetrizamine 28a

2,4,6-Pyrimidinetrizamine (0.575 g, 4.60 mmol) and 1-methyl-4-[(E)-2-nitroethenyl]benzene (0.856 g, 5.25 mmol) were suspended in a mixture of water (20 mL) and ethyl acetate (20 mL) at room temperature. The reaction mixture was left stirring at room temperature for 18 h. The reaction mixture was extracted with ethyl acetate, and dried (Na2SO4). The crude material obtained was purified by column chromatography using silica gel, methanol:ethyl acetate [1:9, Rf = 0.5] to give the required product as yellow solid (1.25 g, 94%), mp 100-103 °C. 1H NMR (DMSO-d6): 7.14 (4H, s), 5.50-5.3 (7H, m, containing 3 x NH2, exchangeable), 5.14-4.99 (2H, m), 2.27 (3H, s). IR (KBr): 1616, 1568, 1439, 1375, 1250, 1042, 802 cm.\(^{-1}\) HRESIMS: Found: 289.1405 Calculated for C13H17N6O2 289.1408.

5-[1-(4-Fluorophenyl)-2-nitroethyl]-2,4,6-pyrimidinetrizamine 28b

2,4,6-Pyrimidinetrizamine (0.575 g, 4.60 mmol) and 1-fluoro-4-[(E)-2-nitroethenyl]benzene (0.877 g, 5.25 mmol) were suspended in a mixture of water (20 mL) and ethyl acetate (20 mL) at room temperature. The reaction mixture was left stirring at room temperature for 18 h. The reaction mixture was extracted with ethyl acetate, and dried (Na2SO4). The crude material obtained was purified by column chromatography using silica gel, methanol:ethyl acetate [1:9, Rf = 0.5] to give the required product as yellow solid (1.130 g, 84%), mp 104-107 °C. 1H NMR (DMSO-d6): 7.30 (1H, d, J = 8.5 Hz), 7.29 (1H, d, J = 8.5 Hz), 7.18 (2H, t, J = 8.9 Hz), 5.48-5.38 (7H, m, containing 3 x NH2, exchangeable), 5.18-5.00 (2H, m). IR (KBr): 1618, 1567, 1508, 1440, 1376, 1228, 1162, 1042, 834, 798 cm.\(^{-1}\) HRESIMS: Found: 293.1160 Calculated for C12H14FN6O2 293.1157.

5-(2-Nitro-1-phenylethyl)-2,4,6-pyrimidinetrizamine 28c

2,4,6-Pyrimidinetrizamine (0.575 g, 4.60 mmol) and [(E)-2-nitroethenyl]benzene (0.783 g, 5.25 mmol) were suspended in a mixture of water (20 mL) and ethyl acetate (20 mL) at room temperature. The reaction mixture was left stirring at room temperature for 18 h. The reaction mixture was extracted with ethyl acetate, and dried (Na2SO4). The crude material obtained was purified by column chromatography using silica gel, methanol:ethyl acetate [1:9, Rf = 0.5] to give the required product as yellow solid (0.500 g, 40%), mp 110-113 °C (transparent). 1H NMR (DMSO-d6): 7.36-7.22 (5H, m), 5.48-5.41 (7H, m, containing 3 x NH2, exchangeable), 5.18-5.04 (2H, m). IR (KBr): 1619, 1567, 1442, 1377, 1254, 1032, 802, 743, 701 cm.\(^{-1}\) HRESIMS: Found: 275.1244 Calculated for C12H13N2O2N6 275.1251.

5-[1-(Nitromethyl)-3-phenylpropyl]-2,4,6-pyrimidinetrizamine 28d
[(3E)-4-Nitro-3-butenyl]benzene (0.627 g, 3.538 mmol) and 2,4,6-pyrimidinetriamine (0.443 g, 3.538 mmol) were dissolved in ethyl acetate (20 mL) and water (20 mL). The reaction mixture was heated in a sealed tube at 50 °C overnight. The organic layer was collected, dried (Na2SO4) and the solvent was removed under reduced pressure. The crude material was purified by gel column chromatography using methanol: dichloromethane (1:9), Rf = 0.4. The required product was obtained as a pale yellow solid (0.510 g, 48%) with no distinct melting point. 1H NMR (DMSO-d6): 7.32 (2H, t, J = 7.3 Hz), 7.24 (1H, t, J = 7.3 Hz), 7.16 (2H, d, J = 7.3 Hz), 4.67-4.57 (2H, m), 4.51 (3H, br), 4.43 (3H, br), 3.48-3.42 (1H, m), 2.75-2.57 (2H, m), 2.09-2.08 (2H, m). IR: 1620, 1566, 1442, 1377, 1254, 1032, 802, 743, 703 cm. 1H NMR (DMSO-d6): 11.90 (1H, s, NH, exchangeable), 7.44 (2H, dd, J = 7.3 Hz), 7.20 (4H, d, J = 8.1 Hz), 7.17 (4H, br, 2 x NH2 exchangeable), 7.07 (1H, d, J = 1.9 Hz). IR (KBr): 1647, 1458, 1206, 1132, 831, 798, 771, 724 cm. 1H NMR (DMSO-d6): 11.90 (1H, s, NH, exchangeable), 7.44 (2H, dd, J = 3.2 Hz & J = 8.7 Hz), 7.31 (2H, t, J = 9.0 Hz), 7.17 (4H, br, 2 x NH2 exchangeable), 7.07 (1H, d, J = 1.9 Hz). IR (KBr): 1661, 1547, 1503, 1459, 1190, 1124, 844, 799, 725 cm. HRESIMS: Found: 244.0989 Calculated for C12H14N5 240.1244.

5-(4-Methylphenyl)-7H-pyrrolo[2,3-d]pyrimidine-2,4-diamine 29a

To a solution of NaOH (0.330 g, 8.25 mmol) in water (5 mL) was added (0.441 g, 1.53 mmol) of 5-[1-(4-methylphenyl)-2-nitroethyl]-2,4,6-pyrimidinetriamine at room temperature. The mixture was stirred for 2 h, and then was slowly added to a solution of sulfuric acid (98%, 1.37 g, 14 mmol) in water (5 mL) at 0 °C [the sequence of the addition is important]. The resulting mixture was stirred at 0 °C for 1 h and at room temperature overnight. The solid material was filtered, washed with water and dried to give the crude product as brown solid (400 mg). The crude material was purified by HPLC, fractions containing the required product were collected and freeze dried to give lilac colored solid (30 mg, 13%), mp 210-213 °C. 1H NMR (DMSO-d6): 11.90 (1H, s, NH, exchangeable), 7.34 (2H, d, J = 8.1 Hz), 7.29 (2H, d, J = 8.1 Hz), 7.20 (4H, br, 2 x NH2 exchangeable), 7.03 (1H, d, J = 1.9 Hz), 2.36 (3H, s). IR (KBr): 1647, 1458, 1206, 1132, 831, 798, 771, 724 cm. 1H NMR (DMSO-d6): 11.90 (1H, s, NH, exchangeable), 7.48-7.44 (2H, dd, J = 3.2 Hz & J = 8.7 Hz), 7.31 (2H, t, J = 9.0 Hz), 7.17 (4H, br, 2 x NH2 exchangeable), 7.07 (1H, d, J = 1.9 Hz). IR (KBr): 1661, 1547, 1503, 1459, 1190, 1124, 844, 799, 725 cm. HRESIMS: Found: 240.0989 Calculated for C12H14N5 240.0993.

5-(4-Fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidine-2,4-diamine 29b

To a solution of NaOH (0.500 g, 12.5 mmol) in water (5 mL) was added (0.400 g, 1.39 mmol) of 5-[1-(4-fluorophenyl)-2-nitroethyl]-2,4,6-pyrimidinetriamine at room temperature. The mixture was stirred for 2 h, and then was slowly added to a solution of sulfuric acid (98%, 1.37 g, 14 mmol) in water (5 mL) at 0 °C [the sequence of the addition is important]. The resulting mixture was stirred at 0 °C for 1 h and at room temperature overnight. The solid material was filtered, washed with water and dried to give the crude product as brown solid (285 mg). The crude material was purified by HPLC, fractions containing the required product were collected and freeze dried to give pale yellow solid (40 mg, 35%), mp 130-134 °C. 1H NMR (DMSO-d6): 11.90 (1H, s, NH, exchangeable), 7.34-7.44 (2H, dd, J = 3.2 Hz & J = 8.7 Hz), 7.31 (2H, t, J = 9.0 Hz), 7.17 (4H, br, 2 x NH2 exchangeable), 7.07 (1H, d, J = 1.9 Hz). IR (KBr): 1661, 1547, 1503, 1459, 1190, 1124, 844, 799, 725 cm. HRESIMS: Found: 244.0989 Calculated for C12H11N5F 244.0993.

5-Phenyl-7H-pyrrolo[2,3-d]pyrimidine-2,4-diamine 29c

To an aqueous solution of NaOH (0.330 g, 8.25 mmol) in 5 mL of water was added (0.441 g, 1.53 mmol) of 5-(2-nitro-1-phenylethyl)-2,4,6-pyrimidinetriamine at room temperature. The mixture was stirred for 2 h, and then was slowly added to a solution of sulfuric acid (98%, 1.37 g, 14 mmol) in water (5 mL) at 0 °C [the sequence of the addition is important]. The resulting mixture was stirred at 0 °C for 1 h and at room temperature overnight. The solid material was filtered, washed with water and dried to give the crude product as brown solid (285 mg). The crude material was purified by HPLC, fractions containing the required product were collected
and freeze dried to give pale yellow solid (50 mg, 29\%). mp 200-203 °C. \(^1\)H NMR (DMSO-d\(_6\)): 11.91 (1H, s), 7.48-7.34 (5H, m), 7.20 (4H, br), 7.08 (1H, d, J = 1.8 Hz.) IR (KBr): 1694, 1651, 1543, 1453, 1390, 1207, 1131, 826, 800, 777, 725 cm\(^{-1}\). HRESIMS: Found: 226.1082 Calculated for C\(_{12}\)H\(_{12}\)N\(_5\) 226.1400.

5-(2-Phenylethyl)-7H-pyrrolo[2,3-d]pyrimidine-2,4-diamine 29d
To a solution of NaOH (0.500 g, 12.5 mmol) in water (5 mL) was added (0.444 g, 1.469 mmol) of 5-[1-(nitromethyl)-3-phenylpropyl]-2,4,6-pyrimidintriamine at room temperature. The mixture was stirred for 2 h and then was slowly added to a solution of sulfuric acid (98\%, 1.37 g, 14 mmol) in water (5 mL) at 0 °C [the sequence of the addition is important]. The resulting mixture was stirred at 0 °C for 1 h and at room temperature overnight. The solid material was filtered, washed with water and dried. The crude material was purified by HPLC, fractions containing the required product were collected and freeze dried to give lilac colored solid (72 mg, 20\%) with no distinct melting point. \(^1\)H NMR (DMSO-d\(_6\)): 11.45 (1H, s), 7.82 (2H, br), 7.29-7.12 (7H, m), 6.69 (1H, s), 3.02 (2H, t, \(J = 8.3 \text{ Hz}\)), 2.90 (2H, t, \(J = 8.3 \text{ Hz}\)). IR: 1650, 1455, 1209, 1133, 833, 800, 777, 725 cm\(^{-1}\). HRMS: Found: 254.1396 calculated for C\(_{14}\)H\(_{16}\)N\(_5\) 254.1400.

5-[1-(4-Fluorophenyl)-2-nitroethyl]-6-isobutoxy-2,4-pyrimidinediamine 30a
6-Isobutoxy-2,4-pyrimidinediamine (195 mg, 1.070 mmol) and 1-fluoro-4-[(E)-2-nitroethenyl]benzene (179 mg, 1.070 mmol) were dissolved in ethyl acetate (20 mL). The reaction mixture was placed in a sealed tube and heated at 50 °C for 2 d. Solvent was removed under reduced pressure and the crude material was applied to a silica gel column chromatography. Elution with ethyl acetate:n-hexane (1:1, \(R_f = 0.1\)) gave the required product (240 mg, 64\%) as pale yellow solid, mp 145-147 °C. \(^1\)H NMR (DMSO-d\(_6\)): 7.35 (2H, dd, \(J = 8.8 \text{ Hz}\) & \(J = 5.5 \text{ Hz}\)), 7.13 (2H, t, \(J = 8.8 \text{ Hz}\)), 6.14 (2H, s), 5.84 (2H, s), 5.32-5.17 (2H, m), 4.89 (1H, t, \(J = 8.0 \text{ Hz}\)), 3.93 (2H, 2xd, \(J = 6.7 \text{ Hz}\) & \(J = 6.7 \text{ Hz}\)), 1.97 (1H, septet, \(J = 6.7 \text{ Hz}\)), 0.89 (6H, 2xd, \(J_1 = 6.7 \text{ Hz}\) & \(J_2 = 6.7 \text{ Hz}\)). IR (KBr): 1619, 1566, 1510, 1441, 1376, 1228, 1015, 800 cm\(^{-1}\). HRESIMS: Found: 350.1621 Calculated for C\(_{16}\)H\(_{15}\)F\(_2\)O\(_2\)N\(_3\)F 350.1623.

\(N^4\)-Cyclohexyl-5-[1-(4-fluorophenyl)-2-nitroethyl]-2,4,6-pyrimidintriamine 30b
\(N^4\)-Cyclohexyl-2,4,6-pyrimidintriamine (200 mg, 0.965 mmol) and 1-fluoro-4-[(E)-2-nitroethenyl]benzene (161 mg, 0.965 mmol) were dissolved in ethyl acetate (20 mL). The reaction mixture was placed in a sealed tube and heated at 50 °C for 2 d. Solvent was removed under reduced pressure and the crude material was applied to a silica gel column chromatography. Elution with ethyl acetate (\(R_f = 0.1\)) gave the required product (210 mg, 58\%) as light brown solid, mp 77-77 °C. Some of this material was further purified by HPLC to give the required material as white solid. \(^1\)H-NMR (DMSO-d\(_6\)): 11.10 (1H, br), 7.37-7.19 (6H, m), 6.81 (2H, s), 6.25 (2H, br), 5.63-5.55 (1H, m), 5.24-5.16 (2H, m), 3.89 (1H, br), 1.52-1.17 (10H, m). IR (KBr): 1618, 1567, 1508, 1440, 1376, 1228, 1015, 797 cm\(^{-1}\). HRESIMS: Found: 375.1936 Calculated for C\(_{18}\)H\(_{24}\)O\(_2\)N\(_4\)F 375.1939.

5-(4-Fluorophenyl)-4-isobutoxy-7H-pyrrolo[2,3-d]pyrimidin-2-amine 31a
5-[1-(4-Fluorophenyl)-2-nitroethyl]-6-isobutoxy-2,4-pyrimidinediamine (105 mg, 0.301 mmol) was dissolved in a solution of NaOH (215 mg, 5.375 mmol) in water (25 mL) at room temperature with stirring. The stirring was continued for 2 h at room temperature. Sulfuric acid
(98%, 0.700 g, 7.00 mmol) was diluted with water (5 mL) and cooled to 0 °C. The sodium hydroxide solution was added to the acid dropwise with stirring at 0 °C, after which time it was left stirring at room temperature overnight. The white solid material formed was collected by filtration. This material was purified by HPLC. The starting material was recovered as well as the required product (5 mg, 4%) as white solid after freeze drying with no distinct melting point. \(^1\)H-NMR (DMSO-d_6): 11.41 (1H, s), 7.66 (2H, dd, \(J = 8.7\) Hz, \(J = 5.7\) Hz), 7.16 (2H, t, \(J = 8.9\) Hz), 7.07 (1H, d, \(J = 2.15\) Hz), 4.14 (2H, d, \(J = 6.4\) Hz), 1.98 (1H, septet, \(J = 6.7\) Hz). 0.91 (6H, d, \(J = 6.7\) Hz). IR (KBr): 1720, 1686, 1658, 1213, 1179, 1140, 833, 727, 705, 688 cm.\(^{-1}\) HRESIMS: Found: 301.1454 calculated for C\(_{16}\)H\(_{12}\)ON\(_2\)F 301.1459.

**\(N^d\)-Cyclohexyl-5-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidine-2,4-diamine 31b**

\(N^d\)-Cyclohexyl-5-[1-(4-fluorophenyl)-2-nitroethyl]-2,4,6-pyrimidinetriamine (150 mg, 0.400 mmol) was dissolved in a solution of NaOH (215 mg, 5.375 mmol) in water (25 mL) at room temperature with stirring. The stirring was continued for 2 h at room temperature. Sulfuric acid (98%, 0.700 g, 7.00 mmol) was diluted with water (5 mL) and cooled to 0 °C. The sodium hydroxide solution was added to the acid dropwise with stirring at 0 °C, after which time it was left stirring at room temperature overnight. The white solid material formed was collected by filtration. This material was purified by HPLC. The starting material was recovered as well as the required product (34 mg, 19%) as white solid after freeze drying with no distinct melting point. \(^1\)H-NMR (DMSO-d_6): 11.93 (1H, s), 7.52-7.28 (6H, m), 7.04 (1H, s), 5.97 (1H, br, s), 4.41 (1H, m), 1.87-1.21 (10H, m). IR (KBr): 1718, 1684, 1658, 1213, 1177, 1141, 833, 723, 707, 686 cm.\(^{-1}\) HRESIMS: Found: 326.1779 calculated for C\(_{18}\)H\(_{18}\)FN\(_5\) 326.1776.

**Leading to 34d, 35c, 36a**

**1,2-Bis(4-fluorophenyl)ethanone**

Aluminium chloride (4.635 g, 34.76 mmol, 1.2 mol eq) was added to fluorobenzene (13.92g, 144.85 mmol, 5.0 mol eq) with stirring and cooling with ice-water, under nitrogen. 2-chloro-1-(4-fluorophenyl)ethanone (5.00 g, 28.97 mmol, 1.05 mol eq) was added dropwise while keeping the temperature below 20 °C. The reaction mixture was stirred for a further 15 min and then it was heated at 50 °C for 5 h, after which time the reaction mixture was left stirring at room temperature for 9 h. Hydrolysis was carried out by diluting with dichloromethane and pouring the reaction mixture onto crushed ice (50 g) and extracting the resulting suspension with 2N aqueous HCl (30 mL). The organic phase was then cautiously washed with a saturated solution of sodium hydrogen carbonate and brine. The organic layer was dried (Na\(_2\)SO\(_4\)), filtered and the solvent removed under reduced pressure to give solid material which was washed with \(n\)-hexane. The desired material (6.260 g, 93%) was obtained as a white crystalline solid, mp 100-102 °C [Lit. mp 94-96 °C]\(^7\), \(R_f = 0.4\) (1:9 ethyl acetate: \(n\)-hexane). \(^1\)H NMR (DMSO-d_6): 8.16 (2H, dd, \(J = 8.9\) Hz & \(J = 5.6\) Hz), 7.40 (2H, t, \(J = 8.9\) Hz), 7.32 (2H, dd, \(J = 8.7\) Hz & \(J = 5.7\) Hz), 7.17(2H, t, \(J = 8.9\) Hz), 4.42 (2H, s). IR: 709, 721, 744, 792, 829, 860, 989, 1093, 1147, 1190, 1234, 1332, 1411, 1500, 1593, 1678 cm.\(^{-1}\) HRESIMS: Found: 233.0775 calculated for C\(_{18}\)H\(_{14}\)F\(_2\)O 233.0772.

**2-Bromo-1,2-bis(4-fluorophenyl)ethanone**

1,2-Bis(4-fluorophenyl)ethanone (5.46 g, 23.51 mmol) was dissolved in chloroform (58 mL) to which hydrobromic acid solution 30% in acetic acid (0.140 mL, 1 mol eq) was added at room temperature with stirring. Bromine (1.32 mL) dissolved in chloroform (5 mL) and added to the
reaction mixture dropwise with stirring. At the end of the reaction, a slight bromine coloration should remain. Sodium sulfite (10% aqueous) solution was added and the reaction mixture was then extracted. The organic layer was collected, washed with a saturated solution of sodium hydrogen carbonate followed by brine then the organic layer was dried (Na$_2$SO$_4$), filtered and the solvent removed under reduced pressure to give the required product (6.460 g, 88%) as a colorless oil. R$_f$ = 0.4 [1:9 ethyl acetate:n-hexane]. $^1$H NMR (DMSO-d$_6$): 8.19 (2H, dd, $J$ = 5.5 Hz & 8.7 Hz), 7.62 (2H, dd, $J$ = 5.5 Hz & 8.7 Hz), 7.40 (2H, t, $J$ = 8.7 Hz), 7.25 (2H, t, 8.7 Hz), 7.19 (1H, s). IR: 683, 717, 735, 752, 791, 822, 833, 852, 993, 1097, 1157, 1192, 1213, 1288, 1300, 1408, 1504, 1593, 1688 cm.$^{-1}$ HRESIMS: Found: 310.9878 Calculated for C$_{14}$H$_{10}$BrF$_2$O $^{310.9878}$

Leading to 34e, 35d, 36b

1,2-Bis(4-chlorophenyl)ethanone$^9$

Aluminium chloride (16.00 g, 0.119 mol) was added to chlorobenzene (50 mL) with stirring and cooling with ice-water, under nitrogen. 2-chloro-1-(4-chlorophenyl)ethanone (14 mL) was added dropwise while keeping the temperature below 20 °C. The reaction mixture was stirred for a further 15 min and then it was heated at 50 °C for 5 h, after which time the reaction mixture was left stirring at room temperature for 9 h. Hydrolysis was carried out by diluting with dichloromethane and pouring the reaction mixture onto crushed ice (50 g) and extracting the resulting suspension with 2N HCl (30 mL). The organic phase was then cautiously washed with a saturated solution of sodium hydrogen carbonate and brine. The organic layer was dried (Na$_2$SO$_4$), filtered and the solvent removed under reduced pressure to give solid material which was washed with n-hexane. The desired material (24.79 g, 98%) was obtained as a white crystalline solid, mp 113-115 °C [Lit. mp 114-115 °C]$^9$, R$_f$ = 0.4 (1:9 ethyl acetate:n-hexane). $^1$H NMR (DMSO-d$_6$): 8.05 (2H, d, $J$ = 8.5 Hz), 7.62 (2H, d, $J$ = 8.5 Hz), 7.38 (2H, d, $J$ = 8.5 Hz), 7.28 (2H, d, $J$ = 8.5 Hz), 4.42 (2H, s). IR: 709, 721, 744, 792, 829, 860, 989, 1093, 1147, 1190, 1234, 1332, 1411, 1500, 1593, 1678 cm.$^{-1}$ HRESIMS: Found: 265.0180 Calculated for C$_{14}$H$_{11}$Cl$_2$O $^{265.0181}$.

2-Bromo-1,2-bis(4-chlorophenyl)ethanone$^{10}$ 33e

1,2-Bis(4-chlorophenyl)ethanone (5.50 g, 20.70 mmol) was dissolved in chloroform (60 mL) to which hydrobromic acid solution 30% in acetic acid (0.140 mL, 1 mol eq) was added at room temperature with stirring. Bromine (1.32 mL) dissolved in chloroform (5 mL) and added to the reaction mixture dropwise with stirring. At the end of the reaction, a slight bromine coloration should remain. Sodium sulfite (10% aqueous) solution was added and the reaction mixture was then extracted. The organic layer was collected, washed with a saturated solution of sodium hydrogen carbonate followed by brine then the organic layer was dried (Na$_2$SO$_4$), filtered and the solvent removed under reduced pressure to give the required product (7.05 g, 99%) as a pale yellow oil. R$_f$ = 0.4 [1:9 ethyl acetate:n-hexane]. $^1$H NMR (CDCl$_3$): 7.96 (2H, d, $J$ = 8.7 Hz), 7.50 (2H, d, $J$ = 8.2 Hz), 7.48 (2H, d, $J$ = 8.4 Hz), 7.39 (2H, d, $J$ = 8.7 Hz), 6.26 (1H, s). $^{13}$C NMR (CDCl$_3$): 189.12, 140.01, 134.88, 133.48, 132.33, 131.77, 130.07, 130.01, 128.76, 128.73, 127.67, 48.41. IR: 660, 733, 743, 797, 829, 845, 990, 1013, 1090, 1179, 1213, 1398, 1489, 1568, 1587, 1688 cm.$^{-1}$

Leading to 34f, 34e, 36e

(4-Methoxyphenyl)acetyl chloride$^{11}$
(4-Methoxyphenyl)acetic acid (3.018 g, 18.161 mmol) was dissolved in dichloromethane (25 mL, dry) to which thionyl chloride (10 mL) was added dropwise at 0 °C with stirring. The reaction mixture was left stirring at room temperature overnight. Solvent and excess of thionyl chloride were removed under reduced pressure and the crude product was used in the next experiment without further purification. The required product was obtained as orange oil in quantitative yield.

1-(4-Fluorophenyl)-2-(4-methoxyphenyl)ethanone

Aluminium chloride (5.416 g, 40.625 mmol, 1.2 mol eq) was added to fluorobenzene (10.411 g, 108.331 mmol; 4.0 mol eq) with stirring and cooling with ice-water, under nitrogen. (4-Methoxyphenyl)acetyl chloride (5.00 g, 27.083 mmol) was added dropwise while keeping the temperature below 20 °C. The reaction mixture was stirred for a further 15 min and then it was heated at 50 °C for 5 h, after which time the reaction mixture was left stirring at room temperature for 9 h. Hydrolysis was carried out by diluting with dichloromethane and pouring the reaction mixture onto crushed ice (50 g) and extracting the resulting suspension with 2N HCl (30 mL). The organic phase was then cautiously washed with a saturated solution of sodium hydrogen carbonate and brine. The organic layer was dried (Na₂SO₄), filtered and the solvent removed under reduced pressure to give white solid material which was washed with n-hexane (4.800 g, 73%), mp 97-100 °C, [Lit. mp 112-113 °C].^1\textsuperscript{1}H-NMR (DMSO-d₆): 8.12 (2H, dd, $J = 5.6$ Hz & $J = 8.9$ Hz), 7.36 (2H, t, $J = 8.9$ Hz), 7.37 (2H, d, $J = 8.6$ Hz), 6.87 (2H, d, $J = 8.6$ Hz), 4.29 (2H, s), 3.71 (3H, s). ^1\textsuperscript{3}C-NMR (DMSO-d₆): 197.0, 166.5, 164.5, 158.5, 133.5, 131.9, 131.8, 131.1, 127.2, 116.3, 116.1, 114.3, 55.5, 44.3 IR: 704, 741, 783, 812, 829, 1032, 1333, 1406, 1499, 1589, 1686 cm⁻¹ HRESIMS: Found: 245.0973 Calculated for C₁₅H₁₄O₂F 245.0972

2-Bromo-1-(4-fluorophenyl)-2-(4-methoxyphenyl)ethanone

1-(4-Fluorophenyl)-2-(4-methoxyphenyl)ethanone (2.500 g, 10.233 mmol) was dissolved in chloroform (50 mL) to which HBr in acetic acid 30% (1 mL) was added at room temperature. Bromine (0.7 mL) in chloroform (5 mL) was added to the reaction mixture at room temperature with stirring. The dropwise addition continued until slight bromine coloration remained. Sodium sulfite (10% aqueous) solution was added and the reaction mixture was then extracted. The organic layer was collected, washed with a saturated solution of sodium hydrogen carbonate followed by brine then the organic layer was dried (Na₂SO₄), filtered and the solvent removed under reduced pressure to give the required product (3.190 g, 96%) as pale yellow oil. ^1\textsuperscript{1}H-NMR (CDCl₃): 8.04 (2H, dd, $J = 5.2$ Hz & $J = 8.9$ Hz), 7.47 (2H, d, $J = 8.9$ Hz), 7.14 (2H, t, $J = 8.9$ Hz), 6.91 (2H, d, $J = 8.9$ Hz), 6.34 (1H, s), 3.81 (3H, s). IR: 721, 831, 997, 1032, 1119, 1179, 1225, 1506, 1597, 1684 cm⁻¹ HRESIMS: Found: 323.0085 calculated for C₁₅H₁₄BrFO 323.0083

Leading to 34g, 35f

(4-Methylphenyl)acetyl chloride

(4-Methylphenyl)acetic acid (10.196 g, 0.068 mol) was dissolved in dichloromethane (20 mL, dry) to which thionyl chloride (15 mL) was added dropwise at 0 °C with stirring. The reaction mixture was left stirring at room temperature overnight. Solvent and excess of thionyl chloride were removed under reduced pressure and the crude product was used in the next experiment without further purification. The required product was obtained as orange oil (11.44 g, 100%).
1,2-Bis(4-methylphenyl)ethanone\textsuperscript{13}

Aluminium chloride (4.635 g, 34.76 mmol, 1.2 mol eq) was added to toluene (13.345 g, 144.83 mmol; 5.0 mol eq) with stirring and cooling with ice-water, under nitrogen. (4-Methylphenyl)acetyl chloride (5.435 g, 28.97 mmol) was added dropwise while keeping the temperature below 20 °C. The reaction mixture was stirred for a further 15 min and then it was heated at 50 °C for 5 h, after which time the reaction mixture was left stirring at room temperature for 9 h. Hydrolysis was carried out by diluting with dichloromethane and pouring the reaction mixture crushed ice (50 g) and extracting the resulting suspension with 2N HCl (30 mL). The organic phase was then cautiously washed with a saturated solution of sodium hydrogen carbonate and brine. The organic layer was dried (Na\textsubscript{2}SO\textsubscript{4}), filtered and the solvent removed under reduced pressure to give white solid material which was washed with n-hexane (6.02 g, 93%), mp 95-98 °C, [Lit. mp 102.5-103.5 °C].\textsuperscript{13} \textsuperscript{1}H-NMR (DMSO-d\textsubscript{6}): 7.93 (2H, d, J = 8.2 Hz), 7.32 (2H, d, J = 8.0 Hz), 7.14 (2H, d, J = 8.0 Hz), 7.10 (2H, d, J = 8.0 Hz), 4.26 (2H, s), 2.36 (3H, s), 2.25 (3H, s). IR: 736, 771, 806, 987, 1001, 1039, 1083, 1182, 1209, 1327, 1402, 1487, 1597, 1681 cm\textsuperscript{-1}. HRESIMS: Found: 225.1271 calculated for C\textsubscript{16}H\textsubscript{17}O 225.1274.

2-Bromo-1,2-bis(4-methylphenyl)ethanone 33g

1,2-Bis(4-methylphenyl)ethanone (2.500 g, 11.146 mmol) was dissolved in chloroform (50 mL) to which HBr in acetic acid 30% (1 mL) was added at room temperature. Bromine (0.7 mL) in chloroform (5 mL) was added to the reaction mixture at room temperature with stirring. The dropwise addition continued until slight bromine coloration remained. Sodium sulfite (10% aqueous) solution was added and the reaction mixture was then extracted. The organic layer was collected, washed with a saturated solution of sodium hydrogen carbonate followed by brine then the organic layer was dried (Na\textsubscript{2}SO\textsubscript{4}), filtered and the solvent removed under reduced pressure to give the required product (3.090 g, 91%) as a yellow solid after trituration with n-hexane. \textsuperscript{1}H-NMR (CDCl\textsubscript{3}): 7.90 (2H, d, J = 8.2 Hz), 7.43 (2H, d, J = 8.1 Hz), 7.12 (2H, d, J = 8.1 Hz), 6.37 (1H, s), 2.40 (3H, s), 2.34 (3H, s). \textsuperscript{13}C-NMR (CDCl\textsubscript{3}): 190.7, 144.7, 139.2, 133.2, 131.7, 129.8, 129.5, 129.3, 128.9, 51.5, 21.7, 21.2. IR: 783, 851, 986, 1063, 1163, 1267, 1371, 1454, 1557, 1674 cm\textsuperscript{-1}. HRESIMS: Found: 303.0383 calculated for C\textsubscript{16}H\textsubscript{16}BrO 303.0379.

Leading to 34h, 35g

1-(4-Bromophenyl)-2-phenylethanone\textsuperscript{14}

Aluminium chloride (4.635 g, 34.76 mmol) was added to bromobenzene (5.374 g, 34.23 mmol) in dichloromethane (20 mL, dry) with stirring and cooling with ice-water, under nitrogen. Phenylacetyl chloride (5.374 g, 34.76 mmol) in dichloromethane (10 mL, dry) was added dropwise while keeping the temperature below 20 °C. The reaction mixture was stirred for a further 15 min and then it was heated at 50 °C for 5 h, after which time the reaction mixture was left stirring at room temperature for 9 h. Hydrolysis was carried out by diluting with dichloromethane and pouring the reaction mixture crushed ice (50 g) and extracting the resulting suspension with 2N HCl (30 mL). The organic phase was then cautiously washed with a saturated solution of sodium hydrogen carbonate and brine. The organic layer was dried (Na\textsubscript{2}SO\textsubscript{4}), filtered and the solvent removed under reduced pressure to give yellow solid material which was washed with n-hexane (8.86 g, 94%), mp 104-106 °C, [Lit mp106-108 °C].\textsuperscript{14} \textsuperscript{1}H-NMR (CDCl\textsubscript{3}): 7.88 (2H, d, J = 8.5 Hz), 7.61 (2H, d, J = 8.5 Hz), 7.34-7.25 (5H, m), 4.26 (2H,
2-Bromo-1-(4-bromophenyl)-2-phenylethanone 33h
1-(4-Bromophenyl)-2-phenylethanone (2.500 g, 9.088 mmol) was dissolved in chloroform (50 mL) to which HBr (1 mL) was added at room temperature. Bromine (0.7 mL) in chloroform (5 mL) was added to the reaction mixture at room temperature with stirring. The dropwise addition continued until slight bromine coloration remained. Sodium sulfite (10% aqueous) solution was added and the reaction mixture was then extracted. The organic layer was collected, washed with a saturated solution of sodium hydrogen carbonate followed by brine then the organic layer was dried (Na$_2$SO$_4$), filtered and the solvent removed under reduced pressure to give the required product (3.300 g, 97%) as light brown oil. Trituration with n-hexane gave pale yellow solid, mp 90-93 °C. $^1$H NMR (CDCl$_3$): 7.86 (2H, d, $J = 8.6$ Hz), 7.61 (2H, d, $J = 8.7$ Hz), 7.52-7.35 (5H, m), 6.30 (1H, s). IR: 693, 734, 752, 842, 989, 1070, 1178, 1213, 1269, 1394, 1448, 1485, 1566, 1581, 1598, 1689 cm$^{-1}$. HRESIMS: Found: 352.9176 calculated for C$_{14}$H$_{11}$BrO 352.9171.

Leading to 34i
2-Bromo-1,4-diphenyl-1-butanone 33a
1,4-Diphenyl-1-butanone (3.015 g, 13.44 mmol) was dissolved in chloroform (25 mL) to which HBr (in acetic acid 30%) 1 mL was added at room temperature. Bromine (0.7 mL) in chloroform (5 mL) was added to the reaction mixture at room temperature with stirring. The dropwise addition continued until slight bromine coloration remained. Sodium sulfite (10% aqueous) solution was added and the reaction mixture was then extracted. The organic layer was collected, washed with a saturated solution of sodium hydrogen carbonate followed by brine then the organic layer was dried (Na$_2$SO$_4$), filtered and the solvent removed under reduced pressure to give the required product (4.00 g, 98%) as light brown oil. Trituration with n-hexane gave pale yellow solid, mp 90-93 °C. $^1$H NMR (CDCl$_3$): 7.95 (2H, dd, $J = 8.1$ Hz & $J = 1.0$ Hz), 7.51-7.46 (2H, m), 7.33-7.21 (6H, m), 5.09-5.06 (1H, m), 2.89-2.79 (2H, m), 2.55-2.43 (2H, m). IR: 802, 854, 960, 979, 1001, 1157, 1176, 1232, 1259, 1446, 1494, 1579, 1595, 1681 cm$^{-1}$. HRESIMS: Found: 303.0380 Calculated for C$_{16}$H$_{16}$BrO 303.0379.

Leading to 34j and 35h
1-(4-Isobutylphenyl)-2-phenylethanone
Aluminium chloride (4.635 g, 34.76 mmol) was added to isobutylbenzene (4.665 g, 34.76 mmol) with stirring and cooling with ice-water, under nitrogen. Phenylacetyl chloride (5.374 g, 34.76 mmol) was added dropwise while keeping the temperature below 20 °C. The reaction mixture was stirred for a further 15 min and then it was stirred at room temperature for 2.5 h. Hydrolysis was carried out by diluting with dichloromethane and pouring the reaction mixture crushed ice (50 g) and extracting the resulting suspension with 2N HCl (30 mL). The organic phase was then cautiously washed with a saturated solution of sodium hydrogen carbonate and brine. The organic layer was dried (Na$_2$SO$_4$), filtered and the solvent removed under reduced pressure to give the required product (4.00 g, 29%), mp 48-50 °C, R$_T$ = 0.5 [1:10 ethyl acetate:n-hexane]. $^1$H-NMR (DMSO-d$_6$): 7.97 (2H, d, $J = 7.2$ Hz), 7.31-7.21 (7H, m), 4.34 (2H, s), 2.52 (2H, d, $J = 7.1$ Hz), 1.91-1.82 (1H, m), 0.86 (6H, d, $J = 6.5$ Hz). $^{13}$C-NMR (DMSO-d$_6$): 197.7, 147.6, 135.7, 134.7, 130.2, 129.8, 128.9, 128.7, 126.9, 45.0, 44.9, 29.9, 22.6. IR: 694, 713, 731, 796, 837, 985, 1076, 1118, 1176, 1217, 1315,
2-Bromo-1-(4-isobutylphenyl)-2-phenylethanone

1-(4-Isobutylphenyl)-2-phenylethanone (2.025 g, 8.025 mmol) was dissolved in chloroform (25 mL) to which HBr (in acetic acid 33%, 1 mL) was added at room temperature. Bromine (0.7 mL) in chloroform (5 mL) was added to the reaction mixture at room temperature with stirring. The dropwise addition continued until slight bromine coloration remained. Sodium sulfite (10% aqueous) solution was added and the reaction mixture was then extracted. The organic layer was collected, washed with a saturated solution of sodium hydrogen carbonate followed by brine then the organic layer was dried (Na$_2$SO$_4$), filtered and the solvent removed under reduced pressure to give the required product (2.600 g, 98%) as pale yellow oil. $^1$H-NMR (CDCl$_3$): 7.92 (2H, d, $J = 8.2$ Hz), 7.56 (2H, d, $J = 8.2$ Hz), 7.23 (2H, d, $J = 8.2$ Hz), 6.38 (1H, s), 2.53 (2H, d, $J = 7.2$ Hz), 1.91 (1H, m), 0.91 (6H, d, $J = 6.7$ Hz). IR: 694, 763, 808, 858, 993, 1078, 1120, 1180, 1219, 1411, 1454, 1566, 1600, 1687, 2922, 2954 cm$^{-1}$. HRESIMS: Found: 331.0690 calculated for C$_{18}$H$_{20}$BrO 331.0692.

Leading to 34k and 35i

1-[4-(Methylsulfanyl)phenyl]-2-phenylethanone$^{15}$

Aluminium chloride (5.20 g, 38.25 mmol) was added to (methylsulfanyl)benzene (3.65 g, 29.40 mmol) in dichloromethane (20 mL, dry) with stirring and cooling with ice-water, under nitrogen. Phenylacetyl chloride (5.00 g, 32.35 mmol) in dichloromethane (10 mL, dry) was added dropwise while keeping the temperature below 20°C. The reaction mixture was stirred for a further 15 min and then it was stirred at room temperature for 2.5 h. Hydrolysis was carried out by diluting with dichloromethane and pouring the reaction mixture onto 50 g of crushed ice (50 g) and extracting the resulting suspension with 2N HCl (30 mL). The organic phase was then cautiously washed with a saturated solution of sodium hydrogen carbonate and brine. The organic layer was washed with n-hexane to give the required product as pale yellow solid (6.900 g, 97%), mp 95-97°C, [Lit. mp 96-97°C]. $^1$H-NMR (DMSO-d$_6$): 7.97 (2H, d, $J = 8.5$ Hz), 7.36 (2H, d, $J = 8.5$ Hz), 7.31-7.20 (5H, m), 4.32 (2H, s), 2.52 (3H, s). $^{13}$C-NMR (DMSO-d$_6$): 197.1, 146.1, 135.7, 132.9, 130.1, 129.4, 126.9, 125.4, 44.9, 14.4. IR: 704, 725, 746, 796, 812, 960, 987, 1028, 1087, 1182, 1200, 1212, 1332, 1398, 1431, 1452, 1494, 1552, 1583, 1678 cm$^{-1}$. HRESIMS: Found: 243.0840 Calculated for C$_{15}$H$_{15}$OS 243.0838.

1-[4-(Methylsulfonyl)phenyl]-2-phenylethanone$^{15}$

1-[4-(Methylsulfonyl)phenyl]-2-phenylethanone (2.290 g, 9.45 mmol) was dissolved in THF (50 mL) to which Oxone$^8$ [Sigma-Aldrich] [2KH$_2$SO$_4$.KH$_2$SO$_4$.K$_2$SO$_4$] (13.74 g) in water (50 mL) was added at room temperature with stirring. The stirring was continued overnight. THF was removed under reduced pressure and the resulting mixture was diluted with dichloromethane and extracted. The organic layer was collected, dried (Na$_2$SO$_4$), filtered and the solvent removed to give the required product as pale yellow solid (2.290 g, 88%), mp 168-170°C [Lit. mp 169-170°C]. $^1$H-NMR (DMSO-d$_6$): 8.27 (2H, d, $J = 8.4$ Hz), 8.08 (2H, d, $J = 8.4$ Hz), 7.33-7.22 (5H, m), 4.47 (2H, s), 3.27 (3H, s). $^{13}$C-NMR (DMSO-d$_6$): 197.7, 144.8, 140.6, 135.0, 130.3, 129.7, 128.8, 127.9, 127.1, 45.6, 43.6. IR: 692, 705, 738, 771, 825, 962, 989, 1087, 1149, 1203, 1292,
1303, 1325, 1344, 1396, 1456, 1498, 1693 cm⁻¹. HRESIMS: Found: 275.0740 Calculated for C₁₅H₁₅O₃S 275.0736.

**2-Bromo-1-[4-(methylsulfonyl)phenyl]-2-phenylethanone**

1-[4-(Methylsulfonyl)phenyl]-2-phenylethanone (1.002 g, 3.645 mmol) was dissolved in chloroform (25 mL) to which HBr (in acetic acid 33%, 0.5 mL) was added at room temperature. Bromine (0.5 mL) in chloroform (5 mL) was added to the reaction mixture at room temperature with stirring. The dropwise addition continued until slight bromine coloration remained. Sodium sulfite (10% aqueous) solution was added and the reaction mixture was then extracted. The organic layer was collected, washed with a saturated solution of sodium hydrogen carbonate followed by brine then the organic layer was dried (Na₂SO₄), filtered and the solvent removed under reduced pressure to give the required product as white solid (1.250 g, 97%), mp 117-120°C.

1H-NMR (CDCl₃): 8.17 (2H, d, J = 8.5 Hz), 8.05 (2H, J = 8.5 Hz), 7.54-7.52 (2H, m), 7.43-7.39 (3H, m), 6.32 (1H, s), 3.08(3H, s). IR: 690, 860, 1122, 1220, 1455, 1604, 1677, 1683 cm⁻¹. HRESIMS: Found: 352.9841 Calculated for C₁₅H₁₄O₃BrS 352.9842.

**Leading to 34l and 35j**

2-(3-Chlorophenyl)-1-(4-fluorophenyl)ethanone

Aluminium chloride (5.20 g, 38.25 mmol) was added to fluorobenzene (5.00 g, 52.03 mmol) in dichloromethane (20 mL, dry) with stirring and cooling with ice-water, under nitrogen. (3-Chlorophenyl)acetyl chloride (5.53 g, 29.31 mmol) in dichloromethane (10 mL, dry) was added dropwise while keeping the temperature below 20°C. The reaction mixture was stirred for a further 15 min and then it was stirred at room temperature for 2.5 h. Hydrolysis was carried out by diluting with dichloromethane and pouring the reaction mixture onto crushed ice (50 g) and extracting the resulting suspension with 2N HCl (30 mL). The organic phase was then cautiously washed with a saturated solution of sodium hydrogen carbonate and brine. The organic layer was dried (Na₂SO₄), filtered and the solvent removed under reduced pressure to give the required product as colorless oil (3.930 g, 54%).

1H-NMR (CDCl₃): 8.05-8.02 (2H, m), 7.17-6.86 (6H, m), 4.24 (2H, s). IR: 682, 756, 788, 833, 991, 1078, 1095, 1155, 1201, 1224, 1328, 1409, 1446, 1477, 1487, 1506, 1595, 1681 cm⁻¹. HRESIMS: Found: 249.0480 Calculated for C₁₄H₁₁ClFO.

2-Bromo-2-(3-chlorophenyl)-1-(4-fluorophenyl)ethanone

2-(3-Chlorophenyl)-1-(4-fluorophenyl)ethanone (1.081 g, 4.347 mmol) was dissolved in chloroform (25 mL). Hydrobromic acid in acetic acid (33%) (1 mL) was added at room temperature with stirring. Bromine (0.5 mL) in chloroform (10 mL) was added to the reaction mixture at room temperature with stirring. The dropwise addition continued until slight bromine coloration remained. The stirring was continued for further 30 minutes. Sodium sulfite (10% aqueous) solution was added and the reaction mixture was then extracted. The organic layer was collected, washed with a saturated solution of sodium hydrogen carbonate followed by brine then the organic layer was dried (Na₂SO₄), filtered and the solvent removed under reduced pressure to give the required product (1.200 g, 84%) as pale yellow oil.

1H NMR (CDCl₃): 8.05-8.02 (2H, m), 7.55 (1H, s), 7.43-7.40 (1H, m), 7.34-7.33 (1H, m), 7.18 (2H, t, J = 8.6 Hz), 6.24 (1H, s). IR: 680, 1506, 1487, 1409, 1213, 1157, 1099, 1080, 991, 850, 837, 779, 752, 711, 1591, 1689 cm⁻¹. HRESIMS: Found: 326.9580 Calculated for C₁₄H₁₀Br₃ClFO.
2-Amino-5-methyl-6-phenyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4(3H)-pyrimidinone (34b) and 2,6-Diamino-5-(1-methyl-2-oxo-2-phenylethyl)-4(3H)-pyrimidinone

2-Bromo-1-phenyl-1-propanone (0.500 g, 2.35 mmol) and 2,6-diamino-4(3H)-pyrimidinone (0.290 g, 2.00 mmol) were dissolved in DMF (6 mL, dry). The reaction mixture was heated at 80°C for 4 d with stirring. The solvent was reduced to around 2 mL in vacuo and the residue was purified by HPLC. Two products were isolated: fraction one: (175 mg, 34%): off-white solid, no distinct mp; uncyclised material and fraction two (the required product) (5 mg, 1%) as off-white solid, no distinct melting point.

Product 34b

1H NMR (DMSO-d6): 11.12 (1H, s), 10.23 (1H, s), 7.55-7.40 (5H, m), 6.68 (2H, br), 2.29 (3H, s). IR: 700, 724, 758, 783, 810, 835, 879, 1157, 1225, 1377, 1441, 1506, 1516, 1544, 1600, 1633 cm⁻¹. HRESIMS: Found: 241.1081 calculated for C13H13N4O 241.1084

By-product: 2,6-diamino-5-(1-methyl-2-oxo-2-phenylethyl)-4(3H)-pyrimidinone

IR: 692, 795, 966, 1036, 1084, 1192, 1229, 1379, 1422, 1451, 1516, 1587, 1650, 1659, 1680 cm⁻¹. HRESIMS: Found: 259.1190 calculated for C13H13N4O2 259.1190

2-Amino-5,6-bis(4-fluorophenyl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one 34d

2-Bromo-1,2-bis(4-fluorophenylethanol) (1.00 g, 3.214 mmol) and 2,6-diamino-4(3H)-pyrimidinone (0.405 g, 3.214 mmol) were dissolved in DMF (4 mL, dry). The reaction mixture was heated at 60 °C for 4 d with stirring under nitrogen. DMF was removed in vacuo and the residue was applied to a silica gel column chromatography and eluted with methanol:ethyl acetate (1:9; Rf = 5). The product was obtained as yellow solid (0.540 g, 50%), mp > 230 °C.

1H NMR (DMSO-d6): 11.50 (1H, s), 10.32 (1H, s), 7.32-7.22 (4H, m), 7.14 (2H, t, J = 9.0 Hz), 7.10 (2H, t, J = 9.0 Hz), 6.16 (2H, s). IR: 698, 723, 758, 783, 810, 835, 879, 1157, 1225, 1377, 1441, 1506, 1516, 1543, 1599, 1634 cm⁻¹. HRESIMS: Found: 339.1053 calculated for C18H13ON4F2 339.1052

2-Amino-5,6-bis(4-chlorophenyl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one 34e

2-Bromo-1,2-bis(4-chlorophenylethanol) (1.00 g, 2.907 mmol) and 2,6-diamino-4(3H)-pyrimidinone (0.367 g, 2.12 mmol) were dissolved in DMF (4 mL, dry). The reaction mixture was heated at 60°C for 4 d with stirring under nitrogen. DMF was removed in vacuo and the residue was applied to a silica gel column chromatography and eluted with methanol:ethyl acetate (1:9; Rf = 5). The product was obtained as yellow solid (0.350 g, 50%), mp > 230 °C.

1H NMR (DMSO-d6): 11.56 (1H, s), 10.32 (1H, s), 7.34-7.21 (8H, m), 6.18 (2H, s). IR: 656, 681, 735, 787, 826, 878, 1092, 1350, 1385, 1433, 1493, 1533, 1593, 1653 cm⁻¹. HRESIMS: Found: 371.0463 calculated for C18H13ON4Cl2 371.0461

2-Amino-6-(4-fluorophenyl)-5-(4-methoxyphenyl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one 34f

2,6-Diamino-4(3H)-pyrimidinone (0.367 g, 2.909 mmol) and 2-Bromo-1-(4-fluorophenyl)-2-(4-methoxyphenylethanol) (0.939 g, 3.965 mmol) were dissolved in DMF (4 mL, dry) with stirring to which KI (0.541 g, 3.26 mmol) and cesium carbonate (1.062 g, 3.26 mmol) were added. The reaction mixture was heated at 60 °C overnight. Solvent was removed in vacuo and the crude material was dissolved in ethyl acetate and extracted with water. The organic layer was collected, dried (Na2SO4) and solvent removed under reduced pressure. This material was applied to a silica gel column chromatography and eluted with (1:9 methanol:ethyl acetate) to give impure material (0.400 g, 39%). This material was further purified by HPLC to give the required
product as a pale yellow solid with no distinct melting point. $^1$H-NMR (DMSO-d$_6$): 11.40 (1H, s), 10.27 (1H, s), 7.26 (2H, dd, $J = 5.6$ Hz & $J = 8.7$ Hz), 7.19 (2H, d, $J = 8.7$ Hz), 7.10 (2H, t, $J = 8.7$ Hz), 6.82 (2H, d, $J = 8.7$ Hz), 6.14 (2H, br), 3.74 (3H, s). IR: 702, 733, 769, 803, 850, 875, 1072, 1184, 1442, 1514, 1537, 1564, 1600, 1658, 1672 cm$^{-1}$. HRESIMS: Found: 351.1256 calculated for C$_{19}$H$_{16}$FN$_4$O$_2$ 351.1252.

2-Amino-5,6-bis(4-methylphenyl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one 34g

2,6-Diamino-4(3H)-pyrimidinone (0.166 g, 1.319 mmol) and 2-bromo-1,2-bis(4-methylphenyl)ethanone (0.400 g, 1.319 mmol) were dissolved in DMF (4 mL, dry) with stirring. The reaction mixture was heated at 60 °C for 48 h. Solvent was removed in vacuo and the crude material was dissolved in ethyl acetate, dried (Na$_2$SO$_4$), filtered and the solvent removed under reduced pressure. This material was applied to a silica gel column chromatography and eluted with (1:9 methanol:ethyl acetate) to give an impure material (0.200 g, 46%). This material was further purified by HPLC to give the required product as light green solid. $^1$H-NMR (DMSO-d$_6$): 11.35 (1H, s), 10.25 (1H, s), 7.17-7.02 (8H, m), 6.12 (2H, br), 2.28 (3H, s), 2.24 (3H, s). IR: 736, 771, 806, 987, 1001, 1039, 1083, 1182, 1209, 1327, 1402, 1487, 1597, 1681 cm$^{-1}$. HRESIMS: Found: 331.1557 calculated for C$_{20}$H$_{19}$N$_4$O 331.1553.

2-Amino-6-(4-bromophenyl)-5-phenyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one 34h

2,6-Diamino-4(3H)-pyrimidinone (0.712 g, 5.65 mmol) and 2-bromo-1-(4-bromophenyl)-2-phenylethanone (1.00 g, 2.82 mmol) were dissolved in DMF (10 mL, dry) with stirring. The reaction mixture was heated at 60 °C for 4 d. Solvent was removed in vacuo and the crude material was dissolved in ethyl acetate, dried (Na$_2$SO$_4$), filtered and the solvent removed under reduced pressure. This material was applied to a silica gel column chromatography and eluted with (1:9 methanol:ethyl acetate) to give an impure material (0.200 g, 19%) as yellow solid. This material was further purified by HPLC to give the required product as light green solid with no distinct melting point. $^1$H NMR (DMSO-d$_6$): 11.52 (1H, s), 10.31 (1H, s), 7.42 (2H, d, $J = 8.6$ Hz), 7.29-7.20 (5H, m), 7.15 (2H, d, $J = 8.6$ Hz), 6.15 (2H, s). IR: 698, 717, 767, 825, 873, 1008, 1072, 1388, 1427, 1438, 1500, 1537, 1562, 1585, 1627, 1664 cm$^{-1}$. HRESIMS: Found: 381.0348 Calculated for C$_{18}$H$_{14}$$^{79}$BrN$_4$O 381.0346.

2-Amino-6-phenyl-5-(2-phenylethyl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one 34i

2,6-Diamino-4(3H)-pyrimidinone (1.664 g, 13.193 mmol) and 2-bromo-1,4-diphenyl-1-butane (2.00 g, 6.596 mmol) were dissolved in DMF (6 mL, dry) with stirring. The reaction mixture was heated at 25 °C for 4 d. Solvent was removed in vacuo and the crude material was dissolved in ethyl acetate, dried (Na$_2$SO$_4$), filtered and the solvent removed under reduced pressure. This material was applied to a silica gel column chromatography and eluted with (1:9 methanol:ethyl acetate) to give an impure material (0.390 g, 18%) as yellow solid. This material was further purified by HPLC to give the required product as pale yellow solid, mp > 230°C. $^1$H NMR (DMSO-d$_6$): 11.10 (1H, s), 10.25 (1H, s), 7.39-7.35 (4H, m), 7.27-7.14 (6H, m), 6.16 (2H, br), 2.95 (4H, s). IR: 694, 721, 771, 798, 844, 1066, 1139, 1195, 1386, 1444, 1494, 1589, 1664, 1697 cm$^{-1}$. HRESIMS: Found: 331.1550 Calculated for C$_{20}$H$_{19}$N$_4$O 331.1553.

2-Amino-6-(4-isobutylphenyl)-5-phenyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one 34j
2,6-Diamino-4(3H)-pyrimidinone (0.523 g, 4.152 mmol) and 2-bromo-1-(4-isobutylphenyl)-2-phenylethanone (1.375 g, 4.152 mmol) were dissolved in DMF (6 mL, dry) with stirring. Cesium carbonate (1.062 g, 3.26 mmol) was added to the reaction mixture. The reaction mixture was heated at 60 °C for 2 d. Solvent was removed in vacuo and the crude material was dissolved in ethyl acetate, dried (Na₂SO₄), filtered and the solvent removed under reduced pressure. This material was applied to a silica gel column chromatography and eluted with (1:9 methanol:ethyl acetate) to give an impure material (0.800 g, 54%) as yellow solid. This material was further purified by HPLC to give the required product as pale yellow solid with no distinct melting point. ¹H-NMR (DMSO-d₆): 11.35 (1H, s), 10.23 (1H, s), 7.28-7.17 (5H, m), 7.13 (2H, d, J = 8.2 Hz), 7.01 (2H, d, J = 8.2 Hz), 2.39 (2H, d, J = 7.2 Hz), 1.82 (1H, m), 0.84 (6H, d, J = 6.7 Hz). IR: 700, 731, 767, 800, 848, 875, 1072, 1184, 1386, 1442, 1514, 1537, 1564, 1600, 1658 cm⁻¹. HRESIMS: Found: 355.0756 calculated for C₇25, 765, 790, 810, 837, 1099, 1139, 1161, 1195, 1433, 1512, 1583, 1662, 1693 cm⁻¹.

2-Amino-6-[4-(methylsulfonyl)phenyl]-5-phenyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one 34k

2,6-Diamino-4(3H)-pyrimidinone (0.223 g, 1.769 mmol) and 2-bromo-1-[4-(methylsulfonyl)phenyl]-2-phenylethanone (0.625 g, 1.769 mmol) were dissolved in DMF (5 mL, dry) with stirring. The reaction mixture was heated at 60 °C for 2 d. Solvent was removed in vacuo and the crude material was dissolved in ethyl acetate, dried (Na₂SO₄), filtered and the solvent removed under reduced pressure. This material was applied to a silica gel column chromatography and eluted with (1:8 methanol:ethyl acetate) to give an impure material (0.170 g, 25%) as yellow solid. This material was further purified by HPLC to give the required product as pale yellow solid with no distinct melting point. ¹H-NMR (DMSO-d₆): 11.68 (1H, s), 10.36 (1H, s), 7.73 (2H, d, J = 8.5 Hz), 7.42 (2H, d, J = 8.5 Hz), 7.30-7.26 (5H, m), 6.26 (2H, br), 3.18 (3H, s). IR: 688, 729, 769, 783, 846, 875, 979, 1087, 1143, 1274, 1319, 1357, 1386, 1535, 1583, 1631, 1660 cm⁻¹. HRESIMS: Found: 381.1019 calculated for C₁₉H₁₇N₄O₃S 381.1016.

2-Amino-5-(3-chlorophenyl)-6-(4-fluorophenyl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one 34l

2,6-Diamino-4(3H)-pyrimidinone (0.231 g, 1.832 mmol) and 2-bromo-2-(3-chlorophenyl)-1-(4-fluorophenylethanone (0.600 g, 1.832 mmol) were dissolved in DMF (5 mL, dry) with stirring. The reaction mixture was heated at 60 °C for 24 h. Solvent was removed in vacuo and the crude material was dissolved in ethyl acetate to which water was added. The reaction mixture was extracted and the organic layer was collected, dried (Na₂SO₄), filtered and the solvent removed under reduced pressure. This material was applied to a silica gel column chromatography and eluted with (1:9 methanol:ethyl acetate; Rₚ = 0.3) to give an impure material as yellow solid. This material was further purified by HPLC to give the required product as pale yellow solid (0.288 g, 34%), with no distinct melting point. ¹H NMR (DMSO-d₆): 11.57 (1H, s), 10.33 (1H, s), 7.36 (1H, s), 7.26-7.23 (4H, m), 7.17-7.11 (3H, m), 6.20 (2H, br). IR: 686, 725, 765, 790, 810, 837, 1099, 1139, 1161, 1195, 1433, 1512, 1583, 1662, 1693 cm⁻¹. HRESIMS: Found: 355.0755 Calculated for C₁₈H₁₃ClFN₃O 355.0756.

5,6-Bis(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidine-2,4-diamine 35c

2-Bromo-1,2-bis(4-fluorophenylethanone (1.00 g, 3.214 mmol) and 2,4,6-pyrimidinetr diamine (0.402 g, 3.214 mmol) were dissolved in DMF (4 mL, dry). The reaction mixture was heated at
60 °C for 4 d with stirring under nitrogen. DMF was removed in vacuo and the residue was applied to a silica gel column chromatography and eluted with methanol:ethyl acetate (1:9; RF = 0.4). The product was obtained as yellow solid (0.110 g, 10%), mp > 230 °C. 1H NMR (DMSO-d6; 400 MHz): 11.33 (1H, s), 7.37-7.23 (6H, m), 7.12 (2H, t, J = 8.9 Hz), 5.65 (2H, s), 5.31 (2H, br). IR: 689, 721, 773, 791, 837, 883, 1074, 1096, 1155, 1215, 1317, 1393, 1412, 1439, 1475, 1514, 1553, 1609 cm⁻¹. HRESIMS: Found: 338.1212 Calculated for C18H14N5F2 338.1212.

5,6-Bis(4-chlorophenyl)-7H-pyrrolo[2,3-d]pyrimidine-2,4-diamine 35d

2-Bromo-1,2-bis(4-chlorophenyl)ethanone (1.00 g, 2.907 mmol) and 2,4,6-pyrimidinetriamine (0.364 g, 2.907 mmol) were dissolved in DMF (4 mL, dry). The reaction mixture was heated at 60 °C for 4 d with stirring under nitrogen. DMF was removed in vacuo and the residue was applied to a silica gel column chromatography and eluted with methanol:ethyl acetate (1:9; RF = 0.2). The product was obtained as yellow solid (0.120 g, 11%), mp > 230 °C. 1H NMR (DMSO-d6): 11.38 (1H, s), 7.49 (2H, d, J = 8.4 Hz), 7.33 (2H, d, J = 8.4 Hz), 7.32 (2H, d, J = 8.4 Hz), 7.22 (2H, d, J = 8.4 Hz), 5.66 (2H, s), 5.34 (2H, br). 13C NMR (DMSO-d6): 158.62, 152.73, 152.02, 133.26, 132.28, 131.96, 131.12, 130.83, 130.74, 129.34, 128.36, 127.59, 125.13, 115.25, 99.25. IR: 720, 737, 795, 829, 1013, 1092, 1395, 1416, 1447, 1568, 1614, 1543, 1478 cm⁻¹. HRESIMS: Found: 370.0625 Calculated for C18H14N5Cl 370.0621.

6-(4-Fluorophenyl)-5-(4-methoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidine-2,4-diamine 35e

2,4,6-Pyrimidinetriamine (0.364 g, 2.907 mmol) and 2-bromo-1-(4-fluorophenyl)-2-(4-methoxyphenyl)ethanone (0.939 g, 3.965 mmol) were dissolved in DMF (4 mL, dry) with stirring to which KI (0.541 g, 3.26 mmol) and cesium carbonate (1.062 g, 3.26 mmol) were added. The reaction mixture was heated at 60 °C overnight. Solvent was removed in vacuo and the crude dried Na2SO4 and solvent removed under reduced pressure. This material was applied to a silica gel column chromatography and eluted with (1:9 methanol:ethyl acetate) to give impure material (0.1760 g, 17%). This material was further purified by HPLC to give the required product as a pale yellow solid with no distinct melting point. 1H-NMR (DMSO-d6): 12.21 (1H, s), 11.65 (1H, br), 7.29-7.23 (6H, m), 7.17 (2H, t, J = 8.7 Hz), 7.03 (2H, d, J = 8.7 Hz), 6.80 (2H, br), 3.80 (3H, s). IR: 701, 732, 766, 805, 846, 876, 1072, 1184, 1386, 1442, 1514, 1537, 1564, 1600, 1658, 1672 cm⁻¹. HRESIMS: Found: 350.1415 calculated for C18H17FN5O 350.1412.

5,6-Bis(4-methylphenyl)-7H-pyrrolo[2,3-d]pyrimidine-2,4-diamine 35f

2,4,6-Pyrimidinetriamine (0.165 g, 1.319 mmol) and 2-bromo-1,2-bis(4-methylphenyl)ethanone (0.400 g, 1.319 mmol) were dissolved in DMF (4 mL, dry) with stirring to which KI (0.218 g, 1.319 mmol) and cesium carbonate (0.430 g, 1.319 mmol) were added. The reaction mixture was heated at 60 °C for 48 h. Solvent was removed in vacuo and the crude material was dissolved in ethyl acetate, dried (Na2SO4), filtered and the solvent removed under reduced pressure. This material was applied to a silica gel column chromatography and eluted with (1:9 methanol:ethyl acetate) to give an impure material (0.120 g, 27%). This material was further purified by HPLC to give the required product as pale yellow solid. 1H-NMR (DMSO-d6): 12.18 (1H, br), 11.63 (1H, br), 7.27-7.08 (10H, m), 6.80 (2H, br, 2.36 (3H, s), 2.25 (3H, s). IR: 700, 733, 766, 805, 846, 877, 1074, 1184, 1386, 1442, 1515, 1540, 1564, 1600, 1660, 1673 cm⁻¹. HRESIMS: Found: 330.1711 calculated for C20H20N5 330.1713.
6-(4-Bromophenyl)-5-phenyl-7H-pyrrolo[2,3-d]pyrimidine-2,4-diamine 35g

2,4,6-Pyrimidinetriamine (0.706 g, 5.64 mmol) and 2-bromo-1-(4-bromophenyl)-2-phenylethanone (1.00 g, 2.82 mmol) were dissolved in DMF (10 mL, dry) with stirring. The reaction mixture was heated at 60 °C for 7 d. Solvent was removed in vacuo and the crude material was dissolved in ethyl acetate, dried (Na₂SO₄), filtered and the solvent removed under reduced pressure. This material was applied to a silica gel column chromatography and eluted with (1:9 methanol:ethyl acetate) to give an impure material (0.165 g, 15%). This material was further purified by HPLC to give the required product as pale yellow solid with no distinct melting point. ¹H NMR (DMSO-d₆): 11.33 (1H, s), 7.45 (2H, d, J = 8.6 Hz), 7.41-7.32 (5H, m), 7.17 (2H, d, J = 8.6 Hz), 5.65 (2H, s), 5.25 (2H, br). IR: 702, 765, 796, 831, 1006, 1085, 1323, 1388, 1411, 1440, 1477, 1543, 1560, 1610 cm⁻¹. HRESIMS: Found: 380.0508 Calculated for C₁₃H₁₇BrN₅ 380.0505.

6-(4-Isobutylphenyl)-5-phenyl-7H-pyrrolo[2,3-d]pyrimidine-2,4-diamine 35h

2,4,6-Pyrimidinetriamine (0.519 g, 4.152 mmol) and 2-Bromo-1-(4-isobutylphenyl)-2-phenylethanone (1.375 g, 4.152 mmol) were dissolved in DMF (10 mL, dry) with stirring. Cesium carbonate (0.256 g, 0.786 mmol) was added to the reaction mixture. The reaction mixture was heated at 60 °C for 2 d. Solvent was removed in vacuo and the crude material was dissolved in ethyl acetate, dried (Na₂SO₄), filtered and the solvent removed under reduced pressure. This material was applied to a silica gel column chromatography and eluted with (1:9 methanol:ethyl acetate) to give an impure material (0.310 g, 21%). Trituration with ethyl acetate in vacuo gave the pure material as light brown solid (0.170 g, 25%). HPLC purification gave the pure material as pale yellow solid with no distinct melting point. ¹H NMR (DMSO-d₆): 11.20 (1H, s), 7.44-7.31 (5H, m), 7.17 (2H, d, J = 8.2 Hz), 6.99 (2H, d, J = 8.2 Hz), 2.37 (2H, d, J = 7.2 Hz), 1.80 (1H, m), 0.83 (6H, d, J = 6.6 Hz). IR: 700, 732, 767, 792, 846, 877, 1020, 1070, 1400, 1435, 1481, 1546, 1564, 1597, 1616 cm⁻¹. HRESIMS: Found: 358.2029 calculated for C₂₂H₂₄N₅ 358.2026.

6-[4-(Methylsulfonyl)phenyl]-5-phenyl-7H-pyrrolo[2,3-d]pyrimidine-2,4-diamine 35i

2,4,6-Pyrimidinetriamine (0.2219 g, 1.769 mmol) and 2-bromo-1-[4-(methylsulfonyl)phenyl]-2-phenylethanone (0.625 g, 1.769 mmol) were dissolved in DMF (5 mL, dry) with stirring. Cesium carbonate (0.225 g, 0.691 mmol) was added to the reaction mixture. The reaction mixture was heated at 60 °C for 2 d. Solvent was removed in vacuo and the crude material was dissolved in ethyl acetate, dried (Na₂SO₄), filtered and the solvent removed under reduced pressure. This material was applied to a silica gel column chromatography and eluted with (1:8 methanol:ethyl acetate) to give an impure material as light brown solid (0.170 g, 25%). HPLC purification gave the pure material as pale yellow solid with no distinct melting point. ¹H NMR (DMSO-d₆): 12.49 (1H, s), 7.81 (2H, d, J = 8.5Hz), 7.51-7.36 (9H, m), 7.24 (2H, br), 3.19 (3H, s). ¹³C-NMR (DMSO-d₆): 139.6, 136.1, 133.2, 130.3, 130.1, 128.9, 128.2, 127.5, 116.8. IR: 707, 723, 777, 798, 839, 956, 1147, 1199, 1305, 1390, 1436, 1595, 1647, 1656 cm⁻¹. HRESIMS: Found: 380.1177 calculated for C₁₅H₁₈N₅O₂S 380.1176.

5-(3-Chlorophenyl)-6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidine-2,4-diamine 35j

2,4,6-Pyrimidinetriamine (0.229 g, 1.832 mmol) and 2-bromo-2-(3-chlorophenyl)-1-(4-fluorophenyl)ethanone (0.600 g, 1.832 mmol) were dissolved in DMF (5 mL, dry) with stirring. The reaction mixture was heated at 60 °C for 24 h. Solvent was removed in vacuo and the crude material was dissolved in ethyl acetate to which water was added. The reaction mixture was
extracted and the organic layer was collected, dried (Na₂SO₄), filtered and the solvent removed under reduced pressure. This material was applied to a silica gel column chromatography and eluted with (1:9 methanol:ethyl acetate; Rₐ = 0.3) to give an impure material as yellow solid. This material was further purified by HPLC to give the required product as pale yellow solid (0.096 g, 11%), with no distinct melting point. ¹H NMR (DMSO-d₆): 12.34 (1H, br), 11.71 (1H, br), 7.47-7.46 (2H, m), 7.34-7.16 (10H, m). IR: 688, 723, 765, 796, 837, 1138, 1161, 1199, 1473, 1512, 1550, 1599, 1643, 1658 cm⁻¹. HRESIMS: Found: 354.0919 Calculated for C₁₈H₃₅ClF₃N₅ 354.0916.

5.6-Bis(4-fluorophenyl)-N⁴,N⁴-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-2,4-diamine 36a

N⁴,N⁴-Dimethyl-2,4,6-pyrimidinetrifluoromethane (0.200 g, 1.306 mmol) and 2-bromo-1,2-bis(4-fluorophenyl)ethanone (0.406 g, 1.306 mmol) were dissolved in DMF (4 mL, dry) to which Hunig’s base (1 mL, dry) was added. The reaction mixture was heated at 60 °C for 24 h. DMF and Hunig’s base were removed in vacuo and the residue was dissolved in ethyl acetate and methanol to which silica gel was added and the solvents were removed under reduced pressure. The residue was applied to a silica gel column chromatography and eluted with (1 methanol:ethyl acetate (Rₐ = 0.5). Fractions containing the required product were combined and the solvents removed under reduced pressure gave the crude material which was triturated with a small amount of methanol and filtered to give the desired product (60 mg, 13%) as a pale yellow solid, mp > 230°C. ¹H NMR (DMSO-d₆): 11.37 (1H, s), 7.23-7.08 (8H, m), 5.74 (2H, s), 2.51 (6H, s). IR: 731, 793, 810, 835, 882, 1030, 1057, 1099, 1225, 1398, 1487, 1508, 1547, 1587, 1609 cm⁻¹. HRESIMS: Found: 366.1526 Calculated for C₂₀H₁₈N₄F₂ 366.1525.

5.6-Bis(4-chlorophenyl)-N⁴,N⁴-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-2,4-diamine 36b

N⁴,N⁴-Dimethyl-2,4,6-pyrimidinetrifluoromethane (0.200 g, 1.306 mmol) and 2-bromo-1,2-bis(4-chlorophenyl)ethanone (0.449 g, 1.306 mmol) were dissolved in DMF (4 mL, dry) to which Hunig’s base (1 mL, dry) was added. The reaction mixture was heated at 60 °C for 24 h. DMF and Hunig’s base were removed in vacuo and the residue was dissolved in ethyl acetate and methanol to which silica gel was added and the solvents were removed under reduced pressure. The residue was applied to a silica gel column chromatography and eluted with 1 methanol:ethyl acetate (Rₐ = 0.5). Fractions containing the required product were combined and the solvents removed under reduced pressure gave the crude material which was triturated with a small amount of methanol and filtered to give the desired product (60 mg, 12%) as a pale yellow solid, mp > 230°C. ¹H NMR (DMSO-d₆): 11.38 (1H, s), 7.42 (2H, d, J = 8.4 Hz), 7.35 (2H, d, J = 8.6 Hz), 7.23 (2H, d, J = 8.4 Hz), 7.19 (2H, d, J = 8.6 Hz), 5.83 (2H, s), 2.52 (6H, s). ¹³C NMR (DMSO-d₆): 132.54, 131.80, 131.69, 131.61, 130.27, 128.90, 128.73, 40.92. IR: 733, 789, 828, 880, 1011, 1057, 1057, 1092, 1398, 1449, 1472, 1545, 1593 cm⁻¹. HRESIMS: Found: 398.0938 Calculated for C₂₀H₁₈N₄Cl₂ 398.0934.

6-(4-Fluorophenyl)-N⁴,N⁴-dimethyl-5-phenyl-7H-pyrrolo[2,3-d]pyrimidine-2,4-diamine 36c

N⁴,N⁴-Dimethyl-2,4,6-pyrimidinetrifluoromethane (0.200 g, 1.306 mmol) and 2-bromo-1-(4-fluorophenyl)-2-phenylethanone (0.383 g, 1.306 mmol) were dissolved in DMF (4 mL, dry) to which Hunig’s base (1 mL, dry) was added. The reaction mixture was heated at 60 °C for 24 h. DMF and Hunig’s base were removed in vacuo and the residue was dissolved in ethyl acetate and methanol to which silica gel was added and the solvents were removed under reduced
pressure. The residue was applied to a silica gel column chromatography and eluted with 1:9 methanol:ethyl acetate (R_F = 0.2). Fractions containing the required product were combined and the solvents removed under reduced pressure gave the crude material which was triturated with a small amount of methanol and filtered to give the desired product (60 mg, 13%) as a pale yellow solid, mp > 230 °C. 1H NMR (DMSO-d_6): 11.34 (1H, s), 7.35-7.27 (3H, m), 7.21-7.17 (4H, m), 7.07 (2H, t, J = 8.9 Hz), 2.49 (6H, s). IR: 700, 774, 837, 1069, 1153, 1227, 1400, 1439, 1481, 1506, 1547, 1591 cm^{-1}. HRESIMS: Found: 348.1621 Calculated for C_{20}H_{19}N_{3}F 348.1619.

N^4,N^4-Dimethyl-5,6-diphenyl-7H-pyrrolo[2,3-d]pyrimidine-2,4-diamine 36d

N^4,N^4-Dimethyl-2,4,6-pyrimidinetriamine (0.500 g, 3.26 mmol) and 2-bromo-1,2-diphenylethanone [desyl bromide] (0.898 g, 3.26 mmol) were dissolved in DMF (4 mL, dry) to which potassium iodide (0.541 g, 3.26 mmol) and cesium carbonate (1.062 g, 3.26 mmol) were added. The reaction mixture was heated at 60 °C for 24 h. DMF was removed in vacuo and the residue was dissolved in ethyl acetate and methanol to which silica gel was added and the solvents were removed under reduced pressure. The residue was applied to a silica gel column chromatography and eluted with ethyl acetate (R_F = 0.3). The required product was obtained as a yellow solid (0.310 g, 29%), mp > 230 °C. 1H NMR (DMSO-d_6): 11.35 (1H, s), 7.36-7.17 (10H, m), 5.74 (2H, s), 2.50 (6H, s). IR: 725, 760, 784, 811, 835, 879, 1155, 1225, 1441, 1508, 1516, 1543, 1600, 1633 cm^{-1}. HRESIMS: Found: 330.1710 Calculated for C_{20}H_{20}N_{3}F 330.1713.

6-(4-Fluorophenyl)-5-(4-methoxyphenyl)-N^4,N^4-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-2,4-diamine 36e

N^4,N^4-Dimethyl-2,4,6-pyrimidinetriamine (0.445 g, 2.907 mmol) and 2-Bromo-1-(4-fluorophenyl)-2-(4-methoxyphenyl)ethanone (0.939 g, 3.965 mmol) were dissolved in DMF (4 mL, dry) with stirring to which KI (0.541 g, 3.26 mmol) and cesium carbonate (1.062 g, 3.26 mmol) were added. The reaction mixture was heated at 60 °C overnight. Solvent was removed in vacuo and the crude material was dissolved in ethyl acetate, dried (Na_2SO_4), filtered and the solvent removed under reduced pressure. This material was applied to a silica gel column chromatography and eluted with (1:9 methanol:ethyl acetate) to give impure material (0.390 g, 35%). This material was further purified by HPLC to give the required product as a pale yellow solid with no distinct melting point. 1H-NMR (DMSO-d_6): 12.41 (1H, br), 7.23-7.12 (8H, m), 6.95 (2H, d, J = 8.7 Hz), 3.77 (3H, s), 2.73 (6H, s). IR: 705, 730, 767, 802, 844, 876, 1072, 1185, 1386, 1442, 1514, 1535, 1563, 1602, 1658 cm^{-1}. HRESIMS: Found: 378.1723 calculated for C_{20}H_{21}FN_{3}O 378.1725.

N^4-Cyclohexyl-5,6-diphenyl-7H-pyrrolo[2,3-d]pyrimidine-2,4-diamine 37

N^4-Cyclohexyl-2,4,6-pyrimidinetriamine (0.150 g, 0.724 mmol) and desyl bromide (0.199 g, 0.724 mmol) were dissolved in DMF (2 mL, dry). The reaction mixture was heated at 60 °C for 4 d. The solvent was removed in vacuo and the residue was applied to a silica gel column chromatography and eluted with 1:10 methanol:ethyl acetate, R_F = 0.5. The product was obtained as yellow solid (30 mg, 11%) after recrystallization from ethyl acetate:n-hexane. 1H-NMR (DMSO-d_6): 11.25 (1H, s), 7.49-7.09 (10H, m), 5.66 (2H, s), 4.39 (1H, d, J = 8.1 Hz), 3.96-3.92 (1H, m), 1.68-0.94 (10H, m). IR: 725, 760, 784, 811, 835, 879, 1155, 1225, 1441, 1508, 1516, 1543, 1600, 1633 cm^{-1}. HRESIMS: Found: 384.2180 Calculated for C_{24}H_{26}N_{5} 384.2183.
HPLC methods used to assess the purity of compounds:

First method:
*All the compounds showed purity of > 95%.
The retention time of these compounds was between (15 and 25 minutes).
Reverse phase HPLC on a water system using a C18 Luna column with the gradient given in the table.
Waters 717plus Autosampler, Waters 1525 Binary HPLC Pump, Waters 2487 Dual lambda Absorbance Detector
Programme for HPLC purification:

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Second method:
*All the compounds showed purity of equal or more than 95%.
The retention time of these compounds was between (8 and 20 minutes).
Instrument used:
Agilent: 1200LC coupled to 6130 Dual source MS, single wavelength detector @ 254nm
ChemStation software,
Method: The material was dissolved in 0.2 mL methanol then 4 drops were taken up into 0.4 mL mobile phase (1:1 acetonitrile/water containing 0.1% formic acid). Mass Range 100-1000 Da, UV@254. Time of run was 30 min.
Zorbax Eclipse column C18 150mm x 4.6mm, 5um

Retention time and purity of selected compounds as measured by HPLC and HPLC/MS

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<th>Method Two</th>
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**Protein Purification and Crystallography**

**Reagents**

PTR1 cofactors NADP⁺ and NADPH were purchased from Melford while all pterin substrates were obtained from Schircks Laboratories. Ligands were prepared in 100 % (v:v) dimethyl sulfoxide (DMSO) to 100 mM based on dry weight. The insolubility of any compound at this concentration was established following the application of sonication and heat (42 °C). Solubilized compounds were stored in glass vials at -20°C and 10-fold serial dilutions (in DMSO) made as working stocks.

**Recombinant protein purification**

Expression and purification of *TbPTR1* by a single affinity chromatography step, was carried out following a published protocol.¹⁶ The protein was buffer exchanged using a PD-10 desalting column (GE Healthcare) to 20 mM Tris-HCl pH 7.5 for crystallization or 50 mM Tris-HCl pH 7.5, 250 mM NaCl, 20 % (v:v) glycerol for assay. Following concentration to 15-20 mg mL⁻¹ in a centrifugal concentrator with 100 kDa molecular mass limit, aliquots of *TbPTR1* were flash cooled in liquid nitrogen and stored at -80 °C until required.

**Spectrophotometric assay**

Inhibition of *TbPTR1* activity was carried out according to an established spectrophotometric assay.¹⁶ In brief, 1 mL samples containing 30 μg *TbPTR1* (0.96 μM), 20 μM dihydriobiopterin and 0-1 mM compound of interest in 20 mM sodium citrate pH 3.7 were warmed to 30 °C in acrylic cuvettes (Sarstedt). Each reaction was started by the addition of 100 μM NADPH. The decrease in absorbance at 340 nm was monitored for 120 s using a Shimadzu UV-2450 spectrophotometer coupled to *UVProbe* (Shimadzu). Dihydrobiopterin stocks were prepared in 0.1 M NaOH to 10 mM and stored at -20 °C. Fresh NADPH was dissolved in water to 10 mM immediately prior to each set of approximately 50 measurements. DMSO to a final concentration of 1 % (v:v) was present throughout. All potential inhibitors were initially assessed in duplicate at 10 μM and 50 μM. Compounds showing inhibition of greater than 60-70 % at 50 μM were assayed in triplicate at a range of concentration points (9-12) to produce a full dose-response curve. Mean PTR1 inhibition (%) was plotted against the log compound concentration and a sigmoidal curve fit using four-parameter non-linear regression in *SigmaPlot*.
IC$_{50}$ values were extracted and $K_i$ values calculated using the Cheng-Prusoff equation for competitive inhibition where $K_i = IC_{50} : (1 + [S] \cdot K_m)$. Note that this assumes stoichiometry of 1:1 and that all inhibitor-binding reactions are reversible. Substrate $K_m$ was used as published (10.9 μM).

**TbPTR1-ligand co-crystallization and structure solution**

*TbPTR1* was crystallized in the presence of cofactor and ligand of interest following published methods. A mixture of 4-6 mg mL$^{-1}$ *TbPTR1*, 1 mM NADP$^+$, 20 mM DTT and 1 mM compound was incubated on ice for 1 h prior to crystallization. The solution was centrifuged to remove any insoluble material. 1-2 μL protein-ligand solution was then mixed with 1 μL crystallization solution containing 1.7-2.7 M NaOAc and 20-50 μM sodium citrate pH 4.5-5.0. Drops were suspended on siliconized glass coverslips above reservoirs containing the latter solution at 18°C.

Crystals grown in an excess of 2.6 M NaOAc were placed in a nylon loop and flash-cooled directly in liquid nitrogen. Otherwise, a solution of 3 M NaOAc was used to cryoprotect the *TbPTR1*-ligand co-crystal prior to cooling to -173°C. Diffraction data were collected in-house or at Diamond light source (Supplementary Table 1). Data were collected to 1.7-2.4 Å resolution and typically covered approximately 180 degrees of rotation. X-ray images were integrated using XDS or MOSFLM and scaled in SCALA or AIMLESS. Molecular replacement was performed by MOLREP or data were refined directly against the *TbPTR1* tetrameric starting model using REFMAC5 (PDB 2c7v). Electron and difference density map inspection and model manipulation with Coot was combined with multiple further refinement cycles. Non-crystallographic symmetry restraints were not applied and geometry restraint weightings were manually adjusted in later refinement calculations. The subset of data used to calculate $R_{free}$ was maintained in all structure analyses. Cofactor and solvent molecules were added to the model in Coot from the associated monomer library. Novel ligands were drawn using JME Molecule Editor and coordinates generated using PRODRG. Geometry restraints were obtained from PRODRG or eLBOW and each ligand placed according to difference density Fourier maps. For compounds 8b and 29a, two conformations were modelled and refined, each with occupancy set to 0.5. All coordinates and structure factors have been deposited in the Protein Data Bank.
Representative kill curves for active compounds against *T. brucei* in culture

**Time to kill *T. brucei* protocol:**

To determine the *in vitro* compounds' exposure required to kill trypanosomes, parasites were seeded at $2 \times 10^4$ cells/ml in either HMI-9 or CMM and cell concentration measured at regular intervals for 48-72 hours after exposure to a range of concentrations (IC$_{50}$, $10 \times$ IC$_{50}$ and $100 \times$ IC$_{50}$) of selected compounds. Untreated trypanosomes were monitored in parallel as negative control.

Growth curves of bloodstream *T. b. brucei* strain 427 treated with selected compounds at different doses in either HMI-9 or CMM. Data represent the average of at least two independent experiments and are given ± SEM.

**Pyrrolopyrimidines**

![Graph showing growth curves for bloodstream *T. b. brucei* strain 427 treated with selected compounds at different doses in either HMI-9 or CMM. Data represent the average of at least two independent experiments and are given ± SEM.](image)
Nitro intermediates
Estimation of physicochemical parameters
Pipeline Pilot ® (Accelrys Inc.) uses an atom-based method to calculate logP. Estimation of pKₐ is carried out using the path fingerprints for the identified ionization sites and comparing them with comparable sites of known pKₐ.

References for supplementary information


17. Cheng, Y., Prusoff, W.H., Relationship between the inhibition constant (K_i) and the concentration of inhibitor which causes 50 per cent inhibition (IC_{50}) of an enzymatic reaction, Biochem. Pharmacol. 1973, 22, 3099–3108.


