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Chemistry & Drug Discovery

Supporting Information

Synthesis and Biological Evaluation of N^2-Substituted 2,4-Diamino-6-cyclohexylmethoxy-5-nitrosopyrimidines and Related 5-Cyano-NNO-azoxy Derivatives as Cyclin-Dependent Kinase 2 (CDK2) Inhibitors

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Chemistry

Materials and methods. Chemicals were obtained from reputable suppliers used without any further purification. Anhydrous solvents were obtained from Acroseal™ or SureSeal™ and stored under nitrogen. Synthetic-purity solvents dichloromethane (DCM), acetonitrile (CH_3CN), methanol (MeOH), diethyl ether (Et_2O), diisopropyl ether (*i*-Pr_2O), dimethylformamide (DMF) and 40–60 petroleum ether (PE) were used. Deuterated solvent for NMR analysis were purchased from Sigma-Aldrich. Thin layer chromatography was performed using plates pre-coated with Si F_{254}, NH_2 F_{254s} or RP-18 F_{254s} and visualized using ultraviolet light. Purifications were carried out using a Biotage SP4 automated purification system with UV monitoring at 290 nm and collection at 254 nm. Grace Resolv pre-packed flash cartridges were used for normal phase separations. Microwave-assisted synthesis was performed in sealed Biotage microwave vials, using the Biotage Initiator Sixty microwave system. ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded at 500 MHz and 125 MHz, respectively, using a Bruker Advance III 500 spectrometer or at 300 MHz and 75 MHz, respectively on a Bruker Advance 300 spectrometer. $CDCl_3$, MeOH-d_4 or DMSO-d_6 were used as solvents. Chemical shift values (δ) are reported in parts per million (ppm) and are referenced against TMS (tetramethylsilane); multiplicities are indicated by *s* = singlet, *d*= doublet, *t* = triplet, *q* = quarted, *m* = multiplet or combination thereof; the prefix *br* = broad was used for broadened peaks. Liquid Chromatography-Mass Spectrometry (LC-MS) was carried out on a Waters Acquity UPLC system, with PDA and ELSD employing both positive and negative ionization modes. When a 2 min gradient was used, the sample was eluted on Acquity UPLC BEH C18, 1.7 µm, 2.1 × 50 mm, with a flow rate of 0.6 mL/min using 5-95% 0.1% HCOOH in MeCN. High resolution mass spectra were measured using a Finnigan MAT 95 XP or Finnigan MAT 900 XLT by the EPSRC National Mass Spectrometry Service, University of Wales, Swansea, Singleton Park. Melting points were determined using a Stuart Scientific SMP3 apparatus. Fourier Transform Infrared (FTIR) spectra were recorded on a Bio-Rad FTS 3000MX diamond ATR apparatus. Ultraviolet (UV) absorption data were obtained using a U-2001 Hitachi Spectrophotometer with the sample dissolved in ethanol. Compounds submitted for biological evaluation were obtained with a purity higher than 95%. Purity was determined using a Waters XTerra RP18, 5 µm (4.6 × 150 mm) column eluted at 1 mL/min under both basic (0.1% aq. ammonia and MeCN) and acidic (0.1% aq. HCOOH and MeCN) conditions with a gradient of 5-100% over 15 min.

5-Methyl-2-(propan-2-yl)cyclohexyl nitrite (Menthyl nitrite) was prepared following the reported procedure[1] with slight modifications. Product was obtained from L-menthol using

$NaNO_2$ in a water/THF mixture and a solution of 4M HCl. The spectroscopic data are consistent with those reported.[2] R_f 0.85 (PE); IR ν_{max}/cm^{-1}: 2966, 2936, 2881, 1642; ^{1}H-NMR (500 MHz, DMSO-*d*$_6$) δ (ppm): 0.74 (3H, d, J = 7.0 Hz, CH(C*H*$_3$)$_2$), 0.86 (3H, d, J = 7.0 Hz, CH(C*H*$_3$)$_2$), 0.89-0.91 (1H, m, CH_2(H4)), 0.92 (3H, d, J = 6.5 Hz, CHC*H*$_3$), 1.14-1.24 (2H, m, 1 × CH_2(H3) and 1 × CH_2(H6), 1.42-1.49 (1H, m, CH(H2)), 1-59-1.75 (4H, 1 × CH(H5), 1 × CH_2(H4), 1 × CH_2(H3) and 1 × C*H*(CH$_3$)$_2$), 1.95-2.02 (1H, m, CH_2(H6), 5.33 (1H, td, J = 11.2 and 4.5 Hz, CHO); ^{13}C-NMR (125 MHz, DMSO-*d*$_6$) δ (ppm): 15.75, 20.42, 21.81, 22.99, 25.60, 30.95, 33.45, 41.37, 46.01, 80.09; MS (CI) *m/z* (%): 139 ([M–HONO+H$^+$]).

6-(Cyclohexylmethoxy)-2-[(cyclohexylmethyl)sulfanyl]pyrimidin-4-amine (5). To 6-amino-2-thioxo-2,3-dihydropyrimidin-4(1*H*)-one **4** (1.00 g, 6.20 mmol) contained in a dry microwave vial was added anhydrous DMF (10 mL). Potassium carbonate (5.13 g, 37.2 mmol) and (bromomethyl)cyclohexane (2.16 mL, 2.74 g, 15.5 mmol) were added, the mixture was degassed with N_2 and then heated at 140 °C by microwave irradiation for 16 min. The solvent was removed under reduced pressure and the residue was taken up in water. The product was extracted with DCM (3 × 15 mL). The organic phases were combined, washed with brine and dried ($MgSO_4$). The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (gradient from 10/90 to 20/80 acetone/PE) to give the title compound as a white solid (1.65 g, 79%). R_f 0.45 (20/80 Acetone/PE); m.p. 111-112 °C; UV λ_{max} (EtOH/nm): 253.0, 224.0; IR ν_{max}/cm^{-1}: 3392, 3293, 2915, 2842; ^{1}H-NMR (500 MHz, DMSO-*d*$_6$) δ (ppm): 0.90-1.28 (10H, m, 5H × C_6H_{11} and 5 × C_6H_{11}), 1.48-1.89 (12H, m, 6H × C_6H_{11} and 6 × C_6H_{11}), 2.90 (2H, d, *J* = 6.8 Hz, CH_2S), 4.00 (2H, d, *J* = 6.5 Hz, CH_2O), 5.37 (1H, s, CH arom.), 6.60 (2H, s, NH_2); ^{13}C-NMR (125 MHz, DMSO-*d*$_6$) δ (ppm): 25.15, 25.57, 25.91, 25.98, 29.15, 32.09, 36.60, 36.82, 37.58, 70.21, 81.59, 165.12, 168.72, 169.29; MS (ES$^+$) *m/z* 336.4 [M+H]$^+$.

6-(Cyclohexylmethoxy)-2-[(cyclohexylmethyl)sulfonyl]pyrimidin-4-amine (6). To 6-(cyclohexylmethoxy)-2-((cyclohexylmethyl)thio)pyrimidin-4-amine **5** (660 mg, 1.97 mmol) in DCM (15 mL) 3-chloroperbenzoic acid (1.70 g, 9.85 mmol) was added portionwise. The reaction mixture was stirred at room temperature for 17 h. The solvent was removed under reduced pressure and the residue was partitioned between water (20 mL) and EtOAc (3 × 15 mL). The combined organic extracts were washed with saturated aq. $NaHCO_3$, brine and dried ($MgSO_4$). The crude product was purified by flash chromatography (gradient from 10/90 to 20/80 acetone/PE) to give the title compound as a white powder (404 mg, 56%). R_f 0.28 (20/80 Acetone/PE); m.p. 139-140°C; UV λ_{max} (EtOH/nm): 245.0, 215.8; IR ν_{max}/cm^{-1}: 3494, 3412, 2923, 2851, 1364 (S=O), 1136 (S=O); ^{1}H-NMR (500 MHz, DMSO-*d*$_6$) δ (ppm): 0.93-1.31 (10H,

m, 5H × C_6H_{11} and 5 × C_6H_{11}), 1.51-1.93 (12H, m, 6H × C_6H_{11} and 6 × C_6H_{11}), 3.34 (2H, d, *J* = 6.3 Hz, CH_2S), 4.04 (2H, d, *J* = 6.3 Hz, CH_2O), 5.81 (1H, s, CH arom.), 7.34 (2H, s, NH_2); ^{13}C-NMR (125 MHz, DMSO-d_6) δ (ppm): 25.15, 25.25, 25.40, 25.90, 29.03, 31.17, 32.27, 36.76, 55.83, 71.45, 86.87, 164.66, 166.07, 169.48; MS (ES^+) *m/z* 368 $[M+H]^+$.

2-{[4-Amino-6-(cyclohexylmethoxy)pyrimidin-2-yl]amino}propan-1-ol (7a). To 6-(cyclohexylmethoxy)-2-((cyclohexylmethyl)sulfonyl)pyrimidin-4-amine **6** (250 mg, 0.68 mmol) contained in a dry microwave vial was added diglyme (3 mL). Ethanolamine (144 µL, 146 mg, 2.38 mmol) was added, the mixture was degassed with N_2 and then heated to 170°C by microwave irradiation for 3h. The solvent was removed under reduced pressure and the residue was partitioned between water (20 mL) and EtOAc (3 × 15 mL). The organic extracts were washed with brine and dried ($MgSO_4$). The crude product was purified by flash chromatography (gradient from 0/100 to 5/95 MeOH/CH_2Cl_2) to give the title compound as a white solid (118 mg, 65 %). R_f 0.17 (5/95 MeOH/CH_2Cl_2); m.p. 74-75 °C; UV λ_{max} (EtOH/nm): 268.6, 238,2, 208.4; IR ν_{max}/cm^{-1}: 3428, 3322, 3274, 2918, 2851, 1552; ^{1}H-NMR (500 MHz, DMSO-d_6) δ (ppm): 0.90-1.27 (5H, m, C_6H_{11}), 1.59-1.75 (6H, m, C_6H_{11}), 3.21-3.27 (2H, m, C*H*$_2$NH), 3.43-3.48 (2H, m, C*H*$_2$OH), 3.90 (2H, d, *J* = 6.5 Hz, CH_2O), 4.63 (1H, t, *J* = 5.4 Hz OH), 5.01 (1H, s, CH arom.), 6.02 (2H, s, NH_2), 6.15 (1H, t, *J* = 5.6 Hz, NH); ^{13}C-NMR (125 MHz, DMSO-d_6) δ (ppm): 25.25, 26.03, 29.30, 36.98, 43.37, 60.37, 69.64, 75.85, 162.04, 165.79, 170.01; MS (ES^+) *m/z* 267 $[M+H]^+$.

(2*S*)-2-{[4-Amino-6-(cyclohexylmethoxy)pyrimidin-2-yl]amino}propan-1-ol (7b). To 6-(cyclohexylmethoxy)-2-((cyclohexylmethyl)sulfonyl)pyrimidin-4-amine **6** (300 mg, 0.82 mmol) contained in a dry microwave vial was added dry THF (2.5 mL). $Yb(OSO_2CF_3)_3$ (253 mg, 0.41 mmol) was added followed by (S)-(+)-2-amino-1-propanol (223 µL, 215 mg, 2.86 mmol), the mixture was degassed with N_2 and then heated to 120°C by microwave irradiation for 30 min. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (gradient from 0/100 to 10/90 MeOH/CH_2Cl_2) to give the title compound as a sticky white solid (60 mg, 26 %). R_f 0.21 (5/95 MeOH/CH_2Cl_2); UV λ_{max} (EtOH/nm): 268.6, 238.6, 208.2; IR ν_{max}/cm^{-1}: 3334, 3217, 2921, 2849, 1566; ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 0.96-1.04 (2H, m, C_6H_{11}), 1.20 (3H, d, *J* = 6.86 Hz, CH_3), 1.13-1.30 (3H, m, C_6H_{11}), 1.66-1.81 (6H, m, C_6H_{11}), 3.56 (1H, dd, *J* = 10.69 and 7.78 Hz, C*H*$_2$OH), 3.72 (1H, dd, *J* = 10.70 and 2.79 Hz, C*H*$_2$OH), 3.91-3.99 (2H, m, CH_2O), 4.04-4.11 (1H, m, CH), 4.47 (2H, s, NH_2), 4.80 (1H, d, *J* = 5.63 Hz, NH), 5.19 (1H, s, CH arom.); ^{13}C-NMR (125 MHz, $CDCl_3$) δ (ppm): 17.92, 25.96, 26.65, 29.97, 37.63, 50.02, 69.91, 71.52, 78.00, 162.56, 164.92, 171.52; MS (ES^+) *m/z* 281 $[M+H]^+$.

(2*R*)-2-{[4-Amino-6-(cyclohexylmethoxy)pyrimidin-2-yl]amino}propan-1-ol (7c). To 6-(cyclohexylmethoxy)-2-((cyclohexylmethyl)sulfonyl)pyrimidin-4-amine **6** (300 mg, 0.82 mmol) contained in a dry microwave vial was added dry THF (2.5 mL). $Yb(OSO_2CF_3)_3$ (253 mg, 0.41 mmol) was added followed by (R)-(-)-2-amino-1-propanol (223 µL, 215 mg, 2.86 mmol), the mixture was degassed with N_2 and then heated to 120°C by microwave irradiation for 30 min. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (gradient from 0/100 to 10/90 MeOH/CH_2Cl_2) to give the title compound as a sticky white solid (33 mg, 14%).R_f 0.21 (5/95 MeOH/CH_2Cl_2); UV λ_{max} (EtOH/nm): 269.0, 238.8, 208.2; IR ν_{max}/cm^{-1}: 3334, 3213, 2921, 2850, 1568; ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 0.94-1.05 (2H, m, C_6H_{11}), 1.19 (3H, d, *J* = 6.86 Hz, CH_3), 1.11-1.30 (3H, m, C_6H_{11}), 1.63-1.83 (6H, m, C_6H_{11}), 3.55 (1H, dd, *J* = 10.7 and 7.6 Hz, C*H*$_2$OH), 3.71 (1H, dd, *J* = 10.7 and 2.7 Hz, C*H*$_2$OH), 3.89-3.99 (2H, m, CH_2O), 4.02-4.11 (1H, m, CH), 4.53 (2H, s, NH_2), 4.88 (1H, d, *J* = 5.77 Hz, NH), 5.18 (1H, s, CH arom.); ^{13}C-NMR (125 MHz, $CDCl_3$) δ (ppm): 17.57, 25.80, 26.49, 29.83, 37.47, 49.31, 68.16, 71.34, 77.45, 162.10, 165.01, 171.24; MS (ES^+) *m/z* 281 $[M+H]^+$.

(2*R*)-2-{[4-Amino-6-(cyclohexylmethoxy)pyrimidin-2-yl]amino}butan-1-ol (7d). To 6-(cyclohexylmethoxy)-2-((cyclohexylmethyl)sulfonyl)pyrimidin-4-amine **6** (200 mg, 0.54 mmol) contained in a dry microwave vial dry THF (2.5 mL) was added. $Yb(OSO_2CF_3)_3$ (169 mg, 0.27 mmol) was added followed by (R)-(-)-2-amino-1-butanol (180 µL, 170 mg, 1.91 mmol), the mixture was degassed with N_2 and then heated to 120°C in the oil bath for 24 h. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (2/98 MeOH/CH_2Cl_2) to give the title compound as a white solid (90 mg, 59%). R_f 0.24 (5/95 MeOH/CH_2Cl_2); m.p. 79-80 °C; ^{1}H-NMR (500 MHz, DMSO-d_6) δ (ppm): 0.84 (3H, t, *J* = 7.3 Hz, CH_3), 0.90-1.31 (5H, m, C_6H_{11}), 1.31-1.47 (1H, m, C*H*$_2$$CH_3$), 1.50-1.80 (7H, m, 6 × C_6H_{11} and 1 × C*H*$_2$$CH_3$), 3.26-3.46 (2H, m, C*H*$_2$OH), 3.62-3.80 (1H, m, C*H*CH_2CH_3), 3.80-3.99 (2H, m, CH_2O), 4.59 (1H, br. s, OH), 5.00 (1H, s, CH arom.), 5.88 (1H, d, *J* = 8.4 Hz, NH), 5.99 (2H, s, NH_2); ^{13}C-NMR (125 MHz, $CDCl_3$) δ (ppm): 10.67, 23.90, 25.33, 26.09, 29.37, 37.03, 53.45, 63.18, 69.70, 75.81, 161.99, 165.75, 170.00; MS (ES^+) *m/z* 295.5 $[M+H]^+$.

2-{[4-amino-6-(cyclohexylmethoxy)pyrimidin-2-yl]amino}-3-methylbutan-1-ol (7e). To 6-(cyclohexylmethoxy)-2-((cyclohexylmethyl)sulfonyl)pyrimidin-4-amine **6** (300 mg, 0.82 mmol) contained in a dry microwave vial was added diglyme (3 mL). 2-amino-3-methyl-1-butanol (315 µL, 295 mg, 2.86 mmol) was added, the solution was degassed with N_2 and then heated to 170 °C by microwave irradiation for 12 h. The solvent was removed under reduced pressure and the residue was partitioned between water (20 mL) and EtOAc (3 × 15 mL). The organic extracts were washed with brine and dried ($MgSO_4$). The crude product was purified by flash

chromatography (gradient from 0/100 to 10/90 MeOH/CH_2Cl_2) to give the title compound as a white solid (131 mg, 52 %). R_f 0.2 (5/95 MeOH/CH_2Cl_2); m.p. 110-111 °C; UV λ_{max} (EtOH/nm): 269.4, 239.0, 208.2; IR ν_{max}/cm^{-1}: 3441, 3341, 3238, 2922, 2850, 1572; ^{1}H-NMR (500 MHz, DMSO-d_6) δ (ppm): 0.85 (3H, d, J = 7.1 Hz, CH_3), 0.87 (3H, d, *J* = 7.1 Hz, CH_3) 0.90-1.02 (2H, m, C_6H_{11}), 1.09-1.29 (3H, m, C_6H_{11}), 1.59-1.77 (6H, m, C_6H_{11}), 1.84-1.94 (1H, m, C*H*CH_3) 3.39-3.46 (2H, m, C*H*$_2$OH), 3.69-3.76 (1H, m, C*H*CH_2OH), 3.87 (1H, dd, *J* = 10.2 and 6.6 Hz, CH_2O), 3.94 (1H, br.s., CH_2O), 4.47 (1H, t, *J* = 5.4 Hz, OH), 5.00 (1H, s, CH arom.), 5.77 (1H, d, *J* = 8.9 Hz, NH), 5.95 (2H, s, NH_2); ^{13}C-NMR (125 MHz, DMSO-d_6) δ (ppm): 18.47, 19.52, 25.26, 26.04, 28.53, 29.30, 36.97, 56.80, 61.48, 69.62, 75.76, 162.25, 165.71, 169.93; MS (ES^+) *m/z* 309 $[M+H]^+$.

3-{[4-Amino-6-(cyclohexylmethoxy)pyrimidin-2-yl]amino}propan-1-ol (7f). To 6-(cyclohexylmethoxy)-2-((cyclohexylmethyl)sulfonyl)pyrimidin-4-amine **6** (250 mg, 0.68 mmol) contained in a dry microwave vial was added dry THF (2.5 mL). $Yb(OSO_2CF_3)_3$ (211 mg, 0.34 mmol) was added followed by 3-amino-1-propanol (201 µL, 179 mg, 2.38 mmol), the solution was degassed with N_2 and then heated to 120°C by microwave irradiation for 30 min. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (gradient from 0/100 to 10/90 MeOH/CH_2Cl_2) to give the title compound as a white solid (77 mg, 40%). R_f 0.18 (5/95 MeOH/CH_2Cl_2); m.p. 108-109°C; UV λ_{max} (EtOH/nm): 269.0, 238.4, 208.0; IR ν_{max}/cm^{-1}: 3439, 3334, 3249, 3207, 3095, 2918, 2849, 1574; ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 0.93-1.07 (2H, m, C_6H_{11}), 1.11-1.32 (3H, m, C_6H_{11}), 1.62-1.86 (8H, m, 6 × C_6H_{11} and 2 × C*H*$_2$OH), 3.50-3.56 (2H, m, C*H*$_2$NH), 3.60-3.64 (2H, m, CH_2C*H*$_2$$CH_2$), 3.93 (2H, d, *J* = 6.5 Hz, CH_2O), 4.47 (2H, s, NH_2), 4.90 (1H, t, *J* = 6.5 Hz, NH) 5.17 (1H, s, CH arom.); ^{13}C-NMR (125 MHz, $CDCl_3$) δ (ppm): 25.89, 26.60, 29.92, 33.52, 37.11, 37.56, 58.34, 71.47, 77.37, 162.94, 165.07, 171.58; MS (ES^+) *m/z* 281 $[M+H]^+$.

***N*^{2}-(2-Aminocyclohexyl)-6-(cyclohexylmethoxy)pyrimidine-2,4-diamine (7g).** To 6-(cyclohexylmethoxy)-2-((cyclohexylmethyl)sulfonyl)pyrimidin-4-amine **6** (400 mg, 1.09 mmol) contained in a dry microwave vial was added dry THF (3 mL). $Yb(OSO_2CF_3)_3$ (68 mg, 0.11 mmol) was added followed by (±)-*trans*-1,2-diaminocyclohexane (436 mg, 3.81 mmol) and the solution was degassed with N_2 then heated to 120 °C by microwave irradiation for 6.5 h. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (gradient from 5/95 to 30/70 MeOH/CH_2Cl_2) to give the title compound as a white solid (203 mg, 58 %). R_f 0.23 (10/90 MeOH/CH_2Cl_2); m.p. 90-91°C; UV λ_{max} (EtOH/nm): 266.8, 209.0; IR ν_{max}/cm^{-1}: 3483, 3432, 3354, 2922, 2851, 1569; ^{1}H-NMR (500 MHz, DMSO-d_6)

δ (ppm): 0.85-1.26 (9H, m, 5 × C_6H_{11} and 4 × C_6H_{11}), 1.53-1.75 (10H, m, 6 × C_6H_{11} and 4 × C_6H_{11}), 2.57-2.65 (1H, m, C*H*NH_2), 3.39-3.51 (1H, m, C*H*NH), 3.81-3.90 (1H, m, CH_2O), 3.91-4.00 (1H, m, CH_2O), 4.19 (2H, br. s., NH_2), 5.02 (1H, s, CH arom.), 6.02 (2H, s, NH_2), 6.22 (1H, d, *J* = 8.1 Hz, NH); ^{13}C-NMR (125 MHz, DMSO-d_6) δ (ppm): 24.52, 24.80, 25.24, 25.76, 26.03, 29.33, 31.87, 36.95, 53.65, 55.56, 69.71, 75.91, 162.04, 165.75, 169.94; MS (ES^+) *m/z* 320 $[M+H]^+$.

***tert*-Butyl {2-[(4-amino-6-(cyclohexylmethoxy)pyrimidin-2-yl)amino]cyclohexyl} carbamate (10).** To N^2-(2-aminocyclohexyl)-6-(cyclohexylmethoxy)pyrimidine-2,4-diamine **7g** (230 mg, 0.721 mmol) in dry THF (3 mL) was added di-*tert*-butyl dicarbonate ($(Boc)_2O$) (173 mg, 0.793 mmol) at room temperature. After 2 h the reaction was complete and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (gradient from 0/100 to 5/95 MeOH/CH_2Cl_2) to give the title compound as a white solid (200 mg, 66 %). R_f 0.24 (5/95 MeOH/CH_2Cl_2); m.p. 86-87 °C; UV λ_{max} (EtOH/nm): 269.6, 238.6, 209.0; IR ν_{max}/cm^{-1}: 3343, 3238, 2922, 2851, 1697, 1571; ^{1}H-NMR (500 MHz, DMSO-d_6) δ (ppm): 0.88-1.27 (9H, m, 5 × C_6H_{11} and 4 × C_6H_{11}), 1.55-2.03 (10H, m, 6 × C_6H_{11} and 4 × C_6H_{11}), 3.14-3.26 (1H, m, C*H*NH), 3.40-3.56 (1H, m, C*H*NH), 3.79-3.99 (2H, m, CH_2O), 5.00 (1H, s, CH arom.), 5.86 (1H, d, *J* = 7.2 Hz, NH), 6.02 (2H, s, NH_2), 6.66 (1H, d, *J* = 7.9 Hz, NH); ^{13}C-NMR (125 MHz, DMSO-d_6) δ (ppm): 24.50, 25.21, 26.03, 28.16, 29.30, 31.87, 36.91, 54.18, 54.49, 69.73, 75.88, 77.53, 155.88, 161.85, 165.77, 169.87; MS (ES^+) *m/z* 420 $[M+H]^+$.

2-{1-[4-Amino-6-(cyclohexylmethoxy)pyrimidin-2-yl]piperidin-4-yl}ethan-1-ol (7h). To 6-(cyclohexylmethoxy)-2-((cyclohexylmethyl)sulfonyl)pyrimidin-4-amine **6** (200 mg, 0.54 mmol) contained in a dry microwave vial was added dry THF (2 mL). $Yb(OSO_2CF_3)_3$ (169 mg, 0.27 mmol) was added followed by 4-piperydinethanol (246 mg, 1.91 mmol), the solution was degassed with N_2 and then heated to 120°C by microwave irradiation for 7 h. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (gradient from 1/99 to 2/98 MeOH/CH_2Cl_2) to give the title compound as a white solid (90 mg, 49 %). R_f 0.25 (5/95 MeOH/CH_2Cl_2); m.p. 89-90°C; ^{1}H-NMR (300 MHz, DMSO-d6) δ (ppm): 0.84-1.30 (9H, m, 5 × C_6H_{11} and 4 × CH_2piperidine), 1.31-1.41 (2H, m, CH_2CH_2CH), 1.53-1.76 (7H, m, 6 × C_6H_{11} and 1 × C*H* piperidine), 2.60-2.76 (2H, m, CH_2N), 3.40-3.50 (2H, m, CH_2OH), 3.91 (2H, d, *J* = 5.8 Hz, CH_2O), 4.36 (1H, t, *J* = 4.7 Hz, O*H*), 4.47-4.61 (2H, m, CH_2N), 5.00 (1H, s, C*H* arom.), 6.06 (2H, s, NH_2); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 25.37, 26.07, 29.42, 31.86, 32.57, 38.61, 40.05, 43.58, 58.24, 69.68, 75.48, 160.94, 165.79, 169.94; MS (ES^+) *m/z* 335 $[M+H]^+$.

6-(Cyclohexylmethoxy)-2-(pyrrolidin-1-yl)pyrimidin-4-amine (7i). To 6-(cyclohexylmethoxy)-2-((cyclohexylmethyl)sulfonyl)pyrimidin-4-amine **6** (200 mg, 0.54 mmol) contained in a dry microwave vial was added dry THF (2 mL). $Yb(OSO_2CF_3)_3$ (169 mg, 0.27 mmol) was added followed by pyrrolidine (159 µL, 138 mg, 1.91 mmol), the solution was degassed with N_2 and then heated to 120°C by microwave irradiation for 2 h. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (gradient from 1/99 to 2/98 MeOH/CH_2Cl_2) to give the title compound as a white solid (120 mg, 80%). R_f 0.3 (5/95 MeOH/CH_2Cl_2); m.p. 140-141 °C; ^{1}H-NMR (300 MHz, DMSO-d_6) δ (ppm): 0.90-1.27 (5H, m, C_6H_{11}), 1.61-1.73 (6H, m, C_6H_{11}), 1.81-1.85 (4H, m, CH_2CH_2 pyrrolidine), 3.34-3.39 (4H, m, 2 × CH_2N pyrrolidine), 3.94 (2H, d, J = 6.0 Hz, CH_2O), 5.02 (1H, s, CH arom.), 6.02 (2H, s, NH_2); ^{13}C-NMR (75 MHz, DMSO-d_6) δ (ppm): 24.99, 25.34, 26.07, 29.41, 37.14, 46.04, 69.52, 75.28, 160.00, 165.74, 169.71; MS (ES$^+$) *m/z* 277 $[M+H]^+$.

General procedure for synthesis of nitroso derivatives 8. The corresponding 6-(cyclohexylmethoxy)-N^2-pyrimidine-2,4-diamine **7** was dissolved in DMSO and the appropriate alkyl nitrite (2.5 eq.) was added at r.t. The reaction mixture was stirred for 24 h when 200 mL of H_2O were added and product was extracted with EtOAc (3 × 15 mL). The organic fractions were combined, washed with brine and dried ($MgSO_4$). The solvent was removed under reduced pressure and the crude product purified by flash chromatography.

2-[(4-Amino-6-cyclohexylmethoxy-5-nitrosopyrimidin-2-yl)amino]ethan-1-ol (8a). Prepared starting from **7a** (44 mg, 0.165 mmol), using isopentyl nitrite (56 µL, 49 mg, 0.413 mmol). The crude product was purified by flash chromatography (gradient from 1/99 to 20/80 MeOH/CH_2Cl_2) to give the title compound as a purple solid (43 mg, 88 %). R_f 0.2 (5/95 MeOH/CH_2Cl_2); m.p. 146-148°C; UV λ_{max} (EtOH/nm): 339.2, 237.6; IR ν_{max}/cm^{-1}: 3236, 3144, 2923, 2852, 1569. The compound exists as two conformers, conformer 1 / conformer 2 ratio = 2 / 1. ^{1}H-NMR (500 MHz, DMSO-d_6) δ (ppm): 0.99-1.32 (10H, m, 5 × C_6H_{11} conformer 1 and 5 × C_6H_{11} conformer 2), 1.61-1.91 (12H, m, 6 × C_6H_{11} conformer 1 and 6 × C_6H_{11} conformer 2), 3.35-3.40 (2H, m, CH_2NH conformer 1), 3.41-3.46 (2H, m, CH_2NH conformer 2), 3.49-3.57 (4H, m, 2 × CH_2OH conformer 1 and 2 × CH_2OH conformer 2), 4.29 (2H, d, J = 6.4 Hz, CH_2O conformer 1), 4.35 (2H, d, J = 6.4 Hz, CH_2O conformer 2), 4.70-4.76 (2H, m, 1 × OH conformer 1 and 1 × OH conformer 2), 7.89 (1H, d, J = 4.4 Hz, NH_2 conformer 2), 8.16 (1H, t, J= 5.9 Hz, NH conformer 2), 8.19 (1H, d, J = 4.4 Hz, NH_2 conformer 1), 8.26 (1H, t, J = 5.8 Hz, NH conformer 1), 9.93 (1H, d, J = 4.4 Hz, NH_2 conformer 2), 10.28 (1H, d, J = 4.4 Hz, NH_2 conformer 1); ^{13}C-

NMR (125 MHz, DMSO-d_6) δ (ppm): conformer 1: 25.14, 25.95, 29.14, 36.69, 43.69, 59.32, 71.47, 139.54, 150.57, 161.49, 169.94; conformer 2: 25.24, 25.95, 29.20, 36.91, 43.88, 59.70, 71.55, 139.67, 150.57, 161.93, 170.71; MS (ES^+) *m/z* 296 $[M+H]^+$; HRMS calcd for $C_{13}H_{21}N_5O_3$ $[M+H]^+$296.1717, found 296.1717.

(2*S*)-2-[(4-Amino-6-cyclohexylmethoxy-5-nitrosopyrimidin-2-yl)amino]propan-1-ol (8b). Prepared starting from **7b** (55 mg, 0.196 mmol), using menthyl nitrite (127 mg, 0.687 mmol). The crude product was purified by flash chromatography (gradient from 0/100 to 5/95 MeOH/CH_2Cl_2) to give the title compound as a purple solid (40 mg, 66%). R_f 0.3 (5/95 MeOH/CH_2Cl_2); m.p. 72-74ºC; UV λ_{max} (EtOH/nm): 339.4, 238.0; IR ν_{max}/cm^{-1}: 3249, 2923, 2851, 1558. The compound exists as two conformers, conformer 1 / conformer 2 ratio = 5 / 3, ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 1.01-1.34 (16H, m, 5 × C_6H_{11} and 3 × CH_3 conformer 1, 5 × C_6H_{11} and 3 × CH_3 conformer 2), 1.53-2.02 (12H, m, 6 × C_6H_{11} conformer 1 and 6 × C_6H_{11} conformer 2), 2.84 (2H, br. s, 1 × OH conformer 1 and 1 × OH conformer 2), 3.60-3.68 (2H, m, 1 × C*H*$_2$OH conformer 1 and 1 × C*H*$_2$OH conformer 2), 3.77 (1H, dd , *J* = 11.0 and 3.6 Hz, C*H*$_2$OH conformer 1), 3.85 (1H, dd , *J* = 10.7 and 3.0 Hz, C*H*$_2$OH conformer 2) 4.21-4.28 (1H, m, C*H*NH conformer 1), 4.30-4.37 (4H, m, 2 xCH_2O conformer 1, 1 × CH_2O conformer 2 and 1 × C*H*NH conformer 2), 4.41 (1H, dd, *J* = 10.4 and 6.5 Hz, CH_2O conformer 2), 5.59 (1H, br. s, NH_2 conformer 1), 5.81 (1H, d, *J* = 7.7 Hz, NH conformer 1), 6.00 (1H, br. s, NH_2 conformer 2), 6.54 (1H, br. s, NH conformer 2), 10.29 (1H, br. s, NH_2 conformer 2), 10.61 (1H, br. s, NH_2 conformer 1); ^{13}C-NMR (125 MHz, $CDCl_3$) δ (ppm): conformer 1: 17.33, 25.79, 26.53, 29.88, 37.23, 49.55, 67.23, 73.07, 140.20, 150.81, 162.23, 171.12; conformer 2: 17.33, 25.86, 26.50, 29.98, 37.45, 49.44, 66.36, 73.28, 140.07, 151.08, 162.28, 171.80; MS (ES^+) *m/z* 310 $[M+H]^+$; HRMS calcd for $C_{14}H_{23}N_5O_3$ $[M+H]^+$ 310.1874, found 310.1876.

(2*R*)-2-[(4-Amino-6-cyclohexylmethoxy-5-nitrosopyrimidin-2-yl)amino]propan-1-ol (8c). Prepared starting from **7c** (46 mg, 0.164 mmol), using menthyl nitrite (106 mg, 0.575 mmol). The crude product was purified by flash chromatography (gradient from 0/100 to 5/95 MeOH/CH_2Cl_2) to give the title compound as a purple solid (30 mg, 60%). R_f 0.3 (5/95 MeOH/CH_2Cl_2); m.p. 94-96 ºC; UV λ_{max} (EtOH/nm): 339.6, 237.8; IR ν_{max}/cm^{-1}: 3235, 2920, 2848, 1563. The compound exists as two conformers, conformer 1 / conformer 2 ratio = 5 / 3. ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 1.00-1.35 (16H, m, 5 × C_6H_{11} and 3 × CH_3 conformer 1, 5 × C_6H_{11} and 3 × CH_3 conformer 2), 1.65-2.02 (12H, m, 6 × C_6H_{11} conformer 1 and 6 × C_6H_{11} conformer 2), 2.58 (1H, br. s, OH conformer 2), 2.78 (1H, br. s, OH conformer 1) 3.61-3.68 (2H, m, 1 × C*H*$_2$OH conformer 1 and 1 × C*H*$_2$OH conformer 2), 3.77 (1H, dd, *J* = 10.9 and 3.6 Hz, C*H*$_2$OH conformer 1), 3.84 (1H, dd , *J*= 10.9 and 3.6 Hz, C*H*$_2$OH conformer 2) 4.20-4.28 (1H,

m, C*H*NH conformer 1), 4.31-4.37 (4H, m, 2 × CH_2O conformer 1, 1 × CH_2O conformer 2 and 1 × C*H*NH conformer 2), 4.42 (1H, dd, *J* = 10.4 and 6.6 Hz, CH_2O conformer 2) 5.58 (1H, br. s, NH_2 conformer 1), 5.80 (1H, d, *J* = 7.6 Hz, NH conformer 1), 5.85 (1H, br. s, NH_2 conformer 2), 6.36 (1H, d, *J* = 7.6 Hz, NH conformer 2), 10.28 (1H, br. d, *J* = 4.7 Hz, NH_2 conformer 2), 10.61 (1H, br. s, NH_2 conformer 1); ^{13}C-NMR (125 MHz, $CDCl_3$) δ (ppm): conformer 1: 17.34, 25.79, 26.53, 29.88, 37.23, 49.54, 67.25, 73.07, 140.18, 150.75, 162.21, 171.12; conformer 2: 17.34, 25.87, 26.50, 29.98, 37.46, 49.42, 66.44, 73.29, 140.15, 151.02, 162.31, 171.86; MS (ES^+) *m/z* 310 $[M+H]^+$; HRMS calcd for $C_{14}H_{23}N_5O_3$ $[M+H]^+$ 310.1874, found 310.1875.

(2*R*)-2-{[4-Amino-6-(cyclohexylmethoxy)-5-nitrosopyrimidin-2-yl]amino}butan-1-ol (8d). Prepared starting from **7d** (70 mg, 0.238 mmol), using isopentyl nitrite (80 µL, 70 mg, 0.595 mmol). The crude product was purified by flash chromatography (2/98 MeOH in CH_2Cl_2) to give the title compound as a purple solid (58 mg, 75 %). R_f 0.27 (5/95 MeOH/CH_2Cl_2); m.p. 84-86 ^oC. The compound exists as two conformers, conformer 1 / conformer 2 ratio = 2 / 1. ^{1}H-NMR (300 MHz, DMSO-d_6) δ (ppm): 0.78-0.92 (6H, m, 3 × CH_3 conformer 1 and 3 × CH_3 conformer 2), 0.94-1.34 (10H, m, 5 × C_6H_{11} conformer 1 and 5 × C_6H_{11} conformer 2), 1.36-1.51 (2H, m, C$H_2$$CH_3$ conformer 1) 1.54-1.92 (14H, m, 6 × C_6H_{11} conformer 1, 6 × C_6H_{11} and 2 × C$H_2$$CH_3$ conformer 2), 3.38-3.49 (4H, m, 2 × CH_2OH conformer 1 and 2 × CH_2OH conformer 2), 3.86-4.07 (2H, m, 1 × C*H*NH conformer 1 and 1 × C*H*NH conformer 2), 4.24-4.42 (4H, m, 2 × CH_2O conformer 1 and 2 × CH_2O conformer 2), 4.66-4.78 (2H, m, 1 × OH conformer 1, 1 × OH conformer 2), 7.81 (1H, br. d, *J* = 4.0 Hz, NH_2, conformer 2), 8.00 (1H, d, *J* = 8.7 Hz, NH, conformer 2), 8.06-8.18 (2H, m, 1 × NH, conformer 1, 1 × NH_2, conformer 1) 9.96 (1H, br. d, *J* = 4.0 Hz, NH_2, conformer 2), 10.27 (1H, br. d, *J* = 4.0 Hz NH_2, conformer 1); ^{13}C-NMR (75 MHz, DMSO-d_6) δ (ppm): conformer 1: 10.50, 23.53, 25.20, 26.00, 29.19, 36.74, 54.60, 62.60, 71.58, 139.56, 150.75, 161.63, 169.89; conformer 2: 10.67, 23.86, 25.30, 26.00, 29.19, 36.92, 55.26, 62.97, 71.58, 139.66, 150.66, 162.10, 170.59; MS (ES^+) *m/z* 324 $[M+H]^+$; HRMS calcd for $C_{15}H_{25}N_5O_3$ $[M+H]^+$ 324.2030, found 324.2044.

2-{[4-Amino-6-(cyclohexylmethoxy)-5-nitrosopyrimidin-2-yl]amino}-3-methylbutan-1-ol (8e). Prepared starting from **7e** (70 mg, 0.227 mmol), using menthyl nitrite (147 mg, 0.795 mmol). The crude product was purified by flash chromatography (gradient from 0/100 to 10/90 MeOH/CH_2Cl_2) to give the title compound as a purple solid (43 mg, 56 %). R_f 0.3 (5/95 MeOH/CH_2Cl_2); m.p. 176-177 ^oC; UV λ_{max} (EtOH/nm): 340.4, 238.4; IR ν_{max}/cm^{-1}: 3242, 2922, 2851, 1561. The compound exists as two conformers, conformer 1 / conformer 2 ratio = 5 / 3. ^{1}H-NMR (500 MHz, DMSO-d_6) δ (ppm): 0.83-0.92 (12H, m, 6 × CH_3 conformer 1 and 6 × CH_3 conformer 2), 1.00-1.32 (10H, m, 5 × C_6H_{11} conformer 1 and 5 × C_6H_{11} conformer 2), 1.62-1.95

(14H, m, 6 × C_6H_{11} and 1 × C*H*(CH_3)$_2$ conformer 1, 6 × C_6H_{11} and 1 × C*H*(CH_3)$_2$ conformer 2), 3.43-3.58 (4H, m, 2 × CH_2OH conformer 1 and 2 × CH_2OH conformer 2), 3.87-3.93 (1H, m, C*H*NH conformer 1), 3.95-4.02 (1H, m, C*H*NH conformer 2), 4.25-4.35 (3H, m, 2 × CH_2O conformer 1 and 1 × CH_2O conformer 2), 4.39 (1H, dd, *J* = 10.6 and 6.2 Hz, CH_2O conformer 2), 4.57-4.63 (2H, m, 1 × OH conformer 1 and 1 × OH conformer 2), 7.76 (1H, d, *J* = 4.3 Hz, NH_2 conformer 2), 8.01 (1H, d, *J* = 9.2 Hz, NH conformer 2), 8.08-8.13 (2H, m, 1 × NH_2 conformer 1 and 1 × NH conformer 1), 9.96 (1H, d, *J* = 4.5 Hz, NH_2 conformer 2), 10.25 (1H, d, *J* = 4.5 Hz, NH_2 conformer 1); ^{13}C-NMR (125 MHz, DMSO-*d*$_6$) δ (ppm): conformer 1: 18.76, 19.30, 25.13, 25.94, 28.63, 29.13, 36.70, 58.32, 60.91, 71.48, 139.51, 150.63, 161.82, 169.80; conformer 2: 18.45, 19.52, 25.21, 25.91, 29.04, 29.24, 36.82, 58.78, 61.08, 71.48, 139.60, 150.56, 162.25, 170.45; MS (ES$^+$) *m/z* 338 [M+H]$^+$; HRMS calcd for $C_{16}H_{27}N_5O_3$ [M+H]$^+$ 338.2187, found 338.2187.

3-{[4-Amino-6-(cyclohexylmethoxy)-5-nitrosopyrimidin-2-yl]amino}propan-1-ol (8f). Prepared starting from **7f** (130 mg, 0.464 mmol), using menthyl nitrite (301 mg, 1.625 mmol). The crude product was purified by flash chromatography (gradient from 0/100 to 5/95 MeOH/CH_2Cl_2) to give the title compound as a purple solid (80 mg, 56 %). R_f 0.2 (5/95 MeOH/CH_2Cl_2); m.p. 168-169 ºC; UV λ_{max} (EtOH/nm): 339.2, 238.2; IR ν_{max}/cm^{-1}: 3301, 2921, 2846, 1580. The compound exists as two conformers, conformer 1 / conformer 2 ratio = 2 / 1. ^{1}H-NMR (500 MHz, DMSO-*d*$_6$) δ (ppm): 1.00-1.32 (10H, m, 5 × C_6H_{11} conformer 1 and 5 × C_6H_{11} conformer 2), 1.62-1.91 (16H, m, 6 × C_6H_{11} and 2 × $CH_2CH_2CH_2$ conformer 1, 6 × C_6H_{11} and 2 × $CH_2CH_2CH_2$ conformer 2), 3.33-3.39 (2H, m, CH_2NH conformer 1), 3.40-3.50 (6H, m, 2 × CH_2OH conformer 1, 2 × CH_2OH and 2 × CH_2NH conformer 2), 4.28 (2H, d, *J* = 6.4 Hz, CH_2O conformer 1), 4.36 (2H, d, *J* = 6.4 Hz, CH_2O conformer 2), 4.46 (1H, t, *J* = 5.1 Hz, OH conformer 1), 4.49 (1H, t , *J* = 5.1 Hz, OH conformer 2), 7.85 (1H, d, *J* = 4.2 Hz, NH_2 conformer 2), 8.16-8.25 (2H, m, 1 × NH_2 conformer 1 and 1 × NH conformer 2), 8.33 (1H, t, *J* = 5.6 Hz, NH conformer 1), 9.93 (1H, d, *J* = 4.2 Hz, NH_2 conformer 2), 10.29 (1H, d, *J* = 4.4 Hz, NH_2 conformer 1); ^{13}C-NMR (125 MHz, DMSO-*d*$_6$) δ (ppm): conformer 1: 25.14, 25.95, 29.14, 31.94, 36.70, 38.38, 58.44, 71.49, 139.50, 150.61, 161.31, 169.88; conformer 2: 25.22, 25.93, 29.19, 32.51, 36.86, 38.55, 58.50, 71.55, 139.85, 150.61, 161.77, 170.17; MS (ES$^+$) *m/z* 310 [M+H]$^+$; HRMS calcd for $C_{14}H_{23}N_5O_3$ [M+H]$^+$ 310.1874, found 310.1874.

***tert*-Butyl {2-[(4-amino-6-(cyclohexylmethoxy)-5-nitrosopyrimidin-2-yl)amino]cyclohexyl} carbamate (11).** Prepared starting from **10** (200 mg, 0.477 mmol), using menthyl nitrite (309 mg, 1.67 mmol). The crude product was purified by flash chromatography (gradient from 0/100 to 2/98 MeOH/CH_2Cl_2) to give the title compound as a purple solid (140 mg, 65 %). R_f 0.4

(2.5/97.5 MeOH/CH_2Cl_2); m.p. 119-120 ^oC; UV λ_{max} (EtOH/nm): 341.0, 237.8, 205.2; IR ν_{max}/cm^{-1}: 3294, 2922, 2851, 1688, 1562. The compound exists as two conformers, conformer 1 / conformer 2 ratio = 2 / 1. ^{1}H-NMR (500 MHz, DMSO-*d*$_6$) δ (ppm): 0.97-1.42 (36H, m, 5 × C_6H_{11}, 4 × C_6H_{11} and 9 × CH_3 conformer 1, 5 × C_6H_{11}, 4 × C_6H_{11} and 9 × CH_3 conformer 2), 1.60-1.92 (20H, m, 6 × C_6H_{11} and 4 × C_6H_{11} conformer 1, 6 × C_6H_{11} and 4 × C_6H_{11} conformer 2), 3.33-3.41 (2H, m, 1 × C*H*NHCO conformer 1 and 1 × C*H*NHCO conformer 2), 3.69-3.85 (2H, m, 1 × C*H*NH conformer 1 and 1 × C*H*NH conformer 2), 4.20-4.31 (3H, m, 2 × CH_2O conformer 1 and 1 × CH_2O conformer 2), 4.35-4.43 (1H, m, CH_2O conformer 2), 6.50 (1H, d, *J* = 8.7 Hz, NHCO conformer 2), 6.57 (1H, d, *J* = 8.7 Hz, NHCO conformer 1), 7.81 (1H, d, *J* = 4.2 Hz, NH_2 conformer 2), 7.97 (1H, d, *J* = 8.6 Hz, NH conformer 2), 8.00 (1H, d, *J* = 8.6 Hz, NH conformer 1), 8.12 (1H, d, *J* = 4.2 Hz, NH_2 conformer 1), 9.94 (1H, d, *J* = 4.2 Hz, NH_2 conformer 2), 10.27 (1H, d, *J* = 4.2 Hz, NH_2 conformer 1); ^{13}C-NMR (125 MHz, DMSO-*d*$_6$) δ (ppm): conformer 1: 24.36, 24.55, 25.11, 25.94, 28.07, 29.11, 31.21, 31.99, 36.61, 53.34, 55.12, 71.41, 77.54, 139.54, 150.62, 155.60, 161.23, 169.85; conformer 2: 24.55, 24.50, 25.23 (C-1, C-5), 25.96, 28.08, 29.34, 31.24, 32.03, 36.92, 53.30, 55.05, 71.71, 77.54, 139.66, 150.57, 155.60, 161.62, 169.79; MS (ES$^+$) *m/z* 449 $[M+H]^+$; HRMS calcd for $C_{22}H_{36}N_6O_4$ $[M+H]^+$ 449.2871, found 449.2861.

***N*^{2}-(2-Aminocyclohexyl)-6-cyclohexylmethoxy-5-nitrosopyrimidine-2,4-diamine (8g).** To **11** (138 mg, 0.308 mmol) in CH_2Cl_2 was added TFA (2 mL / mmol). The reaction was stirred at r.t. for 2 h. The solvent was removed under reduced pressure then the free base was triturated with saturated aq. $NaHCO_3$ (10 mL) and the product extracted with CH_2Cl_2. The organic extracts were washed with brine and dried ($MgSO_4$). The solvent was removed under reduced pressure and the crude product purified by flash chromatography (gradient from 0/100 to 5/95 MeOH/CH_2Cl_2) to give the title compound as a purple solid (73 mg, 68 %). R_f 0.25 (5/95 MeOH/CH_2Cl_2); m.p. 122-123 ^oC; UV λ_{max} (EtOH/nm): 341.0; IR ν_{max}/cm^{-1}: 3235, 3128, 2918, 2847, 1561. The compound exists as two conformers, conformer 1 / conformer 2 ratio = 5 : 2. ^{1}H-NMR (500 MHz, DMSO-*d*$_6$) δ (ppm): 1.00-1.32 (18H, m, 5 × C_6H_{11} and 4 × C_6H_{11} conformer 1, 5 × C_6H_{11} and 4 × C_6H_{11} conformer 2), 1.60-1.93 (24H, m, 6 × C_6H_{11}, 4 × C_6H_{11} and 2 × N*H*$_2$CH conformer 1, 6 × C_6H_{11}, 4 × C_6H_{11} and 2 × N*H*$_2$CH conformer 2), 2.57-2.65 (2H, m, 1 × C*H*NH_2 conformer 1 and 1 × C*H*NH_2 conformer 2), 3.54-3.64 (2H, m, 1 × C*H*NH conformer 1 and 1 × C*H*NH conformer 2), 4.26-4.34 (3H, m, 2 × CH_2O conformer 1 and 1 × CH_2O conformer 2), 4.43 (1H, dd, *J* = 10.6 and 6.2 Hz, CH_2O conformer 2), 7.78 (1H, d, *J* = 4.1 Hz, NH_2 conformer 2), 8.14 (1H, d, *J* = 4.4 Hz, NH_2 conformer 1), 8.20 (1H, d, *J* = 8.5 Hz, NH conformer 2), 8.28 (1H, d, *J* = 8.5 Hz, NH conformer 1), 9.96 (1H, d, *J* = 4.1 Hz, NH_2 conformer 2), 10.27 (1H, d, *J* = 4.4

Hz, NH_2 conformer 1); ^{13}C-NMR (125 MHz, DMSO-d_6) δ (ppm): conformer 1: 24.53, 24.70, 25.12, 25.94, 29.14, 31.40, 34.27, 36.66, 53.36, 57.24, 71.52, 139.57, 150.68, 161.52, 169.85; conformer 2: 24.63, 24.75, 25.19, 25.94, 29.28, 31.88, 34.37, 36.85, 53.19, 57.24, 71.57, 139.65, 150.58, 161.89, 170.52; MS (ES^+) *m/z* 349 $[M+H]^+$; HRMS calcd for $C_{17}H_{28}N_6O_2$ $[M+H]^+$ 349.2347, found 349.2348.

2-{1-[4-Amino-6-(cyclohexylmethoxy)-5-nitrosopyrimidin-2-yl]piperidin-4-yl}ethan-1-ol (8h). Prepared starting from **7h** (80 mg, 0.240 mmol), using isopentyl nitrite (80 µL, 70 mg, 0.60 mmol). The crude product was purified by flash chromatography (gradient from 2/98 to 5/95 MeOH/CH_2Cl_2) to give the title compound as a purple solid (60 mg, 69 %). R_f 0.3 (5/95 MeOH/CH_2Cl_2); m.p. 204-205 °C; ^{1}H-NMR (300 MHz, DMSO-d_6) δ (ppm): 0.98-1.33 (9H, m, 5 × C_6H_{11} and 4 × CH_2 piperidine), 1.33-1.42 (2H, m, CH_2CH_2CH), 1.57-1.91 (7H, m, 6 × C_6H_{11}, 1 × CH piperidine), 2.86-3.07 (2H, m, CH_2N), 3.41-3.51 (2H, m, CH_2OH), 4.31 (2H, d, *J* = 6.1 Hz, CH_2O), 4.39 (1H, t, *J* = 5.0 Hz, OH), 4.68-4.84 (2H, m, CH_2N), 8.06 (1H, d, *J* = 4.4 Hz, NH_2) 10.07 (1H, d, *J* = 4.4 Hz, NH_2); ^{13}C-NMR (75 MHz, DMSO-d_6) δ (ppm): 25.28 (C-1, C-5), 25.95 (C-6), 29.25 (C-2, C-4), 31.78 (2 × C-piperidine), 32.08 (C-14), 36.91 (C-3), 38.82 (C-17), 44.15 (C-piperidine), 44.52 (C-piperidine) 58.14(C-18), 71.58(C-7), 139.03 (C-arom.), 150.36 (C-arom.), 159.06 (C-arom.), 170.13 (C-arom.); MS (ES^+) *m/z* 364 $[M+H]^+$.

6-(Cyclohexylmethoxy)-5-nitroso-2-(pyrrolidin-1-yl)pyrimidin-4-amine (8i). Prepared starting from **7i** (100 mg, 0.360 mmol), using isopentyl nitrite (121 µL, 105 mg, 0.91 mmol). The crude product was purified by flash chromatography (1/99 MeOH/CH_2Cl_2) to give the title compound as a purple solid (86 mg, 78 %). R_f 0.4 (5/95 MeOH/CH_2Cl_2); m.p. 172-173 °C; ^{1}H-NMR (300 MHz, DMSO-d_6) δ (ppm): 1.04-1.27 (5H, m, C_6H_{11}), 1.63-1.83 (10H, m, 6 × C_6H_{11} and 4 × CH_2CH_2 pyrrolidine), 3.49-3.53 (2H, m, CH_2N pyrrolidine), 3.61-3.66 (2H, m, CH_2N pyrrolidine), 4.33 (2H, d, *J* = 6.2 Hz, CH_2O), 8.10 (1H, d, *J* = 4.3 Hz, NH_2), 10.13 (1H, d, *J* = 4.3 Hz, NH_2); ^{13}C-NMR (75 MHz, DMSO-d_6) δ (ppm): δ 24.58, 24.71, 25.25, 25.95, 29.26, 36.89, 47.03, 47.23, 71.48, 139.23, 150.27, 158.46, 169.65; MS (ES^+) *m/z* 306 $[M+H]^+$.

General procedure for the synthesis of cyano-*NNO*-azoxyderivatives. To a stirred suspension of the nitroso species (1 eq.) and cyanamide (NH_2CN) (3 eq.) in CH_3CN, (diacetoxyiodo)benzene (IBA) (2 eq.) was added portion-wise at r.t. The reaction mixture gradually changed in colour from purple to yellow. After 2 h solvent was removed under reduced pressure and the crude product was purified by flash chromatography.

4-Amino-5-[(Z)-cyano-*NNO*-azoxy]-2-[(2-hydroxyethyl)amino]-6-cyclohexylmethoxypyrimidine (9a). Prepared starting from **8a** (58 mg, 0.197 mmol). The crude product was purified by flash chromatography (gradient from 2/98 to 10/90 MeOH/CH_2Cl_2) to give the title compound as a yellow solid (33 mg, 50 %). R_f 0.3 (5/95 MeOH/CH_2Cl_2); m.p. 161-162ºC; UV λ_{max} (EtOH/nm): 397.6, 247.8, 209.0; IR ν_{max}/cm^{-1}: 3360, 2924, 2851, 2197, 1558. The compound exists as two conformers, conformer 1 / Conformer 2 ratio = 2 / 1. ^{1}H-NMR (500 MHz, DMSO-d_6) δ (ppm): 0.99-1.30 (10H, m, 5 × C_6H_{11} conformer 1 and 5 × C_6H_{11} conformer 2), 1.60-1.80 (12H, m, 6 × C_6H_{11} conformer 1 and 6 × C_6H_{11} conformer 2), 3.32-3.37 (4H, m, 2 × CH_2NH conformer 1 and 2 × CH_2NH conformer 2), 3.47-3.53 (4H, m, 2 × CH_2OH conformer 1 and 2 × CH_2OH conformer 2), 4.13 (2H, d, J = 6.3 Hz, CH_2O conformer 1), 4.19 (2H, d, J = 6.1 Hz, CH_2O conformer 2), 4.67-4.72 (2H, m, 1 × OH conformer 1 and 1 × OH conformer 2), 7.83 (1H, t, J = 5.8 Hz, NH conformer 2), 7.93 (1H, t, J = 5.7 Hz, NH conformer 1), 8.05 (2H, s, NH_2 conformer 2), 8.29 (2H, s, NH_2 conformer 1); ^{13}C-NMR (125 MHz, DMSO-d_6) δ (ppm): conformer 1: 25.17, 22.93, 28.96, 36.49, 43.51, 59.36, 72.20, 106.20, 112.44, 159.15, 159.18, 163.64; conformer 2: 25.26, 25.93, 29.02, 36.66, 43.74, 59.67, 72.20, 106.14, 112.36, 158.73, 159.48, 164.23; MS (ES^+) *m/z* 336 $[M+H]^+$; HRMS calcd for $C_{14}H_{21}N_7O_3$ $[M+H]^+$ 336.1779, found 336.1782.

4-Amino-5-[(Z)-cyano-*NNO*-azoxy]-2-{[(2*S*)-1-hydroxypropan-2-yl]amino}-6-cyclohexylmethoxypyrimidine (9b). Prepared starting from **8b** (40 mg, 0.129 mmol). The crude product was purified by flash chromatography (gradient from 0/100 to 10/90 MeOH/CH_2Cl_2) to give the title compound as a yellow solid (35 mg, 78 %). R_f 0.4 (5/95 MeOH/CH_2Cl_2); m.p. 165-167ºC; UV λ_{max} (EtOH/nm): 400.0, 247.6, 207.2; IR ν_{max}/cm^{-1}: 3346, 2922, 2850, 2191, 1554. The compound exists as two conformers, conformer 1 / Conformer 2 ratio = 2 / 1. ^{1}H-NMR (500 MHz, DMSO-d_6) δ (ppm): 0.98-1.29 (16H, m, 5 × C_6H_{11} and 3 × CH_3 conformer 1, 5 × C_6H_{11} and 3 × CH_3 conformer 2), 1.60-1.80 (12H, m, 6 × C_6H_{11} conformer 1 and 6 × C_6H_{11} conformer 2), 3.33-3.36 (2H, m, 1 × CH_2OH conformer 1 and 1 × CH_2OH conformer 2), 3.33-3.36 (2H, m, 1 × CH_2OH conformer 1 and 1 × CH_2OH conformer 2), 3.39.3.45 (2H, m, 1 × CH_2OH conformer 1 and 1 × CH_2OH conformer 2), 3.97-4.09 (2H, m, 1 × C*H*NH conformer 1 and 1 × C*H*NH conformer 2), 4.13 (2H, d, J = 6.3 Hz, CH_2O conformer 1), 4.19 (2H, d, J = 6.0 Hz, CH_2O conformer 2), 4.69-4.74 (2H, m, 1 × OH conformer 1 and 1 × OH conformer 2), 7.68 (1H, d, J = 8.3 Hz, NH conformer 2), 7.79 (1H, d, J = 8.3 Hz, NH conformer 1), 8.01 (2H, br. s, NH_2 conformer 2), 8.28 (2H, s, NH_2 conformer 1); ^{13}C-NMR (125 MHz, DMSO-d_6) δ (ppm): conformer 1: 17.00, 25.17, 25.95, 28.97, 36.49, 48.56, 64.09, 72.23, 106.15, 112.52, 158.64, 159.22, 163.65; conformer 2: 17.06, 25.28, 25.94, 29.02, 36.68, 49.10, 64.27, 72.23, 106.15,

112.52, 158.71, 159.02, 163.69; MS (ES^+) *m/z* 350 $[M+H]^+$; HRMS calcd for $C_{15}H_{23}N_7O_3$ $[M+H]^+$ 350.1935, found 350.1937.

4-Amino-5-[(Z)-cyano-*NNO*-azoxy]-2-{[(2*R*)-1-hydroxypropan-2-yl]amino}-6-cyclohexylmethoxypyrimidine (9c). Prepared starting from **8c** (30 mg, 0.097 mmol). The crude product was purified by flash chromatography (gradient from 0/100 to 10/90 MeOH/CH_2Cl_2) to give the title compound as a yellow solid (26 mg, 76 %). R_f 0.4 (5/95 MeOH/CH_2Cl_2); m.p. 172-173 ^oC; UV λ_{max} (EtOH/nm): 400.0, 249.2; IR ν_{max}/cm^{-1}: 3345, 3300, 2922, 2849, 2190. The compound exists as two conformers, conformer 1 / Conformer 2 ratio = 5 / 3. ^{1}H-NMR (500 MHz, CD_3OD) δ (ppm): 1.06-1.38 (16H, m, 5 × C_6H_{11} and 3 × CH_3 conformer 1, 5 × C_6H_{11} and 3 × CH_3 conformer 2), 1.67-1.89 (12H, m, 6 × C_6H_{11} conformer 1 and 6 × C_6H_{11} conformer 2), 3.51-3.61 (4H, m, 2 × C*H*$_2$OH conformer 1 and 2 × C*H*$_2$OH conformer 2), 4.13-4.21 (4H, m, 2 × CH_2O and 1 × C*H*NH conformer 1, 1 × C*H*NH conformer 2), 4.25 (1H, d, *J* = 6.0 Hz, CH_2O conformer 2); ^{13}C-NMR (125 MHz, CD_3OD) δ (ppm): conformer 1: 17.17, 26.88, 27.53, 30.71, 38.46, 49.97, 66.21, 74.14, 108.10, 113.47, 160.89, 161.18, 165.69; conformer 2: 17.41, 26.94, 27.53, 30.74, 38.62, 50.32, 66.21, 74.37, 108.10, 113.29, 160.98, 161.18, 166.34; MS (ES^+) *m/z* 350 $[M+H]^+$; HMRS calcd for $C_{15}H_{23}N_7O_3$ $[M+H]^+$ 350.1935, found 350.1937.

4-Amino-5-[(*Z*)-cyano-*NNO*-azoxy]-2-{[(2*R*)-1-hydroxybutan-2-yl]amino}-6-cyclohexylmethoxypyrimidine (9d). Prepared starting from **8d** (170 mg, 0.526 mmol). The crude product was purified by flash chromatography (gradient from 0/100 to 5/95 MeOH/CH_2Cl_2) to give the title compound as a yellow solid (90 mg, 47 %). R_f 0.33 (5/95 MeOH/CH_2Cl_2); m.p. 152-154 ^oC; UV λ_{max} (EtOH/nm): 400.0, 248.0, 207.8; IR ν_{max}/cm^{-1}: 3341, 2922, 2850, 2192, 1554. The compound exists as two conformers, conformer 1 / conformer 2 ratio = 5 / 3. ^{1}H-NMR (500 MHz, DMSO-*d*$_6$) δ (ppm): 0.84 (6H, t, *J* = 7.4 Hz, 3 × CH_3 conformer 1 and 3 × CH_3 conformer 2), 1.00-1.28 (10H, m, 5 × C_6H_{11} and 5 × C_6H_{11} conformer 2), 1.36-1.46 (2H, m, CH_3C*H*$_2$conformer 1), 1.57-1.78 (14H, m, 6 × C_6H_{11} conformer 1, 6 × C_6H_{11} and 2 × CH_3C*H*$_2$ conformer 2), 3.36-3.45 (4H, m, 2 × CH_2OH conformer 1 and 2 × CH_2OH conformer 2), 3.82-3.93 (2H, m, 1 × C*H*NH conformer 1 and 1 × C*H*NH conformer 2), 4.14 (2H, d, *J* = 6.3 Hz, CH_2O conformer 1), 4.16-4.22 (2H, m, CH_2O conformer 2), 4.66 (1H, t, *J* = 5.5 Hz, OH conformer 1), 4.67 (1H, t, *J* = 5.5 Hz, OH conformer 2), 7.65 (1H, d, *J* = 8.9 Hz, NH conformer 1), 7.76 (1H, d, *J* = 8.9 Hz, NH conformer 1), 8.01 (2H, br. s, NH_2, conformer 2), 8.25 (2H, s, NH_2, conformer 1); ^{13}C-NMR (125 MHz, DMSO-*d*$_6$) δ (ppm): conformer 1: 10.43, 23.53, 25.18, 25.96, 28.97, 36.50, 54.31, 62.58, 72.24, 112.54, 159.16, 159.24, 163.60; conformer 2: 10.60, 23.79, 25.27, 25.93, 29.06, 36.64, 55.04, 62.91, 72.21, 112.45, 158.68, 159.58, 164.12; MS (ES^+) *m/z* 363 $[M+H]^+$; HRMS calcd for $C_{16}H_{25}N_7O_3$ $[M+H]^+$ 364.21, found 364.21.

4-Amino-5-[(Z)-cyano-*NNO*-azoxy]-2-[(1-hydroxy-3-methylbutan-2-yl)amino]-6-cyclohexylmethoxypyrimidine (9e). Prepared starting from **8e** (60 mg, 0.178 mmol). The crude product was purified by flash chromatography (gradient from 0/100 to 10/90 MeOH/CH_2Cl_2) to give the title compound as a yellow solid (15 mg, 22%). R_f 0.4 (5/95 MeOH/CH_2Cl_2); m.p. 156-157 ^oC; UV λ_{max} (EtOH/nm): 400.0, 249.2; IR ν_{max}/cm^{-1}: 3278, 2920, 2848, 2187, 1548. The compound exists as two conformers, conformer 1 / conformer 2 ratio = 5 / 3. ^{1}H-NMR (500 MHz, DMSO-d_6) δ (ppm): 0.82-0.90 (12H, m, 6 × CH_3 conformer 1 and 6 × CH_3 conformer 2), 0.99-1.30 (10H, m, 5 × C_6H_{11} conformer 1 and 5 × C_6H_{11} conformer 2), 1.60-1.81 (12H, m, 6 × C_6H_{11} conformer 1 and 6 × C_6H_{11} conformer 2), 1.83-1.93 (2H, m, 1 × C*H*$(CH_3)_2$ conformer 1 and 1 × C*H*$(CH_3)_2$ conformer 2), 3.43-3.54 (4H, m, 2 × C*H*$_2$OH conformer 1 and 2 × C*H*$_2$OH conformer 2), 3.81-3.91 (2H, m, 1 × C*H*NH conformer 1 and 1 × C*H*NH conformer 2), 4.12-4.18 (3H, m, 2 × CH_2O conformer 1 and 1 × CH_2O conformer 2), 4.21 (1H, dd, J = 10.7 and 5.7 Hz, CH_2O conformer 2), 4.54-4.61 (2H, m, 1 × OH conformer 1 and 1 × OH conformer 2), 7.66 (1H, d, *J* = 9.2 Hz, NH conformer 2), 7.77 (1H, d, *J* = 9.2 Hz, NH conformer 1), 8.00 (2H, s, NH_2 conformer 2), 8.24 (2H, s, NH_2 conformer 1); ^{13}C-NMR (125 MHz, DMSO-d_6) δ (ppm): conformer 1: 18.67, 19.35, 25.18, 25.95, 28.64, 28.97, 36.52, 58.06, 60.94, 72.23, 106.09, 112.54, 159.09, 159.51, 163.57; conformer 2: 18.40, 19.53, 25.25, 25.91, 28.64, 29.06, 36.59, 58.61, 61.10, 72.19, 106.27, 112.43, 158.65, 159.80, 164.04; MS (ES^+) *m/z* 378 $[M+H]^+$; HRMS calcd for $C_{17}H_{27}N_7O_3$ $[M+H]^+$ 378.2248, found 378.2249.

4-Amino-5-[(Z)-cyano-*NNO*-azoxy]-2-[(3-hydroxypropyl)amino]-6-cyclohexylmethoxypyrimidine (9f). Prepared starting from **8f** (65 mg, 0.210 mmol). The crude product was purified by flash chromatography (gradient from 20/80 to 40/60 EtOAc /CH_2Cl_2) to give the title compound as a yellow solid (12 mg, 16 %). R_f 0.3 (5/95 MeOH/CH_2Cl_2); m.p. 171-172 ^oC; UV λ_{max} (EtOH/nm): 401.0; IR ν_{max}/cm^{-1}: 3350, 3144, 2922, 2850, 2193, 1556. The compound exists as two conformers, conformer 1 / conformer 2 ratio = 5 / 3. ^{1}H-NMR (500 MHz, DMSO-d_6) δ (ppm): 0.98-1.31 (10H, m, 5 × C_6H_{11} conformer 1 and 5 × C_6H_{11} conformer 2), 1.61-1.82 (16H, m, 6 × C_6H_{11} and 2 × $CH_2CH_2CH_2$ conformer 1, 6 × C_6H_{11} and 2 × $CH_2CH_2CH_2$ conformer 2), 3.32-3.38 (4H, m, 2 × C*H*$_2$NH conformer 1 and 2 × C*H*$_2$NH conformer 2), 3.41-3.48 (4H, m, 2 × C*H*$_2$OH conformer 1 and 2 × C*H*$_2$OH conformer 2), 4.12 (2H, d, *J* = 6.3 Hz, CH_2O conformer 1), 4.21 (2H, d, *J* = 5.8 Hz, CH_2O conformer 2) 4.39-4.49 (2H, m, 1 × OH conformer 1 and 1 × OH conformer 2), 7.90 (1H, t, *J* = 5.8 Hz, NH conformer 2), 8.00 (1H, t, *J* = 5.8 Hz, NH conformer 1), 8.03 (2H, br. s, NH_2 conformer 2), 8.30 (2H, s, NH_2 conformer 1); ^{13}C-NMR (125 MHz, DMSO-d_6) δ (ppm): conformer 1: 25.18, 25.94, 28.96, 31.97, 36.50, 38.19, 58.47, 72.22, 106.16, 112.50, 159.01, 159.19, 163.62; conformer 2: 25.25, 25.94, 29.02, 32.44,

36.63, 38.41, 58.51, 72.22, 106.34, 112.41, 158.73, 159.34, 164.22; MS (ES^+) *m/z* 350 $[M+H]^+$; HRMS calcd for $C_{15}H_{23}N_7O_3$ $[M+H]^+$ 350.1935, found 350.1938.

4-Amino-5-[(Z)-cyano-*NNO*-azoxy]-2-[(2-aminocyclohexyl)amino]-6-cyclohexylmethoxypyrimidine (9g). Prepared starting from **8g** (70 mg, 0.20 mmol), cyanamide (25 mg, 0.60 mmol), IBA (129 mg, 0.40 mmol) and CH_3CN (2 mL). Purification by flash chromatography (gradient from 0/100 to 30/70 MeOH/CH_2Cl_2) gave a mixture of products. A second flash chromatography (gradient from 0/100 to 10/90 MeOH/CH_2Cl_2 + HCOOH 0.1 %) was performed to obtain the title compound as a yellow solid (10 mg, 13 %). R_f 0.2 (20/80 MeOH/CH_2Cl_2); m.p. 203-204 ^oC dec.; UV λ_{max} (EtOH/nm): 400.0, 248.2, 209.6; IR ν_{max}/cm^{-1}: 3293, 3145, 2924, 2853, 2191, 1555. ^{1}H-NMR Spectrum: The compound exists as two conformers, conformer 1 / conformer 2 ratio = 5 / 3. ^{1}H-NMR (500 MHz, CD_3OD) δ (ppm): 1.07-1.52 (18H, m, 5 × C_6H_{11} and 4 × C_6H_{11} conformer 1, 5 × C_6H_{11} and 4 × C_6H_{11} conformer 2), 1.66-2.14 (20H, m, 6 × C_6H_{11} and 4 × C_6H_{11} conformer 1, 6 × C_6H_{11} and 4 × C_6H_{11} conformer 2), 2.92-2.99 (2H, m, 1 × C*H*NH_2 conformer 1 and 1 × C*H*NH_2 conformer 2), 3.88-3.95 (2H, m, 1 × C*H*NH conformer 1 and 1 × C*H*NH conformer 2), 4.21 (2H, d, *J* = 6.2 Hz, CH_2O conformer 1), 4.26-4.32 (1H, m, CH_2O conformer 2), 4.32-4.37 (1H, m, CH_2O conformer 2); ^{13}C-NMR (125 MHz, CD_3OD) δ (ppm): conformer 1: 25.59, 27.72, 26.88, 27.54, 30.72, 32.93, 33.14, 38.46, 55.75, 59.57, 74.20, 113.43, 117.69, 161.32, 161.42, 165.80; conformer 2: 25.54, 27.72, 26.94, 27.54, 30.78, 32.78, 33.14, 38.63, 55.96, 58.81, 74.57, 113.19, 117.34, 161.06, 161.50, 166.41; MS (ES^+) *m/z* 389 $[M+H]^+$; HRMS calcd for $C_{18}H_{28}N_8O_2$ $[M+H]^+$ 389.2408, found 389.2408.

4-Amino-5-[(Z)-cyano-*NNO*-azoxy]-2-[4-(2-hydroxyethyl)piperidin-1-yl]-6-cyclohexylmethoxypyrimidine (9h). Prepared starting from **8h** (110 mg, 0.30 mmol). Purification by flash chromatography (20/80 acetone/PE) gave a mixture of products. A second flash chromatography (gradient from 0/100 to 10/90 MeOH/CH_2Cl_2) was performed to obtain the title compound as a yellow solid (20 mg, 16%). R_f 0.4 (5/95 MeOH/CH_2Cl_2); m.p. 135-137 ^oC (dec.); UV λ_{max} (EtOH/nm): 400.0; IR ν_{max}/cm^{-1}: 3483, 3441, 3355, 2922, 2852, 2190. ^{1}H-NMR (300 MHz, DMSO-d_6) δ (ppm): 0.94-1.43 (9H, m, 5 × C_6H_{11} and 4 × CH_2 piperidine), 1.56-1.85 (9H, m, 2 × CH_2CH_2CH, 6 × C_6H_{11} and 1 × CH piperidine), 2.81-3.04 (2H, m, CH_2N), 3.39-3.55 (2H, m, CH_2OH), 4.16 (2H, d, *J* = 5.3 Hz, CH_2O), 4.40 (1H, t, *J* = 4.5 Hz, OH), 4.55-4.75 (2H, m, CH_2N), 8.24 (2H, s, NH_2); ^{13}C-NMR (75 MHz, DMSO-d_6) δ (ppm): 25.34, 25.98, 29.08, 31.76, 32.08, 36.69, 43.86, 44.23, 58.14, 72.33, 105.82, 112.55, 156.99, 158.88, 163.89; MS (ES^+) m/z 404 $[M+H]^+$; HRMS calcd for $C_{19}H_{29}N_7O_3$ $[M+H]^+$ 404.2405, found 404.2403.

4-Amino-5-[(Z)-cyano-*NNO*-azoxy]-2-(pyrrolidin-1-yl)-6-cyclohexylmethoxypyrimidine (9i). Prepared starting from **8i** (40 mg, 0.131 mmol). The crude product was purified by flash chromatography (gradient from 5/95 to 20/80 acetone/PE) to give the title compound as a yellow solid (18 mg, 40%). R_f 0.5 (5/95 MeOH/CH_2Cl_2); m.p. 181-183 ^oC; UV λ_{max} (EtOH/nm): 399.8, 258.4; IR ν_{max}/cm^{-1}: 3464, 3339, 2937, 2851,2183, 1554. ^{1}H-NMR (500 MHz, DMSO-d_6) δ (ppm): 0.99-1.29 (5H, m, C_6H_{11}), 1.60-1.81 (6H, m, C_6H_{11}), 1.86-1.95 (4H, m, CH_2CH_2pyrrolidine), 3.46-3.52 (2H, m, CH_2N pyrrolidine), 3.53-3.59 (2H, m, CH_2N pyrrolidine), 4.19 (2H, d, J = 6.0 Hz, CH_2O), 8.24 (2H, s, NH_2); ^{13}C-NMR (125 MHz, DMSO-d_6) δ (ppm): 24.63, 24.76, 25.26, 25.94, 29.06, 36.64, 46.74, 46.88, 72.19, 106.10, 112.47, 156.32, 158.67, 163.40; MS (ES^+) *m/z* 346 $[M+H]^+$; HRMS calcd for $C_{16}H_{23}N_7O_2$ $[M+H]^+$ 346.1986 found 346.1988.

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