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SYNTHESIS AND BIOLOGICAL EVALUATIONS OF NEW PYRROLO[2,3-*b*]PYRIMIDINE AS SDI ANALOGS

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Abstract – The synthesis of new pyrrolo[2,3-*d*]pyrimidines variously substituted on the N-1 and C-2 atoms are described. Access to these compounds, which have modest activity compared with the first inhibitor SDI, involves, as the key step, the formation of a pyrrolopyrimidine skeleton from the 5-amino-2-(methoxymethyl)pyrimidine.

INTRODUCTION

Sorbitol dehydrogenase (SDH) a member of the medium-chain dehydrogenase/reductase protein family and the second enzyme of the polyol glucose metabolism pathway converts sorbitol to fructose strictly using NAD(+) as a coenzyme.[1] SDH is expressed almost ubiquitously in all mammalian tissues. The enzyme has attracted considerable interest[2,3] due to its implication in the development of diabetic complications and futhermore its tertiary structure may facilitate drug conception.[4,5] Modelling studies suggest that SDH is structurally homologous to mammalian alcohol dehydrogenase with respect to conserving zinc binding motif and a hydrophobic substrate-binding pocket.[6,7] Recently, the three-dimensional (3-D) structure of a mammalian SDH was established, and it was found that while the overall 3-D structure of SDH and alcohol dehydrogenase are similar, the zinc coordination in the active sites of the two enzymes is different.[8] The available structural and biochemical information about SDH is currently being overviewed in a structure-based approach to develop drugs for the treatment or prevention of the complications of diabetes.[9]

The first reported *in vivo* active sorbitol dehydrogenase inhibitor (SDI, Figure 1) is the 4-[4-(*N*,*N*-dimethylsulfanoyl)piperazino]-2-hydroxymethylpyrimidine (WAY 135706) which inhibits SDH with an IC_{50} value of 1 μM.[10] Searching for new potent sorbitol dehydrogenase inhibitors, based on a model of recent modelling studies on the active site of SDH and interesting inhibition of WAY 135706

we decided to synthesize SDI analogs as expected sorbitol dehydrogenase inhibitory activity.

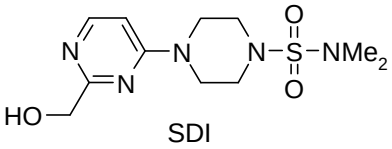


Figure1. Structure of SDI

Herein, we report the synthesis and biological preliminary studies as sorbitol dehydrogenase inhibitor of hydroxymethylpyrimidine derivatives **1**-**5**, (hydroxymethyl)pyrrolo[2,3-*d*]pyrimidine derivatives **6** and **7**, and 6,7,8,9-tetrahydropyrazino[2',1':5,1]pyrrolo[2,3-*d*]pyrimidine derivative **7** (Figure 2).

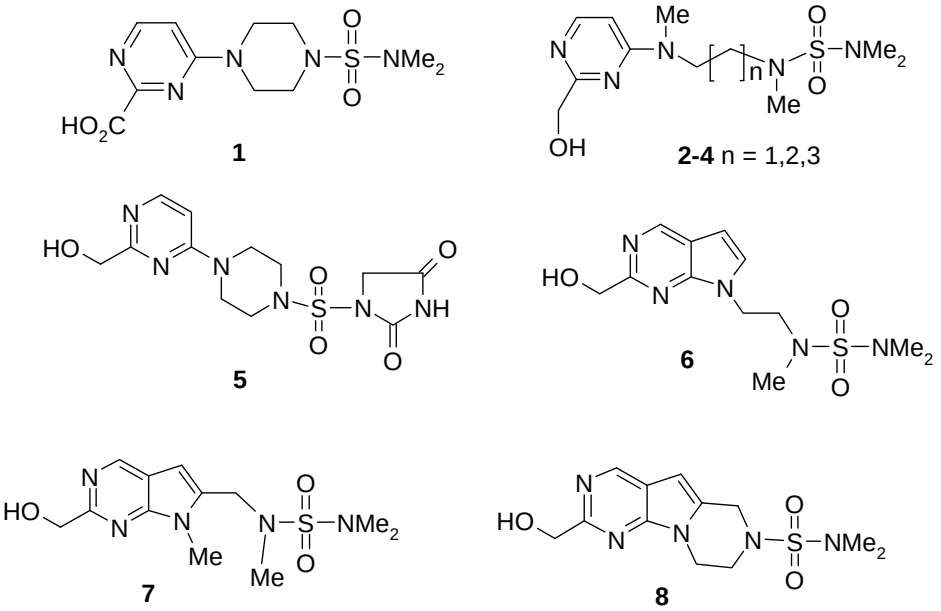
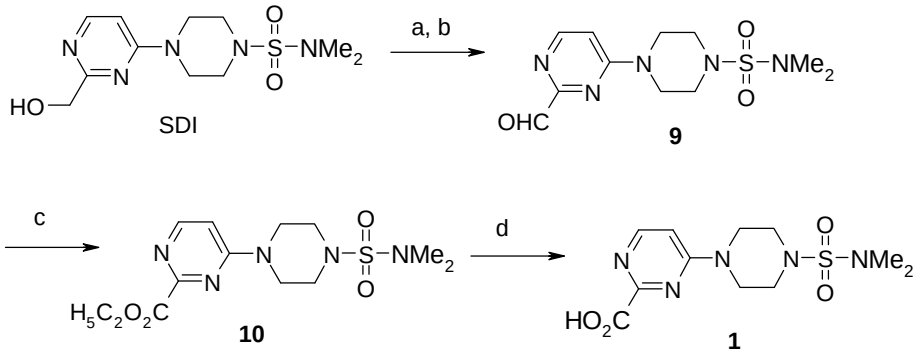


Figure 2. Structures of the target molecules derived from SDI

RESULTS AND DISCUSSION

Synthesis of 4-(4-dimethylsulfamoylpiperazin-1-yl)pyrimidine-2-carboxylic acid 1

The synthesis of aldehyde **9** was achieved under Swern conditions[11] with SDI.[12] Subsequent treatment of **9** by manganese dioxide in the presence of sodium cyanide and acetic acid in ethanol provided the corresponding carboxylic acid ethyl ester **10**. The desired 4-(4-dimethylsulfamoylpiperazin-1-yl)pyrimidine-2-carboxylic acid **1** was then obtained by acidic hydrolysis using Dowex resin with a good yield (Scheme 1).[13]

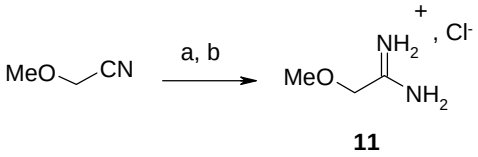


Scheme 1. Synthesis of Compound **1**

Reagents and conditions: a) DMSO, $(COCl)_2$, CH_2Cl_2, -60 °C. b) Et_3N, -60 °C to rt, 70% within 2 steps. c) NaCN, MnO_2, AcOH, EtOH, rt, 24 h, 60%. d) DOWEX, H_2O, reflux, 81%.

Synthesis of *N*-(2-[*N*”-2-(hydroxymethyl)pyrimidin-4-yl)-*N*”-methyl]alkylamino)-*N*,*N*’,*N*’-trimethyl sulfamides 2 and 3

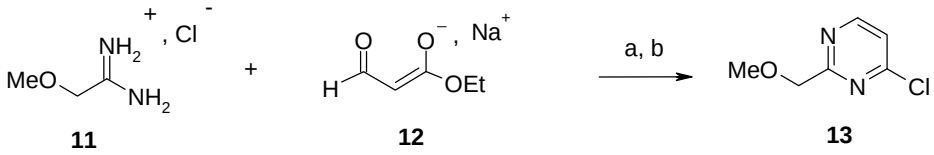
The required 2-methoxyacetamidine hydrochloride **11** was prepared in 2 steps from commercially available methoxyacetonitrile with 86% yield. The first step involved a treatment at 0 °C with hydrogen chloride in ethanol to provide the intermediate imidate. Then, addition of ammonia in methanol gave the corresponding amidine **11** (Scheme 2).[12]



Scheme 2. Synthesis of Compound **11**

Reagents and conditions: a) HCl, EtOH, 0 °C. b) NH_3, MeOH, rt, 86% within 2 steps.

The cyclo-condensation of **11** with ethyl formylacetate sodium salt **12**[14] afforded the corresponding hydroxypyrimidine which was converted using $POCl_3$ under reflux in 24 % yield to its chlorinated derivative **13** (Scheme 3).

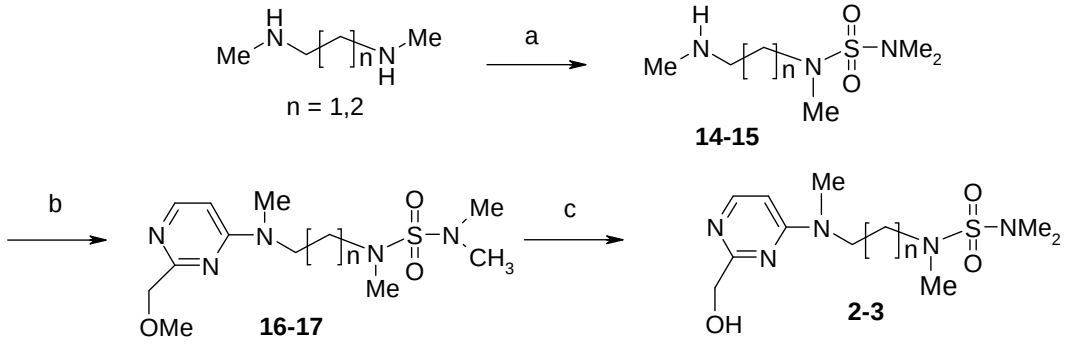


Scheme 3. Synthesis of Compound **13**

Reagents and conditions: a) H_2O, rt. b) $POCl_3$, 70 °C to reflux, 24% within 2 steps.

The target compounds **2** and **3** were prepared as outlined in Scheme 4. *N*,*N*’-alkyldiamines were condensed on *N*,*N*-dimethylsulfamoyl chloride in the presence of potassium carbonate in ethanol at 0 °C to afford the derivatives **14** and **15**. The second step involved a nucleophilic substitution between these

sulfonamide intermediates and the previously described chloropyrimidine **13**, in THF at reflux, providing respectively **16** and **17** in excellent yields. Finally, treatment by boron tribromide in dichloromethane led to the desired compounds **2** and **3** with good yield.

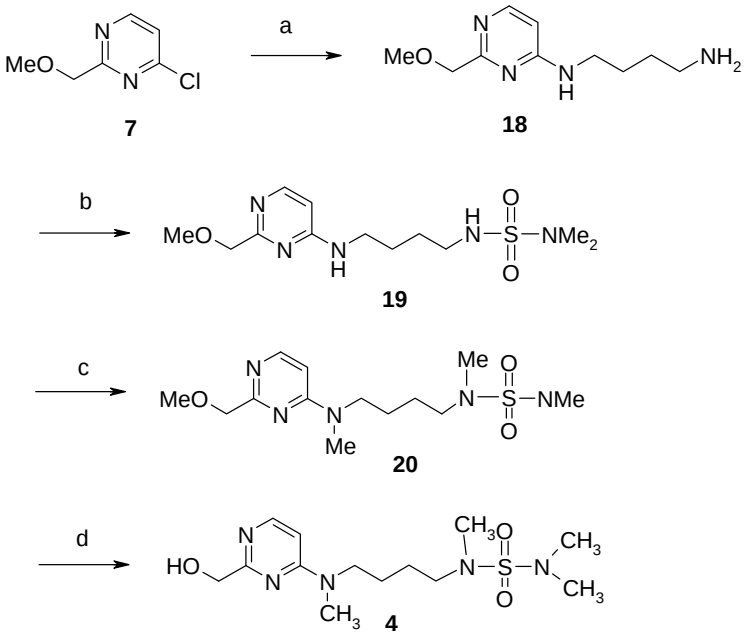


Scheme 4. Synthesis of Compounds **2** and **3**

Reagents and conditions: a) $ClSO_2N(CH_3)_2$, K_2CO_3, EtOH, 0 °C, (**14**, n = 1, 66%), (**15**, n = 2, 41%). b) **13**, THF, reflux; (**16**, n = 1, 95%), (**17**, n = 2, quant.). c) BBr_3, CH_2Cl_2, 0 °C, (**2**, n = 1, quant.), (**3**, n = 2, 90%).

Synthesis of *N*-(2-[*N*”-2-(hydroxymethyl)pyrimidin-4-yl)-*N*”-methyl]butylamino)-*N*,*N*’,*N*’-trimethylsulfamide 4

The reaction of **13** with 1,4-diaminobutane in the presence of triethylamine in refluxing tetrahydrofuran provided **18** in 81% yield. The latter was condensed on *N*,*N*-dimethylsulfamoyl chloride using potassium carbonate to obtain **19** in moderate yield. The introduction of the methyl group was carried out under classic conditions with methyl iodide and sodium hydride leading to the intermediate **20** which was treated by boron tribromide to furnish the final compound **4** (Scheme 5).

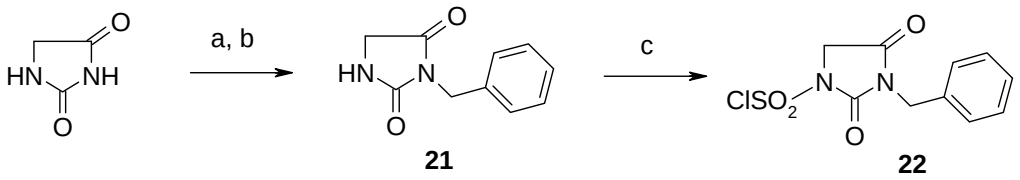


Scheme 5. Synthesis of Compound **4**

Reagents and conditions: a) 1,4-diaminobutane, Et_3N, THF, reflux, 81%. b) $ClSO_2NMe_2$, Et_3N, CH_2Cl_2, rt, 67%. c) NaH, MeI, DMF, rt, 62%. d) BBr_3, CH_2Cl_2, 0 °C, 79%.

Synthesis of 1-[4-(2-hydroxymethylpyrimidin-4-yl)piperazin-1-sulfonyl)imidazolidine-2,4-dione 5

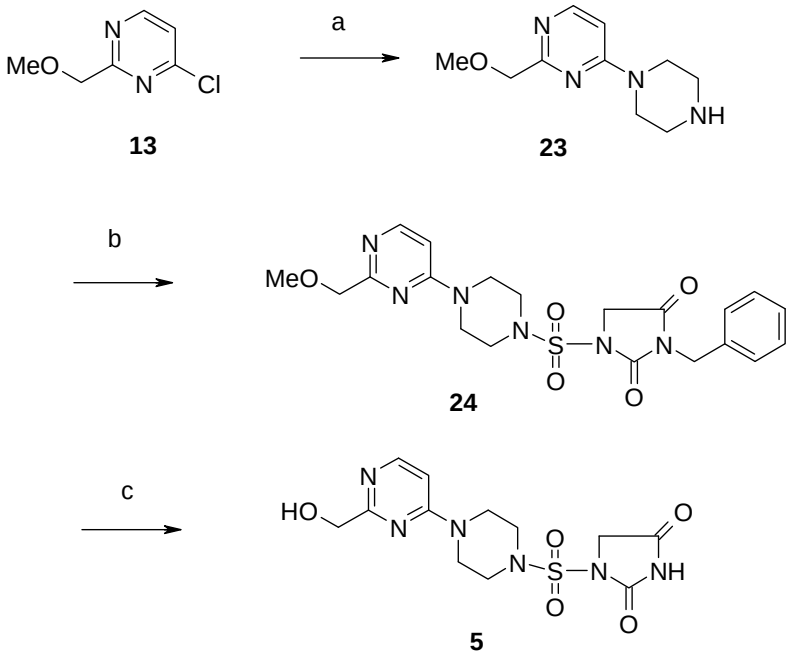
Treatment of hydantoïn with potassium hydroxide in ethanol under reflux followed by reaction with benzyl bromide in the presence of potassium iodide in *N*,*N*-dimethylformamide afforded the 3-benzyl-imidazolidine-2,4-dione **21.**[15] Exposure of **21** to sulfuryl chloride in chloroform at rt yielded to **22** in 81% yield (Scheme 6).



Scheme 6. Synthesis of Compound **22**

Reagents and conditions: a) KOH, EtOH, reflux. b) BnBr, KI, DMF, 80 °C, 49% within 2 steps. c) SO_2Cl_2, Et_3N, $CHCl_3$, rt, 81%.

Finally, the imidazolidine target was prepared according to scheme 7. Reaction of pyrimidine **13** with excess of piperazine in THF gave the 2-(methoxymethyl)-4-(piperazin-1-yl)-pyrimidine **23**. Condensation of **23** and **22** followed by debenzylation with aluminium chloride gave the desired imidazolidine **5**.[16]

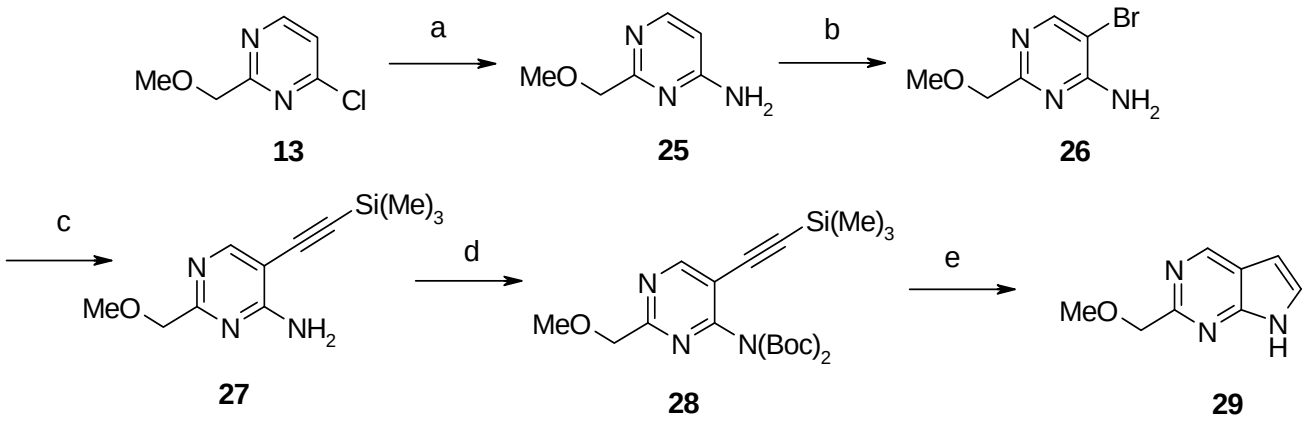


Scheme 7. Synthesis of Compound **5**

Reagents and conditions: a) piperazine, Et_3N, THF, reflux, 91%. b) **22,** NaH, DMF, 80 °C, 24%. c) $AlCl_3$, toluene, 90 °C, 41%.

Synthesis of *N*,*N*,*N*'-trimethyl-*N*'-(2-[2-(hydroxymethyl)pyrrolo[2,3-*d*]pyrimidin-7-yl]ethyl)-sulfamide 6

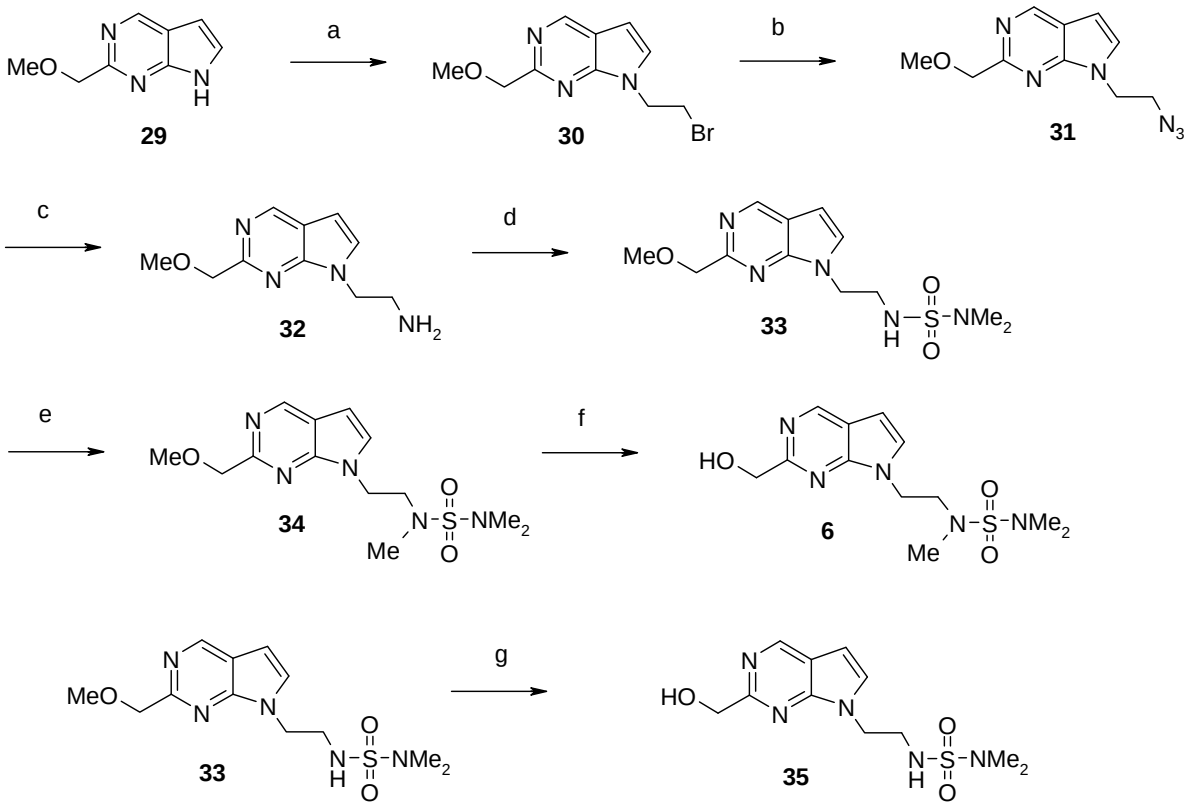
The desired 2-(methoxymethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine **29** was prepared as outlined in Scheme 8 from 4-chloro-2-(methoxymethyl)pyrimidine **13**. The first step involved amination[17] of **13** in a sealed tube at 120 °C with a 30% ammonia solution and provided **25** (91% yield). This amino compound was then treated with bromine in presence of calcium carbonate to give the corresponding bromopyrimidine **26** with moderate yield.[18] In accordance with Kumar conditions,[19] the latter was coupled with trimethylsilylacetylene to form derivative **27**. Finally, treatment of **27** with $(Boc)_2O$ with catalytic amount of DMAP followed by treatment with sodium ethoxide in ethanol led to derivative **29** in a good yield (Scheme 9).[20,21]



Scheme 8. Synthesis of 2-(Methoxymethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine **29**

Reagents and conditions: a) NH_4OH, sealed tube, 91%. b) Br_2, $CaCO_3$, H_2O, 60°C, 59%. c) trimethylsilylacetylene, $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, THF, 40 °C, 91%. d) $(Boc)_2O$, DMAP, THF, rt, quantitative. e) EtONa, EtOH, reflux, 81%.

After, the required sulfamide **33** was prepared in a 4 step sequence from **29**. The first step involved a *N*-alkylation with 1,2-dibromoethane and sodium hydride in *N*,*N*-dimethylformamide to provide **30**. Treatment of **30** with sodium azide in *N*,*N*-dimethylformamide followed by reduction on Lindlar catalyst in methanol provided amine **32** with 83% within 2 steps. This latter was condensed on *N*,*N*-dimethylsulfamoyle chloride in a mixture of methylene chloride and triethylamine at rt to give **33** in a satisfactory yield. **33** was then treated with methyl iodide in the presence of sodium hydride to lead **34** which is demethylated to yield the desired pyrrolo[2,3-*d*]pyrimidine **6**. In the same way the derivative **35** was prepared from **33** in 85% yield (Scheme 9).

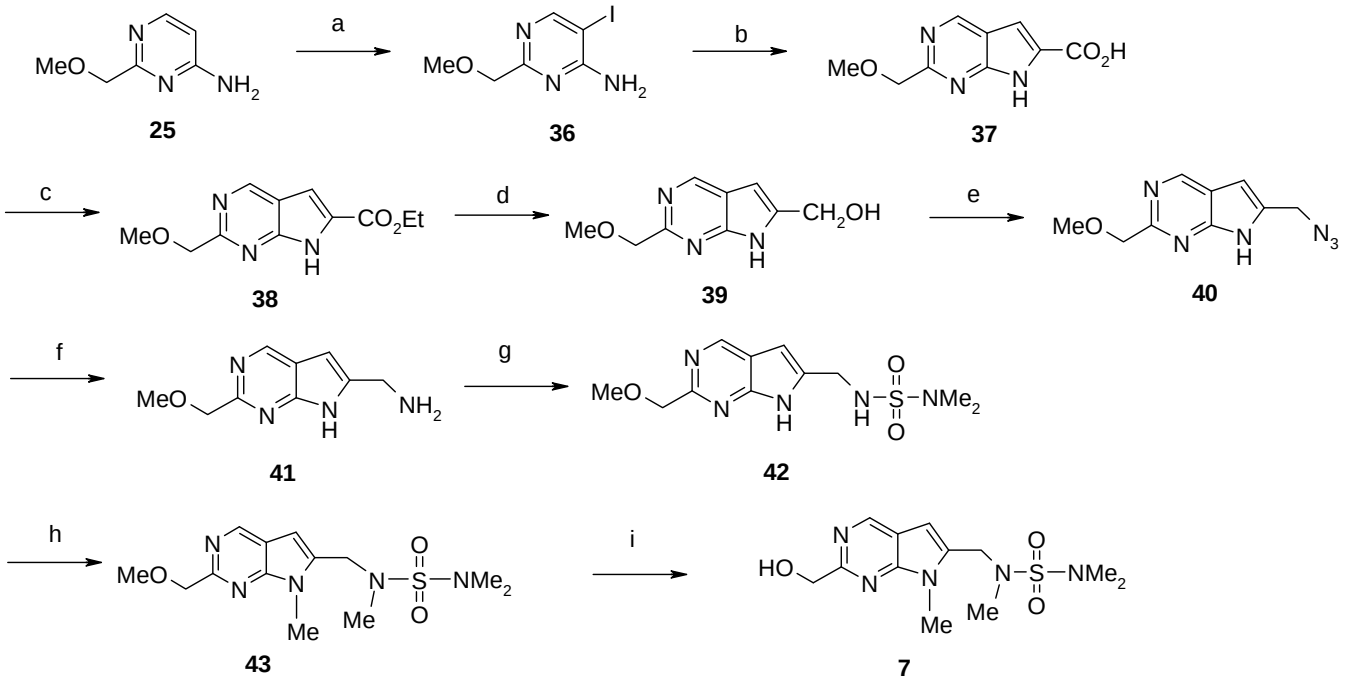


Scheme 9. Synthesis of *N*,*N*,*N*'-Trimethyl-*N*'-(2-[2-(hydroxymethyl)pyrrolo[2,3-*d*]pyrimidin-7-yl]ethyl) sulfamide **6**

Reagents and conditions: a) dibromoethane, NaH, DMF, rt, 85%. b) NaN_3, DMF, rt, 83%. c) H_2, Pd-Lindlar, EtOH, rt, quantitative. d) $ClSO_2NMe_2$, Et_3N, CH_2Cl_2, 73%. e) MeI, NaH, DMF, 91%. f) BBr_3, CH_2Cl_2, 0 °C, 80%. g) BBr_3, CH_2Cl_2, 0 °C, 88%.

Synthesis of *N*-(1-[2-(hydroxymethyl)-7-methylpyrrolo[2,3-*d*]pyrimidin-6-yl]methyl)-*N*,*N*',*N*'-trimethylsulfamide 7

In order to prepare the analog substituted in position 2 by a sulfamide chain, compound **25** was used as starting derivative. Thus, amine **25** was submitted to an iodination reaction with *N*-iodosuccinimide in methanol to give **36** with a yield of 56%.[22] After, the pyrrolopyrimidine **37** was obtained by reaction between compound **36** and pyruvic acid in the presence of triethylamine under palladium catalysis.[23] The next step consisted in the esterification of compound **37** in ethanol with thionyl chloride to form derivative **28** which was then reduced by treatment with lithium aluminium hydride.[24] The azide group was introduced *via* a Mitsunobu–type substitution using zinc azide/bis pyridine complex to afford **40** in a satisfactory yield.[25] Eventually and according to the same sequences as previously described in scheme 3 like reduction,[26] introduction of sulfamide chain, methylation and demethylation, the expected compound **7** was obtained in good yield (Scheme 10).

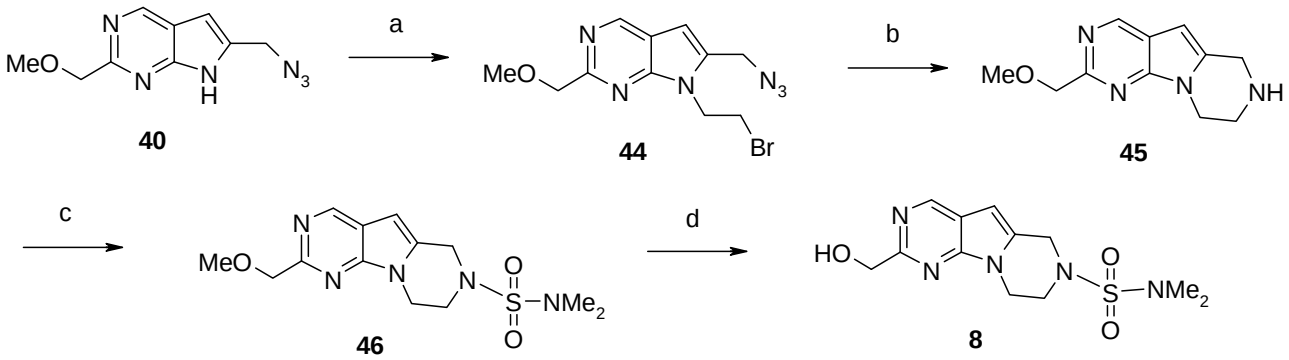


Scheme 10. Synthesis of *N*-(1-[2-(Hydroxymethyl)-7-methylpyrrolo[2,3-*d*]pyrimidin-6-yl]methyl)-*N*,*N*',*N*'-trimethylsulfamide **7**

Reagents and conditions: a) NIS, MeOH, 50 °C, 56%. b) $CH_3COCOOH$, $Pd(OAc)_2$, Et_3N, DMF, 105 °C, 64%. c) $SOCl_2$, EtOH, 0 °C to reflux 71% ; d) $LiAlH_4$, THF, rt, 83%. e) ZnN_6-2Py, DIAD, PPh_3, THF, rt, 50%. f) H_2, Pd, Lindlar, EtOH, rt, quant. g) $ClSO_2N(CH_3)_2$, Et_3N, CH_2Cl_2, rt, 51%. h) MeI, NaH, DMF, rt, 79%. i) BBr_3, CH_2Cl_2, 0 °C, 85%.

Synthesis of *N*,*N*-dimethyl-2-(hydroxymethyl)-6,7,8,9-tetrahydropyrazino[2',1':5,1]pyrrolo[2,3-*d*]-pyrimidine-7-sulfonamide 8

Following our interest in the development of SDI analogs, we decided to introduce a pyrazine ring on the pyrrolopyrimidine skeleton. In order to achieve this, we introduced on position 1 of the azide **40** precedently synthesized, the bromoalkyl chain under Bös *et al*. conditions.[27] Compound **44**, obtained with a yield of 65%, was submitted to reduction using Lindlar palladium as catalyst giving the cyclic derivative **45** in 92% yield. Treatment of **42** with *N*,*N*-dimethylsulfamoyl chloride following the classic method gave the corresponding sulfamide **46** with moderate yield. Finally compound **8** was obtained by demethylation in the presence of boron tribromide in methylene chloride (Scheme 11).



Scheme 11. Synthesis of *N*,*N*-Dimethyl-2-(hydroxymethyl)-6,7,8,9-tetrahydropyrazino[2',1':5,1]-pyrrolo[2,3-*d*]pyrimidine-7-sulfonamide **8**

Reagents and conditions: a) 1,2-dibromoethane, NaOH, Bu_4NBr, H_2O, rt, 65%. b) H_2, Pd, Lindlar, EtOH, rt, 92%. c) $ClSO_2NMe_2$, Et_3N, CH_2Cl_2, rt, 63%. d) BBr_3, CH_2Cl_2, 0 °C, 82%.

The *in vitro* activities of compounds **1-8** were determined by their ability to inhibit sheep liver's SDH. The results of inhibition are presented in Table 1.

Compounds	Formula	% Inhibition for 10^{-5} M
1	$C_{11}H_{17}N_5O_4S$	< 10
2	$C_{11}H_{21}N_5O_3S$	50
9	$C_{11}H_{17}N_5O_3S$	60
3	$C_{12}H_{23}N_5O_3S$	64
4	$C_{13}H_{25}N_5O_3S$	53
5	$C_{12}H_{16}N_6O_5S$	15
24	$C_{19}H_{22}N_6O_5S$	49
6	$C_{12}H_{19}N_5O_3S$	19
7	$C_{12}H_{19}N_5O_3S$	23
8	$C_{12}H_{17}N_5O_3S$	51
35	$C_{11}H_{17}N_5O_3S$	19

As may be seen in Table 1, compounds **3** and **9** exhibited the most potent inhibitory activity (64 and 60 % of inhibition for 10^{-5} M). Compounds **2**, **4**, **8** and **24** had almost the same and modest inhibitory effects which are near 50 %. On the other hand, the other products were practically inactive against SDH.

To conclude, we described the synthesis of eight analogs of sorbitol dehydrogenase which possess an original heterocyclic skeleton. Access to these compounds involves as the key step, the formation of a

pyrrolopyrimidine skeleton from the 5-amino-2-(methoxymethyl)pyrimidine. Unfortunately, among all the molecules synthesized and tested none showed significant activity. Another novel heterocycle is currently under investigation the results of which will be reported elsewhere.

EXPERIMENTAL

Melting points are uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker AM-300 WB (300 MHz). The coupling constants are reported in Hz and the chemical shifts in ppm (δ, ppm) downfield from TMS which was used as an internal standard. IR spectra were obtained with a Perkin-Elmer FT Paragon 1000 PC. MS spectra were registered on a Perkin-Elmer SCIEX API 3000 spectrometer. Reaction products were purified by flash chromatography using silica gel (Merck 230-400 mesh). Analytical TLC was carried out on silica gel F_{254} plates. All anhydrous reactions were performed in over-dried glassware under an atmosphere of argon. Anhydrous solvents were transferred *via* syringe.

The following compounds were prepared by literature methods: 2-methoxyacetamidine hydrochloride **11**,[28] 4-chloro-2-(methoxymethyl)pyrimidine **13**,[29] 3-benzylimidazolin-2,4-dione **21**,[30] 2-(methoxymethyl)-4-(piperazin-1-yl)pyrimidine **23**.[31]

1.1. *N,N*-Dimethyl-4-(2-formylpyrimidin-4-yl)-1-piperazinesulfonamide 9

Under an inert atmosphere, DMSO (0.35 mL, 5 mmol) was added dropwise to a stirred solution of oxalyl chloride (0.22 mL, 2.5 mmol) in dry CH_2Cl_2 (10 mL) at -60°C. After 5 minutes, a solution of SDI (500 mg, 1.66 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise to the mixture. The reaction was stirred an additional time (30 min) with continuous cooling. The triethylamine (2.31 mL, 16.6 mmol) was then added and the mixture was stirred for 12 h, allowing the temperature to slowly reach rt. The residue was taken up in water, basified with saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2. The combined extracts were dried over anhydrous $MgSO_4$. After removal of the solvent in vacuo, the product was purified by flash chromatography on silica gel (eluent: MeOH/EtOAc, 5/95) to afford **9** (347 mg, 70%) as yellow needles. Mp 135-136 °C (*i*-Pr). IR (KBr) ν: 1728, 1346, 1142 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.87 (s, 6H, N(C**H**$_3$)$_2$), 3.36 (t, 4H, *J* = 5.2 Hz, 4 x **H**$_{piperazin}$), 3.84 (t, 4H, *J* = 5.2 Hz, 4 x **H**$_{piperazin}$), 6.65 (d, 1H, *J* = 6.2 Hz, **H**$_5$), 8.46 (d, 1H, *J* = 6.2 Hz, **H**$_6$), 9.91 (s, 1H, C**H**O); ^{13}C-NMR ($CDCl_3$) δ 36.2 (-N(**C**H$_3$)$_2$), 41.5 (2 x **C**$_{piperazin}$), 43.8 (2 x **C**$_{piperazin}$), 102.9 (**C**$_5$), 154.7 (**C**$_6$), 156.9 (**C**$_q$), 159.4 (**C**$_q$), 190.1 (**C**HO); MS (IE) *m/z* = 300 (M+1); *Anal.* Calcd for $C_{11}H_{17}N_5O_3S$: C, 44.14 ; H, 5.72 ; N, 23.40. Found : C, 44.23; H, 5.70; N, 23.15.

1.2. *N,N*-Dimethyl-4-[2-(ethoxycarbonyl)pyrimidin-4-yl]-1-piperazinesulfonamide 10

Under an inert atmosphere, NaCN (712 mg, 14.5 mmol), AcOH (0.27 mL, 4.5 mmol) and MnO_2 (5 g, 58 mmol) were added to a stirred solution of **9** (870 mg, 2.9 mmol) in dry EtOH (12 mL). The mixture was

stirred at rt under nitrogen for 24 h. After filtration on Celite and concentration of the filtrate in vacuo the residue was taken up in CH_2Cl_2, washed with saturated aqueous $NaHCO_3$ solution and dried over anhydrous $MgSO_4$. After removal of the solvent, the crude residue was purified over silica gel (eluent: MeOH/EtOAc, 1/9) to afford **10** (626 mg, 63%) as white needles. Mp 81-82 °C (*i*-Pr). IR (KBr): ν 3000-2800, 1734, 1311, 1179 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.44 (t, 3H, *J* = 7.1 Hz, C**H**$_3$-CH_2-O), 2.88 (s, 6H, N(C**H**$_3$)$_2$), 3.35 (t, 4H, *J* = 5.0 Hz, 4 x **H**$_{piperazin}$), 3.82 (t, 4H, *J* = 5.0 Hz, 4 x **H**$_{piperazin}$), 4.46 (q, 2H, *J* = 7.1 Hz, CH_3-C**H**$_2$-O), 6.63 (d, 1H, *J* = 6.2 Hz, **H**$_5$), 8.39 (d, 1H, *J* = 6.2 Hz, **H**$_6$); ^{13}C-NMR ($CDCl_3$) δ 14.2 (**C**H_3-CH_2-O), 38.3 (N(**C**H_3)$_2$), 43.5 (2 x **C**$_{piperazin}$), 45.9 (2 x **C**$_{piperazin}$), 62.4 (CH_3-**C**H_2-O), 104.4 (**C**$_5$), 156.4 (**C**$_q$), 156.5 (**C**$_6$), 161.8 (**C**$_q$), 164.1 (**C**$_q$); MS (IE) *m/z* = 344 (M+1); *Anal.* Calcd for $C_{13}H_{21}N_5O_4S$: C, 45.47; H, 6.16; N, 20.39. Found: C, 45.21; H, 6.13; N, 20.20.

1.3. *N,N*-Dimethyl-4-(2-carboxypyrimidin-4-yl)-1-piperazinesulfonamide 1

A solution of **10** (400 mg, 1.17 mmol) and Dowex resin (150 mg, 500X8-400) in water (10 mL) was heated under reflux for 15 h. The resin was then filtered off and the filtrate was freeze-dried to give **1** (281 mg, 77%) as a white foam. Mp 107-109 °C (*i*-Pr). IR (KBr): ν 3600-2600**,** 1636, 1355, 1150 cm^{-1}; ^{1}H-NMR (DMSO-d_6+D_2O) δ 2.79 (s, 6H, N(C**H**$_3$)$_2$), 3.26 (t, 2H, *J* = 4.7 Hz, 4 x **H**$_{piperazin}$), 3.78 (sb, 2H, 4 x **H**$_{piperazin}$), 6.99 (d, 1H, *J* = 6.4 Hz, **H**$_5$), 8.30 (d, 1H, *J* = 6.4 H, **H**$_6$); ^{13}C-NMR ($CDCl_3$) δ 38.4 (-N(**C**H_3)$_2$), 43.8 (2 x **C**$_{piperazin}$), 46.2 (2 x **C**$_{piperazin}$), 105.2 (**C**$_5$), 155.6 (**C**$_6$), 157.6 (**C**$_q$), 161.8 (**C**$_q$), 165.5 (**C**$_q$); MS (IE) *m/z* = 316 (M+1); *Anal.* Calcd for $C_{11}H_{17}N_5O_4S$: C, 41.90; H, 5.43; N, 22.21. Found: C, 42.15; H, 5.46; N, 22.15.

1.4. *N*-(2-Methylaminoethyl)-*N,N',N'*-trimethylsulfamide 14

At rt, K_2CO_3 (2.6 g, 18.8 mmol) was added to a solution of *N,N'*-dimethylethane-1,2-diamine (4 mL, 37.6 mmol) in EtOH (50 mL). The mixture was then cooled to 0°C, and *N,N*-dimethylsulfamoyl chloride (1.96 mL, 18.8 mmol) was added dropwise. The reaction was stirred vigorously for an additional time (40 min) under continuous cooling. The mixture was filtered and the filtrate was concentrated in vacuo. The crude was purified on silica gel (eluent: MeOH/CH_2Cl_2, 1/9) to provide **14** (2.43 g, 66%) as a colourless oil. IR (film): ν 3329, 3000-2800, 1324, 1143 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.55 (s, 3H, NH-C**H**$_3$), 2.82 (s, 6H, N(C**H**$_3$)$_2$), 2.87 (s, 3H, C**H**$_3$-N-SO_2), 2.91 (t, 2H, *J* = 6.3 Hz, NH-C**H**$_2$), 3.40 (t, 2H, *J* = 6.3 Hz, C**H**$_2$-N-SO_2), 3.55 (sb, 1H, N**H**); ^{13}C-NMR ($CDCl_3$) δ 35.7 (NH-**C**H_3), 36.2 (**C**H_3-N-SO_2), 38.6 (N(**C**H_3)$_2$), 49.0 (NH-**C**H_2-), 49.7 (**C**H_2-N-SO_2); MS (IE) *m/z* = 196 (M+1); *Anal.* Calcd for $C_6H_{17}N_3O_2S$: C, 36.90; H, 8.77; N, 21.52. Found: C, 36.71; H, 8.53; N, 21.60.

1.5. *N*-(2-Methylaminopropyl)-*N,N',N'*-trimethylsulfamide 15

At rt, K_2CO_3 (1.38 g, 10.0 mmol) was added to a solution of *N,N'*-dimethylpropane-1,3-diamine (2.5 mL,

20.0 mmol) and EtOH (25 mL). The mixture was then cooled to 0 °C, and *N*,*N*-dimethylsulfamoyl chloride (1.07 mL, 10.0 mmol) was added dropwise. The reaction was stirred vigorously for an additional time (2 h) under continuous cooling. The mixture was filtered and the filtrate was concentrated in vacuo. The crude was purified on silica gel (eluent: MeOH/CH_2Cl_2, 2/8) to provide **15** (858 mg, 41%) as a colourless oil. IR (film): ν 3327, 3000-2800, 1322, 1143 cm^{-1}; ^{1}H-NMR ($CDCl_3$+ D_2O) δ 1.76 (m, 2H, CH_2-C**H**$_2$-CH_2), 2.43 (s, 3H, NH-C**H**$_3$), 2.63 (t, 2H, *J* = 7.0 Hz, NH-C**H**$_2$), 2.78 (s, 6H, N(C**H**$_3$)$_2$), 2.81 (s, 3H, C**H**$_3$-N-SO_2), 3.24 (t, 2H, *J* = 7.0 Hz, C**H**$_2$-N-SO_2); ^{13}C-NMR ($CDCl_3$) δ 27.3 (CH_2-**C**H_2-CH_2), 34.5 (NH-**C**H_3), 36.0 (**C**H_3-N-SO_2), 37.6 (N(**C**H_3)$_2$), 48.2 (NH-**C**H_2-CH_2-CH_2), 48.3 (NH-CH_2-CH_2-**C**H_2); MS (IE) *m/z* = 210 (M+1); *Anal.* Calcd for $C_7H_{19}N_3O_2S$: C, 45.41; H, 7.30; N, 22.06. Found: C, 45.12; H, 7.51; N, 21.98.

1.6. *N*-(2-[*N*”-(2-(Methoxymethyl)pyrimidin-4-yl)-*N*”-methyl]ethylamino)-*N*,*N*’,*N*’-trimethylsulfamide 16

Under an Argon atmosphere, 4-chloro-2-(methoxymethyl)pyrimidine **13** (800 mg, 5 mmol) and triethylamine (0.773 mL, 5.5 mmol) were added to a stirred solution of **14** (1.08 g, 5.54 mmol) in dry THF (4 mL). The mixture was heated under reflux for 15 h. After cooling, the solvent was removed and the crude was purified on silica gel (eluent: MeOH/EtOAc, 1/9) to give **16** (1.51 g, 95%) as a colourless oil. IR (film): ν 3000-2800, 1344, 1145 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.73 (s, 6H, -N(C**H**$_3$)$_2$) 2.89 (s, 3H, C**H**$_3$-N-SO_2) 3.09 (s, 3H, N-C**H**$_3$), 3.39 (t, 2H, *J* = 6.3 Hz, C**H**$_2$-N-SO_2), 3.51 (s, 3H, OC**H**$_3$), 3.85 (t, 2H, *J* = 6.3 Hz, N-C**H**$_2$-), 4.46 (s, 2H, OC**H**$_2$-), 6.35 (d, 1H, *J* = 6.1 Hz, **H**$_5$), 8.23 (d, 1H, *J* = 6.1 Hz, **H**$_6$); ^{13}C-NMR ($CDCl_3$) δ 35.7 (N-**C**H_3), 36.0 (C**H**$_3$-N-SO_2), 38.0 (N(**C**H_3)$_2$), 47.0 (N-**C**H_2-), 47.9 (**C**H_2-N-SO_2), 59.0 (O**C**H_3), 75.1 (O**C**H_2), 100.9 (**C**$_5$), 155.8 (**C**$_6$), 161.7 (**C**$_q$), 165.9 (**C**$_q$). MS (IE) *m/z* = 318 (M+1); *Anal.* Calcd for $C_{12}H_{23}N_5O_3S$: C, 43.49; H, 7.60; N, 21.13. Found: C, 43.01; H, 7.45; N, 21.30.

1.7. *N*-(2-[*N*”-(2-(Methoxymethyl)pyrimidin-4-yl)-*N*”-methyl]propylamino)-*N*,*N*’,*N*’-trimethylsulfamide 17

Under an inert atmosphere, 4-chloro-2-(methoxymethyl)pyrimidine **13** (345 mg, 2.2 mmol) and triethylamine (0.33 mL, 2.4 mmol) were added to a stirred solution of **15** (500 mg, 2.4 mmol) in dry THF (4 mL). The mixture was heated under reflux for 15 h. After cooling, the solvent was removed and the crude was purified on silica gel (eluent: MeOH/EtOAc, 1/9) to give **17** (720 mg, 95%) as a colourless oil. IR (film): ν 3000-2800, 1324, 1145 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.90 (m, 2H, CH_2-C**H**$_2$-CH_2), 2.79 (s, 6H, N(C**H**$_3$)$_2$), 2.83 (s, 3H, C**H**$_3$-N-SO_2), 3.06 (s, 3H, N-C**H**$_3$), 3.23 (t, 2H, *J* = 7.1 Hz, C**H**$_2$-N-SO_2), 3.52 (s, 3H, OC**H**$_3$), 3.63 (t, 2H, *J* = 7.1 Hz, N-C**H**$_2$), 4.46 (s, 2H, OC**H**$_2$), 6.29 (d, 1H, *J* = 6.2 Hz, **H**$_5$), 8.20 (d, 1H, *J* = 6.2 Hz, **H**$_6$); ^{13}C-NMR ($CDCl_3$) δ 25.3 (CH_2-**C**H_2-CH_2), 35.0 (N-**C**H_3), 35.5 (**C**H_3-N-SO_2), 38.1

(-N(**C**H_3)$_2$), 46.7 (N-**C**H_2-CH_2-CH_2), 48.5 (NH-CH_2-CH_2-**C**H_2), 59.0 (O**C**H_3), 75.6 (O**C**H_2), 100.9 (**C**$_5$), 155.6 (**C**$_6$), 161.5 (**C**$_q$), 166.0 (**C**$_q$); MS (IE) *m/z* = 332 (M+1); *Anal.* Calcd for $C_{13}H_{25}N_5O_3S$: C, 43.55; H, 6.98; N, 23.09. Found: C, 43.21; H, 6.81; N, 23.15.

1.8. *N*-(2-[*N"*-(2-(Hydroxymethyl)pyrimidin-4-yl)-*N"*-methyl]ethylamino)-*N,N',N'*-trimethylsulfamide 2

Under an inert atmosphere, compound **16** (1.48 g, 4.7 mmol) was dissolved in dry CH_2Cl_2 (7 mL). The mixture was then cooled to 0 °C and a solution of BBr_3 (1.1 mL, 11.6 mmol) in dry CH_2Cl_2 (3.5 mL) was added dropwise. After 2 h at 0 °C, the reaction was hydrolysed, basified with saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo. Finally, purification by flash chromatography on silica gel using 10% MeOH in EtOAc as eluent gave 1.38 g (98%) of *N*-(2-[*N"*-(2-(hydroxymethyl)pyrimidin-4-yl)-*N"*-methyl]-ethylamino)-*N*,*N'*,*N'*-trimethylsulfamide **2** as a colourless oil. IR (film): ν 3425, 2931, 1329, 1143 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 2.64 (s, 6H, N(C**H**$_3$)$_2$), 2.82 (s, 3H, C**H**$_3$-N-SO_2), 3.04 (s, 3H, N-C**H**$_3$), 3.33 (t, 2H, *J* = 6.4 Hz, C**H**$_2$-N-SO_2), 3.77 (sb, 2H, N-C**H**$_2$), 4.36 (d, 2H, *J* = 5.9 Hz, C**H**$_2$OH), 4.74 (t, 1H, *J* = 5.9 Hz, CH_2O**H**), 6.53 (d, 1H, *J* = 6.1 Hz, **H**$_5$), 8.16 (d, 1H, *J* = 6.1 Hz, **H**$_6$); ^{13}C-NMR (DMSO-d_6) δ 33.9 (N-**C**H_3), 34.3 (**C**H_3-N-SO_2), 36.0 (N(**C**H_3)$_2$), 45.3 (N-**C**H_2-), 46.0 (**C**H_2-N-SO_2), 62.2 (**C**H_2OH), 98.9 (**C**$_5$), 153.4 (**C**$_6$), 159.4 (**C**$_q$), 165.2 (**C**$_q$); MS (IE) *m/z* = 304 (M+1). *Anal.* Calcd for $C_{11}H_{21}N_5O_3S$: C, 43.55; H, 6.98; N, 23.09. Found: C, 43.62; H, 6.71; N , 23.15.

1.9. *N*-(2-[*N"*-(2-(Hydroxymethyl)pyrimidin-4-yl)-*N"*-methyl]propylamino)-*N,N',N'*-trimethylsulfamide 3

Under an inert atmosphere, compound **17** (650 mg, 1.95 mmol) was dissolved in dry CH_2Cl_2 (4 mL). The mixture was then cooled to 0 °C and a solution of BBr_3 (0.55 mL, 5.8 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise. After 2 h at 0 °C, the reaction was hydrolysed, basified with saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo. Finally, purification by flash chromatography on silica gel using 4% MeOH in EtOAc as eluent gave 560 mg (90%) of *N*-(2-[*N"*-(2-(hydroxymethyl)pyrimidin-4-yl)-*N"*-methyl]-propylamino)-*N*,*N'*,*N'*-trimethylsulfamide **3** as a colourless oil. IR (film): ν 3417, 3000-2800, 1343, 1143 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 1.78 (m, 2H, CH_2-C**H**$_2$-CH_2), 2.70 (s, 6H, N(C**H**$_3$)$_2$), 2.76 (s, 3H, C**H**$_3$-N-SO_2), 3.03 (s, 3H, N-C**H**$_3$), 3.14 (t, 2H, *J* = 7.2 Hz, C**H**$_2$-N-SO_2), 3.55 (tb, 2H, N-C**H**$_2$), 4.34 (d, 2H, *J* = 5.8 Hz, C**H**$_2$OH), 4.71 (t, 2H, *J* = 5.8 Hz, CH_2O**H**), 6.52 (d, 1H, *J* = 6.2 Hz, **H**$_5$), 8.13 (d, 1H, *J* = 6.2 Hz, **H**$_6$); ^{13}C-NMR ($CDCl_3$) δ 24.7 (CH_2-**C**H_2-CH_2), 34.4 (N-**C**H_3), 35.2 (**C**H_3-N-SO_2), 37.5 (N(**C**H_3)$_2$), 46.3 (N-**C**H_2-CH_2-CH_2), 47.9 (NH-CH_2-CH_2-**C**H_2), 63.5 (O**C**H_2), 100.2 (**C**$_5$), 154.5 (**C**$_6$), 160.5 (**C**$_q$), 166.5 (**C**$_q$); MS (IE) *m/z* = 318 (M+1); *Anal.* Calcd for $C_{12}H_{23}N_5O_3S$: C, 45.41; H, 7.30; N,

22.06. Found: C, 45.31; H, 7.21; N, 21.97.

1.10. *N*-(4-aminobutyl)-2-(methoxymethyl)pyrimidin-4-amine 18

Under an inert atmosphere, 4-chloro-2-(methoxymethyl)pyrimidine **13** (2 g, 12.6 mmol), triethylamine (1.75 mL, 12.6 mmol) was added to a stirred solution of 1,4-diaminobutane (2.5 mL, 25.2 mmol) in dry THF (32 mL). The mixture was heated under reflux for 15 h. After cooling, the solvent was removed and the crude was purified on silica gel (eluent: MeOH/EtOAc, 2/8) to give **18** (2.15 g, 81%) as a colourless oil. IR (film): ν 3500-3000, 3000-2800, 1605 cm^{-1}; ^{1}H-NMR ($CDCl_3$+ D_2O) δ 1.51-1.70 (m, 4H, NH-CH_2-(C**H**$_2$)$_2$-CH_2-NH_2), 2.75 (t, 2H, *J* = 6.7 Hz, C**H**$_2$-NH_2), 3.30 (tb, 2H, NH-C**H**$_2$-), 3.50 (s, 3H, -OC**H**$_3$), 4.45 (s, 2H, OC**H**$_2$), 6.21 (d, 1H, *J* = 5.9 Hz, **H**$_5$), 8.16 (d, 1H, *J* = 5.9 Hz, **H**$_6$); ^{13}C-NMR ($CDCl_3$) δ 26.3 (NH-CH_2-(**C**H$_2$)$_2$-CH_2-NH_2), 30.3 (NH-CH_2-(**C**H$_2$)$_2$-CH_2-NH_2), 40.9 (**C**H$_2$-NH_2), 41.3 (NH-**C**H$_2$), 58.7 (O**C**H$_3$), 75.1 (O**C**H$_2$), 101.3 (**C**$_5$), 155.3 (**C**$_6$), 162.3 (**C**$_q$), 166.0 (**C**$_q$); MS (IE) *m/z* = 211 (M+1); *Anal.* Calcd for $C_{10}H_{18}N_4O$: C, 57.12; H, 8.63; N, 26.64. Found: C, 56.82; H, 8.41; N, 26.61.

1.11. *N,N*-Dimethyl-*N'*-(4-[*N"*-(2-methoxymethyl)pyrimidin-4-yl])butylaminosulfamide 19

Under an inert atmosphere, a solution of *N,N*-dimethylsulfamoyl chloride (2 mL, 10.4 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise to a solution of **18** (2 g, 9.5 mmol) and triethylamine (1.45 mL, 10.4 mmol) in dry CH_2Cl_2 (35 mL). The reaction was then stirred at rt. After 15h, the mixture was hydrolysed and extracted with EtOAc. The combined organic layers were dried over anhydrous $MgSO_4$ and evaporated in vacuo. The crude was purified on silica gel (eluent: MeOH/EtOAc, 5/95) to provide **19** (2.0 g, 67%) as a yellow oil. IR (film): ν 3500-3000, 3000-2800, 1603, 1327, 1145 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.61-1.69 (m, 4H, NH-CH_2-(C**H**$_2$)$_2$-CH_2-NH_2), 2.79 (s, 6H, N(C**H**$_3$)$_2$), 3.11 (m, 2H, C**H**$_2$-NH-SO_2-), 3.32 (m, 2H, NH-C**H**$_2$-), 3.50 (s, 3H, -OC**H**$_3$), 4.45 (s, 2H, OC**H**$_2$), 5.23 (t, 1H, *J* = 3.4 Hz, N**H**), 5.48 (sb, 1H, N**H**), 6.22 (d, 1H, *J* = 6.0 Hz, **H**$_5$), 8.15 (d, 1H, *J* = 6.0 Hz, **H**$_6$); ^{13}C-NMR ($CDCl_3$) δ 26.5 (NH-CH_2-(**C**H$_2$)$_2$-CH_2-NH_2), 27.4 (NH-CH_2-(**C**H$_2$)$_2$-CH_2-NH_2), 38.4 (N(**C**H$_3$)$_2$), 41.1 (**C**H$_2$-NH), 43.5 (**C**H$_2$-NH-SO_2), 59.4 (O**C**H$_3$), 75.7 (O**C**H$_2$), 100.5 (**C**$_5$), 155.8 (**C**$_6$), 162.9 (**C**$_q$), 166.5 (**C**$_q$); MS (IE) *m/z* = 318 (M+1); *Anal.* Calcd for $C_{12}H_{23}N_5O_3S$: C, 45.41; H, 7.30; N, 22.06. Found: C, 45.56; H, 7.26; N, 22.15.

1.12. *N*-(4-(*N"*-[2-(Methoxymethyl)pyrimidin-4-yl]-*N"*-methyl)butylamino)-*N,N',N'*-trimethyl-sulfamide 20

Under an inert atmosphere, NaH (0.34 g, 8.5 mmol) was added portionwise to a stirred solution of **19** (0.90 g, 2.8 mmol) in DMF (12 mL) at rt over 30 min. The mixture was stirred for an additional time (30 min) before MeI (0.53 mL, 8.5 mmol) was added dropwise and the mixture stirred for 3 h. Water was then added, the product was extracted with CH_2Cl_2, purified by flash chromatography on silica gel

(eluent: MeOH/CH_2Cl_2, 1/9) to give compound **20** (0.60 g, 62%) as a colourless oil. IR (film): ν 3000-2800, 1592, 1343, 1143 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.54 (m, 4H, N-CH_2-(C**H**$_2$)$_2$-CH_2-NH-SO_2), 2.71 (s, 6H, N(C**H**$_3$)$_2$), 2.72 (s, 3H, C**H**$_3$-N-SO_2), 2.96 (s, 3H, N-C**H**$_3$), 3.13 (t, 2H, *J* = 6.6 Hz, C**H**$_2$-N-SO_2), 3.42 (s, 3H, OC**H**$_3$), 3.50 (sb, 2H, N-C**H**$_2$), 4.37 (s, 2H, OC**H**$_2$), 6.20 (d, 1H, *J* = 6.2 Hz, **H**$_5$), 8.08 (d, 1H, *J* = 6.0 Hz, **H**$_6$); ^{13}C-NMR ($CDCl_3$) δ 23.9 (N-CH_2-(**C**H$_2$)$_2$-CH_2-N-SO_2), 24.8 (N-CH_2-(**C**H$_2$)$_2$-CH_2-N-SO_2), 34.8 (**C**H$_3$-N), 35.2 (**C**H$_3$-N-SO_2), 38.0 (N(**C**H$_3$)$_2$), 48.4 (N-**C**H$_2$), 50.3 (**C**H$_2$-N-SO_2), 58.9 (O**C**H$_3$), 75.5 (O**C**H$_2$), 100.7 (**C**$_5$), 155.3 (**C**$_6$), 161.5 (**C**$_q$), 165.8 (**C**$_q$); MS (IE) *m/z* = 346 (M+1); *Anal.* Calcd for $C_{14}H_{27}N_5O_3S$: C, 48.67; H, 7.88; N, 20.27. Found: C, 48.33; H, 7.60; N, 20.33.

1.13. *N*-(4-[*N*”-(2-(Hydroxymethyl)pyrimidin-4-yl)-*N*”-methyl]butylamino)-*N*,*N*’,*N*’-trimethylsulfamide 4

Under an inert atmosphere, compound **20** (0.5 g, 1.4 mmol) was dissolved in dry CH_2Cl_2 (15 mL). The mixture was then cooled to 0 °C and a solution of BBr_3 (0.68 mL, 7.2 mmol) in dry CH_2Cl_2 (4 mL) was added dropwise. After 2 h at 0 °C, the reaction was hydrolysed, basified with saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo. Finally, purification by flash chromatography on silica gel using 10% MeOH in CH_2Cl_2 as eluent gave 0.436 g (91%) of *N*-(4-[*N*”-(2-(hydroxymethyl)pyrimidin-4-yl)-*N*”-methyl]-butylamino)-*N*,*N*’,*N*’-trimethylsulfamide **4** as a colourless oil. IR (film): ν 3417, 3000-2800, 1594, 1342, 1143 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.64 (m, 4H, N-CH_2-(C**H**$_2$)$_2$-CH_2-N-SO_2), 2.79 (s, 9H, -N(C**H**$_3$)$_2$ and C**H**$_3$-N-SO_2), 3.07 (s, 3H, N-C**H**$_3$), 3.22 (t, 2H, *J* = 6.6 Hz, C**H**$_2$-N-SO_2), 3.61 (sb, 2H, N-C**H**$_2$), 4.02 (sb, 1H, CH_2O**H**), 4.58 (s, 2H, C**H**$_2$OH), 6.30 (d, 1H, *J* = 6.2 Hz, **H**$_5$), 8.15 (d, 1H, *J* = 6.0 Hz, **H**$_6$); ^{13}C-NMR ($CDCl_3$) δ 23.5 (N-CH_2-(**C**H$_2$)$_2$-CH_2-N-SO_2), 24.5 (N-CH_2-(**C**H$_2$)$_2$-CH_2-N-SO_2), 34.5 (**C**H$_3$-N), 35.1 (**C**H$_3$-N-SO_2), 37.7 (N(**C**H$_3$)$_2$), 48.2 (N-**C**H$_2$), 49.9 (**C**H$_2$-N-SO_2), 63.8 (O**C**H$_2$), 100.4 (**C**$_5$), 154.5 (**C**$_6$), 160.8 (**C**$_q$), 166.8 (**C**$_q$); MS (IE) *m/z* = 332 (M+1); *Anal.* Calcd for $C_{13}H_{25}N_5O_3S$: C, 47.11; H, 7.60; N, 21.13. Found: C, 46.81; H, 7.42; N, 21.22.

1.14. 3-Benzyl-1-(chlorosulfonyl)imidazolidine-2,4-dione 22

A solution of sulfuryl chloride (3.8 mL, 47.3 mmol) in $CHCl_3$ (13 mL) was added dropwise at 0 °C to a solution of **21** (3 g, 15.7 mmol) and triethylamine (4.4 mL, 31.6 mmol) in $CHCl_3$ (35 mL). The reaction was stirred for an additional time (1 h) and the solvent was removed in vacuo. The crude was purified on silica gel (eluent: light petroleum/EtOAc, 7/3) to provide **22** (3.96 g, 81%) as a white solid. Mp 130-131 °C (*i*-Pr). IR (KBr): ν 1740, 1723, 1411, 1174 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 4.42 (s, 2H, C**H**$_2$-N), 4.72 (s, 2H, C**H**$_2$-Ph), 7.33-7.41 (m, 5H, **H**$_{arom}$); ^{13}C-NMR ($CDCl_3$) δ 43.8 (**C**H$_2$-Ph), 50.3 (**C**H$_2$-NH), 128.8 (2 x **C**$_{arom}$), 129.0 (2 x **C**$_{arom}$), 132.1 (**C**$_{arom}$), 133.9 (**C**$_q$), 150.1 (**C**=O), 164.6 (**C**=O); MS (IE) *m/z* =

311 (M+1 for ^{35}Cl), *m/z* = 313 (M+1 for ^{37}Cl); Calcd for $C_{10}H_9ClN_2O_4S$: C, 41.60; H, 3.14; N, 9.70. Found: C, 41.31; H, 3.01; N, 9.41.

1.15. 3-Benzyl-1-([4-(2-(methoxymethyl)pyrimidin-4-yl)piperazin-1-yl]sulfonyl)imidazolidine-2,4-dione 24

Under an inert atmosphere, a suspension of NaH (0.395 mg, 9.9 mmol) and compound **23** (1.15 g, 5.5 mmol) in dry DMF (35 mL) was stirred at 50 °C for 30 min. A solution of **22** (2.4 g, 8.3 mmol) in dry DMF (18 mL) was then added dropwise. The mixture was heated at 80 °C for 15 h. After cooling, the mixture was hydrolysed and extracted with CH_2Cl_2. The combined organic layers were washed with water, dried over anhydrous $MgSO_4$ and concentrated in vacuo. The crude was purified on silica gel (eluent: MeOH/CH_2Cl_2, 4/96) to provide **24** (610 mg, 24%) as a brown solid. Mp 211-212 °C (*i*-Pr). IR (KBr): ν 3000-2800, 1715, 1713, 1411, 1586, 1374, 1175 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.51 (m, 7H, OC**H**$_3$ + 4 x **H**$_{piperazin}$), 3.80 (t, 4H, *J* = 2.5 Hz, **H**$_{piperazin}$), 4.30 (s, 2H, N-C**H**$_2$-CO), 4.48 (s, 2H, OC**H**$_2$), 4.64 (s, 2H, C**H**$_2$Ph), 6.41 (d, 1H, *J* = 6.2 Hz, **H**$_5$), 7.28-7.38 (m, 5H, **H**$_{arom}$), 8.29 (d, 1H, *J* = 6.2 Hz, **H**$_6$); ^{13}C-NMR ($CDCl_3$) δ 43.1 (**C**H$_2$-Ph), 43.2 (2 x **C**$_{piperazin}$), 46.1 (2 x C$_{piperazin}$), 51.1 (N-**C**H$_2$-CO), 59.2 (O**C**H$_3$), 75.4 (O**C**H$_2$), 101.1 (**C**$_5$), 128.5 (2 x **C**$_{arom}$), 128.8 (2 x **C**$_{arom}$), 128.9 (**C**$_{arom}$), 134.6 (**C**$_q$), 153.0 (**C**$_q$), 156.5 (**C**$_6$), 161.4 (**C**$_q$), 166.4 (**C**=O), 167.0 (**C**=O); MS (IE) *m/z* = 461 (M+1); Calcd for $C_{20}H_{24}N_6O_5S$: C, 52.16; H, 5.25; N,18.25. Found: C, 52.23; H, 5.36; N, 18.22.

1.16. 1-([4-(2-(Methoxymethyl)pyrimidin-4-yl)piperazin-1-yl]sulfonyl)imidazolidine-2,4-dione 5

Under an inert atmosphere, $AlCl_3$ (1.38 g, 10.4 mmol) was added to a solution of 3-benzyl-1-([4-(2-(methoxymethyl)pyrimidin-4-yl)piperazin-1-yl]sulfonyl)imidazolidin-2,4-dione **24** (0.6 g, 1.3 mmol) in dry toluene (30 mL). The reaction was stirred at 90 °C for 15 h. After cooling, the solvent was removed in vacuo and the residue was taken up in EtOAc. The mixture was then basified with aqueous NaOH solution (20%) and extracted. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated. The crude was purified on silica gel (eluent : MeOH/CH_2Cl_2, 1/9) to give **5** (190 mg, 41%) as a white needles. Mp > 244 °C (*i*-Pr). IR (KBr): ν 3600-3000, 2933, 2896, 1740, 1593, 1385, 1164 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.39 (tb, 4H, 4 x **H**$_{piperazin}$), 3.77 (bt, 4H, 4 x **H**$_{piperazin}$), 4.30 (s, 2H, N-C**H**$_2$-CO), 4.36 (d, 2H, *J* = 5.5 Hz, C**H**$_2$-OH), 4.85 (t, 1H, *J* = 5.5 Hz, CH$_2$-O**H**), 6.75 (d, 1H, *J* = 6.2 Hz, **H**$_5$), 8.20 (d, 1H, *J* = 6.2 Hz, **H**$_6$); ^{13}C-NMR ($CDCl_3$) δ 42.8 (2 x **C**$_{piperazin}$), 45.8 (2 x C$_{piperazin}$), 52.8 (N-**C**H$_2$-CO), 64.7 (**C**H$_2$-OH), 101.8 (**C**$_5$), 154.0 (**C**$_q$), 155.9 (**C**$_6$), 161.1 (**C**$_q$), 168.3 (**C**=O), 169.9 (**C**=O); MS (IE) *m/z* = 357 (M+1); Calcd for $C_{12}H_{16}N_6O_5S$: C, 40.44; H, 4.53; N, 23.58. Found: C, 40.72; H, 4.58; N, 23.39.

1.17. 4-Amino-2-(methoxymethyl)pyrimidine 25

In a sealed tube, a solution of 4-chloro-2-(methoxymethyl)pyrimidine **13** (1 g, 6.3 mmol) in a 30 %

aqueous (w/w) NH_4OH solution (20 mL) was heated at 120 °C for 15 h. After cooling, the reaction was extracted with CH_2Cl_2. The organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo to give compound **25** (0.797 g, 91%) as a white solid used without further purification. Mp 112-113 °C. IR (KBr): ν 3362, 3312 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.51 (s, 3H, OC**H**$_3$), 4.49 (s, 2H, OC**H**$_2$), 5.11 (bs, 2H, N**H**$_2$), 6.32 (d, 1H, *J* = 5.7 Hz, **H**$_5$), 8.22 (d, 1H, *J* = 5.7 Hz, **H**$_6$); ^{13}C-NMR ($CDCl_3$) δ 59.0(O-**C**H_3), 75.3O-**C**H_2), 103.6 (**C**$_5$), 155.9 (**C**$_6$), 163.2(**C**$_q$), 166.6 (**C**$_q$); MS (IE) *m/z* = 140 (M+1); Calcd for $C_6H_9N_3O$: C, 51.79; H, 6.52; N, 30.20. Found: C, 51.52; H, 6.44; N, 30.11.

1.18. 4-Amino-5-bromo-2-(methoxymethyl)pyrimidine 26

At 60 °C, bromine (1.08 mL, 21.2 mmol) was added dropwise to a solution of **25** (1.47 g, 10.6 mmol) and $CaCO_3$ (0.528 g, 5.3 mmol) in water (15 mL). The reaction was stirred vigorously for 40 min with continuous heating. The mixture was then cooled at rt, neutralised to pH 8 using saturated aqueous $NaHCO_3$ solution and extracted with EtOAc. The combined extracts were dried over anhydrous $MgSO_4$. After removal of the solvent in vacuo, the product was purified by flash chromatography on silica gel (eluent: EtOAc) to afford **2** (1.36 g, 59%) as a yellow solid. Mp 117-118 °C. IR (KBr): ν 3385, 3316 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.49 (s, 3H, OC**H**$_3$), 4.45 (s, 2H, OC**H**$_2$), 5.78 (sb, 2H, N**H**$_2$), 8.34 (d, 1H, **H**$_6$); ^{13}C-NMR ($CDCl_3$) δ 59.0 (O-**C**H_3), 74.6 (O-**C**H_2), 101.8 (**C**$_q$), 156.5 (**C**$_6$), 160.1 (**C**$_q$), 165.3 (Cq); MS (IE) *m/z* = 218 (M+1 for ^{79}Br) m/z 220 (M+1 for ^{81}Br); Calcd for $C_6H_8BrN_3O$: C, 33.05; H, 3.70; N, 19.27. Found: C, 32.95; H, 3.74; N, 19.03.

1.19. 4-Amino-2-(methoxymethyl)-5-[2'-(1,1,1-trimethylsilyl)-1'-ethynyl]pyrimidine 27

Under an argon atmosphere, a mixture of **26** (1.24 g, 5.7 mmol), bis(triphenylphosphine)palladium (II) chloride (0.398 g, 0.57 mmol), CuI (0.108 g, 0.57 mmol), trimethylsilylacetylene (1.6 mL, 11.4 mmol) and triethylamine (33 ml) in dry THF (30 ml) was heated at 40 °C for 15 h. The reaction mixture was evaporated in vacuo and the product was isolated by flash chromatography eluting with EtOAc-light petroleum (1/1) affording **27** (1.22 g, 91%) as a yellow solid. Mp 92-93 °C. IR (KBr): ν 3487, 3277, 2149 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.28 (s, 9H, Si(C**H**$_3$)$_3$), 3.49 (s, 3H, OC**H**$_3$), 4.49 (s, 2H, OC**H**$_2$), 5.52 (sb, 2H, N**H**$_2$), 8.34 (s, 1H, **H**$_6$); ^{13}C-NMR ($CDCl_3$) δ 0.0 (Si(**C**H_3)$_3$), 59.1 (O-**C**H_3), 75.1 (O-**C**H_2), 96.9 (**C**$_q$), 100.3 (**C**$_q$), 104.3 (**C**$_q$), 158.2 (**C**$_6$), 163.2 (**C**$_q$), 165.5 (**C**$_q$); MS (IE) *m/z* = 236 (M+1); Calcd for $C_{17}H_{17}N_3OSi$: C, 56.14; H, 7.28; N, 17.85. Found: C, 55.98; H, 7.34; N, 17.78.

1.20. 4-[(*N*,*N*-Ditertiobutoxycarbonyl)amino]-2-methoxymethyl-5-[2'-(1,1,1-trimethylsilyl)-1'-ethyn-yl]pyrimidine 28

Under an inert atmosphere, 4-amino-2-(methoxymethyl)-5-[2'-(1,1,1-trimethylsilyl)-1'-ethynyl]-

pyrimidine **27** (1.10 g, 4.7 mmol) and 4-*N*,*N*-dimethylaminopyridine (0.057 g, 0.47 mmol) was added to a stirred solution of *tert*-butyl dicarbonate (3.06 g, 14.0 mmol) in dry THF (30 mL). After 1 h stirring at room temperature, the reaction was hydrolysed and extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo. Finally, purification by flash chromatography on silica gel using 20% light petroleum in EtOAc as eluent gave 2.03 g (quant.) of 4-[(*N*,*N*-ditertiobutoxycarbonyl)amino]-2-methoxymethyl-5-[2'-(1,1,1-trimethylsilyl)-1'-ethynyl]-pyramidine **28** as a colourless oil. IR (film): ν 2933, 2890, 2164, 1767, 1731 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.25 (s, 9H, Si(C**H**$_3$)$_3$), 1.41 (s, 18H, N[CO-O-C(C**H**$_3$)$_3$]$_2$), 3.52 (s, 3H, OC**H**$_3$), 4.70 (s, 2H, OC**H**$_2$), 8.34 (s, 1H, **H**$_6$); ^{13}C-NMR ($CDCl_3$) δ 0.0 (Si(**C**H$_3$)$_3$), 28.2 (N[CO-O-C(**C**H$_3$)$_3$]$_2$), 59.4 (O-**C**H$_3$), 75.1 (O-**C**H$_2$), 84.0 (**C**$_q$), 95.8 (**C**$_q$), 106.2 (**C**$_q$), 116.3 (**C**$_q$), 149.5 (**C**$_q$), 161.2 (**C**$_q$), 161.5 (**C**$_6$), 166.4 (**C**$_q$); MS (IE) *m/z* = 436 (M+1); Calcd for $C_{21}H_{33}N_3O_5Si$: C, 57.90; H, 7.64; N, 9.65. Found: C, 57.98; H, 7.66; N, 9.58.

1.21. 2-(Methoxymethyl)-*7H*-pyrrolo[2,3-*d*]pyrimidine 29

Under an inert atmosphere, a solution of **28** (1.8 g, 4.1 mmol) in dry EtOH (12 mL) was added dropwise to a solution of sodium (0.475 g, 20.5 mmol) in dry EtOH (36 mL). The reaction was then heated at reflux for 2.5 h. The mixture was hydrolysed and extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo. The crude was purified on silica gel (eluent: MeOH/EtOAc, 1/99) to give **29** (0.546 g, 81%) as a white solid. Mp 138-139 °C. IR (KBr): ν 3128, 1598 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.61 (s, 3H, OC**H**$_3$), 4.92 (s, 2H, OC**H**$_2$), 6.60 (dd, 1H, *J* = 1.8, 3.5 Hz, **H**$_5$), 7.46 (dd, 1H, *J* = 2.6 Hz, 3.5 Hz, **H**$_6$), 9.00 (s, 1H, **H**$_4$), 12.44 (sb, 1H, N**H**); ^{13}C-NMR ($CDCl_3$) 61.5 (O-**C**H$_3$), 75.7 (O-**C**H$_2$), 100.3 (**C**$_5$), 118.5 (**C**$_q$), 127.9 (**C**$_6$), 150.1 (**C**$_4$), 152.9 (**C**$_q$), 159.5 (**C**$_q$); MS (IE) *m/z* = 164 (M+1); Calcd for $C_8H_9N_3O$: C, 58.89; H, 5.56; N, 25.75. Found: C, 58;74; H, 5.55; N, 25.28.

1.22. 7-(2-Bromoethyl)-2-(methoxymethyl)pyrrolo[2,3-*d*]pyrimidine 30

Under an inert atmosphere, sodium hydride (0.397 g, 9.9 mmol) was added portionwise to a stirred solution of **29** (0.90 g, 5.5 mmol) in DMF (10 mL) at rt over 30 min. The mixture was stirred for an additional time (30 min). 1,2-dibromoethane (4.75 mL, 55.1 mmol) was then added dropwise and the mixture was stirred for 2 h at rt. After water was added, the product was extracted with CH_2Cl_2 and purified by flash chromatography on silica gel (eluent: MeOH/EtOAc, 2/98) to give **30** (1.27 g, 85%) as a yellow oil. IR (film): ν 2927, 2822, 1591 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.56 (s, 3H, OC**H**$_3$), 3.77 (s, 2H, *J* = 6.3 Hz, C**H**$_2$Br), 4.69 (t, 2H, *J* = 6.3 Hz, N-C**H**$_2$), 4.76 (s, 2H, OC**H**$_2$), 6.55 (d, 1H, *J* = 3.6 Hz, **H**$_5$), 7.29 (d, 1H, *J* = 3.6 Hz, **H**$_6$), 8.98 (s, 1H, **H**$_4$); ^{13}C-NMR ($CDCl_3$) 30.3 (**C**H$_2$-Br), 46.2 (N-**C**H$_2$), 59.0 (O-**C**H$_3$), 76.0 (O-**C**H$_2$), 99.6 (**C**$_5$), 117.7 (**C**$_q$), 129.5 (**C**$_6$), 149.8 (**C**$_4$), 151.0 (**C**$_q$), 159.5 (**C**$_q$); MS (IE) *m/z* = 270 (M+1 for ^{79}Br), 272 (M+1 for ^{81}Br); Calcd for $C_{10}H_{12}BrN_3O$: C, 44.46; H, 4.48; N, 15.56. Found: C,

44.76; H, 4.58; N, 16.01.

1.23. 7-(2-Azidoethyl)-2-(methoxymethyl)pyrrolo[2,3-*d*]pyrimidine 31

Under an inert atmosphere, sodium azide (0.866 g, 13.32 mmol) was added portionwise to a stirred solution of **30** (1.2 g, 4.44 mmol) in DMF (25 mL) at rt over 30 min. At the end of the addition, the mixture was stirred for 15 h at rt. Water was added and the product was extracted with CH_2Cl_2 and purified by flash chromatography on silica gel (eluent: MeOH/EtOAc, 3/97) to give **31** (0.852 g, 83%) as a colourless oil. IR (film): ν 2932, 2812, 2101, 1591 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.56 (s, 3H, OC**H**$_3$), 3.75 (s, 2H, *J* = 5.6 Hz, C**H**$_2$N$_3$), 4.45 (t, 2H, *J* = 5.6 Hz, N-C**H**$_2$), 4.76 (s, 2H, OC**H**$_2$), 6.57 (d, 1H, *J* = 3.6 Hz, **H**$_5$), 7.26 (d, 1H, *J* = 3.6 Hz, **H**$_6$), 8.99 (s, 1H, **H**$_4$); ^{13}C-NMR ($CDCl_3$) 43.7 (N-**C**H$_3$), 50.9 (**C**H$_2$-N$_3$), 59.0 (O-**C**H$_3$), 76.1 (O-**C**H$_2$), 100.0 (**C**$_5$), 117.7 (**C**$_q$), 129.4 (**C**$_6$), 149.8 (**C**$_4$), 151.1 (**C**$_q$), 159.6 (**C**$_q$); MS (IE) *m/z* = 233 (M+1); Calcd for $C_{10}H_{12}N_6O$: C, 51.72; H, 5.21; N, 36.19. Found: C, 50.94; H, 5.38; N, 36.15.

1.24. 2-[2-(Methoxymethyl)pyrrolo[2,3-*d*]pyrimidin-7-yl]ethylamine 32

A solution of compound **31** (0.645 g, 2.8 mmol) in EtOH (7 mL) was hydrogenated under pressure (15 psi) over Lindlar palladium catalyst (97 mg) for 1 h at rt. The catalyst was then filtered over Celite and the filtrate concentrated in vacuo to give the title compound **32** (0.573 g, quant.) as a yellow oil. IR (film): ν 3364, 3015, 2865, 1592 cm^{-1}; ^{1}H-NMR ($CDCl_3$ + D_2O) δ 3.15 (t, 2H, *J* = 6.0 Hz, C**H**$_2$NH$_2$), 3.56 (s, 3H, OC**H**$_3$), 4.36 (t, 2H, *J* = 6.0 Hz, N-C**H**$_2$), 4.76 (s, 2H, OC**H**$_2$), 6.56 (d, 1H, *J* = 3.6 Hz, **H**$_5$), 7.27 (d, 1H, *J* = 3.6 Hz, **H**$_6$), 8.99 (s, 1H, **H**$_4$); ^{13}C-NMR ($CDCl_3$) 42.4 (**C**H$_2$-NH$_2$), 47.7 (N-**C**H$_2$), 59.2 (O-**C**H$_3$), 74.3 (O-**C**H$_2$), 97.6 (**C**$_5$), 115.8 (**C**$_q$), 127.6 (**C**$_6$), 147.8 (**C**$_4$), 157.5 (**C**$_q$); MS (IE) *m/z* = 207 (M+1); Calcd for $C_{10}H_{14}N_4O$: C, 58.24; H, 6.84; N, 27.16. Found: C, 58.33; H, 6.57; N, 27.41.

1.25. *N*,*N*-Dimethyl-*N*'-(2-[2-(methoxymethyl)pyrrolo[2,3-*d*]pyrimidin-7-yl]ethyl)sulfamide 33

Under an inert atmosphere, a solution of *N*,*N*-dimethylsulfamoyl chloride (0.69 mL, 6.4 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise to a solution of **32** (0.665 g, 3.2 mmol) and triethylamine (0.9 mL, 6.4 mmol) in dry CH_2Cl_2 (12 mL). After stirring the reaction at rt for 15 h, it was hydrolysed and extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$ and evaporated in vacuo. The crude was purified on silica gel (eluent: MeOH/EtOAc, 3/97) to provide **33** (0.737 g, 73%) as a white solid. Mp 144-145 °C. IR (KBr): ν 3100, 3000-2800, 1595, 1333, 1147 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.72 (s, 6H, N(C**H**$_3$)$_2$), 3.56 (s, 3H, OC**H**$_3$), 3.57 (m, 2H, C**H**$_2$NH), 4.45 (m, 2H, N-C**H**$_2$), 4.74 (s, 2H, OC**H**$_2$), 5.65 (sb, 1H, N**H**), 6.56 (d, 1H, *J* = 3.6 Hz, **H**$_5$), 7.24 (d, 1H, *J* = 3.6 Hz, **H**$_6$), 8.99 (s, 1H, **H**$_4$); ^{13}C-NMR ($CDCl_3$) 38.7 (N(**C**H$_3$)$_2$), 44.4 (**C**H$_2$-NH), 46.3 (N-**C**H$_2$), 59.7 (O-**C**H$_3$), 76.4 (O-**C**H$_2$), 100.5 (**C**$_5$), 118.5 (**C**$_q$), 130.9 (**C**$_6$), 150.4 (**C**$_4$), 151.7 (**C**$_q$), 159.9 (**C**$_q$); MS (IE) *m/z* = 314 (M+1); Calcd for $C_{12}H_{19}N_5O_3S$: C, 45.99; H, 6.11; N, 22.35. Found: C, 46.06; H, 5.98; N, 22.32.

1.26. *N,N,N'*-Trimethyl-*N'*-(2-[2-(methoxymethyl)pyrrolo[2,3-*d*]pyrimidin-7-yl]ethyl)sulfamide 34

Under an inert atmosphere, sodium hydride (0.086 g, 2.15 mmol) was added portionwise to a stirred solution of **33** (0.45 g, 1.44 mmol) in DMF (4 mL) at rt over 30 min. The mixture was stirred an additional time (40 min), before MeI (0.134 mL, 2.15 mmol) was added dropwise and the mixture stirred again for 2 h. Water was then added, the product was extracted with CH_2Cl_2, purified by flash chromatography on silica gel (eluent: MeOH/CH_2Cl_2, 2/98) to give the title compound **34** (0.428 g, 91%) as a white oil. IR (film): ν 3000-2800, 1591, 1324, 1146 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.63 (s, 6H, N(C**H**$_3$)$_2$), 2.66 (s, 3H, NC**H**$_3$), 3.56 (s, 3H, OC**H**$_3$), 3.64 (t, 2H, *J* = 6.0 Hz, C**H**$_2$NSO$_2$), 4.50 (t, 2H, *J* = 6.0 Hz, N-C**H**$_2$), 4.75 (s, 2H, OC**H**$_2$), 6.56 (d, 1H, *J* = 3.6 Hz, **H**$_5$), 7.29 (d, 1H, *J* = 3.6 Hz, **H**$_6$), 8.97 (s, 1H, **H**$_4$); ^{13}C-NMR ($CDCl_3$) 35.9 (N-**C**H$_3$), 37.8 (N-(**C**H$_3$)$_2$), 43.0 (N-**C**H$_2$), 50.4 (**C**H$_2$-N-SO$_2$) 59.0 (O-**C**H$_3$), 76.1 (O-**C**H$_2$), 99.8 (**C**$_5$), 117.6 (**C**$_q$), 129.6 (**C**$_6$), 149.7 (**C**$_4$), 151.1 (**C**$_q$), 159.3 (**C**$_q$); MS (IE) *m/z* = 328.5 (M+1); Calcd for $C_{13}H_{21}N_5O_3S$: C, 47.69; H, 6.47; N, 21.39. Found: C, 47.07; H, 6.33; N, 21.66.

1.27. *N,N,N'*-Trimethyl-*N'*-[2-(2-(hydroxymethyl)pyrrolo[2,3-*d*]pyrimidin-7-yl)ethyl]sulfamide 6

Under an inert atmosphere, compound **34** (0.4 g, 1.2 mmol) was dissolved in dry CH_2Cl_2 (12 mL). The mixture was then cooled to 0 °C and a solution of BBr_3 (0.35 mL, 3.6 mmol) in dry CH_2Cl_2 (4 mL) was added dropwise. After 2 h stirring at 0 °C, the reaction was hydrolysed, basified with saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo. Finally, purification by flash chromatography on silica gel using 2% MeOH in CH_2Cl_2 as eluent gave 0.306 g (80%) of *N,N,N'*-trimethyl-*N'*-(2-[2-(hydroxymethyl)pyrrolo-[2,3-*d*]pyrimidin-7-yl]ethyl)sulfamide **6** as a white solid. Mp 69-70 °C; IR (KBr): ν 3448, 3000-2800, 1594, 1310, 1153 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.62 (s, 6H, N(C**H**$_3$)$_2$), 2.67 (s, 3H, NC**H**$_3$), 3.64 (t, 2H, *J* = 6.0 Hz, C**H**$_2$NSO$_2$), 3.88 (sb, 1H, CH$_2$O**H**), 4.49 (t, 2H, *J* = 6.0 Hz, N-C**H**$_2$), 4.49 (sb, 2H, C**H**$_2$OH), 6.58 (d, 1H, *J* = 3.6 Hz, **H**$_5$), 7.29 (d, 1H, *J* = 3.6 Hz, **H**$_6$), 8.93 (s, 1H, **H**$_4$); ^{13}C-NMR ($CDCl_3$) 35.9 (N-**C**H$_3$), 37.8 (N-(**C**H$_3$)$_2$), 43.0 (**C**H$_2$-NH), 50.3 (**C**H$_2$-N-SO$_2$), 64.6 (**C**H$_2$-OH), 100.0 (**C**$_5$), 117.6 (**C**$_q$), 149.3 (**C**$_5$), 150.8 (**C**$_6$), 160.9 (**C**$_q$); MS (IE) *m/z* = 314 (M+1); Anal. Calcd for $C_{12}H_{19}N_5O_3S$: C, 45.99; H, 6.11; N, 22.35; S, 10.23. Found : C, 46.25; H, 5.92; N, 22.50; S, 10.17.

1.28. *N,N*-Dimethyl-*N'*-(2-[2-(hydroxymethyl)pyrrolo[2,3-*d*]pyrimidin-7-yl]ethyl)sulfamide 35

Under an inert atmosphere, compound **33** (0.2 g, 0.64 mmol) was dissolved in dry CH_2Cl_2 (7 mL). The mixture was then cooled to 0 °C and a solution of BBr_3 (0.18 mL, 1.9 mmol) in dry CH_2Cl_2 (2 mL) was added dropwise. After 2 h at 0 °C, the reaction was hydrolysed, basified with saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo. Finally, purification by flash chromatography on silica gel using 2% MeOH in CH_2Cl_2 as eluent gave 0.162 g (85%) of *N,N*-dimethyl-*N'*-(2-[2-(hydroxymethyl)pyrrolo[2,3-*d*]pyrimidin-

7-yl]ethyl)sulfamide **35** as a white solid. Mp 91-92 °C; IR (KBr): ν 3442, 3171, 3000-2800, 1594, 1341, 1153 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.71 (s, 6H, N(C**H**$_3$)$_2$), 3.54 (m, 2H, C**H**$_2$-NH), 4.13 (sb, 1H, CH_2O**H**), 4.44 (t, 2H, *J* = 5.8 Hz, N-C**H**$_2$), 4.84 (s, 2H, C**H**$_2$OH), 5.88 (sb, 1H, N**H**), 5.53 (d, 1H, *J* = 3.5 Hz, **H**$_5$), 7.28 (d, 1H, *J* = 3.5 Hz, **H**$_6$), 8.80 (s, 1H, **H**$_4$); ^{13}C-NMR ($CDCl_3$) 38.0 (N-(**C**H_3)$_2$), 43.4 (**C**H_2-NH), 45.2 (N-**C**H_2), 64.7 (**C**H_2-OH), 100.0 (**C**$_5$), 117.8 (**C**$_q$), 130.0 (**C**$_6$), 149.3 (**C**$_4$), 150.8 (**C**$_q$), 161.0 (**C**$_q$); MS (IE) *m/z* = 300 (M+1); Anal. Calcd for $C_{11}H_{17}N_5O_3S$: C, 44.13; H, 5.72; N, 23.40; S, 10.71. Found: C, 44.30; H, 5.74; N, 23.29; S, 10.45.

1.29. 4-Amino-5-iodo-2-(methoxymethyl)pyrimidine 36

Under an inert atmosphere, *N*-iodosuccinimide (14.5 g, 64.4 mmol) was added portionwise to a stirred solution of **25** (3 g, 21.42 mmol) in dry MeOH (230 mL). The mixture was then heated at 50 °C for 60 h. More *N*-iodosuccinimide (4.8 g, 21.5 mmol) was put in reaction and the solution was allowed to reflux for 24 h. After cooling of the solution to rt, the product was extracted with $CHCl_3$ and the combined layers were washed with water, brine and dried over anhydrous $MgSO_4$. Finally, purification by flash chromatography on silica gel using 10% light petroleum in EtOAc as eluent gave 3.3 g (58%) of 4-amino-5-iodo-2-(methoxymethyl)pyrimidine **36** as a white solid. Mp 169-170 °C; IR (KBr): ν 3454, 300-2800, 1637 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 3.30 (s, 3H, OC**H**$_3$), 4.25 (s, 2H, OC**H**$_2$), 7.05 (sb, 2H, N**H**$_2$), 8.41 (s, 1H, **H**$_6$); ^{13}C-NMR ($CDCl_3$) 58.9 (O-**C**H_3), 75.2 (O-**C**H_2), 76.2 (**C**$_q$), 163.1 (**C**$_6$), 164.3 (**C**$_q$), 167.3 (**C**$_q$); MS (IE) *m/z* = 266 (M+1); Calcd for $C_6H_8IN_3O$: C, 27.19; H, 3.04; N, 15.85. Found: C, 27.28; H, 3.36; N, 15.80.

1.30. (2-(Methoxymethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-6-yl)carboxylic acid 37

Under an inert atmosphere, pyruvic acid (3.9 mL, 56.6 mmol), palladium acetate (0.254 g, 1.1 mmol) and triethylamine (7.9 mL, 56.6 mmol) were respectively added to a solution of **36** (3 g, 11.3 mmol) in dry DMF (32 mL). The mixture was then heated at 150 °C for 15 h under nitrogen. After cooling of the solution to rt, the solvent was removed under reduced pressure. The residue was purified on silica gel (eluent: Et_3N/MeOH/EtOAc, 1/9/90) to provide **37** (1.5 g, 64%) as a white solid. Mp 284-285 °C. IR (KBr): ν 3440, 3195, 300-2800, 1699, 1602 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 3.37(s, 3H, OC**H**$_3$), 4.60 (s, 2H, OC**H**$_2$), 7.20 (s, 1H, **H**$_5$), 9.12 (s, 1H, **H**$_4$), 12.74 (sb, 1H, N**H**), 13.43 (sb, 1H, CO_2**H**); ^{13}C-NMR (DMSO-d_6) 58.4 (O-**C**H_3), 75.6 (O-**C**H_2), 105.8 (**C**$_5$), 116.7 (**C**$_q$), 130.7 (**C**$_q$), 152.1 (**C**$_q$), 152.5 (**C**$_4$), 161.8 (**C**$_q$), 162.4 (**C**$_q$); MS (IE) *m/z* = 208 (M+1); Calcd for $C_9H_9N_3O_3$: C, 52.17; H, 4.38; N, 20.28. Found: C, 52.72; H, 4.58; N, 20.39.

1.31. (2-(Methoxymethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-6-yl)ethyl carboxylate 38

Under an inert atmosphere, thionyl chloride (1.6 mL, 21.6 mmol) was added dropwise to a solution of **37**

(1.5 g, 7.2 mmol) in EtOH (21 mL) at 0 °C. The mixture was stirred for an additional 30 min, allowing it to rise slowly to rt. The reaction was then heated under reflux for 15 h, cooled at rt and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (eluent: MeOH/CH_2Cl_2, 5/95) to provide **38** (1.2 g, 71%) as a white solid. Mp 122-123 °C; IR (KBr): ν 3422, 3000-2800, 1719, 1610 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.41 (t, 3H, *J* = 7.1 Hz, OCH_2-C**H**$_3$), 3.56 (s, 3H, OC**H**$_3$), 4.44 (q, 2H, *J* = 7.1 Hz, OC**H**$_2$-CH_3), 4.82 (s, 2H, OC**H**$_2$), 7.23 (d, 1H, *J* = 1.2 Hz, **H**$_5$), 9.12 (s, 1H, **H**$_4$), 9.91 (bs, 1H, N**H**); ^{13}C-NMR ($CDCl_3$) 14.4 (O-CH_2-**C**H_3), 59.4 (O-**C**H_3), 62.1 (O-**C**H_2-CH_3), 75.8 (O-**C**H_2), 106.6 (**C**$_5$), 117.4 (**C**$_q$), 129.4 (**C**$_q$), 152.1 (**C**$_q$), 153.2 (**C**$_4$), 161.4 (**C**$_q$), 163.1 (**C**$_q$); MS (IE) *m/z* = 236 (M+1); Calcd for $C_{11}H_{13}N_3O_3$: C, 56.16; H, 5.57; N, 17.86. Found: C, 56.44; H, 5.69; N, 17.45.

1.32. 6-(Hydroxymethyl)-2-(methoxymethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine 39

Under an inert atmosphere, a solution of **38** (0.6 g, 2.55 mmol) in dry THF (9 mL) was added dropwise to a suspension of $LiAlH_4$ (0.145 g, 3.8 mmol) in dry THF (9 mL) at rt. The reaction was then continuously stirred for 1 h at rt. The mixture was taken up in EtOAc (20 mL) and water (5 mL) was added dropwise. The precipitate obtained was filtered off, washed with EtOAc and the filtrate concentrated in vacuo. The residue was purified by flash chromatography on silica gel (eluent: MeOH/CH_2Cl_2, 1/9) to provide **39** (0.409 g, 83%) as a yellow solid. Mp 140-141 °C. IR (KBr): ν 3205, 3124, 3000-2800, 1586 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.51 (s, 3H, OC**H**$_3$), 4.80 (s, 2H, C**H**$_2$OH), 4.82 (s, 2H, OC**H**$_2$), 6.33 (s, 1H, **H**$_5$), 8.81 (s, 1H, **H**$_4$), 11.74 (bs, 1H, N**H**); ^{13}C-NMR ($CDCl_3$) 58.2 (**C**H_2OH), 59.2 (O-**C**H_3), 75.9 (O-**C**H_2), 98.2 (**C**$_5$), 118.5 (**C**$_q$), 141.6 (**C**$_q$), 149.4 (**C**$_4$), 153.2 (**C**$_q$), 158.9 (**C**$_q$); MS (IE) *m/z* = 178 (M+1); Calcd for $C_9H_{11}N_3O$: C, 61.00; H, 6.26; N, 23.73. Found: C, 60.85; H, 6.34; N, 23.39.

1.33. 6-(Azidomethyl)-2-(methoxymethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine 40

Under an inert atmosphere, triphenylphosphine (1.06 g, 4 mmol) and zinc azide/bis pyridine complex (0.465 g, 1.5 mmol) were successively added to a solution of alcohol **39** (0.390 g, 2 mmol) in dry THF (20 mL). Diisopropyl azodicarboxylate (0.8 mL, 4 mmol) was then added dropwise and the reaction was stirred for an additional time (1h) at rt. The precipitate was filtered off, washed with MeOH and the filtrate concentrated in vacuo. The residue was purified by flash chromatography on silica gel (eluent: MeOH/CH_2Cl_2, 1/9) to provide **40** (0.409 g, 83%) as a yellow solid. Mp 105-112 °C. IR (KBr): ν 3111, 3000-2800, 2101, 1584 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.52 (s, 3H, OC**H**$_3$), 4.64 (s, 2H, C**H**$_2N_3$), 4.90 (s, 2H, OC**H**$_2$), 6.56 (1, 1H, **H**$_5$), 8.98 (s, 1H, **H**$_4$), 11.85 (sb, 1H, N**H**); ^{13}C-NMR ($CDCl_3$) 48.1 (**C**H_2-N_3), 59.1 (O-**C**H_3), 75.7 (O-**C**H_2), 100.4 (**C**$_5$), 118.2 (**C**$_q$), 135.5 (**C**$_q$), 150.0 (**C**$_4$), 153.6 (**C**$_q$), 160.2 (**C**$_q$); MS (IE) *m/z* = 219 (M+1); Calcd for $C_9H_{12}N_4O$: C, 49.54; H, 4.62; N, 38.51. Found: C, 49.01; H, 4.58; N, 38.39.

1.34. 1-[2-Methoxymethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-6-yl]methylamine 41

A solution of compound **40** (0.220 g, 1.0 mmol) in EtOH (7 mL) was hydrogenated (15 psi) over Lindlar palladium (33 mg) for 1 h at rt. The catalyst was then filtered over Celite and the filtrate concentrated in vacuo to give the title compound **41** (0.193 g, quant.) as a yellow oil. IR (film): ν 3500-3000, 2881, 1606 cm^{-1}; ^{1}H-NMR ($CDCl_3$+D_2O) 3.49 (s, 3H, OC**H**$_3$), 4.05 (s, 2H, C**H**$_2$NH$_2$), 4.76 (s, 2H, OC**H**$_2$), 6.30 (s, 1H, **H**$_5$), 8.84 (s, 1H, **H**$_4$); ^{13}C-NMR ($CDCl_3$) 39.5 (**C**H$_2$-NH$_2$), 58.8 (O-**C**H$_3$), 75.7 (O-**C**H$_2$), 96.5 (**C**$_5$), 118.0 (**C**$_q$), 132.0 (**C**$_q$), 148.5 (**C**$_4$), 152.6 (**C**$_q$), 158.8 (**C**$_q$); MS (IE) *m/z* = 193 (M+1); Calcd for $C_9H_{12}N_4O$: C, 56.24; H, 6.29; N, 29.15. Found: C, 55.98; H, 6.67; N, 29.39.

1.35. *N*,*N*-Dimethyl-*N*'-(1-[2-(methoxymethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-6-yl]methyl)sulfamide 42

Under an inert atmosphere, a solution of *N*,*N*-dimethylsulfamoyl chloride (0.21 mL, 1.98 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise to a solution of **41** (0.190 g, 0.99 mmol) and triethylamine (0.27 mL, 1.98 mmol) in dry CH_2Cl_2 (4 mL). The reaction was then stirred at rt for 15 h. The mixture was hydrolysed and extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$ and evaporated in vacuo. The crude was purified on silica gel (eluent: MeOH/EtOAc, 5/95) to provide **42** (0.151 g, 51%) as a white solid. Mp 104-105 °C. IR (KBr): ν 3196, 3000-2720, 1345, 1145 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.74 (s, 6H, N(C**H**$_3$)$_2$), 3.50 (s, 3H, OC**H**$_3$), 4.37 (d, 2H, *J* = 6.1 Hz, C**H**$_2$NH), 4.74 (s, 2H, OC**H**$_2$), 6.32 (s, 1H, **H**$_5$), 6.35 (sb, 1H, CH$_2$N**H**), 8.79 (s, 1H, **H**$_4$), 10.68 (sb, 1H, N**H**); ^{13}C-NMR ($CDCl_3$) 38.4 (N(**C**H$_3$)$_2$), 41.2 (**C**H$_2$-NH), 59.3 (O-**C**H$_3$), 75.9 (O-**C**H$_2$), 99.3 (**C**$_5$), 118.1 (**C**$_q$), 138.1 (**C**$_q$), 149.5 (**C**$_4$), 154.0 (**C**$_q$), 160.5 (**C**$_q$); MS (IE) *m/z* = 300 (M+1); Calcd for $C_{11}H_{17}N_5O_3S$: C, 44.14; H, 5.72; N, 23.39. Found: C, 44.12; H, 5.58; N, 23.57.

1.36. *N*-(1-[2-Methoxymethyl)-7-methylpyrrolo[2,3-*d*]pyrimidin-6-yl]methyl)-*N*,*N*',*N*'-trimethyl-sulfamide 43

Under an inert atmosphere, sodium hydride (57 mg, 1.41 mmol) was added portionwise to a stirred solution of **42** (0.140 g, 0.47 mmol) in DMF (2 mL) at rt over 30 min. The mixture was stirred for an additional time (20 min), before MeI (0.088 mL, 1.41 mmol) was added dropwise and the mixture stirred again for 2 h. Water was then added and the product was extracted with CH_2Cl_2, purified by flash chromatography on silica gel (eluent: MeOH/CH_2Cl_2, 2/98) to give the title compound **43** (0.140 g, 91%) as a yellow solid. Mp 104-105 °C IR (KBr): ν 3000-2800, 1352, 1157 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.67 (s, 6H, CH$_2$-N-C**H**$_3$), 2.88 (s, 6H, N(C**H**$_3$)$_2$), 3.55 (s, 3H, OC**H**$_3$), 3.86 (s, 3H, N-C**H**$_3$), 4.50 (s, 2H, C**H**$_2$-N-SO$_2$), 4.72 (s, 2H, OC**H**$_2$), 6.48 (s, 1H, **H**$_5$), 8.87 (s, 1H, **H**$_4$); ^{13}C-NMR ($CDCl_3$) 28.6 (N-**C**H$_3$), 38.3 (N(**C**H$_3$)$_2$), 34.5 (CH$_2$-N-**C**H$_3$), 47.1 (**C**H$_2$-N-SO$_2$), 59.0 (O-**C**H$_2$), 76.1 (O-**C**H$_3$), 100.8 (**C**$_5$), 116.8 (**C**$_q$), 136.0 (**C**$_q$), 149.1 (**C**$_4$), 152.6 (**C**$_q$), 159.7 (**C**$_q$); MS (IE) *m/z* = 328 (M+1); Calcd for $C_{13}H_{21}N_5O_3S$:

C, 47.69; H, 6.47; N, 21.39. Found: C, 47.74; H, 6.58; N, 21.59.

1.37. *N*-(1-[2-(Hydroxymethyl)-7-methylpyrrolo[2,3-*d*]pyrimidin-6-yl]methyl)-*N,N',N'*-trimethylsulfamide 7

Under an inert atmosphere, compound **43** (0.115 g, 0.35 mmol) was dissolved in dry CH_2Cl_2 (4 mL). The mixture was cooled to 0°C and a solution of BBr_3 (0.17 mL, 1.75 mmol) in dry CH_2Cl_2 (2 mL) was added dropwise. After 2 h stirring at 0 °C, the reaction was hydrolysed, basified with saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo. Finally, purification by flash chromatography on silica gel using 3% MeOH in CH_2Cl_2 as eluent gave 0.093 g (85%) of *N*-(1-[2-(hydroxymethyl)-7-methylpyrrolo[2,3-*d*]-pyrimidin-6-yl]methyl)-*N*,*N*',*N*'-trimethylsulfamide **7** as a white solid. Mp 156-157 °C. IR (KBr): ν 3146, 3000-2800, 1593, 1351, 1153 cm^{-1}; ^{1}H-NMR ($CDCl_3$+D_2O) δ 2.71 (s, 3H, CH_2-N-C**H**$_3$), 2.91 (s, 6H, N(C**H**$_3$)$_2$), 3.88 (s, 3H, N-C**H**$_3$), 4.54 (s, 2H, C**H**$_2$-N-SO_2), 4.90 (s, 2H, C**H**$_2$OH), 6.53 (s, 1H, **H**$_5$), 8.87 (s, 1H, **H**$_4$); ^{13}C-NMR ($CDCl_3$) 28.9 (N-**C**H_3), 34.9 (**C**H_2-N-**C**H_3), 38.7 (N(**C**H_3)$_2$), 47.5 (**C**H_2-N-SO_2), 65.0 (**C**H_2OH), 101.4 (**C**$_5$), 117.2 (**C**$_q$), 136.2 (**C**$_q$), 149.1 (**C**$_4$), 152.9 (**C**$_q$), 161.9 (**C**$_q$); MS (IE) *m/z* = 314 (M+1); Anal. Calcd for $C_{12}H_{19}N_5O_3S$: C, 45.99; H, 6.11; N, 22.35; S, 10.23. Found: C, 46.18; H, 6.05; N, 22.55; S, 10.09.

1.38. 6-(Azidomethyl)-7-(2-bromoethyl)-2-(methoxymethyl)pyrrolo[2,3-*d*]pyrimidine 44

A solution of **40** (0.670 g, 3.1 mmol), 1,2-dibromoethane (8.7 mL, 101.0 mmol) and tetrabutylammonium bromide (0.050 g, 0.16 mmol) was added to a 7M NaOH aqueous solution (8.7 mL). The reaction was then stirred at rt for 18 h. The mixture was extracted with EtOAc and the combined organic layers were washed with water, a saturated aqueous NaCl solution then dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The crude was purified on silica gel (eluent: light petroleum/EtOAc, 1/9) to provide **44** (0.649 g, 65%) as a pink oil. IR (film): ν 3000-2800, 2102, 1591 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.55 (s, 1H, OC**H**$_3$), 3.82 (t, 2H, *J* = 6.5 Hz, C**H**$_2$Br), 4.60 (s, 2H, C**H**$_2$N$_3$), 4.65 (t, 2H, *J* = 6.5 Hz, NC**H**$_2$), 4.75 (s, 2H, OC**H**$_2$), 6.57 (s, 1H, **H**$_5$), 8.96 (s, 1H, **H**$_4$); ^{13}C-NMR ($CDCl_3$) 30.5 (**C**H_2-Br), 44.7 (N-**C**H_2), 47.7 (Ar-**C**H_2-N_3), 59.8 (O-**C**H_3), 76.7 (O-**C**H_2), 101.9 (**C**$_5$), 117.6 (**C**$_q$), 135.8 (**C**$_q$), 150.7 (**C**$_4$), 153.1 (**C**$_q$), 161.1 (**C**$_q$); MS (IE) *m/z* = 325 (M+1 for ^{79}Br), 327 (M+1 for ^{81}Br); Calcd for $C_{11}H_{13}BrN_6O$: C, 40.63; H, 4.03; N, 25.85. Found: C, 40.72; H, 4.38; N, 25.39.

1.39. 2-(Methoxymethyl)-6,7,8,9-tetrahydropyrazino [2',1':5,1]pyrrolo[2,3-*d*]pyrimidine 45

A solution of compound **44** (0.620 g, 1.9 mmol) in EtOH (7 mL) was hydrogenated under pressure (15 psi) over Lindlar palladium catalyst (93 mg) for 1 h at rt. After filtration of the catalyst over Celite the filtrate was concentrated in vacuo. The crude was purified on silica gel (eluent: MeOH/CH_2Cl_2, 1/9) to

give the title compound **45** (0.382 g, 92%) as a yellow oil. IR (film): ν 3416, 3000-2800, 1593 cm^{-1}; ^{1}H-NMR ($CDCl_3$ + D_2O) 3.34 (t, 2H, *J* = 5.6 Hz, N-CH_2-C**H**$_2$-NH), 3.54 (s, 3H, OC**H**$_3$), 4.23 (m, 4H, N-C**H**$_2$-CH_2-NH and C**H**$_2$-NH), 4.74 (s, 2H, OC**H**$_2$), 6.20 (s, 1H, **H**$_5$), 8.85 (s, 1H, **H**$_4$); ^{13}C-NMR ($CDCl_3$ 42.1 (N-**C**H_2-CH_2-NH), 43.5 (N-CH_2-**C**H_2-NH), 44.6 (Ar-**C**H_2-NH), 59.3 (O-**C**H_3), 76.4 (O-**C**H_2), 94.2(**C**$_5$), 117.9 (**C**$_q$), 136.9 (**C**$_q$), 148.5 (**C**$_4$), 152.3 (**C**$_q$), 158.7 (**C**$_q$); MS (IE) *m/z* = 219 (M+1); Calcd for $C_{11}H_{14}N_4O$: C, 60.53; H, 6.47; N, 25.67. Found: C, 60.72; H, 6.58; N, 25.39.

1.40. *N*,*N*-Dimethyl-2-(methoxymethyl)-6,7,8,9-tetrahydropyrazino[2',1':5,1]pyrrolo[2,3-*d*]-pyrimidine-7-sulfonamide 46

Under an inert atmosphere, a solution of *N*,*N*-dimethylsulfamoyl chloride (0.24 mL, 2.2 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise to a solution of **45** (0.245 g, 1.1 mmol) and triethylamine (0.31 mL, 2.2 mmol) in dry CH_2Cl_2 (8 mL). The reaction was then stirred at rt for 15 h. After completion of the reaction, the mixture was hydrolysed and extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$ and evaporated in vacuo. The crude was purified on silica gel (eluent: MeOH/EtOAc, 3/97) to provide **46** (0.230 g, 63%) as a yellow oil. IR (film): ν 3000-2800, 1592, 1148 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.89 (s, 6H, N(C**H**$_3$)$_2$), 3.56 (s, 3H, OC**H**$_3$), 3.78 (t, 2H, *J* = 5.6 Hz, N-CH_2-C**H**$_2$-N-SO_2), 4.37 (t, 2H, *J* = 5.6 Hz, N-C**H**$_2$-CH_2-N-SO_2), 4.64 (s, 2H, C**H**$_2$-N-SO_2), 4.75 (s, 2H, OC**H**$_3$), 6.32 (s, 1H, **H**$_5$), 8.90 (s, 1H, **H**$_4$); ^{13}C-NMR ($CDCl_3$) 38.6 (N(**C**H_3)$_2$), 41.2 (N-**C**H_2), 44.3 (CH_2-**C**H_2-N-SO_2), 44.8 (Ar-**C**H_2-N-SO_2), 59.4 (O-**C**H_3), 76.3 (O-**C**H_2), 95.5 (**C**$_5$), 117.9 (**C**$_q$), 133.4 (**C**$_q$), 149.2 (**C**$_4$), 151.5 (**C**$_q$), 159.4 (**C**$_q$); MS (IE) *m/z* = 326 (M+1); Calcd for $C_{13}H_{19}N_5O_3$: C, 47.99; H, 5.89; N, 21.52. Found: C, 47.65; H, 5.90; N, 21.67.

1.41. *N*,*N*-Dimethyl-2-(hydroxymethyl)-6,7,8,9-tetrahydropyrazino[2',1':5,1]pyrrolo[2,3-*d*]-pyrimidine-7-sulfonamide 8

Under an inert atmosphere, compound **46** (0.220 g, 0.68 mmol) was dissolved in dry CH_2Cl_2 (8 mL). The mixture was then cooled to 0°C and a solution of BBr_3 (0.32 mL, 3.4 mmol) in dry CH_2Cl_2 (3 mL) was added dropwise. After 2 h stirring at 0 °C, the reaction was hydrolysed, basified with saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo. Finally, purification by flash chromatography on silica gel using 3% methanol in dichloromethane as eluent gave 0.172 g (82%) of *N*,*N*-dimethyl-2-(hydroxymethyl)-6,7,8,9-tetrahydropyrazino[2',1':5,1]pyrrolo[2,3-*d*]pyrimidine-7-sulfonamide **8** as a yellow solid. Mp 160 °C; IR (KBr): ν 3170, 3000-2800, 1593, 1361, 1161 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.89 (s, 6H, N(C**H**$_3$)$_2$), 3.79 (t, 2H, *J* = 5.6 Hz, N-CH_2-C**H**$_2$-N), 3.85 (sb, 1H, CH_2O**H**), 4.34 (t, 2H, *J* = 5.6 Hz, N-C**H**$_2$-CH_2-N-SO_2), 4.65 (s, 2H, C**H**$_2$-N-SO_2), 4.89 (s, 2H, OC**H**$_2$), 6.34 (s, 1H, **H**$_5$), 8.87 (s, 1H, **H**$_4$); ^{13}C-NMR ($CDCl_3$) 38.2 (N(**C**H_3)$_2$), 40.8 (N-**C**H_2), 43.9 (CH_2-**C**H_2-N-SO_2), 44.5 (Ar-**C**H_2-N-SO_2), 64.6

(**C**H_2-OH), 95.3 (**C**$_5$), 117.6 (**C**$_q$), 132.9 (**C**$_q$), 148.5 (**C**$_4$), 150.8 (**C**$_q$), 160.6 (**C**$_q$); MS (IE) *m/z* = 312 (M+1); Anal. Calcd for $C_{12}H_{17}N_5O_3S$: C, 46.29; H, 5.50; N, 22.49; S, 10.30. Found: C, 46.55; H, 5.52; N, 22.41; S, 10.22.

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