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

Jérôme Guillard and Marie-Claude Viaud-Massuard*

EA 3857 Laboratoire de Synthèse et Physicochimie, Organique et Thérapeutique, University of Tours, 31 avenue Monge, 37200 Tours, Université François Rabelais, Tours, France. Phone: 33 247 36 72 28; Email: guillard@univ-tours.fr

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. SDH is expressed almost ubiquitously in all mammalian tissues. The enzyme has attracted considerable interest due to its implication in the development of diabetic complications and furthermore its tertiary structure may facilitate drug conception. 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. 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. 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.

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 IC50 value of 1 μM. 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.

![Figure 1. Structure of SDI](image)

IC$_{50}$ = 1 µM

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](image)

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, CH₂Cl₂, -60 °C. b) Et₃N, -60 °C to rt, 70% within 2 steps. c) NaCN, MnO₂, AcOH, EtOH, rt, 24 h, 60%. d) DOWEX, H₂O, 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) NH₃, MeOH, rt, 86% within 2 steps.

The cyclo-condensation of 11 with ethyl formylacetate sodium salt 12¹⁴ afforded the corresponding hydroxypyrimidine which was converted using POCl₃ under reflux in 24 % yield to its chlorinated derivative 13 (Scheme 3).

Scheme 3. Synthesis of Compound 13

Reagents and conditions: a) H₂O, rt. b) POCl₃, 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) ClSO₂N(CH₃)₂, K₂CO₃, EtOH, 0 °C, (14, n = 1, 66%), (15, n = 2, 41%). b) 13, THF, reflux; (16, n = 1, 95%), (17, n = 2, quant.). c) BBr₃, CH₂Cl₂, 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, Et₃N, THF, reflux, 81%. b) ClSO₂NMe₂, Et₃N, CH₂Cl₂, rt, 67%. c) NaH, MeI, DMF, rt, 62%. d) BBr₃, CH₂Cl₂, 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. Exposure of 21 to sulfuryl chloride in chloroform at rt yielded to 22 in 81% yield (Scheme 6).

\[ \text{Scheme 6. Synthesis of Compound 22} \]

Reagents and conditions: a) KOH, EtOH, reflux. b) BnBr, KI, DMF, 80 °C, 49% within 2 steps. c) SO\(_2\)Cl\(_2\), Et\(_3\)N, 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.  

\[ \text{Scheme 7. Synthesis of Compound 5} \]

Reagents and conditions: a) piperazine, Et\(_3\)N, 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)\(_2\)O 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](image)

Reagents and conditions: a) NH\(_4\)OH, sealed tube, 91%. b) Br\(_2\), CaCO\(_3\), H\(_2\)O, 60°C, 59%. c) trimethylsilylacetylene, Pd(PPh\(_3\))\(_2\)Cl\(_2\), CuI, Et\(_3\)N, THF, 40 °C, 91%. d) (Boc)\(_2\)O, 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 \(N,N\)-dimethylsulfamoyl 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).

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$_2$NMe$_2$, Et$_3$N, CH$_2$Cl$_2$, 73%. e) Mel, NaH, DMF, 91%. f) BBr$_3$, CH$_2$Cl$_2$, 0 °C, 80%. g) BBr$_3$, CH$_2$Cl$_2$, 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%. After, the pyrrolopyrimidine 37 was obtained by reaction between compound 36 and pyruvic acid in the presence of triethylamine under palladium catalysis. 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. The azide group was introduced via a Mitsunobu–type substitution using zinc azide/bis pyridine complex to afford 40 in a satisfactory yield. Eventually and according to the same sequences as previously described in scheme 3 like reduction, 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) CH₃COOH, Pd(OAc)₂, Et₃N, DMF, 105 °C, 64%. c) SOCl₂, EtOH, 0 °C to reflux 71%; d) LiAlH₄, THF, rt, 83%. e) ZnN₆-2Py, DIAD, PPh₃, THF, rt, 50%. f) H₂, Pd, Lindlar, EtOH, rt, quant. g) ClSO₂N(CH₃)₂, Et₃N, CH₂Cl₂, rt, 51%. h) MeI, NaH, DMF, rt, 79%. i) BBr₃, CH₂Cl₂, 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 \( \text{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, Bu₄NBr, H₂O, rt, 65%. b) H₂, Pd, Lindlar, EtOH, rt, 92%. c) ClSO₂NMe₂, Et₃N, CH₂Cl₂, rt, 63%. d) BBr₃, CH₂Cl₂, 0 °C, 82%.

The \textit{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.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Formula</th>
<th>% Inhibition for 10⁻⁵ M</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C₁₁H₁₇N₅O₄S</td>
<td>&lt; 10</td>
</tr>
<tr>
<td>2</td>
<td>C₁₁H₂₁N₅O₃S</td>
<td>50</td>
</tr>
<tr>
<td>9</td>
<td>C₁₁H₁₇N₅O₃S</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>C₁₂H₂₃N₅O₃S</td>
<td>64</td>
</tr>
<tr>
<td>4</td>
<td>C₁₃H₂₅N₅O₃S</td>
<td>53</td>
</tr>
<tr>
<td>5</td>
<td>C₁₂H₁₆N₆O₅S</td>
<td>15</td>
</tr>
<tr>
<td>24</td>
<td>C₁₉H₂₂N₆O₅S</td>
<td>49</td>
</tr>
<tr>
<td>6</td>
<td>C₁₂H₁₉N₅O₃S</td>
<td>19</td>
</tr>
<tr>
<td>7</td>
<td>C₁₂H₁₉N₅O₃S</td>
<td>23</td>
</tr>
<tr>
<td>8</td>
<td>C₁₂H₁₇N₅O₃S</td>
<td>51</td>
</tr>
<tr>
<td>35</td>
<td>C₁₁H₁₇N₅O₃S</td>
<td>19</td>
</tr>
</tbody>
</table>

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 ($\delta$, 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-methoxacetamidine hydrochloride 11, 4-chloro-2-(methoxymethyl)pyrimidine 13, 3-benzylimidazolin-2,4-dione 21, 2-(methoxymethyl)-4-(piperazin-1-yl)pyrimidine 23.

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$_2$Cl$_2$ (10 mL) at -60°C. After 5 minutes, a solution of SDI (500 mg, 1.66 mmol) in dry CH$_2$Cl$_2$ (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$_2$Cl$_2$. 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) $\nu$: 1728, 1346, 1142 cm$^{-1}$; $^1$H-NMR (CDCl$_3$) $\delta$: 2.87 (s, 6H, N(C$_{6}$H$_3$)$_2$), 3.36 (t, 4H, $J$ = 5.2 Hz, 4 x H$_{\text{piperazin}}$), 3.84 (t, 4H, $J$ = 5.2 Hz, 4 x H$_{\text{piperazin}}$), 6.65 (d, 1H, $J$ = 6.2 Hz, H$_3$), 8.46 (d, 1H, $J$ = 6.2 Hz, H$_6$), 9.91 (s, 1H, CHO); $^{13}$C-NMR (CDCl$_3$) $\delta$: 36.2 (-N(C$_{6}$H$_3$)$_2$), 41.5 (2 x C$_{\text{piperazin}}$), 43.8 (2 x C$_{\text{piperazin}}$), 102.9 (C$_5$), 154.7 (C$_6$), 156.9 (C$_q$), 159.4 (C$_q$), 190.1 (CHO); MS (IE) m/z = 300 (M+1); Anal. Calcd for C$_{11}$H$_{17}$N$_5$O$_3$S : 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 CH₂Cl₂, washed with saturated aqueous NaHCO₃ solution and dried over anhydrous MgSO₄. After removal of the solvent, the crude residue was purified over silica gel (elu: 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; ¹H-NMR (CDCl₃) δ 1.44 (t, 3H, J = 7.1 Hz, CH₃CH₂O), 2.88 (s, 6H, N(CH₃)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, CH₃-C₂H₂O), 6.63 (d, 1H, J = 6.2 Hz, H₅), 8.39 (d, 1H, J = 6.2 Hz, H₆); ¹³C-NMR (CDCl₃) δ 14.2 (C(CH₃)-CH₂-O), 38.3 (N(N(CH₃)₂), 43.5 (2 x C_piperazin), 45.9 (2 x C_piperazin), 62.4 (CH₃-CH₂-O), 104.4 (C₅), 156.4 (C₆), 161.8 (C₇), 164.1 (C₈); MS (IE) m/z = 344 (M+1); Anal. Calcd for C₁₃H₂₁N₅O₄S : 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; ¹H-NMR (DMSO-d₆+D₂O) δ 2.79 (s, 6H, N(CH₃)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, H₅), 8.30 (d, 1H, J = 6.4 Hz, H₆); ¹³C-NMR (CDCl₃) δ 38.4 (-N(N(CH₃)₂), 43.8 (2 x C_piperazin), 46.2 (2 x C_piperazin), 105.2 (C₅), 155.6 (C₆), 157.6 (C₇), 161.8 (C₈), 165.5 (C₉); MS (IE) m/z = 316 (M+1); Anal. Calcd for C₁₁H₁₇N₅O₄S: 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, K₂CO₃ (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 (elu: MeOH/CH₂Cl₂, 1/9) to provide 14 (2.43 g, 66%) as a colourless oil. IR (film): ν 3329, 3000-2800, 1324, 1143 cm⁻¹; ¹H-NMR (CDCl₃) δ 2.79 (s, 6H, N(CH₃)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, H₅), 8.30 (d, 1H, J = 6.4 Hz, H₆); ¹³C-NMR (CDCl₃) δ 38.4 (-N(N(CH₃)₂), 43.8 (2 x C_piperazin), 46.2 (2 x C_piperazin), 105.2 (C₅), 155.6 (C₆), 157.6 (C₇), 161.8 (C₈), 165.5 (C₉); MS (IE) m/z = 316 (M+1); Anal. Calcd for C₁₁H₁₇N₅O₄S: C, 41.90; H, 5.43; N, 22.21. Found: C, 42.15; H, 5.46; N, 22.15.

1.5. N-(2-Methylaminopropyl)-N,N',N'-trimethylsulfamide 15
At rt, K₂CO₃ (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/CH₂Cl₂, 2/8) to provide 15 (858 mg, 41%) as a colourless oil. IR (film): ν 3327, 3000-2800, 1322, 1143 cm⁻¹; ¹H-NMR (CDCl₃+ D₂O) δ 1.76 (m, 2H, CH₂-C₅H₃), 2.43 (s, 3H, NH-C₅H₃), 2.63 (t, 2H, J = 7.0 Hz, NH-CH₂), 2.78 (s, 6H, N(CH₃)₂), 2.81 (s, 3H, CH₃-N-SO₂), 2.78 (s, 6H, N(C₃H₃)₂), 2.81 (s, N(CH₂CH₂-CH₂)), 3.24 (t, 2H, J = 7.0 Hz, CH₂-N-SO₂); ¹³C-NMR (CDCl₃) δ 27.3 (CH₂-C₅H₂-CH₂), 34.5 (NH-C₅H₃), 36.0 (CH₃-N-SO₂), 37.6 (N(CH₃)₂), 48.2 (NH-CH₂CH₂-CH₂), 48.3 (NH-CH₂CH₂-CH₂); MS (IE) m/z = 210 (M+1); Anal. Calcd for C₇H₁₉N₃O₂S: 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’-trimethyl-sulfamide 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; ¹H-NMR (CDCl₃) δ 2.73 (s, 6H, N(C₃H₃)₂), 2.89 (s, 3H, CH₃-N-SO₂), 3.09 (s, 3H, N-C₅H₃), 3.39 (t, 2H, J = 6.3 Hz, CH₂-N-SO₂), 3.51 (s, 3H, OCH₃), 3.85 (t, 2H, J = 6.3 Hz, N-C₅H₂), 4.46 (s, 2H, OCH₂), 6.35 (d, 1H, J = 6.1 Hz, H₅), 8.23 (d, 1H, J = 6.1 Hz, H₆); ¹³C-NMR (CDCl₃) δ 35.7 (N-C₅H₃), 36.0 (CH₃-N-SO₂), 38.0 (N(CH₃)₂), 47.0 (N-CH₂), 47.9 (CH₂-N-SO₂), 59.0 (OCH₃), 75.1 (OCH₂), 100.9 (C₂), 155.8 (C₆), 161.7 (C₇), 165.9 (C₈). MS (IE) m/z = 318 (M+1); Anal. Calcd for C₁₂H₂₅N₅O₃S: 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’-trimethyl-sulfamide 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; ¹H-NMR (CDCl₃) δ 1.90 (m, 2H, CH₂-CH₂-CH₂), 2.79 (s, 6H, N(CH₃)₂), 2.83 (s, 3H, CH₃-N-SO₂), 3.06 (s, 3H, N-CH₃), 3.23 (t, 2H, J = 7.1 Hz, CH₂-N-SO₂), 3.52 (s, 3H, OCH₃), 3.63 (t, 2H, J = 7.1 Hz, N-CH₂), 4.46 (s, 2H, OCH₂), 6.29 (d, 1H, J = 6.2 Hz, H₅), 8.20 (d, 1H, J = 6.2 Hz, H₆); ¹³C-NMR (CDCl₃) δ 25.3 (CH₂-CH₂-CH₂), 35.0 (N-CH₃), 35.5 (CH₃-N-SO₂), 38.1
(-N(CH$_3$)$_2$), 46.7 (N-CH$_2$-CH$_2$-CH$_2$), 48.5 (NH-CH$_2$-CH$_2$-CH$_2$), 59.0 (OCH$_3$), 75.6 (OCH$_2$), 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$_5$O$_3$S: 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’'-trimethyl-sulfamide 2

Under an inert atmosphere, compound 16 (1.48 g, 4.7 mmol) was dissolved in dry CH$_2$Cl$_2$ (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$_2$Cl$_2$ (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$_2$Cl$_2$. 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): $\nu$ 3425, 2931, 1329, 1143 cm$^{-1}$; $^1$H-NMR (DMSO-$d_6$) $\delta$ 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$$_3$), 3.33 (t, 2H, $J$ = 6.4 Hz, C$_H$_$_2$-N-SO$_2$), 3.77 (sb, 2H, N-C$_H$_$_2$), 4.36 (d, 2H, $J$ = 5.9 Hz, C$_H$_$_2$OH), 4.74 (t, 1H, $J$ = 5.9 Hz, CH$_2$O$_H$), 6.53 (d, 1H, $J$ = 6.1 Hz, H$_5$), 8.16 (d, 1H, $J$ = 6.1 Hz, H$_6$); $^{13}$C-NMR (DMSO-$d_6$) $\delta$ 33.9 (N-C$_H$$_3$), 34.3 (C$_H$$_3$-N-SO$_2$), 36.0 (N(C$_H$$_3$)$_2$), 45.3 (N-C$_H$_$_2$), 46.0 (CH$_2$-N-SO$_2$), 62.2 (CH$_2$OH), 98.9 (C$_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$_5$O$_3$S: C, 43.62; H, 6.71; N, 23.15.


Under an inert atmosphere, compound 17 (650 mg, 1.95 mmol) was dissolved in dry CH$_2$Cl$_2$ (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$_2$Cl$_2$ (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$_2$Cl$_2$. 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): $\nu$ 3417, 3000-2800, 1343, 1143 cm$^{-1}$; $^1$H-NMR (DMSO-$d_6$) $\delta$ 2.64 (s, 6H, N(C$_H$$_3$)$_2$), 2.82 (s, 3H, CH$_3$-N-SO$_2$), 3.04 (s, 3H, N-C$_H$$_3$), 3.14 (t, 2H, $J$ = 7.2 Hz, CH$_2$-N-SO$_2$), 3.55 (tb, 2H, N-C$_H$_$_2$), 4.34 (d, 2H, $J$ = 5.8 Hz, CH$_2$OH), 4.71 (t, 2H, $J$ = 5.8 Hz, CH$_2$O$_H$), 6.52 (d, 1H, $J$ = 6.2 Hz, H$_5$), 8.13 (d, 1H, $J$ = 6.2 Hz, H$_6$); $^{13}$C-NMR (CDCl$_3$) $\delta$ 24.7 (CH$_2$-CH$_2$-CH$_2$), 34.4 (N-C$_H$_$_3$), 35.2 (CH$_3$-N-SO$_2$), 37.5 (N(N$_3$)$_2$), 46.3 (N-CH$_2$-CH$_2$-CH$_2$), 47.9 (NH-CH$_2$-CH$_2$-CH$_2$), 63.5 (OCH$_2$), 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$_5$O$_3$S: C, 45.41; H, 7.30; N,
22.06. Found: C, 45.31; H, 7.21; N, 21.97.

1.10. \( \text{N-(4-aminobutyl)-2-(methoxymethyl)pyrimidin-4-amine 18} \)

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): \( \nu \) 3500-3000, 3000-2800, 1605 cm\(^{-1}\); \( ^1\text{H-NMR} \) (CDCl\(_3+\) D\(_2\)O) \( \delta \) 1.51-1.70 (m, 4H, \( \text{NH-CH}_2-(\text{C}_2\text{H}_2)\text{CH}_2-\text{NH}_2 \)), 2.75 (t, 2H, \( \text{J} = 6.7 \text{ Hz, CH}_2-\text{NH}_2 \)), 3.30 (tb, 2H, \( \text{NH-C}_2\text{H}_2-\text{NH}_2 \)), 3.50 (s, 3H, \( \text{-OC}_3\text{H}_3 \)), 4.45 (s, 2H, \( \text{OC}_2\text{H}_2 \)), 6.21 (d, \( \text{J} = 5.9 \text{ Hz, H}_5 \)), 8.16 (d, \( \text{J} = 5.9 \text{ Hz, H}_6 \)); \( ^{13}\text{C-NMR} \) (CDCl\(_3\)) \( \delta \) 26.3 (NH-\( \text{CH}_2-(\text{C}_2\text{H}_2)\text{CH}_2-\text{NH}_2 \)), 30.3 (NH-\( \text{CH}_2-(\text{C}_2\text{H}_2)\text{CH}_2-\text{NH}_2 \)), 40.9 (CH\(_2\)-NH\(_2\)), 41.3 (NH-\( \text{CH}_2 \)), 58.7 (OCH\(_3\)), 75.1 (OCH\(_2\)), 101.3 (C\(_3\)), 155.3 (C\(_6\)), 162.3 (C\(_q\)), 166.0 (C\(_q\)); MS (IE) \( m/z = 211 \) (M+1); \textit{Anal.} Calcd for C\(_{10}\)H\(_{18}\)N\(_4\)O: C, 57.12; H, 8.63; N, 26.64. Found: C, 56.82; H, 8.41; N, 26.61.

1.11. \( \text{N,N-Dimethyl-N’-(4-[N’-(2-methoxymethyl)pyrimidin-4-yl]butylamino)sulfamide 19} \)

Under an inert atmosphere, a solution of \( \text{N,N-dimethylsulfamoyl chloride} \) (2 mL, 10.4 mmol) in dry CH\(_2\)Cl\(_2\) (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\(_2\)Cl\(_2\) (35 mL). The reaction was then stirred at rt. After 15 h, 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): \( \nu \) 3500-3000, 3000-2800, 1603, 1327, 1145 cm\(^{-1}\); \( ^1\text{H-NMR} \) (CDCl\(_3\)) \( \delta \) 1.61-1.69 (m, 4H, \( \text{NH-CH}_2-(\text{C}_2\text{H}_2)\text{CH}_2-\text{NH}_2 \)), 2.79 (s, 6H, \( \text{N(C}_2\text{H}_3)\text{2} \)), 3.11 (m, 2H, \( \text{CH}_2-\text{NH-SO}_2-\)), 3.32 (m, 2H, \( \text{NH-C}_2\text{H}_2-\text{NH}_2 \)), 3.50 (s, 3H, \( \text{-OC}_3\text{H}_3 \)), 4.45 (s, 2H, \( \text{OC}_2\text{H}_2 \)), 5.23 (t, \( \text{J} = 3.4 \text{ Hz, H}_5 \)), 5.48 (sb, 1H, \( \text{NH} \)), 6.22 (d, \( \text{J} = 6.0 \text{ Hz, H}_5 \)), 8.15 (d, \( \text{J} = 6.0 \text{ Hz, H}_6 \)); \( ^{13}\text{C-NMR} \) (CDCl\(_3\)) \( \delta \) 26.5 (NH-\( \text{CH}_2-(\text{C}_2\text{H}_2)\text{CH}_2-\text{NH}_2 \)), 27.4 (NH-\( \text{CH}_2-(\text{C}_2\text{H}_2)\text{CH}_2-\text{NH}_2 \)), 38.4 (N(CH\(_3\)_2)), 41.1 (CH\(_2\)-NH\(_2\)), 43.5 (CH\(_2\)-NH-SO\(_2\)), 59.4 (OCH\(_3\)), 75.7 (OCH\(_2\)), 100.5 (C\(_3\)), 155.8 (C\(_6\)), 162.9 (C\(_q\)), 166.5 (C\(_q\)); MS (IE) \( m/z = 318 \) (M+1); \textit{Anal.} Calcd for C\(_{12}\)H\(_{23}\)N\(_5\)O\(_3\)S: C, 45.41; H, 7.30; N, 22.06. Found: C, 45.56; H, 7.26; N, 22.15.

1.12. \( \text{N-(4-([N’-(2-(Methoxymethyl)pyrimidin-4-yl)]-N’-methylbutylamino)-N,N’,N’-trimethylsulfamide 20} \)

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\(_2\)Cl\(_2\), purified by flash chromatography on silica gel
eluent: MeOH/CH$_2$Cl$_2$, 1/9) to give compound 20 (0.60 g, 62%) as a colourless oil. IR (film): v 3000-2800, 1592, 1343, 1143 cm$^{-1}$; $^1$H-NMR (CDCl$_3$) δ 1.54 (m, 4H, N-CH$_2$-(CH$_2$)$_2$-CH$_2$-NH-SO$_2$), 2.71 (s, 6H, N(CH$_3$)$_2$), 2.72 (s, 3H, CH$_3$-N-SO$_2$), 2.96 (s, 3H, N-CH$_3$), 3.13 (t, 2H, J = 6.6 Hz, CH$_2$-N-SO$_2$), 3.42 (s, 3H, OCH$_3$), 3.50 (sb, 2H, N-CH$_3$), 3.72 (s, 9H, -N(CH$_3$)$_2$ and CH$_3$-N-SO$_2$), 3.86 (s, 3H, N-C$_6$), 3.91 (sb, 2H, N-C$_6$), 4.37 (s, 2H, OCH$_2$), 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$_2$-(CH$_2$)$_2$-CH$_2$-NH-SO$_2$), 24.8 (N-CH$_2$-(CH$_2$)$_2$-CH$_2$-NH-SO$_2$), 34.8 (CH$_3$-N), 35.2 (CH$_3$-N-SO$_2$), 38.0 (N(CH$_3$)$_2$), 48.4 (N-CH$_2$), 50.3 (CH$_2$-N-SO$_2$), 58.9 (OCH$_3$), 75.5 (OCH$_2$), 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$_5$O$_3$S: 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$_2$Cl$_2$ (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$_2$Cl$_2$ (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$_2$Cl$_2$. 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$_2$Cl$_2$ 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): v 3417, 3000-2800, 1594, 1342, 1143 cm$^{-1}$; $^1$H-NMR (CDCl$_3$) δ 1.64 (m, 4H, N-CH$_2$-(CH$_2$)$_2$-CH$_2$-NH-SO$_2$), 2.79 (s, 9H, -N(CH$_3$)$_2$ and CH$_3$-N-SO$_2$), 3.07 (s, 3H, N-C$_6$), 3.22 (t, 2H, J = 6.6 Hz, CH$_2$-N-SO$_2$), 3.61 (sb, 2H, N-CH$_2$), 4.02 (sb, 1H, CH$_2$O), 4.58 (s, 2H, CH$_2$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$_2$-(CH$_2$)$_2$-CH$_2$-NH-SO$_2$), 24.5 (N-CH$_2$-(CH$_2$)$_2$-CH$_2$-NH-SO$_2$), 34.5 (CH$_3$-N), 35.1 (CH$_3$-N-SO$_2$), 37.7 (N(CH$_3$)$_2$), 48.2 (N-CH$_2$), 49.9 (CH$_2$-N-SO$_2$), 63.8 (OCH$_2$), 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$_5$O$_3$S: 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 using 10% MeOH in CH$_2$Cl$_2$ 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): v 3417, 3000-2800, 1594, 1342, 1143 cm$^{-1}$; $^1$H-NMR (CDCl$_3$) δ 1.64 (m, 4H, N-CH$_2$-(CH$_2$)$_2$-CH$_2$-NH-SO$_2$), 2.79 (s, 9H, -N(CH$_3$)$_2$ and CH$_3$-N-SO$_2$), 3.07 (s, 3H, N-CH$_3$), 3.22 (t, 2H, J = 6.6 Hz, CH$_2$-N-SO$_2$), 3.61 (sb, 2H, N-CH$_2$), 4.02 (sb, 1H, CH$_2$OH), 4.58 (s, 2H, CH$_2$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$_2$-(CH$_2$)$_2$-CH$_2$-NH-SO$_2$), 24.5 (N-CH$_2$-(CH$_2$)$_2$-CH$_2$-NH-SO$_2$), 34.5 (CH$_3$-N), 35.1 (CH$_3$-N-SO$_2$), 37.7 (N(CH$_3$)$_2$), 48.2 (N-CH$_2$), 49.9 (CH$_2$-N-SO$_2$), 63.8 (OCH$_2$), 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$_5$O$_3$S: C, 47.11; H, 7.60; N, 21.13. Found: C, 46.81; H, 7.42; N, 21.22.
311 (M+1 for $^{35}$Cl), $m/z$ = 313 (M+1 for $^{37}$Cl); Calcd for C$_{10}$H$_9$ClN$_2$O$_4$S: 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$_2$Cl$_2$. 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$_2$Cl$_2$, 4/96) to provide 24 (610 mg, 24%) as a brown solid. Mp 211-212 °C ($i$-Pr). IR (KBr): $\nu$ 3000-2800, 1715, 1713, 1411, 1586, 1374, 1175 cm$^{-1}$; $^{1}$H-NMR (CDCl$_3$) $\delta$ 3.51 (m, 7H, OC$_3$H$_3$ + 4 x H$_{piperazin}$), 3.80 (t, 4H, $J$ = 2.5 Hz, H$_{piperazin}$), 4.30 (s, 2H, N-C$_2$H$_2$-CO), 4.48 (s, 2H, OC$_2$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$_3$) $\delta$ 43.1 (C$_H_2$-Ph), 43.2 (2 x C$_{piperazin}$), 46.1 (2 x C$_{piperazin}$), 51.1 (N-C$_2$H$_2$-CO), 59.2 (OCH$_3$), 75.4 (OCH$_2$), 101.1 (C$_3$), 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$_6$O$_5$S: 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$_2$Cl$_2$, 1/9) to give 5 (190 mg, 41%) as a white needles. Mp > 244 °C ($i$-Pr). IR (KBr): $\nu$ 3600-3000, 2933, 2896, 1740, 1593, 1385, 1164 cm$^{-1}$; $^{1}$H-NMR (CDCl$_3$) $\delta$ 3.39 (tb, 4H, 4 x H$_{piperazin}$), 3.77 (bt, 4H, 4 x H$_{piperazin}$), 4.30 (s, 2H, N-C$_2$H$_2$-CO), 4.36 (d, 2H, $J$ = 5.5 Hz, C$_H_2$-OH), 4.85 (t, 1H, $J$ = 5.5 Hz, CH$_2$-OH), 6.75 (d, 1H, $J$ = 6.2 Hz, H$_5$), 8.20 (d, 1H, $J$ = 6.2 Hz, H$_6$); $^{13}$C-NMR (CDCl$_3$) $\delta$ 42.8 (2 x C$_{piperazin}$), 45.8 (2 x C$_{piperazin}$), 52.8 (N-CH$_2$-CO), 64.7 (CH$_2$-OH), 101.8 (C$_3$), 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$_6$O$_5$S: 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) NH₄OH solution (20 mL) was heated at 120 °C for 15 h. After cooling, the reaction was extracted with CH₂Cl₂. The organic layers were dried over anhydrous MgSO₄ 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; ¹H-NMR (CDCl₃) δ 3.51 (s, 3H, OC₃H₃), 4.49 (s, 2H, OC₂H₂), 5.11 (bs, 2H, NH₂), 6.32 (d, 1H, J = 5.7 Hz, H₅), 8.22 (d, 1H, J = 5.7 Hz, H₆); ¹³C-NMR (CDCl₃) δ 59.0 (O-CH₃), 75.3 (O-CH₂), 103.6 (C₅), 155.9 (C₆), 163.2 (C₇), 166.6 (C₈); MS (IE) m/z = 140 (M+1); Calcd for C₆H₁₀N₃O: 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 CaCO₃ (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 NaHCO₃ solution and extracted with EtOAc. The combined extracts were dried over anhydrous MgSO₄. After removal of the solvent in vacuo, the product was isolated 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; ¹H-NMR (CDCl₃) δ 3.49 (s, 3H, OC₃H₃), 4.45 (s, 2H, OC₂H₂), 5.78 (sb, 2H, NH₂), 8.34 (d, 1H, H₆); ¹³C-NMR (CDCl₃) δ 59.0 (O-CH₃), 74.6 (O-CH₂), 101.8 (C₅), 156.5 (C₆), 160.1 (C₇), 165.3 (C₈); MS (IE) m/z = 218 (M+1 for ⁷⁹Br) m/z 220 (M+1 for ⁸¹Br); Calcd for C₆H₈BrN₃O: 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), Cul (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; ¹H-NMR (CDCl₃) δ 0.28 (s, 9H, Si(CH₃)₃), 3.49 (s, 3H, OCH₃), 4.49 (s, 2H, OCH₂), 5.52 (sb, 2H, NH₂), 8.34 (s, 1H, H₆); ¹³C-NMR (CDCl₃) δ 0.0 (Si(CH₃)₃), 59.1 (O-CH₃), 75.1 (O-CH₂), 96.9 (C₅), 100.3 (C₆), 104.3 (C₇), 158.2 (C₈), 163.2 (C₉), 165.5 (C₁₀); MS (IE) m/z = 236 (M+1); Calcd for C₁₇H₁₇N₃OSi: 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′-ethynyl]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 CH₂Cl₂. The combined organic layers were dried over anhydrous MgSO₄ 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-ditertiobutyloxycarbonyl)amino]-2-methoxymethyl-5-[2’-(1,1,1-trimethylsilyl)-1’-ethynyl]-pyrimidine 28 as a colourless oil. IR (film): ν 2933, 2890, 2164, 1767, 1731 cm⁻¹; ¹H-NMR (CDCl₃) δ 0.25 (s, 9H, Si(CH₃)₃), 1.41 (s, 18H, N[CO-O-C(CH₃)₃]₂), 3.52 (s, 3H, OC₃H₃), 4.70 (s, 2H, OC₂H₂), 8.34 (s, 1H, H₆); ¹³C-NMR (CDCl₃) δ 0.0 (Si(C₃H₃)₃), 28.2 (N[CO-O-C(CH₃)₃]₂), 59.4 (O-CH₃), 75.1 (O-CH₂), 84.0 (C₅), 95.8 (C₆), 106.2 (C₇), 149.5 (C₈), 161.2 (C₉), 161.5 (C₁₀), 166.4 (C₁₁); MS (IE) m/z = 436 (M+1); Calcd for C₂₁H₃₃N₃O₅Si: 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 CH₂Cl₂. The combined organic layers were dried over anhydrous MgSO₄ 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; ¹H-NMR (CDCl₃) δ 3.61 (s, 3H, OC₃H₃), 4.92 (s, 2H, OCH₂), 6.60 (dd, 1H, J = 1.8, 3.5 Hz, H₅), 7.46 (dd, 1H, J = 2.6 Hz, 3.5 Hz, H₆), 9.00 (s, 1H, H₄); ¹³C-NMR (CDCl₃) 61.5 (O-CH₃), 75.7 (O-CH₂), 100.3 (C₅), 118.5 (C₆), 127.9 (C₇), 150.1 (C₈), 152.9 (C₉), 159.5 (C₁₀); MS (IE) m/z = 164 (M+1); Calcd for C₈H₉N₃O: 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 CH₂Cl₂ 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; ¹H-NMR (CDCl₃) δ 3.56 (s, 3H, OC₃H₃), 3.77 (s, 2H, J = 6.3 Hz, CH₂Br), 4.69 (t, 2H, J = 6.3 Hz, N-CH₂), 4.76 (s, 2H, OCH₂), 6.55 (d, 1H, J = 3.6 Hz, H₅), 7.29 (d, 1H, J = 3.6 Hz, H₆), 8.98 (s, 1H, H₄); ¹³C-NMR (CDCl₃) 30.3 (CH₂-Br), 46.2 (N-CH₂), 59.0 (O-CH₃), 76.0 (O-CH₂), 99.6 (C₅), 117.7 (C₆), 129.5 (C₇), 149.8 (C₈), 151.0 (C₉), 159.5 (C₁₀); MS (IE) m/z = 270 (M+1 for ⁷⁹Br), 272 (M+1 for ⁸¹Br); Calcd for C₁₀H₁₂BrN₃O: 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 CH2Cl2 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; ¹H-NMR (CDCl3) δ 3.56 (s, 3H, OCH3), 3.75 (s, 2H, J = 5.6 Hz, CH2N3), 4.45 (t, 2H, J = 5.6 Hz, OCH2), 4.76 (s, 2H, OCH2), 6.57 (d, 1H, J = 3.6 Hz, H5), 7.26 (d, 1H, J = 3.6 Hz, H6), 8.99 (s, 1H, H4); ¹³C-NMR (CDCl3) 43.7 (N-C3H3), 50.9 (C2H2-N3), 59.0 (O-C3H2), 76.1 (O-CH2), 100.0 (C3), 117.7 (C4), 129.4 (C6), 149.8 (C4), 151.1 (C4), 159.6 (C4); MS (IE) m/z = 233 (M+1); Calcd for C10H12N6O: 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]ethyamine 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; ¹H-NMR (CDCl3 + D2O) δ 3.15 (t, 2H, J = 6.0 Hz, C2H2NH2), 3.56 (s, 3H, OCH3), 4.36 (t, 2H, J = 6.0 Hz, N-C2H2), 4.76 (s, 2H, OCH2), 6.56 (d, 1H, J = 3.6 Hz, H5), 7.27 (d, 1H, J = 3.6 Hz, H6), 8.99 (s, 1H, H4); ¹³C-NMR (CDCl3) 42.4 (C2H2-NH2), 47.7 (N-C2H2), 59.2 (O-C2H2), 74.3 (O-CH2), 97.6 (C3), 115.8 (C4), 127.6 (C6), 147.8 (C4), 157.5 (C4); MS (IE) m/z = 207 (M+1); Calcd for C10H14N4O: 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]ethy)sulfamide 33

Under an inert atmosphere, a solution of N,N-dimethylsulfamoyl chloride (0.69 mL, 6.4 mmol) in dry CH2Cl2 (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 CH2Cl2 (12 mL). After stirring the reaction at rt for 15 h, it was hydrolysed and extracted with CH2Cl2. The combined organic layers were dried over anhydrous MgSO4 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; ¹H-NMR (CDCl3) δ 2.72 (s, 6H, N(CH3)2), 3.56 (s, 3H, OCH3), 3.57 (m, 2H, CH2NH), 4.45 (m, 2H, N-CH2), 4.74 (s, 2H, OCH2), 5.65 (sb, 1H, NH), 6.56 (d, 1H, J = 3.6 Hz, H5), 7.24 (d, 1H, J = 3.6 Hz, H6), 8.99 (s, 1H, H4); ¹³C-NMR (CDCl3) 38.7 (N(CH3)2), 44.4 (CH2-NH), 46.3 (N-CH2), 59.7 (O-CH3), 76.4 (O-CH2), 100.5 (C3), 118.5 (C4), 130.9 (C6), 150.4 (C4), 151.7 (C4), 159.9 (C4); MS (IE) m/z = 314 (M+1); Calcd for C12H19N5O3S: C, 45.99; H, 6.11; N, 22.35. Found: C, 46.06; H, 5.98; N, 22.32.
1.26. \( \text{N,N,N'} \)-Trimethyl-\( \text{N'} \)-(2-[2-(methoxymethyl)pyrrolo[2,3-\text{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\(_2\)Cl\(_2\), purified by flash chromatography on silica gel (eluent: MeOH/CH\(_2\)Cl\(_2\), 2/98) to give the title compound 34 (0.428 g, 91%) as a white oil.

IR (film): \( \nu \) 3000-2800, 1591, 1324, 1146 cm\(^{-1}\);
\[ ^1\text{H-NMR (CDCl}_3 \] \( \delta \) 2.63 (s, 6H, N(CH\(_3\))\(_2\)), 2.66 (s, 3H, NCH\(_3\)), 3.56 (s, 3H, OCH\(_3\)), 3.64 (t, 2H, \( J = 6.0 \) Hz, CH\(_2\)NSO\(_2\)), 4.50 (t, 2H, \( J = 6.0 \) Hz, N-CH\(_2\)), 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\(_4\));
\[ ^{13}\text{C-NMR (CDCl}_3 \] 35.9 (N-CH\(_3\)), 37.8 (N-(CH\(_3\))\(_2\)), 43.0 (N-CH\(_2\)), 50.4 (CH\(_2\)-N-SO\(_2\)), 59.0 (O-C\(_H\)\(_3\)), 76.1 (O-CH\(_2\)), 99.8 (C\(_5\)), 117.6 (C\(_q\)), 129.6 (C\(_o\)), 149.7 (C\(_q\)), 151.1 (C\(_q\)), 159.3 (C\(_q\)); MS (IE) \( m/z = 328.5 \) (M+1); Calcd for C\(_{13}\)H\(_{21}\)N\(_5\)O\(_3\)S: C, 47.69; H, 6.47; N, 21.39. Found: C, 47.07; H, 6.33; N, 21.66.

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

Under an inert atmosphere, compound 34 (0.4 g, 1.2 mmol) was dissolved in dry CH\(_2\)Cl\(_2\) (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\(_2\)Cl\(_2\) (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\(_2\)Cl\(_2\). 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\(_2\)Cl\(_2\) as eluent gave 0.306 g (80%) of \( \text{N,N,N'} \)-trimethyl-\( \text{N'} \)-(2-[2-(hydroxymethyl)pyrrolo[2,3-\text{d}]pyrimidin-7-yl]ethyl)sulfamide 6 as a white solid. Mp 69-70 °C; IR (KBr): \( \nu \) 3448, 3000-2800, 1594, 1310, 1153 cm\(^{-1}\);
\[ ^1\text{H-NMR (CDCl}_3 \] \( \delta \) 2.62 (s, 6H, N(CH\(_3\))\(_2\)), 2.67 (s, 3H, NCH\(_3\)), 3.64 (t, 2H, \( J = 6.0 \) Hz, CH\(_2\)NSO\(_2\)), 3.88 (sb, 1H, CH\(_2\)O), 4.49 (t, 2H, \( J = 6.0 \) Hz, N-CH\(_2\)), 4.49 (sb, 2H, CH\(_2\)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\(_4\));
\[ ^{13}\text{C-NMR (CDCl}_3 \] 35.9 (N-CH\(_3\)), 37.8 (N-(CH\(_3\))\(_2\)), 43.0 (N-CH\(_2\)), 50.4 (CH\(_2\)-N-SO\(_2\)), 64.6 (CH\(_2\)OH), 100.0 (C\(_5\)), 117.6 (C\(_q\)), 149.3 (C\(_s\)), 150.8 (C\(_b\)), 160.9 (C\(_q\)); MS (IE) \( m/z = 314 \) (M+1); Anal. Calcd for C\(_{11}\)H\(_{19}\)N\(_5\)O\(_3\)S: 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. \( \text{N,N-Dimethyl-N'}-(2-[2-(hydroxymethyl)pyrrolo[2,3-\text{d}]pyrimidin-7-yl]ethyl)sulfamide 35

Under an inert atmosphere, compound 33 (0.2 g, 0.64 mmol) was dissolved in dry CH\(_2\)Cl\(_2\) (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\(_2\)Cl\(_2\) (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\(_2\)Cl\(_2\). 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\(_2\)Cl\(_2\) as eluent gave 0.306 g (80%) of \( \text{N,N-dimethyl-N'}-(2-[2-(hydroxymethyl)pyrrolo[2,3-\text{d}]pyrimidin-7-yl]ethyl)sulfamide 35\) as a white solid.
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; ¹H-NMR (CDCl₃) δ 2.71 (s, 6H, N(CH₃)₂), 3.54 (m, 2H, CH₂-NH), 4.13 (sb, 1H, CH₂OH), 4.44 (t, 2H, J = 5.8 Hz, N-CH₂), 4.84 (s, 2H, CH₂OH), 5.88 (sb, 1H, NH), 5.53 (d, 1H, J = 3.5 Hz, H₅), 7.28 (d, 1H, J = 3.5 Hz, H₆), 8.80 (s, 1H, H₄); ¹³C-NMR (CDCl₃) 38.0 (N-(CH₃)₂), 43.4 (CH₂-NH), 45.2 (N-CH₂), 64.7 (CH₂-OH), 100.0 (C₅), 117.8 (C₆), 130.0 (C₆), 149.3 (C₄), 150.8 (C₆), 161.0 (C₄); MS (IE) m/z = 300 (M+1); Anal. Calcd for C₁₁H₁₇N₅O₃S: 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 CHCl₃ and the combined layers were washed with water, brine and dried over anhydrous MgSO₄. Finally, purification by flash chromatography on silica gel using 10% light petrolatum 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; ¹H-NMR (DMSO-d₆) δ 3.30 (s, 3H, OCH₃), 4.25 (s, 2H, OCH₂), 7.05 (sb, 2H, NH₂), 8.41 (s, 1H, H₄); ¹³C-NMR (CDCl₃) 58.9 (O-CH₃), 75.2 (O-CH₂), 76.2 (C₆), 163.1 (C₆), 164.3 (C₅), 167.3 (C₅); MS (IE) m/z = 266 (M+1); Calcd for C₆H₈IN₃O: C, 27.19; H, 3.04; N, 15.85. Found: C, 27.28; H, 3.36; N, 15.80.

1.30. (2-(Methoxymethyl)-7H-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: Et₃N/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, 3000-2800, 1699, 1602 cm⁻¹; ¹H-NMR (DMSO-d₆) δ 3.37 (s, 3H, OCH₃), 4.60 (s, 2H, OCH₂), 7.20 (s, 1H, H₅), 9.12 (s, 1H, H₄), 12.74 (sb, 1H, NH), 13.43 (sb, 1H, CO₂H); ¹³C-NMR (DMSO-d₆) 58.4 (O-CH₃), 75.6 (O-CH₂), 105.8 (C₅), 116.7 (C₆), 130.7 (C₆), 152.1 (C₆), 152.5 (C₄), 161.8 (C₄), 162.4 (C₄); MS (IE) m/z = 208 (M+1); Calcd for C₈H₉N₃O₂: C, 52.17; H, 4.38; N, 20.28. Found: C, 52.72; H, 4.58; N, 20.39.

1.31. (2-(Methoxymethyl)-7H-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/CH2Cl2, 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; ¹H-NMR (CDCl3) δ 1.41 (t, 3H, J = 7.1 Hz, OCH2-C⁶H₃), 3.56 (s, 3H, OC₆H₃), 4.44 (q, 2H, J = 7.1 Hz, OC₆H₂-CH₃), 4.82 (s, 2H, OC₆H₂), 7.23 (d, 1H, J = 1.2 Hz, H₅), 9.12 (s, 1H, H₄), 9.91 (bs, 1H, NH); ¹³C-NMR (CDCl3) 14.4 (O-CH₂-C⁶H₃), 59.4 (O-OC₆H₃), 62.1 (O-OC₆H₂-CH₃), 75.8 (O-CH₂), 106.6 (C₅), 117.4 (C₆), 129.4 (C₇), 152.1 (C₈), 153.2 (C₉), 161.4 (C₉), 163.1 (C₉); MS (IE) m/z = 236 (M+1); Calcd for C₁₁H₁₃N₃O₃: C, 56.16; H, 5.57; N, 17.86. Found: C, 56.44; H, 5.69; N, 17.45.

13.2. 6-(Hydroxymethyl)-2-(methoxymethyl)-7H-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 LiAlH₄ (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/CH₂Cl₂, 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; ¹H-NMR (CDCl3) δ 3.51 (s, 3H, OC₆H₃), 4.80 (s, 2H, C₆H₂OH), 4.82 (s, 2H, OC₆H₂), 6.33 (s, 1H, H₅), 8.81 (s, 1H, H₄), 11.74 (bs, 1H, NH); ¹³C-NMR (CDCl3) 58.2 (CH₂OH), 59.2 (O-OC₆H₃), 75.9 (O-CH₂), 98.2 (C₅), 118.5 (C₆), 141.6 (C₇), 149.4 (C₈), 153.2 (C₉), 158.9 (C₉); MS (IE) m/z = 178 (M+1); Calcd for C₉H₁₁N₃O: C, 61.00; H, 6.26; N, 23.73. Found: C, 60.85; H, 6.34; N, 23.39.

13.3. 6-(Azidomethyl)-2-(methoxymethyl)-7H-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/CH₂Cl₂, 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; ¹H-NMR (CDCl3) δ 3.52 (s, 3H, OC₆H₃), 4.64 (s, 2H, CH₂N₃), 4.90 (s, 2H, OCH₂), 6.56 (1, 1H, H₅), 8.98 (s, 1H, H₄), 11.85 (sb, 1H, NH); ¹³C-NMR (CDCl3) 48.1 (CH₂N₃), 59.1 (O-CH₂), 75.7 (O-CH₂), 100.4 (C₅), 118.2 (C₆), 135.5 (C₇), 150.0 (C₈), 153.6 (C₉), 160.2 (C₉); MS (IE) m/z = 219 (M+1); Calcd for C₉H₁₂N₄O: C, 49.54; H, 4.62; N, 38.51. Found: C, 49.01; H, 4.58; N, 38.39.
1.34. 1-[2-Methoxymethyl]-7H-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): \( \nu = 3500-3000, 2881, 1606 \text{ cm}^{-1} \); 1H-NMR (CDCl3+D2O) 3.49 (s, 3H, OCH3), 4.05 (s, 2H, CH2NH2), 4.76 (s, 2H, OCH2), 6.30 (s, H5), 8.84 (s, 1H, H4); 13C-NMR (CDCl3) 39.5 (CH2-NH2), 58.8 (O-CH2), 75.7 (O-CH2), 96.5 (C4), 118.0 (Cq), 132.0 (Cq), 148.5 (C4), 152.6 (Cq), 158.8 (Cq); MS (IE) \( m/z = 193 \) (M+1); Calcd for C9H12N4O: 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)-7H-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 CH2Cl2 (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 CH2Cl2 (4 mL). The reaction was then stirred at rt for 15 h. The mixture was hydrolysed and extracted with CH2Cl2. The combined organic layers were dried over anhydrous MgSO4 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): \( \nu = 3196, 3000-2720, 1345, 1145 \text{ cm}^{-1} \); 1H-NMR (CDCl3) \( \delta = 2.74 \) (s, 6H, N(CH3)2), 3.50 (s, 3H, OCH3), 4.37 (d, 2H, J = 6.1 Hz, CH2NH), 4.74 (s, 2H, OCH2), 6.32 (s, 1H, H5), 6.35 (sb, 1H, CH2NH), 8.79 (s, 1H, H4), 10.68 (sb, 1H, NH); 13C-NMR (CDCl3) 38.4 (N-C(CH3)2), 41.2 (CH2-NH), 59.3 (O-CH3), 75.9 (O-CH2), 99.3 (C5), 118.1 (Cq), 138.1 (Cq), 149.5 (C4), 154.0 (Cq), 160.5 (Cq); MS (IE) \( m/z = 300 \) (M+1); Calcd for C11H17N5O3S: 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 then 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 CH2Cl2, purified by flash chromatography on silica gel (eluent: MeOH/CH2Cl2, 2/98) to give the title compound 43 (0.140 g, 91%) as a yellow solid. Mp 104-105 °C IR (KBr): \( \nu = 3000-2800, 1352, 1157 \text{ cm}^{-1} \); 1H-NMR (CDCl3) \( \delta = 2.67 \) (s, 6H, CH2-N-CH3), 2.88 (s, 6H, N(CH3)2), 3.55 (s, 3H, OCH3), 3.86 (s, 3H, N-CH3), 4.50 (s, 2H, CH2-N-SO2), 4.72 (s, 2H, OCH2), 6.48 (s, 1H, H5), 8.87 (s, 1H, H4); 13C-NMR (CDCl3) 28.6 (N-CH3), 38.3 (N(CH3)2), 34.5 (CH2-N-CH3), 47.1 (CH2-N-SO2), 59.0 (O-CH2), 76.1 (O-CH3), 100.8 (C5), 116.8 (Cq), 136.0 (Cq), 149.1 (C4), 152.6 (Cq), 159.7 (Cq); MS (IE) \( m/z = 328 \) (M+1); Calcd for C13H21N5O3S:
1.37. \(N\)-(1-[2-(Hydroxymethyl)-7-methylpyrrolo[2,3-d]pyrimidin-6-yl]methyl)-\(N\),\(N\)',\(N\)'-trimethyl-sulfamide 7

Under an inert atmosphere, compound 43 (0.115 g, 0.35 mmol) was dissolved in dry CH\(_2\)Cl\(_2\) (4 mL). The mixture was cooled to 0°C and a solution of BBr\(_3\) (0.17 mL, 1.75 mmol) in dry CH\(_2\)Cl\(_2\) (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\(_2\)Cl\(_2\). 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\(_2\)Cl\(_2\) 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): \(\nu\) 3146, 3000-2800, 1593, 1351, 1153 cm\(^{-1}\); 1H-NMR (CDCl\(_3\)+D\(_2\)O) \(\delta\) 2.71 (s, 3H, CH\(_2\)-N-C\(_6\)H\(_3\)), 2.91 (s, 6H, N(C\(_6\)H\(_3\))\(_2\)), 3.88 (s, 3H, N-C\(_6\)H\(_3\)), 4.54 (s, 2H, CH\(_2\)-N-SO\(_2\)), 4.90 (s, 2H, CH\(_2\)OH), 6.53 (s, 1H, H\(_5\)), 8.87 (s, 1H, H\(_4\)); 13C-NMR (CDCl\(_3\)) 28.9 (N-C\(_6\)H\(_3\)), 34.9 (C\(_6\)H\(_2\)-N-CH\(_3\)), 38.7 (N(C\(_6\)H\(_3\))\(_2\)), 47.5 (C\(_6\)H\(_2\)-N-SO\(_2\)), 65.0 (CH\(_2\)OH), 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\(_5\)O\(_3\)S: 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 Na OH 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, then with a saturated aqueous NaCl solution, then dried over anhydrous MgSO\(_4\), filtered and concentrated in vacuo. The crude was purified by flash chromatography on silica gel (eluent: CH\(_2\)Cl\(_2\)/EtOAc, 1/9) to provide 44 (0.649 g, 65%) as a pink oil. IR (film): \(\nu\) 3000-2800, 2102, 1591 cm\(^{-1}\); 1H-NMR (CDCl\(_3\)) \(\delta\) 3.55 (s, 1H, OC\(_6\)H\(_3\)), 3.82 (t, 2H, \(J\) = 6.5 Hz, CH\(_2\)Br), 4.60 (s, 2H, CH\(_2\)N\(_3\)), 4.65 (t, 2H, \(J\) = 6.5 Hz, NCH\(_2\)), 4.75 (s, 2H, OCH\(_2\)), 6.57 (s, 1H, H\(_5\)), 8.96 (s, 1H, H\(_4\)); 13C-NMR (CDCl\(_3\)) 30.5 (Ar-CH=), 44.7 (N-C\(_6\)H\(_3\)), 47.7 (Ar-CH\(_2\)-N\(_3\)), 59.8 (O-CH\(_3\)), 76.7 (O-CH\(_2\)), 101.9 (C\(_3\)), 117.6 (C\(_q\)), 135.8 (C\(_q\)), 150.7 (C\(_4\)), 153.1 (C\(_q\)), 161.1 (C\(_q\)); MS (IE) \(m/z\) = 314 (M+1); Anal. Calcd for C\(_{11}\)H\(_{13}\)BrN\(_6\)O: 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: CH\(_3\)OH/CH\(_2\)Cl\(_2\), 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; ¹H-NMR (CDCl₃ + D₂O) 3.34 (t, 2H, J = 5.6 Hz, N-CH₂-CH₂-NH), 3.54 (s, 3H, OCH₃), 4.23 (m, 4H, N-CH₂-CH₂-NH and CH₂-NH), 4.74 (s, 2H, OCH₂), 6.20 (s, 1H, H₅), 8.85 (s, 1H, H₄); ¹³C-NMR (CDCl₃) 42.1 (N-CH₂-CH₂-NH), 43.5 (N-CH₂-CH₂-NH), 44.6 (Ar-CH₂-NH), 59.3 (O-CH₃), 76.4 (O-CH₂), 94.2 (C₅), 117.9 (C₆), 136.9 (C₇), 148.5 (C₈), 152.3 (C₉), 158.7 (C₁₀); MS (IE) m/z = 219 (M+1); Calcd for C₁₁H₁₄N₄O: 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 CH₂Cl₂ (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 CH₂Cl₂ (8 mL). The reaction was then stirred at rt for 15 h. After completion of the reaction, the mixture was hydrolysed and extracted with CH₂Cl₂. The combined organic layers were dried over anhydrous MgSO₄ 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; ¹H-NMR (CDCl₃) δ 2.89 (s, 6H, N(CH₃)₂), 3.56 (s, 3H, OCH₃), 4.37 ( t, 2H, J = 5.6 Hz, N-CH₂-CH₂-N), 4.47 (s, 2H, CH₂-N-SO₂), 4.64 (s, 2H, OCH₂), 6.32 (s, 1H, H₅), 8.85 (s, 1H, H₄); ¹³C-NMR (CDCl₃) 38.6 (N(CH₃)₂), 41.2 (N-CH₂), 44.3 (Ar-CH₂-N-SO₂), 44.8 (Ar-CH₂-N-SO₂), 59.4 (O-CH₃), 76.3 (O-CH₂), 95.5 (C₅), 117.9 (C₆), 133.4 (C₇), 149.2 (C₈), 151.5 (C₉), 159.4 (C₁₀); MS (IE) m/z = 326 (M+1); Calcd for C₁₃H₁₉N₅O₃: 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 CH₂Cl₂ (8 mL). The mixture was then cooled to 0°C and a solution of BBr₃ (0.32 mL, 3.4 mmol) in dry CH₂Cl₂ (3 mL) was added dropwise. After 2 h stirring at 0 °C, the reaction was hydrolysed, basified with saturated aqueous NaHCO₃ solution and extracted with CH₂Cl₂. The combined organic layers were dried over anhydrous MgSO₄ 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; ¹H-NMR (CDCl₃) δ 2.89 (s, 6H, N(CH₃)₂), 3.79 (t, 2H, J = 5.6 Hz, N-CH₂-CH₂-N), 3.85 (sβ, 1H, CH₂OH), 4.34 (t, 2H, J = 5.6 Hz, N-CH₂-CH₂-N), 4.65 (s, 2H, CH₂-N-SO₂), 4.89 (s, 2H, OCH₂), 6.34 (s, 1H, H₅), 8.87 (s, 1H, H₄); ¹³C-NMR (CDCl₃) 38.2 (N(CH₃)₂), 40.8 (N-CH₂), 43.9 (CH₂-CH₂-N-SO₂), 44.5 (Ar-CH₂-N-SO₂), 64.6
(CH$_2$-OH), 95.3 (C$_3$), 117.6 (C$_4$), 132.9 (C$_5$), 148.5 (C$_6$), 150.8 (C$_7$), 160.6 (C$_8$); MS (IE) $m/z = 312$ (M+1); Anal. Calcd for C$_{12}$H$_{17}$N$_5$O$_3$S: 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.

ACKNOWLEDGEMENTS

We thank the society ADIR (Courbevoie, France) for its multiform supports.

REFERENCES (AND NOTES)