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Effect of substituent structure on pyrimidine electrophilic substitution

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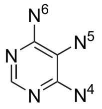
Abstract—In an investigation into the electrophilic nitrosation reactions of a series of 4,6-disubstituted pyrimidine derivatives, a subtle interplay between the electronic nature of the C-4 and C-6 substituents and reactivity was found where these were chloro-, mono- or disubstituted amino groups. Effects such as the presence of an aryl group or two alkyl groups on the amino moiety impede the progress of the reaction despite the presence of a second activating group.

1. Introduction

Purine and pyrimidine ring systems form the backbone of many important biological molecules, such as nucleic acids, cofactors and various toxins. The ability of these molecules to interact with proteins has been extensively exploited in the preparation of inhibitors specific against certain conditions, such as Gleevec (cancer) or aronixil (atherosclerosis), for example. The privileged nature of the purine/pyrimidine structure in terms of their shape and hydrogen-bonding characteristics make them ideal starting points in the search for new chemical entities of biological significance.

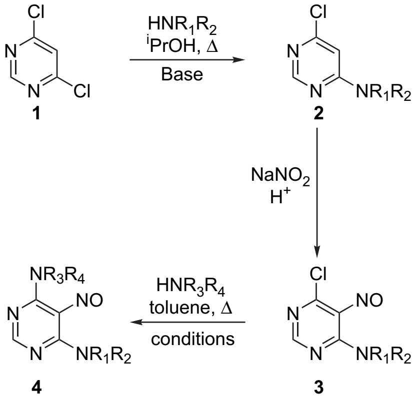
Our research, focussing on biologically relevant metal ions in binding sites of receptors, led us to look at these structures as potential inhibitory compounds from the point of view of ion chelation in the receptor. Both pyrimidines, in the guise of the 4,5-diamino or 4,5,6-triamino structures, and purines could potentially function within this paradigm. With judicious use of substituents on the amino moieties of the pyrimidines, we wanted to generate a diverse selection of the products for screening against a battery of potential targets in the infectious disease area.



2. Results and discussion

2.1. Generation of substituted 4-amino-5-nitrosopyrimidines, followed by amination at C-6

As a starting point, we chose to use 4,6-dichloropyrimidine **1** both for its availability and the well-documented selectivity obtainable by a sequential introduction of different nucleophiles to substitute the chlorine atoms on the ring.[1,2] We planned to use combinations of a primary and a secondary amine for each pyrimidine, in order to probe the selectivity hereof against selected targets (Scheme 1).



Scheme 1. General preparation of bisaminated 5-nitrosopyrimidines **4**.

Refluxing a mixture of **1**, the amine of choice and triethylamine,[1] or alternatively, two-fold excess of the amine in question in isopropyl alcohol according to literature methods[2] afforded the required aminopyrimidines **2a–h** for all the primary and secondary aliphatic amines employed

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Keywords: Pyrimidine; Nitrosation; Alkyl substituted; Aryl substituted.

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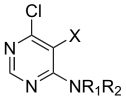
Table 1. Amination of **1** and nitrosation reactions of amines **2a**–**j**



2 X=H
3 X=NO

a R_1 = Me, R_2 = H
b R_1= Bn, R_2 = H
c R_1 = CH_2CH_2OH, R_2 = H
d R_1 = $CH(Bn)CO_2Me$, R_2 = H
e NR_1,R_2 = pyrrolidin-1-yl
f NR_1,R_2 = prolin-1-yl (Me ester)
g NR_1,R_2 = $-N(CH_3)_2$
h NR_1,R_2 = morpholin-1-yl
i NR_1,R_2 = 4-BrPhNH-
j NR_1,R_2 = 2-PyNH-

Amine	Amination of **1**		Nitrosation of **2a**–**i**	
	No.	Yield (%)	No.	Yield (%)/ method[a]
Methylamine	**2a**	75	**3a**	88/A
Benzylamine	**2b**	85	**3b**	90/B
Ethanolamine	**2c**	78	**3c**	80/A
L-Phenylalanine methyl ester	**2d**	11	**3d**	0/A
Pyrrolidine	**2e**	98	**3e**	0/A, B
L-Proline methyl ester	**2f**	83	**3f**	0/A, B
Dimethylamine	**2g**	Quant.	**3g**	0/A, B
Morpholine	**2h**	92	**3h**	0/B
4-Bromoaniline	**2i**	67	**3i**	0/A, C
2-Aminopyridine	**2j**	0[b]	**3j**	—

[a] A: Glacial AcOH, $NaNO_2$; B: concd HCl, $NaNO_2$; C: concd H_2SO_4, $NaNO_2$.
[b] Toluene, KOBu^t, 130 °C, sealed tube.

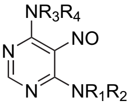
in generally good yield (Table 1). The aromatic amines used proved unpredictable, with 4-bromoaniline readily forming **2i**, while 2-aminopyridine refused to react with **1** even under forcing conditions (potassium *tert*-butoxide, toluene, pressure tube, 130 °C).

To facilitate the introduction of the second amine in **2a**–**i**, electrophilic substitution at C-5 with an electron-withdrawing group was attempted to activate the remaining C–Cl bond to nucleophilic displacement. Otherwise, forcing conditions need to be employed,[3] and we sought to avoid this if possible. In this instance, nitrosation was chosen due to the ease of introducing the group, and its facile reduction. Nitrosation was attempted under classical conditions[4] (glacial acetic acid or mineral acid, aqueous sodium nitrite, room temperature), with the nitroso products **3a**–**c** precipitating out of solution as brilliant yellow, water insoluble products in good yield, at least in the case of secondary amines **2a**–**c**. Surprisingly, phenylalaninyl derivative **2d** failed to react under these conditions. We assumed that this was due to its insolubility in the slightly aqueous medium used in that case, or possibly a slight attenuation of the amino group donor ability through the inductive effect of the adjacent carbonyl. In the instance of the tertiary amines **2e**–**h**, as well as *N*-aryl product **2i**, nitrosation failed. Similarly, when **2e**–**h** were treated with sodium nitrite in sulfuric acid in which *they remained soluble* in the presence of aqueous sodium nitrite, no reaction occurred, indicating that contact was not the issue.

Chlorides **3a**–**c** were subsequently treated with each of the desired secondary amines in dichloromethane at room temperature, smoothly generating the substituted 4,6-di-amino-5-nitrosopyrimidines **4a**–**g** (Table 2). The exceptions were products **4b** and **4g**, which were prepared by heating **3a** and **3c** in neat pyrrolidine at 150 °C for 1 h.

Mechanistically, the nitrosation requires the formation of an intermediate nitramine, with the migration of the nitroso group to the *ortho*- or *para*-position of an aromatic ring.[5] In the instance of a secondary amine, *ortho* substitution occurs, while tertiary anilines favour *direct* electrophilic nitrosation in the *para*-position without the intermediacy of a nitramine.[6] Inability to form the nitramine intermediate may be the reason for the failure of the nitrosation reaction in products **2e**–**h**, with direct *para*-substitution being precluded in this system. Nitramine generation from secondary arylamines using nitrous acid is also known.[5] A possible explanation for the failure of the reaction using **2i** may lie in the slightly poorer electrophilicity of the pyrimidine ring at C-5 due to the chlorine substituent at C-6. Furthermore, the lower basicity of the arylamine nitrogen at C-4 due to being bound to *two* aromatic rings may hinder the formation of a stable nitramine intermediate. Following this line of thought, it would appear that displacement of both the chlorine atoms first, and then nitrosation would avoid these difficulties in the case of amines **2e**–**i**.

Table 2. Aminations of chlorides **3a**–**c**



4

a R_1 = Me, R_2 = H, R_3,R_4 = $-NMe_2$
b R_1 = Me, R_2 = H, NR_3,R_4 = pyrrolidin-1-yl
c R_1 = Bn, R_2 = H, R_3,R_4 = $-NMe_2$
d R_1 = Bn, R_2 = H, NR_3,R_4 = pyrrolidin-1-yl
e R_1 = Bn, R_2 = H, NR_3,R_4 = morpholin-1-yl
f R_1 = CH_2CH_2OH, R_2 = H, R_3,R_4 = $-NMe_2$
g R_1 = CH_2CH_2OH, R_2 = H, NR_3,R_4 = pyrrolidin-1-yl

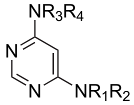
	Dimethylamine		Pyrrolidine		Morpholine	
	No.	Yield (%)	No.	Yield (%)	No.	Yield (%)
3a	**4a**	59	**4b**[a]	83	n/a	—
3b	**4c**	91	**4d**	94	**4e**	85
3c	**4f**	72	**4g**[a]	37	n/a	—

n/a=not attempted.
[a] Neat, 150 °C, 1h.

2.2. Generation of 4,6-diaminopyrimidines, and subsequent electrophilic substitution reactions

In the cases where nitrosation proved problematic, the displacement of the second chlorine moiety in **2e**–**i** was accomplished under forcing conditions (toluene, 130 °C, pressure tube, 18 h) using the required primary or secondary amines.[3]

When using secondary amines as nucleophiles for reaction with secondary amines **2a**–**d**, yields of 4,6-disubstituted pyrimidines **5a**–**f** were modest in most cases attempted, while the reaction with dimethylamine proving problematic due to its volatility (Table 3). In the instance of proline derivative **2d**, the corresponding amide **5e** was isolated from the reaction with pyrrolidine.



5

a R_1 = Me, R_2= H, NR_3,R_4 = morpholin-1-yl
b R_1 = Bn, R_2= H, NR_3,R_4 = morpholin-1-yl
c R_1 = CH_2CH_2OH, R_2 = H, NR_3,R_4 = morpholin-1-yl
d R_1 = Me, R_2 = H, NR_3,R_4 = pyrrolidin-1-yl
e R_1 = $-CH(Bn)CON(C_4H_8)$,
R_2 = H, NR_3,R_4 = pyrrolidin-1-yl
f R_1 = $-CH(Bn)CO_2Me$, R_2 = H, R_3 = R_4 = Me

Similarly, treating tertiary amines **2e** and **2f** with primary aliphatic amines gave modest yields of bisamines **6a**–**c** (Table 4). No reaction was noted for the poorly basic 2-aminopyridine or 4-bromoaniline in the absence of strong base, namely potassium *tert*-butoxide, affording bisamines **6d**–**f**

Table 3. Amination of secondary amines **2a–d**

Amine	2a		2b		2c		2d	
	No.	%	No.	%	No.	%	No.	%
Morpholine	**5a**[a]	77	**5b**[a,c]	55	**5c**[a]	75	n/a	—
Pyrrolidine	**5d**[a]	35	n/a	—	n/a	—	**5e**[b,d]	26
Dimethylamine	n/a	—	n/a	—	n/a	—	**5f**[b]	17

n/a=not attempted.

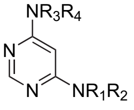
[a] Fused at 250 °C.

[b] Boiled in toluene in a sealed tube at 130 °C.

[c] Potassium *tert*-butoxide added.

[d] Isolated as the 2-hydroxyethyl amide.

Table 4. Amination of tertiary amines **2e** and **f**[a]



6

a R_1 = Bn, R_2 = H, R_3,R_4 = pyrrolidin-1-yl
b R_1= CH_2CH_2OH, R_2 = H, NR_3,R_4 = pyrrolidin-1-yl
c R_1 = CH_2CH_2OH, R_2 = H, R_3,R_4 = prolin-1-yl (ethanolamine amide)
d R_1 = 4-BrPh-, R_2 = H, NR_3,R_4 = pyrrolidin-1-yl
e R_1 = 4-BrPh-, R_2 = H, NR_3,R_4 = prolin-1-yl (free acid form)
f R_1 = 2-Py, R_2 = H, R_3,R_4 = pyrrolidin-1-yl

Amine	2e		2f	
	No.	Yield	No.	Yield
Benzylamine	**6a**	46	n/a	—
Ethanolamine	**6b**	50	**6c**[c]	54
4-Bromoaniline	**6d**[b]	37	**6e**[b,d]	20[a]
2-Aminopyridine	**6f**[b]	15[a]	n/a	—

n/a=not attempted.

[a] Boiled in toluene in a sealed tube at 130 °C.

[b] Potassium *tert*-butoxide added.

[c] Isolated as the pyrrolidin-1-yl amide.

[d] Isolated as the free acid.

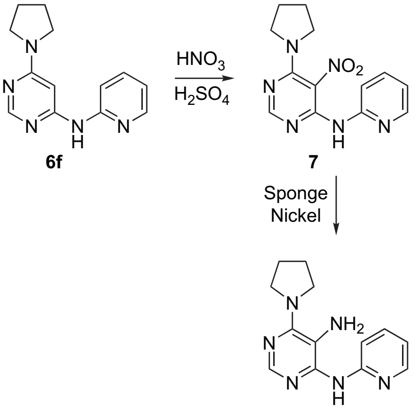
in poor yield. Under these conditions, the amination of **2f** afforded amide **6c** with ethanolamine, while the poorly basic 4-bromoaniline afforded the free acid **6e**.

It was reasoned that the presence of a secondary amine in products **5a–f** and **6a–f**, along with the additional electrophilic activation afforded by the second amino moiety, should be sufficient to allow electrophilic nitrosation to occur at C-5. However, attempted nitrosation of **6d** and **6e** as test cases failed in both acetic acid and concentrated mineral acid, despite their solubility in the latter case.

To assure ourselves of the nucleophilicity of pyrimidines **5a–f** and **6a–f**, a stronger electrophile was used as a test case (Scheme 2). Nitration of **6f** using 65% nitric acid in concentrated sulfuric acid afforded 5-nitropyrimidine **7** (83% yield). Reduction hereof in boiling ethanol using sponge nickel occurred readily, but the amino product decomposed when the filtrate was concentrated after removing the catalyst. This would therefore support the assumption that a stronger, softer electrophile would be better suited to react directly with these bisamines at C-5.

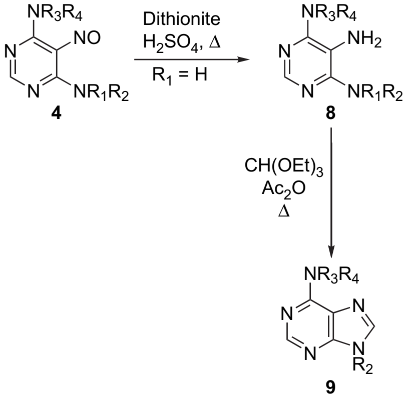
2.3. Reduction of 5-nitrosopyrimidines 4b–f, and ring closure of the amines

Reduction of nitroso products **4b–g** was readily accomplished by treating a warm mixture of the nitroso product



Scheme 2. Nitration of **6f** and reduction of the nitro group.

in aqueous sulfuric acid with sodium dithionite, affording a readily filterable solid (Scheme 3).

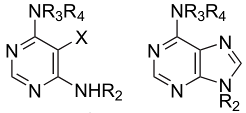


Scheme 3. Reduction and cyclisation of bisaminated 5-nitroso-pyrimidines **4b–g**.

Recrystallisation produced pure products **8b–g** in modest to good yields (Table 5). Portions of the resultant triamines **8b–g** were treated with triethyl orthoformate and acetic anhydride, producing purines **9a–e**. Ethanolamine derivatives **8e** and **8f** produced complex mixtures of products along with the desired systems, the mixtures were not purified sufficiently for conclusive characterisation.

Interestingly, the analysis of the chlorides **2a–h,j**, **3a–c** and **4a–f** proved problematic showing great instability under electrospray mass spectral conditions in most cases. This also adds credence to the observed reactivity of these

Table 5. Reduction of **4b–g** and cyclisation of the 5-amino compounds **8b–g**



4 X = NO
8 X = NH_2
9

b R_2 = Me, NR_3,R_4 = pyrrolidin-1-yl
c R_2= Bn, R_3,R_4 = -NMe_2
d R_2= Bn, NR_3,R_4 = pyrrolidin-1-yl
e R_2= Bn, NR_3,R_4 = morpholin-1-yl
f R_2 = CH_2CH_2OH, R_3,R_4 = -NMe_2
g R_2 = CH_2CH_2OH, NR_3,R_4 = pyrrolidin-1-yl

Nitroso product	Dithionite reduction		Cyclisation	
	No.	Yield (%)	No.	Yield (%)
4b	**8b**	86	**9b**	67
4c	**8c**	80	**9c**	88
4d	**8d**	87	**9d**	80
4e	**8e**	70	**9e**	68
4f	**8f**	54	**9f**	Mixture
4g	**8g**	71	**9g**	Mixture

structures in the above instances. Furthermore, the purines **9b–e** showed similar trends, consistently adding water under the mild ionisation conditions employed to afford stable formamides in the ion trap, along with detectable amounts of the product derived by the loss of formamide in all instances.

3. Conclusion

In summary, we have uncovered a series of unexpected and obscure effects influencing the electrophilic nitrosation of activated pyrimidines. These include structural factors (the inability of trisubstituted amino moieties to promote electrophilic nitrosation in the presence of a competing deactivator **2e–h**,**j** and in bisactivated cases **5a–f** and **6a–f**), despite the precedent for this with trisubstituted anilines, as well as possible electronic factors contributing to a similar inability with *N*-aryl substituted 4-aminopyrimidines. Interestingly, the presence of a C-6 *N*-alkyl amino moiety in **5a–f** and **6a–f** does not promote nitrosation in the presence of a C-4 *N*,*N*-dialkyl- or *N*-aryl group on the same pyrimidine system, despite the mechanistic precedent for the promotion of nitrosation in the presence of such functionality.

4. Experimental

4.1. General procedures

All starting materials used were commercially obtained and used as obtained from the supplier without further purification. Column chromatography was performed using Merck Kiesel gel 60 (particle size 0.040–0.063 mm), while thin layer chromatography was done on Merck aluminium-supported silica gel 60 F_{254}. NMR spectra were recorded on a Varian Gemini 200 NMR spectrometer operating at 200 MHz. Chemical shift data are recorded in parts per million, and coupling constants are quoted in hertz. HPLC data were recorded on a Waters Liquid Chromatograph system using a Varian 9050 UV–vis detector operating at 254 nm. All separations were done using a Phenomenex® Luna™ 5μ C-18(2) 150 mm×4.60 mm column using an isocratic elution system, detecting at 254 nm. Solvents used were either pure methanol (A) or 50% methanol: 25 mM aqueous ammonium acetate buffer at pH 4 (B) as indicated, eluting at a flow rate of 1 cm^3/min. Mass spectra were recorded in the ES+ mode using a 32 V source on a Waters LCT-Premiere TOF MS system with MassLynx V 4.1 software. Samples were dissolved in methanol containing reserpine (100 pg/μL) and recorded by direct infusion at a flow rate of 20 μL/min. The ion abundances were controlled by dilution or by altering the capillary voltages. Infrared spectra were recorded on a Bruker Tensor 22 system. Melting points were determined with a Reichert Hotstage microscope and are uncorrected. Standard workup refers to extraction with an organic solvent, followed by drying with magnesium sulfate, and vacuum distillation of the solvent on a rotary evaporator.

4.2. General method for the monoamination of 4,6-dichloropyrimidine (1)

A solution of **1** in isopropyl alcohol (1.0 M) containing either amine (2.1 equiv) or a mixture of amine (1.2 equiv) and triethylamine (1.2 equiv) was refluxed for 1–5 h, until all the starting material was consumed. The solvent was removed under vacuum, and the resulting viscous mass partitioned between water and ethyl acetate or dichloromethane. Extraction and standard workup, followed by column chromatography afforded the pure products. In this manner the following products were obtained:

4.2.1. 6-Chloro-*N*-methylpyrimidin-4-amine (2a).[7] Compound **1** (10.03 g, 67.12 mmol), isopropyl alcohol (168 cm^3), methylamine hydrochloride (5.06 g, 74.97 mmol) and triethylamine (10.3 cm^3, 73.8 mmol) afforded, after column chromatography using 10% ethyl acetate/hexane as eluent, **2a** (7.26 g, 75%) as a white crystalline solid. Recrystallised to white needles, mp 136–138 °C (hexane), lit.[7b] 137–138 °C (hexane); R_f (50% ethyl acetate/hexane) 0.42; ν_{max} (KBr pellet) 3253, 3111, 1627, 1574, 1434, 1388, 1331, 1228, 1145, 1099, 981, 893, 839, 747 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 8.33 (1H, s, H-2), 6.35 (1H, s, H-5), 5.72 (1H, br s, N*H*) and 2.94 (3H, d, NH*Me*, *J* 5.2); δ_C (50 MHz, $CDCl_3$) 164.0 (C-6), 160.8 (C-4), 158.2 (C-2), 101.3 (br, C-5) and 28.2 (NH*Me*); t_R 3.10 min (B); HRMS (ES): MH^+, found 144.0322. $C_5H_7ClN_3$ requires 144.0323.

4.2.2. *N*-Benzyl-6-chloropyrimidin-4-amine (2b).[3a,8] Compound **1** (10.04 g, 67.36 mmol), isopropyl alcohol (168 cm^3), benzylamine (8.07 cm^3, 73.84 mmol) and triethylamine (10.3 cm^3, 73.8 mmol) afforded, after column chromatography using 10% ethyl acetate/hexane as eluent, **2b** (12.66 g, 85%) as an orange solid. Recrystallised to white rhomboid needles, mp 119–120 °C (hexane), lit.[3a] 121 °C (ethyl acetate/petroleum ether); R_f (20% ethyl acetate/hexane) 0.26; ν_{max} (KBr pellet) 3218, 3073, 2991, 2857, 1594, 1494, 1400, 1346, 1314, 1156, 1099, 979, 936, 907, 824, 757, 740, 696 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 8.09 (1H, s, H-2), 7.19–7.43 (5H, m, aryl H), 6.42 (1H, br s, N*H*), 6.36 (1H, s, H-5) and 4.50 (2H, d, PhC*H*$_2$, *J* 5.4); δ_C (50 MHz, $CDCl_3$) 163.2 (C-6), 159.7 (C-4), 158.2 (C-2), 136.8 (quaternary aryl C), 128.8, 127.9 and 127.4 (aryl C), 101.9 (br, C-5) and 45.6 (Ph*C*H$_2$); t_R 14.28 min (B); *m*/*z* (ES) 221 (40), 220 (36, MH^+), 219 (100, M^+), 218 (65), 185 (15), 106 (96), 91 (98), 79 (37), 77 (19), 65 (49), 52 (23), 51 (27%); HRMS (ES): MH^+, found 220.0726. $C_{11}H_{11}ClN_3$ requires 220.0636.

4.2.3. 2-[(6-Chloropyrimidin-4-yl)amino]ethanol (2c).[9] Compound **1** (10.08 g, 67.64 mmol) in isopropyl alcohol (168 cm^3) containing ethanolamine (4.25 cm^3, 70.48 mmol) and triethylamine (10.3 cm^3, 73.8 mmol) afforded, after column chromatography using 10% ethyl acetate/hexane as eluent, **2c** (9.19 g, 78%) as a beige solid. Recrystallised to white needle clusters, mp 110–112 °C (ethyl acetate/hexane), lit.[9] 115–116 °C (ethyl acetate); R_f (ethyl acetate) 0.40; ν_{max} (KBr pellet) 3600–3100 (br), 2920, 1614, 1403, 1334, 1090, 997, 954, 910, 877, 817, 746, 689 cm^{-1}; δ_H (200 MHz, CDCl$_3$+DMSO-d_6) 8.22 (1H, s, H-2), 6.45 (1H, br s, N*H*), 6.35 (1H, s, H-5), 3.70 (2H, t, OC*H*$_2$, *J* 5.0) and 3.41 (3H, br s, O*H* and NHC*H*$_2$); δ_C (50 MHz, CDCl$_3$+DMSO-d_6) 163.8 (C-6), 158.4 (C-2 and C-4), 103.3 (br, C-5), 61.1 (O*C*H$_2$) and 44.2 (NH*C*H$_2$); t_R 2.40 min (B); HRMS (ES): MH$^+$, found 174.0482. $C_6H_9ClN_3O$ requires 174.0429.

4.2.4. Methyl (2*R*)-2-[(6-chloropyrimidin-4-yl)amino]-3-phenylpropanoate (2d).[10] Compound **1** (10.04 g, 67.38 mmol), isopropyl alcohol (168 cm^3), L-phenylalanine methyl ester hydrochloride [freshly prepared from L-phenylalanine (12.32 g, 74.57 mmol) in methanol (75 cm^3) that was treated with hydrogen chloride gas] and triethylamine (19.6 cm^3, 0.14 mol) afforded, after column chromatography using 10–20% ethyl acetate/hexane as eluent, **2d** (2.08 g, 11%) as an orange oil; R_f (20% ethyl acetate/hexane) 0.28; ν_{max} (solid ATR) 3241, 3091, 2953, 1743, 1572, 1498, 1455, 1236, 1116, 1091, 842, 756, 695 cm^{-1}; δ_H (200 MHz, CDCl$_3$) 8.35 (1H, s, H-2), 7.01–7.35 (5H, m, aryl H), 6.36 (1H, s, H-5), 5.79 (1H, br d, N*H*, *J* 7.6), 4.68–5.21 (1H, br m, C*H*CO), 3.75 (3H, s, OC*H*$_3$) 3.24 (1H, dd, PhCH_aH$_b$, *J* 5.6 and 13.8) and 3.41 (1H, dd, PhCH$_a$$H_b$, *J* 6.4 and 14.0); δ_C (50 MHz, CDCl$_3$) 172.0 (*C*O), 162.1 (C-6), 159.1 (C-4), 158.3 (C-2), 135.5 (quaternary aryl C), 129.1, 128.5 and 127.1 (aryl C), 103.9 (br, C-5), 54.6 (O*C*H$_3$), 52.3 (Ph*C*H$_2$) and 37.8 (*C*HCO); t_R 1.87 min (A); *m*/*z* (ES) 291 (6, M$^+$), 234 (26, MH$^+$−CO$_2$Me), 232 (75), 202 (60), 200 (98), 168 (26), 163 (27), 162 (100), 142 (37), 140 (79), 131 (23), 129 (22), 113 (51), 103 (29), 91 (70), 77 (21), 65 (23), 51 (19%); HRMS (ES): MH$^+$, found 292.0944. $C_{14}H_{15}ClN_3O_2$ requires 292.0853.

4.2.5. 6-Chloro-4-pyrrolidin-1-ylpyrimidine (2e). Compound **1** (15.00 g, 0.10 mol), pyrrolidine (9.37 cm^3, 0.112 mol) and triethylamine (17.1 cm^3, 0.12 mol) in isopropyl alcohol (100 cm^3) were treated as per the general method. Column chromatography (using 10–20% ethyl acetate/hexane as eluent) afforded beige crystals of **2e** (17.85 g, 98%). Recrystallised to white needles, mp 93–94 °C (ethyl acetate/hexane); R_f (20% ethyl acetate/hexane) 0.28; ν_{max} (KBr pellet) 2984, 2871, 1593, 1494, 1416, 1349, 1326, 1177, 1094, 1012, 964, 811, 742 cm^{-1}; δ_H (200 MHz, CDCl$_3$) 8.36 (1H, s, H-2), 6.25 (1H, s, H-5), 3.58 and 3.31 [4H, 2 overlapping br s, N(C*H*$_2$)$_2$] and 2.12 [4H, br s, (C*H*$_2$)$_2$]; δ_C (50 MHz, CDCl$_3$) 160.9 (C-6), 158.9 (C-4), 158.0 (C-2), 101.0 (C-5), 46.3 [N(*C*H$_2$)$_2$] and 25.3 [(*C*H$_2$)$_2$]; t_R 7.13 min (B); *m*/*z* (ES) 185 (21), 183 (48, M$^+$), 156 (39), 155 (63), 154 (100), 121 (18), 120 (33), 70 (27), 52 (18%); HRMS (ES): MH$^+$, found 184.0676. $C_8H_{11}ClN_3$ requires 184.0642.

4.2.6. Methyl 1-(6-chloropyrimidin-4-yl)pyrrolidine-2-carboxylate (2f).[11] A solution of L-proline (14.26 g, 0.12 mol) in methanol (100 cm^3) was treated with hydrogen chloride gas for 30 min, then left to stir for 1 h. The solution was then concentrated to dryness, and the methyl ester hydrochloride was used without characterisation. A solution hereof, **1** (15.01 g, 0.10 mol) and triethylamine (31.3 cm^3, 0.23 mol) in isopropyl alcohol (100 cm^3) was treated as per the general method. Chromatography (using 20% ethyl acetate/hexane as eluent) afforded **2f**, a viscous orange oil (19.74 g, 81%); R_f (20% ethyl acetate/hexane) 0.29; δ_H (200 MHz, CDCl$_3$) 8.39 (1H, s, H-2), 6.39 (1H, br s, H-5), 4.63 (1H, br s, COC*H*), 3.73 (3H, s, O*Me*), 3.81–3.28 (2H, two overlapping br s, NC*H*$_2$) and 2.41–1.95 [4H, m, (C*H*$_2$)$_2$]; δ_C (50 MHz, CDCl$_3$) 172.8 (*C*O), 160.9 (C-6), 159.8 (C-4), 158.0 (C-2), 101.2 (C-5), 59.8 (O*Me*), 52.2 (CO*C*H), 46.5 (N*C*H$_2$), 30.1 and 24.1 [(*C*H$_2$)$_2$]; t_R 5.27 min (B). The product could not be purified sufficiently and was used as-is without further characterisation.

4.2.7. 6-Chloro-*N*,*N*-dimethylpyrimidin-4-amine (2g).[12] Compound **1** (15.03 g, 0.10 mol), dimethylamine (60% in water, 9.20 cm^3, 0.12 mol) and triethylamine (17.07 cm^3, 0.12 mol) in isopropyl alcohol (100 cm^3) were treated as per the general method. Chromatography (using 10–20% ethyl acetate/hexane as eluent) afforded beige crystals of **2g** (16.73 g, quant.). Recrystallised to white blocks, mp 99–100 °C (ethyl acetate/hexane), lit.[12b] 102–103 °C (heptane); R_f (20% ethyl acetate/hexane) 0.29; ν_{max} (KBr pellet) 3080, 2932, 1582, 1499, 1398, 1344, 1299, 1184, 1107, 989, 966, 858, 738 cm^{-1}; δ_H (200 MHz, CDCl$_3$) 8.38 (1H, s, H-2), 6.39 (1H, s, H-5) and 3.14 (6H, s, N*Me*$_2$); δ_C (50 MHz, CDCl$_3$) 159.2 (C-6), 158.9 (C-4), 158.0 (C-2), 101.3 (C-5) and 37.8 (N*Me*$_2$); t_R 4.48 min (B); HRMS (ES): MH$^+$, found 158.0490. $C_6H_9ClN_3$ requires 158.0485.

4.2.8. 4-(6-Chloropyrimidin-4-yl)morpholine (2h).[12a] Compound **1** (15.00 g, 0.10 mol) and morpholine (18.00 g, 0.21 mol) in isopropyl alcohol (100 cm^3) were treated as per the general method. Concentration of the extract afforded a crystalline solid. This was washed on a Büchner funnel with saturated aqueous sodium bicarbonate, followed by the minimum of ethyl acetate to remove water to yield beige crystals of **2h** (18.30 g, 92%). Recrystallised to white needles, mp 154–155 °C (ethyl acetate/hexane), lit.[12a] 151–152 °C (ethyl acetate/hexane); R_f (20% ethyl acetate/hexane) 0.26; ν_{max} (KBr pellet) 3070, 2970, 2870, 1584, 1526, 1492, 1343, 1112, 982, 856 cm^{-1}; δ_H (200 MHz, CDCl$_3$) 8.39 (1H, s, H-2), 6.48 (1H, s, H-5), 3.91–3.72 [4H, m, O(C*H*$_2$)$_2$] and 3.70–3.41 [4H, m, N(C*H*$_2$)$_2$]; δ_C (50 MHz, CDCl$_3$) 162.6 (C-6), 160.2 (C-4), 158.0 (C-2), 101.4 (C-5), 66.3 [O(*C*H$_2$)$_2$] and 44.2 [N(*C*H$_2$)$_2$]; t_R 1.91 min (A); *m*/*z* (ES) 201 (20), 200 (17), 199 (58, M$^+$), 198 (38), 170 (38), 169 (25), 168 (93), 156 (25), 154 (27), 142 (67), 116 (31), 114 (100), 87 (33), 86 (24), 52 (25%); HRMS (ES): MH$^+$, found 200.0633. $C_8H_{11}ClN_3O$ requires 200.0591.

4.2.9. *N*-(4-Bromophenyl)-6-chloropyrimidin-4-amine (2i).[13] Compound **1** (9.98 g, 67.01 mmol) in isopropyl alcohol (168 cm^3) containing 4-bromoaniline (12.10 g, 69.50 mmol) and triethylamine (10.3 cm^3, 73.8 mmol) was heated as per the general procedure. An equal volume of water and ethyl acetate were then added, and the resultant suspension filtered off to yield **2i** (12.73 g, 67%) as a beige powder. Recrystallised to a beige powder, mp 220–222 °C (ethyl acetate/hexane); R_f (20% ethyl acetate/hexane) 0.35; ν_{max} (KBr pellet) 3286, 3152, 3066, 1628, 1596, 1569, 1505, 1488, 1456, 1403, 1327, 1284, 1265, 1228, 1096, 1073, 986, 845, 824, 808, 766 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 9.11 (1H, br s, H-2), 8.05 (1H, s, N*H*), 7.17 (2H, d, aryl H, *J* 8.8), 7.05 (2H, d, aryl H, *J* 9.0) and 6.40 (1H, s, H-5); δ_C (50 MHz, $CDCl_3$+DMSO-d_6) 169.4 (C-6), 161.9 (C-4), 158.1 (C-2), 137.6 (quaternary aryl C), 131.7 and 122.7 (aryl C), 116.3 (quaternary aryl C) and 104.6 (C-5); t_R 2.15 min (A); *m/z* (ES) 286 (34), 285 (68), 284 (100, M$^+$), 283 (55), 282 (87%); HRMS (ES): M$^+$, found 284.1569. $C_{10}H_7{}^{81}Br^{35}ClN_3$ requires 284.9491.

4.3. General method for the nitrosation of pyrimidines

A solution of the pyrimidine in either acetic acid or hydrochloric acid (2 M) was treated dropwise with a solution of sodium nitrite (1.8 equiv) in water (6.3 M). Evolution of a brown gas occurs during addition, and a solid precipitate forms over time. The solid is filtered off, washed with water and dried under suction. In this manner, the following products were obtained.

4.3.1. 6-Chloro-*N*-methyl-5-nitrosopyrimidin-4-amine (3a). Chloride **2a** (7.26 g, 50.58 mmol) in acetic acid (26 cm^3) was treated with a solution of sodium nitrite (6.31 g, 91.38 mmol) in water (84 cm^3) dropwise over 30 min. After stirring for 2 h, **3a** was filtered off (7.68 g, 88%) as a yellow powder. Recrystallised to yellow rhomboid blocks, mp 76–78 °C (hexane); R_f (20% ethyl acetate/hexane) 0.59; ν_{max} (KBr pellet) 3095, 1568, 1490, 1455, 1212, 1145, 1079, 957, 888, 781 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 8.83 (1H, s, H-2), 8.06 (1H, s, N*H*) and 3.45 (3H, s, NH*Me*); δ_C (50 MHz, $CDCl_3$) 161.9 (C-4 and C-6), 158.4 (C-2), 107.9 (C-5) and 27.6 (NH*Me*); t_R 9.10 min (B); *m/z* (ES) 173 (1, MH$^+$), 146 (33, MH$^+$−NO), 145 (21), 144 (100, M$^+$−NO), 143 (39), 130 (18%).

4.3.2. *N*-Benzyl-6-chloro-5-nitrosopyrimidin-4-amine (3b). Chloride **2b** (12.48 g, 56.82 mmol) in concentrated hydrochloric acid (28 cm^3) was treated with sodium nitrite (7.11 g, 0.10 mol) in water (95 cm^3) dropwise over 30 min. The pale beige powder that deposited over 18 h was isolated, affording **3b** (12.75 g, 90%). Recrystallised to small yellow rhomboid blocks, mp 110–112 °C (hexane); R_f (20% ethyl acetate/hexane) 0.64; ν_{max} (KBr pellet) 3093, 1568, 1497, 1458, 1410, 1392, 1128, 1058, 926, 887, 710 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 8.91 (1H, br s, H-2), 8.08 (1H, s, N*H*), 7.29 (5H, br s, aryl H) and 5.37 (2H, s, PhC*H*$_2$); δ_C (50 MHz, $CDCl_3$) 162.1 (C-4 and C-6), 158.4 (C-2), 134.2 (quaternary aryl C), 128.6, 128.3 and 127.9 (aryl C), 108.0 (C-5) and 43.6 (Ph*C*H$_2$); t_R 2.12 min (A); *m/z* (ES) 222 (23), 221 (26), 220 (100), 219 (65, MH$^+$−NO), 218 (80), 106 (12%).

4.3.3. 2-[(6-Chloro-5-nitrosopyrimidin-4-yl)amino]ethanol (3c). Chloride **2c** (9.19 g, 52.96 mmol) in acetic acid (26 cm^3), sodium nitrite (6.65 g, 96.32 mol) and water (132 cm^3) were treated as before. The solids that formed over 18 h were isolated, and the solution extracted with ethyl acetate. The organic phase was washed with 2 M aqueous sodium hydroxide and partially concentrated to an orange oil. This was seeded, and combined with the filtered solids to afford **3c** (8.54 g, 80%) as a pale orange powder. Recrystallised to clumps of yellow blocks, mp 79–80 °C (hexane); R_f (20% ethyl acetate/hexane) 0.18; ν_{max} (KBr pellet) 3377, 3094, 1569, 1455, 1384, 1138, 1080, 1054, 978, 803 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 8.86 (1H, br s, H-2), 8.05 (1H, s, N*H*), 4.36 (2H, t, OC*H*$_2$, *J* 5.5), 3.73 (2H, t, NHC*H*$_2$, *J* 5.6) and 2.25 (1H, br s, O*H*); δ_C (50 MHz, $CDCl_3$) 162.5 (C-6), 158.2 (C-2 and C-4), 108.1 (C-5), 59.6 (O*C*H$_2$) and 42.7 (NH*C*H$_2$); t_R 4.52 min (A); *m/z* (ES) 203 (14, M$^+$), 176 (19), 174 (58, MH$^+$−NO), 172 (25), 156 (8), 145 (32), 144 (38), 143 (100), 142 (98), 130 (28%); HRMS (ES): MH$^+$−NO, found 174.0468. $C_6H_9ClN_3O$ requires 174.0434.

4.4. General method for the amination of 5-nitrosopyrimidines 3a–c

A mixture of the pyrimidine in dichloromethane (2 M) was treated with 2 equiv of the amine required dropwise, resulting in spontaneous heating. The mixture was stirred for 18 h at room temperature. The resultant solution was concentrated and purified by column chromatography. In this manner, the following products were obtained.

4.4.1. *N*,*N*,*N*′-Trimethyl-5-nitrosopyrimidine-4,6-diamine (4a). Pyrimidine **3a** (0.97 g, 5.65 mmol), dichloromethane (2.9 cm^3) and dimethylamine (33% in alcohol, 1.74 cm^3, 12.75 mmol) afforded, after column chromatography using 10–30% ethyl acetate/hexane as eluent, a yellow solid, **4a** (0.60 g, 59%) by the general method. Recrystallised to beige blocks, mp 91–92 °C (ethyl acetate/hexane); R_f (20% ethyl acetate/hexane) 0.42; ν_{max} (KBr pellet) 2930, 1599, 1560, 1459, 1438, 1308, 1185, 1098, 1007, 975, 951, 833, 727 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 8.52 (1H, s, H-2), 7.02 (1H, s, N*H*), 3.47 (3H, s, NC*H*$_3$) and 3.18 [6H, s, N(C*H*$_3$)$_2$]; δ_C (50 MHz, $CDCl_3$) 163.1 (C-6), 160.1 (C-4), 157.4 (C-2), 87.4 (C-5), 37.5 [N(*C*H$_3$)$_2$] and 28.0 (NH*C*H$_3$); HRMS (ES): MH$^+$−NO, found 153.1136. $C_7H_{12}N_4$ requires 153.1140.

4.4.2. *N*-Methyl-5-nitroso-6-pyrrolidin-1-ylpyrimidin-4-amine (4b). Pyrimidine **3a** (0.97 g, 5.61 mmol) and neat pyrrolidine (1.16 cm^3, 13.91 mmol) was heated to 150 °C for 1 h. The resultant black solution was purified by chromatography using 10–30% ethyl acetate/hexane as eluent to yield a yellow solid, **4b** (0.97 g, 83%). Recrystallised to yellow rhomboid plates, mp 93–95 °C (ethyl acetate/hexane); R_f (20% ethyl acetate/hexane) 0.28; ν_{max} (KBr pellet) 3048, 2974, 2868, 1598, 1552, 1510, 1442, 1333, 1300, 1237, 1183, 1153, 1099, 1051, 1021, 960, 861, 819, 788, 728 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 8.44 (1H, s, H-2), 6.80 (1H, s, N*H*), 3.48 [4H, br s, N(C*H*$_2$)$_2$], 3.40 (3H, s, NHC*H*$_3$) and 1.78–2.13 [4H, br m, (C*H*$_2$)$_2$]; δ_C (50 MHz, $CDCl_3$) 160.7 (C-6), 159.5 (C-4), 157.8 (C-2), 88.1 (C-5), 46.5 [N(*C*H$_2$)$_2$], 27.8 (NH*C*H$_3$) and 25.1 [(*C*H$_2$)$_2$]; t_R 11.57 min (B); *m/z* (ES) 208 (1, MH$^+$), 180 (10), 179 (100), 178 (89, MH$^+$−NO), 177 (49, M$^+$−NO), 150 (51), 149 (15), 123 (12%).

4.4.3. *N*-Benzyl-*N*′,*N*′-dimethyl-5-nitrosopyrimidin-4,6-diamine (4c). Pyrimidine **3b** (0.51 g, 2.04 mmol), dichloromethane (1 cm^3) and dimethylamine (33% in alcohol, 1.00 cm^3, 7.32 mmol) afforded, after column chromatography using 10–30% ethyl acetate/hexane as eluent, a pale yellow solid, **4c** (0.48 g, 91%) by the general method. Recrystallised to clusters of yellow needles, mp 84–85 °C (ethyl acetate/hexane); R_f (20% ethyl acetate/hexane) 0.39; ν_{max} (KBr pellet) 3032, 2995, 2930, 1613, 1446, 1197, 1112, 995, 937, 895, 857, 818, 715 cm^{-1}; δ_H (200 MHz, CDCl$_3$) 8.57 (1H, s, H-2), 7.21–7.31 (5H, m, aryl H), 7.05 (1H, s, N*H*), 5.39 (2H, s, PhC*H*$_2$) and 3.18 [6H, s, N(C*H*$_3$)$_2$]; δ_C (50 MHz, CDCl$_3$) 163.2 (C-6), 159.9 (C-4), 157.5 (C-2), 135.1 (quaternary aryl C), 128.3, 128.2 and 127.4 (aryl C), 87.6 (C-5), 43.7 (Ph*C*H$_2$) and 37.5 [N(*C*H$_3$)$_2$]; t_R 2.17 min (A); HRMS (ES): MH$^+$, found 258.1362. $C_{13}H_{16}N_5O$ requires 258.1355.

4.4.4. *N*-Benzyl-5-nitroso-6-pyrrolidin-1-ylpyrimidin-4-amine (4d). Pyrimidine **3b** (0.50 g, 2.00 mmol), dichloromethane (1 cm^3) and pyrrolidine (0.34 cm^3, 4.02 mmol) afforded, after column chromatography using 10–30% ethyl acetate/hexane as eluent, a pale yellow solid, **4d** (0.53 g, 94%) by the general method. Recrystallised to clusters of yellow needles, mp 126–127 °C (ethyl acetate/hexane); R_f (20% ethyl acetate/hexane) 0.36; ν_{max} (KBr pellet) 3035, 2974, 2866, 1598, 1549, 1509, 1475, 1439, 1333, 1319, 1219, 1097, 1078, 1051, 1007, 900, 822, 749, 722, 703 cm^{-1}; δ_H (200 MHz, CDCl$_3$) 8.56 (1H, s, H-2), 7.15–7.31 (5H, m, aryl H), 6.90 (1H, s, N*H*), 5.39 (2H, s, PhC*H*$_2$), 3.53 [4H, br s, N(C*H*$_2$)$_2$] and 1.87–2.21 [4H, br m, (C*H*$_2$)$_2$]; δ_C (50 MHz, CDCl$_3$) 160.9 (C-6), 159.4 (C-4), 157.7 (C-2), 135.1 (quaternary aryl C), 128.3, 128.1 and 127.3 (aryl C), 88.5 (C-5), 46.7 [N(*C*H$_2$)$_2$], 43.6 (Ph*C*H$_2$) and 25.2 [(*C*H$_2$)$_2$]; t_R 2.28 min (A); HRMS (ES): MH$^+$, found 284.1519. $C_{15}H_{18}N_5O$ requires 284.1511.

4.4.5. *N*-Benzyl-6-morpholin-4-yl-5-nitrosopyrimidin-4-amine (4e). A mixture of pyrimidine **3b** (1.46 g, 5.87 mmol) in dichloromethane (10 cm^3) was treated with morpholine (1.23 g, 14.1 mmol) dropwise, resulting in spontaneous heating. The mixture was stirred overnight at room temperature. The resultant deep yellow solution was poured into ethyl acetate (20 cm^3) and washed with an equal volume of water. The solvent was removed to generate a sticky solid that was triturated in hexane. Compound **4e** was collected as a yellow solid by filtration (1.42 g, 85%). Recrystallised to yellow needles, mp 122–124 °C (ethyl acetate/hexane); R_f (20% ethyl acetate/hexane) 0.33; ν_{max} (solid ATR) 2868, 1658, 1438, 1221, 1102, 980, 901, 827, 694 cm^{-1}; δ_H (200 MHz, CDCl$_3$) 8.60 (1H, s, H-2), 7.26 (5H, br s, aryl H), 7.14 (1H, s, N*H*), 5.39 (2H, s, PhC*H*$_2$), 3.80 [4H, m, O(C*H*$_2$)$_2$] and 3.72 [4H, m, N(C*H*$_2$)$_2$]; δ_C (50 MHz, CDCl$_3$) 163.5 (C-6), 161.0 (C-4), 157.5 (C-2), 135.0 (quaternary aryl C), 128.7, 128.5 and 127.7 (aryl C), 87.8 (C-5), 66.5 [O(*C*H$_2$)$_2$], 45.0 [N(*C*H$_2$)$_2$] and 43.5 (Ph*C*H$_2$); t_R 2.11 min (A). Used without further characterisation.

4.4.6. 2-{[6-(Dimethylamino)-5-nitroso-pyrimidin-4-yl]amino}ethanol (4f). Pyrimidine **3c** (1.02 g, 5.03 mmol), dichloromethane (2.5 cm^3) and dimethylamine (33% in alcohol, 1.48 cm^3, 10.86 mmol) afforded, after column chromatography using 20–50% ethyl acetate/hexane as eluent, a yellow solid, **4f** (0.76 g, 72%) by the general method. Recrystallised to yellow needles, mp 76–78 °C (ethyl acetate/hexane); R_f (50% ethyl acetate/hexane) 0.28; ν_{max} (KBr pellet) 3309, 2885, 1602, 1523, 1443, 1410, 1333, 1202, 1122, 1094, 1058, 1013, 983, 864, 840, 814, 762 cm^{-1}; δ_H (200 MHz, CDCl$_3$) 8.48 (1H, s, H-2), 6.97 (1H, s, N*H*), 4.30 (2H, t, OC*H*$_2$, *J* 4.9), 3.69 (2H, t, NHC*H*$_2$, *J* 4.9) and 3.19 [6H, s, N(C*H*$_3$)$_2$]; δ_C (50 MHz, CDCl$_3$) 163.1 (C-6), 159.9 (C-4), 157.0 (C-2), 88.0 (C-5), 60.3 (O*C*H$_2$), 44.1 (NH*C*H$_2$) and 37.5 [N(*C*H$_3$)$_2$]; t_R 3.87 min (B); HRMS (ES): MH$^+$, found 212.1154. $C_8H_{14}N_5O_2$ requires 212.1147.

4.4.7. 2-[(5-Nitroso-6-pyrrolidin-1-ylpyrimidin-4-yl)amino]ethanol (4g). Pyrimidine **3c** (0.96 g, 4.76 mmol) and neat pyrrolidine (0.98 cm^3, 11.85 mmol) were heated to 150 °C for 1 h. The resultant black solution was purified by chromatography using 20–50% ethyl acetate/hexane as eluent to afford a beige solid, **4g** (0.41 g, 37%). Recrystallised to yellow needles, mp 162–164 °C (ethyl acetate/hexane); R_f (50% ethyl acetate/hexane) 0.26; ν_{max} (KBr pellet) 3220, 3102, 2994, 2965, 2868, 2824, 1736, 1589, 1479, 1442, 1253, 1234, 1115, 1097, 1012, 978, 904, 803, 750, 702 cm^{-1}; δ_H (200 MHz, CDCl$_3$) 8.49 (1H, s, H-2), 6.84 (1H, s, N*H*), 4.31 (2H, ca. t, OC*H*$_2$, *J* 4.8), 3.70 (2H, ca. t, NHC*H*$_2$, *J* 4.9), 3.11–3.85 [4H, br m, N(C*H*$_2$)$_2$] and 1.82–2.23 [4H, br m, (C*H*$_2$)$_2$]; δ_C (50 MHz, CDCl$_3$) 160.9 (C-6), 159.5 (C-4), 157.3 (C-2), 89.0 (C-5), 60.4 (O*C*H$_2$), 46.8 [br, N(*C*H$_2$)$_2$], 44.1 (NH*C*H$_2$) and 25.3 [br, (*C*H$_2$)$_2$]; t_R 6.43 min (B); *m*/*z* (ES) 237 (2, M$^+$), 207 (28), 178 (28), 177 (100), 164 (19), 149 (27), 148 (22), 147 (19), 136 (19), 135 (18), 121 (30), 79 (20), 70 (32), 67 (17%); HRMS (ES): MH$^+$, found 238.1348. $C_{10}H_{16}N_5O_2$ requires 238.1304.

4.5. General method for the amination of chloropyrimidines 2a–f

A mixture of the chloride and the required amine (2.1 equiv) were either fused at 250 °C for 1 h or boiled in toluene (0.5 M) in a sealed tube at 130 °C for 18 h. Partitioning between water and ethyl acetate, drying and concentration, followed by column chromatography, affording the following products.

4.5.1. *N*-Methyl-6-morpholin-4-ylpyrimidin-4-amine (5a). Chloride **2a** (1.45 g, 10.11 mmol) and morpholine (2.28 cm^3, 22.23 mmol) were fused, affording a yellow powder, **5a** (1.51 g, 77%) after chromatography with 30–50% ethyl acetate/hexane. Recrystallised to fine beige needles, mp 130–132 °C (ethyl acetate/hexane); R_f (ethyl acetate) 0.21; ν_{max} (KBr pellet) 3249, 3102, 2968, 2856, 1599, 1442, 1234, 1112, 992, 801 cm^{-1}; δ_H (200 MHz, CDCl$_3$) 8.14 (1H, s, H-2), 5.37 (1H, s, H-5), 5.05 (1H, br s, N*H*), 3.77 [4H, t, O(C*H*$_2$)$_2$, *J* 4.9], 3.54 [4H, t, N(C*H*$_2$)$_2$, *J* 4.9] and 2.87 (3H, d, NHC*H*$_3$, *J* 5.2); δ_C (50 MHz, CDCl$_3$) 163.7 and 163.1 (C-4 and C-6), 157.2 (C-2), 79.9 (C-5), 66.5 [O(*C*H$_2$)$_2$], 44.5 [N(*C*H$_2$)$_2$] and 28.4 (NH*C*H$_3$); t_R 2.11 min (B); *m*/*z* (ES) 194 (100, M$^+$), 193 (25), 164 (49), 163 (94), 149 (49), 137 (88), 136 (26), 109 (88), 82 (33), 81 (24), 57 (21%); HRMS (ES): MH$^+$, found 195.1267. $C_9H_{15}N_4O$ requires 195.1246.

4.5.2. *N*-Benzyl-6-morpholin-4-ylpyrimidin-4-amine (5b).[8a] Chloride **2b** (2.29 g, 10.44 mmol) and morpholine (2.00 cm^3, 23.00 mmol) in the presence of potassium *tert*-butoxide (1.28 g, 11.48 mmol) were fused at 250 °C for

1 h. This was taken up in ethyl acetate (50 cm^3), washed with water (50 cm^3), dried (MgSO$_4$) and concentrated to a brown gum. Column chromatography (20–50% ethyl acetate/hexane as eluent) afforded a tacky yellow solid. This was dissolved in acetone, and the solid precipitated with hexane to afford **5b**, a yellow powder (1.56 g, 55%). Recrystallised to a beige powder, mp 160–162 °C (ethyl acetate/hexane); R_f (50% ethyl acetate/hexane) 0.21; ν_{max} (KBr pellet) 3220, 3102, 2994, 2965, 2868, 2824, 1588, 1442, 1233, 1204, 1115, 1012, 978, 904, 803, 766, 750, 702 cm^{-1}; δ_H (200 MHz, CDCl$_3$) 8.16 (1H, s, H-2), 7.48–7.05 (5H, m, aryl H), 5.39 (2H, br m, H-5 and N*H*), 4.46 (2H, d, PhC*H*$_2$, *J* 6.0), 3.74 [4H, t, O(C*H*$_2$)$_2$, *J* 4.9] and 3.48 [4H, t, N(C*H*$_2$)$_2$, *J* 4.9]; δ_C (50 MHz, CDCl$_3$) 162.9 and 162.8 (C-4 and C-6), 157.3 (C-2), 138.0 (quaternary phenyl C), 128.8, 127.5 and 127.2 (phenyl CH), 81.0 (C-5), 66.5 [O(*C*H$_2$)$_2$], 45.8 (Ph*C*H$_2$) and 44.5 [N(*C*H$_2$)$_2$]; t_R 6.82 min (B); HRMS (ES): MH$^+$, found 271.1553. $C_{15}H_{19}N_4O$ requires 271.1559.

4.5.3. 2-[(6-Morpholin-4-ylpyrimidin-4-yl)amino]ethanol (5c). Chloride **2c** (1.88 g, 10.84 mmol) and morpholine (2.08 cm^3, 23.84 mmol) were fused and purified by column chromatography [10–20% methanol/ethyl acetate as eluent]. This afforded a waxy beige solid **5c** (1.82 g, 75%). Recrystallised to a beige powder, mp 123–124 °C (ethyl acetate/hexane); R_f (10% methanol/ethyl acetate) 0.35; ν_{max} (KBr pellet) 3500–3100 (br), 3355, 2963, 2858, 1598, 1543, 1491, 1448, 1230, 1115, 1060, 992, 782 cm^{-1}; δ_H (200 MHz, CDCl$_3$) 7.96 (1H, s, H-2), 5.65 (1H, br m, N*H*), 5.35 (1H, s, H-5), 4.68 (1H, br s, O*H*), 3.59 [6H, t and obscured m, O(C*H*$_2$)$_2$, *J* 4.8 and C*H*$_2$OH], 3.34 [4H, t, N(C*H*$_2$)$_2$, *J* 4.9] and 3.24 (2H, q, NHC*H*$_2$, *J* 5.0); δ_C (50 MHz, CDCl$_3$) 169.2 and 162.4 (C-4 and C-6), 156.8 (C-2), 81.2 (C-5), 66.1 [O(*C*H$_2$)$_2$], 61.0 (*C*H$_2$OH), 44.1 [N(*C*H$_2$)$_2$] and 43.8 (NH*C*H$_2$); t_R 1.91 min (B); HRMS (ES): MH$^+$, found 225.1354. $C_{10}H_{17}N_4O$ requires 225.1352.

4.5.4. *N*-Methyl-6-pyrrolidin-1-ylpyrimidin-4-amine (5d). Chloride **2a** (1.45 g, 10.11 mmol) and pyrrolidine (1.86 cm^3, 22.24 mmol) were fused. Column chromatography (10% methanol/ethyl acetate as eluent) afforded **5d**, a pale brown solid (0.63 g, 35%). Recrystallised to a beige powder, mp 180–181 °C (ethyl acetate/hexane); R_f (10% methanol/ethyl acetate) 0.44; ν_{max} (KBr pellet) 2858, 1539, 1148, 1099, 1021, 973, 795, 698 cm^{-1}; δ_H (200 MHz, CDCl$_3$) 8.11 (1H, s, H-2), 5.13 (1H, s, H-5), 4.89 (1H, br s, N*H*), 3.52–3.28 [4H, m, O(C*H*$_2$)$_2$], 2.85 (3H, d, NHC*H*$_3$, *J* 5.2) and 2.09–1.81 [4H, m, N(C*H*$_2$)$_2$]; δ_C (50 MHz, CDCl$_3$) 162.8 and 160.7 (C-4 and C-6), 157.2 (C-2), 79.5 (C-5), 46.3 [O(*C*H$_2$)$_2$], 28.5 (NH*C*H$_3$) and 25.3 [N(*C*H$_2$)$_2$]; t_R 2.25 min (B); HRMS (ES): MH$^+$, found 179.1292. $C_9H_{15}N_4$ requires 179.1297.

4.5.5. *N*-(1-Benzyl-2-oxo-2-pyrrolidin-1-ylethyl)-6-pyrrolidin-1-ylpyrimidin-4-amine (5e). Chloride **2d** (1.00 g, 3.43 mmol) and pyrrolidine (0.57 cm^3, 6.89 mmol) in toluene (7 cm^3) afforded an orange solid, **5e** (0.33 g, 26%) after chromatography (ethyl acetate to 10% methanol/ethyl acetate as eluent). Recrystallised to a beige powder, mp 170–171 °C (ethyl acetate/hexane; dec.); R_f (10% methanol/ethyl acetate) 0.63; ν_{max} (KBr pellet) 3261, 3156, 2953, 2874, 1629, 1572, 1503, 1456, 1343, 1285, 1225, 1173, 973, 804, 740, 700 cm^{-1}; δ_H (200 MHz, CDCl$_3$) 8.18 (1H, br s, H-2), 7.41–7.09 (5H, m, aryl H), 5.45 (1H, br d, N*H*, *J* 8.8), 5.25 (1H, s, H-5), 5.03 (1H, dt, NHC*H*, *J* 14.2 and 6.0), 3.62–3.19 [3H, m, CONC*H*$_a$H$_b$(C*H*$_2$)–], 3.38 [4H, t, N(C*H*$_2$)$_2$, *J* 7.0], 3.13 (1H, dd, PhC*H*$_a$H$_b$, *J* 13.2 and 7.2), 3.02 (1H, dd, PhCH$_a$*H*$_b$, *J* 13.0 and 9.2), 2.80–2.42 [1H, m, CONCH$_a$*H*$_b$(CH$_2$)–], 2.13–1.82 and 1.82–1.44 [8h, 2×m, 2×(C*H*$_2$)$_2$]; δ_C (50 MHz, CDCl$_3$) 170.6 (*C*O), 161.2 and 160.2 (C-4 and C-6), 157.5 (C-2), 137.0 (quaternary phenyl C), 129.4, 128.2 and 126.7 (phenyl *C*H), 82.9 (C-5), 53.8 (NH*C*H), 46.3 and 45.7 [CON(*C*H$_2$)$_2$], 46.2 [N(*C*H$_2$)$_2$], 39.7 (Ph*C*H$_2$), 25.3, 25.1 and 24.0 [2×(*C*H$_2$)$_2$]; t_R 13.65 min (B); *m*/*z* (ES) 365 (1, M$^+$), 292 (41), 274 (80), 268 (40), 267 (100), 204 (26), 203 (98), 164 (19), 121 (75), 70 (24), 55 (23%); HRMS (ES): MH$^+$, found 366.2252. $C_{21}H_{28}N_5O$ requires 366.2294.

4.5.6. Methyl 2-{[6-(dimethylamino)pyrimidin-4-yl]-amino}-3-phenylpropanoate (5f). Chloride **2d** (0.98 g, 3.37 mmol), dimethylamine (33% in ethanol, 3.0 cm^3, 22.0 mmol) and toluene (7 cm^3) afforded an orange solid, **5f** (0.21 g, 17%) after chromatography (ethyl acetate to 10% methanol/ethyl acetate as eluent). Recrystallised to beige blocks, mp 145–147 °C (ethyl acetate/hexane); R_f (10% methanol/ethyl acetate) 0.63; ν_{max} (KBr pellet) 3284, 2905, 2801, 1645, 1584, 1505, 1454, 1306, 1164, 1119, 974, 805, 716, 699 cm^{-1}; δ_H (200 MHz, CDCl$_3$) 8.20 (1H, br s, H-2), 7.38–7.11 (5H, m, aryl H), 5.47 (1H, br d, N*H*, *J* 8.4), 5.38 (1H, s, H-5), 5.31 (1H, dt, NHC*H*, *J* 8.2 and 6.0), 3.10 (1H, dd, PhC*H*$_a$H$_b$, *J* 13.2 and 5.8), 3.08 (3H, s, OC*H*$_3$), 3.02 (1H, obscured dd? PhCH$_a$*H*$_b$, *J* 13.2 and 3.4), 2.08 and 2.73 (6H, 2×s, 2×C*H*$_3$); δ_C (50 MHz, CDCl$_3$) 172.3 (*C*O), 162.5 and 161.6 (C-4 and C-6), 157.3 (C-2), 136.9 (quaternary phenyl C), 129.4, 128.3 and 126.7 (phenyl *C*H), 82.5 (C-5), 51.4 (O*C*H$_3$), 39.8 (NH*C*H), 37.1 (Ph*C*H$_2$), 36.9 and 35.6 [N(*C*H$_3$)$_2$]; t_R 6.20 min (B); *m*/*z* (ES) 300 (15, M$^+$), 224 (10, MH$^+$−Ph), 207 (15), 206 (100), 178 (35%).

4.5.7. *N*-Benzyl-6-pyrrolidin-1-ylpyrimidin-4-amine (6a). A mixture of chloride **2e** (0.98 g, 5.35 mmol), benzylamine (1.24 cm^3, 11.4 mmol) and toluene (5 cm^3) afforded **6a**, a beige solid (0.62 g, 46%) after chromatography (50% ethyl acetate/hexane to ethyl acetate was used as the eluent). Recrystallised to beige needles, mp 167–169 °C (ethyl acetate/hexane); R_f (ethyl acetate) 0.41; ν_{max} (KBr pellet) 3210, 2962, 2858, 1590, 1446, 1338, 1279, 1100, 978, 796, 749, 699 cm^{-1}; δ_H (200 MHz, CDCl$_3$) 8.15 (1H, s, H-2), 7.21–7.40 (5H, m, aryl H), 5.30 (1H, br t, N*H*), 5.18 (1H, s, H-5), 4.46 (2H, d, PhC*H*$_2$, *J* 5.6), 3.39 [4H, br s, N(C*H*$_2$)$_2$] and 1.90–2.05 [4H, m, (C*H*$_2$)$_2$]; δ_C (50 MHz, CDCl$_3$) 162.1 (C-6), 160.6 (C-4), 157.5 (C-2), 138.4 (aryl quaternary C), 128.6, 127.3 and 127.2 (aryl C), 80.6 (C-5), 46.2 [N(*C*H$_2$)$_2$], 45.9 (Ph*C*H$_2$) and 25.3 [(*C*H$_2$)$_2$]; t_R 10.13 min (B); HRMS (ES): MH$^+$, found 255.1596. $C_{15}H_{19}N_4$ requires 255.1610.

4.5.8. 2-[(6-Pyrrolidin-1-ylpyrimidin-4-yl)amino]ethanol (6b). Chloride **2e** (1.95 g, 5.10 mmol), ethanolamine (1.89 cm^3, 31.37 mmol) and toluene (20 cm^3) gave a beige-brown solid, **6b** (1.10 g, 50%) after chromatography (ethyl acetate to 10% methanol/ethyl acetate was used as the eluent). Recrystallised to a beige blocks, mp 116–117 °C (ethyl acetate/hexane); R_f (10% methanol/ethyl acetate) 0.22; ν_{max} (KBr pellet) 3249, 3097, 2943, 2858, 1600, 1539, 1509, 1435, 1340, 1283, 1222, 1080, 1022, 979, 790 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 8.07 (1H, s, H-2), 5.30 (1H, br t, N*H*), 5.18 (1H, s, H-5), 4.08 (1H, br s, O*H*), 3.78 (2H, t, CH_2OH, *J* 4.6), 3.22–3.49 [6H, br m, N(CH_2)$_2$ and CH_2NH] and 1.90–2.05 [4H, m, (CH_2)$_2$]; δ_C (50 MHz, $CDCl_3$) 162.2 (C-6), 160.4 (C-4), 157.1 (C-2), 80.8 (C-5), 61.6 (*C*H_2OH), 46.3 [N(*C*H_2)$_2$], 44.3 (*C*H_2NH) and 25.2 [(*C*H_2)$_2$]; t_R 2.17 min (B); HRMS (ES): MH$^+$, found 209.1409. $C_{10}H_{17}N_4O$ requires 209.1402.

4.5.9. *N*-(2-Hydroxyethyl)-1-{6-[(2-hydroxyethyl)amino]pyrimidin-4-yl}pyrrolidine-2-carboxamide (6c). Chloride **2f** (1.61 g, 6.67 mmol), ethanolamine (1.21 cm^3, 20.0 mmol) and toluene (20 cm^3) afforded a brown oil, **6c** (1.02 g, 54%) after chromatography (10–20% methanol/ethyl acetate as eluent); R_f (10% methanol/ethyl acetate) 0.23; ν_{max} (liquid ATR) 3288 (br), 2941, 2872, 1650, 1596, 1490, 1307, 1056, 979, 800 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.97 (1H, s, H-2), 7.43 (1H, br t, CON*H*, *J* 5.0), 5.90 (1H, br t, N*H*, *J* 5.6), 5.27 (1H, s, H-5), 4.20–4.35 (1H, br m, C*H*CO), 3.18–3.38 and 3.39–3.75 [10H, 2×m, 2×NH(CH_2)$_2$OH and NCH_2] and 1.74–2.20 [4H, m, (CH_2)$_2$]; δ_C (50 MHz, $CDCl_3$) 172.5 (*C*O), 162.1 (C-6), 160.1 (C-4), 156.4 (C-2), 81.3 (C-5), 60.4 (*C*HCO), 60.2 [2×(*C*H_2)$_2$OH], 46.6 (N*C*H_2), 45.0 [NH(*C*H_2)$_2$], 41.3 [NH(*C*H_2)$_2$], 29.4 and 23.2 [(*C*H_2)$_2$]; t_R 1.77 min (B); HRMS (ES): MH$^+$, found 296.1732. $C_{13}H_{22}N_5O_3$ requires 296.1723.

4.5.10. *N*-4-Bromophenyl-6-pyrrolidin-1-ylpyrimidin-4-amine (6d). Chloride **2e** (1.93 g, 10.50 mmol), 4-bromoaniline (2.73 g, 15.87 mmol) and potassium *tert*-butoxide (3.52 g, 31.37 mmol) in toluene (20 cm^3) yielded a brown powder after chromatography (ethyl acetate to 10% methanol/ethyl acetate as eluent). This was partially dissolved in a minimum of acetone and precipitated with hexane. The solid was isolated by filtration to afford a beige powder, **6d** (1.24 g, 37%). Recrystallised to beige needles, mp 108–110 °C (ethyl acetate/hexane); R_f (ethyl acetate) 0.26; ν_{max} (KBr pellet) 2960, 2863, 1587, 1504, 1480, 1321, 1153, 962, 797 cm^{-1}; δ_H (200 MHz, $CDCl_3$+DMSO-d_6) 8.15 (1H, s, H-2), 7.58 (1H, br s, N*H*), 7.31 (2H, ca. d, aryl H, *J* 6.6), 7.20 (2H, ca. d, aryl H, *J* 6.7), 5.55 (1H, s, H-5), 3.32 [4H, br s, N(CH_2)$_2$] and 1.88–1.98 [4H, m, (CH_2)$_2$]; δ_C (50 MHz, $CDCl_3$) 160.4 (C-6), 159.7 (C-4), 157.4 (C-2), 138.8 (aryl quaternary C), 131.8 and 122.5 (aryl C), 115.2 (aryl quaternary C), 82.8 (C-5), 46.1 [N(*C*H_2)$_2$] and 25.0 [(*C*H_2)$_2$]; t_R 2.23 min (A); *m*/*z* (ES) 322 (13), 321 (100, MH$^+$), 320 (12), 319 (100%, MH$^+$).

4.5.11. 1-{6-[(4-Bromophenyl)amino]pyrimidin-4-yl}-pyrrolidine-2-carboxylic acid (6e). Chloride **2f** (1.61 g, 6.66 mmol), 4-bromoaniline (1.75 g, 10.18 mmol) and potassium *tert*-butoxide (2.26 g, 20.14 mmol) in toluene (20 cm^3) were mixed at room temperature in a reaction tube. Instant heating occurred, with the formation of a dense brown precipitate. The reaction was treated as before to yield **6e**, a beige powder (0.47 g, 20%) after chromatography (ethyl acetate to 10% methanol/ethyl acetate as eluent). Recrystallised to a beige powder, mp 264–265 °C (ethyl acetate/hexane); R_f (ethyl acetate) 0.15; ν_{max} (KBr pellet) 3276, 3072, 2964, 2870, 1684, 1609, 1543, 1489, 1306, 1249, 825, 809 cm^{-1}; δ_H (200 MHz, $CDCl_3$+DMSO-d_6) 9.73 (1H, br s, N*H*), 7.67 (1H, m, H-2), 7.46 (2H, m, aryl H), 7.28 (2H, m, aryl H), 5.07 (1H, ca. d, H-5, *J* 3.2), 4.23–4.61 (1H, br m, NC*H*CO), 3.18–3.39 and 3.39–3.62 (2H, 2×br m, NCH_2) and 1.82–2.25 [4H, m, (CH_2)$_2$]; δ_C (50 MHz, $CDCl_3$) 170.3 (*C*O), 161.6 (C-6), 159.6 (C-4), 147.2 (C-2), 137.0 (aryl quaternary C), 130.3 and 120.4 (aryl C), 114.6 (aryl quaternary C), 85.7 (C-5), 60.3 (N*C*HCO), 46.5 (N*C*H_2), 29.4 and 22.7 [(*C*H_2)$_2$]; t_R 11.30 min (B); *m*/*z* (ES) 364 (22, M$^+$), 362 (24, M$^+$), 192 (20), 165 (34), 164 (100), 70 (44), 68 (28%).

4.5.12. *N*-Pyridin-2-yl-6-pyrrolidin-1-ylpyrimidin-4-amine (6f). Chloride **2e** (1.91 g, 10.40 mmol), 2-aminopyridine (1.51 g, 16.07 mmol) and potassium *tert*-butoxide (3.54 g, 31.51 mmol) in toluene (20 cm^3) were mixed at room temperature in a reaction tube. Instant heating occurred, with the formation of a dense brown precipitate. The tube was sealed and treated as before to yield **6f**, a beige powder (0.38 g, 15%) after chromatography (ethyl acetate to 10% methanol/ethyl acetate as eluent). Recrystallised to a brown powder, mp 203–204 °C (ethyl acetate/hexane; dec.); R_f (ethyl acetate) 0.29; ν_{max} (KBr pellet) 3345, 3258, 3167, 2965, 2879, 2181, 1592, 1547, 1459, 1417, 1365, 1342, 1324, 1285, 1148, 1052, 1029, 980, 791, 778, 688 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 8.35 (1H, s, H-2), 8.30 (1H, dd, pyridine H-6, *J* 2.0 and 7.0), 7.60 (1H, ca. ddd, pyridine H-4, *J* 7.2, 6.8 and 1.8), 7.32 (1H, d, pyridine H-3, *J* 8.2), 6.87 (1H, dd, pyridine H-5, *J* 7.2 and 6.0), 6.78 (1H, s, H-5), 3.52 [4H, br s, N(CH_2)$_2$] and 1.90–2.18 [4H, m, (CH_2)$_2$]; δ_C (50 MHz, $CDCl_3$) 161.0 (C-6), 158.1 (C-4), 157.5 (C-2), 153.8 (pyridine C-2), 147.7 (pyridine C-6), 137.6 (pyridine C-4), 116.7 (pyridine C-3), 112.6 (pyridine C-5), 86.7 (C-5), 46.4 [N(*C*H_2)$_2$] and 25.3 [(*C*H_2)$_2$]; t_R 5.17 min (B); HRMS (ES): MH$^+$, found 242.1409. $C_{13}H_{16}N_5$ requires 242.1406.

4.5.13. 5-Nitro-*N*^{4}-pyridin-2-yl-6-pyrrolidin-1-ylpyrimidin-4-amine (7). A rapidly stirred suspension of pyrimidine **6f** (0.28 g, 1.16 mmol) and concentrated sulfuric acid (2.3 cm^3) were mixed at 0 °C in a conical flask. Nitric acid (65%, 0.24 cm^3, 2.4 mmol) was then added dropwise to the mixture, affording a yellow-orange solution over time that gradually turned deep orange. This was allowed to warm to room temperature over 18 h. The mixture was then decanted onto crushed ice, neutralised with concentrated ammonia and extracted with ethyl acetate. Drying of the organic phase ($MgSO_4$) and concentration, followed by column chromatography of the residue using 10% ethyl acetate/hexane afforded a yellow solid **7** (0.28 g, 83%). Recrystallised to yellow needles, mp 155–157 °C (ethyl acetate/hexane); R_f (20% ethyl acetate/hexane) 0.25; ν_{max} (KBr pellet) 3339, 2977, 2881, 1572, 1519, 1456, 1433, 1358, 1279, 1255, 1224, 1181, 846, 778 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 10.2 (1H, br s, N*H*), 8.42 (1H, dd, pyridine H-6, *J* 8.4 and 0.8), 8.35 (1H, dt, pyridine H-4, *J* 4.8 and 1.0), 8.23 (1H, s, H-2), 7.71 (1H, ddd, H-5, *J* 8.8, 7.8 and 1.9), 7.04 (1H, dd, H-3, *J* 7.2 and 4.8), 3.47 [4H, br s, N(CH_2)$_2$] and 1.96–2.05 [4H, m, (CH_2)$_2$]; δ_C (50 MHz, $CDCl_3$) 156.9 (pyridine C-2), 153.5 (C-6), 151.5 (C-4), 148.2 (pyridine C-6), 137.8 (pyridine C-4), 119.6 (C-2), 115.8 (pyridine C-5), 109.7 (pyridine C-3), 80.2 (C-5), 50.0 [N(*C*H_2)$_2$] and 25.2 [br, (*C*H_2)$_2$]; t_R 2.18 min (A); HRMS (ES): MH$^+$, found 287.1259. $C_{13}H_{15}N_6O_2$ requires 287.1256.

4.6. General procedure for nitroso reduction

The 5-nitrosopyrimidine was suspended in water (1 M) and treated with solid sodium dithionite (2 equiv) portionwise. Aqueous sulfuric acid (50% v/v, 2.5–3 mass equiv) was added dropwise, and the resulting mixture was heated at 130 °C with stirring for 5 min. The reaction mixture became colourless after this time, and was cooled on ice. The pH of the mixture was adjusted to >10 with 2 M aqueous sodium hydroxide, and extracted with dichloromethane. The combined organic extracts were concentrated under reduced pressure, and the crude product recrystallised from dichloromethane/hexane. The following compounds were prepared by this method.

4.6.1. N^4-Methyl-6-pyrrolidin-1-ylpyrimidine-4,5-diamine (8b). Pyrimidine **4b** (0.82 g, 3.98 mmol) in water (4 cm^3), sodium dithionite (1.45 g, 8.36 mmol) and sulfuric acid (50% v/v, 8.2 g) afforded **8b**, a brown solid (0.66 g, 86%). Recrystallised to a beige powder, mp 165–167 °C (CH_2Cl_2/hexane); R_f (10% methanol/ethyl acetate) 0.44; ν_{max} (KBr pellet) 3242, 3170, 3097, 2861, 1600, 1578, 1408, 1333, 1283, 1145, 1098, 1021, 993, 973, 915, 794, 700 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 8.11 (1H, s, H-2), 5.13 (1H, s, N*H*), 4.76 (2H, br s, NH_2), 3.36–3.48 [4H, m, N(CH_2)$_2$], 2.85 (3H, d, NCH_3, *J* 5.4) and 1.94–2.00 [4H, m, (CH_2)$_2$]; δ_C (50 MHz, $CDCl_3$) 163.4 (C-4)[a], 161.8 (C-6)[a], 157.8 (C-2), 79.9 (C-5), 46.5 [N(CH_2)$_2$], 28.7 (NCH_3)[b] and 25.5 [(CH_2)$_2$][b]; t_R 2.23 min (B); HRMS (ES): MH$^+$−NH, found 179.1303. $C_9H_{15}N_4$ requires 179.1297.

4.6.2. N^6-Benzyl-N^4,N^4-dimethylpyrimidine-4,5,6-triamine (8c).[14] Pyrimidine **4c** (0.12 g, 0.48 mmol) in water (0.48 cm^3), sodium dithionite (0.17 g, 1.00 mmol) and sulfuric acid (50% v/v, 1.21 g) afforded **8c**, a beige solid (91.9 mg, 80%). Recrystallised to a beige powder, mp 149–150 °C (CH_2Cl_2/hexane), lit.[13] 181–185 °C (methanol); R_f (50% ethyl acetate/hexane) 0.18; ν_{max} (KBr pellet) 3211, 3071, 2987, 2861, 2808, 1589, 1422, 1317, 1299, 1169, 977, 797, 750, 702 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 8.16 (1H, s, H-2), 7.26–7.35 (5H, m, aryl H), 5.30 and 5.10 (2H, 2×br s, NH_2), 4.45 (2H, d, CH_2Ph, *J* 5.8), 3.01 (6H, s, 2×NCH_3) and 1.78 (1H, br s, N*H*); δ_C (50 MHz, $CDCl_3$) 163.0 (C-4 and C-6), 157.6 (C-2), 138.7 (quaternary aryl C), 128.8 and 127.5 (aryl C), 80.2 (C-5), 46.0 (CH_2Ph) and 37.4 (2×NCH_3); t_R 4.82 min (B); *m/z* (ES) and 229 (31), 228 (100, M$^+$−NH), 227 (59), 213 (29), 199 (33), 123 (68), 106 (67), 96 (25), 91 (81), 81 (23), 65 (21), 57 (21%); HRMS (ES): MH$^+$−NH, found 229.1469. $C_{13}H_{17}N_4$ requires 229.1453.

4.6.3. N^4-Benzyl-6-pyrrolidin-1-ylpyrimidine-4,5-diamine (8d). Pyrimidine **4d** (0.41 g, 1.45 mmol) in water (1.45 cm^3), sodium dithionite (0.53 g, 3.04 mmol) and sulfuric acid (50% v/v, 4.08 g) afforded **8d**, a beige solid (0.34 g, 87%). Recrystallised to a beige powder, mp 165–169 °C (CH_2Cl_2/hexane); R_f (ethyl acetate) 0.32; ν_{max} (KBr pellet) 3210, 2962, 2858, 1657, 1561, 1489, 1337, 1306, 1279, 1219, 1180, 1103, 1024, 978, 917, 795, 748, 698 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 8.10 (1H, s, H-2), 7.25–7.35 (5H, m, aryl H), 5.35 (1H, br s, N*H*), 5.14 (2H, s, NH_2), 4.41 (2H, d, CH_2Ph, *J* 5.8), 3.36 [4H, br s, N(CH_2)$_2$] and 1.90–1.96 [4H, m, (CH_2)$_2$]; δ_C (50 MHz, $CDCl_3$) 162.5 (C-4)[a], 160.9 (C-6)[a], 157.9 (C-2), 138.7 (quaternary aryl C), 128.7, 127.6 and 127.5 (aryl C), 80.9 (C-5), 46.4 [N(CH_2)$_2$], 46.1 (CH_2Ph) and 25.5 [(CH_2)$_2$]; t_R 7.12 min (B); HRMS (ES): MH$^+$−NH, found 255.1599. $C_{15}H_{19}N_4$ requires 255.1610.

4.6.4. N^4-Benzyl-6-morpholin-4-ylpyrimidine-4,5-diamine (8e). Pyrimidine **4e** (1.35 g, 4.63 mmol) in water (50 cm^3), sodium dithionite (1.70 g, 9.74 mmol) and sulfuric acid (50% w/w, 9.09 g) afforded **8e** (0.90 g, 70%) as a white solid. Recrystallised to a white powder, mp 184–185 °C (CH_2Cl_2/hexane); R_f (50% ethyl acetate/hexane) 0.20; ν_{max} (KBr pellet) 3242, 3170, 3097, 2861, 1583, 1401, 1322, 1286, 1105, 1021, 973, 915 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 8.20 (1H, s, H-2), 7.35 (5H, br s, aryl H), 5.41 (1H, s, N*H*), 5.35 (2H, br s, NH_2), 4.48 (2H, d, CH_2Ph, *J* 5.8), 3.75 [4H, m, O(CH_2)$_2$] and 3.51 [4H, m, N(CH_2)$_2$]; δ_C (50 MHz, $CDCl_3$) 164.5 (C-6), 163.0.0 (C-4), 157.5 (C-2), 138.5 (quaternary aryl C), 129.0, 128.0 and 127.5 (aryl C), 81.5 (C-5), 66.5 [O(CH_2)$_2$], 46.0 (PhCH_2) and 44.5 [N(CH_2)$_2$]; t_R 6.33 min (B); HRMS (ES): MH$^+$−NH, found 271.1564. $C_{15}H_{19}N_4O$ requires 271.1559.

4.6.5. 2-[5-Amino-6-(dimethylamino)pyrimidin-4-yl]-aminoethanol (8f).[15] Pyrimidine **4f** (0.58 g, 2.73 mmol) in water (2.7 cm^3), sodium dithionite (1.00 g, 5.74 mmol) and sulfuric acid (50% v/v, 5.8 g) afforded **8f**, a white solid (0.29 g, 54%). Recrystallised to a white powder, mp 110–111 °C (CH_2Cl_2/hexane), lit.[15] 119–120 °C (benzene); R_f (10% methanol/ethyl acetate) 0.31; ν_{max} (KBr pellet) 3225, 3105, 2860, 2807, 1599, 1518, 1420, 1328, 1301, 1073, 1021, 986, 892, 791, 675 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 8.15 (1H, s, H-2), 5.36 and 5.00 (2H, 2×br s, NH_2), 3.80 (2H, t, CH_2OH, *J* 4.9), 3.42–3.50 (2H, m, CH_2NH), 3.05 (6H, s, 2×NCH_3) and 2.87 (1H, br s, N*H*); δ_C (50 MHz, $CDCl_3$) 162.9 (C-4)[a], 162.0 (C-6)[a], 157.3 (C-2), 80.9 (C-5), 62.9 (CH_2OH), 44.8 (CH_2NH) and 37.5 (2×NCH_3); t_R 1.81 min (B); HRMS (ES): MH$^+$−NH, found 183.1241. $C_8H_{15}N_4O$ requires 183.1246.

4.6.6. 2-[(5-Amino-6-pyrrolidin-1-ylpyrimidin-4-yl)amino]ethanol (8g). Pyrimidine **4g** (0.34 g, 1.45 mmol) in water (1.45 cm^3), sodium dithionite (0.53 g, 3.05 mmol) and sulfuric acid (50% v/v, 3.5 g) afforded **8g**, a brown solid (0.23 g, 71%). Recrystallised to a beige powder, mp 117–118 °C (CH_2Cl_2/hexane); R_f (10% methanol/ethyl acetate) 0.27; ν_{max} (KBr pellet) 3321, 3234, 2964, 2862, 1600, 1539, 1509, 1434, 1338, 1280, 1226, 1196, 1110, 1079, 1057, 1025, 977, 798 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 8.12 (1H, s, H-2), 5.22 (1H, s, NH_2), 5.06 (1H, br s, NH_2), 3.79 (2H, t, CH_2OH, *J* 4.9), 3.30–3.48 [7H, m, CH_2NH, N(CH_2)$_2$ and N*H*] and 1.94–2.01 [4H, m, (CH_2)$_2$]; δ_C (50 MHz, $CDCl_3$) 162.6 (C-4)[a], 160.7 (C-6)[a], 157.5 (C-2), 81.4 (C-5), 62.5 (CH_2OH), 46.5 [N(CH_2)$_2$], 44.7 (CH_2NH) and 25.5 [(CH_2)$_2$]; t_R 1.97 min (B); HRMS (ES): MH$^+$−NH, found 209.1408. $C_{10}H_{17}N_4O$ requires 209.1402.

4.7. General procedure for ring closure of triaminopyrimidines 8b–g

The pyrimidine was suspended in a mixture of acetic anhydride (5 mass equiv) and triethyl orthoformate (5 mass equiv) and heated to reflux with stirring. All the starting material dissolves upon heating. After 4 h at reflux, the mixture was cooled and excess acetic anhydride and triethyl orthoformate were removed under reduced pressure. The crude residue was purified by silica gel column chromatography using ethyl acetate as eluent, then by recrystallisation from dichloromethane/hexane mixtures. The following compounds were prepared by this method:

4.7.1. 9-Methyl-6-pyrrolidin-1-yl-9*H*-purine (9b). Triamine **8b** (66.6 mg, 0.35 mmol), acetic anhydride (332.5 mg) and triethyl orthoformate (332.5 mg) afforded a beige solid, **9b** (47.1 mg, 67%). Recrystallised to beige plates, mp 53–56 °C (CH_2Cl_2/hexane); R_f (50% ethyl acetate/hexane) 0.32; ν_{max} (KBr pellet) 3087, 3050, 2973, 2871, 1657, 1595, 1509, 1458, 1349, 1327, 1287, 1180, 1101, 1021, 983, 968, 870, 865, 704, 632 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 8.41 (1H, s, H-2), 6.29 (1H, s, H-8), 3.34–3.56 [4H, m, $N(CH_2)_2$], 3.31 (3H, s, NCH_3) and 1.92–2.04 [4H, m, $(CH_2)_2$]; δ_C (50 MHz, $CDCl_3$) 171.2 (C-6)[a], 161.3 (C-4)[a], 158.4 (C-8), 158.1 (C-2), 96.9 (C-5), 46.8 [$N(CH_2)_2$], 35.0 (NCH_3) and 25.4 [$(CH_2)_2$]; t_R 3.72 min (B); *m*/*z* (ES) 221 (M^++H_2O), 220 (40), 192 (25), 178 (47), 177 (100), 150 (45), 149 (75), 109 (30), 70 (40%); HRMS (ES): MH^++H_2O−NCHO, found 179.1228 ($C_9H_{15}N_4$ requires 179.1297) and M^++H_2O, found 221.1425 ($C_{10}H_{15}N_5O$ requires 221.1277).

4.7.2. 9-Benzyl-6-dimethylamino-9*H*-purine (9c).[14,16] Triamine **8c** (50.2 mg, 0.21 mmol), acetic anhydride (251 mg) and triethyl orthoformate (251 mg) afforded a beige solid, **9c** (46.0 mg, 88%). Recrystallised to a beige powder, mp 116–117 °C (CH_2Cl_2/hexane), lit.[14b] 120–121 °C (ethanol); R_f (10% methanol/ethyl acetate) 0.22; ν_{max} (solid ATR) 2963, 1655, 1588, 1510, 1402, 1286, 1170, 1082, 982, 702 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 8.46 (1H, s, H-2), 7.23–7.32 (5H, m, aryl H), 6.33 (1H, s, H-8), 5.11 (2H, s, CH_2Ph) and 3.04 (6H, s, 2×NCH_3); t_R 9.27 min (B); *m*/*z* (ES) 271 (9, M^++H_2O), 270 (41), 229 (10), 228 (83), 227 (100), 150 (19), 123 (24), 106 (56), 95 (42), 91 (70), 65 (20%); HRMS (ES): MH^++H_2O−NCHO, found 229.1478 ($C_{13}H_{17}N_4$ requires 229.1453) and M^++H_2O, found 271.1592 ($C_{14}H_{17}N_5O$ requires 271.1433).

4.7.3. 9-Benzyl-6-pyrrolidin-1-yl-9*H*-purine (9d).[14] Compound **8d** (39.6 mg, 0.15 mmol), acetic anhydride (143 mg) and triethyl orthoformate (143 mg) afforded **9d** (32.8 mg, 80%) as a wax [lit.[14b] 129–130.5 °C (heptane)]; R_f (50% ethyl acetate/hexane) 0.19; ν_{max} (neat film) 2946, 2870, 1667, 1580, 1504, 1450, 1381, 1220, 1045, 969, 847, 728 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 8.45 (1H, s, H-2), 7.24–7.28 (5H, m, aryl H), 6.19 (1H, s, H-8), 5.11 (2H, s, CH_2Ph), 3.18–3.62 [4H, br s, $N(CH_2)_2$] and 1.90–2.06 [4H, m, $(CH_2)_2$]; δ_C (50 MHz, $CDCl_3$) 171.2 (C-6)[a], 161.3 (C-4)[a], 158.4 (C-8)[a], 158.4 (C-2), 138.0 (quaternary aryl C), 128.7, 127.7 and 127.4 (aryl C), 98.1 (C-5), 50.5 [$N(CH_2)_2$], 46.7 (CH_2Ph) and 25.5 [$(CH_2)_2$]; t_R 15.90 min (B); *m*/*z* (ES) 296 (17), 254 (56), 253 (100), 226(14), 225 (17), 106 (27), 91 (44%); HRMS (ES): MH^++H_2O−NCHO, found 255.1646 ($C_{15}H_{18}N_4$ requires 255.1610) and M^++H_2O, found 297.1736 ($C_{16}H_{19}N_5O$ requires 297.1590).

4.7.4. 9-Benzyl-6-morpholin-1-yl-9*H*-purine (9e). Triamine **8e** (85 mg, 0.30 mmol), acetic anhydride (0.43 g) and triethyl orthoformate (0.43 g) afforded a beige solid, **9e** (59.7 mg, 68%). Recrystallised to a beige powder, mp 104–105 °C (CH_2Cl_2/hexane); R_f (50% ethyl acetate/hexane) 0.22; ν_{max} (solid ATR) 3034, 2965, 2857, 1683, 1577, 1482, 1446, 1211, 984, 968, 754 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 8.49 (1H, s, H-2), 7.21–7.35 (5H, m, aryl H), 6.66 (1H, s, H-8), 5.18 (2H, s, CH_2Ph), 3.74–3.80 [4H, m, $O(CH_2)_2$] and 3.56–3.61 [4H, m, $N(CH_2)_2$]; δ_C (50 MHz, $CDCl_3$) 171.6 (C-6)[a], 163.5 (C-4)[a], 161.35 (C-8), 158.0 (C-2), 137.9 (quaternary aryl C), 128.8, 127.5 and 127.4 (aryl *C*), 96.9 (C-5), 66.6 [$O(CH_2)_2$], 50.4 (CH_2Ph) and 44.6 [$N(CH_2)_2$]; t_R 10.25 min (B); *m*/*z* (ES) 313 (8, M^++H_2O), 312 (36), 270 (72), 269 (100), 239 (25), 213 (23), 106 (39), 91 (63), 65 (15%); HRMS (ES): MH^++H_2O−NCHO, found 271.1591 ($C_{15}H_{19}N_4O$ requires 271.1559) and M^++H_2O, found 313.1695 ($C_{16}H_{19}N_5O_2$ requires 313.1539).

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