Expanding the scope of fused pyrimidines as kinase inhibitor scaffolds: synthesis and modification of pyrido[3,4-d]pyrimidines

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ARTICLE

Expanding the scope of fused pyrimidines as kinase inhibitor scaffolds: synthesis and modification of pyrido[3,4-*d*]pyrimidines

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Fused pyrimidine cores are privileged kinase scaffolds, yet few examples of the 2-amino-pyrido[3,4-*d*]pyrimidine chemotype have been disclosed in the context of kinase inhibitor programs. Furthermore, no general synthetic route has been reported to access 2-amino-pyrido[3,4-*d*]pyrimidine derivatives. Here we report a versatile and efficient chemical approach to this class of molecules. Our strategy involves the concise preparation of 8-chloro-2-(methylthio)pyrido[3,4-*d*]pyrimidine intermediates and their efficient derivatisation to give novel compounds with potential as kinase inhibitors.

Introduction

Kinases are a particularly prevalent class of targets within drug discovery, with inhibitors of approximately 30 distinct targets progressed into phase 1 clinical trials. Deregulation of kinase function has been associated with a wide range of diseases. In particular, many kinases have been found to be closely linked to tumour proliferation and survival and therefore kinase inhibition represents an effective treatment for cancer.[1-3]

Fused pyrimidines have become ubiquitous in medicinal chemistry programs aimed at the discovery of small-molecule kinase inhibitors.[4-8] Among the most striking results of these efforts are Gefitinib, Erlotinib and Vandetanib,[9, 10] molecules based on quinazolines (fused pyrimidine and benzene rings) which are currently widely used as anticancer drugs. However, as fused pyrimidines have been extensively explored by medicinal chemists, the patent landscape has become very crowded making it challenging to discover novel chemotypes that can be exploited for the large fraction of kinase targets that remain to be drugged.

During the course of our own kinase drug discovery program, we were surprised to find that the 2-amino-pyrido[3,4-*d*]pyrimidine core (Figure 1) has been utilised to a much lesser degree than many other fused pyrimidines and no concise and robust route to this kinase preferred chemotype has been reported in the peer reviewed literature. The 2-amino-pyrido[3,4-*d*]pyrimidine core (Figure 1) addresses key pharmacophoric elements of the kinase ATP pocket. The aminopyrimidine/R_1 moiety can interact with the hinge region and the R_2 substituent is ideally situated to access the ribose pocket. Furthermore, modification at positions 5 and 6 creates an opportunity to gain interactions with the gate-keeper residue and back-pockets and thus optimise potency and kinase selectivity. All these features are illustrated in the bottom part of Figure 1, where a simplified core was docked in a representative kinase (CDK2, PDB code 1H08).[1, 11, 12]

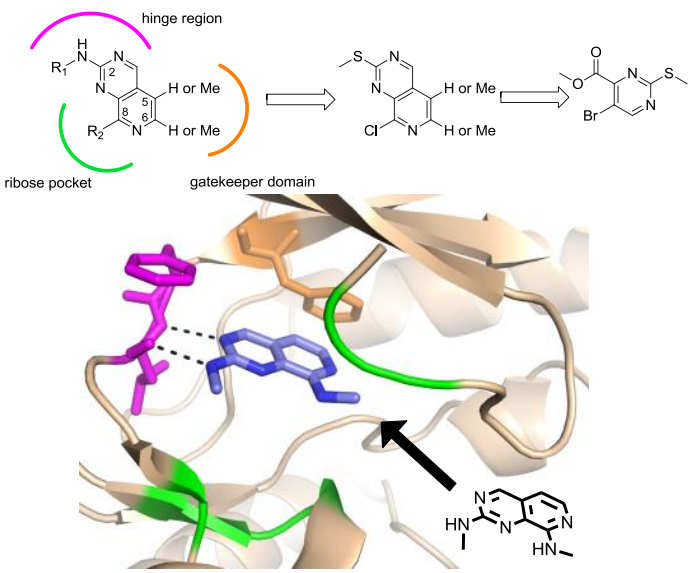


Figure 1 Top: outline of the retrosynthetic strategy towards 2-amino-pyrido[3,4-*d*]pyrimidines. Bottom: docked pose of a pyrido[3,4-*d*]pyrimidine core in CDK2 (PDB code 1H08).

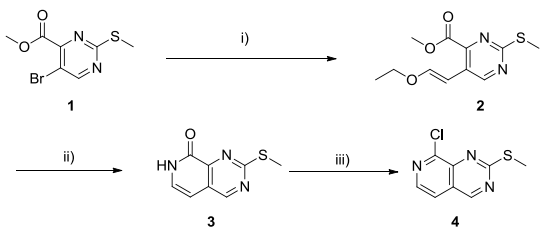
We therefore set out to develop a concise route for the preparation of a wide range of 2-amino-pyrido[3,4-*d*]pyrimidines (Figure 1). We purposefully aimed to design a strategy that would allow us to: a) concisely incorporate a wide variety of substituents at positions 2 and 8, b) introduce different substituents in the 5 and 6 positions, c) upscale to

multigram amounts, d) use a single commercially available building block as a starting material. Our retrosynthetic analysis led us to a novel, 8-chloro-2-(methylthio)pyrido[3,4-*d*]pyrimidine-based class of intermediates (Figure 1) with substituents in positions 5 and 6 in place and perfectly set for derivatisation at positions 2 and 8. We anticipated that these intermediates could be readily prepared, in a few steps, from the commercially available methyl 5-bromo-2-(methylthio)pyrimidine-4-carboxylate.

In the first part of this manuscript we describe concise chemical routes to three representative 8-chloro-2-(methylthio) pyrido[3,4-*d*]pyrimidine intermediates. In the second part we report the efficient chemical modification of these key building blocks to access a wide range of 2-amino-pyrido[3,4-*d*]pyrimidines. Finally we report inhibition data for a selection of compounds, showing that 2-amino-pyrido[3,4-*d*]pyrimidine derivatives have potential as CDK2 inhibitors.

Results and discussion

We have previously reported the use of (2-ethoxyvinyl) borolanes as an efficient coupling partner in Suzuki-Miyaura reactions with halopyridines.[13] Subsequent acid cyclisation gave rise to azaindoles in excellent yields. We explored a similar strategy for the preparation of the 5,6-unsubstituted 8-chloro-2-(methylthio)pyrido[3,4-*d*]pyrimidine intermediate (Scheme 1).

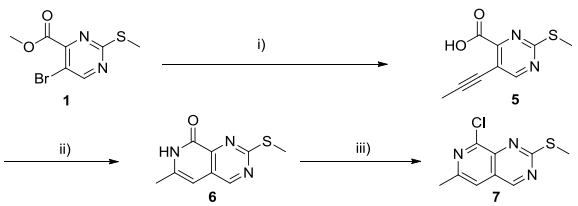


Scheme 1 Synthesis of pyrido[3,4-*d*]pyrimidine core **4**. Reagents and conditions: i) (*E*)-2-(2-ethoxyvinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, $Pd(dppf)Cl_2$.DCM, Na_2CO_3, THF/water, 65 °C, 63 %; ii) NH_3, MeOH, 85 °C followed by pTSA·H_2O, toluene, 90 °C, 84 %; iii) $POCl_3$, 70 °C, 86 %.

The readily accessible methyl ester **1** underwent the key Suzuki-Miyaura coupling with (*E*)-2-(2-ethoxyvinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane under palladium catalysed conditions to give alkene **2**. Subsequent amide formation with ammonia in methanol, followed by cyclisation under acidic conditions yielded the desired pyrido[3,4-*d*]pyrimidinone **3** in excellent yield (84 %). The resulting compound was subjected to chlorination with phosphorus oxychloride giving rise to our key intermediate **4**, ideally set up to allow expedient functionalisation at the 2 and 8 positions, in good overall yield (46 % over three steps).

In order to exemplify 2-amino-pyrido[3,4-*d*]pyrimidines featuring substituents at the 5 and 6 position (Figure 1) we targeted intermediates which carried a methyl substituent at either of these positions. Careful inspection of the literature revealed no precedence for either of these classes of compounds with only a limited number of examples of an aryl group incorporated at position 6.[6, 14] Whilst it should be possible to synthesise these two compounds in a similar manner to **4** described above, the corresponding boron reagents (see Scheme 1) were not readily accessible and therefore, we devised different routes starting from commercially available reagents.

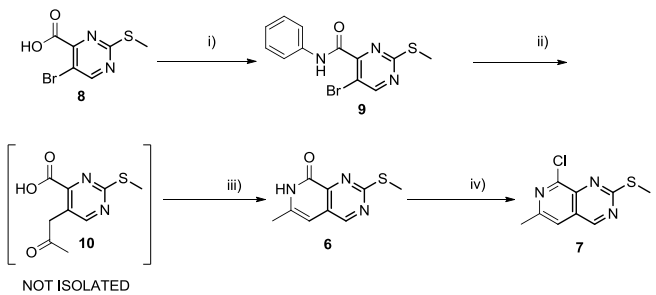
Based on a recent patent application,[6, 14] disclosing the synthesis of pyrido[3,4-*d*]pyrimidine derivatives with aryl substitutions in position 6, we utilised an approach whereby the halopyrimdine was coupled with substituted alkynes, replacing the initial Suzuki reaction carried out for the unsubstituted core (Scheme 2). In order to introduce a methyl group instead of an aromatic ring we needed to utilise a propynyl building block, and for practical ease decided to make use of the corresponding tin reagent, 1-propynyltri-n-butyltin (Scheme 2).



Scheme 2 First generation synthesis of chloride **7**. Reagents and conditions: i) $Pd(PPh_3)_4$, 1-propynyltri-n-butyltin, CuI, Et_3N, DMF, 110 °C, MW, 49 %; ii) pTSA·H_2O, toluene, 90 °C then NH_3, MeOH, 80 °C, 62 %; iii) $POCl_3$, 50 °C, 81 %.

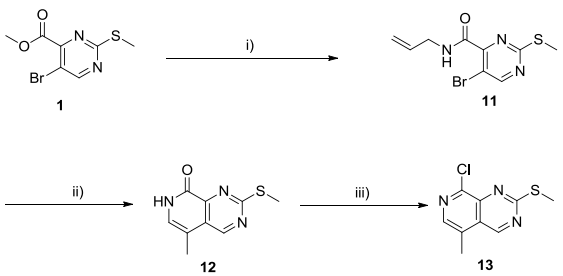
The Stille-type coupling of methyl ester **1** with 1-propynyltri-n-butyltin[6] proceeded more efficiently when performed under microwave irradiation, albeit in moderate yield (49 %) and gave the corresponding acid **5** after work up. Subsequent cyclisation, carried out with pTSA·H_2O followed by treatment of the corresponding lactone intermediate with ammonia, gave rise to the desired pyrimidinone **6** in good yield (62 %). As previously, chlorination of the pyrimidone was carried out in phosphorus oxychloride to furnish pyridopyrimidine **7**.

Whilst this route yielded the desired intermediate, the overall yield was modest (25 % over three steps) and not suited to upscaling due to the use of microwave irradiation and the need for the expensive and toxic tin reagent. We therefore explored an alternative approach based on recently published copper mediated derivatisation of *ortho*-halo-*N*-phenyl amides (Scheme 3).[15]



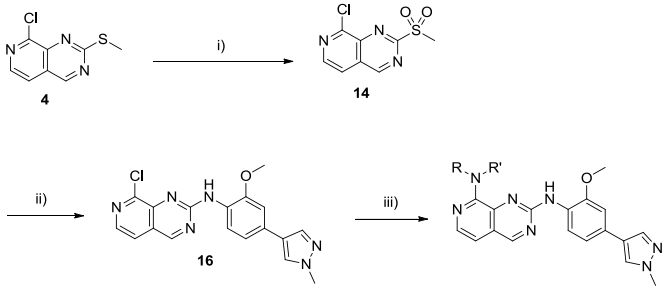
Scheme 3 Second generation synthesis of chloride **7**. Reagents and conditions: i) oxalyl chloride, DCM, DMF, rt; followed by Et_3N, aniline, DCM, rt, 95 %; ii) pentane-2,4-dione, CuI, Cs_2CO_3, MeCN, 85 °C; iii) $AcONH_4$, AcOH, 85 °C, 63 % over two steps; iv) $POCl_3$, 50 °C, 81 %.

Reaction of carboxylic acid **8** with oxalyl chloride followed by treatment with aniline gave the desired phenyl amide **9** in excellent yield (95 %). Gratifyingly, copper promoted coupling of the amide went smoothly in the presence of Cs_2CO_3 and pentane-2,4-dione in acetonitrile to yield the ketoacid **10** which we cyclised without isolation into the corresponding pyrimidone **6** by treatment with ammonium acetate in acetic acid. Reaction with phosphorus oxychloride finally furnished pyridopyrimidine **7** The revised route gave access to the key intermediate **7** in three steps and in good overall yield (48 %) from readily available starting materials and was applicable to multigram scale (Scheme 3). Having found efficient routes to intermediates **4** and **7** we set out to prepare the analogous compound with position 5 substituted with a methyl group (Figure 1). As mentioned previously there were no literature methods, to our knowledge, for the synthesis of the 5-methyl substituted scaffold. Instead of using the strategy employed for the unsubstituted scaffold (Scheme 1), a shorter approach relying on an intramolecular Heck reaction (Scheme 4) was devised.[16]



Scheme 4 Synthesis of intermediate **13**. Reagents and conditions: i) allylamine, MeOH, 90 °C, 90 %; ii) Herrmann's Pd, Hunig's base, DMA, 150 °C, 44 %; iii) $POCl_3$, 70 °C, 77 %.

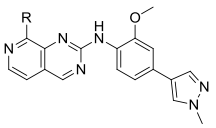
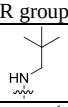
Reaction of the readily accessible methyl ester **1** with allylamine in methanol efficiently gave the corresponding allyl amide **11** in high yield (90 %). The Heck cyclisation was carried out using Herrmann's palladacycle catalyst[17] and Hunig's base in DMA affording the desired pyridopyrimidone **12** in a 44 % yield. Chlorination was again carried out using phosphorus oxychloride, affording the key chloro intermediate **13** in high yield (77 %, Scheme 4).



Scheme 5 Functionalisation of pyridopyrimidine core **4**. Reagents and conditions: i) mCPBA, DCM, 0 °C – rt, 67 %; ii) NaH, *N*-(2-methoxy-4-(1-methyl-1H-pyrazol-4-yl)phenyl)formamide **15**, 0 °C - rt, THF, 79 %; iii) RR'NH or salt thereof, NMP, Et_3N, 120-130 °C.

Once we had successfully completed the synthesis of these versatile intermediates, we focussed on functionalisation of the 2 and 8 positions. Initially, we focused on substitution of the 2 position with anilines since this substitution pattern is prevalent for kinase inhibitors, followed by diversification at the 8 position with a range of different reagents. This route is outlined in Scheme 5. Oxidation of the key pyridopyrimidine **4** with mCPBA in DCM gave sulfone **14** which was reacted with formylated aniline **15**[18] to afford chloride **16**. Diversification through amine displacement of the resulting intermediate **16** was carried out in NMP at elevated temperatures affording the desired products in high yield. A number of different amines were introduced at this position, including primary (**17**, **18**, **19** and **20** Table 1), secondary (**21**, Table 1) and spirocyclic amines (**22**, Table 1), in order to probe the scope of the chemistry.

Table 1 Incorporation of amines at position 8 on pyridopyrimidine core **4**[a]

Product	Compound	Entry	R group	Yield
	**17**	1		73 %
	18	2		90 %
	19	3		68 %
	20	4		100 %
	21	5		87 %
	22	6		70 %[b]

a) Amine (12 eq.), NMP, 120-130 °C; b) 2-oxa-6-azaspiro[3.3]heptane oxalate (5 eq.), Et_3N (20 eq.), NMP, 130 °C

Moreover, diversification at this position was not limited to amine replacement and we were able to introduce a number of substituents by exploring a range of reactions (Figure 2). Aryl and heteroaryl groups could be introduced *via* a Suzuki reaction giving access to pyridopyrimidines **23** and **24**, (Figure 2, conditions 1 and 2). Incorporation of sulfonamides was achieved *via* a palladium catalysed reaction affording compound **25** in good yield (85 %) (Figure 2, conditions 3).[19] Oxygen and sulfur nucleophiles can also be used for displacement affording **26** and **27** in high yields (96 and 94 % respectively) (Figure 2, conditions 4 and 5).

The route shown above (Scheme 5) provided rapid diversification at position 8 as variation was introduced in the final step of the reaction sequence.

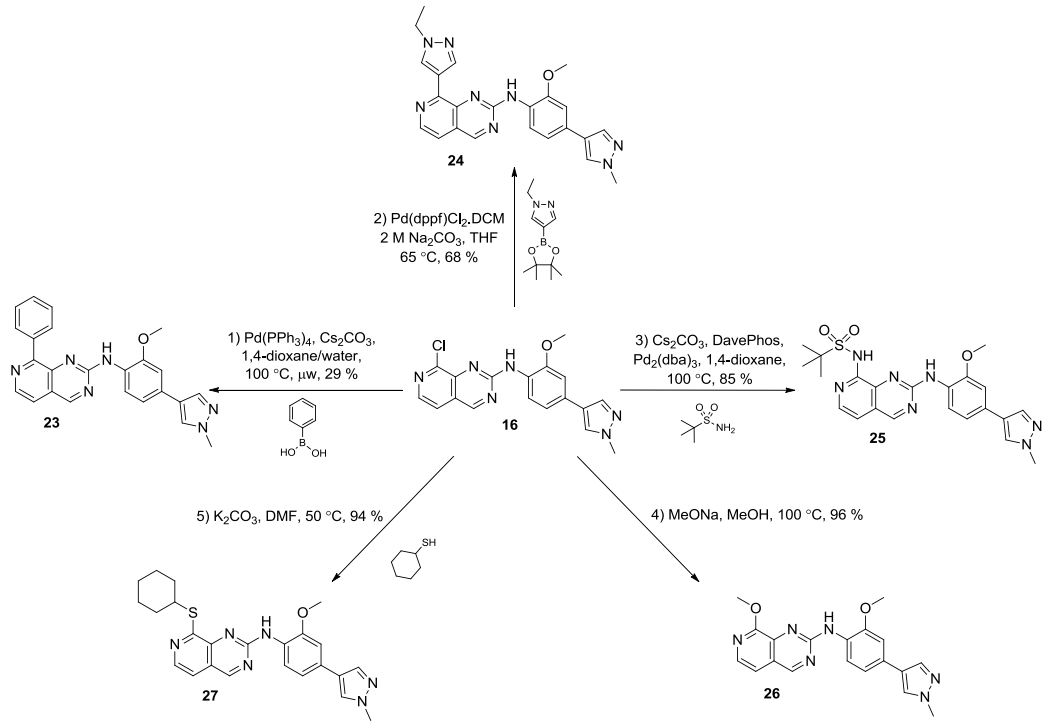
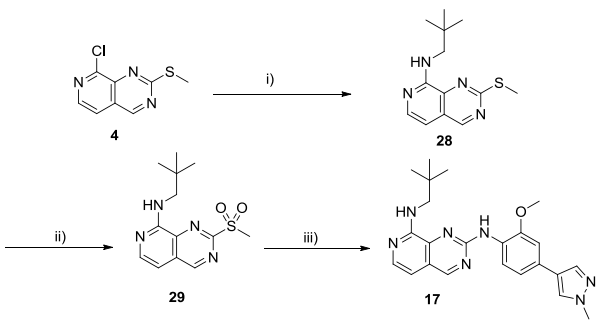


Figure 2 Alternative reactions with chloro intermediate **16**



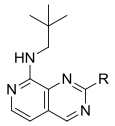
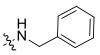
Scheme 6 Alternative reaction sequence from key intermediate **4**. Reagents and conditions: i) neopentylamine, NMP, 80 °C, 74 %; ii) mCPBA, DCM, 0 °C – rt, 68 %; iii) NaH, *N*-(2-methoxy-4-(1-methyl-1H-pyrazol-4-yl)phenyl)formamide **15**, THF, 0 °C – rt, 56 %.

To enable efficient variation at position 2, we reversed the order of the steps. The substituent at position 8 was introduced first, followed by oxidation of the thiomethyl group to the sulfone, to allow subsequent substitution at position 2 (Scheme 6). Amine displacement on intermediate **4** was carried out with neopentylamine at elevated temperature in NMP. Subsequent oxidation of the resulting sulfide **28** with mCPBA gave access to intermediate **29** in high yield (68 %). Displacement of the sulfone with formylated aniline **15** using NaH in THF proceeded in good yield (56 %), to give the expected compound **17** in 28 % over three steps, comparable to the overall yield obtained *via* the alternative route (Scheme 5 and Table 1, entry 1, 38 % over three steps). The reactivity of position 2 on scaffold **29** was then assessed using a range of amines (Table 2), all of which could efficiently be introduced in good yield (56 - 94 %). Treatment with ammonia in 1,4-dioxane satisfactorily afforded primary amine **30** (entry 1).

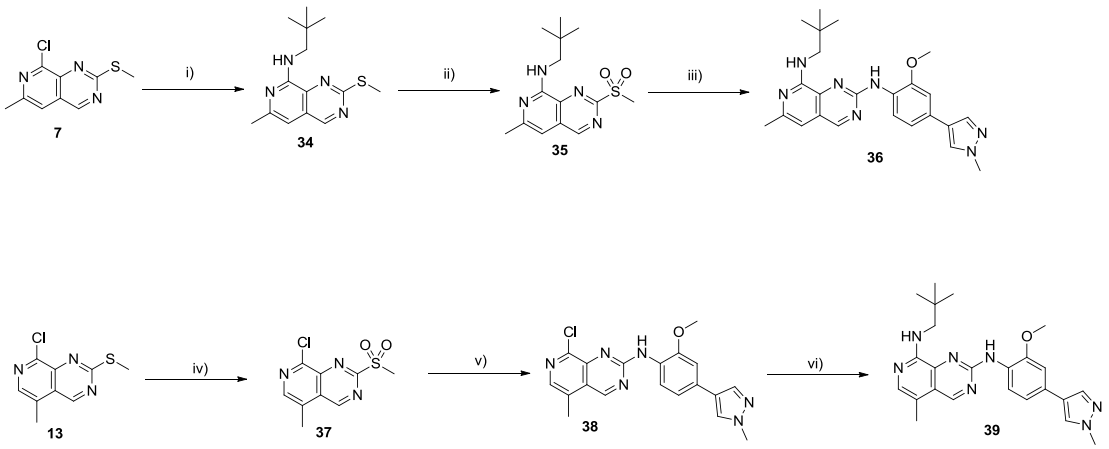
Incorporation of a dimethylamino substituent was performed using a dimethylamine THF solution (entry 2) affording pyridopyrimidine **31** in a 94 % yield. Displacement with cyclohexylamine and benzylamine was also carried out successfully with excess reagent in DMSO furnishing compounds **32** and **33** (entries 3 and 4 respectively). The chemistry shown in Schemes 5 and 6 was also readily applicable to the methyl-substituted cores **7** and **13** illustrating the general applicability of our approach (Scheme 7). Chloride substitution of **7** with neopentylamine gave sulfide **34** which was subsequently oxidised to the sulfoxide **35** with mCPBA. Displacement of the sulfone moiety using formylated aniline **15** finally afforded pyridopyrimidine **36**. Alternatively, oxidation of intermediate **13** furnished sulfone **37**. Displacement with formylated aniline **15** gave chloro derivative **38** which could efficiently be transformed into pyridopyrimidine **39** *via* amine displacement. The ease with which the steps can be reversed, permits rapid and efficient SAR investigation of the 2 and 8 positions of these pyrido[3,4-*d*]pyrimidines.

In order to demonstrate that 2-amino-pyrido[3,4-*d*]pyrimidines have the potential for kinase binding, a selection of compounds were tested for CDK2 inhibition (see Figure 1).[20] The IC_{50} values, presented in Table 3, reach the nanomolar range for tetrahydropyran **19**, alcohol **20** and cyclohexyl derivative **32** (entries 1, 2 and 5 respectively).

Table 2 Introduction of *N*-substituents at position **2**

Compound		Entry	R group	Method	Yield
	**30**	1		a	56 %
	31	2		b	94 %
	32	3		c	85 %
	33	4		c	80 %

a) 0.5 M ammonia in 1,4-dioxane, 100 °C; b) 2 M dimethylamine in THF, 100 °C; c) amine (15 eq), DMSO, 100 °C



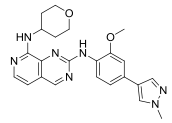
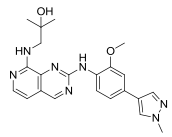
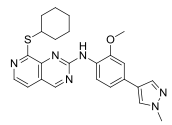
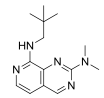
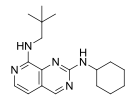
Scheme 7 Modification of 5- and 6-methyl pyridopyrimidines. Reagents and conditions: i) neopentylamine, NMP, 100 °C, 64 %; ii) mCPBA, DCM, 0 °C – rt, 94 %; iii) NaH, *N*-(2-methoxy-4-(1-methyl-1H-pyrazol-4-yl)phenyl)formamide **15**, THF, 0 °C – rt, 32 %; iv) mCPBA, DCM, 0 °C – rt, 72 %; v) NaH, *N*-(2-methoxy-4-(1-methyl-1H-pyrazol-4-yl)phenyl)formamide **15**, THF, 0 °C – rt; vi) neopentylamine, NMP, 130 °C, 31 % over two steps.

On the other hand, sulfur-subtituted compound **27** (entry 3) and dimethylamino pyridopyrimidine **31** (entry 4) are unable to significantly inhibit CDK2 and show IC_{50} values in the high micromolar range. The lack of potency seen for the former is not surprising and can be explained by the absence of the hinge binding motif, whereas in the latter case the large sulfur atom used as a "linker" perhaps prevents the molecule from fitting in the binding pocket.

Conclusions

A significant fraction of small-molecule drug discovery projects target protein kinases and fused pyrimidines have proved to be a particularly successful class of kinase inhibitors. However, due to the large prevalence of fused pyrimidines as kinase inhibitors, the patent landscape has become increasingly crowded making it difficult to discover novel chemotypes. During our work we have identified 2-aminopyrido[3,4-d]pyrimidines as a promising class of fused pyrimidines that have not been utilised to target kinases and for which no comprehensive synthetic approach had been published. We have thus developed robust, reliable and scalable syntheses of suitably substituted 2-aminopyrido[3,4-d]pyrimidine scaffolds 4, 7 and 13 using copper- or palladium-catalysed reactions as key steps. The use of our previously reported ethoxyborolane reagent allowed an ethoxyvinyl group to be efficiently introduced onto an appropriately substituted pyrimidine. Amide formation, cyclisation and chlorination provided the desired pyrido[3,4-d]pyrimidine which was perfectly set up to investigate the structure-activity relationship at both of the required positions. In addition, routes have also been developed to 5- and 6- methyl substituted pyrido[3,4-*d*]pyrimidines intermediates, also *via* the formation of the pyridine ring. These methyl substituted intermediates could be derivatised in a manner similar to the unsubstituted core underscoring the robustness of our approach. The syntheses developed fulfilled the key strategic elements we had set for ourselves, namely the use of a single commercially available starting material, the ability to incorporate a wide range of substituents at position 2 and 8 and the possibility to reverse the order of steps to investigate SAR around both positions through a late stage diversification approach. Finally, the prepared 2-aminopyrido[3,4-*d*]pyrimidines have shown promise as kinase inhibitors by reaching nanomolar IC_{50} values when tested in a CDK2 ATP competitive biochemical assay.

Table 3 CDK2 inhibition data for selected compounds

Compound	Entry	Structure	CDK2 IC_{50} (μM)
19	1		0.016 (0.014, 0.018)
20	2		0.090 ± 0.009
27	3		>100
31	4		44.8 (44.3, 45.3)
32	5		0.274 (0.337, 0.210)

Experimental section

General experimental

Starting materials, reagents and solvents for reactions were reagent grade and used as purchased. Chromatography solvents were HPLC grade and were used without further purification. Thin layer chromatography (TLC) analysis was performed using silica gel 60 F-254 thin layer plates. Flash column chromatography was carried out using columns pre-packed with 40-63 μm silica. Microwave assisted reactions were carried out using a Biotage Initiator microwave system. LCMS and HRMS analyses were performed on a HPLC system with diode array detector operating at 254 nm, fitted with a reverse-phase 50×4.6mm column at a temperature of 22 °C, connected to a Time of Flight (ToF) mass spectrometer (ESI). The following solvent system, at a flow rate of 2 mL/min, was used: solvent A: methanol; solvent B: 0.1 % formic acid in water. Gradient elution was as follows: 1:9 (A:B) to 9:1 (A:B) over 2.5 min., 9:1 (A:B) for 1 min. then reversion back to 1:9 (A:B) over 0.3 min., 1:9 (A:B) for 0.2 min. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 500 MHz spectrometer using an internal deuterium lock. NMR data is given as follows: chemical shift (δ) in ppm, integration, multiplicity and coupling constants (*J*) given in Hz.

Synthetic procedures

(*E*)-Methyl 5-(2-ethoxyvinyl)-2-(methylthio)pyrimidine-4-carboxylate 2

A solution of (*E*)-2-(2-ethoxyvinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane[13] (4.34 g, 21.9 mmol), methyl 5-bromo-2-(methylthio)pyrimidine-4-carboxylate **1** (3.81 g, 14.5 mmol), Pd(dppf)Cl_2·DCM (505 mg, 0.62 mmol) and aq. Na_2CO_3 (2 M, 15 mL) in THF (45 mL) was heated to 65 °C for 18 h. The reaction was quenched with brine and extracted with EtOAc. The combined organics were washed with water and brine, dried and concentrated under reduced pressure. The residue was purified by flash column chromatography (0 – 10 % EtOAc in cyclohexane) to give the title compound (2.30 g, 63 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 8.67 (1H, s), 6.96 (1H, d, *J* = 13.1 Hz), 6.26 (1H, d, *J* = 13.1 Hz), 4.13 – 3.81 (5H, m), 2.60 (3H, s), 1.37 (3H, t, *J* = 7.0 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ_C 169.2, 165.4, 155.8, 151.1, 150.5, 124.8, 98.1, 65.9, 53.0, 14.6, 14.3. HRMS (ESI) m/z calcd for $C_{11}H_{15}N_2O_3S$ $[M+H]^+$ 255.0798, found 255.0797.

2-(Methylthio)pyrido[3,4-*d*]pyrimidin-8(7H)-one 3

(*E*)-Methyl 5-(2-ethoxyvinyl)-2-(methylthio)pyrimidine-4-carboxylate **2** (2.30 g, 9.04 mmol) was treated with NH_3 in MeOH (7 M, 45 mL) and heated to 85 °C for 18 h in a sealed tube. The reaction was concentrated under reduced pressure, the residue was suspended in toluene (50 mL) and pTSA·H_2O (175 mg, 0.92 mmol) was added. The reaction was heated to 90 °C for 2 h. The reaction was concentrated under reduced pressure and the residue purified by flash column chromatography (0 - 5 % MeOH in DCM) to give the title compound (1.47 g, 84 %). ^{1}H NMR (500 MHz, DMSO-d_6) δ_H 11.88 (1H, br s), 9.21 (1H, s), 7.28 (1H, d, *J* = 7.0 Hz), 6.58 (1H, d, *J* = 7.0 Hz), 2.60 (3H, s). ^{13}C NMR (126 MHz, DMSO-d_6) δ_C 169.1, 159.9, 146.8, 130.8, 127.5, 101.3, 14.2. HRMS (ESI) m/z calcd for $C_8H_8N_3OS$ $[M+H]^+$ 194.0383, found 194.0385.

8-Chloro-2-(methylthio)pyrido[3,4-*d*]pyrimidine 4

A solution of 2-(methylthio)pyrido[3,4-*d*]pyrimidin-8(7H)-one **3** (1.47 g, 7.61 mmol) in $POCl_3$ (70 mL) was heated to 70 °C for 18 h. The reaction was concentrated under reduced pressure and partitioned between EtOAc and sat. aq. $NaHCO_3$. The aqueous layer was extracted with EtOAc and the combined organics were washed with water and brine, dried and concentrated under reduced pressure. The residue was purified by flash column chromatography (0 - 20 % EtOAc in cyclohexane) to give the title compound (1.39 g, 86 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 9.24 (1H, s), 8.43 (1H, d, *J* = 5.4 Hz), 7.62 (1H, d, *J* = 5.4 Hz), 2.77 (3H, s). ^{13}C NMR (126 MHz, $CDCl_3$) δ_C 172.6, 159.8, 151.5, 143.0, 142.4, 126.0, 118.5, 14.6. HRMS (ESI) m/z calcd for $C_8H_7ClN_3S$ $[M+H]^+$ 212.0044, found 212.0047.

2-(Methylthio)-5-(prop-1-yn-1-yl)pyrimidine-4-carboxylic acid 5

To a solution of methyl 5-bromo-2-(methylthio)pyrimidine-4-carboxylate **1** (3.00 g, 11.4 mmol) in DMF (30 mL) was added 1-propynyltri-n-butyltin (4.17 mL, 13.7 mmol), $Pd(PPh_3)_4$ (395 mg, 0.34 mmol), copper iodide (65 mg, 0.34 mmol) and Et_3N (1.6 mL, 11 mmol). The reaction was heated to 90 °C under microwave irradiation for 40 min. The reaction was diluted with EtOAc, washed with water and brine, dried and concentrated under reduced pressure. The residue was purified by flash column chromatography (0 - 100 % DCM in cyclohexane) to give the title compound (414 mg, 49 %). ^{1}H NMR (500 MHz, MeOD-d_4) δ_H 8.68 (1H, s), 2.59 (3H, s), 2.10 (3H, s). ^{13}C NMR (126 MHz, MeOD-d_4) δ_C 170.5, 165.8, 161.5 (2C), 112.1, 95.6, 71.6, 12.9, 2.9. HRMS (ESI) m/z calcd for $C_9H_9N_2O_2S$ $[M+H]^+$ 209.0379, found 209.038.

6-Methyl-2-(methylthio)pyrido[3,4-*d*]pyrimidin-8(7*H*)-one 6 (from acid 5)

To a solution of 2-(methylthio)-5-(prop-1-yn-1-yl)pyrimidine-4-carboxylic acid **5** (1.47 g, 7.06 mmol) in toluene (150 mL) was added pTSA·H_2O (300 mg, 1.6 mmol). The reaction was heated to 90 °C for 18 h. Another batch of pTSA·H_2O (200 mg, 1.1 mmol) was added and the reaction heated for a further 18 h. The reaction was concentrated under reduced pressure. The residue was dissolved in NH_3 in MeOH (7 M, 60 mL) and heated to 80 °C for 66 h. The reaction was concentrated under reduced pressure, the residue dissolved in DCM/MeOH and washed with water. The aqueous layer was re-extracted with DCM/MeOH and the washing process repeated twice. The combined organics were dried and concentrated under reduced pressure. The residue was triturated with cyclohexane to give the title compound (909 mg, 62 %). ^{1}H NMR (500 MHz, MeOD-d_4) δ_H 9.03 (1H, s), 6.45 (1H, d, J = 0.9 Hz), 2.67 (3H, s), 2.35 (3H, d, J = 0.9 Hz). ^{13}C NMR (126 MHz, MeOD-d_4) δ_C 169.5, 158.4 (2C), 144.2, 140.0, 127.3, 100.1, 17.7, 13.0. HRMS (ESI) m/z calcd for $C_9H_{10}N_3OS$ $[M+H]^+$ 208.0539, found 208.0544.

8-Chloro-6-methyl-2-(methylthio)pyrido[3,4-*d*]pyrimidine 7

A solution of 6-methyl-2-(methythio)pyrido[3,4-*d*]pyrimidin-8(7H)-one **6** (213 mg, 1.03 mmol) in $POCl_3$ (10 mL) was heated to 50 °C for 25 min. The reaction was concentrated under reduced pressure. The residue was diluted with EtOAc, washed with water, dried and concentrated under reduced pressure to give the title compound (189 mg, 81 %). ^{1}H NMR (500 MHz, MeOD-d_4) δ_H 9.32 (1H, s), 7.70 (1H, d, J = 0.5 Hz), 2.72 (3H, s), 2.66 (3H, d, J = 0.5 Hz). ^{13}C NMR (126 MHz, MeOD-d_4) δ_C 160.6 (2C), 152.3, 140.6, 127.1, 117.6 (2C), 22.2, 13.1. HRMS (ESI) m/z calcd for $C_9H_9ClN_3S$ $[M+H]^+$ 226.0200, found 226.0200.

5-Bromo-2-(methylthio)-*N*-phenylpyrimidine-4-carboxamide 9

A solution of 5-bromo-2-(methylthio)pyrimidine-4-carboxylic acid **8** (20.1 g, 81.0 mmol) in DCM (300 mL) was treated with a drop of DMF and oxalyl chloride (8.63 mL, 102 mmol) at 0 °C. The reaction was stirred for 18 h at rt and then concentrated under reduced pressure. The residue was dissolved in DCM and treated with aniline (12.0 mL, 132 mmol) and Et_3N (24.0 mL, 173 mmol) at 0 °C. The resulting mixture was stirred at rt for 3 days. The reaction was quenched with 0.5 M HCl and extracted with DCM. The combined organics were washed with water and brine, dried and concentrated under reduced pressure to give the title compound (24.9 g, 95 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 9.64 (1H, br s), 8.86 (1H, s), 7.75 (2H, dd, J = 8.5, 1.1 Hz), 7.42 (2H, dd, J = 8.5, 7.5 Hz), 7.22 (1H, t, J = 7.5 Hz), 2.66 (3H, s). ^{13}C NMR (126 MHz, CDCl3) δ_C 170.6, 163.5, 159.3, 152.3, 136.9, 129.2, 125.2, 120.0, 112.5, 14.6. HRMS (ESI) m/z calcd for $C_{12}H_{11}BrN_3OS$ $[M+H]^+$ 323.9801, found 323.9795.

6-Methyl-2-(methylthio)pyrido[3,4-*d*]pyrimidin-8(7H)-one 6 (from amide 9)

A suspension of pentane-2,4-dione (5.10 mL, 49.7 mmol), CuI (487 mg, 2.6 mmol), 5-bromo-2-(methylthio)-*N*-phenylpyrimidine-4-carboxamide **9**, (8.00 g, 24.7 mmol) and Cs_2CO_3 (16.2 g, 49.6 mmol) in MeCN (70 mL) was heated to 85 °C for 18 h. The mixture was treated with AcOH (70 mL) and $AcONH_4$ (28 g, 364 mmol) and heated to 85 °C for 5 h. The reaction was partitioned between sat. aq. $NaHCO_3$ and $CHCl_3$. The aqueous layers were extracted with $CHCl_3$, the combined organics were washed with water and brine, dried and concentrated under reduced pressure. The residue was purified by flash column chromatography (20 - 100 % EtOAc in cyclohexane then 0 - 20 % MeOH in EtOAc) to give the title compound (3.22 g, 63 %). Data consistent with that shown above.

***N*-Allyl-5-bromo-2-(methylthio)pyrimidine-4-carboxamide 11**

A solution of methyl 5-bromo-2-(methylthio)pyrimidine-4-carboxylate **1** (1.00 g, 3.80 mmol) in MeOH (16 mL) was treated with allylamine (3.00 mL, 40.0 mmol) and the reaction heated to 90 °C for 18 h in a sealed tube. The reaction was concentrated under reduced pressure and the residue purified by flash column chromatography (0 - 5 % EtOAc in cyclohexane) to give the title compound (981 mg, 90 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 8.79 (1H, s), 7.73 (1H, br s), 5.94 (1H, ddt, J = 17.1, 10.2, 5.8 Hz), 5.35 – 5.27 (1 H, m), 5.23 (1H, dq, J = 10.2, 1.5 Hz), 4.09 (2H, tt, J = 5.8, 1.5 Hz), 2.60 (3H, s). ^{13}C NMR (126 MHz, $CDCl_3$) δ_C 170.6, 162.9, 161.7, 152.9, 133.4, 117.1, 112.3, 42.0, 14.6. HRMS (ESI) m/z calcd for $C_9H_{11}BrN_3OS$ $[M+H]^+$ 287.9801, found 287.9791.

5-Methyl-2-(methylthio)pyrido[3,4-*d*]pyrimidin-8(7H)-one 12

A solution of *N*-allyl-5-bromo-2-(methylthio)pyrimidine-4-carboxamide **11** (745 mg, 2.6 mmol), Hunig's base (1.80 mL, 10.3 mmol) and Herrmann's catalyst (50 mg, 0.053 mmol) in DMA (14 mL) was heated to 150 °C in a sealed tube for 18 h. The reaction was diluted with DCM and quenched with brine. The aqueous layer was extracted with DCM and the combined organics were washed with water, dried and concentrated under reduced pressure. The residue was purified by flash column chromatography (0 - 5 % MeOH in DCM) to give the title compound (237 mg, 44 %). ^{1}H NMR (500 MHz, DMSO-d_6) δ_H 11.68 (1H, br s), 9.21 (1H, s), 7.07 (1H, dd, *J* = 5.7, 1.2 Hz), 2.61 (3H, s), 2.25 (3H, d, *J* = 1.2 Hz). ^{13}C NMR (126 MHz, DMSO-d_6) δ_C 169.0, 159.5, 157.9, 147.0, 127.9, 127.3, 108.4, 14.2, 13.6. HRMS (ESI) m/z calcd for $C_9H_{10}N_3OS$ $[M+H]^+$ 208.0539, found 208.0536.

8-Chloro-5-methyl-2-(methylthio)pyrido[3,4-*d*]pyrimidine 13

A solution of 5-methyl-2-(methylthio)pyrido[3,4-*d*]pyrimidin-8(7H)-one **12** (235 mg, 1.1 mmol) in $POCl_3$ (8 mL) was heated to 70 °C for 2 h. The reaction was concentrated under reduced pressure and partitioned between EtOAc and sat. aq. $NaHCO_3$. The aqueous layer was extracted with EtOAc and the combined organics were washed with water and brine, dried and concentrated under reduced pressure. The residue was purified by flash column chromatography (0 - 15 % EtOAc in cyclohexane) to give the title compound (197 mg, 77 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 9.38 (1H, s), 8.23 (1H, d, *J* = 1.1 Hz), 2.77 (3H, s), 2.68 (3H, d, *J* = 1.1 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ_C 172.1, 157.5, 149.5, 142.7, 142.1, 127.4, 125.4, 14.6, 14.1. HRMS (ESI) m/z calcd for $C_9H_9ClN_3S$ $[M+H]^+$ 226.0200, found 226.0229.

8-Chloro-2-(methylsulfonyl)pyrido[3,4-*d*]pyrimidine 14

A cooled (0 °C) suspension of 8-chloro-2-(methylthio)pyrido[3,4-*d*]pyrimidine **4** (71.0 mg, 0.34 mmol) in DCM (3 mL) was treated with mCPBA (77 % w/w, 180 mg, 0.80 mmol) and stirred for 18 h, whilst slowly warming to rt. The reaction was quenched with water and extracted with DCM. The combined organics were washed with water, dried and concentrated under reduced pressure. The residue was purified by flash column chromatography (0 - 80 % EtOAc in cyclohexane) to give the title compound (55 mg, 67 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 9.76 (1H, s), 8.77 (1H, d, *J* = 5.5 Hz), 7.89 (1H, d, *J* = 5.5 Hz), 3.59 (3H, s). ^{13}C NMR (126 MHz, $CDCl_3$) δ_C 164.0, 163.4, 154.1, 146.6, 141.7, 129.6, 118.2, 39.1. HRMS (ESI) m/z calcd for $C_8H_7ClN_3O_2S$ $[M+H]^+$ 243.9942, found 243.9945.

***N*-(2-Methoxy-4-(1-methyl-1H-pyrazol-4-yl)phenyl)formamide 15**

A solution of 2-methoxy-4-(1-methyl-1H-pyrazol-4-yl)aniline[21] (110 mg, 0.54 mmol) in formic acid (3 mL) was heated to reflux for 2 h. The reaction was concentrated under reduced pressure and the residue partitioned between sat. aq. $NaHCO_3$ and EtOAc. The aqueous layer was extracted with EtOAc and the combined organics were washed with water and brine, dried and concentrated under reduced pressure. The residue was purified by flash column chromatography (0 - 80 % EtOAc in cyclohexane) to give the title compound (81 mg, 65 %). ^{1}H NMR (500 MHz, DMSO-d_6) δ_H 9.61 (1H, s), 8.27 (1H, d, *J* = 2.0 Hz), 8.15 – 8.05 (2H, m), 7.85 (1H, s), 7.22 (1H, d, *J* = 2.0 Hz), 7.10 (1H, d, *J* = 8.2 Hz), 3.90 (3H, s), 3.85 (3H, s). ^{13}C NMR (126 MHz, DMSO-d_6) δ_C 160.3, 149.4, 136.4, 129.3, 128.1, 125.4, 122.3, 121.1, 117.3, 108.4, 56.3, 39.1. HRMS (ESI) m/z calcd for $C_{12}H_{14}N_3O_2$ $[M+H]^+$ 232.1081, found 232.1081.

8-Chloro-*N*-(2-methoxy-4-(1-methyl-1H-pyrazol-4-yl)phenyl)pyrido[3,4-*d*]pyrimidin-2-amine 16

A cooled (0 °C) solution of *N*-(2-methoxy-4-(1-methyl-1H-pyrazol-4-yl)phenyl)formamide **15** (24 mg, 0.10 mmol) in THF (1 mL) was treated with NaH (60 % w/w in mineral oil, 7.0 mg, 0.18 mmol). After stirring for 20 min at rt, the reaction was cooled to 0 °C and 8-chloro-2-(methylsulfonyl)pyrido[3,4-*d*]pyrimidine **14** (33 mg, 0.14 mmol) was added. The reaction was stirred for 18 h, whilst slowly warming to rt. Aq. NaOH (2 M, 0.5 mL) and MeOH (0.5 mL) were added and the resulting mixture stirred at rt for 1 h. The reaction was concentrated under reduced pressure and the residue partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc and the combined organics were washed with water and brine, dried and concentrated under reduced pressure. The residue was purified by flash column chromatography (0 - 80 % EtOAc in cyclohexane) to give the title compound (30 mg, 79 %). ^{1}H NMR (500 MHz, DMSO-d_6) δ_H 9.47 (1H, s), 8.84 (1H, s), 8.51 (1H, br s), 8.25 (1H, d, *J* = 5.2 Hz), 8.18 (1H, s), 7.92 (1H, s), 7.86 (1H, d, *J* = 5.2 Hz), 7.30 (1H, d, *J* = 1.9 Hz), 7.26 (1H, dd, *J* = 8.3, 1.9 Hz), 3.95 (3H, s), 3.87 (3H, s). ^{13}C NMR (126 MHz, DMSO-d_6) δ_C 163.5, 160.0, 148.7, 143.5, 140.2, 136.5, 129.1, 128.2, 126.1, 124.9, 122.4, 121.1, 120.6, 117.4, 108.3, 56.5, 55.4, 39.1. HRMS (ESI) m/z calcd for $C_{18}H_{16}ClN_6O$ $[M+H]^+$ 367.1069, found 367.1059.

N^2-(2-Methoxy-4-(1-methyl-1H-pyrazol-4-yl)phenyl)-N^8-neopentylpyrido[3,4-*d*]pyrimidine-2,8-diamine 17 (from intermediate 16)

A suspension of 8-chloro-*N*-(2-methoxy-4-(1-methyl-1H-pyrazol-4-yl)phenyl)pyrido[3,4-*d*]pyrimidin-2-amine **16** (27 mg, 0.074 mmol) and neopentylamine (100 µL, 0.86 mmol) in NMP (0.7 mL) was heated to 130 °C in a sealed tube for 5 h. The reaction was quenched with sat. aq. $NaHCO_3$, extracted

with EtOAc, washed with water and brine, dried and concentrated under reduced pressure. The residue was purified by flash column chromatography (0 - 80 % EtOAc in cyclohexane) to give the title compound (22 mg, 73 %). ^{1}H NMR (500 MHz, DMSO-d_6) δ_H 9.17 (1H, s), 8.56 (1H, s), 8.21 – 8.07 (2H, m), 7.88 (1H, d, *J* = 0.8 Hz), 7.76 (1H, d, *J* = 5.7 Hz), 7.28 (1H, d, *J* = 1.8 Hz), 7.15 (1H, dd, *J* = 8.3, 1.8 Hz), 6.85 (1H, d, *J* = 5.7 Hz), 6.65 (1H, t, *J* = 6.2 Hz), 3.93 (3H, s), 3.88 (3H, s), 3.38 (2H, d, *J* = 6.2 Hz), 0.99 (9H, s). ^{13}C NMR (126 MHz, DMSO-d_6) δ_C 161.8, 157.4, 154.7, 150.6, 139.6, 136.9, 136.4, 128.7, 128.1, 126.6, 122.5, 122.0, 121.5, 117.0, 108.5, 106.4, 56.4, 51.5, 39.1, 32.5, 27.7 (3C). HRMS (ESI) m/z calcd for $C_{23}H_{28}N_7O$ $[M+H]^+$ 418.2350, found 418.2352.

N^8-(2-Methoxy-2-methylpropyl)-N^2-(2-methoxy-4-(1-methyl-1H-pyrazol-4-yl)phenyl)pyrido[3,4-*d*]pyrimidine-2,8-diamine 18

A suspension of 8-chloro-*N*-(2-methoxy-4-(1-methyl-1H-pyrazol-4-yl)phenyl)pyrido[3,4-*d*]pyrimidin-2-amine **16** (26 mg, 0.071 mmol) and 2-methoxy-2-methylpropan-1-amine (88 mg, 0.85 mmol) in NMP (0.7 mL) was stirred at 120 °C in a sealed tube for 18 h. The reaction was quenched with sat. aq. $NaHCO_3$ and extracted with EtOAc, washed with water and brine, dried and concentrated under reduced pressure. The residue was purified by flash column chromatography (0 - 90 % EtOAc in cyclohexane) to give the title compound (28 mg, 90 %). ^{1}H NMR (500 MHz, DMSO-d_6) δ_H 9.18 (1H, s), 8.57 (1H, s), 8.17 (1H, d, *J* = 0.9 Hz), 8.12 (1H, d, *J* = 8.2 Hz), 7.89 (1H, d, *J* = 0.9 Hz), 7.77 (1H, d, *J* = 5.7 Hz), 7.29 (1H, d, *J* = 1.9 Hz), 7.15 (1H, dd, *J* = 8.2, 1.9 Hz), 6.88 (1H, d, *J* = 5.7 Hz), 6.67 (1H, t, *J* = 5.5 Hz), 3.93 (3H, s), 3.88 (3H, s), 3.55 (2H, d, *J* = 5.5 Hz), 3.22 (3H, s), 1.19 (6H, s). ^{13}C NMR (126 MHz, DMSO-d_6) δ_C 161.8, 157.3, 154.4, 150.7, 139.6, 136.8, 136.4, 128.7, 128.1, 126.6, 122.5, 122.0, 121.3, 117.0, 108.5, 106.6, 74.6, 56.4, 49.6, 48.2, 39.1, 23.2 (2C). HRMS (ESI) m/z calcd for $C_{23}H_{28}N_7O_2$ $[M+H]^+$ 434.2299, found 434.2296.

N^2-(2-Methoxy-4-(1-methyl-1H-pyrazol-4-yl)phenyl)-N^8-(tetrahydro-2H-pyran-4-yl)pyrido[3,4-*d*]pyrimidine-2,8-diamine 19

A suspension of 8-chloro-N-(2-methoxy-4-(1-methyl-1H-pyrazol-4-yl)phenyl)pyrido[3,4-*d*]pyrimidin-2-amine **16** (26 mg, 0.071 mmol) and tetrahydro-2H-pyran-4-amine (100 µl, 0.97 mmol) in NMP (0.7 mL) was stirred at 135 °C in a sealed tube for 6 h. The reaction was quenched with sat. aq. $NaHCO_3$ and extracted with EtOAc, washed with water and brine, dried and concentrated under reduced pressure. The residue was purified by flash column chromatography (0 - 5 % MeOH in EtOAc) to give the title compound (21 mg, 68 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 8.99 (1H, s), 8.50 (1H, d, *J* = 8.3 Hz), 7.97 (1H, s), 7.89 (1H, d, *J* = 5.7 Hz), 7.80 (1H, d, *J* = 0.8 Hz), 7.66 (1H, d, *J* = 0.8 Hz), 7.18 (1H, dd, *J* = 8.3, 1.9 Hz), 7.06 (1H, d, *J* = 1.8 Hz), 6.79 (1H, d, *J* = 5.7 Hz), 6.40 (1H, d, *J* = 8.0 Hz), 4.37 (1H, dddd, *J* = 14.7, 10.4, 8.3, 4.2 Hz), 4.08 (2H, dt, *J* = 11.9, 3.7 Hz), 4.02 (3H, s), 3.99 (3H, s), 3.68 (2H, td, *J* = 11.5, 2.3 Hz), 2.20 (2H, dd, *J* = 12.9, 2.9 Hz), 1.79 – 1.65 (2H, m). ^{13}C NMR (126 MHz, $CDCl_3$) δ_C 160.7, 156.6, 153.4, 148.5, 139.8, 137.3, 136.6, 127.3, 127.1, 126.7, 123.3, 122.2, 118.4, 117.8, 107.6, 106.2, 66.8, 55.9, 46.3, 39.1, 33.3. HRMS (ESI) m/z calcd for $C_{23}H_{26}N_7O_2$ $[M+H]^+$ 432.2142, found 432.2135.

1-((2-((2-methoxy-4-(1-methyl-1H-pyrazol-4-yl)phenyl)amino)pyrido[3,4-*d*]pyrimidin-8-yl)amino)-2-methylpropan-2-ol 20

A suspension of 8-chloro-N-(2-methoxy-4-(1-methyl-1H-pyrazol-4-yl)phenyl)pyrido[3,4-*d*]pyrimidin-2-amine **16** (26 mg, 0.071 mmol) and 1-amino-2-methylpropan-2-ol (71 mg, 0.80 mmol) in NMP (0.7 mL) was stirred at 130 °C in a sealed tube for 8 h. The reaction was quenched with sat. aq. $NaHCO_3$ and extracted with EtOAc, washed with water and brine, dried and concentrated under reduced pressure. The residue was purified by flash column chromatography (0 - 5 % MeOH in EtOAc) to give the title compound (30 mg, 100 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 8.98 (1H, s), 8.48 (1H, d, *J* = 8.3), 7.97 (1H, s), 7.80 (1H, d, *J* = 5.8 Hz), 7.77 (1H, d, *J* = 0.8 Hz), 7.62 (1H, d, *J* = 0.9 Hz), 7.29 (1H, s), 7.16 (1H, dd, *J* = 8.3, 1.8 Hz), 7.03 (1H, d, *J* = 1.9 Hz), 6.84 (1H, t, *J* = 5.9 Hz), 6.78 (1H, d, *J* = 5.9 Hz), 4.00 (3H, s), 3.97 (3H, s), 3.66 (2H, d, *J* = 5.9 Hz), 1.36 (6H, s). ^{13}C NMR (126 MHz, $CDCl_3$) δ_C 160.7, 156.7, 155.2, 148.4, 138.8, 137.6, 136.5, 127.2, 127.1, 126.7, 123.3, 122.2, 118.4, 117.9, 107.5, 106.8, 71.3, 55.8, 53.4, 39.1, 27.6. HRMS (ESI) m/z calcd for $C_{22}H_{26}N_7O_2$ $[M+H]^+$ 420.2142, found 420.2138.

***N*-(2-Methoxy-4-(1-methyl-1H-pyrazol-4-yl)phenyl)-8-morpholinopyrido[3,4-*d*]pyrimidin-2-amine 21**

A suspension of 8-chloro-*N*-(2-methoxy-4-(1-methyl-1H-pyrazol-4-yl)phenyl)pyrido[3,4-*d*]pyrimidin-2-amine **16** (26 mg, 0.071 mmol) and morpholine (75 µL, 0.86 mmol) in NMP (0.7 mL) was heated to 120 °C in a sealed tube for 3 h. The reaction was quenched with sat. aq. $NaHCO_3$, extracted with EtOAc, washed with water and brine, dried and concentrated under reduced pressure. The residue was purified by flash column chromatography (0 - 100 % EtOAc in cyclohexane) to give the title compound (26 mg, 87 %). ^{1}H NMR (500 MHz, DMSO-d_6) δ_H 9.27 (1H, s), 8.59 (1H, s), 8.20 (1H, s), 8.04 (1H, d, *J* = 8.2 Hz), 7.98 (1H, d, *J* = 5.4 Hz), 7.93 (1H, d, *J* = 0.9 Hz), 7.28 (1H, d, *J* = 1.8 Hz), 7.25 – 7.20 (2H, m), 3.91 (3H, s), 3.88 (3H, s), 3.79 – 3.67 (8H, m). ^{13}C NMR (126 MHz, DMSO-d_6) δ_C 163.0, 156.5, 156.4, 151.0, 139.2, 139.0, 136.5, 129.2, 128.2, 126.5, 124.1, 122.5, 122.3, 117.1, 111.9, 108.3, 66.8, 56.3, 49.2, 39.1. HRMS (ESI) m/z calcd for $C_{22}H_{24}N_7O_2$ $[M+H]^+$ 418.1986, found 418.1983.

N-(2-Methoxy-4-(1-methyl-1H-pyrazol-4-yl)phenyl)-8-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyrido[3,4-*d*]pyrimidin-2-amine 22

A suspension of 8-chloro-*N*-(2-methoxy-4-(1-methyl-1H-pyrazol-4-yl)phenyl)pyrido[3,4-*d*]pyrimidin-2-amine **16** (26 mg, 0.071 mmol), 2-oxa-6-azaspiro[3.3]heptane oxalate (67 mg, 0.35 mmol) and Et_3N (200 µL, 1.5 mmol) in NMP (0.7 mL) was heated to 130 °C in a sealed tube for 6 h. The reaction was quenched with sat. aq. $NaHCO_3$, extracted with EtOAc, washed with water and brine, dried and concentrated under reduced pressure. The residue was purified by flash column chromatography (0 - 5 % MeOH in EtOAc) to give the title compound (22 mg, 70 %). ^{1}H NMR (500 MHz, DMSO-d_6) δ_H 9.18 (1H, s), 8.45 (1H, s), 8.18 (1H, d, *J* = 0.9 Hz), 7.99 (1H, d, *J* = 8.1 Hz), 7.92 (1H, d, *J* = 0.8 Hz), 7.84 (1H, d, *J* = 5.5 Hz), 7.33 – 7.18 (2H, m), 6.97 (1H, d, *J* = 5.4 Hz), 4.73 (4H, s), 4.46 (4H, s), 3.92 (3H, s), 3.89 (3H, s). ^{13}C NMR (126 MHz, DMSO-d_6) δ_C 161.8, 157.0, 155.8, 151.0, 139.5, 138.4, 136.5, 128.9, 128.1, 126.5, 123.4, 122.6, 122.5, 117.1, 108.6, 108.4, 80.5, 62.6, 56.3, 39.6, 39.1. HRMS (ESI) m/z calcd for $C_{23}H_{24}N_7O_2$ $[M+H]^+$ 430.1986, found 430.1990.

N-(2-Methoxy-4-(1-methyl-1H-pyrazol-4-yl)phenyl)-8-phenylpyrido[3,4-*d*]pyrimidin-2-amine 23

To a solution of 8-chloro-*N*-(2-methoxy-4-(1-methyl-1H-pyrazol-4-yl)phenyl)pyrido[3,4-*d*]pyrimidin-2-amine **16** (25 mg, 0.068 mmol) in 1,4-dioxane/water (2:1, 3 mL) was added phenyl boronic acid (17 mg, 0.14 mmol), $Pd(PPh_3)_4$ (16 mg, 0.014 mmol) and Cs_2CO_3 (33 mg, 0.10 mmol). The reaction was heated to 100 °C under microwave irradiation for 30 min. The reaction was diluted with EtOAc and water, dried and concentrated under reduced pressure. The residue was purified by flash column chromatography (0 - 100 % EtOAc in cyclohexane), followed by SCX-2 purification (MeOH – 1M NH_3 in MeOH) to give the title compound (8.1 mg, 29 %). ^{1}H NMR (500 MHz, MeOD-d_4) δ_H 9.37 (1H, s), 8.56 (1H, d, *J* = 8.5 Hz), 8.50 (1H, d, *J* = 5.5 Hz), 8.11-8.09 (2H, m), 7.97 (1H, s), 7.82 (1H, s), 7.79 (1H, d, *J* = 5.5 Hz), 7.61-7.59 (3H, m), 7.19 (1H, d, *J* = 2.0 Hz), 6.99 (1H, dd, *J* = 8.5, 2.0 Hz), 4.02 (3H, s), 3.95 (3H, s). ^{13}C NMR (126 MHz, MeOD-d_4) δ_C 162.0, 157.7, 156.7, 148.1, 144.4, 141.2, 137.9, 136.6, 130.7 (2C), 129.1, 127.9 (2C), 127.1, 127.0, 126.7, 123.8, 123.3, 118.9, 118.1, 118.0, 107.3, 55.8, 39.1. HRMS (ESI) m/z calcd for $C_{24}H_{21}N_6O$ $[M+H]^+$ 409.1777, found 409.1771.

8-(1-Ethyl-1H-pyrazol-4-yl)-N-(2-methoxy-4-(1-methyl-1H-pyrazol-4-yl)phenyl)pyrido[3,4-*d*]pyrimidin-2-amine 24

A solution of 8-chloro-*N*-(2-methoxy-4-(1-methyl-1H-pyrazol-4-yl)phenyl)pyrido[3,4-*d*]pyrimidin-2-amine **16** (35 mg, 0.095 mmol), 1-ethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (32 mg, 0.14 mmol) and $Pd(dppf)Cl_2$·DCM (8.0 mg, 9.8 µmol) in THF (0.6 mL) and aq. Na_2CO_3 (2M, 0.2 mL) was heated to 65 °C for 18 h. The reaction was partitioned between DCM and sat. aq. $NaHCO_3$. The aqueous layer was extracted with DCM three times and the combined organics were dried and concentrated under reduced pressure. The residue was purified by flash column chromatography (0 - 5 % MeOH in EtOAc) to give the title compound (28 mg, 68 %). ^{1}H NMR (500 MHz, DMSO-d_6) δ_H 9.35 (1H, s), 9.10 (1H, s), 8.50 (1H, s), 8.33 (1H, d, *J* = 5.3 Hz), 8.23 (1H, s), 8.21 (1H, s), 7.96 (1H, d, *J* = 0.9 Hz), 7.67 (1H, d, *J* = 8.1 Hz), 7.56 (1H, d, *J* = 5.3 Hz), 7.37 (1H, d, *J* = 1.9 Hz), 7.28 (1H, dd, *J* = 8.1, 1.9 Hz), 3.99 (2H, q, *J* = 7.2 Hz), 3.90 (3H, s), 3.84 (3H, s), 1.22 (3H, t, *J* = 7.2 Hz). ^{13}C NMR (126 MHz, DMSO-d_6) δ_C 163.5, 159.3, 153.8, 150.1, 143.1, 140.3, 139.4, 136.6, 131.6, 131.3, 128.3, 126.5, 126.0, 123.1, 122.4, 120.1, 117.2, 109.0, 56.2, 46.8, 39.2, 16.0. HRMS (ESI) m/z calcd for $C_{23}H_{23}N_8O$ $[M+H]^+$ 427.1989, found 427.1967.

N-(2-(2-Methoxy-4-(1-methyl-1H-pyrazol-4-yl)phenylamino)pyrido[3,4-*d*]pyrimidin-8-yl)-2-methylpropane-2-sulfonamide 25

A suspension of 8-chloro-*N*-(2-methoxy-4-(1-methyl-1H-pyrazol-4-yl)phenyl)pyrido[3,4-*d*]pyrimidin-2-amine **16** (27 mg, 0.074 mmol), *tert*-butylsulfonamide (13 mg, 0.095 mmol), tris(dibenzylideneacetone)dipalladium(0) (2.0 mg, 2.2 µmol), Cs_2CO_3 (34 mg, 0.10 mmol) and DavePhos (3.0 mg, 7.6 µmol) in 1,4-dioxane (0.7 mL) (degassed) was heated to 100 °C for 18 h. The reaction was quenched with water, extracted with EtOAc, washed with brine, dried and concentrated under reduced pressure. The residue was purified by flash column chromatography (0 - 90 % EtOAc in cyclohexane) to give the title compound (29 mg, 85 %). ^{1}H NMR (500 MHz, DMSO-d_6) δ_H 11.97 (1H, s), 9.17 (1H, s), 8.84 (1H, br s), 8.50 (1H, s), 8.16 (1H, s), 7.88 (1H, s), 7.36 (1H, d, *J* = 7.0 Hz), 7.27 (1H, d, *J* = 1.9 Hz), 7.06 (1H, dd, *J* = 8.4, 1.9 Hz), 6.89 (1H, d, *J* = 7.0 Hz), 3.96 (3H, s), 3.88 (3H, s), 1.48 (9H, s). ^{13}C NMR (126 MHz, DMSO-d_6) δ_C 161.3, 158.1, 151.7, 149.3, 145.8, 136.4, 128.0, 127.2, 126.8, 123.0, 122.46, 120.0, 117.1, 108.1, 105.9, 58.2, 56.5, 39.1, 24.2 (3C). HRMS (ESI) m/z calcd for $C_{22}H_{26}N_7O_3S$ $[M+H]^+$ 468.1812, found 468.1808.

8-Methoxy-N-(2-methoxy-4-(1-methyl-1H-pyrazol-4-yl)phenyl)pyrido[3,4-*d*]pyrimidin-2-amine 26

To a solution of 8-chloro-*N*-(2-methoxy-4-(1-methyl-1H-pyrazol-4-yl)phenyl)pyrido[3,4-*d*]pyrimidin-2-amine **16** (26 mg, 0.071 mmol) in MeOH (1 mL) was added NaOMe (42 mg, 0.78 mmol). The reaction was heated to 100 °C for 5 h, before concentration under reduced pressure. The residue was purified by flash column chromatography (0 - 70 % EtOAc in cyclohexane) to give the title compound (25 mg, 96 %). ^{1}H NMR (500 MHz, DMSO-d_6) δ_H 9.33 (1H, s), 8.55 (1H, s), 8.37 (1H, br d, *J* = 8.2 Hz), 8.17 (1H, s), 7.94 (1H, d, *J* = 5.5 Hz), 7.91 (1H, d, *J* = 0.8 Hz), 7.38 (1H, d, *J* = 5.5 Hz), 7.28 (1H, d, *J* = 1.9 Hz), 7.23 (1H, dd, *J* = 8.2, 1.9 Hz), 4.06 (3H, s), 3.94 (3H, s), 3.88 (3H, s). ^{13}C NMR (126 MHz, DMSO-d_6) δ_C 162.1, 159.0, 158.1, 150.3, 138.3, 137.5, 136.5, 128.5, 128.1, 126.7,

124.3, 122.5, 121.1, 117.4, 113.5, 108.3, 56.5, 54.3, 39.1. HRMS (ESI) m/z calcd for $C_{19}H_{19}N_6O_2$ $[M+H]^+$ 363.1564, found 363.1561.

8-(Cyclohexylthio)-*N*-(2-methoxy-4-(1-methyl-1H-pyrazol-4-yl)phenyl)pyrido[3,4-*d*]pyrimidin-2-amine 27

To a suspension of 8-chloro-*N*-(2-methoxy-4-(1-methyl-1H-pyrazol-4-yl)phenyl)pyrido[3,4-*d*]pyrimidin-2-amine **16** (26 mg, 0.071 mmol) and K_2CO_3 (15 mg, 0.11 mmol) in DMF (0.35 mL) was added cyclohexanethiol (12 µL, 0.098 mmol) and the reaction stirred at rt for 4 days. Additional batches of K_2CO_3 (10 mg, 0.070 mmol) and cyclohexanethiol (12 µL, 0.098 mmol) were added and the reaction stirred at 50 °C for 18 h. The reaction was quenched with brine, extracted with EtOAc, washed with water and brine, dried and concentrated under reduced pressure. The residue was purified by flash column chromatography (0 - 80 % EtOAc in cyclohexane) to give the title compound (30 mg, 94 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 9.06 (1H, s), 8.93 (1H, d, *J* = 8.4 Hz), 8.27 (1H, d, *J* = 5.4 Hz), 8.20 (1H, s), 7.80 (1H, d, *J* = 0.8 Hz), 7.65 (1H, d, *J* = 0.8 Hz), 7.32 – 7.26 (1H, m), 7.18 (1H, d, *J* = 5.4 Hz), 7.03 (1H, d, *J* = 1.9 Hz), 4.12 – 4.04 (1H, m), 4.00 (3H, s), 3.98 (3H, s), 2.29 – 2.16 (2H, m), 1.92 – 1.82 (2H, m), 1.75 – 1.49 (6H, m). ^{13}C NMR (126 MHz, $CDCl_3$) δ_C 161.3, 160.5, 156.3, 148.1, 144.4, 140.9, 136.6, 127.2, 126.8, 126.7, 123.5, 121.2, 118.7, 118.5, 113.3, 107.2, 55.8, 41.5, 39.1, 33.2, 26.4, 26.0. HRMS (ESI) m/z calcd for $C_{24}H_{27}N_6OS$ $[M+H]^+$ 447.1962, found 447.1948.

2-(Methylthio)-*N*-neopentylpyrido[3,4-*d*]pyrimidin-8-amine 28

To a solution of 8-chloro-2-(methylthio)pyrido[3,4-*d*]pyrimidine **4** (1 g, 4.72 mmol) in NMP (15 mL) was added neopentylamine (5.5 mL, 4.72 mmol). The reaction was heated to 80 °C in a sealed tube for 20 h before being quenched with sat. aq. $NaHCO_3$ and extracted with EtOAc. The combined organics were washed with water and brine, dried and concentrated under reduced pressure. The residue was purified by flash column chromatography (0 - 100 % EtOAc in cyclohexane) to give the title compound (915 mg, 74 %). ^{1}H NMR (500 MHz, MeOD-d_4) δ_H 9.10 (1H, s), 7.87 (1H, d, *J* = 5.9 Hz), 6.87 (1H, d, *J* = 5.9 Hz), 3.43 (2H, s), 2.66 (3H, s), 1.04 (9H, s). ^{13}C NMR (126 MHz, MeOD-d_4) δ_C 168.4, 159.1, 141.4 (2C), 136.8, 124.4, 105.3, 51.3, 31.9, 26.3 (3C), 13.0. HRMS (ESI) m/z calcd for $C_{13}H_{19}N_4S$ $[M+H]^+$ 263.1330, found 263.1331.

2-(Methylsulfonyl)-*N*-neopentylpyrido[3,4-*d*]pyrimidin-8-amine 29

To a cooled (0 °C) solution of 2-(methylthio)-*N*-neopentylpyrido[3,4-*d*]pyrimidin-8-amine **28** (1.0 g, 4.72 mmol) in DCM (40 mL) was added portion-wise mCPBA (77 % w/w, 2.54 g, 11.3 mmol). The reaction was stirred for 18 h, whilst slowly warming to rt. The reaction was quenched with water and diluted with DCM. The combined organics were washed with sat. aq. $NaHCO_3$ and brine, dried and concentrated under reduced pressure. The residue was purified by flash column chromatography (0 - 100 % EtOAc in cyclohexane) to give the title compound (700 mg, 68 %). ^{1}H NMR (500 MHz, MeOD-d_4) δ_H 9.51 (1H, s), 8.18 (1H, d, *J* = 5.7 Hz), 7.04 (1H, d, *J* = 5.7 Hz), 3.53 (2H, s), 3.48 (3H, s), 1.04 (9H, s). ^{13}C NMR (126 MHz, MeOD-d_4) δ_C 161.2, 160.3, 146.7 (2C), 135.3, 129.5, 104.8, 51.4, 38.5, 32.4, 26.5 (3C). HRMS (ESI) m/z calcd for $C_{13}H_{19}N_4O_2S$ $[M+H]^+$ 295.1229, found 295.1226.

N^2-(2-Methoxy-4-(1-methyl-1H-pyrazol-4-yl)phenyl)-N^8-neopentylpyrido[3,4-*d*]pyrimidine-2,8-diamine 17 (from intermediate 29)

A cooled (0°C) solution of *N*-(2-methoxy-4-(1-methyl-1H-pyrazol-4-yl)phenyl)formamide **15** (19 mg, 0.082 mmol) in THF (3 mL) was treated with NaH (60 % w/w in mineral oil, 4.0 mg, 0.11 mmol). After stirring for 10 mins at rt, the reaction was cooled to 0 °C and 2-(methylsulfonyl)-*N*-neopentylpyrido[3,4-*d*]pyrimidin-8-amine **29** (20 mg, 0.068 mmol) was added. The reaction was stirred for 18 h, whilst slowly warming to rt. Aq. NaOH (2 M, 2 mL) and MeOH (2 mL) were added and the resulting suspension was stirred at rt for 45 min. The reaction was concentrated under reduced pressure and purified by flash column chromatography (0 - 10 % MeOH in DCM then 0-10 % MeOH in EtOAc) to give the title compound (16 mg, 56 %). Data consistent with that shown above.

N^8-Neopentylpyrido[3,4-*d*]pyrimidine-2,8-diamine 30

2-(Methylsulfonyl)-*N*-neopentylpyrido[3,4-*d*]pyrimidin-8-amine **29** (20 mg, 0.068 mmol) was treated with ammonia (0.5 M in 1,4-dioxane, 1 mL, 0.50 mmol) and heated to 100 °C in a sealed tube for 4 days. The reaction was concentrated under reduced pressure. The residue was purified by flash column chromatography (0 - 3 % MeOH in DCM) to give the title compound (9 mg, 56 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 8.89 (1H, s), 7.82 (1H, d, *J* = 5.8 Hz), 6.69 (1H, d, *J* = 5.8 Hz), 6.54 (1H, s), 5.20 (2H, s), 3.42 (2H, d, *J* = 6.1 Hz), 1.06 (9H, s). ^{13}C NMR (126 MHz, $CDCl_3$) δ_C 161.1, 159.9, 154.6, 139.3, 138.1, 121.6, 105.5, 52.0, 32.1, 27.5 (3C). HRMS (ESI) m/z calcd for $C_{12}H_{18}N_5$ $[M+H]^+$ 232.1562, found 232.1558.

N^2,N^2-Dimethyl-N^8-neopentylpyrido[3,4-*d*]pyrimidine-2,8-diamine 31

2-(Methylsulfonyl)-*N*-neopentylpyrido[3,4-*d*]pyrimidin-8-amine **29** (20 mg, 0.068 mmol) was treated with dimethylamine in THF (2 M, 1 mL, 2.00 mmol) and heated to 100 °C in a sealed tube for 18 h. The reaction was concentrated under reduced pressure. The residue was purified by flash column chromatography (0 - 10 % EtOAc in cyclohexane) to give the title compound (17 mg, 94 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ_H

8.87 (1 H, s), 7.75 (1 H, d, *J* = 5.8), 6.66 (1 H, d, *J* = 5.8 Hz), 6.59 (1 H, br s), 3.43 (2 H, d, *J* = 6.0 Hz), 3.30 (6 H, s), 1.06 (9 H, s). ^{13}C NMR (126 MHz, $CDCl_3$) δ_C 160.0, 159.7, 154.6, 138.4, 138.0, 119.5, 105.6, 52.0, 37.2, 32.0, 27.5 (3C). HRMS (ESI) m/z calcd for $C_{14}H_{22}N_5$ $[M+H]^+$ 260.1875, found 260.1880.

N^2-Cyclohexyl-N^8-neopentylpyrido[3,4-*d*]pyrimidine-2,8-diamine 32

To a solution of 2-(methylsulfonyl)-*N*-neopentylpyrido[3,4-*d*]pyrimidin-8-amine **29** (20 mg, 0.068 mmol) in DMSO (1 mL) was added cyclohexylamine (0.12 mL, 1.02 mmol). The reaction was heated to 100 °C in a sealed tube for 18 h. The reaction was diluted with EtOAc and water. The aqueous layer was extracted with EtOAc and the combined organics were dried and concentrated under reduced pressure. The residue was purified by flash column chromatography (0 - 10 % MeOH in DCM) to yield the title compound (18 mg, 85 %). ^{1}H NMR (500 MHz, MeOD-d_4) δ_H 8.88 (1H, s), 7.56 (1H, d, *J* = 5.8 Hz), 6.74 (1H, d, *J* = 5.8 Hz), 3.85 (1H, m), 3.36 (2H, s), 2.16-2.11 (2H, m), 1.87-1.82 (2H, m), 1.72 (1H, m), 1.50-1.28 (6H, m), 1.06 (9H, s). ^{13}C NMR (126 MHz, MeOD-d_4) δ_C 160.6 (2C), 136.3 (2C), 120.2, 105.8 (2C), 51.6, 50.4, 32.0 (3C), 26.3 (3C), 25.6, 25.0 (2C). HRMS (ESI) m/z calcd for $C_{18}H_{28}N_5$ $[M+H]^+$ 314.2345, found 314.2340.

N^2-Benzyl-N^8-neopentylpyrido[3,4-*d*]pyrimidine-2,8-diamine 33

To a solution of 2-(methylsulfonyl)-*N*-neopentylpyrido[3,4-*d*]pyrimidin-8-amine **29** (20 mg, 0.068 mmol) in DMSO (1 mL) was added benzylamine (0.11 mL, 1.02 mmol). The reaction was heated to 100 °C in a sealed tube for 18 h. The reaction was diluted with EtOAc and water. The aqueous layer was extracted with EtOAc and the combined organics were dried and concentrated under reduced pressure. The residue was purified by flash column chromatography (0 - 10 % MeOH in DCM) to yield the title compound (17.5 mg, 80 %). ^{1}H NMR (500 MHz, MeOD-d_4) δ_H 8.92 (1H, s), 7.57 (1H, d, *J* = 6.0 Hz), 7.41 (2H, br d, *J* = 7.6 Hz), 7.30 (2H, app t, *J* = 7.6 Hz), 7.22 (1H, app t, *J* = 7.6 Hz), 6.74 (1H, d, *J* = 6.0 Hz), 4.67 (2H, s), 3.30 (2H, s), 0.98 (9H, s). ^{13}C NMR (126 MHz, MeOD-d_4) δ_C 160.7 (2C), 136.7, 128.2, 128.1 (2C), 127.2, 126.7 (2C), 126.5 (2C), 120.6, 105.7, 51.5, 44.8, 26.4 (3C). HRMS (ESI) m/z calcd for $C_{19}H_{24}N_5$ $[M+H]^+$ 322.2032, found 322.2033.

6-Methyl-2-(methylthio)-*N*-neopentylpyrido[3,4-*d*]pyrimidin-8-amine 34

To a solution of 8-chloro-6-methyl-2-(methythio)pyrido[3,4-*d*]pyrimidine **7** (232 mg, 1.0 mmol) in NMP (10 mL) was added neopentylamine (0.24 mL, 2.1 mmol) and Et_3N (0.72 mL, 5.1 mmol). The reaction was heated to 100 °C in a sealed tube for 18 h. The reaction was diluted with EtOAc and water, dried and concentrated under reduced pressure. The residue was purified by flash column chromatography (0 - 50 % EtOAc in cyclohexane) to give the title compound (133 mg, 64 %). ^{1}H NMR (500 MHz, MeOD-d_4) δ_H 9.02 (1H, s), 6.71 (1H, d, *J* = 0.6 Hz), 3.47 (2H, s), 2.66 (3H, s), 2.44 (3H, d, *J* = 0.6 Hz), 1.04 (9H, s). ^{13}C NMR (126 MHz, MeOD-d_4) δ_C 166.9, 158.6, 154.2, 151.5, 135.1, 125.0, 102.8, 51.2, 31.9, 26.4 (3C), 23.1, 13.0. HRMS (ESI) m/z calcd for $C_{14}H_{21}N_4S$ $[M+H]^+$ 277.1481, found 277.1467.

6-Methyl-2-(methylsulfonyl)-*N*-neopentylpyrido[3,4-*d*]pyrimidin-8-amine 35

A cooled (0 °C) solution of 6-methyl-2-(methylthio)-*N*-neopentylpyrido[3,4-*d*]pyrimidin-8-amine **34** (133 mg, 0.48 mmol) in DCM (30 mL) was treated with mCPBA (77 % w/w, 260 mg, 1.16 mmol) and stirred for 18 h, whilst slowly warming to rt. An additional batch of mCPBA (77 % w/w, 30 mg, 0.13 mmol) was added and the reaction stirred for a further 2 h at rt. The reaction was quenched with sat. aq. $NaHCO_3$ and diluted with DCM. The organic layer was washed with brine, dried and concentrated under reduced pressure. The residue was purified by flash column chromatography (0 - 100 % EtOAc in cyclohexane) to give the title compound (140 mg, 94 %). ^{1}H NMR (500 MHz, MeOD-d_4) δ_H 9.39 (1H, s), 6.89 (1H, s), 3.55 (2H, s), 3.45 (3H, s), 2.52 (3H, s), 1.04 (9H, s). ^{13}C NMR (126 MHz, MeOD-d_4) δ_C 160.3, 159.3, 157.5, 155.7, 133.4, 130.0, 102.6, 51.3, 38.6, 32.5, 26.6 (3C), 23.7. HRMS (ESI) m/z calcd for $C_{14}H_{21}N_4O_2S$ $[M+H]^+$ 309.138, found 309.1364.

N^2-(2-Methoxy-4-(1-methyl-1H-pyrazol-4-yl)phenyl)-6-methyl-N^8-neopentylpyrido[3,4-*d*]pyrimidine-2,8-diamine 36

A cooled (0 °C) suspension of *N*-(2-methoxy-4-(1-methyl-1H-pyrazol-4-yl)phenyl)formamide **15** (8.5 mg, 0.037 mmol) in THF (1 mL) was treated with NaH (60 % w/w dispersion in mineral oil, 2.4 mg, 0.059 mmol). After stirring at rt for 10 min. the reaction was cooled (0 °C) and 6-methyl-2-(methylsulfonyl)-*N*-neopentylpyrido[3,4-*d*]pyrimidin-8-amine **35** (12.5 mg, 0.040 mmol) in THF (1 mL) was added. The reaction was stirred for 5 h, whilst slowly warming to rt. The reaction was concentrated under reduced pressure. The residue was diluted with EtOAc and water. The aqueous layers were re-extracted with EtOAc and DCM. The combined organics were washed with water and brine, dried and concentrated under reduced pressure. The residue was purified by flash column chromatography (50 - 100 % EtOAc in cyclohexane), followed by SCX-2 purification (MeOH - 1M NH_3 in MeOH) to give the title compound (5 mg, 32 %). ^{1}H NMR (500 MHz, MeOD-d_4) δ_H 8.96 (1H, s), 8.41 (1H, d, *J* = 8.3 Hz), 7.95 (1H, s), 7.82 (1H, d, *J* = 0.7 Hz), 7.21 (1H, d, *J* = 1.9 Hz), 7.13 (1H, dd, *J* = 8.3, 1.9 Hz), 6.66 (1H, d, *J* = 0.7 Hz), 4.01 (3H, s), 3.95 (3H, s), 3.44 (2H, s), 2.42 (3H, s), 1.10 (9H, s). ^{13}C NMR (126 MHz, MeOD-d_4) δ_C 160.3, 156.3, 149.2, 148.0, 135.8, 135.4, 127.4, 127.2, 127.1, 123.2, 122.6, 118.8, 116.8, 107.4, 103.4,

55.1, 51.6, 37.5, 31.5, 26.4 (3C), 22.6. HRMS (ESI) m/z calcd for $C_{24}H_{30}N_7O$ $[M+H]^+$ 432.2506, found 432.2502.

8-Chloro-5-methyl-2-(methylsulfonyl)pyrido[3,4-*d*]pyrimidine 37

A cooled (0 °C) suspension of 8-chloro-5-methyl-2-(methylthio)pyrido[3,4-*d*]pyrimidine **13** (53 mg, 0.24 mmol) in DCM (2.5 mL) was treated with mCPBA (77 % w/w, 150 mg, 0.67 mmol) and stirred for 18 h, whilst slowly warming to rt. The reaction was quenched with water and extracted with DCM, washed with water and sat. aq. $NaHCO_3$, dried and concentrated under reduced pressure. The residue was purified by flash column chromatography (0 - 60 % EtOAc in cyclohexane) to give the title compound (44 mg, 72 %). ^{1}H NMR (500 MHz, DMSO-d_6) δ_H 10.19 (1H, s), 8.63 (1H, d, J = 1.0 Hz), 3.56 (3H, s), 2.78 (3H, d, J = 1.1 Hz). ^{13}C NMR (126 MHz, DMSO-d_6) δ_C 163.5, 163.5, 150.0, 146.0, 141.2, 130.1, 129.7, 39.7, 14.4. HRMS (ESI) m/z calcd for $C_9H_9ClN_3O_2S$ $[M+H]^+$ 258.0104, found 258.0095.

N^2-(2-Methoxy-4-(1-methyl-1H-pyrazol-4-yl)phenyl)-5-methyl-N^8-neopentylpyrido[3,4-*d*]pyrimidine-2,8-diamine 39

A cooled (0 °C) solution of *N*-(2-methoxy-4-(1-methyl-1H-pyrazol-4-yl)phenyl)formamide **15** (35 mg, 0.15 mmol) in THF (1 mL) was treated with NaH (60 % w/w dispersion in mineral oil, 8.0 mg, 0.20 mmol). After stirring for 20 min. at rt, the reaction was cooled to 0 °C and 8-chloro-5-methyl-2-(methylsulfonyl)pyrido[3,4-*d*]pyrimidine **37** (42 mg, 0.16 mmol) was added in THF (2 mL). The reaction was stirred for 18 h, whilst slowly warming to rt. Aq. NaOH (2 M, 1 mL) and MeOH (1 mL) were added and the resulting mixture stirred at rt for 1 h. The reaction was concentrated under reduced pressure and the residue partitioned between DCM and water. The aqueous layer was extracted with DCM and the combined organics were dried and concentrated under reduced pressure. The residue was purified by flash column chromatography (0 - 75 % EtOAc in cyclohexane) to give 8-chloro-*N*-(2-methoxy-4-(1-methyl-1H-pyrazol-4-yl)phenyl)-5-methylpyrido[3,4-d]pyrimidin-2-amine **38** (ca. 35 mg).

A mixture of 8-chloro-*N*-(2-methoxy-4-(1-methyl-1H-pyrazol-4-yl)phenyl)-5-methylpyrido[3,4-*d*]pyrimidin-2-amine **38** (ca. 35 mg) and neopentylamine (110 µL, 0.93 mmol) in NMP (0.7 mL) was stirred at 130 °C in a sealed tube for 13 h. An additional batch of neopentylamine (55 uL, 0.47 mmol) was added and the mixture heated to 130 °C for 18 h. The reaction was quenched with sat. aq. $NaHCO_3$ and extracted with EtOAc. The combined organics were washed with water and brine, dried and concentrated under reduced pressure. The residue was purified by preparative reverse phase HPLC (250 X 21.2 mm Phenomenex Gemini C18, 40 - 100 % MeOH in water (0.1 % formic acid)) to give the title compound (20 mg, 31 % over two steps). ^{1}H NMR (500 MHz, DMSO-d_6) δ_H 9.26 (1H, s), 8.56 (1H, s), 8.19 – 8.11 (2H, m), 7.88 (1H, s), 7.55 (1H, d, J = 1.0 Hz), 7.28 (1H, d, J = 1.8 Hz), 7.14 (1H, dd, J = 8.2, 1.8 Hz), 6.52 (1H, t, J = 6.2 Hz), 3.93 (3H, s), 3.88 (3H, s), 3.34 (2H, s), 2.38 (3H, s), 0.98 (9H, s). ^{13}C NMR (126 MHz, DMSO-d_6) δ_C 159.7, 157.2, 153.6, 150.6, 138.3, 137.0, 136.4, 128.7, 128.1, 126.7, 122.5, 121.5, 121.4, 117.0, 113.6, 108.5, 56.4, 51.6, 39.1, 32.5, 27.7 (3C), 13.8. HRMS (ESI) m/z calcd for $C_{24}H_{30}N_7O$ $[M+H]^+$ 432.2506, found 432.2497.

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