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Preparation and evaluation of trisubstituted pyrimidines as phosphatidylinositol 3-kinase inhibitors. 3-Hydroxyphenol analogues and bioisosteric replacements

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ABSTRACT

Two classes of trisubstituted pyrimidines related to PI-103 **1** have been prepared and their inhibitory activities against phosphatidylinositol 3-kinase (PI3K) p110α were determined. From those with direct 6-aryl substitution compound **11a** was the most potent inhibitor with an IC_{50} value of 62 nM, and showed similar activity against other class 1a PI3K isoforms tested, p110β and p110γ. When a linking chain was introduced, as in the second exemplified class, compound **15f** inhibited p110α with IC_{50} 142 nM, and showed greater selectivity towards p110α. Compounds of both classes showed promising inhibition of cellular proliferation in IGROV-1 ovarian cancer cells. Among compounds designed to replace the 3-phenolic motif with structural isosteres, analogues incorporating a 4-indazolyl group possessed enzyme and cellular activities comparable to the parent phenols.

1. Introduction

The phosphatidylinositol 3-kinase (PI3K) family of enzymes occupies a central position in numerous important cellular signaling pathways.[1] Deregulation of activity of specific PI3K isoforms in a variety of disease states including cancer,[2] autoimmune disease[3] and cardiovascular disease[4] has been extensively studied. Further, the lipid products derived from PI3K-catalysed phosphorylation at the 3-position of phosphatidylinositols can interact with important targets downstream of PI3K, notably AKT.[1,5] The phosphorylated form of AKT is also implicated in numerous aspects of cancer progression.[6] The p110α isoform (encoded by the *PIK3CA* gene) is known to be over-expressed or activated by mutation in many human cancer types, while loss of the regulatory phosphatase PTEN also leads to activation of the PI3K pathway.[7–14] Thus a growing body of direct and indirect evidence suggests that PI3K is an attractive target for anti-cancer drug discovery[15–17] and the development of novel small molecule inhibitors of PI3K could represent a beneficial therapeutic intervention strategy in cancer treatment.[18–20] To this end, a number of compounds are entering or have already begun early stage clinical trials.[21–23]

The pyridofuropyrimidine PI-103 **1** (Fig. 1) has been identified as a useful and potent PI3K inhibitor and chemical tool compound,[24,25] with in vitro IC_{50} of 2 nM against PI3K p110α and good levels of cellular potency and selectivity over other classes of PI3K isoforms. However, the compound is cleared rapidly from plasma and has low aqueous solubility. In addition, synthetic approaches to compounds of this type are not particularly amenable to rapid analogue synthesis in the context of lead optimisation. Our goal was therefore to modify the structure of **1** in order to generate structurally simpler analogues with improved physical properties, whilst maintaining potency and drug-likeness.[26,27] In concept we disconnected the bicyclic ring system of **1** at the 5-position of the pyrimidine ring, and set out to prepare synthetically accessible seco-compounds such as **2** and **3** (Fig. 1), where the morpholine and phenol functionalities are conserved. Related compounds have also been reported recently by other groups.[28–31] Previous studies, on the closely related PI3K p110γ isoform[32] using the well-known but non-selective PI3K inhibitor LY294002,[33] have suggested that the morpholine and phenol motifs form important binding interactions in the PI3K catalytic site. We initially chose to target a small set of compounds bearing a pyridyl substituent in the side chain at the 2-position. For **3**, variations of the linking atom **X** (nitrogen or oxygen), the pyrimidine substitution pattern and the length of the linking chain (1 or 2 carbon atoms) were included to study the impact of these structural variations on biological activity. We also

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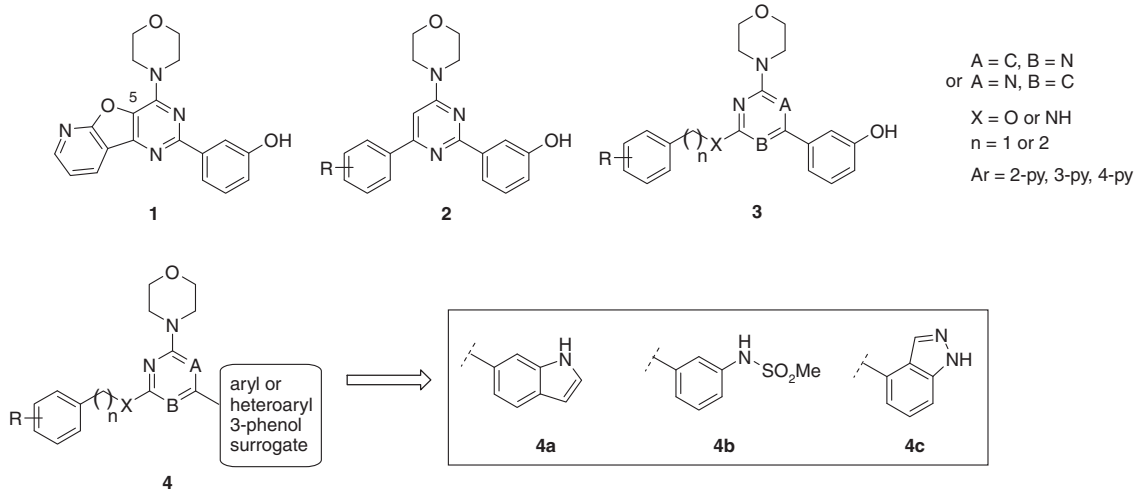
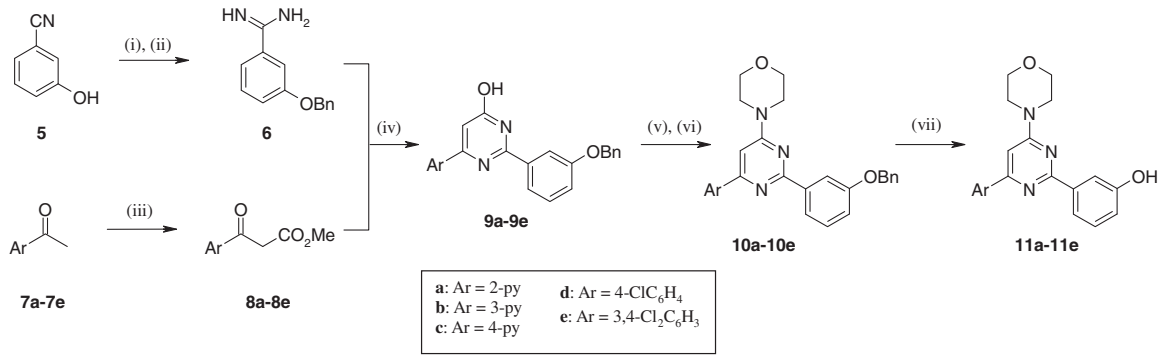


Figure 1. Structure of pyridofuropyrimidine **1** and proposed compound sets **2**, **3** and **4a**–**4c**.



Scheme 1. Reagents and conditions: (i) NaH, BnBr, DMF, reflux; (ii) LiHMDS, HCl, 0 °C to rt; (iii) NaH, $(MeO)_2CO$, THF, rt to reflux; (iv) ^{n}BuOH, 110 °C; (v) $POCl_3$, $PhNEt_2$, 110 °C; (vi) morpholine, $^i Pr_2NEt$, dioxane, 80 °C; (vii) HBr, AcOH, reflux.

decided to prepare structures such as **4**, designed to incorporate bioisosteric replacements of the 3-phenolic motif in **3**. Glucuronidation of such functional groups can result in rapid and undesirable second pass metabolic clearance in vivo;[34] indeed PI-103 has been shown to be metabolized in this way.[24] We chose to evaluate 6-indolyl, 3-(methanesulfonylamino)phenyl and 4-indazolyl bioisosteres (**4a**–**4c**, Fig. 1) in this study.

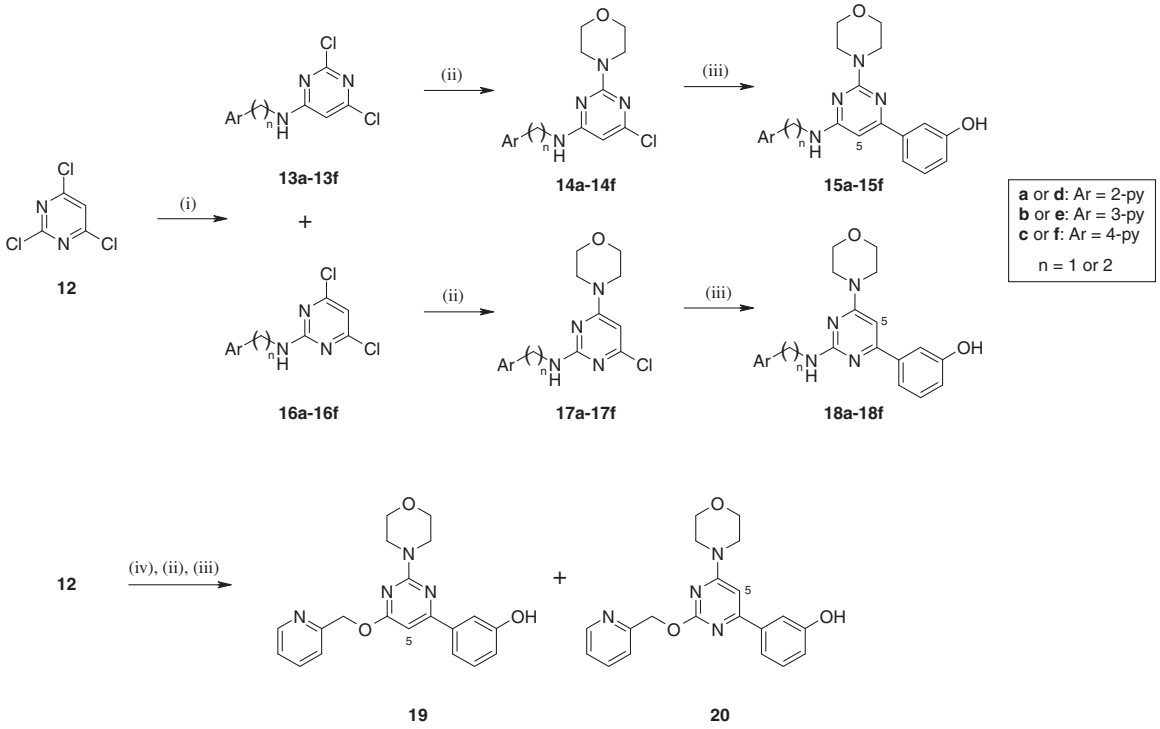
2. Chemical synthesis

6-Aryl compounds[29–31] were synthesised by means of well-precedented condensation chemistry and standard manipulations (Scheme 1). First, the known amidine **6** was prepared in two steps[35,36] from commercially available 3-cyanophenol **5**; and a small set of known aryl β-keto esters **8a–8e** were prepared from the corresponding ketones **7a–7e** by deprotonation and quenching with dimethylcarbonate.[37] Condensation of these crude dicarbonyl compounds with **6** gave pyrimidinones **9a–9e**. These key intermediates were converted to the corresponding chlorides and then reacted with morpholine, generating **10a–10e** and, after deprotection, the desired phenolic targets **11a–11e**. We included two compounds (**11d** and **11e**) that displayed non-pyridine aryl substituents in this part of the study, to monitor the impact of the pyridine nitrogen atoms on the desired biological activity.

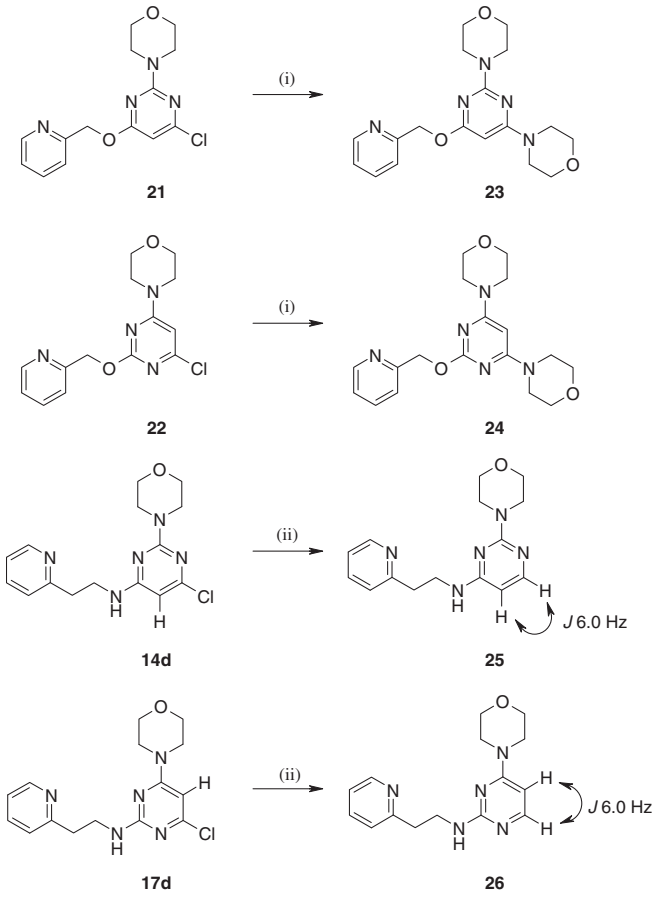
Compounds **15a–15f** containing a 6-amino linked substituent[28] could be prepared from commercially available 2,4,6-trichloropyrimidine **12** by means of two sequential amine displacements;[38,39] first with a small set of amines which contained a linking chain and a pyridine motif, and second with morpholine (Scheme 2). Suzuki–Miyaura coupling with 3-hydroxyphenylboronic acid then afforded the trisubstituted products **15a–15f**. Due to the essentially non-selective nature of the first amine displacement, 2-amino-linked compounds **18a–18f** were also easily available using the same methodology. These desirable structures would allow us to probe the effect of altering the pyrimidine regiochemistry on biological activity. A very similar route was also employed to prepare the two O-linked congeners **19** and **20**.[40] This serves to highlight the flexibility and scope of the approach.

Comparison of ^{1}H NMR spectroscopic data for intermediates **13a–13f/14a–14f** (2-morpholines) and **16a–16f/17a–17f** (4-morpholines) (Scheme 2) showed that the chemical shift of the pyrimidine *H*-5 proton was broadly but not unambiguously diagnostic for each series.[†] Hence two different methods were employed to confirm the regiochemical outcome of the amination steps. For example, reaction of **21** and **22** (the precursors to **19** and **20**, respectively) with morpholine gave adducts **23** and **24**, respectively (Scheme 3). Examination of ^{13}C NMR spectroscopic data showed four distinct quaternary carbon signals for **23**, but only three for the symmetrical pyrimidine **24**. This verified the regiochemistry of the first alkoxide substitution. In addition, reductive removal of the remain-

[†] This proton always appeared at higher field for intermediates in the 2-morpholine series (**13a–f/14a–f**) than those in the 4-morpholine series (**16a–f/17a–f**).[39] See Section 5.



Scheme 2. Reagents and conditions: (i) $Ar(CH_2)_nNH_2$, $^iPr_2NEt$, dioxane, 10 °C; (ii) morpholine, $^iPr_2NEt$, dioxane, 80 °C; (iii) $PdCl_2(dppf)$ (for **15a–15f**) or $Pd(Ph_3P)_4$ (for **18a–18f**), 3-$HOC_6H_4B(OH)_2$, Na_2CO_3 (aq), DME, 80 °C; (iv) NaH, $ArCH_2OH$, THF, 0 °C to rt.



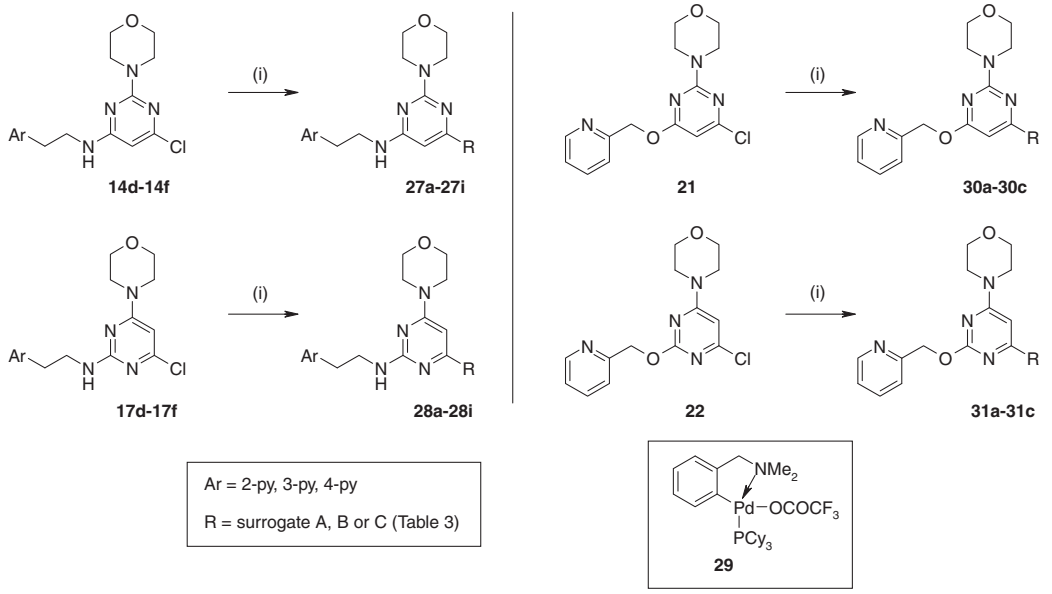
Scheme 3. Reagents and conditions: (i) morpholine, 50 °C; (ii) H_2, Pd/C, KOAc, HOAc, rt.

ing chlorine atom in **14d** and **17d** gave **25** and **26** respectively. Analysis of these two products by ^1H NMR spectroscopy revealed two new aromatic doublets (coupling constant 6 Hz) in each case, establishing the position of the morpholine group. Combination of these methods provided rigorous proof of the regiochemistry in each chemical series.

Analogues bearing isosteric replacements for the 3-phenolic motif were prepared from intermediates **14d–14f** or **17d–17f**, respectively, using modified Suzuki coupling protocols (Scheme 4). Thus using the Bedford palladacycle **29**[41] as catalyst, reaction with the requisite aryl or heteroaryl boronic acid or pinacol boronate ester cleanly provided compounds **27a–27i** and **28a–28i**. The O-linked congeners **30a–30c** and **31a–31c** were similarly prepared from **21** and **22** using the same protocol. We have described the use of palladacycle **29** as an effective catalyst for Suzuki couplings involving a closely related pyrimidine template.[42] Here, the use of automated microwave heating[43] and shortened reaction times considerably enhanced the efficiency and flexibility of the approach. This chemistry represents a useful sequential method for the preparation of compounds of this type, given that access to both regioisomers of the pyrimidine scaffold was again required.

3. Results and discussion

All the newly prepared compounds were assessed for in vitro biological activity against PI3K p110α, using a radiometric scintillation proximity assay.[44] Under these assay conditions the IC_{50} value determined for PI-103 was 2 nm. We first tested compounds bearing a 3-phenolic group (Table 1) and found, as expected, that an unprotected phenol was required for optimal biological activity; *O*-benzyl ethers **10a–10e** showed no appreciable in vitro inhibition of the enzyme (entries 1–5). On revealing the phenol motif, compounds **11a–11e** (entries 6–10) each possessed useful inhibitory activity with **11a** the most promising at 62 nM. We were also encouraged to find that non-pyridine analogues **11d** and **11e**



Scheme 4. Reagents and conditions: (i) 0.05–0.10 equiv **29**, 2.2 equiv R-B(OH)$_2$, 2.2 equiv Na_2CO_3 (aq), 1,2-DME, microwave heating, 150 °C, 30 min.

Table 1
In vitro screening of trisubstituted pyrimidines against PI3K p110α

Entry	Compound No.	Ar[a]	*n*	p110α IC_{50}[b] (μM)	SRB GI_{50}[b] (μM)
1	**10a**	2-py	0	>10	[c]
2	**10b**	3-py	0	>10	[c]
3	**10c**	4-py	0	>10	[c]
4	**10d**	4-ClC_6H_4	0	>10	[c]
5	**10e**	3,4-$Cl_2C_6H_3$	0	>10	[c]
6	**11a**	2-py	0	0.062	0.37
7	**11b**	3-py	0	0.26	0.63
8	**11c**	4-py	0	0.14	1.2
9	**11d**	4-ClC_6H_4	0	0.69	[c]
10	**11e**	3,4-$Cl_2C_6H_3$	0	0.20	[c]
11	**15a**	2-py	1	0.90	[c]
12	**15b**	3-py	1	0.72	[c]
13	**15c**	4-py	1	1.0	[c]
14	**15d**	2-py	2	0.25	2.2
15	**15e**	3-py	2	0.26	1.2
16	**15f**	4-py	2	0.14	0.70
17	**18a**	2-py	1	1.0	[c]
18	**18b**	3-py	1	0.88	[c]
19	**18c**	4-py	1	0.86	[c]
20	**18d**	2-py	2	0.18	1.20
21	**18e**	3-py	2	0.25	0.75
22	**18f**	4-py	2	0.23	0.95
23	**19**	2-py	1	0.11	1.5
24	**20**	2-py	1	0.86	2.5

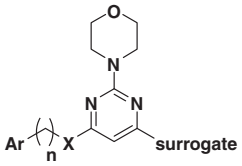
[a] py = pyridyl.
[b] Mean of at least two separate measurements with typical variability <25%.
[c] Not determined.

(entries 9 and 10) retained activity and so a broader exploration of the SAR in this region might be fruitful. When a linking chain containing a nitrogen heteroatom was introduced, inhibition was generally greater when two additional linking carbon atoms were present (entries 11–16 and 17–22). Encouragingly, both regioisomeric series of the pyrimidine scaffold provided useful levels of in vitro activity, although no clear preference for the position of the pyridine nitrogen was observed in either pyrimidine series. We also wanted to probe the effect of changing the nature and hydrogen bonding capability of the linking motif. When an oxygen linking atom was introduced, compound **19** displayed better inhibitory activity than **20** (entries 23–24), and both ethers have comparable activity to the corresponding NH-linked analogues, revealing that the hydrogen bond donating ability of the linking atom is not a critical requirement for good inhibition. It also implies that shorter linkers can be employed to generate useful levels of activity, and that the orientation of the nitrogen atoms in the pyrimidine scaffold may be important for some compounds.

We assessed the cancer cell growth inhibitory activity of the more active compounds using a sulphorhodamine B assay[45] (SRB) in the IGROV-1 human ovarian cancer cell line which has a strongly activated PI3 kinase pathway through a combination of loss of PTEN and mutational activation of *PIK3CA* (Table 1). Where no linking chain was present (entries 6–8), the 2-pyridyl analogue **11a** (entry 6) possessed the best activity in this series with a GI_{50} value for 50% growth inhibition of 0.37 μM, consistent with its potent activity on PI3K. When compounds with a two-carbon linker were considered (entries 14–16 and 20–22), both regioisomeric pyrimidine series again showed similar levels of inhibition. The position of the pyridine nitrogen was again not critical for good activity. The O-linked congeners **19** and **20**, which do not feature a hydrogen bond donor in the side chain, showed levels of cell growth inhibition (entries 23 and 24) similar to those of NH compounds, commensurate with their potencies as inhibitors of p110α .

Assessment of analogues containing structural surrogates of the 3-phenolic motif was carried out using the same two assay protocols (Tables 2 and 3). The key SAR conclusions from these data are that compounds in the 4-morpholinyl series (Table 3) were generally more potent than the corresponding 2-morpholinyl analogues (Table 2); and that compounds incorporating the 6-indolyl or 3-$MeSO_2$NH-phenyl substituents (surrogates A and B, respectively, in Tables 2 and 3) were an order of magnitude less active than the corresponding phenols.[17,24] However compounds **27g–27i** and **28g–28i** with the 4-indazolyl group (surrogate C) had activities comparable to the corresponding phenols. These data strongly suggest that molecular interaction between the phenolic and 4-indazolyl inhibitors and PI3K p110α includes H-bond donation that cannot be mimicked effectively by either sulphonamido or 6-indolyl analogues. The constrained geometries of the bicyclic compounds then lead to the conclusion that the trajectory of the postulated H-bond lies in the *anti*- rather than *syn*- direction with respect to the pyrimidine moieties. The foregoing pattern of activity was broadly followed by the O-linked compounds, with

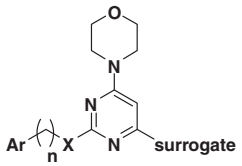
Table 2
In vitro screening of trisubstituted pyrimidines **27a–27i** and **30a–30c** against PI3K p110α



Compound No.	Ar[a]	X	*n*	Surrogate[b]	p110α IC_{50}[c] (μM)	SRB GI_{50}[c] (μM)
27a	2-py	NH	2	A	> 10	12.0
27b	3-py	NH	2	A	> 10	6.0
27c	4-py	NH	2	A	> 10	14.5
27d	2-py	NH	2	B	> 10	15.0
27e	3-py	NH	2	B	> 10	11.6
27f	4-py	NH	2	B	> 10	15.0
27g	2-py	NH	2	C	1.3	7.8
27h	3-py	NH	2	C	0.66	2.9
27i	4-py	NH	2	C	0.77	2.7
30a	2-py	O	1	A	> 10	6.0
30b	2-py	O	1	B	> 10	16.0
30c	2-py	O	1	C	0.50	1.9

[a] py = pyridyl.
[b] A = 6-indole; B = 3-(methanesulfonylamino)phenyl; C = 4-indazole (see Fig. 1 for structures).
[c] Mean of at least two separate measurements with typical variability <25%.

Table 3
In vitro screening of trisubstituted pyrimidines **28a–28i** and **31a–31c** against PI3K p110α



Compound No.	Ar[a]	X	*n*	Surrogate[b]	p110α IC_{50}[c] (μM)	SRB GI_{50}[c] (μM)
28a	2-py	NH	2	A	8.9	3.6
28b	3-py	NH	2	A	7.2	4.2
28c	4-py	NH	2	A	>10	3.0
28d	2-py	NH	2	B	>10	11.5
28e	3-py	NH	2	B	>10	16.2
28f	4-py	NH	2	B	9.1	6.2
28g	2-py	NH	2	C	1.1	2.7
28h	3-py	NH	2	C	0.82	2.9
28i	4-py	NH	2	C	0.44	1.5
31a	2-py	O	1	A	5.2	9.0
31b	2-py	O	1	B	6.2	13.5
31c	2-py	O	1	C	1.35	2.3

[a] py = pyridyl.
[b] A = 6-indole; B = 3-(methanesulfonylamino)phenyl; C = 4-indazole (see Fig. 1 for structures).
[c] Mean of at least two separate measurements with typical variability <25%.

indazoles **30c** and **31c** only slightly less active than the parent phenols **19** and **20**. In the cell growth inhibition assay, again the 6-indolyl and 3-$MeSO_2NH$ analogues were significantly less active than the corresponding phenol parents but the indazoles showed good levels of cancer cell growth inhibitory activity with GI_{50}s generally only twofold greater than the parent phenols. It is interesting to note that several surrogates listed in Tables 2 and 3 are weak inhibitors of p110α but nevertheless show moderate levels of cell growth inhibition, possibly due to inhibition of non-target enzymes.

In summary, indazolyl analogues are inhibitors of p110α and of IGROV-1 human ovarian cancer cell proliferation with activities comparable to the parent phenols and therefore offer an attractive opportunity for further optimisation.

The cellular activities described above might be a consequence of activity of these compounds against more than one target. A small number of the most active phenolic compounds were therefore assessed for selectivity against the class 1a PI3K isoforms p110β and p110γ (Table 4). When no linking chain was present (entries 1–3), compounds **11a–11c** could not effectively discriminate between the three isoforms in vitro. However, compounds **15d–15f** (entries 5–7) showed 5–10-fold selectivity for the p110α target enzyme, particularly over p110β. Such levels of selectivity are very interesting for structurally simple and easily prepared compounds. On changing the pyrimidine scaffold in **15d** to its regioisomeric counterpart in **18d** (entry 8), a different selectivity profile resulted. It is also interesting to note the subtle changes in selectivity when nature and length of the linking chain was

Table 4
Inhibitory activities of key trisubstituted pyrimidines against three PI3K p110 isoforms

Entry	Compound No.	p110α IC_{50}[a] (μM)	p110β IC_{50}[a] (μM)	p110γ IC_{50}[a] (μM)
1	**11a**	0.062	0.10	0.044
2	**11b**	0.26	0.44	0.34
3	**11c**	0.14	0.20	0.15
4	**15a**	0.90	2.3	7.6
5	**15d**	0.25	2.6	0.83
6	**15e**	0.26	1.9	0.96
7	**15f**	0.14	1.6	0.74
8	**18d**	0.18	5.2	0.38
9	**19**	0.11	0.37	0.73

[a] Mean of at least two separate measurements with typical variability <25%.

Table 5
Metabolic stabilities of trisubstituted pyrimidines in mouse liver microsomes

Compound No.	% Metabolised at	
	15 min	30 min
11a	39	57
15f	54	71
27g	58	84
27h	66	98
27i	37	68
28c	38	60
28f	33	53
28i	49	74
30c	44	66

altered. Compound **15a** (entry 4), although not among the most active against the primary oncogenic target p110α, was able to discriminate against p110γ. The O-linked congener **19** (entry 9) showed a very similar profile, but with enhanced activities against all three isoforms. These useful observations should aid the design of further inhibitors against any of the three class 1a PI3K enzymes with improved overall characteristics. Taking into account all the foregoing results, we considered that the 4-pyridyl side chain analogues **15f** and **18f** (entries 16 and 22) showed the best overall profile of activity.

The effect of the structural replacements on metabolic stability was examined by conducting mouse microsomal incubation studies on the most biochemically active phenols **11a** and **15f**, several key indazoles and also on examples of the less active indoles and sulfonamides (**28c** and **28f**, respectively). As expected for phenols[34] compounds **11a** and **15f**, like PI-103,[24] were rapidly metabolised, with glucuronidation an important pathway in each case (Fig. 2). However, the results (Table 5) show that the surrogate compounds are also metabolised at rates similar to the representative phenols with only marginal reductions for analogues **27i**, **28f**, **28c** and **30c** compared to the parent phenol **15f**. It is therefore clear that further structural modifications will be necessary to confer high levels of metabolic stability.

Finally we conducted pharmacodynamic biomarker analysis experiments in the PI3K pathway activated IGROV-1 ovarian cancer cells, utilising key compounds **11a** and **15f** and the known PI3K inhibitor LY294002[33] (Fig. 3). All compounds were found to inhibit constitutive phosphorylation of AKT at Ser^{473} following 24 and 48-h exposure to 1 and 5 times the cellular GI_{50} determined for 96-h exposure. These biomarker data are consistent with cancer cell growth inhibition through blockade of the PI3K pathway. Inhibition of signaling through the PI3K/AKT pathway has previously been demonstrated to decrease expression of cyclin D1 protein.[24] In agreement with this observation, all three compounds also reduced cyclin D1 protein levels at the same two time points. Further, cell cycle analysis experiments with **11a** and **15f** (Fig. 4) revealed a robust G1 arrest with loss of cells from S phase. This profile is similar to that of PI-103[44] and the results are consistent with the interpretation that intracellular inhibition of the p110α target is important for the biological activities observed above.

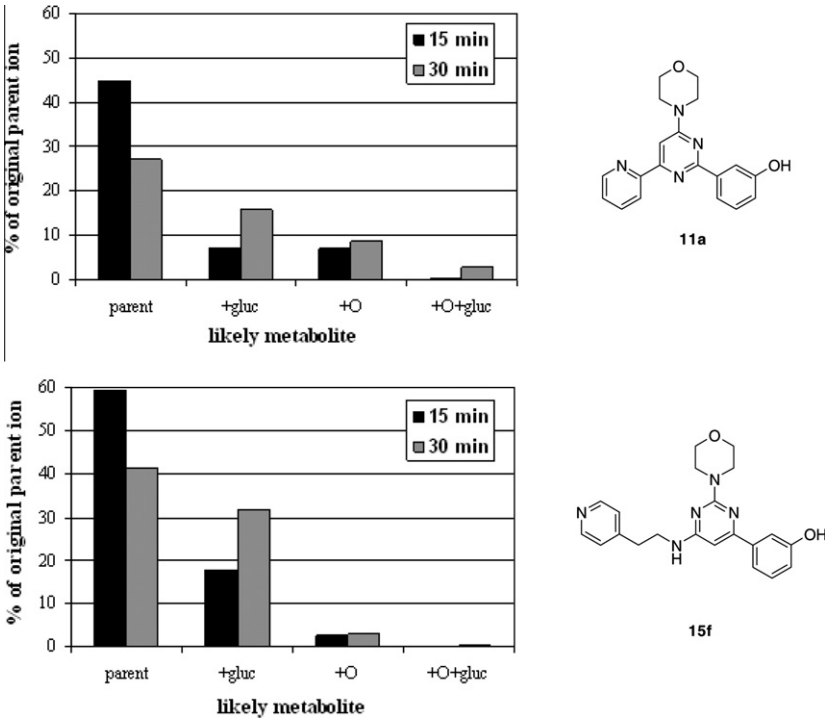


Figure 2. Metabolite identification of compounds **11a** and **15f** by MS analysis (O = oxidation, gluc = glucoronide).

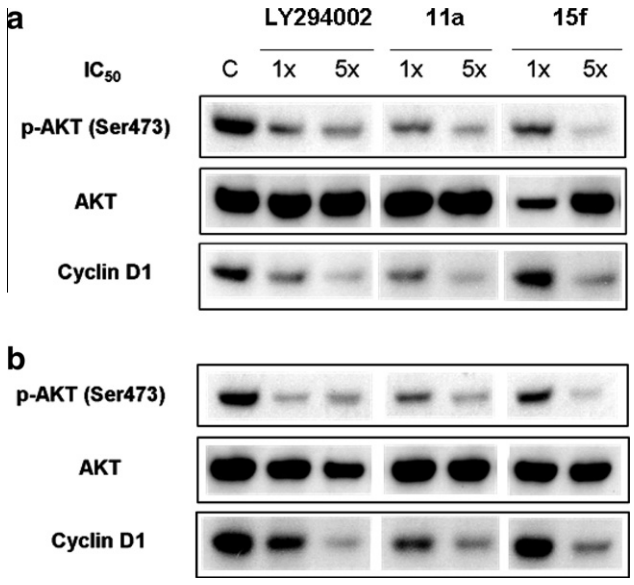


Figure 3. Effect of **11a** and **15f** applied at onefold and fivefold GI_{50} concentrations on levels of phospho-AKT (at Ser473) and cyclin D1 in IGROV-1 cells at 24 h (a) and 48 h (b) time points.

4. Conclusions

In summary, we have prepared two series of 2,4,6-trisubstituted pyrimidines and demonstrated that they are structurally simple and useful inhibitors of the PI3K p110α enzyme, which is a validated and important cancer target. Compounds such as **11a** possessed good inhibitory activity and also showed similar activity against other PI3K isoforms tested, namely p110β and p110γ. When a linking chain was introduced, in compounds like **15f**, potency was maintained and an interesting discrimination between PI3K isoforms was observed. The most active compounds were also able to inhibit growth at sub-micromolar concentrations of IGROV-1 human ovarian cancer cells, which have an activated PI3 kinase pathway. Isosteric replacement of the 3-phenolic motif led to three further sets of compounds, with 4-indazolyl analogues displaying comparably potent enzyme inhibition and antiproliferative active in IGROV-1 cells comparable to the parent phenols. All three surrogate types had metabolic stabilities similar to those of parent phenols, indicating that further optimisation of pharmacokinetic properties will be necessary. Pharmacodynamic biomarker and cell cycle analysis of **11a** and **15f** confirmed that these compounds inhibited the PI3K pathway in genetically relevant cancer cells, consistent with their growth inhibitory effects.

5. Experimental

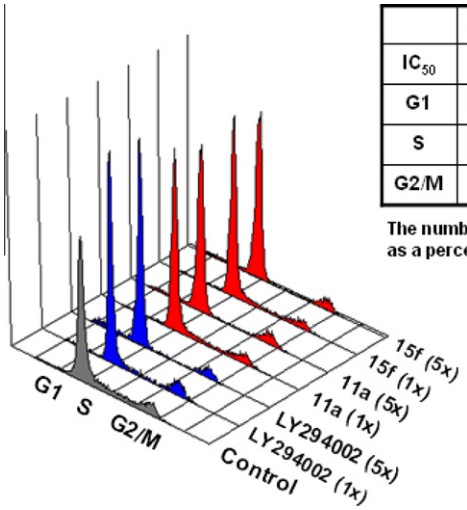
5.1. General synthetic chemistry remarks

Commercially available starting materials, reagents and dry solvents were used as supplied. Flash chromatography was performed using Merck Silica Gel 60 (0.025–0.04 mm). Ion exchange chromatography was performed using acidic Isolute flash SCX-II cartridges. ^{1}H NMR spectra were recorded on a Bruker Avance dpx250 at 250 MHz or a Bruker Avance-500 at 500 MHz. ^{13}C spectra were recorded on a Bruker Avance-500 at 125 MHz. Samples were prepared as solutions in either $CDCl_3$ or DMSO-d_6 and referenced to the appropriate internal non-deuterated solvent peak or tetramethylsilane. Chemical shifts were recorded in ppm (δ) downfield of tetramethylsilane. Coupling constants were recorded in Hz to the nearest 0.5 ppm. HPLC–MS spectra were recorded on a Waters Micromass LCT with a Waters Alliance 2795 separations module, using a Phenomenex Gemini C_{18} column (5 μ, 50 × 4.6 mm) and either a 6 min (a) or 10 min (b) gradient (MeOH/0.1% formic acid), with nominal mass, LC injection, positive ionisation and an injection volume of 2 μL (a) or 3 μL (b). High-resolution mass spectra were obtained to within 5 ppm accuracy using the same instrumental set-up and LC injection with a 10 min gradient (MeOH and 0.1% formic acid), positive ionisation and an injection volume of 4 μL. Analytical HPLC spectra were recorded on a Thermo-Finnigan Surveyor HPLC system at 30 °C, using a Phenomenex Gemini C_{18} column (5 μ, 50 × 4.6 mm) and a 6 min (a) or 10 min (b) gradient of 10→90% MeOH/0.1% formic acid, visualising at 254 nm. Compounds **6**[34,35] and **8a–8e**[36] were prepared according to the reported procedures. All compounds were characterised by ^{1}H NMR spectroscopy and low/high-resolution mass spectrometry—those that were biologically tested were also assessed for purity by HPLC.

5.2. Compound preparation and characterisation

5.2.1. General procedure 1: condensation of 6 with 8a–8e

5.2.1.1. 2-(3-(Benzyloxy)phenyl)-6-(pyridin-2-yl)pyrimidin-4-ol (9a). A solution of the amidine **6** (1.1 equiv, 276 mg, 1.23 mmol) and the β-ketoester **8a** (1 equiv, 200 mg, 1.12 mmol) in ^{n}BuOH (3 mL) was stirred at 110 °C for 18 h. During this time a solid



	C	LY294002		11a		15f	
IC_{50}		1x	5x	1x	5x	1x	5x
G1	60	72	82	76	84	75	87
S	32	21	3	20	5	21	2
G2/M	7	7	15	3	10	4	10

The number of cells in each phase of the cell cycle is expressed as a percentage of gated events.

Figure 4. Cell cycle analysis of compounds **11a** and **15f** applied at one- and fivefold GI_{50} concentrations to IGROV-1 cells for 24 h.

precipitate formed. After cooling to room temperature, the solid was filtered off and air-dried to provide **9a** (190 mg, 48%) as a pale yellow solid; δ_H (500 MHz, DMSO-d_6) 12.89 (1H, br), 8.74 (1H, d, br, *J* 4.5), 8.47 (1H, d, br, *J* 8.0), 8.03 (1H, td, *J* 8.0, 2.0), 7.94 (1H, s, br), 7.90 (1H, d, *J* 7.0), 7.54 (1H, ddd, *J* 7.5, 5.0, 1.0), 7.51–7.49 (1H, m), 7.50 (2H, t, *J* 8.0), 7.42 (2H, t, *J* 8.0), 7.36 (1H, t, br, *J* 7.5), 7.25 (1H, dd, *J* 8.0, 2.0), 7.23 (1H, s), 5.26 (2H, s); HPLC–MS[a] R_t 5.26 min; ($C_{22}H_{17}N_3O_2$): *m/z* (ESI) 356 ([M+H]$^+$, 100%); $C_{22}H_{17}N_3O_2$ requires 356.1399, found: [M+H]$^+$, 356.1396.

5.2.1.2. 2-(3-(Benzyloxy)phenyl)-6-(pyridin-3-yl)pyrimidin-4-ol (9b). Prepared from compounds **6** and **8b** according to general procedure 1; pale yellow solid, 48% yield; δ_H (500 MHz, DMSO-d_6) 12.90 (1H, br), 9.34 (1H, d, *J* 2.0), 8.81 (1H, dd, *J* 4.5, 1.5), 8.61 (1H, dt, *J* 8.0, 2.0), 7.92 (1H, s, br), 7.88 (1H, d, br, *J* 8.0), 7.55 (1H, dd, *J* 8.0, 4.5), 7.51–7.48 (1H, m), 7.50 (2H, t, *J* 8.0), 7.42 (2H, t, *J* 8.0), 7.35 (1H, t, br, *J* 8.0), 7.25 (1H, dd, *J* 8.0, 2.0), 7.05 (1H, s), 5.24 (2H, s); HPLC–MS[a] R_t 5.00 min; ($C_{22}H_{17}N_3O_2$): *m/z* (ESI) 356 ([M+H]$^+$, 100%); $C_{22}H_{17}N_3O_2$ requires 356.1399, found: [M+H]$^+$, 356.1401.

5.2.1.3. 2-(3-(Benzyloxy)phenyl)-6-(pyridin-4-yl)pyrimidin-4-ol (9c). Prepared from compounds **6** and **8c** according to general procedure 1; colourless solid, 44% yield; δ_H (500 MHz, DMSO-d_6) 12.49 (1H, br), 8.67 (2H, d, *J* 6.0), 8.08 (2H, d, *J* 6.0), 7.92 (1H, s, br), 7.88 (1H, d, br, *J* 8.0), 7.51–7.49 (1H, m), 7.50 (2H, t, *J* 8.0), 7.43 (2H, t, *J* 8.0), 7.35 (1H, t, br, *J* 7.5), 7.25 (1H, dd, *J* 8.0, 2.0), 7.09 (1H, s), 5.24 (2H, s); HPLC–MS[a] R_t 4.92 min; ($C_{22}H_{17}N_3O_2$): *m/z* (ESI) 356 ([M+H]$^+$, 100%); $C_{22}H_{17}N_3O_2$ requires 356.1399, found: [M+H]$^+$, 356.1382.

5.2.1.4. 2-(3-(Benzyloxy)phenyl)-6-(4-chlorophenyl)pyrimidin-4-ol (9d). Prepared from compounds **6** and **8d** according to general procedure 1; pale yellow solid, 15% yield; δ_H (250 MHz, DMSO-d_6) 8.21 (2H, d, *J* 8.5), 7.91 (1H, d, br, *J* 8.0), 7.87 (1H, s, br), 7.59 (2H, d, *J* 8.5), 7.53–7.36 (5H, m), 7.26 (1H, dd, *J* 8.0, 2.0), 6.97 (1H, s), 5.24 (2H, s); HPLC–MS[b] R_t 9.27 min; ($C_{23}H_{17}Cl_1N_2O_2$): *m/z* (ESI) 389 ([^{35}M+H]$^+$, 100%), 391 ([^{37}M+H]$^+$, 32); $C_{23}H_{17}Cl_1N_2O_2$ requires 389.1057, found: [^{35}M+H]$^+$, 389.1052.

5.2.1.5. 2-(3-(Benzyloxy)phenyl)-6-(3,4-dichlorophenyl)pyrimidin-4-ol (9e). Prepared from compounds **6** and **8e** according to general procedure 1; pale yellow solid, 30% yield; δ_H (250 MHz, DMSO-d_6) 8.47 (1H, d, *J* 2.0), 8.23 (1H, dd, *J* 8.5, 2.0), 7.95 (1H, d, br, *J* 8.0), 7.89 (1H, s), 7.85 (1H, d, *J* 8.5), 7.59–7.41 (6H, m), 7.31 (1H, dd, *J* 8.0, 2.0), 7.12 (1H, s), 5.30 (2H, s); HPLC–MS[b] R_t 9.85 min; ($C_{23}H_{18}Cl_2N_2O_2$): *m/z* (ESI) 423 ([^{35,35}M+H]$^+$, 100%), 425 ([^{37,35}M+H]$^+$, 53), 427 ([^{37,37}M+H]$^+$, 13); $C_{23}H_{18}Cl_2N_2O_2$ requires 423.0667, found: [^{35,35}M+H]$^+$, 423.0671.

5.2.2. General procedure 2: conversion of 9a–9e to chlorides and nucleophilic displacement

5.2.2.1. 4-(2-(3-(Benzyloxy)phenyl)-6-(pyridin-2-yl)pyrimidin-4-yl)morpholine (10a). Compound **9a** (50 mg, 0.14 mmol) was dissolved in $POCl_3$ (1 mL) and *N*,*N*-diethylaniline (1 equiv, 0.14 mmol, 0.02 mL) was added and the mixture stirred overnight at 110 °C. After cooling the excess $POCl_3$ was removed in vacuo, ice water (2 ml) added to the residue. After extraction with $CHCl_3$ (2 × 2 mL), the combined extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was dissolved in dioxane (1 mL) and diisopropylethylamine (0.5 mL) and morpholine (5 equiv, 0.70 mmol, 0.07 mL) and stirred at 85 °C overnight. The solvents were removed in vacuo and the residue partitioned between water (2 mL) and EtOAc (2 mL)—the organic layer was separated and the aqueous layer was further extracted with EtOAc (2 mL) and $CHCl_3$ (2 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to give crude product. Purification by preparative TLC (hexane/EtOAc, 1:1) gave **10a** (28 mg, 47% for two steps) as a colourless solid; R_f 0.40 (hexane/EtOAc, 1:1); δ_H (500 MHz, $CDCl_3$) 8.70 (1H, ddd, *J* 5.0, 1.5, 1.0), 8.64 (1H, dt, *J* 8.0, 1.5), 8.19–8.16 (2H, m), 7.90 (1H, td, *J* 2.0), 7.61 (1H, s), 7.52 (1H, d, br, *J* 7.5), 7.44–7.36 (5H, m), 7.11 (1H, ddd, *J* 8.0, 3.0, 1.0), 5.21 (2H, s), 3.86 (8H, s, br); HPLC–MS[a] R_t 5.86 min; ($C_{26}H_{24}N_4O_2$): *m/z* (ESI) 425 ([M+H]$^+$, 100%); $C_{26}H_{24}N_4O_2$ requires 425.1978, found: [M+H]$^+$, 425.1974; HPLC[b] R_t 9.13 min, area 99.5%.

5.2.2.2. 4-(2-(3-(Benzyloxy)phenyl)-6-(pyridin-3-yl)pyrimidin-4-yl)morpholine (10b). Prepared from compound **9b** according to general procedure 2; colourless solid, 47% yield for two steps; R_f 0.15 (hexane/EtOAc, 1:1); δ_H (500 MHz, $CDCl_3$) 9.28 (1H, d, br, *J* 2.0), 8.72 (1H, dd, *J* 5.0, 1.5), 8.38 (1H, dt, *J* 8.0, 2.0), 8.16 (1H, s), 8.16–8.12 (1H, m), 7.45–7.26 (7H, m), 7.05–7.01 (1H, m), 6.76 (1H, s), 5.12 (2H, s), 3.82–3.72 (8H, m); HPLC–MS[a] R_t 5.67 min; ($C_{26}H_{24}N_4O_2$): *m/z* (ESI) 425 ([M+H]$^+$, 100%); $C_{26}H_{24}N_4O_2$ requires 425.1978, found: [M+H]$^+$, 425.1981; HPLC[b] R_t 9.89 min, area 95.9%.

5.2.2.3. 4-(2-(3-(Benzyloxy)phenyl)-6-(pyridin-4-yl)pyrimidin-4-yl)morpholine (10c). Prepared from compound **9c** according to general procedure 2; colourless solid, 40% yield for two steps; R_f 0.21 (hexane/EtOAc, 1:1); δ_H (250 MHz, $CDCl_3$) 8.70 (2H, d, *J* 5.0), 8.07–8.04 (2H, m), 7.99 (2H, d, *J* 5.0), 7.44–7.24 (6H, m), 7.04 (1H, ddd, *J* 8.0, 2.5, 1.5), 6.80 (1H, s), 5.12 (2H, s), 3.81–3.74 (8H, m); HPLC–MS[a] R_t 5.67 min; ($C_{26}H_{24}N_4O_2$): *m/z* (ESI) 425 ([M+H]$^+$, 100%); $C_{26}H_{24}N_4O_2$ requires 425.1978, found: [M+H]$^+$, 425.1964; HPLC[b] R_t 9.85 min, area 93.4%.

5.2.2.4. 4-(2-(3-(Benzyloxy)phenyl)-6-(4-chlorophenyl)pyrimidin-4-yl)morpholine (10d). Prepared from compound **9d** according to general procedure 2; colourless solid, 29% yield for two steps; R_f 0.68 (hexane/EtOAc, 1:1); δ_H (250 MHz, $CDCl_3$) 8.08–8.04 (2H, m), 7.99 (2H, d, *J* 8.5), 7.39 (2H, d, *J* 8.5), 7.39–7.26 (6H, m), 7.04–7.00 (1H, m), 6.71 (1H, s), 5.12 (2H, s), 3.82–3.72 (8H, m); HPLC–MS[b] R_t 9.25 min; ($C_{27}H_{24}Cl_1N_3O_2$): *m/z* (ESI) 458 ([^{35}M+H]$^+$, 100%), 460 ([^{37}M+H]$^+$, 33); $C_{27}H_{24}Cl_1N_3O_2$ requires 458.1635, found: [^{35}M+H]$^+$, 458.1626; HPLC[b] R_t 9.45 min, area 96.7%.

5.2.2.5. 4-(2-(3-(Benzyloxy)phenyl)-6-(3,4-dichlorophenyl)pyrimidin-4-yl)morpholine (10e). Prepared from compound **9e** according to general procedure 2; colourless solid, 26% yield for two steps; R_f 0.63 (hexane/EtOAc, 1:1); δ_H (250 MHz, $CDCl_3$) 8.15 (1H, d, *J* 2.0), 8.07–8.04 (2H, m), 7.89 (1H, dd, *J* 8.5, 2.0), 7.48 (1H, d, *J* 8.5), 7.51–7.26 (6H, m), 7.05–7.00 (1H, ddd, *J* 8.0, 4.0, 1.0), 6.69 (1H, s), 5.12 (2H, s), 3.80–3.70 (8H, m); HPLC–MS[a] R_t 9.99 min; ($C_{27}H_{23}Cl_2N_3O_2$): *m/z* (ESI) 496 ([^{37,37}M+H]$^+$, 11%), 494 ([^{37,35}M+H]$^+$, 60), 492 ([^{35,35}M+H]$^+$, 100); $C_{27}H_{23}Cl_2N_3O_2$ requires 492.1246, found: [^{35,35}M+H]$^+$, 492.1241; HPLC[b] R_t 9.38 min, area 99.8%.

5.2.3. General procedure 3: deprotection of 10a–10e

5.2.3.1. 3-(4-Morpholino-6-(pyridin-2-yl)pyrimidin-2-yl)phenol (11a). A solution of compound **10a** (5 mg, 0.012 mmol) in HBr (48% in acetic acid, 0.5 mL) was stirred at reflux for 3 h. The solvents were then removed in vacuo and the residue dried at high vacuum in the presence of sodium hydroxide to give **11a** (3 mg, 61%) as a yellow solid; δ_H (250 MHz, DMSO-d_6) 9.58 (1H, s), 9.17 (1H, d, *J* 8.0), 8.94–8.92 (1H, m), 8.10–8.03 (1H, m), 7.86–7.81 (2H, m), 7.50 (1H, s), 7.23 (1H, t, *J* 8.0), 6.85 (1H, dd, *J* 8.0, 1.5), 3.80–3.67 (8H, m); HPLC–MS[a] R_t 3.90 min; ($C_{19}H_{18}N_4O_2$): *m/z* (ESI) 335 ([M+H]$^+$, 100%); $C_{19}H_{18}N_4O_2$ requires 335.1508, found: [M+H]$^+$, 335.1501; HPLC[a] R_t 5.65 min, area 97.0%.

5.2.3.2. 3-(4-Morpholino-6-(pyridin-3-yl)pyrimidin-2-yl)phenol (11b). Prepared from compound **10b** according to general procedure 3; pale brown solid, 70% yield; δ_H (250 MHz, DMSO-d_6) 8.81 (1H, s), 8.62 (1H, d, *J* 8.0), 8.18 (1H, t, *J* 8.0), 8.00–7.90 (2H, m), 7.72–7.68 (2H, m), 8.34 (1H, t, *J* 7.5), 6.93 (1H, d, *J* 7.5), 3.83–3.79 (8H, m); HPLC–MS[b] R_t 4.14 min; ($C_{19}H_{18}N_4O_2$): *m/z* (ESI) 335 ([M+H]$^+$, 100%); $C_{19}H_{18}N_4O_2$ requires 335.1508, found: [M+H]$^+$, 335.1517; HPLC[a] R_t 5.86 min, area 93.4%.

5.2.3.3. 3-(4-Morpholino-6-(pyridin-4-yl)pyrimidin-2-yl)phenol (11c). Prepared from compound **10c** according to general procedure 3; pale brown solid, 58% yield; δ_H (250 MHz, DMSO-d_6) 8.70 (2H, br), 7.96–7.91 (2H, m), 7.59 (1H, s), 7.32 (1H, t, *J* 8.0), 6.92 (1H, ddd, *J* 7.5, 2.0, 1.0), 3.89–3.86 (4H, m) 3.80–3.75 (4H, m); HPLC–MS[a] R_t 3.72 min; ($C_{19}H_{18}N_4O_2$): *m/z* (ESI) 335 ([M+H]$^+$, 100%); $C_{19}H_{18}N_4O_2$ requires 335.1508, found: [M+H]$^+$, 335.1495; HPLC[a] R_t 5.46 min, area 91.5%.

5.2.3.4. 3-(4-(4-Chlorophenyl)-6-morpholinopyrimidin-2-yl) phenol (11d). Prepared from compound **10d** according to general procedure 3; yellow solid, 72% yield; δ_H (250 MHz, DMSO-d_6) 8.33 (2H, d, *J* 8.5), 7.96–7.89 (2H, m), 7.61 (2H, d, *J* 8.5), 7.37–7.27 (2H, m), 6.90 (1H, ddd, *J* 8.5, 2.5, 1.0), 3.85–3.80 (4H, m), 3.77–3.72 (4H, m); HPLC–MS[a] R_t 5.19 min; ($C_{20}H_{18}Cl_1N_3O_2$): *m/z* (ESI) 368 ([^{35}M+H]$^+$, 100%), 370 ([^{37}M+H]$^+$, 53); $C_{20}H_{18}Cl_1N_3O_2$ requires 368.1166, found: [^{35}M+H]$^+$, 368.1156; HPLC[a] R_t 4.31 min, area 93.6%.

5.2.3.5. 3-(4-(3,4-Dichlorophenyl)-6-morpholinopyrimidin-2-yl)phenol (11e). Prepared from compound **10e** according to general procedure 3; yellow solid, 65% yield; δ_H (250 MHz, DMSO-d_6) 8.56 (1H, d, *J* 2.0), 8.33 (1H, br, d, *J* 8.0), 7.92–7.89 (2H, m), 7.82 (1H, d, *J* 8.0), 7.41 (1H, s), 7.31 (1H, t, *J* 8.0), 6.90 (1H, ddd, *J* 8.0, 2.5, 1.0), 3.87–3.83 (4H, m), 3.77–3.74 (4H, m); HPLC–MS[b] R_t 8.80 min; ($C_{20}H_{17}Cl_2N_3O_2$): *m/z* (ESI) 402 ([^{35,35}M+H]$^+$, 100%), 404 ([^{37,35}M+H]$^+$, 53), 406 ([^{37,37}M+H]$^+$, 13); $C_{20}H_{17}Cl_2N_3O_2$ requires 402.0776, found: [^{35,35}M+H]$^+$, 402.0768; HPLC[a] R_t 5.70 min, area 91.6%.

5.2.4. General procedure 4: treatment of 2,4,6-trichloropyrimidine 12 with amines

5.2.4.1. 4,6-Dichloro-*N*-(pyridin-2-ylmethyl)pyrimidin-2-amine (16a) and 2,6-dichloro-*N*-(pyridin-2-ylmethyl)pyrimidin-4-amine (13a). A solution of 2,4,6-trichloropyrimidine **12** (1.00 g, 5.45 mmol) in dioxane (15 mL) at 10 °C was treated with diisopropylethylamine (1.1 equiv, 6.00 mmol, 1.04 mL) and dropwise with 2-aminomethylpyridine (1.1 equiv, 6.00 mmol, 0.62 mL) and stirred for 2 h at room temperature. TLC analysis (EtOAc/hexane, 3:1) showed conversion to 2 products. The dioxane was evaporated in vacuo, and the residue partitioned between H_2O (15 mL) and $CHCl_3$ (15 mL). The organic layer was separated and the aqueous layer further extracted with $CHCl_3$ (2 × 10 mL). The combined extracts were dried (Na_2SO_4) and concentrated in vacuo. Purification by column chromatography (same eluent) gave **16a** (280 mg, 20%) and **13a** (575 mg, 41%) as pale yellow solids.

Compound **16a**: R_f 0.69 (EtOAc/hexane, 3:1); δ_H (250 MHz, $CDCl_3$) 8.49 (1H, d, *J* 4.5), 7.61 (1H, td, *J* 7.5, 1.5), 7.23 (1H, d, *J* 7.5), 7.14 (1H, dd, *J* 7.5, 5.0), 6.71 (1H, br), 6.56 (1H, s), 4.66 (2H, d, *J* 5.0); HPLC–MS[a] R_t 3.44 min; ($C_{10}H_8Cl_2N_4$): *m/z* (ESI) 259 ([^{37,37}M+H]$^+$, 10), 257 ([^{37,35}M+H]$^+$, 56), 255 ([^{35,35}M+H]$^+$, 100); $C_{10}H_8Cl_2N_4$ requires 255.0204, found: [^{35,35}M+H]$^+$, 255.0201.

Compound **13a**: R_f 0.39 (EtOAc/hexane, 3:1); δ_H (250 MHz, $CDCl_3$) 8.49 (1H, d, *J* 4.5), 7.66 (1H, td, *J* 7.5, 1.5), 7.25–7.17 (2H, m), 6.85 (1H, br), 6.36 (1H, s, br), 4.66 (2H, s, br); HPLC–MS[b] R_t 5.15 min; ($C_{10}H_8Cl_2N_4$): *m/z* (ESI) 259 ([^{37,37}M+H]$^+$, 4%), 257 ([^{37,35}M+H]$^+$, 52), 255 ([^{35,35}M+H]$^+$, 100); $C_{10}H_8Cl_2N_4$ requires 255.0204, found: [^{35,35}M+H]$^+$, 255.0202.

5.2.4.2. 4,6-Dichloro-*N*-(pyridin-3-ylmethyl)pyrimidin-2-amine (16b) and 2,6-dichloro-*N*-(pyridin-3-ylmethyl)pyrimidin-4-amine (13b). Prepared from compound **12** according to general procedure 4; **16b** (19% yield) and **13b** (45% yield) were obtained as off-white solids.

Compound **16b**: R_f 0.54 (EtOAc); δ_H (250 MHz, $CDCl_3$) 8.55 (1H, d, *J* 2.0), 8.47 (1H, dd, *J* 5.0, 1.5), 7.61 (1H, dd, *J* 8.0, 2.0), 7.21 (1H, dd, *J* 7.5, 4.5), 6.59 (1H, s), 6.06 (1H, br), 4.59 (2H, d, *J* 6.0); HPLC–MS[b] R_t 4.20 min; ($C_{10}H_8Cl_2N_4$): *m/z* (ESI) 259 ([^{37,37}M+H]$^+$, 3%), 257 ([^{37,35}M+H]$^+$, 70), 255 ([^{35,35}M+H]$^+$, 100); $C_{10}H_8Cl_2N_4$ requires 255.0204, found: [^{35,35}M+H]$^+$, 255.0200.

Compound **13b**: R_f 0.30 (EtOAc); δ_H (250 MHz, $CDCl_3$) 8.53–8.47 (2H, m), 7.62 (1H, d, *J* 7.5), 7.28–7.25 (1H, m), 6.26 (1H, s), 5.95 (1H, s, br), 4.58 (2H, s, br); HPLC–MS[b] R_t 2.95 min; ($C_{10}H_8Cl_2N_4$): *m/z* (ESI) 259 ([^{37,37}M+H]$^+$, 2%), 257 ([^{37,35}M+H]$^+$, 46), 255 ([^{35,35}M+H]$^+$, 100); $C_{10}H_8Cl_2N_4$ requires 255.0204, found: [^{35,35}M+H]$^+$, 255.0211.

5.2.4.3. 4,6-Dichloro-*N*-(pyridin-4-ylmethyl)pyrimidin-2-amine (16c) and 2,6-dichloro-*N*-(pyridin-4-ylmethyl)pyrimidin-4-amine (13c). Prepared from compound **12** according to general procedure 4; **16c** (21% yield) and **13c** (45% yield) were obtained as pale yellow solids.

Compound **16c**: R_f 0.47 (EtOAc); δ_H (250 MHz, $CDCl_3$) 8.49 (2H, d, *J* 6.0), 7.17 (2H, d, *J* 6.0), 6.60 (1H, s), 6.24 (1H, s, br), 4.61 (2H, d, *J* 6.5); HPLC–MS[a] R_t 2.46 min; ($C_{10}H_8Cl_2N_4$): *m/z* (ESI) 259 ([^{37,37}M+H]$^+$, 4%), 257 ([^{37,35}M+H]$^+$, 51), 255 ([^{35,35}M+H]$^+$, 100); $C_{10}H_8Cl_2N_4$ requires 255.0204, found: [^{35,35}M+H]$^+$, 255.0203.

Compound **13c**: R_f 0.27 (EtOAc); δ_H (250 MHz, $CDCl_3$) 8.62 (2H, d, *J* 6.0), 7.23 (2H, d, *J* 6.0), 6.31 (1H, s), 4.62 (2H, s, br); HPLC–MS[a] R_t 1.80 min; ($C_{10}H_8Cl_2N_4$): *m/z* (ESI) 259 ([^{37,37}M+H]$^+$, 3%), 257 ([^{37,35}M+H]$^+$, 49), 255 ([^{35,35}M+H]$^+$, 100); $C_{10}H_8Cl_2N_4$ requires 255.0204, found: [^{35,35}M+H]$^+$, 255.0204.

5.2.4.4. 4,6-Dichloro-*N*-(2-(pyridin-2-yl)ethyl)pyrimidin-2-amine (16d) and 2,6-dichloro-*N*-(2-(pyridin-2-yl)ethyl)pyrimidin-4-amine (13d). Prepared from compound **12** according to general procedure 4; **16d** (19% yield) and **13d** (44% yield) were obtained as pale yellow solids.

Compound **16d**: R_f 0.64 ($CHCl_3$/MeOH, 9:1); δ_H (250 MHz, $CDCl_3$) 8.48 (1H, d, *J* 6.0), 7.54 (1H, td, *J* 7.5, 2.0), 7.11–7.06 (2H, m), 6.50 (1H, s), 6.20 (1H, br), 3.80 (2H, q, *J* 6.0), 3.01 (2H, t, *J* 6.0); HPLC–MS[a] R_t 3.77 min; ($C_{10}H_8Cl_2N_4$): *m/z* (ESI) 273 ([^{37,37}M+H]$^+$, 10%), 271 ([^{37,35}M+H]$^+$, 72), 269 ([^{35,35}M+H]$^+$, 100); $C_{10}H_8Cl_2N_4$ requires 269.0361, found: [^{35,35}M+H]$^+$, 269.0359.

Compound **13d**: R_f 0.45 ($CHCl_3$/MeOH, 9:1); δ_H (250 MHz, $CDCl_3$) 8.55 (1H, d, *J* 4.0), 7.66 (1H, td, *J* 7.5, 2.0), 7.23–7.19 (2H, m), 6.66 (1H, br), 6.31 (1H, s), 3.92–3.85 (2H, m), 3.12 (2H, t, *J* 6.0); HPLC–MS[a] R_t .88 min; ($C_{10}H_8Cl_2N_4$): *m/z* (ESI) 273 ([^{37,37}M+H]$^+$, 10%), 271 ([^{37,35}M+H]$^+$, 43), 269 ([^{35,35}M+H]$^+$, 100); $C_{10}H_8Cl_2N_4$ requires 269.0361, found: [^{35,35}M+H]$^+$, 269.0361.

5.2.4.5. 4,6-Dichloro-*N*-(2-(pyridin-3-yl)ethyl)pyrimidin-2-amine (16e) and 2,6-dichloro-*N*-(2-(pyridin-3-yl)ethyl)pyrimidin-4-amine (13e). Prepared from compound **12** according to general procedure 4; **16e** (21% yield) and **13e** (37% yield) were obtained as pale yellow solids.

Compound **16e**: R_f 0.45 ($CHCl_3$/MeOH, 9:1); δ_H (250 MHz, $CDCl_3$) 8.43–8.41 (2H, m), 7.50 (1H, dt, *J* 7.5, 2.0), 7.20 (1H, dd, *J* 7.5, 5.0), 6.55 (1H, s), 5.48 (1H, br), 3.64 (2H, q, *J* 7.0), 2.85 (2H, q, *J* 7.0); HPLC–MS[a] R_t 3.77 min; ($C_{10}H_8Cl_2N_4$): *m/z* (ESI) 273 ([^{37,37}M+H]$^+$, 10%), 271 ([^{37,35}M+H]$^+$, 72), 269 ([^{35,35}M+H]$^+$, 100); $C_{10}H_8Cl_2N_4$ requires 269.0361, found: [^{35,35}M+H]$^+$, 269.0359.

Compound **13e**: R_f 0.33 ($CHCl_3$/MeOH, 9:1); δ_H (250 MHz, $CDCl_3$) 8.41–8.37 (2H, m), 7.48 (1H, dt, *J* 7.5, 1.5), 7.20 (1H, dd, *J* 7.5, 5.5), 6.20 (1H, s), 5.75 (1H, br), 3.63–3.61 (2H, m), 2.88 (2H,

t, *J* 7.0); HPLC–MS[a] R_t 2.69 min; ($C_{10}H_8Cl_2N_4$): *m/z* (ESI) 273 ([^{37,37}M+H]$^+$, 5%), 271 ([^{37,35}M+H]$^+$, 45), 269 ([^{35,35}M+H]$^+$, 100); $C_{10}H_8Cl_2N_4$ requires 269.0361, found: [^{35,35}M+H]$^+$, 269.0356.

5.2.4.6. 4,6-Dichloro-*N*-(2-(pyridin-4-yl)ethyl)pyrimidin-2-amine (16f) and 2,6-dichloro-*N*-(2-(pyridin-4-yl)ethyl)pyrimidin-4-amine (13f). Prepared from compound **12** according to general procedure 4; **16f** (27% yield) and **13f** (29% yield) were obtained as pale yellow solids.

Compound **16f**: R_f 0.47 ($CHCl_3$/MeOH, 9:1); δ_H (250 MHz, $CDCl_3$) 8.46 (2H, dd, *J* 4.5, 1.5), 7.09 (2H, dd, *J* 4.5, 1.5), 6.55 (1H, s), 5.54 (1H, br), 3.66 (2H, q, *J* 7.0), 2.84 (2H, t, *J* 7.0); HPLC–MS[a] R_t 2.42 min; ($C_{10}H_8Cl_2N_4$): *m/z* (ESI) 273 ([^{37,37}M+H]$^+$, 5%), 271 ([^{37,35}M+H]$^+$, 45), 269 ([^{35,35}M+H]$^+$, 100); $C_{10}H_8Cl_2N_4$ requires 269.0361, found: [^{35,35}M+H]$^+$, 269.0357.

Compound **13f**: R_f 0.35 ($CHCl_3$/MeOH, 9:1); δ_H (250 MHz, $CDCl_3$) 8.47 (2H, d, *J* 6.0), 7.08 (2H, d, *J* 6.0), 6.20 (1H, s), 5.28 (1H, br), 3.62 (2H, s, br), 2.87 (2H, t, *J* 7.0); HPLC–MS[a] R_t 2.45 min; ($C_{10}H_8Cl_2N_4$): *m/z* (ESI) 273 ([^{37,37}M+H]$^+$, 10%), 271 ([^{37,35}M+H]$^+$, 45), 269 ([^{35,35}M+H]$^+$, 100); $C_{10}H_8Cl_2N_4$ requires 269.0361, found: [^{35,35}M+H]$^+$, 269.0362.

5.2.5. General procedure 5: reaction of 13a–13f with morpholine

5.2.5.1. 6-Chloro-2-morpholino-*N*-(pyridin-2-ylmethyl)pyrimidin-4-amine (14a). A solution of compound **13a** (50 mg, 0.19 mmol) in dioxane (1 mL) was treated with diisopropylethylamine (1.5 equiv, 0.29 mmol, 0.05 mL) and morpholine (1.8 equiv, 0.35 mmol, 0.03 mL) and heated to 70 °C for 8 h. TLC analysis ($CHCl_3$/MeOH, 96:4) showed complete conversion. The dioxane was evaporated in vacuo, and the residue partitioned between H_2O (5 ml) and $CHCl_3$ (5 ml). The organic layer was separated and the aqueous layer further extracted with $CHCl_3$ (2 × 2 mL). The combined extracts were dried (Na_2SO_4) and concentrated in vacuo. Purification by column chromatography (same eluent) gave **14a** (39 mg, 65%) as a colourless solid; R_f 0.60 ($CHCl_3$/MeOH, 9:1); δ_H (250 MHz, $CDCl_3$) 8.49 (1H, d, *J* 4.5), 7.60 (1H, td, *J* 8.0, 2.0), 7.21 (1H, d, *J* 7.5), (1H, dd, *J* 7.5, 5.0), 5.85 (1H, br), 5.75 (1H, s), 4.56 (2H, d, *J* 5.0), 3.68–3.60 (8H, m); HPLC–MS[b] R_t 4.09 min; ($C_{14}H_{16}Cl_1N_5O_1$): *m/z* (ESI) 306 ([^{35}M+H]$^+$, 100%), 308 ([^{37}M+H]$^+$, 29); $C_{14}H_{16}Cl_1N_5O_1$ requires 306.1122, found: [^{35}M+H]$^+$, 306.1122.

5.2.5.2. 6-Chloro-2-morpholino-*N*-(pyridin-3-ylmethyl)pyrimidin-4-amine (14b). Prepared from compound **13b** according to general procedure 5; colourless solid, 76% yield; R_f 0.32 ($CHCl_3$/MeOH, 9:1); δ_H (250 MHz, $CDCl_3$) 8.51 (1H, d, *J* 2.0), 8.46 (1H, dd, *J* 5.0, 1.5), 7.57 (1H, dd, *J* 8.0, 2.0), 7.20 (1H, dd, *J* 8.0, 5.0), 5.68 (1H, s), 5.03 (1H, br), 4.49 (2H, d, *J* 6.0), 3.68–3.60 (8H, m); HPLC–MS[a] R_t 2.63 min; ($C_{14}H_{16}Cl_1N_5O_1$): *m/z* (ESI) 306 ([^{35}M+H]$^+$, 100%), 308 ([^{37}M+H]$^+$, 33); $C_{14}H_{16}Cl_1N_5O_1$ requires 306.1122, found: [^{35}M+H]$^+$, 306.1132.

5.2.5.3. 6-Chloro-2-morpholino-*N*-(pyridin-4-ylmethyl)pyrimidin-4-amine (14c). Prepared from compound **13c** according to general procedure 5; pale yellow solid, 58% yield; R_f 0.43 ($CHCl_3$/MeOH, 9:1); δ_H (250 MHz, $CDCl_3$) 8.52 (2H, d, *J* 6.0), 7.33 (2H, d, *J* 6.0), 5.72 (1H, s), 5.36 (1H, br), 4.57 (2H, d, *J* 6.0), 3.65–3.55 (8H, m); HPLC–MS[b] R_t 2.87 min; ($C_{14}H_{16}Cl_1N_5O_1$): *m/z* (ESI) 306 ([^{35}M+H]$^+$, 100%), 308 ([^{37}M+H]$^+$, 28); $C_{14}H_{16}Cl_1N_5O_1$ requires 306.1122, found: [^{35}M+H]$^+$, 306.1131.

5.2.5.4. 6-Chloro-2-morpholino-*N*-(2-(pyridin-2-yl)ethyl)pyrimidin-4-amine (14d). Prepared from compound **13d** according to general procedure 5; pale yellow solid, 70% yield; R_f 0.18 ($CHCl_3$/MeOH, 9:1); δ_H (250 MHz, $CDCl_3$) 8.48 (1H, dt, *J* 5.0, 1.5), 7.55 (1H, td, *J* 7.5, 2.0), 7.12–7.07 (2H, m), 5.64 (1H, s), 5.39 (1H, br), 3.65–3.62 (10H, m), 2.98 (2H, t, *J* 6.5); HPLC–MS[b] R_t 3.70 min; ($C_{15}H_{18}Cl_1N_5O_1$): *m/z* (ESI) 320 ([^{35}M+H]$^+$, 100%), 322 ([^{37}M+H]$^+$, 29); $C_{15}H_{18}Cl_1N_5O_1$ requires 320.1278, found: [^{35}M+H]$^+$, 320.1269.

5.2.5.5. 6-Chloro-2-morpholino-*N*-(2-(pyridin-3-yl)ethyl)pyrimidin-4-amine (14e). Prepared from compound **13e** according to general procedure 5; pale yellow solid, 51% yield; R_f 0.08 ($CHCl_3$/MeOH, 9:1); δ_H (250 MHz, $CDCl_3$) 8.43 (1H, d, *J* 1.5), 8.39 (1H, dd, br, *J* 5.5, 2.0), 7.45 (1H, dt, *J* 8.0, 2.0), 7.18 (1H, dd, *J* 8.0, 5.0), 5.62 (1H, s), 4.73 (1H, br), 3.66 (8H, br s), 3.52 (2H, br q *J* 6.5), 2.83 (2H, t *J* 7.0); HPLC–MS[b] R_t 3.53 min; ($C_{15}H_{18}Cl_1N_5O_1$): *m/z* (ESI) 320 ([^{35}M+H]$^+$, 100%), 322 ([^{37}M+H]$^+$, 30); $C_{15}H_{18}Cl_1N_5O_1$ requires 320.1278, found: [^{35}M+H]$^+$, 320.1270.

5.2.5.6. 6-Chloro-2-morpholino-*N*-(2-(pyridin-4-yl)ethyl)pyrimidin-4-amine (14f). Prepared from compound **13f** according to general procedure 5; pale brown solid, 51% yield; R_f 0.10 ($CHCl_3$/MeOH, 9:1); δ_H (250 MHz, $CDCl_3$) 8.58 (2H, d, *J* 6.0), 7.24 (2H, d, *J* 6.0), 5.74 (1H, s), 4.88 (1H, br), 3.80–3.63 (10H, m), 2.98 (2H, t, *J* 7.0); HPLC–MS[b] R_t 3.21 min; ($C_{15}H_{18}Cl_1N_5O_1$): *m/z* (ESI) 320 ([^{35}M+H]$^+$, 100%), 322 ([^{37}M+H]$^+$, 15); $C_{15}H_{18}Cl_1N_5O_1$ requires 320.1278, found: [^{35}M+H]$^+$, 320.1277.

5.2.6. General procedure 6: reaction of 16a–16f with morpholine

5.2.6.1. 4-Chloro-6-morpholino-*N*-(pyridin-2-ylmethyl)pyrimidin-2-amine (17a). A solution of compound **16a** (100 mg, 0.39 mmol) in dioxane (1 mL) at room temperature was treated with diisopropylethylamine (1.5 equiv, 0.59 mmol, 0.10 mL) and morpholine (1.5 equiv, 0.59 mmol, 0.05 mL) and stirred at room temperature for 2 h. TLC analysis (EtOAc) then showed complete conversion. The dioxane was evaporated in vacuo, and the residue partitioned between H_2O (5 mL) and $CHCl_3$ (5 mL). The organic layer was separated and the aqueous layer further extracted with $CHCl_3$ (2 × 2 mL). The combined extracts were dried (Na_2SO_4) and concentrated in vacuo. Purification by column chromatography (same eluent) gave **17a** (101 mg, 83%) as a colourless solid; R_f 0.33 (EtOAc); δ_H (250 MHz, $CDCl_3$) 8.47 (1H, d, *J* 4.0), 7.56 (1H, td, *J* 7.5, 2.0), 7.21 (1H, d, *J* 7.5), 7.09 (1H, dd, *J* 7.5, 5.0), 6.07 (1H, br), 5.81 (1H, s), 4.62 (2H, d, *J* 5.5), 3.67–3.60 (4H, m), 3.46–3.42 (4H, m); HPLC–MS[a] R_t 2.48 min; ($C_{14}H_{16}Cl_1N_5O_1$): *m/z* (ESI) 306 ([^{35}M+H]$^+$, 100%), 308 ([^{37}M+H]$^+$, 32); $C_{14}H_{16}Cl_1N_5O_1$ requires 306.1122, found: [^{35}M+H]$^+$, 306.1124.

5.2.6.2. 4-Chloro-6-morpholino-*N*-(pyridin-3-ylmethyl)pyrimidin-2-amine (17b). Prepared from compound **16b** according to general procedure 6; colourless solid, 33% yield; R_f 0.47 ($CHCl_3$/MeOH, 9:1); δ_H (250 MHz, $CDCl_3$) 8.52 (1H, s), 8.43 (1H, d, *J* 4.0), 7.58 (1H, dt, *J* 8.0, 1.5), 7.17 (1H, dd, *J* 8.0, 5.0), 5.83 (1H, s), 5.61 (1H, br), 4.52 (2H, d, *J* 6.0), 3.65–3.62 (4H, m), 3.46–3.42 (4H, m); HPLC–MS[b] R_t 3.21 min; ($C_{14}H_{16}Cl_1N_5O_1$): *m/z* (ESI) 306 ([^{35}M+H]$^+$, 100%), 308 ([^{37}M+H]$^+$, 30); $C_{14}H_{16}Cl_1N_5O_1$ requires 306.1122, found: [^{35}M+H]$^+$, 306.1120.

5.2.6.3. 4-Chloro-6-morpholino-*N*-(pyridin-4-ylmethyl)pyrimidin-2-amine (17c). Prepared from compound **16c** according to general procedure 6; pale yellow solid, 51% yield; R_f 0.43 ($CHCl_3$/MeOH, 9:1); δ_H (250 MHz, $CDCl_3$) 8.50 (2H, d, *J* 6.0), 7.32 (2H, d, *J* 6.0), 5.86 (1H, s), 5.52 (1H, br), 4.57 (2H, d, *J* 6.0), 3.64–3.60 (4H, m), 3.43–3.39 (4H, m); HPLC–MS[b] R_t 2.81 min; ($C_{14}H_{16}Cl_1N_5O_1$): *m/z* (ESI) 306 ([^{35}M+H]$^+$, 100%), 308 ([^{37}M+H]$^+$, 29); $C_{14}H_{16}Cl_1N_5O_1$ requires 306.1122, found: [^{35}M+H]$^+$, 306.1130.

5.2.6.4. 4-Chloro-6-morpholino-*N*-(2-(pyridin-2-yl)ethyl)pyrimidin-2-amine (17d). Prepared from compound **16d** according to general procedure 6; pale yellow solid, 58% yield; R_f 0.13 ($CHCl_3$/

MeOH, 9:1); δ_H (250 MHz, $CDCl_3$) 8.47 (1H, d, *J* 5.0), 7.52 (1H, td, *J* 7.5, 2.0), 7.09–7.04 (2H, m), 5.77 (1H, s), 5.38 (1H, br t, *J* 5.0), 3.78–3.65 (6H, m), 3.57–3.46 (4H, m), 2.98 (2H, t, *J* 6.5); HPLC–MS[b] R_t 3.09 min; ($C_{15}H_{18}Cl_1N_5O_1$): *m/z* (ESI) 320 ([^{35}M+H]$^+$, 100%), 322 ([^{37}M+H]$^+$, 28); $C_{15}H_{18}Cl_1N_5O_1$ requires 320.1278, found: [^{35}M+H]$^+$, 320.1272.

5.2.6.5. 4-Chloro-6-morpholino-*N*-(2-(pyridin-3-yl)ethyl)pyrimidin-2-amine (17e). Prepared from compound **16e** according to general procedure 6; pale yellow solid, 50% yield; R_f 0.08 ($CHCl_3$/MeOH, 9:1); δ_H (250 MHz, $CDCl_3$) 8.41–8.38 (2H, m), 7.45 (1H, dt, *J* 7.5, 1.5), 7.15 (1H, dd, *J* 7.5, 5.0), 5.80 (1H, s), 5.18 (1H, br), 3.74–3.66 (4H, m), 3.56 (2H, q, *J* 7.0), 3.50–3.41 (4H, m), 2.82 (2H, t, *J* 7.0); HPLC–MS[b] R_t 3.12 min; ($C_{15}H_{18}Cl_1N_5O_1$): *m/z* (ESI) 320 ([^{35}M+H]$^+$, 100%), 322 ([^{37}M+H]$^+$, 30); $C_{15}H_{18}Cl_1N_5O_1$ requires 320.1278, found: [^{35}M+H]$^+$, 320.1277.

5.2.6.6. 4-Chloro-6-morpholino-*N*-(2-(pyridin-4-yl)ethyl)pyrimidin-2-amine (17f). Prepared from compound **16f** according to general procedure 6; pale yellow solid, 39% yield; R_f 0.10 ($CHCl_3$/MeOH, 9:1); δ_H (250 MHz, $CDCl_3$) 8.45 (2H, d, *J* 6.0), 7.11 (2H, d, *J* 6.0), 5.82 (1H, s), 4.98 (1H, br), 3.70–3.66 (4H, m), 3.59 (2H, q, *J* 7.0), 3.49 (4H, m), 2.83 (2H, t, *J* 7.0); HPLC–MS[b] R_t 2.87 min; ($C_{15}H_{18}Cl_1N_5O_1$): *m/z* (ESI) 320 ([^{35}M+H]$^+$, 100%), 322 ([^{37}M+H]$^+$, 35); $C_{15}H_{18}Cl_1N_5O_1$ requires 320.1278, found: [^{35}M+H]$^+$, 320.1285.

5.2.7. General procedure 7: Suzuki coupling of 14a–14f and 17a–17f

5.2.7.1. 3-(2-Morpholino-6-(pyridin-2-ylmethylamino)pyrimidin-4-yl)phenol (15a). A mixture of compound **14a** (20 mg, 0.065 mmol) and $PdCl_2$(dppf) (5 mol %, 2.5 mg) in DME (0.5 mL) was stirred at room temperature for 15 min. 3-hydroxyphenylboronic acid (3 equiv, 0.195 mmol, 27 mg), Na_2CO_3 (2.5 equiv, 0.16 mmol, 17 mg) and five drops of water were added and the mixture heated at 80 °C for 18 h. The solvents were then removed in vacuo and the residue partitioned between water (3 mL) and chloroform (4 mL). The organic phase was dried (Na_2SO_4) and concentrated in vacuo. Purification by preparative TLC ($CHCl_3$/MeOH, 95:5) gave **15a** (6 mg, 25%) as an off-white solid; R_f 0.37 $CHCl_3$/MeOH, 9:1); δ_H (250 MHz, $CDCl_3$) 8.50 (1H, d, *J* 4.5), 7.62 (1H, td, *J* 8.0, 2.0), 7.35–7.29 and 7.20–7.15 (5H, 2 × m), 6.83 (1H, br d, *J* 8.0), 5.94 (1H, s), 5.74 (1H, br), 4.64 (2H, d, *J* 5.5), 3.66–3.62 (8H, m); HPLC–MS[b] R_t 3.10 min; ($C_{20}H_{21}N_5O_2$): *m/z* (ESI) 364 ([M+H]$^+$, 100%); $C_{20}H_{21}N_5O_2$ requires 364.1774, found: [M+H]$^+$, 364.1779; HPLC[a] R_t 3.73 min, area 92.2%.

5.2.7.2. 3-(2-Morpholino-6-(pyridin-3-ylmethylamino)pyrimidin-4-yl)phenol (15b). Prepared from compound **14b** according to general procedure 7; pale yellow solid, 25% yield; R_f 0.27 $CHCl_3$/MeOH, 9:1); δ_H (250 MHz, CD_3OD) 8.45 (1H, s), 8.30 (1H, d, *J* 4.0), 7.74 (1H, d, *J* 8.0), 7.32–7.26 (3H, m), 7.12 (1H, t, *J* 8.0), 6.73 (1H, ddd, *J* 8.0, 2.5, 1.0), 6.18 (1H, s), 4.53 (2H, s), 3.67–3.64 (4H, m), 3.60–3.57 (4H, m); HPLC–MS[b] R_t 2.50 min; ($C_{20}H_{21}N_5O_2$): *m/z* (ESI) 364 ([M+H]$^+$, 100%); $C_{20}H_{21}N_5O_2$ requires 364.1774, found: [M+H]$^+$, 364.1786; HPLC[a] R_t 3.24 min, area >99.9%.

5.2.7.3. 3-(2-Morpholino-6-(pyridin-4-ylmethylamino)pyrimidin-4-yl)phenol (15c). Prepared from compound **14c** according to general procedure 7; off-white solid, 40% yield; R_f 0.25 $CHCl_3$/MeOH, 9:1); δ_H (250 MHz, $CDCl_3$) 8.49 (2H, d, *J* 5.0), 7.40–7.36 and 7.23–7.18 (5H, 2 × m), 6.82 (1H, ddd, *J* 8.0, 2.5, 1.0), 6.06 (1H, s), 5.07 (1H, br t, *J* 6.0), 4.56 (2H, d, *J* 6.0), 3.71–3.69 (4H, m), 3.67–3.62 (4H, m); HPLC–MS[b] R_t 2.20 min; ($C_{20}H_{21}N_5O_2$): *m/z* (ESI) 364 ([M+H]$^+$, 100%); $C_{20}H_{21}N_5O_2$ requires 364.1774, found: [M+H]$^+$, 364.1768; HPLC[a] R_t 2.02 min, area 92.4%.

5.2.7.4. 3-(2-Morpholino-6-(2-(pyridin-2-yl)ethylamino)pyrimidin-4-yl)phenol (15d). Prepared from compound **14d** according to general procedure 7. Purification by preparative TLC ($CHCl_3$/MeOH, 95:5) was followed by further purification by 2 g scx cartridge, eluting with MeOH, then 1 M NH_3 in MeOH; this gave **15d** (55% yield) as an off-white solid; R_f 0.33 $CHCl_3$/MeOH, 9:1); δ_H (250 MHz, $CDCl_3$) 8.61 (1H, app dq, *J* 5.0, 1.0), 7.67 (1H, td, *J* 8.0, 2.0), 7.46 (2H, app t, *J* 8.0), 7.30–7.19 (3H, m), 6.91 (1H, ddd, *J* 8.0, 2.0, 1.0), 6.00 (1H, s), 5.25 (1H, br t, *J* 5.5), 3.84–3.72 (10H, m), 3.14 (2H, t, *J* 6.5); HPLC–MS[b] R_t 2.60 min; ($C_{21}H_{23}N_5O_2$): *m/z* (ESI) 378 ([M+H]$^+$, 100%); $C_{21}H_{23}N_5O_2$ requires 378.1930, found: [M+H]$^+$, 378.1940; HPLC[a] R_t 3.40 min, area 92.2%.

5.2.7.5. 3-(2-Morpholino-6-(2-(pyridin-3-yl)ethylamino)pyrimidin-4-yl)phenol (15e). Prepared from compound **14e** according to general procedure 7; pale yellow solid, 52% yield; R_f 0.38 $CHCl_3$/MeOH, 9:1); δ_H (250 MHz, $CDCl_3$) 8.42–8.40 (2H, m), 7.48 (1H, br d, *J* 8.0), 7.39–7.34 (2H, m), 7.21–7.14 (2H, m), 6.82 (1H, dd, *J* 7.0, 1.5), 5.92 (1H, s), 4.75 (1H, br t, *J* 6.0), 3.75–3.65 (8H, m), 3.55 (2H, q, *J* 6.5), 2.81 (2H, t, *J* 6.5); HPLC–MS[b] R_t 2.49 min; ($C_{21}H_{23}N_5O_2$): *m/z* (ESI) 378 ([M+H]$^+$, 100%); $C_{21}H_{23}N_5O_2$ requires 378.1930, found: [M+H]$^+$, 378.1924; HPLC[a] R_t 3.26 min, area 95.5%.

5.2.7.6. 3-(2-Morpholino-6-(2-(pyridin-4-yl)ethylamino)pyrimidin-4-yl)phenol (15f). Prepared from compound **14f** according to general procedure 7; pale yellow solid, 43% yield; R_f 0.29 $CHCl_3$/MeOH, 9:1); δ_H (250 MHz, $CDCl_3$) 8.45 (2H, d, br, *J* 4.5), 7.39–7.37 (2H, m), 7.19 (1H, t, *J* 8.0), 7.09 (2H, d, *J* 6.0), 6.83 (1H, ddd, *J* 8.0, 2.0, 1.0), 5.96 (1H, s), 4.70 (1H, t, *J* 6.0), 3.78–3.74 (4H, m), 3.70–3.67 (4H, m), 3.56 (2H, q, *J* 6.5), 2.86 (2H, t, *J* 6.5); HPLC–MS[b] R_t 2.34 min; ($C_{21}H_{23}N_5O_2$): *m/z* (ESI) 378 ([M+H]$^+$, 100%); $C_{21}H_{23}N_5O_2$ requires 378.1930, found: [M+H]$^+$, 378.1932; HPLC[a] R_t 2.78 min, area 90.1%.

5.2.7.7. 3-(6-Morpholino-2-(pyridin-2-ylmethylamino)pyrimidin-4-yl)phenol (18a). Prepared from compound **17a** according to general procedure 7. Purification by prep TLC ($CHCl_3$/MeOH, 9:1) was followed by further purification by scx cartridge, eluting with MeOH, then 1 M NH_3 in MeOH; this gave **18a** (20% yield) as a pale yellow solid; R_f 0.33 ($CHCl_3$/MeOH, 9:1); δ_H (250 MHz, $CDCl_3$) 8.55 (1H, d, *J* 4.0), 7.64 (1H, td, *J* 8.0, 2.0), 7.42–7.36 (3H, m), 7.33 (1H, d, *J* 8.0), 7.22 (1H, t, *J* 8.0), 6.89 (1H, ddd, *J* 8.0, 2.0, 1.0), 6.20 (1H, s), 6.09 (1H, br), 4.76 (2H, d, *J* 5.5), 3.74–3.71 (4H, m), 3.58–3.54 (4H, m); HPLC–MS[b] R_t 3.08 min; ($C_{20}H_{21}N_5O_2$): *m/z* (ESI) 364 ([M+H]$^+$, 100%); $C_{20}H_{21}N_5O_2$ requires 364.1774, found: [M+H]$^+$, 364.1763; HPLC[a] R_t 3.66 min, area 96.8%.

5.2.7.8. 3-(6-Morpholino-2-(pyridin-3-ylmethylamino)pyrimidin-4-yl)phenol (18b). Prepared from compound **17b** according to general procedure 7; pale yellow solid, 42% yield; R_f 0.25 ($CHCl_3$/MeOH, 9:1); δ_H (250 MHz, $CDCl_3$) 8.73 (1H, br s), 8.51 (1H, d, *J* 3.5), 7.73 (1H, d, *J* 8.0), 7.45 (1H, br, q, *J* 1.5), 7.37–7.24 (3H, m), 7.28 (1H, t, *J* 8.0), 6.93 (1H, ddd, *J* 8.0, 2.5, 1.0), 6.29 (1H, s), 5.66 (1H, br), 4.63 (2H, d, *J* 6.0), 3.79–3.75 (4H, m), 3.63–3.59 (4H, m); HPLC–MS[b] R_t 2.49 min; ($C_{20}H_{21}N_5O_2$): *m/z* (ESI) 364 ([M+H]$^+$, 100%); $C_{20}H_{21}N_5O_2$ requires 364.1774, found: [M+H]$^+$, 364.1765; HPLC[a] R_t 3.19 min, area 92.3%.

5.2.7.9. 3-(6-Morpholino-2-(pyridin-4-ylmethylamino)pyrimidin-4-yl)phenol (18c). Prepared from compound **17c** according to general procedure 7; pale yellow solid, 31% yield; R_f 0.26 ($CHCl_3$/MeOH, 9:1); δ_H (250 MHz, $CDCl_3$) 8.41 (2H, d, *J* 6.0), 7.39 (1H, br, t, *J* 2.0), 7.25–7.20 (2H, m), 7.15 (2H, d, *J* 6.0), 6.80 (1H, ddd, *J* 7.5, 2.5, 1.0), 6.18 (1H, s), 5.94 (1H, br), 4.48 (2H, d, *J* 5.5), 3.67–3.63 (4H, m), 3.51–3.47 (4H, m); HPLC–MS[b] R_t 2.14 min;

($C_{20}H_{21}N_5O_2$): *m/z* (ESI) 364 ([M+H]$^+$, 100%); $C_{20}H_{21}N_5O_2$ requires 364.1774, found: [M+H]$^+$, 364.1758; HPLC[a] R_t 1.67 min, area 95.9%.

5.2.7.10. 3-(6-Morpholino-2-(2-(pyridin-2-yl)ethylamino)pyrimidin-4-yl)phenol (18d). Prepared from compound **17d** according to general procedure 7; pale yellow solid, 14% yield; R_f 0.52 (EtOAc/MeOH, 9:1); δ_H (250 MHz, $CDCl_3$) 8.58 (1H, ddd, *J* 4.0, 2.0, 1.0), 7.64 (1H, td, *J* 8.0, 2.0), 7.56–7.52 (1H, m), 7.38–7.23 (3H, m), 7.16 (1H, ddd, *J* 7.5, 5.0, 1.0), 6.95 (1H, ddd, *J* 8.0, 2.5, 1.0), 6.25 (1H, s), 3.89 (2H, q, *J* 7.0), 3.83–3.80 (4H, m), 3.71–3.67 (4H, m), 3.16 (2H, t, *J* 7.0); HPLC–MS[b] R_t 2.75 min; ($C_{21}H_{23}N_5O_2$): *m/z* (ESI) 378 ([M+H]$^+$, 100%); $C_{21}H_{23}N_5O_2$ requires 378.1930, found: [M+H]$^+$, 378.1935; HPLC[a] R_t 3.42 min, area 99.2%.

5.2.7.11. 3-(6-Morpholino-2-(2-(pyridin-3-yl)ethylamino)pyrimidin-4-yl)phenol (18e). Prepared from compound **17e** according to general procedure 7; pale yellow solid, 23% yield; R_f 0.44 (EtOAc/MeOH, 9:1); δ_H (250 MHz, $CDCl_3$) 8.44 (1H, br s), 8.37 (1H, dd, *J* 5.0, 1.0), 7.46 (1H, dt, *J* 8.0, 2.0), 7.37 (1H, s), 7.27–7.09 (3H, m), 6.80 (1H, ddd, *J* 8.0, 2.5, 1.0), 6.15 (1H, s), 5.28 (1H, br), 3.72–3.68 (4H, m), 3.59–3.53 (6H, m), 2.82 (2H, t, *J* 7.0); HPLC–MS[b] R_t 2.60 min; ($C_{21}H_{23}N_5O_2$): *m/z* (ESI) 378 ([M+H]$^+$, 100%); $C_{21}H_{23}N_5O_2$ requires 378.1930, found: [M+H]$^+$, 378.1928; HPLC[a] R_t 3.35 min, area 94.3%.

5.2.7.12. 3-(6-Morpholino-2-(2-(pyridin-4-yl)ethylamino)pyrimidin-4-yl)phenol (18f). Prepared from compound **17f** according to general procedure 7; pale yellow solid, 28% yield; R_f 0.40 (EtOAc/MeOH, 9:1); δ_H (250 MHz, $CDCl_3$) 8.33 (2H, d, *J* 6.0), 7.36 (1H, s), 7.00 (2H, d, *J* 6.0), 7.24–7.10 (2H, m), 6.81–6.72 (1H, br), 6.13 (1H, s), 5.40 (1H, br), 3.69 (4H, t, *J* 5.0), 3.56–3.50 (6H, m), 2.76 (2H, t, *J* 7.0); HPLC–MS[b] R_t 2.37 min; ($C_{21}H_{23}N_5O_2$): *m/z* (ESI) 378 ([M+H]$^+$, 100%); $C_{21}H_{23}N_5O_2$ requires 378.1930, found: [M+H]$^+$, 378.1934; HPLC[a] R_t 3.15 min, area 90.8%.

5.2.7.13. Preparation of 4-(4-chloro-6-(pyridin-2-ylmethoxy)pyrimidin-2-yl)morpholine 21 and 4-(6-chloro-2-(pyridin-2-ylmethoxy)pyrimidin-4-yl)morpholine 22. 248 mg of NaH (60% in mineral oil, 10.36 mmol) was added to a solution of 2-pyridinemethanol (0.90 equiv, 9.81 mmol, 0.95 mL) in THF (20 ml) at room temperature and stirred for 30 min. After cooling to −78 °C, 2,4,6-trichloropyrimidine **12** (2 g, 10.90 mmol) was added dropwise and the reaction allowed to warm to room temperature and stirred for 3 h. Saturated aqueous NH_4Cl (20 mL) was added and the mixture extracted with EtOAc (20 mL). The organic phase was dried ($MgSO_4$) and evaporated in vacuo. Column chromatography (EtOAc/DCM, 1:1) gave a mixture of two products (491 mg, 18%) as a pale yellow solid and in a ratio of 2.4:1, with the 4-isomer tentatively assigned as the major component; R_f 0.81 ($CHCl_3$/MeOH, 9:1); δ_H (250 MHz, $CDCl_3$) 8.66–8.61 (2H, m, 1 × major, 1 × minor), 7.75 (1H, td, *J* 8.0, 2.0, 1 × major), 7.74 (1H, td, *J* 8.0, 2.0, 1 × minor), 7.53 (1H, d, *J* 8.0, 1 × minor), 7.44 (1H, d, *J* 8.0, 1 × major), 7.32–7.24 (1H, 2H, m, 1 × major, 1 × minor), 7.09 (1H, s, 1 × minor), 6.84 (1H, s, 1 × major), 5.59 (2H, s, 2 × minor), 5.58 (2H, s, 2 × major); HPLC–MS[a] R_t major, 3.99 min; minor, 3.87 min; ($C_{10}H_8Cl_2N_4$): *m/z* (ESI) 260 ([^{37,37}M+H]$^+$, 5%), 258 ([^{37,35}M+H]$^+$, 35), 256 ([^{35,35}M+H]$^+$, 100).

This mixture (100 mg, 0.39 mmol) was treated with diisopropylethylamine (2.5 equiv, 0.98 mmol, 0.17 mL) and morpholine (3.5 equiv, 1.37 mmol, 0.12 mL) in dioxane (1 mL) according to general procedure 5. Purification by preparative TLC ($CHCl_3$/MeOH, 95:5) gave **21** (60 mg, 50%) and **22** (31 mg, 26%) as colourless solids.

Compound **21:** R_f 0.80 ($CHCl_3$/MeOH, 9:1); δ_H (250 MHz, $CDCl_3$) 8.49 (1H, d, *J* 5.0), 7.63 (1H, td, *J* 8.0, 2.0), 7.44 (1H, d, *J* 8.0), 7.14 (1H, dd, *J* 8.0, 5.0), 6.11 (1H, s), 5.41 (2H, s), 3.68–3.64 (4H, m), 3.53–3.50 (4H, m); HPLC–MS[b] R_t 7.16 min; ($C_{14}H_{15}Cl_1N_4O_2$): *m/z* (ESI) 307 ([^{35}M+H]$^+$, 100%), 309 ([^{37}M+H]$^+$, 29); $C_{14}H_{15}Cl_1N_4O_2$ requires 307.0962, found: [^{35}M+H]$^+$, 307.0958.

Compound **22**: R_f 0.63 ($CHCl_3$/MeOH, 9:1); δ_H (250 MHz, $CDCl_3$) 8.51 (1H, d, *J* 4.5), 7.63 (1H, td, *J* 8.0, 2.0), 7.31 (1H, d, *J* 8.0), 7.16 (1H, dd, *J* 7.0, 5.5), 6.08 (1H, s), 5.40 (2H, s), 3.68–3.59 (8H, m); HPLC–MS[b] R_t 5.21 min; ($C_{14}H_{15}Cl_1N_4O_2$): *m/z* (ESI) 307 ([^{35}M+H]$^+$, 100%), 309 ([^{37}M+H]$^+$, 29); $C_{14}H_{15}Cl_1N_4O_2$ requires 307.0962, found: [^{35}M+H]$^+$, 307.0953.

5.2.7.14. 3-(2-Morpholino-6-(pyridin-2-ylmethoxy)pyrimidin-4-yl)phenol (19). Prepared from compound 21 according to general procedure 7. Purification by preparative TLC ($CHCl_3$/MeOH, 95:5) was followed by further purification by 2 g scx cartridge, eluting with MeOH, then 1 M NH_3 in MeOH; this gave **19** (13 mg, 43%) as a colourless solid; R_f 0.44 $CHCl_3$/MeOH, 9:1); δ_H (250 MHz, $CDCl_3$) 8.54 (1H, d, *J* 4.5), 7.67 (1H, td, *J* 7.5, 2.0), 7.42–7.38 and 7.24–7.17 (5H, 2 × m), 6.85 (1H, ddd, *J* 8.0, 2.5, 1.0), 6.39 (1H, s), 5.45 (2H, s), 3.70–3.61 (8H, m); HPLC–MS[b] R_t 7.11 min; ($C_{20}H_{20}N_4O_3$): *m/z* (ESI) 365 ([M+H]$^+$, 100%); $C_{20}H_{20}N_4O_3$ requires 365.1614, found: [M+H]$^+$, 365.1608; HPLC[a] R_t 5.97 min, area 94.6%.

5.2.7.15. 3-(6-Morpholino-2-(pyridin-2-ylmethoxy)pyrimidin-4-yl)phenol (20). Prepared from compound **22** according to general procedure 7; pale yellow solid, 49% yield; R_f 0.46 ($CHCl_3$/MeOH, 9:1); δ_H (250 MHz, $CDCl_3$) 8.50 (1H, d, *J* 4.5), 7.62 (1H, td, *J* 8.0, 1.5), 7.51–7.47 (2H, m), 7.34 (1H, d, *J* 8.0), 7.18 (1H, t, *J* 8.0), 7.16–7.11 (1H, m), 6.86 (1H, ddd, *J* 8.0, 2.5, 1.0), 6.85 (1H, s), 5.52 (2H, s), 3.70–3.65 (4H, m), 3.58–3.54 (4H, m); HPLC–MS[b] R_t 4.85 min; ($C_{20}H_{20}N_4O_3$): *m/z* (ESI) 365 ([M+H]$^+$, 100%); $C_{21}H_{23}N_5O_2$ requires 365.1614, found: [M+H]$^+$, 365.1605; HPLC[a] R_t 4.84 min, area 97.6%.

5.2.7.16. 4,4′-(6-(Pyridin-2-ylmethoxy)pyrimidine-2,4-diyl)dimorpholine (23). Compound **21** (306 mg, 1.0 mmol) was stirred in morpholine (0.5 mL) and heated to 50 °C. After 4 h, the reaction mixture was poured into water and the products extracted into ethyl acetate. The organic layers were rinsed (brine) and dried (Na_2SO_4) and evaporated to give **23** (327 mg, 92%) as a colourless solid; R_f 0.88 ($CHCl_3$/MeOH, 9:1); δ_H (500 MHz, $CDCl_3$) 8.56 (1H, d, *J* 5.0), 7.66 (1H, td, *J* 7.5, 1.5), 7.40 (1H, d, *J* 7.5), 7.18 (1H, dd, *J* 7.5, 5.0), 5.45 (2H, s), 5.40 (1H, s), 3.74 (4H, t, *J* 4.5), 3.68 (8H, br), 3.51 (4H, t, *J* 5.0); δ_C (125 MHz, $CDCl_3$) 170.6 (*C*), 165.2 (*C*), 160.9 (*C*), 157.8 (*C*), 149.1 (*CH*), 136.5 (*CH*), 122.3 (*CH*), 121.1 (*CH*), 76.2 (*CH*), 67.8 (CH_2), 66.8 (CH_2), 66.6 (CH_2), 44.7 (CH_2), 44.4 (CH_2); HPLC–MS[b] R_t 5.93 min; ($C_{18}H_{23}N_5O_3$): *m/z* (ESI) 358 ([M+H]$^+$, 100%); $C_{18}H_{23}N_5O_3$ requires 358.1879, found: [M+H]$^+$, 358.1882.

5.2.7.17. 4,4′-(2-(Pyridin-2-ylmethoxy)pyrimidine-4,6-diyl)dimorpholine (24). Prepared from compound **22** using the same procedure as for **23**; compound **24** was obtained as a colourless solid (91% yield); R_f 0.75 ($CHCl_3$/MeOH, 9:1); δ_H (500 MHz, $CDCl_3$) 8.51 (1H, d, *J* 4.5), 7.62 (1H, td, *J* 7.5, 1.5), 7.46 (1H, d, *J* 8.0), 7.13 (1H, dd, *J* 6.5, 4.5), 5.43 (2H, s), 5.23 (1H, s), 3.69 (8H, t, *J* 5.0), 3.48 (8H, t, *J* 5.0); δ_C (125 MHz, $CDCl_3$) 165.3 (*C*), 164.1 (*C*), 158.1 (*C*), 148.8 (*CH*), 136.5 (*CH*), 122.1 (*CH*), 121.0 (*CH*), 75.9 (*CH*), 68.9 (CH_2), 66.5 (CH_2), 44.7 (CH_2); HPLC–MS[b] R_t 4.37 min; ($C_{18}H_{23}N_5O_3$): *m/z* (ESI) 358 ([M+H]$^+$, 100%); $C_{18}H_{23}N_5O_3$ requires 358.1879, found: [M+H]$^+$, 358.1873.

5.2.7.18. 2-Morpholino-*N*-(2-(pyridin-2-yl)ethyl)pyrimidin-4-amine (25). Compound **14d** (50 mg, 0.16 mmol), 5% palladium on carbon (15 mg, 0.007 mmol, 4 mol %) and potassium acetate (100 mg, 1.02 mmol, 6 equiv) were stirred in AcOH (3 mL) under an atmosphere of H_2 for 18 h. The reaction mixture was added to

saturated $NaHCO_3$ (3 mL), then DCM (2 mL) was added; the organic layer was collected, rinsed (brine), dried (Na_2SO_4) and concentrated to give a yellow oil. The residue was filtered through a plug of Celite to give **25** (30 mg, 68%) as a colourless solid; R_f 0.23 ($CHCl_3$/MeOH 9:1); δ_H (500 MHz, CD_3OD) 8.46 (1H, d, *J* 6.0), 7.74 (1H, td, *J* 6.5, 2.0), 7.67 (1H, d, *J* 6.5), 7.30 (1H, d, *J* 7.0), 7.26 (1H, ddd, *J* 7.0, 5.0, 1.0), 5.80 (1H, d, *J* 6.0), 3.70–3.74 (6H, m), 3.64–3.67 (4H, m), 3.06 (2H, t, *J* 7.0); δ_C (500 MHz, CD_3OD) 161.0 (*C*), 159.2 (*C*), 158.1 (*C*), 152.3 (*CH*), 147.1 (*CH*), 136.9 (*CH*), 122.3 (*CH*), 120.3 (*CH*), 75.9 (*CH*), 65.2 (CH_2), 43.0 (CH_2), 35.9 (CH_2)1 HPLC–MS[a] R_t 0.68 min; ($C_{15}H_{19}N_5O_1$): *m/z* (ESI) 286 ($[M+H]^+$, 100%); $C_{15}H_{19}N_5O_1$ requires 286.1662, found: $[M+H]^+$, 286.1668.

5.2.7.19. 4-Morpholino-*N*-(2-(pyridin-2-yl)ethyl)pyrimidin-2-amine (26). From compound **17d**, and using the same procedure as for **25**; compound **26** was obtained as a colourless solid (78% yield); R_f 0.19 ($CHCl_3$/MeOH 9:1); δ_H (500 MHz, DMSO-d_6, 330 K) 8.49 (1H, d, *J* 6.0), 7.82 (1H, d, *J* 6.0), 7.67 (1H, td, *J* 7.5, 2.0), 7.24 (1H, d, *J* 7.5), 7.19 (1H, dd, *J* 7.5, 5.0), 6.33 (1H, br), 5.99 (1H, d, *J* 6.0), 3.65–3.63 (4H, m), 3.62–3.58 (2H, m), 3.51–3.49 (4H, m), 2.96 (2H, t, *J* 7.5); δ_C (500 MHz, CD_3OD) 164.2 (*C*), 162.8 (*C*), 161.0 (*C*), 156.6 (*CH*), 149.8 (*CH*), 138.5 (*CH*), 125.2 (*CH*), 123.0 (*CH*), 94.1 (*CH*), 67.7 (CH_2), 45.3 (CH_2), 42.1 (CH_2), 38.8 (CH_2); HPLC–MS[a] R_t 0.63 min; ($C_{15}H_{19}N_5O_1$): *m/z* (ESI) 286 ($[M+H]^+$, 100%); $C_{15}H_{19}N_5O_1$ requires 286.1668, found: $[M+H]^+$, 286.1671.

5.2.8. General procedure 8: Suzuki coupling of intermediates 14d–14f, 17d–17f, 21 and 22 with aryl or heteroaryl boronic acids or esters

The chloropyrimidine (1.0 equiv), boronic acid or ester (2.2 equiv), Bedford catalyst **29** (0.05 equiv) and 2 M aqueous Na_2CO_3 (2.2 equiv) were dissolved in 1,2-DME. The solution was degassed and backfilled with nitrogen, then stirred with microwave heating at 150 °C for 30 min. The reaction mixture was cooled, absorbed onto a plug of silica (100 mg) and eluted ($CHCl_3$/MeOH, 9:1). The crude product was obtained by evaporating the filtrate in vacuo and purified by one of the following methods:

Method A: The crude compound was dissolved in methanol and purified using an SCX-2 ion exchange column, eluting first with MeOH, then 2 M NH_3 in MeOH.

Method B: Purification by preparative TLC using the specified eluent.

Method C: Recrystallisation from MeOH/$CHCl_3$/hexane, 1:1:4.

5.2.8.1. 6-(1*H*-indol-6-yl)-2-morpholino-*N*-(2-(pyridin-2-yl)ethyl) pyrimidin-4-amine (27a). Prepared from compound **14d** according to general procedure 8, using **14d** (50 mg, 0.16 mmol), **29** (0.05 equiv, 4.9 mg), indole 6-boronic acid (2.2 equiv, 0.34 mmol, 55 mg), 2 M Na_2CO_3 (2.2 equiv, 0.34 mmol, 0.17 mL) and DME (1 mL). Purification by method A, followed by method B (EtOAc/MeOH, 9:1) gave **27a** (10 mg, 16%) as an off-white solid; mp 204–208 °C; R_f 0.68 ($CHCl_3$/MeOH, 9:1); δ_H (500 MHz, CD_3OD) 8.45 (1H, d, *J* 4.5), 8.05 (1H, s), 7.70 (1H, td, *J* 8.0, 2.0), 7.61 (1H, dd, *J* 8.5, 1.0), 7.57 (1H, d, *J* 8.5), 7.29 (1H, d, *J* 8.0), 7.27 (1H, d, *J* 3.0), 7.22 (1H, dd, *J* 6.5, 4.5), 6.46 (1H, dd, *J* 3.0, 0.5), 6.25 (1H, s), 3.84–3.82 (4H, m), 3.78–3.74 (6H, m), 3.09 (2H, t, *J* 7.0); HPLC–MS R_t 2.89 min; ($C_{22}H_{24}N_6O_1$) *m/z* (ESI) 401 ($[M+H]^+$, 100%); $C_{22}H_{24}N_6O_1$ requires 401.2090 for $[M+H]^+$, found: 401.2107; HPLC[b] R_t 3.80 min, purity 96%.

5.2.8.2. 6-(1*H*-indol-6-yl)-2-morpholino-*N*-(2-(pyridin-3-yl) ethyl)pyrimidin-4-amine (27b). Prepared from compound **14e** according to general procedure 8. Purification by method B ($CHCl_3$/MeOH, 9:1) followed by method C gave **27b** (25% yield) as a pale brown solid; mp 217–218 °C; R_f 0.53 ($CHCl_3$/MeOH, 9:1); δ_H (500 MHz, CD_3OD) 8.40 (1H, s), 8.35 (1H, d, *J* 4.0), 8.04 (1H, s), 7.68 (1H, d, *J* 8.0), 7.60 (1H, dd, *J* 8.5, 1.5) 7.57 (1H, d, *J* 8.5), 7.32 (1H, dd, *J* 7.5, 5.0), 7.27 (1H, d, *J* 3.0), 6.46 (1H, dd, *J* 3.0, 0.5), 6.24 (1H, s), 3.84–3.82 (4H, m), 3.78–3.76 (4H, m), 3.66 (2H, t, *J* 7.0), 2.96 (2H, t, *J* 7.0); HPLC–MS R_t 2.85 min; ($C_{22}H_{24}N_6O_1$) *m/z* (ESI) 401 ($[M+H]^+$, 100%); $C_{22}H_{24}N_6O_1$ requires 401.2090 for $[M+H]^+$, found: 401.2098; HPLC[b] R_t 3.88 min, purity >99%.

5.2.8.3. 6-(1*H*-indol-6-yl)-2-morpholino-*N*-(2-(pyridin-4-yl) ethyl)pyrimidin-4-amine (27c). Prepared from compound **14f** according to general procedure 8. Purification by method C gave **27c** (41% yield) as a pale yellow solid; mp >230 °C; R_f 0.43 ($CHCl_3$/MeOH, 9:1); δ_H (500 MHz, CD_3OD) 8.43 (2H, dd, *J* 4.5, 1.5), 8.07 (1H, br s), 7.60 (1H, dd, *J* 8.5, 1.5), 7.56 (1H, d, *J* 8.5), 7.34 (2H, dd, *J* 4.5, 1.5), 7.31 (1H, d, *J* 3.0), 6.46 (1H, d, *J* 3.0), 6.28 (1H, s), 3.72 (2H, t, *J* 7.0) 3.84–3.82 (4H, m), 3.78–3.76 (4H, m) 3.00 (2H, t, *J* 7.0); HPLC–MS R_t 2.66 min; ($C_{22}H_{24}N_6O_1$) *m/z* (ESI) 401 ($[M+H]^+$, 100%); $C_{22}H_{24}N_6O_1$ requires 401.2090 for $[M+H]^+$, found: 401.2083; HPLC[b] R_t 3.60 min, purity 99%.

5.2.8.4. *N*-(3-(2-Morpholino-6-(2-(pyridin-2-yl)ethylamino)pyrimidin-4-yl)phenyl)methanesulfonamide (27d). Prepared from compound **14d** according to general procedure 8. Purification by method A, followed by method B ($CHCl_3$/MeOH, 9:1) gave **27d** (31% yield) as an off-white solid; mp 155–158 °C; R_f 0.47 ($CHCl_3$/MeOH, 9:1); δ_H (500 MHz, CD_3OD) 8.46 (1H, d, *J* 4.0), 7.90 (1H, t, *J* 2.0), 7.74 (1H, td, *J* 7.5, 2.0), 7.70 (1H, d, *J* 8.0), 7.38 (1H, t, *J* 8.0), 7.33–7.29 (2H, m), 7.25 (1H, dd, *J* 7.5, 1.5), 6.22 (1H, s), 3.81–3.73 (10H, m), 3.09 (2H, t, *J* 7.0), 2.97 (3H, s, *CH*$_3$); HPLC–MS[b] R_t 2.68 min; ($C_{22}H_{26}N_6O_3S_1$) *m/z* (ESI) 455 ($[M+H]^+$, 100%); $C_{22}H_{26}N_6O_3S_1$ requires 455.1865 for $[M+H]^+$, found: 455.1885; HPLC[b] R_t 3.62 min, purity 94%.

5.2.8.5. *N*-(3-(2-Morpholino-6-(2-(pyridin-3-yl)ethylamino)pyrimidin-4-yl)phenyl)methanesulfonamide (27e). Prepared from compound **14e** according to general procedure 8. Purification by method A, followed by method B ($CHCl_3$/MeOH, 9:1) gave **27e** (27% yield) as an off-white solid; mp 208–211 °C; R_f 0.43 ($CHCl_3$/MeOH, 9:1); δ_H (500 MHz, $CDCl_3$) 8.51 (1H, d, *J* 2.0), 8.50 (1H, dd, *J* 5.0, 2.0), 7.81 (1H, br t, *J* 2.0), 7.77 (1H, dt, *J* 8.0, 2.0), 7.55 (1H, dt, *J* 8.0, 2.0), 7.41 (1H, t, *J* 8.0), 7.33 (1H, ddd, *J* 8.0, 2.0, 1.0), 7.26 (1H, dd, *J* 7.5, 5.0), 6.11 (1H, s), 4.79 (1H, br t, *J* 6.5), 3.86–3.84 (4H, m), 3.79–3.77 (4H, m), 3.68 (2H, dt, *J* 7.0, 6.5), 3.01 (3H, s), 2.95 (2H, t, *J* 7.0); HPLC–MS R_t 2.55 min; ($C_{22}H_{26}N_6O_3S_1$) *m/z* (ESI) 455 ($[M+H]^+$, 100%); $C_{22}H_{26}N_6O_3S_1$ requires 455.1865 for $[M+H]^+$, found: 455.1871; HPLC[b] R_t 3.47 min, purity 97%.

5.2.8.6. *N*-(3-(2-Morpholino-6-(2-(pyridin-4-yl)ethylamino)pyrimidin-4-yl)phenyl)methanesulfonamide (27f). Prepared from compound **14f** according to general procedure 8. Purification by method B (EtOAc/MeOH, 9:1), followed by method C gave **27f** (6% yield) as an off-white solid; mp 134–136 °C; R_f 0.43 ($CHCl_3$/MeOH, 9:1; δ_H (500 MHz, $CDCl_3$) 8.57 (2H, d, *J* 5.0), 7.81 (1H, s), 7.77 (1H, d, *J* 8.0), 7.43 (1H, t, *J* 8.0), 7.32 (1H, d, *J* 8.0), 7.18 (2H, d, *J* 5.0), 6.09 (1H, s), 3.89–3.87 (4H, m), 3.81–3.80 (4H, m), 3.73 (2H, dt, *J* 7.0, 6.5), 3.04 (3H, s), 2.27 (2H, t, *J* 7.0); HPLC–MS R_t 2.28 min; ($C_{22}H_{26}N_6O_3S_1$) *m/z* (ESI) 455 ($[M+H]^+$, 100%); $C_{22}H_{26}N_6O_3S_1$ requires 455.1865 for $[M+H]^+$, found: 455.1873; HPLC[a] R_t 1.81 min, purity >99%.

5.2.8.7. 6-(1*H*-Indazol-4-yl)-2-morpholino-*N*-(2-(pyridin-2-yl) ethyl)pyrimidin-4-amine (27g). Prepared from compound **14d** according to general procedure 8. Purification by method B ($CHCl_3$/MeOH, 9:1) gave **27g** (19% yield) as a pale yellow solid; mp 120–130 °C; R_f 0.37 ($CHCl_3$/MeOH, 9:1); δ_H (500 MHz, $CDCl_3$),

8.65 (1H, s), 8.58 (1H, d, *J* 5.0), 7.62 (1H, td, *J* 7.5, 1.5), 7.59 (1H, d, *J* 7.5), 7.53 (1H, d, *J* 7.5), 7.43 (1H, t, *J* 7.5), 7.19 (1H, d, *J* 7.5), 7.16 (1H, dd, *J* 7.5, 5.0), 6.23 (1H, s), 5.39 (1H, br t, *J* 5.0), 3.90–3.83 (6H, m), 3.81–3.79 (4H, m), 3.13 (2 H, t, *J* 6.5); HPLC–MS R_t 2.31 min; ($C_{22}H_{23}N_7O_1$) *m/z* (ESI) 402 ([M+H]$^+$, 100%); $C_{22}H_{23}N_7O_1$ requires 402.2042 for [M+H]$^+$, found: 402.2042; HPLC[b] R_t 3.52 min, purity 96%.

5.2.8.8. 6-(1*H*-Indazol-4-yl)-2-morpholino-*N*-(2-(pyridin-3-yl) ethyl)pyrimidin-4-amine (27h). Prepared from compound **14e** according to general procedure 8. Purification by method A gave **27h** (16% yield) as an off-white solid; mp 100–105 °C; R_f 0.24 ($CHCl_3$/MeOH, 9:1); δ_H (500 MHz, $CDCl_3$) 8.65 (1H, s), 8.54 (1H, d, *J* 1.5), 8.52 (1H, dd, *J* 5.0, 1.5), 7.58–7.54 (2H, m), 7.53 (1H, d, *J* 8.5), 7.41 (1H, dd, *J* 8.0, 7.5), 7.25 (1H, dd, *J* 7.5, 5.0), 6.20 (1H, s), 4.87 (1H, t, *J* 5.5), 3.90–3.88 (4H, m), 3.81–3.79 (4H, m), 3.71–3.67 (2H, m), 2.97 (2H, t, *J* 7.0); HPLC–MS R_t 2.56 min; ($C_{22}H_{23}N_7O_1$) *m/z* (ESI) 402 ([M+H]$^+$, 100%); $C_{22}H_{23}N_7O_1$ requires 402.2042 for [M+H]$^+$, found: 402.2059; HPLC[b] R_t 3.39 min, purity 97%.

5.2.8.9. 6-(1*H*-Indazol-4-yl)-2-morpholino-*N*-(2-(pyridin-4-yl) ethyl)pyrimidin-4-amine (27i). Prepared from compound **14f** according to general procedure 8. Purification by method B ($CHCl_3$/MeOH, 9:1), followed by method C gave **27i** (95% yield) as a pale brown solid; mp 108–115 °C; R_f 0.23 ($CHCl_3$/MeOH, 9:1); δ_H (500 MHz, CD_3OD), 8.65 (1H, s, br), 8.55 (2H, d, *J* 6.0), 7.58 (1H, d, *J* 7.5), 7.55 (1H, d, *J* 8.5), 7.49 (1H, dd, *J* 8.5, 7.5), 7.17 (2H, d, *J* 6.0), 6.21 (1H, s, br), 4.69 (1H, s, br), 3.83–3.82 (4H, t, *J* 5.0), 3.76 (4H, t, *J* 5.0), 3.70 (2H, dt, *J* 7.0, 6.5), 2.95 (2H, t, *J* 7.0); HPLC–MS R_t 2.41 min; ($C_{22}H_{23}N_7O_1$) *m/z* (ESI) 402 ([M+H]$^+$, 100%); $C_{22}H_{23}N_7O_1$ requires 402.2042 for [M+H]$^+$, found: 402.2049; HPLC[b] R_t 3.18 min, purity 96%.

5.2.8.10. 4-(1*H*-Indol-6-yl)-6-morpholino-*N*-(2-(pyridin-2-yl) ethyl)pyrimidin-2-amine (28a). Prepared from compound **17d** according to general procedure 8. Purification by method A gave **28a** (73% yield) as a yellow solid; mp 91–98 °C; R_f 0.35 ($CHCl_3$/MeOH, 9:1); δ_H (250 MHz, $CDCl_3$) 9.78 (1H, br), 8.49 (1H, d, *J* 4.5), 8.19 (1H, s), 7.61 (1H, d, *J* 8.0), 7.58 (1H, d, *J* 8.0), 7.52 (1H, td, *J* 7.5, 1.5), 7.15 (1H, br), 7.12 (1H, d, *J* 7.5), 7.07 (1H, dd, *J* 7.0, 4.5), 6.47 (1H, s), 6.29 (1H, br), 3.86–3.83 (2H, m), 3.76–3.74 (4H, m), 3.62–3.60 (4H, m), 3.09 (2H, t, *J* 7.0); HPLC–MS R_t 3.30 min; ($C_{22}H_{24}N_6O_1$) *m/z* (ESI) 401 ([M+H]$^+$, 100%); $C_{22}H_{24}N_6O_1$ requires 401.2090 for [M+H]$^+$, found: 401.2085; HPLC[b] R_t 4.27 min, purity >99%.

5.2.8.11. 4-(1*H*-indol-6-yl)-6-morpholino-*N*-(2-(pyridin-3-yl) ethyl)pyrimidin-2-amine (28b). Prepared from compound **17e** according to general procedure 8. Purification by method B ($CHCl_3$/MeOH, 9:1) gave **28b** (91% yield) as an off-white solid; mp 188–194 °C; R_f 0.26 ($CHCl_3$/MeOH, 9:1); δ_H (500 MHz, $CDCl_3$) 9.22 (1H, br s), 8.49 (1H, s), 8.44 (1H, dd, *J* 5.0, 1.5), 8.17 (1H, s), 7.65 (1H, d, *J* 8.5), 7.61 (1H, d, *J* 8.5), 7.47 (1H, d, *J* 7.5), 7.20 (1H, t, *J* 3.0), 7.16 (1H, dd, *J* 7.5, 5.0), 6.52 (1H, br), 6.35 (1H, s), 3.79–3.77 (4H, m), 3.64–3.60 (6H, m), 2.87 (2H, t, *J* 7.0); HPLC–MS R_t 3.03 min; ($C_{22}H_{24}N_6O_1$) *m/z* (ESI) 401 ([M+H]$^+$, 100%); $C_{22}H_{24}N_6O_1$ requires 401.2090 for [M+H]$^+$, found: 401.2100; HPLC[b] R_t 4.08 min, purity 97%.

5.2.8.12. 4-(1*H*-Indol-6-yl)-6-morpholino-*N*-(2-(pyridin-4-yl) ethyl)pyrimidin-2-amine (28c). Prepared from compound **17f** according to general procedure 8. Purification by method B ($CHCl_3$/MeOH, 9:1) gave **28c** (87% yield) as an orange solid; mp 133–135 °C; R_f 0.22 ($CHCl_3$/MeOH, 9:1); δ_H (500 MHz, CD_3OD) 8.44 (2H, d, *J* 6.0), 7.96 (1H, s), 7.64 (1H, d, *J* 8.5), 7.54 (1H, d, *J* 8.5), 7.38–7.37 (3H, m), 6.52 (1H, s), 6.51 (1H, dd, *J* 3.0, 0.5), 3.80–3.74 (10H), 3.04 (2H, t, *J* 7.0); HPLC–MS R_t 2.76 min; ($C_{22}H_{24}N_6O_1$) *m/z* (ESI) 401 ([M+H]$^+$, 100%); $C_{22}H_{24}N_6O_1$ requires 401.2090 for [M+H]$^+$, found: 401.2108; HPLC[b] R_t 3.86 min, purity >99%.

5.2.8.13. *N*-(3-(6-Morpholino-2-(2-(pyridin-2-yl)ethylamino) pyrimidin-4-yl)phenyl)methanesulfonamide (28d). Prepared from compound **17d** according to general procedure 8. Purification by method A gave **28d** (75% yield) as an off-white solid; mp 90–95 °C; R_f 0.36 ($CHCl_3$/MeOH, 9:1); δ_H (500 MHz, $CDCl_3$) 8.54 (1H, d, *J* 5.0), 7.76 (1H, br), 7.64 (1H, d, *J* 6.5), 7.59 (1H, td, *J* 7.5, 2.0), 7.35 (1H, t, *J* 7.5), 7.31 (1H, d, *J* 8.0), 7.19 (1H, d, *J* 7.5), 7.12 (1H, dd, *J* 7.5, 5.0), 6.21 (1H, s), 5.60 (1H, br), 3.85 (2H, td, *J* 6.5, 6.0), 3.63 (4H, t, *J* 5.0), 3.52 (4H, t, *J* 4.5), 3.12 (2H, t, *J* 7.0), 2.98 (3H, s); HPLC–MS R_t 2.53 min; ($C_{22}H_{26}N_6O_3S_1$) *m/z* (ESI) 455 ([M+H]$^+$, 100%); $C_{22}H_{26}N_6O_3S_1$ requires 455.1865 for [M+H]$^+$, found: 455.1870; HPLC[b] R_t 3.59 min, purity 98%.

5.2.8.14. *N*-(3-(6-Morpholino-2-(2-(pyridin-3-yl)ethylamino) pyrimidin-4-yl)phenyl)methanesulfonamide (28e). Prepared from compound **17e** according to general procedure 8. Purification by method B ($CHCl_3$/MeOH, 9:1) gave **28e** (95% yield) as a yellow solid; mp 130–138 °C; R_f 0.35 ($CHCl_3$/MeOH, 9:1); δ_H (500 MHz $CDCl_3$) 8.55 (1H, s), 8.47 (1H, d, *J* 5.0, 1.5), 7.72 (1H, s), 7.65 (1H, d, *J* 7.0), 7.58 (1H, d, *J* 8.0), 7.39 (1H, t, *J* 8.0), 7.33 (1H, d, *J* 8.0), 7.23 (1H, d, *J* 8.0, 5.0), 6.25 (1H, s), 3.80–3.78 (4H, m), 3.72 (2H, dt, *J* 7.0, 6.5), 3.66–3.63 (4H, m), 3.02 (3H, s), 2.95 (2H, t, *J* 7.0); HPLC–MS R_t 2.42 min; ($C_{22}H_{26}N_6O_3S_1$) *m/z* (ESI) 455 ([M+H]$^+$, 100%); $C_{22}H_{26}N_6O_3S_1$ requires 455.1865 for [M+H]$^+$, found: 455.1877; HPLC[b] R_t 3.45 min, purity 98%.

5.2.8.15. *N*-(3-(6-Morpholino-2-(2-(pyridin-4-yl)ethyl-amino)pyrimidin-4-yl)phenyl)methanesulfonamide (28f). Prepared from compound **17f** according to general procedure 8. Purification by method B (EtOAc/MeOH, 9:1) gave **28f** (47% yield) as a pale yellow solid; mp 145–152 °C; R_f 0.36 ($CHCl_3$/MeOH, 9:1); δ_H (500 MHz, $CDCl_3$) 9.87 (1H, br), 8.45 (2H, d, *J* 4.5), 8.31 (1H, s), 7.92 (1H, br), 7.76 (1H, d, *J* 7.5), 7.41 (1H, t, *J* 8.0), 7.30–7.27 (3H, m), 6.73 (1H, s), 3.68–3.66 (4H, m), 3.61–3.56 (6H, m), 3.00 (3H, s), 2.90 (2H, t, *J* 7.0); HPLC–MS R_t 2.28 min; ($C_{22}H_{26}N_6O_3S_1$) *m/z* (ESI) 455 ([M+H]$^+$, 100%); $C_{22}H_{26}N_6O_3S_1$ requires 455.1865 for [M+H]$^+$, found: 455.1880; HPLC[b] R_t 3.62 min, purity 98%.

5.2.8.16. 4-(1*H*-Indazol-4-yl)-6-morpholino-*N*-(2-(pyridin-2-yl) ethyl)pyrimidin-2-amine (28g). Prepared from compound **17d** according to general procedure 8. Purification by method B (EtOAc/MeOH, 9:1) gave **28g** (16% yield) as a colourless solid; mp 170–180 °C; R_f 0.33 ($CHCl_3$/MeOH, 9:1); δ_H (500 MHz, $CDCl_3$), 8.61 (1H, s), 8.57 (1H, d, *J* 4.5), 7.61–7.58 (2H, m), 7.52 (1H, d, *J* 8.0), 7.43 (1H, t, *J* 8.0), 7.21 (1H, d, *J* 8.0) 7.13 (1H, dd, *J* 7.5, 5.0), 6.37 (1H, s, br), 5.46 (1H, s, br, N*H*), 3.93 (dt, *J* 7.0, 6.5), 3.81–3.79 (4H, m), 3.68–3.66 (4H, m), 3.15 (2H, t, *J* 7.0); HPLC–MS[b] R_t 2.57 min; ($C_{22}H_{23}N_7O_1$) *m/z* (ESI) 402 ([M+H]$^+$, 100%); $C_{22}H_{23}N_7O_1$ requires 402.2042 for [M+H]$^+$, found: 402.2057; HPLC[b] R_t 3.44 min, purity 98%.

5.2.8.17. 4-(1*H*-Indazol-4-yl)-6-morpholino-*N*-(2-(pyridin-3-yl) ethyl)pyrimidin-2-amine (28h). Prepared from compound **17e** according to general procedure 8. Purification by method B ($CHCl_3$/MeOH, 9:1) gave **28h** (63% yield) as an off-white solid; mp 105–110 °C; R_f 0.26 ($CHCl_3$/MeOH, 9:1); δ_H (500 MHz, CD_3OD), 8.52 (1H, s), 8.52 (1H, d, *J* 1.5), 8.47 (1H, dd, *J* 4.5, 1.5), 7.72 (1H, d, *J* 8.0), 7.61 (1H, d, *J* 8.0), 7.58 (1H, d, *J* 7.0), 7.46–7.43 (1H, dd, *J* 8.0, 7.0) 7.32 (1H, dd, *J* 8.0, 4.5), 6.46 (1H, s), 5.4 (1H, s, br), 3.76–3.74

(4H, m), 3.70–3.67 (2H, m), 3.66–3.64 (4H, m), 2.97 (2H, t, *J* 7.0); HPLC–MS R_t 2.46 min; ($C_{22}H_{23}N_7O_1$) *m/z* (ESI) 402 ([M+H]$^+$, 100%); $C_{22}H_{23}N_7O_1$ requires 402.2042 for [M+H]$^+$, found: 402.2061; HPLC[b] R_t 3.44 min, purity 98%.

5.2.8.18. 4-(1*H*-Indazol-4-yl)-6-morpholino-*N*-(2-(pyridin-4-yl) ethyl)pyrimidin-2-amine (28i). Prepared from compound **17f** according to general procedure 8. Purification B ($CHCl_3$/MeOH, 9:1), followed by method C gave **28i** (38% yield) as a pale yellow solid; mp 182–185 °C; R_f 0.28 ($CHCl_3$/MeOH, 9:1); δ_H (500 MHz, $CDCl_3$) 8.60 (1H, s), 8.52 (2H, d, *J* 5.0), 7.60 (1H, d, *J* 7.0), 7.54 (1H, d, *J* 8.0), 7.45 (1H, dd, *J* 8.0, 7.0), 7.19 (2H, d, *J* 5.0), 6.41 (1H, s), 3.82–3.77 (6H, m), 3.67–3.65 (4H, m), 2.98 (2H, t, *J* 7.0); HPLC–MS R_t 2.31 min; ($C_{22}H_{23}N_7O_1$) *m/z* (ESI) 402 ([M+H]$^+$, 100%); $C_{22}H_{23}N_7O_1$ requires 402.2042 for [M+H]$^+$, found: 402.2059; HPLC[b] R_t 3.22 min, purity 97%.

5.2.8.19. 4-(4-(1*H*-Indol-6-yl)-6-(pyridin-2-ylmethoxy)pyrimidin-2-yl)morpholine (30a). Prepared from compound **21** according to general procedure 8. Purification by method C gave **30a** (28% yield) as a pale yellow solid; m.p. 189–190 °C; R_f 0.63 ($CHCl_3$/MeOH, 9:1); δ_H (500 MHz, CD_3OD) 8.53 (1H, d, *J* 5.5), 8.17 (1H, s), 7.86 (1H, td, *J* 7.5, 2.0), 7.72 (1H, dd, *J* 8.5, 1.5), 7.60 (1H, d, *J* 8.5), 7.56 (1H, d, *J* 7.5), 7.36 (1H, dd, *J* 7.5, 5.5), 7.33 (1H, d, *J* 3.5), 6.69 (1H, s), 6.48 (1H, dd, *J* 3.0), 5.51 (2H, s), 3.84–3.71 (4H, m), 3.32–3.32 (4H, m); HPLC–MS R_t 7.73 min; ($C_{22}H_{21}N_5O_2$) *m/z* (ESI) 388 ([M+H]$^+$, 100%); $C_{22}H_{21}N_5O_2$ requires 388.1873 for [M+H]$^+$, found: 388.1764; HPLC[a] R_t 4.96 min, purity >99%.

5.2.8.20. *N*-(3-(2-Morpholino-6-(pyridin-2-ylmethoxy)pyrimidin-4-yl)phenyl)methanesulfonamide (30b). Prepared from compound **21** according to general procedure 8. Purification by method B ($CHCl_3$/MeOH, 9:1) gave **30b** (12% yield) as a colourless solid; mp 206–210 °C; R_f 0.67 ($CHCl_3$/MeOH, 9:1); δ_H (500 MHz, DMSO-d_6) 9.87 (1H, br s), 8.56 (1H, d, *J* 5.0), 7.96 (1H, t, *J* 2.0), 7.82 (1H, td, *J* 7.5, 2.0), 7.78 (1H, d, *J* 8.0), 7.48 (1H, d, *J* 8.0), 7.43 (1H, t, *J* 7.9), 7.35–7.32 (2H, m), 6.69 (1H, s), 5.47 (2H, s), 3.74–3.72 (4H, m), 3.65–3.63 (4H, m), 3.01 (3H, s); HPLC–MS R_t 6.78 min; ($C_{21}H_{23}N_5O_4S_1$) *m/z* (ESI) 442 ([M+H]$^+$, 100%); $C_{21}H_{23}N_5O_4S_1$ requires 442.1549 for [M+H]$^+$, found: 442.1529; HPLC[b] R_t 7.44 min, purity 99%.

5.2.8.21. 4-(4-(1*H*-Indazol-4-yl)-6-(pyridin-2-ylmethoxy)pyrimidin-2-yl)morpholine (30c). Prepared from compound **21** according to general procedure 8. Purification by method B ($CHCl_3$/MeOH, 9:1), followed by method C gave **30c** (55% yield) as an off-white solid; mp 170–172 °C; R_f 0.33 ($CHCl_3$/MeOH, 9:1); δ_H (500 MHz, $CDCl_3$), 10.20 (1H, br), 8.67 (1H, s, br), 8.62 (1H, d, *J* 4.0), 7.73 (1H, td, *J* 7.5, 1.5), 7.68 (1H, dd, *J* 7.0, 0.5), 7.60 (1H, d, *J* 8.5), 7.50–7.46 (2H, m), 7.25 (1H, dd, *J* 7.0, 5.0), 6.69 (1H, s), 5.59 (2H, s), 3.90 (4H, t, *J* 4.5), 3.78 (4H, t, *J* 5.0); HPLC–MS R_t 7.20 min; ($C_{21}H_{20}N_6O_2$) *m/z* (ESI) 389 ([M+H]$^+$, 100%); $C_{21}H_{20}N_6O_2$ requires 389.1726 for [M+H]$^+$, found: 389.1734; HPLC[b] R_t 7.78 min, purity 99%.

5.2.8.22. 4-(6-(1*H*-Indol-6-yl)-2-(pyridin-2-ylmethoxy)pyrimidin-4-yl)morpholine (31a). Prepared from compound **22** according to general procedure 8. Purification by method B (EtOAc/MeOH, 9:1) gave **31a** (52% yield) as a pale brown solid; mp 186–190 °C; R_f 0.61 ($CHCl_3$/MeOH, 9:1); δ_H (500 MHz, $CDCl_3$) 8.59 (1H, d, *J* 5.0), 8.39 (1H, br), 8.68 (1H, s), 7.70–7.67 (3H, m), 7.59 (1H, d, *J* 8.0), 7.30 (1H, t, *J* 3.0), 7.19 (1H, dd, *J* 7.0, 5.5), 6.67 (1H, s), 6.58 (1H, br), 5.64 (2H, s), 3.79–3.77 (4H, m), 3.69–3.67 (4H, m); HPLC–MS R_t 5.04 min; ($C_{22}H_{21}N_5O_2$) *m/z* (ESI) 388 ([M+H]$^+$, 100%); $C_{22}H_{21}N_5O_2$ requires 388.1873 for [M+H]$^+$, found: 388.1769; HPLC[b] R_t 5.58 min, purity >99%.

5.2.8.23. *N*-(3-(6-Morpholino-2-(pyridin-2-ylmethoxy)pyrimidin-4-yl)phenyl)methanesulfonamide (31b). Prepared from compound **22** according to general procedure 8. Purification by method B (EtOAc/MeOH, 9:1) gave **31b** (55% yield) as a pale yellow solid; mp 80–86 °C; R_f 0.59 ($CHCl_3$/MeOH, 9:1); δ_H (500 MHz, $CDCl_3$) 8.57 (1H, d, *J* 4.5), 7.85 (1H, s), 7.74 (1H, br), 7.69 (1H, t, *J* 8.0), 7.55 (1H, d, *J* 8.0), 7.42–7.41 (2H, m), 7.20 (1H, dd, *J* 7.5, 5.0), 6.57 (1H, s), 5.59 (2H, s), 3.78–3.76 (4H, m), 3.68–3.66 (4H, m), 3.01 (3H, s); HPLC–MS R_t 5.13 min; ($C_{21}H_{23}N_5O_4S_1$) *m/z* (ESI) 442 ([M+H]$^+$, 100%); $C_{21}H_{23}N_5O_4S_1$ requires 442.1549 for [M+H]$^+$, found: 442.1554; HPLC[b] R_t 5.63 min, purity 99%.

5.2.8.24. 4-(6-(1*H*-Indazol-4-yl)-2-(pyridin-2-ylmethoxy)pyrimidin-4-yl)morpholine (31c). Prepared from compound **22** according to general procedure 8. Purification by method B ($CHCl_3$/MeOH, 9:1), followed by method C gave **31c** (89% yield) as a yellow solid; mp 205–209 °C; R_f 0.27 ($CHCl_3$/MeOH, 9:1); δ_H (500 MHz, $CDCl_3$) 10.27 (1H, s, br), 8.61 (1H, d, *J* 4.5), 8.48 (1H, s), 7.70 (1H, td, *J* 8.0, 1.5), 7.68 (1H, d, *J* 7.0), 7.59–7.57 (2H, m), 7.45 (1H, dd, *J* 8.0, 7.5), 7.21 (1H, dd, *J* 7.0, 5.0), 6.71 (1H, s, br), 5.65 (2H, s), 3.80–3.78 (4H, m), 3.72–3.70 (4H, m); HPLC–MS R_t 5.24 min; ($C_{21}H_{20}N_6O_2$) *m/z* (ESI) 389 ([M+H]$^+$, 100%); $C_{21}H_{20}N_6O_2$ requires 389.1726 for [M+H]$^+$, found: 389.1735; HPLC[b] R_t 6.00 min, purity 99%.

5.3. PI3K biochemical screening

Compound inhibition of PI3K was determined in a radiometric (scintillation proximity) assay[44] using purified, recombinant human enzyme and ATP at a concentration of 1 μM. All compounds were serially diluted in 100% DMSO (final concentration = 4%). The kinase reaction was incubated for 1 h at room temperature and the reaction was terminated by the addition of PBS. IC_{50} values were subsequently determined using a sigmoidal dose–response curve fit (variable slope) and represent the means of at least two experiments.

5.4. SRB cellular proliferation assay

The IGROV-1 human ovarian cancer cell line was grown in DMEM (Invitrogen, Paisley, UK) supplemented with 10% FCS (PAA, Somerset, UK). Cell number was measured using the sulforhodamine B assay[45] (SRB). Ten thousand cells per well were seeded in a 96-well plate 48 h before treatment. After an incubation time of 96 h, cells were fixed and stained with SRB. This was then solubilised with 10 mM Tris. The absorbance was read at 540 nm.

5.5. Pharmacodynamic marker analysis

After treating cells as described in the figures, protein extracts were prepared by washing the cells once in ice-cold phosphate-buffered saline and then re-suspended in Cell Lysis Buffer (Cell Signalling Technologies, Hertfordshire, UK), supplemented with protease inhibitors (Boehinger/Roche, Mannheim, Germany). Protein concentration for each lysate was determined using the BCA Protein Assay method (Pierce, Rockford, USA). Equal amounts of protein were analysed by western blotting. Polyclonal antibodies against phospho-Ser^{473}-AKT and AKT were obtained from Cell Signalling Technologies (Hertfordshire, UK), that for Cyclin-D1 was obtained from NeoMarkers (Lab Vision Corporation, California, USA), and GAPDH was obtained from Chemicon International (California, USA). All antibodies were used as recommended by the manufacturer and visualised using the ECL PLUS western blot detection kit (Amersham Biosciences, Buckinghamshire, UK).

5.6. Flow cytometry

For cell cycle analysis, 1000 cells were harvested and fixed in 70% ethanol, then stained with 10 μg/mL propidium iodide (Molecular Probes, Eugene, Oregon, USA) for 24 h, and analysed on a Beckman Coulter EPICS Elite ESP.[24] The data were quantitated using WINMIDI version 2.8 and Cylchred software.

5.7. Microsomal incubation experiments

Compounds (10 mM) were incubated with male CD1 mouse liver microsomes containing 1 mg/mL protein (Tebu-Bio, Peterborough, UK) in the presence of NADPH (1 mM), $MgCl_2$ (3 mM) and UDP-glucuronic acid (2.5 mM) in phosphate buffered saline (10 mM, pH 7.4) at 37 °C. All reagents were supplied by Sigma Aldrich (Gillingham, UK). Incubations were conducted for 0, 15 and 30 min. Control incubations were generated by omitting either cofactors or microsomal protein. Incubations were terminated by the addition of three volumes of methanol containing an analytical internal standard followed by centrifugation at 13000*g* for 5 min at 4 °C. The percentage of compound remaining was determined after analysis by LC–MS.

A Supelcosil Discovery C18 column (5 cm × 4.6 mm ID, 5 μm; Supelco, Gillingham, UK) was used for chromatographic separation. The mobile phase consisted of methanol and 0.1% formic acid in water. After an initial 0.5 min isocratic period, methanol was increased from 10% to 90% over 6 min, held at 90% for 3.5 min, returned to 10% over 0.5 min, and equilibrated for 3.5 min. The flow rate was 1 mL/min and the sample injection volume was 25 μL.

An LCQ ion trap mass spectrometer coupled to a SpectraSYSTEM P4000 pump and an AS3000 autosampler (ThermoFinnigan, Radlett, UK) was used for analysis. The mass spectrometer was equipped with an electrospray source and operated in positive mode. The capillary temperature and spray voltage were operated at 250 °C and 4.5 kV respectively. Sheath and auxiliary gases were set to 80 and 20 arbitrary units, respectively. Spectra were acquired in full scan mode over the *m/z* range 50 to 850.

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References and notes

1. Vanhaesebroeck, B.; Leevers, S. J.; Ahmadi, K.; Timms, J.; Katso, R.; Driscoll, P. C.; Woscholski, R.; Parker, P. J.; Waterfield, M. D. *Annu. Rev. Biochem.* **2001**, *70*, 535.
2. Vivanco, I.; Sawyers, C. L. *Nat. Rev. Cancer* **2002**, *2*, 489.
3. Patel, R. K.; Mohan, C. *Immunol. Res.* **2005**, *31*, 47.
4. Oudit, G. Y.; Sun, H.; Kerfant, B.-G.; Crackower, M. A.; Penninger, J. M.; Backx, P. H. *J. Mol. Cell. Cardiol.* **2004**, *37*, 449.
5. Cantley, L. C. *Science* **2002**, *296*, 1655.
6. Lawlor, M. A.; Alessi, D. R. *J. Cell Sci.* **2001**, *114*, 2903.
7. Shayesteh, L.; Lu, Y.; Kuo, W.-L.; Baldocchi, R.; Godfrey, T.; Collins, C.; Pinkel, D.; Powell, B.; Mills, G. B.; Gray, J. W. *Nat. Genet.* **1999**, *21*, 99.
8. Ma, Y.-Y.; Wei, S.-J.; Lin, Y.-C.; Lung, J.-C.; Chang, T.-C.; Whang-Peng, J.; Liu, J. M.; Yang, D.-M.; Yang, W. K.; Schen, C.-Y. *Oncogene* **2000**, *19*, 2739.
9. Samuels, Y.; Wang, Z.; Bardelli, A.; Silliman, N.; Ptak, J.; Szabo, S.; Yan, H.; Gazdar, A.; Powell, S. M.; Riggins, G. J.; Willson, J. K.; Markowitz, S.; Kinzler, K. W.; Vogelstein, B.; Velculescu, V. E. *Science* **2004**, *304*, 554.
10. Campbell, I. G.; Russell, S. E.; Choong, D. Y.; Montgomery, K. G.; Ciavarella, M. L.; Hooi, C. S.; Cristiano, B. E.; Pearson, R. B.; Phillips, W. A. *Cancer Res.* **2004**, *64*, 7678.
11. Kang, S.; Bader, A. G.; Vogt, P. K. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 802.
12. Parsons, D. W.; Wang, T.-L.; Samuels, Y.; Bardelli, A.; Cummins, J. M.; DeLong, L.; Silliman, N.; Ptak, J.; Szabo, S.; Willson, J. K.; Markowitz, S.; Kinzler, K. W.; Vogelstein, B.; Lengauer, C.; Velculescu, V. E. *Nature* **2005**, *436*, 792.
13. Yuan, T. L.; Cantley, L. C. *Oncogene* **2008**, *27*, 5497.
14. Guillard, S.; Clarke, P. A.; te Poole, R.; Mohri, Z.; Bjerke, L.; Valenti, M.; Raynaud, F.; Eccles, S. A.; Workman, P. *Cell Cycle* **2009**, *8*, 443.
15. Drees, B. A.; Mills, G. B.; Rommel, C.; Prestwich, G. D. *Expert Opin. Ther. Patents* **2004**, *14*, 703.
16. Crabbe, T.; Welham, M. J.; Ward, S. G. *Trends Biochem. Sci.* **2007**, *32*, 450.
17. Workman, P. *Biochem. Soc. Trans.* **2004**, *32*, 393.
18. Workman, P.; Clarke, P. A.; Guillard, S.; Raynaud, F. I. *Nat. Biotechnol.* **2006**, *24*, 794.
19. Folkes, A. J.; Ahmadi, K.; Alderton, W. K.; Alix, S.; Baker, S. J.; Box, G.; Chuckowree, I. S.; Clarke, P. A.; Depledge, P.; Eccles, S. A.; Friedman, L. S.; Hayes, A.; Hancox, T. C.; Kugendadras, A.; Lensun, L.; Moore, P.; Olivero, A. G.; Pang, J.; Patel, S.; Pergl-Wilson, G. H.; Raynaud, F. I.; Robson, A.; Saghir, N.; Salphati, L.; Sohal, S.; Ultsch, M. H.; Valenti, M.; Wallweber, H. J. A.; Wan, N. C.; Wiesmann, C.; Workman, P.; Zhyvoloup, A.; Zvelebil, M. J.; Shuttleworth, S. J. *J. Med. Chem.* **2008**, *51*, 5522.
20. Raynaud, F. I.; Eccles, S. A.; Patel, S.; Alix, S.; Box, G.; Chuckowree, I.; Folkes, A.; Gowna, S.; De Haven Brandon, A.; Di Stefano, F.; Hayes, A.; Henley, A. T.; Lensun, L.; Pergl-Wilson, G.; Robson, A.; Saghir, N.; Zhyvoloup, A.; McDonald, E.; Sheldrake, P.; Shuttleworth, S.; Valenti, M.; Wan, N. C.; Clarke, P. A.; Workman, P. *Mol. Cancer Ther.* **2009**, *8*, 1725.
21. Workman, P.; Clarke, P. A.; Raynaud, F. I.; van Montfort, R. L. M. *Cancer Res.* **2010**, *70*, 2146.
22. Shuttleworth, S.; Silva, F.; Tomassi, C.; Cecil, A.; Hill, T.; Rogers, H.; Townsend, P. In *Progress in Medicinal Chemistry*; Lawton, G., Witty, D. R., Eds.; Elsevier B. V., 2010; Vol. 48, pp 81–131.
23. Maira, S.-M.; Stauffer, F.; Schnell, C.; García-Echeverría, C. *Biochem. Soc. Trans.* **2009**, *37*, 265.
24. Raynaud, F. I.; Eccles, S.; Clarke, P. A.; Hayes, A.; Nutley, B.; Alix, S.; Henley, A.; Di-Stefano, F.; Ahmad, Z.; Guillard, S.; Bjerke, L. M.; Kelland, L.; Valenti, M.; Patterson, L.; Gowan, S.; de Haven Brandon, A.; Hayakawa, M.; Kaizawa, H.; Koizumi, T.; Ohishi, T.; Patel, S.; Saghir, N.; Parker, P.; Waterfield, M.; Workman, P. *Cancer Res.* **2007**, *67*, 5840.
25. Hayakawa, M.; Kaizawa, H.; Moritomo, H.; Koizumi, T.; Ohishi, T.; Yamano, M.; Okada, M.; Ohta, M.; Tsukamoto, S.; Raynaud, F. I.; Workman, P.; Waterfield, M. D.; Parker, P. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2438.
26. Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. *Adv. Drug Deliv. Rev.* **2001**, *46*, 3.
27. Teague, S. J.; Davis, A. M.; Leeson, P. D.; Oprea, T. *Angew. Chem., Int. Ed.* **1999**, *38*, 3743.
28. Nuss, J. M.; Pecchi, S.; Renhowe, P. A. PCT Int. Appl. WO2004048365, 2004; *Chem. Abstr. 141*, 38627.
29. Bailey, J. P.; Giles, M. B.; Pass, M. PCT Int. Appl. WO2006005914, 2006; *Chem. Abstr. 144*, 150379.
30. Pass, M. PCT Int. Appl. WO2006005915, 2006; *Chem. Abstr. 144*, 128997.
31. Pass, M. PCT Int. Appl. WO2006005918, 2006; *Chem. Abstr. 144*, 128996.
32. Walker, E. H.; Pacold, M. E.; Perisic, O.; Stephens, L.; Hawkins, P. T.; Wymann, M. P.; Williams, R. L. *Mol. Cell* **2000**, *6*, 909.
33. Vlahos, C. J.; Matter, W. F.; Hui, K. Y.; Brown, R. F. *J. Biol. Chem.* **1994**, *269*, 5241.
34. For a review see: Magdalou, J.; Fournel-Gigleux, S.; Testa, B.; Ouzzine, M. In *The Practice of Medicinal Chemistry*; Wermuth, C. G., Ed.; Elsevier Academic Press: Oxford, 2003; pp 517–543.
35. Astles, P. C.; Brown, T. J.; Harris, N. V.; Harper, M. F.; McCarthy, C.; Porter, B.; Smith, C.; Walsh, R. J. A. *Eur. J. Med. Chem.* **1997**, *32*, 515.
36. Thurkauf, A.; Hutchison, A.; Peterson, J.; Cornfield, L.; Meade, R.; Huston, K.; Harris, K.; Ross, P. C.; Gerber, K.; Ramabhadran, T. V. *J. Med. Chem.* **1995**, *38*, 2251.
37. Eid, C. N., Jr.; Konopelski, J. P. *Tetrahedron* **1991**, *47*, 975.
38. D'Atri, G.; Gomarasca, P.; Resnati, G.; Tronconi, G.; Scolastico, C.; Sirtori, C. R. *J. Med. Chem.* **1984**, *27*, 1621.
39. Montebugnoli, D.; Bravo, P.; Brenna, E.; Mioskowski, C.; Panzeri, W.; Viani, F.; Volonterio, A.; Wagner, A.; Zanda, M. *Tetrahedron* **2003**, *59*, 7147.
40. Suzuki, M.; Ohdoi, K.; Kato, K.; Matsumoto, H.; Toyama, K.; Kitahara, M.; Yotsumoto, T. PCT Int. Appl. WO9965881, 1999; *Chem. Abstr.* 132, 49974.
41. Bedford, R. B.; Cazin, C. S. J.; Coles, S. J.; Gelbrich, T.; Horton, P. N.; Hursthouse, M. B.; Light, M. E. *Organometallics* **2003**, *22*, 987.
42. Large, J. M.; Clarke, M.; Williamson, D. M.; McDonald, E.; Collins, I. *Synlett* **2006**, 861.
43. For a review see Kappe, C. O.; Stadler, A. *Microwaves in Organic and Medicinal Chemistry*; Wiley-VCH, 2005.
44. Hayakawa, M.; Kaizawa, H.; Moritomo, H.; Koizumi, T.; Ohishi, T.; Okada, M.; Ohta, M.; Tsukamoto, S.; Parker, P.; Workman, P.; Waterfield, M. *Bioorg. Med. Chem.* **2006**, *14*, 6847.
45. Monks, A.; Scudiero, D.; Skehan, P.; Shoemaker, R.; Paull, K.; Vistica, D.; Hose, C.; Langley, J.; Cronise, P.; Vaigro-Wolff, A. *J. Natl. Cancer Inst.* **1991**, *83*, 757.