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Trisubstituted Pyrimidines as Efficacious and Fast-acting Antimalarials

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Abstract

In this paper we describe the optimisation of a phenotypic hit against *Plasmodium falciparum*, based on a tri-substituted pyrimidine scaffold. This led to compounds with good pharmacokinetics and oral activity in a *P. berghei* mouse model of malaria. The most promising compound (13) showed a reduction in parasitaemia of 96% when dosed at 30 mg/kg orally, once a day for 4 days in the *P. berghei* mouse model of malaria. It also demonstrated a rapid rate of clearance of the erythrocytic stage of *P. falciparum* in the SCID mouse model with an ED$_{90}$ 11.7 mg/kg when dosed orally. Unfortunately, the compound is a potent inhibitor of cytochrome P450 enzymes, probably due to a 4-pyridyl substituent. Nevertheless, this is a lead molecule with a potentially useful antimalarial profile, which could either be further optimised or used for target hunting.
Introduction

Malaria is a devastating parasitic disease causing widespread mortality and morbidity across many parts of the developing world. Human malaria is caused by five *Plasmodium* species; *P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae* and *P. knowlesi*. *P. falciparum* causes the most mortality and is found in high levels in Africa, whereas *P. vivax* causes the most morbidity and is more commonly found across Asia and the Americas. In 2013, there were an estimated 198 million cases of malaria worldwide and 584,000 deaths, of which 453,000 were of children under 5 years, with 90% of all malaria deaths in the African region. Many medicines for the treatment of malaria such as chloroquine and pyrimethamine are failing due to increasing development of resistance. Furthermore, there are now cases of drug resistance to artemisinin-based combination therapies (ACT’s), which are the mainstays for the World Health Organisation (WHO) campaign against malaria. Currently, primaquine is the only drug in general use for radical cure of malaria due to *P. vivax*, preventing relapse, but this medicine has a prolonged dosing schedule and is toxic to individuals with glucose 6-phosphate deficiency. Therefore, new therapies for both treatment and prevention of this deadly disease across all of its life cycle stages are urgently needed. Efforts from academic groups and pharmaceutical companies to identify novel antimalarials are now beginning to bear fruit as novel therapies for the treatment of malaria are in clinical trials. However, the discovery of potential new antimalarials remains vital, given the high attrition rates in clinical development, the propensity of the parasite to develop resistance, and the need for additional indications (such as transmission blocking, chemoprevention and radical cure of vivax malaria). Here, we report the design, synthesis and biological evaluation of fast-acting and highly efficacious antimalarials, based on tri-substituted pyrimidines, which were discovered using a whole cell-based screening approach.

Project Initiation

A drug discovery programme for the identification of novel antimalarials was initiated with the high throughput phenotypic screening (HTS) of an in-house library of protein kinase scaffolds (4,731
compounds. This effort identified multiple structurally diverse chemical series that blocked asexual blood stage parasite viability, as measured by a SYBR green assay. In this paper, we describe a chemistry programme based around one of these series, a tri-substituted pyrimidine, which displayed chemical tractability, nanomolar potency against *P. falciparum* cell line 3D7 and excellent selectivity over a mammalian cell line MRC-5 (Table 1). An initial example of this series was inactive against a panel of mammalian kinases up to a concentration of 10 µM.

**Lead Identification**

**Table 1**: Hit series identified from phenotypic screening of kinase-like library

<table>
<thead>
<tr>
<th>Series ID</th>
<th>MMV02</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound ID</td>
<td>1</td>
</tr>
<tr>
<td>EC₅₀ vs. <em>P. falciparum</em> 3D7 (µM)</td>
<td>0.25</td>
</tr>
<tr>
<td>EC₅₀ vs. MRC5 (µM)</td>
<td>31</td>
</tr>
<tr>
<td>clogP</td>
<td>3.2</td>
</tr>
<tr>
<td>MWT</td>
<td>343</td>
</tr>
<tr>
<td>No. of examples with EC₅₀ &lt;1 µM</td>
<td>3</td>
</tr>
</tbody>
</table>

The initial hit from the screen, 1, was followed up by hit expansion through commercially available analogues. Systematic changes of functional groups at R¹, R² and R³ were carried out to try to improve potency and physicochemical properties. Analogues of our original screening hit (1), were also identified from published data from GSK and Novartis (Figure 1). Following re-synthesis and screening in-house, compound 2 (reported by GSK and Novartis), provided a suitable chemical start point for further synthetic modifications. However, due to poor solubility (5 µM), compound 2 was not progressed any further than assessment at the *in vitro* (cellular) level for potency and Absorption,
Distribution, Metabolism, Excretion and Toxicology (ADMET). Analogue design was then directed towards improving potency and solubility and reducing the number of aromatic rings, which can have a beneficial impact on overall development characteristics including solubility.\textsuperscript{11,12} Compound 2 has a high degree of planarity so we sought further improvement by increasing the proportion of sp\textsuperscript{3} to sp\textsuperscript{2} carbon atoms, which is reported to increase the solubility.\textsuperscript{13}

**Figure 1:** Published analogue compound 2. Codes TCMDC-125419 (GSK) and GNF-Pf-1034/ GNF-Pf-1447 (Novartis)

<table>
<thead>
<tr>
<th>Compound ID: 2</th>
<th>Pf(3D7) EC\textsubscript{50} = 0.11 \mu M</th>
<th>MRC5 EC\textsubscript{50} = 14 \mu M</th>
</tr>
</thead>
<tbody>
<tr>
<td>MWT = 365</td>
<td>clogP = 3.3</td>
<td>Mouse Clint = 1.7 ml/min/g</td>
</tr>
<tr>
<td>PSA = 55</td>
<td>Sol = 5 \mu M</td>
<td>PPB = 92%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CYP3A4 = 0.1 \mu M</td>
</tr>
</tbody>
</table>

**Table 2:** Modifications at R\textsuperscript{1}

<table>
<thead>
<tr>
<th>R\textsuperscript{1}</th>
<th>R\textsuperscript{3}</th>
<th>Pf (3D7) EC\textsubscript{50} (\mu M)</th>
<th>MRC5 EC\textsubscript{50} (\mu M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>\begin{array}{c} \text{N} \ \text{N} \end{array}</td>
<td>0.1</td>
<td>14</td>
</tr>
<tr>
<td>3</td>
<td>\begin{array}{c} \text{N} \ \text{N} \end{array}</td>
<td>3.1</td>
<td>30</td>
</tr>
<tr>
<td>4</td>
<td>\begin{array}{c} \text{N} \ \text{N} \end{array}</td>
<td>3.4</td>
<td>49</td>
</tr>
<tr>
<td>5</td>
<td>\begin{array}{c} \text{N} \ \text{O} \end{array}</td>
<td>6.5</td>
<td>24</td>
</tr>
</tbody>
</table>

All parasite assays were run in duplicate.
We were concerned about the inhibition of Cytochrome P450 isoform CYP3A4, which we believed to be due to the 4-pyridyl group (see later for further discussion). Initial attempts to replace the 4-pyridyl functional group at R₁ resulted in a significant loss of antimalarial activity (Table 2). Removal of the pyridine nitrogen at R₁ or simply moving the nitrogen from the 4- to the 3- position resulted in >30-fold drop in potency. In addition, replacing the 4-pyridyl group with a morpholine group reduced potency by almost 60-fold, highlighting the importance of the pyridine nitrogen and suggesting that the vector of the lone pair donor was also crucial for activity. We decided therefore to investigate variations at R² and R³ for improvements in potency, which would render the interaction with the 4-pyridyl less critical.

**Optimisation of R²**

Removal of the tetrahydroisoquinoline (2) and replacement with an amino group (6), gave a 100-fold drop in activity, indicating the tetrahydroisoquinoline group has a significant effect on the potency. Replacement of the tetrahydroisoquinoline moiety of compound 2 with N-methylbenzylamine (7) resulted in a 10-fold loss of potency (Table 3), possibly suggesting that a degree of conformational restraint was necessary. Contracting the aliphatic ring size to a 5-membered ring (8), led to a complete loss in activity. Replacing the phenyl ring in 2 with an imidazole (9) gave a 10-fold drop in activity (EC₅₀ = 1.7 μM). Interestingly, activity was retained when the phenyl was attached to a piperazine, rather than being directly fused onto the piperidine ring (10, EC₅₀ = 0.3 μM), despite the different vector compared to compound 2.

Further work was undertaken to remove an aromatic ring, with a key aim being to increase solubility and improve the potential for clinical development. Replacing the phenyl ring found in 10 with piperidine gave a compound equipotent to the starting point (11, EC₅₀ = 0.1 μM). This compound had marginally improved aqueous solubility (56 μM, measured as the free base) and retained reasonably low microsomal turnover. Replacing the “terminal” piperidine with a morpholine gave a compound with similar activity (12, EC₅₀ = 0.3 μM), but with a significantly increased solubility (>100 μM),...
reduced clogP, and low microsomal turnover. It was also possible to add a flexible linker between the piperidine and the morpholine (13) with only a minimal effect on potency (EC50 = 0.3 μM) and retaining low microsomal turnover, but with a similar solubility (44 μM). It was possible to replace the piperidine of 13 with an alkyl linker to give 14. This compound had the same activity as 13 (EC50 = 0.3 μM), but despite a lower clogP, showed a significantly higher microsomal turnover. Finally, a bicyclic aliphatic system, 15, also showed similar activity (EC50 = 0.3 μM) and good solubility (>100 μM), but increased microsomal turnover. In summary, it is possible to reduce the number of aromatic rings and increase the proportion of sp3 carbon atoms which improves solubility and cLogP without compromising potency and microsomal turnover.

Table 3: Modifications at R2

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>PF (3D7) EC50 (μM)</th>
<th>MRC5 EC50 (μM)</th>
<th>MWT</th>
<th>clogP</th>
<th>Mouse microsomal Clint ml/min/g</th>
<th>Sol (μM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td></td>
<td>0.1</td>
<td>14</td>
<td>365</td>
<td>3.3</td>
<td>1.7</td>
<td>5</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>17</td>
<td>50</td>
<td>249</td>
<td>1.7</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>1.4</td>
<td>28</td>
<td>353</td>
<td>3.4</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>50</td>
<td>50</td>
<td>351</td>
<td>3.0</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>1.7</td>
<td>24</td>
<td>355</td>
<td>2.2</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>0.3</td>
<td>50</td>
<td>394</td>
<td>3.4</td>
<td>1.4</td>
<td>36</td>
</tr>
<tr>
<td>11</td>
<td></td>
<td>0.1</td>
<td>15</td>
<td>400</td>
<td>3.3</td>
<td>3.9</td>
<td>56</td>
</tr>
<tr>
<td>12</td>
<td></td>
<td>0.3</td>
<td>36</td>
<td>402</td>
<td>2.3</td>
<td>1.2</td>
<td>&gt;248</td>
</tr>
</tbody>
</table>
clogP was calculated using StarDrop from Optibrium. Sol is solubility in water for the free base.

<table>
<thead>
<tr>
<th></th>
<th>Structure</th>
<th>clogP</th>
<th>Sol (µg/mL)</th>
<th>pKa</th>
<th>pH</th>
<th>Tert (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td><img src="image13.png" alt="Structure 13" /></td>
<td>0.3</td>
<td>50</td>
<td>416</td>
<td>2.6</td>
<td>3</td>
</tr>
<tr>
<td>14</td>
<td><img src="image14.png" alt="Structure 14" /></td>
<td>0.3</td>
<td>ND</td>
<td>390</td>
<td>2.1</td>
<td>13</td>
</tr>
<tr>
<td>15</td>
<td><img src="image15.png" alt="Structure 15" /></td>
<td>0.3</td>
<td>14</td>
<td>358</td>
<td>2.6</td>
<td>7.0</td>
</tr>
</tbody>
</table>
Optimisation of R³

Replacement of the planar aromatic 3-pyridyl unit at the R³ position with aliphatic substituents was investigated to both reduce the aromatic ring count and increase the sp³ nature. Small aliphatic groups such as the cyclopropyl group of 16 were not tolerated and resulted in around a 30-fold drop in potency (Table 4). Furthermore, replacement of the 3-pyridyl by the flexible aminoalkyl morpholine (17) or aminoalkyl amide (18) resulted in >90 fold drop in potency. In addition, the morpholine moiety 19, was completely inactive. Further examples are given in the supporting information. In summary, attempts to replace R³ with an aliphatic group or heteroaromatics such as the oxazole (20) were unsuccessful. Attempts to replace the pyridyl nitrogen atom with groups such as 3-fluoro phenyl (21) or 4-fluoro phenyl (22) lost around 10-fold activity and led to an increase in clogP. Furthermore, the addition of another nitrogen atom into the pyridyl unit to afford the pyrimidine 23, was less well tolerated (10-fold loss in potency). In summary, despite extensive investigation, we were unable to find a suitable replacement for the 3-pyridyl moiety at R³, and further changes were focused on different substitutions on the 3-pyridyl ring to improve activity and physicochemical properties (Table 5).
Table 4: Modifications at R³

<table>
<thead>
<tr>
<th></th>
<th>R³</th>
<th>R³ (3D7) EC50 (µM)</th>
<th>MRC5 EC50 (µM)</th>
<th>MWT</th>
<th>clogP</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td><img src="image" alt="Image" /></td>
<td>0.3</td>
<td>36</td>
<td>402</td>
<td>2.3</td>
</tr>
<tr>
<td>16</td>
<td><img src="image" alt="Image" /></td>
<td>10</td>
<td>ND</td>
<td>365</td>
<td>2.7</td>
</tr>
<tr>
<td>17</td>
<td><img src="image" alt="Image" /></td>
<td>32</td>
<td>ND</td>
<td>467</td>
<td>2.1</td>
</tr>
<tr>
<td>18</td>
<td><img src="image" alt="Image" /></td>
<td>&gt;50</td>
<td>ND</td>
<td>411</td>
<td>1.1</td>
</tr>
<tr>
<td>19</td>
<td><img src="image" alt="Image" /></td>
<td>&gt;50</td>
<td>ND</td>
<td>410</td>
<td>2.0</td>
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<tr>
<td>20</td>
<td><img src="image" alt="Image" /></td>
<td>16</td>
<td>ND</td>
<td>420</td>
<td>3.0</td>
</tr>
<tr>
<td>21</td>
<td><img src="image" alt="Image" /></td>
<td>4.3</td>
<td>ND</td>
<td>419</td>
<td>3.4</td>
</tr>
<tr>
<td>22</td>
<td><img src="image" alt="Image" /></td>
<td>3.3</td>
<td>ND</td>
<td>419</td>
<td>3.4</td>
</tr>
<tr>
<td>23</td>
<td><img src="image" alt="Image" /></td>
<td>4.3</td>
<td>ND</td>
<td>403</td>
<td>2.5</td>
</tr>
</tbody>
</table>

A variety of modifications were made at different positions around the 3-pyridyl ring. Small electron withdrawing and electron donating substituents at the 5-position of the pyridyl were tolerated (methoxy, 24; nitrile, 25; fluoro, 26). However, the aminomethyl analogue 27 had a 10-fold loss in activity, and the morpholine amide 28 was essentially inactive.
Small functional groups at the 6-position of the pyridine such as amino (29) or methoxy (30) were tolerated, with only a 3- to 6-fold loss in activity compared to 12. Larger groups at the 4-position on the 3-pyridyl moiety, such as the methylamide (31) or morpholine (32) reduced activity by >10-fold. Furthermore, moving the methoxy from the 5-position of the pyridine (24) to the 6-position (33), caused a 20-fold reduction in potency compared to 12. In summary, there appear to be limited opportunities for synthetic modification to enhance activity at the $R^3$ position, based on the pyridyl moiety.

**Table 5: Modifications at $R^3$**

<table>
<thead>
<tr>
<th>$R^3$</th>
<th>Pf (3D7) $EC_{50}$ (µM)</th>
<th>MRC5 $EC_{50}$ (µM)</th>
<th>MWT</th>
<th>clogP</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>0.3</td>
<td>36</td>
<td>402</td>
<td>2.3</td>
</tr>
<tr>
<td>24</td>
<td>0.1</td>
<td>ND</td>
<td>432</td>
<td>2.3</td>
</tr>
<tr>
<td>25</td>
<td>0.4</td>
<td>ND</td>
<td>427</td>
<td>2.2</td>
</tr>
<tr>
<td>26</td>
<td>0.5</td>
<td>ND</td>
<td>420</td>
<td>2.6</td>
</tr>
<tr>
<td>27</td>
<td>3.1</td>
<td>ND</td>
<td>431</td>
<td>1.4</td>
</tr>
<tr>
<td>28</td>
<td>&gt;50</td>
<td>ND</td>
<td>515</td>
<td>1.8</td>
</tr>
<tr>
<td>29</td>
<td>1.1</td>
<td>ND</td>
<td>417</td>
<td>1.9</td>
</tr>
</tbody>
</table>
In Vivo Efficacy

Compounds 12 and 13 were selected for in vivo pharmacokinetic (PK) and efficacy studies, based on their overall profile of properties. Both compounds displayed suitable predicted physicochemical properties consistent with that of an oral drug. In addition, 12 and 13 demonstrated sub-micromolar potency in vitro, reasonable aqueous solubility, were metabolically stable when exposed to mouse liver microsomes and displayed low plasma protein binding. Unfortunately, 13 displayed some binding to the hERG ion channel (Table 6).

In vivo PK studies with 12 showed rapid absorption after oral administration (10mg/kg), but with limited exposure and a short half-life, whereas 13 displayed an improved half-life with a 7-fold increase in AUC. Subsequently, in vivo efficacy experiments were carried out and mice were subjected to oral dosing of compound 12 and 13 up to 30 mg/kg, once a day for four consecutive days using the P. berghei rodent model of infection (Peters’ test, Table 6). Compound 13 displayed superior efficacy compared with 12 with a 96% reduction in parasitaemia (compared to 72% for 12), when dosed at 30 mg/kg, qd, PO. The early lead criteria, stipulated by MMV, required compounds to display both suppression of parasitaemia and an ED$_{50}$ < 50 mg/kg under this protocol.$^{14}$ However, we were unable to obtain complete cures in the rodent model for either compound 12 or 13. For efficacy

### Table 1: Chemical Structures and Properties

<table>
<thead>
<tr>
<th></th>
<th>Chemical Structure</th>
<th>Log P</th>
<th>pKa</th>
<th>Molecular Weight</th>
<th>ClogP</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td><img src="image1" alt="Chemical Structure" /></td>
<td>1.8</td>
<td>ND</td>
<td>432</td>
<td>2.3</td>
</tr>
<tr>
<td>31</td>
<td><img src="image2" alt="Chemical Structure" /></td>
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<td>ND</td>
<td>459</td>
<td>1.7</td>
</tr>
<tr>
<td>32</td>
<td><img src="image3" alt="Chemical Structure" /></td>
<td>4.8</td>
<td>ND</td>
<td>487</td>
<td>2.5</td>
</tr>
<tr>
<td>33</td>
<td><img src="image4" alt="Chemical Structure" /></td>
<td>19</td>
<td>ND</td>
<td>432</td>
<td>2.3</td>
</tr>
</tbody>
</table>
experiments with compound 12, all mice were euthanized by day 14. For compound 13, all mice were euthanized by day 11.
Table 6: *In vitro* and *in vivo* profile of key compounds

<table>
<thead>
<tr>
<th>Compound</th>
<th>12</th>
<th>13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pf (3D7) EC_{50} (µM)</td>
<td>0.34</td>
<td>0.27</td>
</tr>
<tr>
<td>Pf (K1) EC_{50} (µM)</td>
<td>ND</td>
<td>0.28</td>
</tr>
<tr>
<td>MRC5 EC_{50} (µM)</td>
<td>36</td>
<td>50</td>
</tr>
<tr>
<td>MWT</td>
<td>402</td>
<td>416</td>
</tr>
<tr>
<td>logP</td>
<td>2.3</td>
<td>2.5</td>
</tr>
<tr>
<td>PSA</td>
<td>67.3</td>
<td>67.3</td>
</tr>
<tr>
<td>Mouse microsomal Clint (ml/min/g)</td>
<td>1.2</td>
<td>3</td>
</tr>
<tr>
<td>Kinetic Solubility (µM)</td>
<td>&gt;248</td>
<td>106</td>
</tr>
<tr>
<td>PPB (%)</td>
<td>59</td>
<td>78</td>
</tr>
<tr>
<td>CYP inhibition IC_{50} (µM)</td>
<td>1A2, 93; 2C9, 1.9; 2C19, 6.3; 2D6, 0.7; 3A4, 0.1.</td>
<td>1A2, &gt;100; 2C9, 3.5; 2C19, 38; 2D6, 0.7; 3A4, 0.1.</td>
</tr>
<tr>
<td>hERG K^+ ion channel (µM)</td>
<td>ND</td>
<td>6.9</td>
</tr>
<tr>
<td><strong>Intravenous PK (3 mg/kg)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clb (mL/min/kg)</td>
<td>39</td>
<td>N.D.</td>
</tr>
<tr>
<td>Vdss (L/kg)</td>
<td>2.7</td>
<td>N.D.</td>
</tr>
<tr>
<td>T_{1/2} (h)</td>
<td>1.3</td>
<td>N.D.</td>
</tr>
<tr>
<td><strong>Oral PK Parameters (10 mg/kg)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C_{max} (ng/mL)</td>
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<td>1094</td>
</tr>
<tr>
<td>T_{max} (h)</td>
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<td>2</td>
</tr>
<tr>
<td>Oral AUC (0-8) ng.min/mL</td>
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<td>306,000</td>
</tr>
<tr>
<td>F (%)</td>
<td>18</td>
<td>ND</td>
</tr>
</tbody>
</table>
In vivo efficacy in Peters’ test

<table>
<thead>
<tr>
<th>Treatment</th>
<th>% Reduction in Parasitaemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 x 30 mg/kg, qd, PO</td>
<td>72%</td>
</tr>
<tr>
<td>4 x 30 mg/kg, qd, PO</td>
<td>96%</td>
</tr>
</tbody>
</table>

(a) *Pf*(K1) is a chloroquine and pyrimethamine resistant strain of *P. falciparum*. (b) Pharmacokinetic and efficacy studies were carried out using compound 12 as the HCl salt and compound 13 as the fumarate salt.

Compound 13 was also evaluated *in vivo* against *P. falciparum* parasites grown in the peripheral blood of NODscidIL2R-null mice (SCID), engrafted with human erythrocytes. Three days after infection, mice were dosed orally once a day with 13, for 4 days, at concentrations up to 100 mg/kg (Figure 2a). A daily oral dose of ED$_{90}$ = 11.7 mg/kg, or its equivalent estimated daily exposure in blood AUC$_{ED90}$ = 1.4 µg·h/ml, reduced parasitaemia by 90% at day 7 after infection. *In vivo* there was a rapid reduction of parasitaemia at doses ≥ 20 mg/kg or >7.96 µg·h/ml/day in blood. With doses ≥ 30 mg/kg, the parasites levels were reduced below detection limits within 2 days. The rate of parasite clearance *in vivo* was at least as fast as the artemisinins, and only pyknotic parasites are observed in peripheral blood of mice 48 h after treatment at 100 mg/kg (Figure 2c). Interestingly, the *in vitro* parasite reduction ratio (PRR) assay identified 13 as a compound with a moderate rate of killing, displaying 99.9% clearance of parasites in 52 h, when tested at 10 x EC$_{50}$ (Figure 2b). It is possible, that the PRR assay would show a faster killing rate at higher concentrations of compound, more in-line with what is seen *in vivo*. 
Figure 2: (a) The *in vivo* efficacy data for compound 13 in *P. falciparum* infected SCID mice. (b) The levels of compound 13 in blood of the mice of the efficacy experiment during 23h after the first oral dose. The symbols represent the same individuals depicted in plot a. (c) The *in vitro* PRR data for compound 13 when parasites were treated at 10 x EC_{50}. Comparator data for other standard drugs is included for reference (data previously reported\(^1\)). Compound 13 showed a similar rate of kill to pyrimethamine. (d) Comparison of morphology of parasitized human RBC in vehicle and compound 13 treated mice. Erythrocytes with only remnants of parasites showing nuclear condensation were seen following 2-day treatment with compound 13. Compound dosed as the fumarate salt.
To assess the mode of action, given that the compound contained a potential heme binding moiety in the 4-pyridyl, the ability of compound 13 to block haemozoin (β-hematin) formation was also tested. It displayed relatively comparable activity to chloroquine in this assay (27 µM for 13 vs 6.6 µM for chloroquine). It was not known if the primary mode of action is through the same mechanism of action as chloroquine. However when assayed against the chloroquine/pyrimethamine resistant (K1) lines, compound 13 displayed similar activity to sensitive cell lines, so it has a different profile to chloroquine.

**Reducing Affinity for Human CYP Isoforms**

Although the antimalarial properties of the compound series had been demonstrated in mouse models of malaria, further development of the series required compounds that had markedly reduced inhibition of the major CYP enzymes. Subsequent elaboration of 13 focused on reducing inhibition of human CYP isoforms 3A4 and 2D6. Previous work had not been successful in distinguishing the antimalarial activity and the inhibition of human CYP isoforms (Table 1), thought to be due to the 4-pyridyl group at the R1 position. Therefore, two approaches were investigated to reduce CYP inhibition. One approach involved replacement of the 4-pyridyl unit with functional groups that could have similar steric and H-bond acceptor properties (Table 7). In parallel, the possibility of modifying the 4-pyridyl unit with the addition of functional groups adjacent to the pyridine nitrogen was also investigated, which could potentially reduce binding to human CYP isoforms whilst retaining suitable affinity for the unknown target of interest (Table 8). The R2 and R3 positions were fixed with piperidine-morpholine and 3-pyridyl respectively, to use as a reference point for changes in activity and with the view that if it were possible to optimise R1, this should also work with other R2 and R3 substituents (e.g. as found in 13). The key molecules prepared are summarised in the main text. Additional molecules prepared are presented in the supporting information.

**Optimisation of R1**
The initial focus was on placing a hydrogen bond acceptor (HBA) at the 4-position of the phenyl ring to replace the 4-pyridyl moiety at the R1 position. Several nitrile derivatives were prepared. The 4-cyano phenyl (34) gave a 7-fold reduction in potency (EC50 = 2.1 μM) from 12 (EC50 = 0.3 μM). This would place the HBA further from the pyrimidine than the pyridine nitrogen in 12. Therefore, it was decided to attach the nitrile directly onto the pyrimidine ring (35), which gave a similar level of potency (EC50 = 5.3 μM) to the 4-cyano phenyl analogue. Other HBAs such as sulfones (36) gave significantly reduced activity (EC50 = 49 μM). Direct attachment of a hydroxyl to the pyrimidine ring (37) also failed to increase activity (EC50 = 24 μM), although this may be in a different tautomeric form. Amide 38, was also inactive (EC50 = 50 μM). Finally, basic groups were investigated to determine if there was an interaction with an acidic group on the protein. None of these were active (e.g. 39, EC50 = 30 μM).

Table 7: Modifications at R1

<table>
<thead>
<tr>
<th>R1</th>
<th>EC50 (µM)</th>
<th>MRC5 EC50 (µM)</th>
<th>MWT</th>
<th>clogP</th>
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</thead>
<tbody>
<tr>
<td>12</td>
<td>0.3</td>
<td>35.92</td>
<td>402</td>
<td>2.3</td>
</tr>
<tr>
<td>34</td>
<td>2.1</td>
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<td>35</td>
<td>5.3</td>
<td>ND</td>
<td>350</td>
<td>1.6</td>
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<td>36</td>
<td>49</td>
<td>ND</td>
<td>458</td>
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</tr>
<tr>
<td>37</td>
<td>24</td>
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<tr>
<td>38</td>
<td>50</td>
<td>ND</td>
<td>423</td>
<td>1.6</td>
</tr>
</tbody>
</table>
The original 4-pyridyl moiety at R¹ was then returned to with a focus on reducing binding to the human CYP450 isoforms with close analogues incorporating blocking groups adjacent to the pyridine nitrogen, to reduce the interaction with the haem iron. Addition of two methyl groups in the 3- and 5-positions significantly reduced CYP inhibition across all five CYPs investigated (40), which confirmed involvement of the parent 4-pyridyl moiety. However there was a 5-fold drop in activity (EC₅₀ = 1.5 µM). Interestingly having just one methyl group in the 3-positions (41, EC₅₀ = 17 µM) led to a further 10-fold drop in potency compared to disubstitution. Other groups in the 3-position which would alter the electronics of the pyridine nitrogen were also inactive (e.g. the CF₃ group 42, EC₅₀ = 50 µM). The effect of both electron-donating and electron-withdrawing substituents (43 and 44) were also investigated, where both gave a 5- to 10-fold reduction in potency compared to the substituted pyridine 12. Changing the heterocycle to a pyrimidine, pyridone or pyrazole (45-47) also led to a reduction in activity. Therefore, despite a variety of variations on the R¹ position, all modifications investigated led to a marked decrease in potency.

Table 8: Modifications at R¹

<table>
<thead>
<tr>
<th>R¹</th>
<th>Pf(3D7) EC₅₀ (µM)</th>
<th>MRC5 EC₅₀ (µM)</th>
<th>MWT</th>
<th>clogP</th>
<th>CYP inhibition IC₅₀ (µM)</th>
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</thead>
<tbody>
<tr>
<td>12</td>
<td>0.3</td>
<td>36</td>
<td>402</td>
<td>2.3</td>
<td>1A2 93</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2C9 1.9</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>2C19 6.3</td>
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<td></td>
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<td></td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>3A4 0.1</td>
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<tr>
<td>No.</td>
<td>Structure</td>
<td>Property</td>
<td>Activity</td>
<td>Selectivity</td>
<td>Pharmacodynamics</td>
</tr>
<tr>
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<td>ND</td>
<td>403</td>
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</table>

**Concluding remarks and future work**

Compounds 12 and 13 both display suitable physicochemical properties for an oral drug lead, good cellular activity in vitro against *P. falciparum* parasites and good selectivity in a mammalian counterscreen. Compound 13 also demonstrated excellent oral efficacy in vivo with a 96% reduction in levels of parasitaemia (*P. berghei*, 4 x 30 mg/kg, qd, PO) and a fast kill rate in the *P. falciparum* SCID mouse model. Compound 13 was also further profiled in the liver-stage schizont assay (EC50
> 10 μM), and in a stage IV/V gametocyte assay (EC$_{50}$ = 2.4 μM). Initial infection with malaria occurs when *Plasmodium* sporozites injected by the mosquito invade the liver cells. The parasites then undergo a liver-stage life-cycle which involves formation of liver schizonts. Compounds that can prevent liver schizont formation may have potential for chemoprevention. The data for compound 13 suggests that this is not likely to have chemopreventative activity. Blood-stage infection gives rise to the clinical symptoms of malaria. Some of the parasites involved in blood-stage infection differentiate into gametocytes, which are the form of the parasite which can infect a mosquito, completing the life-cycle. Compounds that kill the gametocytes may be able to block transmission of the parasite to mosquitos. The data for compound 13, suggests that these compounds may have transmission blocking activity. Additional studies would be required to assess this in detail.

Unfortunately, further development is hampered by the potent inhibition of major CYP enzymes, where involvement of the 4-pyridyl group has been demonstrated. Focus has now moved towards the identification of the biological target of 13, to see if this information can be used to scaffold-hop to compounds that do not inhibit human cytochrome P450s. Given the rapid development of parasite drug resistance to known antimalarials, the identification of an essential and druggable target associated with the rapid clearance of *P. falciparum* parasites would be significant.

**Chemistry**

Synthesis of 4-pyridyl pyrimidines via a modified literature procedure, was initially undertaken by condensation of 4-pyridylamidine with dimethylmalonate using sodium methoxide as a base, and refluxed in methanol for up to 3 days to afford 2-(pyridin-4-yl)pyrimidine-4,6-diol 48 in 55% yield. However, by employing experiment design software Modde® and transferring the process to a microwave reactor, we were able to rapidly optimise the reaction conditions, improving the reaction yield to 70% and shortening the reaction time from 3 days to 1 h (Scheme 1). Chlorination of diol 48 with phosphorus trichloride at 90°C gave rise to 4,6-dichloro-2-(pyridin-4-yl)pyrimidine 49 with 58% yield. Nucleophilic displacement of one chlorine atom by an amine followed by a Suzuki cross-
coupling reaction with a boronic acid or ester afforded pyrimidines 51, allowing us to investigate substituents at the R2 and R3 positions.

Scheme 1: (i) Dimethylmalonate (DMM), NaOMe, MeOH, reflux, 3 days, 55%; or DMM, NaOMe, N-methyl pyrrolidinone, mw, 1 h, 150°C, 70%; (ii) POCl₃, 90°C, 58%; (iii) amine, DIPEA, THF, rt; (iv) boronic ester/acid, K₃PO₄, Pd(PPh₃)₄, DMF/water, microwave, 120°C, 20 min.

The synthetic route outlined in Scheme 1 is not amenable to explore the influence of changes at the R1 position on antimalarial activity. Therefore a number of synthetic routes that allowed the introduction of a diverse array of substituents at C-2 position on the pyrimidine ring were explored. Firstly, starting from commercially available 2,4,6-trichloropyrimidine 52, nucleophilic displacement with the corresponding amine (1 eq) at -5°C in ethanol gave rise to 53, with substitution at the 4-position as the major product, together with substitution at the 2-position as the minor product (Scheme 2).

Scheme 2: (i) amine, Et₃N, ethanol, -5°C, 4 h; (ii) boronic acid/ester, 2 M aq. sol. Na₂CO₃, Pd(PPh₃)₄, 1,4-dioxane/water, microwave at 120°C, 20 min; (iii) amine, Et₃N, acetonitrile, 40-70°C; (iv) 3-pyridyl boronic acid, K₃PO₄, Pd(PPh₃)₄, DMF/water 3/1, microwave at 120°C, 20 min.

The two reaction products could be easily separated by column chromatography. Suzuki cross-coupling reaction at the 2-position allowed the introduction of aromatic R1 substituents using commercially available boronic esters or acids. Alternatively, amino derivatives at C-2 were prepared by heating 53 in acetonitrile in the presence of the corresponding amine. Finally, the desired
trisubstituted pyrimidines 55 were obtained by Suzuki cross-coupling with 3-pyridylboronic acid. An alternative route allowing the introduction of the R₁ substituent at C-2 as the last step is shown in Scheme 3. Starting from commercially available 4,6-dichloro-2-methylsulfanylpyrimidine 56, reaction with 4-(4-piperidyl)morpholine in acetonitrile at room temperature gave rise to 57 in 56% yield. As above, a Suzuki cross-coupling with 3-pyridylboronic acid led to 58 in excellent yield. Finally, the introduction of the R₁ substituent was carried out following the palladium-catalyzed, copper(I) thiophene-2-carboxylate (CuTC) mediated coupling of boronic acids with heteroaromatic thioethers to yield compounds of type 55, reported by Liebeskind and Srogl. However, this reaction is limited to boronic acids and the more commercially accessible boronic esters led to low yields or failed.

Scheme 3: (i) amine, Et₃N, ethanol, rt, 16 h, 56%; (ii) 3-pyridyl boronic acid, K₃PO₄, Pd(PPh₃)₄, 1,4-Dioxane/water 3/1, microwave at 130°C, 20 min, 96%; (iii) boronic acid, thiophene-2-carbonyloxcopper, Pd(PPh₃)₄, 1,4-Dioxane or THF, microwave at 130°C, 1 h or 85°C, 18 h.

To expand the diversity of substituents at R₁ allowing a comprehensive SAR study, we developed the synthetic route outlined in Scheme 4. Iodination of commercially available 2-aminopyrimidine 59 was performed in good yield using tert-butyl nitrate and diiodomethane as previously described. Subsequent selective displacement of one of the chlorine atoms on intermediate 60 with amines such as 4-(4-piperidyl)morpholine, was carried out to afford substituted pyrimidines as exemplified by 61. Intermediate 61 proved to be a very versatile synthon, allowing the introduction of a diverse array of R₁ groups by a variety of synthetic methods. Pyrimidines bearing alkyl substituents were prepared by Sonogashira cross-coupling with a terminal alkyne followed by reduction of the resulting alkene,
aromatic and heteroaromatic substituents were introduce at C-2 by coupling with boronic acids or esters with good selectivity and nucleophilic displacements of iodine with amines and copper cyanide were also selective. The final step to obtain trisubstituted pyrimidine 55 from intermediate 62 was by Suzuki cross-coupling with 3-pyridylboronic acid.

Scheme 4: (i) CH$_2$I$_2$, t-ButONO, acetonitrile, 80°C, 3 h 30 min, 64%; (ii) amine, Et$_3$N, ethanol, 0°C, 3h; (iii) acetylene, CuI, Et$_3$N, Pd(PPh$_3$)$_2$Cl$_2$, acetonitrile, rt, 18h; (iv) amine, DIPEA, NMP, microwave at 200°C, 15 min; (v) boronic acid/ester, 2M aq. sol. Na$_2$CO$_3$, Pd(PPh$_3$)$_2$Cl$_2$, DME, microwave at 200°C, 20 min; (vi) 3-pyridyl boronic acid, K$_3$PO$_4$, Pd(PPh$_3$)$_4$, DMF, microwave at 120°C, 20 min.

**Experimental**

**General.** Reactions using microwave irradiation were carried out in a Biotage Initiator microwave. Normal phase TLCs were carried out on pre-coated silica plates (Kieselgel 60 F$_{254}$, BDH) with visualisation *via* U.V. light (UV254/365 nm) and/or ninhydrin solution. Flash chromatography was performed using Combiflash Companion Rf (Teledyne ISCO) and prepacked silica gel columns purchased from Grace Davison Discovery Science or SiliCycle. Mass-directed preparative HPLC separations were performed using a Waters HPLC (2545 binary gradient pumps, 515 HPLC make up)
pump, 2767 sample manager) connected to a Waters 2998 photodiode array and a Waters 3100 mass detector. Preparative HPLC separations were performed with a Gilson HPLC (321 pumps, 819 injection module, 215 liquid handler/injector) connected to a Gilson 155 UV/vis detector. On both instruments, HPLC chromatographic separations were conducted using Waters XBridge C18 columns, 19 x 100 mm, 5 um particle size; using 0.1% ammonia in water (solvent A) and acetonitrile (solvent B) as mobile phase. \(^1\)H NMR, \(^{19}\)F NMR spectra were recorded on a Bruker Avance DPX 500 spectrometer (\(^1\)H at 500.1 MHz, \(^{13}\)C at 125 MHz \(^{19}\)F at 470.5 MHz), or a Bruker Avance DPX 300 (\(^1\)H at 300 MHz). Chemical shifts (δ) are expressed in ppm recorded using the residual solvent as the internal reference in all cases. Signal splitting patterns are described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br), or a combination thereof. Coupling constants (J) are quoted to the nearest 0.5 Hz. Low resolution electrospray (ES) mass spectra were recorded on a Bruker MicroTof mass spectrometer, run in positive mode. High resolution mass spectroscopy (HRMS) was performed using a Bruker MicroTof mass spectrometer. LC-MS analysis and chromatographic separation were conducted with a Brucker MicrOTOf mass spectrometer or an Agilent Technologies 1200 series HPLC connected to an Agilent Technologies 6130 quadrupole LC/MS, where both instruments were connected to an Agilent diode array detector. The column used was a Waters XBridge column (50 mm × 2.1 mm, 3.5 μm particle size,) and the compounds were eluted with a gradient of 5 to 95% acetonitrile/water +0.1% Ammonia. All compounds for \textit{in vitro} and \textit{in vivo} experiments displayed >95% purity by LCMS. Unless otherwise stated herein reactions have not been optimised. Solvents and reagents were purchased from commercial suppliers and used without further purification. Dry solvents were purchased in sure sealed bottles stored over molecular sieves.
Chemistry Experimental

Synthetic Routes:

Scheme S1: (i) Dimethylmalonate, NaOMe, NMP, (150°C, mw, 1h), 70%; (ii) POCl₃, 90°C, 58%; (iii) amine, DIPEA, THF, rt; (iv) boronic ester/acid, K₃PO₄, Pd(PPh₃)₄, DMF/water 3/1, microwave at 120°C, 20 min.

Scheme S2: (i) amine, Et₃N, ethanol, -5°C, 4h; (ii) boronic acid/ester, 2M aq. sol. Na₂CO₃, Pd(PPh₃)₄, 1,4-dioxane/water, microwave at 120°C, 20 min; (iii) 3-pyridyl boronic acid, K₃PO₄, Pd(PPh₃)₄, DMF/water 3/1, microwave at 120°C, 20 min.

Scheme S3: (i) amine, Et₃N, ethanol, rt, 16h, 56%; (ii) 3-pyridyl boronic acid, K₃PO₄, Pd(PPh₃)₄, 1,4-Dioxane/water 3/1, microwave at 130°C, 20 min, 96%; (iii) boronic acid, thiophene-2-carboxylxycopper, Pd(PPh₃)₄, 1,4-Dioxane or THF, microwave at 130°C, 1h or 85°C, 18h.
**Scheme S4:** (i) CH$_3$I, t-BuONO, acetonitrile, 80°C, 3 h 30 min, 64%; (ii) amine, Et$_3$N, ethanol, 0°C, 3 h; (iii) acetylene, CuI, Et$_3$N, Pd(PPh)$_3$Cl$_2$, acetonitrile, rt, 18 h; (iv) amine, DIPEA, NMP, microwave at 200°C, 15 min; (v) boronic acid/ester, 2M aq. sol. Na$_2$CO$_3$, Pd(PPh)$_3$Cl$_2$, DME, microwave at 200°C, 20 min; (vi) 3-pyridyl boronic acid, K$_3$PO$_4$, Pd(PPh)$_3$, DMF, microwave at 120°C, 20 min.
Preparation of Compounds

2-(2,6-di(pyridine-3-yl)pyrimidin-4-yl)-1,2,3,4-tetrahydroisoquinoline (3) To a solution of 2,4,6-trichloropyrimidine (52) (1 g, 5.45 mmol) in ethanol (12 ml) at 0°C, a solution of 1,2,3,4-tetrahydroisoquinoline (0.68 ml, 5.45 mmol) in ethanol (5 ml) was added dropwise followed by triethylamine (1.14 ml, 8.19 mmol). Reaction mixture was stirred at 0°C for 1.5 h. Solvents were removed under vacuum and the reaction crude was partitioned between DCM (150 ml) and a saturated aqueous solution of NaHCO₃ (2 x 100 ml). The organic phase was dried over MgSO₄, filtered and solvents removed under reduced pressure. The product was purified by column chromatography (25 g silica cartridge) using A: hexane B: ethyl acetate as eluents and the following gradient: 3 min hold to 100% A, 10 min ramp to 40% B, 1 min hold to 40% B. Fractions containing pure product were pooled together and solvents were removed to obtain 2-(2,6-dichloropyrimidin-4-yl)-1,2,3,4-tetrahydroisoquinoline as a yellow solid (0.98 g, 64% yield). Purity by LCMS (UV chromatogram, 190-450 nm) 98%. 1H-NMR (500 MHz, CDCl₃) δ 7.29-7.22 (m, 4H), 6.49 (s, 1H), 4.76 (broad peak, 2H), 3.81 (broad peak, 4H), 3.01-2.99 (m, 2H); LRMS (ES⁺) m/z 281 [M+H]⁺.

To a stirred solution of 2-(2,6-dichloropyrimidin-4-yl)-1,2,3,4-tetrahydroisoquinoline (0.15 g, 0.54 mmol) and 3-pyridylboronic acid (0.15 g, 1.18 mmol) in 1,4-Dioxane (4.5 ml), a solution of potassium phosphate (0.34 g, 1.61 mmol) in water (1.5 ml) was added. The reaction mixture was degassed by bubbling argon through for 5 min and then Pd(PPh₃)₄ (0.018 g, 0.02 mmol) was added. The reaction was heated at 120°C under microwave irradiation for 30 min. The reaction crude was partitioned between DCM (2 x 50 ml) and saturated aqueous solution of NaHCO₃ (10 ml). The organics phase was dried over MgSO₄ before concentration to dryness. The product was purified by column chromatography (12 g silica cartridge) using A: DCM B: 10% MeOH in DCM as eluents and the following gradient: 3 min hold to 100% A, 15 min ramp to 100% B, 3 min hold to 100% B. The fractions containing product were pooled together and solvents were removed to obtain 3 as an off-white solid (100 mg, 51% yield). Purity by LCMS (UV chromatogram, 190-450 nm) > 98%. 1H-
NMR (500 MHz, CDCl₃) δ 9.75 (dd, 1H, J = 0.8, 2.1 Hz), 9.31 (dd, 1H, J = 0.7, 2.2 Hz), 8.82-8.79 (m, 1H), 8.72-8.70 (m, 2H), 8.49-8.47 (m, 1H), 7.47-7.41 (m, 2H), 7.29-7.24 (m, 4H), 6.92 (s, 1H), 4.95 (broad m, 2H), 4.07 (broad m, 4H), 3.07-3.04 (m, 2H); LRMS (ES⁺) m/z 366 [M+H]+.

4-(4-(3,4-dihydroisoquinolin-2(1H)-yl)-6-(pyridine-3-yl)pyrimidin-2-yl)morpholine (5) To a solution of 2,4,6-trichloropyrimidine (52) (0.63 ml, 5.5 mmol) in ethanol (12 ml) at 0°C, a solution of 1,2,3,4-tetrahydroisoquinoline (0.68 ml, 5.45 mmol) in ethanol (5 ml) was added dropwise followed by triethylamine (1.14 ml, 8.19 mmol). The white suspension was stirred at 0°C for 3 h and then was allowed to reach room temperature. Morpholine (0.48 ml, 5.5 mmol) and acetonitrile (20 ml) was added to the reaction mixture. The clear suspension was stirred at 40°C overnight. Solvents were removed under vacuum and the reaction crude was partitioned between DCM (100 ml) and water (25 ml). The organic phase was washed with a saturated aqueous solution of NaHCO₃ (25 ml), was dried over MgSO₄, filtered and solvents removed under reduced pressure. The product was purified by column chromatography (24 g silica cartridge) using A: hexane B: ethyl acetate as eluents and the following gradient: 3 min hold to 100% A, 18 min ramp to 30% B, 2 min hold to 30% B. Fractions containing product were pooled together and solvents were removed to obtain 4-(4-chloro-6-(3,4-dihydroisoquinolin-2(1H)-yl)pyrimidin-2-yl)morpholine as a white wax (1.25g, 69% yield, 88% purity by LCMS) that was used for the next step without further purification.

To a stirred solution of 4-(4-chloro-6-(3,4-dihydroisoquinolin-2(1H)-yl)pyrimidin-2-yl)morpholine (0.15 g, 0.45 mmol) and 3-pyridylboronic acid (0.17 g, 1.4 mmol) in DMF (6 ml), a solution of potassium phosphate (0.30 g, 1.4 mmol) in water (2 ml) was added. The reaction mixture was degassed by bubbling argon through for 5 min and then Pd(PPh₃)₄ (0.016 g, 0.01 mmol) was added. The reaction was heated at 120°C under microwave irradiation for 30 min. The reaction crude filtered through Celite and partitioned between DCM (2 x 50 ml) and saturated aqueous solution of NaHCO₃ (10 ml). The organics phase was dried over MgSO₄ before concentration to dryness. The product was purified by column chromatography (12 g silica cartridge) using A: hexane B: ethyl acetate as eluents.
and the following gradient: 3 min hold to 100% A, 15 min ramp to 80% B, 2 min ramp to 100% B, 3 min hold to 100% B. The fractions containing product, first eluting peak, were pooled together and solvents were removed to obtain 5 as yellow solid (34 mg, 20% yield). Purity by LCMS (UV chromatogram, 190-450 nm) 95%. 1H-NMR (500 MHz, CDCl3) δ 9.19 (bs, 1H), 8.66-8.65 (m, 1H), 8.312-8.29 (m, 1H), 7.38-7.36 (m, 1H), 7.23-7.18 (m, 4H), 6.38 (s, 1H), 4.79 (broad peak, 2H), 3.93-3.87 (m, 6H), 3.81-3.79 (m, 4H), 2.97 (t, 2H, $J = 5.9$ Hz); LRMS (ES+) m/z 374 [M+H]+.

### 6-(pyridyl-3-yl)-2-(pyridin-4-yl)pyrimidin-4-amine (6)

In a sealed tube a solution of 4,6-dichloro-2-(pyridin-4-yl)pyrimidine (49) (0.13 g, 0.58 mmol) and ammonium hydroxide (2 ml) in methanol (2 ml) was heated at 80°C for 5h. Solvents were removed under reduced pressure and the residue was partitioned between water (10 ml) and DCM (2 x 25 ml). The organic phases were combined, dried over magnesium sulphate and solvents were removed under reduced pressure. The product was purified by column chromatography (12 g silica cartridge) using A: DCM and B: 20% MeOH in DCM as eluents and the following gradient: 2 min hold at 100%A, 18 min ramp to 100%B, 3 min hold at 100% B. The fractions containing product were pooled together and solvents were removed to obtain 6-chloro-2-(pyridin-4-yl)pyrimidin-4-amine as white solid (69 mg, 39% yield, 99% purity by LCMS). Product was used in the next step without further purification.

1H-NMR (500 MHz, d6 DMSO) δ 8.74-8.72 (m, 2H), 8.10-8.08 (m, 2H), 7.50 (bs, 2H), 6.51 (m, 1H); LRMS (ES+) m/z 207 [M+H]+.

To a stirred solution of 6-chloro-2-(pyridin-4-yl)pyrimidin-4-amine (69 mg, 0.33 mmol) and 3-pyridylboronic acid (91 mg, 0.66 mmol) in DMF (3 mL), a solution of potassium phosphate (140 mg, 0.66 mmol) in water (1 mL) was added. The reaction mixture was degassed by bubbling argon through for 5 min and then Pd(PPh3)4 (20 mg, 0.017 mmol) was added. The reaction was heated at 120°C under microwave irradiation for 30 min. Reaction crude was filtered through Celite, quenched with water (10 ml) and extracted with DCM (2 x 25 ml). The organic phases were
combined, dried over magnesium sulphate and solvents were removed under reduced pressure. The product was purified by column chromatography (4 g silica cartridge) using A: DCM and B: 20% MeOH in DCM as eluents and the following gradient: 3 min hold at 100%A, 18 min ramp to 50%B, 3 min hold at 50%B. The fractions containing product were pooled together and solvents were removed to obtain 6 as off-white solid (24 mg, 29% yield). Purity by LCMS (UV chromatogram, 190-450 nm) > 98%. 1H-NMR (500 MHz, d6 DMSO) δ 8.76-8.72 (m, 3H), 8.50-8.47 (m, 1H), 8.31-8.29 (m, 2H), 7.59 (dd, 2H, J = 4.8, 7.4 Hz), 7.29 (m, 1H), 7.02 (m, 1H); LRMS (ES+) m/z 250 [M+H]⁺.

N-benzyl-N-methyl-6-(pyridine-3-yl)-2-(pyridin-4-yl)pyrimidin-4-amine (7) Prepared in an analogous 4-step procedure as that of compound 12: To a stirred solution of N-benzyl-6-chloro-N-methyl-2-(pyridin-4-yl)pyrimidin-4-amine (0.18 g, 0.58 mmol) and 3-pyridylboronic acid (0.21 g, 1.74 mmol) in DMF (3 mL), a solution of potassium phosphate (0.36 g, 1.74 mmol) in water (1 mL) was added. The reaction mixture was degassed by bubbling argon through for 5 min and then Pd(PPh₃)₄ (0.02 g, 0.014 mmol) was added. The reaction was heated at 120°C under microwave irradiation for 30 min. Reaction crude was filtered through Celite, quenched with water (10 ml) and extracted with DCM (2 x 25 ml). The organic phases were combined, dried over magnesium sulphate and solvents were removed under reduced pressure. The product was purified by column chromatography (12 g silica cartridge) using A: DCM and B: 20% MeOH in DCM as eluents and the following gradient: 3 min hold at 100%A, 18 min ramp to 50%B, 3 min hold at 50%B. The fractions containing product were pooled together and solvents were removed to obtain 7 as a white solid (115 mg, 56% yield). Purity by LCMS (UV chromatogram, 190-450 nm) > 98%. 1H-NMR (500 MHz, CDCl₃) δ 9.27 (s, 1H), 8.74-8.73 (m, 2H), 8.70-8.69 (m, 1H), 8.42-8.41 (m, 1H), 8.37-8.35 (m, 2H), 7.43-7.28 (m, 6H), 6.82 (s, 1H), 4.99 (bs, 2H), 3.20 (bs, 3H); LRMS (ES⁺) m/z 354 [M+H]⁺.

2-(6-(pyridin-4-yl)-2-(pyridine-4-yl)pyrimidin-4-yl)isoindoline (8) Prepared in an analogous 4-step procedure as that of compound 12: To a stirred solution of 2-(6-chloro-2-(pyridin-4-
yl)pyrimidin-4-yl)isoindoline (0.21 g, 0.68 mmol) and 3-pyridylboronic acid (2.50 g, 2.04 mmol) in DMF (3 mL), a solution of potassium phosphate (0.63 g, 2.04 mmol) in water (1 mL) was added. The reaction mixture was degassed by bubbling argon through for 5 min and then Pd(PPh$_3$)$_4$ (0.03 g, 0.02 mmol) was added. The reaction was heated at 120°C under microwave irradiation for 30 min. Reaction crude was filtered through Celite, quenched with water (10 mL) and extracted with DCM (2 x 25 mL). The organic phases were combined, dried over magnesium sulphate and solvents were removed under reduced pressure. The product was purified by column chromatography (12 g silica cartridge) using A: DCM and B: 20% MeOH in DCM as eluents and the following gradient: 3 min hold at 100%A, 15 min ramp to 100%B, 3 min hold at 100%B. The fractions containing product were pooled together and solvents were removed to obtain 8 as off-white solid (90 mg, 38% yield). Purity by LCMS (UV chromatogram, 190-450 nm) > 98%. 1H-NMR (500 MHz, CDCl$_3$) $\delta$ 9.35 (d, 1H, $J$ = 1.7 Hz), 8.78-8.73 (m, 2H), 8.74 (dd, 1H, $J$ = 1.5, 4.8 Hz), 8.53-8.50 (m, 1H), 8.44-8.43 (m, 2H), 7.47 (ddd, 1H, $J$ = 0.7, 4.8, 8.0 Hz), 7.43-7.38 (m, 4H), 6.83 (s, 1H), 5.16 (s, 2H), 4.90 (s, 2H); LRMS (ES$^+$) m/z 352 [M+H]$^+$.}

7-(6-(pyridine-4-yl)-2-(pyridine-4-yl)pyrimidin-4-yl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine (9)

Prepared in an analogous 4-step procedure as that of compound 12: To a stirred solution of 7-(6-chloro-2-(pyridine-4-yl)pyrimidin-4-yl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine (?) (0.09 g, 0.29 mmol) and 3-pyridylboronic acid (0.71 g, 0.58 mmol) in DMF (3 mL), a solution of potassium phosphate (0.18 g, 0.86 mmol) in water (1 mL) was added. The reaction mixture was degassed by bubbling argon through for 5 min and then Pd(PPh$_3$)$_4$ (0.01 g, 0.008 mmol) was added. The reaction was heated at 120°C under microwave irradiation for 30 min. Reaction crude was filtered through Celite, quenched with water (10 mL) and extracted with DCM (2 x 25 mL). The organic phases were combined, dried over magnesium sulphate and solvents were removed under reduced pressure. The product was purified by column chromatography (12 g silica cartridge) using A: DCM and B: 20% MeOH in DCM as eluents and the following gradient: 3 min hold at 100%A, 15 min ramp to
100%B, 3 min hold at 100%B. The fractions containing product were pooled together and solvents were removed to obtain 9 as an off-white solid (79 mg, 77% yield). Purity by LCMS (UV chromatogram, 190-450 nm) > 98%. \( ^1\)H-NMR (500 MHz, CDCl\(_3\)) \( \delta \) 9.30 (d, 1H, \( J = 1.7 \) Hz), 8.75-8.74 (m, 2H), 8.72 (dd, 1H, \( J = 1.6, 4.8 \) Hz), 8.43-8.40 (m, 1H), 8.33-8.32 (m, 2H), 7.44 (ddd, 1H, \( J =0.7, 4.8, 8.0 \) Hz), 7.09 (s, 1H), 6.98 (s, 1H), 6.92 (s, 1H), 4.97 (s, 2H), 4.93(t, 2H, \( J = 5.3 \) Hz), 4.20-4.18 (m, 2H) LRMS (ES\(^+\)) m/z 356 [M+H]\(^+\).

4-(4-phenylpiperazin-1-yl)-6-(pyridin-3-yl)-2-(pyridin-4-yl)pyrimidine (10) Prepared in an analogous 4-step procedure as that of compound 12: To a stirred solution of 4-chloro-6-(4-phenylpiperazin-1-yl)-2-(pyridin-4-yl)pyrimidine (0.18 g, 0.53 mmol) and 3-pyridylboronic acid (0.21 g, 1.69 mmol) in DMF (3 mL), a solution of potassium phosphate (0.35 g, 1.69 mmol) in water (1 mL) was added. The reaction mixture was degassed by bubbling argon through for 5 min and then Pd(PPh\(_3\))\(_4\) (0.02 g, 0.014 mmol) was added. The reaction was heated at 120°C under microwave irradiation for 30 min. Reaction crude was filtered through Celite, quenched with water (10 ml) and extracted with DCM (2 x 25 ml). The organic phases were combined, dried over magnesium sulphate and solvents were removed under reduced pressure. The product was purified by column chromatography (12 g silica cartridge) using A: DCM and B: 20% MeOH in DCM as eluents and the following gradient: 3min hold at 100%A, 18 min ramp to 30%B, 3 min hold at 30%B. The fractions containing product were pooled together and solvents were removed to obtain 10 as off-white solid (28 mg, 13% yield). Purity by LCMS (UV chromatogram, 190-450 nm) > 98%. \( ^1\)H-NMR (500 MHz, CDCl\(_3\)) \( \delta \) 9.30 (s, 1H), 8.77-8.74 (m, 3H), 8.47-8.45 (m, 1H), 8.37-8.36 (m, 2H), 7.46 (dd, 1H, \( J = 4.8, 7.7 \) Hz), 7.33-7.31 (m, 2H), 7.01-6.92 (s, 4H), 4.02 (broad peak, 4H), 3.37-3.35 (m, 4H); LRMS (ES\(^+\)) m/z 395 [M+H]\(^+\).

1’-(6-(pyridin-3-yl)-2-(pyridin-4-yl)pyrimidin-4-yl)-1,4’-bipiperidine (11) Prepared in an analogous 4-step procedure as that of compound 12: To a stirred solution of 1’-(6-chloro-2-(pyridin-
4-yl)pyrimidin-4-yl)-1,4’-bipiperidine (0.25 g, 0.71 mmol) and 3-pyridylboronic acid (0.17 g, 1.43 mmol) in DMF (9 mL), a solution of potassium phosphate (0.45 g, 2.14 mmol) in water (3 mL) was added. The reaction mixture was degassed by bubbling argon through for 5 min and then Pd(PPh$_3$)$_4$ (0.02 g, 0.014 mmol) was added. The reaction was heated at 120°C under microwave irradiation for 30 min. Reaction crude was filtered through Celite, quenched with water (20 ml) and extracted with DCM (2 x 50 ml). The organic phases were combined, dried over magnesium sulphate and solvents were removed under reduced pressure. The product was purified by column chromatography (12 g silica cartridge) using A: DCM and B: 20% MeOH in DCM as eluents and the following gradient: 3 min hold at 100%A, 18 min ramp to 100%B, 3 min hold at 100%B. The fractions containing product were pooled together and solvents were removed to obtain **11** as an off-white solid (261 mg, 91% yield). Purity by LCMS (UV chromatogram, 190-450 nm) > 98%. $^1$H-NMR (500 MHz, CDCl$_3$) δ 9.21 (d, 1H, $J$ = 1.8 Hz), 8.68-8.67 (m, 2H), 8.64 (dd, 1H, $J$ = 1.6, 4.8 Hz), 8.36-8.34 (m, 1H), 8.27-8.26 (m, 2H), 7.36 (dd, 1H, $J$ = 4.9, 7.8 Hz), 6.83 (s, 1H), 4.61 (broad peak, 2H), 3.95-3.90 (m, 2H), 2.59-2.49 (m, 5H), 1.96-1.93 (m, 2H), 1.57-1.49 (m, 6H), 1.40-1.39(m, 2H) ; LRMS (ES$^+$) m/z 401 [M+H]$^+$. **4-(1-(6-(pyridin-3-yl)-2-(pyridin-4-yl)pyrimidin-4-yl)piperidin-4-yl)morpholine (12)**

**Scheme S1 (4-step procedure)**

**1. 2-(pyridin-4-yl)pyrimidine-4,6-diol (48)** A mixture of 4-amidinopyridine hydrochloride (0.5 g, 3.17 mmol) and N-methyl-2-pyrolidone (10 mL) was prepared at rt and dimethylmalonate (0.363 mL, 419 mg, 3.17 mmol) added followed by sodium methoxide (686 mg, 12.69 mmol) and the mixture heated in a mw at 150°C for 1h. The mixture was then concentrated under reduced pressure, diluted with water (10 mL) and acidified to pH 6 with concentrated acetic acid. The resulting precipitate was then filtered and dried in vacuo to afford compound **48** (420 mg, 2.22 mmol, 70%) as an off-white
solid. $^1$H-NMR (500 MHz, $d_6$ DMSO) $\delta$ 12.10 (bs, 2H), 8.76-8.75 (m, 2H), 8.02-8.03 (m, 2H), 5.56 (s, 1H); LRMS (ES$^+$) m/z 190 [M+H]$^+$. 

2. 4,6-dichloro-2-(pyridin-4-yl)pyrimidine (49) A stirred solution of 2-(pyridin-4-yl)pyrimidine-4,6-diol (0.62 g, 3.28 mmol) in phosphorus oxychloride (6 ml) was heated at 90°C for 3h. The reaction mixture was slowly added to ice water and 2.5M NaOH was added to adjust to pH 7. The white precipitated was filtered a white solid. The filtrated was extracted with ethyl acetate (2 x 50ml) and the organic phases were combined, dried over magnesium sulphate and solvents were removed under reduced pressure. Precipitated and extracted product were combined to obtain 49 as a brown solid (421 mg, 58% yield). Purity by LCMS (UV chromatogram, 190-450 nm) 90%. $^1$H-NMR (500 MHz, $d_6$ DMSO) $\delta$ 8.81-8.80 (m, 2H), 8.27-8.26 (m, 2H), 7.41 (s, 1H); LRMS (ES$^+$) m/z 225 [M+H]$^+$. 

3. 4-(1-(6-chloro-2-(pyridin-4-yl)pyrimidin-4-yl)piperidin-4-yl)morpholine To a stirred solution of 4,6-dichloro-2-(pyridin-4-yl)pyrimidine (0.13 g, 0.58 mmol) in anhydrous THF (5 ml), 4-morpholinopiperidine (0.11 g, 0.63 mmol) and diisopropylethylamine (0.20 ml, 1.15 mmol) were added at room temperature and the reaction mixture was stirred at room temperature overnight. Water (10 ml) was added and the product was extracted with DCM (2 x 50 ml), the organic phases were combined, dried over magnesium sulphate and solvents were removed under reduced pressure. The product was purified by column chromatography (12 g silica cartridge) using A: DCM and B: 10% MeOH in DCM as eluents and the following gradient: 3 min hold at 100%A, 18 min ramp to 50%B, 3 min hold at 50%B. The fractions containing product were pooled together and solvents were removed to obtain 4-(1-(6-chloro-2-(pyridin-4-yl)pyrimidin-4-yl)piperidin-4-yl)morpholine as white solid (151mg, 73% yield). Purity by LCMS (UV chromatogram, 190-450 nm) 97%. $^1$H-NMR (500 MHz, $d_6$ DMSO) $\delta$ 8.74-8.72 (m, 2H), 8.14-8.13 (m, 2H), 7.03 (s, 1H), 4.58 (broad peak, 2H), 3.57-3.55 (m, 4H), 3.06-3.02 (m, 2H), 2.48-2.46 (m, 4H), 1.90-1.87 (m, 2H), 1.39 (dddd, 2H, $J$ = 4.2, 12.5, 12.6, 12.6 Hz); LRMS (ES$^+$) m/z 360 [M+H]$^+$. 

Commented [Ian2]: Is this the problem?
To a stirred solution of 4-[1-(6-chloro-2-(pyridin-4-yl)pyrimidin-4-yl)-4-piperidyl]morpholine (3x) (0.141 g, 0.39 mmol) and 3-pyridylboronic acid (0.098 g, 0.78 mmol) in DMF (3 mL), a solution of potassium phosphate (0.249 g, 1.17 mmol) in water (1 mL) was added. The reaction mixture was degassed by bubbling argon through for 5 min and then Pd(PPh₃)₄ (0.018 g, 0.016 mmol) was added. The reaction was heated at 120°C under microwave irradiation for 20 min. Reaction crude was diluted with methanol (10 ml) and applied to a SCX 5 g column and product was eluted with 2M NH₃ in MeOH. Solvents were removed. The product was further purified by preparative HPLC. The fractions containing product were pooled together and solvents were removed to obtain compound 12 as off-white solid (38 mg, 24% yield). Purity by LCMS (UV chromatogram, 190-450 nm) > 98%. ¹H-NMR (500 MHz, CDCl₃) δ 9.28-9.27 (m, 1H), 8.76-8.75 (m, 2H), 8.72 (dd, 1H, J = 1.7, 4.8 Hz), 8.45-8.42 (m, 1H), 8.34-8.33 (m, 2H), 7.44 (ddd, 1H, J = 0.7, 4.8, 7.9 Hz), 6.93 (s, 1H), 4.65 (bs, 2H), 3.74-3.72 (m, 4H), 3.12-3.06 (m, 2H), 2.60-2.52 (m, 5H), 2.04-2.01 (m, 2H), 1.59 (ddd, 2H, J = 4.3, 12.3, 24.1 Hz); LRMS (ES⁺) m/z 403 [M+H]⁺. HRMS (ES⁺) calculated for C₂₃H₂₇N₆O m/z [M+H]⁺ 403.2241, Measured m/z [M+H]⁺ 403.2260.

4-((1-(6-(pyridin-3-yl)-2-(pyridin-4-yl)pyrimidin-4-yl)piperidin-4-yl)(methyl)morpholine fumarate (13) Prepared in an analogous 4-step procedure to that of compound 12: A mixture of 4-((1-(6-chloro-2-(pyridin-4-yl)pyrimidin-4-yl)piperidin-4-yl)(methyl)morpholine (312 mg, 0.83 mmol) in DMF (4 mL) was prepared at rt and to it added 3-pyridyl boronic acid (205 mg, 1.70 mmol), potassium phosphate (354 mg, 1.70 mmol) in water (1 mL) and Pd tetraakis (48 mg, 0.04 mmol). The mixture was then heated in mw at 130°C for 1 h. The mixture was then diluted with DCM (10 mL) and filtered through a celite column, filtrate then purified by SCX-2 column, column washed with methanol (2 x 10 mL) then flushed with 7M ammonia in methanol (2 x 10 mL) and the ammonia/methanol filtrate concentrated under reduced pressure. Mixture then purified by column (0-10% 7M ammonia in methanol/dichloromethane) to afford 13 as an off-white solid (276 mg, 0.66 mmol). A sample of 13 (free base) (100 mg, 0.24 mmol) was suspended in ethanol (20.0 mL) and refluxed for 5 minutes until dissolution occurred. Fumaric acid (13.9 mg, 0.12 mmol) was dissolved in ethanol
(5 mL) and added to the mixture and stirred at rt for a further 24h. The mixture was then concentrated under reduced pressure and triturated with ethyl acetate and the resulting precipitate filtered, washed with ethyl acetate (2 x 5 mL) and dried by vacuum filtration to afford compound 13 (82 mg, 0.15 mmol, 21 % yield over 2 steps). Purity by LCMS (UV chromatogram, 190-450 nm) > 95%.  

\[ \text{H-NMR (500 MHz, CDCl}_3) \delta 9.47 (1H, d, J=1.6 Hz), 8.74 (2H, d, J=6.0 Hz), 8.71 (1H, dd, J=1.3, 4.7 Hz), 8.67 - 8.64 (1H, m), 8.33 (2H, d, J=6.0 Hz), 7.57 (1H, dd, J=4.8, 8.0 Hz), 7.49 (1H, s), 6.60 (1H, s), 4.73 - 4.73 (2H, m), 3.59 (4H, dd, J=4.0, 4.0 Hz), 3.04 (2H, t, J=12.5 Hz), 2.35 (4H, s), 2.16 (2H, d, J=7.3 Hz), 1.95 - 1.89 (1H, m), 1.86 (2H, d, J=13.0 Hz), 1.17 - 1.09 (2H, m); LRMS (ES\(^+\)) m/z 417 [M+H]\(^+\)]

N-(4-morpholinobutyl)-6-(pyridin-3-yl)-2-(pyridin-4-yl)pyrimidin-4-amine (14) Prepared in an analogous 4-step procedure to that of compound 12: A mixture of 6-chloro-N-(4-morpholinobutyl)-2-(pyridin-4-yl)pyrimidin-4-amine (187 mg, 0.54 mmol) in DMF (4 mL) was prepared at rt and 3-pyridylboronic acid (132, 1.08 mmol) added followed by potassium phosphate (228 mg, 1.08 mmol) in water (2mL) and Pd tetrais (31 mg, 0.03 mmol) added and the mixture heated in a mw to 130°C for 1h. The mixture was diluted with dichloromethane (10 mL) and filtered through an SCX-2 column, washed with methanol (2 x 10 mL) and flushed with 7M ammonia in methanol (2 x 10 mL) and filtrate concentrated under reduced pressure. The mixture was then purified by mass directed auto prep to afford 14 (161 mg, 0.41 mmol, 77%) as a colourless solid. Purity by LCMS (UV chromatogram, 190-450 nm) > 95%.  

\[ \text{H-NMR (500 MHz, CDCl}_3) \delta 9.27 (1H, d, J=1.8 Hz), 8.75 (dd, 2H, J = 1.6, 4.5 Hz), 8.72 (dd, 1H, J = 1.6, 4.8 Hz), 8.45 (dt, 1H, J = 2.0, 9.9 Hz), 8.32 (d, 2H, J = 8.3 Hz), 7.45 (dd, 1H, J = 3.1, 7.3 Hz), 6.70 (s, 1H), 6.04 (brs, 1H), 3.78 (t, 4H, J = 4.4 Hz), 3.52 (brs, 2H), 2.49 (brs, 4H), 2.43 (t, 2H, J = 7.1 Hz), 1.80 (p, 2H, J = 6.8 Hz), 1.69 (p, 2H, J = 7.1 Hz); LRMS (ES\(^+\)) m/z 389 [M+H]\(^+\)]

(R)-2-(6-(pyridin-3-yl)-2-(pyridine-4-yl)pyrimidin-4-yl)octahydropyrrolo[1,2-a]pyrazine (15) Prepared in an analogous 4-step procedure as that of compound 12: To a stirred solution of (R)-2-
(6-chloro-2-(pyridin-4-yl)pyrimidin-4-yl)octahydropyrrolo[1,2-a]pyrazine (0.14 g, 0.44 mmol) and 3-pyridylboronic acid (0.16 g, 1.31 mmol) in DMF (4.5 mL), a solution of potassium phosphate (0.28 g, 1.31 mmol) in water (1.5 mL) was added. The reaction mixture was degassed by bubbling argon through for 5 min and then Pd(PPh₃)₄ (0.015 g, 0.013 mmol) was added. The reaction was heated at 120°C under microwave irradiation for 30 min. Reaction crude was filtered through Celite, quenched with water (20 ml) and extracted with DCM (2 x 50 ml). The organic phases were combined, dried over magnesium sulphate and solvents were removed under reduced pressure. The product was purified by column chromatography (12 g silica cartridge) using A: DCM and B: 20% MeOH in DCM as eluents and the following gradient: 3 min hold at 100%A, 18 min ramp to 45%B, 3 min hold at 45%B. The fractions containing product were pooled together and solvents were removed to obtain 15 as white solid (119 mg, 75% yield). Purity by LCMS (UV chromatogram, 190-450 nm) > 98%. ¹H-NMR (500 MHz, CDCl₃) δ 9.22 (s, 1H), 8.69-8.65 (m, 3H), 8.37-8.35 (m, 1H), 8.28-8.27 (m, 2H), 7.37 (dd, 1H, J = 4.8, 7.8 Hz), 6.84 (s, 1H), 4.56 (broad peak, 2H), 3.16-3.09 (m, 3H), 2.78-2.74 (m, 1H), 2.27-2.22 (m, 1H), 2.18-2.13 (m, 1), 2.04-1.98 (m, 1H) 1.94-1.82 (m, 2H), 1.78-1.70 (m, 1H), 1.54-1.45 (m, 1H) ; LRMS (ES⁺) m/z 359 [M+H]⁺.

4-[1-(6-cyclopropyl-2-(pyridin-4-yl)pyrimidin-4-yl)piperidin-4-yl)morpholine (16) Prepared in an analogous 4-step procedure to that of compound 12: A mixture of 4-[1-{6-chloro-2-{(pyridyl)pyrimidin-4-yl}-4-piperidyl)morpholine (0.050g, 0.14mmol), potassium phosphate (0.088g, 0.41mmol), Pd(PPh₃)₄ (0.005g, 0.004mmol), cyclopropylboronic acid (0.012g, 0.014mmol) in 1,4-dioxane (1.6ml) and water (0.4ml) was heated at 120°C under microwave irradiation for 30mins. The cooled reaction mixture was evaporated to dryness. The residue was dissolved in MeOH/DCM and purified by SCX 2g column eluting with MeOH then 2M NH₃ in MeOH. The fraction containing product was evaporated to dryness. The residue was dissolved in DMF and purified by mass directed HPLC 5-95% MeCN, basic to afford 16 as a white solid (15mg, 28% yield). Purity by LCMS (UV chromatogram, 190-450 nm) > 98%. ¹H-NMR (500 MHz, CDCl₃) δ 8.68 (d, 2H, J = 5.5Hz), 8.19 (d,
To a mixture of 4-[6-chloro-2-(4-pyridyl)pyrimidin-4-yl]-4-piperidyl]morpholine (0.050g, 0.14mmol) in anhydrous NMP (1ml) was added 3-morpholinopropan-1-amine (60mg, 0.41mmol) and the mixture was heated at 200°C under microwave irradiation for 10mins. The cooled reaction mixture was purified by mass directed HPLC 5-95% MeCN, basic to afford 17 as a yellow solid (38mg, 55% yield). Purity by LCMS (UV chromatogram, 190-450 nm) > 98%. 1H-NMR (500 MHz, CDCl3) δ 8.69-8.65 (m, 2H), 8.18-8.16 (m, 2H), 5.61 (bs, 1H), 5.43 (s, 1H), 4.50-4.45 (m, 2H), 3.80-3.70 (m, 8H), 3.44-3.38 (m, 2H), 2.90 (m, 2H), 2.62-2.44 (m, 11H), 1.97-1.94 (m, 2H), 1.87-1.80 (m, 2H), 1.58-1.48 (m, 2H); LRMS (ES+) m/z 468 [M+H]+.

6-(4-morpholinopiperidin-1-yl)-N-(3-morpholinopropyl)-2-(pyridin-4-yl)pyrimidin-4-amine (17) A mixture of 4-[6-chloro-2-(4-pyridyl)pyrimidin-4-yl]-4-piperidyl]morpholine (0.050g, 0.14mmol), n,n-diisopropylethylamine (0.072ml, 0.41mmol), 3-aminopropanamide hydrochloride (0.052g, 0.41mmol) in anhydrous NMP (1ml) was heated at 200°C under microwave irradiation for 10mins. The cooled reaction mixture was purified by mass directed HPLC 5-95% MeCN, basic to afford 18 as a yellow solid (16mg, 26% yield). Purity by LCMS (UV chromatogram, 190-450 nm) > 98%. 1H-NMR (500 MHz, CD32SO) δ 8.67-8.64 (m, 2H), 8.15-8.12 (m, 2H), 7.33 (bs, 1H), 6.84-6.75 (broad peaks, 2H), 5.7 (s, 1H), 4.41-4.32 (m, 2H), 3.48-3.47 (m, 6H), 2.83 (m, 2H), 2.52-2.34 (m, 7H), 1.88-1.82 (m, 2H), 1.40-1.30 (m, 2H); LRMS (ES+) m/z 412 [M+H]+.

3-((6-(4-morpholinopiperidin-1-yl)-2-(pyridin-4-yl)pyrimidin-4-yl)amino) propanamide (18) A mixture of 4-[6-chloro-2-(4-pyridyl)pyrimidin-4-yl]-4-piperidyl]morpholine (0.050g, 0.14mmol), n,n-diisopropylethylamine (0.072ml, 0.41mmol), 3-aminopropanamide hydrochloride (0.052g, 0.41mmol) in anhydrous NMP (1ml) was heated at 200°C under microwave irradiation for 10mins. The cooled reaction mixture was purified by mass directed HPLC 5-95% MeCN, basic to afford 19 as a yellow solid (16mg, 26% yield). Purity by LCMS (UV chromatogram, 190-450 nm) > 98%. 1H-NMR (500 MHz, CD32SO) δ 8.67-8.64 (m, 2H), 8.15-8.12 (m, 2H), 7.33 (bs, 1H), 6.84-6.75 (broad peaks, 2H), 5.7 (s, 1H), 4.41-4.32 (m, 2H), 3.48-3.47 (m, 6H), 2.83 (m, 2H), 2.52-2.34 (m, 7H), 1.88-1.82 (m, 2H), 1.40-1.30 (m, 2H); LRMS (ES+) m/z 412 [M+H]+.
directed HPLC 5-95% MeCN, basic to afford 19 as a white solid (30mg, 57% yield). Purity by LCMS (UV chromatogram, 190-450 nm) > 98%. \(^1\)H-NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.69-8.67 (m, 2H), 8.20-8.18 (m, 2H), 5.61 (s, 1H), 4.55-4.49 (m, 2H), 3.83-3.80 (m, 4H), 3.68-3.71 (broad peak, 4H), 3.66-3.63, (m, 4H), 2.92 (m, 2H), 2.62-2.57 (broad peak, 5H), 2.00-1.93 (m, 2H), 1.62-1.52 (m, 2H); LRMS (ES\(^+\)) m/z 411 [M+H]\(^+\).

4-(1-(6-(3,5-dimethylisoxazol-4-yl)-2-(pyridin-4-yl)pyrimidin-4-yl)piperidin-4-yl)morpholine (20) Prepared in an analogous 4-step procedure to that of compound 51: A mixture of 4-[1-[6-chloro-2-(4-pyridyl)pyrimidin-4-yl]-4-piperidyl]morpholine (0.050g, 0.14mmol), potassium phosphate (0.088g, 0.41mmol), Pd(PPh\(_3\))\(_4\) (0.005g, 0.004mmol), 3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoxazole (0.093g, 0.41mmol) in 1,4-dioxane (1.6ml) and water (0.4ml) was heated at 120°C under microwave irradiation for 30mins. The cooled reaction mixture was filtered through a celite cartridge (2.5g), washing the cartridge with DCM. The filtrate was partitioned between saturated NaHCO\(_3\) (5ml) and DCM (10ml). The DCM extract was evaporated to dryness. The residue was dissolved in MeOH and purified by SCX 2g column eluting with MeOH then 2M NH\(_3\) in MeOH. The fraction containing product was evaporated to dryness. The residue was dissolved in DMF and purified by mass directed HPLC 5-95% MeCN, basic to afford 20 as a white solid (36mg, 61% yield). Purity by LCMS (UV chromatogram, 190-450 nm) >98%. \(^1\)H-NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.75-8.73 (m, 2H), 8.25-8.23 (m, 2H), 6.51 (s, 1H), 4.61 (bs, 2H), 3.92-3.67 (broad peak, 4H), 3.05 (m, 2H), 2.75-2.55 (m, 8H), 2.53 (s, 3H), 2.16-2.00 (broad peak, 2H), 1.72-1.49 (broad peak, 2H); LRMS (ES\(^+\)) m/z 421 [M+H]\(^+\).

4-(1-(6-(3-fluorophenyl)-2-(pyridin-4-yl)pyrimidin-4-yl)piperidin-4-yl)morpholine (21) Prepared in an analogous 4-step procedure to that of compound 12: A mixture of 4-[1-[6-chloro-2-(4-pyridyl)pyrimidin-4-yl]-4-piperidyl]morpholine (0.050g, 0.14mmol), potassium phosphate (0.088g, 0.41mmol), Pd(PPh\(_3\))\(_4\) (0.005g, 0.004mmol), (3-fluorophenyl)boronic acid (0.058g, 0.41mmol) in 1,4-dioxane (1.6ml) and water (0.4ml) was heated at 120°C under microwave
irradiation for 30mins. The cooled reaction mixture was evaporated to dryness. The residue was dissolved in MeOH/DCM and purified by SCX 2g column eluting with MeOH then 2M NH₃ in MeOH. The fraction containing product was evaporated to dryness. The residue was dissolved in DMF and purified by mass directed HPLC 5-95% MeCN, basic to afford 21 as a white solid (47mg, 76% yield). Purity by LCMS (UV chromatogram, 190-450 nm) > 98%. \(^1\)H-NMR (500 MHz, CDCl₃) δ 8.76-8.74 (m, 2H), 8.35-8.33 (m, 2H), 7.88-7.83 (m, 2H), 7.49-7.44 (m, 1H), 7.2-7.16 (m, 1H), 6.90 (s, 1H), 4.68 (bs, 2H), 3.85-3.73 (broad peak, 4H), 3.06 (m, 2H), 2.76-2.59 (broad peak, 5H), 2.14-2.04 (m, 2H), 1.69-1.54 (m, 2H); LRMS (ES⁺) m/z 420 [M+H]⁺.

4-(1-(6-(4-fluorophenyl)-2-(pyridin-4-yl)pyrimidin-4-yl)piperidin-4-yl)morpholine (22) Prepared in an analogous 4-step procedure to that of compound 12: A mixture of 4-[1-[6-chloro-2-(4-pyridyl)pyrimidin-4-yl]-4-piperidyl]morpholine (0.050g, 0.1389mmol), potassium phosphate (0.088g, 0.41mmol), Pd(PPh₃)₄ (0.005g, 0.004mmol), (4-fluorophenyl)boronic acid (0.058g, 0.41mmol) in 1,4-dioxane (1.6ml) and water (0.4ml) was heated at 120°C under microwave irradiation for 30mins. The cooled reaction mixture was evaporated to dryness. The residue was dissolved in MeOH/DCM and purified by SCX 2g column eluting with MeOH then 2M NH₃ in MeOH. The fraction containing product was evaporated to dryness. The residue was dissolved in DMF and purified by mass directed HPLC 5-95% MeCN, basic to afford 22 as a white solid (38mg, 61% yield). Purity by LCMS (UV chromatogram, 190-450 nm) > 98%. \(^1\)H-NMR (500 MHz, CDCl₃) δ 8.74 (d, 2H, J = 5.35Hz), 8.35-8.32 (m, 2H), 8.14-8.09 (m, 2H), 7.21-7.16 (m, 2H), 6.87 (s, 1H), 4.67 (broad peak, 2H), 3.84-3.7 (broad peak, 4H), 3.05 (m, 2H), 2.71-2.55 (broad peak, 5H), 2.10-2.00 (m, 2H), 1.67-1.52 (m, 2H); LRMS (ES⁺) m/z 420 [M+H]⁺.

4-(1-(2-(pyridin-4-yl)-[4,5'-bipyrimidin]-6-yl)piperidin-4-yl)morpholine (23) Prepared in an analogous 4-step procedure to that of compound 12: A mixture of 4-[1-[6-chloro-2-(4-pyridyl)pyrimidin-4-yl]-4-piperidyl]morpholine (0.050g, 0.14mmol), potassium phosphate (0.088g, 0.41mmol), Pd(PPh₃)₄ (0.005g, 0.004mmol), 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-
yl)pyrimidine (0.085g, 0.41mmol) in 1,4-dioxane (1.6ml) and water (0.4ml) was heated at 120°C under microwave irradiation for 30mins. The cooled reaction mixture was evaporated to dryness. The residue was dissolved in MeOH/DCM and purified by SCX 2g column eluting with MeOH then 2M NH₃ in MeOH. The fraction containing product was evaporated to dryness. The residue was dissolved in DMF and purified by mass directed HPLC 5-95% MeCN, basic to afford 23 as a white solid (26mg, 44% yield). Purity by LCMS (UV chromatogram, 190-450 nm) > 98%. 1H-NMR (500 MHz, CDCl₃) δ 9.41 (s, 2H), 9.32 (s, 1H), 8.78-8.75 (m, 2H), 8.33-8.31 (m, 2H), 6.92 (s, 1H) 4.70 (bs, 2H), 3.99-3.66 (broad peak, 4H), 3.11 (m, 2H), 2.82-2.52 (broad peak, 5H), 2.19-2.01 (broad peak, 2H), 1.77-1.49 (broad peak, 2H); LRMS (ES⁺) m/z 404 [M+H]⁺.

4-({1-(6-(5-methoxy-3-yl)-2-(pyridin-4-yl)pyrimidin-4-yl)piperidin-4-yl)morpholine (24)
Prepared in an analogous 4-step procedure to that of compound 12: A mixture of 4-{1-[6-chloro-2-(4-pyridyl)pyrimidin-4-yl]-4-piperidyl}morpholine (0.050g, 0.14mmol), potassium phosphate (0.088g, 0.41mmol), Pd(PPh₃)₄ (0.005g, 0.004mmol), (5-methoxy-3-pyridyl)boronic acid (0.063g, 0.41mmol) in 1,4-dioxane (1.6ml) and water (0.4ml) was heated at 120°C under microwave irradiation for 30mins. The cooled reaction mixture was evaporated to dryness. The residue was dissolved in MeOH/DCM and purified by SCX 2g column eluting with MeOH then 2M NH₃ in MeOH. The fraction containing product was evaporated to dryness. The residue was dissolved in DMF and purified by mass directed HPLC 5-95% MeCN, basic to afford 24 as a white solid (38mg, 60% yield). Purity by LCMS (UV chromatogram, 190-450 nm) > 98%. 1H-NMR (500 MHz, CDCl₃) δ 8.82 (d, 1H, J = 1.7 Hz), 8.76-8.74 (m, 2H), 8.41 (d, 1H, J = 2.85 Hz), 8.34-8.32 (m, 2H), 8.00-7.98 (m, 1H), 6.93 (s, 1H), 4.71 (broad peak, 2H), 3.98 (s, 3H), 3.86-3.74 (broad peak, 4H), 3.13-3.04 (m, 2H), 2.76-2.04 (broad peak, 5H), 2.16-2.04 (broad peak, 2H), 1.7-1.56 (broad peak, 2H); LRMS (ES⁺) m/z 433 [M+H]⁺.

5-{6-(4-morpholinopiperidin-1-yl)-2-(pyridin-4-yl)pyrimidin-4-yl}nicotinonitrile (25)
Prepared in an analogous 4-step procedure to that of compound 12: A mixture of 4-{1-[6-chloro-2-(4-
pyridyl]pyrimidin-4-yl]-4-piperidyl)morpholine (0.050g, 0.14mmol), potassium phosphate (0.088g, 0.41mmol), Pd(PPh$_3$)$_4$ (0.005g, 0.004mmol), (3-cyanophenyl)boronic acid (0.061g, 0.41mmol) in 1,4-dioxane (1.6ml) and water (0.4ml) was heated at 120°C under microwave irradiation for 60mins. The cooled reaction mixture was evaporated to dryness. The residue was dissolved in MeOH/DCM and purified by SCX 2g column eluting with MeOH then 2M NH$_3$ in MeOH. The fraction containing product was evaporated to dryness. The residue was dissolved in DMF and purified by mass directed HPLC 5-95% MeCN, basic to afford 25 as a white solid (14mg, 22% yield). Purity by LCMS (UV chromatogram, 190-450 nm) > 97%. $^1$H-NMR (500 MHz, CDCl$_3$) δ 9.45 (d, 1H, $J = 2.09$ Hz), 8.97 (d, 1H, $J = 1.94$ Hz), 8.79-8.72 (m, 3H), 8.34-8.29 (m, 2H), 6.94 (s, 1H), 4.69 (broad peak, 2H), 3.84-3.72 (broad peak, 4H), 3.12 (m, 2H), 2.70-2.58 (broad peak, 5H), 2.15-2.03 (m, 2H), 1.71-1.54 (broad peak, 2H); LRMS (ES$^+$) m/z 428 [M+H]$^+$.}

4-(1-(6-(5-fluoropyridin-3-yl)-2-(pyridin-4-yl)pyrimidin-4-yl) piperidin-4-yl)morpholine (26)

Prepared in an analogous 4-step procedure to that of compound 12: A mixture of 4-[1-[6-chloro-2-(4-pyridyl)pyrimidin-4-yl]-4-piperidyl]morpholine (0.050g, 0.14mmol), potassium phosphate (0.088g, 0.41mmol), Pd(PPh$_3$)$_4$ (0.005g, 0.004mmol), (5-fluoropyridin-3-yl)boronic acid (0.058g, 0.41mmol) in 1,4-dioxane (1.6ml) and water (0.4ml) was heated at 120°C under microwave irradiation for 30mins. The cooled reaction mixture was evaporated to dryness. The residue was dissolved in MeOH/DCM and purified by SCX 2g column eluting with MeOH then 2M NH$_3$ in MeOH. The fraction containing product was evaporated to dryness. The residue was dissolved in DMF and purified by mass directed HPLC 5-95% MeCN, basic to afford 26 as a yellow solid (13mg, 21% yield). Purity by LCMS (UV chromatogram, 190-450 nm) > 98%. $^1$H-NMR (500 MHz, CDCl$_3$) δ 9.07 (m, 1H), 8.76 (m, 2H), 8.58 (d, 1H, $J = 2.8$Hz), 8.34 (m, 2H), 8.22-8.19 (m, 1H), 6.94 (s, 1H), 4.67 (bs, 2H), 3.76-3.74 (m, 4H), 3.13-3.07 (m, 2H), 2.64-2.62 (m, 5H), 2.07-2.04 (m, 2H), 1.64-1.56 (m, 2H); LRMS (ES$^+$) m/z 421 [M+H]$^+$.
(5-(6-(4-morpholinopiperidin-1-yl)-2-(pyridin-4-yl)pyrimidin-4-yl)pyridin-3-yl)methanamine) (27) Prepared in an analogous 4-step procedure to that of compound 12: A solution of 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)picolinaldehyde (0.100g, 0.43mmol) in ammonia (7M in MeOH, 2ml) was stirred at room temperature overnight. Sodium borohydride (0.035g, 0.92mmol) was added and the reaction mixture stirred at room temperature under argon for 5 hours. Water (1ml) was added and the reaction mixture evaporated to dryness. The residue was dissolved in MeOH and purified by SCX 2g column eluted with MeOH then 2M NH₃ in MeOH. The fractions containing product were evaporated to dryness to give impure (5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)methanamine (0.090g) as a brown gum. A mixture of impure (5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)methanamine (0.090g, 0.38mmol), 4-[(6-chloro-2-(4-pyridyl)pyrimidin-4-yl]-4-piperidyl]morpholine (0.050g, 0.14mmol), potassium phosphate (0.088g, 0.41mmol), Pd(PPh₃)₄ (0.005g, 0.004mmol), in 1,4-dioxane (1.6ml) and water (0.4ml) was heated at 120°C under microwave irradiation for 30mins. The cooled reaction mixture was evaporated to dryness. The residue was dissolved in MeOH/DCM and purified by SCX 2g column eluting with MeOH then 2M NH₃ in MeOH. The fraction containing product was evaporated to dryness. The residue was dissolved in DMF and purified by mass directed HPLC 5-95% MeCN, basic to afford 27 as a white solid (13mg, 20% yield). Purity by LCMS (UV chromatogram, 190-450 nm) 95%. 1H-NMR (500 MHz, CDCl₃) δ 9.16 (d, 1H, J = 1.9Hz), 8.77-8.74 (m, 2H), 8.34 (d, 1H, J = 1.85Hz), 8.47 (m, 1H), 8.35-8.33 (m, 2H), 6.95 (s, 1H), 6.65 (bs, 2H) 4.04 (s, 2H), 3.76-3.70 (m, 4H), 3.09 (m, 2H), 2.62-2.56 (m, 5H), 2.07-1.99 (m, 2H), 1.65-1.54 (m, 2H); LRMS (ES⁺) m/z 432 [M+H]^⁺.

morpholino(5-(6-(4-morpholinopiperidin-1-yl)-2-(pyridin-4-yl)pyrimidin-4-yl)pyridin-3-yl)methanone (28) Prepared in an analogous 4-step procedure to that of compound 12: A mixture of 4-[(6-chloro-2-(4-pyridyl)pyrimidin-4-yl]-4-piperidyl]morpholine (0.050g, 0.14mmol), potassium phosphate (0.088g, 0.41mmol), Pd(PPh₃)₄ (0.005g, 0.004mmol), morpholino(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)methanone (0.132g, 0.41mmol) in 1,4-dioxane (1.6ml) and
water (0.4ml) was heated at 120°C under microwave irradiation for 30mins. The cooled reaction mixture was evaporated to dryness. The residue was dissolved in MeOH/DCM and purified by SCX 2g column eluting with MeOH then 2M NH₃ in MeOH. The fraction containing product was evaporated to dryness. The residue was dissolved in DMF and purified by mass directed HPLC 5-95% MeCN, basic to afford 28 as a light brown solid (52mg, 68% yield). Purity by LCMS (UV chromatogram, 190-450 nm) > 98%. ¹H-NMR (500 MHz, CDCl₃) δ 9.35 (d, 1H, J = 2.11Hz), 8.77-8.73 (m, 3H), 8.51 (m, 1H), 8.33-8.30 (m, 2H), 6.95 (s, 1H), 4.70 (bs, 2H), 3.92-3.64 (broad peaks, 12H), 3.09 (m, 2H), 2.77-2.55 (broad peak, 5H), 2.17-2.03 (broad peak, 2H), 1.73-1.53, (broad peak, 2H); LRMS (ES⁺) m/z 516 [M+H⁺].

5-(6-(4-morpholinopiperidin-1-yl)-2-(pyridin-4-yl)pyrimidin-4-yl)pyridin-2-amine (29) A mixture of 4-[1-[6-chloro-2-(4-pyridyl)pyrimidin-4-yl]-4-piperidyl]morpholine (0.050g, 0.14mmol), potassium phosphate (0.088g, 0.41mmol), Pd(PPh₃)₄ (0.005g, 0.004mmol), 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (0.091g, 0.41mmol) in 1,4-dioxane (1.6ml) and water (0.4ml) was heated at 120°C under microwave irradiation for 30mins. The cooled reaction mixture was evaporated to dryness. The residue was dissolved in MeOH/DCM and purified by SCX 2g column eluting with MeOH then picolinamide 2M NH₃ in MeOH. The fraction containing product was evaporated to dryness. The residue was dissolved in DMF and purified by mass directed HPLC 5-95% MeCN, basic to afford 29 as a white solid (42mg, 68% yield). Purity by LCMS (UV chromatogram, 190-450 nm) > 96%. ¹H-NMR (500 MHz, (CD₂)SO) δ 8.92 (d, 1H, J = 2.05Hz), 8.74-8.72 (m, 2H), 8.32-8.28 (m, 3H), 7.23 (s, 1H), 6.54 (d, 1H, J = 8.75Hz), 6.48 (bs, 2H), 4.70 (bs, 2H), 3.59-3.55 (m, 4H), 3.04-2.97 (m, 2H), 2.55-2.48 (m, 5H), 1.94-1.88 (m, 2H), 1.45-1.36 (m, 2H); LRMS (ES⁺) m/z 418 [M+H⁺].

4-(1-(6-(6-methoxypyridin-3-yl)-2-(pyridin-4-yl)pyrimidin-4-yl)piperidin-4-yl)morpholine (30) Prepared in an analogous 4-step procedure to that of compound 12: A mixture of 4-[1-[6-chloro-2-(4-pyridyl)pyrimidin-4-yl]-4-piperidyl]morpholine (0.050g, 0.14mmol), potassium phosphate
(0.088g, 0.41mmol), Pd(PPh₃)₄ (0.005g, 0.004mmol), (6-methoxypyridin-3-yl)boronic acid (0.063g, 0.41mmol) in 1,4-dioxane (1.6ml) and water (0.4ml) was heated at 120°C under microwave irradiation for 30mins. The cooled reaction mixture was filtered through a celite cartridge (2.5g), the cartridge was washed with DCM. The filtrate was partitioned between saturated NaHCO₃ (5ml) and DCM (10ml). The DCM extract was evaporated to dryness. The residue was dissolved in MeOH and purified by SCX 2g column eluting with MeOH then 2M NH₃ in MeOH. The fraction containing product was evaporated to dryness. The residue was dissolved in DMF and purified by mass directed HPLC 5-95% basic to afford impure product. The sample was dissolved in DMF and purified by mass directed HPLC 25-75% MeCN, basic to afford 30 as a white solid (17mg, 26% yield). Purity by LCMS (UV chromatogram, 190-450 nm) > 98%. ¹H-NMR (500 MHz, CDCl₃) δ 8.9 (m, 1H), 8.75-8.73 (m, 2H), 8.34-8.31 (m, 3H), 6.88-6.85 (m, 1H), 6.84 (s, 1H), 4.67 (broad peak, 2H), 4.01 (s, 3H), 3.87-3.79 (broad peak, 4H), 3.06 (m, 2H), 2.76-2.58 (broad peak, 5H), 2.14-2.08 (broad peak 2H), 1.69-1.55 (broad peak 2H); LRMS (ES⁺) m/z 433 [M+H]⁺.

N-methyl-5-(6-(4-morpholinopiperidin-1-yl)-2-(pyridin-4-yl)pyrimidin-4-yl)picolinamide (31)

Prepared in an analogous 4-step procedure to that of compound 12: A mixture of 4-[1-[6-chloro-2-(4-pyridyl)pyrimidin-4-yl]-4-piperidyl]morpholine (0.050g, 0.14mmol), potassium phosphate (0.088g, 0.41mmol), Pd(PPh₃)₄ (0.005g, 0.004mmol), N-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)picolinamide (0.109g, 0.41mmol) in 1,4-dioxane (1.6ml) and water (0.4ml) was heated at 120°C under microwave irradiation for 30mins. The cooled reaction mixture was evaporated to dryness. The residue was dissolved in MeOH/DCM and purified by SCX 2g column eluting with MeOH then 2M NH₃ in MeOH. The fraction containing product was evaporated to dryness. The residue was dissolved in DMF and purified by mass directed HPLC 5-95% basic to afford impure product. The sample was dissolved in DMF and purified by mass directed HPLC 25-75% MeCN, basic to afford 31 as a white solid (22mg, 32% yield). Purity by LCMS (UV chromatogram, 190-450 nm) > 98%. ¹H-NMR (500 MHz, CDCl₃) δ 9.25 (m, 1H), 8.77 (bs, 2H), 8.53-8.49 (m, 1H), 8.36-8.30 (m, 3H), 8.10-8.04 (m, 1H), 6.95 (s, 1H), 4.72 (bs, 2H), 3.96-3.67 (broad peak, 4H), 3.013-3.04
(m, 5H), 2.75-2.60 (broad peak, 5H) 2.16-2.03 (broad peak, 2H), 1.75-1.55 (broad peak, 2H); LRMS (ES+) m/z 460 [M+H]+.

4-(5-(4-morpholinopiperidin-1-yl)-2-(pyridin-4-yl)pyrimidin-4-yl)pyridin-2-yl)morpholine (32) Prepared in an analogous 4-step procedure to that of compound 12: A mixture of 4-1-[6-chloro-2-(4-pyridyl)pyrimidin-4-yl]-4-piperidyl]morpholine (0.050g, 0.14mmol), potassium phosphate (0.088g, 0.41mmol), Pd(PPh3)4 (0.005g, 0.004mmol), 4-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)morpholine (0.121g, 0.41mmol) in 1,4-dioxane (1.6ml) and water (0.4ml) was heated at 120°C under microwave irradiation for 30mins. The cooled reaction mixture was filtered through a celite cartridge (2.5g), washing the cartridge with DCM. The filtrate was partitioned between saturated NaHCO3 (5ml) and DCM (10ml). The DCM extract was evaporated to dryness. The residue was dissolved in MeOH and purified by SCX 2g column eluting with MeOH then 2M NH3 in MeOH. The fraction containing product was evaporated to dryness. The residue was dissolved in DMF and purified by mass directed HPLC 25-75%, basic to afford impure product. The sample was dissolved in DMF and purified by mass directed HPLC 25-75%, basic to afford 32 as a white solid (40mg, 56% yield). Purity by LCMS (UV chromatogram, 190-450 nm) 95%. 1H-NMR (500 MHz, (CD3)2SO) δ 9.12-9.09 (m, 1H), 8.72 (d, 2H, J = 5.78Hz), 8.48-8.42 (m, 1H), 8.30 (d, 2H, J = 5.93Hz), 7.3 (s, 1H), 6.95 (d, 1H, J = 9.08Hz), 4.65 (bs, 2H), 3.78-3.50 (m, 12H), 3.01 (m, 2H), 2.58-2.38 (m, 5H), 1.97-1.84 (m, 2H), 1.50-1.29 (m, 2H); LRMS (ES+) m/z 488 [M+H]+.

4-(1-(6-(4-methoxypyridin-3-yl)-2-(pyridin-4-yl)pyrimidin-4-yl)piperidin-4-yl)morpholine (33) Prepared in an analogous 4-step procedure to that of compound 12: A mixture of 4-1-[6-chloro-2-(4-pyridyl)pyrimidin-4-yl]-4-piperidyl]morpholine (0.050g, 0.14mmol), potassium phosphate (0.088g, 0.41mmol), Pd(PPh3)4 (0.005g, 0.004mmol), (4-methoxypyridin-3-yl)boronic acid (0.068g, 0.41mmol) in 1,4-dioxane (1.6ml) and water (0.4ml) was heated at 120°C under microwave irradiation for 30mins. The cooled reaction mixture was evaporated to dryness. The residue was dissolved in MeOH/DCM and purified by SCX 2g column eluting with MeOH then 2M NH3 in
MeOH. The fraction containing product was evaporated to dryness. The residue was dissolved in DMF and purified by mass directed HPLC 5-95% MeCN, basic to afford 33 as a white solid (46mg, 72% yield). Purity by LCMS (UV chromatogram, 190-450 nm) > 98%. 1H-NMR (500 MHz, CDCl3) δ 9.16 (s, 1H), 8.75-8.71 (m, 2H), 8.56 (d, 1H, J = 5.75Hz), 8.32-8.29 (m, 2H), 7.13 (s, 1H), 6.94 (d, 1H, J = 5.80Hz), 4.65 (bs, 2H), 3.97 (s, 3H), 3.85-3.76 (broad peak, 4H), 3.04 (m, 2H), 2.72-2.65 (broad peak, 5H), 2.15-2.02 (m, 2H), 1.67-1.54 (m, 2H); LRMS (ES+ m/z 433 [M+H]+).

4-(4-(morpholinopiperidin-1-yl)-6-(pyridin-3-yl)pyrimidin-2-yl)benzonitrile (34) Prepared in an analogous 3-step procedure to that of compound 43: In a sealed 5 ml microwave vial, a solution of 4-[1-(6-chloro-2-iodo-pyrimidin-4-yl)-4-piperydyl]morpholine (0.075 g, 0.20 mmol) in THF (4 ml) was degassed by bubbling argon through for 5 minutes. (4-cyanophenyl)boronic acid (0.030 g, 0.20 mmol), thioephene-2-carbonyloxy copper (0.058 g, 0.30 mmol) and Pd(PPh3)4 (0.023 g,0.02 mmol) were added at room temperature. The reaction was heated in the sealed tube at 85°C for 18 h. Reaction was filtered through Celite® and partitioned between DCM (10ml) and NH3 aq (5 ml). The organic phase was dried over magnesium sulphate and solvents were removed under reduced pressure. The product was purified by the product was purified by mass directed autopreparative HPLC under basic conditions. The fractions containing product were pooled together and solvents were removed to obtain 34 as off-white solid (12 mg, 14% yield). Purity by LCMS (UV chromatogram, 190-450 nm) > 98%. 1H-NMR (500 MHz, CDCl3) δ 9.27 (d, 1H, J = 1.7 Hz), 8.72 (dd, 1H, J = 1.6z, 4.8 Hz), 8.64-8.61 (m, 2H), 8.44-8.42 (m, 1H), 7.78-7.76 (m, 2H), 7.45 (ddd, 1H, J = 0.7, 4.8, 7.9 Hz), 6.92(s, 1H), 4.74-4.61 (m, 2H), 3.79-3.72 (m, 4H), 3.49 (d, 2H, J = 5.2 Hz), 3.11-3.06 (m, 2H), 2.69-2.52 (m, 5H), 2.08-2.03 (m, 2H), 1.63-1.54 (m, 2H); LRMS (ES+) m/z 427 [M+H]+.

4-(4-(morpholinopiperidin-1-yl)-6-(pyridin-3-yl)pyrimidin-2-carbonitrile (35) In a stirred sealed tube a solution of 4-[1-(6-chloro-2-iodo-pyrimidin-4-yl)-4-piperydyl]morpholine (0.29 g, 0.72 mmol) and copper cyanide (0.077 g, 0.86 mmol) in NMP (3 ml) was heated at 120°C for 5h. Reaction crude
was applied to a SCX cartridge (5g) and the product was diluted with a solution of 2N NH₃ in methanol. The product was further purified by column chromatography (12g silica cartridge) using A: DCM, B: 10% MeOH in DCM as eluents and the following gradient: 1 min hold at 100%A, 10 min ramp to 50% B and 3 min hold at 50% B. The fractions containing product were pooled together and solvents were removed to obtain 4-chloro-6-(4-morpholinopiperidin-1-yl)pyrimidine-2-carbonitrile as an off-white solid (139 mg, 62% yield). Purity by LCMS (UV chromatogram, 190-450 nm) 90%. 1H-NMR (500 MHz, CDCl₃) δ 6.44 (s, 1H), 3.73-3.71 (m, 4H), 3.06-3.01 (m, 2H), 2.56-2.48 (m, 5H), 1.99-1.96 (m, 2H), 1.55-1.47 (m, 2H); LRMS (ES⁺) m/z 308 [M+H]⁺.

To a stirred solution of 6-chloro-4-(4-morpholino-1-piperidyl)-1,6-dihydropyrimidine-2-carbonitrile (0.128 g, 0.41 mmol) and 3-pyridylboronic acid (0.103 g, 0.83 mmol) in DME (4 mL), an aqueous solution of sodium carbonate (2M, 0.26 g, 1.24 mmol) and PdCl₂(PPh₃)₂ (0.014 g, 0.02 mmol) were added. The reaction was heated at 120°C for 20 min under microwave irradiation. The reaction crude was diluted with methanol (5 ml) and applied to a SCX column (5 g) and the product was eluted with 2M NH₃ in MeOH. The product was further purified by preparative HLPC under acidic conditions. The fractions containing product were pooled together and solvents were removed to obtain 35 as an off-white solid (47 mg, 31% yield). Purity by LCMS (UV chromatogram, 190-450 nm) 98%. 1H-NMR (500 MHz, CDCl₃) δ 9.14-9.13 (m, 1H), 8.72 (dd, 1H, J =1.7, 4.8 Hz), 8.36-8.34 (m, 1H), 7.45 (ddd, 1H, J =0.8, 4.8, 8.0 Hz), 6.97 (s, 1H), 4.59-4.56 (m, 2H), 3.76-3.74 (m, 4H), 3.10-3.05 (m, 2H), 2.63-2.57 (m, 5H), 2.04-2.02 (m, 2H), 1.60-1.52 (m, 2H); LRMS (ES⁺) m/z 351 [M+H]⁺.

1-(4-(4-morpholinopiperidin-1-yl)-6-(pyridine-3-yl)pyrimidin-2-yl)thiomorpholine-1,1-dioxide (36) Prepared in an analogous 3-step procedure to that of compound 74: A solution of 4-[1-(6-chloro-2-iodopyrimidin-4-yl)-4-piperidyl]morpholine (0.15 g, 0.37 mmol), thiomorpholine-1,1-dioxide (0.06 mg, 0.40 mmol) and DIPEA (0.13 ml, 040 mmol) in NMP (2 ml) was heated at 200°C for 15 min under microwave irradiation. Reaction crude was diluted with MeOH (5 ml) and applied to a SCX cartridge (5g) and the product was diluted with a solution of 2N NH₃ in methanol. Solvents were
removed under reduced pressure and the product was further purified by column chromatography (12g silica cartridge) using A: DCM, B: 10% MeOH in DCM as eluents and the following gradient: 1 min hold at 100% A, 18 min ramp to 50% B and 3 min hold at 50% B. The fractions containing product were pooled together and solvents were removed to obtain 1-(4-chloro-6-(4-morpholinopiperidin-1-yl)pyrimidin-2-yl)thiomorpholine-1,1-dioxide as an off-white solid (149 mg, 98%, 91% purity by LCMS). The product was used for the next step without further purification.

To a stirred solution of 1-(4-chloro-6-(4-morpholinopiperidin-1-yl)pyrimidin-2-yl)thiomorpholine-1,1-dioxide (0.15 g, 0.36 mmol) and 3-pyridylboronic acid (0.09 g, 0.76 mmol) in DMF (3 mL), Pd(PPh₃)₄ (0.015 g, 0.01 mmol) and an aqueous solution of potassium carbonate (2M, 0.5 ml) were added. The reaction was heated at 120°C for 20 min under microwave irradiation. The reaction crude was diluted with methanol (10 ml) and applied to a SCX column (2 g) and the product was eluted with 2M NH₃ in MeOH. The product was further purified by preparative HPLC under basic conditions. The fractions containing product were pooled together and solvents were removed to obtain 36 as off-white solid (67 mg, 41% yield). Purity by LCMS (UV chromatogram, 190-450 nm) 98%. ¹H-NMR (500 MHz, CDCl₃) δ 9.13 (dd, 1H, J=0.7, 2.2 Hz), 8.66 (dd, 1H, J=1.7, 4.8 Hz), 8.22-8.20 (m, 1H), 7.37 (ddd, 1H, J= 0.8, 4.8, 8.0 Hz), 6.42 (s, 1H), 4.45-4.40 (m, 6H), 3.73-3.71 (m, 4H), 3.07-3.05 (m, 4H), 2.53-2.93 (m, 2H), 2.58-2.56 (m, 4H), 2.52-2.47 (m, 1H), 1.97-1.94 (m, 2H), 1.55-1.47 (m, 2H); LRMS (ES⁺) m/z 459 [M+H]⁺.

4-(4-morpholinopiperidin-1-yl)-6-(pyridin-3-yl)pyrimidin-2-ol (37) To a stirred solution of 4-(2,6-dichloropyrimidin-4-yl)-4-piperidyl)morpholine (0.60 g, 1.89 mmol) in THF (10ml) in a 20 ml microwave vial, a solution of NaOH (1M, 9.8 ml) was added at room temperature. The reaction mixture was heated 150°C for 1 h under microwave irradiation. The reaction crude was washed with ethyl acetate (2 x 100 ml). The pH of the aqueous layer was adjusted to pH 6 with 10% HCl and then MeOH (40 ml) added. The water/methanol mixture was applied onto an SCX column (20 g) and the compound was eluted from the column with 2M NH₃ in Methanol. Solvents were removed under
reduced pressure to obtain 4-chloro-6-(4-morpholinopiperidin-1-yl)pyrimidin-2-ol as a white solid (256 mg, 45% yield). Purity by LCMS (UV chromatogram, 190-450 nm) 86%. $^1$H-NMR (500 MHz, CDCl$_3$) δ 5.86 (s, 1H), 4.26 (broad peak, 2H), 3.69 (broad peak, 4H), 2.94-2.89 (m, 2H), 2.51-2.40 (m, 5H), 1.90-1.87 (m, 2H), 1.46-1.40 (m, 2H); LRMS (ES$^+$) m/z 299 [M+H]$^+$.  

To a stirred suspension of 4-chloro-6-(4-morpholinopiperidin-1-yl)pyrimidin-2-ol (0.26 g, 0.86 mmol) and 3-pyridylboronic acid (0.32 g, 2.57 mmol) in DMF (3 mL), a solution of potassium phosphate (0.55 g, 2.57 mmol) in water (1 mL) was added. The reaction mixture was degassed by bubbling argon through for 5 min and then Pd(PPh$_3$)$_4$ (0.049 g, 0.04 mmol) was added. The reaction was heated at 130°C under microwave irradiation for 20 min. Reaction was filtered through Celite and partitioned between DCM (50 ml) and a saturated aqueous solution of NaHCO$_3$ (15 ml). The organics phase was dried over MgSO$_4$ before concentration to dryness. The crude was then purified by column chromatography (12 g silica cartridge) using A: DCM; B: MeOH as eluents and the following gradient: 1 min hold at 100% A, 20 min ramp to 20% B, 5 min hold to 10%B. The fractions containing product were pooled together and solvents were removed to obtain 37 as a white solid (50 mg, 17% yield). Purity by LCMS (UV chromatogram, 190-450 nm) >98%. $^1$H-NMR (500 MHz, $d_6$ DMSO) δ 11.02 (bs, 1H), 9.07 (d, 1H, $J = 2.0$ Hz), 8.77 (dd, 1H, $J = 1.5$, 4.8 Hz), 8.28-8.25 (m, 1H), 7.61 (dd, 1H, $J = 4.8$, 8.0 Hz), 6.58 (s, 1H), 4.84-4.32 (broad peak, 2H), 3.65-3.63 (m, 4H), 3.02 (broad peak, 2H), 2.54 (broad peak, 5H), 1.93-1.91 (m, 2H), 1.45-1.33 (m, 2H); LRMS (ES$^+$) m/z 342 [M+H]$^+$.  

4(4-(4-morpholinopiperidin-1-yl)-6-(pyridine-3-yl)pyrimidin-2-yl)piperazine-2-one (38)  
Prepared in an analogous 3-step procedure to that of compound 74: A solution of 4-[1-((6-chloro-2-iodo-pyrimidin-4-yl)-4-piperidyl)morpholine (0.15 g, 0.37 mmol), Piperazine-2-one (0.04 mg, 0.40 mmol) and DIPEA (0.13 ml, 0.40 mmol) in NMP (2 ml) was heated at 200°C for 15 min under
microwaved irradiation. Reaction crude was diluted with MeOH (5 ml) and applied to a SCX cartridge (5g) and the product was diluted with a solution of 2N NH₃ in methanol. Solvents were removed under reduced pressure and the product was further purified by column chromatography (12g silica cartridge) using A: DCM, B: 10% MeOH in DCM as eluents and the following gradient: 1 min hold at 100% A, 18 min ramp to 50% B and 3 min hold at 50% B. The fractions containing product were pooled together and solvents were removed to obtain 4-chloro-N-(2-morpholinoethyl)-6-(4-morpholinopiperidin-1-yl)pyrimidin-2-amine as an off-white solid (159 mg, quantitative yield, 83% purity by LCMS). The product was used for the next step without further purification.

To a stirred solution of 4-chloro-N-(2-morpholinoethyl)-6-(4-morpholinopiperidin-1-yl)pyrimidin-2-amine (0.16 g, 0.41 mmol) and 3-pyridylboronic acid (0.10 g, 0.82 mmol) in DMF (3 mL), Pd(PPh₃)₄ (0.015 g, 0.01 mmol) and an aqueous solution of potassium carbonate (2M, 0.5 ml) were added. The reaction was heated at 120°C for 20 min under microwave irradiation. The reaction crude was diluted with methanol (10 ml) and applied to a SCX column (2 g) and the product was eluted with 2M NH₃ in MeOH. The product was further purified by preparative HPLC under basic conditions. The fractions containing product were pooled together and solvents were removed to obtain 38 as an off-white solid (70 mg, 40% yield). Purity by LCMS (UV chromatogram, 190-450 nm) 98%. 

H-NMR (500 MHz, CDCl₃) δ 9.17 (dd, 1H, J = 0.7, 2.2 Hz), 8.67 (dd, 1H, J = 1.7, 4.8 Hz), 8.31-8.29 (m, 1H), 7.38 (ddd, 1H, J = 0.8, 4.8, 8.0 Hz), 6.47 (bs, 1H), 6.41 (s,1H), 4.52-4.49 (m, 4H), 4.16-4.13 (m, 2H), 3.16-3.74 (m, 4H), 3.53-3.50 (m, 2H), 2.99-2.94 (m, 2H), 2.60-2.59 (m, 4H), 2.54-2.48 (m, 1H), 1.98-1.95 (m, 2H), 1.57-1.49 (m, 2H); LRMS (ES⁺) m/z 425 [M+H]⁺.

N¹,N¹-dimethyl-N²-(4-(4-morpholinopiperidin-1-yl)-6-(pyridine-3-yl)pyrimidin-2-yl)ethane-1,2-diamine (39) Prepared in an analogous 3-step procedure to that of compound 5: To a stirred suspension of N¹-(4-chloro-6-(4-morpholinopiperidin-1-yl)pyrimidin-2-yl)-N²,N²-dimethylethane-1,2-diamine (0.04 g, 0.11 mmol) and 3-pyridylboronic acid (0.41 g, 0.33 mmol) in DMF (3 mL), a solution of potassium phosphate (0.07 g, 0.33 mmol) in water (1 mL) was added. The reaction
mixture was degassed by bubbling argon through for 5 min and then Pd(PPh₃)₄ (0.004 g, 0.003 mmol) was added. The reaction was heated at 130°C under microwave irradiation for 20 min. Reaction was filtered through Celite and partitioned between DCM (10 ml) and a saturated aqueous solution of NaHCO₃ (5 ml). The organics phase was dried over MgSO₄ before concentration to dryness. The crude was then purified by preparative mass directed autopreparative HPLC (method: 5-95 basic). The fractions containing product were pooled together and solvents were removed to obtain 39 as a white solid (18 mg, 39% yield). Purity by LCMS (UV chromatogram, 190-450 nm) >98%. ¹H-NMR (500 MHz, d₆ DMSO) δ 9.11 (s, 1H), 8.63 (dd, 1H, J = 1.6, 4.8 Hz), 8.24 (d, 1H, J = 7.9 Hz), 7.35 (dd, 1H, J = 4.8, 7.9 Hz), 6.32 (s, 1H), 4.51-4.48 (m, 2H), 3.73-3.55 (m, 4H), 3.55-3.52 (m, 2H), 2.90 (t, 1H, J = 12.7 Hz), 2.58-2.54 (m, 4H), 2.53-2.51 (m, 2H), 2.49-2.44 (m, 1H), 2.27 (s, 6H), 1.94-1.91 (m, 2H), 1.54-1.45 (m, 2H); LRMS (ES⁺) m/z 412 [M+H]⁺.

4-(1-(2-(2,6-dimethylpyridin-4-yl)-6-(pyridin-3-yl)pyrimidin-4-yl)piperidin-4-yl)morpholine (40) To a stirred solution of 4-[1-[6-chloro-2-(2,6-dimethyl-4-pyridyl)pyrimidin-4-yl]-4-piperidyl]morpholine (0.042 g, 0.11 mmol) and 3-pyridylboronic acid (0.040 g, 0.32 mmol) in DMF (3 mL), a solution of potassium phosphate (0.069 g, 0.32 mmol) in water (1 mL) was added. The reaction mixture was degassed by bubbling argon through for 5 min and then Pd(PPh₃)₄ (0.006 g, 0.005 mmol) was added. The reaction was heated at 130°C under microwave irradiation for 20 min. The reaction crude was partitioned between DCM (15 ml) and saturated aqueous solution of NaHCO₃ (5 ml). The organics phase was dried over MgSO₄ before concentration to dryness. The crude was then purified by preparative HPLC. The fractions containing product were pooled together and solvents were removed to obtain 40 as off-white solid (8 mg, 17% yield). Purity by LCMS (UV chromatogram, 190-450 nm) >98%. ¹H-NMR (500 MHz, CDCl₃) δ 9.27-9.26 (m, 1H), 8.72 (dd, 1H, J = 1.6, 4.8 Hz), 8.45-8.42 (m, 1H), 8.03 (bs, 2H), 7.46 (ddd, 1H, J = 0.6, 4.8, 8.0 Hz), 6.93 (s, 1H), 4.69 (broad m, 2H), 3.78 (broad m, 4H), 3.12-3.06 (m, 2H), 2.67-2.61 (m, 1H), 2.09-2.07 (m, 2H), 1.67-1.57 (m, 2H); LRMS (ES⁺) m/z 431 [M+H]⁺.
4-(1-(2-(2-methylpyridin-4-yl)-6-(pyridin-3-yl)pyrimidin-4-yl)piperidin-4-yl)morpholine (41)

Prepared in an analogous 3-step procedure to that of compound 43: In a sealed 5 ml microwave vial, a solution of 4-[1-[2-methylsulfanyl-6-(3-pyridyl)pyrimidin-4-yl]-4-piperidyl]morpholine (0.07 g, 0.20 mmol) in THF (4 ml) was degassed by bubbling argon through for 5 minutes. (2-methyl-4-pyridyl)boronic acid (0.03 g, 0.20 mmol), thiophene-2-carbonyloxyopper (0.06 g, 0.30 mmol) and Pd(PPh)_3Cl (0.02 g, 0.02 mmol) were added at room temperature. The reaction was heated in a sealed tube at 85 °C for 18h. The reaction crude filtered through Celite and partitioned between DCM (10 ml) and ammonium hydroxide (5 ml). The organic phase was dried over magnesium sulphate and solvents were removed under reduced pressure. The product was purified by mass directed autopreparative HPLC under basic conditions (5-95 prep basic). The fractions containing product were pooled together and solvents were removed to obtain 41 as white solid (9 mg, 10% yield). Purity by LCMS (UV chromatogram, 190-450 nm) 97%. ^H-NMR (500 MHz, CDCl_3) δ 9.26 (d, 1H, J = 2.0 Hz), 8.72-8.71 (m, 1H), 8.62 (d, 1H, J = 5.2 Hz), 8.45-8.42 (m, 1H), 8.19 (s, 1H), 8.13 (d, 1H, J = 5.1 Hz), 7.44 (dd, 1H, J = 4.8, 7.9 Hz), 6.92 (s, 1H), 4.67-4.66 (m, 2H), 3.75-3.73 (m, 4H), 3.10-3.04 (m, 2H), 2.67 (s, 3H), 2.61-2.54 (m, 5H), 2.05-2.00 (m, 2H), 1.63-1.55 (m, 2H); LRMS (ES^+) m/z 417 [M+H]^+. 

4-(1-(6-(pyridine-3-yl)-2-(2-(trifluoromethyl)pyridine-4-yl)pyrimidin-4-yl)piperidin-4-yl)morpholine (42) Prepared in an analogous 3-step procedure to that of compound 63: To a solution of 4-[1-(6-chloro-2-iodo-pyrimidin-4-yl)-4-piperidyl]morpholine (0.15 g, 0.37 mmol) and (2-(trifluoromethyl)pyridine-4-yl)boronic acid (0.07 mg, 0.37) in DME (3 ml) in a 5 ml sealed microwave tube, Pd(PPh_3)Cl_2 (0.01 g, 0.02 mmol) and an aqueous 2M Na_2CO_3 solution (0.55 ml) were added. The reaction was heated at 120°C for 20 min under microwave irradiation. The reaction mixture was diluted with methanol (10 ml) and applied to a SCX column (5 g) and the product was eluted with 2M NH_3 in MeOH. Solvents were removed under reduced pressure and the product was further purified by column chromatography (12g silica cartridge) using A: DCM, B: 10% MeOH in DCM as
eluents and the following gradient: 1 min hold at 100%A, 18 min ramp to 50% B and 3 min hold at 50% B. The fractions containing product were pooled together and solvents were removed to obtain 4-(1-(6-chloro-2-(trifluoromethyl)pyridine-4-yl)pyrimidin-4-yl)piperidin-4-yl)morpholine as an off-white solid (100 mg, 64% yield, 77% purity by LCMS). The product was used for the next step without further purification. To a stirred solution of 4-(1-(6-chloro-2-(trifluoromethyl)pyridine-4-yl)pyrimidin-4-yl)piperidin-4-yl)morpholine (0.10 g, 0.23 mmol) and 3-pyridylboronic acid (0.057 g, 0.46 mmol) in DME (3 ml), Pd(PPh₃)₄ (0.015 g, 0.01 mmol) and an aqueous solution of potassium phosphate (2M, 0.5 ml) were added. The reaction was heated at 120°C for 20 min under microwave irradiation. The reaction crude was diluted with methanol (5 ml) and applied to a SCX column (1 g) and the product was eluted with 2M NH₃ in MeOH. The product was further purified by preparative HPLC under basic conditions. The fractions containing product were pooled together and solvents were removed to obtain 42 as off-white solid (69 mg, 63% yield). Purity by LCMS (UV chromatogram, 190-450 nm) 98%. ¹H-NMR (500 MHz, CDCl₃) δ 9.27 (d, 1H, J = 1.5 Hz), 8.87-8.86 (m, 1H), 8.74 (dd, 1H, J =1.2, 4.6 Hz), 8.74-8.71 (m, 1H), 8.55 (dd, 1H, J =1.1, 5.0 Hz), 8.45-8.43 (m, 2H), 7.47 (dd, 1H, J =5.1, 7.7 Hz), 6.97 (s, 1H), 4.69-4.61 (m, 2H), 3.75-3.73 (m, 4H), 3.15-3.10 (m, 2H), 2.61-2.55 (m, 5H), 2.07-2.04 (m, 2H), 1.64-1.56 (m, 2H); LRMS (ES⁺) m/z 471 [M+H]⁺.

4-(1-(2-(3-methylpyridin-4-yl)-6-(pyridin-3-yl)pyrimidin-4-yl)piperidin-4-yl)morpholine (43)

In a sealed 5 ml microwave vial, a solution of 4-[1-[2-methylsulfanyl-6-(3-pyridyl)pyrimidin-4-yl]-4-piperidyl)morpholine (0.10 g, 0.26 mmol) in 1,4-Dioxane (4 ml) was degassed by bubbling argon through for 5 minutes. (3-methyl-4-pyridyl)boronic acid (0.073 g, 0.54 mmol), thiophene-2-carbonyloxycopper (0.102 g, 0.54 mmol) and Pd(PPh₃)₄ (0.031 g, 0.03 mmol) were added at room temperature. The reaction was heated under microwave irradiation at 130°C for 1h. The reaction crude was applied to a SCX column (2 g) and the product was eluted with 2 M NH₃ in MeOH. Solvents were removed and the product was purified by mass directed autopreparative HPLC under
basic conditions. The fractions containing product were pooled together and solvents were removed to obtain 43 as off-white solid (31 mg, 26% yield). Purity by LCMS (UV chromatogram, 190-450 nm) 95%. 1H-NMR (500 MHz, CDCl₃) δ 9.26-9.21 (m, 1H), 8.72-8.71 (m, 1H), 8.69-8.52 (m, 2H), 8.39-8.37 (m, 1H), 7.87 (d, 1H, J = 4.5 Hz), 7.43 (dd, 1H, J = 4.8, 7.8 Hz), 6.91 (s, 1H), 4.62-4.59 (m, 2H), 3.80-3.72 (m, 4H), 3.10-3.04 (m, 2H), 2.66 (s, 3H), 2.64-2.52 (m, 5H), 2.06-2.03 (m, 2H), 1.65-1.55 (m, 2H); LRMS (ES⁺) m/z 417 [M+H]⁺.

4-(1-(2-(3-fluoropyridin-4-yl)-6-(pyridin-3-yl)pyrimidin-4-yl)piperidin-4-yl)morpholine (44)
Prepared in an analogous 3-step procedure to that of compound 43: In a sealed 5 ml microwave vial, a solution of 4-[1-[2-methylsulfanyl-6-(3-pyridyl)pyrimidin-4-yl]-4-piperidyl]morpholine (0.10 g, 0.26 mmol) in 1,4-Dioxane (4 ml) was degassed by bubbling argon through for 5 minutes. (3-fluoro-4-pyridyl)boronic acid (0.076 g, 0.54 mmol), thiophene-2-carbonyloxycopper (0.102 g, 0.54 mmol) and Pd(PPh₃)₄ (0.031 g, 0.03 mmol) were added at room temperature. The reaction was heated under microwave irradiation at 130 °C for 1h. The reaction crude was applied to a SCX column (2 g) and the product was eluted with 2 M NH₃ in MeOH. Solvents were removed and the product was purified by mass directed autopreparative HPLC under basic conditions. The fractions containing product were pooled together and solvents were removed to obtain 44 as off-white solid (10 mg, 9% yield). Purity by LCMS (UV chromatogram, 190-450 nm) > 98%. 1H-NMR (500 MHz, CDCl₃) δ 9.32-9.31 (m, 1H), 8.58-8.51 (m, 1H), 8.96-8.52 (m, 2H), 8.55-8.54 (m, 1H), 8.49-8.47 (m, 1H), 8.10-8.08 (m, 1H), 7.51-7.47 (m, 1H), 7.00 (s, 1H), 4.88-4.84 (m, 2H), 3.41-3.38 (m, 2H), 3.40-3.36 (m, 3H), 3.08-2.95 (m, 4H), 2.47-2.45 (m, 2H), 2.00-1.91 (m, 2H); LRMS (ES⁺) m/z 421 [M+H]⁺.

4-(4-(4-morpholinopiperidin-1-yl)-6-(pyridin-3-yl)pyrimidin-2-yl)pyridine-2-ol (45)
Prepared in an analogous 3-step procedure to that of compound 43: In a sealed vial, a solution of 4-[1-[2-methylsulfanyl-6-(3-pyridyl)pyrimidin-4-yl]-4-piperidyl]morpholine (0.15 g, 0.40 mmol) in THF (8 ml) was degassed by bubbling argon through for 5 minutes. 4-(4,4,5,5-tetramethyl-1,3,2-
dioxaborolan-2-yl)pyridin-2-ol (0.09 g, 0.40 mmol), thiophene-2-carbonyloxcopper (0.12 g, 0.61 mmol) and Pd(PPh₃)₄ (0.05 g, 0.04 mmol) were added at room temperature. The reaction was heated in a sealed tube at 85°C for 16 h. The reaction crude was applied to a SCX column (2 g) and the product was eluted with 2 M NH₃ in MeOH. Solvents were removed under reduced pressure and the product was purified by mass directed auto-preparative HPLC under basic conditions (5-95 prep basic). The fractions containing product were pooled together and solvents were removed to obtain xx as white solid (10 mg, 6% yield). Purity by LCMS (UV chromatogram, 190-450 nm) >97%. ¹H-NMR (500 MHz, d₆ DMSO) δ 11.73 (bs, 1H), 9.43-9.42 (m, 1H), 8.70-8.69 (m, 1H), 8.61-8.60 (m, 1H), 7.56 (dd, 1H, J =4.8, 8.0 Hz), 7.49 (s, 1H), 7.48 (s, 1H, J =6.8 Hz), 7.32 (s, 1H), 7.13 (d, 1H, J = 6.9 Hz), 4.70-4.67 (m, 2H), 3.57-3.55 (m, 4H), 3.06-3.01 (m, 2H), 1.92-1.90 (m, 2H), 1.44-1.36 (m, 2H); LRMS (ES⁺) m/z 419 [M+H]+.

4-(1-(2-(1-methyl-1H-pyrazol-4-yl)-6-(pyridin-3-yl)pyrimidin-4-yl)piperidin-4-yl)morpholine (46)
Prepared in an analogous 3-step procedure to that of compound 40: To a stirred solution of 4-[1-[6-chloro-2-(1-methylpyrazol-4-yl)pyrimidin-4-yl]-4-piperidyl]morpholine (0.070 g, 0.19 mmol) and 3-pyridylboronic acid (0.071 g, 0.58 mmol) in DMF (3 mL), a solution of potassium phosphate (0.122 g, 0.58 mmol) in water (1 mL) was added. The reaction mixture was degassed by bubbling argon through for 5 min and then Pd(PPh₃)₄ (0.011 g, 0.010 mmol) was added. The reaction was heated at 130°C under microwave irradiation for 20 min. Reaction was filtered through Celite® and partitioned between DCM (15 ml) and a saturated aqueous solution of NaHCO₃ (5 ml). The organics phase was dried over MgSO₄ before concentration to dryness. The crude was then purified by preparative HPLC. The fractions containing product were pooled together and solvents were removed to obtain 46 as off-white solid (27 mg, 35% yield). Purity by LCMS (UV chromatogram, 190-450 nm) 96%. ¹H-NMR (500 MHz, CDCl₃) δ 9.21 (m, 1H), 8.70-8.69 (m, 1H), 8.38-8.36 (m, 1H), 8.17 (s, 1H), 8.10 (s, 1H), 7.43-7.40 (m, 1H), 6.74 (s, 1H), 4.66-4.60 (m, 2H), 3.97 (m, 3H), 3.79-3.68 (m,
4H), 3.03-2.97 (m, 2H), 2.62-2.56 (m, 5H), 2.05-1.95 (m, 2H), 1.58-1.54 (m, 2H); LRMS (ES⁺) m/z 406 [M+H]⁺.

4-(1-(6-(pyridin-3-yl)-[2,4'-bipyrimidin]-4-yl)piperidin-4-yl)morpholine (47) Prepared in an analogous 3-step procedure to that of compound 43: In a sealed 5 ml microwave vial, a solution of 4-[1-[2-methylsulfanyl-6-(3-pyridy1)pyrimidin-4-yl]-4-piperidyl]morpholine (0.075 g, 0.20 mmol) in THF (4 ml) was degassed by bubbling argon through for 5 minutes. Pyrimidin-4-y1boronic acid (0.037 g, 0.30 mmol), thiophene-2-carbonyloxycopper (0.058 g, 0.30 mmol) and Pd(PPh₃)₄ (0.023 g, 0.02 mmol) were added at room temperature. The reaction was heated in the sealed tube at 85°C for 18 h. Reaction was filtered through Celite® and partitioned between DCM (10 ml) and NH₃ aq (5 ml). The organic phase was dried over magnesium sulphate and solvents were removed under reduced pressure. The product was purified by the product was purified by mass directed autopreparative HPLC under basic conditions. The fractions containing product were pooled together and solvents were removed to obtain 47 as off-white solid (10 mg, 12% yield). Purity by LCMS (UV chromatogram, 190-450 nm) > 98%. ¹H-NMR (500 MHz, CDCl₃) δ 9.45 (d, 1H, J = 1.3 Hz), 9.23 (dd, 1H, J = 0.7, 2.3 Hz), 8.93 (d, 1H, J = 5.2 Hz), 8.72 (dd, 1H, J = 1.6, 4.8 Hz), 8.46-8.43 (m, 2H), 7.45 (ddd, 1H, J = 0.8, 4.8, 8.0 Hz), 7.00 (s, 1H), 4.77-4.75 (m, 2H), 3.82-3.70 (m, 2H), 3.67-2.55 (m, 5H), 2.11-2.01 (m, 2H), 1.62-1.61 (m, 2H); LRMS (ES⁺) m/z 404 [M+H]⁺.

Scheme S2 (general procedure for intermediates)

4-(1-(6-chloro-2-(2,6-dimethylpyridin-4-yl)pyrimidin-4-yl)piperidin-4-yl)morpholine (54) To a solution of 2,4,6-trichloropyrimidine (52) (10 g, 54.52 mmol) in ethanol (125 ml) at -5°C (salt ice bath), a solution of 4-(4-piperidyl)morpholine (9.28 g, 54.52 mmol) in ethanol (100 ml) was added dropwise followed by N,N-diethylthelanamine (8.27 g, 81.78 mmol). Reaction mixture was stirred at -5°C for 4h. A white precipitate was formed. Solvents were removed under vacuum and the reaction crude was partitioned between DCM (300 ml) and a saturated aqueous solution of NaHCO₃ (2 x 200 ml). The organic phase was dried over MgSO₄, filtered and solvents removed under reduced pressure.
The product was purified by column chromatography (330 g silica cartridge) using A: DCM B: 5%MeOH in DCM as eluents and the following gradient: 2 min hold to 100% A, 20 min ramp to 50% B, 3 min hold to 50% B. Fractions containing pure product were pooled together and solvents were removed to obtain intermediate 4-(1-(2,6-dichloropyrimidin-4-yl)piperidin-4-yl)morpholine as a white solid (5.6 g). Column fractions that contained a mixture of the desired product and a side product resulting from substitution at C-2 were pooled together and solvents removed under vacuum. The mixture was suspended in methanol and DCM was added to obtain a clear solution that was left standing at -20°C. The precipitate was filtered and dried to obtain 4-(1-(2,6-dichloropyrimidin-4-yl)piperidin-4-yl)morpholine as a white solid (1.7 g). Both product fractions were mix together (7.3 g, 42% yield). Purity by LCMS (UV chromatogram, 190-450 nm) > 98%. 1H-NMR (500 MHz, CDCl3) δ 6.42 (s, 1H), 4.41 (broad peak, 2H), 3.72 (broad peak, 4H), 2.01-2.97 (m, 2H), 2.55-2.47 (m, 5H), 1.97-1.94 (m, 2H), 1.54-1.46 (m, 2H); LRMS (ES+) m/z 317 [M+H]+.

To a stirred solution of 4-[1-(2,6-dichloropyrimidin-4-yl)-4-piperidyl]morpholine (0.20 g, 0.63 mmol) and 2,6-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (0.16 g, 0.69 mmol) in 1,4-Dioxane (6 ml), a solution sodium carbonate (0.20 g, 1.89 mmol) in water (2 mL) was added. The reaction mixture was degassed by bubbling argon through for 5 min and then Pd(PPh3)4 (0.036 g, 0.03 mmol) was added. The reaction was heated at 120°C under microwave irradiation for 1h. The reaction crude filtered through Celite and partitioned between DCM (15 ml) and saturated aqueous solution of NaHCO3 (5 ml). The organics phase was dried over MgSO4 before concentration to dryness. The product was purified by column chromatography (4 g silica cartridge) using A: DCM B: 10%MeOH in DCM as eluents and the following gradient: 1 min hold at 100% A, 18 min ramp to 40% B, 5 min hold at 40% B. The fractions containing product were pooled together and solvents were removed to obtain 54 as an off-white solid (42 mg, 15% yield). Purity by LCMS (UV chromatogram, 190-450 nm) 88%. 1H-NMR (500 MHz, d6 DMSO) δ 7.81 (s, 2H), 6.47 (s, 1H), 4.64
(broad peak, 2H), 3.71-3.69 (m, 4H), 3.02-2.97 (m, 2H), 2.58 (s, 6H), 2.56-2.43 (m, 5H), 1.98-1.86 (m, 2H), 1.55-1.47 (m, 2H); LRMS (ES+) m/z 388 [M+H]+.

S3 (general procedure for intermediates)

4-(1-(2-(methylthio)-6-(pyridin-3-yl)pyrimidin-4-yl)piperidin-4-yl)morpholine (58)

To a stirred solution of 4-(4-piperidyl)morpholine (4.36 g, 25.63 mmol) in ethanol (50 ml), a solution of 4,6-dichloro-2-methylsulfanylpyrimidine (56) (5.00 g, 25.63 mmol) in ethanol (50 ml) was added dropwise at room temperature. N,N-diethylethanamine (3.89 g, 38.45 mmol) was then added and the reaction mixture was stirred at room temperature for 3 h. A white precipitate was formed. Solvents were removed under reduced pressured and the reaction crude was purified by filtration through a silica plug. First, impurities were removed with a mixture 1/1 of petroleum ether and ethyl acetate and then the product eluted with methanol. The fractions containing product were pooled together and methanol was removed to obtain 4-[1-(6-chloro-2-methylsulfanyl-pyrimidin-4-yl)-4-piperidyl]morpholine (57) as off-white solid (7.17 g, 84% yield). Purity by LCMS (UV chromatogram, 190-450 nm) >98%. 1H-NMR (500 MHz, CDCl3) δ 6.19 (s, 1H), 4.37 (broad peak, 2H), 3.76 (broad peak, 4H), 2.95-2.90 (m, 2H), 2.69-2.53 (m, 5H), 2.47 (s, 3H), 1.98-1.96 (m, 2H), 1.54-1.48 (m, 2H); LRMS (ES+) m/z 329 [M+H]+.

A solution of 57 (4.00 g, 12.16 mmol) and 3-pyridylboronic acid (2.99 g, 24.3 mmol) in 1,4-dioxane (60 mL) was divided equally into four 20 ml microwave vials. A solution of K3PO4 (5.16 g, 24.32 mmol) in water (20 mL) was prepared and 5 ml were added to each reaction vial. The reaction mixtures were degassed by bubbling argon through for 5 min. Then, Pd(PPh3)4 (0.70 mg, 0.61 mmol) was added and the reaction mixtures were heated under microwave irradiation at 130°C for 30 min. The contents of the three vials were pooled together and the reaction was filtered through Celite and partitioned between DCM (2 x 200 ml) and a saturated aqueous solution of NaHCO3 (20 ml). The
product was purified by column chromatography (120 g silica cartridge) using A: DCM and B: 10% MeOH in DCM as eluents and the following gradient: 1 min hold at 100% A, 20 min ramp to 50%B, 10 min hold at 50%B. The fractions containing were pooled together and the solvents removed to obtain a dark colour solid. The solid was dissolved in methanol (50 ml) and 3-mercaptopropyl ethyl sulfide Silica (2g, 60-200 uM, Phosphonics SPM-32) was added. The stirred suspension was heated at 50°C overnight. The silica was filtered and washed with methanol (100 ml). Methanol was removed under reduced pressure to obtain the 58 as an off-white solid (2.24 g, 50% yield). Purity by LCMS (UV chromatogram, 190-450 nm) 98%. 1H-NMR (500 MHz, CDCl3) δ 9.14 (dd, 1H, J = 0.6, 2.2 Hz), 8.66 (dd, 1H, J = 1.7, 4.8), 8.32-8.29 (m, 1H), 7.37 (ddd, 1H, J =0.7, 4.8, 7.9 Hz), 6.61 (s, 1H), 4.49-4.51 (m, 2H), 3.73-3.71 (m, 4H), 3.00-2.94 (m, 2H), 2.58-2.56 (m, 1H), 2.53-2.46(m, 1H), 1.97-1.95 (m, 2H), 1.52 (ddd, 2H, J = 4.3, 12.3, 24.2 Hz); LRMS (ES+) m/z 372 [M+H]+.

Scheme S4 (general procedure for intermediates)

4,6-dichloro-2-iodopyrimidine (60) To a stirred solution 4,6-dichloropyrimidin-2-amine (4.23 g, 25.8 mmol) and diiodomethane (6.91 g, 25.8 mmol) in anhydrous acetonitrile (36 ml) was added tert-butyl nitrite (11.97 g, 116.1 mmol) at room temperature under nitrogen. The reaction mixture was heated at 80°C for 3 h and 30 min. The reaction crude was concentrated under reduced pressure and purified by column chromatography (80g silica cartridge) using A: Hex, B: ethyl acetate as eluents and the following gradient: 5 min hold at 100%A, 10 min ramp to 20%B, 1 min hold at 20%B. Fractions containing product were pooled together and solvents removed under reduced pressure to obtain 12 as an off-white solid (4.49 g, 63% yield). Purity by LCMS (UV chromatogram, 190-450 nm) 98%. 1H-NMR (500 MHz, CDCl3) δ 7.42 (m, 1H).

4-(1-(6-chloro-2-iodopyrimidin-4-yl)piperidin-4-yl)morpholine (61) To a stirred solution of 4,6-dichloro-2-ido-pyrimidine (60) (6.14 g, 22.33 mmol) in ethanol (120 ml), a solution of 4-(4-piperidyl)morpholine (3.80 g, 22.33 mmol) in 7 ml of ethanol was added in an ice bath.
Diethylethanamine (6.78 g, 66.98 mmol) was then added and the reaction was stirred for 3h at 0°C. Solvents were removed under reduced pressure and the reaction was partitioned between a saturated aqueous solution of NaHCO₃ (50 ml) and DCM (150 ml). Solvents were removed under vacuum and reaction crude was purified by column chromatography (80 g silica cartridge) using A: Hex, B: ethyl acetate as eluents and the following gradient: 1 min hold at 100%A, 25 min ramp to 100%B, 15min hold at 100% B. Fractions containing product were pooled together and solvents removed under reduced pressure to obtain 61 as yellow solid (7 g, 77 % yield). Purity by LCMS (UV chromatogram, 190-450 nm) 98%. ¹H-NMR (500 MHz, CDCl₃) δ 6.44 (s, 1H), 3.72-3.70 (m, 4H), 2.97-2.93 (m, 2H), 2.55-2.53 (m, 4H), 2.50-2.45 (m, 1H), 1.95-1.92 (m, 2H), 1.52-1.43 (m, 2H); LRMS (ES⁺) m/z 409 [M+H]⁺.

4-chloro-6-(4-morpholinopiperidin-1-yl)pyrimidine-2-carbonitrile (62) In a stirred sealed tube a solution of 4-[1-(6-chloro-2-iodo-pyrimidin-4-yl)-4-piperidyl]morpholine (61) (0.29 g, 0.72 mmol) and copper cyanide (0.077 g, 0.86 mmol) in NMP (3 ml) was heated at 120°C for 5h. Reaction crude was applied to a SCX cartridge (5g) and the product was diluted with a solution of 2N NH₃ in methanol. The product was further purified by column chromatography (12g silica cartridge) using A: DCM, B: 10% MeOH in DCM as eluents and the following gradient: 1 min hold at 100%A, 10 min ramp to 50% B and 3 min hold at 50% B. The fractions containing product were pooled together and solvents were removed to obtain 4-chloro-6-(4-morpholinopiperidin-1-yl)pyrimidine-2-carbonitrile (62) as an off-white solid (139 mg, 62% yield). Purity by LCMS (UV chromatogram, 190-450 nm) 90%. ¹H-NMR (500 MHz, CDCl₃) δ 6.44 (s, 1H), 3.73-3.71 (m, 4H), 3.06-3.01 (m, 2H), 2.56-2.48 (m, 5H), 1.99-1.96 (m, 2H), 1.55-1.47 (m, 2H); LRMS (ES⁺) m/z 308 [M+H]⁺.

Biology Materials and Methods

This is included in the supporting information
Abbreviations

ACT  artemisinin-based combination therapy
MMV  Medicines for Malaria Venture
PRR  Parasite Reduction Ratio
SCX  Strong Cation Exchange
SCID  nonobese diabetic scid IL2Rγcnull
WHO  World Health Organisation

Ethical Statements

In vivo antimalarial efficacy studies in *P. berghei* carried out at the Swiss Tropical and Public Health Institute (Basel, Switzerland) adhere to local and national regulations of laboratory animal welfare in Switzerland (awarded permission no. 1731). Protocols are regularly reviewed and revised following approval by the local authority (Veterinäramt Basel Stadt).

In vivo antimalarial efficacy studies using *P. falciparum* in SCID mice carried out at GSK were approved by the Diseases of the Developing World Ethical Committee on Animal Research and carried out in accordance with European Directive 2010/63/EU and the GSK Policy on the Care, Welfare and Treatment of Animals. The animal studies were performed at DDW Laboratory Animal Science facilities accredited by AAALAC. The human biological samples were sourced ethically and their research use was in accord with the terms of the informed consents.

Mouse pharmacokinetics were carried out at the University of Dundee. All regulated procedures on living animals were carried out under the authority of a licence issued by the Home Office under the Animals (Scientific Procedures) Act 1986, as amended in 2012 (and in compliance with EU Directive
EU/2010/63). Licence applications will have been approved by the University's Ethical Review Committee (ERC) before submission to the Home Office. The ERC has a general remit to develop and oversee policy on all aspects of the use of animals on University premises and is a sub-committee of the University Court, its highest governing body.

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Supporting Information

Synthetic details for all compounds, supplementary data tables, additional information on ADMET and pharmacology. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.
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Graphical Abstract

Antimalarial efficacy;
(SCID) ED$_{90}$ = 11.7 mg/kg
30 mg/kg - reduction of parasitaemia within 48h to undetectable levels