Synthesis of novel pyridine and pyrimidine derivatives as potential inhibitors of HIV-1 reverse transcriptase using palladium-catalysed C-N cross-coupling and nucleophilic aromatic substitution reactions

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Abstract

Palladium-mediated cross-coupling reactions are used in the successful construction of a small library of flexible heteroatom-linked diarylpyridine target compounds, including pyridines bearing a secondary amide substituent. Heteroatom-linked diarylpyrimidine derivatives bearing a chlorine substituent are prepared by base-catalysed nucleophilic aromatic substitution reactions without the need for palladium catalysis.

Y = C or N; R = amide, CN, Cl;
R1 = alkyl, aryl; R2 = aryl; X = N(H) or O.

Keywords: Pyridines, pyrimidines, palladium cross-coupling, nucleophilic aromatic substitution
Introduction

The nitrogen-containing heterocycles are widely distributed in nature\(^1\) and have long been of interest to synthetic organic chemists,\(^2\) for example in the synthesis of a wide range of natural products.\(^3\) They have also become privileged motifs in medicinal chemistry and there is an ongoing need for development of new synthetic methodology towards these heterocycles.\(^4\) Many nitrogen heterocycles are therapeutically useful, for example as anticancer,\(^5\) antifungal,\(^6\) and antiviral\(^7\) agents. In particular, pyridine and pyrimidine derivatives continue to generate much attention due to their inherent biological and pharmacological properties as exemplified by their incorporation into FDA-approved non-nucleoside reverse transcriptase inhibitor (NNRTI) anti-HIV drugs and drug candidates.\(^8\) The NNRTIs are a critical component of highly active antiretroviral therapy (HAART) in the treatment of HIV-AIDS.\(^9\) These drugs target the allosteric site of the HIV-1 reverse transcriptase enzyme to induce conformational changes that slow down the rate of nucleotide incorporation and hence viral replication at the polymerase site.\(^10\) The RT enzyme erroneously incorporates mismatched nucleotide bases to produce mutant viral strains that develop resistance towards the drugs that are currently used in HIV treatment.\(^11\)

We previously reported the use of a scaffold-hopping approach\(^12\) to virtually modify a potent imidazo[1,2-\(a\)]pyridine NNRTI lead candidate 1 (IC\(_{50}=0.18\mu\text{M}\) against wild-type HIV) that had been identified in our laboratory (Fig. 1).\(^13\) We then synthesised a small library of 2,6-disubstituted pyridine targets that were based on three scaffolds (pyridyl-benzamide, -benzylamine and -sulfonamide). The rationale behind this approach was to generate analogues with more torsional freedom than 1 that could translate to better repositioning, reorientation and possibly better binding affinity in the mutated RT allosteric site. Fortunately, a potent and novel 2,6-disubstituted pyridylbenzamide 2 (IC\(_{50}=0.7\mu\text{M}\)) was identified as a promising lead candidate against the wild-type (wt) HI virus. In this paper, we describe our efforts towards the synthesis of novel analogues designed through rational modification and functionalisation of compound 2, with the aim of achieving compounds with improved antiviral activity profiles against the wt HI virus. This approach, informed by molecular modelling, identified a series of tri-functionalised pyridine (3 and 4) and pyrimidine (5) target compounds for synthesis (Fig. 1).

Figure 1. Imidazopyridine lead compound 1, pyridylbenzamide hit compound 2 and general structures for tri-functionalised pyridine (3 and 4) and pyrimidine (5) synthetic targets.
Ruiz-Castello and Buchwald\textsuperscript{14} have reviewed the use of palladium catalysed C-heteroatom cross-coupling reactions in the construction of a wide range of compounds, including compounds of medicinal interest, natural products and catalysts. Many other reports attest to the utility of palladium-catalysed methods in the synthesis of biologically active compounds.\textsuperscript{15,16,17} Herein, we describe the use of cheap and readily available pyridines and pyrimidines as a starting point for accessing tri-functionalised target molecules using a combination of palladium-based protocols and $S_NAr$ (addition-elimination) methodologies.

**Results and Discussion**

Our initial synthetic targets were heterocyclic compounds of general structures 3, 4 and 5 (Fig. 1) containing amino and ether linkages, enabling them to be torsionally flexible. *In silico* docking of virtual analogues into the binding site of the target protein crystal structure was performed to identify these targets. Flexible docking perturbations were used to ensure that the potential analogues interacted effectively with key side chain amino acids lining the targeted chemical space in the binding site. Our molecular modelling results indicated that tri-functionalised analogues bearing polar substituents could optimise electrostatic interactions with the hydrophilic groups in the allosteric site of the RT enzyme crystal structure. In particular, target compounds bearing amide substituents were identified as top hits following docking into the allosteric site of the 3MEG RT/Rilpivirine complex crystal structure.\textsuperscript{18} Their binding hypothesis showed targeted hydrogen-bonding interactions with key side chain amino acids; Lys101, Lys103, and Glu138 lining the putative entrance to the site which could be crucial in enhancing their antiviral potency against the RT enzyme. Compounds bearing a nitrile group were also planned for synthesis, based on the presence of this functional group in a number of FDA-approved NNRTIs.\textsuperscript{11}

The initial compounds targeted for synthesis were 2,3,6-trisubstituted pyridines (3) bearing either a nitrile or amide at position 3 and heteroatom-linked aryl groups at positions 2 and 6. Although we were confident that nitriles 3a and 3b could be accessed using a palladium-catalysed reaction similar to that previously reported for pyridines by Maes and co-workers,\textsuperscript{19} we were not sure whether a similar approach would work for compound 3c as a similar palladium-mediated reaction has never previously been reported for pyridines substituted with either a primary or secondary amide. Synthesis of compounds 3a-c is shown in Scheme 1. Readily available dichloronicotinic acid 6, used as a starting point, was converted to the reactive acid chloride via thionyl chloride activation. Quantitative amination gave carboxamide 7, which was dehydrated using POCl$_3$, in the presence of a quaternary ammonium salt, to yield nitrile 8, the spectroscopic data of which was consistent with that previously reported.\textsuperscript{20} Compound 8 was then cross-coupled with 2 equivalents of 4-chlorophenol to give disubstituted compound 3a. Preparation of compound 3b required initial reaction of compound 8 with 0.5 equivalents of 4-chlorophenol to avoid the second substitution reaction, which occurred very readily. Despite the high reactivity of compound 8, attempts to perform a simple nucleophilic substitution reaction in the absence of palladium catalysis met with failure. Reaction of precursor compound 9 with 2-amino-4-methylbenzonitrile furnished compound 3b. Cross-coupling reactions were achieved using a Pd$_2$dba$_3$/BINAP catalysed protocol that we have reported previously.\textsuperscript{12}
Our attempts to access compound 3c, one of the top hits identified from modelling, from primary amide 7 by means of palladium-mediated cross-coupling with 4-chlorophenol followed by 2-amino-4-methylbenzonitrile met with failure as the initial etherification step proved unsuccessful. Several attempts to change the reaction conditions by varying the solvent polarity (THF, 1,4-dioxane, DMF or DME) and/or strength of base (KOtBu, Cs₂CO₃, K₂CO₃ or K₂PO₄ or KHMDs) did not lead to success, as only starting material was recovered. A change in supporting ligand from rac-BINAP to Xantphos also did not achieve the desired C-O coupling. As a result, compound 3c was obtained indirectly from the nitrile derivative 3b using biocatalysis as a key step for selectively hydrolysing the pyridylcarbonitrile (Scheme 1). Employing methodology developed in our laboratory for the hydrolysis of β-aminonitriles,²¹ purified nitrile hydratase enzyme from the bacterial species *Rhodococcus rhodochrous* ATCC BAA-870²² was successfully used to selectively hydrolyse the pyridyl-nitrile group, leaving the benzonitrile group intact. As confirmatory evidence for successful enzymatic conversion and formation of compound 3c, two additional amide protons were observed as a broad singlet which overlapped with the aryl proton doublet signal at 7.49 ppm (J 8.0 ppm, H-3’) in the range 7.51–7.45 ppm of the ¹H NMR spectrum. ¹³C NMR spectroscopy showed the presence a new carbonyl carbon signal at
165.3 ppm and only one CN signal at 117.9 ppm. More significantly, HMBC analysis confirmed the presence of the unreacted CN group on the 2-amino-4-methylbenzyl moiety as evidenced by strong heteronuclear $^3J$ coupling between H-3' at 7.49 ppm and a quaternary nitrile carbon signal at 117.9 ppm. In addition, weaker $^4J$ heteronuclear coupling was observed between H-6' at 7.31 ppm and the CN signal at 117.9 ppm. The presence of the new amide group on the pyridine ring was confirmed by $^3J$ heteronuclear coupling between the H-4 pyridyl proton (a doublet at 8.18 ppm) and a quaternary amide carbonyl signal at 165.3 ppm.

The next compounds identified from modelling that required synthesis were the cyclopropylamide derivatives 3d-e. We decided to attempt a direct palladium-catalysed etherification on secondary amide 10, despite the failure of this reaction on primary amide 7. Amide 10 was synthesized using a similar method to that described for compound 7 via formation of the acid chloride followed by amidation with cyclopropylamine (Scheme 2). We were delighted to find that compound 10, unlike 7, underwent successful reaction with 4-chlorophenol under Pd$_2$dba$_3$/BINAP catalysis to produce precursor 11 in 68% yield. This appears to be the first such report of successful palladium-catalysed cross-coupling on a 2,6-dichloro-substituted pyridine containing a secondary amide functional group. Cyclopropylamide 10 did not display the high reactivity and the tendency to undergo di-substitution seen for nitrile 8. This is not unexpected considering the strongly electron-withdrawing properties of the nitrile group, rendering the pyridine ring even more electrophilic and activating the C-Cl bond to oxidative addition by palladium.$^{23}$

![Scheme 2](image_url)

**Scheme 2. Reagents and conditions:** (a) SOCl$_2$, 80°C, 24 h; 99%; (b) cyclopropylamine, DCM, Et$_3$N, 0°C - RT, 4 h; 99%; (c) 2 mol% Pd$_2$dba$_3$, 6 mol% rac-BINAP, 1.2 eq. 4-chlorophenol, NaO'Bu, THF, 135-140°C, 24 h; 68%; (d) 2 mol% Pd$_2$dba$_3$, 3 mol% Xantphos, piperidine, dioxane, NaO'Bu, 110-120°C, 24 h; 37% from 10; (e) 2 mol% Pd$_2$dba$_3$, 3 mol% Xantphos, 2-amino-4-methylbenzonitrile, dioxane, NaO'Bu, 100-120°C, 24 h; 43% from 10.

Our initial attempt to aminate 11 with piperidine using the cross-coupling reaction conditions (shown in Scheme 1) surprisingly gave a poor conversion (<5%) to the desired product 3d, as most of the starting material was recovered. An alternative amination protocol employing Xantphos (in place of rac-BINAP) as an
ancillary ligand was tested. This approach was explored given Xantphos’ more flexible backbone and larger bite angle (108°) relative to rac-BINAP (93°). Pleasingly, target 3d was formed in a reasonable yield of 54%. The formation of compound 3d in the presence of Xantphos as supporting ligand is consistent with Buchwald’s and van Leeuwen’s observations that ligands possessing larger bite angles make excellent support systems in cross-coupling reactions. The larger bite angles enable such ligands to “stretch” or reposition in space to facilitate the migration of the metal centre towards the energetically unstable transition state involving the Pd-amido complex in palladium-mediated aminations.

Similarly, amination of 11 using rac-BINAP as supporting ligand gave an extremely low yield (11%) of target compound 3e, in comparison with a superior conversion of 63% obtained using Xantphos as ancillary ligand.

The next set of compounds synthesised was the 2,4,6-trisubstituted pyridines (4). In order to obtain the desired nitrile derivatives 4a-b, a similar approach to that described in Scheme 1 was followed. Conversion of carboxylic acid 12 to the acid chloride was followed immediately by amidation to give compound 13 and dehydration to the corresponding 2,6-dichloroisonicotinonitrile 14. Similar to nicotinonitrile derivative 8, isonicotinonitrile 14 was highly reactive to 4-chlorophenol under Pd$_2$dba$_3$/BINAP cross-coupling conditions and both chlorine atoms were easily displaced to give di-substituted compound 4a (Scheme 3). In order to obtain mono-substituted compound 15, 0.5 equivalents of 4-chlorophenol were used in the reaction. Subsequent reaction of precursor 15 with 2-amino-4-methylbenzonitrile under similar conditions gave 4b.

**Scheme 3. Reagents and conditions:** (a) SOCl$_2$, 80°C, 24 h: 98%; (b) aq. NH$_3$, 0°C - RT, 4 h; 99% (c) SOCl$_2$, 80°C, 24 h: 99%; (d) 2 mol% Pd$_2$dba$_3$, 6 mol% rac-BINAP, 2 eq. 4-chlorophenol, NaO$_i$Bu, THF, 100-110°C, 24 h: 99%; (e) 2 mol% Pd$_2$dba$_3$, 6 mol% rac-BINAP, 0.5 eq. 4-chlorophenol, NaO$_i$Bu, THF, 100-110°C, 24 h; (f) 2 mol% Pd$_2$dba$_3$, 3 mol% rac-BINAP, 2-amino-4-methylbenzonitrile, 1,4-dioxane, NaO$_i$Bu, 110-120°C, 24 h; 83% from 14.

As a result of the successful preparation of compounds 3d and 3e using palladium-catalysed cross-coupling reactions directly on the secondary amide starting material, we used a similar approach for the preparation of cyclopropylamide derivatives 4c-d (Scheme 4). Conversion of 12 to the acid chloride, followed
by amidation with cyclopropylamine gave compound 16. Compound 16 was converted into the mono-substituted precursor 17 using Pd$_2$dba$_3$/BINAP cross-coupling conditions. It is interesting to note that compound 17, being less hindered than the nicotinic acid isomer 11, did undergo cross-coupling using the rac-BINAP supported protocol to give compounds 4c-d in a reasonable yield of 53%. The yields of 4c and 4d did, however, show modest increases to 67% and 75%, respectively, when using Xantphos as ligand.

Scheme 4. Reagents and conditions: (a) SOCl$_2$, 80°C, 24 h; 98%; (b) cyclopropylamine, DCM, DMAP, Et$_3$N, 0°C-RT, 4 h, 99%; (c) 2 mol% Pd$_2$dba$_3$, 6 mol% rac-BINAP, 1.2 eq. 4-chlorophenol, NaO'Bu, THF, 100-110°C, 24 h; 71%; (d) 2 mol% Pd$_2$dba$_3$, 6 mol% rac-BINAP, piperidine, 1,4-dioxane, NaO'Bu, 110-120°C, 24 h; 53%; (e) 2 mol% Pd$_2$dba$_3$, 6 mol% rac-BINAP, 2-amino-4-methylbenzonitrile, 1,4-dioxane, NaO'Bu, 110-120°C, 24 h; 53%.

It is interesting to note that when Brimble and co-workers$^{26}$ used 2,6-dichloro-N,N-diisopropylisonicotinamide as the substrate in a palladium-catalysed cross-coupling reaction with m-anisidine, they found this hindered tertiary amide to be unreactive, returning mostly starting material and only 14% of the desired mono-arylation product from the reaction. This is in stark contrast to the success we achieved using a palladium-catalysed cross-coupling approach on the secondary amide derivative 16.

The tri-functionalised pyrimidine targets of general structure 5, which mimicked the NNRTI diarylpyrimidine (DAPY) type framework, were selected for synthesis given that the presence of one chlorine atom and two hydrophobic aryl substituents were expected to enhance hydrophobic interactions in the RT NNIBP. The starting point for the synthesis of compounds 5a-k was chlorination of commercially available barbituric acid (18) to give 2,4,6-trichloropyrimidine (19) using a previously described POCl$_3$/quaternary ammonium salt-activated methodology.$^{27}$ This method, applied here for the first time on a pyrimidine substrate, appears to represent a significant improvement on the traditional halogenation protocol employing...
secondary amines and POCl₃. Due to the high reactivity of 19, target molecules 5a-k were accessed via a general addition-elimination methodology originally reported by Delia and co-workers (Scheme 5).²⁸

\[ \text{Scheme 5. Reagents and conditions} \]
\[ (a) \text{POCl}_3, \text{Et}_4\text{NCl}, 120^\circ \text{C}, 4 \text{ h}, 78\%; (b) \text{acetone, aq. Na-phenoxide (1.2 eq.), } 0^\circ \text{C-RT, 2 h; (c) 1.1 eq. amine, KO}^\text{t}\text{Bu, THF, RT, 4 h: 5a-k, 46-84\% from 19.} \]

Reaction of 2,4,6-trichloropyrimidine (19) in ice-cold acetone with an aqueous solution of an appropriate sodium phenoxide salt gave crude precursors 20a-e (Scheme 5), which were further reacted with various nitrogen nucleophiles to give the final products. Reaction of 2-aminoo-5-methylpyridine gave products 5a-e in moderate to good yields of 57-84% over two steps from 19 while reaction of 20e with 2-aminoo-5-chloropyrimidine resulted in product 5f in 76% from 19. Ours is the first report of the successful use of aminopyridine or aminopyrimidine nucleophiles on precursors such as 20. It is interesting to note that our reactions proceeded without the need for palladium catalysis, but for substrates lacking the 4-chloro substituent, it has been reported in the patent literature that palladium catalysis was required for reaction with nitrogen nucleophiles.²⁹

Use of various aniline derivatives in the reaction gave products 5g-k in lower yields (46-61% from 19) than seen for the aminopyridine or aminopyrimidine nucleophiles.
Antiviral Assay for novel pyridines and pyrimidines

The synthesised pyridines and pyrimidines were screened against the wild-type HI virus with our pyridylbenzamide lead compound 2 and nevirapine (NVP) being included as positive controls. As shown in Table 1, the results display the activity [concentrations of compounds that were required to inhibit 50% of viral activity (IC\textsubscript{50})] and toxicity [compound concentration reducing cell viability by 50% (CC\textsubscript{50})]. The selectivity index (S.I. = CC\textsubscript{50}/IC\textsubscript{50}) was included as an indicator of the degree to which each tested compound was selective towards reducing viral activity versus cell viability.

Table 1. In vitro anti-HIV assay for novel pyridine target compounds.

<table>
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<th>S. Index</th>
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<td>S. D.</td>
<td>CC\textsubscript{50} (µM)</td>
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As shown in Table 1 unfortunately none of the compounds prepared showed activity against wild-type HIV. However, cytotoxicity data revealed some interesting trends. All the nicotinic acid-derived analogues (carbonitrile, carboxamide, and cyclopropylamide) displayed modest (CC\textsubscript{50} = 30.78 µM for 3a) to excellent (3c-e) cytotoxic profiles in the in vitro assay. In comparison, the isonicotinic acid based targets bearing a cyclopropyl carboxamide (4c: CC\textsubscript{50} = 1.52 µM; 4d: CC\textsubscript{50} = 8.34 µM) were highly toxic and adversely affected cell viability. Interestingly, where a nitrile group replaced the cyclopropylamide, toxicity was dramatically reduced.
(4a: CC<sub>50</sub> = 54.42 µM and 4b: CC<sub>50</sub> > 100 µM). The 2,4,6-trichloropyrimidine-derived compounds 5a-k displayed intermediate to low levels of toxicity.

Although compounds 5a-k are torsionally flexible, the general lack of activity against wild-type HIV displayed by this series of analogues could be attributed to the inefficiency of the 4-Cl group to make meaningful electrostatic contacts through halogen bonding with key hydrophilic amino acid side chains (K101, N103, and E138) that line the putative entrance to the RT allosteric site.

**Conclusions**

We designed and successfully synthesised a small library of novel pyridine and pyrimidine derivatives as potential NNRTIs. These compounds were designed to resemble a DAPY ‘horse-shoe’ type configuration on the premise that they would exhibit torsional flexibility as well as targeted interactions with key hydrophobic and hydrophilic amino acid residues surrounding the allosteric binding pocket of the 3MEG-RT crystal structure. We successfully extended our already developed Pd-catalysed cross-coupling protocol towards accessing a new set of 2,3,6- (3) and 2,4,6-tri-functionalised pyridine derivatives (4), with the reactions also proving successful on pyridine derivative bearing a secondary amide substituent. As expected, 2,6-dichloropyridine derivatives bearing the electron-withdrawing nitrile group were more reactive under palladium catalysed cross-coupling conditions than the corresponding cyclopropylamide derivatives, while a derivative bearing a primary amide was completely unreactive under the same conditions. 2,4,6-Trichloropyrimidine (19) displayed facile sequential C-O and C-N displacement reactions under base-catalysed nucleophilic conditions to afford the corresponding 2,6-disubstituted pyrimidines 5a-k. These reactions did not require application of the more expensive palladium-based protocol. One of the target molecules, 3c, was accessed via the use of a biocatalytic approach as a key step towards the selective hydrolysis of a pyridyl-carbonitrile group in the presence of a benzonitrile group. Despite the favourable binding conformations elicited by the synthetic targets during the preliminary molecular modelling exercise, none of the compounds were found to be active against the wild-type HIV virus.

**Experimental Section**

**General.** All solvents and amines were freshly distilled prior to use. Other reagents were used as purchased from Sigma-Aldrich. All infrared spectra were recorded neat using a Bruker TENSOR 27 single channel infrared infrared spectrometer. All melting points are uncorrected and were performed using open capillary tubes on a Stuart SMP 10 melting point apparatus. ¹H and ¹³C NMR spectra were recorded using either a Bruker AVANCE 111 300 or 500 MHz spectrometer in deuterated chloroform (CDCl₃) with trimethylsilane (TMS) as internal standard (δ = 0) for ¹H NMR, and CDCl₃ (δ = 77.0 ppm) for ¹³C NMR. The chemical shift (δ) is reported in ppm and the coupling constants (J) in Hz. High resolution mass spectral data was collected on a Waters Synapt G2 using an ESI positive source and a cone voltage of 15 V. TLC was performed on aluminium-backed Merck silica gel 60 F₂₅₄ plates. The purification of compounds by column chromatography was performed using gravity (particle size 0.063-0.200 mm) or flash (particle size 0.040-0.063 mm) silica gel 60 purchased from Merck. Where the word ‘dioxane’ is used, it should be taken to mean ‘1.4-dioxane’.

**Synthetic Methods**
General preparation of amides 7 and 13. An appropriate aromatic carboxylic acid 6 or 12 (382 mg, 2.0 mmol) and a magnetic stirrer bar were placed into a 50 ml round-bottomed flask containing thionyl chloride (10 ml). The mixture was gently stirred and refluxed in an oil bath at 80°C for 24 h. After cooling to room temperature, excess thionyl chloride was removed in vacuo to leave a crude residue of the acid chloride that was subsequently used without further purification. A solution of the acid chloride (2.0 mmol) in dichloromethane (5 ml) was cautiously added to an ice-cold mixture of excess 25% aqueous ammonia (5 ml) and pyridine (1 ml) in dichloromethane (15 ml). The mixture was stirred at 0°C (30 min) and then allowed to warm to room temperature for 4 h. The reaction was washed successively with aqueous saturated NaHCO₃ (2 x 10 ml), saturated brine solution (10 ml), distilled water (2 x 10 ml) and finally dried over anhydrous Na₂SO₄. After removal of the solvent, the crude mixture was purified by silica gel flash column chromatography, eluting with 5–10% EtOAc/hexane.

2,6-Dichloronicotinamide (7). Reaction of 2,6-dichloronicotinoyl chloride (411 mg, 2 mmol) gave 2,6-dichloronicotinamide 7 (380 mg, 98%) as a pale yellow solid. ¹H NMR (500 MHz, CDCl₃) δ 8.23 (d, J 7.9 Hz, 1H), 7.40 (d, J 7.9 Hz, 1H), 6.67 (br s, 1H), 6.24 (br s, 1H).

2,6-Dichloroisonicotinamide (13) Reaction of 2,6-dichloroisonicotinoyl chloride (411 mg, 2 mmol) gave 2,6-dichloroisonicotinamide 16 (381 mg, 99%) as a pale yellow solid. ¹H NMR (500 MHz, CDCl₃) δ 7.87 (br s, 1H), 7.85 (br s, 1H), 7.59 (s, 2H).

General preparation of carbonitriles 8 and 14. The appropriate carboxamide 7 or 13 (189 mg, 0.99 mmol) was subjected to catalytic amounts of tetraethylammonium chloride (5% w/w) and POCl₃ (5 ml) and heated under reflux at 80°C for 24 h. Excess POCl₃ was removed in vacuo to leave a crude residue which was diluted with dichloromethane (10 ml) and filtered. The filtrate was washed successively with saturated aqueous K₂CO₃ (2 x 5 ml) and distilled water (5 ml). After drying over anhydrous Na₂SO₄, the solvent was evaporated to yield carbonitrile 8 or 14 which was sufficiently pure for use in the next reaction without purification.

2,6-Dichloronicotinonitrile (8) 2,6-Dichloronicotinonitrile (8) was isolated as an off-white solid (152 mg, 89% yield). ¹H NMR (300 MHz, CDCl₃) δ 7.95 (d, J 8.1 Hz, 1H), 7.43 (d, J 8.1 Hz, 1H). 2,6-Dichloroisonicotinonitrile (14) 2,6-Dichloroisonicotinonitrile (18) was isolated as a white solid (169 mg, 99% yield). ¹H NMR (500 MHz, DMSO-d₆) δ 8.23 (s, 2H).

General preparation of cyclopropylamides 10 and 16. A solution of an appropriate acid chloride (2.0 mmol) in dichloromethane (5 ml) was cautiously added to an ice-cold mixture of cyclopropylamine (120 mg, 2.1 mmol) and pyridine (1 ml) in dichloromethane (15 ml). The mixture was stirred at 0°C (30 min) and then allowed to warm to room temperature for 4 h. The reaction was washed successively with aqueous saturated NaHCO₃ (2 x 10 ml), saturated brine solution (10 ml), distilled water (2 x 10 ml) and finally dried over anhydrous Na₂SO₄. After evaporating the solvent, the crude mixture was purified by silica gel flash column chromatography, eluting compound 10 or 16 with 5–10% EtOAc/hexane.

2,6-Dichloro-N-cyclopropylnicotinamide (10). 2,6-Dichloro-N-cyclopropylnicotinamide 10 (380 mg, 99%) was obtained as a pale yellow solid. ¹H NMR (300 MHz, CDCl₃) δ 8.11 (d, J 7.9 Hz, 1H), 7.37 (d, J 7.9 Hz, 1H), 6.61 (br s, 1H), 2.97-2.89 (m, 1H), 0.95-0.88 (m, 2H), 0.69-0.64 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 164.4, 152.1, 151.5, 146.8, 124.6, 120.6, 23.5, 6.8.
2,6-Dichloro-N-cyclopropylisonicotinamide (16). 2,6-Dichloro-N-cyclopropylisonicotinamide (16) (380 mg, 99%) was obtained as a pale yellow solid. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.55 (s, 2H), 6.43 (s, 1H), 2.96–2.84 (m, 1H), 0.96–0.87 (m, 2H), 0.69–0.62 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$164.8, 151.8, 142.3, 123.6, 23.4, 6.9.

General procedure for the preparation of compounds 3a and 4a. Tris-(dibenzylideneacetone)-di-palladium (0) [Pd$_2$dba$_3$] (28 mg, 3 mol %), rac-BINAP (38 mg, 6 mol %), 1,4-dioxane (3–5 ml) and a magnetic stirrer bar were added to an oven-dried 10 ml round-bottomed flask and purged with nitrogen. The flask was sealed and heated with stirring at 80°C in an oil bath for 5 min. Thereafter, the appropriate carbonitrile substrate (1.0 equivalent), 4-chlorophenol (2.0 equivalents) and sodium tert-butoxide (1.5 mmol) were added and the sealed reaction heated at 110–120°C for 24 h. The cooled reaction mixture was filtered and the excess solvent removed in vacuo to leave a crude mixture which was re-dissolved in dichloromethane and filtered. The filtrate was washed successively with aqueous saturated NaHCO$_3$ (10 ml), and distilled water (2 x 10 ml). After drying over anhydrous Na$_2$SO$_4$ and evaporating excess solvent, the crude mixture was purified by silica gel flash column chromatography, eluting with 0–3% EtOAc/hexane.

2,6-Bis(4-chlorophenoxy)nicotinonitrile (3a).$^{22}$ Reaction of 2,6-dichloronicotinonitrile (9) (173 mg, 1.0 mmol) with 4-chlorophenol (256 mg, 2.0 mmol) gave product 3a (276 mg, 78%) as a white oil. IR (cm$^{-1}$): 3043 (CH str.), 2218 (CN), 1553 (C=N str.), 1457 (C=C); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.94 (d, J 8.3 Hz, 1H), 7.25–7.22 (m, 4H), 6.98–6.93 (m, 2H), 6.91–6.87 (m, 2H), 6.63 (d, J 8.3 Hz, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 164.1, 161.1, 150.8, 145.9, 132.1, 131.1, 129.4, 123.0, 114.8, 104.8; HRMS (ES$^+$) Calculated for C$_{18}$H$_{11}$Cl$_2$N$_2$O$_2$ [M+H]$^+$: 357.0179, found: 357.0183.

2,6-Bis-(4-chlorophenoxy)isonicotinonitrile (4a)$^{22}$ Reaction of 2,6-dichloronicotinonitrile 14 (173 mg, 1.0 mmol) with 4-chlorophenol (256 mg, 2.0 mmol) gave product 4a (354 mg, 99%) as a white oil. IR (cm$^{-1}$): 3001 (CH str.), 2213 (CN), 1566 (C=N str.), 1470 (C=C); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.42–7.38 (m, 2H), 7.29–7.26 (m, 2H), 7.25 (d, J 0.9 Hz, 1H), 7.11–7.07 (m, 2H), 7.06 (d, J 0.9 Hz, 1H), 6.96–6.93 (m, 2H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 162.9, 162.8, 162.5, 151.1, 150.9, 150.6, 131.3, 130.9, 130.0, 129.6, 125.8, 125.3, 122.8, 122.6, 119.9, 115.9, 115.0, 112.1, 106.6; HRMS (ES$^+$) Calculated for C$_{18}$H$_{11}$Cl$_2$N$_2$O$_2$ [M+H]$^+$: 357.0198, found: 357.0181.

General procedure for the preparation of compounds 3b and 4b. Tris-(dibenzylideneacetone)-di-palladium (0) [Pd$_2$dba$_3$] (28 mg, 3 mol %), rac-BINAP (38 mg, 6 mol %), 1,4-dioxane (3–5 ml) and a magnetic stirrer bar were added to an oven-dried 10 ml round-bottomed flask and purged with nitrogen. The flask was sealed and heated with stirring at 80°C in an oil bath for 5 min. Thereafter, the appropriate carbonitrile substrate (2.0 mmol), 4-chlorophenol (128 mg, 1.0 mmol) and sodium tert-butoxide (3.0 mmol) were added and the sealed reaction heated at 110–120°C for 24 h. The cooled reaction mixture was filtered and the excess solvent removed in vacuo to leave a crude mixture which was re-dissolved in dichloromethane and filtered. The filtrate was washed successively with aqueous saturated NaHCO$_3$ (10 ml), and distilled water (2 x 10 ml). After drying over anhydrous Na$_2$SO$_4$ and evaporating excess solvent, the crude mixture was purified by silica gel flash column chromatography, eluting with 0–3% EtOAc/hexane. This precursor (1 equivalent) was subjected to a second palladium-mediated reaction with 2-amino-4-methylbenzonitrile (1.2 equivalents) as described above to give the desired final product after purification by silica gel column chromatography.

6-(4-Chlorophenoxy)-2-((2-cyano-5-methylphenyl)amino)nicotinonitrile (3b)$^{22}$ Reaction of 2,6-dichloronicotinonitrile 8 (346 mg, 2.0 mmol) gave 6-(4-chlorophenoxy)nicotinonitrile 9 (257 mg, 87% with respect to the phenol) as a white oil. $^1$H NMR (300MHz, CDCl$_3$): $\delta$ 7.94 (d, J 8.3 Hz, 1H), 6.63 (d, J 8.3 Hz, 1H), 7.26–7.21 (m, 2H), 6.98–6.94 (m, 1H), 6.91–6.86 (m, 1H);
Further reaction of $6$-(4-chlorophenoxo)nicotinonitrile ($9$) (133 mg, 0.5 mmol) with 2-amino-4-methylbenzonitrile (80 mg, 0.6 mmol) gave product $3b$ (156 mg, 87\%) as a yellow oil. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.94 (d, J 8.3 Hz, 1H), 6.63 (d, J 8.3 Hz, 1H), 7.26–7.21 (m, 2H), 6.98–6.94 (m, 1H), 6.91–6.86 (m, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 160.1, 154.9, 151.2, 145.2, 143.9, 141.7, 132.2, 131.2, 129.8, 127.9, 123.8, 123.6, 120.1, 117.2, 115.4, 106.0, 98.9, 22.2; HRMS (ES$^+$) Calculated for C$_{20}$H$_{14}$ClN$_2$O $[M+H]^+$: 361.0856, found: 361.0837.

2-(4-Chlorophenoxy)-6-((2-cyano-5-methylphenyl)amino)isonicotinonitrile ($4b$). Reaction of 2,6-dichloroisonicotinonitrile ($14$) (346 mg, 2.0 mmol) gave 6-(4-chlorophenoxy)isonicotinonitrile ($18$) (265 mg, 99\% with respect to the phenol) as a white oil. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.43–7.38 (m, 2H), 7.25 (d, J 1.0 Hz, 1H, H-3), 7.11–7.07 (m, 2H), 7.06 (d, J 1.0 Hz, 1H, H-5). Further reaction of 6-(4-chlorophenoxy)isonicotinonitrile ($15$) (133 mg, 0.5 mmol) with 2-amino-4-methylbenzonitrile (80 mg, 0.6 mmol) in the presence of rac-BINAP gave product $4b$ (151 mg, 84\%) as a pale yellow solid. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.14 (d, J 1.0 Hz, 1H), 7.86 (d, J 1.0 Hz, 1H), 7.76 (s, 1H), 7.67 (d, J 8.4 Hz, 1H), 7.41–7.35 (m, 4H), 7.17–7.11 (m, 2H), 2.55 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$): 154.7, 150.9, 145.9, 142.1, 133.2, 129.6, 124.1, 123.3, 120.6, 119.4, 117.2, 115.4, 113.1, 106.7, 99.6, 22.4; HRMS (ES$^+$) Calculated for C$_{20}$H$_{14}$ClN$_2$O $[M+H]^+$: 361.0856, found: 361.0837.

6-(4-Chlorophenoxy)-2-(2-cyano-5-methylphenyl)amino)-nicotinamide ($3c$). 6-(4-Chlorophenoxy)-2-(2-cyano-5-methylphenyl)amino)-nicotinonitrile ($3b$) (20 mg) was dissolved in methanol (1 ml). After addition of Tris buffer (pH 9.0), purified Rhodochrous rhodochrous nitrile hydratase enzyme (20 mg) was added and the reaction mixture was equilibrated at 37°C with agitation for 24–72 h whilst samples were collected at 12 h intervals to monitor the reaction progress. After reaction completion, product $3c$ (13 mg, 64\%) was obtained as a light yellow solid. Mp: 204–205°C; IR (cm$^{-1}$): 3633 and 3480 and 3380 (NH str.), 3010 (CH str.), 2216 (CN). A mixture of these products was dissolved in methanol (1 ml). After addition of K$_2$CO$_3$ (10 eq.) and sealed reaction heated at 135–140°C for 24 h. The cooled reaction mixture was filtered and the excess solvent removed in vacuo to leave a crude reaction which was re-dissolved in dichloromethane and filtered. The filtrate was washed successively with aqueous saturated NaHCO$_3$ (10 ml), and distilled water (2 x 10 ml). After drying over anhydrous Na$_2$SO$_4$ and evaporating excess solvent, the crude mixture was purified by silica gel flash column chromatography, eluting the precursor with 0–3\% EtOAc/hexane. Tris-(dibenzylideneacetone)-di-palladium (0) [Pd$_2$db$_3$] (28 mg, 3 mol\%) and sodium tert-butoxide (2.4 mmol) were added and the sealed reaction heated at 135–140°C for 5 min. The crude reaction mixture was filtered and the excess solvent removed in vacuo to leave a crude mixture which was re-dissolved in dichloromethane and filtered. The filtrate was washed successively with aqueous saturated NaHCO$_3$ (10 ml), and distilled water (2 x 10 ml). After drying over anhydrous Na$_2$SO$_4$ and evaporating excess solvent, the crude mixture was purified by silica gel flash column chromatography, eluting the precursor with 0–3\% EtOAc/hexane.
work-up (as described above) the crude mixture was purified by silica gel flash column chromatography, eluting the products with 10–25% EtOAc/hexane.

2-(4-Chlorophenoxy)-N-cyclopropyl-6-(piperidin-1-yl)nicotinamide (3d). Reaction of 2,6-dichloro-N-cyclopropylnicotinamide 10 (232 mg, 1.0 mmol) gave precursor 11 (220 mg, 68%) as a white solid. 1H NMR (500 MHz, CDCl₃) δ 8.56 (d, (J 8.0 Hz, 1H), 7.68 (s, 1H), 7.41 (d, J 8.3 Hz, 2H), 7.16 (d, J 8.0 Hz, 1H), 7.10 (d, J 8.4 Hz, 2H), 2.98–2.91 (m, 1H), 0.88 (q, (J 5.9, 5.9, 5.5 Hz, 2H), 0.63–0.58 (m, 2H); 13C NMR (126 MHz, CDCl₃) δ 163.7, 158.8, 151.0, 150.5, 144.7, 131.4, 129.9, 123.1, 119.9, 115.3, 23.2, 6.9. 2-Chloro-6-(4-chlorophenoxy)-N-cyclopropylnicotinamide (11) (162 mg, 0.5 mmol) was further reacted with piperidine (51 mg, 0.6 mmol) and with Xantphos (18 mg, 1.5 mol%) as supporting ligand to give compound 3d (99 mg, 54%) as pale yellow oil. IR (cm⁻¹): 3438 (NH str.), 3020 (CH str.), 1680 (C=O), 1572 (C-N); 1452 (C=C); 1H NMR (500 MHz, CDCl₃) δ 8.32 (d, (J 8.7 Hz, 1H), 7.58 (br s, 1H), 7.35 (d, J 8.8 Hz, 2H), 7.07 (d, J 8.8 Hz, 2H), 6.34 (d, J 8.8 Hz, 1H), 3.38–3.31 (m, 4H), 2.94–2.88 (m, 1H), 1.62–1.56 (m, 2H), 1.50–1.44 (m, 4H), 0.85–0.80 (m, 2H), 0.59–0.53 (m, 2H); 13C NMR (126 MHz, CDCl₃) δ 165.7, 159.2, 158.2, 151.4, 143.3, 130.2, 129.2, 123.6, 102.9, 100.9, 45.8, 25.3, 24.6, 22.8, 6.9; HRMS (ES⁺) Calculated for C₂₅H₂₃ClN₂O₂ [M+H⁺]: 372.1471, found: 372.1457.

6-(4-Chlorophenoxy)-2-[(2-cyano-5-methylphenyl)amino]-N-cyclopropylnicotinamide (3e). Precursor 2-chloro-6-(4-chlorophenoxy)-N-cyclopropylnicotinamide (11) (162 mg, 0.5 mmol) was further reacted with 2-amino-4-methylbenzonitrile (80 mg, 0.6 mmol) to give product 3e (24 mg, 11%; rac-BINAP) or Xantphos (142 mg, 63%) as a pale yellow oil. IR (cm⁻¹): 3321 (NH str.) 3029, 2972 (CH str.), 2231 (CN), 1683 (C=O str.); 1H NMR (500 MHz, CDCl₃) δ 8.51 (d, J 8.4 Hz, 1H), 7.64 (br s, 1H), 7.57 (s, 1H), 7.43–7.40 (m, 2H), 7.37 (d, J 7.9 Hz, 1H), 7.16–7.13 (m, 2H), 7.00 (s, 1H), 6.78 (d, J 8.6 Hz, 1H), 6.59 (d, J 8.4 Hz, 1H), 2.97–2.92 (m, 1H), 2.08 (s, 3H), 0.89–0.84 (m, 2H), 0.63–0.58 (m, 2H); 13C NMR (126 MHz, CDCl₃) δ 164.8, 159.6, 154.0, 151.2, 145.3, 143.8, 141.9, 132.1, 131.2, 129.9, 123.8, 123.3, 119.5, 117.2, 107.9, 106.0, 98.1, 23.0, 22.2, 6.9; HRMS (ES⁺) Calculated for C₂₃H₂₂ClN₂O₂ [M+H⁺]: 417.1118, found: 417.1090.

6-(4-Chlorophenoxy)-N-cyclopropyl-2-[(piperidin-1-yl)jisonicotinamide (4c). Reaction of 2,6-dichloro-N-cyclopropylisonicotinamide (16) (232 mg, 1.0 mmol) gave precursor 17 (230 mg, 71%) as a white solid. 1H NMR (500 MHz, CDCl₃) δ 7.39–7.34 (m, 2H), 7.29–7.24 (m, 2H), 7.09–7.06 (m, 2H), 6.30–6.29 (m, 1H), 2.94–2.86 (m, 1H), 0.93–0.88 (m, 2H), 0.67–0.62 (m, 2H); 13C NMR (126 MHz, CDCl₃) δ 165.2, 163.2, 151.7, 149.9, 147.8, 130.7, 129.8, 122.5, 120.6, 116.1, 107.5, 23.4, 6.9. Further reaction of 2-chloro-6-(4-chlorophenoxy)-N-cyclopropylisonicotinamide (17) (162 mg, 0.5 mmol) with piperidine (128 mg, 1.5 mmol) and with rac-BINAP (28 mg, 3 mol%) or Xantphos (18 mg, 2 mol%) as supporting ligand to give compound 4c (99 mg, 53%) or (125 mg, 67%) as a yellow oil, respectively. 1H NMR (CDCl₃, 300 MHz) δ 7.39–7.28 (m, 2H), 7.11–7.03 (m, 2H), 6.89–6.86 and 6.81–6.79 (2 x m, 1H), 6.67–6.64 and 6.61–6.59 (2 x m, 1H), 6.25–6.10 (m, 1H), 3.70–3.26 (m, 4H), 2.95–2.78 (m, 1H), 1.70–1.52 (m, 6H), 0.96–0.91 (m, 2H), 0.70–0.52 (m, 2H); 13C NMR (126 MHz, CDCl₃) δ 167.9, 167.0, 162.7, 159.3, 158.6, 152.8, 146.9, 129.8, 129.3, 122.6, 107.2, 102.9, 98.9, 94.0, 46.0, 25.4, 24.6, 23.2, 6.8; HRMS (ES⁺) Calculated for C₂₀H₁₅ClN₂O₂ [M+H⁺]: 372.1479, found: 372.1424.

2-(4-Chlorophenoxy)-6-[(2-cyano-5-methylphenyl)amino]-N-cyclopropylisonicotinamide (4d). Precursor 2-chloro-6-(4-chlorophenoxy)-N-cyclopropylisonicotinamide (17) (162 mg, 0.5 mmol) was further reacted with 2-amino-4-methylbenzonitrile (80 mg, 0.6 mmol) and with rac-BINAP or Xantphos as supporting ligand to give compound 4d (122 mg, 53%) or (157 mg, 78%) as a brown solid. 1H NMR (500 MHz, CDCl₃) δ 7.94 and 7.68 (2 x br s, 2H), 7.46 (d, J 7.9 Hz, 1H), 7.38–7.33 (m, 1H), 7.17–7.04 (m, 4H), 6.92 (d, J 7.9 Hz, 1H), 6.83–6.69 (m, 1H), 6.49 and 6.42 (2 x br s, 1H), 2.96–2.83 (m, 1H), 2.41 (s, 3H), 0.91–0.85 (m, 2H), 0.68–0.62 (m, 2H); 13C NMR (126 MHz, CDCl₃) δ 165.8, 154.7, 150.4, 146.3, 145.5, 142.1, 132.6, 132.1, 129.6, 124.1, 123.3, 120.6, 119.4,
2,4,6-Trichloropyrimidine (19). Barbituric acid (18) (5.07 g, 44.5 mmol) and tetraethyl ammonium chloride (6.10 g, 44.5 mmol) were added to a 100ml 3-necked round-bottomed flask chilled in ice. After thoroughly mixing the reagents, POCI₃ (15 ml) was cautiously added over 30 min. The reaction mixture was heated at 130–140°C for 24 h. After cooling the reaction to room temperature and removing of excess POCI₃ in vacuo, crushed ice (75 g) was added to the brown mixture. The mixture was stirred and allowed to warm to room temperature over 4 h. The mixture was extracted with ethyl acetate (7 x 100 ml), dried over Na₂SO₄ and the organic solvent was evaporated. The crude product was purified by flash silica gel column chromatography using 3–5% EtOAc/Hex to give 19 (6.33 g, 78%) as a pale-yellow oil. ¹H NMR (500 MHz, CDCl₃) δ 7.39 (s, 1 H).

General preparation of compounds 5a-m. 2,4,6-Trichloropyrimidine (19) (1 eq.) dissolved in acetone (5 ml) was placed in a 25 ml round-bottomed flask chilled in ice (0-5°C). A solution of the appropriate substituted phenoxy (4-chloro-, 2,4-dichloro-, 3,5-dichloro-, 4-fluoro-, 4-trifluoromethyl-), made by mixing the phenol (1.05 eq.) and NaOH (1.05 eq.) in water (5 ml), was slowly added with stirring. The reaction was stirred for 1 h under the same conditions. Thereafter, the mixture was allowed to warm to room temperature while stirring for a further 4 h. After evaporating the excess solvent, the crude product was diluted with ethyl acetate (20 ml) and washed successively with saturated aqueous NaHCO₃ (10 ml) and water (10 ml). The organic layer was dried over Na₂SO₄ and filtered. The solvent was evaporated in vacuo to give the crude 6-(phenoxy)-substituted pyrimidine 20, which was used directly without purification. To a 25 ml round-bottomed flask containing 6-(phenoxy)-substituted pyrimidine 20 (0.5 mmol) dissolved in freshly distilled THF at room temperature was added an appropriate amine (0.55 mmol). KO'Bu (1.5 mmol) of was added portion-wise to the mixture over 1 h with stirring. After evaporating the solvent, the crude residue was dissolved in DCM (25 ml) and washed successively with saturated aqueous NH₄Cl (2 x 20 ml) and water. The organic phase was dried over Na₂SO₄ and evaporated to leave the crude product. The product was purified by flash column chromatography eluting with 5–15% EtOAc/Hex. Product yields are quoted over both steps from 2,4,6-trichloropyrimidine (19).

4-Chloro-6-(4-chlorophenoxy)-N-(5-methylpyridin-2-yl)pyrimidin-2-amine (5a). Reaction of 2,4-dichloro-6-(4-chlorophenoxy)pyrimidine 20a (138 mg, 0.5 mmol) with 5-methylpyridin-2-amine (60 mg, 0.55 mmol) gave compound 5a (162 mg, 84%) as an off-white solid. Mp: 230–233°C; IR (cm⁻¹): 3108 and 2916 (CH str.), 3161 (CN), 1567 (NH bend), 1460 (C=C); ¹H NMR (300 MHz, CDCl₃) δ 8.13–8.05 (m, 2H), 7.63 (d, J 8.3 Hz, 1H), 7.44–7.41 (m, 2H), 7.29–7.25 (m, 1H, overlapping with chloroform), 7.13–7.10 (m, 2H), 6.41 (s, 1H), 2.25 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 170.1, 162.5, 157.4, 156.8, 155.9, 152.3, 132.3, 130.1, 125.1, 124.5, 122.6, 119.0, 100.8, 30.9; HRMS (ES⁺) Calculated for C₁₆H₁₃Cl₂N₄O [M+H]⁺: 347.0466, found: 347.0467.

4-Chloro-6-(2,4-dichlorophenoxy)-N-(5-methylpyridin-2-yl)pyrimidin-2-amine (5b). Reaction of 2,4-dichloro-6-(2,4-dichlorophenoxy)pyrimidine 20b (155 mg, 0.5 mmol) with 5-methylpyridin-2-amine (60 mg, 0.55 mmol) gave compound 5b (149 mg, 70%) as a white solid. Mp: 200–202°C; IR (cm⁻¹): 3234 (NH str.), 3095 and 3016 and 2916 (CH str.), 1614 (C=N str.), 1566 (NH bend), 1453 (C=C); ¹H NMR (500 MHz, CDCl₃) δ 8.15–8.11 (m, 2H), 7.55–7.47 (m, 2H), 7.34 (d, J 8.6 Hz, 1H), 7.23 (d, J 8.5 Hz, 1H), 7.17 (d, J 8.6 Hz, 1H), 6.50 (s, 1H), 2.25 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 169.7, 162.2, 157.9, 149.5, 148.0, 147.5, 138.3, 132.0, 130.3, 128.6, 128.1, 127.7, 125.0, 112.2, 98.0, 17.7; HRMS (ES⁺) Calculated for C₁₆H₁₂Cl₂N₄O [M+H]⁺: 381.0077, found: 381.0068.
4-Chloro-6-(3,5-dichlorophenoxy)-N-(5-methylpyridin-2-yl)pyrimidin-2-amine (5c). Reaction of 2,4-dichloro-6-(3,5-dichlorophenoxy)pyrimidine 20c (196 mg, 0.55 mmol) with 5-methylpyridin-2-amine (60 mg, 0.55 mmol) gave compound 5c (142 mg, 68%) as an off-white solid. Mp: 218–220°C; IR (cm⁻¹): 3083 and 2922 (CH str.), 1563 (C=N str.), 1481 (NH bend), 1402 (C=C); ¹H NMR (300 MHz, CDCl₃) δ 8.15 (d, J 2.0 Hz, 1H), 7.67 (br s, 1H), 7.49 (dd, J 8.3, 2.2 Hz, 1H), 7.41 (s, 1H), 7.26 (d, J 2.4 Hz, 1H, pyrimidyl proton overlaps with solvent signal), 7.10 (d, J 1.8 Hz, 2H), 7.06 (d, J 8.5 Hz, 1H), 2.31 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 170.2, 161.9, 159.1, 153.3, 149.8, 147.7, 139.1, 135.4, 128.1, 126.0, 120.5, 112.6, 90.1, 17.8; HRMS (ES⁺) Calculated for C₁₆H₁₂Cl₃N₄O [M+H]^+: 381.0077, found: 381.0079.

4-Chloro-6-(4-fluorophenoxy)-N-(5-methylpyridin-2-yl)pyrimidin-2-amine (5d). Reaction of 2,4-dichloro-6-(4-fluorophenoxy)pyrimidine 20d (166 mg, 0.55 mmol) with 5-methylpyridin-2-amine (60 mg, 0.55 mmol) gave compound 5d (101 mg, 57%) as an off-white solid. Mp: 238–240°C; IR (cm⁻¹): 2919 (CH str.), 1615 (C=N str.), 1568 (NH bend), 1457 (C=C); ¹H NMR (500 MHz, CDCl₃) δ 8.07 (s, 1H), 7.88 (br s, 1H), 7.66 (br s, 1H), 7.16–7.12 (m, 5H), 6.40 (s, 1H), 2.25 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 170.9, 162.0, 160.4 (d, J analyses).

4-Chloro-N-(5-methylpyridin-2-yl)-6-(3-(trifluoromethyl)phenoxy)pyrimidin-2-amine (5e). Reaction of 2,4-dichloro-6-(3-(trifluoromethyl)phenoxy)pyrimidine 20e (155 mg, 0.5 mmol) with 5-methylpyridin-2-amine (60 mg, 0.55 mmol) gave compound 5e (143 mg, 68%) as a pale yellow solid. Mp: 186–188°C; IR (cm⁻¹): 3210 (NH str.), 3008 (CH str.), 1610 (C=N), 1568 (NH bend), 1442 (C=C); ¹H NMR (500 MHz, CDCl₃) δ 8.60 (br s, 1H), 8.19 (s, 1H), 7.62–7.52 (m, 3H), 7.49 (s, 1H), 7.37 (d, J 7.6 Hz, 1H), 7.19 (d, J 7.6 Hz, 1H), 6.46 (s, 1H), 2.23 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 170.3, 162.2, 158.0, 152.6, 152.3, 149.6, 148.1, 138.3, 132.3 (q, J analyses).

4-Chloro-N-(5-chloropyrimidin-2-yl)-6-(3-(trifluoromethyl)phenoxy)pyrimidin-2-amine (5f). Reaction of 2,4-dichloro-6-(3-(trifluoromethyl)phenoxy)pyrimidine 20e (155 mg, 0.5 mmol) with 5-chloropyrimidin-2-amine (60 mg, 0.55 mmol) gave compound 5f (169 mg, 76%) as an off-white solid. Mp: 206–207°C; IR (cm⁻¹): 3239 (NH str.), 3054 (CH str.), 1553 (C=N str.), 1430 (C=C); ¹H NMR (500 MHz, CDCl₃) δ 8.77 (d, J 4.7 Hz, 1H), 8.49 (s, 2H), 8.25 (s, 1H), 7.63–7.46 (m, 3H), 6.54 (s, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 170.1, 162.5, 157.3, 156.6, 155.8, 152.3, 132.1 (q, J analyses).

2-(4-Chloro-6-(4-chlorophenoxy)pyrimidin-2-yl)amino)-4-methylbenzonitrile (5g). Reaction of 2,4-dichloro-6-(4-chlorophenoxy)pyrimidine 20a (138 mg, 0.5 mmol) with 2-amino-4-methylbenzonitrile (73 mg, 0.55 mmol) gave compound 5g (128 mg, 61%) as a white solid. Mp: 170–172°C; IR cm⁻¹: 3095 (CH str.), 2232 (CN) 1580 (C=N str.), 1557 (NH bend), 1430 (C=C); ¹H NMR (300 MHz, CDCl₃) δ 7.79 (br s, 1H), 7.53 (br s, 1H), 7.45–7.37 (m, 3H), 7.17–7.07 (m, 2H), 6.87–6.82 (m, 1H), 6.52 (s, 1H), 2.18 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 171.0, 162.2, 158.2, 150.8, 145.4, 141.0, 132.3, 131.6, 130.0, 123.9, 123.4, 120.2, 116.8, 99.5, 98.7, 22.5; HRMS (ES⁺) Calculated for C₁₈H₁₃Cl₂N₂O [M+H]^+: 371.0466, found: 371.0467.

2-(4-Chloro-6-(2,4-dichlorophenoxy)pyrimidin-2-yl)amino)-4-methylbenzonitrile (5h). Reaction of 2,4-dichloro-6-(2,4-dichlorophenoxy)pyrimidine 20b (155 mg, 0.5 mmol) with 2-amino-4-methylbenzonitrile (73 mg, 0.55 mmol) gave compound 5j (114 mg, 50%) as a white solid. Mp: 151–152°C; IR cm⁻¹: 3392 and 3382 (NH str.), 3190 (CH str.), 2208 (CN), 1580 (C=N str.), 1526 (NH bend), 1380 (C=C); ¹H NMR (300 MHz, CDCl₃) δ 7.73 (br s, 1H), 7.53–7.49 (m, 2H), 7.39 (d, J 7.9 Hz, 1H), 7.33 (dd, J 8.7, 2.5 Hz, 1H), 7.18 (d, J 8.7 Hz, 1H), 6.84 (d, J 7.9 Hz, 1H), 6.59 (s, 1H), 2.19 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 169.8, 162.3, 158.1, 147.3, 145.0, 140.8,
132.3, 132.2, 130.4, 128.4, 128.3, 124.9, 123.9, 120.1, 116.7, 99.4, 98.7, 22.2; HRMS (ES+) Calculated for C_{16}H_{12}Cl_{3}N_{4}O [M+H]^+: 405.0077, found: 405.0066.

2-((4-Chloro-6-(3,5-dichlorophenoxy)pyrimidin-2-yl)amino)-4-methylbenzonitrile (5i). Reaction of 2,4-dichloro-6-(3,5-dichlorophenoxy)pyrimidine 20c (196 mg, 0.5 mmol) with 2-amino-4-methylbenzonitrile (73 mg, 0.55 mmol) gave compound 5k (124 mg, 56%) as an off-white solid. Mp: 236–238°C; IR (cm\(^{-1}\)): 3295 (NH str.), 2980 (CH str.), 2227 (CN), 1573 (C=N str.), 1432 (C=C); \(^{1}\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.79–7.72 (m, 1H), 7.57 (d, \(J = 8.0\) Hz, 1H), 7.28–7.26 (m, 3H), 7.15–7.07 (m, 2H), 6.65 (s, 1H), 2.48–2.46 (m, 3H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 162.0, 161.5, 160.4, 145.8, 139.5, 133.4, 133.1, 132.7, 128.8, 126.08, 123.7, 121.2, 120.5, 116.2, 103.1, 22.2; HRMS (ES+) Calculated for C_{16}H_{12}Cl_{3}N_{4}O [M+H]^+: 405.0077, found: 405.0070.

2-((4-Chloro-6-(4-fluorophenoxy)pyrimidin-2-yl)amino)-4-methylbenzonitrile (5j). Reaction of 2,4-dichloro-6-(4-fluorophenoxy)pyrimidine 20d (166 mg, 0.5 mmol) with 2-amino-4-methylbenzonitrile (73 mg, 0.55 mmol) gave compound 5l (96 mg, 51%) as an off-white solid. Mp: 166–168°C; IR (cm\(^{-1}\)): 3399 (NH str.), 3111 (CH str.), 2211 (CN), 1563 (C=N str.), 1435 (C=C); \(^{1}\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.81 (br s, 1H), 7.51 (br s, 1H), 7.37 (m, 2H), 6.83 (d, \(J = 7.9\) Hz, 1H), 6.49 (s, 1H), 2.18 (s, 3H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 170.9, 162.1, 160.4, (d, \(J_{CF} = 245\) Hz), 158.2, 148.2 (d, \(J_{CF} = 3\) Hz), 145.0, 142.0, 132.3, 132.8, 123.3 (d, \(J_{CF} = 9\) Hz), 123.0, 116.8, 116.5 (d, \(J_{CF} = 23.5\) Hz), 99.5, 98.7, 22.2; HRMS (ES+) Calculated for C_{16}H_{12}ClF_{4}N_{4}O [M+H]^+: 331.0762, found: 331.0768.

2-((4-Chloro-6-(3-(trifluoromethyl)phenoxy)pyrimidin-2-yl)amino)-4-methylbenzonitrile (5k). Reaction of 2,4-dichloro-6-(3-(trifluoromethyl)phenoxy)pyrimidine 20e (155 mg, 0.5 mmol) with 2-amino-4-methylbenzonitrile (73 mg, 0.55 mmol) gave compound 5m (102 mg, 46%) as an off-white solid. Mp: 132–134°C; IR (cm\(^{-1}\)): 3398 (NH str.), 3130 (CH str.), 2214 (CN), 1529 (NH bend), 1430 (C=C); \(^{1}\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.72 (m, 1H), 7.59–7.57 (m, 2H), 7.51 (s, 1H), 7.45 (s, 1H), 7.39–7.37 (m, 2H), 6.83 (d, \(J = 7.9\) Hz, 1H), 6.55 (s, 1H), 2.10 (s, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 170.4, 162.4, 158.3, 152.5, 145.0, 140.8, 132.3, 130.3, 125.6, 124.0, 122.8 (q, \(J_{CF} = 3.7\) Hz), 120.4, 119.2 (q, \(J_{CF} = 3.9\) Hz), 116.7, 99.7, 99.0, 22.2; HRMS (ES+) Calculated for C_{19}H_{13}ClF_{4}N_{4}O [M+H]^+: 405.0730, found: 405.0733.

**Biological Assays**

The *in vitro* assessment of cellular toxicity and anti-HIV activity of the test compounds were performed in HEK293T human embryonic kidney cells. Test compounds were dissolved in dimethyl sulfoxide (DMSO) to 10 mM, and diluted into complete Dulbecco’s Modified Eagle’s Medium (DMEM medium to 200 μM). Three-fold serial dilutions of test compounds were prepared in 96-well culture plates, after which HEK293T cells were added. A medium control, containing no test compound, was included to provide a reference for 100% cell viability (no toxicity). The culture plates were incubated for 48 hours at 37°C under 5% CO\(_2\) in a humidified atmosphere. Cell viability was assessed through the addition of resazurin dye (i.e. Alamar Blue; Sigma-Aldrich, Missouri, United States), and the quantification of the reduced form (i.e. resoruﬁn) 1 – 2 hours later. The cytotoxic concentration-50 (CC50) for each test compound was calculated using Microsoft Excel (Redmond, WA, United States).

Anti-HIV activity was assessed in an *in vitro* single-cycle non-replicating HIV pseudoviral assay.\(^{34,35}\) Briefly, three-fold serial dilutions of the test compounds were prepared over non-toxic concentrations (as determined in the toxicity screens) in 96-well culture plates. HEK293T cells and HIV-like virus particles were added after which the culture plates were incubated for 48 hours at 37°C under 5% CO\(_2\) in a humidified atmosphere. A medium control, containing no test compound, was included to provide a reference for 100% viral activity (no inhibition). Viral activity was assessed by quantifying the expression of a firefly luciferase reporter gene in the culture plate wells using Bright-Glo™ Luciferase Assay substrate (Promega, Madison, WI, USA). The inhibitory
concentration-50 (IC$_{50}$) for each test compound was calculated using Microsoft Excel (Redmond, WA, United States).

**Supplementary Material**

Copies of $^1$H and $^{13}$C NMR spectra of compounds 3c-3e, 4c-d and 5a-k are given in the Supplementary material file associated with this article.

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