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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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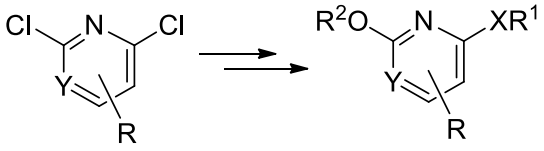
Abstract

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;

R^1 = alkyl, aryl; R^2 = 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}=0.18μM against wild-type HIV) that had been identified in our laboratory (Figure 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}=0.7μM) 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 (Figure 1).

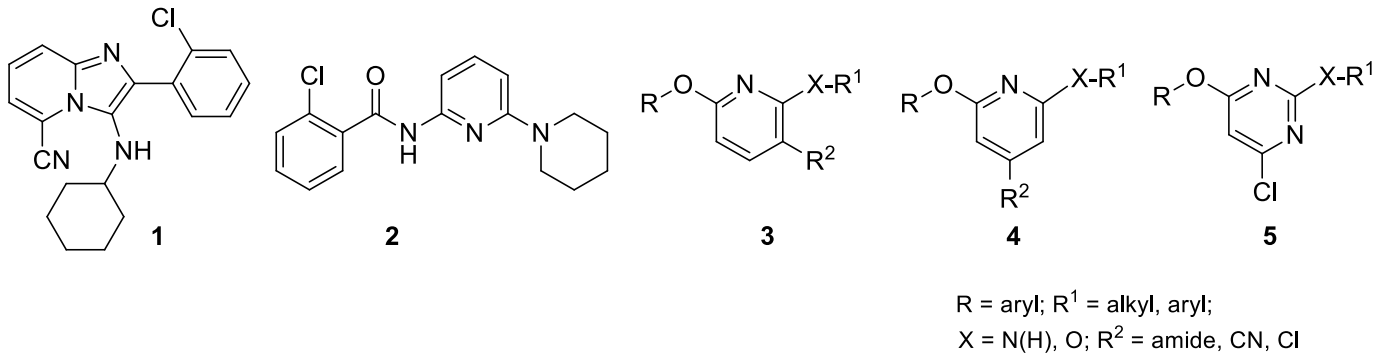


Figure 1. Imidazopyridine lead compound **1**, pyridylbenzamide hit compound **2** and general structures for tri-functionalised pyridine (**3** and **4**) and pyrimidine (**5**) synthetic targets.

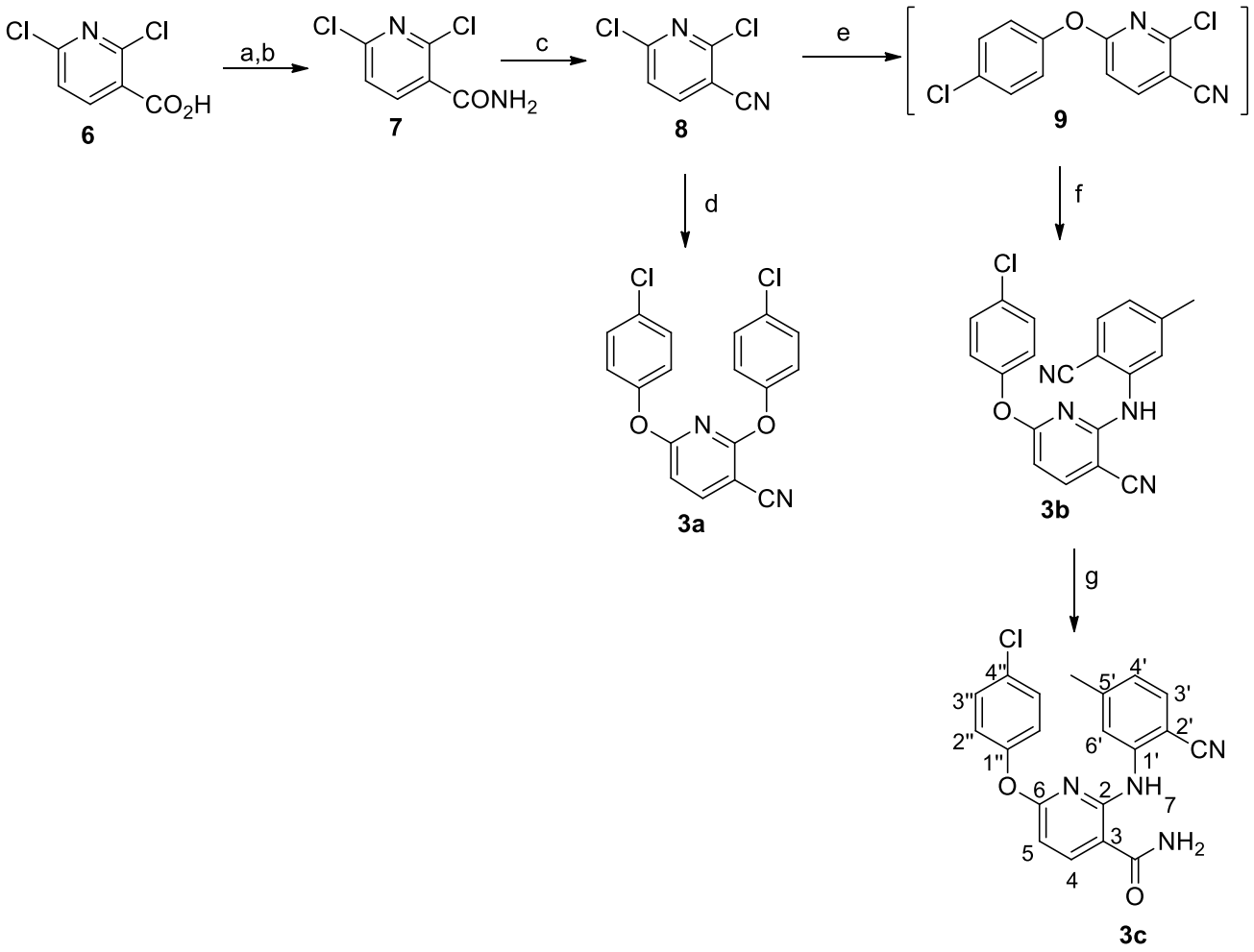
Ruiz-Castello and Buchwald[14] have reviewed the use of palladium catalysed C-heteroatom cross-coupling reactions in the construction of a wide range of compounds, including compounds of medicinal interest, natural products and catalysts. Many other reports attest to the utility of palladium-catalysed methods in the

synthesis of biologically active compounds.[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** (Figure 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.[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.[11]

The initial compounds targeted for synthesis were 2,3,6-trisubstitued pyridines (**3**) bearing either a nitrile or amide at position 3 and heteroatom-linked aryl groups at positons 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,[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.[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_2dba_3/BINAP catalysed protocol that we have reported previously.[12]

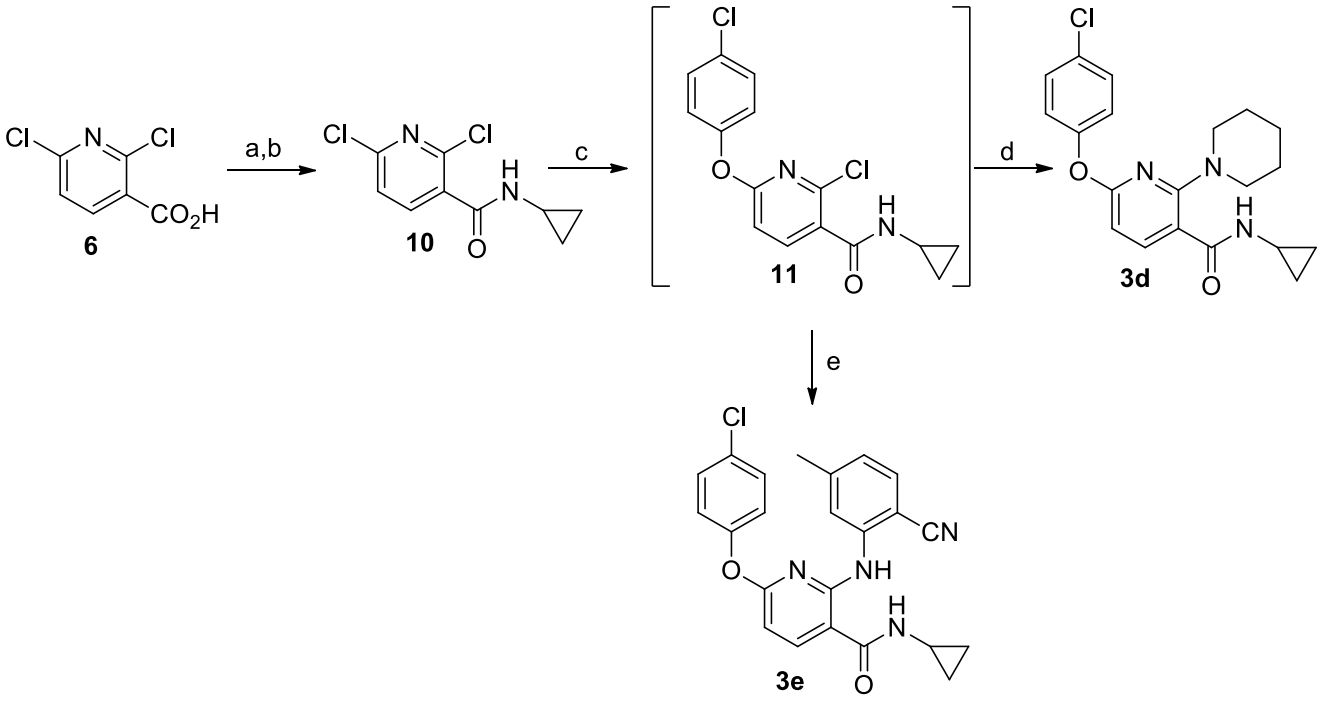


Scheme 1. *Reagents and conditions*: (a) $SOCl_2$, 80°C, 24 h; 99%; (b) aq. NH_3, 0°C - RT, 4 h; 98%; (c) $POCl_3$, Et_4NCl, 120°C, 4 h; 89% (d) 2 mol% Pd_2dba_3, 6 mol % *rac*-BINAP, 2 eq. 4-chlorophenol, NaO^tBu, THF, 100-110°C, 24 h; 78%; (e) 2 mol % Pd_2dba_3, 6 mol% *rac*-BINAP, 0.5 eq. 4-chlorophenol, NaO^tBu, THF, 100-110°C, 24 h (f) 2 mol % Pd_2dba_3, 6 mol % *rac*-BINAP, 1.2 eq. 2-amino-4-methylbenzonitrile, NaO^tBu, THF, 100-110°C, 24 h; 76% from **8**; (g) nitrile hydratase from *R. rhodochrous*, phosphate buffer, 30-37°C, 72 h; 64%.

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 (KO^tBu, Cs_2CO_3, K_2CO_3 or K_2PO_4 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-870[22] 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. ^{13}C 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 ^{3}J coupling between H-3' at 7.49 ppm and a quaternary nitrile carbon signal at 117.9 ppm. In addition, weaker ^{4}J 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 ^{3}J 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_2dba_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]



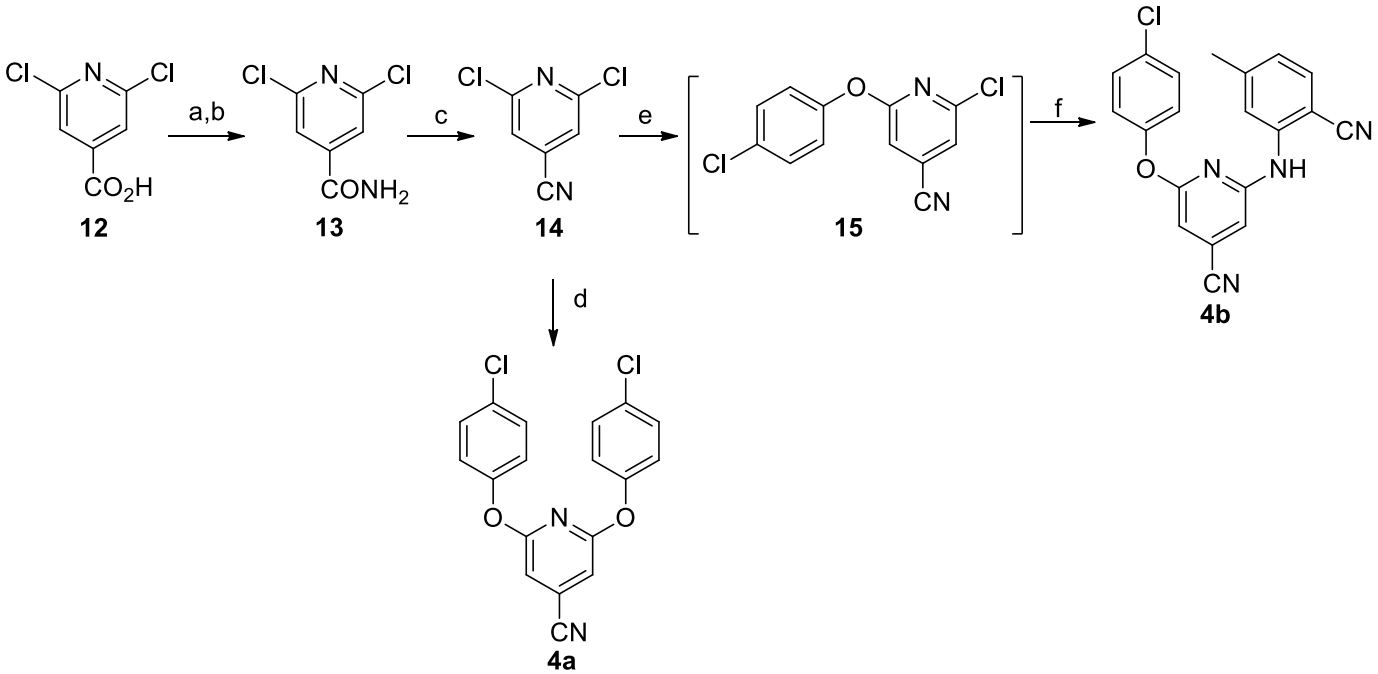
Scheme 2. *Reagents and conditions*: (a) $SOCl_2$, 80°C, 24 h; 99%; (b) cyclopropylamine, DCM, Et_3N, 0°C - RT, 4 h; 99%; (c) 2 mol % Pd_2dba_3, 6 mol % *rac*-BINAP, 1.2 eq. 4-chlorophenol, NaO^{t}Bu, THF, 135-140°C, 24 h; 68%; (d) 2 mol % Pd_2dba_3, 3 mol % Xantphos, piperidine, dioxane, NaO^{t}Bu, 110-120°C, 24 h; 37% from **10**; (e) 2 mol % Pd_2dba_3, 3 mol % Xantphos, 2-amino-4-methylbenzonitrile, dioxane, NaO^{t}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[24] and van Leeuwen's[25] 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.

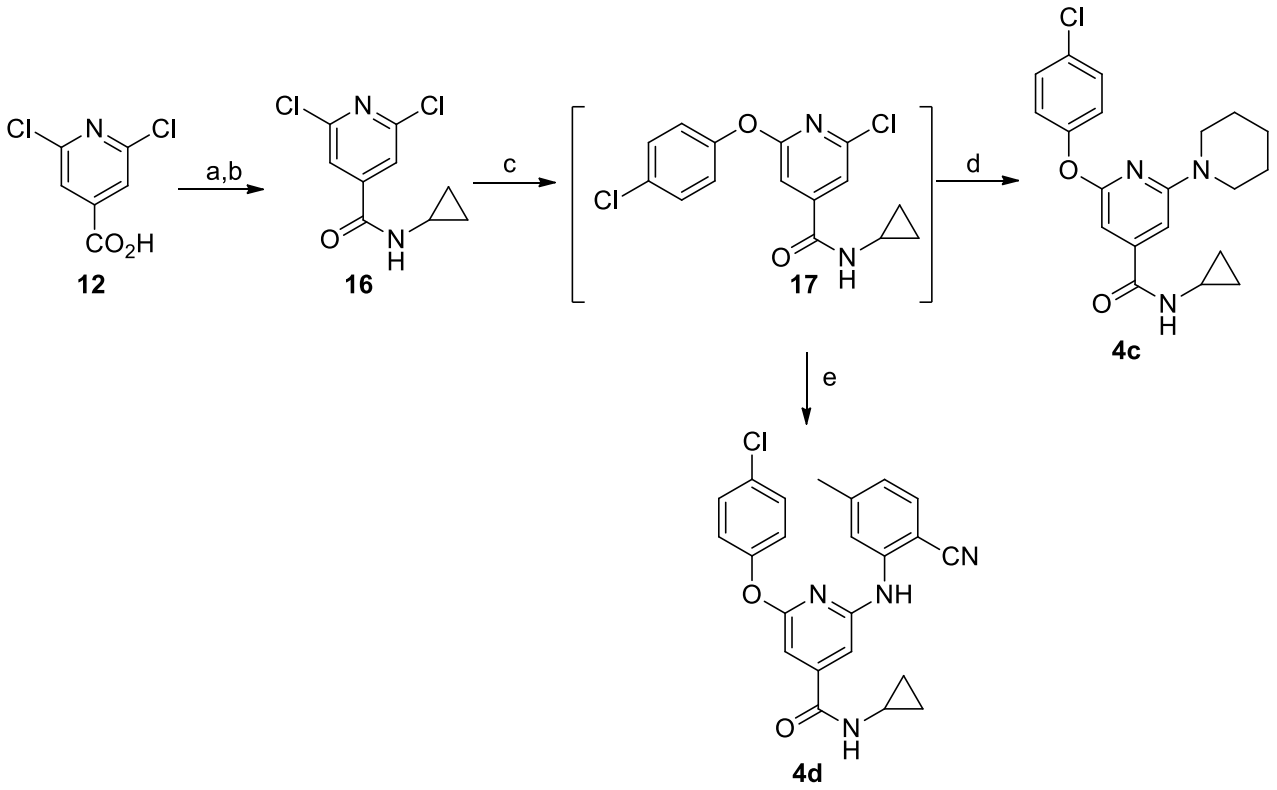
The next set of compounds synthesised was the 2,4,6-trisubstituted pyridines (**4**). In order to obtain the desired nitrile derivatives **4a-b**, a similar approach to that described in Scheme 1 was followed. Conversion of carboxylic acid **12** to the acid chloride was followed immediately by amidation 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_2dba_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_2dba_3, 6 mol % *rac*-BINAP, 2 eq. 4-chlorophenol, NaO^tBu, THF, 100-110°C, 24 h; 99%; (e) 2 mol % Pd_2dba_3, 6 mol % *rac*-BINAP, 0.5 eq. 4-chlorophenol, NaO^tBu, THF, 100-110°C, 24 h; (f) 2 mol % Pd_2dba_3, 3 mol% *rac*-BINAP, 2-amino-4-methylbenzonitrile, 1,4-dioxane, NaO^tBu, 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_2dba_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.

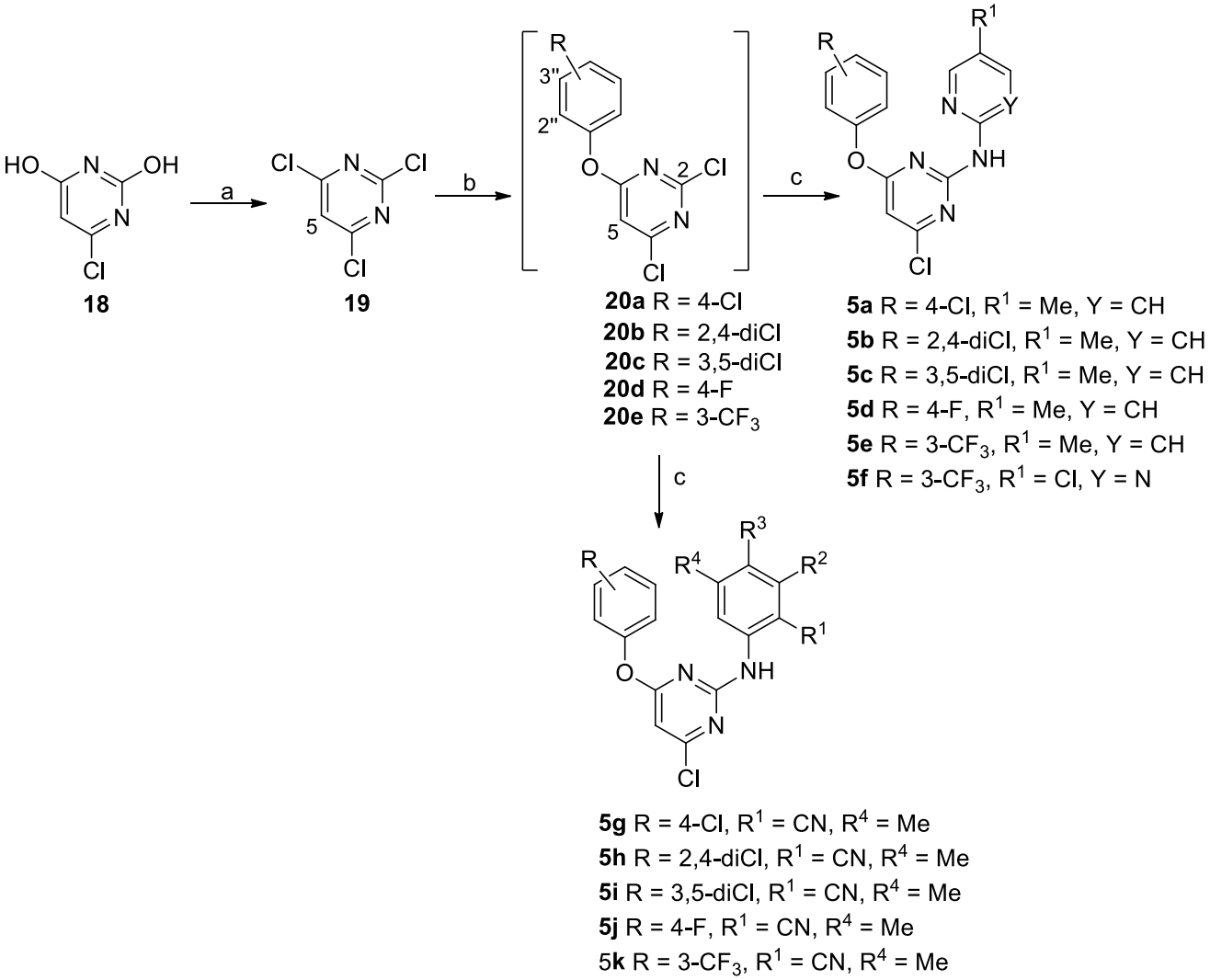


Scheme 4. *Reagents and conditions*: (a) $SOCl_2$, 80°C, 24 h; 98%; (b) cyclopropylamine, DCM, DMAP, Et_3N, 0°-RT, 4 h, 99%; (c) 2 mol % Pd_2dba_3, 6 mol % *rac*-BINAP, 1.2 eq. 4-chlorophenol, NaO^tBu, THF, 100-110°C, 24 h; 71%; (d) 2 mol % Pd_2dba_3, 6 mol % *rac*-BINAP, piperidine, 1,4-dioxane, NaO^tBu, 110-120°C, 24 h; 53%; (e) 2 mol % Pd_2dba_3, 6 mol % *rac*-BINAP, 2-amino-4-methylbenzonitrile, 1,4-dioxane, NaO^tBu, 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 $POCl_3$. 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]



Scheme 5. *Reagents and conditions* (a) $POCl_3$, Et_4NCl, 120°C, 4 h, 78%; (b) acetone, aq. Na-phenoxide (1.2 eq.), 0°C-RT, 2 h; (c) 1.1 eq. amine, KO^{t}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-amino-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-amino-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_{50})] and toxicity [compound concentration reducing cell viability by 50% (CC_{50})]. The selectivity index (S.I. = CC_{50}/IC_{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

Compound	Activity		Toxicity		S. Index
	IC_{50} (μM)	S. D.	CC_{50} (μM)	S. D.	
3a	28.09	1.23	30.78	1.79	1.1
3c	>21.34	-	83.9	14.5	-
3d	60.21	3.28	81.75	11.40	1.4
3e	>100	-	>100	-	-
4a	53.40	1.29	54.42	13.25	1.0
4b	>100	-	>100	-	-
4c	7.61	0.19	1.52	0.63	0.2
4d	27.20	2.92	8.34	1.24	0.3
5a	>49.4	-	>100	-	-
5b	> 4.6	-	53.0	26.5	-
5c	>86.3	-	>100	-	-
5d	>67.2	-	>100	-	-
5e	>100	-	>100	-	-
5f	> 8.6	-	41.5	1.3	-
5g	>60.7	-	>100	-	-
5h	>23.4	-	>100	-	-
5i	>27.8	-	97.4	1.7	-
5j	>52.1	-	>100	-	-
5k	>15.1	-	36.4	3.1	-
2	1.07	0.03	54.25	9.76	50.7
Toxicity Control (DMSO)	-	-	>1%	>1%	-
Activity Control (nevirapine)	0.12	0.0	-	-	-

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_{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_{50} = 1.52 µM; **4d**: CC_{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_{50} = 54.42 µM and **4b**: CC_{50} > 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 derivatives 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 HI 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 spectrometer. All melting points are uncorrected and were performed using open capillary tubes on a Stuart SMP 10 melting point apparatus. ^{1}H and ^{13}C NMR spectra were recorded using either a Bruker AVANCE 111 300 or 500 MHz spectrometer in deuterated chloroform ($CDCl_3$) with trimethylsilane (TMS) as internal standard (δ = 0) for ^{1}H NMR, and $CDCl_3$ (δ = 77.0 ppm) for ^{13}C 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 F_{254} 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 $NaHCO_3$ (2 x 10 ml), saturated brine solution (10 ml), distilled water (2 x 10 ml) and finally dried over anhydrous Na_2SO_4. 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).[20] Reaction of 2,6-dichloronicotinoyl chloride (411 mg, 2 mmol) gave 2,6-dichloronicotinamide **7** (380 mg, 98%) as a pale yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) 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)[30] Reaction of 2,6-dichloroisonicotinoyl chloride (411 mg, 2 mmol) gave 2,6-dichloroisonicotinamide **13** (381 mg, 99%) as a pale yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) 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 $POCl_3$ (5 ml) and heated under reflux at 80°C for 24 h. Excess $POCl_3$ 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 K_2CO_3 (2 x 5 ml) and distilled water (5 ml). After drying over anhydrous Na_2SO_4, 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)[31] 2,6-Dichloronicotinonitrile (**8**) was isolated as an off-white solid (152 mg, 89% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, *J* 8.1 Hz, 1H), 7.43 (d, *J* 8.1 Hz, 1H).

2,6-Dichloroisonicotinonitrile (14)[32] 2,6-Dichloroisonicotinonitrile (**14**) was isolated as a white solid (169 mg, 99% yield). ^{1}H NMR (500 MHz, DMSO-d_6) 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 $NaHCO_3$ (2 x 10 ml), saturated brine solution (10 ml), distilled water (2 x 10 ml) and finally dried over anhydrous Na_2SO_4. 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. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (d, *J* 7.9 Hz, 1H), 7.37 (d, *J* 7.9 Hz, 1H), 6.60 (br s, 1H), 2.97-2.89 (m, 1H), 0.95-0.88 (m, 2H), 0.69-0.64 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) 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 as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ164.8, 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_2dba_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_2SO_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, $CDCl_3$) δ 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, $CDCl_3$) δ 164.1, 161.1, 150.8, 145.9, 132.1, 131.1, 129.4, 123.0, 114.8, 104.8; HRMS (ES^+) Calculated for $C_{18}H_{11}Cl_2N_2O_2$ $[M+H]^+$: 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 (500 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 162.9, 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 $C_{18}H_{11}Cl_2N_2O_2$ $[M+H]^+$: 357.0198, found: 357.0181.

General procedure for the preparation of compounds 3b and 4b. Tris-(dibenzylideneacetone)-di-palladium (0) [Pd_2dba_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_2SO_4 and evaporating excess solvent, the crude mixture was purified by silica gel flash column chromatography, eluting the precursor 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, $CDCl_3$): δ 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, $CDCl_3$) δ 163.0, 150.9, 145.9, 144.8, 131.1, 129.2, 122.9, 114.8, 110.1, 104.8. Further reaction of 6-(4-chlorophenoxy)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 (300MHz, $CDCl_3$): δ 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, $CDCl_3$) δ 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 $C_{20}H_{14}ClN_4O$ $[M+H]^+$: 361.0856, found: 361.0977.

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, $CDCl_3$) δ 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 (300MHz, $CDCl_3$) δ 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 (75MHz, $CDCl_3$) 154.7, 150.4, 146.3, 145.5, 142.1, 132.6, 132.1, 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 $C_{20}H_{14}ClN_4O$ $[M+H]^+$: 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), 1662 (C=O), 1587 (C=N), 1518 (NH bend), 1483 (C=C); ^{1}H NMR (500 MHz, DMSO- d_6) δ 9.40 (br s, 1H, NH), 8.18 (d, *J* 8.4 Hz, 1H, H-4), 7.51–7.45 (m, 3H, H-3', NH_2), 7.43–7.40 (m, 2H, H-2"), 7.31 (s, 1H, H-6'), 7.26–7.21 (m, 2H, H-3"), 6.91 (d, *J* 7.9 Hz, 1H, H-4'), 6.77 (d, *J* 8.4 Hz, 1H, H-5), 2.12 (s, 3H); ^{13}C NMR (126 MHz, DMSO- d_6) δ 165.2 (C=O), 159.5 (C-6), 155.6 (C-2), 152.2 (C-1"), 144.4 (C-1'), 143.1 (C-4), 142.3 (Ar-C), 133.2 (C-3'), 129.7 (Ar-C), 129.5 (Ar-C), 124.7 (C-4'), 124.5 (Ar-C), 123.4 (Ar-C), 117.9 (CN), 107.9 (Ar-C), 105.8 (C-5), 101.8 (C-2'), 21.8; HRMS (ES)$^+$ Calculated for $C_{20}H_{16}ClN_4O_2$ $[M+H]^+$: 379.0962, found: 379.0952.

General procedure for the preparation of compounds 3d-e and 4c-d. Tris-(benzylideneacetone)-di-palladium (0) [Pd_2dba_3] (28 mg, 3 mol %), *rac*-BINAP (38 mg, 6 mol %), 1,4-dioxane or THF (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 dichlorocyclopropylamide derivative (1.0 mmol), 4-chlorophenol (1.2 mmol) and sodium *tert*-butoxide (2.4 mmol) were added and the 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 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_2SO_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_2dba_3] (28 mg, 3 mol %), *rac*-BINAP (38 mg, 6 mol %) or Xantphos (35 mg, 3 mol %), THF (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 mono-substituted cyclopropylamide substrate (1.0 equivalents), amine (1.2 equivalents) and sodium *tert*-butoxide (2.4 mmol) were added and the sealed reaction heated at 100–110°C for 24 h. After 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. ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (126 MHz, $CDCl_3$) 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); ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (126 MHz, $CDCl_3$) 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 $C_{20}H_{23}ClN_3O_2$ $[M+H]^+$: 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.); ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (126 MHz, $CDCl_3$) 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 $C_{23}H_{20}ClN_4O_2$ $[M+H]^+$: 417.1118, found: 417.1090.

6-(4-Chlorophenoxy)-*N*-cyclopropyl-2-(piperidin-1-yl)isonicotinamide (4c). Reaction of 2,6-dichloro-*N*-cyclopropylisonicotinamide (**16**) (232 mg, 1.0 mmol) gave precursor **17** (230 mg, 71%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (126 MHz, $CDCl_3$) 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 gave compound **4c** (99 mg, 53%) or (125 mg, 67%) as a yellow oil, respectively. ^{1}H NMR ($CDCl_3$, 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), 0.96–0.81 (m, 2H), 0.70–0.52 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) 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 $C_{20}H_{23}ClN_3O_2$ $[M+H]^+$: 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. ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (126 MHz, $CDCl_3$) 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, 117.2, 113.1, 106.7, 99.6, 23.4, 22.4, 22.2, 6.7; HRMS (ES^+) Calculated for $C_{23}H_{20}ClN_4O_2$ $[M+H]^+$: 419.1275, found: 419.1240.

2,4,6-Trichloropyrimidine (19).[33] 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, $POCl_3$ (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 $POCl_3$ *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 Na_2SO_4 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. ^{1}H NMR (500 MHz, $CDCl_3$) 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 phenoxide (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 $NaHCO_3$ (10 ml) and water (10 ml). The organic layer was dried over Na_2SO_4 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^{t}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 NH_4Cl (2 x 20 ml) and water. The organic phase was dried over Na_2SO_4, filtered 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.), 1616 (CN), 1567 (NH bend), 1460 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{16}H_{13}Cl_2N_4O$ [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); ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (126 MHz, $CDCl_3$) 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 $C_{16}H_{12}Cl_3N_4O$ [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, 0.5 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); ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{16}H_{12}Cl_3N_4O$ [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, 0.5 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); ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.9, 162.0, 160.4 (d, $^1J_{C\text{-}F}$ = 245 Hz), 158.0, 149.5, 148.3 (d, $^4J_{C\text{-}F}$ = 2.7 Hz), 148.0, 138.4, 127.6, 123.5 (d, $^3J_{C\text{-}F}$ = 8.5 Hz), 116.3 (d, $^2J_{C\text{-}F}$ = 23.5 Hz), 112.3, 98.2, 17.7; HRMS (ES$^+$) Calculated for $C_{16}H_{13}ClFN_4O$ [M+H]$^+$: 331.0762, found: 331.0758.

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); ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.3, 162.2, 158.0, 152.6, 149.6, 148.1, 138.3, 132.3 (q, $^2J_{C\text{-}F}$ = 33 Hz), 130.3, 127.6, 125.6, 123.5 (q, $^1J_{C\text{-}F}$ = 273 Hz), 122.6 (q, $^3J_{C\text{-}F}$ = 3.7 Hz), 119.5 (q, $^3J_{C\text{-}F}$ = 3.6 Hz), 112.3, 98.3, 17.7; HRMS (ES$^+$) Calculated for $C_{17}H_{13}ClF_3N_4O$ $[M+H]^+$: 381.0730, found: 381.0720.

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-chloropyrimidine-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); ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.1, 162.5, 157.3, 156.6, 155.8, 152.3, 132.1 (q, $^2J_{C\text{-}F}$ = 33 Hz), 130.2, 125.1, 124.6, 122.6 (q, $^3J_{C\text{-}F}$ = 3.9 Hz), 121.3 (q, $^1J_{C\text{-}F}$ = 267 Hz), 119.0 (q, $^3J_{C\text{-}F}$ = 4.0 Hz), 100.8; HRMS (ES$^+$) Calculated for $C_{15}H_9Cl_2F_3N_5O$ $[M+H]^+$: 402.0136, found: 402.0131.

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); ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{18}H_{13}Cl_2N_4O$ $[M+H]^+$: 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 **5h** (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); ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{16}H_{12}Cl_3N_4O$ $[M+H]^+$: 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 **5i** (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, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{18}H_{12}Cl_3N_4O$ $[M+H]^+$: 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 **5j** (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, $CDCl_3$) δ 7.81 (br s, 1H), 7.51 (br s, 1H), 7.39 (d, *J* 7.9 Hz, 1H), 7.14–7.11 (m, 4H), 6.84 (d, *J* 7.9 Hz, 1H), 6.49 (s, 1H), 2.18 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.9, 162.1, 160.4, (d, $^1J_{C\text{-}F}$ = 245 Hz), 158.2, 148.2 (d, $^4J_{C\text{-}F}$ = 3 Hz), 145.0, 142.0, 132.3, 123.8, 123.3 (d, $^3J_{C\text{-}F}$ = 9 Hz),

123.0, 116.8, 116.5 (d, $^{2}J_{C\text{-}F}$ = 23.5 Hz), 99.5, 98.7, 22.2; HRMS (ES^{+}) Calculated for $C_{16}H_{13}ClFN_4O$ $[M+H]^{+}$: 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 **5k** (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, $CDCl_3$) δ 7.74 (s, 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, $CDCl_3$) δ 170.4, 162.4, 158.3, 152.5, 145.0, 140.8, 132.3, 130.3, 125.6, 124.0, 122.8 (q, $^{3}J_{C\text{-}F}$ = 3.7 Hz), 120.4, 119.2 (q, $^{3}J_{C\text{-}F}$ = 3.9 Hz), 116.7, 99.7, 99.0, 22.2; HRMS (ES^{+}) Calculated for $C_{19}H_{13}ClFN_4O$ $[M+H]^{+}$: 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 NMR spectra of selected compounds are given in the Supplementary material file associated with this article.

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