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Synthesis of aryl benzamides containing a pyrimidine moiety as possible HIV-1 NNRTIs

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Dedicated to Professor Hans-Günther (Hagga) Schmalz, on the occasion of his retirement

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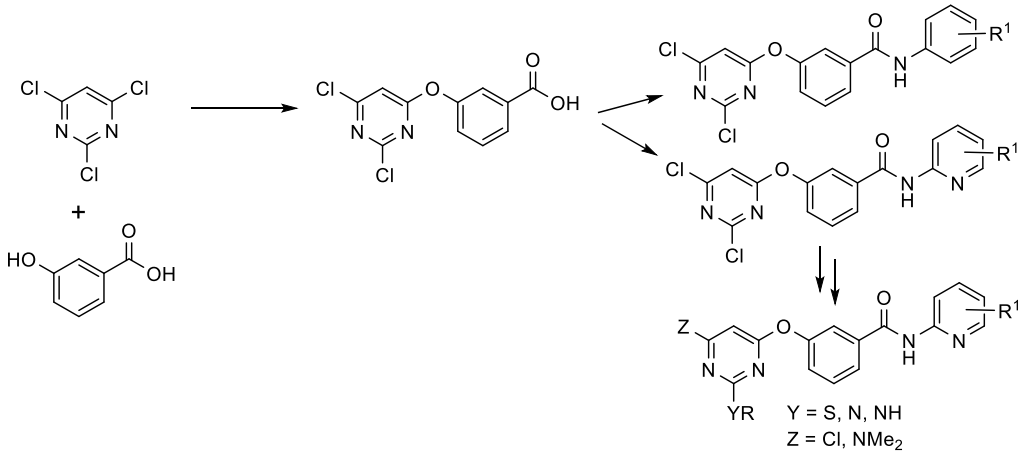
Abstract

A synthetic method is described for the preparation of novel compounds containing both aryl benzamide and pyrimidine moieties linked through an oxygen heteroatom designed as possible torsionally flexible inhibitors of HIV-1 non-nucleoside reverse transcriptase inhibitors (NNRTIs). Initially, reactions were conducted to optimise conditions for benzamide formation using anilines and aminopyridines in reaction with benzoic acid, followed by reactions with 3-hydroxy- and 3-methoxybenzoic acid to determine the best overall reaction sequence. The optimal route was found to be the initial reaction of trichloropyrimidine with 3-hydroxybenzoic acid, followed by reaction with aminopyridine or aniline to form *O*-linked pyrimidine-aryl benzamides that could be further functionalised with sulphur or nitrogen nucleophiles.



Keywords: Aryl benzamide, pyrimidine, trichloropyrimidine, sulphur, nitrogen, NNRTI

Introduction

HIV continues to impact the lives of people across the globe, with 39.9 million people reportedly living with HIV in 2023[1] and there is thus an ongoing need for the development of new antiviral drugs. Despite numerous awareness programs and controls, Southern Africa remains the global epicentre of the disease and South Africa accounts for 25% of recorded new infections.[2] With the increase in other viral and bacterial infections across the world, development of new therapeutics against HIV is of importance to ensure that suppression of HI viral load is as complete as possible to allow the immune system of HIV-AIDS sufferers to fight these new infections.

Current HIV chemotherapy targets different constitutive viral enzymes and proteins to limit viral replication within the human body. One of the targeted enzymes is reverse transcriptase, which controls the replication of viral genetic material. Two types of drugs that have been developed to target this enzyme are the nucleoside reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs). The NNRTIs work by binding to a hydrophobic allosteric site 10 Å away from the active site, which results in conformational alteration of the active site, rendering the enzyme inactive.[3]

Chemical structures of the currently approved NNRTIs can be considered to possess a butterfly, horseshoe or U-like shape.[4] These compounds are electron-rich and have the potential to donate π-electrons to aromatic side chain residues near the binding pocket. Five NNRTIs are currently FDA-approved as part of the highly active antiretroviral therapy (HAART) regimen. Examples of these are nevirapine, which is one of the original 1st generation drugs, whilst etravirine and rilpivirine are 2nd generation drugs with a characteristic diarylpyrimidine (DAPY) motif (Fig. 1).[5] Elsufavirine has received approval as a therapeutic drug for use in Russia alone.[6]

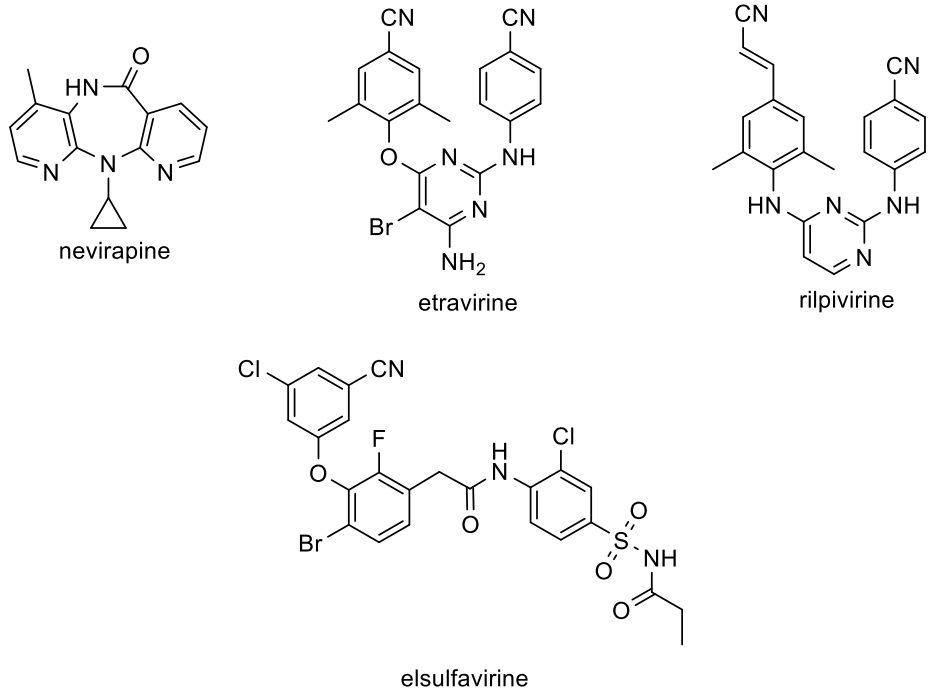


Figure 1. Structures of selected NNRTIs.

The structural rigidity of the first generation of approved NNRTI drugs contributed significantly to the emergence of drug resistance.[7,8,9] Pretreatment resistance has also been detected and this has compounded adverse effects on infected patients as they already have diminished chances of receiving effective antiretroviral therapy. Modelled and predicted levels of pretreatment NNRTI resistance in 2018 ranged from

3.3% in Mozambique to as high as 25% in Eswatini.[10] These results emphasize the need for continual development of new therapeutics. An important element in the design of newer NNRTI drugs has been the introduction of torsional flexibility, where the aromatic rings are linked through heteroatoms. This allows multiple conformations to be adopted by the molecules, resulting in antiviral activity being maintained, even in the presence of viral point mutations.[11]

Ongoing efforts in our laboratory to identify new NNRTIs previously led to the identification of benzamide compounds possessing anti-HIV activity.[12] We identified pyridyl benzamides as potential HIV-1 NNRTIs through a scaffold-hopping approach starting from imidazo[1,2-*a*]pyridines we had earlier demonstrated to have activity as NNRTIs.[13] From the small compound library we synthesised, compound **1** (Fig. 2) was the most active, showing significant antiviral activity of 0.7 µM against the wild-type HIV-1 in an *in vitro* single-cycle assay. This compound bears a structural similarity to elsulfavirine and this led us to further explore methods towards the synthesis of compounds possessing this structural motif. In addition, a large number of compounds displaying NNRTI activity contain a pyrimidine ring, including FDA-approved etravirine and rilpivirine (Fig. 1) and the exploratory NNRTI S-DABO compounds (**2**, Fig. 2).[14] Our interest was thus to focus on the synthesis of torsionally flexible compounds containing the benzamide motif, which our previous work had indicated was advantageous for NNRTI activity, and combine this with a pyrimidine moiety bearing a sulphur substituent linked through a heteroatom, as exemplified by compounds of type **3** (Fig. 2). The pyrimidine ring is of biological importance and is a privileged structure present not only in approved NNRTIs but also in therapeutics used in the treatment of infections, cancer, neurological disorders, chronic pain, and diabetes mellitus.[15] The pyrimidine ring can act as a bioisostere for phenyl and similar aromatic π systems which improves pharmacokinetic and pharmacodynamic properties of drugs.[15, 16]

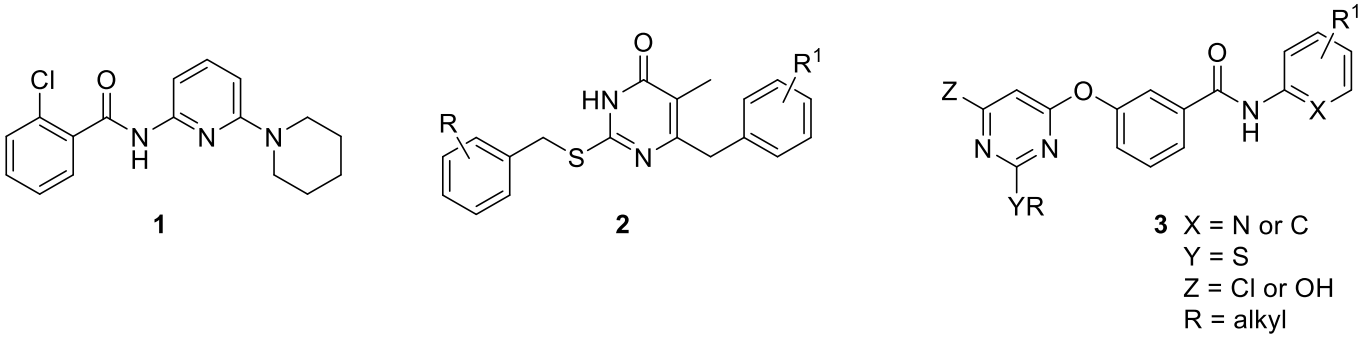
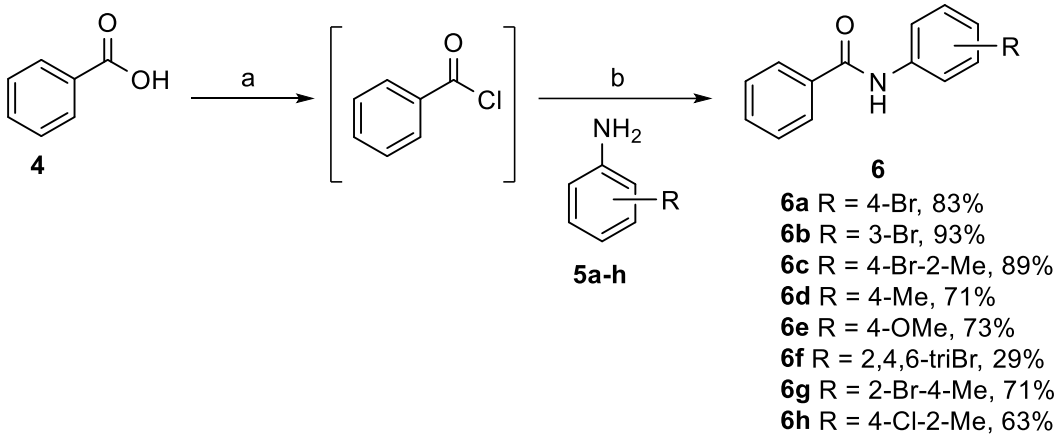


Figure 2. Structure of the most active compound from previous studies **1**, S-DABO compound **2** and proposed motif **3** for synthesis.

Results and Discussion

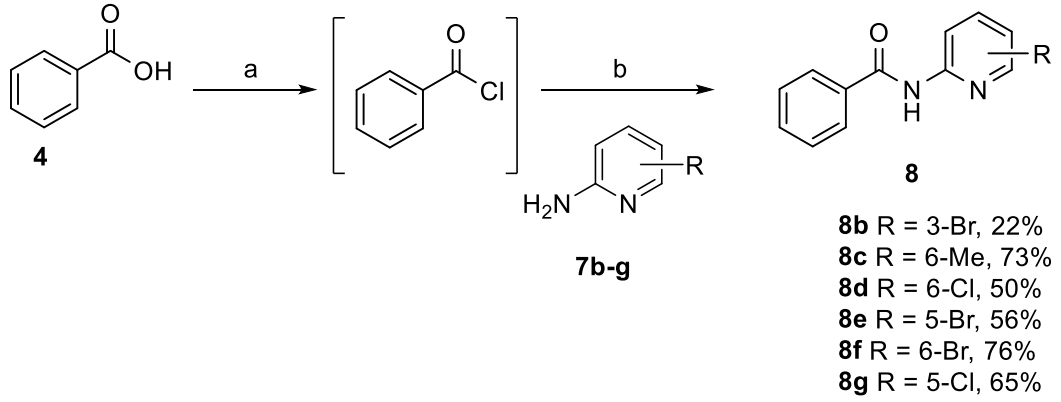
Our starting point for this work was to investigate the best conditions for the key amidation reaction that would be central to the preparation of the desired derivatives **3**. Thus, a small library of compounds was initially prepared from benzoic acid and eight anilines. Benzoic acid **4** was transformed to the corresponding acyl chloride by refluxing in $SOCl_2$ and after removal of excess $SOCl_2$, the crude acyl chloride was reacted with anilines **5a** – **h** (Scheme 1). Pyridine was initially selected as the base of choice but low yields ranging from 3 – 49% were obtained. Improved yields were observed for all substrates when triethylamine was used instead of pyridine. Respectable yields of known products **6a** – **h**, ranging from 63 – 93% were obtained, with the single exception of compound **6f** which was recovered in a low yield of 29%. This low yield, attributed to steric

hindrance by the two bromine atoms adjacent to the amine, was still a significant improvement over the 3% recovered yield when pyridine was used as the base.



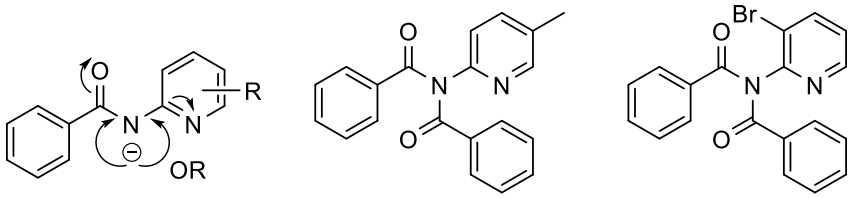
Scheme 1. Reagents and conditions: a) $SOCl_2$, reflux, 24 h; b) aniline (**5**), CH_3CN, triethylamine, 0 °C – rt, 14 – 24 h, 29 – 93% (Note: **6a** and **6c** were prepared using pyridine).

For the next small library of compounds, anilines were replaced by 2-aminopyridines, initially **7a** – **d**, which were reacted with benzoic acid **4** in the presence of triethylamine. Unlike the amidation reactions undertaken using anilines, use of triethylamine as the base for the aminopyridine reactions was not optimal and led to undesired N,N-diacylated products being isolated. Although 2-aminopyridines **7c** – **d** gave the expected products **8c** – **d** (Scheme 2), N,N-diacylated products **9a** – **b** (Fig. 3) were obtained for the reactions of 2-amino-5-methylpyridine (**7a**) and 2-amino-3-bromopyridine (**7b**).



Scheme 2. Reagents and conditions: a) $SOCl_2$, reflux, 24 h; b) aminopyridine (**7**), CH_3CN, pyridine or triethylamine, 0 °C – rt, 8 – 24 h, 22 – 76%.

This problem with diacylation has been previously reported when using 2-aminopyrimidines or aminopyrazines as the amine component, with a single example of a 2-aminopyridine also being reported.[17] Morizo *et al.* also reported similar findings but no further investigations were undertaken to establish the reason behind this outcome.[18] We attribute our results to triethylamine being a strong enough base to deprotonate the acidic amide proton of the mono-acylated product (shown in Fig. 3 for our own compounds **8**), generating a negatively charged nitrogen atom, with the charge being stabilised on one side by a carbonyl group and on the other by what is effectively an imine (**A**, Fig. 3). The increased nucleophilicity of the nitrogen as a result of the negative charge results in attack on a second molecule of benzoyl chloride, furnishing the di-acylated product.



A **9a** **9b**

Figure 3. Stabilisation of negative charge (**A**) and N,N-diacylated products **9a** and **9b**.

As a result of this problem encountered when using triethylamine, the rest of the 2-aminopyridines (**7e** – **g**) were reacted in the presence of pyridine as base. Repeating the reaction of **7b** in the presence of pyridine yielded the desired mono-acylated product in a poor yield of 22%, but no diacylated product was observed under these conditions. The results are summarised in Scheme 2. Synthesis of the monobenzoylated products **8b**,[19] **8c** – **d**,[20] **8g**,[20] **8d**[21]and **8f**[22] has been reported previously using different methods and reaction conditions to those described here. The exception to this is **8b**, which was earlier synthesised under similar conditions to those used here, but with 1,2-dichloroethane as solvent instead of MeCN.[23]

Based on the structure of the desired compounds **3**, a 3-hydroxybenzoic acid or protected 3-hydroxybenzoic acid derivative would be needed for the amidation reaction with an aniline or aminopyridine, with the hydroxyl group subsequently acting as a handle for attachment of the pyrimidine moiety. We thus proceeded to test two possibilities in the amidation reaction, the 3-methoxy and 3-hydroxybenzoic acids to determine if there were significant differences in reaction outcomes. 3-Methoxybenzoic acid **10** was reacted with aminopyridines **7a** – **g** to yield a library of benzamide products **11a** – **g**. Reactions were carried out in the presence of pyridine as a base, having earlier found this to be preferable to triethylamine in reactions with aminopyridines. In test reactions with triethylamine as base to confirm our earlier findings, reaction of 3-methoxybenzoic acid with 2-amino-5-methylpyridine (**7a**) gave the N,N-diacylated product **12a** in 39% yield while reaction with 2-amino-5-bromopyridine (**7e**) have product **12e** in 57% yield. Single X-ray crystal structure determination confirmed the structures of all diacylated compounds, as exemplified by **12e** (Fig. 4). Diacylation reactions appeared more prevalent for aminopyridines substituted at position 5, opposite the amino group, possibly because of increased donation of electron density to nitrogen for these compounds.

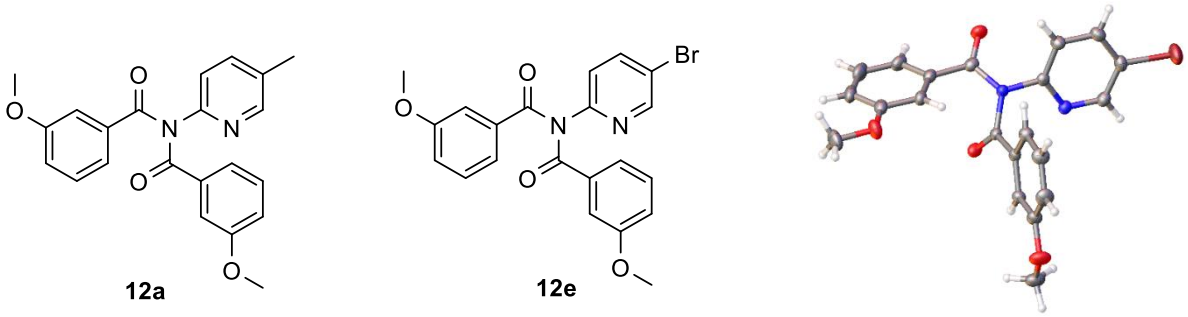
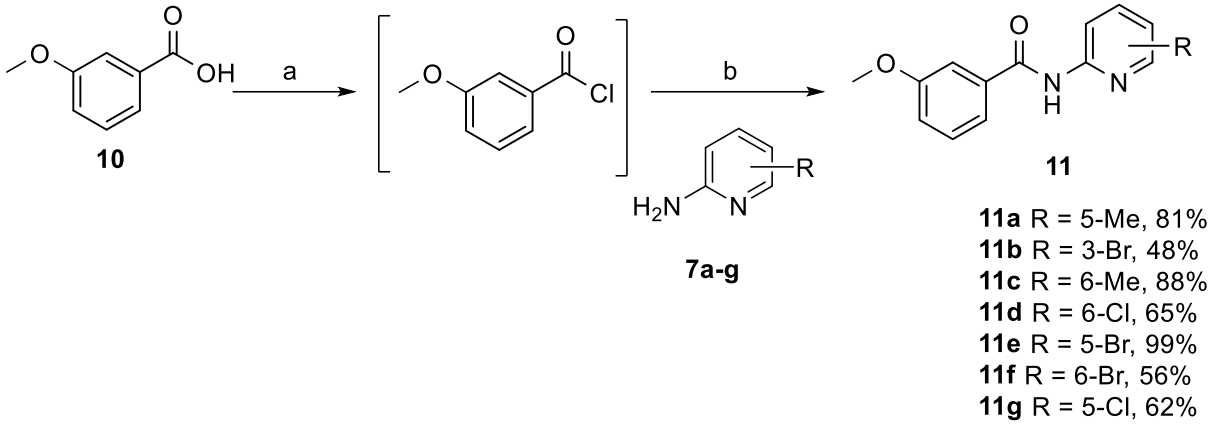


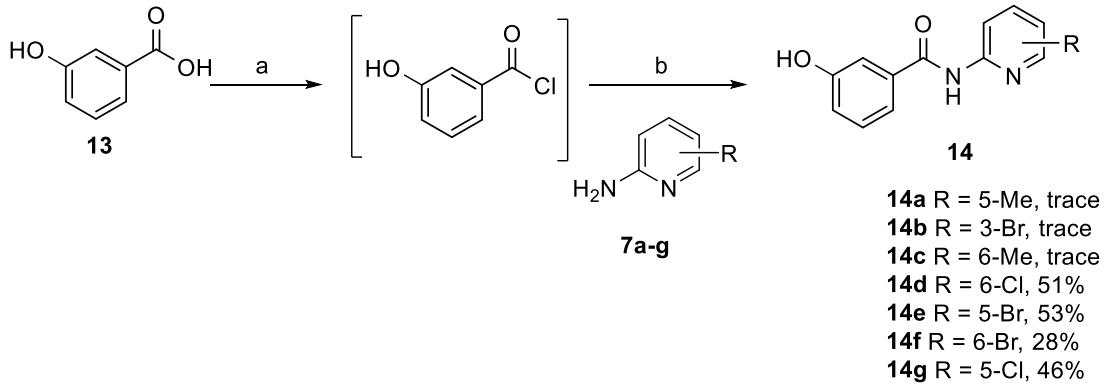
Figure 4. Diacylated compounds **12a** and **12e** and the ORTEP diagram (50% probability ellipsoids) of major disordered component (85%) of the single-crystal X-ray structure of compound **12e**.



Scheme 3. Reagents and conditions: a) $SOCl_2$, reflux, 24 h; b) aminopyridine, pyridine, 0 °C – rt, 10 – 24 h, 48 – 99%.

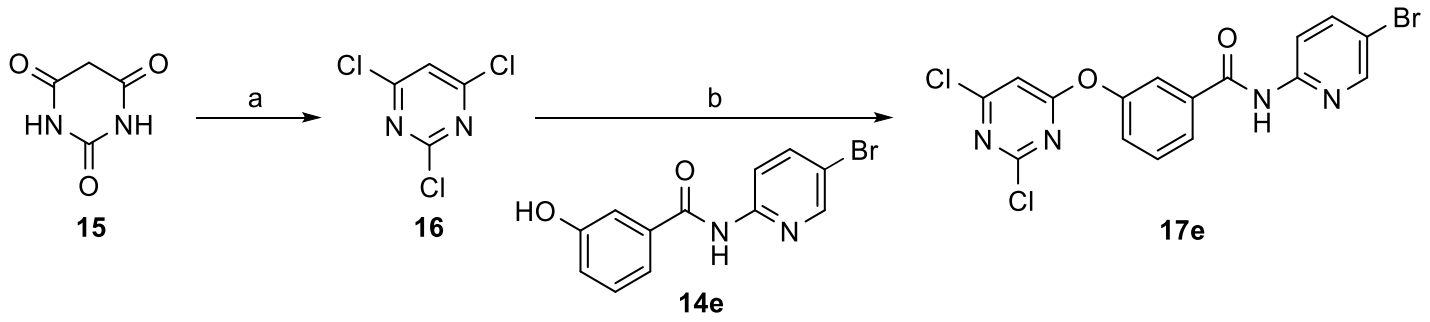
For the rest of the recovered products, positioning of the substituent on the pyridinyl ring had a slight effect on the recovered yield. As with the previous series, the 2-amino-3-bromo pyridine product **11b** was obtained in the lowest yield of 48% although it was double the yield obtained when benzoic acid was used. A quantitative yield was obtained for **11e** whilst **11f** gave a yield of 56%. The chlorinated analogues **11d** and **11g** gave modest yields of 65% and 62%, respectively.

Having established that 3-methoxybenzoic acid **10** performed well in the amidation reactions, 3-hydroxybenzoic acid **13** was tested next. We suspected that the unprotected phenol may complicate generation of the corresponding acyl chloride and this proved to be the case. A complex mixture of products was observed, suggesting that the phenolic oxygen acts as a nucleophile on the acyl chloride yielding a polymerisation product. Nonetheless, the subsequent amidation reaction was carried out in the presence of pyridine. Only four analogues **14d** – **g** were recoverable in this series whilst only trace amounts of compounds **14a** – **c** were recovered as mixtures with uncharacterised side products. The difficulty of isolating the desired products due to product polarity during purification significantly contributed to the low yields.



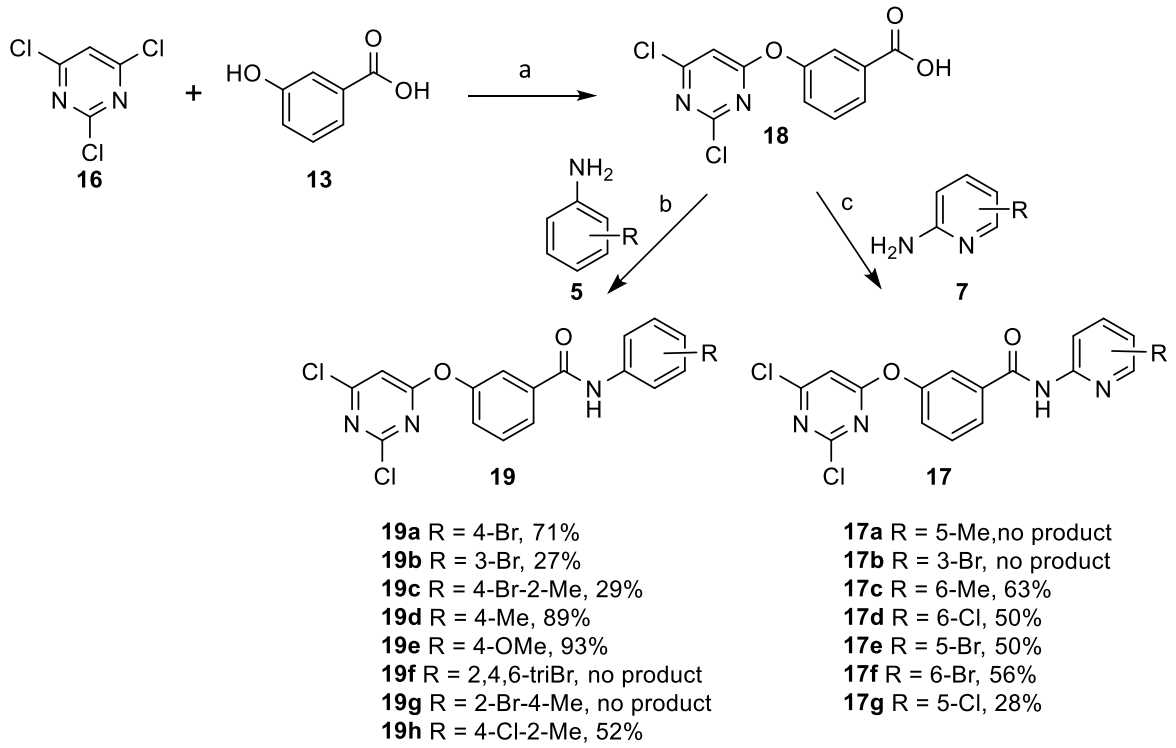
Scheme 4: Reagents and conditions: a) $SOCl_2$, reflux, 24 h; b) Pyridine, 0 °C – rt, 3 – 24 h, 28 – 53%.

Having obtained amides **14d** – **g**, albeit in poor yields, we were in the position to test the use of the phenolic OH of these compounds as a handle for attachment to the pyrimidine ring. Barbituric acid **15** was used as the starting material to synthesise 2,4,6-trichloropyrimidine **16**,[24] followed by nucleophilic substitution of chlorine by the phenolic OH of compound **14e** in the presence of K_2CO_3 as a base (Scheme 5). The reaction was monitored for 24 h but compound **17e** was only obtained in 28% yield, with unreacted starting material also being recovered. NMR spectroscopy confirmed that substitution occurred at position 4 of the pyrimidine ring, as required.



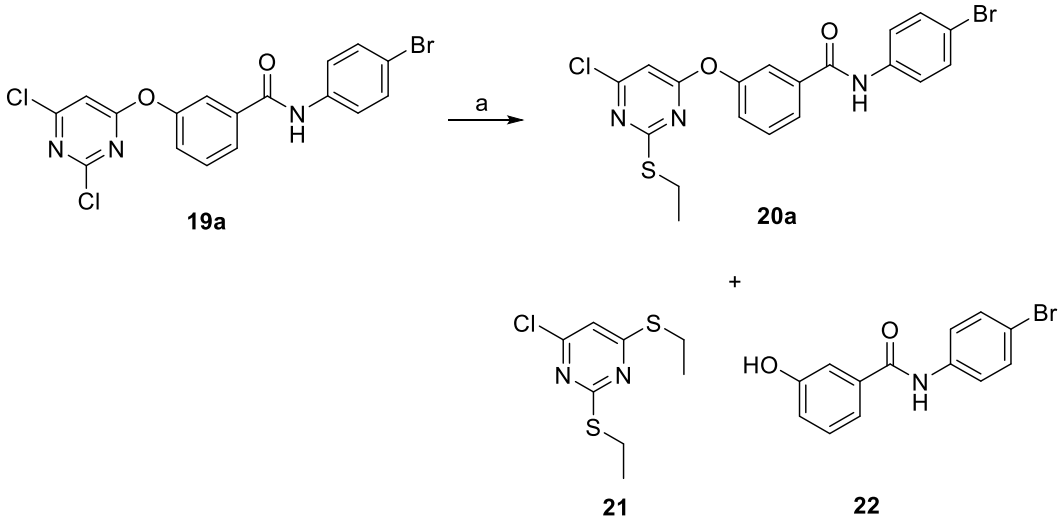
Scheme 5. Reagents and conditions: a) $POCl_3$, tetraethylammonium chloride, reflux, 24 h, 67%; b) acetone, K_2CO_3, 24 h, 28%.

The poor yields obtained using this approach and the success of the amidation reactions using masked phenols, in the form of 3-methoxybenzoic acid, prompted us to change the order of the reactions. Thus, 3-hydroxybenzoic acid **13** was reacted first with trichloropyrimidine **16** to yield complex acid **18** from trichloropyrimidine **16.** Using 1 M NaOH as the base gave **18** in 81% yield (Scheme 6). Acid **18** was reacted with anilines **5a** – **g**, furnishing compounds **19a** – **e** and **19h** in low to moderate yields. Despite several attempts to optimise reaction conditions, analogues **19f** and **19g** were not obtained. Reaction of compound **18** with aminopyridines **7a** – **g** resulted in five analogues (**17b** – **e** and **17g**) being prepared. Purification of these compounds was achieved by column chromatography followed by recrystallisation.



Scheme 6. Reagents and conditions: a) 1 M NaOH, acetone, 0 °C – rt,24 h; b) i) $SOCl_2$, 70 °C, 1 h ii) aniline **5**, pyridine or Et_3N, CH_3CN/THF, 0 °C – rt, 13 – 24 h; c) i) $SOCl_2$, 70 °C, 1 h ii) aminopyridine **7**, pyridine or Et_3N, CH_3CN/THF, 0 °C – rt, 13 – 24 h.

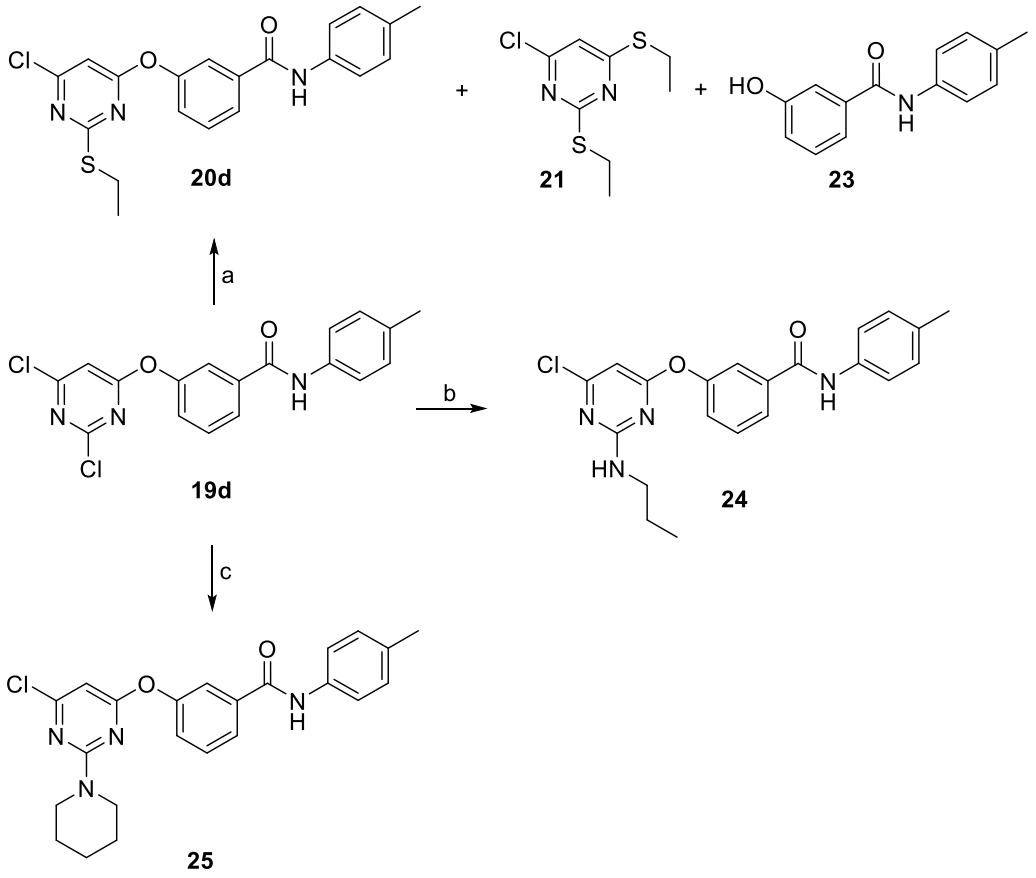
The next step was replacement of a chlorine atom with the desired thioalkyl group. Compound **19a** was reacted with ethanethiol in the presence of 1 M NaOH as base to give compound **20a** in 43% yield. Two other compounds were also isolated from the reaction, which corresponded to cleavage products **21** and **22** (Scheme 7). Presumably, sulphur acted as a nucleophile not only at the pyrimidine carbon carrying chlorine, but also at that carrying the oxygen atom.



Scheme 7. *Reagents and conditions: (a) ethanethiol (1.2 eq.), 1 M NaOH, acetone or THF, rt, 1 h, 43% (**20a**), 22% (**21**), 20% (**22**).*

The reaction was repeated using a different analogue to confirm the outcome obtained with **19a**. Thus, **19d** was reacted under the same conditions and the same outcome was observed, with compound **20d** being

obtained in 38% yield, together with the two cleavage products **21** and **23** (Scheme 8). At this stage we suspected that the strength of the sulphur nucleophile was such that it allowed reaction at two different electrophilic sites on the pyrimidine ring. The sulphur nucleophile, ethanethiol, was thus replaced with a nitrogen nucleophile, *n*-propylamine, to test if the cleavage reaction would still occur with the weaker nitrogen nucleophile. Reaction of compound **19d** with *n*-propylamine gave only the expected product **24** in 66% yield, with no cleavage products being observed. Interestingly, the ^{1}H and ^{13}C NMR spectra for compound **24** clearly show that in solution two different conformations of the compound are present, in approximately equal concentrations. It is possible that this results from restricted rotation about the newly formed N-C bond between *N*-propylamine and the pyrimidine ring, which allows for *cis* and *trans* arrangements about this pseudo-double bond to be observable at the NMR timescale. This phenomenon is generally observed for the amide functional group, but could conceivably also occur through donation of the nitrogen lone pair from *N*-propylamine into the pyrimidine ring. Single X-ray crystal structure determination confirmed the structure of compound **24** (Fig. 5).



Scheme 8. *Reagents and conditions: (a) ethanethiol (1.2 eq.), aq. NaOH, acetone, rt, 1 h, 38% (**20d**), 18% (**21**), 20% (**23**); (b) n-propylamine, aq. NaOH, acetone, rt, 1 h, 66%; (c) piperidine, aq. NaOH, acetone, rt, 5 h, 64%.*

Similarly, reaction with piperidine as the nitrogen nucleophile gave only expected product **25** in 64%, also without any cleavage products. Thus, it seems that the increased nucleophilicity of the sulphur nucleophile compared to that of the nitrogen nucleophiles impacted directly on the reaction outcome, leading to multiple products. Despite this, in both instances the desired products **20a** and **20d** were the major

products isolated and were obtained in adequate yield. Nitrogen nucleophiles, however, were clearly superior in this displacement reaction.

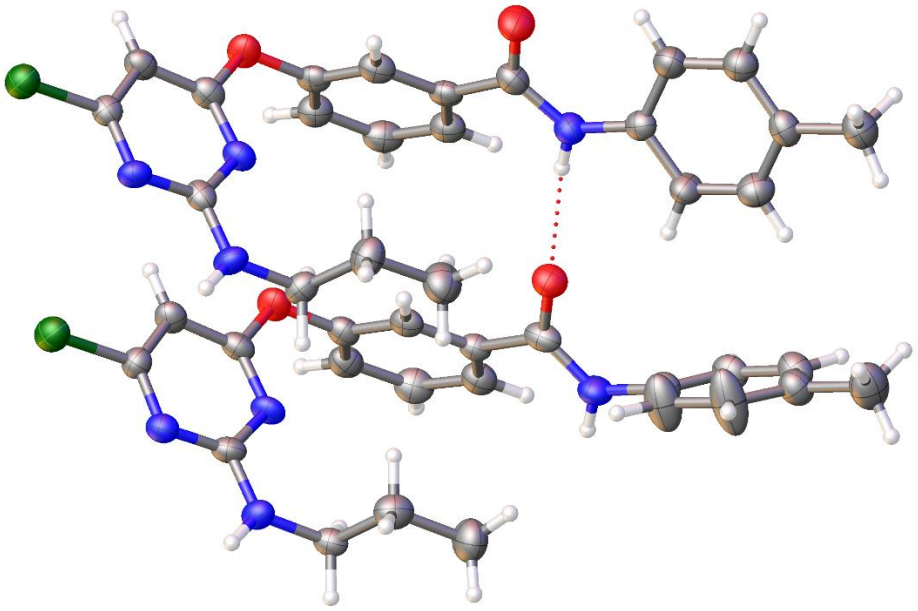
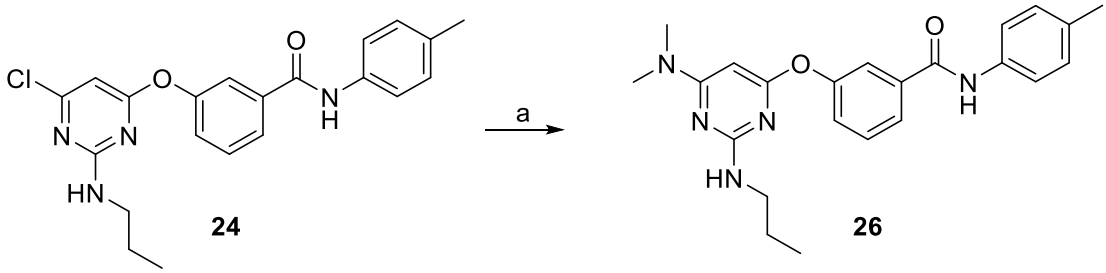


Figure 5. ORTEP diagram (30% probability ellipsoids) showing the asymmetric unit (Z' = 2) of the single-crystal X-ray structure of compound **24**.

Finally, we explored the possibility of displacing the third chlorine atom. Our intention was to displace chlorine with oxygen and so reacted compound **24** first under dilute acidic conditions (aq. HCl), where only starting material was recovered, and then under basic conditions using NaOH in DMF as solvent. Only when the concentration of base was increased significantly did conversion of the starting material occur. The only product isolated was the unexpected compound **26**, obtained in 35% yield. It was clear that decomposition of DMF must have occurred under the conditions of the reaction, liberating dimethylamine into the reaction mixture to act as a nucleophile to displace chlorine.



Scheme 9. *Reagents and conditions: (a) 50% w/v NaOH, DMF, 130 °C, 5 h, 35%.*

Although the intended product was not obtained, this result clearly demonstrated that displacement of all three chlorine atoms of the original trichloropyrimidine, which was a key objective, was indeed possible in the preparation of these novel *O*-linked pyrimidine-aryl benzamides.

Conclusions

Our overall aim of synthesising flexible benzamides containing a pyrimidine moiety for possible inhibition of HIV-1 reverse transcriptase was achieved. The optimal route to these compounds proved to be that where trichloropyrimidine was linked to the acid component prior to reaction with the aminopyridine or aniline to form the benzamides. Based on our results, it is evident that use of triethylamine in some instances results in diacylation for reaction of aminopyridines with benzoic acids, confirming earlier findings by other workers. Mono- acylated products were obtained when the milder base, pyridine, was used. Nucleophilic aromatic substitution reactions with a sulphur nucleophile on the combined benzamide-pyrimidine compounds led not only to the expected displacement of chlorine, but also led to cleavage of the final compound by nucleophilic attack at the carbon carrying oxygen. In contrast, use of nitrogen nucleophiles led only to the desired products. Displacement of the final chlorine atom of the *O*-linked pyrimidine-aryl benzamides proved to be feasible, albeit producing a final product that was unexpected.

Experimental Section

General. All solvents used for column chromatography and dry reactions were purified by distillation. All other solvents and reagents were purchased from commercial suppliers and used without further purification. TLC analysis was performed on aluminium-backed Macherey-Nagel AlugramSil G/UV254 plates and visualisation was done using a lamp operating at λ = 254 nm or λ = 366 nm. Column chromatography purification was performed on Merck silica gel 60 with particle size of 0.063 – 0.200 mm for normal chromatography or 0.040 – 0.063 mm for flash chromatography. Melting points are uncorrected and were measured on a Stuart SMP10 melting point apparatus. FT-IR spectra were recorded using a Bruker Vector 22 Spectrometer and all signals are reported on the wavenumber scale of ν/cm^{-1}. NMR spectra were recorded on a Bruker Avance-300, Bruker Avance-400 or Bruker-Avance-500 spectrometer in deuterated solvents. Chemical shifts (δ) values are reported in ppm relative to TMS (δ = 0) and coupling constant values (*J*) in Hz. High Resolution Mass Spectrometry data was recorded on a Waters Synapt G2 and data for all novel compounds is reported in relative abundance (*m/z*).

Synthetic methods

3-((2,6-Dichloropyrimidin-4-yl)oxy)benzoic acid (**18**). In a round-bottomed flask was added 3-hydroxybenzoic acid **13** (5.04 g, 36.0 mmol) and 1 M NaOH (2.73 g, 68.3 mmol) dissolved in a 500 mL round-bottomed flask. The mixture was stirred at room temperature for 30 min to give 3-carboxyphenoxide. In a separate flask chilled in ice was placed 2,4,6-trichloropyrimidine **16** (6.62 g, 36.0 mmol) dissolved in acetone (70.0 mL) and a solution of 3-carboxyphenoxide was slowly added. The mixture was stirred under similar conditions for 1h. Thereafter, the mixture was allowed to proceed for 24 h whilst the temperature gradually increased to room temperature. The solvent was evaporated under reduced pressure and the residue adjusted to pH 3 with aqueous 1 M HCl. This aqueous mixture was extracted several times with ethyl acetate (7 × 100 mL) and the organic layer dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo* to give product **18** (8.31 g, 81% yield). R_f = 0.2 (7:3 EtOAc/hexane). mp 187-189 °C. IR (*ν*/cm^{-1}): 2800-3200 (OH, br), 1682 (C=O, str), 1533, 1262 (C-O, str), 1102. ^{1}H NMR (500 MHz, DMSO-d_6): δ_H 13.34 (s, 1H, OH), 7.91 (d, *J* = 7.7 Hz, 1H, ArH), 7.79 (s, 1H, ArH), 7.63 (t, *J* = 7.9 Hz, 1H, ArH), 7.55 (dd, *J* = 7.6, 2.2 Hz, 1H, ArH), 7.50 (s, 1H, ArH); ^{13}C NMR (126 MHz, DMSO-d_6): δ_C 170.7 (ArC), 166.4 (C=O), 161.7 (ArC), 158.2 (ArC), 151.5 (ArC), 132.9 (ArC), 130.4 (ArCH), 127.3 (ArCH), 126.1 (ArCH), 122.2 (ArCH), 107.6 (ArCH). HRMS (ES+) calculated for $C_{11}H_7Cl_2N_2O_3$ $[M+H]^+$: 284.9828, found: 284.9821.

General procedure for the preparation of benzamides (17). 3-((2,4-Dichloropyrimidin-4-yl)oxo)benzoic acid **18** (1.00 g, 3.50 mmol) was placed in a round-bottomed flask, and thionyl chloride (2 mL mL) was added. The mixture was stirred and heated at 70 °C in an oil bath for overnight. After cooling the mixture to room-temperature, excess thionyl chloride was removed *in vacuo* leaving a pale yellow 3-(2,4-dichloropyrimidin-4-yl)oxo)benzoyl chloride residue which was dissolved in distilled acetonitrile (4 mL mL) and cautiously added to an ice-cold mixture of aminopyridine (**7**) and pyridine (2 mL mL) in distilled acetonitrile or THF (15 mL mL). The mixture was stirred at 0 °C for 30 min, warmed to room temperature and stirred for 3-13 h. Excess solvent was removed under reduced pressure and the residue dissolved in ethyl acetate (50 mL mL). The organic mixture was washed with aqueous saturated K_2CO_3 (2 × 50 mL mL) and saturated brine solution (50 mL), followed by separation of the organic layer which was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude product purified by normal silica gel chromatography eluting with 30% EtOAc/hexane to obtain derivatives **17**.

3-((2,6-Dichloropyrimidin N-(5-Chloropyridin-2-yl)-3-((2,6-dichloropyrimidin-4-yl)oxy)benzamide (**17g**). **-4-yl)oxy)-*N-(*6-methylpyridin-2-yl)benzamide** (**17c***).* 2-Amino-6-methylpyridine **7c** (0.380 g, 3.50 mmol) was reacted as per the general method for 13 h. Compound **17c** was obtained as a white solid (0.830 g, 63% yield); R_f = 0.3 (7:3 EtOAc/hexane). mp 162-164 °C. IR (*v*/cm^{-1}): 3385 (NH, br), 2920, 1676 (C=O, str), 1518, 1448, 1265 (C-O, str), 1114, 982. ^{1}H NMR (400 MHz, DMSO-d$_6$): δ_H 10.80 (s, 1H, NH), 8.04 – 7.98 (m, 2H, 2xArH), 7.97 – 7.93 (m, 1H, ArH), 7.73 (t, *J* = 7.9 Hz, 1H, ArH), 7.63 (t, *J* = 7.9 Hz, 1H, ArH), 7.56 – 7.50 (m, 2H, 2 x ArH), 7.04 (d, *J* = 7.4 Hz, 1H, ArH), 2.45 (s, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO-d$_6$): δ_C 171.3 (ArC), 165.1 (C=O), 162.2 (ArC), 158.7 (ArC), 151.9 (ArC), 151.8 (ArC), 138.9 (ArCH), 136.5 (ArC), 130.6 (ArCH), 126.5 (ArCH), 125.4 (ArCH), 121.5 (ArCH), 119.7 (ArCH), 112.2 (ArCH), 108.0 (ArCH), 24.0 (CH_3). HRMS (ES+) calculated for $C_{17}H_{13}Cl_2N_4O_2$ [M+H]$^+$: 375.0410, found: 375.0419.

***N*-(6-Chloropyridin-2-yl)-3-((2,6-dichloropyrimidin-4-yl)oxy)benzamide** (**17d**). 2-Amino-6-chloropyridine **7d** (0.460 g, 3.50 mmol) was reacted for 3 h. Compound **17d** was obtained as a white solid (0.670 g, 50% yield). R_f = 0.3 (7:3 EtOAc/hexane). mp 168-170 °C. IR (*v*/cm-1): 3377 (NH, br), 3095, 3072, 1681 (C=O, str), 1512, 1262 (C-O), 1115. ^{1}H NMR (500 MHz, DMSO-d$_6$): δ_H 11.14 (s, 1H, NH), 8.19 (d, *J* = 8.2 Hz, 1H, ArH), 8.01 (d, *J* = 7.8 Hz, 1H, ArH), 7.92 (dd, *J* = 15.8, 7.8 Hz, 2H, 2 x ArH), 7.55 – 7.51 (m, 2H, 2 x ArH), 7.28 (d, *J* = 7.7 Hz, 1H, ArH). ^{13}C NMR (125 MHz, DMSO-d$_6$): δ_C 170.8 (ArC), 164.9 (C=O), 161.7 (ArC), 158.2 (ArC), 152.0 (ArC), 151.4 (ArC), 148.0 (ArC), 141.6 (ArCH), 135.6 (ArC), 130.2 (ArCH), 126.2 (ArCH), 125.3 (ArCH), 121.1 (ArCH), 119.7 (ArCH), 113.3 (ArCH), 107.5 (ArCH). HRMS (ES+) calculated for $C_{16}H_{10}Cl_3N_4O_2$ [M+H]$^+$: 394.9864, found: 394.9856.

***N*-(5-Bromopyridin-2-yl)-3-((2,6-dichloropyrimidin-4-yl)oxy)benzamide** (**17e**). 2-Amino-5-bromopyridine **7e** (0.620 g, 3.50 mmol) was reacted for 3 h. Compound **17e** was obtained as a white solid (0.770 g, 50% yield). R_f = 0.3 (7:3 EtOAc/hexane). mp 168- 176 °C. IR (*v*/cm^{-1}): 3228 (NH, br), 3118, 3078, 1668 (C=O, str), 1560, 1272 (C-O), 1186. ^{1}H NMR (300 MHz, DMSO-d$_6$): δ_H 11.06 (s, 1H, NH), 8.52 (d, *J* = 2.2 Hz, 1H, ArH), 8.18 (d, *J* = 8.9 Hz, 1H, ArH), 8.08 (dd, *J* = 8.9, 2.4 Hz, 1H, ArH), 8.00 (d, *J* = 7.8 Hz, 1H, ArH), 7.92 (s, 1H, ArH), 7.64 (t, *J* = 7.9 Hz, 1H, ArH), 7.54 (d, *J* = 6.1 Hz, 2H, 2 x ArH). ^{13}C NMR (75 MHz, DMSO-d$_6$): δ_C 170.8 (ArC), 164.9 (C=O), 161.7 (ArC), 158.2 (ArC), 151.5 (ArC), 151.0 (ArC), 148.5 (ArCH), 140.6 (ArCH), 135.8 (ArC), 130.2 (ArCH), 126.1 (ArCH), 125.2 (ArCH), 121.1 (ArCH), 116.3 (ArCH), 114.2 (ArC), 107.5 (ArCH). HRMS (ES+) calculated for $C_{16}H_{10}{}^{79}BrCl_2N_4O_2$ [M+H]$^+$: 438.9359, found: 438.9361.

***N*-(6-bromopyridin-2-yl)-3-((2,6-dichloropyrimidin-4-yl)oxy)benzamide** (**17f**). 2-Amino-6-bromopyridine **7f** (0.620 g, 3.50 mmol) was reacted for 3 h and the impure product was washed with 10% EtOAc/hexane. Compound **17f** was obtained as a white solid (0.86 g, 56% yield). R_f = 0.3 (7:3 EtOAc/hexane). mp 185-187 °C. IR (*v*/cm^{-1}): 3374 (NH, br), 3097, 1682 (C=O, str), 1342, 1299 (C-O), 1184. ^{1}H NMR (400 MHz, DMSO-d$_6$): δ_H 11.19 (s, 1H, NH), 8.21 (d, *J* = 8.1 Hz, 1H, ArH), 8.00 (d, *J* = 7.8 Hz, 1H, ArH), 7.92-7.95 (m, 1H, ArH), 7.80 (t, *J* =

8.0 Hz, 1H, ArH), 7.64 (t, *J* = 7.9 Hz, 1H, ArH), 7.57 – 7.53 (m, 2H, 2 x ArH), 7.41 (d, *J* = 7.6 Hz, 1H, ArH). ^{13}C NMR (101 MHz, DMSO-d_6): δ_C 170.8 (ArC), 165.0 (C=O), 161.8 (ArC), 158.2 (ArC), 152.3, (ArC), 151.4 (ArC), 141.4 (ArCH), 138.8 (ArC), 135.6 (ArC), 130.2 (ArCH), 126.3 (ArCH), 125.3 (ArCH), 123.6 (ArCH), 121.2 (ArCH), 113.7 (ArCH), 107.5 (ArCH). HRMS (ES+) calculated for $C_{16}H_{10}{}^{79}BrCl_2N_4O_2$ $[M+H]^+$: 438.9359, found: 438.9352.
2-Amino-5-chloropyridine **7g** (0.450 g, 3.50 mmol) was reacted for 4 h. Compound **17g** was obtained as a white solid (0.410 g, 28% yield). R_f = 0.3 (7:3 EtOAc/hexane). mp 132-137 °C. IR (*v*/cm^{-1}): 3326 (NH, br), 3287, 3073, 1671 (C=O, str), 1515, 1258 (C-O, str), 1108. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.84 (s, 1H, NH), 8.35 (d, *J* = 8.9 Hz, 1H, ArH), 8.18 (d, *J* = 2.3 Hz, 1H, ArH), 7.82 (d, *J* = 7.8 Hz, 1H, ArH), 7.72 (dd, *J* = 8.7, 2.3 Hz, 2H, 2 x ArH), 7.58 (t, *J* = 8.0 Hz, 1H, ArH), 7.40 – 7.34 (m, 1H, ArH), 6.92 (s, 1H, ArH); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 170.5 (ArC), 164.3 (C=O), 162.9 (ArC), 160.0 (ArC), 152.0 (ArC), 149.6 (ArC), 146.6 (ArCH), 138.2 (ArCH), 136.1 (ArC), 130.5 (ArCH), 127.2 (ArC), 125.4 (ArCH), 124.9 (ArCH), 120.8 (ArCH), 115.0 (ArCH), 106.5 (ArCH). HRMS (ES+) calculated for $C_{16}H_{10}Cl_3N_4O_2$ $[M+H]^+$: 394.9864, found: 394.9865.

General procedure for the preparation of benzamides (**19**). 3-((2,4-Dichloropyrimidin-4-yl)oxo)benzoic acid **18** (1.00 g, 3.50 mmol) was placed in a round-bottomed flask, and thionyl chloride (2 mL) was added. The mixture was stirred and heated at 70 °C in an oil bath for overnight. After cooling the mixture to room-temperature, excess thionyl chloride was removed *in vacuo* leaving a pale yellow 3-(2,4-dichloropyrimidin-4-yl)oxo)benzoyl chloride residue which was dissolved in distilled acetonitrile (4 mL) and cautiously added to an ice-cold mixture of aniline (**5**) and triethylamine (2 mL) in distilled acetonitrile or THF (15 mL). The mixture was stirred at 0 °C for 30 min, warmed to room temperature and stirred for 3-22 h. Excess solvent was removed under reduced pressure and the residue dissolved in ethyl acetate (50 mL). The organic mixture was washed with aqueous saturated K_2CO_3 (2 × 50 mL) and saturated brine solution (50 mL) followed by separation of the organic layer which was then dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude product purified by normal silica gel chromatography eluting with 30% EtOAc/hexane to obtain derivatives **19**.
***N*-(4-Bromophenyl)-3-((2,6-dichloropyrimidin-4-yl)oxy)benzamide** (**19a**). 4-Bromoaniline **5a** (0.600 g, 3.50 mmol) was reacted for 5 h. Compound **19a** was obtained as a light brown solid (1.07 g, 70% yield). R_f = 0.4 (7:3 EtOAc/hexane). mp 178-180 ^{o}C. IR (*v*/cm^{-1}): 3341 (NH, br), 3105, 3071, 1661 (C=O, str), 1539, 1259 (C-O, str), 1165. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 10.45 (s, 1H, NH), 7.93 (d, *J* = 7.8 Hz, 1H, ArH), 7.84 – 7.81 (m, 1H, ArH), 7.76 (d, *J* = 8.9 Hz, 2H, 2 x ArH), 7.67 (t, *J* = 7.9 Hz, 1H, ArH), 7.64 – 7.55 (m, 4H, 4 x ArH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 170.8 (ArC), 164.4 (C=O), 161.7 (ArC), 158.2 (ArC), 151.5 (ArC), 138.3 (ArC), 136.7 (ArC), 131.5 (2 x ArCH), 130.2 (ArCH), 125.8 (ArCH), 124.9 (ArCH), 122.3 (2 x ArCH), 120.7 (ArCH), 115.6 (ArC), 107.8 (ArCH). HRMS (ES+) calculated for $C_{17}H_{11}{}^{79}BrCl_2N_3O_2$ $[M+H]^+$: 437.9406, found: 437.9396.
***N*-(3-Bromophenyl)-3-((2,6-dichloropyrimidin-4-yl)oxy)benzamide** (**19b**). 3-Bromoaniline **5b** (0.380 mL, 3.50 mmol) was reacted for 22 h. Compound **19b** was obtained as a light brown solid (0.42 g, 27%). R_f = 0.5 (7:3 EtOAc/hexane). mp 150-152°C. IR (*v*/cm^{-1}): 3301 (NH, br), 1655 (C=O, str), 1275 (C-O, str). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.31 (s, 1H, NH), 7.84 (s, 1H, ArH), 7.71 (d, *J* = 7.7 Hz, 1H, ArH), 7.64 (s, 1H, ArH), 7.49 (q, *J* = 7.9, 7.4 Hz, 2H, 2 x ArH), 7.31 – 7.22 (m, 2H, 2 x ArH), 7.16 (t, *J* = 8.0 Hz, 1H, ArH), 6.86 (s, 1H, ArH); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 170.5 (ArC), 164.7 (C=O), 162.9 (ArC), 159.8 (ArC), 151.8 (ArC), 138.9 (ArC), 136.5 (ArC), 130.4 (ArCH), 127.8 (ArCH), 124.9 (2 x ArC), 123.4 (ArCH), 122.7 (ArC), 120.4 (ArCH), 119.0 (ArCH), 106.5 (ArCH). HRMS (ES+) calculated for $C_{17}H_{11}{}^{79}BrCl_2N_3O_2$ $[M+H]^+$: 437.9406, found: 437.9400.
***N*-(4-Bromo-2-methylphenyl)-3-((2,6-dichloropyrimidin-4-yl)oxy)benzamide** (**19c**). 4-Bromo-2-methylaniline **5c** (0.650 g, 3.50 mmol) was reacted for 22 h. Compound **19c** was obtained as a cream-white solid (0.460 g, 29% yield). R_f = 0.5 (7:3 EtOAc/hexane). mp 138-140 °C. IR (*v*/cm^{-1}): 3086 (NH), 2922, 2854, 1634 (C=O, str),

1551, 1261 (C-O, str), 1110. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.77 – 7.69 (m, 4H, 3 x ArH and NH), 7.56 (t, *J* = 7.9 Hz, 1H, ArH), 7.35 (d, *J* = 8.2 Hz, 3H, 3 x ArH), 6.91 (s, 1H, ArH), 2.29 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 170.6 (ArC), 164.5 (C=O), 163.1 (ArC), 160.1 (ArC), 152.1 (ArC), 136.8 (ArC), 134.7 (ArC), 133.4 (ArCH), 131.9 (ArC), 130.6 (ArCH), 130.0 (ArCH), 125.1 (2 x ArCH), 124.8 (ArCH), 120.7 (ArCH), 118.8 (ArC), 106.7 (ArCH), 17.8 (CH_3). HRMS (ES+) calculated for $C_{18}H_{13}{}^{79}BrCl_2N_3O_2$ $[M+H]^+$: 451.9563, found: 451.9542.

3-((2,6-Dichloropyrimidin-4-yl)oxy)-*N*-(*p*-tolyl)benzamide (**19d**). 4-Methylaniline **5d** (0.380 g, 3.50 mmol) was reacted for 14 h. Compound **19d** was obtained as a white solid (1.17 g, 89% yield). R_f = 0.5 (7:3 EtOAc/hexane). mp 168-170 °C. IR (*v*/cm^{-1}) 3282 (NH, br), 3068, 2920, 1662(C=O, str), 1536, 1301, 1078. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 10.27 (s, 1H, NH), 7.94 (d, *J* = 7.9 Hz, 1H, ArH), 7.85 – 7.81 (m, 1H, ArH), 7.69 – 7.63 (m, 3H, 3 x ArH), 7.56 – 7.50 (m, 2H, 2 x ArH), 7.17 (d, *J* = 8.3 Hz, 2H, 2 x ArH), 2.28 (s, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO-d_6): δ_C 171.3 (ArC), 164.5 (C=O), 162.2 (ArC), 158.7 (ArC), 151.9 (ArC), 137.5 (ArC), 136.8 (ArC), 133.3 (ArC), 130.6 (ArCH), 129.5 (2 x ArCH), 126.1 (ArCH), 125.1 (ArCH), 121.1 (2 x ArCH), 120.9 (ArCH), 108.0 (ArCH), 21.0 (CH_3). HRMS (ES+) calculated for $C_{17}H_{13}Cl_2N_4O_2$ $[M+H]^+$: 375.0410, found: 375.0417.

3-((2,6-Dichloropyrimidin-4-yl)oxy)-*N*-(4-methoxyphenyl)benzamide (**19e**). 4-Methoxyaniline **5e** (0.430 g, 3.50 mmol) was reacted for 3 h. Compound **19e** was obtained as a white solid (1.28 g, 93%). R_f = 0.5 (7:3 EtOAc/hexane). mp 169-171°C. IR (*v*/cm^{-1}) 3297 (NH, br), 3060, 1637 (C=O, str), 1511, 1248 (C-O, str), 1114. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 10.23 (s, 1H, NH), 7.94 (d, *J* = 7.8 Hz, 1H, ArH), 7.83 (s, 1H, ArH), 7.70 – 7.63 (m, 3H, 3 x ArH), 7.56 – 7.50 (m, 2H, 2 x ArH), 6.94 (d, *J* = 9.0 Hz, 2H, 2 x ArH), 3.75 (s, 3H, OCH_3). ^{13}C NMR (101 MHz, DMSO-d_6): δ_C 171.3 (ArC), 164.3 (C=O), 162.2 (ArC), 158.7 (ArC), 156.1 (ArC), 151.9 (ArC), 137.5 (ArC), 132.4 (ArC), 130.6 (ArCH), 126.1 (ArCH), 125.0 (ArCH), 122.5 (ArCH), 121.0 (2 x ArCH), 114.2 (2 x ArCH), 108.0 (ArCH), 55.6 (OCH_3). HRMS (ES+) calculated for $C_{18}H_{14}Cl_2N_3O_3$ $[M+H]^+$: 390.0407, found: 390.0407.

***N*-(4-Chloro-2-methylphenyl)-3-((2,6-dichloropyrimidin-4-yl)oxy)benzamide** (**19h**). 4-Chloro-2-methylaniline **51** (0.500 g, 3.50 mmol) was reacted for 14 h. Compound **19h** was obtained as a white solid (0.740 g, 52% yield). R_f = 0.3 (7:3 EtOAc/hexane). mp 83-85 °C. IR (*v*/cm^{-1}): 3260 (NH, br), 1647 (C=O, str), 1539, 1398, 1262, 1106. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.80 – 7.74 (m, 3H, NH, 2 x ArH), 7.70 – 7.67 (m, 1H, ArH), 7.56 (t, *J* = 8.0 Hz, 1H, ArH), 7.35 (ddd, *J* = 8.2, 2.3, 0.8 Hz, 1H, ArH), 7.20 (d, *J* = 7.5 Hz, 2H, 2 x ArH), 6.91 (s, 1H, ArH), 2.28 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 170.5 (ArC), 164.4 (C=O), 163.0 (ArC), 159.9 (ArC), 151.9 (ArC), 136.7 (ArC), 134.0 (ArC), 131.7 (ArC), 130.8 (ArC), 130.5 (ArCH), 130.4 (ArCH), 126.9 (ArCH), 124.9 (ArCH), 124.7 (ArCH), 120.5 (ArCH), 106.6 (ArCH), 17.8 (CH_3). HRMS (ES+) calculated for $C_{18}H_{13}Cl_3N_3O_2$ $[M+H]^+$: 408.0068, found: 408.0055.

N*-(4-Bromophenyl)-3-((6-chloro-2-(ethylthio)pyrimidin-4-yl)oxy)benzamide** (**20a).* To a round-bottomed flask were added *N*-(4-bromophenyl)-3- ((2,6-dichloropyrimidin-4-yl)oxy)benzamide **19a** (0.50 g, 1.1 mmol) and ethanethiol (0.10 mL, 1.3 mmol) in acetone (15 mL). To the stirring mixture was added NaOH (0.044 g, 1.1 mmol) in water (4.4 mL) and the reaction proceeded for 1 h. Excess solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate (20 mL) and washed successively with aqueous saturated $NaHCO_3$ (2 × 20 mL) and saturated brine solution (20 mL). The organic layer was separated and dried over anhydrous Na_2SO_4. The solvent was evaporated, and the crude mixture was purified by normal silica gel chromatography eluting with 30% ethyl acetate/hexane followed by recrystallization from ethyl acetate and hexane to give **20a** as a white solid (0.22 g, 43% yield). R_f = 0.4 (7:3 EtOAc/hexane). mp 174- 176 °C. IR (*v*/cm^{-1}): 3294 (NH, br), 3100, 1665 (C=O, str), 1535, 1394, 1288 (C-O, str), 1117. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 10.42 (s, 1H, NH), 7.92 (d, *J* = 7.7 Hz, 1H, ArH), 7.85 (s, 1H, ArH), 7.76 (d, *J* = 8.7 Hz, 2H, 2 x ArH), 7.64 (t, *J* = 7.9 Hz, 1H, ArH), 7.54 (t, *J* = 8.4 Hz, 3H, 3 x ArH), 7.11 (s, 1H, ArH), 2.85 (q, *J* = 7.3 Hz, 2H, S-CH_2), 1.11 (t, *J* = 7.2 Hz, 3H, CH_3CH$_2$). ^{13}C NMR (101 MHz, DMSO-d_6): δ_C 172.2 (ArC), 169.7 (ArC), 164.8 (C=O), 161.2 (ArC), 152.1 (ArC), 138.8 (ArC), 136.7 (ArC), 131.9 (2 x ArCH), 130.4 (ArCH), 125.9 (ArCH), 125.6 (ArCH), 122.7 (ArCH), 121.4

(ArCH), 116.0 (ArC), 103.4 (ArCH), 25.3 (CH_2CH_3), 14.7 (CH_2CH_3). HRMS (ES+) calculated for $C_{19}H_{16}{}^{79}BrClN_3O_2S$ $[M+H]^+$: 463.9830, found: 463.9789. Two minor products were also isolated from this reaction: compounds **21** and **22**.

3-((6-Chloro-2-(ethylthio)pyrimidin-4-yl)oxy)-*N* -(*p*-tolyl)benzamide (**20d**).To a round-bottomed flask were added 3-((2,6- dichloropyrimidin-4-yl)oxy)-*N*-(*p*-tolyl)benzamide **19d** (0.50 g, 1.3 mmol) and ethanethiol (0.12 mL, 1.6 mmol) in THF (10 mL) and the mixture was stirred at room temperature. To the stirring mixture was added NaOH (0.068 g, 1.7 mmol) in water (8.5 mL). The reaction mixture was stirred for a further 1 h. The solvent was evaporated under reduced pressure and the residue was dissolved in ethyl acetate (20 mL), followed by washing with aqueous K_2CO_3 (2 × 20 mL) and then saturated brine solution (20 mL). The organic layer was separated and dried over anhydrous Na_2SO_4 and excess solvent was removed under reduced pressure. The crude product was purified by normal silica gel chromatography eluting with 30% EtOAc/hexane. The product was recrystallized from ethyl acetate and hexane to obtain **20d** as a white solid (0.20 g, 38%). R_f = 0.4 (7:3 EtOAc/hexane). mp 168-170 °C. IR (ν/cm^{-1}): 3319 (NH, br), 3090, 1669 (C=O, str), 1534, 1319, 1218 (C-O, str), 1109. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.01 (s, 1H, NH), 7.73 (d, *J* = 7.6 Hz, 1H, ArH), 7.65 (s, 1H, ArH), 7.53 – 7.45 (m, 3H, 3 x ArH), 7.28 (d, *J* = 8.6 Hz, 1H, ArH), 7.15 (d, *J* = 7.8 Hz, 2H, 2 x ArH), 6.54 (s, 1H, ArH), 2.89 (q, *J* = 7.2 Hz, 2H, S-CH_2), 2.33 (s, 3H, CH_3Ar), 1.20 (t, *J* = 7.3 Hz, 3H, CH_3CH_2). ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 173.1 (ArC), 169.2 (ArC), 164.4 (C=O), 161.7 (ArC), 152.2 (ArC), 136.8 (ArC), 135.1 (ArC), 134.5 (ArC), 129.9 (ArCH), 129.6 (2 x ArCH), 125.0 (ArCH), 124.4 (ArCH), 120.6 (ArCH), 120.4 (ArCH), 102.3 (ArCH), 25.6 (CH_2CH_3), 20.9 (CH_3Ar), 14.2 (CH_2CH_3). HRMS (ES+) calculated for $C_{20}H_{19}ClN_3O_2S$ $[M+H]^+$: 400.0881, found: 400.0865. Two minor products were also isolated from this reaction: compounds **21** and **23**.

3-((6-Chloro-2-(propylamino)pyrimidin-4-yl)oxy)-*N*-(*p*-tolyl)benzamide (**24**). To a round-bottomed flask were added 3-((2,6-dichloropyrimidin-4-yl)oxy)-*N*-(*p*-tolyl)benzamide **19d** (0.52 g, 1.3 mmol) and *n*-propylamine (0.11 mL, 1.3 mmol) in THF (10 mL). The mixture was stirred at room temperature and 0.2 M NaOH (0.052 g, 1.3 mmol) was added dropwise. The reaction mixture was stirred for 1 h. Excess solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate (20 mL) followed by washing with aqueous K_2CO_3 (2 × 20 mL) and saturated brine solution (20 mL). The organic layer was separated and dried over anhydrous Na_2SO_4 and the solvent removed *in vacuo*. The crude product was purified by normal silica gel chromatography eluting with 30% EtOAc/hexane. Compound **24** (0.31 g, 66% yield) was obtained as a white amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 10.19 (br s, 1H, NH), 7.91 – 7.82 (m, 2H, 2 x ArH), 7.79 (br s, 0.5H, NH), 7.68 – 7.63 (m, 2.5H, NH, 2 x ArH), 7.59 (t, *J* = 7.9 Hz, ArH), 7.48 – 7.41 (m, 1H, ArH), 7.16 (d, *J* = 7.9 Hz, 2 x ArH), 6.34 and 6.26 (2 x s, 1H, ArH), 3.18 – 3.08 and 2.94 – 2.84 (2 x m, 2H, CH_2NH), 2.28 (s, 3H, CH_3Ar), 1.52 – 1.41 and 1.39 – 1.28 (2 x m, 2H, CH_2CH$_3$), 0.83 and 0.67 (2 x t, *J* = 7.0 Hz, 3H, CH_2CH_3). ^{13}C NMR (101 MHz, DMSO-d_6): δ_C 170.7 and 170.5 (ArC), 164.6 and 164.5 (C=O), 162.0 and 161.9 (ArC), 161.5 and 161.3 (ArC), 152.5 and 152.4 (ArC), 137.0 and 136.6 (ArC), 136.9 (ArC), 133.3 (ArC), 130.4 and 130.0 (ArCH), 129.5 (2 x ArCH), 125.5 and 125.4 (ArCH), 125.3 (ArCH), 121.3 (ArCH), 121.0 (2 x ArCH), 95.2 and 94.1 (ArCH), 43.1 and 42.9 (CH_2NH), 22.3 (CH_2CH_3), 21.0 (CH_3Ar), 11.8 and 11.6 (CH_2CH_3) ; HRMS (ES+) calculated for $C_{21}H_{22}ClN_4O_2$ $[M+H]^+$: 397.1426, found: 397.1412.

3-((6-Chloro-2-(piperidin-1-yl)pyrimidin-4-yl)oxy)-*N*-(*p*-tolyl)benzamide (**25**). To a round-bottomed flask were added 3-((2,6- dichloropyrimidin-4-yl)oxy)-*N*-(*p*-tolyl)benzamide **19d** (0.50 g, 1.3 mmol) and piperidine (0.13 mL, 1.3 mmol) dissolved in THF (10 mL). The mixture was stirred at room temperature and NaOH (0.052 g, 1.3 mmol) in water (1.3 mL) was added dropwise. The mixture was allowed to stir at room temperature for 5 h. The solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate (20 mL) and then washed successively with aqueous K_2CO_3 (2 × 20 mL) and saturated brine solution (20 mL). The organic layer was separated and dried over anhydrous Na_2SO_4. The crude product was purified by normal silica gel

chromatography eluting with 20% EtOAc/hexane. Compound **25** was obtained as a white solid (0.35 g, 64%). R_f = 0.4 (7:3 EtOAc/hexane). mp 155-160 °C. IR (ν/cm^{-1}) 3353 (NH, br), 2947, 2925, 2856, 1647 (C=O, str), 1524, 1314, 1246 (C-O, str). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.91 (s, 1H, NH), 7.72 (d, *J* = 7.8 Hz, 1H, ArH), 7.65 (s, 1H, ArH), 7.53 – 7.44 (m, 3H, 3 x ArH), 7.30 (d, *J* = 8.3 Hz, 1H, ArH), 7.15 (d, *J* = 8.0 Hz, 2H, 2 x ArH), 5.97 (s, 1H, ArH), 3.74 – 3.46 (m, 4H, 4 x piperidinyl-H), 2.33 (s, 3H, CH_3), 1.66 – 1.45 (m, 6H, 6 x piperidinyl-H). ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 170.1 (ArC), 164.6 (C=O), 162.0 (ArC), 160.4 (ArC), 152.8 (ArC), 136.6 (ArC), 135.1 (ArC), 134.5 (ArC), 129.8 (ArCH), 129.6 (2 x ArCH), 125.1 (ArCH), 123.9 (ArCH), 120.5 (ArCH), 120.4 (2 x ArCH), 44.9 (piperidinyl-C), 25.6 (C-piperidinyl-C), 24.6 (C-piperidinyl-C), 20.9 (CH_3Ar). HRMS (ES+) calculated for $C_{23}H_{24}ClN_4O_2$ $[M+H]^+$: 463.9830, found: 463.9789.

3-((6-Hydroxy-2-(propylamino)pyrimidin-4-yl)oxy)-*N*-*(p*-tolyl)benzamide (**26**). To a round bottomed flask were added 3-((6-chloro-2-(propylamino)pyrimidin-4-yl)oxy)-*N*-(p-tolyl)benzamide **24** (0.20 g, 0.50 mmol) dissolved in DMF (10 mL) and 50% w/v NaOH (1 mL) was added. The mixture was heated at 130 °C in an oil bath for 5 h. After cooling the reaction mixture to room temperature, excess solvent was evaporated. The residue was dissolved in ethyl acetate and washed several times (7 × 20 mL) with saturated brine solution and with warm water to remove excess DMF. The organic layer was separated and dried over anhydrous Na_2SO_4, and the solvent was removed *in vacuo*. The crude product was purified by Combiflash column chromatography eluting with 10-40% EtOAc/hexane. A white solid product **26** (0.070 g, 37% yield) was obtained. R_f = 0.3 (7:3 EtOAc/hexane). IR (ν/cm^{-1}): 3289 (NH, br), 1660 (C=O, weak str), 1237 (C-O, str). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.32 (s, 1H, NH-amide), 7.70 – 7.61 (m, 2H, 2 x ArH), 7.52 (d, *J* = 7.8 Hz, 2H, 2 x ArH), 7.40 (t, *J* = 7.8 Hz, 1H, ArH), 7.25 (d, *J* = 8.1 Hz, 1H, ArH), 7.13 (d, *J* = 7.8 Hz, 2H, 2 x ArH), 5.12 (s, 1H, ArH), 4.81 – 4.75 (m, 1H, NH-amine), 3.28 – 3.19 (m, 2H, CH_2N), 2.97 (s, 6H, 2 x CH_3N), 2.31 (s, 3H, CH_3Ar), 1.50 (h, *J* = 7.0 Hz, 2H, CH_3CH_2), 0.87 (t, *J* = 7.3 Hz, 3H, CH_3CH_2). ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 170.5 (ArC), 165.3 (ArC), 165.1 (C=O), 161.8 (ArC), 153.8 (ArC), 136.6 (ArC), 135.4 (ArC), 134.1 (ArC), 129.7 (ArCH), 129.5 (2 x ArCH), 124.7 (ArCH), 123.4 (ArCH), 120.4 (2 x ArCH), 120.1 (ArCH), 76.2 (ArCH), 43.2 (CH_2N), 37.1 ((CH_3)$_2$N), 23.0 (CH_3CH_2), 20.9 (CH_3Ar), 11.5 (CH_3CH_2); HRMS (ES+) calculated for $C_{23}H_{28}N_5O_2$ $[M+H]^+$: 406.2238, found: 406.2252.

X-ray crystallography

Intensity data for compound **12e** were collected on a BRUKER D8 Venture PHOTON II pixel array area detector with Mo Kα graphite monochromated sealed X-ray source (50kV, 30 mA). For compound **24**, data were collected on a Bruker D8 Venture Bio PHOTON III diffractometer with a Cu Kα IμS DIAMOND source (50kV, 1.2 mA). The collection method involved ω- and ϕ-scans, with either 768 × 1024 (PHOTON II) or 1536 × 1024 (PHOTON III) bit data frames. The unit cell and full data set were collected using *APEX4*;[25] *SAINT* was used to integrate the data, and *SADABS* was used to make empirical absorption corrections and scale the data. Space group assignments were made using *XPREP* on all compounds. Using *Olex2*,[26] the crystal structures were solved with the *ShelXT*[27] structure solution program using Intrinsic Phasing and refined with the *ShelXL*[28] refinement package using Least Squares minimization. Non-hydrogen atoms were first refined isotropically followed by anisotropic refinement by full-matrix least-squares calculations based on F^2. The molecule in the crystal structure compound **12e** is fully disordered across the (010) plane. SIMU, RIGU, EADP, and SAME restraints were applied during the final refinements, with the occupancy for the major and minor components being 0.850(2) and 0.150(2), respectively. The crystal structure of compound **24** contains disordered methanol solvent molecules which required a solvent mask (SQUEEZE)[29] to account for the disorder. A solvent mask was calculated, and 60 electrons were found within a volume of 163 Å^3 in one void per unit cell. This is consistent with the presence of two methanol molecules per asymmetric unit (Z'=2) or one methanol solvent molecule per molecule of compound **24**.

Crystal data for 12e: $C_{21}H_{17}BrN_2O_4$ (M =441.27 g/mol): monoclinic, space group $C2/c$ (no. 15), a = 21.3612(9) Å, b = 7.9993(4) Å, c = 22.9711(8) Å, β = 102.2740(10)°, V = 3835.5(3) Å^3, Z = 8, T = 173.00 K, μ(MoKα) = 2.174 mm^{-1}, *Dcalc* = 1.528 g/cm^3, 59065 reflections measured (5.454° ≤ 2Θ ≤ 56.64°), 4768 unique (R_{int} = 0.0395, R_{sigma} = 0.0207) which were used in all calculations. The final R_1 was 0.0387 (I > 2σ(I)) and wR_2 was 0.0886 (all data). CCDC 2469415.

Crystal data for 24: $C_{22}H_{25}ClN_4O_3$ (M =428.91 g/mol): triclinic, space group P-1 (no. 2), a = 9.9951(12) Å, b = 11.5794(14) Å, c = 18.459(2) Å, α = 92.121(6)°, β = 99.267(6)°, γ = 90.313(5)°, V = 2106.9(5) Å^3, Z = 4, T = 173.00 K, μ(CuKα) = 1.868 mm^{-1}, *Dcalc* = 1.352 g/cm^3, 46431 reflections measured (4.854° ≤ 2Θ ≤ 129.984°), 7095 unique (R_{int} = 0.2403, R_{sigma} = 0.2189) which were used in all calculations. The final R_1 was 0.0967 (I > 2σ(I)) and wR_2 was 0.3115 (all data). CCDC 2469416.

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Supplementary Material

Supplementary Material that includes experimental methods, crystal structure data and copies of ^{1}H and ^{13}C NMR spectra is available. The crystallographic data for this paper has been deposited as CCDC 2469415-2469416. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44 1223 336033; E-mail: deposit@ccdc.cam.ac.uk).

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