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A complementary route to diaminopyrimidines through regioselective S_NAr amination reactions

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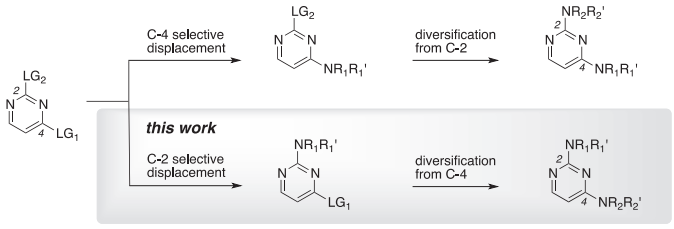
ABSTRACT

A novel approach towards the production of diverse sets of diaminopyrimidines through sequential S_NAr reactions is reported. The readily prepared 2-chloro-4-tetrafluorophenoxypyrymidine reacts regioselectively with amines at the C-2 position. The tetrafluorophenoxy at C-4 can then be replaced with amines in a second S_NAr to afford easy access to a different and complementary set of diaminopyrimidines. The broad utility of this 'C-2 then C-4' two-step sequence has been demonstrated with a range of aromatic and aliphatic amines.

1. Introduction

The pyrimidine nucleus is found in many natural products and has been used as a core scaffold in numerous drug discovery programmes.[1–7] Its widespread presence in pharmaceutical substances can, in part, be attributed to the versatility of readily available reactive pyrimidine building blocks such as 2,4-dichloropyrimidine **1**. Nucleophilic aromatic substitutions (S_NAr) of 2,4-dichloropyrimidine occur preferentially at the most electron-deficient C-4 position.[1–3] However, product mixtures arising from substitution at C-2 in addition to C-4 are generally obtained, with ratios depending on the nature of the nucleophile. While the purification of products from these mixtures can often prove difficult,[8–14] 2,4-dihalopyrimidines have provided privileged blocks for parallel synthesis in drug discovery,[15] mostly through diversification at C-4 followed by a substitution at C-2 (Scheme 1). The complementary set of molecules derived from substitution at C-2 followed by diversification at C-4 can be obtained from a 4-methoxypyrimidine or 4-pyrimidinone with a leaving group at position-2 (e.g., Cl, SMe),[16–19] or 4-thioalkyl-2-chloropyrimidines.[20] In these cases though, an intermediate step is required between the two S_NAr reactions: chlorination of the 4-position (e.g., using phosphoryl chloride) in the first two examples, and oxidation of the thioalkyl group in the third. The need for these intermediate reactions can limit the scope of the final products.



Scheme 1. Two complementary approaches for the S_NAr diamination of pyrimidines where LG_1 and LG_2 are leaving groups.

In this work we describe a new methodology of broad utility, that allows C-2 substitution followed by C-4 on a pyrimidine, without recourse to an intermediate step and its consequential limitations (Scheme 1). For this, we required a 2,4-disubsituted pyrimidine with a leaving group LG_1 that would render the C-2 position more reactive than the C-4 position, when exposed to nucleophiles. An important criterion in our quest was that the pyrimidine starting point should be readily available.

2. Results and discussion

Pentafluorophenoxide is widely used as a leaving group in peptide chemistry[21] and its reactivity is generally considered to be similar to that of chloride. The leaving group capability of the polyfluorophenoxy type can be adjusted according to the number of fluorine substituents.[22] We envisaged using three different polyfluorophenoxy leaving groups at C-4, the pentafluorophenoxy, the

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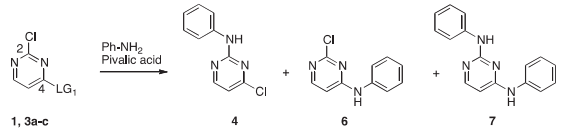
2,3,5,6-tetrafluorophenoxy and the 2,4,6-trifluorophenoxy (as in **3a**, **3b** and **3c**, respectively).

In each case, calculation of the electrophilicity at C-4 was lower than if it had been substituted by a chlorine atom and was also lower than that of the chlorine-substituted C-2 (Fukui indices[23] at C-4: 0.26, 0.08, 0.09 and 0.008 for **1**, **3a**, **3b** and **3c**, respectively; Fukui indices at C-2: 0.01, 0.12, 0.11 and 0.12 for **1**, **3a**, **3b** and **3c**, respectively). Based on these calculations, we predicted S_NAr would take place at the C-2 position preferentially. Interestingly, Fukui indices suggested that the electron density at the polyfluorophenoxy-substituted C-4 was barely affected by the number of fluorine atoms on the benzene ring. Therefore, we carried out a number of experiments to reveal the relative merits of the different polyfluorophenoxy leaving groups.

2-Chloro-4-pentafluorophenoxypyrimidine **3a** was obtained from 2,4-dichloropyrimidine and 1 equiv of pentafluorophenol in the presence of DIPEA, in high yield (82%). The high C-4 regioselectivity obtained for this substitution is in agreement with the literature for S_NAr with species such as phenoxides.[24] 2-Chloro-4-pentafluorophenoxypyrimidine **3a** reacted readily with aniline to provide a mixture of three compounds, where substitution at the C-2 position provided the major product in a 4:1 ratio (Table 1). 2,3,5,6-Tetrafluorophenoxypyrimidine **3b** and the 2,4,6-trifluorophenoxypyrimidine **3c** were prepared in high yields (84% and 90%, respectively) in a similar fashion to their pentafluorophenoxy analogue **3a**. These compounds also reacted readily with aniline, but this time, the products resulting from substitution at C-2, 2-anilino-4-tetrafluorophenoxypyrimidine and 2-anilino-4-trifluorophenoxypyrimidine, were formed almost exclusively. The trifluorophenoxy leaving group, however, was found to be insufficiently reactive to be useful as a starting point for the parallel derivatization to form diamino-substituted pyrimidines. Despite the fact that the pentafluoropyrimidine appeared to have the best reactivity, we chose to use the 2,3,5,6-tetrafluorophenoxypyrimidine variant **3b** because of the regioselectivity advantage in its use in S_NAr reactions.

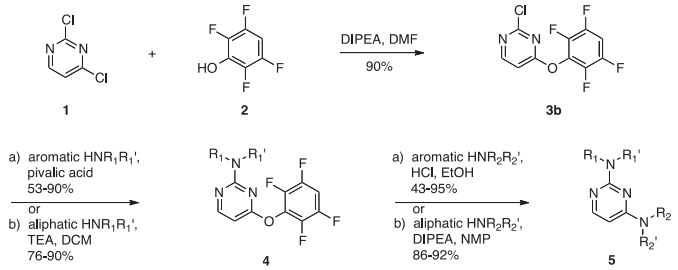
Table 1
Comparison of regioselectivity profiles following S_NAr with aniline



Entry	Substrate	LG_1	Ratio **4**/**6**/**7**
1	**1**	Cl	35:47:18
2	**3a**	Pentafluorophenoxy	80:8:12
3	**3b**	2,3,5,6-Tetrafluorophenoxy	93:1:6
4	**3c**	2,4,6-Trifluorophenoxy	97:1:2

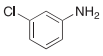
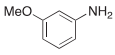
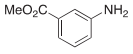
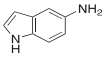
2.1. Scope of regioselective substitution at C-2

We next examined the scope of the regioselectivity with various nucleophilic amines reacting with **3b** under standard conditions: acid catalysis for aromatic amines (pivalic acid) and basic conditions for aliphatic amines (triethylamine) (Scheme 2). With aromatic amines, reaction of **3b** provided the C-2 substituted products **4a**–**h** (Table 2) in moderate to excellent yields (53–90%). Typically, we used 1.5 equiv of amine, in the presence of pivalic acid (10 equiv) at 60 °C for 2 h (method A). The reaction rates were in line with the expectations, dependent on the hindrance and the nucleophilicity of the reacting amine. Similarly good yields (76–87%) were obtained when **3b** was treated with aliphatic amines[25] under basic conditions. Tetrafluorophenoxypyrimidine **3b** was found to react with stoichiometric amount of aliphatic amines in dichloromethane, in the presence of triethylamine (2 equiv) at ambient temperature for ~20 h (method B). S_NAr with aromatic amines were exquisitely selective for the C-2 substitution, the undesired C-4 isomers occasionally being detected only in trace amounts (≤2%), whereas significant amounts of C-4 adducts (5–10%) were observed in reactions with aliphatic amines. We were also able to show that the C2/C4 selectivity, in the case of aliphatic amines could also be undermined by use of inappropriate solvents, such as DMF or DMSO, which have been reported to direct S_NAr towards the C-4 substitution.[10]



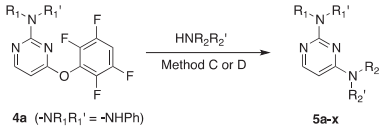
Scheme 2. Synthesis of disubstituted pyrimidines **5** via C-2 then C-4 regioselective S_NAr reactions.

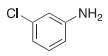
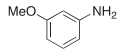
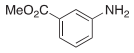
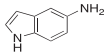
Table 2
First S_NAr displacement of **3b** at C-2 with aromatic and aliphatic amines

Entry	HNR_1R_1'	Method[a]	Product	Yield[b] (%)
1		A	**4a**	83
2		A	**4b**	74
3		A	**4c**	90
4		A	**4d**	89
5		A	**4e**	73
6		A	**4f**	53
7		A	**4g**	76
8		A	**4h**	77
9		B	**4i**	76
10		B	**4j**	90
11		B	**4k**	77
12		B	**4l**	87
13		B	**4m**	85

[a] Method A: amine (1.5 equiv), pivalic acid (10 equiv), 60 °C, 2 h. Method B: amine (1 equiv), TEA (2 equiv), DCM, rt, 12 h.
[b] Isolated yield.

Table 3
Second S_NAr displacement of **4a** and **4j** at C-4 with aromatic and aliphatic amines



Entry	Substrate	$HNR_2R'_2$	Method[a]	Product	Yield[b] (%)
1	**4a**		C	**5a**	84
2	**4j**			**5b**	77
3	**4a**		C	**5c**	86
4	**4j**			**5d**	81
5	**4a**		C	**5e**	83
6	**4j**			**5f**	83
7	**4a**		C	**5g**	84
8	**4j**			**5h**	85
9	**4a**		C	**5i**	86
10	**4j**			**5j**	95
11	**4a**		C	**5k**	43
12	**4j**			**5l**	84
13	**4a**		C	**5m**	70
14	**4j**			**5n**	62
15	**4a**		C	**5o**	50
16	**4j**			**5p**	64
17	**4a**		D	**5q**	89
18	**4j**			**5r**	87
19	**4a**		D	**5s**	92
20	**4j**			**5t**	81
21	**4a**		D	**5u**	90
22	**4j**			**5v**	86
23	**4a**		D	**5w**	89
24	**4j**			**5x**	92

2.2. Scope of regioselective substitution at C-4

We then needed to establish if the 2,3,5,6-tetrafluorophenoxy moiety was a sufficiently good leaving group to ensure versatile and high yielding substitution at C-4 in the presence of an amine at C-2. For this experiment, we chose to use 2-anilinopyrimidine **4a** and 2-morpholino **4j** as representative examples of an aromatic and an aliphatic amine at the C-2 position (Table 3). Both substrates **4a** and **4j** reacted with a variety of aromatic amines under acid-catalyzed conditions. Pivalic acid catalysis, as used in the previous reaction set (method A), led to unacceptable reaction times, whereas catalytic HCl provided universal high yields of the desired products at the C-4 position (**5a**–**p**, 43–95%). Typically, tetrafluorophenoxypyrimidines **4a** and **4j** were treated with 1.5 equiv of aromatic amine, in the presence of a catalytic amount of hydrochloric acid in aqueous ethanol, at 95 °C overnight (method C). The yields of the S_NAr reaction at C-4 were similarly high for both substrates **4a** and **4j** and largely independent of the nature of the aniline substituents. The most hindered 2-chloroaniline and the deactivated 3-aminopyridine gave moderate yields of the C-4 adduct when the anilino substrate **4a** was used (**5k** and **5o**, 43% and 50%, respectively). However, these aromatic amines gave significantly better yields of the C-4 adducts with the more reactive morpholino substrate **4j** (**5l** and **5p**, 84% and 64%, respectively). In addition, this methodology could be extended to secondary aniline (**5m** and **5n**).

Both **4a** and **4j** reacted with aliphatic amines to afford the C-4 substituted products **5q**–**x** in excellent yields (86–92%). Substrates **4a** and **4j** were treated with a slight excess of aliphatic amines in NMP, in the presence of diisopropylethylamine (2 equiv) at 110 °C overnight (method D).

3. Conclusions

We have developed a method that enables the sequential bis-amination of the pyrimidine nucleus, starting with a regioselective S_NAr reaction at the C-2 position, followed by a second S_NAr reaction at the C-4 position. This simple approach is based on the use of 2-chloro-4-tetrafluorophenoxypyrimidine **3b** as a starting building block. The presence of the tetrafluorophenoxy leaving group affects the reactivity of the electrophilic centres at C-2 and C-4, leading to the unconventional C-2 then C-4 regioselective bis-amination. The method is applicable to a wide range of primary/secondary aromatic and aliphatic amines. This novel approach complements the more conventional C-4 then C-2 displacement sequence and is likely to become a valuable tool for researchers aiming at a rapid and facile exploration at position C-4 of the pyrimidine nucleus.

4. Experimental section

4.1. General

^1H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded at 500 MHz, 125 MHz and 470 MHz, respectively. MS samples were analyzed on a mass spectrometer operated in single MS mode with electrospray ionization. Samples were introduced into the mass spectrometer using chromatography. HRMS spectra were recorded on a QTOF spectrometer operating in positive electrospray mode. Flash chromatography were carried out on an automated system, with silica as a solid support and eluting with a 0–100% EtOAc/

[a] Method C: amine (1.5 equiv), HCl, EtOH/H_2O, 95 °C, 12 h. Method D: amine (1.5 equiv), DIPEA (2 equiv), NMP, 110 °C, o/n.
[b] Isolated yield.

petroleum ether gradient. All final products had a purity ≥95%, unless specified otherwise in the experimental details. The purity of the final compounds was determined using HPLC method: analytical reverse phase HPLC equipped with a 5 mm C-18 reverse phase column; the mobile phases were acetonitrile/methanol (1:1) and water (10 mm ammonium acetate). Commercially available reagents and solvents were used without further purification.

4.2. General method for the preparation of compounds 3a–c

To a solution of 2,4-dichloropyrimidine **1** (1 g, 6.71 mmol) in DMF (2 mL) was added the required polyfluorophenol **2** (1 equiv, 6.71 mmol), followed by DIPEA (1.04 g, 1.4 mL, 8.05 mmol) and the mixture heated to 80 °C for 1 h. The reaction mixture was cooled to ambient temperature and partitioned between a mixture of water (50 mL) and diethyl ether (70 mL). The organic layer was washed with water (30 mL×2), aqueous 0.1 M NaOH (30 mL) and brine. The organic layer was then dried ($MgSO_4$), filtered and concentrated in vacuo to yield **3a–c** as colourless oils, which slowly solidified to waxy solids upon standing.

*4.2.1. 2-Chloro-4-(2,3,4,5,6-pentafluorophenoxy)pyrimidine **3a**.* Following the general procedure, the reaction was carried out with pentafluorophenol to provide title compound (1.63 g, 82%) as a white solid, mp 78 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.61 (d, J=5.7 Hz, 1H), 7.11 (d, J=5.7 Hz, 1H);^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9, 161.0, 160.5, 142.5, 140.5, 138.9, 137.2, 106.6; MS m/z: 296.7 $(M+H)^+$; HRMS (ESI): calcd for $C_{10}H_2ClF_5N_2O$ (MH^+) 296.9854; found 296.9858.

*4.2.2. 2-Chloro-4-(2,3,5,6-tetrafluorophenoxy)pyrimidine **3b**.* Following the general procedure, the reaction was carried out with 2,3,5,6-tetrafluorophenol to provide title compound (1.57 g, 84%) as a white solid, mp 90 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.84 (d, J=5.7 Hz, 1H), 8.07–8.0 (m, 1H), 7.61 (d, J=5.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.0, 160.9, 160.5, 146.1 ($^1J_{C-F}$ 253 Hz), 140.9 ($^1J_{C-F}$ 252 Hz), 130.4, 106.6, 103.7 ($^2J_{C-F}$ 23 Hz); MS m/z: 279.0 $(M+H)^+$; HRMS (ESI): calcd for $C_{10}H_3ClF_4N_2O$ (MH^+) 278.9948; found 278.9960.

*4.2.3. 2-Chloro-4-(2,4,6-trifluorophenoxy)pyrimidine **3c**.* Following the general procedure, the reaction was carried out with 2,4,6-trifluorophenol to provide title compound (1.57 g, 90%) as a white solid, mp 95 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.56 (d, J=5.7 Hz, 1H), 7.07 (d, J=5.7 Hz, 1H), 6.82–6.88 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6, 160.6, 160.5, 158.7, 156.4, 154.2, 106.5, 101.4; MS m/z: 260.0 $(M+H)^+$; HRMS (ESI): calcd for $C_{10}H_4ClF_3N_2O$ (MH^+) 261.0043; found 261.0045.

4.3. General procedure for the nucleophilic aromatic substitution of 2-chloro-4-(2,3,5,6-tetrafluorophenoxy)pyrimidine with aromatic amines to afford products 4a–h (method A)

To a mixture of 2-chloro-4-(2,3,5,6-tetrafluorophenoxy)pyrimidine **3b** (200 mg, 0.72 mmol) and 2,2-dimethylpropanoic acid (733 mg, 0.412 mL, 7.2 mmol, 10 equiv) was added the aromatic amine (1.08 mmol, 1.5 equiv) and the mixture was heated to 60 °C for 2 h. The reaction mixture was partitioned between a mixture of water (20 mL) and diethyl ether (30 mL). The organic layer was washed with water (20 mL×2), aqueous 0.1 M NaOH (20 mL) and brine (20 mL). The organic layer was then dried ($MgSO_4$), filtered and concentrated in vacuo to yield light yellow solids, which were triturated in a small amount of 50:50 diethyl ether/petroleum ether, filtered and dried to yield compounds **4a–h** as white solids.

*4.3.1. N-Phenyl-4-(2,3,5,6-tetrafluorophenoxy)pyrimidin-2-amine **4a**.* Following the general procedure, the reaction was carried out with aniline to provide title compound (200 mg, 83%) as a white solid, mp 151 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (d, J=7.0 Hz, 1H), 7.36–7.32 (m, 2H), 7.28–7.25 (m, 1H), 7.25–7.20 (m, 2H), 7.10–7.05 (m, 1H), 7.05–7.00 (m, 1H), 6.56 (d, J=7.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8, 160.3, 159.6, 147.1, 145.2, 142.2, 140.3, 138.6, 131.5, 128.6, 123.0, 119.4, 102.7, 98.2; MS m/z: 336.0 $(M+H)^+$; HRMS (ESI): calcd for $C_{16}H_9F_4N_3O$ (MH^+) 336.0760; found 336.0761.

*4.3.2. N-(3-Chlorophenyl)-4-(2,3,5,6-tetrafluorophenoxy)pyrimidin-2-amine **4b**.* Following the general procedure, the reaction was carried out with 3-chloroaniline to provide title compound (196 mg, 74%) as a white solid, mp 171 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (d, J=7.0 Hz, 1H), 7.54–7.52 (m, 1H), 7.42 (br s, 1H), 7.18–7.05 (m, 3H), 7.01–6.97 (m, 1H), 6.62 (d, J=7.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.0, 159.8, 159.0, 147.2, 145.2, 142.1, 139.7, 134.5, 129.6, 122.9, 118.9, 117.1, 103.3, 98.9; MS m/z: 370.0 $(M+H)^+$; HRMS (ESI): calcd for $C_{16}H_8ClF_4N_3O$ (MH^+) 370.0370; found 370.0378.

*4.3.3. N-(3-Methoxyphenyl)-4-(2,3,5,6-tetrafluorophenoxy)pyrimidin-2-amine **4c**.* Following the general procedure, the reaction was carried out with 3-methoxyaniline to provide title compound (236 mg, 90%) as a white solid, mp 99 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (d, J=5.6 Hz, 1H), 7.22 (br s, 1H), 7.15–7.11 (m, 1H), 7.09–7.03 (m, 2H), 6.90–6.87 (m, 1H), 6.60–6.56 (m, 2H), 3.78 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8, 160.1, 159.5, 147.2, 145.2, 142.2, 139.8, 129.3, 111.8, 107.7, 106.0, 102.8, 98.4, 55.2; MS m/z: 366.0 $(M+H)^+$; HRMS (ESI): calcd for $C_{17}H_{11}F_4N_3O_2$ (MH^+) 366.0866; found 366.0875.

*4.3.4. Methyl 3-((4-(2,3,5,6-tetrafluorophenoxy)pyrimidin-2-yl) amino)benzoate **4d**.* Following the general procedure, the reaction was carried out with methyl 3-aminobenzoate to provide title compound (251 mg, 89%) as a white solid, mp 162 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (d, J=5.6 Hz, 1H), 7.95 (br s, 1H), 7.72–7.68 (m, 2H), 7.33–7.27 (m, 2H), 7.10–7.02 (m, 1H), 6.61 (d, J=5.6 Hz, 1H), 3.93 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8, 166.7, 160.2, 159.4, 147.1, 145.2, 142.1, 140.0, 138.8, 130.8, 128.7, 124.1, 123.9, 120.7, 102.9, 98.9, 52.2; MS m/z: 394.2 $(M+H)^+$; HRMS (ESI): calcd for $C_{18}H_{11}F_4N_3O_3$ (MH^+) 394.0815; found 394.0820.

*4.3.5. N-(4-(2,3,5,6-Tetrafluorophenoxy)pyrimidin-2-yl)-1H-indol-5-amine **4e**.* Following the general procedure, the reaction was carried out with 1*H*-indol-5-amine to provide title compound (196 mg, 73%) as a white solid, mp 168 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41 (d, J=5.6 Hz, 1H), 8.24 (br s, 1H), 7.48–7.42 (m, 1H), 7.38 (s, 1H), 7.20–7.17 (m, 1H), 7.13–7.11 (m, 1H), 7.09–6.98 (m, 2H), 6.58 (d, J=5.6 Hz, 1H), 6.56–6.53 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9, 160.2, 160.0, 147.2, 145.2, 142.3, 140.3, 136.4, 130.9, 123.4, 122.2, 120.1, 110.0, 106.6, 102.6, 98.8, 97.9; MS m/z: 375.1 $(M+H)^+$.

*4.3.6. N-(2-Chlorophenyl)-4-(2,3,5,6-tetrafluorophenoxy)pyrimidin-2-amine **4f**.* Following the general procedure, the reaction was carried out with 2-chloroaniline to provide title compound (141 mg, 53%) as a white solid, mp 119 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (d, J=5.7 Hz, 1H), 7.98 (d, J=8.2 Hz, 1H), 7.52 (s, 1H), 7.37–7.34 (m, 1H), 7.12–7.04 (m, 2H), 6.97–6.93 (m, 1H), 6.63 (d, J=5.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8, 160.3, 159.2, 147.1, 145.2, 142.1, 140.2, 135.4, 129.2, 126.8, 123.3, 122.8, 120.4, 102.8, 99.1; MS m/z: 370.1 $(M+H)^+$.

*4.3.7. N-Methyl-N-phenyl-4-(2,3,5,6-tetrafluorophenoxy)pyrimidin-2-amine **4g**.* Following the general procedure, the reaction was carried out with *N*-methylaniline to provide title compound

(191 mg, 76%) as a white solid, mp 123 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 (d, J=5.5 Hz, 1H), 7.31–7.26 (m, 2H), 7.19–7.15 (m, 2H), 6.93–6.87 (m, 1H), 6.41 (d, J=5.5 Hz, 1H), 3.42 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0, 161.4, 160.0, 146.8, 144.8, 144.6, 142.0, 140.1, 128.6, 126.3, 125.7, 104.0, 102.2, 96.2, 38.1; MS m/z: 349.7 $(M+H)^+$; HRMS (ESI): calcd for $C_{17}H_{11}F_4N_3O$ (MH^+) 350.0916; found 350.0931.

*4.3.8. N-(Pyridin-3-yl)-4-(2,3,5,6-tetrafluorophenoxy)pyrimidin-2-amine **4h**.* Following the general procedure, the reaction was carried out with pyridin-3-amine to provide title compound (186 mg, 77%) as a white solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.20 (d, J=5.7 Hz, 1H), 9.06–9.02 (m, 1H), 8.83–8.78 (m, 1H), 8.17–8.07 (m, 1H), 7.91 (d, J=5.7 Hz, 1H), 7.88–7.86 (m, 2H), 6.98 (s, 1H); MS m/z: 336.8 $(M+H)^+$.

4.4. General procedure for the nucleophilic aromatic substitution of 2-chloro-4-(2,3,5,6-tetrafluorophenoxy)pyrimidine with aliphatic amines to provide compounds 4i–4m (method B)

To a solution of 2-chloro-4-(2,3,5,6-tetrafluorophenoxy)pyrimidine **3b** (30 mg, 0.11 mmol) in CH_2Cl_2 (1 mL) were added the aliphatic amine (0.11 mmol, 1 equiv) and triethylamine (22.2 mg, 30.5 μL, 0.22 mmol, 2 equiv). The mixture was allowed to stir at room temperature for 12 h, diluted with CH_2Cl_2 (10 mL) before being washed with an aqueous saturated solution of bicarbonate (10 mL) and then brine (10 mL). The organic layer was dried ($MgSO_4$) and concentrated to a solid in vacuo. The product was purified by chromatography using a diethyl ether/petroleum ether gradient as eluent to yield compounds **4i**–**4m**.

*4.4.1. 2-(4-Methylpiperazin-1-yl)-4-(2,3,5,6-tetrafluorophenoxy)pyrimidine **4i**.* Following the general procedure, the reaction was carried out with *N*-methylpiperazine to provide title compound (28 mg, 76%) as a white solid, mp 131 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (d, J=5.5 Hz, 1H), 7.07–6.99 (m, 1H), 6.32 (d, J=5.5 Hz, 1H), 3.75–3.6 (m, 4H), 2.45–2.4 (m, 4H), 2.32 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.5, 161.2, 160.0, 146.9, 145.0, 142.1, 140.1, 102.9, 95.22, 54.5, 46.1, 43.6; MS m/z: 343.1 $(M+H)^+$; HRMS (ESI): calcd for $C_{15}H_{14}F_4N_4O$ (MH^+) 343.1182; found 343.1195.

*4.4.2. 4-(4-(2,3,5,6-Tetrafluorophenoxy)pyrimidin-2-yl)morpholine **4j**.* Following the general procedure, the reaction was carried out with morpholine to provide title compound (TFA salt) (43 mg, 90%) as a white solid, mp 111 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.41 (d, J=5.5 Hz, 1H), 8.0–7.92 (m, 1H), 6.56 (d, J=5.5 Hz, 1H), 3.65–3.37 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.6, 161.0, 159.8, 147.0, 145.0, 140.9, 139.5, 106.6, 102.8, 95.8, 66.4, 44.1; MS m/z: 329.9 $(M+H)^+$; HRMS (ESI): calcd for $C_{14}H_{11}F_4N_3O_2$ (MH^+) 330.0866; found 330.0881.

*4.4.3. N-Benzyl-4-(2,3,5,6-tetrafluorophenoxy)pyrimidin-2-amine **4k**.* Following the general procedure, the reaction was carried out with benzylamine to provide title compound (29 mg, 77%) as a white solid, mp 144 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (br s, 1H), 7.39–7.05 (m, 5H), 7.07–6.97 (m, 1H), 6.38 (d, J=5.6 Hz, 1H), 4.60–4.20 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8, 162.1, 160.2, 147.0, 145.0, 142.1, 140.1, 138.6, 131.5, 128.7, 127.3, 102.2, 96.3, 45.5; MS m/z: 351.1 $(M+H)^+$.

*4.4.4. N-Propyl-4-(2,3,5,6-tetrafluorophenoxy)pyrimidin-2-amine **4l**.* Following the general procedure, the reaction was carried out with propylamine to provide title compound (28 mg, 87%) as a white solid, mp 83 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25–8.20 (m, 1H), 7.10–6.99 (m, 1H), 6.43–6.40 (m, 1H), 3.40–3.00 (m, 2H), 1.65–1.40 (m, 2H), 0.93–0.63 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.8, 159.3, 147.0, 145.0, 142.1, 141.1, 102.5, 95.8, 43.2, 22.5, 11.3; MS m/z: 302.8 $(M+H)^+$; HRMS (ESI): calcd for $C_{13}H_{11}F_4N_3O$ (MH^+) 302.0916; found 302.0925.

*4.4.5. N-Cyclopentyl-4-(2,3,5,6-tetrafluorophenoxy)pyrimidin-2-amine **4m**.* Following the general procedure, the reaction was carried out with cyclopentylamine to provide title compound (30 mg, 85%) as a white solid, mp 100 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25–8.05 (m, 1H), 7.18–7.06 (m, 1H), 6.48–6.38 (m, 1H), 3.88–3.70 (m, 1H), 1.93–1.65 (m, 4H), 1.62–1.45 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.4, 154.2, 147.0, 145.0, 142.0, 140.0, 103.0, 96.0, 53.5, 32.5, 23.7; MS m/z: 327.9 $(M+H)^+$; HRMS (ESI): calcd for $C_{15}H_{13}F_4N_3O$ (MH^+) 328.1073; found 328.1079.

4.5. General procedure for the nucleophilic aromatic substitution of 4a and 4j with aromatic amines to form compounds 5a–5p (method C)

To a solution of *N*-phenyl-4-(2,3,5,6-tetrafluorophenoxy)pyrimidin-2-amine **4a** or 4-(4-(2,3,5,6-tetrafluorophenoxy)pyrimidin-2-yl)morpholine **4j** (0.1 mmol) in a mixture of ethanol and water (0.5 mL:0.15 mL) were added the aromatic aniline (0.15 mmol, 1.5 equiv) and a catalytic amount of 2 M HCl. The mixture was heated 95 °C for 12 h, then cooled to ambient temperature and concentrated to a solid in vacuo. Purification by chromatography using an EtOAc/hexane gradient as eluent provided compounds **5a**–**5p**.

*4.5.1. N2,N4-Diphenylpyrimidine-2,4-diamine **5a**.*[26] Following the general procedure, the reaction was carried out with **4a** and aniline to provide title compound (22 mg, 84%) as a white solid, mp 124 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, J=5.8 Hz, 1H), 7.66–7.60 (m, 2H), 7.43–7.38 (m, 4H), 7.36–7.31 (m, 2H), 7.24–7.17 (m, 1H), 7.02–7.08 (m, 1H), 6.79 (s, 1H), 6.22 (d, J=5.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.3, 159.8, 156.8, 139.6, 138.3, 129.2, 128.8, 124.6, 122.3, 119.8, 96.7; MS m/z: 263.1 $(M+H)^+$; HRMS (ESI): calcd for $C_{16}H_{14}N_4$ (MH^+) 263.1297; found 263.1306.

*4.5.2. 2-Morpholino-N-phenylpyrimidin-4-amine **5b**.* Following the general procedure, the reaction was carried out with **4j** and aniline to provide title compound (20 mg, 77%) as a white solid, mp 143 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, J=5.5 Hz, 1H), 7.39–7.36 (m, 4H), 7.18–7.13 (m, 1H), 6.56 (br s, 1H), 6.08 (d, J=5.5 Hz, 1H), 3.83–3.77 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.9, 161.0, 157.1, 138.8, 129.2, 124.0, 121.7, 94.9, 66.9, 44.3; MS m/z: 277.2 $(M+H)^+$; MS m/z: 257.1 $(M+H)^+$; HRMS (ESI): calcd for $C_{14}H_{16}N_4O$ (MH^+) 257.1402; found 257.1408.

*4.5.3. N4-(3-Chlorophenyl)-N2-phenylpyrimidine-2,4-diamine **5c**.* Following the general procedure, the reaction was carried out with **4a** and 3-chloroaniline to provide title compound (26 mg, 86%) as a white solid, mp 141 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, J=5.8 Hz, 1H), 7.64–7.56 (m, 3H), 7.39–7.32 (m, 3H), 7.29–7.23 (m, 2H), 7.15–7.12 (m, 1H), 7.08–7.04 (m, 1H), 6.76 (s, 1H), 6.20 (d, J=5.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.8, 159.8, 157.0, 139.8, 139.4, 134.8, 130.1, 128.9, 124.1, 122.7, 121.5, 119.9, 119.5, 97.3; MS m/z: 297.7 $(M+H)^+$; HRMS (ESI): calcd for $C_{16}H_{13}ClN_4$ (MH^+) 297.0907; found 297.0914.

*4.5.4. N-(3-Chlorophenyl)-2-morpholinopyrimidin-4-amine **5d**.* Following the general procedure, the reaction was carried out with **4j** and 3-chloroaniline to provide title compound (23 mg, 81%) as a white solid, mp 106 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, J=5.7 Hz, 1H), 7.62–7.60 (m, 1H), 7.30–7.25 (m, 1H), 7.23–7.20 (m, 1H), 7.12–7.08 (m, 1H), 6.48 (br s, 1H), 6.03 (d, J=5.7 Hz, 1H),

3.83–3.79 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.8, 160.4, 157.3, 140.2, 134.7, 130.0, 123.7, 121.0, 118.8, 95.4, 66.9, 44.3; MS *m*/*z*: 291.1 $(M+H)^+$; HRMS (ESI): calcd for $C_{14}H_{15}ClN_4O$ (MH^+) 291.1013; found 291.1019.

4.5.5. N4-(3-Methoxyphenyl)-N2-phenylpyrimidine-2,4-diamine ***5e***. Following the general procedure, the reaction was carried out with **4a** and 3-methoxyaniline to provide title compound (24 mg, 83%) as a white solid, mp 133 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, *J*=5.9 Hz, 1H), 7.66–7.59 (m, 2H), 7.38–7.28 (m, 4H), 7.06–7.02 (m, 1H), 7.01–6.99 (m, 2H), 6.96–6.90 (m, 1H), 6.79 (br s, 1H), 6.77–6.74 (m, 1H), 6.25 (d, *J*=5.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.2, 160.4, 159.7, 156.7, 139.6, 130.0, 128.8, 122.5, 119.8, 114.5, 109.9, 108.2, 96.9, 55.4; MS *m*/*z*: 293.3 $(M+H)^+$; HRMS (ESI): calcd for $C_{17}H_{16}N_4O$ (MH^+) 293.1402; found 293.1405.

4.5.6. N-(3-Methoxyphenyl)-2-morpholinopyrimidin-4-amine ***5f***. Following the general procedure, the reaction was carried out with **4j** and 3-methoxyaniline to provide title compound (24 mg, 83%) as a white solid, mp 108 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, *J*=5.6 Hz, 1H), 7.28–7.25 (m, 1H), 7.08–7.06 (m, 1H), 6.93–6.90 (m, 1H), 6.71–6.67 (m, 1H), 6.51 (br s, 1H), 6.08 (d, *J*=5.6 Hz, 1H), 3.84 (s, 3H), 3.83–3.78 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.8, 160.9, 160.3, 157.1, 140.0, 129.9, 113.7, 109.3, 107.4, 95.2, 66.9, 55.3, 44.4; MS *m*/*z*: 287.2 $(M+H)^+$; HRMS (ESI): calcd for $C_{15}H_{18}N_4O_2$ (MH^+) 287.1508; found 287.1506.

4.5.7. Methyl 3-((2-(phenylamino)pyrimidin-4-yl)amino)benzoate ***5g***. Following the general procedure, the reaction was carried out with **4a** and methyl 3-aminobenzoate to provide title compound (27 mg, 84%) as a white solid, mp 172 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, *J*=5.7 Hz, 1H), 8.04–8.01 (m, 1H), 7.85–7.82 (m, 1H), 7.75–7.72 (m, 1H), 7.63–7.58 (m, 2H), 7.46 (t, *J*=7.9 Hz, 1H), 7.34–7.31 (m, 2H), 7.17–7.04 (m, 2H), 6.69 (br s, 1H), 6.21 (d, *J*=5.8 Hz, 1H), 3.93 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6, 160.9, 157.3, 139.5, 138.7, 131.2, 129.3, 128.8, 126.3, 125.3, 122.7, 122.5, 119.7, 97.1, 52.3; MS *m*/*z*: 321.1 $(M+H)^+$; HRMS (ESI): calcd for $C_{18}H_{16}N_4O_2$ (MH^+) 321.1352; found 321.1356.

4.5.8. Methyl 3-((2-morpholinopyrimidin-4-yl)amino)benzoate ***5h***. Following the general procedure, the reaction was carried out with **4j** and methyl 3-aminobenzoate to provide title compound (27 mg, 85%) as a white solid, mp 112 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34–8.32 (m, 1H), 8.07 (d, *J*=5.6 Hz, 1H), 7.80–7.76 (m, 1H), 7.57–7.53 (m, 1H), 7.44–7.41 (m, 1H), 6.21 (br s, 1H), 6.02 (d, *J*=5.6 Hz, 1H), 3.95 (s, 3H), 3.85–3.79 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8, 161.7, 160.5, 157.2, 139.3, 131.1, 129.1, 124.9, 124.4, 121.9, 95.6, 66.9, 55.2, 44.4; MS *m*/*z*: 315.2 $(M+H)^+$; HRMS (ESI): calcd for $C_{16}H_{18}N_4O_3$ (MH^+) 315.1457; found 315.1459.

4.5.9. N4-(1H-Indol-4-yl)-N2-phenylpyrimidine-2,4-diamine ***5i***. Following the general procedure, the reaction was carried out with **4a** and 1*H*-indol-4-amine to provide title compound (26 mg, 86%) as a white solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.35 (s, 1H), 10.58 (s, 1H), 10.53 (s, 1H), 7.98 (d, *J*=7.5 Hz, 1H), 7.54–7.51 (m, 2H), 7.39 (t, *J*=3.0 Hz, 1H), 7.37 (d, *J*=8.0 Hz, 2H), 7.27 (t, *J*=7.7 Hz, 2H), 7.11 (t, *J*=7.7 Hz, 2H), 6.57 (s, 1H), 6.5 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 161.8, 159.2, 152.6, 144.3, 137.2, 136.9, 128.6, 128.5, 125.4, 124.1, 122.4, 121.4, 120.8, 114.2, 109.7, 99.0; MS *m*/*z*: 302.1 $(M+H)^+$; HRMS (ESI): calcd for $C_{18}H_{15}N_5$ (MH^+) 302.1406; found 302.1414.

4.5.10. N-(2-Morpholinopyrimidin-4-yl)-1H-indol-4-amine ***5j***. Following the general procedure, the reaction was carried out with **4j** and 1*H*-indol-4-amine to provide title compound (28 mg, 95%) as a white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (br s, 1H), 8.02 (d, *J*=5.5 Hz, 1H), 7.30–7.20 (m, 3H), 6.75 (br s, 1H), 6.55–6.53 (m, 1H), 6.08 (d, *J*=5.5 Hz, 1H), 3.89–3.83 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.7, 156.9, 136.9, 130.7, 123.8, 122.6, 113.6, 108.3, 100.0, 95.0, 67.0, 44.4; MS *m*/*z*: 296.2 $(M+H)^+$; HRMS (ESI): calcd for $C_{16}H_{17}N_5O$ (MH^+) 296.1511; found 296.1514.

4.5.11. N4-(2-Chlorophenyl)-N2-phenylpyrimidine-2,4-diamine ***5k***. Following the general procedure, the reaction was carried out with **4a** and 2-chloroaniline to provide title compound (13 mg, 43%) as a white solid, mp 140 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.4–10.3 (m, 2H), 8.04 (d, *J*=7.0 Hz, 1H), 7.68 (d, *J*=7.8 Hz, 1H), 7.63–7.6 (m, 1H), 7.46–7.41 (m, 3H), 7.40–7.37 (m, 1H), 7.22 (t, *J*=7.3, 2H), 7.04 (t, *J*=7.3 Hz, 1H), 6.43 (d, *J*=7.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.2, 158.8, 153.5, 146.8, 137.6, 134.3, 129.8, 129.0, 128.6, 128.5, 128.0, 127.7, 123.7, 120.8, 98.4; MS *m*/*z*: 297.1 $(M+H)^+$; HRMS (ESI): calcd for $C_{16}H_{13}ClN_4$ (MH^+) 297.0907; found 297.0909.

4.5.12. N-(2-Chlorophenyl)-2-morpholinopyrimidin-4-amine ***5l***. Following the general procedure, the reaction was carried out with **4j** and 2-chloroaniline to provide title compound (24 mg, 84%) as a white solid, mp 95 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, *J*=5.7 Hz, 1H), 8.02–7.98 (m, 1H), 7.47–7.43 (m, 1H), 7.36–7.31 (m, 1H), 7.13–7.08 (m, 1H), 7.01 (br s, 1H), 6.12 (d, *J*=5.7 Hz, 1H), 3.88–3.82 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.7, 129.8, 127.4, 124.8, 122.9, 96.2, 66.7, 44.6; MS *m*/*z*: 291.1 $(M+H)^+$; HRMS (ESI): calcd for $C_{14}H_{15}ClN_4O$ (MH^+) 291.1013; found 291.1015.

4.5.13. N4-Methyl-N2,N4-diphenylpyrimidine-2,4-diamine ***5m***. Following the general procedure, the reaction was carried out with **4a** and *N*-methylaniline to provide title compound (19 mg, 70%) as a white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, *J*=6.0 Hz, 1H), 7.66–7.62 (m, 2H), 7.50–7.44 (m, 2H), 7.37–7.29 (m, 5H), 7.08–6.98 (m, 2H), 5.84 (d, *J*=6.0 Hz, 1H), 3.52 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.0, 159.6, 155.6, 144.8, 140.2, 129.8, 128.7, 127.2, 126.9, 121.8, 119.0, 96.9, 38.1; MS *m*/*z*: 277.2 $(M+H)^+$.

4.5.14. N-Methyl-2-morpholino-N-phenylpyrimidin-4-amine ***5n***. Following the general procedure, the reaction was carried out with **4j** and *N*-methylaniline to provide title compound (17 mg, 62%) as a white solid, mp 140 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, *J*=6.1 Hz, 1H), 7.47–7.43 (m, 2H), 7.37–7.25 (m, 3H), 5.71 (d, *J*=6.1 Hz, 1H), 3.84–3.80 (m, 8H), 3.47 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.7, 155.2, 144.8, 129.7, 127.0, 126.8, 95.3, 67.0, 44.5, 37.6; MS *m*/*z*: 257.1 $(M+H)^+$; MS *m*/*z*: 271.2 $(M+H)^+$; HRMS (ESI): calcd for $C_{15}H_{18}N_4O$ (MH^+) 271.1559; found 271.1558.

4.5.15. N2-Phenyl-N4-(pyridin-3-yl)pyrimidine-2,4-diamine ***5o***. Following the general procedure, the reaction was carried out with **4a** and pyridin-3-amine to provide title compound (TFA salt) (19 mg, 50%) as a white solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.15–9.13 (m, 1H), 9.00–8.97 (m, 1H), 8.52 (d, *J*=5.8 Hz, 1H), 7.96–7.92 (m, 1H), 7.89–7.86 (m, 1H), 7.70–7.65 (m, 2H), 7.48–7.44 (m, 2H), 7.22–7.18 (m, 1H), 7.06 (d, *J*=5.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.2, 155.9, 154.9, 148.6, 138.1, 130.87, 129.1, 127.6, 126.9, 124.1, 123.9, 120.7; MS *m*/*z*: 264.1 $(M+H)^+$.

4.5.16. 2-Morpholino-N-(pyridin-3-yl)pyrimidin-4-amine ***5p***. Following the general procedure, the reaction was carried out with **4j** and pyridin-3-amine to provide title compound (TFA salt) (24 mg, 64%) as a white solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.88–8.86 (m, 1H), 8.82 (d, *J*=7.0 Hz, 1H), 8.78–8.76 (m, 1H), 7.9–7.83 (m, 2H), 7.32 (d, *J*=7.0 Hz, 1H), 6.9 (br s, 1H), 3.88–3.84 (m, 4H), 3.7–3.65 (m, 4H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.9, 160.8,

158.9, 148.8, 130.7, 128.2, 127.9, 124.8, 100.6, 65.8, 62.0, 44.0; MS *m*/*z*: 258.2 $(M+H)^+$.

4.6. General procedure for the nucleophilic aromatic substitution of 4a and 4j with aliphatic amines to form compounds 5q–5x (method D)

To a solution of **4a** or **4j** (0.1 mmol) in 0.5 mL of NMP were added the aliphatic amine (0.15 mmol, 1.5 equiv) and DIPEA (0.2 mmol, 2 equiv) [in the case of the cyclopentylamine and benzylamine where 3 equiv of the amine and DIPEA was used]. The mixture was heated to 110 °C overnight, before being cooled to ambient temperature and purified directly by chromatography using an EtOAc/hexanes gradient as eluent to provide compounds **5q**–**5x**.

4.6.1. 4-(4-Methylpiperazin-1-yl)-N-phenylpyrimidin-2-amine ***5q***. Following the general procedure, the reaction was carried out with **4a** and *N*-methylpiperazine to provide title compound (24 mg, 89%) as a white solid, mp 138 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, *J*=6.0 Hz, 1H), 7.62–7.58 (m, 2H), 7.36–7.31 (m, 2H), 7.05–7.00 (m, 2H), 6.05 (d, *J*=6.0 Hz, 1H), 3.70–3.65 (m, 4H), 3.55–3.50 (m, 4H), 2.37 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.4, 159.7, 156.6, 140.1, 128.7, 121.8, 119.2, 95.1, 54.7, 46.2, 43.9; MS *m*/*z*: 270.2 $(M+H)^+$; HRMS (ESI): calcd for $C_{15}H_{19}N_5$ (MH^+) 270.1719; found 270.1718.

4.6.2. 4-(4-(4-Methylpiperazin-1-yl)pyrimidin-2-yl)morpholine ***5r***. Following the general procedure, the reaction was carried out with **4j** and *N*-methylpiperazine to provide title compound (23 mg, 87%) as a white solid, mp 76 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, *J*=6.1 Hz, 1H), 5.94 (d, *J*=6.1 Hz, 1H), 3.79–3.75 (m, 8H), 3.78–3.63 (m, 4H), 3.58–3.53 (m, 4H), 2.42 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.2, 161.2, 156.2, 93.3, 67.2, 66.9, 54.5, 45.9, 44.4, 43.4; MS *m*/*z*: 264.2 $(M+H)^+$.

4.6.3. 4-Morpholino-N-phenylpyrimidin-2-amine ***5s***. Following the general procedure, the reaction was carried out with **4a** and morpholine to provide title compound (23 mg, 92%) as a white solid, mp 132 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, *J*=5.5 Hz, 1H), 7.59 (d, *J*=5.5 Hz, 2H), 7.38–7.33 (m, 2H), 7.08 (br s, 1H), 7.06–7.02 (m, 1H), 6.05 (d, *J*=5.5 Hz, 1H), 3.83–3.78 (m, 4H), 3.68–3.63 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.7, 159.6, 156.8, 140.0, 128.8, 122.0, 119.3, 94.9, 66.6, 44.3; MS *m*/*z*: 257.2 $(M+H)^+$; HRMS (ESI): calcd for $C_{14}H_{16}N_4O$ (MH^+) 257.1402; found 257.1411.

4.6.4. 4,4′-(Pyrimidine-2,4-diyl)dimorpholine ***5t***.[27] Following the general procedure, the reaction was carried out with **4j** and morpholine to provide title compound (23 mg, 91%) as a white solid, mp 112 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, *J*=6.1 Hz, 1H), 5.90 (d, *J*=6.1 Hz, 1H), 3.80–3.76 (m, 12H), 3.62–3.58 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.7, 161.5, 156.7, 93.1, 66.9, 66.6, 44.3, 44.1; MS *m*/*z*: 251.1 $(M+H)^+$; HRMS (ESI): calcd for $C_{12}H_{18}N_4O_2$ (MH^+) 251.1508; found 251.1507.

4.6.5. N2-Phenyl-N4-propylpyrimidine-2,4-diamine ***5u***. Following the general procedure, the reaction was carried out with **4a** and propylamine to provide title compound (20 mg, 90%) as a white solid, mp 107 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (br s, 1H), 7.65 (br s, 1H), 7.52 (d, *J*=8.4 Hz, 1H), 7.25–7.17 (m, 2H), 6.88–6.82 (m, 1H), 5.75 (d, *J*=5.9 Hz, 1H), 5.02 (br s, 1H), 3.25–3.15 (m, 2H), 1.60–1.51 (m, 2H), 0.90 (t, *J*=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.1, 159.6, 152.1, 140.2, 128.7, 122.0, 119.4, 98.6, 43.25, 22.7, 11.5; MS *m*/*z*: 229.4 $(M+H)^+$; HRMS (ESI): calcd for $C_{13}H_{16}N_4$ (MH^+) 229.1453; found 229.1456.

4.6.6. 2-Morpholino-N-propylpyrimidin-4-amine ***5v***.[27] Following the general procedure, the reaction was carried out with **4j** and propylamine to provide title compound (19 mg, 86%) as a white solid, mp 56 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90–7.87 (m, 1H), 5.75 (d, *J*=5.9 Hz, 1H), 4.78 (br s, 1H), 3.75–3.80 (m, 8H), 3.30–3.23 (m, 2H), 1.70–1.61 (m, 2H), 1.01 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.9, 160.9, 154.5, 94.5, 66.9, 44.3, 43.0, 22.7, 11.5; MS *m*/*z*: 223.5 $(M+H)^+$; HRMS (ESI): calcd for $C_{11}H_{18}N_4O$ (MH^+) 223.1559; found 223.1558.

4.6.7. N4-Cyclopentyl-N2-phenylpyrimidine-2,4-diamine ***5w***. Following the general procedure, the reaction was carried out with **4a** and cyclopropylamine to provide title compound (23 mg, 89%) as a white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99–7.97 (m, 1H), 7.63 (d, *J*=8.2 Hz, 2H), 7.36–7.31 (m, 2H), 7.15 (br s, 1H), 7.04–6.99 (m, 1H), 5.88 (d, *J*=5.9 Hz, 1H), 4.82 (br s, 1H), 4.15–4.05 (m, 1H), 2.10–2.05 (m, 2H), 1.80–1.65 (m, 4H), 1.55–1.50 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.6, 159.7, 155.9, 140.1, 128.7, 121.9, 119.2, 96.0, 52.9, 33.9, 23.8; MS *m*/*z*: 255.2 $(M+H)^+$; HRMS (ESI): calcd for $C_{15}H_{18}N_4$ (MH^+) 255.1610; found 255.1620.

4.6.8. N-Cyclopentyl-2-morpholinopyrimidin-4-amine ***5x***. Following the general procedure, the reaction was carried out with **4j** and cyclopropylamine to provide title compound (23 mg, 92%) as a white solid, mp 101 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91–7.88 (m, 1H), 5.76 (d, *J*=5.9 Hz, 1H), 4.86–4.81 (m, 1H), 4.13–4.07 (m, 1H), 2.13–2.04 (m, 2H), 1.80–1.73 (m, 2H), 1.70–1.63 (m, 2H), 1.55–1.48 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.5, 152.6, 94.5, 66.9, 44.4, 33.7, 23.8; MS *m*/*z*: 249.2 $(M+H)^+$; HRMS (ESI): calcd for $C_{13}H_{20}N_4O$ (MH^+) 249.1715; found 249.1719.

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Supplementary data

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