Discovery of FLT3 inhibitors for the treatment of acute myeloid leukemia

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Chapter 5

Discovery and development of pyrrolo-pyrimidines as mutant active FLT3 inhibitors*

Introduction

Acute myeloid leukemia (AML) is a cancer of the blood, characterized by excessive proliferation of immature hematopoietic cells and high mortality.[1–3] 20-30% of AML patients harbor an internal tandem duplication (ITD) in the fms-like tyrosine kinase 3 (FLT3) gene, which is thought to enable growth-factor independent proliferation.[4–6] FLT3-ITD has been validated as a target for AML treatment, as evidenced by the approval of midostaurin as a FLT3 inhibitor.[7–9] Nevertheless, successful AML therapy remains a challenge due to the emergence of treatment-resistant point-mutations in the FLT3 tyrosine kinase domain.[9–11] Hence, there is a need for new chemical matter that also inhibits the treatment-resistant FLT3 kinase activity.

To this end a high throughput screen was performed to identify new chemical entities that inhibit FLT3 (as described in Chapter 4). This led to the discovery of SPCE00476_01 and NP_004099_001 (Figure 1A) as qualified hits. In this Chapter, the hit confirmation, optimization of the potency, physico-chemical properties and cellular activity against several mutant FLT3 proteins is described (Figure 1B).

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* The data presented in this chapter was gathered in collaboration with Laura de Paus, Ruud H. Wijdeven, Hengyi You, Hugo van Kessel, Maxime A. Siegler, Constant A. A. van Boeckel, Herman S. Overkleeft, Jacques Neefjes and Mario van der Stelt.

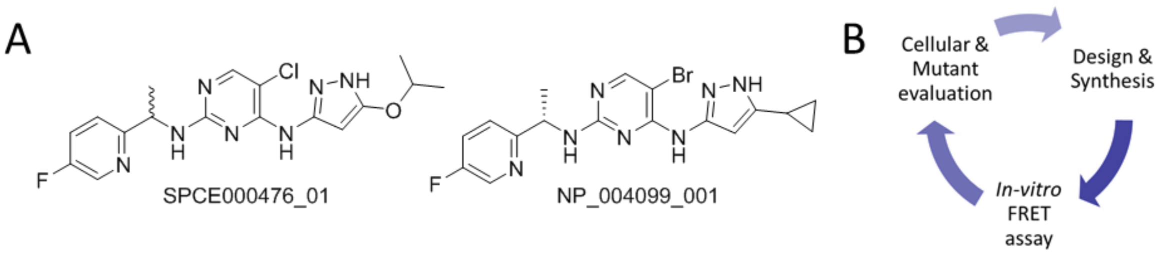


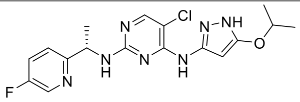
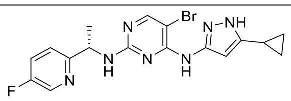
Figure 1: (**A**) The hits discovered in the high-throughput screening campaign described in chapter 4. (**B**) General development strategy employed.

Results and discussion

Confirmation of screening hits

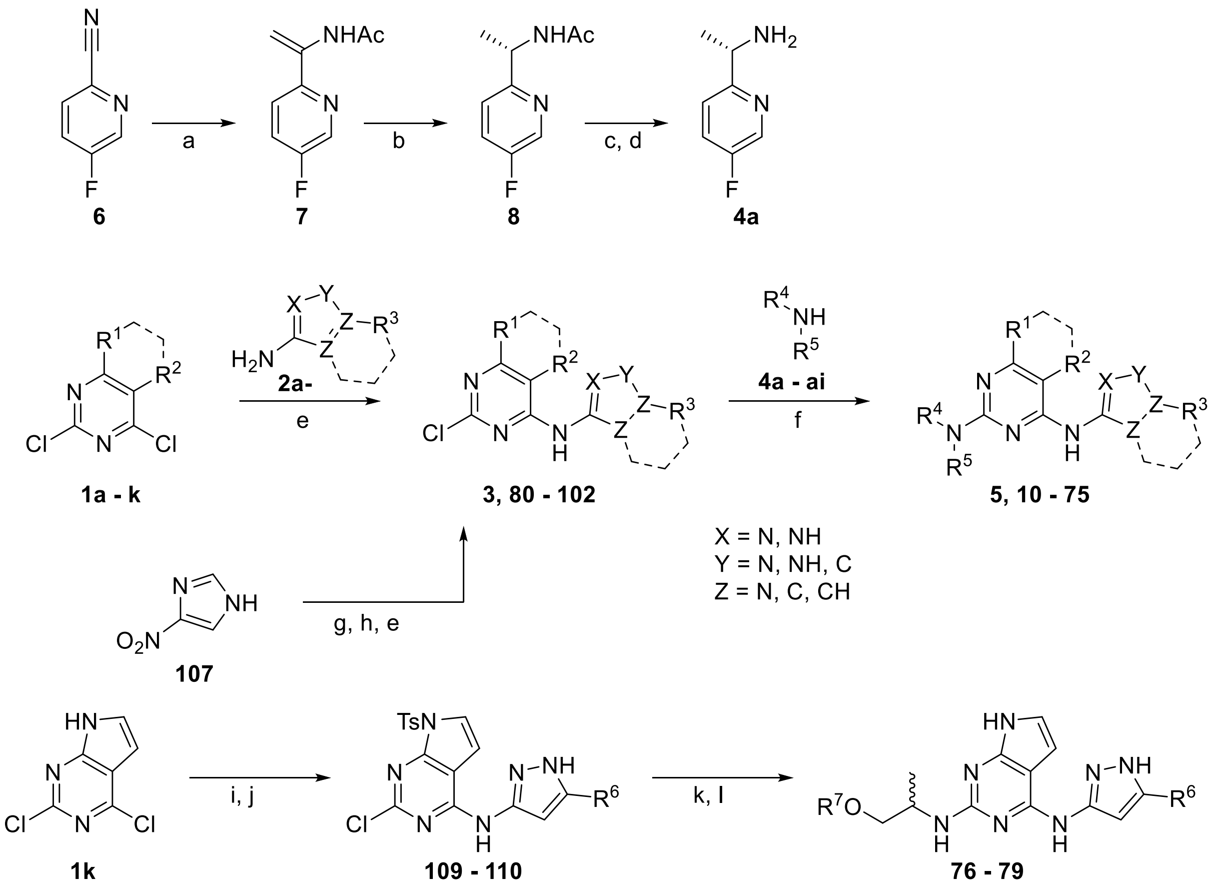
First, SPCE00476_01 and NP_004099_001 were resynthesized to confirm their structure and activity. The synthesis was performed following known literature procedures.[12–16] The general synthetic strategy to produce these compounds is summarized in Scheme 1. In short, SPCE00476_01 was synthesized by coupling the core building block 2,4,5-trichloropyrimidine (**1a**) with 5-isopropoxy-1*H*-pyrazol-3-amine (**2a**) via a nucleophilic aromatic substitution reaction (S_NA_R). The resulting building block (**3**) was reacted with (*S*)-1-(5-fluoropyridin-2-yl)ethan-1-amine (**4a**) in a second S_NA_R, which resulted in the desired compound (SPCE00476_01), subsequently renamed **5**. The chiral amine **4a** was synthesized from 5-fluoropicolinonitrile (**6**), starting with methyl-Grignard reagent, followed by acetylation to yield the corresponding protected enamine **7** (in Scheme 1).[12] The enamine was reduced using a chiral rhodium catalyst to yield **8**. Deprotection resulted in the desired chiral amine **4a**. This synthesis provided a moderate enantiomeric ratio of 76% in favor of the required *S*-enantiomer. This was considered sufficient for confirmation of the activity and subsequent structure-activity studies. NP_004099_001 was synthesized in a similar fashion, starting from 5-bromo-2,4-dichloropyrimidine (**1b**) and 5-cyclopropyl-1*H*-pyrazol-3-amine (**2b**) and was subsequently named **10**.

Table 1: Bioactivities of the resynthesized initial screening hits.

		pIC$_{50}$ ± SEM							
					Ba/F3				
	Structure	***in vitro* FLT3**	**MV4-11**	**U937**	**wt**	**FLT3 ITD**	**FLT3 ITD F691L**	**FLT3 ITD D835H**	**FLT3 ITD D835Y**
5		8.2 ± 0.1	7.2 ± 0.1	5.0 ± 0.2	< 5	7.3 ± 0.2	5.8 ± 0.1	6.7 ± 0.1	6.3 ± 0.1
10		8.5 ± 0.1	7.7 ± 0.1	6.4 ± 0.1	6.2 ± 0.2	7.9 ± 0.2	6.9 ± 0.1	7.1 ± 0.2	6.8 ± 0.2

The two hits were tested in the biochemical FLT3 and cellular assays (MV4-11[6], U937[17] and Ba/F3 derived[18–20]). The activity of the two compounds was confirmed (Table 1). Of note, **5** showed significantly less toxicity towards the U937 and Ba/F3 wt cells compared to **10** and was less active in the cell lines harboring the point-mutant derivatives. This might suggest that off-target activity contributes to the cellular activity of **10**.

Scheme 1: Synthetic strategies used in the synthesis of the FLT3 inhibitors presented in this chapter.[a]

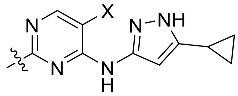


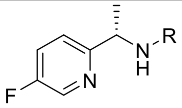
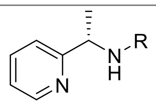
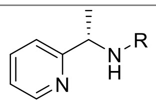
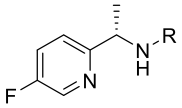
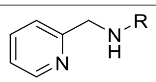
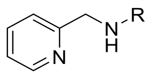
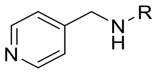
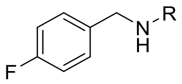
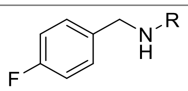
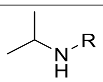
[a]Reagents and conditions: (a) MeMgBr, THF, 0°C, then Ac_2O, RT; (b) (+)-1,2-Bis((2*S*,5*S*)-2,5-diethylphospholano) benzene(cyclooctadiene)rhodium trifluoromethanesulfonate, MeOH, 10 bar H_2, RT; (c) DMAP, Boc_2O, THF, 50°C, then LiOH, H_2O, RT; (d) TFA, $CHCl_3$, 0°C – RT; (e) Heterocycle-amine, Et_3N or DIPEA; (f) alkyl-amine, DIPEA; (g) Alkyl-tosylate or alkyl halide, K_2CO_3, ACN; (h) Pd/C, H_2, EtOH; (i) TsCl, tetrabutylammonium hydrogen sulfate, DCM, H_2O, RT; (j) heterocycle-amine, Et_3N, ACN, 100°C; (k) alkyl-amine, DIPEA, *n*-butanol, 160°C; (l) NaOH, MeOH, 1,4-dioxane, H_2O, 0°C – RT.

Structure activity relationship studies

The SAR study was initiated by using a disjunctive approach in which functional groups were deleted from hit compound **10**. To this end a series of compounds (**11** – **20**) was synthesized and tested. The bioactivities of the compounds are summarized in Table 2.

Table 2: Structure-activity relation study of left-hand side of **10**.

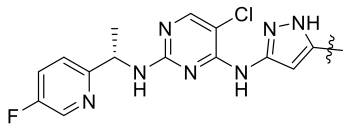
R = 

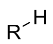
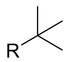
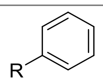
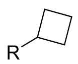
	Structure	X	pIC50 ± SEM							
						Ba/F3				
			in vitro FLT3	MV4-11	U937	wt	FLT3 ITD	FLT3 ITD F691L	FLT3 ITD D835H	FLT3 ITD D835Y
11		Cl	8.44 ± 0.06	7.6 ± 0.1	6.5 ± 0.1	6.4 ± 0.2	7.8 ± 0.1	6.9 ± 0.2	7.1 ± 0.2	6.8 ± 0.2
12		Br	8.49 ± 0.07	7.7 ± 0.1	6.2 ± 0.2	5.8 ± 0.3	7.9 ± 0.2	6.9 ± 0.1	7.2 ± 0.2	6.9 ± 0.2
13		Cl	8.50 ± 0.08	7.5 ± 0.1	6.4 ± 0.1	5.8 ± 0.4	8.0 ± 0.1	7.0 ± 0.2	7.3 ± 0.2	7.0 ± 0.2
14		H	8.44 ± 0.09	7.3 ± 0.1	6.8 ± 0.1	6.8 ± 0.3	7.7 ± 0.2	6.9 ± 0.2	6.9 ± 0.2	6.9 ± 0.2
15		Cl	7.92 ± 0.05	7.4 ± 0.1	5.5 ± 0.2	5.2 ± 0.6	7.2 ± 0.2	6.5 ± 0.2	6.9 ± 0.2	6.7 ± 0.2
16		Br	8.01 ± 0.05	7.3 ± 0.1	5.3 ± 0.3	5.3 ± 0.5	7.2 ± 0.2	6.5 ± 0.2	6.9 ± 0.2	6.7 ± 0.2
17		Cl	7.62 ± 0.10	6.8 ± 0.2	5.7 ± 0.1	< 5	6.6 ± 0.3	6.1 ± 0.3	6.4 ± 0.2	6.4 ± 0.2
18		Br	6.60 ± 0.09				ND			
19		Cl	6.72 ± 0.11				ND			
20		Cl	7.84 ± 0.08	7.5 ± 0.1	5.2 amb.	< 5	7.4 ± 0.2	6.7 ± 0.2	7.0 ± 0.2	6.9 ± 0.2

The substitution of a bromine (**10**) to a chlorine (**11**) or its removal (**14**) did not affect the biochemical or cellular activity of the hit. The same effect was observed for the removal of the para-fluoro substituent on the pyridyl ring (**12** and **13**). Removal of the chiral methyl on the benzyl carbon (**15** and **16**) resulted in a small loss of activity in the *in vitro* assay and in the Ba/F3 ITD, but not for MV4-11, cellular assays. Moving the pyridine nitrogen to the para-position (**17**) or its substitution by a carbon atom (**18** and **19**) resulted in a substantial loss of activity. Remarkably, substituting the chiral pyridine-amine group for an isopropyl amine provided a potent compound (pIC_{50} = 7.8 ± 0.1), while substantially reducing the molecular weight by almost 30% from 418 (original hit, **10**) to 293 g/mol (**20**). All together, these results indicated that the pyridine ring substituent does not make any significant interactions with the FLT3 binding pocket.

Next, the size of the binding pocket accommodating the alkyl substituent on the pyrazole moiety was investigated (Table 3). Smaller substituents, such as hydrogen (**21**) or methyl (**22**) as well as larger substituents (e.g. *tert*-butyl (**23**) and phenyl (**24**)) showed substantially decreased activity against FLT3. The cyclobutyl analog (**25**) showed an increase in potency compared to the hit. This indicated that the cyclopropyl group has an almost optimal fit with a small lipophilic pocket.

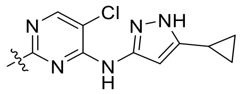
Table 3: SAR study of the cyclopropyl analogs of **10**.

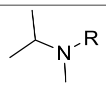
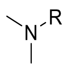
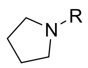
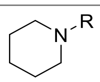
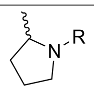
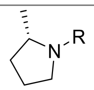
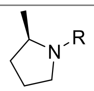
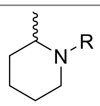
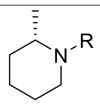
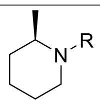
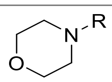
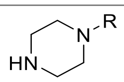
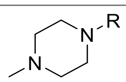
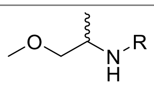
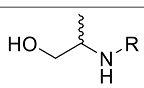
R = 

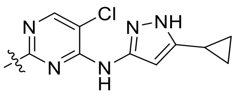
		pIC₅₀ ± SEM							
					Ba/F3				
	Structure	***in vitro* FLT3**	**MV4-11**	**U937**	**wt**	**FLT3 ITD**	**FLT3 ITD F691L**	**FLT3 ITD D835H**	**FLT3 ITD D835Y**
21		6.22 ± 0.12				ND			
22		7.38 ± 0.10	6.6 ± 0.2	6.5 ± 0.1	6.5 ± 0.4	6.9 ± 0.2	6.8 ± 0.3	6.4 ± 0.2	6.3 ± 0.3
23		5.94 ± 0.10				ND			
24		7.11 ± 0.09	6.8 ± 0.2	5.2 ± 0.1	< 5	6.8 ± 0.2	6.0 ± 0.3	6.4 ± 0.2	6.1 ± 0.3
25		8.85 ± 0.15	7.8 ± 0.1	5.9 ± 0.1	5.9 ± 0.4	8.2 ± 0.2	7.0 ± 0.2	7.4 ± 0.2	7.1 ± 0.2

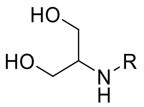
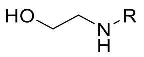
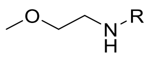
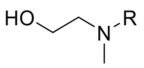
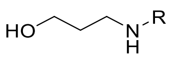
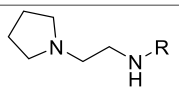
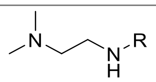
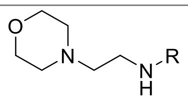
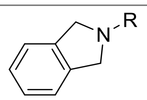
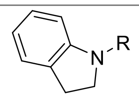
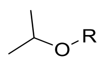
In view of the remarkable activity of the isopropyl analog (**20**), a series of amine analogs (**26** - **51**) was synthesized and evaluated (Table 4). Alkylation (**26**, **27**) and cyclization (**28** - **35**) of the amine did not significantly alter the activity of the compounds, indicating that the N-H group does not form an H-bond interaction with the protein. Of note, pyrrolidine analog (**28**) showed a significant increase in activity in the *in vitro* assay, but this did not translate into increased cellular activity. As observed previously for the hit compound, introduction of chiral methyl substituents (**30** - **35**) on the cyclic amines did not improve the potency of the compounds.

Table 4: Structure-activity relationship investigation of the amine tail substituent.

R = 

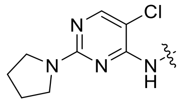
		pIC$_{50}$ ± SEM							
					Ba/F3				
	Structure	***in vitro* FLT3**	**MV4-11**	**U937**	**wt**	**FLT3 ITD**	**FLT3 ITD F691L**	**FLT3 ITD D835H**	**FLT3 ITD D835Y**
26		7.70 ± 0.13	6.8 ± 0.1	5.1 amb.	5.2 ± 0.2	6.9 ± 0.1	6.0 ± 0.2	6.6 ± 0.2	6.4 ± 0.1
27		7.51 ± 0.12	6.5 ± 0.1	5.5 ± 0.2	< 5	6.3 ± 0.2	5.5 ± 0.2	6.0 ± 0.2	5.6 ± 0.2
28		8.39 ± 0.12	7.4 ± 0.1	5.4 ± 0.1	< 5	7.1 ± 0.2	6.3 ± 0.2	6.8 ± 0.2	6.6 ± 0.2
29		7.93 ± 0.10	6.8 ± 0.2	5.3 ± 0.4	< 5	6.8 ± 0.2	6.0 ± 0.3	6.3 ± 0.2	6.4 ± 0.2
30		7.78 ± 0.09	7.2 ± 0.2	5.6 ± 0.2	< 5	7.1 ± 0.3	6.3 ± 0.2	6.7 ± 0.2	6.7 ± 0.2
31		7.81 ± 0.15				ND			
32		7.90 ± 0.08				ND			
33		7.44 ± 0.09	6.5 ± 0.2	5.1 amb.	< 5	6.5 ± 0.3	5.6 ± 0.2	6.1 ± 0.2	5.9 ± 0.2
34		7.75 ± 0.11				ND			
35		7.42 ± 0.11				ND			
36		6.82 ± 0.18				ND			
37		6.87 ± 0.12				ND			
38		6.90 ± 0.18				ND			
39		7.78 ± 0.09	7.2 ± 0.2	5.4 ± 0.2	5.5 ± 0.2	7.2 ± 0.1	6.5 ± 0.2	6.9 ± 0.1	6.7 ± 0.1
40		7.51 ± 0.06	7.1 ± 0.1	5.1 amb.	5.1 amb.	7.3 ± 0.1	6.3 ± 0.2	7.1 ± 0.2	6.9 ± 0.1

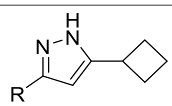
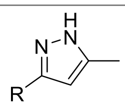
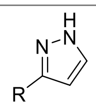
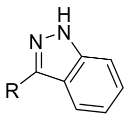
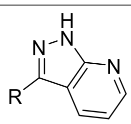
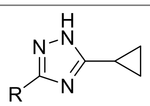
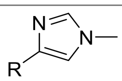
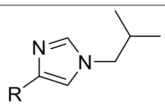
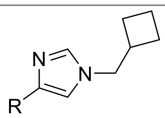
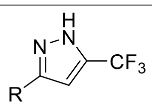
R = 

		pIC$_{50}$ ± SEM							
					Ba/F3				
	Structure	***in vitro* FLT3**	**MV4-11**	**U937**	**wt**	**FLT3 ITD**	**FLT3 ITD F691L**	**FLT3 ITD D835H**	**FLT3 ITD D835Y**
41		7.08 ± 0.07	6.7 ± 0.1	5.0 amb.	< 5	6.5 ± 0.2	5.6 ± 0.2	6.4 ± 0.2	6.3 ± 0.1
42		7.08 ± 0.10	6.6 ± 0.2	< 5	< 5	6.3 ± 0.2	5.1 amb.	6.1 ± 0.1	6.0 ± 0.2
43		7.57 ± 0.12	6.7 ± 0.1	5.2 ± 0.1	< 5	6.4 ± 0.2	5.6 ± 0.2	6.2 ± 0.2	6.2 ± 0.2
44		7.60 ± 0.11	6.8 ± 0.1	< 5	< 5	6.5 ± 0.2	5.5 ± 0.2	6.4 ± 0.1	6.3 ± 0.1
45		7.57 ± 0.08	7.0 ± 0.1	5.1 amb.	< 5	6.6 ± 0.2	5.7 ± 0.2	6.5 ± 0.1	6.4 ± 0.2
46		6.78 ± 0.14	6.0 ± 0.2	< 5	< 5	5.5 ± 0.3	5.3 ± 0.2	5.4 ± 0.2	5.5 ± 0.2
47		6.57 ± 0.13	6.0 ± 0.2	< 5	< 5	5.4 ± 0.2	5.1 ± 0.2	5.2 amb.	5.1 amb.
48		6.81 ± 0.09	6.1 ± 0.2	< 5	< 5	5.6 ± 0.2	5.2 ± 0.2	5.4 ± 0.3	5.4 ± 0.3
49		7.23 ± 0.15	6.5 ± 0.1	5.3 ± 0.2	< 5	6.3 ± 0.2	5.7 ± 0.2	5.8 ± 0.2	5.8 ± 0.2
50		7.00 ± 0.09				ND			
51		7.00 ± 0.16	6.6 ± 0.1	5.1 amb.	< 5	6.4 ± 0.2	5.5 ± 0.2	6.3 ± 0.2	5.7 ± 0.2

To improve the solubility of the compounds, the left hand side substituent was replaced by various solubilizers (**36** - **48**). Morpholines (**36**, **48**) and piperazines (**37**, **38**) or other basic amines (**46**, **47**) were, however, not preferred and resulted in a 10-fold drop in activity. Interestingly, more flexible ethanolamine derivatives (**39** - **45**) retained activity (pIC$_{50}$ > 7). Compounds **49**, **50** and **51** retained strong inhibitor activity in the biochemical assay (pIC$_{50}$ > 7.5), but showed very low activity in the Ba/F3 cells, especially in the cell line expressing the F691L mutation (pIC$_{50}$ < 6). **39** and **40**, with a propanol-2-amine substituent were among the most potent compounds with a favorable cellular activity profile, retaining strong anti-proliferative activity for most of the mutant variations.

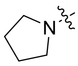
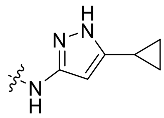
Table 5: Investigation of the pyrazole moiety.

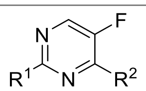
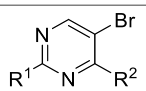
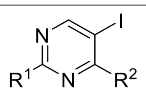
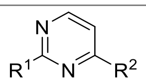
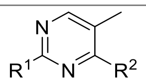
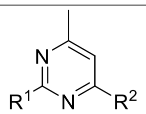
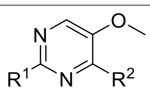
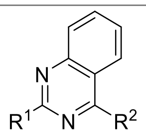
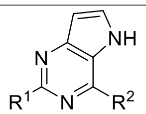
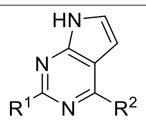
R = 

		pIC$_{50}$ ± SEM							
					Ba/F3				
	Structure	***in vitro* FLT3**	**MV4-11**	**U937**	**wt**	**FLT3 ITD**	**FLT3 ITD F691L**	**FLT3 ITD D835H**	**FLT3 ITD D835Y**
52		7.38 ± 0.10	6.8 ± 0.1	5.1 amb.	< 5	6.9 ± 0.1	5.8 ± 0.2	6.7 ± 0.2	6.4 ± 0.1
53		6.84 ± 0.08	5.9 ± 0.2	ND	< 5	5.5 ± 0.1	5.7 ± 0.2	5.5 ± 0.2	5.6 ± 0.1
54		5.28 ± 0.14				ND			
55		5.46 ± 0.10				ND			
56		7.44 ± 0.08	6.3 ± 0.1	6.8 ± 0.1	6.1 ± 0.2	6.2 ± 0.1	6.2 ± 0.1	6.3 ± 0.1	6.3 ± 0.1
57		5.88 ± 0.18				ND			
58		5.86 ± 0.13				ND			
59		6.34 ± 0.06				ND			
60		6.47 ± 0.13				ND			
61		5.56 ± 0.12				ND			

Compounds **52** – **54** show that the head group alkyl substituents follow the same general trend as with the original tail fragment, albeit the cyclobutyl residue demonstrated a somewhat lower activity compared to the cyclopropyl (Table 5). **55** and **56** were synthesized to investigate the effect of an annulated aromatic ring. Interestingly, while the phenyl derivative completely lost activity, the pyridyl retained its activity. Of note, the cellular activity was very similar across the whole panel of cell lines. Inhibition of U937 cell growth was even stronger than the reduced MV4-11 cell proliferation, indicating that this effect was independent of FLT3 inhibition. Perhaps a change in binding mode, due to the introduction of an additional hydrogen bond donor-acceptor pair in **56** is responsible for additional kinase inhibitory activity. Replacing the pyrazole with a 1, 2, 4-triazole (**57**) or imidazole (**58** - **60**) resulted in loss of activity. Finally, introducing electron-withdrawing groups (i.e. CF_3) on the pyrazole (**61**) also led to a reduction of activity.

Table 6: Optimization of the scaffold of **10**.

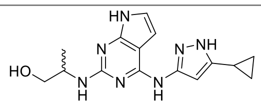
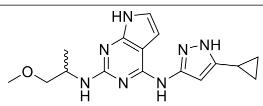
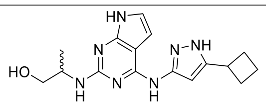
R^1 =  **, R^2 =** 

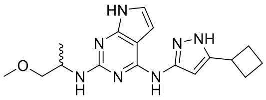
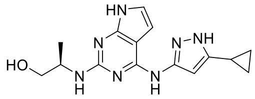
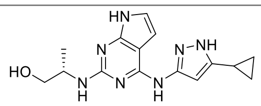
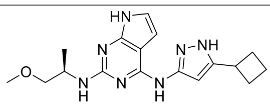
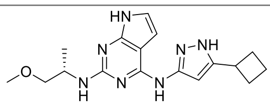
	Structure	pIC$_{50}$ ± SEM							
					Ba/F3				
		in vitro FLT3	MV4-11	U937	wt	FLT3 ITD	FLT3 ITD F691L	FLT3 ITD D835H	FLT3 ITD D835Y
62		7.47 ± 0.15	6.7 ± 0.1	6.0 amb.	5.2 ± 0.3	6.7 ± 0.1	5.8 ± 0.2	6.3 ± 0.1	6.2 ± 0.1
63		7.56 ± 0.11	6.7 ± 0.1	5.1 amb.	< 5	6.8 ± 0.2	5.9 ± 0.2	6.5 ± 0.2	6.3 ± 0.1
64		6.43 ± 0.12	ND						
65		7.50 ± 0.10	7.0 ± 0.1	6.7 ± 0.1	6.3 ± 0.1	7.0 ± 0.2	6.6 ± 0.1	6.8 ± 0.2	6.7 ± 0.1
66		7.46 ± 0.08	6.9 ± 0.1	6.0 amb.	5.6 ± 0.2	6.9 ± 0.1	6.1 ± 0.2	6.5 ± 0.2	6.4 ± 0.1
67		7.73 ± 0.12	6.9 ± 0.1	6.5 amb.	6.4 ± 0.2	6.7 ± 0.1	6.3 ± 0.1	6.5 ± 0.1	6.3 ± 0.1
68		8.17 ± 0.14	7.1 ± 0.1	5.4 ± 0.2	5.2 ± 0.4	7.3 ± 0.1	6.3 ± 0.2	6.8 ± 0.2	6.6 ± 0.1
69		8.84 ± 0.07	7.5 ± 0.1	6.4 ± 0.1	6.1 ± 0.2	7.3 ± 0.1	6.6 ± 0.1	7.0 ± 0.1	7.0 ± 0.1
70		8.66 ± 0.09	7.1 ± 0.1	6.5 amb.	6.2 ± 0.1	7.2 ± 0.2	6.5 ± 0.1	6.9 ± 0.2	6.7 ± 0.1
71		9.23 ± 0.14	7.8 ± 0.1	6.3 ± 0.1	5.6 ± 0.2	7.7 ± 0.1	6.7 ± 0.1	7.4 ± 0.1	7.3 ± 0.1

Next, the central core pyrimidine of **10** was investigated (Table 6). Compounds **62** – **65** were synthesized and tested to explore the influence of the halogen on the scaffold. The original chloro-substituted pyrimidine (**28**) was the most active compound, followed by the almost equipotent fluoro (**62**), bromo (**63**) and hydrogen substitution (**65**). The iodo substituted compound (**64**) lost approximately 100-fold in activity compared to **28**. The cellular activities were comparable, but **65** lacking a halogen showed substantial inhibition of the cellular proliferation of control cell lines U937 and Ba/F3. Introducing electron-donating substituents, such as methyl (**66**, **67**) and methoxy (**68**) groups, did not improve the potency in the biochemical or cellular assays compared to **28**. Of note, annulated ring systems, mimicking the adenosine-base in ATP, such as **69**, **70** and **71**, demonstrated substantially increased potency. **71** reached even subnanomolar potency (pIC_{50} of 9.2 ± 0.1) in the biochemical assay, which was accompanied by good cellular activity.

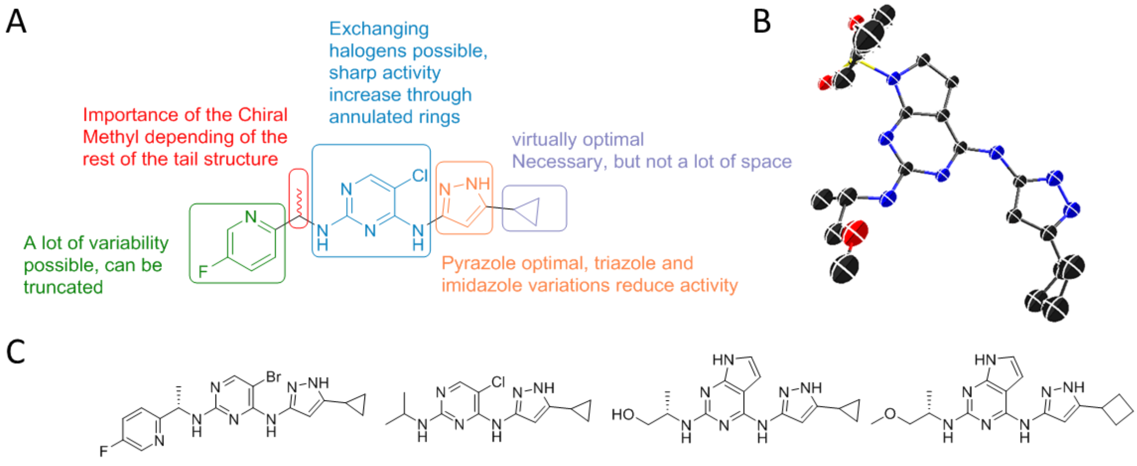
In the final round of optimization, the optimal core (7*H*-pyrrolo[2,3-*d*]pyrimidine) was combined with methoxypropanol-2-amine or propanol-2-amine as the best substituents at the left hand side with cyclopropylpyrazoloamine or cyclobutylpyrazoloamine on the right hand side. This led to the synthesis of **72** - **75** (Table 7). The biochemical potency for these compounds was high and ranged from pIC_{50} 8.7 to 9.1. The cellular activity as measured in the MV4-11 anti-proliferation assay was also excellent (pIC_{50} 7.8 - 8.3). Importantly, **75** also demonstrated high cellular activity against the mutant cell lines. As a last step the chirality of the tail group methyl was revisited. For this purpose **72** and **75** were chosen. **75** was the most active compound *in vitro* and across all cell lines. **72** exhibits slightly lower activity, but also reduced off-target toxicity (Ba/F3 wt) and decreased lipophilicity. For both compounds the two enantiomers were synthesized from enantio pure building blocks (**76** – **79**). A clear preference for the *S*-enantiomer (**77** and **79**) was observed with subnanomolar biochemical activities and a good cellular profile.

Table 7: Combination of optimal substituents.

		pIC_{50} ± SEM							
					Ba/F3				
	Structure	***in vitro* FLT3**	**MV4-11**	**U937**	**wt**	**FLT3 ITD**	**FLT3 ITD F691L**	**FLT3 ITD D835H**	**FLT3 ITD D835Y**
72		8.70 ± 0.10	7.8 ± 0.1	< 5	5.3 ± 0.3	7.4 ± 0.1	6.6 ± 0.1	7.4 ± 0.1	7.2 ± 0.1
73		8.76 ± 0.09	7.9 ± 0.1	5.1 ± 0.3	6.0 ± 0.2	8.0 ± 0.1	7.0 ± 0.1	7.7 ± 0.1	7.5 ± 0.1
74		8.94 ± 0.10	8.0 ± 0.1	< 5	5.1 amb.	7.8 ± 0.1	6.5 ± 0.1	7.6 ± 0.1	7.4 ± 0.1

	Structure	pIC$_{50}$ ± SEM							
					Ba/F3				
		in vitro FLT3	MV4-11	U937	wt	FLT3 ITD	FLT3 ITD F691L	FLT3 ITD D835H	FLT3 ITD D835Y
75		9.12 ± 0.06	8.3 ± 0.1	5.1 ± 0.3	6.0 amb.	8.2 ± 0.1	7.1 ± 0.1	8.0 ± 0.1	7.8 ± 0.1
76		8.64 ± 0.09	7.5 ± 0.1	5.7 ± 0.2			ND		
77		9.31 ± 0.08	8.0 ± 0.1	6.4 ± 0.2	6.1 ± 0.1	8.0 ± 0.1	6.8 ± 0.1	7.6 ± 0.1	7.5 ± 0.1
78		8.99 ± 0.07	7.7 ± 0.1	5.9 amb.			ND		
79		9.67 ± 0.06	8.5 ± 0.1	6.7 ± 0.1	6.4 ± 0.1	8.6 ± 0.1	7.2 ± 0.1	8.2 ± 0.1	8.1 ± 0.1

To confirm the position of the nitrogen atoms in the series, a X-ray study with a crystal from the tosyl-protected intermediate was performed (Figure 2B). This clearly showed the expected substitution pattern.



	10	20	77	79
pIC_{50} FLT3	8.5	7.8	9.3	9.7
pIC_{50} MV4-11	7.7	7.5	8.0	8.5
pIC_{50} Ba/F3 ITD	7.9	7.4	8.0	8.6
MW	418	293	313	341
cLogP	3.5	3.7	2.3	3.6
LipE	5.0	4.1	7.0	6.1

Figure 2: (A) Summary of the established structure-activity relationship in this chapter. (B) Crystal structure of tosyl-protected **79** to confirm the configuration. (C) Milestones in the development process of the series.

Compounds **77** and **79** were selected for further profiling (Figure 2C), because they are subnanomolar FLT3 inhibitors with single digit nanomolar potency in the cellular assays. Furthermore, they retained activity on the cells expressing the mutant FLT3 proteins, while having favorable physico-chemical properties and keeping general cellular toxicity to a minimum (Figure 3).

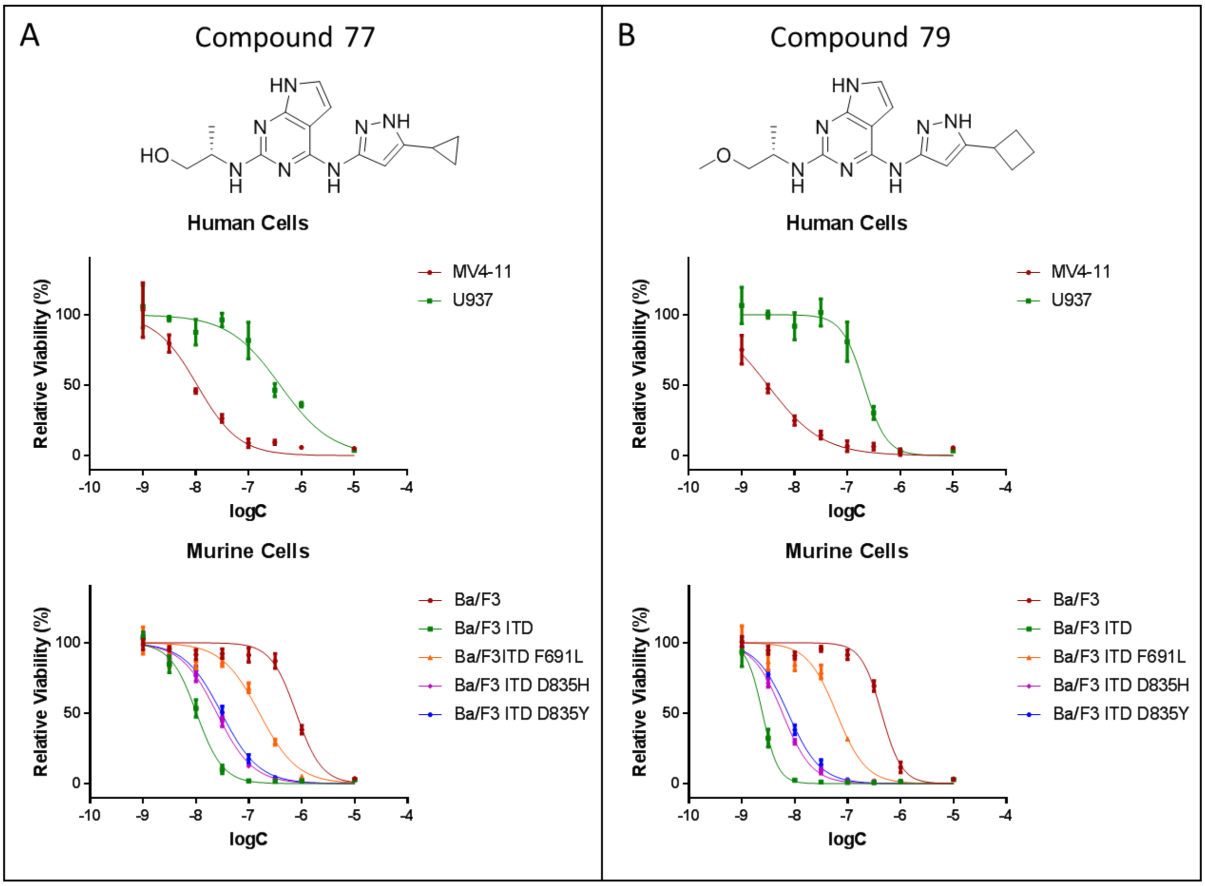


Figure 3: Summary of activity data of the two potent inhibitors X and Y, selected to be further profiled.

In situ selectivity testing using chemical proteomics

The cellular selectivity profile of compound **77** and **79** was determined using chemical proteomics (Chapter 2).[21,22] In this experiment a total of 77 and 53 kinases were identified in MV4-11 and U937 cells, respectively, using the same cut-offs as described in Chapter 2. Next, the two compounds were tested at three different concentrations, 1, 10 and 100 µM in MV4-11 and U937 cells. The results from this study are summarized as a heatmap (Figure 4) and as volcano plots (SI Figure 2). Table 8 lists the off-targets that were dose-dependently inhibited and displayed an IC_{50} < 1 uM. **77** inhibited 19 targets, whereas 34 targets were inhibited by **79**. The target selection procedure is outlined in detail in chapter 2. AURKA, AURKB, CSNK2A1, FYN, GSK3A, GSK3B, IRAK4, JAK1, MAP3K7, MARK2, PTK2, PTK2B, RPS6KA6, SLK, STK11, TBK1 and TEC were inhibited by both compounds. Some of them have been named as drug targets or oncogenes for various disorders, among them AURKB,[23] FYN,[24] IRAK4[25] and MARK2.[26] Furthermore **79** also strongly inhibited tyrosine-protein kinase receptor UFO (AXL), which is being investigated as a target for AML treatment.[27–29]

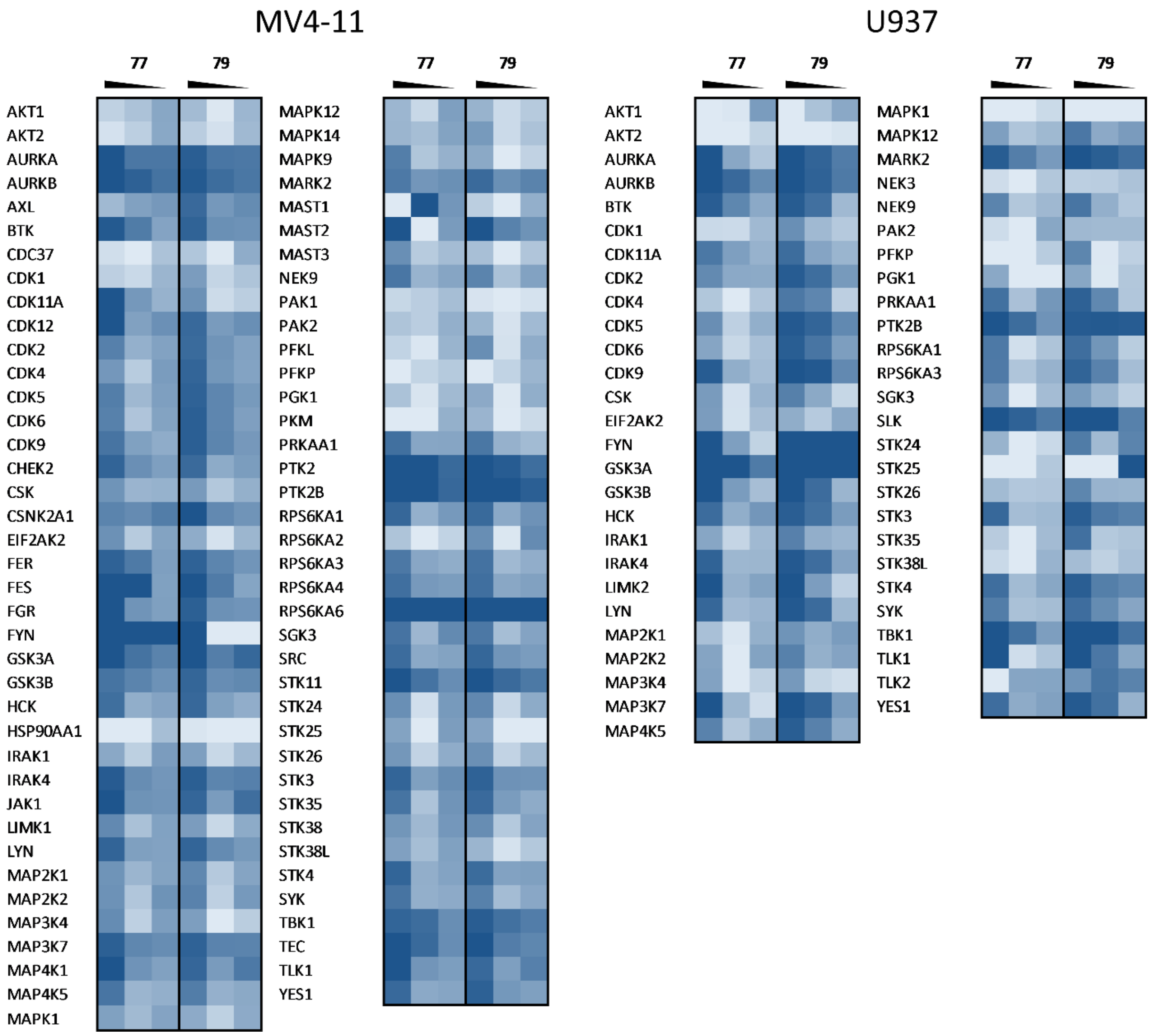


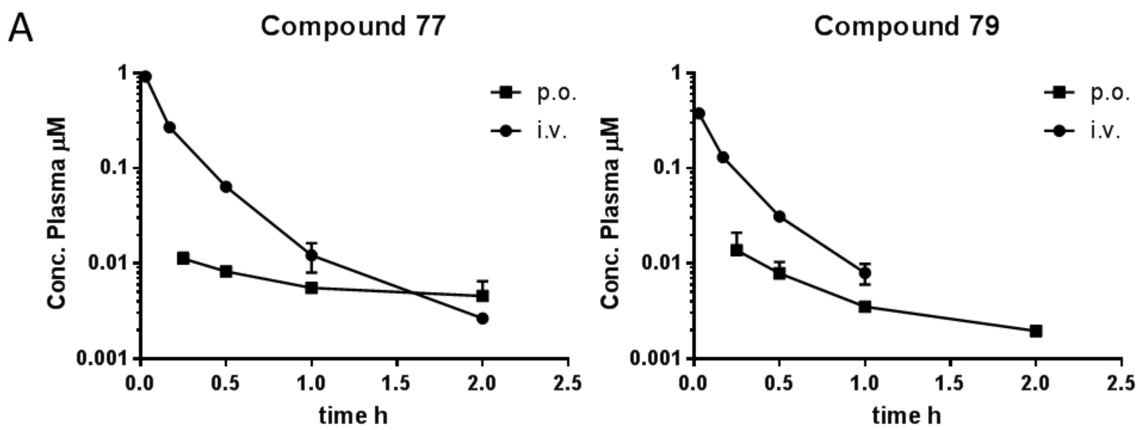
Figure 4: Heatmap of kinase targets of **77** and **79** in MV4-11 and U937. The heatmap shows the ratio of label-free quantification signal from IsoQuant of inhibitor pretreated samples at three concentrations (100, 10 and 1 µM), normalized by only XO44 treatment after subtraction of negative control signal (e.g. 1: no difference in competitor and probe treated sample (light blue) 0: full competition of probe by the inhibitor (dark blue)).

Table 8: Identified targets of **77** and **79** at 1 µM competitor. Targets were selected if there was at least 50% reduction in quantification signal from probe treated samples vs inhibitor pretreated sample in all three concentrations.

Compound 77				Compound 79			
MV4-11		U937		MV4-11		U937	
AURKA	MARK2	AURKB	PTK2B	AURKA	LYN	AURKA	MAP3K7
AURKB	PTK2	GSK3A	SLK	AURKB	MAP3K7	AURKB	MARK2
CSNK2A1	PTK2B	MARK2	TBK1	AXL	MAP4K1	CDK2	PTK2B
FYN	RPS6KA4			BTK	MARK2	CDK5	SLK
GSK3A	RPS6KA6			CDK12	MAST2	CDK6	STK3
GSK3B	STK11			CDK5	PTK2	CDK9	STK4
IRAK4	TBK1			CDK9	PTK2B	FYN	TBK1
JAK1	TEC			CSNK2A1	RPS6KA6	GSK3A	TLK2
MAP3K7	TLK1			FER	SRC	HCK	
				FGR	STK11		
				GSK3A	STK3		
				GSK3B	TBK1		
				IRAK4	TEC		
				JAK1			

In vivo PK study

Next, pharmacokinetic studies were performed to establish whether sufficient plasma concentrations could be obtained to inhibit the FLT3 in mice. To this end, compounds **77** and **79** were administered as a single dose in 5% DMSO, 95% SBE-B-CD (30% w/v) via tail vein injection (i.v.) or via oral gavage (p.o.) (Figure 5A). Unfortunately, the compounds displayed low oral bioavailability (F_{po} < 6 %), which can be explained by the high *in vivo* clearance (CL > 120 ml/min/kg). The volume of distribution was low (V_{ss} = 1.2-2.0 L/kg) as expected for neutral compounds. This resulted in short half live ($t_{1/2}$ < 30 min) and low plasma concentrations.



B

	77		79	
	i.v.	p.o.	i.v.	p.o.
Actual dose [mg/kg]	0.52	1.0	0.32	0.63
CL [mL/min/kg]	122 ± 7	n.a.	160 ± 6	n.a.
V_{ss} [L/Kg]	1.4 ± 0.1	n.a.	2.0 ± 0.2	n.a.
$t_{½}$ [h]	0.25 ± 0.08	0.43 ± 0	0.21 ± 0.02	0.65 ± 0.30
C_{max} [µmol/L]	0.92 ± 0.02	0.011 ± 0.001	0.38 ± 0.02	0.01 ± 0.01
T_{max} [h]	0.03	0.25	0.03	0.25
F [%]	n.a.	3.2 ± 0.1	n.a.	5.5 ± 0.8

Figure 5: Pharmacokinetic studies of **77** and **79** carried out in mice using oral and intravenous dosing. (N = 2; mouse *in vivo* pharmacokinetic studies were carried out in collaboration with AstraZeneca). (A) Plasma concentrations over time after single dosing. (B) Summary of pharmacokinetic parameters.

Conclusion

In this chapter the hit-to-lead optimization of two confirmed hits (Chapter 4) as FLT3 inhibitors for AML treatment is described. **77** and **79** were identified as highly potent and cellular active FLT3 inhibitors with low molecular weight and high lipophilic efficiency. The compounds also potently inhibited the proliferation of cells that expressed the FLT3 mutants (F691L and D835H/Y), which were previously found to confer resistance to the clinically tested drugs, such as quizartinib. Selectivity profiling of **77** and **79** using chemical proteomics in MV4-11 and U937 cells revealed that the compounds possess broad-spectrum kinase activity, comparable to the clinically approved drug midostaurin.[7,8] Pharmacokinetic profiling indicated that the chemical and metabolic stability needs to be improved before these compounds can be tested in *in vivo* models of AML.

Experimental

Biochemical Evaluation of FLT3 inhibitors

In a 384-wells plate (PerkinElmer 384 Flat White), 5 µL kinase/peptide mix (0.06 ng/µL FLT3 (Life Technologies; PV3182; Lot: 1614759F), 200 nM peptide (PerkinElmer; Lance® Ultra ULightTM TK-peptide; TRFO127-M; Lot: 2178856)) in assay buffer (50 mM HEPES pH 7.5, 1 mM EGTA, 10 mM $MgCl_2$, 0.01% Tween-20, 2 mM DTT) was dispensed. Separately inhibitor solutions (10 µM – 0.1 pM) were prepared in assay buffer containing 400 µM ATP and 1% DMSO. 5 µL of these solutions were dispensed and the plate was incubated in the dark at room temperature. After 90 minutes the reaction was quenched by the addition of 10 µL of 20 mM EDTA containing 4 nM antibody (PerkinElmer; Lance® Eu-W1024-anti-phosphotyrosine(PT66); AD0068; Lot: 2342358). After mixing, samples were incubated for 60 minutes in the dark. The FRET fluorescence was measured on a Tecan Infinite M1000 Pro plate reader (excitation 320 nm, emission donor 615 nm, emission acceptor 665 nm). Data was processed using Microsoft Excel 2016, pIC_{50} values were fitted using GraphPad Prism 7.0. Final assay concentrations during reaction: 200 µM ATP, 0.03 ng/µL FLT3, 100 nM Lance TK-peptide, 0.5% DMSO. Compounds were tested in n=2 and N=2. Compounds 14, 16, 17 and 28 – 35 were tested in n=3.

In situ testing of kinase inhibitors

To evaluate inhibitor effect on cell proliferation MV4-11, U937 and Ba/F3 cell lines were grown in RPMI, supplemented with 10% fetal bovine serum in an incubator at 37°C under 5% CO_2 atmosphere. Ba/F cells (wild-type) were grown in the presence of IL-3 (10 ng/mL, PeproTech). For viability assays, 10,000 cells were seeded per well in a 96-wells plate and inhibitors were added at the indicated concentration. After three days, cell viability was measured using the Cell Titer Blue (alamarBlue) viability assay (Promega) and fluorescence was measured using the Clariostar (BMG Labtech). Relative survival was normalized to the untreated control and corrected for background signal. Data was processed using Microsoft Excel 2016, pIC_{50} values were fitted using GraphPad Prism 7.0. Experiments were performed in n=2 – 3.

In vivo pharmacokinetic studies

Mouse in vivo pharmacokinetic studies were carried out in collaboration with AstraZeneca. Compounds were prepared in a solution PO: 5% DMSO, 95% SBE-B-CD (30% w/v) in water and IV: 5% DMSO, 95% SBE-B-CD (30% w/v) in water. Male CD-1 mice (20-40 g) were administered in a single dose with test compound solution either by intravenous tail vein injection or oral gavage, in a cassette dosing fashion. Plasma levels were measured at the indicated time points using LC-MS/MS. Measured mass signal was adjusted using an internal standard and quantified using an external calibration curve from 0.5 nM to 1 µM.

Crystallography

All reflection intensities were measured at 110(2) K using a SuperNova diffractometer (equipped with Atlas detector) with Mo Kα radiation (λ = 0.71073 Å) under the program CrysAlisPro (Version CrysAlisPro 1.171.39.29c, Rigaku OD, 2017). The same program was used to refine the cell dimensions and for data reduction. The structure was solved with the program SHELXS-2014/7[30] and was refined on F2 with SHELXL-2014/7 (Sheldrick, 2015). Numerical absorption correction based on gaussian integration over a multifaceted crystal model was applied using CrysAlisPro. The temperature of the data collection was controlled using the system Cryojet (manufactured by Oxford Instruments). The H atoms were placed at calculated positions (unless otherwise specified) using the instructions AFIX 13, AFIX 23, AFIX 43 or AFIX 137 with isotropic displacement parameters having values 1.2 or 1.5 Ueq of the attached C or N atoms.

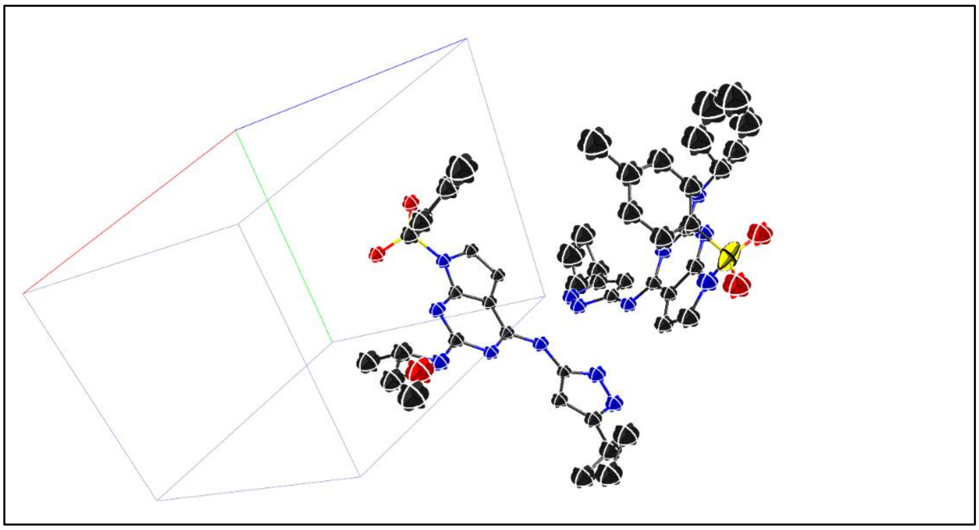
The structure is significantly disordered as the two crystallographically independent molecules A and B are disordered over two orientations. The occupancy factors of the major components of the disorder (i.e., A and B are 0.796(8) and 0.543(10)). The disorder is likely more complicated as there are some unresolved electron density peaks ranging from 0.63-1.42 e– Å–3 near the fragments (N10X→C26X, X = A and B for the major components of the disorder, X = C and D for the minor components of the disorder). This suggests those fragments are disordered over at least three orientations. As the data-to-parameter ratio is low, no attempts were made to model a three-component disorder.

The absolute configuration has been established by anomalous-dispersion effects in diffraction measurements on the crystal, and the Flack and Hooft parameters refine to 0.02(2) and 0.011(18), respectively. The chiral centers C22A/C22B have the S configuration. Used computer programs: *CrysAlis PRO* 1.171.39.29c, *SHELXS2014*/7, *SHELXL2014*/7, *SHELXTL* v6.10.

SI Table 1: Experimental details for compound **105**.

	xs1582a
Crystal data	
Chemical formula	$C_{24}H_{29}N_7O_3S$
M_r	495.60
Crystal system, space group	Triclinic, *P*1
Temperature (K)	110
a, *b*, *c* (Å)	10.0594 (3), 11.8988 (3), 12.4777 (3)
α, β, γ(°)	116.556 (2), 99.359 (2), 95.790 (2)
V (Å^3)	1292.42 (6)
Z	2
Radiation type	Mo *K*α
μ (mm^{-1})	0.16
Crystal size (mm)	0.35 × 0.18 × 0.14
Data collection	
Diffractometer	SuperNova, Dual, Cu at zero, Atlas
Absorption correction	Gaussian *CrysAlis PRO* 1.171.39.29c (Rigaku Oxford Diffraction, 2017) Numerical absorption correction based on gaussian integration over a multifaceted crystal model Empirical absorption correction using spherical harmonics, implemented in SCALE3 ABSPACK scaling
T_{min}, T_{max}	0.546, 1.000
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	34089, 10410, 9470
R_{int}	0.030
$(\sin \Theta/\lambda)_{max}$ (Å^{-1})	0.622

Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.074, 0.214, 1.03
No. of reflections	10410
No. of parameters	1017
No. of restraints	2528
H-atom treatment	H-atom parameters constrained
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	1.42, -0.35
Absolute structure	Flack x determined using 4089 quotients [(I+)-(I-)]/[(I+)+(I-)] (Parsons, Flack and Wagner, Acta Cryst. B69 (2013) 249-259).
Absolute structure parameter	0.02 (2)



SI Figure 1: Crystal-structure of **105**.

Synthetic Procedures

Solvents were purchased from Biosolve, Sigma Aldrich or Fluka and, if necessary dried over 3 Å or 4Å molecular sieves. Reagents purchased from chemical suppliers were used without further purification, unless stated otherwise. Oxygen or H_2O sensitive reactions were performed under argon or nitrogen atmosphere and/or under exclusion of H_2O. Microwave reactions were performed in a Biotage initiator+ microwave. Reactions were followed by thin layer chromatography analysis and was performed using TLC silica gel 60 F_{245} on aluminium sheets, supplied by Merck. Compounds were visualized by UV absorption (254 nm) or spray reagent (permanganate (5 g/L $KMnO_4$, 25 g/L K_2CO_3)). TLCMS was measured thin layer chromatography-mass spectrometer (Advion, EppressionL CMS; Advion, Plate Express). ^{1}H and ^{13}C-NMR spectra were performed on one of the following Bruker spectrometers: DPX 300 NMR spectrometer (300 MHz), equipped with 5mm-BBO-z-gradient-probe; AV-400 NMR spectrometer (400 MHz), equipped with 5mm-BBO-z-gradient-probe; AV-500 NMR spectrometer (500 MHz), equipped with BBFO-z-gradient-probe; AV-600 NMR spectrometer (600 MHz), equipped with 5mm-Cryo-z-gradient probe; AV-850 NMR spectrometer (850 MHz),. NMR spectra were measured in deuterated methanol, chloroform or DMSO and were referenced to the residual protonated solvent signals as internal standards (chloroform-*d* = 7.260 (^{1}H), 77.160 (^{13}C); methanol-*d₄* = 3.310 (^{1}H), 49.000 (^{13}C); DMSO-*d₆* = 2.500 (^{1}H), 39.520

(^{13}C)). Signals multiplicities are written as s (singlet), bs (broad singlet), d (doublet), t (triplet), q (quartet), p (pentet) or m (multiplet). Coupling constants (*J*) are given in Hz. Preparative HPLC (Waters, 515 HPLC pump M; Waters, 515 HPLC pump L; Waters, 2767 sample manager; Waters SFO System Fluidics Organizer; Waters Acquity Ultra Performance LC, SQ Detector; Waters Binary Gradient Module) was performed on a Phenomenex Gemini column (5 µM C18, 150 x 4.6 mm) or a Waters XBridgeTM column (5 µM C18, 150 x 19 mm). Diode detection was done between 210 and 600 nm. Gradient: ACN in (H_2O + 0.2% TFA). HRMS (Thermo, Finnigan LTQ Orbitrap; Thermo, Finnigan LTQ Pump; Thermo, Finnigan Surveyor MS Pump PLUS Thermo, Finnigan Surveyor Autosampler; NESLAB, Merlin M25). Data acquired through direct injection of 1 mM of the sample in ACN/H_2O/*t*-BuOH (1:1:1), with mass spectrometer equipped with an electrospray ion source in positive mode (source voltage 3.5 kV, sheath gas low 10, capillary temperature 275°C) with resolution R = 60,000 at m/z = 400 (mass range = 150-2000) and dioctylphtalate (m/z = 391.28428) as lock mass. All tested compounds were checked for purity by LCMS liquid chromatography-mass spectrometer, a Thermo (Thermo Finnigan LCQ Advantage Max; Thermo Finnigan Surveyor LC-pump Plus; Thermo Finnigan Surveyor Autosampler Plus; Thermo Finnigan Surveyor PDA Plus Detector; Phenomenex Gemini column (5 µm C18, 50 x 4.6 mm)) system and were determined to be >95% pure by integrating UV intensity recorded unless stated otherwise.

General procedure A: Nucleophilic aromatic substitution

A flask was charged with chloropyrimidine derivative (1 eq) dissolved in EtOH. Dropwise addition of aminopyrazole (1.1 - 1.2 eq) dissolved in EtOH brings the concentration of chloropyrimidine in EtOH to 0.4 M. After addition of Et_3N (1.1 – 1.4 eq) the reaction was stirred until completion as was indicated by TLC or LCMS analysis (typically 2-48 h). The reaction mixture was diluted with MeOH, concentrated onto celite and purified via silica-gel flash-column-chromatography.

General procedure B: Nucleophilic aromatic substitution

A flask was charged with chloropyrimidine derivative (eq indicated) and amine (eq indicated) dissolved in the indicated solvent (0.15 M). After addition of DiPEA or Et_3N (eq indicated), the flask was sealed and heated to the indicated temperature until completion (typically 1-4 d) was indicated by TLC or LCMS analysis. The reaction mixture concentrated and purified via silica-gel flash-column-chromatography or when the product precipitated by filtration.

General procedure C: Nucleophilic aromatic substitution

A flask was charged with chloropyrimidine derivative (1 eq) and amine (1.1 eq) dissolved in *n*-butanol (0.15 M). After addition of DiPEA (2.5 eq), the flask was sealed and heated to 120°C until completion was indicated by TLC or LCMS analysis (typically 2-4 d). The reaction mixture concentrated and purified via preparative HPLC.

General procedure D: Nucleophilic aromatic substitution

A flask was charged with chloropyrimidine derivative (1 eq) and amine (1.2 eq) dissolved in *n*-butanol (0.15 M). After addition of DiPEA (2.5 eq), the flask was sealed and heated to 120°C until completion was indicated by TLC or LCMS analysis (typically 2-4 d). The reaction mixture concentrated and purified via preparative HPLC.

General procedure E: Nucleophilic aromatic substitution

A flask was charged with chloropyrimidine derivative (1 eq) and amine (1.1 eq) dissolved in *n*-butanol (0.15 M). After addition of DiPEA (1.5 eq), the flask was sealed and heated to 120°C until completion was indicated by TLC or LCMS analysis (typically 2-4 d). The reaction mixture concentrated and purified via preparative HPLC.

General procedure F: Nucleophilic aromatic substitution

A flask was charged with chloropyrimidine derivative (1 eq) and amine (1.2 eq) dissolved in *n*-butanol (0.15 M). After addition of DiPEA (1.5 eq), the flask was sealed and heated to 120°C until completion was indicated by TLC or LCMS analysis (typically 2-4 d). The reaction mixture concentrated and purified via preparative HPLC.

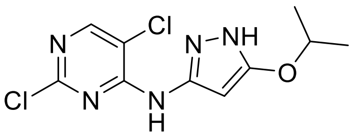
General procedure G: Nucleophilic aromatic substitution

A flask was charged with chloropyrimidine derivative (eq indicated) and amine (eq indicated) dissolved in *n*-butanol. After addition of DiPEA (eq indicated), the flask was sealed and heated to 120°C until completion was indicated by TLC or LCMS analysis. The reaction mixture concentrated and purified via preparative HPLC.

General procedure H: Nucleophilic aromatic substitution

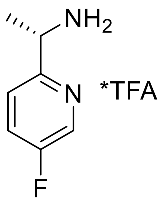
A flask was charged with chloropyrimidine derivative (eq indicated) and amine (eq indicated) dissolved in *n*-butanol. After addition of DiPEA (eq indicated), the flask was sealed and heated in the microwave to the indicated time and temperature. Completion was indicated by TLC or LCMS analysis. The reaction was mixture concentrated and purified via preparative HPLC.

2,5-Dichloro-*N*-(5-isopropoxy-1*H*-pyrazol-3-yl)pyrimidin-4-amine (3)



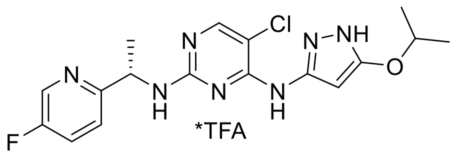
The title compound was synthesized from 2,4,5-trichloropyrimidine (**1a**) and 5-isopropoxy-1*H*-pyrazol-3-amine (**2a**) following General procedure A on a 0.30 mmol scale at RT and purified via flash-column-chromatography (dry-loading, SiO_2, 0% → 100% EtOAc in pentane) to yield the product (40 mg, 47%). ^{1}H NMR (500 MHz, methanol-d_4) δ 8.25 (s, 1H), 5.81 (bs, 1H), 4.60 (bs, 1H), 1.35 (d, J = 6.2 Hz, 6H). ^{13}C NMR (126 MHz, methanol-d_4) δ 158.92, 157.73, 156.14, 114.85, 83.10, 81.72, 76.28, 73.16, 22.36. LCMS (ESI, C_{18}, linear gradient, 10% → 90% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 5.48 min; *m/z* : 288 $[M+H]^+$.

(*S*)-1-(5-Fluoropyridin-2-yl)ethan-1-amine (4a)



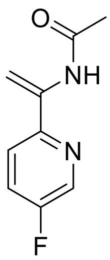
A round-bottom-flask was charged with *tert*-butyl (*S*)-(1-(5-fluoropyridin-2-yl)ethyl)carbamate (**9**) (1.17 g, 4.87 mmol, 1 eq) dissolved in $CHCl_3$ (48 mL). After cooling to 0°C and addition of TFA (12 mL) the mixture was warmed up to RT and stirred for 1 h. The solution was concentrated under reduced pressure and co-evaporated with MeOH (3x50 mL) to yield the product (1.29 g, quant.). ^{1}H NMR (600 MHz, methanol-d_4) δ 8.52 (d, J = 2.9 Hz, 1H), 7.67 (td, J = 8.6, 2.9 Hz, 1H), 7.53 (dd, J = 8.7, 4.3 Hz, 1H), 4.96 (s, 3H), 4.61 (q, J = 6.9 Hz, 1H), 1.61 (d, J = 6.9 Hz, 3H). ^{13}C NMR (151 MHz, methanol-d_4) δ 160.82 (d, J = 255.1 Hz), 154.47 (d, J = 3.8 Hz), 138.54 (d, J = 24.9 Hz), 125.47 (d, J = 19.1 Hz), 124.04 (d, J = 4.9 Hz), 51.59, 20.43.

(*S*)-5-Chloro-*N*²-(1-(5-fluoropyridin-2-yl)ethyl)-*N*⁴-(5-isopropoxy-1*H*-pyrazol-3-yl)pyrimidine-2,4-diamine (5)



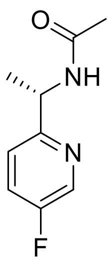
The title compound was synthesized from 2,5-dichloro-*N*-(5-isopropoxy-1H-pyrazol-3-yl)pyrimidin-4-amine (**3**) and (*S*)-1-(5-fluoropyridin-2-yl)ethan-1-amine (**4a**) following General procedure D on a 0.135 mmol scale and was purified by preparative HPLC (Gemini C_{18}, 25% → 35% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (3 mg, 4%). ^{1}H NMR (600 MHz, methanol-d_4) δ 8.42 (d, *J* = 2.9 Hz, 1H), 8.04 (s, 1H), 7.58 (td, *J* = 8.6, 2.9 Hz, 1H), 7.46 (s, 1H), 5.75 (s, 1H), 5.14 (s, 1H), 4.68 – 4.57 (m, 1H), 1.59 (d, *J* = 7.0 Hz, 3H), 1.37 (d, *J* = 6.1 Hz, 6H). ^{13}C NMR (151 MHz, methanol-d_4) δ 161.18, 158.89 (d, *J* = 254.0 Hz), 156.58, 144.95, 141.07, 136.41 (d, *J* = 24.5 Hz), 124.07 (d, *J* = 18.7 Hz), 121.69, 103.65, 73.44, 52.41, 51.73, 20.95, 19.96. HRMS calculated for $C_{17}H_{20}ClFN_7O$ 392.13964 [M+H]$^+$, found 392.1404. LCMS (ESI, C_{18}, linear gradient, 10% → 90% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 5.13 min; *m/z* : 392 [M+H]$^+$.

***N*-(1-(5-Fluoropyridin-2-yl)vinyl)acetamide (7)**



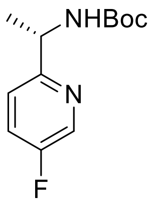
A round-bottom-flask was charged with 2-cyano-5-fluoropyrimidine (**6**) (3.00 g, 23.82 mmol, 1 eq) dissolved in dry THF (120 mL) under nitrogen atmosphere and cooled to 0°C. After dropwise addition of MeMgBr in diethyl ether (3 M, 9.5 mL, 28.62 mmol, 1.2 eq) the reaction mixture was stirred at 0°C for 50 min and after addition of Ac_2O (3.0 mL, 28.62 mmol, 1.2 eq) allowed to warm to RT. The reaction was quenched by addition of saturated $NaHCO_3$ (150 mL) and extracted with DCM (3x100 mL). The combined organic layers where dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting residue was purified via flash-column-chromatography (SiO_2, 15% → 45% EtOAc in pentane) to yield the product (1.89 g, 44%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 9.06 (s, 1H), 8.36 (d, *J* = 2.7 Hz, 1H), 7.90 – 7.69 (m, 1H), 7.50 – 7.42 (m, 1H), 6.47 (s, 1H), 5.46 (s, 1H), 2.22 (s, 3H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 169.34, 159.37 (d, *J* = 257.1 Hz), 148.46 (d, *J* = 3.7 Hz), 136.81, 135.71 (d, *J* = 24.6 Hz), 124.34 (d, *J* = 19.1 Hz), 120.35 (d, *J* = 4.6 Hz), 99.11, 25.19.

(*S*)-*N*-(1-(5-Fluoropyridin-2-yl)ethyl)acetamide (8)



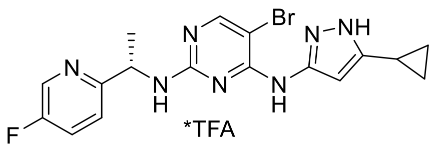
A round-bottom-flask was charged with *N*-(1-(5-fluoropyridin-2-yl)vinyl)acetamide (**7**) (1.68 g, 9.1 mmol, 1 eq) dissolved in dry Methanol (20 mL) under inert atmosphere. After addition of (+)-1,2-bis((2*S*,5*S*)-2,5-diethylphospholano) benzene(cyclooctadiene)rhodium trifluoromethanesulfonat (135 mg, 0.18 mmol, 0.02 eq) the mixture was transferred into a high-pressure reaction vessel and stirred under a 10 bar H_2 atmosphere ON. The resulting solution was concentrated under reduced pressure and purified via flash-column-chromatography (SiO_2, 0% → 1% MeOH in EtOAc) to yield the product (1.63 g, 96%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.39 (d, *J* = 2.8 Hz, 1H), 7.46 – 7.33 (m, 1H), 7.32 – 7.23 (m, 1H), 6.85 (s, 1H), 5.16 (p, *J* = 7.0 Hz, 1H), 2.03 (s, 3H), 1.45 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 169.42, 158.66 (d, *J* = 254.9 Hz), 157.15 (d, *J* = 3.8 Hz), 137.20 (d, *J* = 23.9 Hz), 123.76 (d, *J* = 18.5 Hz), 122.50 (d, *J* = 4.2 Hz), 49.30 (d, *J* = 1.0 Hz), 23.51, 22.65.

***tert*-Butyl (*S*)-(1-(5-fluoropyridin-2-yl)ethyl)carbamate (9)**



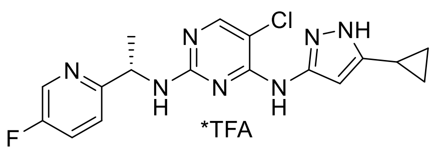
A round-bottom-flask was charged with (*S*)-*N*-(1-(5-fluoropyridin-2-yl)ethyl)acetamide (**8**) (1.24 g, 5.49 mmol, 1 eq) and DMAP (135 mg, 1.10 mmol, 0.2 eq). After addition of Boc_2O (4.20 g, 19.22 mmol, 3.5 eq) in THF (10 mL) and heating to 50°C for 3 d, the reaction was cooled to RT and LiOH (826 mg, 19.69 mmol, 3.59 eq) and H_2O (15 mL) were added. The mixture was stirred ON at RT, diluted with diethyl ether (100 mL), washed with brine (1x100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified via flash-column-chromatography (SiO_2, 0% → 20% EtOAc in pentane) to yield the product (1.40 g, quant.). ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.39 (d, *J* = 3.0 Hz, 1H), 7.39 – 7.33 (m, 1H), 7.28 – 7.23 (m, 1H), 5.54 (s, 1H), 4.85 (s, 1H), 1.63 – 1.25 (m, 12H). chiral-LC (Chiralcel OD, isocratic, 0.5 *i*PrOH in heptane): 76% (*S*). LCMS (ESI, C_{18}, linear gradient, 10% → 90% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 5.76 min; *m/z* : 241 [M+H]$^+$.

(*S*)-5-Chloro-*N*^{4}-(5-cyclopropyl-1*H*-pyrazol-3-yl)-*N*^{2}-(1-(5-fluoropyridin-2-yl)ethyl) pyrimidine-2,4-diamine (10)



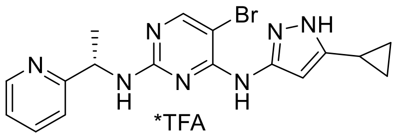
The title compound was synthesized from 5-bromo-2-chloro-*N*-(5-cyclopropyl-1*H*-pyrazol-3-yl)pyrimidin-4-amine (**80**) and (*S*)-1-(5-fluoropyridin-2-yl)ethan-1-amine (**4a**) following General procedure C on a 0.13 mmol scale and was purified by preparative HPLC (Gemini C_{18}, 20% → 30% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (29 mg, 42%). ^{1}H NMR (600 MHz, methanol-*d*$_4$) δ 8.43 (d, *J* = 2.9 Hz, 1H), 8.13 (s, 1H), 7.57 (td, *J* = 8.6, 2.9 Hz, 1H), 7.38 (bs, 1H), 6.06 (bs, 1H), 5.13 (bs, 1H), 2.00 – 1.93 (m, 1H), 1.59 (d, *J* = 7.0 Hz, 3H), 1.09 – 1.03 (m, 2H), 0.79 (bs, 2H). ^{13}C NMR (151 MHz, methanol-*d*$_4$) δ 160.27 (d, *J* = 253.9 Hz), 159.12, 158.55, 154.30, 149.44, 145.99, 145.87, 138.06 (d, *J* = 24.5 Hz), 125.29 (d, *J* = 18.8 Hz), 123.08 (d, *J* = 4.7 Hz), 96.48, 92.48, 53.69, 21.49, 8.48, 7.84. HRMS calculated for $C_{17}H_{18}BrFN_7$ 418.07856 [M+H]$^+$, found 418.0795. LCMS (ESI, C_{18}, linear gradient, 0% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 7.45 min; *m/z* : 418 [M+H]$^+$.

(*S*)-5-Chloro-*N*^{4}-(5-cyclopropyl-1*H*-pyrazol-3-yl)-*N*^{2}-(1-(5-fluoropyridin-2-yl)ethyl)pyrimidine-2,4-diamine (11)



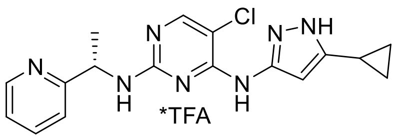
The title compound was synthesized from 2,5-dichloro-*N*-(5-cyclopropyl-1*H*-pyrazol-3-yl)pyrimidin-4-amine (**81**) and (*S*)-1-(5-fluoropyridin-2-yl)ethan-1-amine (**4a**) following General procedure C on a 0.13 mmol scale and was purified by preparative HPLC (Gemini C_{18}, 20% → 30% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (28 mg, 44%). ^{1}H NMR (600 MHz, methanol-*d*$_4$) δ 8.43 (d, *J* = 2.8 Hz, 1H), 8.05 (s, 1H), 7.61 – 7.54 (m, 1H), 7.40 (bs, 1H), 6.07 (s, 1H), 5.14 (s, 1H), 2.00 – 1.93 (m, 1H), 1.60 (d, *J* = 7.0 Hz, 3H), 1.11 – 1.03 (m, 2H), 0.79 (s, 2H). ^{13}C NMR (151 MHz, methanol-*d*$_4$) δ 160.27 (d, *J* = 253.7 Hz), 158.61, 158.57, 154.06, 149.41, 145.83, 142.93, 138.04 (d, *J* = 24.6 Hz), 125.31 (d, *J* = 18.8 Hz), 123.09 (d, *J* = 4.6 Hz), 105.55, 96.47, 53.74, 21.50, 8.48, 7.84. HRMS calculated for $C_{17}H_{18}ClFN_7$ 374.12908 [M+H]$^+$, found 374.1304. LCMS (ESI, C_{18}, linear gradient, 0% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 7.35 min; *m/z* : 374 [M+H]$^+$.

(*S*)-5-Bromo-*N*^{4}-(5-cyclopropyl-1*H*-pyrazol-3-yl)-*N*^{2}-(1-(pyridin-2-yl)ethyl) pyrimidine -2,4-diamine (12)



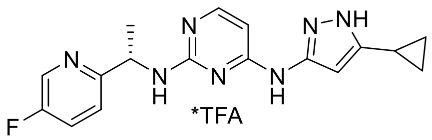
The title compound was synthesized from 5-bromo-2-chloro-*N*-(5-cyclopropyl-1*H*-pyrazol-3-yl)pyrimidin-4-amine (**80**) and (*S*)-1-(pyridin-2-yl)ethan-1-amine (**4b**) following General procedure E on a 0.20 mmol scale and was purified by preparative HPLC (Gemini C_{18}, 15% → 25% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (58 mg, 56%). ^{1}H NMR (600 MHz, methanol-d_4) δ 8.63 (d, *J* = 5.5 Hz, 1H), 8.27 (s, 1H), 8.15 (s, 1H), 7.78 (s, 1H), 7.71 (s, 1H), 5.96 (s, 1H), 5.23 (q, *J* = 7.1 Hz, 1H), 2.03 – 1.94 (m, 1H), 1.71 (d, *J* = 7.1 Hz, 3H), 1.13 – 1.05 (m, 2H), 0.79 (s, 2H). ^{13}C NMR (151 MHz, methanol-d_4) δ 159.67, 158.91, 155.24, 149.38, 147.70, 146.17, 145.46, 144.39, 125.88, 124.19, 96.52, 92.99, 52.18, 20.06, 8.58, 7.82. HRMS calculated for $C_{17}H_{19}BrN_7$ 400.08798 [M+H]$^+$, found 400.0892. LCMS (ESI, C_{18}, linear gradient, 0% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 5.76 min; *m/z* : 400 [M+H]$^+$.

(*S*)-5-Chloro-*N*^{4}-(5-cyclopropyl-1*H*-pyrazol-3-yl)-*N*^{2}-(1-(pyridin-2-yl)ethyl) pyrimidine-2,4-diamine (13)



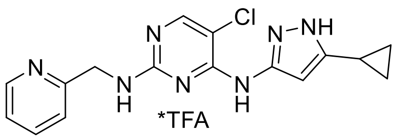
The title compound was synthesized from 2,5-dichloro-*N*-(5-isopropoxy-1H-pyrazol-3-yl)pyrimidin-4-amine (**81**) and (*S*)-1-(pyridin-2-yl)ethan-1-amine (**4b**) following General procedure F on a 0.25 mmol scale and was purified by preparative HPLC (Gemini C_{18}, 15% → 25% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (60 mg, 51%). ^{1}H NMR (600 MHz, methanol-d_4) δ 8.62 (d, *J* = 5.4 Hz, 1H), 8.24 (s, 1H), 8.05 (s, 1H), 7.77 (s, 1H), 7.68 (s, 1H), 5.98 (s, 1H), 5.23 (q, *J* = 7.1 Hz, 1H), 2.01 – 1.94 (m, 1H), 1.70 (d, *J* = 7.1 Hz, 3H), 1.11 – 1.04 (m, 2H), 0.79 (s, 2H). ^{13}C NMR (151 MHz, methanol-d_4) δ 159.98, 158.20, 155.30, 149.39, 146.16, 145.75, 145.29, 144.01, 125.76, 124.06, 105.90, 96.39, 52.30, 20.14, 8.57, 7.83. HRMS calculated for $C_{17}H_{19}ClN_7$ 356.13850 [M+H]$^+$, found 356.1394. LCMS (ESI, C_{18}, linear gradient, 0% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 5.68 min; *m/z* : 356 [M+H]$^+$.

(*S*)-*N*^{4}-(5-Cyclopropyl-1*H*-pyrazol-3-yl)-*N*^{2}-(1-(5-fluoropyridin-2-yl)ethyl) pyrimidine-2,4-diamine (14)



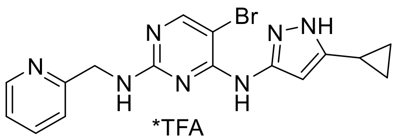
The title compound was synthesized from 2-chloro-*N*-(5-cyclopropyl-1*H*-pyrazol-3-yl)pyrimidin-4-amine (**82**) and (*S*)-1-(5-Fluoropyridin-2-yl)ethan-1-amine (**4b**) following General procedure D on a 0.30 mmol scale and was purified by preparative HPLC (Gemini C_{18}, 20% → 30% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (46 mg, 34%). ^{1}H NMR (500 MHz, methanol-d_4) δ 8.44 (d, *J* = 2.8 Hz, 1H), 7.73 (d, *J* = 7.3 Hz, 1H), 7.57 (td, *J* = 8.6, 2.9 Hz, 1H), 7.49 – 7.44 (m, 1H), 6.32 (s, 1H), 6.11 (s, 1H), 5.35 – 5.19 (m, 1H), 1.96 – 1.89 (m, 1H), 1.62 (d, *J* = 7.0 Hz, 3H), 1.04 – 1.00 (m, 2H), 0.77 – 0.74 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 159.40, 158.25 (d, *J* = 251.6 Hz), 157.90, 153.24, 146.22, 145.90, 142.20, 136.85 (d, *J* = 22.9 Hz), 124.20 (d, *J* = 18.4 Hz), 121.46, 98.12, 93.42, 51.94, 21.46, 7.93, 6.83. HRMS calculated for $C_{17}H_{19}FN_7$ 340.16805 [M+H]$^+$, found 340.1688. LCMS (ESI, C_{18}, linear gradient, 0% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 7.22 min; *m/z* : 340 [M+H]$^+$.

5-Chloro-N^4-(5-cyclopropyl-1*H*-pyrazol-3-yl)-N^2-(pyridin-2-ylmethyl)pyrimidine-2,4-diamine (15)



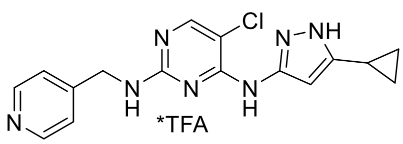
The title compound was synthesized from 2,5-dichloro-*N*-(5-isopropoxy-1H-pyrazol-3-yl)pyrimidin-4-amine (**81**) and pyridin-2-ylmethanamine (**4c**) following General procedure E on a 0.185 mmol scale and was purified by preparative HPLC (Gemini C_{18}, 10% → 20% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (45 mg, 53%). ^{1}H NMR (600 MHz, methanol-d_4) δ 8.61 (d, *J* = 5.2 Hz, 1H), 8.19 (t, *J* = 7.8 Hz, 1H), 8.04 (s, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.65 (t, *J* = 6.5 Hz, 1H), 5.95 (s, 1H), 4.78 (s, 2H), 1.93 – 1.87 (m, 1H), 1.04 – 0.99 (m, 2H), 0.69 (s, 2H). ^{13}C NMR (151 MHz, methanol-d_4) δ 157.69, 156.44, 149.46, 147.56, 146.51, 146.23, 143.42, 125.52, 125.34, 105.72, 95.56, 45.75, 8.47, 7.77. HRMS calculated for $C_{16}H_{17}ClN_7$ 342.12285 [M+H]$^+$, found 342.1242. LCMS (ESI, C_{18}, linear gradient, 0% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 5.42 min; *m/z* : 342 [M+H]$^+$.

5-Bromo-N^4-(5-cyclopropyl-1*H*-pyrazol-3-yl)-N^2-(pyridin-2-ylmethyl)pyrimidine -2,4-diamine (16)



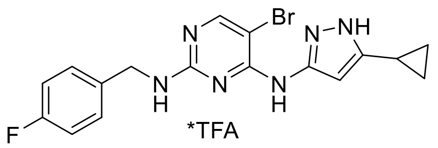
The title compound was synthesized from 5-bromo-2-chloro-*N*-(5-cyclopropyl-1*H*-pyrazol-3-yl)pyrimidin-4-amine (**80**) and pyridin-2-ylmethanamine (**4c**) following General procedure E on a 0.20 mmol scale and was purified by preparative HPLC (Gemini C_{18}, 10% → 20% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (71 mg, 71%). ^{1}H NMR (600 MHz, methanol-d_4) δ 8.65 (d, *J* = 5.2 Hz, 1H), 8.28 (t, *J* = 7.9 Hz, 1H), 8.16 (s, 1H), 7.79 – 7.75 (m, 1H), 7.73 (t, *J* = 6.6 Hz, 1H), 5.95 (s, 1H), 4.81 (s, 2H), 1.95 – 1.88 (m, 1H), 1.05 – 1.00 (m, 2H), 0.70 (s, 2H). ^{13}C NMR (151 MHz, methanol-d_4) δ 158.63, 156.77, 155.66, 149.09, 146.48, 145.55, 144.42, 125.89, 95.96, 93.13, 45.29, 8.52, 7.74. HRMS calculated for $C_{16}H_{17}BrN_7$ 386.07233 [M+H]$^+$, found 342.12340. LCMS (ESI, C_{18}, linear gradient, 0% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 5.51 min; *m/z* : 386 [M+H]$^+$.

5-Chloro-N^4-(5-cyclopropyl-1*H*-pyrazol-3-yl)-N^2-(pyridin-4-ylmethyl)pyrimidine-2,4-diamine (17)



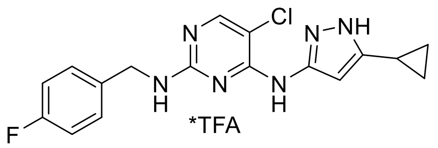
The title compound was synthesized from 2,5-dichloro-*N*-(5-isopropoxy-1H-pyrazol-3-yl)pyrimidin-4-amine (**81**) and pyridin-4-ylmethanamine (**4d**) following General procedure F on a 0.25 mmol scale and was purified by preparative HPLC (Gemini C_{18}, 10% → 20% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (49 mg, 43%). ^{1}H NMR (500 MHz, methanol-d_4) δ 8.78 – 8.75 (m, 2H), 8.14 (s, 1H), 7.94 (s, 2H), 5.84 (s, 1H), 4.85 (s, 2H), 1.89 (s, 1H), 1.06 – 1.01 (m, 2H), 0.62 (s, 2H). NO C NMR. HRMS calculated for $C_{16}H_{17}ClN_7$ 342.12285 [M+H]$^+$, found 342.1242. LCMS (ESI, C_{18}, linear gradient, 0% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 5.12 min; *m/z* : 342 [M+H]$^+$.

5-Bromo-*N*⁴-(5-cyclopropyl-1*H*-pyrazol-3-yl)-*N*²-(4-fluorobenzyl)pyrimidine-2,4-diamine (18)



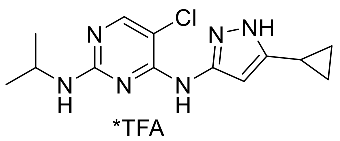
The title compound was synthesized from 5-bromo-2-chloro-*N*-(5-cyclopropyl-1*H*-pyrazol-3-yl)pyrimidin-4-amine (**80**) and (4-fluorophenyl)methanamine (**4e**) following General procedure E on a 0.20 mmol scale and was purified by preparative HPLC (Gemini C_{18}, 25% → 35% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (66 mg, 64%). ^{1}H NMR (600 MHz, methanol-*d*$_4$) δ 8.12 (s, 1H), 7.29 (s, 2H), 7.05 (t, *J* = 8.6 Hz, 2H), 6.09 (s, 1H), 4.55 (s, 2H), 1.94 – 1.85 (m, 1H), 1.02 – 0.93 (m, 2H), 0.60 (s, 2H). ^{13}C NMR (151 MHz, methanol-*d*$_4$) δ 163.62 (d, *J* = 244.6 Hz), 159.58, 154.78, 149.23, 146.29, 145.36, 134.73, 130.33 (d, *J* = 8.1 Hz), 116.35 (d, *J* = 21.8 Hz), 96.83, 92.39, 45.37, 8.37, 7.69. HRMS calculated for $C_{17}H_{17}BrFN_6$ 403.06766 [M+H]$^+$, found 403.0686. LCMS (ESI, C_{18}, linear gradient, 10% → 90% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 5.28 min; *m/z* : 403 [M+H]$^+$.

5-Chloro-*N*⁴-(5-cyclopropyl-1*H*-pyrazol-3-yl)-*N*²-(4-fluorobenzyl)pyrimidine-2,4-diamine (19)



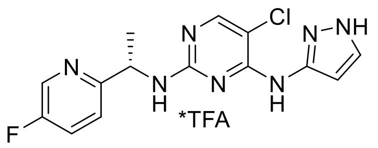
The title compound was synthesized from 2,5-dichloro-*N*-(5-isopropoxy-1H-pyrazol-3-yl)pyrimidin-4-amine (**81**) and (4-fluorophenyl)methanamine (**4e**) following General procedure F on a 0.25 mmol scale and was purified by preparative HPLC (Gemini C_{18}, 25% → 35% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (71 mg, 60%). ^{1}H NMR (600 MHz, methanol-*d*$_4$) δ 8.05 (s, 1H), 7.30 (s, 2H), 7.05 (t, *J* = 8.6 Hz, 2H), 6.10 (s, 1H), 4.56 (s, 2H), 1.92 – 1.86 (m, 1H), 1.00 – 0.94 (m, 2H), 0.61 (s, 2H). ^{13}C NMR (151 MHz, methanol-*d*$_4$) δ 163.62 (d, *J* = 244.4 Hz), 159.01, 154.53, 149.19, 146.16, 142.38, 134.75, 130.32 (d, *J* = 8.3 Hz), 116.35 (d, *J* = 21.7 Hz), 105.55, 96.84, 45.41, 8.37, 7.68. HRMS calculated for $C_{17}H_{17}ClFN_6$ 359.11818 [M+H]$^+$, found 359.1194. LCMS (ESI, C_{18}, linear gradient, 10% → 90% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 5.21 min; *m/z* : 359 [M+H]$^+$.

5-Chloro-*N*⁴-(5-cyclopropyl-1*H*-pyrazol-3-yl)-*N*²-isopropylpyrimidine-2,4-diamine (20)



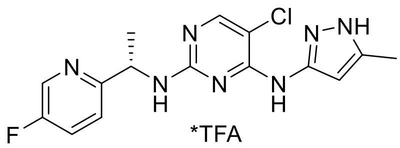
The title compound was synthesized from 2,5-dichloro-*N*-(5-isopropoxy-1H-pyrazol-3-yl)pyrimidin-4-amine (**81**) and propan-2-amine (**4f**) following General procedure F on a 0.25 mmol scale and was purified by preparative HPLC (Gemini C_{18}, 20% → 30% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (21 mg, 21%). ^{1}H NMR (600 MHz, methanol-*d*$_4$) δ 8.00 (s, 1H), 6.35 (s, 1H), 4.09 (bs, 1H), 1.98 – 1.91 (m, 1H), 1.29 (d, *J* = 6.6 Hz, 6H), 1.06 – 1.00 (m, 2H), 0.74 (s, 2H). ^{13}C NMR (151 MHz, methanol-*d*$_4$) δ 158.54, 153.51, 149.20, 146.35, 142.03, 105.11, 96.07, 45.52, 22.20, 8.40, 7.71. HRMS calculated for $C_{13}H_{18}ClN_6$ 293.12760 [M+H]$^+$, found 293.1280. LCMS (ESI, C_{18}, linear gradient, 0% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 7.15 min; *m/z* : 293 [M+H]$^+$.

(*S*)-5-Chloro-*N*²-(1-(5-fluoropyridin-2-yl)ethyl)-*N*⁴-(1*H*-pyrazol-3-yl)pyrimidine-2,4-diamine (21)



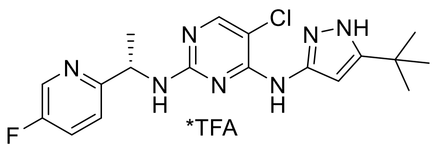
The title compound was synthesized from 2,5-dichloro-*N*-(1*H*-pyrazol-3-yl)pyrimidin-4-amine (**83**) and (*S*)-1-(5-fluoropyridin-2-yl)ethan-1-amine (**4a**) following General procedure D on a 0.25 mmol scale and was purified by preparative HPLC (Gemini C_{18}, 15% → 25% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (79 mg, 71%). ^1H NMR (600 MHz, methanol-d_4) δ 8.42 (d, *J* = 2.9 Hz, 1H), 8.08 (s, 1H), 7.68 (d, *J* = 2.4 Hz, 1H), 7.59 – 7.53 (m, 1H), 7.38 (bs, 1H), 6.41 (bs, 1H), 5.20 – 5.09 (m, 1H), 1.58 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, methanol-d_4) δ 160.33 (d, *J* = 253.7 Hz), 159.01, 158.23, 153.62, 145.95, 142.15, 137.99 (d, *J* = 24.6 Hz), 131.19, 125.39 (d, *J* = 18.8 Hz), 123.42, 105.69, 100.62, 53.64, 21.50. HRMS calculated for $C_{14}H_{14}ClFN_7$ 334.09778 $[M+H]^+$, found 334.0994. LCMS (ESI, C_{18}, linear gradient, 0% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 6.09 min; *m/z* : 334 $[M+H]^+$.

(*S*)-5-Chloro-*N*²-(1-(5-fluoropyridin-2-yl)ethyl)-*N*⁴-(5-methyl-1*H*-pyrazol-3-yl)pyrimidine-2,4-diamine (22)



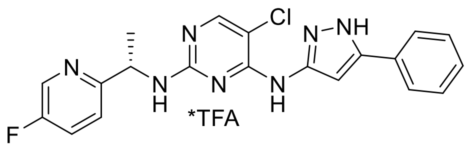
The title compound was synthesized from 2,5-dichloro-*N*-(5-methyl-1*H*-pyrazol-3-yl)pyrimidin-4-amine (**84**) and (*S*)-1-(5-fluoropyridin-2-yl)ethan-1-amine (**4a**) following General procedure D on a 0.25 mmol scale and was purified by preparative HPLC (Gemini C_{18}, 15% → 25% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (52 mg, 45%). ^1H NMR (600 MHz, methanol-d_4) δ 8.43 (d, *J* = 2.9 Hz, 1H), 8.06 (s, 1H), 7.58 (td, *J* = 8.6, 2.9 Hz, 1H), 7.42 (bs, 1H), 6.09 (bs, 1H), 5.13 (d, *J* = 7.2 Hz, 1H), 2.34 (s, 3H), 1.60 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, methanol-d_4) δ 160.30 (d, *J* = 253.7 Hz), 158.65, 158.58, 153.94, 146.00, 142.69, 142.08, 137.91 (d, *J* = 24.6 Hz), 125.39 (d, *J* = 18.8 Hz), 123.20 (d, *J* = 4.8 Hz), 105.61, 99.49, 53.78, 21.52, 11.05. HRMS calculated for $C_{15}H_{16}ClFN_7$ 348.11343 $[M+H]^+$, found 348.1147. LCMS (ESI, C_{18}, linear gradient, 0% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 6.52 min; *m/z* : 348 $[M+H]^+$.

(*S*)-*N*⁴-(5-(*tert*-Butyl)-1*H*-pyrazol-3-yl)-5-chloro-*N*²-(1-(5-fluoropyridin-2-yl)ethyl)pyrimidine-2,4-diamine (23)



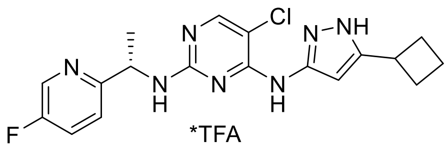
The title compound was synthesized from *N*-(5-(*tert*-butyl)-1*H*-pyrazol-3-yl)-2,5-dichloropyrimidin-4-amine (**85**) and (*S*)-1-(5-fluoropyridin-2-yl)ethan-1-amine (**4a**) following General procedure D on a 0.25 mmol scale and was purified by preparative HPLC (Gemini C_{18}, 25% → 35% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (89 mg, 71%). ^1H NMR (600 MHz, methanol-d_4) δ 8.41 (d, *J* = 2.9 Hz, 1H), 8.07 (s, 1H), 7.55 (td, *J* = 8.6, 2.9 Hz, 1H), 7.37 (s, 1H), 6.38 (s, 1H), 5.22 (s, 1H), 1.60 (d, *J* = 7.0 Hz, 3H), 1.37 (s, 9H). ^{13}C NMR (151 MHz, methanol-d_4) δ 160.28 (d, *J* = 253.8 Hz), 158.63, 158.20, 155.97, 153.98, 145.78, 142.69, 138.09 (d, *J* = 24.4 Hz), 125.21 (d, *J* = 18.7 Hz), 123.18 (d, *J* = 4.6 Hz), 105.53, 96.69, 53.50, 32.30, 30.45, 21.41. HRMS calculated for $C_{18}H_{22}ClFN_7$ 390.16038 $[M+H]^+$, found 390.1614. LCMS (ESI, C_{18}, linear gradient, 10% → 90% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 5.37 min; *m/z* : 390 $[M+H]^+$.

(*S*)-5-Chloro-*N*²-(1-(5-fluoropyridin-2-yl)ethyl)-*N*⁴-(5-phenyl-1*H*-pyrazol-3-yl)pyrimidine-2,4-diamine (24)



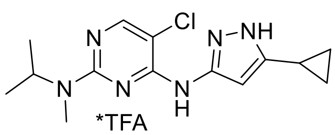
The title compound was synthesized from 2,5-dichloro-*N*-(5-phenyl-1*H*-pyrazol-3-yl)pyrimidin-4-amine (**86**) and (*S*)-1-(5-fluoropyridin-2-yl)ethan-1-amine (**4a**) following General procedure D on a 0.25 mmol scale and was purified by preparative HPLC (Gemini C_{18}, 25% → 35% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (57 mg, 44%). ^{1}H NMR (600 MHz, methanol-d_4) δ 8.24 (s, 1H), 8.10 (s, 1H), 7.75 (d, *J* = 7.7 Hz, 2H), 7.52 (t, *J* = 7.6 Hz, 2H), 7.43 (t, *J* = 7.3 Hz, 2H), 7.35 (bs, 1H), 6.70 (s, 1H), 5.19 (bs, 1H), 1.60 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, methanol-d_4) δ 160.13 (d, *J* = 253.8 Hz), 158.77, 158.74, 153.80, 146.60, 145.70, 142.53, 137.92 (d, *J* = 24.4 Hz), 130.75, 130.19, 129.88, 126.61, 125.26 (d, *J* = 18.8 Hz), 122.82, 105.57, 97.83, 54.02, 21.62. HRMS calculated for $C_{20}H_{18}ClFN_7$ 410.12908 $[M+H]^+$, found 410.1299. LCMS (ESI, C_{18}, linear gradient, 10% → 90% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 5.47 min; *m/z* : 410 $[M+H]^+$.

(*S*)-5-Chloro-*N*⁴-(5-cyclobutyl-1*H*-pyrazol-3-yl)-*N*²-(1-(5-fluoropyridin-2-yl)ethyl)pyrimidine-2,4-diamine (25)



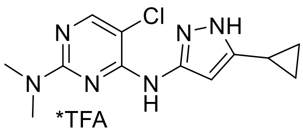
The title compound was synthesized from 2,5-dichloro-*N*-(5-cyclobutyl-1*H*-pyrazol-3-yl)pyrimidin-4-amine (**87**) and (*S*)-1-(5-fluoropyridin-2-yl)ethan-1-amine (**4a**) following General procedure D on a 0.25 mmol scale and was purified by preparative HPLC (Gemini C_{18}, 25% → 35% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (90 mg, 72%). ^{1}H NMR (600 MHz, methanol-d_4) δ 8.42 (d, *J* = 2.9 Hz, 1H), 8.06 (s, 1H), 7.55 (td, *J* = 8.5, 2.9 Hz, 1H), 7.39 (s, 1H), 6.29 (s, 1H), 5.18 (s, 1H), 3.60 (p, *J* = 8.6 Hz, 1H), 2.46 – 2.39 (m, 2H), 2.30 – 2.19 (m, 2H), 2.16 – 2.07 (m, 1H), 2.00 – 1.93 (m, 1H), 1.60 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, methanol-d_4) δ 160.27 (d, *J* = 253.9 Hz), 158.60, 158.54, 154.10, 150.85, 146.00, 142.91, 138.02 (d, *J* = 24.5 Hz), 125.25 (d, *J* = 18.8 Hz), 123.12 (d, *J* = 4.7 Hz), 105.54, 97.41, 53.66, 33.06, 30.25, 21.49, 19.50. HRMS calculated for $C_{18}H_{20}ClFN_7$ 388.14473 $[M+H]^+$, found 388.1453. LCMS (ESI, C_{18}, linear gradient, 10% → 90% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 5.22 min; *m/z* : 388 $[M+H]^+$.

5-Chloro-*N*⁴-(5-cyclopropyl-1H-pyrazol-3-yl)-*N*²-isopropyl-*N*²-methylpyrimidine-2,4-diamine (26)



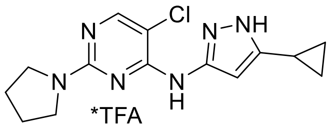
The title compound was synthesized from 2,5-dichloro-*N*-(5-isopropoxy-1H-pyrazol-3-yl)pyrimidin-4-amine (**81**) and *N*-methylpropan-2-amine (**4g**) following General procedure F on a 0.30 mmol scale and was purified by preparative HPLC (Gemini C_{18}, 20% → 30% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (96 mg, 76%). ^{1}H NMR (600 MHz, methanol-d_4) δ 8.01 (s, 1H), 6.25 (s, 1H), 4.78 (s, 1H), 3.02 (s, 3H), 1.99 – 1.92 (m, 1H), 1.26 (d, *J* = 6.8 Hz, 6H), 1.06 – 1.01 (m, 2H), 0.75 – 0.69 (m, 2H). ^{13}C NMR (151 MHz, methanol-d_4) δ 157.76, 153.56, 149.22, 146.47, 142.49, 105.49, 96.02, 49.87, 29.10, 19.45, 8.45, 7.67. HRMS calculated for $C_{14}H_{20}ClN_6$ 307.14325 $[M+H]^+$, found 307.1431. LCMS (ESI, C_{18}, linear gradient, 0% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 7.18 min; *m/z* : 307 $[M+H]^+$.

5-Chloro-*N*⁴-(5-cyclopropyl-1*H*-pyrazol-3-yl)-*N*²,*N*²-dimethylpyrimidine-2,4-diamine (27)



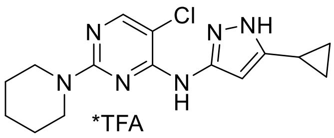
A vial was charged with NaH (60% in mineral oil, 32 mg, 0.80 mmol, 2.7 eq) dissolved in *i*PrOH (1 mL). After drop-wise addition of 2,5-dichloro-*N*-(5-isopropoxy-1*H*-pyrazol-3-yl)pyrimidin-4-amine (**81**) (80 mg, 0.30 mmol, 1 eq) dissolved in *i*PrOH (0.7 mL) and DMF (1 mL), the vial was sealed and the mixture stirred at 120°C ON, concentrated under reduced pressure and purified by preparative HPLC (Gemini C_{18}, 15% → 25% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (79 mg, 67%). ^{1}H NMR (500 MHz, methanol-d_4) δ 8.01 (s, 1H), 6.32 (s, 1H), 3.22 (s, 6H), 1.98 – 1.90 (m, 1H), 1.05 – 0.96 (m, 2H), 0.76 – 0.69 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6, 1% TFA, 75°C) δ 155.01, 154.85, 147.00, 145.73, 144.53, 102.59, 94.28, 37.24, 7.44, 6.66. HRMS calculated for $C_{12}H_{16}ClN_6$ 279.11195 [M+H]$^+$, found 279.11198. LCMS (ESI, C_{18}, linear gradient, 0% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 6.31 min; *m/z* : 279 [M+H]$^+$.

5-Chloro-*N*-(5-cyclopropyl-1*H*-pyrazol-3-yl)-2-(pyrrolidin-1-yl)pyrimidin-4-amine (28)



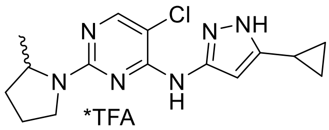
The title compound was synthesized from 2,5-dichloro-*N*-(5-isopropoxy-1*H*-pyrazol-3-yl)pyrimidin-4-amine (**81**) and pyrrolidine (**4h**) following General procedure F on a 0.30 mmol scale and was purified by preparative HPLC (Gemini C_{18}, 20% → 25% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (23 mg, 18%). ^{1}H NMR (500 MHz, methanol-d_4) δ 8.02 (s, 1H), 6.40 (s, 1H), 3.67 (s, 2H), 3.51 (s, 2H), 2.13 (s, 2H), 2.07 (s, 2H), 2.01 – 1.90 (m, 1H), 1.05 – 1.00 (m, 2H), 0.76 – 0.71 (m, 2H). ^{13}C NMR (126 MHz, methanol-d_4) δ 157.35, 151.78, 149.03, 146.58, 141.89, 105.39, 96.09, 49.85, 47.83, 26.67, 25.74, 8.34, 7.73. HRMS calculated for $C_{14}H_{18}ClN_6$ 305.12760 [M+H]$^+$, found 305.1267. LCMS (ESI, C_{18}, linear gradient, 0% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 7.03 min; *m/z* : 305 [M+H]$^+$.

5-5-Chloro-*N*-(5-cyclopropyl-1*H*-pyrazol-3-yl)-2-(piperidin-1-yl)pyrimidin-4-amine (29)



The title compound was synthesized from 2,5-dichloro-*N*-(5-isopropoxy-1*H*-pyrazol-3-yl)pyrimidin-4-amine (**81**) and piperidine (**4i**) following General procedure F on a 0.30 mmol scale and was purified by preparative HPLC (Gemini C_{18}, 20% → 30% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (95 mg, 73%). ^{1}H NMR (500 MHz, methanol-d_4) δ 8.01 (s, 1H), 6.21 (s, 1H), 3.75 – 3.69 (m, 4H), 2.02 – 1.88 (m, 1H), 1.79 – 1.72 (m, 2H), 1.72 – 1.66 (m, 4H), 1.05 – 1.00 (m, 2H), 0.75 – 0.69 (m, 2H). ^{13}C NMR (126 MHz, methanol-d_4) δ 158.01, 153.22, 149.25, 146.37, 142.92, 105.23, 96.20, 47.44, 26.39, 24.89, 8.41, 7.68. HRMS calculated for $C_{15}H_{20}ClN_6$ 319.14325 [M+H]$^+$, found 319.1441. LCMS (ESI, C_{18}, linear gradient, 0% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 7.56 min; *m/z* : 319 [M+H]$^+$.

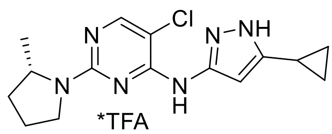
5-Chloro-*N*-(5-cyclopropyl-1*H*-pyrazol-3-yl)-2-(2-methylpyrrolidin-1-yl)pyrimidin-4-amine (30)



The title compound was synthesized from 2,5-dichloro-*N*-(5-isopropoxy-1*H*-pyrazol-3-yl)pyrimidin-4-amine (**81**) and 2-methylpyrrolidine (**4j**) following General procedure D on a 0.30 mmol scale and was purified by preparative HPLC (Gemini C_{18}, 20% → 30% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (32 mg, 25%). ^{1}H NMR (500 MHz, methanol-d_4) δ

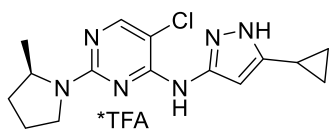
7.98 (s, 1H), 6.35 (s, 1H), 4.30 (s, 1H), 3.70 – 3.62 (m, 1H), 3.54 – 3.46 (m, 1H), 2.26 – 2.15 (m, 2H), 2.15 – 2.05 (m, 1H), 1.98 – 1.90 (m, 1H), 1.85 – 1.79 (m, 1H), 1.27 (d, *J* = 6.4 Hz, 3H), 1.06 – 0.94 (m, 2H), 0.77 – 0.68 (m, 2H). ^{13}C NMR (126 MHz, methanol-d_4) δ 157.60, 152.17, 149.34, 146.59, 142.85, 105.43, 95.94, 56.92, 33.30, 24.06, 19.08, 8.27, 8.18, 7.68. HRMS calculated for $C_{15}H_{20}ClN_6$ 319.14325 [M+H]$^+$, found 319.14322. LCMS (ESI, C_{18}, linear gradient, 0% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 7.41 min; *m/z* : 319 [M+H]$^+$.

(*S*)-5-Chloro-*N*-(5-cyclopropyl-1*H*-pyrazol-3-yl)-2-(2-methylpyrrolidin-1-yl)pyrimidin-4-amine (31)



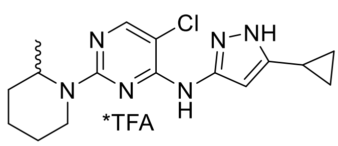
The title compound was synthesized from 2,5-dichloro-*N*-(5-isopropoxy-1*H*-pyrazol-3-yl)pyrimidin-4-amine (**81**) and (*S*)-2-methylpyrrolidine (**4k**) following General procedure D on a 0.30 mmol scale and was purified by preparative HPLC (Gemini C_{18}, 20% → 30% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (68 mg, 52%). ^{1}H NMR (500 MHz, methanol-d_4) δ 7.99 (s, 1H), 6.34 (s, 1H), 4.31 (s, 1H), 3.72 – 3.60 (m, 1H), 3.60 – 3.49 (m, 1H), 2.26 – 2.16 (m, 2H), 2.16 – 2.06 (m, 1H), 1.98 – 1.91 (m, 1H), 1.86 – 1.81 (m, 1H), 1.28 (d, *J* = 6.4 Hz, 3H), 1.06 – 0.99 (m, 2H), 0.75 – 0.68 (m, 2H). ^{13}C NMR (126 MHz, methanol-d_4) δ 157.65, 151.80, 149.31, 146.53, 142.27, 105.52, 96.02, 56.98, 33.27, 24.06, 19.04, 8.28, 8.19, 7.66. HRMS calculated for $C_{15}H_{20}ClN_6$ 319.14325 [M+H]$^+$, found 319.14337. LCMS (ESI, C_{18}, linear gradient, 0% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 7.55 min; *m/z* : 319 [M+H]$^+$.

(*R*)-5-Chloro-*N*-(5-cyclopropyl-1*H*-pyrazol-3-yl)-2-(2-methylpyrrolidin-1-yl)pyrimidin-4-amine (32)



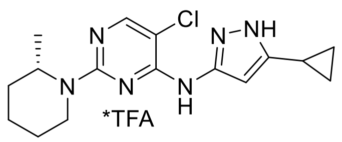
The title compound was synthesized from 2,5-dichloro-*N*-(5-isopropoxy-1*H*-pyrazol-3-yl)pyrimidin-4-amine (**81**) and (*R*)-2-methylpyrrolidine (**4l**) following General procedure D on a 0.30 mmol scale and was purified by preparative HPLC (Gemini C_{18}, 20% → 30% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (102 mg, 79%. ^{1}H NMR (500 MHz, methanol-d_4) δ 7.98 (s, 1H), 6.34 (s, 1H), 4.31 (s, 1H), 3.71 – 3.63 (m, 1H), 3.56 – 3.47 (m, 1H), 2.26 – 2.15 (m, 2H), 2.14 – 2.08 (m, 1H), 1.99 – 1.91 (m, 1H), 1.86 – 1.80 (m, 1H), 1.28 (d, *J* = 6.5 Hz, 3H), 1.05 – 0.99 (m, 2H), 0.77 – 0.69 (m, 2H). ^{13}C NMR (126 MHz, methanol-d_4) δ 157.63, 151.85, 149.32, 146.53, 142.36, 105.50, 96.00, 56.98, 33.27, 24.06, 19.05, 8.28, 8.19, 7.67. HRMS calculated for $C_{15}H_{20}ClN_6$ 319.14325 [M+H]$^+$, found 319.14330. LCMS (ESI, C_{18}, linear gradient, 0% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 7.51 min; *m/z* : 319 [M+H]$^+$.

5-Chloro-*N*-(5-cyclopropyl-1*H*-pyrazol-3-yl)-2-(2-methylpiperidin-1-yl)pyrimidin-4-amine (33)



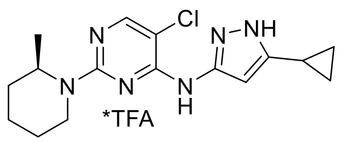
The title compound was synthesized from 2,5-dichloro-*N*-(5-isopropoxy-1*H*-pyrazol-3-yl)pyrimidin-4-amine (**81**) and 2-methylpiperidine (**4m**) following General procedure D on a 0.30 mmol scale and was purified by preparative HPLC (Gemini C_{18}, 25% → 28% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (47 mg, 35%). ^{1}H NMR (500 MHz, methanol-d_4) δ 8.01 (s, 1H), 6.21 (s, 1H), 4.65 (s, 1H), 4.30 – 4.05 (m, 1H), 3.22 (td, *J* = 13.4, 3.1 Hz, 1H), 1.98 – 1.90 (m, 1H), 1.85 – 1.74 (m, 3H), 1.73 – 1.62 (m, 2H), 1.62 – 1.48 (m, 1H), 1.30 (d, *J* = 6.9 Hz, 3H), 1.11 – 0.98 (m, 2H), 0.78 – 0.63 (m, 2H). ^{13}C NMR (126 MHz, methanol-d_4) δ 158.02, 153.14, 149.25, 146.42, 142.85, 105.25, 96.04, 49.91, 41.32, 30.80, 26.05, 19.07, 15.61, 8.48, 7.68. HRMS calculated for $C_{16}H_{22}ClN_6$ 333.15890 $[M+H]^+$, found 333.15891. LCMS (ESI, C_{18}, linear gradient, 0% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 7.97 min; *m/z* : 333 $[M+H]^+$.

(*S*)-5-Chloro-*N*-(5-cyclopropyl-1*H*-pyrazol-3-yl)-2-(2-methylpiperidin-1-yl)pyrimidin-4-amine (34)



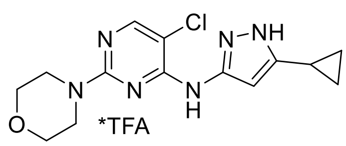
The title compound was synthesized from 2,5-dichloro-*N*-(5-isopropoxy-1*H*-pyrazol-3-yl)pyrimidin-4-amine (**81**) and (*S*)-2-methylpiperidine (**4n**) following General procedure D on a 0.30 mmol scale and was purified by preparative HPLC (Gemini C_{18}, 25% → 28% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (92 mg, 69%). ^1H NMR (500 MHz, methanol-d_4) δ 7.93 (d, *J* = 1.6 Hz, 1H), 6.12 (d, *J* = 2.9 Hz, 1H), 4.55 (s, 1H), 4.15 – 3.98 (m, 1H), 3.20 – 3.06 (m, 1H), 1.92 – 1.80 (m, 1H), 1.80 – 1.66 (m, 3H), 1.66 – 1.55 (m, 2H), 1.55 – 1.39 (m, 1H), 1.30 – 1.14 (m, 3H), 1.00 – 0.88 (m, 2H), 0.72 – 0.52 (m, 2H). ^{13}C NMR (126 MHz, methanol-d_4) δ 158.10, 152.86, 149.31, 146.36, 142.37, 105.37, 96.14, 50.05, 41.40, 30.79, 26.00, 19.03, 15.65, 8.44, 7.65. HRMS calculated for $C_{16}H_{22}ClN_6$ 333.15890 $[M+H]^+$, found 333.15909. LCMS (ESI, C_{18}, linear gradient, 0% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 7.96 min; *m/z* : 333 $[M+H]^+$.

(*R*)-5-Chloro-*N*-(5-cyclopropyl-1*H*-pyrazol-3-yl)-2-(2-methylpiperidin-1-yl)pyrimidin-4-amine (35)



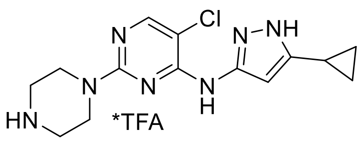
The title compound was synthesized from 2,5-dichloro-*N*-(5-isopropoxy-1*H*-pyrazol-3-yl)pyrimidin-4-amine (**81**) and (*R*)-2-methylpiperidine (**4o**) following General procedure D on a 0.30 mmol scale and was purified by preparative HPLC (Gemini C_{18}, 25% → 28% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (75 mg, 56%). ^1H NMR (500 MHz, methanol-d_4) δ 8.02 (s, 1H), 6.21 (s, 1H), 4.64 (s, 1H), 4.21 – 4.09 (m, 1H), 3.28 – 3.18 (m, 1H), 2.00 – 1.91 (m, 1H), 1.88 – 1.75 (m, 3H), 1.75 – 1.64 (m, 2H), 1.65 – 1.46 (m, 1H), 1.31 (d, *J* = 6.9 Hz, 3H), 1.14 – 0.93 (m, 2H), 0.81 – 0.61 (m, 2H). ^{13}C NMR (126 MHz, methanol-d_4) δ 158.07, 152.96, 149.30, 146.38, 142.53, 105.34, 96.11, 50.02, 41.38, 30.79, 26.01, 19.04, 15.65, 8.43, 7.66. HRMS calculated for $C_{16}H_{22}ClN_6$ 333.15890 $[M+H]^+$, found 333.15878. LCMS (ESI, C_{18}, linear gradient, 0% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 7.98 min; *m/z* : 333 $[M+H]^+$.

5-Chloro-*N*-(5-cyclopropyl-1*H*-pyrazol-3-yl)-2-morpholinopyrimidin-4-amine (36)



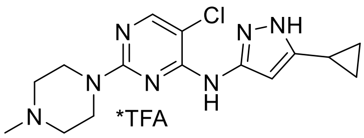
The title compound was synthesized from 2,5-dichloro-*N*-(5-isopropoxy-1*H*-pyrazol-3-yl)pyrimidin-4-amine (**81**) and morpholine (**4p**) following General procedure D on a 0.30 mmol scale and was purified by preparative HPLC (Gemini C_{18}, 15% → 25% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (106 mg, 81%). ^1H NMR (500 MHz, methanol-d_4) δ 8.09 (s, 1H), 6.21 (s, 1H), 3.83 – 3.76 (m, 4H), 3.73 – 3.68 (m, 4H), 1.96 (tt, *J* = 8.5, 5.1 Hz, 1H), 1.06 – 1.00 (m, 2H), 0.77 – 0.71 (m, 2H). ^{13}C NMR (126 MHz, methanol-d_4) δ 157.85, 155.02, 149.52, 146.17, 145.04, 105.71, 96.28, 67.00, 46.19, 8.51, 7.75. HRMS calculated for $C_{14}H_{18}ClN_6O$ 321.12251 $[M+H]^+$, found 321.12246. LCMS (ESI, C_{18}, linear gradient, 0% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 6.48 min; *m/z* : 321 $[M+H]^+$.

5-Chloro-*N*-(5-cyclopropyl-1*H*-pyrazol-3-yl)-2-(piperazin-1-yl)pyrimidin-4-amine (37)



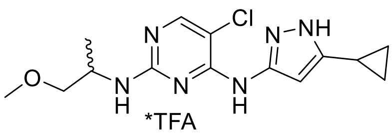
The title compound was synthesized from 2,5-dichloro-*N*-(5-isopropoxy-1*H*-pyrazol-3-yl)pyrimidin-4-amine (**81**) and piperazine (**4q**) following General procedure D on a 0.30 mmol scale and was purified by preparative HPLC (Gemini C_{18}, 10% → 20% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (106 mg, 65%). ^{1}H NMR (500 MHz, methanol-d_4) δ 8.11 (s, 1H), 6.21 (s, 1H), 4.07 – 3.95 (m, 4H), 3.32 – 3.30 (m, 4H), 1.98 (tt, J = 8.5, 5.0 Hz, 1H), 1.12 – 0.99 (m, 2H), 0.85 – 0.72 (m, 2H). ^{13}C NMR (126 MHz, methanol-d_4) δ 159.30, 157.09, 153.50, 150.24, 146.54, 105.71, 95.47, 44.17, 42.46, 8.61, 7.92. HRMS calculated for $C_{14}H_{19}ClN_7$ 320.13850 [M+H]$^+$, found 320.13869. LCMS (ESI, C_{18}, linear gradient, 0% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 5.37 min; *m/z* : 320 [M+H]$^+$.

5-Chloro-*N*-(5-cyclopropyl-1*H*-pyrazol-3-yl)-2-(4-methylpiperazin-1-yl)pyrimidin-4-amine (38)



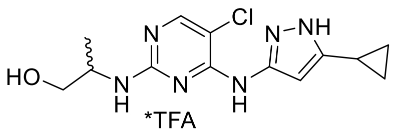
The title compound was synthesized from 2,5-dichloro-*N*-(5-isopropoxy-1*H*-pyrazol-3-yl)pyrimidin-4-amine (**81**) and 1-methylpiperazine (**4r**) following General procedure D on a 0.30 mmol scale and was purified by preparative HPLC (Gemini C_{18}, 10% → 20% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (136 mg, 81%). ^{1}H NMR (500 MHz, methanol-d_4) δ 8.04 (s, 1H), 6.18 (s, 1H), 4.03 (bs, 4H), 3.33 (bs, 4H), 2.93 (s, 3H), 1.94 (tt, J = 8.5, 5.1 Hz, 1H), 1.09 – 0.95 (m, 2H), 0.82 – 0.67 (m, 2H). ^{13}C NMR (126 MHz, methanol-d_4) δ 159.65, 157.03, 154.31, 150.08, 146.71, 105.78, 95.38, 54.09, 43.63, 42.71, 8.58, 7.93. HRMS calculated for $C_{15}H_{21}ClN_7$ 334.15415 [M+H]$^+$, found 334.15438. LCMS (ESI, C_{18}, linear gradient, 0% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 5.50 min; *m/z* : 334 [M+H]$^+$.

5-Chloro-*N*^{4}-(5-cyclopropyl-1*H*-pyrazol-3-yl)-*N*^{2}-(1-methoxypropan-2-yl)pyrimidine-2,4-diamine (39)



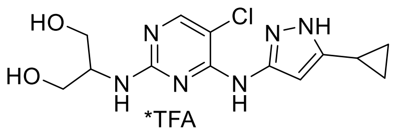
The title compound was synthesized from 2,5-dichloro-*N*-(5-isopropoxy-1*H*-pyrazol-3-yl)pyrimidin-4-amine (**81**) and 1-methoxypropan-2-amine (**4s**) following General procedure F on a 0.30 mmol scale and was purified by preparative HPLC (Gemini C_{18}, 20% → 30% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (75 mg, 57%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.08 (s, 1H), 6.23 (s, 1H), 4.07 (q, J = 6.1 Hz, 1H), 3.45 – 3.41 (m, 1H), 3.38 – 3.34 (m, 1H), 3.29 (s, 3H), 1.97 – 1.86 (m, 1H), 1.19 (d, J = 6.7 Hz, 3H), 0.99 – 0.91 (m, 2H), 0.74 – 0.68 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 155.81, 153.99, 147.27, 144.46, 143.93, 102.66, 94.23, 74.48, 57.97, 46.88, 16.49, 7.12, 6.58. HRMS calculated for $C_{14}H_{20}ClN_6O$ 323.13816 [M+H]$^+$, found 323.1391. LCMS (ESI, C_{18}, linear gradient, 0% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 6.81 min; *m/z* : 323 [M+H]$^+$.

2-((5-Chloro-4-((5-cyclopropyl-1*H*-pyrazol-3-yl)amino)pyrimidin-2-yl)amino)propan-1-ol (40)



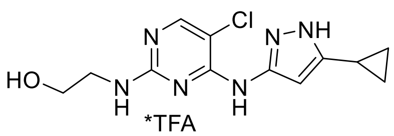
The title compound was synthesized from 2,5-dichloro-*N*-(5-isopropoxy-1*H*-pyrazol-3-yl)pyrimidin-4-amine (**81**) and 2-aminopropan-1-ol (**4t**) following General procedure D on a 0.30 mmol scale and was purified by preparative HPLC (Gemini C_{18}, 15% → 25% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (112 mg, 88%). ^{1}H NMR (500 MHz, methanol-d_4) δ 8.02 (s, 1H), 6.34 (s, 1H), 4.11 (s, 1H), 3.66 (dd, J = 11.1, 4.6 Hz, 1H), 3.57 (dd, J = 11.0, 6.3 Hz, 1H), 2.01 – 1.89 (m, 1H), 1.26 (d, J = 6.7 Hz, 3H), 1.09 – 0.94 (m, 2H), 0.92 – 0.67 (m, 2H). ^{13}C NMR (151 MHz, methanol-d_4) δ 158.52, 154.06, 149.29, 146.19, 142.10, 105.24, 96.10, 65.57, 51.31, 16.79, 8.43, 7.73. HRMS calculated for $C_{13}H_{18}ClN_6O$ 309.12251 $[M+H]^+$, found 309.12245. LCMS (ESI, C_{18}, linear gradient, 0% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 6.18 min; *m/z* : 309 $[M+H]^+$.

2-((5-Chloro-4-((5-cyclopropyl-1*H*-pyrazol-3-yl)amino)pyrimidin-2-yl)amino)propane-1,3-diol (41)



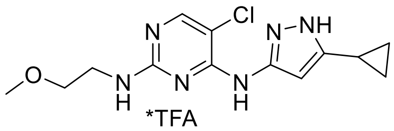
The title compound was synthesized from 2,5-dichloro-*N*-(5-isopropoxy-1*H*-pyrazol-3-yl)pyrimidin-4-amine (**81**) and 2-aminopropane-1,3-diol (**4u**) following General procedure D on a 0.30 mmol scale and was purified by preparative HPLC (Gemini C_{18}, 10% → 20% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (91 mg, 69%). ^{1}H NMR (600 MHz, methanol-d_4) δ 8.04 (s, 1H), 6.35 (s, 1H), 4.13 (s, 1H), 3.78 – 3.74 (m, 2H), 3.73 – 3.68 (m, 2H), 1.94 (tt, J = 8.5, 5.1 Hz, 1H), 1.04 – 0.98 (m, 2H), 0.82 – 0.77 (m, 2H). ^{13}C NMR (151 MHz, methanol-d_4) δ 158.40, 154.61, 149.44, 146.12, 142.16, 105.40, 96.13, 61.65, 57.06, 8.48, 7.77. HRMS calculated for $C_{13}H_{18}ClN_6O_2$ 325.11743 $[M+H]^+$, found 325.11740. LCMS (ESI, C_{18}, linear gradient, 0% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 5.18 min; *m/z* : 325 $[M+H]^+$.

2-((5-Chloro-4-((5-cyclopropyl-1*H*-pyrazol-3-yl)amino)pyrimidin-2-yl)amino)ethan-1-ol (42)



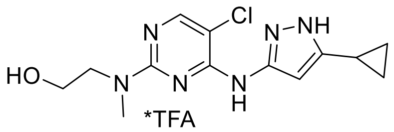
The title compound was synthesized from 2,5-dichloro-*N*-(5-isopropoxy-1*H*-pyrazol-3-yl)pyrimidin-4-amine (**81**) and 2-aminopropane-1,3-diol (**4v**) following General procedure D on a 0.30 mmol scale and was purified by preparative HPLC (Gemini C_{18}, 15% → 25% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (111 mg, 91%). ^{1}H NMR (500 MHz, DMSO-d_6, 1% TFA, 75°C) δ 8.14 (s, 1H), 6.30 (s, 1H), 3.59 (t, J = 5.7 Hz, 2H), 3.41 (t, J = 5.7 Hz, 2H), 1.92 (tt, J = 8.5, 5.1 Hz, 1H), 1.00 – 0.90 (m, 2H), 0.76 – 0.67 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6, 1% TFA, 75°C) δ 155.93, 153.57, 147.16, 144.09, 142.49, 102.94, 94.60, 59.06, 43.74, 7.47, 6.70. HRMS calculated for $C_{12}H_{16}ClN_6O$ 295.10686 $[M+H]^+$, found 295.10714. LCMS (ESI, C_{18}, linear gradient, 0% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 5.71 min; *m/z* : 295 $[M+H]^+$.

5-Chloro-*N*4-(5-cyclopropyl-1*H*-pyrazol-3-yl)-*N*2-(2-methoxyethyl)pyrimidine-2,4-diamine (43)



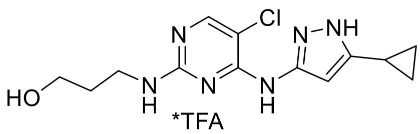
The title compound was synthesized from 2,5-dichloro-*N*-(5-isopropoxy-1*H*-pyrazol-3-yl)pyrimidin-4-amine (**81**) and 2-methoxyethan-1-amine (**4w**) following General procedure D on a 0.30 mmol scale and was purified by preparative HPLC (Gemini C_{18}, 15% → 25% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (59 mg, 47%). ^{1}H NMR (500 MHz, methanol-d_4) δ 8.02 (s, 1H), 6.34 (s, 1H), 3.57 (s, 4H), 3.37 (s, 3H), 2.00 – 1.89 (m, 1H), 1.10 – 0.97 (m, 2H), 0.83 – 0.67 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6, 1% TFA, 75°C) δ 155.94, 153.80, 147.16, 144.07, 143.25, 102.91, 94.51, 69.69, 57.75, 40.73, 7.41, 6.68. HRMS calculated for $C_{13}H_{18}ClN_6O$ 309.12251 [M+H]$^+$, found 309.12237. LCMS (ESI, C_{18}, linear gradient, 0% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 6.30 min; *m/z* : 309 [M+H]$^+$.

2-((5-Chloro-4-((5-cyclopropyl-1*H*-pyrazol-3-yl)amino)pyrimidin-2-yl)(methyl)amino) ethan-1-ol (44)



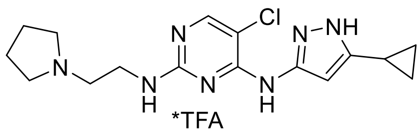
The title compound was synthesized from 2,5-dichloro-*N*-(5-isopropoxy-1*H*-pyrazol-3-yl)pyrimidin-4-amine (**81**) and 2-(methylamino)ethan-1-ol (**4x**) following General procedure D on a 0.30 mmol scale and was purified by preparative HPLC (Gemini C_{18}, 15% → 25% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (112 mg, 88%). ^{1}H NMR (500 MHz, DMSO-d_6, 1% TFA, 75°C) δ 8.09 (s, 1H), 6.25 (s, 1H), 3.65 (s, 4H), 3.16 (s, 3H), 1.92 (tt, J = 8.4, 5.1 Hz, 1H), 1.01 – 0.92 (m, 2H), 0.75 – 0.67 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6, 1% TFA, 75°C) δ 155.03, 154.31, 147.19, 145.06, 144.44, 102.74, 94.11, 58.21, 52.05, 36.47, 7.51, 6.64. HRMS calculated for $C_{13}H_{18}ClN_6O$ 309.12251 [M+H]$^+$, found 309.12259. LCMS (ESI, C_{18}, linear gradient, 0% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 5.90 min; *m/z* : 309 [M+H]$^+$.

3-((5-Chloro-4-((5-cyclopropyl-1*H*-pyrazol-3-yl)amino)pyrimidin-2-yl)amino)propan-1-ol (45)



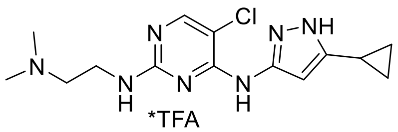
The title compound was synthesized from 2,5-dichloro-*N*-(5-isopropoxy-1*H*-pyrazol-3-yl)pyrimidin-4-amine (**81**) and 3-aminopropan-1-ol (**4y**) following General procedure D on a 0.30 mmol scale and was purified by preparative HPLC (Gemini C_{18}, 15% → 20% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (107 mg, 84%). ^{1}H NMR (500 MHz, DMSO-d_6, 1% TFA, 75°C) δ 8.14 (s, 1H), 6.31 (s, 1H), 3.51 (t, J = 6.2 Hz, 2H), 3.40 (t, J = 6.9 Hz, 2H), 1.93 (tt, J = 8.5, 5.1 Hz, 1H), 1.73 (p, J = 6.4 Hz, 2H), 0.99 – 0.91 (m, 2H), 0.78 – 0.66 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6, 1% TFA, 75°C) δ 156.00, 153.24, 147.00, 144.13, 142.23, 102.84, 94.71, 58.20, 38.61, 31.32, 7.41, 6.67. HRMS calculated for $C_{13}H_{18}ClN_6O$ 309.12251 [M+H]$^+$, found 309.12280. LCMS (ESI, C_{18}, linear gradient, 0% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 5.94 min; *m/z* : 309 [M+H]$^+$.

5-Chloro-*N*⁴-(5-cyclopropyl-1*H*-pyrazol-3-yl)-*N*²-(2-(pyrrolidin-1-yl)ethyl)pyrimidine-2,4-diamine (46)



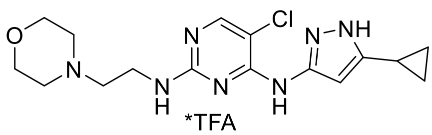
The title compound was synthesized from 2,5-dichloro-*N*-(5-isopropoxy-1*H*-pyrazol-3-yl)pyrimidin-4-amine (**81**) and 2-(pyrrolidin-1-yl)ethan-1-amine (**4z**) following General procedure D on a 0.30 mmol scale and was purified by preparative HPLC (Gemini C_{18}, 10% → 20% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (113 mg, 65%). ^1H NMR (500 MHz, methanol-d_4) δ 8.11 (s, 1H), 6.16 (s, 1H), 3.73 (t, *J* = 5.7 Hz, 2H), 3.60 (bs, 2H), 3.39 (t, *J* = 5.7 Hz, 2H), 3.01 (bs, 2H), 2.09 (bs, 2H), 2.02 – 1.93 (m, 3H), 1.08 – 1.03 (m, 2H), 0.81 – 0.75 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6, 1% TFA, 75°C) δ 156.10, 147.42, 144.12, 103.17, 94.91, 53.51, 53.07, 37.34, 22.32, 7.40, 6.79. HRMS calculated for $C_{16}H_{23}ClN_7$ 348.16980 [M+H]$^+$, found 348.16994. LCMS (ESI, C_{18}, linear gradient, 0% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 5.26 min; *m/z* : 348 [M+H]$^+$.

5-Chloro-*N*⁴-(5-cyclopropyl-1*H*-pyrazol-3-yl)-*N*²-(2-(dimethylamino)ethyl)pyrimidine-2,4-diamine (47)



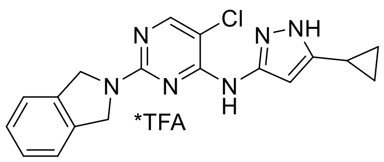
The title compound was synthesized from 2,5-dichloro-*N*-(5-isopropoxy-1*H*-pyrazol-3-yl)pyrimidin-4-amine (**81**) and *N*¹,*N*¹-dimethylethane-1,2-diamine (**4aa**) following General procedure D on a 0.30 mmol scale and was purified by preparative HPLC (Gemini C_{18}, 10% → 20% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (70 mg, 42%). ^1H NMR (500 MHz, DMSO-d_6, 1% TFA, 75°C) δ 8.14 (s, 1H), 6.19 (s, 1H), 3.63 (t, *J* = 6.0 Hz, 2H), 3.27 (t, *J* = 6.0 Hz, 2H), 2.80 (s, 6H), 1.93 (tt, *J* = 8.5, 5.1 Hz, 1H), 1.01 – 0.90 (m, 2H), 0.79 – 0.68 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 155.97, 147.40, 144.16, 103.18, 94.81, 55.76, 42.53, 36.23, 7.38, 6.79. HRMS calculated for $C_{14}H_{21}ClN_7$ 322.15415 [M+H]$^+$, found 322.15397. LCMS (ESI, C_{18}, linear gradient, 0% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 5.11 min; *m/z* : 322 [M+H]$^+$.

5-Chloro-*N*⁴-(5-cyclopropyl-1*H*-pyrazol-3-yl)-*N*²-(2-morpholinoethyl)pyrimidine-2,4-diamine (48)



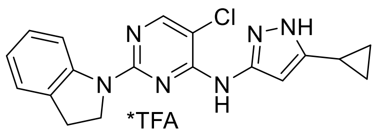
The title compound was synthesized from 2,5-dichloro-*N*-(5-isopropoxy-1*H*-pyrazol-3-yl)pyrimidin-4-amine (**81**) and 2-morpholinoethan-1-amine (**4ab**) following General procedure D on a 0.30 mmol scale and was purified by preparative HPLC (Gemini C_{18}, 10% → 20% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (134 mg, 75%). ^1H NMR (500 MHz, DMSO-d_6, 1% TFA, 75°C) δ 8.15 (s, 1H), 6.19 (s, 1H), 3.81 (s, 4H), 3.66 (t, *J* = 6.0 Hz, 2H), 3.31 (t, *J* = 6.0 Hz, 2H), 3.26 (bs, 4H), 1.99 – 1.88 (m, 1H), 1.03 – 0.91 (m, 2H), 0.78 – 0.68 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6, 1% TFA, 75°C) δ 156.06, 147.44, 144.13, 103.22, 94.88, 62.98, 55.22, 51.30, 35.46, 7.41, 6.80. HRMS calculated for $C_{16}H_{23}ClN_7O$ 364.16471 [M+H]$^+$, found 364.16477. LCMS (ESI, C_{18}, linear gradient, 0% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 5.12 min; *m/z* : 364 [M+H]$^+$.

5-Chloro-*N*-(5-cyclopropyl-1*H*-pyrazol-3-yl)-2-(isoindolin-2-yl)pyrimidin-4-amine (49)



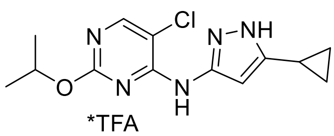
The title compound was synthesized from 2,5-dichloro-*N*-(5-isopropoxy-1*H*-pyrazol-3-yl)pyrimidin-4-amine (**81**) and isoindoline (**4ac**) following General procedure D on a 0.30 mmol scale and was purified by preparative HPLC (Gemini C_{18}, 30% → 35% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (108 mg, 77%). ^1H NMR (500 MHz, DMSO-d_6, 1% TFA, 75°C) δ 8.16 (s, 1H), 7.41 – 7.36 (m, 2H), 7.35 – 7.30 (m, 2H), 6.43 (s, 1H), 4.85 (s, 4H), 1.99 (tt, *J* = 8.5, 5.1 Hz, 1H), 1.07 – 0.94 (m, 2H), 0.84 – 0.68 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6, 1% TFA, 75°C) δ 154.90, 154.09, 147.87, 147.39, 144.57, 135.93, 127.26, 122.49, 103.07, 94.06, 52.81, 7.59, 6.84. HRMS calculated for $C_{18}H_{18}ClN_6$ 353.12760 $[M+H]^+$, found 353.12745. LCMS (ESI, C_{18}, linear gradient, 0% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 8.49 min; *m/z* : 353 $[M+H]^+$.

5-Chloro-*N*-(5-cyclopropyl-1*H*-pyrazol-3-yl)-2-(indolin-1-yl)pyrimidin-4-amine (50)



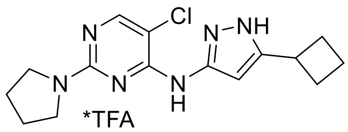
The title compound was synthesized from 2,5-dichloro-*N*-(5-isopropoxy-1*H*-pyrazol-3-yl)pyrimidin-4-amine (**81**) and indoline (**4ad**) following General procedure D on a 0.30 mmol scale and was purified by preparative HPLC (Gemini C_{18}, 30% → 40% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (66 mg, 47%). ^1H NMR (500 MHz, methanol-d_4) δ 8.14 (s, 1H), 7.97 (d, *J* = 8.1 Hz, 1H), 7.21 (d, *J* = 7.3 Hz, 1H), 7.07 (t, *J* = 7.7 Hz, 1H), 7.01 – 6.93 (m, 1H), 6.20 (s, 1H), 4.21 – 4.06 (m, 2H), 3.22 (t, *J* = 8.5 Hz, 2H), 2.00 (tt, *J* = 8.4, 5.1 Hz, 1H), 1.09 – 1.01 (m, 2H), 0.82 – 0.75 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6, 1% TFA, 75°C) δ 165.02, 164.90, 161.75, 157.02, 154.14, 152.11, 141.43, 135.87, 133.76, 130.87, 124.65, 113.31, 104.62, 58.01, 35.96, 16.94, 16.29. HRMS calculated for $C_{18}H_{18}ClN_6$ 353.12760 $[M+H]^+$, found 353.12734. LCMS (ESI, C_{18}, linear gradient, 0% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 9.27 min; *m/z* : 353 $[M+H]^+$.

5-Chloro-*N*-(5-cyclopropyl-1*H*-pyrazol-3-yl)-2-isopropoxypyrimidin-4-amine (51)



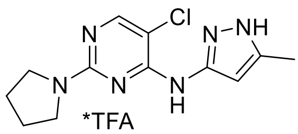
A vial was charged with NaH (60% in mineral oil, 35 mg, 0.88 mmol, 3.0 eq) dissolved in *i*PrOH (**4ae**) (1 mL) and cooled to 0°C. After drop-wise addition of 2,5-dichloro-*N*-(5-isopropoxy-1*H*-pyrazol-3-yl)pyrimidin-4-amine (**81**) (80 mg, 0.30 mmol, 1 eq) dissolved in *i*PrOH (2 mL), the vial was sealed and the mixture stirred at 110°C for 3.5 h, concentrated under reduced pressure and purified by preparative HPLC (Gemini C_{18}, 25% → 35% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (38 mg, 31%). ^1H NMR (500 MHz, methanol-d_4) δ 8.24 (s, 1H), 6.29 (s, 1H), 5.24 (m, 1H), 1.96 (tt, *J* = 8.4, 5.0 Hz, 1H), 1.40 (d, *J* = 6.2 Hz, 6H), 1.08 – 1.01 (m, 2H), 0.79 – 0.72 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 160.99, 156.61, 152.46, 147.19, 144.52, 106.58, 94.38, 70.66, 21.32, 7.39, 6.70. HRMS calculated for $C_{13}H_{17}ClN_5O$ 294.11161 $[M+H]^+$, found 294.11171. LCMS (ESI, C_{18}, linear gradient, 0% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 7.51 min; *m/z* : 294 $[M+H]^+$.

5-Chloro-*N*-(5-cyclobutyl-1*H*-pyrazol-3-yl)-2-(pyrrolidin-1-yl)pyrimidin-4-amine (52)



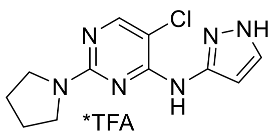
The title compound was synthesized from 2,5-dichloro-*N*-(5-cyclobutyl-1*H*-pyrazol-3-yl)pyrimidin-4-amine (**87**) and pyrrolidine (**4h**) following General procedure D on a 0.176 mmol scale and was purified by preparative HPLC (Gemini C_{18}, 20% → 30% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (66 mg, 87%). ^{1}H NMR (500 MHz, methanol-d_4) δ 8.02 (s, 1H), 6.60 (s, 1H), 3.69 (bs, 2H), 3.59 (p, *J* = 8.6 Hz, 1H), 3.51 (bs, 2H), 2.47 – 2.35 (m, 2H), 2.25 – 2.16 (m, 2H), 2.16 – 2.01 (m, 5H), 1.99 – 1.87 (m, 1H). ^{13}C NMR (126 MHz, methanol-d_4) δ 157.27, 152.00, 150.46, 146.69, 142.26, 105.29, 96.93, 49.85, 47.81, 33.03, 30.29, 26.68, 25.73, 19.50. HRMS calculated for $C_{15}H_{20}ClN_6$ 319.14325 [M+H]$^+$, found 319.14330. LCMS (ESI, C_{18}, linear gradient, 0% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 7.60 min; *m/z* : 319 [M+H]$^+$.

5-Chloro-*N*-(5-methyl-1*H*-pyrazol-3-yl)-2-(pyrrolidin-1-yl)pyrimidin-4-amine (53)



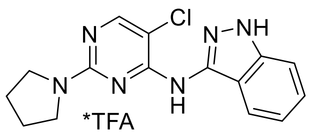
The title compound was synthesized from 2,5-dichloro-*N*-(5-methyl-1*H*-pyrazol-3-yl)pyrimidin-4-amine (**84**) and pyrrolidine (**4h**) following General procedure D on a 0.11 mmol scale and was purified by preparative HPLC (Gemini C_{18}, 15% → 25% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (39 mg, 90%). ^{1}H NMR (500 MHz, methanol-d_4) δ 8.03 (s, 1H), 6.52 (s, 1H), 3.70 (s, 2H), 3.51 (s, 2H), 2.33 (s, 3H), 2.14 (s, 2H), 2.07 (s, 2H). ^{13}C NMR (126 MHz, methanol-d_4) δ 157.35, 151.54, 146.79, 141.67, 141.46, 105.43, 99.08, 49.98, 47.85, 26.68, 25.72, 10.97. HRMS calculated for $C_{12}H_{16}ClN_6$ 279.11195 [M+H]$^+$, found 279.11170. LCMS (ESI, C_{18}, linear gradient, 0% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 5.90 min; *m/z* : 279 [M+H]$^+$.

***N*-(5-Cyclopropyl-1*H*-pyrazol-3-yl)-2-(pyrrolidin-1-yl)-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-amine (54)**



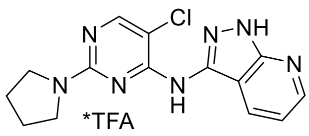
The title compound was synthesized from 2,5-dichloro-*N*-(1*H*-pyrazol-3-yl)pyrimidin-4-amine (**83**) and pyrrolidine (**4h**) following General procedure D on a 0.190 mmol scale and was purified by preparative HPLC (Gemini C_{18}, 15% → 20% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (52 mg, 72%). ^{1}H NMR (500 MHz, methanol-d_4) δ 8.03 (s, 1H), 7.67 (d, *J* = 2.4 Hz, 1H), 6.78 (d, *J* = 2.4 Hz, 1H), 3.69 (s, 2H), 3.51 (s, 2H), 2.13 (s, 2H), 2.05 (s, 2H). ^{13}C NMR (126 MHz, methanol-d_4) δ 157.43, 151.68, 146.70, 141.77, 130.79, 105.38, 99.84, 49.97, 47.83, 26.68, 25.68. HRMS calculated for $C_{11}H_{14}ClN_6$ 265.09630 [M+H]$^+$, found 265.09640. LCMS (ESI, C_{18}, linear gradient, 0% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 5.78 min; *m/z* : 265 [M+H]$^+$.

***N*-(5-Chloro-2-(pyrrolidin-1-yl)pyrimidin-4-yl)-1*H*-indazol-3-amine (55)**



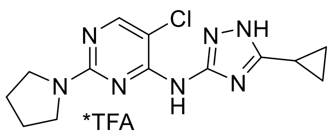
The title compound was synthesized from *N*-(2,5-dichloropyrimidin-4-yl)-1*H*-indazol-3-amine (**88**) and pyrrolidine (**4h**) following General procedure D on a 0.323 mmol scale and was purified by preparative HPLC (Gemini C_{18}, 20 → 30% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (103 mg, 74%). ^{1}H NMR (500 MHz, methanol-d_4) δ 8.09 (s, 1H), 7.64 (d, *J* = 8.2 Hz, 1H), 7.54 (d, *J* = 8.5 Hz, 1H), 7.48 – 7.37 (m, 1H), 7.23 – 7.10 (m, 1H), 3.44 (s, 2H), 3.15 (s, 2H), 2.03 (s, 2H), 1.80 (s, 2H). ^{13}C NMR (126 MHz, DMSO-d_6, 1% TFA, 75°C) δ 157.47, 150.88, 142.99, 141.01, 138.25, 126.14, 120.96, 119.56, 117.19, 110.37, 103.02, 46.82, 24.25. HRMS calculated for $C_{15}H_{16}ClN_6$ 315.11195 [M+H]$^+$, found 315.11195. LCMS (ESI, C_{18}, linear gradient, 0% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 6.91 min; *m/z* : 315 [M+H]$^+$.

***N*-(5-Chloro-2-(pyrrolidin-1-yl)pyrimidin-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-amine (56)**



The title compound was synthesized from *N*-(2,5-dichloropyrimidin-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-amine (**89**) and pyrrolidine (**4h**) following General procedure D on a 0.308 mmol scale and was purified by preparative HPLC (Gemini C_{18}, 15% → 25% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (82 mg, 62%). ^1H NMR (500 MHz, methanol-d_4) δ 8.58 (dd, *J* = 4.5, 1.5 Hz, 1H), 8.23 (dd, *J* = 8.1, 1.5 Hz, 1H), 8.14 (s, 1H), 7.26 (dd, *J* = 8.1, 4.5 Hz, 1H), 3.47 (s, 2H), 3.19 (s, 2H), 2.07 (s, 2H), 1.84 (s, 2H). ^{13}C NMR (126 MHz, DMSO-d_6, 1% TFA, 75°C) δ 157.31, 151.75, 151.36, 149.05, 143.99, 137.53, 130.88, 115.97, 109.31, 102.90, 46.84, 24.28. HRMS calculated for $C_{14}H_{15}ClN_7$ 316.10720 [M+H]$^+$, found 316.10694. LCMS (ESI, C_{18}, linear gradient, 0% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 5.91 min; *m/z* : 316 [M+H]$^+$.

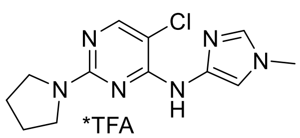
5-Chloro-*N*-(5-cyclopropyl-1*H*-1,2,4-triazol-3-yl)-2-(pyrrolidin-1-yl)pyrimidin-4-amine (57)



<u>**Step 1:**</u> 2,5-dichloro-*N*-(5-cyclopropyl-1*H*-1,2,4-triazol-3-yl) pyrimidin-4-amine was synthesized from 2,4-dichloroquinazoline (**1a**) (1 eq) and 5-cyclopropyl-1*H*-1,2,4-triazol-3-amine (**2c**) (1 eq) following General procedure A with DiPEA (3.4 eq) in THF on a 1.11 mmol scale at RT. The precipitating product was collected by filtration (43 mg, 58%). LCMS (ESI, C_{18}, linear gradient, 10% → 90% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 5.05 min; *m/z* : 271 [M+H]$^+$.

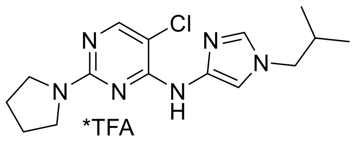
<u>**Step 2:**</u> The title compound was synthesized from the product of step 1 (1 eq), pyrrolidine (**4h**) (2.3 eq) and DiPEA (3.6 eq) in *n*-butanol (0.08 M), at 120°C for 24 h, on a 0.159 mmol scale following General procedure G and was purified by preparative HPLC (Gemini C_{18}, 28% → 31% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (5 mg, 7%). ^1H NMR (500 MHz, methanol-d_4) δ 8.38 (s, 1H), 3.56 (bs, 4H), 2.06 – 2.01 (m, 4H), 1.91 – 1.85 (m, 1H), 1.29 (bs, 2H), 0.95 – 0.92 (m, 2H). HRMS calculated for $C_{13}H_{17}ClN_7$ 306.12285 [M+H]$^+$, found 306.12302. LCMS (ESI, C_{18}, linear gradient, 0% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 8.49 min; *m/z* : 306 [M+H]$^+$.

5-Chloro-*N*-(1-methyl-1*H*-imidazol-4-yl)-2-(pyrrolidin-1-yl)pyrimidin-4-amine (58)



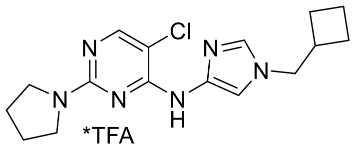
The title compound was synthesized from 2,5-dichloro-*N*-(1-methyl-1*H*-imidazol-4-yl)pyrimidin-4-amine (**90**) and pyrrolidine (**4h**) following General procedure D on a 0.246 mmol scale and was purified by preparative HPLC (Gemini C_{18}, 5 → 15% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (101 mg, quant.). ^1H NMR (500 MHz, DMSO-d_6, 1% TFA, 75°C) δ 8.82 (s, 1H), 8.35 (s, 1H), 7.63 (s, 1H), 3.88 (s, 3H), 3.58 (s, 2H), 3.48 (s, 2H), 1.98 (s, 2H), 1.95 (s, 2H). ^{13}C NMR (126 MHz, DMSO-d_6, 1% TFA, 75°C) δ 155.44, 151.97, 145.87, 132.87, 128.84, 112.59, 102.95, 48.16, 47.19, 35.99, 25.31, 24.63. HRMS calculated for $C_{12}H_{16}ClN_6$ 279.11195 [M+H]$^+$, found 279.11202. LCMS (ESI, C_{18}, linear gradient, 0% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 4.71 min; *m/z* : 279 [M+H]$^+$.

5-Chloro-*N*-(1-methyl-1*H*-imidazol-4-yl)-2-(pyrrolidin-1-yl)pyrimidin-4-amine (59)



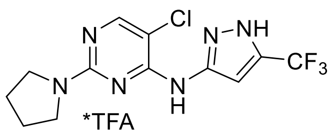
The title compound was synthesized from 2,5-dichloro-*N*-(1-isobutyl-1*H*-imidazol-4-yl)pyrimidin-4-amine (**91**) and pyrrolidine (**4h**) following General procedure D on a 0.30 mmol scale and was purified by preparative HPLC (Gemini C_{18}, 15 → 25% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (90 mg, 69%). ^{1}H NMR (600 MHz, DMSO-d_6, 1% TFA, 75°C) δ 8.86 (d, J = 1.3 Hz, 1H), 8.33 (s, 1H), 7.68 (d, J = 1.5 Hz, 1H), 4.05 (d, J = 7.2 Hz, 2H), 3.51 (s, 2H), 3.48 (s, 2H), 2.14 – 2.08 (m, 1H), 1.97 (s, 2H), 1.93 (s, 2H), 0.88 (d, J = 6.7 Hz, 6H). ^{13}C NMR (151 MHz, DMSO-d_6, 1% TFA, 75°C) δ 155.65, 152.24, 146.29, 132.60, 129.10, 112.34, 102.89, 55.60, 47.98, 47.06, 28.95, 25.30, 24.58, 19.12. HRMS calculated for $C_{15}H_{22}ClN_6$ 321.15890 [M+H]$^+$, found 321.15912. LCMS (ESI, C_{18}, linear gradient, 0% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 6.06 min; *m/z* : 321 [M+H]$^+$.

5-Chloro-*N*-(1-(cyclobutylmethyl)-1*H*-imidazol-4-yl)-2-(pyrrolidin-1-yl)pyrimidin-4-amine (60)



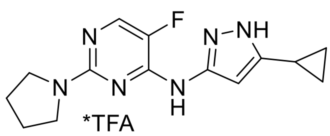
The title compound was synthesized from 2,5-dichloro-*N*-(1-(cyclobutylmethyl)-1*H*-imidazol-4-yl)pyrimidin-4-amine (**92**) and pyrrolidine (**4h**) following General procedure D on a 0.222 mmol scale and was purified by preparative HPLC (Gemini C_{18}, 15 → 25% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (24 mg, 24%). ^{1}H NMR (500 MHz, DMSO-d_6, 1% TFA, 75°C) δ 8.86 (s, 1H), 8.33 (s, 1H), 7.66 (s, 1H), 4.25 (d, J = 7.5 Hz, 2H), 3.54 (s, 2H), 3.48 (s, 2H), 2.85 – 2.69 (m, 1H), 2.05 – 1.70 (m, 10H). ^{13}C NMR (126 MHz, DMSO-d_6, 1% TFA, 75°C) δ 155.51, 152.23, 146.25, 132.18, 129.20, 111.69, 102.92, 53.37, 48.07, 47.11, 35.07, 25.32, 24.83, 24.60, 17.59. HRMS calculated for $C_{16}H_{22}ClN_6$ 333.1589 [M+H]$^+$, found 333.15905. LCMS (ESI, C_{18}, linear gradient, 0% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 6.34 min; *m/z* : 333 [M+H]$^+$.

2-(Pyrrolidin-1-yl)-*N*-(5-(trifluoromethyl)-1*H*-pyrazol-3-yl)quinazolin-4-amine (61)



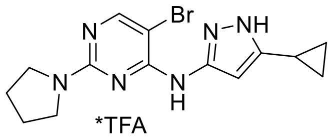
The title compound was synthesized from 2,5-dichloro-*N*-(5-(trifluoromethyl)-1*H*-pyrazol-3-yl)pyrimidin-4-amine (**93**) (1 eq), pyrrolidine (**4h**) (2.8 eq) and DiPEA (2.6 eq) in *n*-butanol (0.06 M), at 120°C for 70 h, on a 0.116 mmol scale following General procedure G and was purified by preparative HPLC (Gemini C_{18}, 25% → 35% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (36 mg, 69%). ^{1}H NMR (600 MHz, methanol-d_4) δ 8.10 (s, 1H), 6.80 (s, 1H), 3.59 (s, 4H), 2.08 (s, 4H). ^{13}C NMR (151 MHz, methanol-d_4) δ 157.67, 153.60, 146.22, 122.35 (q, J = 266.2 Hz), 104.83, 97.29, 48.02, 26.23 (bs). HRMS calculated for $C_{12}H_{13}ClF_3N_6$ 333.08368 [M+H]$^+$, found 333.08380. LCMS (ESI, C_{18}, linear gradient, 0% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 7.50 min; *m/z* : 333 [M+H]$^+$.

***N*-(5-Cyclopropyl-1*H*-pyrazol-3-yl)-5-fluoro-2-(pyrrolidin-1-yl)pyrimidin-4-amine (62)**



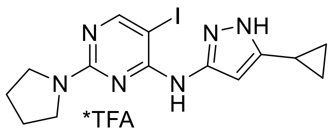
The title compound was synthesized from 2-chloro-*N*-(5-cyclopropyl-1*H*-pyrazol-3-yl)-5-fluoropyrimidin-4-amine (**94**) and pyrrolidine (**4h**) following General procedure D on a 0.30 mmol scale and was purified by preparative HPLC (Gemini C_{18}, 20% → 30% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (80 mg, 66%). ^{1}H NMR (600 MHz, methanol-d_4) δ 7.93 (d, *J* = 5.4 Hz, 1H), 6.44 (s, 1H), 3.68 (bs, 2H), 3.52 (bs, 2H), 2.10 (bs, 4H), 1.95 (tt, *J* = 8.5, 5.1 Hz, 1H), 1.06 – 0.99 (m, 2H), 0.78 – 0.66 (m, 2H). ^{13}C NMR (151 MHz, methanol-d_4) δ 153.04 (d, *J* = 12.8 Hz), 150.95, 148.82, 146.58, 139.92 (d, *J* = 248.8 Hz), 127.60, 127.59 (d, *J* = 31.8 Hz), 49.92, 47.81, 26.70, 25.86, 8.36, 7.71. HRMS calculated for $C_{14}H_{18}FN_6$ 289.15715 [M+H]$^+$, found 289.15690. LCMS (ESI, C_{18}, linear gradient, 0% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 6.72 min; *m/z* : 289 [M+H]$^+$.

5-Bromo-*N*-(5-cyclopropyl-1*H*-pyrazol-3-yl)-2-(pyrrolidin-1-yl)pyrimidin-4-amine (63)



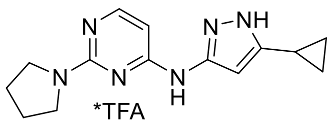
The title compound was synthesized from 5-bromo-2-chloro-*N*-(5-cyclopropyl-1*H*-pyrazol-3-yl)pyrimidin-4-amine (**80**) and pyrrolidine (**4h**) following General procedure F on a 0.30 mmol scale and was purified by preparative HPLC (Gemini C_{18}, 20% → 30% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (95 mg, 68%). ^{1}H NMR (600 MHz, methanol-d_4) δ 8.09 (s, 1H), 6.39 (s, 1H), 3.66 (s, 2H), 3.50 (s, 2H), 2.13 (s, 2H), 2.06 (s, 2H), 1.98 – 1.92 (m, 1H), 1.06 – 1.00 (m, 2H), 0.76 – 0.71 (m, 2H). ^{13}C NMR (151 MHz, methanol-d_4) δ 157.71, 151.92, 149.00, 146.72, 144.80, 95.92, 92.35, 49.83, 47.84, 26.67, 25.70, 8.43, 7.76. HRMS calculated for $C_{14}H_{18}BrN_6$ 349.07708 [M+H]$^+$, found 349.0783. LCMS (ESI, C_{18}, linear gradient, 0% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 7.04 min; *m/z* : 349 [M+H]$^+$.

***N*-(5-Cyclopropyl-1*H*-pyrazol-3-yl)-5-iodo-2-(pyrrolidin-1-yl)pyrimidin-4-amine (64)**



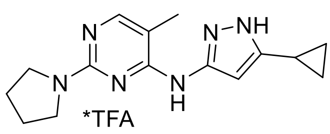
The title compound was synthesized from 2-chloro-*N*-(5-cyclopropyl-1*H*-pyrazol-3-yl)-5-iodopyrimidin-4-amine (**95**) and pyrrolidine (**4h**) following General procedure D on a 0.30 mmol scale and was purified by preparative HPLC (Gemini C_{18}, 20% → 23% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (28 mg, 18%). ^{1}H NMR (500 MHz, methanol-d_4) δ 8.12 (s, 1H), 6.41 (s, 1H), 3.68 (bs, 2H), 3.50 (bs, 2H), 2.12 (bs, 2H), 2.07 (bs, 2H), 1.95 (tt, *J* = 8.5, 5.1 Hz, 1H), 1.06 – 0.99 (m, 2H), 0.76 – 0.71 (m, 2H). ^{13}C NMR (151 MHz, methanol-d_4) δ 159.32, 152.39, 150.68, 149.07, 147.13, 95.62, 62.18, 49.69, 47.77, 26.65, 25.70, 8.41, 7.76. HRMS calculated for $C_{14}H_{18}IN_6$ 397.06321 [M+H]$^+$, found 397.06254. LCMS (ESI, C_{18}, linear gradient, 0% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 7.25 min; *m/z* : 397 [M+H]$^+$.

***N*-(5-Cyclopropyl-1*H*-pyrazol-3-yl)-2-(pyrrolidin-1-yl)pyrimidin-4-amine (65)**



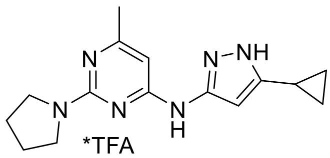
The title compound was synthesized from 2-chloro-*N*-(5-cyclopropyl-1*H*-pyrazol-3-yl)pyrimidin-4-amine (**82**) and pyrrolidine (**4h**) following General procedure F on a 0.30 mmol scale and was purified by preparative HPLC (Gemini C_{18}, 20% → 30% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (85 mg, 74%). ^{1}H NMR (600 MHz, methanol-d_4) δ 7.69 (d, *J* = 7.2 Hz, 1H), 6.47 (s, 1H), 6.29 (d, *J* = 7.2 Hz, 1H), 3.81 – 3.72 (m, 2H), 3.58 – 3.48 (m, 2H), 2.19 – 2.12 (m, 2H), 2.10 – 2.03 (m, 2H), 1.96 – 1.90 (m, 1H), 1.04 – 0.99 (m, 2H), 0.75 – 0.71 (m, 2H). ^{13}C NMR (151 MHz, methanol-d_4) δ 160.94, 152.68, 147.55, 144.13, 142.24, 99.14, 95.28, 49.50, 47.50, 26.63, 25.64, 8.35, 7.71. HRMS calculated for $C_{14}H_{19}N_6$ 271.16657 [M+H]$^+$, found 271.1673. LCMS (ESI, C_{18}, linear gradient, 0% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 6.87 min; *m/z* : 271 [M+H]$^+$.

***N*-(5-Cyclopropyl-1*H*-pyrazol-3-yl)-5-methyl-2-(pyrrolidin-1-yl)pyrimidin-4-amine (66)**



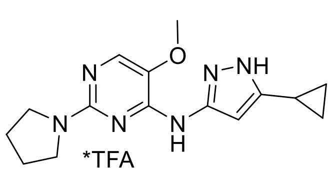
The title compound was synthesized from 2-chloro-*N*-(5-cyclopropyl-1*H*-pyrazol-3-yl)-5-methylpyrimidin-4-amine (**96**) and pyrrolidine (**4h**) following General procedure D on a 0.30 mmol scale and was purified by preparative HPLC (Gemini C_{18}, 20% → 30% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (99 mg, 83%). ^{1}H NMR (600 MHz, methanol-d_4) δ 7.60 (d, *J* = 1.1 Hz, 1H), 6.42 (s, 1H), 3.68 (bs, 2H), 3.48 (bs, 2H), 2.14 (s, 3H), 2.14 (bs, 2H), 2.06 (bs, 2H), 1.95 (tt, *J* = 8.5, 5.1 Hz, 1H), 1.04 – 0.99 (m, 2H), 0.76 – 0.71 (m, 2H). ^{13}C NMR (151 MHz, methanol-d_4) δ 161.30, 152.08, 148.98, 147.12, 147.06, 140.21, 107.57, 96.28, 49.43 (bs), 47.38, 26.66, 25.70, 8.39, 7.79. HRMS calculated for $C_{15}H_{21}N_6$ 285.18222 $[M+H]^+$, found 285.18205. LCMS (ESI, C_{18}, linear gradient, 0% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 7.00 min; *m/z* : 285 $[M+H]^+$.

***N*-(5-Cyclopropyl-1*H*-pyrazol-3-yl)-6-methyl-2-(pyrrolidin-1-yl)pyrimidin-4-amine (67)**



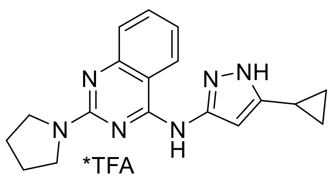
The title compound was synthesized from 2-chloro-*N*-(5-cyclopropyl-1*H*-pyrazol-3-yl)-6-methylpyrimidin-4-amine (**97**) and pyrrolidine (**4h**) following General procedure D on a 0.48 mmol scale and was purified by preparative HPLC (Gemini C_{18}, 20% → 25% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (52 mg, 27%). ^{1}H NMR (500 MHz, DMSO-d_6, 1% TFA, 75°C) δ 10.67 (bs, 1H), 6.28 (bs, 1H), 3.66 – 3.50 (m, 4H), 2.32 (s, 3H), 2.06 – 1.98 (m, 4H), 1.96 – 1.86 (m, 1H), 1.01 – 0.89 (m, 2H), 0.73 – 0.65 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6, 1% TFA, 75°C) δ 151.44, 146.17, 145.89, 96.11, 93.65, 47.22, 24.40, 18.36, 7.35, 6.47. HRMS calculated for $C_{15}H_{21}N_6$ 285.18222 $[M+H]^+$, found 285.18211. LCMS (ESI, C_{18}, linear gradient, 0% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 7.09 min; *m/z* : 285 $[M+H]^+$.

***N*-(5-Cyclopropyl-1*H*-pyrazol-3-yl)-5-methoxy-2-(pyrrolidin-1-yl)pyrimidin-4-amine (68)**



The title compound was synthesized from 2-chloro-*N*-(5-cyclopropyl-1*H*-pyrazol-3-yl)-5-methoxypyrimidin-4-amine (**98**) and pyrrolidine (**4h**) following General procedure D on a 0.30 mmol scale and was purified by preparative HPLC (Gemini C_{18}, 20% → 30% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (95 mg, 76%). ^{1}H NMR (600 MHz, methanol-d_4) δ 7.34 (s, 1H), 6.45 (s, 1H), 3.91 (s, 3H), 3.58 (s, 4H), 2.10 (s, 4H), 1.94 (tt, *J* = 8.5, 5.1 Hz, 1H), 1.05 – 0.98 (m, 2H), 0.77 – 0.69 (m, 2H). ^{13}C NMR (151 MHz, methanol-d_4) δ 154.75, 149.97, 148.90, 146.77, 134.91, 119.67, 95.56, 57.60, 47.61, 26.26, 8.37, 7.76. HRMS calculated for $C_{15}H_{21}N_6O$ 301.17714 $[M+H]^+$, found 301.17711. LCMS (ESI, C_{18}, linear gradient, 0% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 7.10 min; *m/z* : 301 $[M+H]^+$.

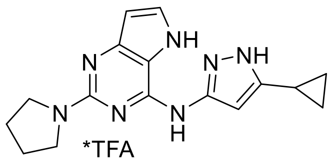
***N*-(5-Cyclopropyl-1*H*-pyrazol-3-yl)-2-(pyrrolidin-1-yl)quinazolin-4-amine (69)**



The title compound was synthesized from 2-chloro-*N*-(5-cyclopropyl-1*H*-pyrazol-3-yl)quinazolin-4-amine (**99**) (1 eq), pyrrolidine (**4h**) (3.5 eq) and DiPEA (4.8 eq) in *n*-butanol (0.15 M) at 120°C for 25 h on a 0.30 mmol scale following General procedure G and was purified by preparative HPLC (Gemini C_{18}, 25% → 35% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (78 mg, 60%). ^{1}H NMR (500 MHz, methanol-d_4) δ 8.32 (d, *J* = 7.5 Hz, 1H), 7.89 – 7.81 (m, 1H), 7.66 (d, *J* = 7.9 Hz, 1H), 7.54 – 7.45 (m, 1H), 6.52

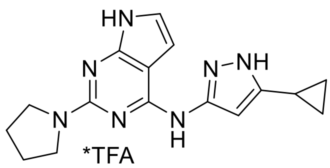
(s, 1H), 3.83 (t, *J* = 6.6 Hz, 2H), 3.68 (t, *J* = 6.6 Hz, 2H), 2.26 – 2.15 (m, 2H), 2.15 – 2.06 (m, 2H), 1.98 (tt, *J* = 8.5, 5.1 Hz, 1H), 1.08 – 0.98 (m, 2H), 0.81 – 0.71 (m, 2H). ^{13}C NMR (126 MHz, DMSO-*d*$_6$, 1% TFA, 75°C) δ 156.54, 150.02, 146.18, 145.46, 139.52, 134.88, 124.27, 116.96, 109.43, 95.12, 47.68, 24.39, 7.45, 6.55. HRMS calculated for $C_{18}H_{21}N_6$ 321.18222 [M+H]$^+$, found 321.18246. LCMS (ESI, C$_{18}$, linear gradient, 0% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t$_R$ = 7.88 min; *m/z* : 321 [M+H]$^+$.

N-(5-Cyclopropyl-1*H*-pyrazol-3-yl)-2-(pyrrolidin-1-yl)-5*H*-pyrrolo[3,2-d]pyrimidin-4-amine (70)



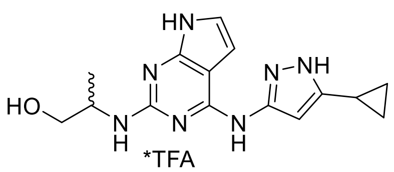
The title compound was synthesized from 2-chloro-*N*-(5-cyclopropyl-1*H*-pyrazol-3-yl)-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-amine (**100**) and pyrrolidine (**4h**) following General procedure D on a 0.372 mmol scale and was purified by preparative HPLC (Gemini C$_{18}$, 22% → 27% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (56 mg, 36%). ^{1}H NMR (600 MHz, methanol-*d*$_4$) δ 7.46 (d, *J* = 2.9 Hz, 1H), 6.48 (bs, 1H), 6.32 (d, *J* = 2.9 Hz, 1H), 3.63 (s, 4H), 2.11 (s, 4H), 1.95 (tt, *J* = 8.5, 5.1 Hz, 1H), 1.09 – 0.98 (m, 2H), 0.80 – 0.69 (m, 2H). ^{13}C NMR (151 MHz, methanol-*d*$_4$) δ 150.95, 149.49, 149.01, 147.85, 137.64, 130.56, 109.49, 97.08, 94.89, 48.86, 26.28, 8.36, 7.70. HRMS calculated for $C_{16}H_{20}N_7$ 310.17747 [M+H]$^+$, found 310.17727. LCMS (ESI, C$_{18}$, linear gradient, 0% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t$_R$ = 7.69 min; *m/z* : 310 [M+H]$^+$.

N-(5-Cyclopropyl-1*H*-pyrazol-3-yl)-2-(pyrrolidin-1-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (71)



The title compound was synthesized from 2-chloro-*N*-(5-cyclopropyl-1*H*-pyrazol-3-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (**101**) and pyrrolidine (**4h**) following General procedure D on a 0.275 mmol scale and was purified by preparative HPLC (Gemini C$_{18}$, 25% → 30% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (42 mg, 36%). ^{1}H NMR (500 MHz, methanol-*d*$_4$) δ 7.03 (d, *J* = 3.7 Hz, 1H), 6.65 (d, *J* = 3.5 Hz, 1H), 5.90 (s, 1H), 3.74 – 3.65 (m, 4H), 2.20 – 2.09 (m, 4H), 1.97 (tt, *J* = 8.5, 5.0 Hz, 1H), 1.11 – 1.01 (m, 2H), 0.84 – 0.74 (m, 2H). ^{13}C NMR (126 MHz, DMSO-*d*$_6$, 1% TFA, 75°C) δ 148.51, 148.18, 147.83, 147.39, 147.20, 121.23, 100.59, 94.77, 92.22, 46.71, 24.51, 7.59, 6.38. HRMS calculated for $C_{16}H_{20}N_7$ 310.17747 [M+H]$^+$, found 310.17742. LCMS (ESI, C$_{18}$, linear gradient, 0% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t$_R$ = 7.78 min; *m/z* : 310 [M+H]$^+$.

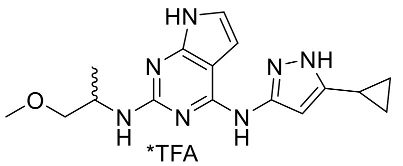
2-((4-((5-Cyclopropyl-1*H*-pyrazol-3-yl)amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)amino)propan-1-ol (72)



The title compound was synthesized from 2-chloro-*N*-(5-cyclopropyl-1*H*-pyrazol-3-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (**101**) (1 eq), 2-aminopropan-1-ol (**4t**) (2.7 eq) and DiPEA (1.85 eq), in *n*-butanol (0.12 M), at 200°C for 12 h, on a 0.31 mmol scale following General procedure H and was purified by preparative HPLC (Gemini C$_{18}$, 23% → 26% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (8 mg, 6%). ^{1}H NMR (500 MHz, methanol-*d*$_4$) δ 7.03 (d, *J* = 3.5 Hz, 1H), 6.68 (s, 1H), 5.88 (s, 1H), 4.23 – 4.13 (m, 1H), 3.71 – 3.62 (m, *J* = 24.8, 11.1, 5.4 Hz, 2H), 2.04 – 1.97 (m, 1H), 1.32 (d, *J* = 6.7

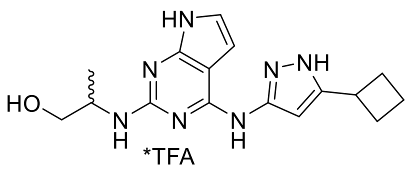
Hz, 3H), 1.11 – 1.05 (m, 2H), 0.82 – 0.77 (m, 2H). HRMS calculated for $C_{15}H_{20}N_7O$ 314.17238 $[M+H]^+$, found 314.1732. LCMS (ESI, C_{18}, linear gradient, 10% → 90% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 4.33 min; *m/z* : 314 $[M+H]^+$.

N^4-(5-Cyclopropyl-1*H*-pyrazol-3-yl)-N^2-(1-methoxypropan-2-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine (73)



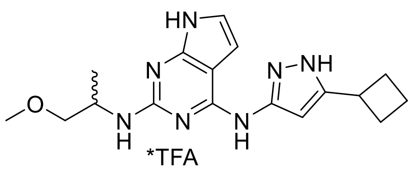
The title compound was synthesized from 2-chloro-*N*-(5-cyclopropyl-1*H*-pyrazol-3-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (**101**) (1 eq), 1-methoxypropan-2-amine (**4s**) (2.6 eq) and DiPEA (1.85 eq), in *n*-butanol (0.12 M), at 200°C for 12 h, on a 0.31 mmol scale following General procedure H and was purified by preparative HPLC (Gemini C_{18}, 20% → 30% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (9 mg, 7%). ^1H NMR (500 MHz, methanol-d_4) δ 7.05 – 7.00 (m, 1H), 6.68 (s, 1H), 5.89 (s, 1H), 4.35 – 4.25 (m, 1H), 3.56 – 3.45 (m, 2H), 3.41 (s, 3H), 2.04 – 1.96 (m, *J* = 8.5, 5.1 Hz, 1H), 1.31 (d, *J* = 5.6 Hz, 3H), 1.11 – 1.04 (m, 2H), 0.82 – 0.76 (m, 2H). ^{13}C NMR (126 MHz, methanol-d_4) δ 149.09, 148.54, 147.55, 121.82, 120.96, 100.05, 94.80, 90.83, 75.37, 75.07, 57.88, 46.89, 15.99, 7.18, 6.08. HRMS calculated for $C_{16}H_{22}N_7O$ 328.18803 $[M+H]^+$, found 328.1883. LCMS (ESI, C_{18}, linear gradient, 0% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 7.46 min; *m/z* : 328 $[M+H]^+$; purity 83%.

2-((4-((5-Cyclobutyl-1*H*-pyrazol-3-yl)amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)amino) propan-1-ol (74)



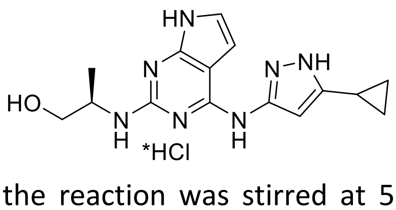
The title compound was synthesized from 2-chloro-*N*-(5-cyclobutyl-1*H*-pyrazol-3-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (**102**) (1 eq), 2-aminopropan-1-ol (**4t**) (2.8 eq) and DiPEA (1.85 eq), in *n*-butanol (0.12 M), at 200°C for 12 h, on a 0.30 mmol scale following General procedure H and was purified by preparative HPLC (Gemini C_{18}, 20% → 30% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (11 mg, 8%). ^1H NMR (850 MHz, methanol-d_4) δ 7.03 (d, *J* = 3.3 Hz, 1H), 6.70 (s, 1H), 6.11 (s, 1H), 4.25 – 4.16 (m, 1H), 3.72 – 3.68 (m, 1H), 3.68 – 3.60 (m, 2H), 2.50 – 2.38 (m, 2H), 2.31 – 2.21 (m, 2H), 2.17 – 2.08 (m, 1H), 2.02 – 1.93 (m, 1H), 1.30 (d, 3H). ^{13}C NMR (214 MHz, methanol-d_4) δ 153.01, 151.42, 150.71, 149.18, 148.74, 123.41, 101.60, 96.31, 93.58, 65.97, 50.53, 32.81, 30.37, 19.63, 17.25. HRMS calculated for $C_{16}H_{22}N_7O$ 328.18803 $[M+H]^+$, found 328.1883. LCMS (ESI, C_{18}, linear gradient, 10% → 90% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 4.73 min; *m/z* : 328 $[M+H]^+$.

N^4-(5-Cyclobutyl-1*H*-pyrazol-3-yl)-N^2-(1-methoxypropan-2-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine (75)



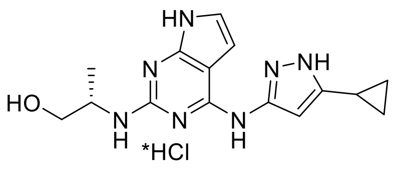
The title compound was synthesized from 2-chloro-*N*-(5-cyclobutyl-1*H*-pyrazol-3-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (**102**) (1 eq), 1-methoxypropan-2-amine (**4s**) (2.6 eq) and DiPEA (1.85 eq), in *n*-butanol (0.12 M), at 200°C for 12 h, on a 0.31 mmol scale following General procedure H and was purified by preparative HPLC (Gemini C_{18}, 25% → 35% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (8 mg, 6%). ^1H NMR (850 MHz, methanol-d_4) δ 7.04 (d, *J* = 3.2 Hz, 1H), 6.70 (s, 1H), 6.11 (s, 1H), 4.34 – 4.27 (m, 1H), 3.68 – 3.62 (m, *J* = 8.7 Hz, 1H), 3.55 – 3.52 (m, *J* = 9.7, 5.9 Hz, 1H), 3.51 – 3.48 (m, 1H), 3.40 (s, 3H), 2.46 – 2.41 (m, 2H), 2.30 – 2.22 (m, 2H), 2.15 – 2.09 (m, 1H), 2.01 – 1.95 (m, 1H), 1.32 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (214 MHz, methanol-d_4) δ 149.85, 149.04, 147.57, 121.86, 117.52, 100.04, 94.76, 92.08, 75.05, 57.88, 46.87, 31.27, 28.83, 18.08, 15.99. HRMS calculated for $C_{17}H_{24}N_7O$ 342.20368 $[M+H]^+$, found 342.2045. LCMS (ESI, C_{18}, linear gradient, 10% → 90% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 5.20 min; *m/z* : 342 $[M+H]^+$; purity 85%.

(*R*)-2-((4-((5-Cyclopropyl-1*H*-pyrazol-3-yl)amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)amino)propan-1-ol (76)



A vial was charged with (*R*)-2-((4-((5-cyclopropyl-1*H*-pyrazol-3-yl)amino)-7-tosyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)amino)propan-1-ol (**103**) (78 mg, 0.167 mmol, 1 eq) dissolved in MeOH (0.11 mL) and 1,4-dioxane (0.58 mL). After addition of aqueous NaOH (50%, 9.33 mL, 0.117 mmol, 20 eq) the reaction was stirred at 55°for 2 h and quenched with sat. aqueous NH_4Cl (3 mL) and extracted with chloroform (5x6 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC (Gemini C_{18}, 20% → 30% ACN in H_2O 0.2% TFA, 10 min gradient) and concentrated under reduced pressure. The resulting product re-dissolved in chloroform and sat. aqueous $NaHCO_3$ and after phase separation the aqueous layer was extracted with 10% MeOH in chloroform (5x8 mL). The combined organic layers were dried (Na_2SO_4), filtered and after addition of excess HCl in 1,4-dioxane concentrated under reduced pressure to yield the compound as a HCl-salt after lyophilisation (13 mg, 22%). ^1H NMR (500 MHz, methanol-d_4) δ 7.04 (d, *J* = 3.6 Hz, 1H), 6.78 (d, *J* = 3.6 Hz, 1H), 6.14 (s, 1H), 4.20 – 4.11 (m, 1H), 3.82 – 3.77 (m, 1H), 3.69 – 3.63 (m, 1H), 2.08 (tt, *J* = 8.4, 5.0 Hz, 1H), 1.34 (d, *J* = 6.6 Hz, 3H), 1.27 – 1.16 (m, 2H), 0.99 – 0.86 (m, 2H). ^{13}C NMR (126 MHz, methanol-d_4) δ 153.53, 153.44, 153.40, 152.73, 145.01, 122.73, 102.01, 98.78, 92.81, 67.21, 51.52, 17.00, 9.70, 7.77. HRMS calculated for $C_{15}H_{20}N_7O$ 314.17238 $[M+H]^+$, found 314.1727. LCMS (ESI, C_{18}, linear gradient, 10% → 90% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 4.30 min; *m/z* : 314 $[M+H]^+$.

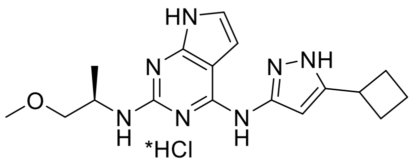
(*S*)-2-((4-((5-Cyclopropyl-1*H*-pyrazol-3-yl)amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)amino)propan-1-ol (77)



A round bottom flask was charged with (*S*)-2-((4-((5-cyclopropyl-1*H*-pyrazol-3-yl)amino)-7-tosyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)amino)propan-1-ol (**104**) (2.3 g, 5.83 mmol, 1 eq) dissolved in MeOH (16 mL) and 1,4-dioxane (20 mL). After cooling to 0°C and addition of aqueous NaOH (50%, 9.33 mL, 117 mmol, 20 eq) the reaction was allowed to warm to RT and stirred for another 90 min. The mixture was acidified with HCl (20 mL 6M) and concentrated under reduced pressure, re-dissolved in MeOH, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC (Gemini C_{18}, 20% → 30% ACN in H_2O 0.2% TFA, 10 min gradient) and concentrated under reduced pressure. The resulting product was exchanged to a HCl salt by re-dissolving in HCl in H_2O/ACN (1/1, pH ~2) and concentrating under reduced pressure (3x) to yield the compound as a HCl-salt after lyophilisation (0.93 g, 46%). ^1H NMR (500 MHz, methanol-d_4) δ 7.04 (d, *J* = 3.6 Hz, 1H), 6.75 (d, *J* = 3.6 Hz, 1H), 6.08 (s, 1H), 4.20 – 4.11 (m, 1H), 3.78 (dd, *J* = 11.2, 4.2 Hz, 1H), 3.66 (dd, *J* = 11.1, 7.1 Hz, 1H), 2.06 (tt, *J* = 8.5, 5.0 Hz, 1H), 1.33 (d, *J* = 6.7 Hz, 3H), 1.22 – 1.15 (m, 2H), 0.94 – 0.88 (m, 2H). ^{13}C

NMR (126 MHz, methanol-d_4) δ 152.79, 152.75, 152.59, 152.32, 145.80, 122.85, 101.89, 98.28, 92.64, 66.95, 51.31, 17.02, 9.52, 7.72. HRMS calculated for $C_{15}H_{20}N_7O$ 314.17238 $[M+H]^+$, found 314.1723. LCMS (ESI, C_{18}, linear gradient, 10% → 90% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 4.51 min; *m/z* : 314 $[M+H]^+$.

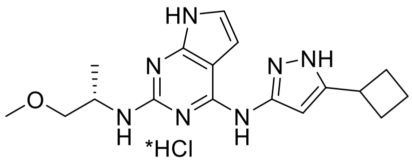
(*R*)-*N*⁴-(5-Cyclobutyl-1*H*-pyrazol-3-yl)-*N*²-(1-methoxypropan-2-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine (78)



Step 1: A vial was charged with 2-chloro-*N*-(5-cyclobutyl-1*H*-pyrazol-3-yl)-7-tosyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (**110**) (0.28 g, 0.63 mmol, 1 eq), (*R*)-1-methoxypropan-2-amine hydrochloride (**4ah**) (119 mg, 0.945 mmol, 1.5 eq) dissolved in *n*-butanol (1.6 mL). After addition of DiPEA (0.33 mL, 1.89 mmol, 3.0 eq) the vial was sealed and the mixture heated in the microwave to 160°C for 13h. The reaction mixture was concentrated under reduced pressure and purified via flash-column-chromatography (SiO_2, dry-loading, 0% → 10% (10% of sat. aqueous NH_3 in MeOH) in DCM) to yield the product, which was used directly in step 2.

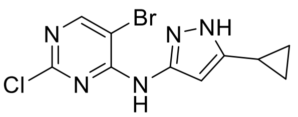
Step 2: A round bottom flask was charged with product from step 1, dissolved in MeOH (1.3 mL) and 1,4-dioxane (1.7 mL). After addition of aqueous NaOH (50%, 0.80 mL, 9.8 mmol, 20 eq) the reaction was stirred for 60 min at 55°C and quenched with sat. aqueous NH_4Cl (3 mL) and extracted with chloroform (5x6 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC (Gemini C_{18}, 28% → 31% ACN in H_2O 0.2% TFA, 10 min gradient) and concentrated under reduced pressure. The resulting product re-dissolved in chloroform and sat. aqueous $NaHCO_3$ and after phase separation the aqueous layer was extracted with 10% MeOH in chloroform (5x8 mL). The combined organic layers were dried over Na_2SO_4, filtered and after addition of excess HCl in 1,4-dioxane concentrated under reduced pressure to yield the compound as a HCl-salt after lyophilisation (145 mg, 61%). ^1H NMR (850 MHz, methanol-d_4) δ 7.05 (d, J = 3.6 Hz, 1H), 6.78 (d, J = 3.6 Hz, 1H), 6.37 (s, 1H), 4.27 – 4.21 (m, 1H), 3.73 – 3.68 (m, 1H), 3.61 – 3.56 (m, 1H), 3.53 – 3.48 (m, 1H), 3.41 (s, 3H), 2.51 – 2.43 (m, 2H), 2.33 – 2.26 (m, 2H), 2.20 – 2.10 (m, 1H), 2.02 – 1.96 (m, 1H), 1.35 (d, J = 6.7 Hz, 3H). ^{13}C NMR (214 MHz, methanol-d_4) δ 153.52, 152.50, 152.08, 146.14, 145.83, 122.90, 101.91, 98.23, 94.35, 77.30, 59.44, 32.42, 29.80, 19.53, 17.29. HRMS calculated for $C_{17}H_{24}N_7O$ 342.20368 $[M+H]^+$, found 342.2043. LCMS (ESI, C_{18}, linear gradient, 0% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 8.23 min; *m/z* : 342 $[M+H]^+$.

(*S*)-*N*⁴-(5-Cyclobutyl-1*H*-pyrazol-3-yl)-*N*²-(1-methoxypropan-2-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine (79)



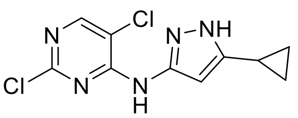
A round bottom flask was charged with (*S*)-*N*⁴-(5-cyclobutyl-1*H*-pyrazol-3-yl)-*N*²-(1-methoxypropan-2-yl)-7-tosyl-7*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine (**105**) (3.0 g, 6.05 mmol, 1 eq) dissolved in MeOH (17 mL) and 1,4-dioxane (21 mL). After cooling to 0°C and addition of aqueous NaOH (50%, 9.7 mL, 121 mmol, 20 eq) the reaction was allowed to warm to RT and stirred for another 3 h. The mixture was acidified with HCl (20 mL, 6M) and concentrated under reduced pressure, re-dissolved in MeOH, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC (Gemini C_{18}, 25% → 35% ACN in H_2O 0.2% TFA, 10 min gradient) and concentrated under reduced pressure. The resulting product was exchanged to a HCl salt by re-dissolving in HCl in H_2O/ACN (1/1, pH ~2) and concentrating under reduced pressure (3x) to yield the compound as a HCl-salt after lyophilisation (1.07 g, 47%). ^{1}H NMR (500 MHz, methanol-d_4) δ 7.04 (d, *J* = 3.6 Hz, 1H), 6.77 (d, *J* = 3.6 Hz, 1H), 6.34 (s, 1H), 4.29 – 4.21 (m, 1H), 3.72 – 3.64 (m, 1H), 3.58 (dd, *J* = 9.6, 4.5 Hz, 1H), 3.51 (dd, *J* = 9.6, 6.8 Hz, 1H), 3.40 (s, 3H), 2.50 – 2.42 (m, 2H), 2.34 – 2.24 (m, 2H), 2.19 – 2.09 (m, 1H), 2.04 – 1.95 (m, 1H), 1.34 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, methanol-d_4) δ 151.97, 150.68, 150.55, 145.63, 145.00, 121.62, 100.58, 96.66, 93.10, 75.89, 58.11, 31.17, 31.15, 28.54, 18.21, 16.00. HRMS calculated for $C_{17}H_{24}N_7O$ 342.20368 $[M+H]^+$, found 342.2040. LCMS (ESI, C_{18}, linear gradient, 0% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 8.13 min; *m/z* : 342 $[M+H]^+$.

5-Bromo-2-chloro-*N*-(5-cyclopropyl-1*H*-pyrazol-3-yl)pyrimidin-4-amine (80)



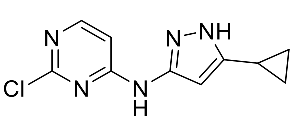
The title compound was synthesized from 5-bromo-2,4-dichloropyrimidine (**1b**) and 5-cyclopropyl-1*H*-pyrazol-3-amine (**2b**) following General procedure A on a 2.19 mmol scale at RT and purified via flash-column-chromatography (dry-loading, SiO_2, 50% → 100% EtOAc in pentane) to yield the product (523 mg, 75%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.36 (s, 1H), 9.26 (s, 1H), 8.41 (s, 1H), 6.16 (s, 1H), 2.02 – 1.75 (m, 1H), 1.03 – 0.82 (m, 2H), 0.77 – 0.63 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 158.19, 157.95, 157.79, 146.04, 145.65, 102.76, 95.68, 7.87, 6.90.

2,5-Dichloro-*N*-(5-cyclopropyl-1*H*-pyrazol-3-yl)pyrimidin-4-amine (81)



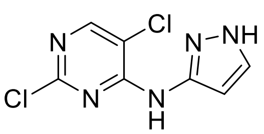
A round-bottom-flask was charged with 2,4,5-trichloropyrimidine (**1a**) (5.00 g, 27.26 mmol, 1 eq) dissolved in EtOH (35 mL). Et_3N (4.18 mL, 29.99 mmol, 1.1 eq) and 5-cyclopropyl-1*H*-pyrazol-3-amine (**2b**) (3.69 g, 29.99 mmol, 1.1 eq) dissolved in EtOH (35 mL) were added dropwise and the reaction mixture was stirred ON at RT until a colourless precipitate was formed. The formed precipitate was filtered off, washed with ice-cold EtOH and dried under reduced pressure to yield the product (7.40 g, quant.). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.37 (s, 1H), 9.70 (s, 1H), 8.32 (s, 1H), 6.19 (s, 1H), 2.03 – 1.80 (m, 1H), 1.04 – 0.87 (m, 2H), 0.81 – 0.60 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 157.14, 156.97, 155.25, 145.99, 145.64, 113.26, 95.69, 7.92, 6.94. LCMS (ESI, C_{18}, linear gradient, 10% → 90% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 5.66 min; *m/z* : 270 $[M+H]^+$.

2-Chloro-*N*-(5-cyclopropyl-1*H*-pyrazol-3-yl)pyrimidin-4-amine (82)



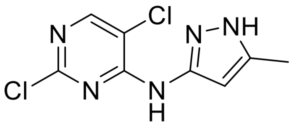
The title compound was synthesized from 2,4-dichloropyrimidine (**1c**) and 5-cyclopropyl-1*H*-pyrazol-3-amine (**2b**) following General procedure A on a 3.36 mmol scale at 80°C and purified via flash-column-chromatography (dry-loading, SiO_2, 50% → 100% EtOAc in pentane) to yield the product (290 mg, 37%). ^{1}H NMR (500 MHz, methanol-d_4) δ 8.07 (d, *J* = 6.0 Hz, 1H), 7.00 (bs, 1H), 6.08 (bs, 1H), 1.99 – 1.83 (m, 1H), 1.07 – 0.95 (m, 2H), 0.83 – 0.70 (m, 2H). ^{13}C NMR (126 MHz, methanol-d_4) δ 163.00, 161.23, 157.74, 148.69, 105.59, 94.43, 8.25, 7.62.

2,5-Dichloro-*N*-(1*H*-pyrazol-3-yl)pyrimidin-4-amine (83)



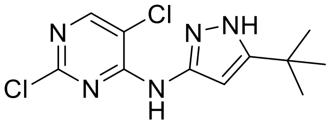
The title compound was synthesized from 2,4,5-trichloropyrimidine (**1a**) and 1*H*-pyrazol-3-amine (**2d**) following General procedure A on a 0.60 mmol scale at RT and purified via flash-column-chromatography (dry-loading, SiO_2, 0% → 100% EtOAc in pentane) to yield the product (123 mg, 89%). ^{1}H NMR (600 MHz, methanol-d_4) δ 8.23 (s, 1H), 7.62 (d, *J* = 2.4 Hz, 1H), 6.71 (s, 1H). ^{13}C NMR (151 MHz, methanol-d_4) δ 159.11, 158.20, 155.77, 147.53, 130.42, 114.79, 99.42. LCMS (ESI, C_{18}, linear gradient, 10% → 90% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 4.79 min; *m/z* : 230 [M+H]$^+$.

2,5-Dichloro-*N*-(5-methyl-1*H*-pyrazol-3-yl)pyrimidin-4-amine (84)



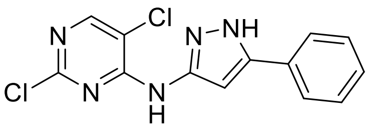
The title compound was synthesized from 2,4,5-trichloropyrimidine (**1a**) and 5-methyl-1*H*-pyrazol-3-amine (**2e**) following General procedure A on a 0.60 mmol scale at RT and purified via flash-column-chromatography (dry-loading, SiO_2, 40% → 100% EtOAc in pentane) to yield the product (128 mg, 88%). ^{1}H NMR (600 MHz, methanol-d_4) δ 8.21 (s, 1H), 6.47 (s, 1H), 2.32 (s, 3H). ^{13}C NMR (151 MHz, methanol-d_4) δ 159.11, 158.09, 155.66, 147.72, 141.29, 114.73, 98.78, 10.92. LCMS (ESI, C_{18}, linear gradient, 10% → 90% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 4.84 min; *m/z* : 244 [M+H]$^+$.

***N*-(5-(*tert*-Butyl)-1*H*-pyrazol-3-yl)-2,5-dichloropyrimidin-4-amine (85)**



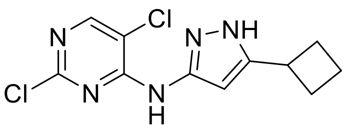
The title compound was synthesized from 2,4,5-trichloropyrimidine (**1a**) and 5-(*tert*-butyl)-1*H*-pyrazol-3-amine (**2f**) following General procedure A on a 0.60 mmol scale at RT and purified via flash-column-chromatography (dry-loading, SiO_2, 20% → 100% EtOAc in pentane) to yield the product (159 mg, 92%). ^{1}H NMR (600 MHz, methanol-d_4) δ 8.22 (s, 1H), 6.50 (s, 1H), 1.36 (s, 9H). ^{13}C NMR (151 MHz, methanol-d_4) δ 159.12, 158.06, 155.65, 155.26, 147.17, 114.73, 95.71, 32.16, 30.44. LCMS (ESI, C_{18}, linear gradient, 10% → 90% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 6.60 min; *m/z* : 286 [M+H]$^+$.

2,5-Dichloro-*N*-(5-phenyl-1*H*-pyrazol-3-yl)pyrimidin-4-amine (86)



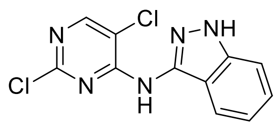
The title compound was synthesized from 2,4,5-trichloropyrimidine (**1a**) and 5-phenyl-1*H*-pyrazol-3-amine (**2g**) following General procedure A on a 0.60 mmol scale at RT and purified via flash-column-chromatography (dry-loading, SiO_2, 0% → 100% EtOAc in pentane) to yield the product (169 mg, 92%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.16 (s, 1H), 9.87 (s, 1H), 8.37 (s, 1H), 7.74 (d, *J* = 7.1 Hz, 2H), 7.48 (t, *J* = 7.6 Hz, 2H), 7.38 (t, *J* = 7.4 Hz, 1H), 6.89 (d, *J* = 2.2 Hz, 1H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 157.13, 157.09, 155.37, 146.53, 142.36, 129.11, 128.67, 128.35, 125.02, 113.29, 96.83. LCMS (ESI, C_{18}, linear gradient, 10% → 90% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 7.02 min; *m/z* : 306 [M+H]$^+$.

2,5-Dichloro-*N*-(5-cyclobutyl-1*H*-pyrazol-3-yl)pyrimidin-4-amine (87)



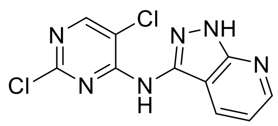
The title compound was synthesized from 2,4,5-trichloropyrimidine (**1a**) and 5-cyclobutyl-1*H*-pyrazol-3-amine (**2h**) following General procedure A on a 0.60 mmol scale at RT and purified via flash-column-chromatography (dry-loading, SiO_2, 0% → 100% EtOAc in pentane) to yield the product (156 mg, 91%). ^{1}H NMR (600 MHz, methanol-d_4) δ 8.22 (s, 1H), 6.52 (s, 1H), 3.58 (p, *J* = 8.7 Hz, 1H), 2.50 – 2.34 (m, 2H), 2.30 – 2.18 (m, 2H), 2.14 – 2.00 (m, 1H), 2.01 – 1.86 (m, 1H). ^{13}C NMR (151 MHz, methanol-d_4) δ 159.13, 158.09, 155.68, 150.15, 147.50, 114.75, 96.59, 33.07, 30.24, 19.47. LCMS (ESI, C_{18}, linear gradient, 10% → 90% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 6.38 min; *m/z* : 284 [M+H]$^+$.

_N_-(2,5-Dichloropyrimidin-4-yl)-1_H_-indazol-3-amine (88)



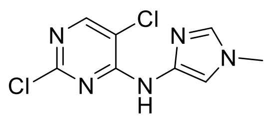
The title compound was synthesized from 2,4,5-trichloropyrimidine (**1a**) (1 eq) and 1*H*-indazol-3-amine (**2i**) (1.3 eq) following General procedure B with DiPEA (1.8 eq) in THF on a 1.0 mmol scale at RT. The crude product was purified via flash-column-chromatography (dry-loading, SiO_2, 20% → 60% EtOAc in pentane) to yield the product (174 mg, 78%). ^1H NMR (400 MHz, DMSO-d_6) δ 13.01 (s, 1H), 10.08 (bs, 1H), 8.41 (s, 1H), 7.59 – 7.49 (m, 2H), 7.45 – 7.34 (m, 1H), 7.16 – 7.06 (m, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 158.76, 157.30, 155.71, 141.31, 138.76, 126.68, 120.67, 120.44, 117.87, 113.41, 110.78. LCMS (ESI, C_{18}, linear gradient, 10% → 90% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 5.79 min; *m/z* : 280 $[M+H]^+$.

_N_-(2,5-Dichloropyrimidin-4-yl)-1_H_-pyrazolo[3,4-_b_]pyridin-3-amine (89)



The title compound was synthesized from 2,4,5-trichloropyrimidine (1 eq) (**1a**) and 1*H*-pyrazolo[3,4-*b*]pyridin-3-amine (**2j**) (1.1 eq) following General procedure B with Et_3N (1.3 eq) in EtOH (2 mL) and THF (1.5 mL) on a 1.0 mmol scale at 60°C. The precipitating product was collected by filtration (184 mg, 65%). ^1H NMR (500 MHz, DMSO-d_6) δ 13.55 (s, 1H), 10.22 (bs, 1H), 8.54 (dd, *J* = 4.5, 1.6 Hz, 1H), 8.41 (s, 1H), 8.10 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.19 (dd, *J* = 8.1, 4.5 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 158.28, 157.19, 155.92, 152.03, 149.52, 138.00, 131.00, 116.78, 113.47, 109.79. LCMS (ESI, C_{18}, linear gradient, 10% → 90% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 4.82 min; *m/z* : 281 $[M+H]^+$.

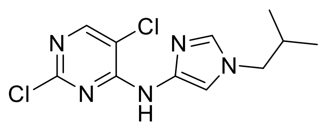
2,5-Dichloro-_N_-(1-methyl-1_H_-imidazol-4-yl)pyrimidin-4-amine (90)



<u>**Step 1:**</u> A round-bottom-flask was charged with 1-methyl-4-nitro-1*H*-imidazole (**106**) (0.25 g, 1.95 mmol, 1.15 eq) and Pd/C (10%, 207 mg) suspended in EtOH (10 mL). The mixture was degassed and H_2 gas was bubbled through while sonicating for 20 min. The reaction was stirred for another 16 h under H_2 atmosphere until full conversion was detected by TLC. The mixture was filtered and because the resulting product is unstable, the resulting filtrated was used directly in step 2.

<u>**Step 2:**</u> After Et_3N (0.353 mL, 2.53 mmol, 1.5 eq) was added to the filtrate from step 1, a solution of 2,4,5-trichloropyrimidine (**1a**) (0.32 g, 1.7 mmol, 1 eq) in EtOH (5 mL) was added dropwise and the mixture was stirred for 16 h. The mixture was concentrated under reduced pressure onto celite and purified via flash-column-chromatography (dry-loading, SiO_2, 50% → 100% EtOAc in pentane) to yield the product (117 mg, 25%). ^1H NMR (500 MHz, methanol-d_4) δ 8.21 (s, 1H), 7.48 (d, *J* = 1.1 Hz, 1H), 7.41 (d, *J* = 1.6 Hz, 1H), 3.76 (s, 3H). ^{13}C NMR (126 MHz, methanol-d_4) δ 159.16, 157.10, 155.16, 137.49, 135.78, 114.75, 111.38, 34.17.

2,5-Dichloro-_N_-(1-isobutyl-1_H_-imidazol-4-yl)pyrimidin-4-amine (91)



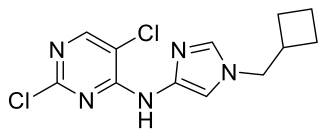
<u>**Step 1:**</u> A round-bottom-flask was charged with 4-nitro-1*H*-imidazole (**107**) (0.57 g, 5 mmol, 1 eq) and K_2CO_3 (1.04 g, 7.5 mmol, 1.5 eq) suspended in DMF (6.25 mL). After addition of 1-bromo-2-methylpropane (0.82 g, 6 mmol, 1.2 eq) the reaction mixture was stirred at 50°C overnight. The resulting mixture was filtered and the filtrate concentrated and the crude product used without further purification.

<u>**Step 2:**</u> A round-bottom-flask was charged with crude product from step 1 (0.25 g, 1.48 mmol, 1.1 eq) and Pd/C (10%) suspended in MeOH (10 mL). The mixture was degassed and H_2 gas

was bubbled through while sonicating for 20 min. The reaction was stirred for another 16 h under H_2 atmosphere until full conversion was detected by TLC. The mixture was filtered and because the resulting product is unstable, the resulting filtrated was used directly in step 2.

Step 3: Et_3N (0.30 mL, 2.15 mmol, 1.6 eq) and 2,4,5-trichloropyrimidine (**1a**) (0.25 g, 1.34 mmol, 1 eq) was added and the mixture was stirred for 16 h. The mixture was concentrated under reduced pressure onto celite and purified via flash-column-chromatography (dry-loading, SiO_2, 20% → 50% EtOAc in pentane) to yield the product (108 mg, 28%). ^1H NMR (500 MHz, DMSO-d_6) δ 9.77 (bs, 1H), 8.30 (s, 1H), 7.56 (s, 1H), 7.33 (s, 1H), 3.81 (d, J = 7.0 Hz, 2H), 2.09 – 1.94 (m, 1H), 0.85 (d, J = 6.5 Hz, 6H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 157.03, 155.56, 154.54, 136.18, 134.32, 113.21, 109.15, 53.71, 29.41, 19.49. LCMS (ESI, C_{18}, linear gradient, 10% → 90% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 4.4 min; *m/z* : 286 $[M+H]^+$.

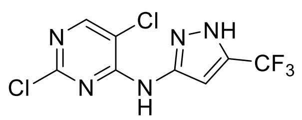
2,5-Dichloro-*N*-(1-(cyclobutylmethyl)-1*H*-imidazol-4-yl)pyrimidin-4-amine (92)



Step 1: A round-bottom-flask was charged with 1-(cyclobutylmethyl)-4-nitro-1*H*-imidazole (**108**) (0.045 g, 0.248 mmol, 1 eq) and Pd/C (10%) suspended in MeOH (2 mL). The mixture was degassed and H_2 gas was bubbled through while sonicating for 20 min. The reaction was stirred for another 16 h under H_2 atmosphere until full conversion was detected by TLC. The mixture was filtered over celite and the resulting oil used directly in step 2.

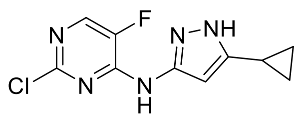
Step 2: The product from step 1 was dissolved in EtOH (7 mL) and 2,4,5-trichloropyrimideine (**1a**) (48 mg, 0.262 mmol, 1.1 eq) was added. After dropwise addition of Et_3N (50 µL, 0.360 mmol, 1.5 eq) the reaction was stirred to 35 h at RT. The mixture was concentrated under reduced pressure onto celite and purified via flash-column-chromatography (dry-loading, SiO_2, 40% → 80% EtOAc in pentane) to yield the product (66 mg, 85%). ^1H NMR (400 MHz, methanol-d_4) δ 8.21 (s, 1H), 7.50 (s, 1H), 7.41 (s, 1H), 4.04 (d, J = 7.4 Hz, 2H), 2.86 – 2.71 (m, 1H), 2.15 – 2.05 (m, 2H), 2.03 – 1.89 (m, 2H), 1.89 – 1.79 (m, 2H). ^{13}C NMR (101 MHz, methanol-d_4) δ 159.15, 157.06, 155.14, 137.36, 134.93, 114.75, 110.22, 53.65, 37.58, 26.76, 18.86.

2,5-Dichloro-*N*-(5-(trifluoromethyl)-1*H*-pyrazol-3-yl)pyrimidin-4-amine (93)



The title compound was synthesized from 2,4,5-trichloropyrimidine (**1a**) (1 eq) and 5-(trifluoromethyl)-1*H*-pyrazol-3-amine (**2k**) (1.1 eq) following General procedure B with Et_3N (1.4 eq) in EtOH on a 1.0 mmol scale at 60°C. The crude product was purified via flash-column-chromatography (dry-loading, SiO_2, 20% → 60% EtOAc in pentane) to yield the product (35 mg, 19%). ^1H NMR (500 MHz, methanol-d_4) δ 8.34 (s, 1H), 6.69 (s, 1H). LCMS (ESI, C_{18}, linear gradient, 10% → 90% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 6.62 min; *m/z* : 298 $[M+H]^+$.

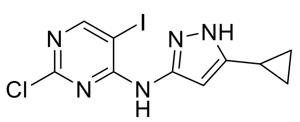
2-Chloro-*N*-(5-cyclopropyl-1*H*-pyrazol-3-yl)-5-fluoropyrimidin-4-amine (94)



The title compound was synthesized from 2,4-dichlo-5-fluororopyrimidine (**1d**) and 5-cyclopropyl-1*H*-pyrazol-3-amine (**2b**) following General procedure A on a 1.0 mmol scale at RT and purified via flash-column-chromatography (dry-loading, SiO_2, 30% → 80% EtOAc in pentane) to yield the product (220 mg, 87%). ^1H NMR (400 MHz, DMSO-d_6) δ 12.27

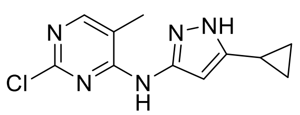
(s, 1H), 10.34 (s, 1H), 8.22 (d, J = 3.4 Hz, 1H), 6.24 (s, 1H), 1.96 – 1.86 (m, 1H), 0.97 – 0.90 (m, 2H), 0.72 – 0.65 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 153.23 (d, J = 3.1 Hz), 150.87 (d, J = 12.1 Hz), 145.87, 144.94 (d, J = 259.2 Hz), 141.38 (d, J = 20.6 Hz), 94.66, 48.74, 7.87, 7.02. LCMS (ESI, C_{18}, linear gradient, 10% → 90% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 5.00 min; *m/z* : 254 $[M+H]^+$.

2-Chloro-*N*-(5-cyclopropyl-1*H*-pyrazol-3-yl)-5-iodopyrimidin-4-amine (95)



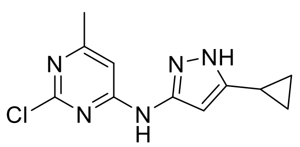
The title compound was synthesized from 2,4-dichlo-5-iodoropyrimidine (**1e**) and 5-cyclopropyl-1*H*-pyrazol-3-amine (**2b**) following General procedure A on a 1.0 mmol scale at 60°C and purified via flash-column-chromatography (dry-loading, SiO_2, 60% → 80% EtOAc in pentane) to yield the product (200 mg, 55%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.35 (s, 1H), 8.62 (s, 1H), 8.51 (s, 1H), 6.16 (s, 1H), 1.96 – 1.87 (m, 1H), 0.98 – 0.90 (m, 2H), 0.72 – 0.66 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 164.20, 159.88, 159.09, 146.19, 145.99, 95.20, 77.55, 7.90, 6.97. LCMS (ESI, C_{18}, linear gradient, 10% → 90% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 6.18 min; *m/z* : 362 $[M+H]^+$.

2-Chloro-*N*-(5-cyclopropyl-1*H*-pyrazol-3-yl)-5-methylpyrimidin-4-amine (96)



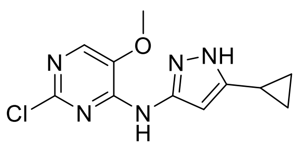
The title compound was synthesized from 2,4-dichloro-5-methylpyrimidine (**1f**) and 5-cyclopropyl-1*H*-pyrazol-3-amine (**2b**) following General procedure A on a 1.0 mmol scale at 60°C and purified via flash-column-chromatography (dry-loading, SiO_2, 70% → 80% EtOAc in pentane) to yield the product (122 mg, 49%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.22 (s, 1H), 9.27 (s, 1H), 8.03 – 7.91 (m, 1H), 6.27 (s, 1H), 2.12 (s, 3H), 1.92 (tt, J = 8.5, 5.1 Hz, 1H), 0.98 – 0.89 (m, 2H), 0.72 – 0.65 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 160.23, 157.43, 156.30, 147.18, 146.05, 114.36, 95.28, 13.81, 8.15, 7.39. LCMS (ESI, C_{18}, linear gradient, 10% → 90% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 5.70 min; *m/z* : 250 $[M+H]^+$.

2-Chloro-*N*-(5-cyclopropyl-1*H*-pyrazol-3-yl)-6-methylpyrimidin-4-amine (97)



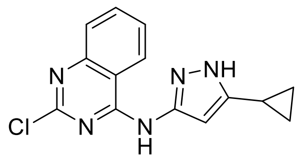
The title compound was synthesized from 2,4-dichloro-6-methylpyrimidine (**1g**) and 5-cyclopropyl-1*H*-pyrazol-3-amine (**2b**) following General procedure A on a 1.0 mmol scale at 60°C and purified via flash-column-chromatography (dry-loading, SiO_2, 40% → 60% EtOAc in pentane) to yield the product (119 mg, 48%). ^{1}H NMR (500 MHz, methanol-d_4) δ 6.84 (s, 1H), 6.02 (s, 1H), 2.31 (s, 3H), 1.90 (tt, J = 8.5, 5.1 Hz, 1H), 1.01 – 0.95 (m, 2H), 0.76 – 0.71 (m, 2H). ^{13}C NMR (126 MHz, methanol-d_4) δ 160.08, 159.07, 153.08, 152.97, 120.67, 95.09, 26.12, 9.21, 8.26. LCMS (ESI, C_{18}, linear gradient, 10% → 90% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 4.55 min; *m/z* : 250 $[M+H]^+$.

2-Chloro-*N*-(5-cyclopropyl-1*H*-pyrazol-3-yl)-5-methoxypyrimidin-4-amine (98)



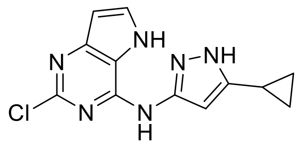
The title compound was synthesized from 2,4-dichloro-5-methoxypyrimidine (**1h**) and 5-cyclopropyl-1*H*-pyrazol-3-amine (**2b**) following General procedure A on a 1.0 mmol scale at 60°C and purified via flash-column-chromatography (dry-loading, SiO_2, 50% → 80% EtOAc in pentane) to yield the product (209 mg, 79%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.22 (s, 1H), 9.20 (s, 1H), 7.87 (s, 1H), 6.25 (s, 1H), 3.89 (s, 3H), 2.00 – 1.84 (m, 1H), 0.99 – 0.86 (m, 2H), 0.78 – 0.60 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 152.31, 149.87, 146.24, 145.77, 139.62, 135.28, 94.52, 56.63, 7.83, 6.98. LCMS (ESI, C_{18}, linear gradient, 10% → 90% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 4.58 min; *m/z* : 266 $[M+H]^+$.

2-Chloro-*N*-(5-cyclopropyl-1*H*-pyrazol-3-yl)quinazolin-4-amine (99)



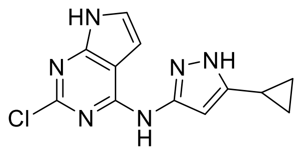
The title compound was synthesized from 2,4-dichloroquinazoline (**1i**) (1 eq) and 5-cyclopropyl-1*H*-pyrazol-3-amine (**2b**) (1.3 eq) following General procedure B with DiPEA (1.1 eq) in EtOH on a 1.0 mmol scale at RT. The precipitating product was collected by filtration (166 mg, 58%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.26 (s, 1H), 10.60 (s, 1H), 8.58 (d, *J* = 8.2 Hz, 1H), 7.87 – 7.80 (m, 1H), 7.72 – 7.64 (m, 1H), 7.60 – 7.52 (m, 1H), 6.45 (s, 1H), 1.95 (tt, *J* = 8.5, 5.1 Hz, 1H), 0.99 – 0.93 (m, 2H), 0.74 – 0.70 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 158.70, 156.35, 150.74, 146.76, 145.65, 133.88, 126.69, 126.49, 123.49, 113.43, 95.33, 7.56, 6.85. LCMS (ESI, C_{18}, linear gradient, 10% → 90% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 5.51 min; *m/z* : 286 [M+H]$^+$.

2-Chloro-*N*-(5-cyclopropyl-1*H*-pyrazol-3-yl)-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-amine (100)



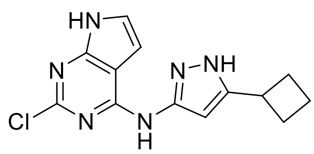
The title compound was synthesized from 2,4-dichloro-5*H*-pyrrolo[3,2-*d*]pyrimidine (**1j**) and 5-cyclopropyl-1*H*-pyrazol-3-amine (**2b**) following General procedure A on a 1.0 mmol scale at 120°C and purified via flash-column-chromatography (dry-loading, SiO_2, 2% → 7% (10% of sat. aqueous NH_3 in MeOH) in DCM) to yield the product (123 mg, 45%). ^{1}H NMR (500 MHz, methanol-d_4) δ 7.55 (d, *J* = 3.0 Hz, 1H), 6.42 (d, *J* = 3.0 Hz, 1H), 5.26 (s, 1H), 1.93 (tt, *J* = 8.5, 5.1 Hz, 1H), 1.04 – 0.97 (m, 2H), 0.79 – 0.74 (m, 2H). ^{13}C NMR (126 MHz, methanol-d_4) δ 152.23, 151.26, 148.88, 148.52, 131.08, 113.79, 102.11, 93.95, 89.11, 8.02, 7.70. LCMS (ESI, C_{18}, linear gradient, 10% → 90% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 4.58 min; *m/z* : 275 [M+H]$^+$.

2-Chloro-*N*-(5-cyclopropyl-1*H*-pyrazol-3-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (101)



A round-bottom-flask was charged with 2,4-dichloro-7*H*-pyrrolo[2,3-*d*]pyrimidine (**1k**) (1.91 g, 10.13 mmol, 1 eq), 5-cyclopropyl-1*H*-pyrazol-3-amine (**2b**) (2.05 g, 16.65 mmol, 1.64 eq) dissolved in *n*-butanol (30 mL). After addition of DiPEA (2.6 mL, 14.91 mmol, 1.47 eq) the mixture was stirred for 5 d at 120°C. The resulting mixture was concentrated under reduced pressure onto celite and purified via flash-column-chromatography (dry-loading, SiO_2, 0% → 10% MeOH in EtOAc) to yield the product (1.10 mg, 40%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.12 (s, 1H), 11.81 (s, 1H), 10.18 (s, 1H), 7.25 – 7.05 (m, 1H), 6.75 (s, 1H), 6.40 (s, 1H), 1.99 – 1.83 (m, 1H), 1.00 – 0.84 (m, 2H), 0.76 – 0.63 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 153.80, 151.97, 151.44, 122.20, 101.65, 99.80, 94.37, 7.72, 7.03. LCMS (ESI, C_{18}, linear gradient, 0% → 90% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 4.42 min; *m/z* : 275 [M+H]$^+$.

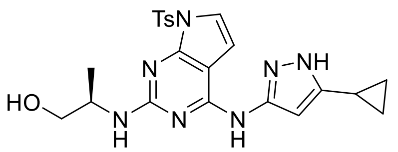
2-Chloro-*N*-(5-cyclobutyl-1*H*-pyrazol-3-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (102)



A vial was charged with 2,4-dichloro-7*H*-pyrrolo[2,3-*d*]pyrimidine (**1k**) (0.404 g, 2.15 mmol, 1 eq), 5-cyclobutyl-1*H*-pyrazol-3-amine (**2h**) (0.487 g, 3.55 mmol, 1.65 eq) and DiPEA (0.5 mL, 2.87 mmol, 1.34 eq) dissolved in *n*-butanol. The reaction mixture was heated for 4 d at 120°C, concentrated onto celite under reduced pressure and purified via flash-column-chromatography (dry-loading, SiO_2, 40% → 100% EtOAc in pentane) to yield the product (0.35 mg, 56%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.19 (s, 1H), 11.81 (s, 1H), 10.21 (s, 1H), 7.15 (s, 1H), 6.85 (s, 1H), 6.56 (s, 1H), 3.63 – 3.42 (m, 1H), 2.37 – 2.25 (m, 2H), 2.23 – 2.07 (m, 2H), 2.06 – 1.92 (m, 1H), 1.91 – 1.76 (m, 1H). ^{13}C NMR (101 MHz, DMSO-

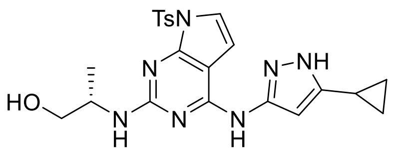
d$_6$) δ 152.40, 151.83, 147.95, 147.50, 122.55, 102.08, 100.24, 31.62, 29.47, 18.58. LCMS (ESI, C_{18}, linear gradient, 10% → 90% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 7.32 min; *m/z* : 289 $[M+H]^+$.

(*R*)-2-((4-((5-Cyclopropyl-1*H*-pyrazol-3-yl)amino)-7-tosyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)amino)propan-1-ol (103)



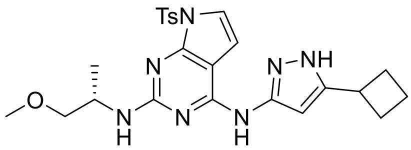
A vial was charged with 2-chloro-*N*-(5-cyclopropyl-1*H*-pyrazol-3-yl)-7-tosyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (**109**) (0.22 g, 0.47 mmol, 1 eq), (*R*)-2-aminopropan-1-ol (**4af**) (67 mg, 0.892 mmol, 1.9 eq) dissolved in *n*-butanol (1.3 mL). After addition of DiPEA (0.18 mL, 1.02 mmol, 2.2 eq) the vial was sealed and the mixture heated in the microwave to 150°C for 6 h. The reaction mixture was concentrated under reduced pressure and purified via flash-column-chromatography (SiO_2, dry-loading, 50% → 100% EtOAc in pentane) to yield the product (85 mg, 36%). ^{1}H NMR (500 MHz, methanol-*d*$_4$) δ 7.95 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 7.9 Hz, 2H), 7.16 (d, *J* = 4.0 Hz, 1H), 6.58 (d, *J* = 4.0 Hz, 1H), 5.91 (bs, 1H), 4.16 – 4.08 (m, 1H), 3.67 – 3.62 (m, 1H), 3.62 – 3.57 (m, 1H), 2.31 (s, 3H), 1.85 (tt, *J* = 8.5, 5.0 Hz, 1H), 1.23 (d, *J* = 6.7 Hz, 3H), 0.93 – 0.84 (m, 2H), 0.73 – 0.62 (m, 2H). ^{13}C NMR (126 MHz, Methanol-*d*$_4$) δ 160.89, 154.89, 154.44, 152.25, 146.84, 145.80, 136.56, 130.70, 129.14, 119.95, 104.30, 99.22, 91.85, 67.38, 49.98, 21.55, 17.74, 8.85, 8.20. LCMS (ESI, C_{18}, linear gradient, 10% → 90% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 5.90 min; *m/z* : 468 $[M+H]^+$.

(*S*)-2-((4-((5-Cyclopropyl-1*H*-pyrazol-3-yl)amino)-7-tosyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)amino)propan-1-ol (104)



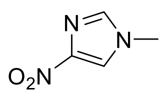
A vial was charged with 2-chloro-*N*-(5-cyclopropyl-1*H*-pyrazol-3-yl)-7-tosyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (**109**) (2.57 g, 6.0 mmol, 1 eq), (*S*)-2-aminopropan-1-ol (**4ag**) (0.676 g, 9.0 mmol, 1.5 eq) dissolved in *n*-butanol (15 mL). After addition of DiPEA (2.09 mL, 12 mmol, 2 eq) the vial was sealed and the mixture heated in the microwave to 160°C for 10 h. The reaction mixture was concentrated under reduced pressure and purified via flash-column-chromatography (SiO_2, dry-loading, 0% → 8% (10% of sat. aqueous NH_3 in MeOH) in DCM) to yield the product (2.81 g, 50%). ^{1}H NMR (500 MHz, methanol-*d*$_4$) δ 7.94 (d, *J* = 8.1 Hz, 2H), 7.26 (d, *J* = 8.2 Hz, 2H), 7.15 (d, *J* = 4.0 Hz, 1H), 6.58 (bs, 1H), 5.60 (bs, 1H), 4.17 – 4.08 (m, 1H), 3.68 – 3.63 (m, 1H), 3.61 – 3.56 (m, 1H), 2.28 (s, 3H), 1.84 (tt, *J* = 8.5, 5.1 Hz, 1H), 1.23 (d, *J* = 6.7 Hz, 3H), 0.91 – 0.82 (m, 2H), 0.71 – 0.62 (m, 2H). ^{13}C NMR (126 MHz, methanol-*d*$_4$) δ 161.01, 154.86, 154.43, 148.89, 146.79, 136.52, 130.67, 129.11, 119.89, 104.30, 99.23, 95.54, 88.66, 67.40, 49.95, 21.55, 17.75, 8.91, 8.20. LCMS (ESI, C_{18}, linear gradient, 10% → 90% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 6.11 min; *m/z* : 468 $[M+H]^+$.

(*S*)-*N*^{4}-(5-Cyclobutyl-1*H*-pyrazol-3-yl)-*N*^{2}-(1-methoxypropan-2-yl)-7-tosyl-7*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine (105)



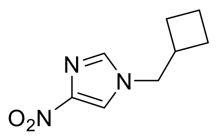
A vial was charged with 2-chloro-*N*-(5-cyclobutyl-1*H*-pyrazol-3-yl)-7-tosyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (**110**) (2.66 g, 6.0 mmol, 1 eq), (*S*)-1-methoxypropan-2-amine (**4ai**) (0.80 g, 9.0 mmol, 1.5 eq) dissolved in *n*-butanol (15 mL). After addition of DiPEA (2.09 mL, 12 mmol, 2 eq) the vial was sealed and the mixture heated in the microwave to 160°C for 13 h. The reaction mixture was concentrated under reduced pressure and purified via flash-column-chromatography (SiO_2, dry-loading, 0% → 8% (10% of sat. aqueous NH_3 in MeOH) in DCM) to yield the product (2.36 g, 79%). ^{1}H NMR (500 MHz, methanol-d_4) δ 7.94 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 8.1 Hz, 2H), 7.17 (bs, 1H), 6.60 (bs, 1H), 5.79 (bs, 1H), 4.26 – 4.18 (m, 1H), 3.56 – 3.43 (m, 2H), 3.34 (s, 3H), 3.32 (bs, 1H), 2.31 (s, 3H), 2.30 – 2.23 (m, 2H), 2.20 – 2.09 (m, 2H), 2.03 – 1.93 (m, 1H), 1.82 (bs, *J* = 9.8 Hz, 1H), 1.21 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (126 MHz, methanol-d_4) δ 159.57, 156.27, 154.50, 153.41, 148.50, 145.45, 135.43, 129.40, 127.88, 118.51, 103.04, 97.89, 95.47, 88.30, 75.98, 58.02, 46.41, 28.94, 20.29, 18.16, 16.85. LCMS (ESI, C_{18}, linear gradient, 10% → 90% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 6.97 min; *m/z* : 496 [M+H]$^+$.

1-Methyl-4-nitro-1*H*-imidazole (106)



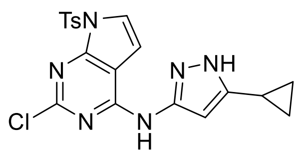
A round-bottom-flask was charged with 4-nitro-1*H*-imidazole (**107**) (0.57 g, 5 mmol, 1 eq) and K_2CO_3 (1.04 g, 7.5 mmol, 1.5 eq) suspended in ACN (6.25 mL). After addition of methyl iodine (0.85 g, 6 mmol, 1.2 eq) the reaction mixture was stirred at 65°C overnight. The resulting mixture was filtered and the filtrate concentrated after witch the crude product was recrystallized from 20 mL *i*PrOH to yield the product (0.31 g, 49%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.36 (d, *J* = 1.4 Hz, 1H), 7.81 (d, *J* = 1.2 Hz, 1H), 3.75 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 138.04, 122.55, 34.22.

1-(Cyclobutylmethyl)-4-nitro-1*H*-imidazole (108)



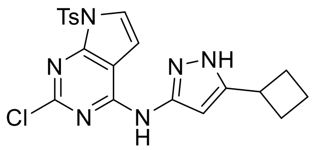
A vial was charged with cyclobutylmethyl 4-methylbenzenesulfonate (**111**) (0.288 g, 1.2 mmol, 1.13 eq) and K_2CO_3 (0.237 g, 1.7 mmol, 1.6 eq) dissolved in ACN (1.25 mL). After addition of 4-nitro-1*H*-imidazole (**107**) (0.120 g, 1.06 mmol, 1 eq) the reaction mixture was stirred for 70 h at 60°C. The reaction mixture was filtered, concentrated onto celite and purified via flash-column-chromatography (dry-loading, SiO_2, 50% EtOAc in pentane) to yield the product (61 mg g, 64%, 2 regio-isomers 4:1, major isomer reported). ^{1}H NMR (500 MHz, methanol-d_4) δ 8.13 (d, *J* = 1.5 Hz, 1H), 7.74 (d, *J* = 1.3 Hz, 1H), 4.13 (d, *J* = 7.6 Hz, 2H), 2.86 – 2.74 (m, 1H), 2.11 – 2.03 (m, 2H), 1.98 – 1.86 (m, 2H), 1.86 – 1.76 (m, 2H). ^{13}C NMR (126 MHz, methanol-d_4) δ 148.55, 138.13, 121.46, 54.13, 37.10, 26.42, 18.73.

2-Chloro-*N*-(5-cyclopropyl-1*H*-pyrazol-3-yl)-7-tosyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (109)



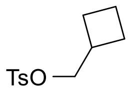
A vial was charged with 2,4-dichloro-7-tosyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (**112**) (2.00 g, 5.84 mmol, 1 eq), 5-cyclopropyl-1*H*-pyrazol-3-amine (**2b**) (0.90 g, 7.31 mmol, 1.25 eq) and Et_3N (1.22 mL, 8.77 mmol, 1.5 eq) dissolved in ACN (15 mL), sealed and heated in the microwave to 100°C for 2.5 h. The reaction mixture was concentrated under reduced pressure and purified via flash-column-chromatography (SiO_2, 30% → 75% EtOAc in pentane) to yield the product (1.36 g, 54%). ^{1}H NMR (500 MHz, methanol-d_4) δ 7.99 (d, *J* = 8.4 Hz, 2H), 7.49 (d, *J* = 4.0 Hz, 1H), 7.33 (d, *J* = 7.9 Hz, 2H), 6.66 (bs, 1H), 6.28 (bs, 1H), 2.34 (s, 3H), 1.89 (tt, *J* = 8.5, 5.1 Hz, 1H), 0.98 – 0.92 (m, 2H), 0.74 – 0.67 (m, 2H). ^{13}C NMR (126 MHz, methanol-d_4) δ 156.03, 155.94, 152.49, 148.60, 147.53, 135.98, 130.89, 129.33, 124.22, 105.43, 104.12, 95.86, 21.60, 8.20, 7.90. LCMS (ESI, C_{18}, linear gradient, 10% → 90% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 7.00 min; *m/z* : 429 [M+H]$^+$.

2-Chloro-*N*-(5-cyclobutyl-1*H*-pyrazol-3-yl)-7-tosyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (110)



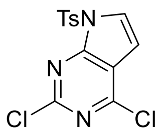
A vial was charged with 2,4-dichloro-7-tosyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (**112**) (2.00 g, 5.84 mmol, 1 eq), 5-cyclobutyl-1*H*-pyrazol-3-amine (**2h**) (1.00 g, 7.31 mmol, 1.25 eq) and Et_3N (1.22 mL, 8.77 mmol, 1.5 eq) dissolved in ACN (15 mL), sealed and heated in the microwave to 100°C for 4 h. The reaction mixture was concentrated under reduced pressure and purified via flash-column-chromatography (SiO_2, 30% → 80% EtOAc in pentane) to yield the product (1.52 g, 59%). ^1H NMR (500 MHz, methanol-d_4) δ 8.00 (d, *J* = 8.5 Hz, 2H), 7.50 (d, *J* = 4.0 Hz, 1H), 7.35 (d, *J* = 7.9 Hz, 2H), 6.65 (bs, 1H), 6.46 (bs, 1H), 3.58 – 3.49 (m, 1H), 2.36 (s, 3H), 2.38 – 2.31 (m, 2H), 2.24 – 2.15 (m, 2H), 2.09 – 1.98 (m, 1H), 1.94 – 1.86 (m, 1H). ^{13}C NMR (126 MHz, methanol-d_4) δ 156.11, 156.05, 152.53, 150.84, 147.89, 147.56, 136.03, 130.91, 129.35, 124.22, 105.45, 104.16, 96.65, 33.26, 30.23, 21.61, 19.45. LCMS (ESI, C_{18}, linear gradient, 10% → 90% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 7.51 min; *m/z* : 443 $[M+H]^+$.

Cyclobutylmethyl 4-methylbenzenesulfonate (111)



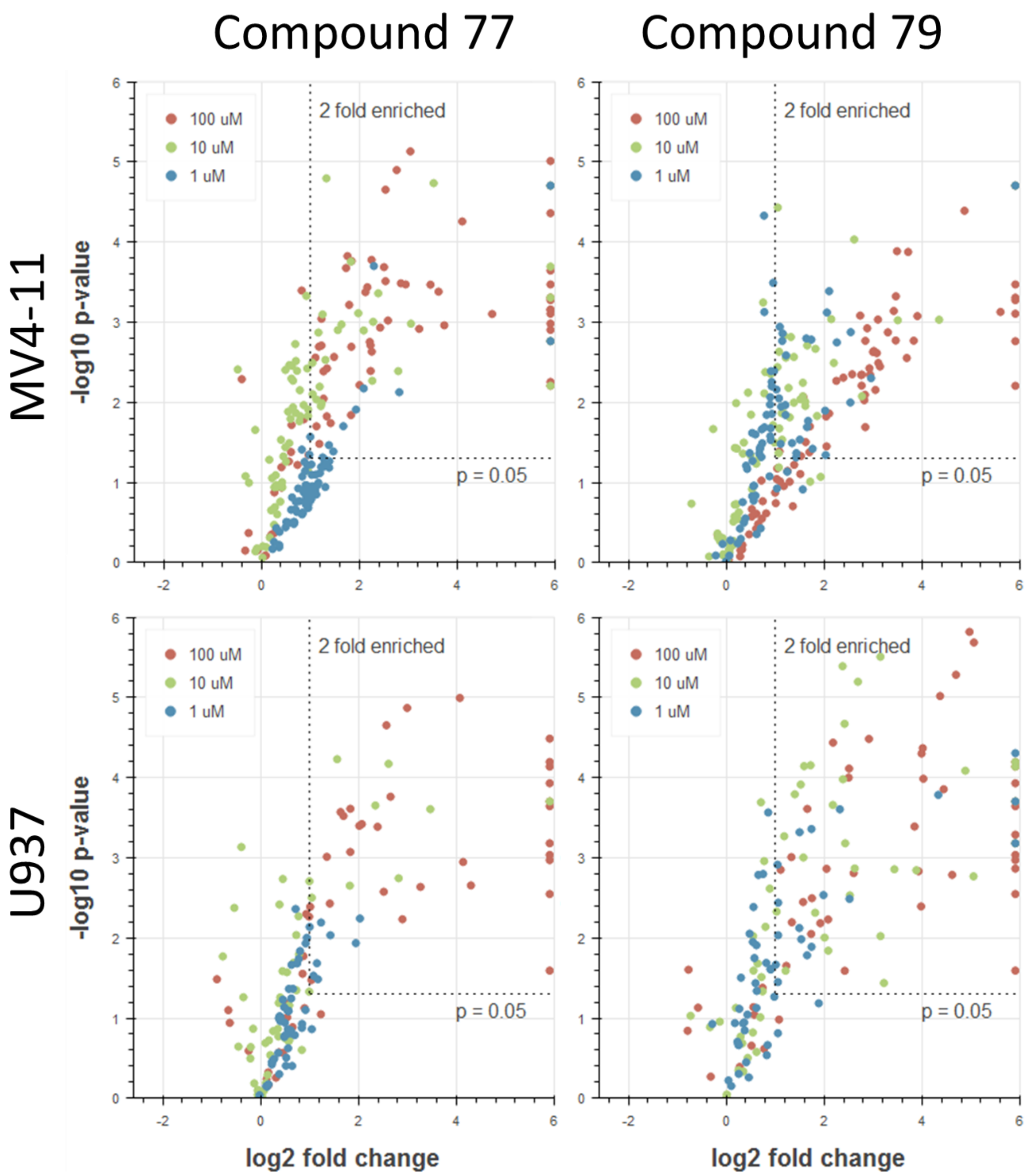
A round-bottom-flask was charged with cyclobutylmethanol (1.92 g, 22.33 mmol, 1.1 eq) dissolved in 20 mL chloroform. After dropwise addition of pyridine (3.53 g, 44.66 mmol, 2.2 mL), a solution of 4-methylbenzenesulfonyl chloride (3.87 g, 20.30 mmol, 1 eq) in 13 mL chloroform was added dropwise and the resulting mixture stirred overnight at RT. The reaction was diluted with 100 mL Et_2O, washed with aqueous HCl (0.1M, 4x40 mL) and with brine (1x100 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting residue was purified via flash-column-chromatography (SiO_2, 2% → 10% EtOAc in pentane) to yield the product (1.96 g, 40%). ^1H NMR (300 MHz, chloroform-*d*) δ 7.79 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.7 Hz, 2H), 3.98 (d, *J* = 6.6 Hz, 2H), 2.69 – 2.54 (m, 1H), 2.45 (s, 3H), 2.08 – 1.95 (m, 2H), 1.95 – 1.78 (m, 2H), 1.77 – 1.64 (m, 2H). ^{13}C NMR (75 MHz, chloroform-*d*) δ 144.75, 133.30, 129.91, 127.98, 74.21, 33.96, 24.37, 21.75, 18.25.

2,4-Dichloro-7-tosyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (112)



A round bottom flask was charged with 2,4-dichloro-7*H*-pyrrolo[2,3-*d*]pyrimidine (**1k**) (6.21 g, 33.0 mmol, 1 eq), 4-methylbenzenesulfonyl chloride (6.29 g, 33.0 mmol, 1 eq) and tetrabutylammonium hydrogen sulfate (0.56 g, 1.69 mmol, 0.05 eq) suspended in DCM (124 mL). Aqueous NaOH (50%, 6.21 mL) was added and after the mixture was stirred at RT for 90 min, H_2O (120 mL) was added. The phases were separated and the organic aqueous layer was extracted with DCM (4x100 mL). the combined organic layers were washed with brine (1x80 mL), dried (Na_2SO_4), filtered over a SiO_2 plug and concentrated under reduced pressure to yield the product (11.12 g, 98%). ^1H NMR (400 MHz, chloroform-*d*) δ 8.11 (d, *J* = 8.4 Hz, 2H), 7.76 (d, *J* = 4.0 Hz, 1H), 7.37 (d, *J* = 7.8 Hz, 2H), 6.69 (d, *J* = 4.0 Hz, 1H), 2.43 (s, 3H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 153.87, 153.69, 151.66, 146.85, 133.87, 130.17, 128.82, 127.77, 118.56, 102.91, 21.90.

Supplementary Information



SI Figure 2: Competition of **77** and **79** with XO44 in living cells. Volcano plot of the label-free quantification signal from IsoQuant for target kinases, pretreated with three different inhibitor concentrations in two cell lines. To enable plotting of all targets, infinite fold change (XO44 treated divided by competitor treated) was set to 60. A kinase was named a target if there was at least 50% reduction in quantification signal from probe treated samples vs inhibitor pretreated sample.

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