Discovery of BUB1 kinase inhibitors for the treatment of cancer

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Hit optimization of benzimidazoles towards highly potent BUB1 inhibitors

Introduction

Millions of people are diagnosed with cancer worldwide each year.[1] In 2020 the number of new cases was estimated to be 19.3 million and about 10 million cancer-related deaths were reported.[1] In a healthy individual, cell division is tightly controlled and homeostasis of cell number is thereby ensured.[2] One of the hallmarks of cancer includes uncontrolled cell proliferation, which may involve aberrant signaling of receptor tyrosine kinases.[2] Insights into these molecular mechanisms have led to the development of small molecule inhibitors that target these receptor tyrosine kinases and thereby block cell proliferation.[3] However, new molecular targets are urgently needed for cancer types that do not respond well to the currently available anti-cancer therapies. Budding uninhibited by benzimidazole 1 (BUB1) kinase has recently emerged as such a potential target for anti-cancer therapy.[4–6]

BUB1 plays an important role in the spindle assembly checkpoint (SAC), which is a safety mechanism during the prometaphase of mitosis. The SAC induces a mitotic arrest when chromosomes are not yet, or not properly, attached to the mitotic spindle.[7] This arrest is crucial for genomic integrity since mitotic progression with unattached chromosomes can result in aneuploidy which subsequently may contribute to tumorigenesis.[5] Many cancer cells have a weakened spindle assembly checkpoint and interference with these diminished checkpoints, for example by pharmacological inhibition of SAC proteins, has been hypothesized as a strategy to kill cancer cells.[4,5]

BUB1 participates in SAC signaling by recruiting several SAC proteins to unattached kinetochores.[8–11] Kinetochores, which are located at the centromeres of sister chromatids, are thought to catalyze mitotic checkpoint complex (MCC) formation.[12] The MCC is an inhibitor of the anaphase promoting complex/cyclosome (APC/C) and inhibition of APC/C results in a mitotic arrest.[12] BUB1 has been found to phosphorylate histone H2A[13], but the relevance of its kinase activity in SAC function has been debated.[14–16] Recently, the first BUB1 inhibitor, BAY1816032 (**Figure 4.1A,B**), was published and its potential as anti-cancer agent was investigated in a mouse xenograft model of human triple-negative breast cancer.[6] BAY1816032 was found to synergistically inhibit tumor growth when combined with paclitaxel, but did not exhibit efficacy as a single agent.[6] Of interest, residual BUB1 activity may be sufficient for a functional SAC[17], which suggests that more potent BUB1 inhibitors could act as single agents.

In **Chapter 2**, the results of a high-throughput screening campaign, to identify novel BUB1 inhibitors, are described. AT-9283 (**1**) (**Figure 4.1A**) was the most potent hit with a half maximal inhibitory concentration (IC_{50}) of 219 nM. AT-9283 has been investigated in several phase I clinical trials in patients with leukemia, solid tumors and non-Hodgkin's lymphoma[18–21] and as such may represent an excellent starting point for a new drug discovery program. AT-9283 potently inhibits multiple kinases, including FGFR1-3, VEGFR1-3, FLT3, PDGFRα, JAK2-3 and ABL.[22] AT-9283 is also a potent inhibitor of Aurora kinase (Aurora) A and B, which

both have an important role during mitosis. Aurora A participates in centrosome maturation, separation and bipolar spindle assembly. Aurora B is responsible for correcting erroneous kinetochore-microtubule attachments, contributes to SAC signaling and is involved in cytokinesis.[23–28] The binding mode of AT-9283 in Aurora A is shown in **Figure 4.1C** and involves three hydrogen bonds between the benzimidazole-pyrazole scaffold and amide backbones of hinge amino acids Glu211 and Ala213.[22] In addition, the urea linker adopts a cis/trans configuration, which causes the cyclopropyl group to bind in the front pocket of Aurora A. The gatekeeper residue of Aurora A, Leu210, is relatively large and thereby hinders access to its back pocket (**Figure 4.1C**). In contrast, BUB1 has a small gatekeeper residue (Gly866) and this feature can be exploited by inhibitors to target its back pocket (**Figure 4.1B**), which will contribute to their selectivity for BUB1. In this chapter, the structure-activity relationship (SAR) of AT-9283 (**1**) on BUB1 kinase activity was systematically investigated by changing its molecular structure. This resulted in the discovery of novel and highly potent BUB1 inhibitors.

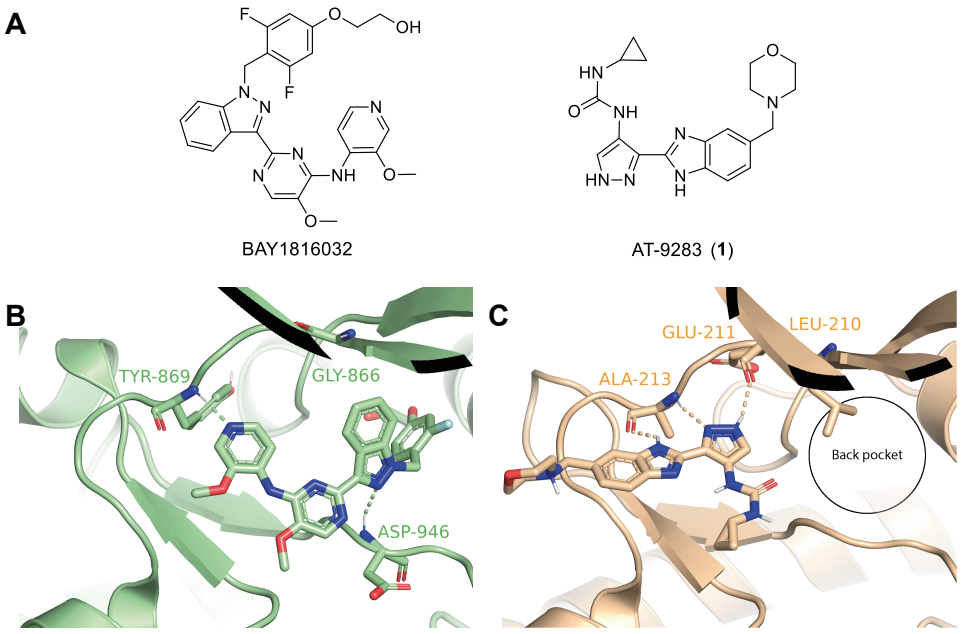


Figure 4.1 | (A) Chemical structures of BAY1816032 and AT-9283 (**1**). **(B)** Crystal structure of BAY1816032 bound to BUB1 (PDB code: 6F7B).[6] **(C)** Crystal structure of AT-9283 bound to Aurora A (PDB code: 2W1G).[22] Hydrogen bonds are indicated by dashed lines.

Results & Discussion

Biochemical evaluation of structural analogues 2 – 60 of AT-9283

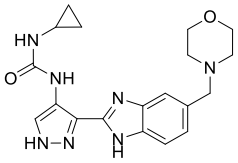
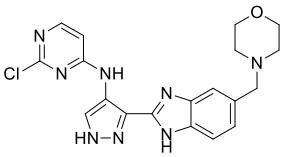
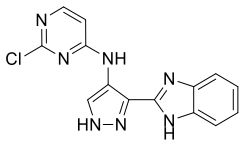
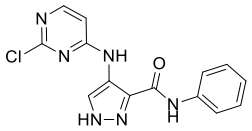
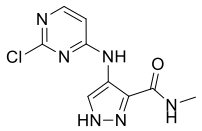
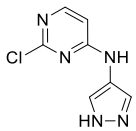
To study the structure-activity relationship (SAR) of AT-9283 (**1**), analogues **2** – **60** were synthesized by employing different synthetic routes (see Experimental section). Compounds **2** – **60** were subsequently evaluated in a biochemical fluorescence polarization assay to

determine the half maximal inhibitory concentrations (IC_{50}) as described in **Chapter 2**. The data are reported in **Table 4.1** – **Table 4.6** and activities are expressed as pIC_{50} ± SEM (N=2, n=2).

To tune the activity towards BUB1 and to dial out potency for Aurora A, the cyclopropyl urea of **1** was replaced with a 2-chloro-4-aminopyrimidine as bioisoster, in which the chlorine was hypothesized to be oriented towards the back pocket of BUB1 and functioned as a synthetic handle to introduce substituents. Surprisingly, synthetic intermediate 2-chloropyrimidine **2** already showed a 3-fold increase in potency compared to compound **1** (**Table 4.1**). A disjunctive approach was applied to identify essential functional groups that constitute the pharmacophore of compound **2**. Removal of the morpholine (**3**) reduced potency 2.5-fold, which suggested that the morpholine does not only act as a solubilizer, but may also have important interactions with BUB1. Substituting the benzimidazole of **3** for a phenyl amide (**4**) was not tolerated and reduced potency over 30-fold. Methyl amide **5** further reduced potency and similarly, compound **6**, which completely lacked the benzimidazole was inactive. Overall, the benzimidazole was found to be crucial for activity, probably due to hydrogen bond formation between the benzimidazole –NH and the hinge region of BUB1 and also the morpholine contributed to the potency.

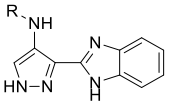
The SAR of the 2-chloropyrimidine in **3** was systematically investigated by evaluation of compound **7** – **14** (**Table 4.2**). Removal of the chlorine (**7**), one (**8**, **9**) or two nitrogens (**10**) of the pyrimidine moiety significantly reduced the potency or led to a completely inactive compound. Addition of an extra chlorine at the 5-position (**12**), but not at the 6-position (**11**), was tolerated. Introducing electron donating groups at the 5-position, such as a methyl (**13**) or methoxy group (**14**), significantly increased potency. Altogether, this suggested that the 2-chloropyrimidine substituent has favorable hydrophobic interactions with the back pocket, the pyrimidine nitrogens may form hydrogen bond interactions and the pyrimidine ring could form pi-pi or pi-sigma interactions with for example amino acids present in the β-strands 1–3.

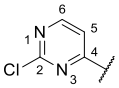
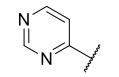
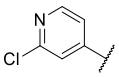
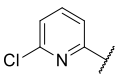
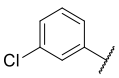
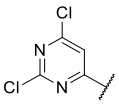
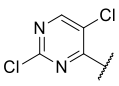
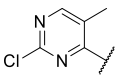
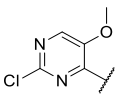
Table 4.1 | Half maximal inhibitory concentrations (expressed as pIC_{50} ± SEM) of **1** – **6** determined by a fluorescence polarization assay on BUB1 kinase activity (N=2, n=2).

ID	Structure	pIC_{50} ± SEM	app. K_i (nM)[a]	cLogP[b]	LipE[c]	tPSA[d]	MW[e]
1		6.66 ± 0.02	77	0.4	6.7	102	381
2		7.13 ± 0.01	26	1.6	5.9	98	411
3		6.73 ± 0.03	66	2.1	5.1	86	312
4		5.23 ± 0.04	2070	1.9	3.8	90	315
5		< 5	–	0.2	–	90	253
6		< 5	–	0.7	–	61	196

[a] Apparent K_i ; [b] cLogP, calculated by DataWarrior (v.5.2.1); [c] Lipophilic efficiency, defined as $\mathrm{LipE} = \mathrm{app.\,p}K_i - \mathrm{cLogP}$; [d] Topological polar surface area (Å^2), calculated by Chemdraw (v.19.1); [e] Molecular weight (g/mol).

Table 4.2 | Half maximal inhibitory concentrations (expressed as pIC_{50} ± SEM) of **7** – **14** determined by a fluorescence polarization assay on BUB1 kinase activity (N=2, n=2).

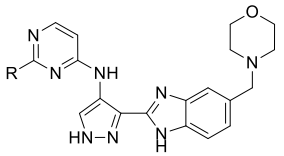


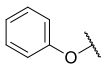
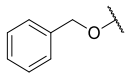
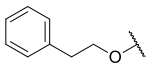
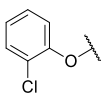
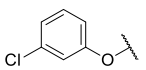
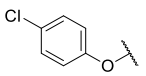
ID	R =	pIC_{50} ± SEM	app. K_i (nM)[a]	cLogP[b]	LipE[c]
3		6.73 ± 0.03	66	2.1	5.1
7		5.87 ± 0.04	474	1.2	5.1
8		5.71 ± 0.03	685	2.1	4.0
9		5.20 ± 0.03	2228	2.5	3.2
10		< 5	–	3.0	–
11		5.61 ± 0.07	865	2.8	3.3
12		6.56 ± 0.02	96	2.7	4.4
13		7.60 ± 0.02	9	2.4	5.6
14		7.52 ± 0.01	11	2.0	6.0

[a] Apparent K_i ; [b] cLogP, calculated by DataWarrior (v.5.2.1); [c] Lipophilic efficiency, defined as $\mathrm{LipE} = \mathrm{app.\,p}K_i - \mathrm{cLogP}$.

To explore the size of the back pocket, the activity of compounds **15** – **25** (**Table 4.3**) was evaluated. Substitution of the chlorine with an acetylene (**15**) retained potency, whereas substitution with a larger phenyl ring (**16**) reduced potency about 3-fold. Compounds with a phenoxy (**17**) or benzyloxy (**18**) group were tolerated, but not with a phenethyloxy group (**19**), which suggested that a flexible ether linker is allowed, but that its length should not be too large. Substituting phenoxy analogue **17** with a chlorine on the *ortho*-, *meta*- or *para*-position (**23** – **25**) further reduced potency. Similarly, replacing the chlorine of **2** with small heteroaryl groups, such as pyrazole (**20**) or thiophenes (**21**, **22**) showed on average a 10-fold decrease in potency as well.

Table 4.3 | Half maximal inhibitory concentrations (expressed as pIC_{50} ± SEM) of **15** – **25** determined by a fluorescence polarization assay on BUB1 kinase activity (N=2, n=2).



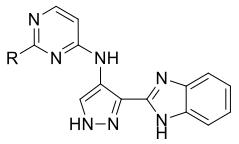
ID	R =	pIC_{50} ± SEM	app. K_i (nM)[a]	cLogP[b]	LipE[c]	tPSA[d]	MW[e]
2		7.13 ± 0.01	26	1.6	5.9	98	411
15		6.96 ± 0.03	39	0.8	6.6	98	400
16		6.61 ± 0.04	86	2.4	4.6	98	453
17		6.45 ± 0.01	125	2.6	4.3	107	469
18		6.41 ± 0.04	138	2.5	4.3	107	483
19		5.67 ± 0.02	758	2.9	3.2	107	497
20		6.08 ± 0.03	294	0.6	5.9	114	442
21		6.28 ± 0.02	184	2.2	4.5	98	459
22		6.11 ± 0.02	272	2.5	4.1	98	459
23		6.01 ± 0.02	347	3.2	3.3	107	503
24		6.18 ± 0.02	234	3.2	3.5	107	503
25		6.09 ± 0.03	289	3.2	3.4	107	503

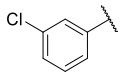
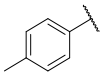
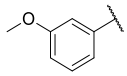
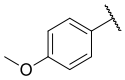
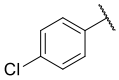
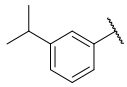
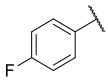
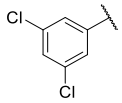
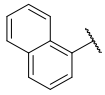
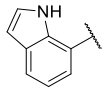
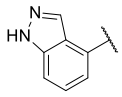
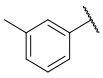
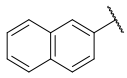
[a] Apparent K_i ; [b] cLogP, calculated by DataWarrior (v.5.2.1); [c] Lipophilic efficiency, defined as $\mathrm{LipE} = \mathrm{app.}\, pK_i - \mathrm{cLogP}$; [d] Topological polar surface area (Å^2), calculated by Chemdraw (v.19.1); [e] Molecular weight (g/mol).

Based on the activity of phenylpyrimidine **16** (Table 4.3), a series of substituted phenylpyrimidines (**26** – **43**) was explored (Table 4.4). For synthetic reasons, this series was initially based on the scaffold lacking the morpholine group. Compared to **16**, unsubstituted phenyl **26** showed a 5-fold decrease in potency upon removal of the morpholine. Substituting the phenyl ring with either electron withdrawing or electron donating groups at

the *para* position (**27** – **30**) further decreased the potency. The presence of small lipophilic groups at the *ortho* (**31**, **32**) or *meta* position (**34**, **35**) retained or gained potency, respectively, whereas compounds with a methoxy-substituent at the *ortho* (**33**) or *meta* (**36**) position lost or retained potency, respectively. A *meta*-pyridyl (**37**) was also not allowed and neither a larger lipophilic isopropyl-substituent (**38**) or a 3,5-dichloro-substitution (**39**) were tolerated. In addition, introduction of fused rings (**40** – **43**) did not improve potency.

Table 4.4 | Half maximal inhibitory concentrations (expressed as pIC_{50} ± SEM) of **26** – **43** determined by a fluorescence polarization assay on BUB1 kinase activity (N=2, n=2).

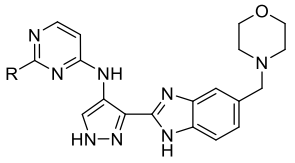


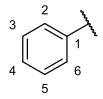
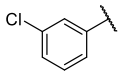
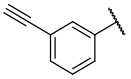
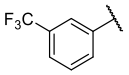
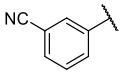
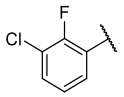
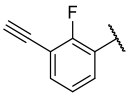
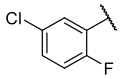
ID	R =	pIC_{50} ± SEM	app. K_i (nM)[a]	ID	R =	pIC_{50}	app. K_i (nM)[a]
26		5.91 ± 0.03	435	**35**		6.37 ± 0.05	151
27		5.74 ± 0.05	643	**36**		6.08 ± 0.07	290
28		5.54 ± 0.03	1016	**37**		< 5	–
29		5.19 ± 0.05	2306	**38**		5.08 ± 0.04	2923
30		< 5	–	**39**		< 5	–
31		5.99 ± 0.03	362	**40**		5.98 ± 0.02	370
32		6.05 ± 0.02	314	**41**		< 5	–
33		5.59 ± 0.03	908	**42**		5.64 ± 0.04	809
34		6.32 ± 0.03	167	**43**		5.21 ± 0.06	2182

[a] Apparent K_i

Next, *meta*-substituents were further explored and introduced to the original benzimidazole-morpholine scaffold (**44** – **50**, Table 4.5). Substituting phenyl **16** with a chlorine (**44**) or acetylene (**45**) at position 3, significantly increased the potency. Strong electron withdrawing groups at this position (**46**, **47**) resulted in a substantial drop in activity. Introduction of an additional fluorine at position 2 in compound **48** or **49** increased the potency 10-fold, thereby providing single digit nanomolar potent inhibitors. Of note, changing the position of the fluorine to position 6 (**50**) boosted potency even further with a 25-fold increase compared to **16**.

Table 4.5 | Half maximal inhibitory concentrations (expressed as pIC_{50} ± SEM) of **44** – **50** determined by a fluorescence polarization assay on BUB1 kinase activity (N=2, n=2).



ID	R =	pIC_{50} ± SEM	app. K_i (nM)[a]	cLogP[b]	LipE[c]	tPSA[d]	MW[e]
16		6.61 ± 0.04	86	2.4	4.6	98	453
44		7.08 ± 0.02	29	3.0	4.5	98	487
45		7.57 ± 0.01	10	2.5	5.5	98	477
46		6.03 ± 0.03	329	3.3	3.2	98	521
47		6.24 ± 0.02	201	2.3	4.4	122	478
48		7.63 ± 0.02	8	3.1	4.9	98	505
49		7.89 ± 0.01	5	2.6	5.7	98	495
50		8.03 ± 0.01	3	3.1	5.4	98	505

[a] Apparent K_i ; [b] cLogP, calculated by DataWarrior (v.5.2.1); [c] Lipophilic efficiency, defined as $\mathrm{LipE} = \mathrm{app.\,p}K_i - \mathrm{cLogP}$; [d] Topological polar surface area (Å^2), calculated by Chemdraw (v.19.1); [e] Molecular weight (g/mol).

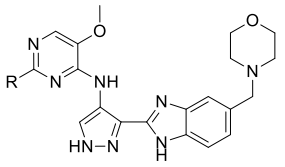
Finally, a series of compounds (**51** – **60**, **Table 4.6**) with mono-, di- and trisubstituted phenyl groups was investigated on the 5-methoxypyrimidine moiety, since this was the most potent scaffold (based on **Table 4.2** and **Table 4.5**). Compounds **51** – **57** showed a 2- to 10-fold increased potency compared to their corresponding analogues **44** – **50**. Compounds with a trifluoromethyl or nitril at position 3 (**53**, **54**) showed the lowest activity among this series, which may be attributed to their strong electron withdrawing property. Potencies of molecules with chlorine (**51**) or acetylene (**52**) at position 3 were high and could be further increased by introducing a fluorine at position 6 (**57**, **58**), but not at position 2 (**55**, **56**). Accordingly, the activities of difluorophenyl substituted **59** and **60** were similar to monofluorophenyl substituted **57** and **58**, respectively. Of note, the most active compounds identified here (**57** – **60**) showed activities near the detection limit (pIC_{50} of 8.79) of the biochemical assay. Overall, this series of substituted phenyl-5-methoxypyrimidines showed several inhibitors with pIC_{50} values near 8 or higher and compound **58** was the most potent inhibitor in this study.

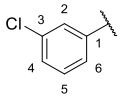
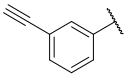
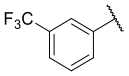
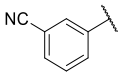
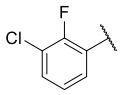
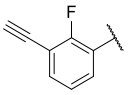
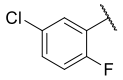
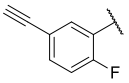
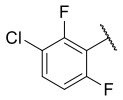
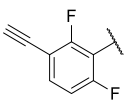
Crystal structure of 58 bound to BUB1

To investigate the binding mode of **58**, the crystal structure of this inhibitor bound to the kinase domain of human BUB1 was determined at 2.1 Å resolution. The inhibitor was well defined by the electron density (**Figure 4.2A**). Compound **58** binds in the ATP-pocket of BUB1 and interacts with the hinge region via multiple hydrogen bonds. The benzimidazole forms a hydrogen bond with the backbone carbonyl of hinge amino acid Tyr869 and hydrophobic interactions were observed with the side chains of Leu793 and Ile924 (**Figure 4.2B**). Two more hydrogen bonds are formed between the pyrazole and hinge residues Tyr869 and Glu867. In addition, the hydrophobic side chains of Val819 and Ile924 interact with the pyrazole. The amine between the pyrazole and pyrimidine forms an intramolecular hydrogen bond with the benzimidazole nitrogen which favors the planar conformation of the molecule. The pyrimidine is sandwiched between the hydrophobic side chains of Ile945 and Val801 and the *N*1 nitrogen forms a water-mediated hydrogen bond with Lys821. The substituted phenyl ring occupies the so called gate area[29] which is located between residues of the DFG-motif (DLG in BUB1), the conserved lysine in β-sheet 3 (Lys821) and the gatekeeper residue (Gly866). The phenyl ring interacts with several residues in close proximity to this area, such as Lys821, Met850 and Phe852. Due to the small size of BUB1's gatekeeper residue (Gly866), a small pocket is available which is occupied by the acetylene moiety (**Figure 4.2D**). This allows for non-polar interactions with Val819, Lys821, Met850, Phe852 and Leu864 and explains the potency increase upon substituting the phenyl ring with this acetylene. The fluorine interacts with aforementioned water molecule, the –NH of DLG-Asp946 as well as with the alkyl side chain of Ile945. To classify **58** to a specific type of kinase inhibitor, the regulatory (R) spine was inspected, which is a spatial motif that consist of four non-consecutive hydrophobic residues.[30] Previous crystallography studies of ADP bound to BUB1's kinase domain revealed that both unphosphorylated[31] and pSer969[32] BUB1 had an assembled R-spine. This indicated that BUB1 is a constitutively active kinase.[32] Compound

58 was found to preserve this assembled R-spine upon BUB1 binding (**Figure 4.2C**) and can therefore be classified as a type I inhibitor.[33]

Table 4.6 | Half maximal inhibitory concentrations (expressed as pIC_{50} ± SEM) of **51** – **60** determined by a fluorescence polarization assay on BUB1 kinase activity (N=2, n=2).



ID	R =	pIC_{50} ± SEM	app. K_i (nM)[a]	cLogP[b]	LipE[c]	tPSA[d]	MW[e]
51		7.96 ± 0.02	3.9	3.0	5.4	107	517
52		8.37 ± 0.02	1.5	2.5	6.2	107	507
53		6.80 ± 0.03	55	3.2	4.0	107	551
54		7.24 ± 0.04	20	2.2	5.5	131	508
55		7.98 ± 0.02	3.7	3.1	5.3	107	535
56		8.34 ± 0.02	1.6	2.6	6.1	107	525
57		8.57 ± 0.02	0.94	3.1	5.9	107	535
58		8.68 ± 0.02	0.74	2.6	6.4	107	525
59		8.62 ± 0.03	0.84	3.2	5.8	107	553
60		8.64 ± 0.02	0.80	2.7	6.3	107	543

[a] Apparent K_i ; [b] cLogP, calculated by DataWarrior (v.5.2.1); [c] Lipophilic efficiency, defined as $\mathrm{LipE} = \mathrm{app.\,p}K_i - \mathrm{cLogP}$; [d] Topological polar surface area (Å^2), calculated by Chemdraw (v.19.1); [e] Molecular weight (g/mol).

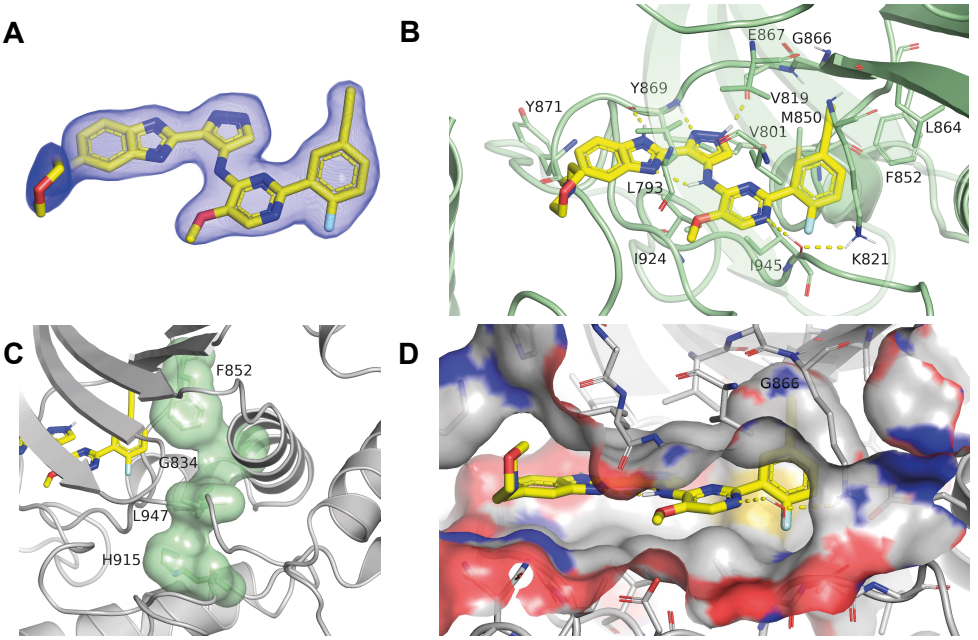
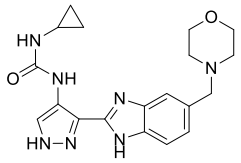
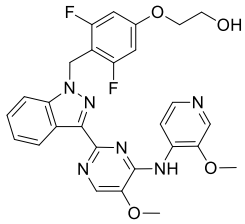
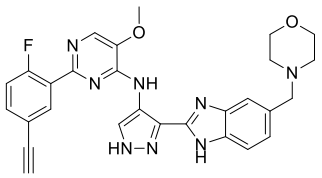


Figure 4.2 | Crystal structure of 58 bound to the kinase domain of human BUB1. **(A)** $2mF_o$-DF_c electron density map of **58** contoured at 1.0 σ. **(B)** Crystal structure of **58** bound to BUB1. Hydrogen bonds are visualized by dashed lines (yellow) and a water molecule is represented by small sticks. β-sheets 1–3 are semi-transparent for visualization purposes. **(C)** Representation of the surface around the R-spine amino acids of BUB1 reveals an intact R-spine. **(D)** Representation of the surface around amino acids within 8 Å from **58**.

Conclusion

In this chapter, the structure-activity relationship of AT-9283 (**1**) on BUB1 kinase inhibition was investigated by the synthesis and biochemical evaluation of 59 analogues based on its structure. Replacement of the cyclopropyl urea of AT-9283 (**1**) by a 2-chloro-4-aminopyrimidine (compound **2**) increased potency. The benzimidazole moiety was found to be crucial for activity and forms a hydrogen bond with the backbone of hinge amino acid Tyr869 of BUB1. In addition, the *N*1 nitrogen of the pyrimidine ring was crucial for activity and forms a water-mediated hydrogen bond with the side chain of Lys821. Substituting the chlorine of the 2-chloro-4-aminopyrimidine **2** with a phenyl ring and optimization of its substitution pattern increased potency significantly. Overall, five compounds (**56** – **60**) matched or exceeded the activity of BAY1816032. Among these compounds, **58** was the most active BUB1 inhibitor found in this study and a crystal structure of this molecule revealed that **58** can be classified as a type I inhibitor.[33] A summary of the activities and physicochemical properties of compound **58**, AT-9283 (**1**) and BAY1816032 is shown in **Table 4.7**. Compound **58** is 100-fold more active compared to original hit **1**. Compound **58** showed excellent activity (apparent K_i = 0.74 nM) and favorable physicochemical properties (cLogP = 2.6, LipE = 6.4, tPSA = 107 Å^2) which are in a similar range or better than the published[6] BUB1 inhibitor BAY1816032.

Table 4.7 | Properties of initial hit **1**, BAY1816032 and optimized hit **58**.

ID	R =	pIC_{50} ± SEM	app. K_i (nM)[a]	cLogP[b]	LipE[c]	tPSA[d]	MW[e]
1		6.66 ± 0.02	77	0.4	6.7	102	381
BAY-1816032		8.34 ± 0.03	1.6	2.9	5.8	113	535
58		8.68 ± 0.02	0.74	2.6	6.4	107	525

[a] Apparent K_i ; [b] cLogP, calculated by DataWarrior (v.5.2.1); [c] Lipophilic efficiency, defined as $\mathrm{LipE} = \mathrm{app.\,p}K_i - \mathrm{cLogP}$; [d] Topological polar surface area (Å^2), calculated by Chemdraw (v.19.1); [e] Molecular weight (g/mol).

Acknowledgements

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Experimental – Biochemistry

Biochemical evaluation of BUB1 inhibitors

Assays were performed in 384-well plates (Greiner, black, flat bottom, 781076) by sequential addition (final concentrations are indicated) of inhibitor (5 µL, 0.3 nM – 1 µM or 3 nM – 10 µM), BUB1/BUB3 (5 µL, 3.26 nM, Carna Biosciences (05-187), lot: 15CBS-0644 D), ATP (5 µL, 15 µM) and BUB1/BUB3 substrate (5 µL, 75 nM, Carna Biosciences (05-187MSSU)), all as 4x working solutions. The final concentration of DMSO was 1%. Assay reactions were stopped by addition of IMAP progressive binding reagent (20 µL, 1200x diluted (see below), Molecular Devices (R8155), lot: 3117896). Each assay included the following controls: (i) a background control (treated with vehicle instead of inhibitor and BUB1/BUB3 substrate), (ii) MIN controls (treated with 5 µM BAY1816032 (MedChem Express) as inhibitor, defined as 0% BUB1 activity) and (iii) MAX controls (treated with vehicle instead of inhibitor, defined as 100% BUB1 activity). All inhibitors were tested in two separate assays and all inhibitor concentrations were tested in duplicate per assay (N=2, n=2).

For each assay, assay buffer (AB) was freshly prepared and consisted of 20 mM HEPES (prepared by diluting 1 M HEPES, pH 7.2), 5 mM $MgCl_2$, 0.01% (v/v) Tween-20 and 1 mM DTT. Stocks of inhibitors (in DMSO) were diluted in AB to obtain 4x working solutions (4% DMSO) and 5 µL was added to the assay plate. BUB1/BUB3 (3.26 µM (486 µg/mL) in storage buffer) was diluted in AB to obtain 13.0 nM of which 5 µL was added to all wells of the assay plate. The assay plate was centrifuged (1 min, 200 *g*) and incubated at RT for 30 min. ATP (4 mM in MilliQ) was diluted in AB to obtain 60 µM of which 5 µL was added to each well. BUB1/BUB3 substrate (1 mM) was diluted in 20 mM HEPES (prepared by diluting 1 M HEPES (pH 7.2) in MilliQ) to obtain 80 µM (this solution was freshly prepared every assay) and further diluted in AB to obtain 300 nM after which 5 µL was added to each well of the assay plate except for background control wells. The assay plate was centrifuged (1 min, 200 *g*) and incubated at RT in the dark for 180 min. IMAP progressive binding buffer A (5x) and IMAP progressive binding buffer B (5x) were mixed in a ratio to obtain 30% buffer A and 70% buffer B, which was subsequently diluted 5x in MilliQ. IMAP progressive binding reagent was diluted 600x in aforementioned mixture of buffer A and B (to obtain a 2x working solution) of which 20 µL was added to each well of the assay plate. The assay plate was centrifuged (1 min, 200 *g*) and incubated at RT in the dark for 90 min. Fluorescence polarization was measured on a CLARIOstar plate reader using the following settings: (i) optic settings → excitation = F: 482-16, dichroic = F: LP 504, emission = F: 530-40, (ii) optic = top optic, (iii) speed/precision = maximum precision, (iv) focus adjustment was performed for every assay and (v) gain adjustment was done by setting the target mP value to 35 mP for one of the MIN control wells. Data was normalized between MIN and MAX controls and data was plotted using GraphPad Prism 8.0 using "Nonlinear regression (curve fit)" and "log(inhibitor) vs. normalized response – Variable slope" to determine pIC_{50} values. The Cheng-Prusoff equation was used to calculate K_i values using 8.13 µM as the apparent K_M of ATP (determined as described in the experimental section of **Chapter 2**).

Protein production

The synthetic construct for BUB1, spanning the residues 725-1085, was ordered from GeneArt (Thermo Fisher). The construct was subcloned in pET-NKI-His-3C-LIC vector[34] for expression in Sf9 cells. Recombinant bacmid for transfection was generated according to the protocols in the Invitrogen manual (Bac-to-Bac® Baculovirus Expression Systems). For expression, 3 L of Sf9 cells were transfected with the P1 virus. The cultures were grown at 27°C for 72 hours. Cells were harvested by centrifugation at 1200 *g* for 10 min and pellets were stored at -20°C. All the steps of the protein purification were carried out at 4 °C. The cell pellet was resuspended in lysis buffer (40 mM HEPES (pH 7.5), 500 mM NaCl, 1 mM TCEP) supplemented with protease inhibitor tablet (Roche). Cells were lysed by sonication (5 sec ON/ 15 sec OFF; 50% amplitude; 150 sec). The lysate was centrifuged at 53,000 *g* for 45 min. The supernatant was incubated with 1 mL of Ni-Sepharose beads on a rotator for 1 h. The beads were washed with 50 mL of washing buffer (40 mM HEPES (pH 7.5), 1 M NaCl, 20 mM imidazole, 1 mM TCEP). The NaCl concentration of the beads was reduced to 100 mM by washing with buffer containing 40 mM HEPES (pH 7.5) and 1 mM TCEP and the protein was eluted with the elution buffer (40 mM HEPES (pH 7.5), 100 mM NaCl, 500 mM imidazole, 1 mM TCEP). The elution fractions containing the protein were pooled together and the

His-tag was cleaved by incubation overnight with 3C-protease. The protein was filtered through a 0.22 µm filter, the NaCl concentration was reduced to 50 mM by dilution with buffer containing 40 mM HEPES pH 7.5 and 1 mM TCEP, and the protein was loaded on a 6 mL ResourceQ anion exchange column. The protein eluted in the flowthrough which was concentrated and loaded onto a Superdex S75 10/300 Increase column, equilibrated with buffer containing 20 mM HEPES (pH 7.5), 150 mM NaCl and 1 mM TCEP. Peak fractions were analyzed by SDS-PAGE, pooled together and concentrated to 14.2 mg/mL.

Crystallization, data collection, structure solution and refinement

Protein was mixed with **58** (1:2 molar ratio, protein:compound), incubated at room temperature for 5 min and briefly centrifuged before setting up the plates. Crystals were obtained in 0.1 M Tris (pH 7.0), 19% PEG 6000 and 0.2 M $CaCl_2$. Crystals were cryoprotected in mother liquor containing 20% glycerol before flash cooling in liquid N_2. Data were collected at the MASSIF-1 beamline at the European synchrotron radiation facility (ESRF). The structure was solved by molecular replacement using BUB1 (PDB: 6F7B)[6] as the search model. Molecular replacement and initial refinement was done by the MOLREP[35] program of the ccp4i2 suite[36]. The CIF and the PDB files for the ligands were generated from the SMILES strings by AceDRG[37]. Ligand fitting was done in Coot[38] and subsequent refinement cycles were carried out in REFMAC[39]. Data collection and refinement statistics are reported in **Table 4.8**. Figures were generated using PyMOL[40].

Table 4.8 | Data collection and structure refinement statistics for human BUB1 kinase domain-**58** complex.

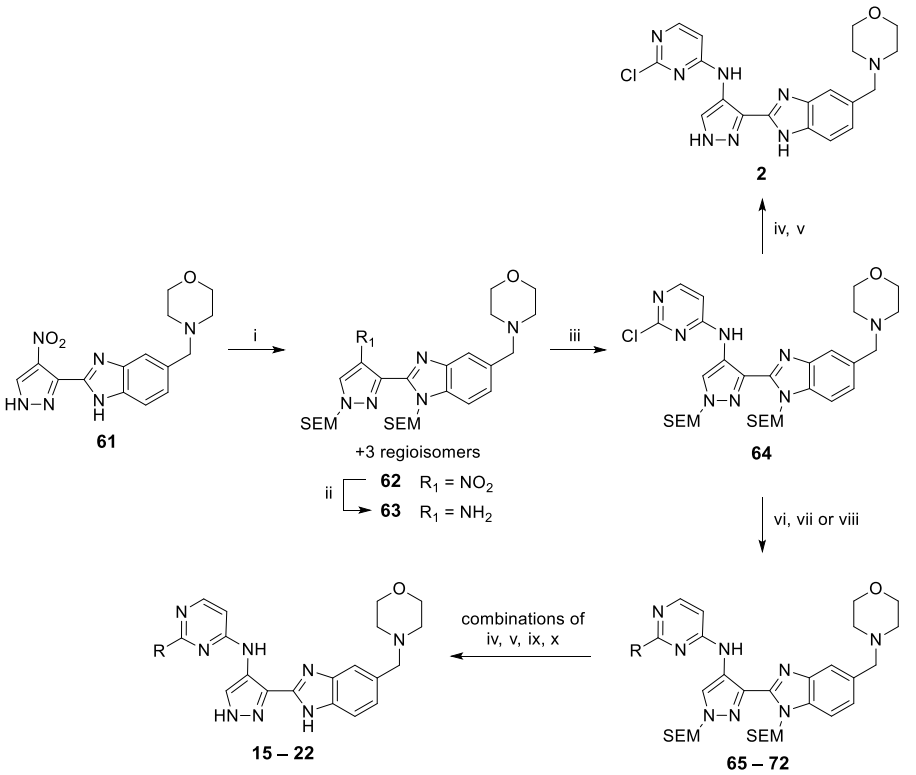
Data Collection[a]	
Wavelength (Å)	0.965
Resolution (Å)	46.52-2.10 (2.16-2.10)
Space Group	P 2_1 2 2_1
Unit Cell a, b, c (Å)	50.27, 59.32, 122.77
Unit Cell α, β, γ (°)	90, 90, 90
$CC_{1/2}$	0.998 (0.536)
R_{merge}	0.044 (0.572)
<I/σ(I)>	16.6 (2.0)
Completeness (%)	99.3 (99.2)
Multiplicity	3.8 (3.6)
Refinement	
Reflections work/test (nr)	20813/1111
Atoms protein/ligand/other (nr)	2803/39/91
B-factors protein/ligand/other ($Å^2$)	50/42/48
R_{work}/R_{free}[b] (%)	20.4/24.9
rmsZ bond lengths/bond angles[b]	0.260/0.519
Model validation	
Ramachandran plot, preferred/outliers[c] (%)	97.3/0.0
Ramachandran Z-score[d]	-0.11 ± 0.50
Rotamers preferred/outliers (%)[c]	96.4/0.3
Rotamer Z-score[d]	-1.06 ± 0.52
Clashscore (%-ile)[c]	99
MolProbity score (%-ile)[c]	100

[a] Values in parenthesis describe the highest resolution shell, [b] As reported by Refmac, [c] As reported by MolProbity, [d] As reported by Tortoize.

Experimental – Chemistry

Synthetic routes

The synthesis of **2** (Scheme 4.1) started from **61**, which is an intermediate for the synthesis of AT-9283 (**1**) and was synthesized as described in Chapter 2.[22] The amines of **61** were protected by SEM groups resulting in the formation of four separable regioisomers (Scheme 4.1). All of these regioisomers could be used in subsequent reactions. The nitro group of **62** was reduced to an amine, which was subsequently used for a nucleophilic aromatic substitution with 2,4-dichloropyrimidine to form **64**. The SEM groups were removed under acidic conditions and required a second reaction with ethylenediamine to completely remove the *N*-hydroxymethyl intermediate[41] to obtain **2**. Intermediate **64** was used to synthesize substituted pyrimidines **15** – **22** by employing series of transformations. A Sonogashira reaction was used to introduce a TMS-protected acetylene (**65**). Suzuki couplings led to the formation of phenylpyrimidine **66** and thiophenes **71** and **72**. Nucleophilic aromatic substitutions were used to synthesize **67** – **70**. Corresponding deprotection methods yielded **15** – **22**.

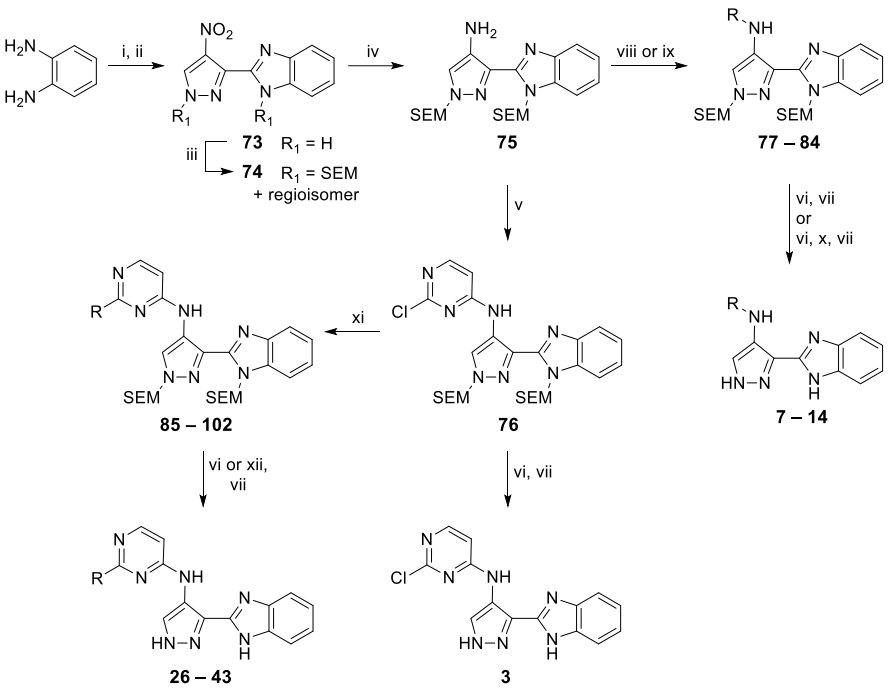


Scheme 4.1 | Synthesis of 2 and 15 – 22. Reagents and conditions: **i)** SEM-Cl, DIPEA, DCM, 0°C → RT, 60%. **ii)** 10% Pd/C, MeOH, 72 – 99%. **iii)** 2,4-dichloropyrimidine, DIPEA, EtOH, 40°C, 54%. **iv)** TFA, DCM. **v)** ethylenediamine, DCM/MeOH (1:1), 50°C. **vi)** ethynyltrimethylsilane, Et_3N, $PdCl_2(PPh_3)_2$, CuI, 89°C, 17%. **vii)** phenylboronic acid (for **66**), thiophene-3-boronic acid pinacol ester (for **71**) or thiophene-2-boronic acid pinacol ester (for **72**), K_2CO_3, Pd(dppf)Cl_2·DCM, dioxane/H_2O (4:1), 90°C. **viii)** phenol (for **67**), benzyl alcohol (for **68**), phenethyl alcohol (for **69**) or 1*H*-pyrazole (for **70**), NaH, dioxane, 0 → 90°C, 44 – 71%. **ix)** TBAF, THF, RT or 80°C (sealed tube). **x)** HCl (in dioxane), EtOH or DCM, 50°C (sealed tube).

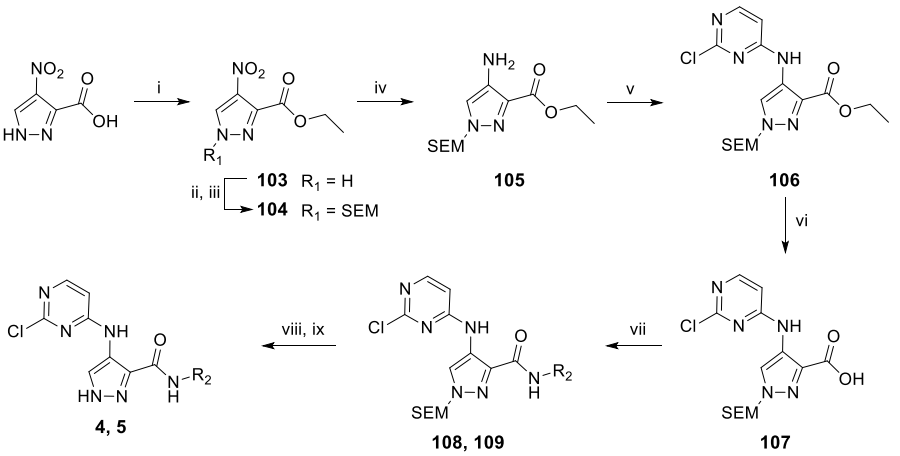
Next, compound **3**, which lacked the morpholine group, was synthesized as depicted in Scheme 4.2. Benzene-1,2-diamine was coupled to 4-nitro-1*H*-pyrazole-3-carboxylic acid and subsequently cyclized to form benzimidazole **73**. *N*-SEM protection resulted in the formation of two separable regioisomers and by applying the reaction sequence as described for the synthesis of **2** (Scheme 4.1), compound **3** was obtained. Aminopyrazole **75** and chloropyrimidine **76** were used for the synthesis of a small library

of analogues (**7** – **14** and **26** – **43**, respectively). Synthesis of **7** – **14** proceeded via **77** – **84** by performing either Buchwald-Hartwig aminations or nucleophilic aromatic substitutions with **75** followed by SEM deprotection. For the synthesis of **26** – **43**, Suzuki couplings with **76** provided intermediates **85** – **102** and subsequent SEM deprotection afforded the desired products.

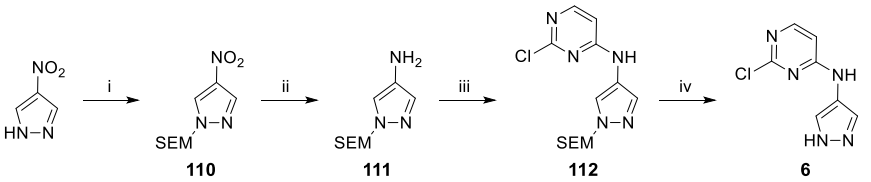
Compound **4** and **5**, in which the benzimidazole was substituted by amides, were synthesized as depicted in **Scheme 4.3** and started with esterification of 4-nitro-1*H*-pyrazole-3-carboxylic to obtain **103**. *N*-SEM protection and subsequent SEM-switch procedure[42] led to the formation of one SEM-protected regioisomer (**104**). Nitro reduction and nucleophilic aromatic substitution formed chloropyrimidine **106**. Mild ester hydrolysis[43] resulted in the formation of **107** of which the carboxylic acid was coupled to different amines to form **4** and **5** after SEM deprotection. A part of this reaction sequence was performed to synthesize compound **6** (**Scheme 4.4**), which completely lacked the benzimidazole.



Scheme 4.2 | Synthesis of 3, 7 – 14 and 26 – 43. Reagents and conditions: **i)** 4-nitro-1*H*-pyrazole-3-carboxylic acid, EDC·HCl, HOBt, DMF. **ii)** AcOH, 118°C, 70%. **iii)** SEM-Cl, DIPEA, DCM, 0°C → RT, 81%. **iv)** 10% Pd/C, MeOH, 95%. **v)** 2,4-dichloropyrimidine, DIPEA, EtOH, 40°C, 74%. **vi)** TFA, DCM. **vii)** ethylenediamine, DCM/MeOH (1:1), RT or 50°C, 20% – quant. **viii)** corresponding (hetero)aryl halide, xantphos, Cs_2CO_3, $Pd(OAc)_2$, DMF, 90°C, 34 – 76%. **ix)** corresponding chloropyrimidine, DIPEA, EtOH, 40°C or 50°C, 45 – 63%. **x)** HCl (aq.), MeOH. **xi)** corresponding boronic acid (pinacol ester), K_2CO_3, $Pd(dppf)Cl_2$·DCM, dioxane/H2O (4:1), 90°C, 18 – 92%. **xii)** TBAF, THF, 80°C (sealed tube).

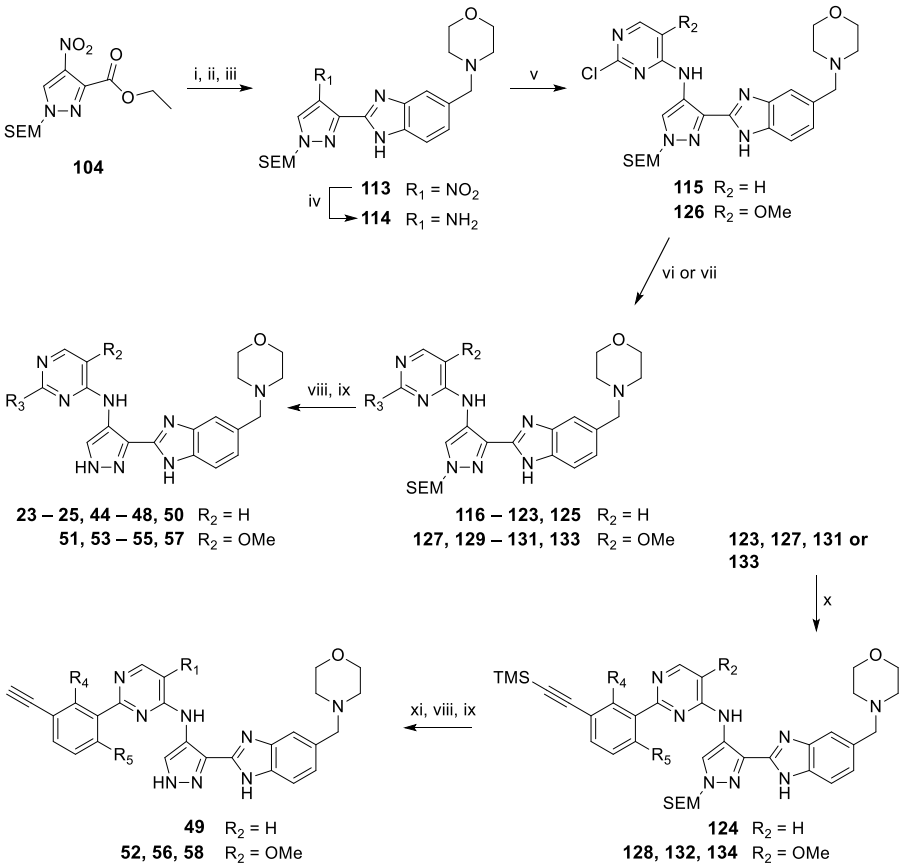


Scheme 4.3 | Synthesis of 4 and 5. Reagents and conditions: **i)** $SOCl_2$, EtOH, 0°C – RT, 96%. **ii)** SEM-Cl, DIPEA, DCM, 0°C – RT. **iii)** SEM-Cl (5 mol%), MeCN, 95°C, microwave irradiation, 83%. **iv)** 10% Pd/C, EtOH, 99%. **v)** 2,4-dichloropyrimidine, DIPEA, EtOH, 70°C, 90%. **vi)** Et_3N, LiBr, MeCN/H2O (50:1), quant. **vii)** aniline (for **108**) or methylamine (33 wt. % in EtOH, for **109**), EDC·HCl, DCM, 58 – 75%. **viii)** TFA, DCM. **ix)** ethylenediamine, DCM/MeOH (1:1), 50°C, 46 – 52%.

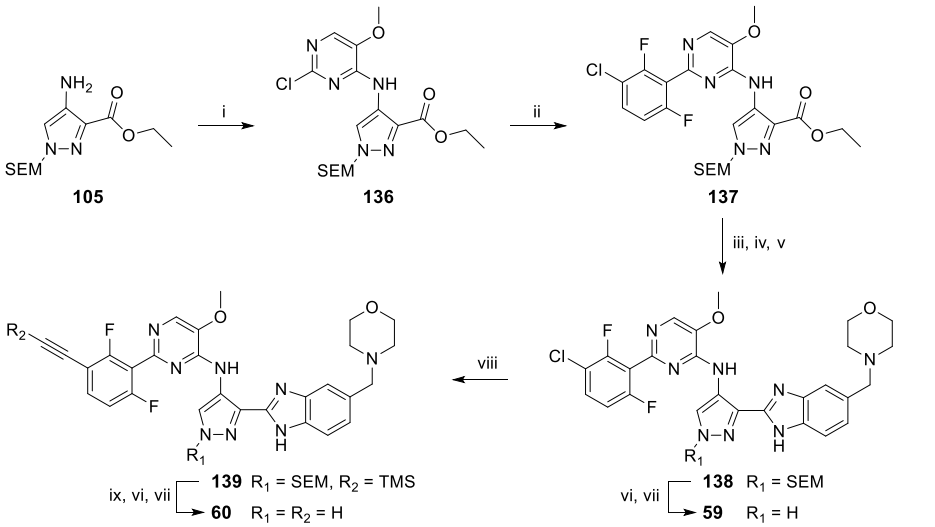


Scheme 4.4 | Synthesis of 6. Reagents and conditions: **i)** SEM-Cl, DIPEA, DCM, 0°C – RT, quant. **ii)** 10% Pd/C, MeOH, 82%. **iii)** 2,4-dichloropyrimidine, DIPEA, EtOH, 64%. **iv)** TFA, DCM, 86%.

Alternatively to the synthetic route as depicted in **Scheme 4.1**, a small library of analogues (**23** – **25** and **44** – **58**) containing the morpholine group was synthesized according to **Scheme 4.5**. The ester of **104** (synthesized as depicted in **Scheme 4.3**) was saponified, coupled to 4-(morpholinomethyl)benzene-1,2-diamine (synthesized as described in **Chapter 2**) and cyclized to form benzimidazole **113**. Nitro reduction and subsequent nucleophilic aromatic substitution with either 2,4-dichloropyrimidine or 2,4-dichloro-5-methoxypyrimidine yielded **115** and **126**, respectively. From these two intermediates, either Suzuki couplings or nucleophilic aromatic substitutions were performed to obtain substituted pyrimidines. Of these substituted pyrimidines, 3-chlorophenyl analogues **123**, **127**, **131** and **133** were also subjected to a Stille coupling to transform the chlorine into a TMS protected acetylene to form **124**, **128**, **132** and **134**.[44,45] SEM or TMS and SEM group deprotection of intermediates **116** – **125** and **127** – **134** resulted in the formation of **23** – **25** and **44** – **58**. Synthesis of **59** and **60** was performed according to **Scheme 4.6** and started from **105** (synthesized as depicted in **Scheme 4.3**) to which a 2-chloro-5-methoxypyrimidine was introduced. Subsequent coupling of the chloro-difluorophenyl proved to be challenging due to deboronation of the boronic acid and therefore required different Suzuki coupling conditions[46] to yield **137**. Analogous to the synthetic route as depicted in **Scheme 4.5**, compound **59** and **60** were subsequently obtained.



Scheme 4.5 | Synthesis of 23 – 25 and 44 – 58. Reagents and conditions: **i)** LiOH, MeOH/H2O (1:1). **ii)** 4-(morpholinomethyl)benzene-1,2-diamine (synthesized in **Chapter 2**, compound 28), EDC·HCl, HOBt, DMF. **iii)** AcOH, 118°C, 58%. **iv)** 10% Pd/C, MeOH, 97%. **v)** 2,4-dichloropyrimidine (for **115**) or 2,4-dichloro-5-methoxypyrimidine (for **126**), DIPEA, EtOH, RT or 40°C, 66 – 70%. **vi)** corresponding boronic acid (pinacol ester), K_2CO_3, Pd(dppf)Cl_2·DCM, dioxane/H2O (4:1), 90°C, 28 – 82%. **vii)** 2-chlorophenol (for **116**), 3-chlorophenol (for **117**) or 4-chlorophenol (for **118**), K_2CO_3, dioxane, 120°C (sealed tube), 81 – 91%. **vii)** TFA, DCM. **ix)** ethylenediamine, DCM/MeOH (1:1), RT or 50°C, 44 – 90%. **x)** trimethyl((tributylstannyl)ethynyl)silane, XPhos, $Pd_2(dba)_3$, THF, 135°C (sealed tube), 78 – 96%. **xi)** TBAF, THF.



Scheme 4.6 | Synthesis of 59 and 60. Reagents and conditions: **i)** 2,4-dichloro-5-methoxypyrimidine, DIPEA, EtOH, 50°C, 78%. **ii)** (3-chloro-2,6-difluorophenyl)boronic acid, K_2CO_3, XPhos Pd G2, THF/H2O (1:2). **iii)** LiOH, MeOH/H2O (1:1), DCM, 65°C. **iv)** 4-(morpholinomethyl)benzene-1,2-diamine (synthesized in **Chapter 2**, compound 28), EDC·HCl, HOBt, DMF. **v)** AcOH, 118°C, 9% over two steps. **vi)** TFA, DCM. **vii)** ethylenediamine, DCM/MeOH (1:1), 88 – 95%. **viii)** trimethyl((tributylstannyl)ethynyl)silane, XPhos, $Pd_2(dba)_3$, THF, 135°C (sealed tube), quant. **ix)** TBAF, THF.

General procedures

All reagents were purchased from chemical suppliers (Fluorochem, Sigma-Aldrich, Merck, Fisher Scientific) and used without further purification. Solvents (Honeywell, VWR, Biosolve) indicated with "dry" were stored on activated 3 Å (EtOH) or 4 Å (other solvents) molecular sieves (8 to 12 mesh, Acros Organics). Solvents indicated by "degassed" were sonicated while bubbling N_2 through the solvent for 20 min. All reactions were performed at room temperature (RT) under a nitrogen atmosphere, unless stated otherwise. Microwave reactions were performed in a Biotage Initiator+ reactor. Reactions were monitored by thin layer chromatography (TLC, silica gel 60, UV_{254}, Macherey-Nagel, ref: 818333) and compounds were visualized by UV absorption (254 nm and/or 366 nm) or spray reagent (permanganate (5 g/L $KMnO_4$, 25 g/L K_2CO_3)) followed by heating. Alternatively, reactions were monitored by liquid chromatography-mass spectrometry (LCMS), either on a Thermo Finnigan (Thermo Finnigan LCQ Advantage MAX ion-trap mass spectrometer (ESI+) coupled to a Surveyor HPLC system (Thermo Finnigan) equipped with a Nucleodur C18 Gravity column (50x4.6 mm, 3 µm particle size, Macherey-Nagel)) or a Thermo Fleet (Thermo LCQ Fleet ion-trap mass spectrometer (ESI+) coupled to a Vanquish UHPLC system). LCMS eluent consisted of MeCN in 0.1% TFA (aq.) and LCMS methods were as follows: 0.5 min cleaning with starting gradient, 8 min using specified gradient (linear), 2 min cleaning with 90% MeCN in 0.1% TFA (aq.). LCMS data is reported as follows: instrument (Finnigan or Fleet), gradient (% MeCN in 0.1% TFA (aq.)), retention time (t_r) and mass (as m/z: $[M+H]^+$). Purity of final compounds was determined to be ≥ 95% by integrating UV intensity of spectra generated by either of the LCMS instruments. ^1H and ^{13}C NMR spectra were recorded on a Bruker AV300 (300 and 75 MHz, respectively), Bruker AV400 (400 and 101 MHz, respectively), Bruker AV500 (500 and 126 MHz, respectively) or Bruker AV600 (600 and 150 MHz, respectively) NMR spectrometer. NMR samples were prepared in deuterated chloroform, methanol or DMSO. Chemical shifts are given in ppm (δ) relative to residual protonated solvent signals ($CDCl_3$ → δ 7.260 (^1H), δ 77.160 (^{13}C), MeOD → δ 3.310 (^1H), δ 49.000 (^{13}C), DMSO → δ 2.500 (^1H), δ 39.520 (^{13}C)). Data was processed by using MestReNova (v. 14) and is reported as follows: chemical shift (δ), multiplicity, coupling constant (*J* in Hz) and integration. Multiplicities are abbreviated as follows: s = singlet, br s = broad singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets, td = triplet of doublets, t = triplet, dt = doublet of triplets, q = quartet, hept = heptet, m = multiplet, br m = broad multiplet. For some molecules about 1:1 rotamer and/or tautomer peaks were observed, resulting in extra splitting of peaks. For these compounds, chemical shifts were

reported as ranges and multiplicity was denoted by "2x", followed by the multiplicities specified above (i.e. 2x d = twice a doublet). The reported coupling constant corresponds to either of the multiplet peaks (of note, coupling constants were the same for both multiplet peaks). Purification was done either by manual silica gel column chromatography (using 40-63 µm, 60 Å silica gel, Macherey-Nagel) or automated flash column chromatography on a Biotage Isolera machine (using pre-packed cartridges with 40-63 µm, 60 Å silica gel (4, 12, 25 or 40 g), Screening Devices). High-performance liquid chromatography (HPLC) purifications were performed on either an Agilent 1200 preparative HPLC system (equipped with a Gemini C18 column (250x10 mm, 5 µm particle size, Phenomenex) coupled to a 6130 quadrupole mass spectrometer) or a Waters Acquity UPLC system (equipped with a Gemini C18 column (150x21 mm, 5 µm particle size, Phenomenex) coupled to a SQ mass spectrometer). Specified gradients for HPLC purifications (MeCN in 0.2% TFA (aq.)) were linear (5 mL/min for 12 min (Agilent) or 25 mL/min for 10 min (Waters)). High resolution mass spectrometry (HRMS) spectra were recorded through direct injection of a 1 µM sample either on a Thermo Scientific Q Exactive Orbitrap equipped with an electrospray ion source in positive mode coupled to an Ultimate 3000 system (source voltage = 3.5 kV, capillary temperature = 275 °C, resolution R = 240,000 at m/z 400, external lock, mass range m/z = 150-2000) or on a Synapt G2-Si high definition mass spectrometer (Waters) equipped with an electrospray ion source in positive mode (ESI-TOF) coupled to a NanoEquity system with Leu-enkephalin (m/z = 556.2771) as internal lock mass. The eluent for HRMS measurements consisted of a 1:1 (v/v) mixture of MeCN in 0.1% formic acid (aq.) using a flow of 25 mL/min. Compound names were generated by ChemDraw (v. 19.1.21).

General procedure A – SEM deprotection

SEM-protected amine starting material was dissolved in DCM (2 mL) after which TFA (2 mL) was added dropwise. The mixture was stirred for the indicated time and subsequently concentrated under a flow of N_2. The mixture was suspended in EtOAc (25 mL) and poured into 1 M $NaHCO_3$ (aq.) (20 mL). The organic layer was separated and the water layer extracted with EtOAc (1 or 2x25 mL). The combined organic layers were concentrated as such, suspended/dissolved in 1:1 MeOH/DCM (2 mL) and transferred to a microwave vial. Ethylenediamine (50 µL, 746 µmol) was added after which the vial was sealed and the mixture was stirred at 50°C for 30 – 60 min. The mixture was poured into H_2O (20 mL) and when required, brine (0.5 – 1 mL) was added, and the product extracted with EtOAc (2x20 mL). The combined organic layers were concentrated as such. Purification was performed as indicated.

General procedure B – SEM deprotection

SEM-protected amine starting material was dissolved in DCM (0.5 mL) after which TFA (0.5 mL) was added dropwise. The mixture was stirred for the indicated time and subsequently quenched by addition of sat. $NaHCO_3$ (aq.) (20 mL). The product was extracted with EtOAc (2x20 mL) and the combined organic layers were concentrated as such. The mixture was suspended/dissolved in 1:1 MeOH/DCM (3 mL) and ethylenediamine (50 µL, 746 µmol) was added after which the mixture was stirred for 1 h. The mixture was poured into H_2O (20 mL) and when required, brine (1 mL) was added, and the product extracted with EtOAc (2x20 mL). The combined organic layers were concentrated as such. Purification was performed as indicated.

General procedure C – SEM deprotection

A microwave vial was charged with SEM-protected amine starting material dissolved in DCM (± 0.2 M) after which HCl (4 M in dioxane, 24 eq.) was added and the vial was sealed. The mixture was stirred at 50°C for the indicated time and subsequently concentrated. The mixture was dissolved in $CHCl_3$ (20 mL) and poured into 1 M $NaHCO_3$ (aq.) (20 mL). The organic layer was separated and the water layer extracted with $CHCl_3$ (20 mL). The combined organic layers were concentrated as such and purified as indicated.

General procedure D – TMS and SEM deprotection

TMS- and SEM-protected starting material was dissolved in TBAF (1 M in THF, 0.5 mL) and the mixture was stirred for 1.5 h. The mixture was poured into H_2O (20 mL) and brine (1 mL), and the intermediate extracted with EtOAc (2x15 mL). The combined organic layers were concentrated as such. The intermediate was dissolved in DCM (0.5 mL) after which TFA (0.5 mL) was added dropwise. The mixture

was stirred for the indicated time and subsequently quenched by addition of sat. $NaHCO_3$ (aq.) (15 mL). The product was extracted with EtOAc (2x15 mL) and the combined organic layers were concentrated as such. The mixture was suspended/dissolved in 1:1 MeOH/DCM (3 mL) and ethylenediamine (50 µL, 746 µmol) was added after which the mixture was stirred for 1 h. The mixture was poured into H_2O (20 mL) and when required, brine (1 mL) was added, and the product extracted with EtOAc (2x15 mL). The combined organic layers were concentrated as such. Purification was performed as indicated.

General procedure E – Buchwald coupling

A microwave vial was charged with **75** (150 mg, 326 µmol), Cs_2CO_3 (319 mg, 979 µmol), xantphos (28.3 mg, 48.9 µmol), indicated (hetero)aryl halide (359 µmol) and DMF (1.5 mL). N_2 was bubbled through the mixture for 1 min after which $Pd(OAc)_2$ (7.3 mg, 33 µmol) was added. N_2 was bubbled through the mixture for 30 sec after which the vial was sealed and the mixture was stirred at 90°C for 16 h. The mixture was diluted in EtOAc (15 mL) and filtered over Celite. The filtrate was diluted in EtOAc (15 mL) and poured into H_2O (30 mL) and brine (2 mL). The organic layer was isolated and the water layer extracted with EtOAc (30 mL). The combined organic layers were washed with brine (30 mL) and concentrated as such. Purification was performed as indicated.

General procedure F – Suzuki coupling

A microwave vial was charged with **76** (300 mg, 524 µmol), K_2CO_3 (290 mg, 2.10 mmol), corresponding boronic acid (786 µmol) and $Pd(dppf)Cl_2$·DCM (30 mg, 37 µmol) after which the vial was sealed. The tube was evacuated and backfilled with argon (3x) via a Schlenk setup after which degassed 4:1 dioxane/H_2O (2.6 mL) was added. The mixture was heated to 90°C, stirred for 16 h and subsequently poured into H_2O (30 mL). The product was extracted with EtOAc (2x30 mL) and the combined organic layers were concentrated as such. Purification was performed as indicated.

General procedure G – Suzuki coupling

A microwave vial was charged with 2-chloropyrimidine analogue (1 eq.), K_2CO_3 (4 eq.), corresponding boronic acid (pinacol ester) (1.02 – 1.5 eq.) and 4:1 dioxane/H_2O (0.2 M). N_2 was bubbled through the mixture for 1 min after which $Pd(dppf)Cl_2$·DCM (0.07 eq.) was added. N_2 was bubbled through the mixture for 30 sec after which the vial was sealed. The mixture was heated to 90°C, stirred for indicated time and subsequently poured into H_2O (20 mL) and when required, brine (1 mL) was added. The product was extracted with DCM (2x20 mL) and the combined organic layers were concentrated as such. Purification was performed as indicated.

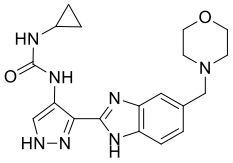
General procedure H – Stille coupling

A microwave vial was charged with chlorophenyl analogue (1 eq.), XPhos (0.6 eq.) and $Pd_2(dba)_3$ (0.15 eq.). THF (0.15 M) was added and N_2 was bubbled through the mixture for 30 sec after which the vial was sealed and trimethyl((tributylstannyl)ethynyl)silane (1.5 eq.) was added via syringe. The vial was put into a heating block and the top of the vial was covered with cotton and aluminum foil. The mixture was heated to 135°C and stirred for 1 h. The mixture was cooled down to RT and filtered over a pre-wetted mixture of K_2CO_3/silica gel (~750 mg/10 mL). Elution was done by EtOAc (10 mL) and subsequently 5% MeOH/EtOAc (4x10 mL). Product containing fractions were concentrated and purified as indicated.

General procedure I – Nucleophilic aromatic substitution

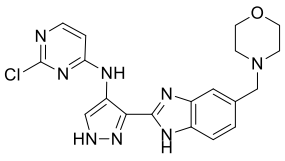
A microwave vial was charged with **115** (90.0 mg, 166 µmol), K_2CO_3 (46.0 mg, 333 µmol) and dry dioxane (0.2 mL) after which corresponding phenol analogue (1.05 eq.) was added. The vial was sealed, stirred at 120°C for 16 h and subsequently poured into H_2O (20 mL). The product was extracted with DCM (2x20 mL) and the combined organic layers were concentrated as such. Purification was done by automated column chromatography (0 – 25% MeOH/DCM) to afford the product.

1-Cyclopropyl-3-(3-(5-(morpholinomethyl)-1*H*-benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)urea (1)



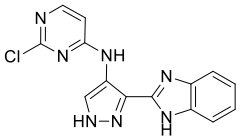
The title compound was synthesized as described in **Chapter 2** (compound 1).

2-Chloro-*N*-(3-(5-(morpholinomethyl)-1*H*-benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)pyrimidin-4-amine (2)



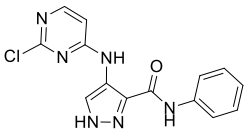
64 (77.0 mg, 115 µmol) was dissolved in DCM (1 mL) after which TFA (1 mL) was added and the mixture was stirred for 16 h. The mixture was concentrated under a flow of N_2, suspended in $CHCl_3$ (20 mL) and poured into sat. $NaHCO_3$ (aq.) (20 mL). The organic layer was separated, the water layer extracted with $CHCl_3$ (2x20 mL) and the combined organic layers were concentrated as such. The crude was dissolved in 1:1 MeOH/DCM (1 mL) and transferred to a microwave vial. Ethylenediamine (50 µL, 746 µmol) was added after which the vial was sealed and the mixture was stirred at 50°C for 1 h. The mixture was poured into H_2O (20 mL) and the product extracted with $CHCl_3$ (2x15 mL). The combined organic layers were concentrated as such. The crude was purified by automated column chromatography (2 – 15% MeOH/DCM) to afford the product (22.4 mg, 54.5 µmol, 48%). ^{1}H NMR (500 MHz, MeOD) δ 8.37 (br s, 1H), 8.05 (d, *J* = 6.0 Hz, 1H), 7.71 – 7.42 (br m, 2H), 7.22 (d, *J* = 8.2 Hz, 1H), 6.86 (d, *J* = 5.9 Hz, 1H), 3.71 – 3.66 (m, 4H), 3.61 (s, 2H), 2.53 – 2.45 (m, 4H). ^{13}C NMR (126 MHz, MeOD) δ 161.50, 156.76, 148.86, 144.09, 134.27, 132.68, 126.01, 125.62, 122.23, 121.96, 120.76, 119.16, 113.36, 112.05, 107.18, 67.71, 64.71, 54.61 (not all quaternary carbons were observed). LCMS (Fleet, 0 → 50%): t_r = 4.74 min, m/z: 411.3. HRMS $[C_{19}H_{19}ClN_8O + H]^+$: 411.14431 calculated, 411.1444 found.

***N*-(3-(1*H*-Benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)-2-chloropyrimidin-4-amine (3)**



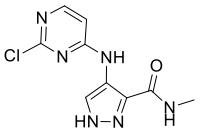
76 (58.0 mg, 101 µmol) was treated as described for the preparation of compound **2**. The crude was purified by automated column chromatography (30% EtOAc/DCM) to afford the product (8.5 mg, 27 µmol, 29%). ^{1}H NMR (500 MHz, DMSO) δ 13.51 (br s, 2H), 10.29 (br s, 1H), 8.34 (s, 1H), 8.21 (d, *J* = 5.9 Hz, 1H), 7.69 – 7.62 (m, 2H), 7.32 – 7.25 (m, 2H), 7.04 (br s, 1H). ^{13}C NMR (126 MHz, DMSO) δ 160.14 (br), 159.57, 156.93 (br), 146.40 (br), 136.91 (br), 130.98 (br), 122.90, 121.68 (br), 120.59, 114.89 (br), 106.63 (br). LCMS (Finnigan, 0 → 90%): t_r = 4.82 min, m/z: 312.1. HRMS $[C_{14}H_{10}ClN_7 + H]^+$: 312.07590 calculated, 312.0764 found.

4-((2-Chloropyrimidin-4-yl)amino)-*N*-phenyl-1*H*-pyrazole-3-carboxamide (4)



The title compound was synthesized from **108** (76.3 mg, 171 µmol) according to general procedure A (reaction time: 3 h). The crude was purified by automated column chromatography (15 – 55% EtOAc/DCM) to afford the product (28 mg, 89 mmol, 52%). ^{1}H NMR (400 MHz, DMSO) δ 13.50 (br s, 1H), 10.26 (s, 1H), 9.69 (br s, 1H), 8.35 (s, 1H), 8.16 (d, *J* = 5.9 Hz, 1H), 7.84 (d, *J* = 7.3 Hz, 2H), 7.36 – 7.30 (m, 2H), 7.22 – 7.05 (m, 2H). ^{13}C NMR (101 MHz, DMSO) δ 161.86 (br), 160.21 (br), 159.44, 156.77 (br), 138.42, 133.55 (br), 128.60, 123.76, 122.55 (br), 121.42 (br), 120.55, 106.68 (br). LCMS (Fleet, 10 → 90%): t_r = 5.91 min, m/z: 315.2. HRMS $[C_{14}H_{11}ClN_6O + H]^+$: 315.07556 calculated, 315.07550 found.

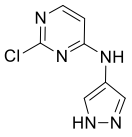
4-((2-Chloropyrimidin-4-yl)amino)-*N*-methyl-1*H*-pyrazole-3-carboxamide (5)



The title compound was synthesized from **109** (46.1 mg, 120 µmol) according to general procedure A (reaction time: 4 h). The crude was loaded onto Celite and purified by automated column chromatography (15 – 100% EtOAc/DCM) to afford the product (14 mg, 55 µmol, 46%). ^{1}H NMR (500 MHz, DMSO) δ 13.21 (br s, 1H), 9.76 (br s, 1H), 8.37 – 8.30 (m, 1H), 8.25 (s, 1H), 8.14 (d, *J* = 5.9 Hz, 1H), 7.06 (br s,

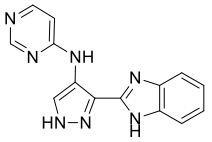
1H), 2.78 (d, *J* = 4.5 Hz, 3H). ^{13}C NMR (126 MHz, DMSO) δ 163.62, 159.92 (br), 159.43, 156.65 (br), 133.17 (br), 121.99, 120.81 (br), 106.59 (br), 25.29. LCMS (Fleet, 10 → 90%): t_r = 3.47 min, m/z: 253.2. HRMS $[C_9H_9ClN_6O + H]^+$: 253.05991 calculated, 253.05970 found.

2-Chloro-*N*-(1*H*-pyrazol-4-yl)pyrimidin-4-amine (6)



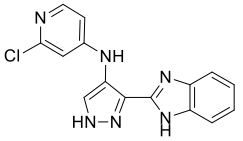
112 (70.0 mg, 215 µmol) was dissolved in DCM (1 mL) after which TFA (1 mL) was added dropwise. The mixture was stirred for 2 h and subsequently concentrated under a flow of N_2. The mixture was dissolved in $CHCl_3$ (20 mL) and poured into 1 M $NaHCO_3$ (aq.) (20 mL). The organic layer was separated and the water layer extracted with $CHCl_3$ (2x20 mL) and subsequently with EtOAc (2x20 mL). The combined organic layers were concentrated as such and purified by automated column chromatography (5% MeOH/DCM) to afford the product (36.0 mg, 184 µmol, 86%). ^{1}H NMR (500 MHz, MeOD) δ 7.97 (d, *J* = 6.0 Hz, 1H), 7.84 (br s, 2H), 6.56 (d, *J* = 6.0 Hz, 1H). ^{13}C NMR (126 MHz, MeOD) δ 162.01, 161.54, 156.20, 127.09 (br), 122.67, 106.35. LCMS (Finnigan, 0 → 90%): t_r = 4.22 min, m/z: 196.1. HRMS $[C_7H_6ClN_5 + H]^+$: 196.03845 calculated, 196.0387 found.

N-(3-(1*H*-Benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)pyrimidin-4-amine (7)



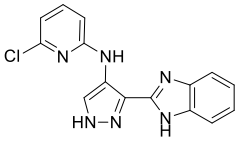
The title compound was synthesized from **77** (59.2 mg, 110 µmol) according to general procedure A (reaction time: 2 h). The crude was purified by automated column chromatography (25 – 55% EtOAc/DCM) to afford the product (27.8 mg, 80.3 µmol, 52%). ^{1}H NMR (500 MHz, DMSO) δ 13.09 (br s, 2H), 10.06 (br s, 1H), 8.72 (d, *J* = 0.8 Hz, 1H), 8.48 (s, 1H), 8.32 (d, *J* = 6.0 Hz, 1H), 7.67 – 7.58 (m, 2H), 7.25 – 7.20 (m, 2H), 7.07 (dd, *J* = 5.9, 1.2 Hz, 1H). ^{13}C NMR (126 MHz, DMSO) δ 158.38, 158.25, 155.22, 147.46, 130.68 (br), 122.21, 121.70, 120.21 (br), 114.68 (br), 107.17 (br) (not all quaternary carbons were observed). LCMS (Finnigan, 0 → 50%): t_r = 4.81 min, m/z: 278.3. HRMS $[C_{14}H_{11}N_7 + H]^+$: 278.11487 calculated, 278.11462 found.

N-(3-(1*H*-Benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)-2-chloropyridin-4-amine (8)



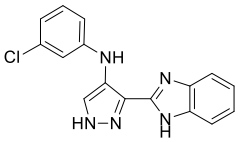
The title compound was synthesized from **78** (142 mg, 248 µmol) according to general procedure A (reaction time: 3 h). The crude was purified by automated column chromatography (70 – 100% EtOAc/DCM) to afford the product (49.5 mg, 159 µmol, 64%). ^{1}H NMR (500 MHz, DMSO) δ 13.45 (br s, 1H), 12.96 (br s, 1H), 9.36 (s, 1H), 8.28 (s, 1H), 8.01 (d, *J* = 5.6 Hz, 1H), 7.78 – 7.44 (br m, 2H), 7.24 – 7.17 (m, 2H), 6.99 – 6.92 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 152.83, 151.38, 149.67, 146.94, 143.20 (br), 133.76 (br), 133.44, 122.61 (br), 121.75, 121.37, 118.68 (br), 111.54 (br), 108.67, 107.18. LCMS (Finnigan, 0 → 50%): t_r = 5.52 min, m/z: 311.2. HRMS $[C_{15}H_{11}ClN_6 + H]^+$: 311.08065 calculated, 311.08044 found.

N-(3-(1*H*-Benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)-6-chloropyridin-2-amine (9)



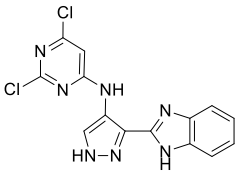
The title compound was synthesized from **79** (102 mg, 178 µmol) according to general procedure A (reaction time: 3 h). The crude was purified by automated column chromatography (15 – 50% EtOAc/DCM) to afford the product (29.6 mg, 95.2 µmol, 54%). ^{1}H NMR (500 MHz, DMSO) δ 13.06 (br s, 2H), 9.91 (br s, 1H), 8.36 (s, 1H), 7.64 (dd, *J* = 8.2, 7.5 Hz, 1H), 7.61 (br s, 2H), 7.26 – 7.19 (m, 2H), 7.00 (d, *J* = 8.2 Hz, 1H), 6.82 (d, *J* = 7.5 Hz, 1H). ^{13}C NMR (126 MHz, DMSO) δ 154.26, 148.29, 147.71, 140.34, 130.10 (br), 122.92, 122.15, 118.49 (br), 112.74, 108.64 (not all quaternary carbons were observed). LCMS (Finnigan, 10 → 90%): t_r = 5.06 min, m/z: 311.2. HRMS $[C_{15}H_{11}ClN_6 + H]^+$: 311.08065 calculated, 311.08054 found.

3-(1*H*-Benzo[*d*]imidazol-2-yl)-*N*-(3-chlorophenyl)-1*H*-pyrazol-4-amine (10)



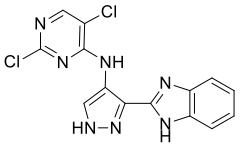
80 (125 mg, 219 µmol) was dissolved in DCM (2 mL) after which TFA (2 mL) was added and the mixture was stirred for 2.5 h. The mixture was concentrated under a flow of N_2 and subsequently dissolved in a mixture of 2 M HCl (aq.) (3 mL) and MeOH (3 mL). The mixture was stirred for 2 h and subsequently concentrated under a flow of N_2 to about half of the volume. The mixture was poured into 1 M $NaHCO_3$ (aq.) (30 mL) and the product extracted with EtOAc (2x20 mL). The combined organic layers were concentrated as such after which the mixture was dissolved in 1:1 MeOH/DCM (2 mL) and transferred to a microwave vial. Ethylenediamine (50 µL, 746 µmol) was added after which the vial was sealed and the mixture was stirred at 50°C for 1 h. The mixture was poured into H_2O (20 mL) and the product extracted with EtOAc (2x20 mL). The combined organic layers were concentrated as such and purified by automated column chromatography (25 – 60% EtOAc/DCM) to afford the product (31.6 mg, 102 µmol, 47%). ^{1}H NMR (500 MHz, MeOD) δ 7.81 (s, 1H), 7.64 – 7.55 (br m, 2H), 7.24 – 7.19 (m, 2H), 7.14 (t, *J* = 8.1 Hz, 1H), 7.00 (t, *J* = 2.1 Hz, 1H), 6.92 (ddd, *J* = 8.2, 2.3, 0.7 Hz, 1H), 6.72 (ddd, *J* = 7.9, 1.9, 0.8 Hz, 1H). ^{13}C NMR (126 MHz, MeOD) δ 148.34 (br), 147.46, 135.98, 133.30 (br), 131.44, 126.39, 123.62, 120.06 (br), 119.50, 115.81 (br), 115.09, 113.80. LCMS (Fleet, 10 → 90%): t_r = 4.77 min, m/z: 310.3. HRMS [$C_{16}H_{12}ClN_5$ + H]$^+$: 310.08540 calculated, 310.08534 found.

***N*-(3-(1*H*-Benzo[*d*]imidazol-2-yl)-1H-pyrazol-4-yl)-2,6-dichloropyrimidin-4-amine (11)**



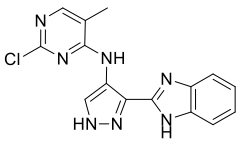
The title compound was synthesized from **81** (94.6 mg, 156 µmol) according to general procedure A (reaction time: 4 h). The crude was purified by automated column chromatography (25 – 55% EtOAc/DCM) to afford the product (27.8 mg, 80.3 µmol, 52%). ^{1}H NMR (500 MHz, DMSO) δ 13.16 (br s, 2H), 10.61 (br s, 1H), 8.33 (s, 1H), 7.80 – 7.46 (br m, 2H), 7.34 (br s, 1H), 7.26 – 7.19 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 160.48, 158.85, 157.73, 146.94, 142.86 (br), 133.76 (br), 131.54, 122.67 (br), 121.97 (br), 121.20, 120.30, 118.63 (br), 111.59 (br), 105.07. LCMS (Fleet, 10 → 90%): t_r = 4.32 min, m/z: 346.3. HRMS [$C_{14}H_9Cl_2N_7$ + H]$^+$: 346.03693 calculated, 346.03665 found.

***N*-(3-(1*H*-Benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)-2,5-dichloropyrimidin-4-amine (12)**



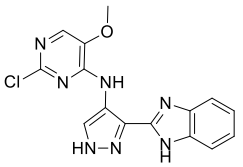
The title compound was synthesized from **82** (103 mg, 169 µmol) according to general procedure A (reaction time: 2.5 h). The crude was purified by automated column chromatography (twice, first 20 – 50% EtOAc/DCM, second 1 – 10% MeOH/DCM) to afford the product (35.5 mg, 103 µmol, 61%). ^{1}H NMR (500 MHz, DMSO) δ 13.29 (br s, 2H), 11.42 (s, 1H), 8.39 (s, 1H), 8.35 (s, 1H), 7.69 (d, *J* = 7.1 Hz, 1H), 7.52 (d, *J* = 7.0 Hz, 1H), 7.28 – 7.19 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 157.28, 154.96, 154.29, 147.14, 142.44, 133.47, 130.98, 122.91, 121.93, 120.65, 119.87, 118.46, 114.02, 111.61. LCMS (Fleet, 10 → 90%): t_r = 5.20 min, m/z: 346.3. HRMS [$C_{14}H_9Cl_2N_7$ + H]$^+$: 346.03693 calculated, 346.03683 found.

***N*-(3-(1*H*-Benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)-2-chloro-5-methylpyrimidin-4-amine (13)**



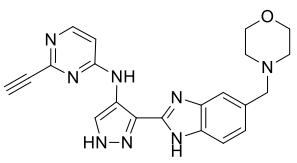
The title compound was synthesized from **83** (57.5 mg, 98.1 µmol) according to general procedure B (reaction time: 5 h). The crude was loaded onto Celite and purified by automated column chromatography (20 – 50% EtOAc/DCM) to afford the product (21.7 mg, 66.6 µmol, 68%). ^{1}H NMR (400 MHz, DMSO) δ 13.21 (br s, 2H), 10.76 (br s, 1H), 8.35 (s, 1H), 8.10 – 8.08 (2x s, 1H), 7.70 – 7.48 (br m, 2H), 7.27 – 7.20 (m, 2H), 2.34 – 2.31 (2x s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 158.41, 157.34, 155.28, 147.55, 142.44 (br), 133.86 (br), 130.67, 122.42 (br), 121.59, 119.66, 118.11 (br), 114.18, 111.75 (br), 12.61. LCMS (Fleet, 10 → 90%): t_r = 4.13 min, m/z: 326.3. HRMS [$C_{15}H_{12}ClN_7$ + H]$^+$: 326.09155 calculated, 326.09140 found.

_N_-(3-(1_H_-Benzo[_d_]imidazol-2-yl)-1_H_-pyrazol-4-yl)-2-chloro-5-methoxypyrimidin-4-amine (14)



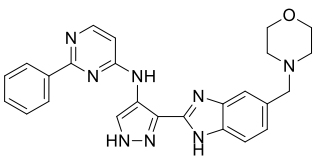
The title compound was synthesized from **84** (104 mg, 172 µmol) according to general procedure B (reaction time: 5.5 h). The crude was loaded onto Celite and purified by automated column chromatography (20 – 50% EtOAc/DCM) to afford the product (48.7 mg, 142 µmol, 83%). ^{1}H NMR (400 MHz, DMSO) δ 13.24 (br s, 2H), 10.93 (br s, 1H), 8.40 (s, 1H), 7.96 (s, 1H), 7.72 (br s, 1H), 7.52 (br s, 1H), 7.28 – 7.21 (m, 2H), 4.08 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 150.99, 149.93, 147.34, 142.69, 139.89, 134.58, 133.59, 130.89, 122.83, 121.90, 121.07, 119.51, 118.52, 111.60, 56.89. LCMS (Fleet, 10 → 90%): t_r = 3.96 min, m/z: 342.3. HRMS [$C_{15}H_{12}ClN_7O$ + H]$^+$: 342.08646 calculated, 342.08629 found.

2-Ethynyl-_N_-(3-(5-(morpholinomethyl)-1_H_-benzo[_d_]imidazol-2-yl)-1_H_-pyrazol-4-yl)pyrimidin-4-amine (15)



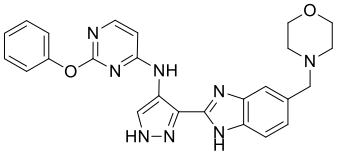
65 (19.1 mg, 26.1 µmol) was dissolved in TBAF (1 M in THF, 0.5 mL) and stirred for 2.5 h. The mixture was poured into H_2O (10 mL) and the intermediate extracted with 10% MeOH/EtOAc (3x4 mL). The combined organic layers were concentrated as such and subsequently dissolved in DCM (1.2 mL) after which TFA (0.3 mL) was added dropwise. The mixture was stirred for 6 h, subsequently poured into 1 M $NaHCO_3$ (aq.) (10 mL) and the product extracted with 10% MeOH/EtOAc (3x3 mL). The combined organic layers were concentrated as such and purified by automated column chromatography (2 – 14% MeOH/DCM) to afford the product (5.5 mg, 14 µmol, 53%). ^{1}H NMR (500 MHz, MeOD) δ 8.48 (br s, 1H), 8.18 (d, J = 6.1 Hz, 1H), 7.76 – 7.42 (br m, 2H), 7.25 (d, J = 8.2 Hz, 1H), 6.95 (d, J = 6.1 Hz, 1H), 3.72 – 3.68 (m, 4H), 3.66 (s, 1H), 3.64 (s, 2H), 2.54 – 2.47 (m, 4H). ^{13}C NMR (126 MHz, MeOD) δ 160.22, 155.23, 152.51, 149.02, 132.70 (br), 125.67 (br), 122.62, 121.89, 120.58 (br), 119.05 (br), 113.49 (br), 112.13 (br), 108.11, 83.10, 82.70, 76.34, 67.73, 64.73, 54.63 (not all quaternary carbons were observed). LCMS (Fleet, 0 → 50%): t_r = 4.25 min, m/z: 401.3. HRMS [$C_{21}H_{20}N_8O$ + H]$^+$: 401.18328 calculated, 401.18305 found.

_N_-(3-(5-(Morpholinomethyl)-1_H_-benzo[_d_]imidazol-2-yl)-1_H_-pyrazol-4-yl)-2-phenylpyrimidin-4-amine (16)



The title compound was synthesized from **66** (29.8 mg, 41.8 µmol) according to general procedure C (reaction time: 4.5 h). The crude was purified by automated column chromatography (3 – 15% MeOH/DCM) to afford the product (8.6 mg, 19 µmol, 46%). ^{1}H NMR (500 MHz, MeOD) δ 8.64 (s, 1H), 8.30 (d, J = 5.9 Hz, 1H), 8.29 – 8.25 (m, 2H), 7.70 (br s, 1H), 7.51 – 7.43 (m, 4H), 7.27 – 7.20 (br m, 1H), 6.81 (d, J = 5.9 Hz, 1H), 3.71 (t, J = 4.4 Hz, 4H), 3.64 (s, 2H), 2.58 – 2.43 (m, 4H). ^{13}C NMR (126 MHz, MeOD) δ 165.28, 159.50, 154.94, 148.06, 143.62, 143.08, 138.77, 133.85, 133.18, 132.33, 131.57, 131.14, 130.86, 128.86, 128.48, 125.47, 124.61, 122.71, 120.80, 120.08, 118.65, 112.57, 111.40, 106.03, 67.10, 64.16, 53.80. LCMS (Finnigan, 0 → 50%): t_r = 5.53 min, m/z: 453.1. HRMS [$C_{25}H_{24}N_8O$ + H]$^+$: 453.21458 calculated, 453.2146 found.

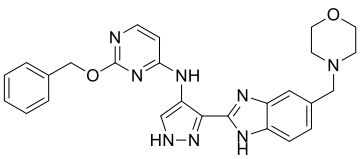
_N_-(3-(5-(Morpholinomethyl)-1_H_-benzo[_d_]imidazol-2-yl)-1_H_-pyrazol-4-yl)-2-phenoxypyrimidin-4-amine (17)



The title compound was synthesized from **67** (28.0 mg, 38.4 µmol) according to general procedure C (reaction time: 6 h). The crude was dissolved in 1:1 MeOH/DCM (1 mL) and transferred to a microwave vial. Ethylenediamine (50 µL, 746 µmol) was added after which the vial was sealed and the mixture was stirred at 50°C for 40 min. The mixture was poured into H_2O (20 mL) and the product extracted with $CHCl_3$ (2x20 mL). The combined organic layers were concentrated as such and purified by automated column chromatography (2 – 15% MeOH/DCM) to afford the product (7.5 mg, 16 µmol, 42%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.21 – 10.75 (br m, 2H), 10.11 (s, 1H), 8.11 (d, J = 5.5 Hz, 1H), 7.70 (s, 1H), 7.54 (d, J = 15.5 Hz, 1H), 7.41 – 7.29 (m, 3H), 7.24 – 7.13 (m, 4H), 6.51 – 6.43 (2x d, J = 5.4 Hz, 1H),

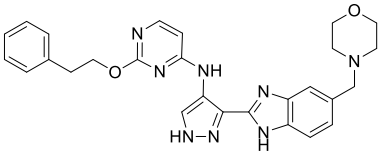
3.79 – 3.52 (m, 6H), 2.56 – 2.39 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.83, 160.33, 156.95, 153.50, 147.26 (br), 143.40, 142.78, 133.18, 133.05, 132.21, 132.01, 131.21 (br), 129.63, 125.20, 124.37, 122.63, 122.52, 120.72 (br), 119.94, 118.83, 111.69, 110.72, 102.41 (br), 67.09, 66.95, 63.89, 63.85, 53.70. LCMS (Finnigan, 0 → 50%): t_r = 5.88 min, m/z: 469.1. HRMS $[C_{25}H_{24}N_8O_2 + H]^+$: 469.20950 calculated, 469.2097 found.

2-(Benzyloxy)-*N*-(3-(5-(morpholinomethyl)-1*H*-benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)pyrimidin-4-amine (18)



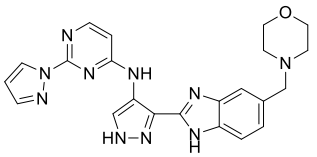
A microwave vial was charged with **68** (55 mg, 74 µmol) and TBAF (1 M in THF, 0.5 mL) was added. The vial was sealed and the mixture was stirred at 80°C for 7 days. The mixture was poured into H_2O (20 mL) and the product extracted with 10% MeOH/$CHCl_3$ (2x20 mL). The combined organic layers were concentrated as such, dissolved in 1:1 MeOH/DCM (1 mL) and transferred to a microwave vial. Ethylenediamine (50 µL, 746 µmol) was added after which the vial was sealed and the mixture was stirred at 50°C for 1 h. The mixture was poured into H_2O (20 mL) and the product extracted with $CHCl_3$ (2x20 mL). The combined organic layers were concentrated as such and purified by automated column chromatography (twice, 0 – 10% MeOH/EtOAc) to afford the product (6.9 mg, 14 µmol, 19%). ^{1}H NMR (600 MHz, MeOD) δ 8.30 (s, 1H), 8.03 (d, *J* = 5.9 Hz, 1H), 7.66 (br s, 1H), 7.50 (br s, *J* = 1.2 Hz, 1H), 7.47 – 7.44 (m, 2H), 7.38 – 7.34 (m, 2H), 7.31 – 7.28 (m, 1H), 7.24 (d, *J* = 8.1 Hz, 1H), 6.58 (d, *J* = 5.9 Hz, 1H), 5.45 (s, 2H), 3.72 – 3.68 (m, 4H), 3.65 (s, 2H), 2.55 – 2.48 (m, 4H). ^{13}C NMR (151 MHz, MeOD) δ 166.08, 161.99, 156.83, 148.77, 137.90, 129.32, 128.74, 128.32, 125.85, 125.12, 122.55, 121.55, 120.43, 119.15, 113.16, 111.85, 102.12, 69.69, 67.52, 64.56, 54.34. LCMS (Fleet, 0 → 50%): t_r = 5.48 min, m/z: 483.4. HRMS $[C_{26}H_{26}N_8O_2 + H]^+$: 483.22515 calculated, 483.22509 found.

***N*-(3-(5-(Morpholinomethyl)-1*H*-benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)-2-phenethoxypyrimidin-4-amine (19)**



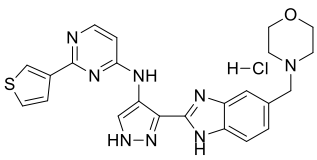
69 (30 mg, 40 µmol) was dissolved in DCM (1 mL) after which TFA (1 mL) was added dropwise and the mixture was stirred for 2.5 h. The mixture was concentrated under a flow of N_2, dissolved in 5% MeOH/DCM (20 mL), poured into 1 M $NaHCO_3$ (aq.) (20 mL) and the layers were separated. The water layer was extracted with 5% MeOH/DCM (20 mL) and the combined organic layers were concentrated as such. The mixture was dissolved in 1:1 MeOH/DCM (1 mL) and transferred to a microwave vial. Ethylenediamine (50 µL, 746 µmol) was added after which the vial was sealed and the mixture was stirred at 50°C for 80 min. The mixture was poured into H_2O (20 mL) and the product extracted with 5% MeOH/DCM (2x20 mL). The combined organic layers were concentrated as such and purified by HPLC (Agilent, 19 – 25% MeCN in 0.2% TFA (aq.)). The fractions were concentrated and traces of TFA were removed by coevaporation with 1:1 MeCN/H_2O (20 mL). The residue was dissolved in $CHCl_3$ (20 mL) and poured into 1 M $NaHCO_3$ (aq.) (20 mL). The organic layer was separated and the water layer extracted with $CHCl_3$ (20 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated to afford the product (8.6 mg, 17 µmol, 44%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.46 – 11.12 (br m, 1H), 10.00 (s, 1H), 8.39 (s, 1H), 7.99 (d, *J* = 5.2 Hz, 1H), 7.70 (d, *J* = 5.8 Hz, 1H), 7.40 – 7.22 (m, 6H), 7.23 – 7.14 (m, 2H), 6.36 – 6.30 (m, 1H), 4.50 (t, *J* = 7.3 Hz, 2H), 3.74 – 3.64 (m, 4H), 3.63 – 3.55 (m, 2H), 3.08 (t, *J* = 7.3 Hz, 2H), 2.52 – 2.41 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.26, 160.63, 156.33, 147.25 (br), 143.46, 142.85, 138.20, 133.29, 132.37, 131.91, 131.26 (br), 129.13, 128.63, 126.63, 125.19, 124.31, 122.82, 120.71 (br), 119.91, 118.82, 111.73, 110.75, 101.68, 67.87, 67.05, 66.95, 63.88, 53.71, 35.51. LCMS (Fleet, 0 → 50%): t_r = 5.76 min, m/z: 497.4. HRMS $[C_{27}H_{28}N_8O_2 + H]^+$: 497.24080 calculated, 497.24093 found.

N-(3-(5-(Morpholinomethyl)-1*H*-benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)-2-(1*H*-pyrazol-1-yl)pyrimidin-4-amine (20)



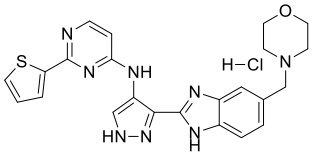
70 (60 mg, 85 µmol) was dissolved in DCM (1 mL) after which TFA (1 mL) was added dropwise and the mixture was stirred for 3 h. The mixture was concentrated under a flow of N_2, dissolved in $CHCl_3$ (20 mL) and poured into 1 M $NaHCO_3$ (aq.) (20 mL). The organic layer was separated and the water layer extracted with $CHCl_3$ (20 mL). The combined organic layers were concentrated as such, dissolved in 1:1 MeOH/DCM (1 mL) and transferred to a microwave vial. Ethylenediamine (50 µL, 746 µmol) was added after which the vial was sealed and the mixture was stirred at 50°C for 1 h. The mixture was poured into H_2O (20 mL) and the product extracted with $CHCl_3$ (2x20 mL). The combined organic layers were concentrated as such and purified by automated column chromatography (2 – 15% MeOH/DCM) to afford the product (16.5 mg, 37.3 µmol, 44%). ^{1}H NMR (500 MHz, MeOD) δ 8.60 (br s, 1H), 8.54 (d, *J* = 2.5 Hz, 1H), 8.22 (d, *J* = 5.9 Hz, 1H), 7.78 – 7.77 (m, 1H), 7.67 (br s, 1H), 7.45 (br s, 1H), 7.22 (d, *J* = 8.0 Hz, 1H), 6.77 (d, *J* = 5.8 Hz, 1H), 6.50 (dd, *J* = 2.6, 1.7 Hz, 1H), 3.72 – 3.68 (m, 4H), 3.63 (s, 2H), 2.55 – 2.46 (m, 4H). ^{13}C NMR (126 MHz, MeOD) δ 160.31 (br), 156.08, 155.93 (br), 147.96 (br), 143.61 (br), 143.35, 143.05 (br), 133.92 (br), 133.27 (br), 132.37 (br), 131.74 (br), 131.18 (br), 129.55, 125.53 (br), 124.67 (br), 122.11 (br), 121.41 (br), 120.08 (br), 118.66 (br), 112.65 (br), 111.47 (br), 108.70, 105.74 (br), 67.11, 64.17, 53.82. LCMS (Fleet, 0 → 50%): t_r = 4.78 min, m/z: 443.3. HRMS $[C_{22}H_{22}N_{10}O + H]^+$: 443.20508 calculated, 443.20488 found.

N-(3-(5-(Morpholinomethyl)-1*H*-benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)-2-(thiophen-3-yl)pyrimidin-4-amine hydrochloride (21)



71 (43.2 mg, 60.0 µmol) was dissolved in EtOH (0.5 mL) and HCl (4 M in dioxane, 0.5 mL) was added. The mixture was stirred at 50°C for 16 h. The reaction was concentrated under a flow of N_2, subsequently 2 M K_2CO_3 (2 mL) was added and the mixture was stirred for 30 min. The mixture was diluted with DCM (10 mL) and H_2O (10 mL), the organic layer was separated and subsequently concentrated as such. The crude was purified by HPLC (Agilent, 13 – 19% MeCN in 0.2% TFA (aq.)) after which the fractions were concentrated and traces of TFA were removed by coevaporation with 1:1 MeCN/H_2O (3x20 mL). The residue was dissolved in 1:1 MeCN/H_2O (2x40 mL) to which 0.4 mL HCl (2 M aq.) was added and subsequently concentrated to afford the product as HCl salt (14.8 mg, 32.3 µmol, 54%). ^{1}H NMR (500 MHz, MeOD) δ 8.46 (s, 1H), 8.37 (s, 1H), 8.25 (d, *J* = 4.5 Hz, 1H), 8.17 (s, 1H), 7.86 (d, *J* = 6.1 Hz, 1H), 7.80 (d, *J* = 6.3 Hz, 1H), 7.60 (d, *J* = 4.1 Hz, 1H), 7.58 – 7.53 (m, 1H), 7.32 (d, *J* = 4.0 Hz, 1H), 4.55 (s, 2H), 4.05 – 3.89 (m, 4H), 3.31 – 3.21 (m, 4H). ^{13}C NMR (126 MHz, MeOD) δ 162.80, 155.49, 145.12, 143.67, 133.98, 133.36, 132.64, 130.50, 130.43, 129.39, 127.65, 127.51, 126.81, 119.69, 118.55, 115.54, 106.94, 64.41, 60.91, 52.42. LCMS (Finnigan, 0 → 50%): t_r = 5.44 min, m/z: 459.1. HRMS $[C_{23}H_{23}ClN_8OS + H]^+$: 459.17100 calculated, 459.1712 found.

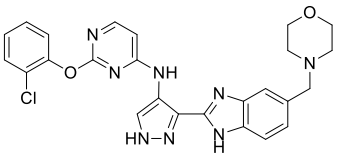
N-(3-(5-(Morpholinomethyl)-1*H*-benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)-2-(thiophen-2-yl)pyrimidin-4-amine hydrochloride (22)



72 (59.6 mg, 82.8 µmol) was dissolved in EtOH (0.5 mL) and HCl (4 M in dioxane, 0.5 mL) was added. The mixture was stirred at 50°C for 16 h. The reaction was concentrated under a flow of N_2, subsequently 2 M K_2CO_3 (2 mL) was added and the mixture was stirred for 30 min. The mixture was diluted with DCM (10 mL) and H_2O (10 mL), the organic layer was separated and subsequently concentrated as such. The crude was purified by HPLC (Agilent, 13 – 19% MeCN in 0.2% TFA (aq.)) after which the fractions were concentrated and traces of TFA were removed by coevaporation with 1:1 MeCN/H_2O (3x20 mL). The residue was dissolved in 1:1 MeCN/H_2O (2x40 mL) to which 0.4 mL HCl (2 M aq.) was added and subsequently concentrated to afford the product as HCl salt (21.7 mg, 47.3 µmol, 57%). ^{1}H NMR (500 MHz, MeOD) δ 8.37 (s, 1H), 8.24 (d, *J* = 5.1 Hz, 1H), 8.20 – 8.12 (m, 2H), 7.87 (s, 2H), 7.81 – 7.76 (m, 1H), 7.26 (d, *J* = 5.0 Hz, 1H), 7.24 – 7.20 (m, 1H), 4.56 (s, 2H), 4.05 – 3.97 (m, 2H), 3.96 – 3.87 (m, 2H), 3.33 –

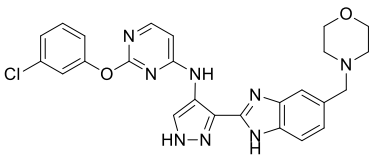
3.21 (m, 4H). ^{13}C NMR (126 MHz, MeOD) δ 162.45, 155.24, 145.39, 143.75, 136.75, 135.01, 133.72, 133.41, 133.04, 130.70, 130.44, 127.53, 119.83, 118.69, 115.63, 106.79, 64.50, 61.06, 52.53. LCMS (Finnigan, 0 → 50%): t_r = 5.54 min, m/z: 459.1. HRMS [$C_{23}H_{23}ClN_8OS$ + H]$^+$: 459.17100 calculated, 459.1710 found.

2-(2-Chlorophenoxy)-*N*-(3-(5-(morpholinomethyl)-1*H*-benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)pyrimidin-4-amine (23)



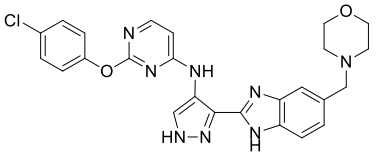
The title compound was synthesized from **116** (95.5 mg, 151 µmol) according to general procedure B (reaction time: 4 h). The crude was purified by automated column chromatography (0 – 50% MeOH/DCM) to afford the product (38.1 mg, 75.8 µmol, 50%). ^{1}H NMR (400 MHz, DMSO) δ 13.15 (br s, 1H), 13.03 – 12.94 (2x s, 1H), 10.35 – 10.14 (2x s, 1H), 8.19 – 8.15 (2x d, *J* = 5.8 Hz, 1H), 7.69 – 7.62 (m, 2H), 7.53 – 7.28 (m, 5H), 7.20 – 7.11 (2x dd, *J* = 8.3, 1.5 Hz, 1H), 6.88 – 6.79 (2x d, *J* = 5.8 Hz, 1H), 3.59 – 3.51 (m, 6H), 2.40 – 2.30 (m, 4H). ^{13}C NMR (101 MHz, DMSO) δ 164.42, 159.96 (br), 157.22 (br), 149.01, 147.58 (br), 147.45 (br), 142.85, 142.12, 133.65, 132.75, 132.57, 131.34, 130.58 (br), 130.29, 128.66, 127.04, 126.77, 124.76, 124.16, 123.21, 121.34, 121.25, 119.46 (br), 118.90, 118.00, 111.66, 111.03, 102.80 (br), 66.27, 62.99, 62.92, 53.25, 53.21. LCMS (Fleet, 10 → 90%): t_r = 3.43 min, m/z: 503.2. HRMS [$C_{25}H_{23}ClN_8O_2$ + H]$^+$: 503.17053 calculated, 503.17069 found.

2-(3-Chlorophenoxy)-*N*-(3-(5-(morpholinomethyl)-1*H*-benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)pyrimidin-4-amine (24)



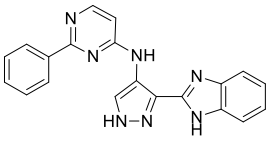
The title compound was synthesized from **117** (85.8 mg, 135 µmol) according to general procedure B (reaction time: 3 h). The crude was purified by automated column chromatography (2 – 40% MeOH/DCM) to afford the product (46 mg, 91 µmol, 67%). ^{1}H NMR (400 MHz, DMSO) δ 13.22 (br s, 1H), 13.00 (br s, 1H), 10.40 – 10.18 (2x s, 1H), 8.17 (d, *J* = 5.8 Hz, 1H), 7.67 – 7.62 (m, 1H), 7.57 (br s, 1H), 7.52 (t, *J* = 8.1 Hz, 1H), 7.44 (t, *J* = 2.2 Hz, 1H), 7.42 (br s, 1H), 7.39 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.26 (dd, *J* = 7.9, 2.1 Hz, 1H), 7.20 – 7.12 (m, 1H), 6.87 – 6.78 (2x d, *J* = 5.8 Hz, 1H), 3.58 – 3.51 (m, 6H), 2.39 – 2.30 (m, 4H). ^{13}C NMR (101 MHz, DMSO) δ 164.86, 160.01 (br), 157.09 (br), 153.86, 147.58 (br), 147.48 (br), 142.87, 142.14, 133.68, 133.58, 132.77, 132.58, 131.35, 131.02, 130.65 (br), 125.34, 124.16, 123.22, 122.72, 121.35 (br), 121.25, 119.65 (br), 118.90, 118.00, 111.68, 111.04, 102.89 (br), 66.28, 62.97, 53.24. LCMS (Fleet, 10 → 90%): t_r = 3.50 min, m/z: 503.2. HRMS [$C_{25}H_{23}ClN_8O_2$ + H]$^+$: 503.17053 calculated, 503.17040 found.

2-(4-Chlorophenoxy)-*N*-(3-(5-(morpholinomethyl)-1*H*-benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)pyrimidin-4-amine (25)



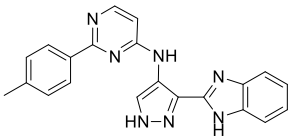
The title compound was synthesized from **118** (95.5 mg, 151 µmol) according to general procedure B (reaction time: 3 h). The crude was purified by automated column chromatography (2 – 14% MeOH/DCM) to afford the product (59.6 mg, 118 µmol, 79%). ^{1}H NMR (400 MHz, DMSO) δ 13.24 (br s, 1H), 13.01 (br s, 1H), 10.39 – 10.18 (2x s, 1H), 8.15 (d, *J* = 5.8 Hz, 1H), 7.71 (br s, 1H), 7.67 – 7.63 (m, 1H), 7.55 – 7.50 (m, 2H), 7.46 – 7.40 (m, 1H), 7.33 – 7.27 (m, 2H), 7.16 (t, *J* = 8.8 Hz, 1H), 6.85 – 6.77 (2x d, *J* = 5.8 Hz, 1H), 3.59 – 3.51 (m, 6H), 2.39 – 2.31 (m, 4H). ^{13}C NMR (101 MHz, DMSO) δ 164.88, 160.12 (br), 157.02 (br), 151.89, 147.61 (br), 147.50 (br), 142.88, 142.15, 133.68, 132.78, 132.59, 131.36, 130.68 (br), 129.52, 129.27, 124.17, 124.07, 123.23, 121.40, 121.31, 119.69 (br), 118.90, 118.01, 111.69, 111.05, 102.84 (br), 66.28, 63.01, 62.96, 53.25, 53.23. LCMS (Fleet, 10 → 90%): t_r = 3.44 min, m/z: 503.2. HRMS [$C_{25}H_{23}ClN_8O_2$ + H]$^+$: 503.17053 calculated, 503.17050 found.

_N_-(3-(1_H_-Benzo[_d_]imidazol-2-yl)-1_H_-pyrazol-4-yl)-2-phenylpyrimidin-4-amine (26)



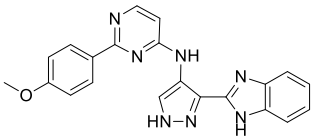
The title compound was synthesized from **85** (114 mg, 186 µmol) according to general procedure A (reaction time: 4.5 h). The crude was loaded onto Celite and purified by silica gel column chromatography (2 – 4% MeOH/DCM) to afford the product (50.6 mg, 143 µmol, 77%). ^{1}H NMR (400 MHz, DMSO) δ 13.20 (br s, 2H), 10.20 (br s, 1H), 8.63 (br s, 1H), 8.46 (d, *J* = 5.8 Hz, 1H), 8.44 – 8.39 (m, 2H), 7.75 (br s, 1H), 7.65 – 7.45 (m, 4H), 7.29 – 7.20 (m, 2H), 7.01 (d, *J* = 5.8 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 163.42, 158.66, 155.68, 147.55, 142.92 (br), 138.11, 133.65 (br), 130.86 (br), 130.51, 128.59, 127.77, 122.53 (br), 121.84, 119.80, 118.57 (br), 111.56 (br), 105.74 (br). LCMS (Fleet, 10 → 90%): t_r = 3.08 min, m/z: 354.3. HRMS [$C_{20}H_{15}N_7$ + H]$^+$: 354.14617 calculated, 354.14637 found.

_N_-(3-(1_H_-Benzo[_d_]imidazol-2-yl)-1_H_-pyrazol-4-yl)-2-(_p_-tolyl)pyrimidin-4-amine (27)



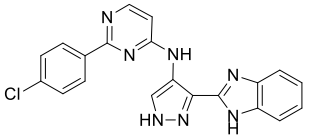
The title compound was synthesized from **86** (100 mg, 190 µmol) according to general procedure A (reaction time: 3 h). The crude was loaded onto Celite and purified by silica gel column chromatography (2% MeOH/DCM) to afford the product (40.0 mg, 106 µmol, 56%). ^{1}H NMR (400 MHz, DMSO) δ 13.19 (br s, 2H), 10.15 (br s, 1H), 8.60 (s, 1H), 8.43 (d, *J* = 5.8 Hz, 1H), 8.32 – 8.28 (m, 2H), 7.65 (br s, 2H), 7.37 – 7.33 (m, 2H), 7.28 – 7.22 (m, 2H), 6.98 (d, *J* = 5.8 Hz, 1H), 2.39 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 163.47, 158.61, 155.65 (br), 147.52 (br), 142.68 (br), 140.23, 135.43, 134.07 (br), 130.77 (br), 129.20, 127.75, 122.21 (br), 121.89, 119.71 (br), 118.27 (br), 111.60 (br), 105.45 (br), 21.05. LCMS (Fleet, 10 → 90%): t_r = 3.35 min, m/z: 368.3. HRMS [$C_{21}H_{17}N_7$ + H]$^+$: 368.16182 calculated, 368.16204 found.

_N_-(3-(1_H_-Benzo[_d_]imidazol-2-yl)-1_H_-pyrazol-4-yl)-2-(4-methoxyphenyl)pyrimidin-4-amine (28)



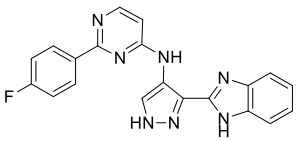
The title compound was synthesized from **87** (110 mg, 171 µmol) according to general procedure A (reaction time: 3 h), using 10% MeOH/EtOAc as organic layers in the work-up. The crude was purified by silica gel column chromatography (2% MeOH/DCM) to afford the product (66 mg, 171 µmol, quant.). ^{1}H NMR (400 MHz, DMSO) δ 13.35 (br s, 1H), 13.06 (br s, 1H), 10.16 (br s, 1H), 8.61 (br s, 1H), 8.41 (d, *J* = 5.8 Hz, 1H), 8.39 – 8.35 (m, 2H), 7.83 – 7.73 (br m, 1H), 7.58 – 7.50 (br m, 1H), 7.28 – 7.21 (m, 2H), 7.12 – 7.06 (m, 2H), 6.93 (d, *J* = 5.9 Hz, 1H), 3.84 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 163.27, 161.30, 158.55, 155.64 (br), 147.60, 142.94, 133.66, 130.82 (br), 130.60, 129.41, 122.72, 121.97, 121.79, 119.65, 118.56, 113.90, 111.53, 104.92 (br), 55.29. LCMS (Fleet, 10 → 90%): t_r = 3.26 min, m/z: 384.3. HRMS [$C_{21}H_{17}N_7O$ + H]$^+$: 384.15673 calculated, 384.15699 found.

_N_-(3-(1_H_-Benzo[_d_]imidazol-2-yl)-1_H_-pyrazol-4-yl)-2-(4-chlorophenyl)pyrimidin-4-amine (29)



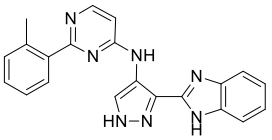
The title compound was synthesized from **88** (141 mg, 218 µmol) according to general procedure A (reaction time: 5 h). The crude was purified by HPLC (Waters, 15 – 25% MeCN in 0.2% TFA (aq.)) after which the fractions were concentrated and traces of TFA were removed by coevaporation with 1:1 MeCN/H_2O (20 mL). The residue was dissolved in EtOAc (20 mL) and poured into 1 M $NaHCO_3$ (aq.) (20 mL). The organic layer was separated and the water layer extracted with EtOAc (20 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated to afford the product (24 mg, 62 µmol, 28%). ^{1}H NMR (500 MHz, DMSO) δ 12.74 (br s, 2H), 10.25 (br s, 1H), 8.56 (br s, 1H), 8.44 (d, *J* = 5.8 Hz, 1H), 8.42 – 8.39 (m, 2H), 7.66 – 7.62 (m, 2H), 7.61 – 7.57 (m, 2H), 7.25 – 7.21 (m, 2H), 7.01 (d, *J* = 5.8 Hz, 1H). ^{13}C NMR (126 MHz, DMSO) δ 162.40, 158.68, 155.60 (br), 147.52, 138.38 (br), 136.91, 135.32, 130.65 (br), 129.50, 128.63, 122.10, 121.64, 120.42 (br), 114.94 (br), 105.96 (br). LCMS (Fleet, 10 → 90%): t_r = 3.72 min, m/z: 388.3. HRMS [$C_{20}H_{14}ClN_7$ + H]$^+$: 388.10720 calculated, 388.10714 found.

_N_-(3-(1_H_-Benzo[_d_]imidazol-2-yl)-1_H_-pyrazol-4-yl)-2-(4-fluorophenyl)pyrimidin-4-amine (30)



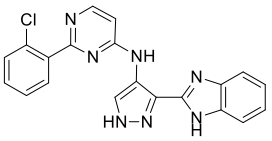
The title compound was synthesized from **89** (125 mg, 198 µmol) according to general procedure A (reaction time: 3 h). The crude was purified by HPLC (Waters, 15 – 25% MeCN in 0.2% TFA (aq.)) after which the fractions were concentrated and traces of TFA were removed by coevaporation with 1:1 MeCN/H_2O (20 mL). The residue was dissolved in EtOAc (20 mL) and poured into 1 M $NaHCO_3$ (aq.) (20 mL). The organic layer was separated and the water layer extracted with EtOAc (20 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated to afford the product (18.5 mg, 49.8 µmol, 25%). ^{1}H NMR (500 MHz, DMSO) δ 13.36 (s, 1H), 13.05 (br s, 1H), 10.19 (s, 1H), 8.58 (s, 1H), 8.46 (d, _J_ = 5.8 Hz, 1H), 8.45 – 8.42 (m, 2H), 7.65 (br s, 2H), 7.36 (t, _J_ = 8.8 Hz, 2H), 7.26 – 7.22 (m, 2H), 7.00 (d, _J_ = 5.8 Hz, 1H). ^{13}C NMR (126 MHz, DMSO) δ 164.75, 162.78, 162.46, 158.65, 155.60 (br), 147.49, 142.49 (br), 134.53, 133.94 (br), 130.91 (br), 130.10, 130.04, 122.23 (br), 121.70, 119.82, 118.05 (br), 115.53, 115.36, 111.62 (br), 105.61 (br). LCMS (Fleet, 10 → 90%): t_r = 3.42 min, m/z: 372.3. HRMS $[C_{20}H_{14}FN_7 + H]^+$: 372.13675 calculated, 372.13647 found.

_N_-(3-(1_H_-Benzo[_d_]imidazol-2-yl)-1_H_-pyrazol-4-yl)-2-(_o_-tolyl)pyrimidin-4-amine (31)



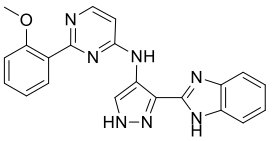
The title compound was synthesized from **90** (177 mg, 281 µmol) according to general procedure A (reaction time: 2 h). The crude was loaded onto Celite and purified by automated column chromatography (40 – 70% EtOAc/DCM) to afford the product (75.2 mg, 205 µmol, 73%). ^{1}H NMR (500 MHz, DMSO) δ 13.16 (br s, 2H), 10.19 (br s, 1H), 8.47 – 8.43 (m, 2H), 7.80 (dd, _J_ = 7.2, 1.4 Hz, 1H), 7.77 – 7.49 (br m, 2H), 7.38 – 7.29 (m, 3H), 7.28 – 7.22 (m, 2H), 7.00 (d, _J_ = 5.9 Hz, 1H), 2.52 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 166.47, 158.41 (br), 155.27 (br), 147.59 (br), 142.94 (br), 139.19, 136.38, 133.74 (br), 130.98, 129.92, 128.86, 125.71, 122.16 (br), 121.95, 119.79 (br), 118.50 (br), 111.63 (br), 104.79 (br), 20.80 (not all quaternary carbons were observed). LCMS (Fleet, 10 → 90%): t_r = 3.21 min, m/z: 368.3. HRMS $[C_{21}H_{17}N_7 + H]^+$: 368.16182 calculated, 368.16163 found.

_N_-(3-(1_H_-Benzo[_d_]imidazol-2-yl)-1_H_-pyrazol-4-yl)-2-(2-chlorophenyl)pyrimidin-4-amine (32)



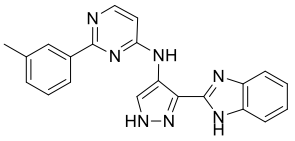
The title compound was synthesized from **91** (120 mg, 185 µmol) according to general procedure A (reaction time: 4.5 h). The crude was loaded onto Celite and purified by silica gel column chromatography (2 – 4% MeOH/DCM) to afford the product (48.1 mg, 124 µmol, 67%). ^{1}H NMR (400 MHz, DMSO) δ 13.14 (br s, 2H), 10.22 (br s, 1H), 8.50 (s, 1H), 8.47 (d, _J_ = 5.9 Hz, 1H), 7.80 – 7.75 (m, 1H), 7.65 (br s, 2H), 7.62 – 7.58 (m, 1H), 7.52 – 7.44 (m, 2H), 7.27 – 7.21 (m, 2H), 7.08 (d, _J_ = 6.0 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 164.33, 158.21 (br), 155.43 (br), 147.49 (br), 138.55, 131.68, 131.37, 130.72 (br), 130.46, 130.26, 127.17, 122.26 (br), 121.72, 120.23 (br), 105.83 (not all quaternary carbons were observed, neither were two –CH's of the benzimidazole). LCMS (Fleet, 10 → 90%): t_r = 3.01 min, m/z: 388.3. HRMS $[C_{20}H_{14}ClN_7 + H]^+$: 388.10720 calculated, 388.10741 found.

_N_-(3-(1_H_-Benzo[_d_]imidazol-2-yl)-1_H_-pyrazol-4-yl)-2-(2-methoxyphenyl)pyrimidin-4-amine (33)



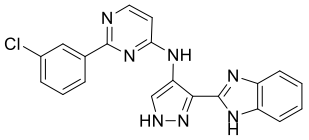
The title compound was synthesized from **92** (110 mg, 171 µmol) according to general procedure A (reaction time: 3 h). The crude was purified by silica gel column chromatography (2 – 3% MeOH/DCM) to afford the product (60.0 mg, 156 µmol, 91%). ^{1}H NMR (400 MHz, DMSO) δ 13.43 – 12.94 (br m, 2H), 10.07 (s, 1H), 8.67 (s, 1H), 8.44 (d, _J_ = 5.8 Hz, 1H), 7.76 (d, _J_ = 7.4 Hz, 2H), 7.53 (br s, 1H), 7.46 (ddd, _J_ = 8.3, 7.3, 1.8 Hz, 1H), 7.27 – 7.22 (m, 2H), 7.20 (dd, _J_ = 8.4, 1.0 Hz, 1H), 7.07 (td, _J_ = 7.5, 1.0 Hz, 1H), 7.00 (d, _J_ = 5.9 Hz, 1H), 3.87 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 164.51, 157.98 (br), 157.48, 155.44 (br), 147.69, 142.96 (br), 133.68 (br), 131.33, 130.70, 130.51 (br), 128.73, 122.65 (br), 122.13, 121.78 (br), 120.23, 120.14, 118.53 (br), 112.34, 111.50 (br), 104.95 (br), 55.57. LCMS (Fleet, 10 → 90%): t_r = 3.22 min, m/z: 384.3. HRMS $[C_{21}H_{17}N_7O + H]^+$: 384.15673 calculated, 384.15685 found.

***N*-(3-(1*H*-Benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)-2-(*m*-tolyl)pyrimidin-4-amine (34)**



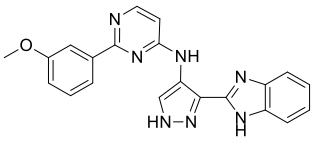
The title compound was synthesized from **93** (120 mg, 191 µmol) according to general procedure A (reaction time: 4 h). The crude was loaded onto Celite and purified by silica gel chromatography (3 – 5% MeOH/DCM) to afford the product (59.5 mg, 162 µmol, 85%). ^{1}H NMR (400 MHz, DMSO) δ 13.59 – 12.82 (br m, 2H), 10.18 (br s, 1H), 8.63 (br s, 1H), 8.45 (d, *J* = 5.9 Hz, 1H), 8.26 – 8.18 (m, 2H), 7.77 (br s, 1H), 7.57 (br s, 1H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.33 (d, *J* = 7.5 Hz, 1H), 7.30 – 7.21 (m, 2H), 6.99 (d, *J* = 5.8 Hz, 1H), 2.43 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 163.55, 158.65 (br), 155.65 (br), 147.58 (br), 142.94 (br), 138.11, 137.64, 133.69 (br), 131.15, 130.86 (br), 128.48, 128.41, 124.99, 122.55 (br), 121.90, 119.78 (br), 118.59 (br), 111.58 (br), 105.63 (br), 21.24. LCMS (Fleet, 10 → 90%): t_r = 3.33 min, m/z: 368.3. HRMS [$C_{21}H_{17}N_7$ + H]$^+$: 368.16182 calculated, 368.16206 found.

***N*-(3-(1*H*-Benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)-2-(3-chlorophenyl)pyrimidin-4-amine (35)**



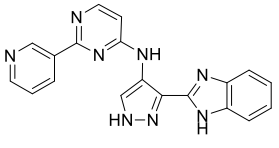
The title compound was synthesized from **94** (111 mg, 171 µmol) according to general procedure A (reaction time: 4 h), using 10% MeOH/EtOAc as organic layers in the work-up. The crude was purified by HPLC (Waters, 15 – 25% MeCN in 0.2% TFA (aq.)) after which the fractions were concentrated and traces of TFA were removed by coevaporation with 1:1 MeCN/H_2O (20 mL). The residue was dissolved in EtOAc (20 mL) and poured into 1 M $NaHCO_3$ (aq.) (20 mL). The organic layer was separated and the water layer extracted with EtOAc (20 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated to afford the product (53.0 mg, 137 µmol, 80%). ^{1}H NMR (500 MHz, DMSO) δ 13.53 – 12.90 (br m, 2H), 10.21 (br s, 1H), 8.56 (br s, 1H), 8.46 (d, *J* = 5.8 Hz, 1H), 8.37 – 8.32 (m, 2H), 7.76 (br s, 1H), 7.62 – 7.57 (m, 2H), 7.53 (br s, 1H), 7.27 – 7.21 (m, 2H), 7.04 (d, *J* = 5.8 Hz, 1H). ^{13}C NMR (126 MHz, DMSO) δ 161.99, 158.72 (br), 155.62 (br), 147.45, 142.93 (br), 140.18, 133.63 (br), 133.44, 131.03 (br), 130.56, 130.25, 127.32, 126.29, 122.68 (br), 121.79 (br), 121.57, 119.87, 118.53 (br), 111.51 (br), 106.32 (br). LCMS (Fleet, 10 → 90%): t_r = 3.66 min, m/z: 388.3. HRMS [$C_{20}H_{14}ClN_7$ + H]$^+$: 388.10720 calculated, 388.10706 found.

***N*-(3-(1*H*-Benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)-2-(3-methoxyphenyl)pyrimidin-4-amine (36)**



The title compound was synthesized from **95** (184 mg, 286 µmol) according to general procedure A (reaction time: 2 h). The crude was loaded onto Celite and purified by automated column chromatography (30 – 60% EtOAc/DCM) to afford the product (76.8 mg, 200 µmol, 70%). ^{1}H NMR (500 MHz, DMSO) δ 13.23 (br s, 2H), 10.21 (br s, 1H), 8.64 (br s, 1H), 8.46 (d, *J* = 5.8 Hz, 1H), 8.03 (d, *J* = 7.7 Hz, 1H), 7.99 – 7.97 (m, 1H), 7.75 (br s, 1H), 7.61 (br s, 1H), 7.46 (t, *J* = 7.9 Hz, 1H), 7.29 – 7.23 (m, 2H), 7.09 (dd, *J* = 8.1, 2.5 Hz, 1H), 7.00 (d, *J* = 5.8 Hz, 1H), 3.88 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 163.21, 159.47, 158.62 (br), 155.59 (br), 147.56 (br), 142.92 (br), 139.63, 133.79 (br), 130.91 (br), 129.61, 122.21 (br), 121.89, 120.15, 119.78 (br), 118.56 (br), 116.31, 112.76, 111.49 (br), 105.80 (br), 55.09. LCMS (Fleet, 10 → 90%): t_r = 3.44 min, m/z: 384.3. HRMS [$C_{21}H_{17}N_7O$ + H]$^+$: 384.15673 calculated, 384.15663 found.

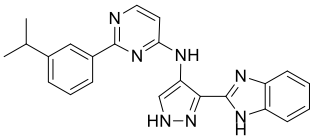
***N*-(3-(1*H*-Benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)-2-(pyridin-3-yl)pyrimidin-4-amine (37)**



The title compound was synthesized from **96** (148 mg, 240 µmol) according to general procedure A (reaction time: 4 h), using 10% MeOH/EtOAc as organic layers in the work-up. The crude was purified by silica gel column chromatography (3 – 5% MeOH/DCM) to afford the product (17 mg, 48 µmol, 20%). ^{1}H NMR (400 MHz, DMSO) δ 13.20 (br s, 2H), 10.24 (br s, 1H), 9.53 (dd, *J* = 2.2, 0.9 Hz, 1H), 8.73 (dd, *J* = 4.8, 1.7 Hz, 1H), 8.68 (dt, *J* = 8.0, 1.9 Hz, 1H), 8.59 (br s, 1H), 8.48 (d, *J* = 5.9 Hz, 1H), 7.64 (br s, 2H), 7.58 (ddd, *J* = 7.9, 4.7, 0.9 Hz, 1H), 7.26 – 7.21 (m, 2H), 7.07 (d, *J* = 5.9 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 161.81, 158.70, 155.65 (br), 151.16, 148.98, 147.37 (br), 143.05 (br), 135.16, 133.43, 130.80 (br), 123.77, 122.24 (br), 121.54,

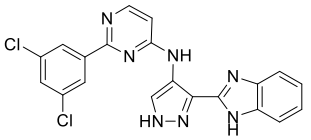
120.36 (br), 118.67 (br), 111.80 (br), 106.40 (br) (not all quaternary carbons were observed). LCMS (Fleet, 10 → 90%): t_r = 2.62 min, m/z: 355.3. HRMS $[C_{19}H_{14}N_8 + H]^+$: 355.14142 calculated, 355.14143 found.

***N*-(3-(1*H*-Benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)-2-(3-isopropylphenyl)pyrimidin-4-amine (38)**



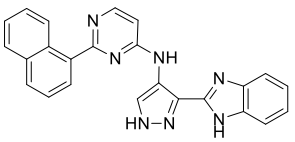
The title compound was synthesized from **97** (72.4 mg, 110 µmol) according to general procedure A (reaction time: 2 h). The crude was loaded onto Celite and purified by automated column chromatography (20 – 55% EtOAc/DCM) to afford the product (35.5 mg, 89.8 µmol, 81%). ^{1}H NMR (500 MHz, DMSO) δ 13.24 (br s, 2H), 10.19 (br s, 1H), 8.63 (br s, 1H), 8.46 (d, *J* = 5.8 Hz, 1H), 8.30 (t, *J* = 1.8 Hz, 1H), 8.22 (dt, *J* = 7.6, 1.5 Hz, 1H), 7.66 (br s, 2H), 7.45 (t, *J* = 7.6 Hz, 1H), 7.39 (dt, *J* = 7.7, 1.5 Hz, 1H), 7.28 – 7.22 (m, 2H), 7.01 (d, *J* = 5.9 Hz, 1H), 3.01 (hept, *J* = 6.9 Hz, 1H), 1.29 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (126 MHz, DMSO) δ 163.61, 158.60, 155.66 (br), 148.56, 147.55, 142.89 (br), 138.15, 133.73 (br), 130.83 (br), 128.75, 128.56, 125.53, 125.39, 122.22 (br), 121.91, 119.68 (br), 118.50 (br), 111.57 (br), 105.68 (br), 33.51, 23.98. LCMS (Fleet, 10 → 90%): t_r = 4.11 min, m/z: 396.3. HRMS $[C_{23}H_{21}N_7 + H]^+$: 396.19312 calculated, 396.19308 found.

***N*-(3-(1*H*-Benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)-2-(3,5-dichlorophenyl)pyrimidin-4-amine (39)**



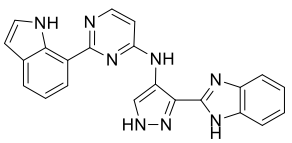
The title compound was synthesized from **98** (128 mg, 188 µmol) according to general procedure A (reaction time: 2 h). The crude was purified by HPLC (Agilent, 25 – 31% MeCN in 0.2% TFA (aq.)) after which the fractions were concentrated and traces of TFA were removed by coevaporation with 1:1 MeCN/H_2O (20 mL). The residue was dissolved in EtOAc (20 mL) and poured into 1 M $NaHCO_3$ (aq.) (20 mL). The organic layer was separated and the water layer extracted with EtOAc (20 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated to afford the product (35.4 mg, 83.8 µmol, 45%). ^{1}H NMR (400 MHz, DMSO) δ 13.43 (s, 1H), 13.04 (br s, 1H), 10.20 (br s, 1H), 8.46 (s, 1H), 8.41 (d, *J* = 5.9 Hz, 1H), 8.22 (d, *J* = 2.0 Hz, 2H), 7.70 (t, *J* = 2.0 Hz, 1H), 7.62 (br s, 2H), 7.28 – 7.19 (m, 2H), 7.01 (d, *J* = 5.9 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 160.69, 158.72, 155.49 (br), 147.40, 142.78 (br), 141.42, 134.44, 133.64 (br), 131.16 (br), 129.69, 126.09, 122.23 (br), 121.38, 119.92, 118.55 (br), 111.54 (br), 106.78 (br). LCMS (Finnigan, 10 → 90%): t_r = 5.15 min, m/z: 422.4. HRMS $[C_{20}H_{13}Cl_2N_7 + H]^+$: 422.06823 calculated, 422.06827 found.

***N*-(3-(1*H*-Benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)-2-(naphthalen-1-yl)pyrimidin-4-amine (40)**



The title compound was synthesized from **99** (134 mg, 201 µmol) according to general procedure A (reaction time: 2 h). The crude was purified by automated column chromatography (20 – 55% EtOAc/DCM) to afford the product (49.3 mg, 122 µmol, 61%). ^{1}H NMR (500 MHz, DMSO) δ 13.15 (br s, 2H), 10.27 (br s, 1H), 8.77 – 8.72 (m, 1H), 8.56 (d, *J* = 5.9 Hz, 1H), 8.42 (s, 1H), 8.09 – 8.05 (m, 2H), 8.04 – 7.99 (m, 1H), 7.74 (br s, 2H), 7.66 (dd, *J* = 8.2, 7.1 Hz, 1H), 7.59 – 7.55 (m, 2H), 7.29 – 7.24 (m, 2H), 7.11 (d, *J* = 5.9 Hz, 1H). ^{13}C NMR (126 MHz, DMSO) δ 165.78, 158.37 (br), 155.55 (br), 147.57 (br), 142.97 (br), 136.79, 133.80 (br), 133.64, 130.85 (br), 130.49, 129.78, 128.48, 128.41, 126.46, 126.10, 125.90, 125.34, 122.47 (br), 121.87, 119.89 (br), 118.55 (br), 111.55 (br), 105.33 (br). LCMS (Fleet, 10 → 90%): t_r = 3.52 min, m/z: 404.3. HRMS $[C_{24}H_{17}N_7 + H]^+$: 404.16182 calculated, 404.16171 found.

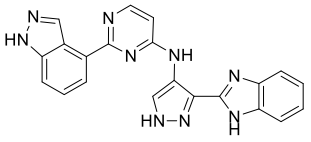
***N*-(3-(1*H*-Benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)-2-(1*H*-indol-7-yl)pyrimidin-4-amine (41)**



A microwave vial was charged with **100** (92.6 mg, 142 µmol) after which TBAF (1 M in THF, 2.5 mL) and ethylenediamine (28.6 µL, 425 µmol) were added. The mixture heated to 80°C, stirred for 2 days and subsequently poured into H_2O (20 mL). The product was extracted with EtOAc (2x20 mL) and the combined organic layers were concentrated as such. The mixture was dissolved in 1:1 MeOH/DCM (2 mL) and transferred to a microwave vial. Ethylenediamine (50 µL, 746 µmol) was added after which the vial was sealed and the

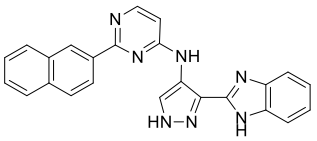
mixture was stirred at 50°C for 1 h. The mixture was poured into H_2O (20 mL) and the product extracted with EtOAc (2x20 mL). The combined organic layers were concentrated as such, the crude was loaded onto Celite and purified by automated column chromatography (25 – 100% EtOAc/DCM) to afford the product (16.5 mg, 42.0 µmol, 30%). ^{1}H NMR (400 MHz, DMSO) δ 13.40 (br s, 1H), 13.05 (br s, 1H), 11.57 (br s, 1H), 10.14 (br s, 1H), 8.65 (br s, 1H), 8.53 (d, *J* = 5.9 Hz, 1H), 8.30 (dd, *J* = 7.5, 1.1 Hz, 1H), 7.78 (d, *J* = 7.6 Hz, 1H), 7.75 (br s, 1H), 7.53 (br s, 1H), 7.47 (t, *J* = 2.8 Hz, 1H), 7.29 – 7.20 (m, 3H), 6.98 (br s, 1H), 6.57 (dd, *J* = 3.1, 2.1 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 164.17, 158.70 (br), 155.22 (br), 147.43 (br), 143.04 (br), 134.39, 133.72 (br), 131.46 (br), 129.23, 126.06, 123.35, 122.74 (br), 121.78 (br), 121.57 (br), 121.43, 120.68, 120.58 (br), 118.88, 118.62 (br), 111.55 (br), 105.11 (br), 101.47. LCMS (Fleet, 10 → 90%): t_r = 3.77 min, m/z: 393.3. HRMS [$C_{22}H_{16}N_8$ + H]$^+$: 393.15707 calculated, 393.15677 found.

N-(3-(1*H*-Benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)-2-(1*H*-indazol-4-yl)pyrimidin-4-amine (42)



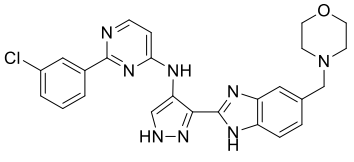
The title compound was synthesized from **101** (101 mg, 155 µmol) according to general procedure A (reaction time: 2.5 h). The crude was loaded onto Celite and purified by automated column chromatography (60 – 100% EtOAc/DCM) to afford the product (36.5 mg, 92.8 µmol, 60%). ^{1}H NMR (500 MHz, DMSO) δ 13.66 – 12.82 (br m, 3H), 10.22 (br s, 1H), 8.87 (br s, 1H), 8.59 (br s, 1H), 8.57 (d, *J* = 5.8 Hz, 1H), 8.23 (d, *J* = 7.2 Hz, 1H), 7.77 (br s, 1H), 7.75 (d, *J* = 8.3 Hz, 1H), 7.58 (br s, 1H), 7.55 (dd, *J* = 8.3, 7.2 Hz, 1H), 7.29 – 7.22 (m, 2H), 7.04 (d, *J* = 5.9 Hz, 1H). ^{13}C NMR (126 MHz, DMSO) δ 164.02, 158.77, 155.86 (br), 147.54, 143.00 (br), 140.85, 135.20, 133.71 (br), 131.23, 125.79, 122.65 (br), 121.80, 121.16, 121.11, 120.10, 118.56 (br), 112.58, 111.58 (br), 105.48 (br). LCMS (Fleet, 10 → 90%): t_r = 2.83 min, m/z: 394.3. HRMS [$C_{21}H_{15}N_9$ + H]$^+$: 394.15232 calculated, 394.15214 found.

N-(3-(1*H*-Benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)-2-(naphthalen-2-yl)pyrimidin-4-amine (43)



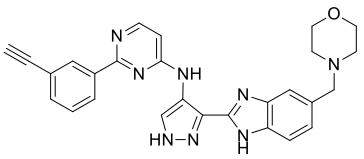
The title compound was synthesized from **102** (68.5 mg, 103 µmol) according to general procedure A (reaction time: 2 h). The crude was loaded onto Celite and purified by automated column chromatography (25 – 100% EtOAc/DCM) to afford the product (30.8 mg, 76.3 µmol, 74%). ^{1}H NMR (500 MHz, DMSO) δ 13.23 (br s, 2H), 10.23 (br s, 1H), 9.00 (s, 1H), 8.72 (br s, 1H), 8.53 (dd, *J* = 8.7, 1.8 Hz, 1H), 8.51 (d, *J* = 5.8 Hz, 1H), 8.17 – 8.12 (m, 1H), 8.07 (d, *J* = 8.6 Hz, 1H), 8.02 – 7.96 (m, 1H), 7.67 (br s, 2H), 7.62 – 7.55 (m, 2H), 7.28 – 7.23 (m, 2H), 7.05 (d, *J* = 5.8 Hz, 1H). ^{13}C NMR (126 MHz, DMSO) δ 163.44, 158.76 (br), 155.74 (br), 147.56 (br), 142.82 (br), 135.56, 134.10, 133.87 (br), 132.84, 130.92 (br), 129.08, 128.06, 127.81, 127.65, 127.22, 126.49, 124.98, 122.27 (br), 121.83, 119.98 (br), 118.48 (br), 111.59 (br), 105.76 (br). LCMS (Finnigan, 10 → 90%): t_r = 4.53 min, m/z: 404.4. HRMS [$C_{24}H_{17}N_7$ + H]$^+$: 404.16182 calculated, 404.16163 found.

2-(3-Chlorophenyl)-*N*-(3-(5-(morpholinomethyl)-1*H*-benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)pyrimidin-4-amine (44)



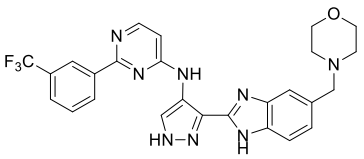
The title compound was synthesized from **119** (87.3 mg, 141 µmol) according to general procedure A (reaction time: 1.5 h). The crude was purified by automated column chromatography (0 – 10% MeOH/EtOAc) to afford the product (53.6 mg, 110 µmol, 78%). ^{1}H NMR (500 MHz, DMSO) δ 13.73 – 12.63 (br m, 2H), 10.22 (br s, 1H), 8.55 (s, 1H), 8.44 (d, *J* = 5.8 Hz, 1H), 8.35 – 8.33 (m, 2H), 7.67 – 7.44 (m, 4H), 7.17 (dd, *J* = 8.3, 0.9 Hz, 1H), 7.02 (d, *J* = 5.9 Hz, 1H), 3.58 – 3.55 (m, 4H), 3.54 (s, 2H), 2.40 – 2.32 (m, 4H). ^{13}C NMR (126 MHz, DMSO) δ 162.02, 158.70, 155.56 (br), 147.54 (br), 142.27 (br), 140.20, 133.70 (br), 133.45, 132.07 (br), 130.92 (br), 130.48, 130.21, 127.35, 126.28, 123.61 (br), 121.62, 119.80 (br), 118.04 (br), 111.54 (br), 106.31 (br), 66.27, 62.98, 53.22. LCMS (Fleet, 10 → 90%): t_r = 3.19 min, m/z: 487.3. HRMS [$C_{25}H_{23}ClN_8O$ + H]$^+$: 487.17561 calculated, 487.17545 found.

2-(3-Ethynylphenyl)-*N*-(3-(5-(morpholinomethyl)-1*H*-benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)pyrimidin-4-amine (45)



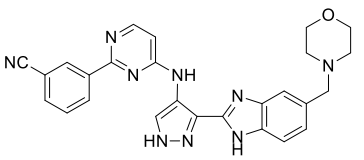
The title compound was synthesized from **120** (44.0 mg, 64.8 µmol) according to general procedure D (reaction time: 2 h). The crude was purified by automated column chromatography (0 – 10% MeOH/EtOAc) to afford the product (13.7 mg, 28.7 µmol, 44%). ^{1}H NMR (500 MHz, DMSO) δ 13.40 (br s, 1H), 13.02 (br s, 1H), 10.20 (br s, 1H), 8.55 (br s, 1H), 8.46 (d, *J* = 5.8 Hz, 1H), 8.44 – 8.41 (m, 2H), 7.67 (br s, 1H), 7.65 (dt, *J* = 7.6, 1.5 Hz, 1H), 7.58 (t, *J* = 7.7 Hz, 1H), 7.45 (br s, 1H), 7.18 (d, *J* = 8.2 Hz, 1H), 7.04 (d, *J* = 5.9 Hz, 1H), 4.30 (s, 1H), 3.61 – 3.54 (m, 6H), 2.44 – 2.32 (m, 4H). ^{13}C NMR (126 MHz, DMSO) δ 162.40, 158.74 (br), 155.65 (br), 147.48 (br), 142.91 (br), 142.19 (br), 138.49, 133.73 (br), 133.57, 132.54 (br), 131.32 (br), 130.88 (br), 130.77, 129.18, 128.26, 124.11 (br), 123.19 (br), 122.04, 121.64 (br), 119.98 (br), 118.96 (br), 118.01 (br), 111.67 (br), 111.04 (br), 106.37 (br), 83.35, 81.09, 66.27, 62.97, 53.24 (not all quaternary carbons were observed). LCMS (Fleet, 10 → 90%): t_r = 3.13 min, m/z: 477.3. HRMS $[C_{27}H_{24}N_8O + H]^+$: 477.21458 calculated, 477.21467 found.

***N*-(3-(5-(Morpholinomethyl)-1*H*-benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)-2-(3-(trifluoromethyl)phenyl)pyrimidin-4-amine (46)**



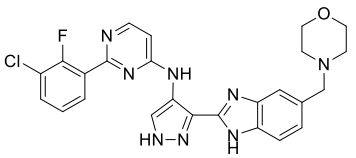
The title compound was synthesized from **121** (112 mg, 173 µmol) according to general procedure A (reaction time: 2.5 h). The crude was purified by automated column chromatography (0 – 10% MeOH/EtOAc) to afford the product (62.6 mg, 120 µmol, 70%). ^{1}H NMR (400 MHz, DMSO) δ 13.59 – 12.90 (br m, 2H), 10.26 (br s, 1H), 8.68 – 8.63 (m, 2H), 8.54 (br s, 1H), 8.45 (d, *J* = 5.8 Hz, 1H), 7.86 (d, *J* = 7.7 Hz, 1H), 7.76 (t, *J* = 8.0 Hz, 1H), 7.63 (br s, 1H), 7.50 (br s, 1H), 7.16 (d, *J* = 8.2 Hz, 1H), 7.03 (d, *J* = 5.9 Hz, 1H), 3.58 – 3.54 (m, 4H), 3.53 (s, 2H), 2.40 – 2.30 (m, 4H). ^{13}C NMR (101 MHz, DMSO) δ 161.86, 158.75, 155.59 (br), 147.56 (br), 142.95 (br), 142.25 (br), 139.01, 133.76 (br), 132.49 (br), 131.48, 130.98 (br), 129.85, 129.58, 129.27, 128.95, 128.35, 126.96 (br), 126.92 (br), 126.89 (br), 126.85 (br), 125.65, 124.20 (br), 124.04 (br), 124.00 (br), 123.97 (br), 123.93 (br), 123.39 (br), 122.94, 121.62, 119.83 (br), 118.91 (br), 118.05 (br), 111.65 (br), 111.08 (br), 106.48 (br), 66.28, 63.00, 53.25. LCMS (Fleet, 10 → 90%): t_r = 3.60 min, m/z: 521.25. HRMS $[C_{26}H_{23}F_3N_8O + H]^+$: 521.20197 calculated, 521.20212 found.

3-(4-((3-(5-(Morpholinomethyl)-1*H*-benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)amino)pyrimidin-2-yl)benzonitrile (47)



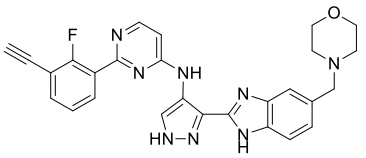
122 (100 mg, 165 mmol) was dissolved in DCM (1 mL) after which TFA (0.33 mL) was added dropwise. The mixture was stirred for 7.5 h and subsequently sat. $NaHCO_3$ (aq.) (10 mL) was added. The mixture was poured into H_2O (10 mL) and the product extracted with EtOAc (2x20 mL). The combined organic layers were concentrated as such and suspended in 1:1 MeOH/DCM (5 mL). Ethylenediamine (50 µL, 746 µmol) was added after which the mixture was stirred for 30 min. The mixture was poured into H_2O (20 mL), the product extracted with DCM (20 mL) and subsequently with 5% MeOH/DCM (20 mL). The combined organic layers were concentrated as such. The crude was purified by automated column chromatography (1 – 20% MeOH/DCM) to afford the product (34.5 mg, 72.2 µmol, 44%). ^{1}H NMR (400 MHz, DMSO) δ 13.39 (s, 1H), 13.03 – 12.96 (2x s, 1H), 10.35 – 10.16 (2x s, 1H), 8.69 – 8.62 (m, 2H), 8.56 (br s, 1H), 8.47 – 8.42 (2x d, *J* = 5.9 Hz, 1H), 7.96 (dt, *J* = 7.7, 1.5 Hz, 1H), 7.73 (t, *J* = 8.1 Hz, 1H), 7.69 – 7.64 (m, 1H), 7.47 – 7.42 (m, 1H), 7.21 – 7.13 (2x dd, *J* = 8.3, 1.5 Hz, 1H), 7.07 – 6.99 (2x d, *J* = 5.9 Hz, 1H), 3.61 – 3.51 (m, 6H), 2.43 – 2.31 (m, 4H). ^{13}C NMR (101 MHz, DMSO) δ 161.50, 158.72, 155.52 (br), 147.68 (br), 147.55 (br), 142.95, 142.23, 139.14, 133.87, 133.71, 132.82, 132.49 (br), 132.24, 131.24 (br), 131.06, 129.96, 124.14, 123.18, 121.52, 121.42, 120.02 (br), 118.93, 118.78, 118.03, 111.82, 111.68, 111.05, 106.62 (br), 66.26, 63.01, 62.93, 53.25, 53.20. LCMS (Fleet, 10 → 90%): t_r = 3.04 min, m/z: 478.2. HRMS $[C_{26}H_{23}N_9O + H]^+$: 478.20983 calculated, 478.21008 found.

2-(3-Chloro-2-fluorophenyl)-*N*-(3-(5-(morpholinomethyl)-1*H*-benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)pyrimidin-4-amine (48)



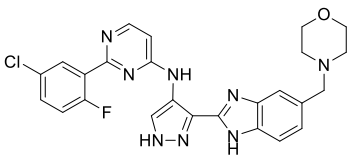
The title compound was synthesized from **123** (86.8 mg, 137 µmol) according to general procedure B (reaction time: 3 h). The crude was purified by automated column chromatography (0 – 10% MeOH/EtOAc) to afford the product (56.1 mg, 111 µmol, 81%). ^{1}H NMR (500 MHz, DMSO) δ 13.31 (br s, 1H), 12.99 (br s, 1H), 10.40 – 10.16 (br m, 1H), 8.55 (s, 1H), 8.46 (d, *J* = 5.8 Hz, 1H), 8.08 – 8.03 (m, 1H), 7.71 (ddd, *J* = 8.3, 6.7, 1.7 Hz, 1H), 7.68 (s, 1H), 7.45 (br s, 1H), 7.35 (td, *J* = 7.9, 1.0 Hz, 1H), 7.21 – 7.13 (br m, *J* = 8.4 Hz, 1H), 7.10 – 7.03 (br m, 1H), 3.61 – 3.51 (m, 6H), 2.42 – 2.31 (m, 4H). ^{13}C NMR (126 MHz, DMSO) δ 161.16, 161.12, 158.28, 156.74, 155.42 (br), 154.71, 147.62 (br), 142.95 (br), 142.22 (br), 133.72 (br), 132.81 (br), 132.53 (br), 131.90, 131.32 (br), 130.75 (br), 130.53, 128.47, 128.39, 125.15, 125.11, 124.10 (br), 123.17 (br), 121.70 (br), 121.15, 121.01, 119.82 (br), 118.89 (br), 117.99 (br), 111.66 (br), 111.03 (br), 106.25 (br), 66.27, 62.98, 53.23. LCMS (Fleet, 10 → 90%): t_r = 3.07 min, m/z: 505.3. HRMS $[C_{25}H_{22}ClFN_8O + H]^+$: 505.16619 calculated, 505.16584 found.

2-(3-Ethynyl-2-fluorophenyl)-*N*-(3-(5-(morpholinomethyl)-1*H*-benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)pyrimidin-4-amine (49)



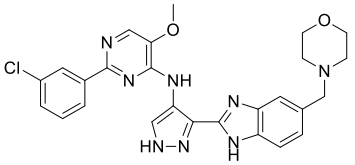
The title compound was synthesized from **124** (74.7 mg, 107 µmol) according to general procedure D (reaction time with TFA: 4 h). The crude was purified by automated column chromatography (0 – 10% MeOH/EtOAc) to afford the product (33.7 mg, 68.1 µmol, 64%). ^{1}H NMR (400 MHz, DMSO) δ 13.31 (br s, 1H), 13.02 (br s, 1H), 10.25 (br s, 1H), 8.56 (s, 1H), 8.47 (d, *J* = 5.9 Hz, 1H), 8.13 (td, *J* = 7.6, 1.8 Hz, 1H), 7.71 (ddd, *J* = 8.0, 6.4, 1.8 Hz, 1H), 7.66 (br s, 1H), 7.46 (br s, 1H), 7.36 (t, *J* = 7.7 Hz, 1H), 7.18 (d, *J* = 8.3 Hz, 1H), 7.08 (d, *J* = 5.9 Hz, 1H), 4.59 (s, 1H), 3.59 – 3.53 (m, 6H), 2.42 – 2.32 (m, 4H). ^{13}C NMR (101 MHz, DMSO) δ 162.15, 161.31, 161.27, 159.58, 158.27, 155.48 (br), 147.58 (br), 142.89 (br), 142.20 (br), 135.27, 133.73 (br), 132.83 (br), 132.56, 132.54, 131.35 (br), 130.51 (br), 127.24, 127.15, 124.56, 124.51, 124.11 (br), 123.29 (br), 121.74, 120.02 (br), 118.90 (br), 118.07 (br), 111.69 (br), 111.55, 111.38, 111.04 (br), 106.16 (br), 86.59, 86.55, 77.03, 77.02, 66.28, 62.99, 53.25. LCMS (Fleet, 10 → 90%): t_r = 3.01 min, m/z: 495.2. HRMS $[C_{27}H_{23}FN_8O + H]^+$: 495.20516 calculated, 495.20496 found.

2-(5-Chloro-2-fluorophenyl)-*N*-(3-(5-(morpholinomethyl)-1*H*-benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)pyrimidin-4-amine (50)



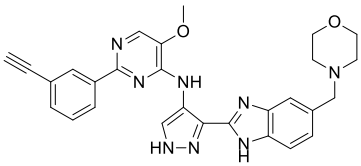
The title compound was synthesized from **125** (65.5 mg, 103 µmol) according to general procedure B (reaction time: 4 h). The crude was purified by automated column chromatography (0 – 10% MeOH/EtOAc) to afford the product (41.3 mg, 81.7 µmol, 79%). ^{1}H NMR (400 MHz, DMSO) δ 13.09 (br s, 2H), 10.28 (br s, 1H), 8.55 (s, 1H), 8.46 (d, *J* = 5.9 Hz, 1H), 8.09 (dd, *J* = 6.6, 2.8 Hz, 1H), 7.61 (ddd, *J* = 8.8, 4.0, 2.8 Hz, 1H), 7.55 (br s, 2H), 7.44 (dd, *J* = 10.8, 8.8 Hz, 1H), 7.17 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.07 (d, *J* = 5.9 Hz, 1H), 3.59 – 3.52 (m, 6H), 2.41 – 2.32 (m, 4H). ^{13}C NMR (101 MHz, DMSO) δ 160.65, 160.60, 160.49, 158.28, 157.97, 155.42 (br), 147.59, 131.94 (br), 131.53, 131.44, 130.92, 130.90, 130.66 (br), 128.33, 128.30, 128.19, 123.62 (br), 121.69, 119.99 (br), 119.16, 118.91, 106.35 (br), 66.28, 62.99, 53.25 (not all quaternary carbons were observed, neither were two –CH's of the benzimidazole). LCMS (Fleet, 10 → 90%): t_r = 3.04 min, m/z: 505.2. HRMS $[C_{25}H_{22}ClFN_8O + H]^+$: 505.16619 calculated, 505.16603 found.

2-(3-Chlorophenyl)-5-methoxy-*N*-(3-(5-(morpholinomethyl)-1*H*-benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)pyrimidin-4-amine (51)



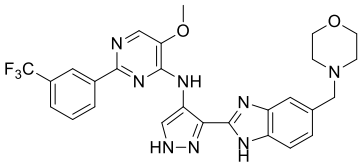
The title compound was synthesized from **127** (50 mg, 77 µmol) according to general procedure B (reaction time: 5.5 h). The crude was purified by automated column chromatography (1 – 20% MeOH/EtOAc) to afford the product (34.4 mg, 66.5 µmol, 86%). ^{1}H NMR (500 MHz, DMSO) δ 13.67 – 12.76 (br m, 2H), 10.72 (br s, 1H), 8.61 (s, 1H), 8.31 – 8.25 (m, 2H), 8.19 (s, 1H), 7.64 (br s, 1H), 7.57 – 7.50 (m, 2H), 7.45 (br s, 1H), 7.21 – 7.17 (br m, 1H), 4.14 (s, 3H), 3.61 – 3.53 (m, 6H), 2.42 – 2.33 (m, 4H). ^{13}C NMR (126 MHz, DMSO) δ 154.03, 149.70, 147.62 (br), 142.87 (br), 142.11 (br), 140.27, 139.76, 133.69 (br), 133.51, 133.38, 132.78 (br), 132.57 (br), 131.39 (br), 130.84 (br), 130.48, 129.22, 126.77, 125.76, 124.14 (br), 123.20 (br), 121.70, 119.00 (br), 118.90 (br), 117.99 (br), 111.71 (br), 111.11 (br), 66.28, 62.96, 56.62, 53.25. LCMS (Fleet, 10 → 90%): t_r = 3.79 min, m/z: 517.3. HRMS [$C_{26}H_{25}ClN_8O_2$ + H]$^+$: 517.18618 calculated, 517.18628 found.

2-(3-Ethynylphenyl)-5-methoxy-*N*-(3-(5-(morpholinomethyl)-1*H*-benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)pyrimidin-4-amine (52)



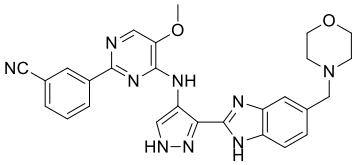
The title compound was synthesized from **128** (52.9 mg, 74.6 µmol) according to general procedure D (reaction time with TFA: 5 h). The crude was purified by automated column chromatography (1 – 15% MeOH/EtOAc) to afford the product (30.1 mg, 59.4 µmol, 80%). ^{1}H NMR (400 MHz, DMSO) δ 13.39 (br s, 1H), 13.03 (br s, 1H), 10.81 – 10.61 (2x s, 1H), 8.65 – 8.62 (2x s, 1H), 8.39 – 8.36 (m, 2H), 8.23 – 8.20 (2x s, 1H), 7.68 – 7.62 (m, 1H), 7.59 (dt, *J* = 7.6, 1.6 Hz, 1H), 7.57 – 7.53 (m, 1H), 7.49 – 7.43 (m, 1H), 7.25 – 7.15 (2x d, *J* = 8.2 Hz, 1H), 4.29 (s, 1H), 4.17 – 4.12 (2x s, 3H), 3.61 – 3.53 (m, 6H), 2.42 – 2.33 (m, 4H). ^{13}C NMR (101 MHz, DMSO) δ 154.46, 149.72, 147.70 (br), 147.61 (br), 142.87, 142.12, 139.69, 138.56, 133.68 (br), 133.61, 132.78 (br), 132.60, 131.39 (br), 130.84 (br), 130.22, 129.10, 127.76, 124.17 (br), 123.20 (br), 121.96, 121.75, 118.91 (br), 118.00 (br), 111.69 (br), 111.09 (br), 83.54, 80.93, 66.28, 62.96, 56.68, 56.60, 53.25. LCMS (Fleet, 10 → 90%): t_r = 3.68 min, m/z: 507.3. HRMS [$C_{28}H_{26}N_8O_2$ + H]$^+$: 507.22515 calculated, 507.22522 found.

5-Methoxy-*N*-(3-(5-(morpholinomethyl)-1*H*-benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)-2-(3-(trifluoromethyl)phenyl)pyrimidin-4-amine (53)



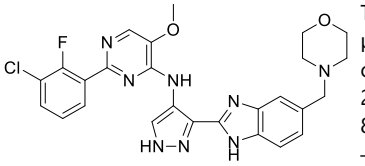
The title compound was synthesized from **129** (74.0 mg, 109 µmol) according to general procedure B (reaction time: 7 h). The crude was purified by automated column chromatography (1 – 20% MeOH/EtOAc) to afford the product (52.4 mg, 95.2 µmol, 88%). ^{1}H NMR (400 MHz, DMSO) δ 13.66 – 12.74 (br m, 2H), 10.74 (s, 1H), 8.63 – 8.56 (m, 3H), 8.19 (s, 1H), 7.82 – 7.78 (m, 1H), 7.73 (t, *J* = 7.7 Hz, 1H), 7.67 – 7.60 (br m, 1H), 7.48 – 7.42 (br m, 1H), 7.23 – 7.14 (br m, 1H), 4.14 (s, 3H), 3.62 – 3.52 (m, 6H), 2.43 – 2.30 (m, 4H). ^{13}C NMR (101 MHz, DMSO) δ 153.88, 149.75, 147.63 (br), 142.90 (br), 142.15 (br), 139.87, 139.07, 133.71 (br), 133.44, 132.81 (br), 132.58 (br), 131.38 (br), 130.93, 129.83 (br), 129.79, 129.51, 129.20, 128.88, 128.43, 125.93 (br), 125.90 (br), 125.86 (br), 125.83 (br), 125.73, 124.16 (br), 123.42 (br), 123.39 (br), 123.34 (br), 123.30 (br), 123.21 (br), 123.02, 121.71, 118.94 (br), 118.00 (br), 111.70 (br), 111.10 (br), 66.29, 62.98, 56.61, 53.26. LCMS (Fleet, 10 → 90%): t_r = 4.22 min, m/z: 551.3. HRMS [$C_{27}H_{25}F_3N_8O_2$ + H]$^+$: 551.21253 calculated, 551.21229 found.

3-(5-Methoxy-4-((3-(5-(morpholinomethyl)-1*H*-benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)amino)pyrimidin-2-yl)benzonitrile (54)



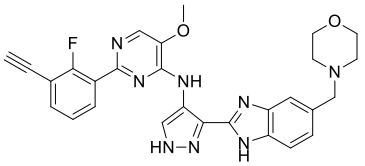
The title compound was synthesized from **130** (62.4 mg, 97.8 µmol) according to general procedure B (reaction time: 7 h). The crude was purified by automated column chromatography (1 – 20% MeOH/EtOAc) to afford the product (44.6 mg, 87.9 µmol, 90%). ^{1}H NMR (400 MHz, DMSO) δ 13.50 – 12.66 (br m, 2H), 10.71 (s, 1H), 8.60 (s, 1H), 8.60 – 8.55 (m, 2H), 8.14 (s, 1H), 7.87 (dt, *J* = 7.7, 1.4 Hz, 1H), 7.67 (t, *J* = 7.8 Hz, 1H), 7.62 (br s, 1H), 7.45 (br s, 1H), 7.22 – 7.14 (m, 1H), 4.13 (s, 3H), 3.61 – 3.53 (m, 6H), 2.43 – 2.32 (m, 4H). ^{13}C NMR (101 MHz, DMSO) δ 153.43, 149.71, 147.61 (br), 142.85 (br), 142.17 (br), 139.89, 139.18, 133.69 (br), 133.31, 132.82, 132.53 (br), 131.67, 131.44 (br), 130.80 (br), 130.42, 129.83, 124.14 (br), 123.21 (br), 121.60, 119.25 (br), 118.94, 118.01 (br), 111.71, 111.08 (br), 66.30, 62.99, 56.60, 53.27. LCMS (Fleet, 10 → 90%): t_r = 3.66 min, m/z: 508.2. HRMS [$C_{27}H_{25}N_9O_2$ + H]$^+$: 508.22040 calculated, 508.22051 found.

2-(3-Chloro-2-fluorophenyl)-5-methoxy-*N*-(3-(5-(morpholinomethyl)-1*H*-benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)pyrimidin-4-amine (55)



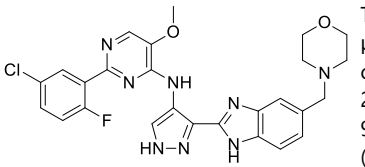
The title compound was synthesized from **131** (60.3 mg, 90.6 µmol) according to general procedure B (reaction time: 4 h). The crude was purified by automated column chromatography (2 – 20% MeOH/EtOAc) to afford the product (42.1 mg, 78.7 µmol, 87%). ^{1}H NMR (400 MHz, DMSO) δ 13.72 – 12.72 (br m, 2H), 10.74 – 10.68 (2x s, 1H), 8.60 (s, 1H), 8.23 (s, 1H), 8.05 (td, *J* = 7.8, 1.6 Hz, 1H), 7.70 – 7.60 (m, 2H), 7.48 – 7.42 (m, 1H), 7.33 (td, *J* = 7.9, 1.0 Hz, 1H), 7.24 – 7.14 (m, 1H), 4.18 – 4.12 (2x s, 3H), 3.60 – 3.53 (m, 6H), 2.41 – 2.33 (m, 4H). ^{13}C NMR (101 MHz, DMSO) δ 156.79, 154.26, 152.83, 152.78, 149.38, 147.68, 147.59, 142.89, 142.15, 139.41, 133.71, 133.58, 132.81, 132.56, 131.37, 131.18, 130.57, 130.29, 130.28, 128.37, 128.28, 125.09, 125.04, 124.16, 123.20, 121.77, 121.17, 120.98, 119.37 (br), 118.93, 117.99, 111.71, 111.09, 66.29, 62.97, 56.64, 56.57, 53.26. LCMS (Fleet, 10 → 90%): t_r = 3.70 min, m/z: 535.3. HRMS [$C_{26}H_{24}ClFN_8O_2$ + H]$^+$: 535.17675 calculated, 535.17673 found.

2-(3-Ethynyl-2-fluorophenyl)-5-methoxy-*N*-(3-(5-(morpholinomethyl)-1*H*-benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)pyrimidin-4-amine (56)



The title compound was synthesized from **132** (85.7 mg, 118 µmol) according to general procedure D (reaction time with TFA: 3 h). The crude was purified by automated column chromatography (1 – 20% MeOH/EtOAc) to afford the product (50.2 mg, 95.7 µmol, 81%). ^{1}H NMR (400 MHz, DMSO) δ 13.32 (s, 1H), 13.02 (s, 1H), 10.73 – 10.66 (2x s, 1H), 8.64 – 8.61 (2x s, 1H), 8.27 – 8.22 (2x s, 1H), 8.13 (td, *J* = 7.7, 1.8 Hz, 1H), 7.68 – 7.63 (m, 2H), 7.47 – 7.43 (m, 1H), 7.34 (t, *J* = 7.8 Hz, 1H), 7.23 – 7.16 (2x dd, *J* = 8.2, 1.5 Hz, 1H), 4.58 (s, 1H), 4.17 – 4.13 (2x s, 3H), 3.60 – 3.55 (m, 6H), 2.42 – 2.33 (m, 4H). ^{13}C NMR (101 MHz, DMSO) δ 161.95, 159.38, 152.98, 152.94, 149.34, 147.72, 147.62, 142.87, 142.13, 139.34, 134.53, 133.69, 133.65, 132.78, 132.58, 132.31, 132.28, 131.38, 130.74, 127.09, 127.00, 124.45, 124.41, 124.16, 123.19, 121.77, 119.13, 118.92, 117.99, 111.69, 111.51, 111.34, 111.08, 86.41, 86.38, 77.19, 77.17, 66.38, 66.28, 62.96, 56.65, 56.57, 53.26, 53.24. LCMS (Fleet, 10 → 90%): t_r = 3.61 min, m/z: 525.3. HRMS [$C_{28}H_{25}FN_8O_2$ + H]$^+$: 525.21573 calculated, 525.21579 found.

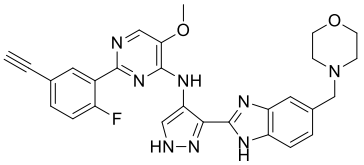
2-(5-Chloro-2-fluorophenyl)-5-methoxy-*N*-(3-(5-(morpholinomethyl)-1*H*-benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)pyrimidin-4-amine (57)



The title compound was synthesized from **133** (56.6 mg, 85.1 µmol) according to general procedure B (reaction time: 7 h). The crude was purified by automated column chromatography (1 – 20% MeOH/EtOAc) to afford the product (40.9 mg, 76.5 µmol, 90%). ^{1}H NMR (400 MHz, DMSO) δ 13.61 – 12.81 (br m, 2H), 10.70 (s, 1H), 8.61 – 8.60 (2x s, 1H), 8.22 (s, 1H), 8.07 (dd, *J* = 6.7, 2.8 Hz,

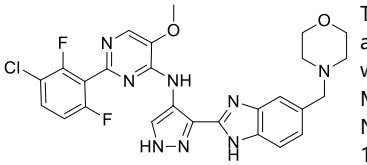
1H), 7.68 – 7.59 (br m, 1H), 7.55 (ddd, *J* = 8.8, 4.0, 2.8 Hz, 1H), 7.45 (br s, 1H), 7.41 (dd, *J* = 10.9, 8.8 Hz, 1H), 7.24 – 7.14 (br m, 1H), 4.15 (s, 3H), 3.61 – 3.53 (m, 6H), 2.42 – 2.32 (m, 4H). ^{13}C NMR (101 MHz, DMSO) δ 160.27, 157.76, 152.33, 152.28, 149.35, 147.64 (br), 142.89 (br), 142.14 (br), 139.43, 133.70 (br), 133.54, 132.80 (br), 132.58 (br), 131.40, 130.72, 130.63, 130.60, 130.58, 128.24, 128.21, 128.20, 128.09, 124.17 (br), 123.22 (br), 121.76, 119.12, 118.87, 118.00 (br), 111.71 (br), 111.09 (br), 66.29, 62.98, 56.61, 53.26. LCMS (Fleet, 10 → 90%): t_r = 3.68 min, m/z: 535.2. HRMS [$C_{26}H_{24}ClFN_8O_2$ + H]$^+$: 535.17675 calculated, 535.17674 found.

2-(5-Ethynyl-2-fluorophenyl)-5-methoxy-*N*-(3-(5-(morpholinomethyl)-1*H*-benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)pyrimidin-4-amine (58)



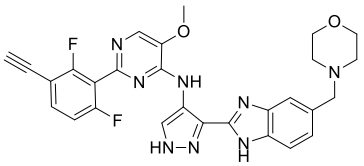
The title compound was synthesized from **134** (86.1 mg, 118 µmol) according to general procedure D (reaction time with TFA: 5 h). The crude was purified by automated column chromatography (1 – 20% MeOH/EtOAc) to afford the product (46.9 mg, 89.4 µmol, 75%). ^{1}H NMR (500 MHz, DMSO) δ 13.31 (br s, 1H), 13.02 (br s, 1H), 10.74 – 10.65 (2x s, 1H), 8.63 – 8.60 (2x s, 1H), 8.25 – 8.22 (2x s, 1H), 8.18 (dd, *J* = 7.5, 2.3 Hz, 1H), 7.68 – 7.60 (m, 2H), 7.48 – 7.43 (m, 1H), 7.40 (dd, *J* = 11.1, 8.5 Hz, 1H), 7.21 (2x dd, *J* = 8.2, 1.5 Hz, 1H), 4.24 (s, 1H), 4.18 – 4.13 (2x s, 3H), 3.62 – 3.53 (m, 6H), 2.43 – 2.32 (m, 4H). ^{13}C NMR (126 MHz, DMSO) δ 161.29, 159.26, 152.66, 152.63, 149.37, 147.70, 147.60, 142.88, 142.13, 139.38, 134.73, 134.34, 134.27, 133.69, 133.63, 132.79, 132.58, 131.38, 130.76, 127.08, 126.99, 124.16, 123.20, 121.80, 119.10, 118.92, 118.07, 118.04, 117.99, 117.84, 117.65, 111.69, 111.08, 82.37, 80.75, 66.28, 62.96, 56.65, 56.57, 53.26. LCMS (Fleet, 10 → 90%): t_r = 3.59 min, m/z: 525.2. HRMS [$C_{28}H_{25}FN_8O_2$ + H]$^+$: 525.21573 calculated, 525.21586 found.

2-(3-Chloro-2,6-difluorophenyl)-5-methoxy-*N*-(3-(5-(morpholinomethyl)-1*H*-benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)pyrimidin-4-amine (59)



The title compound was synthesized from 137 (10 mg, 15 µmol) according to general procedure B (reaction time: 5 h). The crude was purified by automated column chromatography (1 – 15% MeOH/EtOAc) to afford the product (7.1 mg, 13 µmol, 88%). ^{1}H NMR (600 MHz, DMSO) δ 13.41 – 12.84 (br m, 2H), 10.72 (br s, 1H), 8.36 (s, 1H), 8.26 (s, 1H), 7.77 (td, *J* = 8.7, 5.5 Hz, 1H), 7.71 – 7.57 (br m, 1H), 7.52 – 7.40 (br m, 1H), 7.34 (td, *J* = 9.0, 1.7 Hz, 1H), 7.23 – 7.18 (br m, 1H), 4.17 (s, 3H), 3.61 – 3.56 (m, 6H), 2.43 – 2.36 (m, 4H). ^{13}C NMR (151 MHz, DMSO) δ 159.49, 159.46, 157.84, 157.80, 156.10, 156.05, 154.43, 154.38, 149.50, 148.65, 147.52 (br), 142.04 (br), 139.64, 134.67 (br), 133.56, 132.77 (br), 131.43 (br), 130.84, 130.77, 124.11 (br), 123.15 (br), 121.50, 119.14 (br), 119.07, 118.95, 118.94, 118.82, 117.97 (br), 116.06, 116.03, 115.94, 115.91, 113.36, 113.34, 113.20, 113.18, 111.67 (br), 111.05 (br), 66.25, 62.91, 56.66, 53.23. LCMS (Fleet, 10 → 90%): t_r = 3.80 min, m/z: 553.3. HRMS [$C_{26}H_{23}ClF_2N_8O_2$ + H]$^+$: 553.16733 calculated, 553.16754 found.

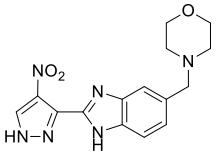
2-(3-Ethynyl-2,6-difluorophenyl)-5-methoxy-*N*-(3-(5-(morpholinomethyl)-1*H*-benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)pyrimidin-4-amine (60)



The title compound was synthesized from 138 (24 mg, 32 µmol) according to general procedure D (reaction time with TFA: 5 h). The crude was purified by automated column chromatography (1 – 15% MeOH/EtOAc) to afford the product (16.6 mg, 30.6 µmol, 95%). ^{1}H NMR (400 MHz, DMSO) δ 13.38 – 12.90 (br m, 2H), 10.72 (s, 1H), 8.36 (s, 1H), 8.26 (s, 1H), 7.73 (td, *J* = 8.2, 6.1 Hz, 1H), 7.69 – 7.60 (br m, 1H), 7.49 – 7.41 (br m, 1H), 7.31 (td, *J* = 8.9, 1.3 Hz, 1H), 7.25 – 7.16 (br m, 1H), 4.57 (s, 1H), 4.17 (s, 3H), 3.64 – 3.53 (m, 6H), 2.44 – 2.33 (m, 4H). ^{13}C NMR (101 MHz, DMSO) δ 161.99, 161.92, 161.33, 161.27, 159.46, 159.39, 158.81, 158.75, 149.50, 148.72, 147.55 (br), 142.88 – 142.61 (m), 142.16 – 142.02 (m), 139.61, 134.45, 134.35, 133.67 (br), 133.58, 132.76 (br), 132.62 (br), 131.43 (br), 130.73 (br), 124.15 (br), 123.19 (br), 121.56, 119.18 (br), 118.93 (br), 118.27, 118.09, 118.01 (br), 117.90, 112.86, 112.82, 112.63, 112.60, 111.70 (br), 111.11 (br), 107.21, 107.17, 107.04, 107.00, 86.36, 76.02, 66.27,

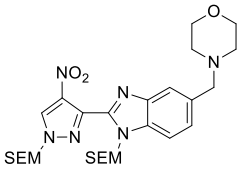
62.94, 56.67, 53.25. LCMS (Fleet, 10 → 90%): t_r = 3.69 min, m/z: 543.3. HRMS $[C_{28}H_{24}F_2N_8O_2 + H]^+$: 543.20630 calculated, 543.20646 found.

4-((2-(4-Nitro-1*H*-pyrazol-3-yl)-1*H*-benzo[*d*]imidazol-5-yl)methyl)morpholine (61)



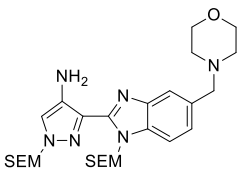
The title compound was synthesized as described in **Chapter 2** (compound 29)

4-((2-(4-Nitro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-benzo[*d*]imidazol-5-yl)methyl)morpholine (62) & 3 regioisomers



61 (3.07 g, 9.35 mmol) was suspended in dry DCM (45 mL) and cooled down to 0°C. DIPEA (5.1 mL, 29 mmol) was added after which SEM-Cl (3.56 mL, 20.1 mmol) was added dropwise. The mixture was left to stir at 0°C and allowed to warm to RT overnight. The mixture was poured into 0.05 M $NaHCO_3$ (aq.) (150 mL) and the product extracted with DCM (2x100 mL). The combined organic layers were washed with brine (200 mL) and the layers were separated. The brine layer was extracted with DCM (30 mL) after which the combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude was purified several times either by manual or automated column chromatography to separate all four regioisomers (total yield: 3.26 g, 5.54 mmol, 60%). NMR data (sorted on descending isomer lipophilicity as determined by TLC analysis): Regioisomer 1 – yield (1.34 g, 2.28 mmol, 25%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.79 (d, *J* = 8.3 Hz, 1H), 7.61 (s, 1H), 7.39 (dd, *J* = 8.4, 1.3 Hz, 1H), 5.83 – 5.40 (br m, 2H), 5.32 (br s, 2H), 3.75 – 3.70 (m, 4H), 3.67 (s, 2H), 3.62 (br s, 2H), 3.43 – 3.36 (m, 2H), 2.56 – 2.45 (m, 4H), 0.89 – 0.72 (m, 4H), -0.05 (s, 9H), -0.08 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.58, 139.22, 136.37, 136.13, 135.38, 135.30, 131.10, 125.13, 120.56, 111.35, 79.55, 74.39, 68.22, 67.14, 67.05, 63.81, 53.82, 17.94, 17.83, -1.33, -1.42. LCMS (Finnigan, 10 → 90%): t_r = 7.89 min, m/z: 589.1. Regioisomer 2 – yield (765 mg, 1.30 mmol, 14%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.78 (s, 1H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.45 (dd, *J* = 8.4, 1.2 Hz, 1H), 5.77 – 5.38 (br m, 2H), 5.31 (br s, 2H), 3.74 – 3.70 (m, 4H), 3.65 (s, 2H), 3.60 (br s, 2H), 3.42 – 3.35 (m, 2H), 2.52 – 2.46 (m, 4H), 0.87 – 0.72 (m, 4H), -0.06 (s, 9H), -0.09 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.24, 139.27, 136.31, 136.11, 134.47, 133.60, 131.05, 126.36, 121.20, 110.85, 79.53, 74.45, 68.17, 67.12, 67.01, 63.57, 53.71, 17.89, 17.77, -1.38, -1.46. LCMS (Finnigan, 10 → 90%): t_r = 8.00 min, m/z: 589.1. Regioisomer 3 – yield (502 mg, 0.853 mmol, 9%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.48 (s, 1H), 7.75 (d, *J* = 8.3 Hz, 1H), 7.55 (s, 1H), 7.31 (dd, *J* = 8.3, 1.3 Hz, 1H), 5.51 (s, 2H), 5.50 (s, 2H), 3.72 – 3.68 (m, 4H), 3.68 – 3.64 (m, 2H), 3.63 (s, 2H), 3.36 – 3.31 (m, 2H), 2.50 – 2.42 (m, 4H), 0.97 – 0.92 (m, 2H), 0.76 – 0.71 (m, 2H), -0.02 (s, 9H), -0.15 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.02, 142.38, 137.77, 135.63, 135.12, 134.29, 130.01, 124.66, 120.26, 111.10, 82.14, 73.76, 68.47, 67.04, 66.36, 63.79, 53.69, 17.90, 17.65, -1.36, -1.48. LCMS (Finnigan, 10 → 90%): t_r = 7.53 min, m/z: 589.1. Regioisomer 4 – yield (649 mg, 1.10 mmol, 12%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49 (s, 1H), 7.76 (s, 1H), 7.53 (d, *J* = 8.4 Hz, 1H), 7.38 (dd, *J* = 8.4, 1.2 Hz, 1H), 5.51 (s, 2H), 5.50 (s, 2H), 3.71 – 3.68 (m, 4H), 3.68 – 3.64 (m, 2H), 3.63 (s, 2H), 3.36 – 3.31 (m, 2H), 2.50 – 2.44 (m, 4H), 0.98 – 0.93 (m, 2H), 0.77 – 0.72 (m, 2H), -0.01 (s, 9H), -0.15 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.15, 143.09, 137.79, 135.69, 134.31, 132.95, 129.99, 125.68, 121.13, 110.56, 82.19, 73.88, 68.53, 67.09, 66.40, 63.64, 53.64, 17.94, 17.65, -1.33, -1.46. LCMS (Finnigan, 10 → 90%): t_r = 7.70 min, m/z: 589.1.

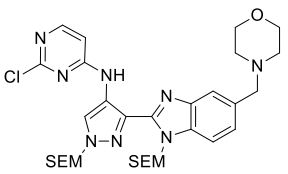
3-(5-(Morpholinomethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-benzo[*d*]imidazol-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-amine (63)



62 (502 mg, 853 µmol) was dissolved in degassed MeOH (10 mL). 10% Pd/C (60 mg) was added and the atmosphere was exchanged for H_2. The reaction was vigorously stirred for 3.5 h while bubbling H_2 through the mixture. The atmosphere was exchanged for N_2, the mixture was filtered over Celite and concentrated to afford the product, which was used as such in subsequent

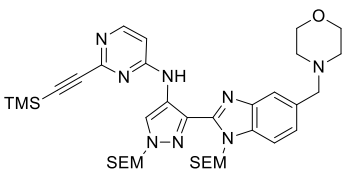
reaction (471 mg, 853 µmol, 99%). LCMS (Finnigan, 10 → 90%): t_r = 6.59 min, m/z: 559.1.

2-Chloro-*N*-(3-(5-(morpholinomethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-benzo[*d*]imidazol-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)pyrimidin-4-amine (64)



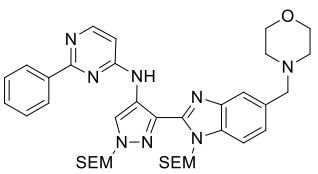
63 (471 mg, 843 µmol) was dissolved in EtOH (2 mL) after which DIPEA (450 µL, 2.69 mmol) and 2,4-dichloropyrimidine (119 mg, 801 µmol) were added. The mixture was stirred at 40°C for 3 days and subsequently poured into H_2O (50 mL). The product was extracted with DCM (2x50 mL) and the combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated. The crude was purified by silica gel column chromatography (1 – 4% MeOH/DCM) to afford the product (305 mg, 455 µmol, 54%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.00 (s, 1H), 8.57 (s, 1H), 8.11 (d, *J* = 5.8 Hz, 1H), 7.70 (d, *J* = 8.2 Hz, 1H), 7.56 (s, 1H), 7.32 (dd, *J* = 8.3, 1.4 Hz, 1H), 6.68 (d, *J* = 5.8 Hz, 1H), 6.26 (s, 2H), 5.50 (s, 2H), 3.75 – 3.69 (m, 4H), 3.69 – 3.60 (m, 6H), 2.54 – 2.44 (m, 4H), 0.99 – 0.94 (m, 2H), 0.90 – 0.85 (m, 2H), 0.00 (s, 9H), -0.12 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.95, 159.52, 156.33, 146.84, 141.60, 135.03, 133.84, 131.70, 124.71, 124.39, 121.18, 118.78, 111.47, 106.27, 81.29, 73.92, 67.17, 67.10, 66.15, 63.87, 53.76, 17.96, 17.83, -1.29, -1.34. LCMS (Finnigan, 10 → 90%): t_r = 8.73 min, m/z: 671.1.

***N*-(3-(5-(Morpholinomethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-benzo[*d*]imidazol-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-4-yl)-2-((trimethylsilyl)ethynyl)pyrimidin-4-amine (65)**



A microwave vial was charged with **64** (104 mg, 155 µmol) and Et_3N (1 mL). N_2 was bubbled through the mixture for 1 min after which $PdCl_2(PPh_3)_2$ and Cu(I)I were added. N_2 was bubbled through the mixture for 30 sec after which ethynyltrimethylsilane (100 µL, 722 µmol) was added and the vial was sealed. The mixture was heated to 89°C and stirred for 5 h. Ethynyltrimethylsilane (50 µL, 361 µmol) was added via syringe and the mixture was stirred at 90°C for 16 h. The mixture was diluted in MeOH (15 mL), filtered over Celite and subsequently concentrated. The crude was purified by automated column chromatography (0 – 10% MeOH/EtOAc) to afford the product (19.1 mg, 26.1 µmol, 17%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, *J* = 6.0 Hz, 1H), 8.05 (br s, 1H), 7.76 (br s, 1H), 7.72 (s, 1H), 7.44 (d, *J* = 8.3 Hz, 1H), 7.39 (dd, *J* = 8.4, 1.3 Hz, 1H), 6.49 (d, *J* = 6.0 Hz, 1H), 5.54 (s, 2H), 5.38 (s, 2H), 3.73 – 3.69 (m, 4H), 3.63 (s, 2H), 3.58 – 3.49 (m, 4H), 2.52 – 2.43 (m, 4H), 0.98 – 0.92 (m, 2H), 0.79 – 0.73 (m, 2H), 0.24 (s, 9H), -0.06 (s, 9H), -0.09 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.37, 152.04, 143.31, 142.29, 134.75, 134.56, 133.52, 125.97, 120.95, 110.24, 102.89, 92.42, 79.05, 73.79, 67.68, 67.30, 67.13, 63.58, 53.70, 17.99, 17.95, -0.30, -1.34, -1.42 (not all quaternary carbons were observed). LCMS (Finnigan, 10 → 90%): t_r = 6.64 min, m/z: 661.2.

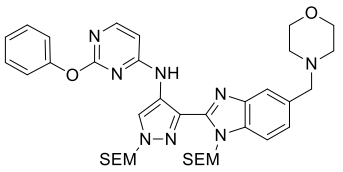
N-(3-(5-(Morpholinomethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-benzo[*d*]imidazol-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)-2-phenylpyrimidin-4-amine (66)



A microwave vial was charged with **64** (65.8 mg, 98.0 µmol), phenylboronic acid (20.3 mg, 167 µmol), K_2CO_3 (4.7 M (aq.), 83 µL, 392 µmol) and dioxane (0.33 mL). N_2 was bubbled through the mixture for 1 min after which $Pd(dppf)Cl_2$·DCM (4.0 mg, 4.9 µmol) was added. N_2 was bubbled through the mixture for 30 sec after which the vial was sealed. The mixture was heated to 90°C, stirred for 3.5 h and subsequently poured into H_2O (20 mL). The product was extracted with DCM (2x20 mL) and the combined organic layers were washed with brine (40 mL), dried over Na_2SO_4, filtered and concentrated. The crude was purified by automated column chromatography (50 – 100% EtOAc/pentane) to afford the product (34.2 mg, 47.9 µmol, 49%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.72 (s, 1H), 8.79 (s, 1H), 8.44 – 8.38 (m, 3H), 7.75 (d, *J* = 8.2 Hz, 1H), 7.58 (s, 1H), 7.56 – 7.48 (m, 3H), 7.35 (dd, *J* = 8.3, 1.4 Hz, 1H), 6.74 (d, *J* = 5.8 Hz, 1H), 6.30 (s, 2H), 5.56 (s, 2H), 3.77 – 3.73 (m, 4H), 3.72 – 3.62 (m, 6H), 2.54 – 2.48 (m, 4H), 1.02 – 0.96 (m, 2H), 0.92 – 0.87 (m, 2H), -0.01 (s, 9H), -0.10 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.85, 158.81, 155.36, 147.17, 141.86, 138.87, 135.14, 133.62, 131.67, 130.41,

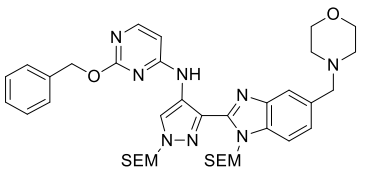
128.60, 128.22, 125.52, 124.69, 120.44, 118.90, 111.51, 106.05, 81.46, 73.99, 67.20, 67.15, 66.14, 63.96, 53.80, 18.01, 17.92, -1.24, -1.29. LCMS (Finnigan, 10 → 90%): t_r = 7.03 min, m/z: 713.3.

_N_-(3-(5-(Morpholinomethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1_H_-benzo[_d_]imidazol-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1_H_-pyrazol-4-yl)-2-phenoxypyrimidin-4-amine (67)



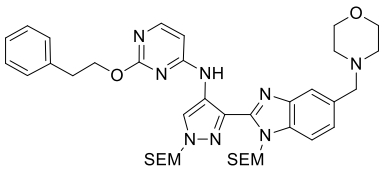
NaH (60% in mineral oil, 46 mg, 1.15 mmol) was suspended in dioxane (4 mL) and cooled down to 0°C. Phenol (116 mg, 1.23 mmol) was carefully added (H_2 evolution) and the mixture was allowed to warm to RT and stirred for 30 min. Of this mixture, 400 µL was added to a microwave vial charged with **64** (27.6 mg, 41.1 µmol) after which the vial was sealed and the mixture was stirred at 100°C for 16 h. Extra sodium phenolate was prepared freshly as described above, of which 100 µL was added to the mixture which was continued to stir at 100°C for 24 h. The mixture was poured into 1 M $NaHCO_3$ (aq.) (20 mL) and the product extracted with DCM (2x20 mL). The combined organic layers were concentrated as such and purified by automated column chromatography (0 – 15% MeOH/DCM) to afford the product (18 mg, 24.7 µmol, 60%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.76 (s, 1H), 8.19 (d, _J_ = 5.8 Hz, 1H), 7.73 (s, 1H), 7.56 – 7.45 (m, 4H), 7.36 – 7.31 (m, 2H), 7.30 – 7.27 (m, 2H), 6.52 (d, _J_ = 5.8 Hz, 1H), 6.23 (s, 2H), 5.19 (s, 2H), 3.76 – 3.71 (m, 4H), 3.66 (s, 2H), 3.59 – 3.55 (m, 2H), 3.54 – 3.50 (m, 2H), 2.55 – 2.45 (m, 4H), 0.94 – 0.89 (m, 2H), 0.88 – 0.83 (m, 2H), -0.00 (s, 9H), -0.13 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.10, 160.02, 157.35, 153.79, 147.16, 142.48, 134.32, 131.71, 129.76, 125.20, 124.60, 123.03, 121.44, 119.76, 110.78, 102.42, 80.96, 74.03, 67.16, 66.95, 66.06, 63.85, 53.75, 17.95, 17.87, -1.21, -1.33. LCMS (Finnigan, 10 → 90%): t_r = 7.37 min, m/z: 729.2.

2-(Benzyloxy)-_N_-(3-(5-(morpholinomethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1_H_-benzo[_d_]imidazol-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1_H_-pyrazol-4-yl)pyrimidin-4-amine (68)



NaH (60% in mineral oil, 90.0 mg, 2.25 mmol) was suspended in dioxane (3 mL) and cooled down to 0°C. Benzyl alcohol (250 µL, 2.41 mmol) was carefully added (H_2 evolution) and the mixture was allowed to warm to RT and stirred for 2 h. Of this mixture, 300 µL was added to a microwave vial charged with **64** (80.9 mg, 120 µmol) after which the vial was sealed and the mixture was stirred at 90°C for 16 h. The mixture was poured into H_2O (20 mL) and brine (0.5 mL), and the product extracted with DCM (2x20 mL). The combined organic layers were concentrated as such and purified by automated column chromatography (1 – 10% MeOH/DCM) to afford the product (63.3 mg, 85.2 µmol, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (br s, 1H), 8.05 (br s, 1H), 8.01 (d, _J_ = 5.8 Hz, 1H), 7.65 (d, _J_ = 8.3 Hz, 1H), 7.46 – 7.40 (m, 3H), 7.35 – 7.30 (m, 2H), 7.30 – 7.26 (m, 2H), 6.21 (d, _J_ = 5.8 Hz, 1H), 5.52 (s, 2H), 5.35 (s, 2H), 5.34 (s, 2H), 3.74 – 3.67 (m, 4H), 3.61 (s, 2H), 3.54 – 3.46 (m, 4H), 2.53 – 2.41 (m, 4H), 0.93 – 0.86 (m, 2H), 0.78 – 0.70 (m, 2H), -0.09 (s, 9H), -0.10 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.11, 162.37 (br), 157.83 (br), 142.48, 142.37, 136.83, 135.17, 134.75 (br), 134.53, 128.42, 127.91, 127.86, 124.89, 124.49 (br), 119.84, 110.94, 99.29 (br), 78.83, 73.75, 68.68, 67.38, 67.12, 67.06, 63.74, 53.72, 17.99, 17.87, -1.40, -1.46. LCMS (Finnigan, 10 → 90%): t_r = 6.82 min, m/z: 743.3.

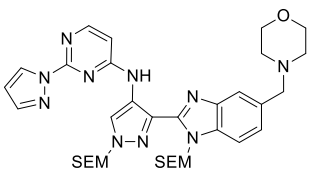
_N_-(3-(5-(Morpholinomethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1_H_-benzo[_d_]imidazol-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1_H_-pyrazol-4-yl)-2-phenethoxypyrimidin-4-amine (69)



NaH (60% in mineral oil, 120 mg, 3.02 mmol) was suspended in dioxane (6 mL), phenethyl alcohol (400 µL, 3.34 mmol) was carefully added and the mixture was stirred at 45°C for 3 h. The mixture was cooled down to RT and 300 µL was added to a microwave vial charged with **64** (61.3 mg, 91.3 µmol) after which the vial was sealed and the mixture was stirred at 90°C for 16 h. The mixture was poured into H_2O (20 mL) and the product extracted with DCM (2x20 mL). The combined organic layers were concentrated as such and purified by automated column chromatography (50 – 100% EtOAc/pentane) to afford the product (30.6 mg, 40.4 µmol, 44%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.72 (s, 1H), 8.57 (s, 1H), 8.11 (d, _J_ = 5.7 Hz, 1H), 7.75

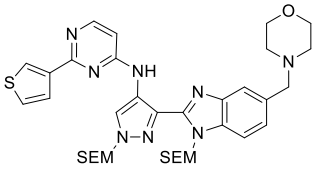
(s, 1H), 7.54 (d, *J* = 8.3 Hz, 1H), 7.38 – 7.30 (m, 5H), 7.26 – 7.22 (m, 1H), 6.46 (d, *J* = 5.8 Hz, 1H), 6.27 (s, 2H), 5.45 (s, 2H), 4.61 (t, *J* = 7.5 Hz, 2H), 3.77 – 3.71 (m, 4H), 3.67 (s, 2H), 3.66 – 3.57 (m, 4H), 3.19 (t, *J* = 7.5 Hz, 2H), 2.55 – 2.47 (m, 4H), 0.98 – 0.90 (m, 2H), 0.93 – 0.84 (m, 2H), -0.01 (s, 9H), -0.11 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.42, 160.49, 156.54, 147.18, 142.49, 138.32, 134.32, 132.80, 131.60, 129.13, 128.62, 126.57, 125.22, 125.20, 120.69, 119.79, 110.73, 101.95, 81.26, 74.02, 67.77, 67.14, 67.09, 66.08, 63.84, 53.73, 35.52, 17.94, 17.85, -1.25, -1.33. LCMS (Finnigan, 10 → 90%): t_r = 7.75 min, m/z: 757.3.

_N_-(3-(5-(Morpholinomethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1_H_-benzo[_d_]imidazol-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1_H_-pyrazol-4-yl)-2-(1_H_-pyrazol-1-yl)pyrimidin-4-amine (70)



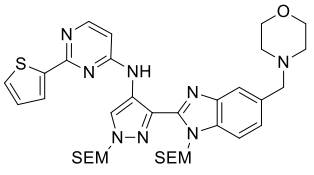
NaH (60% in mineral oil, 74 mg, 1.85 mmol) was suspended in dioxane (2 mL) and cooled down to 0°C. 1*H*-Pyrazole (155 mg, 2.28 mmol) was carefully added (H_2 evolution) and the mixture was allowed to warm to RT and stirred for 1.5 h. Of this mixture, 300 µL was added to a microwave vial charged with **64** (136 mg, 203 µmol) after which the vial was sealed and the mixture was stirred at 90°C for 45 min. The mixture was poured into H_2O (20 mL) and the product extracted with DCM (2x20 mL). The combined organic layers were concentrated as such and purified by automated column chromatography (70 – 100% EtOAc/pentane, then 0 – 10% MeOH/EtOAc) to afford the product (78.2 mg, 111 µmol, 55%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.98 (s, 1H), 8.86 (s, 1H), 8.56 – 8.52 (m, 1H), 8.29 (d, *J* = 5.8 Hz, 1H), 7.84 – 7.80 (m, 1H), 7.76 – 7.74 (m, 1H), 7.54 (d, *J* = 8.3 Hz, 1H), 7.33 (dd, *J* = 8.3, 1.4 Hz, 1H), 6.69 (d, *J* = 5.8 Hz, 1H), 6.48 (dd, *J* = 2.6, 1.6 Hz, 1H), 6.27 (s, 2H), 5.55 (s, 2H), 3.76 – 3.70 (m, 4H), 3.72 – 3.65 (m, 2H), 3.66 (s, 2H), 3.65 – 3.59 (m, 2H), 2.50 (s, 4H), 1.01 – 0.94 (m, 2H), 0.91 – 0.85 (m, 2H), -0.02 (s, 9H), -0.12 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.45, 156.01, 147.12, 143.05, 142.40, 134.28, 132.84, 131.67, 128.80, 125.20, 124.97, 121.25, 119.71, 110.72, 108.15, 105.21, 81.36, 74.00, 67.19, 67.09, 66.08, 63.79, 53.69, 17.92, 17.83, -1.30, -1.37. LCMS (Finnigan, 10 → 90%): t_r = 8.03 min, m/z: 703.2.

_N_-(3-(5-(Morpholinomethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1_H_-benzo[_d_]imidazol-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1_H_-pyrazol-4-yl)-2-(thiophen-3-yl)pyrimidin-4-amine (71)



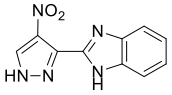
A microwave vial was charged with **64** (75.0 mg, 112 µmol), thiophene-3-boronic acid pinacol ester (27.5 mg, 134 µmol), K_2CO_3 (61.8 mg, 447 µmol), dioxane (0.8 mL) and H_2O (0.2 mL). N_2 was bubbled through the mixture for 1 min after which Pd(dppf)Cl_2·DCM (6.5 mg, 8.0 µmol) was added. N_2 was bubbled through the mixture for 30 sec after which the vial was sealed and the mixture was stirred at 100°C for 6 h. The mixture was diluted in 1:1:1 EtOAc/H_2O/brine (9 mL) and filtered over Celite. The mixture was poured into H_2O (10 mL) and EtOAc (10 mL) and the layers were separated. The organic layer was washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated. The crude was purified by automated column chromatography (0 – 10% MeOH/DCM) and used as such in subsequent reaction (yield: 43.2 mg). LCMS m/z: 719.3.

_N_-(3-(5-(Morpholinomethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1_H_-benzo[_d_]imidazol-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1_H_-pyrazol-4-yl)-2-(thiophen-2-yl)pyrimidin-4-amine (72)



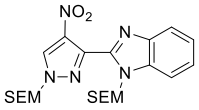
A microwave vial was charged with **64** (75.0 mg, 112 µmol), thiophene-2-boronic acid pinacol ester (27.5 mg, 134 µmol), K_2CO_3 (61.8 mg, 447 µmol), dioxane (0.8 mL) and H_2O (0.2 mL). N_2 was bubbled through the mixture for 1 min after which Pd(dppf)Cl_2·DCM (6.5 mg, 8.0 µmol) was added. N_2 was bubbled through the mixture for 30 sec after which the vial was sealed and the mixture was stirred at 100°C for 6 h. The mixture was poured into H_2O (10 mL) and the product extracted with DCM (10 mL). The organic layer was concentrated as such and purified by automated column chromatography (0 – 10% MeOH/DCM) and used as such in subsequent reaction (yield: 59.6 mg). LCMS (Finnigan, 10 → 90%): t_r = 7.31 min, m/z: 719.3.

2-(4-Nitro-1*H*-pyrazol-3-yl)-1*H*-benzo[*d*]imidazole (73)



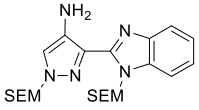
Benzene-1,2-diamine (9.39 g, 87.0 mmol), 4-nitro-1H-pyrazole-3-carboxylic acid (13.6 g, 87.0 mmol), EDC·HCl (16.7 g, 87.0 mmol) and HOBt (11.7 g, 87.0 mmol) were mixed in DMF (140 mL) and stirred for 18 h. The mixture was concentrated at 60°C after which AcOH (110 mL) was added and the reaction was stirred at 118°C for 75 min. Sat. $NaHCO_3$ (aq.) (440 mL) was added carefully while the mixture was stirred vigorously. The mixture was stirred for 1 h, filtered and the solids were washed with H_2O (2x50 mL). The solids were collected and traces of water were removed by coevaporation with MeOH to afford the product (14.0 g, 60.9 mmol, 70%). ^{1}H NMR (400 MHz, DMSO) δ 14.55 (br s, 1H), 13.01 (br s, 1H), 8.84 (br s, 1H), 7.74 – 7.67 (m, 2H), 7.33 – 7.24 (m, 2H). ^{13}C NMR (101 MHz, DMSO) δ 158.83, 141.58, 135.26, 134.13, 132.96, 122.89, 115.69 (br). LCMS (Finnigan, 0 → 90%): t_r = 4.51 min, m/z: 230.1.

2-(4-Nitro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-benzo[*d*]imidazole (74)



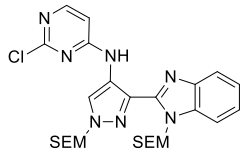
73 (10.0 g, 43.6 mmol) was suspended in DCM (220 mL) and cooled down to 0°C. DIPEA (22.8 mL, 131 mmol) was added after which SEM-Cl (17 mL, 96 mmol) was added dropwise. The mixture was stirred at 0°C for 15 min and then allowed to warm to RT and stirred for 1.5 h. The mixture was poured into 0.05 M $NaHCO_3$ (aq.) (300 mL) and the organic layer was separated. The water layer was extracted with DCM (150 mL) after which the combined organic layers were washed with brine (300 mL). The brine layer was extracted with DCM (100 mL) after which the organic layers were combined, dried over Na_2SO_4, filtered and concentrated. The crude was purified by silica gel chromatography (twice, 0 – 3% MeOH/DCM) to afford both regioisomers in pure form (total yield: 17.2 g, 35.2 mmol, 81%). NMR data (sorted on descending isomer lipophilicity): Regioisomer 1 – yield (8.45 g, 17.3 mmol, 40%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.86 (dd, *J* = 7.3, 1.0 Hz, 1H), 7.65 – 7.62 (m, 1H), 7.44 (td, *J* = 7.7, 1.3 Hz, 1H), 7.39 (td, *J* = 7.7, 1.3 Hz, 1H), 5.75 – 5.40 (br m, 2H), 5.39 – 5.29 (br m, 2H), 3.70 – 3.54 (br m, 2H), 3.44 – 3.36 (m, 2H), 0.90 – 0.70 (m, 4H), -0.05 (s, 9H), -0.08 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.11, 139.14, 136.31, 136.11, 135.19, 131.04, 124.92, 123.60, 120.90, 111.13, 79.52, 74.38, 68.15, 67.00, 17.86, 17.76, -1.40, -1.47. LCMS (Finnigan, 10 → 90%): t_r = 10.86 min, m/z: 490.0. Regioisomer 2 – yield (8.78 g, 17.9 mmol, 41%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 1H), 7.85 (dd, *J* = 7.1, 1.4 Hz, 1H), 7.60 (dd, *J* = 7.0, 1.3 Hz, 1H), 7.41 – 7.32 (m, 2H), 5.53 (s, 2H), 5.52 (s, 2H), 3.72 – 3.65 (m, 2H), 3.39 – 3.32 (m, 2H), 1.00 – 0.94 (m, 2H), 0.79 – 0.73 (m, 2H), 0.00 (s, 9H), -0.13 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.03, 142.98, 137.81, 135.71, 135.04, 129.99, 124.23, 123.20, 120.73, 110.85, 82.21, 73.84, 68.55, 66.43, 17.95, 17.68, -1.32, -1.45. LCMS (Finnigan, 10 → 90%): t_r = 9.48 min, m/z: 490.0.

1-((2-(Trimethylsilyl)ethoxy)methyl)-3-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-amine (75)



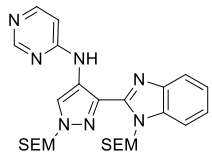
74 (8.78 g, 17.9 mmol) was dissolved in degassed MeOH (220 mL). 10% Pd/C (900 mg) was added and the atmosphere was exchanged for H_2. The reaction was vigorously stirred for 5.5 h while bubbling H_2 through the mixture. The atmosphere was exchanged for N_2, the mixture was filtered over Celite and concentrated to afford the product (7.87 g, 17.1 mmol, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 – 7.72 (m, 1H), 7.60 – 7.54 (m, 1H), 7.32 – 7.26 (m, 2H), 7.21 (s, 1H), 6.23 (s, 2H), 5.36 (s, 2H), 4.75 (s, 2H), 3.64 – 3.55 (m, 4H), 0.96 – 0.91 (m, 2H), 0.91 – 0.85 (m, 2H), -0.01 (s, 9H), -0.10 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.51, 143.12, 135.09, 133.80, 131.81, 123.01, 122.63, 119.29, 115.95, 110.77, 81.07, 73.88, 66.78, 65.80, 17.92, 17.85, -1.29, -1.36. LCMS (Finnigan, 10 → 90%): t_r = 8.61 min, m/z: 460.1.

2-Chloro-*N*-(1-((2-(trimethylsilyl)ethoxy)methyl)-3-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)pyrimidin-4-amine (76)



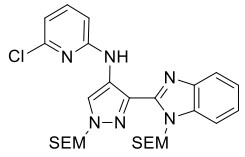
75 (6.00 g, 13.1 mmol) was dissolved in EtOH (14 mL). DIPEA (6.8 mL, 39 mmol) and 2,4-dichloropyrimidine (2.33 g, 15.7 mmol) were added after which the mixture was stirred at 40°C for 2 days. 2,4-dichloropyrimidine (388 mg, 2.61 mmol) was added and the mixture was stirred for another day at 40°C. The mixture was poured into H_2O (200 mL) and the product extracted with DCM (2x200 mL). The combined organic layers were concentrated as such and purified by silica gel column chromatography (10 – 20% EtOAc/pentane) to afford the product (5.53 g, 9.66 mmol, 74%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.03 (s, 1H), 8.57 (s, 1H), 8.11 (d, *J* = 5.8 Hz, 1H), 7.79 – 7.74 (m, 1H), 7.62 – 7.58 (m, 1H), 7.36 – 7.31 (m, 2H), 6.67 (d, *J* = 5.8 Hz, 1H), 6.26 (s, 2H), 5.50 (s, 2H), 3.69 – 3.65 (m, 2H), 3.65 – 3.61 (m, 2H), 1.00 – 0.95 (m, 2H), 0.91 – 0.86 (m, 2H), 0.01 (s, 9H), -0.11 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.90, 159.46, 156.28, 146.67, 142.15, 134.88, 131.60, 124.41, 123.72, 123.20, 121.14, 119.15, 111.06, 106.26, 81.26, 73.89, 67.15, 66.09, 17.90, 17.80, -1.29, -1.37. LCMS (Finnigan, 50 → 90%): t_r = 11.35 min, m/z: 572.1.

***N*-(1-((2-(Trimethylsilyl)ethoxy)methyl)-3-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)pyrimidin-4-amine (77)**



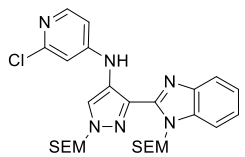
The title compound was synthesized according to general procedure E using 4-chloropyrimidine hydrochloride (54.2 mg, 359 µmol). The crude was purified by automated column chromatography (0 – 3% MeOH/EtOAc) to afford the product (59.2 mg, 110 µmol, 34%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.69 (s, 1H), 8.81 – 8.80 (m, 1H), 8.70 (s, 1H), 8.31 (dd, *J* = 5.9, 0.5 Hz, 1H), 7.83 – 7.77 (m, 1H), 7.64 – 7.58 (m, 1H), 7.37 – 7.31 (m, 2H), 6.81 (dd, *J* = 6.0, 1.3 Hz, 1H), 6.29 (s, 2H), 5.51 (s, 2H), 3.69 – 3.60 (m, 4H), 0.99 – 0.94 (m, 2H), 0.91 – 0.86 (m, 2H), -0.00 (s, 9H), -0.11 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.80, 158.39, 154.80, 146.99, 142.41, 135.03, 131.61, 125.30, 123.67, 123.18, 120.89, 119.26, 111.10, 108.01, 81.32, 73.99, 67.13, 66.11, 17.97, 17.86, -1.25, -1.33. LCMS (Finnigan, 10 → 90%): t_r = 7.80 min, m/z: 538.1.

6-Chloro-*N*-(1-((2-(trimethylsilyl)ethoxy)methyl)-3-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)pyridin-2-amine (79)



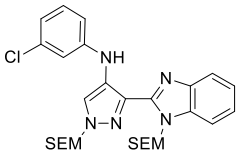
The title compound was synthesized according to general procedure E using 2,6-dichloropyrimidine (53.1 mg, 359 µmol). The crude was purified by automated column chromatography (15 – 35% EtOAc/pentane) to afford the product (102 mg, 178 µmol, 55%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (s, 1H), 8.06 (s, 1H), 7.74 – 7.70 (m, 1H), 7.44 – 7.40 (m, 1H), 7.35 (t, *J* = 7.7 Hz, 1H), 7.30 – 7.25 (m, 2H), 6.66 (dd, *J* = 7.5, 0.4 Hz, 1H), 6.59 (dd, *J* = 8.2, 0.4 Hz, 1H), 5.53 (s, 2H), 5.41 (s, 2H), 3.54 – 3.44 (m, 4H), 0.95 – 0.88 (m, 2H), 0.77 – 0.71 (m, 2H), -0.08 (s, 9H), -0.09 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.02, 149.75, 143.00, 142.62, 139.79, 134.87, 134.06, 125.74, 124.19, 123.27, 122.10, 119.85, 113.71, 110.77, 105.82, 78.74, 73.78, 67.13, 66.92, 17.81, -1.47, -1.49. LCMS (Finnigan, 50 → 90%): t_r = 7.79 min, m/z: 571.0.

2-Chloro-*N*-(1-((2-(trimethylsilyl)ethoxy)methyl)-3-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)pyridin-4-amine (78)



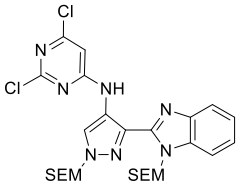
The title compound was synthesized according to general procedure E using 2-chloro-4-iodopyridine (86.0 mg, 359 µmol). The crude was purified by automated column chromatography (25 – 60% EtOAc/pentane) to afford the product (142 mg, 248 µmol, 76%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.00 (s, 1H), 7.94 (d, *J* = 5.7 Hz, 1H), 7.61 (s, 1H), 7.49 – 7.45 (m, 1H), 7.20 – 7.17 (m, 1H), 7.14 – 7.09 (m, 2H), 6.79 (d, *J* = 2.1 Hz, 1H), 6.71 (dd, *J* = 5.8, 2.1 Hz, 1H), 5.46 (s, 2H), 5.21 (s, 2H), 3.47 – 3.42 (m, 2H), 3.30 – 3.25 (m, 2H), 0.75 – 0.70 (m, 2H), 0.69 – 0.65 (m, 2H), -0.14 (s, 18H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.57, 152.54, 149.85, 142.20, 141.69, 134.17, 134.14, 124.36, 124.25, 123.77, 123.28, 118.93, 110.96, 107.55, 107.03, 78.67, 73.67, 67.05, 66.90, 17.72, 17.69, -1.54, -1.58. LCMS (Finnigan, 50 → 90%): t_r = 5.82 min, m/z: 571.2.

_N_-(3-Chlorophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-3-(1-((2-(trimethylsilyl)ethoxy)methyl)-1_H_-benzo[_d_]imidazol-2-yl)-1_H_-pyrazol-4-amine (80)



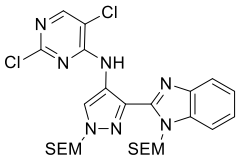
The title compound was synthesized according to general procedure E using 1-chloro-3-iodobenzene (44.4 µL, 359 µmol) which was added just before sealing the microwave vial. The crude was purified by automated column chromatography (10 – 40% EtOAc/pentane) to afford the product (140 mg, 245 µmol, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.50 (s, 1H), 7.87 – 7.80 (m, 1H), 7.76 (s, 1H), 7.64 – 7.58 (m, 1H), 7.38 – 7.31 (m, 2H), 7.22 (t, _J_ = 8.0 Hz, 1H), 7.13 (t, _J_ = 2.0 Hz, 1H), 7.01 (dd, _J_ = 8.1, 2.1 Hz, 1H), 6.85 (dd, _J_ = 7.6, 1.5 Hz, 1H), 6.27 (s, 2H), 5.49 (s, 2H), 3.72 – 3.60 (m, 4H), 1.03 – 0.96 (m, 2H), 0.94 – 0.88 (m, 2H), 0.04 (s, 9H), -0.08 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.94, 144.85, 142.60, 135.14, 135.01, 131.73, 130.40, 129.36, 123.45, 122.96, 119.37, 119.31, 115.49, 114.92, 113.86, 110.88, 81.39, 73.92, 67.09, 66.01, 17.94, 17.88, -1.24, -1.33. LCMS (Finnigan, 10 → 90%): t_r = 10.86 min, m/z: 570.1.

2,6-Dichloro-_N_-(1-((2-(trimethylsilyl)ethoxy)methyl)-3-(1-((2-(trimethylsilyl)ethoxy)methyl)-1_H_-benzo[_d_]imidazol-2-yl)-1_H_-pyrazol-4-yl)pyrimidin-4-amine (81)



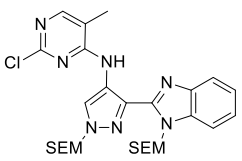
75 (150 mg, 326 µmol) was dissolved in EtOH (0.45 mL). DIPEA (170 µL, 979 µmol) and 2,4,6-trichloropyrimidine (48.8 µL, 424 µmol) were added after which the mixture was stirred at 40°C for 2.5 h. The mixture was poured into H_2O (30 mL) and the product extracted with DCM (2x30 mL). The combined organic layers were concentrated as such and purified by automated column chromatography (5 – 25% Et_2O/pentane) to afford the product (94.6 mg, 156 µmol, 48%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.24 (s, 1H), 8.50 (s, 1H), 7.80 – 7.72 (m, 1H), 7.61 – 7.56 (m, 1H), 7.37 – 7.31 (m, 2H), 6.68 (s, 1H), 6.24 (s, 2H), 5.49 (s, 2H), 3.72 – 3.59 (m, 4H), 1.04 – 0.94 (m, 2H), 0.94 – 0.84 (m, 2H), 0.02 (s, 9H), -0.10 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.22, 159.83, 159.01, 146.45, 142.00, 134.82, 131.64, 124.11, 123.82, 123.28, 121.27, 119.18, 111.05, 104.57, 81.31, 73.89, 67.23, 66.14, 17.91, 17.82, -1.28, -1.36. LCMS (Finnigan, 70 → 90%): t_r = 12.06 min, m/z: 606.1.

2,5-Dichloro-_N_-(1-((2-(trimethylsilyl)ethoxy)methyl)-3-(1-((2-(trimethylsilyl)ethoxy)methyl)-1_H_-benzo[_d_]imidazol-2-yl)-1_H_-pyrazol-4-yl)pyrimidin-4-amine (82)



75 (150 mg, 326 µmol) was dissolved in EtOH (0.45 mL). DIPEA (170 µL, 979 µmol) and 2,4,5-trichloropyrimidine (48.6 µL, 424 µmol) were added after which the mixture was stirred at 40°C for 5.5 h. The mixture was poured into H_2O (30 mL) and the product extracted with DCM (2x30 mL). The combined organic layers were concentrated as such and purified by automated column chromatography (1 – 20% EtOAc/pentane) to afford the product (103 mg, 169 µmol, 52%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.87 (s, 1H), 8.47 (s, 1H), 8.05 (s, 1H), 7.72 – 7.66 (m, 1H), 7.61 – 7.54 (m, 1H), 7.36 – 7.28 (m, 2H), 6.23 (s, 2H), 5.47 (s, 2H), 3.71 – 3.59 (m, 4H), 1.03 – 0.94 (m, 2H), 0.94 – 0.81 (m, 2H), 0.01 (s, 9H), -0.10 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.12, 155.37, 153.77, 146.32, 142.05, 134.79, 132.08, 123.90, 123.78, 123.18, 121.00, 119.23, 114.59, 110.98, 81.30, 73.86, 67.20, 66.09, 17.92, 17.83, -1.28, -1.34. LCMS (Finnigan, 10 → 90%): t_r = 10.15 min, m/z: 606.1.

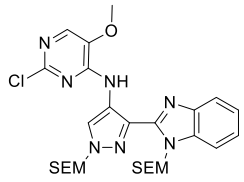
2-Chloro-5-methyl-_N_-(1-((2-(trimethylsilyl)ethoxy)methyl)-3-(1-((2-(trimethylsilyl)ethoxy)methyl)-1_H_-benzo[_d_]imidazol-2-yl)-1_H_-pyrazol-4-yl)pyrimidin-4-amine (83)



A microwave vial was charged with **75** (100 mg, 218 µmol) which was dissolved in EtOH (0.2 mL). DIPEA (114 µL, 653 µmol) and 2,4-dichloro-5-methylpyrimidine (46.1 mg, 283 µmol) were added after which the vial was sealed and stirred at 50°C for 7 days. The mixture was poured into H_2O (30 mL) and the product extracted with DCM (2x20 mL). The combined organic layers were concentrated as such. The crude was purified by automated column chromatography (10 – 25% EtOAc/pentane) to afford the product (57.5 mg, 98.1 µmol, 45%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.22 (s, 1H), 8.56 (s, 1H), 7.91 (s, 1H), 7.71 – 7.64 (m, 1H), 7.64 – 7.55 (m, 1H), 7.39 – 7.28 (m, 2H), 6.27 (s, 2H), 5.50 (s, 2H), 3.71 – 3.57 (m, 4H), 2.32 (s, 3H), 1.01 – 0.94 (m, 2H), 0.93 –

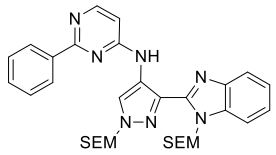
0.86 (m, 2H), 0.01 (s, 9H), -0.10 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.78, 158.46, 155.11, 146.83, 142.10, 134.81, 131.80, 124.85, 123.76, 123.18, 120.86, 118.95, 113.91, 111.12, 81.30, 73.92, 67.16, 66.11, 17.94, 17.84, 13.30, -1.27, -1.34. LCMS (Finnigan, 70 → 90%): t_r = 8.94 min, m/z: 586.3.

2-Chloro-5-methoxy-*N*-(1-((2-(trimethylsilyl)ethoxy)methyl)-3-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)pyrimidin-4-amine (84)



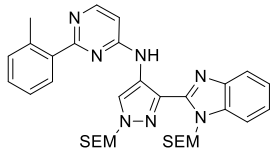
75 (125 mg, 272 µmol) was dissolved in EtOH (0.3 mL). DIPEA (142 µL, 816 µmol) and 2,4-dichloro-5-methoxypyrimidine (63.3 mg, 353 µmol) were added after which the mixture was stirred at 50°C for 4 days. The mixture was poured into H_2O (20 mL) and the product extracted with DCM (2x20 mL). The combined organic layers were concentrated as such and purified by automated column chromatography (10 – 25% EtOAc/pentane) to afford the product (104 mg, 172 µmol, 63%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.33 (s, 1H), 8.55 (s, 1H), 7.73 – 7.68 (m, 1H), 7.60 (s, 1H), 7.60 – 7.56 (m, 1H), 7.36 – 7.29 (m, 2H), 6.25 (s, 2H), 5.46 (s, 2H), 3.99 (s, 3H), 3.68 – 3.58 (m, 4H), 0.99 – 0.93 (m, 2H), 0.90 – 0.85 (m, 2H), -0.01 (s, 9H), -0.12 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.45, 151.25, 146.62, 142.30, 140.15, 134.89, 133.40, 131.92, 124.26, 123.59, 123.02, 120.78, 119.14, 111.02, 81.22, 73.85, 67.08, 65.99, 56.49, 17.88, 17.78, -1.32, -1.39. LCMS (Finnigan, 70 → 90%): t_r = 11.57 min, m/z: 602.3.

2-Phenyl-*N*-(1-((2-(trimethylsilyl)ethoxy)methyl)-3-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)pyrimidin-4-amine (85)



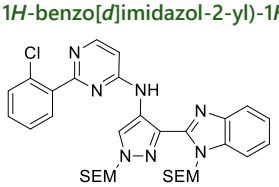
The title compound was synthesized according to general procedure F using phenylboronic acid. The crude was purified by silica gel column chromatography (40 – 50% Et_2O/pentane) to afford the product (57 mg, 93 µmol, 18%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.77 (s, 1H), 8.77 (s, 1H), 8.44 – 8.40 (m, 3H), 7.85 – 7.81 (m, 1H), 7.63 – 7.59 (m, 1H), 7.56 – 7.49 (m, 3H), 7.38 – 7.34 (m, 2H), 6.72 (d, *J* = 5.8 Hz, 1H), 6.29 (s, 2H), 5.54 (s, 2H), 3.74 – 3.69 (m, 2H), 3.68 – 3.63 (m, 2H), 1.04 – 0.98 (m, 2H), 0.96 – 0.87 (m, 2H), 0.01 (s, 9H), -0.08 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.66, 158.69, 155.08, 146.90, 142.35, 142.23, 142.20, 138.68, 134.95, 131.53, 131.44, 130.37, 128.53, 128.18, 125.43, 123.57, 123.09, 120.36, 119.22, 111.00, 105.98, 81.37, 73.90, 67.12, 66.03, 17.91, 17.84, -1.29, -1.37. LCMS (Finnigan, 70 → 90%): t_r = 3.55 min, m/z: 614.4.

2-(*o*-Tolyl)-*N*-(1-((2-(trimethylsilyl)ethoxy)methyl)-3-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)pyrimidin-4-amine (90)



The title compound was synthesized from **76** (200 mg, 349 µmol) and *o*-tolylboronic acid (71.3 mg, 524 µmol) according to general procedure G (reaction time 1.5 h). The crude was purified by automated column chromatography (40 – 60% EtOAc/pentane) to afford the product (177 mg, 281 µmol, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (br s, 1H), 8.39 (d, *J* = 5.9 Hz, 1H), 8.14 (br s, 1H), 7.80 (d, *J* = 7.3 Hz, 1H), 7.75 – 7.68 (m, 1H), 7.42 – 7.36 (m, 1H), 7.34 – 7.25 (m, 5H), 6.61 (d, *J* = 5.9 Hz, 1H), 5.55 (s, 2H), 5.38 (s, 2H), 3.56 – 3.45 (m, 4H), 2.56 (s, 3H), 0.93 – 0.87 (m, 2H), 0.80 – 0.73 (m, 2H), -0.07 (s, 9H), -0.09 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.43, 160.34, 155.89, 142.74, 142.35, 138.70, 136.94, 134.78, 134.67, 131.09, 130.20, 128.99, 125.68, 124.60, 124.32, 123.34, 119.60, 110.81, 78.71, 73.72, 67.17, 66.96, 21.22, 17.77, -1.53 (not all quaternary carbons were observed, neither was one –CH of the pyrimidine). LCMS (Finnigan, 50 → 90%): t_r = 5.18 min, m/z: 628.3.

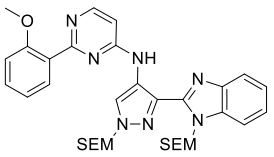
2-(2-Chlorophenyl)-*N*-(1-((2-(trimethylsilyl)ethoxy)methyl)-3-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)pyrimidin-4-amine (91)



The title compound was synthesized according to general procedure F using 2-chlorophenylboronic acid. The crude was purified by silica gel column chromatography (40 – 50% Et_2O/pentane) to afford the product (268 mg, 413 µmol, 79%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.82 (s, 1H), 8.80 (s, 1H), 8.45 (d, *J* = 5.9 Hz, 1H), 7.87 – 7.78 (m, 2H), 7.66 – 7.58 (m, 1H), 7.57

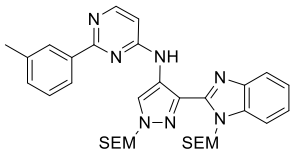
– 7.50 (m, 1H), 7.44 – 7.31 (m, 4H), 6.79 (d, *J* = 5.9 Hz, 1H), 6.30 (s, 2H), 5.47 (s, 2H), 3.69 – 3.59 (m, 4H), 0.99 – 0.85 (m, 4H), -0.02 (s, 9H), -0.10 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.14, 158.24, 155.06, 147.01, 142.41, 138.80, 135.00, 132.49, 131.86, 131.61, 130.62, 130.02, 126.80, 125.12, 123.58, 123.11, 121.31, 119.23, 111.06, 106.06, 81.27, 73.96, 67.11, 66.04, 17.93, 17.86, -1.33, -1.36. LCMS (Finnigan, 70 → 90%): t_r = 3.72 min, m/z: 648.4.

2-(2-Methoxyphenyl)-*N*-(1-((2-(trimethylsilyl)ethoxy)methyl)-3-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)pyrimidin-4-amine (92)



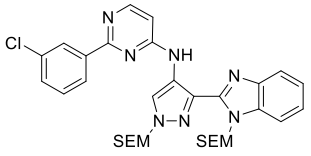
The title compound was synthesized according to general procedure F using 2-methoxyphenylboronic acid. The crude was purified by silica gel column chromatography (70 – 100% EtOAc/pentane) to afford the product (300 mg, 466 µmol, 89%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (br s, 1H), 8.39 (s, 1H), 8.35 (d, *J* = 5.9 Hz, 1H), 7.75 – 7.69 (m, 2H), 7.42 – 7.35 (m, 2H), 7.31 – 7.25 (m, 2H), 7.04 – 6.97 (m, 2H), 6.54 (d, *J* = 5.9 Hz, 1H), 5.51 (s, 2H), 5.37 (s, 2H), 3.88 (s, 3H), 3.52 – 3.43 (m, 4H), 0.86 (t, *J* = 8.2 Hz, 2H), 0.75 – 0.70 (m, 2H), -0.12 (s, 9H), -0.13 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.31, 157.69, 155.72, 142.88, 142.37, 134.80, 134.50, 131.70, 130.78, 128.44, 124.34, 123.42, 120.48, 119.83, 111.74, 110.80, 78.74, 73.76, 67.23, 66.99, 55.85, 17.85, 17.81, -1.51, -1.52 (not all quaternary carbons were observed, neither was one –CH of the pyrimidine). LCMS (Finnigan, 50 → 90%): t_r = 5.24 min, m/z: 644.3.

2-(*m*-Tolyl)-*N*-(1-((2-(trimethylsilyl)ethoxy)methyl)-3-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)pyrimidin-4-amine (93)



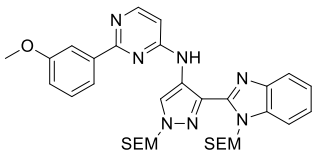
The title compound was synthesized according to general procedure F using *m*-tolylboronic acid. The crude was purified by silica gel chromatography (20 – 40% Et_2O/pentane) to afford the product (286 mg, 456 µmol, 87%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.74 (s, 1H), 8.79 (s, 1H), 8.42 (d, *J* = 5.8 Hz, 1H), 8.27 (s, 1H), 8.23 (d, *J* = 7.8 Hz, 1H), 7.87 – 7.78 (m, 1H), 7.66 – 7.57 (m, 1H), 7.44 (t, *J* = 7.6 Hz, 1H), 7.39 – 7.30 (m, 3H), 6.70 (d, *J* = 5.8 Hz, 1H), 6.29 (s, 2H), 5.52 (s, 2H), 3.76 – 3.63 (m, 4H), 2.50 (s, 3H), 1.07 – 0.97 (m, 2H), 0.97 – 0.85 (m, 2H), 0.02 (s, 9H), -0.08 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.79, 158.64, 155.16, 146.92, 142.37, 138.70, 137.97, 134.95, 131.53, 131.09, 128.91, 128.41, 125.46, 125.28, 123.52, 123.04, 120.41, 119.21, 110.97, 105.85, 81.37, 73.90, 67.09, 65.74, 21.66, 17.92, 17.84, -1.30, -1.37. LCMS (Finnigan, 70 → 90%): t_r = 4.15 min, m/z: 628.4.

2-(3-Chlorophenyl)-*N*-(1-((2-(trimethylsilyl)ethoxy)methyl)-3-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)pyrimidin-4-amine (94)



The title compound was synthesized according to general procedure F using 3-chlorophenylboronic acid. The crude was purified by silica gel column chromatography (45% EtOAc/pentane) and used as such in subsequent reaction (yield: 258 mg). LCMS (Finnigan, 70 → 90%): t_r = 2.86 min, m/z: 648.3.

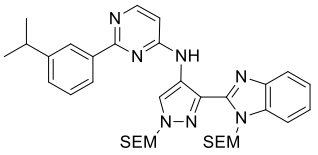
2-(3-Methoxyphenyl)-*N*-(1-((2-(trimethylsilyl)ethoxy)methyl)-3-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)pyrimidin-4-amine (95)



The title compound was synthesized from **76** (200 mg, 349 µmol) and 3-methoxyphenylboronic acid (80.0 mg, 524 µmol) according to general procedure G (reaction time 1.5 h). The crude was purified by automated column chromatography (40 – 60% EtOAc/pentane) to afford the product (184 mg, 286 µmol, 82%).^{1}H NMR (400 MHz, $CDCl_3$) δ 9.32 (br s, 1H), 8.39 (d, *J* = 5.8 Hz, 1H), 8.27 (br s, 1H), 8.08 – 8.01 (m, 2H), 7.69 – 7.63 (m, 1H), 7.37 (t, *J* = 7.9 Hz, 1H), 7.35 – 7.29 (m, 1H), 7.28 – 7.19 (m, 2H), 7.03 (dd, *J* = 8.1, 2.6 Hz, 1H), 6.66 (d, *J* = 5.8 Hz, 1H), 5.54 (s, 2H), 5.38 (s, 2H), 3.88 (s, 3H), 3.55 – 3.49 (m, 3H), 3.47 – 3.40 (m, 2H), 0.91 – 0.82 (m, 2H), 0.79 – 0.70 (m, 2H), -0.08 (s, 8H), -0.11 (s, 9H). ^{13}C NMR (101 MHz,

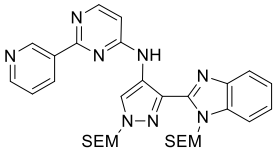
$CDCl_3$) δ 164.18, 160.51, 159.74, 156.07, 142.55, 142.25, 139.46, 134.58, 134.44, 129.33, 124.61, 124.28, 123.28, 120.65, 119.26, 117.04, 112.55, 110.89, 78.61, 73.64, 66.99, 66.91, 55.25, 17.70, -1.57 (not all quaternary carbons were observed, neither was one –CH of the pyrimidine). LCMS (Finnigan, 50 → 90%): t_r = 5.38 min, m/z: 644.3.

2-(3-Isopropylphenyl)-*N*-(1-((2-(trimethylsilyl)ethoxy)methyl)-3-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)pyrimidin-4-amine (97)



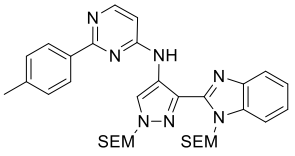
The title compound was synthesized from **76** (170 mg, 297 µmol), 3-isopropylphenylboronic acid (68.0 mg, 445 µmol), K_2CO_3 (165 mg, 1.19 mmol) and Pd(dppf)Cl_2·DCM (17 mg, 21 µmol) according to general procedure F (reaction time: 2 h). The crude was purified by silica gel column chromatography (40 – 60% EtOAc/pentane) to afford the product (89.6 mg, 137 µmol, 46%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.76 (s, 1H), 8.84 (s, 1H), 8.44 (d, *J* = 5.8 Hz, 1H), 8.33 (t, *J* = 1.6 Hz, 1H), 8.23 (dt, *J* = 7.7, 1.4 Hz, 1H), 7.85 – 7.79 (m, 1H), 7.65 – 7.59 (m, 1H), 7.46 (t, *J* = 7.6 Hz, 1H), 7.40 – 7.33 (m, 3H), 6.75 (d, *J* = 5.9 Hz, 1H), 6.32 (s, 2H), 5.54 (s, 2H), 3.72 – 3.61 (m, 4H), 3.06 (hept, *J* = 6.8 Hz, 1H), 1.37 (d, *J* = 6.9 Hz, 6H), 1.02 – 0.93 (m, 2H), 0.93 – 0.86 (m, 2H), -0.01 (s, 9H), -0.11 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.98, 158.76, 155.15, 149.15, 147.03, 142.46, 138.67, 135.07, 131.71, 128.93, 128.65, 126.30, 125.85, 125.56, 123.69, 123.21, 120.65, 119.32, 111.12, 105.95, 81.50, 74.04, 67.17, 66.14, 34.37, 24.25, 18.00, 17.91, -1.24, -1.31. LCMS (Finnigan, 70 → 90%): t_r = 5.70 min, m/z: 656.5.

2-(Pyridin-3-yl)-*N*-(1-((2-(trimethylsilyl)ethoxy)methyl)-3-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)pyrimidin-4-amine (96)



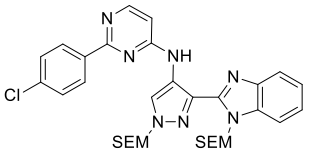
The title compound was synthesized according to general procedure F using pyridin-3-ylboronic acid. The crude was purified by silica gel column chromatography (EtOAc) to afford the product (226 mg, 367 µmol, 70%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.54 (s, 1H), 9.34 (br s, 1H), 8.63 – 8.56 (m, 2H), 8.32 (d, *J* = 5.8 Hz, 1H), 8.19 (br s, 1H), 7.66 – 7.58 (m, 1H), 7.36 – 7.27 (m, 2H), 7.25 – 7.15 (m, 2H), 6.64 (d, *J* = 5.9 Hz, 1H), 5.49 (s, 2H), 5.34 (s, 2H), 3.52 – 3.45 (m, 2H), 3.44 – 3.35 (m, 2H), 0.85 – 0.77 (m, 2H), 0.75 – 0.66 (m, 2H), -0.13 (s, 9H), -0.17 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.08, 162.38, 160.67, 156.03, 150.53, 149.37, 142.48, 142.05, 135.60, 134.61, 134.49, 133.58, 124.43, 124.34, 123.36, 123.26, 119.41, 110.83, 78.66, 73.66, 67.05, 66.99, 17.71, -1.59 (one –CH of the pyrimidine was not observed). LCMS (Finnigan, 10 → 90%): t_r = 7.77 min, m/z: 615.3.

2-(*p*-Tolyl)-*N*-(1-((2-(trimethylsilyl)ethoxy)methyl)-3-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)pyrimidin-4-amine (86)



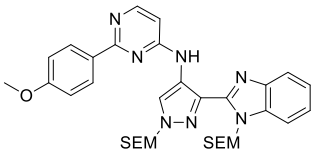
The title compound was synthesized according to general procedure F using *p*-tolylboronic acid. The crude was purified by silica gel column chromatography (20 – 80% Et_2O/pentane) to afford the product (175 mg, 279 µmol, 53%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.72 (s, 1H), 8.78 (s, 1H), 8.41 (d, *J* = 5.8 Hz, 1H), 8.35 – 8.29 (m, 2H), 7.86 – 7.79 (m, 1H), 7.66 – 7.58 (m, 1H), 7.41 – 7.30 (m, 4H), 6.69 (d, *J* = 5.8 Hz, 1H), 6.29 (s, 2H), 5.54 (s, 2H), 3.76 – 3.62 (m, 4H), 2.46 (s, 3H), 1.06 – 0.97 (m, 2H), 0.95 – 0.88 (m, 2H), 0.02 (s, 9H), -0.08 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.78, 158.69, 155.21, 146.96, 142.41, 140.46, 136.10, 134.99, 131.54, 129.28, 128.14, 125.54, 123.55, 123.08, 120.37, 119.24, 111.01, 105.71, 81.38, 73.94, 67.12, 66.03, 21.55, 17.94, 17.89, -1.27, -1.35. LCMS (Finnigan, 70 → 90%): t_r = 3.97 min, m/z: 628.4.

2-(4-Chlorophenyl)-*N*-(1-((2-(trimethylsilyl)ethoxy)methyl)-3-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)pyrimidin-4-amine (88)



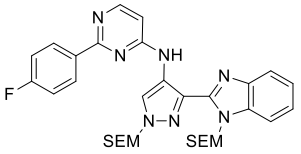
The title compound was synthesized according to general procedure F using 4-chlorophenylboronic acid. The crude was purified by silica gel column chromatography (25 – 35% EtOAc/pentane) and used as such in subsequent reaction (yield: 254 mg). LCMS (Finnigan, 70 → 90%): t_r = 2.23 min, m/z: 648.3.

2-(4-Methoxyphenyl)-*N*-(1-((2-(trimethylsilyl)ethoxy)methyl)-3-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)pyrimidin-4-amine (87)



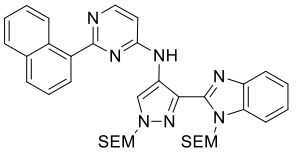
The title compound was synthesized according to general procedure F using 4-methoxyphenylboronic acid. The crude was purified by silica gel column chromatography (20% EtOAc/pentane) to afford the product (258 mg, 401 µmol, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.70 (s, 1H), 8.76 (s, 1H), 8.41 – 8.35 (m, 3H), 7.85 – 7.79 (m, 1H), 7.64 – 7.59 (m, 1H), 7.39 – 7.32 (m, 2H), 7.06 – 7.02 (m, 2H), 6.68 (d, *J* = 5.8 Hz, 1H), 6.30 (s, 2H), 5.56 (s, 2H), 3.90 (s, 3H), 3.73 – 3.68 (m, 2H), 3.68 – 3.62 (m, 2H), 1.04 – 0.97 (m, 2H), 0.94 – 0.87 (m, 2H), 0.01 (s, 9H), -0.10 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.47, 161.62, 158.71, 155.21, 146.99, 142.43, 135.02, 131.57, 131.42, 129.75, 125.62, 123.61, 123.13, 120.30, 119.28, 113.89, 111.05, 105.40, 81.44, 73.98, 67.17, 66.08, 55.46, 17.97, 17.91, -1.24, -1.33. LCMS (Finnigan, 70 → 90%): t_r = 3.43 min, m/z: 644.4.

2-(4-Fluorophenyl)-*N*-(1-((2-(trimethylsilyl)ethoxy)methyl)-3-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)pyrimidin-4-amine (89)



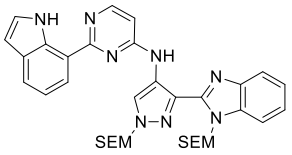
The title compound was synthesized according to general procedure F using 4-fluorophenylboronic acid. The crude was purified by silica gel column chromatography (35% EtOAc/pentane) and used as such in subsequent reaction (yield: 229 mg).

2-(Naphthalen-1-yl)-*N*-(1-((2-(trimethylsilyl)ethoxy)methyl)-3-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)pyrimidin-4-amine (99)



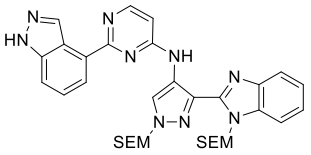
The title compound was synthesized from **76** (125 mg, 218 µmol) and naphthalen-1-boronic acid (43.2 mg, 251 µmol) according to general procedure G (reaction time 2 h). The crude was purified by automated column chromatography (40 – 60% EtOAc/pentane) to afford the product (134 mg, 201 µmol, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (br s, 1H), 8.73 (d, *J* = 8.1 Hz, 1H), 8.45 (d, *J* = 5.8 Hz, 1H), 8.23 (br s, 1H), 8.04 (d, *J* = 7.1 Hz, 1H), 7.95 (d, *J* = 8.2 Hz, 1H), 7.93 – 7.89 (m, 1H), 7.78 – 7.72 (m, 1H), 7.59 – 7.55 (m, 1H), 7.54 – 7.50 (m, 2H), 7.43 – 7.38 (m, 1H), 7.33 – 7.28 (m, 2H), 6.66 (d, *J* = 5.9 Hz, 1H), 5.57 (s, 2H), 5.39 (s, 2H), 3.56 – 3.46 (m, 4H), 0.92 – 0.86 (m, 2H), 0.80 – 0.74 (m, 2H), -0.07 (s, 9H), -0.14 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.86, 160.45, 156.03, 142.81, 142.35, 136.53, 134.79, 134.53, 134.02, 131.04, 130.02, 128.70, 128.30, 126.49, 126.21, 125.72, 125.10, 124.74, 124.33, 123.37, 119.76, 110.72, 78.76, 73.69, 67.27, 67.00, 17.78, 17.76, -1.53, -1.59 (not all quaternary carbons were observed, neither was one –CH of the pyrimidine). LCMS (Finnigan, 50 → 90%): t_r = 5.46 min, m/z: 664.3.

2-(1*H*-Indol-7-yl)-*N*-(1-((2-(trimethylsilyl)ethoxy)methyl)-3-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)pyrimidin-4-amine (100)



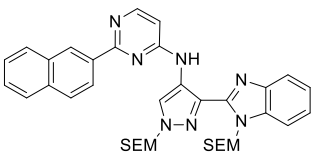
The title compound was synthesized from **76** (125 mg, 218 µmol) and indole-7-boronic acid pinacol ester (61.1 mg, 251 µmol) according to general procedure G (reaction time 16 h). The crude was purified by automated column chromatography (30 – 50% EtOAc/pentane) to afford the product (111 mg, 169 µmol, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.22 (s, 1H), 9.44 (br s, 1H), 8.46 (d, *J* = 5.9 Hz, 1H), 8.44 (dd, *J* = 7.7, 1.0 Hz, 1H), 8.14 (br s, 1H), 7.80 (d, *J* = 7.7 Hz, 1H), 7.66 – 7.60 (m, 1H), 7.33 – 7.28 (m, 1H), 7.26 – 7.17 (m, 3H), 7.09 (br s, 1H), 6.65 (d, *J* = 5.9 Hz, 1H), 6.56 (t, *J* = 2.7 Hz, 1H), 5.57 (s, 2H), 5.36 (s, 2H), 3.56 – 3.47 (m, 2H), 3.40 (dd, *J* = 8.8, 7.4 Hz, 2H), 0.84 – 0.78 (m, 2H), 0.76 – 0.70 (m, 2H), -0.10 (s, 9H), -0.15 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.23, 160.43, 156.00, 142.46, 142.23, 135.32, 134.77, 134.42, 129.17, 124.49, 124.46, 123.90, 123.43, 122.55, 120.19, 119.35, 119.32, 111.00, 102.01, 78.81, 73.76, 67.07, 67.04, 17.76, 17.72, -1.53, -1.56 (not all quaternary carbons were observed). LCMS (Finnigan, 10 → 90%): t_r = 9.13 min, m/z: 653.3.

2-(1*H*-Indazol-4-yl)-*N*-(1-((2-(trimethylsilyl)ethoxy)methyl)-3-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)pyrimidin-4-amine (101)



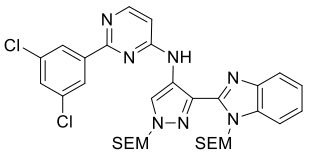
The title compound was synthesized from **76** (130 mg, 227 µmol) and indazole-4-boronic acid hydrochloride (63.1 mg, 318 µmol) according to general procedure G (reaction time 16 h). The crude was purified by automated column chromatography (40 – 100% EtOAc/pentane) to afford the product (101 mg, 155 µmol, 68%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.00 (s, 1H), 8.89 (br s, 1H), 8.44 (d, *J* = 5.9 Hz, 1H), 8.29 – 8.12 (m, 2H), 7.76 – 7.72 (m, 1H), 7.54 (d, *J* = 8.3 Hz, 1H), 7.44 – 7.39 (m, 2H), 7.29 – 7.23 (m, 2H), 6.60 (d, *J* = 5.9 Hz, 1H), 5.57 (s, 2H), 5.42 (s, 2H), 3.60 – 3.54 (m, 2H), 3.51 – 3.44 (m, 2H), 0.88 – 0.82 (m, 2H), 0.80 – 0.75 (m, 2H), -0.10 (s, 9H), -0.17 (s, 9H) (the –NH of the benzimidazole was not observed). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.66, 160.96 (br), 156.32 (br), 142.80, 142.27, 141.00, 136.36, 135.37, 134.84, 131.55, 126.37, 124.87, 124.43, 123.52, 122.09, 121.61, 119.88, 112.37, 110.81, 103.04 (br), 78.96, 73.83, 67.29, 67.17, 17.84, -1.48, -1.54. LCMS (Finnigan, 50 → 90%): t_r = 4.10 min, m/z: 654.3.

2-(Naphthalen-2-yl)-*N*-(1-((2-(trimethylsilyl)ethoxy)methyl)-3-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)pyrimidin-4-amine (102)



The title compound was synthesized from **76** (200 mg, 349 µmol), 2-naphthylboronic acid (90.1 mg, 524 µmol), K_2CO_3 (193 mg, 1.40 mmol) and Pd(dppf)Cl_2·DCM (20 mg, 24 µmol) according to general procedure F (reaction time: 2 h). The crude was purified by silica gel column chromatography (40 – 60% EtOAc/pentane) to afford the product (100 mg, 150 µmol, 43%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.81 (s, 1H), 8.96 (s, 1H), 8.89 (s, 1H), 8.51 (dd, *J* = 8.6, 1.5 Hz, 1H), 8.48 (d, *J* = 5.8 Hz, 1H), 8.03 – 8.00 (m, 1H), 7.99 (d, *J* = 8.6 Hz, 1H), 7.93 – 7.88 (m, 1H), 7.87 – 7.80 (m, 1H), 7.65 – 7.60 (m, 1H), 7.57 – 7.51 (m, 2H), 7.39 – 7.34 (m, 2H), 6.78 (d, *J* = 5.8 Hz, 1H), 6.32 (s, 2H), 5.59 (s, 2H), 3.76 – 3.70 (m, 2H), 3.68 – 3.62 (m, 2H), 1.04 – 0.97 (m, 2H), 0.94 – 0.87 (m, 2H), -0.01 (s, 9H), -0.10 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.76, 158.89, 155.20, 147.02, 142.48, 136.03, 135.09, 134.70, 133.43, 131.76, 129.30, 128.56, 128.24, 127.84, 127.12, 126.36, 125.55, 125.33, 123.70, 123.22, 120.61, 119.33, 111.12, 106.07, 81.57, 77.41, 77.16, 76.91, 74.06, 67.28, 66.16, 18.02, 17.98, -1.23, -1.30. LCMS (Finnigan, 70 → 90%): t_r = 5.14 min, m/z: 664.4.

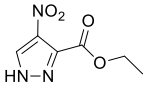
2-(3,5-Dichlorophenyl)-*N*-(1-((2-(trimethylsilyl)ethoxy)methyl)-3-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)pyrimidin-4-amine (98)



The title compound was synthesized from **76** (125 mg, 218 µmol) and 3,5-dichlorophenylboronic acid (47.9 mg, 251 µmol) according to general procedure G (reaction time 2 h). The crude was purified by automated column chromatography (25 – 45% EtOAc/pentane) to afford the product (128 mg, 188 µmol, 86%). ^{1}H NMR (400 MHz, $CDCl_3$)

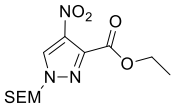
δ 8.96 (br s, 1H), 8.33 (d, *J* = 5.8 Hz, 1H), 8.26 (d, *J* = 1.9 Hz, 2H), 8.14 (br s, 1H), 7.71 – 7.63 (m, 1H), 7.40 (t, *J* = 2.0 Hz, 1H), 7.38 – 7.32 (m, 1H), 7.30 – 7.22 (m, 2H), 6.63 (d, *J* = 5.8 Hz, 1H), 5.52 (s, 2H), 5.37 (s, 2H), 3.54 – 3.45 (m, 4H), 0.93 – 0.84 (m, 2H), 0.75 – 0.69 (m, 2H), -0.11 (s, 9H), -0.12 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.07, 160.81 (br), 156.30 (br), 142.75, 142.21, 141.10, 140.60, 140.21, 135.11, 134.76, 134.56, 130.16, 126.59, 124.50, 124.41, 123.51, 119.70, 110.77, 78.82, 73.68, 67.38, 67.13, 17.85, 17.82, -1.49 (one –CH of the pyrimidine was not observed). LCMS (Finnigan, 70 → 90%): t_r = 7.15 min, m/z: 682.3.

Ethyl 4-nitro-1*H*-pyrazole-3-carboxylate (103)



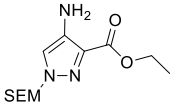
4-Nitro-1*H*-pyrazole-3-carboxylic acid (10.0 g, 63.7 mmol) was suspended in dry EtOH (160 mL) and cooled down to 0°C. $SOCl_2$ (6.0 mL, 83 mmol) was added dropwise, after which the mixture was allowed to warm to RT and stirred for 16 h. The mixture was concentrated and traces of $SOCl_2$ were removed by coevaporation with toluene (2x20 mL). The resulting solids were suspended in pentane and filtered to afford the product (11.3 g, 63.7 mmol, 96%). ^{1}H NMR (500 MHz, DMSO) δ 14.42 (br s, 1H), 8.95 (br s, 1H), 4.35 (q, *J* = 7.0 Hz, 2H), 1.29 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, DMSO) δ 160.81, 138.53, 133.14, 130.81, 61.83, 13.83.

Ethyl 4-nitro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-3-carboxylate (104)



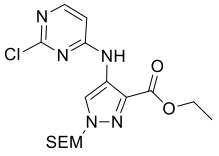
103 (15.0 g, 81.0 mmol) was suspended in DCM (81 mL). DIPEA (18.4 mL, 105 mmol) was added after which the mixture was cooled down to 0°C. SEM-Cl (15.2 mL, 85.9 mmol) was added dropwise after which the mixture was stirred at 0°C for 10 min. The reaction was allowed to warm to RT and continued to stir for 10 min. The mixture was poured into H_2O (150 mL), the layers were separated and the organic layer was washed with H_2O (75 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated. The crude was split in half, transferred to a microwave vial and MeCN (8 mL) was added to each vial. Argon was bubbled through the mixture for 1 min after which SEM-Cl (357 µL, ~5 mol%) was added to each vial. The vials were sealed and heated to 95°C in a microwave reactor for 8 h. The content of both vials were combined and subsequently concentrated. The crude was purified by automated column chromatography (20 – 60% Et_2O/pentane) to afford the product (21.1 g, 67.0 mmol, 83%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (s, 1H), 5.45 (s, 2H), 4.42 (q, *J* = 7.1 Hz, 2H), 3.65 – 3.57 (m, 2H), 1.36 (t, *J* = 7.1 Hz, 3H), 0.94 – 0.87 (m, 2H), -0.04 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.14, 138.98, 134.89, 129.80, 82.02, 68.33, 62.54, 17.80, 13.99, -1.46.

Ethyl 4-amino-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-3-carboxylate (105)



104 (4.00 g, 12.7 mmol) was dissolved in degassed EtOH (140 mL). 10% Pd/C (400 mg) was added and the atmosphere was exchanged for H_2. The reaction was vigorously stirred for 5 h while bubbling H_2 through the mixture. The atmosphere was exchanged for N_2, the mixture was filtered over Celite and concentrated to afford the product (3.57 g, 12.5 mmol, 99%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.09 (s, 1H), 5.30 (s, 2H), 4.35 (q, *J* = 7.1 Hz, 2H), 4.09 (br s, 2H), 3.50 – 3.44 (m, 2H), 1.34 (t, *J* = 7.1 Hz, 3H), 0.86 – 0.80 (m, 2H), -0.09 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.71, 135.54, 130.56, 115.82, 81.43, 66.89, 60.59, 17.79, 14.48, -1.46. LCMS (Finnigan, 10 → 90%): t_r = 5.88 min, m/z: 286.0.

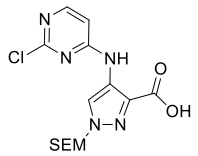
Ethyl 4-((2-chloropyrimidin-4-yl)amino)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-3-carboxylate (106)



105 (3.53 g, 12.4 mmol) was dissolved in EtOH (12.4 mL). DIPEA (4.3 mL, 24.7 mmol) and 2,4-dichloropyrimidine (2.76 g, 18.6 mmol) were added after which the mixture was stirred at 70°C for 4 days. The mixture was concentrated, suspended in DCM (100 mL) and poured into H_2O (100 mL). The organic layer was separated and the water layer was extracted with DCM (50 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated. The crude was purified by silica gel column chromatography (50% Et_2O/pentane) to afford the product (4.41 g, 11.1 mmol, 90%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.91 (s, 1H), 8.51 (s, 1H), 8.13 (d, *J* = 5.8 Hz, 1H), 6.55 (d, *J* = 5.9 Hz, 1H), 5.49 (s, 2H), 4.45 (q, *J* = 7.1 Hz, 2H), 3.63 – 3.55 (m, 2H), 1.42 (t, *J* = 7.2 Hz, 3H), 0.96 – 0.88 (m, 2H), -0.04 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.47,

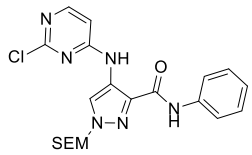
160.95, 159.42, 156.97, 130.53, 126.28, 121.41, 105.78, 81.78, 67.37, 61.64, 17.84, 14.47, -1.36. LCMS (Fleet, 10 → 90%): t_r = 8.29 min, m/z: 398.3.

4-((2-Chloropyrimidin-4-yl)amino)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-3-carboxylic acid (107)



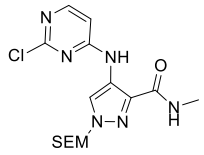
106 (250 mg, 628 µmol) was dissolved in MeCN (2.5 mL) and H_2O (50 µL). Et_3N (263 µL, 1.89 mmol) and LiBr (546 mg, 6.28 mmol) were added and the mixture was stirred for 3 days. The mixture was concentrated, suspended in DCM (30 mL) and poured into H_2O (30 mL). The pH of the water layer was adjusted (2 < pH < 5) by addition of 2 M HCl (aq.). The organic layer was separated and the water layer was extracted with DCM (30 mL). The combined organic layers were concentrated as such to afford the product (232 mg, 628 µmol, quant.). LCMS (Finnigan, 10 → 90%): t_r = 7.48 min, m/z: 370.1.

4-((2-Chloropyrimidin-4-yl)amino)-*N*-phenyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-3-carboxamide (108)



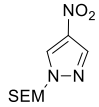
107 (85.0 mg, 230 µmol) was dissolved in DCM (0.9 mL). Aniline (25.2 µL, 276 µmol) and EDC·HCl (48.5 mg, 253 µmol) were added and the mixture was stirred for 16 h. The mixture was poured into H_2O (10 mL) and brine (1 mL), and the product extracted with DCM (2x10 mL). The combined organic layers were concentrated and purified by automated column chromatography (50 – 75% Et_2O/pentane) to afford the product (76.3 mg, 171 µmol, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.41 (s, 1H), 8.64 (s, 1H), 8.47 (s, 1H), 8.09 (d, *J* = 5.8 Hz, 1H), 7.65 – 7.60 (m, 2H), 7.39 – 7.33 (m, 2H), 7.17 – 7.11 (m, 1H), 6.53 (d, *J* = 5.8 Hz, 1H), 5.42 (s, 2H), 3.65 – 3.56 (m, 2H), 1.00 – 0.90 (m, 2H), -0.01 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.86, 160.77, 159.34, 156.72, 137.08, 132.77, 129.18, 124.93, 124.71, 122.13, 119.99, 105.79, 81.22, 67.24, 17.71, -1.36. LCMS (Finnigan, 50 → 90%): t_r = 7.84 min, m/z: 445.3.

4-((2-Chloropyrimidin-4-yl)amino)-*N*-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-3-carboxamide (109)



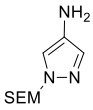
In a microwave vial, **107** (77.0 mg, 208 µmol) and EDC·HCl (47.9 mg, 250 µmol) were suspended in DCM (0.6 mL) after which methylamine (33 wt. % in EtOH, 39 µL, 312 µmol) was added. The vial was sealed and the mixture was stirred for 16 h. The mixture was poured into H_2O (10 mL) and brine (1 mL), and the product extracted with DCM (2x10 mL). The combined organic layers were concentrated as such and the crude was purified by automated column chromatography (65 – 100% Et_2O/pentane) to afford the product (46.1 mg, 120 µmol, 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.52 (s, 1H), 8.42 (s, 1H), 8.08 (d, *J* = 5.9 Hz, 1H), 6.91 (q, *J* = 5.1 Hz, 1H), 6.51 (d, *J* = 5.8 Hz, 1H), 5.39 (s, 2H), 3.59 – 3.50 (m, 2H), 2.97 (d, *J* = 5.1 Hz, 3H), 0.96 – 0.86 (m, 2H), -0.04 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.51, 160.84, 159.40, 156.63, 132.89, 124.46, 121.80, 105.78, 81.19, 67.14, 25.54, 17.73, -1.36. LCMS (Finnigan, 10 → 90%): t_r = 8.31 min, m/z: 383.1.

4-Nitro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole (110)



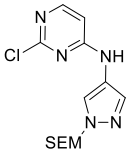
4-Nitro-1H-pyrazole (300 mg, 2.65 mmol) was dissolved in dry DCM (4.5 mL) and DIPEA (462 µL, 2.65 mmol was added. The mixture was cooled down to 0°C, SEM-Cl (510 µL, 2.92 mmol) was added dropwise and the reaction was stirred for 30 min at 0°C. The reaction was allowed to warm to RT and continued to stir for 30 min. The mixture was poured into H_2O (50 mL) and the product extracted with DCM (3x50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated to afford the product (646 mg, 2.65 mmol, quant.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 8.09 (s, 1H), 5.45 (s, 2H), 3.63 – 3.59 (m, 2H), 0.95 – 0.91 (m, 2H), -0.02 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.89, 135.95, 128.57, 81.65, 68.07, 17.90, -1.36.

1-((2-(Trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-amine (111)



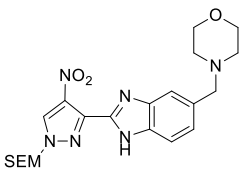
110 (330 mg, 1.36 mmol) was dissolved in degassed MeOH (14 mL). 10% Pd/C (70 mg) was added and the atmosphere was exchanged for H_2. The reaction was vigorously stirred for 3 h while bubbling H_2 through the mixture. The atmosphere was exchanged for N_2, the mixture was filtered over Celite and concentrated to afford the product (238 mg, 1.11 mmol, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, *J* = 0.9 Hz, 1H), 7.15 (d, *J* = 0.9 Hz, 1H), 5.29 (s, 2H), 3.53 – 3.47 (m, 2H), 2.65 (br s, 2H), 0.92 – 0.85 (m, 2H), -0.03 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.27, 130.07, 117.88, 80.58, 66.51, 17.93, -1.32. LCMS (Finnigan, 10 → 90%): t_r = 4.84 min, m/z: 214.0.

2-Chloro-*N*-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)pyrimidin-4-amine (112)



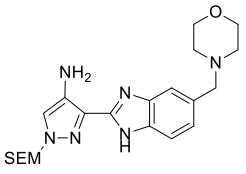
111 (220 mg, 1.03 mmol) was dissolved in EtOH (1.5 mL). DIPEA (629 µL, 3.61 mmol) and 2,4-dichloropyrimidine (180 mg, 1.21 mmol) were added. The mixture was stirred for 24 h, subsequently poured into half sat. $NaHCO_3$ (aq.) (20 mL) and the product was extracted with DCM (2x50 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated. The crude was purified by silica gel column chromatography (1% MeOH (containing 10% sat. NH_4OH (aq.))/DCM) to afford the product (214 mg, 0.665 µmol, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 5.9 Hz, 1H), 7.85 (br s, 2H), 7.52 (d, *J* = 0.7 Hz, 1H), 6.43 (d, *J* = 5.9 Hz, 1H), 5.40 (s, 2H), 3.60 – 3.52 (m, 2H), 0.94 – 0.84 (m, 2H), -0.05 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.36 (br), 160.65, 157.28 (br), 135.88 (br), 131.93 (br), 125.13 (br), 121.30 (br), 102.85 (br), 80.85, 67.02, 17.83, -1.38. LCMS (Finnigan, 10 → 90%): t_r = 7.38 min, m/z: 326.1.

4-((2-(4-Nitro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-3-yl)-1*H*-benzo[*d*]imidazol-5-yl)methyl)morpholine (113)



104 (2.00 g, 6.34 mmol) was suspended in a mixture of MeOH and H_2O (1:1, 12 mL), LiOH·H_2O (1.06 g, 25.3 mmol) was added and the mixture was stirred vigorously for 1.5 h. The mixture was poured into a mixture of H_2O (60 mL) and DCM (75 mL). The pH of the water layer was adjusted by addition of 2 M HCl (aq.) to pH ~2. The organic layer was separated and the water layer extracted with DCM (75 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to yield the free acid intermediate. The intermediate was dissolved in DMF (10 mL), after which 4-(morpholinomethyl)benzene-1,2-diamine (1.45 g, 6.98 mmol), EDC·HCl (1.22 g, 6.34 mmol) and HOBt (857 mg, 6.34 mmol) were added and the mixture was stirred for 1 h. The mixture was concentrated after which AcOH (7 mL) was added and the mixture was stirred at 118°C for 30 min. The mixture was cooled down to RT, 10 M NaOH (aq.) was added until the pH was about 8. The mixture was poured into a mixture of H_2O (60 mL) and DCM (70 mL) after which the organic layer was separated. The water layer was extracted with DCM (70 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude was purified by automated column chromatography twice (0 – 10% MeOH/EtOAc) to afford the product (1.69 g, 3.69 mmol, 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.42 (s, 1H), 8.51 (s, 1H), 7.85 – 7.66 (br m, 1H), 7.60 – 7.44 (br m, 1H), 7.35 – 7.22 (br m, 1H), 5.53 (s, 2H), 3.70 – 3.62 (m, 6H), 3.60 (s, 2H), 2.49 – 2.38 (m, 4H), 0.97 – 0.87 (m, 2H), -0.06 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.44 (br), 142.72 (br), 142.17, 136.67, 134.34 (br), 134.08, 133.41 (br), 132.80 (br), 132.56 (br), 131.56, 125.91 (br), 124.87 (br), 120.89 (br), 120.09 (br), 111.96 (br), 111.42 (br), 82.43, 68.65, 66.97, 63.60, 53.55, 17.98, -1.42. LCMS (Finnigan, 10 → 90%): t_r = 5.57 min, m/z: 459.1.

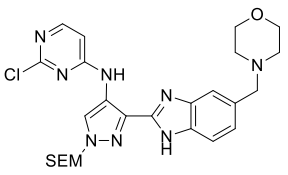
3-(5-(Morpholinomethyl)-1*H*-benzo[*d*]imidazol-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-amine (114)



113 (1.17 g, 2.56 mmol) was dissolved in degassed MeOH (30 mL). 10% Pd/C (120 mg) was added and the atmosphere was exchanged for H_2. The reaction was vigorously stirred for 30 min while bubbling H_2 through the mixture. The atmosphere was exchanged for N_2, the mixture was filtered over Celite and concentrated to afford the product (1.07 g, 2.49 mmol, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (br s, 1H), 7.50 (br s, 1H), 7.21 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.18 (s, 1H), 5.29 (s, 2H), 4.18 (s, 2H), 3.76 – 3.72 (m, 4H), 3.67 (s, 2H), 3.55 – 3.49

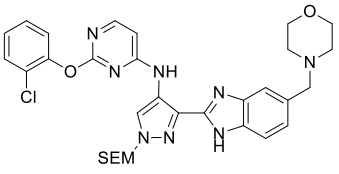
(m, 2H), 2.58 – 2.50 (m, 4H), 0.91 – 0.85 (m, 2H), -0.06 (s, 9H) (the –NH of the benzimidazole was not observed). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.94, 131.91, 130.54 (br), 124.38 (br), 117.17, 80.90, 66.83, 66.56, 63.56, 53.29, 17.83, -1.35 (not all quaternary carbons were observed, neither were two –CH's of the benzimidazole). LCMS (Finnigan, 10 → 90%): t_r = 4.85 min, m/z: 429.2.

2-Chloro-*N*-(3-(5-(morpholinomethyl)-1*H*-benzo[*d*]imidazol-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)pyrimidin-4-amine (115)



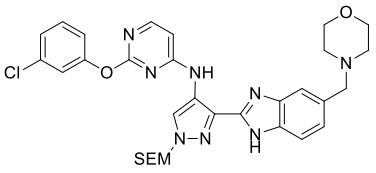
114 (445 mg, 1.04 mmol) was dissolved in EtOH (1 mL). DIPEA (0.54 mL, 3.1 mmol) and 2,4-dichloropyrimidine (232 mg, 1.56 mmol) were added and the mixture was stirred for 4 days. The mixture was poured into H_2O (75 mL) and the product extracted with DCM (2x75 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude was purified by automated column chromatography to afford the product (371 mg, 685 µmol, 66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.79 – 10.63 (2x s, 1H), 10.39 – 10.30 (2x s, 1H), 8.51 – 8.47 (2x s, 1H), 8.19 – 8.15 (2x d, *J* = 5.8 Hz, 1H), 7.74 – 7.67 (m, 1H), 7.44 – 7.36 (m, 1H), 7.30 – 7.22 (2x dd, *J* = 8.3, 1.3 Hz, 1H), 6.73 – 6.68 (2x d, *J* = 5.6 Hz, 1H), 5.44 (s, 2H), 3.76 – 3.70 (m, 4H), 3.66 – 3.57 (m, 4H), 2.56 – 2.45 (m, 4H), 0.97 – 0.90 (m, 2H), -0.02 – -0.04 (2x s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.90, 160.88, 159.55, 156.46, 147.11, 146.93, 143.26, 142.55, 133.59, 132.91, 132.23, 132.04, 131.66, 131.62, 125.28, 124.24, 123.00, 122.96, 121.91, 119.80, 118.77, 111.54, 110.74, 106.09, 81.09, 81.07, 67.11, 67.10, 67.07, 63.84, 63.77, 53.72, 53.68, 17.81, -1.33. LCMS (Fleet, 10 → 90%): t_r = 5.56 min, m/z: 541.2.

2-(2-Chlorophenoxy)-*N*-(3-(5-(morpholinomethyl)-1*H*-benzo[*d*]imidazol-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)pyrimidin-4-amine (116)



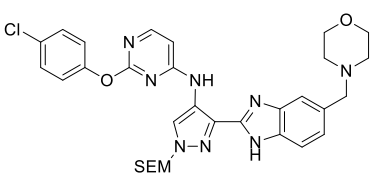
The title compound was synthesized according to general procedure I using 2-chlorophenol to afford the product (95.5 mg, 151 µmol, 91%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.37 – 11.31 (2x s, 1H), 10.26 – 10.20 (2x s, *J* = 9.8 Hz, 1H), 8.33 – 8.30 (2x d, *J* = 5.8 Hz, 1H), 7.73 – 7.67 (m, 1H), 7.54 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.47 – 7.33 (m, 3H), 7.30 – 7.24 (m, 2H), 7.24 – 7.19 (m, 1H), 6.58 – 6.52 (2x d, *J* = 5.4 Hz, 1H), 5.11 (s, 2H), 3.74 – 3.64 (m, 4H), 3.63 – 3.55 (2x s, 2H), 3.44 (t, *J* = 8.1 Hz, 2H), 2.56 – 2.38 (m, 4H), 0.92 – 0.83 (m, 2H), -0.03 – -0.05 (2x s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.93, 160.03, 157.30, 157.28, 149.75, 147.21, 147.08, 143.26, 142.58, 133.11, 133.04, 132.25, 131.78, 131.70, 131.63, 130.54, 128.34, 128.01, 126.36, 125.00, 124.80, 124.01, 123.09, 123.04, 121.57, 119.69, 118.60, 111.83, 110.82, 102.52, 80.72, 66.99, 66.94, 66.71, 66.69, 63.79, 63.73, 53.59, 53.55, 17.77, -1.34, -1.37. LCMS (Fleet, 10 → 90%): t_r = 5.78 min, m/z: 633.2.

2-(3-Chlorophenoxy)-*N*-(3-(5-(morpholinomethyl)-1*H*-benzo[*d*]imidazol-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)pyrimidin-4-amine (117)



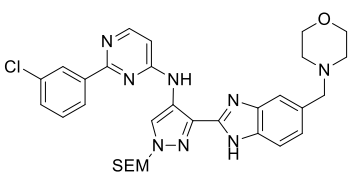
The title compound was synthesized according to general procedure I using 3-chlorophenol to afford the product (85.8 mg, 135 µmol, 81%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.21 – 11.10 (m, 1H), 10.28 – 10.19 (m, 1H), 8.30 – 8.24 (2x d, *J* = 5.8 Hz, 1H), 7.73 – 7.68 (m, 1H), 7.48 – 7.44 (2x s, 1H), 7.43 – 7.35 (m, 2H), 7.35 – 7.33 (2x t, *J* = 2.3 Hz, 1H), 7.31 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.26 – 7.22 (2x dd, *J* = 8.3, 1.5 Hz, 1H), 7.20 – 7.16 (2x dt, *J* = 8.1, 2.5 Hz, 1H), 6.58 – 6.52 (2x d, *J* = 5.8 Hz, 1H), 5.20 (s, 2H), 3.76 – 3.68 (m, 4H), 3.65 – 3.57 (2x s, 2H), 3.49 – 3.43 (m, 2H), 2.56 – 2.43 (m, 4H), 0.91 – 0.85 (m, 2H), -0.04 – -0.05 (2x s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.46, 159.98, 159.88, 157.24, 157.21, 154.09, 147.19, 147.05, 146.92, 143.27, 142.60, 134.65, 133.19, 133.06, 132.92, 132.19, 132.04, 131.87, 131.66, 130.47, 125.49, 125.08, 124.07, 123.51, 123.00, 122.96, 122.88, 122.83, 121.76, 121.27, 119.78, 118.66, 111.68, 111.62, 110.72, 110.67, 102.63, 102.55, 80.86, 67.01, 66.97, 66.81, 66.79, 63.81, 63.75, 53.62, 17.75, -1.32. LCMS (Fleet, 10 → 90%): t_r = 5.76 min, m/z: 633.2.

2-(4-Chlorophenoxy)-*N*-(3-(5-(morpholinomethyl)-1*H*-benzo[*d*]imidazol-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)pyrimidin-4-amine (118)



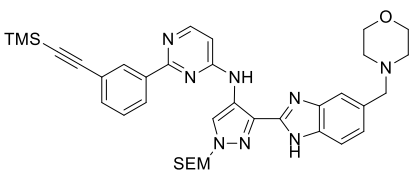
The title compound was synthesized according to general procedure I using 4-chlorophenol to afford the product (95.5 mg, 151 µmol, 91%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.62 – 11.53 (2x s, 1H), 10.21 – 10.12 (2x s, 1H), 8.18 – 8.14 (2x d, *J* = 5.9 Hz, 1H), 7.70 – 7.64 (m, 1H), 7.44 – 7.37 (m, 3H), 7.31 (s, 1H), 7.24 – 7.16 (m, 3H), 6.57 – 6.53 (2x d, *J* = 5.8 Hz, 1H), 5.15 (s, 2H), 3.72 – 3.65 (m, 4H), 3.62 – 3.56 (2x s, 2H), 3.50 – 3.43 (m, 2H), 2.51 – 2.43 (m, 4H), 0.91 – 0.85 (m, 2H), -0.05 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.46, 159.92, 159.82, 156.84, 151.96, 146.97, 146.85, 146.74, 143.07, 142.46, 133.20, 133.07, 132.67, 132.40, 132.26, 131.84, 131.38, 130.43, 129.64, 125.14, 124.39, 124.15, 124.13, 122.74, 122.70, 122.61, 122.58, 121.93, 119.67, 118.45, 111.88, 110.88, 102.45, 102.40, 80.72, 66.81, 66.76, 66.72, 63.71, 53.48, 53.44, 17.70, -1.43, -1.49. LCMS (Fleet, 10 → 90%): t_r = 5.70 min, m/z: 633.2.

2-(3-Chlorophenyl)-*N*-(3-(5-(morpholinomethyl)-1*H*-benzo[*d*]imidazol-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)pyrimidin-4-amine (119)



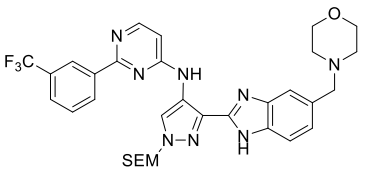
The title compound was synthesized from **115** (125 mg, 231 µmol) and 3-chlorophenylboronic acid (36.8 mg, 236 µmol) according to general procedure G (reaction time 16 h). The crude was purified by automated column chromatography (0 – 10% MeOH/EtOAc) to afford the product (87.3 mg, 141 µmol, 61%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.96 – 10.79 (2x s, 1H), 10.14 – 10.06 (2x s, 1H), 8.58 (s, 1H), 8.41 – 8.37 (2x d, *J* = 5.9 Hz, 1H), 8.37 (s, 1H), 8.25 (d, *J* = 7.5 Hz, 1H), 7.76 – 7.71 (m, 1H), 7.45 – 7.42 (m, 1H), 7.40 (t, *J* = 7.7 Hz, 1H), 7.37 – 7.31 (m, 1H), 7.27 – 7.23 (m, 1H), 6.70 (d, *J* = 5.8 Hz, 1H), 5.43 (s, 2H), 3.79 – 3.70 (m, 4H), 3.68 – 3.60 (m, 4H), 2.57 – 2.48 (m, 4H), 0.98 – 0.93 (m, 2H), -0.05 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.40, 158.67, 155.27, 147.26, 147.10, 143.42, 142.74, 140.50, 134.53, 133.18, 133.00, 132.17, 131.89, 131.64, 130.26, 129.77, 128.39, 126.21, 125.18, 124.20, 123.80, 121.18, 119.93, 118.79, 111.56, 110.64, 106.21, 81.12, 67.16, 67.00, 63.77, 63.73, 53.64, 17.81, -1.35. LCMS (Fleet, 10 → 90%): t_r = 5.44 min, m/z: 617.1.

***N*-(3-(5-(Morpholinomethyl)-1*H*-benzo[*d*]imidazol-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)-2-(3-((trimethylsilyl)ethynyl)phenyl)pyrimidin-4-amine (120)**



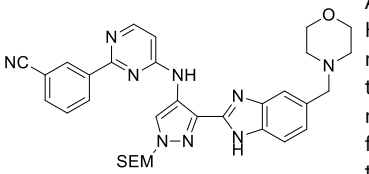
A microwave vial was charged with **115** (125 mg, 231 µmol), K_2CO_3 (128 mg, 924 µmol), 3-[(trimethylsilyl)ethynyl]phenylboronic acid pinacol ester (74.2 mg, 247 µmol) and 4:1 dioxane/H_2O (1.2 mL). N_2 was bubbled through the mixture for 1 min after which Pd(dppf)Cl_2·DCM (13.2 mg, 16.2 µmol) was added. N_2 was bubbled through the mixture for 30 sec after which the vial was sealed. The mixture was heated to 90°C and stirred for 16 h. Then, extra K_2CO_3 (64.0 mg, 462 µmol), 3-[(trimethylsilyl)ethynyl]phenylboronic acid pinacol ester (37.1 mg, 124 µmol) and Pd(dppf)Cl_2·DCM (6.7 mg, 8.0 µmol) were added, N_2 was bubbled through the mixture for 30 sec after which the vial was sealed and stirred at 90°C for another 8 h. The mixture was poured into H_2O (20 mL). The product was extracted with DCM (2x20 mL) and the combined organic layers were concentrated as such. The crude was purified by automated column chromatography (0 – 10% MeOH/EtOAc) to afford the product (44 mg, 65 µmol, 28%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.87 – 10.70 (2x s, 1H), 10.13 – 10.06 (2x s, 1H), 8.65 (s, 1H), 8.52 (s, 1H), 8.44 – 8.39 (2x d, *J* = 5.5 Hz, 1H), 8.33 (d, *J* = 7.6 Hz, 1H), 7.77 – 7.71 (m, 1H), 7.58 (dt, *J* = 7.7, 1.4 Hz, 1H), 7.43 (t, *J* = 7.8 Hz, 1H), 7.41 – 7.35 (m, 1H), 7.26 (dd, *J* = 8.3, 1.3 Hz, 1H), 6.73 (d, *J* = 5.8 Hz, 1H), 5.48 – 5.45 (2x s, 2H), 3.78 – 3.70 (m, 4H), 3.68 – 3.59 (m, 4H), 2.57 – 2.47 (m, 4H), 0.97 – 0.91 (m, 2H), 0.28 (s, 9H), -0.06 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.88, 158.72, 155.34, 147.28, 147.13, 143.42, 142.75, 138.69, 133.61, 133.20, 133.01, 132.25, 132.16, 132.00, 131.90, 131.66, 128.52, 128.16, 125.24, 124.86, 124.25, 123.87, 123.48, 121.37, 119.96, 118.82, 111.64, 110.71, 106.12, 105.13, 94.37, 81.07, 67.05, 63.82, 63.78, 53.67, 53.64, 17.82, 0.12, -1.34. LCMS (Fleet, 10 → 90%): t_r = 6.60 min, m/z: 679.2.

_N_-(3-(5-(Morpholinomethyl)-1_H_-benzo[_d_]imidazol-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1_H_-pyrazol-4-yl)-2-(3-(trifluoromethyl)phenyl)pyrimidin-4-amine (121)



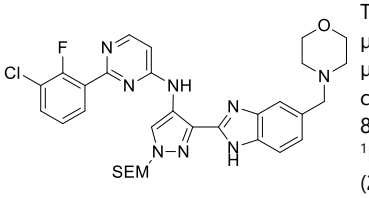
The title compound was synthesized from **115** (125 mg, 231 µmol) and (3-(trifluoromethyl)phenyl)boronic acid (46.9 mg, 247 µmol) according to general procedure G (reaction time 16 h). The crude was purified by automated column chromatography (0 – 10% MeOH/EtOAc) to afford the product (112 mg, 173 µmol, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.12 – 10.91 (2x s, 1H), 10.16 (s, 1H), 8.67 (s, 1H), 8.58 (s, 1H), 8.55 (d, _J_ = 7.8 Hz, 1H), 8.41 (d, _J_ = 5.8 Hz, 1H), 7.74 (br s, 1H), 7.72 (d, _J_ = 7.7 Hz, 1H), 7.58 (t, _J_ = 7.8 Hz, 1H), 7.41 – 7.31 (m, 1H), 7.25 (dd, _J_ = 8.1, 1.8 Hz, 1H), 6.72 (d, _J_ = 5.8 Hz, 1H), 5.41 (s, 2H), 3.79 – 3.71 (m, 4H), 3.69 – 3.58 (m, 4H), 2.60 – 2.49 (m, 4H), 0.97 – 0.90 (m, 2H), -0.06 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.16, 158.64, 155.29, 147.17 (br), 147.08 (br), 143.35 (br), 142.71 (br), 139.34, 133.06 (br), 132.89 (br), 132.26 (br), 131.72, 131.57 (br), 131.27, 130.95, 130.63, 129.08, 126.85 (br), 126.81 (br), 125.70, 125.27 (br), 125.08 (br), 125.04 (br), 125.00 (br), 124.97 (br), 124.28 (br), 123.71, 122.99, 121.31, 120.00 (br), 118.77 (br), 111.75 (br), 110.74 (br), 106.39, 81.08, 67.13, 66.90, 63.67, 53.53, 17.74, -1.44. LCMS (Fleet, 10 → 90%): t_r = 5.85 min, m/z: 651.1.

3-(4-((3-(5-(Morpholinomethyl)-1_H_-benzo[_d_]imidazol-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1_H_-pyrazol-4-yl)amino)pyrimidin-2-yl)benzonitrile (122)



A microwave vial was charged with **115** (125 mg, 231 µmol), K_2CO_3 (128 mg, 924 µmol), (3-cyanophenyl)boronic acid (37.3 mg, 254 µmol) and 4:1 dioxane/H_2O (1.2 mL). N_2 was bubbled through the mixture for 1 min after which Pd(dppf)Cl_2·DCM (13.2 mg, 16.2 µmol) was added. N_2 was bubbled through the mixture for 30 sec after which the vial was sealed. The mixture was heated to 90°C and stirred for 5 h. Then, extra K_2CO_3 (60.0 mg, 434 µmol), (3-cyanophenyl)boronic acid (15.0 mg, 102 µmol) and Pd(dppf)Cl_2·DCM (6.0 mg, 7.3 µmol) were added, N_2 was bubbled through the mixture for 30 sec after which the vial was sealed and stirred at 90°C for another 4.5 h. The mixture was poured into H_2O (20 mL) and brine (1 mL). The product was extracted with 5% MeOH/DCM (20 mL) and DCM (3x20 mL) and the combined organic layers were concentrated as such. The crude was purified by automated column chromatography (0 – 15% MeOH/EtOAc) to afford the product (101 mg, 167 µmol, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.80 – 10.63 (2x s, 1H), 10.18 – 10.11 (2x s, 1H), 8.66 – 8.62 (2x t, _J_ = 1.7 Hz, 1H), 8.59 – 8.54 (2x dt, _J_ = 8.1, 1.5 Hz, 1H), 8.51 – 8.48 (2x s, 1H), 8.41 – 8.36 (2x d, _J_ = 5.8 Hz, 1H), 7.75 – 7.68 (m, 2H), 7.55 (t, _J_ = 7.8 Hz, 1H), 7.35 – 7.30 (m, 1H), 7.27 – 7.23 (m, 1H), 6.73 (d, _J_ = 5.8 Hz, 1H), 5.47 – 5.42 (2x s, 2H), 3.79 – 3.70 (m, 4H), 3.67 – 3.59 (m, 4H), 2.58 – 2.46 (m, 4H), 0.94 (t, _J_ = 8.2 Hz, 2H), -0.06 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.50, 162.47, 158.68, 155.25, 147.18, 147.00, 143.34, 142.62, 139.76, 133.36, 132.86, 132.10, 132.01, 131.90, 131.59, 131.57, 129.30, 125.17, 124.18, 123.67, 123.61, 120.80, 119.84, 118.84, 118.75, 112.63, 111.42, 110.56, 106.60, 81.17, 67.14, 67.05, 67.00, 63.79, 63.74, 53.68, 53.64, 17.76, -1.38. LCMS (Fleet, 10 → 90%): t_r = 5.24 min, m/z: 608.3.

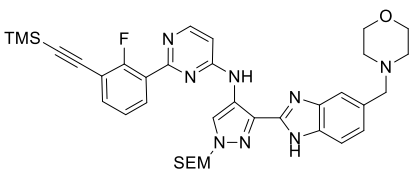
2-(3-Chloro-2-fluorophenyl)-_N_-(3-(5-(morpholinomethyl)-1_H_-benzo[_d_]imidazol-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1_H_-pyrazol-4-yl)pyrimidin-4-amine (123)



The title compound was synthesized from **115** (115 mg, 213 µmol) and (3-chloro-2-fluorophenyl)boronic acid (37.8 mg, 217 µmol) according to general procedure G (reaction time 16 h). The crude was purified by automated column chromatography (0 – 8% MeOH/EtOAc) to afford the product (104 mg, 164 µmol, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.90 – 10.75 (m, 1H), 10.16 – 10.08 (2x s, 1H), 8.72 – 8.69 (2x s, 1H), 8.46 – 8.41 (2x d, _J_ = 5.9 Hz, 1H), 8.05 – 7.99 (m, 1H), 7.77 – 7.70 (m, 1H), 7.52 – 7.46 (m, 1H), 7.33 – 7.28 (m, 1H), 7.27 – 7.22 (m, 1H), 7.20 – 7.14 (m, 1H), 6.76 (dd, _J_ = 5.9, 2.5 Hz, 1H), 5.44 – 5.41 (2x s, 2H), 3.77 – 3.70 (m, 4H), 3.67 – 3.58 (m, 4H), 2.56 – 2.45 (m, 4H), 0.98 – 0.91 (m, 2H), -0.06 – -0.07 (2x s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.09,

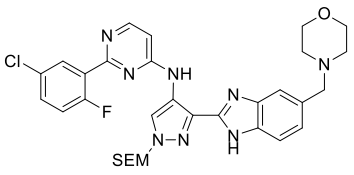
162.06, 162.04, 162.02, 158.35, 157.95, 155.40, 155.21, 155.18, 147.36, 147.20, 143.40, 142.70, 133.32, 132.95, 132.09, 132.05, 131.84, 131.70, 131.66, 130.29, 130.28, 128.75, 128.66, 125.10, 124.42, 124.38, 124.12, 123.57, 123.52, 122.49, 122.31, 122.01, 121.96, 119.82, 118.75, 111.46, 110.61, 106.12, 81.05, 67.09, 67.04, 63.85, 63.79, 53.70, 53.67, 17.74, -1.40. LCMS (Fleet, 10 → 90%): t_r = 5.37 min, m/z: 635.3.

2-(2-Fluoro-3-((trimethylsilyl)ethynyl)phenyl)-*N*-(3-(5-(morpholinomethyl)-1*H*-benzo[*d*]imidazol-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)pyrimidin-4-amine (124)



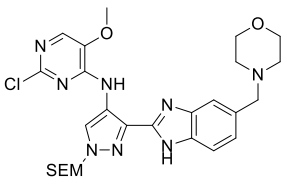
The title compound was synthesized from **123** (42 mg, 66 µmol) according to general procedure H. The crude was purified by automated column chromatography (0 – 8% MeOH/EtOAc) to afford the product (37.4 mg, 53.7 µmol, 81%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.90 – 10.76 (2x s, 1H), 10.14 – 10.05 (2x s, 1H), 8.75 (s, 1H), 8.47 – 8.43 (2x d, *J* = 6.3 Hz, 1H), 8.12 – 8.06 (2x d, *J* = 7.3 Hz, 1H), 7.78 – 7.70 (m, 1H), 7.55 (ddd, *J* = 7.8, 6.3, 1.6 Hz, 1H), 7.36 – 7.29 (m, 1H), 7.27 – 7.23 (m, 1H), 7.18 (t, *J* = 7.7 Hz, 1H), 6.75 (d, *J* = 5.9 Hz, 1H), 5.43 (s, 2H), 3.78 – 3.71 (m, 4H), 3.69 – 3.57 (m, 4H), 2.61 – 2.45 (m, 4H), 0.96 – 0.87 (m, 2H), 0.29 (s, 9H), -0.08 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.61, 162.31, 162.28, 160.54, 158.35, 155.21, 147.42, 147.27, 143.43, 142.78, 135.09, 132.98, 132.16, 131.70, 127.36, 127.29, 125.13, 124.17, 123.78, 123.74, 123.59, 122.20, 119.92, 118.78, 113.31, 113.17, 111.58, 110.67, 105.95, 100.41, 100.38, 98.16, 80.95, 66.96, 66.92, 63.73, 53.60, 17.70, 0.00, -1.38. LCMS (Fleet, 10 → 90%): t_r = 6.51 min, m/z: 697.3.

2-(5-Chloro-2-fluorophenyl)-*N*-(3-(5-(morpholinomethyl)-1*H*-benzo[*d*]imidazol-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)pyrimidin-4-amine (125)



The title compound was synthesized from **115** (100 mg, 185 µmol) and (5-chloro-2-fluorophenyl)boronic acid (33.2 mg, 190 µmol) according to general procedure G (reaction time 16 h). The crude was purified by automated column chromatography (0 – 6% MeOH/EtOAc) to afford the product (65.5 mg, 103 µmol, 56%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.76 – 10.61 (2x s, 1H), 10.17 – 10.08 (2x s, 1H), 8.71 – 8.68 (2x s, 1H), 8.45 – 8.41 (2x d, *J* = 6.2 Hz, 1H), 8.19 – 8.15 (2x dd, *J* = 6.7, 2.6 Hz, 1H), 7.76 – 7.71 (m, 1H), 7.40 – 7.35 (2x ddd, *J* = 8.6, 3.9, 2.7 Hz, 1H), 7.35 – 7.29 (m, 1H), 7.28 – 7.22 (2x dd, *J* = 8.1, 1.6 Hz, 1H), 7.16 – 7.10 (2x dd, *J* = 10.1, 8.8 Hz, 1H), 6.76 – 6.74 (2x d, *J* = 5.9 Hz, 1H), 5.45 – 5.42 (2x s, 2H), 3.79 – 3.69 (m, 4H), 3.67 – 3.57 (m, 4H), 2.57 – 2.45 (m, 4H), 0.97 – 0.90 (m, 2H), -0.05 – -0.07 (2x s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.64, 161.61, 161.59, 161.56, 161.04, 158.52, 158.37, 155.20, 155.16, 147.36, 147.19, 143.42, 142.72, 133.39, 132.92, 132.10, 132.06, 131.70, 131.68, 131.63, 131.60, 131.20, 131.11, 129.37, 129.33, 128.42, 128.32, 125.12, 124.15, 123.64, 123.59, 121.89, 121.84, 121.82, 119.85, 118.79, 118.47, 118.22, 111.42, 110.59, 106.18, 106.15, 81.11, 67.10, 67.08, 67.06, 63.86, 63.79, 53.72, 53.69, 17.79, -1.38. LCMS (Fleet, 10 → 90%): t_r = 5.41 min, m/z: 635.2.

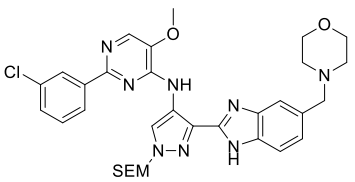
2-Chloro-5-methoxy-*N*-(3-(5-(morpholinomethyl)-1*H*-benzo[*d*]imidazol-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)pyrimidin-4-amine (126)



114 (1.20 g, 2.80 mmol) was dissolved in EtOH (3 mL) after which DIPEA (1.5 mL 8.4 mmol) and 2,4-dichloro-5-methoxypyrimidine (752 mg, 4.20 mmol) were added. The mixture was heated to 40°C and stirred for 6 days. The mixture was poured into H_2O (75 mL) and the product extracted with DCM (2x50 mL). The combined organic layers were concentrated as such. The crude was purified by automated column chromatography (0 – 10% MeOH/EtOAc) to afford the product (1.12 g, 1.97 mmol, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.65 – 10.59 (2x s, 1H), 10.58 – 10.49 (2x s, 1H), 8.54 – 8.48 (2x s, 1H), 7.72 – 7.66 (m, 2H), 7.43 – 7.35 (m, 1H), 7.28 – 7.24 (m, 1H), 5.45 – 5.42 (2x s, 2H), 4.06 – 4.02 (2x s, 3H), 3.76 – 3.70 (m, 4H), 3.66 – 3.62 (2x s, 2H), 3.62 – 3.56 (m, 2H), 2.55 – 2.45 (m, 4H), 0.96 – 0.90 (m, 2H), -0.03 – -0.05 (2x s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.56, 151.54, 151.29, 147.07, 146.90,

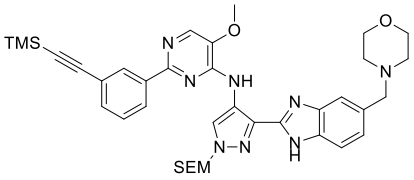
143.48, 142.73, 140.15, 140.13, 133.70, 133.67, 133.52, 132.94, 132.09, 132.07, 132.06, 132.01, 125.29, 124.11, 122.83, 121.72, 121.67, 119.99, 118.90, 111.52, 110.65, 81.08, 81.05, 67.09, 63.92, 63.82, 56.71, 56.63, 53.74, 17.81, -1.34. LCMS (Fleet, 10 → 90%): t_r = 6.13 min, m/z: 571.1.

2-(3-Chlorophenyl)-5-methoxy-*N*-(3-(5-(morpholinomethyl)-1*H*-benzo[*d*]imidazol-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)pyrimidin-4-amine (127)



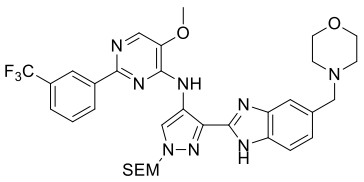
The title compound was synthesized from **126** (175 mg, 306 µmol) and (3-chlorophenyl)boronic acid (55.1 mg, 352 µmol) according to general procedure G (reaction time 16 h). The crude was purified by HPLC (Waters, 35 – 45% MeCN in 0.2% TFA (aq.)), the pH of the combined fractions was adjusted to pH ~8 using 10 M NaOH after which the mixture was concentrated. The product was dissolved in a mixture of H_2O (20 mL) and DCM (20 mL). The organic layer was separated and the water layer extracted with DCM (20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to afford the product (103 mg, 159 µmol, 52%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.89 – 10.81 (2x s, 1H), 10.47 – 10.41 (2x s, 1H), 8.61 – 8.58 (m, 1H), 8.32 – 8.29 (m, 1H), 8.20 – 8.15 (m, 1H), 7.93 – 7.88 (2x s, 1H), 7.74 – 7.69 (m, 1H), 7.41 – 7.36 (m, 2H), 7.32 – 7.27 (m, 1H), 7.27 – 7.22 (m, 1H), 5.39 (s, 2H), 4.06 – 4.03 (2x s, 3H), 3.78 – 3.70 (m, 4H), 3.68 – 3.58 (m, 4H), 2.51 (dt, *J* = 16.7, 4.7 Hz, 4H), 0.96 – 0.89 (m, 2H), -0.07 – -0.08 (2x s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.41, 155.39, 150.21, 150.19, 147.28, 147.12, 143.60, 142.85, 140.51, 140.04, 140.02, 134.39, 134.37, 133.21, 133.01, 132.69, 132.66, 132.16, 132.02, 131.98, 131.88, 129.69, 129.25, 127.85, 125.65, 125.15, 124.01, 123.57, 120.93, 120.87, 120.02, 118.87, 111.46, 110.52, 81.07, 67.07, 67.06, 67.03, 63.91, 63.82, 56.35, 56.26, 53.71, 17.76, -1.38. LCMS (Fleet, 10 → 90%): t_r = 6.04 min, m/z: 647.3.

5-Methoxy-*N*-(3-(5-(morpholinomethyl)-1*H*-benzo[*d*]imidazol-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)-2-(3-((trimethylsilyl)ethynyl)phenyl)pyrimidin-4-amine (128)



The title compound was synthesized from **127** (50 mg, 77 µmol) according to general procedure H. The crude was purified by automated column chromatography (0 – 10% MeOH/EtOAc) to afford the product (52.6 mg, 74.2 µmol, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.46 – 10.43 (2x s, 1H), 10.41 – 10.37 (2x s, 1H), 8.71 – 8.68 (2x s, 1H), 8.47 – 8.45 (2x t, *J* = 1.6 Hz, 1H), 8.29 – 8.25 (2x dt, *J* = 7.8, 1.3 Hz, 1H), 7.99 – 7.96 (2x s, 1H), 7.74 – 7.71 (m, 1H), 7.53 (dt, *J* = 7.5, 1.5 Hz, 1H), 7.41 (t, *J* = 8.1 Hz, 1H), 7.39 – 7.34 (m, 1H), 7.28 – 7.25 (m, 1H), 5.47 – 5.43 (2x s, 2H), 4.12 – 4.07 (2x s, 3H), 3.77 – 3.71 (m, 4H), 3.68 – 3.58 (m, 4H), 2.57 – 2.45 (m, 4H), 0.96 – 0.90 (m, 2H), 0.28 (s, 9H), -0.06 – -0.08 (2x s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.03, 150.36, 150.34, 147.31, 147.14, 143.67, 142.92, 140.04, 140.03, 138.72, 133.39, 132.94, 132.69, 132.08, 132.07, 132.01, 132.00, 131.48, 128.46, 127.69, 125.24, 124.09, 123.69, 123.35, 121.17, 121.13, 120.12, 119.00, 111.42, 110.54, 105.37, 94.12, 81.12, 67.12, 67.10, 67.04, 67.02, 63.96, 63.87, 56.46, 56.38, 53.76, 0.15, -1.33. LCMS (Fleet, 10 → 90%): t_r = 7.08 min, m/z: 709.4.

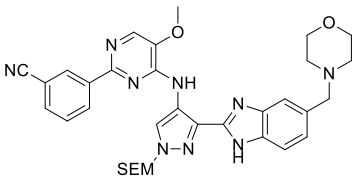
5-Methoxy-*N*-(3-(5-(morpholinomethyl)-1*H*-benzo[*d*]imidazol-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)-2-(3-(trifluoromethyl)phenyl)pyrimidin-4-amine (129)



The title compound was synthesized from **126** (75.8 mg, 133 µmol) and (3-(trifluoromethyl)phenyl)boronic acid (29.0 mg, 153 µmol) according to general procedure G (reaction time 16 h). The crude was purified by automated column chromatography (0 – 10% MeOH/EtOAc) to afford the product (74.0 mg, 109 µmol, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.68 – 10.57 (2x s, 1H), 10.50 – 10.42 (2x s, 1H), 8.65 – 8.61 (m, 2H), 8.52 – 8.47 (m, 1H), 7.98 – 7.93 (2x s, 1H), 7.74 – 7.70 (m, 1H), 7.69 – 7.65 (m, 1H), 7.57 (t, *J* = 7.8 Hz, 1H), 7.37 – 7.30 (m, 1H), 7.28 – 7.23 (m, 1H), 5.40 – 5.37 (2x s, 2H), 4.09 – 4.05 (2x s, 3H), 3.78 – 3.70 (m, 4H), 3.68 – 3.58 (m, 4H),

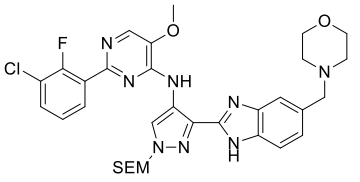
2.58 – 2.46 (m, 4H), 0.95 – 0.90 (m, 2H), -0.06 – -0.08 (2x s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.28, 155.26, 150.30, 150.28, 147.28, 147.12, 143.64, 142.89, 140.21, 140.19, 139.42, 133.36, 132.98, 132.80, 132.77, 132.16, 132.13, 132.12, 131.99, 130.89, 130.69, 130.57, 128.99, 125.88, 125.85, 125.80, 125.22, 124.57, 124.54, 124.50, 124.46, 124.08, 123.53, 123.10, 121.06, 121.01, 120.08, 118.95, 111.44, 110.54, 81.15, 67.11, 67.08, 63.94, 63.85, 56.42, 56.33, 53.75, 17.75, -1.43. LCMS (Fleet, 10 → 90%): t_r = 6.41 min, m/z: 681.3.

3-(5-Methoxy-4-((3-(5-(morpholinomethyl)-1*H*-benzo[*d*]imidazol-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)amino)pyrimidin-2-yl)benzonitrile (130)



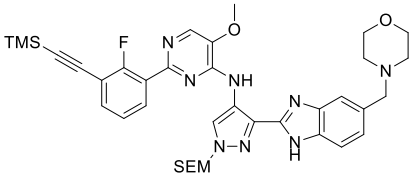
A microwave vial was charged with **126** (72,6 mg, 127 µmol), K_2CO_3 (70.3 mg, 508 µmol), (3-cyanophenyl)boronic acid (21.5 mg, 146 µmol) and 4:1 dioxane/H_2O (0.65 mL). N_2 was bubbled through the mixture for 1 min after which Pd(dppf)Cl_2·DCM (7.3 mg, 8.9 µmol) was added. N_2 was bubbled through the mixture for 30 sec after which the vial was sealed. The mixture was heated to 90°C and stirred for 16 h. Extra K_2CO_3 (70.3 mg, 508 µmol), (3-cyanophenyl)boronic acid (21.5 mg, 146 µmol), 4:1 dioxane/H_2O (0.2 mL) and Pd(dppf)Cl_2·DCM (7.3 mg, 8.9 µmol) were added and the mixture was continued to stir for another 16 h. The mixture was poured into H_2O (20 mL) and brine (2 mL). The product was extracted with DCM (2x20 mL) and the combined organic layers were concentrated as such. The crude was purified by automated column chromatography (0 – 10% MeOH/EtOAc) to afford the product (62.4 mg, 97.8 µmol, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.64 – 10.44 (m, 2H), 8.59 – 8.57 (2x t, *J* = 1.8 Hz, 1H), 8.55 – 8.53 (2x s, 1H), 8.51 – 8.47 (2x dt, *J* = 7.9, 1.4 Hz, 1H), 7.97 – 7.90 (2x s, 1H), 7.73 – 7.69 (m, 1H), 7.68 – 7.64 (2x dt, *J* = 7.7, 2.0 Hz, 1H), 7.53 (t, *J* = 7.8 Hz, 1H), 7.38 – 7.32 (m, 1H), 7.29 – 7.24 (m, 1H), 5.44 – 5.41 (2x s, *J* = 1.3 Hz, 2H), 4.11 – 4.07 (2x s, 3H), 3.77 – 3.70 (m, 4H), 3.68 – 3.58 (m, 4H), 2.57 – 2.46 (m, 4H), 0.96 – 0.90 (m, 2H), -0.06 – -0.08 (2x s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.55, 154.52, 150.33, 150.32, 147.18, 147.01, 143.57, 142.81, 140.33, 140.31, 139.81, 133.38, 132.93, 132.67, 132.65, 132.46, 132.08, 132.00, 131.96, 131.60, 131.38, 129.24, 125.24, 124.10, 123.50, 120.67, 120.62, 120.04, 119.05, 118.91, 112.54, 111.43, 110.54, 81.17, 67.14, 67.13, 67.08, 67.05, 63.91, 63.82, 56.47, 56.38, 53.73, 17.78, -1.37. LCMS (Fleet, 10 → 90%): t_r = 5.80 min, m/z: 638.3.

2-(3-Chloro-2-fluorophenyl)-5-methoxy-*N*-(3-(5-(morpholinomethyl)-1*H*-benzo[*d*]imidazol-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)pyrimidin-4-amine (131)



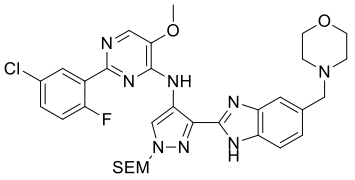
The title compound was synthesized from **126** (200 mg, 350 µmol) and (3-chloro-2-fluorophenyl)boronic acid (65.3 mg, 375 µmol) according to general procedure G (reaction time 64 h). The crude was purified by automated column chromatography (0 – 10% MeOH/EtOAc) to afford the product (160 mg, 241 µmol, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.71 – 10.58 (2x s, 1H), 10.53 – 10.45 (2x s, 1H), 8.81 – 8.75 (2x s, 1H), 8.07 – 8.04 (2x s, 1H), 8.01 (t, *J* = 7.8 Hz, 1H), 7.78 – 7.71 (m, 1H), 7.48 (t, *J* = 7.2 Hz, 1H), 7.39 – 7.31 (m, 1H), 7.31 – 7.24 (m, 1H), 7.18 (t, *J* = 7.9 Hz, 1H), 5.46 (s, 2H), 4.20 – 4.09 (2x s, 3H), 3.80 – 3.72 (m, 4H), 3.70 – 3.61 (m, 4H), 2.58 – 2.48 (m, 4H), 0.97 (t, *J* = 8.1 Hz, 2H), -0.03 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.74, 155.20, 154.02, 153.97, 150.06, 150.04, 147.35, 147.18, 143.64, 142.90, 139.82, 133.30, 132.99, 132.89, 132.87, 132.14, 132.09, 131.94, 131.10, 130.00, 128.74, 128.65, 125.13, 124.31, 124.27, 124.00, 123.42, 122.44, 122.25, 121.81, 121.76, 120.04, 118.93, 111.43, 110.55, 81.06, 67.11, 67.08, 63.94, 63.85, 56.42, 56.34, 53.74, 17.75, -1.40. LCMS (Finnigan, 10 → 90%): t_r = 6.71 min, m/z: 665.1.

2-(2-Fluoro-3-((trimethylsilyl)ethynyl)phenyl)-5-methoxy-*N*-(3-(5-(morpholinomethyl)-1*H*-benzo[*d*]imidazol-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)pyrimidin-4-amine (132)



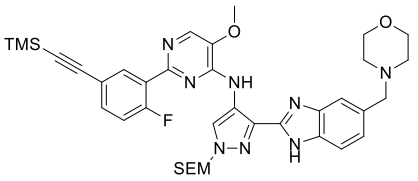
The title compound was synthesized from **131** (100 mg, 150 µmol) according to general procedure H. The crude was purified by automated column chromatography (0 – 10% MeOH/EtOAc) to afford the product (85.7 mg, 118 µmol, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.76 – 10.67 (2x s, 1H), 10.47 – 10.40 (2x s, *J* = 16.9 Hz, 1H), 8.80 – 8.77 (2x d, *J* = 1.9 Hz, 1H), 8.08 – 8.00 (m, 2H), 7.74 – 7.70 (m, 1H), 7.54 – 7.48 (m, 1H), 7.32 – 7.28 (m, 1H), 7.27 – 7.22 (m, 1H), 7.15 (td, *J* = 7.7, 1.4 Hz, 1H), 5.43 (s, 2H), 4.12 – 4.07 (2x s, 3H), 3.77 – 3.69 (m, 4H), 3.67 – 3.56 (m, 4H), 2.56 – 2.45 (m, 4H), 0.94 – 0.87 (m, 2H), 0.29 (s, 9H), -0.08 – -0.10 (2x s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.65, 160.07, 154.25, 154.21, 150.04, 150.02, 147.38, 147.21, 143.65, 142.91, 139.72, 139.70, 134.35, 133.20, 133.01, 132.91, 132.88, 132.18, 132.17, 132.13, 131.92, 131.89, 131.83, 127.33, 127.24, 125.11, 123.98, 123.67, 123.62, 123.44, 121.97, 121.92, 121.87, 120.03, 118.92, 113.21, 113.03, 111.44, 110.55, 100.15, 100.11, 98.40, 98.38, 80.97, 67.08, 67.04, 66.90, 66.88, 63.92, 63.82, 56.38, 56.30, 53.71, 17.70, 0.03, -1.39. LCMS (Finnigan, 10 → 90%): t_r = 7.71 min, m/z: 727.3.

2-(5-Chloro-2-fluorophenyl)-5-methoxy-*N*-(3-(5-(morpholinomethyl)-1*H*-benzo[*d*]imidazol-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)pyrimidin-4-amine (133)



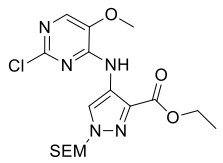
The title compound was synthesized from **126** (100 mg, 175 µmol) and (5-chloro-2-fluorophenyl)boronic acid (35.1 mg, 201 µmol) according to general procedure G (reaction time: 16 h). The crude was purified by automated column chromatography (0 – 10% MeOH/EtOAc) to afford the product (90.0 mg, 135 µmol, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.62 – 10.50 (2x s, 1H), 10.49 – 10.42 (2x s, 1H), 8.76 – 8.72 (2x d, *J* = 1.8 Hz, 1H), 8.15 – 8.11 (2x dd, *J* = 2.8, 1.9 Hz, 1H), 8.03 – 7.99 (2x s, 1H), 7.74 – 7.70 (m, 1H), 7.37 – 7.30 (m, 2H), 7.28 – 7.23 (m, 1H), 7.15 – 7.08 (2x dd, *J* = 10.3, 8.7 Hz, 1H), 5.45 – 5.42 (2x s, 2H), 4.13 – 4.09 (2x s, 3H), 3.77 – 3.70 (m, 4H), 3.66 – 3.58 (m, 4H), 2.56 – 2.45 (m, 4H), 0.96 – 0.89 (m, 2H), -0.06 – -0.07 (2x s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.81, 158.29, 153.53, 153.48, 150.05, 150.03, 147.33, 147.16, 143.64, 142.89, 139.83, 133.34, 132.98, 132.82, 132.80, 132.12, 132.08, 132.03, 131.96, 131.38, 131.36, 130.39, 130.30, 129.23, 129.22, 129.20, 129.18, 128.40, 128.29, 125.16, 124.03, 123.47, 121.71, 121.66, 121.61, 120.06, 118.94, 118.40, 118.15, 111.42, 110.54, 81.10, 67.11, 67.08, 67.06, 63.95, 63.85, 56.42, 56.34, 53.74, 17.79, -1.38. LCMS (Fleet, 10 → 90%): t_r = 6.01 min, m/z: 665.2.

2-(2-Fluoro-5-((trimethylsilyl)ethynyl)phenyl)-5-methoxy-*N*-(3-(5-(morpholinomethyl)-1*H*-benzo[*d*]imidazol-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)pyrimidin-4-amine (134)



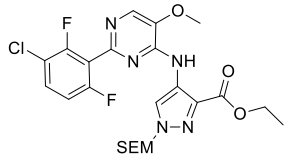
The title compound was synthesized from **133** (90.0 mg, 135 µmol) according to general procedure H. The crude was purified by automated column chromatography (0 – 10% MeOH/EtOAc) to afford the product (86.1 mg, 118 µmol, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.03 (br s, 1H), 10.59 – 10.47 (2x s, 1H), 8.79 – 8.76 (2x d, *J* = 1.9 Hz, 1H), 8.26 (dd, *J* = 7.6, 2.2 Hz, 1H), 8.05 – 8.01 (2x s, 1H), 7.73 – 7.69 (m, 1H), 7.48 (ddd, *J* = 8.5, 4.5, 2.3 Hz, 1H), 7.43 – 7.36 (m, 1H), 7.27 – 7.22 (m, 1H), 7.11 (dd, *J* = 11.1, 8.5 Hz, 1H), 5.42 (s, 2H), 4.13 – 4.06 (2x s, 3H), 3.77 – 3.71 (m, 4H), 3.71 – 3.64 (2x s, 2H), 3.62 – 3.56 (m, 2H), 2.61 – 2.49 (m, 4H), 0.96 – 0.88 (m, 2H), 0.25 (s, 9H), -0.08 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.08, 159.53, 153.88, 153.83, 150.01, 147.20, 147.04, 143.56, 142.94, 139.74, 135.63, 135.60, 134.12, 134.03, 133.19, 132.82, 132.46, 132.39, 132.03, 131.99, 130.94, 127.02, 126.92, 125.31, 124.19, 123.58, 121.99, 121.94, 120.27, 119.45, 119.41, 118.92, 117.21, 116.97, 111.93, 110.80, 104.05, 94.02, 80.88, 67.04, 66.77, 63.61, 56.40, 56.32, 53.43, 53.38, 17.76, 0.05, -1.41. LCMS (Fleet, 10 → 90%): t_r = 7.07 min, m/z: 727.3.

Ethyl 4-((2-chloro-5-methoxypyrimidin-4-yl)amino)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-3-carboxylate (135)



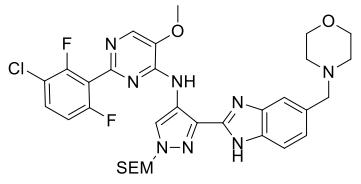
105 (1.54 g, 5.38 mmol) was dissolved in EtOH (5 mL) after which DIPEA (1.90 mL, 10.8 mmol) and 2,4-dichloro-5-methoxypyrimidine (1.45 g, 8.07 mmol) were added. The mixture heated to 40°C and stirred for 4 days and subsequently stirred at 50°C for 4 days. The mixture was poured into H_2O (75 mL) and the product extracted with DCM (2x75 mL). The organic layers were dried over Na_2SO_4, filtered and concentrated. The crude was purified by silica gel column chromatography (50% Et_2O/pentane) to afford the product (1.81 g, 4.22 mmol, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.21 (s, 1H), 8.52 (s, 1H), 7.67 (s, 1H), 5.48 (s, 2H), 4.45 (q, *J* = 7.1 Hz, 2H), 3.94 (s, 3H), 3.59 – 3.53 (m, 2H), 1.41 (t, *J* = 7.1 Hz, 3H), 0.92 – 0.86 (m, 2H), -0.06 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.90, 151.14, 151.02, 139.81, 134.01, 130.84, 125.79, 121.11, 81.72, 67.27, 61.49, 56.45, 17.78, 14.42, -1.41. LCMS (Fleet, 10 → 90%): t_r = 8.76 min, m/z: 428.3.

Ethyl 4-((2-(3-chloro-2,6-difluorophenyl)-5-methoxypyrimidin-4-yl)amino)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-3-carboxylate (136)



A microwave vial was charged with **135** (250 mg, 584 µmol), (3-chloro-2,6-difluorophenyl)boronic acid (169 mg, 876 µmol) and XPhos Pd G2 (92 mg, 117 µmol) after which the vial was purged with argon and subsequently sealed. Degassed THF (1 mL) and degassed 0.5 M K_3PO_4 (aq.) (2 mL) were added via syringe and the mixture was stirred for 1 h. The mixture was poured into H_2O (20 mL) and the product extracted with DCM (2x20 mL). The combined organic layers were concentrated as such. The crude was purified by automated column chromatography (50 – 80% Et_2O/pentane) to afford a mixture of starting material and product. The reaction was performed again using (3-chloro-2,6-difluorophenyl)boronic acid (113 mg, 584 µmol), XPhos Pd G2 (30 mg, 38 µmol), THF (0.5 mL) and 0.5 M K_3PO_4 (aq.) (1 mL). Performing a workup and purification as stated above, afforded a mixture of starting material and product which was subjected to another reaction using (3-chloro-2,6-difluorophenyl)boronic acid (169 mg, 876 µmol), XPhos Pd G2 (45 mg, 57 µmol) and THF (2 mL). The mixture was homogenized by stirring for 1 minute after which 1 M K_3PO_4 (aq.) (1 mL) was added and the mixture was stirred for 1 h. Performing a workup and purification as stated above, afforded a mixture of starting material and product (257 mg) which was used as such in subsequent reaction. LCMS (Fleet, 10 → 90%): t_r = 8.66 min, m/z: 540.3.

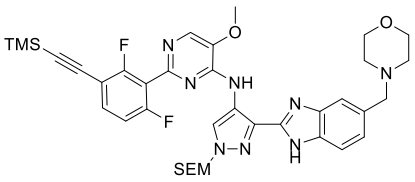
2-(3-Chloro-2,6-difluorophenyl)-5-methoxy-*N*-(3-(5-(morpholinomethyl)-1*H*-benzo[*d*]imidazol-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)pyrimidin-4-amine (137)



136 (257 mg, crude) was suspended in MeOH:H_2O (1:1) (2 mL) after which LiOH·H_2O (232 mg, 5.53 mmol) was added. DCM (1 mL) was added to dissolve some insoluble parts of the mixture after which the reaction was heated to 65°C and stirred for 16 h. The mixture was poured into H_2O (30 mL) and DCM (30 mL), and the pH of the water layer was adjusted by addition of 2 M HCl (aq.) to pH ~ 2. The organic layer was separated and the water layer extracted with DCM (30 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. To the obtained intermediate was added 4-(morpholinomethyl)benzene-1,2-diamine (143 mg, 690 µmol), EDC·HCl (109 mg, 569 µmol), HOBt (77.3 mg, 572 µmol) and DMF (1 mL) after which the reaction was stirred for 16 h. The mixture was concentrated, AcOH (1.5 mL) was added and the reaction was stirred at 118°C for 1 h. The mixture was cooled down to RT and the pH was adjusted by addition of 10 M NaOH (aq.) (until 9 > pH > 7). The mixture was poured into H_2O (40 mL) and brine (1 mL) and the product extracted with DCM (2x40 mL). The combined organic layers were concentrated as such. The crude was purified by HPLC (Waters, 39 – 42% MeCN in 0.2% TFA (aq.)), the pH of the combined fractions was adjusted to pH ~8 using 10 M NaOH after which the mixture was concentrated. The product was dissolved in a mixture of H_2O (20 mL) and DCM (15 mL). The organic layer was separated and the water layer extracted with DCM (15 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to afford the product (32.5 mg, 49.8 µmol, 9% over 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ

10.54 – 10.47 (2x s, 1H), 10.32 – 10.21 (2x s, 1H), 8.56 – 8.53 (2x s, 1H), 8.09 – 8.06 (2x s, 1H), 7.75 – 7.72 (m, 1H), 7.45 – 7.35 (m, 2H), 7.29 – 7.25 (m, 1H), 7.01 – 6.94 (m, 1H), 5.44 – 5.41 (2x s, 2H), 4.18 – 4.13 (2x s, 3H), 3.77 – 3.70 (m, 4H), 3.67 – 3.62 (2x s, 2H), 3.61 – 3.55 (m, 2H), 2.56 – 2.45 (m, 4H), 0.94 – 0.88 (m, 2H), -0.06 – -0.07 (2x s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.65, 160.60, 158.15, 158.10, 157.71, 157.65, 155.19, 155.13, 150.37, 150.35, 149.94, 147.24, 147.07, 143.66, 142.91, 140.14, 133.51, 132.91, 132.84, 132.81, 132.11, 132.06, 132.01, 130.29, 130.20, 125.24, 124.10, 123.44, 121.56, 121.53, 120.12, 119.52, 119.34, 119.15, 119.05, 117.35, 117.17, 112.65, 112.61, 112.41, 112.37, 111.38, 110.55, 81.11, 81.10, 67.15, 67.13, 67.05, 67.03, 63.96, 63.87, 56.51, 56.44, 53.78, 17.81, -1.39. LCMS (Fleet, 10 → 90%): t_r = 6.10 min, m/z: 683.3.

2-(2,6-Difluoro-3-((trimethylsilyl)ethynyl)phenyl)-5-methoxy-*N*-(3-(5-(morpholinomethyl)-1*H*-benzo[*d*]imidazol-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)pyrimidin-4-amine (138)



The title compound was synthesized from **137** (22 mg, 32 µmol) according to general procedure H. The crude was purified by automated column chromatography (0 – 10% MeOH/EtOAc) to afford the product (24 mg, 32 µmol, quant.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.52 – 10.43 (2x s, 1H), 10.25 – 10.15 (2x s, 1H), 8.56 – 8.53 (2x s, 1H), 8.08 – 8.05 (2x s, *J* = 4.9 Hz, 1H), 7.76 – 7.71 (m, 1H), 7.51 – 7.45 (m, 1H), 7.43 – 7.36 (m, 1H), 7.30 – 7.25 (m, 1H), 6.99 – 6.91 (2x d, *J* = 8.8 Hz, 1H), 5.45 – 5.42 (2x s, 2H), 4.18 – 4.13 (2x s, 3H), 3.76 – 3.70 (m, 4H), 3.67 – 3.62 (2x s, 2H), 3.61 – 3.55 (m, 2H), 2.54 – 2.46 (m, 4H), 0.94 – 0.87 (m, 2H), 0.25 (s, 9H), -0.06 – -0.07 (2x s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.89, 162.82, 162.01, 161.95, 160.34, 160.27, 159.48, 159.42, 150.36, 150.33, 150.16, 150.15, 147.27, 147.09, 143.67, 142.92, 140.06, 133.85, 133.74, 133.53, 132.91, 132.87, 132.85, 132.13, 132.06, 132.04, 132.00, 125.24, 124.11, 123.48, 121.65, 121.63, 120.13, 119.06, 118.55, 118.37, 118.20, 112.07, 112.03, 111.84, 111.81, 111.38, 110.56, 108.91, 108.87, 108.74, 108.70, 100.09, 100.05, 97.26, 97.25, 81.09, 81.07, 67.17, 67.15, 67.01, 66.99, 63.98, 63.89, 56.50, 56.43, 53.79, 17.80, -0.02, -1.35. LCMS (Fleet, 10 → 90%): t_r = 7.11 min, m/z: 745.3.

References

1. Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A. & Bray, F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA. Cancer J. Clin.* **71**, 209–249 (2021).
2. Hanahan, D. & Weinberg, R. A. Hallmarks of Cancer: The Next Generation. *Cell* **144**, 646–674 (2011).
3. Zhong, L., Li, Y., Xiong, L., Wang, W., Wu, M., Yuan, T., Yang, W., Tian, C., Miao, Z., Wang, T. & Yang, S. Small molecules in targeted cancer therapy: advances, challenges, and future perspectives. *Signal Transduct. Target. Ther.* **6**, 201 (2021).
4. Dominguez-Brauer, C., Thu, K. L., Mason, J. M., Blaser, H., Bray, M. R. & Mak, T. W. Targeting Mitosis in Cancer: Emerging Strategies. *Mol. Cell* **60**, 524–536 (2015).
5. Kops, G. J. P. L., Weaver, B. A. A. & Cleveland, D. W. On the road to cancer: aneuploidy and the mitotic checkpoint. *Nat. Rev. Cancer* **5**, 773–785 (2005).
6. Siemeister, G., Mengel, A., Fernández-Montalván, A. E., Bone, W., Schröder, J., Zitzmann-Kolbe, S., Briem, H., Prechtl, S., Holton, S. J., Mönning, U., von Ahsen, O., Johanssen, S., Cleve, A., Pütter, V., Hitchcock, M., von Nussbaum, F., Brands, M., Ziegelbauer, K. & Mumberg, D. Inhibition of BUB1 Kinase by BAY 1816032 Sensitizes Tumor Cells toward Taxanes, ATR, and PARP Inhibitors *In Vitro* and *In Vivo*. *Clin. Cancer Res.* **25**, 1404–1414 (2019).
7. Musacchio, A. & Salmon, E. D. The spindle-assembly checkpoint in space and time. *Nat. Rev. Mol. Cell Biol.* **8**, 379–393 (2007).
8. Zhang, G., Kruse, T., López-Méndez, B., Sylvestersen, K. B., Garvanska, D. H., Schopper, S., Nielsen, M. L. & Nilsson, J. Bub1 positions Mad1 close to KNL1 MELT repeats to promote checkpoint signalling. *Nat. Commun.* **8**, 15822 (2017).
9. Zhang, G., Lischetti, T., Hayward, D. G. & Nilsson, J. Distinct domains in Bub1 localize RZZ and BubR1 to kinetochores to regulate the checkpoint. *Nat. Commun.* **6**, 7162 (2015).
10. Di Fiore, B., Davey, N. E., Hagting, A., Izawa, D., Mansfeld, J., Gibson, T. J. & Pines, J. The ABBA Motif Binds APC/C Activators and Is Shared by APC/C Substrates and Regulators. *Dev. Cell* **32**, 358–372 (2015).
11. Ciossani, G., Overlack, K., Petrovic, A., Huis in 't Veld, P. J., Koerner, C., Wohlgemuth, S., Maffini, S. & Musacchio, A. The kinetochore proteins CENP-E and CENP-F directly and specifically interact with distinct BUB mitotic checkpoint Ser/Thr kinases. *J. Biol. Chem.* **293**, 10084–10101 (2018).
12. Musacchio, A. & Salmon, E. D. The spindle-assembly checkpoint in space and time. *Nat. Rev. Mol. Cell Biol.* **8**, 379–393 (2007).
13. Kawashima, S. A., Yamagishi, Y., Honda, T., Ishiguro, K. & Watanabe, Y. Phosphorylation of H2A by Bub1 Prevents Chromosomal Instability Through Localizing Shugoshin. *Science* **327**, 172–177 (2010).
14. Bolanos-Garcia, V. M. & Blundell, T. L. BUB1 and BUBR1: multifaceted kinases of the cell cycle. *Trends Biochem. Sci.* **36**, 141–150 (2011).
15. Elowe, S. Bub1 and BubR1: at the Interface between Chromosome Attachment and the Spindle Checkpoint. *Mol. Cell. Biol.* **31**, 3085–3093 (2011).
16. Funabiki, H. & Wynne, D. J. Making an effective switch at the kinetochore by phosphorylation and dephosphorylation. *Chromosoma* **122**, 135–158 (2013).
17. Zhang, G., Kruse, T., Guasch Boldú, C., Garvanska, D. H., Coscia, F., Mann, M., Barisic, M. & Nilsson, J. Efficient mitotic checkpoint signaling depends on integrated activities of Bub1 and the RZZ complex. *EMBO J.* **38**, (2019).
18. Foran, J., Ravandi, F., Wierda, W., Garcia-Manero, G., Verstovsek, S., Kadia, T., Burger, J., Yule, M., Langford, G., Lyons, J., Ayrton, J., Lock, V., Borthakur, G., Cortes, J. & Kantarjian, H. A Phase I and Pharmacodynamic Study of AT9283, a Small-Molecule Inhibitor of Aurora Kinases in Patients With Relapsed/Refractory Leukemia or Myelofibrosis. *Clin. Lymphoma Myeloma Leuk.* **14**, 223–230 (2014).
19. Dent, S. F., Gelmon, K. A., Chi, K. N., Jonker, D. J., Wainman, N., Capier, C. A., Chen, E. X., Lyons, J. F. & Seymour, L. NCIC CTG IND.181: Phase I study of AT9283 given as a weekly 24 hour infusion in advanced malignancies. *Invest. New Drugs* **31**, 1522–1529 (2013).
20. Arkenau, H.-T., Plummer, R., Molife, L. R., Olmos, D., Yap, T. A., Squires, M., Lewis, S., Lock, V., Yule, M., Lyons, J., Calvert, H. & Judson, I. A phase I dose escalation study of AT9283, a small molecule inhibitor of aurora kinases, in patients with advanced solid malignancies. *Ann. Oncol.* **23**, 1307–1313 (2012).
21. Moreno, L., Marshall, L. V., Pearson, A. D. J., Morland, B., Elliott, M., Campbell-Hewson, Q., Makin, G., Halford, S. E. R., Acton, G., Ross, P., Kazmi-Stokes, S., Lock, V., Rodriguez, A., Lyons, J. F., Boddy, A. V., Griffin, M. J., Yule, M. & Hargrave, D. A Phase I Trial of AT9283 (a Selective Inhibitor of Aurora Kinases) in Children and Adolescents with Solid Tumors: A Cancer Research UK Study. *Clin. Cancer Res.* **21**, 267–273 (2015).
22. Howard, S., Berdini, V., Boulstridge, J. A., Carr, M. G., Cross, D. M., Curry, J., Devine, L. A., Early, T. R., Fazal, L., Gill, A. L., Heathcote, M., Maman, S., Matthews, J. E., McMenamin, R. L., Navarro, E. F., O'Brien, M. A., O'Reilly, M., Rees, D. C., Reule, M., Tisi, D., Williams, G., Vinković, M. & Wyatt, P. G. Fragment-Based Discovery of the Pyrazol-4-yl Urea (AT9283), a Multitargeted Kinase Inhibitor with Potent Aurora Kinase Activity. *J. Med. Chem.* **52**, 379–388 (2009).

23. Vader, G. & Lens, S. M. A. The Aurora kinase family in cell division and cancer. *Biochim. Biophys. Acta BBA - Rev. Cancer* **1786**, 60–72 (2008).
24. Lampson, M. A., Renduchitala, K., Khodjakov, A. & Kapoor, T. M. Correcting improper chromosome–spindle attachments during cell division. *Nat. Cell Biol.* **6**, 232–237 (2004).
25. Knowlton, A. L., Lan, W. & Stukenberg, P. T. Aurora B Is Enriched at Merotelic Attachment Sites, Where It Regulates MCAK. *Curr. Biol.* **16**, 1705–1710 (2006).
26. Santaguida, S., Vernieri, C., Villa, F., Ciliberto, A. & Musacchio, A. Evidence that Aurora B is implicated in spindle checkpoint signalling independently of error correction: Aurora B is directly implicated in spindle checkpoint. *EMBO J.* **30**, 1508–1519 (2011).
27. Maldonado, M. & Kapoor, T. M. Constitutive Mad1 targeting to kinetochores uncouples checkpoint signalling from chromosome biorientation. *Nat. Cell Biol.* **13**, 475–482 (2011).
28. Ruchaud, S., Carmena, M. & Earnshaw, W. C. Chromosomal passengers: conducting cell division. *Nat. Rev. Mol. Cell Biol.* **8**, 798–812 (2007).
29. van Linden, O. P. J., Kooistra, A. J., Leurs, R., de Esch, I. J. P. & de Graaf, C. KLIFS: A Knowledge-Based Structural Database To Navigate Kinase–Ligand Interaction Space. *J. Med. Chem.* **57**, 249–277 (2014).
30. Taylor, S. S. & Kornev, A. P. Protein kinases: evolution of dynamic regulatory proteins. *Trends Biochem. Sci.* **36**, 65–77 (2011).
31. Kang, J., Yang, M., Li, B., Qi, W., Zhang, C., Shokat, K. M., Tomchick, D. R., Machius, M. & Yu, H. Structure and Substrate Recruitment of the Human Spindle Checkpoint Kinase Bub1. *Mol. Cell* **32**, 394–405 (2008).
32. Lin, Z., Jia, L., Tomchick, D. R., Luo, X. & Yu, H. Substrate-Specific Activation of the Mitotic Kinase Bub1 through Intramolecular Autophosphorylation and Kinetochore Targeting. *Structure* **22**, 1616–1627 (2014).
33. Roskoski, R. Classification of small molecule protein kinase inhibitors based upon the structures of their drug-enzyme complexes. *Pharmacol. Res.* **103**, 26–48 (2016).
34. Luna-Vargas, M. P. A., Christodoulou, E., Alfieri, A., van Dijk, W. J., Stadnik, M., Hibbert, R. G., Sahtoe, D. D., Clerici, M., Marco, V. D., Littler, D., Celie, P. H. N., Sixma, T. K. & Perrakis, A. Enabling high-throughput ligation-independent cloning and protein expression for the family of ubiquitin specific proteases. *J. Struct. Biol.* **175**, 113–119 (2011).
35. Vagin, A. & Teplyakov, A. *MOLREP*: an Automated Program for Molecular Replacement. *J. Appl. Crystallogr.* **30**, 1022–1025 (1997).
36. Potterton, L., Agirre, J., Ballard, C., Cowtan, K., Dodson, E., Evans, P. R., Jenkins, H. T., Keegan, R., Krissinel, E., Stevenson, K., Lebedev, A., McNicholas, S. J., Nicholls, R. A., Noble, M., Pannu, N. S., Roth, C., Sheldrick, G., Skubak, P., Turkenburg, J., Uski, V., von Delft, F., Waterman, D., Wilson, K., Winn, M. & Wojdyr, M. *CCP* 4 *i* 2: the new graphical user interface to the *CCP* 4 program suite. *Acta Crystallogr. Sect. Struct. Biol.* **74**, 68–84 (2018).
37. Long, F., Nicholls, R. A., Emsley, P., Gražulis, S., Merkys, A., Vaitkus, A. & Murshudov, G. N. *AceDRG*: a stereochemical description generator for ligands. *Acta Crystallogr. Sect. Struct. Biol.* **73**, 112–122 (2017).
38. Emsley, P. & Cowtan, K. *Coot*: model-building tools for molecular graphics. *Acta Crystallogr. D Biol. Crystallogr.* **60**, 2126–2132 (2004).
39. Murshudov, G. N., Skubák, P., Lebedev, A. A., Pannu, N. S., Steiner, R. A., Nicholls, R. A., Winn, M. D., Long, F. & Vagin, A. A. *REFMAC* 5 for the refinement of macromolecular crystal structures. *Acta Crystallogr. D Biol. Crystallogr.* **67**, 355–367 (2011).
40. The PyMOL Molecular Graphics System, Version 2.3.0 Schrödinger, LLC.
41. Yamagishi, H., Shirakami, S., Nakajima, Y., Tanaka, A., Takahashi, F., Hamaguchi, H., Hatanaka, K., Moritomo, A., Inami, M., Higashi, Y. & Inoue, T. Discovery of 3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one derivatives as novel JAK inhibitors. *Bioorg. Med. Chem.* **23**, 4846–4859 (2015).
42. Joo, J. M., Touré, B. B. & Sames, D. C−H Bonds as Ubiquitous Functionality: A General Approach to Complex Arylated Imidazoles via Regioselective Sequential Arylation of All Three C−H Bonds and Regioselective *N* -Alkylation Enabled by SEM-Group Transposition. *J. Org. Chem.* **75**, 4911–4920 (2010).
43. Mattsson, S., Dahlström, M. & Karlsson, S. A mild hydrolysis of esters mediated by lithium salts. *Tetrahedron Lett.* **48**, 2497–2499 (2007).
44. Dineen, T. A., Weiss, M. M., Williamson, T., Acton, P., Babu-Khan, S., Bartberger, M. D., Brown, J., Chen, K., Cheng, Y., Citron, M., Croghan, M. D., Dunn, R. T., Esmay, J., Graceffa, R. F., Harried, S. S., Hickman, D., Hitchcock, S. A., Horne, D. B., Huang, H., Imbeah-Ampiah, R., Judd, T., Kaller, M. R., Kreiman, C. R., La, D. S., Li, V., Lopez, P., Louie, S., Monenschein, H., Nguyen, T. T., Pennington, L. D., San Miguel, T., Sickmier, E. A., Vargas, H. M., Wahl, R. C., Wen, P. H., Whittington, D. A., Wood, S., Xue, Q., Yang, B. H., Patel, V. F. & Zhong, W. Design and Synthesis of Potent, Orally Efficacious Hydroxyethylamine Derived β-Site Amyloid Precursor Protein Cleaving Enzyme (BACE1) Inhibitors. *J. Med. Chem.* **55**, 9025–9044 (2012).
45. Harrowven, D. C., Curran, D. P., Kostiuk, S. L., Wallis-Guy, I. L., Whiting, S., Stenning, K. J., Tang, B., Packard, E. & Nanson, L. Potassium carbonate–silica: a highly effective stationary phase for the chromatographic removal of organotin impurities. *Chem. Commun.* **46**, 6335 (2010).
46. Kinzel, T., Zhang, Y. & Buchwald, S. L. A New Palladium Precatalyst Allows for the Fast Suzuki−Miyaura Coupling Reactions of Unstable Polyfluorophenyl and 2-Heteroaryl Boronic Acids. *J. Am. Chem. Soc.* **132**, 14073–14075 (2010).