Supporting Information

ADDRESSING THE OSIMERTINIB RESISTANCE MUTATION EGFR-L858R/C797S WITH REVERSIBLE AMINOPYRIMIDINES

Tobias Grabe, Kirujan Jeyakumar[+], Janina Niggenaber[+], Tom Schulz, Sandra Koska, Silke Kleinboelting, Michael E. Beck[†], Matthias P. Müller and Daniel Rauh*

Faculty of Chemistry and Chemical Biology, TU Dortmund University and Drug Discovery Hub Dortmund (DDHD) am Zentrum für Integrierte Wirkstoffforschung (ZIW), Otto-Hahn-Strasse 4a, 44227 Dortmund (Germany), E-mail: daniel.rauh@tu-dortmund.de.

1. Protein Expression and Crystallization

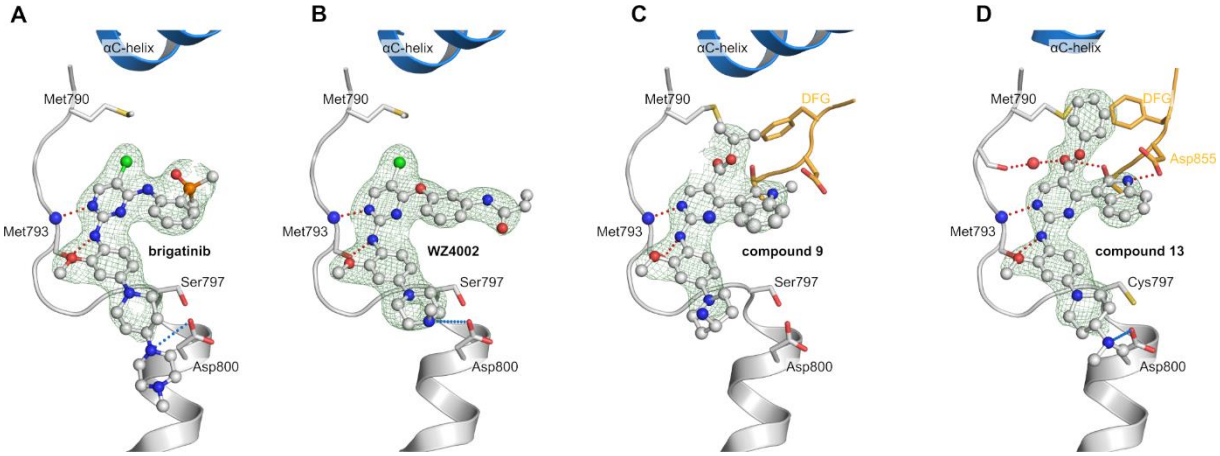
Construct Design of EGFR-T790M/C797S and EGFR-T790M/V948R.
For crystallographic studies, codon-optimized DNA encoding residues 696-1022 of the human EGFR with a N-terminal His6-tag and thrombin cleavage site was cloned into a pIEX/Bac-3 vector. Point mutations T790M, C797S, E865A, E866A and K867A as well as T790M and V948R were introduced by site-directed mutagenesis (QuikChange, Stratagene/Agilent Technologies). Transfection, virus generation, amplification, and expression were carried out in *Spodoptera frugiperda* cell line *Sf9* following the flashBAC protocol.

Protein Expression and Purification.
After three days of expression (27 °C, 110 rpm) the Sf9-cells were harvested (3000 g, 20 min), resuspended in lysis buffer (600 mM NaCl, 50 mM Tris-HCl pH 7.5, 15% glycerol, 1 mM TCEP) supplemented with a protease-inhibitor cocktail (Complete EDTA-free), lysed and incubated with CHAPS (1 h, 4 °C) followed by centrifugation (20500 rpm, 1 h, 4 °C). The filtered supernatant was loaded onto a nickel-affinity column. The protein was eluted with 500 mM NaCl, 25 mM Tris-HCl pH 8, 250 mM imidazole, 10% glycerol, and 1 mM TCEP followed by cleavage with thrombin to remove the His6-tag and a second nickel-affinity chromatography capturing the flow through. Finally, the protein was purified by size-exclusion chromatography (100 mM NaCl, 25 mM Tris-HCl pH 8, 10% glycerol, and 1 mM TCEP) and concentrated to 3.5-5.5 and 6.4 mg/mL. Protein identity was confirmed by ESI-MS analysis.

Crystallization of EGFR-T790M/C797S.
The concentrated protein EGFR-T790M/C797S (3.5-5.5 mg/mL) was incubated with a three-fold excess of brigatinib, WZ4002 or **compound 9** (10 mM DMSO stock) for 2 h on ice. Crystals were grown at 20 °C by hanging drop vapor diffusion method. The protein-compound-complex was mixed in a 1:1 ratio (1 µL protein and 1 µL reservoir solution containing 1.3-1.7 M K-Na-tartrate, 100 mM Na-MES pH 5.5-7.5, 0-4% 1,3-propanediol). Crystals grew within one to two weeks and were harvested and flash-cooled in liquid nitrogen. Diffraction data were collected at the PXII X10SA beamline at the Swiss Light Source (PSI, Villigen, Switzerland). The data were processed using XDS and scaled using XSCALE (W. Kabsch, XDS. Acta Cryst. 2010, D66, 125-132).

Crystallization of EGFR-T790M/V948R.
The concentrated protein EGFR-T790M/V948R (6.4 mg/mL) was incubated with a three-fold excess of **compound 13** (10 mM DMSO stock) for 2 h on ice. Crystals were grown at 20 °C by hanging drop vapor diffusion method. The protein-compound-complex was mixed in a 1:1 ratio (1 µL protein and 1 µL reservoir solution containing 15-37.5% PEG3350, 100 mM $MgSO_4$, 0-4% ethylene glycol). Crystals grew within one to two weeks and were harvested and flash-cooled in liquid nitrogen. Diffraction data were collected at the PXII X10SA beamline at the Swiss Light Source (PSI, Villigen, Switzerland). The data were processed using XDS and scaled using XSCALE (W. Kabsch, XDS. Acta Cryst. 2010, D66, 125-132).

Structure Determination and Refinement.
The complex crystal structures of EGFR-T790M/C797S and EGFR-T790M/V948R were solved by molecular replacement with PHASER (R.J. Read, Acta Crystallogr D Biol Crystallogr 2001, 57, 1373-1382) using structure PDB ID: 6S8A as template. The molecules in the asymmetric unit were manually adjusted using the program COOT (P. Emsley, K. Cowtan, Acta Crystallogr D Biol Crystallogr 2004, 60, 2126-2132). The refinement was performed with Phenix.refine 1.17.1 (P.D. Adams, P.V. Afonine, G. Bunkoczi, V.B. Chen, I.W. Davis, N. Echols, J.J. Headd, L.W. Hung, G.J. Kapral, R.W. Grosse-Kunstleve, A.J. McCoy, N.W. Moriarty, R. Oeffner, R.J. Read, D.C. Richardson, J.S. Richardson, T.C. Terwilliger, P.H. Zwart, Acta Cryst 2010, D66, 213-221). Inhibitor topology files were generated using eLBOW of the Phenix1.17.1 program package (P.D. Adams, P.V. Afonine, G. Bunkoczi, V.B. Chen, I.W. Davis, N. Echols, J.J. Headd, L.W. Hung, G.J. Kapral, R.W. Grosse-Kunstleve, A.J. McCoy, N.W. Moriarty, R. Oeffner, R.J. Read, D.C. Richardson, J.S. Richardson, T.C. Terwilliger, P.H. Zwart, Acta Cryst 2010, D66, 213-221). The angles of the atoms of the solubility groups were adapted to the calculations shown in the manuscript supplement below (Chapter 7). Refined structures were validated with the PDB validation server. Data collection, structure refinement statistics, PDB-ID codes, and further details for data collection are provided in Table S1. PyMOL (W.L. DeLano, The PyMOL Molecular Graphics System) was used for generating the figures.



Supplementary Figure S1: Simulated Annealing |Fo-Fc| omit electron density maps shown for all ligands that were cocrystallized with EGFR in this study (r.m.s.d. = 2.8). **A** – Brigatinib in EGFR-T790M/C797S (PDB: 7ZYM). **B** – WZ4002 in EGFR-T790M/C797S (PDB: 7ZYN). **C** – Compound 9 in EGFR-T790M/C797S (PDB: 7ZYP). **D** – Compound 13 in EGFR-T790M/V948R (PDB: 7ZYQ).

Table S1. Data collection and refinement statistics of complex crystal structures.[a]

	EGFR-T790M/C797S with **Brigatinib** PDB ID: 7ZYM	EGFR-T790M/C797S with **WZ4002** PDB ID: 7ZYN	EGFR-T790M/C797S with **9** PDB ID: 7ZYP	EGFR-T790M/V948R with **13** PDB ID: 7ZYQ
Data collection				
Space group	I 2 3 (197)	I 2 3 (197)	I 2 3 (197)	P 2_1 2_1 2_1 (19)
Cell dimensions				
a, b, c [Å]	146.10, 146.10, 146.10	144.60, 144.60, 144.60	141.80, 141.80, 141.80	75.89, 79.59, 89.57
α, β, γ [°]	90.0, 90.0, 90.0	90.0, 90.0, 90.0	90.0, 90.0, 90.0	90.0, 90.0, 90.0
Resolution [Å]	42.18-2.50 (2.60-2.50)	41.74-2.30 (2.40-2.30)	44.84-2.80 (2.90-2.80)	46.82-2.10 (2.20-2.10)
R_{meas} [%]	16.6 (146.4)	8.3 (122.8)	13.9 (283.1)	6.6 (78.1)
$I / \sigma I$	12.51 (2.10)	27.45 (2.91)	21.67 (2.11)	16.92 (2.75)
Completeness [%]	100.0 (100.0)	100.0 (100.0)	100.0 (100.0)	99.9 (100.0)
$CC_{1/2}$	99.6 (77.3)	100.0 (86.0)	100.0 (68.1)	99.9 (80.9)
Redundancy	19.66 (19.47)	20.33 (20.98)	38.28 (42.91)	6.73 (6.66)
Refinement				
Resolution [Å]	42.18-2.50 (2.60-2.50)	41.74-2.30 (2.40-2.30)	44.84-2.80 (2.90-2.80)	46.82-2.10 (2.20-2.10)
No. reflections	18104	22472	11850	32296
R_{work} / R_{free}	19.39 / 22.37 (27.38 / 30.62)	19.29 / 22.32 (26.66 / 29.42)	19.87 / 22.81 (28.06 / 31.29)	19.78 / 22.30 (26.57 / 31.84)
No. atoms				
Protein	2486	2468	2268	4139 (chain A= 2105, chain B=2034)
Ligand	40	35	38	84 (chain A= 42, chain B= 42)
Ligand 2 (MES)	-	12	12	-
Ions	-	-	-	23
Water	22	64	2	129
B-factors				
Protein	70.34	66.98	87.15	50.92 (chain A= 47.54, chain B=54.30)
Ligand	80.06	73.78	85.50	44.41 (chain A= 44.45, chain B=44.37)

Ligand 2 (MES)	-	91.64	111.55	-
Ions	-	-	-	61.61
Water	62.54	60.25	89.05	49.22
R.m.s. deviations				
Bond lengths [Å]	0.003	0.002	0.003	0.006
Bond angles [°]	0.561	0.603	0.601	0.457

[a] Diffraction data from a single crystal was used to determine the complex structure. Values in parenthesis are referring to the highest resolution shell.

2. HTRF and CTG and Microsomal Stability Assays

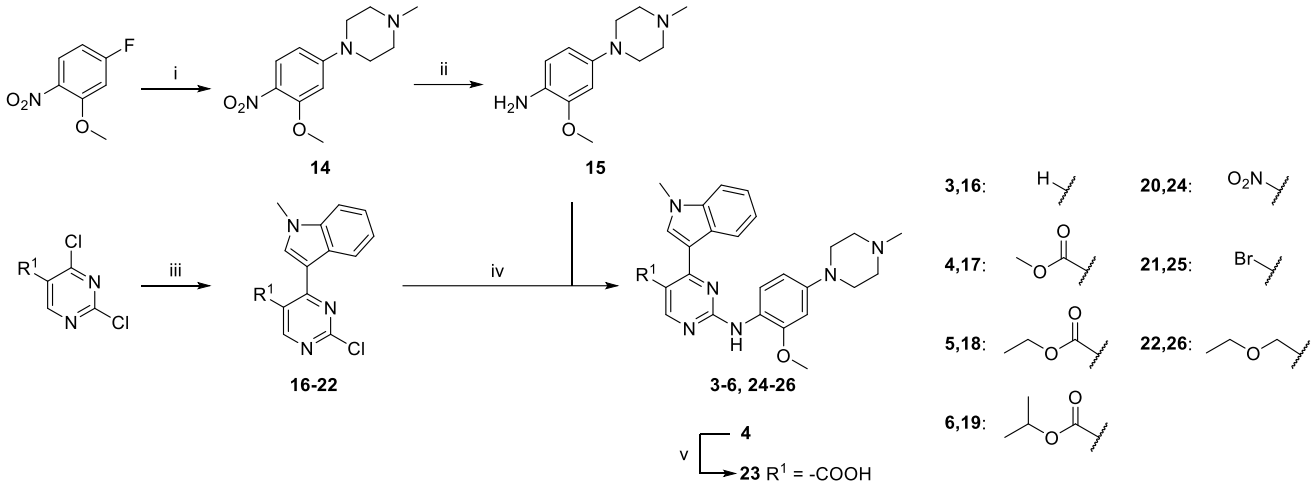
Biochemical IC_{50}-Determination of EGFR-mutants: Activity-based IC_{50} determination for EGFR and its mutants (Carna Biosciences lot13CBS-0005K for EGFR-wt; Carna, lot13CBS-0537B for EGFR-L858R and Carna, lot12CBS-0765B for EGFR-L858R/T790M, SignalChem lot2219-3 for LR/CS, for LR/TM/CS expression see Lategahn *et. al.* doi.org/10.1039/C9SC03445E) were performed with commercially available HTRF KinEASE-TK assay from Cisbio according to the manufacturer's instructions. Briefly, the amount of EGFR in each reaction well was set to 0.60 ng EGFR-wt (0.67 nM), 0.10 ng EGFR-L858R (0.11 nM), 0.07 ng EGFR-T790M/L858R (0.08 nM), 0.05 ng EGFR-L858R/C797S (0.06 nM) and 0.8 ng EGFR-L858R/T790M/C797S (0.88 nM). An artificial substrate peptide (TK-substrate from Cisbio) was phosphorylated by EGFR. After completion of the reaction, the reaction was stopped by addition of buffer containing EDTA, an anti-phosphotyrosine antibody labeled with europium cryptate and streptavidin labeled with the fluorophore XL665. FRET between europium cryptate and XL665 was measured after an additional hour of incubation to quantify the phosphorylation of the substrate peptide. ATP concentrations were set at their respective K_m-values (9.5 µM for EGFR-wt, 25 µM for EGFR-L858R, 20 µM for EGFR-L858R/T790M, 75 µM for EGFR-L858R/C797S, and 11 µM for EGFR-L858R/T790M/C797S) while a substrate concentration of 1 µM, 0.225 µM, and 0.275 µM, 1 µM, and 0.325 µM respectively, was used. After kinase and inhibitor were preincubated for 30 min, the reaction (reaction time: 25 min for EGFR-wt, 15 min for EGFR-L858R, 20 min for EGFR-T790M/L858R, 20 min for EGFR-L858R/C797S, and 10 min for EGFR-L858R/T790M/C797S) was started by addition of ATP and substrate peptide. An EnVision multimode plate reader (Perkin Elmer) was used to measure the fluorescence of the samples at 620 nm (Eu^{3+}-labeled antibody) and 665 nm (XL665 labeled streptavidin) 50 µs after excitation at 320 nm. The quotient of both intensities for reactions made with eight different inhibitor concentrations was then analyzed using the Quattro Software Suite for IC_{50}-determination. Each reaction was performed in duplicate, and at least three independent determinations of each IC_{50} were made if not noted otherwise.

Cell viability assay: A431 cells were obtained from the American Type Culture Collection (ATCC), Ba/F3-EGFR-L858R and Ba/F3-EGFR-L858R/C797S were obtained by Crown Bioscience. Ba/F3 cells were cultivated in RPMI-1640 GlutaMAX (Life Technologies, Germany) supplemented with 10% FBS Good (PanBiotech, Germany) and 1% PenStrep (Life Technologies, Germany) in a humidified incubator at 37 °C and 5% CO_2. A431 cells were cultivated in Dulbecco's modified Eagle's medium high-glucose GlutaMAX (Life Technologies, Germany) supplemented with 10% FBS Good (PanBiotech, Germany) and 1% PenStrep (Life Technologies, Germany) in a humidified incubator at 37 °C and 5% CO_2. Cells were seeded at cell numbers that assure linearity and optimal signal intensity 150–300 cells/well, 25 µL) and cultured for 24 hours in serum- and antibiotics-containing media in humidified chambers at 37 °C and 5% CO_2. The cells were then treated with EGFR inhibitors in serial dilutions (1.4 nM to 30 µM) with DMSO and Staurosporine as control and incubated for 96 hours. Afterwards viability studies were carried out using CellTiter-Glo Assay (Promega, USA) that is a homogeneous method of determining the number of viable cells in culture. It is based on quantification of ATP, indicating the presence of metabolically active cells. For these studies, CellTiter-Glo reagent was prepared according to the instructions of the kit and diluted 1:1 with the complete growth medium suitable for the corresponding cell line. Thereon, reagent and assay plates were equilibrated at room temperature for 30 min. Equal volumes of the reagent were added to the volume of culture medium present in each well (25 µL). The plates were mixed for 2 minutes on an orbital shaker to induce cell lysis. The microplates were then incubated at room temperature for 20 minutes for stabilization of the luminescent signal. Following incubation, the luminescence was recorded on an EnVision microplate reader (Perkin Elmer) using 500 ms integration time. The data was then analyzed using the Quattro Research Software Suite for EC_{50}-determination. As quality control the Z'-factor was calculated from 16 positive and negative control values. Only assay results showing a Z'-factor ≥0.5 were used for further analysis. All data points were measured in duplicates for each plate and were replicated in at least three plates if not noted otherwise.

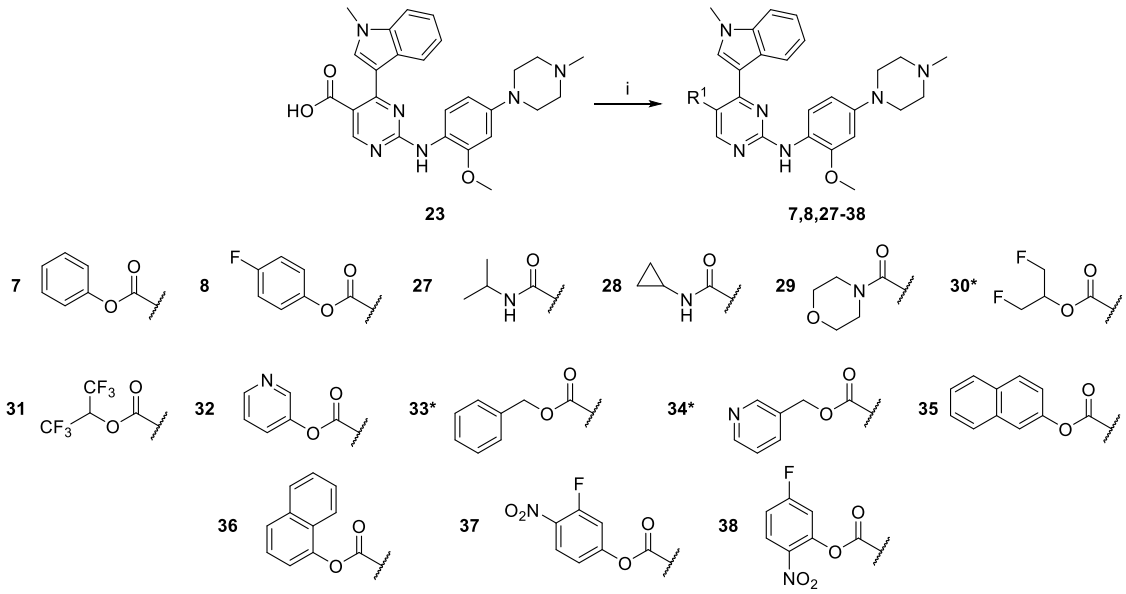
Microsomal Stability Assay: Microsomal metabolic stability (CLint) of test compounds under oxidative conditions was determined at a final concentration of 1 µM by incubation with liver microsomes (XenoTech, tebu-bio, Germany) derived from different species supplemented with NADP, glucose-6-phosphate (G6P), and G6P-dihydrogenase. Compound depletion was measured over time by LC-MS/MS to calculate compound half-life $t_{1/2}$. Conversion to the in vitro intrinsic clearance CLint expressed in [µL/min/mg] was performed using the following equation: Clint [µL/min/mg] = (0.693/t1/2 [min]) × (reaction volume [µL]/microsomal protein [mg]).

Compound	**Microsomal Stability Phase I, mouse** **CLint [µL/min/mg]**
1 (Osimertinib)	81.1
2 (Mobocertinib)	149.4
11 (Isopropyl ester)	49.3
13 (Phenol ester)	55.0

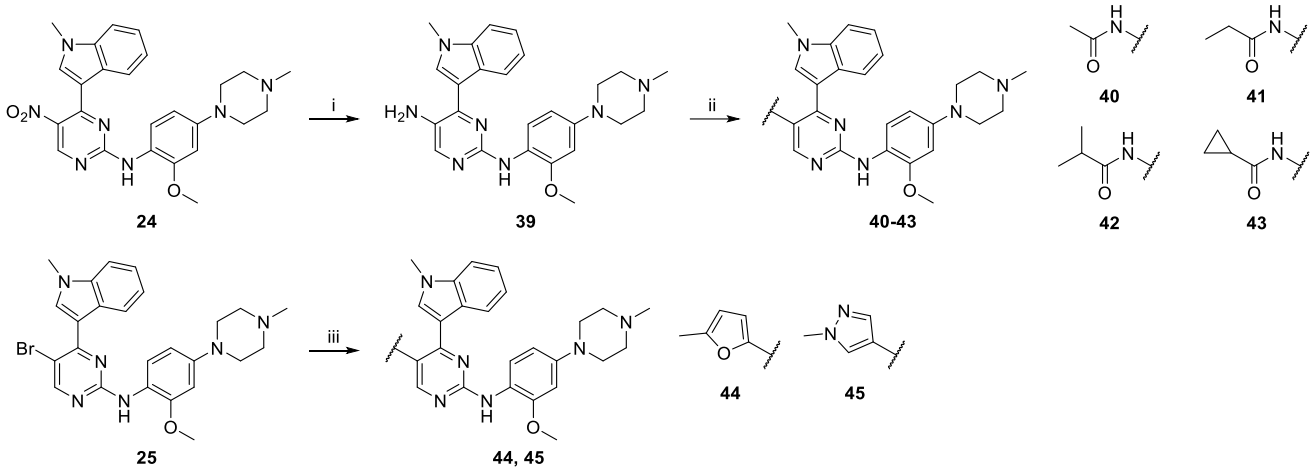
3. Synthetic Schemes



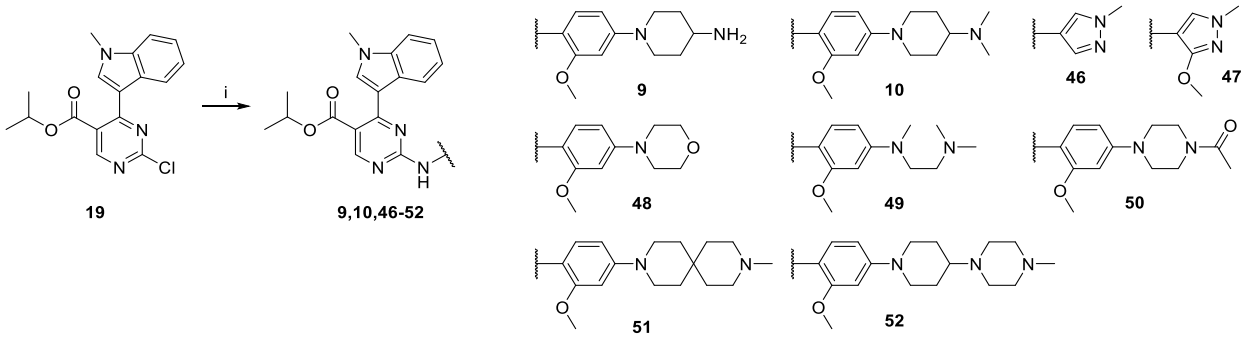
Scheme S1 – Reagents and conditions: (i) Methylpiperazine, K_2CO_3, DMF, 50° C (quant. yield); (ii) Hydrogen-flow-reactor, Pd/C(10%)-cartridge, 1 atm, 60 °C, MeOH (quant. yield); (iii) $AlCl_3$, DME, 55 °C (69-97%); (iv) TFA, *i*-PrOH, 85 °C (72-96%); (v) aq. KOH, THF, 90 °C (quant. yield). Intermediate **16** was acquired from Sigma Aldrich.



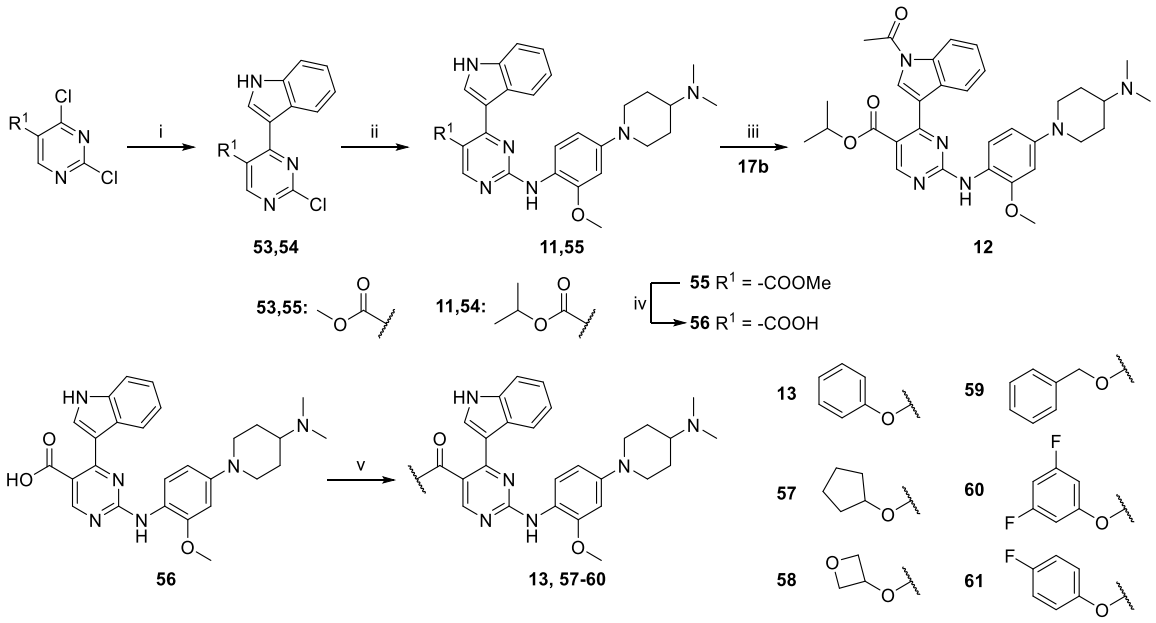
Scheme S2 – Reagents and conditions: (i) 1. TBTU, TEA, DCM, 0 °C; 2. alcohol/amine. * NaH was used for activation of the alcohol prior to addition to active ester.



Scheme S3 - Reagents and conditions: (i) Hydrogen-flow-reactor, Pd/C(10%)-cartridge, 1 atm, 60 °C, MeOH (quant. yield); (ii) acid chloride, DIPEA, DCM/THF, 0 °C (16-73%); (iii) Boronic acid pinacol ester, $Pd(PPh_3)_4$, K_2CO_3, dioxane, 100 °C (20-24%).



Scheme S4 - Reagents and conditions: (i) Anilines 16a-g, *i*-PrOH, TFA, 90 °C, 4-16 h, 37-78%.



Scheme S5 - Reagents and conditions: (i) $AlCl_3$, indole, DCE, 70 °C, 2 h, 36%. (ii) aniline, TFA, *i*-PrOH, 90 °C, 16 h, 57-76%. (iii) acetylchloride, DIPEA, DMAP, THF, 0 °C, 4 h, 73%. (iv) 1 M NaOH, THF, 90 °C, 16 h, quantitative. (v) TBTU, DIPEA, DCM, 0 °C, 3-39%.

4. Synthetic Procedures and Analysis

Safety statement: No unexpected or unusually high safety hazards were encountered. Unless otherwise noted, all commercially available compounds, reagents, solvents, and anhydrous solvents were used as provided without further purification. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance III HD NanoBay - 400 MHz, Bruker Avance NEO – 500 MHz, Bruker Avance III HD – 600 MHz und Agilent DD2 – 500 MHz. Chemical shifts (δ) are reported in parts per million (ppm) and are referenced to the residual solvent signal DMSO-d6 (2.50 or 39.52 ppm), $CDCl_3$ (7.26 or 77.16 ppm), or CD_3OD (1.94 or 49.00 ppm, respectively). High-resolution ESI mass spectra (ESI-Fourier transform mass spectrometry) were recorded on a Thermo LTQ Orbitrap (high-resolution mass spectrometer from Thermo Electron) coupled to an "Accela" HPLC system supplied with a "Hypersil GOLD" column (Thermo Electron). Compounds were purified by flash chromatography on a Biotage Isolera One using Büchi Reveleris or Büchi FlashPure EcoFlex C18 columns and monitored by UV at λ = 254 and 280 nm. Preparative HPLC was conducted on a Büchi Reveleris Prep System with a VP 250/21 Nucleodur C18 column from Macherey-Nagel and monitored by UV at λ = 210, 254, and 280 nm. All final compounds were purified to ≥95% purity confirmed by NMR analysis as well as LC/MS analysis on LCQ Advantage MAX (1200 series, Agilent) with Eclipse XDB- C18-column (5 µM 150 × 1.6 mm, Phenomenex).

General method for Friedel-Crafts arylation: To a solution of 5-substituted 2,4-dichloropyrimidine in dimethoxyethane (0.5 M), anhydrous $AlCl_3$ (2.0 eq) was added at 0 °C. The reaction was stirred for 15 min before *N*-methylindole (1.1 eq) was added. The reaction mixture was slowly heated up to 55 °C and stirred for 2 h. Afterwards the reaction mixture was quenched with MeOH at 0 °C and separated between EtOAc and 0.1 M HCl solution. The aqueous phase was extracted two additional times with DCM. The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (PE:EtOAc) which resulted in the desired product.

General method for nucleophilic aromatic substitution with *p*-fluoronitrobenzenes: 2-Nitro-5-fluoroanisole was dissolved in DMF (0.5 M) and the secondary amine (1.0 eq) was added. K_2CO_3 (2.0 eq) was added and the reaction was stirred at 50 °C for 24 h. The reaction mixture was separated between water and DCM with sufficient amount for resolving the precipitate. The organic fraction was dried with Na_2SO_4 and concentrated to a residual DMF-product solution. The product was recrystallized by addition of water and heating the suspension until it cleared. Slow cooling and filtering off the crystals resulted in the desired product.

General method for aromatic nitro reduction: The nitro-derivative was dissolved in MeOH (0.05 M) and treated in a hydrogen-flow-reactor using a Pd/C (10%) cartridge at 1 atm and 60 °C with a flow rate of 2 mL/min. The flow-through was concentrated *in vacuo* yielding the desired product. If not noted otherwise no further purification was performed.

General method for nucleophilic aromatic substitution of 2-chloropyrimidines: The 4,5-substituted 2-chloropyrimidine and the aniline (1.0-1.5 eq) were dissolved in *n*-BuOH or *i*-PrOH and TFA (1.5 eq) was added. The reaction was stirred at 80-110 °C for 2 to 48 h until sufficient product formation was observed. The cooled down reaction mixture was separated between $NaHCO_3$ solution and DCM and extracted two additional times with DCM. The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (DCM:MeOH) which resulted in the desired product.

General method for amide and ester couplings: The acid was dissolved in DCM (0.1 M) and TEA or DIPEA (10.0 eq) was added. At 0 °C TBTU (1.2 eq) was added and the mixture was stirred for 10 min. Afterwards the amine or alcohol was added and the reaction was stirred for 2 h at room temperature. The mixture was separated between $NaHCO_3$ solution and DCM and extracted two additional times with DCM. The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (DCM:MeOH) which resulted in the desired product.

Compound 3: *N*-(2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)-4-(1-methyl-1*H*-indol-3-yl)pyrimidin-2-amine: The reaction was performed according to the *General method for nucleophilic aromatic substitution of 2-chloropyrimidines* with 3-(2-chloropyrimidin-4-yl)-1-methyl-1*H*-indole (0.20 mmol, 49 mg) and **15** (0.24 mmol, 53 mg) in *i*-PrOH (0.1 M) at 85 °C. The product was obtained as an off-white solid in 72% yield (0.14 mmol, 62 mg). **^{1}H NMR** (700 MHz, $CDCl_3$) δ ppm 2.40 (s, 3 H) 2.65 (t, *J* = 4.8 Hz, 4 H) 3.22 (t, *J* = 4.8 Hz, 4 H) 3.87 (s, 3 H) 3.91 (s, 3 H) 6.60 (d, *J* = 2.6 Hz, 1 H) 6.63 (dd, *J* = 8.8, 2.6 Hz, 1 H) 7.01 (d, *J* = 5.2 Hz, 1 H) 7.25 - 7.29 (m, 1 H) 7.32 (td, *J* = 7.5, 1.1 Hz, 1 H) 7.38 (d, *J* = 8.2 Hz, 1 H) 7.44 (s, 1 H) 7.80 (s, 1 H) 8.33 (d, *J* = 5.4 Hz, 1 H) 8.39 (d, *J* = 8.8 Hz, 1 H) 8.40 (d, *J* = 7.74 Hz, 1 H). **^{13}C NMR** (176 MHz, $CDCl_3$) δ ppm 33.3, 46.0, 50.3, 55.2, 55.7, 100.8, 107.6, 108.4, 109.7, 114.2, 120.3, 121.1, 121.9, 122.5, 123.0, 126.0, 131.1, 137.9, 146.9, 149.2, 157.2, 160.3, 162.2. **HRMS** (ESI^+) (m/z) calculated for $[C_{25}H_{29}N_6O]^+$ 429.2397, found 429.2392.

Compound 4: methyl 2-((2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)-4-(1-methyl-1*H*-indol-3-yl)pyrimidine-5-carboxylate: The reaction was performed according to the *General method for nucleophilic aromatic substitution of 2-chloropyrimidines* with **17** (3.0 mmol, 0.91 g) and **15** (3.6 mmol, 0.80 g) in *i*-PrOH (0.1 M) at 85 °C. The product was obtained as a yellow solid in 95% yield (2.85 mmol, 1.39 g). **^{1}H NMR** (500 MHz, DMSO-d_6) δ ppm 2.25 (s, 3 H) 2.49 (t, *J* = 4.9 Hz, 4 H) 3.17 (t, *J* = 4.9 Hz, 4 H) 3.74 (s, 3 H) 3.78 (s, 3 H) 3.85 (s, 3 H) 6.51 (dd, *J* = 8.7, 2.6 Hz, 1 H) 6.67 (d, *J* = 2.44 Hz, 1 H) 7.04 (br. s., 1 H) 7.21 (t, *J* = 7.5 Hz, 1 H) 7.47 (d, *J* = 8.5 Hz, 2 H) 7.92 (s, 1 H) 7.95 (br. s., 1 H) 8.62 (s, 1 H) 8.67 (s, 1 H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ ppm 33.0, 45.8, 48.6, 51.8, 54.7, 55.5, 100.0, 106.7, 110.1, 111.3, 119.3, 120.6, 122.0, 122.1, 126.2, 126.5, 134.4, 136.7, 149.7, 153.3, 160.2, 161.2, 161.3, 167.3. **HRMS** (ESI^+) (m/z) calculated for $[C_{27}H_{31}N_6O_3]^+$ 487.24456, found 487.24522.

Compound 5: ethyl 2-((2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)-4-(1-methyl-1*H*-indol-3-yl)pyrimidine-5-carboxylate: The reaction was performed according to the *General method for nucleophilic aromatic substitution of 2-chloropyrimidines* with **18** (0.10 mmol, 32 mg) and **15** (0.12 mmol, 27 mg) in *i*-PrOH (0.1 M) at 85 °C. The product was obtained as a yellow solid in 96% yield (96 µmol, 48 mg). **^{1}H NMR** (500 MHz, DMSO-d_6) δ ppm 1.15 (t, *J* = 7.2 Hz, 3 H) 2.23 (s, 3 H) 2.47 (t, *J* = 4.9 Hz, 4 H) 3.16 (t, *J* = 4.9 Hz, 4 H) 3.77 (s, 3 H) 3.85 (s, 3 H) 4.20 (q, *J* = 7.0 Hz, 2 H) 6.50 (dd, *J* = 8.7, 2.6 Hz, 1 H) 6.66 (d, *J* = 2.4 Hz, 1 H) 7.03 (br. s., 1 H) 7.20 (t, *J* = 7.6 Hz, 1 H) 7.44 - 7.51 (m, 2 H) 7.91 (s, 1 H) 7.93 (br. s., 1 H) 8.62 (s, 1 H) 8.64 (s, 1 H) **^{13}C NMR** (126 MHz, DMSO-d_6) δ ppm 13.9, 32.9, 45.8, 48.6, 54.7, 55.5, 60.5, 100.0, 106.7, 110.1, 111.4, 119.3, 120.6, 121.9, 122.0, 126.0, 126.6, 134.4, 136.7, 149.7, 153.2, 160.2, 161.2, 161.2, 166.8. **HRMS** (ESI^+) (m/z) calculated for $[C_{28}H_{33}N_6O_3]^+$ 501.2609, found 501.2604.

Compound 6: isopropyl 2-((2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)-4-(1-methyl-1*H*-indol-3-yl)pyrimidine-5-carboxylate: The reaction was performed according to the *General method for nucleophilic aromatic substitution of 2-chloropyrimidines* with **19** (0.10 mmol, 33 mg) and **15** (0.12 mmol, 27 mg) in *i*-PrOH (0.1 M) at 85 °C. The product was obtained as a yellow solid in 87% yield (87 µmol, 45 mg). **^{1}H NMR** (600 MHz, CDCl3) δ ppm 1.20 (d, *J* = 6.2 Hz, 6 H) 2.39 (s, 3 H) 2.63 (t, *J* = 4.8 Hz, 4 H) 3.21 (t, *J* = 4.8 Hz, 4 H) 3.87 (s, 3 H) 3.90 (s, 3 H) 5.10 (spt, *J* = 6.2 Hz, 1 H) 6.52 - 6.60 (m, 2 H) 7.17 - 7.23 (m, 1 H) 7.25 - 7.31 (m, 1 H) 7.36 (d, *J* = 8.4 Hz, 1 H) 7.74 (s, 1 H) 7.81 (s, 1 H) 8.04 (d, *J* = 8.1 Hz, 1 H) 8.38 (d, *J* = 8.4 Hz, 1 H) 8.86 (s, 1 H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ ppm 21.7, 33.3, 46.0, 49.9, 55.1, 55.6, 68.3, 100.4, 108.2, 109.5, 113.2, 113.8, 120.7, 120.8, 121.7, 122.3, 127.1, 133.1, 137.1, 147.6, 149.4, 160.0, 160.9, 162.2, 166.3. **HRMS** (ESI^+) (m/z) calculated for $[C_{29}H_{35}N_6O_3]^+$ 515.2765, found 515.2760.

Compound 7: phenyl 2-((2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)-4-(1-methyl-1*H*-indol-3-yl)pyrimidine-5-carboxylate: The reaction was performed according to the *General method for amide and ester couplings* with **23** (0.10 mmol, 70 mg) and phenol (0.15 mmol, 14 mg). The product was obtained as a yellow solid in 56% yield (56 µmol, 31 mg). **^{1}H NMR** (600 MHz, $CDCl_3$) δ ppm 2.42 (s, 3 H) 2.67 (t, *J* =4.8 Hz, 4 H) 3.24 (t, *J* =4.8 Hz, 4 H) 3.85 (s, 3 H) 3.92 (s, 3 H) 6.56 (δ, *J* =8.4 Hz, 1 H) 6.58 (d, *J* =2.6 Hz, 1 H) 7.04 (d, *J* =7.7 Hz, 2 H) 7.21 - 7.26 (m, 2 H) 7.29 - 7.32 (m, 1 H) 7.35 - 7.40

(m, 3 H) 7.83 (s, 1 H) 7.95 (s, 1 H) 8.18 (d, *J* =8.1 Hz, 1 H) 8.34 - 8.48 (m, 1 H) 9.14 (s, 1 H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ ppm 33.4, 46.0, 49.8, 55.1, 55.7, 100.3, 108.3, 109.6, 111.9, 112.9, 121.06, 121.13, 121.4, 121.7, 122.0, 122.5, 125.7, 127.2, 129.4, 134.0, 137.1, 147.8, 149.6, 150.8, 160.3, 162.0, 163.3, 165.0. **HRMS** (ESI^+) (m/z) calculated for $[C_{32}H_{33}N_6O_3]^+$ 549.26087, found 549.26014.

Compound 8: 4-fluorophenyl 2-((2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)-4-(1-methyl-1*H*-indol-3-yl)pyrimidin-5-carboxylate: The reaction was performed according to the *General method for amide and ester couplings* with **23** (0.10 mmol, 70 mg) and 4-fluorophenol (0.15 mmol, 14 mg). The product was obtained as a yellow solid in 86% yield (86 µmol, 49 mg). **^{1}H NMR** (700 MHz, DMSO-d_6) δ ppm 2.26 (s, 3 H) 2.51 (br. s., 4 H) 3.19 (br. s., 4 H) 3.79 (s, 3 H) 3.84 (s, 3 H) 6.52 (d, *J* =8.6 Hz, 1 H) 6.68 (br. s., 1 H) 7.04 (br. s., 1 H) 7.21 (br. s., 1 H) 7.26 (d, *J* =6.7 Hz, 4 H) 7.44 - 7.51 (m, 2 H) 7.92 (br. s., 1 H) 8.09 (s, 1 H) 8.85 (s, 1 H) 8.91 (s, 1 H). **^{13}C NMR** (176 MHz, DMSO-d_6) δ ppm 33.0, 45.7, 48.5, 54.6, 55.5, 100.0, 106.7, 110.2, 111.4, 115.9, 116.0, 119.0, 120.7, 122.0, 123.8, 123.8, 126.2, 126.5, 134.8, 136.7, 146.6, 146.6, 149.8, 153.5, 158.9, 160.3, 161.4, 161.5, 162.2, 165.0. **HRMS** (ESI^+) (m/z) calculated for $[C_{32}H_{32}FN_6O_3]^+$ 567.2514, found 567.2509.

Compound 9: isopropyl-2-((4-(4-aminopiperidin-1-yl)-2-methoxyphenyl)amino)-4-(1-methyl-1*H*-indol-3-yl)pyrimidin-5-carboxylate: The reaction was performed according to the *General method for nucleophilic aromatic substitution of 2-chloropyrimidines* with **19** (0.10 mmol, 33 mg) and *tert*-butyl (1-(4-amino-3-methoxyphenyl)piperidin-4-yl)carbamate (0.12 mmol, 39 mg) in *i*-PrOH (0.1 M) at 85 °C. The crude product was deprotected in a mixture of DCM (1 mL) and TFA (1 mL) at rt for 60 min. The product was obtained as a yellow solid in 55% yield (55 µmol, 28 mg). **^{1}H NMR** (600 MHz, DMSO-d_6) δ ppm 1.16 (d, *J* =6.2 Hz, 6 H) 1.23 (br. s., 2 H) 1.33 - 1.42 (m, 2 H) 1.78 - 1.84 (m, 2 H) 2.70 - 2.77 (m, 3 H) 3.64 (d, *J* =12.8 Hz, 2 H) 3.77 (s, 3 H) 3.85 (s, 3 H) 5.04 (spt, *J* =6.2 Hz, 1 H) 6.50 (dd, *J* =8.8, 2.57 Hz, 1 H) 6.65 (d, *J* =2.6 Hz, 1 H) 7.04 (br. s., 1 H) 7.20 (t, *J* =7.5 Hz, 1 H) 7.44 - 7.50 (m, 2 H) 7.89 (s, 1 H) 7.92 (br. s., 1 H) 8.58 (s, 1 H) 8.59 (s, 1 H). The amino group is not observable. **^{13}C NMR** (151 MHz, DMSO-d_6) δ ppm 21.4, 32.9, 34.7, 48.1, 48.2, 55.5, 67.8, 100.4, 107.1, 110.1, 111.5, 112.4, 119.0, 120.5, 121.9, 125.7, 126.5, 134.1, 136.7, 149.7, 153.1, 160.1, 161.1, 161.1, 166.3. **HRMS** (ESI^+) (m/z) calculated for $[C_{29}H_{35}N_6O_3]^+$ 515.2765, found 515.2757.

Compound 10: isopropyl 2-((4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenyl)amino)-4-(1-methyl-1*H*-indol-3-yl)pyrimidine-5-carboxylate: The reaction was performed according to the *General method for nucleophilic aromatic substitution of 2-chloropyrimidines* with **19** (0.20 mmol, 66 mg) and 1-(4-amino-3-methoxyphenyl)-*N,N*-dimethylpiperidin-4-amine (0.20 mmol, 50 mg) in *i*-PrOH (0.1 M) at 85 °C. The product was obtained as a yellow solid in 64% yield (0.13 mmol, 70 mg). **^{1}H NMR** (700 MHz, DMSO-d_6) δ ppm 1.17 (d, *J* =6.2 Hz, 6 H) 1.51 (qd, *J* =12.0, 3.76 Hz, 2 H) 1.85 (d, *J* =12.0 Hz, 2 H) 2.21 (m, 7 H) 2.69 (td, *J* =12.0, 2.15 Hz, 2 H) 3.73 (d, *J* =12.5 Hz, 2 H) 3.78 (s, 3 H) 3.86 (s, 3 H) 5.05 (spt, *J* =6.2 Hz, 1 H) 6.51 (dd, *J* =8.6, 2.6 Hz, 1 H) 6.66 (d, *J* =2.4 Hz, 1 H) 7.05 (br. s., 1 H) 7.21 (t, *J* =7.5 Hz, 1 H) 7.46 - 7.53 (m, 2 H) 7.90 (s, 1 H) 7.93 (br. s., 1 H) 8.56 - 8.62 (m, 2 H). **^{13}C NMR** (176 MHz, DMSO-d_6) δ ppm 21.4, 27.9, 32.9, 41.5, 48.6, 55.5, 61.4, 67.8, 100.5, 107.2, 110.1, 111.5, 119.0, 119.1, 120.5, 121.9, 126.5, 134.1, 136.7, 149.6, 153.1, 160.1, 161.0, 161.1, 161.1, 166.2, 166.3. **HRMS** (ESI^+) (m/z) calculated for $[C_{31}H_{39}N_6O_3]^+$ 543.3078, found 543.3069.

Compound 11: isopropyl-2-((4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenyl)amino)-4-(1*H*-indol-3-yl)pyrimidin-5-carboxylate: The reaction was performed according to the *General method for nucleophilic aromatic substitution of 2-chloropyrimidines* with **54** (35 µmol, 11 mg) and 1-(4-amino-3-methoxyphenyl)-*N,N*-dimethylpiperidin-4-amine (53 µmol, 13 mg) in *i*-PrOH (0.1 M) at 85 °C. The product was obtained as a yellow solid in 76% yield (27 µmol, 14 mg). **^{1}H NMR** (500 MHz, DMSO-d_6) δ ppm 1.16 (d, *J* =6.1 Hz, 6 H) 1.54 (qd, *J* =11.9, 3.66 Hz, 2 H) 1.89 (d, *J* =12.2 Hz, 2 H) 2.30 (s, 6 H) 2.40 (br. s., 1 H) 2.69 (td, *J* =12.1, 2.0 Hz, 2 H) 3.76 (d, *J* =12.5 Hz, 2 H) 3.79 (s, 3 H) 5.02 (spt, *J* =6.3 Hz, 1 H) 6.51 (dd, *J* =8.5, 2.4 Hz, 1 H) 6.67 (d, *J* =2.4 Hz, 1 H) 7.00 (br. s., 1 H) 7.13 (t, *J* =7.5 Hz, 1 H) 7.43 (d, *J* =7.9 Hz, 1 H) 7.50 (d, *J* =8.9 Hz, 1 H) 7.87 (d, *J* =3.1 Hz, 1 H) 7.90 (br. s., 1 H) 8.59 (s, 1 H) 8.61 (s, 1 H) 11.61 - 11.75 (m, 1 H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ ppm 21.4, 27.5, 41.2, 48.5, 55.5, 61.6, 67.9, 100.5, 107.2, 111.8, 112.5, 119.3, 120.2, 121.7, 121.8, 126.1, 130.3, 136.2, 149.5, 153.2, 160.0, 161.2, 161.5, 166.5. **HRMS** (ESI^+) (m/z) calculated for $[C_{30}H_{37}N_6O_3]^+$ 529.2922, found 529.2912.

Compound 12: isopropyl-4-(1-acetyl-1*H*-indol-3-yl)-2-((4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenyl)amino)pyrimidin-5-carboxylate: The indole **11** (20 µmol, 10.6 mg) was dissolved in THF (0.02 M) and DIPEA (100 µmol, 18 µL) and DMAP (20 µmol, 2.4 mg) were added. At 0 °C acetyl chloride (30 µmol, 2.4 mg) was added and the reaction was stirred at rt for 4 h. The mixture was separated between $NaHCO_3$ solution and DCM and extracted two additional times with DCM. The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (DCM:MeOH) to give the desired product as a yellow solid in 73% yield (15 µmol, 8.3 mg). **^{1}H NMR** (700 MHz, DMSO-d_6) δ ppm 1.02 (br. s., 6 H) 1.45 - 1.57 (m, 2 H) 1.86 (d, *J* =11.6 Hz, 2 H) 2.27 (br. s, 6 H) 2.31 - 2.43 (m, 1 H) 2.64 - 2.73 (m, 5 H) 3.73 (d, *J* =12.3 Hz, 2 H) 3.79 (s, 3 H) 4.89 (br. s., 1 H) 6.49 (d, *J* =8.2 Hz, 1 H) 6.64 (d, *J* =2.2 Hz, 1 H) 7.25 (br. s., 1 H) 7.36 (t, *J* =7.6 Hz, 1 H) 7.45 (d, *J* =8.6 Hz, 1 H) 7.63 (d, *J* =8.0 Hz, 1 H) 8.22 (s, 1 H) 8.36 (d, *J* =8.2 Hz, 1 H) 8.78 (s, 1 H) 8.91 (s, 1 H). **^{13}C NMR** (176 MHz, DMSO-d_6) δ ppm 21.2, 23.8, 27.5, 29.0, 41.2, 48.3, 55.5, 61.5, 68.0, 100.4, 107.1, 115.8, 118.7, 123.7, 125.0, 125.8, 128.7, 134.8, 149.7, 153.2, 160.5, 160.9, 161.4, 165.0, 169.7. **HRMS** (ESI$^+$) (m/z) calculated for $[C_{32}H_{39}N_6O_4]^+$ 571.30273, found 571.30223.

Compound 13: phenyl-2-((4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenyl)amino)-4-(1*H*-indol-3-yl)pyrimidin-5-carboxylate: The reaction was performed according to the *General method for amide and ester couplings* with **56** (0.10 mmol, 105 mg), DIPEA (2.00 mmol, 348 µL) and phenol (1.00 mmol, 94 mg). The product was obtained as a yellow solid in 39% yield (39 µmol, 21.7 mg). **^{1}H NMR** (600 MHz, DMSO-d_6) δ ppm 1.55 (qd, *J* =11.9, 3.7 Hz, 2 H) 1.89 (d, *J* =11.7 Hz, 2 H) 2.29 (br. s., 6 H) 2.33 - 2.44 (m, 1 H) 2.71 (td, *J* =12.2, 2.0 Hz, 2 H) 3.77 (d, *J* =12.5 Hz, 2 H) 3.80 (s, 3 H) 6.53 (dd, *J* =8.8, 2.6 Hz, 1 H) 6.68 (d, *J* =2.6 Hz, 1 H) 7.02 (br. s., 1 H) 7.14 (t, *J* =7.2 Hz, 1 H) 7.20 (d, *J* =7.7 Hz, 2 H) 7.27 (t, *J* =7.3 Hz, 1 H) 7.41 - 7.45 (m, 3 H) 7.48 (d, *J* =8.4 Hz, 1 H) 7.94 (br. s., 1 H) 8.05 (d, *J* =2.9 Hz, 1 H) 8.83 (s, 1 H) 8.90 (s, 1 H) 11.71 (br. s., 1 H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ ppm 27.7, 41.3, 48.6, 55.6, 61.7, 100.6, 107.3, 111.9, 112.5, 119.0, 120.5, 121.9, 122.0, 122.1, 122.1, 125.9, 126.3, 126.4, 129.5, 131.1, 136.3, 149.9, 150.7, 153.6, 161.4, 161.6, 162.7, 165.3. **HRMS** (ESI$^+$) (m/z) calculated for $[C_{33}H_{35}N_6O_3]^+$ 563.27652, found 563.27570.

Compound 14: 1-(3-methoxy-4-nitrophenyl)-4-methylpiperazine: The reaction was performed according to the *General method for nucleophilic aromatic substitution with p-fluoronitrobenzenes* from 4-fluoro-2-methoxy-1-nitrobenzene (50.0 mmol, 8.56 g) and 1-methylpiperazine (50.0 mmol, 5.56 mL). The product was obtained as yellow crystals in quantitative yield (49.9 mmol, 12.55 g). **^{1}H NMR** (500 MHz, DMSO-d_6) δ ppm 2.21 (s, 3 H) 2.36 - 2.47 (m, 4 H) 3.38 - 3.48 (m, 4 H) 3.90 (s, 3 H) 6.51 (d, *J* =2.2 Hz, 1 H) 6.57 (dd, *J* =9.5, 2.2 Hz, 1 H) 7.87 (d, *J* =9.5 Hz, 1 H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ ppm 30.8, 35.8, 45.6, 46.3, 54.2, 56.3, 96.9, 105.3, 128.0, 128.2, 155.5, 156.0. **LC-MS** (ESI$^+$) (m/z) calculated for $[C_{12}H_{18}N_3O_3]^+$ 252.13, found 252.14.

Compound 15: 2-methoxy-4-(4-methylpiperazin-1-yl)aniline: The reaction was performed according to the *General method for aromatic nitro reduction* of **14** (20.0 mmol, 5.03 g). The product was obtained as a deep purple gum in quantitative yield (20.0 mmol, 4.42 g). **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm 2.22 (s, 3 H) 2.45 (t, J = 4.8, 4 H) 2.94 (t, J = 4.8, 4 H) 3.74 (s, 3 H) 4.18 (br. s., 2 H) 6.28 (d, *J* = 8.3, 2.5 Hz, 1 H) 6.48 (d, J = 2.0 Hz, 1 H) 6.52 (d, *J* = 8.3 Hz, 1 H). **^{13}C NMR** (176 MHz, DMSO-d_6) δ ppm 45.1, 49.7, 54.5, 55.2, 101.9, 108.6, 114.2, 131.1, 143.0, 147.0. **LC-MS** (ESI$^+$) (m/z) calculated for $[C_{12}H_{20}N_3O]^+$ 222.16, found 222.17.

Compound 17: methyl 2-chloro-4-(1-methyl-1*H*-indol-3-yl)pyrimidine-5-carboxylate: The reaction was performed according to the *General method for Friedel-Crafts arylation* from methyl 2,4-dichloropyrimidine-5-carboxylate (5.27 mmol, 1.10 g). The product was obtained as a yellow solid in 97% yield (5.10 mmol, 1.54 g). **^{1}H-NMR** (600 MHz, $CDCl_3$) δ ppm 3.87 (s, 3 H) 3.88 (s, 3 H) 7.29 - 7.36 (m, 2 H) 7.37 - 7.40 (m, 1 H) 7.98 (s, 1 H) 8.18 (dt, *J* = 8.3, 0.8 Hz, 1 H) 8.83 (s, 1 H). **^{13}C-NMR** (151 MHz, $CDCl_3$) δ ppm 33.6, 52.8, 109.9, 111.5, 120.0, 121.8, 122.2, 123.2, 126.7, 135.0, 137.4, 160.6, 162.2, 162.6, 166.7. **LC-MS** (ESI+) (m/z) calculated for $[C_{15}H_{13}ClN_3O_2]^+$ 302.07, found 302.17.

Compound 18: ethyl 2-chloro-4-(1-methyl-1*H*-indol-3-yl)pyrimidine-5-carboxylate: The reaction was performed according to the *General method for Friedel-Crafts arylation* from ethyl 2,4-dichloropyrimidine-5-carboxylate (1.0 mmol, 221 mg). The product was obtained as a yellow solid in 69% yield (0.69 mmol, 218 mg). **^{1}H-NMR** (600 MHz, $CDCl_3$) δ ppm 1.25 (t, *J* = 7.2 Hz, 3 H) 3.89 (s, 3 H) 4.34 (q, *J* = 7.2 Hz, 2 H) 7.28 - 7.36 (m, 2 H) 7.37 - 7.40 (m, 1 H) 7.97 (s, 1 H) 8.18 (d, *J* = 8.1 Hz, 1 H) 8.83 (s, 1 H). **^{13}C-NMR** (151 MHz, $CDCl_3$) δ ppm 13.9, 33.6, 62.1, 109.9, 111.6, 120.4, 121.8, 122.1, 123.2, 126.7, 134.8, 137.4, 160.6, 162.1, 162.6, 166.3. **LC-MS** (ESI+) (m/z) calculated for $[C_{16}H_{15}ClN_3O_2]^+$ 316.08, found 316.14.

Compound 19: isopropyl 2-chloro-4-(1-methyl-1*H*-indol-3-yl)pyrimidine-5-carboxylate: The reaction was performed according to the *General method for Friedel-Crafts arylation* from isopropyl 2,4-dichloropyrimidine-5-carboxylate (5.0 mmol, 1.18 g). The product was obtained as a yellow solid in 64% yield (3.22 mmol, 1.06 g). **^{1}H-NMR** (700 MHz, $CDCl_3$) δ ppm 1.26 (d, *J* = 6.2 Hz, 6 H) 3.88 (s, 3 H) 5.21 (spt, *J* = 6.3 Hz, 1 H) 7.28 - 7.36 (m, 2 H) 7.37 - 7.40 (m, 1 H) 7.96 (s, 1 H) 8.17 - 8.21 (m, 1 H) 8.79 (s, 1 H). **^{13}C-NMR** (176 MHz, $CDCl_3$) δ ppm 21.6, 33.6, 70.0, 109.9, 111.6, 121.0, 121.9, 122.1, 123.2, 126.8, 134.7, 137.4, 160.4, 162.0, 162.5, 165.9. **LC-MS** (ESI+) (m/z) calculated for $[C_{17}H_{17}ClN_3O_2]^+$ 330.10, found 330.10.

Compound 20: 3-(2-chloro-5-nitropyrimidin-4-yl)-1-methyl-1*H*-indole: The reaction was performed according to the *General method for Friedel-Crafts arylation* from 2,4-dichloro-5-nitropyrimidine (15.00 mmol, 2.91 g). The product was obtained as a red crystalline solid in 56% yield (8.47 mmol, 2.45 g). **^{1}H NMR** (600 MHz, $CDCl_3$) δ ppm 3.90 (s, 3 H) 7.34 - 7.45 (m, 3 H) 7.86 (s, 1 H) 8.23 (dd, *J* =6.6, 1.8 Hz, 1 H) 8.83 (s, 1 H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ ppm 33.9, 108.4, 110.3, 122.4, 123.2, 124.0, 126.3, 135.4, 137.5, 140.2, 154.7, 156.1, 161.7. **LC-MS** (ESI+) (m/z) calculated for $[C_{13}H_{10}ClN_4O_2]^+$ 289.05, found 289.16.

Compound 21: 3-(5-bromo-2-chloropyrimidin-4-yl)-1-methyl-1*H*-indole: The reaction was performed according to the *General method for Friedel-Crafts arylation* from 5-bromo-2,4-dichloropyrimidine (5.00 mmol, 1.14 g). The product was obtained as an off-white crystalline solid in 42% yield (2.09 mmol, 0.67 g). **^{1}H-NMR** (600 MHz, $CDCl_3$) δ ppm 3.91 (s, 3 H) 7.34 - 7.42 (m, 3 H) 8.52 (s, 1 H) 8.60 (s, 1 H) 8.63 - 8.67 (m, 1 H). **^{13}C-NMR** (151 MHz, $CDCl_3$) δ ppm 33.8, 109.6, 110.9, 113.9, 122.5, 123.4, 123.6, 127.1, 134.9, 137.0, 159.0, 161.2, 161.5. **LC-MS** (ESI+) (m/z) calculated for $[C_{13}H_{10}BrClN_3]^+$ 321.97, found 322.16.

Compound 22: 3-(2-Chloro-5-(ethoxymethyl)pyrimidin-4-yl)-1-methyl-1*H*-indole: The reaction was performed according to the *General method for Friedel-Crafts arylation* from 2,4-dichloro-5-(ethoxymethyl)pyrimidin (1.0 mmol, 207 mg). The product was obtained as a brown solid in 56% yield (0.57 mmol, 171 g). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 1.32 (t, *J* =7.0 Hz, 3 H) 3.64 (q, *J* =7.0 Hz, 2 H) 3.91 (s, 3 H) 4.55 (s, 2 H) 7.31 - 7.42 (m, 3 H) 7.93 (s, 1 H) 8.50 (s, 1 H) 8.53 - 8.58 (m, 1 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 15.2, 33.6, 65.6, 68.3, 109.5, 111.3, 122.1, 122.7, 123.3, 124.0, 126.9, 134.2, 137.4, 160.1, 160.3, 164.3. **LC-MS** (ESI+) (m/z) calculated for $[C_{16}H_{17}ClN_3O]^+$ 302.1, found 301.4.

Compound 23: 2-((2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)-4-(1-methyl-1*H*-indol-3-yl)pyrimidine-5-carboxylic acid ditrifluoroacetate: methyl 2-((2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)-4-(1-methyl-1H-indol-3-yl)pyrimidine-5-carboxylate **4** (2.80 mmol, 1.36 g) was dissolved in THF/MeOH (4:1, 0.1 M) and KOH solution (1 M, 5.6 mL) was added. The reaction was stirred at 40 °C for 16 h. The reaction mixture was concentrated *in vacuo*, resolved in water (100 mL) and acidified with TFA to pH 3. To separate excess KOH, the solution was purified over a C_{18}-flash column (TFA in water 0.5%, TFA in MeCN 0.5%) to yield the product as an orange crystalline solid in a quantitative yield (2.80 mmol, 1.96 g, double TFA salt). **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm 2.88 (s, 3 H) 2.99 (t, *J* =12.2 Hz, 2 H) 3.11 - 3.27 (m, 2 H) 3.55 (d, *J* =11.7 Hz, 2 H) 3.80 (s, 3 H) 3.85 (s, 3 H) 3.86 – 3.92 (m, 2 H) 3.98 (br. s., water/TFA) 6.58 (dd, *J* =8.8, 2.45 Hz, 1 H) 6.75 (d, *J* =2.5 Hz, 1 H) 7.05 (t, *J* =7.6 Hz, 1 H) 7.17 - 7.26 (m, 1 H) 7.48 (d, *J* =8.3 Hz, 1 H) 7.58 (d, *J* =8.8 Hz, 1 H) 7.99 (br. s., 1 H) 8.00 (s, 1 H) 8.64 (s, 1 H) 8.70 (s, 1 H) 10.00 (br. s., 1 H). **LC-MS** (ESI+) (m/z) calculated for $[C_{26}H_{29}N_6O_3]^+$ 473.23, found 473.46.

Compound 24: *N*-(2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)-4-(1-methyl-1*H*-indol-3-yl)-5-nitropyrimidin-2-amine: The reaction was performed according to the *General method for nucleophilic aromatic substitution of 2-chloropyrimidines* with **20**; 4.25 mmol, 1.23 g) and **15** (4.25 mmol, 0.94 g) in *n*-BuOH (0.1 M) at 85 °C. The product was obtained as a red crystalline solid in 78% yield (3.31 mmol, 1.57 g). **^{1}H NMR** (500 MHz, DMSO-d_6) δ ppm 2.58 (br. s., 3 H) 2.96 (br. s., 4 H) 3.33 (br. s., 4 H) 3.77 (s, 3 H) 3.86 (br. s., 3 H) 6.57 (dd, *J* =8.7, 2.3 Hz, 1 H) 6.72 (br. s., 1 H) 6.97 (br. s., 1 H) 7.23 (br. s., 1 H) 7.36 (d, *J* =8.5 Hz, 1 H) 7.50 (br. s., 1 H) 7.62 (br. s., 1 H) 7.97 (br. s., 1 H) 8.89 (br. s., 1 H) 9.38 (s, 1 H). Due to the strong mesomeric effect of the nitro group many peaks are distorted. **LC-MS** (ESI+) (m/z) calculated for $[C_{25}H_{28}N_7O_3]^+$ 474.22, found 474.33.

Compound 25: 5-bromo-*N*-(2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)-4-(1-methyl-1*H*-indol-3-yl)pyrimidin-2-amine: The reaction was performed according to the *General method for nucleophilic aromatic substitution of 2-chloropyrimidines* with **21** (2.50 mmol, 0.81 g) and **15** (2.75 mmol, 0.61 g) in *n*-BuOH (0.1 M) at 110 °C for 72 h. The product was obtained as an off-white solid in 11% yield (0.26 mmol, 134 mg). **^{1}H NMR** (700 MHz, DMSO-d_6) δ ppm 2.38 (br. s., 3 H) 2.68 (br. s., 4 H) 3.22 (br. s., 4 H) 3.76 (s, 3 H) 3.89 (s, 3 H) 6.50 (dd, *J* =8.6, 2.2 Hz, 1 H) 6.68 (d, *J* =2.2 Hz, 1 H) 7.02 (br. t, *J* =7.6, 7.6 Hz, 1 H) 7.23 (t, *J* =7.6 Hz, 1 H) 7.45 (d, *J* =8.6 Hz, 1 H) 7.49 (d, *J* =8.2 Hz, 1 H) 8.19 (br. s., 1 H) 8.29 (s, 1 H) 8.41 (s, 1 H) 8.56 (s, 1 H). **^{13}C NMR** (176 MHz, DMSO-d_6) δ ppm 33.6, 45.4, 48.6, 54.7, 56.0, 100.8, 103.4, 107.4, 110.5, 111.3, 120.7, 121.2, 122.8, 123.8, 126.5, 127.2, 134.7, 137.0, 149.6, 153.9, 159.1, 160.3, 160.5. **LC-MS** (ESI+) (m/z) calculated for $[C_{25}H_{28}BrN_6O]^+$ 507.15, found 507.32.

Compound 26: 5-(ethoxymethyl)-*N*-(2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)-4-(1-methyl-1*H*-indol-3-yl)pyrimidin-2-amine: The reaction was performed according to the *General method for nucleophilic aromatic substitution of 2-chloropyrimidines* with **22** (0.20 mmol, 60 mg) and **15** (0.24 mmol, 53 mg) in *n*-BuOH (0.2 M) at 100 °C for 16 h. **^{1}H NMR** (700 MHz, DMSO-d_6) δ ppm 1.23 (t, J = 7.0, 3 H) 2.26 (br. s., 3 H) 3.15 (br. s., 4 H) 3.59 (q, *J* =7.1 Hz, 2 H) 3.80 (s, 3 H) 3.88 (s, 3 H) 4.42 (s, 2 H) 6.47 (dd, *J* =8.6, 2.6 Hz, 1 H) 6.67 (d, *J* =2.6 Hz, 1 H) 7.06 (t, *J* =7.4 Hz, 1 H) 7.23 (td, *J* =7.6, 1.18 Hz, 1 H) 7.50 (d, *J* =8.2 Hz, 1 H) 7.71 (d, *J* =8.6 Hz, 1 H) 7.96 (s, 2 H) 8.28 (d, *J* =6.9 Hz, 1 H) 8.30 (br. s., 1 H), piperazine (4 H) overlays with DMSO. **^{13}C NMR** (176 MHz, DMSO-d_6) δ ppm 15.1, 33.1, 45.6, 48.7, 54.6, 55.5, 64.3, 68.1, 100.2, 106.8, 109.9, 111.5, 116.2, 120.4, 120.8, 122.2, 122.8, 124.1, 126.7, 133.4, 136.9, 148.4, 151.9, 159.7, 160.5, 161.7. **LC-MS** (ESI+) (m/z) calculated for $[C_{28}H_{35}N_6O_2]^+$ 487.28, found 487.34.

Compound 27: *N*-isopropyl-2-((2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)-4-(1-methyl-1*H*-indol-3-yl)pyrimidine-5-carboxamide: 2-((2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)-4-(1-methyl-1H-indol-3-yl)pyrimidine-5-carboxylic acid ditrifluoroacetate **23** (100.0 µmol, 70 mg) was dissolved in DCM (0.1 M) and cooled down to 0 °C. TEA (1.00 mmol, 139 µL) and TBTU (0.12 mmol) were added and the reaction was stirred for 15 min. Afterwards, isopropyl amine (0.15 mmol, 13 µL) was added and the reaction was stirred at rt for 16 h. The reaction mixture was separated between $NaHCO_3$ solution and DCM and the aqueous phase was extracted twice with DCM. The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (DCM:MeOH) which gave the desired product as a pale yellow solid in 41% yield (40.7 µmol, 21 mg). **^{1}H NMR** (500 MHz, DMSO-d_6) δ ppm 1.11 (d, *J* =6.7 Hz, 6 H) 2.24 (s, 3 H) 2.48 (br. s., 4 H, mixed with DMSO signal) 3.16 (t, *J* =4.8 Hz, 4 H) 3.78 (s, 3 H) 3.82 (s, 3 H) 3.99 - 4.10 (m, 1 H) 6.51 (dd, *J* =8.7, 2.6 Hz, 1 H) 6.67 (d, *J* =2.6 Hz, 1 H) 7.03 (t, *J* =7.5 Hz, 1 H) 7.18 - 7.24 (m, 1 H) 7.47 (d, *J* =8.2 Hz, 1 H) 7.56 (d, *J* =8.9 Hz, 1 H) 7.82 (s, 1 H) 8.15 (s, 1 H) 8.20 (br. s., 1 H) 8.21 (s, 1 H) 8.30 (d, *J* =7.9 Hz, 1 H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ ppm 22.1, 33.0, 40.9, 45.8, 48.7, 54.7, 55.5, 100.2, 106.8, 110.0, 111.4, 118.9, 120.2, 120.5, 122.1, 123.0, 125.3, 126.5, 133.0, 136.8, 149.1, 156.5, 158.5, 160.6, 167.1. **HRMS** (ESI+) (m/z) calculated for $[C_{29}H_{36}N_7O_2]^+$ 514.2925, found 514.2916.

Compound 28: *N*-Cyclopropyl-2-((2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)-4-(1-methyl-1*H*-indol-3-yl)pyrimidin-5-carboxamide: The reaction was performed according to the *General method for amide and ester couplings* with **23** (100 µmol, 70 mg) and cyclopropyl amine (150 µmol, 9 mg) and TEA (1.0 mmol, 139 µL). The desired product was obtained as an off-white solid

in 49% yield (49 µmol, 25 mg). **^{1}H NMR** (600 MHz, DMSO-d_6) δ ppm 0.43 - 0.51 (m, 2 H) 0.64 - 0.72 (m, 2 H) 2.28 (s, 3 H) 2.53 (br. s., 4 H) 2.84 (tq, *J* =7.4, 3.97 Hz, 1 H) 3.18 (t, *J* =4.7 Hz, 4 H) 3.78 (s, 3 H) 3.85 (s, 3 H) 6.51 (dd, *J* =8.8, 2.6 Hz, 1 H) 6.68 (d, *J* =2.6 Hz, 1 H) 7.04 (t, *J* =7.3 Hz, 1 H) 7.18 - 7.26 (m, 1 H) 7.48 (d, *J* =8.1 Hz, 1 H) 7.55 (d, *J* =8.8 Hz, 1 H) 7.80 (s, 1 H) 8.16 (s, 1 H) 8.20 (br. s., 1 H) 8.22 (s, 1 H) 8.47 (d, *J* =4.4 Hz, 1 H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ ppm 5.5, 22.9, 33.0, 45.6, 48.6, 54.6, 55.5, 100.2, 106.8, 110.0, 111.4, 118.5, 120.2, 120.5, 122.1, 122.9, 125.4, 126.5, 133.0, 136.8, 149.1, 152.9, 156.4, 158.6, 160.6, 169.3. **LC-MS** (ESI+) (m/z) calculated for $[C_{29}H_{34}N_7O_2]^+$ 512.27685, found 512.27609.

Compound 29: (2-((2-Methoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)-4-(1-methyl-1*H*-indol-3-yl)pyrimidin-5-yl)(morpholino)methanone: The reaction was performed according to the *General method for amide and ester couplings* with **23** (100 µmol, 70 mg) and morpholine (150 µmol, 13 mg) and TEA (1.0 mmol, 139 µL). The desired product was obtained as an off-white solid in 62% yield (62 µmol, 33 mg). **^{1}H NMR** (500 MHz, DMSO-d_6) δ ppm 2.26 (s, 3 H) 2.46 - 2.51 (m, 4 H) 2.88 - 3.02 (m, 2 H) 3.17 (t, *J* =4.8 Hz, 4 H) 3.43 - 3.53 (m, 2 H) 3.53 - 3.70 (m, 4 H) 3.79 (s, 3 H) 3.88 (s, 3 H) 6.52 (dd, *J* =8.7, 2.6 Hz, 1 H) 6.68 (d, *J* =2.4 Hz, 1 H) 7.06 (t, *J* =7.2 Hz, 1 H) 7.21 - 7.28 (m, 1 H) 7.50 (d, *J* =8.2 Hz, 1 H) 7.57 (d, *J* =8.9 Hz, 1 H) 7.64 (s, 1 H) 8.18 (s, 1 H) 8.24 (br. s., 1 H) 8.31 (s, 1 H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ ppm 33.1, 41.7, 45.8, 46.8, 48.7, 51.6, 54.7, 55.5, 65.6, 65.7, 66.2, 100.1, 106.7, 110.2, 111.2, 116.1, 120.0, 120.7, 122.4, 122.8, 125.5, 126.2, 132.3, 136.9, 149.2, 156.3, 157.9, 160.7, 167.7. **LC-MS** (ESI+) (m/z) calculated for $[C_{30}H_{36}N_7O_3]^+$ 542.29, found 542.33.

Compound 30: 1,3-difluoropropan-2-yl 2-((2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)-4-(1-methyl-1*H*-indol-3-yl)pyrimidin-5-carboxylate: The reaction was performed according to the *General method for amide and ester couplings* with **23** (100 µmol, 70 mg) and 1,3-difluoropropanol (150 µmol, 14 mg) and TEA (1.0 mmol, 139 µL). After 1 h reaction time further 1,3-difluoropropanol (150 µmol, 14 mg) which was prestirred with sodium hydride (150 µmol) in THF (1 mL) was added. The desired product was obtained as a yellow solid in 32% yield (32 µmol, 18 mg). **^{1}H NMR** (500 MHz, DMSO-d_6) δ ppm 2.25 (s, 3 H) 3.18 (t, *J* =4.8 Hz, 4 H) 3.77 (s, 3 H) 3.82 (s, 3 H) 4.57 - 4.81 (m, 4 H) 5.34 - 5.50 (m, 1 H) 6.51 (dd, *J* =8.7, 2.6 Hz, 1 H) 6.67 (d, *J* =2.4 Hz, 1 H) 7.02 (br. s., 1 H) 7.20 (t, *J* =7.5 Hz, 1 H) 7.40 - 7.45 (m, 1 H) 7.47 (d, *J* =8.5 Hz, 1 H) 7.90 (br. s., 1 H) 7.93 (s, 1 H) 8.66 (s, 1 H) 8.79 (s, 1 H). Piperazine peak (4H) overlayed by DMSO peak. **^{13}C NMR** (126 MHz, DMSO-d_6) δ ppm 32.9, 45.7, 48.5, 54.6, 55.5, 70. 8 (t, *J* =19.50 Hz, 1 C) 81.1 (dd, *J* =168.0, 8.00 Hz, 2 C) 100.0, 106.7, 110.1, 111.0, 119.1, 120.6, 122.0, 122.2, 126.5, 134.8, 136.7, 149.9, 160.7, 161.5, 161.6, 165.9. **LC-MS** (ESI+) (m/z) calculated for $[C_{29}H_{33}F_2N_6O_3]^+$ 551.26, found 551.32.

Compound 31: 1,1,1,3,3,3-Hexafluoropropan-2-yl 2-((2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)-4-(1-methyl-1*H*-indol-3-yl)pyrimidin-5-carboxylate: The reaction was performed according to the *General method for amide and ester couplings* with **23** (100 µmol, 70 mg), hexafluoropropanol (500 µmol, 53 µL), TEA (1.0 mmol, 139 µL) and additional DMAP (10 µmol, 1.2 mg). The desired product was obtained as a yellow solid in 75% yield (75 µmol, 47 mg). **^{1}H NMR** (500 MHz, DMSO-d_6) δ ppm 2.24 (s, 3 H) 2.48 (t, *J* =4.8 Hz, 3 H) 3.19 (t, *J* =4.8 Hz, 4 H) 3.77 (s, 3 H) 3.83 (br. s., 3 H) 6.51 (dd, *J* =8.9, 2.4 Hz, 1 H) 6.68 (br. s., 1 H) 6.88 - 7.08 (m, 2 H) 7.22 (br. s., 1 H) 7.38 (d, *J* =8.9 Hz, 1 H) 7.49 (br. s., 1 H) 7.73 (br. s., 1 H) 7.92 (s, 1 H) 8.77 (br. s., 1 H) 9.19 (s, 1 H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ ppm 33.1, 45.8, 48.5, 54.7, 55.5, 65.6, 65.9, 66.1, 99.9, 106.7, 110.2, 111.0, 118.4, 120.8, 122.2, 126.5, 136.7, 161.5, 161.9, 162.4. **LC-MS** (ESI+) (m/z) calculated for $[C_{29}H_{29}F_6N_6O_3]^+$ 623.22, found 623.29.

Compound 32: Pyridin-3-yl 2-((2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)-4-(1-methyl-1*H*-indol-3-yl)pyrimidin-5-carboxylate: The reaction was performed according to the *General method for amide and ester couplings* with **23** (100 µmol, 70 mg) and 3-hydroxypyridine (150 µmol, 14 mg) and TEA (1.0 mmol, 139 µL). The desired product was obtained as a yellow solid in 54% yield (54 µmol, 30 mg). **^{1}H NMR** (700 MHz, $CDCl_3$) δ ppm 2.40 (s, 3 H) 2.64 (t, *J* =4.8 Hz, 4 H) 3.23 (t, *J* =4.8 Hz, 4 H) 3.87 (s, 3 H) 3.92 (s, 3 H) 6.57 (d, *J* =7.3 Hz, 1 H) 6.58 (d, *J* =2.6 Hz, 1 H) 7.23 (t, *J* =7.4 Hz, 1 H) 7.28 - 7.34 (m, 2 H) 7.39 (d, *J* =8.2 Hz, 2 H) 7.86 (s, 1 H) 7.90 (s, 1 H) 8.08 (d, *J* =8.0 Hz, 1 H) 8.28 (br. d, *J*

=2.2 Hz, 1 H) 8.39 (br. s., 1 H) 8.46 (dd, *J* =4.7, 1.29 Hz, 1 H) 9.14 (br. s., 1 H). **^{13}C NMR** (176 MHz, $CDCl_3$) δ ppm 33.4, 46.1, 49.8, 55.1, 55.7, 100.3, 108.2, 109.8, 121.1, 121.3, 122.6, 123.8, 127.1, 129.4, 133.7, 137.1, 143.6, 146.8, 147.4, 148.1, 149.7, 160.3, 162.2, 163.5, 164.5. **LC-MS** (ESI+) (m/z) calculated for $[C_{31}H_{32}N_7O_3]^+$ 550.26, found 550.21.

Compound 33: Benzyl-2-((2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)-4-(1-methyl-1*H*-indol-3-yl)pyrimidin-5-carboxylate: The reaction was performed according to the *General method for amide and ester couplings* with **23** (100 µmol, 70 mg) and benzyl alcohol (150 µmol, 16 mg) and TEA (1.0 mmol, 139 µL). After 1 h reaction time further benzyl alcohol (150 µmol, 16 mg) which was prestirred with sodium hydride (150 µmol) in THF (1 mL) was added. The desired product was obtained as a yellow solid in 42% yield (42 µmol, 23 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 2.41 (s, 3 H) 2.66 (t, *J* =4.7 Hz, 4 H) 3.23 (t, *J* =4.7 Hz, 4 H) 3.76 (s, 3 H) 3.89 (s, 3 H) 5.20 (s, 2 H) 6.51 - 6.60 (m, 2 H) 7.15 - 7.24 (m, 3 H) 7.27 - 7.39 (m, 5 H) 7.67 (s, 1 H) 7.75 (s, 1 H) 8.05 (d, *J* =7.9 Hz, 1 H) 8.37 (d, *J* =8.2 Hz, 1 H) 8.92 (s, 1 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 33.2, 45.9, 49.8, 55.0, 55.6, 66.6, 100.4, 108.2, 109.6, 113.0, 120.8, 121.0, 121.6, 122.3, 126.9, 126.9, 128.1, 128.3, 128.4, 133.3, 135.7, 137.1, 147.6, 149.4, 160.1, 161.2, 162.5, 166.6. **LC-MS** (ESI+) (m/z) calculated for $[C_{33}H_{35}N_6O_3]^+$ 563.28, found 563.25.

Compound 34: Pyridin-3-ylmethyl 2-((2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)-4-(1-methyl-1*H*-indol-3-yl)pyrimidin-5-carboxylate: The reaction was performed according to the *General method for amide and ester couplings* with **23** (100 µmol, 70 mg) and *m*-pyridinemethanol (150 µmol, 16 mg) and TEA (1.0 mmol, 139 µL). After 1 h reaction time further *m*-pyridinemethanol (150 µmol, 16 mg) which was prestirred with sodium hydride (150 µmol) in THF (1 mL) was added. The desired product was obtained as a yellow solid in 55% yield (55 µmol, 31 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 2.40 (s, 3 H) 2.66 (t, *J* =4.8 Hz, 4 H) 3.22 (t, *J* =4.8 Hz, 4 H) 3.80 (s, 3 H) 3.89 (s, 3 H) 5.15 (s, 2 H) 6.52 - 6.58 (m, 2 H) 7.14 - 7.22 (m, 2 H) 7.24 - 7.31 (m, 1 H) 7.32 - 7.36 (m, 1 H) 7.36 - 7.41 (m, 1 H) 7.67 (s, 1 H) 7.78 (s, 1 H) 7.92 (d, *J* =7.9 Hz, 1 H) 8.31 - 8.40 (m, 2 H) 8.53 (dd, *J* =4.9, 1.5 Hz, 1 H) 8.91 (s, 1 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 33.3, 45.9, 49.8, 55.0, 55.6, 64.0, 100.3, 108.2, 109.7, 113.4, 120.8, 121.0, 121.2, 121.5, 122.4, 123.3, 126.8, 131.2, 132.8, 134.7, 136.0, 137.1, 147.6, 148.9, 149.4, 149.6, 160.1, 161.3, 162.5, 166.5. **LC-MS** (ESI+) (m/z) calculated for $[C_{32}H_{34}N_7O_3]^+$ 564.27, found 564.23.

Compound 35: Naphthalen-2-yl 2-((2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)-4-(1-methyl-1*H*-indol-3-yl)pyrimidin-5-carboxylate: The reaction was performed according to the *General method for amide and ester couplings* with **23** (100 µmol, 70 mg), 2-naphthol (1.0 mmol, 144 mg), TEA (1.0 mmol, 139 µL) and additional DMAP (10 µmol, 1.2 mg). The desired product was obtained as a yellow solid in 74% yield (74 µmol, 44 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 2.43 (s, 3 H) 2.69 (t, *J* =4.8 Hz, 4 H) 3.25 (t, *J* =4.8 Hz, 4 H) 3.84 (s, 3 H) 3.92 (s, 3 H) 6.57 (d, *J* =9.5 Hz, 1 H) 6.58 - 6.61 (m, 1 H) 7.19 (dd, *J* =8.9, 2.14 Hz, 1 H) 7.22 - 7.27 (m, 1 H) 7.30 - 7.36 (m, 1 H) 7.36 - 7.41 (m, 1 H) 7.42 - 7.52 (m, 3 H) 7.74 - 7.79 (m, 1 H) 7.84 (d, *J* =8.6 Hz, 2 H) 7.88 (s, 1 H) 7.97 (s, 1 H) 8.20 (d, *J* =7.9 Hz, 1 H) 8.43 (d, *J* =7.6 Hz, 1 H) 9.20 (s, 1 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 33.3, 45.8, 49.7, 55.0, 55.7, 100.3, 108.3, 109.7, 118.7, 121.0, 121.2, 121.2, 121.5, 122.5, 125.6, 126.5, 127.2, 127.6, 127.7, 129.2, 131.3, 133.7, 134.0, 137.1, 147.7, 148.3, 149.5, 160.2, 162.0, 163.3, 165.2. **LC-MS** (ESI+) (m/z) calculated for $[C_{36}H_{35}N_6O_3]^+$ 599.28, found 599.24.

Compound 36: Naphthalen-1-yl 2-((2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)-4-(1-methyl-1*H*-indol-3-yl)pyrimidin-5-carboxylate: The reaction was performed according to the *General method for amide and ester couplings* with **23** (100 µmol, 70 mg), 1-naphthol (1.0 mmol, 144 mg), TEA (1.0 mmol, 139 µL) and additional DMAP (10 µmol, 1.2 mg). The desired product was obtained as a yellow solid in 69% yield (69 µmol, 41 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 2.44 (s, 3 H) 2.70 (t, *J* =4.8 Hz, 4 H) 3.27 (t, *J* =4.8 Hz, 4 H) 3.78 (s, 3 H) 3.93 (s, 3 H) 6.57 (d, *J* =7.9 Hz, 1 H) 6.60 (d, *J* =2.4 Hz, 1 H) 7.22 - 7.27 (m, 1 H) 7.27 - 7.33 (m, 2 H) 7.33 - 7.37 (m, 1 H) 7.44 - 7.53 (m, 3 H) 7.76 (d, *J* =8.5 Hz, 1 H) 7.82 - 7.86 (m, 1 H) 7.86 - 7.91 (m, 2 H) 8.00 (s, 1 H) 8.26 - 8.33 (m, 1 H) 8.44 (d, *J* =7.0 Hz, 1 H) 9.37 (s, 1 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 33.3, 45.8, 49.7, 54.9, 55.7, 100.4, 108.3, 109.6, 118.2, 121.1, 121.2, 121.3, 121.4, 122.5, 125.4, 125.9, 126.4, 127.0, 127.3, 128.0, 134.6, 137.1,

146.7, 147.7, 149.6, 160.3, 162.1, 163.7, 164.8. **LC-MS** (ESI+) (m/z) calculated for $[C_{36}H_{35}N_6O_3]^+$ 599.28, found 599.23.

Compound 37: 3-Fluoro-4-nitrophenyl-2-((2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)-4-(1-methyl-1*H*-indol-3-yl)pyrimidin-5-carboxylate: The reaction was performed according to the *General method for amide and ester couplings* with **23** (100 µmol, 70 mg) and 3-fluoro-4-nitrophenol (0.50 mmol, 79 mg) and TEA (1.0 mmol, 139 µL). The desired product was obtained as a yellow solid in 69% yield (69 µmol, 42 mg). **^{1}H NMR** (600 MHz, DMSO-d_6) δ ppm 2.25 (s, 3 H) 2.49 (t, *J* =4.7 Hz, 4 H) 3.19 (t, *J* =4.7 Hz, 4 H) 3.78 (s, 3 H) 3.84 (s, 3 H) 6.52 (dd, *J* =8.8, 2.6 Hz, 1 H) 6.62 - 6.73 (m, 1 H) 7.02 (br. s., 1 H) 7.21 (br. s., 1 H) 7.39 (d, *J* =8.4 Hz, 1 H) 7.43 (d, *J* =8.8 Hz, 1 H) 7.47 (d, *J* =7.0 Hz, 1 H) 7.67 (d, *J* =10.6 Hz, 1 H) 7.82 (br. s., 1 H) 8.16 (s, 1 H) 8.27 (t, *J* =8.8 Hz, 1 H) 8.96 (s, 1 H) 9.00 (s, 1 H). **LC-MS** (ESI+) (m/z) calculated for $[C_{32}H_{31}FN_7O_5]^+$ 612.24, found 612.08.

Compound 38: 5-Fluoro-2-nitrophenyl-2-((2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)-4-(1-methyl-1*H*-indol-3-yl)pyrimidin-5-carboxylate: The reaction was performed according to the *General method for amide and ester couplings* with **23** (100 µmol, 70 mg) and 5-fluoro-2-nitrophenol (0.50 mmol, 79 mg) and TEA (1.0 mmol, 139 µL). The desired product was obtained as a yellow solid in 65% yield (65 µmol, 40 mg). **^{1}H NMR** (600 MHz, DMSO-d_6) δ ppm 2.25 (s, 3 H) 2.49 (t, *J* =4.7 Hz, 4 H) 3.19 (t, *J* =4.7 Hz, 4 H) 3.78 (s, 3 H) 3.82 (br. s., 3 H) 6.53 (dd, *J* =8.4, 2.57 Hz, 1 H) 6.69 (br. s., 1 H) 6.97 (br. s., 1 H) 7.21 (br. s., 1 H) 7.39 (d, *J* =8.4 Hz, 1 H) 7.47 (ddd, *J* =9.2, 7.7, 2.6 Hz, 2 H) 7.68 (br. s., 1 H) 7.80 (br. s., 1 H) 8.08 (s, 1 H) 8.31 (dd, *J* =9.2, 5.9 Hz, 1 H) 8.99 (br. s., 1 H) 9.10 (s, 1 H). **LC-MS** (ESI+) (m/z) calculated for $[C_{32}H_{31}FN_7O_5]^+$ 612.24, found 612.14.

Compound 39: N^2-(2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)-4-(1-methyl-1*H*-indol-3-yl)pyrimidine-2,5-diamine: The reaction was performed according to the *General method for aromatic nitro reduction* of **24** (3.00 mmol, 1.42 g). The product was obtained as a pale green crystalline solid in 95% yield (2.86 mmol, 4.17 g). **^{1}H NMR** (500 MHz, DMSO-d_6) δ ppm 2.23 (s, 3 H) 2.47 (t, *J* = 4.8 Hz, 4 H) 3.09 (t, *J* = 4.8 Hz, 4 H) 3.83 (s, 3 H) 3.87 (s, 3 H) 4.56 (s, 2 H) 6.44 (dd, *J* = 8.7, 2.6 Hz, 1 H) 6.65 (d, *J* = 2.4 Hz, 1 H) 7.10 (t, *J* = 7.5 Hz, 1 H) 7.21 - 7.28 (m, 2 H) 7.50 (d, *J* = 7.9 Hz, 1 H) 7.96 (dd, *J* = 8.7, 1.4 Hz, 1 H) 8.00 - 8.05 (m, 1 H) 8.18 (s, 1 H) 8.43 (d, *J* = 7.9 Hz, 1 H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ ppm 32.9, 45.8, 49.2, 54.8, 55.6, 100.4, 106.9, 109.8, 110.9, 120.2, 120.4, 122.1, 122.7, 123.0, 126.6, 130.9, 132.6, 136.6, 145.6, 146.6, 148.4, 149.6, 154.0. **HRMS** (ESI+) (m/z) calculated for $[C_{25}H_{30}N_7O]^+$ 444.2506, found 444.2496.

Compound 40: *N*-(2-((2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)-4-(1-methyl-1*H*-indol-3-yl)pyrimidin-5-yl)acetamide: N^2-(2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)-4-(1-methyl-1H-indol-3-yl)pyrimidine-2,5-diamine (**39**; 0.15 mmol, 67 mg) was dissolved in DCM/THF (50:50, 0.05 M) and DIPEA (0.75 mmol, 131 µL) was added. At 0 °C acetyl chloride (0.23 mmol, 16 µL) was added and the reaction was stirred at rt for 2 h. The reaction mixture was separated between $NaHCO_3$ solution and DCM and extracted two additional times with DCM. The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. Flash chromatography on silica gel (DCM:MeOH) and subsequent HPLC-purification (water:MeCN) gave the desired product as an off-white solid in 16% yield (23.7 µmol, 11.5 mg). **^{1}H NMR** (500 MHz, DMSO-d_6) δ ppm 2.11 (s, 3 H) 2.24 (s, 3 H) 3.16 (t, *J* = 5.0 Hz, 4 H) 3.79 (s, 3 H) 3.87 (s, 3 H) 6.50 (dd, *J* = 8.5, 2.4 Hz, 1 H) 6.67 (d, *J* = 2.4 Hz, 1 H) 7.04 (t, *J* = 7.5 Hz, 1 H) 7.22 (t, *J* = 7.5 Hz, 1 H) 7.48 (d, *J* = 8.2 Hz, 1 H) 7.59 (d, *J* = 8.5 Hz, 1 H) 7.99 (s, 1 H) 8.01 (s, 1 H) 8.09 (s, 1 H) 8.29 (d, *J* = 7.32 Hz, 1 H) 9.43 (s, 1 H). One of the piperazine peaks (t, 4 H) mixed with DMSO-signal. **^{13}C NMR** (126 MHz, DMSO-d_6) δ ppm 23.2, 33.1, 45.8, 48.8, 54.7, 55.5, 100.2, 106.8, 109.9, 110.2, 118.7, 120.5, 120.7, 122.2, 123.3, 124.9, 126.6, 133.0, 136.5, 148.8, 152.5, 157.7, 157.8, 159.2, 169.6. **HRMS** (ESI+) (m/z) calculated for $[C_{27}H_{32}N_7O_2]^+$ 486.2612, found 486.2602.

Compound 41: *N*-(2-((2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)-4-(1-methyl-1*H*-indol-3-yl)pyrimidin-5-yl)propionamide: N^2-(2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)-4-(1-methyl-1H-indol-3-yl)pyrimidine-2,5-diamine (**39**; 0.15 mmol, 67 mg) was dissolved in DCM/THF (50:50, 0.05 M) and DIPEA (0.75 mmol, 131 µL) was added. At 0 °C propionyl chloride (0.15 mmol, 13 µL) was added and the reaction was stirred at rt for 16 h. The reaction mixture was separated between $NaHCO_3$ solution

and DCM and extracted two additional times with DCM. The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. Flash chromatography on silica gel (DCM:MeOH) and subsequent HPLC-purification (water:MeCN) gave the desired product as an off-white solid in 72% yield (0.11 mmol, 54 mg). **HRMS** (ESI+) (m/z) $_{calculated}$ for $[C_{28}H_{34}N_7O_2]^+$ 500.2769, found 500.2765.

Compound 42: *N*-(2-((2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)-4-(1-methyl-1*H*-indol-3-yl)pyrimidin-5-yl)isobutyramide: N^2-(2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)-4-(1-methyl-1H-indol-3-yl)pyrimidine-2,5-diamine (**39**; 0.15 mmol, 67 mg) was dissolved in DCM/THF (50:50, 0.05 M) and DIPEA (0.75 mmol, 131 µL) was added. At 0 °C isobutyryl chloride (0.15 mmol, 13 µL) was added and the reaction was stirred at rt for 2 h. The reaction mixture was separated between $NaHCO_3$ solution and DCM and extracted two additional times with DCM. The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. Flash chromatography on silica gel (DCM:MeOH) and subsequent HPLC-purification (water:MeCN) gave the desired product as an off-white solid in 49% yield (73.8 µmol, 38 mg). **^{1}H NMR** (500 MHz, DMSO-d_6) δ ppm 1.15 (d, *J* =6.7 Hz, 6 H) 2.26 (s, 3 H) 2.69 (spt, *J* =6.7 Hz, 1 H) 3.17 (t, *J* =4.7 Hz, 4 H) 3.80 (s, 3 H) 3.85 (s, 3 H) 6.51 (dd, *J* =8.5, 2.44 Hz, 1 H) 6.68 (d, *J* =2.4 Hz, 1 H) 7.05 (t, *J* =7.5 Hz, 1 H) 7.23 (t, *J* =7.6 Hz, 1 H) 7.49 (d, *J* =7.9 Hz, 1 H) 7.62 (d, *J* =8.5 Hz, 1 H) 7.95 (s, 1 H) 8.03 (s, 1 H) 8.08 (s, 1 H) 8.27 (d, *J* =7.6 Hz, 1 H) 9.36 (s, 1 H). One of the piperazine peaks (t, 4 H) mixed with DMSO-signal. **^{13}C NMR** (126 MHz, DMSO-d_6) δ ppm 19.4, 33.1, 34.2, 45.8, 48.8, 54.7, 55.5, 100.2, 106.8, 109.9, 110.3, 118.8, 120.5, 120.8, 122.2, 123.1, 124.7, 126.6, 132.9, 136.5, 148.8, 152.4, 157.8, 158.1, 159.2, 176.2. **HRMS** (ESI+) (m/z) calculated for $[C_{29}H_{36}N_7O_2]^+$ 514.2925, found 514.2911.

Compound 43: *N*-(2-((2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)-4-(1-methyl-1*H*-indol-3-yl)pyrimidin-5-yl)cyclopropanecarboxamide: N^2-(2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)-4-(1-methyl-1H-indol-3-yl)pyrimidine-2,5-diamine (**39**; 0.15 mmol, 67 mg) was dissolved in DCM/THF (50:50, 0.05 M) and DIPEA (0.75 mmol, 131 µL) was added. At 0 °C cyclopropane carbonyl chloride (0.23 mmol, 20 µL) was added and the reaction was stirred at rt for 2 h. The reaction mixture was separated between $NaHCO_3$ solution and DCM and extracted two additional times with DCM. The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. Flash chromatography on silica gel (DCM:MeOH) and subsequent HPLC-purification (water:MeCN) gave the desired product as an off-white solid in 73% yield (109 µmol, 56 mg). **^{1}H NMR** (600 MHz, DMSO-d6) δ ppm 0.77 - 0.86 (m, 4 H) 1.85 - 1.94 (m, 1 H) 2.25 (s, 3 H) 2.49 (t, J=4.8 Hz, 3 H) 3.16 (t, J=4.8 Hz, 4 H) 3.80 (s, 3 H) 3.87 (s, 3 H) 6.51 (dd, J=8.4, 2.6 Hz, 1 H) 6.68 (d, J=2.6 Hz, 1 H) 7.05 (t, J=7.5 Hz, 1 H) 7.20 - 7.28 (m, 1 H) 7.50 (d, J=8.1 Hz, 1 H) 7.61 (d, J=8.8 Hz, 1 H) 7.95 (s, 1 H) 8.01 (s, 1 H) 8.10 (s, 1 H) 8.28 (d, J=7.3 Hz, 1 H) 9.68 (s, 1 H). **^{13}C NMR** (151 MHz, DMSO-d6) δ ppm 6.7, 14.0, 33.1, 45.8, 48.8, 54.7, 55.5, 100.2, 106.8, 109.9, 110.3, 118.8, 120.5, 120.7, 122.2, 123.2, 124.8, 126.6, 132.9, 136.5, 148.8, 152.5, 157.6, 157.9, 159.1, 172.9. **HRMS** (ESI+) (m/z) calculated for $[C_{29}H_{34}N_7O_2]^+$ 512.27685, found 512.27591.

Compound 44: N-(2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)-4-(1-methyl-1*H*-indol-3-yl)-5-(5-methylfuran-2-yl)pyrimidin-2-amine trifluoroacetate: 5-bromo-*N*-(2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)-4-(1-methyl-1H-indol-3-yl)pyrimidin-2-amine (50.0 µmol, 25 mg) and 4,4,5,5-tetramethyl-2-(5-methylfuran-2-yl)-1,3,2-dioxaborolane (75.0 µmol, 16 mg) were dissolved in dioxane (0.05 M) and degassed with an argon stream for 15 min. K_2CO_3 (100.0 µmol, 14 mg) and $Pd(PPh_3)_4$ (5.0 µmol, 6 mg) werde added and the reaction was stirred at 100 °C for 16 h. The cooled down reaction mixture was separated between $NaHCO_3$ solution and DCM and the aqueous phase was extracted two additional times with DCM. The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. Flash chromatography on silica gel (DCM:MeOH) and subsequent HPLC-purification (water:MeCN) gave the desired product as a yellow solid in 20% yield (9.8 µmol, 6 mg). **^{1}H NMR** (600 MHz, Methanol-d_4) δ ppm 2.35 (s, 3 H) 3.01 (s, 3 H) 3.14 (br. s., 2 H) 3.66 (br. s., 2 H) 3.77 (s, 3 H) 3.89 (s, 3 H) 3.96 (br. s., 2 H) 6.25 - 6.29 (m, 1 H) 6.46 - 6.50 (m, 1 H) 6.73 (dd, *J* =8.6, 2.4 Hz, 1 H) 6.74 - 6.78 (m, 1 H) 6.84 - 6.85 (m, 1 H) 7.13 (t, *J* =7.3 Hz, 1 H) 7.29 (t, *J* =7.7 Hz, 1 H) 7.46 (d, *J* =8.1 Hz, 1 H) 7.59 - 7.67 (m, 1 H) 8.04 (br. s., 1 H) 8.26 (br. s., 1 H). **HRMS** (ESI+) (m/z) calculated for $[C_{30}H_{33}N_6O_2]^+$ 509.2660, found 509.2652.

Compound 45: *N*-(2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)-4-(1-methyl-1*H*-indol-3-yl)-5-(1-methyl-1*H*-pyrazol-4-yl)pyrimidin-2-amine: 5-bromo-*N*-(2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)-4-(1-methyl-1H-indol-3-yl)pyrimidin-2-amine (50.0 µmol, 25 mg) and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (75.0 µmol, 16 mg) were dissolved in dioxane (0.05 M) and degassed with an argon stream for 15 min. K_2CO_3 (100.0 µmol, 14 mg) and $Pd(PPh_3)_4$ (5.0 µmol, 6 mg) werde added and the reaction was stirred at 100 °C for 16 h. The cooled down reaction mixture was separated between $NaHCO_3$ solution and DCM and the aqueous phase was extracted two additional times with DCM. The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. Flash chromatography on silica gel (DCM:MeOH) and subsequent HPLC-purification (water:MeCN) gave the desired product as an off-white solid in 24% yield (11.8 µmol, 6 mg). **^{1}H NMR** (700 MHz, DMSO-d_6) δ ppm 2.25 (s, 3 H) 2.49 (t, *J* = 4.6 Hz, 4 H) 3.14 (t, *J* = 4.6 Hz, 4 H) 3.64 (s, 3 H) 3.83 (s, 3 H) 3.94 (s, 3 H) 6.44 - 6.49 (m, 2 H) 6.67 (d, *J* = 2.4 Hz, 1 H) 7.11 (t, *J* = 7.5 Hz, 1 H) 7.25 (t, *J* = 7.5 Hz, 1 H) 7.54 (d, *J* = 8.2 Hz, 1 H) 7.63 (s, 1 H) 7.69 (d, *J* = 8.8 Hz, 1 H) 7.83 (s, 1 H) 8.06 (s, 1 H) 8.11 (d, *J* = 5.4 Hz, 1 H) 8.22 (d, *J* = 7.5 Hz, 1 H). **^{13}C NMR** (176 MHz, DMSO-d_6) δ ppm 30.5, 38.7, 45.7, 48.8, 54.7, 55.6, 100.1, 106.8, 109.2, 110.1, 110.6, 111.7, 120.6, 120.9, 121.4, 122.2, 123.3, 125.9, 131.9, 133.8, 136.9, 139.6, 148.1, 151.3, 156.7, 160.7, 162.4. **HRMS** (ESI+) (m/z) calculated for $[C_{29}H_{33}N_8O]^+$ 509.2772, found 509.2764.

Compound 46: isopropyl 4-(1-methyl-1*H*-indol-3-yl)-2-((1-methyl-1*H*-pyrazol-4-yl)amino)pyrimidine-5-carboxylate: The reaction was performed according to the *General method for nucleophilic aromatic substitution of 2-chloropyrimidines* with **19** (0.15 mmol, 49 mg) and 1-methyl-1H-pyrazol-4-amine (0.15 mmol, 13 µL) in *n*-BuOH (0.1 M) at 90 °C. The product was obtained as a yellow solid in 63% yield (95 µmol, 37 mg). **^{1}H NMR** (700 MHz, $CDCl_3$) δ ppm 1.22 (d, *J* =6.2 Hz, 6 H) 3.82 (br. s., 3 H) 3.85 (br. s., 3 H) 5.12 (spt, *J* =6.2 Hz, 1 H) 7.20 (t, *J* =7.6 Hz, 1 H) 7.29 (t, *J* =7.6 Hz, 1 H) 7.36 (d, *J* =8.0 Hz, 1 H) 7.49 (s, 1 H) 7.80 (br. s., 1 H) 7.83 (s, 1 H) 7.88 (br. s., 1 H) 8.03 (d, *J* =8.0 Hz, 1 H) 8.86 (br. s., 1 H). **HRMS** (ESI+) (m/z) calculated for $[C_{21}H_{23}N_6O_2]^+$ 391.1877, found 391.1885.

Compound 47: isopropyl 2-((3-methoxy-1-methyl-1H-pyrazol-4-yl)amino)-4-(1-methyl-1*H*-indol-3-yl)pyrimidine-5-carboxylate: The reaction was performed according to the *General method for nucleophilic aromatic substitution of 2-chloropyrimidines* with **19** (0.15 mmol, 49 mg) and 3-methoxy-1-methyl-1H-pyrazol-4-amine hydrochloride (0.15 mmol, 25 mg) in *n*-BuOH (0.1 M) at 90 °C. The product was obtained as a yellow solid in 65% yield (97 µmol, 41 mg). **^{1}H NMR** (700 MHz, $CDCl_3$) δ ppm 1.23 (br. s., 6 H) 3.69 (br. s., 3 H) 3.87 (s, 3 H) 3.98 (s, 3 H) 5.13 (br. s., 1 H) 7.21 (t, *J* =7.1 Hz, 1 H) 7.29 (t, *J* =7.5 Hz, 1 H) 7.37 (d, *J* =8.0 Hz, 1 H) 7.44 (br. s., 1 H) 7.84 (br. s., 2 H) 8.09 (br. s., 1 H) 8.86 (br. s., 1 H). **^{13}C NMR** (176 MHz, $CDCl_3$) δ ppm 21.7, 33.3, 39.0, 56.4, 68.3, 106.4, 109.6, 113.0, 120.8, 122.2, 122.5, 124.3, 127.1, 133.1, 133.9, 137.1, 154.3, 160.6, 161.3, 166.1. **HRMS** (ESI+) (m/z) calculated for $[C_{22}H_{25}N_6O_3]^+$ 421.1983, found 421.1978.

Compound 48: isopropyl 2-((2-methoxy-4-morpholinophenyl)amino)-4-(1-methyl-1*H*-indol-3-yl)pyrimidine-5-carboxylate: The reaction was performed according to the *General method for nucleophilic aromatic substitution of 2-chloropyrimidines* with **19** (0.10 mmol, 33 mg) and 2-methoxy-4-morpholinoaniline (0.12 mmol, 25 mg) in *i*-PrOH (0.1 M) at 90 °C. The product was obtained as a yellow solid in 69% yield (69 µmol, 35 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 1.21 (d, *J* =6.3 Hz, 6 H) 3.15 (t, *J* =4.7 Hz, 4 H) 3.86 - 3.92 (m, 10 H) 5.11 (spt, *J* =6.3 Hz, 1 H) 6.51 - 6.59 (m, 2 H) 7.20 (t, *J* =7.1 Hz, 1 H) 7.26 - 7.32 (m, 1 H) 7.37 (d, *J* =8.3 Hz, 1 H) 7.78 (s, 1 H) 7.82 (s, 1 H) 8.05 (d, *J* =8.3 Hz, 1 H) 8.40 (d, *J* =8.3 Hz, 1 H) 8.86 (s, 1 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 21.7, 33.3, 50.3, 55.7, 66.9, 68.3, 100.0, 107.9, 109.5, 113.2, 113.9, 120.8, 120.8, 121.8, 122.0, 122.3, 127.1, 133.2, 137.1, 147.6, 149.5, 159.9, 160.8, 162.3, 166.3. **HRMS** (ESI+) (m/z) calculated for $[C_{28}H_{32}N_5O_4]^+$ 502.2449, found 502.2442.

Compound 49: isopropyl 2-((4-((2-(dimethylamino)ethyl)(methyl)amino)-2-methoxyphenyl)amino)-4-(1-methyl-1*H*-indol-3-yl)pyrimidine-5-carboxylate: The reaction was performed according to the *General method for nucleophilic aromatic substitution of 2-chloropyrimidines* with **19** (0.10 mmol, 33 mg) and *N*1-(2-(dimethylamino)ethyl)-3-methoxy-*N*1-methylbenzene-1,4-diamine (0.12 mmol, 27 mg) in *n*-BuOH (0.1 M) at 80 °C. The product was obtained as a yellow solid in 49% yield (49 µmol, 25 mg). **^{1}H NMR** (700 MHz, DMSO-d_6) δ ppm 1.17 (d, *J* = 6.0 Hz, 6 H) 2.20 (s, 6

H) 2.41 (t, *J* = 7.1 Hz, 2 H) 2.95 (s, 3 H) 3.44 (t, *J* = 7.1 Hz, 2 H) 3.76 (s, 3 H) 3.84 (s, 3 H) 5.05 (spt, *J* = 6.2, 1 H) 6.27 (dd, *J* = 8.6, 2.6 Hz, 1 H) 6.38 (s, 1 H) 7.01 (br. s., 1 H) 7.19 (t, *J* = 6.8 Hz, 1 H) 7.36 (d, *J* = 8.6 Hz, 1 H) 7.46 (d, *J* = 8.0 Hz, 1 H) 7.90 (br. s, 2 H) 8.57 (d, *J* = 6.0 Hz, 2 H). **^{13}C NMR** (176 MHz, DMSO-d_6) δ ppm 21.9, 33.4, 39.0, 46.1, 50.8, 55.8, 56.1, 68.3, 96.7, 103.9, 110.5, 112.0, 116.9, 120.9, 122.3, 122.6, 127.1, 127.5, 134.6, 137.1, 148.4, 154.4, 160.6, 161.6, 162.0, 166.8. **HRMS** (ESI+) (m/z) calculated for $[C_{29}H_{37}N_6O_3]^+$ 517.2922, found 517.2912.

Compound 50: isopropyl 2-((4-(4-acetylpiperazin-1-yl)-2-methoxyphenyl)amino)-4-(1-methyl-1H-indol-3-yl)pyrimidine-5-carboxylate: The reaction was performed according to the *General method for nucleophilic aromatic substitution of 2-chloropyrimidines* with **19** (0.10 mmol, 33 mg) and 1-(4-(4-amino-3-methoxyphenyl)piperazin-1-yl)ethan-1-one (0.12 mmol, 30 mg) in *i*-PrOH (0.1 M) at 90 °C. The product was obtained as a yellow solid in 78% yield (78 µmol, 42 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 1.20 (d, *J* =6.3 Hz, 6 H) 2.15 (s, 3 H) 3.13 (dt, *J* =11.1, 5.4 Hz, 4 H) 3.63 (t, *J* =5.4 Hz, 2 H) 3.80 (t, *J* =5.4 Hz, 2 H) 3.87 (s, 3 H) 3.90 (s, 3 H) 5.11 (spt, *J* =6.3 Hz, 1 H) 6.51 - 6.60 (m, 2 H) 7.16 - 7.22 (m, 1 H) 7.26 - 7.31 (m, 1 H) 7.36 (d, *J* =8.3 Hz, 1 H) 7.79 (s, 1 H) 7.82 (s, 1 H) 8.05 (d, *J* =8.3 Hz, 1 H) 8.41 (d, *J* =8.8 Hz, 1 H) 8.86 (s, 1 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 21.3, 21.6, 33.3, 41.4, 46.3, 50.4, 50.7, 55.7, 68.3, 101.1, 108.8, 109.6, 113.1, 114.0, 120.7, 120.8, 121.7, 122.3, 122.5, 127.0, 133.2, 137.1, 147.2, 149.4, 159.9, 160.8, 162.2, 166.2, 168.9. **HRMS** (ESI+) (m/z) calculated for $[C_{30}H_{35}N_6O_4]^+$ 543.2714, found 543.2708.

Compound 51: isopropyl 2-((2-methoxy-4-(9-methyl-3,9-diazaspiro[5.5]undecan-3-yl)phenyl)amino)-4-(1-methyl-1*H*-indol-3-yl)pyrimidine-5-carboxylate: The reaction was performed according to the *General method for nucleophilic aromatic substitution of 2-chloropyrimidines* with **19** (0.20 mmol, 66 mg) and 2-methoxy-4-(9-methyl-3,9-diazaspiro[5.5]undecan-3-yl)aniline (0.20 mmol, 58 mg) in *i*-PrOH (0.1 M) at 85 °C. The product was obtained as a yellow solid in 37% yield (74 µmol, 43 mg). **^{1}H NMR** (500 MHz, DMSO-d_6) δ ppm 1.16 (d, *J* =6.2 Hz, 6 H) 1.47 (t, *J* =5.3 Hz, 4 H) 1.54 (t, *J* =5.5 Hz, 4 H) 2.16 (s, 3 H) 2.29 (br. s., 4 H) 3.14 (t, *J* =5.3 Hz, 4 H) 3.77 (s, 3 H) 3.85 (s, 3 H) 5.04 (spt, *J* =6.2 Hz, 1 H) 6.49 (dd, *J* =8.5, 2.4 Hz, 1 H) 6.64 (d, *J* =2.1 Hz, 1 H) 7.04 (br. s., 1 H) 7.20 (t, *J* =7.6 Hz, 1 H) 7.43 - 7.54 (m, 2 H) 7.89 (s, 1 H) 7.92 (br. s., 1 H) 8.59 (d, *J* =2.8 Hz, 2 H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ ppm 21.4, 28.3, 32.9, 35.1, 44.6, 46.2, 50.7, 55.5, 67.9, 73.8, 100.0, 107.0, 110.1, 111.6, 118.9, 120.5, 121.9, 125.7, 126.5, 134.2, 136.7, 149.9, 153.0, 160.2, 161.1, 161.1, 166.3. **LC-MS** (ESI^+) (m/z) calculated for $[C_{34}H_{43}N_6O_3]^+$ 583.34, found 583.33.

Compound 52: isopropyl 2-((2-methoxy-4-(4-(4-methylpiperazin-1-yl)piperidin-1-yl)phenyl)amino)-4-(1-methyl-1*H*-indol-3-yl)pyrimidine-5-carboxylate: The reaction was performed according to the *General method for nucleophilic aromatic substitution of 2-chloropyrimidines* with **19** (0.20 mmol, 66 mg) and 2-methoxy-4-(4-(4-methylpiperazin-1-yl)piperidin-1-yl)aniline (0.20 mmol, 61 mg) in *i*-PrOH (0.1 M) at 85 °C. The product was obtained as a yellow solid in 48% yield (95 µmol, 57 mg). **^{1}H NMR** (600 MHz, Methanol-d_4) δ ppm 2.72 (d, *J* =6.2 Hz, 6 H) 3.21 (qd, *J* =12.1, 4.0 Hz, 2 H) 3.56 (d, *J* =12.5 Hz, 2 H) 3.85 (s, 3 H) 3.92 (tt, *J* =11.6, 3.7 Hz, 1 H) 3.95 - 4.45 (m, 8 H) 5.28 (d, *J* =12.5 Hz, 2 H) 5.43 (s, 3 H) 5.44 (s, 3 H) 6.62 (spt, *J* =6.2 Hz, 1 H) 8.12 (dd, *J* =8.8, 2.6 Hz, 1 H) 8.25 (d, *J* =2.6 Hz, 1 H) 8.67 (t, *J* =7.5 Hz, 1 H) 8.77 - 8.83 (m, 1 H) 8.99 (d, *J* =8.1 Hz, 1 H) 9.38 (s, 1 H) 9.44 (d, *J* =8.1 Hz, 1 H) 9.56 (d, *J* =8.8 Hz, 1 H) 10.*24* (s, 1 H). **^{13}C NMR** (151 MHz, Methanol-d_4) δ ppm 22.0, 29.4, 33.5, 46.1, 50.0, 51.4, 56.0, 56.5, 63.2, 70.1, 102.5, 109.9, 111.0, 114.3, 114.9, 122.0, 122.3, 122.7, 123.5, 124.3, 128.4, 134.9, 138.9, 150.5, 152.8, 161.6, 162.0, 163.9, 168.4. **LC-MS** (ESI^+) (m/z) calculated for $[C_{34}H_{44}N_7O_3]^+$ 598.35, found 598.28.

Compound 53: methyl 2-chloro-4-(1H-indol-3-yl)pyrimidin-5-carboxylate: methyl 2,4-dichloropyrimidin-5-carboxylate (2.0 mmol, 414 mg) were dissolved in 1,2-dichloroethane (0.2 M) and $AlCl_3$ (2.4 mmol, 320 mg) were added at rt. The reaction mixture was stirred at 70 °C for 20 min before 1*H*-indole (2.0 mmol, 234 mg) was added. After 20 min the reaction mixture was cooled down and separated between hydrochlorid acid (0.1 M, 10 mL) and DCM. The aqueous phase was extracted two additional times with DCM. The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. Flash chromatography on silica gel (PE:EtOAc) gave the desired product as an off-white solid in 36% yield (0.72 mmol, 206 mg). **^{1}H NMR** (500 MHz, DMSO-d6) δ ppm 3.87 (s, 3 H) 7.20 - 7.28 (m, 2 H)

7.47 - 7.56 (m, 1 H) 8.07 (s, 1 H) 8.17 - 8.27 (m, 1 H) 8.84 (s, 1 H) 12.11 (br. s., 1 H). **^{13}C NMR** (126 MHz, DMSO-*d*6) δ ppm 53.1, 110.4, 112.5, 120.6, 121.3, 121.6, 122.9, 125.6, 132.4, 136.6, 160.1, 160.8, 162.0, 166.6. **LC-MS** (ESI+) (m/z) calculated for $[C_{14}H_{11}ClN_3O_2]^+$ 288.05, found 288.10.

Compound 54: isopropyl 2-chloro-4-(1H-indol-3-yl)pyrimidin-5-carboxylate: isopropyl 2,4-dichloropyrimidin-5-carboxylate (0.20 mmol, 47 mg) was dissolved in 1,2-dichloroethane (0.2 M) and $AlCl_3$ (0.22 mmol, 29 mg) was added at rt. The reaction mixture was stirred at 70 °C for 20 min before 1*H*-indole (0.2 mmol, 23 mg) was added. After 20 min the reaction mixture was cooled down and separated between hydrochloric acid (0.1 M, 10 mL) and DCM. The aqueous phase was extracted two additional times with DCM. The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. Flash chromatography on silica gel (PE:EtOAc) gave the desired product as an off-white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 1.23 (d, *J* =6.3 Hz, 6 H) 5.18 (spt, *J* =6.3 Hz, 1 H) 7.27 - 7.33 (m, 2 H) 7.40 - 7.46 (m, 1 H) 8.03 (d, *J* =3.1 Hz, 1 H) 8.12 - 8.19 (m, 1 H) 8.74 (br. s., 1 H) 8.83 (s, 1 H). **LC-MS** (ESI+) (m/z) calculated for $[C_{16}H_{15}ClN_3O_2]^+$ 316.08, found 316.00.

Compound 55: methyl 2-((4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenyl)amino)-4-(1*H*-indol-3-yl)pyrimidin-5-carboxylate: The reaction was performed according to the *General method for nucleophilic aromatic substitution of 2-chloropyrimidines* with **53** (0.50 mmol, 144 mg) and 1-(4-amino-3-methoxyphenyl)-*N,N*-dimethylpiperidin-4-amine (0.60 mmol, 150 mg) in *i*-PrOH (0.1 M) at 85 °C. The product was obtained as a yellow solid in 57% yield (0.28 mmol, 142 mg). **^{1}H NMR** (600 MHz, DMSO-d_6) δ ppm 1.50 (qd, *J* =12.0, 4.0 Hz, 2 H) 1.85 (d, *J* =12.0 Hz, 2 H) 2.17 - 2.24 (m, 7 H) 2.65 - 2.73 (m, 2 H) 3.72 (m, 5 H) 3.77 (s, 3 H) 6.50 (dd, *J* =8.8, 2.6 Hz, 1 H) 6.66 (d, *J* =2.6 Hz, 1 H) 6.99 (br. s., 1 H) 7.13 (t, *J* =7.3 Hz, 1 H) 7.42 (d, *J* =8.1 Hz, 1 H) 7.46 (d, *J* =8.8 Hz, 1 H) 7.89 (d, *J* =2.6 Hz, 1 H) 7.94 (br. s., 1 H) 8.61 (d, *J* =3.7 Hz, 2 H) 11.66 (br. s., 1 H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ ppm 27.9, 41.5, 48.6, 51.8, 54.9, 55.5, 61.4, 100.5, 107.1, 111.7, 112.3. 119.0, 120.3, 121.8, 126.1, 130.5, 136.1, 149.7, 153.3, 160.1, 161.2, 161.7, 167.3. **LC-MS** (ESI+) (m/z) calculated for $[C_{28}H_{33}N_6O_3]^+$ 501.26, found 501.22.

Compound 56: 2-((4-(4-(Dimethylamino)piperidin-1-yl)-2-methoxyphenyl)amino)-4-(1*H*-indol-3-yl)pyrimidin-5-carboxylic acid tri-trifluoroacetate: methyl ester **55** (0.43 mmol, 216 mg) was dissolved in THF (0.1 M) and sodium hydroxide solution (1 M, 4.3 mmol). LiOH (4.3 mmol, 103 mg) was added, and the reaction was stirred at 90 °C for 16 h. The cooled down reaction mixture was concentrated *in vacuo* and the crude product was dissolved in aqueous TFA-solution and further acidified to pH=2. The crude solution was purified by reverse-phase chromatography using a C_{18}-column and an TFA-acidic water/acetonitrile gradient. The flow-though was dried in an air stream giving the desired product as an orange TFA-salt in a quantitative yield (0.43 mmol, 454 mg). **LC-MS** (ESI+) (m/z) calculated for $[C_{27}H_{31}N_6O_3]^+$ 487.25, found 487.21.

Compound 57: Cyclopentyl 2-((4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenyl)amino)-4-(1*H*-indol-3-yl)pyrimidin-5-carboxylate: The reaction was performed according to the *General method for amide and ester couplings* with **56** (0.10 mmol, 106 mg), DIPEA (2.00 mmol, 348 µL) and cyclopentyl alcohol (2.0 mmol, 172 mg). After 1 h reaction time further cyclopentyl alcohol (1.0 mmol, 86 mg) which was prestirred with sodium hydride (1.0 mmol) in THF (1 mL) was added. The product was obtained as a yellow solid in 4% yield (4.3 µmol, 2.4 mg). **^{1}H NMR** (600 MHz, DMSO-d_6) δ ppm 1.44 - 1.53 (m, 6 H) 1.53 - 1.61 (m, 2 H) 1.76 (dq, *J* =13.8, 6.8 Hz, 2 H) 1.85 (d, *J* =12.5 Hz, 2 H) 2.17 - 2.27 (m, 7 H) 2.68 (td, *J* =12.2, 2.0 Hz, 2 H) 3.73 (d, *J* =12.5 Hz, 2 H) 3.78 (s, 3 H) 5.15 - 5.22 (m, 1 H) 6.50 (dd, *J* =8.8, 2.6 Hz, 1 H) 6.65 (d, *J* =2.6 Hz, 1 H) 6.99 (br. s., 1 H) 7.13 (t, *J* =7.5 Hz, 1 H) 7.42 (d, *J* =8.1 Hz, 1 H) 7.48 (d, *J* =8.4 Hz, 1 H) 7.85 (d, *J* =2.9 Hz, 1 H) 7.88 (br. s., 1 H) 8.58 (d, *J* =4.8 Hz, 2 H) 11.65 (br. d, *J* =2.0 Hz, 1 H). **^{13}C NMR** (151 MHz, DMSO-*d*6) δ ppm 23.2, 27.9, 32.0, 41.5, 48.6, 55.5, 61.4, 77.0, 100.5, 107.2, 111.7, 112.7, 119.1, 120.2, 121.6, 121.8, 125.8, 126.1, 130.1, 136.1, 149.6, 153.1, 160.1, 161.2, 161.6, 166.6. **LC-MS** (ESI+) (m/z) calculated for $[C_{32}H_{39}N_6O_3]^+$ 555.31, found 555.22.

Compound 58: oxetan-3-yl 2-((4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenyl)amino)-4-(1*H*-indol-3-yl)pyrimidin-5-carboxylate: The reaction was performed according to the *General method for amide and ester couplings* with **56** (0.10 mmol, 106 mg), DIPEA (2.00 mmol, 348 µL) and oxentan-

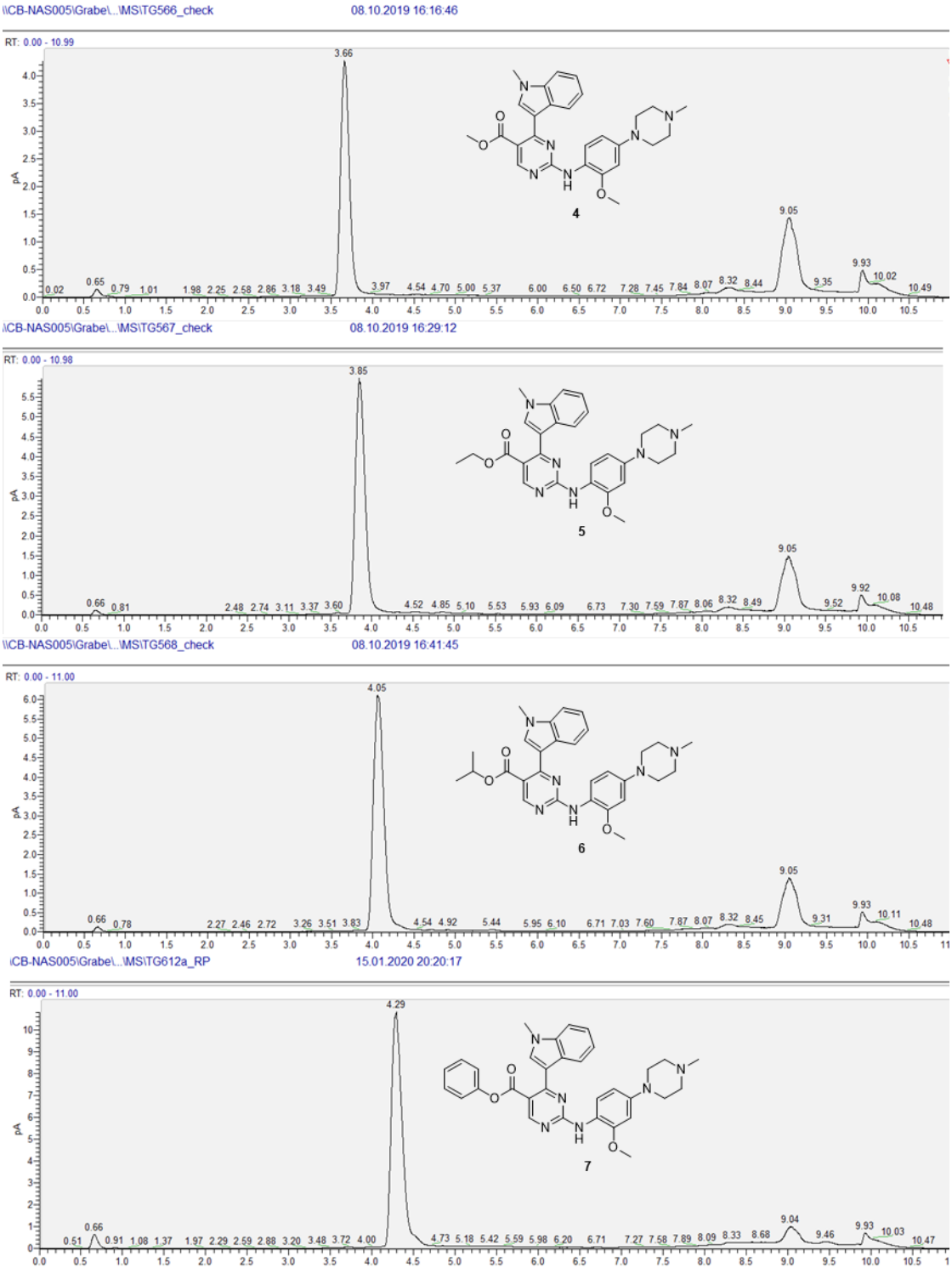
2-ol (2.0 mmol, 132 µL). After 1 h reaction time further oxentan-2-ol (1.0 mmol, 66 µL) which was prestirred with sodium hydride (1.0 mmol) in THF (1 mL) was added. The product was obtained as a yellow solid in 3% yield (3.1 µmol, 1.7 mg). **^{1}H NMR** (600 MHz, DMSO-d_6) δ ppm 1.51 (qd, *J* =11.8, 3.9 Hz, 2 H) 1.85 (d, *J* =12.5 Hz, 2 H) 2.18 - 2.28 (m, 7 H) 2.69 (td, *J* =12.0, 2.0 Hz, 2 H) 3.74 (d, *J* =12.5 Hz, 2 H) 3.77 (s, 3 H) 4.51 (t, *J* =5.9 Hz, 2 H) 4.77 (t, *J* =7.0 Hz, 2 H) 5.49 - 5.56 (m, 1 H) 6.51 (dd, *J* =8.8, 2.6 Hz, 1 H) 6.66 (d, *J* =2.6 Hz, 1 H) 6.99 (br. s., 1 H) 7.12 (t, *J* =7.2 Hz, 1 H) 7.41 (d, *J* =8.1 Hz, 1 H) 7.45 (d, *J* =8.8 Hz, 1 H) 7.88 (br. s., 1 H) 7.95 (d, *J* =2.9 Hz, 1 H) 8.72 (s, 1 H) 8.75 (s, 1 H) 11.66 (br. s., 1 H). **LC-MS** (ESI+) (m/z) calculated for $[C_{30}H_{35}N_6O_4]^+$ 543.27, found 543.21.

Compound 59: benzyl 2-((4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenyl)amino)-4-(1*H*-indol-3-yl)pyrimidin-5-carboxylate: The reaction was performed according to the *General method for amide and ester couplings* with **56** (50 µmol, 53 mg), TEA (2.00 mmol, 348 µL) and benzyl alcohol (2.5 mmol, 0.26 mL). The product was obtained as a yellow solid in 4% yield (1.9 µmol, 1.1 mg). **TLC-MS** (APCI+) (m/z) calculated for $[C_{34}H_{37}N_6O_3]^+$ 577.29, found 577.31.

Compound 60: 3,5-difluorophenyl 2-((4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenyl)-amino)-4-(1*H*-indol-3-yl)pyrimidin-5-carboxylate: The reaction was performed according to the *General method for amide and ester couplings* with **56** (60 µmol, 63 mg), DIPEA (1.20 mmol, 209 µL) and 3,5-difluorophenol (0.60 mmol, 78 mg). The product was obtained as a yellow solid in 35% yield (21 µmol, 12.5 mg). **^{1}H NMR** (600 MHz, $CDCl_3$) δ ppm 1.75 - 1.85 (m, 2 H) 2.01 - 2.16 (m, 2 H) 2.50 (br. s., 6 H) 2.56 (br. s., 1 H) 2.71 - 2.79 (m, 2 H) 3.72 (d, *J* =12.5 Hz, 2 H) 3.92 (s, 3 H) 6.50 - 6.57 (m, 3 H) 6.58 (d, *J* =2.2 Hz, 1 H) 6.68 (tt, *J* =8.9, 2.3 Hz, 1 H) 7.21 - 7.26 (m, 1 H) 7.27 - 7.31 (m, 1 H) 7.47 (d, *J* =8.1 Hz, 1 H) 7.90 (s, 1 H) 7.97 (d, *J* =2.9 Hz, 1 H) 8.05 (d, *J* =8.1 Hz, 1 H) 8.39 (br. s., 1 H) 8.63 (br. s., 1 H) 9.10 (br. s., 1 H). **LC-MS** (ESI+) (m/z) calculated for $[C_{33}H_{33}F_2N_6O_3]^+$ 599.26, found 599.20.

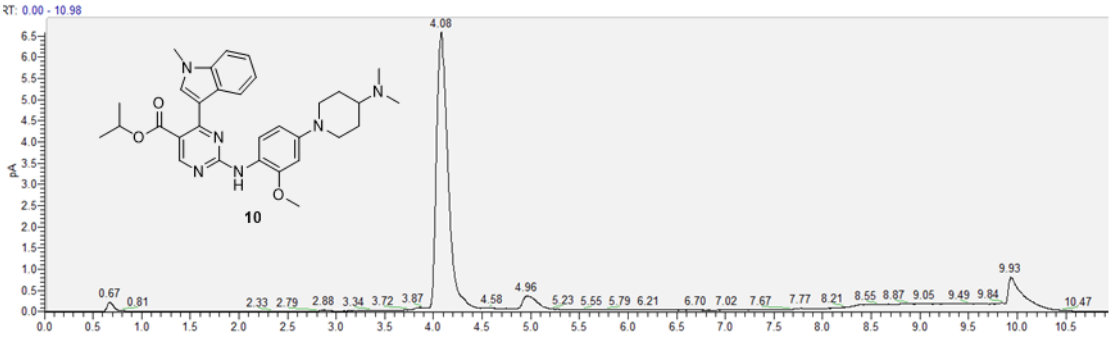
Compound 61: 4-fluorophenyl 2-((4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenyl)- amino)-4-(1*H*-indol-3-yl)pyrimidin-5-carboxylate: The reaction was performed according to the *General method for amide and ester couplings* with **56** (60 µmol, 63 mg), DIPEA (1.20 mmol, 209 µL) and 4-fluorophenol (0.60 mmol, 67 mg). The product was obtained as a yellow solid in 39% yield (24 µmol, 13.7 mg). **^{1}H NMR** (600 MHz, $CDCl_3$) δ ppm 1.75 - 1.84 (m, 3 H) 2.08 (d, *J* =8.8 Hz, 2 H) 2.50 (br. s., 6 H) 2.71 - 2.79 (m, 2 H) 3.71 (d, *J* =12.5 Hz, 2 H) 3.92 (s, 3 H) 6.55 (d, *J* =8.1 Hz, 1 H) 6.58 (d, *J* =2.6 Hz, 1 H) 6.91 - 6.96 (m, 2 H) 7.01 - 7.05 (m, 2 H) 7.23 (t, *J* =7.3 Hz, 1 H) 7.27 - 7.30 (m, 1 H) 7.45 (d, *J* =8.1 Hz, 1 H) 7.88 (s, 1 H) 8.00 (d, *J* =2.6 Hz, 1 H) 8.09 (d, *J* =8.1 Hz, 1 H) 8.41 (br. s., 1 H) 8.61 (br. s., 1 H) 9.12 (s, 1 H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ ppm 1.0, 27.4, 40.8, 49.9, 55.7, 62.6, 101.0, 108.7, 111.5, 115.9, 116.1, 120.9, 121.4, 122.9, 123.0, 123.1, 126.4, 129.1, 136.0, 146.5, 146.5, 147.8, 149.5, 159.4, 160.3, 161.0, 161.9, 163.5, 165.0. **LC-MS** (ESI+) (m/z) calculated for $[C_{33}H_{34}FN_6O_3]^+$ 581.27, found 581.27.

5. LC-MS spectra of title compounds

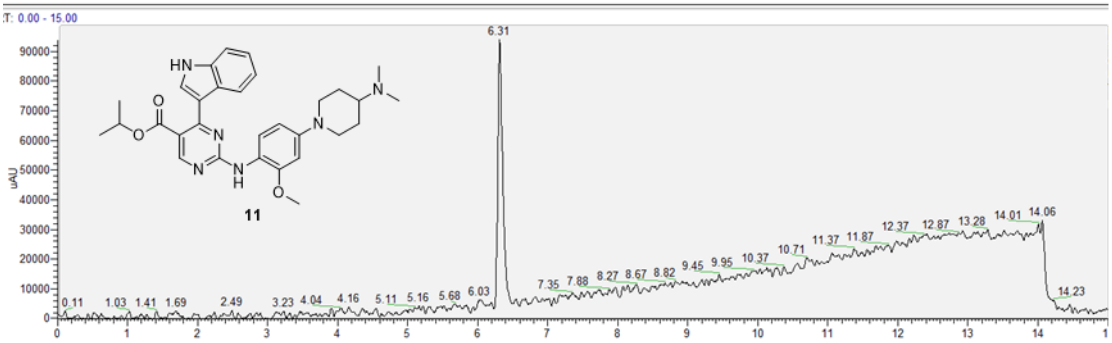


Peaks at 9.0 min from Acetonitrile Flush.

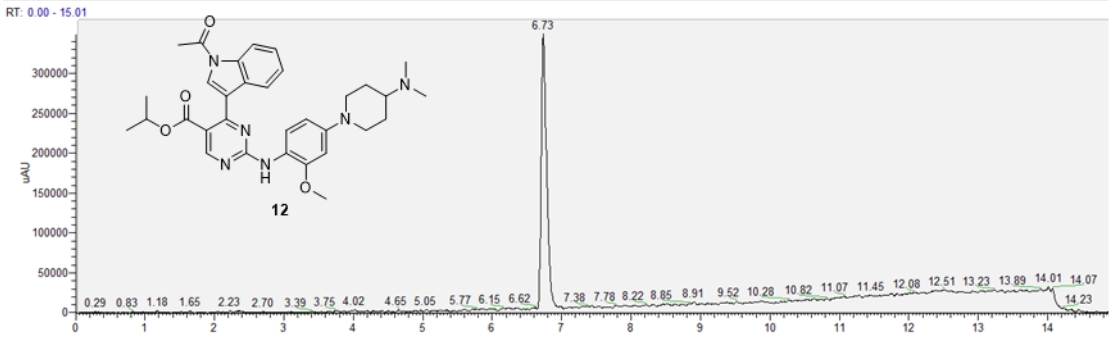
CB-NAS005\Grabe\...\MS\TG635a_DMN 27.02.2020 17:54:37



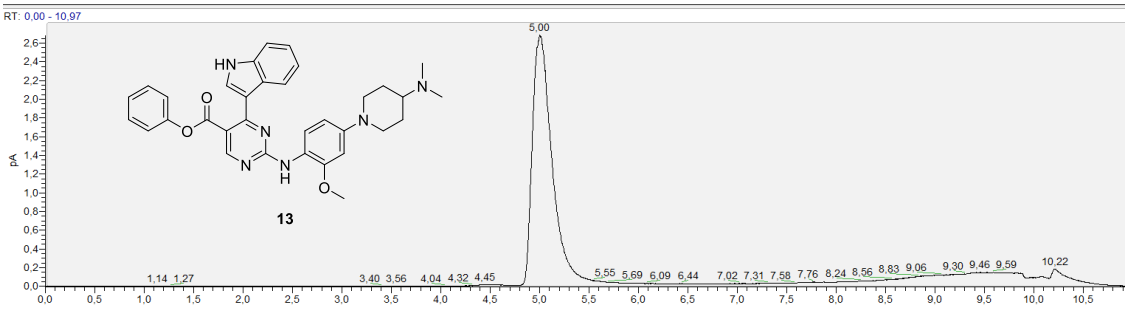
:\GrabeLockdown\MS\TG673a_prep13 10.06.2020 15:59:57



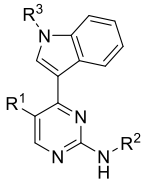
C:\GrabeLockdown\MS\TG673a_prep19 10.06.2020 15:43:01

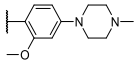
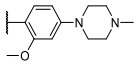
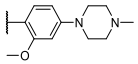
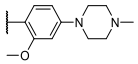
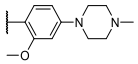
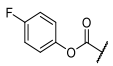
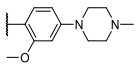
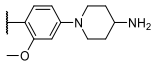
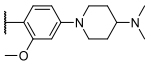
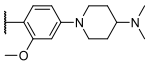
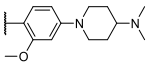
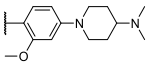
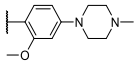
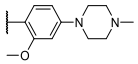
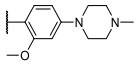


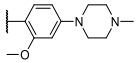
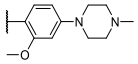
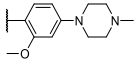
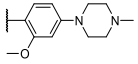
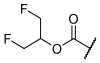
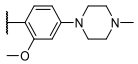
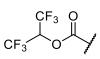
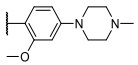
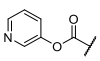
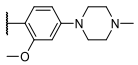
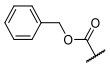
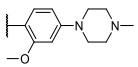
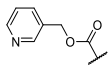
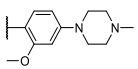
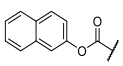
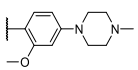
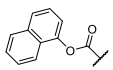
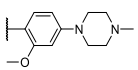
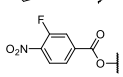
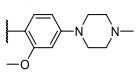
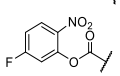
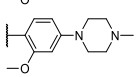
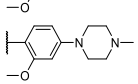
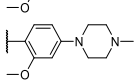
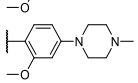
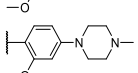
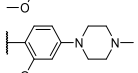
C:\Users\...\Rar$DIa5492.18479\TG696 24.11.2022 17:09:50

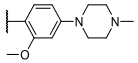
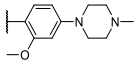
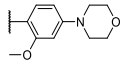
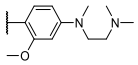
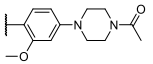
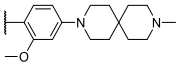
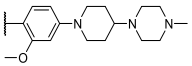
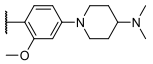
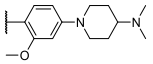
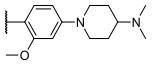
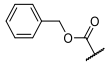
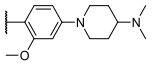
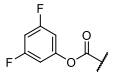
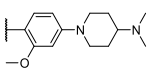
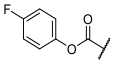
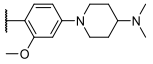


6. Complete Structure-Activity-Relationship of Reversible Aminopyrimidines – Table S2



				HTRF EGFR [nM]					CTG [µM]				
	R1	R2	R3	Wild type	L858R	L858R/T790M	L858R/C797S	L858R/T790M/ C797S	A431	Ba/F3 Parental	Ba/F3-EGFR L858R	Ba/F3-EGFR L858R/C797S	Ba/F3-EGFR L858R/T790M /C797S
Osimertinib	-	-	-	0.24 ± 0.01	0.05 ± 0.02	0.03 ± 0.01	354 ± 129	151 ± 77	0.83 ± 0.43	2.3 ± 0.13**	0.006 ± 0.003	3.0 ± 1.2	1.0 ± 0.2
Mobocertinib	-	-	-	0.03 ± 0.01	0.01 ± 0.001	0.03 ± 0.003	25 ± 11	364 ± 139	1.7 ± 1.1	2.3 ± 0.65**	0.001 ± 0.0003	2.7 ± 1.1	2.4 ± 0.3
Erlotinib	-	-	-	0.03 ± 0.01	0.005 ± 0.002	17 ± 5	0.06 ± 0.02	313 ± 101	2.8 ± 0.3	8.1 ± 1.9	0.013 ± 0.001	0.016 ± 0.004	> 2
3	-H		-Me	34 ± 13	5.4 ± 0.3	3.8 ± 0.3	125 ± 51	37 ± 19	> 30	3.0 ± 0.3**	3.6 ± 1.4	2.1 ± 1.1	1.9 ± 0.6
4			-Me	23 ± 8	3.4 ± 1.2	29 ± 17	73 ± 18	265 ± 165	11.0 ± 0.4	n.d.	3.3 ± 1.0	3.8 ± 0.3	2.7 ± 0.8
5			-Me	5.2 ± 1.5	0.68 ± 0.10	15 ± 5	17 ± 9	156 ± 130	> 3	n.d.	1.9 ± 0.6	1.9 ± 0.1	3.5 ± 2.5
6			-Me	1.0 ± 0.2	0.17 ± 0.02	5.0 ± 2.5	1.6 ± 0.2	35 ± 24	8.0 ± 1.0	1.0 ± 0.1**	0.61 ± 0.32	0.61 ± 0.22	1.9 ± 0.4
7			-Me	0.053 ± 0.015	0.023 ± 0.014	0.69 ± 0.14	0.064 ± 0.029	8.8 ± 2.3	2.6 ± 0.7	9.1 ± 0.9**	0.081 ± 0.021	0.094 ± 0.054	0.90 ± 0.63
8			-Me	0.28 ± 0.21	0.12 ± 0.05	0.68 ± 0.37	0.15 ± 0.06	6.2 ± 2.3	1.4 ± 0.1	3.4 ± 1.1**	0.23 ± 0.11	0.23 ± 0.04	n.d.
9			-Me	0.35 ± 0.07	0.077 ± 0.005	1.3 ± 0.2	0.56 ± 0.15	12 ± 5	4.0 ± 0.2	1.6 ± 0.04**	0.41 ± 0.09	0.35 ± 0.12	1.8 ± 0.4
10			-Me	0.40 ± 0.09	0.13 ± 0.10	0.97 ± 0.28	0.42 ± 0.21	19 ± 6	3.7 ± 0.4	1.1 ± 0.2**	0.17 ± 0.03	0.20 ± 0.07	0.88 ± 0.41
11			-H	0.16 ± 0.04	0.097 ± 0.055	0.54 ± 0.15	0.32 ± 0.13	15 ± 6	3.9 ± 0.4	1.2 ± 0.3**	0.11 ± 0.02	0.11 ± 0.03	1.3 ± 0.1
12			-Acetyl	0.86 ± 0.24	0.36 ± 0.20	5.2 ± 0.6	3.0 ± 1.1	78 ± 10	3.9 ± 0.5	1.4 ± 0.01**	0.15 ± 0.06	0.22 ± 0.03	n.d.
13			-H	0.008 ± 0.001	0.007 ± 0.001	0.033 ± 0.002	0.020 ± 0.005	0.64 ± 0.20	1.8 ± 0.3	1.2 ± 0.1**	0.008 ± 0.002	0.007 ± 0.003	0.47 ± 0.17
23	-COOH		-Me	131 ± 15	32 ± 2	2089 ± 208	1336 ± 268	n.d.	> 30	n.d.	> 30	> 30	n.d.
24	$-NO_2$		-Me	21 ± 4	3.0 ± 0.3	2.5 ± 0.6	44 ± 12	138 ± 15	2.0 ± 0.4	n.d.	4.1 ± 0.3	4.0 ± 0.5	n.d
25	-Br		-Me	34 ± 10	3.9 ± 0.6	0.39 ± 0.29	52 ± 6	n.d.	3.1 ± 0.4	n.d.	5.2 ± 1.4	4.4 ± 0.2	n.d

#	R1	R2	R3	Wild type	L858R	L858R/T790M	L858R/C797S	L858R/T790M/ C797S	A431	Ba/F3 parental	Ba/F3-EGFR L858R	Ba/F3-EGFR L858R/C797S	Ba/F3-EGFR L858R/T790M /C797S
26	-CH_2OEt		-Me	172 ± 26	29 ± 16	180 ± 44	277 ± 31	2258 ± 800	11.4 ± 0.4	n.d.	3.9 ± 1.4	5.6 ± 1.2	n.d.
27			-Me	22 ± 6	3.7 ± 1.4	244 ± 78	27 ± 11	1767 ± 650	27 ± 4	n.d.	1.4 ± 0.4	1.7 ± 0.6	n.d.
28			-Me	285 ± 100	50 ± 32	942 ± 110	317 ± 175	n.d.	> 30	n.d.	0.70 ± 0.12	7.2 ± 1.7	n.d.
29			-Me	60 ± 12	14 ± 12	1887 ± 147	103 ± 23	n.d.	> 30*	n.d.	3.5 ± 1.9	3.6 ± 1.4	n.d.
30			-Me	0.95 ± 0.16	0.21 ± 0.12	3.2 ± 0.3	1.2 ± 0.5	38 ± 23	5.9 ± 1.4	n.d.	0.36 ± 0.09	0.29 ± 0.04	n.d.
31			-Me	15 ± 3	3.0 ± 1.7	3.8 ± 1.0	18 ± 5	32 ± 10	5.6 ± 0.7	n.d.	2.8 ± 1.1	3.0 ± 0.3	n.d.
32			-Me	6.7 ± 1.0	1.3 ± 0.5	26 ± 3	0.89 ± 0.07	29 ± 11	1.5 ± 0.02	n.d.	0.26 ± 0.10	0.37 ± 0.03	n.d.
33			-Me	3.2 ± 1.0	0.22 ± 0.06	11 ± 2	2.8 ± 0.5	159 ± 23	5.2 ± 0.5	n.d.	2.9 ± 0.2	1.2 ± 0.7	n.d.
34			-Me	57 ± 13	4.3 ± 0.2	65 ± 14	57 ± 13	1152 ± 315	7.1 ± 0.1	n.d.	2.3 ± 0.8	1.4 ± 0.9	n.d.
35			-Me	60 ± 24	8.9 ± 0.9	45 ± 11	98 ± 9	111 ± 47**	3.2 ± 0.2	n.d.	3.0 ± 0.1	2.5 ± 0.6	n.d.
36			-Me	19 ± 15	1.0 ± 0.5	89 ± 9	12 ± 2	930 ± 415**	4.7 ± 1.7	n.d.	3.8 ± 0.6	2.4 ± 0.7	n.d.
37			-Me	16 ± 4	4.8 ± 1.3	30 ± 3	62 ± 6	3114*	4.2 ± 1.0	n.d.	4.1 ± 1.0	2.4 ± 1.5	n.d.
38			-Me	16 ± 8	0.91 ± 0.32	589 ± 126	10 ± 1	n.d.	3.2 ± 0.5	n.d.	6.0 ± 2.3	3.3 ± 1.3	n.d.
39	-NH_2		-Me	13 ± 5	2.3 ± 0.5	14 ± 3	129 ± 38	470 ± 36	13.8 ± 2.3	n.d.	2.7 ± 0.4	3.1 ± 0.6	n.d.
40			-Me	452 ± 175	90 ± 66	2037 ± 564	744 ± 143	15834 ± 3702	8.7 ± 1.1	n.d.	4.2 ± 0.1	5.8 ± 0.2	n.d.
41			-Me	241 ± 193	60 ± 43	8048 ± 4105	178 ± 128	n.d.	7.6 ± 2.3	n.d.	4.5 ± 0.2	4.3 ± 0.7	n.d.
42			-Me	435 ± 226	137 ± 60	1514 ± 742	1063 ± 360	17921 ± 1956	3.3 ± 0.8	n.d.	3.2 ± 0.5	2.1 ± 0.7	n.d.
43			-Me	82 ± 70	13 ± 6	306 ± 84	76 ± 11	n.d.	5.7 ± 1.2	n.d.	4.3 ± 1.6	4.5 ± 2.0	n.d.

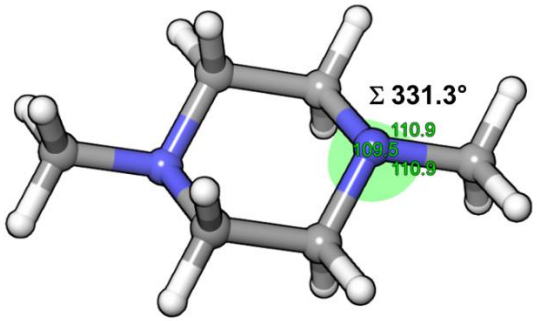
#	R1	R2	R3	Wild type	L858R	L858R/T790M	L858R/C797S	L858R/T790M/ C797S	A431	Ba/F3 parental	Ba/F3-EGFR L858R	Ba/F3-EGFR L858R/C797S	Ba/F3-EGFR L858R/T790M /C797S
44			-Me	0.60 ± 0.18	0.11 ± 0.01	16 ± 3	2.7 ± 0.9	128 ± 26	13.3 ± 1.9	n.d.	2.4 ± 0.7	3.0 ± 0.4	n.d.
45			-Me	9.6 ± 3.4	1.1 ± 0.3	20 ± 4	21 ± 2	141 ± 50	7.8 ± 1.1	n.d.	2.9 ±0.2	3.5 ± 0.5	n.d.
46			-Me	10 ± 4	1.4 ± 0.1	63 ± 11	12 ± 1	n.d.	22 ± 5	n.d.	2.0 ± 0.2	1.6 ± 0.3	n.d.
47			-Me	9.1 ± 2.6	1.3 ± 0.1	49 ± 10	23 ± 5	n.d.	> 30	n.d.	2.2 ± 0.4	2.1 ± 0.5	n.d.
48			-Me	3.2 ± 0.9	0.48 ± 0.05	17 ± 3	8.2 ± 1.3	n.d.	> 30	n.d.	1.8 ± 0.2	2.4 ± 0.5	n.d.
49			-Me	4.5 ± 1.0	0.67 ± 0.15	18 ± 3	3.8 ± 0.5	141 ± 50	8.1 ± 1.1	n.d.	2.1 ± 0.2	2.2 ± 0.7	n.d.
50			-Me	2.0 ± 0.4	0.28 ± 0.02	10 ±1	4.8 ± 0.5	n.d.	27 ± 3	n.d.	0.70 ± 0.06	1.0 ± 0.2	n.d.
51			-Me	0.57 ± 0.08	0.13 ± 0.02	2.0 ± 0.2	0.94 ± 0.27	32 ± 8	3.1 ± 0.1	n.d.	0.43 ± 0.04	0.40 ± 0.14	n.d.
52			-Me	0.26 ± 0.03	0.063 ± 0.008	0.91 ± 0.12	0.51 ± 0.14	20 ± 4	5.2 ± 1.2	n.d.	0.18 ± 0.07	0.25 ± 0.05	n.d.
55			-H	3.7 ± 0.4	0.48 ± 0.21	3.4 ± 1.0	9.3 ± 0.5	81 ± 28	3.9 ± 0.5	n.d.	0.76 ± 0.19	0.52 ± 0.08	n.d.
57			-H	0.84 ± 0.13	0.17 ± 0.02	7.4 ± 2.1	2.1 ± 0.4	89 ± 7	3.7 ± 0.3	n.d.	1.1 ± 0.3	0.56 ± 0.29	n.d.
58			-H	3.8 ± 0.4	0.64 ± 0.03	12 ± 2	9.8 ± 1.0	187 ± 97	11.9 ± 1.3	n.d.	0.91 ± 0.41	0.61 ± 0.10	n.d.
59			-H	3.3 ± 0.9	0.60 ± 0.04	12 ± 2	5.7 ± 0.7	171 ± 37	7.5 ± 0.3	n.d.	2.0 ± 0.5	1.8 ± 0.9	n.d.
60			-H	0.097 ± 0.018	0.027 ± 0.003	0.60 ± 0.19	0.30 ± 0.03	n.d.	3.0 ± 0.6	1.3 ± 0.04**	0.28 ± 0.10	0.19 ± 0.12	0.85 ± 0.29
61			-H	0.016 ± 0.002	0.011 ± 0.004	0.036 ± 0.005	0.044 ± 0.012	n.d.	1.7 ± 0.2	1.3 ± 0.06**	0.024 ± 0.009	0.014 ± 0.006	0.32 ± 0.13

n.d. = not determinded, * single measurement, ** double measurement.

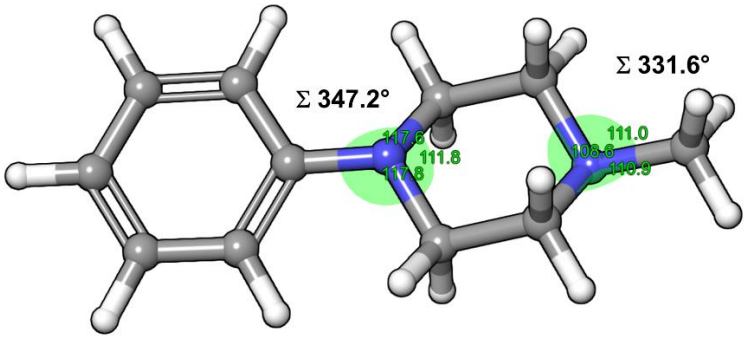
7. Quantum chemical calculations to confirm coordinates of the solubility group

Table S3: Optimized geometries, selected bond angles and sum of these bond angles for model systems of solubilizing groups. a1) and a2): Model systems of solubilizing groups in compounds **3**-**8**, b1)/b2) compound **9**, c1)/c2) **10**-**13**, and d1)/d2) **1** and **2**.

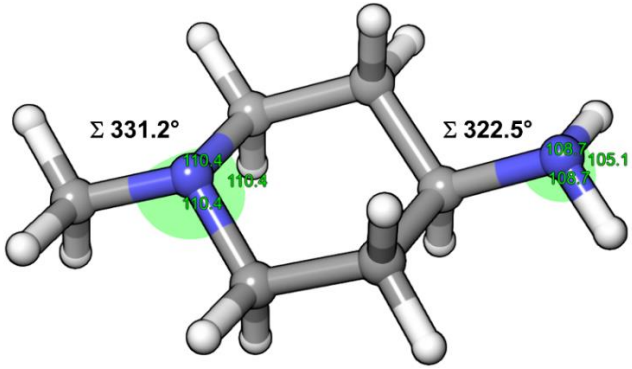
a1)



a2)



b1)



b2)

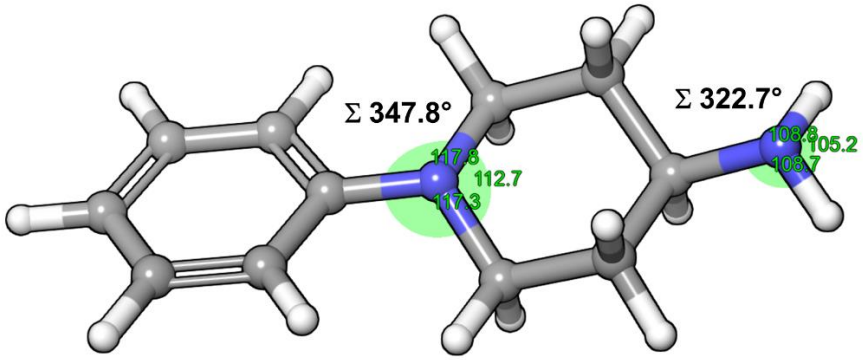
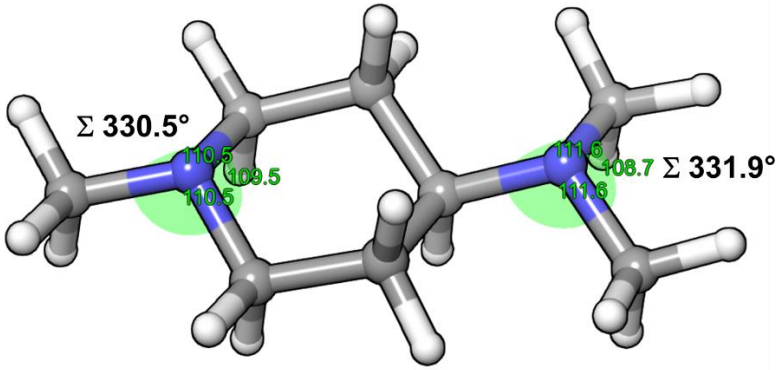
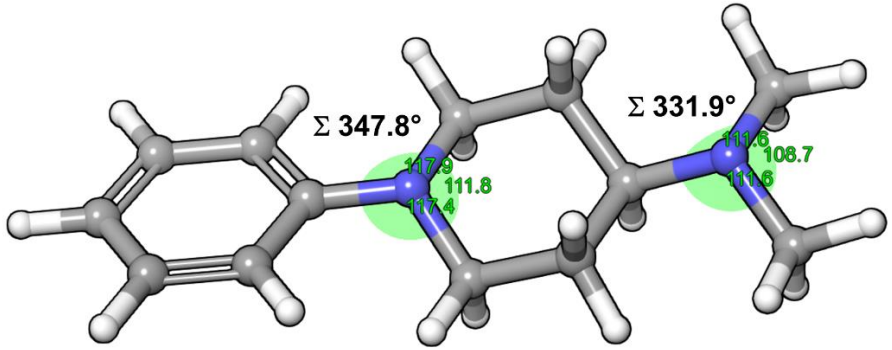


Table S3. continued:

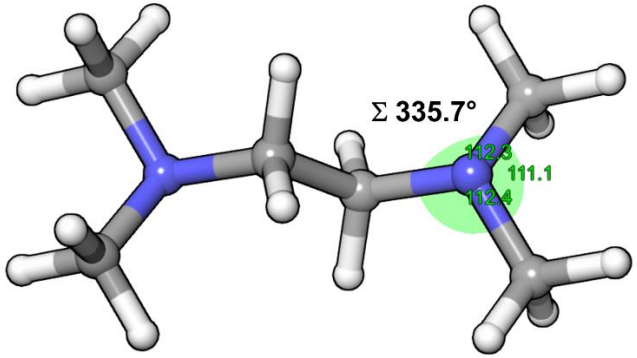
c1)



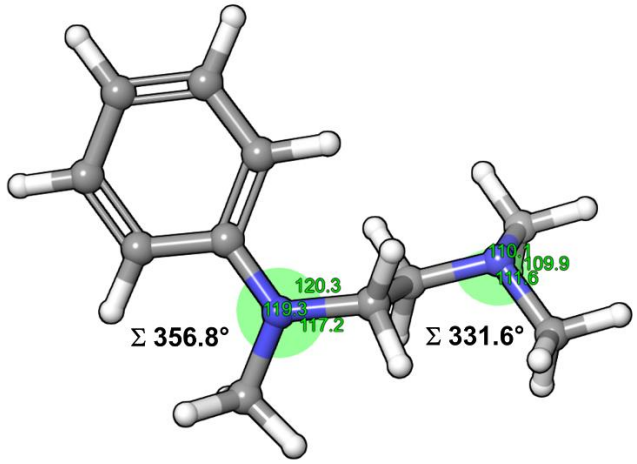
c2)



d1)



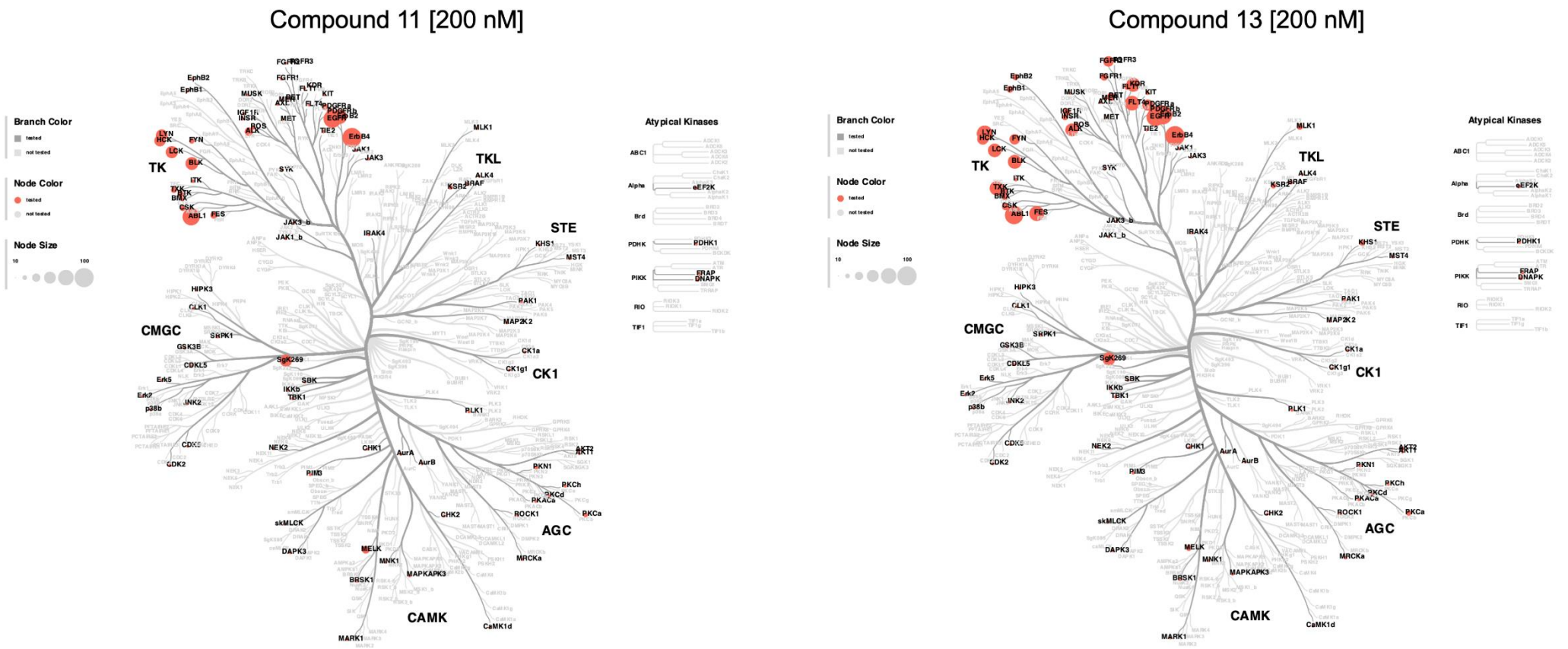
d2)



When fitting models to the electron densities obtained from x-ray crystallography, we found that parametrization with phenix.elbow (P.D. Adams, P.V. Afonine, G. Bunkoczi, V.B. Chen, I.W. Davis, N. Echols, J.J. Headd, L.W. Hung, G.J. Kapral, R.W. Grosse-Kunstleve, A.J. McCoy, N.W. Moriarty, R. Oeffner, R.J. Read, D.C. Richardson, J.S. Richardson, T.C. Terwilliger, P.H. Zwart, Acta Cryst 2010, D66, 213-221) led to unreasonably planar, sp2-like configuration of aliphatic nitrogen atoms in the pyridazine and piperidine solubilizing groups of the ligands. That planar arrangements of these nitrogen atoms must be considered numerical artifacts is already clear when comparing to high resolution X-structures as available from the Cambridge Crystallographic Database CSD [C. R. Groom, I. J. Bruno, M. P. Lightfoot and S. C. Ward, Acta Cryst. (2016). B72, 171-179] (data not shown, see for instance CSD structures with CSD-codes BAPLIQ or BEJMEJ in which the sum over all C-N-C angles is approximately 340°). To confirm the sp3 nature of the N-atoms for our systems at hand, we performed geometry optimizations for model systems representing ligands **1**-**13**, the results are summarized in Table S-3. With the exception of the phenyl-substituted open structure d2), the sums over the C-N-C angles strongly deviate from planarity (i.e. 360°), by at least ~12°, thus confirming significant sp3 character of the respective N-atoms in the solubilizing moieties. In the case of model system d2, the anilinic nitrogen comes very close to the ideal sp2-planarity, deviating by just 3° from 360°. However, note that after formally opening the piperazine ring, the relative highly flexible sidechain does not easily reside in a ring-like conformation. Compared to the closed piperazine ring in model system a2, the distance of the two nitrogen atoms in the relaxed geometry d2) is larger by almost 1 Å (3.8 Å as compares to 2.9Å).

Computational details: Molecular geometries were prepared using Maestro 13.1 [Schrödinger Release 2022-2: Maestro, Schrödinger, LLC, New York, NY, 2021]. Quantum chemical calculations were carried out using the ORCA 5.0 suite of programs, as set forth in the below [Neese, Frank (2012). "The ORCA program system". Wiley Interdisciplinary Reviews: Computational Molecular Science. 2 (1): 73–78. doi:10.1002/wcms.81.; Neese, Frank (2018). "Software update: The ORCA program system, version 4.0". Wiley Interdisciplinary Reviews: Computational Molecular Science. 8 (1): e1327. doi:10.1002/wcms.132]. Visualization and analysis of results were again carried out in Maestro. Molecular geometries were optimized at B3LYP level of theory [A.D. Becke, J.Chem.Phys. 98 (1993) 5648-5652, C. Lee, W. Yang, R.G. Parr, Phys. Rev. B 37 (1988) 785-789, S.H. Vosko, L. Wilk, M. Nusair, Can. J. Phys. 58 (1980) 1200-1211, P.J. Stephens, F.J. Devlin, C.F. Chabalowski, M.J. Frisch, J.Phys.Chem. 98 (1994) 11623-11627], with an Ahlrichs def2-TZVP(-F) basis set [Jankowski, K.; Becherer, R.; Scharf, P.; Ahlrichs, R. The impact of higher polarization basis functions on molecular ab initio results. J. Chem. Phys.1985, 82, 1413−1419]. To mimic solvent effects in water, optimizations employed the CPCM model [V.Barone and M. Cossi, Quantum Calculation of Molecular Energies and Energy Gradients in Solution by a Conductor Solvent Model, J. Phys. Chem. A 1998, 102, 11, 1995–2001] (with a COSMO [Klamt, A.; Schürmann, G. COSMO: A new approach to dielectric sreening in solvents with explicit expressions for the screening energy and its gradient. J. Chem. Soc., Perkin Trans.1993, 2, 799−805] epsilon function). To better describe non-bonded weak interactions, Grimme's D3 correction[S.Grimme, S.Ehrlich, L.Goerigk, J Comput Chem, (2011), 32, 1456–1465; S.Grimme, J.Antony, S.Ehrlich and H.Krieg, J.Chem.Phys., 132, (2010), 154104] was used throughout all calculations.

8. Kinome-Selectivity Panel



Supplementary Figure S2: Kinome Selectivity Screening from ThermoFisherScientific – SelectScreen Z'Lyte™ Biochemical Kinase Profiling Service. %-Inhibition measured at 200 nM concentration of compound **11** (left) and compound **13** (right). Kinome Panel prepared with CORAL (Phanstiel-Lab, https://doi.org/10.1016/j.cels.2018.07.001).

Table S4: Kinome Selectivity Screening from ThermoFisherScientific – SelectScreen Z'Lyte™ Biochemical Kinase Profiling Service. %-Inhibition measured at 200 nM compound concentration. Inhibition above 40% is highlighted in red, and inhibition above 80% is highlighted in bold red.

Kinase	Compound 11 [%-Inhibition at 200 nM]	Compound 13 [%-Inhibition at 200 nM]
ABL1	**88**	**94**
ACVR1B (ALK4)	0	5
ADRBK1 (GRK2)	5	2
AKT1 (PKB alpha)	5	10
AKT2 (PKB beta)	14	16
ALK	40	64
AURKA (Aurora A)	10	8
AURKB (Aurora B)	7	7
AXL	4	8
BLK	64	70
BMX	17	23
BRAF	13	16
BRSK1 (SAD1)	5	7
BTK	28	43
CAMK1D (CaMKI delta)	6	7
CDC42 BPA (MRCKA)	7	13
CDK2/cyclin A	11	10
CDK5/p25	1	3
CDKL5	12	8
CHEK1 (CHK1)	9	14
CHEK2 (CHK2)	3	7
CLK1	2	4
CSK	24	33
CSNK1A1 (CK1 alpha 1)	5	9
CSNK1G1 (CK1 gamma 1)	5	4
DAPK3 (ZIPK)	3	5
DNA-PK	14	16
EEF2K	12	13
EGFR (ErbB1) C797S	78	**93**
EGFR (ErbB1) L858R	**84**	**90**
EGFR (ErbB1) T790M C797S	74	**92**
EGFR (ErbB1) T790M L858R	**90**	**93**
EGFR (ErbB1) T790M	**93**	**97**
EGFR (ErbB1)	**91**	**91**
EPHB1	11	31
EPHB2	7	28
ERBB2 (HER2)	74	**98**
ERBB4 (HER4)	**99**	**101**
FES (FPS)	32	76
FGFR1	12	33
FGFR2	4	51
FGFR3	2	5
FLT1 (VEGFR1)	5	30
FLT4 (VEGFR3)	7	74
FRAP1 (mTOR)	3	2
FYN	23	51
GSK3B (GSK3 beta)	6	9
HCK	56	56
HIPK3 (YAK1)	3	4
IGF1R	11	34

Kinase	Compound 11 [%-Inhibition at 200 nM]	Compound 13 [%-Inhibition at 200 nM]
IKBKB (IKK beta)	6	6
INSR	10	26
IRAK4	10	8
ITK	13	14
JAK1	2	4
JAK3	2	0
KDR (VEGFR2)	9	70
KIT	6	15
KSR2	19	24
LCK	60	68
LYN A	58	**80**
MAP2K2 (MEK2)	2	5
MAP3K9 (MLK1)	8	27
MAP4K5 (KHS1)	7	24
MAPK1 (ERK2)	2	5
MAPK11 (p38 beta)	10	11
MAPK14 (p38 alpha) Direct	8	26
MAPK3 (ERK1)	3	6
MAPK7 (ERK5)	8	3
MAPK9 (JNK2)	-2	5
MARK1 (MARK)	7	9
MELK	36	25
MERTK (cMER)	5	-2
MET (cMet)	6	8
MKNK1 (MNK1)	7	8
MST4	10	11
MUSK	8	11
MYLK2 (skMLCK)	5	9
NEK2	5	8
PAK1	6	9
PDGFRA (PDGFR alpha)	28	55
PDGFRB (PDGFR beta)	35	44
PDK1 Direct	0	-3
PEAK1	59	64
PIM3	10	9
PKN1 (PRK1)	13	7
PLK1	1	3
PRKACA (PKA)	10	9
PRKCA (PKC alpha)	19	22
PRKCD (PKC delta)	5	4
PRKCH (PKC eta)	5	8
RET	7	39
ROCK1	-1	-1
ROS1	16	26
SBK1	4	4
SRPK1	9	9
SYK	6	4
TBK1	11	12
TEK (Tie2)	13	9
TXK	27	72