Supporting information for

Discovery and optimisation of pyrazolo[1,5-a]pyrimidines as aryl hydrocarbon receptor antagonists

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1 Additional data

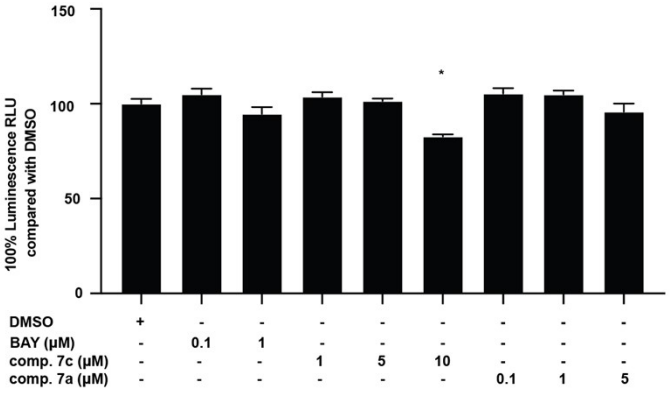


Figure SI1. Select AHR antagonists have minimum effects on cell viability. Cell viability of HuH-7 cells treated with different concentrations of AHR antagonists for 4 days. Cell viability was determined using celltiter Glo assays. Data are shown as mean ± s.e.m. of n = 3 biological replicates.

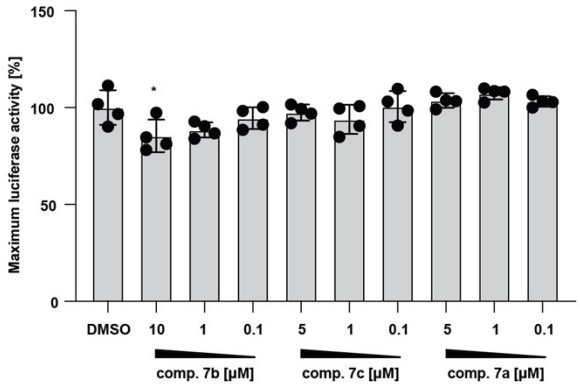


Figure SI2. Inhibition of luciferase catalytic activity. HuH7 cells were transfected with pGL4.51[luc2/CMV/Neo] and CMV-regulated luciferase-expressing plasmid for 24 h. Cells were lysed and the lysate containing luciferase was incubated for 30 min with tested compounds or vehicle (DMSO). The bar graph shows the percentage of luciferase activity relative to control (vehicle). Data are presented as mean ± SD from three independent replicates (n=3).

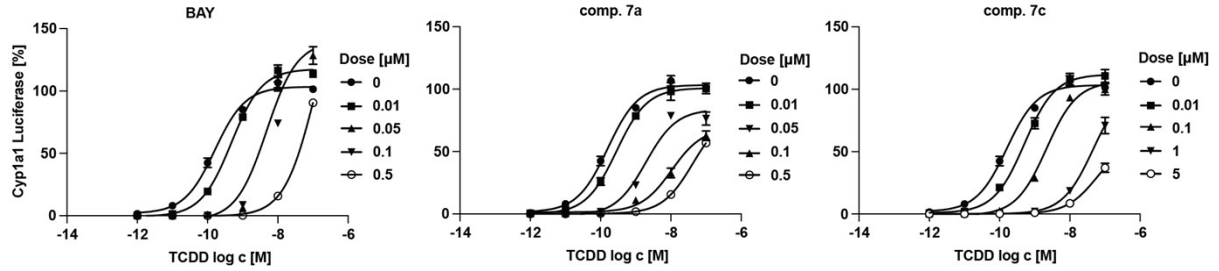


*Figure SI3. Antagonism of AHR by BAY2416964 (BAY), comp. **7a** and **7c**. Transfected HuH-7 cells were incubated with combinations of with a fixed concentration of antagonists (BAY2416964, comp. **7a** and **7c**) and TCDD for 20 h. These data reveal that all three compounds act as competitive antagonists. Data are shown as mean ± s.e.m. of n = 3 biological replicates.*

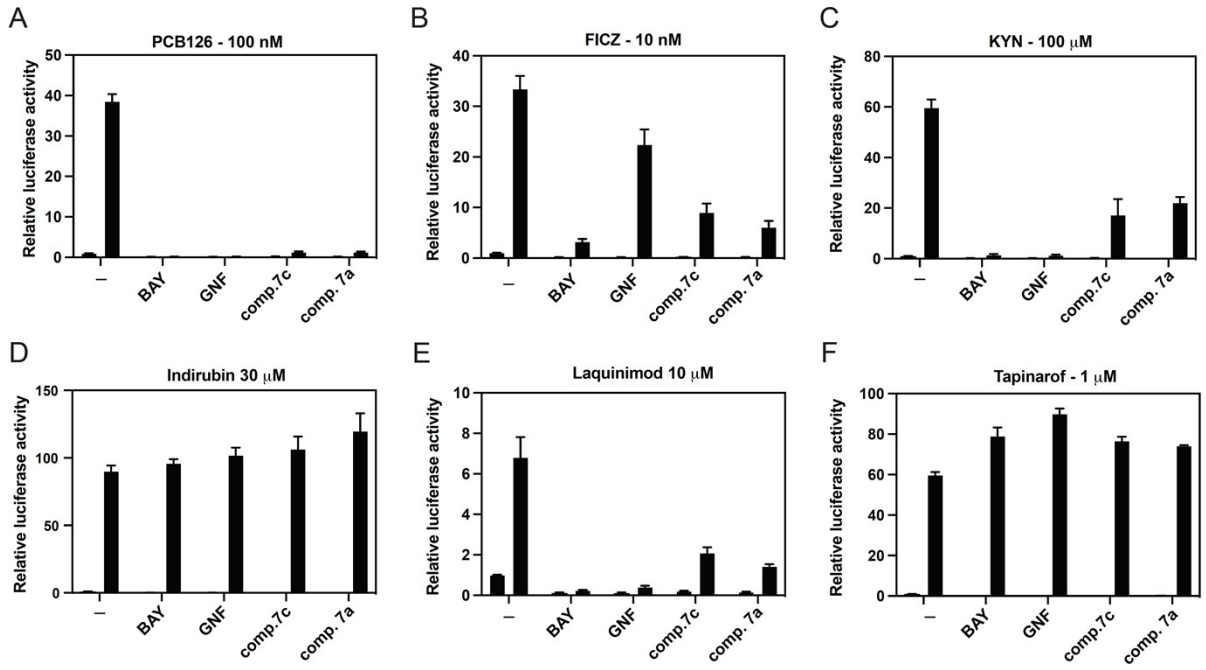
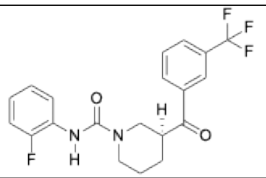
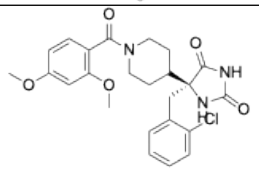
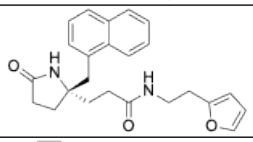
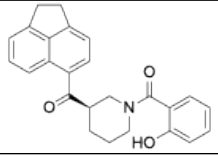
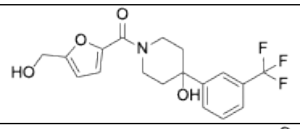
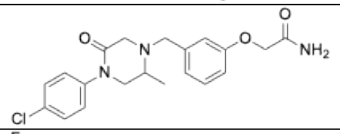
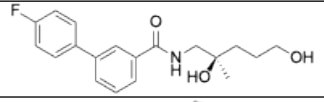
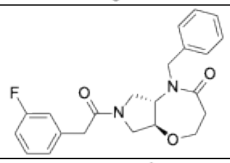
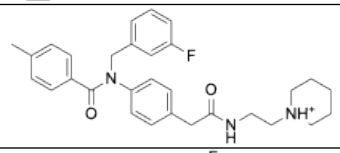
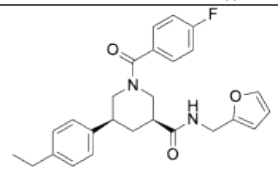
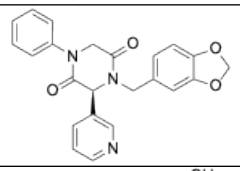
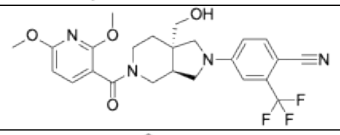
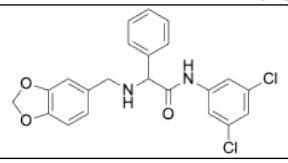
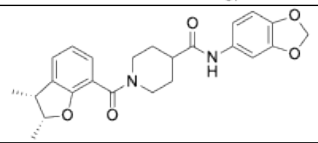
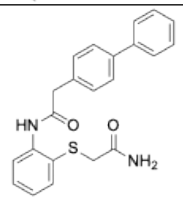
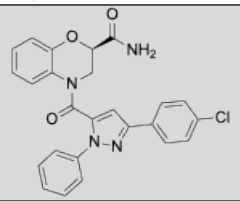
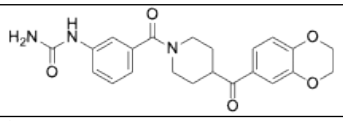
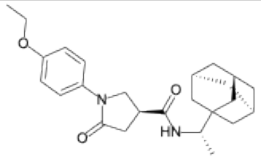
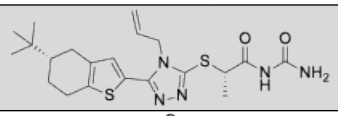
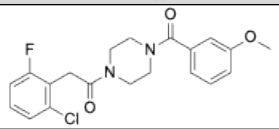
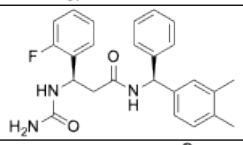
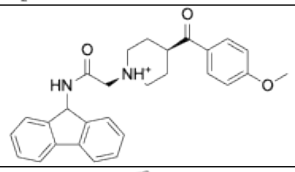
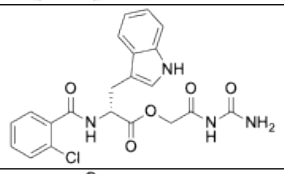
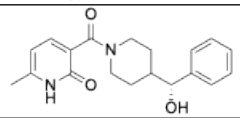
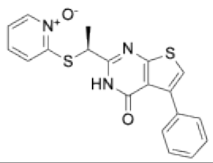
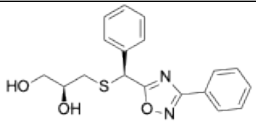
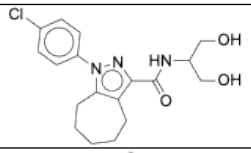
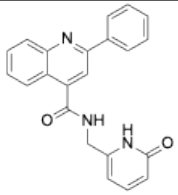
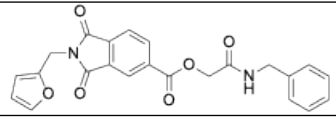


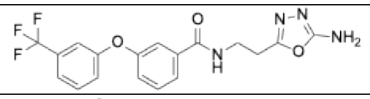
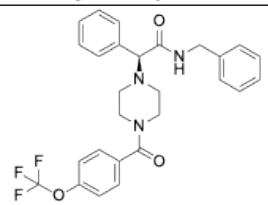
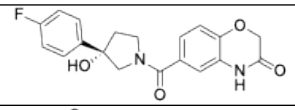
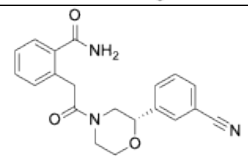
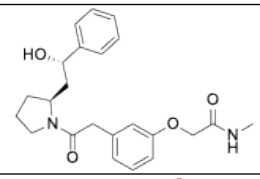
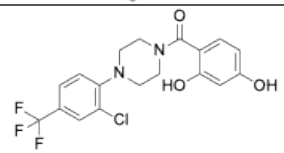
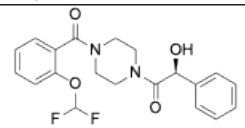
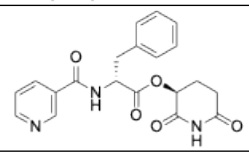
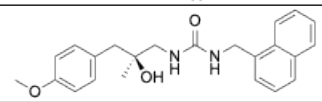
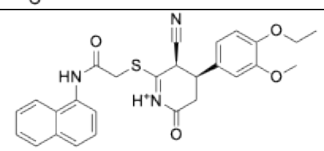
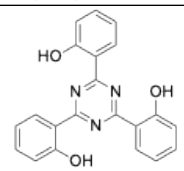
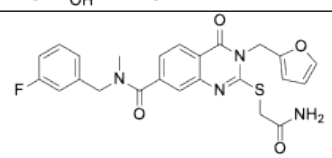
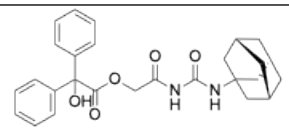
*Figure SI4. AHR antagonists differentially inhibit structurally diverse AHR agonists. HuH-7 cells were transfected as described in materials and methods and treated for 20 h with the indicated doses of structurally diverse AHR agonists in the presence or absence of 1 μM BAY2416964 (BAY), GNF351 (GNF), comp. **7a** or **7c**. Data are shown as mean ± s.e.m. of n = 3 biological replicates.*

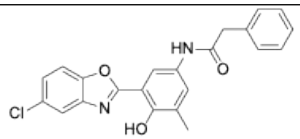
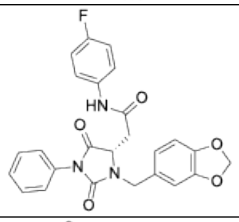
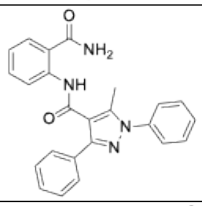
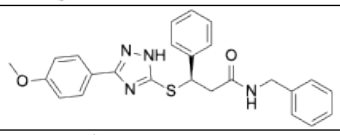
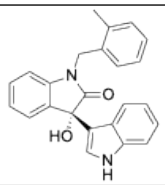
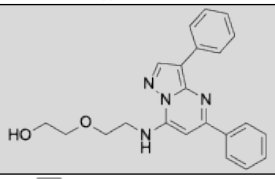
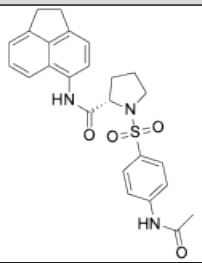
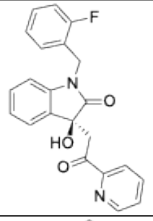
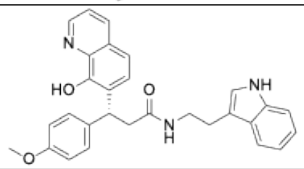
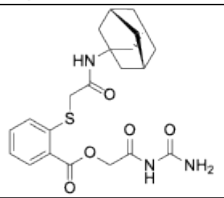
Table SI1. Measured AHR activity of virtual screening hits and reference compounds. AHR activity (in % with respect to untreated AHR) was measured in the presence of 25 μM compound and in the presence of 25 μM compound in combination with 10 nM AHR agonist TCDD.

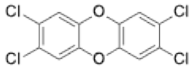
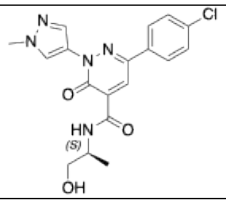
No	**Molport ID (Vendor ID)**	**Structure**	**AHR activity in the presence of 25 μM compound, %**	**AHR activity in the presence of 10 nM AHR agonist TCDD and 25 μM compound, %**
1	MolPort-005-024-151 (19151294)		5.2±0.4	52±2
2	MolPort-005-049-091 (29133790)		16.25±0.16	93.7±0.8
3	MolPort-005-164-569 (99074978)		11.4±0.5	107±2
4	MolPort-020-201-429 (40144815)		16±2	56.2±0.7

5	MolPort-021-769-244 (77393003)		6.4±0.4	90.3±1.6
6	MolPort-023-329-719 (99432551)		19.8±0.7	79±4
7	MolPort-039-219-881 (44571204)		23.4±1.8	107±6
8	MolPort-047-527-265 (51216576)		6.1±0.4	97.4±0.5
9	MolPort-006-592-195 (V022-6060)		42±3	91±7
10	MolPort-006-604-851 (V017-9980)		7.2±0.6	50±2
11	MolPort-010-946-911 (T413-2887)		36.4±1.4	96±3
12	MolPort-046-603-167 (S948-5007)		35.8±0.7	59±2
13	MolPort-004-029-927 (Z44489993)		29±2	69.41±0.00
14	MolPort-004-157-611 (Z146228738)		14.4±0.3	68.43±0.18
15	MolPort-005-552-654 (Z91114709)		43±2	64.1±1.3
16	MolPort-005-623-396 (Z28777212)		38±5	23.6±1.8

17	MolPort-005-691-740 (Z232011892)		4.37±0.00	73.16±0.00
18	MolPort-005-874-766 (Z26510884)		7.81±0.19	86±2
19	MolPort-009-238-731 (Z17466857)		1.4±0.9	21±4
20	MolPort-009-259-389 (Z316629048)		1.27±0.15	101±5
21	MolPort-009-283-970 (Z356645216)		10.2±0.3	85±6
22	MolPort-009-623-146 (Z229450066)		2.70±0.13	58±5
23	MolPort-009-939-126 (Z18937604)		86.7±0.6	62.4±1.0
24	MolPort-019-661-699 (Z642334286)		7.1±0.9	105±5
25	MolPort-027-711-887 (Z18546375)		24.5±0.5	113±7
26	MolPort-027-904-216 (Z1363088827)		10.0±1.6	105±7
27	MolPort-027-933-161 (Z1574523376)		7.5±0.8	115±5
28	MolPort-028-793-158 (Z1610478325)		14.14±1.06	93±3
29	MolPort-028-806-928 (Z16725709)		11.4±1.8	81.4±0.4

30	MolPort-035-848-560 (Z1820365879)		5.4±0.4	96.4±0.6
31	MolPort-038-980-924 (Z2006089628)		32.0±1.6	112.6±0.4
32	MolPort-044-445-019 (Z1610730473)		29.8±0.4	108±8
33	MolPort-044-456-442 (Z1851718509)		9±6	127±5
34	MolPort-046-432-405 (Z1474170243)		11.9±1.1	97.9±1.2
35	MolPort-046-452-452 (Z2092607227)		16.6±0.5	56±5
36	MolPort-046-718-587 (Z1312807648)		6.6±0.9	94±5
37	MolPort-046-895-949 (Z1985588874)		7.4±0.3	93.3±1.7
38	MolPort-023-201-602 (F5857-4160)		15±2	43.4±0.4
39	MolPort-000-785-444 (PHAR118748)		53±9	85.6±0.7
40	MolPort-035-717-384 (ST103005)		105±2	96±4
41	MolPort-004-129-581 (PB120069862)		28±2	57±6
42	MolPort-004-669-539 (PB15592620)		15±7	76±8

43	MolPort-000-859-994 (STK319859)		33±2	86±5
44	MolPort-001-587-677 (STK130729)		27.4±1.3	121±9
45	MolPort-001-641-108 (STK301846)		35.3±0.4	124±8
46	MolPort-001-730-226 (STK807698)		18.57±0.10	38±4
47	MolPort-002-000-883 (STK053588)		24±2	45±7
48	MolPort-002-650-228 (STK848347)		1.3±0.5	1.0±0.5
49	MolPort-002-730-043 (STK231337)		5.6±0.2	34±2
50	MolPort-002-981-074 (STK237361)		25.8±1.0	49±6
51	MolPort-046-853-741 (STL561654)		6.7±1.2	71±3
52	MolPort-028-806-139 (PB15781798)		49±8	46±8

	Dimethyl sulfoxide (DMSO) *(Solvent control)*		2.5±0.3	
	2,3,7,8-tetrachlorodibenzo para dioxin (TCDD) *(AHR agonist)*		100±2	
	BAY 2416964 *(Positive control)*		0.28±0.14	0.38±0.01

2 Methods

2.1 Homology modelling

Since no crystal structure of human AHR PAS-B domain homology model was available at the beginning of the project, homology model used in structure-based drug design was constructed using HIF-2α (hypoxia-inducible factor) PAS-B domain in complex with a tetrazole-containing antagonist as a template (PDB: 4XT2). The selected template has 26% identity and 51% similarity to the human AHR PAS-B domain sequence. The homology model was generated using the Schrodinger Maestro software package[1]. Multiple sequence alignment was performed using Muscle[2] and the model was built using a knowledge-based homology modelling tool. The loops of the obtained homology models were refined using Prime[3]. The homology model obtained had a backbone atom rmsd of 1.8 Å to the agonist-bound AHR structure that became available recently[4].

2.2 Molecular docking

Potential AHR PAS-B domain binders were identified *via* high throughput virtual screening (HTVS) of MolPort commercially available compound library (~6.3M comp., 2021) against the homology model created. MolPort in-stock drug-like compound library was prepared using LigPrep[5] by desalting the molecules, generating possible tautomers and ionisation states at pH 7.0±2.0. The stereochemistry of the compounds was retained as specified in the library.

The prepared library was docked in the homology model created. The homology model was prepared for docking using Maestro Protein Preparation Wizard by optimising loops using Prime, adjusting side chain protonation states at pH 7.0, and minimising heavy atoms with convergence up to 0.30 Å. Molecular docking was performed using Glide[6], with scaling of the van der Waals radii set to 0.9 for protein and ligand heavy atoms, and docking compounds flexibly. The top-scoring 5000 compounds were clustered into 300 representative compounds by calculating the Linear Fingerprints from Daylight invariant atom types and evaluating compound similarity using Tanimoto similarity metrics. The top-scoring compound was retained for each cluster. The top-ranked 300 representative compounds for each homology model were visually inspected for their ability to form hydrogen bonds similar to those established by the co-crystallised ligand, with molecules showing internal strains or unsatisfied hydrogen bond donors being deprioritised. A total of 52 compounds were selected and purchased from MolPort. Docked poses were visualised using PyMOL[7].

2.3 Luciferase Reporter Gene Assay

HuH-7 cells, human hepatoma cells, were plated on 24-well dishes at a density of 8.0×10^4 cells with 1 mL media per well. The following day, each well was transfected with 1 µL Lipofectamine 2000 and 1 µg DNA consisting of 350 ng pGudLuc 4.1, 100 ng pRenilla, and 50 ng pEGFP. pGudLuc 4.1 is an AHR-driven reporter construct containing a luciferase gene downstream of the *Cyp1a1* promoter. After 6 hours, the cells were treated with either DMSO, 10 nM TCDD alone or in combination with test compounds (0.001 to 10 µM). For the mechanism of antagonism studies cells were treated with increasing concentrations of TCDD alone or in

combination with increasing concentrations of test compounds. For AHR agonist screening, transfected cells were treated with DMSO, 100 nM PCB126, 10 nM FICZ, 100 µM kynurenine, 30 µM indirubin, 10 µM laquinimod or 1 µM tapinarof. After a 20-hour incubation, the cells were lysed, and the luciferase activity was measured using Dual luciferase assay and normalised to Renilla activity.

2.4 Celltiter Glo assay

CellTiter-Glo® assay (Promega G7571) was used to assess cell viability following exposure of HuH-7 cells to different concentrations of AHR antagonists. HuH-7 cells, human hepatoma cells, were plated in 96-well dishes at a density of 2.0×10^3 cells per well. The following day the cells were treated with increasing concentrations of BAY2416964, GNF351, comp. **7a** and **7c**. Plates were incubated at 37 °C for 4 days after which CellTiter-Glo® Substrate and CellTiter-Glo® Buffer were mixed to produce CellTiter-Glo® Reagent which was added in a 1:1 ratio to the wells (50 µL). The plate was then incubated on a rocker for 20 minutes (protected from light) at room temperature. Luminescence was measured using the Synergy H1 (Biotek).

2.5 Western blot

HuH-7 cells were plated in 6-well dishes at a density of 2.0×10^5 cells per well. The next morning, cells were treated with DMSO or 1 µM of BAY2416964, GNF351, comp. **7a** and **7c**. After 24 h incubation, the cells were harvested and lysed using 10 mM Tris-Cl buffer containing 1 mM EDTA and 1% SDS, with pH of 8.0. Samples were sonicated at low intensity for 2×30 seconds on/off. Protein concentration was measured using Pierce™ BCA Protein Assay Kit (Thermofischer Scientific) according to the manufacturer's instructions. Twenty µg of protein were separated on a 4-20% SDS-PAGE gel and transferred to a polyvinylidene fluoride (PVDF) membrane. The membranes were incubated with primary antibodies dissolved in 5% skim milk over night at 4 °C, following appropriate secondary antibodies for 1 hour at room temperature. Protein bands were visualised with SuperSignal™ West PICO or DURA extended Duration Substrate.

2.6 Inhibition of luciferase catalytic activity

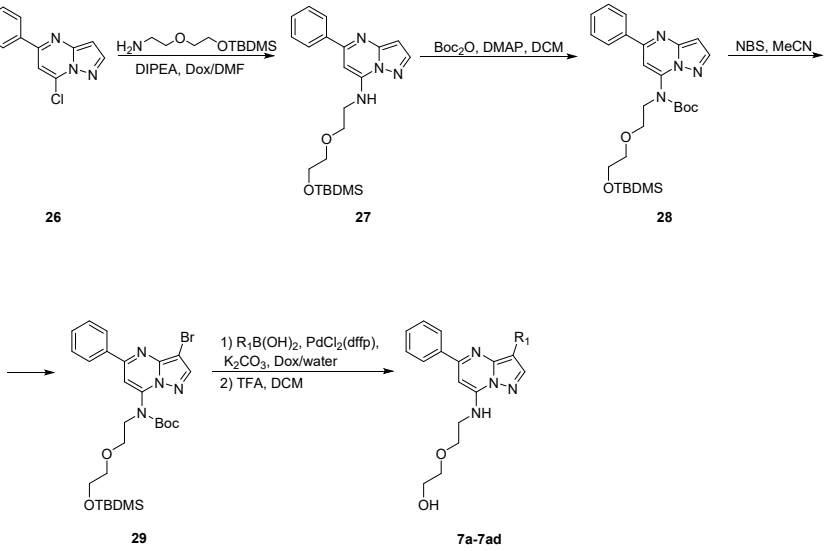
HuH-7 cells were transiently transfected with 350 ng of pGL4.51[luc2/CMV/Neo], 100 ng pRenilla, and 50 ng pEGFP. The following morning cells were lysed and the lysate containing luciferase was incubated for 30 min with test compounds or vehicle (control). Luciferase activity was measured using Dual luciferase assay and normalised to Renilla activity.

2.7 Organic synthesis

2.7.1 General Experimental Procedures

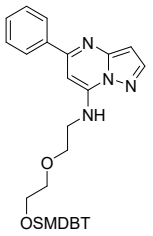
The NMR spectra were recorded on Varian 400-MR instruments (working frequencies 400 and 100 MHz for ^{1}H and ^{13}C, respectively) and 300-MR instruments (working frequencies 300 for ^{1}H) with the residual signals of the protons of DMSO (2.50 ppm for ^{1}H-NMR and 39.52 ppm for ^{13}C-NMR), of $CHCl_3$ (7.26 ppm for ^{1}H-NMR and 77.16 ppm for ^{13}C-NMR) and of MeOH (3.31 ppm for ^{1}H-NMR and 49.00 ppm for ^{13}C-NMR) as internal standards. Chemical shifts (δ) are expressed in ppm and coupling constants (*J*) are given in Hz. The low-resolution mass spectra were obtained with an Acquity UPLC liquid chromato-mass spectrometer of the (Wasters)-Q-TOF (Micromass) system with an Acquity UPLC BEH C18 chromatographic column (1.7 µm, 2.1×50 mm), gradient elution MeOH–HCOOH (0.1%) in water, ESI ionization, for positive and negative ions. The purity of the compounds was determined by HPLC on a Waters Alliance 2695 liquid chromatograph with a Waters 2489 UV/Vis detector, an Apollo C18 column or Adamas column (5 µm, 4.6×150 mm), and gradient elution with MeCN–0.1% H_3PO_4 in water. All compounds are >95% pure by HPLC analysis.

2.7.2 The general procedure of 2-(2-((3-aryl-5-phenylpyrazolo[1,5-a]pyrimidin-7-yl)amino)ethoxy)ethan-1-ole preparation



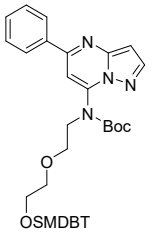
Scheme 1.

2.7.2.1 Synthesis of N-(2-(2-((tert-butyldimethylsilyl)oxy)ethoxy)ethyl)-5-phenylpyrazolo[1,5-a]pyrimidin-7-amine (27)



7-Chloro-5-phenylpyrazolo[1,5-a]pyrimidine (**26**, 1.2 g, 5.2 mmol) was suspended in the mixture of Dox (35 mL) and DMF (3 mL) followed by addition of DIPEA (3.6 mL, 4 eq) and 2-(2-((tert-butyldimethylsilyl)oxy)ethoxy)ethan-1-amine (1.7 g, 1.5 eq). The reaction mixture was stirred by reflux for 18h, and then cooled to RT. The solvent was removed to give an oily residue that was dissolved in EtOAc (50 mL). The obtained solution was washed with brine (2x15 mL), dried over Na_2SO_4 and the solvent was removed to give oil that was purified by column chromatography (EtOAc/PE 1:2) to afford the desired product **27** as colorless oil (1.1 g , yield 50%).
^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.06-7.98 (m, 3H), 7.52-7.41 (m, 3H), 6.67 (t, *J* = 5.4 Hz, 1H), 6.55 (d, *J* = 2.3 Hz, 1H), 6.38 (s, 1H), 3.85 (t, *J*= 5.4 Hz, 2H), 3.82-3.77 (m, 2H), 3.67 (t, *J*= 5.4 Hz, 2H), 3.64-3.59 (m, 2H), 0.88 (s, 9H), 0.06 (s, 6H). MS: 413.3 $[M+H]^+$.

2.7.2.2 Synthesis of tert-butyl (2-(2-((tert-butyldimethylsilyl)oxy)ethoxy)ethyl)(5-phenylpyrazolo[1,5-a]pyrimidin-7-yl)carbamate (28)

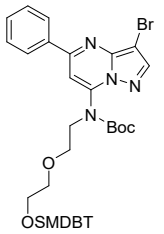


To a stirred solution of N-(2-(2-((tert-butyldimethylsilyl)oxy)ethoxy)ethyl)-5-phenylpyrazolo[1,5-a]pyrimidin-7-amine (**27**, 4.0 g, 9.7 mmol) in DCM (100 mL) was added di-*tert*-butyl dicarbonate (4.2 g, 2 eq) followed by a catalytic amount of 4-dimethylaminopyridine (120 mg, 0.1 eq). The reaction mixture was stirred at RT for 18h, then washed with water (2× 50 mL), dried over Na_2SO_4,

concentrated in vacuo. The obtained colourless oil was used in the next step without purification.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.14-8.06 (m, 3H), 7.55-7.43 (m, 3H), 7.39 (s, 1H), 6.75 (d, *J* = 2.3 Hz, 1H), 4.02 (t, *J* = 5.2 Hz, 2H), 3.73 (t, *J* = 5.2 Hz, 2H), 3.57 (t, *J* = 5.4 Hz, 2H), 3.42 (t, *J* = 5.4 Hz, 2H), 1.36 (s, 9H), 0.81 (s, 9H), 0.04 (s, 6H). MS: 513.4 $[M+H]^+$.

2.7.2.3 Synthesis of tert-butyl (3-bromo-5-phenylpyrazolo[1,5-a]pyrimidin-7-yl)(2-(2-((tert-butyldimethylsilyl)oxy)ethoxy)ethyl)carbamate (29)

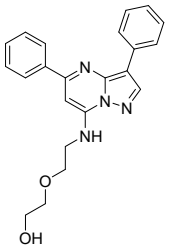


N-bromosuccinimide (1.7 g) was added to crude tert-butyl (2-(2-((tert-butyldimethylsilyl)oxy)ethoxy)ethyl)(5-phenylpyrazolo[1,5-a]pyrimidin-7-yl)carbamate (**28**) in MeCN (80 mL) at RT. The reaction mixture was stirred at RT for 5h, and then the solvent was evaporated in vacuo. The residue was dissolved in DCM (200 mL), the obtained solution was washed with water (3×50 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was subjected to column chromatography (EA/PE 1:2) to give brominated product **29** as yellow oil (4.7 g, yield 82% calculated from **27**).
^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.22-8.15 (m, 2H), 8.09 (s, 1H), 7.55-7.49 (m, 3H), 7.47 (s, 1H), 4.00 (t, *J* = 5.1 Hz, 2H), 3.72 (t, *J* = 5.1 Hz, 2H), 3.56 (t, *J* = 5.3 Hz, 2H), 3.41 (t, *J* = 5.3 Hz, 2H), 1.36 (s, 9H), 0.81 (s, 9H), 0.04 (s, 6H). MS: 591.2 $[M\ (^{79}Br)+H]^+$, 593.2 $[M\ (^{81}Br)+H]^+$.

2.7.2.4 General method A for the synthesis of 2-(2-((3-aryl-5-phenylpyrazolo[1,5-a]pyrimidin-7-yl)amino)ethoxy)ethan-1-ols

$PdCl_2$(dffp) (20 mg, 5 mol-%) was added to a mixture of tert-butyl (3-bromo-5-phenylpyrazolo[1,5-a]pyrimidin-7-yl)(2-(2-((tert-butyldimethylsilyl)oxy)ethoxy)ethyl)carbamate (**29**, 0.59 mmol), aryl boronic acid (1.5 eq) and K_3PO_4 (0.5 g, 4 eq) in Dox (9 mL) and water (3 mL) under argon. The reaction mixture was stirred and heated at 80°C. The course of the reaction was controlled by LC-MS. The obtained mixture was then cooled to RT, diluted with DCM (40 mL) and washed with brine (10 mL). The water layer was additionally extracted with DCM (2×15 mL). The combined organics were dried over Na_2SO_4 and concentrated in vacuo. The residue was dissolved in DCM (5 mL) and TFA (3 mL) and stirred for 18h at RT, then concentrated in vacuo. The obtained oil was basified by stirring with K_2CO_3 (0.4 g, 5eq) in 90% aq MeOH for 2h. The obtained mixture was concentrated in vacuo, the residue was dissolved in mixture of DCM (40 mL) and water (20 mL). The organic layer was separated, dried over Na_2SO_4 and concentrated in vacuo. The desired reaction product was isolated by purification via column chromatography.

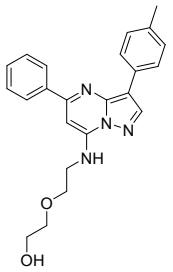
2-(2-((3,5-Diphenylpyrazolo[1,5-a]pyrimidin-7-yl)amino)ethoxy)ethan-1-ol [internal ID: Pir-8-1] (7)



Instead of $PdCl_2$(dffp), $Pd(PPh_3)_4$ was used as catalyst. The purification was carried out using MeOH/DCM (1:20) as eluent to afford **7** as yellow oil (40 mg, yield 20%, HPLC purity 99% at 254 nm, 97% at 210 nm). ^{1}H-NMR (400 MHz, Methanol-d_4) δ 8.43 (s, 1H), 8.25-8.14 (m, 4H), 7.45-7.36 (m, 3H), 7.44-7.34 (m, 2H), 7.19 (t, *J* = 7.3 Hz, 1H), 6.72 (s, 1H), 3.87-3.80 (m, 2H), 3.79-3.74

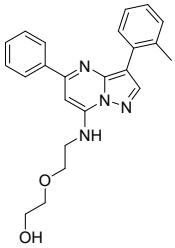
(m, 2H), 3.74-3.67 (m, 2H), 3.65-3.60 (m, 2H); ^{13}C-NMR (101 MHz, Methanol-d_4) δ 158.7, 148.9, 146.8, 142.8, 140.1, 134.5, 130.8, 129.6, 129.5, 128.4, 126.9, 126.4, 110.2, 83.6, 73.7, 70.3, 62.2, 42.9; LC-MS: 375 $[M+H]^+$;373 $[M-H]^-$.

2-(2-((5-Phenyl-3-(p-tolyl)pyrazolo[1,5-a]pyrimidin-7-yl)amino)ethoxy)ethan-1-ol [Pir-8-2] (7i)



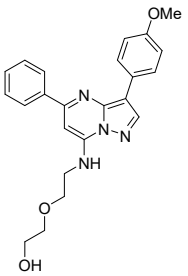
The purification was carried out using MeOH/DCM (1:15) as eluent to afford **7i** as white solid (100 mg, yield 44%, HPLC purity 97% at 254 nm, 97% at 210 nm). ^{1}H-NMR (400 MHz, Methanol-d_4) δ 8.39 (s, 1H), 8.24-8.19 (m, 2H), 8.08 (d, J = 8.9 Hz, 2H), 7.56-7.45 (m, 3H), 7.24 (d, J = 8.9 Hz, 2H), 6.72 (s, 1H), 3.87-3.81 (m, 2H), 3.80-3.75 (m, 2H), 3.73-3.68 (m, 2H), 3.66-3.61 (m, 2H), 2.37 (s, 3H); ^{13}C-NMR (101 MHz, Methanol-d_4) δ 158.5, 148.8, 146.6, 142.6, 140.1, 136.0, 131.5, 130.7, 130.1, 129.6, 128.4, 126.8, 110.3, 83.4, 73.7, 70.3, 62.2, 42.9, 21.2; LC-MS: 389.3 $[M+H]^+$; 387.2 $[M-H]^-$.

2-(2-((5-Phenyl-3-(o-tolyl)pyrazolo[1,5-a]pyrimidin-7-yl)amino)ethoxy)ethan-1-ol [Pir-8-3] (7m)



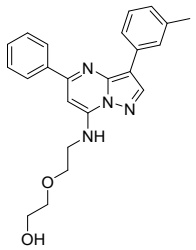
The purification was carried out using MeOH/DCM (1:15) as eluent to afford **7m** as white solid (100 mg, yield 44%, HPLC purity 91% at 254 nm, 92% at 210 nm). ^{1}H-NMR (400 MHz, Methanol-d_4) δ 8.09 (s, 1H), 8.08-8.04 (m, 2H), 7.58-7.53 (m, 1H), 7.49-7.41 (m, 3H), 7.32-7.28 (m, 1H), 7.28-7.18 (m, 2H), 6.67 (s, 1H), 3.86-3.80 (m, 2H), 3.80-3.74 (m, 2H), 3.73-3.67 (m, 2H), 3.66-3.60 (m, 2H), 2.43 (s, 3H); ^{13}C-NMR (101 MHz, Methanol-d_4) δ 158.9, 149.0, 146.9, 145.0, 140.1, 138.0, 133.3, 131.9, ,131.3, 130.7, 129.6, 128.5, 127.9, 126.6, 111.3, 83.7, 73.7, 70.4, 62.3, 43.0, 21.3; LC-MS: 389.3$[M+H]^+$; 387.2 $[M-H]^-$.

2-(2-((3-(4-Methoxyphenyl)-5-phenylpyrazolo[1,5-a]pyrimidin-7-yl)amino)ethoxy)ethan-1-ol [Pir-8-4] (7b)



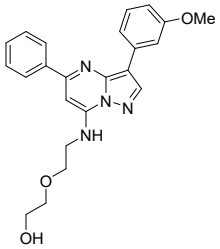
The purification was carried out using acetone/DCM (1:5) as eluent to afford **7b** as yellow oil (86 mg, yield 36%, HPLC purity 92% at 254 nm, 93% at 210 nm). ^{1}H-NMR (400 MHz, Methanol-d_4) δ 8.36 (s, 1H), 8.18-8.24 (m, 2H), 8.11 (d, J = 8.9 Hz, 2H), 7.45-7.56 (m, 3H), 7.00 (d, J = 8.9 Hz, 2H), 6.71 (s, 1H), 3.84 (m, 3H), 3.80-3.88 (m, 2H),3.74-3.80 (m, 2H), 3.67-3.73 (m, 2H), 3.60-3.66 (m, 2H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 157.9, 157.1, 147.1, 145.2, 141.4, 139.0, 129.9, 128.9, 127.5, 127.2, 125.7, 114.3, 109.7, 82.5, 72.7, 69.2, 62.0, 55.5, 42.2; LC-MS: 405.3$[M+H]^+$.

2-(2-((5-Phenyl-3-(m-tolyl)pyrazolo[1,5-a]pyrimidin-7-yl)amino)ethoxy)ethan-1-ol [Pir-8-5] (7c)



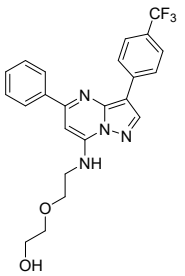
The purification was carried out using MeOH/DCM (1:15) as eluent to afford **7c** as yellow solid (80 mg, yield 35%, HPLC purity 99% at 254 nm, 99% at 210 nm). ^{1}H-NMR (400 MHz, Methanol-d_4) δ 8.42 (s, 1H), 8.25-8.19 (m, 2H), 8.03-8.00 (m, 1H), 8.00-7.99 (m, 1H), 7.56-7.46 (m, 3H), 7.30 (t, *J* = 7.8 Hz, 1H), 7.03 (d, J = 7.8 Hz, 1H), 6.73 (s, 1H), 3.88-3.81 (m, 2H), 3.81-3.74 (m, 2H), 3.74-3.67 (m, 2H), 3.66-3.60(m, 2H), 2.42 (s, 3H); ^{13}C-NMR (101 MHz, Methanol-d_4) δ 158.6, 148.8, 146.7, 142.8, 140.1, 139.0, 134.3, 130.8, 129.6, 129.4, 128.4, 127.5, 127.2, 124.1, 110.3, 83.5, 73.7, 70.3, 62.2, 42.9, 21.8; LC-MS: 389.3[M+H]$^{+}$.

2-(2-((3-(3-Methoxyphenyl)-5-phenylpyrazolo[1,5-a]pyrimidin-7-yl)amino)ethoxy)ethan-1-ol [Pir-8-6] (7n)



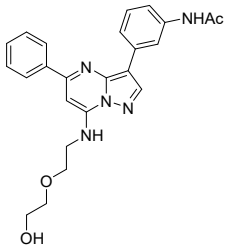
The purification was carried out using acetone/DCM (1:5) as eluent to afford **7n** as yellow semisolid (100 mg, yield 42%, HPLC purity 97% at 254 nm, 98% at 210 nm). ^{1}H-NMR (400 MHz, Methanol-d_4) δ 8.40 (s, 1H), 8.18-8.23 (m, 2H), 7.99 (dd, *J* =2.5;1.5 Hz, 1H), 7.66 (ddd, *J* = 8.2; 1.5; 0.9 Hz, 1H), 7.44-7.53 (m, 3H), 7.29 (t, *J* = 8.2 Hz, 1H), 6.76 (ddd, *J* = 8.2; 2.5; 0.9 Hz, 1H), 6.69 (s, 1H), 3.79-3.85 (m, 2H), 3.77-3.72(m, 2H), 3.72-3.68 (m, 2H), 3.65-3.60 (m, 2H), 3.89 (s, 3H). ^{13}C-NMR (101 MHz, Methanol-d_4) δ 161.4, 158.6, 148.9, 146.8, 142.9, 140.0, 135.8, 130.8, 130.4, 129.6, 128.4, 119.0, 112.3, 112.2, 109.9, 83.6, 73.7, 70.4, 62.2, 55.6, 43.0; LC-MS: 405.2 [M+H]$^{+}$.

2-(2-((5-Phenyl-3-(4-(trifluoromethyl)phenyl)pyrazolo[1,5-a]pyrimidin-7-yl)amino)ethoxy)-ethan-1-ol [Pir-8-7] (7g)



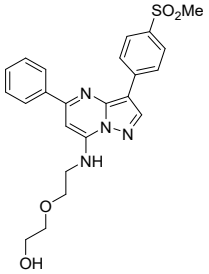
The purification was carried out using acetone/DCM (1:5) as eluent to afford **7g** as yellow solid (70 mg, yield 28%, HPLC purity 91% at 254 nm, 95% at 210 nm). ^{1}H-NMR (400 MHz, Methanol-d_4) δ 8.42 (s, 1H), 8.33 (d, *J* = 8.2 Hz, 2H), 8.18-8.13 (m, 2H), 7.63 (d, *J* = 8.2 Hz, 2H), 7.51-7.42 (m, 3H), 6.64 (s, 1H), 3.80 (t, 2H, *J* = 5.2 Hz), 3.73-3.66 (m, 4H), 3.64-3.59 (m, 2H); ^{13}C-NMR (101 MHz, Methanol-d_4) δ 159.1, 148.9, 147.2, 143.1, 139.8, 138.6, 130.9, 129.6, 128.4, 127.6 (q, *J* = 32.3 Hz), 126.55, 126.3 (q, *J* = 3.8 Hz), 126.1(q, *J* = 270.0 Hz), 108.4, 84.1, 73.7, 70.3, 62.2, 43.0; LC-MS: 443.2 [M+H]$^{+}$.

N-(3-(7-((2-(2-Hydroxyethoxy)ethyl)amino)-5-phenylpyrazolo[1,5-a]pyrimidin-3-yl)phenyl)acetamide [Pir-8-8] (7v)



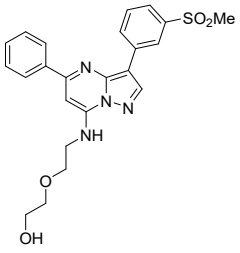
The purification was carried out using 10-50% acetone/DCM as eluent to afford **7v** as yellow oil (65 mg, yield 25%, HPLC purity 99% at 254 nm, 99% at 210 nm). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1H), 8.24 (t, *J* = 1.3 Hz, 1H), 8.18-8.13 (m, 2H), 7.95 (dt, *J* = 7.9; 1.3 Hz,1H), 7.55-7.44 (m, 4H), 7.40 (t, *J* = 7.9 Hz, 1H), 7.23 (br s, 1H), 6.74 (t, *J* = 5.5 Hz, 1H), 6.46 |(s, 1H), 3.87 (t, *J* = 5.2 Hz, 2H), 3.84-3.79 (m, 2H), 3.73-3.66 (m, 4H), 2.30 (br s, 1H), 2.21 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 168.4, 157.7, 147.1, 145.6, 142.0, 139.0, 138.3, 133.8, 129.9, 129.4, 128.8, 127.6, 122.0, 117.3, 117.1, 109.2, 83.0, 72.8, 69.1, 62.0, 42.2, 24.9; LC-MS: 432.3 $[M+H]^+$.

2-(2-((3-(4-(Methylsulfonyl)phenyl)-5-phenylpyrazolo[1,5-a]pyrimidin-7-yl)amino)ethoxy)-ethan-1-ol [Pir-8-9] (7o)



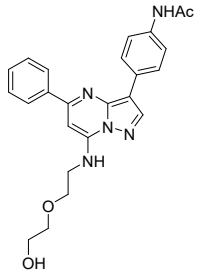
The purification was carried out using 10-40% acetone/DCM as eluent to afford **7o** as yellow solid (180 mg, yield 67%, HPLC purity 96% at 254 nm, 97% at 210 nm). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 1H), 8.38 (d, *J* = 8.6 Hz, 2H), 8.16-8.11 (m, 2H), 7.97 (d, *J* = 8.6 Hz, 2H), 7.56-7.47 (m, 3H), 6.80 (t, *J*= 5.5 Hz, 1H), 6.51 (s, 1H), 3.89 (t, *J* = 5.5 Hz, 2H), 3.84-3.79 (m, 2H), 3.72 (t, *J* = 5.5 Hz, 2H),3.70-3.67 (m, 2H), 3.07 (s, 3H), 2.24 (s, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 158.4, 147.3, 146.3, 142.2, 139.0, 138.5, 136.5, 130.3, 129.0, 127.9, 127.5, 126.0, 107.8, 83.6, 72.7, 69.1, 62.0, 44.7, 42.3; LC-MS: 453.3 $[M+H]^+$.

2-(2-((3-(3-(Methylsulfonyl)phenyl)-5-phenylpyrazolo[1,5-a]pyrimidin-7-yl)amino)ethoxy)ethan-1-ol [Pir-8-10] (7p)



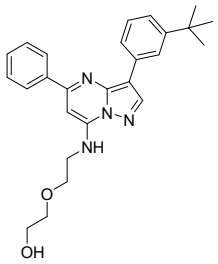
The purification (carried out using acetone/DCM, 1:5, as eluent) followed by crystallization from MeOH afforded product **7p** as yellow solid (80 mg, yield 30%, HPLC purity 98% at 254 nm, 99% at 210 nm). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.79 (t, *J* = 1.7 Hz, 1H), 8.56 (ddd, *J* = 7.8; 1.7, 1.1 Hz, 1H), 8.41 (s, 1H), 8.19-8.15 (m, 2H), 7.76 (ddd, *J* = 7.8, 1.7, 1.1 Hz, 1H), 7.63 (t, *J* = 7.8 Hz, 1H), 7.57-7.47 (m, 3H), 6.79 (t, *J* = 5.8 Hz, 1H), 6.53 (s, 1H), 3.85-3.78 (m, 2H), 3.74 (t, *J* = 5.3 Hz, 2H), 3.71-3.68 (m, 2H), 3.89 (t, *J* = 5.3 Hz, 2H), 3.13 (s, 3H), 2.15 (t, *J* = 5.3 Hz, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 158.0, 147.3, 141.7, 145.9, 140.9, 138.4, 134.8, 130.6, 130.3, 129.7, 128.9, 127.5, 124.2, 123.7, 107.6, 83.2, 72.8, 69.1, 62.0, 44.7, 42.3; LC-MS: 453.2 $[M+H]^+$.

N-(4-(7-((2-(2-Hydroxyethoxy)ethyl)amino)-5-phenylpyrazolo[1,5-a]pyrimidin-3-yl)phenyl)acetamide [Pir-8-11] (7l)



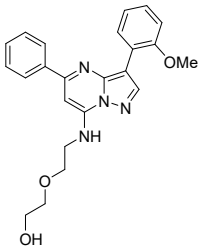
The purification was carried out using acetone/DCM (1:1.7) as eluent to afford **7l** as yellow solid (170 mg, yield 66%, HPLC purity 98% at 254 nm, 98% at 210 nm). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.32 (s, 1H), 8.17 (d, *J* = 8.6 Hz, 2H), 8.16-8.13 (m, 2H), 7.58 (d, *J* = 8.6 Hz, 2H), 7.55-7.44 (m, 3H), 7.16 (s, 1H), 6.73 (t, *J* = 5.5 Hz, 1H), 6.46 (s, 1H), 3.88 (t, *J* = 5.2 Hz, 2H), 3.84-3.77 (m, 2H), 3.71(t, *J* = 5.5 Hz, 2H), 3.70-3.66 (m, 2H), 2.20 (s, 3H), 1.26-1.23 (m, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 168.1, 155.9, 147.3, 144.8, 141.3, 138.2, 136.7, 129.8, 128.7, 127.9, 127.2, 125.4, 119.2, 107.6, 82.4, 72.2, 68.7, 60.3, 41.4, 24.0; LC-MS: 432.3 [M+H]+.

2-(2-((3-(3-(Tert-butyl)phenyl)-5-phenylpyrazolo[1,5-a]pyrimidin-7-yl)amino)ethoxy)ethan-1-ol [Pir-8-13] (7ac)



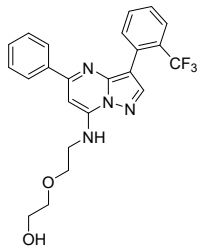
The purification was carried out using acetone/DCM (1:5) as eluent to afford **7ac** as yellow solid (46 mg, yield 18%, HPLC purity 98% at 254 nm, 99% at 210 nm). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1H), 8.45 (t, *J* = 1.8 Hz, 1H), 8.22-8.17 (m, 2H), 7.88 (ddd, *J* = 7.8; 1.8; 1.2 Hz, 1H), 7.54 -7.44 (m, 3H), 7.39 (t, *J* = 7.8 Hz, 1H), 7.29 (ddd, *J* = 7.8, 1.8, 1.2 Hz, 1H), 6.47 (s, 1H), 6.74 (t, *J* = 5.5 Hz, 1H),3.87 (t, *J* = 5.4 Hz, 2H), 3.83-3.78 (m, 2H), 3.71 (t, *J* = 5.5 Hz, 2H), 3.69-3.66 (m, 2H), 1.44 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 157.1, 151.5, 147.2, 145.6, 141.9, 138.9, 132.6, 129.9, 128.7, 128.4, 127.4, 123.5, 123.1, 122.9, 110.3, 82.5, 72.8, 69.2, 62.0, 42.3, 35.0, 31.6; LC-MS: 431.4 $[M+H]^+$; 430.2 $[M-H]^-$.

2-(2-((3-(2-Methoxyphenyl)-5-phenylpyrazolo[1,5-a]pyrimidin-7-yl)amino)ethoxy)ethan-1-ol [Pir-8-14] (7y)



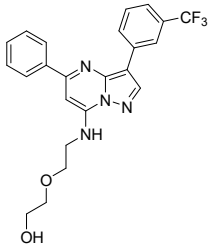
The purification was carried out using acetone/DCM (1:5) as eluent to afford **7y** as yellow solid (24 mg, yield 10%, HPLC purity 94% at 254 nm, 96% at 210 nm). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.70 (dd, *J* = 7.4; 1.8 Hz, 1H), 8.14-8.09 (m, 2H), 7.51-7.41 (m, 3H), 7.24 (ddd, *J* = 8.2; 7.4; 1.8 Hz, 1H), 7.14 (td, *J* = 7.4; 1.2 Hz, 1H), 6.81 (t, *J* = 5.5 Hz, 1H), 6.99 (dd, *J* = 8.2; 1.2 Hz, 1H), 6.39 (s, 1H), 3.92 (s, 1H), 3.83-3.75 (m, 4H), 3.66-3.58 (m, 4H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 157.0, 156.3, 147.0, 145.9, 145.1, 138.8, 129.7, 129.5, 128.7, 127.4, 126.7, 121.8, 121.0, 111.1, 105.9, 82.6, 72.7, 67.0, 61.8, 55.5, 42.1; LC-MS: 405.3 $[M+H]^+$.

2-(2-((5-Phenyl-3-(2-(trifluoromethyl)phenyl)pyrazolo[1,5-a]pyrimidin-7-yl)amino)ethoxy)ethan-1-ol [Pir-8-15] (7x)



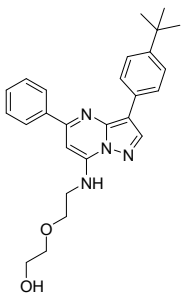
The purification was carried out using acetone/DCM (1:5) as eluent to afford **7x** as white solid (10 mg, yield 4%, HPLC purity 97% at 254 nm, 96% at 210 nm). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 8.06-8.02 (m, 2H), 7.49-7.39 (m, 4H), 7.98 (d, *J* = 7.8 Hz, 1H), 7.78 (d, *J* = 7.8 Hz, 1H), 7.63 (t, *J* = 7.8 Hz, 1H), 6.79 (t, *J* = 5.4 Hz, 1H), 6.40 (s, 1H), 3.90 (t, *J* = 5.2 Hz, 2H), 3.85-3.80 (m, 2H), 3.73 (t, *J* = 5.4 Hz, 2H), 3.71-3.68 (m, 2H), 2.14 (t, *J* = 5.8 Hz, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 158.1, 147.4, 145.5, 144.4 (q, *J* = 4.0 Hz), 137.9, 133.6, 131.6, 130.7 (q, *J* = 1.7 Hz), 130.2, 128.8, 128.6 (q, *J* = 30.0 Hz), 127.6, 127.0, 126.5 (q, J = 5.5 Hz), 124.6(q, *J* =274.7 Hz), 107.6, 83.5, 72.8, 69.0, 61.9, 42.3; LC-MS: 443.3 $[M+H]^+$.

2-(2-((5-Phenyl-3-(3-(trifluoromethyl)phenyl)pyrazolo[1,5-a]pyrimidin-7-yl)amino)ethoxy)ethan-1-ol [Pir-8-16] (7a)



The purification was carried out using 0-30% acetone/DCM as eluent to afford **7a** as yellow solid (70 mg, yield 27%, HPLC purity 97% at 254 nm, 98% at 210 nm). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.53 (s, 1H), 8.39-8.34 (m, 2H), 8.18-8.12 (m, 2H), 7.56-7.42 (m, 5H), 6.77 (t, *J* = 5.6 Hz, 1H), 6.40 (s, 1H), 3.88 (t, *J* = 5.2 Hz, 2H), 3.82 (m, 2H), 3.71 (t, *J* = 5.4 Hz, 2H), 3.70-3.67 (m, 2H), 2.39 (t, *J* = 5.7 Hz, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 157.2, 147.2, 145.8, 141.7, 138.5, 133.9, 131.0 (q, J = 31.9 Hz), 130.2, 129.1, 128.9, 128.8, 127.4, 124.6 (q, J = 272.7 Hz), 122.5 (q, *J* = 4.0 Hz), 122.1 (q, *J* = 3.7 Hz), 108.3, 83.0, 72.8, 69.1, 62.0, 42.3; MS: 443.3 $[M+H]^+$; 441.3 $[M-H]^-$.

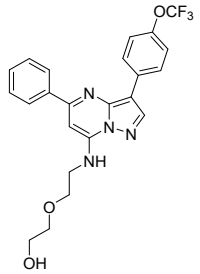
2-(2-((3-(4-(Tert-butyl)phenyl)-5-phenylpyrazolo[1,5-a]pyrimidin-7-yl)amino)ethoxy)ethan-1-ol [Pir-8-17] (7t)



The purification was carried out using 0-50% acetone/DCM as eluent to afford **7t** as yellow solid (172 mg, yield 68%, HPLC purity 97% at 254 nm, 98% at 210 nm). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 1H), 8.19-8.14 (m, 2H), 8.12 (d, *J* = 8.7 Hz, 2H), 7.54-7.42 (m, 5H), 6.73 (t, *J* = 5.7 Hz, 1H), 6.45 (s, 1H), 3.87 (t, *J* = 5.2 Hz, 2H), 3.83-3.78 (m, 2H), 3.71 (t, *J* = 5.4 Hz, 2H), 3.70-3.66 (m, 2H), 2.30 (br s, 1H), 1.37 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 157.2, 148.6, 147.1, 145.5,

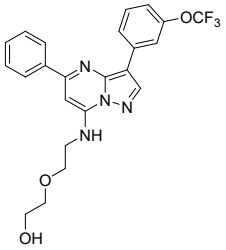
141.8, 139.0, 130.1, 129.8, 128.8, 127.5, 125.8, 125.7, 109.9, 82.6, 72.7, 69.2, 62.0, 42.2, 34.6, 31.5; MS: 431.3 $[M+H]^+$.

2-(2-((5-Phenyl-3-(4-(trifluoromethoxy)phenyl)pyrazolo[1,5-a]pyrimidin-7-yl)amino)ethoxy)ethan-1-ol [Pir-8-18] (7e)



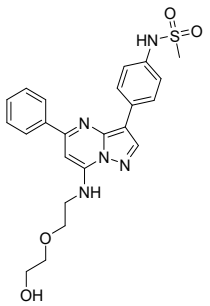
The purification was carried out using 15-40% acetone/DCM as eluent to afford **7e** as white solid (70 mg, yield 26%, HPLC purity 98% at 254 nm, 99% at 210 nm). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 1H), 8.22 (d, *J* = 8.7 Hz, 2H), 8.17-8.12 (m, 2H), 7.57-7.45 (m, 3H), 7.30 (d, *J* = 8.7 Hz, 2H), 6.76 (t, *J* = 5.6 Hz, 1H), 6.49 (s, 1H), 3.89 (t, *J* = 5.6 Hz, 2H), 3.85-3.78 (m, 2H), 3.73 (t, *J* = 5.3 Hz, 2H), 3.71-3.67 (m, 2H), 2.15 (t, *J* = 5.9 Hz, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 157.8, 147.2, 147.1 (q, *J* = 1.8 Hz), 145.7, 141.8, 138.8, 132.0, 130.1, 128.9, 127.5, 127.1, 121.5, 120.8 (q, *J* = 256.7 Hz), 108.5, 83.0, 72.7, 69.2, 62.0, 42.3; MS: 459.2 $[M+H]^+$.

2-(2-((5-Phenyl-3-(3-(trifluoromethoxy)phenyl)pyrazolo[1,5-a]pyrimidin-7-yl)amino)ethoxy)ethan-1-ol [Pir-8-19] (7h)



The purification was carried out using 15-40% acetone/DCM as eluent to afford **7h** as yellow semisolid (57 mg, yield 21%, HPLC purity 91% at 254 nm, 95% at 210 nm). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 1H), 8.23 (m, 1H), 8.17-8.12 (m, 2H), 8.03 (ddd, *J* = 7.9; 1.5; 0.9 Hz, 1H), 7.55-7.43 (m, 3H), 7.43 (t, *J* = 7.9Hz, 1H), 7.05 (m, 1H), 6.76 (t, *J* = 5.6 Hz, 1H), 6.48 (s, 1H), 3.87 (t, *J* = 5.1 Hz, 2H), 3.84-3.78 (m, 2H), 3.72-3.65 (m, 4H), 2.42 (br s, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 157.8, 149.9 (q, *J* = 1.8 Hz), 147.2, 145.8, 141.8, 138.5, 135.1, 130.1, 129.9, 128.8, 127.5, 123.8, 120.8 (q, *J* = 256.6 Hz), 118.2, 117.7, 108.3, 83.0, 72.8, 69.1, 62.0, 42.2; MS: 459.2 $[M+H]^+$.

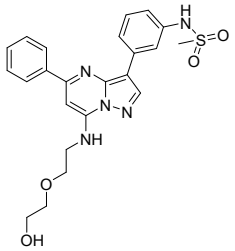
N-(4-(7-((2-(2-Hydroxyethoxy)ethyl)amino)-5-phenylpyrazolo[1,5-a]pyrimidin-3-yl)phenyl)methanesulfonamide [Pir-8-20] (7r)



The purification was carried out using 15-70% acetone/DCM as eluent to afford **7r** as white semisolid (195 mg, yield 71%, HPLC purity 99% at 254 nm, 99% at 210 nm). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1H), 8.20-8.16 (m, 2H), 8.16-8.12 (m, 2H), 7.55-7.45 (m, 3H), 7.33-7.28 (m,

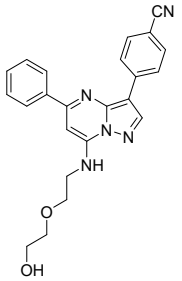
2H), 6.75 (t, *J* = 5.5 Hz, 1H), 6.47 (s, 1H), 6.42 (br s, 1H),3.89 (t, *J* = 5.2 Hz, 2H), 3.85-3.79 (m, 2H), 3.72 (t, *J* = 5.4 Hz, 2H), 3.71-3.67 (m, 2H), 3.02 (s, 3H), 2.26 (t, *J* = 5.9 Hz, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 157.7, 147.2, 145.6, 141.6, 138.8, 133.9, 131.0, 130.11, 129.0, 127.5, 127.1, 122.0, 108.8, 82.9, 72.7, 69.2, 62.0, 42.3, 39.3; MS: 468.3 $[M+H]^+$.

N-(3-(7-((2-(2-Hydroxyethoxy)ethyl)amino)-5-phenylpyrazolo[1,5-a]pyrimidin-3-yl)phenyl)methanesulfonamide [Pir-8-21] (7w)



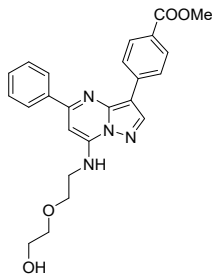
The purification was carried out using 15-50% acetone/DCM as eluent, followed by repeated column chromatography using 70-90% EtOAc/PE as eluent, to afford **7w** as yellow solid (115 mg, yield 42%, HPLC purity 99% at 254 nm, 99% at 210 nm). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 9.79 (s, 1H), 8.59 (s, 1H), 8.39-8.34 (m, 2H), 8.31 (t, *J* = 1.8 Hz, 1H), 7.99-7.93 (m, 1H), 7.86 (ddd, *J* = 8.0;1.8;1.0 Hz, 1H), 7.58-7.48 (m, 3H), 7.38 (t, *J* = 8.0 Hz, 1H), 7.02 (ddd, *J* = 8.0; 1.8;1.0 Hz, 1H), 6.90 (s, 1H), 4.66-4.59 (m, 1H), 3.79-3.70 (m, 4H), 3.54-3.47 (m, 4H), 3.06 (s, 3H); ^{13}C-NMR (101 MHz, DMSO-d_6) δ 156.3, 147.4, 145.1, 141.7, 138.7, 138.0, 134.1, 129.9, 129.4, 128.6, 127.4, 120.7, 116.9, 116.5, 107.3, 82.6, 72.2, 68.7, 60.3, 41.4, one signal was overlapping with DMSO; MS: 468.3 $[M+H]^+$.

4-(7-((2-(2-Hydroxyethoxy)ethyl)amino)-5-phenylpyrazolo[1,5-a]pyrimidin-3-yl)benzonitrile [Pir-8-22] (7u)



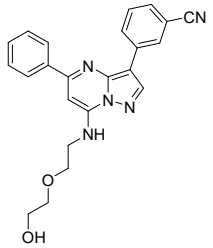
The purification was carried out using 20-40% acetone/DCM as eluent to afford **7u** as yellow solid (47 mg, yield 20%, HPLC purity 98% at 254 nm, 99% at 210 nm). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.36 (s, 1H), 8.30 (d, *J* = 8.5 Hz, 2H), 8.15-8.10 (m, 2H), 7.68 (d, *J* = 8.5 Hz, 2H), 7.56-7.48 (m, 3H), 6.80 (t, *J* = 5.5 Hz, 1H), 6.51 (s, 1H), 3.89 (t, *J* = 5.1 Hz, 2H), 3.85-3.78 (m, 2H), 3.72 (t, *J* = 5.3 Hz, 2H), 3.71-3.67 (m, 2H), 2.27 (br s, 1H); ^{13}C-NMR (101 MHz, DMSO-d_6) δ 158.4, 147.3, 146.2, 142.1, 138.5, 138.0, 132.6, 130.3, 128.9, 127.5, 125.8, 119.8, 108.2, 107.8, 83.5, 72.8, 69.1, 62.0, 42.3; MS: 400.3 $[M+H]^+$.

Methyl 4-(7-((2-(2-hydroxyethoxy)ethyl)amino)-5-phenylpyrazolo[1,5-a]pyrimidin-3-yl)-benzoate [Pir-8-23] (7f)



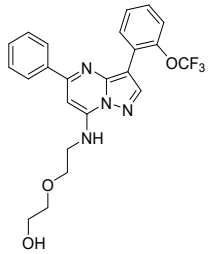
The purification was carried out using 15-30% acetone/DCM as eluent to afford **7f** as yellow solid (100 mg, yield 45%, HPLC purity 99% at 254 nm, 99% at 210 nm). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 8.18-8.14 (m, 2H), 8.30 (d, *J* = 8.6 Hz, 2H), 8.11 (d, *J* = 8.6 Hz, 2H), 7.56-7.45 (m, 3H), 6.50 (s, 1H), 6.77 (t, *J* = 5.6 Hz, 1H), 3.93 (s, 3H), 3.88 (t, *J* = 5.2 Hz, 2H), 3.85-3.80 (m, 2H), 3.72 (t, *J* = 5.4 Hz, 2H), 3.70-3.67 (m, 2H), 2.22 (t, *J* = 5.1 Hz, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 167.4, 158.0, 147.2, 146.1, 142.2, 138.6, 138.0, 130.22, 130.20, 128.9, 127.5, 126.8, 125.3, 108.7, 83.2, 72.7, 69.2, 62.0, 52.0, 42.3; MS: 433.3 $[M+H]^+$.

3-(7-((2-(2-Hydroxyethoxy)ethyl)amino)-5-phenylpyrazolo[1,5-a]pyrimidin-3-yl)benzonitrile [Pir-8-24] (7d)



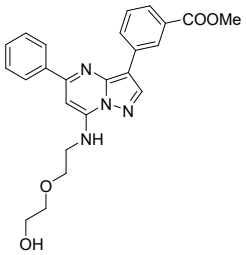
The purification was carried out using 15-30% acetone/DCM as eluent to afford **7d** as yellow solid (118 mg, yield 50%, HPLC purity 99% at 254 nm, 99% at 210 nm). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.47-8.43 (m, 1H), 8.36 (dt, *J* = 7.6;1.7 Hz, 1H), 8.28 (s, 1H), 8.12-8.07 (m, 2H), 7.55-7.41 (m, 5H), 6.78 (t, *J* = 5.5 Hz, 1H), 6.45 (s, 1H), 3.87 (t, J = 5.2 Hz, 2H), 3.85-3.79 (m, 2H), 3.73-3.66 (m, 4H), 2.56 (t, *J*= 5.5 Hz, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 158.1, 147.2, 145.8, 141.6, 138.4, 134.4, 130.3, 129.7, 129.4, 129.0, 128.9, 128.7, 127.4, 119.6, 112.7, 107.3, 83.3, 72.8, 69.0, 61.9, 42.2; MS: 400.2 $[M+H]^+$.

2-(2-((5-Phenyl-3-(2-(trifluoromethoxy)phenyl)pyrazolo[1,5-a]pyrimidin-7-yl)amino)-ethoxy)ethan-1-ol [Pir-8-25] (7aa)



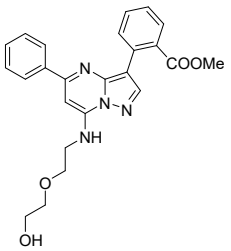
The purification was carried out using 15-30% acetone/DCM as eluent to afford **7aa** as white solid (97 mg, yield 36%, HPLC purity 98% at 254 nm, 98% at 210 nm). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.72 (dd, *J* = 7.9; 1.4 Hz, 1H), 8.52 (s, 1H), 8.14-8.08 (m, 2H), 7.54-7.45 (m, 3H), 7.42 (ddd, *J* = 7.9;7.2;1.4Hz, 1H), 7.35 (m, 1H), 7.25 (ddd, *J* = 8.2;7.2;1.5 Hz, 1H, the signals overlapped with $CDCl_3$), 6.48 (s, 1H), 6.83 (t, *J* = 5.4 Hz, 1H), 3.87 (t, *J* = 5.2 Hz, 2H), 3.84-3.78 (m, 2H), 3.72-3.66 (m, 4H), 2.42 (br s, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 157.9, 147.2, 146.3, 145.9, 144.3, 138.8, 130.5, 130.0, 128.8, 127.5, 127.1, 126.6, 126.3, 120.9, 120.8 (q, J = 257.5 Hz), 104.5, 83.1, 72.8, 69.2, 62.0, 42.2; MS: 459.3 $[M+H]^+$.

Methyl 3-(7-((2-(2-hydroxyethoxy)ethyl)amino)-5-phenylpyrazolo[1,5-a]pyrimidin-3-yl)benzoate [Pir-8-26] (7k)



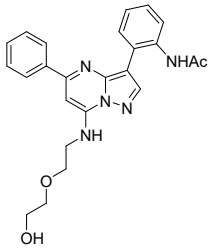
The purification was carried out using 15-30% acetone/DCM as eluent to afford **7k** as white solid (107 mg, yield 42%, HPLC purity 99% at 254 nm, 99% at 210 nm). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.87 (dd, *J* = 1.9;1.6 Hz, 1H), 8.51 (ddd, *J* = 7.8;1.9;1.2 Hz, 1H), 8.41 (s, 1H), 8.22-8.16 (m, 2H), 7.90 (ddd, *J* = 7.7;1.6;1.2 Hz, 1H), 7.57-7.46 (m, 4H), 6.77 (t, *J* = 5.5 Hz, 1H), 6.50 (s, 1H), 3.98 (s, 3H), 3.89 (t, *J* = 5.2 Hz, 2H), 3.85-3.78 (m, 2H), 3.73 (t, *J* = 5.5 Hz, 2H), 3.72-3.66 (m, 2H), 2.20 (t, *J* = 5.2 Hz, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 167.6, 157.6, 147.2, 145.8, 141.8, 138.7, 133.4, 130.5, 130.2, 130.1, 128.8 (2C), 127.5, 126.8, 126.6, 108.7, 82.8, 72.8, 69.2, 62.0, 52.2, 42.3; MS: 433.3 $[M+H]^+$; 431.3 $[M-H]^-$.

Methyl 2-(7-((2-(2-hydroxyethoxy)ethyl)amino)-5-phenylpyrazolo[1,5-a]pyrimidin-3-yl)benzoate [Pir-8-27] (7z)



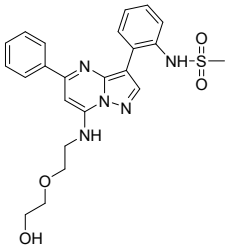
The purification was carried out using 5-15% acetone/DCM as eluent to afford **7z** as brown solid (10 mg, yield 5%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 1H), 8.14-8.10 (m, 2H), 7.86 (ddd, *J* = 7.8; 1.4; 0.4 Hz, 1H), 7.70 (ddd, *J* = 7.8; 1.4; 0.4 Hz, 1H), 7.54 (td, *J* = 7.8; 1.4 Hz, 1H), 7.50-7.40 (m, 3H), 7.34 (td, *J* = 7.8; 1.4 Hz, 1H), 6.77 (t, *J* = 5.6 Hz, 1H), 6.46 (s, 1H), 3.87 (t, *J* = 5.2 Hz, 2H), 3.83-3.79 (m, 2H), 3.72-3.66 (m, 4H), 3.57 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 170.0, 157.3, 147.2, 145.9, 143.0, 138.4, 132.0, 131.4, 131.1, 130.9, 130.3, 130.0, 128.8, 127.4, 126.3, 110.0, 82.5, 72.7, 69.2, 62.0, 52.1, 42.3; MS: 433.3 $[M+H]^+$; 431.1 $[M-H]^-$.

N-(2-(7-((2-(2-hydroxyethoxy)ethyl)amino)-5-phenylpyrazolo[1,5-a]pyrimidin-3-yl)phenyl)acetamide [Pir-8-28] (7ad)



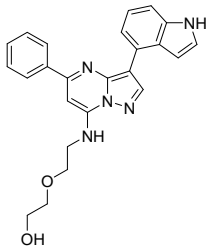
The purification was carried out using 10-30% acetone/DCM as eluent to afford **7ad** as yellow solid (80 mg, yield 36%, HPLC purity 98% at 254 nm, 98% at 210 nm). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 11.32 (s, 1H), 8.14 (s, 1H), 8.11-8.06 (m, 2H), 8.04 (dd, *J* = 8.2; 1.1 Hz, 1H), 7.56-7.47 (m, 4H), 7.35 (ddd, *J* = 8.2; 7.6; 1.6 Hz, 1H), 7.20 (td, *J* = 7.6; 1.1Hz, 1H), 6.99 (t, *J* = 5.5 Hz, 1H), 6.49 (s, 1H), 3.89 (t, *J* = 5.2 Hz, 2H), 3.84-3.79 (m, 2H), 3.72 (t, *J* = 5.5 Hz, 2H), 3.70-3.67 (m, 2H), 1.73 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 169.0, 156.9, 147.8, 144.3, 144.2, 137.7, 135.5, 130.7, 129.5, 129.1, 127.4, 127.2, 125.2, 124.9, 124.7, 109.4, 82.2, 72.8, 69.1, 62.0, 42.4, 24.3; MS: 432.3 $[M+H]^+$; 430.3 $[M-H]^-$.

N-(2-(7-((2-(2-hydroxyethoxy)ethyl)amino)-5-phenylpyrazolo[1,5-a]pyrimidin-3-yl)phenyl)methanesulfonamide [Pir-8-30] (7ab)



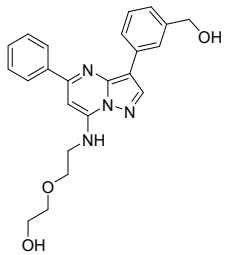
The purification was carried out using acetone/DCM (1:5) as eluent to afford **7ab** as white solid (33 mg, yield 12%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.11 (s, 1H), 8.57 (s, 1H), 8.35 (t, *J* = 5.9 Hz, 1H), 8.25-8.18 (m, 2H), 7.80-7.74 (m, 1H), 7.59-7.47 (m, 4H), 7.38-7.30 (m, 2H), 6.93 (s, 1H), 4.63 (m, 1H), 3.82-3.71 (m, 4H), 3.51 (d, *J* = 2.7 Hz, 4H), 2.58 (s, 3H). ^{13}C-NMR (101 MHz, DMSO-d_6) δ 156.5, 148.0, 143.9, 143.8, 137.3, 133.7, 130.3, 129.6, 128.8, 127.4, 127.2, 127.1, 126.5, 126.3, 106.6, 83.1, 72.2, 68.7, 60.3, 41.6. The signal of SO_2Me is overlapped with DMSO-d_6. MS: 468.3 $[M+H]^+$; 466.2 $[M-H]^-$.

2-(2-((3-(1H-Indol-4-yl)-5-phenylpyrazolo[1,5-a]pyrimidin-7-yl)amino)ethoxy)ethan-1-ol [Pir-8-32] (7s)



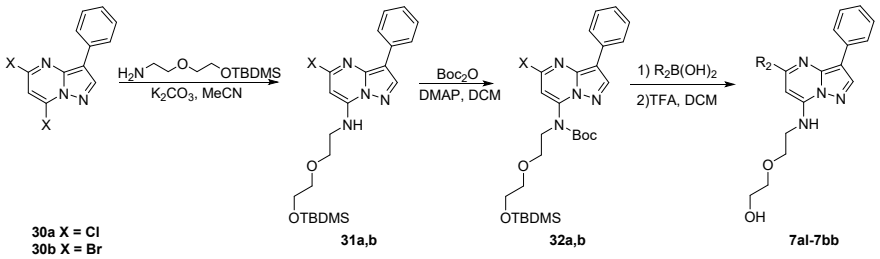
The purification was carried out using 5%-30% acetone/DCM as eluent to afford **7s** as brown solid (22 mg, yield 9%). ^{1}H-NMR (300 MHz, CD_3OD) δ 8.49 (s, 1H), 8.20-8.16 (m, 2H), 7.81 (dd, *J* = 7.3;0.8 Hz, 1H), 7.52-7.43 (m, 3H), 7.34 (dt, *J* = 8.1;0.8 Hz, 1H), 7.30 (d, *J* = 3.2 Hz, 1H), 7.23 (dd, *J* = 8.1;7.3 Hz, 1H), 6.82 (dd, *J* = 3.2;0.8 Hz, 1H), 6.73 (s, 1H), 3.89-3.83 (m, 2H), 3.82-3.77 (m, 2H), 3.74-3.69 (m, 2H), 3.67-3.62 (m, 2H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 157.2, 147.2, 145.9, 143.7, 139.0, 136.6, 129.8, 128.7, 127.5, 126.1, 125.2, 124.0, 122.6, 120.0, 110.5, 109.3, 103.0, 82.7, 72.7, 69.2, 62.0, 42.3. MS: 414.3 $[M+H]^+$.

2-(2-((3-(3-(Hydroxymethyl)phenyl)-5-phenylpyrazolo[1,5-a]pyrimidin-7-yl)amino)ethoxy)ethan-1-ol [Pir-8-33] (7j)



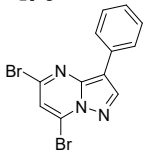
The purification was carried out using 15%-40% acetone/DCM as eluent to afford **7j** as yellow solid (114 mg, yield 48%, HPLC purity 99% at 254 nm, 99% at 210 nm). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 8.16-8.06 (m, 4H), 7.53-7.44 (m, 3H), 7.40 (t, *J* = 7.7 Hz, 1H), 7.21 (dt, *J* = 7.7;1.3 Hz, 1H), 6.71 (t, *J* = 5.5 Hz, 1H), 6.39 (s, 1H), 4.75 (s, 2H), 3.86 (t, *J* = 5.2 Hz, 2H), 3.83-3.79 (m, 2H), 3.70-3.63 (m, 4H), 2.74 (br s, 1H), 2.31 (br s, 1H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 157.4, 147.1, 145.6, 141.8, 141.2, 138.8, 133.2, 130.0, 129.0, 128.8, 127.5, 125.2, 124.6, 124.5, 109.4, 82.8, 72.9, 69.0, 65.9, 62.0, 42.2. MS: 405.3 $[M+H]^+$; 403.3 $[M-H]^-$

2.7.3 The general procedure of 2-(2-((5-aryl-3-phenylpyrazolo[1,5-a]pyrimidin-7-yl)amino)ethoxy)ethan-1-ole preparation



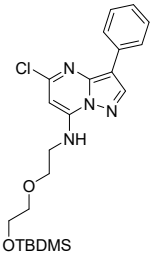
Scheme 2

2.7.3.1 5,7-Dibromo-3-phenylpyrazolo[1,5-a]pyrimidine (30b)



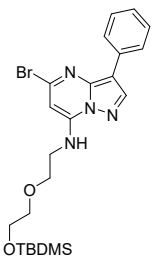
5,7-Dibromo-3-phenylpyrazolo[1,5-a]pyrimidine (**30b**) (yield 47%) was prepared using the method described in Journal of Heterocyclic Chemistry (1985), 22(3), 601-34 using $POBr_3$ instead of $POCl_3$. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.51 (s, 1H), 8.01-7.96 (m, 2H), 7.51-7.42 (m, 2H), 7.35-7.29 (m, 2H). MS: 351.95 [M (^{79,79}Br)+H]$^+$, 353.93 [M (^{79,81}Br)+H]$^+$, 355.91 [M (^{81,81}Br)+H]$^+$.

2.7.3.2 Synthesis of N-(2-(2-((tert-butyldimethylsilyl)oxy)ethoxy)ethyl)-5-chloro-3-phenylpyrazolo[1,5-a]pyrimidin-7-amine (31a)



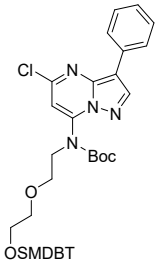
A mixture of 5,7-dichloro-3-phenylpyrazolo[1,5-*a*]pyrimidine (**30a**, 3.3 g, 12.5 mmol), 2-(2-((tert-butyldimethylsilyl)oxy)ethoxy)ethan-1-amine (4.1 g, 1.5 eq) and K_2CO_3 (8.6 g, 5 eq) in MeCN (100 mL) was stirred at RT for 18h. The solvent was removed to give an oily residue that was dissolved in EtOAc (50 mL). The obtained solution was washed with brine (2x15 mL), dried over Na_2SO_4 and the solvent was removed to give oil that was purified by column chromatography (5%-20% EtOAc/PE) to afford the desired product **31** as colourless oil (5.0 g, yield 90%).
^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.30 (s, 1H), 8.00 (d, *J* = 7.8 Hz, 2H), 7.43 (t, *J* = 7.8 Hz, 2H), 7.24 (t, *J* = 7.8 Hz, 1H, overlapped with $CDCl_3$), 6.76 (t, *J* = 5.3 Hz, 1H), 6.00 (s, 1H), 3.86-3.77 (m, 4H), 3.64-3.54 (m, 4H), 0.90 (s, 9H), 0.08 (s, 6H); MS: 447.3 [M (^{35}Cl)+H]$^+$, 449.2 [M (^{37}Cl)+H]$^+$.

2.7.3.3 5-Bromo-N-(2-(2-((tert-butyldimethylsilyl)oxy)ethoxy)ethyl)-3-phenylpyrazolo[1,5-a]pyrimidin-7-amine (31b)



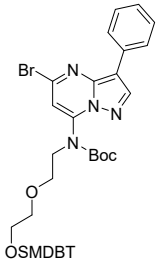
31b (yield 78%) as a yellow solid was prepared from 5,7-dibromo-3-phenylpyrazolo[1,5-*a*]pyrimidine (**30b**) using the method described previously for *N*-(2-(2-((tert-butyldimethylsilyl)oxy)ethoxy)ethyl)-5-chloro-3-phenylpyrazolo[1,5-a]pyrimidin-7-amine (**31a**). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.28 (s, 1H), 8.03-8.97 (m, 2H), 7.46-7.38 (m, 2H), 7.27-7.17 (m, 1H, overlapped with $CDCl_3$), 6.73 (t, *J* = 5.5 Hz, 1H), 6.14 (s, 1H), 3.84-3.77 (m, 4H), 3.36-3.52 (m, 4H), 0.90 (s, 9H), 0.08 (s, 6H); MS: 491.29 [M (^{79}Br)+H]$^+$, 493.27 [M (^{81}Br)+H]$^+$.

2.7.3.4 t-Butyl (2-(2-((tert-butyldimethylsilyl)oxy)ethoxy)ethyl)(5-chloro-3-phenylpyrazolo[1,5-a]pyrimidin-7-yl)carbamate (32a)



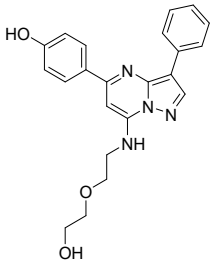
Compound **32a** was prepared using the method described previously for tert-butyl (2-(2-((tert-butyldimethylsilyl)oxy)ethoxy)ethyl)(5-phenylpyrazolo[1,5-a]pyrimidin-7-yl)carbamate (**28**, see Scheme 1). Isolated crude product was purified by column chromatography (10%-30% EtOAc/PE) to give the desired product as colorless oil (yield 90%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.42 (s, 1H), 8.04-7.98 (m, 2H), 7.49-7.41 (m, 2H), 7.32-7.24 (m, 1H, overlapped with $CDCl_3$), 6.96 (s, 1H), 3.99 (t, *J* = 5.2 Hz, 2H), 3.71 (t, *J* = 5.2 Hz, 2H), 3.58-3.52 (m, 2H), 3.43-3.38 (m, 2H), 1.37 (s, 9H), 1.84 (s, 9H), 0.01 (s, 6H); MS: 447.3 [M (^{35}Cl)+H]$^+$, 449.3 [M (^{37}Cl)+H]$^+$.

2.7.3.5 t-Butyl (5-bromo-3-phenylpyrazolo[1,5-a]pyrimidin-7-yl)(2-(2-((tert-butyldimethylsilyl)oxy)ethoxy)ethyl)carbamate (32b)



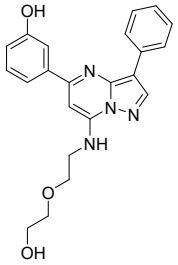
Compound **32b** was prepared using the method described previously for tert-butyl (2-(2-((tert-butyldimethylsilyl)oxy)ethoxy)ethyl)(5-phenylpyrazolo[1,5-a]pyrimidin-7-yl)carbamate (**28**, see Scheme 1). Isolated crude product was purified by column chromatography (5%-25% EtOAc/PE) to give the desired product as yellow oil (yield 93%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.40 (s, 1H), 8.05-7.99 (m, 2H), 7.49-7.41 (m, 2H), 7.32-7.26 (m, 1H, overlapped with $CDCl_3$), 7.07 (s, 1H), 3.98 (t, *J* = 5.1 Hz, 2H), 7.31 (t, *J* = 5.1 Hz, 2H), 3.58-3.52 (m, 2H), 3.43-3.37 (m, 2H), 1.37 (s, 9H), 0.85 (s, 9H), 0.00 (s, 6H); MS: 591.35 [M (^{79}Br)+H]$^+$, 593.36 [M (^{81}Br)+H]$^+$.

4-(7-((2-(2-Hydroxyethoxy)ethyl)amino)-3-phenylpyrazolo[1,5-a]pyrimidin-5-yl)phenol [Pir-10-1] (7ao)



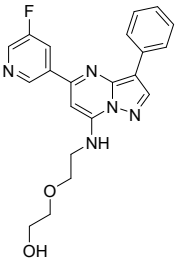
7ao was prepared from tert-butyl (2-(2-((tert-butyldimethylsilyl)oxy)ethoxy)ethyl)(5-chloro-3-phenylpyrazolo[1,5-a]pyrimidin-7-yl)carbamate (**32a**) and 4-hydroxyphenylboronic acid by following the procedure described in general method **A**. The purification was carried out using 10-30% acetone/DCM as eluent to afford **7ao** white solid (yield 42%, HPLC purity 98% at 254 nm, 97% at 210 nm). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.60 (s, 1H), 8.28-8.22 (m, 2H), 8.15 (d, *J* = 8.7 Hz, 2H), 7.82-7.76 (m, 1H), 7,43 (t, *J* = 7.7 Hz, 2H), 7.22-7.15 (m, 1H), 6.93 (d, *J* = 8.7 Hz, 2H), 6.76 (s, 1H), 4.69-4.62 (m, 1H), 3.77-3.68 (m, 4H), 3.56-3.48 (m, 4H). ^{13}C-NMR (101 MHz, DMSO-d_6) δ 159.3, 156.3, 147.2, 145.2, 141.5, 133.2, 129.0, 128.8, 128.6, 125.1, 125.0, 115.4, 107.2, 81.6, 72.3, 68.7, 60.3, 41.3. MS: 391.3 $[M+H]^+$; 389.2 $[M-H]^-$.

3-(7-((2-(2-Hydroxyethoxy)ethyl)amino)-3-phenylpyrazolo[1,5-a]pyrimidin-5-yl)phenol [Pir-10-2] (7as)



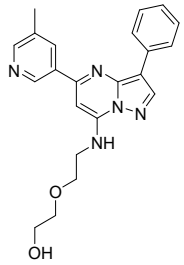
7as was prepared from tert-butyl (2-(2-((tert-butyldimethylsilyl)oxy)ethoxy)ethyl)(5-chloro-3-phenylpyrazolo[1,5-a]pyrimidin-7-yl)carbamate (**32a**) and 3-hydroxyphenylboronic acid by following the procedure described in general method **A**. The purification was carried out using 10-30% acetone/DCM as eluent to afford **7as** as white solid (yield 80%, HPLC purity 99% at 254 nm, 99% at 210 nm). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 9.64 (s, 1H), 8.65 (s, 1H), 8.29-8.22 (m, 2H), 7.94-7.86 (m, 1H), 7.72-7.63 (m, 2H), 7.44 (t, *J* = 7.7 Hz, 2H), 7.34 (t, *J* = 7.9 Hz, 1H), 7.24-7.16 (m, 1H), 6.90 (dd, *J* = 7.9; 0.7 Hz, 1H), 6.77 (s, 1H), 4.67-4.60 (m, 1H), 3.73 (s, 4H), 3.53-3.48 (m, 4H). ^{13}C-NMR (101 MHz, DMSO-d_6) δ 157.6, 156.3, 147.3, 145.0, 141.7, 139.7, 133.1, 129.7, 128.6, 125.2 (2C), 118.1, 116.9, 114.0, 107.6, 82.6, 72.3, 68.7, 60.3, 41.4. MS: 391.3 $[M+H]^+$; 389.2 $[M-H]^-$.

2-(2-((5-(5-Fluoropyridin-3-yl)-3-phenylpyrazolo[1,5-a]pyrimidin-7-yl)amino)ethoxy)ethan-1-ol [Pir-10-23] (7am)



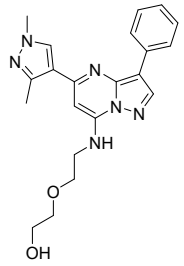
7am was prepared from tert-butyl (2-(2-((tert-butyldimethylsilyl)oxy)ethoxy)ethyl)(5-chloro-3-phenylpyrazolo[1,5-a]pyrimidin-7-yl)carbamate (**32a**) and (5-fluoropyridin-3-yl)boronic acid by following the procedure described in general method **A**. The purification was carried out using 20-100% acetone/DCM as eluent to afford **7am** as yellow solid (yield 83%, HPLC purity 99% at 254 nm, 99% at 210 nm). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.14 (t, *J* = 1.7 Hz, 1H), 8.56 (d, *J* = 2.7 Hz, 1H), 8.38 (s, 1H), 8.24 (ddd, *J* = 9.5, 2.7, 1.7 Hz, 1H), 8.18-8.11 (m, 2H), 7.50-7.44 (m, 2H), 7.29-7.24 (m, 1H, overlapped with $CDCl_3$), 6.88 (t, *J* = 5.6 Hz, 1H), 6.45 (s, 1H), 3.90 (t, *J* = 5.2 Hz, 2H), 3.85-3.80 (m, 2H), 3.74 (t, *J* = 5.3 Hz, 2H), 3.72-3.68 (m, 2H), 2.22 (t, *J* = 5.6 Hz, 1H). ^{13}C NMR (101 MHz,$CDCl_3$) δ 159.9 (d, *J* = 256.7 Hz), 153.1(d, *J* = 2.0 Hz),147.4,145.3, 144.4 (d, *J* = 3.9 Hz),142.2, 139.0 (d, *J* = 23.6 Hz), 136.2 (d, *J* = 3.9 Hz), 132.6, 128.9, 126.2, 126.1, 121.6 (d, *J* = 19.4 Hz), 110.5, 82.4, 72.8, 69.2, 62.0, 42.4. ^{19}F NMR (376 MHz, $CDCl_3$) δ -126.7 (d, *J* = 9.7 Hz). MS: 394.3 $[M+H]^+$; 392.3 $[M-H]^-$.

2-(2-((5-(5-Methylpyridin-3-yl)-3-phenylpyrazolo[1,5-a]pyrimidin-7-yl)amino)ethoxy)ethan-1-ol [Pir-10-22] (7aq)



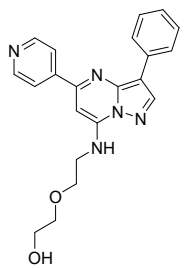
7aq was prepared from (2-(2-((tert-butyldimethylsilyl)oxy)ethoxy)ethyl)(5-chloro-3-phenylpyrazolo[1,5-a]pyrimidin-7-yl)carbamate (**32a**) and (5-methylpyridin-3-yl)boronic acid by following the procedure described in general method **A**. The purification was carried out using 20-100% acetone/DCM as eluent to afford **7aq** as yellow solid (yield 84%, HPLC purity 99% at 254 nm, 98% at 210 nm). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.14 (dq, *J* = 2.1; 0.6 Hz, 1H), 8.52 (dq, *J* = 2.1; 0.6 Hz, 1H), 8.37 (s, 1H), 8.26 (tq, *J* = 2.1; 0.6 Hz,1H), 8.19-8.15 (m, 2H), 7.49-7.43 (m, 2H), 7.28-7.23 (m, 1H, overlapped with $CDCl_3$), 6.82 (t, *J* = 5.6 Hz, 1H), 6.44 (s, 1H), 3.91-3.88 (m, 2H), 3.85-3.79 (m, 2H), 3.76-3.68 (m, 4H), 2.47 (q, *J* = 0.6 Hz, 3H), 2.27 (br s, 1H). ^{13}C NMR (101 MHz,$CDCl_3$) δ 155.0, 151.3, 147.3, 146.1, 145.5, 142.0, 135.3, 134.0, 133.2, 132.8, 128.9, 126.1, 126.0, 110.2, 82.5, 72.8, 69.2, 62.0, 42.3, 18.7. MS: 390.3 $[M+H]^+$; 388.3 $[M-H]^-$.

2-(2-((5-(1,3-Dimethyl-1H-pyrazol-4-yl)-3-phenylpyrazolo[1,5-a]pyrimidin-7-yl)amino)ethoxy)ethan-1-ol [Pir-10-21] (7ay)



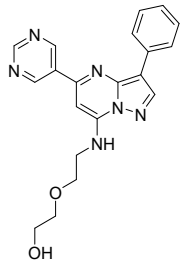
7ay was prepared from (2-(2-((tert-butyldimethylsilyl)oxy)ethoxy)ethyl)(5-chloro-3-phenylpyrazolo[1,5-a]pyrimidin-7-yl)carbamate (**32a**) and (1,3-dimethyl-1H-pyrazol-4-yl)boronic acid by following the procedure described in general method **A**. The purification was carried out using 50-100% acetone/DCM as eluent to afford **7ay** as white solid (yield 19%, HPLC purity 99% at 254 nm, 99% at 210 nm). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 8.15-8.10 (m, 2H), 7.74 (s, 1H), 7.44-7.38 (m, 2H), 7.24-7.18 (m, 1H), 6.59 (t, *J* = 5.5 Hz, 1H), 6.00 (s, 1H), 3.86 (s, 3H), 3.83-3.78 (m, 4H), 3.68-3.63 (m, 2H), 3.54 (q, *J* = 5.3 Hz, 2H), 2.66 (s, 3H). ^{13}C NMR (101 MHz,$CDCl_3$) δ 153.2, 148.0, 146.7, 145.5, 141.4, 133.1, 131.2, 128.6, 125.8, 125.5, 120.1, 108.9, 82.8, 72.8, 69.0, 61.8, 42.1, 38.9, 14.9. MS: 393.3 $[M+H]^+$; 391.3 $[M-H]^-$.

2-(2-((3-Phenyl-5-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-7-yl)amino)ethoxy)ethan-1-ol [Pir-10-14] (7au)



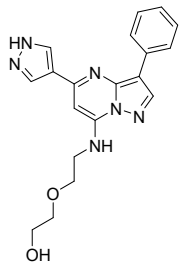
7au was prepared from (2-(2-((tert-butyldimethylsilyl)oxy)ethoxy)ethyl)(5-chloro-3-phenylpyrazolo[1,5-a]pyrimidin-7-yl)carbamate (**32a**) and pyridine-4-boronic acid by following the procedure described in general method **A**. The purification was carried out using 20-50% acetone/DCM as eluent to afford **7au** as yellow solid (yield 82%, HPLC purity 99% at 254 nm, 99% at 210 nm). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (dd, *J* = 4.5; 1.7 Hz, 2H), 8.39 (s, 1H), 8.19-8.15 (m, 2H), 8.02 (dd, *J* = 4.5; 1.7 Hz, 2H), 7.49-7.44 (m, 2H), 7.29-7.24 (m, 1H, overlapped with $CDCl_3$), 6.86 (t, *J* = 5.6 Hz, 1H), 6.48 (s, 1H), 3.92-3.88 (m, 2H), 3.85-3.80 (m, 2H), 3.75-3.68 (m, 4H), 2.25 (t, *J* = 5.4 Hz, 1H). ^{13}C NMR (101 MHz,$CDCl_3$) δ 154.4, 150.5, 147.3, 146.0, 145.3, 142.1, 132.6, 128.9, 126.1 (2C), 121.5, 110.5, 82.4, 72.8, 69.1, 62.0, 42.3. MS: 376.3 $[M+H]^+$; 374.2 $[M-H]^-$.

2-(2-((3-Phenyl-5-(pyrimidin-5-yl)pyrazolo[1,5-a]pyrimidin-7-yl)amino)ethoxy)ethan-1-ol [Pir-10-19] (7an)



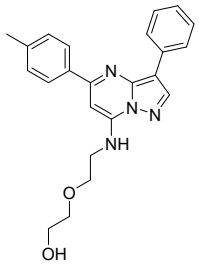
7an was prepared from (2-(2-((tert-butyldimethylsilyl)oxy)ethoxy)ethyl)(5-chloro-3-phenylpyrazolo[1,5-a]pyrimidin-7-yl)carbamate (**32a**) and pyrimidine-5-boronic acid by following the procedure described in general method **A**. The purification was carried out using 20-50% acetone/DCM as eluent to afford **7an** as yellow solid (yield 68%, HPLC purity 99% at 254 nm, 99% at 210 nm). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.46 (s, 2H), 9.30 (s, 1H), 8.37 (s, 1H), 8.18-8.12 (m, 2H), 7.49-7.43 (m, 2H), 7.29-7.24 (m, 1H, overlapped with $CDCl_3$), 6.91 (t, *J* = 5.4 Hz, 1H), 6.38 (s, 1H), 3.92-3.88 (m, 2H), 3.86-3.81 (m, 2H), 3.74-3.68 (m, 4H), 2.38 (t, *J* = 5.6 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 158.9, 155.4, 151.3, 147.6, 145.0, 142.0, 132.7, 131.3, 128.6, 125.4, 125.4, 108.2, 82.7, 72.2, 68.6, 60.3, 41.4. MS: 377.3 $[M+H]^+$; 375.3 $[M-H]^-$.

2-(2-((3-Phenyl-5-(1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-7-yl)amino)ethoxy)ethan-1-ol [Pir-10-12] (7ax)



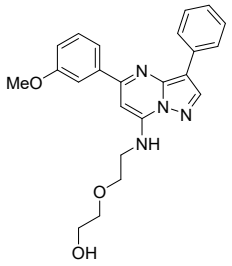
7ax was prepared from (2-(2-((tert-butyldimethylsilyl)oxy)ethoxy)ethyl)(5-chloro-3-phenylpyrazolo[1,5-a]pyrimidin-7-yl)carbamate (**32a**) and (1-(tert-butoxycarbonyl)-1H-pyrazol-4-yl)boronic acid by following the procedure described in general method **A**. The purification was carried out using acetone/DCM (2:1) as eluent to afford **7ax** as white solid (yield 50%, HPLC purity 98% at 254 nm, 94% at 210 nm). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.2 (br s, 1H), 8.57 (s, 1H), 8.50 (br s, 1H), 8.27-8.18 (m, 3H), 7.74 (t, *J* = 5.9 Hz, 1H), 7.44-7.38 (m, 2H), 7.20-7.14 (m, 1H), 6.65 (s, 1H), 4.66-4.61 (m, 4H), 3.76-3.63 (m, 4H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 152.2, 147.1, 145.2, 141.2, 138.1, 133.2, 128.5 (2C), 125.1, 124.9, 122.0, 106.6, 82.2, 72.2, 68.5, 60.3, 41.3. MS: 365.2 $[M+H]^+$; 363.2 $[M-H]^-$.

2-(2-((3-Phenyl-5-(p-tolyl)pyrazolo[1,5-a]pyrimidin-7-yl)amino)ethoxy)ethan-1-ol [Pir-10-11] (7bb)



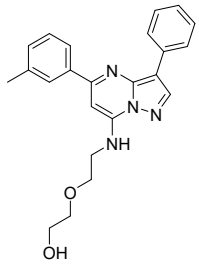
7bb was prepared from (2-(2-((tert-butyldimethylsilyl)oxy)ethoxy)ethyl)(5-chloro-3-phenylpyrazolo[1,5-a]pyrimidin-7-yl)carbamate (**32a**) and p-tolylboronic acid by following the procedure described in general method **A**. The purification was carried out using acetone/DCM (1:5) as eluent to afford **7bb** as yellow solid (yield 50%, HPLC purity 99% at 254 nm, 99% at 210 nm). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1H), 8.23-8.18 (m, 2H), 8.08-8.03 (m, 2H), 7.48-7.42 (m, 2H), 7.31 (d, *J* = 7.96 Hz, 2H), 7.25-7.20 (m, 1H), 6.71 (t, *J* = 5.6 Hz, 1H), 6.43 (s, 1H), 3.86 (t, *J* = 5.2 Hz, 2H), 3.83-3.77 (m, 2H), 3.72-3.65 (m, 4H), 2.44 (s, 3H), 2.36 (t, *J* = 5.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.4, 147.1, 145.7, 141.8, 140.1, 136.1, 133.1, 129.5, 128.8, 127.4, 126.0, 125.7, 109.6, 82.5, 72.7, 69.2, 62.0, 42.2, 21.5. MS: 389.3 $[M+H]^+$.

2-(2-((5-(3-Methoxyphenyl)-3-phenylpyrazolo[1,5-a]pyrimidin-7-yl)amino)ethoxy)ethan-1-ol [Pir-10-9-b] (7av)



7av was prepared from 5-bromo-N-(2-(2-((tert-butyldimethylsilyl)oxy)ethoxy)ethyl)-3-phenylpyrazolo[1,5-a]pyrimidin-7-amine (**32b**) and 3-methoxyphenylboronic acid by following the procedure described in general method **A**. The purification was carried out using acetone/DCM (1:5) as eluent to afford **7av** as yellow oil (yield 68%, HPLC purity 95% at 254 nm, 93% at 210 nm). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1H), 8.22-8.17 (m, 2H), 7.76 (dd, *J* = 2.6; 1.6 Hz, 1H), 7.70 (ddd, *J* = 7.7; 1.6; 1.0 Hz, 1H), 7.47-7.39 (m, 3H), 7.25-7.20 (m, 1H), 7.02 (ddd, *J* = 8.2; 2.6; 1.0 Hz, 1H), 6.47 (t, *J* = 5.6 Hz, 1H), 6.44 (s, 1H), 3.92 (s, 3H), 3.88-3.83 (m, 2H), 3.82-3.79 (m, 2H), 3.71-3.65 (m, 4H), 2.37 (br s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.1, 157.2, 147.1, 145.5, 141.9, 140.4, 133.0, 129.8, 128.8, 126.0, 125.7, 119.9, 115.4, 113.2, 109.8, 82.9, 72.7, 69.2, 62.0, 55.5, 42.2. MS: 405.3 $[M+H]^+$

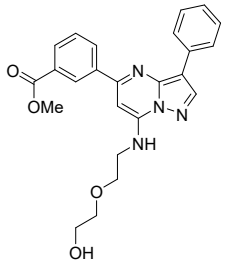
2-(2-((3-Phenyl-5-(m-tolyl)pyrazolo[1,5-a]pyrimidin-7-yl)amino)ethoxy)ethan-1-ol [Pir-10-9] (7ap)



7ap was prepared from 5-bromo-N-(2-(2-((tert-butyldimethylsilyl)oxy)ethoxy)ethyl)-3-phenylpyrazolo[1,5-a]pyrimidin-7-amine (**32b**) and m-tolylboronic acid by following the procedure described in general method **A**. The purification was carried out using acetone/DCM (1:5) as eluent to afford **7ap** as yellow solid (yield 47%, HPLC purity 99% at 254 nm, 99% at 210 nm). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1H), 8.22-8.17 (m, 2H), 7.97-7.92 (m, 2H), 7.48-7.42 (m, 2H),

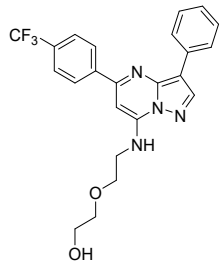
7.42-7.37 (m, 1H), 7.31-7.27 (m, 1H), 7.26-7.21 (m, 1H, overlapped with $CDCl_3$), 6.73 (t, *J* = 5.5 Hz, 1H), 6.44 (s, 1H), 3.89-3.85 (m, 2H), 3.84-3.78 (m, 2H), 3.71 (t, *J* = 5.5 Hz, 2H), 3.69-3.66 (m, 2H), 2.48 (s, 3H), 2.33 (br s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.7, 147.1, 145.6, 141.9, 138.9, 138.4, 133.1, 130.7, 128.8, 128.7, 128.1, 126.1, 125.7, 124.7, 109.8, 82.9, 72.7, 69.2, 62.0, 42.2, 21.8. MS: 389.3 $[M+H]^+$; 387.2 $[M-H]^-$.

Methyl 3-(7-((2-(2-hydroxyethoxy)ethyl)amino)-3-phenylpyrazolo[1,5-a]pyrimidin-5-yl)benzoate [Pir-10-6] (7ba)



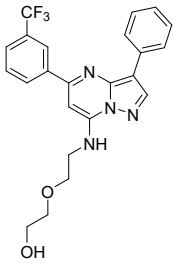
7ba was prepared from 5-bromo-N-(2-(2-((tert-butyldimethylsilyl)oxy)ethoxy)ethyl)-3-phenylpyrazolo[1,5-a]pyrimidin-7-amine (**32b**) and 3-methoxycarbonylphenylboronic acid by following the procedure described in general method **A**. The purification was carried out using 10-50% acetone/DCM as eluent to afford **7ba** as yellow solid (yield 38%, HPLC purity 99% at 254 nm, 99% at 210 nm). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (t, *J* = 1.7 Hz, 1H), 8.49 (ddd, *J* = 7.8; 1.7; 1.2 Hz, 1H), 8.36 (s, 1H), 8.20-8.16 (m, 2H), 8.13 (ddd, *J* = 7.8; 1.7; 1.2 Hz, 1H), 7.59 (t, *J* = 7.8 Hz, 1H), 7.49-7.42 (m, 2H), 7.27-7.21 (m, 1H overlapped with $CDCl_3$), 6.78 (t, *J* = 5.6 Hz, 1H), 6.52 (s, 1H), 3.98 (s, 3H), 3.88 (t, *J* = 5.1 Hz, 2H), 3.85-3.80 (m, 2H), 3.75-3.66 (m, 4H), 2.53 (br s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 156.2, 147.3, 145.5, 142.0, 139.2, 132.9, 132.3, 130.8, 130.6, 129.0, 128.8, 128.3, 126.1, 125.8, 110.0, 82.7, 72.8, 69.4, 62.0, 52.5, 42.4. MS: 433.3 $[M+H]^+$; 431.2 $[M-H]^-$.

2-(2-((3-Phenyl-5-(4-(trifluoromethyl)phenyl)pyrazolo[1,5-a]pyrimidin-7-yl)amino)ethoxy)ethan-1-ol [Pir-10-5] (7az)



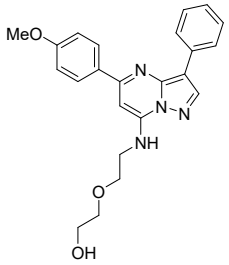
7az was prepared from 5-bromo-N-(2-(2-((tert-butyldimethylsilyl)oxy)ethoxy)ethyl)-3-phenylpyrazolo[1,5-a]pyrimidin-7-amine (**32b**) and 4-(trifluoromethyl)phenylboronic acid by following the procedure described in general method **A**. The purification was carried out using 10-50% acetone/DCM as eluent to afford **7az** as yellow solid (yield 75%, HPLC purity 99% at 254 nm, 99% at 210 nm). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.37 (s, 1H), 8.23 (d, *J* = 8.1 Hz, 2H), 8.18-8.13 (m, 2H), 7.75 (d, *J* = 8.1 Hz, 2H), 7.45 (t *J* = 7.8 Hz, 2H), 7.27-7.23 (m, 1H, overlapped with , $CDCl_3$), 6.81 (t, *J* = 5.6 Hz, 1H), 6.42 (s, 1H), 3.88 (t, *J* = 5.2 Hz, 2H), 3.84-3.80 (m, 2H), 3.71-3.70 (m, 4H), 2.24 (t, *J* = 5.9 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 155.7, 147.3, 145.4, 142.2, 142.1, 132.8, 131.5 (q, *J* = 32.7 Hz), 128.8, 127.8, 126.1, 126.0, 125.7 (q, *J* = 3.5 Hz), 124.3 (q, *J* = 273.4 Hz), 110.3, 82.7, 72.8, 69.1, 62.0, 42.3; MS: 443.2 $[M+H]^+$; 441.2 $[M-H]^-$.

2-(2-((3-Phenyl-5-(3-(trifluoromethyl)phenyl)pyrazolo[1,5-a]pyrimidin-7-yl)amino)ethoxy)ethan-1-ol [Pir-10-3] (7aw)



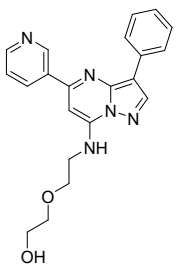
7aw was prepared from 5-bromo-N-(2-(2-((tert-butyldimethylsilyl)oxy)ethoxy)ethyl)-3-phenylpyrazolo[1,5-a]pyrimidin-7-amine (**32b**) and 3-(trifluoromethyl)phenylboronic acid by following the procedure described in general method **A**. The purification was carried out using 10-30% acetone/DCM as eluent to afford **7aw** as yellow solid (yield 62%, HPLC purity 99% at 254 nm, 99% at 210 nm). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 7.7 Hz, 1H), 8.36 (s, 1H), 8.33 (br s, 1H), 8.19-8.14 (m, 2H), 7.72 (d, *J* = 7.7 Hz, 1H), 7.63 (t, *J* = 7.7 Hz, 1H), 7.49-7.41 (m, 2H), 7.25-7.22 (m, 1H overlapped with $CDCl_3$), 6.82 (t, *J* = 5.6 Hz, 1H), 6.43 (s, 1H), 3.90-3.86 (m, 2H), 3.85-3.79 (m, 2H), 3.74-3.67 (m, 4H), 2.41 (br s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.7, 147.3, 145.4, 142.1, 139.7, 132.8, 131.2 (*J* = 32.3 Hz), 130.8, 129.3, 128.8, 126.4 (*J* = 3.6 Hz), 126.1, 125.9, 124.3 (*J* = 272.3 Hz), 124.1 (*J* = 3.8 Hz), 110.2, 82.5, 72.8, 69.2, 62.0, 42.3. MS: 443.3 $[M+H]^+$.

2-(2-((5-(4-Methoxyphenyl)-3-phenylpyrazolo[1,5-a]pyrimidin-7-yl)amino)ethoxy)ethan-1-ol [Pir-10-4] (7ar)



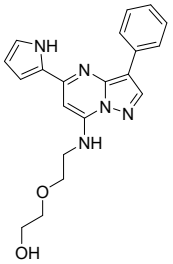
7ar was prepared from 5-bromo-N-(2-(2-((tert-butyldimethylsilyl)oxy)ethoxy)ethyl)-3-phenylpyrazolo[1,5-a]pyrimidin-7-amine (**32b**) and 4-methoxyphenylboronic acid by following the procedure described in general method **A**. The purification was carried out using 10-50% acetone/DCM as eluent to afford **7ar** as yellow solid (yield 63%, HPLC purity 99% at 254 nm, 99% at 210 nm). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 1H), 8.23-8.16 (m, 2H), 8.16-8.1 (m, 2H), 7.48-7.42 (m, 2H), 7.26-7.20 (m, 1H overlapped with $CDCl_3$), 7.06-7.00 (m, 2H), 6.69 (t, *J* = 5.6 Hz, 1H), 6.41 (s, 1H), 3.89 (s, 3H), 3.87 (t, *J* = 5.3 Hz, 2H), 3.83-3.78 (m, 2H), 3.73-3.65 (m, 4H), 2.22 (br s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.3, 157.0, 147.0, 145.6, 141.7, 133.2, 131.3, 128.9, 127.8, 125.9, 125.6, 114.1, 109.4, 82.1, 72.7, 69.1, 61.9, 55.5, 42.1. MS: 405.3 $[M+H]^+$; 403.2 $[M+H]^-$.

2-(2-((3-phenyl-5-(pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-7-yl)amino)ethoxy)ethan-1-ol [Pir-10-7] ***(7al)***



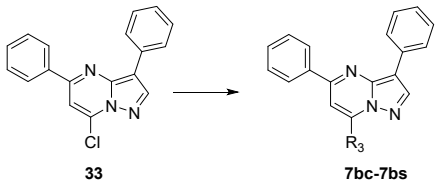
7al was prepared from 5-bromo-N-(2-(2-((tert-butyldimethylsilyl)oxy)ethoxy)ethyl)-3-phenylpyrazolo[1,5-a]pyrimidin-7-amine (**32b**) and 3-pyridinylboronic acid by following the procedure described in general method **A**. The purification was carried out using 30-70% acetone/DCM as eluent to afford **7al** as yellow solid (yield 43%, HPLC purity 99% at 254 nm, 99% at 210 nm). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.34 (dd, *J* = 2.3; 0.7 Hz, 1H), 8.69 (dd, *J* = 4.8; 1.7 Hz, 1H), 8.45 (ddd, *J* = 8.0; 2.3; 1.7 Hz, 1H), 8.35 (s, 1H), 8.19-8.14 (m, 2H), 7.48-7.40 (m, 3H), 7.28-7.22 (m, 1H, overlapped with $CDCl_3$), 6.81 (t, *J* = 5.5 Hz, 1H), 6.41 (s, 1H), 3.90-3.86 (m, 2H), 3.85-3.80 (m, 2H), 3.73-3.66 (m, 4H), 2.51 (br s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.6, 150.7, 148.8, 147.3, 145.5, 142.0, 134.9, 134.4, 132.8, 128.8, 126.1, 126.0, 123.7, 110.2, 82.3, 72.8, 69.1, 62.0, 42.3. MS: 376.2 $[M+H]^+$; 374.2 $[M-H]^-$.

2.7.3.6 Synthesis of 2-(2-((3-phenyl-5-(1H-pyrrol-2-yl)pyrazolo[1,5-a]pyrimidin-7-yl)amino)-ethoxy)ethan-1-ol [Pir-10-20] (7at)



THF (2 mL) and aq 0.5M K_3PO_4 (4 mL, 8eq) were added to the mixture X-Phos Pd G2 (6 mg, 3mol-%), 2-(2-((tert-butyldimethylsilyl)oxy)ethoxy)ethyl)(5-chloro-3-phenylpyrazolo[1,5-a]pyrimidin-7-yl)carbamate (**32a**, 150 mg, 0.27mmol) and N-Boc-2-pyrroleboronic acid (114 mg, 2.0 eq) under argon. The reaction mixture was stirred for 2h at 40°C, then cooled to RT and extracted with DCM (2x20 mL). The combined organics were dried over Na_2SO_4 and concentrated in vacuo. The residue was dissolved in mixture of DCM (5 mL) and TFA (1.3 mL) and stirred for 18h at RT, then concentrated in vacuo. The obtained oil was stirred with K_2CO_3 (0.4 g, 5eq) in 90% aq MeOH for 2h. The obtained mixture was concentrated in vacuo, the residue was dissolved in mixture of DCM (40 mL) and water (20 mL). The organic layer was separated, dried over Na_2SO_4 and concentrated in vacuo. The oily residue was subjected to column chromatography (5-20% acetone/DCM as eluent) to give the desired reaction product **7at** as brown semi-solid (40 mg, yield 41%, HPLC purity 99% at 254 nm, 98% at 210 nm). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (br s, 1H), 8.26 (s, 1H), 8.08-8.04 (m, 2H), 7.47-7.41 (m, 2H), 7.26-7.21 (m, 1H, overlapped with $CDCl_3$), 7.00 (td, *J* = 2.6; 1.4, 1H), 6.79 (ddd, *J* = 3.7, 2.6, 1.4 Hz, 1H), 6.66 (t, *J* = 5.7 Hz ,1H), 6.33 (dt, *J* = 3.7, 2.6 Hz, 1H), 6.25 (s, 1H), 3.87-3.83 (m, 2H), 3.82-3.78 (m, 2H), 3.69-3.62 (m, 4H), 2.32 (br s, 1H). ^{13}C NMR (101 MHz,$CDCl_3$) δ 150.3, 146.9, 145.4, 141.8, 133.2, 131.1, 128.8, 126.1, 125.7, 121.1, 110.6, 109.2, 109.0, 80.76, 72.7, 69.2, 62.0, 42.2. MS: 364.3 $[M+H]^+$; 362.3 $[M-H]^-$.

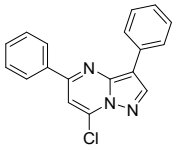
2.7.4 The general procedure of 7-substituted 3,5-diphenylpyrazolo[1,5-a]pyrimidine preparation



33 **7bc-7bs**

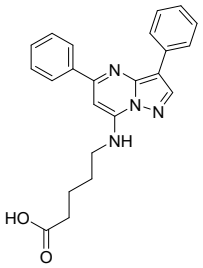
Scheme 3

2.7.4.1 7-Chloro-3,5-diphenylpyrazolo[1,5-a]pyrimidine (33)



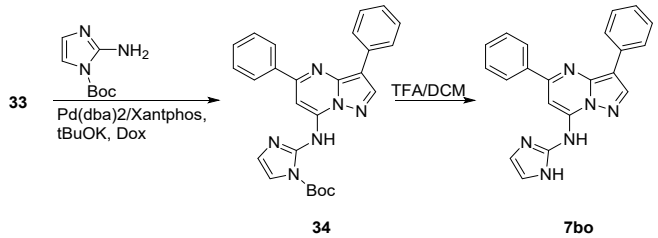
33 was prepared by method described by Yin L., 2005, Synthesis of new calcineurin inhibitors via palladium catalysis cross coupling reactions, (20121004).

2.7.4.2 Synthesis of 5-((3,5-diphenylpyrazolo[1,5-a]pyrimidin-7-yl)amino)pentanoic acid [Pir-9-1] (7br)



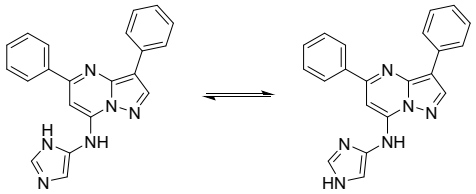
A mixture of **33** (300 mg, 1.0 mmol), 5-aminopentanoic acid (172 mg, 1.5 eq) and DIPEA (0.9 mL, 5 eq) in DMAA (5 mL) was stirred at 80°C for 5h, then cooled to RT and poured on ice. The solid was filtered off and dried in air. The crude product was purified by column chromatography (acetone /DCM 1:5) to afford desired **7br** as yellow solid (100 mg, yield 26%, HPLC purity 99% at 254 nm, 98% at 210 nm). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 12.04 (br s, 1H), 8.65 (s, 1H), 8.31-8.23 (m, 4H), 8.13 (t, *J* = 6.1 Hz, 1H), 7.59-7.48 (m, 3H), 7.47-7.40 (m, 2H), 7.19 (tt, *J* = 7.3; 1.1 Hz, 1H), 6.78 (s, 1H), 3.56 (m, 2H), 2.30 (t, *J* = 7.2 Hz, 2H), 1.79-1.68 (m, 2H), 1.68-1.58 (m, 2H). ^{13}C-NMR (101 MHz, DMSO-d_6) δ 174.5, 156.2, 147.2, 145.1, 141.7, 138.3, 133.1, 129.8, 128.7, 128.6, 127.2, 125.2, 125.2, 107.6, 82.2, 40.95, 33.3, 27.9, 21.9. MS: 387.3 $[M+H]^+$; 385.2 $[M-H]^-$.

2.7.4.3 Synthesis of N-(1H-imidazol-2-yl)-3,5-diphenylpyrazolo[1,5-a]pyrimidin-7-amine [Pir-9-2] (7bo)



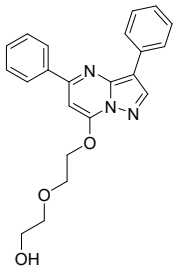
In a flask were charged **33** (100 mg, 0.32 mmol), 2-amino-1-Boc-imidazole (88 mg, 1.5 eq), *t*-BuOK (90 mg, 2.5 eq), $Pd(dba)_2$ (15 mg, 5mol-%) and dioxane (5 mL), then Xantphos (18 mg, 10 mol-%) was introduced under argon. The reaction mixture was heated and stirred at 100°C for 18h, then cooled to RT, diluted with water (10 mL) and extracted with EtOAc (3×10 mL). Combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The obtained residue was subjected to column chromatography (10%-100% EtOAc/PE). Isolated **34** was dissolved in DCM (5 mL) and TFA (1 mL) and stirred for 2h at RT, then concentrated in vacuo. The obtained oil was dissolved in EtOAc (20 mL) and washed with aq $NaHCO_3$ (2×5 mL). EtOAc layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was crystallized from toluene to give **7bo** as yellow solid (25 mg, yield 22%, HPLC purity 99% at 254 nm, 98% at 210 nm); ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.02 (br s, 1H), 8.78 (s, 1H), 8.33-8.27 (m, 2H), 8.23-8.12 (m, 3H), 7.65-7.52 (m, 3H), 7.47 (t, *J* = 7.8 Hz , 2H), 7.26-7.19 (m, 1H), 6.97 (s, 2H). ^{13}C-NMR (101 MHz, DMSO-d_6) δ 156.5 (2C), 145.1, 143.2, 141.8, 141.5, 138.0, 132.8, 130.1, 129.0, 128.7, 127.0, 125.5, 125.4, 108.4, 87.2. MS: 353.2 $[M+H]^+$; 351.2 $[M-H]^-$.

2.7.4.4 Synthesis of N-(1H-imidazol-5-yl)-3,5-diphenylpyrazolo[1,5-a]pyrimidin-7-amine [Pir-9-3] (7bq)



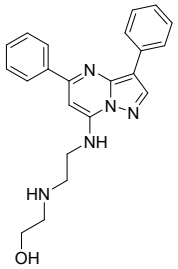
A suspension of 1H-imidazol-4-amine hydrochloride (38 mg, 1.5 eq) and NaH (40 mg, 6 eq, 60% suspension in mineral oil) in DMAA (4 mL) was stirred for 1h at RT, then **33** (50 mg, 0.16 mmol) was added and the reaction mixture was stirred at 60°C for 2h. After cooling to RT, the mixture was quenched with 5% aq AcOH (5 mL) and extracted with EtOAc (3×15 mL). Combined organics were dried over Na_2SO_4, concentrated in vacuo. The obtained residue was subjected to column chromatography (0%-50% MeOH/DCM) to afford **7bq** as a mixture of tautomers in ratio 1:1 (10 mg, yield 18%, HPLC purity 93% at 254 nm, 95% at 210 nm). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 12.46 (s, 0.5H), 11.60 (s, 0.5H), 8.78 (s, 0.5H), 8.74 (s, 0.5H), 8.39-8.19 (m, 4H), 7.91 (s, 0.5H), 7.75 (s, 0.5H), 7.66-7.50 (m, 3.5 H), 7.51-7.42 (m, 2.5H), 7.24 (t, *J* = 7.4 Hz, 1H), 7.19 (s, 1H), 6.40 (s, 1H). ^{13}C-NMR (101 MHz, CD_3OD) δ 156.9 (2C), 147.3, 142.4, 139.0, 133.8, 131.0, 129.8, 129.6, 129.4, 129.1, 128.3, 127.0, 126.7, 126.2, 110.3, 100.1. MS: 353.2 $[M+H]^+$.

2.7.4.5 Synthesis of 2-(2-((3,5-diphenylpyrazolo[1,5-a]pyrimidin-7-yl)oxy)ethoxy)ethan-1-ol [Pir-9-5] (7bm)



Potassium bis(trimethylsilil)amide (1M in THF, 0.2 mL, 1.2 eq) was added to a suspension of 7-chloro-3,5-diphenylpyrazolo[1,5-a]pyrimidine (**33,** 50 mg, 0.16 mmol) in bis(hydroxyethyl)-ether (1 mL). The reaction mixture was heated at 120°C for 5h, then cooled to RT and diluted with DCM (50 mL). The obtained solution was washed with brine (2×15 mL). Organic phase was dried over Na_2SO_4 and concentrated in vacuo. The obtained residue was subjected to column chromatography (10-50% acetone/DCM) to afford **7bm** (10 mg, yield 17%, HPLC purity 99% at 254 nm, 98% at 210 nm). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 8.20-8.14 (m, 4H), 7.57-7.50 (m, 3H), 7.50-7.44 (m, 2H), 7.30-7.24 (m, 1H overlapped witj $CDCl_3$), 6.73 (s, 1H), 4.66-4.61 (m, 2H), 4.15-4.09 (m, 2H), 3.85-3.80 (m, 2H), 3.78-3.74 (m, 2H), 2 95 (br s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 158.2, 155.4, 146.7, 143.4, 137.9, 132.4, 130.6, 129.0, 128.9, 127.5, 126.3, 126.2, 110.7, 84.9, 73.2, 70.0, 68.6, 61.8; MS: 376.2 $[M+H]^+$;

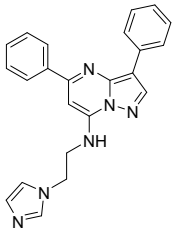
2.7.4.6 Synthesis of 2-((2-((3,5-diphenylpyrazolo[1,5-a]pyrimidin-7-yl)amino)ethyl)amino)ethan-1-ol [IDR-Pir-9-6] (7bn)



A mixture of 7-chloro-3,5-diphenylpyrazolo[1,5-a]pyrimidine (33, 200 mg, 0.65 mmol), K_2CO_3 (0.45 g, 5 eq) and *N*-(2-hydroxyethyl)ethylenediamine (0.2 mL, 3 eq) in MeCN (10 mL) was

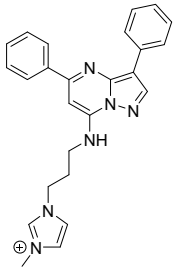
refluxed for 4h. The cooled reaction mixture was evaporated in vacuo, the residue was dissolved in mixture of water (60 mL) and DCM (60 mL) and acidified with 1N HCl (~1.7 mL) to pH 7. The organic layer was separated, dried and concentrated. The residue was treated with TBME (10 mL) to give desired product as yellow solid (160 mg, yield 66%, HPLC purity 97% at 254 nm, 97% at 210 nm). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 1H), 8.19 (dd, *J* = 8.3; 1.0 Hz, 2H), 8.16-8.12 (m, 2H), 7.53-7.41 (m, 5H), 7.23 (td, J = 7.4; 1.3 Hz, 1H), 6.84 (br s, 1H), 6.39 (s, 1H), 3.73-3.68 (m, 2H), 3.58-3.49 (m, 2H), 3.04 (t, *J* = 5.8 Hz, 2H), 2.86-2.81 (m, 2H), 2.29 (br s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.4, 147.0, 145.6, 141.8, 138.8, 133.1, 129.9, 128.9 (2C), 127.5, 126.0, 125.7, 109.7, 82.7, 61.4, 51.1, 47.7, 41.8. MS: 374.2 $[M+H]^+$.

2.7.4.7 N-(2-(1H-imidazol-1-yl)ethyl)-3,5-diphenylpyrazolo[1,5-a]pyrimidin-7-amine [Pir-9-8] (7bp)



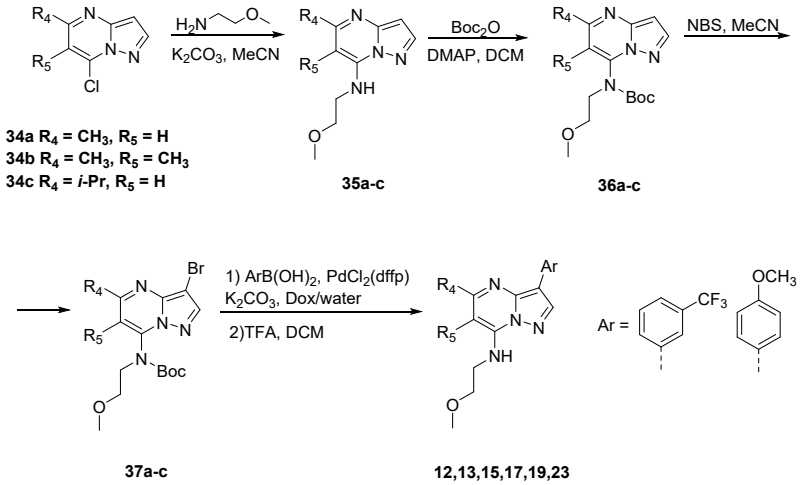
7bp (a white solid, yield 36%, HPLC purity 99% at 254 nm, 99% at 210 nm) was prepared by method described previously for **7bn** using 2-(1H-imidazol-1-yl)ethanamine instead of *N*-(2-hydroxyethyl)ethylenediamine. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 1H), 8.18 (dd, *J* = 8.3; 1.2 Hz, 2H), 8.12-8.07 (m, 2H), 7.56-7.42 (m, 6H), 7.28-7.22 (m, 1H overlapped with $CDCl_3$), 7.11 (t, *J* = 1.0 Hz, 1H), 7.00 (t, *J* = 1.2 Hz, 1H), 6.54 (t, *J* = 6.5 Hz, 1H), 6.23 (s, 1H), 4.33-4.26 (m, 2H), 3.88-3.79 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.5, 146.4, 145.4, 142.0, 138.6, 137.4, 132.8, 130.7, 130.1, 128.9, 128.8, 127.5, 126.1, 125.9, 119.0, 110.2, 82.2, 46.3, 43.4. MS: 381.2 $[M+H]^+$; 379.2 $[M-H]^-$.

2.7.4.8 1-(3-((3,5-Diphenylpyrazolo[1,5-a]pyrimidin-7-yl)amino)propyl)-3-methyl-1H-imidazol-3-ium [Pir-9-7] (7bs)



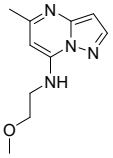
7bs (a yellow semisolid, yield 36%, HPLC purity 91% at 254 nm, 92% at 210 nm) was prepared by the method described previously for **7bn** using 1-(3-((3,5-diphenylpyrazolo[1,5-a]pyrimidin-7-yl)amino)propyl)-3-methyl-1H-imidazol-3-ium iodide instead of *N*-(2-hydroxyethyl)ethylenediamine. ^{1}H NMR (300 MHz, CD_3OD) δ 8.95 (s, 1H), 8.48 (s, 1H), 8.27-8.20 (m, 4H), 7.68 (t, *J* = 1.8 Hz, 1H), 7.58-7.48 (m, 4H), 7.43 (t, *J* = 7.7 Hz, 2H), 7.22 (t, *J* = 7.4 Hz, 1H), 6.66 (s, 1H), 4.44 (t, *J* = 7.0 Hz, 2H), 3.85 (s, 3H), 3.73 (t, *J* = 6.5 Hz, 2H), 2.42 (m, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 156.2, 147.1, 145.1, 141.6, 138.2, 136.8, 133.0, 129.9, 128.6, 128.5, 127.2, 125.2 (2xC), 123.6, 122.3, 107.7, 82.3, 46.7, 38.3, 35.7, 28.7; MS: 409.2 $[M+H]^+$; 407.2 $[M-H]^-$.

2.7.5 Synthesis of N-(2-methoxyethyl)-3-arylpyrazolo[1,5-a]pyrimidin-7-amines



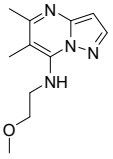
Scheme 4

2.7.5.1 Synthesis of N-(2-methoxyethyl)-5-methylpyrazolo[1,5-a]pyrimidin-7-amine (35a)



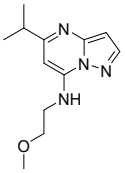
A mixture of 7-chloro-5-methylpyrazolo[1,5-a]pyrimidine (**34a**, 1.5 g, 9.0 mmol), 2-methoxyethylamine (1.2 mL, 1.5 eq) and K_2CO_3 (6.2 g, 5 eq) in MeCN (40 mL) was refluxed for 18h, then cooled to RT and concentrated in vacuo. The resulting residue was dissolved in water (30 mL) and DCM (30 mL). The phases were separated, and the water layer was extracted with DCM (1×25 mL). Combined organics were dried over Na_2SO_4 and concentrated in vacuo. The desired product **35a** was isolated as colorless oil (1.6 g, yield 90 %). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.95 (d, *J* = 2.3 Hz, 1H), 6.49 (br s, 1H), 6.37 (d, *J* = 2.3 Hz, 1H), 5.82 (s, 1H), 3.70-3.66 (m, 2H), 3.57-3.51 (m, 2H), 3.42 (s, 3H), 2.50 (s, 3H); MS: 207.1 $[M+H]^+$.

N-(2-methoxyethyl)-5,6-dimethylpyrazolo[1,5-a]pyrimidin-7-amine (35b)



35b was prepared from 7-chloro-5,6-dimethylpyrazolo[1,5-a]pyrimidine (**34b)** using the method described previously for the synthesis of N-(2-methoxyethyl)-5-methylpyrazolo[1,5-a]pyrimidin-7-amine (**35a**). The isolated crude product was purified by column chromatography (10%-30% EtOAc/PE) to afford desired product as colorless oil (yield 78%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.90 (d, *J* = 2.3 Hz), 6.35 (d, *J* = 2.3 Hz), 6.28 (br s, 1H), 3.93-3.85 (m, 2H), 3.62 (t, *J* = 5.2 Hz, 2H), 3.41 (s, 3H), 2.50 (s, 3H), 2.31 (s, 3H); MS: 221.1 $[M+H]^+$.

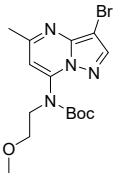
5-i-Propyl-N-(2-methoxyethyl)pyrazolo[1,5-a]pyrimidin-7-amine (35c)



35c was prepared in 90% yield from 7-chloro-5-isopropylpyrazolo[1,5-a]pyrimidine **34c** using the method described previously for the synthesis of N-(2-methoxyethyl)-5-methylpyrazolo[1,5-

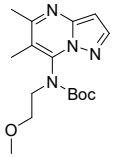
a]pyrimidin-7-amine (**35a**). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.95 (d, *J* = 2.3 Hz, 1H), 6.50 (br s, 1H), 6.41 (d, *J* = 2.3 Hz, 1H), 5.83 (s, 1H), 3.71-3.64 (m, 2H), 3.59-3.52 (m, 2H), 3.41 (s, 3H), 2.98 (septet, *J* = 6.9 Hz, 1H), 1.31 (d, *J* = 6.9 Hz, 6H); MS: 235.1 $[M+H]^+$.

2.7.5.2 Synthesis of t-butyl (3-bromo-5-methylpyrazolo[1,5-a]pyrimidin-7-yl)(2-methoxyethyl)carbamate (37a)



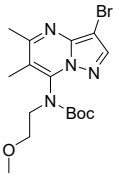
To a stirred solution of N-(2-methoxyethyl)-5-methylpyrazolo[1,5-a]pyrimidin-7-amine (**35a**, 1.6 g, 7.8 mmol) in DCM (50 mL) was added di-*t*-butyl dicarbonate (4.2 g, 2.5 eq) followed by 4-dimethylaminopyridine (94 mg, 0.1 eq). The reaction mixture was stirred at RT for 18h, then washed with water (2×50 mL), dried over Na_2SO_4, concentrated in vacuo to obtain crude t-butyl (2-methoxyethyl)(5-methylpyrazolo[1,5-a]pyrimidin-7-yl)carbamate (**36a**) as colorless oil.
N-bromosuccinimide (1.2 g) was added to the crude *t*-butyl (2-methoxyethyl)(5-methylpyrazolo[1,5-a]pyrimidin-7-yl)carbamate (**36a**) in MeCN (80 mL) at RT. After stirring the reaction mixture for 18h the solvent was evaporated in vacuo. The resulting semisolid was dissolved in DCM (50 mL). The obtained solution was washed with water (30 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was subjected to column chromatography (10%-50% EtOAc/PE) to give brominated product **37a** as yellow solid (1.2 g, yield 40%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.04 (s, 1H), 6.77 (s, 1H), 3.92 (t, *J* = 5.2 Hz, 2H), 3.56 (t, *J* = 5.2 Hz, 2H), 3.20 (s, 3H), 2.66 (s, 3H), 1.34 (s, 9H); MS: 385.2 $[M\ (^{79}Br)+H]^+$, 387.2 $[M\ (^{81}Br)+H]^+$.

2.7.5.3 Synthesis of t-butyl (5,6-dimethylpyrazolo[1,5-a]pyrimidin-7-yl)(2-methoxyethyl)-carbamate (36b)



A mixture of N-(2-methoxyethyl)-5,6-dimethylpyrazolo[1,5-a]pyrimidin-7-amine (**35b**, 5.0 g, 22.7 mmol), di-*t*-butyl dicarbonate (9.9 g, 2 eq), TEA (9.6 mL, 3eq) and 4-dimethylaminopyridine (280 mg, 0.1 eq) in DCM was stirred for 18h at RT. Additional amount (2 eq) of di-*tert*-butyl dicarbonate was added portionwise to reaction mixture and stirring was continued until all starting material was converted to the desired Boc-product (LC-MS control). After the usual workup (see previously) the isolated crude product was purified by column chromatography (10%-50% EtOAc/PE) to give the desired Boc-product **36b** as colorless oil 5.8 g (yield 78%). ^{1}H-NMR (400 MHz, $CDCl_3$, mixture of two rotamers) δ 8.00-7.97 (m, 1H), 6.56 (d, *J* = 2.3 Hz, 1H), 4.18-4.12 (m, 0.3H), 4.12-4.03 (m, 0.7H), 3.84-3.73 (m, 1H), 3.65-3.58 (m, 0.7H), 3.58-3.51 (m, 0.3H), 3.46-3.36 (m, 1H), 3.22 (s, 0.9H), 3.16 (s, 2.1 H), 2.59 (s, 2.1 H), 2.58 (s, 0.9H), 2.25 (s, 2.1 H), 2.23 (s, 0.9H), 1.56 (s, 2.7H), 1.28 (s, 6.3 H); MS: 321.2 $[M+H]^+$.

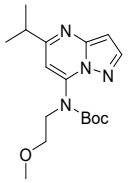
2.7.5.4 t-Butyl (3-bromo-5,6-dimethylpyrazolo[1,5-a]pyrimidin-7-yl)(2-methoxyethyl)carbamate (37b)



37b as white solid (yield 90%) was prepared by reacting *t*-butyl (5,6-dimethylpyrazolo[1,5-a]pyrimidin-7-yl)(2-methoxyethyl)carbamate (**36b**) with N-bromosuccinimide (1.2 eq) using the

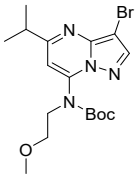
method described previously for the synthesis of *t*-butyl (3-bromo-5-methylpyrazolo[1,5-a]pyrimidin-7-yl)(2-methoxyethyl)carbamate (**37a**).
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 0.7H), 7.97 (s, 0.3H), 4.10-4.06 (m, 0.3H), 4.06-3.97 (m, 0.7H), 3.82-3.74 (m, 0.7H), 3.74-3.70 (m, 0.3H), 3.64-3.57 (m, 0.7H), 3.57-3.51 (m, 0.3H), 3.45-3.38 (m, 0.7H), 3.38-3.33 (m, 0.3H), 3.20 (s, 0.9H), 3.13 (s, 2.1H), 2.65 (s, 2.1H), 2.64 (s, 0.9H), 2.26 (s, 2.1H), 2.24 (s, 0.9H), 1.55 (s, 2.7H), 1.28 (s, 6.3 H); MS: 399.2 [M (^{79}Br)+H]$^{+}$, 401.2 [M (^{81}Br)+H]$^{+}$.

2.7.5.5 t-Butyl (5-isopropylpyrazolo[1,5-a]pyrimidin-7-yl)(2-methoxyethyl)carbamate (36c)



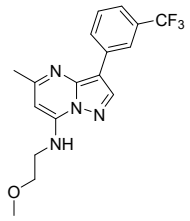
36c as colorless oil (yield 90%) was prepared from 5-*i*-propyl-N-(2-methoxyethyl)pyrazolo[1,5-a]pyrimidin-7-amine (**35c**) using the method described previously for the synthesis of *t*-butyl (5,6-dimethylpyrazolo[1,5-a]pyrimidin-7-yl)(2-methoxyethyl)carbamate (**36b**). The crude product was purified by column chromatography (0%-20% acetone/DCM) ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 2.3 Hz, 1H), 6.76 (s, 1H), 6.63 (d, *J* = 2.3 Hz, 1H), 3.98 (t, *J* = 5.4 Hz, 2H), 3.57 (t, *J* = 5.4 Hz, 2H), 3.24 (s, 3H), 3.10 (septet, *J* = 6.9 Hz, 1H), 1.38-1.33 (m, 15H); MS: 335.2 [M+H]$^{+}$.

2.7.5.6 tert-Butyl (3-bromo-5-isopropylpyrazolo[1,5-a]pyrimidin-7-yl)(2-methoxyethyl)carbamate (37c)



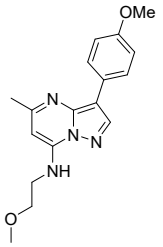
37c as brown oil (yield 68%) was prepared in reaction of *t*-butyl (5-isopropylpyrazolo[1,5-a]pyrimidin-7-yl)(2-methoxyethyl)carbamate (**36c**) with N-bromosuccinimide (1.2 eq) using the method described previously for the synthesis of **37a**. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 6.82 (s, 1H), 3.94 (t, *J* = 5.2 Hz, 2H), 3.55 (t, *J* = 5.2 Hz, 2H), 3.22 (s, 3H), 3.17 (septet, *J* = 6.9 Hz, 1H), 1.38-1.33 (m, 15H); MS: 413.1 [M (^{79}Br)+H]$^{+}$, 415.1 [M (^{81}Br)+H]$^{+}$.

N-(2-Methoxyethyl)-5-methyl-3-(3-(trifluoromethyl)phenyl)pyrazolo[1,5-a]pyrimidin-7-amine [Pir-11-1] (13)



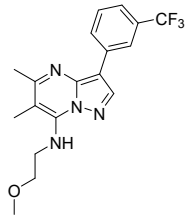
13 was prepared from **37a** and (3-(trifluoromethyl)phenylboronic acid by following the procedure described in general method **A**. The purification was carried out using 0-10% acetone/DCM as eluent to afford **13** as brown solid (yield 28%, HPLC purity 99% at 254 nm, 99% at 210 nm). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.33 (br s, 1H), 8.31 (d, *J* = 7.7 Hz , 1H), 8.30 (s, 1H), 7.51 (t, *J* = 7.7 Hz, 1H), 7.43 (d, *J* = 7.7 Hz, 1H), 6.53 (t, *J* = 5.4 Hz, 1H), 5.90 (s, 1H), 3.69 (t, *J* = 5.4 Hz, 2H), 3.56 (q, *J* = 5.4 Hz, 2H), 3.43 (s, 3H), 2.58 (s, 3H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 160.6, 146.5, 145.7, 141.4, 134.05, 131.0 (q, *J* = 31.9 Hz), 129.1, 129.0, 124.7 (q, *J* = 271.6 Hz), 122.4 (q, *J* = 3.8 Hz), 122.0 (q, *J* = 3.8 Hz), 107.2, 86.2, 70.3, 59.2, 41.9, 25.6. MS: 351.2 [M+H]$^{+}$; 349.1 [M-H]$^{-}$.

N-(2-Methoxyethyl)-3-(4-methoxyphenyl)-5-methylpyrazolo[1,5-a]pyrimidin-7-amine [Pir-11-2] (23)



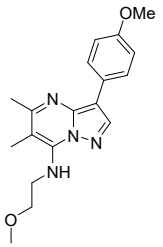
23 was prepared from **37a** and 4-methoxyphenylboronic acid by following the procedure described in general method **A**. The purification was carried out using 0-10% acetone/DCM as eluent to afford **23** as white solid (yield 48%, HPLC purity 99% at 254 nm, 98% at 210 nm). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 8.01-7.96 (m, 2H), 7.01-6.95 (m, 2H), 6.47 (t, *J* = 5.4 Hz, 1H), 5.85 (s, 1H), 3.84 (s, 3H), 3.69 (t, *J* = 5.5 Hz, 2H), 3.55 (q, *J* = 5.5 Hz, 2H), 3.43 (s, 3H), 2.56 (s, 3H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 159.7, 157.8, 146.4, 145.1, 141.1, 127.3, 125.9, 114.3, 108.6, 85.6, 70.4, 59.32, 55.5, 41.9, 25.6. MS: 313.2 $[M+H]^+$.

N-(2-Methoxyethyl)-5,6-dimethyl-3-(3-(trifluoromethyl)phenyl)pyrazolo[1,5-a]pyrimidin-7-amine [Pir-12-1] (15)



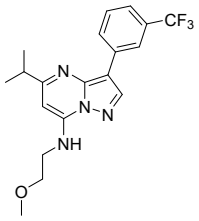
15 was prepared from **37b** and (3-(trifluoromethyl)phenylboronic acid by following the procedure described in general method **A**. The purification was carried out using 0-50% acetone/DCM as eluent to afford **15** as white solid (yield 16% after recrystallization from TBME, HPLC purity 99% at 254 nm, 99% at 210 nm). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1H), 8.29 (d, *J* = 7.8 Hz, 1H), 8.27 (s, 1H), 7.51 (t, *J* = 7.8 Hz, 1H), 7.42 (d, *J* = 7.8 Hz, 1H), 6.33 (t, *J* = 5.4 Hz, 1H), 3.93 (q, *J* = 5.4 Hz, 2H), 3.65 (t, *J* = 5.4 Hz, 2H), 3.43 (s, 3H), 2.59 (s, 3H), 2.36 (s, 3H). ^{13}C-NMR (101 MHz, DMSO) δ 160.7, 145.9, 144.2, 140.5, 134.2, 131.0 (q, *J* = 31.7 Hz), 129.1, 128.8, 124.6 (q, *J* = 272.0 Hz), 122.3 (q, *J* = 3.9 Hz), 121.8 (q, *J* = 3.9 Hz), 106.8, 97.3, 71.7, 59.2, 45.5, 24.8, 13.6. MS: 365.2 $[M+H]^+$; 363.1 $[M-H]^-$

N-(2-Methoxyethyl)-3-(4-methoxyphenyl)-5,6-dimethylpyrazolo[1,5-a]pyrimidin-7-amine [Pir-12-2] (17)



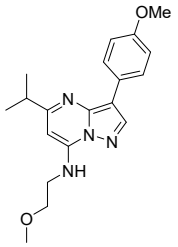
17 was prepared from **37b** and 4-methoxyphenylboronic acid by following the procedure described in general method **A**. The purification was carried out using 0-50% acetone/DCM as eluent to afford **17** as white solid (yield 61%, HPLC purity 99% at 254 nm, 99% at 210 nm). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 1H), 8.01-7.96 (m, 2H), 7.00-6.95 (m, 2H), 6.28 (t, *J* = 5.6 Hz, 1H), 3.92-3.87 (m, 2H), 3.84 (s, 3H), 3.64 (t, *J* = 5.2 Hz, 2H), 3.43 (s, 3H), 2.57 (s, 3H), 2.34 (s, 3H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 159.8, 157.7, 145.8, 143.7, 140.1, 127.1, 126.0, 114.3, 108.2, 96.8, 71.8, 59.2, 55.5, 45.5, 24.7, 13.6. MS: 327.2 $[M+H]^+$.

5-Isopropyl-N-(2-methoxyethyl)-3-(3-(trifluoromethyl)phenyl)pyrazolo[1,5-a]pyrimidin-7-amine [(Pir-14-1] (12)



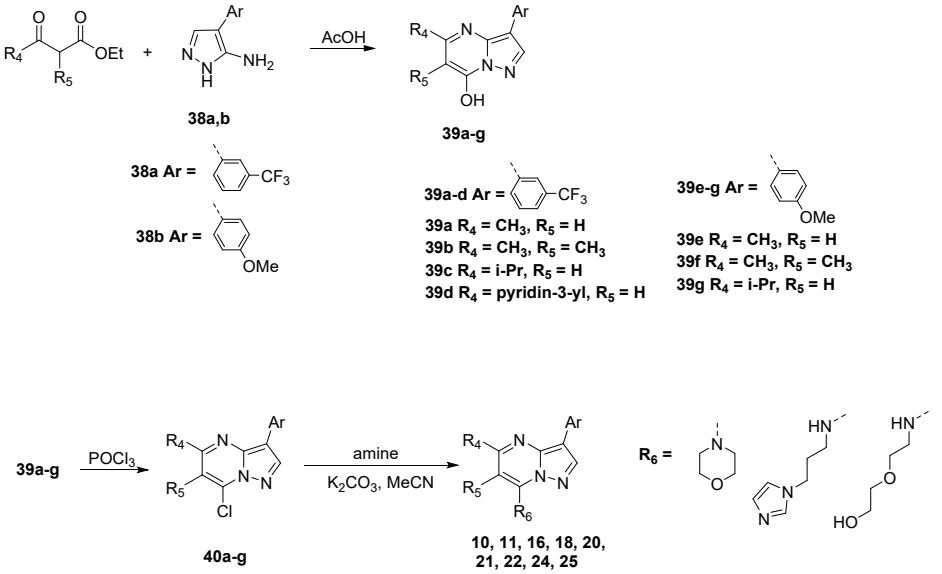
12 was prepared from **37c** and (3-(trifluoromethyl)phenylboronic acid by following the procedure described in general method **A**. The purification was carried out using 0-10% acetone/DCM as eluent to afford **12** as yellow solid (yield 82%, HPLC purity 98% at 254 nm, 99% at 210 nm). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1H), 8.33 (s, 1H), 8.30 (d, *J* = 7.8 Hz, 1H), 7.51 (t, *J* = 7.8 Hz, 1H), 7.42 (d, *J* = 7.8 Hz, 1H), 6.52 (t, *J* = 5.5 Hz, 1H), 5.93 (s, 1H), 3.72-3.68 (m, 2H), 3.61-3.55 (m, 2H), 3.44 (s, 3H), 3.05 (septet, *J* = 6.9 Hz, 1H), 1.38 (d, *J* = 6.9 Hz, 6H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 169.2, 146.9, 145.8, 141.2, 134.2, 130.9 (q, *J* = 31.7 Hz), 129.0, 128.5, 124.6 (q, *J* = 273.1 Hz), 122.4 (q, *J* = 4.0 Hz), 121.7 (q, *J* = 3.8 Hz), 107.1, 84.1, 70.3, 59.2, 42.0, 37.0, 22.3. MS: 379.2 $[M+H]^+$; 377.2 $[M+H]^-$.

5-Isopropyl-N-(2-methoxyethyl)-3-(4-methoxyphenyl)pyrazolo[1,5-a]pyrimidin-7-amine [Pir-14-2] (19)



19 was prepared from **37c** and 4-methoxyphenylboronic acid by following the procedure described in general method **A**. The purification was carried out using 0-10% acetone/DCM as eluent to afford **19** as brown solid (yield 85%, HPLC purity 99% at 254 nm, 98% at 210 nm). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1H), 8.10-8.03 (m, 2H), 7.02-6.94 (m, 2H), 6.45 (t, *J* = 5.5 Hz, 1H), 5.87 (s, 1H), 3.85 (s, 3H), 3.71-3.67 (m, 2H), 3.60-3.54 (m, 2H), 3.43 (s, 3H), 3.04 (septet, *J* = 6.9 Hz, 1H), 1.36 (d, J = 6.9 Hz, 6H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 168.3, 157.7, 146.8, 145.1, 140.9, 127.1, 126.1, 114.2, 108.4, 83.3, 70.4, 59.2, 55.5, 41.9, 37.1, 22.4. MS: 341.2 $[M+H]^+$.

2.7.6 Synthesis of *N*-substituted 3-arylpyrazolo[1,5-a]pyrimidin-7-amines

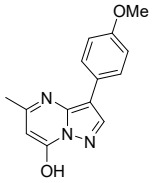


Scheme 5

2.7.6.1 General method B for the synthesis of 3-arylpyrazolo[1,5-a]pyrimidin-7-ols (39a-g)

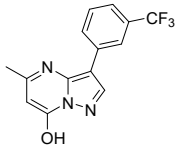
A mixture of 4-aryl-1H-pyrazol-5-amine (8.0 mmol) **38 a,b** and corresponding β-keto ester (1.2 eq) in AcOH (10 mL) was stirred at 100°C. The obtained mixture was then cooled to RT and diluted with TBME (30 mL). The resulting white solid was filtered off and dried in air.

3-(4-Methoxyphenyl)-5-methylpyrazolo[1,5-a]pyrimidin-7-ol (39e)



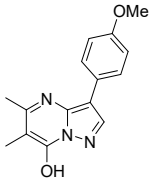
39e was prepared in 78% yield (1.6 g) from 4-(4-methoxyphenyl)-1H-pyrazol-5-amine (**38b**) and ethyl acetoacetate by heating for 4h. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.81 (s, 1H), 8.02 (s, 1H), 7.47 (d, *J*= 8.8 Hz, 2H), 7.03 (d, *J*= 8.8 Hz, 2H), 5.63 (s, 1H), 3.80 (s, 3H), 2.33 (s, 3H). MS: 256.1 $[M+H]^+$.

5-Methyl-3-(3-(trifluoromethyl)phenyl)pyrazolo[1,5-a]pyrimidin-7-ol (39a)



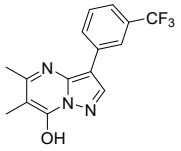
39a was prepared in 43% yield (1.0 g) from 4-(3-(trifluoromethyl)phenyl)-1H-pyrazol-5-amine (**38a**) and ethyl acetoacetate by heating for 18h. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 12.02 (s, 1H), 8.21 (s, 1H), 7.90-7.82 (m, 2H), 7.74-7.63 (m, 2H), 5.70 (s, 1H), 2.35 (s, 3H). MS: 294.0 $[M+H]^+$.

3-(4-Methoxyphenyl)-5,6-dimethylpyrazolo[1,5-a]pyrimidin-7-ol (39f)



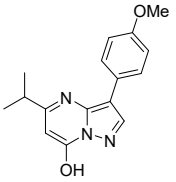
39f was prepared in 60% yield (1.2 g) from 4-(4-methoxyphenyl)-1H-pyrazol-5-amine (**38b**) and ethyl 2-methyl-3-oxobutanoate by heating for 2h. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.59 (s, 1H), 7.99 (s, 1H), 7.46 (d, *J* = 8.8 Hz, 2H), 7.02 (d, *J* = 8.8 Hz, 2H), 3.79 (s, 3H), 2.36 (s, 3H), 1.99 (s, 3H). MS: 270.0 $[M+H]^+$.

5,6-Dimethyl-3-(3-(trifluoromethyl)phenyl)pyrazolo[1,5-a]pyrimidin-7-ol (39b)



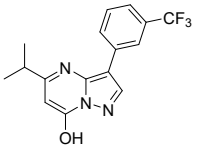
39b was prepared in 46% yield (1.1 g) from 4-(3-(trifluoromethyl)phenyl)-1H-pyrazol-5-amine (**38a**) and ethyl 2-methyl-3-oxobutanoate by heating for 2h. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 11.80 (s, 1H), 8.19 (s, 1H), 7.88-7.83 (m, 2H), 7.72-7.61 (m, 2H), 2.38 (s, 3H), 2.00 (s, 3H). MS: 308.1 $[M+H]^+$.

5-Isopropyl-3-(4-methoxyphenyl)pyrazolo[1,5-a]pyrimidin-7-ol (39g)



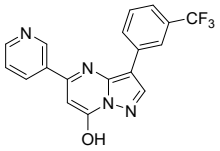
39g was prepared in 50% yield (1.1 g) from 4-(4-methoxyphenyl)-1H-pyrazol-5-amine (**38b**) and ethyl 4-methyl-3-oxopentanoate by heating for 2h. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 11.70 (s, 1H), 8.01 (s, 1H), 7.46 (d, *J* = 8.9 Hz, 2H), 7.04 (d, *J* = 8.9 Hz, 2H), 5.65 (s, 1H), 3.80 (s, 3H), 3.03 (septet, *J* = 6.9 Hz, 1H), 1.25 (d, *J*= 6.9 Hz, 6H). MS: 284.1 $[M+H]^+$.

5-Isopropyl-3-(3-(trifluoromethyl)phenyl)pyrazolo[1,5-a]pyrimidin-7-ol (39c)



39c was prepared in 60% yield (1.5 g) from 4-(3-(trifluoromethyl)phenyl)-1H-pyrazol-5-amine (**38a**) and ethyl 4-methyl-3-oxopentanoate by heating for 3h. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 11.88 (s, 1H), 8.20 (s, 1H), 7.90-7.78 (m, 2H), 7.75-7.63 (m, 2H), 5.72 (s, 1H), 3.00 (septet, *J* = 6.9 Hz, 1H), 1.26 (d, *J* = 6.9 Hz, 6H).

5-(Pyridin-3-yl)-3-(3-(trifluoromethyl)phenyl)pyrazolo[1,5-a]pyrimidin-7-ol (39d)



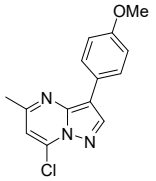
39d was prepared in 60% yield (1.5 g) from 4-(3-(trifluoromethyl)phenyl)-1H-pyrazol-5-amine (**38a**) and ethyl 3-oxo-3-(pyridin-3-yl)propanoate by heating for 18h. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 12.47 (br s, 1H), 9.07 (br s, 1H), 8.76 (dd, *J* = 4.85;1,54 Hz, 1H), 8.40 (br s, 1H), 8.30 (br s, 1H), 8.07 (br s, 2H), 7.73-7.58 (m, 3H), 6.23 (s, 1H).

2.7.7 General method C for the synthesis of 3-aryl-7-chloropyrazolo[1,5-a]pyrimidines (40a-g)

N,*N*-dimethylaniline (0.1 mL, 0.3 eq) was added to a suspension of **39a-g** (3.0 mmol) in $POCl_3$ (5 mL). The reaction mixture was stirred at 100°C. The course of the reaction was controlled by LC-MS. The obtained solution was cooled to RT and evaporated in vacuo. Obtained oily residue was

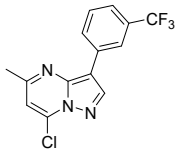
dissolved in DCM (40 mL), washed with aq $NaHCO_3$ (2×15 mL). Organic layer was dried over Na_2SO_4 and filtered through a SiO_2 pad. The filtrate was concentrated to give the desired chloro compound **40a-g** as yellow solid.

7-Chloro-3-(4-methoxyphenyl)-5-methylpyrazolo[1,5-a]pyrimidine (40e)



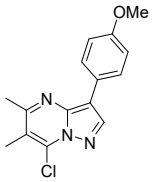
40e was prepared in 78% yield (0.64 g) from 3-(4-methoxyphenyl)-5-methylpyrazolo[1,5-a]pyrimidin-7-ol (**39e**). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.97 (d, *J* = 8.9 Hz, 2H), 7.00 (d, *J* = 8.9 Hz, 2H), 6.85 (s, 1H), 3.86 (s, 3H), 2.65 (s, 3H). MS: 274.1 [M (^{35}Cl)+H]$^+$, 276.1 [M (^{37}Cl)+H]$^+$.

7-Chloro-5-methyl-3-(3-(trifluoromethyl)phenyl)pyrazolo[1,5-a]pyrimidine (40a)



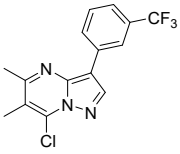
40a was prepared in 90% yield (0.84 g) from 5-methyl-3-(3-(trifluoromethyl)phenyl)pyrazolo[1,5-a]pyrimidin-7-ol (**39a**). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.51 (s, 1H), 8.34 (br s, 1H), 8.26 (d, *J*= 7.20 Hz, 1H), 7.60-7.48 (m, 2H), 6.93 (s, 1H), 2.69 (s, 3H). MS: 312.0 [M (^{35}Cl)+H]$^+$, 314.0 [M (^{37}Cl)+H]$^+$.

7-Chloro-3-(4-methoxyphenyl)-5,6-dimethylpyrazolo[1,5-a]pyrimidine (40f)



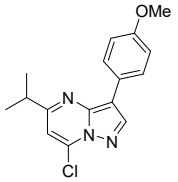
40f was prepared in 77% yield (0.66 g) from 3-(4-methoxyphenyl)-5,6-dimethylpyrazolo[1,5-a]pyrimidin-7-ol (**39f**). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.97 (d, *J* = 8.9 Hz, 2H), 6.99 (d, *J* = 8.9 Hz, 2H), 3.85 (s, 3H), 2.65 (s, 3H), 2.44 (s, 3H). MS: 288.0 [M (^{35}Cl)+H]$^+$, 290.0 [M (^{37}Cl)+H]$^+$.

7-Chloro-5,6-dimethyl-3-(3-(trifluoromethyl)phenyl)pyrazolo[1,5-a]pyrimidine (40b)



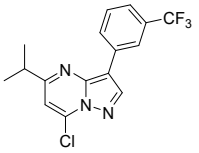
40b was prepared in 79% yield (0.77 g) from 5,6-dimethyl-3-(3-(trifluoromethyl)-phenyl)pyrazolo[1,5-a]pyrimidin-7-ol (**39b**). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.44 (s, 1H), 8.36 (br s, 1H), 8.25 (d, *J* = 7.4 Hz, 1H), 7.59-7.46 (m, 2H), 2.63 (s, 3H), 2.47 (s, 3H). MS: 326.0 [M (^{35}Cl)+H]$^+$, 328.0 [M (^{37}Cl)+H]$^+$.

7-Chloro-5-isopropyl-3-(4-methoxyphenyl)pyrazolo[1,5-a]pyrimidine (40g)



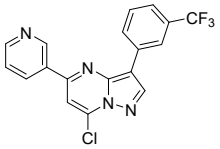
40g was prepared in 83% yield (0.75 g) from 5-iso-propyl-3-(4-methoxyphenyl)pyrazolo[1,5-a]pyrimidin-7-ol (**39g**). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.43 (s, 1H), 8.03 (d, *J* = 8.9 Hz, 2H), 7.01 (d, *J* = 8.9 Hz, 2H), 6.89 (s, 1H), 3.86 (s, 3H), 3.14 (septet, *J* = 6.9 Hz, 1H), 1.39 (d, *J*= 6.9 Hz, 6H). MS: 302.1 [M (^{35}Cl)+H]$^+$, 304.1 [M (^{37}Cl)+H]$^+$.

7-Chloro-5-isopropyl-3-(3-(trifluoromethyl)phenyl)pyrazolo[1,5-a]pyrimidine (40c)



40c was prepared in 44% yield (0.45 g) from 5-iso-propyl-3-(3-(trifluoromethyl)-phenyl)pyrazolo[1,5-a]pyrimidin-7-ol (**39c**). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.52 (s, 1H), 8.50 (br s, 1H), 8.23 (d, *J* = 7.3 Hz, 1H), 7.59-7.46 (m, 2H), 6.95 (s, 1H), 3.15 (septet, *J* = 6.9 Hz, 1H), 1.40 (d, *J*= 6.9 Hz, 6H). MS: 340.1 [M (^{35}Cl)+H]$^+$, 342.1 [M (^{37}Cl)+H]$^+$.

7-Chloro-5-(pyridin-3-yl)-3-(3-(trifluoromethyl)phenyl)pyrazolo[1,5-a]pyrimidine (40d)

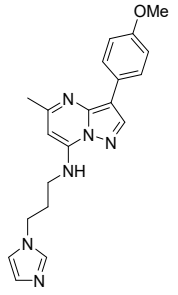


40d was prepared in 40% yield (0.44 g) from 5-(pyridin-3-yl)-3-(3-(trifluoromethyl)phenyl)pyrazolo[1,5-a]pyrimidin-7-ol (**39d**). ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.15 (s, 1H), 8.70 (d, *J* = 4.6 Hz, 1H), 8.43-8.28 (m, 3H), 8.17 (br s, 1H), 7.69-7.50 (m, 3H), 6.21 (s, 1H). MS: 375.07 [M (^{35}Cl)+H]$^+$, 377.05 [M (^{37}Cl)+H]$^+$.

2.7.7.1 General method D for the synthesis of N-substituted 3-arylpyrazolo[1,5-a]pyrimidin-7-amines (11, 14, 16, 18, 20, 21, 22, 24, 25)

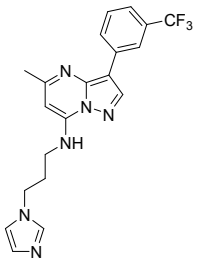
A mixture of **40a-g** (2.0 mmol), corresponding amine (1.5 eq) and K_2CO_3 (1.38 g, 5 eq) in MeCN (10 mL) was refluxed. The course of the reaction was controlled by LC-MS. The obtained mixture was then cooled to RT. The solvent was removed in vacuo to give a residue that was dissolved in DCM (30 mL) and water (30 mL). The organic layer was collected, dried over Na_2SO_4 and the solvent was removed in vacuo to give crude product, which was purified by crystallization or by column chromatography.

N-(3-(1H-imidazol-1-yl)propyl)-3-(4-methoxyphenyl)-5-methylpyrazolo[1,5-a]pyrimidin-7-amine [IDR-Pir-11-5b] (24)



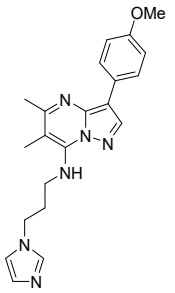
24 was prepared from 7-chloro-3-(4-methoxyphenyl)-5-methylpyrazolo[1,5-a]pyrimidine (**40e**). After crystallization from MeOH **24** was isolated as white solid (0.3g, yield 46%, HPLC purity 99% at 254 nm, 99% at 210 nm). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 8.00-7.95 (m, 2H), 7.51 (t, *J* = 1.1 Hz, 1H), 7.12 (t, *J* = 1.1 Hz, 1H), 7.00-6.96 (m, 2H), 6.95 (t, *J* = 1.1 Hz, 1H), 6.22 (t, *J* = 5.9 Hz, 1H), 5.72 (s, 1H), 4.13 (t, *J* = 6.7 Hz, 2H), 3.84 (s, 3H), 3.40-3.33 (m, 2H), 2.55 (s, 3H), 2.24 (pentet, *J* = 6.7 Hz, 2H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 159.8, 157.9, 146.1, 145.0, 141.2, 137.3, 130.3, 127.3, 125.6, 118.8, 114.3, 108.9, 85.6, 55.5, 44.1, 38.8, 30.4, 25.6. MS: 363.2 $[M+H]^+$; 361.1 $[M+H]^-$.

N-(3-(1H-imidazol-1-yl)propyl)-5-methyl-3-(3-(trifluoromethyl)phenyl)pyrazolo[1,5-a]pyrimidin-7-amine [Pir-11-5c] (20)



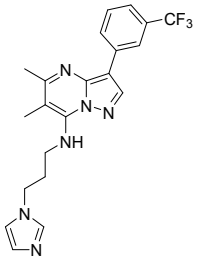
20 was prepared from 7-chloro-5-methyl-3-(3-(trifluoromethyl)phenyl)pyrazolo[1,5-a]pyrimidine (**40a**). After crystallization from *i*-PrOH **20** was isolated as white solid (0.4 g, yield 50%, HPLC purity 99% at 254 nm, 99% at 210 nm). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.35-8.27 (m, 3H), 7.55-7.48 (m, 2H), 7.44 (d, *J* = 7.8 Hz, 1H), 7.13 (t, *J* = 1.1 Hz, 1H), 6.95 (t, *J* = 1.1 Hz, 1H), 6.28 (t, *J* = 5.9 Hz, 1H), 5.76 (s, 1H), 4.13 (t, *J* = 6.7 Hz, 2H), 3.41-3.33 (m, 2H), 2.56 (s, 3H), 2.25 (pentet, *J* = 6.7 Hz, 2H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 160.6, 146.0, 145.4, 141.3, 137.2, 133.7, 130.9 (q, *J* = 31.8 Hz), 130.3, 129.0, 128.9, 124.4 (q, *J* = 271.5 Hz), 122.3 (q, *J* = 3.9 Hz), 122.0 (q, *J* = 3.9 Hz),118.6, 107.4, 86.0, 43.9, 38.8, 30.3, 25.3. MS: 401.2 $[M+H]^+$; 399.2 $[M+H]^-$.

N-(3-(1H-imidazol-1-yl)propyl)-3-(4-methoxyphenyl)-5,6-dimethylpyrazolo[1,5-a]pyrimidin-7-amine [Pir-12-3] (18)



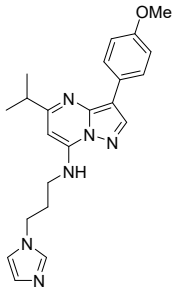
18 was prepared from 7-chloro-3-(4-methoxyphenyl)-5,6-dimethylpyrazolo[1,5-a]pyrimidine (**40f**). The purification was carried out using 20%-100% acetone/DCM as eluent to afford **18** as white solid (0.30 g, yield 39%, HPLC purity 99% at 254 nm, 99% at 210 nm). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.99-7.94 (m, 2H), 7.46 (t, *J* = 1.1 Hz, 1H), 7.07 (t, *J* = 1.1 Hz, 1H), 6.99-6.94 (m, 2H), 6.88 (t, *J* = 1.1 Hz, 1H), 5.99 (t, *J* = 6.7 Hz, 1H), 4.07 (t, *J* = 6.7 Hz, 2H), 3.82 (s, 3H), 3.58 (q, *J* = 6.7 Hz, 2H), 2.54 (s, 3H), 2.20 (s, 3H), 2.14 (pentet, *J* = 6.7 Hz, 2H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 160.1, 157.8, 145.2, 143.4, 140.0, 137.2, 130.1, 127.1, 125.7, 118.8, 114.3, 108.6, 97.4, 55.4, 43.8, 42.3, 32.2, 24.6, 13.4. MS: 377.2 $[M+H]^+$; 375.1 $[M+H]^-$.

N-(3-(1H-imidazol-1-yl)propyl)-5,6-dimethyl-3-(3-(trifluoromethyl)phenyl)pyrazolo[1,5-a]pyrimidin-7-amine [Pir-12-5c] (25)



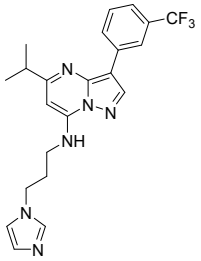
25 was prepared from 7-chloro-5,6-dimethyl-3-(3-(trifluoromethyl)phenyl)pyrazolo[1,5-a]pyrimidine (**40b**). The purification was carried out using acetone as eluent to afford **25** as brown semisolid (0.37 g, yield 45%, HPLC purity 99% at 254 nm, 99% at 210 nm). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 1H), 8.27 (d, *J* = 7.7 Hz, 1H), 8.25 (s, 1H), 7.49 (t, *J* = 7.7 Hz, 1H), 7.47 (s, 1H), 7.42 (d, *J* = 7.7 Hz, 1H), 7.08 (s, 1H), 6.89 (s, 1H), 6.03 (t, *J* = 6.3 Hz, 1H), 4.08 (t, *J* = 6.7 Hz, 2H), 3.64-3.56 (m, 2H), 2.55 (s, 3H), 2.21 (s, 3H), 2.20-2.11 (m, 2H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 161.0, 145.3, 143.9, 140.4, 137.2, 133.9, 130.9 (q, *J* = 31.9 Hz), 130.1, 129.1, 128.7, 124.5 (q, *J* = 271.9 Hz), 122.2 (q, *J* = 3.9 Hz), 121.9 (q, *J* = 3.8 Hz), 118.8, 107.1, 97.8, 43.8, 42.4, 32.2, 24.7, 13.4. MS: 415.2 $[M+H]^+$; 413.2 $[M+H]^-$.

N-(3-(1H-imidazol-1-yl)propyl)-5-isopropyl-3-(4-methoxyphenyl)pyrazolo[1,5-a]pyrimidin-7-amine [Pir-14-3] (11)



11 was prepared from 7-chloro-5-isopropyl-3-(4-methoxyphenyl)pyrazolo[1,5-a]pyrimidine (**40g**). After crystallization from MeOH **11** was isolated as white solid (0.3 g, yield 38%, HPLC purity 99% at 254 nm, 98% at 210 nm). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1H), 8.09-8.03 (m, 2H), 7.51 (t, *J* = 1.1 Hz, 1H), 7.13 (t, *J* = 1.1 Hz, 1H), 7.00-6.97 (m, 2H), 6.94 (t, *J* = 1.1 Hz, 1H), 6.20 (t, *J* = 6.0 Hz, 1H), 5.74 (s, 1H), 4.13 (t, *J* = 6.7 Hz , 2H), 3.84 (s, 3H), 3.40-3.34 (m, 2H), 3.02 (septet, *J* = 6.9 Hz, 1H), 2.24 (pentet, *J* = 6.7 Hz, 2H), 1.35 (d, J = 6.9 Hz, 6H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 168.4, 157.8, 146.4, 145.0, 140.9, 137.3, 130.3, 127.1, 125.8, 118.8, 114.2, 108.8, 83.3, 55.5, 44.0, 38.8, 37.1, 30.5, 22.4. MS: 391.2 $[M+H]^+$; 389.2 $[M+H]^-$.

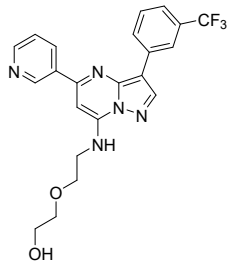
N-(3-(1H-imidazol-1-yl)propyl)-5-isopropyl-3-(3-(trifluoromethyl)phenyl)pyrazolo[1,5-a]pyrimidin-7-amine [Pir-14-5c] (22)



22 was prepared from 7-chloro-5-isopropyl-3-(3-(trifluoromethyl)phenyl)pyrazolo[1,5-a]pyrimidine (**40c**). The purification was carried out using acetone as eluent to afford **Pir-14-5c** as white solid (0.54 g, yield 63%, HPLC purity 99% at 254 nm, 99% at 210 nm). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.52 (s, 1H), 8.33 (s, 1H), 8.30 (d, *J* = 7.8 Hz, 1H), 7.55-7.47 (m, 2H), 7.43 (d, *J*

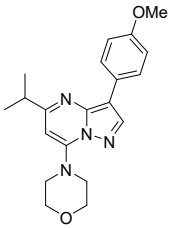
= 7.8 Hz, 1H), 7.13 (s, 1H), 6.95 (s, 1H), 6.26 (t, *J* = 5.9 Hz, 1H), 5.79 (s, 1H), 4.14 (t, *J* = 6.7 Hz, 2H), 3.43-3.36 (m, 2H), 3.03 (septet, *J* = 6.8 Hz, 1H), 2.26 (pentet, *J* = 6.7 Hz, 2H), 1.36 (d, J = 6.8 Hz, 6H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 169.3, 146.5, 145.6, 141.3, 137.3, 134.0, 130.96 (q, *J* = 31.8 Hz), 130.4,129.0, 128.6, 124.6 (q, *J* = 273.0 Hz), 122.4 (q, *J* = 3.9 Hz), 121.9 (q, *J* = 3.7 Hz), 118.8, 107.4, 84.1, 44.0, 38.8, 37.0, 30.4, 22.3. MS: 429.2 $[M+H]^+$; 427.2 $[M+H]^-$.

2-(2-((5-(Pyridin-3-yl)-3-(3-(trifluoromethyl)phenyl)pyrazolo[1,5-a]pyrimidin-7-yl)amino)ethoxy)-ethan-1-ol [Pir-10-18] (10)



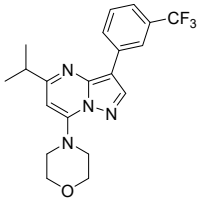
10 was prepared from 7-chloro-5-(pyridin-3-yl)-3-(3-(trifluoromethyl)-phenyl)pyrazolo[1,5-a]pyrimidine (**40d**). The purification was carried out using 0-50% acetone/DCM as eluent to afford **10** as yellow solid (0.24 g, yield 27%, HPLC purity 95% at 254 nm, 95% at 210 nm). ^{1}H NMR (400 MHz, CD_3OD) δ 9.40 (d, *J* = 1.8 Hz, 1H), 8.71 (br s, 1H), 8.68-8.62 (m, 2H), 8.55 (s, 1H), 8.36 (d, *J* = 7.8 Hz, 1H), 7.63-7.55 (m, 2H), 7.47 (d, *J* = 7.8 Hz, 1H), 6.86 (s, 1H), 3.88-3.78 (m, 4H), 3.73-3.68 (m, 2H), 3.66-3.61 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 154.4, 150.7, 148.4, 147.7, 145.4, 142.2, 134.5, 134.1, 133.4, 129.6, 129.5 (q, *J* = 31.1 Hz), 128.6, 124.5 (q, *J* = 271.2 Hz), 123.7, 121.4 (q, *J* = 4.2 Hz), 121.3 (q, *J* = 3.7 Hz), 106.2, 83.2, 72.2, 68.6, 60.3, 41.4. MS: 444.2 $[M+H]^+$, 442.2 $[M-H]^-$.

4-(5-i-Propyl-3-(4-methoxyphenyl)pyrazolo[1,5-a]pyrimidin-7-yl)morpholine [Pir-16] (21)



21 was prepared from 7-chloro-5-isopropyl-3-(4-methoxyphenyl)pyrazolo[1,5-a]pyrimidine (**40g**). After crystallization from TBME **21** was isolated as yellow solid (0.28 g, yield 40%, HPLC purity 97% at 254 nm, 98% at 210 nm). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 8.09-8.03 (m, 2H), 7.02-6.96 (m, 2H), 6.03 (s, 1H), 4.02-3.95 (m, 4H), 3.85 (s, 3H), 3.73-3.65 (m, 4H), 3.07 (septet, *J* = 6.9 Hz, 1H), 1.37 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.8, 157.9, 150.7, 146.6, 141.1, 127.3, 125.6, 114.2, 108.6, 91.3, 66.5, 55.5, 48.6, 36.9, 22.3. MS: 353.2 $[M+H]^+$.

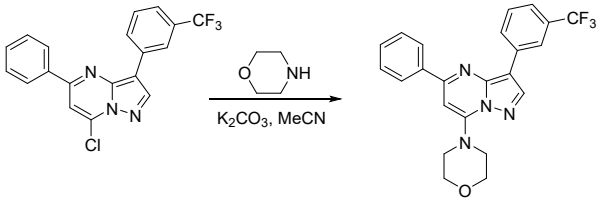
4-(5-i-Propyl-3-(3-(trifluoromethyl)phenyl)pyrazolo[1,5-a]pyrimidin-7-yl)morpholine [Pir-10-10] (16)



16 was prepared from 7-chloro-5-isopropyl-3-(3-(trifluoromethyl)phenyl)pyrazolo[1,5-a]pyrimidine (**40c**). The purification was carried out using acetone/DCM (1:5) as eluent to afford **16** as yellow solid (0.41g, yield 53%, HPLC purity 99% at 254 nm, 99% at 210 nm). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (br s, 1H), 8.37 (s, 1H), 8.27 (d, *J* = 7.8 Hz, 1H), 7.52 (t, *J* = 7.8 Hz, 1H), 7.45 (d, *J* = 7.8 Hz, 1H), 6.09 (s, 1H), 4.02-3.95 (m, 4H), 3.76-3.68 (m, 4H), 3.08 (septet, *J* = 6.9

Hz, 1H), 1.39 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.8, 150.8, 147.3, 141.4, 133.8, 131.0 (q, *J* = 31.9 Hz), 129.0, 128.8, 124.6 (q, *J* = 272.6 Hz), 122.8 (q, *J* = 4.0 Hz), 122.1 (q, *J* = 3.8 Hz), 107.2, 92.1, 66.5, 48.7, 36.8, 22.1. MS: 391.3 $[M+H]^+$.

2.7.7.2 4-(5-Phenyl-3-(3-(trifluoromethyl)phenyl)pyrazolo[1,5-a]pyrimidin-7-yl)morpholine [Pir-10-17] (14)



14 was prepared from 7-chloro-5-phenyl-3-(3-(trifluoromethyl)phenyl)pyrazolo[1,5-a]pyrimidine and morpholine by following the procedure described in general method **D**. After crystallization from TBME **14** was isolated as yellow solid (0.55 g, yield 66%, HPLC purity 99% at 254 nm, 99% at 210 nm). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 1H), 8.42 (s, 1H), 8.35 (d, *J* = 7.81 Hz, 1H), 8.19-8.14 (m, 2H), 7.59-7.46 (m, 5H), 6.65 (s, 1H), 4.07-3.98 (m, 4H), 3.86-3.77 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.4, 151.1, 147.5, 141.8, 137.9, 133.6, 131.1 (q, *J* = 32.9 Hz), 130.5, 129.2, 129.1, 129.0, 127.4, 124.6(q, *J* = 272.0 Hz), 122.9 (q, *J* = 3.9 Hz), 122.3 (q, *J* = 3.7 Hz), 108.3, 90.5, 66.5, 48.8. MS: 425.2 $[M+H]^+$.

3 References

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