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Discovery of BUB1 kinase inhibitors for the treatment of cancer

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Hit optimization of quinazolines as BUB1 inhibitors

Introduction

Many types of cancer cells suffer from a diminished spindle assembly checkpoint (SAC) and further weakening of these checkpoints has emerged as a potential strategy to kill cancer cells.[1,2] During mitosis, the SAC prevents anaphase initiation before all chromosomes are properly attached to the mitotic spindle.[3] Proper SAC functioning is essential for genomic integrity, since mitotic progression in the presence of unattached or incorrectly attached chromosomes may lead to aneuploidy.[3] It has been hypothesized that reducing SAC integrity contributes to the killing of malignant cells.[1] Kinases of the SAC, in particular budding uninhibited by benzimidazole 1 (BUB1), are, therefore, considered interesting drug targets.[1] To date, only one chemotype as BUB1 inhibitor, BAY1816032 (**Figure 3.1A**), has been published.[4] BAY1816032 was evaluated *in vivo* using mouse xenograft models of human triple-negative breast cancer and synergistically inhibited tumor growth when co-treated with a microtubule targeting drug (paclitaxel) or PARP inhibitor olaparib.[4] Of note, BAY1816032 did not show efficacy as single agent which suggests that more potent BUB1 inhibitors are required.

In the search for novel inhibitors for SAC kinase BUB1, quinazoline OSI-420 (**1**) (**Figure 3.1A**) was identified as a hit via high-throughput screening (**Chapter 2**) and showed a half maximum inhibitory concentration (IC_{50}) of 525 nM. Compound **1** is a metabolite of FDA-approved drug erlotinib (**2**) (**Figure 3.1A**), which inhibits the epidermal growth factor receptor (EGFR, also known as HER1 or ERBB1).[5] EGFR is part of the ERBB family of receptor tyrosine kinases and contains an extracellular ligand binding domain.[6] Ligand binding induces receptor dimerization, which in turn activates the intracellular kinase domain.[6] Subsequent autophosphorylation results in receptor activation which initiates a signaling cascade that, among other physiological processes, involves cell proliferation and inhibition of apoptosis.[7] Erlotinib blocks the intracellular kinase domain and thereby inhibits cell proliferation. Erlotinib is used for the treatment of advanced non-small cell lung cancer since 2004.[8] Of note, also erlotinib (**2**) was identified as a BUB1 inhibitor in the high-throughput screen, albeit, with lower potency (IC_{50} = 1072 nM). This may suggest that the free hydroxyl group of compound **1** plays a role in the binding activity. The binding mode of erlotinib (**2**) in EGFR (PDB code: 4HJO)[9] (**Figure 3.1B**) shows that the molecule forms a hydrogen bond between one of the quinazoline nitrogens and the amide backbone of the hinge region in EGFR. The substituents at R_1 and R_2 are solvent exposed and the phenylacetylene substituent at R_3 binds the so-called gate area of EGFR and contributes to selectivity (**Figure 3.1A, B**).[10,11] In this chapter, the structure-activity relationship of compound **1** on BUB1 kinase activity was investigated by systematically changing three distinct regions of its structure (R_1 – R_3, **Figure 3.1A**).

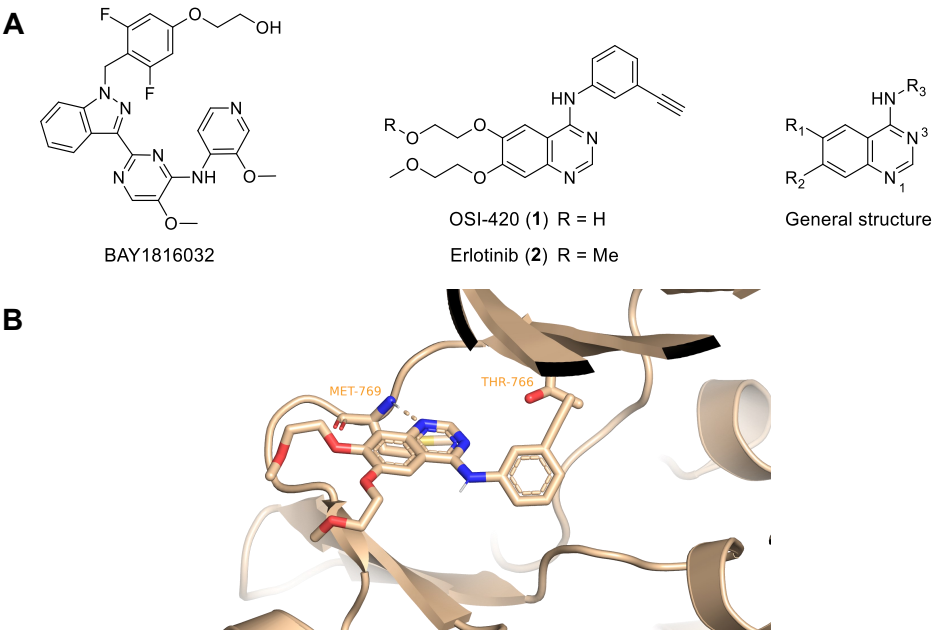


Figure 3.1 | (A) Left: chemical structure of BAY1816032. Middle: chemical structure of OSI-420 (**1**) and erlotinib (**2**). Right: regions R_1 – R_3 of the quinazoline scaffold used to investigate the structure-activity relationship of OSI-420. **(B)** Crystal structure of erlotinib (**2**) in EGFR (PDB code: 4HJO).[9] A hydrogen bond (dashed line) is formed between the quinazoline and the amide backbone of hinge amino acid Met769.

Results & Discussion

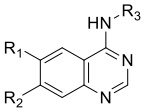
Biochemical evaluation of structural analogues 2 – 49 of hit 1

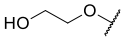
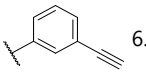
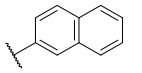
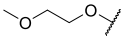
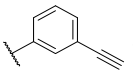
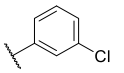
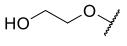
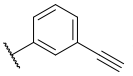
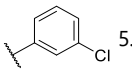
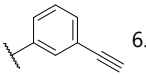
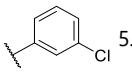
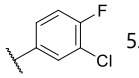
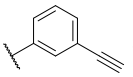
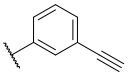
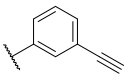
To study the structure-activity relationship (SAR) of compound **1**, analogues **2** – **49** were synthesized according to the routes reported in the Experimental section. Compounds **2** – **49** were subsequently evaluated in a biochemical fluorescence polarization assay to determine the half maximal inhibitory concentrations (IC_{50}) as described in Chapter 2. The data are reported in Table 3.1 – Table 3.6 and activities are expressed as pIC_{50} ± SEM (N=2, n=2).

First, a disjunctive approach was used to identify substituents contributing to BUB1 inhibitory activity. Compound **3**, which lacked the acetylene on the R_3-phenyl group, showed a more than 10-fold loss in potency compared to compound **1** (Table 3.1). Substitution of the phenylacetylene with a naphthyl group (**4**), to probe the size of the binding pocket, also resulted in a loss of potency. These results suggested that the acetylene group may form an important interaction with BUB1 in a relatively small hydrophobic pocket. Next, it was found methylation of the alcohol at R_1 (**2**, erlotinib) reduced potency about 4-fold, which was in agreement with data obtained from the high-throughput screen (Chapter 2). This suggests that a hydrogen bond donating property may be important. Of note, removing the methyl group at R_2 to obtain two hydroxyl groups (**6**) slightly reduced potency as well, which points towards a different role of the two solubilizers. In contrast, shortening R_1 and R_2 to methoxy

groups (**8**) retained potency compared to compound **1**, whereas complete removal of either R_1 or R_2 (**11**, **12**) reduced potency on average about 10-fold. In line, removal of both R_1 and R_2 (**13**), reduced potency at least 20-fold. Substituting the acetylene on the R_3-phenyl ring for a chlorine (**5**, **7**, **9**), reduced potency to a similar extent (on average about 6-fold) compared to analogues **2**, **6**, **8**, respectively. This observation suggested that the acetylene may form a specific contact and its activity is not due to only hydrophobic interactions. Alternatively, the electron withdrawing properties of the chlorine may be detrimental for the binding activity. Of note, an additional fluorine (**10**) did not further reduce potency.

Table 3.1 | Half maximal inhibitory concentrations (expressed as pIC_{50} ± SEM) of **1** – **13** determined by a fluorescence polarization assay on BUB1 kinase activity (N=2, n=2).

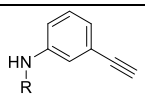


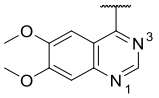
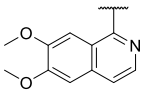
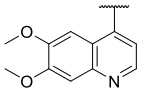
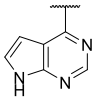
	ID	R_3	pIC_{50} ± SEM	ID	R_3	pIC_{50} ± SEM	ID	R_3	pIC_{50} ± SEM
R_1  R_2	**1**		6.28 ± 0.05	**3**		< 5	**4**		< 5
R_1  R_2	**2**		5.67 ± 0.04	**5**		< 5			
R_1  R_2	**6**		5.94 ± 0.04	**7**		5.27 ± 0.05			
R_1 R_2	**8**		6.17 ± 0.05	**9**		5.31 ± 0.05	**10**		5.37 ± 0.03
R_1 R_2	**11**		5.10 ± 0.02						
R_1 R_2	**12**		5.35 ± 0.03						
R_1 R_2	**13**		< 5						

Next, the importance of the nitrogens of the quinazoline scaffold was investigated. Removal of the *N*1 nitrogen (**14**, **Table 3.2**), reduced potency by more than 10-fold, suggesting that this nitrogen might be involved in hydrogen bond formation with the hinge region of BUB1. In contrast, removal of the *N*3 nitrogen (**15**), barely affected potency. Changing the quinazoline scaffold to a pyrrolopyrimidine (**16**), reduced potency significantly.

To further investigate the scope of the R_3 substituents (**Figure 3.1**), compounds **17** – **29** were evaluated (**Table 3.3**). Compared to **6**, substituting the acetylene by an ethyl (**17**) or isopropyl (**18**), reduced potency by at least 10-fold (**Table 3.3**). In contrast, replacing the acetylene for a phenyl (**19**) as bioisostere only slightly reduced potency. Subsequent substitution of this phenyl ring in compounds **20** – **24** with electron donating substituents (*o*, *m*, or *p*-methyl (**20**, **21**, **23**)) was not allowed. An electron withdrawing group, such as a *m*- or *p*-cyano group (**22**, **24**), was tolerated, but did not improve potency. Modification of the phenyl ring of **6** with both small (**25**, **27**) and large (**26**, **28**, **29**) ether substituents reduced potency as well.

Table 3.2 | Half maximal inhibitory concentrations (expressed as pIC_{50} ± SEM) of **14** – **16** determined by a fluorescence polarization assay on BUB1 kinase activity (N=2, n=2).

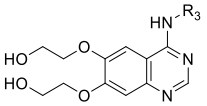


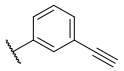
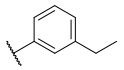
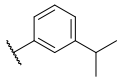
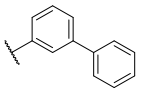
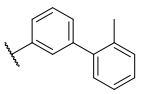
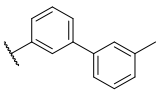
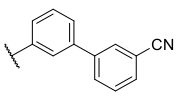
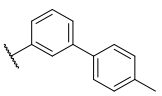
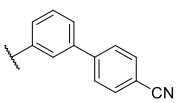
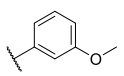
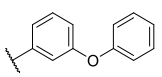
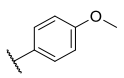
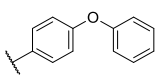
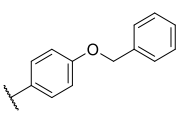
ID	R =	pIC_{50} ± SEM	app. K_i (nM)[a]	cLogP[b]	LipE[c]
8		6.17 ± 0.05	236	3.3	3.4
14		< 5	–	3.7	–
15		5.97 ± 0.03	373	3.5	3.0
16		< 5	–	2.4	–

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

Due to the observed decrease in potency for biphenyl and phenyl ether analogues (**Table 3.3**), a small series of substituted pyrazoles (**30** – **41**) was evaluated (**Table 3.4**). The different size and exit vectors of a pyrazole may allow substituents to address different subpockets of the enzyme. In addition, the different electronic properties of a pyrazole ring may affect the binding affinity and its nitrogens may form additional hydrogen bonds. Changing the phenylacetylene of **6** for a pyrazole (**30**) decreased potency significantly. Compared to unsubstituted phenyl **3** (**Table 3.1**), compound **30** still showed some activity. In addition, due to lower lipophilicity, the lipophilic efficiency (LipE, calculated as defined in **Table 3.4**) of **30** was significantly improved when compared to **6**. Alkylation of the pyrazole by methyl (**31**) or ethyl (**32**) further decreased potency. In contrast, substitution with a benzyl group (**33**) showed similar activity compared to **6**, but improved in LipE. Extending the alkyl linker between pyrazole and phenyl (**34**, **35**) decreased potency, indicating that a methylene is the most optimal linker. Based on the activity of **33**, different electron donating and withdrawing substituents on the phenyl ring were explored (**36** – **41**), but none of them improved potency.

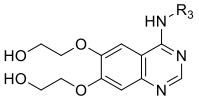
Table 3.3 | Half maximal inhibitory concentrations (expressed as pIC_{50} ± SEM) of **17** – **29** determined by a fluorescence polarization assay on BUB1 kinase activity (N=2, n=2).

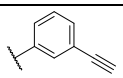
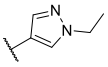
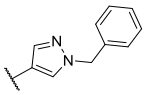
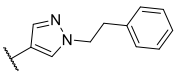
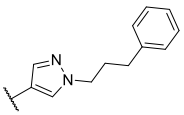
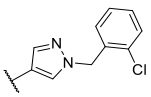
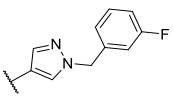
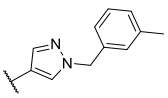
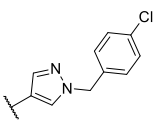
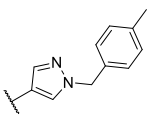
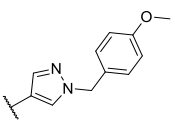


ID	R_3 =	pIC_{50} ± SEM	app. K_i (nM)[a]	cLogP[b]	LipE[c]
6		5.94 ± 0.04	407	2.2	4.2
17		< 5	–	2.9	–
18		< 5	–	3.3	–
19		5.63 ± 0.03	828	3.8	2.3
20		< 5	–	4.1	–
21		5.00 ± 0.03	–	4.1	–
22		5.66 ± 0.03	769	3.6	2.5
23		< 5	–	4.1	–
24		5.52 ± 0.04	1064	3.6	2.4
25		< 5	–	2.0	–
26		< 5	–	3.5	–
27		< 5	–	2.0	–
28		< 5	–	3.5	–
29		< 5	–	3.5	–

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

Table 3.4 | Half maximal inhibitory concentrations (expressed as pIC_{50} ± SEM) of **30** – **41** determined by a fluorescence polarization assay on BUB1 kinase activity (N=2, n=2).

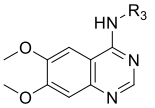


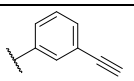
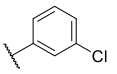
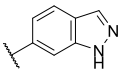
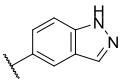
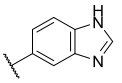
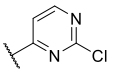
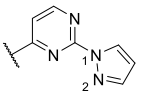
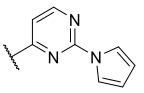
ID	R_3 =	pIC_{50} ± SEM	app. K_i (nM)[a]	cLogP[b]	LipE[c]
6		5.94 ± 0.04	407	2.2	4.2
30		5.09 ± 0.05	2877	0.0	5.5
31		< 5	–	0.2	–
32		< 5	–	0.4	–
33		5.92 ± 0.04	420	1.5	4.8
34		5.18 ± 0.09	2322	1.9	3.8
35		< 5	–	2.3	–
36		5.04 ± 0.03	3198	2.1	3.4
37		5.87 ± 0.02	474	1.6	4.7
38		5.19 ± 0.03	2274	1.9	3.8
39		< 5	–	2.1	–
40		< 5	–	1.9	–
41		< 5	–	1.5	–

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

Since pyrazoles at R_3 resulted in an active compound with lower lipophilicity, other heterocycles were explored at this position (**42** – **47**, Table 3.5). Indazole or benzimidazole at R_3 (**42** – **44**) were not found to be tolerated. In contrast, chloropyrimidine **45** showed similar activity compared to its chlorophenyl analogue (**9**), which may indicate that the pyrimidine nitrogens do not form additional hydrogen bonds with the enzyme. Substituting the chlorine of **45** for a pyrazole (**46**) significantly improved potency (over 15-fold), and this compound had the highest LipE (5.1) of this study. Substituting the chlorine for a pyrrole (**44**) abolished activity, suggesting that the *N*2 nitrogen of the pyrazole of **46** interacts with the protein via a hydrogen bond. Overall, compound **46** was the most potent BUB1 inhibitor identified in this study with a pIC_{50} of 6.4.

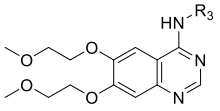
Table 3.5 | Half maximal inhibitory concentrations (expressed as pIC_{50} ± SEM) of **42** – **47** determined by a fluorescence polarization assay on BUB1 kinase activity (N=2, n=2).

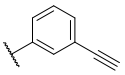
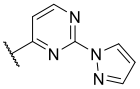
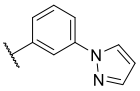


ID	R_3 =	pIC_{50} ± SEM	app. K_i (nM)[a]	cLogP[b]	LipE[c]
8		6.17 ± 0.05	236	3.3	3.4
9		5.31 ± 0.05	1733	3.8	2.0
42		< 5	–	2.4	–
43		< 5	–	2.4	–
44		< 5	–	2.8	–
45		5.18 ± 0.04	2333	2.8	2.8
46		6.41 ± 0.04	136	1.7	5.1
47		< 5	–	2.8	–

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

Table 3.6 | Half maximal inhibitory concentrations (expressed as pIC_{50} ± SEM) of **48** and **49** determined by a fluorescence polarization assay on BUB1 kinase activity (N=2, n=2).



ID	R_3 =	pIC_{50} ± SEM	app. K_i (nM)[a]	cLogP[b]	LipE[c]
2		5.67 ± 0.04	746	3.1	3.1
48		6.25 ± 0.04	197	1.6	5.1
49		5.43 ± 0.02	1306	2.1	3.7

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

Finally, the R_3 substituent of **46** was grafted on the original scaffold of erlotinib (**2**) , thereby providing compound **48** (Table 3.6). Pyrazole-pyrimidine **48** showed improved potency compared to phenylacetylene **2** (Table 3.6), but was less active than compound **46** (Table 3.5). Strikingly, removal of the pyrimidine nitrogens (**49**) decreased the potency significantly, even below the activity of compound **2**, which indicated the importance of the pyrimidine nitrogens. The observed activities of chlorophenyl **9** and chloropyrimidine **45** (Table 3.5), for which the pyrimidine nitrogens were not found to increase activity, suggests a different binding mode for pyrazole-pyrimidines **46** and **48**.

Proposed binding mode of compound 1 and 46 in BUB1

Based on the obtained biochemical data, a binding model of compound **1** and **46** was generated by docking these molecules into the crystal structure of the kinase domain of human BUB1 (in complex with BAY1816032 (PDB code: 6F7B)[4]). Docking was performed using a published plugin[12] of AutoDock Vina[13] for PyMOL[14]. The proposed binding mode of compound **1** (Figure 3.2A) closely resembled the binding mode of erlotinib (**2**) in EGFR (PDB code: 4HJO) (Figure 3.1B).[9] Like erlotinib, R_1 and R_2 of compound **1** are solvent exposed, R_3 is positioned near the gatekeeper residue and the quinazoline of compound **1** is proposed to form a hydrogen bond between the *N*1 nitrogen and the amide backbone of hinge amino acid Tyr869 (Figure 3.2A). The proposed hydrogen bond is supported by the 15-fold decrease in potency when this nitrogen is removed (**14** vs. **8**, Table 3.2). The acetylene is hypothesized to interact with Val819, Lys821 and Leu864 (Figure 3.2A), which is supported by the observation that removal of this acetylene dropped potency by more than 10-fold (**3** vs. **1**, Table 3.1). The difference in activity between compound **1** and erlotinib (**2**) could not be explained based on the proposed binding mode. The position of the quinazoline ring of compound **1** is in line with the binding mode of the hinge binding pyridine ring of BAY1816032 and the acetylene of compound **1** points in the direction where the indazole

phenyl of BAY1816032 is located (**Figure 3.2B**). Molecular docking of **46** revealed a binding mode in which one of the pyrimidine nitrogens forms a hydrogen bond with Lys821 and the *N*2 nitrogen of the pyrazole forms a hydrogen bond with both Lys821 and Asp946 (**Figure 3.2C**). These proposed hydrogen bonds are supported by the 6-fold potency drop upon removal of both pyrimidine nitrogens (**49** vs. **48**, **Table 3.6**) as well as by the more than 25-fold decrease in potency upon removal of the corresponding pyrazole nitrogen (**47** vs. **46**, **Table 3.5**). When compared to the proposed binding mode of compound **1**, the quinazoline of **46** is slightly shifted and this shift hinders the formation of a hydrogen bond with Tyr869 (**Figure 3.2C**). In addition, this shift in position might explain why the activities of chlorophenyl **9** and chloropyrimidine **45** (**Table 3.5**) indicated no hydrogen bond interactions with the pyrimidine nitrogens of **45**, whereas the activities of compound **48** and **49** suggested that at least one of these nitrogens are involved in the formation of a hydrogen bond. The proposed binding mode of **46** closely resembles part of BAY1816032 which also forms two hydrogen bonds with Lys821 and one hydrogen bond with Asp946 (**Figure 3.2D**).

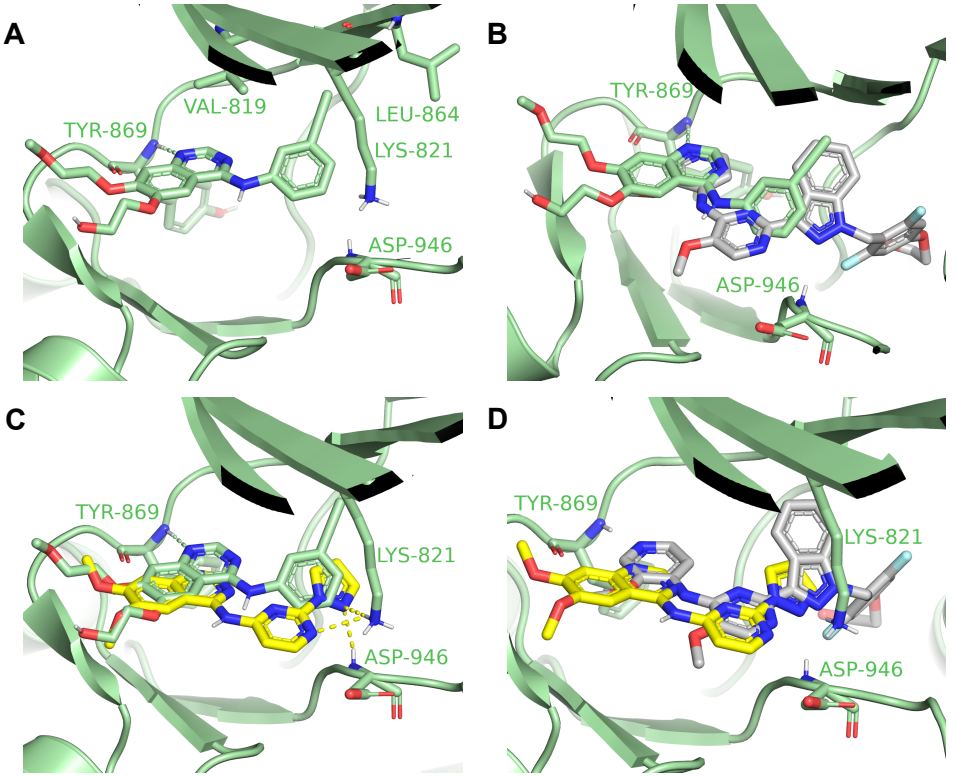
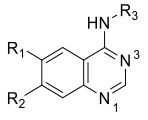


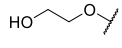
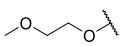
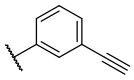
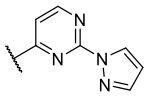
Figure 3.2 | Proposed binding mode of hit 1 and compound 46 in BUB1. (A) Proposed binding mode of compound **1** in BUB1. A hydrogen bond is formed with the amide backbone of hinge amino acid Tyr869 (dashed line). **(B)** Proposed binding mode of compound **1** compared to the binding mode of BAY1816032 (grey). **(C)** Proposed binding mode of compound **46** (yellow) compared with the proposed binding mode of compound **1**. Hydrogen bonds are indicated with dashed lines (green for compound **1**, yellow for compound **46**). **(D)** Proposed binding mode of compound **46** compared to the binding mode of BAY1816032 (grey).

Conclusion

In this chapter, the structure-activity relationship of compound **1** on BUB1 inhibition was investigated by synthesizing 48 analogues. The size of the substituents at R_1 and R_2 (**Figure 3.1A**) could significantly be reduced without losing much potency. The *N*1 nitrogen of the quinazoline scaffold was found to be crucial for activity, since its removal reduced potency over 10-fold. This nitrogen is hypothesized to form a hydrogen bond with hinge amino acid Tyr869 of BUB1. Modifications at R_3 showed that the acetylene is crucial for activity as well and optimization of potency in this region was found to be challenging. A summary of the activity and physicochemical properties of most active inhibitor **46** is shown in **Table 3.7**. A pyrazole-pyrimidine group at R_3 (**46**) was found to show the best activity (pIC_{50} = 6.41) which increased compared to compound **1**. In addition, **46** showed an almost 10-fold decrease in lipophilicity which contributed to the 10-fold increase in lipophilic efficiency. Furthermore, the molecular weight of **46** was reduced which contributed to better ligand efficiency.

Table 3.7 | Properties of initial hit **1** and optimized hit **46**.



ID	R_1/R_2	R_3 =	pIC_{50} ± SEM	app. K_i (nM)[a]	cLogP[b]	LipE[c]	LE[d]	tPSA[e]	MW[f]
1	R_1  R_2 		6.28 ± 0.05	185	2.6	4.1	0.33	85	379
46	R_1 R_2		6.41 ± 0.04	136	1.7	5.1	0.36	96	349

[a] Apparent K_i ; [b] cLogP, calculated by DataWarrior (v.5.2.1); [c] Lipophilic efficiency, defined as $\mathrm{LipE} = \mathrm{app.\,p}K_i - \mathrm{cLogP}$; [d] Ligand efficiency, defined as: $\mathrm{LE} = (-RT * \ln(\mathrm{app.}\,K_i))/\mathrm{HA}$, where HA stands for the number of 'heavy atoms' (non-hydrogen atoms); [e] Topological surface area (Å^2), calculated by Chemdraw (v.19.1); [f] Molecular weight (g/mol).

Acknowledgements

Julian Clijncke, Jessica Domínguez Alfaro, Na Zhu, Bas de Man and Joel Rüegger are kindly acknowledged for their contribution with regard to compound synthesis and biochemical testing. Anthe Janssen is kindly acknowledged for his help in molecular docking and Hans van den Elst for HRMS measurements.

Experimental – Biochemistry

Molecular docking

The crystal structure of human BUB1 kinase domain in complex with BAY1816032 (PDB code: 6F7B)[4] was fetched into PyMOL[14]. Reduce[15] was used to add hydrogens to the protein structure and the ligand (BAY1816032) was extracted to a new object. The published plugin[12] of AutoDock Vina[13] for PyMOL was used for molecular docking. The AutoDock Vina grid box was based on the position of BAY1816032 and modified to obtain the following settings: grid size X = 54, Y = 34 and Z = 42 Å (grid spacing = 0.375 Å) centered at X = 12.68 Y = -31.93 and Z = -12.25. The number of docking poses was arbitrarily set to 60 to generate the maximum number of docking poses. Only docking poses which resembled the binding mode of erlotinib (**2**) in EGFR (PDB code: 4HJO)[9] were evaluated.

Biochemical evaluation of BUB1 inhibitors

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

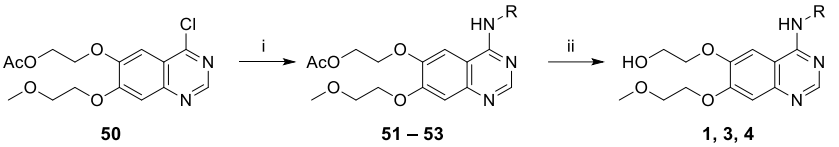
For each assay, assay buffer (AB) was freshly prepared and consisted of 20 mM HEPES (prepared by diluting 1 M HEPES, pH 7.2), 5 mM $MgCl_2$, 0.01% (v/v) Tween-20 and 1 mM DTT. Stocks of inhibitors (in DMSO) were diluted in AB to obtain 4x working solutions (4% DMSO) and 5 µL was added to the assay plate.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

Experimental – Chemistry

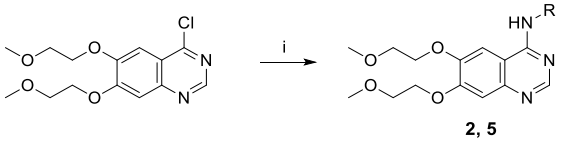
Synthetic routes

The synthesis of OSI-420 (**1**), **3** and **4** (**Scheme 3.1**) involved the synthesis of **50** as described in **Chapter 2**.[16–18] From **50**, three groups were introduced at R_3 (**Figure 3.1A**) by nucleophilic aromatic

substitutions to afford **51** – **53**. Deacetylation resulted in the formation of the desired compounds. Erlotinib (**2**) and **5**, in which the free hydroxyl of R_1 (**Figure 3.1A**) was methylated, were synthesized from commercially available 4-chloro-6,7-bis(2-methoxyethoxy)quinazoline by nucleophilic aromatic substitutions (**Scheme 3.2**).

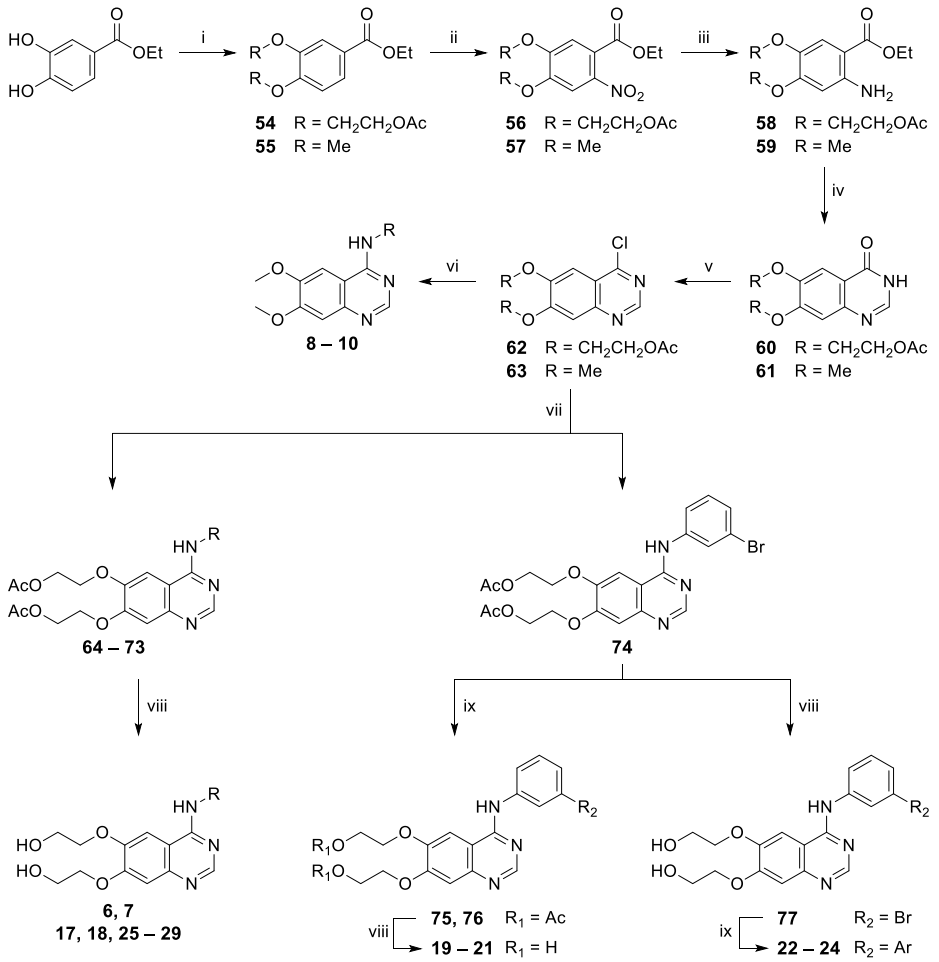


Scheme 3.1 | Synthesis of 1, 3 and 4. Reagents and conditions: **i)** 3-ethynylaniline (for **51**), aniline (for **52**) or naphthalen-2-amine (for **53**), 2-propanol, 82°C, 95% – quant. **ii)** 0.4 M NaOH in MeOH, 27 – 89%.



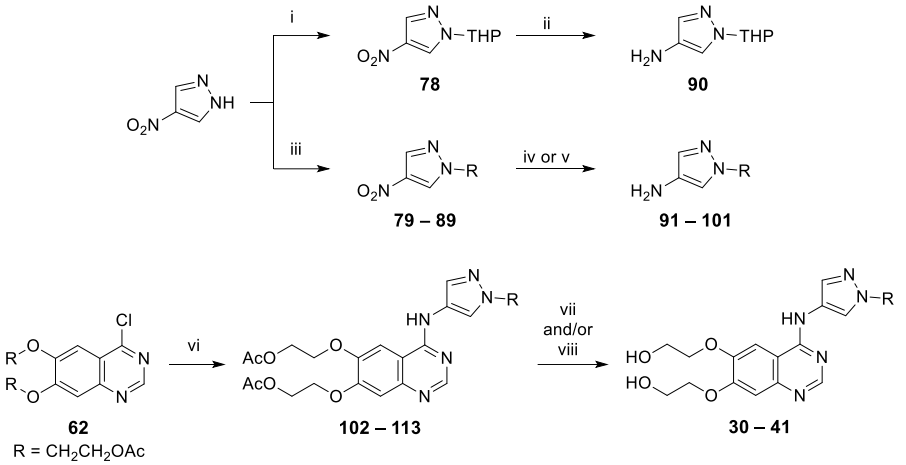
Scheme 3.2 | Synthesis of 2 and 5. Reagents and conditions: **i)** 3-ethynylaniline (for **2**) or 3-chloroaniline (for **5**), 2-propanol, 82°C, 97 – 98%.

Next, several analogues were prepared which either contained methoxy (**8** – **10**) or glycol groups (**6**, **7** and **17** – **41**) at R_1 and R_2 (**Figure 3.1A**, **Scheme 3.3**, **Scheme 3.4**). In addition, this small array of compounds contained derivatives involving R_3 (**Figure 3.1A**). Synthesis of these compounds started from 3,4-dihydroxybenzoate which was alkylated with either 2-bromoethyl acetate or iodomethane to yield **54** and **55**, respectively (**Scheme 3.3**). Compounds **56** – **63** were subsequently synthesized analogous to the synthetic route as described for OSI-420 (**1**) (**Chapter 2**). Compounds **8** – **10** were prepared from **63** via nucleophilic aromatic substitutions. Similarly, nucleophilic aromatic substitutions with **62** resulted in the formation of intermediates **64** – **73** and yielded **6**, **7**, **17**, **18**, **25** – **29** after deacetylation. Synthesis of analogues **19** – **24** involved a Suzuki coupling with **74** and subsequent deacetylation or *vice versa*, which saved one synthetic step per final compound. To obtain pyrazole derivatives **30** – **41**, aminopyrazoles **90** – **101** were first prepared as depicted in **Scheme 3.4**. Protection or alkylation of 4-nitro-1*H*-pyrazole resulted in the formation intermediates **78** – **89**. Nitro group reduction yielded aminopyrazoles **90** – **101** which were subsequently coupled to **62** to form intermediates **102** – **113** (**Scheme 3.4**). Deacetylation resulted in the formation of compounds **30** – **41**.

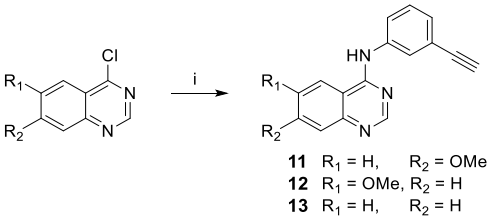


Scheme 3.3 | Synthesis of 6 – 10 and 17 – 29. Reagents and conditions: **i)** 2-bromoethyl acetate (for **54**) or iodomethane (for **55**), K_2CO_3, DMF, 100°C, 62 – 97%. **ii)** $Cu(NO_3)_2 \cdot 3H_2O$, Ac_2O, 0°C → RT, 62 – 71%. **iii)** 5% Pt/C, MeOH, 69 – 95%. **iv)** NH_4HCO_2, formamide, 160°C, 27 – 39%. **v)** $POCl_3$, 105°C, 14 – 84%. **vi)** 3-ethynylaniline (for **8**), 3-chloroaniline (for **9**) or 3-chloro-4-fluoroaniline (for **10**), 2-propanol, 82°C, 68 – 95%. **vii)** corresponding amine, 2-propanol, 82°C, 71 – 99%. **viii)** 0.4 M NaOH in MeOH, 45 – 97%. **ix)** corresponding boronic acid, K_2CO_3, Pd(dppf)Cl_2·DCM, dioxane/H_2O (4:1), 100°C, 55 – 80%.

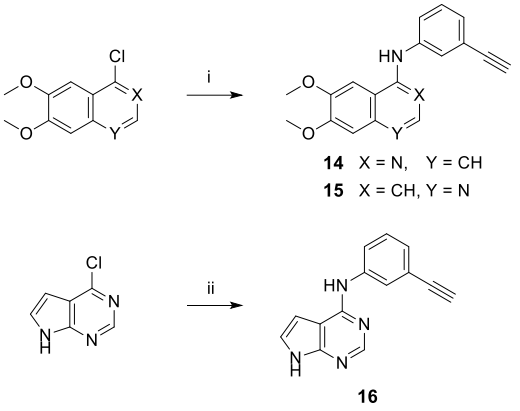
Further reducing the size of the substituents at R_1 and R_2 (**Figure 3.1A**) involved the synthesis of **11** – **13** (**Scheme 3.5**) which only required a nucleophilic aromatic substitution from commercial building blocks. Similarly, analogues involving the quinazoline scaffold were synthesized from commercial building blocks to obtain compound **14** – **16** (**Scheme 3.6**).[19] Compound **42** – **47**, which contained different heterocycles at R_3 (**Figure 3.1A**), were synthesized as depicted in **Scheme 3.7**. Nucleophilic aromatic substitutions with commercially available 4-chloro-6,7-dimethoxyquinazoline yielded compound **42** – **44**.[20] For the synthesis of **45**, a chloropyrimidine was coupled using a Buchwald-Hartwig amination and this compound also served as building block for the synthesis of **46** and **47** by using nucleophilic aromatic substitutions. Similarly, the R_3 substituent of **46** was attached to the scaffold of erlotinib (**2**) using 4-chloro-6,7-bis(2-methoxyethoxy)quinazoline (**Scheme 3.8**) to form **114** and yielded **48** after an nucleophilic aromatic substitution. To investigate the importance of the pyrimidine nitrogens in this molecule, compound **49** was synthesized (**Scheme 3.8**) and required the synthesis of **116** via an Ullmann reaction[21,22] and subsequent reduction of the nitro group.



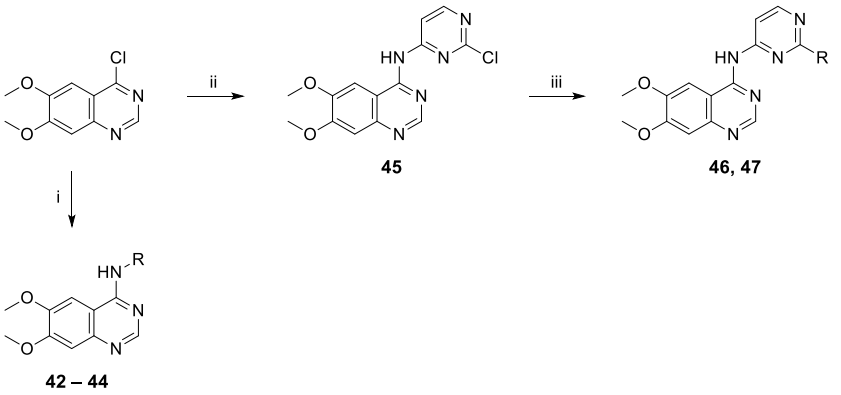
Scheme 3.4 | Synthesis of 30 – 41. Reagents and conditions: **i)** 3,4-dihydro-2*H*-pyran, *p*-TsOH·H_2O, DCM. **ii)** 5% Pt/C, MeOH, 74% over two steps. **iii)** corresponding halide, K_2CO_3, DMF, RT – 90°C, 97% – quant. **iv)** 10% Pd/C, MeOH, 68% – quant. **v)** Fe, NH_4Cl, H_2O/EtOH (1:1), 60°C, 34 – 99%. **vi)** corresponding amine, 2-propanol, 82°C, 73 – 97%. **vii)** 0.16 M HCl (aq.), MeOH. **viii)** 0.4 M NaOH in MeOH, 68 – 92%.



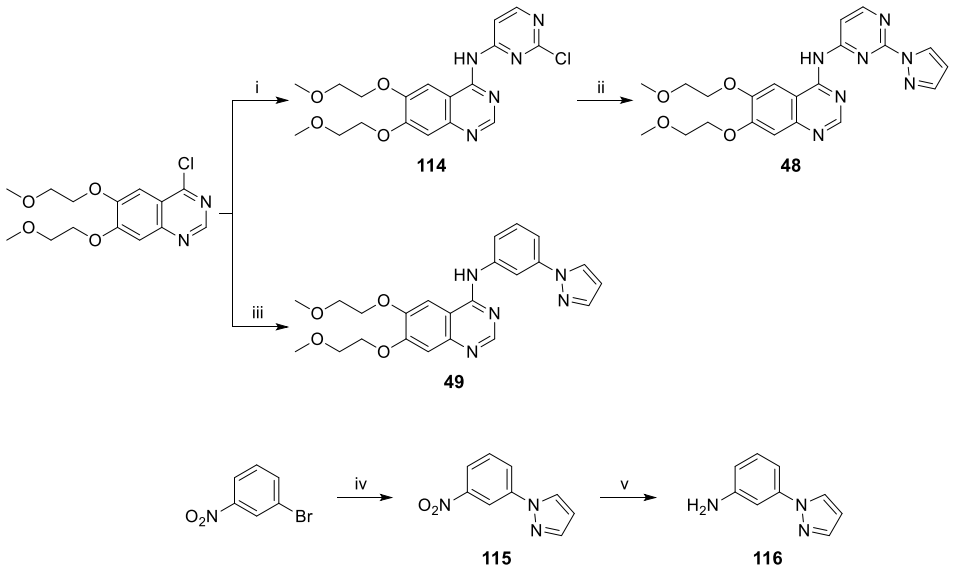
Scheme 3.5 | Synthesis of 11 – 13. Reagents and conditions: **i)** 3-ethynylaniline, 2-propanol, 82°C, 66 – 98%.



Scheme 3.6 | Synthesis of 14 – 16. Reagents and conditions: **i)** 3-ethynylaniline, cat. HCl (aq.), 2-propanol, 82°C, 32 – 43%. **ii)** 3-ethynylaniline, 2-propanol, 82°C, 35%.



Scheme 3.7 | Synthesis of 42 – 47. Reagents and conditions: **i)** 1*H*-indazol-6-amine (for **42**), 1*H*-indazol-5-amine (for **43**) or 1*H*-benzo[*d*]imidazole-5-amine (for **44**), MeCN, 80°C, 48 – 74%. **ii)** 2-chloropyrimidin-4-amine, Cs_2CO_3, xantphos, $Pd(OAc)_2$, DMF, 90°C, 67%. **iii)** 1*H*-pyrazole (for **46**) or 1*H*-pyrrole (for **47**), NaH, dioxane, 90 – 100°C, 38 – 70%.



Scheme 3.8 | Synthesis of 48 and 49. Reagents and conditions: **i)** 2-chloropyrimidin-4-amine, Cs_2CO_3, xantphos, $Pd(OAc)_2$, DMF, 90°C, 63%. **ii)** 1*H*-pyrazole, K_2CO_3, dioxane, 95°C, 19%. **iii)** **116**, 2-propanol, 82°C, 45%. **iv)** 1*H*-pyrazole, ethyl 2-oxocyclohexane-1-carboxylate, Cs_2CO_3, Cu_2O, MeCN, 82°C, 55%. **v)** NH_4Cl, Fe, $EtOH/H_2O$ (30:1), 80°C, 98%.

General procedures

All reagents were purchased from chemical suppliers (Fluorochem, Sigma-Aldrich, Merck, Fisher Scientific) and used without further purification. Solvents (Honeywell, VWR, Biosolve) indicated with "dry" were stored on activated 3 Å (MeCN) or 4 Å (other solvents) molecular sieves (8 to 12 mesh, Acros Organics). Solvents indicated by "degassed" were sonicated while bubbling N_2 through the solvent for 20 min. All reactions were performed at room temperature (RT) under a nitrogen atmosphere, unless stated otherwise. Reactions were monitored by thin layer chromatography (TLC, silica gel 60, UV_{254}, Macherey-Nagel, ref: 818333) and compounds were visualized by UV absorption (254 nm and/or 366 nm) or spray reagent (permanganate (5 g/L $KMnO_4$, 25 g/L K_2CO_3)) followed by heating. Alternatively, reactions were monitored by liquid chromatography-mass spectrometry (LCMS), either on a Thermo Finnigan (Thermo Finnigan LCQ Advantage MAX ion-trap mass spectrometer (ESI+) coupled to a

Surveyor HPLC system (Thermo Finnigan) equipped with a Nucleodur C18 Gravity column (50x4.6 mm, 3 µm particle size, Macherey-Nagel)) or a Thermo Fleet (Thermo LCQ Fleet ion-trap mass spectrometer (ESI+) coupled to a Vanquish UHPLC system). LCMS eluent consisted of MeCN in 0.1% TFA (aq.) and LCMS methods were as follows: 0.5 min cleaning with starting gradient, 8 min using specified gradient (linear), 2 min cleaning with 90% MeCN in 0.1% TFA (aq.). LCMS data is reported as follows: instrument (Finnigan or Fleet), gradient (% MeCN in 0.1% TFA (aq.)), retention time (t_r) and mass (as m/z: $[M+H]^+$). Purity of final compounds was determined to be ≥ 95% by integrating UV intensity of spectra generated by either of the LCMS instruments. ^1H and ^{13}C NMR spectra were recorded on a Bruker AV300 (300 and 75 MHz, respectively), Bruker AV400 (400 and 101 MHz, respectively) or Bruker AV500 (500 and 126 MHz, respectively) NMR spectrometer. NMR samples were prepared in deuterated chloroform, water, methanol or DMSO. Chemical shifts are given in ppm (δ) relative to residual protonated solvent signals ($CDCl_3$ → δ 7.260 (^1H), δ 77.160 (^{13}C), D_2O → δ 4.790 (^1H), MeOD → δ 3.310 (^1H), δ 49.000 (^{13}C), DMSO → δ 2.500 (^1H), δ 39.520 (^{13}C)). Data was processed by using MestReNova (v. 14) and is reported as follows: chemical shift (δ), multiplicity, coupling constant (*J* in Hz) and integration. Multiplicities are abbreviated as follows: s = singlet, br s = broad singlet, app. s = apparent singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets, td = triplet of doublets, t = triplet, dt = doublet of triplets, tt = triplet of triplets, q = quartet, p = pentet, hept = heptet, m = multiplet, br m = broad multiplet. Purification was done either by manual silica gel column chromatography (using 40-63 µm, 60 Å silica gel, Macherey-Nagel) or automated flash column chromatography on a Biotage Isolera machine (using pre-packed cartridges with 40-63 µm, 60 Å silica gel (4, 12, 25 or 40 g), Screening Devices). High resolution mass spectrometry (HRMS) spectra were recorded through direct injection of a 1 µM sample either on a Thermo Scientific Q Exactive Orbitrap equipped with an electrospray ion source in positive mode coupled to an Ultimate 3000 system (source voltage = 3.5 kV, capillary temperature = 275 °C, resolution R = 240,000 at m/z 400, external lock, mass range m/z = 150-2000) or on a Synapt G2-Si high definition mass spectrometer (Waters) equipped with an electrospray ion source in positive mode (ESI-TOF) coupled to a NanoEquity system with Leu-enkephalin (m/z = 556.2771) as internal lock mass. The eluent for HRMS measurements consisted of a 1:1 (v/v) mixture of MeCN in 0.1% formic acid (aq.) using a flow of 25 mL/min. Compound names were generated by ChemDraw (v. 19.1.21).

General procedure A – Aromatic substitution

4-Chloroquinazoline analogue (1 eq.) was dissolved in 2-propanol (~0.18 M) after which corresponding aniline or amine analogue (1 – 1.2 eq.) was added. DIPEA (2 eq.) was added only if the aniline or amine analogue was an HCl salt. The mixture was heated to 82°C, stirred for indicated time and subsequently poured into 0.1 M $NaHCO_3$ (aq.) (30 mL). The product was extracted with DCM (3x30 mL) or EtOAc (3x30 mL), the combined organic layers washed with brine (100 mL) and subsequently dried over Na_2SO_4, filtered and concentrated. Purification was performed as indicated.

General procedure B – Acetyl deprotection

Acetyl-protected alcohol starting material was dissolved in a solution of 0.4 M NaOH in MeOH (2.7 eq.) and the mixture was stirred for indicated time. The mixture was diluted in H_2O (30 mL) and the product extracted with EtOAc (3x30 mL) or 20% MeOH in DCM (3x30 mL) and brine was added when required. The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated. For water soluble products, the mixture was concentrated directly and purified as indicated.

General procedure C – Suzuki coupling

A microwave tube was charged with 3-bromoaniline analogue (1 eq.), corresponding boronic acid (1.2 eq.), K_2CO_3 (4 eq.) and 4:1 dioxane/H_2O (~0.15 M). N_2 was bubbled through the mixture for 1 min after which Pd(dppf)Cl_2·DCM (0.07 eq.) was added. N_2 was bubbled through the mixture for 30 sec after which the vial was sealed. The mixture was heated to 100°C, stirred for 1.5 h and subsequently poured into H_2O (20 mL). The product was extracted with EtOAc (3x20 mL) and the combined organic layers were washed with brine (50 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated. Purification was performed as indicated.

General procedure D – Nucleophilic aromatic substitution

4-Chloro-6,7-dimethoxyquinazoline (50.0 mg, 223 µmol) was suspended in MeCN (0.11 M) after which corresponding amine analogue (1 eq.) was added. The mixture was heated to 80°C, stirred for indicated time and subsequently poured into 1 M $NaHCO_3$ (aq.) (20 mL). The product was extracted with EtOAc (3x20 mL) and the combined organic layers were concentrated as such. Purification was performed as indicated.

General procedure E – Alkylation

4-Nitro-1*H*-pyrazole (1 eq.) and K_2CO_3 (1.2 eq.) were mixed in dry DMF (at indicated reaction molarity). Corresponding halide (1 – 1.2 eq.) was added and the mixture was stirred for 16 h at indicated temperature. The mixture was poured into H_2O (30 mL) and the product extracted with EtOAc (3x20 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated. The crude was purified by silica gel column chromatography (5 – 30% EtOAc/pentane) to afford the product.

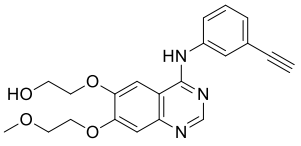
General procedure F – Reduction

4-Nitropyrazole analogue (1 eq.) was dissolved in degassed MeOH (3 mL). 10% Pd/C (10 mass%) was added and the atmosphere was exchanged for H_2. The mixture was vigorously stirred for indicated time while bubbling H_2 through the mixture. The atmosphere was exchanged for N_2, after which the mixture was filtered over Celite and concentrated to afford the product.

General procedure G – Reduction

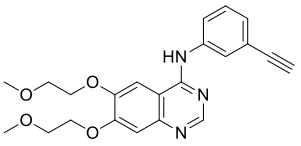
4-Nitropyrazole analogue (1 eq.) and NH_4Cl (4 eq.) were mixed in a 1:1 mixture of H_2O/EtOH (~0.1 M). Iron powder (3 eq.) was added and the mixture was stirred at 60°C for 2 h. The hot mixture was filtered over Celite and concentrated. The residue was diluted in DCM (20 mL) and poured into H_2O (20 mL). The organic layer was separated and the water layer washed with DCM (20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated to afford the product.

2-((4-((3-Ethynylphenyl)amino)-7-(2-methoxyethoxy)quinazolin-6-yl)oxy)ethan-1-ol (1)



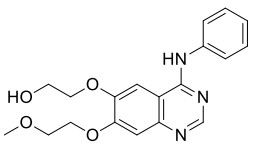
The title compound was synthesized as described in **Chapter 2** (compound 3)

N-(3-Ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (2)



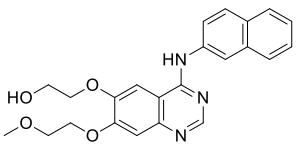
The title compound was synthesized from 4-chloro-6,7-bis(2-methoxyethoxy)quinazoline (40.0 mg, 128 µmol) and 3-ethynylaniline (15.9 µL, 141 µmol) according to general procedure A (reaction time: 1.5 h). The crude was purified by silica gel column chromatography (1 – 10% MeOH/DCM) to afford the product (49.0 mg, 125 µmol, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (s, 1H), 7.84 (t, *J* = 1.9 Hz, 1H), 7.72 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.64 (s, 1H), 7.32 (t, *J* = 7.9 Hz, 1H), 7.28 – 7.21 (m, 2H), 7.14 (s, 1H), 4.24 – 4.13 (m, 4H), 3.80 – 3.73 (m, 4H), 3.41 (s, 3H), 3.40 (s, 3H), 3.08 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.43, 154.60, 153.70, 148.88, 147.63, 138.96, 129.10, 127.85, 125.23, 122.88, 122.49, 109.26, 108.74, 102.56, 83.48, 77.58, 71.05, 70.48, 69.17, 68.36, 59.42, 59.34. LCMS (Finnigan, 10 → 90%): t_r = 5.38 min, m/z: 394.2. HRMS $[C_{22}H_{23}N_3O_4 + H]^+$: 394.17613 calculated, 394.1764 found.

2-((7-(2-Methoxyethoxy)-4-(phenylamino)quinazolin-6-yl)oxy)ethan-1-ol (3)



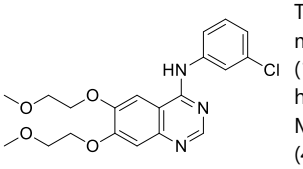
The title compound was synthesized from **52** (36.1 mg, 90.8 µmol) according to general procedure B (reaction time: 3 h). The crude was purified by automated column chromatography (4 – 20% MeOH/DCM) to afford the product (28.7 mg, 80.8 µmol, 89%). ^{1}H NMR (500 MHz, MeOD) δ 8.36 (s, 1H), 7.70 (s, 1H), 7.69 (d, *J* = 7.6 Hz, 2H), 7.37 (t, *J* = 7.9 Hz, 2H), 7.18 – 7.11 (m, 2H), 4.31 – 4.27 (m, 2H), 4.27 – 4.24 (m, 2H), 3.98 – 3.94 (m, 2H), 3.85 – 3.81 (m, 2H), 3.45 (s, 3H). LCMS (Finnigan, 10 → 90%): t_r = 4.50 min, m/z: 356.2. HRMS $[C_{19}H_{21}N_3O_4 + H]^+$: 356.16048 calculated, 356.1613 found.

2-((7-(2-Methoxyethoxy)-4-(naphthalen-2-ylamino)quinazolin-6-yl)oxy)ethan-1-ol (4)



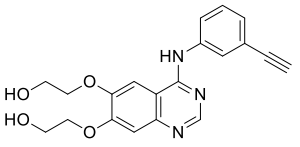
The title compound was synthesized from **53** (36.7 mg, 82.0 µmol) according to general procedure B (reaction time: 3 h). The crude was purified by automated column chromatography (4 – 20% MeOH/DCM) to afford the product (28.8 mg, 71.0 µmol, 87%). ^{1}H NMR (500 MHz, MeOD) δ 8.45 (s, 1H), 8.17 (s, 1H), 7.83 (d, *J* = 8.8 Hz, 1H), 7.81 – 7.72 (m, 4H), 7.43 (t, *J* = 7.4 Hz, 1H), 7.39 (t, *J* = 7.3 Hz, 1H), 7.15 (s, 1H), 4.31 – 4.27 (m, 2H), 4.26 – 4.21 (m, 2H), 4.00 – 3.95 (m, 2H), 3.87 – 3.82 (m, 2H), 3.46 (s, 3H). ^{13}C NMR (126 MHz, MeOD) δ 157.97, 154.88, 153.33, 149.49, 146.41, 136.76, 134.41, 131.50, 128.86, 127.99, 127.95, 126.74, 125.57, 123.25, 120.24, 110.27, 107.64, 103.74, 71.39, 70.88, 68.55, 60.92, 59.27. LCMS (Finnigan, 0 → 50%): t_r = 8.31 min, m/z: 406.2. HRMS $[C_{23}H_{23}N_3O_4 + H]^+$: 406.17613 calculated, 406.1764 found.

***N*-(3-Chlorophenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (5)**



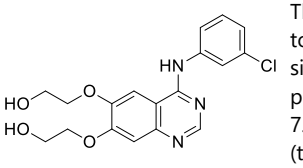
The title compound was synthesized from 4-chloro-6,7-bis(2-methoxyethoxy)quinazoline (41.0 mg, 131 µmol) and 3-chloroaniline (15.3 µL, 144 µmol) according to general procedure A (reaction time: 1.5 h). The crude was purified by silica gel column chromatography (1 – 4% MeOH/DCM) to afford the product (52.0 mg, 129 µmol, 98%). ^{1}H NMR (400 MHz, MeOD) δ 8.39 (s, 1H), 7.88 (s, 1H), 7.63 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.60 (d, *J* = 1.5 Hz, 1H), 7.30 (t, *J* = 8.1 Hz, 1H), 7.09 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.03 (s, 1H), 4.26 (t, *J* = 4.7 Hz, 2H), 4.25 – 4.18 (m, 2H), 3.86 – 3.77 (m, 4H), 3.46 (s, 3H), 3.44 (s, 3H). ^{13}C NMR (101 MHz, MeOD) δ 157.88, 155.63, 153.48, 150.03, 147.16, 141.47, 134.99, 130.61, 124.66, 123.14, 121.31, 110.33, 107.87, 103.71, 71.69, 71.44, 69.68, 69.31, 59.53, 59.48. LCMS (Finnigan, 10 → 90%): t_r = 5.43 min, m/z: 404.1. HRMS $[C_{20}H_{22}ClN_3O_4 + H]^+$: 404.13716 calculated, 404.1378 found.

2,2'-((4-((3-Ethynylphenyl)amino)quinazoline-6,7-diyl)bis(oxy))bis(ethan-1-ol) (6)



The title compound was synthesized from **64** (36 mg, 80 µmol) according to general procedure B (reaction time: 1 h). The crude was purified by silica gel column chromatography (4 – 20% MeOH/DCM) to afford the product (22.9 mg, 62.7 µmol, 78%). ^{1}H NMR (400 MHz, MeOD) δ 8.42 (s, 1H), 7.91 (t, *J* = 1.9 Hz, 1H), 7.77 (ddd, *J* = 8.2, 2.3, 1.1 Hz, 1H), 7.73 (s, 1H), 7.37 (t, *J* = 7.9 Hz, 1H), 7.25 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.15 (s, 1H), 4.28 – 4.24 (m, 2H), 4.24 – 4.20 (m, 2H), 4.02 – 3.97 (m, 4H), 3.52 (s, 1H). ^{13}C NMR (101 MHz, MeOD) δ 158.47, 156.08, 153.92, 150.57, 147.63, 140.62, 129.91, 128.74, 127.06, 124.30, 124.18, 110.61, 108.04, 103.69, 84.30, 78.72, 72.01, 71.71, 61.45, 61.25. LCMS (Finnigan, 10 → 90%): t_r = 4.54 min, m/z: 366.3. HRMS $[C_{20}H_{19}N_3O_4 + H]^+$: 366.14483 calculated, 366.1448 found.

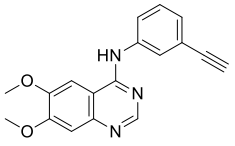
2,2'-((4-((3-Chlorophenyl)amino)quinazoline-6,7-diyl)bis(oxy))bis(ethan-1-ol) (7)



The title compound was synthesized from **65** (39 mg, 85 µmol) according to general procedure B (reaction time: 1 h). The crude was purified by silica gel column chromatography (10% MeOH/DCM) to afford the product (30 mg, 80 µmol, 94%). ^{1}H NMR (400 MHz, MeOD) δ 8.43 (s, 1H), 7.87 – 7.80 (m, 1H), 7.69 (s, 1H), 7.60 (ddd, *J* = 8.2, 2.1, 1.0 Hz, 1H), 7.30 (t, *J* = 8.1 Hz, 1H), 7.13 – 7.06 (m, 2H), 4.27 – 4.17 (m, 4H), 4.02 – 3.96 (m,

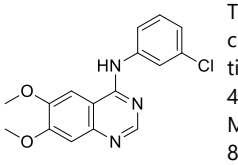
4H). ^{13}C NMR (101 MHz, MeOD) δ 157.79, 155.29, 153.30, 149.77, 146.93, 140.99, 134.84, 130.40, 124.68, 123.14, 121.23, 110.23, 107.49, 103.22, 71.33, 71.06, 60.91, 60.68. LCMS (Finnigan, 10 → 90%): t_r = 4.77 min, m/z: 376.2. HRMS $[C_{18}H_{18}ClN_3O_4 + H]^+$: 376.10586 calculated, 376.1064 found.

N-(3-Ethynylphenyl)-6,7-dimethoxyquinazolin-4-amine (8)



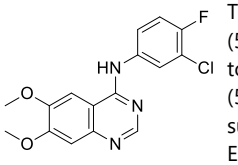
The title compound was synthesized from **63** (16.7 mg, 74.3 µmol) and 3-ethynylaniline (8.4 µL, 74.3 µmol) according to general procedure A (reaction time: 1.5 h). The crude was purified by silica gel column chromatography (1 – 10% MeOH/DCM) to afford the product (21 mg, 69 µmol, 93%). ^{1}H NMR (400 MHz, MeOD) δ 8.42 (s, 1H), 7.84 (t, *J* = 1.8 Hz, 1H), 7.75 – 7.67 (m, 2H), 7.34 (t, *J* = 7.9 Hz, 1H), 7.25 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.14 (s, 1H), 4.03 (s, 3H), 4.01 (s, 3H), 3.33 (s, 1H). ^{13}C NMR (101 MHz, MeOD) δ 158.15, 155.97, 153.37, 150.58, 147.03, 139.86, 129.54, 128.67, 126.98, 124.17, 123.69, 110.32, 106.67, 102.18, 83.94, 78.24, 56.77, 56.57. LCMS (Finnigan, 10 → 90%): t_r = 5.15 min, m/z: 306.3. HRMS $[C_{18}H_{15}N_3O_2 + H]^+$: 306.12370 calculated, 306.1244 found.

N-(3-Chlorophenyl)-6,7-dimethoxyquinazolin-4-amine (9)



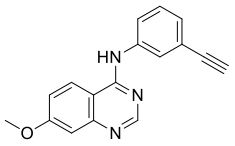
The title compound was synthesized from **63** (15.8 mg, 70.3 µmol) and 3-chloroaniline (7.4 µL, 70.3 µmol) according to general procedure A (reaction time: 1.5 h). The crude was purified by silica gel column chromatography (0 – 4% MeOH/DCM) to afford the product (21 mg, 67 µmol, 95%). ^{1}H NMR (400 MHz, MeOD) δ 8.45 (s, 1H), 7.83 (t, *J* = 2.1 Hz, 1H), 7.71 (s, 1H), 7.61 (ddd, *J* = 8.2, 2.1, 1.0 Hz, 1H), 7.31 (t, *J* = 8.1 Hz, 1H), 7.13 (s, 1H), 7.10 (ddd, *J* = 8.0, 2.1, 1.0 Hz, 1H), 4.03 (s, 3H), 4.01 (s, 3H). ^{13}C NMR (101 MHz, MeOD) δ 157.82, 155.74, 153.25, 150.38, 147.03, 140.96, 134.82, 130.37, 124.68, 123.18, 121.26, 110.24, 106.65, 101.95, 56.71, 56.54, 49.86. LCMS (Finnigan, 10 → 90%): t_r = 5.26 min, m/z: 316.3. HRMS $[C_{16}H_{14}ClN_3O_2 + H]^+$: 316.08473 calculated, 316.0852 found.

N-(3-Chloro-4-fluorophenyl)-6,7-dimethoxyquinazolin-4-amine (10)



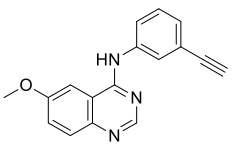
The title compound was synthesized from 4-chloro-6,7-dimethoxyquinazoline (50.0 mg, 223 µmol) and 3-chloro-4-fluoroaniline (32.4 mg, 223 µmol) according to general procedure A (reaction time: 16 h). The crude was suspended in DCM (5 mL) and filtered. The solids were collected, loaded onto Celite and subsequently purified by automated column chromatography (50 – 100% EtOAc/DCM) to afford the product (50.7 mg, 152 µmol, 68%). ^{1}H NMR (400 MHz, DMSO) δ 9.50 (s, 1H), 8.49 (s, 1H), 8.11 (dd, *J* = 6.9, 2.6 Hz, 1H), 7.79 (ddd, *J* = 9.0, 4.3, 2.7 Hz, 1H), 7.75 (s, 1H), 7.42 (t, *J* = 9.1 Hz, 1H), 7.16 (s, 1H), 3.94 (s, 3H), 3.92 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 156.00, 154.36, 152.62, 151.94, 149.01, 147.04, 136.87 (d, $J_{(C–F)}$ = 3.0 Hz), 123.39, 122.21 (d, $J_{(C–F)}$ = 6.7 Hz), 118.80 (d, $J_{(C–F)}$ = 18.3 Hz), 116.50 (d, $J_{(C–F)}$ = 21.6 Hz), 108.78, 107.19, 101.62, 56.20, 55.82. LCMS (Fleet, 10 → 90%): t_r = 4.68 min, m/z: 334.3. HRMS $[C_{16}H_{13}ClFN_3O_2 + H]^+$: 334.07531 calculated, 334.07508 found.

N-(3-Ethynylphenyl)-7-methoxyquinazolin-4-amine (11)



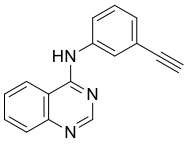
The title compound was synthesized from 4-chloro-7-methoxyquinazoline (50.0 mg, 257 µmol) and 3-ethynylaniline (26.9 µL, 257 µmol) according to general procedure A (reaction time: 3 h). The crude was purified by automated column chromatography (20 – 60% EtOAc/DCM) to afford the product (69.2 mg, 251 µmol, 98%). ^{1}H NMR (400 MHz, DMSO) δ 9.68 (s, 1H), 8.58 (s, 1H), 8.43 (d, *J* = 9.2 Hz, 1H), 8.09 (t, *J* = 1.9 Hz, 1H), 7.91 (ddd, *J* = 8.4, 2.3, 1.1 Hz, 1H), 7.38 (t, *J* = 7.9 Hz, 1H), 7.26 – 7.19 (m, 2H), 7.18 (d, *J* = 2.6 Hz, 1H), 4.19 (s, 1H), 3.90 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 162.76, 157.25, 154.90, 152.18, 139.74, 128.87, 126.50, 124.78, 124.55, 122.56, 121.77, 117.74, 109.42, 107.00, 83.63, 80.51, 55.61. LCMS (Fleet, 10 → 90%): t_r = 4.39 min, m/z: 276.3. HRMS $[C_{17}H_{13}N_3O + H]^+$: 276.11314 calculated, 276.11296 found.

_N_-(3-Ethynylphenyl)-6-methoxyquinazolin-4-amine (12)



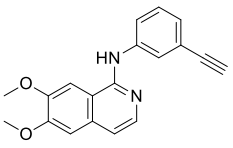
The title compound was synthesized from 4-chloro-6-methoxyquinazoline (50.0 mg, 257 µmol) and 3-ethynylaniline (26.9 µL, 257 µmol) according to general procedure A (reaction time: 3 h). The crude was purified by automated column chromatography (20 – 60% EtOAc/DCM) to afford the product (58.1 mg, 211 µmol, 82%). ^{1}H NMR (500 MHz, DMSO) δ 9.62 (s, 1H), 8.54 (s, 1H), 8.05 (t, *J* = 1.9 Hz, 1H), 7.94 (ddd, *J* = 8.3, 2.3, 1.1 Hz, 1H), 7.88 (d, *J* = 2.7 Hz, 1H), 7.72 (d, *J* = 9.0 Hz, 1H), 7.47 (dd, *J* = 9.1, 2.7 Hz, 1H), 7.41 (t, *J* = 7.9 Hz, 1H), 7.24 (dt, *J* = 7.6, 1.3 Hz, 1H), 4.19 (s, 1H), 3.93 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 157.42, 156.77, 152.18, 145.18, 139.64, 129.45, 128.88, 126.62, 124.98, 124.23, 122.75, 121.79, 115.66, 102.10, 83.51, 80.54, 55.99. LCMS (Fleet, 10 → 90%): t_r = 4.42 min, m/z: 276.3. HRMS [$C_{17}H_{13}N_3O$ + H]$^+$: 276.11314 calculated, 276.11305 found.

_N_-(3-Ethynylphenyl)quinazolin-4-amine (13)



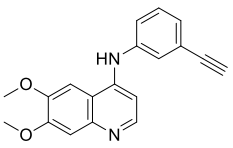
The title compound was synthesized from 4-chloroquinazoline (50.0 mg, 304 µmol) and 3-ethynylaniline (34.2 µL, 257 µmol) according to general procedure A (reaction time: 3 h). The crude was purified by automated column chromatography (1 – 10% MeOH/DCM) to afford the product (49.3 mg, 201 µmol, 66%). ^{1}H NMR (500 MHz, MeOD) δ 8.52 (s, 1H), 8.31 (dd, *J* = 8.4, 0.7 Hz, 1H), 7.93 (t, *J* = 1.9 Hz, 1H), 7.81 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 7.79 – 7.72 (m, 2H), 7.58 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 7.34 (t, *J* = 7.9 Hz, 1H), 7.25 (dt, *J* = 7.7, 1.3 Hz, 1H), 3.50 (s, 1H). ^{13}C NMR (126 MHz, MeOD) δ 159.83, 155.49, 150.31, 140.17, 134.54, 129.86, 129.09, 128.03, 128.01, 127.20, 124.42, 124.15, 123.51, 116.61, 84.23, 78.81. LCMS (Fleet, 0 → 50%): t_r = 6.61 min, m/z: 246.1. HRMS [$C_{16}H_{11}N_3$ + H]$^+$: 246.10257 calculated, 246.10253 found.

_N_-(3-Ethynylphenyl)-6,7-dimethoxyisoquinolin-1-amine (14)



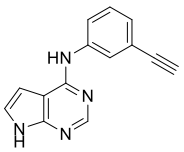
A microwave tube charged with 1-chloro-6,7-dimethoxyisoquinoline (100 mg, 447 µmol) was mixed in 2-propanol (3 mL) after which 3-ethynylaniline (50 µL, 447 µmol) and a catalytic amount of 2 M HCl (aq., 50 µL) were added. The vial was sealed and the mixture was stirred at 82°C for 16 h. This mixture was poured into sat. $NaHCO_3$ (aq.) (20 mL) and the product extracted with $CHCl_3$/MeOH (4:1) (3x20 mL). The combined organic layers were washed with H_2O (30 mL), dried over Na_2SO_4, filtered and concentrated. The crude was purified by silica gel column chromatography (0 – 5% MeOH/DCM) to afford the product (44.0 mg, 145 µmol, 32%). ^{1}H NMR (400 MHz, DMSO) δ 8.96 (s, 1H), 8.00 (t, *J* = 1.9 Hz, 1H), 7.92 – 7.87 (m, 2H), 7.78 (s, 1H), 7.32 (t, *J* = 7.9 Hz, 1H), 7.25 (s, 1H), 7.12 (d, *J* = 5.7 Hz, 1H), 7.07 (dt, *J* = 7.5, 1.3 Hz, 1H), 4.15 (s, 1H), 3.97 (s, 3H), 3.91 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 152.11, 151.03, 149.24, 141.86, 138.85, 133.51, 128.73, 124.38, 122.85, 121.57, 120.76, 113.30, 112.64, 105.99, 102.87, 84.02, 80.04, 56.06, 55.61. LCMS (Fleet, 10 → 90%): t_r = 4.50 min, m/z: 305.3. HRMS [$C_{19}H_{16}N_2O_2$ + H]$^+$: 305.12845 calculated, 305.12840 found.

_N_-(3-Ethynylphenyl)-6,7-dimethoxyquinolin-4-amine (15)



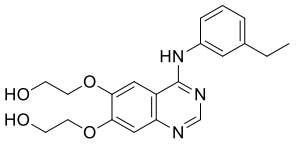
A microwave tube charged with 1-chloro-6,7-dimethoxyisoquinoline (100 mg, 447 µmol) was mixed in 2-propanol (3 mL) after which 3-ethynylaniline (50 µL, 447 µmol) and a catalytic amount of 2 M HCl (aq., 50 µL) were added. The vial was sealed and the mixture was stirred at 82°C for 16 h. This mixture was poured into sat. $NaHCO_3$ (aq.) (20 mL) and the product extracted with $CHCl_3$/MeOH (4:1) (3x20 mL). The combined organic layers were washed with H_2O (30 mL), dried over Na_2SO_4, filtered and concentrated. The crude was purified by silica gel column chromatography (0 – 5% MeOH/DCM) to afford the product (58.3 mg, 192 µmol, 43%). ^{1}H NMR (400 MHz, DMSO) δ 8.88 (br s, 1H), 8.33 (d, *J* = 5.4 Hz, 1H), 7.65 (s, 1H), 7.42 – 7.39 (m, 3H), 7.27 (s, 1H), 7.24 – 7.18 (m, 1H), 6.89 (d, *J* = 5.4 Hz, 1H), 4.22 (s, 1H), 3.93 (s, 3H), 3.91 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 151.91, 148.42, 147.88, 146.02, 145.48, 141.36, 129.85, 126.34, 124.46, 122.76, 122.17, 114.21, 107.84, 101.57, 101.02, 83.28, 80.97, 55.94, 55.57. LCMS (Fleet, 10 → 90%): t_r = 4.66 min, m/z: 305.3. HRMS [$C_{19}H_{16}N_2O_2$ + H]$^+$: 305.12845 calculated, 305.12831 found.

_N_-(3-Ethynylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (16)



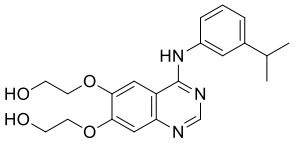
The title compound was synthesized from 4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine (50.0 mg, 326 µmol) and 3-ethynylaniline (36.6 µL, 326 µmol) according to general procedure A, using 5% MeOH/$CHCl_3$ for the extraction (reaction time 18 h). The crude was purified by automated column chromatography (1 – 10% MeOH/DCM) to afford the product (26.6 mg, 114 µmol, 35%). ^{1}H NMR (500 MHz, MeOD) δ 8.26 (s, 1H), 7.89 (t, *J* = 1.8 Hz, 1H), 7.70 (ddd, *J* = 8.2, 2.2, 1.0 Hz, 1H), 7.28 (t, *J* = 7.9 Hz, 1H), 7.17 (dt, *J* = 7.6, 1.2 Hz, 1H), 7.14 (d, *J* = 3.5 Hz, 1H), 6.66 (d, *J* = 3.5 Hz, 1H), 3.40 (s, 1H). ^{13}C NMR (126 MHz, MeOD) δ 155.43, 151.61, 151.36, 141.02, 129.72, 127.73, 125.68, 123.93, 123.29, 122.94, 105.41, 99.87, 84.39, 78.29. LCMS (Fleet, 0 → 50%): t_r = 6.19 min, m/z: 235.1. HRMS [$C_{14}H_{10}N_4$ + H]$^+$: 235.09782 calculated, 235.09760 found.

2,2'-((4-((3-Ethylphenyl)amino)quinazoline-6,7-diyl)bis(oxy))bis(ethan-1-ol) (17)



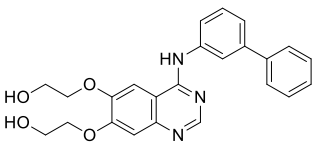
The title compound was synthesized from **66** (28 mg, 62 µmol) according to general procedure B (reaction time: 1 h). The crude was purified by silica gel column chromatography (5 – 8% MeOH/DCM) to afford the product (19 mg, 51 µmol, 83%). ^{1}H NMR (400 MHz, MeOD) δ 8.34 (s, 1H), 7.68 (s, 1H), 7.55 – 7.49 (m, 2H), 7.29 (t, *J* = 7.7 Hz, 1H), 7.09 (s, 1H), 7.02 (dt, *J* = 7.6, 1.2 Hz, 1H), 4.26 – 4.21 (m, 2H), 4.21 – 4.17 (m, 2H), 4.01 – 3.94 (m, 4H), 2.67 (q, *J* = 7.6 Hz, 2H), 1.27 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, MeOD) δ 158.64, 155.92, 153.87, 150.39, 147.20, 146.24, 140.11, 129.73, 125.20, 123.72, 121.71, 110.50, 107.86, 103.81, 71.97, 71.65, 61.45, 61.24, 29.89, 16.11. LCMS (Finnigan, 10 → 90%): t_r = 4.92 min, m/z: 370.2. HRMS [$C_{20}H_{23}N_3O_4$ + H]$^+$: 370.17613 calculated, 370.17599 found.

2,2'-((4-((3-Isopropylphenyl)amino)quinazoline-6,7-diyl)bis(oxy))bis(ethan-1-ol) (18)



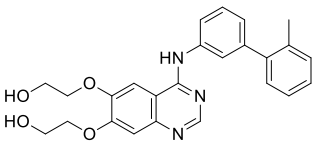
The title compound was synthesized from **67** (28.8 mg, 61.6 µmol) according to general procedure B (reaction time: 1 h). The crude was purified by silica gel column chromatography (5 – 8% MeOH/DCM) to afford the product (20 mg, 52 µmol, 85%). ^{1}H NMR (400 MHz, MeOD) δ 8.34 (s, 1H), 7.70 (s, 1H), 7.57 (ddd, *J* = 8.1, 2.2, 1.1 Hz, 1H), 7.53 (t, *J* = 1.9 Hz, 1H), 7.30 (t, *J* = 7.8 Hz, 1H), 7.10 (s, 1H), 7.05 (dt, *J* = 7.8, 1.1 Hz, 1H), 4.26 – 4.22 (m, 2H), 4.22 – 4.17 (m, 2H), 4.02 – 3.94 (m, 4H), 2.93 (hept, *J* = 6.9 Hz, 1H), 1.29 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, MeOD) δ 158.64, 155.90, 153.96, 150.91, 150.38, 147.38, 140.14, 129.72, 123.73, 122.28, 121.90, 110.54, 107.97, 103.81, 71.97, 71.65, 61.45, 61.25, 35.45, 24.43. LCMS (Fleet, 10 → 90%): t_r = 4.46 min, m/z: 384.3. LCMS (Fleet, 10 → 90%): t_r = 4.46 min, m/z: 384.3. HRMS [$C_{21}H_{25}N_3O_4$ + H]$^+$: 384.19178 calculated, 384.19186 found.

2,2'-((4-([1,1'-Biphenyl]-3-ylamino)quinazoline-6,7-diyl)bis(oxy))bis(ethan-1-ol) (19)



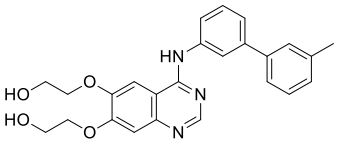
The title compound was synthesized from **68** (39 mg, 78 µmol) according to general procedure B (reaction time: 1 h). The crude was purified by silica gel column chromatography (5 – 8% MeOH/DCM) to afford the product (28.8 mg, 69.0 µmol, 89%). ^{1}H NMR (400 MHz, DMSO) δ 9.57 (s, 1H), 8.47 (s, 1H), 8.06 (t, *J* = 1.9 Hz, 1H), 7.90 (s, 1H), 7.87 (ddd, *J* = 8.0, 2.0, 0.9 Hz, 1H), 7.72 – 7.67 (m, 2H), 7.52 – 7.46 (m, 3H), 7.42 – 7.36 (m, 2H), 7.22 (s, 1H), 4.99 (t, *J* = 5.4 Hz, 1H), 4.96 (t, *J* = 5.4 Hz, 1H), 4.24 – 4.16 (m, 4H), 3.89 – 3.79 (m, 4H). ^{13}C NMR (101 MHz, DMSO) δ 156.36, 153.83, 152.89, 148.38, 146.95, 140.53, 140.24, 140.07, 129.05, 129.01, 127.57, 126.72, 121.72, 121.35, 120.57, 108.93, 108.15, 103.06, 70.78, 70.40, 59.39, 59.26. LCMS (Finnigan, 10 → 90%): t_r = 5.45 min, m/z: 418.2. HRMS [$C_{24}H_{23}N_3O_4$ + H]$^+$: 418.17613 calculated, 418.17623 found.

2,2'-((4-((2'-Methyl-[1,1'-biphenyl]-3-yl)amino)quinazoline-6,7-diyl)bis(oxy))bis(ethan-1-ol) (20)



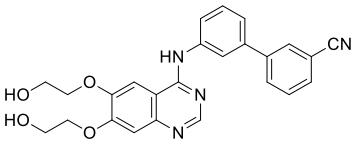
The title compound was synthesized from **75** (26 mg, 50 µmol) according to general procedure B (reaction time: 1 h). The crude was purified by silica gel column chromatography (5 – 8% MeOH/DCM) to afford the product (20 mg, 46 µmol, 92%). ^{1}H NMR (400 MHz, MeOD) δ 8.36 (s, 1H), 7.74 – 7.70 (m, 2H), 7.67 (t, *J* = 1.8 Hz, 1H), 7.42 (t, *J* = 7.9 Hz, 1H), 7.28 – 7.21 (m, 4H), 7.12 – 7.07 (m, 2H), 4.24 (t, 2H), 4.20 (t, 2H), 4.00 – 3.94 (m, 4H), 2.31 (s, 3H). ^{13}C NMR (101 MHz, MeOD) δ 158.61, 155.94, 153.99, 150.43, 147.49, 143.99, 142.99, 140.12, 136.37, 131.37, 130.63, 129.53, 128.43, 126.85, 126.24, 124.84, 122.49, 110.60, 108.00, 103.77, 71.98, 71.66, 61.45, 61.25, 20.69. LCMS (Finnigan, 10 → 90%): t_r = 5.74 min, m/z: 432.3. HRMS $[C_{25}H_{25}N_3O_4 + H]^+$: 432.19178 calculated, 432.19188 found.

2,2'-((4-((3'-Methyl-[1,1'-biphenyl]-3-yl)amino)quinazoline-6,7-diyl)bis(oxy))bis(ethan-1-ol) (21)



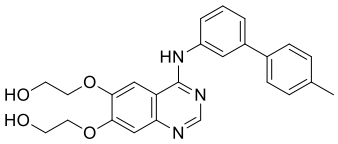
The title compound was synthesized from **76** (24.5 mg, 47.5 µmol) according to general procedure B (reaction time: 1 h). The crude was purified by silica gel column chromatography (4 – 8% MeOH/DCM) to afford the product (18 mg, 42 µmol, 88%). ^{1}H NMR (400 MHz, DMSO) δ 9.56 (s, 1H), 8.47 (s, 1H), 8.01 (t, *J* = 1.8 Hz, 1H), 7.92 – 7.85 (m, 2H), 7.54 – 7.43 (m, 3H), 7.42 – 7.33 (m, 2H), 7.22 (s, 1H), 7.20 (d, *J* = 7.5 Hz, 1H), 5.00 (t, *J* = 5.4 Hz, 1H), 4.96 (t, *J* = 5.4 Hz, 1H), 4.25 – 4.15 (m, 4H), 3.86 (q, *J* = 5.3 Hz, 2H), 3.82 (q, *J* = 5.3 Hz, 2H), 2.39 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 156.37, 153.83, 152.90, 148.38, 146.95, 140.63, 140.19, 140.02, 138.12, 128.98, 128.90, 128.20, 127.37, 123.84, 121.71, 121.31, 120.53, 108.93, 108.15, 103.06, 70.79, 70.40, 59.40, 59.27, 21.16. LCMS (Fleet, 10 → 90%): t_r = 4.94 min, m/z: 432.3. HRMS $[C_{25}H_{25}N_3O_4 + H]^+$: 432.19178 calculated, 432.19157 found.

3'-((6,7-Bis(2-hydroxyethoxy)quinazolin-4-yl)amino)-[1,1'-biphenyl]-3-carbonitrile (22)



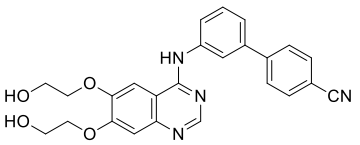
The title compound was synthesized from **77** (50.0 mg, 119 µmol) according to general procedure C using (3-cyanophenyl)boronic acid. The crude was purified by silica gel column chromatography (2 – 8% MeOH/DCM) to afford the product (39 mg, 88 µmol, 74%). ^{1}H NMR (400 MHz, DMSO) δ 9.59 (s, 1H), 8.48 (s, 1H), 8.16 (t, *J* = 1.5 Hz, 1H), 8.11 (t, *J* = 1.7 Hz, 1H), 8.04 (dt, *J* = 7.9, 1.4 Hz, 1H), 7.93 (dt, *J* = 7.8, 1.5 Hz, 1H), 7.88 (s, 1H), 7.85 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.70 (t, *J* = 7.8 Hz, 1H), 7.52 (t, *J* = 7.7 Hz, 1H), 7.48 (dt, *J* = 7.7, 1.6 Hz, 1H), 7.22 (s, 1H), 5.01 (t, *J* = 5.4 Hz, 1H), 4.97 (t, *J* = 5.4 Hz, 1H), 4.25 – 4.15 (m, 4H), 3.86 (q, *J* = 5.4 Hz, 2H), 3.82 (q, *J* = 5.2 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ 156.34, 153.88, 152.88, 148.41, 146.98, 141.34, 140.27, 138.35, 131.54, 131.19, 130.26, 129.29, 122.24, 121.91, 120.76, 118.83, 112.17, 108.93, 108.14, 103.01, 70.80, 70.42, 59.40, 59.28. LCMS (Fleet, 10 → 90%): t_r = 4.45 min, m/z: 443.3. HRMS $[C_{25}H_{22}N_4O_4 + H]^+$: 443.17138 calculated, 443.17105 found.

2,2'-((4-((4'-Methyl-[1,1'-biphenyl]-3-yl)amino)quinazoline-6,7-diyl)bis(oxy))bis(ethan-1-ol) (23)



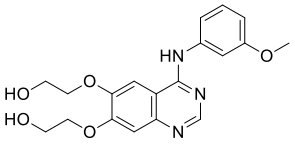
The title compound was synthesized from **77** (34 mg, 81 µmol) according to general procedure C using *p*-tolylboronic acid. The crude was purified by silica gel column chromatography (4 – 8% MeOH/DCM) to afford the product (28 mg, 65 µmol, 80%). ^{1}H NMR (400 MHz, DMSO) δ 9.55 (s, 1H), 8.47 (s, 1H), 8.02 (t, *J* = 1.8 Hz, 1H), 7.89 (s, 1H), 7.87 – 7.83 (m, 1H), 7.61 – 7.57 (m, 2H), 7.46 (t, *J* = 7.9 Hz, 1H), 7.37 (ddd, *J* = 7.7, 1.8, 1.1 Hz, 1H), 7.31 – 7.27 (m, 2H), 7.22 (s, 1H), 5.00 (t, *J* = 5.4 Hz, 1H), 4.96 (t, *J* = 5.4 Hz, 1H), 4.24 – 4.16 (m, 4H), 3.86 (q, *J* = 5.5 Hz, 2H), 3.82 (q, *J* = 5.3 Hz, 2H), 2.35 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 156.38, 153.83, 152.90, 148.38, 146.95, 140.42, 140.03, 137.32, 136.85, 129.60, 128.98, 126.53, 121.48, 121.12, 120.30, 108.94, 108.15, 103.08, 70.79, 70.40, 59.40, 59.27, 20.71. LCMS (Fleet, 10 → 90%): t_r = 4.96 min, m/z: 432.3. HRMS $[C_{25}H_{25}N_3O_4 + H]^+$: 432.19178 calculated, 432.19187 found.

3'-((6,7-Bis(2-hydroxyethoxy)quinazolin-4-yl)amino)-[1,1'-biphenyl]-4-carbonitrile (24)



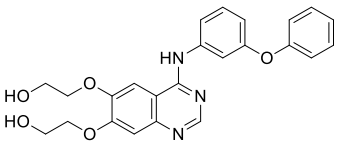
The title compound was synthesized from **77** (45.0 mg, 107 µmol) according to general procedure C using (4-cyanophenyl)boronic acid. The crude was purified by silica gel column chromatography (2 – 8% MeOH/DCM) to afford the product (26 mg, 59 µmol, 55%). ^{1}H NMR (400 MHz, DMSO) δ 9.61 (s, 1H), 8.48 (s, 1H), 8.15 (t, *J* = 1.7 Hz, 1H), 7.99 – 7.86 (m, 6H), 7.53 (t, *J* = 7.8 Hz, 1H), 7.48 (dt, *J* = 8.2, 1.4 Hz, 1H), 7.22 (s, 1H), 5.00 (t, *J* = 5.2 Hz, 1H), 4.96 (t, *J* = 5.3 Hz, 1H), 4.24 – 4.16 (m, 4H), 3.86 (q, *J* = 5.3 Hz, 2H), 3.81 (q, *J* = 5.2 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ 156.31, 153.89, 152.84, 148.42, 146.99, 144.73, 140.32, 138.59, 132.97, 129.35, 127.60, 122.51, 121.99, 120.78, 118.91, 110.14, 108.93, 108.15, 103.02, 70.78, 70.42, 59.39, 59.27. LCMS (Fleet, 10 → 90%): t_r = 4.45 min, m/z: 443.3. HRMS $[C_{25}H_{22}N_4O_4 + H]^+$: 443.17138 calculated, 443.17117 found.

2,2'-((4-((3-Methoxyphenyl)amino)quinazoline-6,7-diyl)bis(oxy))bis(ethan-1-ol) (25)



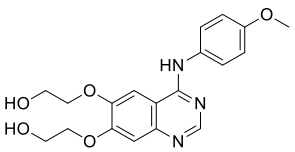
The title compound was synthesized from **69** (49.5 mg, 109 µmol) according to general procedure B (reaction time: 1 h). The crude was purified by silica gel column chromatography (5 – 20% MeOH/DCM) to afford the product (32.5 mg, 87.5 µmol, 81%). ^{1}H NMR (400 MHz, MeOD) δ 8.34 (s, 1H), 7.63 (s, 1H), 7.39 (s, 1H), 7.31 – 7.22 (m, 2H), 7.03 (s, 1H), 6.71 (d, *J* = 7.6 Hz, 1H), 4.22 (t, 2H), 4.15 (t, 2H), 4.03 – 3.91 (m, 4H), 3.81 (s, 3H). ^{13}C NMR (101 MHz, MeOD) δ 161.47, 158.39, 155.78, 154.31, 150.28, 147.21, 141.38, 130.40, 116.14, 110.83, 110.49, 109.78, 107.81, 103.62, 71.91, 71.58, 61.41, 61.20, 55.73. LCMS (Finnigan, 10 → 90%): t_r = 4.39 min, m/z: 372.2. HRMS $[C_{19}H_{21}N_3O_5 + H]^+$: 372.15540 calculated, 372.1557 found.

2,2'-((4-((3-Phenoxyphenyl)amino)quinazoline-6,7-diyl)bis(oxy))bis(ethan-1-ol) (26)



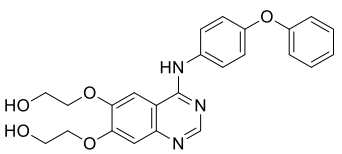
The title compound was synthesized from **70** (32 mg, 62 µmol) according to general procedure B (reaction time: 1 h). The crude was purified by silica gel column chromatography (4 – 10% MeOH/DCM) to afford the product (22 mg, 51 µmol, 82%). ^{1}H NMR (400 MHz, MeOD) δ 8.32 (s, 1H), 7.60 (s, 1H), 7.51 (ddd, *J* = 8.1, 2.0, 0.8 Hz, 1H), 7.46 (t, *J* = 2.1 Hz, 1H), 7.37 – 7.28 (m, 3H), 7.12 – 7.07 (m, 1H), 7.06 – 7.01 (m, 3H), 6.73 (ddd, *J* = 8.2, 2.4, 0.8 Hz, 1H), 4.19 (t, 2H), 4.15 (t, 2H), 3.99 – 3.91 (m, 4H). ^{13}C NMR (101 MHz, MeOD) δ 159.05, 158.49, 158.26, 155.87, 153.67, 150.37, 147.18, 141.85, 130.87, 130.72, 124.48, 120.08, 118.39, 115.23, 114.02, 110.48, 107.76, 103.58, 71.91, 71.61, 61.42, 61.22. LCMS (Finnigan, 10 → 90%): t_r = 5.56 min, m/z: 434.2. HRMS $[C_{24}H_{23}N_3O_5 + H]^+$: 434.17105 calculated, 434.1709 found.

2,2'-((4-((4-Methoxyphenyl)amino)quinazoline-6,7-diyl)bis(oxy))bis(ethan-1-ol) (27)



The title compound was synthesized from **71** (42 mg, 92 µmol) according to general procedure B (reaction time: 1.5 h). The crude was loaded onto Celite and purified by silica gel column chromatography (7 – 10% MeOH/DCM) to afford the product (15.4 mg, 41.5 µmol, 45%). ^{1}H NMR (500 MHz, MeOD) δ 8.35 (s, 1H), 7.74 (s, 1H), 7.52 – 7.48 (m, 2H), 7.14 (s, 1H), 6.97 – 6.94 (m, 2H), 4.27 – 4.20 (m, 4H), 4.02 – 3.97 (m, 4H), 3.82 (s, 3H). ^{13}C NMR (126 MHz, MeOD) δ 158.83, 158.30, 155.76, 152.90, 150.10, 144.93, 131.87, 126.29, 114.88, 109.84, 106.53, 103.90, 71.60, 71.37, 61.03, 60.82, 55.84. LCMS (Finnigan, 10 → 90%): t_r = 4.30 min, m/z: 372.1. HRMS $[C_{19}H_{21}N_3O_5 + H]^+$: 372.15540 calculated, 372.1555 found.

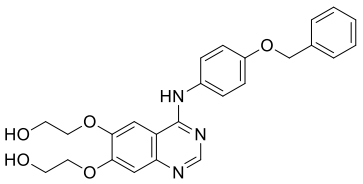
2,2'-((4-((4-Phenoxyphenyl)amino)quinazoline-6,7-diyl)bis(oxy))bis(ethan-1-ol) (28)



The title compound was synthesized from **72** (31.5 mg, 60.9 µmol) according to general procedure B (reaction time: 1 h). The crude was purified by silica gel column chromatography (5 – 10% MeOH/DCM) to afford the product (21 mg, 48 µmol, 80%). ^{1}H NMR (400 MHz, MeOD) δ 8.38 (s, 1H), 7.69 (s, 1H), 7.62 – 7.57 (m, 2H),

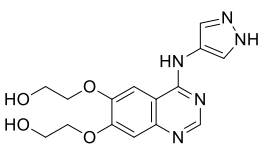
7.35 – 7.29 (m, 2H), 7.12 (s, 1H), 7.10 – 7.05 (m, 1H), 7.05 – 6.99 (m, 4H), 4.25 – 4.19 (m, 4H), 4.02 – 3.96 (m, 4H). ^{13}C NMR (101 MHz, MeOD) δ 158.17, 158.07, 155.03, 154.65, 153.50, 149.47, 146.75, 134.62, 130.25, 125.48, 123.72, 119.81, 119.09, 110.04, 107.53, 103.37, 71.23, 70.94, 60.86, 60.63. LCMS (Finnigan, 10 → 90%): t_r = 5.52 min, m/z: 434.2. HRMS [$C_{24}H_{23}N_3O_5$ + H]$^+$: 434.17105 calculated, 434.1713 found.

2,2'-((4-((4-(Benzyloxy)phenyl)amino)quinazoline-6,7-diyl)bis(oxy))bis(ethan-1-ol) (29)



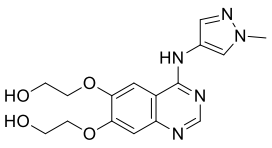
The title compound was synthesized from **73** (19 mg, 36 µmol) according to general procedure B (reaction time: 1 h). The crude was purified by silica gel column chromatography (5 – 10% MeOH/DCM) to afford the product (13 mg, 29 µmol, 81%). ^{1}H NMR (400 MHz, MeOD) δ 8.32 (s, 1H), 7.69 (s, 1H), 7.51 – 7.47 (m, 2H), 7.45 – 7.41 (m, 2H), 7.39 – 7.33 (m, 2H), 7.32 – 7.27 (m, 1H), 7.11 (s, 1H), 7.03 – 6.99 (m, 2H), 5.08 (s, 2H), 4.26 – 4.19 (m, 4H), 4.02 – 3.96 (m, 4H). ^{13}C NMR (101 MHz, MeOD) δ 158.50, 156.94, 155.11, 153.62, 149.55, 146.64, 137.83, 132.39, 129.13, 128.54, 128.10, 125.97, 115.83, 110.07, 107.52, 103.56, 71.34, 71.04, 70.90, 60.92, 60.71. LCMS (Fleet, 10 → 90%): t_r = 4.79 min, m/z: 448.3. HRMS [$C_{25}H_{25}N_3O_5$ + H]$^+$: 448.18670 calculated, 448.1870 found.

2,2'-((4-((1*H*-Pyrazol-4-yl)amino)quinazoline-6,7-diyl)bis(oxy))bis(ethan-1-ol) (30)



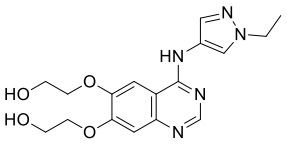
102 (30 mg, 60 µmol) was mixed in MeOH (2 mL). 0.16 M HCl in dioxane was prepared by diluting 12 M HCl (aq.). in dioxane of which 0.4 mL was added to the reaction mixture. The mixture was stirred for 3 h and subsequently concentrated. The title compound was synthesized from the remaining solids according to general procedure B (reaction time: 2 h). Since the product was soluble in water, the crude reaction mixture was concentrated directly and purified twice by silica gel column chromatography (first 30% MeOH/DCM, then, 20% MeOH (containing 10% sat. NH_4OH (aq.))/DCM) to afford the product (13.5 mg, 40.7 µmol, 68%). ^{1}H NMR (400 MHz, D_2O) δ 8.17 (s, 1H), 7.51 (s, 2H), 6.88 (s, 1H), 6.41 (s, 1H), 3.90 – 3.79 (m, 8H). ^{13}C NMR (101 MHz, D_2O) δ 155.38, 154.49, 149.56, 148.41, 134.43, 127.07 (br), 120.02, 106.51, 102.75, 100.58, 71.34, 71.27, 60.02, 59.93. LCMS (Finnigan, 0 → 50%): t_r = 5.10 min, m/z: 332.2. HRMS [$C_{15}H_{17}N_5O_4$ + H]$^+$: 332.13533 calculated, 332.1358 found.

2,2'-((4-((1-Methyl-1*H*-pyrazol-4-yl)amino)quinazoline-6,7-diyl)bis(oxy))bis(ethan-1-ol) (31)



The title compound was synthesized from **103** (32 mg, 75 µmol) according to general procedure B (reaction time: 2 h). Since the product was soluble in water, the crude reaction mixture was concentrated directly and purified by silica gel column chromatography (5 – 10% MeOH (containing 10% sat. NH_4OH (aq.))/DCM) to afford the product (23.7 mg, 68.6 µmol, 92%). ^{1}H NMR (400 MHz, DMSO) δ 10.10 (s, 1H), 8.51 (s, 1H), 8.24 (s, 1H), 7.95 (s, 1H), 7.75 (s, 1H), 7.18 (s, 1H), 5.00 (br s, 2H), 4.20 (t, *J* = 5.2 Hz, 2H), 4.16 (t, *J* = 4.9 Hz, 2H), 3.86 (s, 3H), 3.85 – 3.79 (m, 4H). ^{13}C NMR (101 MHz, DMSO) δ 155.25, 153.79, 152.52, 148.34, 144.27, 131.22, 122.77, 122.02, 108.40, 106.84, 103.45, 70.80, 70.45, 59.30, 59.24, 38.83. LCMS (Fleet, 0 → 50%): t_r = 4.76 min, m/z: 346.3. HRMS [$C_{16}H_{19}N_5O_4$ + H]$^+$: 346.15098 calculated, 346.1516 found.

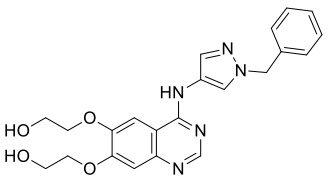
2,2'-((4-((1-Ethyl-1*H*-pyrazol-4-yl)amino)quinazoline-6,7-diyl)bis(oxy))bis(ethan-1-ol) (32)



The title compound was synthesized from **104** (33 mg, 74 µmol) according to general procedure B (reaction time: 2 h). The crude reaction mixture was concentrated directly and purified by silica gel column chromatography (5 – 10% MeOH/DCM) to afford the product (22 mg, 61 µmol, 82%). ^{1}H NMR (400 MHz, MeOD) δ 8.45 (s, 1H), 8.20 (d, *J* = 0.7 Hz, 1H), 7.72 (d, *J* = 0.7 Hz, 1H), 7.62 (s, 1H), 7.06 (s, 1H), 4.23 – 4.14 (m, 6H), 4.02 – 3.94 (m, 4H), 1.49 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, MeOD) δ 156.88, 154.89, 153.76, 149.48, 145.98, 132.15, 122.86, 122.64, 109.82, 107.38, 103.21, 71.29, 71.02, 60.93, 60.73, 47.80, 15.82.

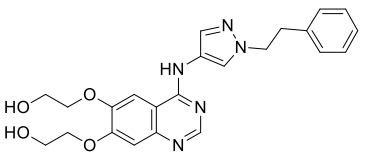
LCMS (Fleet, 0 → 50%): t_r = 5.09 min, m/z: 360.3. HRMS $[C_{17}H_{21}N_5O_4 + H]^+$: 360.16663 calculated, 360.1671 found.

2,2'-((4-((1-Benzyl-1*H*-pyrazol-4-yl)amino)quinazoline-6,7-diyl)bis(oxy))bis(ethan-1-ol) (33)



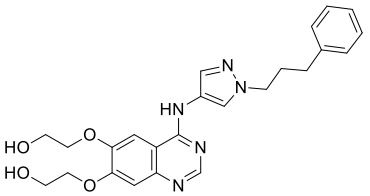
The title compound was synthesized from **105** (40 mg, 79 µmol) according to general procedure B (reaction time: 2 h). The crude reaction mixture was concentrated directly and purified by silica gel column chromatography (3 – 10% MeOH (containing 10% sat. NH_4OH (aq.))/DCM) to afford the product (28 mg, 66 µmol, 84%). ^{1}H NMR (400 MHz, MeOD) δ 8.46 (s, 1H), 8.25 (s, 1H), 7.79 (d, *J* = 0.8 Hz, 1H), 7.65 (s, 1H), 7.35 – 7.26 (m, 3H), 7.26 – 7.21 (m, 2H), 7.09 (s, 1H), 5.31 (s, 2H), 4.24 – 4.16 (m, 4H), 4.01 – 3.95 (m, 4H). ^{13}C NMR (101 MHz, MeOD) δ 156.70, 154.91, 153.54, 149.49, 145.58, 137.15, 132.51, 129.31, 128.59, 128.03, 123.37, 123.30, 109.74, 107.14, 103.20, 71.23, 70.99, 60.85, 60.65, 56.63. LCMS (Finnigan, 0 → 50%): t_r = 7.17 min, m/z: 422.3. HRMS $[C_{22}H_{23}N_5O_4 + H]^+$: 422.18228 calculated, 422.1821 found.

2,2'-((4-((1-Phenethyl-1*H*-pyrazol-4-yl)amino)quinazoline-6,7-diyl)bis(oxy))bis(ethan-1-ol) (34)



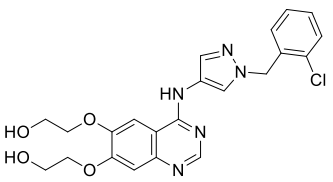
The title compound was synthesized from **106** (31 mg, 60 µmol) according to general procedure B (reaction time: 1 h). The crude reaction mixture was concentrated directly and purified by silica gel column chromatography (4 – 10% MeOH (containing 10% sat. NH_4OH (aq.))/DCM) to afford the product (21 mg, 48 µmol, 81%). ^{1}H NMR (400 MHz, MeOD) δ 8.26 (s, 1H), 7.87 (d, *J* = 0.7 Hz, 1H), 7.74 (d, *J* = 0.5 Hz, 1H), 7.41 (s, 1H), 7.26 – 7.20 (m, 2H), 7.19 – 7.14 (m, 1H), 7.12 – 7.08 (m, 2H), 6.94 (s, 1H), 4.30 (t, *J* = 7.1 Hz, 2H), 4.19 – 4.08 (m, 4H), 4.00 – 3.97 (m, 2H), 3.97 – 3.93 (m, 2H), 3.10 (t, *J* = 7.1 Hz, 2H). ^{13}C NMR (101 MHz, MeOD) δ 157.03, 154.90, 153.94, 149.46, 146.04, 139.27, 132.98, 129.75, 129.55, 127.63, 124.30, 122.82, 109.75, 107.55, 103.26, 71.63, 71.41, 61.10, 60.95, 54.54, 37.46. LCMS (Finnigan, 10 → 90%): t_r = 4.84 min, m/z: 436.3. HRMS $[C_{23}H_{25}N_5O_4 + H]^+$: 436.19793 calculated, 436.1981 found.

2,2'-((4-((1-(3-Phenylpropyl)-1*H*-pyrazol-4-yl)amino)quinazoline-6,7-diyl)bis(oxy))bis(ethan-1-ol) (35)



The title compound was synthesized from **108** (40.8 mg, 76.5 µmol) according to general procedure B (reaction time: 1 h). The crude reaction mixture was concentrated directly and purified by silica gel column chromatography (4 – 10% MeOH (containing 10% sat. NH_4OH (aq.))/DCM) to afford the product (31.4 mg, 69.9 µmol, 91%). ^{1}H NMR (400 MHz, MeOD) δ 8.41 (s, 1H), 8.21 (s, 1H), 7.76 (s, 1H), 7.52 (s, 1H), 7.29 – 7.21 (m, 2H), 7.21 – 7.11 (m, 3H), 7.00 (s, 1H), 4.18 (t, *J* = 4.4 Hz, 2H), 4.17 – 4.08 (m, 4H), 4.01 – 3.91 (m, 4H), 2.64 – 2.55 (m, 2H), 2.16 (p, *J* = 7.2 Hz, 2H). ^{13}C NMR (101 MHz, MeOD) δ 157.19, 155.58, 154.06, 150.17, 146.10, 142.34, 132.66, 129.50, 129.47, 127.09, 123.98, 123.48, 110.01, 107.51, 103.44, 71.87, 71.59, 61.41, 61.23, 52.61, 33.63, 33.15. LCMS (Finnigan, 10 → 90%): t_r = 5.18 min, m/z: 450.3. HRMS $[C_{24}H_{27}N_5O_4 + H]^+$: 450.21358 calculated, 450.21345 found.

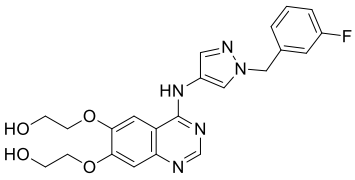
2,2'-((4-((1-(2-Chlorobenzyl)-1*H*-pyrazol-4-yl)amino)quinazoline-6,7-diyl)bis(oxy))bis(ethan-1-ol) (36)



The title compound was synthesized from **107** (42 mg, 78 µmol) according to general procedure B (reaction time: 2 h). The crude reaction mixture was concentrated directly and purified by silica gel column chromatography (2 – 20% MeOH (containing 10% sat. NH_4OH (aq.))/DCM) to afford the product (30 mg, 66 µmol, 85%). ^{1}H NMR (400 MHz, DMSO) δ 9.69 (s, 1H), 8.46 (s, 1H), 8.34 (d, *J* = 0.7 Hz, 1H), 7.81 (d, *J* = 0.7 Hz, 1H), 7.79 (s, 1H), 7.50 (dd, *J* = 7.4, 1.8

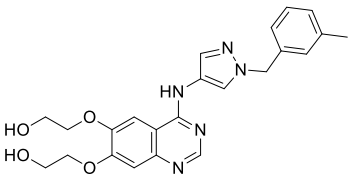
Hz, 1H), 7.38 – 7.30 (m, 2H), 7.18 (s, 1H), 7.01 (dd, *J* = 7.1, 2.2 Hz, 1H), 5.47 (s, 2H), 4.99 (t, *J* = 5.4 Hz, 1H), 4.94 (t, *J* = 5.4 Hz, 1H), 4.20 – 4.14 (m, 4H), 3.84 (q, *J* = 5.3 Hz, 2H), 3.80 (q, *J* = 5.2 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ 155.15, 153.53, 153.26, 148.16, 146.30, 135.18, 132.08, 131.90, 129.69, 129.57, 129.40, 127.55, 122.65, 122.22, 108.60, 108.18, 102.96, 70.72, 70.34, 59.37, 59.26, 52.69. LCMS (Fleet, 10 → 90%): t_r = 4.16 min, m/z: 456.3. HRMS $[C_{22}H_{22}ClN_5O_4 + H]^+$: 456.14331 calculated, 456.14322 found.

2,2'-((4-((1-(3-Fluorobenzyl)-1*H*-pyrazol-4-yl)amino)quinazoline-6,7-diyl)bis(oxy))bis(ethan-1-ol) (37)



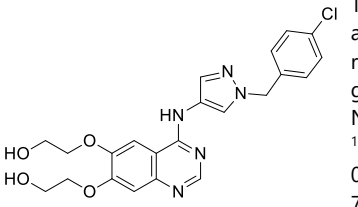
The title compound was synthesized from **109** (35 mg, 67 µmol) according to general procedure B (reaction time: 1 h). The crude reaction mixture was concentrated directly and purified by silica gel column chromatography (4 – 10% MeOH (containing 10% sat. NH_4OH (aq.))/DCM) to afford the product (25.5 mg, 58.0 µmol, 87%). ^{1}H NMR (400 MHz, DMSO) δ 9.69 (s, 1H), 8.47 (s, 1H), 8.37 (s, 1H), 7.79 (s, 1H), 7.78 (d, *J* = 0.7 Hz, 1H), 7.40 (td, *J* = 8.0, 6.1 Hz, 1H), 7.18 (s, 1H), 7.16 – 7.02 (m, 3H), 5.39 (s, 2H), 4.99 (t, *J* = 5.4 Hz, 1H), 4.94 (t, *J* = 5.4 Hz, 1H), 4.20 – 4.14 (m, 4H), 3.84 (q, *J* = 5.5 Hz, 2H), 3.80 (q, *J* = 5.2 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ 162.17 (d, $J_{(C–F)}$ = 243.9 Hz), 155.15, 153.54, 153.26, 148.16, 146.28, 140.75 (d, $J_{(C–F)}$ = 7.3 Hz), 131.81, 130.58 (d, $J_{(C–F)}$ = 8.3 Hz), 123.54 (d, $J_{(C–F)}$ = 2.7 Hz), 122.69, 122.01, 114.38 (d, $J_{(C–F)}$ = 20.9 Hz), 114.21 (d, $J_{(C–F)}$ = 21.8 Hz), 108.60, 108.17, 102.99, 70.72, 70.35, 59.37, 59.27, 54.32. LCMS (Finnigan, 10 → 90%): t_r = 4.73 min, m/z: 440.3. HRMS $[C_{22}H_{22}FN_5O_4 + H]^+$: 440.17286 calculated, 440.17262 found.

2,2'-((4-((1-(3-Methylbenzyl)-1*H*-pyrazol-4-yl)amino)quinazoline-6,7-diyl)bis(oxy))bis(ethan-1-ol) (38)



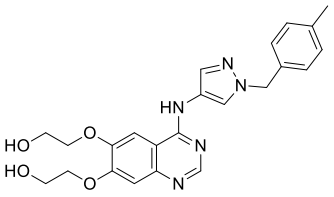
The title compound was synthesized from **110** (38.8 mg, 74.7 µmol) according to general procedure B (reaction time: 1 h). The crude reaction mixture was concentrated directly and purified by silica gel column chromatography (4 – 10% MeOH (containing 10% sat. NH_4OH (aq.))/DCM) to afford the product (29 mg, 67 µmol, 89%). ^{1}H NMR (400 MHz, DMSO) δ 9.66 (s, 1H), 8.45 (s, 1H), 8.29 (d, *J* = 0.7 Hz, 1H), 7.78 (s, 1H), 7.75 (d, *J* = 0.7 Hz, 1H), 7.24 (t, *J* = 7.5 Hz, 1H), 7.17 (s, 1H), 7.12 – 7.03 (m, 3H), 5.31 (s, 2H), 4.99 (t, *J* = 5.4 Hz, 1H), 4.94 (t, *J* = 5.4 Hz, 1H), 4.20 – 4.13 (m, 4H), 3.84 (q, *J* = 5.4 Hz, 2H), 3.80 (q, *J* = 5.2 Hz, 2H), 2.28 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 155.14, 153.51, 153.29, 148.13, 146.28, 137.72, 137.68, 131.46, 128.47, 128.25, 128.16, 124.73, 122.57, 121.72, 108.59, 108.18, 102.97, 70.71, 70.34, 59.37, 55.06, 21.02. LCMS (Fleet, 10 → 90%): t_r = 4.16 min, m/z: 436.3. HRMS $[C_{23}H_{25}N_5O_4 + H]^+$: 436.19793 calculated, 436.19809 found.

2,2'-((4-((1-(4-Chlorobenzyl)-1*H*-pyrazol-4-yl)amino)quinazoline-6,7-diyl)bis(oxy))bis(ethan-1-ol) (39)



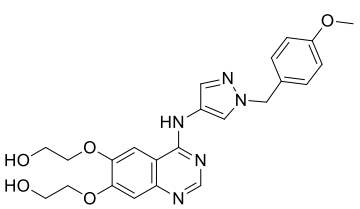
The title compound was synthesized from **111** (40 mg, 74 µmol) according to general procedure B (reaction time: 1 h). The crude reaction mixture was concentrated directly and purified by silica gel column chromatography (4 – 10% MeOH (containing 10% sat. NH_4OH (aq.))/DCM) to afford the product (30 mg, 66 µmol, 89%). ^{1}H NMR (400 MHz, DMSO) δ 9.79 (s, 1H), 8.48 (s, 1H), 8.36 (d, *J* = 0.7 Hz, 1H), 7.82 (s, 1H), 7.79 (d, *J* = 0.7 Hz, 1H), 7.43 – 7.39 (m, 2H), 7.30 – 7.25 (m, 2H), 7.18 (s, 1H), 5.36 (s, 2H), 5.01 (br s, 2H), 4.17 (q, *J* = 5.3 Hz, 4H), 3.84 (t, *J* = 5.2 Hz, 2H), 3.80 (t, *J* = 4.8 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ 155.18, 153.65, 153.07, 148.25, 145.70, 136.89, 132.28, 131.81, 129.45, 128.55, 122.62, 121.98, 108.56, 107.79, 103.09, 70.77, 70.41, 59.38, 59.29, 54.24. LCMS (Finnigan, 10 → 90%): t_r = 5.10 min, m/z: 456.2. HRMS $[C_{22}H_{22}ClN_5O_4 + H]^+$: 456.14331 calculated, 456.1434 found.

2,2'-((4-((1-(4-Methylbenzyl)-1*H*-pyrazol-4-yl)amino)quinazoline-6,7-diyl)bis(oxy))bis(ethan-1-ol) (40)



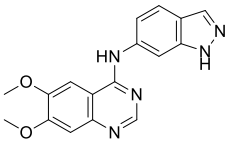
The title compound was synthesized from **112** (36 mg, 69 µmol) according to general procedure B (reaction time: 1 h). The crude reaction mixture was concentrated directly and purified by silica gel column chromatography (4 – 10% MeOH (containing 10% sat. NH_4OH (aq.))/DCM) to afford the product (26.5 mg, 60.9 µmol, 88%). ^{1}H NMR (400 MHz, DMSO) δ 9.72 (s, 1H), 8.47 (s, 1H), 8.28 (d, *J* = 0.8 Hz, 1H), 7.79 (s, 1H), 7.76 (d, *J* = 0.7 Hz, 1H), 7.23 – 7.07 (m, 5H), 5.29 (s, 2H), 5.06 – 4.89 (br m, 2H), 4.19 – 4.14 (m, 4H), 3.84 (t, *J* = 5.0 Hz, 2H), 3.80 (t, *J* = 4.8 Hz, 2H), 2.27 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 155.17, 153.60, 153.19, 148.21, 145.93, 136.88, 134.77, 131.45, 129.11, 127.66, 122.55, 121.69, 108.58, 107.95, 103.04, 70.76, 70.39, 59.40, 59.30, 54.91, 20.74. LCMS (Finnigan, 10 → 90%): t_r = 4.97 min, m/z: 436.3. HRMS [$C_{23}H_{25}N_5O_4$ + H]$^+$: 436.19793 calculated, 436.1983 found.

2,2'-((4-((1-(4-Methoxybenzyl)-1*H*-pyrazol-4-yl)amino)quinazoline-6,7-diyl)bis(oxy))bis(ethan-1-ol) (41)



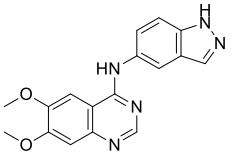
The title compound was synthesized from **113** (41 mg, 77 µmol) according to general procedure B (reaction time: 1 h). The crude reaction mixture was concentrated directly and purified by silica gel column chromatography (5 – 10% MeOH (containing 10% sat. NH_4OH (aq.))/DCM) to afford the product (30 mg, 66 µmol, 87%). ^{1}H NMR (400 MHz, DMSO) δ 9.71 (s, 1H), 8.47 (s, 1H), 8.27 (d, *J* = 0.7 Hz, 1H), 7.79 (s, 1H), 7.75 (d, *J* = 0.7 Hz, 1H), 7.27 – 7.22 (m, 2H), 7.17 (s, 1H), 6.93 – 6.88 (m, 2H), 5.26 (s, 2H), 5.11 – 4.88 (br m, 2H), 4.19 – 4.14 (m, 4H), 3.84 (t, *J* = 5.1 Hz, 2H), 3.80 (t, *J* = 4.8 Hz, 2H), 3.72 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 158.85, 155.18, 153.60, 153.20, 148.21, 145.95, 131.40, 129.67, 129.21, 122.53, 121.51, 113.95, 108.59, 107.97, 103.04, 70.76, 70.39, 59.40, 59.30, 55.14, 54.64. LCMS (Finnigan, 10 → 90%): t_r = 4.70 min, m/z: 452.3. HRMS [$C_{23}H_{25}N_5O_5$ + H]$^+$: 452.19285 calculated, 452.1931 found.

***N*-(1*H*-Indazol-6-yl)-6,7-dimethoxyquinazolin-4-amine (42)**



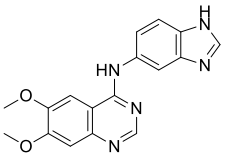
The title compound was synthesized from 1*H*-indazol-6-amine according to general procedure D (reaction time: 16 h). The crude was purified by automated column chromatography (10 – 40% EtOAc/pentane) to afford the product (52.9 mg, 165 µmol, 74%). ^{1}H NMR (400 MHz, DMSO) δ 13.02 (br s, 1H), 9.59 (s, 1H), 8.54 (s, 1H), 8.35 – 8.33 (m, 1H), 8.02 (d, *J* = 1.0 Hz, 1H), 7.90 (s, 1H), 7.73 (dd, *J* = 8.6, 0.7 Hz, 1H), 7.48 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.20 (s, 1H), 3.98 (s, 3H), 3.93 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 156.47, 154.28, 152.88, 148.98, 147.01, 140.53, 137.85, 133.36, 120.12, 119.31, 117.07, 109.13, 107.25, 101.99, 101.97, 56.30, 55.83. LCMS (Fleet, 10 → 90%): t_r = 3.54 min, m/z: 322.3. HRMS [$C_{17}H_{15}N_5O_2$ + H]$^+$: 322.12985 calculated, 322.12969 found.

***N*-(1*H*-Indazol-5-yl)-6,7-dimethoxyquinazolin-4-amine (43)**



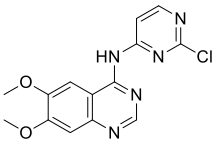
The title compound was synthesized from 1*H*-indazol-5-amine according to general procedure D (reaction time: 16 h). The crude was purified by automated column chromatography (1 – 20% EtOAc/pentane). The residue was suspended in a mixture of MeOH (1 mL) and DCM (2 mL) after which the mixture was warmed to ~50°C and subsequently cooled down. The suspension was filtered and the solids were collected to afford the product (38.6 mg, 120 µmol, 54%). ^{1}H NMR (400 MHz, DMSO) δ 13.08 (s, 1H), 9.56 (s, 1H), 8.42 (s, 1H), 8.14 (d, *J* = 1.8 Hz, 1H), 8.09 (t, *J* = 1.2 Hz, 1H), 7.87 (s, 1H), 7.64 (dd, *J* = 8.9, 1.9 Hz, 1H), 7.58 (d, *J* = 8.8 Hz, 1H), 7.17 (s, 1H), 3.96 (s, 3H), 3.93 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 156.98, 154.13, 153.18, 148.82, 146.83, 137.40, 133.48, 132.21, 124.03, 122.92, 113.86, 109.87, 108.84, 107.20, 102.00, 56.22, 55.79. LCMS (Fleet, 10 → 90%): t_r = 3.39 min, m/z: 322.3. HRMS [$C_{17}H_{15}N_5O_2$ + H]$^+$: 322.12985 calculated, 322.12974 found.

_N_-(1_H_-Benzo[d]imidazol-5-yl)-6,7-dimethoxyquinazolin-4-amine (44)



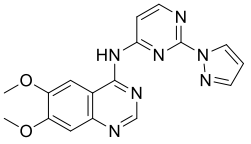
The title compound was synthesized from 1*H*-benzo[*d*]imidazol-5-amine according to general procedure D (reaction time: 16 h). The crude was purified by automated column chromatography (25 – 55% EtOAc/DCM) to afford the product (34.6 mg, 108 µmol, 48%). ^{1}H NMR (500 MHz, DMSO) δ 12.47 (br s, 1H), 9.55 (s, 1H), 8.44 (s, 1H), 8.22 (s, 1H), 8.14 (br s, 1H), 7.89 (s, 1H), 7.62 (br s, 1H), 7.50 (d, *J* = 8.6 Hz, 1H), 7.18 (s, 1H), 3.96 (s, 3H), 3.93 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 156.77, 154.12, 153.11, 148.82, 146.85, 142.19 (br), 139.69 (br), 134.24 (br), 133.38 (br), 119.20 (br), 118.50 (br), 117.78 (br), 113.82 (br), 111.10 (br), 108.91, 107.21, 105.79 (br), 102.04, 56.23, 55.79. LCMS (Fleet, 0 → 50%): t_r = 4.68 min, m/z: 322.3. HRMS $[C_{17}H_{15}N_5O_2 + H]^+$: 322.12985 calculated, 322.12980 found.

_N_-(2-Chloropyrimidin-4-yl)-6,7-dimethoxyquinazolin-4-amine (45)



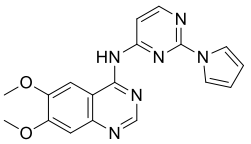
A microwave tube was charged with 4-chloro-6,7-dimethoxyquinazoline (100 mg, 0.445 mmol), Cs_2CO_3 (435 mg, 1.34 mmol), xantphos (38.6 mg, 66.7 µmol), 2-chloropyrimidin-4-amine (69.2 mg, 0.534 mmol) and DMF (2 mL). N_2 was bubbled through the mixture for 30 sec after which $Pd(OAc)_2$ (10 mg, 45 µmol) was added. N_2 was bubbled through the mixture for 10 sec after which the vial was sealed and the mixture was stirred at 90°C for 16 h. The mixture was diluted in EtOAc (20 mL) and filtered over Celite. The filtrate was diluted in EtOAc (20 mL) and poured into H_2O (40 mL) and brine (1 mL). The organic layer was separated, washed with brine (40 mL) and isolated. The water layer was extracted with EtOAc (15 mL) and the combined organic layers were concentrated as such. The crude was purified by automated column chromatography (30 – 50% EtOAc/DCM) to afford the product (95.4 mg, 300 µmol, 67%). ^{1}H NMR (500 MHz, DMSO) δ 11.03 (s, 1H), 8.72 (s, 1H), 8.56 (d, *J* = 5.9 Hz, 1H), 8.51 (d, *J* = 5.9 Hz, 1H), 8.02 (s, 1H), 7.28 (s, 1H), 3.97 (s, 3H), 3.95 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 160.82, 159.97, 159.00, 155.14, 154.93, 151.82, 149.58, 148.06, 110.02, 109.29, 106.97, 102.10, 56.33, 56.01. LCMS (Finnigan, 10 → 90%): t_r = 5.53 min, m/z: 318.1. HRMS $[C_{14}H_{12}ClN_5O_2 + H]^+$: 318.07523 calculated, 318.07521 found.

_N_-(2-(1_H_-Pyrazol-1-yl)pyrimidin-4-yl)-6,7-dimethoxyquinazolin-4-amine (46)



To an oven dried flask was added NaH (60% in mineral oil, 32.7 mg, 818 µmol) and dioxane (2 mL). 1*H*-pyrazole (68.5 mg, 1.01 mmol) was carefully added after which the mixture was stirred for 1 h. Of this mixture, 0.5 mL was added to a microwave tube charged with **45** (30 mg, 94 µmol). The vial was sealed, heated to 90°C and stirred for 72 h. The mixture was poured into H_2O (10 mL) and the product extracted with EtOAc (2x10 mL) and then with 10% MeOH/EtOAc (4x10 mL). The combined organic layers were concentrated as such. The crude was loaded onto Celite and purified by automated column chromatography (0 – 3% MeOH/EtOAc) to afford the product (23.1 mg, 66.1 µmol, 70%). ^{1}H NMR (400 MHz, DMSO) δ 10.86 (br s, 1H), 8.71 (s, 1H), 8.67 (dd, *J* = 2.6, 0.6 Hz, 1H), 8.64 (d, *J* = 5.8 Hz, 1H), 8.32 (d, *J* = 5.3 Hz, 1H), 8.01 (s, 1H), 7.85 (dd, *J* = 1.5, 0.6 Hz, 1H), 7.26 (s, 1H), 6.59 (dd, *J* = 2.6, 1.6 Hz, 1H), 3.98 (s, 3H), 3.95 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 160.54 (br), 158.77, 155.28, 155.12, 155.08, 151.87 (br), 149.41, 148.01, 142.74, 129.40, 110.22, 108.49, 108.41, 106.95, 102.40, 56.29, 55.99. LCMS (Finnigan, 10 → 90%): t_r = 3.82 min, m/z: 350.3. HRMS $[C_{17}H_{15}N_7O_2 + H]^+$: 350.13600 calculated, 350.13593 found.

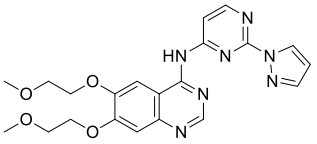
_N_-(2-(1_H_-Pyrrol-1-yl)pyrimidin-4-yl)-6,7-dimethoxyquinazolin-4-amine (47)



To an oven dried flask was added NaH (60% in mineral oil, 64.9 mg, 1.62 mmol) and dioxane (0.5 mL). 1*H*-pyrrole (250 µL, 3.60 mmol) was carefully added after which the mixture was stirred at 50°C for 1 h. Of this mixture, 0.5 mL was added to a microwave tube charged with **45** (74.8 mg, 235 µmol). The vial was sealed, heated to 100°C and stirred for 16 h. The mixture was poured into H_2O (20 mL) and the product extracted with EtOAc (3x20 mL). The combined organic layers were concentrated as such. The crude was loaded onto Celite and purified by silica gel column chromatography (10 – 100% EtOAc/DCM) to afford the product (31.3 mg, 89.8 µmol,

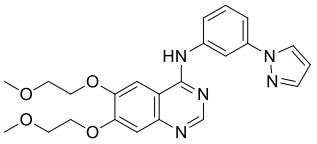
38%). ^{1}H NMR (500 MHz, DMSO) δ 10.54 (br s, 1H), 8.71 (s, 1H), 8.58 (d, *J* = 5.8 Hz, 1H), 8.22 (d, *J* = 5.9 Hz, 1H), 7.96 (s, 1H), 7.80 (t, *J* = 2.4 Hz, 2H), 7.27 (s, 1H), 6.34 – 6.30 (m, 2H), 3.99 (s, 3H), 3.95 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 160.08, 158.80, 155.25, 155.10, 155.05, 151.98, 149.45, 148.02, 118.70, 111.55, 110.09, 107.27, 107.01, 102.28, 56.36, 56.00. LCMS (Fleet, 10 → 90%): t_r = 4.83 min, m/z: 349.3. HRMS $[C_{18}H_{16}N_6O_2 + H]^+$: 349.14075 calculated, 349.14069 found.

N-(2-(1*H*-Pyrazol-1-yl)pyrimidin-4-yl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (48)



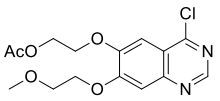
114 (100 mg, 246 µmol), 1*H*-pyrazole (17.6 mg, 259 µmol) and K_2CO_3 (68.1 mg, 493 µmol) were mixed dioxane (1 mL) after which the mixture was heated to 95°C and stirred for 140 h. The mixture poured into H_2O (20 mL) and the product extracted with EtOAc (3x20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude was loaded onto Celite and purified by automated column chromatography (2 – 10% MeOH/DCM). The residue was dissolved in DCM (0.5 mL), heated to 40°C for 10 min and subsequently cooled to 0°C. Heptane (0.5 mL) was added and the mixture was stirred for 20 min at 0°C. The solids were collected by filtration and washed with ice cold DCM (0.1 mL) to afford the product (20 mg, 46 µmol, 19%). ^{1}H NMR (400 MHz, DMSO) δ 10.83 (s, 1H), 8.72 (s, 1H), 8.68 (dd, *J* = 2.7, 0.8 Hz, 1H), 8.66 (d, *J* = 5.9 Hz, 1H), 8.36 (d, *J* = 5.8 Hz, 1H), 8.05 (s, 1H), 7.86 (dd, *J* = 1.6, 0.7 Hz, 1H), 7.31 (s, 1H), 6.60 (dd, *J* = 2.6, 1.6 Hz, 1H), 4.37 – 4.28 (m, 4H), 3.81 – 3.73 (m, 4H), 3.37 (s, 3H), 3.35 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 160.44, 158.85, 155.34, 155.14, 154.38, 152.02, 148.66, 147.97, 142.77, 129.42, 110.13, 108.49, 108.45, 107.90, 103.33, 70.04, 70.02, 68.39, 68.24, 58.41, 58.38. LCMS (Fleet, 10 → 90%): t_r = 4.03 min, m/z: 438.3. HRMS $[C_{21}H_{23}N_7O_4 + H]^+$: 438.18843 calculated, 438.18818 found.

N-(3-(1*H*-Pyrazol-1-yl)phenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (49)



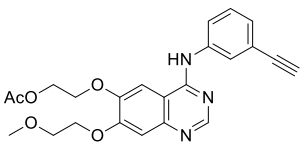
The title compound was synthesized from 4-chloro-6,7-bis(2-methoxyethoxy)quinazoline (45.2 mg, 144 µmol) and **116** (23.0 mg, 144 µmol) according to general procedure A (reaction time: 2 h). The crude was purified by automated column chromatography (2 – 10% MeOH/DCM) to afford the product (28 mg, 64 µmol, 45%). ^{1}H NMR (400 MHz, DMSO) δ 9.62 (s, 1H), 8.51 (s, 1H), 8.50 (dd, *J* = 2.6, 0.6 Hz, 1H), 8.34 (t, *J* = 2.1 Hz, 1H), 7.92 (s, 1H), 7.87 (ddd, *J* = 7.9, 2.2, 1.2 Hz, 1H), 7.77 (dd, *J* = 1.8, 0.5 Hz, 1H), 7.55 (ddd, *J* = 8.1, 2.1, 1.1 Hz, 1H), 7.49 (t, *J* = 8.0 Hz, 1H), 7.23 (s, 1H), 6.56 (dd, *J* = 2.5, 1.7 Hz, 1H), 4.33 – 4.26 (m, 4H), 3.81 – 3.77 (m, 2H), 3.77 – 3.73 (m, 2H), 3.37 (s, 3H), 3.35 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 156.28, 153.67, 152.85, 148.16, 147.01, 140.92, 140.71, 139.93, 129.45, 127.79, 119.69, 112.95, 112.22, 109.00, 108.18, 107.90, 103.17, 70.15, 70.08, 68.40, 68.07, 58.43, 58.38. LCMS (Fleet, 10 → 90%): t_r = 4.34 min, m/z: 436.3. HRMS $[C_{23}H_{25}N_5O_4 + H]^+$: 436.19793 calculated, 436.19760 found.

2-((4-Chloro-7-(2-methoxyethoxy)quinazolin-6-yl)oxy)ethyl acetate (50)



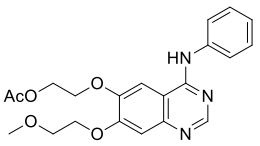
The title compound was synthesized as described in **Chapter 2** (compound 43)

2-((4-((3-Ethynylphenyl)amino)-7-(2-methoxyethoxy)quinazolin-6-yl)oxy)ethyl acetate (51)



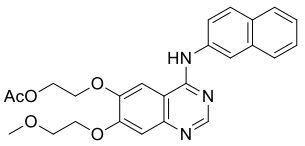
The title compound was synthesized as described in **Chapter 2** (compound 44)

2-((7-(2-Methoxyethoxy)-4-(phenylamino)quinazolin-6-yl)oxy)ethyl acetate (52)



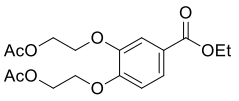
The title compound was synthesized from **50** (31.3 mg, 91.9 µmol) and aniline (9.3 µL, 102 µmol) according to general procedure A (reaction time: 1.25 h). The crude was purified by automated column chromatography (1 – 10% MeOH/DCM) to afford the product (36.1 mg, 90.8 µmol, 99%). ^{1}H NMR (400 MHz, MeOD) δ 8.32 (s, 1H), 7.70 (d, *J* = 7.6 Hz, 2H), 7.64 (s, 1H), 7.37 (t, *J* = 7.9 Hz, 2H), 7.15 (t, *J* = 7.4 Hz, 1H), 7.05 (s, 1H), 4.52 – 4.45 (m, 2H), 4.37 – 4.29 (m, 2H), 4.26 – 4.19 (m, 2H), 3.85 – 3.77 (m, 2H), 3.45 (s, 3H), 2.07 (s, 3H). ^{13}C NMR (101 MHz, MeOD) δ 172.67, 158.50, 155.84, 154.01, 149.92, 147.40, 140.20, 129.76, 125.47, 124.10, 110.41, 108.21, 104.43, 71.71, 69.68, 68.50, 63.80, 59.49, 20.77.

2-((7-(2-Methoxyethoxy)-4-(naphthalen-2-ylamino)quinazolin-6-yl)oxy)ethyl acetate (53)



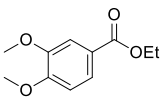
The title compound was synthesized from **50** (29.4 mg, 86.3 µmol) and naphthalen-2-amine (14.5 mg, 101 µmol) according to general procedure A (reaction time: 1.5 h). The crude was purified by automated column chromatography (1 – 10% MeOH/DCM) to afford the product (36.7 mg, 82.0 µmol, 95%). ^{1}H NMR (400 MHz, MeOD) δ 8.39 (s, 1H), 8.14 (s, 1H), 7.75 – 7.63 (m, 5H), 7.43 – 7.34 (m, 2H), 6.88 (s, 1H), 4.50 – 4.45 (m, 2H), 4.36 – 4.31 (m, 2H), 4.16 – 4.11 (m, 2H), 3.77 – 3.72 (m, 3H), 3.43 (s, 3H), 2.08 (s, 3H). LCMS (Finnigan, 0 → 50%): t_r = 8.80 min, m/z: 448.2.

((4-(Ethoxycarbonyl)-1,2-phenylene)bis(oxy))bis(ethane-2,1-diyl) diacetate (54)



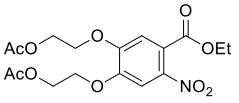
Ethyl 3,4-dihydroxybenzoate (7.00 g, 38.4 mmol) and K_2CO_3 (21.24 g, 10.98 mmol) were mixed in dry DMF (35 mL). 2-bromoethyl acetate (12.8 mL, 8.23 mmol) was added and the mixture was stirred at 100°C for 2 h. The mixture was poured into H_2O (150 mL) and the product extracted with EtOAc (3x150 mL). The combined organic layers were washed with brine (100 mL), dried with over Na_2SO_4, filtered and concentrated. The crude was purified by silica gel column chromatography (25 – 40% Et_2O/pentane) to afford the product (8.40 g, 23.7 mmol, 62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.54 (d, *J* = 2.0 Hz, 1H), 6.86 (d, *J* = 8.5 Hz, 1H), 4.43 – 4.35 (m, 4H), 4.28 (q, *J* = 7.1 Hz, 2H), 4.24 – 4.18 (m, 4H), 2.04 (s, 3H), 2.03 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.89, 170.86, 166.04, 152.60, 148.02, 124.32, 123.85, 115.83, 113.21, 67.55, 67.07, 62.80, 62.56, 60.86, 20.81, 20.79, 14.34. LCMS (Finnigan, 10 → 50%): t_r = 10.09 min, m/z: 355.0.

Ethyl 3,4-dimethoxybenzoate (55)



Ethyl 3,4-dihydroxybenzoate (2.00 g, 11.0 mmol) and K_2CO_3 (6.00 g, 43.9 mmol) were mixed in DMF (10.9 mL). Iodomethane (4.8 mL, 77 mmol) was added and the mixture stirred at 100°C for 1.25 h. The mixture was poured into H_2O (50 mL) and the product extracted with DCM (3x100 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated. The crude was purified by silica gel column chromatography (5 – 20% MeOH/DCM) to afford the product (2.24 g, 10.7 mmol, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.34 (d, *J* = 2.0 Hz, 1H), 6.66 (d, *J* = 8.5 Hz, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.72 (s, 3H), 3.70 (s, 3H), 1.18 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.83, 152.47, 148.16, 123.05, 122.56, 111.46, 109.80, 60.31, 55.47, 55.46, 13.99. LCMS (Finnigan, 10 → 90%): t_r = 6.46 min, m/z: 211.0.

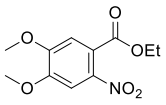
((4-(Ethoxycarbonyl)-5-nitro-1,2-phenylene)bis(oxy))bis(ethane-2,1-diyl) diacetate (56)



54 (8.40 g, 23.7 mmol) was dissolved in acetic anhydride (65 mL) and cooled down to 0°C. Copper(II) nitrate trihydrate (14.5 g, 60.0 mmol) was added and the mixture was stirred at 0°C for 1 h. The mixture was then allowed to warm to RT after which a mild exothermic reaction (NO_2 escapes) was observed. After TLC analysis showed completion of the reaction, the mixture was diluted with water (30 mL) and the product extracted with DCM (3x150 mL). The combined organic layers were washed with 1 M $NaHCO_3$ (400 mL, until pH 7) and brine (100 mL), and subsequently dried over Na_2SO_4, filtered and

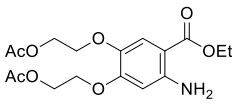
concentrated. The crude was purified by silica gel column chromatography (40 – 60% Et_2O/pentane) to afford the product (5.80 g, 14.5 mmol, 62%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.47 (s, 1H), 7.10 (s, 1H), 4.47 – 4.41 (m, 4H), 4.37 – 4.25 (m, 6H), 2.07 (s, 3H), 2.07 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.82, 165.52, 151.97, 149.74, 141.56, 122.46, 113.32, 109.61, 67.82, 67.69, 62.54, 62.33, 62.30, 20.84, 13.82. Regioselectivity was confirmed by ^1H-^1H-NOESY NMR analysis. LCMS (Finnigan, 10 → 90%): t_r = 7.09 min, m/z: not observed.

Ethyl 4,5-dimethoxy-2-nitrobenzoate (57)



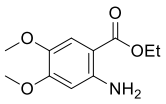
55 (1.00 g, 4.76 mmol) was dissolved in acetic anhydride (12.5 mL) and cooled down to 0°C. Copper(II) nitrate trihydrate (2.91 g, 12.0 mmol) was added and the mixture was stirred at 0°C for 2 h after which TLC analysis showed completion of the reaction. The mixture was poured into 1 M $NaHCO_3$ (aq.) (20 mL) and the product extracted with DCM (3x25mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated at 80°C. The residue was coevaporated with toluene several times to remove the remaining acetic anhydride. The crude was purified by silica gel column chromatography (10 – 30% EtOAc/pentane) to afford the product (862 mg, 3.38 mmol, 71%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (s, 1H), 6.93 (s, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 3.83 (s, 3H), 3.83 (s, 3H), 1.20 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.43, 152.20, 150.04, 140.86, 121.56, 110.45, 106.64, 62.08, 56.33, 56.27, 13.48. Regioselectivity was confirmed by ^1H-^1H-NOESY NMR analysis after subsequent step (compound **59**). LCMS (Finnigan, 10 → 90%): t_r = 6.83 min, m/z: no mass observed.

((4-Amino-5-(ethoxycarbonyl)-1,2-phenylene)bis(oxy))bis(ethane-2,1-diyl) diacetate (58)



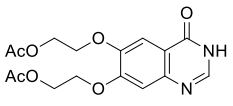
56 (5.80 g, 14.5 mmol) was dissolved in degassed MeOH (45 mL). 5% Pt/C (0.58 g) was added and the atmosphere was exchanged for H_2. The mixture was vigorously stirred for 2.75 h while bubbling H_2 through the mixture. The atmosphere was exchanged for N_2, the mixture was filtered over Celite and concentrated to afford the product (5.10 g, 13.8 mmol, 95%). ^1H NMR (400 MHz, MeOD) δ 7.37 (s, 1H), 6.30 (s, 1H), 4.84 (br s, 2H), 4.42 – 4.37 (m, 2H), 4.33 – 4.29 (m, 2H), 4.25 (q, *J* = 7.1 Hz, 2H), 4.17 – 4.13 (m, 2H), 4.09 – 4.04 (m, 2H), 2.05 (app. s, 6H), 1.33 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, MeOD) δ 172.67, 172.57, 168.84, 156.66, 150.42, 139.85, 120.45, 103.44, 101.57, 70.54, 67.63, 64.49, 63.73, 61.05, 20.80, 20.75, 14.76. LCMS (Finnigan, 10 → 90%): t_r = 6.25 min, m/z: 370.0.

Ethyl 2-amino-4,5-dimethoxybenzoate (59)



57 (1.84 g, 7.21 mmol) was dissolved in degassed MeOH (20 mL). 5% Pt/C (288 mg) was added and the atmosphere was exchanged for H_2. The mixture was vigorously stirred for 45 min while bubbling H_2 through the mixture. The atmosphere was exchanged for N_2, after which the mixture was filtered over Celite and concentrated. The crude was purified by automated column chromatography (40 – 60% Et_2O/pentane) to afford the product (1.11 g, 4.94 mmol, 69%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (s, 1H), 6.09 (s, 1H), 5.58 (s, 2H), 4.26 (q, *J* = 7.1 Hz, 2H), 3.78 (s, 3H), 3.78 (s, 3H), 1.33 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.75, 154.69, 147.15, 140.40, 112.68, 102.18, 99.29, 60.03, 56.38, 55.66, 14.45. LCMS (Finnigan, 10 → 90%): t_r = 5.04 min, m/z: 225.9.

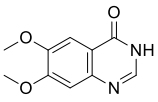
((4-Oxo-3,4-dihydroquinazoline-6,7-diyl)bis(oxy))bis(ethane-2,1-diyl) diacetate (60)



58 (5.09 g, 13.8 mmol) was dissolved in formamide (7.3 mL) and ammonium formate (0.902 g, 14.3 mmol) was added. The mixture was stirred at 160°C for 5.5 h and subsequently poured into H_2O (100 mL). The product was extracted with DCM (3x150 mL) and the combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated. The crude was purified by silica gel column chromatography (1 – 3% MeOH/DCM) to afford the product (1.30 g, 3.71 mmol, 27%), which was slightly contaminated with side-product in which one of the acetyl groups had been substituted by a formyl group. ^1H NMR (400 MHz, MeOD) δ 7.95 (s, 1H), 7.60 (s, 1H), 7.12 (s, 1H), 4.52 – 4.45 (m, 4H), 4.37 – 4.29 (m, 4H), 2.08 (app. s, 6H). ^{13}C NMR (101 MHz, MeOD) δ 172.22, 172.17, 162.07, 155.44, 149.27, 145.68,

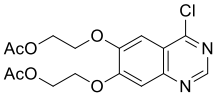
144.36, 116.86, 109.61, 108.48, 67.97, 67.74, 63.34, 63.12, 20.95, 20.93. LCMS (Finnigan, 10 → 90%): t_r = 4.22 min, m/z: 351.1.

6,7-Dimethoxyquinazolin-4(3*H*)-one (61)



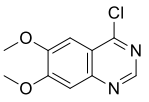
59 (1.01 g, 4.51 mmol) and ammonium formate (284 mg, 4.51 mmol) were mixed in formamide (2.4 mL) after which the mixture was heated to 160°C, stirred for 5.5 h and continued to stir at 120°C for 16 h. The mixture was poured into H_2O (50 mL) which was extracted DCM (4x50 mL). The water layer was concentrated and the residue suspended in MeOH (10 mL). The suspension was heated to about 60°C and immediately filtered as such to afford the product (360 mg, 1.75 mmol, 39%). ^{1}H NMR (400 MHz, DMSO) δ 12.03 (br s, 1H), 7.99 (s, 1H), 7.44 (s, 1H), 7.13 (s, 1H), 3.90 (s, 3H), 3.86 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 160.12, 154.48, 148.57, 144.91, 143.91, 115.62, 108.04, 104.91, 55.97, 55.72. LCMS (Finnigan, 0 → 50%): t_r = 5.33 min, m/z: 207.2.

((4-Chloroquinazoline-6,7-diyl)bis(oxy))bis(ethane-2,1-diyl) diacetate (62)



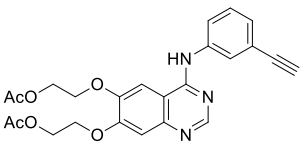
60 (500 mg, 1.43 mmol) was mixed in $POCl_3$ (2.8 ml, 30 mmol). The mixture was stirred at 105°C for 2 h and subsequently concentrated. The residue was dissolved in DCM (100 mL) and poured into H_2O (100 mL). The organic layer was separated and the water layer washed with DCM (3x100 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated. The crude was purified by silica gel column chromatography (0 – 3 % MeOH/DCM) to afford the product (440 mg, 1.19 mmol, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (s, 1H), 7.40 (s, 1H), 7.30 (s, 1H), 4.56 – 4.51 (m, 4H), 4.39 – 4.35 (m, 4H), 2.11 (s, 3H), 2.10 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.97, 170.90, 159.28, 155.96, 152.75, 150.58, 149.02, 119.62, 108.40, 104.64, 67.37, 67.22, 62.35, 62.07, 20.96, 20.93. LCMS (Finnigan, 10 → 90%): t_r = 5.98 min, m/z: 369.0.

4-Chloro-6,7-dimethoxyquinazoline (63)



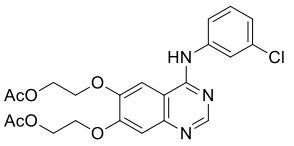
61 (285 mg, 1.38 mmol) was mixed in $POCl_3$ (2.7 mL) and the mixture was stirred at 105°C for 1.5 h. Subsequently, the mixture was concentrated, diluted in DCM (100 mL) and carefully poured into H_2O (100 mL). The organic layer was separated and the water layer extracted with DCM (3x100 mL). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, filtered and concentrated. The crude was purified by silica gel column chromatography (1 – 3% MeOH/DCM) to afford the product (42.5 mg, 189 µmol, 14%). ^{1}H NMR (300 MHz, DMSO) δ 8.84 (s, 1H), 7.35 (s, 1H), 7.30 (s, 1H), 4.05 (app. s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.12, 156.82, 152.59, 151.50, 149.14, 119.62, 106.98, 102.72, 56.73, 56.54. LCMS (Finnigan, 10 → 90%): t_r = 5.46 min, m/z: 225.2.

((4-((3-Ethynylphenyl)amino)quinazoline-6,7-diyl)bis(oxy))bis(ethane-2,1-diyl) diacetate (64)



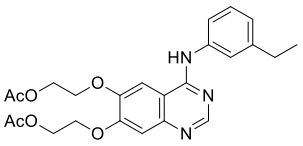
The title compound was synthesized from **62** (39.6 mg, 107 µmol) and 3-ethynylaniline (13.4 µL, 119 µmol) according to general procedure A (reaction time: 1.5 h). The crude was purified by silica gel column chromatography (8% MeOH/DCM) to afford the product (39 mg, 87 µmol, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (s, 1H), 7.98 (t, *J* = 1.9 Hz, 1H), 7.87 (ddd, *J* = 8.2, 2.3, 1.1 Hz, 1H), 7.73 (s, 1H), 7.55 (s, 1H), 7.35 (t, *J* = 7.9 Hz, 1H), 7.26 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.23 (s, 1H), 4.54 – 4.48 (m, 4H), 4.37 – 4.29 (m, 4H), 3.09 (s, 1H), 2.16 (s, 3H), 2.11 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.88, 171.01, 156.41, 154.06, 153.99, 148.16, 147.66, 139.13, 129.14, 127.68, 124.73, 121.86, 109.51, 109.36, 102.88, 83.57, 77.48, 66.95, 66.66, 62.33, 61.41, 21.14, 21.02. LCMS (Finnigan, 10 → 90%): t_r = 5.62 min, m/z: 450.1.

((4-((3-Chlorophenyl)amino)quinazoline-6,7-diyl)bis(oxy))bis(ethane-2,1-diyl) diacetate (65)



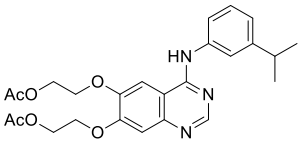
The title compound was synthesized from **62** (40.0 mg, 108 µmol) and 3-chloroaniline (12.7 µL, 120 µmol) according to general procedure A (reaction time: 1 h). The crude was purified by silica gel column chromatography (1 – 10% MeOH/DCM) to afford the product (39 mg, 85 µmol, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.02 (t, *J* = 2.0 Hz, 1H), 7.77 (br s, 1H), 7.75 (ddd, *J* = 8.3, 2.2, 1.0 Hz, 1H), 7.61 (s, 1H), 7.32 (t, *J* = 8.1 Hz, 1H), 7.25 (s, 1H), 7.11 (ddd, *J* = 8.0, 2.1, 0.9 Hz, 1H), 4.55 – 4.51 (m, 4H), 4.42 – 4.31 (m, 4H), 2.19 (s, 3H), 2.12 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.85, 171.00, 156.41, 154.06, 153.71, 148.23, 147.22, 140.28, 134.56, 129.99, 123.89, 121.38, 119.31, 109.49, 108.91, 103.02, 66.92, 66.67, 62.26, 61.46, 21.09, 20.96. LCMS (Finnigan, 10 → 90%): t_r = 5.68 min, m/z: 460.1.

((4-((3-Ethylphenyl)amino)quinazoline-6,7-diyl)bis(oxy))bis(ethane-2,1-diyl) diacetate (66)



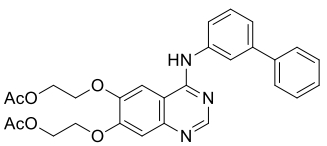
The title compound was synthesized from 62 (30.0 mg, 81.3 µmol) and 3-ethylaniline (11.1 µL, 89.5 µmol) according to general procedure A (reaction time 1.5 h). The crude was purified by silica gel column chromatography (0 – 2% MeOH/DCM) to afford the product (28 mg, 62 µmol, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (s, 1H), 7.78 (s, 1H), 7.63 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.54 (t, *J* = 1.8 Hz, 1H), 7.49 (s, 1H), 7.29 (t, *J* = 7.8 Hz, 1H), 7.21 (s, 1H), 6.98 (d, *J* = 7.6 Hz, 1H), 4.52 – 4.44 (m, 4H), 4.32 – 4.24 (m, 4H), 2.66 (q, *J* = 7.6 Hz, 2H), 2.12 (s, 3H), 2.09 (s, 3H), 1.24 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.58, 170.99, 156.75, 154.27, 153.90, 148.06, 147.58, 145.32, 138.78, 129.03, 123.98, 121.24, 119.23, 109.54, 109.28, 103.29, 66.93, 66.87, 62.32, 61.74, 28.98, 21.05, 20.97, 15.56. LCMS (Finnigan, 10 → 90%): t_r = 5.91 min, m/z: 454.1.

((4-((3-Isopropylphenyl)amino)quinazoline-6,7-diyl)bis(oxy))bis(ethane-2,1-diyl) diacetate (67)



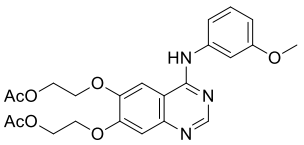
The title compound was synthesized from **62** (30.0 mg, 81.3 µmol) and 3-ethylaniline (12.1 mg, 89.5 µmol) according to general procedure A (reaction time: 1.5 h). The crude was purified by silica gel column chromatography (0 – 2% MeOH/DCM) to afford the product (28.8 mg, 61.6 µmol, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (s, 1H), 7.72 (ddd, *J* = 8.1, 2.3, 1.0 Hz, 1H), 7.67 (s, 1H), 7.53 (t, *J* = 1.7 Hz, 1H), 7.50 (s, 1H), 7.32 (t, *J* = 7.8 Hz, 1H), 7.22 (s, 1H), 7.02 (dt, *J* = 7.6, 1.4 Hz, 1H), 4.55 – 4.45 (m, 4H), 4.35 – 4.28 (m, 4H), 2.93 (hept, *J* = 6.9 Hz, 1H), 2.14 (s, 3H), 2.10 (s, 3H), 1.27 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.65, 171.01, 156.69, 154.32, 153.90, 150.00, 148.05, 147.63, 138.79, 129.06, 122.56, 119.72, 119.32, 109.54, 109.38, 103.21, 66.90, 66.88, 62.35, 61.66, 34.24, 24.09, 21.09, 21.00. LCMS (Finnigan, 10 → 90%): t_r = 6.23 min, m/z: 468.1.

((4-([1,1'-Biphenyl]-3-ylamino)quinazoline-6,7-diyl)bis(oxy))bis(ethane-2,1-diyl) diacetate (68)



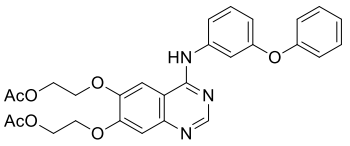
The title compound was synthesized from **62** (30.0 mg, 81.3 µmol) and [1,1'-biphenyl]-3-amine (15.1 mg, 89.2 µmol) according to general procedure A (reaction time: 1.5 h). The crude was purified by silica gel column chromatography (0 – 5% MeOH/DCM) to afford the product (39 mg, 78 µmol, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.01 – 7.91 (m, 2H), 7.87 (d, *J* = 7.1 Hz, 1H), 7.62 – 7.56 (m, 3H), 7.48 – 7.39 (m, 3H), 7.38 – 7.31 (m, 2H), 7.21 (s, 1H), 4.52 – 4.44 (m, 4H), 4.33 – 4.24 (m, 4H), 2.12 (s, 3H), 2.09 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.71, 170.99, 156.71, 154.16, 153.92, 148.10, 147.51, 142.11, 140.90, 139.36, 129.50, 128.85, 127.57, 127.22, 122.94, 120.52, 120.40, 109.57, 109.21, 103.11, 66.89, 66.73, 62.30, 61.55, 21.07, 20.97. LCMS (Finnigan, 10 → 90%): t_r = 6.38 min, m/z: 502.1.

((4-((3-Methoxyphenyl)amino)quinazoline-6,7-diyl)bis(oxy))bis(ethane-2,1-diyl) diacetate (69)



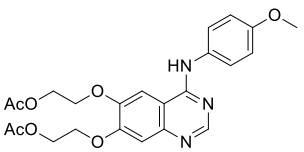
The title compound was synthesized from **62** (40.0 mg, 108 µmol) and 3-methoxyaniline (13.4 mg, 108 µmol) according to general procedure A (reaction time: 3 h). The crude was purified by silica gel column chromatography (0 – 2% MeOH/DCM) to afford the product (49.0 mg, 108 µmol, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 7.99 (br s, 1H), 7.55 (s, 1H), 7.54 (t, *J* = 2.1 Hz, 1H), 7.36 – 7.32 (m, 1H), 7.31 – 7.25 (m, 1H), 7.22 (s, 1H), 6.69 (ddd, *J* = 8.0, 2.5, 1.1 Hz, 1H), 4.54 – 4.44 (m, 4H), 4.33 – 4.26 (m, 4H), 3.83 (s, 3H), 2.14 (s, 3H), 2.11 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.61, 170.98, 160.21, 156.67, 153.95, 153.94, 148.12, 147.26, 140.08, 129.77, 113.94, 109.62, 109.54, 109.01, 107.72, 103.21, 66.88, 66.83, 62.29, 61.65, 55.40, 21.06, 20.97. LCMS (Finnigan, 10 → 90%): t_r = 5.36 min, m/z: 456.1.

((4-((3-Phenoxyphenyl)amino)quinazoline-6,7-diyl)bis(oxy))bis(ethane-2,1-diyl) diacetate (70)



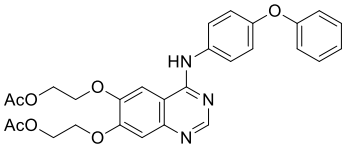
The title compound was synthesized from **62** (25 mg, 68 µmol) and 3-phenoxyaniline (12.6 mg, 68.0 µmol) according to general procedure A (reaction time 1.5 h). The crude was purified by silica gel column chromatography (2% MeOH/DCM) to afford the product (32 mg, 62 µmol, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (s, 1H), 7.95 (s, 1H), 7.62 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.54 (s, 1H), 7.52 (t, *J* = 1.7 Hz, 1H), 7.36 – 7.29 (m, 3H), 7.20 (s, 1H), 7.11 – 7.06 (m, 1H), 7.06 – 7.02 (m, 2H), 6.76 (dd, *J* = 8.1, 2.3 Hz, 1H), 4.49 (t, 2H), 4.44 (t, *J* = 5.7 Hz, 2H), 4.31 – 4.23 (m, 4H), 2.08 (s, 3H), 2.06 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.71, 170.98, 157.89, 157.08, 156.48, 154.00, 153.91, 148.10, 147.51, 140.44, 130.07, 129.83, 123.48, 119.19, 116.11, 114.16, 111.86, 109.57, 109.16, 103.04, 66.88, 66.73, 62.29, 61.52, 21.01, 20.96. LCMS (Finnigan, 10 → 90%): t_r = 6.44 min, m/z: 518.1.

((4-((4-Methoxyphenyl)amino)quinazoline-6,7-diyl)bis(oxy))bis(ethane-2,1-diyl) diacetate (71)



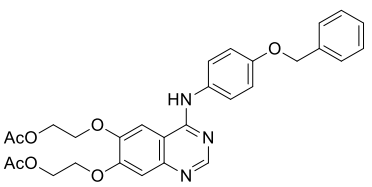
The title compound was synthesized from **62** (40.0 mg, 108 µmol) and 4-methoxyaniline (13.4 mg, 108 µmol) according to general procedure A (reaction time: 3 h). The crude was purified by silica gel column chromatography (3% MeOH/DCM) to afford the product (42.7 mg, 93.7 µmol, 86%). ^{1}H NMR (400 MHz, MeOD) δ 8.35 (s, 1H), 7.72 (s, 1H), 7.51 – 7.46 (m, 2H), 7.12 (s, 1H), 6.95 – 6.91 (m, 2H), 4.53 – 4.48 (m, 4H), 4.38 – 4.33 (m, 4H), 3.81 (s, 3H), 2.10 (app. s, 6H). ^{13}C NMR (101 MHz, MeOD) δ 172.27, 172.12, 158.44, 157.71, 154.80, 153.67, 149.07, 146.40, 131.85, 125.83, 114.68, 110.07, 108.08, 104.64, 67.89, 67.45, 63.25, 63.05, 55.77, 20.98, 20.96. LCMS (Finnigan, 10 → 90%): t_r = 5.27 min, m/z: 456.1.

((4-((4-Phenoxyphenyl)amino)quinazoline-6,7-diyl)bis(oxy))bis(ethane-2,1-diyl) diacetate (72)



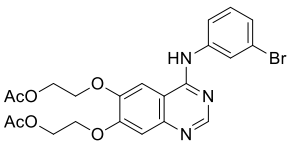
The title compound was synthesized from **62** (30.0 mg, 81.4 µmol) and 4-phenoxyaniline (15.1 mg, 81.5 µmol) according to general procedure A (reaction time: 2 h). The crude was purified by silica gel column chromatography (0 – 2% MeOH/DCM) to afford the product (34.3 mg, 66.3 µmol, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (s, 1H), 7.98 (br s, 1H), 7.73 – 7.68 (m, 2H), 7.55 (s, 1H), 7.35 – 7.29 (m, 2H), 7.21 (s, 1H), 7.11 – 7.06 (m, 1H), 7.05 – 6.99 (m, 4H), 4.52 – 4.47 (m, 2H), 4.46 (t, *J* = 5.7 Hz, 2H), 4.32 – 4.25 (m, 4H), 2.12 (s, 3H), 2.09 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.65, 170.99, 157.50, 156.78, 154.01, 153.96, 153.68, 148.11, 147.19, 134.14, 129.84, 123.58, 123.27, 119.57, 118.72, 109.37, 109.00, 103.25, 66.89, 66.85, 62.28, 61.63, 21.08, 20.97. LCMS (Finnigan, 10 → 90%): t_r = 6.33 min, m/z: 518.1.

((4-((4-(Benzyloxy)phenyl)amino)quinazoline-6,7-diyl)bis(oxy))bis(ethane-2,1-diyl) diacetate (73)



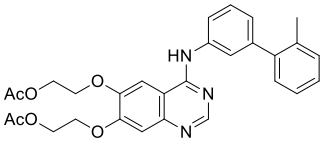
The title compound was synthesized from **62** (31.5 mg, 85.4 µmol) and 4-(benzyloxy)aniline hydrochloride (20.2 mg, 85.7 µmol) according to general procedure A (reaction time: 2 h). The crude was purified by silica gel column chromatography (0 – 3% MeOH/DCM) to afford the product (35 mg, 66 µmol, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (s, 1H), 7.93 (br s, 1H), 7.60 – 7.55 (m, 2H), 7.48 (s, 1H), 7.45 – 7.40 (m, 2H), 7.40 – 7.35 (m, 2H), 7.34 – 7.29 (m, 1H), 7.18 (s, 1H), 6.97 (d, *J* = 9.0 Hz, 2H), 5.04 (s, 2H), 4.50 – 4.45 (m, 2H), 4.42 (t, *J* = 5.5 Hz, 2H), 4.28 – 4.24 (m, 2H), 4.22 (t, *J* = 5.5 Hz, 2H), 2.09 (s, 3H), 2.08 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.47, 170.96, 157.09, 155.94, 154.17, 153.75, 148.02, 147.18, 137.03, 131.80, 128.67, 128.07, 127.54, 124.19, 115.34, 109.33, 109.03, 103.50, 70.37, 67.02, 66.85, 62.28, 61.85, 21.02, 20.94. LCMS (Finnigan, 10 → 90%): t_r = 6.37 min, m/z: 532.1.

((4-((3-Bromophenyl)amino)quinazoline-6,7-diyl)bis(oxy))bis(ethane-2,1-diyl) diacetate (74)



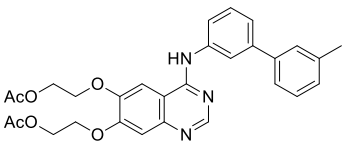
The title compound was synthesized from **62** (300 mg, 814 µmol) and 3-bromoaniline (96.8 µL, 891 µmol) according to general procedure A (reaction time: 1.5 h). The crude was purified by silica gel column chromatography (0 – 2% MeOH/DCM) to afford the product (289 mg, 573 µmol, 71%). ^{1}H NMR (400 MHz, MeOD) δ 8.43 (s, 1H), 8.01 – 7.98 (m, 1H), 7.72 – 7.62 (m, 2H), 7.27 – 7.21 (m, 2H), 7.11 (s, 1H), 4.54 – 4.46 (m, 4H), 4.40 – 4.30 (m, 4H), 2.10 (s, 3H), 2.09 (s, 3H). ^{13}C NMR (101 MHz, MeOD) δ 172.39, 172.27, 157.83, 155.14, 153.68, 149.50, 147.29, 141.28, 130.78, 127.63, 125.93, 122.85, 121.63, 110.46, 108.37, 104.37, 68.11, 67.67, 63.41, 63.22, 20.95, 20.92. LCMS (Finnigan, 10 → 90%): t_r = 5.82 min, m/z: 504.0.

((4-((2'-Methyl-[1,1'-biphenyl]-3-yl)amino)quinazoline-6,7-diyl)bis(oxy))bis(ethane-2,1-diyl) diacetate (75)



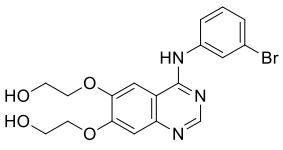
The title compound was synthesized from **74** (40 mg, 79 µmol) according to general procedure C using *o*-tolylboronic acid. The crude was purified by silica gel column chromatography (1 – 5% MeOH/DCM) to afford the product (26 mg, 50 µmol, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 7.89 – 7.85 (m, 2H), 7.74 (t, *J* = 1.8 Hz, 1H), 7.57 (s, 1H), 7.45 (t, *J* = 7.9 Hz, 1H), 7.29 – 7.24 (m, 5H), 7.12 (dt, *J* = 7.6, 1.1 Hz, 1H), 4.54 – 4.47 (m, 4H), 4.36 – 4.29 (m, 4H), 2.34 (s, 3H), 2.13 (s, 3H), 2.11 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.72, 171.00, 156.62, 154.17, 153.95, 148.12, 147.52, 142.85, 141.63, 138.66, 135.50, 130.48, 129.83, 128.84, 127.50, 125.88, 125.08, 122.41, 119.95, 109.55, 109.27, 103.11, 66.92, 66.79, 62.33, 61.56, 21.07, 21.00, 20.66. LCMS (Finnigan, 10 → 90%): t_r = 6.74 min, m/z: 516.1.

((4-((3'-Methyl-[1,1'-biphenyl]-3-yl)amino)quinazoline-6,7-diyl)bis(oxy))bis(ethane-2,1-diyl) diacetate (76)



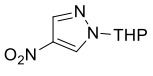
The title compound was synthesized from **74** (35 mg, 69 µmol) according to general procedure C using *m*-tolylboronic acid. The crude was purified by silica gel column chromatography (1 – 3% MeOH/DCM) to afford the product (24.6 mg, 47.7 µmol, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (s, 1H), 7.94 (t, *J* = 2.0 Hz, 1H), 7.90 (ddd, *J* = 8.1, 2.3, 1.1 Hz, 1H), 7.87 (s, 1H), 7.58 (s, 1H), 7.46 (t, *J* = 7.9 Hz, 1H), 7.45 – 7.38 (m, 2H), 7.36 (ddd, *J* = 7.7, 1.8, 1.1 Hz, 1H), 7.32 (td, *J* = 7.3, 1.1 Hz, 1H), 7.24 (s, 1H), 7.21 – 7.13 (m, 1H), 4.54 – 4.46 (m, 4H), 4.37 – 4.28 (m, 4H), 2.42 (s, 3H), 2.15 (s, 3H), 2.11 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.75, 171.01, 156.70, 154.16, 153.95, 148.12, 147.50, 142.31, 140.94, 139.31, 138.45, 129.49, 128.79, 128.35, 128.04, 124.39, 123.05, 120.45, 120.39, 109.56, 109.27, 103.10, 66.93, 66.75, 62.34, 61.54, 21.69, 21.11, 21.01. LCMS (Fleet, 10 → 90%): t_r = 5.96 min, m/z: 516.2.

2,2'-((4-((3-Bromophenyl)amino)quinazoline-6,7-diyl)bis(oxy))bis(ethan-1-ol) (77)



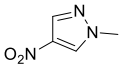
The title compound was synthesized from **74** (360 mg, 714 µmol) according to general procedure B (reaction time: 1 h). The crude was purified by silica gel column chromatography (4 – 8% MeOH/DCM) to afford the product (292 mg, 695 µmol, 97%). ^{1}H NMR (400 MHz, MeOD) δ 8.39 (s, 1H), 8.09 – 8.03 (m, 1H), 7.74 – 7.68 (m, 1H), 7.60 (s, 1H), 7.28 – 7.23 (m, 2H), 7.04 (s, 1H), 4.22 (t, 2H), 4.17 (t, 2H), 4.01 – 3.94 (m, 4H). ^{13}C NMR (101 MHz, MeOD) δ 158.08, 155.93, 153.73, 150.44, 147.49, 142.06, 131.15, 127.72, 126.13, 123.06, 121.95, 110.49, 107.92, 103.45, 71.94, 71.63, 61.45, 61.24. LCMS (Finnigan, 10 → 90%): t_r = 4.82 min, m/z: 420.1.

4-Nitro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazole (78)



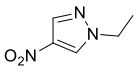
4-Nitro-1*H*-pyrazole (50.0 mg, 0.442 mmol) was dissolved in dry DCM (0.2 mL). 3,4-dihydro-2*H*-pyran (202 µL, 2.21 mmol) and 4-methylbenzenesulfonic acid monohydrate (4.2 mg, 0.022 mmol) were added and the mixture was stirred for 1 h. The mixture was poured into H_2O (20 mL) and the product extracted with DCM (3x20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated. The crude was purified by silica gel column chromatography (10 – 30% EtOAc/pentane) and used as such in subsequent reaction (yield: 100 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 1H), 8.04 (s, 1H), 5.36 (dd, *J* = 9.0, 2.8 Hz, 1H), 4.07 – 4.00 (m, 1H), 3.73 – 3.64 (m, 1H), 2.16 – 2.08 (m, 1H), 2.01 – 1.89 (m, 2H), 1.71 – 1.58 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.42, 127.09, 88.38, 67.80, 30.61, 24.67, 21.59 (the quaternary carbon was not observed). LCMS (Finnigan, 10 → 90%): t_r = 5.67 min, m/z: no mass observed.

1-Methyl-4-nitro-1*H*-pyrazole (79)



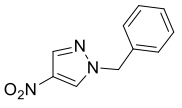
The title compound was synthesized from 4-nitro-1*H*-pyrazole (80.0 mg, 707 µmol) and iodomethane (52.9 µL, 849 µmol) according to general procedure E (1.4 M, at RT) to afford the product (88.0 mg, 692 µmol, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.99 (s, 1H), 3.93 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.72, 129.28, 40.11 (the quaternary carbon was not observed).

1-Ethyl-4-nitro-1*H*-pyrazole (80)



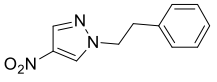
The title compound was synthesized from 4-nitro-1*H*-pyrazole (80.0 mg, 707 µmol) and iodoethane (67.9 µL, 849 µmol) according to general procedure E (1.4 M, at RT) to afford the product (98.0 mg, 694 µmol, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.98 (s, 1H), 4.17 (q, *J* = 7.3 Hz, 2H), 1.47 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.52, 127.82, 48.36, 14.87 (the quaternary carbon was not observed).

1-Benzyl-4-nitro-1*H*-pyrazole (81)



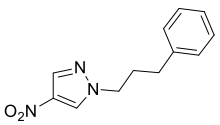
The title compound was synthesized from 4-nitro-1*H*-pyrazole (80.0 mg, 707 µmol) and benzyl bromide (101 µL, 849 µmol) according to general procedure E (1.4 M, at RT) to afford the product (144 mg, 707 µmol, quant.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 8.05 (s, 1H), 7.41 – 7.33 (m, 3H), 7.30 – 7.25 (m, 2H), 5.29 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.96 (br), 135.82, 134.05, 129.16, 128.95, 128.49, 128.24, 57.19.

4-Nitro-1-phenethyl-1*H*-pyrazole (82)



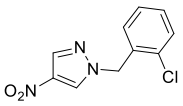
The title compound was synthesized from 4-nitro-1*H*-pyrazole (100 mg, 884 µmol) and (2-bromoethyl)benzene (145 µL, 1061 µmol) according to general procedure E (1.5 M, at 90°C) to afford the product (192 mg, 884 µmol, quant.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.82 (s, 1H), 7.32 – 7.18 (m, 3H), 7.07 – 7.02 (m, 2H), 4.35 (t, *J* = 7.0 Hz, 2H), 3.17 (t, *J* = 7.0 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.77, 135.90, 135.33 (br), 128.86, 128.81, 128.56, 127.18, 54.83, 36.07.

4-Nitro-1-(3-phenylpropyl)-1*H*-pyrazole (83)



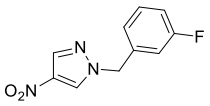
The title compound was synthesized from 4-nitro-1*H*-pyrazole (100 mg, 884 µmol) and (3-bromopropyl)benzene (122 µL, 804 µmol, 0.91 eq.) according to general procedure E (1.3 M, at 85°C, using 3 eq. of K_2CO_3) to afford the product (180 mg, 778 µmol, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 0.7 Hz, 1H), 8.07 (d, *J* = 0.7 Hz, 1H), 7.33 – 7.28 (m, 2H), 7.24 – 7.19 (m, 1H), 7.19 – 7.15 (m, 2H), 4.14 (t, *J* = 7.1 Hz, 2H), 2.65 (t, *J* = 7.5 Hz, 2H), 2.25 (p, *J* = 7.3 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.98, 135.77, 135.62 (br), 128.67, 128.54, 128.38, 126.43, 52.62, 32.37, 30.98.

1-(2-Chlorobenzyl)-4-nitro-1*H*-pyrazole (84)



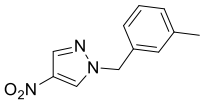
The title compound was synthesized from 4-nitro-1*H*-pyrazole (80.0 mg, 707 µmol) and 1-(bromomethyl)-2-chlorobenzene (83.0 µL, 641 µmol, 0.91 eq.) according to general procedure E (0.4 M, at RT, using 1.05 eq. of K_2CO_3) to afford the product (150 mg, 631 µmol, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 8.08 (s, 1H), 7.45 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.39 – 7.25 (m, 3H), 5.44 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.10, 136.06 (br), 133.97, 131.77, 130.93, 130.74, 130.19, 128.92, 127.72, 54.74.

1-(3-Fluorobenzyl)-4-nitro-1*H*-pyrazole (85)



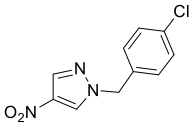
The title compound was synthesized from 4-nitro-1*H*-pyrazole (100 mg, 884 µmol) and 1-(bromomethyl)-3-fluorobenzene (108 µL, 884 µmol) according to general procedure E (1.5 M, at RT, using 3 eq. of K_2CO_3) to afford the product (194 mg, 877 µmol, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 8.07 (s, 1H), 7.39 – 7.32 (m, 1H), 7.10 – 7.00 (m, 2H), 6.97 (dt, *J* = 9.4, 1.9 Hz, 1H), 5.30 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.00 (d, $J_{(C–F)}$ = 248.0 Hz), 136.54 (d, $J_{(C–F)}$ = 7.7 Hz), 136.23 (br), 136.11, 130.95 (d, $J_{(C–F)}$ = 8.3 Hz), 128.69, 123.80 (d, $J_{(C–F)}$ = 3.1 Hz), 116.05 (d, $J_{(C–F)}$ = 21.0 Hz), 115.19 (d, $J_{(C–F)}$ = 22.3 Hz).

1-(3-Methylbenzyl)-4-nitro-1*H*-pyrazole (86)



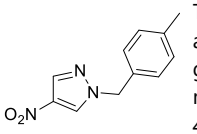
The title compound was synthesized from 4-nitro-1*H*-pyrazole (80.0 mg, 707 µmol) and 1-(bromomethyl)-3-methylbenzene (87.0 µL, 644 µmol, 0.91 eq.) according to general procedure E (0.4 M, at RT, using 1.05 eq. of K_2CO_3) to afford the product (138 mg, 635 µmol, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 8.06 (s, 1H), 7.31 – 7.26 (m, 1H), 7.21 – 7.17 (m, 1H), 7.12 – 7.07 (m, 2H), 5.26 (s, 2H), 2.36 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.19, 136.07, 135.91, 133.87, 129.89, 129.19, 129.11, 128.45, 125.48, 57.38, 21.39.

1-(4-Chlorobenzyl)-4-nitro-1*H*-pyrazole (87)



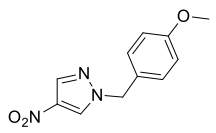
The title compound was synthesized from 4-nitro-1*H*-pyrazole (110 mg, 973 µmol) and 1-(bromomethyl)-4-chlorobenzene (182 mg, 884 µmol, 0.91 eq.) according to general procedure E (1.8 M, at RT, using 1.1 eq. of K_2CO_3) to afford the product (208 mg, 875 µmol, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 8.06 (s, 1H), 7.37 – 7.33 (m, 2H), 7.25 – 7.20 (m, 2H), 5.28 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.19 (br), 136.10, 135.10, 132.61, 129.68, 129.46, 128.52, 56.56.

1-(4-Methylbenzyl)-4-nitro-1*H*-pyrazole (88)



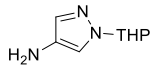
The title compound was synthesized from 4-nitro-1*H*-pyrazole (110 mg, 973 µmol) and 1-(bromomethyl)-4-methylbenzene (164 mg, 884 µmol, 0.91 eq.) according to general procedure E (1.8 M, at RT, using 1.1 eq. of K_2CO_3) to afford the product (192 mg, 884 µmol, quant.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 8.05 (s, 1H), 7.20 (s, 4H), 5.25 (s, 2H), 2.35 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.00, 135.91 (br), 135.78, 130.92, 129.86, 128.38, 128.33, 57.03, 21.13.

1-(4-Methoxybenzyl)-4-nitro-1*H*-pyrazole (89)



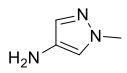
The title compound was synthesized from 4-nitro-1*H*-pyrazole (110 mg, 973 µmol) and 1-(chloromethyl)-4-methoxybenzene (110 µL, 884 µmol, 0.91 eq.) according to general procedure E (1.8 M, at RT, using 1.1 eq. of K_2CO_3) to afford the product (205 mg, 879 µmol, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 0.8 Hz, 1H), 8.01 (d, *J* = 0.8 Hz, 1H), 7.24 – 7.19 (m, 2H), 6.89 – 6.85 (m, 2H), 5.19 (s, 2H), 3.75 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.91, 135.72 (br), 135.63, 129.82, 128.18, 125.86, 114.38, 56.56, 55.14.

1-(Tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-4-amine (90)



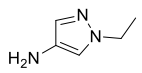
78 (100 mg) was dissolved in degassed MeOH (3 mL). 5% Pt/C (17.7 mg) was added and the atmosphere was exchanged for H_2. The mixture was vigorously stirred for 2 h while bubbling H_2 through the mixture. The atmosphere was exchanged for N_2, the mixture was filtered over Celite and subsequently concentrated. The crude was purified by silica gel column chromatography (10% MeOH (containing 10% sat. NH_4OH (aq.))/DCM) to afford the product (52.0 mg, 311 µmol, 74% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (s, 1H), 7.17 (s, 1H), 5.22 (dd, *J* = 9.6, 2.4 Hz, 1H), 4.04 – 3.97 (m, 1H), 3.68 – 3.60 (m, 1H), 2.88 (s, 2H), 2.08 – 1.94 (m, 3H), 1.68 – 1.53 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.09, 129.42, 116.35, 87.87, 67.77, 30.22, 25.03, 22.61.

1-Methyl-1*H*-pyrazol-4-amine (91)



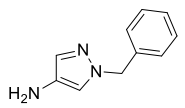
The title compound was synthesized from **79** (88.0 mg, 692 µmol) according to general procedure F (reaction time: 2 h) to afford the product (58.0 mg, 596 µmol, 86%). ^{1}H NMR (400 MHz, MeOD) δ 7.15 (s, 1H), 7.11 (s, 1H), 3.75 (s, 3H). ^{13}C NMR (101 MHz, MeOD) δ 131.75, 130.39, 121.44, 38.79.

1-Ethyl-1*H*-pyrazol-4-amine (92)



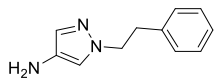
The title compound was synthesized from **80** (98.0 mg, 694 µmol) according to general procedure F (reaction time: 2 h) to afford the product (65.0 mg, 585 µmol, 84%). ^{1}H NMR (400 MHz, MeOD) δ 7.19 (d, *J* = 1.0 Hz, 1H), 7.12 (d, *J* = 0.9 Hz, 1H), 4.02 (q, *J* = 7.3 Hz, 2H), 1.37 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, MeOD) δ 131.63, 130.20, 119.83, 47.73, 16.01.

1-Benzyl-1*H*-pyrazol-4-amine (93)



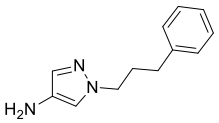
81 (144 mg, 707 µmol) and iron powder (300 mg, 5.37 mmol) were mixed in MeOH (10 mL) and AcOH (4.5 mL). The mixture was stirred at 60°C for 2 h after which the hot mixture was filtered over Celite and concentrated. The residue was diluted in 1 M $NaHCO_3$ (aq.) (30 mL) and the product extracted with EtOAc (3x25 mL). The combined organic layers were concentrated as such. The crude was purified by silica gel column chromatography (1 – 3% MeOH (containing 10% sat. NH_4OH (aq.))/DCM) to afford the product as a mixture of 1-benzyl-1H-pyrazol-4-amine and N-(1-benzyl-1H-pyrazol-4-yl)acetamide (40 mg). This mixture was dissolved in MeOH (1 mL) and 37% HCl (aq.) (0.3 mL) and stirred for 7 h. The mixture was concentrated and the residue diluted with 1 M $NaHCO_3$ (aq.) (30 mL). The product was extracted with DCM (3x20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 and concentrated. The crude was purified by silica gel column chromatography (1 – 2% MeOH in DCM) to afford the product (20.0 mg, 115 µmol, 16%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.25 (m, 3H), 7.20 – 7.16 (m, 3H), 6.96 (d, *J* = 0.9 Hz, 1H), 5.17 (s, 2H), 2.77 (br s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.02, 131.46, 129.43, 128.82, 128.00, 127.63, 118.48, 56.28. LCMS (Finnigan, 0 → 50%): t_r = 5.00 min, m/z: 174.1.

1-Phenethyl-1*H*-pyrazol-4-amine (94)



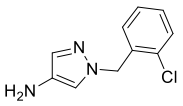
The title compound was synthesized from **82** (60.0 mg, 276 µmol) according to general procedure F (reaction time: 1 h) to afford the product (35.0 mg, 187 µmol, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.19 (m, 3H), 7.16 (d, *J* = 0.8 Hz, 1H), 7.12 – 7.07 (m, 2H), 6.82 (d, *J* = 0.8 Hz, 1H), 4.20 (t, *J* = 7.4 Hz, 2H), 3.10 (t, *J* = 7.5 Hz, 2H), 2.71 (br s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.31, 131.35, 128.80, 128.63, 128.60, 126.67, 118.79, 53.75, 37.00. LCMS (Finnigan, 10 → 50%): t_r = 4.38 min, m/z: 188.1.

1-(3-Phenylpropyl)-1*H*-pyrazol-4-amine (95)



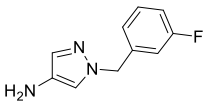
The title compound was synthesized from **83** (127 mg, 549 µmol) according to general procedure F (reaction time: 2 h) to afford the product (110 mg, 547 µmol, quant.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.22 (m, 2H), 7.19 – 7.13 (m, 4H), 6.96 (d, *J* = 0.9 Hz, 1H), 3.98 (t, *J* = 7.0 Hz, 2H), 2.83 (br s, 2H), 2.58 (t, *J* = 7.4 Hz, 2H), 2.12 (p, *J* = 7.2 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.00, 131.01, 128.68, 128.44, 128.43, 126.03, 118.39, 51.45, 32.62, 31.79. LCMS (Finnigan, 0 → 50%): t_r = 6.70 min, m/z: 202.1.

1-(2-Chlorobenzyl)-1*H*-pyrazol-4-amine (96)



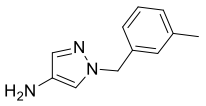
The title compound was synthesized from **84** (75.0 mg, 316 µmol) according to general procedure G to afford the product (60.0 mg, 289 µmol, 92%). ^{1}H NMR (400 MHz, MeOD) δ 7.41 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.31 – 7.24 (m, 3H), 7.22 (d, *J* = 0.8 Hz, 1H), 6.92 (dd, *J* = 7.3, 1.9 Hz, 1H), 5.32 (s, 2H). ^{13}C NMR (101 MHz, MeOD) δ 136.18, 133.88, 132.62, 130.56, 130.53, 130.50 (br), 130.39, 128.40, 121.25, 54.04. LCMS (Finnigan, 10 → 90%): t_r = 4.06 min, m/z: 208.1.

1-(3-Fluorobenzyl)-1*H*-pyrazol-4-amine (97)



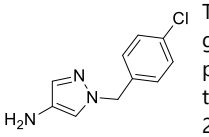
The title compound was synthesized from **85** (126 mg, 570 µmol) according to general procedure G (using 32 eq. NH_4Cl) to afford the product (69.0 mg, 361 µmol, 63%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.23 (m, 1H), 7.19 (s, 1H), 7.02 – 6.91 (m, 3H), 6.84 (dt, *J* = 9.6, 2.1 Hz, 1H), 5.16 (s, 2H), 2.87 (br s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.99 (d, $J_{(C–F)}$ = 246.6 Hz), 139.60 (d, $J_{(C–F)}$ = 7.2 Hz), 131.69, 130.30 (d, $J_{(C–F)}$ = 8.2 Hz), 129.64, 122.92 (d, $J_{(C–F)}$ = 2.9 Hz), 118.42, 114.84 (d, $J_{(C–F)}$ = 21.1 Hz), 114.33 (d, $J_{(C–F)}$ = 22.0 Hz), 55.52 (d, $J_{(C–F)}$ = 1.5 Hz). LCMS (Finnigan, 0 → 50%): t_r = 5.63 min, m/z: 192.1.

1-(3-Methylbenzyl)-1*H*-pyrazol-4-amine (98)



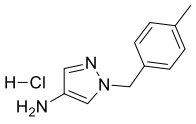
The title compound was synthesized from **86** (115 mg, 529 µmol) according to general procedure G to afford the product (98.0 mg, 523 µmol, 99%). ^{1}H NMR (400 MHz, MeOD) δ 7.35 (d, *J* = 0.8 Hz, 1H), 7.25 (d, *J* = 0.8 Hz, 1H), 7.19 (t, *J* = 7.6 Hz, 1H), 7.09 (d, *J* = 7.6 Hz, 1H), 7.02 (s, 1H), 6.98 (d, *J* = 8.0 Hz, 1H), 5.17 (s, 2H), 2.29 (s, 3H). ^{13}C NMR (101 MHz, MeOD) δ 139.55, 138.31, 132.58, 129.61, 129.60, 129.14, 127.76 (br), 125.60, 121.80, 56.69, 21.38. LCMS (Finnigan, 10 → 50%): t_r = 4.98 min, m/z: 188.1.

1-(4-Chlorobenzyl)-1*H*-pyrazol-4-amine (99)



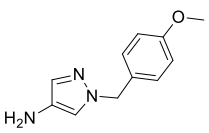
The title compound was synthesized from **87** (80.0 mg, 337 µmol) according to general procedure G (using 5 eq. of iron powder and 32 eq. NH_4Cl). The crude was purified by automated column chromatography (0 – 10% MeOH/DCM) to afford the product (23.5 mg, 113 µmol, 34%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.27 (m, 2H), 7.19 (d, *J* = 0.9 Hz, 1H), 7.13 – 7.08 (m, 2H), 6.97 (d, *J* = 0.9 Hz, 1H), 5.14 (s, 2H), 2.65 (br s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.59, 133.91, 131.74, 129.65, 129.01, 128.95, 118.39, 55.55. LCMS (Finnigan, 0 → 50%): t_r = 6.53 min, m/z: 208.1.

1-(4-Methylbenzyl)-1*H*-pyrazol-4-amine hydrochloride (100)



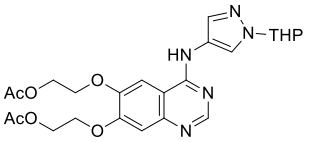
The title compound was synthesized from **88** (73.0 mg, 337 µmol) according to general procedure G (using 5 eq. of iron powder and 32 eq. NH_4Cl). The crude was diluted in a mixture of 0.5 M HCl (aq.) (10 mL) and DCM (10 mL). The organic layer was separated and the water layer extracted with DCM (10 mL). The water layer was concentrated to afford the product (29.3 mg, 156 µmol, 47%). ^{1}H NMR (400 MHz, MeOD) δ 7.97 (s, 1H), 7.64 (s, 1H), 7.20 – 7.12 (m, 4H), 5.30 (s, 2H), 2.30 (s, 3H). ^{13}C NMR (101 MHz, MeOD) δ 139.24, 134.73, 134.43, 130.39, 128.93, 126.62, 114.18, 57.10, 21.13. LCMS (Finnigan, 0 → 50%): t_r = 6.27 min, m/z: 188.1.

1-(4-Methoxybenzyl)-1*H*-pyrazol-4-amine (101)



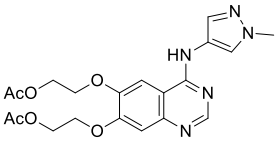
The title compound was synthesized from 89 (78.0 mg, 336 µmol) according to general procedure G (using 5 eq. of iron powder and 32 eq. NH_4Cl). The crude was purified by automated column chromatography (0 – 10% MeOH/DCM) to afford the product (25.0 mg, 123 µmol, 37%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (d, *J* = 0.8 Hz, 1H), 7.15 – 7.12 (m, 2H), 6.93 (d, *J* = 0.8 Hz, 1H), 6.87 – 6.83 (m, 2H), 5.09 (s, 2H), 3.77 (s, 3H), 2.72 (br s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.39, 131.32, 129.30, 129.17, 128.97, 118.26, 114.17, 55.77, 55.36. LCMS (Finnigan, 0 → 50%): t_r = 5.74 min, m/z: 204.1.

((4-((1-(Tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-4-yl)amino)quinazoline-6,7-diyl)bis(oxy))bis(ethane-2,1-diyl) diacetate (102)



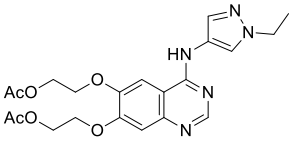
The title compound was synthesized from **62** (30.0 mg, 81.4 µmol) and **90** (13.7 mg, 81.9 µmol) according to general procedure A (also DIPEA (21.0 µL, 122 µmol) was added, reaction time: 6 h). The crude was purified by silica gel column chromatography (2% MeOH/DCM) to afford the product (30 mg, 60 µmol, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 2H), 8.48 (s, 1H), 7.66 (s, 1H), 7.55 (s, 1H), 7.18 (s, 1H), 5.35 (d, *J* = 9.9 Hz, 1H), 4.49 – 4.42 (m, 2H), 4.36 (t, *J* = 5.0 Hz, 2H), 4.29 – 4.22 (m, 2H), 4.09 (t, *J* = 5.1 Hz, 2H), 4.00 (d, *J* = 11.3 Hz, 1H), 3.63 (t, *J* = 10.0 Hz, 1H), 2.23 – 2.12 (m, 1H), 2.09 – 1.98 (m, 8H), 1.72 – 1.52 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.52, 170.95, 155.75, 154.33, 153.68, 148.07, 146.84, 132.15, 122.81, 120.52, 109.33, 108.98, 103.33, 88.12, 67.92, 66.94, 66.87, 62.29, 62.00, 30.33, 24.99, 22.63, 20.99, 20.92. LCMS (Fleet, 10 → 90%): t_r = 4.34 min, m/z: 500.2.

((4-((1-Methyl-1*H*-pyrazol-4-yl)amino)quinazoline-6,7-diyl)bis(oxy))bis(ethane-2,1-diyl) diacetate (103)



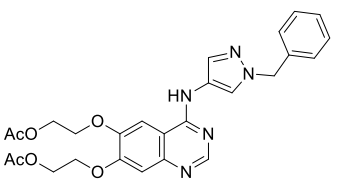
The title compound was synthesized from **62** (30.0 mg, 81.4 µmol) and **91** (9.5 mg, 98 µmol) according to general procedure A (reaction time: 2 h). The crude was purified by silica gel column chromatography (2 – 5% MeOH/DCM) to afford the product (32 mg, 75 µmol, 92%). ^{1}H NMR (500 MHz, MeOD) δ 8.48 (s, 1H), 8.17 (s, 1H), 7.59 (s, 1H), 7.58 (s, 1H), 7.08 (s, 1H), 4.46 – 4.42 (m, 4H), 4.28 – 4.24 (m, 4H), 3.86 (s, 3H), 2.05 (s, 3H), 2.05 (s, 3H). ^{13}C NMR (126 MHz, MeOD) δ 171.67, 171.35, 156.01, 153.79, 148.19, 146.15, 131.34, 123.29, 122.41, 109.42, 108.11, 103.77, 67.27, 66.80, 62.66, 62.44, 39.04, 20.82, 20.77. LCMS (Finnigan, 10 → 90%): t_r = 4.43 min, m/z: 430.1.

((4-((1-Ethyl-1*H*-pyrazol-4-yl)amino)quinazoline-6,7-diyl)bis(oxy))bis(ethane-2,1-diyl) diacetate (104)



The title compound was synthesized from **62** (30.0 mg, 81.4 µmol) and **92** (10.9 mg, 98.1 µmol) according to general procedure A (reaction time: 2 h). The crude was purified by silica gel column chromatography (5% MeOH/DCM) to afford the product (33 mg, 74 µmol, 91%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 (s, 1H), 8.18 (s, 1H), 7.56 (s, 1H), 7.55 (s, 1H), 7.04 (s, 1H), 4.42 – 4.37 (m, 4H), 4.25 – 4.19 (m, 4H), 4.09 (q, *J* = 7.3 Hz, 2H), 2.01 (s, 3H), 2.01 (s, 3H), 1.42 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.56, 171.22, 155.85, 153.72, 153.67, 148.07, 146.02, 130.96, 122.09, 121.49, 109.30, 108.02, 103.66, 67.15, 66.69, 62.53, 62.32, 47.20, 20.71, 20.67, 15.33. LCMS (Finnigan, 10 → 90%): t_r = 4.66 min, m/z: 444.1.

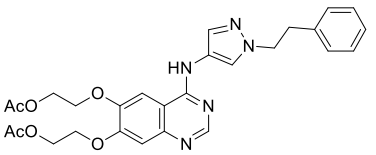
((4-((1-Benzyl-1*H*-pyrazol-4-yl)amino)quinazoline-6,7-diyl)bis(oxy))bis(ethane-2,1-diyl) diacetate (105)



The title compound was synthesized from **62** (30.0 mg, 81.4 µmol) and **93** (15.5 mg, 89.5 µmol) according to general procedure A (reaction time: 2 h). The crude was purified by silica gel column chromatography (1 – 3% MeOH/DCM) to afford the product (40 mg, 79 µmol, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.56 (br s, 1H), 8.28 (s, 1H), 7.64 (s, 1H), 7.51 (s, 1H), 7.31 – 7.15 (m, 6H),

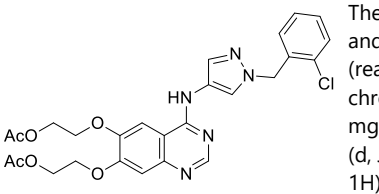
5.27 (s, 2H), 4.48 – 4.43 (m, 2H), 4.36 (t, *J* = 5.4 Hz, 2H), 4.29 – 4.22 (m, 2H), 4.07 (t, *J* = 5.4 Hz, 2H), 2.06 (s, 3H), 2.06 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.60, 170.97, 155.67, 154.35, 153.64, 148.00, 146.88, 136.53, 131.69, 128.87, 128.15, 127.74, 122.75, 122.23, 109.29, 109.03, 103.20, 66.88, 66.85, 62.28, 61.89, 56.53, 21.02, 20.94. LCMS (Finnigan, 10 → 90%): t_r = 5.50 min, m/z: 506.1.

((4-((1-Phenethyl-1*H*-pyrazol-4-yl)amino)quinazoline-6,7-diyl)bis(oxy))bis(ethane-2,1-diyl) diacetate (106)



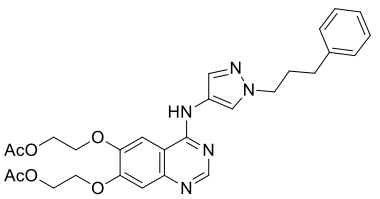
The title compound was synthesized from **62** (30.0 mg, 81.4 µmol) and **94** (15.3 mg, 81.7 µmol) according to general procedure A (reaction time: 1 h). The crude was purified by silica gel column chromatography (0 - 5% MeOH/DCM) to afford the product (31 mg, 60 µmol, 73%). ^{1}H NMR (400 MHz, MeOD) δ 8.44 (s, 1H), 8.04 (d, *J* = 0.7 Hz, 1H), 7.75 (d, *J* = 0.7 Hz, 1H), 7.66 (s, 1H), 7.27 – 7.11 (m, 5H), 7.10 (s, 1H), 4.52 – 4.46 (m, 4H), 4.38 – 4.29 (m, 6H), 3.15 (t, *J* = 7.3 Hz, 2H), 2.08 (s, 3H), 2.08 (s, 3H). ^{13}C NMR (101 MHz, MeOD) δ 172.34, 172.24, 156.93, 154.71, 154.26, 149.18, 146.61, 138.73, 132.37, 129.40, 129.24, 127.32, 123.51, 122.87, 110.16, 108.44, 104.45, 68.07, 67.62, 63.43, 63.22, 54.47, 37.50, 20.94, 20.92. LCMS (Finnigan, 0 → 90%): t_r = 6.33 min, m/z: 520.2.

((4-((1-(2-Chlorobenzyl)-1*H*-pyrazol-4-yl)amino)quinazoline-6,7-diyl)bis(oxy))bis(ethane-2,1-diyl) diacetate (107)



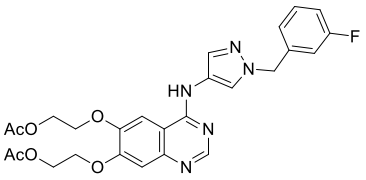
The title compound was synthesized from **62** (30.0 mg, 81.4 µmol) and **96** (16.9 mg, 81.4 µmol) according to general procedure A (reaction time: 1 h). The crude was purified by silica gel column chromatography (2 – 4% MeOH/DCM) to afford the product (42 mg, 78 µmol, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (s, 1H), 8.33 (d, *J* = 0.7 Hz, 1H), 8.30 (br s, 1H), 7.72 (d, *J* = 0.8 Hz, 1H), 7.52 (s, 1H), 7.35 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.22 – 7.13 (m, 3H), 7.02 (dd, *J* = 7.5, 1.8 Hz, 1H), 5.42 (s, 2H), 4.51 – 4.47 (m, 2H), 4.42 (t, *J* = 5.6 Hz, 2H), 4.32 – 4.26 (m, 2H), 4.19 – 4.12 (m, 2H), 2.10 (s, 3H), 2.08 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.75, 170.99, 155.66, 154.38, 153.70, 148.02, 146.94, 134.43, 133.14, 132.07, 129.69, 129.51, 127.36, 122.72, 122.67, 109.25, 109.13, 103.09, 66.90, 66.87, 62.32, 61.76, 53.90, 21.10, 20.98. LCMS (Finnigan, 10 → 90%): t_r = 5.86 min, m/z: 540.0.

((4-((1-(3-Phenylpropyl)-1*H*-pyrazol-4-yl)amino)quinazoline-6,7-diyl)bis(oxy))bis(ethane-2,1-diyl) diacetate (108)



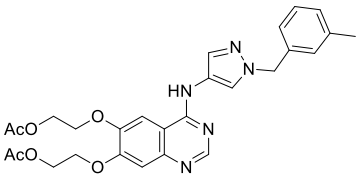
The title compound was synthesized from **62** (30.0 mg, 81.4 µmol) and **95** (16.4 mg, 81.5 µmol) according to general procedure A (reaction time: 1.5 h). The crude was purified by silica gel column chromatography (1 – 4% MeOH/DCM) to afford the product (40.8 mg, 76.5 µmol, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 – 8.62 (m, 2H), 8.28 (d, *J* = 0.7 Hz, 1H), 7.65 (d, *J* = 0.7 Hz, 1H), 7.60 (s, 1H), 7.28 – 7.23 (m, 2H), 7.22 – 7.13 (m, 4H), 4.50 – 4.45 (m, 2H), 4.40 (t, *J* = 5.3 Hz, 2H), 4.30 – 4.25 (m, 2H), 4.17 – 4.09 (m, 4H), 2.62 (t, *J* = 7.6 Hz, 2H), 2.21 (p, *J* = 7.4 Hz, 2H), 2.08 (s, 3H), 2.08 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.60, 170.99, 155.74, 154.32, 153.67, 148.03, 146.77, 140.82, 131.21, 128.55, 128.49, 126.19, 122.15, 122.13, 109.30, 108.91, 103.31, 66.96, 66.84, 62.27, 61.94, 51.89, 32.73, 31.83, 21.01, 20.92. LCMS (Finnigan, 10 → 90%): t_r = 6.05 min, m/z: 534.2.

((4-((1-(3-Fluorobenzyl)-1*H*-pyrazol-4-yl)amino)quinazoline-6,7-diyl)bis(oxy))bis(ethane-2,1-diyl) diacetate (109)



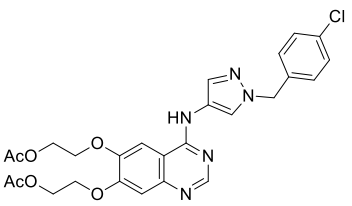
The title compound was synthesized from **62** and **97** (15.6 mg, 81.6 µmol) according to general procedure A (reaction time: 1.5 h). The crude was purified by silica gel column chromatography (1 – 4% MeOH/DCM) to afford the product (35 mg, 67 µmol, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.64 (br s, 1H), 8.33 (s, 1H), 7.65 (d, *J* = 0.8 Hz, 1H), 7.53 (s, 1H), 7.26 – 7.19 (m, 1H), 7.18 (s, 1H), 6.97 (ddd, *J* = 7.6, 1.7, 0.9 Hz, 1H), 6.94 – 6.88 (m, 1H), 6.86 (dt, *J* = 9.5, 1.9 Hz, 1H), 5.27 (s, 2H), 4.47 – 4.43 (m, 2H), 4.37 (t, *J* = 5.4 Hz, 2H), 4.27 – 4.23 (m, 2H), 4.08 (t, *J* = 5.5 Hz, 2H), 2.06 (s, 3H), 2.06 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.64, 170.98, 163.01 (d, $J_{(C–F)}$ = 246.9 Hz), 155.64, 154.28, 153.70, 148.04, 146.82, 139.12 (d, $J_{(C–F)}$ = 7.2 Hz), 131.88, 130.44 (d, $J_{(C–F)}$ = 8.3 Hz), 123.15 (d, $J_{(C–F)}$ = 2.9 Hz), 122.94, 122.29, 115.07 (d, $J_{(C–F)}$ = 21.1 Hz), 114.52 (d, $J_{(C–F)}$ = 22.1 Hz), 109.28, 108.95, 103.21, 66.90, 66.86, 62.26, 61.87, 55.83 (d, $J_{(C–F)}$ = 1.8 Hz), 21.01, 20.92. LCMS (Finnigan, 10 → 90%): t_r = 5.64 min, m/z: 524.1.

((4-((1-(3-Methylbenzyl)-1*H*-pyrazol-4-yl)amino)quinazoline-6,7-diyl)bis(oxy))bis(ethane-2,1-diyl) diacetate (110)



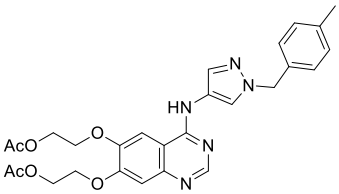
The title compound was synthesized from **62** (30.0 mg, 81.4 µmol) and **98** (15.3 mg, 81.7 µmol) according to general procedure A (reaction time: 1 h). The crude was purified by silica gel column chromatography (1 – 4% MeOH/DCM) to afford the product (38.8 mg, 74.7 µmol, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.32 (br s, 1H), 8.28 (d, *J* = 0.7 Hz, 1H), 7.67 (d, *J* = 0.8 Hz, 1H), 7.49 (s, 1H), 7.21 – 7.12 (m, 2H), 7.09 – 7.00 (m, 3H), 5.25 (s, 2H), 4.50 – 4.46 (m, 2H), 4.41 (t, *J* = 5.5 Hz, 2H), 4.31 – 4.27 (m, 2H), 4.12 (t, *J* = 5.6 Hz, 2H), 2.25 (s, 3H), 2.09 (s, 3H), 2.08 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.71, 170.99, 155.64, 154.36, 153.66, 147.98, 146.91, 138.65, 136.44, 131.70, 128.94, 128.78, 128.56, 124.87, 122.65, 122.20, 109.25, 109.11, 103.11, 66.88, 62.32, 61.83, 56.60, 21.42, 21.08, 20.97. LCMS (Finnigan, 10 → 90%): t_r = 5.84 min, m/z: 520.1.

((4-((1-(4-Chlorobenzyl)-1*H*-pyrazol-4-yl)amino)quinazoline-6,7-diyl)bis(oxy))bis(ethane-2,1-diyl) diacetate (111)



The title compound was synthesized from **62** (30.0 mg, 81.4 µmol) and **99** (16.9 mg, 81.4 µmol) according to general procedure A (reaction time: 2 h). The crude was purified by silica gel column chromatography (0 – 5% MeOH/DCM) to afford the product (40 mg, 74 µmol, 91%). ^{1}H NMR (400 MHz, MeOD) δ 8.45 (s, 1H), 8.31 (d, *J* = 0.7 Hz, 1H), 7.77 (d, *J* = 0.7 Hz, 1H), 7.63 (s, 1H), 7.30 – 7.25 (m, 2H), 7.20 – 7.16 (m, 2H), 7.07 (s, 1H), 5.28 (s, 2H), 4.50 – 4.45 (m, 4H), 4.33 – 4.28 (m, 4H), 2.08 (s, 3H), 2.07 (s, 3H). ^{13}C NMR (101 MHz, MeOD) δ 172.32, 172.22, 156.77, 154.71, 154.20, 149.18, 146.52, 136.24, 134.53, 132.72, 129.65, 129.51, 123.75, 123.42, 110.11, 108.35, 104.33, 68.05, 67.61, 63.42, 63.20, 55.87, 20.94, 20.92. LCMS (Finnigan, 10 → 90%): t_r = 5.94 min, m/z: 540.1.

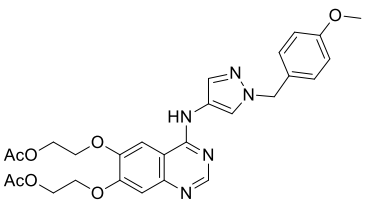
((4-((1-(4-Methylbenzyl)-1*H*-pyrazol-4-yl)amino)quinazoline-6,7-diyl)bis(oxy))bis(ethane-2,1-diyl) diacetate (112)



The title compound was synthesized from **62** (30.0 mg, 81.4 µmol) and **100** (18.2 mg, 81.4 µmol) according to general procedure A (reaction time: 6 h). The crude was purified by automated column chromatography (0 – 5% MeOH/DCM) to afford the product (36 mg, 69 µmol, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (s, 1H), 8.57 (br s, 1H), 8.26 (d, *J* = 0.7 Hz, 1H), 7.62 (d, *J* = 0.7 Hz, 1H), 7.48 (s, 1H), 7.18 (s, 1H), 7.13 – 7.09 (m, 2H), 7.08 – 7.04 (m, 2H), 5.23 (s,

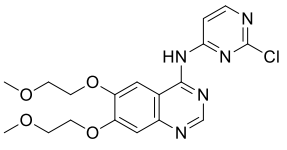
2H), 4.49 – 4.44 (m, 2H), 4.36 (t, *J* = 5.4 Hz, 2H), 4.29 – 4.24 (m, 2H), 4.06 (t, *J* = 5.4 Hz, 2H), 2.26 (s, 3H), 2.07 (s, 3H), 2.06 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.59, 170.98, 155.66, 154.31, 153.61, 147.97, 146.80, 137.94, 133.46, 131.62, 129.52, 127.82, 122.68, 122.14, 109.29, 108.98, 103.20, 66.90, 66.85, 62.30, 61.94, 56.34, 21.18, 21.02, 20.94. LCMS (Finnigan, 10 → 90%): t_r = 5.85 min, m/z: 520.1.

((4-((1-(4-Methoxybenzyl)-1*H*-pyrazol-4-yl)amino)quinazoline-6,7-diyl)bis(oxy))bis(ethane-2,1-diyl) diacetate (113)



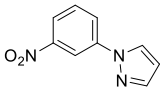
The title compound was synthesized from **62** (30.0 mg, 81.4 µmol) and **101** (16.6 mg, 81.7 µmol) according to general procedure A (reaction time: 1.5 h). The crude was purified by automated column chromatography (0 – 5% MeOH/DCM) to afford the product (41 mg, 77 µmol, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (s, 1H), 8.62 (s, 1H), 8.24 (d, *J* = 0.6 Hz, 1H), 7.61 (d, *J* = 0.8 Hz, 1H), 7.47 (s, 1H), 7.18 – 7.12 (m, 3H), 6.79 – 6.74 (m, 2H), 5.19 (s, 2H), 4.48 – 4.43 (m, 2H), 4.35 (t, *J* = 5.3 Hz, 2H), 4.25 (t, 2H), 4.03 (t, *J* = 5.3 Hz, 2H), 3.71 (s, 3H), 2.06 (s, 3H), 2.05 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.57, 170.97, 159.46, 155.67, 154.32, 153.60, 147.97, 146.83, 131.61, 129.30, 128.46, 122.67, 122.03, 114.19, 109.30, 108.98, 103.19, 66.89, 66.83, 62.28, 61.97, 56.04, 55.31, 21.00, 20.93. LCMS (Finnigan, 10 → 90%): t_r = 6.18 min, m/z: 536.2.

***N*-(2-Chloropyrimidin-4-yl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (114)**



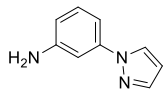
4-Chloro-6,7-bis(2-methoxyethoxy)quinazoline (1.50 g, 4.80 mmol), Cs_2CO_3 (4.69 g, 14.4 mmol), xantphos (416 mg, 0.719 mmol) and 2-chloropyrimidin-4-amine (746 mg, 5.76 mmol) were mixed in DMF (22 mL). N_2 was bubbled through the mixture for 1 min after which $Pd(OAc)_2$ (108 mg, 0.48 mmol) was added. N_2 was bubbled through the mixture for 30 sec after which the mixture was heated to 90°C and stirred for 16 h. The mixture was filtered over Celite and subsequently concentrated. The residue was suspended in EtOAc (100 mL) and poured into H_2O (100 mL) and brine (10 mL). The organic layer was separated and the water layer extracted with EtOAc (50 mL). The combined organic layers were washed with brine (100 mL) and subsequently isolated. The water layer was extracted with EtOAc (50 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude was purified by silica gel column chromatography (1% MeOH/EtOAc) to afford the product (1.23 g, 3.03 mmol, 63%). ^{1}H NMR (500 MHz, DMSO) δ 11.01 (s, 1H), 8.71 (s, 1H), 8.57 (d, *J* = 5.9 Hz, 1H), 8.53 (d, *J* = 5.8 Hz, 1H), 8.04 (s, 1H), 7.30 (s, 1H), 4.34 – 4.28 (m, 4H), 3.80 – 3.77 (m, 2H), 3.76 – 3.73 (m, 2H), 3.37 (s, 3H), 3.35 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 160.79, 159.97, 158.99, 154.91, 154.39, 151.83, 148.77, 147.91, 109.98, 109.33, 107.91, 102.95, 69.97, 68.34, 68.23, 58.37, 58.34, 40.11, 40.02, 39.95, 39.85, 39.78, 39.69, 39.61, 39.52, 39.35, 39.19, 39.02.

1-(3-Nitrophenyl)-1*H*-pyrazole (115)



An oven dried microwave tube was charged with 1*H*-pyrazole (33.7 mg, 495 µmol), 1-bromo-3-nitrobenzene (150 mg, 743 µmol), ethyl 2-oxocyclohexane-1-carboxylate (7.9 µl, 50 µmol), Cs_2CO_3 (323 mg, 990 µmol) and dry MeCN (1 mL). Argon was bubbled through the mixture for 30 sec after which copper(I) oxide (7.1 mg, 50 µmol) was added. The microwave tube was sealed, the mixture was heated to 82°C and stirred for 16 h. The mixture was poured into H_2O (10 mL) and the product extracted with EtOAc (3x10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated. The crude was purified by automated column chromatography (10 – 50% EtOAc/heptane) to afford the product (51.0 mg, 270 µmol, 55%). ^{1}H NMR (400 MHz, DMSO) δ 8.73 (dd, *J* = 2.7, 0.6 Hz, 1H), 8.64 (t, *J* = 2.2 Hz, 1H), 8.32 (ddd, *J* = 8.2, 2.2, 0.9 Hz, 1H), 8.13 (ddd, *J* = 8.3, 2.2, 0.9 Hz, 1H), 7.84 (dd, *J* = 1.7, 0.5 Hz, 1H), 7.78 (t, *J* = 8.2 Hz, 1H), 6.62 (dd, *J* = 2.6, 1.8 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 148.62, 142.05, 140.36, 131.13, 128.57, 124.13, 120.52, 112.75, 108.83. LCMS (Finnigan, 10 → 90%): t_r = 7.49 min, m/z: 190.1.

3-(1*H*-Pyrazol-1-yl)aniline (116)



115 (28.0 mg, 148 µmol) was dissolved in EtOH/H_2O (30:1, 3.3 mL) after which iron powder (41.3 mg, 444 µmol) and NH_4Cl (41.3 mg, 740 µmol) were added. The mixture was heated to 80°C, stirred for 2.5 h and subsequently filtered over Celite. The filtrate was diluted in 10% MeOH/DCM (10 mL) and poured into 1 M $NaHCO_3$ (10 mL). The organic layer was separated and the water layer extracted with DCM (2x10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated to afford the product (23.0 mg, 144 µmol, 98%). ^{1}H NMR (400 MHz, DMSO) δ 8.29 (dd, *J* = 1.9, 0.6 Hz, 1H), 7.66 (d, *J* = 1.8 Hz, 1H), 7.11 – 7.06 (m, 2H), 6.91 (ddd, *J* = 7.9, 2.2, 0.9 Hz, 1H), 6.50 (ddd, *J* = 8.0, 2.2, 0.9 Hz, 1H), 6.47 (dd, *J* = 2.5, 1.8 Hz, 1H), 5.56 (br s, 2H). ^{13}C NMR (101 MHz, DMSO) δ 149.51, 140.61, 140.38, 129.80, 127.41, 112.10, 107.40, 105.92, 104.19. LCMS (Fleet, 0 → 20%): t_r = 6.34 min, m/z: 160.1.

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