Discovery of FLT3 inhibitors for the treatment of acute myeloid leukemia

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Chapter 3

Comprehensive structure-activity-relationship of azaindoles as highly potent FLT3 inhibitors*

Introduction

Acute myeloid leukemia (AML) is a cancer of the blood and bone marrow that is characterized by a failure in differentiation of stem cells during hematopoiesis, resulting in flooding of the bloodstream with immature myeloid blood cells. These blast cells fatally disrupt normal hematopoietic function and their abundance in blood obstruct the normal flow in capillaries resulting in a high mortality.[1,2] While in younger patients cure rates can reach up to 35-40%, elderly patients, who are often unable to cope with the intensive chemotherapy regimen, do not experience this benefit.[3] AML is a genetically diverse disease, but in 20-30% of patients an internal tandem duplication (ITD) in the juxtamembrane domain of the Fms-like tyrosine kinase 3 (FLT3) receptor has been identified as a driver mutation.[4,5] The validation of FLT3 as a drug target led to clinical development of several small molecule inhibitors, culminating in the recent FDA approval of midostaurin for treatment of FLT3-dependent AML in conjunction with standard treatment.[6–9] Although the initial response to treatment with FLT3 inhibitors shows therapeutic promise, many AML patients relapse due to the emergence of drug-resistant cancer cells.[10–12] Resistance-inducing mutations have thus far been observed in

* The data presented in this chapter was gathered in collaboration with Berend Gagestein, Jordi F. Keijzer, Nora Liu, Ruud H. Wijdeven, Eelke B. Lenselink, Adriaan W. Tuin, Adrianus M. C. H. van den Nieuwendijk, Gerard J. P. van Westen, Constant A. A. van Boeckel, Herman S. Overkleeft, Jacques Neefjes, Mario van der Stelt.

treatments with several FLT3 inhibitors, among which the highly potent experimental drug quizartinib.[12–14] The discovery of new chemical entities to target FLT3 represents, therefore, a medical need.

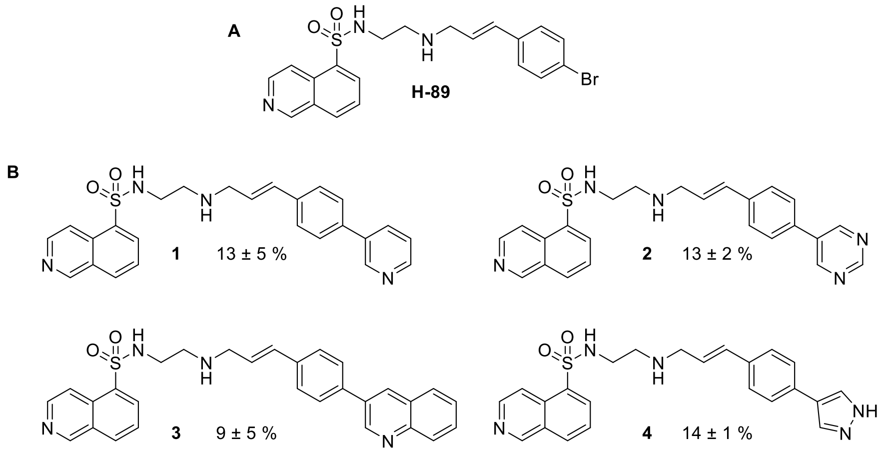


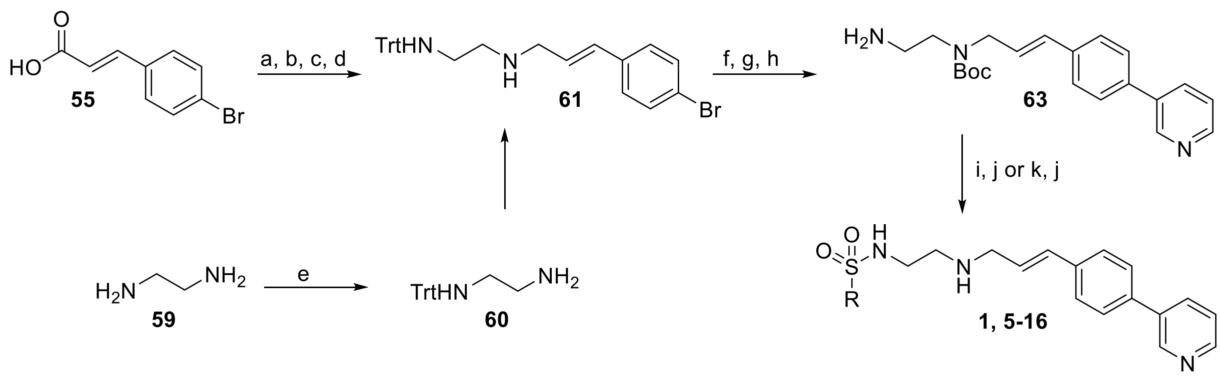
Figure 1: FLT3 screening hits (**1-4**) from an H-89 library.[15] Data represent residual *in vitro* FLT3 activity at 2 µM.

N-[2-(*p*-Bromocinnamylamino)ethyl]-5-isoquinolinesulfonamide (H-89) is a prototypical and intensely-studied kinase inhibitor (Figure 1A). It was one of the first non-natural, synthetic inhibitors that competitively inhibited the binding of ATP to the structurally conserved binding domain of cAMP-dependent protein kinase (PKA).[16,17] The binding mode of H-89 to PKA has been studied in great detail at the atomic level using crystallization studies.[18] This contributed to the understanding of kinase function and provided general principles to develop drug-like kinase inhibitors. The isoquinoline sulfonamide mimics the binding mode of adenosine. The nitrogen of the isoquinoline ring forms a crucial H-bond bridge to the backbone of Val-123, located in the hinge region of PKA.[18] This binding mode of H-89 is not specific to PKA, but has also been observed with Haspin, as shown in structural data (PDB: 3FMD). Furthermore, H-89 activity has been shown for several other kinases, including S6K1, MSK1 and ROCK-II.[19,20] Consequently, H-89 is used as a starting point in several drug discovery programs. For example, this lab has previously described the use of H-89 and its analogs as RAC-alpha serine/threonine-protein kinase (AKT1) inhibitors to combat bacterial infections, such as *Salmonella typhimurium* and *Mycobacterium tuberculosis*.[15,21] During the hit optimization program of H-89 analogs as AKT1 inhibitors, four compounds (**1**-**4**) were identified that demonstrated substantial activity against FLT3 (Figure 1B).[15] In this chapter the optimization and structure-activity relationships of H-89-derived compounds as new FLT3 inhibitors is presented.

Results and Discussion

To confirm the structure and activity of compound **1**, the synthesis was started with the commercially available building blocks as outlined in Scheme 1. After methylation and reduction, the resulting alcohol was exchanged for a chlorine and a trityl protected ethylenediamine linker was introduced via nucleophilic substitution. Subsequent Boc-protection, Suzuki-coupling with 3-pyridinylboronic acid and trityl-deprotection yielded the primary amine, which could be coupled with isoquinoline sulfonyl chloride to provide the desired product **1**. The activity of compound **1** was confirmed in a biochemical assay using purified, recombinantly expressed human FLT3 with a time-resolved fluorescence resonance energy transfer (FRET) method. Compound **1** showed potent inhibition with a half maximum inhibitory concentration (IC_{50}) in the low nanomolar range (pIC_{50} = 8.02 ± 0.05), which was comparable to the inhibitory activity of the reference inhibitor quizartinib (pIC_{50} = 8.30 ± 0.07). Compound **1** demonstrated favorable physico-chemical properties with a molecular weight (MW) of 445 and a logD (pH 7.4) of 1.5.[22] This resulted in a lipophilic efficiency (LipE = pIC_{50} - logD) of 6.5.[23] In summary, compound **1** was defined as an excellent starting point to develop new FLT3 inhibitors.

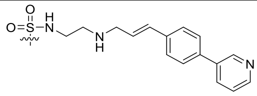
Scheme 1: Synthetic route towards the derivatives **1**, **5**-**16**.[a]

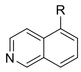
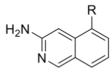
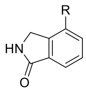
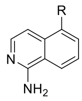
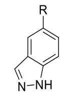
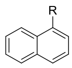
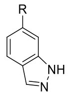
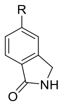
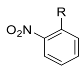
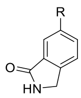
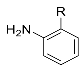
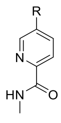


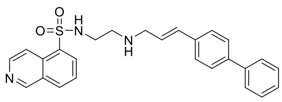
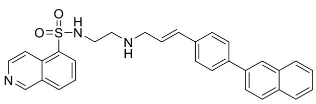
[a]Reagents and conditions: (a) K_2CO_3, dimethyl sulfate, ACN, 80°C, overnight; (b) DIBAL-H, toluene, -80 – 0°C; (c) $SOCl_2$, DCM, RT; (d) **60**, K_2CO_3, ACN, 70°C, 2 h; (e) TrtCl, K_2CO_3, RT, 40 min; (f) $NaHCO_3$, Boc_2O, THF, RT, overnight; (g) 3-pyridinylboronic acid, $Pd(PPh_3)_4$, K_2CO_3, DCM/DMF, 85°C, 6 h; (h) TFA, TES, DCM 0°C – RT, 5 h; (i) heteroaryl-bromide, $K_2S_2O_5$, HCOONa, $Pd(OAc)_2$, PPh_3, 1,10-phenanthroline, DMSO then DiPEA, **63**, NBS, THF, 0°C – RT, 1 h; (j) TFA, $CHCl_3$, 1 h; (k) aryl-sulfonylchloride, Et_3N, DCM/DMF, 0°C – RT.

A topological exploration of the structure-activity relationship of isoquinolinesulfonamides was employed guided by the observed binding mode of H-89 in other kinases.[18] First, the isoquinoline substituent was replaced by various other hinge binding moieties inspired by kinase drugs, including indolones (sunitinib and nintedanib),[24–27] aminoisoquinolines (crizotinib and palbociclib),[24,28,29] indazoles (axitinib)[24,30] and picolinamides (sorafenib).[24,31,32] The analogs (**5**-**16**) were synthesized in a similar manner as compound **1** using a palladium-catalyzed sulfination of heteroaryl halides and subsequent coupling with the primary amine as shown in Scheme 1.[33] Interestingly, compounds **5**-**12** displayed similar or slightly weaker activity compared to compound **1** with a range of pIC_{50}s between 7.6 and 8.0 (Table 1). Indazolone **6** was the most potent compound of the series with a pIC_{50} of 8.01 ± 0.08.

Table 1: *In vitro* FLT3 activity and LipE of compounds **1** – **18**.

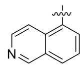
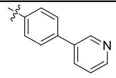
R = 

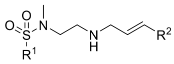
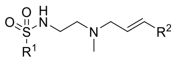
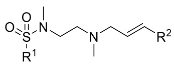
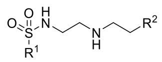
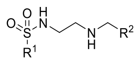
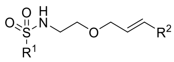
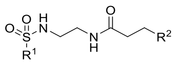
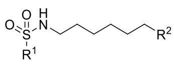
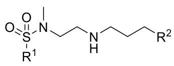
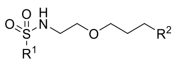
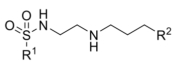
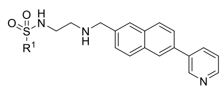
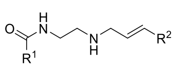
Entry		**pIC_{50} ± SEM**	**LipE**	**Entry**		**pIC_{50} ± SEM**	**LipE**
1		8.02 ± 0.05	6.5	**11**		7.71 ± 0.10	6.4
5		7.70 ± 0.11	7.0	**12**		7.62 ± 0.16	6.3
6		8.01 ± 0.08	6.6	**13**		7.21 ± 0.14	4.6
7		7.77 ± 0.09	6.6	**14**		6.19 ± 0.15	6.2
8		7.74 ± 0.11	7.0	**15**		8.07 ± 0.07	6.6
9		7.32 ± 0.12	6.6	**16**		7.57 ± 0.18	6.6
10		7.86 ± 0.10	7.6				

Entry		**pIC_{50} ± SEM**	**LipE**
17		< 5	n.a.
18		< 5	n.a.

Moreover, substantially more polar groups such as picolinamide were well tolerated (as observed in compound **10**), resulting in a high lipE of 7.6. Surprisingly, the nitrogen atom, which plays an important role in the hinge binding to other kinases, was not required for activity. Compounds **13** and **14** retained activity with a pIC_{50} of 7.21 ± 0.34 and 6.19 ± 0.15, respectively. The same was true for the nitro and amino phenyl derivatives **15** and **16**. All together, these results suggested that the binding orientation of the isoquinolinesulfonamides might be different than the one of H-89 in PKA. It was envisioned that the nitrogen atom of the pyridyl ring could act as a potential H-bond acceptor to interact with the hinge region, which may potentially explain the activity of compounds **13-16**. To test this hypothesis compounds (**17**-**18**), in which the pyridine ring was substituted for a carbacycle, were synthesized (SI Scheme 1). The pIC_{50} of these novel derivatives dropped to < 5 (Table 1). This suggested that the nitrogen in the pyridine is indeed important for the interaction with FLT3 and the isoquinolinesulfonamide may have a flipped binding orientation in the ATP-pocket of FLT3 compared to PKA.

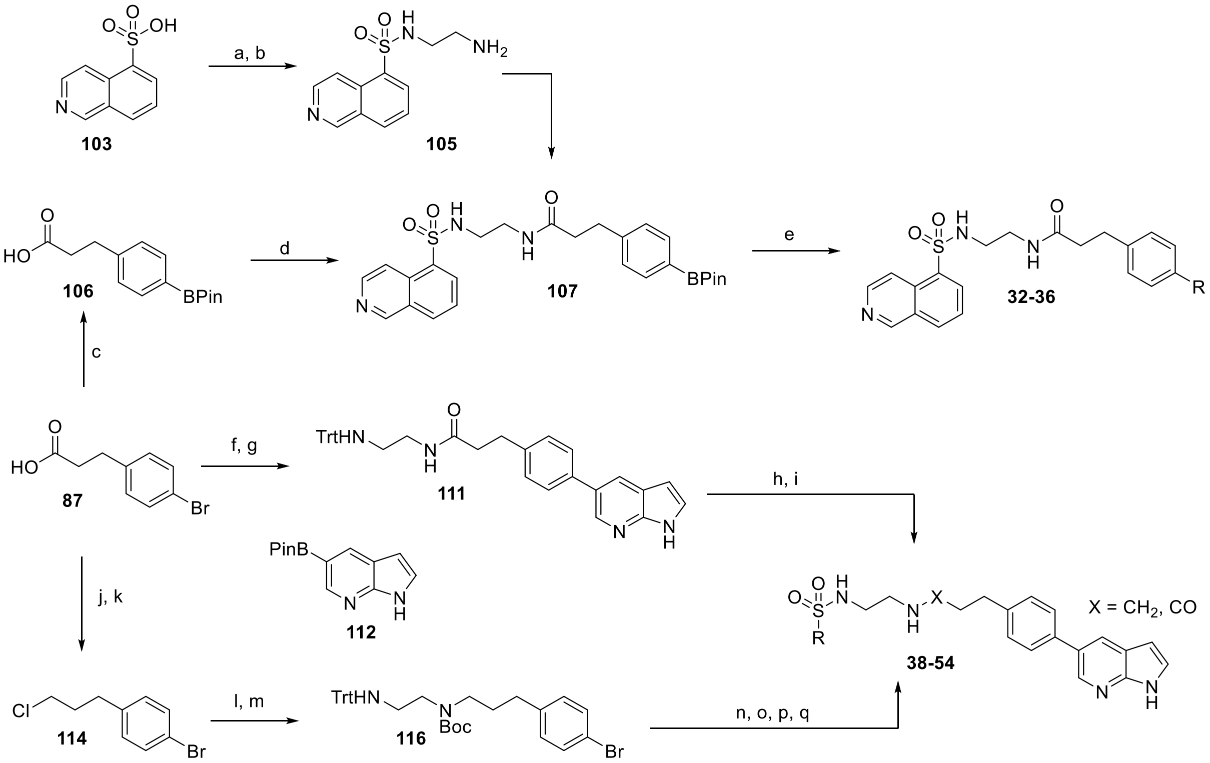
Table 2: FLT3 activity and LipE of compounds **19** – **31**.

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

Entry		pIC_{50} ± SEM	LipE
19		6.74 ± 0.26	5.0
20		6.87 ± 0.20	4.6
21		6.90 ± 0.19	4.3
22		6.57 ± 0.21	5.4
23		6.80 ± 0.17	5.6
24		8.08 ± 0.09	5.3
25		7.49 ± 0.14	5.3
26		6.77 ± 0.17	2.2
27		7.32 ± 0.15	5.5
28		7.41 ± 0.13	4.3
29		8.05 ± 0.07	6.4
30		6.25 ± 0.21	3.7
31		< 5	n.a.

To further understand the SAR of our chemical series, the importance of the linker between the isoquinoline and the pyridyl moieties was investigated (**19**-**31**). The results from this study are summarized in Table 2. The synthetic schemes for these compounds (**19**-**31**) are shown in the SI (SI Scheme 1-4). Several analogs were made to investigate possible hydrogen bond donor capability of the sulfonamide and secondary amine group. To this end, the nitrogens of sulfonamide (**19**), amine (**20**) or both (**21**) were substituted with a methyl group. This led to a > 10-fold drop in potency for all compounds, which indicated that these NH donors could be important for the interaction with FLT3. Next, the linker length between the secondary amine and the phenyl was investigated. Compounds with reduced length of one (**22**) and two (**23**) methylene groups showed decreased activity. The importance of the basicity of the linker moiety was tested by replacing the amine with an ether (**24**), amide (**25**), or a methylene (**26**) containing linker. **24** and **25** were equally active as the corresponding amine derivative, while **26** was > 10-fold less active (Table 2). These results suggested that the basic center of the linker is not required. Of note, reduction of the double bond (**27** - **29**) in the linker resulted in an almost identical inhibitory activity as the parent compound, whereas increasing the conformational restriction in compound **30** reduced its activity. This indicated that the reduced conformational flexibility by the double bond in compound **1** is not beneficial for its activity as has recently been noted for other kinase inhibitors.[34] Finally, the substitution of the sulfonamide for an amide did result in an inactive compound (**31**) (pIC_{50} < 5), which could possibly be due to a difference in the spatial orientation of the (sulfon)amide substituents. These data indicate that a flexible linker of 6 atoms with or without a basic amine is optimal between the sulfonamide and phenyl-pyridyl rings.

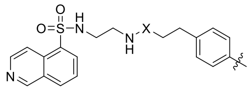
Scheme 2: Synthetic route towards the derivatives **32** - **36** and **38** - **54**.[a]

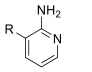
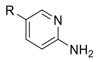
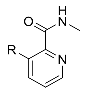
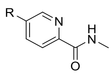
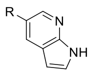
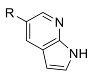


[a]Reagents and conditions: (a) $SOCl_2$, DMF, reflux, 4 h; (b) ethylenediamine, DCM, 0°C – RT; (c) B_2Pin_2, KOAc, Pd(dppf)Cl_2, 1,4-dioxane, 100°C, overnight; (d) **105**, EDC, HOBt, DiPEA, DCM, 4 h; (e) heteroaryl-bromide, Pd(PPh_3)$_4$, K_2CO_3, DMF, 85°C, overnight; (f) **60**, EDC, HOBt, DiPEA, DCM, 4 h; (g) **112**, Pd(PPh_3)$_4$, K_2CO_3, DMF, 90°C; (h) TFA, TES, DCM, 0°C – RT, 16 h; (i) aryl-sulfonylchloride, Et_3N, DCM/DMF, 0°C – RT, 16 h; (j) $NaBH_4$, BF_3, THF, 0° - RT, 16 h; (k) $SOCl_2$, DMF, 0°C – RT, 19 h; (l) **60**, K_2CO_3, ACN, 70°C, 72 h; (m) $NaHCO_3$, Boc_2O, THF, RT, 36 h; (n) **112**, Pd(PPh_3)$_4$, K_2CO_3, DMF, 90°C; (o) TFA, TES, DCM, 0°C – RT, 20 h; (p) aryl-sulfonylchloride, Et_3N, DCM/DMF, 0°C – 30°C, 16 h (q) TFA, DCM, 0°C – RT, 16 h.

Having established the optimal linker features, an additional array of compounds (**32**-**37**) was synthesized in which the pyridyl ring was replaced with other (substituted) heteroaryls to optimize the hinge-binding interaction (Scheme 2 and SI Scheme 5). In contrast to the isoquinoline replacements, a wide range of activities was observed (pIC_{50}: 5 – 8.9) (Table 3). While the picolinamide variations (**34**-**35**) were inactive (pIC_{50} < 5), the azaindoles **36** and **37** demonstrated a significantly increased pIC_{50} of 8.87 ± 0.06. and 8.78 ± 0.05, respectively. Of note, **37** demonstrated a LipE of 6.7. Altogether, the optimization of the potential hinge-binding pyridyl moiety resulted in the discovery of the azaindoles as a potent FLT3 inhibitor scaffold.

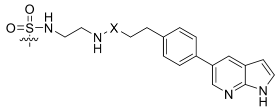
Table 3: FLT3 activity and LipE of compounds **32** - **37**.

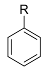
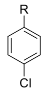
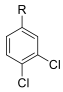
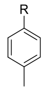
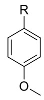
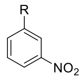
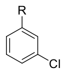
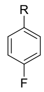
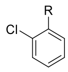
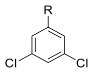
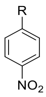
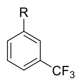
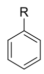
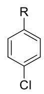
R = 

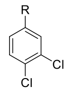
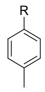
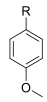
Entry		X	pIC_{50} ± SEM	LipE
32		CO	6.82 ± 0.14	4.8
33		CO	7.63 ± 0.11	5.6
34		CO	< 5	n.a.
35		CO	< 5	n.a.
36		CO	8.87 ± 0.06	6.2
37		CH_2	8.78 ± 0.05	6.7

Next, a matched-molecular pair analysis was performed using the azaindole scaffold with amide (**38**-**49**) and amine linker (**50**-**54**) series.[35] The goal was to study the influence of the substitution pattern of the phenyl ring.[36] Compounds (**38**-**54**) were prepared as shown in Scheme 2. Compounds with electron-withdrawing groups, such as Cl (**39**), *p*-NO_2 (**43**), *p*-F (**45**), or electron donating groups (*p*-Me (**41**) and *p*-OMe (**42**)) both displayed high potency (pIC_{50} > 8.0). No correlation could be found between the Hammett constants of the substituents and the activity of the compounds (SI Figure 1). In fact, non-substituted compound **38** was the most potent compound identified in this study with a pIC_{50} of 9.49 ± 0.08. The matched-molecular pair analysis of LipE values of the amine and amide series showed good correlation, which supports the hypothesis that both series bind in a similar fashion to FLT3 (Figure 2).

Table 4: FLT3 activity and LipE of compounds **38** - **54**

R = 

Entry		**X**	**pIC$_{50}$ ± SEM**	**LipE**
38		CO	9.49 ± 0.08	6.5
39		CO	8.62 ± 0.05	5.0
40		CO	8.39 ± 0.05	4.1
41		CO	8.67 ± 0.06	5.2
42		CO	8.74 ± 0.08	5.8
43		CO	8.80 ± 0.08	5.9
44		CO	8.72 ± 0.06	5.1
45		CO	9.39 ± 0.18	6.2
46		CO	9.32 ± 0.09	5.7
47		CO	8.16 ± 0.08	3.9
48		CO	7.97 ± 0.09	5.0
49		CO	8.37 ± 0.09	4.5
50		CH$_2$	8.88 ± 0.06	6.5
51		CH$_2$	8.36 ± 0.08	6.4

52		CH_2	8.13 ± 0.09	4.5
53		CH_2	8.69 ± 0.07	5.9
54		CH_2	8.62 ± 0.10	6.3

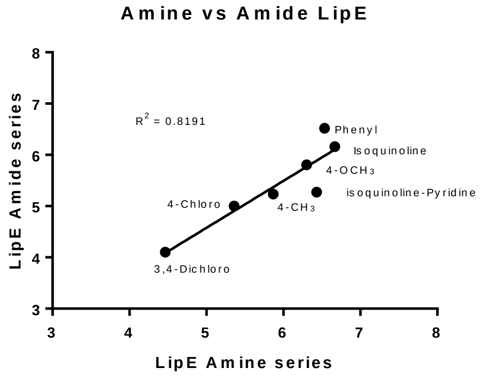


Figure 2: Matched molecular pair analysis of amine and amide containing compounds. Data shows a high correlation (R^2 = 0.82), indicating a similar binding mode for both linker series.

Finally, to explain our structure activity relationships a structure based study was performed with compound **1** and compound **38** using a published DFG-out crystal structure (4RT7), and a DFG-in model (see methods). Induced fit docking was performed in combination with an previously established binding pose metadynamics protocol[45], in order to determine a feasible binding mode. On the basis of these results and overlap in binding mode with quizartinib (SI Figure 2) it was established that compound **1** and compound **38** bind DFG-out (Figure 3A). The pyridine moiety of **1** is engaged in a hydrogen bond interaction with the backbone of C694 (hinge) and the adjacent phenyl engages in a π-interaction with F691 (Figure 3A). Moreover, in the induced fit docking, no poses were observed in which the isoquinoline interacted with the hinge of FLT3. As shown in Figure 3B the resulting docking pose of **38** is similar to the binding mode of **1** with an additional hydrogen-bond-interaction to C694, which may explain the increased potency. To conclude, the observed binding mode is in agreement with the obtained structure activity relations.

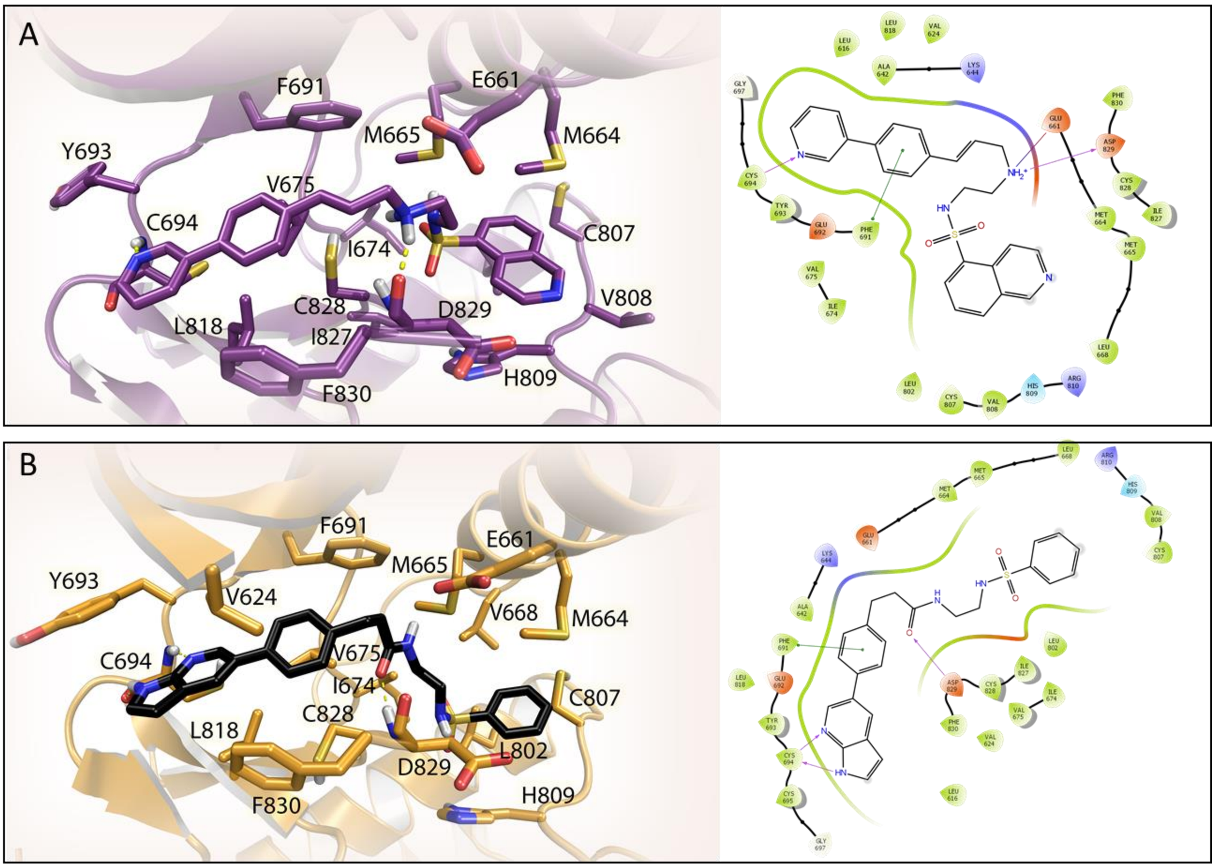


Figure 3: Proposed "flipped" binding mode of **1** and **38** in FLT3. (A-left) **1** and (B-left) **38** docked in FLT3 crystal structure (PDB: 4RT7) On the right a 2D-interaction diagram is shown depicting the interactions between the ligand and FLT3.

In summary, azaindole **38** was identified as a new, highly potent inhibitor of FLT3-ITD with favorable physico-chemical properties. Our structure-activity relationships and modeling studies suggest that **38** has an alternative flipped binding mode compared to other kinase inhibitors derived from the prototypical kinase inhibitor H-89. **38** forms an excellent starting point for further lead optimization studies to obtain clinical candidates to modulate FLT3-ITD in AML patients.

Experimental

Biochemical Evaluation of FLT3 inhibitors

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

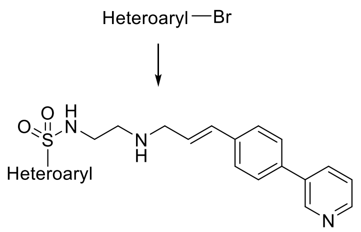
Structure based modeling on FLT3

All structure based modeling was performed in the Schrödinger suite (Schrödinger Release 2017-4: Maestro, Schrödinger, LLC, New York, NY, 2017). Crystal structures were prepared using the protein preparation wizard,[37] ligands were prepared using LigPrep.[38] Both the DFG-out structure co-crystalized with quizartinib (4RT7)[39] and a DFG-in model were used in order to dock our initial compound **1**. The DFG-in model was constructed on the basis of 4RT7 and 3LCD, in a similar fashion as has been done before,[40] using the knowledge based potential in prime.[41, 42] Docking was done using induced fit docking and using H-bond constraints on C694.[43] In order to determine to correct binding pose, induced fit docking was followed by the conformer cluster script, using the Kelley criterion[44] to determine the optimal number of clusters. The highest scoring poses of every cluster were used in a previously published workflow to determine binding poses[45], which is based on metadynamics. The highest scoring pose was selected by adding the Metadynamics CompScore to the docking score. Based on this workflow the highest scoring pose was visualized and rendered using PyMol.[46]

Synthetic Procedures

Solvents were purchased from Biosolve, Sigma Aldrich or Fluka and, if necessary dried over 3Å or 4Å molecular sieves. Reagents purchased from chemical suppliers were used without further purification, unless stated otherwise. Oxygen or H_2O sensitive reactions were performed under argon or nitrogen atmosphere and/or under exclusion of H_2O. Reactions were followed by thin layer chromatography which was performed using TLC silica gel 60 F_{245} on aluminium sheets, supplied by Merck. Compounds were visualized by UV absorption (254 nm) or spray reagent (permanganate (5 g/L $KMnO_4$, 25 g/L K_2CO_3)). TLCMS was measured with a thin layer chromatography-mass spectrometer (Advion, Eppression LCMS; Advion, Plate Express). ^1H- and ^{13}C-NMR spectra were performed on one of the following Bruker spectrometers: DPX 300 NMR spectrometer (300 MHz), equipped with 5mm-BBO-z-gradient-probe; AV-400 NMR spectrometer (400 MHz), equipped with 5mm-BBO-z-gradient-probe; AV-500 NMR spectrometer (500 MHz), equipped with BBFO-z-gradient-probe; AV-600 NMR spectrometer (600 MHz), equipped with 5mm-Cryo-z-gradient probe. NMR spectra were measured in deuterated methanol, chloroform or DMSO and were referenced to the residual protonated solvent signals as internal standards (chloroform-*d* = 7.260 (^{1}H), 77.160 (^{13}C); methanol-d_4 = 3.310 (^{1}H), 49.000 (^{13}C); DMSO-d_6 = 2.500 (^{1}H), 39.520 (^{13}C)). Signals multiplicities are written as s (singlet), bs (broad singlet), d (doublet), t (triplet), q (quartet), p (pentet) or m (multiplet). Coupling constants (*J*) are given in Hz. Preparative HPLC (Waters, 515 HPLC pump M; Waters, 515 HPLC pump L; Waters, 2767 sample manager; Waters SFO System Fluidics Organizer; Waters Acquity Ultra Performance LC, SQ Detector; Waters Binary Gradient Module) was performed on a Phenomenex Gemini column (5 µM C18, 150 x 4.6 mm) or a Waters XBridgeTM column (5 µM C18, 150 x 19 mm). Diode detection was done between 210 and 600 nm. Gradient: ACN in (H_2O + 0.2% TFA). HRMS (Thermo, Finnigan LTQ Orbitrap; Thermo, Finnigan LTQ Pump; Thermo, Finnigan Surveyor MS Pump PLUS Thermo, Finnigan Surveyor Autosampler; NESLAB, Merlin M25). Data acquired through direct injection of 1 mM of the sample in ACN/H_2O/*t*-BuOH (1:1:1), with mass spectrometer equipped with an electrospray ion source in positive mode (source voltage 3.5 kV, sheath gas low 10, capillary temperature 275°C) with resolution R = 60.000 at m/z = 400 (mass range = 150-2000) and dioctylphtalate (m/z = 391.28428) as lock mass. All tested compounds were checked for purity by HPLC, either on a Thermo (Thermo Finnigan LCQ Advantage Max; Thermo Finnigan Surveyor LC-pump Plus; Thermo Finnigan Surveyor Autosampler Plus; Thermo Finnigan Surveyor PDA Plus Detector; Phenomenex Gemini column (5 µm C18, 50 x 4.6 mm)) or a Waters (Waters 515 HPLC pump M; Waters 515 HPLC pump L; Waters 2767 sample manager; Waters SFO System Fluidics Organizer; Waters Acquity Ultra Performance LC, SQ Detector; Waters binary gradient module; Phenomenex Gemini column (5 µm C18, 150 x 4.6 mm)) system and were determined to be >95% pure by integrating UV intensity recorded.

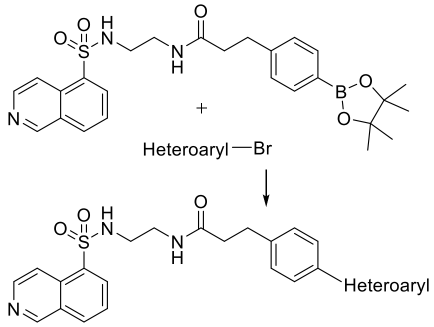
General procedure A: Sulfonamide coupling



<u>Step 1:</u> A glass vial was charged with corresponding bromo-heteroaryl compound (0.20 mmol, 1 eq), potassium metabisulfite (88 mg, 0.40 mmol, 2 eq), tetrabutylammonium bromide (70 mg, 0.22 mmol, 1.1 eq), sodium formate (15 mg, 0.22 mmol, 1.1 eq), palladium(II) acetate (5 mg, 0.02 mmol, 0.1 eq), triphenylphosphine (16 mg, 0.06 mmol, 0.3 eq), 1,10-phenanthroline (11 mg, 0.06 mmol, 0.3 eq). After sealing, the vial was flushed with argon for 30 min and the reagents were suspended in dry, degassed DMSO (1 mL) and the reaction mixture was stirred for 4 h at 70°C. After cooling to RT *N*,*N*-Diisopropylethylamine (70 µL, 0.40 mmol, 2 eq) and a solution of *tert*-butyl (*E*)-(2-aminoethyl)(3-(4-(pyridin-3-yl)phenyl)allyl)carbamate (**63**) (106 mg, 0.30 mmol, 1.5 eq) in dry THF (1 mL) were added and the reaction mixture was cooled to 0°C. Subsequently a solution of *N*-bromosuccinimide (62 mg, 0.40 mmol, 2 eq) in dry THF (1 mL) was added and the reaction mixture was allowed to come to RT. After stirring for 1 h the reaction was quenched by adding H_2O (1 mL) and brine (2 mL). The resulting mixture was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and the solvent removed under reduced pressure. The residue was purified via flash-column-chromatography (SiO_2, 0% → 5% MeOH in DCM) to yield the desired Boc-protected product, which was used directly in step 2.

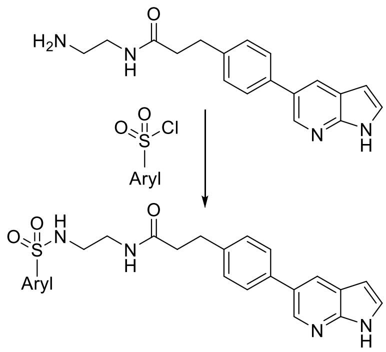
Step 2: The Boc-protected product was dissolved in chloroform (1.6 mL) and cooled to 0°C. After drop-wise addition of TFA (0.4 mL), the reaction mixture was allowed to come to RT and stirred for 1 h. Chloroform (10 mL) was added to the reaction mixture and subsequently concentrated in vacuum. After co-evaporating with chloroform (1x10 mL), the residue was purified by reverse phase HPLC.

General procedure B: Suzuki Coupling



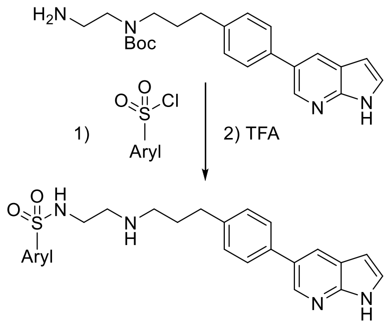
A glass vial was charged with the corresponding bromo-heteroaryl compound (0.15 mmol, 1.5 eq), *N*-(2-(isoquinoline-5-sulfonamido)ethyl)-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propanamide (**107**) (51 mg, 0.10 mmol, 1 eq) and $Pd(PPh_3)_4$ (6 mg, 0.005 mmol, 0.05 eq). The vial was put under an argon atmosphere and degassed DMF (0.35 mL) and 2 M degassed aqueous K_2CO_3 (0.125 mL, 0.25 mmol, 2.5 eq) were added. The reaction mixture was stirred at 85°C overnight, diluted with DCM (10 mL) and half-saturated aq. $NaHCO_3$ solution (10 mL), extracted with DCM (3x10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by reverse phase HPLC.

General procedure C: Sulfonamide formation



3-(4-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)phenyl)-*N*-(2-aminoethyl)propanamide (**113**) (50 mg, 0.16 mmol, 1.0 eq) and Et_3N (45 µL,0.32 mmol, 2.0 eq) were dissolved in DMF (1.6 mL). The reaction mixture was cooled to 0°C and corresponding sulfonylchloride (194.6 µmol, 1.2 eq) dissolved in DCM (1.6 mL) or DMF (1.6 mL) was added. After 15 min the mixture was warmed up to RT and stirred for 5-16 h. The mixture was quenched with saturated aqueous $NaHCO_3$ (50 mL), the phases were separated and the aqueous layer was extracted with DCM or with a mixture of 10% MeOH in $CHCl_3$ (3x40 mL). The combined organic layers were washed with brine (1x100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified via flash column chromatography and preparative HPLC.

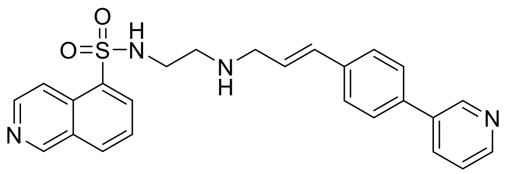
General Procedure D: Sulfonamide formation and debocylation



Step 1: *tert*-Butyl (3-(4-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)phenyl)propyl)(2-aminoethyl) carbamate (**117**) (90 mg, 228.3 µmol, 1.0 eq) and Et_3N (63 µL, 456.3 µmol, 2.0 eq) were dissolved in DCM (1 mL). The mixture was cooled to 0°C, corresponding sulfonylchloride (0.27 mmol, 1.2 eq) dissolved in DCM (1 mL) was added and the mixture was allowed to warm up and stirred at 30°C until full conversion was confirmed by TLC (4 – 40 h). The mixture was quenched with saturated aqueous $NaHCO_3$ (50 mL), the phases were separated and the aqueous layer was extracted with DCM (3x70 mL). The combined organic layers were washed with brine (1x120 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by flash-column-chromatography (SiO_2, dry-loading, 5% → 7% (10% of sat. aqueous NH_3 in MeOH) in DCM) and used in step 2.

Step 2: The product from step 1 was dissolved in DCM (1 mL) and subsequently cooled to 0°C. TFA (250 µL) was added dropwise to the solution and warmed to RT and stirred for 19 h. The mixture was diluted with 15 mL $CHCl_3$ and concentrated under reduced pressure. The resulting crude was purified by flash-column-chromatography and preparative HPLC to yield the desired compound after lyophilisation.

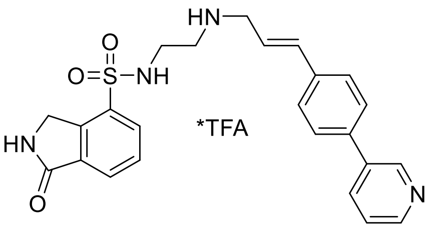
(*E*)-*N*-(2-((3-(4-(Pyridin-3-yl)phenyl)allyl)amino)ethyl)isoquinoline-5-sulfonamide (1)



A round-bottom-flask was charged with *tert*-butyl (*E*)-(2-(isoquinoline-5-sulfonamido)ethyl)(3-(4-(pyridin-3-yl)phenyl) allyl)carbamate (**64**) (610 mg, 1.12 mmol, 1 eq) dissolved in $CHCl_3$ (50 mL). After cooling the solution to 0°C and dropwise addition of TFA (12.5 mL), it was allowed to warm to RT and stirred for 30 min. The reaction was quenched by slow addition of sat. aqueous Na_2CO_3 solution (70 mL) until a pH of ~12 was reached and the mixture was extracted with DCM (3x50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified via flash-column-chromatography (SiO_2, 0% → 15% (10% of sat. aqueous NH_3 in MeOH) in DCM) to yield the desired product (329 mg, 66%). ^1H NMR (400 MHz, methanol-*d*$_4$) δ 9.32 (d, *J* = 0.7 Hz, 1H), 8.80 (dd, *J* = 2.3, 0.7 Hz, 1H), 8.61 (d, *J* = 6.2 Hz, 1H), 8.55 (d, *J* = 6.2 Hz, 1H), 8.50 (dd, *J* = 4.9, 1.5 Hz, 1H), 8.47 (dd, *J* = 7.4, 1.2 Hz, 1H), 8.33 (d, *J* = 8.3 Hz, 1H), 8.11 – 8.06 (m, 1H), 7.81 – 7.74 (m, 1H), 7.62 (d, *J* = 8.3 Hz, 2H), 7.53 – 7.48 (m, 1H), 7.46 (d, *J* = 8.3 Hz, 2H), 6.44 (d, *J* = 15.9 Hz, 1H), 6.17 (dt, *J* = 15.9, 6.5 Hz, 1H), 3.21 (dd, *J* = 6.5, 1.1 Hz, 2H), 3.03 (t, *J* = 6.4 Hz, 2H), 2.60 (t, *J* = 6.4 Hz, 2H). ^{13}C NMR (101 MHz, methanol-*d*$_4$) δ 154.33, 148.68, 148.12, 144.87, 138.41, 138.10, 137.49, 136.36, 136.24, 134.88, 134.75, 132.65, 132.60, 130.62, 128.72, 128.25, 128.21, 127.72, 125.49, 119.15, 68.12, 51.73, 43.06. HRMS calculated for $C_{25}H_{25}N_4O_2S$ 445.16927 $[M+H]^+$, found

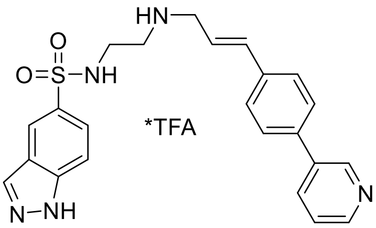
445.16891. LCMS (ESI, Waters, C_{18}, linear gradient, 5% → 50% ACN in H_2O 0.2% TFA, 10 min): t_R = 5.17 min; *m/z* : 445 $[M+H]^+$.

(*E*)-1-Oxo-*N*-(2-((3-(4-(pyridin-3-yl)phenyl)allyl)amino)ethyl)isoindoline-4-sulfonamide (5)



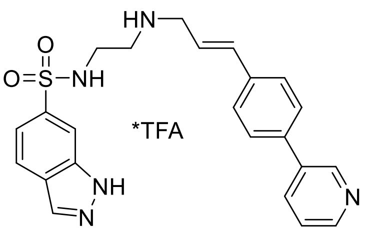
The title compound was synthesized from 4-bromoisoindolin-1-one following general procedure A on a 0.2 mmol scale and purified by preparative HPLC (XBridge, C_{18}, 0% → 20% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA salt after lyophilisation (27 mg, 24%). ^{1}H NMR (600 MHz, methanol-d_4) δ 8.98 (s, 1H), 8.66 (d, *J* = 4.8 Hz, 1H), 8.45 (dt, *J* = 8.1, 1.6 Hz, 1H), 8.07 (dd, *J* = 17.2, 7.6 Hz, 2H), 7.82 – 7.72 (m, 4H), 7.66 (d, *J* = 8.3 Hz, 2H), 6.95 (d, *J* = 15.9 Hz, 1H), 6.41 (dt, *J* = 15.7, 7.2 Hz, 1H), 4.76 (s, 2H), 3.90 (d, *J* = 7.1 Hz, 2H), 3.23 (s, 4H). ^{13}C NMR (151 MHz, methanol-d_4) δ 170.09, 144.52, 143.92, 141.94, 138.51, 137.84, 137.75, 136.29, 136.01, 134.98, 134.39, 130.70, 129.02, 127.63, 127.55, 127.28, 125.41, 119.05, 49.03, 46.21, 45.73, 38.79. HRMS calculated for $C_{24}H_{25}N_4O_3S$ 449.16419 $[M+H]^+$, found 449.16397. LCMS (ESI, Waters, C_{18}, linear gradient, 5% → 50% ACN in H_2O 0.2% TFA, 10 min): t_R = 5.59 min; *m/z* : 449 $[M+H]^+$.

(*E*)-*N*-(2-((3-(4-(Pyridin-3-yl)phenyl)allyl)amino)ethyl)-1*H*-indazole-5-sulfonamide (6)



The title compound was synthesized from 5-bromo-1*H*-indazole following general procedure A on a 0.2 mmol scale and purified by preparative HPLC (XBridge, C_{18}, 0% → 20% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA salt after lyophilisation (11 mg, 10%). ^{1}H NMR (600 MHz, methanol-d_4) δ 9.03 (s, 1H), 8.69 (d, *J* = 4.7 Hz, 1H), 8.54 (d, *J* = 8.1 Hz, 1H), 8.43 – 8.42 (m, 1H), 8.25 (s, 1H), 7.88 – 7.84 (m, 2H), 7.79 (d, *J* = 8.3 Hz, 2H), 7.74 (d, *J* = 8.9 Hz, 1H), 7.68 (d, *J* = 8.3 Hz, 2H), 6.96 (d, *J* = 15.9 Hz, 1H), 6.42 (dt, *J* = 15.8, 7.2 Hz, 1H), 3.90 (d, *J* = 7.1 Hz, 2H), 3.22 (t, *J* = 5.5 Hz, 2H), 3.17 (t, *J* = 5.5 Hz, 2H). ^{13}C NMR (151 MHz, methanol-d_4) δ 145.10, 144.55, 142.82, 140.89, 139.64, 139.03, 137.93, 137.01, 136.53, 132.92, 129.00, 128.74, 127.18, 125.40, 123.58, 123.43, 120.67, 112.49, 50.36, 47.65, 40.33. HRMS calculated for $C_{23}H_{24}N_5O_2S$ 434.16452 $[M+H]^+$, found 434.16414. LCMS (ESI, Waters, C_{18}, linear gradient, 5% → 50% ACN in H_2O 0.2% TFA, 10 min): t_R = 5.80 min; *m/z* : 434 $[M+H]^+$.

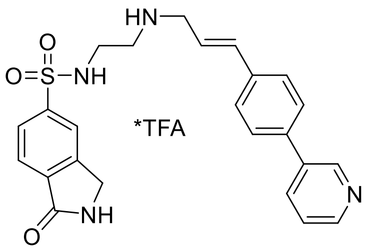
(*E*)-*N*-(2-((3-(4-(Pyridin-3-yl)phenyl)allyl)amino)ethyl)-1*H*-indazole-6-sulfonamide (7)



The title compound was synthesized from 6-bromo-1*H*-indazole following general procedure A on a 0.2 mmol scale and purified by preparative HPLC (XBridge C_{18}, 10% → 35% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA salt after lyophilisation (27 mg, 25%). ^{1}H NMR (600 MHz, methanol-d_4) δ 9.02 (d, *J* = 1.9 Hz, 1H), 8.71 – 8.68 (m, 1H), 8.54 (dt, *J* = 8.1, 1.6 Hz, 1H), 8.20 (d, *J* = 0.9 Hz, 1H), 8.15 (s, 1H), 8.03 – 7.96 (m, 1H), 7.86 (dd, *J* = 8.1, 5.4 Hz, 1H), 7.79 (d, *J* = 8.4 Hz, 2H), 7.68 (d, *J* = 8.3 Hz, 2H), 7.62 (dd, *J* = 8.5, 1.5 Hz, 1H), 6.96 (d, *J* = 15.9 Hz, 1H), 6.42 (dt, *J* = 15.8, 7.2 Hz, 1H), 3.90 (d, *J* = 7.2 Hz, 2H), 3.22 (d, *J* = 4.9 Hz, 2H), 3.19 (d, *J* = 4.7 Hz, 2H). ^{13}C NMR (151 MHz, methanol-d_4) δ 143.67, 143.12, 139.51, 139.06, 138.23, 137.65, 137.34, 136.51, 135.59, 133.75, 127.59, 127.33, 125.77, 125.07, 122.03, 119.22, 117.78, 110.40, 48.97, 46.24, 38.96. HRMS calculated for $C_{23}H_{24}N_5O_2S$

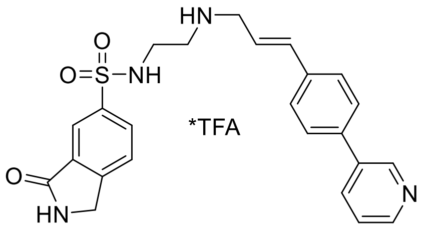
434.16452 [M+H]$^+$, found 434.16410. LCMS (ESI, Waters, C_{18}, linear gradient, 5% → 50% ACN in H_2O 0.2% TFA, 10 min): t_R = 6.02 min; *m/z* : 434 [M+H]$^+$.

(*E*)-1-Oxo-*N*-(2-((3-(4-(pyridin-3-yl)phenyl)allyl)amino)ethyl)isoindoline-5-sulfonamide (8)



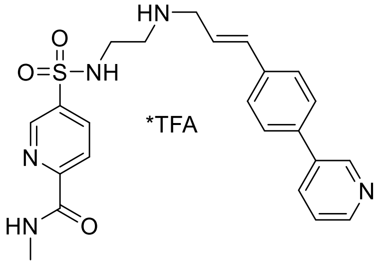
The title compound was synthesized from 5-bromoisoindolin-1-one following general procedure A on a 0.2 mmol scale and purified by preparative HPLC (Gemini C_{18}, 0% → 20% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA salt after lyophilisation (9 mg, 8%). ^{1}H NMR (600 MHz, methanol-d_4) δ 8.99 (s, 1H), 8.67 (d, *J* = 5.0 Hz, 1H), 8.48 (d, *J* = 7.7 Hz, 1H), 8.13 (s, 1H), 8.03 (d, *J* = 8.5 Hz, 1H), 7.98 (d, *J* = 8.0 Hz, 1H), 7.84 – 7.80 (m, 1H), 7.78 (d, *J* = 8.2 Hz, 2H), 7.68 (d, *J* = 8.3 Hz, 2H), 6.97 (d, *J* = 15.9 Hz, 1H), 6.45 – 6.37 (m, 1H), 4.56 (s, 2H), 3.91 (d, *J* = 7.1 Hz, 2H), 3.22 (s, 4H). ^{13}C NMR (126 MHz, methanol-d_4) δ 170.33, 145.49, 145.25, 144.82, 142.88, 137.93, 137.60, 137.53, 136.56, 136.15, 136.06, 127.59, 127.33, 126.64, 125.14, 124.05, 122.52, 118.94, 49.10, 46.30, 45.60, 39.02. HRMS calculated for $C_{24}H_{25}N_4O_3S$ 449.16419 [M+H]$^+$, found 449.16390. LCMS (ESI, Waters, C_{18}, linear gradient, 5% → 50% ACN in H_2O 0.2% TFA, 10 min): t_R = 5.35 min; *m/z* : 449 [M+H]$^+$.

(*E*)-3-Oxo-*N*-(2-((3-(4-(pyridin-3-yl)phenyl)allyl)amino)ethyl)isoindoline-5-sulfonamide (9)



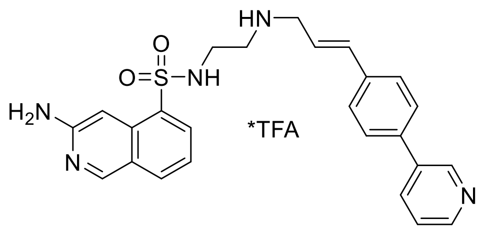
The title compound was synthesized from 6-bromoisoindolin-1-one following general procedure A on a 0.2 mmol scale and purified by preparative HPLC (XBridge, C_{18}, 0% → 20% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA salt after lyophilisation (16 mg, 14%). ^{1}H NMR (600 MHz, methanol-d_4) δ 9.04 (s, 1H), 8.70 (d, *J* = 5.0 Hz, 1H), 8.57 (d, *J* = 8.2 Hz, 1H), 8.27 (s, 1H), 8.13 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.88 (dd, *J* = 8.1, 5.4 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.79 (d, *J* = 8.3 Hz, 2H), 7.69 (d, *J* = 8.3 Hz, 2H), 6.97 (d, *J* = 15.9 Hz, 1H), 6.47 – 6.37 (m, 1H), 4.57 (s, 2H), 3.91 (d, *J* = 7.2 Hz, 2H), 3.26 – 3.22 (m, 2H), 3.22 – 3.17 (m, 2H). ^{13}C NMR (151 MHz, methanol-d_4) δ 171.74, 150.24, 144.77, 144.25, 141.27, 141.26, 139.78, 139.04, 138.01, 136.84, 134.58, 131.36, 129.02, 128.76, 127.30, 126.15, 123.29, 120.70, 50.40, 47.67, 47.05, 40.34. HRMS calculated for $C_{24}H_{25}N_4O_3S$ 449.16419 [M+H]$^+$, found 449.16386. LCMS (ESI, Waters, C_{18}, linear gradient, 5% → 50% ACN in H_2O 0.2% TFA, 10 min): t_R = 5.39 min; *m/z* : 449 [M+H]$^+$.

(*E*)-*N*-Methyl-5-(*N*-(2-((3-(4-(pyridin-3-yl)phenyl)allyl)amino)ethyl)sulfamoyl) picolinamide (10)



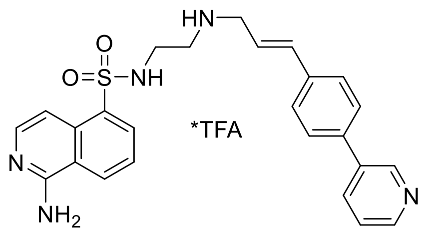
The title compound was synthesized from 5-bromo-*N*-methylpicolinamide following general procedure A on a 0.2 mmol scale and purified by preparative HPLC (XBridge C_{18}, 0% → 20% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA salt after lyophilisation (17 mg, 15%). ^{1}H NMR (600 MHz, methanol-d_4) δ 9.07 (d, *J* = 2.0 Hz, 1H), 9.03 (s, 1H), 8.70 (d, *J* = 5.2 Hz, 1H), 8.57 (d, *J* = 8.2 Hz, 1H), 8.40 (dd, *J* = 8.2, 2.2 Hz, 1H), 8.27 (d, *J* = 8.2 Hz, 1H), 7.88 (dd, *J* = 8.0, 5.4 Hz, 1H), 7.79 (d, *J* = 8.3 Hz, 2H), 7.68 (d, *J* = 8.3 Hz, 2H), 6.97 (d, *J* = 15.9 Hz, 1H), 6.42 (dt, *J* = 15.7, 7.2 Hz, 1H), 3.91 (d, *J* = 7.1 Hz, 2H), 3.29 – 3.23 (m, 4H), 2.98 (s, 3H). ^{13}C NMR (151 MHz, methanol-d_4) δ 165.72, 154.28, 148.04, 144.92, 144.39, 141.12, 139.78, 139.70, 139.10, 137.95, 137.76, 136.94, 129.01, 128.76, 127.25, 123.41, 120.64, 50.43, 47.67, 40.30, 26.53. HRMS calculated for $C_{23}H_{26}N_5O_3S$ 452.17509 [M+H]$^+$, found 452.17469. LCMS (ESI, Waters, C_{18}, linear gradient, 5% → 50% ACN in H_2O 0.2% TFA, 10 min): t_R = 5.62 min; *m/z* : 452 [M+H]$^+$.

(*E*)-3-Amino-*N*-(2-((3-(4-(pyridin-3-yl)phenyl)allyl)amino)ethyl)isoquinoline-5-sulfonamide (11)



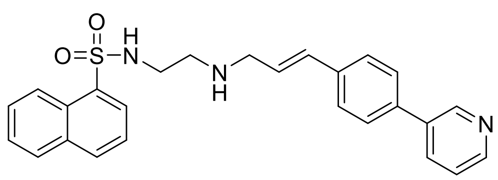
The title compound was synthesized from 5-bromoisoquinolin-3-amine following general procedure A on a 0.2 mmol scale and purified by preparative HPLC (XBridge C_{18}, 10% → 20% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA salt after lyophilisation (19 mg, 17%). ^{1}H NMR (400 MHz, methanol-d_4) δ 9.06 (s, 1H), 8.98 (s, 1H), 8.72 (d, *J* = 5.2 Hz, 1H), 8.61 (d, *J* = 8.2 Hz, 1H), 8.29 (d, *J* = 7.3 Hz, 1H), 8.13 (d, *J* = 8.2 Hz, 1H), 7.92 (dd, *J* = 8.0, 5.5 Hz, 1H), 7.80 (d, *J* = 8.3 Hz, 2H), 7.68 (d, *J* = 8.3 Hz, 2H), 7.60 (s, 1H), 7.36 (t, *J* = 7.8 Hz, 1H), 6.94 (d, *J* = 15.9 Hz, 1H), 6.46 – 6.36 (m, 1H), 3.89 (d, *J* = 7.2 Hz, 2H), 3.19 (m, *J* = 8.6, 4.4 Hz, 4H). ^{13}C NMR (101 MHz, methanol-d_4) δ 156.42, 150.93, 144.36, 143.86, 141.72, 139.95, 138.95, 138.10, 136.93, 136.62, 136.47, 136.13, 132.35, 129.04, 128.77, 127.47, 124.30, 122.66, 120.79, 99.56, 50.39, 47.72, 40.16. HRMS calculated for $C_{25}H_{26}N_5O_2S$ 460.18017 [M+H]$^+$, found 460.17998. LCMS (ESI, Waters, C_{18}, linear gradient, 5% → 50% ACN in H_2O 0.2% TFA, 10 min): t_R = 5.51 min; *m/z* : 460 [M+H]$^+$.

(*E*)-1-Amino-*N*-(2-((3-(4-(pyridin-3-yl)phenyl)allyl)amino)ethyl)isoquinoline-5-sulfonamide (12)



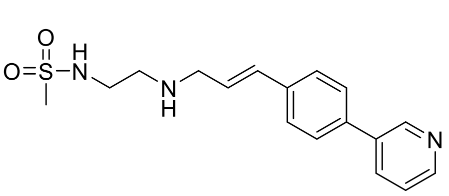
The title compound was synthesized from 5-bromoisoquinolin-1-amine following general procedure A on a 0.2 mmol scale and purified by preparative HPLC (XBridge C_{18}, 0% → 20% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA salt after lyophilisation (32 mg, 28%). ^{1}H NMR (600 MHz, methanol-d_4) δ 8.96 (s, 1H), 8.71 (d, *J* = 8.4 Hz, 1H), 8.64 (d, *J* = 4.3 Hz, 1H), 8.60 (d, *J* = 8.7 Hz, 1H), 8.41 (dt, *J* = 8.1, 1.8 Hz, 1H), 7.94 – 7.88 (m, 2H), 7.79 – 7.73 (m, 4H), 7.66 (d, *J* = 8.3 Hz, 2H), 6.95 (d, *J* = 15.9 Hz, 1H), 6.41 (dt, *J* = 15.8, 7.2 Hz, 1H), 3.90 (d, *J* = 7.1 Hz, 2H), 3.22 (s, 4H). ^{13}C NMR (151 MHz, methanol-d_4) δ 156.25, 146.32, 145.70, 139.44, 139.12, 139.05, 137.61, 137.58, 137.46, 137.05, 135.36, 131.46, 130.51, 128.98, 128.93, 128.65, 126.65, 121.02, 120.43, 109.12, 50.47, 47.69, 40.15. HRMS calculated for $C_{25}H_{26}N_5O_2S$ 460.18017 [M+H]$^+$, found 460.18005. LCMS (ESI, Waters, C_{18}, linear gradient, 5% → 50% ACN in H_2O 0.2% TFA, 10 min): t_R = 5.45 min; *m/z* : 460 [M+H]$^+$.

(*E*)-*N*-(2-((3-(4-(Pyridin-3-yl)phenyl)allyl)amino)ethyl)naphthalene-1-sulfonamide (13)



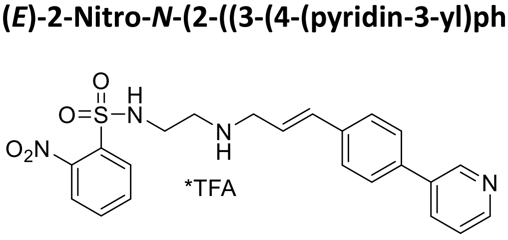
To a solution of *tert*-butyl (*E*)-(2-(naphthalene-1-sulfonamido)ethyl)(3-(4-(pyridin-3-yl)phenyl) allyl) carbamate (**65**) (0.270 g, 0.50 mmol, 1 eq) in DCM (5 mL) at 0 °C was added TFA (1 mL). The reaction was allowed to warm to RT and stirred for 1 h before it was concentrated under reduced pressure and re-dissolved in DCM (20 mL) and sat. aqueous Na_2CO_3 solution (20 mL). The organic layer was collected and the aqueous layer extracted with DCM (4x20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified via flash-column-chromatography (SiO_2 (neutralized with 1% Et_3N in DCM), 1.25% → 1.5% MeOH in DCM) to yield the product (0.18 g, 81%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.85 (d, *J* = 1.9 Hz, 1H), 8.70 (d, *J* = 8.6 Hz, 1H), 8.58 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.29 (dd, *J* = 7.3, 1.1 Hz, 1H), 8.05 (d, *J* = 8.2 Hz, 1H), 7.93 (d, *J* = 7.9 Hz, 1H), 7.89 – 7.84 (m, 1H), 7.67 – 7.61 (m, 1H), 7.59 – 7.54 (m, 1H), 7.53 – 7.49 (m, 3H), 7.39 – 7.33 (m, 3H), 6.35 (d, *J* = 15.9 Hz, 1H), 6.06 (dt, *J* = 15.9, 6.3 Hz, 1H), 3.17 (bs, 2H), 3.09 (dd, *J* = 6.3, 1.1 Hz, 2H), 3.03 – 2.98 (m, 2H), 2.66 – 2.61 (m, 2H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 148.45, 148.07, 136.81, 136.69, 136.20, 134.52, 134.30, 134.29, 134.22, 130.69, 129.82, 129.20, 128.50, 128.42, 128.18, 127.26, 127.01, 126.95, 124.45, 124.26, 123.71, 50.87, 47.34, 42.51. HRMS calculated for $C_{26}H_{26}N_3O_2S$ 444.17402 $[M+H]^+$, found 444.17370. LCMS (ESI, Waters, C_{18}, linear gradient, 5% → 90% ACN in H_2O 0.2% TFA, 10 min): t_R = 5.32 min; *m/z* : 444 $[M+H]^+$.

(*E*)-*N*-(2-((3-(4-(Pyridin-3-yl)phenyl)allyl)amino)ethyl)methanesulfonamide (14)



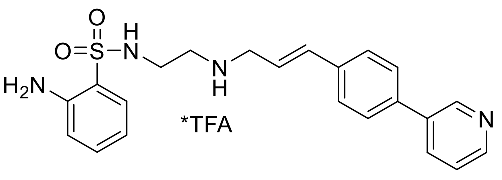
A round-bottom-flask was charged with *tert*-butyl (*E*)-(2-(isoquinoline-5-sulfonamido)ethyl)(3-(4-(pyridin-3-yl)phenyl) allyl)carbamate (**66**) (107 mg, 0.25 mmol, 1 eq) dissolved in $CHCl_3$ (8 mL). After cooling the solution to 0°C and dropwise addition of TFA (2 mL), it was allowed to warm to RT and stirred for 60 min. The reaction was quenched by slow addition of sat. aqueous Na_2CO_3 solution (12 mL) until a pH of ~12 was reached and the mixture was extracted with DCM (3x10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified via flash-column-chromatography (SiO_2, 0% → 15% (10% of sat. aqueous NH_3 in MeOH) in DCM) to yield the product (52 mg, 63%). ^{1}H NMR (600 MHz, methanol-d_4) δ 8.80 (d, *J* = 2.3 Hz, 1H), 8.50 (dd, *J* = 4.9, 1.4 Hz, 1H), 8.09 (d, *J* = 8.0 Hz, 1H), 7.63 (d, *J* = 8.2 Hz, 2H), 7.55 (d, *J* = 8.3 Hz, 2H), 7.51 (dd, *J* = 8.0, 4.9 Hz, 1H), 6.65 (d, *J* = 15.9 Hz, 1H), 6.40 (dt, *J* = 15.9, 6.5 Hz, 1H), 3.46 – 3.42 (m, 2H), 3.23 (t, *J* = 6.3 Hz, 2H), 2.96 (s, 3H), 2.80 (t, *J* = 6.3 Hz, 2H). ^{13}C NMR (151 MHz, methanol-d_4) δ 148.66, 148.11, 138.58, 138.15, 137.49, 136.26, 132.78, 129.03, 128.26, 128.23, 125.49, 51.91, 49.46, 43.26, 39.68. HRMS calculated for $C_{17}H_{22}N_3O_2S$ 332.14272 $[M+H]^+$, found 332.14267. LCMS (ESI, Waters, C_{18}, linear gradient, 5% → 50% ACN in H_2O 0.2% TFA, 10 min): t_R = 4.49 min; *m/z* : 332 $[M+H]^+$.

(*E*)-2-Nitro-*N*-(2-((3-(4-(pyridin-3-yl)phenyl)allyl)amino)ethyl)benzenesulfonamide (15)



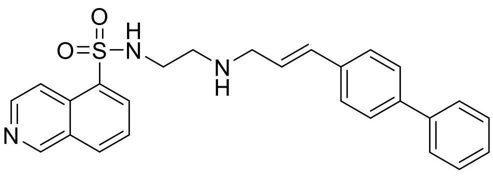
To a solution of *tert*-butyl (*E*)-(2-((2-nitrophenyl)sulfonamido)ethyl)(3-(4-(pyridin-3-yl)phenyl)allyl)carbamate (**67**) (0.347 g, 0.64 mmol, 1 eq) dissolved in $CHCl_3$ (4.8 mL) at 0 °C was added dropwise TFA (1.2 mL). The reaction was allowed to warm to RT and stirred for 2 h before it was concentrated under reduced pressure. It was re-dissolved in DCM (20 mL) and sat. aqueous Na_2CO_3 solution (20 mL). The organic layer was collected and the aqueous layer extracted with DCM (3x20 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated under reduced pressure and purified by preparative HPLC (Gemini, C_{18}, 10% → 35% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA salt after lyophilisation (11 mg, 3%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.99 (s, 1H), 8.86 (bs, 2H), 8.63 (dd, *J* = 3.5, 1.3 Hz, 1H), 8.36 (d, *J* = 5.4 Hz, 1H), 8.23 (d, *J* = 6.9 Hz, 1H), 8.03 (dt, *J* = 6.1, 3.2 Hz, 2H), 7.91 (dd, *J* = 5.9, 3.3 Hz, 2H), 7.81 (d, *J* = 8.2 Hz, 2H), 7.61 (d, *J* = 8.3 Hz, 3H), 6.87 (d, *J* = 15.9 Hz, 1H), 6.40 – 6.30 (m, 1H), 3.81 (d, *J* = 5.1 Hz, 2H), 3.23 (d, *J* = 6.1 Hz, 2H), 3.10 (s, 2H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 148.40, 147.98, 136.77, 136.61, 136.06, 134.11, 133.57, 133.39, 132.69, 131.07, 130.73, 128.68, 127.20, 126.98, 125.25, 123.65, 51.03, 47.46, 43.16. HRMS calculated for $C_{22}H_{23}N_4O_4S$ 439.14345 $[M+H]^+$, found 439.14302. LCMS (ESI, Waters, C_{18}, linear gradient, 5% → 50% ACN in H_2O 0.2% TFA, 10 min): t_R = 6.71min; *m/z* : 439 $[M+H]^+$.

(*E*)-2-Amino-*N*-(2-((3-(4-(pyridin-3-yl)phenyl)allyl)amino)ethyl) benzenesulfonamide (16)



(*E*)-2-Nitro-*N*-(2-((3-(4-(pyridin-3-yl)phenyl) allyl) amino) ethyl)benzenesulfonamide (**15**) (84 mg, 0.19 mmol, 1 eq) was dissolved in EtOH (0.32 mL), AcOH (0.32 mL) and H_2O (0.16 mL) after which iron powder (30 mg) was added and the vial was sonicated for 2.5 h. The mixture was basified with aqueous NaOH (1 M, 5.5 mL) solution, concentrated under reduced pressure, re-suspended in DCM (5 mL) and sat. aqueous Na_2CO_3 (5 mL) and filtered over filter paper. The filter was rinsed with sat. aqueous Na_2CO_3 (50 mL) and the filtrate was extracted with DCM (5x40 mL). The combined organic layers were dried over $MgSO_4$, concentrated under reduced pressure and purified by preparative HPLC (XBridge C_{18}, 10% → 35% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA salt after lyophilisation (48 mg, 48%). ^1H NMR (500 MHz, DMSO-d_6) δ 9.00 (d, *J* = 1.8 Hz, 1H), 8.78 (bs, 2H), 8.65 (dd, *J* = 4.9, 1.5 Hz, 1H), 8.26 (d, *J* = 8.1 Hz, 1H), 7.86 – 7.79 (m, 3H), 7.65 – 7.59 (m, 3H), 7.50 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.31 – 7.27 (m, 1H), 6.88 – 6.82 (m, 2H), 6.64 (t, *J* = 7.0 Hz, 1H), 6.34 (dt, *J* = 15.8, 6.9 Hz, 1H), 4.37 (bs, 2H), 3.83 – 3.72 (m, 2H), 3.08 – 2.96 (m, 4H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 147.26, 146.41, 146.19, 136.36, 136.18, 135.59, 135.56, 135.41, 133.90, 129.13, 127.40, 127.35, 124.52, 120.42, 118.72, 117.12, 115.31, 48.38, 45.42, 38.47. HRMS calculated for $C_{22}H_{25}N_4O_2S$ 409.16927 $[M+H]^+$, found 409.16884. LCMS (ESI, Waters, C_{18}, linear gradient, 5% → 90% ACN in H_2O 0.2% TFA, 10 min): t_R = 4.62 min; *m/z* : 409 $[M+H]^+$.

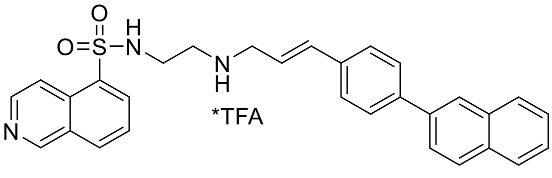
(*E*)-*N*-(2-((3-([1,1'-Biphenyl]-4-yl)allyl)amino)ethyl)isoquinoline-5-sulfonamide (17)



To a solution of *tert*-butyl (*E*)-(3-([1,1'-biphenyl]-4-yl)allyl)(2-(isoquinoline-5-sulfonamido) ethyl) carbamate (**71**) (0.387 g, 0.70 mmol, 1 eq) in DCM (3.1 mL) at 0 °C was added TFA (3.1 mL) after which the mixture was allowed to warm to RT. After stirring for 30 min it was concentrated under reduced pressure, re-dissolved in sat. aqueous $NaHCO_3$ (30 mL) and DCM (30 mL), the organic layer was collected and the aqueous layer extracted with DCM (3x30 mL). The combined organic layers were washed with brine (1x50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified via flash-column-chromatography (SiO_2, 3% → 4% (10% of sat. aqueous NH_3 in MeOH) in DCM) to yield the desired product (0.150 g, 48%). ^1H NMR (400 MHz, chloroform-*d*) δ 9.35 (d, *J* = 0.8 Hz, 1H), 8.71 (d, *J* = 6.1 Hz, 1H), 8.48 – 8.42 (m, 2H), 8.18 (d, *J* = 8.2 Hz, 1H), 7.72 – 7.64 (m, 1H), 7.63 – 7.58 (m, 2H), 7.55 (d, *J* = 8.3 Hz, 2H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.40 – 7.32 (m, 3H), 6.40 (d, *J* = 15.9 Hz, 1H), 6.08 (dt, *J* = 15.9, 6.4 Hz, 1H), 3.31 (bs, 2H), 3.17 (dd, *J* = 6.4, 1.3 Hz, 2H), 3.01 (dd, *J* = 6.4, 4.8 Hz, 2H), 2.69 (dd, *J* = 6.4, 4.9 Hz, 2H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 153.49, 145.39, 140.69, 140.44, 135.78, 134.27, 133.70, 133.49, 131.49, 131.36, 129.13, 128.92, 127.46, 127.40, 127.39, 127.02, 126.81, 126.02, 117.30, 51.01, 47.18, 42.41. HRMS calculated for $C_{26}H_{26}N_3O_2S$ 444.17402

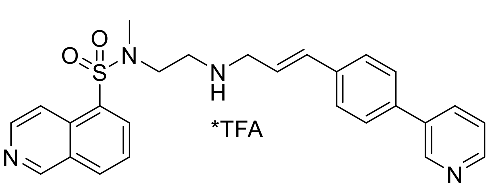
$[M+H]^+$, found 444.17354. LCMS (ESI, Waters, C_{18}, linear gradient, 5% → 90% ACN in H_2O 0.2% TFA, 10 min): t_R = 6.27 min; *m/z* : 444 $[M+H]^+$.

(*E*)-*N*-(2-((3-(4-(Naphthalen-2-yl)phenyl)allyl)amino)ethyl)isoquinoline-5-sulfonamide (18)



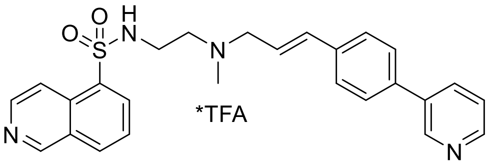
To a solution of *tert*-butyl (*E*)-(2-(isoquinoline-5-sulfonamido)ethyl)(3-(4-(naphthalene-2-yl)phenyl)allyl)carbamate (**72**) (0.339 g, 0.62 mmol, 1 eq) in DCM (3.1 mL) at 0 °C was added TFA (3.1 mL) after which the mixture was allowed to warm to RT. After stirring for 30 min it was concentrated under reduced pressure, re-dissolved in sat. aqueous $NaHCO_3$ (30 mL) and DCM (30 mL), the organic layer was collected and the aqueous layer extracted with DCM (3x30 mL). The combined organic layers were washed with brine (1x50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude was purified by flash-column-chromatography (SiO_2, 3% → 4% (10% of sat. aqueous NH_3 in MeOH) in DCM) and preparative HPLC (XBridge C_{18}, 25% → 50% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the desired compound as a TFA salt after lyophilisation (23 mg, 6%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.51 (s, 1H), 8.74 (d, *J* = 6.1 Hz, 3H), 8.48 (d, *J* = 8.2 Hz, 1H), 8.44 – 8.41 (m, 2H), 8.38 (dd, *J* = 7.4, 1.1 Hz, 1H), 8.28 – 8.25 (m, 1H), 8.02 (t, *J* = 8.6 Hz, 2H), 7.95 (d, *J* = 7.8 Hz, 1H), 7.91 – 7.84 (m, 4H), 7.60 (d, *J* = 8.3 Hz, 2H), 7.58 – 7.51 (m, 2H), 6.84 (d, *J* = 15.9 Hz, 1H), 6.30 (dt, *J* = 15.8, 7.0 Hz, 1H), 3.81 – 3.76 (m, 2H), 3.10 – 3.00 (m, 4H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 153.46, 144.67, 139.92, 136.67, 136.49, 134.63, 133.91, 133.72, 133.30, 132.88, 132.34, 130.31, 128.72, 128.55, 128.22, 127.51, 127.31, 127.30, 126.50, 126.27, 125.16, 124.82, 119.70, 117.04, 48.43, 45.42, 38.69. HRMS calculated for $C_{30}H_{28}N_3O_2S$ 494.18967 $[M+H]^+$, found 494.18922. LCMS (ESI, Waters, C_{18}, linear gradient, 5% → 90% ACN in H_2O 0.2% TFA, 10 min): t_R = 6.80 min; *m/z* : 494 $[M+H]^+$.

(*E*)-*N*-Methyl-*N*-(2-((3-(4-(pyridin-3-yl)phenyl)allyl)amino)ethyl)isoquinoline-5-sulfonamide (19)



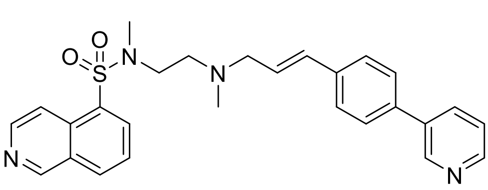
A solution of *tert*-butyl (*E*)-(2-(*N*-methylisoquinoline-5-sulfonamido)ethyl)(3-(4-(pyridine-3-yl)phenyl)allyl)carbamate (**75**) (0.768 g, 1.4 mmol, 1 eq) in $CHCl_3$ (10.4 mL) and TFA (2.6 mL) was stirred for 1.5 h. The reaction mixture was concentrated under reduced pressure and re-dissolved in sat. aqueous Na_2CO_3 solution (20 mL) and DCM (20 mL) by stirring vigorously until both phases became clear. The organic layer was collected and the aqueous layer extracted with DCM (3x20 mL), after which the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified via flash-column-chromatography (SiO_2, 0% → 10% (10% of sat. aqueous NH_3 in MeOH) in DCM) and then further by preparative HPLC (XBridge C_{18}, 0% → 20% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA salt after lyophilisation (44 mg, 5%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.54 (s, 1H), 9.05 (s, 1H), 8.90 (bs, 2H), 8.72 (d, *J* = 6.2 Hz, 1H), 8.69 (s, 2H), 8.53 (d, *J* = 8.1 Hz, 1H), 8.47 (d, *J* = 6.1 Hz, 1H), 8.37 (d, *J* = 7.4 Hz, 1H), 7.91 (t, *J* = 7.8 Hz, 1H), 7.84 (d, *J* = 7.4 Hz, 2H), 7.71 (bs, 1H), 7.65 (d, *J* = 7.8 Hz, 2H), 6.88 (d, *J* = 15.9 Hz, 1H), 6.44 – 6.35 (m, 1H), 3.86 – 3.81 (m, 2H), 3.44 (t, *J* = 6.4 Hz, 2H), 3.26 – 3.18 (m, 2H), 2.90 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 153.88, 146.69, 145.68, 145.07, 137.10, 136.54, 136.35, 136.23, 136.20, 134.81, 133.87, 132.43, 131.44, 129.27, 127.87, 127.84, 127.18, 125.35, 121.03, 117.60, 48.96, 46.15, 43.95, 35.48, 31.71. HRMS calculated for $C_{26}H_{27}N_4O_2S$ 459.18492 $[M+H]^+$, found 459.18464. LCMS (ESI, Waters, C_{18}, linear gradient, 5% → 90% ACN in H_2O 0.2% TFA, 10 min): t_R = 4.12 min; *m/z* : 459 $[M+H]^+$.

(*E*)-*N*-(2-(Methyl(3-(4-(pyridin-3-yl)phenyl)allyl)amino)ethyl)isoquinoline-5-sulfonamide (20)



(*E*)-*N*-(2-((3-(4-(pyridin-3-yl)phenyl)allyl) amino) ethyl) isoquinoline-5-sulfonamide (**1**) (158 mg, 0.35 mmol, 1 eq), formaldehyde in H_2O (36%, 30 µL, 0.39 mmol, 1.1 eq) and $NaHB(OAc)_3$ (188 mg, 0.89 mmol, 2.5 eq) were dissolved in THF (13 mL) and MeOH (2 mL) and after activated molecular sieves (3 Å) were added to the reaction, it was stirred under argon atmosphere for 16 h. The reaction was quenched with sat. aqueous NH_4Cl (2.5 mL), H_2O (7.5 mL), diluted with sat. aqueous Na_2CO_3 (25 mL) and Et_2O (30 mL) after which the organic phase was collected and the aqueous layer extracted with DCM (3x20 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated under reduced pressure and purified by preparative HPLC (Gemini C_{18}, 0% → 20% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA salt after lyophilisation (11 mg, 5%). ^1H NMR (600 MHz, DMSO-d_6) δ 9.79 (bs, 1H), 9.52 (s, 1H), 9.04 (s, 1H), 8.74 (d, *J* = 6.1 Hz, 1H), 8.71 – 8.66 (m, 1H), 8.49 (t, *J* = 5.8 Hz, 2H), 8.42 (d, *J* = 6.1 Hz, 1H), 8.39 (dd, *J* = 7.4, 1.0 Hz, 1H), 8.33 (d, *J* = 8.0 Hz, 1H), 7.87 (t, *J* = 7.8 Hz, 1H), 7.83 (d, *J* = 8.3 Hz, 2H), 7.70 – 7.66 (m, 1H), 7.65 (s, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 15.8 Hz, 1H), 6.40 (dt, *J* = 15.6, 7.2 Hz, 1H), 3.94 (dd, *J* = 19.5, 6.4 Hz, 2H), 3.30 – 3.21 (m, 1H), 3.21 – 3.11 (m, 3H), 2.81 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 153.35, 146.67, 145.63, 144.42, 138.38, 136.35, 136.31, 135.67, 135.54, 133.97, 133.70, 133.02, 130.36, 128.71, 127.69, 127.35, 126.59, 124.79, 118.39, 117.13, 57.12, 53.29, 40.06, 37.38. HRMS calculated for $C_{26}H_{27}N_4O_2S$ 459.18592 $[M+H]^+$, found 459.18460. LCMS (ESI, Waters, C_{18}, linear gradient, 5% → 90% ACN in H_2O 0.2% TFA, 10 min): t_R = 5.23 min; *m/z* : 459 $[M+H]^+$.

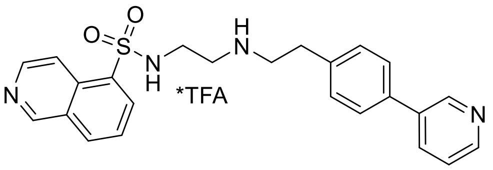
(*E*)-*N*-Methyl-*N*-(2-(methyl(3-(4-(pyridin-3-yl)phenyl)allyl)amino) ethyl)isoquinoline-5-sulfonamide (21)



To a solution of (*E*)-*N*-methyl-*N*-(2-((3-(4-(pyridin-3-yl)phenyl)allyl)amino)ethyl)isoquinoline-5-sulfonamide (**19**) (0.261 g, 0.57 mmol, 1 eq), formaldehyde in H_2O (36%, 48 µL, 0.63 mmol, 1.1 eq) and $NaHB(OAc)_3$ (300 mg, 1.4 mmol, 2.5 eq) were dissolved in THF (21 mL) and MeOH (3.5 mL) and after activated molecular sieves (3 Å) were added to the reaction, it was stirred under argon atmosphere for 16 h. The reaction was was quenched with sat. aqueous NH_4Cl (2.5 mL), H_2O (7.5 mL), diluted with sat. aqueous Na_2CO_3 (25 mL) and Et_2O (30 mL) after which the organic phase was collected and the aqueous layer extracted with DCM (3x40 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure and the resulting residue was purified via flash-column-chromatography (SiO_2, 2% → 4% MeOH in DCM, 0.5% Et_3N) to yield the product (222 mg, 82%). ^1H NMR (400 MHz, chloroform-*d*) δ 9.33 (s, 1H), 8.86 (d, *J* = 2.1 Hz, 1H), 8.68 (d, *J* = 6.1 Hz, 1H), 8.59 (dd, *J* = 4.8, 1.4 Hz, 1H), 8.52 (d, *J* = 6.1 Hz, 1H), 8.39 (d, *J* = 7.3 Hz, 1H), 8.18 (d, *J* = 8.2 Hz, 1H), 7.88 (dt, *J* = 7.9, 1.8 Hz, 1H), 7.68 (t, *J* = 7.8 Hz, 1H), 7.55 (d, *J* = 8.2 Hz, 2H), 7.46 (d, *J* = 8.2 Hz, 2H), 7.36 (dd, *J* = 7.9, 4.8 Hz, 1H), 6.53 (d, *J* = 15.9 Hz, 1H), 6.21 (dt, *J* = 15.8, 6.6 Hz, 1H), 3.37 (t, *J* = 6.9 Hz, 2H), 3.17 (d, *J* = 6.6

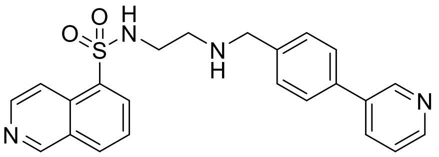
Hz, 2H), 2.92 (s, 3H), 2.61 (t, *J* = 6.9 Hz, 2H), 2.27 (s, 3H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 153.24, 148.53, 148.15, 145.11, 136.85, 136.75, 136.13, 134.13, 133.78, 133.55, 133.47, 132.12, 131.86, 129.17, 127.60, 127.32, 127.05, 125.88, 123.64, 117.83, 60.37, 54.88, 47.65, 42.41, 34.99. HRMS calculated for $C_{27}H_{29}N_4O_2S$ 473.20057 [M+H]$^+$, found 473.20031. LCMS (ESI, Waters, C_{18}, linear gradient, 5% → 90% ACN in H_2O 0.2% TFA, 10 min): t_R = 4.25 min; *m/z* : 473 [M+H]$^+$.

N-(2-((4-(Pyridin-3-yl)phenethyl)amino)ethyl)isoquinoline-5-sulfonamide (22)



2-(4-(Pyridin-3-yl)phenyl)ethan-1-ol (**77**) (96 mg, 0.48 mmol, 1 eq) was dissolved in DCM (5 mL) to which was added Dess–Martin periodinane (0.24 g, 0.58 mmol, 1.2 eq). The reaction was stirred for 2 h before it was quenched using aqueous $Na_2S_2O_3$ (3 mL), then diluted with sat. aqueous Na_2CO_3 (30 mL) and DCM (15 mL) after which the organic layer was collected and the aqueous layer extracted with DCM (5x20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure after which a silica filtration with 50% EtOAc in pentane and concentrating under reduced pressure afforded the crude aldehyde. It was re-dissolved in dry THF (2.6 mL) together with *N*-(2-aminoethyl)isoquinoline-5-sulfonamide (**105**) (0.13 g, 0.52 mmol, 1.1 eq), glacial acetic acid (15 µL, 0.26 mmol, 0.5 eq), $NaHB(OAc)_3$ (0.11 g, 0.52 mmol, 1.2 eq) and activated molecular sieves (3 Å). The reaction was stirred under argon atmosphere for 16 h after which it was diluted with sat. aqueous Na_2CO_3 (10 mL) and Et_2O (10 mL). The organic layer was collected and the aqueous layer extracted with DCM (3x10 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated under reduced pressure and purified by preparative HPLC (Gemini C_{18}, 0% → 20% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA salt after lyophilisation (13 mg, 5%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.54 (d, *J* = 0.8 Hz, 1H), 8.99 (d, *J* = 2.1 Hz, 1H), 8.74 (d, *J* = 6.1 Hz, 1H), 8.69 – 8.59 (m, 3H), 8.50 (d, *J* = 8.2 Hz, 1H), 8.44 (t, *J* = 5.8 Hz, 2H), 8.39 (dd, *J* = 7.4, 1.2 Hz, 1H), 8.29 (d, *J* = 8.1 Hz, 1H), 7.92 – 7.85 (m, 1H), 7.76 (d, *J* = 8.3 Hz, 2H), 7.67 (dd, *J* = 8.0, 5.0 Hz, 1H), 7.40 (d, *J* = 8.3 Hz, 2H), 3.22 (bs, 2H), 3.06 (s, 4H), 2.99 – 2.91 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 153.36, 146.43, 145.56, 144.44, 137.47, 136.35, 136.02, 134.77, 133.95, 133.75, 132.96, 130.38, 129.57, 128.72, 127.25, 126.59, 124.78, 117.14, 47.51, 46.28, 38.59, 31.20. HRMS calculated for $C_{24}H_{25}N_4O_2S$ 433.16927 [M+H]$^+$, found 433.16897. LCMS (ESI, Waters, C_{18}, linear gradient, 5% → 50% ACN in H_2O 0.2% TFA, 10 min): t_R = 4.89 min; *m/z* : 433 [M+H]$^+$.

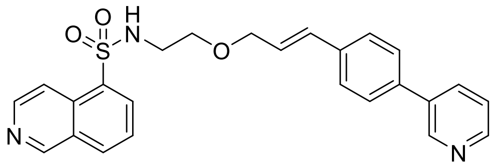
N-(2-((4-(Pyridin-3-yl)benzyl)amino)ethyl)isoquinoline-5-sulfonamide (23)



To a solution *tert*-butyl (2-(isoquinoline-5-sulfonamido)ethyl)(4-(pyridin-3-yl)benzyl)carbamate (**81**) (0.290 g, 0.56 mmol, 1 eq) in DCM (4 mL) at 0°C was added TFA (1 mL). The reaction was allowed to warm to RT and stirred for 2 h before the solvents were removed under reduced pressure. $CHCl_3$ (5 mL) and sat. aqueous Na_2CO_3 solution (10 mL) were added and the mixture was stirred vigorously until both phases became clear. The organic layer was collected and the aqueous layer extracted with $CHCl_3$ (3x15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified via flash-column-chromatography (SiO_2, 6% → 8% (10% of sat. aqueous NH_3 in MeOH) in DCM) to yield the product (174 mg, 74%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.46 (s, 1H), 8.87

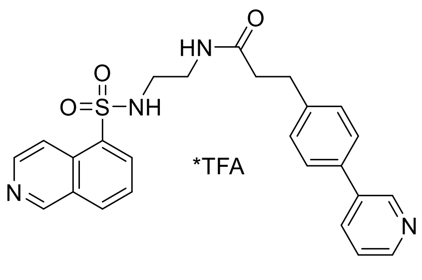
(d, *J* = 2.4 Hz, 1H), 8.68 (d, *J* = 6.0 Hz, 1H), 8.56 (dd, *J* = 4.7, 1.6 Hz, 1H), 8.45 – 8.40 (m, 2H), 8.35 (dd, *J* = 7.4, 1.1 Hz, 1H), 8.08 – 8.02 (m, 1H), 7.85 – 7.78 (m, 1H), 7.60 (d, *J* = 8.2 Hz, 2H), 7.51 – 7.44 (m, 1H), 7.25 (d, *J* = 8.1 Hz, 2H), 3.52 (s, 2H), 3.32 (bs, 2H), 2.91 (t, *J* = 6.5 Hz, 2H), 2.43 (t, *J* = 6.6 Hz, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 153.38, 148.30, 147.53, 144.56, 140.55, 135.42, 135.29, 134.91, 133.91, 133.35, 132.42, 130.34, 128.67, 128.50, 126.54, 126.40, 123.85, 117.15, 51.92, 47.76, 42.35. HRMS calculated for $C_{23}H_{23}N_4O_2S$ 419.15362 [M+H]$^+$, found 419.15328. LCMS (ESI, Waters, C_{18}, linear gradient, 5% → 50% ACN in H_2O 0.2% TFA, 10 min): t_R = 4.58 min; *m/z* : 419 [M+H]$^+$.

(*E*)-*N*-(2-((3-(4-(Pyridin-3-yl)phenyl)allyl)oxy)ethyl)isoquinoline-5-sulfonamide (24)



To a solution of (*E*)-2-((3-(4-(pyridin-3-yl)phenyl)allyl)oxy)ethan-1-amine (**84**) (95 mg, 0.37 mmol, 1 eq) and Et_3N (62 µL, 0.45 mmol, 1.2 eq) in DCM (11.6 mL) at 0°C was added dropwise an isoquinoline-5-sulfonyl chloride solution which was prepared by extracting from a solution of isoquinoline-5-sulfonyl chloride hydrochloride (**104**) (0.12 g, 0.45 mmol, 1.2 eq) in sat. aqueous $NaHCO_3$ with DCM (3x1 mL). The reaction was allowed to warm to RT and stirred for 2 h before it was quenched with aqueous NaOH (1 M, 1 mL) and subsequently diluted with sat. aqueous Na_2CO_3 solution (20 mL). The organic phase was collected and the aqueous layer was extracted with DCM (3x20 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated under reduced pressure and the crude was purified via flash-column-chromatography (SiO_2, 2% → 5% (10% of sat. aqueous NH_3 in MeOH) in DCM) and the further by preparative HPLC (C_{18}, 10% → 35% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound after lyophilisation (32 mg, 19%). ^{1}H NMR (600 MHz, methanol-d_4) δ 9.46 (s, 1H), 9.13 (s, 1H), 8.82 – 8.69 (m, 3H), 8.65 (d, *J* = 5.5 Hz, 1H), 8.61 – 8.55 (m, 1H), 8.43 (d, *J* = 7.4 Hz, 1H), 8.08 – 7.99 (m, 1H), 7.89 (dd, *J* = 12.6, 5.1 Hz, 1H), 7.77 (d, *J* = 8.3 Hz, 2H), 7.52 (d, *J* = 7.1 Hz, 2H), 6.45 (d, *J* = 15.9 Hz, 1H), 6.10 (dt, *J* = 15.9, 5.7 Hz, 1H), 3.85 (d, *J* = 5.7 Hz, 2H), 3.38 (t, *J* = 5.3 Hz, 2H), 3.21 (t, *J* = 5.2 Hz, 2H). ^{13}C NMR (151 MHz, methanol-d_4) δ 153.01, 143.08, 142.86, 142.60, 142.06, 140.85, 139.77, 137.70, 135.58, 135.08, 134.79, 133.65, 131.74, 130.51, 128.84, 128.64, 128.62, 128.56, 127.97, 120.68, 72.04, 69.80, 43.92. HRMS calculated for $C_{25}H_{24}N_3O_3S$ 446.15329 [M+H]$^+$, found 446.15301. LCMS (ESI, Waters, C_{18}, linear gradient, 5% → 50% ACN in H_2O 0.2% TFA, 10 min): t_R = 6.77 min; *m/z* : 446 [M+H]$^+$.

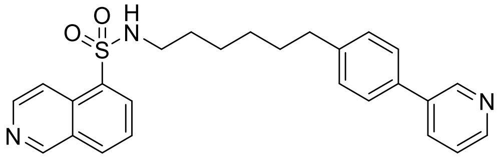
***N*-(2-(Isoquinoline-5-sulfonamido)ethyl)-3-(4-(pyridin-3-yl)phenyl)propanamide (25)**



A vial was charged with 3-(4-bromophenyl)-*N*-(2-(isoquinoline-5-sulfonamido)ethyl)propanamide (**91**) (374 mg, 0.81 mmol, 1 eq), pyridin-3-ylboronic acid (149 mg, 1.21 mmol, 1.5 eq) and $Pd(PPh_3)_4$ (10 mg, 0.01 mmol, 0.01 eq) dissolved in DCM (0.8 mL) and DMF (1.8 mL). The vial is put under an argon atmosphere and degassed aqueous K_2CO_3 (2 M, 1.0 mL, 2.02 mmol, 2.5 eq) was added. The reaction mixture was stirred at 85°C for 2.5 h, filtered over celite, concentrated under reduced pressure and purified by preparative HPLC (XBridge C_{18}, 0% → 20% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA salt after lyophilisation (27 mg, 6%). ^{1}H NMR (600 MHz, methanol-d_4) δ 9.53 (s, 1H), 9.08 (s, 1H), 8.77 – 8.71 (m, 2H), 8.67 (q, *J* = 6.4 Hz, 2H), 8.52 (dd, *J* = 7.4, 1.1 Hz, 1H), 8.47 (d, *J* = 8.2 Hz, 1H), 8.02 (dd, *J* = 8.1, 5.6 Hz, 1H), 7.91 – 7.87 (m, 1H), 7.70 (d, *J* = 8.3 Hz, 2H), 7.40

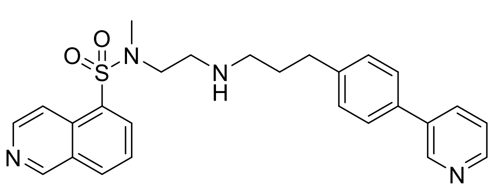
(d, *J* = 8.3 Hz, 2H), 3.15 (t, *J* = 6.3 Hz, 2H), 2.93 (t, *J* = 6.4 Hz, 4H), 2.42 (t, *J* = 7.7 Hz, 2H). ^{13}C NMR (151 MHz, methanol-*d*$_4$) δ 175.17, 153.05, 144.47, 143.63, 142.21, 142.09, 142.02, 141.27, 136.83, 135.80, 135.36, 133.49, 133.45, 130.76, 130.52, 128.65, 128.49, 128.09, 120.50, 43.07, 40.27, 38.29, 32.27. HRMS calculated for $C_{25}H_{25}N_4O_3S$ 461.16419 [M+H]$^+$, found 461.16406. LCMS (ESI, Waters, C$_{18}$, linear gradient, 5% → 50% ACN in H_2O 0.2% TFA, 10 min): t$_R$ = 5.58 min; *m/z* : 461 [M+H]$^+$.

***N*-(6-(4-(Pyridin-3-yl)phenyl)hexyl)isoquinoline-5-sulfonamide (26)**



To a solution of 6-(4-(pyridin-3-yl)phenyl)hexan-1-amine (**97**) (62 mg, 0.24 mmol, 1 eq) and Et_3N (41 µL, 0.30 mmol, 1.25 eq) in DCM (1.2 mL) at 0°C was added dropwise an isoquinoline-5-sulfonyl chloride solution which was prepared by extracting from a solution of isoquinoline-5-sulfonyl chloride hydrochloride (**104**) (77 mg, 0.29 mmol, 1.2 eq) in sat. aqueous $NaHCO_3$ with DCM (2x0.7 mL). The reaction was allowed to warm to RT and after 3 h of stirring it was concentrated onto Celite and purified via flash-column-chromatography (SiO_2, 0% → 10% (10% of sat. aqueous NH_3 in MeOH) in DCM) to yield the product (105 mg, 98%). ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 9.47 (s, 1H), 8.87 (d, *J* = 2.4 Hz, 1H), 8.70 (d, *J* = 6.1 Hz, 1H), 8.55 (dd, *J* = 4.8, 1.5 Hz, 1H), 8.45 (d, *J* = 6.1 Hz, 1H), 8.42 (d, *J* = 8.2 Hz, 1H), 8.33 (d, *J* = 7.3 Hz, 1H), 8.08 – 8.02 (m, 2H), 7.82 (t, *J* = 7.8 Hz, 1H), 7.62 (d, *J* = 8.1 Hz, 2H), 7.47 (dd, *J* = 7.9, 4.8 Hz, 1H), 7.24 (d, *J* = 8.1 Hz, 2H), 2.79 (q, *J* = 6.6 Hz, 2H), 2.45 (t, *J* = 7.5 Hz, 2H), 1.36 – 1.29 (m, 2H), 1.27 – 1.20 (m, 2H), 1.10 – 0.97 (m, 4H). ^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ 153.36, 148.13, 147.42, 144.49, 142.32, 135.51, 135.08, 134.39, 133.92, 133.28, 132.38, 130.39, 129.01, 128.67, 126.72, 126.41, 123.86, 117.25, 42.19, 34.50, 30.55, 28.76, 27.92, 25.56. HRMS calculated for $C_{26}H_{28}N_3O_2S$ 446.18967 [M+H]$^+$, found 446.18926. LCMS (ESI, Waters, C$_{18}$, linear gradient, 5% → 90% ACN in H_2O 0.2% TFA, 10 min): t$_R$ = 5.69 min; *m/z* : 446 [M+H]$^+$.

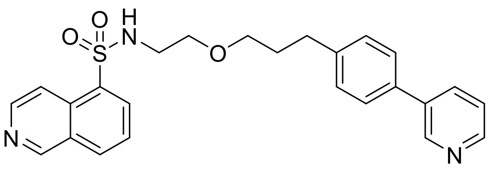
***N*-Methyl-*N*-(2-((3-(4-(pyridin-3-yl)phenyl)propyl)amino)ethyl)isoquinoline-5-sulfonamide (27)**



Acetyl chloride (35 µL, 0.49 mmol, 3 eq) was added to a vial containing MeOH (2.3 mL) and after 10 minutes of stirring (*E*)-*N*-methyl-*N*-(2-((3-(4-(pyridin-3-yl) phenyl) allyl)amino)ethyl)isoquinoline-5-sulfonamide (**19**) (75 mg, 0.16 mmol, 1 eq) and Pd/C (30 w%, 22 mg) were added and the vial was sealed. The mixture was degassed and H_2 gas was bubbled through under vigorous stirring for 1 h. The reaction was stirred for another 16 h under H_2 atmosphere until full conversion, after which aqueous NaOH (1 M, 1 mL) was added to neutralize the acid. The mixture was dried over $MgSO_4$, filtered and concentrated onto Celite. The resulting crude was purified via flash-column-chromatography (SiO_2, dry-loading, 0% → 10% (10% of sat. aqueous NH_3 in MeOH) in DCM) to yield the product (12 mg, 16%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 9.34 (s, 1H), 8.84 (d, *J* = 1.7 Hz, 1H), 8.69 (d, *J* = 6.2 Hz, 1H), 8.58 (dd, *J* = 4.8, 1.5 Hz, 1H), 8.51 (d, *J* = 6.1 Hz, 1H), 8.39 (dd, *J* = 7.4, 1.1 Hz, 1H), 8.21 (d, *J* = 8.2 Hz, 1H), 7.89 – 7.84 (m, 1H), 7.70 (t, *J* = 7.6 Hz, 1H), 7.51 (d, *J* = 8.2 Hz, 2H), 7.36 (dd, *J* = 7.9, 4.8 Hz, 1H), 7.29 (d, *J* = 8.1 Hz, 2H), 3.30 (t, *J* = 6.2 Hz, 2H), 2.89 (s, 3H), 2.82 (t, *J* = 6.2 Hz, 2H), 2.73 – 2.58 (m, 4H), 1.91 – 1.74 (m, 3H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 153.40, 148.40, 148.34, 145.32, 142.14, 136.58, 135.53, 134.29, 133.81, 133.79, 133.40, 131.98, 129.28, 129.25, 127.24, 126.02, 123.66, 117.77, 49.55, 49.06, 47.21, 34.97, 33.21, 31.50. HRMS calculated for $C_{26}H_{29}N_4O_2S$ 461.20057 [M+H]$^+$, found

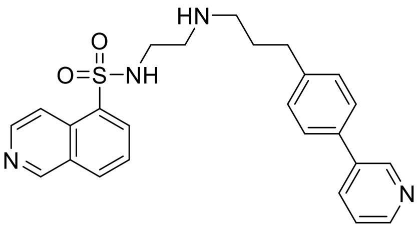
461.20029. LCMS (ESI, Waters, C_{18}, linear gradient, 5% → 90% ACN in H_2O 0.2% TFA, 10 min): t_R = 4.07 min; *m/z* : 461 $[M+H]^+$.

***N*-(2-(3-(4-(Pyridin-3-yl)phenyl)propoxy)ethyl)isoquinoline-5-sulfonamide (28)**



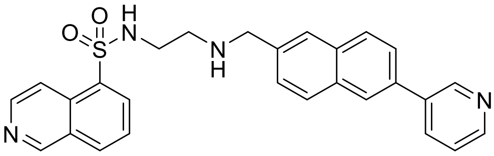
(*E*)-*N*-(2-((3-(4-(pyridin-3-yl)phenyl)allyl)oxy) ethyl) isoquinoline-5-sulfonamide (**24**) (38 mg, 0.086 mmol, 1 eq), *p*-toluenesulfonyl hydrazide (48 mg, 0.26 mmol, 3 eq) and NaOAc (21 mg, 0.26 mmol, 3 eq) were suspended in THF (0.9 mL) and heted to reflux for 3 days with daily addition of both *p*-toluenesulfonyl hydrazide and NaOAc (3x0.17 mmol). It was then diluted with sat. aqueous Na_2CO_3 and extracted with DCM (3x5 mL) after which the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified via flash-column-chromatography (SiO_2, 1% → 5% (10% of sat. aqueous NH_3 in MeOH) in DCM) and then further by preparative HPLC (C_{18}, 10% → 35% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound after lyophilisation (13 mg, 34%). ^1H NMR (500 MHz, DMSO-d_6) δ 9.51 (s, 1H), 9.06 (d, *J* = 2.1 Hz, 1H), 8.73 – 8.69 (m, 2H), 8.50 (d, *J* = 6.2 Hz, 1H), 8.48 – 8.42 (m, 2H), 8.39 (dd, *J* = 7.4, 1.2 Hz, 1H), 8.27 (t, *J* = 5.8 Hz, 1H), 7.85 (dd, *J* = 8.1, 7.5 Hz, 1H), 7.79 (dd, *J* = 8.0, 5.3 Hz, 1H), 7.71 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.3 Hz, 2H), 3.25 (t, *J* = 5.6 Hz, 2H), 3.10 (t, *J* = 6.4 Hz, 2H), 3.02 (q, *J* = 5.7 Hz, 2H), 2.50 – 2.45 (m, 2H), 1.54 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 152.92, 144.52, 143.90, 143.59, 142.77, 138.16, 137.00, 135.43, 133.41, 132.90, 132.56, 130.68, 129.19, 128.64, 127.02, 126.63, 125.43, 117.74, 69.17, 68.49, 42.29, 31.09, 30.41. HRMS calculated for $C_{25}H_{26}N_3O_3S$ 448.16894 $[M+H]^+$, found 448.16847. LCMS (ESI, Waters, C_{18}, linear gradient, 5% → 90% ACN in H_2O 0.2% TFA, 10 min): t_R = 5.01 min; *m/z* : 448 $[M+H]^+$.

***N*-(2-((3-(4-(Pyridin-3-yl)phenyl)propyl)amino)ethyl)isoquinoline-5-sulfonamide (29)**



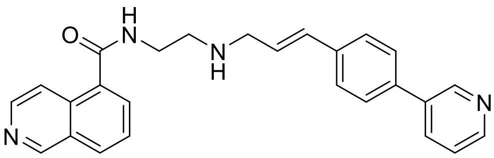
A round-bottom-flask was charged with 3-(4-(pyridin-3-yl)phenyl)propanal (**90**) (167 mg, 0.79 mmol, 1 eq), *N*-(2-aminoethyl)isoquinoline-5-sulfonamide (**105**) (397 mg, 1.58 mmol, 2 eq) and $NaHB(OAc)_3$ (318 mg, 1.58 mmol, 2 eq) suspended in DCM (79 mL). The reaction mixture was stirred overnight and half sat. aqueous Na_2CO_3 (80 mL) was added and the product was extracted with DCM (3x80 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure and the resulting residue was purified via flash-column-chromatography (SiO_2, 1% → 4% (10% of sat. aqueous NH_3 in MeOH) in DCM) to yield the product (220 mg, 62%). ^1H NMR (400 MHz, methanol-d_4) δ 9.34 (s, 1H), 8.75 (d, *J* = 2.2 Hz, 1H), 8.61 (d, *J* = 6.2 Hz, 1H), 8.54 (d, *J* = 6.2 Hz, 1H), 8.47 (dd, *J* = 4.9, 1.3 Hz, 1H), 8.45 (d, *J* = 7.4 Hz, 1H), 8.33 (d, *J* = 8.2 Hz, 1H), 8.02 (dt, *J* = 8.0, 1.8 Hz, 1H), 7.77 (t, *J* = 7.8 Hz, 1H), 7.53 (d, *J* = 8.1 Hz, 2H), 7.47 (dd, *J* = 8.0, 4.9 Hz, 1H), 7.25 (d, *J* = 8.1 Hz, 2H), 2.98 (t, *J* = 6.3 Hz, 2H), 2.61 – 2.51 (m, 4H), 2.45 – 2.36 (m, 2H), 1.63 (p, *J* = 7.6 Hz, 2H). ^{13}C NMR (101 MHz, methanol-d_4) δ 154.32, 148.45, 148.13, 144.90, 143.60, 138.40, 136.34, 136.23, 136.03, 134.82, 134.69, 132.58, 130.60, 130.26, 128.05, 127.69, 125.40, 119.12, 49.55, 49.45, 43.02, 33.96, 32.03. HRMS calculated for $C_{25}H_{27}N_4O_2S$ 447.18492 $[M+H]^+$, found 447.18461. LCMS (ESI, Waters, C_{18}, linear gradient, 5% → 50% ACN in H_2O 0.2% TFA, 10 min): t_R = 5.25 min; *m/z* : 447 $[M+H]^+$.

N-(2-(((6-(Pyridin-3-yl)naphthalen-2-yl)methyl)amino)ethyl)isoquinoline-5-sulfonamide (30)



A vial containing *tert*-butyl ((6-bromonaphthalen-2-yl)methyl)(2-(isoquinoline-5-sulfonamido) ethyl)carbamate (**102**) (0.448 g, 0.79 mmol, 1 eq), $Pd(PPh_3)_4$ (18 mg, 0.016 mmol, 0.02 eq) and pyridine-3-boronic acid (0.14 g, 1.2 mmol, 1.5 eq) was sealed and flushed with argon, after which a deoxygenated mixture of DCM (0.8 mL), DMF (1.7 mL) and aqueous K_2CO_3 solution (2M, 1 mL, 2.0 mmol, 2.5 eq) was added. After stirring at 80°C for 4 h, the mixture was cooled to ambient temperature, concentrated under reduced pressure, diluted with EtOAc, filtered over silica and concentrated again. It was re-dissolved in DCM (8 mL) and TFA (1.6 mL) and stirred for 4 h before the reaction was neutralized with sat. aqueous Na_2CO_3 solution (30 mL). DCM (30 mL) was added and the mixture was stirred vigorously until two clear phases were formed. The organic layer was collected and the aqueous layer was extracted with DCM (5x30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified via flash-column-chromatography (SiO_2, 2% → 4% (10% of sat. aqueous NH_3 in MeOH) in DCM) to yield the product (301 mg, 81%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 9.27 (s, 1H), 8.92 (d, *J* = 2.1 Hz, 1H), 8.62 – 8.56 (m, 2H), 8.47 (d, *J* = 6.1 Hz, 1H), 8.42 (d, *J* = 7.3 Hz, 1H), 8.09 (d, *J* = 8.2 Hz, 1H), 7.96 (d, *J* = 7.9 Hz, 1H), 7.91 (s, 1H), 7.78 (d, *J* = 8.5 Hz, 1H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.64 – 7.57 (m, 2H), 7.54 (s, 1H), 7.38 (dd, *J* = 7.9, 4.8 Hz, 1H), 7.26 (d, *J* = 8.4 Hz, 1H), 4.03 (bs, 2H), 3.69 (s, 2H), 3.10 – 3.04 (m, 2H), 2.70 (t, *J* = 5.6 Hz, 2H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 153.26, 148.34, 148.26, 144.98, 137.72, 136.47, 134.74, 134.66, 134.46, 133.42, 133.21, 132.70, 131.21, 128.96, 128.64, 128.50, 126.97, 126.10, 125.92, 125.85, 125.19, 123.76, 117.31, 53.18, 47.68, 42.54. HRMS calculated for $C_{27}H_{25}N_4O_2S$ 469.16927 $[M+H]^+$, found 469.16903. LCMS (ESI, Waters, C_{18}, linear gradient, 5% → 90% ACN in H_2O 0.2% TFA, 10 min): t_R = 4.17 min; *m/z* : 469 $[M+H]^+$.

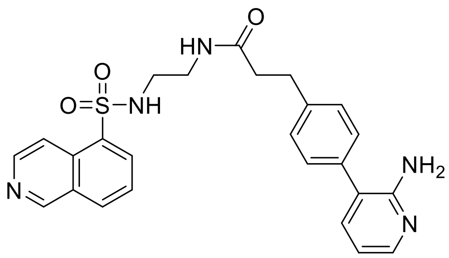
(*E*)-*N*-(2-((3-(4-(Pyridin-3-yl)phenyl)allyl)amino)ethyl)isoquinoline-5-carboxamide (31)



A round-bottom-flask was charged with *tert*-butyl (*E*)-(2-(isoquinoline-5-carboxamido)ethyl) (3-(4-(pyridin-3-yl)phenyl) allyl)carbamate (**73**) (57 mg, 0.112 mmol, 1 eq) dissolved in $CHCl_3$ (4 mL). After cooling the solution to 0°C and dropwise addition of TFA (1 mL), it was allowed to warm to RT and stirred for 60 min. The reaction was quenched by slow addition of sat. aqueous Na_2CO_3 solution (10 mL) until a pH of ~12 was reached and the mixture was extracted with DCM (3x10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified via flash-column-chromatography (SiO_2, 0% → 10% (10% of sat. aqueous NH_3 in MeOH) in DCM) to yield the product (25 mg, 55%). ^{1}H NMR (400 MHz, methanol-d_4) δ 9.28 (s, 1H), 8.79 (d, *J* = 2.1 Hz, 1H), 8.50 (dd, *J* = 4.9, 1.4 Hz, 1H), 8.46 (d, *J* = 6.1 Hz, 1H), 8.24 – 8.19 (m, 2H), 8.09 (dt, *J* = 8.0, 1.9 Hz, 1H), 8.04 – 7.99 (m, 1H), 7.75 – 7.69 (m, 1H), 7.62 (d, *J* = 8.3 Hz, 2H), 7.54 (d, *J* = 8.3 Hz, 2H), 7.50 (dd, *J* = 8.0, 4.9 Hz, 1H), 6.69 (d, *J* = 15.9 Hz, 1H), 6.44 (dt, *J* = 15.9, 6.5 Hz, 1H), 3.67 (t, *J* = 6.4 Hz, 2H), 3.53 (d, *J* = 6.5 Hz, 2H), 2.98 (t, *J* = 6.4 Hz, 2H). ^{13}C NMR (101 MHz, methanol-d_4) δ 169.53, 152.33, 147.35, 146.78, 142.47, 137.17, 136.77, 136.23, 134.89, 133.17, 132.89, 131.72, 130.34, 130.18, 128.84, 127.42, 126.92, 126.90, 126.73, 124.12, 118.65, 50.64, 47.56, 39.07. HRMS calculated for $C_{26}H_{25}N_4O$ 409.20229 $[M+H]^+$, found

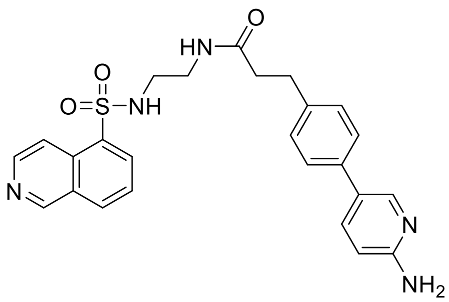
409.20208. LCMS (ESI, Waters, C_{18}, linear gradient, 5% → 50% ACN in H_2O 0.2% TFA, 10 min): t_R = 4.69 min; *m/z* : 409 $[M+H]^+$.

3-(4-(2-Aminopyridin-3-yl)phenyl)-*N*-(2-(isoquinoline-5-sulfonamido) ethyl)propanamide (32)



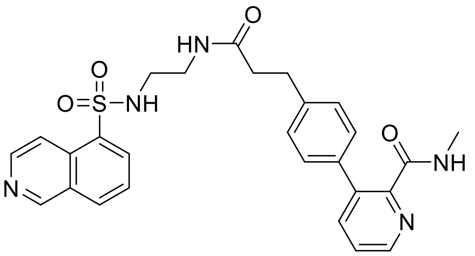
The title compound was synthesized from 3-bromopyridin-2-amine following general procedure B on a 0.29 mmol scale and purified by preparative HPLC (Gemini C_{18}, 10% → 35% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound after lyophilisation (52 mg, 38%). ^1H NMR (600 MHz, methanol-d_4) δ 9.44 (s, 1H), 8.63 (d, *J* = 6.2 Hz, 1H), 8.59 (d, *J* = 6.2 Hz, 1H), 8.48 (dd, *J* = 7.3, 1.1 Hz, 1H), 8.42 (d, *J* = 8.2 Hz, 1H), 7.88 (dd, *J* = 6.4, 1.6 Hz, 1H), 7.86 – 7.83 (m, 1H), 7.81 (dd, *J* = 7.3, 1.2 Hz, 1H), 7.36 (s, 4H), 7.00 (t, *J* = 6.8 Hz, 1H), 3.17 (t, *J* = 6.3 Hz, 2H), 2.93 (t, *J* = 6.3 Hz, 2H), 2.89 (t, *J* = 7.7 Hz, 2H), 2.40 (t, *J* = 7.7 Hz, 2H). ^{13}C NMR (151 MHz, methanol-d_4) δ 175.24, 154.38, 153.72, 145.07, 143.82, 143.63, 143.59, 136.55, 135.68, 135.14, 135.07, 132.99, 132.77, 130.61, 129.79, 128.20, 128.13, 119.81, 114.36, 43.09, 40.28, 38.26, 32.38. HRMS calculated for $C_{25}H_{26}N_5O_3S$ 476.17509 $[M+H]^+$, found 476.17485. LCMS (ESI, Thermo, C_{18}, linear gradient, 10% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 4.70 min; *m/z* : 476 $[M+H]^+$.

3-(4-(6-Aminopyridin-3-yl)phenyl)-*N*-(2-(isoquinoline-5-sulfonamido) ethyl)propanamide (33)



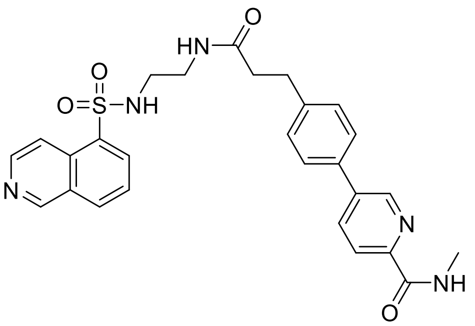
The title compound was synthesized from 5-bromopyridin-2-amine following general procedure B on a 0.1 mmol scale and purified by preparative HPLC (Gemini C_{18}, 10% → 35% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound after lyophilisation (24 mg, 50%). ^1H NMR (600 MHz, methanol-d_4) δ 9.44 (s, 1H), 8.64 (d, *J* = 6.2 Hz, 1H), 8.58 (d, *J* = 6.2 Hz, 1H), 8.46 (dd, *J* = 7.3, 1.1 Hz, 1H), 8.42 (d, *J* = 8.2 Hz, 1H), 8.22 (dd, *J* = 9.3, 2.3 Hz, 1H), 8.05 (d, *J* = 2.1 Hz, 1H), 7.84 (dd, *J* = 8.2, 7.3 Hz, 1H), 7.50 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.3 Hz, 2H), 7.08 (dd, *J* = 9.3, 0.8 Hz, 1H), 3.14 (t, *J* = 6.3 Hz, 2H), 2.92 – 2.85 (m, 4H), 2.38 (t, *J* = 7.7 Hz, 2H). ^{13}C NMR (151 MHz, methanol-d_4) δ 175.27, 154.78, 153.84, 144.47, 143.80, 142.84, 136.58, 135.02, 134.99, 133.77, 133.21, 132.96, 130.64, 130.46, 128.07, 127.66, 127.33, 119.74, 115.09, 43.06, 40.26, 38.43, 32.24. HRMS calculated for $C_{25}H_{26}N_5O_3S$ 476.17509 $[M+H]^+$, found 476.17485. LCMS (ESI, Thermo, C_{18}, linear gradient, 10% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 4.75 min; *m/z* : 476 $[M+H]^+$.

3-(4-(3-((2-(Isoquinoline-5-sulfonamido)ethyl)amino)-3-oxopropyl)phenyl)-*N*-methylpicolinamide (34)



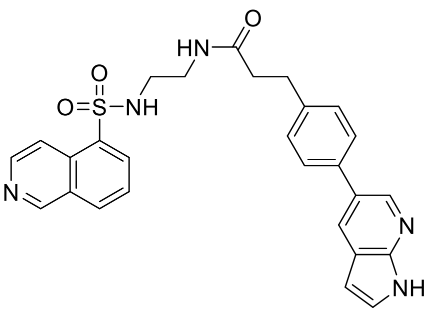
The title compound was synthesized from 3-bromo-*N*-methylpicolinamide following general procedure B on a 0.1 mmol scale and purified by preparative HPLC (Gemini C_{18}, 10% → 35% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound after lyophilisation (15 mg, 29%). ^{1}H NMR (600 MHz, methanol-d_4) δ 9.40 (s, 1H), 8.62 (d, *J* = 6.2 Hz, 1H), 8.55 (d, *J* = 6.3 Hz, 2H), 8.45 (dd, *J* = 7.3, 1.0 Hz, 1H), 8.38 (d, *J* = 8.2 Hz, 1H), 7.83 – 7.78 (m, 2H), 7.55 (dd, *J* = 7.8, 4.8 Hz, 1H), 7.27 (d, *J* = 8.2 Hz, 2H), 7.21 (d, *J* = 8.2 Hz, 2H), 3.15 (t, *J* = 6.4 Hz, 2H), 2.89 (t, *J* = 6.4 Hz, 2H), 2.86 (t, *J* = 7.6 Hz, 2H), 2.77 (s, 3H), 2.36 (t, *J* = 7.7 Hz, 2H). ^{13}C NMR (151 MHz, methanol-d_4) δ 175.36, 170.25, 154.02, 152.51, 148.26, 144.18, 142.01, 140.40, 137.67, 137.38, 136.48, 134.94, 134.90, 132.84, 130.65, 129.60, 129.50, 127.91, 126.33, 119.57, 43.05, 40.36, 38.67, 32.43, 26.43. HRMS calculated for $C_{27}H_{28}N_5O_4S$ 518.18565 $[M+H]^+$, found 518.18541. LCMS (ESI, Thermo, C_{18}, linear gradient, 10% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 5.09 min; *m/z* : 518 $[M+H]^+$.

5-(4-(3-((2-(Isoquinoline-5-sulfonamido)ethyl)amino)-3-oxopropyl)phenyl)-*N*-methylpicolinamide (35)



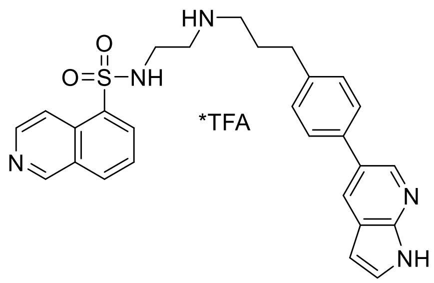
The title compound was synthesized from 5-bromo-*N*-methylpicolinamide following general procedure B on a 0.1 mmol scale and purified by preparative HPLC (Gemini C_{18}, 10% → 35% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound after lyophilisation (26 mg, 50%). ^{1}H NMR (600 MHz, methanol-d_4) δ 9.50 (s, 1H), 8.81 (s, 1H), 8.68 – 8.63 (m, 2H), 8.49 (dd, *J* = 7.4, 1.1 Hz, 1H), 8.44 (d, *J* = 8.2 Hz, 1H), 8.14 – 8.06 (m, 2H), 7.89 – 7.84 (m, 1H), 7.59 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.2 Hz, 2H), 3.16 (t, *J* = 6.4 Hz, 2H), 2.99 (s, 3H), 2.89 (t, *J* = 7.3 Hz, 4H), 2.40 (t, *J* = 7.7 Hz, 2H). ^{13}C NMR (151 MHz, methanol-d_4) δ 175.29, 167.27, 153.16, 149.51, 147.91, 143.02, 142.26, 140.22, 136.83, 136.39, 135.98, 135.63, 135.28, 133.43, 130.52, 130.41, 128.55, 128.31, 123.00, 120.40, 43.03, 40.32, 38.49, 32.34, 26.41. HRMS calculated for $C_{27}H_{28}N_5O_4S$ 518.18565 $[M+H]^+$, found 518.18522. LCMS (ESI, Thermo, C_{18}, linear gradient, 10% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 6.41 min; *m/z* : 518 $[M+H]^+$.

3-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-5-yl)phenyl)-*N*-(2-(isoquinoline-5-sulfonamido) ethyl)propanamide (36)



The title compound was synthesized from 5-bromo-1*H*-pyrrolo[2,3-*b*]pyridine following general procedure B on a 0.1 mmol scale and purified by preparative HPLC (Gemini C_{18}, 10% → 35% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound after lyophilisation (36 mg, 72%). ^{1}H NMR (600 MHz, methanol-d_4) δ 9.53 (s, 1H), 8.72 (d, *J* = 6.4 Hz, 1H), 8.65 (d, *J* = 6.4 Hz, 1H), 8.59 (d, *J* = 1.8 Hz, 1H), 8.54 – 8.50 (m, 2H), 8.45 (d, *J* = 8.2 Hz, 1H), 7.89 (t, *J* = 7.8 Hz, 1H), 7.62 (d, *J* = 3.5 Hz, 1H), 7.59 (d, *J* = 8.1 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 6.76 (d, *J* = 3.5 Hz, 1H), 3.16 (t, *J* = 6.4 Hz, 2H), 2.94 – 2.89 (m, 4H), 2.42 (t, *J* = 7.7 Hz, 2H). ^{13}C NMR (151 MHz, methanol-d_4) δ 173.94, 151.16, 141.78, 140.76, 139.63, 135.65, 134.97, 134.91, 134.67, 134.04, 132.38, 132.21, 129.63, 129.02, 128.99, 128.64, 127.51, 127.03, 124.37, 119.51, 101.97, 41.68, 38.90, 37.13, 30.89. HRMS calculated for $C_{27}H_{26}N_5O_3S$ 500.17509 [M+H]$^+$, found 500.17487. LCMS (ESI, Thermo, C_{18}, linear gradient, 10% → 90% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 4.19 min; *m/z* : 486 [M+H]$^+$.

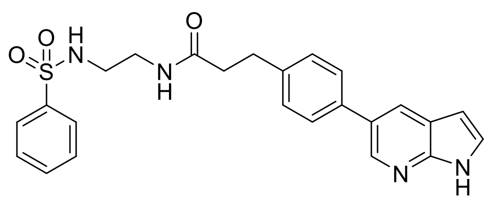
***N*-(2-((3-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-5-yl)phenyl)propyl)amino)ethyl)isoquinoline-5-sulfonamide (37)**



Step 1: A round-bottom-flask was charged with 3-(4-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)phenyl) propan-1-ol (**109**) (182 mg, 0.72 mmol, 1 eq) dissolved in DCM (4 mL). After addition of Dess–Martin periodinane (337 mg, 0.79 mmol, 1.1 eq) the reaction-mixture was stirred for 60 min and the reaction mixture was quenched with sat. aqueous $NaHCO_3$ (5 mL) and aqueous $Na_2S_2O_3$ (1 M, 5 mL). The product was extracted with DCM (3x15 mL), the combined organic layers dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was used without further purification in step 2.

Step 2: A round-bottom-flask was charged with crude from step 1 (181 mg, 0.72 mmol, 1 eq), *N*-(2-aminoethyl)isoquinoline-5-sulfonamide (**105**) (364 mg, 1.45 mmol, 2 eq) and $NaHB(OAc)_3$ (307 mg, 1.45 mmol, 2 eq) suspended in DCM (8 mL). After addition of AcOH (90 µL, 1.45 mmol, 2 eq) the reaction mixture was stirred overnight, diluted with DCM (10 mL) and sat. aqueous Na_2CO_3 (10 mL) and extracted with DCM (3x25 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated under reduced pressure and the resulting residue was purified by preparative HPLC (Gemini C_{18}, 15% → 25% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA-salt after lyophilisation (53 mg, 12% over 2 steps). ^{1}H NMR (400 MHz, methanol-d_4) δ 9.63 (s, 1H), 8.78 (d, *J* = 6.5 Hz, 1H), 8.71 – 8.68 (m, 2H), 8.63 – 8.53 (m, 3H), 7.96 (t, *J* = 7.9 Hz, 1H), 7.70 – 7.64 (m, 3H), 7.41 (d, *J* = 8.1 Hz, 2H), 6.82 (d, *J* = 3.5 Hz, 1H), 3.17 (bs, 4H), 3.14 – 3.07 (m, 2H), 2.80 (t, *J* = 7.7 Hz, 2H), 2.13 – 2.04 (m, 2H). ^{13}C NMR (101 MHz, methanol-d_4) δ 151.11, 140.95, 140.47, 139.42, 135.46, 134.88, 134.68, 134.51, 133.88, 133.08, 132.49, 129.61, 129.09, 129.07, 129.02, 127.69, 127.25, 125.01, 119.53, 102.23, 47.07, 47.04, 38.66, 31.73, 27.32. HRMS calculated for $C_{27}H_{28}N_5O_2S$ 486.19582 [M+H]$^+$, found 486.19561. LCMS (ESI, Thermo, C_{18}, linear gradient, 10% → 90% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 4.19 min; *m/z* : 486 [M+H]$^+$.

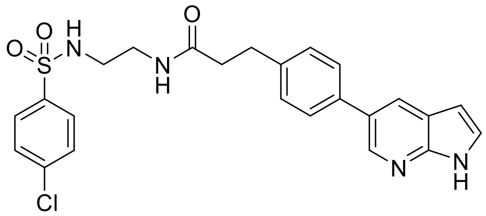
3-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-5-yl)phenyl)-*N*-(2-(phenylsulfonamido)ethyl) propanamide (38)



The title compound was synthesized from benzenesulfonyl chloride following general procedure C and purified by flash-column-chromatography (SiO_2, 2% → 8% (10% of sat. aqueous NH_3 in MeOH) in DCM) and preparative HPLC (Gemini C_{18}, 30% → 40% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound after lyophilisation (48 mg, 66%). ^{1}H NMR (500 MHz, methanol-d_4) δ 8.70 (d, *J* = 1.4 Hz, 1H), 8.57 (s, 1H), 7.82 – 7.78 (m, 2H), 7.66 (d, *J* = 3.5 Hz, 1H), 7.62 (d, *J* = 8.1 Hz, 2H), 7.57 (d, *J* = 7.2 Hz, 1H), 7.52 (t, *J* = 7.4 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 6.82 (d, *J* = 3.5 Hz, 1H), 3.20 (t, *J* = 6.4

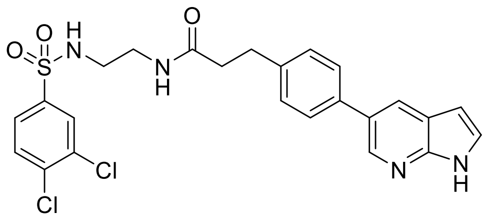
Hz, 2H), 2.96 (t, *J* = 7.6 Hz, 2H), 2.87 (t, *J* = 6.4 Hz, 2H), 2.50 (t, *J* = 7.6 Hz, 2H). ^{13}C NMR (126 MHz, methanol-d_4) δ 175.39, 162.13, 142.45, 142.12, 141.68, 135.93, 135.17, 134.70, 133.64, 131.18, 130.47, 130.23, 128.48, 127.90, 126.49, 103.69, 43.26, 40.28, 38.61, 32.35. HRMS calculated for $C_{24}H_{25}N_4O_3S$ 449.16419 [M+H]$^+$, found 449.16412. LCMS (ESI, Thermo, C_{18}, linear gradient, 0% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 7.73 min; *m/z* : 449 [M+H]$^+$.

3-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-5-yl)phenyl)-*N*-(2-((4-chlorophenyl)sulfonamido) ethyl)propanamide (39)



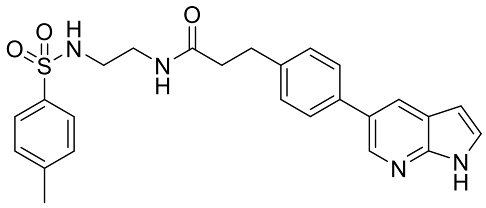
The title compound was synthesized from 4-chlorophenylsulfonylchloride following general procedure C and purified by flash-column-chromatography (SiO_2, 0% → 4% (10% of sat. aqueous NH_3 in MeOH) in DCM) and preparative HPLC (Gemini C_{18}, 30% → 40% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound after lyophilisation (38 mg, 49%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.69 (s, 1H), 8.47 (d, *J* = 2.0 Hz, 1H), 8.15 (d, *J* = 1.9 Hz, 1H), 7.91 (t, *J* = 5.8 Hz, 1H), 7.84 – 7.76 (m, 3H), 7.66 (d, *J* = 8.6 Hz, 2H), 7.59 (d, *J* = 8.1 Hz, 2H), 7.53 – 7.48 (m, 1H), 7.27 (d, *J* = 8.1 Hz, 2H), 6.49 (dd, *J* = 3.2, 1.6 Hz, 1H), 3.08 (q, *J* = 6.5 Hz, 2H), 2.82 (t, *J* = 7.7 Hz, 2H), 2.76 (d, *J* = 6.9 Hz, 2H), 2.36 (t, *J* = 7.8 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.56, 147.96, 141.38, 139.89, 139.19, 137.29, 136.74, 129.39, 128.85, 128.45, 128.04, 126.90, 126.75, 125.82, 119.67, 100.11, 42.01, 38.42, 36.92, 30.57. HRMS calculated for $C_{24}H_{24}ClN_4O_3S$ 483.12522 [M+H]$^+$, found 483.12522. LCMS (ESI, Thermo, C_{18}, linear gradient, 10% → 90% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 5.64 min; *m/z* : 483 [M+H]$^+$.

3-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-5-yl)phenyl)-*N*-(2-((3,4-dichlorophenyl) sulfonamido)ethyl)propanamide (40)



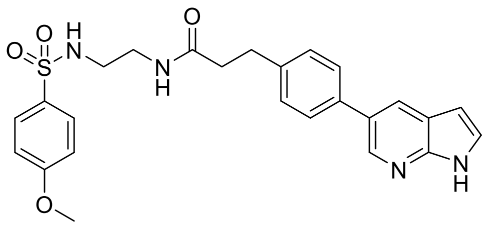
The title compound was synthesized from 3,4-dichlorobenzenesulfonyl chloride following general procedure C and purified by flash-column-chromatography (SiO_2, 0% → 5% (10% of sat. aqueous NH_3 in MeOH) in DCM) and preparative HPLC (Gemini C_{18}, 35% → 45% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound after lyophilisation (40 mg, 48%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.70 (s, 1H), 8.47 (d, *J* = 2.1 Hz, 1H), 8.16 (d, *J* = 1.9 Hz, 1H), 7.97 (d, *J* = 2.1 Hz, 1H), 7.95 – 7.90 (m, 2H), 7.87 (d, *J* = 8.4 Hz, 1H), 7.74 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.59 (d, *J* = 8.2 Hz, 2H), 7.52 – 7.48 (m, 1H), 7.28 (d, *J* = 8.2 Hz, 2H), 6.49 (dd, *J* = 3.4, 1.8 Hz, 1H), 3.09 (q, *J* = 6.5 Hz, 2H), 2.81 (p, *J* = 7.2, 6.6 Hz, 4H), 2.41 – 2.33 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.59, 147.91, 141.33, 140.70, 139.83, 136.73, 135.53, 132.15, 131.71, 128.84, 128.30, 128.04, 126.91, 126.76, 126.69, 125.87, 119.71, 100.12, 42.03, 38.41, 36.91, 30.57. HRMS calculated for $C_{24}H_{23}Cl_2N_4O_3S$ 517.08624 [M+H]$^+$, found 517.08602. LCMS (ESI, Thermo, C_{18}, linear gradient, 0% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 9.07 min; *m/z* : 517 [M+H]$^+$.

3-(4-(1*H*-Pyrrolo[2,3-b]pyridin-5-yl)phenyl)-*N*-(2-((4-methylphenyl) sulfonamido)ethyl)propanamide (41)



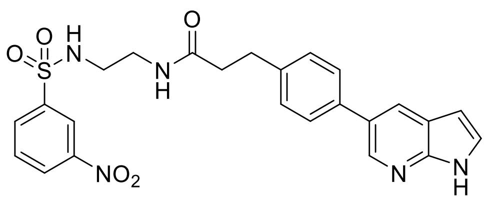
The title compound was synthesized from *p*-tosylsulfonylchloride following general procedure C and purified by preparative HPLC (Gemini, C_{18}, 30% → 40% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound after lyophilisation (71 mg, 95%). ^1H NMR (500 MHz, DMSO-d_6) δ 11.88 (s, 1H), 8.52 (d, *J* = 2.1 Hz, 1H), 8.27 (d, *J* = 2.0 Hz, 1H), 7.91 (t, *J* = 5.8 Hz, 1H), 7.65 (d, *J* = 8.2 Hz, 2H), 7.62 – 7.58 (m, 3H), 7.57 – 7.54 (m, 1H), 7.36 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 8.2 Hz, 2H), 6.55 (dd, *J* = 3.3, 1.9 Hz, 1H), 3.07 (q, *J* = 6.6 Hz, 2H), 2.82 (t, *J* = 7.7 Hz, 2H), 2.70 (q, *J* = 6.6 Hz, 2H), 2.38 – 2.35 (m, 2H), 2.34 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 171.57, 146.64, 142.72, 140.17, 140.14, 137.39, 136.28, 129.69, 128.94, 128.17, 127.48, 127.13, 126.84, 126.56, 120.55, 100.53, 42.07, 36.93, 30.61, 20.97. HRMS calculated for $C_{25}H_{27}N_4O_3S$ 463.17984 $[M+H]^+$, found 463.17975. LCMS (ESI, Thermo, C_{18}, linear gradient, 10% → 90% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 5.47 min; *m/z* : 463 $[M+H]^+$.

3-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-5-yl)phenyl)-*N*-(2-((4-methoxyphenyl) sulfonamido)ethyl)propanamide (42)



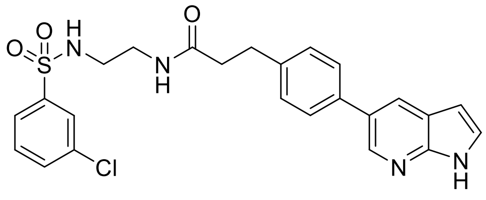
The title compound was synthesized from 4-methoxybenzenesulfonyl chloride following general procedure C and purified by preparative HPLC (Gemini, C_{18}, 30% → 40% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound after lyophilisation (64 mg, 83%). ^1H NMR (500 MHz, DMSO-d_6) δ 11.98 (s, 1H), 8.55 (d, *J* = 1.9 Hz, 1H), 8.34 (d, *J* = 1.9 Hz, 1H), 7.91 (t, *J* = 5.8 Hz, 1H), 7.73 – 7.68 (m, 2H), 7.61 (d, *J* = 8.2 Hz, 2H), 7.59 – 7.57 (m, 1H), 7.52 (t, *J* = 6.0 Hz, 1H), 7.29 (d, *J* = 8.2 Hz, 2H), 7.12 – 7.05 (m, 2H), 6.58 (dd, *J* = 3.4, 1.8 Hz, 1H), 3.80 (s, 3H), 3.07 (q, *J* = 6.5 Hz, 2H), 2.83 (t, *J* = 7.7 Hz, 2H), 2.70 (q, *J* = 6.5 Hz, 2H), 2.37 (t, *J* = 7.8 Hz, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 171.60, 162.18, 145.82, 140.36, 139.35, 136.00, 131.92, 128.98, 128.72, 128.24, 127.94, 127.83, 126.91, 121.10, 114.39, 100.79, 55.66, 42.10, 38.45, 36.94, 30.63. HRMS calculated for $C_{25}H_{27}N_4O_4S$ 479.17475 $[M+H]^+$, found 479.17450. LCMS (ESI, Thermo, C_{18}, linear gradient, 0% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 7.85 min; *m/z* : 479 $[M+H]^+$.

3-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-5-yl)phenyl)-*N*-(2-((3-nitrophenyl)sulfonamido) ethyl)propanamide (43)



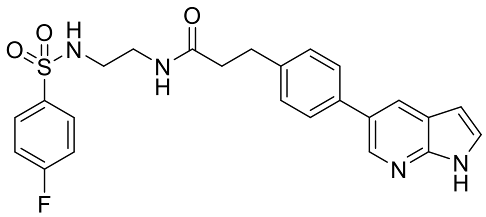
The title compound was synthesized from 3-nitrobenzenesulfonyl chloride following general procedure C and purified by flash-column-chromatography (SiO_2, 5% (10% of sat. aqueous NH_3 in MeOH) in DCM) and preparative HPLC (Gemini C_{18}, 30% → 40% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound after lyophilisation (33 mg, 41%). ^1H NMR (400 MHz, methanol-d_4) δ 8.73 (d, *J* = 1.8 Hz, 1H), 8.62 – 8.53 (m, 2H), 8.42 (dd, *J* = 8.2, 1.4 Hz, 1H), 8.18 (d, *J* = 7.9 Hz, 1H), 7.80 (t, *J* = 8.0 Hz, 1H), 7.67 (d, *J* = 3.5 Hz, 1H), 7.64 (d, *J* = 8.2 Hz, 2H), 7.38 (d, *J* = 8.2 Hz, 2H), 6.84 (d, *J* = 3.5 Hz, 1H), 3.21 (t, *J* = 6.4 Hz, 2H), 2.97 (t, *J* = 7.6 Hz, 2H), 2.93 (t, *J* = 6.4 Hz, 2H), 2.51 (t, *J* = 7.6 Hz, 2H). ^{13}C NMR (101 MHz, methanol-d_4) δ 175.41, 149.72, 143.98, 142.55, 141.77, 135.80, 135.07, 134.77, 133.58, 132.03, 131.23, 130.65, 130.50, 128.49, 128.00, 126.75, 122.79, 103.82, 43.24, 40.27, 38.56, 32.32. HRMS calculated for $C_{24}H_{24}N_5O_5S$ 494.14927 [M+H]$^+$, found 494.14886. LCMS (ESI, Thermo, C_{18}, linear gradient, 10% → 90% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 5.36 min; *m/z* : 494 [M+H]$^+$.

3-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-5-yl)phenyl)-*N*-(2-((3-chlorophenyl)sulfonamido) ethyl)propanamide (44)



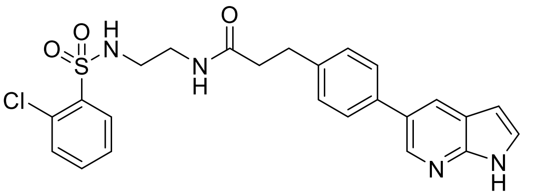
The title compound was synthesized from 3-chlorobenzenesulfonyl chloride following general procedure C and purified by flash-column-chromatography (SiO_2, 5% (10% of sat. aqueous NH_3 in MeOH) in DCM) and preparative HPLC (Gemini C_{18}, 30% → 40% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound after lyophilisation (14 mg, 18%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.76 (s, 1H), 8.48 (d, *J* = 2.0 Hz, 1H), 8.21 (d, *J* = 2.0 Hz, 1H), 7.92 (t, *J* = 5.7 Hz, 1H), 7.85 (t, *J* = 5.9 Hz, 1H), 7.78 (t, *J* = 1.7 Hz, 1H), 7.76 – 7.68 (m, 2H), 7.64 – 7.56 (m, 3H), 7.54 – 7.49 (m, 1H), 7.28 (d, *J* = 8.1 Hz, 2H), 6.55 – 6.49 (m, 1H), 3.09 (q, *J* = 6.5 Hz, 2H), 2.82 (t, *J* = 7.7 Hz, 2H), 2.79 – 2.73 (m, 2H), 2.36 (t, *J* = 7.7 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.82, 147.31, 142.29, 140.78, 140.11, 136.57, 133.99, 132.57, 131.48, 128.99, 128.21, 127.29, 126.89, 126.65, 126.17, 125.32, 120.26, 100.47, 42.10, 38.53, 37.00, 30.67. HRMS calculated for $C_{24}H_{24}ClN_4O_3S$ 483.12522 [M+H]$^+$, found 483.12498. LCMS (ESI, Thermo, C_{18}, linear gradient, 10% → 90% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 5.53 min; *m/z* : 483 [M+H]$^+$.

3-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-5-yl)phenyl)-*N*-(2-((4-fluorophenyl)sulfonamido) ethyl)propanamide (45)



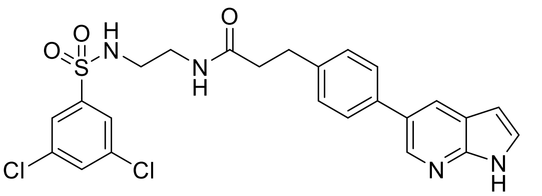
The title compound was synthesized from 4-fluorobenzenesulfonyl chloride following general procedure C and purified by flash-column-chromatography (SiO_2, 5% (10% of sat. aqueous NH_3 in MeOH) in DCM) and preparative HPLC (Gemini, C_{18}, 25% → 35% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound after lyophilisation (18 mg, 24%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.72 (s, 1H), 8.48 (d, *J* = 2.1 Hz, 1H), 8.19 (d, *J* = 2.0 Hz, 1H), 7.92 (t, *J* = 5.8 Hz, 1H), 7.87 – 7.80 (m, 2H), 7.73 (t, *J* = 6.0 Hz, 1H), 7.58 (d, *J* = 8.2 Hz, 2H), 7.52 – 7.49 (m, 1H), 7.45 – 7.37 (m, 2H), 7.27 (d, *J* = 8.2 Hz, 2H), 6.51 (dd, *J* = 3.4, 1.8 Hz, 1H), 3.08 (q, *J* = 6.5 Hz, 2H), 2.82 (t, *J* = 7.7 Hz, 2H), 2.74 (q, *J* = 6.5 Hz, 2H), 2.36 (t, *J* = 7.7 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.84, 164.22 (d, *J* = 250.8 Hz), 147.57, 141.03, 140.07, 136.76 (d, *J* = 3.1 Hz), 136.66, 129.62 (d, *J* = 9.5 Hz), 129.00, 128.20, 127.20, 126.89, 126.42, 120.11, 116.50 (d, *J* = 22.6 Hz), 100.42, 42.10, 38.55, 37.02, 30.69. HRMS calculated for $C_{24}H_{24}FN_4O_3S$ 467.15477 [M+H]$^+$, found 467.15439. LCMS (ESI, Thermo, C_{18}, linear gradient, 10% → 90% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 5.24 min; *m/z* : 467 [M+H]$^+$.

3-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-5-yl)phenyl)-*N*-(2-((2-chlorophenyl) sulfonamido)ethyl)propanamide (46)



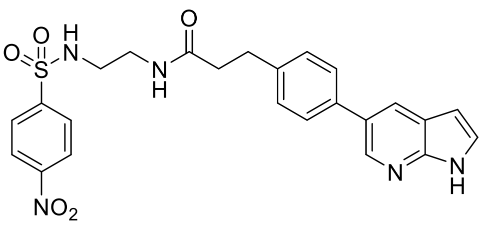
The title compound was synthesized from 2-chlorobenzenesulfonyl chloride following general procedure C and purified by flash-column-chromatography (SiO_2, 5% (10% of sat. aqueous NH_3 in MeOH) in DCM) and preparative HPLC (Gemini C_{18}, 25% → 35% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound after lyophilisation (38 mg, 49%). ^1H NMR (400 MHz, methanol-d_4) δ 8.66 (d, *J* = 1.8 Hz, 1H), 8.55 (d, *J* = 1.6 Hz, 1H), 8.03 – 7.98 (m, 1H), 7.64 (d, *J* = 3.5 Hz, 1H), 7.62 (d, *J* = 8.2 Hz, 2H), 7.56 – 7.53 (m, 2H), 7.47 – 7.40 (m, 1H), 7.36 (d, *J* = 8.2 Hz, 2H), 6.81 (d, *J* = 3.5 Hz, 1H), 3.21 (t, *J* = 6.4 Hz, 2H), 2.97 (t, *J* = 7.6 Hz, 2H), 2.91 (t, *J* = 6.4 Hz, 2H), 2.50 (t, *J* = 7.6 Hz, 2H). ^{13}C NMR (101 MHz, methanol-d_4) δ 175.42, 142.57, 142.36, 138.97, 136.14, 135.66, 134.97, 134.30, 132.90, 132.70, 132.09, 131.15, 130.46, 130.29, 128.47, 128.39, 126.22, 103.57, 43.13, 40.31, 38.64, 32.34. HRMS calculated for $C_{24}H_{24}ClN_4O_3S$ 483.12522 $[M+H]^+$, found 483.12502. LCMS (ESI, Thermo, C_{18}, linear gradient, 10% → 90% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 5.28 min; *m/z* : 483 $[M+H]^+$.

3-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-5-yl)phenyl)-*N*-(2-((3,5-dichlorophenyl) sulfonamido)ethyl)propanamide (47)



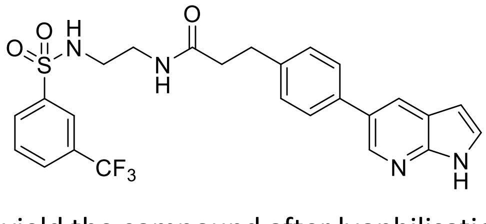
The title compound was synthesized from 3,5-dichlorobenzenesulfonyl chloride following general procedure C and purified by flash-column-chromatography (SiO_2, 5% (10% of sat. aqueous NH_3 in MeOH) in DCM) and preparative HPLC (Gemini, C_{18}, 30% → 40% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound after lyophilisation (29 mg, 35%). ^1H NMR (400 MHz, DMSO-d_6) δ 11.78 (s, 1H), 8.49 (s, 1H), 8.22 (s, 1H), 7.99 (t, *J* = 5.9 Hz, 1H), 7.96 – 7.90 (m, 2H), 7.76 (d, *J* = 1.9 Hz, 2H), 7.59 (d, *J* = 8.2 Hz, 2H), 7.52 (t, *J* = 2.7 Hz, 1H), 7.28 (d, *J* = 8.2 Hz, 2H), 6.53 (dd, *J* = 3.0, 1.6 Hz, 1H), 3.10 (q, *J* = 6.4 Hz, 2H), 2.87 – 2.77 (m, 4H), 2.37 (t, *J* = 7.7 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.85, 147.08, 143.59, 140.57, 140.15, 136.51, 135.22, 132.26, 129.00, 128.22, 127.37, 126.90, 125.19, 120.40, 100.54, 42.13, 38.52, 37.00, 30.68. HRMS calculated for $C_{24}H_{23}Cl_2N_4O_3S$ 517.08624 $[M+H]^+$, found 517.08618. LCMS (ESI, Thermo, C_{18}, linear gradient, 10% → 90% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 6.00 min; *m/z* : 517 $[M+H]^+$.

3-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-5-yl)phenyl)-*N*-(2-((4-nitrophenyl) sulfonamido)ethyl)propanamide (48)



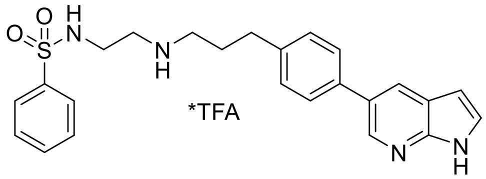
The title compound was synthesized from 4-nitrobenzenesulfonyl chloride following general procedure C and purified by flash-column-chromatography (SiO_2, 5% (10% of sat. aqueous NH_3 in MeOH) in DCM) and preparative HPLC (Gemini, C_{18}, 25% → 35% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound after lyophilisation (29 mg, 36%). ^1H NMR (400 MHz, DMSO-d_6) δ 11.87 (s, 1H), 8.51 (d, *J* = 1.8 Hz, 1H), 8.40 (d, *J* = 8.8 Hz, 2H), 8.28 (d, *J* = 1.6 Hz, 1H), 8.09 (t, *J* = 5.9 Hz, 1H), 8.03 (d, *J* = 8.8 Hz, 2H), 7.94 (t, *J* = 5.7 Hz, 1H), 7.60 (d, *J* = 8.1 Hz, 2H), 7.56 – 7.52 (m, 1H), 7.28 (d, *J* = 8.1 Hz, 2H), 6.55 (dd, *J* = 3.3, 1.6 Hz, 1H), 3.09 (q, *J* = 6.4 Hz, 2H), 2.82 (m, 4H), 2.36 (t, *J* = 7.8 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 171.88, 149.69, 146.44, 146.07, 140.28, 139.94, 136.27, 129.03, 128.27, 128.18, 127.65, 127.47, 126.95, 124.75, 120.82, 100.74, 42.11, 38.62, 36.99, 30.68. HRMS calculated for $C_{24}H_{24}N_5O_5S$ 494.14927 [M+H]$^+$, found 494.14870. LCMS (ESI, Thermo, C_{18}, linear gradient, 10% → 90% ACN in H_2O, 0.1% TFA, 10.5 min): t$_R$ = 5.39 min; *m/z* : 494 [M+H]$^+$.

3-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-5-yl)phenyl)-*N*-(2-((3-(trifluoromethyl) phenyl)sulfonamido)ethyl)propanamide (49)



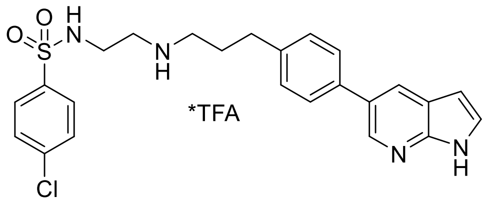
The title compound was synthesized from 3-(trifluoromethyl)benzenesulfonyl chloride following general procedure C and purified by flash-column-chromatography (SiO_2, 5% (10% of sat. aqueous NH_3 in MeOH) in DCM) and preparative HPLC (Gemini, C_{18}, 30% → 40% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound after lyophilisation (25 mg, 30%). ^{1}H NMR (400 MHz, methanol-*d*$_4$) δ 8.52 (d, *J* = 7.1 Hz, 2H), 8.11 – 8.04 (m, 2H), 7.90 (d, *J* = 7.8 Hz, 1H), 7.74 (t, *J* = 7.8 Hz, 1H), 7.62 – 7.56 (m, 3H), 7.35 (d, *J* = 8.1 Hz, 2H), 6.73 (d, *J* = 3.5 Hz, 1H), 3.22 (t, *J* = 6.4 Hz, 2H), 2.96 (t, *J* = 7.6 Hz, 2H), 2.91 (t, *J* = 6.4 Hz, 2H), 2.51 (t, *J* = 7.6 Hz, 2H). ^{13}C NMR (101 MHz, methanol-*d*$_4$) δ 175.48, 144.23, 143.31, 142.02, 137.42, 136.80, 132.70, 131.61, 131.53, 131.00, 130.34, 130.22, 130.18, 129.59, 128.42, 125.16, 124.69, 103.06, 43.22, 40.32, 38.67, 32.36. HRMS calculated for $C_{25}H_{24}F_3N_4O_3S$ 517.15157 [M+H]$^+$, found 517.15101. LCMS (ESI, Thermo, C_{18}, linear gradient, 10% → 90% ACN in H_2O, 0.1% TFA, 10.5 min): t$_R$ = 5.82 min; *m/z* : 517 [M+H]$^+$.

***N*-(2-((3-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-5-yl)phenyl)propyl)amino)ethyl) benzenesulfonamide (50)**



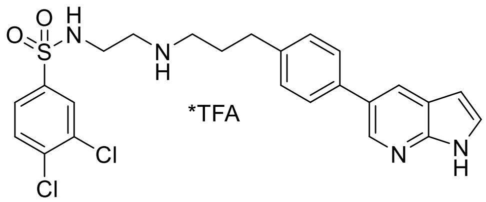
The title compound was synthesized from benzenesulfonyl chloridefollowing general procedure D and purified by flash-column-chromatography (SiO_2, 7% → 10% (10% of sat. aqueous NH_3 in MeOH) in DCM) and preparative HPLC (Gemini, C_{18}, 23% → 26% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound after lyophilisation (4 mg, 3%). ^{1}H NMR (400 MHz, methanol-*d*$_4$) δ 8.50 (d, *J* = 1.7 Hz, 1H), 8.46 (d, *J* = 1.9 Hz, 1H), 7.90 – 7.86 (m, 2H), 7.70 – 7.64 (m, 3H), 7.63 – 7.57 (m, 2H), 7.54 (d, *J* = 3.5 Hz, 1H), 7.40 (d, *J* = 8.2 Hz, 2H), 6.69 (d, *J* = 3.5 Hz, 1H), 3.18 – 3.14 (m, 2H), 3.14 – 3.07 (m, 4H), 2.81 (t, *J* = 7.6 Hz, 2H), 2.08 (dd, *J* = 9.3, 6.3 Hz, 2H). ^{13}C NMR (126 MHz, methanol-*d*$_4$) δ 145.70, 141.11, 140.70, 138.89, 137.72, 134.17, 131.30, 130.72, 130.48, 130.27, 129.10, 128.60, 128.12, 124.30, 102.63, 49.46, 48.37, 40.18, 33.15, 28.75. HRMS calculated for $C_{24}H_{27}N_4O_2S$ 435.18492 [M+H]$^+$, found 435.18503. LCMS (ESI, Thermo, C_{18}, linear gradient, 10% → 90% ACN in H_2O, 0.1% TFA, 10.5 min): t$_R$ = 4.61 min; *m/z* : 435 [M+H]$^+$.

N-(2-((3-(4-(1H-Pyrrolo[2,3-b]pyridin-5-yl)phenyl)propyl)amino)ethyl)-4-chlorobenzenesulfonamide (51)



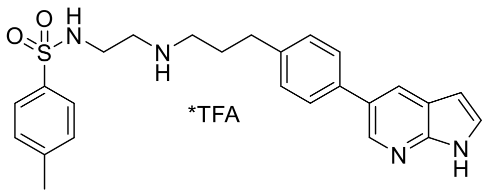
The title compound was synthesized from 4-chlorobenzenesulfonyl chloride on a 127 µmol scale following general procedure D and purified by flash-column-chromatography (SiO_2, 5% → 10% (10% of sat. aqueous NH_3 in MeOH) in DCM) and preparative HPLC (Gemini C_{18}, 25% → 28% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA salt after lyophilisation (13 mg, 18%). ^{1}H NMR (400 MHz, methanol-d_4) δ 8.47 (d, J = 1.9 Hz, 1H), 8.38 (d, J = 2.0 Hz, 1H), 7.87 – 7.83 (m, 2H), 7.66 – 7.59 (m, 4H), 7.51 (d, J = 3.5 Hz, 1H), 7.38 (d, J = 8.2 Hz, 2H), 6.65 (d, J = 3.5 Hz, 1H), 3.17 – 3.13 (m, 4H), 3.12 – 3.07 (m, 2H), 2.80 (t, J = 7.6 Hz, 2H), 2.12 – 2.04 (m, 2H). ^{13}C NMR (101 MHz, methanol-d_4) δ 146.46, 140.93, 140.38, 139.69, 139.52, 138.02, 132.76, 130.68, 130.55, 130.22, 129.88, 128.77, 128.57, 123.81, 102.40, 49.28, 48.33, 40.17, 33.14, 28.74. HRMS calculated for $C_{24}H_{26}ClN_4O_2S$ 469.14595 $[M+H]^+$, found 469.14604. LCMS (ESI, Thermo, C_{18}, linear gradient, 0% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 7.65 min; *m/z* : 469 $[M+H]^+$.

N-(2-((3-(4-(1H-Pyrrolo[2,3-b]pyridin-5-yl)phenyl)propyl)amino)ethyl)-3,4-dichlorobenzenesulfonamide (52)



The title compound was synthesized from 3,4-dichlorobenzenesulfonyl chloride on a 80 µmol scale following general procedure D and purified by flash-column-chromatography (SiO_2, 5% → 9% (10% of sat. aqueous NH_3 in MeOH) in DCM) and preparative HPLC (Gemini, C_{18}, 29% → 32% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA salt after lyophilisation (23 mg, 47%). ^{1}H NMR (500 MHz, chloroform-d) δ 10.38 (bs, 1H), 8.50 (d, J = 2.0 Hz, 1H), 8.12 (d, J = 2.0 Hz, 1H), 7.97 (d, J = 2.1 Hz, 1H), 7.68 (dd, J = 8.4, 2.1 Hz, 1H), 7.55 – 7.50 (m, 3H), 7.37 (d, J = 3.5 Hz, 1H), 7.23 (d, J = 8.1 Hz, 2H), 6.55 (d, J = 3.5 Hz, 1H), 3.08 – 3.04 (m, 2H), 2.77 – 2.73 (m, 2H), 2.66 (t, J = 7.6 Hz, 2H), 2.59 (t, J = 7.2 Hz, 2H), 2.51 (bs, 2H), 1.80 (p, J = 7.4 Hz, 2H). ^{13}C NMR (126 MHz, chloroform-d) δ 147.78, 141.92, 140.65, 140.06, 137.36, 137.22, 133.74, 131.23, 129.61, 129.12, 129.00, 127.52, 127.48, 126.20, 126.00, 120.59, 101.14, 48.93, 48.30, 42.55, 33.22, 31.54. HRMS calculated for $C_{24}H_{25}Cl_2N_4O_2S$ 503.10698 $[M+H]^+$, found 503.10711. LCMS (ESI, Thermo, C_{18}, linear gradient, 10% → 90% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 5.33 min; *m/z* : 503 $[M+H]^+$.

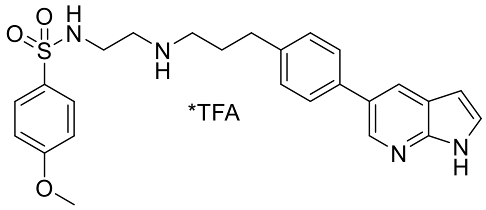
N-(2-((3-(4-(1H-Pyrrolo[2,3-b]pyridin-5-yl)phenyl)propyl)amino)ethyl)-4-methylbenzenesulfonamide (53)



The title compound was synthesized from *p*-tosyl chloride following general procedure D and purified by flash-column-chromatography (SiO_2, 4% → 7% (10% of sat. aqueous NH_3 in MeOH) in DCM) and preparative HPLC (Gemini, C_{18}, 24% → 27% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA salt after lyophilisation (8 mg, 6%). ^{1}H NMR (600 MHz, methanol-d_4) δ 8.46 (d, J = 1.5 Hz, 1H), 8.33 (d, J = 1.9 Hz, 1H), 7.75 (d, J = 8.2 Hz, 2H), 7.64 (d, J = 8.1 Hz, 2H), 7.49 (d, J = 3.4 Hz, 1H), 7.42 – 7.35 (m, 4H), 6.62 (d, J = 3.5 Hz, 1H), 3.15 (t, J = 5.8 Hz, 2H), 3.12 – 3.05 (m, 4H), 2.80 (t, J =

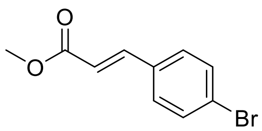
7.6 Hz, 2H), 2.42 (s, 3H), 2.08 (p, *J* = 7.8 Hz, 2H). ^{13}C NMR (151 MHz, methanol-d_4) δ 147.09, 145.35, 140.79, 140.36, 138.28, 137.72, 130.97, 130.60, 130.19, 129.96, 128.56, 128.43, 128.19, 123.42, 102.21, 48.35, 48.34, 40.14, 33.14, 28.72, 21.44. HRMS calculated for $C_{25}H_{29}N_4O_2S$ 449.20057 [M+H]$^+$, found 449.20051. LCMS (ESI, Thermo, C_{18}, linear gradient, 10% → 90% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 4.83 min; *m/z* : 449 [M+H]$^+$.

_N_-(2-((3-(4-(1_H_-Pyrrolo[2,3-_b_]pyridin-5-yl)phenyl)propyl)amino)ethyl)-4-methoxybenzenesulfonamide (54)



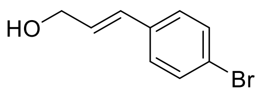
The title compound was synthesized from 4-methoxybenzenesulfonyl chloride following general procedure D and purified by flash-column-chromatography (SiO_2, 4% → 7% (10% of sat. aqueous NH_3 in MeOH) in DCM) and preparative HPLC (Gemini, C_{18}, 24% → 27% ACN in H_2O 0.2% TFA, 10 min gradient) to yield the compound as a TFA salt after lyophilisation (19 mg, 14%). ^{1}H NMR (400 MHz, methanol-d_4) δ 8.52 (s, 1H), 8.51 – 8.50 (m, 1H), 7.82 – 7.78 (m, 2H), 7.67 (d, *J* = 8.2 Hz, 2H), 7.57 (d, *J* = 3.5 Hz, 1H), 7.40 (d, *J* = 8.2 Hz, 2H), 7.11 – 7.06 (m, 2H), 6.71 (d, *J* = 3.5 Hz, 1H), 3.86 (s, 3H), 3.17 – 3.13 (m, 2H), 3.11 – 3.06 (m, 4H), 2.83 – 2.78 (m, 2H), 2.12 – 2.03 (m, 2H). ^{13}C NMR (101 MHz, methanol-d_4) δ 164.78, 145.02, 141.26, 138.17, 137.42, 132.01, 131.93, 130.78, 130.33, 130.30, 129.37, 128.60, 124.72, 115.53, 102.83, 56.24, 48.31 (2C), 40.12, 33.14, 28.71. HRMS calculated for $C_{25}H_{29}N_4O_3S$ 465.19549 [M+H]$^+$, found 465.19543. LCMS (ESI, Thermo, C_{18}, linear gradient, 10% → 90% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 4.70 min; *m/z* : 465 [M+H]$^+$.

Methyl (_E_)-3-(4-bromophenyl)acrylate (56)



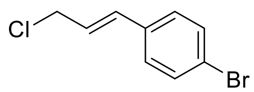
A round-bottom-flask was charged with (*E*)-3-(4-bromophenyl)acrylic acid (18.2 g, 80 mmol, 1 eq) and K_2CO_3 (55.3 g, 400 mmol, 5 eq). After suspending in ACN (120 mL), dimethyl sulfate (8.0 mL, 84 mmol, 1.05 eq) was added dropwise and the mixture was stirred at 80°C for 20 h. The reaction mixture was filtered and concentrated under reduced pressure to yield the product (quant.) without further purification. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.62 (d, *J* = 16.0 Hz, 1H), 7.55 – 7.49 (m, 2H), 7.41 – 7.35 (m, 2H), 6.42 (d, *J* = 16.0 Hz, 1H), 3.81 (s, 3H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 167.29, 143.62, 133.44, 132.29, 129.58, 124.69, 118.64, 51.95.

(_E_)-3-(4-Bromophenyl)prop-2-en-1-ol (57)



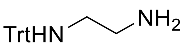
A round-bottom-flask was charged with methyl (*E*)-3-(4-bromophenyl)acrylate (**56**) (19.3 g, 80 mmol, 1 eq) and dissolved in toluene (300 mL). After cooling to -80°C, diisobutylaluminium hydride solution (1 M, 176 mL, 176 mmol, 2.2 eq) was added dropwise and the reaction mixture was allowed to warm to 0°C. The mixture was quenched with EtOAc (80 mL) and diluted with Et_2O (150 mL). H_2O (7.2 mL), aqueous NaOH (10%, 7.2 mL) and H_2O (18 mL) were added sequentially and the mixture was stirred at RT overnight. Drying over Na_2SO_4, filtering and concentration under reduced pressure yielded the product (14.9 g, 86%) which was used without further purification. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.44 (d, *J* = 8.1 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 6.56 (d, *J* = 15.9 Hz, 1H), 6.44 – 6.24 (m, 1H), 4.32 (s, 1H), 1.54 (s, 1H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 135.77, 131.84, 129.93, 129.46, 128.11, 121.58, 63.66.

(*E*)-1-Bromo-4-(3-chloroprop-1-en-1-yl)benzene (58)



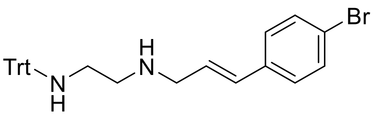
A round-bottom-flask was charged with (*E*)-3-(4-bromophenyl)prop-2-en-1-ol (**57**) (14.9 g, 70 mmol, 1 eq) dissolved in DCM (230 mL). Thionyl chloride (15.2 mL) was added dropwise and the evolving gas was neutralized with aqueous $NaHCO_3$ solution. After confirming complete conversion with TLC, the reaction mixture was concentrated under reduced pressure and co-evaporated with DCM to yield the product (16.2 g, quant.) without further purification. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.45 (d, *J* = 8.5 Hz, 2H), 7.25 (d, *J* = 8.5 Hz, 2H), 6.60 (d, *J* = 15.6 Hz, 1H), 6.31 (dt, *J* = 15.6, 7.1 Hz, 1H), 4.22 (dd, *J* = 7.1, 1.2 Hz, 2H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 134.97, 133.03, 131.94, 128.35, 125.82, 122.29, 45.28.

***N*^{1}-Tritylethane-1,2-diamine (60)**



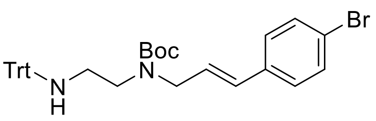
A round-bottom-flask was charged with ethylenediamine (267 mL, 4 mol, 10 eq), K_2CO_3 (66.3 g, 440 mmol, 1.1 eq) suspended in DCM (700 mL) and a solution of (chloromethanetriyl)tribenzene (111.5 g, 400 mmol, 1 eq) in DCM (700 mL) was added dropwise over 40 min. The reaction-mixture was stirred overnight at RT, filtered, concentrated under reduced pressure and co-evaporated with toluene to yield the product (122.8 g, quant.) which was used without further purification. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.48 (d, *J* = 7.6 Hz, 6H), 7.26 (t, *J* = 7.7 Hz, 6H), 7.17 (t, *J* = 7.3 Hz, 3H), 2.79 (t, *J* = 5.9 Hz, 2H), 2.21 (t, *J* = 6.0 Hz, 2H), 1.51 (bs, 3H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 146.24, 128.76, 127.89, 126.34, 70.77, 46.60, 42.89.

(*E*)-*N*^{1}-(3-(4-Bromophenyl)allyl)-*N*^{2}-tritylethane-1,2-diamine (61)



A round-bottom-flask was charged with *N*^{1}-tritylethane-1,2-diamine (**60**) (72.6 g, 240 mmol, 4 eq), (*E*)-1-bromo-4-(3-chloroprop-1-en-1-yl)benzene (**58**) (13.9 g, 60 mmol, 1 eq) and K_2CO_3 (9.1 g, 66 mmol, 1.1 eq) suspended in ACN (1200 mL). The reaction mixture is stirred at 70°C for 2 h. After confirming complete conversion with TLC the reaction mixture was filtrated and concentrated under reduced pressure. The residue was purified via flash-column-chromatography (SiO_2, 10% → 40% EtOAc in pentane, 1% Et_3N) to yield the product (22.4 g, 75%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.50 – 7.45 (m, 6H), 7.43 – 7.38 (m, 2H), 7.29 – 7.14 (m, 11H), 6.43 (d, *J* = 16.0 Hz, 1H), 6.24 (dt, *J* = 15.9, 6.2 Hz, 1H), 3.32 (dd, *J* = 6.2, 1.5 Hz, 2H), 2.79 – 2.73 (m, 2H), 2.34 – 2.27 (m, 2H), 1.91 (bs, 2H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 146.16, 136.12, 131.72, 130.17, 129.32, 128.76, 127.90, 126.36, 121.16, 70.86, 51.56, 49.66, 43.24.

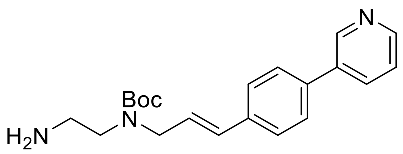
***tert*-Butyl (*E*)-(3-(4-bromophenyl)allyl)(2-(tritylamino)ethyl)carbamate (62)**



A flask was charged with (*E*)-*N*^{1}-(3-(4-bromophenyl)allyl)-*N*^{2}-tritylethane-1,2-diamine (**61**) (22.4 g, 45.0 mmol, 1 eq), di-tert-butyl dicarbonate (11.8 g, 54.0 mmol, 1.2 eq) and $NaHCO_3$ (4.54 g, 54.0 mmol, 1.2 eq) suspended in THF (150 mL). The reaction-mixture was stirred overnight at RT and after confirming complete conversion with TLC, sat. aqueous $NaHCO_3$ (300 mL) was added. The phases were separated and the aqueous layer was extracted with DCM (3x200 mL). The combined organic layers were washed with brine (1x200 mL), dried over Na_2SO_4, filtered and the solvent removed under reduced pressure. The residue was purified via flash-column-chromatography (SiO_2, 1% → 8% EtOAc in pentane) to yield the product (20.6 g, 76%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.49 (d, *J* = 8.5

Hz, 2H), 7.38 (d, *J* = 7.2 Hz, 6H), 7.30 (d, *J* = 8.6 Hz, 2H), 7.25 (t, *J* = 7.7 Hz, 6H), 7.16 (t, *J* = 7.3 Hz, 3H), 6.39 (d, *J* = 15.9 Hz, 1H), 6.20 (dt, *J* = 15.9, 6.0 Hz, 1H), 3.93 (d, *J* = 5.7 Hz, 2H), 3.30 (t, *J* = 6.4 Hz, 2H), 2.63 (bs, *J* = 9.8 Hz, 1H), 2.19 (q, *J* = 6.8 Hz, 2H), 1.36 (s, 9H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 164.02, 155.35, 145.14, 140.73, 139.09, 137.60, 137.49, 136.91, 136.61, 135.32, 129.62, 88.45, 87.92, 79.64, 56.49, 52.01, 37.39.

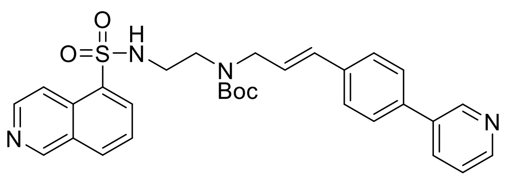
***tert*-Butyl (*E*)-(2-aminoethyl)(3-(4-(pyridin-3-yl)phenyl)allyl)carbamate (63)**



Step 1: A round-bottom-flask was charged with *tert*-butyl (*E*)-(3-(4-bromophenyl)allyl)(2-(tritylamino)ethyl)carbamate (**62**) (19.8 g, 33.20 mmol, 1 eq), 3-pyridinylboronic acid (6.1 g, 49.80 mmol, 1.5 eq) and Pd(PPh_3)$_4$ (0.415 g, 0.33 mmol, 0.01 eq) dissolved in DCM (34 mL) and DMF (73 mL). After addition of aqueous K_2CO_3 (2 M, 41.5 mL, 83.0 mmol, 2.5 eq) the reaction mixture was heated to 85°C for 6 h and after confirming complete conversion with TLC the reaction mixture was filtered over celite and concentrated under reduced pressure. Excess reagents were removed via silica flash column chromatography, eluting with a gradient from 10% to 100% EtOAc in pentane. The resulting product was then directly used in step 2.

Step 2: A round bottom flask was charged with *tert*-butyl (*E*)-(3-(4-(pyridin-3-yl)phenyl)allyl)(2-(tritylamino)ethyl)carbamate (19.78 g, 33.20 mmol, 1 eq) and dissolved in DCM (1025 mL). The flask was cooled down to 0°C and after adding TFA (15.35 mL, 199.20 mmol, 6 eq) the solution turns bright yellow and turns colorless again after addition of triethylsilane (42.42 mL, 265 mmol, 8 eq). The solution was allowed to warm to RT and was stirred for 5 h. The reaction was basified by adding sat. aqueous Na_2CO_3 (300 mL). The phases were separated and the aqueous layer was extracted with DCM (5x300 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent removed under reduced pressure. The residue was purified via flash-column-chromatography (SiO_2, 2% → 10% (10% of sat. aqueous NH_3 in MeOH) in DCM) to yield the product (9.61 g, 82% over 2 steps). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.91 (d, *J* = 2.0 Hz, 1H), 8.56 (dd, *J* = 4.7, 1.5 Hz, 1H), 8.15 – 7.99 (m, 1H), 7.72 (d, *J* = 8.3 Hz, 2H), 7.57 (d, *J* = 8.3 Hz, 2H), 7.48 (dd, *J* = 7.9, 4.8 Hz, 1H), 6.53 (d, *J* = 15.8 Hz, 1H), 6.34 (bs, 1H), 3.98 (s, 2H), 3.39 (bs, 2H), 2.94 (t, *J* = 6.5 Hz, 2H), 1.43 (s, 9H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 148.53, 147.52, 136.27, 136.13, 135.06, 133.91, 131.09, 130.71, 127.11, 126.28, 123.94, 79.43, 49.36, 48.54, 44.35, 37.62, 28.09. LCMS (ESI, Thermo, C_{18}, linear gradient, 10% → 90% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 4.37 min; *m/z* : 354 [M+H]$^+$.

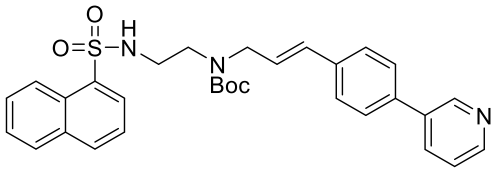
***tert*-Butyl (*E*)-(2-(isoquinoline-5-sulfonamido)ethyl)(3-(4-(pyridin-3-yl)phenyl)allyl) carbamate (64)**



A round-bottom-flask equipped with an addition funnel was charged with *tert*-butyl (*E*)-(2-aminoethyl)(3-(4-(pyridin-3-yl)phenyl)allyl) carbamate (**63**) (500 mg, 1.41 mmol, 1 eq) and Et_3N (0.47 mL, 3.39 mmol, 2.4 eq) dissolved in DCM (14 mL). Isoquinoline-5-sulfonyl chloride (**104**) (0.45 g) was dissolved in sat. aqueous $NaHCO_3$ (5 mL) and extracted with DCM (3x4 mL). The resulting solution was dried over Na_2SO_4, filtered, transferred into the addition funnel and after cooling the reaction mixture to 0°C added dropwise. The reaction mixture was allowed to warm to RT and after stirring for 60 min sat. aqueous $NaHCO_3$ (50 mL) was added. The mixture was extracted with DCM (3x50 mL), the combined organic layers were dried over

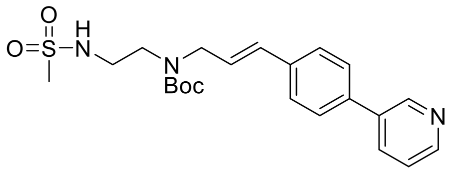
Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified via flash-column-chromatography (SiO_2, 1% → 10% MeOH in DCM) to yield the product (0.61 g, 66%). ^1H NMR (400 MHz, chloroform-*d*) δ 9.34 (s, 1H), 8.86 (d, *J* = 1.8 Hz, 1H), 8.65 (d, *J* = 6.0 Hz, 1H), 8.60 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.46 – 8.36 (m, 2H), 8.17 (d, *J* = 8.2 Hz, 1H), 7.89 (dt, *J* = 7.9, 2.0 Hz, 1H), 7.63 (t, *J* = 7.8 Hz, 1H), 7.55 (d, *J* = 8.2 Hz, 2H), 7.43 (d, *J* = 8.3 Hz, 2H), 7.38 (dd, *J* = 7.6, 4.5 Hz, 1H), 6.43 (d, *J* = 15.9 Hz, 1H), 6.17 – 6.06 (m, 1H), 3.91 (d, *J* = 6.0 Hz, 2H), 3.36 (t, *J* = 5.0 Hz, 2H), 3.13 (s, 2H), 1.45 (s, 9H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 153.38, 148.58, 148.12, 145.33, 137.16, 136.34, 136.18, 134.32, 133.58, 133.21, 131.61, 131.34, 129.15, 127.43, 127.24, 125.92, 125.76, 123.78, 117.39, 80.98, 50.63, 46.64, 42.98, 28.48. LCMS (ESI, Thermo, C_{18}, linear gradient, 10% → 90% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 5.12 min; *m/z* : 545 $[M+H]^+$.

***tert*-Butyl (*E*)-(2-(naphthalene-1-sulfonamido)ethyl)(3-(4-(pyridin-3-yl)phenyl) allyl) carbamate (65)**



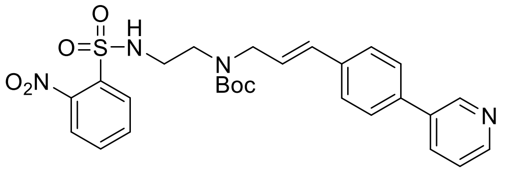
To a solution of *tert*-butyl (*E*)-(2-aminoethyl) (3-(4-(pyridin-3-yl)phenyl)allyl)carbamate (**63**) (0.181 g, 0.51 mmol, 1 eq) and Et_3N (100 µL, 0.72 mmol, 1.4 eq) in DCM (5.1 mL) at 0 °C was added dropwise a solution of 1-naphthalenesulfonyl chloride (0.12 g, 0.56 mmol 1.1 eq) in DCM (5.6 mL). It was allowed to warm to RT and stirred for 30 min before sat. aqueous Na_2CO_3 (20 mL) was added. The organic layer was collected and the aqueous layer extracted with DCM (2x20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified via flash-column-chromatography (SiO_2, 0.5% → 0.7% (10% of sat. aqueous NH_3 in MeOH) in DCM) to yield the product (0.270 g, 98%). ^1H NMR (400 MHz, chloroform-*d*) δ 8.85 (s, 1H), 8.66 (d, *J* = 8.3 Hz, 1H), 8.58 (d, *J* = 4.1 Hz, 1H), 8.22 (d, *J* = 7.2 Hz, 1H), 8.02 (d, *J* = 8.1 Hz, 1H), 7.94 – 7.84 (m, 2H), 7.62 – 7.55 (m, 2H), 7.55 – 7.49 (m, 2H), 7.45 (t, *J* = 7.8 Hz, 1H), 7.42 – 7.33 (m, 3H), 6.38 (d, *J* = 15.8 Hz, 1H), 6.28 (s, 1H), 6.07 (dt, *J* = 15.8, 6.2 Hz, 1H), 3.86 (d, *J* = 5.8 Hz, 2H), 3.33 (s, 2H), 3.11 (s, 2H), 1.43 (s, 9H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 148.40, 147.97, 136.86, 136.42, 136.16, 134.29, 134.25, 134.17, 131.27, 129.47, 129.08, 128.34, 128.15, 127.27, 127.16, 126.89, 125.89, 124.56, 124.12, 123.73, 80.55, 50.45, 46.61, 42.52, 28.40.

***tert*-Butyl (*E*)-(2-(methylsulfonamido)ethyl)(3-(4-(pyridin-3-yl)phenyl)allyl) carbamate (66)**



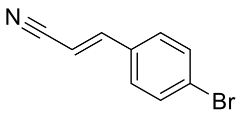
A round-bottom-flask was charged with *tert*-butyl (*E*)-(2-aminoethyl)(3-(4-(pyridin-3-yl)phenyl)allyl) carbamate (**63**) (100 mg, 0.28 mmol, 1 eq) and Et_3N (80 µL, 0.57 mmol, 2 eq) dissolved in DCM (2.8 mL). After cooling the mixture to 0°C a solution of methane sulfonyl chloride (25 µL, 0.31 mmol, 1.2 eq) in DCM (2.8 mL) was added dropwise and the reaction was slowly allowed to warm to RT. After 50 min half sat. aqueous $NaHCO_3$ solution (4 mL) was added, the mixture was extracted with DCM (3x5 mL), the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified via flash-column-chromatography (SiO_2, 0% → 15% MeOH in DCM) to yield the product (107 mg, 88%). ^1H NMR (400 MHz, chloroform-*d*) δ 8.83 (d, *J* = 1.9 Hz, 1H), 8.56 (dd, *J* = 4.8, 1.5 Hz, 1H), 7.86 (dt, *J* = 7.9, 1.9 Hz, 1H), 7.53 (d, *J* = 8.2 Hz, 2H), 7.46 (d, *J* = 8.3 Hz, 2H), 7.35 (dd, *J* = 7.9, 4.8 Hz, 1H), 6.50 (d, *J* = 15.8 Hz, 1H), 6.20 (d, *J* = 15.4 Hz, 1H), 4.03 (bs, 2H), 3.45 (bs, 2H), 3.31 (bs, 2H), 2.93 (s, 3H), 1.47 (s, 9H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 156.59, 148.48, 148.07, 137.05, 136.40, 136.15, 134.26, 131.51, 127.38, 127.20, 125.83, 123.71, 80.77, 50.35, 46.75, 42.42, 40.39, 28.48.

tert-Butyl (_E_)-(2-((2-nitrophenyl)sulfonamido)ethyl)(3-(4-(pyridin-3-yl)phenyl)allyl) carbamate (67)



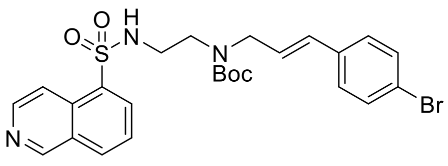
To a solution of *tert*-butyl (*E*)-(2-aminoethyl) (3-(4-(pyridin-3-yl)phenyl)allyl)carbamate (**63**) (0.335 g, 0.95 mmol, 1 eq) and Et_3N (170 µL, 1.3 mmol, 1.4 eq) in DCM (8 mL) at 0 °C was added dropwise a solution of 2-nitrobenzenesulfonyl chloride (0.23 g, 1.1 mmol, 1.1 eq) in DCM (4 mL). The reaction was allowed to warm to RT and stirred for 1 h before it was washed with H_2O (2x20 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified via flash-column-chromatography (SiO_2, 0.5% → 0.7% (10% of sat. aqueous NH_3 in MeOH) in DCM) to yield the product (0.404 g, 79%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.89 – 8.84 (m, 1H), 8.58 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.06 (d, *J* = 7.0 Hz, 1H), 7.92 – 7.85 (m, 1H), 7.79 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.71 – 7.61 (m, 2H), 7.55 (d, *J* = 8.0 Hz, 2H), 7.45 (d, *J* = 8.2 Hz, 2H), 7.39 – 7.34 (m, 1H), 6.49 (d, *J* = 15.9 Hz, 1H), 6.31 (s, 1H), 6.19 (dt, *J* = 15.8, 6.1 Hz, 1H), 4.00 (d, *J* = 5.7 Hz, 2H), 3.50 – 3.42 (m, 2H), 3.31 (s, 2H), 1.48 (s, 9H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 148.40, 147.96, 147.93, 136.88, 136.40, 136.05, 134.18, 133.56, 132.69, 131.31, 130.80, 127.25, 127.15, 125.91, 125.23, 123.68, 80.60, 50.52, 46.60, 42.55, 28.36. LCMS (ESI, Thermo, C_{18}, linear gradient, 10% → 90% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 6.33 min; *m/z* : 539 $[M+H]^+$.

(_E_)-3-(4-Bromophenyl)acrylonitrile (69)



Diethyl cyanomethylphosphonate (35.43 g, 200 mmol, 1 eq) was added slowly to a solution of NaH (8.80 g, 220 mmol, 1.1 eq) in DMF (900 mL) at 0°C. After the mixture was allowed to stir for 30 min, a solution of 4-bromobenzaldehyde (40.70 g, 220 mmol, 1.1 eq) dissolved in DMF (100 mL) was added dropwise. The mixture was allowed to warm up to RT, stirred overnight and quenched by addition of saturated aqueous $NaHSO_3$ (800 mL). After further dilution with H_2O (800 mL), the mixture was extracted with Et_2O (4x600 mL). The combined organic layers were washed with sat. aqueous $NaHSO_3$ and brine, before being dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude was purified via flash-column-chromatography (SiO_2, 10% EtOAc in pentane) to yield the product (25.4 g, 61%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.51 (d, *J* = 8.8 Hz, 2H), 7.33 – 7.29 (m, 3H), 5.89 (d, *J* = 16.8 Hz, 1H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 149.89, 132.12, 132.03, 128.52, 125.26, 117.67, 96.84.

tert-Butyl (_E_)-(3-(4-bromophenyl)allyl)(2-(isoquinoline-5-sulfonamido)ethyl) carbamate (70)

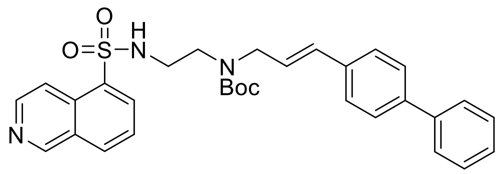


<u>**Step 1:**</u> A solution of (*E*)-3-(4-bromophenyl)acrylonitrile (**69**) (10.40 g, 50 mmol, 1 eq) in Et_2O (250 mL) was cooled to -87°C, before DiBAL-H in hexanes (1 M, 100 mL, 100 mmol, 2 eq) was added dropwise and the reaction was allowed to warm up to 0°C. After stirring at 0°C for 2 h the mixture was cooled to -100°C, followed by rapid addition of MeOH (100 mL) and after 5 min stirring a solution of *N*-(2-aminoethyl)isoquinoline-5-sulfonamide (**105**) (25.18 g, 100 mmol, 2 eq) in MeOH (100 mL) was added dropwise. The resulting mixture was allowed

to warm up to RT and stirred overnight. After cooling to 0°C, $NaBH_4$ (3.78 g, 100 mmol, 2 eq) was added and the mixture was stirred for 4 h and then diluted with aqueous NaOH (2 M, 250 mL). The phases were separated and the aqueous layer was extracted with DCM (3x250 mL). The combined organic layers were washed with H_2O (3x250 mL) and brine, before being dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was used in step 2 without further purification.

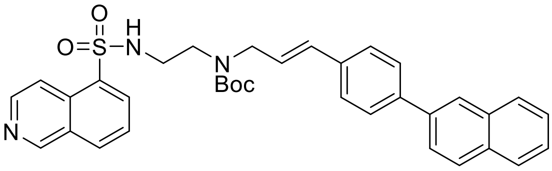
Step 2: The crude product from step 1 was dissolved in THF (250 mL) and cooled to 0°C before Boc_2O (27.28 g, 125 mmol, 2.5 eq) was added and the reaction was allowed to warm up to RT and stirred overnight. The reaction mixture was diluted with H_2O and extracted with EtOAc (4x250 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (2x250 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified via flash-column-chromatography (SiO_2, 0.1% → 2% MeOH in DCM) to yield the product (14.9 g, 55%). ^1H NMR (400 MHz, chloroform-*d*) δ 9.32 (s, 1H), 8.59 (d, *J* = 6.4 Hz, 1H), 8.44 (d, *J* = 6.0 Hz, 1H), 8.36 (d, *J* = 7.2 Hz, 1H), 8.14 (d, *J* = 8.0 Hz, 1H), 7.59 (t, *J* = 7.6 Hz, 1H), 7.38 (s, 2H), 7.15 (d, *J* = 7.6 Hz, 2H), 6.77 (bs, 1H), 6.30 (d, *J* = 16 Hz, 1H), 6.06 – 5.99 (m, 1H), 3.87 (d, *J* = 5.2 Hz, 2H), 3.35 (bs, 2H), 3.12 (bs, 2H), 1.42 (s, 9H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 152.93, 144.54, 135.13, 134.33, 133.23, 132.82, 131.43, 131.00, 128.80, 127.70, 125.72, 121.23, 117.25, 80.38, 50.16, 46.45, 42.11, 29.41, 28.12.

***tert*-Butyl (*E*)-(3-([1,1'-biphenyl]-4-yl)allyl)(2-(isoquinoline-5-sulfonamido)ethyl)carbamate (71)**



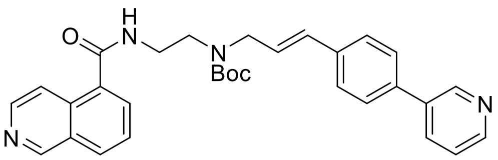
A vial containing *tert*-butyl (*E*)-(3-(4-bromophenyl)allyl)(2-(isoquinoline-5- sulfon amido) ethyl)carbamate (**70**) (0.55 g, 1.0 mmol, 1 eq), $Pd(PPh_3)_4$ (13 mg, 0.012 mmol, 0.012 eq) and phenylboronic acid (0.182 g, 1.5 mmol, 1.5 eq) was sealed and flushed with argon, after which a deoxygenated mixture of DCM (1 mL), DMF (2.2 mL) and aqueous K_2CO_3 (2 M, 1.25 mL, 2.5 mmol, 2.5 eq) was added. After stirring at 90 °C for 21 h, the mixture was cooled to ambient temperature, concentrated under reduced pressure, re-suspended with EtOAc, filtered over silica and concentrated again. The resulting crude was purified via flash-column-chromatography (SiO_2, 45% → 65% EtOAc in pentane) to yield the product (0.378 g, 70%). ^1H NMR (400 MHz, chloroform-*d*) δ 9.29 (s, 1H), 8.58 (d, *J* = 6.1 Hz, 1H), 8.46 (d, *J* = 6.1 Hz, 1H), 8.36 (dd, *J* = 7.4, 1.1 Hz, 1H), 8.07 (d, *J* = 8.1 Hz, 1H), 7.61 – 7.48 (m, 5H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.38 – 7.29 (m, 3H), 6.85 (t, *J* = 5.7 Hz, 1H), 6.40 (d, *J* = 15.9 Hz, 1H), 6.10 – 6.01 (m, 1H), 3.90 (s, 2H), 3.35 (s, 2H), 3.12 (s, 2H), 1.42 (s, 9H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 156.32, 153.07, 144.70, 140.34, 140.31, 135.34, 134.48, 133.31, 132.97, 131.61, 131.12, 129.16, 128.93, 128.75, 127.32, 127.13, 126.76, 125.83, 124.95, 117.41, 80.43, 50.45, 46.57, 42.31, 28.28. LCMS (ESI, Thermo, C_{18}, linear gradient, 10% → 90% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 7.63 min; *m/z* : 544 $[M+H]^+$.

***tert*-Butyl (*E*)-(2-(isoquinoline-5-sulfonamido)ethyl)(3-(4-(naphthalen-2-yl)phenyl)allyl)carbamate (72)**



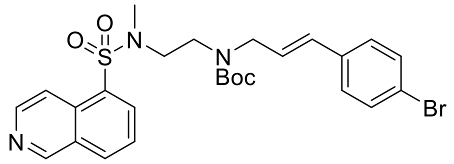
A vial containing *tert*-butyl (*E*)-(3-(4-bromophenyl)allyl)(2-(isoquinoline-5-sulfon amido)ethyl)carbamate (**70**) (0.55 g, 1.0 mmol, 1 eq), $Pd(PPh_3)_4$ (13 mg, 0.012 mmol, 0.012 eq) and 2-naphthaleneboronic acid (0.26 mg, 1.5 mmol, 1.5 eq) was sealed and flushed with argon, after which a deoxygenated mixture of DCM (1 mL), DMF (2.2 mL) and aqueous K_2CO_3 (2 M, 1.25 mL, 2.5 mmol, 2.5 eq) was added. After stirring at 90 °C for 21 h, the mixture was cooled to ambient temperature, concentrated under reduced pressure, re-suspended with EtOAc, filtered over silica and concentrated again. The crude was purified via flash-column-chromatography (SiO_2, 40% → 70% EtOAc in pentane) to yield the desired product (0.370 g, 62%). ^1H NMR (400 MHz, chloroform-*d*) δ 9.31 (s, 1H), 8.63 (d, *J* = 6.0 Hz, 1H), 8.42 (d, *J* = 5.7 Hz, 1H), 8.37 (dd, *J* = 7.4, 1.0 Hz, 1H), 8.11 (d, *J* = 8.2 Hz, 1H), 8.04 (s, 1H), 7.93 – 7.82 (m, 3H), 7.74 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.67 (d, *J* = 8.2 Hz, 2H), 7.57 (t, *J* = 7.8 Hz, 1H), 7.51 – 7.46 (m, 2H), 7.41 (d, *J* = 8.3 Hz, 2H), 6.43 (d, *J* = 15.9 Hz, 1H), 6.38 (s, 1H), 6.13 – 6.02 (m, 1H), 3.90 (d, *J* = 5.8 Hz, 2H), 3.35 (s, 2H), 3.11 (s, 2H), 1.45 (s, 9H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 171.12, 162.61, 153.17, 144.91, 140.27, 137.77, 135.55, 134.66, 133.66, 133.34, 132.99, 132.65, 131.72, 131.24, 129.04, 128.51, 128.19, 127.63, 127.47, 126.95, 126.36, 126.01, 125.86, 125.49, 125.20, 117.47, 80.51, 50.56, 46.68, 42.48, 28.37. LCMS (ESI, Thermo, C_{18}, linear gradient, 10% → 90% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 8.24 min; *m/z* : 594 $[M+H]^+$.

***tert*-Butyl (*E*)-(2-(isoquinoline-5-carboxamido)ethyl)(3-(4-(pyridin-3-yl)phenyl) allyl)carbamate (73)**



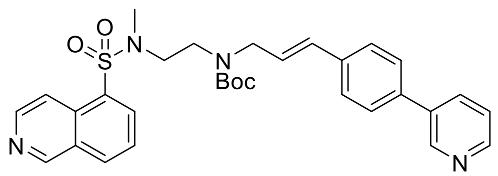
A round bottom flask was charged with isoquinoline-5-carboxylic acid (50 mg, 0.29 mmol, 1.05 eq) suspended in $SOCl_2$ (2 mL). After addition of 3 drops of DMF the reaction was heated to 70°C for 60 min and excess $SOCl_2$ was removed under reduced pressure. The resulting solid was re-dissolved in DCM (3 mL) and after addition of DiPEA (140 µL, 0.41 mmol, 3 eq) a solution of *tert*-butyl(*E*)-(2-aminoethyl)(3-(4-(pyridin-3-yl)phenyl) allyl) carbamate (**63**) (97 mg, 0.275 mmol, 1 eq) and DMAP (3 mg, 0.03 mmol, 0.1 eq) dissolved in DCM (5 mL) was added dropwise at 0°C. The reaction mixture was allowed to warm up to RT. After 75 min half saturated aqueous $NaHCO_3$ solution (10 mL) was added, the mixture was extracted with DCM (3x15 mL), the combined organic layers were washed with brine (1x40 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified via flash-column-chromatography (SiO_2, 0% → 15% MeOH in DCM) to yield the product (57 mg, 41%). ^1H NMR (400 MHz, chloroform-*d*) δ 9.26 (s, 1H), 8.85 (s, 1H), 8.62 – 8.51 (m, 2H), 8.36 – 8.16 (m, 1H), 8.03 (d, *J* = 8.2 Hz, 1H), 7.88 (d, *J* = 7.7 Hz, 2H), 7.62 – 7.33 (m, 7H), 6.55 (d, *J* = 15.9 Hz, 1H), 6.32 – 6.19 (m, 1H), 4.09 (bs, 2H), 3.73 (d, *J* = 5.3 Hz, 2H), 3.62 (bs, 2H), 1.41 (s, 9H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 168.47, 157.28, 152.82, 148.61, 148.18, 144.24, 137.20, 136.37, 136.16, 134.26, 133.35, 132.83, 131.68, 130.61, 129.46, 128.84, 127.45, 127.21, 126.24, 125.80, 123.73, 118.58, 80.77, 50.08, 45.59, 40.30, 28.42. LCMS (ESI, Thermo, C_{18}, linear gradient, 10% → 90% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 4.67 min; *m/z* : 509 $[M+H]^+$.

tert-Butyl (E)-(3-(4-bromophenyl)allyl)(2-(N-methylisoquinoline-5-sulfonamido)ethyl) carbamate (74)



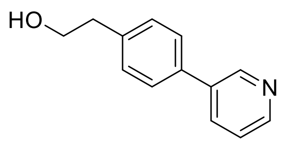
To a solution of (*E*)-(3-(4- bromophenyl)allyl)(2-(isoquinoline-5-sulfon amido)ethyl)carbamate (**70**) (2.51 g, 4.6 mmol, 1 eq), and cesium carbonate (2.2 g, 6.9 mmol, 1.5 eq) in DMF (45 mL) was added methyl iodide (357 µL, 5.7 mmol, 1.25 eq). The mixture was stirred for 21 h and concentrated under reduced pressure at 75°C, after which the resulting solids were re-dissolved in DCM (100 mL) and H_2O (100 mL). The organic layer was collected and the aqueous layer extracted with DCM (2x100 mL), the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified via flash-column-chromatography (SiO_2, 40% → 65% EtOAc in pentane) to yield the product (2.57 g, quant.). ^{1}H NMR (400 MHz, chloroform-*d*) δ 9.33 (s, 1H), 8.64 (d, *J* = 6.1 Hz, 1H), 8.49 – 8.38 (m, 1H), 8.26 (s, 1H), 8.18 (d, *J* = 8.2 Hz, 1H), 7.68 – 7.53 (m, 1H), 7.49 – 7.35 (m, 2H), 7.24 (d, *J* = 7.9 Hz, 2H), 6.41 (d, *J* = 15.5 Hz, 1H), 6.14 (dt, *J* = 15.9, 6.3 Hz, 1H), 3.99 (s, 2H), 3.51 – 3.24 (m, 4H), 2.93 – 2.85 (m, 3H), 1.45 (s, 9H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 155.37, 153.27, 145.16, 135.51, 133.59, 133.33, 131.74, 130.84, 129.17, 129.06, 127.99, 126.16, 125.88, 121.57, 121.51, 117.64, 80.27, 50.12, 47.69, 44.90, 35.11, 28.44. LCMS (ESI, Thermo, C_{18}, linear gradient, 10% → 90% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 7.51 min; *m/z* : 560, 562 [M+1]$^+$.

tert-Butyl (E)-(2-(N-methylisoquinoline-5-sulfonamido)ethyl)(3-(4-(pyridin-3-yl)phenyl)allyl)carbamate (75)



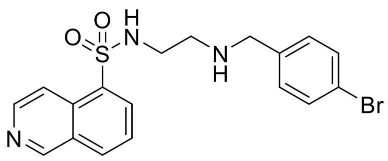
tert-Butyl (*E*)-(3-(4-bromophenyl)allyl)(2-(*N*-methyl isoquinoline-5-sulfonamido)ethyl)carbamate (**74**) (2.57 g, 4.6 mmol, 1 eq), $Pd(PPh_3)_4$ (106 mg, 0.092 mmol, 0.02 eq) and pyridine-3-boronic acid (0.85 g, 6.9 mmol, 1.5 eq) were dissolved in a deoxygenated mixture of DCM (4.6 mL), DMF (10.1 mL) and aqueous K_2CO_3 solution (2 M, 5.7 mL, 11.4 mmol, 2.5 eq) and the reaction was heated under argon atmosphere to 80°C for 17 h. After cooling to ambient temperature, the mixture was concentrated under reduced pressure, diluted with EtOAc, filtered over silica and concentrated again. The residue was purified via flash-column-chromatography (SiO_2, 0% → 2% MeOH in EtOAc) to yield the product (1.91 g, 74%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 9.33 (d, *J* = 0.4 Hz, 1H), 8.87 (d, *J* = 1.9 Hz, 1H), 8.64 (d, *J* = 6.2 Hz, 1H), 8.59 (dd, *J* = 4.8, 1.5 Hz, 1H), 8.46 (bs, 1H), 8.29 (bs, 1H), 8.17 (d, *J* = 8.2 Hz, 1H), 7.89 (dt, *J* = 8.0, 2.0 Hz, 1H), 7.64 – 7.53 (m, 3H), 7.50 (d, *J* = 7.9 Hz, 2H), 7.37 (dd, *J* = 7.7, 4.9 Hz, 1H), 6.53 (d, *J* = 15.6 Hz, 1H), 6.23 (dt, *J* = 15.8, 6.3 Hz, 1H), 4.04 (s, 2H), 3.56 – 3.21 (m, 4H), 2.93 (t, *J* = 7.8 Hz, 3H), 1.48 (s, 9H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 155.38, 154.99, 153.23, 148.50, 148.07, 145.15, 136.99, 136.44, 136.03, 134.12, 133.55, 133.33, 131.72, 131.26, 129.13, 127.31, 127.15, 126.06, 125.83, 123.62, 117.61, 80.22, 50.16, 48.08, 44.89, 35.07, 28.42. LCMS (ESI, Thermo, C_{18}, linear gradient, 10% → 90% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 5.38 min; *m/z* : 559 [M+1]$^+$.

2-(4-(Pyridin-3-yl)phenyl)ethan-1-ol (77)



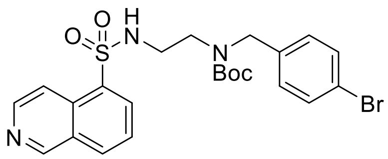
A vial containing 2-(4-bromophenyl)ethanol (420 µL, 3.0 mmol, 1 eq), $Pd(PPh_3)_4$ (69 mg, 0.060 mmol, 0.02 eq) and pyridine-3-boronic acid (0.55 g, 4.5 mmol, 1.5 eq) was sealed and flushed with argon, after which a deoxygenated mixture of DCM (3 mL), DMF (6.6 mL) and aqueous K_2CO_3 solution (2 M, 3.8 mL, 7.6 mmol, 2.5 eq) was added. After stirring at 80°C for 3 h, the mixture was cooled to ambient temperature, concentrated under reduced pressure, diluted with EtOAc, filtered over silica and concentrated again. The residue was purified via flash-column-chromatography (SiO_2, 80% → 100% EtOAc in pentane) to yield the product (96 mg, 16%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.78 (s, 1H), 8.55 (d, *J* = 4.7 Hz, 1H), 7.86 (d, *J* = 7.9 Hz, 1H), 7.59 – 7.43 (m, 2H), 7.36 (d, *J* = 7.9 Hz, 3H), 3.91 (t, *J* = 6.7 Hz, 2H), 2.97 – 2.90 (m, 2H), 2.80 (bs, 1H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 148.20, 148.07, 139.18, 136.47, 135.76, 134.31, 132.14, 129.85, 123.63, 63.40, 38.95.

***N*-(2-((4-Bromobenzyl)amino)ethyl)isoquinoline-5-sulfonamide (79)**



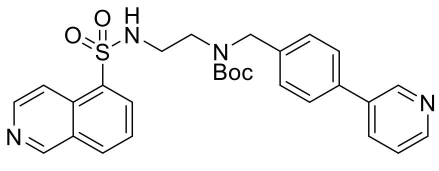
4-Bromobenzaldehyde (0.283 g, 1.5 mmol, 1 eq) and *N*-(2-aminoethyl)isoquinoline-5-sulfonamide (**105**) (0.77 g, 3.1 mmol, 2.05 eq) were dissolved in THF (15 mL). Subsequently, activated molecular sieves (3 Å), glacial acetic acid (87 µL, 1.5 mmol, 1 eq) and $NaHB(OAc)_3$ (0.65 g, 3.1 mmol, 2.05 eq) were added and the reaction was stirred for 18 h. Sat. aqueous Na_2CO_3 solution (35 mL) and Et_2O (40 mL) were added, the organic layer was collected and the aqueous layer extracted with DCM (3x50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified via flash-column-chromatography (SiO_2, 6% → 8% (10% of sat. aqueous NH_3 in MeOH) in DCM) to yield the product (633 mg, quant.). ^{1}H NMR (400 MHz, chloroform-*d*) δ 9.32 (s, 1H), 8.61 (d, *J* = 6.1 Hz, 1H), 8.45 (d, *J* = 6.1 Hz, 1H), 8.41 (dd, *J* = 7.3, 1.0 Hz, 1H), 8.17 (d, *J* = 8.2 Hz, 1H), 7.67 (t, *J* = 7.8 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 6.98 (d, *J* = 8.3 Hz, 2H), 4.77 (bs, 2H), 3.51 (s, 2H), 3.08 – 2.97 (m, 2H), 2.64 (t, *J* = 5.6 Hz, 2H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 153.28, 144.90, 138.03, 134.33, 133.58, 133.24, 131.45, 131.19, 129.74, 128.97, 126.03, 120.96, 117.31, 52.25, 47.48, 42.32.

***tert*-Butyl (4-bromobenzyl)(2-(isoquinoline-5-sulfonamido)ethyl)carbamate (80)**



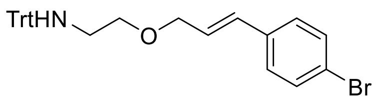
To a solution of *N*-(2-((4-bromobenzyl)amino) ethyl)isoquinoline-5-sulfonamide (**79**) (0.633 g, 1.5 mmol, 1 eq) and $NaHCO_3$ (0.14 g, 1.7 mmol, 1.1 eq) in THF (15 mL) at 0°C was added di-*tert*-butyl dicarbonate (0.36 g, 1.7 mmol, 1.1 eq). The reaction was allowed to warm to RT and stirred for 2 h before it was diluted with sat. aqueous Na_2CO_3 solution (30 mL) and DCM (30 mL). The organic layer was collected and the aqueous layer was extracted with DCM (3x20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified via flash-column-chromatography (SiO_2, 50% → 80% EtOAc in pentane) to yield the product (0.570 g, 73%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 9.36 (s, 1H), 8.63 (d, *J* = 6.1 Hz, 1H), 8.39 (d, *J* = 6.0 Hz, 1H), 8.35 (dd, *J* = 7.4, 1.2 Hz, 1H), 8.21 (d, *J* = 8.1 Hz, 1H), 7.68 (t, *J* = 7.7 Hz, 1H), 7.39 – 7.31 (m, 2H), 6.97 (s, 2H), 6.45 (s, 1H), 4.27 (s, 2H), 3.31 (s, 2H), 3.00 (s, 2H), 1.41 (s, 9H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 153.28, 145.06, 136.90, 134.31, 133.55, 133.20, 131.72, 131.22, 129.09, 128.88, 125.98, 121.28, 117.38, 81.13, 51.31, 46.76, 42.37, 28.35.

***tert*-Butyl (2-(isoquinoline-5-sulfonamido)ethyl)(4-(pyridin-3-yl)benzyl)carbamate (81)**



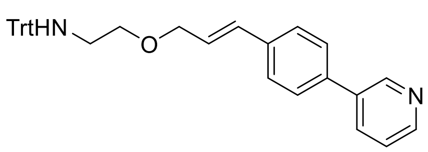
A vial containing *tert*-butyl (4-bromobenzyl)(2-(isoquinoline-5-sulfonamido)ethyl)carbamate (**80**) (0.633 g, 1.1 mmol, 1 eq), $Pd(PPh_3)_4$ (38 mg, 0.033 mmol, 0.03 eq) and pyridine-3-boronic acid (0.20 g, 1.6 mmol, 1.45 eq) was sealed and flushed with argon, after which a deoxygenated mixture of DCM (1.1 mL), DMF (2.2 mL) and aqueous K_2CO_3 solution (2 M, 1.4 mL, 2.8 mmol, 2.5 eq) was added. After stirring at 80°C for 26 h, the mixture was cooled to ambient temperature, concentrated under reduced pressure, diluted with EtOAc, filtered over silica and concentrated again. The residue was purified via flash-column-chromatography (SiO_2, 80% → 100% EtOAc in pentane) to yield the product (0.289 g, 51%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 9.33 (s, 1H), 8.81 (s, 1H), 8.66 – 8.54 (m, 2H), 8.43 (d, *J* = 5.9 Hz, 1H), 8.38 (dd, *J* = 7.3, 0.9 Hz, 1H), 8.16 (d, *J* = 8.0 Hz, 1H), 7.86 (d, *J* = 7.1 Hz, 1H), 7.63 (t, *J* = 7.8 Hz, 1H), 7.46 (d, *J* = 8.2 Hz, 2H), 7.39 (dd, *J* = 7.8, 4.9 Hz, 1H), 7.22 (s, 2H), 6.87 (s, 1H), 4.40 (s, 2H), 3.36 (s, 2H), 3.08 (s, 2H), 1.43 (s, 9H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 153.23, 148.44, 148.03, 145.02, 137.93, 136.81, 136.12, 134.58, 134.36, 133.38, 133.04, 131.24, 129.07, 127.94, 127.31, 125.88, 123.72, 117.41, 80.95, 51.48, 46.72, 42.27, 28.35. LCMS (ESI, Thermo, C_{18}, linear gradient, 10% → 50% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 6.50 min; *m/z* : 519 [M+1]$^+$.

(*E*)-2-((3-(4-Bromophenyl)allyl)oxy)-*N*-tritylethan-1-amine (82)



To a solution of 2-(tritylamino)ethan-1-ol (**60**) (0.91 g, 3.0 mmol, 1.11 eq) in ACN (20 mL) was added NaH (60% in mineral oil, 0.12 g, 3.0 mmol) and (*E*)-1-bromo-4-(3-chloroprop-1-en-1-yl)benzene (**58**) (0.63 g, 2.7 mmol, 1 eq), after which the reaction was stirred at 70°C for 4 h. The solvents were removed under reduced pressure and the mixture was re-dissolved in DCM (60 mL) and washed with sat. aqueous $NaHCO_3$ (40 mL) after which the organic layer was collected and the aqueous layer extracted with DCM (4x25 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified via flash-column-chromatography (SiO_2, 3% → 7% EtOAc in pentane) to yield the product (0.492 g, 37%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.51 – 7.46 (m, 6H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 7.3 Hz, 6H), 7.23 (d, *J* = 8.5 Hz, 2H), 7.18 (t, *J* = 7.3 Hz, 3H), 6.51 (d, *J* = 16.0 Hz, 1H), 6.23 (dt, *J* = 15.9, 5.8 Hz, 1H), 4.06 (dd, *J* = 5.8, 1.2 Hz, 2H), 3.61 (t, *J* = 5.3 Hz, 2H), 2.38 (t, *J* = 5.2 Hz, 2H), 2.07 (bs, 1H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 146.20, 135.80, 131.79, 130.87, 128.82, 128.11, 127.94, 127.23, 126.39, 121.52, 71.29, 70.79, 70.65, 43.38.

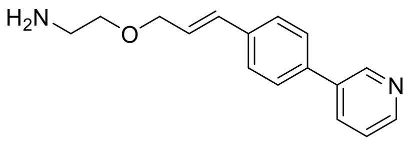
(*E*)-2-((3-(4-(Pyridin-3-yl)phenyl)allyl)oxy)-*N*-tritylethan-1-amine (83)



(*E*)-2-((3-(4-bromophenyl)allyl)oxy)-*N*-trityl ethan-1-amine (**82**) (0.491 g, 0.86 mmol, 1 eq), $Pd(PPh_3)_4$ (20 mg, 0.017 mmol, 0.02 eq) and pyridine-3-boronic acid (0.16 g, 1.3 mmol, 1.5 eq) were dissolved in a deoxygenated mixture of DCM (0.9 mL), DMF (1.9 mL) and aqueous K_2CO_3 solution (2 M, 1.1 mL, 2.2 mmol, 2.5 eq) and the reaction was stirred under argon atmosphere at 80°C for 3 h and at 70 °C for 16 h. After cooling to ambient temperature, the mixture was concentrated under reduced pressure, diluted with EtOAc, filtered over silica and concentrated again. The residue was purified via flash-column-chromatography (SiO_2, 40% → 60% EtOAc in pentane) to yield the product (0.383 g, 78%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.85 (d, *J* = 2.0 Hz, 1H), 8.55 (dd, *J* = 4.8, 1.5 Hz, 1H), 7.82 (dt, *J* = 8.0, 2.0 Hz, 1H), 7.54 – 7.44

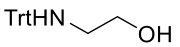
(m, 10H), 7.32 – 7.29 (m, 1H), 7.28 – 7.20 (m, 6H), 7.16 (t, *J* = 7.3 Hz, 3H), 6.61 (d, *J* = 16.0 Hz, 1H), 6.31 (dt, *J* = 15.9, 5.8 Hz, 1H), 4.11 – 4.06 (m, 2H), 3.63 (t, *J* = 5.3 Hz, 2H), 2.40 (t, *J* = 5.3 Hz, 2H), 2.19 (bs, 1H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 148.51, 148.16, 146.11, 136.89, 136.65, 136.10, 134.07, 131.22, 128.72, 127.85, 127.26, 127.19, 127.09, 126.29, 123.58, 71.29, 70.71, 70.49, 43.32.

(*E*)-2-((3-(4-(Pyridin-3-yl)phenyl)allyl)oxy)ethan-1-amine (84)



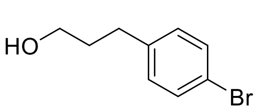
To a solution of (*E*)-2-((3-(4-(pyridin-3-yl)phenyl)allyl)oxy)-*N*-tritylethan-1-amine (**83**) (0.322 g, 0.65 mmol, 1 eq) in DCM (20 mL) was added dropwise TFA (0.30 mL), after which triethylsilane (0.83 mL, 5.2 mmol, 8 eq) was added and the reaction was stirred for 1 h. It was quenched with sat. aqueous Na_2CO_3 (30 mL), the organic layer was collected and the aqueous layer extracted with DCM (3x25 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure after which filtration over silica (DCM, 0.5% Et_3N) yielded the product without further purification (103 mg, 62%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.85 (dd, *J* = 2.4, 0.7 Hz, 1H), 8.58 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.89 – 7.82 (m, 1H), 7.58 – 7.47 (m, 4H), 7.35 (ddd, *J* = 7.9, 4.8, 0.8 Hz, 1H), 6.66 (d, *J* = 16.0 Hz, 1H), 6.37 (dt, *J* = 15.9, 6.0 Hz, 1H), 4.20 (dd, *J* = 6.0, 1.4 Hz, 2H), 3.55 (t, *J* = 5.2 Hz, 2H), 2.92 (t, *J* = 5.2 Hz, 2H), 1.43 (bs, 2H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 148.49, 148.13, 136.93, 136.56, 136.07, 134.07, 131.49, 127.24, 127.18, 126.89, 123.57, 72.68, 71.56, 41.99.

2-(Tritylamino)ethan-1-ol (86)



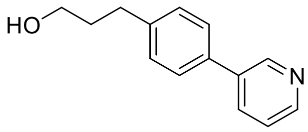
To a solution of trityl chloride (1.39 g, 5.0 mmol, 1 eq) and K_2CO_3 (0.76 g, 5.5 mmol, 1.1 eq) in DCM (17 mL) at 0°C was added dropwise ethanolamine (1.51 mL, 25.0 mmol, 5 eq). The reaction was allowed to warm to RT and stirred for 3 h before it was mixed with sat. aqueous $NaHCO_3$ (15 mL) and H_2O (15 mL). The organic layer was collected and the aqueous layer extracted with DCM (3x30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified via flash-column-chromatography (SiO_2, 15% → 25% EtOAc in pentane) to yield the product (1.52 g, quant.). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.49 – 7.44 (m, 6H), 7.31 – 7.24 (m, 6H), 7.22 – 7.16 (m, 3H), 3.68 (t, *J* = 5.2 Hz, 2H), 2.34 (t, *J* = 5.2 Hz, 2H), 2.04 (bs, 1H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 145.89, 128.74, 128.02, 126.52, 70.71, 62.76, 45.76.

3-(4-Bromophenyl)propan-1-ol (88)



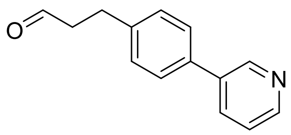
A round-bottom-flask was charged with 3-(4-bromophenyl) propanoic acid (1.00 g, 4.37 mmol, 1 eq) dissolved in dry THF (8.8 mL). After cooling the solution to 0°C $NaBH_4$ (331 mg, 8.73 mmol, 2 eq) was added in small portions and thereafter $BF_3{\cdot}Et_2O$ (1.10 mL, 8.73 mmol, 2 eq) was added dropwise. The resulting mixture was stirred overnight and then quenched by slowly adding MeOH (6 mL), aqueous HCl (1 M, 5 mL) and brine (50 mL). The mixture was then extracted with EtOAc (3x50 mL), the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was re-dissolved in DCM and filtered over Celite to yield the product (0.92 g, 97%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.40 (d, *J* = 8.4 Hz, 2H), 7.07 (d, *J* = 8.4 Hz, 2H), 3.66 (t, *J* = 6.4 Hz, 2H), 2.70 – 2.61 (m, 2H), 1.92 – 1.80 (m, 2H), 1.54 (s, 1H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 140.88, 131.55, 130.33, 119.70, 62.10, 34.11, 31.56.

3-(4-(Pyridin-3-yl)phenyl)propan-1-ol (89)



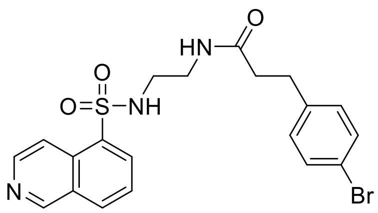
A round-bottom-flask was charged with 3-(4-bromophenyl)propan-1-ol (**88**) (406 mg, 1.89 mmol, 1 eq), pyridin-3-ylboronic acid (348 mg, 2.83 mmol, 1.5 eq) and $Pd(PPh_3)_4$ (20 mg, 0.02 mmol, 0.01 eq) dissolved in DCM (1.9 mL) and DMF (4.2 mL). The flask was put under an argon atmosphere and aqueous K_2CO_3 (2 M, 2.36 mL, 4.73 mmol, 2.5 eq) was added. The reaction mixture was stirred at 85°C for 2.5 h, filtered over celite and concentrated under reduced pressure. The residue was purified via flash-column-chromatography (SiO_2, 50% → 90% EtOAc in pentane) to yield the product (296 mg, 74%). ^1H NMR (400 MHz, chloroform-*d*) δ 8.83 (d, *J* = 1.9 Hz, 1H), 8.57 (dd, *J* = 4.8, 1.3 Hz, 1H), 7.88 (dt, *J* = 7.9, 1.9 Hz, 1H), 7.51 (d, *J* = 8.1 Hz, 2H), 7.37 (dd, *J* = 7.8, 4.9 Hz, 1H), 7.32 (d, *J* = 8.1 Hz, 2H), 3.72 (t, *J* = 6.4 Hz, 2H), 2.83 – 2.74 (m, 2H), 2.59 (s, 1H), 1.94 (dt, *J* = 13.9, 6.4 Hz, 2H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 148.12, 148.09, 142.25, 136.70, 135.37, 134.49, 129.34, 127.23, 123.75, 62.13, 34.28, 31.85.

3-(4-(Pyridin-3-yl)phenyl)propanal (90)



A round-bottom-flask was charged with 3-(4-(pyridin-3-yl)phenyl)propan-1-ol (**89**) (265 mg, 1.19 mmol, 1 eq) dissolved in DCM (4 mL). After addition of Dess–Martin periodinane (553 mg, 1.30 mmol, 1.1 eq) the reaction-mixture was stirred for 60 min, diluted with DCM (10 mL) and quenched with aqueous $Na_2S_2O_3$ (1 M, 15 mL). The mixture was then extracted with DCM (3x15 mL), the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified via flash-column-chromatography (SiO_2, 40% → 80% EtOAc in pentane) to yield the product (204 mg, 74%). ^1H NMR (400 MHz, chloroform-*d*) δ 9.85 (t, *J* = 1.2 Hz, 1H), 8.84 (d, *J* = 1.9 Hz, 1H), 8.59 (dd, *J* = 4.8, 1.5 Hz, 1H), 7.87 (dt, *J* = 7.9, 2.2 Hz, 1H), 7.52 (d, *J* = 8.2 Hz, 2H), 7.42 – 7.35 (m, 1H), 7.32 (d, *J* = 8.2 Hz, 2H), 3.02 (t, *J* = 7.5 Hz, 2H), 2.84 (t, *J* = 7.4 Hz, 2H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 201.41, 148.23, 148.05, 140.59, 136.46, 135.86, 134.46, 129.18, 127.41, 123.73, 45.23, 27.79.

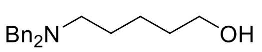
3-(4-Bromophenyl)-*N*-(2-(isoquinoline-5-sulfonamido)ethyl)propanamide (91)



A round-bottom-flask was charged with 3-(4-bromophenyl)propanoic acid (200 mg, 0.87 mmol, 1.05 eq), *N*-(2-aminoethyl)isoquinoline-5-sulfonamide (**105**) (208 mg, 0.83 mmol, 1 eq), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (184 mg, 0.96 mmol, 1.15 eq) and hydroxybenzotriazole (130 mg, 0.96 mmol, 1.15 eq) suspended in DCM (9 mL). After addition of DiPEA (0.23 mL, 1.31 mmol, 1.5 eq) the reaction mixture was stirred for 4 h, quenched with half sat. aqueous $NaHCO_3$ (10 mL) and extracted with DCM (3x10 mL). The combined organic layers were washed with brine (1x50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified via flash-column-chromatography (SiO_2, 0.5% → 4% MeOH in DCM) to yield the desired product (0.41 g, quant.). ^1H NMR (400 MHz, chloroform-*d*) δ 9.36 (s, 1H), 8.67 (d, *J* = 6.1 Hz, 1H), 8.45 – 8.38 (m, 2H), 8.22 (d, *J* = 8.2 Hz, 1H), 7.75 – 7.68 (m, 1H), 7.35 (d, *J* = 8.3 Hz, 2H), 7.00 (d, *J* = 8.3 Hz, 2H), 6.20 (t, *J* = 5.5 Hz, 1H), 6.12 (t, *J* = 5.5 Hz, 1H), 3.30 (q, *J* = 5.7 Hz, 2H), 3.01 (q, *J* = 5.7 Hz, 2H), 2.83 (t, *J* = 7.6 Hz, 2H), 2.36 (t, *J* = 7.6 Hz, 2H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 173.29, 153.31, 145.07, 139.63, 134.20, 133.91, 133.48, 131.69, 131.31, 130.22, 129.16, 126.19, 120.18, 117.45, 43.47, 39.56, 37.89, 30.92. LCMS (ESI,

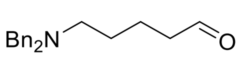
C_{18}, linear gradient, 10% → 90% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 5.39 min; *m/z* : 462, 464 $[M+1]^+$.

5-(Dibenzylamino)pentan-1-ol (93)



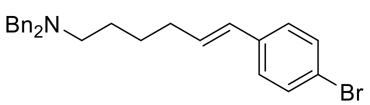
5-Amino-1-pentanol (0.57 mL, 5.0 mmol, 1 eq) and benzaldehyde (1.28 mL, 13 mmol, 2.6 eq) were dissolved in dry THF (50 mL), after which $NaH(OAc)_3$ (3.2 g, 15 mmol, 3 eq) and activated molecular sieves (3 Å) were added. The mixture was stirred for 23 h before sat. aqueous Na_2CO_3 (150 mL) and Et_2O (100 mL) were added, the organic layer was collected and the aqueous layer extracted with DCM (3x50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified via flash-column-chromatography (SiO_2, 1% → 10% (10% of sat. aqueous NH_3 in MeOH) in DCM) to yield the product (1.37 g, 96%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.39 – 7.19 (m, 10H), 3.59 – 3.53 (m, 6H), 2.41 (t, *J* = 7.1 Hz, 2H), 1.57 – 1.48 (m, 2H), 1.48 – 1.40 (m, 2H), 1.38 – 1.27 (m, 3H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 140.05, 128.91, 128.26, 126.87, 63.06, 58.44, 53.28, 32.62, 26.88, 23.39.

5-(Dibenzylamino)pentanal (94)



A solution of oxalyl chloride (0.8 mL, 9.5 mmol, 3.2 eq) in DCM (15 mL) was cooled to -78 °C under argon atmosphere, after which DMSO (1.3 mL, 18 mmol, 6 eq) was added dropwise, 15 min later a solution of 5-(dibenzylamino)pentan-1-ol (**93**) (0.857 g, 3.0 mmol, 1 eq) in DCM (5 mL) was added dropwise and 1 h later Et_3N (3.4 mL, 24 mmol, 8 eq) was added dropwise after which the reaction was allowed to warm to RT over 1 h. The reaction was quenched with sat. aqueous NH_4Cl (2 mL), diluted with sat. aqueous $NaHCO_3$ (100 mL) and DCM (50 mL), after which the organic layer was collected and the aqueous layer extracted with DCM (3x60 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified via flash-column-chromatography (SiO_2, 10% → 30% EtOAc in pentane) to yield the product (0.774 g, 93%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 9.67 (s, 1H), 7.38 – 7.33 (m, 4H), 7.33 – 7.27 (m, 4H), 7.26 – 7.20 (m, 2H), 3.53 (s, 4H), 2.42 (t, *J* = 6.8 Hz, 2H), 2.27 (td, *J* = 7.3, 1.7 Hz, 2H), 1.71 – 1.56 (m, 2H), 1.56 – 1.47 (m, 2H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 202.87, 139.93, 128.92, 128.31, 126.96, 58.51, 52.70, 43.59, 26.55, 19.69.

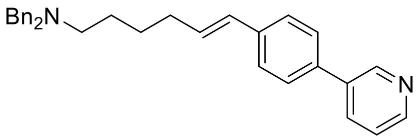
(*E*)-*N*,*N*-Dibenzyl-6-(4-bromophenyl)hex-5-en-1-amine (95)



To a solution of NaH (60% in mineral oil, 6 mg, 0.15 mmol, 1.05 eq) in dry THF (0.2 mL) at 0°C was added dropwise a solution of diethyl (4-bromobenzyl)phosphonate (44 mg, 0.14 mmol, 1 eq) in dry THF (0.2 mL) and the reaction was allowed to warm to RT over 1 h. The solution was cooled to 0°C and a solution of 5-(dibenzylamino)pentanal (**94**) (40 mg, 0.14 mmol, 1 eq) in dry THF (0.4 mL) was added dropwise before the reaction was allowed to warm to RT. After 16 h the reaction was quenched with sat. aqueous NH_4Cl (0.5 mL) and diluted with sat. aqueous $NaHCO_3$ (10 mL) and DCM (10 mL), after which the organic layer was collected and the aqueous layer was extracted with DCM (3x10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified via flash-column-chromatography (SiO_2, 5% → 20% EtOAc in pentane) to yield the product (30 mg, 48%). ^{1}H NMR (400 MHz, chloroform-d) δ 7.41 – 7.39 (m, 1H), 7.37 (dd, *J* = 6.7, 4.5 Hz, 5H), 7.33 – 7.27 (m, 4H), 7.25 – 7.19 (m, 2H), 7.19 – 7.14 (m, 2H), 6.23 (d, *J* = 15.9 Hz, 1H), 6.14 (dt, *J* = 15.8, 6.5 Hz, 1H), 3.54 (s, 4H), 2.42 (t, *J* = 7.0 Hz, 2H), 2.09 (q, *J* = 6.7 Hz, 2H), 1.60 – 1.50 (m, 2H), 1.49 –

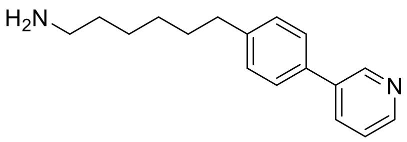
1.39 (m, 2H). ^{13}C NMR (101 MHz, chloroform-d) δ 140.11, 136.91, 131.98, 131.63, 128.89, 128.84, 128.28, 127.59, 126.88, 120.49, 58.48, 53.18, 32.87, 26.83, 26.63.

(*E*)-*N*,*N*-Dibenzyl-6-(4-(pyridin-3-yl)phenyl)hex-5-en-1-amine (96)



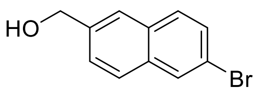
(*E*)-*N*,*N*-dibenzyl-6-(4-bromophenyl)hex-5-en-1-amine (**95**) (0.272 g, 0.63 mmol, 1 eq), $Pd(PPh_3)_4$ (44 mg, 0.038 mmol, 0.06 eq) and pyridine-3-boronic acid (0.12 g, 0.94 mmol, 1.5 eq) were dissolved in a deoxygenated mixture of DCM (0.6 mL), DMF (1.4 mL) and aqueous K_2CO_3 (2 M, 0.8 mL, 1.6 mmol, 2.5 eq) and the reaction was stirred at 80°C for 27 h under argon atmosphere. After cooling to ambient temperature, the mixture was concentrated under reduced pressure, diluted with EtOAc, filtered over silica and concentrated again. The resulting residue was purified via flash-column-chromatography (SiO_2, 20% → 50% EtOAc in pentane) to yield the product (224 mg, 83%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.85 (d, *J* = 1.7 Hz, 1H), 8.57 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.85 (ddd, *J* = 7.9, 2.3, 1.7 Hz, 1H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.42 (d, *J* = 8.3 Hz, 2H), 7.39 – 7.36 (m, 4H), 7.36 – 7.33 (m, 1H), 7.33 – 7.28 (m, 4H), 7.25 – 7.19 (m, 2H), 6.34 (d, *J* = 15.9 Hz, 1H), 6.23 (dt, *J* = 15.8, 6.7 Hz, 1H), 3.55 (s, 4H), 2.44 (t, *J* = 6.9 Hz, 2H), 2.14 (q, *J* = 6.8 Hz, 2H), 1.57 (dt, *J* = 14.0, 6.9 Hz, 2H), 1.53 – 1.42 (m, 2H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 148.42, 148.24, 140.10, 137.92, 136.41, 136.16, 134.13, 132.00, 129.27, 128.89, 128.27, 127.28, 126.87, 126.71, 123.64, 58.46, 53.19, 32.95, 26.91, 26.63.

6-(4-(Pyridin-3-yl)phenyl)hexan-1-amine (97)



A vial containing (*E*)-*N*,*N*-dibenzyl-6-(4-(pyridin-3-yl)phenyl)hex-5-en-1-amine (**96**) (0.204 g, 0.47 mmol, 1 eq) in a mixture of *t*-BuOH/dioxane/H_2O (1:1:0.1, 5 mL) was flushed with argon. $Pd(OH)_2$ (30 wt%, 61 mg) was added and the vial was sealed. The mixture was flushed with H_2 gas for 1 h under vigorous stirring and heated to 50 °C for 3 days under H_2 atmosphere, with periodical H_2 flushing (3x1 h). The mixture was concentrated under reduced pressure and purified via flash-column-chromatography (SiO_2, 15% → 40% (10% of sat. aqueous NH_3 in MeOH) in DCM) to yield the product (75 mg, 63%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.84 (dd, *J* = 2.3, 0.7 Hz, 1H), 8.56 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.88 – 7.81 (m, 1H), 7.55 – 7.46 (m, 2H), 7.37 – 7.30 (m, 1H), 7.30 – 7.24 (m, 2H), 3.53 (bs, 2H), 2.75 (t, *J* = 7.2 Hz, 2H), 2.65 (t, *J* = 7.6 Hz, 2H), 1.66 (dd, *J* = 10.2, 4.7 Hz, 2H), 1.58 – 1.46 (m, 2H), 1.43 – 1.33 (m, 4H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 148.19, 148.18, 142.83, 136.55, 135.16, 134.16, 129.16, 127.01, 123.54, 41.61, 35.52, 32.29, 31.33, 29.04, 26.71.

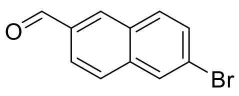
(6-Bromonaphthalen-2-yl)methanol (99)



To a solution of 6-bromo-2-naphthoic acid (1.48 g, 5.9 mmol, 1 eq) dissolved in dry THF (75 mL) at 0°C was added dropwise a lithium aluminium hydride solution (2.4 M, 5 mL, 12 mmol, 2 eq). The reaction was allowed to warm to RT, and after 1 h of stirring it was quenched by addition of H_2O (0.5 mL), queous NaOH (10%, 1 mL) solution and H_2O (3 mL), after which it was stirred for 16 h. The mixture was dried by addition of $MgSO_4$, filtered and the filtrate was concentrated under reduced pressure. The residue was purified via flash-column-chromatography (SiO_2, 10% → 40% EtOAc in pentane) to yield the product (0.872 g, 63%). ^{1}H NMR (400 MHz, chloroform-d) δ 7.99 (s, 1H), 7.79 – 7.72 (m, 2H), 7.69 (d, *J* = 8.7 Hz, 1H), 7.55 (dd, *J* = 8.7, 1.9 Hz, 1H), 7.53 –

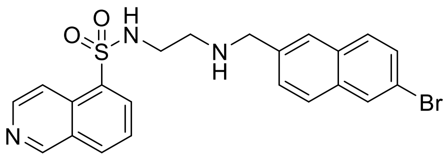
7.46 (m, 1H), 4.84 (s, 2H), 1.79 (s, 1H). ^{13}C NMR (101 MHz, chloroform-d) δ 138.94, 134.07, 131.89, 129.90, 129.71, 129.67, 127.55, 126.29, 125.41, 119.95, 65.37.

6-Bromo-2-naphthaldehyde (100)



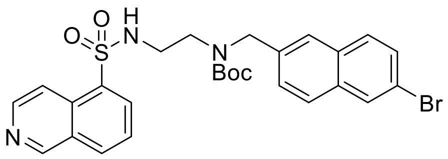
(6-bromonaphthalen-2-yl)methanol (**99**) (0.106 g, 0.45 mmol, 1 eq) and Dess–Martin periodinane (0.23 g, 0.54 mmol, 1.2 eq) were dissolved in DCM (5.4 mL) and subsequently stirred for 1 h at RT. Aqueous $Na_2S_2O_3$ solution (1 M, 10 mL) was added to quench excess reagent, after which the mixture was diluted with H_2O (10 mL). The phases were separated, the aqueous layer was extracted with DCM (3x20 mL), the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified via flash-column-chromatography (SiO_2, 5% → 6% EtOAc in pentane) to yield the product (0.105 g, quant.). ^{1}H NMR (400 MHz, chloroform-*d*) δ 10.13 (s, 1H), 8.27 (s, 1H), 8.04 (s, 1H), 7.96 (d, *J* = 8.4 Hz, 1H), 7.82 (t, *J* = 9.6 Hz, 2H), 7.68 – 7.58 (m, 1H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 191.93, 137.31, 134.36, 134.18, 131.11, 131.05, 130.70, 130.32, 128.23, 124.06, 123.67.

***N*-(2-(((6-Bromonaphthalen-2-yl)methyl)amino)ethyl)isoquinoline-5-sulfonamide (101)**



6-bromo-2-naphthaldehyde (**100**) (0.538 g, 2.3 mmol, 1 eq) and *N*-(2-aminoethyl)isoquinoline-5-sulfonamide (**105**) (1.2 g, 4.6 mmol, 2 eq) were dissolved in dry THF (23 mL) by sonication, after which glacial acetic acid (0.13 mL, 2.3 mmol, 1 eq) and $NaHB(OAc)_3$ (0.97 g, 4.6 mmol, 2 eq) were added and the reaction was stirred for 19 h at RT. The reaction was diluted with EtOAc (100 mL), sat. aqueous K_2CO_3 solution (100 mL) was added, the phases separated and the aqueous layer was extracted with EtOAc (3x50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified via flash-column-chromatography (SiO_2, 1.5% → 2.5% (10% of sat. aqueous NH_3 in MeOH) in DCM) to yield the product (788 mg, 74%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 9.19 (s, 1H), 8.53 (d, *J* = 6.1 Hz, 1H), 8.45 (d, *J* = 6.1 Hz, 1H), 8.36 (d, *J* = 7.3 Hz, 1H), 7.95 (d, *J* = 8.2 Hz, 1H), 7.81 (s, 1H), 7.55 – 7.43 (m, 3H), 7.43 – 7.36 (m, 2H), 7.15 (d, *J* = 9.4 Hz, 1H), 4.21 (bs, 2H), 3.58 (s, 2H), 3.03 (t, *J* = 5.6 Hz, 2H), 2.62 (t, *J* = 5.6 Hz, 2H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 152.99, 144.50, 137.49, 134.17, 133.25, 133.19, 132.96, 131.32, 130.91, 129.37, 129.12, 129.10, 128.66, 127.09, 126.88, 125.93, 125.78, 119.25, 117.17, 52.80, 47.56, 42.38.

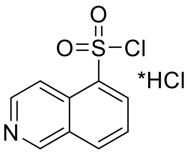
***tert*-Butyl ((6-bromonaphthalen-2-yl)methyl)(2-(isoquinoline-5-sulfonamido) ethyl)carbamate (102)**



A solution of *N*-(2-(((6-bromonaphthalen-2-yl)methyl)amino)ethyl)isoquinoline-5-sulfonamide (**101**) (0.788 g, 1.7 mmol, 1 eq) and $NaHCO_3$ (0.17 g, 2.0 mmol, 1.2 eq) in THF (8.4 mL) was cooled to 0°C after which di-*tert*-butyl dicarbonate (0.55 g, 2.5 mmol, 1.5 eq) were added and the reaction was allowed to warm to RT. After stirring for 24 hours sat. aqueous $NaHCO_3$ solution (20 mL) and DCM (20 mL) were added after which the organic layer was collected and the aqueous layer was extracted with DCM (3x20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified via flash-column-chromatography (SiO_2, 40% → 70% EtOAc in pentane) to yield the product (0.448 g, 46%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 9.33 (s, 1H), 8.63 (d, *J* = 5.4 Hz, 1H), 8.37 (s, 1H), 8.26 (s, 1H), 8.13 (d, *J* = 8.2 Hz, 1H), 7.95 (s, 1H), 7.62 (d, *J* = 3.3 Hz, 1H), 7.60

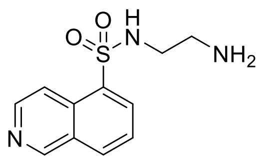
(d, J = 3.1 Hz, 1H), 7.58 – 7.52 (m, 2H), 7.50 (s, 1H), 7.24 (s, 1H), 6.22 (s, 1H), 4.46 (s, 2H), 3.35 (s, 2H), 3.01 (s, 2H), 1.44 (s, 9H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 153.35, 145.26, 135.83, 134.36, 133.84, 133.52, 133.17, 131.69, 131.27, 129.84, 129.48, 129.10, 127.82, 127.75, 126.29, 125.96, 125.86, 124.89, 120.03, 117.39, 81.28, 51.98, 46.66, 42.63, 28.47.

Isoquinoline-5-sulfonyl chloride (104)



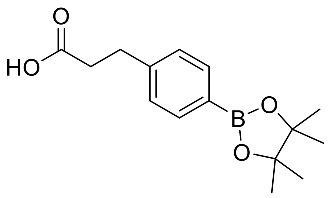
A flask was charged with isoquinoline-5-sulfonic acid (3.20 g, 15.30 mmol, 1 eq) dissolved in $SOCl_2$ (20 mL). After addition of DMF (0.5 mL) the mixture was heated to reflux for 4 h. Excess $SOCl_2$ was removed under reduced pressure, the resulting solid was re-suspended in DCM, filtered over a glass-filter and washed with DCM to yield the product (3.83 g, 95%). Due to the unstable nature of the product it was used without further purification.

***N*-(2-Aminoethyl)isoquinoline-5-sulfonamide (105)**



A solution of isoquinoline-5-sulfonic acid (4.01 g, 19.16 mmol, 1 eq) and catalytic DMF (0.1 mL) in $SOCl_2$ (25 mL) was stirred under reflux for three hours. The mixture was filtered over a glass filter and the resulting white powder was washed thoroughly with DCM and dried under reduced pressure. It was dissolved in a 4°C sat. aqueous $NaHCO_3$ solution and extracted with DCM (3x40 mL). The combined organic layers were dried over $MgSO_4$, filtered and added dropwise over half an hour to an ice cold solution of ethylenediamine (7.6 mL, 114 mmol, 6 eq) in DCM (200 mL). The reaction was allowed to warm to RT and 1.5 h later sat. aqueous Na_2CO_3 (200 mL) were added. The mixture was extracted with DCM (3x150 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified via flash-column-chromatography (SiO_2, 3% → 10% (10% of sat. aqueous NH_3 in MeOH) in DCM) to yield the desired product (3.78 g, 79%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 9.37 (s, 1H), 8.68 (d, J = 6.1 Hz, 1H), 8.48 – 8.41 (m, 2H), 8.22 (d, J = 8.2 Hz, 1H), 7.76 – 7.66 (m, 1H), 2.96 (dd, J = 6.5, 4.8 Hz, 2H), 2.77 (dd, J = 6.5, 4.8 Hz, 2H), 2.66 (s, 3H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 153.41, 145.21, 134.50, 133.67, 133.38, 131.37, 129.16, 126.08, 117.38, 45.25, 40.91. LCMS (ESI, Thermo, C_{18}, linear gradient, 10% → 90% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 0.8 min; *m/z* : 252 $[M+1]^+$.

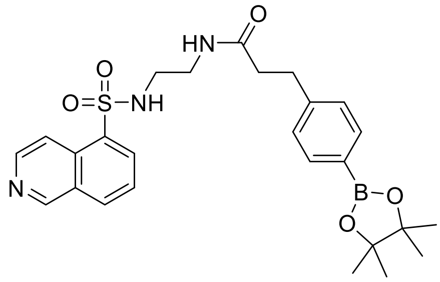
3-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propanoic acid (106)



A round-bottom-flask was charged with 3-(4-bromophenyl)propanoic acid (2.00 g, 8.73 mmol, 1 eq), bis(pinacolato)diboron (3.33 g, 13.10 mmol, 1.5 eq), potassium acetate (4.28 g, 43.65 mmol, 5 eq) and [1,1′-bis (diphenylphosphino)ferrocene]dichloropalladium (357 mg, 0.44 mmol, 0.05 eq) suspended in dry and degassed 1,4-dioxane (44 mL). The reaction mixture was degassed for 30 min by passing N_2 through it while sonicating and stirred at 100°C overnight. The resulting black solution was concentrated in vacuum, re-suspended in EtOAc (100 mL) and extracted with aqueous NaOH (2 M, 3x100 mL). The combined aqueous layers where acidified to pH ~4 with conc. aqueous HCl and extracted with EtOAc (3x100 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentration under reduced pressure yielded the product (2.47 g, quant.), which was used without further purification. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.75 (d, J = 8.0 Hz, 1H), 7.22

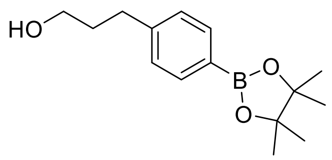
(d, *J* = 7.9 Hz, 1H), 2.97 (t, *J* = 7.8 Hz, 1H), 2.68 (t, *J* = 7.8 Hz, 1H), 1.34 (s, 12H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 178.18, 143.60, 135.23, 127.85, 83.88, 35.39, 30.91, 25.00.

N-(2-(Isoquinoline-5-sulfonamido)ethyl)-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propanamide (107)



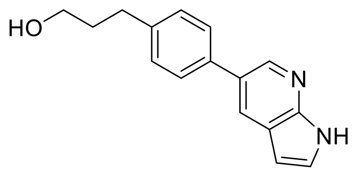
A round-bottom-flask was charged with 3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl) propanoic acid (**106**) (1.00 g, 3.62 mmol, 1 eq), *N*-(2-aminoethyl)isoquinoline-5-sulfonamide (**105**) (0.96 g, 3.80 mmol, 1.05 eq), *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (764 mg, 3.98 mmol, 1.1 eq) and hydroxybenzotriazole (538 mg, 3.98 mmol, 1.1 eq) suspended in DCM (36 mL). After addition of DiPEA (0.95 mL, 5.43 mmol, 1.5 eq) the reaction mixture was stirred for 4 h, diluted with H_2O (100 mL) and extracted with DCM (3x100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified via flash-column-chromatography (SiO_2, 3% → 10% MeOH in DCM) to yield the product (1.45 g, 79%). ^1H NMR (400 MHz, chloroform-*d*) δ 9.35 (s, 1H), 8.70 (d, *J* = 6.0 Hz, 1H), 8.44 – 8.36 (m, 2H), 8.20 (d, *J* = 8.2 Hz, 1H), 7.75 – 7.66 (m, 3H), 7.14 (d, *J* = 7.9 Hz, 2H), 5.92 (dt, *J* = 11.4, 5.6 Hz, 2H), 3.24 (q, *J* = 5.7 Hz, 2H), 2.98 (q, *J* = 5.6 Hz, 2H), 2.88 (t, *J* = 7.5 Hz, 2H), 2.37 (t, *J* = 7.6 Hz, 2H), 1.33 (s, 12H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 173.49, 153.29, 145.16, 143.99, 135.22, 134.39, 133.80, 133.42, 131.35, 129.17, 127.92, 126.15, 117.54, 83.94, 75.17, 43.45, 39.67, 38.09, 31.89, 25.01. LCMS (ESI, Thermo, C_{18}, linear gradient, 10% → 90% ACN in H_2O, 0.1% TFA, 10.5 min): t_R = 5.81 min; *m/z* : 510 $[M+1]^+$.

3-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propan-1-ol (108)



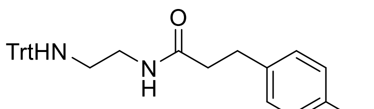
A round-bottom-flask was charged with 3-(4-bromophenyl)propan-1-ol (**88**) (916 mg, 4.26 mmol, 1 eq), bis (pinacolato)diboron (1.63 g, 6.39 mmol, 1.5 eq), potassium acetate (2.09 g, 21.29 mmol, 5 eq) and [1,1′-bis (diphenylphosphino) ferrocene]dichloropalladium (174 mg, 0.21 mmol, 0.05 eq). The flask was put under argon atmosphere and after the reactants were suspended in 1,4-dioxane (22 mL) the mixture was heated to 100°C overnight and then concentrated under reduced pressure. The residue was purified via flash-column-chromatography (SiO_2, 0% → 20% EtOAc in pentane) to yield the product (1.03 g, 92%). ^1H NMR (400 MHz, chloroform-*d*) δ 7.74 (d, *J* = 7.4 Hz, 2H), 7.22 (d, *J* = 7.4 Hz, 2H), 3.66 (t, *J* = 6.3 Hz, 2H), 2.72 (t, *J* = 7.6 Hz, 2H), 1.89 (p, *J* = 6.7 Hz, 2H), 1.34 (s, 12H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 145.40, 135.09, 128.05, 83.80, 62.35, 34.20, 32.40, 24.98.

3-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-5-yl)phenyl)propan-1-ol (109)



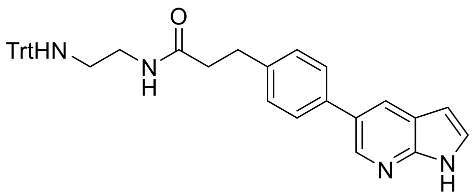
A round-bottom-flask was charged with 3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propan-1-ol (**108**) (0.51 g, 1.95 mmol, 1 eq), 5-bromo-7-azindole (0.58 g, 2.92 mmol, 1.5 eq) and $Pd(PPh_3)_4$ (112 mg, 0.097 mmol, 0.05 eq). The flask was put under an argon atmosphere and degassed DMF (7 mL) and degassed aqueous K_2CO_3 solution (2 M, 2.43 mL, 4.88 mmol, 2.5 eq) were added. After the reaction mixture was stirred at 85°C overnight, sat. aqueous $NaHCO_3$ (40 mL) was added and the product was extracted with DCM (3x40 mL). The combined organic layers were washed with brine (1x100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified via flash-column-chromatography (SiO_2, 50% → 70% EtOAc in pentane) to yield the desired product (0.248 g, 51%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.69 (s, 1H), 8.49 (d, *J* = 1.9 Hz, 1H), 8.20 – 8.13 (m, 1H), 7.60 (d, *J* = 8.0 Hz, 2H), 7.51 – 7.48 (m, 1H), 7.29 (d, *J* = 8.0 Hz, 2H), 6.49 (s, 1H), 4.50 (t, *J* = 5.0 Hz, 1H), 3.45 (q, *J* = 6.1 Hz, 2H), 2.70 – 2.62 (m, 2H), 1.75 (p, *J* = 6.6 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 147.96, 141.40, 140.81, 136.48, 128.96, 128.15, 126.85, 126.76, 125.82, 119.68, 100.10, 60.11, 34.29, 31.25.

3-(4-Bromophenyl)-*N*-(2-(tritylamino)ethyl)propanamide (110)



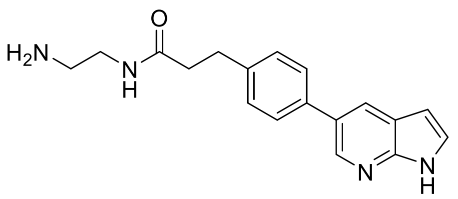
3-(4-Bromophenyl) propionic acid (3.00 g, 13.10 mmol, 1.05 eq), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (3.63 g, 13.72 mmol, 1.1 eq), hydroxybenzotriazole (1.85 g, 13.7 mmol, 1.1 eq) and N^1-tritylethane-1,2-diamine (**60**) (3.77 g, 12.47 mmol, 1.0 eq) were dissolved in DCM (130 mL). DiPEA (3.26 mL, 18.71 mmol, 1.5 eq) was added and the mixture stirred for 16 h at RT. The mixture was quenched with saturated aqueous $NaHCO_3$ (300 mL). The phases were separated and the aqueous layer was extracted with DCM (3x200 mL). The combined organic layers were washed with brine (1x250 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified via flash-column-chromatography (SiO_2, 20% → 60% EtOAc in pentane) to yield the product (4.52 g, 71%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.45 – 7.39 (m, 6H), 7.37 – 7.31 (m, 2H), 7.30 – 7.24 (m, 7H), 7.22 – 7.17 (m, 3H), 7.09 – 7.03 (m, 2H), 5.68 (s, 1H), 3.33 (q, *J* = 6.0 Hz, 2H), 2.92 (t, *J* = 7.6 Hz, 2H), 2.44 (t, *J* = 7.6 Hz, 2H), 2.26 (t, *J* = 6.1 Hz, 2H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 171.82, 145.75, 140.01, 131.70, 130.26, 128.64, 128.05, 126.61, 120.16, 43.55, 40.15, 38.39, 31.13. TLCMS (ESI): *m/z* : 513 [M+1]$^+$.

3-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-5-yl)phenyl)-*N*-(2-(tritylamino)ethyl) propanamide (111)



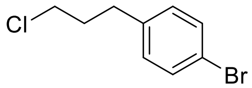
3-(4-Bromophenyl)-*N*-(2-(tritylamino) ethyl) propanamide (**110**) (1.00 g, 1.95 mmol, 1.0 eq), 5-(4,4,5,5- tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-*b*]pyridine (710 mg, 2.92 mmol, 1.5 eq) and $Pd(PPh_3)_4$ (45 mg, 0.039 mmol, 0.02 eq) were dissolved in deoxygenated DMF (8 mL) and aqueous K_2CO_3 (2 M, 2.43 mL, 4.87 mmol, 2.5 eq). The mixture was stirred for 18 h at 85°C. The reaction mixture was filtered over silica, washed with EtOAc and concentrated under reduced pressure. The resulting residue was purified via flash-column-chromatography (SiO_2, 50% → 100% EtOAc in pentane) to yield the product (0.91 g, 85%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 10.41 – 10.07 (m, 1H), 8.54 – 8.52 (m, 1H), 8.09 (d, *J* = 1.8 Hz, 1H), 7.53 (d, *J* = 8.1 Hz, 2H), 7.45 (d, *J* = 7.4 Hz, 6H), 7.40 (s, 1H), 7.34 (d, *J* = 8.1 Hz, 2H), 7.32 – 7.25 (m, 7H), 7.20 (t, *J* = 7.2 Hz, 3H), 6.59 – 6.57 (m, 1H), 5.87 (s, 1H), 3.40 (q, *J* = 5.8 Hz, 2H), 3.07 (t, *J* = 7.6 Hz, 2H), 2.58 (t, *J* = 7.6 Hz, 2H), 2.32 (t, *J* = 6.0 Hz, 2H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 172.18, 148.09, 145.71, 142.18, 139.81, 137.59, 129.52, 128.98, 128.57, 127.96, 127.55, 127.29, 126.50, 125.81, 120.35, 101.20, 70.82, 43.48, 40.12, 38.58, 31.37. TLCMS (ESI): *m/z* : 551 [M+1]$^+$.

3-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-5-yl)phenyl)-*N*-(2-aminoethyl)propanamide (113)



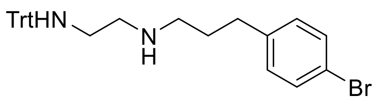
3-(4-(1*H*-pyrrolo[2,3-b]pyridin-5-yl)phenyl)-*N*-(2-(tritylamino) ethyl) propanamide (**111**) (0.827 g, 1.50 mmol, 1.0 eq) was dissolved in DCM (48 mL). TFA (0.67 mL, 9.01 mmol, 6.0 eq) was added dropwise over 10 min at 0°C. Subsequently, triethylsilane (1.92 mL, 12.0 mmol, 8.0 eq) was added to the reaction mixture and it was stirred for 16 h at RT. The mixture was quenched with sat. aqueous Na_2CO_3 (250 mL). The phases were separated and the aqueous layer was extracted with a mixture of 5% MeOH in $CHCl_3$ (3x100 mL). The combined organic layers were washed with brine (1x250 mL), dried over Na_2SO_4, filtered and concentrated onto celite under reduced pressure. The resulting residue was purified via flash-column-chromatography (SiO_2, 10% → 25% (10% of sat. aqueous NH_3 in MeOH) in DCM) to yield the product (0.404 g, 86%). ^{1}H NMR (400 MHz, methanol-*d*$_4$) δ 8.35 (d, *J* = 2.0 Hz, 1H), 8.08 (s, 1H), 7.47 (d, *J* = 7.8 Hz, 2H), 7.36 (d, *J* = 3.5 Hz, 1H), 7.23 (d, *J* = 7.9 Hz, 2H), 6.47 (d, *J* = 3.5 Hz, 1H), 3.18 (d, *J* = 6.2 Hz, 2H), 2.90 (t, *J* = 7.5 Hz, 2H), 2.61 (t, *J* = 6.2 Hz, 2H), 2.48 (t, *J* = 7.5 Hz, 2H). ^{13}C NMR (101 MHz, methanol-*d*$_4$) δ 175.45, 148.67, 142.12, 140.97, 138.57, 130.41, 130.08, 128.31, 128.22, 127.72, 122.25, 101.71, 42.74, 41.82, 38.87, 32.46. TLCMS (ESI): *m/z* : 309 $[M+H]^+$.

1-Bromo-4-(3-chloropropyl)benzene (114)



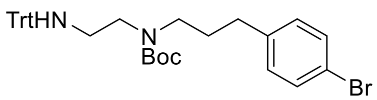
3-(4-Bromophenyl)propan-1-ol (**88**) (3.5 g, 15 mmol, 1.0 eq) was dissolved in DMF (30 mL). The solution was cooled to 0°C and thionyl chloride (2.36 mL, 32.54 mmol, 2.2 eq) was added and the resulting mixture stirred for 19 h at RT. The mixture was quenched with H_2O (1x100 mL) and washed with H_2O (2x100 mL). The phases were separated and the combined aqueous layers were extracted with Et_2O (2x100 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent removed under reduced pressure. The resulting residue was purified via flash-column-chromatography (SiO_2, 100% pentane) to yield the product (3.75 g, 99%). ^{1}H NMR (300 MHz, chloroform-*d*) δ 7.46 – 7.37 (m, 2H), 7.08 (d, *J* = 8.4 Hz, 2H), 3.51 (t, *J* = 6.4 Hz, 2H), 2.74 (t, *J* = 7.4 Hz, 2H), 2.12 – 1.98 (m, 2H). ^{13}C NMR (75 MHz, chloroform-*d*) δ 139.74, 131.68, 130.44, 120.04, 44.11, 33.90, 32.24.

***N*^{1}-(3-(4-Bromophenyl)propyl)-*N*^{2}-tritylethane-1,2-diamine (115)**



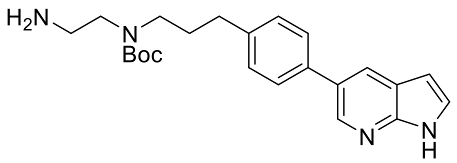
1-Bromo-4-(3-chloropropyl)benzene (**114**) (3.70 g, 15.8 mmol, 1.0 eq), *N*^{1}-tritylethane-1,2-diamine (**60**) (14.37 g, 47.53 mmol, 3.0 eq) and K_2CO_3 (4.38 g, 31.69 mmol, 2.0 eq) were suspended in ACN (55 mL). The mixture was heated to 70°C and stirred for 72 h. The reaction mixture was cooled to RT, filtered and the solvent removed under reduced pressure. The reaction mixture was concentrated onto celite and purified via flash-column-chromatography (SiO_2, dry-loading, 0.5% → 3% (10% of sat. aqueous NH_3 in MeOH) in DCM) to yield the product (5.56 g, 70%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.46 (dt, *J* = 8.5, 1.9 Hz, 6H), 7.39 – 7.34 (m, 2H), 7.29 – 7.23 (m, 6H), 7.20 – 7.14 (m, 3H), 7.04 (d, *J* = 8.4 Hz, 2H), 2.71 (t, *J* = 5.9 Hz, 2H), 2.61 – 2.56 (m, 2H), 2.56 – 2.51 (m, 2H), 2.28 (t, *J* = 5.9 Hz, 2H), 1.88 (bs, 2H), 1.77 (p, *J* = 7.4 Hz, 2H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 146.21, 141.10, 131.49, 130.26, 128.78, 127.90, 126.36, 119.61, 70.87, 50.13, 48.94, 43.07, 33.06, 31.49. TLCMS (ESI): *m/z* : 499 $[M+H]^+$.

***tert*-Butyl (3-(4-bromophenyl)propyl)(2-(tritylamino)ethyl)carbamate (116)**



N[1]-(3-(4-Bromophenyl)propyl)-*N*[2]-tritylethane-1,2-diamine (**115**) (5.51 g, 11.0 mmol, 1.0 eq), di-*tert*-butyl dicarbonate (3.86 g, 17.6 mmol, 1.6 eq) and $NaHCO_3$ (1.11 g, 13.2 mmol, 1.2 eq) were dissolved in THF (37 mL). The reaction mixture was stirred for 36 h at RT. The mixture was quenched with sat. aqueous $NaHCO_3$ (300 mL). The phases were separated and the aqueous layer was extracted with DCM (3x200 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent removed under reduced pressure. The resulting residue was purified via flash-column-chromatography (SiO_2, 5% → 40% Et_2O in pentane) to yield the product (6.62 g, quant.). ^1H NMR (400 MHz, chloroform-*d*) δ 7.47 – 7.41 (m, 6H), 7.37 (d, *J* = 8.1 Hz, 2H), 7.29 – 7.21 (m, 6H), 7.17 (t, *J* = 7.2 Hz, 3H), 7.00 (d, *J* = 8.3 Hz, 2H), 3.28 (s, 2H), 3.17 (s, 2H), 2.54 – 2.44 (m, 2H), 2.27 (bs, 2H), 1.74 (p, *J* = 7.7 Hz, 2H), 1.62 (bs, 1H), 1.50 – 1.30 (m, 9H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 155.72, 146.08, 140.88, 131.51, 130.18, 128.66, 127.95, 126.40, 119.66, 79.53, 70.84, 48.01, 47.41, 42.56, 32.74, 29.91, 28.54. TLCMS (ESI): *m/z* : 599 $[M+H]^+$.

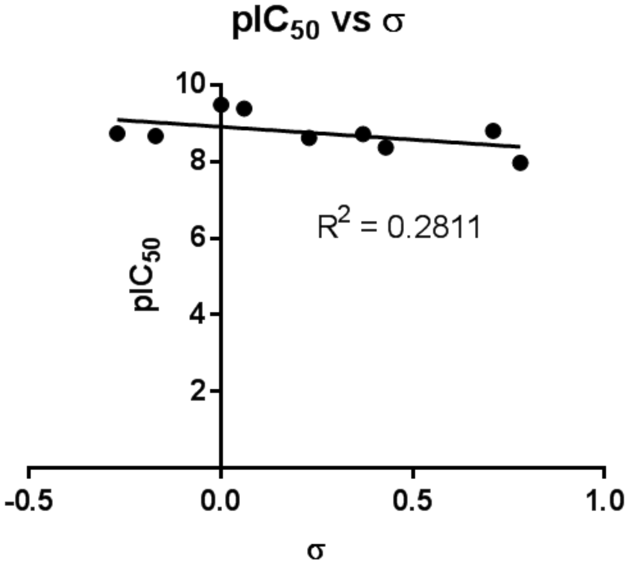
***tert*-Butyl (3-(4-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)phenyl)propyl)(2-aminoethyl) carbamate (117)**



<u>**Step 1:**</u> *tert*-Butyl (3-(4-bromophenyl)propyl)(2-(tritylamino)ethyl)carbamate (**116**) (6.62 g, 11.04 mmol, 1.0 eq), 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (4.03 g, 16.56 mmol, 1.5 eq) and $Pd(PPh_3)_4$ (255 mg, 0.26 mmol, 0.02 eq) were dissolved in deoxygenated DMF (48 mL) and aqueous K_2CO_3 (2 M, 13.80 mL, 26.60 mmol, 2.5 eq). The mixture was stirred for 17 h at 90°C and then filtered over celite and silica. The resulting residue was purified via flash-column-chromatography (SiO_2, 50% → 100% Et_2O in pentane) and used directly in the following step.

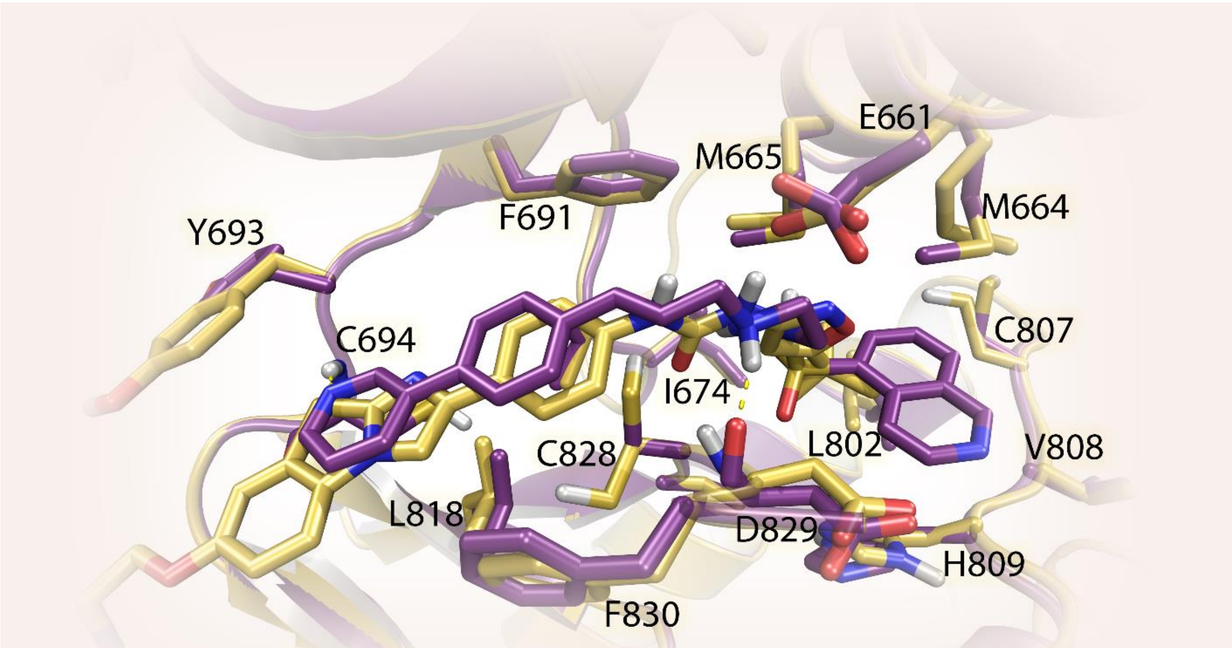
<u>**Step 2:**</u> Crude product from step 1 (2.90 g, 5.27 mmol, 1.0 eq) was dissolved in DCM (163 mL) and cooled to 0°C. TFA (2.35 mL) was added dropwise and after 10 min, triethylsilane (6.73 mL, 42.13 mmol, 8.0 eq) was added. The mixture was stirred for 20 h at RT and was then quenched with sat. aqueous $NaHCO_3$ (150 mL). The phases were separated and the aqueous layer was extracted with DCM (3x100 mL). The combined organic layers were washed with brine (1x200 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified via flash-column-chromatography (SiO_2, dry-loading, 7% (10% of sat. aqueous NH_3 in MeOH) in DCM) to yield the desired product (0.903 g, 21% over 2 steps). ^1H NMR (600 MHz, chloroform-*d*, 330K) δ 10.22 (s, 1H), 8.54 (d, *J* = 2.1 Hz, 1H), 8.09 (d, *J* = 2.1 Hz, 1H), 7.53 (d, *J* = 8.1 Hz, 2H), 7.36 (d, *J* = 3.5 Hz, 1H), 7.27 (d, *J* = 8.1 Hz, 2H), 6.53 (d, *J* = 3.5 Hz, 1H), 3.31 – 3.25 (m, 4H), 2.85 (t, *J* = 6.6 Hz, 2H), 2.69 – 2.63 (m, 2H), 1.92 (p, *J* = 7.7 Hz, 2H), 1.59 (bs, *J* = 35.1 Hz, 2H), 1.45 (d, *J* = 6.7 Hz, 9H). ^{13}C NMR (151 MHz, chloroform-*d*, 330K) δ 156.11, 148.40, 142.42, 140.70, 137.57, 129.92, 128.99, 127.59, 127.25, 125.80, 120.51, 101.29, 79.70, 50.59, 47.83, 41.06, 33.06, 30.33, 28.66.

Supplementary Information



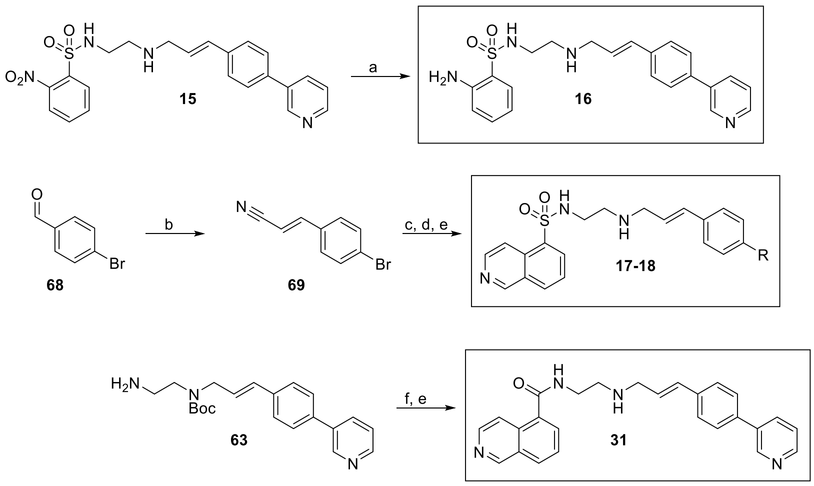
Substituent	σ
H	0
4-Cl	0.23
$4\text{-}CH_3$	-0.17
$4\text{-}OCH_3$	-0.27
$3\text{-}NO_2$	0.71
3-Cl	0.37
4-F	0.06
$4\text{-}NO_2$	0.78
$3\text{-}CF_3$	0.43

SI Figure 1: Plot of pIC_{50}-values of the amide series versus the corresponding substituent σ-values and the used σ-values for each substituent.[36]



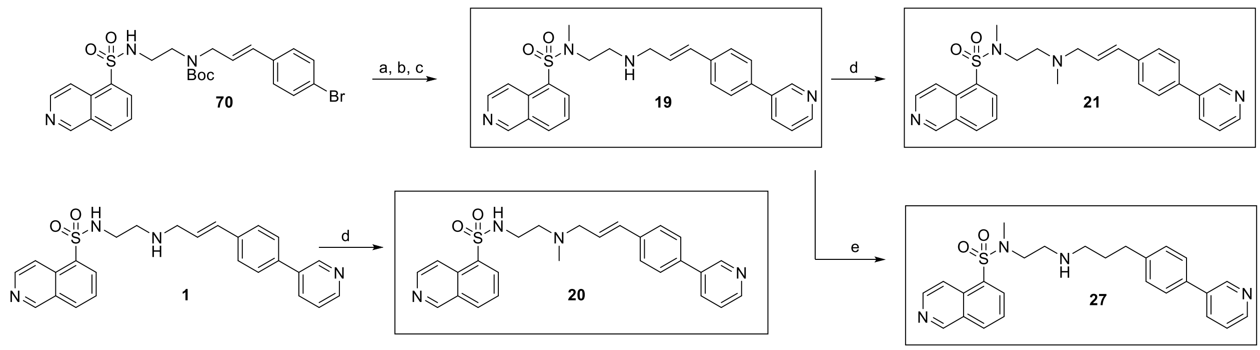
SI Figure 2: Proposed binding mode of **1** (purple) overlaid with the crystal structure of FLT3 co-crystalized with quizartinib (yellow) (PDB: 4RT7).

SI Scheme 1: Synthetic route towards the derivatives **16** - **18**, **31**.[a]



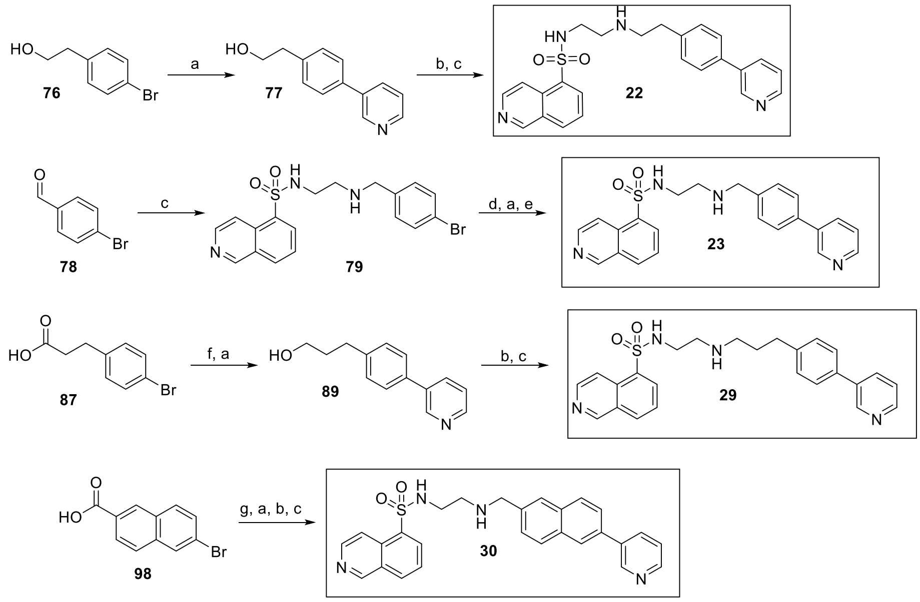
[a]Reagents and conditions: (a) Fe, AcOH, EtOH/H_2O; (b) diethyl cyanomethylphosphonate, NaH, DMF, 0°C – RT; (c) DiBAL-H, Et_2O, -80°C – 0°C, then **105**, $NaBH_4$, MeOH, -100°C – 0°C, then Boc_2O; (d) arylboronic acid, $Pd(PPh_3)_4$, K_2CO_3, DMF/DCM/H_2O, 90°C; (e) TFA, DCM, 0°C – RT; (f) isoquinoline-5-carboxylic acid, $SOCl_2$, then DiPEA, DMAP, substrate, DCM, 0°C – RT.

SI Scheme 2: Synthetic route towards the derivatives **19** – **21**, **27**.[a]



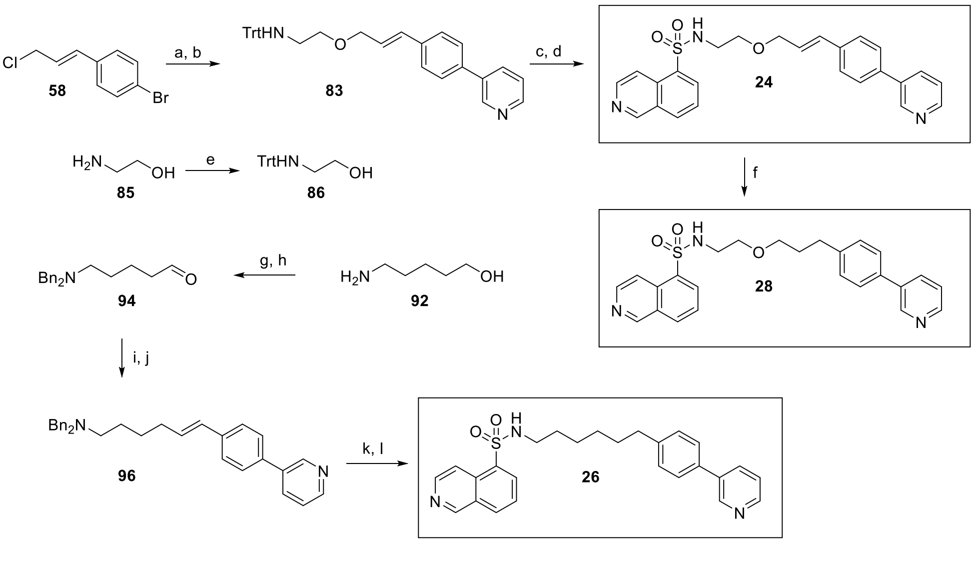
[a]Reagents and conditions: (a) MeI, Cs_2CO_3, DMF, RT; (b) arylboronic acid, $Pd(PPh_3)_4$, K_2CO_3, DMF/DCM/H_2O, 80°C; (c) TFA, $CHCl_3$, 0°C – RT; (d) formaldehyde, $NaHB(OAc)_3$, THF/MeOH, RT; (e) Pd/C, H_2, MeOH.

SI Scheme 3: Synthetic route towards the derivatives **22**, **23**, **29** and **30**.[a]



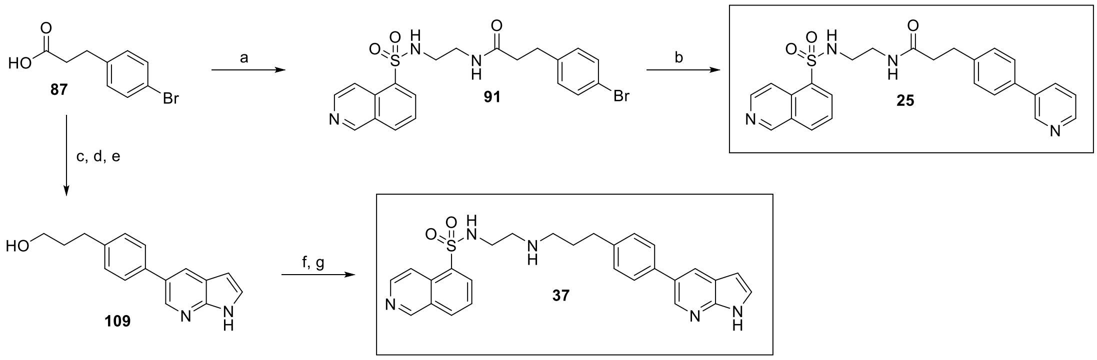
[a]Reagents and conditions: (a) arylboronic acid, $Pd(PPh_3)_4$, K_2CO_3, DMF/DCM/H_2O, 90°C; (b) DMP, DCM, 0°C – RT; (c) **105**, $NaHB(OAc)_3$, THF or DCM, RT; (d) Boc_2O, $NaHCO_3$, THF, RT; (e) TFA, DCM, 0°C – RT; (f) $NaBH_4$, BF_3, THF, 0° - RT; (g) $LiAlH_4$, THF, 0° - RT.

SI Scheme 4: Synthetic route towards the derivatives **24**, **26**, **28**.[a]



[a]Reagents and conditions: (a) **86**, NaH, ACN, 70°C; (b) arylboronic acid, $Pd(PPh_3)_4$, K_2CO_3, DMF/DCM/H_2O, 80°C; (c) TFA, TES, DCM, 0°C – RT; (d) **104**, Et_3N, DCM, 0°C – RT; (e) TrtCl, K_2CO_3, DCM, RT; (f) *p*-toluenesulfonyl hydrazide, NaOAc, THF, 66°C; (g) benzaldehyde, $NaBH(OAc)_3$, THF, RT; (h) oxalyl chloride, DMSO, Et_3N, DCM, -80°C – RT; (i) diethyl (4-bromobenzyl)phosphonate, NaH, THF, 0°C – RT; (j) arylboronic acid, $Pd(PPh_3)_4$, K_2CO_3, DMF/DCM/H_2O, 80°C; (k) $Pd(OH)_2$, *t*-BuOH/1,4-dioxane/H_2O, H_2, RT; (l) **104**, Et_3N, DCM, 0°C – RT.

SI Scheme 5: Synthetic route towards the derivatives **25** and **37**.[a]



[a]Reagents and conditions: (a) **105**, EDC, HOBt, DiPEA, DCM, RT; (b) arylboronic acid, $Pd(PPh_3)_4$, K_2CO_3, DMF/DCM/H_2O, 85°C; (c) $NaBH_4$, BF_3, THF, 0° - RT; (d) B_2Pin_2, KOAc, Pd(dppf)Cl_2, 1,4-dioxane, 100°C, overnight; (e) arylbromide, $Pd(PPh_3)_4$, K_2CO_3, DMF/DCM/H_2O, 85°C; (f) DMP, DCM, 0°C – RT; (g) **105**, $NaHB(OAc)_3$, DCM, RT.

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