Discovery of antibiotics and their targets in multidrug-resistant bacteria

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Chapter 5

Identification of LEI-800 as a potent antibiotic against Gram-negative bacteria

Introduction

The global threat posed by antimicrobial resistance (AMR) continues to rise every year and is associated with an ever-increasing death toll. In 2019, an estimated 1.27 million deaths worldwide were directly attributable to AMR, 20% of which were linked to antibiotic resistant strains of *Escherichia coli*.[1] Multidrug-resistant (MDR) Gram-negative pathogens, such as *E. coli* and *Klebsiella pneumoniae* strains that display resistance to third generation cephalosporins, carbapenems, and fluoroquinolones, are now widespread[2] and pose a daunting challenge to healthcare systems. At the same time, resistance to antibiotics of last resort[3] has also been detected in several countries. The emergence of mobilized colistin resistance-1 (mcr-1) in 2015[4] and tigecycline resistance (tetX3–tetX5) genes in 2019[5] threatens

to render Gram-negative MDR infections untreatable. Clearly, new antibiotics with a novel mode-of-action (MoA) are urgently needed to keep pace with drug-resistant Gram-negative bacteria.

In Chapter 2, a diverse chemical library was screened to identify molecules with antibacterial activity against Gram-negative species *E. coli* (Figure 5.1). *N*-(2-((4-(pyridin-3-yl)benzyl)amino)ethyl)isoquinoline-5-sulfonamide, or compound **1**, was identified as most potent hit. Compound **1** was previously synthesized as part of a SAR study[6] around human kinase inhibitor H-89.[7]

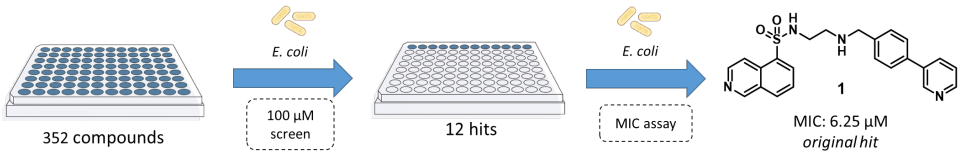


Figure 5.1 | Summary of the in-house library screen in Chapter 2 that led to compound **1**.

Here, a medicinal chemistry program was employed to map the structure-activity relationships (SAR) of **1**. This led to the rational design of LEI-800, a compound with enhanced antimicrobial activity against *E. coli* and *K. pneumoniae*.

Results and discussion

Identification pharmacophore of hit 1 through extended screening. To explore the antibacterial properties of this scaffold, 45 analogs (**2**-**46**, Figure S5.1) were rescreened, which were previously synthesized as part of the original SAR study.[6] These compounds were screened at a single 50 µM concentration against the *E. coli* W3110 strain. Interestingly, we observed steep activity-cliffs, as no other compound than hit **1** showed antimicrobial activity (MIC > 50 µM). A striking distinction between compound **1** and the other compounds was the 6-atom linker between the isoquinoline and the inner phenyl ring (Figure 5.2) suggesting that the distance between these two hydrophobic, aromatic moieties is of key importance.

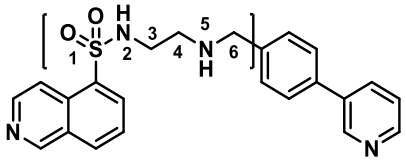
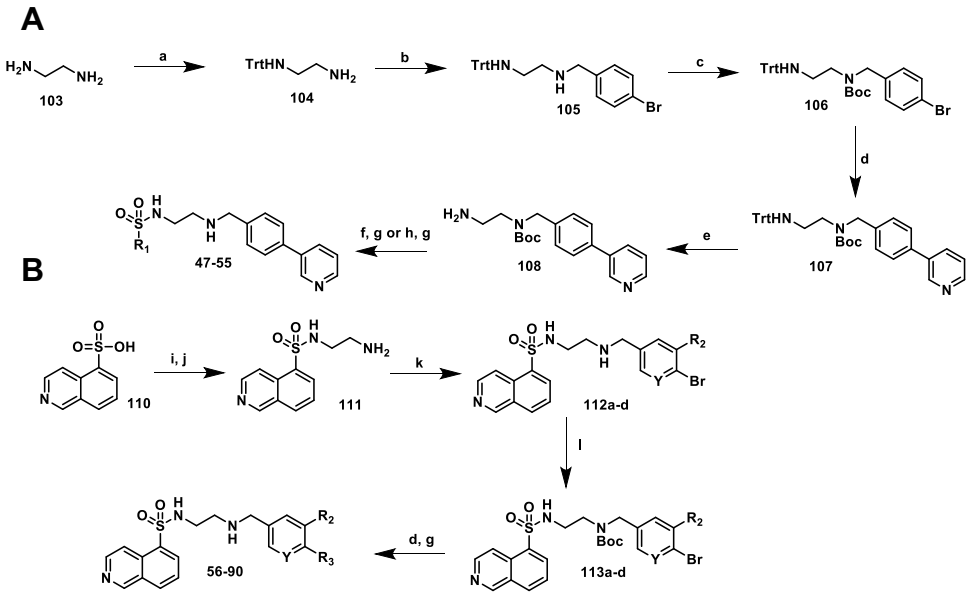


Figure 5.2 | Hit **1** contains a linker region, indicated with brackets and numbers, that differentiates it from similar compounds in its series.

Structure-activity relationship study reveals steep activity-cliffs. To further study the SAR of compound **1**, a variety of synthetic routes were followed to generate compounds **47**-**95** (Scheme 5.1)**.** Variations of the isoquinoline and the inner and outer aromatic rings were investigated, while keeping the linker length constant. The antibacterial activity of these compounds was evaluated using the minimum inhibitory concentration (MIC) assay described in Chapter 2. Gram-negative strains *E. coli* W3110, and *K. pneumoniae* ATCC 29655 were used for biological evaluation of the compounds.

Synthesis of the left-side isoquinoline derivatives (Scheme 5.1A) started with monotritylation of ethylenediamine (**103**) to form **104**. Reductive amination with 4-bromobenzaldehyde resulted in benzylation of the primary amine (**105**), which was subsequently protected with a Boc-group (**106**). Suzuki coupling of the aryl bromide with 3-pyridinyl boronic acid afforded **107**, which was detritylated to form primary amine building block **108**. Amine **108** was then reacted with either *in situ* generated sulfinates[8] or commercially available sulfonyl chlorides, followed by Boc-deprotection, to form final compounds **47**-**55**.



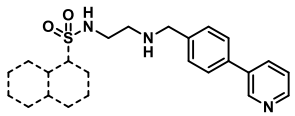
Scheme 5.1 | A) General synthetic route for left ring derivatives of compound **1**. **B)** General synthetic route for inner and outer ring derivatives of compound **1**. Reagents and conditions: a) trityl chloride, K_2CO_3, DCM, RT, quant.; b) bromobenzaldehyde, $NaBH_4$, THF, MeOH, 40%; c) Boc_2O, Et_3N, DCM, 59%; d) $R_3(BOH)_2$, $Pd(PPh_3)_4$, K_2CO_3, H_2O, dioxane, 90°C, 76%; e) triethylsilane, TFA, DCM, RT, 91%; f) R_1SO_2Cl, Et_3N, DCM, 0°C; g) TFA, DCM, 0°C, 3 – 89% (over two or three steps); h) R_1Br, TBAB, sodium formate, $Pd(OAc)_2$, PPh_3, 1-10-phenathroline, *N*-chlorosuccinimide, DIPEA, DMSO, THF, 70°C to RT; i) $SOCl_2$, DMF, 60°C; j) ethylene diamine, DCM, 0°C to RT, 93% (over two steps); k) R_2-bromobenzaldehyde, $NaBH(Oac)_3$, AcOH, THF, RT, 73 – 91%; l) Boc_2O, $NaHCO_3$, THF, 0°C to RT, 86%.

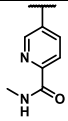
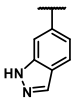
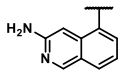
Synthesis of right-side derivatives started with isoquinoline sulfonic acid (**110**) being transformed into the sulfonyl chloride followed by a reaction with ethylenediamine to form **111**. Reductive amination of **111** with a variety of 4-bromobenzaldehydes formed secondary amines **112a**-**d**, which were then Boc-protected to form bromides **113a**-**d**. These

intermediates were coupled to a variety of boronic acids, and subsequently deprotected to form final compounds **56**-**90**. Linker derivatives **91**-**95** were synthesized following Schemes S5.1-5.

First, the importance of the isoquinoline was investigated (**47**-**55**, Table 5.1). Compound **47**, in which the nitrogen of the isoquinoline was substituted for a carbon atom, showed a four-fold reduced activity, whereas compound **48**, with a phenyl ring, lost all activity. This suggests that reduced electron density of the isoquinoline ring might be important for activity and/or that the nitrogen accepts a hydrogen-bond.

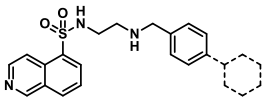
Table 5.1 | Isoquinoline derivatives of hit **1**.



ID	R	MIC (μM)		ID	R	MIC (μM)	
		E. coli	*K. pneumoniae*			*E. coli*	*K. pneumoniae*
1		6.25	12.5	**51**		>50	>50
47		25	>50	**52**		>50	>50
48		>50	>50	**53**		>50	>50
49		>50	>50	**54**		>50	>50
50		>50	>50	**55**		>50	>50

Compounds **49**-**55** contain structural motifs that were previously shown to form more hydrogen bonds with backbone amides of proteins than an isoquinoline, thereby enhancing the potency or specificity of the interaction. In this case, compounds **49**-**55** were inactive, which was taken to suggest that the isoquinoline might reside in a hydrophobic pocket or that the groups lead to reduced cell permeability.

Table 5.2 | Outer ring derivatives of hit **1**.



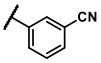
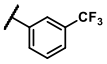
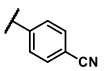
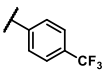
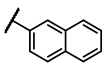
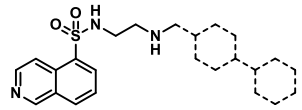
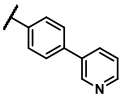
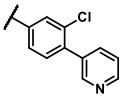
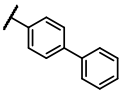
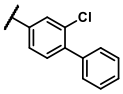
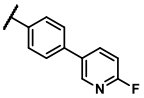
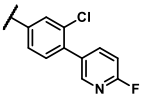
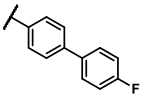
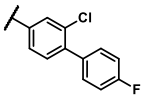
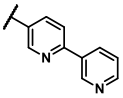
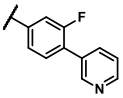
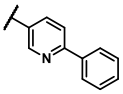
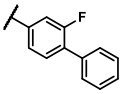
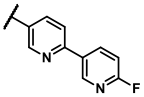
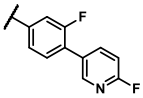
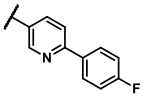
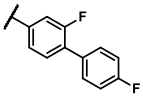
ID	R	MIC (μM)		ID	R	MIC (μM)	
		E. coli	*K. pneumoniae*			*E. coli*	*K. pneumoniae*
1		6.25	12.5	**67**		>50	>50
56		6.25	12.5	**68**		12.5	25
57		6.25	12.5	**69**		25	>50
58		25	25	**70**		25	50
59		3.1	6.25	**71**		12.5	50
60		6.25	6.25	**72**		25	50
61		6.25	>50	**73**		25	50
62		>50	>50	**74**		25	>50
63		6.25	12.5	**75**		>50	>50
64		>50	>50	**76**		>50	>50
65		12.5	25	**77**		>50	>50
66		12.5	25	**78**		>50	>50

Table 5.3 | Inner ring derivatives of hit **1**.



ID	R	MIC (μM)		ID	R	MIC (μM)	
		E. coli	*K. pneumoniae*			*E. coli*	*K. pneumoniae*
1		6.25	12.5	**83**		>50	>50
6		6.25	12.5	**84**		>50	>50
60		6.25	6.25	**85**		>50	>50
59		3.1	6.25	**86**		50	>50
79		>50	>50	**87**		25	50
80		>50	>50	**88**		12.5	25
81		>50	>50	**89**		6.25	12.5
82		>50	>50	**90**		12.5	12.5

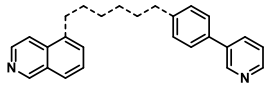
Next, the electronic and hydrophobic properties of the outer aryl ring were systematically studied (**56**-**78**, Table 5.2) by applying the Topliss-scheme. The nitrogen in pyridyl (**1**) was shown not to be important, because compound **56** with a phenyl ring or a thiophene as a phenyl bioisoster (**57**), but not furan (**58**), were equally potent. Electron withdrawing substituents (e.g., a fluoro (**59, 60**), chloro (**61**) or cyano (**63**)), but not more polar or donating substituents (**62, 64, 65**), were tolerated.

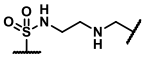
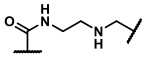
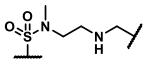
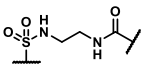
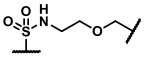
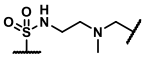
Of note, compound **59** with a *para*-fluoro group showed a two-fold increase in potency with a MIC of 3.1 μM on *E. coli* and was the most potent compound identified in this series, while all compounds with *ortho*- or *meta* substituents (**66**-**75**) demonstrated a reduced potency (Table 5.2). Introduction of a second ring on the phenyl group (compounds **76**-**78**) resulted

in a complete loss of potency, which may indicate the presence of a restricted binding pocket or lack of cell penetration.

Introducing a nitrogen in the inner phenyl ring (compounds **79-82**) to reduce lipophilicity or an *ortho* substituent (compounds **83-90**) to create a rotational barrier did not improve potency (Table 5.3).

Table 5.4 | Linker derivatives of hit **1**.



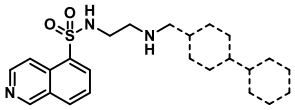
ID	R	MIC (μM)	
		E. coli	*K. pneumoniae*
1		6.25	12.5
91		>50	>50
92		>50	>50
93		>50	>50
94		>50	>50
95		>50	50

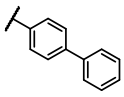
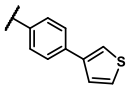
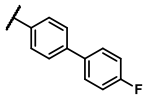
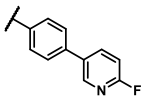
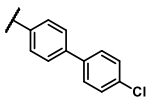
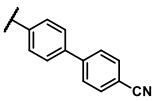
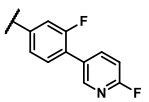
Finally, the importance was investigated of the sulfonamide and secondary amine in the six-atom linker (Table 5.4). Replacement of the sulfonamide with an amide (**91**) or substituting the nitrogen with a methyl group (**92**) led to a loss of activity, suggesting that the sulfonamide is important for directing the isoquinoline into a specific orientation. Replacing the secondary amine with an amide (**93**) or ether (**94**), as well as substituting it with a methyl group (**95**), abolished all activity, thereby suggesting the secondary amine may form an important hydrogen bond or is essential for cellular uptake. Similar trends of the SAR were observed in *K. pneumoniae* (Table 5.1-5.4), although the isoquinolines were generally less potent than in *E. coli*.

Next, the most active compounds (**56, 57, 59, 60, 61, 63** and **89**) were tested for cytotoxicity using human kidney (HEK293T) and liver (HepG2) cell lines by means of an MTT assay measuring metabolic activity as an indicator of cell viability, and compound cytotoxicity

(Table 5.5). In contrast to the other compounds, **60** was found to be non-cytotoxic (IC_{50} > 50 μM). In comparison, the most potent compound **59** was toxic for human cell lines (IC_{50} HEK293T = 2.6 μM, IC_{50} HepG2 = 1.7 μM) at a concentration similar to its MIC. Thus, compound **60** was selected as the lead molecule for further development.

Table 5.5 | Human cytotoxicity data of hit **1** derivatives.



ID	R	MIC (μM)		IC_{50} (μM)	
		E. coli	*K. pneumoniae*	HEK293T (human)	HepG2 (human)
56		6.25	12.5	10.4	16.7
57		6.25	12.5	6.6	8.2
59		3.1	6.25	2.6	1.7
60		6.25	6.25	>50	>50
61		6.25	50	1.0	2.8
63		6.25	12.5	14.7	38
89		6.25	12.5	8.9	6.8

Conformational restriction results in discovery of LEI-800. The initial SAR study, as described above, revealed that the isoquinoline sulfonamides have strict structural requirements to act as antibiotics for Gram-negative bacteria (Figure 5.3A). This steep SAR can be potentially explained by a defined binding pocket on a specific target in combination with a need for essential molecular features to enhance their cellular uptake and/or prevent their efflux. Since it has previously been observed that cell penetration of antibiotics in Gram-negative bacteria can be enhanced by conformational restriction and enhanced target affinity can be obtained due to a reduced loss in entropy,[9] it was hypothesized that reducing the number of rotatable bonds of the linker in the isoquinoline sulfonamide series might increase their antibiotic activity. To this end, four conformationally restricted diastereomeric derivatives (**96**-**99**) based on compound **60** were designed, in which the secondary amine linker was replaced with a 2,5-disubstituted pyrrolidine motif (Figure 5.3B), followed by additional synthesis of **100**-**102**, based on the most potent stereoisomer.

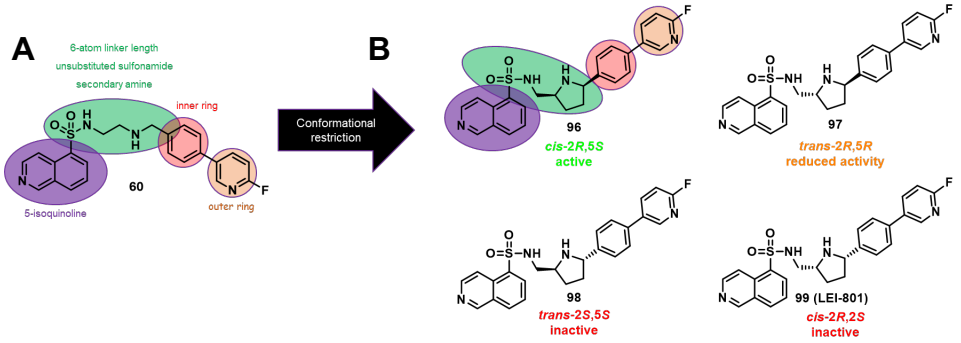
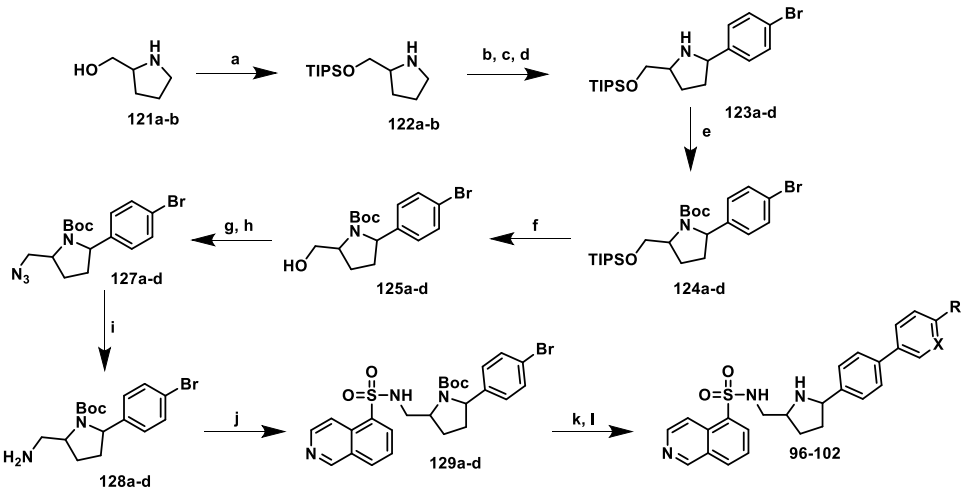


Figure 5.3 | A) SAR overview of **60**. The 5-isoquinoline (purple), linker (green), inner ring (red), and outer ring (orange) were systemically modified using structure **1** as reference. The essential groups are noted in corresponding colors. **B)** Conformational restriction using a pyrrolidine linker retains all the core molecular features, while reducing loss of entropy upon binding. The *cis*-2*R*,5*S* isomer (green) is the only diastereomer that is more potent than the parent compound. The *trans*-2*R*,5*R* isomer (orange) still inhibits growth but at higher concentrations, while the *cis*-2*S*,5*R* and the *trans*-2*S*,5*S* isomers (red) both do not show activity.

The synthesis of compounds **96**-**102** was started by protecting the alcohol of enantiomerically pure prolinol (*R* or *S*) with a triisopropylsilyl (TIPS) group (**122a**-**b**), after which the second chiral center was introduced through alpha-functionalization of the pyrrolidine with lithiated dibromobenzene, forming a new carbon-carbon bond (Scheme 5.2). Following the procedures of Seidel *et al.* [10,11] both *cis* and *trans* isomers in a 4:1 ratio (35% total yield) were obtained (**123a**-**d**), which were separated by column chromatography. After Boc-protection of the pyrrolidine (**124a**-**d**), the TIPS-*O* could be converted into a primary amine in four steps. First the TIPS was deprotected using TBAF (**125a**-**d**), then the alcohol was functionalized with a mesyl group (**126a**-**d**) that was substituted by an azide (**127a**-**d**), which could be reduced under Staudinger conditions (**128a**-**d**). The isoquinoline group was introduced by coupling of the amines with isoquinoline-5-sulfonylchloride to form **129a**-**d**. On the opposite side of the structure, Suzuki-coupling with a variety of boronic acids, followed by acidic deprotection of the Boc group gave final compounds **96**-**102**.

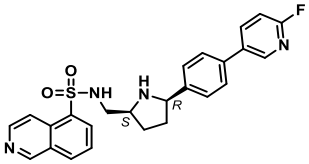
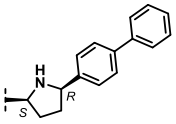
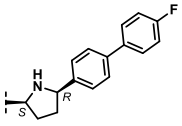
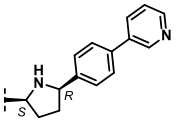


Scheme 5.2 | General synthetic route for conformationally restricted variants of compound **60**. Reagents and conditions: a) TIPS-Cl, imidazole, DMAP, DCM, RT, 23-31%; b) benzophenone; c) *n*-BuLi, Et_2O, -78°C to RT; d) BrPhLi, Et_2O, -78°C to RT, 34 – 35% (over two steps); e) Boc_2O, Et_3N, DCM, RT, 28 – 68%; f) TBAF, MECN, RT, 57% –quant.; g) MsCl, Et_3N, DCM, RT, quant.; h) NaN_3, DMSO, 64°C, 53 – 69%; i) PPh_3, H_2O, THF, 70°C, 63 – 83%; j) 5-isoquinoline-SO_2Cl, Et_3N, DCM, 0°C to RT, 84 – 98%; k) $FpyrB(OH)_2$, $Pd(PPh_3)_4$, K_2CO_3, dioxane, H_2O, 90°C, 51 – 94%; l) TFA, DCM, 0°C to RT, 33 – 74%.

With the four diastereomers in hand (**96**-**99**), we tested their activity in the *E. coli* and *K. pneumoniae* growth assays. Notably, we found that the diastereomer bearing the *cis*-2*R*,5*S* configuration (compound **96**) was much more active than the others and also showed a two-fold increase in potency compared to compound **60** (Table 5.5). The other diastereomers were either 4-fold less active (*trans*-2*R*,5*R,* **97**) or completely inactive (*trans*-2*S*,5*S* (**98**) and *cis*-2*S*,2*R* (**99**)).

Building from this finding, three outer ring derivatives of **96,** based on the SAR described above**,** were synthesized (**100**-**102**) and tested in the MIC and cytotoxicity assays (Table 5.6). Compounds **100** and **101**, phenyl and *p*-fluorophenyl analogs, respectively, were the most potent isoquinoline sulfonamides of this study with a MIC = 1.6 μM, but they also displayed cytotoxicity in a similar concentration range (3-37 μM). Compound **102** with a pyridyl substituent was the most potent compound with a MIC of 3.1 μM, with no cytotoxicity or hemolytic activity (Figure S5.2) observed.

Table 5.6 | Antibacterial activity and cytotoxicity of conformationally restricted isoquinoline sulfonamides.

ID	Structure	MIC (μM)		IC_{50} (μM)	
		E. coli	*K. pneumoniae*	HEK293T (human)	HepG2 (human)
96		3.1	12.5	22	>50
97		12.5	25	39	>50
98		>50	>50	49	>50
99 (LEI-801)		>50	>50	>50	>50
100		1.6	6.25	8.1	37
101		1.6	3.1	3.2	13
102 (LEI-800)		3.1	6.25	>50	>50

In keeping with the activity profile of the parent compounds, **102** showed selectivity towards the Gram-negative strains *E. coli* and *K. pneumoniae* among a selection of pathogenic species (Table 5.7). Furthermore, this activity was maintained when **102** was tested on several clinical isolates of *E. coli*, including multidrug resistant (MDR), mcr-1 positive, and extended-spectrum beta lactamase (ESBL) producing strains.

Table 5.7 | MICs of key compounds **60**, **101**, **102** and control compound ciprofloxacin against a panel of bacteria, including clinical isolates of *E. coli*.

Organism	Strain	Resistance profile	MIC (μM)			
			60	**101**	**102**	CIP
Gram-positive						
Staphylococcus aureus	ATCC 29213		>50	>50	>50	0.755
	ATCC BAA1717		>50	>50	>50	>0.755
Gram-negative						
Klebsiella pneumoniae	ATCC 29665		12.5	3.1	6.25	0.012
Acinetobacter baumannii			>50	25	25	0.755
Pseudomonas aeruginosa	ATCC 27853		>50	>50	>50	0.377
E. coli	W3110		6.25	1.6	3.1	0.024
	BW25113		6.25	1.6	3.1	0.024
	ATCC 25922		12.5	3.1	6.25	0.024
	mcr-1	*MCR*	50	12.5	25	>32
	NCTC13463	*ESBL*	12.5	3.1	3.1	1
	NCTC13846	*MDR (mcr-1)*	>50	12.5	50	>32
	MVAST0072[#]	*MDR*	50	12.5	25	>32
	552059.1[#]		50	12.5	25	1
	552060.1[#]		50	12.5	25	1

CIP: ciprofloxacin, MCR: mobile colistin resistance, MDR: multidrug resistant, ESBL: extended spectrum beta lactamase, [#] urinary tract infection isolates.

Also of note, compound **102** was found to be able to time-dependently kill *E. coli*, when evaluated at higher concentrations (Figure 5.4).

In view of this excellent profile, we selected compound **102** for further profiling (Chapter 6) and termed it LEI-800, whereas closely related inactive compound **99** (LEI-801) was chosen as a negative control compound.

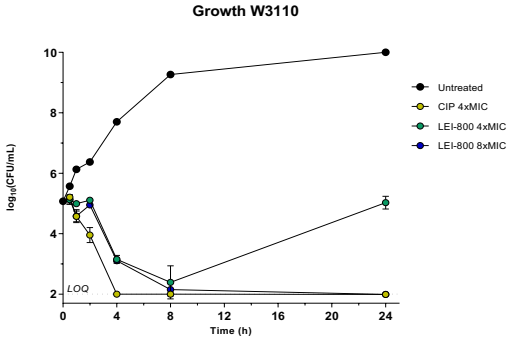
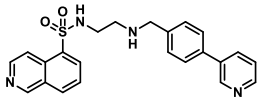
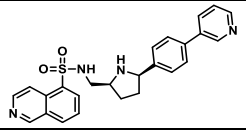


Figure 5.4 | Time-dependent killing of *E. coli* W3110 by compound LEI-800. Ciprofloxacin (CIP) is used as a control compound. LOQ = limit-of-quantification.

Conclusion

In this chapter, an extensive SAR study of hit **1** has been performed, which led to the identification of a) isoquinoline sulfonamide, b) six-atom linker and c) biaryl as key elements of the pharmacophore required for *in vitro* antibiotic activity against *E. coli* and *K. pneumoniae*. Subsequently, conformational restriction led to the identification of compound LEI-800, which has favorable physicochemical properties and exhibits potent, Gram-negative-specific antibacterial activity with little mammalian cell toxicity (Table 5.8). In Chapter 6 the target identification of LEI-800 will be described.

Table 5.8 | Physicochemical properties of lead compound LEI-800 compared to original hit **1**.

ID	Structure	MIC *E. coli* (μM)	MIC KP (μM)	MW (Da)	cLogP	PSA (Å^2)	HBA	HBD	RB
1		6.25	12.5	419	2.49	92.4	6	2	7
LEI-800		3.1	6.25	444	3.31	92.4	6	2	5

KP = *K. pneumoniae*; PSA = polar surface area; HBA = hydrogen bond acceptors; HBD = hydrogen bond donors; RB = rotatable bonds.

Acknowledgments

The following people are kindly acknowledged for their contribution to this chapter. Bing Liu, Diana Piermarini, and Jeroen Punt for assisting with the synthesis of new compounds. Ioli Kotsogianni for assisting with the MIC assays, as well as with the time-kill assay.

Methods

Reagents & materials. Buffers and salts were of ACS reagent grade or higher and were purchased commercially, from Carl Roth GmbH (Karlsruhe, Germany) and Sigma-Aldrich (Darmstadt, Germany), biological materials and growth media were purchased from Sigma-Aldrich, Scharlab S.L. (Barcelona, Spain) and Fisher Scientific (Landsmeer, Netherlands). Antibiotics trimethoprim (Sigma-Aldrich), ceftazidime (ceftazidime pentahydrate, Thermo Scientific, Landsmeer, Netherlands) and kanamycin (kanamycin monosulfate, MP biomedicals, Illkirch, France) were dissolved in DMSO and stored at -20°C, apart from ciprofloxacin, which was used from a 3 M aqueous solution containing 0.01% AcOH. All test compounds were used from 10 mM DMSO stock solutions made from the freeze-dried powder and stored at -20°C.

Bacterial strains. *Klebsiella pneumoniae* ATCC 29665 (NCTC 11228), *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853, *Acinetobacter baumannii* ATCC BAA747 and *Staphylococcus aureus* USA300 (ATCC BAA1717) belong to the American Type Culture Collection (ATCC). *E. coli* NCTC 13463 and 13846 belong to the National Collection of Type Cultures (UK Health Security Agency). *E. coli* JW5503, JW3600, JW3602, JW3605 JW3594, JW3596 belong to the Keio Collection1 of single-gene knockouts. *E. coli* NCTC 13463 and 13846 belong to the National Collection of Type Cultures (NCTC, UK Health Security Agency). *E. coli* strains 552059.1 and 552060.1 were isolated from urine and acquired from the clinical Medical Microbiology department at the University Medical Center Utrecht. *E. coli* mcr-1 (EQAS 2016 412016126, mcr-1 positive, recovered during international antimicrobial resistance programs), W3110, BW25113, belong to the laboratory collection of N.I.M. The following reagents were obtained through BEI Resources, NIAID, NIH: *E. coli*, Strain MVAST0072, NR-51488.

Minimum inhibitory concentration (MIC). From glycerol stocks, bacterial strains were cultured on blood agar plates by overnight incubation at 37°C. A single colony was transferred to TSB. In case of VRSA strains, 6 μg/mL vancomycin was supplemented to the media. The cultures were grown to exponential phase (OD600: 0.5) at 37°C. The bacterial suspensions were diluted 100-fold in CAMHB and 50 μL was added to a 2-fold serial dilution series of test compounds (50 μL per well) in polypropylene 96-well microtiter plates to reach a volume of 100 μL. The plates were sealed with breathable membranes and incubated overnight at 37°C with constant shaking (600 rpm). For Enterococci species direct colony suspension was used by immediately suspending multiple colonies from fresh blood agar plates in CAMHB to an OD600 of 0.5 and subsequent 100-fold dilution. The MIC was determined as the lowest concentration at which no visible bacterial growth was observed, as compared to the inoculum controls, from the median of a minimum of triplicates.

Mammalian cell culture. HepG2 and HEK293T cell lines (ATCC) were cultured at 37 °C and 7% CO_2 in DMEM (Sigma Aldrich, D6546) with GlutaMax, penicillin (100 μg ml−1), streptomycin (100 μg ml−1) and 10% Fetal Calf serum. Cells were passaged twice a week by first detaching using 0.05% trypsin in PBS, and then diluting to appropriate confluence.

Cytotoxicity assay (MTT). Compound cytotoxicity was evaluated against HepG2 and HEK293T human cell lines using standard (3-(4,5-dimethylthiazol-2-yl)−2,5-diphenyltetrazolium bromide (MTT) assay protocol with slight changes.[12] HepG2 and HEK293T cells were seeded at a density of 1.5×10^4 cells per well in a clear 96-well tissue culture treated plate in a final volume of 100 μL in Dulbecco's Modified Eagle Medium (DMEM), supplemented with Fetal Bovine Serum (1%), Glutamax and Pen/Strep. Cells were incubated for 24 h at 37°C, 7% CO_2 to allow cells to attach to the plates. In addition to a single vehicle control, compounds (diluted from DMSO stock) were added into each well at eight concentrations ranging from 100 μM to 0.046 μM in three-fold dilutions (final DMSO concentration 0.5%). Incubation was done for 24 h at 37°C, 7% CO_2. After the incubation, MTT was added to each well at a final concentration of 0.40 mg/mL. The plates were then incubated for 2 h at 37°C, 7% CO_2. Medium was carefully removed via suction, and purple formazan crystals were resuspended in 100 μL DMSO. Absorbance was read at 570 nm using a Clariostar plate reader. The data was then analysed with GraphPad Prism software. IC_{50} values were calculated using non-linear fitted curve with variable slope

settings, with values adjusted for background (plotted $ABS_{SAMPLE} = (ABS_{SAMPLE} - ABS_{BACKGROUND}) / (ABS_{VEHICLE} - ABS_{BACKGROUND})$). Technical triplicates for each condition were used, along with two biological replicates. The reported IC_{50} was obtained by averaging the calculated IC_{50} of both biological replicates.

Minimum bactericidal concentration (MBC). For minimum bactericidal concentration (MBC) determination, 96-well plates were prepared likewise in biological duplicate. After incubation, 100 µL of each bacterial culture corresponding to 1, 2, 4, 8 and 16× MIC was centrifuged for 5 min (12500 rpm). The supernatant was discarded and pellets were washed once with filter-sterilized PBS, then resuspended in an equal volume of fresh buffer and samples were diluted with a 10-fold factor. 10 µL of the appropriate dilutions were inoculated on Lysogeny Broth (LB) agar plates in technical duplicates, allowed to evaporate and incubated at 37°C for 18 h. The colonies were counted and used to calculate the CFU/mL of the original culture. The MBC was determined as the lowest concentration of the test compound that was able to produce a 99.9% decrease in viable bacterial cells.

Time-kill assay. From glycerol stocks, bacterial strains were cultured on blood agar plates by overnight incubation at 37°C. Subsequently, a single colony was cultured in TSB overnight at 37°C. The culture was diluted 100-fold in fresh CAMHB and grown until early exponential phase (OD600: 0.25) followed by 100-fold dilution in media (OD600: 0.0025). The culture was split in separate culture tubes containing 2 mL. Test compounds were added to the cultures at concentration 3.1 µM and 6.2 µM (corresponding to 4 and 8× MIC) and incubated at 37°C for a total of 24 h. At indicated time points (t: 0, 1/2, 1, 2, 4, 8 and 24 h) 100 µL of each culture was centrifuged for 5 min (12500 rpm). The supernatant was discarded and pellets were washed once with filter-sterilized PBS, then resuspended in an equal volume of fresh buffer and samples were 10-fold serially diluted until 10^5 dilution. 10 µL of the appropriate dilutions were inoculated on LB agar plates in technical duplicates, allowed to evaporate and incubated at 37°C for 18 h. 10 µL of the appropriate dilutions were inoculated on LB agar plates in technical duplicates, subsequently allowed to evaporate and incubated at 37°C for 18 ± 2 h. The colonies were counted and used to calculate the CFU/mL remaining in the original culture by taking the dilution factors into account. Experiment was performed in biological duplicates.

Synthetic procedures

General remarks

All chemicals (Sigma-Aldrich, Fluka, Acros, Merck, Combi-Blocks, Fluorochem, TCI) were used as received. All solvents used for reactions were of analytical grade. THF, Et_2O, DMF, MECN and DCM were dried over activated 4 Å molecular sieves, MeOH over 3 Å molecular sieves. H_2O used in synthesis procedures was of Milli-Q-grade quality. Column chromatography was performed on silica gel (Screening Devices BV, 40-63 µm, 60 Å). The eluent EtOAc was of technical grade and distilled before use. Triethylamine was distilled over KOH, and triethylamine and pyridine were stored over KOH pellets. Starting materials were coevaporated with toluene (3×) before use in water-sensitive reactions.

Reactions were monitored by thin layer chromatography (TLC) analysis using Merck aluminium sheets (Silica gel 60, F254). Compounds were visualized by UV-absorption (254 nm) and spraying for general compounds: $KMnO_4$ (20 g/L) and K_2CO_3 (10 g/L) in H_2O, or for amines: ninhydrin (0.75 g/L) and acetic acid (12.5 mL/L) in ethanol, followed by charring at 150°C. ^1H and ^{13}C NMR experiments were recorded on a Bruker AV-300 (300/75 MHz), Bruker AV-400 (400/101 MHz), Bruker DMX-400 (400/101 MHz), Bruker AV- 500 (500/126 MHz) and Bruker AV-600 (600/151 MHz). Chemical shifts are given in ppm (δ) relative to tetramethylsilane, as internal standard. Multiplicity: s = singlet, bs = broad singlet, d = doublet, dd = doublet of doublet, t = triplet, q = quartet, quint = quintet, non = nonet m = multiplet. Coupling constants (*J*) are given in Hz. LC-MS measurements were performed on a Thermo Finnigan LCQ Advantage MAX ion-trap mass spectrometer (ESI+) coupled to a Surveyor HPLC system (Thermo Finnigan) equipped with a standard C18 (Gemini, 4.6 mm D x 50 mm L, 5 µm particle size, Phenomenex) analytical column and buffers A: H_2O, B: MECN, C: 0.1% aq. TFA. High resolution mass spectra were recorded on a LTQ Orbitrap (Thermo Finnigan) mass spectrometer or a Synapt G2-Si high definition mass spectrometer (Waters) equipped with an electrospray ion source in positive mode (source voltage 3.5 kV, sheath gas flow 10 mL/min, capillary temperature 250°C) with resolution R = 60000 at m/z 400 (mass range m/z = 150-2000) and dioctylphtalate (m/z = 391.28428) as a lock mass. Preparative HPLC was performed on a Waters Acquity Ultra Performance LC with a C18 column (Gemini, 150 x 21.2 mm, Phenomenex) using an MECN in H_2O (+0.2% TFA) gradient. All final compounds were determined to be > 95% pure by LC-UV analysis.

General procedure A: Boc deprotection

The Boc protected compound (1 equiv.) was dissolved in DCM (0.1 M). TFA was added dropwise (17% v/v) at 0°C and the mixture was allowed to steer at RT for 4 h. The reaction was quenched with sat. aq. Na_2CO_3, diluted with water and extracted with DCM (3×). The combined organic layers were dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the crude material by column chromatography (0% → 10% MeOH (10% aq. NH_3) in DCM) afforded the pure product.

General procedure B: Sulfonation with sulfonyl chloride

A solution of amine (1 equiv.) and triethylamine (2 equiv.) in DCM (0.1 M) was cooled to 0°C after which dropwise a solution of the corresponding sulfonyl chloride (1.5 equiv.) in DCM (0.1 M) was added. The reaction mixture was allowed to warm to RT and stirred for 1 h before sat. aq. Na_2CO_3 was added. The mixture was extracted with DCM (2×), and the combined organic layers were dried over Mg_2SO_4, filtrated and concentrated *in vacuo*. The residue was purified by column chromatography (2% → 5% MeOH (10% aq. NH_3) in DCM) to afford the product.

General procedure C: Sulfonation with arylbromide

To a microwave reaction tube equipped with a magnetic stir bar was added potassium metabisulfite (2 equiv.), TBAB (1.2 equiv.), sodium formate (2.2 equiv.), palladium acetate (0.1 equiv.), triphenylphosphine (0.3 equiv.), 1,10-phenathroline (0.3 equiv.) and DMSO (0.25 M). The mixture was put under nitrogen flow for 10 min before the corresponding bromide (1 equiv.) was added. After that, the reaction vessel was immersed in a 70°C preheated heating block for 4 h. After cooling, DIPEA (1.5 equiv.) the amine (1.5 equiv.) and THF (0.5 M) were added to the reaction mixture. Subsequently, a solution of *N*-chlorosuccinimide (2 equiv.) in THF (0.5 M) was added and the reaction was stirred at RT overnight. The mixture was then diluted with water and extracted with ethyl acetate. The organic layer was washed with brine and dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography (2% → 5% MeOH (10% aq. NH_3) in DCM).

General procedure D: Suzuki-Miyaura cross-coupling

The bromobenzyl compound (1 equiv.) was reacted with the corresponding boronic acid (1.2 equiv.), $Pd(PPh_3)_4$ (0.015 equiv.), K_2CO_3 (4 equiv.) in 1,4-dioxane and water (1:3, 0.1 M) in a sealed microwave tube. The reaction mixture was degassed under nitrogen flow for 15 min and then stirred overnight at 90°C. The reaction mixture was then filtered over a silica gel pad with EtOAc and concentrated *in vacuo*. The crude product was purified by column chromatography (1% → 10% MeOH (10% aq. NH_3) in DCM) to give the pure product.

General procedure E: TIPS protection

The prolinol was co-evaporated *in vacuo* twice with toluene. The prolinol (1 equiv.), imidazole (1.5 equiv.) and DMAP (0.05 equiv.) were dissolved in dry DCM (0.5 M). TIPS-Cl was added dropwise at 0°C after which the reaction mixture was allowed to warm to RT and was stirred for 16 h. The mixture was then poured onto sat. aq. NH_4Cl and extracted with DCM (4×). The combined organic layers were washed with brine (2×), dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the crude material by column chromatography (80% → 100% Et_2O in pentane with 1% triethylamine) afforded the pure product.

General procedure F: Pyrrolidine α-arylation

The amine (1 equiv.) and benzophenone (1.2 equiv.) were combined and co-evaporated *in vacuo* twice with toluene. These were then dissolved in dry Et_2O (0.5 M) and transferred to a flame dried flask under argon atmosphere. *n*-Butyllithium (1 equiv.) was added dropwise at -78°C and the solution was stirred for 10 min. Subsequently, the corresponding aryllithium solution (1.5 equiv, prepared according to general procedure G) was dropwise added at -78°C after which the mixture was removed from the cooling bath and left to stir for 2 h while reaching RT. The mixture was then quenched with MeOH at -78°C and diluted with Et_2O. This was then washed with water and brine. The aqueous layer was extracted with Et_2O (3×) and the combined organic layers were dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the crude material by column chromatography (2% → 20% Et_2O in pentane with 1% triethylamine and 10% toluene) afforded the separate stereoisomers as crude products.

General procedure G: Preparation of aryllithium

1,4-Dibromobenzene (1.5 equiv. to amine general procedure F) was co-evaporated *in vacuo* twice with toluene. This was then dissolved in dry Et_2O (0.75 M) and transferred to a flame dried flask under argon atmosphere. *n*-Butyllithium (1.5 equiv. to amine) was added dropwise at -78°C and the mixture was stirred for 10 min. The mixture

was then warmed to RT and stirred for an additional 30 min before addition to the appropriate solution with imine intermediate.

General procedure H: Boc protection

The crude product of the pyrrolidine alkylation reaction (1 equiv.) was dissolved with di-*tert*-butyl dicarbonate (2.5 equiv.) and triethylamine (2 equiv.) in DCM (0.06 M) and the mixture was stirred at RT. Upon completion, the reaction was diluted with DCM and washed with water and brine. The organic layer was dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the crude material by column chromatography (1% → 3% EtOAc in pentane) afforded the pure product.

General procedure I: TIPS deprotection

The TIPS protected starting material (1 equiv.) was dissolved in MECN (0.09 M). To this was added TBAF (5 equiv., 1 M in THF) and the mixture was stirred at RT. The mixture was subsequently concentrated *in vacuo* on silica. Purification of the crude material by column chromatography (5% → 40% EtOAc in pentane) afforded the pure product.

General procedure J: Mesylation

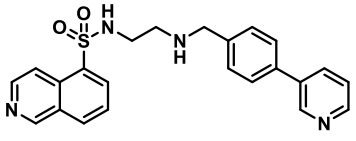
The primary alcohol (1 equiv.) and triethylamine (3 equiv.) were dissolved in dry DCM (0.05 M). A solution of MsCl (1.5 equiv.) in dry DCM (0.05 M) was added dropwise at 0°C and the mixture was stirred at RT for 1.5 h. The mixture was quenched with the addition of water and extracted with DCM (3×). The combined organic layers were washed with brine, dried with $MgSO_4$, filtered and concentrated *in vacuo*. After characterization, the crude product was immediately used for further reactions.

General procedure K: Azide substitution

The crude mesylated starting material (1 equiv.) and sodium azide (6 equiv.) were dissolved in dry DMF (0.1 M). The mixture was heated to 65°C and left to steer overnight. The reaction was diluted with Et_2O and washed with water (3×) and brine. The organic layer was dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the crude material by column chromatography (15% → 20% EtOAc in pentane) afforded the pure product.

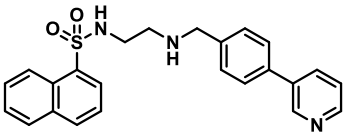
General procedure L: Staudinger reduction of azide

The azide compound (1 equiv.), $(Ph)_3P$ (2 equiv.) and water (2 equiv.) were dissolved in THF (0.1 M). The mixture was then refluxed at 60°C for 64 h. The reaction mixture was concentrated *in vacuo* and redissolved in Et_2O. This solution was thereafter extracted with 1 M aq. HCl (2×) and the aqueous layer washed with Et_2O (2×). The pH of the aqueous layer was then adjusted to >12 with 2 M aq. NaOH and extracted with DCM (6×). The combined organic layers were dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the crude material by column chromatography (5% → 50% MeOH (10% aq. NH_3) in EtOAc) afforded the pure product.

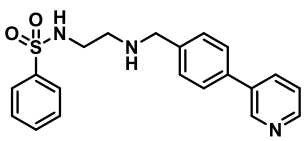


***N*-(2-((4-(Pyridin-3-yl)benzyl)amino)ethyl)isoquinoline-5-sulfonamide (1). 1** (12 mg, 29 µmol, 62%) was synthesized from **109** (20 mg, 38 µmol) according to general procedure A. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.33 (d, *J* = 1.1 Hz, 1H), 8.79 (dd, *J* = 2.4, 0.9 Hz, 1H), 8.63 (d, *J* = 6.1 Hz, 1H), 8.58 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.50 – 8.42 (m, 2H), 8.17 (dt, *J* = 8.4, 1.1 Hz, 1H), 7.85 (ddd, *J* = 7.9, 2.4, 1.6 Hz, 1H), 7.68 (dd, *J* = 8.2, 7.3 Hz, 1H), 7.45 (d, *J* = 8.6 Hz, 2H), 7.37 (ddd, *J* = 7.9, 4.8, 0.9 Hz, 1H), 7.22 (d, *J* = 8.6 Hz, 2H), 3.59 (s, 2H), 3.04 (t, *J* = 5.7 Hz, 2H),

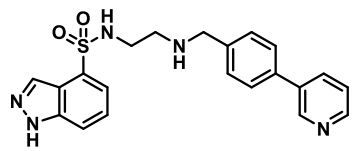
2.69 (t, *J* = 6.1 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.37, 148.40, 148.10, 145.14, 139.67, 136.58, 136.30, 134.46, 134.41, 133.55, 133.35, 131.31, 129.08, 128.69, 127.19, 126.01, 123.74, 117.33, 52.78, 47.60, 42.56. HRMS $[C_{23}H_{22}N_4O_2S + H]^+$: 419.15335 calculated, 419.15335 found.



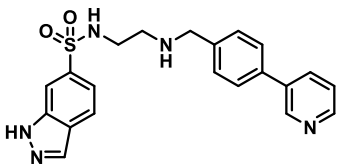
***N*-(2-((4-(Pyridin-3-yl)benzyl)amino)ethyl)naphthalene-1-sulfonamide (47). 47** (50 mg, 39 µmol, 53% over two steps) was synthesized from **108** (24 mg, 73 µmol) and naphthalene 1-sulfonyl chloride (25 mg, 0.11 mmol) according to general procedure B, followed by general procedure A. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (dd, *J* = 2.4, 0.9 Hz, 1H), 8.68 (dt, *J* = 8.6, 1.0 Hz, 1H), 8.59 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.28 (dd, *J* = 7.3, 1.3 Hz, 1H), 8.06 (dt, *J* = 8.2, 1.1 Hz, 1H), 7.97 – 7.91 (m, 1H), 7.85 (ddd, *J* = 7.9, 2.4, 1.6 Hz, 1H), 7.69 – 7.50 (m, 3H), 7.48 – 7.42 (m, 2H), 7.37 (ddd, *J* = 7.9, 4.8, 0.9 Hz, 1H), 7.23 – 7.16 (m, 2H), 3.52 (s, 2H), 3.02 – 2.94 (m, 2H), 2.67 – 2.58 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.55, 148.30, 139.77, 136.70, 136.40, 134.53, 134.39, 134.36, 129.91, 129.27, 128.76, 128.50, 128.26, 127.24, 127.00, 124.46, 124.31, 123.72, 52.73, 47.37, 42.60. HRMS $[C_{24}H_{23}N_3O_2S+H]^+$: 418.15837 calculated, 418.15767 found.



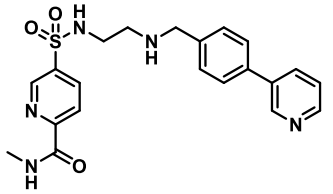
***N*-(2-((4-(Pyridin-3-yl)benzyl)amino)ethyl)benzenesulfonamide (48). 108** (24 mg, 73 µmol) and benzenesulfonyl chloride (19 mg, 0.11 mmol) were reacted according to general procedure B, followed by general procedure A to yield title compound **48** (8.8 mg, 24 µmol, 33% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (dd, *J* = 2.4, 0.9 Hz, 1H), 8.59 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.91 – 7.83 (m, 3H), 7.61 – 7.46 (m, 5H), 7.41 – 7.31 (m, 3H), 3.72 (s, 2H), 3.08 – 3.02 (m, 2H), 2.79 – 2.71 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.55, 148.29, 139.89, 139.85, 136.81, 136.39, 134.41, 132.73, 129.22, 128.91, 127.35, 127.16, 123.73, 52.90, 47.58, 42.56. HRMS $[C_{20}H_{21}N_3O_2S + H]^+$: 368.14272 calculated, 368.14201 found.



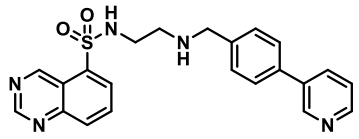
***N*-(2-((4-(Pyridin-3-yl)benzyl)amino)ethyl)-1H-indazole-4-sulfonamide (49). 49** (8.0 mg, 20 µmol, 13% over two steps) was synthesized from **108** (50 mg, 0.15 mmol) and 4-bromo-1*H*-indazole (25 mg, 0.12 mmol) according to general procedure C followed by general procedure A. ^{1}H NMR (400 MHz, MeOD) δ 8.91 (d, *J* = 2.3 Hz, 1H), 8.63 (dd, *J* = 5.1, 1.5 Hz, 1H), 8.41 (d, *J* = 1.0 Hz, 1H), 8.30 (dt, *J* = 8.2, 1.9 Hz, 1H), 7.88 (d, *J* = 8.4 Hz, 1H), 7.85 – 7.80 (m, 3H), 7.72 (d, *J* = 7.1 Hz, 1H), 7.69 – 7.64 (m, 2H), 7.57 (dd, *J* = 8.5, 7.2 Hz, 1H), 4.34 (s, 2H), 3.23 – 3.17 (m, 4H). HRMS $[C_{21}H_{21}N_5O_2S+H]^+$: 408.14887 calculated, 408.14866 found.



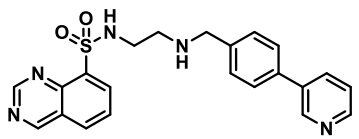
***N*-(2-((4-(Pyridin-3-yl)benzyl)amino)ethyl)-1H-indazole-6-sulfonamide (50). 50** (5.3 mg, 13 µmol, 9% over two steps) was synthesized from **108** (50 mg, 0.15 mmol) and 6-bromo-1*H*-indazole (47 mg, 0.24 mmol) according to general procedure C followed by general procedure A. ^{1}H NMR (400 MHz, MeOD) δ 8.80 (dd, *J* = 2.4, 0.9 Hz, 1H), 8.51 (dd, *J* = 4.9, 1.6 Hz, 1H), 8.37 (d, *J* = 5.0 Hz, 1H), 8.10 (ddd, *J* = 8.0, 2.3, 1.6 Hz, 1H), 7.61 (dd, *J* = 6.0, 2.3 Hz, 3H), 7.55 – 7.48 (m, 2H), 7.37 – 7.30 (m, 2H), 6.92 (d, *J* = 3.5 Hz, 1H), 3.67 (s, 2H), 3.07 (t, *J* = 6.3 Hz, 2H), 2.62 (t, *J* = 6.3 Hz, 2H). HRMS $[C_{21}H_{21}N_5O_2S+H]^+$: 408.14887 calculated, 408.14838 found.



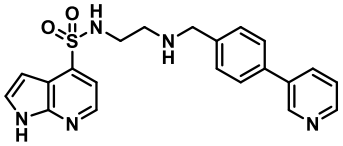
***N*-Methyl-5-(*N*-(2-((4-(pyridin-3-yl)benzyl)amino)ethyl)sulfamoyl)picolinamide (51). 51** (4.0 mg, 9.0 µmol, 6% over two steps) was synthesized from **108** (50 mg, 0.15 mmol) and 5-bromo-*N*-methylpicolinamide (52 mg, 0.24 mmol) according to general procedure C followed by general procedure A. ^{1}H NMR (400 MHz, MeOD) δ 9.02 (dd, *J* = 2.3, 0.8 Hz, 1H), 8.80 (dd, *J* = 2.4, 0.9 Hz, 1H), 8.51 (dd, *J* = 4.9, 1.6 Hz, 1H), 8.36 (dd, *J* = 8.2, 2.3 Hz, 1H), 8.22 (dd, *J* = 8.2, 0.9 Hz, 1H), 8.10 (ddd, *J* = 8.0, 2.4, 1.6 Hz, 1H), 7.65 – 7.60 (m, 2H), 7.53 (ddd, *J* = 8.0, 4.9, 0.9 Hz, 1H), 7.44 – 7.38 (m, 2H), 7.24 – 7.09 (m, 2H), 3.77 (s, 2H), 3.09 (t, *J* = 6.4 Hz, 2H), 2.95 (s, 3H), 2.68 (t, *J* = 6.4 Hz, 2H). HRMS $[C_{21}H_{23}N_5O_3S+H]^+$: 426.15944 calculated, 426.15879 found.



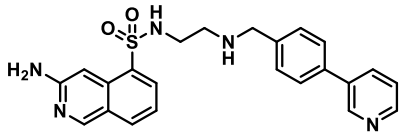
***N*-(2-((4-(Pyridin-3-yl)benzyl)amino)ethyl)quinazoline-6-sulfonamide (52). 52** (12 mg, 29 µmol, 19% over two steps) was synthesized from **108** (50 mg, 0.15 mmol) and 5-bromoquinazoline (25 mg, 0.12 mmol) according to general procedure C followed by general procedure A. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.51 (d, *J* = 0.8 Hz, 1H), 9.45 (s, 1H), 8.82 (dd, *J* = 2.3, 0.9 Hz, 1H), 8.60 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.55 (dd, *J* = 2.0, 0.6 Hz, 1H), 8.27 (dd, *J* = 8.9, 2.0 Hz, 1H), 8.18 – 8.13 (m, 1H), 7.86 (ddd, *J* = 7.9, 2.4, 1.6 Hz, 1H), 7.53 – 7.48 (m, 2H), 7.38 (ddd, *J* = 7.9, 4.8, 0.9 Hz, 1H), 7.35 – 7.30 (m, 2H), 3.73 (s, 2H), 3.17 – 3.06 (m, 2H), 2.83 – 2.72 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.48, 157.48, 151.46, 148.64, 148.30, 139.65, 139.50, 136.96, 136.27, 134.40, 130.89, 130.45, 128.83, 127.81, 127.40, 124.14, 123.75, 52.94, 47.60, 42.63. HRMS $[C_{22}H_{21}N_5O_2S+H]^+$: 420.14887 calculated, 420.14850 found.



***N*-(2-((4-(Pyridin-3-yl)benzyl)amino)ethyl)quinazoline-7-sulfonamide (53). 108** (50 mg, 0.15 mmol) and 8-bromoquinazoline (27 g, 0.13 µmol) were reacted according to general procedure C, followed by general procedure A to yield title compound **53** (13 mg, 31 µmol, 5% over two steps). ^{1}H NMR (400 MHz, MeOD) δ 9.62 (d, *J* = 0.9 Hz, 1H), 9.36 (s, 1H), 8.78 (dd, *J* = 2.4, 0.9 Hz, 1H), 8.54 – 8.48 (m, 2H), 8.31 (dd, *J* = 8.6, 0.7 Hz, 1H), 8.12 (dd, *J* = 8.6, 1.7 Hz, 1H), 8.08 (ddd, *J* = 8.0, 2.4, 1.6 Hz, 1H), 7.61 – 7.56 (m, 2H), 7.56 – 7.50 (m, 1H), 7.42 – 7.37 (m, 2H), 3.75 (s, 2H), 3.11 (t, *J* = 6.4 Hz, 2H), 2.70 (t, *J* = 6.4 Hz, 2H). HRMS $[C_{22}H_{21}N_5O_2S+H]^+$: 420.14887 calculated, 420.14857 found.

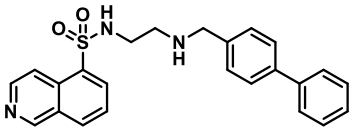


***N*-(2-((4-(Pyridin-3-yl)benzyl)amino)ethyl)-1*H*-pyrrolo[2,3-b]pyridine-4-sulfonamide (54). 108** (50 mg, 0.15 mmol) and 4-bromo-7-azaindole (47 mg, 0.24 mmol) were reacted according to general procedure C, followed by general procedure A to yield title compound **54** (1.8 mg, 4.6 µmol, 3% over two steps). ^{1}H NMR (400 MHz, MeOD) δ 8.97 (s, 1H), 8.67 (d, *J* = 5.0 Hz, 1H), 8.41 (d, *J* = 5.0 Hz, 2H), 7.85 (d, *J* = 8.2 Hz, 2H), 7.76 (d, *J* = 6.1 Hz, 1H), 7.71 – 7.62 (m, 3H), 7.55 (d, *J* = 5.0 Hz, 1H), 6.93 (d, *J* = 3.5 Hz, 1H), 4.34 (s, 2H), 3.25 – 3.16 (m, 4H). HRMS $[C_{21}H_{21}N_5O_2S+H]^+$: 408.14887 calculated, 408.14856 found.

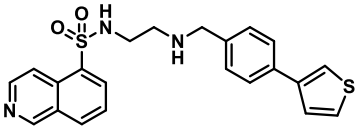


3-Amino-*N*-(2-((4-(pyridin-3-yl)benzyl)amino)ethyl)isoquinoline-5-sulfonamide (55). 108 (50 mg, 0.15 mmol) and 5-bromoisoquinolin-3-amine (54 g, 0.24 mmol) were reacted according to general procedure C, followed

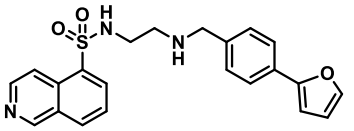
by general procedure A to yield title compound **55** (5.3 mg, 12 µmol, 8% over two steps). ^{1}H NMR (400 MHz, MeOD) δ 8.86 (d, *J* = 0.9 Hz, 1H), 8.79 (dd, *J* = 2.3, 0.8 Hz, 1H), 8.52 (dd, *J* = 4.9, 1.6 Hz, 1H), 8.20 (dd, *J* = 7.3, 1.3 Hz, 1H), 8.09 (dt, *J* = 8.0, 2.0 Hz, 1H), 8.03 (dt, *J* = 8.2, 1.2 Hz, 1H), 7.61 – 7.55 (m, 2H), 7.54 – 7.50 (m, 1H), 7.40 (d, *J* = 1.1 Hz, 1H), 7.32 – 7.05 (m, 5H), 3.59 (s, 2H), 3.02 (t, *J* = 6.2 Hz, 2H), 2.57 (t, *J* = 6.2 Hz, 2H). ^{13}C NMR (101 MHz, MeOD) δ 154.08, 148.69, 148.27, 140.76, 138.36, 137.37, 136.45, 135.54, 135.39, 135.23, 132.96, 130.43, 130.19, 128.17, 125.50, 124.89, 121.58, 97.10, 53.45, 48.94, 43.08. HRMS $[C_{23}H_{24}N_5O_2S+H]^+$: 434.16452 calculated, 434.16422 found.



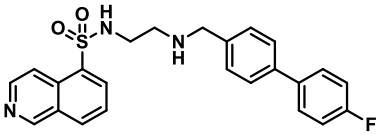
***N*-(2-(([1,1'-Biphenyl]-4-ylmethyl)amino)ethyl)isoquinoline-5-sulfonamide (56).** Phenylboronic acid (28 mg, 0.23 mmol) was subjected to general procedure D with **113a** (0.10 g, 0.19 mmol) followed by general procedure A to yield the title compound **56** (60 mg, 33 µmol, 17% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.32 (d, *J* = 1.0 Hz, 1H), 8.66 (d, *J* = 6.1 Hz, 1H), 8.44 (ddd, *J* = 7.4, 5.8, 1.1 Hz, 2H), 8.15 (dt, *J* = 8.2, 1.1 Hz, 1H), 7.66 (dd, *J* = 8.2, 7.3 Hz, 1H), 7.59 – 7.53 (m, 2H), 7.50 – 7.40 (m, 4H), 7.39 – 7.31 (m, 1H), 7.19 – 7.14 (m, 2H), 3.57 (s, 2H), 3.07 – 2.94 (m, 2H), 2.71 – 2.62 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.45, 145.31, 140.78, 140.23, 138.59, 134.36, 133.65, 133.42, 131.37, 129.12, 128.91, 128.44, 127.43, 127.28, 127.12, 126.01, 117.31, 52.86, 47.39, 42.52. HRMS $[C_{24}H_{23}N_3O_2S+H]^+$: 418.15837 calculated, 418.15782 found.



***N*-(2-((4-(Thiophen-3-yl)benzyl)amino)ethyl)isoquinoline-5-sulfonamide (57).** Thien-3-ylboronic acid (31 mg, 0.23 mmol) was subjected to general procedure D with **113a** (0.10 g, 0.19 mmol) followed by general procedure A to provide **57** (39 mg, 90 µmol, 47% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.33 (d, *J* = 1.0 Hz, 1H), 8.67 (d, *J* = 6.1 Hz, 1H), 8.45 – 8.41 (m, 2H), 8.16 (dt, *J* = 8.2, 1.1 Hz, 1H), 7.67 (dd, *J* = 8.2, 7.3 Hz, 1H), 7.51 – 7.45 (m, 2H), 7.43 (dd, *J* = 2.9, 1.4 Hz, 1H), 7.41 – 7.35 (m, 2H), 7.16 – 7.09 (m, 2H), 3.54 (s, 2H), 3.02 – 2.94 (m, 2H), 2.70 – 2.62 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.46, 145.34, 141.97, 138.42, 134.93, 134.31, 133.67, 133.45, 131.36, 129.13, 128.49, 126.59, 126.42, 126.36, 126.01, 120.35, 117.30, 52.89, 47.34, 42.50. HRMS $[C_{22}H_{21}N_3O_2S_2+H]^+$: 424.11479 calculated, 424.11473 found.

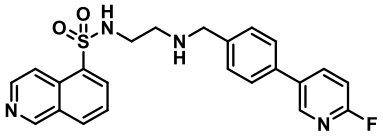


***N*-(2-((4-(Furan-3-yl)benzyl)amino)ethyl)isoquinoline-5-sulfonamide (58).** Furan-3-ylboronic acid (26 mg, 0.23 mmol) was subjected to general procedure D with **113a** (0.10 g, 0.19 mmol) followed by general procedure A to provide **58** (6.0 mg, 15 µmol, 8% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.34 (d, *J* = 1.0 Hz, 1H), 8.68 (d, *J* = 6.1 Hz, 1H), 8.48 – 8.39 (m, 2H), 8.18 (dt, *J* = 8.4, 1.1 Hz, 1H), 7.72 (dd, *J* = 1.5, 0.9 Hz, 1H), 7.68 (dd, *J* = 8.2, 7.4 Hz, 1H), 7.48 (t, *J* = 1.7 Hz, 1H), 7.41 – 7.36 (m, 2H), 7.17 – 7.09 (m, 2H), 6.69 (dd, *J* = 1.9, 0.9 Hz, 1H), 3.56 (s, 2H), 3.04 – 2.95 (m, 2H), 2.71 – 2.62 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.50, 145.41, 143.85, 138.59, 138.33, 134.32, 133.68, 133.46, 131.52, 131.38, 129.14, 128.49, 126.18, 126.05, 126.01, 117.28, 108.91, 52.90, 47.26, 42.50. HRMS $[C_{22}H_{21}N_3O_3S+H]^+$: 408.13764 calculated, 408.13725 found.

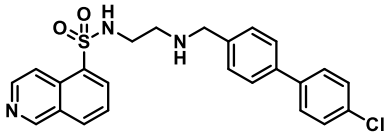


***N*-(2-(((4'-Fluoro-[1,1'-biphenyl]-4-yl)methyl)amino)ethyl)isoquinoline-5-sulfonamide (59).** (4-Fluorophenyl)boronic acid (32 mg, 0.23 mmol) was subjected to general procedure D with **113a** (0.10 g, 0.19 mmol) followed by general procedure A to provide **59** (41 mg, 99 µmol, 52% over two

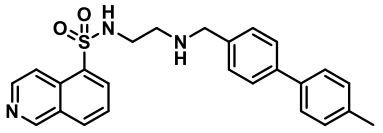
steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.33 (d, *J* = 0.9 Hz, 1H), 8.67 (d, *J* = 6.1 Hz, 1H), 8.47 – 8.41 (m, 2H), 8.17 (dt, *J* = 8.3, 1.2 Hz, 1H), 7.67 (dd, *J* = 8.2, 7.3 Hz, 1H), 7.55 – 7.48 (m, 2H), 7.46 – 7.40 (m, 2H), 7.20 – 7.08 (m, 4H), 3.57 (s, 2H), 3.03 – 2.97 (m, 2H), 2.70 – 2.65 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.57 (d, *J* = 243 Hz), 161.34, 153.46, 145.34, 139.27, 138.52, 136.91, 136.88, 134.31, 133.66, 133.44, 131.35, 129.12, 128.66 (d, *J* = 8.0 Hz), 128.52, 127.15, 126.01, 117.29, 115.76 (d, *J* = 23 Hz), 52.78, 47.35, 42.47. HRMS $[C_{24}H_{22}FN_3O_2S+H]^+$: 436.14895 calculated, 436.14842 found.



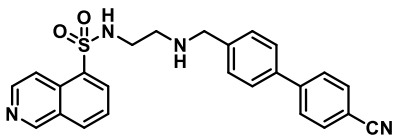
***N*-(2-((4-(6-Fluoropyridin-3-yl)benzyl)amino)ethyl)isoquinoline-5-sulfonamide (60).** (6-Fluoropyridin-3-yl)boronic acid (32 mg, 0.23 mmol) was subjected to general procedure D with **113a** (0.10 g, 0.19 mmol) followed by general procedure A to provide **60** (26 mg, 60 µmol, 32% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.34 (d, *J* = 0.9 Hz, 1H), 8.67 (d, *J* = 6.1 Hz, 1H), 8.45 (dt, *J* = 7.1, 1.3 Hz, 2H), 8.39 (dt, *J* = 2.7, 0.9 Hz, 1H), 8.19 (dt, *J* = 8.2, 1.1 Hz, 1H), 7.95 (ddd, *J* = 8.5, 7.6, 2.6 Hz, 1H), 7.69 (dd, *J* = 8.2, 7.3 Hz, 1H), 7.46 – 7.41 (m, 2H), 7.26 – 7.21 (m, 2H), 7.01 (ddd, *J* = 8.5, 3.0, 0.7 Hz, 1H), 3.60 (s, 2H), 3.05 – 2.98 (m, 2H), 2.73 – 2.65 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.22 (d, *J* = 243 Hz), 153.47, 145.80 (d, *J* = 14.5 Hz) 145.34, 139.76 (d, *J* = 8.1 Hz), 139.69, 135.69, 134.52 (d, *J* = 4.5 Hz), 134.30, 133.69, 133.48, 131.35, 129.14, 128.79, 127.21, 126.04, 117.27, 109.61 (d, *J* = 23 Hz), 52.76, 47.41, 42.51. HRMS $[C_{23}H_{21}FN_4O_2S+H]^+$: 437.14420 calculated, 437.14402 found.



***N*-(2-(((4'-Chloro-[1,1'-biphenyl]-4-yl)methyl)amino)ethyl)isoquinoline-5-sulfonamide (61).** (4-Chlorophenyl)boronic acid (36 mg, 0.23 mmol) was subjected to general procedure D with **113a** (0.10 g, 0.19 mmol) followed by general procedure A to provide **61** (80 mg, 0.14 mmol, 74% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.32 (d, *J* = 1.0 Hz, 1H), 8.68 – 8.62 (m, 1H), 8.49 – 8.41 (m, 2H), 8.20 – 8.11 (m, 1H), 7.70 – 7.50 (m, 2H), 7.50 – 7.35 (m, 6H), 7.24 – 7.14 (m, 2H), 3.59 (d, *J* = 6.9 Hz, 2H), 3.05 – 2.95 (m, 2H), 2.73 – 2.60 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.42, 145.27, 139.17, 138.97, 138.73, 134.31, 133.65, 133.48, 133.41, 131.33, 129.10, 129.03, 128.60, 128.33, 127.09, 126.01, 117.31, 52.74, 47.40, 42.43. HRMS $[C_{24}H_{22}ClN_3O_2S+H]^+$: 452.11940 calculated, 452.11913 found.

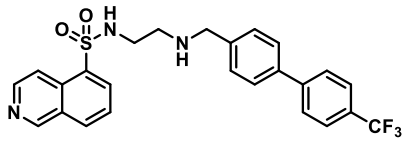


***N*-(2-(((4'-Methyl-[1,1'-biphenyl]-4-yl)methyl)amino)ethyl)isoquinoline-5-sulfonamide (62).** *p*-Tolylboronic acid (31 mg, 0.23 mmol) was subjected to general procedure D with **113a** (0.10 g, 0.19 mmol) followed by general procedure A to provide **62** (46 mg, 0.11 mmol, 58% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.32 (d, *J* = 1.1 Hz, 1H), 8.67 (d, *J* = 6.1 Hz, 1H), 8.47 – 8.39 (m, 2H), 8.16 (dt, *J* = 8.2, 1.1 Hz, 1H), 7.66 (dd, *J* = 8.2, 7.3 Hz, 1H), 7.49 – 7.42 (m, 4H), 7.28 – 7.21 (m, 2H), 7.18 – 7.12 (m, 2H), 3.55 (s, 2H), 3.02 – 2.96 (m, 2H), 2.69 – 2.63 (m, 2H), 2.40 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.46, 145.35, 140.17, 138.29, 137.89, 137.22, 134.34, 133.66, 133.42, 131.37, 129.63, 129.13, 128.41, 127.08, 126.96, 126.00, 117.30, 52.87, 47.34, 42.51, 21.22. HRMS $[C_{25}H_{25}N_3O_2S+H]^+$: 432.17402 calculated, 432.17384 found.

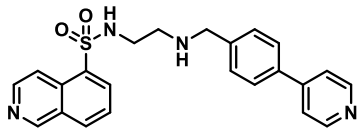


***N*-(2-(((4'-Cyano-[1,1'-biphenyl]-4-yl)methyl)amino)ethyl)isoquinoline-5-sulfonamide (63).** (4-Cyanophenyl)boronic acid (34 mg, 0.23 mmol) was subjected to general procedure D with **113a** (0.10 g, 0.19 mmol) followed by

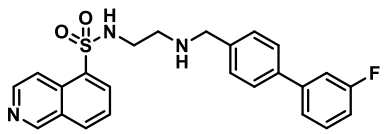
general procedure A to provide **63** (17 mg, 40 µmol, 21% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.33 (d, *J* = 1.0 Hz, 1H), 8.65 (dd, *J* = 6.1, 1.2 Hz, 1H), 8.45 (ddd, *J* = 7.4, 2.2, 1.1 Hz, 2H), 8.18 (dt, *J* = 8.2, 1.0 Hz, 1H), 7.74 – 7.62 (m, 5H), 7.51 – 7.45 (m, 2H), 7.26 – 7.20 (m, 2H), 3.61 (s, 2H), 3.06 – 2.99 (m, 2H), 2.73 – 2.61 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.40, 145.22, 145.20, 140.23, 138.03, 134.29, 133.65, 133.44, 132.69, 131.30, 129.09, 128.70, 127.64, 127.34, 126.03, 119.03, 117.29, 110.87, 52.72, 47.49, 42.51. HRMS $[C_{25}H_{22}N_4O_2S+H]^+$: 443.15362 calculated, 443.15333 found.



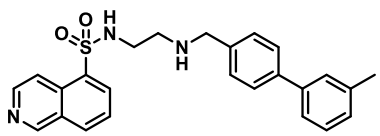
***N*-(2-(((4'-(Trifluoromethyl)-[1,1'-biphenyl]-4-yl)methyl)amino)ethyl)isoquinoline-5-sulfonamide (64).** (4-(Trifluoromethyl)phenyl)boronic acid (44 mg, 0.23 mmol) was subjected to general procedure D with **113a** (0.10 g, 0.19 mmol) followed by general procedure A to provide **64** (64 mg, 0.13 mmol, 68% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.33 (d, *J* = 1.0 Hz, 1H), 8.67 (d, *J* = 6.1 Hz, 1H), 8.48 – 8.42 (m, 2H), 8.18 (dt, *J* = 8.2, 1.1 Hz, 1H), 7.72 – 7.63 (m, 5H), 7.52 – 7.47 (m, 2H), 7.24 – 7.18 (m, 2H), 3.59 (s, 2H), 3.04 – 2.96 (m, 2H), 2.72 – 2.64 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.44, 145.27, 144.30, 139.70, 138.68, 134.29, 133.66, 133.46, 131.33, 129.36 (q, *J* = 32 Hz), 129.12, 128.60, 127.40, 127.36, 126.03, 125.82 (q, *J* = 3.9 Hz), 124.40 (q, *J* = 273 Hz), 117.28, 52.77, 47.42, 42.51. HRMS $[C_{25}H_{22}F_3N_3O_2S+H]^+$: 486.14576 calculated, 486.14555 found.



***N*-(2-((4-(Pyridin-4-yl)benzyl)amino)ethyl)isoquinoline-5-sulfonamide (65).** Pyridin-4-ylboronic acid (28 mg, 0.23 mmol) was subjected to general procedure D with **113a** (0.10 g, 0.19 mmol) followed by general procedure A to provide **65** (38 mg, 91 µmol, 48% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.33 (d, *J* = 1.0 Hz, 1H), 8.66 – 8.60 (m, 3H), 8.48 – 8.42 (m, 2H), 8.18 (dt, *J* = 8.3, 1.2 Hz, 1H), 7.69 (dd, *J* = 8.2, 7.3 Hz, 1H), 7.55 – 7.50 (m, 2H), 7.49 – 7.45 (m, 2H), 7.26 – 7.21 (m, 2H), 3.61 (s, 2H), 3.08 – 2.99 (m, 2H), 2.74 – 2.65 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.41, 150.22, 148.04, 145.21, 140.77, 136.91, 134.43, 133.61, 133.42, 131.34, 129.11, 128.74, 127.12, 126.04, 121.61, 117.33, 52.80, 47.59, 42.56. HRMS $[C_{23}H_{22}N_4O_2S+H]^+$: 419.15362 calculated, 419.15335 found.

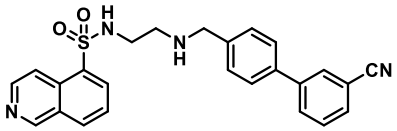


***N*-(2-(((3'-Fluoro-[1,1'-biphenyl]-4-yl)methyl)amino)ethyl)isoquinoline-5-sulfonamide (66).** (3-Fluorophenyl)boronic acid (32 mg, 0.23 mmol) was subjected to general procedure D with **113a** (0.10 g, 0.19 mmol) followed by general procedure A to provide **66** (29 mg, 70 µmol, 37% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.34 (d, *J* = 1.0 Hz, 1H), 8.68 (d, *J* = 6.1 Hz, 1H), 8.47 – 8.39 (m, 2H), 8.18 (dt, *J* = 8.1, 1.1 Hz, 1H), 7.68 (dd, *J* = 8.2, 7.3 Hz, 1H), 7.50 – 7.44 (m, 2H), 7.44 – 7.31 (m, 2H), 7.28 – 7.23 (m, 1H), 7.22 – 7.16 (m, 2H), 7.07 – 7.00 (m, 1H), 3.58 (s, 2H), 3.04 – 2.95 (m, 2H), 2.71 – 2.64 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.53, 153.49, 145.40, 143.08 (d, *J* = 8.7 Hz), 139.24, 138.98, 134.30, 133.70, 133.49, 131.38, 130.40 (d, *J* = 8.7 Hz), 129.15, 128.56, 127.28, 126.02, 122.76 (d, *J* = 2.8 Hz), 117.29, 114.22 (d, *J* = 23 Hz), 114.00 (d, *J* = 23 Hz), 52.82, 47.36, 42.50. HRMS $[C_{24}H_{22}FN_3O_2S+H]^+$: 436.14895 calculated, 436.14864 found.

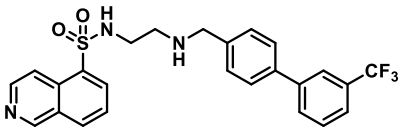


***N*-(2-(((3'-Methyl-[1,1'-biphenyl]-4-yl)methyl)amino)ethyl)isoquinoline-5-sulfonamide (67).** *m*-Tolylboronic acid (31 mg, 0.23 mmol) was subjected to general procedure D with **113a** (0.10 g, 0.19 mmol) followed by general procedure A to provide **67** (59 mg, 0.14 mmol, 74% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.31 (d, *J* = 1.0

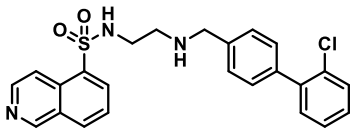
Hz, 1H), 8.65 (d, *J* = 6.1 Hz, 1H), 8.49 – 8.39 (m, 2H), 8.14 (dt, *J* = 8.2, 1.1 Hz, 1H), 7.65 (dd, *J* = 8.2, 7.3 Hz, 1H), 7.50 – 7.41 (m, 2H), 7.39 – 7.29 (m, 3H), 7.19 – 7.10 (m, 3H), 3.56 (s, 2H), 3.03 – 2.97 (m, 2H), 2.70 – 2.63 (m, 2H), 2.42 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.40, 145.23, 140.72, 140.29, 138.46, 138.44, 134.36, 133.62, 133.38, 131.34, 129.09, 128.79, 128.38, 128.15, 127.88, 127.25, 126.00, 124.19, 117.32, 52.84, 47.41, 42.50, 21.64. HRMS $[C_{25}H_{25}N_3O_2S+H]^+$: 432.17402 calculated, 432.17371 found.



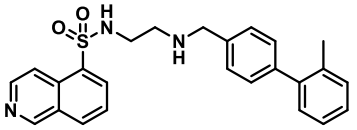
***N*-(2-(((3'-Cyano-[1,1'-biphenyl]-4-yl)methyl)amino)ethyl)isoquinoline-5-sulfonamide (68).** (3-Cyanophenyl)boronic acid (34 mg, 0.23 mmol) was subjected to general procedure D with **113a** (0.10 g, 0.19 mmol) followed by general procedure A to provide **68** (21 mg, 50 µmol, 26% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.35 (d, *J* = 1.0 Hz, 1H), 8.69 (d, *J* = 6.1 Hz, 1H), 8.45 (ddd, *J* = 7.1, 4.9, 1.1 Hz, 2H), 8.20 (dt, *J* = 8.2, 1.1 Hz, 1H), 7.86 – 7.82 (m, 1H), 7.80 (ddd, *J* = 7.8, 1.9, 1.2 Hz, 1H), 7.70 (dd, *J* = 8.2, 7.4 Hz, 1H), 7.64 (dt, *J* = 7.7, 1.4 Hz, 1H), 7.55 (d, *J* = 7.7, 1H), 7.50 – 7.44 (m, 2H), 7.25 – 7.20 (m, 2H), 3.61 (s, 2H), 3.05 – 2.96 (m, 2H), 2.74 – 2.64 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.51, 145.43, 142.08, 139.86, 137.96, 134.27, 133.73, 133.53, 131.52, 131.38, 130.86, 130.71, 129.79, 129.16, 128.79, 127.31, 126.04, 118.97, 117.27, 113.10, 52.76, 47.38, 42.48. HRMS $[C_{25}H_{22}N_4O_2S+H]^+$: 443.15362 calculated, 443.15321 found.



***N*-(2-(((3'-(Trifluoromethyl)-[1,1'-biphenyl]-4-yl)methyl)amino)ethyl)isoquinoline-5-sulfonamide (69).** (3-(Trifluoromethyl)phenyl)boronic acid (43 mg, 0.23 mmol) was subjected to general procedure D with **113a** (0.10 g, 0.19 mmol) followed by general procedure A to provide **69** (37 mg, 80 µmol, 42% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.33 (d, *J* = 1.0 Hz, 1H), 8.68 (d, *J* = 6.1 Hz, 1H), 8.48 – 8.42 (m, 2H), 8.17 (dt, *J* = 8.3, 1.1 Hz, 1H), 7.79 (d, *J* = 1.8 Hz, 1H), 7.74 (dt, *J* = 7.5, 1.7 Hz, 1H), 7.68 (dd, *J* = 8.2, 7.3 Hz, 1H), 7.62 – 7.53 (m, 2H), 7.51 – 7.45 (m, 2H), 7.24 – 7.19 (m, 2H), 3.59 (s, 2H), 3.04 – 2.97 (m, 2H), 2.72 – 2.63 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.45, 145.31, 141.59, 139.52, 138.71, 134.31, 133.65, 133.45, 131.35, 131.21 (q, *J* = 32 Hz), 130.41, 129.39, 129.12, 128.63, 127.32, 126.02, 124.27 (q, *J* = 273 Hz), 124.06, 123.87, 117.27, 52.79, 47.41, 42.52. HRMS $[C_{25}H_{22}F_3N_3O_2S+H]^+$: 486.14576 calculated, 486.14540 found.

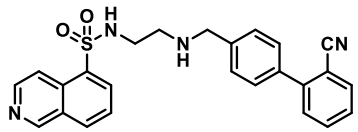


***N*-(2-(((2'-Chloro-[1,1'-biphenyl]-4-yl)methyl)amino)ethyl)isoquinoline-5-sulfonamide (70).** (2-Chlorophenyl)boronic acid (36 mg, 0.23 mmol) was subjected to general procedure D with **113a** (0.10 g, 0.19 mmol) followed by general procedure A to provide **70** (11 mg, 24 µmol, 13% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.35 (d, *J* = 1.0 Hz, 1H), 8.68 (d, *J* = 6.1 Hz, 1H), 8.49 – 8.42 (m, 2H), 8.19 (dt, *J* = 8.3, 1.1 Hz, 1H), 7.69 (dd, *J* = 8.2, 7.4 Hz, 1H), 7.47 (dt, *J* = 7.1, 1.3 Hz, 1H), 7.39 – 7.23 (m, 6H), 7.23 – 7.16 (m, 2H), 3.61 (s, 2H), 3.06 – 2.99 (m, 2H), 2.77 – 2.67 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.47, 145.38, 140.16, 138.95, 138.42, 134.32, 133.68, 133.46, 132.53, 131.45, 131.37, 130.08, 129.68, 129.55, 129.14, 128.70, 127.66, 127.36, 127.00, 126.03, 117.29, 52.90, 47.40, 42.50. HRMS $[C_{24}H_{22}ClN_3O_2S+H]^+$: 452.11940 calculated, 452.11901 found.

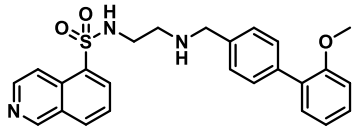


***N*-(2-(((2'-Methyl-[1,1'-biphenyl]-4-yl)methyl)amino)ethyl)isoquinoline-5-sulfonamide (71).** *o*-Tolylboronic acid (31 mg, 0.23 mmol) was subjected to general procedure D with **113a** (0.10 g, 0.19 mmol) followed by general procedure A to provide **71** (37 mg, 80 µmol, 42% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.35 (d, *J* = 1.1

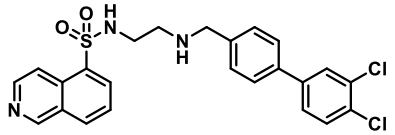
Hz, 1H), 8.68 (d, *J* = 6.1 Hz, 1H), 8.48 – 8.43 (m, 2H), 8.19 (dt, *J* = 8.2, 1.1 Hz, 1H), 7.69 (dd, *J* = 8.2, 7.3 Hz, 1H), 7.30 – 7.12 (m, 8H), 3.58 (s, 2H), 3.03 – 2.98 (m, 2H), 2.72 – 2.67 (m, 2H), 2.26 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.47, 145.37, 141.54, 141.03, 137.97, 135.41, 134.31, 133.69, 133.47, 131.38, 130.47, 129.87, 129.42, 129.15, 127.74, 127.41, 126.02, 125.91, 117.30, 52.93, 47.38, 42.47, 20.60. HRMS $[C_{25}H_{25}N_3O_2S+H]^+$: 432.17402 calculated, 432.17368 found.



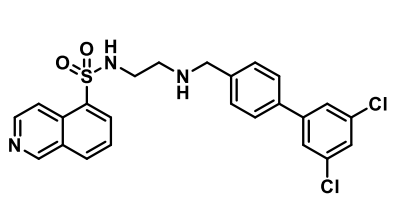
***N*-(2-(((2'-Cyano-[1,1'-biphenyl]-4-yl)methyl)amino)ethyl)isoquinoline-5-sulfonamide (72).** (2-Cyanophenyl)boronic acid (34 mg, 0.23 mmol) was subjected to general procedure D with **113a** (0.10 g, 0.19 mmol) followed by general procedure A to provide **72** (44 mg, 0.10 mmol, 53% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.34 (d, *J* = 1.0 Hz, 1H), 8.67 (d, *J* = 6.1 Hz, 1H), 8.49 – 8.42 (m, 2H), 8.19 (dt, *J* = 8.2, 1.1 Hz, 1H), 7.76 (ddd, *J* = 7.8, 1.3, 0.6 Hz, 1H), 7.72 – 7.59 (m, 2H), 7.52 – 7.41 (m, 4H), 7.25 – 7.19 (m, 2H), 3.59 (s, 2H), 3.06 – 2.97 (m, 2H), 2.72 – 2.63 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.44, 145.30, 145.17, 140.10, 137.14, 134.31, 133.84, 133.69, 133.44, 133.01, 131.34, 130.11, 129.12, 128.97, 128.30, 127.69, 126.05, 118.88, 117.31, 111.22, 52.75, 47.45, 42.49. HRMS $[C_{25}H_{22}N_4O_2S+H]^+$: 443.15362 calculated, 443.15325 found.



***N*-(2-(((2'-Methoxy-[1,1'-biphenyl]-4-yl)methyl)amino)ethyl)isoquinoline-5-sulfonamide (73).** (2-Methoxyphenyl)boronic acid (35 mg, 0.23 mmol) was subjected to general procedure D with **113a** (0.10 g, 0.19 mmol) followed by general procedure A to provide **73** (28 mg, 80 µmol, 42% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.33 (d, *J* = 1.0 Hz, 1H), 8.68 (d, *J* = 6.1 Hz, 1H), 8.48 – 8.40 (m, 2H), 8.17 (dt, *J* = 8.2, 1.1 Hz, 1H), 7.67 (dd, *J* = 8.2, 7.3 Hz, 1H), 7.48 – 7.41 (m, 2H), 7.36 – 7.27 (m, 2H), 7.17 – 7.12 (m, 2H), 7.05 – 6.96 (m, 2H), 3.81 (s, 3H), 3.56 (s, 2H), 3.04 – 2.97 (m, 2H), 2.71 – 2.65 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.52, 153.46, 145.39, 138.04, 137.62, 134.34, 133.66, 133.42, 131.38, 130.89, 130.27, 129.75, 129.13, 128.80, 127.68, 126.00, 120.96, 117.31, 111.29, 55.62, 52.92, 47.30, 42.46. HRMS $[C_{25}H_{25}N_3O_3S+H]^+$: 448.16894 calculated, 448.16854 found.

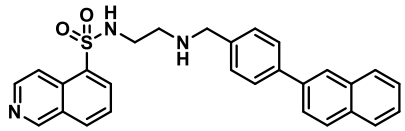


***N*-(2-(((3',4'-Dichloro-[1,1'-biphenyl]-4-yl)methyl)amino)ethyl)isoquinoline-5-sulfonamide (74).** (3,4-Dichlorophenyl)boronic acid (44 mg, 0.23 mmol) was subjected to general procedure D with **113a** (0.10 g, 0.19 mmol) followed by general procedure A to provide **74** (13 mg, 27 µmol, 14% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.34 (d, *J* = 1.0 Hz, 1H), 8.68 (d, *J* = 6.1 Hz, 1H), 8.48 – 8.41 (m, 2H), 8.19 (dt, *J* = 8.3, 1.1 Hz, 1H), 7.69 (dd, *J* = 8.2, 7.3 Hz, 1H), 7.64 (d, *J* = 2.1 Hz, 1H), 7.50 (d, *J* = 8.3 Hz, 1H), 7.46 – 7.41 (m, 2H), 7.39 (dd, *J* = 8.3, 2.2 Hz, 1H), 7.22 – 7.17 (m, 2H), 3.58 (s, 2H), 3.04 – 2.92 (m, 2H), 2.74 – 2.63 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.50, 145.42, 140.85, 139.61, 137.82, 134.29, 133.71, 133.51, 131.58, 131.38, 130.85, 129.16, 128.95, 128.66, 127.15, 126.38, 126.03, 117.27, 52.79, 47.36, 42.50. HRMS: found $[C_{24}H_{21}Cl_2N_3O_2S+H]^+$ calculated for $[C_{24}H_{21}Cl_2N_3O_2S+H]^+$ 486.08043 calculated, 486.07992 found.

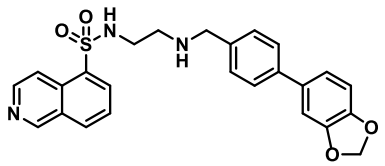


***N*-(2-(((3',5'-Dichloro-[1,1'-biphenyl]-4-yl)methyl)amino)ethyl)isoquinoline-5-sulfonamide (75).** (3,5-Dichlorophenyl)boronic acid (44 mg, 0.23 mmol) was subjected to general procedure D with **113a** (0.10 g, 0.19 mmol) followed by general procedure A to provide **75** (5.0 mg, 10 µmol, 5% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.35 (d, *J* = 1.0 Hz, 1H), 8.70 (d, *J* = 6.1 Hz, 1H), 8.48 – 8.41 (m, 2H), 8.20

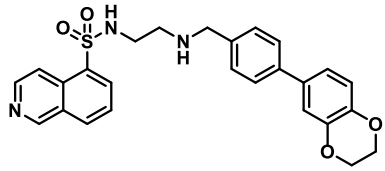
(dt, *J* = 8.2, 1.1 Hz, 1H), 7.70 (dd, *J* = 8.2, 7.3 Hz, 1H), 7.46 – 7.41 (m, 4H), 7.34 (t, *J* = 1.9 Hz, 1H), 7.23 – 7.18 (m, 2H), 3.59 (s, 2H), 3.02 – 2.96 (m, 2H), 2.71 – 2.65 (m, 2H). HRMS $[C_{24}H_{21}Cl_2N_3O_2S+H]^+$: 486.08043 calculated, 486.08022 found.



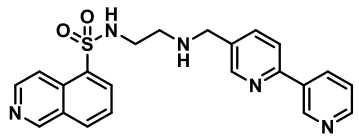
***N*-(2-((4-(Naphthalen-2-yl)benzyl)amino)ethyl)isoquinoline-5-sulfonamide (76).** Naphthalen-2-ylboronic acid (40 mg, 0.23 mmol) was subjected to general procedure D with **113a** (0.10 g, 0.19 mmol) followed by general procedure A to provide **76** (80 mg, 0.17 mmol, 89% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.28 (d, *J* = 1.1 Hz, 1H), 8.65 (dd, *J* = 6.2, 1.0 Hz, 1H), 8.46 (dd, *J* = 6.1, 1.0 Hz, 1H), 8.41 (dd, *J* = 7.4, 1.2 Hz, 1H), 8.09 (dq, *J* = 8.2, 1.4 Hz, 1H), 7.98 (d, *J* = 1.8 Hz, 1H), 7.91 – 7.81 (m, 3H), 7.68 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.65 – 7.56 (m, 3H), 7.53 – 7.40 (m, 2H), 7.22 – 7.15 (m, 2H), 3.58 (s, 2H), 3.04 – 2.94 (m, 2H), 2.73 – 2.55 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.37, 145.18, 140.01, 138.45, 137.98, 134.35, 133.70, 133.59, 133.33, 132.66, 131.31, 129.06, 128.58, 128.54, 128.25, 127.71, 127.46, 126.43, 126.06, 125.98, 125.67, 125.44, 117.35, 52.79, 47.45, 42.44. HRMS $[C_{28}H_{25}N_3O_2S+H]^+$: 468.17402 calculated, 468.17387 found.



***N*-(2-((4-(Benzo[*d*][1,3]dioxol-5-yl)benzyl)amino)ethyl)isoquinoline-5-sulfonamide (77).** Benzo[*d*][1,3]dioxol-5-ylboronic acid (38 mg, 0.23 mmol) was subjected to general procedure D with **113a** (0.10 g, 0.19 mmol) followed by general procedure A to provide **77** (24 mg, 50 µmol, 26% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.34 (d, *J* = 1.0 Hz, 1H), 8.68 (d, *J* = 6.1 Hz, 1H), 8.47 – 8.40 (m, 2H), 8.18 (dt, *J* = 8.2, 1.1 Hz, 1H), 7.68 (dd, *J* = 8.2, 7.3 Hz, 1H), 7.45 – 7.38 (m, 2H), 7.18 – 7.11 (m, 2H), 7.06 – 7.00 (m, 2H), 6.93 – 6.85 (m, 1H), 6.01 (s, 2H), 3.56 (s, 2H), 3.05 – 2.96 (m, 2H), 2.74 – 2.62 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.49, 148.27, 147.24, 145.44, 140.06, 138.07, 135.18, 134.31, 133.69, 133.47, 131.38, 129.15, 128.48, 127.06, 126.01, 120.65, 117.29, 108.74, 107.68, 101.30, 52.80, 47.28, 42.44. HRMS $[C_{25}H_{23}N_3O_4S+H]^+$: 462.14820 calculated, 462.14761 found.

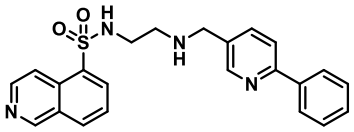


***N*-(2-((4-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)benzyl)amino)ethyl)isoquinoline-5-sulfonamide (78).** (2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)boronic acid (41 mg, 0.23 mmol) was subjected to general procedure D with **113a** (0.10 g, 0.19 mmol,) followed by general procedure A to provide **78** (20 mg, 42 µmol, 22% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.33 (d, *J* = 1.0 Hz, 1H), 8.68 (d, *J* = 6.1 Hz, 1H), 8.48 – 8.40 (m, 2H), 8.17 (dt, *J* = 8.1, 1.1 Hz, 1H), 7.67 (dd, *J* = 8.2, 7.3 Hz, 1H), 7.44 – 7.38 (m, 2H), 7.16 – 7.10 (m, 2H), 7.10 – 7.03 (m, 2H), 6.93 (d, *J* = 8.3 Hz, 1H), 4.30 (s, 4H), 3.55 (s, 2H), 3.02 – 2.96 (m, 2H), 2.70 – 2.62 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.48, 145.41, 143.82, 143.32, 139.69, 137.96, 134.37, 134.33, 133.68, 133.43, 131.38, 129.14, 128.46, 126.90, 126.00, 120.16, 117.71, 117.29, 115.85, 64.60, 64.57, 52.81, 47.28, 42.45. HRMS $[C_{26}H_{25}N_3O_4S+H]^+$: 476.16385 calculated, 476.16340 found.

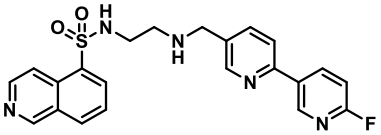


***N*-(2-(([2,3'-Bipyridin]-5-ylmethyl)amino)ethyl)isoquinoline-5-sulfonamide (79).** Pyridin-3-ylboronic acid (27 mg, 0.23 mmol) was subjected to general procedure D with **113b** (0.10 g, 0.21 mmol) followed by general procedure A to provide **79** (10 mg, 24 µmol, 11% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.33 (d, *J* = 1.0 Hz, 1H), 9.15 (dd, *J* = 2.4, 0.9 Hz, 1H), 8.68 – 8.61 (m, 2H), 8.49 (dd, *J* = 2.3, 0.9 Hz, 1H), 8.47 – 8.43 (m, 2H), 8.29 (ddd,

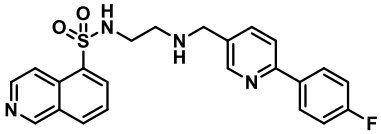
J = 8.0, 2.4, 1.7 Hz, 1H), 8.18 (d, 8.3 Hz), 7.72 – 7.55 (m, 3H), 7.41 (ddd, *J* = 8.0, 4.8, 0.9 Hz, 1H), 3.64 (s, 2H), 3.12 – 2.98 (m, 2H), 2.77 – 2.63 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.78, 153.46, 149.92, 149.79, 148.18, 145.28, 136.73, 134.65, 134.41, 134.39, 134.30, 133.68, 133.44, 131.32, 129.11, 126.06, 123.78, 120.40, 117.26, 50.33, 47.75, 42.60. HRMS $[C_{22}H_{21}N_5O_2S+H]^+$: 420.14887 calculated, 420.14839 found.



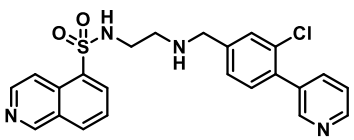
***N*-(2-(((6-Phenylpyridin-3-yl)methyl)amino)ethyl)isoquinoline-5-sulfonamide (80).** Phenylboronic acid (27 mg, 0.23 mmol) was subjected to general procedure D with **113b** (0.10 g, 0.21 mmol) followed by general procedure A to provide **80** (24 mg, 57 µmol, 27% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.32 (d, *J* = 1.0 Hz, 1H), 8.66 (d, *J* = 6.1 Hz, 1H), 8.47 – 8.41 (m, 1H), 8.16 (dt, *J* = 8.2, 1.1 Hz, 1H), 7.97 – 7.92 (m, 2H), 7.67 (dd, *J* = 8.2, 7.3 Hz, 1H), 7.61 (dd, *J* = 8.1, 0.9 Hz, 1H), 7.54 – 7.37 (m, 4H), 3.59 (s, 2H), 3.10 – 2.95 (m, 2H), 2.71 – 2.61 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.60, 153.47, 149.36, 145.30, 139.08, 136.57, 134.33, 133.71, 133.45, 133.37, 131.32, 129.10, 128.89, 126.94, 126.05, 120.42, 117.26, 50.35, 47.58, 42.58. HRMS $[C_{23}H_{22}N_4O_2S+H]^+$: 419.15362 calculated, 419.15334 found.



***N*-(2-(((6'-Fluoro-[2,3'-bipyridin]-5-yl)methyl)amino)ethyl)isoquinoline-5-sulfonamide (81).** (6-Fluoropyridin-3-yl)boronic acid (30 mg, 0.23 mmol) was subjected to general procedure D with **113b** (0.10 g, 0.21 mmol) followed by general procedure A to provide **81** (20 mg, 46 µmol, 22% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.34 (d, *J* = 1.0 Hz, 1H), 8.77 (dt, *J* = 2.6, 0.8 Hz, 1H), 8.68 (d, *J* = 6.1 Hz, 1H), 8.50 – 8.39 (m, 4H), 8.20 (dt, *J* = 8.2, 1.1 Hz, 1H), 7.70 (dd, *J* = 8.2, 7.3 Hz, 1H), 7.65 – 7.56 (m, 2H), 7.04 (ddd, *J* = 8.6, 3.0, 0.7 Hz, 1H), 3.64 (s, 2H), 3.08 – 3.00 (m, 2H), 2.73 – 2.67 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.06, (d, *J* = 243 Hz), 153.50, 152.83, 149.77, 146.20 (d, *J* = 14.5 Hz), 145.36, 139.88 (d, *J* = 8.1 Hz), 136.80, 134.27 (d, *J* = 4.5 Hz), 133.76, 133.52, 132.93, 131.32, 129.13, 126.07, 120.13, 117.21, 109.70 (d, *J* = 23 Hz), 50.29, 47.63, 42.57. HRMS $[C_{22}H_{20}FN_5O_2S+H]^+$: 438.13945 calculated, 438.13902 found.

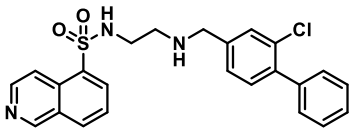


***N*-(2-(((6-(4-Fluorophenyl)pyridin-3-yl)methyl)amino)ethyl)isoquinoline-5-sulfonamide (82).** (4-Fluorophenyl)boronic acid (30 mg, 0.23 mmol) was subjected to general procedure D with **113b** (0.10 g, 0.21 mmol) followed by general procedure A to provide **82** (25 mg, 57 µmol, 27% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.34 (d, *J* = 1.0 Hz, 1H), 8.68 (d, *J* = 6.1 Hz, 1H), 8.48 – 8.40 (m, 3H), 8.18 (dt, *J* = 8.2, 1.1 Hz, 1H), 7.99 – 7.92 (m, 2H), 7.69 (dd, *J* = 8.2, 7.4 Hz, 1H), 7.59 (dd, *J* = 8.1, 0.9 Hz, 1H), 7.52 (dd, *J* = 8.2, 2.3 Hz, 1H), 7.19 – 7.09 (m, 2H), 3.60 (s, 2H), 3.05 – 2.98 (m, 2H), 2.70 – 2.64 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.63 (d, *J* = 243 Hz), 155.65, 153.52, 149.38, 145.39, 136.61, 135.26, 134.25, 133.76, 133.51, 133.28, 131.33, 129.13, 128.75 (d, *J* = 8.0 Hz), 126.05, 120.08, 117.22, 115.81 (d, *J* = 23 Hz), 50.33, 47.52, 42.56. HRMS $[C_{23}H_{21}FN_4O_2S+H]^+$: 437.14420 calculated, 437.14383 found.

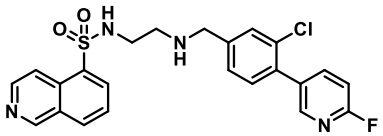


***N*-(2-((3-Chloro-4-(pyridin-3-yl)benzyl)amino)ethyl)isoquinoline-5-sulfonamide (83).** Pyridin-3-ylboronic acid (27 mg, 0.23 mmol) was subjected to general procedure D with **113c** (0.10 g, 0.23 mmol) followed by general procedure A to provide **83** (11 mg, 24 µmol, 10% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.35 (d, *J* = 1.0 Hz, 1H), 8.69 (d, *J* = 6.1 Hz, 1H), 8.66 (dd, *J* = 2.2, 0.9 Hz, 1H), 8.63 (dd, *J* = 4.9, 1.7 Hz, 1H), 8.49 – 8.43 (m, 2H), 8.21 (dt, *J* = 8.2, 1.1 Hz, 1H), 7.82 – 7.76 (m, 1H), 7.71 (dd, *J* = 8.2, 7.3 Hz, 1H), 7.38 (ddd, *J* = 7.9, 4.9, 0.9 Hz, 1H),

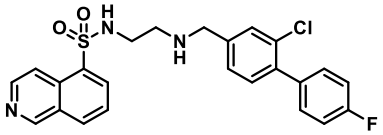
7.31 (d, *J* = 1.7 Hz, 1H), 7.25 (dd, *J* = 7.5, 1.5 Hz, 2H), 7.20 – 7.07 (m, 2H), 3.59 (s, 2H), 3.07 – 2.98 (m, 2H), 2.73 – 2.64 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.51, 150.08, 148.90, 145.43, 141.53, 137.03, 135.83, 134.92, 134.29, 133.76, 133.54, 132.87, 131.41, 131.37, 129.54, 129.16, 126.72, 126.06, 123.06, 117.23, 52.33, 47.49, 42.56. HRMS $[C_{23}H_{21}ClN_4O_2S+H]^+$: 453.11466 calculated, 453.11422 found.



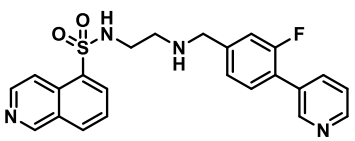
***N*-(2-(((2-Chloro-[1,1'-biphenyl]-4-yl)methyl)amino)ethyl)isoquinoline-5-sulfonamide (84).** Phenylboronic acid (27 mg, 0.23 mmol) was subjected to general procedure D with **113c** (0.10 g, 0.23 mmol) followed by general procedure A to provide **84** (23 mg, 51 µmol, 22% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.41 – 9.29 (m, 1H), 8.70 (d, *J* = 6.1 Hz, 1H), 8.50 – 8.39 (m, 2H), 8.20 (d, *J* = 8.2 Hz, 1H), 7.70 (t, *J* = 7.8 Hz, 1H), 7.48 – 7.35 (m, 5H), 7.32 – 7.18 (m, 2H), 7.07 (dd, *J* = 7.8, 1.7 Hz, 1H), 3.56 (s, 2H), 3.07 – 2.97 (m, 2H), 2.72 – 2.62 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.50, 145.43, 140.42, 139.43, 139.12, 134.28, 133.75, 133.51, 132.58, 131.53, 131.36, 129.54, 129.34, 129.14, 128.19, 127.76, 126.43, 126.04, 117.23, 52.33, 47.39, 42.53. HRMS $[C_{24}H_{22}ClN_3O_2S+H]^+$: 452.11940 calculated, 452.11890 found.



***N*-(2-((3-Chloro-4-(6-fluoropyridin-3-yl)benzyl)amino)ethyl)isoquinoline-5-sulfonamide (85).** (6-Fluoropyridin-3-yl)boronic acid (30 mg, 0.23 mmol) was subjected to general procedure D with **113c** (0.10 g, 0.23 mmol) followed by general procedure A to provide **85** (16 mg, 34 µmol, 15% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.34 (d, *J* = 1.0 Hz, 1H), 8.68 (d, *J* = 6.1 Hz, 1H), 8.49 – 8.42 (m, 2H), 8.27 – 8.23 (m, 1H), 8.20 (dt, *J* = 8.3, 1.1 Hz, 1H), 7.89 (ddd, *J* = 8.5, 7.6, 2.5 Hz, 1H), 7.70 (dd, *J* = 8.2, 7.4 Hz, 1H), 7.33 – 7.08 (m, 3H), 7.00 (ddd, *J* = 8.4, 3.0, 0.7 Hz, 1H), 3.57 (s, 2H), 3.06 – 2.97 (m, 2H), 2.71 – 2.63 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.11 (d, *J* = 243 Hz), 153.51, 147.92 (d, *J* = 14.5 Hz), 145.42, 142.32 (d, *J* = 8.1 Hz), 141.78, 137.99, 134.68, 134.24, 133.77, 133.55, 132.91, 131.34, 129.57, 129.16, 128.35, 126.76, 126.05, 125.42, 117.20, 108.99 (d, *J* = 23 Hz), 52.28, 47.47, 42.55. HRMS $[C_{23}H_{20}ClFN_4O_2S+H]^+$: 471.10523 calculated, 471.10486 found.

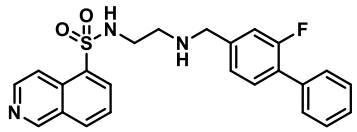


***N*-(2-(((2-Chloro-4'-fluoro-[1,1'-biphenyl]-4-yl)methyl)amino)ethyl)isoquinoline-5-sulfonamide (86).** (4-Fluorophenyl)boronic acid (30 mg, 0.23 mmol) was subjected to general procedure D with **113c** (0.10 g, 0.23 mmol) followed by general procedure A to provide **86** (20 mg, 43 µmol, 19% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.35 (d, *J* = 1.0 Hz, 1H), 8.71 (d, *J* = 6.1 Hz, 1H), 8.49 – 8.41 (m, 2H), 8.21 (dt, *J* = 8.3, 1.2 Hz, 1H), 7.71 (dd, *J* = 8.2, 7.4 Hz, 1H), 7.43 – 7.36 (m, 2H), 7.25 – 7.16 (m, 2H), 7.16 – 7.09 (m, 2H), 7.07 (dd, *J* = 7.8, 1.8 Hz, 1H), 3.56 (s, 2H), 3.05 – 2.96 (m, 2H), 2.72 – 2.61 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.73 (d, *J* = 243 Hz), 153.53, 145.50, 140.62, 138.59, 135.13, 134.25, 133.78, 133.57, 131.50, 131.37, 131.26 (d, *J* = 8.0 Hz), 129.40, 129.16, 126.49, 126.04, 117.21, 115.20 (d, *J* = 23 Hz), 52.32, 47.37, 42.52. HRMS $[C_{24}H_{21}ClFN_3O_2S+H]^+$: 470.10998 calculated, 470.10941 found.

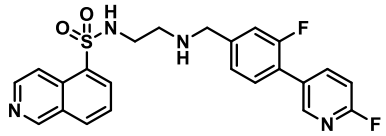


***N*-(2-((3-Fluoro-4-(pyridin-3-yl)benzyl)amino)ethyl)isoquinoline-5-sulfonamide (87).** Pyridin-3-ylboronic acid (27 mg, 0.23 mmol) was subjected to general procedure D with **113d** (0.10 g, 0.20 mmol) followed by general procedure A to provide **87** (10 mg, 23 µmol, 12% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.35 (d, *J* = 1.0 Hz, 1H),

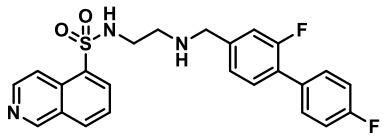
8.77 (dq, *J* = 2.3, 1.0 Hz, 1H), 8.70 (d, *J* = 6.1 Hz, 1H), 8.61 (dd, *J* = 4.8, 1.7 Hz, 1H), 8.50 – 8.42 (m, 2H), 8.21 (dt, *J* = 8.2, 1.1 Hz, 1H), 7.87 (ddt, *J* = 7.9, 2.3, 1.7 Hz, 1H), 7.71 (dd, *J* = 8.2, 7.3 Hz, 1H), 7.42 – 7.31 (m, 2H), 7.05 – 6.97 (m, 2H), 3.61 (s, 2H), 3.04 – 2.98 (m, 2H), 2.71 – 2.67 (m, 2H). HRMS $[C_{23}H_{21}FN_4O_2S+H]^+$: 437.14420 calculated, 437.14402 found.



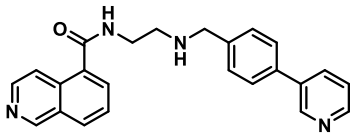
***N*-(2-(((2-Fluoro-[1,1'-biphenyl]-4-yl)methyl)amino)ethyl)isoquinoline-5-sulfonamide (88).** Phenylboronic acid (27 mg, 0.23 mmol) was subjected to general procedure D with **113d** (0.10 g, 0.20 mmol) followed by general procedure A to provide **88** (34 mg, 78 µmol, 39% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.34 (d, *J* = 1.0 Hz, 1H), 8.68 (d, *J* = 6.1 Hz, 1H), 8.50 – 8.40 (m, 2H), 8.18 (dt, *J* = 8.3, 1.1 Hz, 1H), 7.68 (dd, *J* = 8.2, 7.4 Hz, 1H), 7.52 (dt, *J* = 8.2, 1.5 Hz, 2H), 7.48 – 7.41 (m, 2H), 7.41 – 7.28 (m, 2H), 7.01 – 6.92 (m, 2H), 3.57 (s, 2H), 3.08 – 2.95 (m, 2H), 2.74 – 2.62 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.77 (d, *J* = 250 Hz), 153.48, 145.37, 141.23 (d, *J* = 7.2 Hz), 135.57, 134.30, 133.72, 133.48, 131.35, 130.82 (d, *J* = 3.9 Hz), 129.04 (d, *J* = 3.0 Hz), 129.13, 128.59, 127.93, 127.80, 126.03, 123.78 (d, *J* = 3.4 Hz), 117.25, 115.49 (d, *J* = 23 Hz), 52.42, 47.40, 42.55. HRMS $[C_{24}H_{22}FN_3O_2S+H]^+$: 436.14895 calculated, 436.14876 found.



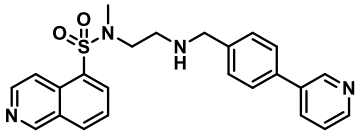
***N*-(2-((3-Fluoro-4-(6-fluoropyridin-3-yl)benzyl)amino)ethyl)isoquinoline-5-sulfonamide (89).** (6-Fluoropyridin-3-yl)boronic acid (30 mg, 0.23 mmol) was subjected to general procedure D with **113d** (0.10 g, 0.20 mmol) followed by general procedure A to provide **89** (18 mg, 40 µmol, 20% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.35 (d, *J* = 0.9 Hz, 1H), 8.69 (d, *J* = 6.1 Hz, 1H), 8.45 (td, *J* = 7.3, 1.1 Hz, 2H), 8.36 (dq, *J* = 2.1, 1.0 Hz, 1H), 8.21 (dt, *J* = 8.3, 1.1 Hz, 1H), 7.97 (dddd, *J* = 8.5, 7.6, 2.6, 1.6 Hz, 1H), 7.70 (dd, *J* = 8.2, 7.4 Hz, 1H), 7.31 (t, *J* = 8.0 Hz, 1H), 7.07 – 6.97 (m, 3H), 3.60 (s, 2H), 3.04 – 2.98 (m, 2H), 2.71 – 2.64 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.14 (d, *J* = 243 Hz), 159.79 (d, *J* = 250 Hz), 153.52, 147.45 (dd, *J* = 15, 3.2 Hz), 145.43, 142.67, 141.65 (dd, *J* = 8.2, 3.7 Hz), 134.25, 133.76, 133.54, 131.36, 130.38, 129.44 (dd, *J* = 4.4, 1.4 Hz), 129.15, 126.05, 124.14, 123.31 (d, *J* = 14 Hz), 117.21, 115.69 (d, *J* = 23 Hz), 109.43 (d, *J* = 38 Hz), 52.37, 47.46, 42.57. HRMS $[C_{23}H_{20}F_2N_4O_2S+H]^+$: 455.13478 calculated, 455.13426 found.



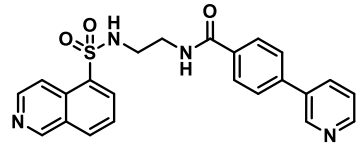
***N*-(2-(((2,4'-Difluoro-[1,1'-biphenyl]-4-yl)methyl)amino)ethyl)isoquinoline-5-sulfonamide (90).** (4-Fluorophenyl)boronic acid (30 mg, 0.23 mmol) was subjected to general procedure D with **113d** (0.10 g, 0.20 mmol) followed by general procedure A to provide **90** (27 mg, 60 µmol, 30% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.34 (d, *J* = 0.9 Hz, 1H), 8.69 (d, *J* = 6.1 Hz, 1H), 8.48 – 8.41 (m, 2H), 8.20 (dt, *J* = 8.3, 1.2 Hz, 1H), 7.70 (dd, *J* = 8.2, 7.4 Hz, 1H), 7.53 – 7.45 (m, 2H), 7.29 (t, *J* = 8.0 Hz, 1H), 7.16 – 7.10 (m, 2H), 7.00 – 6.90 (m, 2H), 3.57 (s, 2H), 3.06 – 2.97 (m, 2H), 2.71 – 2.63 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.35 (d, *J* = 288 Hz), 159.89 (d, *J* = 288 Hz), 153.51, 145.43, 141.34 (d, *J* = 7.1 Hz), 134.26, 133.75, 133.53, 131.55 (d, *J* = 1.9 Hz), 131.36, 130.75 (d, *J* = 3.0 Hz), 130.67 (d, *J* = 2.9 Hz), 129.15, 126.92 (d, *J* = 13 Hz), 126.03, 123.84 (d, *J* = 3.3 Hz), 117.23, 115.67 (d, *J* = 1.8 Hz), 115.44 (d, *J* = 3.3 Hz), 52.40, 47.38, 42.54. HRMS $[C_{23}H_{21}F_2N_3O_2S+H]^+$: 454.13953 calculated, 454.13915 found.



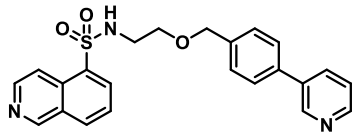
***N*-(2-((4-(Pyridin-3-yl)benzyl)amino)ethyl)isoquinoline-5-carboxamide (91).** To a solution of **108** (14 mg, 44 µmol), DIPEA (11.5 µL, 66 µmol) and the isoquinoline-5-carboxylic acid (8.3 mg, 48 µmol.) in DCM (2 mL) was added HATU (17 mg, 44 µmol). The reaction mixture was stirred at RT overnight. after which the mixture was washed with water. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*, after which the residue was purified by column chromatography (5% MeOH (10% aq. NH_3) in DCM). The product was then subjected to general procedure A to yield title compound **91** (13 mg, 33 µmol, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.26 (d, *J* = 1.0 Hz, 1H), 8.80 (dd, *J* = 2.4, 0.9 Hz, 1H), 8.61 – 8.52 (m, 2H), 8.20 (dt, *J* = 6.0, 1.0 Hz, 1H), 8.04 (dt, *J* = 8.3, 1.1 Hz, 1H), 7.88 – 7.80 (m, 2H), 7.58 (dd, *J* = 8.2, 7.1 Hz, 1H), 7.54 – 7.49 (m, 2H), 7.46 – 7.40 (m, 2H), 7.36 (ddd, *J* = 7.9, 4.8, 0.9 Hz, 1H), 6.81 (t, *J* = 5.3 Hz, 1H), 3.90 (s, 2H), 3.67 (q, *J* = 5.6 Hz, 2H), 2.99 (d, *J* = 6.3 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.31, 152.94, 148.61, 148.30, 144.32, 139.86, 136.93, 136.29, 134.34, 133.32, 133.17, 130.50, 129.37, 129.02, 128.82, 127.38, 126.34, 123.71, 118.36, 53.18, 48.10, 39.67. HRMS $[C_{24}H_{22}N_4O+H]^+$: 383.18664 calculated, 383.18628 found.



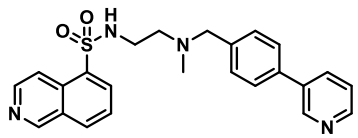
***N*-Methyl-*N*-(2-((4-(pyridin-2-yl)benzyl)amino)ethyl)isoquinoline-5-sulfonamide (92).** *tert*-Butyl (2-(isoquinoline-5-sulfonamido)ethyl)(4-(pyridin-2-yl)benzyl)carbamate (**109**) (7.0 mg, 38 µmol), iodomethane (3.0 µL, 46 µmol) and NaOH (1.0 mg, 19 µmol) were dissolved in DMF (1 mL). The reaction mixture was stirred overnight at 80°C and then diluted with brine (3 mL) and extracted with DCM (3×). The crude product was subjected to general procedure A to give **92** (1.0 mg, 15% over 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.33 (d, *J* = 1.0 Hz, 1H), 8.85 (dd, *J* = 2.4, 0.9 Hz, 1H), 8.67 (d, *J* = 6.2 Hz, 1H), 8.59 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.51 (dt, *J* = 6.2, 0.9 Hz, 1H), 8.40 (dd, *J* = 7.4, 1.2 Hz, 1H), 8.20 (dt, *J* = 8.2, 1.1 Hz, 1H), 7.88 (ddd, *J* = 7.9, 2.4, 1.6 Hz, 1H), 7.71 (dd, *J* = 8.2, 7.4 Hz, 1H), 7.57 – 7.53 (m, 2H), 7.37 (m, 3H), 3.82 (s, 2H), 3.34 (t, *J* = 6.1 Hz, 2H), 2.86 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.41, 148.60, 148.42, 145.35, 138.08, 136.93, 136.29, 134.40, 134.11, 133.80, 133.52, 131.42, 129.68, 128.91, 127.36, 126.01, 123.72, 117.78, 53.15, 49.64, 46.54, 34.88. HRMS $[C_{24}H_{24}N_4O_2S+H]^+$: 433.16927 calculated, 433.16907 found.



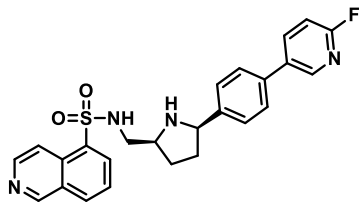
***N*-(2-(Isoquinoline-5-sulfonamido)ethyl)-4-(pyridin-3-yl)benzamide (93). 93** (79 mg, 0.18 mmol, 79%) was synthesized from **114** (100 mg, 0.23 mmol) and pyridin-3-ylboronic acid (30 mg, 0.25 mmol) according to general procedure D. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.23 (s, 1H), 8.70 (d, *J* = 2.2 Hz, 1H), 8.54 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.50 – 8.41 (m, 2H), 8.39 (dd, *J* = 7.4, 1.2 Hz, 1H), 8.08 (d, *J* = 8.2 Hz, 1H), 7.77 (dt, *J* = 8.0, 2.0 Hz, 1H), 7.71 (t, *J* = 8.6 Hz, 3H), 7.60 (t, *J* = 7.8 Hz, 1H), 7.43 – 7.37 (m, 2H), 7.32 (dd, *J* = 8.0, 4.8 Hz, 1H), 3.64 – 3.53 (m, 2H), 3.30 – 3.16 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.82, 153.19, 148.83, 147.83, 144.78, 140.50, 135.39, 134.63, 134.41, 133.60, 133.25, 133.16, 131.14, 129.02, 127.86, 126.99, 126.06, 123.91, 117.44, 67.10, 42.78, 40.35. HRMS $[C_{23}H_{20}N_4O_3S+H]^+$: 433.13289 calculated, 433.13252 found.



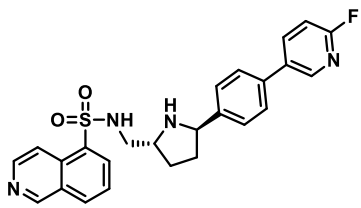
***N*-(2-((4-(Pyridin-3-yl)benzyl)oxy)ethyl)isoquinoline-5-sulfonamide (94). 94** (136 mg, 0.32 mmol, 76%) was synthesized from **119** (0.10 g, 0.44 mmol) and isoquinoline-5-sulfonyl chloride (106 mg, 0.40 µmol) according to general procedure B. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.34 (d, *J* = 1.0 Hz, 1H), 8.80 (dd, *J* = 2.4, 0.9 Hz, 1H), 8.63 (d, *J* = 6.1 Hz, 1H), 8.60 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.48 – 8.42 (m, 2H), 8.17 (dt, *J* = 8.2, 1.1 Hz, 1H), 7.85 (ddd, *J* = 7.9, 2.4, 1.6 Hz, 1H), 7.67 (dd, *J* = 8.2, 7.3 Hz, 1H), 7.49 – 7.43 (m, 2H), 7.37 (ddd, *J* = 7.9, 4.8, 0.9 Hz, 1H), 7.22 (d, *J* = 8.2 Hz, 2H), 6.30 (t, *J* = 5.9 Hz, 1H), 4.33 (s, 2H), 3.46 (t, *J* = 5.0 Hz, 2H), 3.27 – 3.17 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.36, 148.55, 148.17, 145.17, 137.45, 137.35, 136.22, 134.90, 134.47, 133.56, 133.13, 131.37, 129.11, 128.39, 127.22, 126.00, 123.74, 117.41, 72.79, 68.66, 43.15. HRMS $[C_{23}H_{21}N_3O_3S$ +H]$^+$: 420.13764 calculated, 420.13728 found.



***N*-(2-(Methyl(4-(pyridin-3-yl)benzyl)amino)ethyl)isoquinoline-5-sulfonamide (95).** Pyridin-3-ylboronic acid (34 mg, 28 µmol) was subjected to general procedure D with **120** (0.10 g, 0.23 mmol) to provide **95** (45 mg, 0.10 mmol, 45%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.32 (d, *J* = 1.0 Hz, 1H), 8.84 (dd, *J* = 2.4, 0.9 Hz, 1H), 8.65 (d, *J* = 6.1 Hz, 1H), 8.60 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.48 – 8.41 (m, 2H), 8.18 (dt, *J* = 8.2, 1.1 Hz, 1H), 7.88 (ddd, *J* = 7.9, 2.4, 1.6 Hz, 1H), 7.68 (dd, *J* = 8.2, 7.3 Hz, 1H), 7.54 – 7.46 (m, 2H), 7.39 (ddd, *J* = 7.9, 4.9, 0.9 Hz, 1H), 7.29 – 7.23 (m, 2H), 3.38 (s, 2H), 3.06 – 2.97 (m, 2H), 2.49 – 2.38 (m, 2H), 1.91 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.42, 148.57, 148.27, 145.27, 138.08, 136.93, 136.27, 134.41, 134.21, 133.60, 133.42, 131.36, 129.61, 129.08, 127.20, 125.97, 123.72, 117.27, 61.72, 55.03, 41.24, 40.24. HRMS $[C_{24}H_{24}N_4O_2S$+H]$^+$: 433.16927 calculated, 433.16896 found.

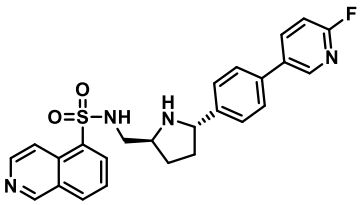


***N*-(((2*S*,5*R*)-5-(4-(6-Fluoropyridin-3-yl)phenyl)pyrrolidin-2-yl)methyl)isoquinoline-5-sulfonamide (96).** Following general procedure A, **175a** (53 mg, 94 µmol) was reacted with TFA to afford the title compound as a white solid (14 mg, 31 µmol, 33%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.37 (s, 1H), 8.71 (d, *J* = 6.1 Hz, 1H), 8.49 – 8.47 (m, 1H), 8.47 (d, *J* = 1.2 Hz, 1H), 8.40 (d, *J* = 2.7 Hz, 1H), 8.22 (d, *J* = 8.2 Hz, 1H), 7.96 (ddd, *J* = 8.5, 7.6, 2.6 Hz, 1H), 7.75 – 7.68 (m, 1H), 7.42 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.02 (ddd, *J* = 8.5, 3.0, 0.7 Hz, 1H), 4.23 (dd, *J* = 8.7, 6.5 Hz, 1H), 3.50 – 3.42 (m, 1H), 3.04 (dd, *J* = 12.0, 4.2 Hz, 1H), 2.84 (dd, *J* = 12.0, 6.4 Hz, 1H), 2.14 – 2.05 (m, 1H), 1.96 – 1.86 (m, 1H), 1.63 – 1.49 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.18 (d, *J* = 239 Hz), 153.56, 145.82 (d, *J* = 15 Hz), 145.40, 144.40, 139.76 (d, *J* = 8.0 Hz), 135.55, 134.65 (d, *J* = 4.8 Hz), 134.33, 133.70, 133.52, 131.38, 129.18, 127.18, 127.09, 126.08, 117.29, 109.61 (d, *J* = 37 Hz), 62.19, 56.05, 47.98, 34.48, 28.76. HRMS $[C_{25}H_{23}FN_4O_2S$ + H]$^+$: 463.15985 calculated, 463.15927 found. $[\alpha]_D^{25}$ +47,9° (c = 1.00, $CHCl_3$).

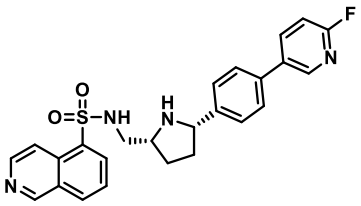


***N*-(((2*R*,5*R*)-5-(4-(6-Fluoropyridin-3-yl)phenyl)pyrrolidin-2-yl)methyl)isoquinoline-5-sulfonamide (97).** Following general procedure A, **175d** (36 mg, 64 mmol) was reacted with TFA to afford the title compound as a white solid (22 mg, 48 µmol, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.37 (d, *J* = 1.1 Hz, 1H), 8.70 (d, *J* = 6.1 Hz, 1H), 8.51 – 8.47 (m, 1H), 8.46 (dd, *J* = 4.7, 1.2 Hz, 1H), 8.39 (dt, *J* = 2.6, 0.9 Hz, 1H), 8.22 (d, *J* = 8.2 Hz, 1H), 7.95 (ddd, *J* = 8.5, 7.6, 2.6 Hz, 1H), 7.72 (dd, *J* = 8.2, 7.4 Hz, 1H), 7.47 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 6.4 Hz, 2H), 7.01 (ddd, *J* = 8.5, 3.1, 0.7 Hz, 1H), 4.02 (dd, *J* = 8.4, 6.3 Hz, 1H), 3.60

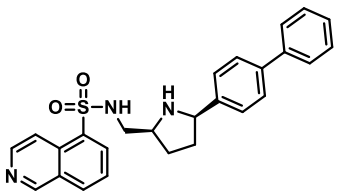
– 3.49 (m, 1H), 3.01 (dd, *J* = 12.3, 4.4 Hz, 1H), 2.79 (dd, *J* = 12.3, 7.9 Hz, 1H), 2.23 – 2.13 (m, 1H), 2.08 – 1.96 (m, 1H), 1.75 – 1.63 (m, 1H), 1.54 – 1.41 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.22 (d, *J* = 239 Hz), 153.50, 145.83 (d, *J* = 15 Hz), 145.39, 143.87, 139.74 (d, *J* = 8.0 Hz), 135.73, 134.52, 134.48, 133.69, 133.42, 131.39, 129.16, 127.33, 127.15, 126.06, 117.31, 109.62 (d, *J* = 38 Hz), 61.39, 57.24, 47.50, 34.76, 29.47. HRMS $[C_{25}H_{23}FN_4O_2S + H]^+$: 463.15985 calculated, 463.15925 found. $[\alpha]_D^{25}$ + 29.5° (c = 1.00, $CHCl_3$).



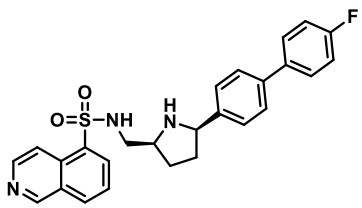
***N*-(((2*S*,5*S*)-5-(4-(6-Fluoropyridin-3-yl)phenyl)pyrrolidin-2-yl)methyl)isoquinoline-5-sulfonamide (98).** Following general procedure A, **175b** (5.8 mg, 10 µmol) was reacted with TFA to afford the title compound as a white solid (3.4 mg, 7.4 µmol, 71%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.37 (s, 1H), 8.71 (d, *J* = 6.1 Hz, 1H), 8.47 (dd, *J* = 7.3, 1.2 Hz, 1H), 8.46 – 8.43 (m, 1H), 8.40 (dt, *J* = 2.7, 0.8 Hz, 1H), 8.22 (d, *J* = 8.2 Hz, 1H), 7.95 (ddd, *J* = 8.4, 7.6, 2.6 Hz, 1H), 7.72 (dd, *J* = 8.2, 7.3 Hz, 1H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 7.9 Hz, 2H), 7.01 (ddd, *J* = 8.5, 3.0, 0.7 Hz, 1H), 4.03 (dd, *J* = 8.4, 6.3 Hz, 1H), 3.58 – 3.52 (m, 1H), 3.01 (dd, *J* = 12.3, 4.4 Hz, 1H), 2.79 (dd, *J* = 12.3, 7.9 Hz, 1H), 2.23 – 2.16 (m, 1H), 2.06 – 1.99 (m, 1H), 1.70 (dq, *J* = 12.5, 8.6 Hz, 1H), 1.53 – 1.44 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.27 (d, *J* = 239 Hz), 153.53, 145.89 (d, *J* = 15 Hz), 145.48, 143.68, 139.75 (d, *J* = 8.0 Hz), 135.85, 134.52, 134.49, 133.71, 133.44, 131.43, 129.20, 127.39, 127.20, 126.06, 117.32, 109.64 (d, *J* = 38 Hz), 61.48, 57.30, 47.44, 34.72, 29.48. HRMS $[C_{25}H_{23}FN_4O_2S + H]^+$: 463.15985 calculated, 463.15937 found. $[\alpha]_D^{25}$ = - 23.5° (c = 0.31, $CHCl_3$).



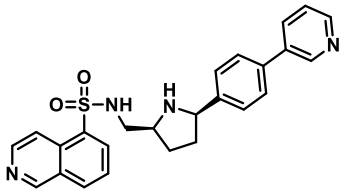
***N*-(((2*R*,5*S*)-5-(4-(6-Fluoropyridin-3-yl)phenyl)pyrrolidin-2-yl)methyl)isoquinoline-5-sulfonamide (99).** Following general procedure A, **175c** (96 mg, 0.18 mmol) was reacted with TFA to afford the title compound as a white solid (54 mg, 0.12 mmol, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.37 (s, 1H), 8.69 (d, *J* = 6.1 Hz, 1H), 8.51 – 8.47 (m, 1H), 8.47 – 8.45 (m, 1H), 8.39 (dt, *J* = 2.7, 0.9 Hz, 1H), 8.21 (d, *J* = 8.2 Hz, 1H), 7.96 (ddd, *J* = 8.5, 7.6, 2.6 Hz, 1H), 7.71 (dd, *J* = 8.2, 7.4 Hz, 1H), 7.41 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.02 (ddd, *J* = 8.5, 3.0, 0.7 Hz, 1H), 4.22 (dd, *J* = 8.6, 6.5 Hz, 1H), 3.46 (ddt, *J* = 8.8, 6.5, 4.4 Hz, 1H), 3.04 (dd, *J* = 12.1, 4.3 Hz, 1H), 2.84 (dd, *J* = 12.0, 6.5 Hz, 1H), 2.14 – 2.05 (m, 1H), 1.97 – 1.84 (m, 1H), 1.63 – 1.46 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.13 (d, *J* = 239 Hz), 153.52, 145.76 (d, *J* = 15 Hz), 145.32, 144.46, 139.74 (d, *J* = 7.9 Hz), 135.45, 134.63 (d, *J* = 4.8 Hz), 134.33, 133.65, 133.47, 131.35, 129.14, 127.15, 127.03, 126.07, 117.29, 109.58 (d, *J* = 37 Hz), 62.13, 56.07, 48.03, 34.45, 28.74. HRMS $[C_{25}H_{23}FN_4O_2S + H]^+$: 463.15985 calculated, 463.15918 found. $[\alpha]_D^{25}$ – 51.2° (c = 1.00, $CHCl_3$).



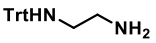
***N*-(((2*S*,5*R*)-5-([1,1'-Biphenyl]-4-yl)pyrrolidin-2-yl)methyl)isoquinoline-5-sulfonamide (100).** Following general procedure A, **175e** (7.4 mg, 14 µmol) was reacted with TFA to afford the title compound as a white solid (6.4 mg, 9.9 µmol, 73%). ^{1}H NMR (850 MHz, $CDCl_3$) δ 9.37 (s, 1H), 8.72 (d, *J* = 6.0 Hz, 1H), 8.47 (d, *J* = 6.1 Hz, 2H), 8.21 (d, *J* = 8.2 Hz, 1H), 7.71 (t, *J* = 7.8 Hz, 1H), 7.58 (d, *J* = 6.9 Hz, 2H), 7.48 (d, *J* = 8.1 Hz, 2H), 7.47 – 7.44 (m, 2H), 7.37 – 7.34 (m, 1H), 7.29 (d, *J* = 8.1 Hz, 2H), 4.22 (dd, *J* = 8.7, 6.5 Hz, 1H), 3.48 – 3.45 (m, 1H), 3.03 (dd, *J* = 12.1, 4.2 Hz, 1H), 2.84 (dd, *J* = 12.1, 6.4 Hz, 1H), 2.11 – 2.07 (m, 1H), 1.93 – 1.88 (m, 1H), 1.61 – 1.55 (m, 2H). ^{13}C NMR (214 MHz, $CDCl_3$) δ 153.57, 145.47, 143.05, 140.96, 140.22, 134.31, 133.70, 133.50, 131.39, 129.18, 128.93, 127.37, 127.22, 127.19, 126.83, 126.05, 117.30, 62.36, 55.95, 47.90, 34.39, 28.78. HRMS $[C_{26}H_{25}N_3O_2S + H]^+$: 444.17402 calculated, 444.17390 found.



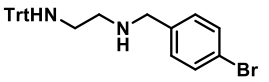
***N*-(((2*S*,5*R*)-5-(4'-Fluoro-[1,1'-biphenyl]-4-yl)pyrrolidin-2-yl)methyl)isoquinoline-5-sulfonamide (101).** Following general procedure A, **175f** (9.0 mg, 16 µmol) was reacted with TFA to afford the title compound as a white solid (1.5 mg, 3.2 µmol, 20%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.37 (d, *J* = 1.0 Hz, 1H), 8.71 (d, *J* = 6.1 Hz, 1H), 8.47 (m, 1H), 8.46 (m, 1H), 8.21 (d, *J* = 8.2 Hz, 1H), 7.71 (dd, *J* = 8.2, 7.3 Hz, 1H), 7.58 – 7.48 (m, 2H), 7.45 – 7.39 (m, 2H), 7.31 – 7.24 (m, 2H), 7.18 – 7.09 (m, 2H), 4.20 (dd, *J* = 8.8, 6.5 Hz, 1H), 3.51 – 3.39 (m, 1H), 3.03 (dd, *J* = 12.0, 4.2 Hz, 1H), 2.83 (dd, *J* = 11.9, 6.4 Hz, 1H), 2.13 – 2.03 (m, 1H), 1.97 – 1.82 (m, 1H), 1.63 – 1.51 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.55 (d, *J* = 246 Hz), 153.56, 145.42, 143.28, 139.17, 137.08 (d, *J* = 3.3 Hz), 134.33, 133.68, 133.51, 131.39, 129.18, 128.69 (d, *J* = 8.0 Hz), 127.05, 126.86, 126.06, 117.30, 115.77 (d, *J* = 21 Hz), 62.27, 55.93, 47.97, 34.44, 28.80. HRMS [$C_{26}H_{24}FN_3O_2S$ + H]$^+$: 462.16460 calculated, 462.16440 found.



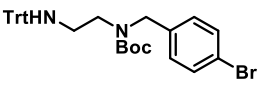
***N*-(((2*S*,5*R*)-5-(4-(Pyridin-3-yl)phenyl)pyrrolidin-2-yl)methyl)isoquinoline-5-sulfonamide (102).** Following general procedure A, **175g** (7.5 mg, 14 µmol) was reacted with TFA to afford the title compound as a white solid (4.2 mg, 9.3 µmol, 68%). ^{1}H NMR (850 MHz, $CDCl_3$) δ 9.38 (s, 1H), 8.84 (d, *J* = 2.4 Hz, 1H), 8.71 (d, *J* = 6.0 Hz, 1H), 8.60 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.49 – 8.47 (m, 1H), 8.47 (s, 1H), 8.22 (d, *J* = 8.2 Hz, 1H), 7.89 – 7.86 (m, 1H), 7.72 (t, *J* = 7.5 Hz, 1H), 7.47 (d, *J* = 8.2 Hz, 2H), 7.38 (ddd, *J* = 7.8, 4.8, 0.9 Hz, 1H), 7.35 – 7.32 (m, 2H), 4.23 (dd, *J* = 8.8, 6.5 Hz, 1H), 3.49 – 3.44 (m, 1H), 3.04 (dd, *J* = 12.1, 4.2 Hz, 1H), 2.83 (dd, *J* = 12.1, 6.4 Hz, 1H), 2.13 – 2.08 (m, 1H), 1.94 – 1.88 (m, 1H), 1.60 – 1.54 (m, 2H). ^{13}C NMR (214 MHz, $CDCl_3$) δ 153.58, 148.57, 148.38, 145.45, 144.32, 136.73, 136.44, 134.40, 134.32, 133.71, 133.54, 131.39, 129.19, 127.22, 127.13, 126.08, 123.74, 117.29, 62.24, 55.98, 47.99, 34.51, 28.78. HRMS [$C_{25}H_{24}N_4O_2S$ + H]$^+$: 445.16927 calculated, 445.16913 found.



***N*^{1}-Tritylethane-1,2-diamine (104).** Ethylenediamine (**103**) (267 mL, 4.00 mol) and K_2CO_3 (66.3 g, 440 mmol) were suspended in DCM (700 mL) after which a solution of trityl chloride (112 g, 400 mmol) in DCM (700 mL) was added dropwise over 40 min. The reaction-mixture was stirred overnight at RT, filtered, concentrated *in vacuo* and co-evaporated with toluene to yield the product (123 g, quant.) which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) 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 (100 MHz, $CDCl_3$) δ 146.24, 128.76, 127.89, 126.34, 70.77, 46.60, 42.89.

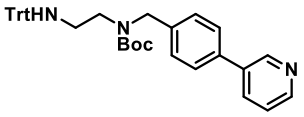


***N*^{1}-(4-Bromobenzyl)-*N*^{2}-tritylethane-1,2-diamine (105).** 4-Bromobenzaldehyde (0.95 g, 5.1 mmol) was dissolved in MeOH (10 mL), and **104** (1.7 g, 5.6 mmol, 1.1 equiv.) was dissolved in THF (5 mL) and added thereto. The mixture was stirred at RT for 1 h, after which sodium borohydride (0.29 g, 7.6 mmol, 1.5 equiv.) was slowly added, followed by stirring overnight. Water (40 mL) was added to the mixture and the mixture was extracted with DCM (3× 30 mL). The organic layers were combined, dried with Na_2SO_4, filtered and purified by column chromatography (2% → 5% MeOH (10% aq. NH_3) in DCM) to yield title compound **105** (1.04 g, 2.04 mmol, 40%).

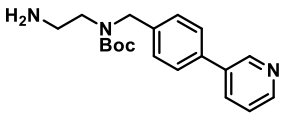


***tert*-Butyl (4-bromobenzyl)(2-(tritylamino)ethyl)carbamate (106).** Di-*tert*-butyl-dicarbonate (0.16 g, 0.73 mmol) was dissolved in DCM (1 mL) and slowly added to a mixture of **105** (0.52 g, 1.10 mmol) and triethylamine (0.30 mL, 2.16 mmol) in DCM (5 mL). The reaction mixture was stirred at RT overnight, after which it was concentrated *in vacuo*.

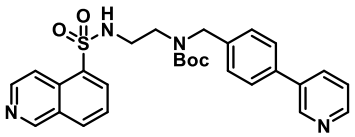
The residue was purified by column chromatography (5% → 10% EtOAc in pentane) to yield the title product **106** (0.33 g, 0.65 mmol, 59%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 6.94 (m, 19H), 4.34 (s, 2H), 3.42 – 3.19 (m, 2H), 2.36 – 2.14 (m, 2H), 1.64 (bs, 1H), 1.54 – 1.32 (m, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.21, 146.02, 137.50, 131.68, 128.63, 127.96, 127.35, 126.41, 121.28, 80.10, 70.86, 50.16, 47.43, 42.22, 28.51.



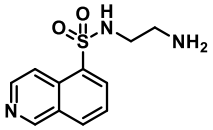
***tert*-Butyl (4-(pyridin-3-yl)benzyl)(2-(tritylamino)ethyl)carbamate (107).** The mixture of **106** (0.30 g, 0.52 mmol), 3-pyridinylboronic acid (86 mg, 0.70 mmol), $Pd(PPh_3)_4$ (30 mg, 26 µmol), potassium carbonate (0.31 g, 2.2 mmol) in water (2 mL) and 1,4-dioxane (6 mL) was deoxygenated under nitrogen flow and sealed. The mixture was heated to 90°C and stirred overnight. The reaction mixture was then filtrated, concentrated and was purified by column chromatography (30% EtOAc in pentane) to yield **107** (0.23 g, 0.40 mmol, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (s, 1H), 8.58 (dd, *J* = 4.8, 1.7 Hz, 1H), 7.90 – 7.73 (m, 1H), 7.59 – 7.09 (m, 21H), 4.47 (s, 2H), 3.47 – 3.20 (m, 2H), 2.39 – 2.17 (m, 2H), 1.59 – 1.34 (m, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.11, 148.56, 148.35, 146.05, 138.61, 136.79, 136.37, 134.35, 128.65, 127.94, 127.36, 126.39, 123.67, 80.04, 70.87, 50.35, 47.50, 42.25, 28.54.



***tert*-Butyl (2-aminoethyl)(4-(pyridin-3-yl)benzyl)carbamate (108).** To a solution of **107** (0.20 g, 0.35 mmol) and triethylsilane (0.40 mL, 2.5 mmol) in DCM (10 mL) on ice bath, was added TFA (0.15 mL). The reaction mixture was stirred at RT overnight, after which it was basified by adding sat. aq. Na_2CO_3 (10 mL), extracted with DCM (3× 25 mL). The combined organic layers were dried over Na_2SO_4, filtered and purified by column chromatography (5% MeOH (10% aq. NH_3) in DCM) to yield **108 (**0.10 g, 0.32 mmol, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (d, *J* = 2.4 Hz, 1H), 8.58 (dd, *J* = 4.8, 1.7 Hz, 1H), 7.87 (dt, *J* = 7.9, 2.0 Hz, 1H), 7.55 (d, *J* = 8.1 Hz, 2H), 7.42 – 7.31 (m, 3H), 4.53 (s, 2H), 3.30 (d, *J* = 27.2 Hz, 2H), 2.97 – 2.68 (m, 2H), 1.47 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.20, 148.51, 148.27, 138.59, 136.80, 136.26, 134.28, 128.46, 127.33, 123.61, 80.10, 50.89, 50.06, 40.57, 28.49.

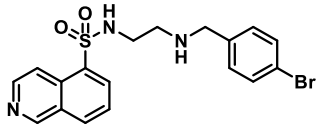


***tert*-Butyl (2-(isoquinoline-5-sulfonamido)ethyl)(4-(pyridin-3-yl)benzyl)carbamate (109). 109** (100 mg, 0.19 mmol, 83%) was synthesized from **108** (79 mg, 0.23 mmol) according to general procedure B. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.36 – 9.30 (m, 1H), 8.81 (s, 1H), 8.63 – 8.55 (m, 2H), 8.43 (d, *J* = 6.1 Hz, 1H), 8.38 (dd, *J* = 7.4, 1.2 Hz, 1H), 8.16 (d, *J* = 8.2 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.64 (t, *J* = 8.2 Hz, 1H), 7.46 (d, *J* = 8.6 Hz, 2H), 7.39 (dd, *J* = 8.0, 4.8 Hz, 1H), 7.22 (dd, *J* = 8.2, 3.2 Hz, 2H), 4.39 (s, 2H), 3.41 – 3.24 (m, 2H), 3.13 – 2.99 (m, 2H), 1.43 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.57, 153.18, 148.34, 147.93, 144.90, 137.92, 136.71, 136.11, 134.55, 134.35, 133.36, 133.00, 131.19, 129.03, 127.90, 127.24, 125.88, 123.70, 117.37, 51.37, 46.66, 42.19, 28.26.

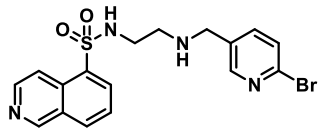


***N*-(2-Aminoethyl)isoquinoline-5-sulfonamide (111).** Isoquinoline-5-sulfonic acid (**110**) (10.0 g, 47.8 mmol) was dissolved in $SOCl_2$ (60 mL) and DMF (1.2 mL). The mixture was refluxed at 60°C until TLC analysis showed the complete conversion of the starting material. The $SOCl_2$ was evaporated *in vacuo*, and the reaction mixture was washed with DCM and then filtered. The crude sulfonyl chloride formed was immediately used in the following reaction. Ethylene diamine (15.1 mL, 227 mmol) was added dropwise to a cooled (0°C) and stirred solution of the crude sulfonyl chloride (10.0 g, 37.7 mmol) in DCM (600 mL). The mixture was then stirred at RT for 2 h. The reaction mixture was diluted with sat. aq. Na_2CO_3 (10 mL), washed with brine (50 mL) and extracted with DCM

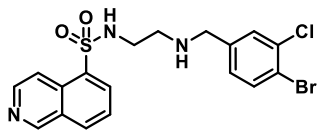
(3×). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The residue was then co-evaporated with toluene to remove the remaining ethylene diamine giving **111** (10.3 g, 35.0 mmol, 93%) as a dark yellow solid that was used without further purification.



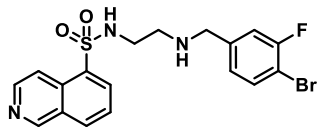
***N*-(2-((4-Bromobenzyl)amino)ethyl)isoquinoline-5-sulfonamide (112a). 111** (0.10 g, 3.96 mmol) and 4-bromobenzaldehyde (0.36 g, 1.93 mmol) were dissolved in THF (20 mL) in the presence of activated 3 Å molecular sieves. Then, sodium triacetoxyborohydride (0.84 g, 3.96 mmol) and glacial acetic acid (110 µL, 1.93 mmol) were added. The reaction mixture was stirred overnight, after which sat. aq. Na_2CO_3 (5 mL) was added to quench the reaction. The mixture was then diluted with brine (5 mL), extracted with Et_2O (10 mL) and DCM (3×). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product purified by column chromatography (1% → 10% MeOH (10% aq. NH_3) in DCM) to give **112A** (0.64 g, 1.52 mmol, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.35 (d, *J* = 1.0 Hz, 1H), 8.65 (d, *J* = 6.1 Hz, 1H), 8.45 – 8.40 (m, 2H), 8.20 (dt, *J* = 8.2, 1.2 Hz, 1H), 7.69 (dd, *J* = 8.2, 7.4 Hz, 1H), 7.38 – 7.31 (m, 2H), 7.00 – 6.95 (m, 2H), 3.49 (s, 2H), 3.02 – 2.96 (m, 2H), 2.65 – 2.59 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.46, 145.24, 138.59, 134.28, 133.70, 133.44, 131.59, 131.30, 129.67, 129.10, 126.05, 121.01, 117.26, 52.53, 47.42, 42.54.



***N*-(2-(((6-Bromopyridin-3-yl)methyl)amino)ethyl)isoquinoline-5-sulfonamide (112b). 111** (1.00 g, 3.98 mmol) and 6-bromonicotinaldehyde (0.36 g, 1.94 mmol) were dissolved in THF (20 mL) in the presence of activated 3 Å molecular sieves. Then, sodium triacetoxyborohydride (0.84 g, 3.98 mmol) and glacial acetic acid (122 µL, 1.94 mmol) were added. The reaction mixture was stirred overnight. Sat. aq. Na_2CO_3 (5 mL) was added to the reaction, which was then diluted with brine (10 mL) and extracted with Et_2O (10 mL) and DCM (3×). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (1% → 10% MeOH (10% aq. NH_3) in DCM) to afford title compound **112b** (0.73 g, 1.73 mmol, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.39 (bs, 1H), 8.73 – 7.70 (m, 1H), 8.51 – 8.41 (m, 2H), 8.26 – 8.21 (m, 1H), 8.19 – 8.16 (m, 1H), 7.78 – 7.68 (m, 1H), 7.49 – 7.36 (m, 2H), 3.59 (s, 2H), 3.13 – 3.00 (m, 2H), 2.72 – 2.65 (m, 2H).

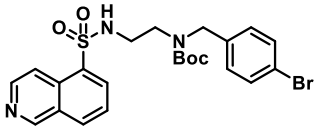


***N*-(2-((4-Bromo-3-chlorobenzyl)amino)ethyl)isoquinoline-5-sulfonamide (112c). 111** (1.00 g, 3.98 mmol) and 3-chloro-4-bromobenzaldehyde (0.43 g, 1.94 mmol) were dissolved in THF (20 mL) in the presence of activated 3 Å molecular sieves. Then, sodium triacetoxyborohydride (0.84 g, 3.98 mmol) and glacial acetic acid (122 µL, 1.94 mmol) were added. The reaction mixture was stirred overnight. Sat. aq. Na_2CO_3 (5 mL) was added to quench the reaction, which was then diluted with brine (10 mL) and extracted with Et_2O (10 mL) and DCM (3×). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (1% → 10% MeOH (10% aq. NH_3) in DCM) to afford title compound **112c** (0.8 g, 1.76 mmol, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.39 (bs, 1H), 8.77 – 8.67 (m, 1H), 8.51 – 8.41 (m, 2H), 8.26 – 8.22 (m, 1H), 7.78 – 7.67 (m, 1H), 7.55 – 7.50 (m, 1H), 7.29 – 7.27 (m, 1H), 6.93 – 6.89 (m, 1H), 3.53 (s, 2H), 3.13 – 2.99 (m, 2H), 2.70 – 2.62 (m, 2H).

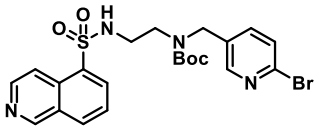


***N*-(2-((4-Bromo-3-fluorobenzyl)amino)ethyl)isoquinoline-5-sulfonamide (112d). 111** (1.00 g, 3.98 mmol) and 3-fluoro-4-bromobenzaldehyde (0.39 g, 1.9 mmol) were dissolved in THF (20 mL) in the presence of activated 3 Å molecular sieves. Then, sodium

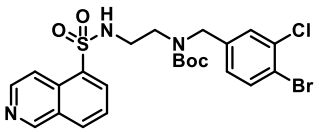
triacetoxyborohydride (0.84 g, 4.0 mmol) and glacial acetic acid (122 µL, 1.94 mmol) were added. The reaction mixture was stirred overnight. Sat. aq. Na_2CO_3 (5 mL) was added to the reaction, which was then diluted with brine (10 mL) and extracted with Et_2O (10 mL) and DCM (3×). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (1% → 10% MeOH (10% aq. NH_3) in DCM) to afford title compound **112d** (0.62 g, 1.4 mmol, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.39 (bs, 1H), 8.74 – 8.70 (m, 1H), 8.50 – 8.39 (m, 2H), 8.26 – 8.21 (m, 1H), 7.75 – 7.70 (m, 1H), 7.48 – 7.43 (m, 1H), 6.99 – 6.94 (m, 1H), 6.86 – 6.81 (m, 1H), 3.58 (s, 2H), 3.10 – 3.00 (m, 2H), 2.71 – 2.64 (m, 2H).



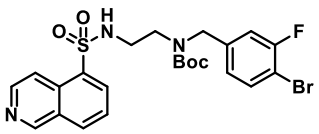
***tert*-Butyl (4-bromobenzyl)(2-(isoquinoline-5-sulfonamido)ethyl)carbamate (113a). 112a** (2.26 g, 5.38 mmol) and $NaHCO_3$ (500 mg, 5.92 mmol) were suspended in THF (15 mL) and cooled to 0°C. Boc_2O (1.26 g, 5.92 mmol) was then carefully added to this mixture, followed by 6 h of stirring. The reaction was diluted with sat. aq. Na_2CO_3 (5 mL), followed by dilution with brine (10 mL) and extraction with DCM (3×). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (20% → 40% EtOAc in pentane) to give title compound **113a** (2.42 g, 4.65 mmol, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.37 (s, 1H), 8.66 (d, *J* = 6.1 Hz, 1H), 8.45 – 8.32 (m, 2H), 8.21 (d, *J* = 8.2 Hz, 1H), 7.69 (t, *J* = 7.8 Hz, 1H), 7.39 – 7.30 (m, 2H), 6.96 (d, *J* = 8.2 Hz, 2H), 4.27 (s, 2H), 3.39 – 3.20 (m, 2H), 3.11 – 2.89 (m, 2H), 1.43 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.93, 153.37, 145.25, 136.89, 133.64, 133.29, 131.83, 131.32, 129.17, 128.94, 126.00, 121.41, 117.41, 81.25, 51.35, 46.77, 42.63, 28.43.



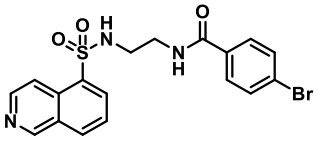
***tert*-Butyl ((6-bromopyridin-3-yl)methyl)(2-(isoquinoline-5-sulfonamido)ethyl)carbamate (113b). 112b** (0.73 g, 1.7 mmol) and $NaHCO_3$ (0.16 g, 1.9 mmol) were dissolved in THF (10 mL) and cooled to 0°C. Boc_2O (0.4 g, 1.9 mmol) was carefully added and the mixture was stirred overnight. The reaction was quenched with sat. aq. Na_2CO_3 (5 mL), washed with brine (10 mL) and extracted with DCM (3×). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. This yielded crude product **113b** (1.1 g, 1.73 mmol, 100%), which was directly used in the next step.



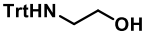
***tert*-Butyl ((6-bromopyridin-3-yl)methyl)(2-(isoquinoline-5-sulfonamido)ethyl)carbamate (113c). 112c** (0.8 g, 1.76 mmol) and $NaHCO_3$ (0.16 g, 1.94 mmol) were dissolved in THF (10 mL) and cooled to 0°C. Boc_2O (0.4 g, 1.9 mmol) was carefully added and the mixture was stirred overnight. The reaction was diluted with sat. aq. Na_2CO_3 (5 mL), washed with brine (10 mL) and extracted with DCM (3×). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. This yielded crude product **113c** (0.98 g, 1.76 mmol, 100%) which was directly used in the next step.



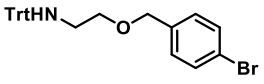
***tert*-Butyl ((6-bromopyridin-3-yl)methyl)(2-(isoquinoline-5-sulfonamido)ethyl)carbamate (113d). 112d** (0.60 g, 1.4 mmol) and $NaHCO_3$ (0.16 g, 1.9 mmol) were dissolved in THF (10 mL) and cooled to 0°C. Boc_2O (0.4 g, 1.9 mmol) was carefully added and the mixture was stirred overnight. The reaction was diluted with sat. aq. Na_2CO_3 (5 mL), washed with brine (10 mL) and extracted with DCM (3×). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. This yielded crude product **113d** (1.0 g, 1.4 mmol, 100%) which was directly used in the next step.



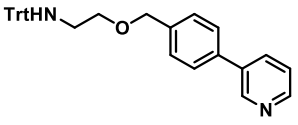
4-Bromo-*N*-(2-(isoquinoline-5-sulfonamido)ethyl)benzamide (114). To a mixture of **111** (0.25 g, 1.0 mmol), 4-bromobenzonic acid (0.26 g, 1.3 mmol) and HATU (0.38 g, 1.0 mmol) in DCM (30 mL) was added DIPEA (0.18 mL, 1.0 mmol), followed by stirring overnight. The reaction mixture was then washed with brine, and the organic layer was dried over Na_2SO_4, filtered and purified by column chromatography (3% MeOH (10% aq. NH_3) in DCM) to yield title compound **114** (0.20 g, 0.43 mmol, 43%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.25 (s, 1H), 8.56 (d, *J* = 6.2 Hz, 1H), 8.42 – 8.36 (m, 2H), 8.14 (d, *J* = 8.2 Hz, 1H), 7.66 (t, *J* = 7.8 Hz, 1H), 7.52 – 7.46 (m, 2H), 7.46 – 7.39 (m, 2H), 7.13 (t, *J* = 5.7 Hz, 1H), 3.76 – 3.63 (m, 2H), 3.54 – 3.48 (m, 2H), 3.23 – 3.18 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.62, 153.25, 145.03, 134.15, 133.84, 133.37, 132.40, 131.81, 131.18, 129.10, 128.68, 126.51, 126.15, 117.42, 43.60, 40.12.



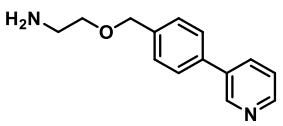
(Tritylamino)ethan-1-ol (116). To a solution of trityl chloride (1.4 g, 5.0 mmol) and K_2CO_3 (0.76 g, 5.5 mmol) in DCM (17 mL) at 0°C was added dropwise ethanolamine (**115**) (1.5 mL, 25 mmol). The reaction was allowed to warm to RT and stirred for 3 h before sat. aq. $NaHCO_3$ (15 mL) and H_2O (15 mL) were added. The organic layer was collected and the aqueous layer extracted with DCM (3× 30 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (20% EtOAc in pentane) to yield **116** (1.5 g, 4.95 mmol, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.52 (m, 6H), 7.42 – 7.31 (m, 6H), 7.27 (t, *J* = 7.3 Hz, 3H), 3.71 (t, *J* = 5.3 Hz, 2H), 2.69 (bs, 1H), 2.41 (t, *J* = 5.3 Hz, 2H), 2.06 (bs, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.88, 128.62, 127.85, 126.34, 70.55, 62.47, 45.60.



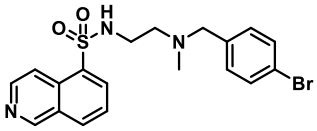
2-((4-Bromobenzyl)oxy)-*N*-tritylethan-1-amine (117). A solution of **116** (1.5 g, 4.95 mmol) in DMF (4 mL) was cooled on ice, and carefully NaH (60% in oil, 0.25 g, 6.25 mmol) was added. 4-Bromo-benzylbromide (0.92 g, 3.3 mmol) was added. The reaction mixture was stirred at RT overnight, after which the reaction was quenched with water (10 mL). The mixture was extracted with EtOAc (3× 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (20% EtOAc in pentane) to yield title compound **117** (0.78 g, 1.65 mmol, 50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.41 (m, 8H), 7.29 – 7.22 (m, 6H), 7.20 – 7.12 (m, 5H), 4.37 (s, 2H), 3.58 (t, *J* = 5.3 Hz, 2H), 2.37 (t, *J* = 5.3 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.17, 137.60, 131.56, 129.30, 128.78, 127.93, 126.38, 121.47, 72.10, 70.76, 70.60, 43.32.



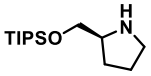
2-((4-(Pyridin-3-yl)benzyl)oxy)-*N*-tritylethan-1-amine (118). 118 (400 mg, 0.85 mmol, 51%) was synthesized from **117** (780 mg, 1.65 mmol) according to general procedure D. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (dd, *J* = 2.3, 0.9 Hz, 1H), 8.58 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.86 (ddd, *J* = 7.9, 2.4, 1.6 Hz, 1H), 7.60 – 7.53 (m, 2H), 7.52 – 7.46 (m, 6H), 7.44 – 7.38 (m, 2H), 7.35 (ddd, *J* = 7.9, 4.8, 0.9 Hz, 1H), 7.30 – 7.23 (m, 6H), 7.20 – 7.15 (m, 3H), 4.50 (s, 2H), 3.65 (t, *J* = 5.3 Hz, 2H), 2.41 (t, *J* = 5.3 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.51, 148.32, 146.17, 138.63, 137.13, 136.45, 134.38, 128.77, 128.34, 127.88, 127.21, 126.33, 123.64, 72.42, 70.75, 70.64, 43.33.



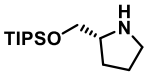
2-((4-(Pyridin-3-yl)benzyl)oxy)ethan-1-amine (119). 119 (100 mg, 0.44 mmol, 54%) was synthesized from **118** (380 mg, 0.81 mmol) according to general procedure A. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (dd, *J* = 2.4, 0.9 Hz, 1H), 8.59 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.87 (ddd, *J* = 7.9, 2.4, 1.6 Hz, 1H), 7.61 – 7.55 (m, 2H), 7.50 – 7.44 (m, 2H), 7.37 (ddd, *J* = 7.9, 4.8, 0.9 Hz, 1H), 4.60 (s, 2H), 3.57 (t, *J* = 5.3 Hz, 2H), 2.93 (t, *J* = 5.3 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.56, 148.35, 138.44, 137.28, 136.42, 134.40, 128.50, 127.29, 123.66, 72.79, 72.66, 41.99.



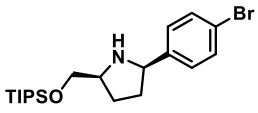
***N*-(2-((4-Bromobenzyl)(methyl)amino)ethyl)isoquinoline-5-sulfonamide (120). 112a** (0.58 g, 1.4 mmol), formaldehyde (46 mg, 1.5 mmol) and sodium triacetoxyborohydride (0.59 g, 2.8 mmol) were suspended in THF (15 mL) and MeOH (2.5 mL). The reaction mixture was stirred at RT overnight, after which it was diluted with sat. aq. $NaHCO_3$ (10 mL) and extracted with DCM (3×). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by column chromatography (1% → 10% MeOH (10% aq. NH_3) in DCM) to give title compound **120** (0.38 g, 0.88 mmol, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.37 (d, *J* = 1.0 Hz, 1H), 8.66 (d, *J* = 6.1 Hz, 1H), 8.50 – 8.38 (m, 2H), 8.21 (dt, *J* = 8.2, 1.1 Hz, 1H), 7.71 (dd, *J* = 8.2, 7.4 Hz, 1H), 3.00 – 2.94 (m, 2H), 2.79 – 2.72 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.40, 145.15, 134.57, 133.61, 133.30, 131.35, 129.14, 126.07, 117.37, 45.37, 40.97.



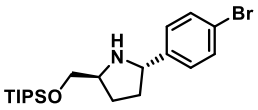
(*S*)-2-(((Triisopropylsilyl)oxy)methyl)pyrrolidine (122a). Following general procedure E, L-prolinol (**121a**) (5.00 g, 49.4 mmol) was reacted with TIPS-Cl (12.7 mL, 59.3 mmol), imidazole (6.73 g, 99.0 mmol) and DMAP, (0.302 g, 2.47 mmol) to afford the title compound as a colorless oil (2.89 g, 11.2 mmol, 23%) which was stored at -20°C to avoid degradation. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.71 – 3.61 (m, 2H), 3.23 – 3.13 (m, 1H), 3.03 – 2.98 (m, 1H), 2.87 – 2.87 (m, 1H), 2.05 (s, 1H), 1.82 – 1.70 (m, 2H), 1.54 – 1.46 (m, 1H), 1.13 – 1.04 (m, 21H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 65.92, 60.19, 46.50, 27.35, 25.41, 17.90, 11.87.



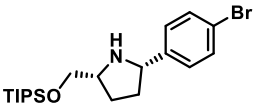
(*R*)-2-(((Triisopropylsilyl)oxy)methyl)pyrrolidine (122b). Following general procedure E, R-prolinol (**121b**) (3.00 g, 29.7 mmol) was reacted with TIPS-Cl (7.62 mL, 35.6 mmol), imidazole (4.04 g, 59.3 mmol) and DMAP (0.181 g, 1.48 mmol) to afford the title compound as a colorless oil (2.40 g, 9.30 mmol, 31%) which was stored at -20°C to avoid degradation. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.78 – 3.56 (m, 2H), 3.26 – 3.09 (m, 1H), 3.09 – 2.93 (m, 1H), 2.93 – 2.76 (m, 1H), 2.02 (s, 1H), 1.88 – 1.61 (m, 3H), 1.60 – 1.41 (m, 1H), 1.21 – 0.91 (m, 21H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 66.00, 60.27, 46.58, 27.43, 25.49, 17.99, 11.94.



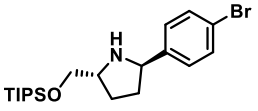
(2*R*,5*S*)-2-(4-Bromophenyl)-5-(((triisopropylsilyl)oxy)methyl)pyrrolidine (123a). Following general procedure F, **122a** (1.57 g, 6.09 mmol) was reacted with *n*-BuLi (1.6 M in hexanes, 3.8 mL, 6.1 mmol), benzophenone (1.33 g, 7.31 mmol) and bromobenzenelithium (9.13 mmol, prepared according to general procedure G) to afford the title compound as a crude mixture with benzhydrol (1.5 g crude, 35% purity, 1.6 mmol product, 26%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.05 (m, 4H + benzhydrol-Ar), 3.89 – 3.83 (m, 2H), 3.70 – 3.61 (m, 2H), 3.12 (tt, *J* = 7.6, 4.2 Hz, 1H), 2.07 – 1.97 (m, 1H), 1.79 – 1.68 (m, 2H), 1.60 – 1.50 (m, 1H), 1.07 – 1.00 (m, 21H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.78, 131.38, 128.29 – 61 (+ benzhydrol-Ar), 75.78, 65.26, 62.11, 60.26, 34.26, 27.79, 18.02, 11.90.



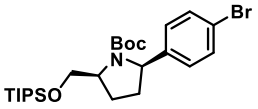
(2*S*,5*S*)-2-(4-Bromophenyl)-5-(((triisopropylsilyl)oxy)methyl)pyrrolidine (123b). Following general procedure F, **122a** (1.57 g, 6.09 mmol) was reacted with *n*-BuLi (1.6 M in hexanes, 3.8 mL, 6.1 mmol), benzophenone (1.33 g, 7.31 mmol) and bromobenzenelithium (9.13 mmol, prepared according to general procedure G) to afford the title compound as a crude mixture with benzophenone (0.35 g crude, 60% purity, 0.49 mmol product, 8%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.13 (m, 4H + benzophenone-Ar), 4.23 – 4.15 (m, 1H), 3.63 (dd, *J* = 5.7, 1.7 Hz, 2H), 3.53 – 3.45 (m, 1H), 2.21 – 2.12 (m, 1H), 2.03 – 1.92 (m, 1H), 1.66 – 1.53 (m, 2H), 1.09 – 1.04 (m, 21H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.45, 131.38-127.46 (+ benzophenone-Ar), 120.37, 66.05, 60.42, 59.86, 35.09, 27.70, 18.13, 12.04.



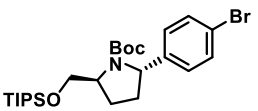
(2*S*,5*R*)-2-(4-Bromophenyl)-5-(((triisopropylsilyl)oxy)methyl)pyrrolidine (123c). Following general procedure F, **122b** (2.39 g, 9.28 mmol) was reacted with *n*-BuLi (1.6 M in hexanes, 5.8 mL, 9.3 mmol), benzophenone (2.03 g, 11.1 mmol) and bromobenzenelithium (13.9 mmol, prepared according to general procedure G) to afford the title compound as a crude mixture with benzhydrol (2.15 g crude, 50% purity, 2.61 mmol product, 28%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41– 7.13 (m, 4H + benzhydrol-Ar), 4.08 – 3.87 (m, 1H), 3.79 – 3.57 (m, 2H), 3.32 – 3.11 (m, 2H), 2.16 – 1.98 (m, 1H), 1.90 – 1.67 (m, 2H), 1.67 – 1.47 (m, 1H), 1.18 – 0.93 (m, 21H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.13, 130.44, 127.50-125.63 (+ benzhydrol-Ar), 126.49, 119.59, 65.14, 61.23, 59.48, 33.43, 26.85, 17.14, 11.05.



(2*R*,5*R*)-2-(4-Bromophenyl)-5-(((triisopropylsilyl)oxy)methyl)pyrrolidine (123d). Following general procedure F, **122b** (2.39 g, 9.28 mmol) was reacted with *n*-BuLi (1.6 M in hexanes, 5.8 mL, 9.3 mmol), benzophenone (2.03 g, 11.1 mmol) and bromobenzenelithium (13.9 mmol, prepared according to general procedure G) to afford the title compound as a crude mixture with benzophenone (0.430 g crude, 60% purity, 0.625 mmol product, 7%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 – 7.21 (m, 4H + benzophenone-Ar), 4.26 – 4.15 (m, 1H), 3.68 – 3.58 (m, 2H), 3.56 – 3.46 (m, 1H), 2.21 – 2.13 (m, 1H), 2.03 – 1.93 (m, 1H), 1.74 – 1.53 (m, 2H), 1.08 – 1.04 (m, 21H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.60, 130.61-125.14 (+ benzophenone-Ar), 119.36, 65.12, 59.43, 58.92, 34.16, 26.73, 17.15, 11.07.

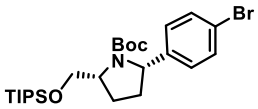


***tert*-Butyl (2*R*,5*S*)-2-(4-bromophenyl)-5-(((triisopropylsilyl)oxy)methyl)pyrrolidine-1-carboxylate (124a).** Following general procedure H, **123a** (0.85 g crude, 35% purity, 0.91 mmol product) was reacted with Boc_2O (494 mg, 2.26 mmol) and triethylamine (0.252 mL, 1.81 mmol) for 1.5 h to afford the title compound as a colorless oil (0.315 g, 0.615 mmol, 68%). ^{1}H NMR (500 MHz, 333 K, $CDCl_3$) δ 7.38 (d, *J* = 8.4 Hz, 2H), 7.16 (d, *J* = 8.4 Hz, 2H), 4.69 (bs, 1H), 4.07 – 3.99 (m, 1H), 3.98 – 3.76 (m, 2H), 2.25 – 2.15 (m, 1H), 2.13 – 2.04 (m, 1H), 1.99 – 1.91 (m, 1H), 1.91 – 1.83 (m, 1H), 1.32 – 1.23 (m, 9H), 1.10 – 1.05 (m, 21H). ^{13}C NMR (126 MHz, 333 K, $CDCl_3$) δ 155.22, 144.18, 131.36, 127.76, 120.25, 79.79, 64.84, 62.84, 60.89, 34.60, 28.48, 27.21, 18.22, 12.35.

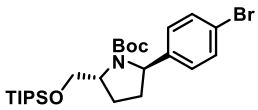


***tert*-Butyl (2*S*,5*S*)-2-(4-bromophenyl)-5-(((triisopropylsilyl)oxy)methyl)pyrrolidine-1-carboxylate (124b).** Following general procedure H, **123b** (0.16 g crude, 60% purity, 0.23 mmol product) was reacted with Boc_2O (36 mg, 0.16 mmol) and triethylamine (18 µL, 0.13 mmol) for 4.5 h to afford the title compound as a colorless oil (45 mg, 65 µmol, 28%). Rotamer equilibrium (3:2). Major rotamer ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.5 Hz, 2H), 7.00 (d, *J* = 8.4 Hz, 2H), 4.79 (d, *J* = 8.5 Hz, 1H),

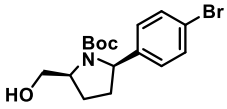
4.18 (ddt, *J* = 7.7, 5.2, 2.6 Hz, 1H), 3.98 (dd, *J* = 9.8, 5.2 Hz, 1H), 3.80 (dd, *J* = 9.8, 2.8 Hz, 1H), 2.66 – 2.50 (m, 1H), 2.10 – 1.90 (m, 2H), 1.60 (dd, *J* = 12.5, 6.1 Hz, 1H), 1.15 (s, 9H), 1.11 – 1.03 (m, 21H). Major rotamer ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.98, 145.26, 131.28, 127.12, 120.02, 79.33, 63.61, 61.95, 59.77, 33.46, 28.24, 25.18, 18.14, 12.10. Minor rotamer ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.5 Hz, 2H), 7.00 (d, *J* = 8.4 Hz, 2H), 4.91 (d, *J* = 8.5 Hz, 1H), 4.12 – 4.01 (m, 1H), 3.91 (dd, *J* = 9.3, 3.4 Hz, 1H), 3.61 (dd, *J* = 9.4, 7.8 Hz, 1H), 2.50 – 2.31 (m, 1H), 2.00 (m, 2H), 1.60 (dd, *J* = 12.5, 6.1 Hz, 1H), 1.44 (s, 9H), 1.13 – 1.03 (m, 21H). Minor rotamer ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.98, 143.67, 131.55, 126.98, 120.02, 79.93, 63.61, 61.32, 59.74, 31.97, 28.64, 25.18, 18.14, 12.10.



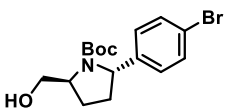
***tert*-Butyl (2*S*,5*R*)-2-(4-bromophenyl)-5-(((triisopropylsilyl)oxy)methyl)pyrrolidine-1-carboxylate (124c).** Following general procedure H, **123c** (2.15 g crude, 50% purity, 2.61 mmol product) was reacted with Boc_2O (1.42 g, 6.52 mmol) and triethylamine (0.727 mL, 5.22 mmol) for 1.5 h to afford the title compound as a colorless oil (0.904 g, 1.76 mmol, 67%). ^{1}H NMR (500 MHz, 333 K, $CDCl_3$) δ 7.38 (d, *J* = 8.4 Hz, 2H), 7.16 (d, *J* = 8.4 Hz, 2H), 4.69 (bs, 1H), 4.06 – 3.99 (m, 1H), 3.97 (dd, *J* = 9.4, 3.7 Hz, 1H), 3.86 (s, 1H), 2.28 – 2.14 (m, 1H), 2.14 – 2.03 (m, 1H), 2.03 – 1.91 (m, 1H), 1.91 – 1.82 (m, 1H), 1.27 (s, 9H), 1.13 – 1.03 (m, 21H). ^{13}C NMR (126 MHz, 333 K, $CDCl_3$) δ 155.24, 144.32, 131.37, 127.77, 120.26, 79.80, 64.85, 62.85, 60.91, 34.55, 28.49, 27.20, 18.23, 12.36.



***tert*-Butyl (2*R*,5*R*)-2-(4-bromophenyl)-5-(((triisopropylsilyl)oxy)methyl)pyrrolidine-1-carboxylate (124d).** Following general procedure H, **123d** (0.430 g crude, 60% purity, 0.625 mmol product) was reacted with Boc_2O (0.341 g, 1.56 mmol) and triethylamine (0.174 mL, 1.25 mmol) for 4.5 h to afford the title compound as a colorless oil (0.133 g, 0.259 mmol, 44%). Rotamer equilibrium (3:2). Major rotamer ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.5 Hz, 2H), 7.00 (d, *J* = 8.4 Hz, 2H), 4.79 (d, *J* = 8.5 Hz, 1H), 4.18 (ddt, *J* = 7.7, 5.2, 2.6 Hz, 1H), 3.98 (dd, *J* = 9.8, 5.2 Hz, 1H), 3.81 (dd, *J* = 9.8, 2.8 Hz, 1H), 2.66 – 2.48 (m, 1H), 2.13 – 1.87 (m, 2H), 1.60 (dd, *J* = 11.0, 6.2 Hz, 1H), 1.15 (s, 9H), 1.11 – 1.01 (m, 21H). Major rotamer ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.94, 145.22, 131.25, 127.09, 120.00, 79.28, 63.59, 61.92, 59.74, 33.44, 28.21, 25.16, 18.12, 12.08. Minor rotamer ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.5 Hz, 2H), 7.00 (d, *J* = 8.4 Hz, 2H), 4.91 (d, *J* = 8.4 Hz, 1H), 4.12 – 4.02 (m, 1H), 3.91 (dd, *J* = 9.3, 3.4 Hz, 1H), 3.61 (dd, *J* = 9.4, 7.8 Hz, 1H), 2.48 – 2.35 (m, 1H), 2.13 – 1.89 (m, 2H), 1.60 (dd, *J* = 11.4, 5.8 Hz, 1H), 1.44 (s, 9H), 1.12 – 1.04 (m, 21H). Minor rotamer ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.80, 143.64, 131.52, 126.95, 120.27, 79.88, 63.59, 61.29, 59.71, 31.94, 28.61, 25.16, 18.12, 12.08.

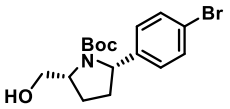


***tert*-Butyl (2*R*,5*S*)-2-(4-bromophenyl)-5-(hydroxymethyl)pyrrolidine-1-carboxylate (125a).** Following general procedure I, **124a** (0.494 g, 0.963 mmol) was reacted with TBAF (1 M in THF, 4.82 mL, 4.82 mmol) for 2.5 h to afford the title compound as a colorless oil (0.313 g, 0.877 mmol, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.4 Hz, 2H), 7.13 (d, *J* = 8.5 Hz, 2H), 4.79 (t, *J* = 7.0 Hz, 1H), 4.16 (p, *J* = 6.3 Hz, 1H), 3.78 (d, *J* = 6.9 Hz, 2H), 2.34 – 2.15 (m, 1H), 2.11 – 1.91 (m, 1H), 1.90 – 1.73 (m, 1H), 1.63 (bs, 1H), 1.21 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.41, 131.49, 127.42, 120.43, 80.97, 67.55, 62.96, 61.68, 34.36, 28.17, 27.19.

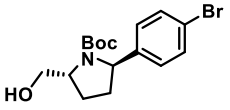


***tert*-Butyl (2*S*,5*S*)-2-(4-bromophenyl)-5-(hydroxymethyl)pyrrolidine-1-carboxylate (125b).** Following general procedure I, **124b** (48 mg, 94 µmol) was reacted with TBAF (1 M in THF, 0.468 mL, 0.468 mmol) for 1.25 h to afford the title compound as a colorless oil (19 mg, 53 µmol, 57%). ^{1}H NMR (300 MHz, $CDCl_3$) δ

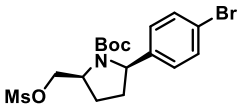
7.43 (d, *J* = 8.4 Hz, 2H), 6.99 (d, *J* = 8.1 Hz, 2H), 4.83 (dd, *J* = 8.1, 2.4 Hz, 1H), 4.31 (tt, *J* = 7.3, 3.4 Hz, 1H), 3.85 – 3.64 (m, 2H), 2.45 – 2.26 (m, 1H), 2.17 – 1.98 (m, 1H), 1.75 – 1.57 (m, 2H), 1.16 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.33, 144.10, 131.45, 127.04, 120.35, 80.68, 67.35, 62.46, 61.27, 33.51, 28.16, 26.18.



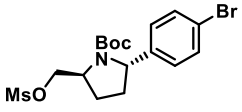
***tert*-Butyl (2*S*,5*R*)-2-(4-bromophenyl)-5-(hydroxymethyl)pyrrolidine-1-carboxylate (125c).** Following general procedure I, **124c** (0.910 g, 1.78 mmol) was reacted with TBAF (1 M in THF, 8.87 mL, 8.87 mmol) for 2.5 h to afford the title compound as a colorless oil (0.527 g, 1.478 mmol, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.4 Hz, 2H), 7.13 (d, *J* = 8.2 Hz, 2H), 4.80 (t, *J* = 7.0 Hz, 2H), 4.22 – 4.12 (m, 1H), 3.78 (t, *J* = 5.4 Hz, 2H), 2.33 – 2.19 (m, 1H), 2.08 – 1.96 (m, 2H), 1.88 – 1.75 (m, 1H), 1.62 (bs, 1H), 1.21 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 131.53, 127.45, 120.48, 81.05, 67.73, 63.01, 61.75, 34.38, 28.21, 27.20.



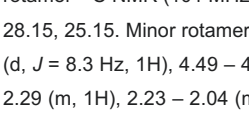
***tert*-Butyl (2*R*,5*R*)-2-(4-bromophenyl)-5-(hydroxymethyl)pyrrolidine-1-carboxylate (125d).** Following general procedure I, **124d** (0.133 g, 0.259 mmol) was reacted with TBAF (1 M in THF, 1.30 mL, 1.30 mmol) for 1.25 h to afford the title compound as a colorless oil (98 mg, quant.). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.4 Hz, 2H), 6.99 (d, *J* = 8.4 Hz, 2H), 4.83 (dd, *J* = 8.2, 2.4 Hz, 1H), 4.30 (tt, *J* = 7.2, 3.2 Hz, 1H), 3.87 – 3.55 (m, 2H), 2.51 – 2.23 (m, 2H), 2.19 – 1.98 (m, 1H), 1.77 – 1.57 (m, 2H), 1.16 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.26, 144.09, 131.43, 127.02, 120.32, 80.63, 67.16, 62.42, 61.22, 33.46, 28.14, 26.11.



***tert*-Butyl (2*R*,5*S*)-2-(4-bromophenyl)-5-(((methylsulfonyl)oxy)methyl)pyrrolidine-1-carboxylate (126a).** Following general procedure J, **125a** (0.313 g, 0.877 mmol) was reacted with MsCl (0.102 mL, 1.32 mmol) and triethylamine (0.367 mL, 2.63 mmol) to afford the crude title compound (0.393 g, quant.). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.4 Hz, 2H), 7.11 (d, *J* = 8.4 Hz, 2H), 4.68 (bs, 1H), 4.49 (dd, *J* = 9.5, 3.5 Hz, 1H), 4.39 (bs, 1H), 4.23 (bs, 1H), 3.04 (s, 3H), 2.39 – 2.18 (m, 1H), 2.17 – 1.95 (m, 2H), 1.94 – 1.78 (m, 1H), 1.40 – 1.06 (m, 9H).

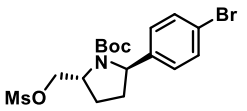


***tert*-Butyl (2*S*,5*S*)-2-(4-bromophenyl)-5-(((methylsulfonyl)oxy)methyl)pyrrolidine-1-carboxylate (126b).** Following general procedure J, **125b** (19 mg, 53 µmol) was reacted with MsCl (6.2 µL, 80 µmol) and triethylamine (22 µL, 0.16 mmol) to afford the crude title compound (24 mg, quant.). Rotamer equilibrium (3:1). Major rotamer ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.4 Hz, 2H), 6.97 (d, *J* = 8.4 Hz, 2H), 4.85 (d, *J* = 8.3 Hz, 1H), 4.49 – 4.40 (m, 1H), 4.40 – 4.32 (m, 2H), 3.05 (s, 3H), 2.55 – 2.34 (m, 1H), 2.21 – 2.05 (m, 1H), 1.96 (dd, *J* = 13.3, 7.2 Hz, 1H), 1.72 (dd, *J* = 12.6, 7.1 Hz, 1H), 1.17 (s, 9H). Major rotamer ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.89, 131.48, 126.92, 120.46, 80.40, 69.28, 61.62, 56.86, 37.19, 32.98, 28.15, 25.15. Minor rotamer ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.4 Hz, 2H), 6.97 (d, *J* = 8.4 Hz, 2H), 4.97 (d, *J* = 8.3 Hz, 1H), 4.49 – 4.41 (m, 1H), 4.30 – 4.24 (m, 1H), 4.19 (dd, *J* = 9.6, 7.3 Hz, 1H), 3.05 (s, 3H), 2.59 – 2.29 (m, 1H), 2.23 – 2.04 (m, 1H), 1.96 (dd, *J* = 13.3, 7.2 Hz, 1H), 1.72 (dd, *J* = 12.6, 7.1 Hz, 1H), 1.47 (s, 9H). Minor rotamer ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.89, 131.71, 126.80, 120.46, 80.40, 68.74, 61.13, 56.78, 37.70, 31.92, 28.53, 25.72.

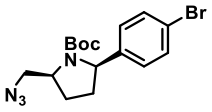


***tert*-Butyl (2*S*,5*R*)-2-(4-bromophenyl)-5-(((methylsulfonyl)oxy)methyl)pyrrolidine-1-carboxylate (126c).** Following general procedure J, **125c** (0.526 g, 1.48 mmol) was reacted with MsCl (0.171 mL, 2.22 mmol) and triethylamine (0.618 mL, 4.43 mmol) to afford the crude title compound (0.691 g, quant.). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.5 Hz, 2H), 7.12 (d, *J* = 8.5 Hz, 2H), 4.68

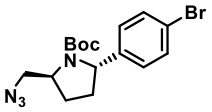
(bs, 1H), 4.49 (dd, *J* = 9.5, 3.5 Hz, 1H), 4.39 (bs, 1H), 4.28 – 4.15 (m, 1H), 3.04 (s, 3H), 2.38 – 2.20 (m, 1H), 2.19 – 1.95 (m, 2H), 1.95 – 1.80 (m, 1H), 1.19 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.85, 146.74, 131.45, 127.37, 120.45, 80.58, 69.62, 62.46, 57.62, 45.95, 37.39, 28.17, 27.17.



***tert*-Butyl (2*R*,5*R*)-2-(4-bromophenyl)-5-(((methylsulfonyl)oxy)methyl)pyrrolidine-1-carboxylate (126d).** Following general procedure J, **125d** (98 mg, 0.28 mmol) was reacted with MsCl (32 µL, 0.41 mmol) and triethylamine (0.115 mL, 0.824 mmol) to afford the crude title compound (0.121 g, quant.). Rotamer equilibrium (3:1). Major rotamer ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.4 Hz, 2H), 6.98 (d, *J* = 8.3 Hz, 2H), 4.85 (d, *J* = 8.3 Hz, 1H), 4.54 – 4.31 (m, 3H), 3.05 (s, 3H), 2.56 – 2.31 (m, 1H), 2.25 – 2.04 (m, 1H), 1.96 (dd, *J* = 13.3, 7.3 Hz, 1H), 1.72 (dd, *J* = 12.5, 7.0 Hz, 1H), 1.17 (s, 9H). Major rotamer ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.94, 143.84, 131.38, 126.86, 120.36, 80.27, 69.18, 61.53, 56.78, 37.10, 32.89, 28.06, 25.06. Minor rotamer ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.4 Hz, 2H), 6.98 (d, *J* = 8.3 Hz, 2H), 4.96 (d, *J* = 8.3 Hz, 1H), 4.64 – 4.30 (m, 1H), 4.27 (dd, *J* = 7.6, 2.6 Hz, 1H), 4.20 (dd, *J* = 9.4, 7.3 Hz, 1H), 3.06 (s, 3H), 2.61 – 2.31 (m, 1H), 2.25 – 2.04 (m, 1H), 1.96 (dd, *J* = 13.3, 7.3 Hz, 1H), 1.72 (dd, *J* = 12.5, 7.0 Hz, 1H), 1.47 (s, 9H). Minor rotamer ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.94, 143.84, 131.61, 126.75, 120.36, 80.90, 68.73, 61.04, 56.70, 37.60, 31.85, 28.43, 25.64.

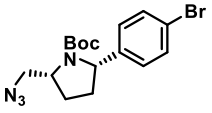


***tert*-Butyl (2*S*,5*R*)-2-(azidomethyl)-5-(4-bromophenyl)pyrrolidine-1-carboxylate (127a).** Following general procedure K, **126a** (0.391 g, 0.905 mmol) was reacted with NaN_3 (0.353 g, 5.43 mmol) for 65 h to afford the title compound as a colorless oil (0.239 g, 0.627 mmol, 69%). ^{1}H NMR (500 MHz, 333 K, $CDCl_3$) δ 7.42 (d, *J* = 8.4 Hz, 2H), 7.12 (d, *J* = 8.4 Hz, 2H), 4.73 (t, *J* = 7.2 Hz, 1H), 4.08 (h, *J* = 3.7 Hz, 1H), 3.70 (dd, *J* = 12.0, 3.9 Hz, 1H), 3.49 (dd, *J* = 12.0, 7.5 Hz, 1H), 2.31 – 2.20 (m, 1H), 2.10 – 1.97 (m, 1H), 1.93 – 1.80 (m, 2H), 1.29 (s, 9H). ^{13}C NMR (126 MHz, 333 K, $CDCl_3$) δ 154.10, 142.40, 130.60, 126.58, 119.60, 79.54, 61.74, 57.63, 53.52, 33.15, 27.42, 27.23.



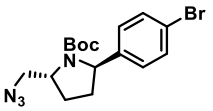
***tert*-Butyl (2*S*,5*S*)-2-(azidomethyl)-5-(4-bromophenyl)pyrrolidine-1-carboxylate (127b).** Following general procedure K, **126b** (24 mg, 55 µmol) was reacted with NaN_3 (21 mg, 55 µmol) for 17 h to afford the title compound as a colorless oil (11 mg, 29 µmol, 53%). Rotamer equilibrium (7:3). Major rotamer ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.4 Hz, 2H), 6.98 (d, *J* = 8.4 Hz, 2H), 4.86 (d, *J* = 7.7 Hz, 1H), 4.30 – 4.19 (m, 1H), 3.66 (dd, *J* = 12.1, 6.5 Hz, 1H), 3.50 (dd, *J* = 12.1, 2.9 Hz, 1H), 2.57 – 2.35 (m, 1H), 2.15 – 2.00 (m, 1H), 1.89 – 1.77 (m, 1H), 1.76 – 1.63 (m, 1H), 1.17 (s, 9H). Major rotamer ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.02, 143.21, 130.46, 125.99, 119.39, 79.20, 60.78, 56.50, 51.49, 32.06, 27.20, 24.93. Minor rotamer ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.4 Hz, 2H), 6.98 (d, *J* = 8.4 Hz, 2H), 4.96 (d, *J* = 8.4 Hz, 1H), 4.14 (td, *J* = 8.1, 2.9 Hz, 1H), 3.57 (dd, *J* = 11.9, 2.7 Hz, 1H), 3.33 (dd, *J* = 11.9, 8.0 Hz, 1H), 2.64 – 2.29 (m, 1H), 2.15 – 1.96 (m, 1H), 1.93 – 1.79 (m, 1H), 1.78 – 1.64 (m, 1H), 1.47 (s, 9H).

Minor rotamer ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.02, 141.83, 130.69, 125.87, 119.59, 79.71, 60.18, 56.45, 52.49, 30.94, 27.59, 25.55.

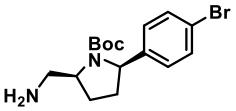


***tert*-Butyl (2*R*,5*S*)-2-(azidomethyl)-5-(4-bromophenyl)pyrrolidine-1-carboxylate (127c).** Following general procedure K, **126c** (0.691 g, 1.60 mmol) was reacted with NaN_3 (0.621 g, 9.55 mmol) for 65 h to afford the title compound as a colorless oil (0.370 g, 0.970 mmol, 61%). ^{1}H NMR (126 MHz, 333 K, $CDCl_3$) δ 7.42 (d, *J* = 8.5 Hz, 2H), 7.12 (d, *J* = 8.4 Hz, 2H), 4.72 (t, *J* = 7.1 Hz, 1H), 4.08 (h, *J* = 3.7 Hz, 1H), 3.70 (dd, *J* = 11.9, 3.8 Hz, 1H), 3.49

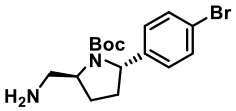
(dd, *J* = 11.7, 7.4 Hz, 1H), 2.31 – 2.18 (m, 1H), 2.11 – 1.96 (m, 1H), 1.93 – 1.78 (m, 2H), 1.29 (s, 9H). ^{13}C NMR (126 MHz, 333 K, $CDCl_3$) δ 154.09, 142.41, 130.60, 126.58, 119.59, 79.53, 61.74, 57.62, 53.52, 33.16, 27.42, 27.22.



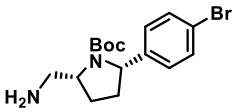
***tert*-Butyl (2*R*,5*R*)-2-(azidomethyl)-5-(4-bromophenyl)pyrrolidine-1-carboxylate (127d).** Following general procedure K, **126d** (0.121 g, 0.278 mmol) was reacted with NaN_3 (0.109 g, 1.67 mmol) for 17 h to afford the title compound as a colorless oil (56 mg, 0.147 mmol, 53%). Rotamer equilibrium (7:3). Major rotamer ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.5 Hz, 2H), 6.98 (d, *J* = 8.4 Hz, 2H), 4.86 (d, *J* = 8.2 Hz, 1H), 4.33 – 4.21 (m, 1H), 3.66 (dd, *J* = 12.1, 6.5 Hz, 1H), 3.50 (dd, *J* = 12.1, 2.9 Hz, 1H), 2.56 – 2.32 (m, 1H), 2.17 – 2.00 (m, 1H), 1.89 – 1.76 (m, 1H), 1.76 – 1.62 (m, 1H), 1.17 (s, 9H). Major rotamer ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.97, 143.19, 130.42, 125.96, 119.35, 79.14, 60.75, 56.47, 51.45, 32.02, 27.16, 24.90. Minor rotamer ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.5 Hz, 2H), 6.98 (d, *J* = 8.4 Hz, 2H), 4.96 (d, *J* = 8.3 Hz, 1H), 4.20 – 4.04 (m, 1H), 3.57 (dd, *J* = 12.0, 2.9 Hz, 1H), 3.33 (dd, *J* = 11.9, 7.9 Hz, 1H), 2.60 – 2.31 (m, 1H), 2.20 – 2.00 (m, 1H), 1.90 – 1.76 (m, 1H), 1.76 – 1.60 (m, 1H), 1.47 (s, 9H). Minor rotamer ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.97, 141.80, 130.64, 125.84, 119.55, 79.65, 60.14, 56.42, 52.46, 30.91, 27.55, 25.52.



***tert*-Butyl (2*S*,5*R*)-2-(aminomethyl)-5-(4-bromophenyl)pyrrolidine-1-carboxylate (128a).** Following general procedure L, **127a** (0.221 g, 0.597 mmol) was reacted with PPh_3 (0.304 g, 1.16 mmol) and water (21 µL, 1.16 mmol) to afford the tile compound as a colorless oil that crystalized upon storage (0.130 g, 0.366 mmol, 63%). ^{1}H NMR (500 MHz, 333K, $CDCl_3$) δ 7.41 (d, *J* = 8.4 Hz, 2H), 7.11 (d, *J* = 8.4 Hz, 2H), 4.73 (t, *J* = 7.3 Hz, 1H), 3.98 – 3.93 (m, 1H), 3.09 (dd, *J* = 12.6, 5.6 Hz, 1H), 2.77 (dd, *J* = 12.6, 7.3 Hz, 1H), 2.30 – 2.19 (m, 1H), 2.08 – 1.96 (m, 1H), 1.88 – 1.73 (m, 2H), 1.49 (s, 2H), 1.28 (s, 9H). ^{13}C NMR (126 MHz, 333K, $CDCl_3$) δ 154.64, 142.98, 130.56, 126.58, 119.41, 79.03, 61.73, 61.07, 45.74, 33.35, 27.44, 27.29.

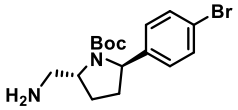


***tert*-Butyl (2*S*,5*S*)-2-(aminomethyl)-5-(4-bromophenyl)pyrrolidine-1-carboxylate (128b).** Following general procedure L, **127b** (11 mg, 29 µmol) was reacted with PPh_3 (17 mg, 65 µmol) and water (2 µL, 0.1 mmol) to afford the tile compound as a colorless oil that crystalized upon storage (8.7 mg, 24 µmol, 83%). Rotamer equilibrium (8:2). Major rotamer ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.4 Hz, 2H), 6.98 (d, *J* = 8.5 Hz, 2H), 4.82 (d, *J* = 6.3 Hz, 1H), 4.34 – 4.13 (m, 1H), 3.95 (bs, 2H), 3.14 (dd, *J* = 12.9, 5.9 Hz, 1H), 2.94 (dd, *J* = 12.9, 5.6 Hz, 1H), 2.42 – 2.27 (m, 1H), 2.20 – 2.03 (m, 1H), 1.87 – 1.74 (m, 1H), 1.74 – 1.62 (m, 1H), 1.15 (s, 9H). Major rotamer ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.33, 142.97, 130.46, 126.04, 119.41, 79.59, 76.48, 61.06, 58.44, 44.14, 31.99, 27.16, 25.47. Minor rotamer ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.4 Hz, 2H), 6.98 (d, *J* = 8.5 Hz, 2H), 4.94 (d, *J* = 8.4 Hz, 1H), 3.95 (bs, 3H), 3.05 (dd, *J* = 12.5, 3.3 Hz, 1H), 2.69 (dd, *J* = 12.6, 8.3 Hz, 1H), 2.42 – 2.27 (m, 1H), 2.20 – 2.03 (m, 1H), 1.87 – 1.74 (m, 1H), 1.74 – 1.62 (m, 1H), 1.45 (s, 9H). Minor rotamer ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.33, 142.16, 130.61, 125.95, 119.41, 79.16, 76.48, 60.07, 59.71, 43.79, 31.01, 27.61, 24.87.

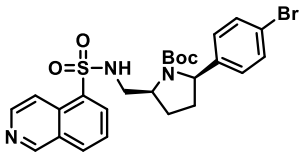


***tert*-Butyl (2*R*,5*S*)-2-(aminomethyl)-5-(4-bromophenyl)pyrrolidine-1-carboxylate (128c).** Following general procedure L, **127c** (0.359 g, 0.942 mmol) was reacted with PPh_3 (0.494 g, 1.83 mmol) and water (34 µL, 1.9 mmol) to afford the title compound as a colorless oil that crystalized upon storage (0.236 g, 0.066 mmol, 70%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.4 Hz, 2H), 7.11 (d, *J* = 8.4 Hz, 2H), 4.73 (t, *J* = 7.3 Hz, 1H), 4.00 – 3.88 (m, 1H), 3.09 (dd, *J* = 12.6, 5.7 Hz, 1H), 2.78 (dd, *J* = 12.6, 7.3 Hz, 1H), 2.30 – 2.20 (m, 1H),

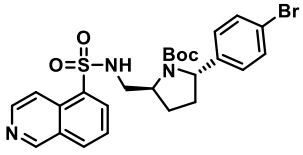
2.06 – 1.96 (m, 1H), 1.87 – 1.75 (m, 2H), 1.28 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.65, 142.97, 130.55, 126.57, 119.41, 79.04, 61.74, 61.04, 45.73, 33.34, 27.44, 27.29.



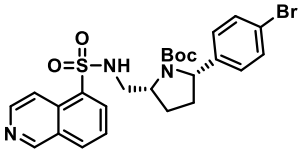
***tert*-Butyl (2*R*,5*R*)-2-(aminomethyl)-5-(4-bromophenyl)pyrrolidine-1-carboxylate (128d).** Following general procedure L, **127d** (56 mg, 0.147 mmol) was reacted with PPh_3 (77 mg, 0.30 mmol) and water (5.3 µL, 0.23 mmol) to afford the title compound as a colorless oil that crystalized upon storage (34 mg, 95 µmol, 65%). Rotamer equilibrium (8:2). Major rotamer ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.4 Hz, 2H), 6.98 (d, *J* = 8.5 Hz, 2H), 4.82 (d, *J* = 6.3 Hz, 1H), 4.25 (bs, 3H), 3.14 (dd, *J* = 12.8, 5.5 Hz, 1H), 2.91 (dd, *J* = 12.8, 6.1 Hz, 1H), 2.45 – 2.23 (m, 1H), 2.19 – 2.03 (m, 1H), 1.92 – 1.75 (m, 1H), 1.75 – 1.59 (m, 1H), 1.15 (s, 9H). Major rotamer ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.11, 144.02, 131.41, 127.01, 120.35, 80.41, 61.95, 59.46, 44.82, 32.91, 28.14, 26.21. Minor rotamer ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.4 Hz, 2H), 6.98 (d, *J* = 8.5 Hz, 2H), 4.94 (d, *J* = 8.4 Hz, 1H), 4.25 (bs, 3H), 3.98 (td, *J* = 8.2, 3.3 Hz, 1H), 3.06 (dd, *J* = 12.7, 3.4 Hz, 1H), 2.70 (dd, *J* = 12.6, 8.5 Hz, 1H), 2.45 – 2.23 (m, 1H), 2.19 – 2.03 (m, 1H), 1.92 – 1.75 (m, 1H), 1.75 – 1.59 (m, 1H), 1.45 (s, 9H). Minor rotamer ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.86, 143.13, 131.58, 126.92, 120.40, 80.14, 61.03, 60.58, 44.65, 31.98, 28.58, 25.82.



***tert*-Butyl (2*R*,5*S*)-2-(4-bromophenyl)-5-((isoquinoline-5-sulfonamido)methyl)pyrrolidine-1-carboxylate (129a).** Following general procedure B, **128a** (0.113 g, 0.318 mmol) was reacted with isoquinoline-5-sulfonylchloride·HCl (87 mg, 0.38 mmol) and triethylamine (0.100 mL, 0.716 mmol) to afford the title compound as an off-white solid (0.166 g, 0.304 mmol, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.40 (s, 1H), 8.66 (d, *J* = 6.2 Hz, 1H), 8.49 (d, *J* = 6.2 Hz, 1H), 8.45 (dd, *J* = 7.4, 1.2 Hz, 1H), 8.25 (d, *J* = 8.2 Hz, 1H), 7.72 (t, *J* = 7.3 Hz, 1H), 7.56 (bs, 1H), 7.20 (d, *J* = 8.0 Hz, 2H), 6.75 (d, *J* = 7.9 Hz, 2H), 4.62 (t, *J* = 7.5 Hz, 1H), 4.10 (t, *J* = 8.8 Hz, 1H), 3.29 – 2.95 (m, 2H), 2.23 – 2.12 (m, 1H), 2.07 – 1.90 (m, 1H), 1.73 – 1.56 (m, 2H), 1.15 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.78, 153.18, 145.19, 142.60, 134.41, 133.33, 133.14, 131.30, 131.22, 129.05, 126.92, 125.92, 120.29, 117.47, 81.15, 62.97, 58.07, 48.92, 34.35, 29.66, 27.95.

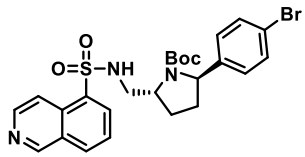


***tert*-Butyl (2*S*,5*S*)-2-(4-bromophenyl)-5-((isoquinoline-5-sulfonamido)methyl)pyrrolidine-1-carboxylate (129b).** Following general procedure B, **128b** (8.7 mg, 24 µmol) was reacted with isoquinoline-5-sulfonylchloride·HCl (8 mg, 0.04 mmol) and triethylamine (10 µL, 73 µmol) to afford the title compound as an off-white solid (11 mg, 20 µmol, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.37 (s, 1H), 8.70 (d, *J* = 6.2 Hz, 1H), 8.45 (d, *J* = 6.1 Hz, 1H), 8.43 (dd, *J* = 7.4, 1.2 Hz, 1H), 8.21 (d, *J* = 8.2 Hz, 1H), 7.79 – 7.64 (m, 1H), 7.40 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 4.72 (d, *J* = 6.5 Hz, 1H), 4.25 – 4.17 (m, 1H), 3.16 (dd, *J* = 12.4, 3.9 Hz, 1H), 3.06 (dd, *J* = 12.4, 7.5 Hz, 1H), 2.37 – 2.17 (m, 1H), 2.12 – 2.00 (m, 1H), 1.67 – 1.58 (m, 2H), 1.11 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.82, 152.35, 144.41, 142.58, 133.80, 132.49, 132.07, 130.49, 130.44, 128.22, 125.85, 124.96, 119.49, 116.54, 79.97, 61.23, 57.05, 47.66, 32.03, 27.08, 26.01.

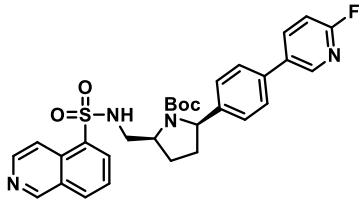


***tert*-Butyl (2*S*,5*R*)-2-(4-bromophenyl)-5-((isoquinoline-5-sulfonamido)methyl)pyrrolidine-1-carboxylate (129c).** Following general procedure B, **128c** (0.144 g, 0.630 mmol) was reacted with isoquinoline-5-sulfonylchloride·HCl (0.172 g, 0.757 mmol) and triethylamine (0.207 mL, 1.48 mmol) to afford the title compound as an off-white solid

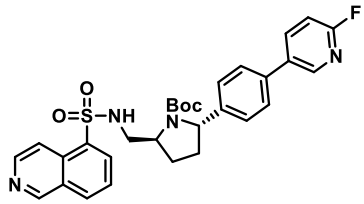
(0.324 g, 0.593 mmol, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.40 (s, 1H), 8.65 (d, *J* = 6.1 Hz, 1H), 8.49 (d, *J* = 6.2 Hz, 1H), 8.45 (d, *J* = 7.4 Hz, 1H), 8.25 (d, *J* = 8.2 Hz, 1H), 7.72 (t, *J* = 7.8 Hz, 1H), 7.61 (bs, 1H), 7.20 (d, *J* = 8.0 Hz, 2H), 6.75 (d, *J* = 8.0 Hz, 2H), 4.62 (t, *J* = 7.2 Hz, 1H), 4.19 – 3.98 (m, 1H), 3.38 – 2.91 (m, 2H), 2.29 – 2.10 (m, 1H), 2.10 – 1.89 (m, 1H), 1.76 – 1.53 (m, 2H), 1.14 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.69, 153.10, 145.03, 142.56, 134.30, 133.26, 133.05, 131.17, 131.09, 128.94, 126.85, 125.88, 120.15, 117.37, 80.96, 62.87, 57.99, 48.85, 34.25, 28.40, 27.85.



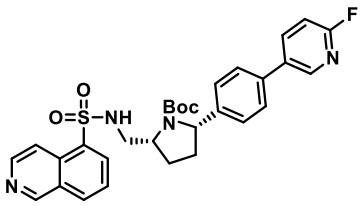
***tert*-Butyl (2*R*,5*R*)-2-(4-bromophenyl)-5-((isoquinoline-5-sulfonamido)methyl)pyrrolidine-1-carboxylate (129d).** Following general procedure B, **128d** (38 mg, 0.11 mmol) was reacted with isoquinoline-5-sulfonylchloride·HCl (37 mg, 0.16 mmol) and triethylamine (34 µL, 0.24 mmol) to afford the title compound as an off-white solid (57 mg, 0.10 mmol, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.36 (s, 1H), 8.67 (d, *J* = 6.1 Hz, 1H), 8.45 (d, *J* = 5.8 Hz, 1H), 8.43 (dd, *J* = 7.4, 1.2 Hz, 1H), 8.20 (d, *J* = 8.2 Hz, 1H), 7.70 (t, *J* = 7.6 Hz, 1H), 7.40 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 8.4 Hz, 2H), 4.72 (d, *J* = 6.4 Hz, 1H), 4.27 – 4.16 (m, 1H), 3.16 (dd, *J* = 12.4, 4.4 Hz, 1H), 3.08 (dd, *J* = 12.4, 7.1 Hz, 1H), 2.36 – 2.19 (m, 1H), 2.09 – 2.00 (m, 1H), 1.78 – 1.52 (m, 2H), 1.10 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.65, 152.30, 144.27, 142.60, 133.79, 132.46, 132.03, 130.44, 130.38, 128.17, 125.83, 124.96, 119.43, 116.53, 79.84, 61.13, 57.00, 47.24, 31.92, 27.04, 25.75.



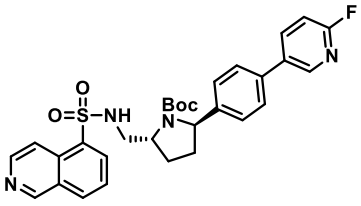
***tert*-Butyl (2*R*,5*S*)-2-(4-(6-fluoropyridin-3-yl)phenyl)-5-((isoquinoline-5-sulfonamido)methyl)pyrrolidine-1-carboxylate (175a).** Following general procedure D, **129a** (84 mg, 0.15 mmol) was reacted with (6-fluoropyridin-3-yl)boronic acid (26 mg, 0.18 mmol), K_2CO_3 (85 mg, 0.62 mmol) and $Pd(PPh_3)_4$ (2.7 mg, 2.3 µmol) to afford the title compound as an off-white solid (78 mg, 0.14 mmol, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.41 (s, 1H), 8.68 (d, *J* = 6.1 Hz, 1H), 8.52 (s, 1H), 8.48 (dd, *J* = 7.3, 1.3 Hz, 1H), 8.38 (d, *J* = 2.8 Hz, 1H), 8.25 (d, *J* = 8.2 Hz, 1H), 7.94 (dd, *J* = 7.9, 2.7 Hz, 1H), 7.72 (t, *J* = 7.4 Hz, 1H), 7.24 (d, *J* = 7.9 Hz, 2H), 7.03 (dd, *J* = 8.4, 2.9 Hz, 1H), 6.98 (d, *J* = 9.4 Hz, 2H), 4.73 (t, *J* = 6.2 Hz, 1H), 4.20 – 4.11 (m, 1H), 3.28 – 3.05 (m, 2H), 2.30 – 2.18 (m, 1H), 2.09 – 1.96 (m, 3H), 1.79 – 1.71 (m, 1H), 1.70 – 1.61 (m, 1H), 1.17 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.19 (d, *J* = 239 Hz), 152.26, 144.72 (d, *J* = 15 Hz), 144.45, 142.76, 138.64 (d, *J* = 7.9 Hz), 134.28, 133.66, 133.42 (d, *J* = 4.5 Hz), 132.36, 130.45, 128.25, 125.96, 125.13, 125.02, 116.68, 108.61 (d, *J* = 37.5 Hz), 80.33, 62.25, 57.16, 48.29, 33.54, 27.85, 27.12.



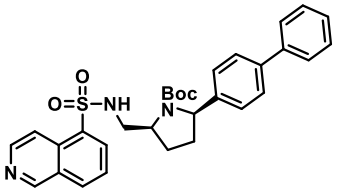
***tert*-Butyl (2*S*,5*S*)-2-(4-(6-fluoropyridin-3-yl)phenyl)-5-((isoquinoline-5-sulfonamido)methyl)pyrrolidine-1-carboxylate (175b).** Following general procedure D, **129b** (11 mg, 20 µmol) was reacted with (6-fluoropyridin-3-yl)boronic acid (3.5 mg, 25 µmol), K_2CO_3 (11 mg, 82 µmol) and $Pd(PPh_3)_4$ (0.4 mg, 0.3 µmol) to afford the title compound as an off-white solid (5.9 mg, 10 µmol, 51%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.37 (s, 1H), 8.71 (d, *J* = 6.0 Hz, 1H), 8.47 (d, *J* = 6.2 Hz, 1H), 8.44 (dd, *J* = 7.3, 1.2 Hz, 1H), 8.40 (d, *J* = 2.6 Hz, 1H), 8.22 (d, *J* = 8.2 Hz, 1H), 7.95 (td, *J* = 8.1, 2.8 Hz, 1H), 7.75 – 7.67 (m, 1H), 7.46 (d, *J* = 8.1 Hz, 2H), 7.11 (d, *J* = 8.3 Hz, 2H), 7.00 (dd, *J* = 8.5, 2.9 Hz, 1H), 4.82 (d, *J* = 7.8 Hz, 1H), 4.31 – 4.22 (m, 1H), 3.26 – 3.05 (m, 2H), 2.39 – 2.25 (m, 1H), 2.18 – 2.06 (m, 1H), 1.79 – 1.66 (m, 2H), 1.11 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.37 (d, *J* = 412 Hz), 155.8, 152.36, 144.82 (d, *J* = 15 Hz), 144.43, 143.67, 138.69 (d, *J* = 8.3 Hz), 134.33, 133.84, 133.43 (d, *J* = 4.6 Hz), 132.51, 132.10, 130.48, 128.25, 126.00, 125.00, 124.98, 116.58, 108.62 (d, *J* = 37 Hz), 79.88, 61.47, 57.12, 47.79, 32.15, 27.09, 26.16.



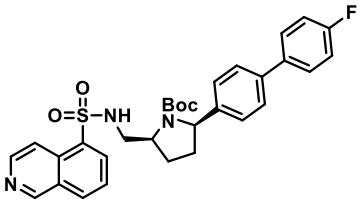
***tert*-Butyl (2*S*,5*R*)-2-(4-(6-fluoropyridin-3-yl)phenyl)-5-((isoquinoline-5-sulfonamido)methyl)pyrrolidine-1-carboxylate (175c).** Following general procedure D, **129c** (0.10 g, 0.18 mmol) was reacted with (6-fluoropyridin-3-yl)boronic acid (31 mg, 0.22 mmol), K_2CO_3 (0.101 g, 0.732 mmol) and $Pd(PPh_3)_4$ (3.2 mg, 2.7 µmol) to afford the title compound as an off-white solid (97 mg, 0.17 mmol, 94%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.41 (s, 1H), 8.67 (d, *J* = 6.2 Hz, 1H), 8.50 (s, 2H), 8.48 (s, 1H), 8.38 (s, 1H), 8.25 (d, *J* = 8.2 Hz, 1H), 7.95 (t, *J* = 6.4 Hz, 1H), 7.73 (t, *J* = 7.7 Hz, 1H), 7.25 (d, *J* = 7.8 Hz, 2H), 7.04 (s, 1H), 7.01 (s, 2H), 4.74 (s, 1H), 4.16 (s, 1H), 3.48 – 2.81 (m, 2H), 2.34 – 2.14 (m, 1H), 2.10 – 1.92 (m, 1H), 1.82 – 1.57 (m, 2H), 1.18 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.09 (d, *J* = 239 Hz), 153.21, 145.61 (d, *J* = 15 Hz), 145.31, 143.72, 139.60 (d, *J* = 7.8 Hz), 135.16, 134.58, 134.37 (d, *J* = 5.1 Hz), 133.30, 131.36, 129.17, 126.87, 126.07, 126.00, 117.60, 109.54 (d, *J* = 38 Hz), 81.19, 63.17, 58.12, 49.15, 34.46, 28.73, 28.04.



***tert*-Butyl (2*R*,5*R*)-2-(4-(6-fluoropyridin-3-yl)phenyl)-5-((isoquinoline-5-sulfonamido)methyl)pyrrolidine-1-carboxylate (175d).** Following general procedure D, **129d** (57 mg, 0.10 mmol) was reacted with (6-fluoropyridin-3-yl)boronic acid (18 mg, 0.13 mmol), K_2CO_3 (58 mg, 0.42 mmol) and $Pd(PPh_3)_4$ (1.8 mg, 1.6 µmol) to afford the title compound as an off-white solid (36 mg, 64 µmol, 61%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.37 (s, 1H), 8.70 (d, *J* = 6.1 Hz, 1H), 8.47 (d, *J* = 5.9 Hz, 1H), 8.44 (dd, *J* = 7.4, 1.3 Hz, 1H), 8.40 (d, *J* = 2.6 Hz, 1H), 8.21 (d, *J* = 8.3 Hz, 1H), 7.95 (td, *J* = 7.9, 2.6 Hz, 1H), 7.71 (t, *J* = 8.0 Hz, 1H), 7.46 (d, *J* = 8.2 Hz, 2H), 7.11 (d, *J* = 8.2 Hz, 2H), 7.00 (dd, *J* = 8.6, 3.1 Hz, 1H), 4.82 (d, *J* = 7.1 Hz, 1H), 4.35 – 4.14 (m, 1H), 3.33 – 3.05 (m, 2H), 2.43 – 2.21 (m, 1H), 2.21 – 2.01 (m, 1H), 1.76 – 1.62 (m, 2H), 1.11 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.22 (d, *J* = 240 Hz), 155.87, 153.34, 145.80 (d, *J* = 15 Hz), 145.37, 144.70, 139.67 (d, *J* = 8.0 Hz), 135.31, 133.46, 133.05, 131.46, 129.23, 126.98, 125.99, 117.58, 109.59 (d, *J* = 37 Hz), 80.81, 62.43, 58.13, 48.56, 33.10, 28.08, 27.04.

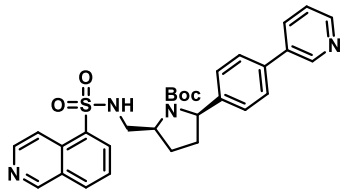


***tert*-Butyl (2*R*,5*S*)-2-([1,1'-biphenyl]-4-yl)-5-((isoquinoline-5-sulfonamido)methyl)pyrrolidine-1-carboxylate (175e).** Following general procedure D, **129a** (15 mg, 27 µmol) was reacted with phenylboronic acid (4.0 mg, 33 µmol), K_2CO_3 (15 mg, 0.11 mmol) and $Pd(PPh_3)_4$ (0.5 mg, 0.4 µmol) to afford the title compound as an off-white solid (12 mg, 22 µmol, 80%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.40 (d, *J* = 1.0 Hz, 1H), 8.69 (d, *J* = 6.1 Hz, 1H), 8.52 (d, *J* = 6.2 Hz, 1H), 8.47 (dd, *J* = 7.3, 1.2 Hz, 1H), 8.23 (dt, *J* = 8.3, 1.1 Hz, 1H), 7.71 (dd, *J* = 8.2, 7.3 Hz, 1H), 7.55 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.46 (t, *J* = 7.7 Hz, 2H), 7.40 – 7.32 (m, 1H), 7.27 (d, *J* = 8.0 Hz, 2H), 6.88 (d, *J* = 7.7 Hz, 2H), 4.70 (s, 1H), 4.19 – 4.09 (m, 1H), 3.24 (s, 1H), 3.13 – 3.04 (m, 1H), 2.27 – 2.17 (m, 1H), 2.08 – 1.98 (m, 2H), 1.81 – 1.69 (m, 1H), 1.66 – 1.59 (m, 2H), 1.15 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.31, 144.57, 141.60, 139.78, 138.85, 133.70, 132.37, 130.53, 128.30, 127.98, 126.44, 126.07, 125.00, 124.76, 116.76, 80.34, 62.44, 57.17, 48.60, 33.58, 28.03, 27.13.



***tert*-Butyl (2*R*,5*S*)-2-(4'-fluoro-[1,1'-biphenyl]-4-yl)-5-((isoquinoline-5-sulfonamido)methyl)pyrrolidine-1-carboxylate (175f).** Following general procedure D, **129a** (15 mg, 27 µmol) was reacted with pyridin-3-ylboronic acid (4.6 mg, 33 µmol), K_2CO_3 (15 mg, 0.11 mmol) and $Pd(PPh_3)_4$ (0.5 mg, 0.4 µmol) to afford the title compound as an off-white solid (12 mg, 21 µmol, 75%). ^{1}H NMR (500

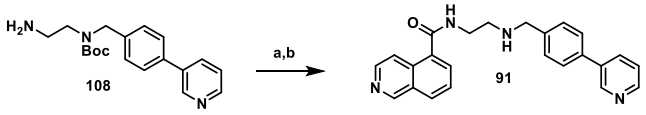
MHz, $CDCl_3$) δ 9.40 (d, *J* = 1.0 Hz, 1H), 8.69 (d, *J* = 6.1 Hz, 1H), 8.51 (d, *J* = 6.0 Hz, 1H), 8.48 (dd, *J* = 7.3, 1.3 Hz, 1H), 8.23 (d, *J* = 8.2 Hz, 1H), 7.71 (t, *J* = 7.3 Hz, 1H), 7.52 – 7.44 (m, 2H), 7.22 (d, *J* = 7.9 Hz, 2H), 7.14 (t, *J* = 8.7 Hz, 2H), 6.90 (d, *J* = 7.6 Hz, 2H), 4.71 (s, 1H), 4.18 – 4.10 (m, 1H), 3.22 (s, 1H), 3.13 – 3.05 (m, 1H), 2.27 – 2.17 (m, 1H), 2.07 – 1.98 (m, 1H), 1.79 – 1.70 (m, 1H), 1.62 (s, 1H), 1.16 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.61 (d, *J* = 247 Hz), 156.30, 152.30, 144.55, 141.65, 137.91, 135.91, 133.70, 132.39, 130.54, 128.30, 127.62 (d, *J* = 7.9 Hz), 125.94, 125.01, 124.84, 116.76, 114.83 (d, *J* = 21 Hz), 80.36, 62.39, 57.17, 48.52, 33.58, 27.99, 27.14.



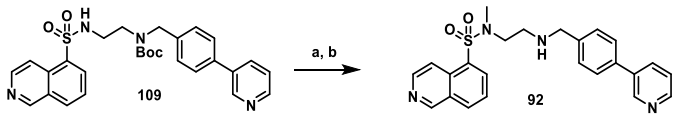
***tert*-Butyl (2*S*,5*R*)-2-((isoquinoline-5-sulfonamido)methyl)-5-(4-(pyridin-3-yl)phenyl)pyrrolidine-1-carboxylate (175g).** Following general procedure D, **129a** (15 mg, 27 µmol) was reacted with pyridin-3-ylboronic acid (4.0 mg, 33 µmol), K_2CO_3 (15 mg, 0.11 mmol) and $Pd(PPh_3)_4$ (0.5 mg, 0.4 µmol) to afford the title compound as an off-white solid (11 mg, 21 µmol, 76%).

^1H NMR (400 MHz, $CDCl_3$) δ 9.41 (d, *J* = 0.8 Hz, 1H), 8.80 (d, *J* = 1.5 Hz, 1H), 8.69 (d, *J* = 6.1 Hz, 1H), 8.60 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.51 (d, *J* = 6.1 Hz, 1H), 8.48 (dd, *J* = 7.3, 1.2 Hz, 1H), 8.25 (d, *J* = 8.2 Hz, 1H), 7.84 (dt, *J* = 7.9, 1.8 Hz, 1H), 7.72 (t, *J* = 7.6 Hz, 1H), 7.39 (dd, *J* = 7.0, 4.8 Hz, 1H), 7.29 (s, 2H), 6.96 (d, *J* = 7.8 Hz, 2H), 4.73 (s, 1H), 4.23 – 4.10 (m, 1H), 3.31 – 3.18 (m, 1H), 3.10 (t, *J* = 10.9 Hz, 1H), 2.30 – 2.19 (m, 1H), 2.10 – 2.00 (m, 2H), 1.79 – 1.69 (m, 1H), 1.66 – 1.58 (m, 1H), 1.16 (s, 9H).

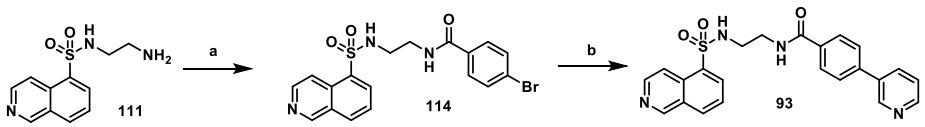
Supplementary information



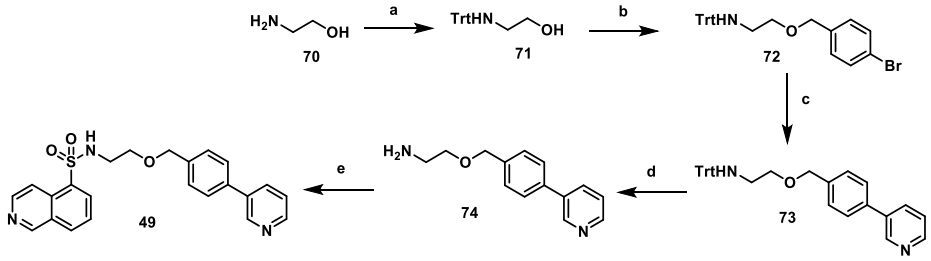
Scheme S5.1 | Synthesis of compound **91**. Reagents and conditions: a) 5-isoquinoline-COOH, HATU, DIPEA, DCM, RT; b) TFA, DCM, 0°C to RT, 81% (over two steps).



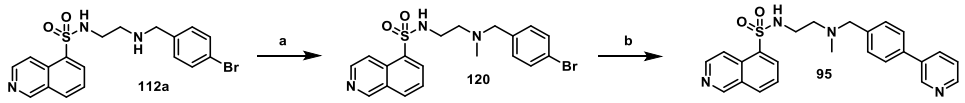
Scheme S5.2 | Synthesis of compound **92**. Reagents and conditions: a) CH_3I, NaOH, DMF, 80°C; b) TFA, DCM, 0°C to RT, 15% (over two steps).



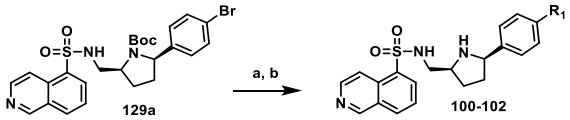
Scheme S5.3 | Synthesis of compound **93**. Reagents and conditions: a) 4-bromobenzoic acid, HATU, DIPEA, DCM, RT, 43%; b) $PyrB(OH)_2$; $Pd(PPh_3)_4$, K_2CO_3, H_2O, dioxane, 90°C, 79%.



Scheme S5.4 | Synthesis of compound **94**. Reagents and conditions: a) Trt-Cl, K_2CO_3, DCM, 0°C to RT, 99%; b) 4-bromobenzylbromide, NaH, DMF, 0°C to RT, 50%; $PyrB(OH)_2$, $Pd(PPh_3)_4$, K_2CO_3, H_2O, dioxane, 90°C, 51%; d) TFA, DCM, 0°C to RT, 54%; e) 5-isoquinoline-SO_2Cl, Et_3N, DCM, 0°C to RT, 76%.



Scheme S5.5 | Synthesis of compound **95**. Reagents and conditions: a) $NaBH(OAc)_3$, CH_2O, THF, MeOH, RT, 64%; b) $PyrB(OH)_2$, $Pd(PPh_3)_4$, K_2CO_3, H_2O, dioxane, 90°C, 45%.



Scheme S5.6 | Synthesis of compound **100-102**. Reagents and conditions: a) $R_1B(OH)_2$, $Pd(PPh_3)_4$, K_2CO_3, dioxane, H_2O, 90°C, 51 – 94%; l) TFA, DCM, 0°C to RT, 20 – 73%.

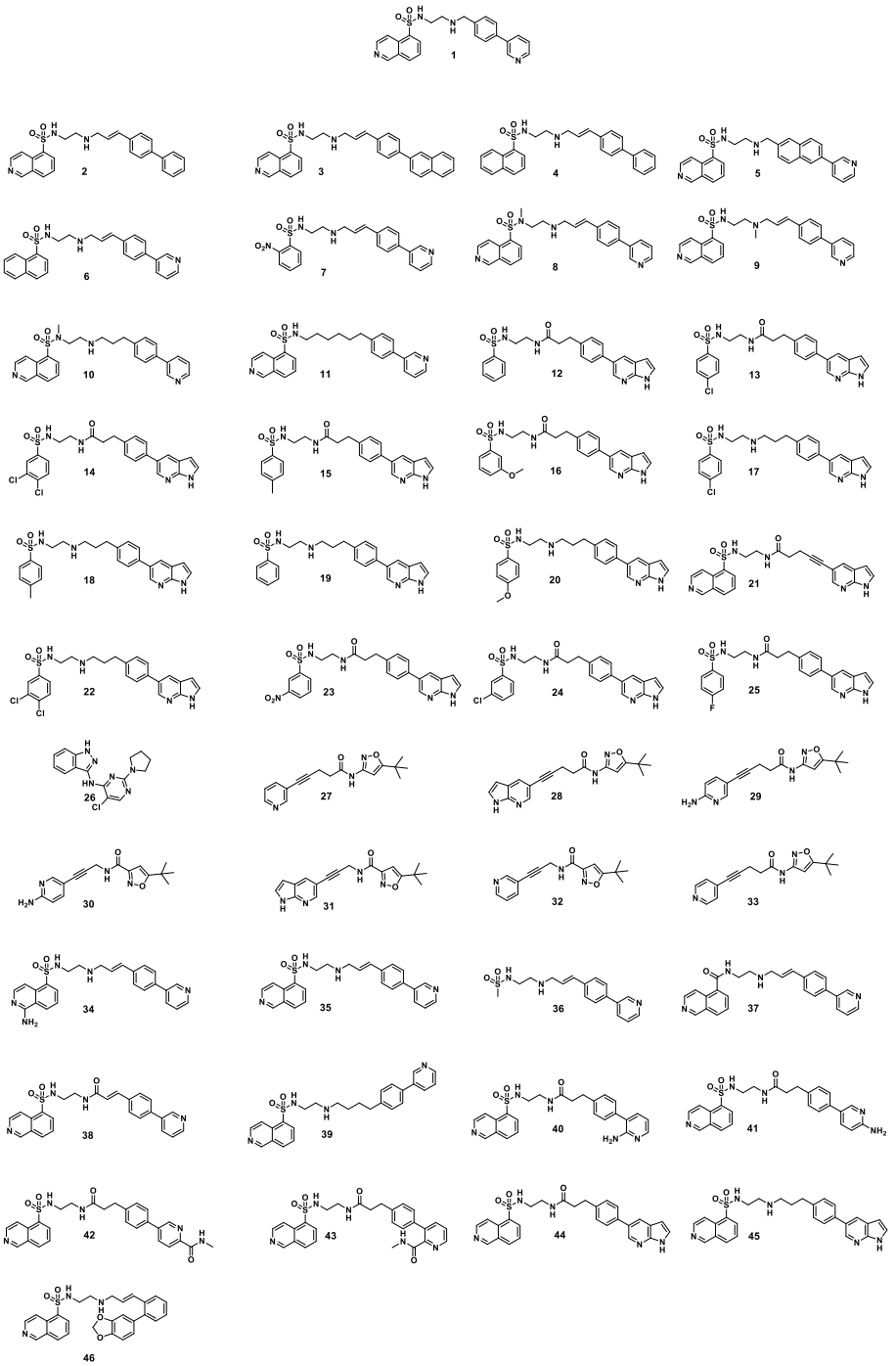


Figure S5.1. Structures of hit **1** and tested kinase inhibitor analogs **2**-**46**. All compounds showed no antibacterial activity against *E. coli* at 50 µM and lower except hit **1**.

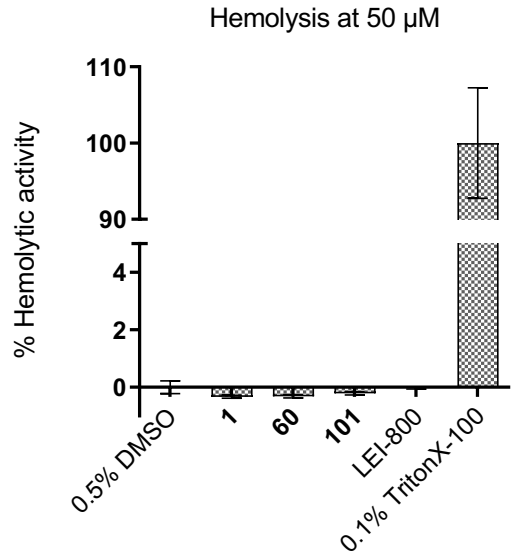


Figure S5.2 | Normalized hemolytic activity of compound **1**, **60**, **101**, and LEI-800 at 50 µM after 20 h incubation time.

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