Synthetic studies on kinase inihbitors and cyclic peptides : strategies towards new antibiotics

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Chapter 3 | Synthesis and Biological Evaluation of Novel Isoquinolinesulfonamide Based PKB/Akt1 Inhibitors

Introduction

A variety of bacterial strains, including *Salmonella typhimurium* and *Mycobacterium tuberculosis*, invade specific host cells and alter the activity of PKB/Akt1 to evade the host immune system and to promote intracellular survival. The discovery of this host / pathogen interaction was described in detail in chapter 2, and the overview includes a summary of PKB/Akt inhibitors that are described in the literature which, in addition to anticancer drugs, can now also be viewed as potential antibiotics. Briefly, infection with one of the above bacterial strains results in the uptake of these pathogens into the host cell where they reside in membrane enclosed vesicles. Effector molecules, expressed and excreted by the bacteria into the host cell cytosol, result in elevated PKB/Akt1 activity. This up-regulation of PKB/Akt1 blocks lysosomal interaction with these vesicles, thus escaping lysosomal degradation. Inhibition of PKB/Akt1 restores this interaction resulting in the destruction of the bacteria.

The development of PKB/Akt1 inhibitors is therefore of great interest, not only as potential antitumor agents (elevated PKB/Akt activity has been shown in several cancers including breast-, ovarian-, lung-, pancreatic-, prostate-, stomach- and melanocytic cancer)[1] but also as novel antibiotic, targeting host cell kinases rather than pathogen specific proteins.

The discovery of the involvement of PKB/Akt1 in bacterial infection was made with the aid of the literature compound H-89 (**1**)[2] and its derivative developed in the context of this theme (**2**, Figure 1). H-89 (**1**) was originally developed as a protein kinase A (PKA) inhibitor, which is closely related to PKB/Akt. However, it was established that the inhibition of PKB/Akt1, not PKA, gave rise to its antibiotic potency and eventually led to the identification of two positions (R^1 and R^2 in **2**, Figure 1) on the H89 scaffold amiable for functionalization towards developing more potent and selective inhibitors of PKB/Akt1.

In this chapter, novel functional variations of the isoquinolinesulfonamide scaffold are discussed. First, a literature survey on the development of this pharmacophore is presented. Next, the introduction of substituents on positions R^1 and R^2 (Figure 1) are discussed, ultimately leading to **3** as most potent and selective PKB/Akt1 inhibitor of this series.

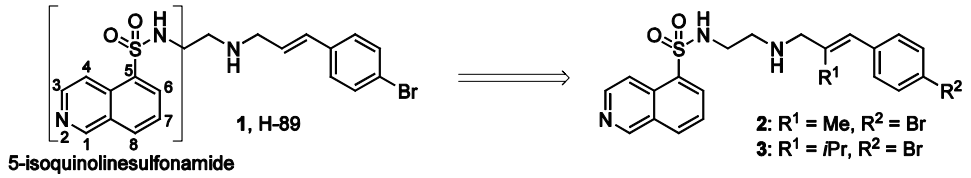


Figure 1; H-89 derived PKB/Akt1 inhibitors **2** and **3**

Isoquinolinesulfonamides as scaffold for small molecule kinase inhibitors

During the eighties and early nineties, the group of Hidaka[3] has published several isoquinolinesulfonamide based small molecule inhibitors for protein kinases. The first 5-isoquinolinesulfonamides to be used as kinase inhibitors were comprised of an isoquinoline moiety attached *via* a sulfonamide to a short diamino spacer exemplified by H-7 (**4**), H-8 (**5**), and H-9 (**6**), Figure 2. These compounds were shown to have low micromolar K_i-values against a small panel of kinases (PKA, PKC, PKG, MLC kinase) which allowed these compounds to be used as ligands in affinity chromatography for the isolation of kinases from different biological samples For this purpose, H-9 (**6**) an be directed attached to cyanogen bromide activated sepharose[4] or equipped with a photoreactive group in combination with a fluorescent label (**7**) or a functionalization handle for solid phase attachment (**8**).[5] A more

recent application of **4** - **6** is their ability to inhibit, albeit with moderate *in vitro* potency, two members of the aminoglycoside kinase family namely APH(3')-IIIA and AAC(6')-APH(2''), preventing the O-phosphorylation (and thereby the inactivation) of antibiotic aminoglycosides.[6] Even though these compounds were not able to inverse antibiotic resistance *in vivo*, this study does present a noteworthy novel application of isoquinolinesulfonamides.

Interestingly, expanding the piperazine ring in H-7 (**4**) to a homopiperazine, (HMN-1179, **9**) resulted in a markedly different inhibition profile (Figure 2). A methyl scan covering all carbon atoms[7] of the homopiperazine moiety (**9** - **13**) had only marginal effect on the inhibitory potency against PKA with IC_{50} values between 1.2 and 5.5 µM.[8] A similar trend was observed for calmodulin Kinase II (IC_{50} between 2.0 and 23 µM). Interestingly, 7-methylated HMN-1180 (**13**) was found to selectively inhibit neuronal nitric oxide synthase (nNOS) with respect to endothelial- (eNOS) and inducible nitric oxide synthase (iNOS). Removing the methyl group altogether (HA1077, **14**) rendered it an antivasospasm drug with unidentified target.[9]

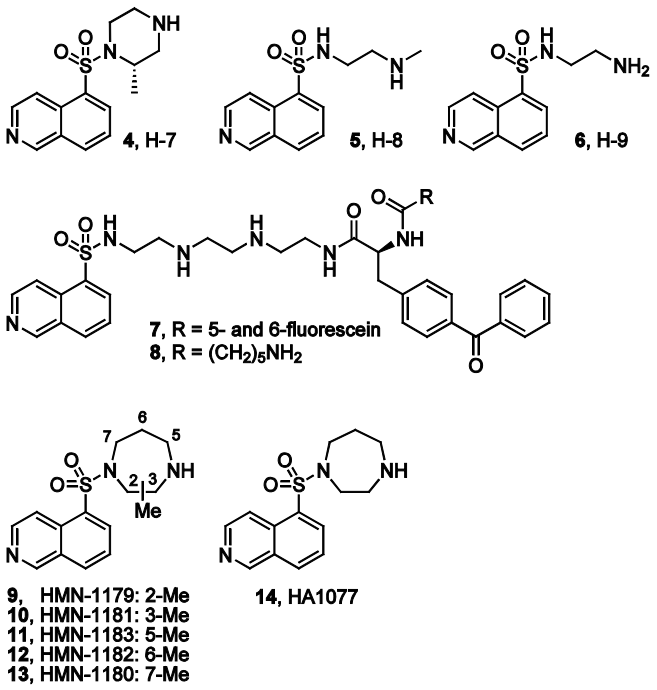


Figure 2; Isoquinolinsulfonamide based kinase inhibitors

In later years, more potent and selective inhibitors were developed (Figure 3). The tyrosinyl based bis-isoquinoline KN-62 (**15**) is a non-ATP-competitive inhibitor of Ca^{2+}/CaM kinase II (K_i = 0.9 µM) that has no significant inhibitory potency against Myosin Light Chain

kinase (MLCK), PKA or PKC at concentrations up to 100 µM.[10] The H-9 (**6**) derivative CKA-1306 (**16**) was found to inhibit PKA (IC_{50} = 1.6 µM) and Ca^{2+}/CaM kinase I (IC_{50} = 2.5 µM).[11]

From a series of *N*-methylated isoquinolinesulfonamides **17** was identified as potent (MIC = 2 µg/mL) inhibitor of plasmodium falciparum MO15 related kinase (Pfmrk), a cyclin dependent kinase with important physiological properties in the life cycle of malaria.[12] An interesting attempt to optimize the potency of H-9 (**6**) towards PKC has been described by Sergheraert and Houdin.[13] Sequence analysis of different PKC isoforms indicated the presence of a possible second ATP binding site in PKCα, PKCβ and PKCγ. Although they were unable to bridge the distance between the two binding sites, these constructs could serve a role in the distinction between free cytosolic, inactive PKC, and membrane bound, active PKC, due to the increased local concentration of inhibitor.

Several groups have published conjugates of H-9 (**6**) and peptide sequences derived from or resembling a kinase substrate protein (**19**-**21**).[14] Although the potency of these conjugates improved significantly with respect to H-9 (**6**), selectivity did not.

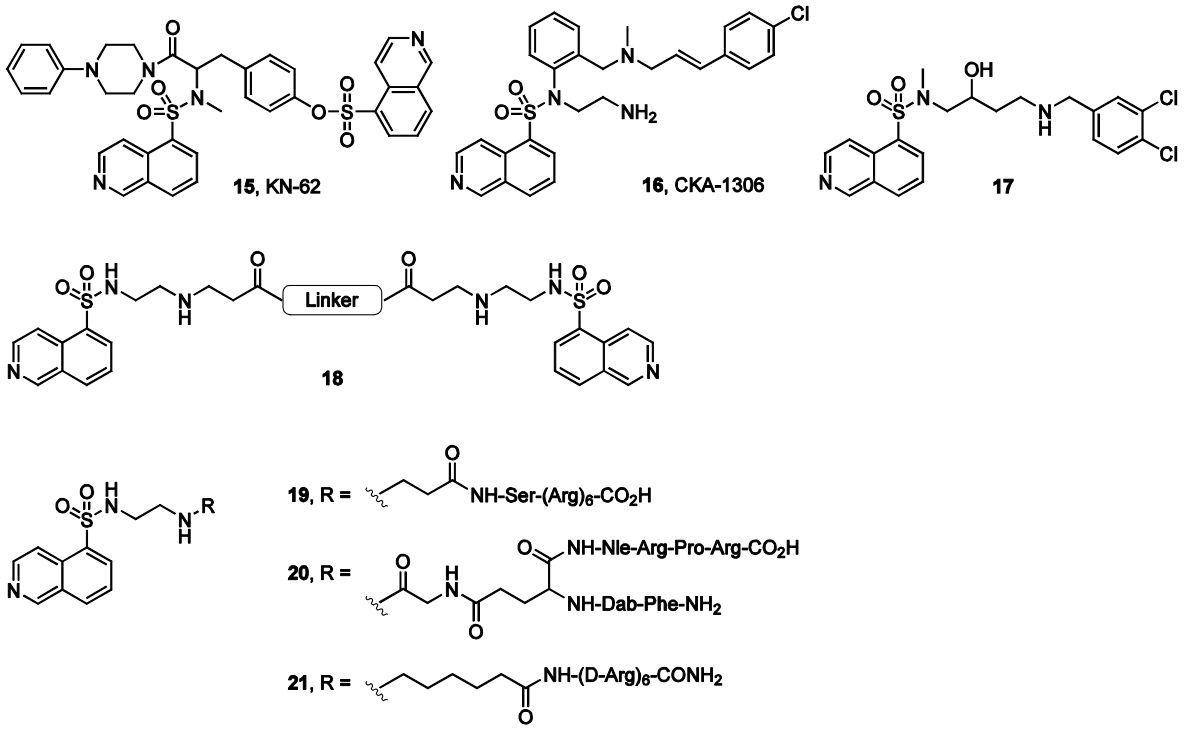


Figure 3; Advanced isoquinolinesulfonamide based kinase inhibitors

Analogues of 2-(Cinnamyl)-ethylamino-5-isoquinolinsulfonamides

In 1990, two novel isoquinolinesulfonamides (H-88 (**22**) and H-89 (**1**), Figure 4) appeared in the literature as part of a study aimed at the synthesis of selective inhibitors against PKA.[2] Whereas H-88 (**22**) was only marginally selective for PKA *vs*. PKG (K_i = 0.38 and 0.76 µM resp.), H-89 (**1**) was ten-fold more potent for PKA than for PKG (K_i = 0.048 and 0.48 µM resp.). Both inhibitors showed only double digit activities against a panel of 5 other related kinases (PKC, MLCK, CaMK II, Casein kinase I and II). Although highly controversial, H-89 (**1**)[15] has long been considered a selective inhibitor for PKA, and is commercially available as reference compound for PKA inhibition,[16] even though 10 µM H-89 (**1**) is able to inhibit at least eight different kinases by 80 - 100%, three of which with a similar or even greater potency then PKA.[17] These results necessitate critical evaluation of earlier findings regarding the biological activity of H-89 (**1**) and evidence of PKA involvement should not solely rely on H-89-based experiments. Despite the drawbacks involved in H-89 (**1**) based assays, the chemical core structure of H-89 (**1**) has contributed to a great number of biochemical studies. The derivatization of H-89 (**1**) with a radiolabeled methylgroup on the sulfonamide nitrogen (**23**) allowed PET based experiments of PKA activity in the brain.[18]

The high sequence homology between PKA and PKB[19] allowed the scaffold of H-89 (**1**) to be used as lead compound in the development of PKB inhibitors. Levitzki and co-workers[20] varied the H-89 (**1**) scaffold in the isoquinoline-, diamine- and styrene-region resulting in the identification of NL-71-101 (**24**) as kinase inhibitor with a 2.4 fold selectivity for PKB over PKA. In a similar study by McDonald and co-workers[21] attempts were made to improve the pharmacological properties of this type of compounds by retaining the isoquinoline moiety and varying the linker region and the aryl group. This yielded **25** as most potent compound. Despite the loss of selectivity over PKA, the similar activity with respect to H-89 (**1**) indicated that the metabolically labile alkene moiety could be replaced by a more stable, and more hydrophilic, ether linkage.

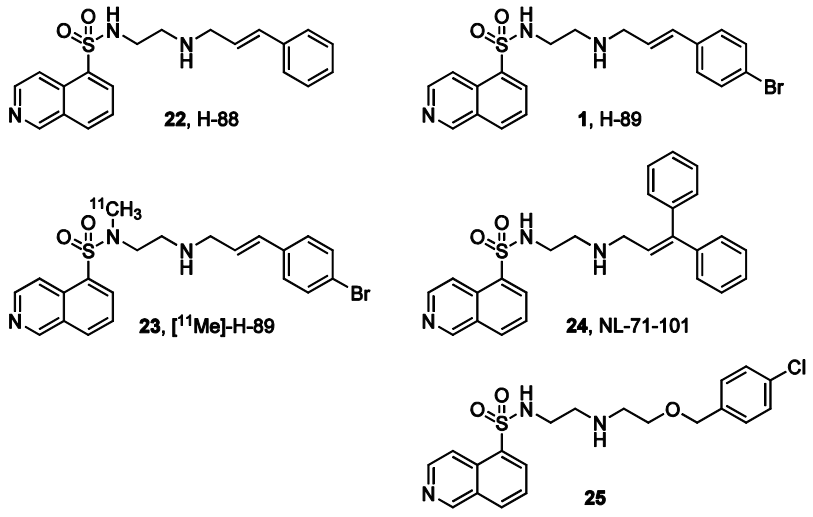


Figure 4; H-89 derivatives

Results and discussion

In the following section, the synthetic efforts of the transformation of H-89 into a potent and more selective inhibitor will be described. First, a small set of analogues is designed, aimed at identifying features of the H-89 (**1**) scaffold that can be modified to increase potency and selectivity. Next, the synthetic strategy to the lead compound resulting from this first library is adapted to allow larger quantities to be synthesized. Finally, a new strategy is described for the construction of a larger and more diverse library.

First small diversity set

A first set of H-89 (**1**) analogues was designed varying the degree of unsaturation, substitution of the linker and the presence or absence of the bromine on the styrene moiety (Figure 5).

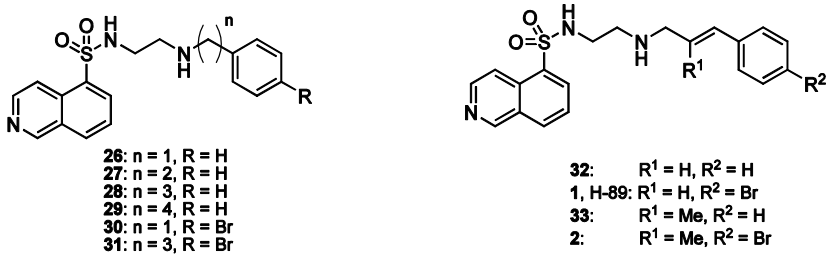
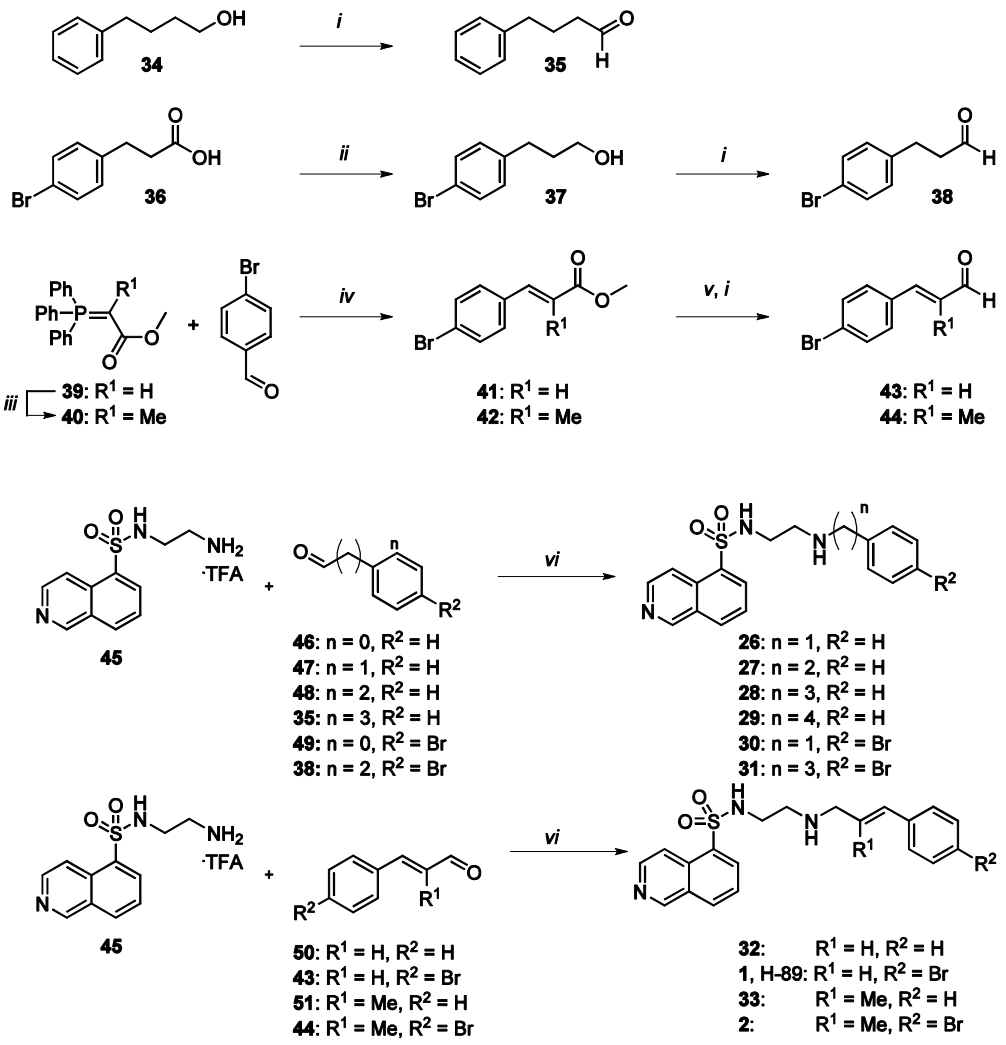


Figure 5; First library of isoquinolinesulfonamides

The synthesis of these isoquinolinesulfonamides is based on the reductive amination of amine **45**[22] and the corresponding aldehydes (**35**, **38**, **43**, **44** and **46** - **51**, Scheme 1). Aldehydes (**46** - **51**) were commercially available, aldehyde **35** was prepared from 4-phenylbutanol by means of a Dess-Martin periodinane mediated oxidation and aldehyde **38** was synthesized from 3-[4-bromophenyl]-propionic acid *via* $BH_3 \cdot Me_2S$ mediated reduction (**37**) followed by Dess-Martin oxidation. Aldehydes **43** and **44** were obtained *via* the following sequence of reactions. Firstly, olefination of *p*-bromo-benzaldehyde with commercially available Wittig-reagent **39** or the methylated derivative **40**[23] in THF at 0°C using NaH as the base afforded methyl esters **41** and **42** in good yield. Performing this reaction in a different solvent (like DMF or DCM) or with another base (such as *n*-BuLi, KOtBu, DBU or NaH) suffered from an increase in side product formation and the requirement of longer reaction time according to TLC analysis. Selective reduction using DiBAl-H and Dess-Martin oxidation afforded the cinnamic aldehydes **43** and **44** which were purified by extraction only and were used as such in the following reactions. The crude aldehydes (**43** and **44**) were treated with amine **45** in MeOH under the agency of AcOH, Na_2SO_4, followed by reduction with $NaBH_4$ to afford isoquinolinesulfonamides **1**, **2** and **26** – **33** in reasable to good yields after HPLC purification.

Biological results

This first set of isoquinolinesulfonamides (**1**, **2**, **26** – **33**) was tested against *Salmonella Thyphimurium* in primary human macrophages, (Figure 6). These results identified several features of the isoquinolinesulfonamides that determine potency against kinases. The optimal length of the linker connecting the phenyl group with the secondary amine proved to be three carbon atoms. The presence of a double bond in that linker improved potency, as does the bromine on the phenyl moiety. A small methyl substituent was well tolerated on the R^1 position (Scheme 1). This first SAR identified possible sites of the H-89 (**1**) scaffold suitable for modification that might increase potency and selectivity. At this stage it was decided to produce **2** on a sufficiently large scale to allow animal testing and to further diversify the library of H-89 (**1**) analogues by incorporating different alkyl substituents on the double bond and to replace the bromine with other halogens.



Scheme 1; *Reagents and conditions*: (*i*) 6 eq. Dess-Martin periodinane, DCM (*ii*) 5 eq. $BH_3{\cdot}Me_2S$, THF, 0°C, 96% (*iii*) ref.23 (*iv*) 1.2 eq. MeLi (1.6M in Et_2O, THF, 0°C, 97% **41**, 99% **42** (*v*) 2.2 eq. DiBAl-H (1M in hexanes (*vi*) Na_2SO_4, 0.2 eq. AcOH then 1.5 eq. $NaCNBH_3$ 43% **26**, 31% **27**, 27% **28**, 22% **29**, 10% **30**, 7% **31**, 41% **32**, 44% **1**, 44% **33**

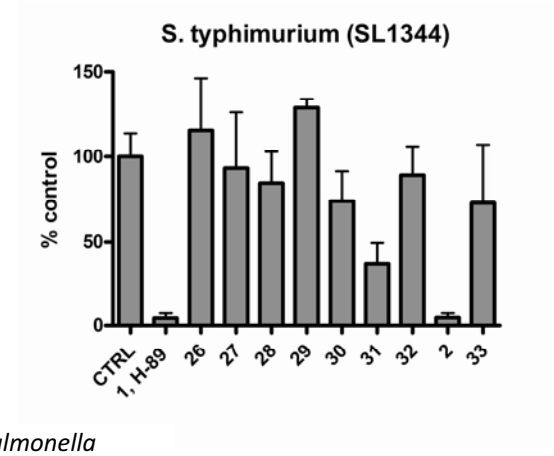
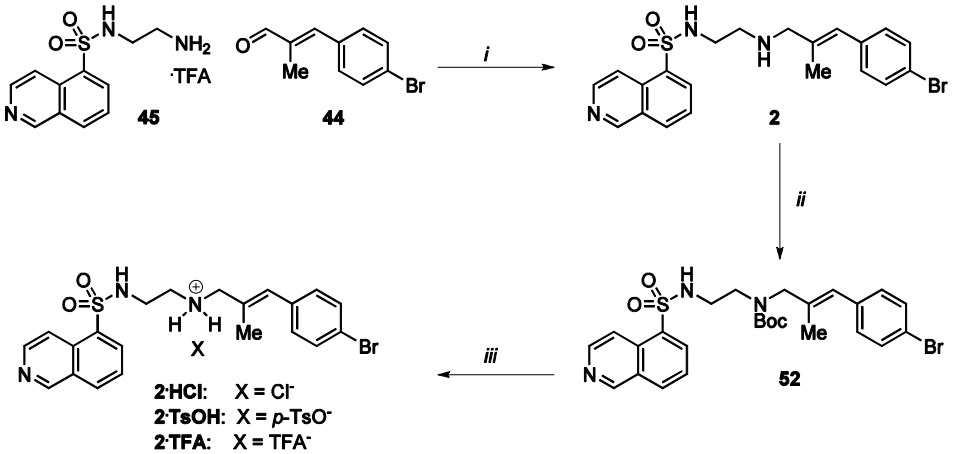


Figure 6; Potency against *salmonella*

Large scale synthesis of 2

Both aldehyde **44** and amine **45** could be prepared on a multi gram scale without difficulties using the small scale procedures. The reductive amination proved to be more scale sensitive. Applying the small scale procedure on a 5 gram scale yielded less than 10% of the desired product. The use of titanium isopropoxide (acting as Lewis acid) and Na_2SO_4 instead of acetic acid/Na_2SO_4 increased the yield after silica column chromatography. However, the product could not be purified beyond a 90 - 95% purity as determined by ^{1}H-NMR. In order to remove the unidentified side product, compound **2** was *N*-protected using Boc-anhydride in THF to afford **52** in a 93% yield. Neither silica column chromatography nor HPLC resulted in complete removal of the side product as judged by ^{1}H-NMR analysis. Acidic treatment of **52** was expected to cause removal of the Boc protecting group and coinciding ammonium salt formation and, depending on the nature of the acid used, possibly enabling selective crystallization. Boc removal using an excess of a freshly prepared dry a methanolic HCl solution or a 2M stock solution of HCl in dioxane resulted in the formation of a crystalline product. Unfortunately, attempts to separate the byproducts by re-crystallization from different solvent systems failed. Boc removal using *p*-TsOH in dioxane, followed by recrystalization from dioxane/ether did result in the pure tosylate salt of **2** (X = tosylate) as determined by NMR. Salt exchange by alkaline extraction and re-acidification using TFA/DCM afforded pure **2** as the TFA salt (X = trifluoroacetate).[24] Further experiments revealed that the bocylation step could be omitted from the purification strategy and *p*-TsOH treatment followed by re-crystallization and anion exchange enabled the synthesis of **2** starting from 6.3 g **45** and 3.2 g **44** resulting in 1.6 g of the desired amine in 24% yield.

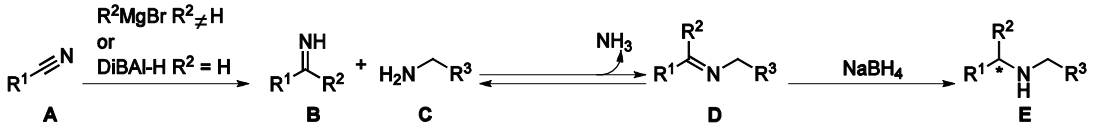


Scheme 2; Reagents and conditions: (*i*) 1.4 eq. Ti(O*i*Pr)$_4$, Na_2SO_4, MeOH, 3h. then 2.8 eq. $NaCNBH_4$ 16h. (*ii*) 1.5 eq. Boc_2O, THF, 93% (*iii*) 5 eq. HCl/MeOH, or 5 eq. HCl/dioxane or 5 eq. p-TsOH/dioxane

Transimination library

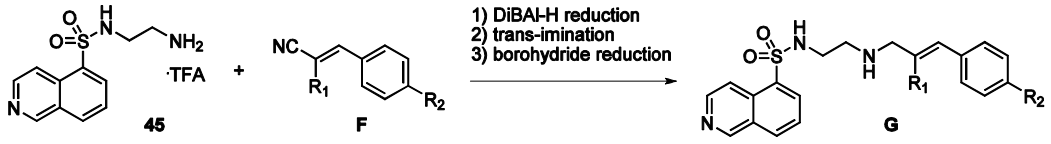
The promising *in vitro* results obtained with the first set of isoquinolinesulfonamides fomented the design of a synthesis scheme that would allow rapid diversification of the core isoquinolinesulfonamide scaffold focusing on bromine replacements and the double bond substitution. The new strategy should require starting materials which are readily available, and easily modified into building blocks that can be efficiently coupled with minimal purification steps yielding the desired library. The laborious preparation of α-alkylated cinnamic aldehydes (such as **43** and **44**, Scheme 1), together with the facile synthesis of amine **45**, directed our attention towards the development of an alternative strategy for the assembly of the secondary amine functionality as the final synthesis step.

An appealing alternative for the reductive amination was published by Van der Gen and Brussee[25] where they described the so-called one-pot Grignard-Transimination-Reduction sequence (Scheme 3). Grignard addition to a nitrile **A** yields primary imine **B** ($R^2 \neq H$), which upon addition of a primary amine **C**, undergoes a transimination reaction forming a secondary imine **D** under the liberation of ammonia. Sodium borohydride reduction of the secondary imine affords the α-alkylated amine **E**. Generating unalkylated imines **B** ($R^2 = H$)[26] could be accomplished *via* DiBAl-H reduction of nitriles **A** ultimately leading to secondary amines **D** after transimination and borohydride reduction in good yields.



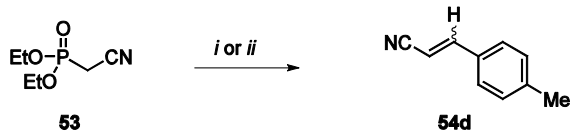
Scheme 3; General scheme for the trans iminationprotocol

Applying this reduction-transimination-reduction-sequence to generate a diverse library of isoquinolinesulfonamides of the general structure **G** would, besides amine **45**, require facile synthesis of nitriles **F**, bearing different substituents on positions R^1 and R^2 (Scheme 4).



Scheme 4; General synthesis of isoquinolinesulfonamides

First the synthesis of unsubstituted cinnamonitriles **F** was investigated (R^1 = H, Scheme 5). It was envisaged that a Horner-Wadsworth-Emmons (HWE) reaction between *p*-substituted benzaldehydes and commercially available diethyl cyanomethylphosphonate **53** would result in α,β-unsaturated cinnamonitriles **54a-i** (R^1 = H). This reaction proceeded in excellent yields with good selectivity (E/Z > 10/1). Attempts to increase the selectivity were met with moderate success and proved to be dependent on many variables including the nature of R^2, reaction temperature and the speed of addition of the aldehyde. These findings prompted us to investigate reaction conditions that would result in a more equalized E/Z ratio resulting in an additional set of derivatives containing a Z-substituted double bond. Indeed, performing the reaction in the presence of additional sodium cations was found[27] to favor the formation of Z-substituted cinnamonitriles resulting in E/Z ratio ranging from 4/1 to 1/1 according to ^{1}H-NMR.



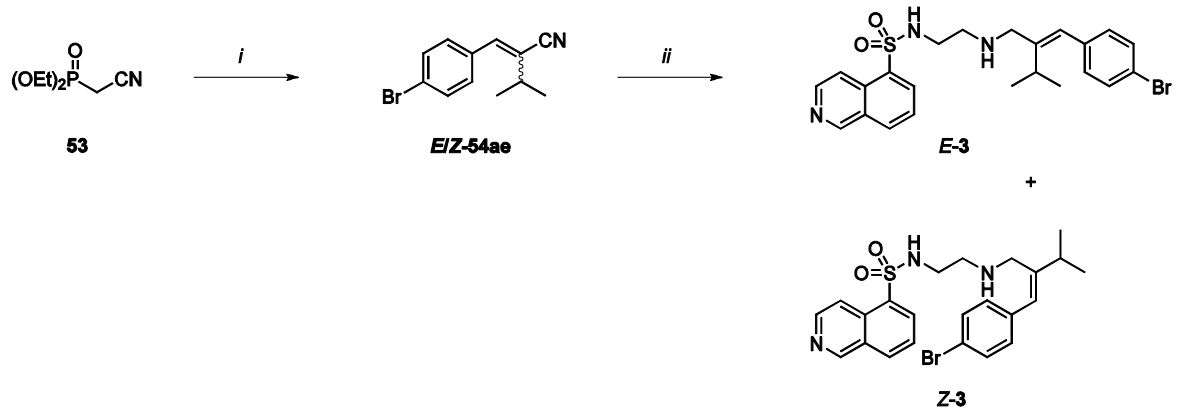
53 **54d**

Scheme 5; Reagents and conditions: (*i*) 1.1 eq. NaH, 0.9 eq. p-tolylbenzaldehyde, DMF, E/Z = 20/1. (*ii*) 1.1 eq. NaH, 2.0 eq. NaI, 0.9 eq. p-tolylbenzaldehyde, DMF, E/Z = 3:1.

The synthesis of α-substituted cinnamonitriles **54e**-**p** (Scheme 6) involved alkylation of phosphonate **53** using NaH and alkyliodide followed by HWE reaction in a one-pot fashion. In these cases an increased prevalence of the Z-isomers was observed, probably arising from both steric hindrance and the presence of an additional equivalent of sodium cations.[27] Since separation of the isomers in the nitrile-stage was at best partially successful, and the nitriles were shown to isomerize during the trans-imination sequence, the nitriles were used in the following reactions as E/Z mixtures.

The thus obtained nitriles were subsequently used in the four-step-one-pot trans-imination procedure according to Brussee *et al*. (Scheme 6).[26] For example, diethyl cyanomethylphopshonate **54** is treated with NaH and alkylated using 2-iodopropane. The intermediate phosphonate is again deprotonated using NaH followed by the Horner-Wadsworth-Emmons reaction with 4-bromobenzaldehyde to afford **54ae** as 3/2 mixture of E/Z isomers in 73% yield. The nitrile is used as isomeric mixture and as such dissolved in dry ether at -78°C and treated with an excess DiBAl-H at -78°C before the excess reagent is quenched at -100°C with concomitant methanolysis of the iminium salt intermediate

towards the primary imine. Reaction with amine **45** at room temperature under the liberation of ammonia followed by overnight reduction of the resulting secondary imine with $NaBH_4$ furnished the final isoquinolinesulfonamides **55ae** as crude E/Z mixture in 80% yield after alkaline extraction. HPLC purification allowed the separation and isolation of both isomers. The remaining isoquinoline sulfonamides **55a-aj** could be synthesized in a similar fashion (Table 1). The separation of the E/Z isomers using HPLC was met with varying results. In most cases one or both of the isomers were obtained in a >95% purity. In some cases, however, neither of the two isomers could be obtained in >95% purity.



Scheme 6; Example of a HWE reaction and trans-imination sequence: *Reagents and conditions*: (*i*) a: NaH (1.2 eq.), 2-iodopropane (1.5 eq.), DMF, 1h., 0°C; b: NaH (1.2 eq.) 4-bromobenzaldehyde, 0°C tot r.t.; 16h. (*ii*) a: DiBAl-H (2 eq.), Et_2O, -78°C to 0°C, 30 min. b: MeOH, -100°C c: **45** (1.5 eq.), r.t., 3h. d: $NaBH_4$ (2 eq.) -18°C to r.t., 16h. Yields and E/Z ratios of the complete library are given in Table 1 and in the experimental section.

Table 1:

	R^1	R^2	**53 → 54** % (E:Z)	**54 → 55** % (E), % (Z)
a	H	H	91 (4:1)	31.6 (E)
b	H	F	84 (5:2)	34.0 (E)
c	H	Cl	88 (2:1)	18.2 (E)
d	H	Br	87 (5:2)	19.4 (E)
e	H	Me	quant (5:2)	38.3 (E)
f	H	CF_3	92 (5:2)	14.0 (E)
g	H	OMe	quant (3:1)	45.8 (E)
h	H	OPh	90 (3:1)	23.2 (E)
i	H	NO_2	92 (2:1)	27.7 (E)
j	Me	H	60 (1:1)	9.1 (E), 2.5 (Z)
k	Me	F	45 (1:1)	11.5 (E), 4.2 (Z)
l	Me	Cl	38 (3:2)	10.5 (E)
m	Me	Br	63 (1:1)	12.4 (E), 2.0 (E/Z = 5/3)
n	Me	Me	35 (1:0)	10.5 (E), 13.5 (Z)
o	Me	CF_3	58 (1:1)	8.5 (E), 7.0 (Z)
p	Me	OMe	20 (1:1)	21.9 (E), 5.7 (Z)
q	Me	OPh	45 (1:1)	10.3 (E)
r	Me	NO_2	56 (1:1)	7.4 (E/Z = 6/1), 7.1 (Z)
s	Et	H	49 (1:1)	14.1 (E), 4.6 (E/Z = 1/5)
t	Et	F	55 (4:3)	8.5 (E), 5.9 (E/Z = 1/4)
u	Et	Cl	39 (1:1)	2.4% (E)
v	Et	Br	64 (1:1)	6.5 (E/Z = 5/1), 2.6 (Z)
w	Et	Me	16 (1:1)	19.0 (E/Z = 1/2), 10.7 (Z)
x	Et	CF_3	60 (3:2)	0.8 (E), 7.4 (Z)
y	Et	OMe	51 (1:1)	5.6 (E/Z = 5/1)
z	Et	OPh	51 (1:1)	14.2 (E), 4.8 (Z)
aa	Et	NO_2	55 (1:1)	10.1% (E/Z = 3/2)
ab	iPr	H	67 (3:2)	3.1 (E), 3.3 (Z)
ac	iPr	F	67 (3:2)	4.6 (E), 4.2 (E/Z = 3/2)
ad	iPr	Cl	34 (3:2)	13.4 (E), 7.5 (Z)
ae	iPr	Br	73 (3:2)	8.3 (E), 16.6 (Z)
af	iPr	Me	67 (1:1)	1.6 (E), 7.8 (Z)
ag	iPr	CF_3	62 (3:2)	15.2 (E), 13.3 (Z)
ah	iPr	OMe	84 (1:1)	6.6 (E/Z = 1/4)
ai	iPr	OPh	34 (1:1)	9.6 (E/Z = 1/1)
aj	iPr	NO_2	23 (5:1)	20.6 (E), 10.7 (Z)

Biological evaluation

In a preliminary *in vitro* biological evaluation, the inhibitory effect of the isoquinolinesulfonamides ***E*-55a-d, j-m, s-v, ab-ae** (R^1 = H, Me, Et or *i*Pr; R^2 = H, F, Cl or Br) against PKA and PKB/Akt1 are depicted in Figure 7A and B. Activity against *salmonella* in primary human macrophages is depicted in Figure 7C.[28] In the case of PKA, with a proton or a methyl group on the double bond, larger halogens provided better inhibition. With an ethyl or isopropyl, however, the bromine is no longer tolerated on that position. Inhibitory potency against PKB increases with halogen size and is largely unaffected by the size of R^1. The potency of ***E*-55a-d, j-m** (R^1 = H or Me) is strongly dependent on the nature of R^2. Compounds **E-55s-v, ab-ae** (R^1 = Et or *i*Pr) are generally more active and less dependent on the nature of R^2.

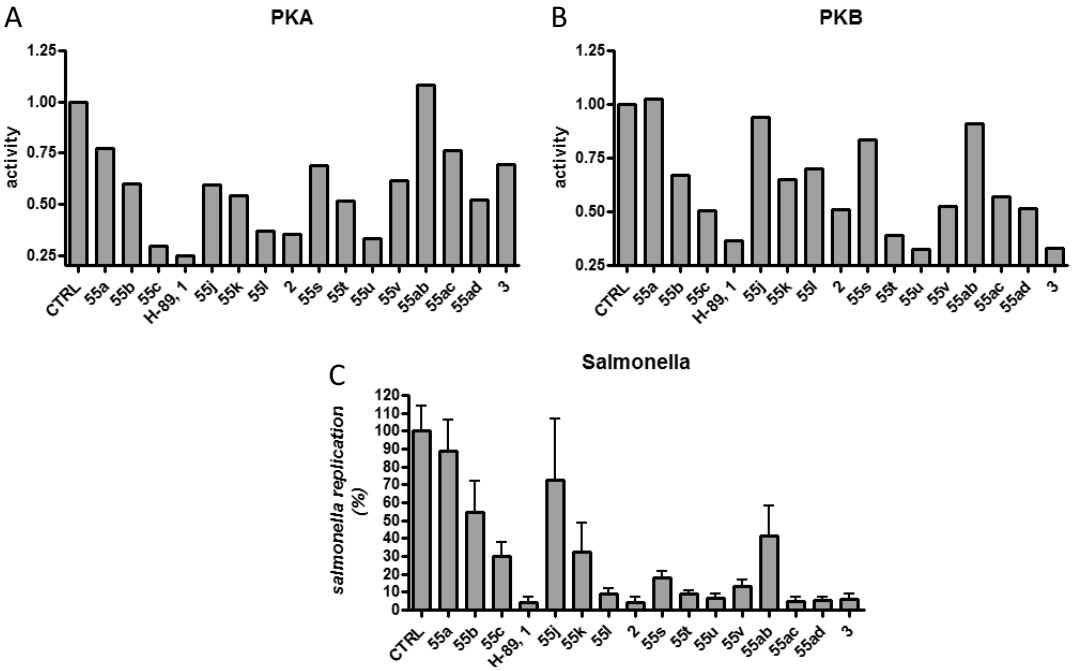


Figure 7; a: PKA activity as determined in an *in vitro* kinase reaction in the absence or presence of 10 µM compound. Results are normalized to the activity detected in the absence of any compound (CTRL, containing DMSO only). b: Similar for PKB. c: Effect of 10µM compound in intracellular growth of *Salmonella* in human primary macrophages compared to DMSO.

Conclusion

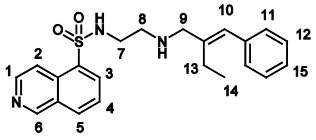
Initial SAR has identified a novel substitution site on the skeleton of H-89 that allows for the construction of more selective inhibitors for PKB. Substitution of the double bond with aliphatic sidechains with increasing size reduces potency against PKA rendering it more selective towards PKB. These results indicate that the ATP binding pocket of PKB, although very similar to PKA in amino acid composition, does contain a cavity situated around the double bond that can be occupied by a bulky apolar group. Replacing the bromine does not result in increased selectivity, however, activity is changed. Smaller halogens decrease activity probably due to reduced van der Waals interaction. Up-scaling the synthesis of the lead compound **2** proved to be less than trivial and could only be optimized to a maximum yield of 24% after silica column purification and re-crystallization, whereas the small scale procedure yielded 44% after HPLC purification. Diversification of the isoquinolinesulfonamide scaffold was achieved *via* the transimination protocol allowing the synthesis of 64 novel H-89 derivatives varying in the double bond configuration, the double bond substitution and the aromatic substituent. HPLC purification and separation of the two geometrical isomers was successful in most cases. Preliminary *in vitro* biological tests show a

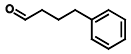
decrease activity against PKA with bulky groups for R^1 while activity against PKB is unaffected. Activity against both enzymes increases with increasing size of R^2. In the *in vivo* experiments, the effect of R^2 seems to correlate with the size of R^1. For R^1 = H or Me, activity increases with the size of R^2. For R^1 = Et or *i*Pr, the influence of R^2 on the inhibitory potency is largely abolished.

Experimental Section:

General: PE with a boiling range of 40 - 60°C was used. THF and Et_2O were distilled over $LiAlH_4$ prior to use. DCM was distilled over CaH_2 prior to use. All other solvents used under anhydrous conditions were stored over molecular sieves (4Å) except for methanol which was stored over 3Å molecular sieves. Solvents used for work-up and column chromatography were of technical grade and distilled before use. Unless stated otherwise, solvents were removed by rotary evaporation under reduced pressure at 40°C. Reactions were monitored by TLC-analysis using Merck 25 DC plastikfolien 60 F_{254} with detection by spraying with 20% H_2SO_4 in EtOH, $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (25 g/L) and $(NH_4)_4Ce(SO_4)_4\cdot 2H_2O$ (10 g/L) in 10% sulfuric acid or by spraying with a solution of ninhydrin (3 g/L) in EtOH / AcOH (20/1 v/v), followed by charring at approx. 150°C. Column chromatography was performed on Fluka silicagel (0.04 – 0.063 mm). For LC/MS analysis, an JASCO HPLC-system (detection simultaneously at 214 and 254 nm) equipped with an analytical C_{18} column (4.6 mmD × 250 mmL, 5μ particle size) in combination with buffers A: H_2O, B: MeCN and C: 0.5% aq. TFA and coupled to a mass instrument with a custom-made Electronspray Interface (ESI) was used. For reversed-phase HPLC purification of the final compounds, an automated HPLC system supplied with a semi-preperative C_{18} column (10.0 mmD × 250 mmL, 5μ particle size) was used. The applied buffers were A: H_2O, B: MeCN and C: 1.0% aq. TFA. High resolution mass spectra were recorded by direct injection (2 μL of a 2 μM solution in water/acetonitrile; 50/50; v/v and 0.1% formic acid) on a mass spectrometer (Thermo Finnigan LTQ Orbitrap) equipped with an electrospray ion source in positive mode (source voltage 3.5 kV, sheath gas flow 10, capillary temperature 250 °C) with resolution R = 60000 at m/z 400 (mass range m/z = 150-2000) and dioctylpthalate (m/z = 391.28428) as a "lock mass".[29] The high resolution mass spectrometer was calibrated prior to measurements with a calibration mixture (Thermo Finnigan). ^{1}H- en ^{13}C-NMR spectra were measured on a Joel JNM-FX-200 (200/50 Mhz), a Brüker AV-400 (400/100 MHz), a Brüker AV-500 (500/125 MHz) or a Brüker DMX-600 (600/125 MHz). Chemical shifts are given in ppm (δ) relative to TMS (0 ppm) or MeOD (3.30 ppm) and coupling constants are given in Hz.

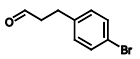
The Isoquinoline sulfonic acid-(2-amino-ethyl) amides are numbered as follows:



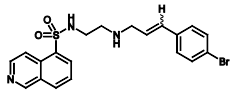


4-Phenyl-butyraldehyde **35**: Dess-Martin periodinane (2.4 g, 6 mmol, 6 equiv.) was added to a solution of 4-phenyl-1-butanol (150 mg, 1 mmol) in CH_2Cl_2 (30 mL). After stirring the reaction

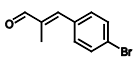
mixture at room temperature for 1 h a solution of 1M $Na_2S_2O_3$ (30 mL) was added and stirred vigorously for 5 min. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The aldehyde was used without further purification.



3-(4-Bromophenyl)propanal **38**: 3-(4-Bromophenyl)propionic acid (2.0 g, 8.7 mmol) was treated for 16 h with Me_2S in THF at 0°C to rt after which TLC analysis (20% EtOAc/PE) indicated complete conversion of the starting material into a higher running spot. The reaction mixture was cooled to 0°C and MeOH (10 mL) was slowly added (gas evolution) and stirring was continued for 1 h. Evaporation of all volatiles yielded the intermediate 3-(4-bromophenyl)propanol **37** (1.8 g, 8.4 mmol, 96%). All physical data was in agreement with published data[30]. 3-(4-bromophenyl)propanol was oxidized to 3-(4-bromophenyl)propanal **38** using the same procedure as described for **35** and was used as crude aldehyde in the next reaction.

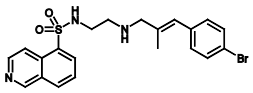


H-89 **1**: Amine **45** (276 mg, 1.1 mmol, 1.1 eq.) was co-evaporated with dry toluene/MeOH 1/1 to remove traces of water and dissolved in dry methanol and Na_2SO_4. Crude aldehyde **43** and acetic acid (11 µl, 0.2 mmol, 0.2 eq.) were added and stirring was continued until TLC analysis indicated complete disappearance of the aldehyde after which $NaCNBH_3$ (100 mg, 1.6 mmol, 1.6 eq.) was added. The reaction mixture was allowed to stir overnight before it was concentrated, redissolved in DCM (10 ml) and washed with brine. Filtration over a path of silica and reversed phase HPLC purification afforded the title compound (202 mg, 0.44mmol, 44%) as colorless oil. ^{1}H NMR (400 MHz, MeOD): δ 9.34 (s, 1H, H6), 8.63 – 8.60 (d, 1H, H1, *J* = 6.2), 8.56 – 8.53 (d, 1H, H2, *J* = 6.2*)*, 8.49 – 8.45 (dd, 1H, H3, *J* = 1.1, 7.3), 8.38 – 8.34 (d, 1H, H5, *J* = 8.4), 7.83 – 7.76 (t, 1H, H4, *J* = 6.9, 8.1), 7.49 – 7.44 (d, 2H, CH_{phenyl}, *J* = 8.8), 7.12 – 7.08 (d, 2H, CH_{phenyl}, *J* = 8.4), 6.19 (s, 1H, =CHPh), 3.10 (s, 2H, NCH_2), 3.07 – 3.00 (t, 2H, H8, *J* = 6.2), 2.58 – 2.51 (t, 2H, H7, *J* = 6.2), 1.72 (d, 3H, CH_3, *J* = 1.1); ^{13}C-NMR (100 MHz, MeOD) : δ 154.1, 144.8, 137.6, 137.0, 136.0, 134.7, 134.5, 132.3, 132.1 – 131.5, 130.2, 127.5, 126.8, 121.0, 118.9, 57.7, 48.5, 42.8, 16.7. MS: *m/z* = 460.1, 461.2 1 : 1 $(M+H)^+$



(E)-3-(4-bromophenyl)-2-methylacrylaldehyde **44**: The aldehyde was prepared *via* the intermediate (E)-3-(4-bromo-phenyl)-2-methyl-prop-2-en-1-ol which was prepared according to literature procedures[31] on a 5 mmol scale from *p*-bromobenzaldehyde *via* a Wittig reaction with [(methoxycarbonyl)methyl]triphenylphosphonium iodide[23] followed by a DiBAl-H reduction affording the intermediate alcohol as off white solid (3.4 mmol, 67% over two steps). All physical data was in agreement with published data[31]. Oxidation using Dess-Martin periodiane as described for **36** afforded crude aldehyde **52** which was used without further purification.

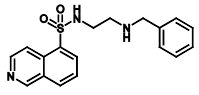
Large scale synthesis of Isoquinoline-5-sulfonic acid (2-((E)-3-(4-bromo-phenyl)-2-methyl-allylamino)-ethyl)-amide 2.



Dess-Martin Periodinane (12.7 g, 30 mmol, 1.5 eq.) was dissolved in DCM (50 mL) under an argon atmosphere before a solution of (E)-3-(4-bromo-phenyl)-2-methyl-prop-2-en-1-ol (4.5 g, 20 mmol) in DCM (50 mL) was added. Stirring was continued until TLC analysis indicated complete disappearance of the starting material. The reaction was quenched by addition of NaS_2O_3 (25 ml, 2M) and sat. aq. $NaHCO_3$ (25 mL) and stirring was continued for 30 minutes after which the organic phase was separated, washed with brine, dried ($MgSO_4$) and concentrated. The residue was applied to silica column chromatography using diethylether / hexanes to afford aldehyde **44** as white solid (3.19 g, 14.3 mmol, 91%). ^{1}H-NMR (200 MHz, MeOD): δ 9.46 (s, 1H, C*H*O), 7.43 (d, 2H, 2x H_{arom}, *J* = 8.8, 7.4 (d, 2H, 2x H_{arom}, *J* = 8.8, 7.1 (s, 1H, C*H*=C), 1.93 (s, 3H, CH_3). ^{13}C-NMR (50 MHz, $CDCl_3$) : δ 194.7 (CH=O), 147.7 (C=*C*H), 138.3 Me*C*=CH), 133.6 ($C_q$arom), 131.5 (CHarom), 131.1 (CHarom), 123.5 ($C_q$arom), 10.5 (CH_3). MS: *m/z* = 224.8, 226.8 1: 1 $(M+H)^+$.

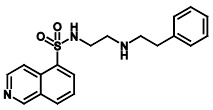
Amine **45** (6.3 g, 25 mmol, 1.8 eq.) was co-evaporated with dry toluene / dry methanol 1/1 to remove traces of water and dissolved in dry methanol (250 mL). Na_2SO_4 was added as drying agent. Aldehyde **44** (3.19 g, 14.3 mmol, 1 eq.) and Ti(O*i*Pr)$_4$ (5.8 mL, 20 mmol, 1.4 eq.) were added and stirring was continued until TLC indicated complete disappearance of the aldehyde. The reaction mixture was cooled to 0°C and $NaCNBH_3$ (2.5 g, 40 mmol, 2.8 eq.) was added. The reaction mixture was allowed to stir overnight at r.t. before it was diluted with water (500 mL) and extracted with DCM (3x, 250 mL). The combined organic fractions were washed with sat. aq. $NaHCO_3$ (200 mL) and brine 200 mL), dried ($MgSO_4$), filtrated and concentrated. The residue was purified using column chromatography (MeOH / DCM) to afford the title compound with a minor impurity (~5% according to NMR). The compound was further purified as follows. The residue was dissolved in dioxane and *p*-toluenesulfonic acid monohydrate was added. The resulting precipitate was collected by filtration and washed with ether. ^{1}H-NMR (200 MHz, MeOD): 9.91 (s, 1H, H6), 9.13 (d, 1H, H1, *J* = 7.0), 8.83 (dd, 1H, H3, *J* = 1.1, 7.3), 8.78 (m, 2H, H2 + H5), 8.13 (dd, 1H, H4, *J* = 8.4, 7.3), 7.66 (m, 4H, 4x H_{arom}), 7.51 (d, 2H, 2x H_{arom}), 7.21 (m, 6H, 6x H_{arom}), 6.63 (s, 1H, C*H*=C), 3.79 (s, 2H, N-CH_2-), 3.28 – 3.24 (m, 4H, H7 + H8), 2.35 (s, 6H, 2x CH_3 pTsOH), 1.95 (d, 3H, =C-CH_3, *J* = 1.5 *Hz*). MS: *m/z* = 460.1, 461.2 1 : 1 $(M+H)^+$

Anion exchange was performed as follows. The solid was suspended in DCM (100 mL) and neutralized with sat. aq. $NaHCO_3$ (50 mL). The organic layer was washed with brine, dried ($MgSO_4$), filtered and concentrated to afford the title compound as colorless oil (1.6 g, 3.5 mmol, 24%). Analytical data were identical to those obtained by the small scale procedure.

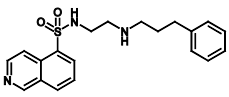


N-(2-(benzylamino)ethyl)isoquinoline-5-sulfonamide **26**: Isoquinolinesulfonamide **26** was prepared according to the procedure described for **1** yielding the title compound (30 mg, 0.09 mmol, 43 %) as light yellow oil. ^{1}H-NMR (200 MHz, MeOD) : δ 9.34 (s, 1H, H6), 8.60 – 8.57 (d, 1H, H1, *J* = 6.2), 8.53 – 8.50 (d, 1H, H2, *J* = 6.2), 8.45 – 8.42 (d, 1H, H3, *J* = 7.3), 8.36 – 8.32 (d, 1H, H5, *J* = 8.4), 7.81 – 7.73 (t, 1H, H4, *J* = 7.3, 8.4), 7.27 – 7.10 (m, 5H, H_{arom}), 3.54 (s, 2H, N-CH_2-Ph), 3.03 – 2.97 (t, 2H, H7, *J* = 6.2), 2.57 – 2.50 (t, 2H, H8, *J* = 6.2). ^{13}C-NMR (50 MHz, MeOD) : δ 154.0 (C6), 144.6 (C1), 139.8 (CqPh), 136.1 (C9), 134.6 (C3),

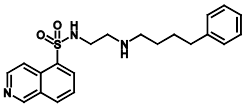
134.4 (C5), 132.3 (C10), 130.3 (C11), 129.2, 129.0 (CH_{phenyl}), 127.9 (C4), 127.4 (CH_{phneyl}), 118.8 (C2), 53.6 (C8), 49.6 (CH_2Ph), 42.7 (C7); MS: *m/z* = 342.0 $(M+H)^+$



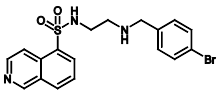
N-(2-(phenethylamino)ethyl)isoquinoline-5-sulfonamide **27**: Isoquinolinesulfonamide **27** was synthesized according to the procedure described for **1** yielding the title compound (22 mg, 0.06 mmol, 31 %) as colorless oil. ^{1}H-NMR (200 MHz, MeOD) : δ 9.37 (s, 1H, H6), 8.62 – 8.59 (d, 1H, H1 , *J* = 6.2), 8.54 – 8.50 (d, 1H, H2 , *J* = 6.2), 8.47 – 8.43 (d, 1H, H3, *J* = 7.3), 8.40 – 8.35 (d, 1H, H5, *J* = 8.4), 7.84 – 7.76 (dd, 1H, H4, *J* = 8.0, *J* = 7.3), 7.29 – 7.08 (m, 5H, CH_{arom}), 2.99 – 2.93 (t, 2H, H7, *J* = 6.2), 2.62 – 2.55 (m, 6H, 2x NH-CH_2 + CH_2-Ph). ^{13}C-NMR (50 MHz, MeOD) : δ 154.1 (C6), 144.6 (C1), 140.4 (Cq_{phenyl}), 136.0 (C9), 134.6 (C3), 134.5 (C5), 132.3 (C10), 130.4 (C11), 129.3, (2x CH_{phenyl}), 127.4 (C4), 127.0 (CH_{phenyl}), 118.9 (C2), 51.2 (C8), 49.0 (NCH_2-CH_2Ph) 42.7 (C7), 36.4 (NCH_2-*C*H_2Ph); MS: *m/z* = 356.1 $(M+H)^+$.



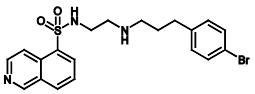
N-(2-(3-phenylpropylamino)ethyl)isoquinoline-5-sulfonamide **28**: Product **28** was synthesized according to the procedure described for **1** yielding the title compound (20 mg, 0.05 mmol. 27 %) as a colorless oil. ^{1}H-NMR (200 MHz, MeOD) : δ 9.39 – 9.38 (d, 1H, H6, *J* = 1.1), 8.65 – 8.62 (d, 1H, H1, *J* = 6.2), 8.56 – 8.52 (dt, 1H, H2, *J* = 1.1, 6.2), 8.49 – 8.44 (dd, 1H, H3, *J* = 1.09, 7.3) 8.41 – 8.37 (d, 1H, H5, *J* = 8.4), 7.86 – 7.78 (dd, 1H, H4, *J* = 7.3, 8.4), 7.27 – 7.09 (m, CH_{phenyl}), 3.03 – 2.97 (t, 2H, H7, *J* = 6.6), 2.68 – 2.48 (m, 6H, 2x, NH-CH_2 + CH_2-Ph, 1.76 – 1.61 (m, 2H, CH_2-CH_2-Ph). ^{13}C-NMR (50 MHz, MeOD) : δ 154.1 (C6), 144.6 (C1), 142.7 (Cq_{phneyl}), 136.1 (C9), 134.6 (C3), 134.5 (C5), 132.4 (C10), 130.4 (C11), 129.1 (2x CH_{phenyl}), 127.5 (C4), 126.6 ($CH_{phernyl}$), 50.0 (C8), 49.2 (NH-*C*H_2), 42.6 (C7), 34.1 (*C*H_2-Ph), 31.8 (*C*H_2-CH_2-Ph); MS: *m/z* = 370.1 $(M+H)^+$



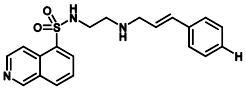
N-(2-(4-phenylbutylamino)ethyl)isoquinoline-5-sulfonamide **29**: This product was synthesized analogously to the procedure described for **1** using 4-phenyl-butyraldehyde **35** (30 mg, 0.2 mmol, 0.8 equiv.) to give **29** (17 mg, 0.04 mmol, 22%) as a colorless oil. ^{1}H NMR (200 MHz, MeOD) : δ 9.38 (s, 1H, H6), 8.64 – 8.61 (d, 1H, H2, *J* = 6.2*)*, 8.55 – 8.52 (d, 1H, H2, *J* = 6.2), 8.48 – 8.44 (d, 1H, H3, *J* = 7.3), 8.40 – 8.36 (d, 1H, H5, *J* = 8.0), 7.85 – 7.77 (dd, 1H, H4, *J* = 7.3, 8.4), 7.28 – 7.09 (m, 5H, CH_{phenyl}), 3.06 – 2.99 (t, 2H, H8, *J* = 6.6), 2.70 – 2.53 (m, 4H, CH_2-Ph + NH-CH_2), 2.49 – 2.42 (t, 2H, H7, *J* = 6.9), 1.61 – 1.19 (m, 4H, NH-CH_2-CH_2 + CH_2-CH_2-Ph); MS: *m/z* = 384.2 $(M+H)^+$.



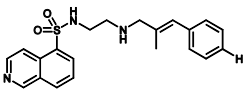
N-(2-(4-bromobenzylamino)ethyl)isoquinoline-5-sulfonamide **30**: This compound is prepared according to the procedure described for **1** using *p*-bromobenzaldeyde. Yield: 5.3 mg, 9.85 µmol 10%. ^{1}H NMR (200 MHz, MeOD): δ 9.65 (bs, 1H, H6), 8.78 – 8.77 (d, 1H, H2, *J* = 5.6), 8.70 (bs, 1H, H1), 8.61 – 8.60 (d, 1H, H5, *J* = 7.3), 8.56 – 8..55 (d, 1H, H3, *J* =8.2), 7.96 – 7.94 (t, 1H, H4, *J* = 7.8, 7.9), 7.59 – 7.58 (d, 2H, H10 , *J* = 8.3), 7.40 – 7.38 (d, 2H, H11, *J* = 8.3), 3.2 (s, 2H, H9), 3.18 – 3.15 (m, 4H, H7+H8); ^{13}C NMR (50 MHz, MeOD): δ 152.4, 140.5, 137.0, 136.2, 136.0, 134.0, 133.4, 133.0, 131.5, 129.2, 124.9, 121.1, 51.4, 48.0, 39.9; MS: *m/z* = 420.5, 422.2 1:1 $(M+H)^+$; HRMS: calcd for $[C_{18}H_{18}BrN_3O_2S + H]^+$ = 420.03759, found 420.03757



N-(2-(3-(4-bromophenyl)propylamino)ethyl)isoquinoline-5-sulfonamide **31**: This compound is prepared according to the general procedure using 3-(4-bromophenyl)-propanal. Yield: 4.2 mg, 7.45 µmol 7.5%. ^{1}H-NMR (MeOD): δ 9.47 (bs, 1H, H6), 8.66 (bs, 1H, H1), 8.57 – 8.56 (d, 1H, H2,J_1 = 5.46 *Hz*), 8.48 – 8.44 (m, 2H, H3/5), 7.87 – 7.84 (t, 1H, H4, J_1 = 7.80 *Hz*, J_2 = 7.86 *Hz*), 7.45 – 7.43 (d, 2H, H12, J_1 =8.22 *Hz*), 7.16 – 7.15 (d, 2H, H13, J_1 = 8.22 *Hz*), 3.11 – 3.07 (m, 4H, H7/8), 3.03 – 3.00 (t, 2H, H9, J_1 = 8.16 *Hz*), J_2 = 7.92 *Hz*), 2.69 – 2.66 (t, 2H, H11, J_1 = J_2 = 7.26 *Hz*), 2.00 – 1.95 (m, 2H, H10) ; ^{13}C-NMR (MeOD): δ 154.11, 144.33, 140.80, 135.55, 135.38, 135.33, 132.77, 131.41, 128.01, 121.16, 48.29, 39.97, 32.86, 28.58; MS: *m/z* = 448.40, 450.27 1:1 $(M+H)^+$; HRMS: calcd for $[C_{20}H_{22}BrN_3O_2S + H]^+$ = 448.06889, found 448.06890

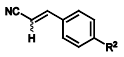


Isoquinoline-5-sulfonic acid (2-((E)-3-phenyl-allylamino)-ethyl)-amide **32**: Compound **32** was synthesized according to the general procedure using cynnamic aldehyde (191 µl, 1.36 mmol) yielding, after HPLC purification, **32** (233 mg, 0.56 mmol, 41%) as yellowish oil. ^{1}H NMR ($CDCl_3$) : δ 9.76 (bs, 1H, H6), 8.97 – 8.93 (d, 1H, H1, *J* = 6.57 *Hz*), 8.72 – 8.59 (m, 3H, H2, H3, H5), 8.05 – 7.97 (t, 1H, H4, *J* = 8.04 *Hz*), 7.34 – 7.26 (m, 5H, H_{arom}), 6.85 – 6.77 (d, 1H, PhC*H*=, *J* = 16.08 *Hz*), 6.29 – 6.21 (m, 1H, CH_2CH=), 3.85 – 3.62 (d, 2H, NCH_2, *J* = 7.30 *Hz*), 3.21 (bs, 4H, H7, H8).). ^{13}C-NMR ($CDCl_3$): δ 151.59 (C6), 139.88 (C1), 137.03 (C3), 136.57 (C9), 136.57 (C5), 135.58 (C10), 129.57 – 127.69 (CH_2*C*H=, CH_{phenyl}), 121.35 (CH, C2), 118.83 (CH=, C14), 50.30 (CH_2, C12), 47.30 (CH_2, C11), 39.92 (CH_2, C10). MS: *m/z* = 368.1 $(M+H)^+$

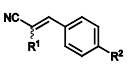


Isoquinoline-5-sulfonic acid (2-((E)-2-methyl-3-phenyl-allylamino)-ethyl)-amide **33**: Compound **33** was synthesized according to the general procedure using α-methyl cynnamic aldehyde (1.36 mmol) yielding, after HPLC purification, **33** (0.6 mmol, 44%) as yellowish oil. ^{1}H NMR ($CDCl_3$): δ 9.60 (s, 1H, H6), 8.74 (m, 2H, H1, H2), 8.64 – 8.46 (m, 2H, H3, H5), 7.99 – 7.91 (dd, 1H, H4, J_1 = 7.31 *Hz*, J_2 = 8.04 *Hz*), 7.42 – 7.17 (m, 5H, H_{phenyl}) 6.71 (s, 1H, CMe=C*H*Ph), 3.80 (s, 2H, NCH_2), 3.21 (s, 4H, H7, H8), 1.98 (s, 3H, CH_3). ^{13}C-NMR ($CDCl_3$): δ 152.9, 144.4, 137.2, 135.5, 134.2, 133.3, 133.0, 130.9, 128.7, 128-5 – 129.9, 125.8, 117.2, 57.0, 47.1, 42.1, 16.1. MS: *m/z* = 382.2 $(M+H)^+$

General procedure for the synthesis of cinnamonitriles.

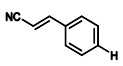
a) para-substituted cinamonitriles with the general structure  were prepared as follows:

To an ice-cold solution of NaH (516 mg, 12.9 mmol, 60% mineral oil) and NaI (1.9 g, 12.9 mmol) in DMF (40 mL) diethyl cyanomethylphosphonate (2.27 g, 12.8 mmol) was slowly added and allowed to stir for 15 minutes before addition of the aldehyde (13.5 mmol). The reaction was allowed to stir until completion (TLC 10% EtOAc/PE) and quenched by addition of freshly prepared sat. aq. Na_2HSO_3(50 mL). The mixture was diluted with H_2O (150 mL) and Et_2O (50 mL), the layers were separated, the aqueous phase washed with Et_2O (3 x 50 mL) and the combined organic phase was washed with sat. aq. bicarb. (1 x 25 mL) and brine (1 x 25 mL), dried over Na_2SO_4, filtered and concentrated. The residue was further purified by silica collumn chromatography (0 - 3% Et_2O/PE) to afford the cinnamonitriles.

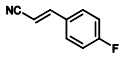
b) para-substituted, α-alkylated cinnamonitriles with the general structure  were prepared similarly to the cinnamonitriles described above with the following adaptations:

- No NaI was used

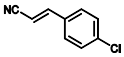
- diethyl cyanomethylphosphonate was first deprotonated at 0°C using NaH (516mg, 12.9 mmol, 60% mineral oil) and subsequently alkylated with alkyliodide (13 mmol) for 1h at r.t. after which the reaction mixture was cooled to 0°C and treated as described above to afford the α-alkylated cinnamonitriles as E/Z mixtures which were used as E/Z mixtures in the following reactions.



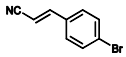
(E/Z)-Cinnamonitrile **54a** was obtained *via* method A in 91% yield as white solid (E/Z = 4/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 – 7.81 (m, 2H), 7.48 – 7.42 (m, 7H), 7.41 (s, 1H), 7.37 (s, 1H), 7.15 (d, *J* = 12.1, 1H), 5.89 (d, *J* = 16.7, 1H), 5.47 (d, *J* = 12.1, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.3, 148.5, 133.4, 133.2, 131.09, 130.7, 128.9, 128.8, 128.7, 127.2, 118.0, 117.2, 96.1, 94.8. MS: *m/z* = 130.0 $(M+H)^+$.



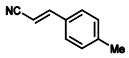
(E/Z)-3-(4-fluorophenyl)acrylonitrile **54b** was obtained *via* method A in 84 % yield as white solid with an E/Z ratio of 5/2. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.74 – 7.65 (m, 2H), 7.39 – 7.31 (m, 3H), 7.23 (d, *J* = 16.7, 1H), 7.03 – 6.94 (m, 4H), 5.75 (d, *J* = 16.7, 1H), 5.37 (d, *J* = 12.1, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.84, 164.4, 162.3, 161.9, 148.4, 146.6, 130.6, 130.5, 129.4, 129.4, 129.3, 129.0, 128.9, 117.6, 116.8, 115.6, 115.4, 115.2, 95.5, 95.5, 94.1, 77.2, 53.2. MS: *m/z* = 148.3 $(M+H)^+$.



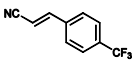
(E/Z)-3-(4-chlorophenyl)acrylonitrile **54c** was obtained *via* method A in 88 % yield as white solid with an E/Z ratio of 2/1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.5, 2H), 7.45 – 7.33 (m, 7H), 7.12 (d, *J* = 10.0, 1H), 5.88 (d, *J* = 16.7, 1H), 5.50 (d, *J* = 12.1, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0, 147.1, 137.1, 131.9, 130.1, 129.3, 129.0, 128.4, 117.7, 96.9, 95.6. MS: *m/z* = 163.9 $(M+H)^+$.



(E/Z)-3-(4-bromophenyl)acrylonitrile **54d** was obtained *via* method A in 87 % yield as a white solid with an E/Z ratio of 5/2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.6, 2H), 7.59 – 7.51 (m, 3H), 7.38 – 7.30 (m, 4H), 7.08 (d, *J* = 12.1, 1H), 5.90 (d, *J* = 16.6, 1H), 5.51 (d, *J* = 12.1, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0=1, 147.2, 132.2, 132.0, 130.2, 128.6, 125.5, 125.2, 117. 7, 97.0, 95.7. MS: *m/z* = 207.9 : 209.9 1:1 $(M+H)^+$.

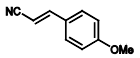


(E)-3-p-tolylacrylonitrile **54e** was obtained *via* method A in 99 % yield as white solid with an E/Z ratio of 5/2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.1, 2H), 7.25 – 7.09 (m, 7H), 6.99 (d, *J* = 12.1, 1H), 5.70 (d, *J* = 16.6, 1H), 5.30 (d, *J* = 12.1, 1H), 2.34 (s, 3H), 2.30 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.3, 147.0, 141.0, 140.7, 130.4, 130.2, 129.1, 129.0, 128.9, 128.3, 126.7, 117.8, 117.0, 94.3, 93.0, 20.7. MS: *m/z* = 144.0 $(M+H)^+$.

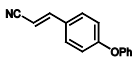


(E/Z)-3-(4-(trifluoromethyl)phenyl)acrylonitrile **54f** was obtained *via* method A in 92 % yield as yellowish solid with an E/Z ratio of 5/2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.2, 2H), 7.75 – 7.66 (m, 3H), 7.59 (d, *J* = 8.2, 2H), 7.45 (d, *J* = 16.7, 2H), 7.21 (d, *J* = 12.1, 1H), 6.02 (d, *J* = 16.7, 1H), 5.63 (d, *J* =

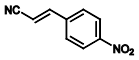
12.1, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148. 7, 146.9, 136.7, 132.4, 129.1, 127.5, 126.0, 126.0, 125.8, 125.8, 124.9, 122.2, 117.3, 116.6, 99.2, 97.9. MS: *m/z* = 197.8 $(M+H)^+$.



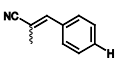
(E/Z)-3-(4-methoxyphenyl)acrylonitrile **54g**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.8, 2H), 7.27 (d, *J* = 16.6, 1H), 6.90 (d, *J* = 8.8, 2H), 5.68 (d, *J* = 16.6, 1H), 3.82 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7, 149.6, 128.8, 126.0, 118.4, 114.2, 93.0, 55.1. MS: m/z = 160.2 $(M+H)^+$



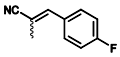
(E/Z)-3-(4-phenoxyphenyl)acrylonitrile **54h** was obtained *via* method A in 90 % yield as white solid with an E/Z ratio of 3/1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.7, 2H), 7.47 – 7.34 (m, 7H), 7.22 (t, *J* = 7.4, 1H), 7.06 (m, 9H), 5.79 (d, *J* = 16.6, 1H), 5.38 (d, *J* = 12.1, 1H). ^{13}C NMR (100 MHz, CDCl3) δ 160.23, 155.64, 149.53, 147.62, 130.83, 129.92, 129.02, 128.12, 124.33, 124.29, 119.80, 119.76, 118.23, 117.98, 94.58, 93.15. MS: *m/z* = 222.0 $(M+H)^+$.



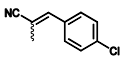
(E/Z)-3-(4-(trifluoromethyl)phenyl)acrylonitrile **54i** was obtained *via* method A in 92 % yield as yellow solid with an E/Z ratio of 2/1. ^{1}H NMR (400 MHz, CDCl3) δ 8.29 (m, 3H), 7.97 (d, *J* = 8.7, 2H), 7.66 (m, 3H), 7.49 (d, *J* = 16.7, 1H), 7.27 (d, *J* = 12.2, 1H), 6.09 (d, *J* = 16.7, 1H), 5.73 (d, *J* = 12.1, 1H). ^{13}C NMR (100 MHz, CDCl3) δ 147.71, 146.01, 139.16, 129.68, 129.57, 128.10, 124.27, 124.03, 123.81, 116.96, 100.93, 99.56, 44.16, 30.22.



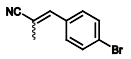
(E/Z)-2-methyl-3-phenylacrylonitrile **54j** was obtained *via* method B in 60 % yield as off white solid with an E/Z ratio of 1/1. ^{1}H NMR (400 MHz, CDCl3) δ 7.74 – 7.68 (m, 2H), 7.46 – 7.33 (m, 6H), 7.31 (d, *J* = 7.0, 2H), 7.16 (s, 1H), 6.92 (s, 1H), 2.12 (s, 3H), 2.10 (d, *J* = 1.3, 3H). ^{13}C NMR (100 MHz, CDCl3) δ 149.96, 148.20, 143.85, 143.55, 133.65, 133.46, 130.72, 130.47, 129.35, 128.93, 128.86, 128.64, 128.56, 128.46, 128.32, 128.25, 127.98, 126.97, 120.81, 118.78, 109.20, 105.63, 95.95, 94.64, 21.63, 16.32.



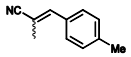
(E/Z)-3-(4-fluorophenyl)-2-methylacrylonitrile **54k** was obtained *via* method B in 45 % yield as colorless oil with an E/Z ratio of 1/1. ^{1}H NMR (400 MHz, CDCl3) δ 7.72 – 7.48 (m, 2H), 7.33 – 7.18 (m, 2H), 7.13 – 6.92 (m, 5H), 6.87 – 6.77 (m, 1H), 2.11 – 2.00 (m, 6H). ^{13}C NMR (100 MHz, CDCl3) δ 163.93, 163.62, 161.44, 161.13, 142.48, 142.11, 130.99, 130.91, 129.99, 129.91, 129.83, 129.72, 120.62, 118.58, 115.36, 115.15, 108.95, 105.38, 21.29, 16.07.



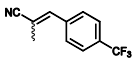
(E/Z)-3-(4-chlorophenyl)-2-methylacrylonitrile **54l** was obtained *via* method B in 38 % yield as yellowish solid with an E/Z ratio of 3/2. ^{1}H NMR (400 MHz, CDCl3) δ 7.56 (d, *J* = 8.5, 2H), 7.34 – 7.24 (m, 4H), 7.19 (d, *J* = 8.5, 2H), 7.05 (s, 1H), 6.81 (s, 1H), 2.07 (s, 3H), 2.04 (d, *J* = 1.0, 3H). ^{13}C NMR (100 MHz, CDCl3) δ 142.37, 142.01, 134.97, 134.67, 132.03, 131.86, 130.19, 129.19, 128.42, 120.45, 118.40, 109.80, 106.36, 21.54, 16.29. MS: *m/z* = 177.9 $(M+H)^+$.



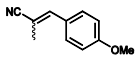
(E/Z)-3-(4-bromophenyl)-2-methylacrylonitrile **54m** was obtained *via* method B in 63 % yield as white solid with an E/Z ratio of 1/1. ^{1}H NMR (400 MHz, CDCl3) δ 7.57 – 7.45 (m, 6H), 7.17 (d, *J* = 8.4, 2H), 7.09 (s, 1H), 6.85 (s, 1H), 2.12 (s, 3H), 2.09 (s, 3H). ^{13}C NMR (100 MHz, CDCl3) δ 142.67, 142.30, 132.59, 132.39, 131.60, 131.57, 130.50, 129.54, 123.59, 123.25, 120.60, 118.56, 110.10, 106.68, 21.82, 16.53.



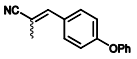
(E/Z)-2-methyl-3-p-tolylacrylonitrile **54n** was obtained *via* method B in 35 % yield as colorless oil with an E/Z ratio of 1/1. ^{1}H NMR (400 MHz, CDCl3) δ 7.63 (d, *J* = 8.1, 1H), 7.24 – 7.16 (m, 7H), 7.12 (s, 1H), 6.87 (s, 1H), 2.38 (s, 3H), 2.37 (s, 3H), 2.11 (s, 6H). ^{13}C NMR (100 MHz, CDCl3) δ 143.83, 143.53, 139.60, 139.13, 130.95, 130.76, 129.01, 128.96, 128.65, 127.98, 121.06, 118.99, 108.03, 104.26, 21.57, 20.91, 16.36. MS: *m/z* = 157.9 $(M+H)^{+}$.



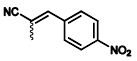
(E/Z)-2-methyl-3-(4-(trifluoromethyl)phenyl)acrylonitrile **54o** was obtained *via* method B in 58 % yield as yellow oil with an E/Z ratio of 1/1. Yield 58%, colorless oil. ^{1}H NMR (400 MHz, CDCl3) δ 7.77 (d, *J* = 8.2, 2H), 7.65 (d, *J* = 8.1, 2H), 7.61 (d, *J* = 8.1, 2H), 7.42 (d, *J* = 8.1, 2H), 7.20 (s, 1H), 6.97 (s, 1H), 2.16 (s, 3H), 2.11 (s, 3H). ^{13}C NMR (100 MHz, CDCl3) δ 148.67, 146.93, 136.67, 132.35, 129.08, 127.52, 126.00, 125.96, 125.79, 125.75, 124.89, 122.19, 117.32, 116.55, 99.16, 97.90. MS: *m/z* = 212.1 $(M+H)^{+}$.



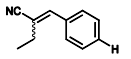
(E/Z)-3-(4-methoxyphenyl)-2-methylacrylonitrile **54p** was obtained *via* method B in 20 % yield as yellow oil with an E/Z ratio of 1/0. ^{1}H NMR (400 MHz, CDCl3) δ 7.63 (d, *J* = 8.8, 2H), 6.86 (d, *J* = 8.8, 2H), 6.78 (s, 1H), 3.74 (s, 3H), 2.04 (s, 3H). ^{13}C NMR (100 MHz, CDCl3) δ 160.28, 143.07, 129.61, 126.14, 119.26, 113.63, 102.35, 54.76, 21.39. MS: *m/z* = 174.1 $(M+H)^{+}$.



(E/Z)-2-methyl-3-(4-phenoxyphenyl)acrylonitrile **54q** was obtained *via* method B in 45 % yield as colorless oil with an E/Z ratio of 1/1. ^{1}H NMR (400 MHz, CDCl3) δ 7.72 (d, *J* = 8.7, 2H), 7.43 – 7.33 (m, 4H), 7.30 (d, *J* = 8.7, 2H), 7.18 (dd, *J* = 7.0, 13.5, 2H), 7.13 (s, 1H), 7.10 – 6.97 (m, 8H), 6.87 (s, 1H), 2.12 (s, 3H), 2.11 (s, 3H). ^{13}C NMR (100 MHz, CDCl3) δ 158.34, 158.02, 155.58, 142.99, 142.67, 130.81, 129.73, 129.54, 129.50, 128.37, 128.20, 123.77, 123.67, 121.01, 119.23, 119.20, 118.95, 117.67, 117.65, 107.67, 103.94, 21.48, 16.33. MS: *m/z* = 236.1 $(M+H)^{+}$.

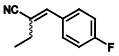


(E/Z)-2-methyl-3-(4-nitrophenyl)acrylonitrile **54r** was obtained *via* method B in 56 % yield as yellow oil with an E/Z ratio of 1/1. ^{1}H NMR (400 MHz, CDCl3) δ 8.30 – 8.16 (m, 4H), 7.84 (d, *J* = 8.6, 2H), 7.51 (d, *J* = 8.7, 2H), 7.26 (s, 1H), 7.05 (s, 1H), 2.22 (s, 3H), 2.16 (s, 3H). ^{13}C NMR (100 MHz, CDCl3) δ 147.71, 147.48, 141.61, 141.20, 139.94, 139.62, 129.88, 128.98, 123.72, 123.63, 120.01, 118.06, 113.42, 110.79, 22.09, 16.74. MS: *m/z* = 188.9 $(M+H)^{+}$.

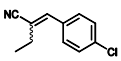


(E/Z)-2-benzylidenebutanenitrile **54s** was obtained *via* method B in 49 % yield as colorless oil with an E/Z ratio of 1/1. ^{1}H NMR (400 MHz, CDCl3) δ 7.77 – 7.70 (m, 2H), 7.45 – 7.33 (m, 6H), 7.28 (d, *J* = 7.1, 2H), 7.15 (s, 1H), 6.93 (s, 1H), 2.47 (dd, *J* = 7.5, 15.0, 2H), 2.44 (dd, *J* = 7.5, 15.0, 2H), 1.28 – 1.21 (m, 6H).

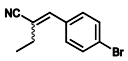
^{13}C NMR (100 MHz, CDCl3) δ 142.95, 141.98, 133.59, 133.45, 129.32, 128.76, 128.65, 128.28, 128.24, 128.07, 119.64, 118.22, 116.71, 112.42, 29.09, 22.48, 12.50, 12.30. MS: *m/z* = 158.0 $(M+H)^+$.



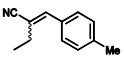
(E/Z)-2-(4-fluorobenzylidene)butanenitrile **54t** was obtained *via* method B in 55 % yield as colorless oil with an E/Z ratio of 4/3. ^{1}H NMR (400 MHz, CDCl3) δ 7.73 – 7.66 (m, 2H), 7.31 – 7.23 (m, 2H), 7.11 – 7.01 (m, 4H), 6.88 (s, 1H), 2.49 – 2.35 (m, 4H), 1.27 – 1.19 (m, 6H). ^{13}C NMR (100 MHz, CDCl3) δ 164.16, 163.83, 161.67, 161.34, 141.87, 140.79, 130.86, 130.77, 130.27, 130.18, 129.88, 129.85, 119.65, 118.25, 116.76, 115.59, 115.55, 115.37, 115.34, 112.38, 29.12, 22.54, 12.55, 12.32. MS: *m/z* = 176.1 $(M+H)^+$.



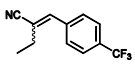
(E/Z)-2-(4-chlorobenzylidene)butanenitrile **54u** was obtained *via* method B in 39 % yield as colorless oil with an E/Z ratio of 1/1. ^{1}H NMR (400 MHz, CDCl3) δ 7.37 – 7.30 (m, 7H), 7.20 (d, *J* = 8.5, 2H), 7.09 (s, 1H), 2.48 – 2.37 (m, 4H), 1.26 – 1.19 (m, 6H). ^{13}C NMR (100 MHz, CDCl3) δ 141.68, 140.62, 136.68, 134.75, 132.11, 131.68, 130.06, 129.87, 129.41, 128.94, 128.75, 128.55, 128.25, 119.48, 117.49, 117.45, 29.13, 22.59, 12.49, 12.32. MS: *m/z* = 191.1 $(M+H)^+$.



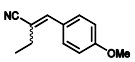
(E/Z)-2-(4-bromobenzylidene)butanenitrile **54v** was obtained *via* method B in 64 % yield as colorless oil with an E/Z ratio of 1/1. 1H NMR (400 MHz, CDCl3) δ 7.59 – 7.55 (m, 2H), 7.54 – 7.47 (m, 4H), 7.19 – 7.13 (m, 2H), 7.10 (s, 1H), 6.87 (s, 1H), 2.49 – 2.39 (m, 4H), 1.27 – 1.22 (m, 6H). 13C NMR (100 MHz, CDCl3) δ 141.98, 140.90, 132.67, 132.49, 132.20, 131.74, 131.72, 130.75, 130.40, 129.78, 123.74, 123.30, 119.66, 118.22, 117.73, 113.57, 29.40, 22.80, 12.69, 12.54. MS: *m/z* = 235.9 : 238.1 1:1 $(M+H)^+$.



(E/Z)-2-(4-methylbenzylidene)butanenitrile **54w** was obtained *via* method B in 16 % yield as yellow oil with an E/Z ratio of 1/1. ^{1}H NMR (400 MHz, CDCl3) δ 7.66 (d, *J* = 8.1, 2H), 7.24 – 7.19 (m, 4H), 7.13 (s, 1H), 6.91 (s, 1H), 2.51 (q, *J* = 7.5, 3H), 2.47 – 2.41 (m, 3H), 2.39 (s, 3H), 2.38 (s, 3H), 1.30 – 1.23 (m, 6H). ^{13}C NMR (100 MHz, CDCl3) δ 143.10, 142.09, 139.71, 139.15, 130.98, 130.83, 129.09, 129.07, 128.84, 128.19, 120.01, 118.56, 115.79, 111.25, 29.20, 22.62, 21.02, 20.96, 12.68, 12.41. MS: *m/z* = 172.0 $(M+H)^+$.

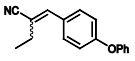


(E/Z)-2-(4-(trifluoromethyl)benzylidene)butanenitrile **54x** was obtained *via* method B in 60 % yield as colorless oil with an E/Z ratio of 3/2. ^{1}H NMR (400 MHz, CDCl3) δ 7.81 (d, *J* = 8.2, 2H), 7.68 – 7.61 (m, 4H), 7.40 (d, *J* = 8.2, 2H), 7.20 (s, 1H), 6.99 (s, 1H), 2.52 – 2.42 (m, 4H), 1.30 – 1.23 (m, 6H). ^{13}C NMR (100 MHz, CDCl3) δ 141.50, 140.44, 137.31, 137.10, 131.13, 130.81, 130.48, 129.09, 128.55, 127.70, 125.43, 125.40, 125.36, 124.99, 122.29, 119.47, 119.24, 117.85, 115.83, 29.35, 22.81, 12.42, 12.36. MS: *m/z* = 226.2 $(M+H)^+$.

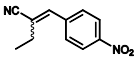


(E/Z)-2-(4-methoxybenzylidene)butanenitrile **54y** was obtained *via* method B in 51 % yield as colorless oil with an E/Z ratio of 1/1. ^{1}H NMR (400 MHz, CDCl3) δ 7.69 (d, *J* = 8.8, 2H), 7.25 (d, *J* = 8.8, 2H), 7.07 (s, 1H), 6.93 – 6.88 (m, 4H), 6.84 (s, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 2.48 (q, *J* = 7.5, 2H), 2.39 (q, *J* = 7.5, 2H), 1.28 – 1.19 (m, 6H). ^{13}C NMR (100 MHz, CDCl3) δ 160.47, 160.07, 142.78, 141.74, 130.66, 129.90,

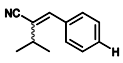
126.42, 126.30, 120.35, 118.90, 114.24, 113.86, 113.82, 109.52, 55.00, 54.98, 29.38, 29.15, 22.60, 12.79, 12.41. MS: *m/z* = 187.9 $(M+H)^+$.



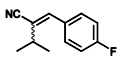
(E/Z)-2-(4-phenoxybenzylidene)butanenitrile **54z** was obtained *via* method B in 51 % yield as yellow oil with an E/Z ratio of 1/1. ^{1}H NMR (400 MHz, CDCl3) δ 7.82 (d, *J* = 6.9, 2H), 7.72 (d, *J* = 8.8, 1H), 7.44 – 6.95 (m, 16H), 6.89 (s, 1H), 2.49 (q, *J* = 7.5, 2H), 2.40 (q, *J* = 7.5, 2H), 1.29 – 1.21 (m, 6H). ^{13}C NMR (100 MHz, CDCl3) δ 190.27, 158.48, 158.14, 155.72, 154.75, 142.35, 141.31, 131.55, 130.93, 130.66, 129.94, 129.79, 129.61, 129.57, 128.38, 128.28, 124.55, 123.83, 123.74, 119.98, 119.94, 119.32, 119.28, 118.52, 117.81, 117.19, 116.01, 115.40, 110.89, 29.09, 22.55, 12.66, 12.36. MS: *m/z* = 250.1 $(M+H)^+$.



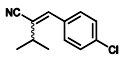
(E/Z)-2-(4-nitrobenzylidene)butanenitrile **54aa** was obtained *via* method B in 55 % yield as yellow oil with an E/Z ratio of 1/1. ^{1}H NMR (400 MHz, CDCl3) δ 8.20 – 8.12 (m, 4H), 7.81 (d, *J* = 8.8, 2H), 7.45 (d, *J* = 8.7, 2H), 7.20 (s, 1H), 7.03 (s, 1H), 2.51 – 2.41 (m, 4H), 1.26 – 1.18 (m, 6H). ^{13}C NMR (100 MHz, CDCl3) δ 147.47, 147.26, 140.60, 139.85, 139.59, 139.51, 129.58, 129.51, 128.93, 123.47, 123.44, 120.41, 118.80, 117.43, 117.26, 29.27, 22.79, 12.25. MS: *m/z* = 203.0 $(M+H)^+$.



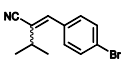
(E/Z)-2-benzylidene-3-methylbutanenitrile **54ab** was obtained *via* method B in 67 % yield as colorless oil with an E/Z ratio of 3/2. ^{1}H NMR (400 MHz, CDCl3) δ 7.78 – 7.72 (m, 2H), 7.47 – 7.33 (m, 6H), 7.29 (d, *J* = 7.0, 2H), 7.11 (s, 1H), 6.97 (s, 1H), 3.19 – 3.08 (m, 1H), 2.74 – 2.62 (m, 1H), 1.27 (d, *J* = 6.8, 6H), 1.23 (d, *J* = 6.8, 6H). ^{13}C NMR (100 MHz, CDCl3) δ 141.74, 140.65, 133.74, 133.55, 129.41, 128.75, 128.63, 128.51, 128.38, 128.29, 122.80, 118.37, 117.96, 117.48, 34.72, 27.31, 21.16, 21.07. MS: *m/z* = 172.2 $(M+H)^+$.



(E/Z)-2-(4-fluorobenzylidene)-3-methylbutanenitrile **54ac** was obtained *via* method B in 67 % yield as colorless oil with an E/Z ratio of 3/2. ^{1}H NMR (400 MHz, CDCl3) δ 7.74 – 7.67 (m, 2H), 7.29 – 7.23 (m, 2H), 7.11 – 7.01 (m, 5H), 6.91 (s, 1H), 3.06 (hept, *J* = 6.7, 1H), 2.65 (hept, *J* = 6.8, 1H), 1.23 (d, *J* = 6.8, 6H), 1.20 (d, *J* = 6.7, 6H). ^{13}C NMR (100 MHz, CDCl3) δ 140.33, 139.20, 135.13, 134.69, 132.15, 132.04, 129.86, 129.56, 128.61, 128.56, 123.46, 118.72, 118.07, 117.22, 34.72, 27.39, 21.10, 21.00. MS: *m/z* = 189.9 $(M+H)^+$.

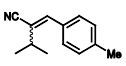


(E/Z)-2-(4-chlorobenzylidene)-3-methylbutanenitrile **54ad** was obtained *via* method B in 34 % yield as colorless oil with an E/Z ratio of 3/2. ^{1}H NMR (400 MHz, CDCl3) δ 7.63 (d, *J* = 8.6, 2H), 7.37 – 7.28 (m, 4H), 7.19 (d, *J* = 8.5, 2H), 7.02 (s, 1H), 6.89 (s, 1H), 3.04 (hept, *J* = 6.7, 1H), 2.65 (hept, *J* = 6.8, 1H), 1.23 (d, *J* = 6.9, 6H), 1.19 (d, *J* = 6.8, 6H). ^{13}C NMR (100 MHz, CDCl3) δ 140.33, 139.20, 135.13, 134.69, 132.15, 132.04, 129.86, 129.56, 128.61, 128.56, 123.46, 118.72, 118.07, 117.22, 34.72, 27.39, 21.10, 21.00. MS: *m/z* = 206.1 $(M+H)^+$.

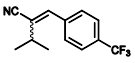


(E/Z)-2-(4-bromobenzylidene)-3-methylbutanenitrile **54ae** was obtained *via* method B in 73 % yield as yellowish oil with an E/Z ratio of 3/2. ^{1}H NMR (400 MHz, CDCl3) δ 7.56 (d, *J* = 8.6, 2H), 7.52 – 7.45 (m, 4H), 7.12 (d, *J* = 8.4, 2H), 7.01 (s, 1H), 6.88 (s, 1H), 3.03 (hept, *J* = 6.7, 1H), 2.65 (hept, *J* = 6.7,

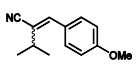
1H), 1.23 (d, *J* = 6.8, 6H), 1.19 (d, *J* = 6.8, 6H). ^{13}C NMR (100 MHz, CDCl3) δ 140.49, 139.36, 132.60, 132.46, 131.63, 131.59, 130.10, 129.79, 123.57, 123.04, 118.89, 118.13, 117.26, 34.78, 27.45, 21.14, 21.06. MS: *m/z* = 249.8 : 252.0 1:1 $(M+H)^+$.



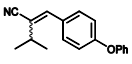
(E/Z)-3-methyl-2-(4-methylbenzylidene)butanenitrile **54af** was obtained *via* method B in 67 % yield as yellow oil with an E/Z ratio of 1/1. ^{1}H NMR (400 MHz, CDCl3) δ 7.67 (d, *J* = 8.2, 2H), 7.25 – 7.17 (m, 6H), 7.07 (s, 1H), 6.93 (s, 1H), 3.16 (hept, *J* = 6.7, 1H), 2.67 (hept, *J* = 6.8, 1H), 2.39 (s, 3H), 2.38 (s, 3H), 1.27 (d, *J* = 6.8, 6H), 1.24 (d, *J* = 6.8, 6H). ^{13}C NMR (100 MHz, CDCl3) δ 141.72, 140.58, 139.61, 138.92, 130.92, 130.80, 129.04, 128.57, 128.26, 121.80, 118.53, 117.64, 116.62, 34.65, 27.24, 21.16, 21.02. MS: *m/z* = 185.9 $(M+H)^+$.



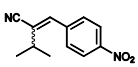
(E/Z)-3-methyl-2-(4-(trifluoromethyl)benzylidene)butanenitrile **54ag** was obtained *via* method B in 62 % yield as yellow oil with an E/Z ratio of 3/2. ^{1}H NMR (400 MHz, CDCl3) δ 7.82 (d, *J* = 8.3, 2H), 7.69 – 7.61 (m, 4H), 7.40 (d, *J* = 8.2, 2H), 7.14 (s, 1H), 7.01 (s, 1H), 3.05 (hept, *J* = 6.7, 1H), 2.72 (hept, *J* = 6.8, 1H), 1.28 (d, *J* = 6.8, 6H), 1.22 (d, *J* = 6.8, 6H). ^{13}C NMR (100 MHz, CDCl3) δ 140.13, 139.04, 137.42, 137.17, 131.14, 130.81, 130.44, 128.89, 128.66, 127.72, 125.46, 125.42, 125.39, 125.01, 122.31, 121.24, 119.60, 117.88, 117.06, 34.96, 27.72, 21.06, 21.03. MS: *m/z* = 239.9 $(M+H)^+$.



(E/Z)-2-(4-methoxybenzylidene)-3-methylbutanenitrile **54ah** was obtained *via* method B in 84 % yield as yellow oil with an E/Z ratio of 1/1. ^{1}H NMR (400 MHz, CDCl3) δ 7.71 (d, *J* = 8.8, 2H), 7.25 (d, *J* = 8.8, 2H), 7.03 (s, 1H), 6.95 – 6.87 (m, 5H), 3.82 (s, 3H), 3.82 (s, 3H), 3.15 (hept, *J* = 6.7, 1H), 2.64 (hept, *J* = 6.8, 1H), 1.27 – 1.21 (m, 12H). ^{13}C NMR (100 MHz, CDCl3) δ 160.51, 160.05, 141.55, 140.34, 130.47, 130.07, 126.41, 126.35, 120.54, 118.99, 118.11, 115.06, 113.95, 113.87, 55.06, 55.04, 34.73, 27.29, 21.37, 21.18. MS: *m/z* = 202.0 $(M+H)^+$.



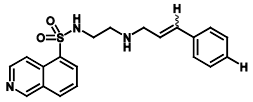
(E/Z)-3-methyl-2-(4-phenoxybenzylidene)butanenitrile **54ai** was obtained *via* method B in 34 % yield as yellow oil with an E/Z ratio of 1/1. ^{1}H NMR (400 MHz, CDCl3) δ 7.75 (d, *J* = 5.8, 2H), 7.42 – 7.35 (m, 4H), 7.29 (d, *J* = 8.6, 2H), 7.22 – 7.15 (m, 2H), 7.11 – 6.99 (m, 9H), 6.94 (s, 1H), 3.17 (hept, *J* = 6.7, 1H), 2.69 (hept, *J* = 6.8, 1H), 1.30 – 1.24 (m, 12H). ^{13}C NMR (100 MHz, CDCl3) δ 158.52, 158.14, 155.82, 155.76, 141.10, 139.92, 130.47, 130.11, 129.67, 129.63, 128.40, 128.36, 123.88, 123.78, 121.61, 119.38, 119.32, 118.62, 117.91, 117.76, 116.43, 34.71, 27.32, 21.28, 21.13. MS: *m/z* = 263.9 $(M+H)^+$.



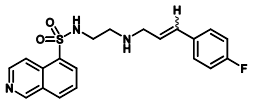
(E/Z)-3-methyl-2-(4-nitrobenzylidene)butanenitrile **54aj** was obtained *via* method B in 23 % yield as colorless oil with an E/Z ratio of 5/1. ^{1}H NMR (400 MHz, CDCl3) δ 8.18 (d, *J* = 8.8, 2H), 8.15 (d, *J* = 8.8, 2H), 7.82 (d, *J* = 8.8, 2H), 7.43 (d, *J* = 8.6, 2H), 7.13 (s, 1H), 7.04 (s, 1H), 3.00 (hept, *J* = 6.7, 1H), 2.71 (hept, *J* = 6.7, 1H), 1.23 (d, *J* = 6.9, 6H), 1.18 (d, *J* = 6.7, 6H). ^{13}C NMR (100 MHz, CDCl3) δ 147.46, 147.26, 140.00, 139.95, 139.67, 139.17, 138.08, 130.19, 129.47, 129.38, 129.03, 123.44, 122.98, 122.60, 117.44, 116.63, 34.86, 27.70, 23.85, 21.38, 20.89. MS: *m/z* = 216.9 $(M+H)^+$.

General procedure for the transimination

A solution of nitrile (1 mmol) in anhydrous Et_2O (5 mL) is cooled to -78°C before dropwise addition of DiBAl-H (2 mL, 2 mmol, 1M soln. in hexanes) and the reaction mixture was allowed to warm to 0°C in 30 min. under stirring. The reaction mixture was cooled to -100°C followed by rapid addition of MeOH (5 mL). After 5 min., a soln. of amine **45** (2 mmol) in MeOH (5 mL) was slowly added and the reaction mixture was allowed to stir at r.t. for 3 h. Then, the reaction mixture was cooled to -18°C and $NaBH_4$ (2mmol) was added and the reaction mixture was allowed to stir for 16 h. at r.t.. The reaction mixture was diluted with 0.5M aq. NaOH (10 mL), the layers were separated and the aqueous phase was washed with $CHCl_3$ (3 x 10 mL). The combined organic phase was washed with H_2O (3 x 10 mL) and brine (5 mL), dried, filtered and concentrated. The residue was purified by HPLC. The LCMS spectrum often showed the presence of a minor sideproduct with a mass of four daltons higher than the expected mass of the desired product. This probably arises from reduction of the isoquinoline ring towards the 1,2,3,4-tetrahydroisoquinoline analogue under the agency of residual $NaBH_4$ and TFA from the HPLC eluens. This product could, in most cases, be separated from the desired product except for **55l**, **55q** and **55u**. The Z isomer usually has a shorter retention time then the E isomer. This allowed, in most cases, the isolation of the individual isomers. However, in some cases, neither of the isomers could be obtained in >95% purity and were used as mixtures. The double bond configuration could be established based on the coupling constants of the double bond protons (**55a** – **55i**) or by NOESY analysis (**55j** – **55aj**).

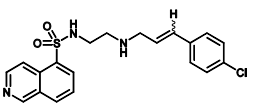


(E)-N-(2-(cinnamylamino)ethyl)isoquinoline-5-sulfonamide **55a**. Yield: 152.2 mg, 316 µmol, 31.6 %. ^{1}H NMR (400 *MHz*, MeOH) δ 9.59 (bs, 1H), 8.79 (d, *J* = 6.3, 1H), 8.68 (bs, 1H), 8.61 (d, *J* = 7.4, 1H), 8.49 (d, *J* = 8.2, 1H), 7.96 – 7.88 (m, 1H), 7.41 (d, *J* = 6.8, 2H), 7.35 – 7.25 (m, 3H), 6.81 (d, *J* = 15.8, 1H), 6.31 – 6.22 (m, 1H), 3.84 (d, *J* = 7.2, 2H), 3.24 (d, *J* = 4.4, 2H), 3.21 (d, *J* = 4.3, 2H). ^{13}C NMR (100 *MHz*, MeOH) δ 152.05, 140.17, 139.98, 137.00, 136.69, 136.05, 135.85, 133.84, 129.76, 129.70, 129.14, 127.81, 121.10, 118.98, 50.44, 49.85, 47.44, 40.07. HRMS: calcd for [C20H21N3O2S + H]+ = 368.14272 , found 368.14286.



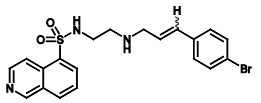
(E)-N-(2-(3-(4-fluorophenyl)allylamino)ethyl)isoquinoline-5-sulfonamide **55b.** Yield: 228.7 mg, 458 µmol, 34%.

^{1}H-NMR (MeOD): δ 9.42 (s, 1H, H6), 8.63 – 8.59 (m, 2H, H1/2), 8.50 – 8.49 (d, 1H, J_1 = 7.38 *Hz*, H5), 8.37 – 8.35 (d, 1H, J_1 = 8.22 *Hz*, H3), 7.81 – 7.86 (t, 1H, J_1 = 7.80 *Hz*, H4), 7.39 – 7.37 (dd, 2H, J_1 = 5.46 *Hz*, J_2 = 8.58 *Hz*, H11), 7.00 – 6.97 (t, 1H, J_1 = 8.73 *Hz*, H12), 6.76 – 6.74 (d, 1H, J_1 = 15.84 *Hz*, H10), 6.20 – 6.15 (dt, 1H, J_1 = 7.74 *Hz*, J_2 = 15.84 *Hz*, H13), 3.81 – 3.80 (d, 2H, J_1 = 7.26 *Hz*, H9), 3.21 – 3.15 (m, 4H); ^{13}C-NMR (MeOD): δ 169.88, 167.42, 156.13, 143.83, 143.16, 141.85, 140.69, 140.43, 138.57, 137.61, 134.68, 134.24, 133.89, 125.96, 123.43, 121.85, 121.05, 120.84, 54.88, 54.34, 51.9, 44.57; MS: *m/z* = 386.13 $(M+H)^+$. HRMS: calcd for $[C_{20}H_{20}FN_3O_2S + H]^+$ = 386.13330 , found 386.13377.



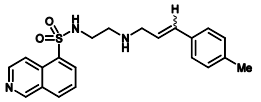
(E)-N-(2-(3-(4-chlorophenyl)allylamino)ethyl)isoquinoline-5-sulfonamide **55c.** Yield: 93.7 mg, 182 µmol, 18.2 %. ^{1}H-NMR (MeOD): δ 9.70 (bs, 1H, H6), 8.87 – 8.86 (d, 1H,

H2, J_1 = 5.94 *Hz*), 8.70 (bs, 1H, H1), 8.65 – 8.64 (d, 1H, H5, J_1 = 7.32 *Hz*), 8.58 – 8.56 (d, 1H, H3, J_1 = 8.28 *Hz*), 7.98 – 7.96 (t, 1H, H4, $J_1 = J_2$ = 7.80 *Hz*), 7.40 – 7.38 (d, 2H, H11, J_1 = 8.40 *Hz*), 7.30 – 7.28 (d, 2H, H12, J_1 = 8.40 *Hz*), 6.80 – 6.77 (d, 1H, H10, J_1 = 15.84 *Hz*), 6.28 – 6.24 (dt, 1H, H13, J_1 = 7.20 *Hz*, J_2 = 7.80 *Hz*, J_3 = 15.84 *Hz*), 3.82 – 3.81 (d, 2H, H9, J_1 = 7.14 *Hz*), 3.19 – 3.14 (m, 4H, H7/8); ^{13}C-NMR (MeOD): δ 151.43, 138.61, 137.8, 136.43, 136.15, 135.54, 135.44, 129.87, 129.75, 129.33, 121.93, 120.02, 50.35, 47.55, 40.12; MS: *m/z* = 402.27, 404.07 3:1 $(M+H)^+$; HRMS: calcd for $[C_{20}H_{20}ClN_3O_2S + H]^+$ = 402.10375 , found 402.10349

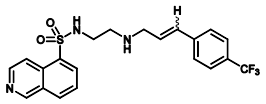


(E)-N-(2-(3-(4-bromophenyl)allylamino)ethyl)isoquinoline-5-sulfonamide, **55d**. Yield: 108.5 mg, 194 µmol, 18%

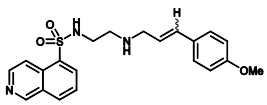
^{1}H NMR (600 MHz, MeOD) δ 9.67 (s, 1H), 8.83 (d, *J* = 5.8, 1H), 8.69 (s, 1H), 8.63 (d, *J* = 6.6, 1H), 8.54 (d, *J* = 8.2, 1H), 7.95 (t, *J* = 7.8, 1H), 7.44 (d, *J* = 8.5, 2H), 7.32 (d, *J* = 8.5, 2H), 6.77 (d, *J* = 15.9, 1H), 6.27 (dt, *J* = 7.2, 7.2, 14.7, 1H), 3.81 (d, *J* = 7.2, 2H), 3.22 – 3.15 (m, 4H). ^{13}C NMR (150 MHz, MeOD) δ 152.21, 140.42, 138.68, 136.96, 136.08, 135.93, 135.91, 133.88, 132.87, 129.58, 129.16, 123.53, 120.12, 50.35, 49.85, 49.43, 49.28, 49.14, 49.00, 48.86, 48.72, 48.57, 47.57, 40.11. HRMS: calcd for $[C_{20}H_{20}BrN_3O_2S + H]^+$ = 446.05324, found 446.05330.



(E)-N-(2-(3-p-tolylallylamino)ethyl)isoquinoline-5-sulfonamide **55e.** Yield: 189 mg, 382 µmol, 38%. ^{1}H NMR (600 MHz, MeOD) δ 9.43 (s, 1H), 8.62 (s, 2H), 8.49 (d, *J* = 7.3, 1H), 8.35 (d, *J* = 8.2, 1H), 7.79 (t, *J* = 7.8, 1H), 7.26 (d, *J* = 8.0, 2H), 7.08 (d, *J* = 7.9, 2H), 6.73 (d, *J* = 15.8, 1H), 6.17 (dt, 1H), 3.79 (d, *J* = 7.2, 2H), 3.19 (d, *J* = 4.6, 2H), 3.17 (d, *J* = 4.6, 2H). ^{13}C NMR (100 MHz, MeOH) δ 139.97, 139.92, 137.27, 136.17, 135.94, 134.01, 133.89, 130.31, 129.34, 127.76, 117.80, 50.54, 49.43, 49.21, 49.00, 48.79, 48.57, 48.36, 47.38, 40.07, 21.23. HRMS: calcd for $[C_{21}H_{23}N_3O_2S + H]^+$ = 382.15837, found 382.15876.

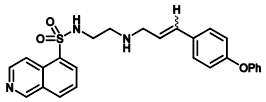


(E)-N-(2-(3-(4-(trifluoromethyl)phenyl)allylamino)ethyl)isoquinoline-5-sulfonamide **55f**. Yield: 77mg, 140 µmol, 13% ^{1}H NMR (600 MHz, MeOD) δ 9.66 (s, 1H), 8.82 (d, *J* = 5.6, 1H), 8.70 (s, 1H), 8.62 (d, *J* = 7.4, 1H), 8.54 (d, *J* = 8.3, 1H), 7.95 (t, *J* = 7.8, 1H), 7.61 (s, 4H), 6.90 (d, *J* = 15.9, 1H), 6.45 – 6.38 (m, 1H), 3.87 (d, *J* = 7.1, 2H), 3.20 (s, 4H). ^{13}C NMR (150 MHz, MeOD) δ 152.52, 141.04, 140.63, 138.27, 136.73, 135.99, 135.85, 133.74, 131.68, 131.47, 131.25, 131.04, 130.03, 128.99, 128.39, 128.21, 126.67, 126.64, 126.62, 126.41, 124.61, 122.30, 120.88, 50.24, 49.85, 49.43, 49.28, 49.14, 49.00, 48.86, 48.72, 48.57, 47.71, 40.13. HRMS: calcd for $[C_{21}H_{20}F_3N_3O_2S + H]^+$ =436.13011, found 436.13001.

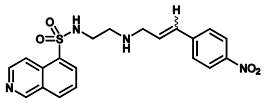


(E)-N-(2-(3-(4-methoxyphenyl)allylamino)ethyl)isoquinoline-5-sulfonamide **55g**. Yield: 234.5 mg, 459 µmol, 46% ^{1}H NMR (600 MHz, MeOD) δ 9.32 (s, 1H), 8.58 (s, 1H), 8.54 (d, *J* = 5.3, 1H), 8.45 (d, *J* = 7.3, 1H), 8.29 (d, *J* = 8.2, 1H), 7.74 (t, *J* = 7.8, 1H), 7.29 (d, *J* = 8.6, 2H), 6.80 (d, *J* = 8.6, 2H), 6.69 (d, *J* = 15.8, 1H), 6.10 – 6.03 (m, 1H), 3.78 (d, *J* = 7.3, 2H), 3.72 (s, 3H), 3.20 (t, *J* = 9.2, 2H), 3.17 (d, *J* = 4.8, 2H). ^{13}C NMR (100 MHz, MeOH) δ 161.48, 152.91, 142.13, 139.66, 136.05, 135.64, 135.50, 133.16, 129.28, 129.17, 128.45, 120.18, 116.32, 115.02, 55.69, 50.61, 49.85, 49.63,

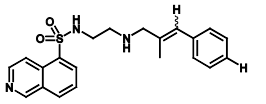
49.43, 49.21, 49.00, 48.79, 48.57, 48.36, 47.30, 40.04. HRMS: calcd for $[C_{21}H_{24}N_3O_3S + H]^+$ = 398.15329, found 398.15289.



(E)-N-(2-(3-(4-phenoxyphenyl)allylamino)ethyl)isoquinoline-5-sulfonamide **55h**. Yield: 133 mg, 232 µmol, 21% ^{1}H NMR (600 MHz, MeOD) δ 9.28 (s, 1H), 8.49 (s, 2H), 8.37 (d, *J* = 7.3, 1H), 8.24 (d, *J* = 8.2, 1H), 7.67 (t, *J* = 7.8, 1H), 7.26 (d, *J* = 8.7, 2H), 7.19 (t, *J* = 8.0, 2H), 6.97 (t, *J* = 7.4, 1H), 6.85 – 6.80 (m, 2H), 6.76 (d, *J* = 8.7, 2H), 6.65 (d, *J* = 15.8, 1H), 6.08 – 6.01 (m, 1H), 3.69 (d, *J* = 7.3, 2H), 3.07 (s, 4H). ^{13}C NMR (150 MHz, MeOD) δ 159.29, 157.86, 153.45, 143.26, 139.23, 135.62, 135.47, 135.36, 132.89, 131.75, 130.91, 130.80, 130.38, 129.44, 128.14, 124.79, 120.19, 119.69, 119.46, 117.86, 50.48, 49.85, 49.43, 49.28, 49.14, 49.00, 48.86, 48.72, 48.57, 47.40, 40.04. HRMS: calcd for $[C_{26}H_{25}N_3O_3S + H]^+$ = 460.16894, found 460.16891.

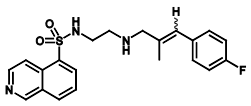


(E)-N-(2-(3-(4-nitrophenyl)allylamino)ethyl)isoquinoline-5-sulfonamide **55i**. Yield: 146 mg, 278 µmol, 28% ^{1}H NMR (600 MHz, MeOD) δ 9.53 (s, 2H), 8.72 – 8.63 (m, 5H), 8.56 (d, *J* = 7.4, 1H), 8.52 – 8.46 (m, 3H), 8.24 (dd, *J* = 8.8, 17.3, 4H), 7.90 (dt, *J* = 7.8, 11.5, 2H), 7.70 (d, *J* = 8.8, 2H), 7.51 (d, *J* = 8.6, 2H), 6.99 (d, *J* = 4.8, 1H), 6.96 (d, *J* = 9.1, 1H), 6.51 (dt, *J* = 7.1, 15.8, 1H), 5.99 – 5.93 (m, 1H), 4.03 (dd, *J* = 1.7, 6.7, 2H), 3.90 (d, *J* = 7.1, 2H), 3.21 (d, *J* = 4.9, 2H), 3.19 (d, *J* = 4.7, 2H), 3.17 – 3.14 (m, 3H), 3.09 (t, *J* = 5.8, 3H). ^{13}C NMR (100 MHz, MeOH) δ 151.34, 143.23, 138.31, 137.95, 137.48, 136.51, 136.25, 134.99, 134.63, 130.89, 129.87, 128.79, 124.95, 124.73, 124.18, 50.16, 49.64, 49.43, 49.21, 49.00, 48.79, 48.57, 48.36, 47.81, 46.24, 40.17, 40.04. HRMS: calcd for $[C_{20}H_{20}N_4O_4S + H]^+$ = 413.12780, found 413.12771.

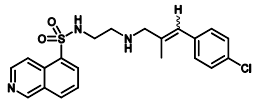


(E)-N-(2-(2-methyl-3-phenylallylamino)ethyl)isoquinoline-5-sulfonamide **55j.**

Data for the E-isomer Yield: 45.2 mg, 91 µmol, 9.1 %. ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.60 (s, 1H, H6), 8.74 (m, 2H, H1, H2), 8.64 – 8.46 (m, 2H, H3, H5), 7.99 – 7.91 (dd, 1H, H4, J_1 = 7.31 *Hz*, J_2 = 8.04 *Hz*), 7.42 – 7.17 (m, 5H, H_{phenyl}) 6.71 (s, 1H, CMe=C*H*Ph), 3.80 (s, 2H, NCH_2), 3.21 (s, 4H, H7, H8), 1.98 (s, 3H, CH_3). ^{13}C-NMR ($CDCl_3$): δ 152.9 (C6), 144.4 (C1), 137.2 (Cq_{phenyl}), 135.5 Me*C*=CH), 134.2 (C9), 133.3 (C3), 133.0 (C5), 130.9 (C10), 128.7 (C11), 128-5 – 129.9 (CH_{phenyl}, H*C*=CMe), 125.8 (C4), 117.2 (C2), 57.0 (C8), 47.1 (NCH_2), 42.1 (C7), 16.1 CH_3) . HRMS: calcd for $[C_{21}H_{23}N_3O_2S + H]^+$ = 382.15837, found 382.15874. **Data for the Z-isomer**: Yield: 12.2 mg, 24.6 µmol, 2.5 %. ^{1}H NMR (600 MHz, MeOD) δ 9.68 (s, 1H), 8.76 (s, 2H), 8.59 (d, *J* = 8.2, 1H), 8.52 (d, *J* = 7.3, 1H), 7.98 (t, *J* = 7.8, 1H), 7.40 (t, *J* = 7.5, 2H), 7.31 (t, *J* = 7.3, 1H), 7.21 (d, *J* = 7.5, 2H), 6.84 (s, 1H), 3.93 (s, 2H), 3.05 (s, 5H). ^{13}C NMR (150 MHz, MeOD) δ 161.83, 161.59, 152.65, 141.10, 137.33, 136.74, 136.08, 135.78, 135.59, 133.76, 130.87, 130.78, 130.03, 129.78, 129.71, 129.41, 129.03, 129.02, 128.63, 120.81, 66.91, 49.43, 49.28, 49.14, 49.00, 48.86, 48.72, 48.68, 48.57, 47.98, 47.62, 39.63, 36.53, 30.82, 30.45, 30.32, 30.23, 28.11, 26.92, 21.41, 15.44. HRMS: calcd for $[C_{21}H_{23}N_3O_2S + H]^+$ = 382.15837, found 382.15861.

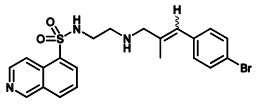


(E)-N-(2-(3-(4-fluorophenyl)-2-methylallylamino)ethyl)isoquinoline-5-sulfonamide **55k**. **Data for the E-isomer**: Yield: 50.5 mg, 111.5 µmol, 11.2 ^{1}H-NMR (MeOD): δ 9.09 (bs, 1H, H1), 8.75 – 8.74 (d, 1H, H5*, J_1* = 7.26 *Hz*), 8.67 – 8.66 (d, 1H, H3*, J_1* = 8.10 *Hz*), 8.08 – 8.05 (t, 1H, H4*, J_1* = 7.62 *Hz, J_2* = 7.74 *Hz*), 7.35 – 7.33 (m, 2H, H11), 7.13 – 7.10 (t, 2H, H12*, J_1* =8.60 *Hz*), 6.94 (s, 1H, H10), 3.82 (s, 2H, H9), 3.28 – 3.24 (m, 4H, H7/8), 1.99 (s, 3H, H13); ^{13}C-NMR (MeOD): δ 1647.23, 162.60, 137.89, 136.64, 136.42, 134.30, 133.81, 133.78, 133.36, 132.04, 131.99, 130.07, 129.60, 116.27, 116.13, 66.93, 56.44, 47.86, 39.96, 16.57; HRMS: calcd for $[C_{21}H_{22}FN_3O_2S + H]^+$ = 400.14895, found 400.14842. **Data for the Z-isomer:** Yield: 19.0 mg, 41.9 µmol, 4.2 %. ^{1}H NMR (600 MHz, MeOD) δ 9.87 (s, 1H), 8.89 (s, 2H), 8.64 (d, *J* = 8.2, 1H), 8.59 (d, *J* = 7.3, 1H), 8.03 (t, *J* = 7.8, 1H), 7.28 – 7.20 (m, 2H), 7.12 (t, *J* = 8.6, 2H), 6.79 (s, 1H), 3.91 (s, 2H), 3.08 (s, 4H). ^{13}C NMR (150 MHz, MeOD) δ 164.26, 162.63, 137.32, 136.37, 136.05, 134.30, 134.12, 133.55, 133.53, 131.74, 131.69, 129.52, 129.43, 116.59, 116.44, 66.90, 49.43, 49.28, 49.14, 49.00, 48.86, 48.72, 48.63, 48.57, 47.70, 39.68, 21.38, 15.44. HRMS: calcd for $[C_{21}H_{22}FN_3O_2S + H]^+$ = 400.14895, found 400.14851.

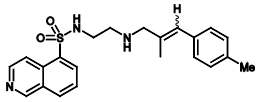


(E)-N-(2-(3-(4-chlorophenyl)-2-methylallylamino)ethyl)isoquinoline-5-sulfonamide **55l.**

Data for E-isomer: Yield: 55.5 mg, 105 µmol, 10.5 %. ^{1}H-NMR (MeOD): δ 9.65 (bs, 1H, H6), 8.81 – 8.80 (d, 1H, H2*, J_1* = 6.48 *Hz*), 8.70 – 8.69 (d, 1H, H1*, J_1* = 6.18 *Hz*), 8.64 – 8.63 (d, 1H, H5*, J_1* = 7.26 *Hz*), 8.57 – 8.55 (d, 1H, H3*, J_1* = 8.22 *Hz*), 7.97 – 7.95 (t, 1H, H4*, J_1* = 7.80 *Hz, J_2* = 7.86 *Hz*), 7.36 – 7.34 (d, 2H, H11*, J_1* = 8.40 *Hz*), 7.28 – 7.26 (d, 2H, H12*, J_1* = 8.46 *Hz*), 6.64 (s, 1H, H10), 3.78 (s, 2H, H9), 3.22 – 3.18 (m, 4H, H7/8), 1.95 (s, 3H, H13); ^{13}C NMR (150 MHz, MeOD) δ 162.27, 162.03, 152.22, 140.19, 137.17, 136.21, 136.16, 136.01, 134.35, 134.08, 133.07, 131.57, 131.36, 130.42, 129.84, 129.52, 129.30, 121.24, 61.53, 56.29, 49.57, 49.43, 49.28, 49.14, 49.00, 48.86, 48.72, 48.57, 47.86, 39.90, 16.61, 14.45. HRMS: calcd for $[C_{21}H_{22}ClN_3O_2S + H]^+$ = 416.11940, found 416.11928. The HPLC fractions of the Z-isomers were contaminated with the 1,2,3,4-tetrahydroisoquinoline based sideproduct.

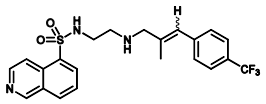


(E)-N-(2-(3-(4-bromophenyl)-2-methylallylamino)ethyl)isoquinoline-5-sulfonamide **55m. Data for E isomer**: Yield: 71.2 mg, 124.2 µmol, 12.4 %. ^{1}H NMR (600 MHz, MeOD) δ 9.70 (s, 1H), 8.86 (d, *J* = 6.4, 1H), 8.72 (s, 1H), 8.67 (d, *J* = 7.4, 1H), 8.59 (d, *J* = 8.3, 1H), 7.99 (t, *J* = 7.8, 1H), 7.50 (d, *J* = 8.4, 2H), 7.21 (d, *J* = 8.4, 2H), 6.63 (s, 1H), 3.97 (s, 2H), 3.78 (s, 2H), 3.24 (d, *J* = 4.9, 2H), 3.21 (d, *J* = 5.1, 2H), 1.95 (s, 3H). **Data for 3/5 EZ mixture**: ^{1}H NMR (600 MHz, MeOD) δ 9.66 (s, 1H), 8.72 (s, 2H), 8.61 (d, *J* = 7.3, 1H), 8.54 (d, *J* = 8.2, 1H), 8.48 (d, *J* = 7.3, 1H), 7.94 (t, *J* = 6.5, 3H), 7.57 – 7.45 (m, 9H), 7.24 (d, *J* = 8.2, 4H), 7.12 (d, *J* = 8.1, 2H), 6.73 (s, 1H), 6.66 (s, 1H), 3.88 (s, 2H), 3.80 (s, 2H), 3.54 (d, *J* = 5.3, 2H), 3.52 (d, *J* = 5.4, 4H), 3.25 (d, *J* = 5.0, 2H), 3.22 (d, *J* = 5.2, 4H), 2.03 (s, 3H), 1.97 (s, 3H). ^{13}C NMR (150 MHz, MeOD) δ 153.49, 143.06, 135.74, 134.16, 133.08, 132.88, 132.56, 132.34, 131.86, 131.64, 130.56, 130.09, 128.36, 56.29, 49.43, 49.28, 49.14, 49.00, 48.86, 48.72, 48.57, 48.03, 47.64, 45.79, 42.04, 39.84, 39.58, 23.96, 16.63, 15.44. HRMS: calcd for $[C_{21}H_{22}BrN_3O_2S + H]^+$ = 460.06889, found 460.06910.



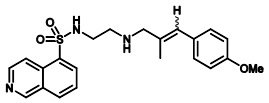
(E)-N-(2-(2-methyl-3-p-tolylallylamino)ethyl)isoquinoline-5-sulfonamide **55n**.

Data for the E-isomer: Yield: 53.4 mg, 104.9 µmol, 10.5 %. ^{1}H NMR (600 MHz, MeOD) δ 9.58 (s, 1H), 8.71 (s, 2H), 8.58 (d, *J* = 6.6, 1H), 8.48 (d, *J* = 8.2, 1H), 7.90 (t, *J* = 7.8, 1H), 7.23 – 7.17 (m, 4H), 6.66 (s, 1H), 3.79 (s, 2H), 3.25 (t, *J* = 5.6, 2H), 3.21 (t, *J* = 5.6, 2H), 2.34 (d, *J* = 12.7, 3H), 1.98 (d, *J* = 1.0, 3H). ^{13}C NMR (150 MHz, MeOD) δ 158.77, 153.29, 142.73, 138.57, 135.98, 135.71, 135.63, 135.47, 134.56, 134.55, 133.18, 130.84, 130.75, 130.32, 129.98, 129.97, 129.60, 128.76, 128.47, 128.46, 116.95, 115.06, 56.62, 49.43, 49.28, 49.14, 49.00, 48.86, 48.72, 48.57, 47.69, 39.86, 31.11, 30.79, 30.29, 28.09, 26.90, 21.22, 16.63. HRMS: calcd for $[C_{22}H_{25}N_3O_2S + H]^+$ = 396.17402, found 396.17351. **Data for the Z-isomer**: Yield: 68.7 mg, 135.0 µmol, 13.5 %. ^{1}H NMR (600 MHz, MeOD) δ 9.60 (s, 1H), 8.70 (s, 2H), 8.52 (d, *J* = 8.2, 1H), 8.49 (d, *J* = 7.3, 1H), 7.91 (t, *J* = 7.8, 1H), 7.18 (d, *J* = 7.8, 2H), 7.07 (d, *J* = 7.9, 2H), 6.75 (s, 1H), 3.91 (s, 2H), 3.09 – 3.01 (m, 4H), 2.33 (s, 3H), 2.03 (d, *J* = 1.1, 3H). ^{13}C NMR (150 MHz, MeOD) δ 152.97, 142.03, 138.49, 136.23, 135.83, 135.60, 135.44, 134.35, 133.36, 130.32, 129.96, 129.60, 128.63, 128.45, 49.43, 49.28, 49.14, 49.00, 48.86, 48.71, 48.57, 47.57, 39.63, 21.44, 21.19. HRMS: calcd for $[C_{22}H_{25}N_3O_2S + H]^+$ = 396.17402, found 396.17341.



(E)-N-(2-(2-methyl-3-(4-(trifluoromethyl)phenyl)allylamino)ethyl)isoquinoline-5-sulfonamide **55o**.

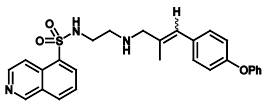
Data for the E-isomer: Yield: 48.1 mg, 85.4 µmol, 8.5%. ^{1}H NMR (600 MHz, MeOD) δ 9.63 (s, 1H), 8.75 (s, 2H), 8.61 (d, *J* = 6.8, 1H), 8.52 (d, *J* = 8.1, 1H), 7.94 (t, *J* = 7.8, 1H), 7.69 (d, *J* = 8.2, 2H), 7.51 (d, *J* = 8.1, 2H), 6.78 (s, 1H), 3.86 (s, 2H), 3.26 (s, 4H), 2.02 (s, 3H). ^{13}C NMR (150 MHz, MeOD) δ 153.13, 142.36, 141.47, 136.18, 135.81, 135.68, 133.32, 132.65, 132.15, 130.57, 130.43, 130.21, 128.61, 126.27, 126.24, 56.04, 49.43, 49.28, 49.14, 49.00, 48.86, 48.72, 48.57, 47.98, 39.89, 16.63. HRMS: calcd for $[C_{22}H_{22}F_3N_3O_2S + H]^+$ = 450.14576, found 450.14559. **Data for 1/4 E/Z mix**: Yield: 39.2 mg, 69.6 µmol, 7.0 %. ^{1}H NMR (600 MHz, MeOD) δ 9.64 (s, 1H), 8.70 (s, 2H), 8.51 (d, *J* = 8.3, 1H), 8.48 (d, *J* = 7.3, 1H), 7.95 (d, *J* = 7.5, 1H), 7.90 (t, *J* = 7.8, 1H), 7.67 (d, *J* = 7.9, 2H), 7.55 – 7.46 (m, 1H), 7.39 (d, *J* = 8.0, 2H), 6.82 (s, 1H), 6.76 (s, 1H), 3.89 (s, 2H), 3.84 (s, 1H), 3.25 (dd, *J* = 4.1, 7.8, 1H), 3.06 (s, 4H), 2.07 (s, 3H), 2.00 (s, 1H). ^{13}C NMR (150 MHz, MeOD) δ 152.99, 142.05, 141.31, 139.18, 136.22, 135.89, 135.63, 133.72, 133.37, 133.08, 132.64, 132.34, 132.20, 132.04, 131.44, 130.59, 130.53, 130.42, 130.32, 130.14, 128.66, 128.33, 126.61, 126.59, 126.25, 66.89, 56.06, 49.43, 49.28, 49.14, 49.00, 48.86, 48.81, 48.72, 48.57, 48.12, 47.96, 45.78, 42.02, 39.84, 39.74, 23.94, 21.52, 16.65, 15.43. HRMS: calcd for $[C_{22}H_{22}F_3N_3O_2S + H]^+$ = 450.14576, found 450.14574.



(E)-N-(2-(3-(4-methoxyphenyl)-2-methylallylamino)ethyl)isoquinoline-5-sulfonamide **55p**.

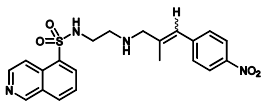
Data for the E-isomer: Yield: 115.2 mg, 219.4 µmol, 21.9 %. ^{1}H NMR (600 MHz, MeOD) δ 9.56 (s, 1H), 8.73 (s, 1H), 8.60 (s, 1H), 8.52 (d, *J* = 7.3, 1H), 8.42 (d, *J* = 8.3, 1H), 7.83 (t, *J* = 7.8, 1H), 7.08 (d, *J* = 8.7, 2H), 6.74 (d, *J* = 8.8, 2H), 6.46 (s, 1H), 3.64 (s, 3H), 3.13 (t, *J* = 6.1, 2H), 3.06 (t, *J* = 6.1, 2H), 1.83 (s, 3H). ^{1}H NMR (600 MHz, MeOD) δ 9.56 (s, 1H), 8.73 (s, 1H), 8.60 (s, 1H), 8.52 (d, *J* = 7.3, 1H), 8.42 (d, *J* = 8.3, 1H), 7.83 (t, *J* = 7.8, 1H), 7.08 (d, *J* = 8.7, 2H), 6.74 (d, *J* = 8.8, 2H), 6.46 (s, 1H), 3.64 (s, 3H), 3.13 (t, *J* = 6.1, 2H), 3.06 (t, *J* = 6.1, 2H), 1.83 (s, 3H). HRMS: calcd for $[C_{22}H_{25}N_3O_3S + H]^+$ = 412.16894, found 412.16883

Data for the Z-isomer: Yield: 27.6 mg, 52.6 µmol, 5.7 %. ^{1}H NMR (600 MHz, MeOD) δ 9.63 (s, 1H), 8.76 (s, 2H), 8.71 (s, 1H), 8.60 (s, 1H), 8.52 (d, *J* = 8.3, 2H), 7.93 (t, *J* = 6.9, 4H), 7.51 – 7.43 (m, 6H), 7.37 (d, *J* = 8.7, 4H), 7.25 (d, *J* = 8.7, 5H), 6.90 (dd, *J* = 8.7, 12.2, 9H), 6.62 (s, 2H), 3.78 (d, *J* = 5.6, 17H), 3.76 (s, 6H), 3.52 (d, *J* = 5.3, 5H), 3.50 (d, *J* = 5.2, 6H), 3.23 (t, *J* = 5.9, 5H), 3.21 – 3.13 (m, 12H), 1.97 (s, 8H). ^{13}C NMR (150 MHz, MeOD) δ 161.79, 160.57, 139.96, 139.24, 136.45, 135.92, 135.86, 134.39, 133.58, 133.08, 132.32, 132.04, 131.43, 130.11, 129.94, 129.44, 129.30, 128.82, 128.35, 127.35, 116.29, 115.19, 114.79, 56.88, 55.77, 55.72, 50.70, 49.85, 49.43, 49.28, 49.14, 49.00, 48.86, 48.72, 48.57, 47.82, 47.39, 45.78, 42.03, 40.13, 39.84, 23.94, 16.67. HRMS: calcd for $[C_{22}H_{25}N_3O_3S + H]^+$ = 412.16894, found 412.16883.



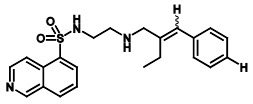
(E)-N-(2-(2-methyl-3-(4-phenoxyphenyl)allylamino)ethyl)isoquinoline-5-sulfonamide **55q**.

Data for the E-isomer: Yield: ^{1}H NMR (600 MHz, MeOD) δ 9.64 (s, 1H), 8.79 (s, 1H), 8.64 (s, 1H), 8.57 (d, *J* = 7.3, 1H), 8.49 (d, *J* = 8.2, 1H), 7.88 (t, *J* = 7.8, 1H), 7.22 (dd, *J* = 7.5, 8.5, 2H), 7.17 (d, *J* = 8.6, 2H), 6.99 (t, *J* = 7.4, 1H), 6.88 – 6.85 (m, 2H), 6.83 (d, *J* = 8.7, 2H), 6.54 (s, 1H), 3.66 (s, 2H), 3.12 (d, *J* = 5.2, 2H), 3.09 (d, *J* = 5.3, 2H), 1.86 (s, 3H). ^{13}C NMR (150 MHz, MeOD) δ 158.21, 158.18, 151.51, 138.74, 137.77, 136.44, 136.20, 134.44, 133.84, 132.44, 131.66, 130.94, 129.75, 128.64, 124.72, 120.15, 119.28, 56.62, 49.43, 49.28, 49.14, 49.00, 48.86, 48.72, 48.57, 47.74, 39.90, 16.65. HRMS: calcd for $[C_{27}H_{27}N_3O_3S + H]^+$ = 474.18459, found 474.18443. The HPLC fractions of the Z-isomers were contaminated with the 1,2,3,4-tetrahydroisoquinoline based sideproduct.



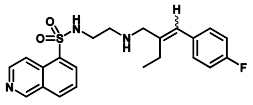
(E)-N-(2-(2-methyl-3-(4-nitrophenyl)allylamino)ethyl)isoquinoline-5-sulfonamide **55r**.

Data for 6/1 E/Z mix: Yield: 40.1, 74.3 µmol, 7.4%. ^{1}H NMR (600 MHz, MeOD) δ 9.63 (s, 1H), 8.77 (d, *J* = 4.8, 1H), 8.70 (s, 1H), 8.64 (s, 1H), 8.59 – 8.55 (m, 1H), 8.53 (d, *J* = 7.4, 1H), 8.49 (d, *J* = 8.3, 1H), 8.47 (s, 1H), 8.44 (d, *J* = 7.4, 1H), 8.10 (d, *J* = 8.8, 2H), 8.08 (d, *J* = 8.7, 1H), 8.04 (d, *J* = 8.7, 1H), 7.89 (t, *J* = 7.8, 1H), 7.86 (t, *J* = 7.8, 1H), 7.41 (d, *J* = 8.7, 2H), 7.35 – 7.29 (m, 1H), 6.72 (s, 1H), 6.66 (s, 1H), 3.80 (s, 1H), 3.73 (s, 2H), 3.13 (s, 4H), 3.00 – 2.95 (m, 1H), 1.97 (s, 1H), 1.89 (d, *J* = 1.0, 3H). ^{13}C NMR (150 MHz, MeOD) δ 151.73, 148.14, 144.23, 144.07, 139.14, 137.63, 137.39, 136.40, 136.14, 134.36, 133.63, 133.09, 132.71, 131.95, 131.31, 131.03, 130.91, 129.65, 129.57, 124.79, 124.61, 124.52, 55.95, 49.43, 49.28, 49.14, 49.00, 48.86, 48.72, 48.57, 48.07, 47.96, 39.92, 39.73, 33.80, 21.67, 16.80. HRMS: calcd for $[C_{21}H_{23}N_4O_4S + H]^+$ = 427.14345, found 427.14322. **Data for the Z-isomer**: Yield: 38.4 mg, 71.1 µmol, 7.1%. ^{1}H NMR (600 MHz, MeOD) δ 9.67 (s, 1H), 8.75 (d, *J* = 5.3, 1H), 8.70 (s, 1H), 8.55 (d, *J* = 8.3, 1H), 8.51 (d, *J* = 7.3, 1H), 8.18 (d, *J* = 8.7, 2H), 7.93 (t, *J* = 7.8, 1H), 7.52 (d, *J* = 8.6, 1H), 7.42 (d, *J* = 8.6, 2H), 6.83 (s, 1H), 6.76 (s, 1H), 3.96 (s, 1H), 3.90 (s, 2H), 3.10 – 3.03 (m, 4H), 2.07 (s, 3H), 2.00 (s, 1H). ^{13}C NMR (150 MHz, MeOD) δ 152.56, 148.28, 144.06, 141.00, 136.55, 136.05, 135.80, 133.74, 133.14, 132.67, 131.98, 131.03, 130.90, 128.96, 124.80, 124.52, 55.96, 49.85, 49.43, 49.28, 49.14, 49.00, 48.86, 48.71, 48.57, 47.98, 39.73, 21.66. HRMS: calcd for $[C_{21}H_{23}N_4O_4S + H]^+$ = 427.14345, found 427.14334.



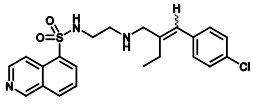
(E)-N-(2-(2-benzylidenebutylamino)ethyl)isoquinoline-5-sulfonamide **55s**.

Data for the E-isomer: Yield: 71.9 mg, 142.3 µmol, 14.2 %. ^{1}H-NMR (MeOD): δ 9.57 (bs, 1H, H6), 8.78 – 8.71 (m, 2H, H1/2), 8.58 – 8.56 (dd, 1H, H5, J_1 = 0.80 *Hz*, J_2 = 7.30 *Hz*), 8.47 – 8.46 (d, 1H, H3, J_1 = 8.16 *Hz*), 7.90 – 7.87 (t, 1H, H4, J_1 = 7.68 *Hz*, J_2 = 7.92 *Hz*), 7.35 – 7.24 (m, 5H, H11/12/15), 6.65 (s, 1H, H10), 3.80 (s, 1H, H9), 3.25 – 3.21 (m, 4H, H7/8), 2.35 – 2.31 (dd, 2H, H13, J_1 = 7.48 *Hz*, J_2 = 15.00 *Hz*), 1.11 – 1.08 (t, 3H, H14, J_1 = 7.50 *Hz*, J_2 = 7.62 *Hz*); ^{13}C-NMR (MeOD): δ 152.24, 140.53, 137.84, 137.62, 136.66, 136.51, 136.13, 134.47, 134.25, 130.04, 139.90, 129.80, 129.02, 53.29, 50.32, 48.48, 40.35, 23.57, 13.45; HRMS: calcd for $[C_{22}H_{25}N_3O_2S + H]^+$ = 396.16402, found 396.17339. **Data for the 1/5 E/Z mix**: Yield: 232. mg, 45.8 µmol, 4.6 %. ^{1}H NMR (400 MHz, MeOH) δ 10.50 – 9.17 (m, 1H), 8.74 (s, 1H), 8.62 (d, *J* = 7.3, 1H), 8.53 (d, *J* = 8.2, 1H), 8.48 (d, *J* = 6.8, 1H), 7.93 (t, *J* = 7.8, 1H), 7.38 (t, *J* = 7.4, 2H), 7.30 (d, *J* = 7.4, 2H), 7.20 (d, *J* = 7.5, 2H), 6.83 (s, 1H), 6.70 (s, 1H), 3.92 (s, 2H), 3.83 (s, 1H), 3.01 (s, 4H), 2.39 – 2.30 (m, 2H), 1.24 (t, *J* = 7.4, 3H), 1.14 (dd, *J* = 5.7, 9.3, 1H). ^{13}C NMR (100 MHz, MeOH) δ 137.42, 136.16, 135.87, 135.66, 134.75, 134.13, 133.79, 129.80, 129.71, 129.60, 129.48, 128.70, 128.60, 49.64, 49.43, 49.21, 49.00, 48.79, 48.57, 48.36, 48.06, 47.59, 47.22, 39.56, 27.99, 13.01, 12.67. HRMS: calcd for $[C_{22}H_{25}N_3O_2S + H]^+$ = 396.16402, found 396.17340.



(E)-N-(2-(2-(4-fluorobenzylidene)butylamino)ethyl)isoquinoline-5-sulfonamide **55t**.

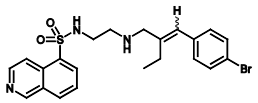
Data for the E-isomer: Yield: 44.8 mg, 85.0 µmol, 8.5 %. ^{1}H-NMR (MeOD): δ 9.65 (bs, 1H, H6), 8.77 (bs, 1H, H2), 8.71 (bs, 1H, H1), 8.62 – 8.60 (dd, 1H, H5, J_1 = 0.84 *Hz*, J_2 = 7.32 *Hz*), 8.57 – 8.52 (d, 1H, H3, J_1 = 8.22 *Hz*), 7.95 – 7.92 (t, 1H, H4, J_1 = 7.74 *Hz*, J_2 = 7.86 *Hz*), 7.29 – 7.26 (dd, 1H, H11, J_1 = 5.46 *Hz*, J_2 = 8.46 *Hz*), 7.09 – 7.06 (t, 1H, H12, J_1 = J_2 = 8.76 *Hz*), 6.62 (s, 1H, H10), 3.79 (s, 2H, H9), 3.23 -3.20 (m, 4H, H7/8), 2.33 – 2.30 (dd, 2H, H13, J_1 = 7.50 *Hz*, J_2 = 15.06 *Hz*), 1.11 – 1.08 (t, 3H, H14, J_1 = 7.50 *Hz*, J_2 = 7.62 *Hz*); ^{13}C-NMR (MeOD): δ 164.27, 162.64, 152.78, 141.55, 136.52, 135.95, 135.87, 133.62, 133.61, 132.61, 131.60, 131.54, 128.87, 116.32, 116.17, 53.05, 49.85, 48.07, 39.88, 23.09, 12.91; HRMS: calcd for $[C_{22}H_{24}FN_3O_2S + H]^+$ = 414.16460, found 414.16438. **Data for the 1/4 E/Z mix**: Yield: 31.2 mg, 59.2 µmol, 5.9 %. ^{1}H NMR (600 MHz, MeOD) δ 9.63 (s, 3H), 8.76 (s, 1H), 8.70 (s, 6H), 8.53 (d, *J* = 7.9, 4H), 8.48 (d, *J* = 7.3, 3H), 7.96 – 7.87 (m, 5H), 7.52 – 7.43 (m, 3H), 7.29 (dd, *J* = 5.6, 8.4, 3H), 7.22 – 7.15 (m, 7H), 7.13 – 7.04 (m, 10H), 6.75 (s, 3H), 6.65 (s, 1H), 3.87 (s, 7H), 3.80 (s, 2H), 3.53 (d, *J* = 5.3, 2H), 3.50 (d, *J* = 5.3, 3H), 3.26 – 3.19 (m, 6H), 3.00 (s, 14H), 2.38 – 2.24 (m, 10H), 1.19 (t, *J* = 7.4, 11H), 1.11 (t, *J* = 7.5, 4H). ^{13}C NMR (150 MHz, MeOD) δ 164.28, 162.65, 152.94, 141.88, 139.23, 136.29, 135.91, 135.68, 135.12, 133.61, 133.59, 133.47, 133.07, 132.91, 132.58, 132.33, 132.05, 131.75, 131.70, 131.61, 131.55, 130.12, 128.72, 128.34, 116.63, 116.48, 116.31, 116.17, 53.08, 49.85, 49.43, 49.28, 49.14, 49.00, 48.86, 48.72, 48.57, 48.22, 47.67, 47.17, 45.79, 42.04, 39.82, 39.60, 27.98, 23.94, 23.12, 12.93, 12.64. HRMS: calcd for $[C_{22}H_{24}FN_3O_2S + H]^+$ = 414.16460, found 414.16458.



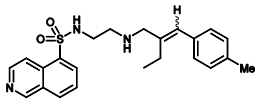
(E)-N-(2-(2-(4-chlorobenzylidene)butylamino)ethyl)isoquinoline-5-sulfonamide **55u**.

Data for the E-isomer: Yield: 13.1 mg, 24.1 µmol, 2.4%. ^{1}H-NMR (MeOD): δ 9.68 (bs, 1H, H6), 8.85 – 8.84 (d, 1H, H2, J_1 = 6.18 *Hz*), 8.71 (bs, 1H, H1), 8.66 – 8.65 (d, 1H, H5, J_1 = 7.38 *Hz*), 8.58 – 8.57 (d, 1H, H3, J_1 =8.22 *Hz*), 7.99 – 7.96 (t, 1H, H4, J_1 = J_2 = 7.73 *Hz*), 7.35 – 7.33 (d, 2H,

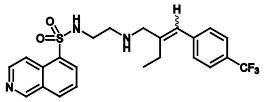
H11*, J_1* = 8.28 *Hz*), 7.24 – 7.23 (d, 2H, H12*, J_1* = 8.28 *Hz*), 6.62 (s, 1H, H10), 3.79 (s, 2H, H9), 3.23 – 3.21 (m, 4H, H7/8), 2.34 – 2.30 (dd, 2H, H13*, J_1* = 7.56 *Hz, J_2* = 15.12 *Hz*), 1.11 – 1.08 (t, 3H, H14*, J_1* = 7.44 *Hz, J_2* = 7.56 *Hz*); ^{13}C-NMR (MeOD): δ 151.85, 139.41, 137.50, 136.67, 136.33, 136.13, 136.06, 134.35, 134.29, 132.29, 131.19, 129.59, 129.55, 121.61, 52.95, 48.09, 39.88, 23.17, 12.92; HRMS: calcd for $[C_{22}H_{24}ClN_3O_2S + H]^+$ = 430.13505, found 430.13503. The HPLC fractions of the Z-isomer were contaminated with the 1,2,3,4-tetrahydroisoquinoline based sideproduct.



(E)-N-(2-(2-(4-bromobenzylidene)butylamino)ethyl)isoquinoline-5-sulfonamide **55v**. **Data for the E-isomer**: Yield: 38.3 mg, 65.1 µmol, 6.5 %. ^{1}H-NMR (MeOD): δ 9.43 (bs, 1H, H6), 8.94 (bs, 1H, H2), 8.57 (bs, 1H, H1), 8.50 – 8.49 (d, 1H, H5*, J_1* = 7.20 *Hz*), 8.41 – 8.40 (d, 1H, H3*, J_1* = 7.98 *Hz*), 7.84 – 7.81 (t, 1H, H4*, J_1 = J_2* = 7.61 *Hz*), 7.50 – 7.49 (d, 2H, H1*, J_1* = 8.34 *Hz*), 7.18 – 1.17 (d, 2H, H12*, J_1* = 8.22 *Hz*), 6.59 (s, 1H, H10), 3.78 (s, 2H, H9), 3.20 (m, 4H, H7/8), 2.32 – 2.29 (dd, 2H, H13*, J_1* = 7.44 *Hz, J_2* = 15.00 *Hz*), 1.10 – 1.08 (t, 3H, H14*, J_1* = 7.44 *Hz, J_2* = 7.50 *Hz*); ^{13}C-NMR (MeOD): δ 154.05, 144.37, 136.73, 136.46, 135.44, 135.39, 132.89, 132.72, 132.69, 132.62, 132.31, 131.67, 131.47, 127.93, 122.39, 122.05, 121.44, 52.92, 49.85, 48.08, 26.47, 23.19, 12.92; HRMS: calcd for $[C_{22}H_{24}BrN_3O_2S + H]^+$ = 474.08454, found 474.08461. **Data for the Z-isomer**: Yield: 15.1 mg, 25.7 µmol, 2.6 %. ^{1}H NMR (600 MHz, MeOD) δ 9.32 (s, 11H), 8.53 (s, 12H), 8.40 (s, 13H), 8.31 (d, *J* = 8.2, 14H), 8.25 (d, *J* = 7.3, 12H), 7.73 (t, *J* = 7.8, 13H), 7.40 (d, *J* = 8.3, 28H), 7.33 (d, *J* = 7.1, 8H), 7.09 (d, *J* = 8.3, 3H), 7.00 (d, *J* = 8.2, 23H), 6.62 (s, 11H), 6.51 (s, 1H), 3.76 (s, 22H), 2.91 – 2.84 (m, 52H), 2.53 (s, 39H), 2.26 – 2.14 (m, 27H), 1.09 (dd, *J* = 6.1, 8.6, 38H), 1.00 (t, *J* = 7.5, 5H). ^{13}C NMR (150 MHz, MeOD) δ 154.27, 144.84, 136.51, 135.70, 135.40, 135.20, 135.05, 132.92, 132.72, 132.58, 131.71, 130.96, 130.28, 127.84, 122.47, 49.85, 49.43, 49.28, 49.14, 49.00, 48.86, 48.72, 48.57, 47.63, 47.10, 40.42, 39.52, 28.07, 12.61. HRMS: calcd for $[C_{22}H_{24}BrN_3O_2S + H]^+$ = 474.08454, found 474.08451.

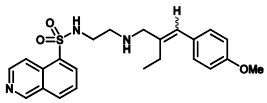


(E)-N-(2-(2-(4-methylbenzylidene)butylamino)ethyl)isoquinoline-5-sulfonamide **55w**. **Data for the E-isomer**: Yield: 55.7 mg, 106.5 µmol, 10.7 %. ^{1}H NMR (400 MHz, MeOH) δ 9.64 (s, 1H), 8.81 (s, 1H), 8.72 (s, 1H), 8.63 (d, *J* = 7.2, 1H), 8.52 (d, *J* = 8.2, 1H), 7.94 (t, *J* = 7.8, 1H), 7.14 (s, 4H), 6.62 (s, 1H), 3.80 (s, 2H), 3.27 (d, *J* = 5.0, 2H), 3.24 (d, *J* = 5.0, 2H), 2.35 (dd, *J* = 5.7, 13.3, 2H), 2.31 (s, 3H), 1.11 (t, *J* = 7.5, 3H). ^{13}C NMR (100 MHz, MeOH) δ 152.09, 140.21, 138.50, 137.02, 136.09, 135.94, 134.79, 134.37, 133.87, 133.83, 130.01, 129.51, 129.19, 53.28, 49.64, 49.43, 49.21, 49.00, 48.79, 48.57, 48.36, 47.91, 39.85, 23.06, 21.18, 12.95. HRMS: calcd for $[C_{23}H_{27}N_3O_2S + H]^+$ = 410.18967, found 410.18936. **Data for the 1/2 E/Z mix**: Yield: 99.6 mg, 190.4 µmol, 19.0 %. ^{1}H NMR (400 MHz, MeOH) δ 9.70 (s, 3H), 8.85 (s, 2H), 8.79 (s, 3H), 8.77 – 8.70 (m, 3H), 8.67 (d, *J* = 7.4, 2H), 8.59 (d, *J* = 8.3, 4H), 8.55 (d, *J* = 7.4, 3H), 7.99 (dd, *J* = 7.3, 15.3, 4H), 7.19 (d, *J* = 6.8, 11H), 7.08 (d, *J* = 8.0, 6H), 6.78 (s, 3H), 6.64 (s, 1H), 3.92 (s, 6H), 3.81 (s, 3H), 3.26 (d, *J* = 4.5, 2H), 3.24 (d, *J* = 4.6, 2H), 3.09 – 2.95 (m, 12H), 2.39 – 2.20 (m, 21H), 1.22 (t, *J* = 7.4, 9H), 1.13 (t, *J* = 7.5, 4H). ^{13}C NMR (150 MHz, MeOD) δ 152.66, 140.72, 139.01, 137.59, 137.45, 136.62, 136.38, 135.31, 134.90, 134.64, 134.53, 134.43, `30.84, 130.52, 130.09, 130.02, 129.77, 129.67, 53.76, 48.05, 47.73, 40.33, 40.06, 28.49, 23.58, 21.63, 13.16, 13.42. HRMS: calcd for [C23H27N3O2S + H]+ = 410.18967, found 410.18942.



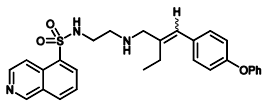
(E)-N-(2-(2-(4-(trifluoromethyl)benzylidene)butylamino)ethyl)isoquinoline-5-sulfonamide **55x**.

Data for the E-isomer: Yield: 4.9 mg, 8.5 µmol, 0.9%. ^{1}H NMR (600 MHz, MeOD) δ 9.64 (s, 1H), 8.79 (d, *J* = 5.0, 1H), 8.71 (s, 1H), 8.62 (d, *J* = 6.6, 1H), 8.53 (d, *J* = 8.2, 1H), 7.94 (t, *J* = 7.8, 1H), 7.64 (d, *J* = 8.2, 2H), 7.44 (d, *J* = 8.1, 2H), 6.71 (s, 1H), 3.83 (s, 2H), 3.24 (s, 4H), 2.33 (q, *J* = 7.5, 2H), 1.11 (t, *J* = 7.5, 3H). ^{13}C NMR (150 MHz, MeOD) δ 152.80, 141.62, 141.44, 138.21, 136.50, 135.92, 135.84, 133.60, 131.89, 130.84, 130.71, 130.50, 130.29, 130.21, 130.07, 128.84, 128.30, 126.50, 126.38, 126.35, 126.33, 126.30, 124.70, 122.91, 120.70, 52.77, 49.85, 49.43, 49.28, 49.14, 49.00, 48.86, 48.72, 48.57, 48.22, 39.89, 30.28, 23.30, 12.93. HRMS: calcd for $[C_{23}H_{24}F_3N_3O_2S + H]^+$ = 464.16141, found 464.16121. **Data for the Z-isomer**: Yield: 42.6 mg, 73.8 µmol, 7.4 %. ^{1}H NMR (600 MHz, MeOD) δ 9.59 (s, 1H), 8.69 (s, 2H), 8.51 (d, *J* = 8.2, 1H), 8.49 (dd, *J* = 0.9, 7.4, 1H), 7.90 (t, *J* = 7.8, 1H), 7.66 (d, *J* = 8.1, 2H), 7.38 (d, *J* = 8.1, 2H), 6.82 (s, 1H), 3.88 (s, 2H), 3.03 (t, *J* = 4.0, 4H), 2.34 (q, *J* = 7.3, 2H), 1.22 (t, *J* = 7.4, 3H). ^{13}C NMR (150 MHz, MeOD) δ 153.03, 142.09, 141.49, 136.95, 136.20, 135.86, 135.63, 133.43, 132.35, 130.79, 130.57, 130.46, 130.36, 130.23, 130.14, 130.12, 128.63, 128.34, 128.29, 126.67, 126.64, 126.62, 126.59, 126.49, 126.35, 124.70, 122.90, 120.37, 49.85, 49.43, 49.28, 49.14, 49.00, 48.86, 48.72, 48.57, 48.38, 47.96, 47.46, 39.70, 28.03, 12.94, 12.53. HRMS: calcd for $[C_{23}H_{24}F_3N_3O_2S + H]^+$ = 464.16141, found 464.16121.



(E)-N-(2-(2-(4-methoxybenzylidene)butylamino)ethyl)isoquinoline-5-sulfonamide **55y**.

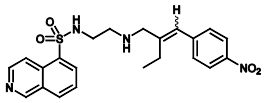
Data for the 5/1 E/Z mix: Yield: 30.2 mg, 56.0 µmol, 5.6 %. ^{1}H NMR (600 MHz, MeOD) δ 9.34 (s, 1H), 8.59 (d, *J* = 6.1, 1H), 8.52 (d, *J* = 6.1, 1H), 8.46 (d, *J* = 7.4, 1H), 8.34 (d, *J* = 8.2, 1H), 8.31 (d, *J* = 7.3, 1H), 7.82 – 7.73 (m, 1H), 7.65 (d, *J* = 8.6, 1H), 7.27 (d, *J* = 8.6, 1H), 7.18 (d, *J* = 8.6, 2H), 7.06 (d, *J* = 8.6, 1H), 6.92 (d, *J* = 8.8, 1H), 6.88 (t, *J* = 8.8, 3H), 6.68 (s, 1H), 6.55 (s, 1H), 3.81 – 3.72 (m, 7H), 3.19 (d, *J* = 5.0, 2H), 3.16 (t, *J* = 11.4, 2H), 2.96 (dd, *J* = 3.9, 6.7, 1H), 2.32 (q, *J* = 7.5, 2H), 2.28 – 2.22 (m, 1H), 1.09 (t, *J* = 7.5, 3H). ^{13}C NMR (150 MHz, MeOD) δ 160.50, 160.42, 154.15, 144.65, 143.47, 142.42, 135.29, 135.09, 135.04, 133.75, 133.70, 133.65, 133.41, 132.56, 132.50, 131.96, 131.34, 130.98, 130.56, 129.63, 129.53, 127.78, 127.73, 119.14, 115.17, 115.11, 115.05, 114.81, 55.80, 55.68, 53.42, 49.43, 49.28, 49.14, 49.00, 48.86, 48.72, 48.57, 47.84, 47.33, 46.93, 39.80, 39.44, 35.97, 28.56, 28.03, 23.03, 21.96, 21.74, 12.95, 12.77. HRMS: calcd for $[C_{23}H_{27}N_3O_3S + H]^+$ = 426.18459, found 426.18456.



(E)-N-(2-(2-(4-phenoxybenzylidene)butylamino)ethyl)isoquinoline-5-sulfonamide **55z**.

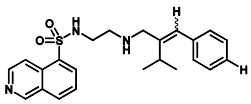
Data for the E-isomer: Yield: 85.3 mg, 141.9 µmol, 14.2 %. ^{1}H NMR (600 MHz, MeOD) δ 9.38 (s, 1H), 8.60 (s, 1H), 8.55 (s, 1H), 8.48 (d, *J* = 7.2, 1H), 8.37 (d, *J* = 8.1, 1H), 7.80 (t, *J* = 7.8, 1H), 7.32 (dd, *J* = 7.6, 8.3, 2H), 7.24 (d, *J* = 8.5, 2H), 7.09 (t, *J* = 7.4, 1H), 6.96 (d, *J* = 7.8, 2H), 6.93 (d, *J* = 8.6, 2H), 6.60 (s, 1H), 3.77 (s, 2H), 3.19 (dd, *J* = 4.0, 5.9, 4H), 2.34 (q, *J* = 7.4, 2H), 1.09 (t, *J* = 7.5, 3H). ^{13}C NMR (150 MHz, MeOD) δ 158.22, 158.15, 154.02, 144.37, 135.37, 135.34, 135.24, 134.98, 133.08, 132.67, 132.26, 131.25, 130.93, 130.57, 127.89, 124.70, 120.13, 119.67, 119.37, 119.29, 53.19, 49.85, 49.43, 49.28, 49.14, 49.00, 48.86,

48.72, 48.57, 47.93, 39.81, 23.09, 12.96. HRMS: calcd for $[C_{28}H_{29}N_3O_3S + H]^+$ = 488.20024, found 488.20013. **Data for the Z-isomer**: Yield: 28.9 mg, 48.1 µmol, 4.8 %. ^{1}H NMR (600 MHz, MeOD) δ 9.37 (s, 1H), 8.60 (d, *J* = 6.0, 1H), 8.47 (d, *J* = 5.9, 1H), 8.38 (d, *J* = 8.3, 1H), 8.36 (d, *J* = 7.4, 1H), 7.80 (t, *J* = 7.8, 1H), 7.32 (dd, *J* = 9.0, 17.3, 3H), 7.16 (d, *J* = 8.4, 2H), 7.10 (t, *J* = 7.4, 1H), 7.01 – 6.93 (m, 5H), 6.75 (s, 1H), 3.90 (s, 2H), 2.98 (d, *J* = 4.2, 2H), 2.97 (d, *J* = 4.2, 2H), 2.29 (q, *J* = 7.0, 2H), 1.19 (t, *J* = 7.4, 3H). ^{13}C NMR (150 MHz, MeOD) δ 158.27, 158.14, 154.36, 145.00, 135.34, 135.16, 134.99, 134.41, 133.39, 132.51, 132.24, 131.37, 130.97, 130.66, 127.73, 124.78, 120.16, 119.71, 119.41, 118.98, 49.43, 49.28, 49.14, 49.00, 48.86, 48.72, 48.57, 47.49, 47.05, 39.51, 28.06, 12.73. HRMS: calcd for $[C_{28}H_{29}N_3O_3S + H]^+$ = 488.20024, found 488.20006.



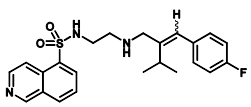
(E)-N-(2-(2-(4-nitrobenzylidene)butylamino)ethyl)isoquinoline-5-sulfonamide **55aa**.

Data for the 3/2 E/Z mix: Yield: 55.9 mg, 100.9 µmol, 10.1 %. ^{1}H NMR (600 MHz, MeOD) δ 9.40 (s, 2H), 8.63 (bs, 2H), 8.54 (d, *J* = 5.8, 1H), 8.49 (d, *J* = 7.2, 1H), 8.47 (d, *J* = 5.8, 1H), 8.44 – 8.38 (m, 2H), 8.35 (d, *J* = 7.2, 1H), 8.26 – 8.16 (m, 4H), 7.83 (t, *J* = 7.8, 1H), 7.79 (t, *J* = 7.8, 1H), 7.56 (d, *J* = 8.6, 1H), 7.50 (d, *J* = 8.6, 2H), 7.43 (d, *J* = 8.5, 1H), 6.84 (s, 1H), 6.73 (s, 1H), 3.90 (s, 1H), 3.85 (s, 2H), 3.22 (d, *J* = 4.3, 2H), 3.20 (d, *J* = 4.2, 2H), 3.02 (d, *J* = 5.0, 1H), 3.00 (d, *J* = 5.0, 1H), 2.39 – 2.31 (m, 4H), 1.23 (t, *J* = 7.3, 3H), 1.13 (t, *J* = 7.5, 4H). ^{13}C NMR (150 MHz, MeOD) δ 154.25, 148.26, 144.76, 144.27, 144.16, 139.54, 138.08, 135.39, 135.31, 135.15, 134.93, 132.65, 131.74, 131.07, 130.98, 130.73, 127.84, 127.75, 124.85, 124.65, 119.16, 52.62, 49.43, 49.28, 49.14, 49.00, 48.86, 48.72, 48.57, 48.28, 47.87, 47.26, 39.83, 39.59, 28.17, 23.48, 12.92, 12.48. HRMS: calcd for $[C_{22}H_{24}N_4O_4S + H]^+$ = 441.15910, found 441.15893.



(E)-N-(2-(2-benzylidene-3-methylbutylamino)ethyl)isoquinoline-5-sulfonamide **55ab**.

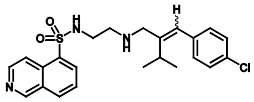
Data for the E-isomer: Yield: 16.2 mg, 31.0 µmol, 3.1 %. ^{1}H-NMR (MeOD): δ 8.76 (m, 2H, H1/2), 8.60 – 8.59 (d, 1H, H5, J_1 = 7.20 *Hz*), 8.52- 8.51 (d, 1H, H3, J_1 = 8.16 *Hz*), 7.94 – 7.91 (t, 1H, H4, $J_1 = J_2$ = 7.80 *Hz*), 7.37 – 7.23 (m, 5H, H11/12/15), 6.56 (s, 1H, H10), 3.83 (s, 2H, H9), 3.30 – 3.29 (m, 4H, H7/8), 3.16 – 3.11 (m, 1H, H13), 1.10 – 1.09 (d, 6H, H14, J_1 = 6.96 *Hz*); ^{13}C-NMR (MeOD): δ 143.08, 140.48, 139.89, 139.08, 138.97, 132.43, 132.28, 132.20, 131.59, 131.18, 42.78, 32.60, 23.79; HRMS: calcd for $[C_{23}H_{27}N_3O_2S + H]^+$ = 410.18967, found 410.18936. **Data for the 1/10 EZ-mix**: Yield: 17.3 mg, 33.1 µmol, 3.3 %. ^{1}H NMR (600 MHz, MeOD) δ 10.08 – 9.51 (m, 1H), 8.76 (bs, 2H), 8.66 – 8.61 (m, 1H), 8.55 (d, *J* = 8.1, 1H), 8.49 (d, *J* = 7.2, 1H), 7.99 – 7.92 (m, 1H), 7.36 (t, *J* = 7.6, 2H), 7.27 (t, *J* = 7.4, 1H), 7.25 – 7.21 (m, 1H), 7.18 (d, *J* = 7.6, 2H), 6.87 (s, 1H), 6.58 – 6.54 (m, 1H), 3.93 (s, 2H), 3.83 (s, 1H), 3.28 – 3.23 (m, 1H), 2.97 (bs, 4H), 2.55 – 2.46 (m, 1H), 1.63 – 1.56 (m, 1H), 1.24 (s, 3H), 1.23 (s, 3H), 1.10 (s, 1H), 1.09 (s, 1H). ^{13}C NMR (100 MHz, MeOH) δ 139.70, 137.73, 137.55, 136.52, 136.19, 134.42, 132.88, 129.87, 129.82, 129.72, 129.60, 129.45, 128.64, 87.53, 49.64, 49.43, 49.21, 49.00, 48.79, 48.57, 48.36, 47.72, 46.90, 39.56, 32.01, 22.22, 20.97. HRMS: calcd for $[C_{23}H_{27}N_3O_2S + H]^+$ = 410.18967, found 410.18939.



(E)-N-(2-(2-(4-fluorobenzylidene)-3-methylbutylamino)ethyl)isoquinoline-5-sulfonamide **55ac**.

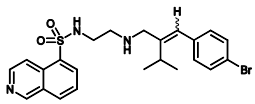
Data for the E-isomer: Yield: 24.9 mg, 46.0 µmol, 4.6 %. ^{1}H-NMR (MeOD): δ 9.58 (bs,

1H, H6), 8.73 – 8.72 (d, 1H, H2, J_1 = 6.00 *Hz*), 8.68 (bs, 1H, H1), 8.60 – 8.59 (dd, 1H, H5, J_1 = 0.78 *Hz*, J_2 = 7.38 *Hz*), 8.53 – 8.51 (d, 1H, H3, J_1 = 8.16 *Hz*), 7.94 – 7.91 (t, 1H, H4, J_1 = J_2 = 7.76 *Hz*), 7.25 – 7.07 (m, 5H, H11/12/15), 6.50 (s, 1H, H10), 3.80 (s, 2H, H9), 3.29 – 3.27 (m, 4H, H7/8), 3.09 – 3.05 (m, 1H, H13), 1.08 – 1.07 (d, 6H, H14, J_1 = 7.02 *Hz*); ^{13}C-NMR (MeOD): δ 164.16, 162.53, 152.94, 141.77, 140.60, 136.48, 135.95, 135.81, 133.82, 133.79, 133.60, 131.58, 131.52, 128.82, 127.41, 120.55, 116.30, 116.1548.28, 39.90, 29.76, 20.91; HRMS: calcd for $[C_{23}H_{26}FN_3O_2S + H]^+$ = 428.18025, found 428.12813. **Data for the 1/3 EZ mix**: Yield: 22.7 mg, 42.0 µmol, 4.2 %. ^{1}H NMR (600 MHz, MeOD) δ 9.44 (s, 1H), 8.63 – 8.50 (m, *J* = 13.2, 26.1, 3H), 8.48 (d, *J* = 7.3, 1H), 8.42 – 8.38 (m, 1H), 8.34 (dd, *J* = 1.0, 7.3, 1H), 7.84 – 7.76 (m, 1H), 7.16 – 7.12 (m, *J* = 8.3, 1H), 7.11 – 7.07 (m, 2H), 7.02 – 6.95 (m, 3H), 6.71 (s, 1H), 6.40 (s, 1H), 3.79 (s, 2H), 3.71 (s, 1H), 3.13 (t, *J* = 5.6, 1H), 2.97 (dt, *J* = 7.0, 13.9, 1H), 2.92 – 2.83 (m, 4H), 2.44 – 2.32 (m, 1H), 1.12 (s, 3H), 1.11 (s, 3H), 0.98 (s, 1H), 0.97 (s, 1H). ^{13}C NMR (150 MHz, MeOD) δ 164.29, 164.16, 162.66, 162.53, 162.29, 153.14, 142.22, 140.60, 139.99, 136.28, 136.18, 135.87, 135.74, 135.56, 133.79, 133.77, 133.69, 133.67, 133.46, 133.39, 131.77, 131.72, 131.70, 131.57, 131.52, 130.86, 130.77, 130.58, 128.67, 128.61, 127.38, 120.26, 116.70, 116.56, 116.31, 116.16, 49.85, 49.43, 49.28, 49.14, 49.00, 48.94, 48.86, 48.72, 48.57, 48.28, 47.69, 46.71, 39.90, 39.51, 31.97, 30.82, 30.31, 29.77, 26.93, 22.20, 20.92. HRMS: calcd for $[C_{23}H_{26}FN_3O_2S + H]^+$ = 428.18025, found 428.18016.



(E)-N-(2-(2-(4-chlorobenzylidene)-3-methylbutylamino)ethyl)isoquinoline-5-sulfonamide **55ad**.

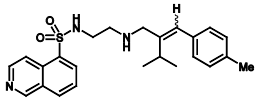
Data for the E-isomer: Yield: 74.6 mg, 133.9 µmol, 13.4 %. ^{1}H-NMR (MeOD): δ 9.68 (bs, 1H, H6), 8.84 – 8.83 (d, 1H, H2, J_1 = 6.06 *Hz*), 8.71 (bs, 1H, H1), 8.66 – 8.65 (d, 1H, H5, J_1 = 7.32 *Hz*), 8.59 – 8.57 (d, 1H, H3, J_1 = 8.22 *Hz*), 7.99 – 7.97 (t, 1H, H4, J_1 = 7.14 *Hz*, J_1 = 7.80 *Hz*), 7.35 – 7.34 (d, 2H, H11, J_1 = 8.28 *Hz*), 7.21 – 7.19 (d, 2H, H12, J_1 = 8.22 *Hz*), 6.49 (s, 1H, H10), 3.81 (s, 2H, H9), 3.29 – 3.26 (m, 4H, H7/8), 3.08 – 3.00 (m, 1H, H13), 1.08 – 1.07 (d, 6H, H14, J_1 = 7.02 *Hz*); ^{13}C-NMR (MeOD): δ 152.02, 141.22, 139.76, 137.35, 136.31, 136.29, 136.10, 134.20, 134.14, 131.22, 129.56, 129.45, 127.16, 121.47, 48.93, 48.26, 39.93, 29.84, 20.88; HRMS: calcd for $[C_{23}H_{26}ClN_3O_2S + H]^+$ = 444.15070, found 444.15066. **Data for the Z-isomer**: Yield: 41.8 mg, 75.0 µmol, 7.5 %. ^{1}H NMR (600 MHz, MeOD) δ 9.51 (s, 1H), 8.69 (s, 1H), 8.57 (d, *J* = 6.1, 1H), 8.50 (d, *J* = 8.2, 1H), 8.42 (d, *J* = 7.3, 1H), 7.91 (t, *J* = 7.8, 1H), 7.42 (d, *J* = 8.3, 2H), 7.22 (d, *J* = 8.3, 2H), 6.87 (s, 1H), 3.96 (s, 2H), 3.02 (d, *J* = 5.3, 2H), 2.99 (d, *J* = 5.3, 2H), 2.52 (dt, *J* = 6.7, 13.4, 1H), 1.28 (d, *J* = 6.7, 6H), . ^{13}C NMR (150 MHz, MeOD) δ 154.01, 144.13, 140.43, 136.17, 135.60, 135.33, 135.28, 134.59, 132.68, 131.68, 131.42, 131.42, 131.05, 130.00, 130.00, 129.99, 129.63, 128.01, 60.79, 49.43, 49.43, 49.42, 49.29, 49.28, 49.28, 49.15, 49.14, 49.14, 49.01, 49.00, 49.00, 48.86, 48.86, 48.85, 48.72, 48.72, 48.71, 48.58, 48.57, 48.57, 47.67, 46.68, 39.45, 32.06, 22.20. HRMS: calcd for $[C_{23}H_{26}ClN_3O_2S + H]^+$ = 444.15070, found 444.15069.



(E)-N-(2-(2-(4-bromobenzylidene)-3-methylbutylamino)ethyl)isoquinoline-5-sulfonamide **55ae**.

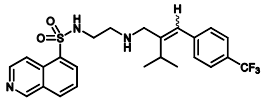
Data for the E-isomer: Yield: 50 mg, 83.2 µmol, 8.3 %. ^{1}H-NMR (MeOD): δ 9.69 (bs, 1H, H6), 8.80 (m, 2H, H1/2), 8.66 – 8.64 (d, 1H, H5, J_1 = 7.30 *Hz*), 8.58 – 8.56 (d, 1H, H3, J_1 = 8.20 *Hz*), 7.99 – 7.96 (t, 1H, H4, J_1 = J_2 =7.80 *Hz*), 7.55 – 7.53 (d, 2H, H11, J_1 = 8.30 *Hz*), 7.19 – 7.17 (d, 2H, H12, J_1 = 8.30 *Hz*), 6.52 (s, 1H, H10), 3.85 (s, 2H, H9),

3.33 – 3.29 (m, 4H, H7/8), 3.12 – 3.07 (m, 1H, H13), 1.12 – 1.11 (d, 6H, H14, J_1 = 6.95 *Hz*); ^{13}C-NMR (MeOD): δ 154.50, 145.19, 141.40, 136,69, 135.43, 135.32, 134.98, 132.69, 132.60, 131.54, 127.74, 127.13, 122.27, 118.95, 39.91, 29.90, 20.92; HRMS: calcd for $[C_{23}H_{26}BrN_3O_2S + H]^+$ = 488.10019, found 488.10000. **Data for the Z-isomer**: yield: 100.0 mg, 166.4 µmol, 16.6 %. ^{1}H NMR (500 *MHz*, MeOD) δ 10.28 – 9.33 (m, 1H), 8.84 (s, 2H), 8.58 (d, *J* = 8.2, 1H), 8.54 (d, *J* = 7.3, 1H), 7.98 (t, *J* = 7.8, 1H), 7.48 (d, *J* = 8.3, 3H), 7.10 (d, *J* = 8.2, 3H), 6.76 (s, 1H), 3.89 (s, 3H), 3.02 (s, 6H), 2.56 – 2.44 (m, 2H), 1.21 (d, *J* = 6.7, 9H). ^{13}C NMR (MeOD) δ 140.64, 137.40, 136.55, 136.37, 136.03, 134.12, 132.88, 131.61, 131.45, 129.63, 122.42, 47.79, 46.82, 39.54, 31.96, 22.13.



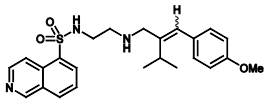
(E)-N-(2-(3-methyl-2-(4-methylbenzylidene)butylamino)ethyl)isoquinoline-5-sulfonamide **55af**.

Data for the E-isomer: Yield: 8.7 mg, 16.2 µmol, 1.6%. ^{1}H NMR (400 MHz, MeOH) δ 9.65 (bs, 1H), 8.73 (s, 2H), 8.61 (d, *J* = 6.4, 1H), 8.54 (d, *J* = 8.2, 1H), 8.00 – 7.90 (m, 1H), 7.21 (d, *J* = 8.0, 2H), 7.16 (d, *J* = 8.1, 2H), 6.54 (s, 1H), 3.84 (s, 2H), 3.24 – 3.11 (m, 2H), 2.36 (s, 3H), 1.13 (s, 3H), 1.11 (s, 3H). HRMS: calcd for $[C_{24}H_{29}N_3O_2S + H]^+$ = 424.20532, found 424.20530. **Data for the Z-isomer**: Yield: 42.0 mg, 78.2 µmol, 7.8 %. ^{1}H NMR (600 MHz, MeOD) δ 9.53 (s, 1H), 8.67 (d, *J* = 22.1, 1H), 8.62 (d, *J* = 6.2, 1H), 8.49 (d, *J* = 8.2, 1H), 8.45 (dd, *J* = 0.9, 7.4, 1H), 7.88 (t, *J* = 7.8, 1H), 7.17 (d, *J* = 7.8, 2H), 7.05 (d, *J* = 7.9, 2H), 6.81 (s, 1H), 3.92 (s, 2H), 2.98 (s, 4H), 2.48 (dt, *J* = 6.7, 13.3, 1H), 2.30 (s, 3H), 1.22 (s, 3H), 1.21 (s, 3H). ^{13}C NMR (100 MHz, MeOH) δ 151.92, 139.60, 139.17, 138.60, 137.31, 136.29, 136.00, 134.52, 134.20, 132.73, 130.47, 129.62, 129.44, 121.44, 49.64, 49.43, 49.21, 49.00, 48.79, 48.57, 48.36, 47.73, 46.97, 39.58, 32.07, 22.22, 21.20. HRMS: calcd for $[C_{24}H_{29}N_3O_2S + H]^+$ = 424.20532, found 424.20514.



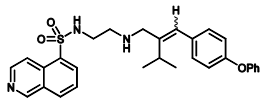
(E)-N-(2-(3-methyl-2-(4-(trifluoromethyl)benzylidene)butylamino)ethyl)isoquinoline-5-sulfonamide **55ag**.

Data for the E-isomer: Yield: 89.8 mg, 151.9 µmol, 15.2 %. ^{1}H NMR (600 MHz, MeOD) δ 9.53 (s, 1H), 8.66 (s, 1H), 8.61 (s, 1H), 8.52 (dd, *J* = 1.0, 7.4, 1H), 8.44 (d, *J* = 8.2, 1H), 7.84 (t, *J* = 7.8, 1H), 7.55 (d, *J* = 8.1, 2H), 7.31 (d, *J* = 8.1, 2H), 6.47 (s, 1H), 3.75 (s, 2H), 3.20 (d, *J* = 6.0, 1H), 3.15 (d, *J* = 5.5, 2H), 2.94 (dt, *J* = 6.9, 13.9, 1H), 0.99 (s, 3H), 0.98 (s, 3H). ^{13}C NMR (150 MHz, MeOD) δ 152.63, 142.54, 141.81, 141.13, 136.77, 136.06, 135.91, 133.78, 130.36, 130.29, 130.14, 129.03, 128.35, 126.69, 126.55, 126.36, 126.34, 124.76, 122.96, 49.43, 49.28, 49.14, 49.00, 48.86, 48.72, 48.57, 48.13, 39.93, 30.01, 20.87. HRMS: calcd for $[C_{24}H_{26}F_3N_3O_2S + H]^+$ = 478.17706, found 478.17681. **Data for the Z-isomer**: Yield: 78.6 mg, 133.0 µmol, 13.3%. ^{1}H NMR (600 MHz, MeOD) δ 9.75 (s, 1H), 8.86 (d, *J* = 6.0, 1H), 8.72 (s, 1H), 8.61 (d, *J* = 8.3, 1H), 8.59 (d, *J* = 7.3, 1H), 7.99 (t, *J* = 7.8, 1H), 7.66 (d, *J* = 8.1, 2H), 7.38 (d, *J* = 8.1, 2H), 6.87 (s, 1H), 3.90 (s, 2H), 3.05 (d, *J* = 4.6, 2H), 3.04 (d, *J* = 4.7, 2H), 2.54 (dt, *J* = 6.6, 13.2, 1H), 1.24 (s, 3H), 1.23 (s, 3H). ^{13}C NMR (150 MHz, MeOD) δ 151.95, 141.83, 141.64, 139.70, 137.26, 136.29, 135.97, 134.17, 131.27, 130.81, 130.60, 130.45, 130.38, 130.24, 130.17, 129.40, 128.28, 126.68, 126.65, 126.63, 126.48, 126.29, 125.89, 124.69, 122.83, 121.47, 116.95, 115.07, 49.85, 49.43, 49.28, 49.14, 49.00, 48.86, 48.72, 48.57, 48.07, 47.08, 39.69, 32.02, 29.88, 22.17, 20.90. HRMS: calcd for $[C_{24}H_{26}F_3N_3O_2S + H]^+$ = 478.17706, found 478.17683.



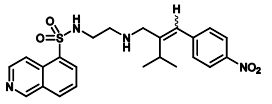
(E)-N-(2-(2-(4-methoxybenzylidene)-3-methylbutylamino)ethyl)isoquinoline-5-sulfonamide **55ah**.

Data for the 1/4 EZ mix: Yield: 36.5 mg, 66.0 µmol, 6.6 %. ^{1}H NMR (600 MHz, MeOD) δ 9.64 (s, 4H), 8.78 (s, 1H), 8.71 (s, 4H), 8.62 (s, 3H), 8.58 (d, *J* = 7.4, 2H), 8.50 (t, *J* = 7.5, 5H), 8.44 – 8.41 (m, 4H), 7.89 (dt, *J* = 7.9, 15.7, 5H), 7.05 (d, *J* = 8.5, 3H), 6.99 (d, *J* = 8.4, 8H), 6.83 – 6.77 (m, 10H), 6.67 (s, 4H), 6.38 (s, 1H), 3.83 (s, 7H), 3.67 (s, 4H), 3.66 (s, 11H), 3.18 – 3.15 (m, 4H), 3.08 – 2.99 (m, 1H), 2.87 (p, *J* = 5.6, 15H), 2.36 (dt, *J* = 6.6, 13.4, 4H), 1.10 (s, 12H), 1.09 (s, 11H), 0.98 (s, 4H), 0.97 (s, 3H). ^{13}C NMR (150 MHz, MeOD) δ 160.54, 160.39, 151.68, 139.02, 138.80, 138.45, 137.68, 137.57, 136.42, 136.25, 136.07, 134.43, 134.34, 132.45, 131.02, 130.92, 129.83, 129.71, 129.66, 129.64, 128.73, 115.25, 114.83, 55.74, 55.70, 49.43, 49.28, 49.14, 49.00, 48.86, 48.72, 48.57, 47.51, 46.74, 39.93, 39.49, 32.10, 29.65, 22.24, 20.99. HRMS: calcd for $[C_{24}H_{29}N_3O_3S + H]^+$ = 440.20024, found 440.20019.



(E)-N-(2-(3-methyl-2-(4-phenoxybenzylidene)butylamino)ethyl)isoquinoline-5-sulfonamide **55ai**.

Data for the 1/1 EZ mix: Yield: 59.0 mg, 95.9 µmol, 9.6%. ^{1}H NMR (600 MHz, MeOD) δ 9.27 (s, 2H), 8.51 (s, 2H), 8.44 (d, *J* = 5.8, 1H), 8.41 – 8.36 (m, 2H), 8.31 – 8.25 (m, 3H), 7.75 – 7.67 (m, 2H), 7.25 – 7.18 (m, 4H), 7.11 (d, *J* = 8.5, 2H), 7.05 (d, *J* = 8.4, 2H), 6.99 (t, *J* = 7.4, 2H), 6.89 – 6.81 (m, 8H), 6.69 (s, 1H), 6.41 (s, 1H), 3.83 (s, 2H), 3.70 (s, 2H), 3.16 (d, *J* = 5.5, 2H), 3.12 (d, *J* = 5.4, 1H), 3.07 – 2.97 (m, 1H), 2.88 (d, *J* = 4.1, 2H), 2.86 (d, *J* = 4.2, 2H), 2.42 – 2.32 (m, 1H), 1.11 (s, 3H), 1.09 (s, 3H), 0.98 (s, 3H), 0.97 (s, 3H). ^{13}C NMR (150 MHz, MeOD) δ 158.28, 158.10, 158.04, 154.22, 144.74, 139.86, 139.34, 135.36, 135.32, 135.17, 135.12, 135.07, 132.62, 132.56, 132.51, 132.28, 132.07, 131.35, 131.24, 130.96, 130.94, 130.66, 128.05, 127.82, 127.80, 124.78, 124.65, 120.17, 120.07, 119.73, 119.46, 119.11, 49.85, 49.43, 49.28, 49.14, 49.00, 48.86, 48.72, 48.57, 48.39, 47.79, 47.60, 46.72, 39.87, 39.47, 32.05, 29.74, 22.23, 20.98. HRMS: calcd for $[C_{29}H_{31}N_3O_3S + H]^+$ = 502.21589, found 502.21576.



(E)-N-(2-(3-methyl-2-(4-nitrobenzylidene)butylamino)ethyl)isoquinoline-5-sulfonamide **55aj**.

Data for the 10/1 E/Z mix: yield: 117.0 mg, 206.0 µmol, 20.6%. ^{1}H NMR (600 MHz, MeOD) δ 9.71 (s, 1H), 8.81 (s, 1H), 8.74 (s, 1H), 8.64 (d, *J* = 7.4, 1H), 8.57 (d, *J* = 8.2, 1H), 8.56 – 8.53 (m, 1H), 8.49 (d, *J* = 7.3, 1H), 8.24 (d, *J* = 8.7, 2H), 8.21 (d, *J* = 8.8, 1H), 7.97 (t, *J* = 7.8, 1H), 7.93 (t, *J* = 7.8, 1H), 7.47 (d, *J* = 8.4, 2H), 7.44 (d, *J* = 8.5, 1H), 6.91 (s, 1H), 6.59 (s, 1H), 3.93 (s, 1H), 3.88 (s, 2H), 3.31 (d, *J* = 5.6, 2H), 3.26 (d, *J* = 5.5, 2H), 3.11 – 3.00 (m, 1H), 2.59 – 2.51 (m, 1H), 1.11 (s, 3H), 1.10 (s, 3H). ^{13}C NMR (150 MHz, MeOD) δ 152.42, 148.23, 144.57, 143.73, 140.64, 136.95, 136.18, 135.98, 133.90, 131.00, 130.79, 129.21, 125.97, 124.90, 124.64, 49.43, 49.28, 49.14, 49.06, 49.00, 48.86, 48.72, 48.57, 48.09, 39.95, 30.18, 20.84. HRMS: calcd for $[C_{23}H_{26}N_4O_4S + H]^+$ =455.17475, found 455.17455. **Data for the 1/10 E/Z mix**: Yield: 60.8 mg, 107.0 µmol, 10.7 %. ^{1}H NMR (600 MHz, MeOD) δ 9.60 (s, 1H), 8.69 (s, 1H), 8.65 (s, 1H), 8.60 (d, *J* = 7.4, 1H), 8.53 (d, *J* = 9.4, 1H), 8.51 (d, *J* = 8.2, 1H), 8.45 (dd, *J* = 1.0, 7.4, 1H), 8.28 – 8.23 (m, 1H), 8.22 (d, *J* = 8.7, 2H), 7.97 – 7.92 (m, 1H), 7.89 (t, *J* = 7.8, 1H), 7.49 – 7.46 (m, 1H), 7.44 (d, *J* = 8.4, 2H), 6.92 (s, 1H), 6.58 (s, 1H), 3.93 (s, 2H), 3.03 (t, *J* = 5.4, 2H), 2.99 (t, *J* = 5.4, 2H), 2.57 –

2.50 (m, 1H), 1.26 (s, 4H), 1.25 (s, 3H), 1.12 (s, 1H), 1.11 (s, 1H). ^{13}C NMR (150 MHz, MeOD) δ 153.00, 144.43, 142.81, 141.87, 136.16, 135.97, 135.65, 133.49, 131.00, 130.84, 128.72, 124.91, 49.43, 49.28, 49.14, 49.00, 48.86, 48.72, 48.57, 47.96, 46.80, 39.56, 32.25, 22.15. HRMS: calcd for $[C_{23}H_{26}N_4O_4S + H]^+$ =455.17475, found 455.17463.

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