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Sulfonamides as Selective $Na_V1.7$ Inhibitors: Optimizing Potency and Pharmacokinetics While Mitigating Metabolic Liabilities

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ABSTRACT

Several reports have recently emerged regarding the identification of heteroarylsulfonamides as $Na_V1.7$ inhibitors that demonstrate high levels of selectivity over other Na_V isoforms. The optimization of a series of internal $Na_V1.7$ leads that address a number of metabolic liabilities including bioactivation, PXR activation, as well as CYP3A4 induction and inhibition led to the identification of potent and selective inhibitors that demonstrated favorable pharmacokinetic profiles and were devoid of the aforementioned liabilities. Key to achieving this within a series prone to transporter-mediated clearance was the identification of a small range of optimal cLogD values and the discovery of subtle PXR SAR that was not lipophilicity-dependent. This enabled the identification of compound **20** which was advanced into a target engagement pharmacodynamic model where it exhibited robust reversal of histamine-induced scratching bouts in mice.

INTRODUCTION

The transmembrane voltage-gated sodium channel $Na_V1.7$ has received considerable attention as a target for the treatment of pain.[1] There is a wealth of genetic evidence linking $Na_V1.7$ and the pain processing pathway. This evidence comes mostly in the form of loss-of-function and gain-of-function mutations in SCN9A, the gene encoding for $Na_V1.7$. The former leads to a rare condition known as congenital indifference to pain (CIP), which manifests in the inability of individuals to sense painful stimuli while not significantly impacting motor or cognitive function.[2] The latter leads to numerous painful conditions including primary inherited erythromelalgia, paroxysmal extreme pain disorder, and small fiber neuropathy.[3] These observations have spurred considerable efforts towards the development of potent and selective

inhibitors of $Na_V1.7$.[4] One of the primary challenges associated with these efforts has been the identification of isoform-selective inhibitors, in particular those that demonstrate suitable levels of selectivity over $Na_V1.5$, which is expressed in cardiac myocytes and plays a key role in cardiovascular function.[5]

Over the past several years, novel leads within a class of highly isoform-selective heteroarylsulfonamide-containing $Na_V1.7$ inhibitors were initially reported by Pfizer/Icagen[6] and later advanced by Genentech/Xenon.[7] We recently published findings detailing efforts associated with a novel series of isoform-selective heteroarylsulfonamides.[8] While this work culminated in the identification of a moderately potent, isoform-selective $Na_V1.7$ inhibitor that demonstrated excellent rodent pharmacokinetics and robust activity in a $Na_V1.7$-dependent pharmacodynamic model, this compound and generally those in this class suffered from several metabolic liabilities, including the activation of the nuclear hormone receptor pregnane X receptor (PXR) which can manifest in the induction of multiple drug metabolizing enzymes, including CYP3A4. Additionally, lead compounds contained a 2-aminothiazole, a motif prone to bioactivation, and as such represented a toxicity liability.[9] Herein we report efforts to obviate the metabolic liabilities associated with this class of compounds while improving potency and maintaining isoform selectivity and favorable pharmacokinetics.

RESULTS AND DISCUSSION

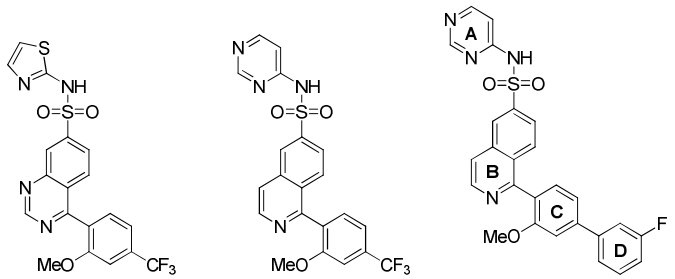
The series of $Na_V1.7$ inhibitors that we previously disclosed are represented by quinazoline **1** (Table 1).[8] This class of compounds suffered from metabolic liabilities that included activation of the nuclear hormone receptor PXR, a ligand-dependent transcription factor that serves a critical role in regulating detoxifying genes such as CYP3A4.[10] Consistent with PXR activation,

incubation of **1** with human hepatocytes led to the induction of CYP3A4.[11] Given the wealth of therapeutics metabolized by this CYP isoform and the potential for induction to lead to drug-drug interactions (DDIs), we focused on mitigating this liability.[12] Previous work found that the incorporation of a 2-aminothiazole warhead afforded inhibitors with a unique balance of potency and favorable pharmacokinetics, however this moiety presented a potential bioactivation risk. It has been well established that 2-aminothiazoles are prone to epoxidation and subsequent scission to yield a reactive thiourea metabolite that is capable of oxidizing glutathione (GSH) and hence has the potential for idiosyncratic adverse drug reactions (IADRs).[13] It was demonstrated that upon incubation of **1** with human liver microsomes (HLMs), GSH, and nicotinamide adenine dinucleotide phosphate (NADPH), both the corresponding thiourea and the GSH-adduct were observed. The adducts observed were presumably the result of oxidation of the C4-C5 double bond followed by subsequent nucleophillic attach of GSH at the carbon adjacent to the thiazole nitrogen (C4). While the amount of these potentially reactive intermediates could be reduced upon the introduction of substituents onto the thiazole, the steep SAR limited what was tolerated (e.g., CH_3, F, Cl, CN) and in none of these cases could the formation of the thiourea and the GSH-adduct be completely obviated. With the goal of identifying a clinically useful $Na_V1.7$ inhibitor, efforts focused on addressing these liabilities while improving potency and achieving a preclinical pharmacokinetic profile that would portend favorable human pharmacokinetics.

To address the issue of bioactivation, we considered the utility of a compound previously reported by Amgen wherein the 2-aminothiazole had been replaced with a 4-aminopyrimidine (**2**). While this ring mitigated the potential for the formation of reactive metabolites, and maintained a favorable pharmacokinetic profile, the 4-aminopyrimidine brought with it a loss in

potency, a modest level of CYP3A4 inhibition (IC_{50} ~ 7 μM) and significant induction of CYP3A4.

Table 1. Representative Amgen $Na_V1.7$ Inhibitors



Compound	**1**	**2**	**3**
$Na_V1.7$ IC_{50} (μM)	0.16	0.73	0.15
$Na_V1.5$ IC_{50} (μM)	>30	>30	>30
Rat iv CL[a] [CLu] (L/hr/kg)	0.54 [27]	0.26 [11]	1.7 [390]
Dog iv CL[b] [CLu] (L/hr/kg)	0.013 [12]	0.055 [1.6]	0.049 [9.1]
CYP3A4 induction (%)[c]	128	177	12
CYP3A4 inhibition IC_{50} (μM)	>50	7.2	1.3
cLogD	2.1	1.7	2.1

[a]0.5 mg/kg in DMSO to male rats. CLu = unbound clearance = total clearance/f_{up}. [b]0.25 mg/kg in DMSO to male dogs. CLu = unbound clearance = total clearance/f_{up} where f_{up} is the unbound fraction in plasma. [c]Expressed as a percentage of the induction seen with rifampicin when both compounds are incubated with human hepatocytes at a concentration of 10 μM.

Utilizing **2** as a starting point, our efforts were focused on improving potency, mitigating CYP3A4 inhibition and reducing PXR activation and/or CYP3A4 induction. One strategy frequently used to help mitigate PXR activation is the incorporation of polarity.[14] Our previous efforts had demonstrated that while potency could be retained upon introduction of polarity within the core of the heterocyclic sulfonamide the increased polar surface area (PSA) brought

with it a significant increase in the rate of in vivo clearance.[8,15] This latter trend was attributed to the observation that this series was prone to transporter-mediated clearance. LogD is one of the most important molecular properties correlating with biliary clearance, wherein reduced LogD often trends with an increase in biliary clearance.[16] Thus, it was anticipated that an approach wherein polarity would be incorporated to attenuate PXR activation would be challenging due to the anticipated detrimental impact this would have on the pharmacokinetic profile. An alternative strategy that was also pursued was one focused on the strategic introduction of substituents to induce unfavorable steric interactions between the inhibitor and the nuclear receptor. These approaches would be undertaken with the goal of identifying an inhibitor with a cLogD between 1.5 – 3.0, a range that we believed could give rise to an inhibitor with a favorable pharmacokinetic profile and also fall within the generally acceptable range for drug-like molecules.[17, 18]

Earlier work within this series had revealed a significant amount of latitude when additional lipophilicity was incorporated at the *para* position of the aryl C-ring. While we were mindful of the already elevated cLogD of compound **2**, we were optimistic that the acidic nature of these molecules would allow for the incorporation of additional lipophilicity and added molecular weight without a detrimental effect on physicochemical properties (e.g., solubility) and key in vitro assays (e.g., microsomal clearance assays). As an initial foray into this area, the *para*-CF_3 moiety of **2** was replaced with a *meta*-fluoro substituted aryl ring to provide **3**. This compound demonstrated a 5-fold increase in $Na_V1.7$ potency, maintained a high level of selectivity over $Na_V1.5$ and interestingly, did not lead to CYP3A4 induction. Compound **3** demonstrated low turnover in human, rat and dog liver microsomes (CL_{int} <14 μL/min/mg), excellent passive permeability (27 μcm/sec) and high aqueous solubility (344 μM in PBS). Furthermore **3**

exhibited low to moderate iv clearance (CL), both total and unbound (CLu), in rat and dog. The disparity in the rates of clearance across species (~40x) was partially attributed to the involvement of hepatobiliary transporters. A series of hepatocyte experiments were undertaken where it was found that compound **3** was rapidly removed from the medium when incubated with attached rat hepatocytes. This process could then be inhibited by the organic anion-transporting polypeptide 1B1 (OATP1B1) and multidrug resistance-associated protein 2 (MRP2) inhibitor MK-571 ((E)-3-(((3-(2-(7-chloroquinolin-2-yl)vinyl)phenyl)((3-(dimethylamino)-3-oxopropyl)thio)methyl)thio)propanoic acid) demonstrating that this compound was a substrate for uptake transporters.[19] It has been reported that for biliary-excreted drugs there can be a significant species differences in clearance. For these reasons, we chose to drive this program on both rat and dog iv CL given the uncertainties associated with the translation of preclinical pharmacokinetics to humans for drugs cleared via a biliary mechanism.[16]

A brief exploration of SAR around the C and D rings found that the ideal substitution pattern was one wherein both were substituted at the *meta* position and the C-ring was further substituted with a methoxy group at the carbon *ortho* to the B-ring core (vide infra). Early in these explorations it was found that a ~3-fold boost in potency could be obtained by incorporation of chlorine on the C-ring (**4**; Table 2). This modification did not lead to an increase in turnover in liver microsomes, hence this functionality was maintained in subsequent SAR efforts.

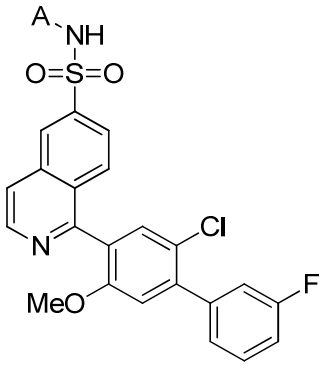
Table 2 illustrates efforts undertaken to identify a suitable alternative to the 4-aminopyrimidine that would retain the potency, but lack the CYP3A4 inhibition, associated with this ring.[20] A number of heteroaromatic A-rings were evaluated and generally it was found that 5-membered heterocycles were more potent than their 6-membered congeners (**7** – **10** vs. **4** – **6**). All of the

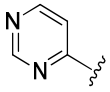
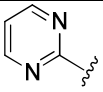
compounds, with the exception of 2-aminoxazole **9**, exhibited low turnover in both human and rat liver microsomes. Additionally, apart from **7**, which was a potent inhibitor of CYP3A4 (0.80 μM) and was only modestly selective over $Na_V1.5$ (1.5 μM), all of the compounds in Table 2 were devoid of CYP3A4 inhibition (>27 μM) and demonstrated high levels of selectivity over $Na_V1.5$ (IC_{50}s > 10 μM). The $Na_V1.7$ potencies are noteworthy as we had previously observed that compounds lacking an aryl D-ring were not tolerant of a wide range of A-rings and exhibited steep SAR in this region of the molecule.[8] Specifically, without a D-ring, compounds containing a 1,2,4-aminothiadiazole were considerably more potent than their 2-aminothiazole and 4-aminopyrimidine counterparts which were in turn significantly more potent than a variety of other A-rings evaluated. However, the 1,2,4-aminothiadiazole generally conferred poor passive permeability (<5 μcm/sec) and high in vivo CL, hence the decision to initially pursue compounds containing a 2-aminothiazole. Despite the aforementioned bioactivation risk associated with this moiety, it was somewhat unique within compounds without a D-ring in that it could provide compounds with an overall good balance of potency and favorable pharmacokinetics. Interestingly, within the context of aryl D-ring-containing compounds, the previously observed steep SAR associated with the A-ring was no longer apparent. A wide range of heterocycles were tolerated in this region and the 1,2,4-aminothiadiazole (**7**) did not stand out with respect to $Na_V1.7$ potency. In light of their potent inhibition of $Na_V1.7$ and lack of CYP3A4 inhibition, compounds **8** and **10** were further profiled to evaluate their in vivo pharmacokinetics.

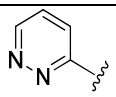
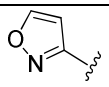
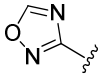
Upon measurement of their rates of iv clearance in both rat and dog, it was found that **8** stood out in this regard, exhibiting a significantly better pharmacokinetic profile in both species. The elevated clearance associated with **10** was attributed to the slightly reduced cLogD (1.9) and hence a likely increased susceptibility to transporter-mediated clearance. While **8** was found to

activate PXR and lead to CYP3A4 induction (58% POC @ 10 μM),[21] it was unique in that it merged potent inhibition of $Na_V1.7$ (<50 nM) and favorable pharmacokinetics, a previously elusive profile within this series of inhibitors. It should be noted that the need to identify very low clearance molecules was particularly important within this class of compounds. It is well known that most acidic molecules demonstrate volume of distribution (V_{dss}) at or below extracellular fluid volume, hence the identification of compounds that will demonstrate half-lives suitable for once-daily dosing requires very low clearance values.[21] We hypothesized that the addition of polarity and/or modifications elsewhere in the molecule could address the PXR activation observed with this compound. Ultimately the potency and pharmacokinetics of **8** outweighed the induction and we chose to conduct subsequent SAR efforts utilizing the 3-aminoisoxazole A-ring.

Table 2. Selected A-Ring SAR



Cpd	A	$Na_V1.7$ IC_{50} (μM)	HLM / RLM CL_{int} (μL/min/mg)	PXR activation[a]	cLogD	Rat iv CL[b] [CLu] (L/hr/kg)	Dog iv CL[c] [CLu] (L/hr/kg)
4		0.065	<14 / <14	24	2.6	--	--
5		0.12	<14 / 32	31	2.6	--	--

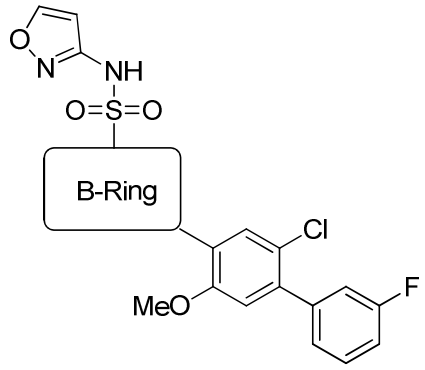
6		0.14	<14 / 29	52	3.2	--	--
7		0.023	<14 / <14	5.9	1.9	--	--
8		0.049	<14 / 18	68	2.6	0.047 [42]	0.003 [1.6]
9		0.22	46 / 98	38	2.7	--	--
10		0.047	<14 / 20	10	1.9	1.6 [940]	0.17 [154]

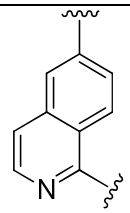
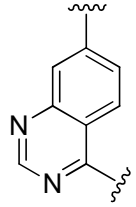
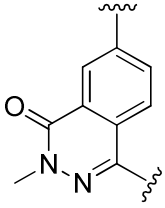
[a]Expressed as a percentage of the induction seen with rifampicin when both compounds are used at a concentration of 10 μM. [b]0.5 mg/kg in DMSO to male rats. CLu = unbound clearance = total clearance/f_{up} where f_{up} is the unbound fraction in plasma. [c]0.25 mg/kg in DMSO to male dogs. CLu = unbound clearance = total clearance/f_{up}.

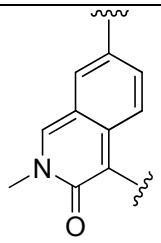
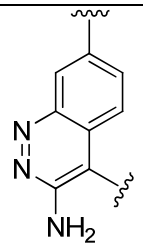
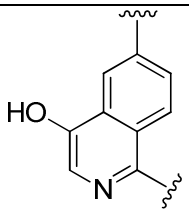
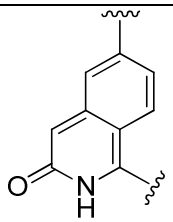
Attempting to alleviate PXR via a judicious reduction in LogD, we turned our attention to the incorporation of polarity into the central core of this class of compounds and prepared a number of different [6,6]-heterocyclic sulfonamides, representatives of which are illustrated in Table 3. As previously observed, it was found that an increase in PSA was generally well tolerated, with compounds showing potency values comparable to **8**. This was true for compounds that spanned a range of cLogDs (1.3 – 2.8). Unfortunately, in most cases the addition of polarity did not help mitigate PXR activation (**11** – **14**). Compounds **15** and **16** both demonstrated reduced levels of PXR activation and were evaluated in vivo to understand the implications that increased polarity would have on the pharmacokinetics. In both cases, the added polarity manifested in a significant increase in both the total and unbound clearance, further highlighting the challenges associated with designing a potent compound without PXR activation from within this series of inhibitors without adversely impacting pharmacokinetics. Interestingly, while compounds **11** – **13** and **15** demonstrated high levels of selectivity over $Na_V1.5$ (>10 μM), **14** and **16** were

somewhat unique in that they both showed modest-to-potent inhibition of this isoform (0.14 and 0.82 μM, respectively).

Table 3. Selected modifications to the central B-ring core



Cpd	X_1	$Na_v1.7$ IC_{50} (μM)	HLM/RLM CL_{int} (μL/min/mg)	PXR activation[a]	cLogD	Rat iv CL[b] [CLu] (L/hr/kg)	Dog iv CL[c] [CLu] (L/hr/kg)
8		0.051	<14 / 18	68	2.6	0.047 [42]	0.003 [1.9]
11		0.037	21 / 58	59	1.9	--	0.12 [25]
12		0.12	16 / 25	54	1.1	2.1 [620]	0.11 [31]

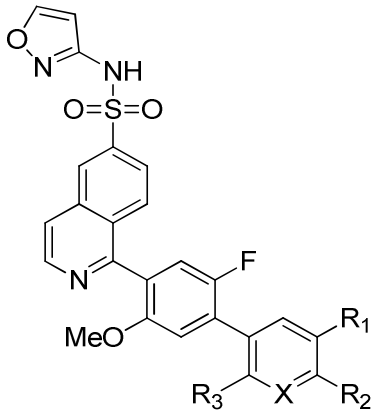
13		0.039	<14 / 21	69	2.8	--	--
14		0.028	<14 / <14	95	1.7	--	--
15		0.085	15 / 28	28	1.8	--	0.13 [140]
16		0.041	<14 / 18	27	1.3	2.1 [1,500]	0.82 [510]

[a]Expressed as a percentage of the activation response seen with rifampicin when both compounds are used at a concentration of 10 μM. [b]0.5 mg/kg in DMSO to male rats. CLu = unbound clearance = total clearance/f_{up} where f_{up} is the unbound fraction in plasma. [c]0.25 mg/kg in DMSO to male dogs. CLu = unbound clearance = total clearance/f_{up}

Focusing on D-ring SAR, it was found that substituting the fluorine and chlorine atoms on **8** to provide **17** did not significantly impact potency or PXR activation, hence subsequent D-ring SAR was explored within the context of a *meta*-fluoro substituted C-ring (Table 4). A wide range of substituents and substitution patterns were tolerated although substitution at the *meta* and *para* positions generally led to more potent inhibitors. All compounds were highly selective over $Na_V1.5$ (>10 μM) and demonstrated low turnover in rat and human liver microsomes. After a significant amount of SAR, a trend emerged wherein potency could be maintained and PXR

activation could reliably be avoided with D-rings that contained relatively bulky substituents at the *meta* and/or *para* positions. This can be seen by comparing compounds **17** – **18** and **22** with **19** – **21** wherein the latter, despite being more lipophilic, do not lead to PXR activation. The decreased PXR activation observed with compounds like **20** may be the result of a steric clash between the inhibitor and the nuclear hormone receptor. The strategy was routinely employed as it allowed for balancing the lipophilicity needed for potency and good pharmacokinetics with low PXR activation. The incorporation of polarity, while tolerated from a potency perspective, did not reduce PXR activation (**23**).

Table 4. Exploration of D-Ring SAR

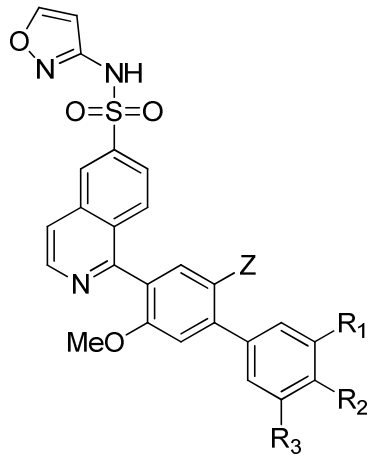


Cpd	R_1	R_2	R_3	X	$Na_v1.7$ IC_{50} (μM)	HLM/RLM CL_{int} (μL/min/mg)	PXR activation[a]	cLogD
17	Cl	H	H	C(H)	0.037	36 / 34	34	2.7
18	F	H	H	C(F)	0.040	30 / <14	47	2.3
19	CH_3	Cl	H	C(H)	0.060	35 / 21	1	3.1
20	CF_3	H	H	C(H)	0.036	<14 / <14	1	2.9
21	H	CF_3	H	C(H)	0.24	<14 / <14	0	2.9
22	CH_3	H	H	C(H)	0.047	36 / 34	54	2.5
23	F	H	OCH_3	N	0.068	<14 / 21	151	1.2

[a]Expressed as a percentage of the activation response seen with rifampicin when both compounds are used at a concentration of 10 μM.

To further support the trend outlined in Table 4, a number of analogs were prepared to probe the impact of a bulky *meta* substituent on PXR activation. Illustrated in Table 5 are additional representative examples, within the context of differentially substituted C-rings, wherein the incorporation of a trifluoromethyl group on the D-ring obviated the PXR activation associated with analogs that lacked this bulky substituent (**24** vs. **25**; **26** vs **27**). These examples provide another illustration of PXR activation being presumably being mitigated by the introduction of substituents which lead to steric interactions between the inhibitor and the nuclear receptor.

Table 5. Obviating PXR activation with the incorporation of a bulky substituent on the D-ring



Cpd	R_1	R_2	R_3	Z	$Na_v1.7$ IC_{50} (μM)	PXR activation[a]	cLogD

24	F	H	F	H	0.17	38	2.1
25	CF_3	H	H	H	0.061	7	2.7
26	F	H	F	CN	0.14	54	1.9
27	CF_3	H	H	CN	0.028	5	2.4

[a]Expressed as a percentage of the activation response seen with rifampicin when both compounds are used at a concentration of 10 μM.

In light of the favorable balance of potency and lack of both PXR activation and CYP3A4 induction (7% POC @ 10 μM)[21] demonstrated by **20**, this compound was further profiled. The pharmacokinetic profile across rat and dog is illustrated in Table 6. The total and unbound clearance in both rat and dog were acceptable and consistent with the previously observed trend of higher clearance in rat vs. dog, resulting in a shorter $t_{1/2}$ in rat vs dog (6.2 vs. 20 hr). In accord with the high aqueous solubility (432 μM in simulated intestinal fluid, pH 6.8), the compound demonstrated good oral absorption and acceptable bioavailability in both rat and dog (%F = 54 – 60).

Table 6. Pharmacokinetic Profiles and Plasma Protein Binding of **20**

	iv[a]			po[b]			
species	CL [CLu][c] (L/h/kg)	V_{dss} (L/kg)	$t_{1/2}$ (h)	AUC (μM*hr)	tmax (h)	%F	plasma protein binding (f_{up})
rat	0.23 [37]	2.1	6.2	44.2	6.0	54	0.0087
dog	0.023 [3.6]	0.56	20	101	2.0	63	0.0066

[a]rat: 0.5 mg/kg in DMSO; dog: 0.25 mg/kg in DMSO. CLu = unbound clearance = total clearance/f_{up}. [b]rat: 10 mg/kg oral dose as a solution in 1%Tween 80/2% HPMC/97%water/KOH at pH = 10; dog: 2 mg/kg (dog) oral dose as a solution in 30% HPBCD/70%water/NaOH at pH = 10. [c]CLu = unbound clearance = total clearance/f_{up}, where f_{up} is the unbound fraction in plasma.

The selectivity of **20** across the Na_V isoforms was determined by evaluation using the IonWorks Quattro (IWQ) electrophysiology platform. As illustrated in Table 7, **20** demonstrated very high levels of selectivity (>400-fold) against the Na_V isoforms that were evaluated. No

inhibition of hERG was observed (hERG PatchXpress IC_{50} >10 μM)[23] and while the compound was devoid of activity on CYP3A4, 2D6 and 1A2 (IC_{50} >15 μM), it did show potent inhibition of CYP2C9 (IC_{50} = 0.43 μM). Addressing this latter liability will be the subject of a subsequent manuscript.

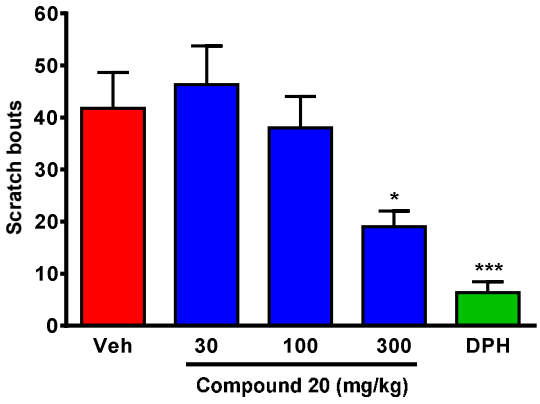
Table 7. Selectivity profile of **20** against $Na_V1.1$ – $Na_V1.6$

$Na_V1.1$ IC_{50} (μM)	$Na_V1.3$ IC_{50} (μM)	$Na_V1.4$ IC_{50} (μM)	$Na_V1.5$ IC_{50} (μM)	$Na_V1.6$ IC_{50} (μM)	$Na_V1.7$ IC_{50} (μM)
17	6.9	12	12	16	0.017

The state-dependent block of $Na_V1.7$ observed with our previously reported heteroarylsulfonamides was also evident with the inhibitors reported herein and was confirmed with manual electrophysiology measurements.[8] When **20** was evaluated at a holding potential wherein the channels were in a closed, fully-inactivated state (-140 mV), the IC_{50} was right-shifted ~200-fold [4.0 μM], clearly demonstrating the state-dependent block of $Na_V1.7$.

The observation that **20** was potent against mouse, but not rat, $Na_V1.7$ (mouse / rat $Na_V1.7$ Patch-Xpress IC_{50}: 0.036 / 4.0 μM) necessitated the evaluation of in vivo pharmacology in mice. The aforementioned lack of potency on rat $Na_V1.7$ was not particulalry surprising as this has previously been observed with compounds from this general class of inhibitors.[8] As a means to measure $Na_V1.7$ target engagement in vivo, **20** was evaluated in a mouse histamine-induced scratching model. There is a significant amount of data implicating $Na_V1.7$ as an important mediator in the itch pathway, including human genetic evidence that SCN9A gain-of-function mutations can lead to paroxysmal itch,[22] as well as the near complete lack of scratching behavior in $Na_V1.7$ knockout mice in response to an intradermal histamine challenge.[23] It has also been demonstrated that the transmission of both pruriceptive and nociceptive sensory information into

the spinal cord occurs via axons of C-fibers and hence supports the utility of a histamine-induced scratching model in preclinical and clinical settings. Oral administration of **20** to C57Bl/6 mice demonstrated a robust reduction in the number of scratching bouts induced by the intradermal injection of histamine (Figure 1). It should be noted that this dose, and a similar exposure, did not lead to a significant reduction in activity in a separate open-field activity study in naïve mice. The high level of target coverage required to elicit a robust response (45-fold over the mouse $Na_V1.7$ IC_{50}; mouse plasma protein binding (f_{up}): 0.0116) and the steep dose-response are in line with the pharmacokinetic/pharmacodynamic (PK/PD) relationship that has been generated with a range of internal compounds that span a number of different chemotypes and will be the subject of a future publication.[8, 26]



(A)

Dose (mg/kg)	$[plasma]_{total}$ (μM)	$[plasma]_{unbound}$ (μM)
30	21.2 ± 9.55	0.246
100	106 ± 22.3	1.23
300	137 ± 25.7	1.59

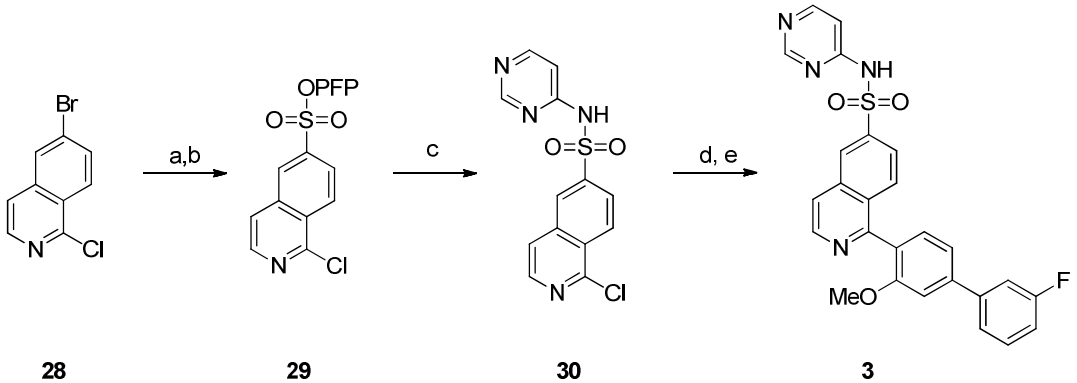
(B)

Figure 1. (A) Reduction of scratch bouts in a mouse histamine-induced scratch model with vehicle, **20**, and DPH (diphenhydramine, 30 mg/kg po dosing). *, $p < 0.05$, ***, $p < 0.0001$ versus vehicle group (one-way ANOVA followed by Dunnett's tests). (B) Total and unbound plasma exposure levels of **20**.

CHEMISTRY

The synthesis of pyrimidine **3** is outlined in Scheme 1. Benzyl mercaptan was coupled with 6-bromo-1-chloroisoquinoline (**28**) to provide an intermediate that was converted to pentafluorophenyl (PFP) ester **29** following oxidation of the thioether to the sulfonyl chloride and treatment with pentafluorophenol.[25] Pyrimidine **30** was obtained following the deprotonation of 4-aminopyrimidine with lithium bis(trimethylsilyl)amide (LHMDS) and the addition of this anion into the activated PFP ester. These conditions proved to be applicable for the incorporation of a wide-range of heterocyclic amines. Coupling of **30** with 4-chloro-2-methoxyphenyl)boronic acid proceeded smoothly to deliver an intermediate that could subsequently be elaborated to **3** using standard Suzuki coupling conditions.

Scheme 1. Synthesis of pyrimidine analog **3**[a].

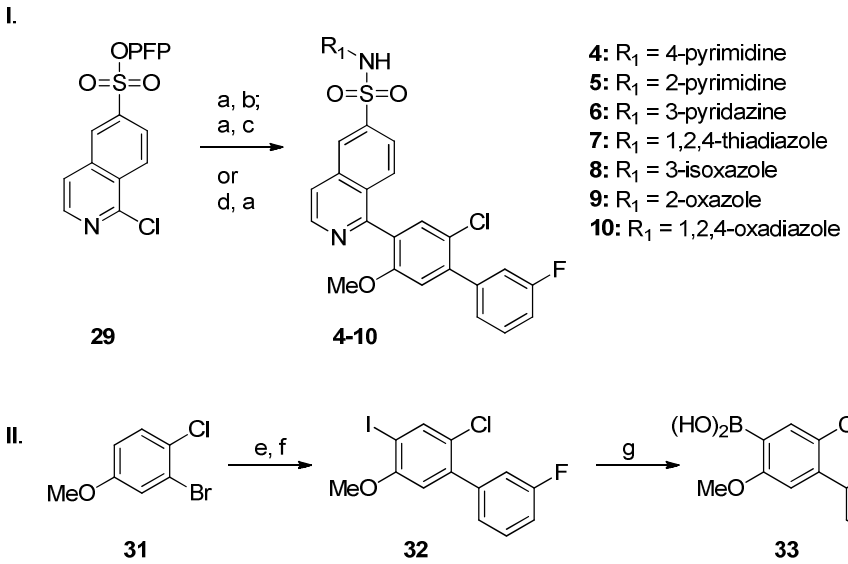


28 **29** **30** **3**

[a]Reagents and conditions: (a) Xantphos, $Pd_2(dba)_3$, benzyl mercaptan, DIPEA, dioxane, 120 ºC, 50%; (b) i) 1,3-dichloro-5,5-dimethylimidazolidine-2,4-dione, MeCN, AcOH, H_2O, 0 ºC, ii) pentafluorophenol, TEA, DCM, 68%; (c) pyrimidin-4-amine, LHMDS, THF, 60%; (d) (4-chloro-2-methoxyphenyl)boronic acid, K_2CO_3, $Pd(PPh_3)_4$, dioxane, H_2O, μW, 100 °C, 71%; (e) (3-fluorophenyl)boronic acid, dicyclohexyl(2',6'-dimethoxy-[1,1'-biphenyl]-2-yl)phosphine, chloro(2-dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl)[2-(2-aminoethylphenyl)]Pd(II) DCM, K_3PO_4, dioxane, H_2O, μW, 120 °C, 52%.

Scheme 2 illustrates the routes that were used to access isoquinoline analogs **4** – **10** wherein modifications were made to the A-ring region of the molecule. Synthesis of these compounds necessitated the preparation of (2-chloro-3'-fluoro-5-methoxy-[1,1'-biphenyl]-4-yl)boronic acid (**33**), which was prepared in an efficient three step sequence starting with 2-bromo-1-chloro-4-methoxybenzene (**31**) and proceeding through iodide **32**. The derived boronic acid was coupled to chloroisoquinoline **29** to provide a PFP-ester that enabled diversification to compounds **4** – **6** and **8** – **9** using the aforementioned LHMDS-mediated conditions. The coupling of **29** and 1,2,4-aminothiadiazole to furnish **7** was carried under slightly modified conditions that utilized cesium carbonate. The synthesis of **10** necessitated the preparation of *tert*-butyl 1,2,4-oxadiazol-3-ylcarbamate[26] to enable smooth addition of this aminoheterocycle into PFP-ester **29** which was subsequently coupled with **33** to provide the fully elaborated compound (**10**) in acceptable yield.

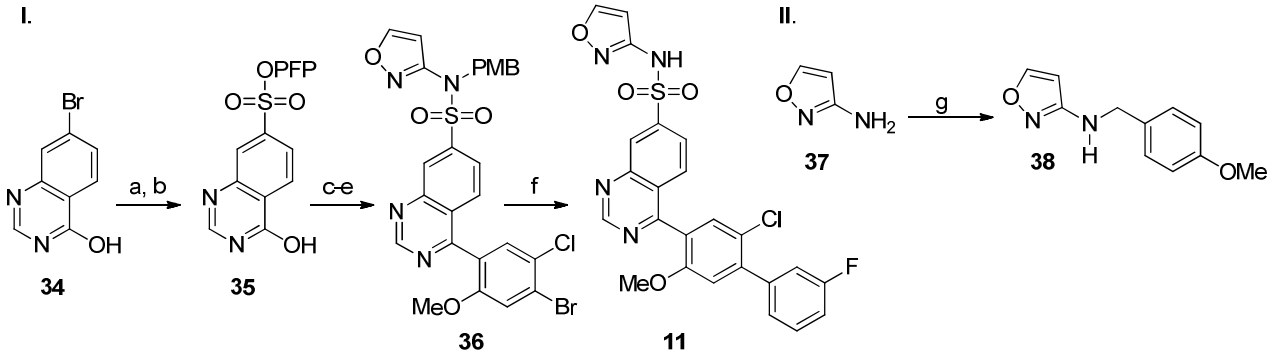
Scheme 2. Synthesis of A-ring analogs **4** – **10**[a]



[a]Reagents and conditions: (a) **28**, K_2CO_3, $Pd(PPh_3)_4$, dioxane, H_2O, 50 °C, 80%; (b) R_1-NH_2, LHMDS, THF, 0 °C, 34 – 91%; (c) 1,2,4-thiadiazole-5-amine, Cs_2CO_3, CH_3CN, 64%; (d) *tert*-butyl 1,2,4-oxadiazol-3-ylcarbamate, Cs_2CO_3, DMF, 50%; (e) (3-fluorophenyl)boronic acid, K_2CO_3, $Pd(PPh_3)_4$, dioxane, H_2O, 90 °C, 74%; (f) NIS, H_2SO_4, AcOH, DCM, 85%; (g) *n*-BuLi, $B(iOPr)_3$, THF, -78 °C; NaOH, 66%.

The synthesis of quinazoline **11** is detailed in Scheme 3. The sequence involves the two-step conversion of 7-bromoquinazolin-4-ol (**34**) to PFP ester **35** using conditions similar to those described above. Installation of protected amine **38**, which was derived from 3-aminoisoxazole (**37**), delivered a hydroxyquinazoline that was chlorinated with $POCl_3$ to furnish an intermediate that was subsequently converted to **36** using standard Suzuki conditions. Coupling of this bromide with the appropriate boronic acid followed by acid-mediated removal of the PMB protecting group furnished **11** in good overall yield.

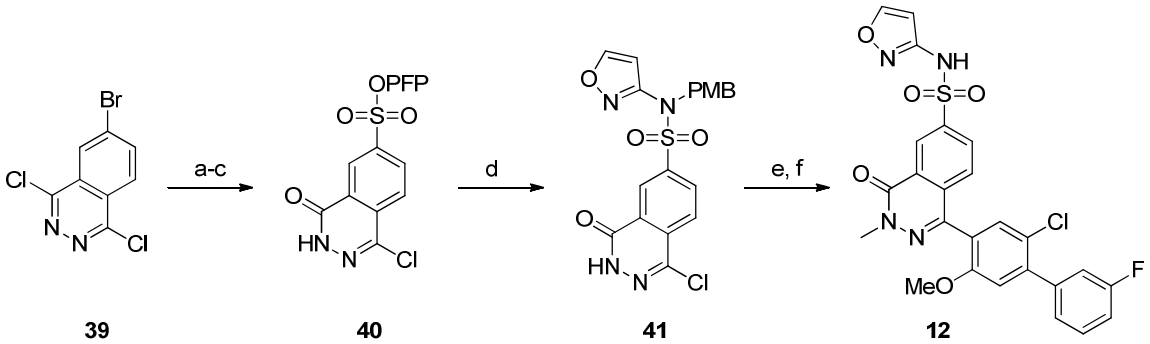
Scheme 3. Synthesis of quinazoline **11**[a]



[a]Reagents and conditions: (a) Xantphos, $Pd_2(dba)_3$, benzyl mercaptan, DIPEA, dioxane, 50 ºC, 97%; (b) i) 1,3-dichloro-5,5-dimethylimidazolidine-2,4-dione, MeCN, AcOH, H_2O, 0 ºC, ii) pentafluorophenol, TEA, DCM, 15%; (c) **38**, LHMDS, THF, -78 ºC, 90%; (d) $POCl_3$, DIPEA, DCE, 70 ºC, 52%; (e) $Pd(PPh_3)_4$, K_2CO_3, 4-bromo-5-chloro-(2-methoxyphenyl)boronic acid, dioxane, H_2O, 60 ºC, 65%; (f) i) $Pd(PPh_3)_4$, K_2CO_3, (3-fluorophenyl)boronic acid, H_2O, 100 ºC, ii) TFA, 80 ºC, 67%; (g) 4-methoxybenzaldehyde, acetic acid, molybdenum dichloride dioxide, phenylsilane, CH_3OH, water, 74%.

The preparation of phthalazinone **12** followed the seven step, six-pot sequence outlined in Scheme 4. This sequence was initiated with the hydrolysis of 6-bromo-1,4-dichlorophthalazine (**39**) which gave rise to an inseparable mixture of isomeric chlorophthalazinones that were carried forward through the benzyl thioether installation and oxidation sequence highlighted in Scheme 1. Separation of the isomers by silica gel chromatography provided PFP ester **40** in 38% overall yield. Installation of PMB-protected 2-aminoisoxazole furnished **41** in modest yield. Completion of the synthesis involved coupling of **41** with boronic acid **33**, methylation of the phthalazinone and removal of the PMB protecting group to deliver **12** in good yield.

Scheme 4. Synthesis of phthalazinone **12**[a]

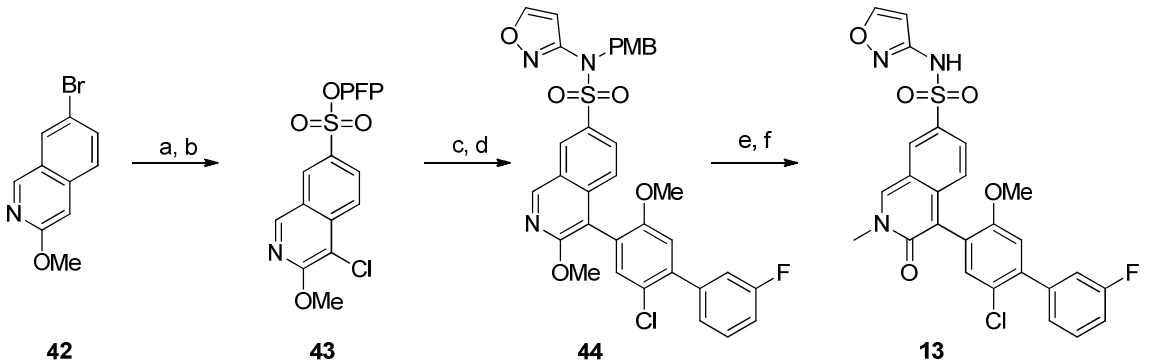


39 **40** **41** **12**

[a]Reagents and conditions: (a) DMSO, H_2O, 100 ºC, 99%; (b) Xantphos, $Pd_2(dba)_3$, benzyl mercaptan, DIPEA, dioxane, 50 ºC, 84%; (c) i) 1,3-dichloro-5,5-dimethylimidazolidine-2,4-dione, MeCN, AcOH, H_2O, 0 ºC, ii) pentafluorophenol, TEA, DCM, 38%; (d) N-(4-methoxybenzyl)isoxazol-3-amine, LHMDS, THF, -78 ºC, 26%; (e) (2-chloro-3'-fluoro-5-methoxy-[1,1'-biphenyl]-4-yl)boronic acid, chloro(2-dicyclohexylphosphino-2′,6′-dimethoxy-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)]palladium(II), K_3PO_4, dioxane, H_2O, μW, 100 ºC, 51%; (f) i) CH_3I, K_2CO_3, DMF, ii) TFA, triflic acid, DCM, 74%.

Isoquinolinone **13** was prepared utilizing the Scheme illustrated in Scheme 5 and mirrors that used for the preparation of **11**. The sequence started with 7-bromo-3-methoxyisoquinoline (**42**) and involved installation of the benzyl mercaptan which upon oxidation and trapping with pentafluorophenol led to concomitant chlorination at the 4-position to provide PFP ester **43** in excellent yield. Advancement to elaborated biaryl **44** proceeded uneventfully as previously described. Exposure of **44** to methyl iodide unveiled the methylated dihydroisoquinolinone core which following removal of the protecting group provided **13.**

Scheme 5. Synthesis of isoquinolinone **13**[a]

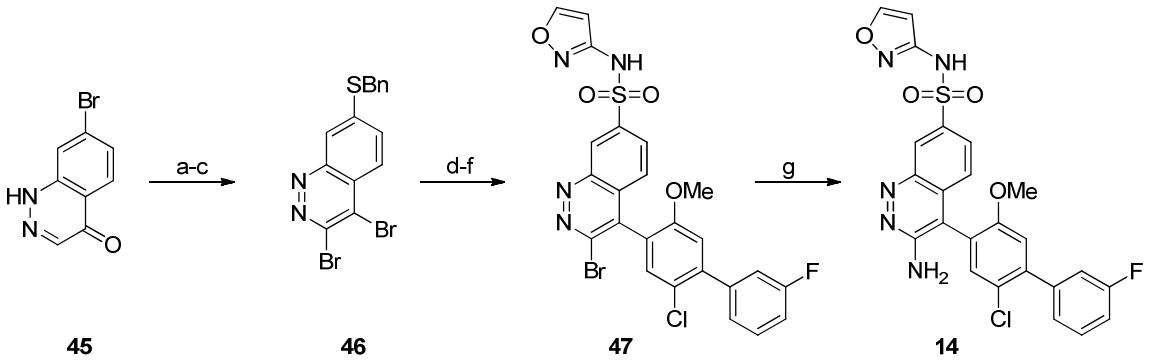


42 **43** **44** **13**

[a]Reagents and conditions: (a) Xantphos, $Pd_2(dba)_3$, benzyl mercaptan, DIPEA, dioxane, 60 ºC, 100%; (b) i) 1,3-dichloro-5,5-dimethylimidazolidine-2,4-dione, MeCN, AcOH, H_2O, 0 ºC, ii) pentafluorophenol, TEA, DCM, 94%; (c) **38**, LHMDS, THF, -78 ºC, 52%; (d) 2-chloro-3'-fluoro-5-methoxy-[1,1'-biphenyl]-4-yl)boronic acid, $Cl_2Pd(AmPhos)_2$, K_3PO_4, dioxane, H_2O, 100 °C, 49%; (e) NaI, CH_3I, CH_3CN, 80 °C, 38%; (f) TFA, 80 ºC, 91%.

The preparation of aminophthalazine **14** commences with conversion of 7-bromocinnolin-4(1H)-one (**45**) to the corresponding benzyl thioether which upon sequential treatment with N-bromosuccinimide (NBS) and $POBr_3$ gave dibromide **461** in 58% overall yield (Scheme 6). An efficient three step sequence similar to the one described above afforded sulfonamide **47**, which upon Pd-mediated installation of *tert*-butylsulfinamide and deprotection furnished **14** in modest overall yield.

Scheme 6. Synthesis of aminophthalazine **14**[a]



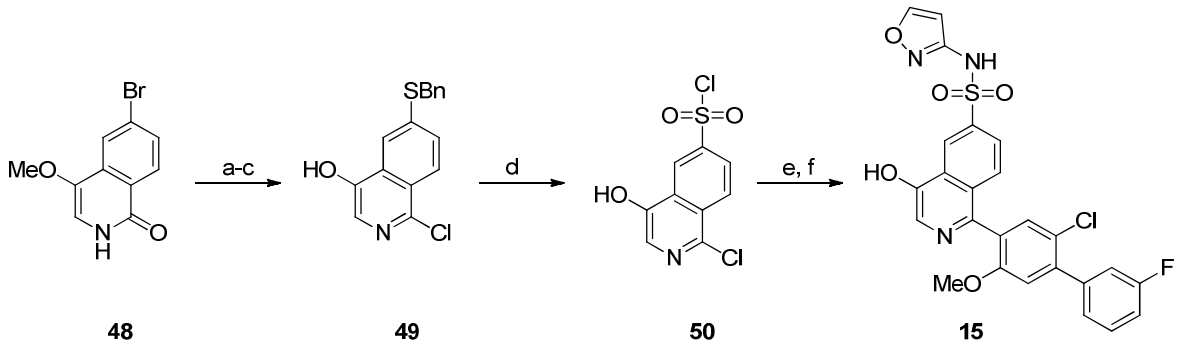
45 46 47 14

[a]Reagents and conditions: (a) Xantphos, $Pd_2(dba)_3$, benzyl mercaptan, DIPEA, dioxane, 110 ºC, 98%; (b) NBS, DMSO, 90 ºC, 73%; (c) $POBr_3$, CH3CN, DIPEA, 90 ºC, 82%; (d) (2-chloro-3'-fluoro-5-methoxy-[1,1'-biphenyl]-4-yl)boronic acid, $Cl_2Pd(dppf)$ DCM, K_2CO_3, dioxane, H_2O, 53%; (e) i) 1,3-dichloro-5,5-dimethylimidazolidine-2,4-dione, MeCN, AcOH, H_2O, 0 ºC, ii) pentafluorophenol, TEA, DCM, 88%; (f) isoxazol-3-amine, LHMDS, THF, -78 ºC, 100%; (g) i) *tert*-butylsulfinamide, $Pd(OAc)_2$, Xantphos, Cs_2CO_3, dioxane, 100 °C; ii) HCl, dioxane, 28%.

Scheme 7 outlines the protocol used to access hydroxyisoquinoline **15**. The sequence was initiated with the conversion of **48** to the benzyl thioether which upon chlorination with $POCl_3$ and deprotection of the methoxy group with BBr_3 provided **49** in excellent yield. Completion of

the synthesis involved preparation of the sulfonyl chloride, direct addition of aminoisoxazole **38** into this intermediate (**50**) followed by Suzuki coupling and deprotection.

Scheme 7. Synthesis of hydroxyisoquinoline **15**[a]

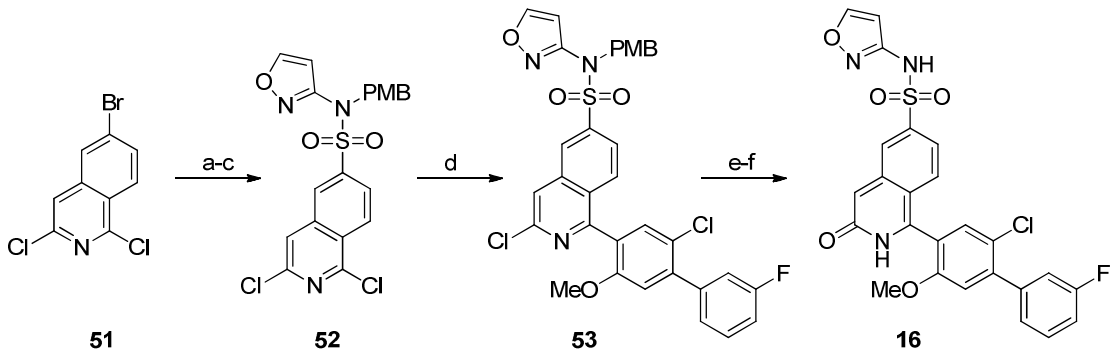


48 **49** **50** **15**

[a]Reagents and conditions: (a) Xantphos, $Pd_2(dba)_3$, benzyl mercaptan, DIPEA, dioxane, 110 ºC, 100%; (b) $POCl_3$, DCE, 90 ºC, 99%; (c) BBr_3, DCM, 0 ºC, 98%; (d) AcOH, sulfuryl chloride, CH_3CN, H_2O, 65%; (e) **33**, LHMDS, THF, -78 ºC, 59%; (f) i) (2-chloro-3'-fluoro-5-methoxy-[1,1'-biphenyl]-4-yl)boronic acid, $Pd(PPh_3)_4$, K_2CO_3, dioxane, H_2O, μW, 100 ºC, ii) triflic acid, 21%.

The synthesis of isoquinolinone **16** was initiated with the conversion of 6-bromo-1,3-dichloroisoquinoline (**51**) to protected sulfonamide **52** using a three step sequence similar to those already described (Scheme 8). Coupling of this intermediate with boronic acid **33** gave rise exclusively to **53** in excellent yield. Palladium-mediated conversion of the chloroisoquinoline to the dihydroisoquinolinone followed by removal of the PMB protecting group furnished **16** in good to excellent yield.

Scheme 8. Synthesis of Isoquinolinone **16**[a]

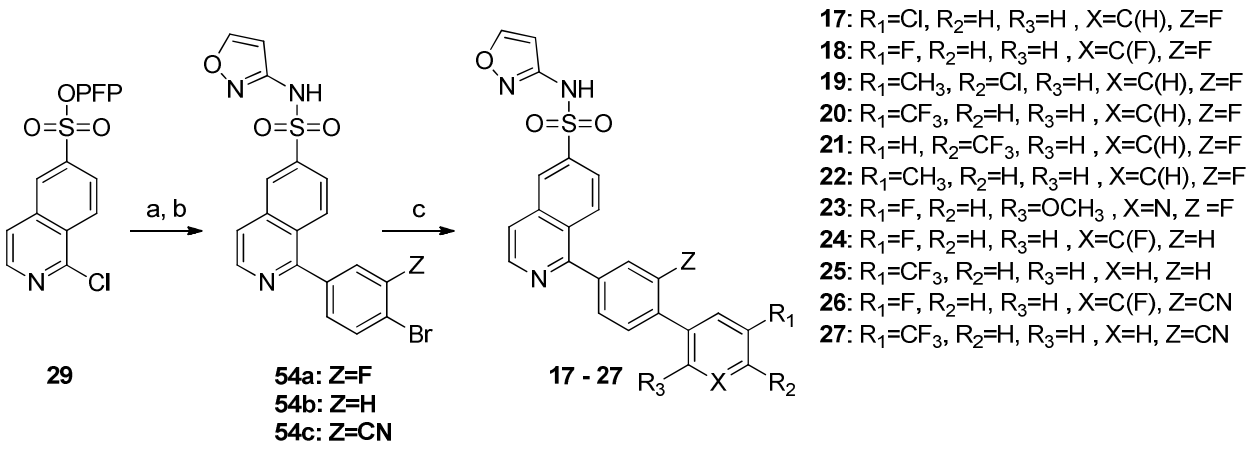


51 **52** **53** **16**

[a]Reagents and conditions: (a) Xantphos, $Pd_2(dba)_3$, benzyl mercaptan, DIPEA, dioxane, 60 ºC, 100%; (b) i) 1,3-dichloro-5,5-dimethylimidazolidine-2,4-dione, MeCN, AcOH, H_2O, 0 ºC, ii) pentafluorophenol, TEA, DCM, 94%; (c) **38**, LHMDS, THF, -78 ºC, 100%; (d) Cl_2Pd(dppf) DCM, (2-chloro-3'-fluoro-5-methoxy-[1,1'-biphenyl]-4-yl)boronic acid **33**, Na_2CO_3, dioxane, 50 °C, 84%; (e) KOH, $Pd_2(dba)_3$, 2-di-*tert*-butylphosphino-2',4',6'-triisopropylbiphenyl, 100 °C, 100%; (f) TFA, 80 °C, 98%.

Preparation of compounds **17** – **23** followed chemistry similar to that described above and is outlined in Scheme 9. Conversion of **29** to biaryl sulfonamide **54a-c** was followed by coupling to the appropriate boronic acid to deliver final compounds **17** – **27**.

Scheme 9. Synthesis C- and D-ring isoquinoline analogs **17** – **27**[a]



29 **54a: Z=F** **54b: Z=H** **54c: Z=CN** **17 - 27**

17: R_1=Cl, R_2=H, R_3=H , X=C(H), Z=F
18: R_1=F, R_2=H, R_3=H , X=C(F), Z=F
19: R_1=CH_3, R_2=Cl, R_3=H, X=C(H), Z=F
20: R_1=CF_3, R_2=H, R_3=H , X=C(H), Z=F
21: R_1=H, R_2=CF_3, R_3=H , X=C(H), Z=F
22: R_1=CH_3, R_2=H, R_3=H , X=C(H), Z=F
23: R_1=F, R_2=H, R_3=OCH_3 , X=N, Z =F
24: R_1=F, R_2=H, R_3=H , X=C(F), Z=H
25: R_1=CF_3, R_2=H, R_3=H , X=H, Z=H
26: R_1=F, R_2=H, R_3=H , X=C(F), Z=CN
27: R_1=CF_3, R_2=H, R_3=H , X=H, Z=CN

[a]Reagents and conditions: (a) boronic acid, K_2CO_3, $Pd(PPh_3)_4$, dioxane, H_2O, 50 °C, 72 – 85%, (b) isoxazol-3-amine, LHMDS, THF, -78 ºC, 69 – 97%; (c) boronic acid, Pd catalyst, ligand, base, dioxane, water, μW, 120 °C, 11 – 56%.

CONCLUSIONS

In conclusion, optimization efforts successfully addressed a number of metabolic liabilities associated with a previously reported series of bicyclic sulfonamide $Na_V1.7$ inhibitors. These efforts focused on improving potency, removing a bioactivation risk and mitigating CYP induction and inhibition liabilities. Critically important to overcoming these liabilities while retaining favorable pharmacokinetics within a series prone to transporter-mediated clearance was maintaining the cLogD within a tight range and the discovery of subtle PXR SAR that was not dependent solely on lipophilicity but leveraged a molecular recognition approach. While this approach required an increase in molecular weight, rigorous attention to key in vitro metabolic properties enabled the idnetification of inhibitors devoid of the liabilities associated with the strating point from which this series was derived. Ultimately, this was achieved with the strategic introduction and substitution of an aromatic ring and led to **20** which demonstrated a robust response in a $Na_V1.7$ target engagement pharmacodynamic model. Additional efforts to further improve the potency and pharmacokinetics while addressing remaining metabolic liabilities (i.e., CYP2C9 inhibition) of the bicyclic sulfonamide series will be reported in due course.

EXPERIMENTAL SECTION

Chemistry. All reagents were purchased from commercial suppliers and used as is unless otherwise noted. Anhydrous solvents were obtained from Aldrich or EM Science. An inert atmosphere of nitrogen or argon was used for reactions involving air- or moisture-sensitive reagents. A Biotage Initiator reactor from Biotage AB, Uppsala, Sweden was used for all microwave assisted reactions. ^{1}H NMR spectra were recorded on a Bruker AV-400 (400 MHz)

spectrometer at ambient temperature or on a Varian 400 MHz spectrometer. Chemical shifts are reported in parts per million (ppm, δ units) downfield from tetramethylsilane. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants, and number of protons. Purity for final compounds was greater than 95% and was measured using Agilent 1100 series high performance liquid chromatography (HPLC) systems with UV detection at 254 nm (system A, Agilent Zorbax Eclipse XDB-C8 4.6 mm × 150 mm, 5 μm, 5−100% CH_3CN in H_2O with 0.1% TFA for 15 min. at 1.5 mL/min.; system B, Waters Xterra 4.6 mm × 150 mm, 3.5 μm, 5−95% CH_3CN in H2O with 0.1% TFA for 15 min. at 1.0 mL/min.). Exact mass confirmation was performed on an Agilent 1100 series high performance liquid chromatography (HPLC) system (Santa Clara, CA, U.S.) by flow injection analysis, eluting with a binary solvent system A and B (A, water with 0.1% FA; B, ACN with 0.1% FA) under isocratic conditions (50% A/50% B) at 0.2 mL/min. with MS detection by an Agilent G1969A time-of-flight (TOF) mass spectrometer (Santa Clara, CA, U.S.).

1-(3'-fluoro-3-methoxy-[1,1'-biphenyl]-4-yl)-N-(pyrimidin-4-yl)isoquinoline-6-sulfonamide (3). Step 1: A 2-neck round-bottom flask was charged with 6-bromo-1-chloro-isoquinoline **28** (5.43 mL, 37.5 mmol), Xantphos (1.08 g, 1.87 mmol), and $Pd_2(dba)_3$ (0.858 g, 0.937 mmol). The flask was flushed with Ar (g), then dioxane (74.9 mL) and N,N-diisopropylethylamine (13.1 mL, 74.9 mmol) were added in sequence. The flask was fitted with a reflux condenser and placed in a 120 °C heating bath for 10 min., at which point the mixture was at a gentle reflux. Benzyl thioether (4.65 mL, 39.3 mmol) was added dropwise via syringe over 3 min. The reaction was maintained at 120 °C for 1 hr at which point the mixture was cooled to rt. After 2 h, a solid had crystallized out. The mixture was filtered, the filtrate was

concentrated, and the crude product was purified by chromatography on silica gel (120-g Redi-Sep Gold column, 0-30% EtOAc/Heptane) to give 6-(benzylthio)-1-chloroisoquinoline (5.34 g, 18.7 mmol, 50% yield) as an off-white solid that was used directly in the next step.

Step 2: A round-bottom flask was charged with 6-(benzylthio)-1-chloroisoquinoline (601 mg, 2.10 mmol), acetonitrile (19.8 mL), acetic acid (742 µl), and water (495 µl) to give a thin suspension. The flask was cooling in an ice-bath for 10 min., then 1,3-dichloro-5,5-dimethylimidazolidine-2,4-dione (829 mg, 4.21 mmol) was added in one portion. After stirring for 30 min., 2,3,4,5,6-pentafluorophenol (774 mg, 4.21 mmol) was added followed by triethylamine (730 µl, 5.26 mmol). The cooling bath was removed and the reaction was stirred for 1 hour. The mixture was diluted with EtOAc (50 mL), washed with water (2 × 50 mL), washed with brine, and dried over sodium sulfate. The mixture was concentrated and purified by chromatography on silica gel (40-g Redi-Sep Gold column, 0-20% EtOAc/Heptane) to give perfluorophenyl 1-chloroisoquinoline-6-sulfonate **29** (0.590 g, 1.44 mmol, 68% yield) as white powder. ^{1}H NMR (400 MHz ,$CDCl_3$) δ = 8.63 (d, *J* = 8.9 Hz, 1 H), 8.57 (d, *J* = 1.8 Hz, 1 H), 8.52 (d, *J* = 5.7 Hz, 1 H), 8.18 (dd, *J* = 1.9, 8.9 Hz, 1 H), 7.85 - 7.76 (m, 1 H). Mass Spectrum (ESI) *m/z* 410.0 $[M+H]^+$.

Step 3: A round-bottom flask was charged with perfluorophenyl 1-chloroisoquinoline-6-sulfonate **29** (1.035 g, 2.53 mmol), pyrimidin-4-amine (0.264 g, 2.78 mmol), and THF (12.6 mL) to give a cloudy, yellow suspension. The flask was cooled in an ice-bath for 10 min., then lithium bis(trimethylsilyl)amide (1M in THF) (5.30 mL, 5.30 mmol) was added dropwise over 1 min. to give an orange mixture. After 20 min. trifluoroacetic acid (0.584 mL, 7.58 mmol) was added dropwise, then the mixture was diluted with DCM (ca. 30 mL). The mixture was stirred for 10 min. while warming to room temperature and was then filtered. The collected solid was

washed with DCM (2×), then dried under a stream of N_2 (g) for 20 min. The collected solid was washed with a minimal amount of MeOH (2×), then dried under a stream of N_2 (g) to give 1-chloro-N-(pyrimidin-4-yl)isoquinoline-6-sulfonamide 2,2,2-trifluoroacetate **30** (658 mg, 1.513 mmol, 60% yield) as a light-yellow solid. Mass Spectrum (ESI) *m/z* 321.0 $[M+H]^+$.

Step 4: A vial was charged with 1-chloro-N-(pyrimidin-4-yl)isoquinoline-6-sulfonamide 2,2,2-trifluoroacetate **30** (326 mg, 0.750 mmol), (4-chloro-2-methoxyphenyl)boronic acid (210 mg, 1.12 mmol), potassium carbonate (518 mg, 3.75 mmol), and $Pd(PPh_3)_4$ (87 mg, 0.075 mmol). The vial was flushed with Ar (g), then dioxane (2800 µl) and water (937 µl) were added. The vial was sealed and heated to 100 °C for 30 min. in a Biotage Initiator microwave reactor. The reaction was cooled to rt, extracted with EtOAc (3×), and the combined organic extracts were concentrated. The residue was purified by chromatography on silica gel (25-g SNAP column, 5-10% MeOH/DCM) to give 1-(4-chloro-2-methoxyphenyl)-N-(pyrimidin-4-yl)isoquinoline-6-sulfonamide (227.4 mg, 0.533 mmol, 71 % yield). ^{1}H NMR (400MHz, DMSO-d_6) δ = 13.09 (br. s., 1 H), 8.77 - 8.63 (m, 2 H), 8.57 (s, 1 H), 8.25 (d, *J* = 6.2 Hz, 1 H), 8.12 (d, *J* = 5.7 Hz, 1 H), 7.95 (dd, *J* = 1.8, 8.8 Hz, 1 H), 7.72 (d, *J* = 8.9 Hz, 1 H), 7.58 (dd, *J* = 2.7, 8.9 Hz, 1 H), 7.39 (s, 1 H), 7.25 (d, *J* = 9.0 Hz, 1 H), 7.03 (d, *J* = 4.5 Hz, 1 H), 3.64 (s, 3 H). Mass Spectrum (ESI) *m/z* 427.2 $[M+H]^+$.

Step 5: A vial was charged with 1-(4-chloro-2-methoxyphenyl)-N-(pyrimidin-4-yl)isoquinoline-6-sulfonamide (410 mg, 0.960 mmol), (3-fluorophenyl)boronic acid (269 mg, 1.921 mmol), dicyclohexyl(2',6'-dimethoxy-[1,1'-biphenyl]-2-yl)phosphine (19 mg, 0.048 mmol), chloro(2-dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl)[2-(2-aminoethylphenyl)]palladium(ii) dichloromethane (73 mg, 0.096 mmol), and potassium phosphate (612 mg, 2.88 mmol). The vial was flushed with Ar (g), then dioxane (4.4 mL) and water (0.4 mL) were added in sequence. The

vial was sealed and heated in a Biotage Initiator microwave reactor for 30 min. at 120 °C. The mixture was cooled to rt. The organic layer was separated, and the aqueous layer was extracted with DCM (2×), EtOAc (2×), and MeOH-DCM (1×). The combined organic extracts were concentrated. The residue was purified by chromatography on silica gel (50-g SNAP Ultra column, 4% MeOH/DCM) to give 1-(3'-fluoro-3-methoxy-[1,1'-biphenyl]-4-yl)-N-(pyrimidin-4-yl)isoquinoline-6-sulfonamide (**3**) (244 mg, 0.502 mmol, 52% yield) as a light-yellow/off-white. ^{1}H NMR (400MHz, DMSO-d_6) δ = 8.75 - 8.67 (m, 2 H), 8.59 (s, 1 H), 8.26 (br. s., 1 H), 8.15 (d, *J* = 5.7 Hz, 1 H), 7.98 (dd, *J* = 1.9, 8.9 Hz, 1 H), 7.81 (d, *J* = 8.9 Hz, 1 H), 7.74 - 7.67 (m, 2 H), 7.57 (dt, *J* = 6.3, 8.0 Hz, 1 H), 7.53 - 7.43 (m, 3 H), 7.27 (dt, *J* = 2.1, 8.7 Hz, 1 H), 7.05 (br. s., 1 H), 3.77 (s, 3 H). [M+H]+ = 487.2. HRMS *m/z* Calcd for $C_{26}H_{20}FN_4O_3S$ $[M+1]^+$ = 487.1235. Found $[M+1]^+$ = 487.1230.

1-(2-chloro-3'-fluoro-5-methoxy-[1,1'-biphenyl]-4-yl)-N-(pyrimidin-4-yl)isoquinoline-6-sulfonamide (4).

Step 1: A round-bottom flask was charged with perfluorophenyl 1-chloroisoquinoline-6-sulfonate **29** (500 mg, 1.22 mmol), (2-chloro-3'-fluoro-5-methoxy-[1,1'-biphenyl]-4-yl)boronic acid (479 mg, 1.71 mmol), potassium carbonate (506 mg, 3.66 mmol), and $Pd(PPh_3)_4$ (141 mg, 0.122 mmol). The vial was flushed with Ar (g), then dioxane (4.6 mL) and water (1.5 mL) were added. The flask was fitted with a reflux condenser and heated in a 50 °C heating bath for 2 hours. The reaction was cooled to rt and partitioned between water and EtOAc. The layers were separated, and the organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated. The residue was purified by chromatography on silica gel (40-g Redi-Sep Gold column, 25-g silica gel loading column, 0-50% EtOAc/Heptane) to give perfluorophenyl 1-(2-chloro-3'-fluoro-5-methoxy-[1,1'-biphenyl]-4-yl)isoquinoline-6-sulfonate (594 mg, 0.973 mmol,

80% yield) as a white foam. ^{1}H NMR (400MHz ,DMSO-d_6) δ = 8.95 (d, *J* = 2.0 Hz, 1 H), 8.85 (d, *J* = 5.7 Hz, 1 H), 8.23 (d, *J* = 5.6 Hz, 1 H), 8.10 (dd, *J* = 2.0, 9.0 Hz, 1 H), 8.00 (d, *J* = 9.0 Hz, 1 H), 7.65 (s, 1 H), 7.59 (dt, *J* = 6.3, 8.1 Hz, 1 H), 7.48 - 7.43 (m, 2 H), 7.36 - 7.27 (m, 2 H), 3.72 (s, 3 H). Mass Spectrum (ESI) *m/z* 609.9 $[M+H]^+$.

Step 2: A round-bottom flask was charged with perfluorophenyl 1-(2-chloro-3'-fluoro-5-methoxy-[1,1'-biphenyl]-4-yl)isoquinoline-6-sulfonate (73 mg, 0.12 mmol), pyrimidin-4-amine (13 mg, 0.13 mmol), and THF (0.6 mL) to give a clear, lightly-colored solution. The flask was cooled in an ice-bath for 5 min., then lithium bis(trimethylsilyl)amide (1M in THF) (251 µl, 0.251 mmol) was added dropwise over 30 sec to give a yellow suspension. After stirring for 1 hr, the mixture was concentration and purified by chromatography on silica gel (12-g Redi-Sep Gold column, 3.5 MeOH/DCM, then 3.5-10% MeOH/DCM) to give 1-(2-chloro-3'-fluoro-5-methoxy-[1,1'-biphenyl]-4-yl)-N-(pyrimidin-4-yl)isoquinoline-6-sulfonamide **4** (40.8 mg, 0.078 mmol, 65% yield) as an off-white solid. ^{1}H NMR (400MHz ,DMSO-d_6) δ = 13.12 (br. s., 1 H), 8.71 (s, 1 H), 8.67 (s, 1 H), 8.57 (s, 1 H), 8.24 (d, *J* = 6.6 Hz, 1 H), 8.14 (d, *J* = 5.8 Hz, 1 H), 7.99 (dd, *J* = 1.8, 8.9 Hz, 1 H), 7.81 (d, *J* = 8.9 Hz, 1 H), 7.58 (dt, *J* = 6.3, 8.0 Hz, 1 H), 7.54 (s, 1 H), 7.49 - 7.40 (m, 2 H), 7.35 - 7.29 (m, 1 H), 7.27 (s, 1 H), 7.02 (d, *J* = 6.6 Hz, 1 H), 3.70 (s, 3 H). m/z (ESI) 521.2 $(M+H)^+$. HRMS *m/z* Calcd for $C_{26}H_{19}ClFN_4O_3S$ $[M+1]^+$ = 521.0845. Found $[M+1]^+$ = 521.0856.

1-(2-chloro-3'-fluoro-5-methoxy-[1,1'-biphenyl]-4-yl)-N-(pyrimidin-2-yl)isoquinoline-6-sulfonamide (5).

A vial was charged with perfluorophenyl 1-(2-chloro-3'-fluoro-5-methoxy-[1,1'-biphenyl]-4-yl)isoquinoline-6-sulfonate (80 mg, 0.13 mmol), pyrimidin-2-amine (14 mg, 0.14 mmol), and

THF (1.4 mL) to give a clear solution. The vial was cooled in an ice-water bath for 10 min., then lithium bis(trimethylsilyl)amide (1M in THF) (277 µl, 0.277 mmol) was added dropwise. After 30 min., the mixture was diluted with 1N aqueous HCl, water, and EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc (2×). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated. The residue was purified by chromatography on silica gel (12-g Redi-Sep Gold column, 0-4% MeOH/DCM) to give 1-(2-chloro-3'-fluoro-5-methoxy-[1,1'-biphenyl]-4-yl)-N-(pyrimidin-2-yl)isoquinoline-6-sulfonamide **5** (62 mg, 0.119 mmol, 90% yield) as a white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ = 12.17 (s, 1 H), 8.77 (s, 1 H), 8.73 (d, *J* = 5.7 Hz, 1 H), 8.50 (d, *J* = 4.9 Hz, 2 H), 8.19 (d, *J* = 5.5 Hz, 1 H), 8.06 (dd, *J* = 1.9, 8.9 Hz, 1 H), 7.85 (d, *J* = 9.0 Hz, 1 H), 7.64 - 7.54 (m, 2 H), 7.48 - 7.42 (m, 2 H), 7.36 - 7.29 (m, 1 H), 7.27 (s, 1 H), 7.05 (t, *J* = 4.8 Hz, 1 H), 3.70 (s, 3 H). HRMS *m/z* Calcd for $C_{26}H_{19}ClFN_4O_3S$ $[M+1]^+$ = 521.0845. Found $[M+1]^+$ = 521.0863.

1-(2-chloro-3'-fluoro-5-methoxy-[1,1'-biphenyl]-4-yl)-N-(pyridazin-3-yl)isoquinoline-6-sulfonamide (6).

A vial was charged with perfluorophenyl 1-(2-chloro-3'-fluoro-5-methoxy-[1,1'-biphenyl]-4-yl)isoquinoline-6-sulfonate (63 mg, 0.10 mmol), pyridazin-3-amine (11 mg, 0.11 mmol), and THF (517 µl) to give a clear solution. The vial was cooled in an ice-water bath for 10 min., then lithium bis(trimethylsilyl)amide (1M in THF) (124 µl, 0.124 mmol) was added dropwise. After 10 min., the mixture was diluted with 1N aqueous HCl and EtOAc. A yellow solid formed. The mixture was filtered, and the collected solid was washed with EtOAc, washed with water (2×), then dried under a stream of N_2 (g) to give 1-(2-chloro-3'-fluoro-5-methoxy-[1,1'-biphenyl]-4-yl)-N-(pyridazin-3-yl)isoquinoline-6-sulfonamide hydrochloride **6** (41 mg, 0.074 mmol, 72% yield) as a yellow solid. ^{1}H NMR (400MHz, DMSO-d_6) δ = 8.72 (d, *J* = 5.8 Hz, 1 H), 8.67 (d, *J*

= 1.8 Hz, 1 H), 8.36 (d, *J* = 3.4 Hz, 1 H), 8.18 (d, *J* = 5.7 Hz, 1 H), 8.02 - 7.96 (m, 2 H), 7.84 (d, *J* = 8.9 Hz, 1 H), 7.73 (dd, *J* = 4.2, 9.6 Hz, 1 H), 7.63 - 7.55 (m, 2 H), 7.49 - 7.43 (m, 2 H), 7.36 - 7.30 (m, 1 H), 7.29 (s, 1 H), 3.72 (s, 3 H). HRMS *m/z* Calcd for $C_{26}H_{19}ClFN_4O_3S$ $[M+1]^+$ = 521.0845. Found $[M+1]^+$ = 521.0827.

1-(2-chloro-3'-fluoro-5-methoxy-[1,1'-biphenyl]-4-yl)-N-(1,2,4-thiadiazol-5-yl)isoquinoline-6-sulfonamide (7).

A vial was charged with perfluorophenyl 1-(2-chloro-3'-fluoro-5-methoxy-[1,1'-biphenyl]-4-yl)isoquinoline-6-sulfonate (72 mg, 0.12 mmol), 1,2,4-thiadiazol-5-amine (13 mg, 0.13 mmol), and cesium carbonate (115 mg, 0.353 mmol). The vial was flushed with Ar (g), then acetonitrile (589 µl) was added and the mixture was stirred for 2 hrs. The mixture was diluted with EtOAc and 0.5 N aqueous HCl. The layers were separated, and the aqueous layer was extracted with EtOAc (2x). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated. The residue was then taken up in MeOH and filtered. The collected solid was washed with MeOH (1×), dried under a stream of N_2 (g) to give 1-(2-chloro-3'-fluoro-5-methoxy-[1,1'-biphenyl]-4-yl)-N-(1,2,4-thiadiazol-5-yl)isoquinoline-6-sulfonamide **7** (40 mg, 0.076 mmol, 64% yield) as an off-white solid. ^{1}H NMR (400MHz ,DMSO-d_6) δ = 8.72 (d, *J* = 5.7 Hz, 1 H), 8.60 (d, *J* = 1.7 Hz, 1 H), 8.48 (s, 1 H), 8.16 (d, *J* = 5.7 Hz, 1 H), 7.95 - 7.90 (m, 1 H), 7.88 - 7.81 (m, 1 H), 7.63 - 7.54 (m, 2 H), 7.50 - 7.41 (m, 2 H), 7.36 - 7.29 (m, 1 H), 7.27 (s, 1 H), 3.71 (s, 3 H). HRMS *m/z* Calcd for $C_{27}H_{17}ClFN_4O_3S_2$ $[M+1]^+$ = 527.0409. Found $[M+1]^+$ = 527.0400.

1-(2-chloro-3'-fluoro-5-methoxy-[1,1'-biphenyl]-4-yl)-N-(isoxazol-3-yl)isoquinoline-6-sulfonamide (8).

A round-bottom flask was charged with perfluorophenyl 1-(2-chloro-3'-fluoro-5-methoxy-[1,1'-biphenyl]-4-yl)isoquinoline-6-sulfonate (597 mg, 0.979 mmol), THF (4.9 mL), and isoxazol-3-amine (80 µl, 1.07 mmol) to give a clear, light-yellow solution. The flask was cooled in an ice-water bath for 10 min., then lithium bis(trimethylsilyl)amide (1M in THF) (2153 µl, 2.153 mmol) was added dropwise and stirred for 30 min. The mixture was taken up in EtOAc, and the organic mixture was washed with 1N aqueous HCl (3×), washed with brine, dried over sodium sulfate, filtered, and concentrated to give 1-(2-chloro-3'-fluoro-5-methoxy-[1,1'-biphenyl]-4-yl)-N-(isoxazol-3-yl)isoquinoline-6-sulfonamide **8** (452 mg, 0.886 mmol, 91% yield) as an off-white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ = 11.92 (br. s., 1 H), 8.78 - 8.72 (m, 2 H), 8.69 (d, *J* = 1.7 Hz, 1 H), 8.16 (d, *J* = 5.5 Hz, 1 H), 8.01 - 7.84 (m, 2 H), 7.64 - 7.53 (m, 2 H), 7.49 - 7.40 (m, 2 H), 7.37 - 7.29 (m, 1 H), 7.27 (s, 1 H), 6.50 (d, *J* = 1.9 Hz, 1 H), 3.70 (s, 3 H). HRMS *m/z* Calcd for $C_{25}H_{18}ClFN_3O_4S$ $[M+1]^+$ = 510.0685. Found $[M+1]^+$ = 510.0699.

1-(2-chloro-3'-fluoro-5-methoxy-[1,1'-biphenyl]-4-yl)-N-(oxazol-2-yl)isoquinoline-6-sulfonamide (9).

A round-bottom flask was charged with perfluorophenyl 1-(2-chloro-3'-fluoro-5-methoxy-[1,1'-biphenyl]-4-yl)isoquinoline-6-sulfonate (137 mg, 0.224 mmol), oxazol-2-amine (24.5 mg, 0.291 mmol) and THF (2241 µl) to give a clear, orange mixture. The flask was cooled in an ice-water bath for 10 min., then lithium bis(trimethylsilyl)amide (1M in THF) (471 µl, 0.471 mmol) was added dropwise. After 10 min., the mixture was diluted with 1N aqueous HCl and water and extracted with EtOAc (3×). The combined organic extracts were concentrated. The residue was dissolved in DMSO and filtered through a 0.2 micron filter. The filtrate was purified by reverse-phase HPLC (0.1 NH_4OH) to give 1-(2-chloro-3'-fluoro-5-methoxy-[1,1'-biphenyl]-4-yl)-N-(oxazol-2-yl)isoquinoline-6-sulfonamide **9** (39.0 mg, 0.077 mmol, 34% yield) as a white solid.

^{1}H NMR (500MHz, DMSO-d_6) δ = 12.23 (br. s, 1 H), 8.70 (d, *J* = 5.7 Hz, 1 H), 8.60 (d, *J* = 1.2 Hz, 1 H), 8.10 (d, *J* = 5.7 Hz, 1 H), 7.96 (dd, *J* = 1.7, 8.9 Hz, 1 H), 7.80 (d, *J* = 8.9 Hz, 1 H), 7.64 - 7.52 (m, 3 H), 7.44 (d, *J* = 8.2 Hz, 2 H), 7.36 - 7.24 (m, 3 H), 3.71 (s, 3 H). HRMS *m/z* Calcd for $C_{25}H_{18}ClFN_3O_4S$ $[M+1]^+$ = 510.0685. Found $[M+1]^+$ = 510.0699.

1-(2-chloro-3'-fluoro-5-methoxy-[1,1'-biphenyl]-4-yl)-N-(1,2,4-oxadiazol-3-yl)isoquinoline-6-sulfonamide (10).

Step 1: A round-bottom flask was charged with perfluorophenyl 1-chloroisoquinoline-6-sulfonate **29** (828 mg, 2.02 mmol), *tert*-butyl-1,2,4-oxadiazol-3-ylcarbamate (486 mg, 2.63 mmol), and cesium carbonate (987 mg, 3.03 mmol). The flask was flushed with Ar (g), then DMF (1 mL) was added. After 1 hr, 10 mL of EtOAc was added and the solution was washed with water (2×). The organic layer was then dried over sodium sulfate, filtered, and concentrated. The residue was then taken up in EtOAc, sonicated, and filtered. The collected solid was washed with EtOAc (2×), dried under a stream of N_2 (g) to give *tert*-butyl (1-chloroisoquinolin-6-yl)sulfonyl(1,2,4-oxadiazol-3-yl)carbamate (419 mg, 1.02 mmol, 50% yield) as a white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ = 9.98 (s, 1 H), 8.97 (d, *J* = 2.0 Hz, 1 H), 8.68 (d, *J* = 9.0 Hz, 1 H), 8.57 (d, *J* = 5.7 Hz, 1 H), 8.34 - 8.27 (m, 2 H), 1.23 (s, 9 H). Mass Spectrum (ESI) *m/z* 411.0 $[M+H]^+$.

Step 2: A vial was charged with *tert*-butyl (1-chloroisoquinolin-6-yl)sulfonyl(1,2,4-oxadiazol-3-yl)carbamate (92 mg, 0.22 mmol), (2-chloro-3'-fluoro-5-methoxy-[1,1'-biphenyl]-4-yl)boronic acid (88 mg, 0.313 mmol), potassium carbonate (93 mg, 0.671 mmol), and $Pd(PPh_3)_4$ (26 mg, 0.022 mmol). The vial was flushed with Ar (g), then dioxane (0.8 mL) and water (0.3 mL) were added. The vial was heated to 50 °C in a Biotage Initiator microwave reactor for 2 h. The reaction was cooled to rt and the layers were separated, and the aqueous layer was extracted with

EtOAc (3×). The combined organic extracts were concentrated. The residue was dissolved in DCM (1 mL) and TFA (0.5 mL) was added and the mixture was stirred for 2 hrs. The mixture was concentrated. The residue was dissolved in MeOH, and the resulting solution was purified by reverse-phase HPLC (40-85% CH_3CN/H_2O with 0.1% TFA) to give 1-(2-chloro-3'-fluoro-5-methoxy-[1,1'-biphenyl]-4-yl)-N-(1,2,4-oxadiazol-3-yl)isoquinoline-6-sulfonamide 2,2,2-trifluoroacetate **10** (74 mg, 0.12 mmol, 53% yield) as a yellow solid. ^{1}H NMR (400MHz, DMSO-d_6) δ = 9.36 (s, 1 H), 8.81 - 8.69 (m, 2 H), 8.23 (d, *J* = 5.6 Hz, 1 H), 8.03 (dd, *J* = 1.9, 8.9 Hz, 1 H), 7.92 (d, *J* = 9.0 Hz, 1 H), 7.64 - 7.53 (m, 2 H), 7.49 - 7.40 (m, 2 H), 7.36 - 7.27 (m, 2 H), 3.71 (s, 3 H). HRMS *m/z* Calcd for $C_{24}H_{17}ClFN_4O_4$ $[M+1]^+$ = 511.0638. Found $[M+1]^+$ = 511.0612.

4-(2-chloro-3'-fluoro-5-methoxy-[1,1'-biphenyl]-4-yl)-N-(isoxazol-3-yl)quinazoline-7-sulfonamide (11).

Step 1: A 3 L three-neck RBF equipped with mechanical stirrer, thermocouple and reflux condenser with nitrogen inlet was charged with 7-bromoquinazolin-4-ol **34** (100 g, 444 mmol), $Pd_2(dba)_3$ (10.1 g, 11.1 mmol), Xantphos (12.86 g, 22.22 mmol), dioxane (900 mL), benzyl mercaptan (54.8 mL, 467 mmol) and DIPEA (155 mL, 889 mmol). The mixture was heated at 90 ^{o}C for 70 min. before being cooled to rt and diluted with cold water (1000 mL). The resulting mixture was filtered through a frit, washed with water (~1000 mL) and dried on the glass filter for 24 hrs. The derived solid was suspended in EtOAc (1200 mL) and stirred for 18 hrs before being isolated by filtration. The obtained solid was washed with EtOAc (~200 mL) and dried on the glass filter to provide 7-(benzylthio)quinazolin-4-ol (116 g, 432 mmol, 97%) that was used in the next step without further purification.

Step 2: 5L three-neck RBF equipped with mechanical, thermocouple and addition funnel with nitrogen inlet 7-(benzylthio)quinazolin-4-ol (103.5 g, 386 mmol) charged, followed by acetonitrile (2000 mL), acetic acid (75 mL) and water (50.0 mL). The mixture was cooled to 2 ^{o}C and 1,3-dichloro-5,5-dimethylhydantoin (152 g, 772 mmol) was added portionwise over 10 min. Stirring was continued for 30 minutes at which time 2,3,4,5,6-pentafluorophenol (92 g, 502 mmol) in MeCN (250 mL) was added dropwise followed by triethylamine (188 mL, 1350 mmol). Reaction was stirred for 1 hr before the mixture was diluted with EtOAc (500 mL) and water (2000 mL). Phases were separated and the organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo leading to a wet yellow solid. The solid was taken up in acetone (1 L) and concentrated in vacuo to ~ 300 mL. The solid which formed was isolated by filtration to provide perfluorophenyl 4-oxo-3,4-dihydroquinazoline-7-sulfonate **35** (25.0 g, 63.7 mmol, 15% yield).

Step 3: A solution of N-(4-methoxybenzyl)isoxazol-3-amine **38** (1.09 g, 5.35 mmol) in THF (19.6 mL) was cooled in a dry ice-acetone bath for 5 min. lithium bis(trimethylsilyl)amide (1M in THF) (5.61 mL, 5.61 mmol) was added dropwise, then the flask was removed from the cooling bath for 5 min. The flask was again cooled into a dry ice-acetone bath for 20 min., resulting in the formation of a thick slurry. A solution of perfluorophenyl 4-oxo-3,4-dihydroquinazoline-7-sulfonate **35** (2.0 g, 5.10 mmol) in THF (20 mL) was added dropwise, and the reaction was stirred for 30 min. The reaction was warmed to room temperature and quenched with saturated ammonium chloride solution, diluted with ethyl acetate and washed with water. The aqueous layer was extracted three times with ethyl acetate, and the combined organic layers were dried with sodium sulfate, filtered and concentrated. The material was triturated in DCM and filtered. The solids were washed with DCM and vacuum dried to afford

N-(isoxazol-3-yl)-N-(4-methoxybenzyl)-4-oxo-3,4-dihydroquinazoline-7-sulfonamide (1.89 g, 4.58 mmol, 90% yield) as a light yellow solid. Mass Spectrum (ESI) *m/z* 413.1 $[M+H]^+$.

Step 4: N-(isoxazol-3-yl)-N-(4-methoxybenzyl)-4-oxo-3,4-dihydroquinazoline-7-sulfonamide (1.0 g, 2.42 mmol) was dissolved in DCE (10 mL). N,N-diisopropylethyl amine (1.27 mL, 7.27 mmol) was added followed by a solution of phosphoryl trichloride (0.66 g, 4.85 mmol) in DCE (5 mL). The reaction was stirred at 70 ºC for two hours before being diluted with DCM and washed with saturated sodium bicarbonate. The aqueous layer was extracted with DCM, and the combined organic layers were dried with sodium sulfate, filtered, and concentrated. The material was purified via column chromatography (40-g Redi-Sep Gold column, gradient elution 0-50% EtOAc:Heptane) to afford 4-chloro-N-(isoxazol-3-yl)-N-(4-methoxybenzyl)quinazoline-7-sulfonamide (0.543 g, 1.26 mmol, 52% yield) as a white solid. Mass Spectrum (ESI) *m/z* 431.1 $[M+H]^+$.

Step 5: A vial was charged with 4-chloro-N-(isoxazol-3-yl)-N-(4-methoxybenzyl)quinazoline-7-sulfonamide (0.28 g, 0.65 mmol), (4-bromo-5-chloro-2-methoxyphenyl)boronic acid (0.175 g, 0.659 mmol), $Pd(PPh_3)_4$ (0.076 g, 0.066 mmol), and potassium carbonate (0.455 g, 3.30 mmol). Dioxane (3.3 mL) and Water (1.1 mL) were added and the reaction was stirred at 60 ºC for two hours. The reaction was diluted with ethyl acetate and washed with water. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were dried with sodium sulfate, filtered, and concentrated. The material was purified via column chromatography (Redi-Sep Gold 12g, gradient elution 0-100% EtOAc:Heptane) to afford 4-(4-bromo-5-chloro-2-methoxyphenyl)-N-(isoxazol-3-yl)-N-(4-methoxybenzyl)quinazoline-7-sulfonamide **36** (0.264 g, 0.429 mmol, 65% yield) as a white solid. Mass Spectrum (ESI) *m/z* 615.0 $[M+H]^+$.

Step 6: A vial was charged with 4-(4-bromo-5-chloro-2-methoxyphenyl)-N-(isoxazol-3-yl)-N-(4-methoxybenzyl)quinazoline-7-sulfonamide **36** (0.045 g, 0.072 mmol), (3-fluorophenyl)boronic acid (0.011 g, 0.072 mmol), $Pd(PPh_3)_4$ (0.011 g, 9.74 μmol), and potassium carbonate (0.050 g, 0.365 mmol). Dioxane (0.40 mL) and water (0.14 mL) were added and the reaction was stirred at 100 ºC for 30 min. The reaction was cooled to rt, diluted with ethyl acetate and washed with water. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were dried with sodium sulfate, filtered, and concentrated. The material was dissolved in neat TFA (1 mL, 12.98 mmol) and stirred at 80 ºC for one hour. The reaction was concentrated and purified via column chromatography (Redi-Sep Gold 80g, gradient elution 0-10% MeOH:DCM) to afford 4-(2-chloro-3'-fluoro-5-methoxy-[1,1'-biphenyl]-4-yl)-N-(isoxazol-3-yl)quinazoline-7-sulfonamide **11** (0.033 g, 0.061 mmol, 67% yield) as an off-white solid. ^{1}H NMR (400MHz ,DMSO-d_6) δ = 12.06 (br. s., 1 H), 9.53 (s, 1 H), 8.77 (d, *J* = 1.9 Hz, 1 H), 8.52 (d, *J* = 1.6 Hz, 1 H), 8.08 - 8.05 (m, 1 H), 8.04 - 8.00 (m, 1 H), 7.68 (s, 1 H), 7.59 (dt, *J* = 6.3, 8.1 Hz, 1 H), 7.47 - 7.42 (m, 2 H), 7.37 - 7.30 (m, 2 H), 6.54 (d, *J* = 1.9 Hz, 1 H), 3.74 (s, 3 H). HRMS *m/z* Calcd for $C_{24}H_{17}ClFN_4O_4S$ $[M+1]^+$ = 511.0638. Found $[M+1]^+$ = 511.0668.

1-(2-chloro-3'-fluoro-5-methoxy-[1,1'-biphenyl]-4-yl)-N-(isoxazol-3-yl)-3-methyl-4-oxo-3,4-dihydrophthalazine-6-sulfonamide (12).

Step 1: A vial was charged with 6-bromo-1,4-dichlorophthalazine **39** (5.0 g, 18 mmol), DMSO (20 mL), and water (4.00 mL). The reaction was heated to 100 ºC and stirred for one hour. The reaction was cooled to rt, diluted with water, cooled to 0 ºC and stirred for 5 min. The solids were filtered, thoroughly washed with water, and dried under a nitrogen blanket to afford an inseparable mixture of 7-bromo-4-chlorophthalazin-1(2H)-one and 6-bromo-4-chlorophthalazin-

1(2H)-one (4.62 g, 17.8 mmol, 99 % yield) as a white solid. Mass Spectrum (ESI) *m/z* 259.0 $[M+H]^+$.

Step 2: A vial was charged with a mixture of 6-bromo-4-chlorophthalazin-1(2H)-one and 7-bromo-4-chlorophthalazin-1(2H)-one (4.62 g, 17.80 mmol), Xantphos (0.51 g, 0.89 mmol), and $Pd_2(dba)_3$ (0.408 g, 0.445 mmol). The flask was flushed with Ar (g), then dioxane (35.6 mL), benzyl mercaptan (2.21 mL, 18.6 mmol), and N,N-diisopropylethylamine (6.22 mL, 35.6 mmol) were added in sequence. The reaction was heated to 50 ºC and stirred for two hours before the reaction was cooled to rt, diluted with water and filtered. The solids were washed with water and dried overnight under a nitrogen blanket. The resulting solid was triturated with ethyl acetate and stirred until a uniform heterogeneous mixture was obtained. The solids were filtered, washed with ethyl acetate, and dried overnight under a nitrogen blanket to afford an inseparable mixture of 7-(benzylthio)-4-chlorophthalazin-1(2H)-one and 6-(benzylthio)-4-chlorophthalazin-1(8aH)-one (4.55 g, 15.0 mmol, 84% yield) as a yellow solid. Mass Spectrum (ESI) *m/z* 303.0 $[M+H]^+$.

Step 3: A round-bottom flask was charged with a mixture of 7-(benzylthio)-4-chlorophthalazin-1(2H)-one and 6-(benzylthio)-4-chlorophthalazin-1(8aH)-one (4.55 g, 15.03 mmol), MeCN (141 mL), acetic acid (5.3 mL), and water (3.5 mL) to give a thin suspension. The flask was cooled in an ice-bath for 10 min., then 1,3-dichloro-5,5-dimethylimidazolidine-2,4-dione (7.40 g, 37.6 mmol) was added in one portion, leading to a solution. The reaction was stirred for 15 min. before 2,3,4,5,6-pentafluorophenol (3.15 mL, 30.1 mmol) was added followed by dropwise addition of triethylamine (5.24 mL, 37.6 mmol). The reaction was stirred for 30 min. The reaction was concentrated and purified via column chromatography (40-g Redi-Sep Gold column, gradient elution 0-25% EtOAc:Heptane) to afford perfluorophenyl 1-chloro-4-oxo-4,4a-

dihydrophthalazine-6-sulfonate (3.16 g, 7.41 mmol, 49% yield) and 1-chloro-4-oxo-3,4-dihydrophthalazine-6-sulfonate **40** (2.42 g, 5.67 mmol, 38% yield) both as white solids. Mass Spectrum (ESI) *m/z* 427.0 $[M+H]^+$.

Step 4: A solution of N-(4-methoxybenzyl)isoxazol-3-amine **38** (0.327 g, 1.60 mmol) in THF (5.8 mL) was cooled in a dry ice-acetone bath for 5 min. Lithium bis(trimethylsilyl)amide (1M in THF) (3.06 mL, 3.06 mmol) was added dropwise, then the flask was removed from the cooling bath for 5 min. The flask was again cooled into a dry ice-acetone bath for 20 min., resulting in the formation of a thick slurry. A solution of perfluorophenyl 1-chloro-4-oxo-3,4-dihydrophthalazine-6-sulfonate **40** (0.621 g, 1.45 mmol) in THF (6 mL) was added dropwise, and the reaction was stirred for one hour at which point the reaction was quenched with saturated ammonium chloride solution, diluted with ethyl acetate and washed with water. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were dried with sodium sulfate, filtered, and concentrated. The filtrate was purified by chromatography on an 80-g Redi-Sep Gold column with 0-100% EtOAc/Heptane to afford 1-chloro-N-(isoxazol-3-yl)-N-(4-methoxybenzyl)-4-oxo-3,4-dihydrophthalazine-6-sulfonamide **41** (0.169 g, 0.378 mmol, 26% yield) as an off-white solid. Mass Spectrum (ESI) *m/z* 447.0 $[M+H]^+$.

Step 5: A microwave vial was charged with 1-chloro-N-(isoxazol-3-yl)-N-(4-methoxybenzyl)-4-oxo-3,4-dihydrophthalazine-6-sulfonamide **41** (.169 g, 0.378 mmol), (2-chloro-3'-fluoro-5-methoxy-[1,1'-biphenyl]-4-yl)boronic acid (0.11 g, 0.41 mmol), Chloro(2-dicyclohexylphosphino-2′,6′-dimethoxy-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)]palladium(II) (0.014 g, 0.019 mmol) and potassium phosphate (0.241 g, 1.13 mmol). The vial was flushed with Ar (g), then dioxane (2.1 mL) and water (0.42 mL) were added. The reaction was microwaved at 100 ºC for 30 min. before the reaction was diluted with ethyl acetate and washed with water.

The aqueous layer was extracted with ethyl acetate, and the combined organic layers were dried with sodium sulfate, filtered, and concentrated. The material was purified via column chromatography (40-g Redi-Sep Gold column, gradient elution 0-100% EtOAc:Heptane) to afford 1-(2-chloro-3'-fluoro-5-methoxy-[1,1'-biphenyl]-4-yl)-N-(isoxazol-3-yl)-N-(4-methoxybenzyl)-4-oxo-3,4-dihydrophthalazine-6-sulfonamide (0.125 g, 0.193 mmol, 51% yield). Mass Spectrum (ESI) *m/z* 527.2 $[M+H]^+$.

Step 6: A vial was charged with 1-(2-chloro-3'-fluoro-5-methoxy-[1,1'-biphenyl]-4-yl)-N-(isoxazol-3-yl)-N-(4-methoxybenzyl)-4-oxo-3,4-dihydrophthalazine-6-sulfonamide (0.065 g, 0.100 mmol), potassium carbonate (0.028 g, 0.20 mmol), and DMF (1.0 mL). Iodomethane (9.4 µl, 0.15 mmol) was added and the reaction was stirred for three hours at room temperature. The reaction was diluted with ethyl acetate and washed with water. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were dried with sodium sulfate, filtered, and concentrated. The material was dissolved in DCM and TFA (.15 mL, 1.947 mmol) and triflic acid (0.1 mL, 1.126 mmol) were added. The reaction was stirred for 30 min. at room temperature before being concentrated and purified via Gilson HPLC (50-95% MeCN:H2O w/ .1% TFA modifier) to afford 1-(2-chloro-3'-fluoro-5-methoxy-[1,1'-biphenyl]-4-yl)-N-(isoxazol-3-yl)-3-methyl-4-oxo-3,4-dihydrophthalazine-6-sulfonamide **12** (0.040 g, 0.074 mmol, 74% yield) as a white solid. ^{1}H NMR (400MHz ,DMSO-d_6) δ = 11.98 (br. s., 1 H), 8.77 (d, *J* = 1.9 Hz, 1 H), 8.75 (dd, *J* = 0.5, 2.0 Hz, 1 H), 8.26 (dd, *J* = 2.0, 8.6 Hz, 1 H), 7.64 (dd, *J* = 0.5, 8.5 Hz, 1 H), 7.62 - 7.55 (m, 2 H), 7.44 - 7.39 (m, 2 H), 7.35 - 7.29 (m, 1 H), 7.27 (s, 1 H), 6.47 (d, *J* = 1.9 Hz, 1 H), 3.79 (s, 3 H), 3.75 (s, 3 H). HRMS *m/z* Calcd for $C_{25}H_{19}ClFN_4O_5S$ $[M+1]^+$ = 541.0743. Found $[M+1]^+$ = 541.0711.

4-(2-chloro-3'-fluoro-5-methoxy-[1,1'-biphenyl]-4-yl)-N-(isoxazol-3-yl)-2-methyl-3-oxo-2,3-dihydroisoquinoline-7-sulfonamide (13)

Step 1: A round-bottom flask was charged with 7-bromo-3-methoxyisoquinoline **42** (327 mg, 1.37 mmol), Xantphos (39.7 mg, 0.069 mmol), and $Pd_2(dba)_3$ (31.4 mg, 0.034 mmol). The flask was flushed with Ar (g), then dioxane (2.7 mL), N,N-diisopropylethylamine (480 µl, 2.75 mmol), and benzyl mercaptan (171 µl, 1.442 mmol) were added in sequence. The flask was heated at 60 °C for 4.5 hrs. The mixture was cooled and concentrated in vacuo. The crude product was purified by chromatography on silica gel (12-g Redi-Sep Gold column, 25-g silica gel loading column, 0-40% EtOAc/Heptane) to give 7-(benzylthio)-3-methoxyisoquinoline (387 mg, 1.37 mmol, 100% yield) as an off-white powder.

Step 2: A round-bottom flask was charged with 7-(benzylthio)-3-methoxyisoquinoline (387 mg, 1.375 mmol), acetonitrile (12.9 mL), acetic acid (0.48 mL), and water (0.3 mL) to give a yellow suspension. The flask was cooling in an ice-bath for 10 min., then 1,3-dichloro-5,5-dimethylimidazolidine-2,4-dione (542 mg, 2.75 mmol) was added in one portion, leading to a yellow solution. After 1 hour 2,3,4,5,6-pentafluorophenol (506 mg, 2.75 mmol) was added followed by triethylamine (0.479 mL, 3.44 mmol). After 10 min. the mixture was diluted with EtOAc (20 mL) and washed with water (2 × 20 mL). The organic layers were combined and concentrated. The crude material was purified by chromatography on silica gel (40-g Redi-Sep Gold column, 0-20% EtOAc/Heptane) to give perfluorophenyl 4-chloro-3-methoxyisoquinoline-7-sulfonate (570 mg, 94% yield).

Step 3: A round-bottom flask was charged with perfluorophenyl 4-chloro-3-methoxyisoquinoline-7-sulfonate (520 mg, 1.18 mmol), THF (12 mL) and N-(4-

methoxybenzyl)isoxazol-3-amine (241 mg, 1.18 mmol). The flask was cooled in an ice-bath for 10 min., then lithium bis(trimethylsilyl)amide (2.48 mL, 2.48 mmol) was added dropwise. After 15 min. the mixture was diluted with 1 N aqueous HCl and extracted with EtOAc (2×). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated. The residue was purified by chromatography on silica gel (40-g Redi-Sep Gold column, 0-20% EtOAc/Heptane) to give 4-chloro-N-(isoxazol-3-yl)-3-methoxy-N-(4-methoxybenzyl)isoquinoline-7-sulfonamide **43** (282 mg, 0.613 mmol, 52% yield) as a white foam.

Step 4: A vial was charged with 4-chloro-N-(isoxazol-3-yl)-3-methoxy-N-(4-methoxybenzyl)isoquinoline-7-sulfonamide **43** (282 mg, 0.613 mmol), (2-chloro-3'-fluoro-5-methoxy-[1,1'-biphenyl]-4-yl)boronic acid (172 mg, 0.613 mmol), $Pd(AmPhos)_2Cl_2$ (43.4 mg, 0.061 mmol), potassium phosphate (390 mg, 1.84 mmol), dioxane (3.1 mL), and water (1.0 mL). The vial was sealed and heated at 100 °C for 2 h. After cooling to rt, the crude material was absorbed onto a plug of silica gel and purified by chromatography using a Redi-Sep pre-packed silica gel column (12 g), eluting with a gradient of 0% to 100% EtOAc in hexane, to provide 4-(2-chloro-3'-fluoro-5-methoxy-[1,1'-biphenyl]-4-yl)-N-(isoxazol-3-yl)-3-methoxy-N-(4-methoxybenzyl)isoquinoline-7-sulfonamide **44** (200 mg, 0.303 mmol, 49% yield) as white solid.

Step 5: To a 2 mL microwave vial, was added 4-(2-chloro-3'-fluoro-5-methoxy-[1,1'-biphenyl]-4-yl)-N-(isoxazol-3-yl)-3-methoxy-N-(4-methoxybenzyl)isoquinoline-7-sulfonamide **44** (180 mg, 0.273 mmol) in MeCN (1.4 mL), sodium iodide (163 mg, 1.09 mmol) and iodomethane (339 µl, 5.45 mmol) at rt. The reaction mixture was heated at 80 °C for 24 hrs. After cooling to rt, the crude material was purified by chromatography using a Redi-Sep pre-packed silica gel column (12 g), eluting with a gradient of 0% to 10% MeOH in DCM, to provide 4-(2-chloro-3'-fluoro-5-

methoxy-[1,1'-biphenyl]-4-yl)-N-(isoxazol-3-yl)-N-(4-methoxybenzyl)-2-methyl-3-oxo-2,3-dihydroisoquinoline-7-sulfonamide as yellow solid (70 mg, 38% yield) that was used directly in the next step.

Step 6: To a 1 mL vial was added 4-(2-chloro-3'-fluoro-5-methoxy-[1,1'-biphenyl]-4-yl)-N-(isoxazol-3-yl)-N-(4-methoxybenzyl)-2-methyl-3-oxo-2,3-dihydroisoquinoline-7-sulfonamide (70 mg, 0.106 mmol) in TFA (1320 µl). The reaction mixture was warmed to 80 °C and stirred for 45 min. After cooling to rt, the reaction mixture was concentrated in vacuo. The crude material was absorbed onto a plug of silica gel and purified by chromatography using a 40-g Redi-Sep Gold column eluting with a gradient of 0% to 10% MeOH in DCM, to provide 4-(2-chloro-3'-fluoro-5-methoxy-[1,1'-biphenyl]-4-yl)-N-(isoxazol-3-yl)-2-methyl-3-oxo-2,3-dihydroisoquinoline-7-sulfonamide 2,2,2-trifluoroacetate **13** (69 mg, 91% yield) as a yellow solid. ^{1}H NMR (400MHz ,DMSO-d_6) δ = 11.61 (s, 1 H), 9.22 (s, 1 H), 8.74 (d, *J* = 1.8 Hz, 1 H), 8.30 (s, 1 H), 7.57 - 7.55 (m, 1 H), 7.47 - 7.44 (m, 1 H), 7.42 - 7.40 (m, 1 H), 7.37 - 7.31 (m, 2 H), 7.17 (s, 1 H), 6.98 (d, *J* = 1.8 Hz, 1 H), 6.43 (s, 1 H), 3.76 (s, 3 H), 3.31 (s, 3 H). HRMS *m/z* Calcd for $C_{26}H_{20}ClFN_3O_5S$ $[M+1]^+$ = 540.0791. Found $[M+1]^+$ = 540.0801.

3-amino-4-(2-chloro-3'-fluoro-5-methoxy-[1,1'-biphenyl]-4-yl)-N-(isoxazol-3-yl)cinnoline-7-sulfonamide (14).

Step 1: A vial was charged with 7-bromocinnolin-4(1H)-one **45** (9.10 g, 40.4 mmol), Xantphos (1.17 g, 2.02 mmol), and $Pd_2(dba)_3$ (0.926 g, 1.011 mmol). The flask was flushed with Ar (g), then dioxane (81 mL), benzyl mercaptan (5.26 mL, 44.5 mmol), and N,N-diisopropylethylamine (14.12 mL, 81 mmol) were added in sequence. The reaction was heated to 110 ºC and stirred for 30 min. before the reaction was diluted with water and filtered. The solids were washed with

water and dried under a nitrogen blanket. The solid was triturated with ethyl acetate and stirred for one hour. The solids were filtered, washed with ethyl acetate, and dried under a nitrogen blanket to afford 7-(benzylthio)cinnolin-4(1H)-one (10.6 g, 39.6 mmol, 98% yield) as a light yellow solid. Mass Spectrum (ESI) *m/z* 269.1 $[M+H]^+$.

Step 2: A round bottom flask was charged with 7-(benzylthio)cinnolin-4(1H)-one (8.42 g, 31.4 mmol), NBS (8.38 g, 47.1 mmol) and DMSO (209 mL) and heated to 90 ºC for one hour. The reaction was cooled to room temperature and water was added. The resulting suspension was stirred for 30 min. and filtered. The solids were washed with water and dried overnight under a nitrogen blanket. The material was dissolved in 100 mL of DMSO and 0.5 eq. of NBS was added (2.8 g). The reaction was heated at 90 ºC for one hour before being cooled to room temperature, submerged in an ice bath, and water was added. The resulting suspension was stirred for 30 min and filtered. The solids were washed with water and dried overnight under a nitrogen blanket to afford 7-(benzylthio)-3-bromocinnolin-4(1H)-one (8.0 g, 23 mmol, 73% yield) as a light yellow solid that was used without further purification. Mass Spectrum (ESI) *m/z* 349.0 $[M+H]^+$.

Step 3: A flask was charged with 7-(benzylthio)-3-bromocinnolin-4(1H)-one (4.00 g, 11.52 mmol), acetonitrile (46.1 mL), and DIPEA (6.04 mL, 34.6 mmol). Phosphorus oxybromide (4.62 g, 16.13 mmol) was added and the reaction was stirred at 90 ºC for 4 hours. The reaction was cooled to rt, poured into ice water and stirred for 15 min. The mixture was neutralized to pH ~7 with concentrated HCl. The solids were filtered, washed with water, and dried overnight under a nitrogen blanket to afford 7-(benzylthio)-3,4-dibromocinnoline **46** (3.89 g, 9.48 mmol, 82% yield) as a brown solid that was used without further purification. Mass Spectrum (ESI) *m/z* 409.1 $[M+H]^+$.

Step 4: A vial was charged with 7-(benzylthio)-3,4-dibromocinnoline (2.0 g, 4.88 mmol), (2-chloro-3'-fluoro-5-methoxy-[1,1'-biphenyl]-4-yl)boronic acid (1.50 g, 5.36 mmol), $PdCl_2$(dppf)-DCM (0.398 g, 0.488 mmol), and potassium carbonate (3.37 g, 24.3 mmol). Dioxane (18 mL) and water (6 mL) were added, the vial was flushed with argon and sealed, and stirred for three days at room temperature. The reaction was cooled to rt, diluted with DCM, and washed with water. The aqueous layer was extracted with DCM, and the combined organic layers were dried with sodium sulfate, filtered, and concentrated. The material was purified via column chromatography (40-g Redi-Sep Gold column, gradient elution 0-100% EtOAc:Heptane) to afford 7-(benzylthio)-3-bromo-4-(2-chloro-3'-fluoro-5-methoxy-[1,1'-biphenyl]-4-yl)cinnoline (1.46 g, 2.58 mmol, 53% yield) as a yellow solid. Mass Spectrum (ESI) *m/z* 565.0 $[M+H]^+$.

Step 5: A round-bottom flask was charged with 7-(benzylthio)-3-bromo-4-(2-chloro-3'-fluoro-5-methoxy-[1,1'-biphenyl]-4-yl)cinnoline (1.46 g, 2.58 mmol), DCM (24.28 mL), acetic acid (0.91 mL), and water (0.6 mL) to give a thin suspension. The flask was cooled in an ice-bath for 10 min., then 1,3-dichloro-5,5-dimethylimidazolidine-2,4-dione (1.27 g, 6.45 mmol) was added in one portion, leading to a solution. The reaction was stirred for 15 min. at which time 2,3,4,5,6-pentafluorophenol (0.541 mL, 5.16 mmol) was added followed by the dropwise addition of triethylamine (0.899 mL, 6.45 mmol). The reaction was stirred for 30 min. before being concentrated and purified via column chromatography (40-g Redi-Sep Gold column, gradient elution 0-50% EtOAc:Heptane) to afford perfluorophenyl 3-bromo-4-(2-chloro-3'-fluoro-5-methoxy-[1,1'-biphenyl]-4-yl)cinnoline-7-sulfonate (1.57 g, 2.27 mmol, 88% yield) as a yellow solid. Mass Spectrum (ESI) *m/z* 688.8 $[M+H]^+$.

Step 6: A round bottom flask was charged with perfluorophenyl 3-bromo-4-(2-chloro-3'-fluoro-5-methoxy-[1,1'-biphenyl]-4-yl)cinnoline-7-sulfonate (1.57 g, 2.27 mmol), isoxazol-3-amine

(0.185 mL, 2.50 mmol), and THF (11.38 mL) to give a clear solution. The flask was cooled to 0 ºC for 10 min., then lithium bis(trimethylsilyl)amide (1M in THF) (5.01 mL, 5.01 mmol) was added dropwise. The reaction was stirred for 30 min. The reaction was diluted with 1 N aqueous HCl and EtOAc. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were washed with 1N aqueous HCl, washed with brine, dried with sodium sulfate, filtered, and concentrated to afford crude 3-bromo-4-(2-chloro-3'-fluoro-5-methoxy-[1,1'-biphenyl]-4-yl)-N-(isoxazol-3-yl)cinnoline-7-sulfonamide **47** (1.5 g, 2.3 mmol, 100% yield) as an orange solid.

Step 7: A vial was charged with 3-bromo-4-(2-chloro-3'-fluoro-5-methoxy-[1,1'-biphenyl]-4-yl)-N-(isoxazol-3-yl)cinnoline-7-sulfonamide **47** (0.125 g, 0.212 mmol), $Pd(OAc)_2$ (0.014 g, 0.064 mmol), Xantphos (0.074 g, 0.127 mmol), *tert*-butylsulfinamide (0.051 g, 0.424 mmol) and cesium carbonate (0.207 g, 0.636 mmol). The vial was capped, evacuated and backfilled with N_2 (g). Dioxane (1.413 mL) was added and the mixture was heated at 100 °C for 3 hours. The reaction was cooled to room temperature. Hydrogen chloride (4.0M in dioxane) (0.85 mL, 3.39 mmol) was added and the reaction was stirred overnight at room temperature. The reaction was diluted with ethyl acetate and washed with 1N HCl. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were dried with sodium sulfate, filtered, and concentrated. The material was purified via column chromatography (40-g Redi-Sep Gold column, gradient elution 10-75% [3:1 EtOAc/EtOH]:Heptane) to afford 3-amino-4-(2-chloro-3'-fluoro-5-methoxy-[1,1'-biphenyl]-4-yl)-N-(isoxazol-3-yl)cinnoline-7-sulfonamide **14** (0.031 g, 0.059 mmol, 28% yield) as a yellow solid. ^{1}H NMR (400MHz ,DMSO-d_6) δ = 11.79 (s, 1 H), 8.74 (d, *J* = 1.8 Hz, 1 H), 8.64 (d, *J* = 1.8 Hz, 1 H), 7.79 (dd, *J* = 2.0, 9.1 Hz, 1 H), 7.64 - 7.54

(m, 1 H), 7.48 (s, 1 H), 7.45 - 7.26 (m, 5 H), 6.52 (d, *J* = 1.8 Hz, 1 H), 3.73 (s, 3 H), 1.10 (s, 2 H). HRMS *m/z* Calcd for $C_{24}H_{18}ClFN_5O_4S$ $[M+1]^+$ = 526.0747. Found $[M+1]^+$ = 526.0771.

1-(2-chloro-3'-fluoro-5-methoxy-[1,1'-biphenyl]-4-yl)-4-hydroxy-N-(isoxazol-3-yl)isoquinoline-6-sulfonamide (15).

Step 1: A vial was charged with 6-bromo-4-methoxyisoquinolin-1(2H)-one **48** (7.91 g, 31.1 mmol), Xantphos (0.901 g, 1.55 mmol), and $Pd_2(dba)_3$ (0.713 g, 0.778 mmol). The flask was flushed with Ar (g), then dioxane (6 mL), benzyl mercaptan (4.05 mL, 34.2 mmol), and N,N-diisopropylethylamine (10.87 mL, 62.3 mmol) were added in sequence. The reaction was heated to 110 ºC and stirred for 30 min. before being cooled to rt. The reaction was diluted with water, stirred vigorously for 10 min., and filtered. The solids were washed with water and dried. The resulting yellow solid was triturated with ethyl acetate and stirred for one hour. The mixture was filtered and the solids were washed with ethyl acetate and dried under a nitrogen blanket overnight to afford 6-(benzylthio)-4-methoxyisoquinolin-1(2H)-one (9.08 g, 31.1 mmol, 100% yield) as a yellow solid. Mass Spectrum (ESI) *m/z* 298.3 $[M+H]^+$.

Step 2: A vial was charged with 6-(benzylthio)-4-methoxyisoquinolin-1(2H)-one (9.26 g, 31.1 mmol) and DCE (156 mL). $POCl_3$ (5.81 mL, 62.3 mmol) was added and the reaction was stirred overnight at 90 ºC. One additional equivalent of $POCl_3$ was added (3 mL) and the reaction was stirred at 100 ºC for two hours. The reaction was cooled to rt, washed with water and the layers were separated. The aqueous layer was extracted several times with ethyl acetate and several times with DCM, and the combined organic layers were concentrated to afford crude 6-(benzylthio)-1-chloro-4-methoxyisoquinoline (10 g, 31 mmol, 99% yield) as a yellow solid that was immediately used in the next step. Mass Spectrum (ESI) *m/z* 317.1 $[M+H]^+$.

Step 3: 6-(benzylthio)-1-chloro-4-methoxyisoquinoline (9.83 g, 31.1 mmol) was dissolved in DCM (156 mL) and cooled to 0 ºC. Boron tribromide (8.83 mL, 93 mmol) was added and the reaction was warmed to room temperature and stirred for 24 hours. The reaction was cooled to 0 ºC and carefully quenched with saturated sodium bicarbonate solution. The reaction was diluted with water and filtered to afford a gummy orange solid. The solid was dissolved in ethyl acetate, washed with brine, concentrated to afford 6-(benzylthio)-1-chloroisoquinolin-4-ol **49** (9.36 g, 29.

Step 4: A round-bottom flask was charged with 6-(benzylthio)-1-chloroisoquinolin-4-ol (9.39 g, 31.1 mmol), MeCN (296 mL), acetic acid (7.4 mL) and water (7.4 mL). The flask was cooled in an ice-bath for 10 min., then sulfuryl chloride (7.57 mL, 93 mmol) was added in one portion. The resulting solution was allowed to warm to rt, where it was maintained for 1 hour. The reaction was diluted with ethyl acetate and washed with water. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were washed with brine, dried with sodium sulfate, filtered, and concentrated. The material was purified via column chromatography (40-g Redi-Sep Gold column, gradient elution 0-100% EtOAc:Heptane) to afford 1-chloro-4-hydroxyisoquinoline-6-sulfonyl chloride **50** (5.62 g, 20.21 mmol, 65% yield) as a light pink solid. Mass Spectrum (ESI) *m/z* 280.1 $[M+H]^+$.

Step 5: A flask was charged with 1-chloro-4-hydroxyisoquinoline-6-sulfonyl chloride **50** (1.3 g, 4.67 mmol), N-(4-methoxybenzyl)isoxazol-3-amine **38** (1.00 g, 4.91 mmol), and THF (31.2 mL) and cooled to -78 ºC in a dry ice/acetone bath for 10 min. LHMDS (1.0M in THF) (9.82 mL, 9.82 mmol) was added dropwise and the reaction was stirred for 30 min. The reaction was warmed to room temperature and quenched with saturated ammonium chloride solution, diluted with ethyl acetate and washed with water. The aqueous layer was extracted three times with ethyl acetate, and the combined organic layers were dried with sodium sulfate, filtered, and

concentrated. The material was purified by chromatography on a 40-g Redi-Sep Gold column with 0-100% EtOAc/Heptane to afford 1-chloro-4-hydroxy-N-(isoxazol-3-yl)-N-(4-methoxybenzyl)isoquinoline-6-sulfonamide (1.24 g, 2.78 mmol, 59% yield) as a light yellow solid. Mass Spectrum (ESI) *m/z* 446.1 $[M+H]^+$.

Step 6: A microwave vial was charged with 1-chloro-4-hydroxy-N-(isoxazol-3-yl)-N-(4-methoxybenzyl)isoquinoline-6-sulfonamide (.200 g, 0.449 mmol), (2-chloro-3'-fluoro-5-methoxy-[1,1'-biphenyl]-4-yl)boronic acid (0.138 g, 0.493 mmol), $Pd(PPh_3)_4$ (0.052 g, 0.045 mmol), and potassium carbonate (0.310 g, 2.24 mmol). Dioxane (2.2 mL) and water (0.7 mL) were added, the vial was flushed with argon and sealed, and microwaved at 100 ºC for 30 min. The reaction was cooled to rt, diluted with ethyl acetate and washed with water. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were dried with sodium sulfate, filtered, and concentrated. The material was purified via column chromatography (40-g Redi-Sep Gold column, gradient elution 0-100% EtOAc:Heptane) to afford 1-(2-chloro-3'-fluoro-5-methoxy-[1,1'-biphenyl]-4-yl)-4-hydroxy-N-(isoxazol-3-yl)-N-(4-methoxybenzyl)isoquinoline-6-sulfonamide (0.253 g, 0.392 mmol, 87% yield) as a yellow solid. A portion 75 mg of material was dissolved in DCM and TFA (0.1 mL, 1.29 mmol) was added, followed by triflic acid (0.1 mL, 1.12 mmol). The reaction was stirred for 30 min. at room temperature before being concentrated and purified via column chromatography (40-g Redi-Sep Gold column, gradient elution 0-10% MeOH:DCM) to afford 1-(2-chloro-3'-fluoro-5-methoxy-[1,1'-biphenyl]-4-yl)-4-hydroxy-N-(isoxazol-3-yl)isoquinoline-6-sulfonamide **15** (0.049 g, 0.093 mmol, 21% yield) as a yellow solid. ^{1}H NMR (400MHz ,DMSO-d_6) δ = 11.86 (br. s., 1 H), 11.19 (s, 1 H), 8.73 (dd, *J* = 1.7, 13.5 Hz, 2 H), 8.29 (s, 1 H), 7.93 (dd, *J* = 2.0, 8.9 Hz, 1 H), 7.79 (d, *J* = 8.8 Hz, 1 H), 7.63 - 7.54 (m, 1 H), 7.49 (s, 1 H), 7.46 - 7.40 (m, 2 H), 7.35 - 7.28 (m, 1

H), 7.23 (s, 1 H), 6.47 (d, J = 1.8 Hz, 1 H), 3.70 (s, 3 H). HRMS *m/z* Calcd for $C_{25}H_{18}ClFN_3O_5S$ $[M+1]^+$ = 526.0634. Found $[M+1]^+$ = 526.0641.

1-(2-chloro-3'-fluoro-5-methoxy-[1,1'-biphenyl]-4-yl)-N-(isoxazol-3-yl)-3-oxo-2,3-dihydroisoquinoline-6-sulfonamide (16).

Step 1: A round-bottom flask was charged with 6-bromo-1,3-dichloroisoquinoline **51** (2 g, 7.22 mmol), Xantphos (0.209 g, 0.361 mmol), and $Pd_2(dba)_3$ (0.165 g, 0.181 mmol). dioxane (14 mL), DIPEA (2.52 mL, 14.44 mmol), and benzyl mercaptan (0.897 mL, 7.58 mmol) were added. The flask was placed in a 60 °C heating bath for 25 min. The mixture was cooled to room temperature, the crude material was absorbed onto a plug of silica gel and purified by chromatography through a (40-g Redi-Sep Gold column, eluting with a gradient of 0% to 40% EtOAc in hexane, to provide 6-(benzylthio)-1,3-dichloroisoquinoline (2.31 g, 7.22 mmol, 100% yield) as yellow solid.

Step 2: A round-bottom flask was charged with 6-(benzylthio)-1,3-dichloroisoquinoline (2.4 g, 7.49 mmol), acetonitrile (70 mL), acetic acid (2.6 mL), and water (1.7 mL) to give a yellow suspension. The flask was cooling in an ice-bath for 10 min., then 1,3-dichloro-5,5-dimethylimidazolidine-2,4-dione (2.95 g, 14.9 mmol) was added in one portion, leading to an orange red solution. After 1 hr 2,3,4,5,6-pentafluorophenol (2.76 g, 14.9 mmol) was added followed by triethylamine (2.61 mL, 18.74 mmol). After 10 min the mixture was diluted with EtOAc (50 mL), washed with water (2 × 50 mL) and washed with brine. The organic layers were combined and concentrated. The crude material was purified by chromatography on silica gel (40-g Redi-Sep Gold column, 0-20% EtOAc/Heptane) to give perfluorophenyl 1,3-dichloroisoquinoline-6-sulfonate (3.12 g, 7.02 mmol, 94% yield) as yellow solid.

Step 3: A round-bottom flask was charged with perfluorophenyl 1,3-dichloroisoquinoline-6-sulfonate (4 g, 9.01 mmol), THF (90 mL) and N-(4-methoxybenzyl)isoxazol-3-amine (1.83 g, 9.01 mmol). The flask was cooled in an ice-bath for 10 min., then lithium bis(trimethylsilyl)amide (18.91 mL, 18.91 mmol) was added dropwise. After 15 min. the mixture was diluted with 1 N aqueous HCl and extracted with EtOAc (2×). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated. The residue was purified by chromatography on silica gel (40-g Redi-Sep Gold column, 0-5% MeOH/DCM) to give 1,3-dichloro-N-(isoxazol-3-yl)-N-(4-methoxybenzyl)isoquinoline-6-sulfonamide **52** (4.40 g, 9.01 mmol, 100% yield) as a white foam.

Step 4: A solution of $Cl_2Pd(dppf)$ DCM (0.088 g, 0.108 mmol), 1,3-dichloro-N-(isoxazol-3-yl)-N-(4-methoxybenzyl)isoquinoline-6-sulfonamide **52** (1 g, 2.15 mmol), (2-chloro-3'-fluoro-5-methoxy-[1,1'-biphenyl]-4-yl)boronic acid (0.604 g, 2.15 mmol) , and sodium carbonate (2.15 mL, 4.31 mmol) in dioxane (4.31 mL) was heated to 50°C for 1 hr. After cooling to rt, the crude material was absorbed onto a plug of silica gel and purified by chromatography through a Redi-Sep pre-packed silica gel column (120 g), eluting with a gradient of 0 % to 60% EtOAc in hexane, to provide 3-chloro-1-(2-chloro-3'-fluoro-5-methoxy-[1,1'-biphenyl]-4-yl)-N-(isoxazol-3-yl)-N-(4-methoxybenzyl)isoquinoline-6-sulfonamide **53** (1.2 g, 1.8 mmol, 84% yield).

Step 5: A glass microwave reaction vessel was charged with 3-chloro-1-(2-chloro-3'-fluoro-5-methoxy-[1,1'-biphenyl]-4-yl)-N-(isoxazol-3-yl)-N-(4-methoxybenzyl)isoquinoline-6-sulfonamide (100 mg, 0.150 mmol), potassium hydroxide (16.8 mg, 0.301 mmol), $Pd_2(dba)_3$ (13.7 mg, 0.015 mmol), and 2-di-*tert*-butylphosphino-2',4',6'-triisopropylbiphenyl (12.7 mg, 0.030 mmol). The vial was capped and was evacuated and backfilled with N_2 (2×). The solvents were added under vacuum followed by backfilling of N_2. The reaction mixture was stirred and

heated at 100° for 8 hours. After cooling to rt, the crude material was absorbed onto a plug of silica gel and purified by chromatography through a (40-g Redi-Sep Gold column, eluting with a gradient of 0 % to 10% MeOH in DCM, to provide 1-(2-chloro-3'-fluoro-5-methoxy-[1,1'-biphenyl]-4-yl)-3-hydroxy-N-(isoxazol-3-yl)-N-(4-methoxybenzyl)isoquinoline-6-sulfonamide (96 mg, 0.15 mmol, 100% yield).

Step 6: To a 1 mL vial was added 1-(2-chloro-3'-fluoro-5-methoxy-[1,1'-biphenyl]-4-yl)-3-hydroxy-N-(isoxazol-3-yl)-N-(4-methoxybenzyl)isoquinoline-6-sulfonamide (95 mg, 0.15 mmol) in TFA (3670 µl). The reaction mixture was warmed to 80 °C, and stirred for 1 hr. After cooling to rt, the reaction mixture was concentrated in vacuo. The crude material was purified by reverse-phase preparative HPLC using 0.1% TFA in CH_3CN/H_2O, gradient 10% to 90% over 20 min. to provide 1-(2-chloro-3'-fluoro-5-methoxy-[1,1'-biphenyl]-4-yl)-N-(isoxazol-3-yl)-3-oxo-2,3-dihydroisoquinoline-6-sulfonamide 2,2,2-trifluoroacetate **16** (94 mg, 0.14 mmol, 98% yield) as a yellow solid. ^{1}H NMR (400MHz ,DMSO-d_6) δ = 11.82 (br. s., 1 H), 11.19 (s, 1 H), 8.73 (dd, *J* = 1.4, 13.8 Hz, 1 H), 8.43 (s, 1 H), 7.92 - 7.90 (m, 1 H), 7.73 - 7.71 (m, 1 H), 7.63 - 7.60 (m, 1 H), 7.57 - 7.52 (m, 2 H), 7.48 - 7.64 (m, 2 H), 7.33 - 7.30 (m, 1 H), 7.29 - 7.27 (m, 1 H), 6.50 (d, *J* = 1.9 Hz, 1 H), 3.71 (s, 3 H). HRMS *m/z* Calcd for $C_{25}H_{18}ClFN_3O_5S$ $[M+1]^+$ = 526.0634. Found $[M+1]^+$ = 526.0638.

1-(3'-chloro-2-fluoro-5-methoxy-[1,1'-biphenyl]-4-yl)-N-(isoxazol-3-yl)isoquinoline-6-sulfonamide (17).

Step 1: A round-bottom flask was charged with perfluorophenyl 1-chloroisoquinoline-6-sulfonate **29** (1.7 g, 4.15 mmol), (4-bromo-5-fluoro-2-methoxyphenyl)boronic acid (1.10 g, 6.22 mmol), potassium carbonate (1.72 g, 12.45 mmol), and $Pd(PPh_3)_4$ (0.479 g, 0.415 mmol). The vial was flushed with Ar (g), then dioxane (15 mL) and water (5 mL) were added. The flask was

fitted with a reflux condenser and heated in a 50 °C heating bath for one hour. The mixture was cooled to rt, diluted with water and extracted with EtOAc (2×). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated. The residue was purified by chromatography on silica gel (40-g Redi-Sep Gold column, 0-50% EtOAc/Heptane) to give perfluorophenyl 1-(4-bromo-5-fluoro-2-methoxyphenyl)isoquinoline-6-sulfonate (1.73 g, 3.54 mmol, 85% yield) as a white foam. Mass Spectrum (ESI) *m/z* 578.0 $[M+H]^+$.

Step 2: A round-bottom flask was charged with perfluorophenyl 1-(4-chloro-5-fluoro-2-methoxyphenyl)isoquinoline-6-sulfonate (527 mg, 1.07 mmol), THF (1 mL) and isoxazol-3-amine (87 µl, 1.18 mmol). The flask was cooled in an ice-bath for 10 min., then lithium bis(trimethylsilyl)amide (1M in THF) (225 µl, 2.25 mmol) was added dropwise. After 15 min. the mixture was diluted with 1 N aqueous HCl and extracted with EtOAc (2×). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated. The residue was purified by chromatography on silica gel (40-g Redi-Sep Gold column, 0-5% MeOH/DCM) to give 1-(4-bromo-5-fluoro-2-methoxyphenyl)-N-(isoxazol-3-yl)isoquinoline-6-sulfonamide **54a** (417 mg, 1.04 mmol, 97% yield) as a white foam. Mass Spectrum (ESI) *m/z* 478.1 $[M+H]^+$.

Step 3: A vial was charged with 1-(4-bromo-5-fluoro-2-methoxyphenyl)-N-(isoxazol-3-yl)isoquinoline-6-sulfonamide (94 mg, 0.23 mmol), (3-chlorophenyl)boronic acid (55.5 mg, 0.355 mmol), chloro(2-dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl)[2-(2-aminoethylphenyl)]palladium(ii) dichloromethane (8.9 mg, 0.012 mmol), and potassium phosphate (251 mg, 1.183 mmol). The vial was flushed with Ar (g), then dioxane (1.1 mL) and water (0.1 mL) were added. The vial was sealed and heated in a Biotage Initiator microwave reactor for 1 h at 120 °C before being cooled to rt. The mixture was extracted with EtOAc (4×). The combined organic extracts were concentrated. The residue was taken up in MeOH, then

filtered through a 0.2 micron filter. The filtrate was purified by reverse-phase HPLC (40-85% CH_3CN/H_2O with 0.1% TFA) to give 1-(3'-chloro-2-fluoro-5-methoxy-[1,1'-biphenyl]-4-yl)-N-(isoxazol-3-yl)isoquinoline-6-sulfonamide 2,2,2-trifluoroacetate **17** (16.4 mg, 0.026 mmol, 11% yield) as a yellow solid. ^{1}H NMR (400MHz, DMSO-d_6) δ = 11.92 (br. s., 1 H), 8.75 (dd, *J* = 2.0, 3.7 Hz, 2 H), 8.69 (d, *J* = 1.8 Hz, 1 H), 8.17 (d, *J* = 5.4 Hz, 1 H), 8.00 - 7.86 (m, 2 H), 7.78 (s, 1 H), 7.72 - 7.66 (m, 1 H), 7.62 - 7.50 (m, 2 H), 7.39 (d, *J* = 10.5 Hz, 1 H), 7.35 (d, *J* = 6.5 Hz, 1 H), 6.50 (d, *J* = 1.8 Hz, 1 H), 3.72 (s, 3 H). HRMS *m/z* Calcd for $C_{25}H_{18}ClFN_3O_4S$ $[M+1]^+$ = 510.0685. Found $[M+1]^+$ = 510.0652.

N-(isoxazol-3-yl)-1-(2,3',5'-trifluoro-5-methoxy-[1,1'-biphenyl]-4-yl)isoquinoline-6-sulfonamide (18).

A vial was charged with 1-(4-bromo-5-fluoro-2-methoxyphenyl)-N-(isoxazol-3-yl)isoquinoline-6-sulfonamide **54a** (94.4 mg, 0.197 mmol), (3,5-difluorophenyl)boronic acid (46.7 mg, 0.296 mmol), potassium carbonate (82 mg, 0.59 mmol), and $Pd(PPh_3)_4$ (22.8 mg, 0.020 mmol). The vial was flushed with Ar (g), then dioxane (0.7 mL) and water (0.3 mL) were added. The vial was heated to 120 °C in a Biotage Initiator microwave reactor for 3 hrs. The mixture was cooled to rt diluted with water and extracted with EtOAc (3×). The combined organic extracts were concentrated. The residue was purified by reverse-phase HPLC (30-85% CH_3CN/H_2O with 0.1% TFA) to give N-(isoxazol-3-yl)-1-(2,3',5'-trifluoro-5-methoxy-[1,1'-biphenyl]-4-yl)isoquinoline-6-sulfonamide 2,2,2-trifluoroacetate **18** (69 mg, 0.11 mmol, 56% yield) as a yellow solid. ^{1}H NMR (400MHz, DMSO-d_6) δ = 11.92 (br. s., 1 H), 8.78 - 8.73 (m, 2 H), 8.70 (d, *J* = 1.9 Hz, 1 H), 8.18 (d, *J* = 5.3 Hz, 1 H), 8.00 - 7.93 (m, 1 H), 7.91 - 7.85 (m, 1 H), 7.49 (dd, *J* = 1.1, 6.4 Hz, 2 H), 7.45 - 7.33 (m, 3 H), 6.50 (d, *J* = 1.9 Hz, 1 H), 3.72 (s, 3 H). HRMS *m/z* Calcd for $C_{25}H_{17}F_3N_3O_4S$ $[M+1]^+$ = 512.0886. Found $[M+1]^+$ = 512.0869.

1-(3'-chloro-2-fluoro-5-methoxy-4'-methyl-[1,1'-biphenyl]-4-yl)-N-(isoxazol-3-yl)isoquinoline-6-sulfonamide (19).

A vial was charged with 1-(4-bromo-5-fluoro-2-methoxyphenyl)-N-(isoxazol-3-yl)isoquinoline-6-sulfonamide **54a** (80 mg, 0.167 mmol), potassium carbonate (69 mg, 0.50 mmol), (3-chloro-4-methylphenyl)boronic acid (43 mg, 0.25 mmol) and $Pd(PPh_3)_4$ (19.3 mg, 0.017 mmol). The vial was flushed with Ar (g), then dioxane (627 µl) and water (209 µl) were added. The vial was heated to 120 °C in a Biotage Initiator microwave reactor for 8 hours. The mixture was cooled to rt and diluted with water and extracted with EtOAc (3×). The combined organic extracts were concentrated. The residue was dissolved in DMSO, and the resulting solution was filtered through a 0.2 micron filter. The filtrate was purified by DAS using singleton purification (reverse-phase HPLC using 0.1% NH_4OH) to give 1-(3'-chloro-2-fluoro-5-methoxy-4'-methyl-[1,1'-biphenyl]-4-yl)-N-(isoxazol-3-yl)isoquinoline-6-sulfonamide **19** (28.7 mg, 0.055 mmol, 33% yield) as a light-yellow solid. ^{1}H NMR (500MHz, DMSO-d_6) δ = 11.97 (br. s., 1 H), 8.75 - 8.69 (m, 2 H), 8.66 (s, 1 H), 8.14 (d, *J* = 5.7 Hz, 1 H), 7.94 (dd, *J* = 1.7, 8.9 Hz, 1 H), 7.89 - 7.84 (m, 1 H), 7.76 (s, 1 H), 7.59 (d, *J* = 7.9 Hz, 1 H), 7.54 - 7.49 (m, 1 H), 7.38 - 7.29 (m, 2 H), 6.48 (d, *J* = 1.6 Hz, 1 H), 3.71 (s, 3 H), 2.42 (s, 3 H). HRMS *m/z* Calcd for $C_{26}H_{20}ClFN_3O_4S$ $[M+1]^+$ = 524.0842. Found $[M+1]^+$ = 524.0831.

1-(2-fluoro-5-methoxy-3'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)-N-(isoxazol-3-yl)isoquinoline-6-sulfonamide (20).

A vial was charged with 1-(4-bromo-5-fluoro-2-methoxyphenyl)-N-(isoxazol-3-yl)isoquinoline-6-sulfonamide **54a** (74 mg, 0.17 mmol), (3-(trifluoromethyl)phenyl)boronic acid (64.4 mg, 0.339 mmol), chloro(2-dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl)[2-(2-

aminoethylphenyl)]palladium(ii) DCM (6.43 mg, 8.48 μmol), and potassium phosphate (180 mg, 0.848 mmol). The vial was flushed with Ar (g), then dioxane (771 μl) and water (77 μl) were added. The vial was sealed and heated in a Biotage Initiator microwave reactor for 1.5 h at 120 °C. After cooled to rt, the mixture was extracted with EtOAc (3×). The combined organic extracts were concentrated. The residue was dissolved in DMSO (2.5 mL), and the resulting solution was filtered through a 0.2 micron filter. The crude product was purified by reverse-phase HPLC using 0.1% NH_4OH in ACN and water as mobile phase to give 1-(2-fluoro-5-methoxy-3'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)-N-(isoxazol-3-yl)isoquinoline-6-sulfonamide **20** (29.2 mg, 0.056 mmol, 33.3 % yield) as a light-yellow solid. ^{1}H NMR (500MHz, DMSO-d_6) δ = 11.90 (br. s., 1 H), 8.77 - 8.69 (m, 2 H), 8.66 (s, 1 H), 8.14 (d, *J* = 5.7 Hz, 1 H), 7.94 (dd, *J* = 1.7, 8.9 Hz, 1 H), 7.89 - 7.83 (m, 1 H), 7.70 (s, 1 H), 7.60 - 7.51 (m, 3 H), 7.36 (d, *J* = 10.4 Hz, 1 H), 7.30 (d, *J* = 6.4 Hz, 1 H), 6.48 (d, *J* = 1.7 Hz, 1 H), 3.71 (s, 3 H). HRMS *m/z* Calcd for $C_{26}H_{18}F_4N_3O_4S$ $[M+1]^+$ = 544.0949. Found $[M+1]^+$ = 544.0962.

1-(2-fluoro-5-methoxy-4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)-N-(isoxazol-3-yl)isoquinoline-6-sulfonamide (21).

A vial was charged with 1-(4-bromo-5-fluoro-2-methoxyphenyl)-N-(isoxazol-3-yl)isoquinoline-6-sulfonamide **54a** (300 mg, 0.63 mmol), (4-(trifluoromethyl)phenyl)boronic acid (230 mg, 1.211 mmol), S-Phos Precatalyst (30.6 mg, 0.040 mmol), dicyclohexyl(2',6'-dimethoxy-[1,1'-biphenyl]-2-yl)phosphine (16.57 mg, 0.040 mmol), potassium phosphate (514 mg, 2.421 mmol) dioxane (2 mL) and water (1 mL). The vial was heated in the microwave at 120 °C for 30 min. The mixture was cooled to rt and extracted with EtOAc (5×), and the combined organic extracts were concentrated. The residue was purified by chromatography on silica gel (40-g Redi-Sep Gold column, 25-g silica gel column, 0-3% MeOH/DCM) to give ca 400 mg of a yellow solid.

The solid was dissolved in EtOAc, and the solution was aged overnight allowing some of the solvent to evaporate and leave a suspension. The suspension was diluted with EtOAc and filtered. The collected solid was washed with EtOAc (2×), dried under a stream of N_2 (g), then dried under vacuum to give 1-(2-fluoro-5-methoxy-4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)-N-(isoxazol-3-yl)isoquinoline-6-sulfonamide **21** (132 mg, 0.243 mmol, 38% yield) as an off-white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ = 11.92 (br. s., 1 H), 8.77 - 8.73 (m, 2 H), 8.69 (d, *J* = 1.6 Hz, 1 H), 8.17 (d, *J* = 5.7 Hz, 1 H), 7.99 - 7.86 (m, 6 H), 7.46 - 7.34 (m, 2 H), 6.50 (d, *J* = 1.9 Hz, 1 H), 3.72 (s, 3 H). HRMS *m/z* Calcd for $C_{26}H_{18}F_4N_3O_4S$ $[M+1]^+$ = 544.0949. Found $[M+1]^+$ = 544.0927.

1-(2-fluoro-5-methoxy-3'-methyl-[1,1'-biphenyl]-4-yl)-N-(isoxazol-3-yl)isoquinoline-6-sulfonamide (22).

A vial was charged with 1-(4-bromo-5-fluoro-2-methoxyphenyl)-N-(isoxazol-3-yl)isoquinoline-6-sulfonamide **54a** (62.3 mg, 0.130 mmol), (3-methylphenyl)boronic acid (26.1 mg, 0.195 mmol), potassium carbonate (54 mg, 0.39 mmol), and $Pd(PPh_3)_4$ (14.5 mg, 0.013 mmol). The vial was flushed with Ar (g), then dioxane (0.7 mL) and water (0.3 mL) were added. The vial was heated to 120 °C in a Biotage Initiator microwave reactor for 3 hrs. The mixture was cooled to rt diluted with water and extracted with EtOAc (3×). The combined organic extracts were concentrated. The residue was purified by reverse-phase HPLC (30-85% CH_3CN/H_2O with 0.1% TFA) to give 1-(2-fluoro-5-methoxy-3'-methyl-[1,1'-biphenyl]-4-yl)-N-(isoxazol-3-yl)isoquinoline-6-sulfonamide **22** (47 mg, 0.079 mmol, 62% yield) as a yellow solid. ^{1}H NMR (400MHz, DMSO-d_6) δ = 11.92 (br. s., 1 H), 8.75 (dd, *J* = 2.0, 3.7 Hz, 2 H), 8.69 (d, *J* = 1.8 Hz, 1 H), 8.17 (d, *J* = 5.4 Hz, 1 H), 8.00 - 7.86 (m, 2 H), 7.78 (s, 1 H), 7.72 - 7.66 (m, 1 H), 7.62 -

7.50 (m, 2 H), 7.39 (d, *J* = 10.5 Hz, 1 H), 7.35 (d, *J* = 6.5 Hz, 1 H), 6.50 (d, *J* = 1.8 Hz, 1 H), 3.72 (s, 3 H), 2.31 (s, 3 H). HRMS *m/z* Calcd for $C_{26}H_{21}FN_3O_4S$ $[M+1]^+$ = 490.1231. Found $[M+1]^+$ = 490.1232.

1-(5-fluoro-4-(5-fluoro-2-methoxypyridin-3-yl)-2-methoxyphenyl)-N-(isoxazol-3-yl)isoquinoline-6-sulfonamide (23).

A vial was charged with 1-(4-chloro-5-fluoro-2-methoxyphenyl)-N-(isoxazol-3-yl)isoquinoline-6-sulfonamide **54a** (122.6 mg, 0.283 mmol), (5-fluoro-2-methoxypyridin-3-yl)boronic acid (97 mg, 0.565 mmol), chloro(2-dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl)[2-(2-aminoethylphenyl)]palladium(II) DCM (10.70 mg, 0.014 mmol), and potassium phosphate (300 mg, 1.413 mmol). The vial was flushed with Ar (g), then dioxane (1280 µl) and water (120 µl) were added. The vial was sealed and heated in a Biotage Initiator microwave reactor for 6 h at 120 °C. The mixture was diluted with water and extracted with EtOAc (3×). The combined organic extracts were concentrated. The residue was dissolved in DMSO and filtered through a 0.2 micron filter. The filtrate was purified by reverse-phase HPLC (35-80% CH_3CN/H_2O with 0.1% TFA) to give 1-(5-fluoro-4-(5-fluoro-2-methoxypyridin-3-yl)-2-methoxyphenyl)-N-(isoxazol-3-yl)isoquinoline-6-sulfonamide 2,2,2-trifluoroacetate **23** (24.9 mg, 0.039 mmol, 14% yield) as an orange solid. ^{1}H NMR (400MHz, DMSO-d_6) δ = 11.93 (br. s., 1 H), 8.77 - 8.73 (m, 2 H), 8.70 (d, *J* = 1.9 Hz, 1 H), 8.30 (d, *J* = 2.9 Hz, 1 H), 8.18 (d, *J* = 5.4 Hz, 1 H), 7.99 - 7.96 (m, 1 H), 7.92 (dd, *J* = 3.0, 8.4 Hz, 1 H), 7.90 - 7.87 (m, 1 H), 7.35 (d, *J* = 9.7 Hz, 1 H), 7.30 (d, *J* = 5.9 Hz, 1 H), 6.51 (d, *J* = 1.9 Hz, 1 H), 3.91 (s, 3 H), 3.66 (s, 3 H). HRMS *m/z* Calcd for $C_{25}H_{19}F_2N_4O_5S$ $[M+1]^+$ = 525.1039. Found $[M+1]^+$ = 525.1044.

1-(3',5'-difluoro-3-methoxy-[1,1'-biphenyl]-4-yl)-N-(isoxazol-3-yl)isoquinoline-6-sulfonamide (24).

Step 1: A round-bottom flask was charged with perfluorophenyl 1-chloroisoquinoline-6-sulfonate **24** (0.85 g, 2.04 mmol), (4-bromo-2-methoxyphenyl)boronic acid (0.506 g, 3.11 mmol), potassium carbonate (0.86 g, 6.22 mmol), and $Pd(PPh_3)_4$ (0.48 g, 0.41 mmol). The vial was flushed with Ar (g), then dioxane (10 mL) and water (5 mL) were added. The flask was fitted with a reflux condenser and heated in a 50 °C heating bath for one hour. The mixture was cooled to rt, diluted with water and extracted with EtOAc (2×). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated. The residue was purified by chromatography on silica gel (40-g Redi-Sep Gold column, 0-50% EtOAc/Heptane) to give perfluorophenyl 1-(4-bromo-2-methoxyphenyl)isoquinoline-6-sulfonate (0.71 g, 1.59 mmol, 72% yield) as a white foam. Mass Spectrum (ESI) *m/z* 560.0 $[M+H]^+$.

Step 2: A round-bottom flask was charged with perfluorophenyl 1-(4-bromo-2-methoxyphenyl)isoquinoline-6-sulfonate (278 mg, 0.588 mmol), THF (1 mL) and isoxazol-3-amine (48 µl, 0.649 mmol). The flask was cooled in an ice-bath for 10 min., then lithium bis(trimethylsilyl)amide (1M in THF) (123 µl, 1.23 mmol) was added dropwise. After 15 min. the mixture was diluted with 1 N aqueous HCl and extracted with EtOAc (2×). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated. The residue was purified by chromatography on silica gel (40-g Redi-Sep Gold column, 0-5% MeOH/DCM) to give 1-(4-bromo-2-methoxyphenyl)-N-(isoxazol-3-yl)isoquinoline-6-sulfonamide **54b** (209 mg, 0.54 mmol, 92% yield) as a white foam. Mass Spectrum (ESI) *m/z* 460.1 $[M+H]^+$.

Step 3: A vial was charged with 1-(4-bromo-2-methoxyphenyl)-N-(isoxazol-3-yl)isoquinoline-6-sulfonamide (135 mg, 0.34 mmol), (3,5-difluorophenyl)boronic acid (84 mg, 0.53 mmol), chloro(2-dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl)[2-(2-aminoethylphenyl)]palladium(ii) dichloromethane (18 mg, 0.024 mmol), and potassium

phosphate (500 mg, 2.4 mmol). The vial was flushed with Ar (g), then dioxane (2 mL) and water (0.1 mL) were added. The vial was sealed and heated in a Biotage Initiator microwave reactor for 1 h at 120 °C before being cooled to rt. The mixture was extracted with EtOAc (4×). The combined organic extracts were concentrated. The residue was taken up in MeOH, then filtered through a 0.2 micron filter. The filtrate was purified by reverse-phase HPLC (40-85% CH_3CN/H_2O with 0.1% TFA) to give 1-(3',5'-difluoro-3-methoxy-[1,1'-biphenyl]-4-yl)-N-(isoxazol-3-yl)isoquinoline-6-sulfonamide **24** (50 mg, 0.078 mmol, 22% yield) as a yellow solid. ^{1}H NMR (400MHz, DMSO-d_6) δ = 11.89 (br. s., 1 H), 8.78 (dd, *J* = 2.1, 3.4 Hz, 2 H), 8.68 (d, *J* = 1.8 Hz, 1 H), 8.19 (d, *J* = 5.6 Hz, 1 H), 8.01 - 7.89 (m, 2 H), 7.79 (s, 1 H), 7.74 - 7.66 (m, 1 H), 7.62 - 7.54 (m, 2 H), 7.41 (d, *J* = 10.5 Hz, 1 H), 7.32 (d, *J* = 6.3 Hz, 1 H), 6.90 (d, *J* = 2.1 Hz, 1 H), 3.76 (s, 3 H). HRMS *m/z* Calcd for $C_{25}H_{18}F_2N_3O_4S$ $[M+1]^+$ = 494.0981. Found $[M+1]^+$ = 494.0972.

N-(isoxazol-3-yl)-1-(3-methoxy-3'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)isoquinoline-6-sulfonamide (25).

A vial was charged with 1-(4-bromo-2-methoxyphenyl)-N-(isoxazol-3-yl)isoquinoline-6-sulfonamide **54b** (100 mg, 0.217 mmol), (3-(trifluoromethyl)phenyl)boron30 acid (52 mg, 0.275 mmol), potassium carbonate (80 mg, 0.57 mmol), and $Pd(PPh_3)_4$ (23 mg, 0.026 mmol). The vial was flushed with Ar (g), then dioxane (1 mL) and water (0.3 mL) were added. The vial was heated to 120 °C in a Biotage Initiator microwave reactor for 3 hrs. The mixture was cooled to rt diluted with water and extracted with EtOAc (3×). The combined organic extracts were concentrated. The residue was purified by reverse-phase HPLC (30-85% CH_3CN/H_2O with 0.1% TFA) to give N-(isoxazol-3-yl)-1-(3-methoxy-3'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)isoquinoline-6-sulfonamide **25** (86 mg, 0.16 mmol, 73% yield) as a white solid. ^{1}H NMR

(400MHz, DMSO-d_6) δ = 11.92 (br. s., 1 H), 8.75 (dd, *J* = 2.0, 3.7 Hz, 2 H), 8.69 (d, *J* = 1.8 Hz, 1 H), 8.17 (d, *J* = 5.4 Hz, 1 H), 8.00 - 7.86 (m, 2 H), 7.78 (s, 1 H), 7.72 - 7.66 (m, 1 H), 7.62 - 7.50 (m, 2 H), 7.39 (d, *J* = 10.5 Hz, 1 H), 7.35 (d, *J* = 6.5 Hz, 1 H), 6.95 (d, *J* = 7.2 Hz, 1 H), 6.50 (d, *J* = 1.8 Hz, 1 H), 3.72 (s, 3 H). HRMS *m/z* Calcd for $C_{26}H_{19}F_3N_3O_4S$ $[M+1]^+$ = 526.1043. Found $[M+1]^+$ = 526.1029.

1-(2-cyano-3',5'-difluoro-5-methoxy-[1,1'-biphenyl]-4-yl)-N-(isoxazol-3-yl)isoquinoline-6-sulfonamide (26).

Step 1: A round-bottom flask was charged with perfluorophenyl 1-chloroisoquinoline-6-sulfonate **24** (1.9 g, 4.64 mmol), (4-bromo-5-cyano-2-methoxyphenyl)boronic acid (1.25 g, 4.90 mmol), potassium carbonate (1.63 g, 11.9 mmol), and $Pd(PPh_3)_4$ (0.55 g, 0.47 mmol). The vial was flushed with Ar (g), then dioxane (10 mL) and water (5 mL) were added. The flask was fitted with a reflux condenser and heated in a 50 °C heating bath for one hour. The mixture was cooled to rt, diluted with water and extracted with EtOAc (2×). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated. The residue was purified by chromatography on silica gel (40-g Redi-Sep Gold column, 0-50% EtOAc/Heptane) to give perfluorophenyl 1-(4-bromo-5-cyano-2-methoxyphenyl)isoquinoline-6-sulfonate (0.71 g, 1.59 mmol, 72% yield) as a white solid.

Step 2: A round-bottom flask was charged with perfluorophenyl 1-(4-bromo-5-cyano-2-methoxyphenyl)isoquinoline-6-sulfonate (300 mg, 0.512 mmol), THF (1.5 mL) and isoxazol-3-amine (50 µl, 0.66 mmol). The flask was cooled in an ice-bath for 10 min., then lithium bis(trimethylsilyl)amide (1 M in THF) (150 µl, 1.50 mmol) was added dropwise. After 30 min. the mixture was diluted with 1 N aqueous HCl and extracted with EtOAc (3×). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated. The residue was

purified by chromatography on silica gel (12-g Redi-Sep Gold column, 0-5% MeOH/DCM) to give 1-(4-bromo-5-cyano-2-methoxyphenyl)-N-(isoxazol-3-yl)isoquinoline-6-sulfonamide **54c** (186 mg, 69% yield) as an off-white solid. Mass Spectrum (ESI) *m/z* 485.2 $[M+H]^+$.

Step 3: A vial was charged with 1-(4-bromo-5-cyano-2-methoxyphenyl)-N-(isoxazol-3-yl)isoquinoline-6-sulfonamide (250 mg, 0.51 mmol), (3,5-difluorophenyl)boronic acid (101 mg, 0.63 mmol), chloro(2-dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl)[2-(2-aminoethylphenyl)]palladium(ii) dichloromethane (20 mg, 0.026 mmol), and potassium phosphate (500 mg, 2.4 mmol). The vial was flushed with Ar (g), then dioxane (2 mL) and water (0.1 mL) were added. The vial was sealed and heated in a Biotage Initiator microwave reactor for 1.5 h at 130 °C before being cooled to rt. The mixture was extracted with EtOAc (2×). The combined organic extracts were concentrated. The residue was taken up in MeOH, then filtered through a 0.2 micron filter. The filtrate was purified by reverse-phase HPLC (40-85% CH_3CN/H_2O with 0.1% TFA) to give 1-(2-cyano-3',5'-difluoro-5-methoxy-[1,1'-biphenyl]-4-yl)-N-(isoxazol-3-yl)isoquinoline-6-sulfonamide 26 (141 mg, 0.27 mmol, 53% yield) as a white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ = 12.01 (br. s., 1 H), 8.75 - 8.71 (m, 2 H), 8.60 (d, *J* = 1.6 Hz, 1 H), 8.14 (d, *J* = 5.8 Hz, 1 H), 8.00 - 7.90 (m, 1 H), 7.88 - 7.84 (m, 1 H), 7.48 (dd, *J* = 1.3, 6.3 Hz, 2 H), 7.43 - 7.33 (m, 3 H), 6.53 (d, *J* = 1.7 Hz, 1 H), 3.73 (s, 3 H). HRMS *m/z* Calcd for $C_{26}H_{17}F_2N_4O_4S$ $[M+1]^+$ = 519.0933. Found $[M+1]^+$ = 519.0900.

1-(2-cyano-5-methoxy-3'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)-N-(isoxazol-3-yl)isoquinoline-6-sulfonamide (27).

A vial was charged with 1-(4-bromo-2-methoxyphenyl)-N-(isoxazol-3-yl)isoquinoline-6-sulfonamide **49c** (300 mg, 0.618 mmol), (3-(trifluoromethyl)phenyl)boronic acid (150 mg, 0.793 mmol), potassium carbonate (160 mg, 1.15 mmol), and $Pd(PPh_3)_4$ (61 mg, 0.052 mmol). The vial

was flushed with Ar (g), then dioxane (5 mL) and water (1 mL) were added. The vial was heated to 120 °C in a Biotage Initiator microwave reactor for 4 hrs. The mixture was cooled to rt diluted with water and extracted with EtOAc (3×). The combined organic extracts were concentrated. The residue was purified by reverse-phase HPLC (30-85% CH_3CN/H_2O with 0.1% TFA) to give 1-(2-cyano-5-methoxy-3'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)-N-(isoxazol-3-yl)isoquinoline-6-sulfonamide **27** (204 mg, 0.37 mmol, 60% yield) as a white solid. ^{1}H NMR (500MHz, DMSO-d_6) δ = 11.88 (br. s., 1 H), 8.78 - 8.68 (m, 2 H), 8.60 (s, 1 H), 8.13 (d, *J* = 5.5 Hz, 1 H), 7.98 (dd, *J* = 1.8, 8.9 Hz, 1 H), 7.88 - 7.83 (m, 1 H), 7.68 (s, 1 H), 7.61 - 7.52 (m, 2 H), 7.38 (d, *J* = 10.0 Hz, 1 H), 7.35 (d, *J* = 6.5 Hz, 1 H), 7.13 (d, *J* = 6.7 Hz, 1 H), 6.45 (d, *J* = 1.8 Hz, 1 H), 3.69 (s, 3 H). HRMS *m/z* Calcd for $C_{27}H_{18}F_3N_4O_4S$ $[M+1]^+$ = 551.0995. Found $[M+1]^+$ = 551.0999.

(2-chloro-3'-fluoro-5-methoxy-[1,1'-biphenyl]-4-yl)boronic acid (33).

Step 1: A round-bottom flask was charged with 3-bromo-4-chloroanisole **31** (1.62 ml, 7.34 mmol), (3-fluorophenyl)boronic acid (1.12 g, 8.07 mmol), potassium carbonate (3.04 g, 22.0 mmol), and $Pd(PPh_3)_4$ (0.424 g, 0.367 mmol). The flask was flushed with Ar (g), then dioxane (19 ml) and water (4 ml) were added. A reflux condenser was attached, and the flask was lowered into a 90 °C heating bath for 2 hrs. The mixture was cooled to rt, diluted with ethyl acetate, and washed with brine. The organic layer was dried over sodium sulfate, filtered, and concentrated. The residue was purified by chromatography on silica gel (80-g Redi-Sep Gold column, 0-10% EtOAc/Heptane) to give 2-chloro-3'-fluoro-5-methoxy-1,1'-biphenyl (1.28 g, 5.44 mmol, 74% yield) as a clear oil that was used immediately in the next step.

Step 2: A round-bottom flask was charged with 2-chloro-3'-fluoro-5-methoxy-1,1'-biphenyl (1.28 g, 5.44 mmol), DCM (8.00 ml), AcOH (8.00 ml), and sulfuric acid (0.160 ml, 2.99 mmol)

to give a clear solution. N-iodosuccinimide (1.22 g, 5.44 mmol) was added in one portion to give a maroon-colored solution that was maintained for 6 hours. The mixture was diluted with DCM, washed with water, washed with saturated aqueous sodium thiosulfate, dried over sodium sulfate, filtered, and concentrated. The residue was purified by chromatography on silica gel (40-g Redi-Sep Gold column, 25-g silica gel column, 0-5% EtOAc/Heptane) to give 2-chloro-3'-fluoro-4-iodo-5-methoxy-1,1'-biphenyl **32** (1.68 g, 4.63 mmol, 85% yield) as a clear oil.

Step 3: A round-bottom flask was charged with 2-chloro-3'-fluoro-4-iodo-5-methoxy-1,1'-biphenyl **32** (1.68 g, 4.63 mmol), triisopropyl borate (1.3 ml, 6.02 mmol), and THF (23 ml). The flask was cooled in a dry ice-acetone bath for 10 min., then n-butyllithium (2.5 M in hexane) (2.40 ml, 6.02 mmol) was added dropwise over 1 min. After 1 hr the mixture was allowed to warm to rt and a solution of 2N aq. NaOH (25 mL) was added. The resulting biphasic mixture was stirred for 10 min., then partitioned between water and ether. The layers were separated, and the ethereal layer was extracted with water (2×). The combined aqueous extracts were washed with ether, and the ethereal layer was back-extracted with water. The combined aq. layers were acidified with 3N aqueous HCl (50 mL), and the aqueous mixture was extracted with DCM (3x). The combined DCM-layers were dried over sodium sulfate, filtered, and concentrated to give (2-chloro-3'-fluoro-5-methoxy-[1,1'-biphenyl]-4-yl)boronic acid **33** (0.859 g, 3.06 mmol, 66% yield) as an oily solid.

N-(4-methoxybenzyl)isoxazol-3-amine (38)

A flask was charged with 4-methoxybenzaldehyde (3.62 mL, 29.8 mmol), 3-aminoisoxazole **37** (2 mL, 27.1 mmol), MeOH (135 mL), water (2.4 mL, 130 mmol), and acetic acid (1.7 mL, 29 mmol). The reaction was stirred for 15 min., after which molybdenum dichloride dioxide (0.269 g, 1.35 mmol) and phenylsilane (5.0 mL, 41 mmol) were added. The reaction was stirred

overnight at room temperature. The reaction was filtered through a pad of Celite, which was washed with ethyl acetate. The filtrate was concentrated, diluted with ethyl acetate and washed with saturated sodium bicarbonate solution. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were washed with water, washed with brine, dried with sodium sulfate, filtered, and concentrated. The material was purified via column chromatography (40-g Redi-Sep Gold column, gradient elution 0-50% EtOAc:Heptane) to afford N-(4-methoxybenzyl)isoxazol-3-amine (4.10, 20.0 mmol, 74% yield) as a light yellow solid. Mass Spectrum (ESI) *m/z* 205.1 $[M+H]^+$.

Human Stable Cell Lines, Rodent Stable Cell Line Development, PatchXpress 7000A Electrophysiology, IonWorks Quattro Electrophysiology, Manual Patch-Clamp Electrophysiology, DRG Neuron Isolation and Manual Patch Clamp Electrophysiology and IonWorks Quattro Electrophysiology, Rat and Human Liver Microsomal Assays and Plasma Protein Binding. All were carried out in a manner identical to that reported in reference 24.

Solubility Determination. Solubilities were determined according to an automated procedure.[27]

CYP Inhibition IC_{50}. Inhibition of CYP3A4, 2D6, and 2C9 was determined as described.[26]

Rat and Dog Pharmacokinetic Studies. Carried out in a manner identical to that reported in reference 8.

Histamine-Induced Scratching in Mice. All procedures were approved and carried out in accordance with Amgen Inc.'s Institutional Animal Care and Use Committee. Subjects were C57Bl/6 male mice (Charles River Labs, Kingston, NY) aged between 9-10 weeks and housed 1-

4 per cage with *ad libitum* access to food and water. Animals were kept on a 12/12 h light/dark cycle with lights on at 6:30 a.m. Following arrival from the vendor, mice were allowed to acclimate to the animal facility for 1 week prior to the start of the experiment. One day prior to behavioral testing, mice were anesthetized under 3% isoflurane and the area at the nape of the neck was shaved. Immediately afterward, mice were transported to the testing room and acclimated to individual sound-attenuated chambers (12"l X 9.5"w X 8.25"h, Med Associates VFC-008, NIR-022MD, St. Albans, VT) for 15-20 minutes. Testing was performed the following day between the hours of 8:00 am and 3:00 pm. Four hours prior to histamine treatment, mice were orally administered either Compound **20** (30, 100 and 300 mg/kg body weight), a vehicle control formulation (30% Hydroxypropyl beta-cyclodextrin, 70% H_2O, pH10), or the antihistamine Diphenhydramine (30 mg/kg in phosphate-buffered saline, Sigma D3630) which served as a positive control. Histamine dichloride (8.15 mM in a volume of 100 µL, Sigma Aldrich H7250) was injected intradermally to the shaved area, mice were placed into the sound-attenuated testing chambers, and behavior was recorded on digital video files for a period of 15 minutes. Video recordings were later reviewed, and individual scratching bouts scored, by trained experimenters blinded to test article treatment. A scratching bout was defined as a rapid head tilt accompanied by a hind paw directed at the site of intradermal injection. Termination of a scratching bout was deemed to have occurred when the hind paw was placed back on the chamber floor or into the animal's mouth. Data was analyzed statistically via GraphPad Prism 5 software (GraphPad Software Inc., La Jolla, CA) using a one-way ANOVA to assess the overall test article treatment effect and followed by Dunnett's multiple comparison post-hoc tests.

Open-Field Locomotor Activity in Mice. All procedures were approved and carried out in accordance with Amgen Inc.'s Institutional Animal Care and Use Committee. Subjects were

C57Bl/6 male mice (Charles River Labs, Kingston, NY) aged between 9-10 weeks and housed 1-4 per cage with *ad libitum* access to food and water. Animals were kept on a 12/12 h light/dark cycle with lights on at 6:30 a.m. Following arrival from the vendor, mice were allowed to acclimate to the animal facility for 1 week prior to the start of the experiment. On the day of testing, animals were orally administered either Compound **20** (30, 100 and 300 mg/kg body weight) or a vehicle control formulation (30% Hydroxypropyl beta-cyclodetrin, 70% H_2O, pH10) between the hours of 7:00 a.m. and 5:00 p.m. Four hours following test article treatment, animals were placed into dimly-lit (15-20 Lux) open-field chambers (16" x 16", Kinder Scientific, San Diego, CA) and behavior was monitored over a 60-minute period during which horizontal movement parameters were measured in an automated manner via infrared photo beam breaks. Data was analyzed statistically via GraphPad Prism 5 software (GraphPad Software Inc., La Jolla, CA) using a one-way ANOVA to assess the overall test article treatment effect and followed by Dunnett's multiple comparison post-hoc tests.

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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ABBREVIATIONS USED

hERG, human ether-a-go-go related gene; μW, microwave; CL, clearance; CLu, unbound clearance; PPB, plasma protein binding; AUC, area under the curve; V_{dss}, volume of distribution; OATP, organic anion-transporting polypeptide; SCN9A, sodium channel protein type 9 subunit alpha; F, bioavailability; PX, Patch-Express; CYP, cytochrome P450; PXR, pregnane X-receptor; DDI, drug-drug interaction; CIP, congenital indifference to pain; SAR, structure activity relationship; POC, percentage of control; IWQ, IonWorks Quattro; PSA, polar surface area.

Supporting Information

Molecular Formula Strings

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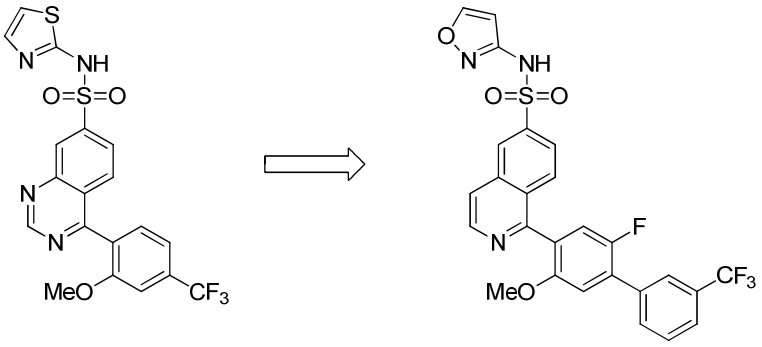

1

$Na_V1.7$ IC_{50} (μM): 0.16
$Na_V1.5$ IC_{50} (μM): >30
Rat iv CL (L/h/kg) [CLu]: 0.54 [33]
PXR Activation (POC @ 10 μM): 130
Contains 2-aminothiazole structural alert

20

$Na_V1.7$ IC_{50} (μM): 0.035
$Na_V1.5$ IC_{50} (μM): >30
Rat iv CL (L/h/kg) [CLu]: 0.23 [26]
PXR Activation (POC @ 10 μM): <1