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Article

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# Development of new benzenesulfonamides as potent and selective $Na_v1.7$ inhibitors for the treatment of pain

Yong-Jin Wu,* Jason Guernon, Jianliang Shi, Jonathan Ditta, Kevin J. Robbins, Ramkumar Rajamani, Amy Easton, Amy Newton, Clotilde Bourin, Kathleen Mosure, Matthew G. Soars, Ronald J. Knox, Michele Matchett, Rick L. Pieschl, Debra J. Post-Munson, Shuya Wang, James Herrington, John Graef, Kimberly Newberry, Linda J. Bristow, Nicholas A. Meanwell, Richard Olson, Lorin A. Thompson, and Carolyn Dzierba

Bristol-Myers Squibb Research and Development, 5 Research Parkway, Wallingford, CT 06492-7660, USA

*Supporting Information Placeholder*

ABSTRACT: By taking advantage of certain features in piperidine **4**, we developed a novel series of cyclohexylamine- and piperidine-based benzenesulfonamides as potent and selective $Na_v1.7$ inhibitors. However, compound **24**, one of the early analogs, failed to reduce phase 2 flinching in the mouse formalin test even at a dose of 100 mpk PO due to insufficient DRG exposure attributed to poor membrane permeability. Two analogs with improved membrane permeability showed much increased DRG concentrations at doses of 30 mpk PO but, confoundingly, only one of these was effective in the formalin test. More data are needed to understand the disconnect between efficacy and exposure relationships.

## INTRODUCTION

The voltage-gated sodium channel $Na_v1.7$, which is encoded by the SCN9A gene, has been shown to play an important role in painful disorders in humans. For example, gain-of-function mutations in the SCN9A gene lead to painful conditions such as inherited erythromelalgia and paroxysmal extreme pain disorder[1,2] whereas loss-of-function mutations in the SCN9A gene result in congenital insensitivity to pain, a rare disorder characterized by a complete inability to sense painful stimuli.[3-5] Apart from anosmia, humans and mice deficient in $Na_v1.7$ are apparently normal,[6,7] suggesting that $Na_v1.7$ inhibitors would not incur safety-related, on-target toxicity. The $Na_v1.7$ isoform is expressed predominantly in the peripheral nervous system (PNS) and, therefore, a non-brain penetrant inhibitor would be expected to have reduced potential for eliciting central nervous system (CNS)-related adverse effects.[8] Thus, $Na_v1.7$ is viewed as a promising analgesic drug target for acute, inflammatory and neuropathic pain.[9-12] As the blocking of the cardiac sodium channel $Na_v1.5$ may lead to arrhythmia,[13] recent efforts have focused on the development of isoform-selective inhibitors. These efforts have led to the discovery of the sulfonamide GNE-131 (**1**)[14] and benzenesulfonamides **2**[15] and **3**[16] as potent and isoform-selective $Na_v1.7$ inhibitors that demonstrate efficacy in various rodent pain models. These compounds bind to a unique site in the voltage sensor domain 4 (VSD4) of $Na_v1.7$ that is distinct from the pore binding sites of tetrodotoxin or local anesthetics.[17]

The crystal structure of a chimera consisting of human $Na_v1.7$ VSD4 and a bacterial pore domain in complex with an aryl sulfonamide has been recently disclosed.[18] Recently, we embarked on identifying new leads from within the heteroaryl sulfonamide class of inhibitors that exhibit high levels of potency and selectivity over the $hNa_v1.5$ cardiac channel.[19] More specifically, we sought to discover potent $Na_v1.7$ inhibitors that combine favorable pharmacokinetic properties, with oral efficacy in rodent pain models. This report describes the development of these new benzenesulfonamides.

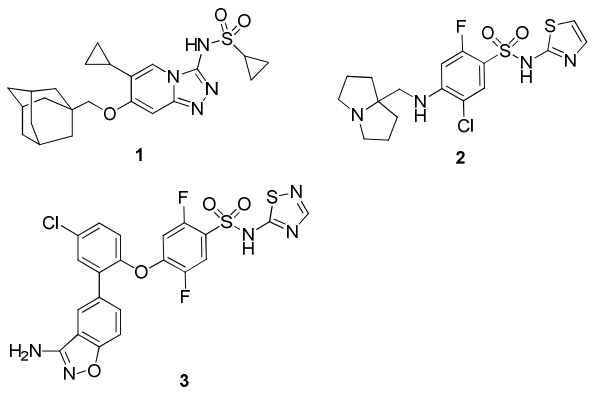



**Figure 1.** Structures of $Na_v1.7$ inhibitors

## RESULTS AND DISCUSSION

The inhibitory activity of test compounds towards $hNa_v1.7$ and $hNa_v1.5$ channels was assessed using an automated 384-well IonWorks Barracuda® patch-clamp assay designed to measure potency on the inactivated channel. The Barracuda data generally correlated well with manual patch clamp electrophysiology results (data not shown). The inhibitory activity of these compounds toward cytochrome P450 isoforms was also monitored closely since heteroaryl sulfonamides are known to exhibit potent CYP inhibition, especially for CYP3A4.[16,19]

In 2014, Sun *et al.* reported the discovery of piperidine **4** as a potent and selective $Na_v1.7$ isoform inhibitor ($IC_{50}$ = 1.1 nM in a PatchXpress assay).[19] As the sulfonamide functionality and the thiadiazole ring that form the acidic element are essential for binding to the protein *via* a salt bridge to a positively charged arginine in the domain 4 voltage sensor,[17,18] we undertook modification of **4** by relocating the aryloxymethyl group from C3 to C4 of the piperidine ring to form the 4,4-disubstituted piperidine **5** (Figure

2). This compound exhibited an $IC_{50}$ value of 0.9 μM, significantly less potent than **4** ($IC_{50}$ = 2 nM in the Barracuda assay). Nevertheless, we felt that it could serve as a useful new lead based on the reasoning that the linkage between the benzenesulfonamide and 4-chlorophenyl moieties in **5** might be spatially too close. Indeed, extension of the linker by just one carbon as in **6** increased channel inhibitory activity by 12-fold ($IC_{50}$ = 78 nM). With the spatial orientation between the benzenesulfonamide moiety and 4-chlorophenyl established, we investigated the impact of the position of the piperidine nitrogen, an effort that led to identification of the *cis* (amine vs. the ethylene linker) cyclohexylamine **7** as a potent ($IC_{50}$ = 8 nM) $hNa_v1.7$ inhibitor with more than 3000-fold selectivity over the $hNa_v1.5$ isoform. As the 4-chlorophenyl analog **7** was analogous to the unsubstituted 4-phenyl counterpart **9** ($IC_{50}$ = 15 nM) (Table 1), structure-activity relationship studies focused on the more readily accessible 4-phenyl analogs. Monoalkyl homologues of the primary amine in **11** ($IC_{50}$ = 10 nM) with methyl as in **13** ($IC_{50}$ = 64 nM) and cyclopropyl as in **15** ($IC_{50}$ = 105 nM) decreased potency by 6- and 10-fold, respectively, indicating a tight pocket in this area of the channel. The 2,5-difluoro- and 2-fluoro-5-chloro benzenesulfonamides **9** and **11** were equally potent in $hNa_v1.7$ activity, but both also suffered from CYP3A4 inhibition with submicromolar $IC_{50}$ values. Thus, replacing the 5-fluoro with chloro made little impact on both $Na_v1.7$ activity and CYP3A4 inhibition. The amine-linked *N*-(thiazolyl)benzenesulfonamide **17** ($IC_{50}$ = 9 nM) displayed comparable $hNa_v1.7$ potency as the corresponding ether-linked *N*-(thiadiazolyl)benzenesulfonamide **9** ($IC_{50}$ = 15 nM), but its liability for CYP3A4 inhibition was significantly ameliorated ($IC_{50}$ = 6.7 μM for **17** vs. 0.43 μM for **9**). As the favorable contribution from the 5-chloro substituent of **17** was likely to be limited, we concluded that the thiazole heterocycle together with the amine linkage contributed to the favorable CYP3A4 inhibition profile of **17**. In an effort to reduce molecular weight, we replaced the phenyl in **9** with a methyl group, and the resulting analog **19** still maintained moderate activity ($IC_{50}$ = 78 nM), thus disproving our long held belief that an aryl or heteroaryl moiety besides the *N*-(heteroaryl)benzenesulfonamide core was essential for $Na_v1.7$ inhibitory activity.[20] Next, we eliminated the phenyl ring of the amine-linked *N*-(thiazolyl)benzenesulfonamide **17**, which was chosen over the ether linked *N*-(thiadiazolyl)benzenesulfonamide **9** because of its reduced potential for

CYP3A4 inhibition. The resulting *cis* and *trans* isomers **21** ($IC_{50}$ = 8 nM) and **22** ($IC_{50}$ = 14 nM) were nearly as potent as the progenitor **17** ($IC_{50}$ = 9 nM) while preserving the favorable CYP3A4 inhibition profile of the latter compound. Interestingly, in the 4-desphenyl benzenesulfonamide series, both two carbon (as in **21** and **22**) and one carbon (as in **23** and **24**) linkages resulted in comparable $Na_v1.7$ inhibitory activity, a trend contrary to that observed with the 4-phenyl piperidine-based chemotype. With respect to the 4,4-disubstituted cyclohexylamine series **7**-**20**, the *cis* (amine vs. linker) isomers were consistently more potent than the *trans* isomers. Within the 4-monosubstituted series **21**, **22**, **24**, and **25**, stereochemical recognition was dependent on the linker: a methylene linker resulted in comparable activity for both isomers **21** and **22**, while an ethylene linker showed a strong preference for the *cis* isomer **24** ($IC_{50}$ = 6 nM) over the *trans* isomer **25** ($IC_{50}$ = 398 nM). In terms of CYP3A4 inhibition, no significant difference was observed between *cis* and *trans* isomers.

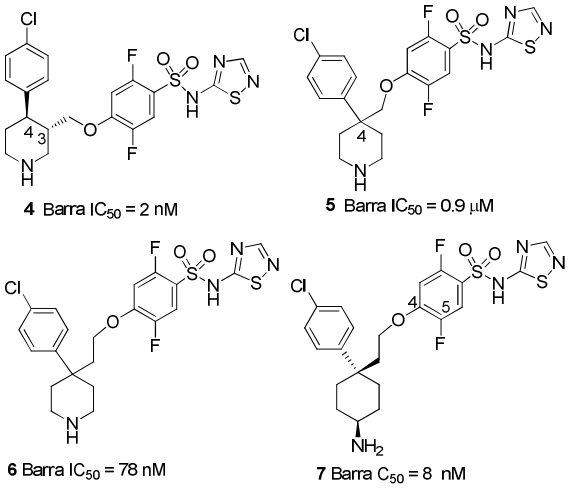
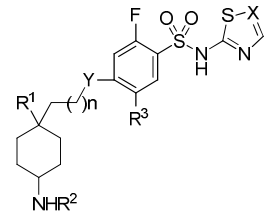



**Figure 2.** Structures of $Na_v1.7$ inhibitors

**Table 1**. $hNa_v1.7$, $hNa_v1.5$ and CYP3A4 inhibition $IC_{50}$ data of **7**-**25**[a]



| Compd. | $R^1$ | $R^2$ | $R^3$ | Y | X | n | Config.[f] | $hNa_v1.7$ $IC_{50}$ (nM)[b] | $hNa_v1.5$ $IC_{50}$ (μM)[c] | CYP3A4 $IC_{50}$ (μM)[d] |
|---|---|---|---|---|---|---|---|---|---|---|
| **7** | 4-Cl-Ph | H | F | O | N | 1 | *cis* | 8.0 ± 1.8 | >30 | 0.28 |
| **8** | 4-Cl-Ph | H | F | O | N | 1 | *trans* | 388[e] | >30 | NT |
| **9** | Ph | H | F | O | N | 1 | *cis* | 15 ± 8 | >30 | 0.43 |
| **10** | Ph | H | F | O | N | 1 | *trans* | 473 ± 111 | >30 | 0.68 |
| **11** | Ph | H | Cl | O | N | 1 | *cis* | 10 ± 1 | >30 | 0.27 |
| **12** | Ph | H | Cl | O | N | 1 | *trans* | 458 ± 45 | >30 | 0.58 |
| **13** | Ph | Me | F | O | N | 1 | *cis* | 64 ± 26 | >30 | 0.45 |
| **14** | Ph | Me | F | O | N | 1 | *trans* | 963[e] | >30 | NT |
| **15** | Ph | *c*-Pr | F | O | N | 1 | *cis* | 105 ± 93 | >30 | 0.09 |
| **16** | Ph | *c*-Pr | F | O | N | 1 | *trans* | 1820[e] | >30 | NT |
| **17** | Ph | H | Cl | NH | CH | 1 | *cis* | 9.0 ± 1.2 | >30 | 6.7 |
| **18** | Ph | H | Cl | NH | CH | 1 | *trans* | 164 ± 15 | >30 | 9.8 |
| **19** | Me | H | F | O | N | 1 | *cis* | 78 ± 21 | >30 | 0.78 |
| **20** | Me | H | F | O | N | 1 | *trans* | 383 ± 114 | >30 | 3.0 |
| **21** | H | H | Cl | NH | CH | 1 | *cis* | 8.0 ± 2.0 | 4.9 | 20 |
| **22** | H | H | Cl | NH | CH | 1 | *trans* | 14 ± 7 | NT | 9.0 |
| **23** | H | H | Cl | NH | N | 0 | *cis* | 16[e] | 2.6 | 2.3 |
| **24** | H | H | Cl | NH | CH | 0 | *cis* | 6.0 ± 1.3 | 1.9 | 20 |
| **25** | H | H | Cl | NH | CH | 0 | *trans* | 398 ± 194 | >30 | NT |

[a]All values are the mean of at least two separate assay determinations. [b]$hNa_v1.7$ data were collected using an Ion Works Barracuda® automated electrophysiology platform using a protocol where cells were held at -60 mV. [c]$hNa_v1.5$ data were collected on the same platform using a protocol where cells were held at -50 mV. [d]For assay conditions, see Ref. 21. [e]Tested only once. [f]Relative stereochemistry between $NHR^2$ and $(CH_2)_nY$ moiety. NT: not tested.

The discovery of cyclohexylamine **24** via phenyl truncation of **17** prompted us to explore the 4-des-aryl piperidine benzenesulfonamides (Figure 3). Thus, we prepared 4-monosubstituted piperidine **26** ($IC_{50}$ = 42 nM), which was 2-fold more potent than the 4-aryl-substituted ether-linked counterpart **6** ($IC_{50}$ = 78 nM). Again, compound **26** was 200-fold less potent than **6** in CYP3A4 inhibition as the result of combining the amine linkage with a thiazole moiety. Both the 3- and the 2-substituted piperidines **27** and **29** showed $IC_{50}$ values in the 10 nM range, 4-fold more potent than the 4-substituted counterpart **26** ($IC_{50}$ = 42 nM). The 3-substituted piperidine **27** ($IC_{50}$ = 12 nM) and pyrrolidine **31** ($IC_{50}$ = 14 nM) were 2-fold more potent than azetidine **32** ($IC_{50}$ = 29 nM). Most of the analogs in Table 2 were prepared as racemates and evaluation of the two pairs of enantiomers **33** and **34** or **37** and **38** revealed no stereochemical preference. With respect to the linkage between the cyclic amine and benzenesulfonamide core, ethylene as in **27** and **32** was preferred over methylene as in **33**, **34** and **40**. Interestingly, the direct-linked sterically hindered piperidine **41** ($IC_{50}$ = 27 nM) was 2-fold more active than the ethylene linked homolog **30** ($IC_{50}$ = 70 nM). The introduction of an additional oxygen to form a morpholine, as in **35** ($IC_{50}$ = 69 nM), was tolerated. Methylation, hydroxylation and acetylation of the piperidine nitrogen as in **36**, **37**, **38** and **39** brought about a significant decrease in potency. Finally, we examined the impact of attaching a ring nitrogen directly to the linker, an effort that led to pyrrolidine **42** with an $IC_{50}$ value of 11 nM.

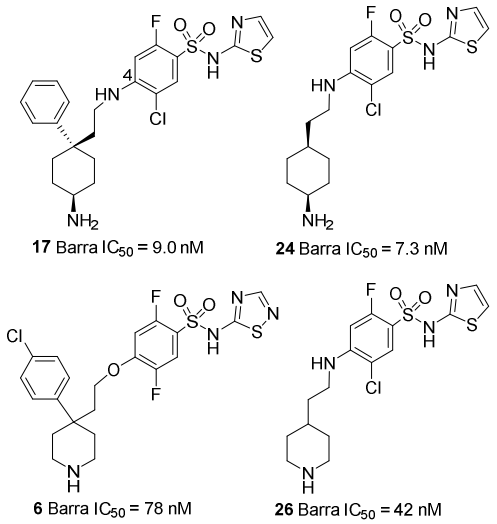
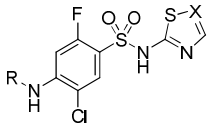
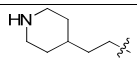
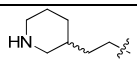
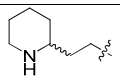
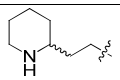
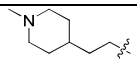
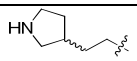
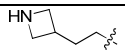
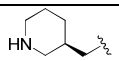
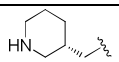
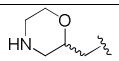
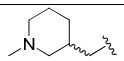
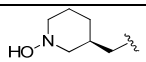
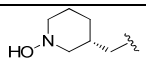
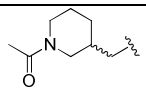
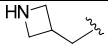
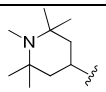
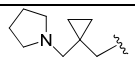



**Figure 3.** Structures of **h**$Na_v1.7$ inhibitors

**Table 2**. $hNa_v1.7$, $hNa_v1.5$ CYP3A4 inhibition $IC_{50}$ data of **26-42**[a]



| Compd. | R | X | $hNa_v1.7$ $IC_{50}$ (nM)[b] | $hNa_v1.5$ $IC_{50}$ (μM)[c] | CYP3A4 $IC_{50}$ (μM)[d] |
|---|---|---|---|---|---|
| **26** |  | CH | 42 ± 6 | >30 | 20 |
| **27** |  | CH | 12 ± 5 | NT | 6.7 |
| **28** |  | N | 15 ± 6 | NT | 5.9 |
| **29** |  | CH | 8.4 ± 0.5 | NT | 20 |
| **30** |  | CH | 70 ± 17 | >30 | 20 |
| **31** |  | CH | 14 ± 3 | >30 | 20 |

| | | | | | |
|---|---|---|---|---|---|
| **32** |  | CH | 29 ± 2 | >30 | 20 |
| **33** |  | CH | 49 ± 16 | >30 | 20 |
| **34** |  | CH | 57[e] | NT | 20 |
| **35** |  | CH | 69 ± 2 | >30 | 20 |
| **36** |  | CH | 264 ± 74 | >30 | NT |
| **37** |  | CH | 186 ± 6 | NT | 7.9 |
| **38** |  | CH | 207 ± 148 | NT | 17 |
| **39** |  | CH | 324 ± 177 | >30 | NT |
| **40** |  | CH | 339 ± 55 | >30 | 20 |
| **41** |  | CH | 27 ± 6 | >30 | 20 |
| **42** |  | CH | 11 ± 6 | 5.1 | 20 |

[a,b,c,d,e] see footnotes in Table 1.

As a result of its potent cellular activity in the Barracuda assay, compound **24** was tested in a manual patch clamp electrophysiology (EP) assay. The results showed that **24** potently inhibited recombinant $Na_v1.7$ channel activity across species with EP $IC_{50}$ values of 4.0, 7.5 and 12.3 nM for the human, mouse and rat $Na_v1.7$ isoforms, respectively, at −70 mV holding potential (partially inactivated state), which is thought to be representative of pain states.[12] However, when the holding potential was set at −120 mV (resting closed state), the $IC_{50}$ value at human $Na_v1.7$ was shifted rightwards by >2,000-fold to 9.4 μM (Figure 4) and, as such, **24** was determined to be a state-dependent inhibitor of $Na_v1.7$ function. Compound **24** was also tested for inhibition of sodium channel currents recorded from cell bodies of individual sensory neurons dissociated from rat dorsal root ganglia (DRG). In this assay, **24** potently inhibited fast-inactivating, tetrodotoxin-sensitive (TTX-S) sodium currents measured in adult mouse DRG

sensory neurons with an $IC_{50}$ of 6.0 nM. Finally, using the Maestro microelectrode array (MEA) platform, **24** was shown to potently block spontaneous firing of rat embryonic DRG cells ($IC_{50}$ = 1.2 nM).

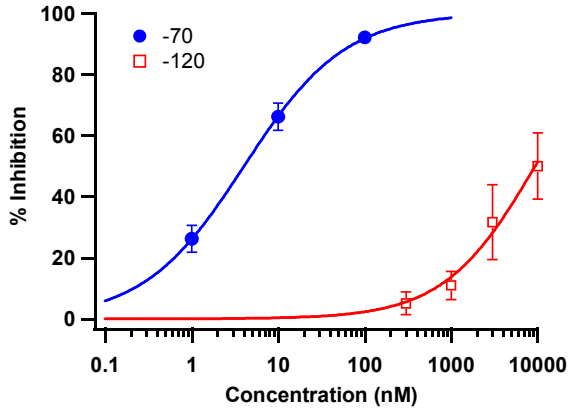



**Figure 4.** Compound **24** shows state-dependent inhibition of $hNa_v1.7$ at -70 mV (blue, $IC_{50}$ = 4.0 nM) and -120 mV (red, $IC_{50}$ = 9.4 μM).

Compound **24** was then examined in the formalin test which measures spontaneous, nociceptive-like paw flinching/licking responses after peripheral nociceptor activation. This model was chosen for in vivo efficacy screening since formalin-induced nociceptive behaviors are abolished in global $Na_v1.7$ knockout mice.[6] Male CD1 mice were injected subcutaneously in the dorsal surface of the right hind paw with 20 μL of 5% formalin solution and nociceptive behavior recorded for 45 min using an automated system (Automated Nociception Analyzer, UCSD, La Jolla, CA, USA). Formalin injection elicits a biphasic behavioral response; phase I occurs during the first 5 min and results from direct nociceptor activation whereas phase II occurs 15-45 min after injection and is thought to involve spinal sensitization. Treatment with compound **2** (60 mpk, PO) 60 minutes prior to formalin injection had no effect on phase I responses (data not shown) but abolished phase II nociceptive behaviors (Figure 5). In contrast, no significant effect on either phase I or phase II responses was seen in mice treated with **24** at 100 mpk PO (Figure 5). Plasma exposures, measured in a subset (n = 3/group) of experiment subjects on completion of testing (i.e. ~ 110 minutes post dose), were similar for both compounds (mean ± SD total drug concentration: compound **2** = 1.2 ± 0.37 μM; compound **24** = 2.8 ± 0.15 μM).

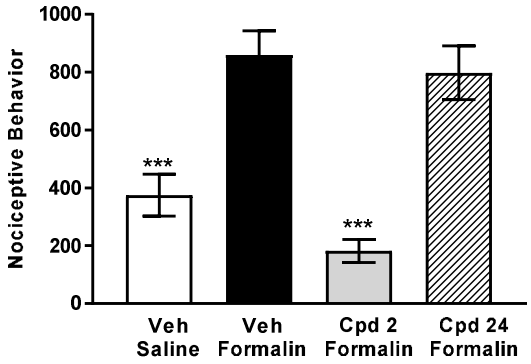



**Figure 5.** Effect oral administration of **2** (60 mpk) or **24** (100 mpk) on phase II formalin-induced nociceptive behaviors. Results are presented as the mean ± SEM response (n=12-14/group) and were analyzed by ANOVA followed by Dunnett's post-hoc tests; ***P<0.001 compared to vehicle/formalin group.

To further examine tissue drug concentrations we treated male CD1 mice with compound **2** (60 mpk PO) or **24** (100 mpk PO) and collected plasma and DRG samples 60 minutes later. The $Na_v1.7$ channel is highly expressed in the DRG and inhibition of channel function in this region may be a primary site of action for analgesic effect. Consistent with our previous results, the total plasma drug concentrations were similar for both agents (mean ± SD: compound **2** = 5.3 ± 1.8 μM; compound **24** = 4.0 ± 0.9 μM). Determination of mouse plasma protein binding, however, showed that the unbound fraction for **24** was 3-fold lower than **2** (8% versus 24%; Table 3) resulting in a lower average free plasma drug concentration (0.32 μM versus 1.27 μM respectively; Table 3). Compound **24** also showed ~ 5 fold lower total drug concentration in DRG (Table 3). While we did not measure protein binding specifically in mouse DRG tissue; if the differences observed in plasma protein binding extend to DRG then free DRG concentrations of **24** may be further reduced compared to compound **2**. Compound **24** was also 2-fold weaker at inhibiting recombinant mouse $Na_v1.7$ currents determined by manual EP (Table 3). Using these results we calculated the free DRG concentration/mouse $Na_v1.7$ $IC_{50}$ ratio (using plasma protein binding as an estimate of tissue binding) and showed that the ratio was >20-fold lower for **24** (ratio = 0.8 versus 21 for **24** and **2**

respectively). Taken together, we concluded that free DRG concentrations of **24** were insufficient to achieve the level of $Na_v1.7$ inhibition required for efficacy in the formalin test.

We speculated that the poor DRG exposure of **24** resulted from its poor membrane permeability as shown by the PAMPA data ($P_{app}$: 0 at both pH 5.5 and 7.4 compared to 8.0 and 142 nm/sec for **2**). To test this hypothesis, we evaluated two analogs **41** and **42** with improved membrane permeability based on PAMPA data (Table 3) in the formalin model. In this study mice were treated with 30 mpk PO of **41** or **42,** 30 minutes prior to formalin injection, and nociceptive behaviors monitored for 45 min as previously described. On completion of testing (i.e. ~ 75 minutes post-treatment) plasma and DRG samples were collected from a subset of animals to determine exposure. Both compounds achieved DRG concentrations of 1.5 μM when dosed at 30 mpk orally in mice, a 19-fold improvement compared to 100 mpk **24** (Table 3). These results are consistent with our hypothesis that improving membrane permeability can enhance DRG exposure. Intriguingly, compound **42** fully reversed formalin-induced phase II nociceptive behaviors at the 30 mpk dose whereas **41** was not effective (Figure 6). The explanation for these discrepant results is unclear given that $Na_v1.7$ potency, mouse plasma protein binding and exposures in plasma and DRG were similar for both compounds (Table 3). Nevertheless similar discrepancies between PK and efficacy have also been reported with aminotriazine $Na_v1.7$ inhibitors in the formalin test.[22] A direct measure of target occupancy may be helpful in understanding the inactivity of **41**.

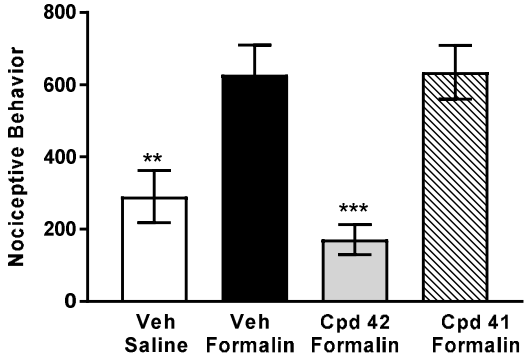


**Figure 6**. Effect of oral administration of **41** (30 mpk) or **42** (30 mpk) on phase II formalin-induced nociceptive behaviors. Results are presented as the mean ± SEM response (n=10-14/group) and were analyzed by ANOVA followed by Dunnett's post-hoc tests; **P<0.01, ***P<0.001.

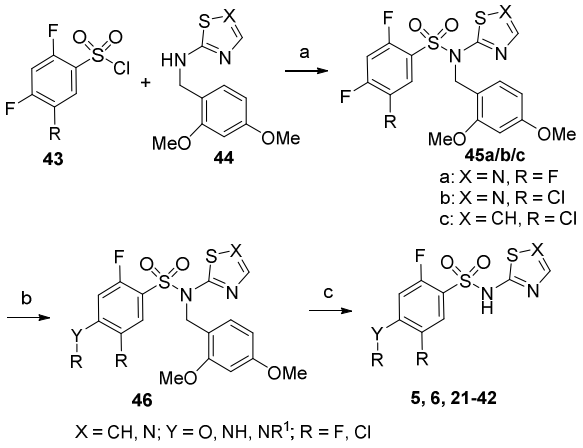
**Table 3**. Miscellaneous Data for **2, 24, 41 and 42**

| Compd. | $hNa_v1.7$ EP $IC_{50}$ | $mNa_v1.7$ EP $IC_{50}$ | $P_{app}$ *p*H 5.5/7.4[c] | $F_u$[a] | Dose PO | Plasma Conc.[b] | Free Plasma Conc. | DRG Conc.[b] | Active in Formalin Test |
|---|---|---|---|---|---|---|---|---|---|
| **2** | 2.4 nM | 3.9 nM | 8.0/142 | 24% | 60 mpk | 5.3 ± 1.8 μM | 1.27 ± 0.43 | 0.34 ± 0.19 μM | Yes |
| **24** | 4.0 nM | 7.5 nM | 0/0 | 8% | 100 mpk | 4.0 ± 0.9 μM | 0.32 ± 0.07 | 72 ± 33 nM | No |
| **41** | 17 nM | 30 nM | 23/241 | 23% | 30 mpk | 1.1 ± 1.0 μM | 0.28 ± 0.23 | 1.5 ± 0.4 μM | No |
| **42** | 12 nM | 51 nM | 47/949 | 20% | 30 mpk | 1.2 ± 0.7 μM | 0.24 ± 0.14 | 1.5 ± 0.6 μM | Yes |

[a]Unbound fraction in mouse plasma. [b]Compound dosed PO to male mice in 0.5% Methocel/0.1% Tween/99.4% water (10 mL/kg). Results are presented as the mean (SD), N = 3–9/group. [C]nm/sec.

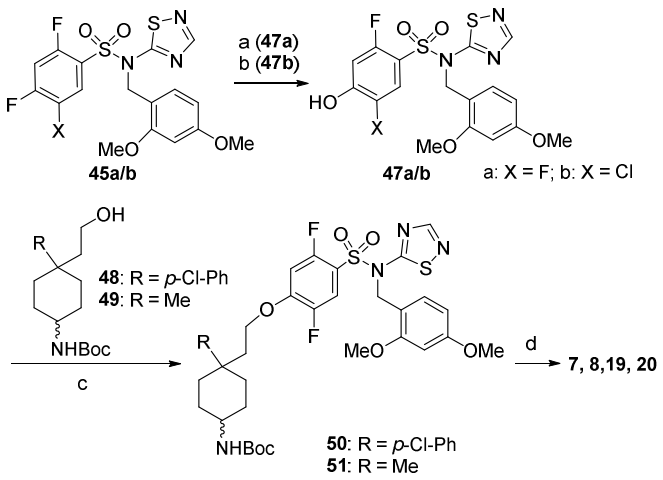
## CHEMISTRY

Scheme 1 describes a general synthesis of benzenesulfonamides **5**, **6** and **21**−**42** from **44a/b/c**, which were readily available through reductive amination of 2,4-dimethoxybenzaldehyde with 2-aminothiazole or 2-aminothiadiazole. Treatment of **44** with benzenesulfonyl chloride **43** under basic conditions afforded the benzenesulfonamides **45a/b/c**.[15,19] A nucleophilic aromatic substitution reaction of an amine or alcohol with **45a/b** using $K_2CO_3$ as the base gave **46**, which underwent deprotection with TFA to afford final analogs.



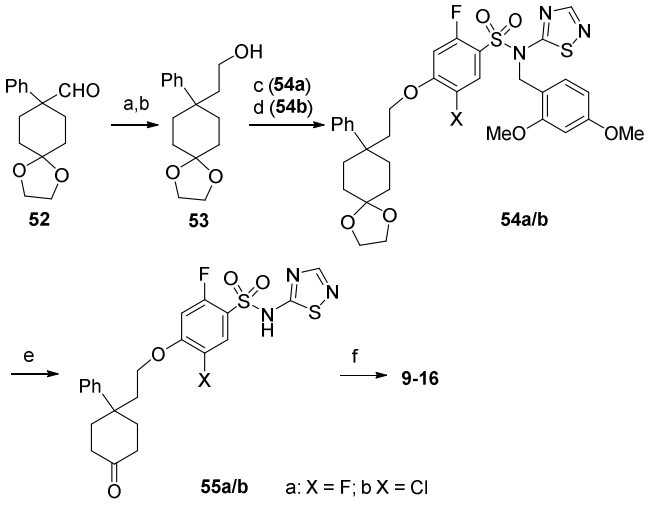

**Scheme 1**. Reagents and conditions: (a) LHMDS, THF, -78 °C, 80% (**45a**), 91% (**45b**), 55% (**45c**); (b) RYH, $K_2CO_3$, DMF, rt, 40-85%; (c) TFA, DCM, rt, 50-95%.

Scheme 2 describes the synthesis of analogs **7**, **8**, **19** and **20**. Treatment of the electron deficient 2,4,5-trifluorobenzenesulfonamides **45a/b** with 2-(methylsulfonyl)ethanol in the presence of excessive potassium *tert*-butoxide in DMSO or $Cs_2CO_3$ in DMF, respectively, brought about a regioselective nucleophilic aromatic substitution followed by spontaneous elimination of vinyl sulfoxide to give 4-hydroxy-2,5-difluorobenzenesulfonamide **47a/b** on a multiple gram scale in good yields.[23] Mitsunobu reaction of alcohols **48** and **49** with phenol **47a** gave **50** and **51**, respectively, and subsequent deprotection with trifluoroacetic acid provided compounds **7**, **8**, **19** and **20**.



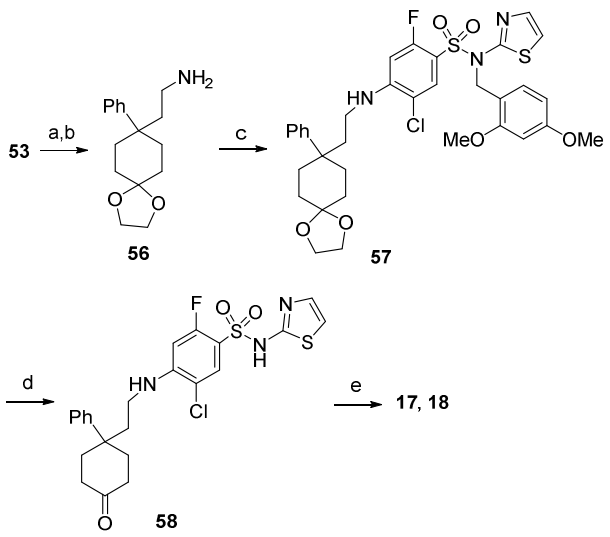

**Scheme 2**. Reagents and conditions: (a) 2-(methylsulfonyl)ethanol, *t*-BuOK, DMSO, rt, 1 h, 62%; (b) 2-(methylsulfonyl)ethanol, $Cs_2CO_3$, DMF, rt, 1 h, 70%; (c) **47a**, DEAD, $Ph_3P$, THF, rt, 85% (**50**), 75% (**51**); (d) TFA, 7-51%.

Scheme 3 describes the synthesis of benzenesulfonamides **9−16**. Aldehyde **52** underwent Wittig reaction with methyl triphenylphosphonium bromide and *n*-BuLi, and the resulting vinyl compound was converted to the primary alcohol **53** via hydroboration. Treatment of **53** with **45a** and $K_2CO_3$ gave **54a**, and Mitsunobu reaction of **53** with phenol **47b** (Scheme 2) furnished **54b**. Compounds **54a/b** underwent global deprotection with TFA to afford ketones **55a/b**, and reductive amination with appropriate amines generated compounds **9-16**.



**Scheme 3**. Reagents and conditions: (a) triphenylphosphonium bromide and *n*-BuLi, THF, -78 °C to 0 °C, 54%; (b) $BH_3$·THF, THF, 0 °C; NaOH, $H_2O_2$, 65%; (c) LHMDS, **45a/b**, $K_2CO_3$, DMF, rt, 73%; (d) DEAD, $Ph_3P$, THF, rt, 30%; (e) 1N HCl, acetone, reflux, 73% (**55a**), 100% (**55b**); (f) $NH_4OAc$ or amine, $NaBH_3CN$, methanol, 6-37%.

Scheme 4 describes the synthesis of analogs **17** and **18**. Alcohol **53** was converted to amine **56** in two steps: Mitsunobu reaction with phthalimide and hydrazinolysis of the resulting phthalimide moiety. The transformation of amine **56** was to **17** and **18** was analogous to that of **53** to **9**-**16** (Scheme 3).




**Scheme 4**. Reagents and conditions: (a) phthalimide, $Ph_3P$, DEAD, THF, rt; (b) hydrazine, THF/methanol; (c) **45c**, $K_2CO_3$, DMF, rt, 12% for 3 steps; (d) HCl, acetone, refluxt, 100%; (e) $NH_4OAc$, $NaBH_3CN$, rt, 6% (**17**) and 16% (**18**).

## CONCLUSIONS

We recognized certain features in **4** and used them to develop new benzenesulfonamides, an approach that culminated in the discovery of a novel series of cyclohexylamine- and piperidine-based benzenesulfonamides as potent and selective $Na_v1.7$ inhibitors. One of the early analogs, compound **24**, was ineffective in the mouse formalin test which was attributed to insufficient DRG exposure. We then identified two analogs, compounds **41** and **42**, with much improved DRG exposure; however, only compound **42** demonstrated efficacy in the formalin model. While the reason for this disconnect is unclear, a direct measure of occupancy at the VSD4 binding site on $Na_v1.7$ would improve our understanding of the efficacy/exposure relationship and potentially explain the different results for these compounds.

## EXPERIMENTAL SECTION

**Patch clamp electrophysiology.** $Na_v1.7$ currents were recorded using whole-cell patch clamp of HEK293 cells stably expressing recombinant human or mouse $Na_v1.7$. Glass microelectrodes filled with internal solution containing (in mM) 50 CsCl, 90 CsF, 10 NaF, 2 $MgCl_2$, 10 EGTA, 10 HEPES, pH 7.2 with CsOH had resistances of 1-4 MOhms. The external solution was (in mM): 150 NaCl, 4 KCl, 1 $MgCl_2$, 1.8 $CaCl_2$, 10 HEPES, 10 glucose, pH 7.4 with NaOH. Series resistance was kept below 10 MOhms and electronically compensated at least 50%. Currents were acquired at 50 kHz via an EPC-10 amplifier with Patchmaster software (HEKA Instruments Inc., Bellmore, NY). Leakage subtraction was performed with the P/N method. Solution exchange was performed with a 16-well Dynaflow Resolve glass chip (Cellectricon, Sweden). The holding potential was -70 mV unless otherwise indicated. Following a 100 msec prepulse to -130 mV, $Na_v1.7$ current was elicited by a 10 msec step to +10 mV. Peak inward current was measured with PatchMaster software and percent inhibition calculated. $IC_{50}$ values were obtained by fits of the Hill equation to the average percent inhibition data. Data are presented as mean ± S.E.M.

**Automated Electrophysiology Methods: Ion Works Barracuda population patch clamp (PPC).** Population patch clamp (PPC) measurements from HEK 293 cells expressing $Na_v1.7$ and $Na_v1.5$ channels were performed using an IonWorks Barracuda instrument (Molecular Devices Corporation, Union City, CA) using a proprietary PPC PatchPlate™ substrate (Molecular Devices Corporation) with 64 patch clamp apertures per well. The ability to average $Na_v1.x$ currents from 64 recordings from each well greatly improves data consistency and recording success rates in the measurement of $Na_v1.x$ mediated ionic currents. Calculated leak current was digitally subtracted from the total cell $Na_v1.x$ current for each sample data point acquired.

$Na_v1.7$ currents were elicited by a voltage clamp protocol designed to strongly bias the $Na_v1.7$ channels toward their inactivated state as follows. From a holding potential of –60 mV cells were briefly hyperpolarized to -100 mV for 1.25 sec, then stepped to -20 mV for 20 sec to inactivate the channels. This was followed by a relatively brief hyperpolarization to -100 mV for 300 ms, then a 20 msec test pulse to -20 mV to elicit the $Na_v1.7$ current used to measure the pharmacology of all test compounds. Compounds were incubated for 600 sec between the pre- and post-compound reads. The external recording solution used was (in mM) 137 NaCl, 4 KCl, 1 $MgCl_2$, 1.8 $CaCl_2$, 10 Hepes, 10 glucose, pH to 7.4 with NaOH, and the internal solution used was (in mM) 100 K-gluconate, 40KCl, 3.2 $MgCl_2$, 5 EGTA, 10 HEPES pH to 7.2 with KOH. The same solutions were used to record $Na_v1.5$ currents, with the following voltage clamp protocol. $Na_v1.5$ currents were elicited by a voltage clamp protocol designed to bias the $Na_v1.5$ channels to their inactivated state as follows. From holding potential of –40 mV cells were briefly hyperpolarized to -100 mV for 300 ms, then stepped to -10 mV for 20 sec to inactivate the channels. This was followed by a relatively brief hyperpolarization to -100 mV for 30 ms, then a 20 msec test pulse to -10 mV to elicit the $Na_v1.5$ current used to measure the pharmacology of all test compounds.

HEK 293 cells expressing $Na_v1.7$ and $Na_v1.5$ channels, were used (Essen Biosciences, Ann Arbor, Michigan). Cells were cultured in T-175 flasks and passaged every 2 to 3 days at 1:3 to 1:6 seeding density dilutions. Cells were grown to 70% to 90% confluence in a flask and removed from the incubator (37° C, 5% CO2) 1 to 3 days after plating. Growth medium was aspirated from the culture flasks. Cells were gently rinsed with 10 mL of Phosphate buffered saline (PBS) to remove residual media. Next a total of 2 mL TrypLE (Gibco) solution was added, and the flasks containing cells sat for 3 min at rt, after which, the cells became visibly rounded and were easily dislodged from the bottom of the flask with a few brief taps on a solid surface. A total of 8 mL of media was added to the flask to inactivate the TrypLE, and the mixture was centrifuged at 910 rpm for 4 min. The cell supernatant was decanted, and the cell pellets were resuspended in 5-6 mL of external solution followed by gentle trituration using a 10 mL pipette, and transferred to a 15 mL conical tube and immediately brought to the IW Barracuda instrument. The cell suspension had a final concentration of ~2 to 3 million cells per mL; this corresponds to 10,000 cells added per well.

Peak membrane currents were analyzed with IW Barracuda software and exported to Excel for further analysis. Concentration response curve fitting was performed with BMS in-house software. $IC_{50}$ values were obtained by fits of the Hill equation to the average percent inhibition data plotted versus compound concentration. Concentration-response curves for all test compounds were fitted to a 4-parameter equation: % of control = 100 (1 + ([drug]/$IC_{50}$)p)–1, where $IC_{50}$ is the concentration of drug required to inhibit current by 50% and p is the Hill slope.

**Formalin test.** Persistent pain was induced with an injection of formalin in the dorsum of one hind paw as previously described.[24] Formalin-induced flinching was quantified with an automated system (Automated Nociception Analyzer, UCSD, La Jolla, CA, USA). A metal band was glued on the right hind paw, the mouse was then acclimated for 60 min in an individual Plexiglas test chamber. Each mouse was dosed (10 mL/kg PO) orally with the compound or vehicle, 30 min before formalin injec-

tion. The right hind paw was injected with 20 μL of 5% formalin (SC of formalin w/v in saline, Sigma), and the animal was immediately placed back into the chamber. Each time the band breaks the electro-magnetic field located under the mouse a signal was generated and nociceptive behavior, paw flinches and licking, were recorded with the automated system for 45 minutes.

**Chemistry**. Proton magnetic resonance ($^1$H NMR) spectra were recorded on either a Bruker Avance 400 or a JEOL Eclipse 500 spectrometer and are reported in ppm relative to the reference solvent of the sample in which they were run. HPLC and LC−MS analyses were conducted using a Shimadzu SCL-10A liquid chromatograph and a SPD UV−vis detector at 220 nm with the MS detection performed with either a Micromass Platform LC spectrometer or a Waters Micromass ZQ spectrometer. All flash column chromatography was performed on EM Science silica gel 60 (particle size of 40−60 μm). All reagents were purchased from commercial sources and used without further purification unless otherwise noted. All reactions were performed under an inert atmosphere. HPLC analyses were performed using the following conditions. All final compounds had an HPLC purity of ≥ 95% unless specifically mentioned.

**HPLC Methods**. Analytical HPLC analyses were carried out following methods A and B, and preparatory reverse-phase scale purifications were performed using methods C and D.

**Method A**. A linear gradient using 5% acetonitrile, 95% water, and 0.05% TFA (solvent A) and 95% acetonitrile, 5% water, and 0.05% TFA (solvent B) (t = 0 min, 10% B; t = 15 min, 100% B) was employed on a SunFire C18 3.5 μm 3.5 mm × 150 mm column. Flow rate was 0.5 mL/min, and UV detection was set to 220 nm. The LC column was maintained at ambient temperature.

**Method B**. A linear gradient using 5% acetonitrile, 95% water, and 0.05% TFA (solvent A) and 95% acetonitrile, 5% water, and 0.05% TFA (solvent B) (t = 0 min, 10% B; t = 15 min, 100% B (20

min)) was employed on a XBridge Ph 3.5 μm 3.0 mm × 150 mm column. Flow rate was 0.5 mL/min, and UV detection was set to 220 nm. The LC column was maintained at ambient temperature.

**Method C**. Column: Waters XBridge C18, 19 x 200 mm, 5 μm particles; Guard Column: Waters XBridge C18, 19 x 10 mm, 5 μm particles; Mobile Phase A: water with 20 mM ammonium acetate; Mobile Phase B: 95:5 methanol:water with 20 mM ammonium acetate; Gradient: 25-65% B over 40 minutes, then a 5-minute hold at 100% B; Flow: 20 mL/min.

**4-((4-(4-Chlorophenyl)piperidin-4-yl)methoxy)-2,5-difluoro-*N*-(1,2,4-thiadiazol-5-yl)benzenesulfonamide (5)**. To a solution of *tert*-butyl 4-(4-chlorophenyl)-4-(hydroxymethyl)piperidine-1-carboxylate[25] (35 mg, 0.11 mmol) in THF (0.54 mL) at rt was added LHMDS in THF (0.12 mL, 0.12 mmol), and the reaction mixture was stirred at rt for 30 min. A solution of **45a** (48 mg, 0.11 mmol) in THF (0.54 mL) was added and the reaction mixture was stirred at rt for 1 h. Water was added and the aqueous layer was extracted with EtOAc (x3). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to give the crude product. This crude product was dissolved in DCM (0.54 mL), TFA (0.49 mL, 6.4 mmol) was added, and the reaction mixture was stirred at rt for 1 h. The solvents were removed, and the product was purified via preparative HPLC (Method C) to give **5** (15 mg, 56% over 2 steps). $^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.95 (s, 1H), 7.87 (s, 1H), 7.55 - 7.40 (m, 5H), 7.18 - 7.08 (m, 1H), 4.10 (s, 2H), 3.23 (br d, *J* = 12.8 Hz, 2H), 2.81 (br t, *J* = 10.5 Hz, 2H), 2.33 (br d, *J* = 15.4 Hz, 2H), 2.13 (br t, *J* = 11.0 Hz, 2H). LC/MS *m/z*: $(M + H)^+$ calcd for $C_{20}H_{20}ClF_2N_4O_3S_2$, 501.06; found 501.2.

**4-(2-(4-(4-Chlorophenyl)piperidin-4-yl)ethoxy)-2,5-difluoro-*N*-(1,2,4-thiadiazol-5-yl)benzenesulfonamide (6)**. Prepared from *tert*-butyl 4-(4-chlorophenyl)-4-(2-hydroxyethyl)piperidine-1-carboxylate[26] in 72% yield using the procedures described for **5**. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.88 (s, 1H), 7.48 - 7.34 (m, 5H), 6.97 (dd, *J* = 11.0, 7.0 Hz, 1H), 3.79 (t, *J* = 6.2 Hz, 2H), 3.22 (br. s.,

2H), 2.90 - 2.77 (m, 2H), 2.25 (br. s., 2H), 2.15 - 1.97 (m, 4H). LC/MS *m/z*: $(M + H)^+$ calcd for $C_{21}H_{22}ClF_2N_4O_3S_2$, 515.08; found 515.2.

**4-(2-((1*R*,4*R*)-4-Amino-1-(4-chlorophenyl)cyclohexyl)ethoxy)-2,5-difluoro-*N*-(1,2,4-thiadiazol-5-yl)benzenesulfonamide (7) and 4-(2-((1*S*,4*S*)-4-amino-1-(4-chlorophenyl)cyclohexyl)ethoxy)-2,5-difluoro-*N*-(1,2,4-thiadiazol-5-yl)benzenesulfonamide (8)**. To a solution of **50** (45 mg, 0.06 mmol) in DCM (0.5 mL) was added TFA (0.09 mL, 1.2 mmol). The mixture was stirred at rt for 3 h and then concentrated. The residue was purified by preparative HPLC (Method C) to give **8** (2 mg, 7%) and **7** (16 mg, 51%). Compound **8**: $^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.87 (s, 1H), 7.47 - 7.37 (m, 5H), 6.93 (dd, *J* = 11.4, 6.6 Hz, 1H), 3.80 (t, *J* = 6.8 Hz, 2H), 2.85 - 2.72 (m, 1H), 2.45 - 2.30 (m, 2H), 1.87 (2H, m), 1.70 - 1.46 (m, 5H). LC/MS *m/z*: $(M + H)^+$ calcd for $C_{22}H_{24}ClF_2N_4O_3S_2$, 529.09; found 529.1. Compound **7**: $^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.96 (s, 1H), 7.87 (s, 1H), 7.50 - 7.31 (m, 5H), 6.99 (dd, *J* = 11.0, 7.0 Hz, 1H), 3.75 (t, *J* = 6.6 Hz, 2H), 3.01 (br. s., 1H), 2.22 - 2.07 (m, 4H), 1.84 - 1.53 (m, 6H). LC/MS *m/z*: $(M + H)^+$ calcd for $C_{22}H_{24}ClF_2N_4O_3S_2$, 529.09; found 529.1.

**4-(2-((1*R*,4*R*)-4-Amino-1-phenylcyclohexyl)ethoxy)-2,5-difluoro-*N*-(1,2,4-thiadiazol-5-yl)benzenesulfonamide (9) and 4-(2-((1*S*,4*S*)-4-amino-1-phenylcyclohexyl)ethoxy)-2,5-difluoro-*N*-(1,2,4-thiadiazol-5-yl)benzenesulfonamide (10)**. A mixture of **55a** (100 mg, 0.20 mmol), $NH_4OAc$ (156 mg, 2.0 mmol), $NaBH_3CN$ (19 mg, 0.30 mmol) and 4Å MS (200 mg) in methanol (1.4 mL) was stirred at rt for 2 h. The crude material was purified via preparative HPLC (Method C) to give **9** (6 mg, 6%) and **10** (20 mg, 20%) and Compound **9**: $^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.88 (s, 1H), 7.47 - 7.37 (m, 3H), 7.34 (t, *J* = 7.5 Hz, 2H), 7.24 - 7.18 (m, 1H), 6.94 (dd, *J* = 10.6, 6.6 Hz, 1H), 3.75 (t, *J* = 6.6 Hz, 2H), 3.06 (br. s., 1H), 2.17 (br. s., 4H), 1.86 - 1.57 (m, 6H). LC/MS *m/z*: $(M + H)^+$ calcd for $C_{22}H_{25}F_2N_4O_3S_2$, 495.13; found 495.2. Compound **10**: $^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.96 (s, 1H), 7.87 (s, 1H), 7.49 - 7.29 (m, 5H), 7.22 (t, *J* = 7.0 Hz, 1H), 6.88 (dd, *J* = 11.2, 6.8 Hz, 1H), 3.79 (t, *J* =

6.8 Hz, 2H), 3.36 (br. s., 2H), 3.11 - 3.01 (m, 1H), 2.57 - 2.52 (m, 2H), 1.88 (t, *J* = 6.4 Hz, 2H), 1.76 (d, *J* = 11.7 Hz, 2H), 1.58 (t, *J* = 13.4 Hz, 2H), 1.30 - 1.14 (m, 2H). LC/MS *m/z*: $(M + H)^+$ calcd for $C_{22}H_{25}F_2N_4O_3S_2$, 495.13; found 495.2.

**4-(2-((1*R*,4*R*)-4-Amino-1-phenylcyclohexyl)ethoxy)-5-chloro-2-fluoro-*N*-(1,2,4-thiadiazol-5-yl)benzenesulfonamide (11) and 4-(2-((1*S*,4*S*)-4-Amino-1-phenylcyclohexyl)ethoxy)-5-chloro-2-fluoro-*N*-(1,2,4-thiadiazol-5-yl)benzenesulfonamide (12)**. A mixture of **55b** (60 mg, 0.12 mmol), $NH_4OAc$ (91 mg, 1.176 mmol), $NaBH_3CN$ (11 mg, 0.18 mmol) and 4Å MS (100 mg) in methanol (0.78 mL) was stirred at rt for 12 h. This reaction mixture was diluted with methanol and then filtered, and the filtrate was purified by preparative HPLC (Method C) to give **11** (4 mg, 6%) and **12** (12 mg, 20%). Compound **11**: $^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.88 (s, 1H), 7.66 (s, 1H), 7.64 (s, 1H), 7.43 - 7.38 (m, 2H), 7.34 (t, *J* = 7.7 Hz, 2H), 7.25 - 7.19 (m, 1H), 6.92 (d, *J* = 11.0 Hz, 1H), 3.52 - 3.38 (m, 2H), 3.04 (br. s., 1H), 2.29 - 2.14 (m, 4H), 1.85 - 1.50 (m, 6H).LC/MS *m/z*: $(M + H)^+$ calcd for $C_{22}H_{25}ClFN_4O_3S_2$, 511.10; found 511.2. MS: 511.2 $(M + H)^+$. Compound **12**: $^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.88 (s, 1H), 7.64 (d, *J* = 7.3 Hz, 1H), 7.47 - 7.34 (m, 5H), 7.22 (s, 1H), 6.86 (d, *J* = 11.0 Hz, 1H), 3.79 (br t, *J* = 6.8 Hz, 2H), 3.05 (br s, 1H), 1.93 - 1.84 (m, 3H), 1.76 (br d, *J* = 9.9 Hz, 2H), 1.60 (br t, *J* = 12.7 Hz, 2H), 1.22 (br d, *J* = 12.8 Hz, 2H). LC/MS *m/z*: $(M + H)^+$ calcd for $C_{22}H_{25}ClFN_4O_3S_2$, 511.10; found 511.2.

**2,5-Difluoro-4-(2-((1*R*,4*R*)-4-(methylamino)-1-phenylcyclohexyl)ethoxy)-*N*-(1,2,4-thiadiazol-5-yl)benzenesulfonamide (13) and 2,5-Difluoro-4-(2-((1*S*,4*S*)-4-(methylamino)-1-phenylcyclohexyl)ethoxy)-*N*-(1,2,4-thiadiazol-5-yl)benzenesulfonamide (14)**. A solution of methylamine (122 µL, 0.12 mmol) (1M in THF) and **55a** (30 mg, 0.06 mmol) in methanol (304 µl) was heated at 65 °C for 1 h. After cooling, sodium borohydride (4.6 mg, 0.12 mmol) was added. The reaction mixture was stirred at rt for 2 h. The crude material was purified via preparative HPLC (Method C) to give **13** (7 mg, 24%) and **14** (9 mg, 28%). $^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.87 (s, 1H), 7.46 - 7.30 (m, 5H),

7.22 (t, *J* = 7.2 Hz, 1H), 6.94 (dd, *J* = 11.2, 6.8 Hz, 1H), 3.74 (t, *J* = 6.8 Hz, 2H), 3.55 (br. s., 3H), 2.93 (br. s., 1H), 2.25 - 2.08 (m, 4H), 1.90 - 1.82 (m, 2H), 1.74 - 1.55 (m, 4H). LC/MS *m/z*: $(M + H)^+$ calcd for $C_{23}H_{27}F_2N_4O_3S_2$, 509.15; found 509.1. Compound **14**: $^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.87 (s, 1H), 7.47 - 7.34 (m, 6H), 7.22 (br t, *J* = 7.2 Hz, 1H), 6.88 (dd, *J* = 11.0, 7.0 Hz, 1H), 3.79 (br t, *J* = 6.4 Hz, 2H), 3.06 - 2.94 (m, 1H), 2.56 (br d, *J* = 12.8 Hz, 2H), 1.93 - 1.85 (m, 4H), 1.55 (br t, *J* = 12.7 Hz, 2H), 1.30 - 1.09 (m, 3H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 185.8, 162.8, 159.4, 156.0, 154.0, 149.4 (t, *J* = 11.0 Hz, 1C), 147.5, 145.5, 143.2, 129.2, 127.4, 126.5, 123.8 (dd, *J* = 19.1, 3.8 Hz, 1C), 115.8 (br dd, *J* = 22.4, 2.4 Hz, 1C), 104.1, 103.9, 66.7, 57.6, 44.0, 40.9, 40.6, 36.3, 33.4, 31.3, 30.2, 25.2. LC/MS *m/z*: $(M + H)^+$ calcd for $C_{23}H_{27}F_2N_4O_3S_2$, 509.15; found 509.1.

**4-(2-((1*R*,4*R*)-4-(Cyclopropylamino)-1-phenylcyclohexyl)ethoxy)-2,5-difluoro-*N*-(1,2,4-thiadiazol-5-yl)benzenesulfonamide (15) and 4-(2-((1*S*,4*S*)-4-(cyclopropylamino)-1-phenylcyclohexyl)ethoxy)-2,5-difluoro-*N*-(1,2,4-thiadiazol-5-yl)benzenesulfonamide (16)**. A solution of cyclopropylamine (8 µL, 0.12 mmol) (1M in THF) and **55a** (30 mg, 0.06 mmol) in ethanol (0.3 mL) was heated at 65 °C for 2 h. After cooling, sodium borohydride (5 mg, 0.12 mmol) was added, and the reaction mixture was stirred at rt for 2 h. The crude material was purified via preparative HPLC (Method C) to give **15** (4 mg, 13%) and **16** (12 mg, 37%). $^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.96 (s, 1H), 7.87 (s, 1H), 7.46 - 7.30 (m, 5H), 7.22 (t, *J* = 7.5 Hz, 1H), 7.00 - 6.88 (m, 1H), 3.75 (br. s., 2H), 3.39 - 3.27 (m, 2H), 3.11 (br. s., 1H), 2.66 (br. s., 1H), 2.26 - 2.10 (m, 4H), 1.95 (br. s., 2H), 1.77 - 1.53 (m, 4H), 0.73 (d, *J* = 9.5 Hz, 4H). LC/MS *m/z*: $(M + H)^+$ calcd for $C_{25}H_{29}F_2N_4O_3S_2$, 535.16; found 535.0. Compound **16**: $^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.96 (s, 1H), 7.87 (s, 1H), 7.45 - 7.39 (m, 3H), 7.34 (br t, *J* = 7.3 Hz, 2H), 7.22 (br t, *J* = 7.5 Hz, 1H), 6.99 - 6.88 (m, 1H), 3.81 - 3.73 (m, 2H), 3.41 - 3.25 (m, 1H), 3.11 (br s, 1H), 2.66 (br s, 1H), 2.24 - 2.13 (m, 4H), 2.01 - 1.90 (m, 2H), 1.79 - 1.52 (m, 4H), 0.73 (br d, *J* = 9.5 Hz, 4H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 185.4, 172.1, 162.3, 158.9, 155.5, 153.6, 149.0 (t, *J* = 11.4 Hz, 1C), 147.0, 145.1, 145.0, 143.6, 128.6, 127.0, 125.8, 123.2 (dd, *J*= 19.1,

4.8 Hz, 1C), 115.3 (br dd, *J* = 21.9, 2.9 Hz, 1C), 103.6, 103.4, 66.3, 57.1, 40.4, 40.3, 35.8, 33.5, 30.8, 27.7, 27.6, 21.1, 5.0. LC/MS *m/z*: $(M + H)^+$ calcd for $C_{25}H_{29}F_2N_4O_3S_2$, 535.16; found 535.0.

**4-(2-((1*R*,4*R*)-4-Amino-1-phenylcyclohexyl)ethoxy)-5-chloro-2-fluoro-*N*-(thiazol-2-yl)benzenesulfonamide (17) and 4-(2-((1*S*,4*S*)-4-amino-1-phenylcyclohexyl)ethoxy)-5-chloro-2-fluoro-*N*-(thiazol-2-yl)benzenesulfonamide (18)**. A mixture of **58** (50 mg, 0.10 mmol), $NH_4OAc$ (76 mg, 0.98 mmol), $NaBH_3CN$ (12 mg, 0.20 mmol) and 4Å MS (100 mg) in methanol (0.7 mL) was stirred at rt for 2 h. This reaction mixture was diluted with methanol and then filtered. The crude material was purified via preparative HPLC (Method C) to give **18** (8 mg, 16%) and **17** (3 mg, 6%). Compound **17**: $^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.51 (d, *J* = 7.3 Hz, 1H), 7.44 - 7.35 (m, 4H), 7.29 - 7.21 (m, 1H), 7.02 (d, *J* = 4.0 Hz, 1H), 6.55 (d, *J* = 3.7 Hz, 1H), 6.03 - 5.96 (m, 2H), 3.05 (br. s., 1H), 2.74 (d, *J* = 4.0 Hz, 2H), 2.13 (br. s., 2H), 1.94 - 1.75 (m, 4H), 1.72 - 1.58 (m, 4H). LC/MS *m/z*: $(M + H)^+$ calcd for $C_{23}H_{27}ClFN_4O_2S_2$, 509.12; found 509.2. Compound **18**: $^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.51 - 7.38 (m, 1H), 7.27 (t, *J* = 7.0 Hz, 1H), 6.93 (d, *J* = 4.0 Hz, 1H), 6.45 (d, *J* = 3.7 Hz, 1H), 5.81 - 5.75 (m, 1H), 5.70 (d, *J* = 12.5 Hz, 1H), 3.06 (br. s., 1H), 2.87 - 2.78 (m, 2H), 1.77 (d, *J* = 10.6 Hz, 2H), 1.67 - 1.59 (m, 2H), 1.51 (t, *J* = 12.5 Hz, 2H), 1.22 (d, *J* = 12.8 Hz, 2H). LC/MS *m/z*: $(M + H)^+$ calcd for $C_{23}H_{27}ClFN_4O_2S_2$, 509.12; found 509.2.

**4-(2-((1*S*,4*S*)-4-Amino-1-methylcyclohexyl)ethoxy)-2,5-difluoro-*N*-(1,2,4-thiadiazol-5-yl)benzenesulfonamide (19) and 4-(2-((1*R*,4*R*)-4-amino-1-methylcyclohexyl)ethoxy)-2,5-difluoro-*N*-(1,2,4-thiadiazol-5-yl)benzenesulfonamide (20)**. A solution of **51** (50 mg, 0.07 mmol) TFA (0.11 mL, 1.5 mmol) in DCM (0.5 mL) was stirred at rt for 3 h. DCM was removed, and the crude material was purified via preparative HPLC (Method C) to give **19** (11 mg, 35%) and **20** (3 mg, 9%). Compound **19**: $^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.88 (s, 1H), 7.51 - 7.44 (m, 1H), 7.24 (dd, *J* = 11.2, 7.2 Hz, 1H), 4.14 (t, *J* = 7.0 Hz, 2H), 2.95 (br. s., 1H), 1.82 - 1.65 (m, 4H), 1.62 - 1.43 (m, 4H), 1.27 - 1.09 (m, 2H). LC/MS *m/z*: $(M + H)^+$ calcd for $C_{17}H_{23}F_2N_4O_3S_2$, 433.12; found 433.0. Compound **20**: $^1$H NMR (500

MHz, DMSO-$d_6$) δ 7.88 (s, 1H), 7.45 (dd, *J* = 10.8, 6.4 Hz, 1H), 7.21 (dd, *J* = 10.8, 6.8 Hz, 1H), 4.15 (t, *J* = 6.8 Hz, 2H), 2.9 (br s, 1H), 1.76 - 1.61 (m, 4H), 1.55 - 1.39 (m, 4H), 1.31 (d, *J* = 13.9 Hz, 2H). LC/MS *m/z*: $(M + H)^+$ calcd for $C_{17}H_{23}F_2N_4O_3S_2$, 433.12; found 433.0.

**4-((2-((1*S*,4*S*)-4-Aminocyclohexyl)ethyl)amino)-5-chloro-2-fluoro-*N*-(thiazol-2-yl)benzenesulfonamide (21)**. Prepared using the procedures described for **26**. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.55 (d, *J* = 7.3 Hz, 1H), 6.97 (d, *J* = 3.7 Hz, 1H), 6.50 (s, 1H), 6.48 - 6.43 (m, 1H), 5.98 (br s, 1H), 3.20 - 3.11 (m, 2H), 1.71 - 1.37 (m, 13H). LC/MS *m/z*: $(M + H)^+$ calcd for $C_{17}H_{23}ClFN_4O_2S_2$, 433.09.; found 433.0.

**4-((2-((1*R*,4*R*)-4-Aminocyclohexyl)ethyl)amino)-5-chloro-2-fluoro-*N*-(thiazol-2-yl)benzenesulfonamide (22)**. Prepared using the procedures described for **26**. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.54 (d, *J* = 7.0 Hz, 1H), 6.96 (d, *J* = 3.7 Hz, 1H), 6.49 (d, *J* = 3.5 Hz, 1H), 6.48 - 6.41 (m, 1H), 5.89 (br s, 1H), 3.18 - 3.12 (m, 2H), 2.95 - 2.88 (m, 1H), 1.93 - 1.87 (m, 3H), 1.86 - 1.76 (m, 2H), 1.42 (q, *J* = 6.8 Hz, 2H), 1.31 - 1.20 (m, 3H), 0.97 (q, *J* = 11.4 Hz, 2H). LC/MS *m/z*: $(M + H)^+$ calcd for $C_{17}H_{23}ClFN_4O_2S_2$, 433.09; found 433.0.

**4-((((1*S*,4*S*)-4-Aminocyclohexyl)methyl)amino)-5-chloro-2-fluoro-*N*-(1,2,4-thiadiazol-5-yl)benzenesulfonamide (23)**. Prepared using the procedures described for **26**. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.88 (s, 1H), 7.71 (br s, 2H), 7.52 (d, *J* = 7.3 Hz, 1H), 6.51 (d, *J* = 12.8 Hz, 1H), 6.20 (br t, *J* = 5.5 Hz, 1H), 3.20 (br s, 1H), 3.09 (t, *J* = 6.6 Hz, 2H), 1.76 (br s, 1H), 1.63 (q, *J* = 5.9 Hz, 4H), 1.55 - 1.41 (m, 4H). LC/MS *m/z*: $(M + H)^+$ calcd for $C_{15}H_{20}ClFN_5O_2S_2$, 420.07; found 420.0.

**4-((((1*S*,4*S*)-4-Aminocyclohexyl)methyl)amino)-5-chloro-2-fluoro-*N*-(thiazol-2-yl)benzenesulfonamide (24)**. Prepared using the procedures described for **26**. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.54 (d, *J* = 7.3 Hz, 1H), 6.94 (d, *J* = 3.8 Hz, 1H), 6.50 - 6.41 (m, 2H), 6.03 (br t, *J* = 5.3

Hz, 1H), 3.17 - 3.12 (m, 1H), 3.11 - 3.02 (m, 2H), 1.75 (br d, *J* = 6.0 Hz, 1H), 1.65 - 1.56 (m, 4H), 1.56 - 1.39 (m, 4H). LC/MS *m/z*: $(M + H)^+$ calcd for $C_{16}H_{21}ClFN_4O_2S_2$, 419.08; found 419.1.

**4-((((1*R*,4*R*)-4-Aminocyclohexyl)methyl)amino)-5-chloro-2-fluoro-*N*-(thiazol-2-yl)benzenesulfonamide (25)**. Prepared using the procedures described for **26**. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.54 (d, *J* = 7.3 Hz, 1H), 6.97 (d, *J* = 3.7 Hz, 1H), 6.60 - 6.44 (m, 2H), 6.03 (br. s., 1H), 3.18 (s, 1H), 3.01 (t, *J* = 6.4 Hz, 2H), 2.92 (t, *J* = 11.9 Hz, 1H), 1.98 - 1.88 (m, 2H), 1.78 (d, *J* = 12.5 Hz, 2H), 1.53 (br. s., 1H), 1.31 - 1.17 (m, 2H), 1.10 - 0.83 (m, 2H). LC/MS *m/z*: $(M + H)^+$ calcd for $C_{16}H_{21}ClFN_4O_2S_2$, 419.08; found 419.1.

**5-Chloro-2-fluoro-4-((2-(piperidin-4-yl)ethyl)amino)-*N*-(thiazol-2-yl)benzenesulfonamide (26)**. To a mixture of *tert*-butyl 4-(2-aminoethyl)piperidine-1-carboxylate (53 mg, 0.23 mmol) and 5-chloro-*N*-(2,4-dimethoxybenzyl)-2,4-difluoro-*N*-(thiazol-2-yl)benzenesulfonamide (**45c**) (107 mg, 0.23 mmol) in DMF (2.3 mL) was added cesium carbonate (151 mg, 0.46 mmol). The resulting mixture was stirred at rt for 1 h. The mixture was then diluted with EtOAc, washed with water, brine, dried over $MgSO_4$, filtered and concentrated to give *tert*-butyl 4-(2-((2-chloro-4-(*N*-(2,4-dimethoxybenzyl)-*N*-(thiazol-2-yl)sulfamoyl)-5-fluorophenyl)amino)ethyl)piperidine-1-carboxylate as a crude mixture which was used in the next step without further purification. The crude product was dissolved in DCM (2 mL), and TFA (0.4 mL 5.2 mmol) was added. The resulting mixture was stirred at rt for 15 min. The mixture was then concentrated. The crude material was purified via preparative HPLC (Method C) to give **26** (17 mg, 12%). $^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.55 (d, *J* = 7.3 Hz, 1H), 7.00 (br d, *J* = 3.8 Hz, 1H), 6.57 - 6.44 (m, 2H), 5.97 (br t, *J* = 5.1 Hz, 1H), 3.24 (br d, *J* = 12.7 Hz, 2H), 3.21 - 3.14 (m, 2H), 2.83 (td, *J* = 12.6, 2.5 Hz, 2H), 1.85 (br d, *J* = 12.4 Hz, 2H), 1.70 - 1.54 (m, 1H), 1.49 (q, *J* = 6.9 Hz, 2H), 1.38 - 1.19 (m, 2H). LC/MS *m/z*: $(M + H)^+$ calcd for $C_{16}H_{21}ClFN_4O_2S_2$, 419.08; found 418.9.

**5-Chloro-2-fluoro-4-((2-(piperidin-3-yl)ethyl)amino)-*N*-(thiazol-2-yl)benzenesulfonamide (27)**. Prepared using the procedures described for **26**. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.56 (d, *J* = 7.3 Hz, 1H), 6.99 (d, *J* = 4.0 Hz, 1H), 6.53 (s, 1H), 6.52 - 6.49 (m, 1H), 6.07 - 5.94 (m, 1H), 3.28 - 3.15 (m, 3H), 2.81 - 2.64 (m, 1H), 2.57 (s, 1H), 2.55 (s, 2H), 1.86 (br d, *J* = 12.8 Hz, 1H), 1.81 - 1.70 (m, 2H), 1.63 - 1.41 (m, 3H), 1.15 (br d, *J* = 9.5 Hz, 1H). LC/MS *m/z*: $(M + H)^+$ calcd for $C_{16}H_{21}ClFN_4O_2S_2$, 419.08; found 418.9.

**5-Chloro-2-fluoro-4-((2-(piperidin-2-yl)ethyl)amino)-*N*-(thiadizol-2-yl)benzenesulfonamide (28).** Prepared using the procedures described for **26**. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.85 (s, 1H), 7.54 (d, *J* = 7.0 Hz, 1H), 6.58 (d, *J* = 12.8 Hz, 1H), 6.25 (s, 1H), 3.33 - 3.17 (m, 1H), 3.03 (br. s., 1H), 2.92 - 2.79 (m, 1H), 1.97 (d, *J* = 11.7 Hz, 1H), 1.87 - 1.63 (m, 4H), 1.52 (d, *J* = 13.2 Hz, 1H), 1.43 (d, *J* = 12.5 Hz, 1H), 1.36 - 1.28 (m, 1H). LC/MS *m/z*: $(M + H)^+$ calcd for $C_{15}H_{20}ClFN_5O_2S_2$, 420.07; found 420.1.

**5-Chloro-2-fluoro-4-((2-(piperidin-2-yl)ethyl)amino)-*N*-(thiazol-2-yl)benzenesulfonamide (29)**. Prepared using the procedures described for **26**. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.56 (d, *J* = 7.3 Hz, 1H), 6.98 (d, *J* = 4.0 Hz, 1H), 6.55 - 6.48 (m, 2H), 6.21 (br t, *J* = 5.1 Hz, 1H), 3.25 (br dd, *J* = 5.9, 3.0 Hz, 3H), 3.09 - 2.93 (m, 1H), 2.81 (td, *J* = 12.5, 2.8 Hz, 1H), 1.95 - 1.88 (m, 1H), 1.85 - 1.77 (m, 1H), 1.77 - 1.61 (m, 3H), 1.56 - 1.25 (m, 3H). LC/MS *m/z*: $(M + H)^+$ calcd for $C_{16}H_{21}ClFN_4O_2S_2$, 419.08; found 419.1.

**5-Chloro-2-fluoro-4-((2-(1-methylpiperidin-4-yl)ethyl)amino)-*N*-(thiazol-2-yl)benzenesulfonamide (30)**. Prepared using the procedures described for **26**. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.56 (d, *J* = 7.3 Hz, 1H), 7.10 (d, *J* = 4.0 Hz, 1H), 6.65 (d, *J* = 4.0 Hz, 1H), 6.53 (d, *J* = 12.8 Hz, 1H), 6.10 (br s, 1H), 3.18 (q, *J* = 6.4 Hz, 2H), 3.14 - 2.99 (m, 2H), 2.47 (s, 3H), 2.43 (br s, 2H), 1.79 (br d, *J* = 13.2 Hz, 2H), 1.51 - 1.38 (m, 3H), 1.38 - 1.19 (m, 2H). LC/MS *m/z*: $(M + H)^+$ calcd for $C_{17}H_{23}ClFN_4O_2S_2$, 433.09; found 433.0.

**5-Chloro-2-fluoro-4-((2-(pyrrolidin-3-yl)ethyl)amino)-*N*-(thiazol-2-yl)benzenesulfonamide (31)**. Prepared using the procedures described for **26**. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.56 (d, *J* = 7.3 Hz, 1H), 6.99 (d, *J* = 4.0 Hz, 1H), 6.59 - 6.48 (m, 2H), 6.07 (br. s., 1H), 3.26 - 3.15 (m, 2H), 3.12 - 3.01 (m, 1H), 2.70 (dd, *J* = 11.4, 9.2 Hz, 1H), 2.26 - 2.08 (m, 2H), 1.72 - 1.41 (m, 3H). LC/MS *m/z*: $(M + H)^+$ calcd for $C_{15}H_{19}ClFN_4O_2S_2$, 405.06; found 405.0.

**4-((2-(Azetidin-3-yl)ethyl)amino)-5-chloro-2-fluoro-*N*-(thiazol-2-yl)benzenesulfonamide (32)**. Prepared using the procedures described for **26**. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.59 (d, *J* = 7.3 Hz, 1H), 7.26 (d, *J* = 4.4 Hz, 1H), 6.83 (d, *J* = 4.4 Hz, 1H), 6.69 (d, *J* = 13.2 Hz, 1H), 6.43 (t, *J* = 5.9 Hz, 1H), 4.11 - 3.84 (m, 2H), 3.75 - 3.53 (m, 2H), 3.18 (q, *J* = 6.6 Hz, 2H), 2.83 (dt, *J* = 15.7, 8.1 Hz, 1H), 1.83 (q, *J* = 6.7 Hz, 2H). LC/MS *m/z*: $(M + H)^+$ calcd for $C_{14}H_{17}ClFN_4O_2S_2$, 391.05; found 391.1.

**(*S*)-5-Chloro-2-fluoro-4-((piperidin-3-ylmethyl)amino)-*N*-(thiazol-2-yl)benzenesulfonamide (33)**. Prepared using the procedures described for **26**. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.65 (d, *J* = 8.4 Hz, 1H), 6.99 (d, *J* = 3.7 Hz, 1H), 6.75 (d, *J* = 12.8 Hz, 1H), 6.61 - 6.40 (m, 2H), 3.52 (d, *J* = 10.6 Hz, 1H), 3.08 - 3.07 (m, 1H), 3.27 - 3.04 (m, 2H), 3.29 - 3.00 (m, 2H), 2.83 - 2.76 (m, 1H), 2.66 (t, *J* = 11.9 Hz, 1H), 2.00 - 1.93 (m, 1H), 1.86 - 1.75 (m, 2H), 1.63 - 1.48 (m, 1H), 1.28 - 1.17 (m, 1H). LC/MS *m/z*: $(M + H)^+$ calcd for $C_{15}H_{19}ClFN_4O_2S_2$, 405.06; found 405.0.

**(*R*)-5-Chloro-2-fluoro-4-((piperidin-3-ylmethyl)amino)-*N*-(thiazol-2-yl)benzenesulfonamide (34)**. Prepared using the procedures described for **33**. $^1$H NMR and MS identical to those of **33**.

**5-Chloro-2-fluoro-4-((morpholin-2-ylmethyl)amino)-*N*-(thiazol-2-yl)benzenesulfonamide (35).** Prepared using the procedures described for **26**. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.57 (d, *J* = 7.3 Hz, 1H), 7.10 (d, *J* = 4.0 Hz, 1H), 6.68 - 6.60 (m, 2H), 6.19 - 6.04 (m, 1H), 3.84 (d, *J* = 8.4 Hz, 1H),

3.66 (br. s., 1H), 3.32 - 3.16 (m, 1H), 2.99 (d, *J* = 11.4 Hz, 1H), 2.92 - 2.74 (m, 2H), 2.58 (d, *J* = 12.1 Hz, 2H). LC/MS *m/z*: $(M + H)^+$ calcd for $C_{14}H_{17}ClFN_4O_3S_2$, 407.04; found 407.0.

**5-Chloro-2-fluoro-4-(((1-methylpiperidin-3-yl)methyl)amino)-*N*-(thiazol-2-yl)benzenesulfonamide (36).** Prepared using the procedures described for **26**. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.57 (d, *J* = 7.3 Hz, 1H), 7.14 (d, *J* = 4.4 Hz, 1H), 6.69 (d, *J* = 4.4 Hz, 1H), 6.62 (d, *J* = 12.8 Hz, 1H), 6.38 - 6.29 (m, 1H), 3.10 (br t, *J* = 6.2 Hz, 2H), 2.91 - 2.76 (m, 2H), 2.37 (1H, m), 2.34 (s, 3H), 2.28 - 2.18 (m, 1H), 2.08 - 1.98 (m, 1H), 1.69 (br d, *J* = 10.3 Hz, 2H), 1.57 - 1.42 (m, 1H), 1.09 - 0.92 (m, 1H). LC/MS *m/z*: $(M + H)^+$ calcd for $C_{16}H_{21}ClFN_4O_2S_2$, 419.08; found 418.9.

**(*R*)-5-Chloro-2-fluoro-4-(((1-hydroxypiperidin-3-yl)methyl)amino)-*N*-(thiazol-2-yl)benzenesulfonamide (37)**. To a mixture of **33** (150 mg, 0.370 mmol) and disodium hydrogen phosphate (263 mg, 1.85 mmol) in THF (2.4 mL) was added benzoyl peroxide (135 mg, 0.56 mmol). The resulting mixture was brought to 80 °C and stirred for 1 h. Additional benzoyl peroxide (135 mg, 0.56 mmol) was added and the resulting mixture was stirred at 80 °C for an additional 1 h. The mixture was then diluted with EtOAc, washed with water, brine, dried over $MgSO_4$, filtered and concentrated. Purification of the crude product by flash chromatography eluting with 0 - 100% EtOAc/hexanes to give (*R*)-3-(((2-chloro-5-fluoro-4-(N-(thiazol-2-yl)sulfamoyl)phenyl)amino)methyl)piperidin-1-yl benzoate (65 mg, 33%). LC/MS *m/z*: $(M + H)^+$ calcd for $C_{22}H_{23}ClFN_4O_2S_2$, 525.08; found 525.1. Step B: To a mixture of (*R*)-3-(((2-chloro-5-fluoro-4-(*N*-(thiazol-2-yl)sulfamoyl)phenyl)amino)methyl)piperidin-1-yl benzoate (34 mg, 0.07 mmol) in THF (1.4 mL), MeOH (0.6 mL), and water (0.15 mL) was added LiOH (8 mg, 0.32 mmol). The resulting mixture was stirred at rt for 10 min and quenched by the addition of saturated aqueous ammonium chloride. The resulting mixture was extracted with EtOAc, and the combined extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by preparative HPLC (Method C) to give **37** (8 mg, 30%). $^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.60 - 7.54 (m, 1H), 7.24 (d, *J* = 4.8 Hz, 1H), 6.80 (d, *J* = 4.8 Hz, 1H), 6.66 (br d, *J* = 12.5 Hz, 1H),

6.42 (br s, 1H), 3.19 - 2.94 (m, 3H), 2.24 - 2.12 (m, 1H), 2.02 - 1.82 (m, 2H), 1.71 - 1.57 (m, 3H), 1.50 - 1.36 (m, 1H), 0.88 - 0.65 (m, 1H). LC/MS *m/z*: $(M + H)^+$ calcd for $C_{16}H_{21}ClFN_4O_2S_2$, 421.06; found 421.0.

**(S)-5-Chloro-2-fluoro-4-(((1-hydroxypiperidin-3-yl)methyl)amino)-*N*-(thiazol-2-yl)benzenesulfonamide (38)**. Prepared from **34** using the same procedures as **37**. $^1$ HNMR and MS data are identical to those of **37**.

**4-(((1-Acetylpiperidin-3-yl)methyl)amino)-5-chloro-2-fluoro-*N*-(thiazol-2-yl)benzenesulfonamide (39)**. Prepared using the procedures described for **26.** $^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.54 (s, 2H), 7.26 (dd, *J* = 4.6, 2.4 Hz, 2H), 6.84 - 6.80 (m, 2H), 6.74 (d, *J* = 12.8 Hz, 1H), 6.66 (d, *J* = 12.8 Hz, 1H), 6.44 (br t, *J* = 5.3 Hz, 2H), 4.14 (br d, *J* = 9.2 Hz, 1H), 4.02 (br d, *J* = 12.5 Hz, 1H), 3.74 - 3.53 (m, 2H), 3.21 - 3.00 (m, 6H), 2.86 (dd, *J* = 13.6, 9.5 Hz, 1H), 2.78 - 2.67 (m, 1H), 1.97 (s, 3H), 1.94 (s, 3H), 1.85 - 1.58 (m, 6H), 1.42 - 1.34 (m, 1H), 1.30 - 1.15 (m, 3H). LC/MS *m/z*: $(M + H)^+$ calcd for $C_{17}H_{21}ClFN_4O_3S_2$, 447.07; found 447.0.

**4-((Azetidin-3-ylmethyl)amino)-5-chloro-2-fluoro-*N*-(thiazol-2-yl)benzenesulfonamide (40)**. Prepared using the procedures described for **26.** $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7.55 (d, *J* = 7.3 Hz, 1H), 6.94 (d, *J* = 4.0 Hz, 1H), 6.58 (d, *J* = 12.8 Hz, 1H), 6.46 (d, *J* = 3.8 Hz, 1H), 6.31 - 6.19 (m, 1H), 3.99 - 3.85 (m, 2H), 3.73 - 3.61 (m, 2H), 3.44 - 3.20 (m, 4H), 3.08 - 2.97 (m, 1H). LC/MS *m/z*: $(M + H)^+$ calcd for $C_{13}H_{15}ClFN_4O_2S_2$, 377.03; found 377.0.

**5-Chloro-2-fluoro-4-((1,2,2,6,6-pentamethylpiperidin-4-yl)amino)-*N*-(thiazol-2-yl)benzenesulfonamide (41)**. Prepared using the procedures described for **26.** $^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.59 (d, *J* = 7.3 Hz, 1H), 7.17 (d, *J* = 4.4 Hz, 1H), 6.75 - 6.59 (m, 2H), 5.65 (br. s., 1H), 3.85 - 3.67 (m, 1H), 1.86 - 1.78 (m, 1H), 1.86 (d, *J* = 11.4 Hz, 2H), 1.55 (t, *J* = 11.6 Hz, 2H), 1.20 (d, *J* = 7.7 Hz, 12H). LC/MS *m/z*: $(M + H)^+$ calcd for $C_{19}H_{27}ClFN_4O_2S_2$, 461.12; found 461.2.

**5-Chloro-2-fluoro-4-(((1-(pyrrolidin-1-ylmethyl)cyclopropyl)methyl)amino)-*N*-(thiazol-2-yl)benzenesulfonamide (42)**. Prepared using the procedures described for **26.** $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7.57 (d, *J* = 7.3 Hz, 1H), 7.28 (br. s., 1H), 7.23 (d, *J* = 4.5 Hz, 1H), 6.79 (d, *J* = 4.5 Hz, 1H), 6.70 (d, *J* = 13.1 Hz, 1H), 3.14 (d, *J* = 5.0 Hz, 2H), 2.59 (m, 6H), 1.75 (br. s., 4H), 0.58 - 0.48 (m, 2H), 0.44 - 0.36 (m, 2H). LC/MS *m/z*: $(M + H)^+$ calcd for $C_{18}H_{23}ClFN_4O_2S_2$, 445.09; found 445.0.

***N*-(2,4-Dimethoxybenzyl)-2,5-difluoro-4-hydroxy-*N*-(1,2,4-thiadiazol-5-yl)benzenesulfonamide (47a)**. To a solution of **45a** (25 g, 56 mmol) and 2-(methylsulfonyl)ethanol (14 g, 112 mmol) in DMSO (140 mL) at rt was added potassium *tert*-butoxide (15.7 g, 140 mmol), and the reaction mixture was stirred at rt for 1 h. The reaction mixture was cooled to 0 ºC, and 1N HCl (168 mL, 168 mmol) in water (200 mL) was added, and the aqueous layer was extracted with EtOAc (x3). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to give the crude product. The crude product was purified by silica gel chromatography eluting with 40-50% EtOAc/hexanes to give **47a** (15.5 g, 62%) as a white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.54 (dd, *J* = 9.0, 6.6 Hz, 1H), 7.19 (d, *J* = 8.3 Hz, 1H), 6.74 (dd, *J* = 10.3, 6.6 Hz, 1H), 6.39 (dd, *J* = 8.4, 2.3 Hz, 1H), 6.28 (d, *J* = 2.2 Hz, 1H), 5.33 (s, 2H), 3.78 (s, 3H), 3.74 (s, 3H). LC/MS *m/z*: $(M + H)^+$ calcd for $C_{17}H_{16}F_2N_3O_5S_2$, 444.05; found 444.0.

**5-Chloro-N-(2,4-dimethoxybenzyl)-2-fluoro-4-hydroxy-N-(1,2,4-thiadiazol-5-yl)benzenesulfonamide (47b)**. To a solution of **45b** (4.6 g, 9.9 mmol) and $Cs_2CO_3$ (6.5 g, 19.9 mmol) in DMF (40 mL) was added 2-(methylsulfonyl)ethanol (1.9 mL, 19.9 mmol), and the reaction mixture was stirred at rt for 12 h. Water was added, the aqueous layer was extracted with EtOAc (x3), and the combined organic layers were dried over sodium sulfate and concentrated. The crude product was diluted with a minimum amount of EtOAc, and the product started to precipitate while petroleum ether was added. Filtration gave **47b** as a white solid (3.5 g, 70%). $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.43 (s, 1H), 7.61 (d, *J* = 7.6 Hz), 7.05 (1H, d, *J* = 8.4 Hz), 6.81 (1H, d, *J* = 11.6 Hz), 6.41 (1H, dd, *J* = 2.4,

8.4 Hz), 6.35 (1H, d, *J* = 2.4 Hz), 5.19 (2H, s), 3.70 (3H, s) and 3.68 (3H, s). LC/MS *m/z*: $(M + H)^+$ calcd for $C_{17}H_{16}ClFN_3O_5S_2$, 460.02; found 460.0.

***tert*-Butyl (4-(4-chlorophenyl)-4-(2-hydroxyethyl)cyclohexyl)carbamate (48)**. To a solution of ethyl 2-(4-((*tert*-butoxycarbonyl)amino)-1-(4-chlorophenyl)cyclohexyl)acetate[27] (70 mg, 0.18 mmol) in THF (1 mL) was added 2.0 M $LiAlH_4$ in THF (0.097 mL, 0.19 mmol) at -20 °C. The mixture was warmed to rt over 1 h, and ether was added followed by $Na_2SO_4 \cdot 10H_2O$ (200 mg). After stirring for 1 h at rt, the solid was removed by filtration, and the filtrate was concentrated. The residue was purified via silica gel chromatography eluting with 0-100% EtOAc/hexanes to give **48** (48 mg, 77 %). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.37 - 7.20 (m, 4H), 4.68 - 4.48 (m, 1H), 3.49 (q, *J* = 7.0 Hz, 1H), 3.33 (t, *J* = 7.4 Hz, 2H), 1.99 - 1.90 (m, 3H), 1.88 - 1.71 (m, 4H), 1.59 - 1.49 (m, 2H), 1.46 (s, 9H). LC/MS *m/z*: $(M - Boc + H)^+$ calcd for $C_{14}H_{21}ClFNO$, 254.13; found 254.1.

***tert*-Butyl (4-(2-hydroxyethyl)-4-methylcyclohexyl)carbamate (49)**. To a solution of 2-(4-((*tert*-butoxycarbonyl)amino)-1-methylcyclohexyl)acetic acid[27] (100 mg, 0.37 mmol) in THF (1.5 mL) cooled in an ice-salt bath was added *N*-methylmorpholine (0.07 mL, 0.59 mmol) followed by isobutyl chloroformate (0.06 mL, 0.48 mmol), and the reaction mixture was stirred at 0 °C for 2 h. The reaction mixture was filtered, and the filtrate was added to a solution of $NaBH_4$ (35 mg, 0.92 mmol) in 0.5 mL of THF and 0.2 mL of water at 10 °C. The reaction mixture was warmed to rt and stirred for 1 h. Water was added, the aqueous layer was extracted with EtOAc, and the combined organic layers were dried over sodium sulfate, and concentrated. The residue was purified via silica gel chromatography eluting with 0-100% EtOAc/hexanes to give **49** (65 mg, 69% ). This material was used as crude for the next step without any purification.

***tert*-Butyl (4-(4-chlorophenyl)-4-(2-(4-(*N*-(2,4-dimethoxybenzyl)-*N*-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2,5-difluorophenoxy)ethyl)cyclohexyl)carbamate (50)**. To a solution of alcohol **48** (24 mg, 0.07 mmol), phenol **47** (36 mg, 0.08 mmol), $Ph_3P$ (27 mg, 0.10 mmol) in THF (1 mL) was added

DEAD (16 μL, 0.10 mmol) dropwise at rt. The mixture was stirred at rt for 3 h and then concentrated, and the residue was purified via silica gel chromatography eluting with 30-100% EtOAc/hexanes to give **50** (45 mg, 85% ). $^1$H NMR (500 MHz, $CDCl_3$) δ 8.21 - 8.14 (m, 1H), 7.49 (dd, *J* = 9.9, 6.4 Hz, 1H), 7.38 - 7.26 (m, 4H), 7.17 (d, *J* = 8.4 Hz, 1H), 6.38 - 6.29 (m, 2H), 6.25 (d, *J* = 2.3 Hz, 1H), 5.28 (s, 2H), 3.75 (s, 3H), 3.72 (s, 3H), 3.67 (t, *J* = 6.7 Hz, 2H), 3.58 - 3.45 (m, 1H), 2.20 (br t, *J* = 6.7 Hz, 2H), 2.04 - 1.97 (m, 2H), 1.94 - 1.80 (m, 4H), 1.58 (br d, *J* = 10.1 Hz, 2H), and 1.46 (9H, s). LC/MS *m/z*: $(M + H)^+$ calcd for $C_{36}H_{42}ClF_2N_4O_7S_2$, 779.22; found 779.2.

***tert*-Butyl (4-(2-(4-(N-(2,4-dimethoxybenzyl)-*N*-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2,5-difluorophenoxy)ethyl)-4-methylcyclohexyl)carbamate (51)**. To a solution of **49** (25 mg, 0.097 mmol), *N*-(2,4-dimethoxybenzyl)-2,5-difluoro-4-hydroxy-*N*-(1,2,4-thiadiazol-5-yl)benzenesulfonamide (52 mg, 0.12 mmol) and $Ph_3P$ (38 mg, 0.15 mmol) in THF (0.5 mL) was added DEAD (0.023 mL, 0.15 mmol) at rt, and the reaction mixture was stirred at rt for 16 h. The solvents were removed, and the residue was purified via silica gel chromatography eluting with 40%-100% EtOAc/hexanes to give **51** (50 mg, 75%). $^1$H NMR (500 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.54 (dd, *J* = 10.1, 6.4 Hz, 1H), 7.19 (d, *J* = 8.4 Hz, 1H), 6.59 (dd, *J* = 11.0, 6.3 Hz, 1H), 6.36 (dd, *J* = 8.5, 2.4 Hz, 1H), 6.27 (d, *J* = 2.3 Hz, 1H), 5.31 (s, 2H), 4.05 (t, *J* = 6.9 Hz, 2H), 3.76 (s, 3H), 3.74 (3H, s), 3.52 - 3.40 (m, 1H), 1.88 (t, *J* = 6.9 Hz, 2H), 1.85 - 1.80 (m, 2H), 1.59 - 1.51 (m, 2H), 1.46 (s, 9H), 1.40 - 1.30 (m, 4H), 0.99 (s, 3H). LC/MS *m/z*: $(M + H)^+$ calcd for $C_{31}H_{41}ClF_2N_4O_7S_2$, 683.24; found 683.3.

**2-(8-Phenyl-1,4-dioxaspiro[4.5]decan-8-yl)ethanol** (**53**). Step A: to a suspension of methyl triphenylphosphonium bromide (19.0 g, 53.3 mmol) in THF (50.8 mL) at -78 °C was added 2.5 M *n*-BuLi (21.3 mL, 53.3 mmol) dropwise, and an orange milky suspension was formed. The reaction mixture was stirred at 0 °C for 30 min. A solution of aldehyde **52**[28] in THF (20 mL) was added, and the reaction mixture was stirred at rt for 2 h. Water was added and the aqueous layer was extracted with EtOAc (x3). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to give the crude product. The crude product was puri-

fied by silica gel chromatography eluting with 0-20% EtOAc/hexanes to give 8-phenyl-8-vinyl-1,4-dioxaspiro[4.5]decane (2 g, 54%). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.42 - 7.37 (m, 2H), 7.36 - 7.30 (m, 2H), 7.24 - 7.18 (m, 1H), 5.87 (dd, *J* = 17.5, 10.6 Hz, 1H), 5.12 (d, *J* = 10.8 Hz, 1H), 4.95 (d, *J* = 17.6 Hz, 1H), 4.11 - 3.86 (m, 4H), 2.23 (ddd, *J* = 13.3, 9.2, 3.9 Hz, 2H), 2.08 - 1.96 (m, 2H), 1.83 - 1.73 (m, 2H), 1.72 - 1.61 (m, 2H). Step B: To a solution of 8-phenyl-8-vinyl-1,4-dioxaspiro[4.5]decane (2 g, 8.2 mmol) in THF (29 mL) at rt was added borane THF complex (12.3 mL, 12.3 mmol), and the reaction mixture was stirred at rt for 1 h. Water was added to quench excessive borane. 1N sodium hydroxide (13 mL, 13 mmol) and 37% hydrogen peroxide (33 mL) were added. The aqueous layer was extracted with EtOAc (x3), and the combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to give the crude product. The crude product was purified by silica gel chromatography eluting with 0-40% EtOAc/hexanes to give **53** (1.4 g, 65%) as a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.42 - 7.32 (m, 4H), 7.26 - 7.18 (m, 1H), 4.03 - 3.86 (m, 4H), 3.42 (br. s., 2H), 2.30 (d, *J* = 14.2 Hz, 2H), 1.93 - 1.80 (m, 4H), 1.76 - 1.64 (m, 2H), 1.63 - 1.51 (m, 3H).

***N*-(2,4-Dimethoxybenzyl)-2,5-difluoro-4-(2-(8-phenyl-1,4-dioxaspiro[4.5]decan-8-yl)ethoxy)-*N*-(1,2,4-thiadiazol-5-yl)benzenesulfonamide (54a)**. To a solution of 2-(8-phenyl-1,4-dioxaspiro[4.5]decan-8-yl)ethanol (34 mg, 0.13 mmol) and *N*-(2,4-dimethoxybenzyl)-2,5-difluoro-4-hydroxy-*N*-(1,2,4-thiadiazol-5-yl)benzenesulfonamide (63 mg, 0.14 mmol) in DMF (1 mL) at rt was added $K_2CO_3$, and the reaction mixture was stirred at rt for 12 h. Water was added and the aqueous layer was extracted with EtOAc (x3). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to give the crude product. The crude product was purified by preparative TLC on silica gel eluting with 40% EtOAc/hexanes to give **54a** (70 mg, 79 %). $^1$H NMR (500 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.46 (dd, *J* = 9.9, 6.4 Hz, 1H), 7.39 - 7.34 (m, 4H), 7.24 (td, *J* = 5.6, 2.7 Hz, 1H), 7.16 (d, *J* = 8.4 Hz, 1H), 6.37 - 6.34 (m, 1H), 6.28 - 6.20

(m, 2H), 5.28 (s, 2H), 4.02 - 3.88 (m, 4H), 3.79 - 3.65 (m, 8H), 2.33 (d, *J* = 14.0 Hz, 2H), 2.08 (t, *J* = 7.2 Hz, 2H), 1.97 - 1.89 (m, 2H), 1.76 - 1.58 (m, 4H).

**5-Chloro-N-(2,4-dimethoxybenzyl)-2-fluoro-4-(2-(8-phenyl-1,4-dioxaspiro[4.5]decan-8-yl)ethoxy)-N-(1,2,4-thiadiazol-5-yl)benzenesulfonamide (54b)**. To a solution of **53** (187 mg, 0.713 mmol) and **47b** (393 mg, 0.86 mmol) in THF (4.8 mL) at rt was added DEAD (169 µL, 1.1 mmol) , and the reaction mixture was stirred at rt for 30 min. Water was added and the aqueous layer was extracted with EtOAc (x3). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and filtered, and the filltrate was evaporated in vacuo to give the crude product. The crude product was purified by preparative TLC on silica gel eluting with 50% EtOAc/hexanes to give **54b** (152 mg, 30%) as a sticky oil. $^1$H NMR (500 MHz, $CDCl_3$) δ 8.20 (d, *J* = 0.8 Hz, 1H), 7.70 (dd, *J* = 7.2, 1.4 Hz, 1H), 7.41 - 7.34 (m, 4H), 7.27 - 7.23 (m, 1H), 7.17 (d, *J*=8.5 Hz, 1H), 6.34 (dt, *J* = 8.5, 1.0 Hz, 1H), 6.24 - 6.13 (m, 2H), 5.30 (s, 2H), 4.27 - 4.18 (m, 3H), 4.12 (q, *J*=7.1 Hz, 2H), 4.01 - 3.89 (m, 5H), 3.74 (s, 3H), 3.69 (3H, s), 2.35 (br d, *J* = 14.0 Hz, 2H), 2.10 (t, *J* = 6.7 Hz, 2H), 2.00 - 1.90 (m, 2H), 1.76 - 1.69 (m, 2H), 1.67 - 1.57 (m, 2H).

**2,5-Difluoro-4-(2-(4-oxo-1-phenylcyclohexyl)ethoxy)-*N*-(1,2,4-thiadiazol-5-yl)benzenesulfonamide (55a)**. To a solution of **54a** (23 mg, 0.033 mmol) in acetone (0.7 mL) at rt was added 1N HCl (0.13 mL, 0.13 mmol), and the reaction mixture was heated at 60 °C for 1 h. Acetone was removed, water was added and the aqueous layer was extracted with EtOAc (x3). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to give the crude product. The crude product was purified by preparative TLC on silica gel eluting with 70% acetone/hexanes to give **55a** (12 mg, 73%). $^1$H NMR (500 MHz, $CD_3COCD_3$) δ 7.82 (s, 1H), 7.62 - 7.51 (m, 3H), 7.42 (t, *J* = 7.8 Hz, 2H), 7.31 - 7.25 (m, 1H), 6.71 (d, *J* = 7.8 Hz, 1H), 3.93 (t, *J* = 6.9 Hz, 2H), 2.72 - 2.64 (m, 2H), 2.39 - 2.12 (m, 8H). LC/MS *m/z*: $(M + H)^+$ calcd for $C_{22}H_{22}F_2N_3O_4S_2$, 494.10; found 494.2.

**5-Chloro-2-fluoro-4-(2-(4-oxo-1-phenylcyclohexyl)ethoxy)-N-(1,2,4-thiadiazol-5-yl)benzenesulfonamide (55b)**. To a solution of **54b** (150 mg, 0.213 mmol) in acetone (4.3 mL) at rt was added HCl (0.85 mL, 0.85 mmol), and the reaction mixture was stirred at rt for 30 min. Water was added and the aqueous layer was extracted with EtOAc (x3). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated in vacuo to give **55b** as a white solid (110 mg, 100%). LC/MS *m/z*: $(M + H)^+$ calcd for $C_{22}H_{22}ClFN_3O_4S_2$, 494.10; found 494.2.

**2-(8-Phenyl-1,4-dioxaspiro[4.5]decan-8-yl)ethanamine (56)**. Step A: To a solution **53** (210 mg, 0.80 mmol), phthalimide (141 mg, 0.96 mmol) and $Ph_3P$ (252 mg, 0.96 mmol) in THF (4 mL) at rt was added DEAD (152 µl, 0.96 mmol), and the reaction mixture was stirred at rt for 12 h. THF was removed, and the crude product was purified by preparative TLC on silica gel eluting with 40% EtOAc/hexanes to give 2-(2-(8-phenyl-1,4-dioxaspiro[4.5]decan-8-yl)ethyl)isoindoline-1,3-dione (325 mg, 100% ) as white foam. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.76 - 7.72 (m, 2H), 7.66 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.37 (dd, *J* = 8.4, 1.1 Hz, 2H), 7.26 (t, *J* = 7.9 Hz, 2H), 7.08 - 7.03 (m, 1H), 4.01 - 3.91 (m, 4H), 3.52 - 3.35 (m, 2H), 2.31 (d, *J* = 14.0 Hz, 2H), 2.06 - 1.99 (m, 2H), 1.96 - 1.85 (m, 2H), 1.76 - 1.67 (m, 2H), 1.66 - 1.54 (m, 4H). Step B: To a solution of 2-(2-(8-phenyl-1,4-dioxaspiro[4.5]decan-8-yl)ethyl)isoindoline-1,3-dione (325 mg, 0.83 mmol) in methanol/THF (1:1) (4 mL) at rt was added hydrazine hydrate (0.60 mL, 12.5 mmol), and the reaction mixture was stirred at rt for 12 h. White precipitate was formed 2 h after addition. The reaction mixture was filtered through a pad of Celite and the pad was shed with DCM. The filtrate was evaporated to give crude **56** (217 mg, 100%) as a yellow oil material. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.38 - 7.30 (m, 4H), 7.23 - 7.17 (m, 1H), 3.99 - 3.94 (m, 2H), 3.93 - 3.89 (m, 2H), 2.44 - 2.38 (m, 2H), 2.32 - 2.22 (m, 2H), 1.86 - 1.78 (m, 2H), 1.74 - 1.64 (m, 4H), 1.61 - 1.53 (m, 2H).

**5-Chloro-*N*-(2,4-dimethoxybenzyl)-2-fluoro-4-((2-(8-phenyl-1,4-dioxaspiro[4.5]decan-8-yl)ethyl)amino)-*N*-(thiazol-2-yl)benzenesulfonamide (57)**. A mixture of crude amine **56** (217 mg, 0.83 mmol), **45c** (402 mg, 0.87 mmol) and cesium carbonate (298 mg, 0.91 mmol) in DMF (5.5 mL) was stirred at rt for 12 h. Water was added and the aqueous layer was extracted with EtOAc (x3). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated *in vacuo* to give the crude product. The crude product was purified by preparative TLC on silica gel eluting with 50% EtOAc/hexanes to give **57** (71 mg, 12%). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.0 Hz, 1H), 7.41 - 7.37 (m, 5H), 7.28 - 7.24 (m, 1H), 7.21 (d, *J* = 8.9 Hz, 1H), 6.96 (d, *J* = 3.5 Hz, 1H), 6.42 - 6.35 (m, 2H), 5.87 (d, *J* =12.5 Hz, 1H), 5.19 (s, 2H), 4.64 (br s, 1H), 4.01 - 3.96 (m, 2H), 3.95 - 3.91 (m, 2H), 3.77 (s, 3H), 3.76 (s, 3H), 2.94 - 2.85 (m, 2H), 2.33 (br d, *J* = 13.9 Hz, 2H), 1.94 - 1.81 (m, 4H), 1.73 - 1.50 (m, 4H). LC/MS *m/z*: $(M - H)^+$ calcd for $C_{34}H_{36}ClFN_3O_6S_2$, 700.17; found 700.3.

**5-Chloro-2-fluoro-4-((2-(4-oxo-1-phenylcyclohexyl)ethyl)amino)-*N*-(thiazol-2-yl)benzenesulfonamide (58)**. A solution of **57** (71 mg, 0.10 mmol) and HCl (0.4 mL, 0.40 mmol) in acetone (2 mL) was heated under reflux for 2 h. Water was added and the aqueous layer was extracted with EtOAc (x3). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated *in vacuo* to give **58** (50 mg, 97% ) as a white solid. LC/MS *m/z*: $(M + H)^+$ calcd for $C_{23}H_{24}ClFN_3O_3S_2$, 508.09; found 508.1. This material was used directly for the next reaction.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Molecular formula strings (cvs).

## AUTHOR INFORMATION

### Corresponding Author

* Tel: 203-677-7485. E-mail: Yong-jin.wu@bms.com

### Notes

The authors declare no competing financial interest.

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## ABBREVIATIONS USED

EtOAc, ethyl acetate; TFA, trifluoroacetic acid; rt, room temperature; DCM, dichloromethane; CYP, cytochrome P450 enzymes; PO, oral administration; SC, subcutaneous injection; DRG: Dorsal root ganglion; PK/PD, Pharmacokinetic/Pharmacodynamic.

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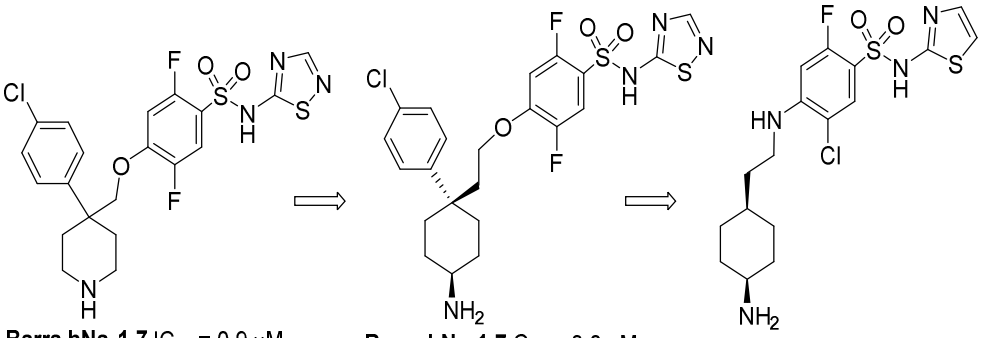
# Table of Contents Graphic



**Barra hNa$_V$1.7** $IC_{50}$ = 0.9 μM

**Barra hNa$_V$1.7** $C_{50}$ = 8.0 nM

**Barra hNa$_V$1.7** $IC_{50}$ = 6.0 nM

EP **hNa$_V$1.7** $IC_{50}$ = 4.0 nM