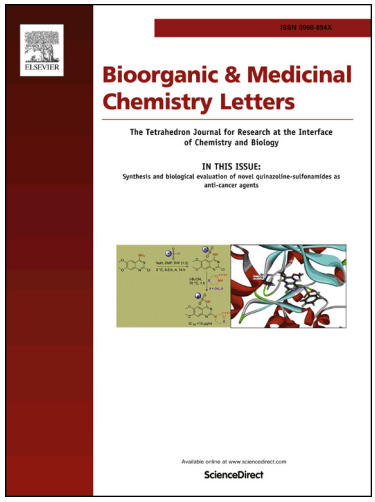


# Benzoxazolinone aryl sulfonamides as potent, selective $Na_v1.7$ inhibitors with in vivo efficacy in a preclinical pain model

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## Graphical Abstract

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**Benzoxazolinone aryl sulfonamides as potent, selective $Na_v1.7$ inhibitors with in vivo efficacy in a preclinical pain model**

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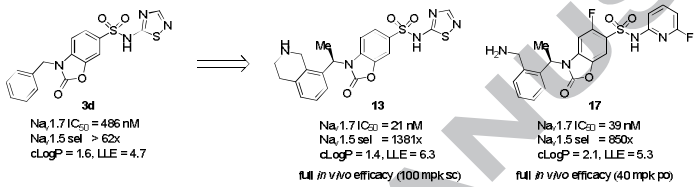

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# Benzoxazolinone aryl sulfonamides as potent, selective $Na_v1.7$ inhibitors with in vivo efficacy in a preclinical pain model

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ABSTRACT

Studies on human genetics have suggested that inhibitors of the $Na_v1.7$ voltage-gated sodium channel hold considerable promise as therapies for the treatment of chronic pain syndromes. Herein, we report novel, peripherally-restricted benzoxazolinone aryl sulfonamides as potent $Na_v1.7$ inhibitors with excellent selectivity against the $Na_v1.5$ isoform, which is expressed in the heart muscle. Elaboration of initial lead compound **3d** afforded exemplar **13**, which featured attractive physicochemical properties, outstanding lipophilic ligand efficiency and pharmacological selectivity against $Na_v1.5$ exceeding 1,000-fold. Key structure-activity relationships associated with oral bioavailability were leveraged to discover compound **17**, which exhibited a comparable potency/selectivity profile as well as full efficacy following oral administration in a preclinical model indicative of antinociceptive behavior.



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Despite many years of intense research, the development of safe and effective therapeutics for the treatment of chronic pain remains an unmet medical need. Recent epidemiological studies have found that 10-55% of people in various countries suffer from chronic pain.[1] In the United States alone, approximately 35% of the population lives with chronic pain syndromes, with roughly 50 million Americans experiencing partial or total disability as a consequence. Furthermore, chronic pain is associated with an increased prevalence of other disorders such as depression, anxiety, insomnia and weight gain.[2,3] In addition, severe chronic pain has been linked to elevated mortality rates, particularly from heart and respiratory diseases.[4]

Pharmacological treatments for chronic pain have historically included opioids (i.e. morphine, oxycodone)[5], non-steroidal anti-inflammatory drugs (NSAIDs, i.e. naproxen, ibuprofen)[6], anti-convulsants (i.e. pregabalin, gabapentin)[7] and serotonin-norepinephrine reuptake inhibitors (SNRIs, i.e. duloxetine, venlafaxine).[8] While each of these modalities can be effective, complete and sustained relief from pain syndromes is unfortunately rare. Furthermore, utility is limited due to a multitude of adverse side effects including addiction (opioids), insomnia (SNRIs), sexual dysfunction (SNRIs) and gastrointestinal issues (NSAIDs).

An alternative therapy for the treatment of chronic pain involves the use of local anesthetics. In particular, lidocaine has been widely leveraged for the rapid relief of pain in both injectable and topical (Lidoderm®) formats.[9] Its putative mode of action involves the non-selective blockade of $Na_v1$ voltage-gated sodium channels (VGSCs), which are key regulators of electrical signaling pathways. As such, VGSCs are responsible for the rising phase of action potentials in excitatory cells such as sensory neurons in response to changes in membrane potential.[10] The nine reported VGSCs have varying tissue distribution patterns and pharmacology.[11] $Na_v1.1$ and $Na_v1.2$ are localized in the central nervous system (CNS) whereas $Na_v1.3$ is embryonically expressed. $Na_v1.4$ and 1.5 are largely localized in skeletal muscle and cardiac myocytes, respectively. While $Na_v1.6$ is expressed in both the CNS and peripheral nervous system (PNS), $Na_v1.7$, 1.8 and 1.9 are primarily localized in the PNS.

Studies on human genetics suggest that the $Na_v1.7$ isoform may be a principle driver of pain signaling. In particular, loss-of-function (LOF) mutations in $Na_v1.7$ lead to channelopathy-associated indifference to pain[12] while gain-of-function (GOF) mutations elicit debilitating pain syndromes such as erythromelalgia.[13] While inhibition of $Na_v1.7$ may contribute to the efficacy of local anesthetics, the CNS and cardiovascular side effects associated with their systemic exposure may be attributed to a lack of pharmacological selectivity with respect to the $Na_v1.1$/$Na_v1.2$ and $Na_v1.5$ channels, respectively.

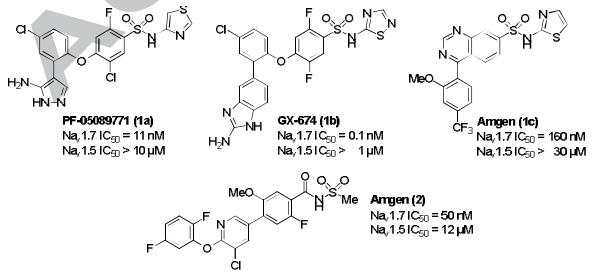


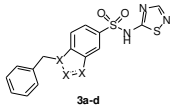

**Figure 1.** Aryl sulfonamide $Na_v1.7$ inhibitors from Pfizer (**1a**), Genentech (**1b**) and Amgen (**1c**). Acyl sulfonamide $Na_v1.7$ inhibitor from Amgen (**2**).

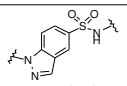
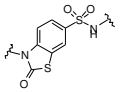
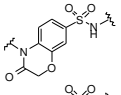
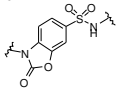
The significant therapeutic potential of pharmacologically-selective, peripherally-restricted $Na_v1.7$ blockers has attracted considerable interest from the pharmaceutical industry. To this end, Pfizer has disclosed a series of arylsulfonamide $Na_v1.7$ inhibitors exemplified by PF-05089771 (**1a**, Figure 1)[14] with high (>1,000-fold) pharmacological selectivity over $Na_v1.5$. The binding site of this structural class (voltage-sensor domain 4, transmembrane segments S2-S3) is distinct from the homologous pore region in which the local anesthetics reside and most likely confers the observed pharmacological selectivity.[15]

In addition to this pioneering work, other scientists have designed compounds to exploit this novel binding site. Genentech[16] and Amgen[17] have recently disclosed structurally distinct aryl sulfonamides exemplified by compounds **1b** and **1c**, respectively. In addition, potent and selective acyl sulfonamides have been reported by Amgen (i.e. compound **2**)[18], Pfizer[19] and Merck,[20] with competitive binding studies suggesting a similar binding mode to the aryl sulfonamides.

We were interested in developing a unique class of conformationally-restricted, bicyclic aryl sulfonamides in hopes of bringing structural novelty to the field with potential improvements in pharmacokinetic and/or physicochemical properties. Targeting scaffolds of generic structure **3**, a series of (6,5)- and (6,6)-frameworks were explored with an emphasis on maximizing ligand efficiency (LE)[21], lipophilic ligand efficiency (LLE)[22] and selectivity against $Na_v1.5$ (Table 1). The *in vitro* profiling of compounds leveraged a PatchXpress® (PX) automated patch clamp system with a protocol tuned to assess inhibition of channels in their inactivated states.[23] From an initial investigation of structure-activity relationships (SAR), thiazolinone **3b**, dihydro-benzoxazinone **3c** and benzoxazolinone **3d** were each inactive against $Na_v1.5$ ($IC_{50}$ > 30 μM). Among these encouraging bicyclic scaffolds, benzoxazolinone **3d** emerged with the most promise due to its superior $Na_v1.7$ activity ($IC_{50}$ = 486 nM), LE (0.33) and LLE (4.7).[24,25]

**Table 1.** Bicyclic aryl sulfonamide structure-activity relationships[a]

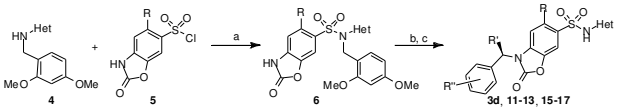



| Cmpd | Bicycle | $Na_v1.7$ $IC_{50}$ (nM) | $Na_v1.5$ sel | cLogP[26] | LE | LLE |
|---|---|---|---|---|---|---|
| **3a** |  | 3026 | 6x | 2.5 | 0.30 | 3.0 |
| **3b** |  | 970 | >31x | 2.5 | 0.30 | 3.5 |
| **3c** |  | 815 | >37x | 1.7 | 0.32 | 4.4 |
| **3d** |  | 486 | >62x | 1.6 | 0.33 | 4.7 |

[a] $Na_v1.7$ and $Na_v1.5$ *in vitro* activity measured by PatchXpress®[23] protocols; $Na_v1.5$ sel = selectivity against $Na_v1.5$; LE = ligand efficiency; LLE = lipophilic ligand efficiency.

The synthesis of benzoxazolinone **3d** and related analogs (**11-13**, **15-17**) utilized the general sequence detailed in Scheme 1.[24] Lithiation of amino-heterocycle **4** with sulfonyl chloride **5** provided intermediate **6**. Mitsunobu coupling with an alcohol building block mediated by diethyl azodicarboxylate (DEAD) and triphenylphosphine gave the ultimate intermediate, which subsequently underwent a global deprotection with trifluoroacetic acid (TFA) to afford the described compounds.

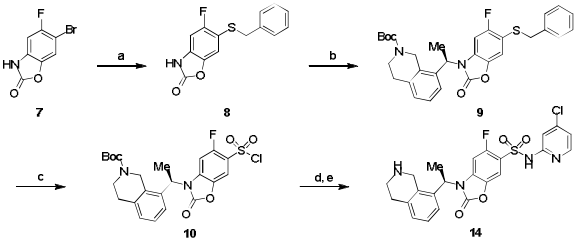
**Scheme 1.** Synthetic strategy for benzoxazolinones **3d**, **11**-**13**, **15**-**17**[a]



[a]Reagents and conditions: (a) LHMDS, THF, -78 °C to RT, 18 h, 23-79%; (b) alcohol, DEAD, $Ph_3P$, THF, 0 °C - RT, 3 h, 43-65%; (c) TFA, DCM, RT, 30 min, 48-90%.

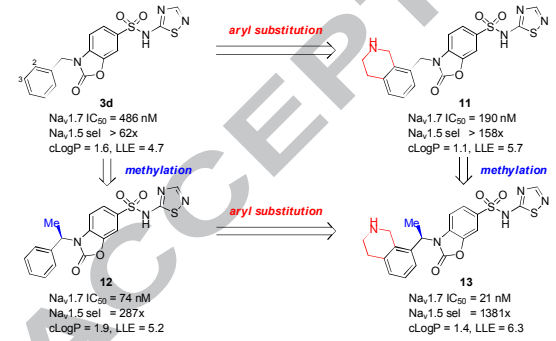
The synthesis of compound **14** leveraged a complimentary sequence featuring the sulfonamide formation as the penultimate step (Scheme 2). This strategy facilitated the investigation of an array of heteroaryl sulfonamides and greatly aided our understanding of the underlying SAR.[27] Here, palladium-catalyzed cross coupling of 6-bromo-5-fluorobenzo[*d*]oxazol-2(3*H*)-one (**7**) with benzyl mercaptan afforded versatile intermediate **8**. The preparation of compound **14** required a Mitsunobu coupling with (*S*)-*tert*-butyl 8-(1-hydroxyethyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate to provide **9**. Oxidation with 1,3-dichloro-5,5-dimethylimidazolidine-2,4-dione gave sulfonyl chloride **10**, which was then subjected to standard sulfonamide formation conditions and acid-mediated deprotection to afford **14**.[27]

**Scheme 2.** Synthesis of benzoxazolinone **14**[a]



[a]Reagents and conditions: (a) benzyl mercaptan, $Pd_2(dba)_3$, Xantphos, DIPEA, THF, 120 °C, 2 h, 52%; (b) (*S*)-*tert*-butyl 8-(1-hydroxyethyl)-3,4-dihydroiso-quinoline-2(1*H*)-carboxylate, DEAD, *n*-$Bu_3P$, THF, 0 °C, 2 h, 43%; (c) 1,3-dichloro-5,5-dimethylimidazolidine-2,4-dione, AcOH, THF, $H_2O$, 0 °C, 5 min, 52%; (d) 4-chloro-*N*-(2,4-dimethoxybenzyl)pyridin-2-amine, DCM, pyridine, RT, 12 h, then TFA, DCM, RT.

**Figure 2.** Combination of two potency-enhancers to give **13**.




Early lead optimization efforts involving the benzoxazolinone structural class revealed two distinct potency-enhancers. For one, incorporation of polar substituents at the 2- or 3-positions of the phenyl group was generally found to increase $Na_v1.7$ activity while lowering cLogP. In a key example, tetrahydroisoquinoline **11** featured a potency increase exceeding two-fold relative to parent compound **3d** (Figure 2). With a cLogP of 1.1, its LLE (5.7) also increased significantly. Importantly, this modification did not increase activity with respect to $Na_v1.5$ ($IC_{50}$ > 30 μM). An additional potency enhancement was found by incorporating a methyl group at the benzyl carbon, providing (*R*)-eutomer **12**. This resulted in nearly a seven-fold improvement in $Na_v1.7$ activity relative to **3d**, potentially by providing a gearing effect which positioned the phenyl ring into a more bioactive orientation.

Gratifyingly, these potency enhancements were found to be additive. Exemplar **13**, incorporating both the tetrahydroisoquinoline and methyl groups, featured a $Na_v1.7$ $IC_{50}$ of 21 nM and a 1.6-unit increase in LLE relative to initial lead compound **3d**. Furthermore, its $Na_v1.5$ selectivity exceeded 1,000-fold and was thus comparable with previously-reported aryl sulfonamides (Figure 1).

The *in vitro* activity of compound **13** was also assessed by investigating the inhibition of tetrodotoxin (TTX)-sensitive $Na_v$ current in freshly-harvested neurons of the dorsal root ganglion (DRG).[28] $Na_v$ potency measured for human in this format ($IC_{50}$ = 31 nM) was consistent with that exhibited in the recombinant $Na_v1.7$ PatchXpress® protocol (PX $IC_{50}$ = 21 nM). The activity of compound **13** in mouse DRG's ($IC_{50}$ = 82 nM) was comparable to that of human. This contrasted sharply with rat, however, as the inhibition of TTX-sensitive sodium current in rat DRG's featured an $IC_{50}$ of 2371 nM. This species-dependent *in vitro* activity is consistent with previously-reported aryl sulfonamides and may be due to specific amino acid differences in domain 4 of the voltage-sensor region (VSD4).[15]

In probing its ancillary profile, benzoxazolinone **13** was inactive against CYP's, PXR, hERG (IKr) and $Ca_v1.2$. Unfortunately, it was non-selective against the $Na_v1.2$ channel (PX $IC_{50}$ = 29 nM). However, the brain/plasma and CSF/plasma ratios in rat were found to be 1% and 0%, respectively. Considering that $Na_v1.2$ is localized in the CNS, this peripheral restriction helped mitigate our concerns with respect to the observed $Na_v1.2$ activity.

The pharmacokinetic properties of compound **13** in rat featured an unbound clearance ($CL_{u,p}$)[29] of 360 mL/min/kg (fraction unbound ($f_u$) = 0.133 in rat) and a half-life ($T_{1/2}$) of 0.8 h following iv dosing (2 mpk). Disappointingly, the compound exhibited poor oral bioavailability (F = 2% following 10 mpk po dose), possibly due to a lack of cell permeability ($P_{app}$ < 2 x $10^{-6}$ cm/sec).

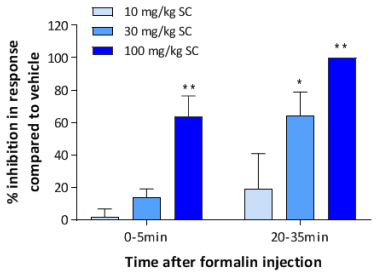
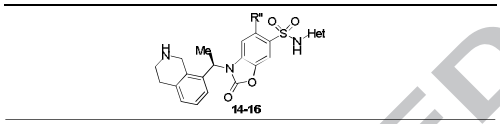



**Figure 3.** %Inhibition of formalin-induced nociceptive behavior compared to vehicle-treated mice after subcutaneous (sc) administration (10/30/100 mpk, 90 min pre-treatment time to align with $T_{max}$ measured in pharmacokinetic studies) of compound **13**. Compound **13** significantly attenuated Phase 2 responses after the 30 and 100 mpk doses (ANOVA followed by Dunnett's multiple comparison test; * P< 0.05, ** P<0.01). Exposures were measured for compound **13** at 3 h post-administration.

Utilizing subcutaneous (sc) administration, the *in vivo* activity of compound **13** was assessed in a mouse formalin paw assay, which has been frequently leveraged as a preclinical indicator of antinociceptive behavior.[30] In this experiment, formalin was injected into the hind paw of a mouse, resulting in a number of nociceptive behaviors including licking, biting and flinching. The total time spent exhibiting nociceptive behaviors was recorded in

5 min intervals for a maximum of 60 min. The 0 – 5 min period post formalin injection (Phase 1) is generally indicative of direct activation of nociceptors while the 25 – 30 min period following administration (Phase 2) is characteristic of a more complex response involving inflammation, injured afferents and central sensitization. Data was normalized and expressed as %inhibition compared to the amount of nociceptive behavior observed in vehicle-treated mice. A 100 mpk sc dose of compound **13** administered 90 min prior to the formalin injection significantly attenuated this behavior for both time intervals (Figure 3). Full efficacy was observed for Phase 2, and subsequent analysis of the terminal exposure provided an $IC_{50}$ of 23 µM. With a fraction unbound ($f_u$) of 0.065 in mice, the unbound efficacious drug exposure ($IC_{50,u}$) for **13** was 1.5 µM, which is approximately 50-fold above its mouse PX $IC_{50}$ (30 nM). This is consistent with previously-reported aryl sulfonamide PK/PD relationships in preclinical pain models.[16,17]

In order to further progress the benzoxazolinone structural class, the lack of oral bioavailability of compounds such as **13** needed to be addressed. One component of our strategy to enhance oral exposure centered on reducing polar surface area (PSA) through modification of the aryl sulfonamide moiety (Table 2). In particular, replacing the thiadiazole with substituted pyridines was most effective at modulating PSA while maintaining acceptable physicochemical properties (i.e. cLogP < 4). While these modifications each proceeded with significant erosion of $Na_v1.7$ potency, a portion of this activity was recovered through the installation of a potency-enhancing fluoro-substituent on the benzoxazolinone scaffold (R = F, Scheme 1). Ultimately, of the initial set of compounds investigated, 6-fluoropyridyl sulfonamide **16** featured the most attractive balance of $Na_v1.7$ potency (150 nM), $Na_v1.5$ selectivity (210x) and LLE




| Cmpd | R'' | Het | $Na_v1.7$ $IC_{50}$ (nM) | $Na_v1.5$ sel | PSA | cLogP | LLE |
|---|---|---|---|---|---|---|---|
| **13** | H |  | 21 | 1381x | 119 | 1.4 | 6.3 |
| **14** | F |  | 134 | 88x | 106 | 3.2 | 3.7 |
| **15** | F |  | 535 | 108x | 106 | 2.6 | 3.7 |
| **16** | F |  | 150 | 210x | 106 | 2.6 | 4.2 |

(4.2) while lowering PSA (106) relative to compound **13**.

**Table 2.** Adjusting PSA through modification of aryl sulfonamide[a]

[a]Het = heterocycle; Nav1.7 and $Na_v1.5$ *in vitro* activity measured by PatchXpress®[23] protocols; $Na_v1.5$ sel = selectivity against $Na_v1.5$; PSA = polar surface area; LLE = lipophilic ligand efficiency.

| Cmpd | ΔpKa | PSA | $P_{app}$ (x$10^{-6}$ cm/sec) | F (%) | $CL_{u,p}$ (mL/min/kg) | $T_{1/2}$ (h) |
|---|---|---|---|---|---|---|
| **13** | 5.4 | 119 | < 2 | 2 | 360 | 0.8 |
| **16** | 3.6 | 106 | 2.5 | 30 | 300 | 1.9 |

**Table 3.** Physicochemical and rat pharmacokinetic properties of **13** and **16**[a]

[a]ΔpKa = pKa difference between conjugate acid of tetrahydroisoquinoline (8.9) and aryl sulfonamide; PSA = polar surface area; $P_{app}$ = permeability coefficient; $CL_{u,p}$ = unbound clearance; $T_{1/2}$ = half-life.

Further inspection of the properties of benzoxazolinone **16** revealed that the 2-fluoropyridyl sulfonamide exhibited lower acidity (pKa = 5.3) than the thiadiazole sulfonamide of exemplar **13** (pKa = 3.5), thus reducing the relative zwitterionic character (ΔpKa) of the compound (Table 3). Gratifyingly, the oral bioavailability of **16** in rat was 30% (10 mpk po dose), constituting a significant improvement over benzoxazolinone **13**. Surprisingly, despite the reduction in PSA and zwitterionic character, compound **16** featured a $P_{app}$ of only 2.5 x $10^{-6}$ cm/sec. With high permeability not required for oral bioavailability, this suggested that active transport may have been a driving factor in the observed oral exposure. Notably, compound **16** also featured improvements in unbound clearance and half-life in comparison to exemplar **13**.

In an effort to more effectively balance $Na_v1.7$ activity, selectivity and desirable pharmacokinetic properties, the structure-activity relationships of the *N*-benzoxazolinone substituent were re-examined with the 6-fluoropyridyl sulfonamide in place. This culminated in the discovery of benzylamine **17** (Figure 4a), which featured four-fold improvements in $Na_v1.7$ activity ($IC_{50}$ = 39 nM) and selectivity against $Na_v1.5$ (850x) in relation to compound **16**. Furthermore, benzoxazolinone **17** exhibited reduced unbound clearance ($CL_{u,p}$ = 170 mL/min/kg; $f_u$ (rat) = 0.133), an extended half-life ($T_{1/2}$ = 3 h) and 50% oral bioavailability in rat, which may be attributed to a slight improvement in permeability ($P_{app}$ = 4 x 10-6 cm/sec). Importantly, following oral administration, **17** demonstrated robust *in vivo* efficacy in the mouse formalin paw test with a Phase 2 interval $IC_{50}$ of 7.4 µM (Figure 4b,c). The corresponding unbound drug level ($IC_{50,u}$ = 1.1 µM; $f_u$ (mouse) = 0.145) is 100-fold above the mouse PX potency ($IC_{50}$ = 11 nM) and thereby comparable to the *in vitro/in vivo* relationship of **13**.

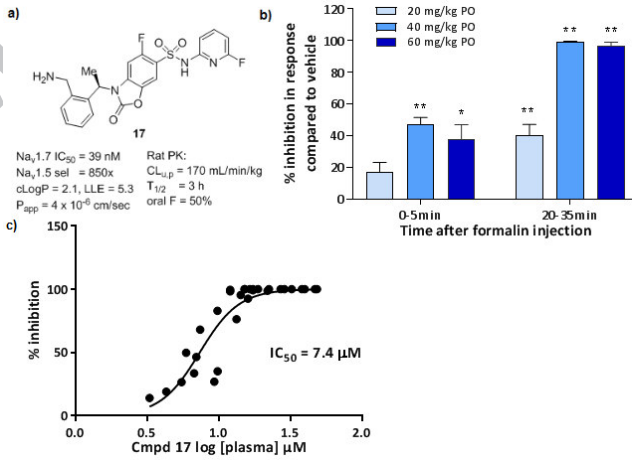



**Figure 4.** (a) Profile of compound **17**. (b) %Inhibition (* P< 0.05, ** P<0.01) of formalin-induced nociceptive behavior compared to vehicle-treated mice after oral (po) administration (20/40/60 mpk, 60 min pre-treatment time) of **17**. (c) Phase 2 exposure-response ($IC_{50}$ = 7.4 µM) of **17**.

In summary, novel, conformationally-restricted aryl sulfonamides have been discovered with high potency against $Na_v1.7$ and excellent pharmacological selectivity against $Na_v1.5$. Initial SAR investigations unearthed two distinct potency enhancers which, when combined, led to compound **13** with outstanding lipophilic ligand efficiency, exquisite selectivity against $Na_v1.5$, limited CNS penetration and dose-dependent *in vivo* efficacy. Tractability with respect to improving oral bioavailability was established with relatively minor structural modification, leading to exemplar **17** (F = 50% in rat) which exhibited comparable potency, selectivity and *in vivo* activity relative to benzoxazolinone **13**. Efforts to leverage these small

molecules to further probe the viability of $Na_v1.7$ as a pain target for drug discovery remain in progress.

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**A. Supplementary data**

Supplementary data associated with this article can be found in the online version, at http://xxx

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