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1,2,4-Triazolsulfone: A novel isosteric replacement of acylsulfonamides in the context of $Na_V1.7$ inhibition

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ABSTRACT

Recently, the identification of several classes of aryl sulfonamides and acyl sulfonamides that potently inhibit $Na_V1.7$ and demonstrate high levels of selectivity over other Na_V isoforms have been reported. The fully ionizable nature of these inhibitors has been shown to be an important part of the pharmacophore for the observed potency and isoform selectivity. The requirement of this functionality, however, has presented challenges associated with optimization toward inhibitors with drug-like properties and minimal off-target activity. In an effort to obviate these challenges, we set out to develop an orally bioavailable, selective $Na_V1.7$ inhibitor, lacking these acidic functional groups. Herein, we report the discovery of a novel series of inhibitors wherein a triazolesulfone has been designed to serve as a bioisostere for the acyl sulfonamide. This work culminated in the delivery of a potent series of inhibitors which demonstrated good levels of selectivity over $Na_V1.5$ and favorable pharmacokinetics in rodents.

The voltage-gated sodium channel $Na_V1.7$, which serves as a primary driver of action potential firing and neuronal excitability in nociceptors, has received considerable attention for its involvement in the pain processing pathway.[1] Genetic evidence supports the role of $Na_v1.7$ in a range of inherited chronic pain syndromes and as such, selective inhibition of $Na_v1.7$ represents a potential method for the management of pain.[2] Within this area, two classes of inhibitors that have recently garnered significant interest are aryl sulfonamides (*i.e.*, **1**)[3] and acyl sulfonamides (*i.e.*, **2**)[4] (Fig. 1). Both classes of compounds were initially reported by Pfizer and have since been investigated by numerous groups,[5] including our own. These classes of inhibitors represented a breakthrough in the field as they exhibited very high levels of selectivity over many of the related Na_V isoforms, most importantly $Na_V1.5$, as inhibition of this isoform has been tied to cardiotoxicities associated with elongation of the QRS interval.[6] A key pharmacophore associated with these inhibitors is the presence of an acidic functionality that can be fully ionized at physiological pH. Studies have shown that this moiety engages two arginine residues within VSD4 $Na_V1.7$ while a portion of the lipophilic "tail" resides within the lipid bilayer[7] and is also key to the observed inhibition.

Recently, we published several reports detailing our own efforts within this area. Representative compounds from this work are illustrated in Fig. 1 (**3**[8] and **4**[9]). In light of some of the challenges that we encountered in the course of optimizing these series of inhibitors, notably transporter-mediated clearance and numerous metabolic liabilities,[10] we sought to identify alternative warheads to engage the aforementioned arginine residues within $Na_V1.7$.

We initiated these efforts by replacing the acyl sulfonamide moiety in **2** with a number of functional groups commonly employed as bioisosteres for the acyl sulfonamide and/or carboxylic acid functionality. Table 1 illustrates a subset of the bioisosteres that were evaluated. Despite their ionic character, none of these compounds demonstrated an appreciable level of $Na_V1.7$ inhibition.

In light of the lack of potency observed with the compounds shown in Table 1, we set out to design a novel bioisostere for the

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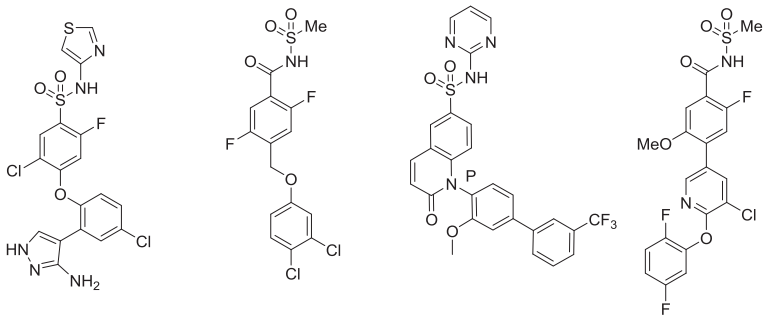


1 (PF-05089771)
$hNa_V1.7$ IC_{50}: 0.203 μM[a]
$hNa_V1.5$ IC_{50}: >30.0 μM[b]
pK_a 5.9[c]

2
$hNa_V1.7$ IC_{50}: 0.076 μM[a]
$hNa_V1.5$ IC_{50}: 11.0 μM[b]
pK_a 3.1[c]

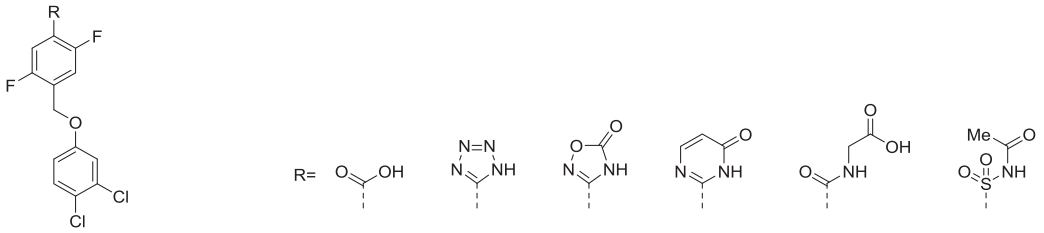
3 (AM-0466)
$hNa_V1.7$ IC_{50}: 0.021 μM[a]
$hNa_V1.5$ IC_{50}: >30.0 μM[b]
pK_a 5.5[c]

4
$hNa_V1.7$ IC_{50}: 0.094 μM[a]
$hNa_V1.5$ IC_{50}: 6.89 μM[b]
pK_a 3.3[c]

[a]$Na_V1.7$ data were collected using a PatchXpress automated electrophysiology platform using a protocol where cells were held at a voltage yielding 20-50% channel inactivation. [b]$Na_V1.5$ data were collected on the same platform using a protocol where cells were held at -50 mV and briefly stepped to -120 mV. [c]Determined by Analiza.

Fig. 1. Reported selective $Na_V1.7$ inhibitors. [a]$Na_V1.7$ data were collected using a PatchXpress automated electrophysiology platform using a protocol where cells were held at a voltage yielding 20–50% channel inactivation. [b]$Na_V1.5$ data were collected on the same platform using a protocol where cells were held at −50 mV and briefly stepped to −120 mV. [c]Determined by Analiza.

Table 1
Bioisosteres evaluated to replace the acyl sulfonamide in **2**.



Compounds	5	6	7	8	9	10
$Na_V1.7$ inhibition @ 5μM[a]	4%	4%	4%	6%	5%	13%
pK_a[b]	3.1	NA[c]	4.3	NA[c]	3.4	3.7

[a] $Na_V1.7$ Inhibition @ 5 μM using a PatchXpress automated electrophysiology platform using a protocol where cells were held at a voltage yielding 20–50% channel inactivation.
[b] Determined by Analiza.
[c] Out of range (p*H* range 1.7–11.2).

acyl sulfonamide. Fig. 2a illustrates the global energy minimum for an acyl sulfonamide. This conformation is such that the three hydrogen bond acceptors—one from the lone pair of electrons on the acyl sulfonamide, one from a carbonyl of the sulfonamide and one from the negatively charged nitrogen—are aligned in a single plane that is distorted to the appended aromatic ring.

Utilizing this as a starting point, we hypothesized that the incorporation of a methyl sulfone onto an appropriate heterocycle could provide a scaffold capable of exhibiting the common pharmacophore described above. Specifically, it was envisioned that a 3-(methylsulfonyl)-1,2,4-triazole would satisfy these requirements (Fig. 2b). To test this hypothesis, triazolesulfone **11** was prepared. The experimental pK_a (4.8) aligned well with the calculated value[11] and when evaluated, the compound demonstrated an encouraging level of $Na_V1.7$ potency (IC_{50} = 4.3 μM). Having successfully demonstrated the utility of the 3-(methylsulfonyl)-1,2,4-triazole-moiety, our focus shifted toward improving the potency of inhibitors containing this central core. To expedite these efforts, we embarked on several strategies that would rely heavily on parallel synthesis and thereby enable the rapid generation of SAR. One approach involved the Suzuki coupling of 3-bromo-5-(methylsulfonyl)-4*H*-1,2,4-triazole with a number of commercially available boronic acids/esters (Scheme 1). Both the preparation and subsequent purification were done using automated technologies, hence enabling the rapid preparation of 74 compounds. While a large percentage of the compounds prepared did not show appreciable inhibition of $Na_V1.7$ (<5% at 5 μM), a small set of weakly potent compounds were identified.[12] One of these compounds was **14**, which showed very weak inhibition of $Na_V1.7$ and was hence utilized as a starting point for subsequent efforts. Leveraging SAR generated in the exploration of an alternative biaryl core (*vide infra*), **14** was advanced to a modestly potent compound **15.** While this strategy allowed for the efficient and rapid generation of SAR, the compounds derived from this approach were deprioritized to focus on leads identified in an alternative approach outlined below.

An alternative chemistry approach was investigated, while increasing the diversity of the central ring to which the triazolesulfone was appended. This work was inspired by our earlier efforts which revealed that subtle changes about the central ring