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# Subtype-selective Na<sub>v</sub>1.8 sodium channel blockers: Identification of potent, orally active nicotinamide derivatives

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# ABSTRACT

A series of aryl-substituted nicotinamide derivatives with selective inhibitory activity against the Na<sub>v</sub>1.8 sodium channel is reported. Replacement of the furan nucleus and homologation of the anilide linker in subtype-selective blocker A-803467 (1) provided potent, selective derivatives with improved aqueous solubility and oral bioavailability. Representative compounds from this series displayed efficacy in rat models of inflammatory and neuropathic pain.

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Voltage-gated sodium (Nav1.x) channels are heteromeric transmembrane protein complexes which open in response to changes in membrane potential to enable selective permeability for sodium ions.<sup>1</sup> The Na<sub>v</sub>1.x channels are critical for the initiation and propagation of action potentials in primary sensory neurons<sup>2</sup>; in both the peripheral and central nervous systems, they play a central role in pain signaling.<sup>3</sup> The nine known sodium channel isoforms can be distinguished pharmacologically on the basis of their sensitivity to blockade by natural toxins, particularly tetrodotoxin (TTx).<sup>4</sup> Nociceptive neurons express a number of voltage-gated sodium channel subtypes (Na<sub>v</sub>1.3, Na<sub>v</sub>1.7, Na<sub>v</sub>1.8, Na<sub>v</sub>1.9) that may contribute to the ectopic hyperexcitability characteristic of chronic pain states.<sup>5</sup> Consistent with this hypothesis, nonselective blockade of sodium channels contributes to the analgesic activity of a number of clinically used agents, including mexiletine, lamotrigine, and carbamazepine. Unfortunately, the utility of these drugs is limited by their relatively narrow therapeutic index versus CNS and cardiovascular adverse events.<sup>6</sup> Subtype-selective small molecule Nav1.x channel blockers have the potential to deliver the therapeutic efficacy of their nonselective counterparts with a concomitant

We recently have described the discovery of A-803467 (1, Fig. 1), an isoform-selective inhibitor of the TTx-resistant (TTx-r) sodium channel Na<sub>v</sub>1.8, that is efficacious in a variety of preclinical pain models.<sup>8,9</sup> This 5-aryl furfuranilide derivative potently blocks recombinant human Na<sub>v</sub>1.8 (IC<sub>50</sub> 8 nM) under conditions (-40 mV) where the channels reside at half-maximal inactivation.<sup>10</sup> Comparable electrophysiology protocols run against other subtypes (Na<sub>v</sub>1.2, Na<sub>v</sub>1.3 and Na<sub>v</sub>1.5) demonstrated a selectivity ratio of 100- to 1000-fold for **1**. In dissociated dorsal root ganglion (DRG) neurons from rats, **1** displays a modest right-shift (IC<sub>50</sub> 125 nM) in its inhibitory potency against native TTx-resistant currents. Although dose-dependent attenuation of mechanical allodynia was observed in neuropathic pain models with **1** upon intraperitoneal (ip) administration, the poor oral bioavailability



Figure 1. Expansion of the furfuramide SAR for Nav1.8.

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amelioration of side effects, and are therefore an attractive class of therapeutic agents for the treatment of pain.<sup>7</sup>

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(~10%) of this compound, a result of limited aqueous solubility (<0.1  $\mu$ g/mL) and metabolic susceptibility (CL<sub>int</sub> 140  $\mu$ L/min/mg, rat microsomes), precluded its further development. Therefore, attention was directed toward the development of agents with enhanced physicochemical and pharmacokinetic properties. Herein, we disclose the in vitro and in vivo profiles of selective, orally-efficacious nicotinamide-derived Na<sub>v</sub>1.8 blockers.

It was anticipated that replacement of the furan nucleus in **1** with less oxidatively labile nitrogen-containing heterocyclic moieties (e.g., **2**) would offer an incremental improvement in aqueous solubility, and potentially, in systemic exposure (Fig. 1). To this end, a collection of five- and six-membered ring analogs could be readily fashioned from known or commercially available bromoester building blocks **3** (Scheme 1).<sup>11</sup> Cross-coupling of these activated precursors with commercially available arylboronic acids under standard Suzuki–Miyaura conditions<sup>12</sup> afforded aryl esters **4**, which were saponified subsequently to give the corresponding carboxylic acids **5**. Activated ester coupling using EDCI and 3,5dimethylaniline, a fragment which produced optimal Na<sub>v</sub>1.8 in vitro potency in the furfuramide series,<sup>10</sup> generated the desired anilides **6–18**.

Relative to 2,5-furfuramide 6 (Table 1), the oxazole 7 possessed essentially equipotent activity in recombinant mouse Nav1.8 (isotopic flux assay), but was considerably less active when characterized electrophysiologically in recombinant human and native rat Na<sub>v</sub>1.8.<sup>10,13</sup> Five-membered oxygen-containing heterocycles wherein the aryl and carboxamide residues are spaced by a nitrogen atom, as in regioisomeric oxazole 8 and 1,2,4-oxadiazole 9, also were less potent across species. Interestingly, structurally complementary sulfur analogs such as 2-aryl thiazole 10 and 5-aryl-1,2,4-thiadiazole **11** restored significant potency at mouse and human Na<sub>v</sub>1.8, although both were characterized by unacceptably low microsomal stability (CL<sub>int</sub> >300 µL/min/mg, rat and human). In accord with the observations with 10 and 11, the isosteric six-membered ring heterocyclic core variants, pyrazine (12) and 2,6-pyridine (13), displayed favorable hNa<sub>v</sub>1.8 inhibitory profiles (IC<sub>50</sub> <100 nM), as did the 3,5-pyridine isomer 14. Interestingly, the corresponding 4,6pyridine 15 was markedly less active at both mouse and human Na<sub>v</sub>1.8 than its regioisomeric cohorts. The greater basicity of pyridine relative to pyrazine, and the qualitatively improved kinetic aqueous solubility of 14 versus 13 prompted the evaluation of additional related 3,5-pyridine derivatives (16-18). Among these, the 4-cyano (16) and 4-chloro (18) congeners offered in vitro po-



**Scheme 1.** Reagents and conditions: (a) arylboronic acid, PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, Na<sub>2</sub>CO<sub>3</sub>, *i*-PrOH, reflux; (b) LiOH, aq dioxane, 23 °C; (c) 3,5-dimethylaniline, EDCI, Et<sub>3</sub>N, DMF, 23 °C.

#### Table 1

In vitro structure-activity relationships for 3,5-dimethylanilide derivatives

п

| Compd | R                | Ar       | mNa <sub>v</sub> 1.8<br>IC <sub>50</sub> (μM) | hNa <sub>v</sub> 1.8<br>IC <sub>50</sub> <sup>a</sup> (μM) | TTx-r<br>IC <sub>50</sub> <sup>a</sup> (µM) |  |
|-------|------------------|----------|-----------------------------------------------|------------------------------------------------------------|---------------------------------------------|--|
| 6     | OCF <sub>3</sub> |          | 0.29                                          | 0.002                                                      | 0.13                                        |  |
| 7     | OCF <sub>3</sub> | ₹<br>N₹  | 0.34                                          | 0.28                                                       | 0.95                                        |  |
| 8     | OCF <sub>3</sub> |          | 1.4                                           | 0.18                                                       | 2.0*                                        |  |
| 9     | OCF <sub>3</sub> | ξ<br>N−O | 0.87                                          | 0.47                                                       | 0.82                                        |  |
| 10    | OCF <sub>3</sub> | N<br>S   | 0.40                                          | 0.051                                                      | 0.38                                        |  |
| 11    | OCF <sub>3</sub> | N<br>S-N | 0.28                                          | 0.008                                                      | 0.52                                        |  |
| 12    | OCF <sub>3</sub> | N Star   | 0.057                                         | 0.021                                                      | 0.034                                       |  |
| 13    | OCF <sub>3</sub> | N Start  | 1.5                                           | 0.064                                                      | 0.51                                        |  |
| 14    | OCF <sub>3</sub> | N        | 0.53                                          | 0.026                                                      | 0.097                                       |  |
| 15    | OCF <sub>3</sub> | N N      | 11                                            | 0.78                                                       | ND                                          |  |
| 16    | CN               | N        | 0.19                                          | 0.023                                                      | 0.091                                       |  |
| 17    | F                | N N      | 1.9                                           | 0.10                                                       | 0.21                                        |  |
| 18    | Cl               |          | 0.61                                          | 0.009                                                      | 0.087                                       |  |

ND = not determined.

<sup>a</sup> Estimated IC<sub>50</sub> values from electrophysiology data generated at multiple testing concentrations (see note 13; a description of \* values is included).

tency comparable to **6**. All of the anilide derivatives in Table 1 possessed selectivity versus  $Na_v 1.2$  and the hERG channel in the range of 30- to 300-fold (data not shown).

With the 3,5-pyridine scaffold established as a more tractable starting point than the 2,5-furan motif, improvements in solubility-limited oral absorption were required to enable the broad in vivo characterization necessary for clinical development. To reduce the crystallinity imparted by the highly planar biaryl anilide system and refine the physicochemical properties of the chemotype, an extensive survey of one-carbon homologated amide substituents was undertaken, employing 5-(4-chlorophenyl)nicotinic acid (**19**) as a starting material (Scheme 2).

For elaboration of the amide, a diverse array of substituted benzylic amines (**20**) and picolinamines (**21**) were chosen from commercial sources. Because the presence of a basic nitrogen in **21** was a particularly attractive design element, a number of these heteroatom-substituted (R = N- and *O*-containing functionality) picolinamine building blocks were fashioned from substituted 2chloro-3-cyano pyridines via a known nucleophilic addition, nitrile reduction sequence.<sup>14</sup> Coupling of the two fragments was accomplished either with BOP reagent<sup>15</sup> or via the intermediacy of the



**Scheme 2.** Reagents and conditions: (a) BOP reagent,  $Et_3N$ ,  $CH_2Cl_2$ , 23 °C; (b) **19**, (COCl)<sub>2</sub>, cat. DMF,  $CH_2Cl_2$ , 23 °C; (c) **20** or **21**,  $Et_3N$ ,  $CH_2Cl_2$ , 23 °C.

acid chloride, with the latter proving more practical for gram-scale syntheses.

As shown in Table 2, several substituted benzyl (22-26) and 3picolinyl (27-33) carboxamides were potent and subtype-selective Nav1.8 blockers. This finding stands in contrast to the SAR generated for the fufuramides, wherein aniline derivatives delivered optimal activity.<sup>10</sup> The potent benzyl amide **22** possessed an attractive profile with 22 nM hNav1.8 potency and 86-fold selectivity versus Nav1.2 (electrophysiology characterization in recombinant human cell line). Introduction of an ortho-methyl group on the benzylic residue  $(22 \rightarrow 23)$  provided a 10-fold boost in Na<sub>v</sub>1.8 activity across species. Comparable increases in potency at mouse and human Nav1.8 were also observed for the corresponding chloro analog 24, which showed a Nav1.2 selectivity profile superior to that of 23. Target potency was also enhanced for piperidine and morpholine derivatives 25 and 26, respectively, albeit with a concomitant erosion in selectivity at Nav1.2. The unsubstituted 3picoline analog 27 had greatly enhanced aqueous solubility, but was a markedly less efficient Nav1.8 blocker; the regioisomeric 2and 4-picolines were essentially inactive (Na<sub>v</sub>1.8 IC<sub>50</sub> >30  $\mu$ M, data not shown). With **27**, introduction of a 2-methyl group (**28**) had negligible impact on in vitro activity, though potency was restored to some degree with ortho-chloro substitution (29). Encouraged by the results with 29, it was discovered that heteroatom appendages containing oxygen (30 and 31) or nitrogen (32 and 33) restored potency and selectivity levels observed with 23, while affording a significant enhancement in solubility (e.g., 28 µg/mL for piperidine

### Table 2

In vitro structure-activity relationships for amide substitution<sup>a</sup>

O R N X

**32**). Unfortunately, Na<sub>v</sub>1.2 selectivity was eroded in **32** and **33**. Morpholine functionality provided still greater aqueous solubility (>50  $\mu$ g/mL for **33**), but reduced hNa<sub>v</sub>1.8 inhibitory potency approximately 6-fold compared with **32**. We also examined the effects of halogenation of the central nicotinamide core and embellishment of the flanking picolinamide residue at various locations with additional sterically unencumbered (one-carbon appendages); a detailed discussion of these structure–activity relation-ships will be the subject of a subsequent publication.

The potency, selectivity, pharmacokinetic profiles, and analgesic effects of two representative 3-nicotinamide derived  $Na_v 1.8$  blockers (**16** and **31**) are summarized in Table 3. Consistent with their improved metabolic stability in rat microsomes and improved aqueous solubility relative to the furfuramides, **16** and **31** were more orally bioavailable and provided plasma concentrations that were multiple-fold above their respective in vitro  $IC_{50}$  values (3 mg/kg dose). These derivatives were further characterized by uniformly high levels of serum protein binding (>97%) and appreciable CNS penetration. Both displayed dose-dependent attenuation of mechanical allodynia in the L5/L6 spinal nerve ligation

| Table 3   |                  |        |      |                       |       |          |
|-----------|------------------|--------|------|-----------------------|-------|----------|
| In vitro, | pharmacokinetic, | and in | vivo | profiles <sup>a</sup> | of 16 | 5 and 31 |

|                                                         | 16       | 31         |
|---------------------------------------------------------|----------|------------|
| hNa <sub>v</sub> 1.8 IC <sub>50</sub> (μM)              | 0.023    | 0.003      |
| Rat TTx-r IC <sub>50</sub> (µM)                         | 0.091    | 0.028      |
| hNa <sub>v</sub> 1.2 IC <sub>50</sub> (μM)              | 3.4      | 2.8        |
| hNa <sub>v</sub> 1.5 IC <sub>50</sub> (μM) <sup>b</sup> | >30      | 4.7        |
| hERG IC <sub>50</sub> ( $\mu$ M) <sup>c</sup>           | 16       | 19         |
| CL <sub>int</sub> , (µL/min/mg) <sup>d</sup>            | 270      | 68         |
| Aq solubility (µg/mL)                                   | 1.4      | 3.1        |
| F, po, 3 mg/kg (%) <sup>e</sup>                         | 17       | 95         |
| $C_{\rm max}$ (µg/mL)                                   | 0.74     | 0.35       |
| CLp (L/(h kg))                                          | 1.0      | 0.6        |
| V <sub>ss</sub> (L/kg)                                  | 0.5      | 2.0        |
| Brain/plasma                                            | 1.3      | 1.0        |
| Plasma protein binding, rat (%)                         | 99.5     | 98.7       |
| Chung ED <sub>50</sub> , (mg/kg) [% effect, max]        | 72 [60%] | 65 [66%]   |
| Cerep (>70 @ 10 µM) <sup>e</sup>                        | BZD      | Cl channel |

<sup>a</sup> Values shown for n = 6 per dose group.

<sup>b</sup> Estimated IC<sub>50</sub> values from electrophysiology data generated at multiple testing concentrations (see note 13).

<sup>c</sup> hERG flux assay determination (see Ref. 10).

<sup>d</sup> Incubation with rat microsomes (1 h, 37 °C).

<sup>e</sup> Determined in rats (n = 6).

| N 💝   |    |                                  |                                                  |                                                               |                                                |                                                               |
|-------|----|----------------------------------|--------------------------------------------------|---------------------------------------------------------------|------------------------------------------------|---------------------------------------------------------------|
| Compd | Х  | R                                | mNa <sub>v</sub> 1.8 IC <sub>50</sub> ( $\mu$ M) | hNa <sub>v</sub> 1.8 IC <sub>50</sub> <sup>a</sup> ( $\mu$ M) | TTx-r IC <sub>50</sub> <sup>a</sup> ( $\mu$ M) | hNa <sub>v</sub> 1.2 IC <sub>50</sub> <sup>a</sup> ( $\mu$ M) |
| 22    | СН | Н                                | 0.62                                             | 0.022                                                         | 0.085                                          | 1.9                                                           |
| 23    | CH | Me                               | <0.030 <sup>b</sup>                              | 0.002                                                         | 0.009                                          | 0.11                                                          |
| 24    | CH | Cl                               | 0.081                                            | 0.004                                                         | 0.066                                          | 1.2                                                           |
| 25    | CH | N-Piperidinyl                    | <0.030 <sup>b</sup>                              | 0.008*                                                        | 0.045                                          | 0.050                                                         |
| 26    | CH | N-Morpholino                     | 0.032                                            | 0.010                                                         | 0.130                                          | 0.12*                                                         |
| 27    | Ν  | Н                                | 7.9                                              | ND                                                            | ND                                             | ND                                                            |
| 28    | Ν  | Me                               | 2.6                                              | ND                                                            | ND                                             | ND                                                            |
| 29    | Ν  | Cl                               | 0.68                                             | 0.14                                                          | 0.56                                           | 18 <sup>°</sup>                                               |
| 30    | Ν  | OEt                              | 0.088                                            | 0.007                                                         | 0.032                                          | $0.67^{*}$                                                    |
| 31    | Ν  | OCH <sub>2</sub> CF <sub>3</sub> | 0.087                                            | 0.003                                                         | 0.028                                          | 2.8                                                           |
| 32    | Ν  | N-Piperidinyl                    | 0.026                                            | 0.014                                                         | 0.008                                          | 0.070                                                         |
| 33    | Ν  | N-Morpholino                     | 0.34                                             | 0.087                                                         | 0.098                                          | 1.6                                                           |

ND = not determined.

<sup>a</sup> Estimated IC<sub>50</sub> values from electrophysiology data generated at multiple testing concentrations (see note 13; a description of \* values is included).

<sup>b</sup> An IC<sub>50</sub> value could not be calculated due to high potency.

(Chung) model<sup>16</sup> of neuropathic pain in the absence of discernable sedative effects. Compounds **16** and **31** also were tested against other channels and receptors expressed in peripheral sensory neurons, including TRPV1, P2X<sub>2/3</sub>, Ca<sub>v</sub>2.2 calcium channels, and KCNQ2/3 potassium channels; neither had significant activity at these channels (IC<sub>50</sub> >10  $\mu$ M). In addition, both showed minimal cross-reactivity upon evaluation (10  $\mu$ M) in a broad screening panel (*n* = 70) of cell-surface receptors, ion channels, and enzymes (CEREP, Poitiers, France).

In summary, we have identified a novel series of potent, selective, orally active pyridine-based blockers of the Nav1.8 sodium channel by expansion of the central core of our previously disclosed furan, A-803467 (1).8,10 The present SAR studies indicate that potency, confirmed at recombinant human Nav1.8 channels and in isolated rat DRG neurons using electrophysiological recordings, and selectivity (against hNav1.2 and hERG) can be modulated with core permutations and judicious choice of amine monomers for amide elaboration. The tolerability of a one-carbon homologation of the amide linkage set the stage for production of compounds with significantly enhanced physicochemical properties relative to their furfuramide predecessors. Oral administration of 16 and 31 produced dose-dependant reversal of allodynia in the spinal nerve ligation (Chung) model of neuropathic pain in rat. The results presented herein reinforce the hypothesis that selective pharmacological blockade of Nav1.8 can produce significant antinociceptive effects in animal models of pain while minimizing observed side-effects.

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