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Subtype-selective $Na_v1.8$ sodium channel blockers: Identification of potent, orally active nicotinamide derivatives

Michael E. Kort [a,*], Robert N. Atkinson [b], James B. Thomas [b], Irene Drizin [a], Matthew S. Johnson [b], Matthew A. Secrest [b], Robert J. Gregg [a], Marc J. C. Scanio [a], Lei Shi [a], Ahmed H. Hakeem [a], Mark A. Matulenko [a], Mark L. Chapman [b], Michael J. Krambis [b], Dong Liu [b], Char-Chang Shieh [a], XuFeng Zhang [a], Gricelda Simler [a], Joseph P. Mikusa [a], Chengmin Zhong [a], Shailen Joshi [a], Prisca Honore [a], Rosemarie Roeloffs [b], Stephen Werness [b], Brett Antonio [b], Kennan C. Marsh [a], Connie R. Faltynek [a], Douglas S. Krafte [b], Michael F. Jarvis [a], Brian E. Marron [b,*]

[a] Global Pharmaceutical Research and Development, Abbott Laboratories, 100 Abbott Park Road, Abbott Park, IL 60064-6100, USA
[b] Icagen, Inc., 4222 Emperor Blvd., Durham, NC 27703, USA

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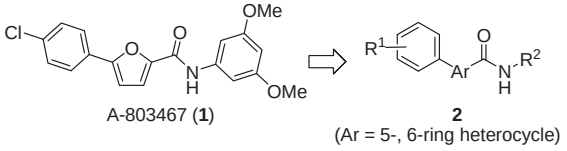
ABSTRACT

A series of aryl-substituted nicotinamide derivatives with selective inhibitory activity against the $Na_v1.8$ 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.

Voltage-gated sodium ($Na_v1.x$) channels are heteromeric transmembrane protein complexes which open in response to changes in membrane potential to enable selective permeability for sodium ions.[1] The $Na_v1.x$ channels are critical for the initiation and propagation of action potentials in primary sensory neurons[2]; in both the peripheral and central nervous systems, they play a central role in pain signaling.[3] The nine known sodium channel isoforms can be distinguished pharmacologically on the basis of their sensitivity to blockade by natural toxins, particularly tetrodotoxin (TTx).[4] Nociceptive neurons express a number of voltage-gated sodium channel subtypes ($Na_v1.3$, $Na_v1.7$, $Na_v1.8$, $Na_v1.9$) that may contribute to the ectopic hyperexcitability characteristic of chronic pain states.[5] 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.[6] Subtype-selective small molecule $Na_v1.x$ channel blockers have the potential to deliver the therapeutic efficacy of their nonselective counterparts with a concomitant amelioration of side effects, and are therefore an attractive class of therapeutic agents for the treatment of pain.[7]

We recently have described the discovery of A-803467 (**1**, Fig. 1), an isoform-selective inhibitor of the TTx-resistant (TTx-r) sodium channel $Na_v1.8$, that is efficacious in a variety of preclinical pain models.[8,9] This 5-aryl furfuranilide derivative potently blocks recombinant human $Na_v1.8$ (IC_{50} 8 nM) under conditions (−40 mV) where the channels reside at half-maximal inactivation.[10] Comparable electrophysiology protocols run against other subtypes ($Na_v1.2$, $Na_v1.3$ and $Na_v1.5$) 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_{50} 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



A-803467 (**1**) **2** (Ar = 5-, 6-ring heterocycle)

Figure 1. Expansion of the furfuramide SAR for $Na_v1.8$.

* Corresponding authors. Tel.: +1 847 935 4945 (M.E.K.).
E-mail addresses: michael.e.kort@abbott.com (M.E. Kort), bmarron@icagen.com (B.E. Marron).

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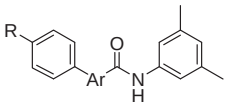
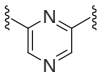
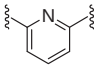
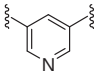
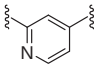
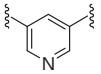
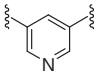
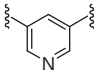
(~10%) of this compound, a result of limited aqueous solubility (<0.1 μg/mL) and metabolic susceptibility (CL_{int} 140 μL/min/mg, rat microsomes), precluded its further development. Therefore, attention was directed toward the development of agents with enhanced physicochemical and pharmacokinetic properties. Herein, we disclose the in vitro and in vivo profiles of selective, orally-efficacious nicotinamide-derived $Na_v1.8$ 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).[11] Cross-coupling of these activated precursors with commercially available arylboronic acids under standard Suzuki–Miyaura conditions[12] afforded aryl esters **4**, which were saponified subsequently to give the corresponding carboxylic acids **5**. Activated ester coupling using EDCI and 3,5-dimethylaniline, a fragment which produced optimal $Na_v1.8$ in vitro potency in the furfuramide series,[10] generated the desired anilides **6**–**18**.

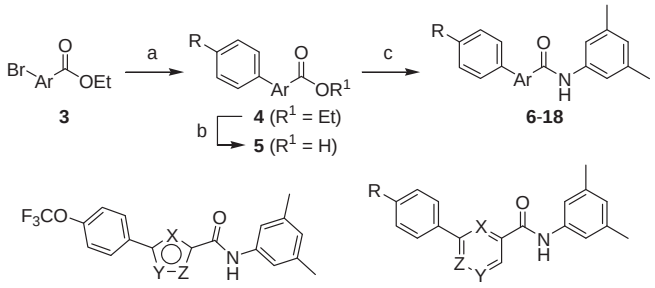
Relative to 2,5-furfuramide **6** (Table 1), the oxazole **7** possessed essentially equipotent activity in recombinant mouse $Na_v1.8$ (isotopic flux assay), but was considerably less active when characterized electrophysiologically in recombinant human and native rat $Na_v1.8$.[10,13] Five-membered 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 $Na_v1.8$, although both were characterized by unacceptably low microsomal stability (CL_{int} >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 $hNa_v1.8$ inhibitory profiles (IC_{50} <100 nM), as did the 3,5-pyridine isomer **14**. Interestingly, the corresponding 4,6-pyridine **15** was markedly less active at both mouse and human $Na_v1.8$ 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 potency comparable to **6**. All of the anilide derivatives in Table 1 possessed selectivity versus $Na_v1.2$ and the hERG channel in the range of 30- to 300-fold (data not shown).

Table 1
In vitro structure–activity relationships for 3,5-dimethylanilide derivatives



Compd	R	Ar	$mNa_v1.8$ IC_{50} (μM)	$hNa_v1.8$ IC_{50}[a] (μM)	TTx-r IC_{50}[a] (μM)
6	OCF_3		0.29	0.002	0.13
7	OCF_3		0.34	0.28	0.95
8	OCF_3		1.4	0.18	2.0*
9	OCF_3		0.87	0.47	0.82
10	OCF_3		0.40	0.051	0.38
11	OCF_3		0.28	0.008	0.52
12	OCF_3		0.057	0.021	0.034
13	OCF_3		1.5	0.064	0.51
14	OCF_3		0.53	0.026	0.097
15	OCF_3		11	0.78	ND
16	CN		0.19	0.023	0.091
17	F		1.9	0.10	0.21
18	Cl		0.61	0.009	0.087

ND = not determined.
[a] Estimated IC_{50} values from electrophysiology data generated at multiple testing concentrations (see note 13; a description of * values is included).



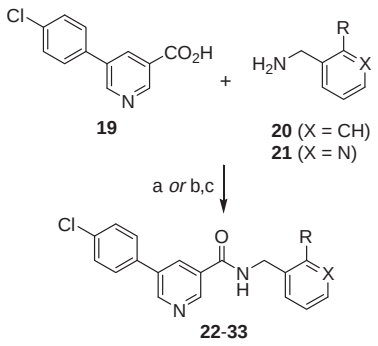
Cmpd	X	Y	Z
6	O	CH	CH
7	O	N	CH
8	N	O	CH
9	N	N	O
10	N	S	CH
11	N	S	N

Cmpd	R	X	Y	Z
12	OCF_3	N	N	CH
13	OCF_3	N	CH	CH
14	OCF_3	CH	N	CH
15	OCF_3	CH	CH	N
16	CN	CH	N	CH
17	F	CH	N	CH
18	Cl	CH	N	CH

Scheme 1. Reagents and conditions: (a) arylboronic acid, $PdCl_2(PPh_3)_2$, Na_2CO_3, *i*-PrOH, reflux; (b) LiOH, aq dioxane, 23 °C; (c) 3,5-dimethylaniline, EDCI, Et_3N, DMF, 23 °C.

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 2-chloro-3-cyano pyridines via a known nucleophilic addition, nitrile reduction sequence.[14] Coupling of the two fragments was accomplished either with BOP reagent[15] or via the intermediacy of the



Scheme 2. Reagents and conditions: (a) BOP reagent, Et_3N, CH_2Cl_2, 23 °C; (b) **19**, $(COCl)_2$, 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 3-picolinyl (**27**–**33**) carboxamides were potent and subtype-selective $Na_v1.8$ blockers. This finding stands in contrast to the SAR generated for the fufuramides, wherein aniline derivatives delivered optimal activity.[10] The potent benzyl amide **22** possessed an attractive profile with 22 nM $hNa_v1.8$ potency and 86-fold selectivity versus $Na_v1.2$ (electrophysiology characterization in recombinant human cell line). Introduction of an *ortho*-methyl group on the benzylic residue (**22**→**23**) provided a 10-fold boost in $Na_v1.8$ activity across species. Comparable increases in potency at mouse and human $Na_v1.8$ were also observed for the corresponding chloro analog **24**, which showed a $Na_v1.2$ 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 $Na_v1.2$. The unsubstituted 3-picoline analog **27** had greatly enhanced aqueous solubility, but was a markedly less efficient $Na_v1.8$ blocker; the regioisomeric 2- and 4-picolines were essentially inactive ($Na_v1.8$ IC_{50} >30 μM, 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 **32**). Unfortunately, $Na_v1.2$ selectivity was eroded in **32** and **33**. Morpholine functionality provided still greater aqueous solubility (>50 μg/mL for **33**), but reduced $hNa_v1.8$ 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 relationships will be the subject of a subsequent publication.

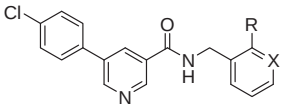
The potency, selectivity, pharmacokinetic profiles, and analgesic effects of two representative 3-nicotinamide derived $Na_v1.8$ blockers (**16** and **31**) are summarized in Table 3. Consistent with their improved metabolic stability in rat microsomes and improved aqueous solubility relative to the 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[a] of **16** and **31**

	16	**31**
$hNa_v1.8$ IC_{50} (μM)	0.023	0.003
Rat TTx-r IC_{50} (μM)	0.091	0.028
$hNa_v1.2$ IC_{50} (μM)	3.4	2.8
$hNa_v1.5$ IC_{50} (μM)[b]	>30	4.7
hERG IC_{50} (μM)[c]	16	19
CL_{int}, (μL/min/mg)[d]	270	68
Aq solubility (μg/mL)	1.4	3.1
F, po, 3 mg/kg (%)[e]	17	95
C_{max} (μg/mL)	0.74	0.35
CLp (L/(h kg))	1.0	0.6
V_{ss} (L/kg)	0.5	2.0
Brain/plasma	1.3	1.0
Plasma protein binding, rat (%)	99.5	98.7
Chung ED_{50}, (mg/kg) [% effect, max]	72 [60%]	65 [66%]
Cerep (>70 @ 10 μM)[e]	BZD	Cl channel

[a] Values shown for $n = 6$ per dose group.
[b] Estimated IC_{50} values from electrophysiology data generated at multiple testing concentrations (see note 13).
[c] hERG flux assay determination (see Ref. 10).
[d] Incubation with rat microsomes (1 h, 37 °C).
[e] Determined in rats ($n = 6$).

Table 2
In vitro structure–activity relationships for amide substitution[a]



Compd	X	R	$mNa_v1.8$ IC_{50} (μM)	$hNa_v1.8$ IC_{50}[a] (μM)	TTx-r IC_{50}[a] (μM)	$hNa_v1.2$ IC_{50}[a] (μM)
22	CH	H	0.62	0.022	0.085	1.9
23	CH	Me	<0.030[b]	0.002	0.009	0.11
24	CH	Cl	0.081	0.004	0.066	1.2
25	CH	*N*-Piperidinyl	<0.030[b]	0.008*	0.045	0.050
26	CH	*N*-Morpholino	0.032	0.010	0.130	0.12*
27	N	H	7.9	ND	ND	ND
28	N	Me	2.6	ND	ND	ND
29	N	Cl	0.68	0.14	0.56	18*
30	N	OEt	0.088	0.007	0.032	0.67*
31	N	OCH_2CF_3	0.087	0.003	0.028	2.8
32	N	*N*-Piperidinyl	0.026	0.014	0.008	0.070
33	N	*N*-Morpholino	0.34	0.087	0.098	1.6

ND = not determined.
[a] Estimated IC_{50} values from electrophysiology data generated at multiple testing concentrations (see note 13; a description of * values is included).
[b] An IC_{50} value could not be calculated due to high potency.

(Chung) model[16] 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, $P2X_{2/3}$, $Ca_v2.2$ calcium channels, and KCNQ2/3 potassium channels; neither had significant activity at these channels (IC_{50} >10 μM). In addition, both showed minimal cross-reactivity upon evaluation (10 μM) 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 $Na_v1.8$ 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 $Na_v1.8$ channels and in isolated rat DRG neurons using electrophysiological recordings, and selectivity (against $hNa_v1.2$ 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 $Na_v1.8$ can produce significant antinociceptive effects in animal models of pain while minimizing observed side-effects.

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13. For ease of comparison, the indicated IC_{50} values are estimates calculated from electrophysiology data (−40 mV for $Na_v1.8$ and TTx-r, −60 mV for $Na_v1.2$, −90 mV for $Na_v1.5$) obtained at multiple ($n = 2–5$) testing concentrations using the following equation: (tested concentration, μM) × [(100 − % inhibition)/(% inhibition)]. Inhibition values <20% and >80% were excluded from the calculation unless indicated otherwise (* in the Table).
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