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Discovery of potent furan piperazine sodium channel blockers for treatment of neuropathic pain

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ABSTRACT

The synthesis and pharmacological characterization of a novel furan-based class of voltage-gated sodium channel blockers is reported. Compounds were evaluated for their ability to block the tetrodotoxin-resistant sodium channel $Na_v1.8$ (PN3) as well as the $Na_v1.2$ and $Na_v1.5$ subtypes. Benchmark compounds from this series possessed enhanced potency, oral bioavailability, and robust efficacy in a rodent model of neuropathic pain, together with improved CNS and cardiovascular safety profiles compared to the clinically used sodium channel blockers mexiletine and lamotrigine.

1. Introduction

Chronic pain comprises a breadth of heterogeneous symptoms that can be characterized as inflammatory or neuropathic in nature. Neuropathic pain results from injury to the peripheral and/or central sensory pathways where the painful state exists without apparent noxious input, and is associated with hyperexcitability and spontaneous action potential firing in sensory neurons. Current treatment options do not provide adequate relief for many patients and a significant number of the agents used have dose-limiting side effects.[1,2]

Voltage-gated sodium channels (VGSCs) are critical modulators for the transduction of action potentials in tissues such as nerve and muscle.[3] Considerable medical and experimental evidence implicates abnormal sodium channel activity in the peripheral nervous system in the pathophysiology of chronic pain,[4] making them attractive molecular targets for therapeutic intervention.[5–7] Several therapeutic classes of drugs, including antiarrhythmics (e.g., mexiletine), anticonvulsants (e.g., lamotrigine), and local anesthetics (e.g., lidocaine), share the common mechanism of blocking VGSCs and some have been used clinically to treat neuropathic pain (Fig. 1).[8] These non-selective agents provide effective analgesia despite their relatively weak in vitro potency against sodium channel blockade, but possess a relatively narrow therapeutic index which limits their clinical utility.[9]

The VGSCs are a family of nine transmembrane proteins that control the flow of sodium ions across cell membranes.[10]

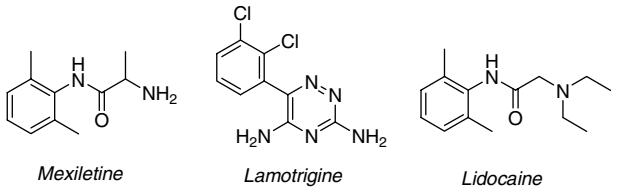

Figure 1. Clinically used sodium channel blockers.

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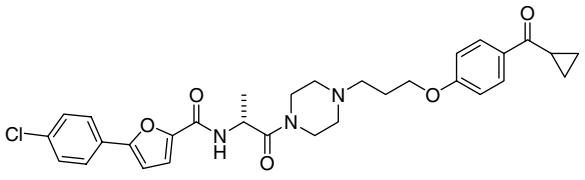
Susceptibility to blockade by natural toxins has been used to classify sodium channel currents in cells; the pufferfish toxin tetrodotoxin (TTx) is the most widely used of the toxins for classification.[11] Activation of tetrodotoxin-resistant sodium channels contributes to action potential electrogenesis in neurons. Among the sodium channel subtypes expressed in primary sensory neurons and dorsal root ganglia, $Na_v1.3$,[12] $Na_v1.7$ (PN1),[13] $Na_v1.8$ (PN3),[14,15] and $Na_v1.9$ (NAN)[16] present the best opportunities for pain therapeutics. In particular, the tetrodotoxin-resistant (TTx-r) subtype $Na_v1.8$ carries a major portion of the TTx-r current in peripheral nerves[17] and has been strongly implicated in pain transmission pathways.[18]

The objective of these efforts was to identify structurally novel, orally bioavailable sodium channel blockers with enhanced potency over existing agents such as lamotrigine and mexiletine. The furfuryl glycinamide derivative **1** (Fig. 2)[19,20] was identified as a hit from a focused screening strategy using an $Na_v1.8$ isotopic flux assay.[21] Herein we describe structure-activity relationships observed with this chemotype as they pertain to piperazine-based amides, and summarize the ability of representative analogs to block VGSCs and dose-dependently reduce neuropathic pain in an experimental rodent model.

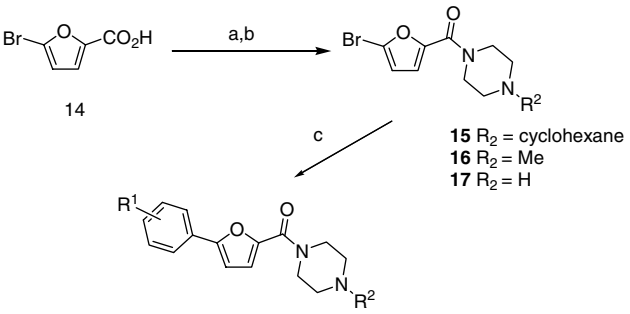
2. Chemistry

In our previous paper,[20] we disclosed potent and selective arylfuran amides with limited oral exposure. The relatively limited synthetic complexity of this family of structures facilitated the generation of a wide array of derivatives. The focus of the present work was directed toward molecules containing piperazine or piperazine-like moieties in efforts to improve the drug-like properties of this class of compounds. The commercially available 5-chlorophenyl-furoic acid **2** was transformed to amides **4**–**13** via the acid chloride intermediate **3** as shown in Scheme 1. Once a set of preferential amides was established, aromatic substitution at the 5-position of the furan carboxamides was examined. To this end,



1 $hNa_V1.8$ IC_{50} ~1 μM

Figure 2. Furan glycinamide screening hit.



18 R^1 = 4-OCF_3, R^2 = cyclohexane
19 R^1 = 4-*t*-butyl, R^2 = cyclohexane
20 R^1 = 4-NMe_2, R^2 = cyclohexane
21 R^1 =3- Cl, R^2 = cyclohexane
22 R^1=2,4-Cl, R^2 = cycloheaxane
23 R^1 = 4-phenoxy, R^2 = cyclohexane
24 R^1 =4-*o*-phenoxy, R^2 = Me
25 R^1 = 4-*t*-butyl, R^2 = Me
26 R^1 = 4-phenoxy, R^2 =H,
27 R^1 =4-*t*-butyl, R^2 = H

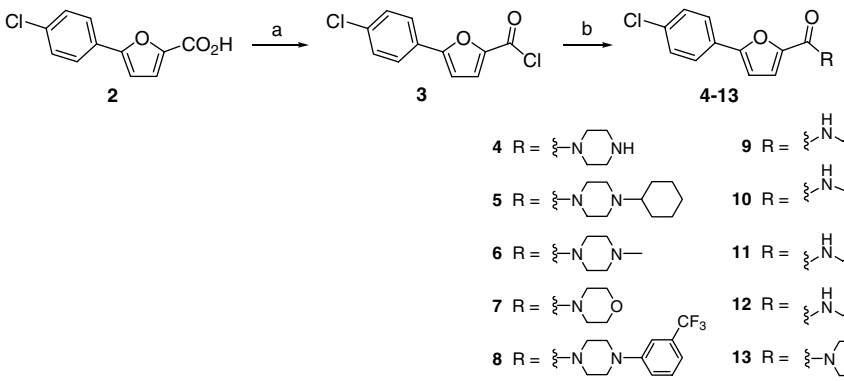
Scheme 2. Reagents and conditions: (a) $(COCl)_2$, cat. DMF, CH_2Cl_2, 23 °C; (b) amine, Et_3N, CH_2Cl_2, 23 °C; (c) arylboronic acid, $PdCl_2(PPh_3)_2$, aq Na_2CO_3, *i*-PrOH, reflux.

the 5-bromo-furoic acid **14** was converted to the amides (**15**–**17**) for subsequent Suzuki coupling to provide **18**–**27** (Scheme 2).

3. Results and discussion

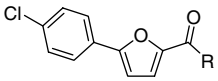
Compounds were evaluated for their ability to block the recombinant mouse $Na_v1.8$ sodium channel stably expressed in HEK293 cells, using an isotopic efflux assay.[21] The activity of potent blockers was confirmed subsequently using conventional voltage-clamp electrophysiology by measuring inhibition of TTx-r currents in dissociated rat DRG neurons and inhibition of sodium currents in HEK293 cells stably expressing recombinant human $Na_v1.8$. Selected analogs were also further examined for their selectivity versus $Na_v1.2$ and $Na_v1.5$ stably expressed in HEK293 cells. As sodium channel blockers bind preferentially to the inactivated states of the channel, electrophysiological protocols were designed to set the membrane potential to the midpoint of voltage-dependent steady-state inactivation (i.e., the voltage at which 50% of channels are inactivated) to allow a direct comparison of compound effects across channel subtypes.[19,20]

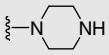
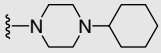
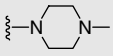
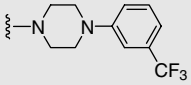
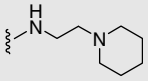
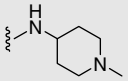
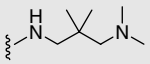
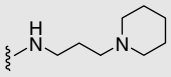
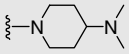
As indicated in Table 1, preliminary studies of the truncated analogs of **1** revealed that the piperazine moiety is an important part of the pharmacophore. Replacement of the basic nitrogen atom of **4** with oxygen (e.g., **7**) led to significant loss of activity in the mouse flux assay. Certain substituents at the terminus of the piperazine, such as cyclohexane, provided analogs (e.g., **5**) with submicromolar potency as assessed by both the native rat (DRG



Scheme 1. Reagents and conditions: (a) $(COCl)_2$, cat. DMF, CH_2Cl_2, 23 °C; (b) amine, Et_3N, CH_2Cl_2, 23 °C.

Table 1
SAR of amide variations



Compound	R	mNa$_v$1.8 IC$_{50}$[a] (μM)	Rat DRG TTx-r[b]		hNa$_v$1.8[b]	
			Conc (μM)	% Inhibition $V_{1/2}$[c]	Conc (μM)	% Inhibition $V_{1/2}$[c]
4		2.9	0.3	41 ± 2	0.3	55 ± 11
5		1.0	0.3	50 ± 5	0.3	58 ± 5
6		9.9	3	31 ± 3		
7		32				
8		14				
9		0.9	0.3	59 ± 8	0.1	29 ± 2
10		1.9	0.3	51 ± 19		
11		2.4	0.3	65 ± 9		
12		1.6	0.3	52 ± 6		
13		5.2				

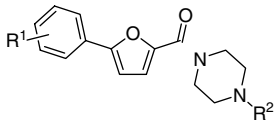
[a] IC$_{50}$ values were determined by least squares fitting of a logistic equation to data from full eight-point, half-log concentration response curves using an Na$_v$1.8 isotopic efflux assay as described in the experimental methods (mean of two to five separate determinations).
[b] Data shown with standard error (±SEM) represent the mean of two to six separate determinations.
[c] Inactivated state protocol: the pre-pulse voltage at which 50% of channels are inactivated ($V_{1/2}$ = −40 mV).[19]

TTx-r current) and recombinant (hNa$_v$1.8) assays. In contrast, substitution with a methyl group as in **6** led to diminished Na$_v$1.8 potency, a somewhat surprising observation given the activity of the unsubstituted piperazine **4**. Attachment of a variety of functionalized aryl groups, such as in **8**, also resulted in a dramatic loss in activity, possibly due to the reduced basicity of the piperazine nitrogen. To assess the effects of conformational rigidity and spacing between the nitrogen atoms, compounds **9**–**13** were prepared. Compounds **9**, **11**, and **12** displayed in vitro potency (DRG TTx-r IC$_{50}$ ⩽300 nM) comparable to **5**. These findings support the conclusion that a basic nitrogen enhances sodium channel activity for this chemotype. The positioning of the amide linkage and proximal basic nitrogen is not unimportant however as evidenced by the moderate decrease in activity of **13** relative to piperidine **10**, **5**, and the open-chain analogs.

Continued examination of the pharmacophore was focused on modifications of the C-5 substituent of the furan ring employing three piperazinyl amides. The results of this effort are summarized in Table 2. It was determined that the 4-Cl group could be replaced effectively by 4-*tert*-butyl, 4-OCF$_3$, and 4-phenoxy substituents, thereby providing a boost in potency for sodium channel block (hNa$_v$1.8 characterization) compared to **5**. The increase in potency was greater with cyclohexyl than with methyl or unsubstituted (R^2 = H) derivatives as exemplified by **19** and **23**, which possessed an estimated IC$_{50}$ potency of <30 nM at human Na$_v$1.8. Although difficult to rationalize at the molecular level, we speculate that the enhanced potency of these two derivatives arises from their increased lipophilicity relative to other examples, a property which, based on our work with a closely related series of molecules,[20] we believe to be important for interactions with hydrophobic regions of the Na$_v$1.8 channel. The compounds in Tables 1 and 2 demonstrated voltage-dependent sodium channel blockade since they did not have significant (>20%) current block (DRG TTx-r and hNa$_v$1.8) at voltages that set all channels to a resting state (data not shown).[22]

This new class of sodium channel blockers was surveyed for cross-reactivity with other sodium channels and compared with reference compounds as summarized in Table 3. Significantly, furan piperazines **4**, **5**, and **19** were 100- to 1000-fold more potent in blocking human Na$_v$1.8 channels compared to mexiletine or lamotrigine. Their enhanced potency in blockade of native TTx-r currents in rat DRG neurons relative to the reference standards was only slightly less profound. Compounds **4**, **5**, and **19** also were more potent than lamotrigine and mexiletine versus Na$_v$1.2 and Na$_v$1.5,

Table 2
SAR of aromatic substitution for piperazine amides



Compound	R^1	R^2	Rat DRG TTx-r[a]		$hNa_v1.8$[a]	
			Concn (μM)	% Inhibition $V_{1/2}$[b]	Concn (μM)	% Inhibition $V_{1/2}$[b]
18	4-OCF_3	Cyclohexyl			0.3	89 ± 5
					0.1	42 ± 3
19	4-*tert*-Butyl	Cyclohexyl	0.1	58 ± 2	0.1	81 ± 10
			0.03	20 ± 3	0.03	57 ± 6
20	4-NMe_2	Cyclohexyl			1	65 ± 4
21	3-Cl	Cyclohexyl			1	80 ± 5
					0.1	22 ± 2
22	2,4-Cl	Cyclohexyl			0.3	12 ± 4
23	4-Phenoxy	Cyclohexyl	1	67 ± 11	0.3	93 ± 1
					0.03	68 ± 10
24	4-Phenoxy	Me	1	90 ± 10	0.3	87 ± 2
			0.1	55 ± 8	0.1	35 ± 1
25	4-*tert*-Butyl	Me	1	55 ± 5	0.3	32 ± 6
26	4-Phenoxy	H	1	56 ± 9	1	93 ± 1
					0.1	39 ± 3
27	4-*tert*-Butyl	H	10	86 ± 3	1	85 ± 5
					0.1	44 ± 6

[a] Data shown with standard error (±SEM) represent the mean of two to six separate determinations.
[b] Inactivated state protocol: the pre-pulse voltage at which 50% of channels are inactivated ($V_{1/2} = -40$ mV).[19]

Table 3
Na channel selectivity of the lead compounds: voltage clamp electrophysiological characterization

	4	**5**	**19**	Lamotrigine	Mexiletine
Rat TTx-r, IC_{50}[a] (μM)	0.43	0.39	0.09	25	31
$hNa_v1.8$, IC_{50}[a] (μM)	0.28	0.30	0.03	96	56
$hNa_v1.2$, IC_{50}[a] (μM)	1.1	0.35	0.1	10	2.9
$hNa_v1.5$, IC_{50}[a] (μM)	4.6	2.3	0.1	62	13

[a] Data shown with standard error (±SEM) represent the mean of two to six separate determinations. Data were collected using an inactivated state protocol (the pre-pulse voltage at which 50% of channels are inactivated). $V_{1/2} = -60$ mV for $hNa_v1.2$, $hNa_v1.8$, rat TTx-r; $V_{1/2} = -90$ mV for $hNa_v1.5$.[19]

and showed marginal selectivity for the $hNa_v1.8$ subtype. The voltage-dependent behavior noted above for $Na_v1.8$ also was observed with $Na_v1.2$ and $Na_v1.5$ for all compounds in Table 3 (data not shown).

Assessment of pharmacokinetic properties revealed that compounds **4**, **5**, and **19** afforded sufficient plasma levels upon oral administration to enable evaluation in animal pain models. The results of these studies are summarized in Table 4. In the spinal nerve ligation (Chung) model of neuropathic pain,[23] the potency of compounds **4** and **5** for reversing mechanical allodynia was somewhat greater than mexiletine and lamotrigine. It is noteworthy that increased in vitro sodium channel potency translated to improved in vivo potency, as exemplified by **19**. On the other hand, lamotrigine is approximately 60-fold less active than **4** and **5** on $Na_v1.8$ (rat TTx-r), yet is only modestly (<2-fold) less active in the Chung model despite an approximately 10-fold greater systemic exposure (C_{max}) relative to these two compounds. These results lead us to speculate that pharmacological activities other than sodium channel blockade contribute to the analgesic activity of lamotrigine and mexiletine. Treatment with **4**, **5**, or **19** resulted in no impairment of locomotor activity at doses substantially greater than required for analgesic efficacy, despite a large degree of partitioning into the CNS (brain/plasma >8) in all three cases. Similar findings were observed in the rotarod and edge tests. Assessment of cardiovascular safety for **4** and **5** in anesthetized rats indicated no sustained changes in mean arterial pressure or heart rate at doses that yielded plasma levels 30- and 10-fold higher than the therapeutic plasma level, respectively.

Table 4
Efficacy, safety profile, and PK properties of lead compounds

	4	**5**	**19**	Lamotrigine	Mexiletine[b]
Chung, po ED_{50} (μmol/kg)	24	37	4.7	47	102
Locomotor, po ED_{50} (μmol/kg)	>300	>300	38% at 230	>390	45 (lethal at 460)
Edge test, po ED_{50} (μmol/kg)	>300	>300	>300	>390	lethal at 460
Rotorod, p.o. ED_{50} (μmol/kg)	>300	>300	>300	>390	>140
MAP effect[c]	None (30×)	None (10×)	↓ 11% (3×)		
Heart rate effect	None (30×)	None (10×)	↓ 27% (10×)		
Brain/Plasma	50	9	8	26	1.4
CLp (L/h kg)[a]	21	2.7	7.6	0.06	
C_{max} po (μg/mL)[a]	0.13	0.47	0.57	3.5	
V_{ss}[a] (L/kg)	24	7.8	13.4	0.98	
F (po)[a]	42	48	7	79	

[a] Administered at 10 mg/kg, 10% DMSO/PEG400.
[b] Administered ip in all cases.
[c] MAP (mean arterial pressure).

With the exception of weak binding to $5HT_{1A}$ and $5HT_{1B}$ receptors (60% and 86% at 10 μM, respectively), **4** was found to be highly selective for sodium channels compared to a diverse set of cell-surface receptors, ion channels, and enzymes (CEREP, Poitiers, France; 70 receptor panel) and a number of other channels and receptors expressed in peripheral sensory neurons.[24]

4. Conclusions

We have discovered a novel series of voltage-dependent furan-based sodium channel blockers with enhanced potency for blockade of sodium channels relative to clinically used agents, mexiletine and lamotrigine. Structure–activity relationship studies identified the preferred amide substituents (e.g., cyclohexylpiperazine, methylpiperazine, and piperazine) and established the preferential aromatic substitution for this class of compounds. Incorporation of a basic nitrogen imparted enhanced solubility and a generally favorable pharmacokinetic profile, but little selectivity among the sodium channels subtypes. Analgesic efficacy in the spinal nerve ligation model of neuropathic pain was observed for these analogs. For example, the novel furan piperazine **19** exhibited a >10-fold increase in potency in the Chung model relative to lamotrigine and mexiletine. Interestingly, the activity at $Na_v1.2$ and $Na_v1.5$ exhibited by these furan derivatives did not manifest itself appreciably in the form of adverse CNS or cardiovascular effects, respectively. Furans **4** and **5** demonstrated favorable in vivo efficacy in the Chung model of neuropathic pain compared to lamotrigine and mexiletine, along with a benign CNS and cardiovascular safety profile.

5. Experimental

5.1. General procedures

Nuclear magnetic resonance spectra were obtained on a General Electric QE 300 MHz instrument with chemical shifts (δ) reported relative to tetramethylsilane as internal standard. Mass spectra determinations were obtained using an electrospray (ESI) technique or by direct chemical ionization (DCI) methods employing ammonia. Melting points were determined with capillary apparatus and are uncorrected. Elemental analyses were performed by Robertson Microlit Laboratories, Inc., Madison, NJ. Analytical thin layer chromatography was done on 2 × 6 cm Kieselgel 60 F-254 plates pre-coated with 0.25 mm thick silica gel distributed by E. Merck. LC-MS analyses were performed on ThermoQuest Navigator systems using 10–100% acetonitrile: 10 mM ammonium acetate gradient with MS data obtained using atmospheric pressure chemical ionization (APCI) positive ionization over the range of m/z from 170 to 1200. Unless otherwise specified, column chromatography was performed on silica gel (230–400 mesh). The term in vacuo refers to solvent removal using a rotary evaporator at 30 mm Hg.

5.2. High-throughput mouse $Na_v1.8$ and hERG flux assays

HEK293 cells stably expressing mouse $Na_v1.8$ or hERG were loaded overnight with $^{86}Rb^+$, followed by stimulation with deltamethrin as previously described.[21] The deltamethrin-stimulated $^{86}Rb^+$ flux was measured for 30 min in the presence and absence of test compounds.

5.3. Electrophysiology[19]

5.3.1. Rat Dorsal Root Ganglion (DRG) neurons

Whole-cell patch clamp recordings were performed at room temperature on rat small diameter DRG neurons (18–25 μm) from the L4 and L5 lumbar region. For current clamp recordings, the pipette solution contained (mM): KCl 140, $MgCl_2$ 2, EGTA 5, HEPES 10, pH 7.2 (osmolarity, 285). The external solution contained (mM): NaCl 140, KCl 5, $CaCl_2$ 2, $MgCl_2$ 2, HEPES 10, pH 7.4 (osmolarity, 310). For voltage clamp recordings, pipette solution contained (mM): CsF 135, NaCl 5, CsCl 10, EGTA 5, HEPES 10, pH 7.2 (osmolarity, 285). The external solution contained (mM): NaCl 22, cholineCl 110, $CaCl_2$ 1.8, $MgCl_2$ 0.8, HEPES 10, Glucose 5, pH 7.4 (osmolarity, 310).

5.3.2. Recombinant human sodium channels

Human embryonic kidney (HEK293) cells expressing recombinant sodium channels were grown in DMEM/High Glucose Dulbecco's Mod, 10% Fetal Bovine Serum, 2 mM Sodium Pyruvate, G418. For whole-cell voltage clamp recordings, patch pipettes were pulled from borosilicate glass on a Flaming–Brown micropipette puller (Sutter Instruments, Inc). Pipettes had a tip resistance of 0.8–2.5 MΩ using the internal solutions (mM): 135 CsF, 10 CsCl, 5 EGTA, 5 NaCl, 10 HEPES-free acid, pH to 7.3 with 5M CsOH and voltage offset was zeroed prior to seal formation. The external buffer consisted of (mM) 132 NaCl, 5.4 KCl, 0.8 $MgCl_2$, 1.8 $CaCl_2$, 5 Glucose, 10 HEPES-free acid, pH to 7.3 with 6N NaOH. After establishment of a whole-cell recording, cellular capacitance was minimized using the analog compensation available on the recording amplifier (Axopatch 200B). Series resistance was less than 5 MΩ and was compensated >85% in all experiments, resulting in a final series resistance no greater than 0.75 MΩ . Signals were low-pass filtered at 5–10 kHz, digitized at 20–50 kHz, and stored on a computer for later analysis. Voltage protocols were generated and data acquisition and analysis were performed using pCLAMP software (Version 8.1, Axon Instruments, Inc.). All experiments were performed at room temperature. Liquid junction potentials were <10 mV and were not corrected.

5.4. In vivo evaluation

Male Sprague–Dawley rats (Charles River, Wilmington, MA) weighing 200–300 g were utilized. All animals were group-housed in AAALAC approved facilities at Abbott Laboratories in a temperature-regulated environment with lights on between 0700 and 2000 h. Food and water was available ad libitum except during testing. All animal handling and experimental protocols were approved by an institutional animal care and use committee (IACUC). All experiments were performed during the light cycle. Unless otherwise noted, all experimental and control groups contained at least six animals per group and data are expressed as mean ± SEM. Data analysis was conducted using analysis of variance and appropriate post-hoc comparisons ($P < 0.05$) as previously described.[25] ED_{50} values were estimated using least squares linear regression.

5.4.1. Spinal nerve (L5/L6) ligation model of neuropathic pain

As previously described in detail by Kim and Chung,[23] a 1.5-cm incision was made dorsal to the lumbosacral plexus. In anesthetized rats, the paraspinal muscles (left side) were separated from the spinous processes, the L5 and L6 spinal nerves isolated, and tightly ligated with 3–0 silk threads. Following hemostasis, the wound was sutured and coated with antibiotic ointment. The rats were allowed to recover and then placed in a cage with soft bedding for 14 days before behavioral testing for mechanical allodynia.

5.4.2. Motor function

Locomotor activity was measured in an open field using photobeam activity monitors (AccuScan Instruments, Columbus, OH), and rotorod performance was measured using an accelerating rotorod apparatus (Omnitech Electronics, Inc. Columbus, OH). For the rotorod assay, rats were allowed a 30-min acclimation period in the testing room and then placed on a 9-cm diameter rod that increased in speed from 0 to 20 rpm over a 60-s period. The time required for

the rat to fall from the rod was recorded, with a maximum score of 60 s. Each rat was given three training sessions. To test for balance, rats were also assessed for their ability to remain on top of a 0.5-cm-thick edges of a 40 × 40 × 36 cm plexiglass box. The rats had to pull themselves up on to the edge and avoid falling with a cut-off time of 2 min. The average (latency to fall) of two trials was recorded.

5.4.3. Cardiovascular safety

Male Sprague–Dawley inaction-anesthesized rats were used to measure mean arterial pressure and heart rate. Following a 30-min control period, a sodium channel blocker or vehicle (PEG-400) was administered intravenously over five, 30-min infusions at 1×, 3×, 10×, 30×, and 100× of calculated therapeutic dose. A blood sample and hematocrit were collected immediately after the infusion.

6. Chemistry

6.1. Representative procedure for conversion of carboxylic acid derivatives to amides via acid chlorides (Method A) 5-(4-Chlorophenyl)-2-furoyl chloride (3)

5-(4-Chlorophenyl)-2-furoic acid (1.10 g, 5.00 mmol) in dichloromethane (50 mL) was treated with oxalyl chloride (0.650 mL, 7.50 mmol) and a catalytic amount of *N,N*-dimethylformamide (100 μL). The mixture was stirred at ambient temperature for 2 h and the solvent and excess oxalyl chloride were removed under reduced pressure to provide 1.11 g of **3** which was used without further purification.

6.2. 1-[5-(4-Chlorophenyl)-2-furoyl]piperazine hydrochloride (4)

A solution of **3** (0.55 g, 2.50 mmol) in dichloromethane (10 mL) was treated with *tert*-butyl-1-piperazine carboxylate (0.46 g, 2.50 mmol) and triethylamine (0.3 mL). The mixture was stirred at ambient temperature for 16 h. The mixture was diluted with dichloromethane (25 mL) and washed with 5% $NaHCO_3$ solution (25 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. The obtained residue was purified by silica gel chromatography (elution with 5% ethanol/dichloromethane).

The purified material was redissolved in dichloromethane (50 mL) and treated with trifluoroacetic acid (15 mL). The mixture was stirred at room temperature for 1 h after which the solvent was removed in vacuo and the residue was partitioned in dichloromethane/1 M NaOH solution (25 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. The obtained residue was converted to HCl salt by treatment of the ethanolic solution of the residue with ethereal HCl to provide 0.550 g (68%) of 4, mp 251 °C. MS (DCI/NH_3) *m/z* 291 $(M+H)^+$. ^1H NMR (DMSO-d_6) δ 9.04 (br s, 1H), 7.82 (d, 2H, J = 8.81 Hz), 7.55 (d, 2H, J = 8.81 Hz), 7.22 (d, 2H, J = 3.73 Hz), 7.21 (d, 2H, J = 3.73 Hz), 3.93 (br s, 4H), 3.21 (br s, 4H). Anal. ($C_{15}H_{15}N_2O_2Cl$·HCl) C, H, N.

6.3. [5-(4-Chlorophenyl)furan-2-yl]-(4-cyclohexylpiperazin-1-yl)-methanone hydrochloride (5)

A solution of **3** (0.3 g, 1.2 mmol) in dichloromethane was reacted with 1-cyclohexylpiperazine (0.20 g, 1.2 mmol) as described in Method A to yield 0.28 g (63%) of **5** as a white powder, mp 256 °C. MS (DCI/NH_3) *m/z* 373 $(M+H)^+$. ^1H NMR (DMSO-d_6) δ 10.49 (s (HCl), 1H), 7.83 (d, 2H, J = 8.82 Hz), 7.55 (d, 2H, J = 8.82 Hz), 7.24 (d, 1H, J = 3.39 Hz), 7.21 (d, 1H, J = 3.39 Hz), 4.58 (d, 2H, J = 13.56 Hz), 3.52 (m, 4H), 3.22 (m, 2H) 2.11 (d, 2H, J = 10.85 Hz), 1.83 (d, 2H, J = 11.87 Hz), 1.62 (d, 1H, J = 12.21 Hz), 1.49–1.03 (m, 5H). Anal. ($C_{21}H_{25}N_2O_2Cl$·HCl) C, H, N.

6.4. [5-(4-Chlorophenyl)furan-2-yl]-(4-methylpiperazin-1-yl)-methanone hydrochloride (6)

A solution of **3** (0.100 g, 0.415 mmol) in dichloromethane was reacted with 1-methylpiperazine (0.042 g, 0.415 mmol) by Method A to yield 0.100 g (79%) of **6**, mp 243–245 °C. MS (DCI/NH_3) *m/z* 305 $(M+H)^+$. ^1H NMR (DMSO-d_6) δ 10.44 (br s, 1H), 7.82 (d, 1H, J = 8.48 Hz), 7.23 (d, 2H, J = 8.48 Hz), 7.23 (d, 1H, J = 3.73 Hz), 7.21 (d, 1H, J = 3.39 Hz), 4.54 (d, 2H, J = 14.24 Hz), 3.58 (m, 4H), 3.13 (m, 2H), 2.80 (s, 3H). Anal. ($C_{16}H_{17}ClN_2O_2$·HCl·0.25 H_2O) C, H, N.

6.5. [5-(4-Chlorophenyl)furan-2-yl]-morpholin-4-yl-methanone (7)

A solution of **3** (0.120 g, 0.500 mmol) in dichloromethane was reacted with morpholine (0.044 g, 0.500 mmol) by Method A to yield 0.070 g of **7**, mp 152–153 °C. MS (DCI/NH_3) *m/z* 292 $(M+H)^+$. ^1H NMR (DMSO-d_6) δ 7.79 (d, 2H, J = 8.81 Hz), 7.54 (d, 2H, J = 8.81 Hz), 7.17 (d, 1H, J = 3.73 Hz), 7.14 (d, 1H, J = 3.72 Hz), 3.67 (m, 8H). Anal ($C_{15}H_{14}ClNO_3$) C, H, N.

6.6. [5-(4-Chlorophenyl)-furan-2-yl]-[4-(3-trifluoromethylphenyl)-piperazin-1-yl]-methanone (8)

A solution of **3** (0.100 g, 0.415 mmol) in dichloromethane was reacted with 1-(3-trifluoromethylphenyl) piperazine (0.096 g, 0.415 mmol) by Method A to yield 0.125 g of **8**, mp 150–151 °C. MS (DCI/NH_3) *m/z* 435 $(M+H)^+$. ^1H NMR (DMSO-d_6) δ 7.82 (d, 2H, J = 8.48 Hz), 7.55 (d, 2H, J = 8.48 Hz), 7.46 (t, 1H, J = 7.97 Hz), 7.27–7.18 (m, 4H), 7.10 (d, 1H, J = 7.46 Hz), 3.90 (m, 2H), 3.38 (m, 6H). Anal. ($C_{22}H_{18}ClF_3N_2O_2$·0.5 H_2O) C, H, N.

6.7. 5-(4-Chlorophenyl)furan-2-carboxylic acid-(2-piperidin-1-yl-ethyl)amide hydrochloride (9)

A solution of **3** (0.240 g, 1.00 mmol) in dichloromethane was reacted with 1-(2-aminoethyl)piperidine (0.130 g, 1.00 mmol) by Method A to yield 0.160 g of free base of **9** as an oil that was converted to its hydrochloride salt, mp 225–227 °C. MS (ESI) *m/z* 333 $(M+H)^+$. ^1H NMR (DMSO-d_6) δ 9.50 (br s, 1H), 8.84 (t, 1H, J = 5.93 Hz), 7.96 (d, 2H, J = 8.48 Hz), 7.58 (d, 2H, J = 8.48 Hz), 7.24 (d, 1H, J = 3.73 Hz), 7.17 (d, 1H, J = 3.73 Hz), 3.66 (q, 2H, J = 5.88 Hz), 3.55 (d, 2H, J = 11.19 Hz), 3.23 (q, 2H, J = 5.65 Hz), 2.93 (m, 2H), 1.83 (m, 2H), 1.70 (m, 3H), 1.40 (m, 1H). Anal. ($C_{18}H_{21}ClN_2O_2$·HCl) C, H, N.

6.8. 5-(4-Chlorophenyl)furan-2-carboxylic acid (1-methylpiperidine-4-yl)amide hydrochloride (10)

A solution of **3** (0.100 g, 0.400 mmol) in dichloromethane was reacted with 1-methylpiperidine-4-ylamine (0.050 g, 0.440 mmol) by Method A to yield 0.100 g of free base of **10** as an oil that was converted to hydrochloride salt, MS (ESI) *m/z* 319 $(M+H)^+$. ^1H NMR (DMSO-d_6) δ 9.97 (br s, 1H), 8.53 (d, 1H, J = 7.8 Hz), 7.93 (d, 2H, J = 8.82 Hz), 7.55 (d, 2H, J = 8.82 Hz), 7.21 (d, 1H, J = 3.39 Hz), 7.17 (d, 1H, J = 3.73 Hz), 4.0 (m, 1H), 3.47 (m, 2H), 3.10 (m, 2H), 2.74 (s, 3H), 1.75–2.05 (m, 4H), mp 220–222 °C. Anal. ($C_{17}H_{19}ClN_2O_2$·HCl·0.75 H_2O) C, H, N.

6.9. 5-(4-Chlorophenyl)furan-2-carboxylic acid (3-dimethylamino-2,2-dimethylpropyl)amide hydrochloride (11)

A solution of **3** (0.100 g, 0.400 mmol) in dichloromethane was reacted with *N,N*-2-tetramethyl-1,3-propanediamine (0.570 g, 0.440 mmol) by Method A to yield 0.120 g of free base of **11** as

an oil that was converted to hydrochloride salt. MS (ESI) *m/z* 335 $(M+H)^+$. ^1H NMR (DMSO-d_6) δ 8.61 (t, 1H, J = 5.76 Hz), 7.88 (d, 2H, J = 8.48 Hz), 7.55 (d, 2H, J = 8.48 Hz), 7.16 (d, 1H, J = 3.39 Hz), 7.13 (d, 1H, J = 3.73 Hz), 3.18 (d, 2H, J = 6.1 Hz), 2.28 (s, 6H), 2.20 (s, 2H), 0.89 (s, 6H). Anal. ($C_{18}H_{23}ClN_2O_2$·HCl·0.5 H_2O) C, H, N.

6.10. 5-(4-Chlorophenyl)furan-2-carboxylic acid (3-piperidin-1-yl-propyl)amide hydrochloride (12)

A solution of 5-(4-Chlorophenyl)-2-furoyl chloride (0.100 g, 0.400 mmol) in dichloromethane was reacted with 1-(3-aminopropyl)piperidine (0.063 g, 0.440 mmol) by Method A to yield 0.100 g of free base of **12** as an oil that was converted to hydrochloride salt, mp 160–162 °C MS (ESI) *m/z* 347$(M+H)^+$. ^1H NMR (DMSO-d_6) δ 9.94 (br s, 1H), 8.75 (t, 1H, J = 6.1 Hz), 7.94 (d, 2H, J = 8.48 Hz), 7.56 (d, 2H, J = 8.48 Hz), 7.17 (d, 1H, J = 3.39 Hz), 7.15 (d, 1H, J = 3.73 Hz), 3.39 (m, 2H), 3.05 (m, 2H), 2.87 (m, 2H), 1.95 (m, 2H), 1.65–1.82 (m, 5H), 1.35 (m, 1H). Anal. ($C_{19}H_{23}ClN_2O_2$·HCl·0.5 H_2O) C, H, N.

6.11. [5-(4-Chlorophenyl)furan-2-yl-(4-dimethylamino-piperidin-1-yl)-methanone (13)

A solution of **3** (0.240 g, 1.00 mmol) in dichloromethane was reacted with 4-dimethylamino-piperidine-1-yl-amine (0.140 g, 1.10 mmol) by method A to yield 0.140 g of **13** as an oil that, upon trituration with 30% ethylacetate/hexane, was converted to white crystalline powder, mp 81–82 °C. MS (ESI) *m/z* 333$(M+H)^+$. ^1H NMR (DMSO-d_6) δ 7.78 (d, 2H, J = 8.82 Hz), 7.54 (d, 2H, J = 8.82 Hz), 7.15 (d, 1H, J = 3.39 Hz), 7.08 (d, 1H, J = 3.73 Hz), 3.01 (m, 2H), 2.21 (s, 6H), 1.85 (d, 2H, J = 10.51 Hz), 1.38 (m, 2H). Anal. ($C_{19}H_{23}ClN_2O_2$·HCl·0.6H_2O) C, H, N.

6.12. (5-Bromofuran-2-yl)-(4-cyclohexylpiperazine-1-yl)methanone (15)

A solution of 5-bromo-2-furoic acid (1.00 g, 5.00 mmol) in dichloromethane (50 mL) was treated with oxalyl chloride (0.650 mL, 7.50 mmol) and a catalytic amount of *N*,*N*-dimethylformamide (100 μL). The mixture was stirred at ambient temperature for 2 h and the solvent and excess oxalyl chloride were removed under reduced pressure to provide the intermediate 5-bromo-furoyl chloride which was used without further purification.

The acid chloride (840 mg, 4.00 mmol) was dissolved in dichloromethane (10 mL) and treated with 1-cyclohexylpiperazine (740 mg, 4.40 mmol) and triethylamine (0.750 mL, 5.40 mmol) at ambient temperature. The mixture was stirred for 16 lh at ambient temperature and was then was diluted with dichloromethane (20 mL) and washed with saturated $NaHCO_3$ solution (10 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated in vacuo. The obtained residue was crystallized from hexane/ethyl acetate to provide 1.15 g (84%) of **15**, mp 128–130 °C. MS (DCI/NH_3) *m/z* 343 $(M+H)^+$. ^1H NMR (DMSO-d_6) 7.0 (d, 1H, J = 3.73 Hz), 6.75 (d, 1H, J = 3.73 Hz), 3.59 (m, 4H), 2.55 (m, 4H), 2.25 (m, 1H), 1.73 (m, 4H), 1.57 (m, 1H), 1.18 (m, 4H), 1.07 (m, 1H).

6.13. (5-Bromofuran-2-yl)-(4-methylpiperazine-1-yl)methanone (16)

5-Bromo-2-furoic acid (0.450 g, 2.00 mmol) was reacted with oxalyl chloride and the resulting product was treated with 1-methylpiperazine (0.218 g, 2.20 mmol) as described in **15** to provide 0.460 g of **16**, mp 93–94 °C. MS (DCI/NH_3) *m/z* 273 $(M+H)^+$.^1H NMR (DMSO-d_6) 7.02 (d, 1H, J = 3.39 Hz), 6.75 (d, 1H, J = 3.39 Hz), 3.63 (m, 4H), 2.34 (m, 4H), 2.16 (s, 3H). Anal ($C_{10}H_{13}BrN_2O_2$) C, H, N.

6.14. (5-bromofuran-2-yl)(piperazine-1-yl)methanone. (17)

5-Bromo-2-furoic acid (1.0 g, 5.0 mmol) was treated with oxalyl chloride (0.650 mL, 7.50 mmol) and the resulting product was treated with *t*-butyl-1-piperazine carboxylate (0.930 g, 5.00 mmol) as described in **15** to yield 1.40 g of 4-(5-Bromofuran-2-carbonyl)-piperazine-1-carboxylic acid *tert*-butyl ester, mp 83–84 °C. ^1H NMR (DMSO-d_6) δ 7.05 (d, 1H, J = 3.39 Hz), 6.78 (d, 1H, J = 3.39 Hz), 3.62 (br s, 4H), 3.41 (m, 4H), 1.38 (s, 9H). 4-(5-Bromofuran-2-carbonyl)-piperazine-1-carboxylic acid *tert*-butyl ester (1.4 g, 3.9 mmol) was dissolved in methylene chloride (10 mL) and reacted with trifluroacetic acid (2 mL) at ambient temperature for 1h. The reaction mixture was concentrated and partitioned in $NaHCO_3$ sol./dichloromethane. The organic layer was separated, dried over MgSO4 and concentrated to yield 0.85 of **17**. MS (DCI/NH_3) *m/z* 260 $(M+H)^+$.^1H NMR ($CDCl_3$) δ ppm 6.96 (d, J = 3.57 Hz, 1 H), 6.42 (d, J = 3.57 Hz, 1 H), 3.75 (m, 4 H), 2.93 (m, 4 H). Anal ($C_9H_{11}BrN_2O_2$) C, H, N.

6.15. Representative procedure for Suzuki coupling (Method B): (4-Cyclohexylpiperazin-1-yl)-{[5-(4-trifluoromethoxy)phenyl]furan-2-yl}-methanone (18)

A solution of **15** (100 mg, 0.300 mmol) in 2:1 toluene–water (5 mL) was reacted with 4-(trifluoromethoxy)phenylboronic acid (80 mg, 0.39 mmol) in the presence of Na_2CO_3 (80 mg, 0.80 mmol) and $PdCl_2(PPh_3)_2$ (10 mg) at 80 °C for 16 h. The reaction mixture was concentrated and purified by chromatography on silica gel, eluting with ethylacetate to yield 85 mg (66%) of **18**, mp 108–109 °C. MS (DCI/NH_3) *m/z* 423 $(M+H)^+$. ^1H NMR (DMSO-d_6) δ 7.90 (d, 2H, J = 8.82 Hz), 7.48 (d, 2H, J = 8.82 Hz), 7.18 (d, 1H, J = 3.39 Hz), 7.10 (d, 1H, J = 3.39 Hz), 3.69 (m, 4H), 2.60 (m, 4H), 2.25 (m, 1H), 1.75 (m, 4H), 1.60 (m, 1H), 1.20 (m, 4H), 1.11 (m, 1H). Anal. ($C_{22}H_{25}F_3N_2O_3$) C, H, N.

6.16. [5-(4-*tert*-Butylphenyl)furan-2-yl]-(4-cyclohexylpiperazin-1-yl)-methanone hydrochloride (19)

Compound **15** (1.10 g, 3.20 mmol) was treated with 4-*tert*-butylphenylboronic acid (0.800 g, 5.00 mmol) by Method B. The obtained free base of **19** (0.700 g, 55%) was converted to HCl salt, mp >250 °C. MS (DCI/NH_3) *m/z* 395$(M+H)^+$. ^1H NMR (DMSO-d_6) δ 10.02 (br s, 1H), 7.72 (d, 2H, J = 8.48 Hz), 7.50 (d, 2H, J = 8.48 Hz), 7.21 (d, 1H, J = 3.73 Hz), 7.08 (d, 1H, J = 3.39 Hz), 4.61 (d, 2H, J = 13.56 Hz), 3.55 (m, 4H), 3.22 (m, 2H,), 2.58 (m, 1H), 2.09 (d, 2H, J = 13.56 Hz), 1.82 (d, 2H, J = 10.85 Hz), 1.62 (m, 1H), 1.45–1.22 (m, 4H), 1.20 (m, 1H), 1.15 (s, 9H). Anal. Calcd. for ($C_{25}H_{34}N_2O_2$·HCl) C, H, N.

6.17. (4-Cyclohexylpiperazin-1-yl)-{[5-(4-dimethylamino)-phenyl]-furan-2-yl}-methanone (20)

Compound **15** (0.100 g, 0.300 mmol) was treated with 4-dimethylaminophenylboronic acid (0.060 g, 0.360 mmol) by Method B to provide **20**, mp 124–125 °C. MS (DCI/NH_3) *m/z* 382 $(M+H)^+$. ^1H NMR (DMSO-d_6) δ 7.56 (d, 2H, J = 9.15 Hz), 7.02 (d, 1H, J = 3.73 Hz), 6.78 (m, 3H), 3.68 (m, 4H), 2.96 (s, 6H), 2.55 (m, 4H), 2.28 (m, 1H), 1.76 (m, 4H), 1.56 (m, 1H), 1.20 (m, 5H). Anal. ($C_{23}H_{31}N_3O_2$) C, H, N.

6.18. (4-Cyclohexylpiperazin-1-yl)-{[5-(3-chloro)phenyl]furan-2-yl}-methanone hydrochloride (21)

Compound **15** (0.100 g, 0.300 mmol) was reacted with 3-chlorophenylboronic acid (0.056 g, 0.360 mmol) by Method B to provide

21, mp 236–238 °C. MS (DCI/NH_3) *m/z* 373 $(M+H)^+$. ^1H NMR (DMSO-d_6) (free base) δ 7.85 (t, 1H, J = 1.87 Hz), 7.72 (dt, 1H, J = 7.71, 1.4 Hz), 7.51 (t, 1H, J = 7.97 Hz), 7.43 (ddd, 1H, J = 7.97, 2.03, 1.19 Hz), 7.28 (d, 1H, J = 3.66 Hz), 7.22 (d, 1H, J = 3.66 Hz), 3.68 (m, 4H), 2.58 (m, 4H), 2.27 (m, 1H), 1.75 (m, 4H), 1.58 (m, 1H), 1.22 (m, 4H), 1.12 (m, 1H).). Anal. ($C_{21}H_{26}ClN_2O_2$. HCl·0.5H_2O) C, H, N.

6.19. (4-Cyclohexylpiperazin-1-yl)-{[5-(2,4-dichloro)phenyl]-furan-2-yl}-methanone hydrochloride (22)

Compound **15** (0.100 g, 0.300 mmol) was reacted with 2,4-dichlorophenylboronic acid (0.068 g, 0.036 mmol) by Method B to provide **22**, mp 238–240 °C. MS (DCI/NH_3) *m/z* 407 $(M+H)^+$. ^1H NMR (DMSO-d_6) (free base) δ 7.87 (d, 1H, J = 8.48 Hz), 7.78 (d, 1H, J = 2.03 Hz), 7.55 (d, 1H, J = 2.03 Hz), 7.24 (d, 1H, J = 3.73 Hz), 7.13 (d, 1H, J = 3.39 Hz), 3.68 (m, 4H), 2.58 (m, 4H), 2.27 (m, 1H), 1.75 (m, 4H), 1.58 (m, 1H), 1.22 (m, 4H), 1.12 (m, 1H). Anal. ($C_{21}H_{24}Cl_2N_2O_2$·HCl) C, H, N.

6.20. (4-Cyclohexylpiperazine-1-yl)(5-(4-phenoxyphenyl)furan-2-yl)methanone (23)

Compound **15** (0.100 g, 0.300 mmol) was reacted with 4-phenoxyphenylboronic acid (0.077 g, 0.036 mmol) by Method B to provide **23**, mp 210–212 °C. MS (DCI/NH_3) *m/z* 431$(M+H)^+$. ^1H NMR (DMSO-d_6) (free base) δ 7.77 (d, 2H, J = 8.81 Hz), 7.43 (t, 2H,J = 8.47 Hz), 7.20 (t, 1H,J = 7.46 Hz), 7.09 (m, 5H), 7.02 (d, 1H, J = 3.39 Hz), 3.68 (m, 4H), 2.57 (t, 4H, J = 5.09 Hz), 2.27 (m, 1H), 1.75 (m, 4H), 1.55 (d, 1H, J = 11.53 Hz), 1.20 (m, 4H), 1.15 (m, 1H). Anal ($C_{27}H_{30}N_2O_3$· HCl), C, H, N.

6.21. (4-Methylpiperazin-1-yl)-[5-(4-phenoxyphenyl)furan-2-yl]-methanone hydrochloride (24)

Compound **16** (0.430 g, 1.60 mmol) was treated with (4-phenoxy)phenylboronic acid (0.420 g, 2.00 mmol) by Method B to provide 0.390 g of free base of **24**, that was converted to HCl salt, mp 181–182 °C. MS (DCI/NH_3) *m/z* 363 $(M+H)^+$. ^1H NMR (DMSO-d_6) (free base) δ 7.71 (d, 2H, J = 8.48 Hz), 7.44 (t, 2H, J = 7.46 Hz), 7.19 (t, 1H, J = 8.48 Hz), 7.09 (m, 5H), 7.02 (d, 1H, J = 3.73 Hz), 3.70 (br s, 4H), 2.36 (t, 4H, J = 5.08 Hz), 2.21 (s, 3H). Anal.($C_{22}H_{22}N_2O_2$·HCl·H_2O) C, H, N.

6.22. (4-Methylpiperazin-1-yl)-[5-(4-t-butylphenyl)furan-2-yl]-methanone hydrochloride (25)

Compound **16** (0.100 g, 0.360 mmol) was treated with (4-phenoxy)phenylboronic acid (0.078 g, 0.430 mmol) by Method B to provide 0.100 g of free base of **25**, that was converted to HCl salt, mp 250–251 °C. MS (DCI/NH_3) *m/z* 327 $(M+H)^+$. ^1H NMR (DMSO-d_6) (free base) δ 7.68 (d, 2H, J = 8.74 Hz), 7.49 (d, 2H, J = 8.74 Hz), 7.08 (d, 2H, J = 3.57 Hz), 7.02 (d, 1H, J = 3.57 Hz), 3.70 (br s, 4H), 2.38 (t, 4H, J = 5.15 Hz), 2.21 (s, 3H), 1.3 (s, 9H). Anal.($C_{20}H_{26}N_2O_2$·HCl·0.25H_2O) C, H, N.

6.23. [5-(4-Phenoxyphenyl)-furan-2-yl]-piperazin-1-yl-methanone hydrochloride (26)

Compound **17** (0.120 g, 0.300 mmol) and 4-phenoxyphenylboronic acid (0.077 g, 0.36 mmol) were processed by Method B to yield **26**, mp 195–196 °C. MS (DCI/NH_3) *m/z* 349 $(M+H)^+$. ^1H NMR (DMSO-d_6)(free base) δ 7.76 (d, 2H J = 8.82 Hz), 7.42 (t, 2H, J = 7.46 Hz), 7.18 (t, 1H, J = 8.48 Hz), 7.09 (m, 5H), 7.02 (d, 1H, J = 3.39 Hz), 3.65 (br s, 4H), 2.80 (m, 4H). Anal ($C_{21}H_{20}N_2O_3$·HCl·0.5 H_2O) C, H, N.

6.24. [5-(4-*tert*-Butylphenyl)-furan-2-yl]-piperazin-1-yl-methanone (27)

A solution of **17** (0.120 g, 0.300 mmol) was reacted by method B with 4-*tert*-butylphenylboronic acid (0.064 g, 0.36 mmol) to provide **27**. MS (DCI/NH_3) *m/z* 313 $(M+H)^+$. ^1H NMR (DMSO-d_6) δ 7.68 (d, 2H, J = 8.33 Hz), 7.49 (d, 2H, J = 8.74 Hz), 7.08 (d, 2H, J = 3.57 Hz), 7.02 (d, 1H, J = 3.57 Hz), 3.63 (br s, 4H), 2.75 (t, 4H, J = 5.15 Hz), 1.30 (s, 9H). Anal ($C_{19}H_{24}N_2O_2$·HCl·0.25H_2O) C, H, N.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2008.05.003.

References and notes

1. (a) Marron, B. *Ann. Rep. Med. Chem.* **2006**, 59–72; (b) Kyle, D. J.; Ilyin, V. I. *J. Med. Chem.* **2007**, *50*, 2583–2888.
2. Hargus, N. J.; Patel, M. K. *Expert Opin. Invest. Drugs* **2007**, *16*, 625–646.
3. Lai, J.; Hunter, J. C.; Porreca, F. *Curr. Opin. Neurobiol.* **2003**, *13*, 291–297.
4. Waxman, S. G.; Cummins, T. R.; Dib-Hajj, S.; Fjell, J.; Black, J. A. *Muscle & Nerve* **1999**, *22*, 1177–1187.
5. Liang, Jun; Brochu, R. M.; Cohe, C.; Dick, I. E.; Felix, J. P.; Fisher, M. H.; Garcia, M. L.; Kaczorowski, G. J.; Lyons, K. A.; Meinke, P. T.; Priest, B. T.; Schmalhofer, W. A.; Smith, McHardy M.; Tarpley, J. W.; Williams, B. S.; Martin, W. J.; Parsons, W. H. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2943–2947.
6. Liberatore, A. M.; Schulz, J.; Favre-Guilmard, C.; Pommier, J.; Lannoy, J.; Pawlowski, E.; Barthelemy, M. A.; Huchet, M.; Auguet, M.; Chabrier, P.-E.; Bigg, D. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1746–1749.
7. Ok, D.; Li, C.; Abbadie, C.; Felix, J. P.; Fisher, M. H.; Garcia, M. L.; Kaczorowski, G. J.; Lyons, K. A.; Martin, W. J.; Priest, B. T.; Smith, M. M.; Williams, B. S.; Wyvratt, M. J.; Parsons, W. H. *Bioorg. Med. Chem.Lett.* **2006**, *16*, 1358–1361.
8. Anger, T.; Madge, D. J.; Mulla, M.; Riddall, D. *J. Med. Chem.* **2001**, *44*, 115–137.
9. Kinloch, R. A.; Cox, P. J. *Expert Opin. Ther. Targets* **2005**, *9*, 685–698.
10. Goldin, A. L.; Barchi, R. L.; Caldwell, J. H.; Hofmann, F.; Howe, J. R.; Hunter, J. C.; Kallen, R. G.; Mandel, G.; Meisler, M. H.; Netter, Y. B.; Noda, M.; Tamkun, M. M.; Waxman, S. G.; Wood, J. N.; Catterall, W. A. *Neuron* **2000**, *28*, 365–368.
11. Catterall, W. A. *Neuron* **2000**, *26*, 13–25.
12. Lindia, J. A.; Kohler, M. G.; Martin, W. J.; Abbadie, C. *Pain* **2005**, *117*, 145–153.
13. Nassar, M. A.; Stirling, L. C.; Forlani, G.; Baker, M. D.; Matthews, E. A.; Dickenson, A. H.; Wood, J. N. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 12706–12711.
14. Akopian, A. N.; Souslova, V.; England, S.; Okuse, K.; Ogata, N.; Ure, J.; Smith, A.; Kerr, B. J.; McMahon, S. B.; Boyce, S.; Hill, R.; Stanfa, L. C.; Dickenson, A. H.; Wood, J. N. *Nat. Neurosci.* **1999**, *2*, 541–548.
15. Coggeshall, R. E.; Tate, S.; Carlton, S. M. *Neurosci. Lett.* **2004**, *355*, 45–48.
16. Priest, B. T.; Murphy, B. A.; Lindia, J. A.; Diaz, C.; Abbadie, C.; Ritter, A. M.; Liberatore, P.; Iyer, L. M.; Kash, S. F.; Kohler, M. G.; Kaczorowski, G. J.; MacIntyre, D. E.; Martin, W. J. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 9382–9387.
17. Renganathan, M.; Cummins, T. R.; Waxman, S. G. *J. Neurophysiol.* **2001**, *86*, 629–640.
18. Lai, J.; Gold, M. S.; Kim, C.-S.; Bian, D.; Ossipov, M. H.; Hunter, J. C.; Porreca, F. *Pain* **2002**, *95*, 143–152.
19. Jarvis, M. F.; Honore, P.; Shieh, C. C.; Chapman, M.; Joshi, S.; Zhang, X.; Kort, M.; Carroll, W. A.; Marron, B.; Atkinson, R.; Thomas, J.; Liu, D.; Krambis, M.; Liu, Y.; McGaraughty, S.; Chu, K.; Roeloffs, R.; Zhong, C.; Mikusa, J. P.; Hernandez, G.; Gauvin, D.; Wade, C.; Zhu, C.; Pai, M.; Scanio, M.; Shi, L.; Drizin, I.; Gregg, R.; Matulenko, M.; Hakeem, A.; Gross, M.; Johnson, M.; Marsh, K.; Wagoner, P. K.; Sullivan, J.; Faltynek, C.; Krafte, D. *Proc. Natl. Acad. Sci. U.S.A.* **2007**, *104*, 8520–8525.
20. Kort, M. E.; Drizin, I.; Gregg, R. J.; Scanio, M. J.; Shi, L.; Gross, M. F.; Atkinson, R. N.; Johnson, M. S.; Pacofsky, G. J.; Thomas, J. B.; Carroll, W. A.; Krambis, M. J.; Liu, D.; Shieh, C. C.; Zhang, X.; Hernandez, G.; Mikusa, J. P.; Zhong, C.; Joshi, S.; Honore, P.; Roeloffs, R.; Marsh, K. C.; Murray, B. P.; Liu, J.; Werness, S.; Faltynek, C. R.; Krafte, D. S.; Jarvis, M. F.; Chapman, M. L.; Marron, B. E. *J. Med. Chem.* **2008**, *1*, 407–416.
21. Daniel, S.; Malkowitz, L.; Wang, H.-C.; Beer, B.; Blume, A. J.; Ziai, M. R. *J. Pharmacol. Methods* **1991**, *25*, 185–193.
22. For the inactivated state protocol, a pre-pulse voltage at which 50% of channels are inactivated ($V_{1/2}$ = −40 mV) was employed. For the resting state protocol, a pre-pulse voltage at which 100% of channels are available to be activated (V_0 = −100 mV) was employed. Additional details are provided in Ref. 19.
23. Kim, S. H.; Chung, J. M. *Pain* **1992**, *50*, 355–363.
24. Jarvis, M. F.; Burgard, E. C.; McGaraughty, S.; Honore, P.; Lynch, K.; Brennan, T. J.; Subieta, A.; van Biesen, T.; Cartmell, J.; Bianchi, B.; Niforatos, W.; Kage, K.; Yu, H.; Mikusa, J.; Wismer, C. T.; Zhu, C. Z.; Chu, K.; Lee, C. H.; Stewart, A. O.; Polakowski, J.; Cox, B. F.; Kowaluk, E.; Williams, M.; Sullivan, J.; Faltynek, C. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 17179–17184.
25. Joshi, S. K.; Honore, P. *Expert Opin. Drug Discov.* **2006**, *1*, 323–334.