# Phenoxyphenyl Pyridines as Novel State-Dependent, High-Potency Sodium Channel Inhibitors

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*Received February 28, 2004*

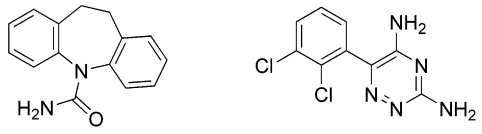
In the search for more efficacious drugs to treat neuropathic pain states, a series of phenoxyphenyl pyridines was designed based on 4-(4-flurophenoxy)benzaldehyde semicarbazone. Through variation of the substituents on the pyridine ring, several potent state-dependent sodium channel inhibitors were identified. From these compounds, **23** dose dependently reversed tactile allodynia in the Chung model of neuropathic pain. Administered orally at 10 mg/kg the level of reversal was ca. 50%, comparable to the effect of carbamazepine administered orally at 100 mg/kg.

## Introduction

Voltage-gated sodium channels play an important role in the molecular pathophysiology of pain. They are essential for the initiation and propagation of neuronal impulses and are dynamically regulated in animal models of neuropathic pain states.[1] Sodium channels can be distinguished pharmacologically according to their sensitivity to tetrodotoxin (TTX) as either TTX-sensitive (TTX-S), or TTX-resistant (TTX-R).[2]

Current evidence suggests that both TTX-S and TTX-R channels expressed in primary afferent neurons play roles in the pathological firing patterns that are established following nerve injury.[3] Thus, a potentially powerful approach to control neuropathic pain is to selectively suppress the repetitive firing that is common in these states.[4] Consistent with this idea, drugs that block sodium channels, such as carbamazepine[5] and lamotrigine,[6] have clinical utility in treating neuropathic pain (Figure 1). However, these agents were developed as anticonvulsants with no view to optimizing the sodium channel activity for pain states. At present, due to limited efficacy and problematic CNS side effects, there are few available options for treating neuropathic pain.

Sodium channels can be thought of as existing in three states: a closed resting state, an open state, and a closed inactivated state. Driven by membrane voltage, the channel is able to cycle through these states within a few milliseconds. It is thought that to achieve a desirable side effect profile it is important to have a state-dependent mechanism of inhibition. The most desirable molecules should have higher affinity for the inactivated state versus the resting or open states of the channel. Thus, during episodes of hyperexcitability, when sodium channels accumulate in inactivated states, this class of inhibitors selectively blocks the pathological state while leaving the remainder of the nervous system to function normally.




Carbamazepine Lamotrigine

**Figure 1.** Structures of carbamazepine and lamotrigine.

4-(4-Fluorophenoxy)benzaldehyde semicarbazone (Scheme 1) was originally identified as a compound with anticonvulsant properties in animals.[7] It was subsequently found to be a state-dependent sodium channel blocker with submicromolar affinities ($K_i$) for inactivated states for a variety of TTX-S sodium channels, including recombinant rBIIa (0.37 $\mu$M) and hSkM1 (0.2 $\mu$M), and wild-type sodium currents in acutely dissociated rat hippocampal neurons (0.6 $\mu$M).[8] It has a minimum effective dose of 2.5 mg/kg in the rat Chung model of neuropathic pain[9] following oral administration.[10] In addition, 4-(4-fluorophenoxy)benzaldehyde semicarbazone does not have obvious CNS side effects. Despite the attractive in vitro and in vivo properties, this compound carries a number of concerns for development including the possible formation of a reactive species during metabolism (Scheme 1).[11]

Toward the discovery of a second-generation compound, we embarked on a systematic structure−activity investigation aiming to replace the labile semicarbazone moiety with various heterocycles as bioisosteric replacements.

It is conceivable that one such direct transformation is to replace one nitrogen atom of the semicarbazone with a carbon atom and incorporate the resulting moiety into a pyridine ring (Figure 2). By doing so, the double bond character between the carbon and nitrogen atom would be kept intact. Most importantly, this would retain the relative spatial relationship between the

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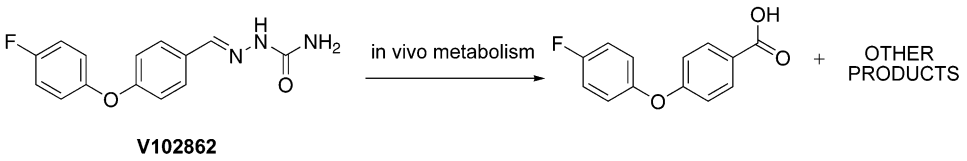
10.1021/jm040048d CCC: $27.50 
Published on Web 07/16/2004

**Scheme 1**




carboxamide and the phenoxyphenol moiety present in 4-(4-fluorophenoxy)benzaldehyde semicarbazone. With this design, we significantly departed from the original structure and entered into a new series of structures, the phenoxyphenyl pyridines. During the progress of our work, a report by Itoh et al.[12] on a sodium/calcium channel blocker NS-7 (Figure 3) triggered our curiosity on the role of the carboxamide of phenoxyphenyl pyridines in determining the potency of sodium inhibitors. On the basis of the structure of NS-7 we designed compound **22c,** analogous to NS-7 (Figure 3), to probe the importance of the carboxamide on activity of the new series.

In this paper, we report our work toward the effective replacement of the semicarbazone moiety with a pyridine scaffold, which leads to the discovery of a new potent and state-dependent sodium channel inhibitor, compound **6**. In addition, we will report a brief structure−activity relationship study of the pyridine ring system, carried out to maximize the potential of these scaffolds. The structure−activity investigation started with the synthesis of analogues designed to probe the importance of the spatial relationship of the carboxamide group relative to the phenoxyphenyl moiety. Several analogues with substituents at either the 4-position of the pyridine or at the carboxamide nitrogen atom were prepared in attempt to improve the pharmaceutical profile of the molecules while maintaining their potency and state dependence.

## Chemistry

Pyridine carboxamides **6**−**9** were prepared in a one-step Suzuki coupling reaction between the corresponding halopyridine carboxamides **2**−**5** and 4-(4-fluorophenoxy)benzene boronic acid (Scheme 2). In a similar fashion, compounds **12**, **15**, and **18** were synthesized with the corresponding halopyridine carboxamides **11**, **14**, and **17**, which were easily obtained from commercially available **10**, **13**, and **16**.

The reaction sequence shown in Scheme 3 was utilized to prepare several 4-substituted pyridine analogues (**22**−**25**).[13] 2,4-Pentanedione (**19**) was converted to a keto-enamine intermediate through its reaction with aniline in the presence of *p*-toluenesulfonic acid as catalyst. Treatment of this intermediate with lithium 2,2,6,6-tetramethylpiperidide (LTMTP) at low temperature resulted in the generation of a dianion that was subsequently reacted with 4-(4-fluorophenoxy) benzonitrile to obtain hydroxypyridine **20**. Brief treatment of **20** with $POCl_3$ at elevated temperature yielded chloropyridine **21**. Serving as a key intermediate, compound **21** was reacted with several nucleophiles including dimethylamine, morpholine, 2-piperidinyl ethanol, and methanol in the presence of NaH at elevated temperatures to produce **22a**−**22d**. Oxidation of **22a** with $SeO_2$ in refluxing pyridine failed to provide the corresponding carboxylic acid; only starting material **22a** was recovered. Extended reaction time and excess $SeO_2$ did not change the outcome. In contrast, the oxidation of **22b** with $SeO_2$ in refluxing pyridine provided the corresponding acid in good yield, which was then converted to the desired amide **23**. This process involved the conversion of the acid to the corresponding methyl ester, followed by the treatment with $NH_3$ in methanol to complete the synthesis of the primary amide. In a similar reaction sequence, **22d** was converted to methoxy-substituted pyridines **24** and **25** with $NH_3$ and *N*,*N*-dimethylethylenediamine, respectively.

## Results and Discussion

The extent of sodium channel inhibition was measured with the rat brain NaIIa ($rNa_v1.2$) -B2 cell line hosted in HEK-293 cells. In addition, the activity of selected compounds was confirmed by assaying for the

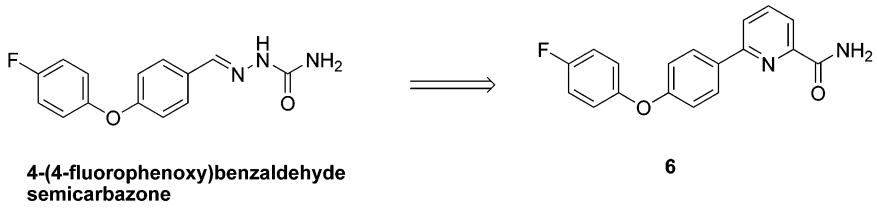



**Figure 2.** Replacement of semicarbazone with pyridine-2-carboxylic acid amide.

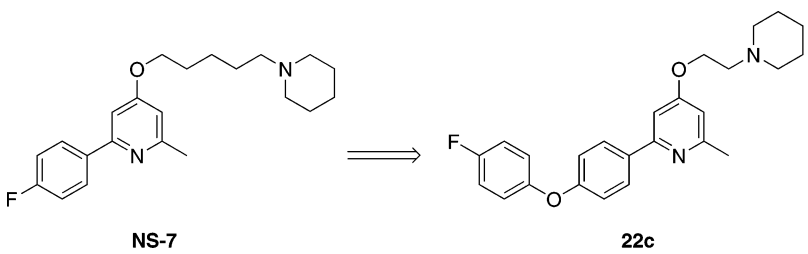
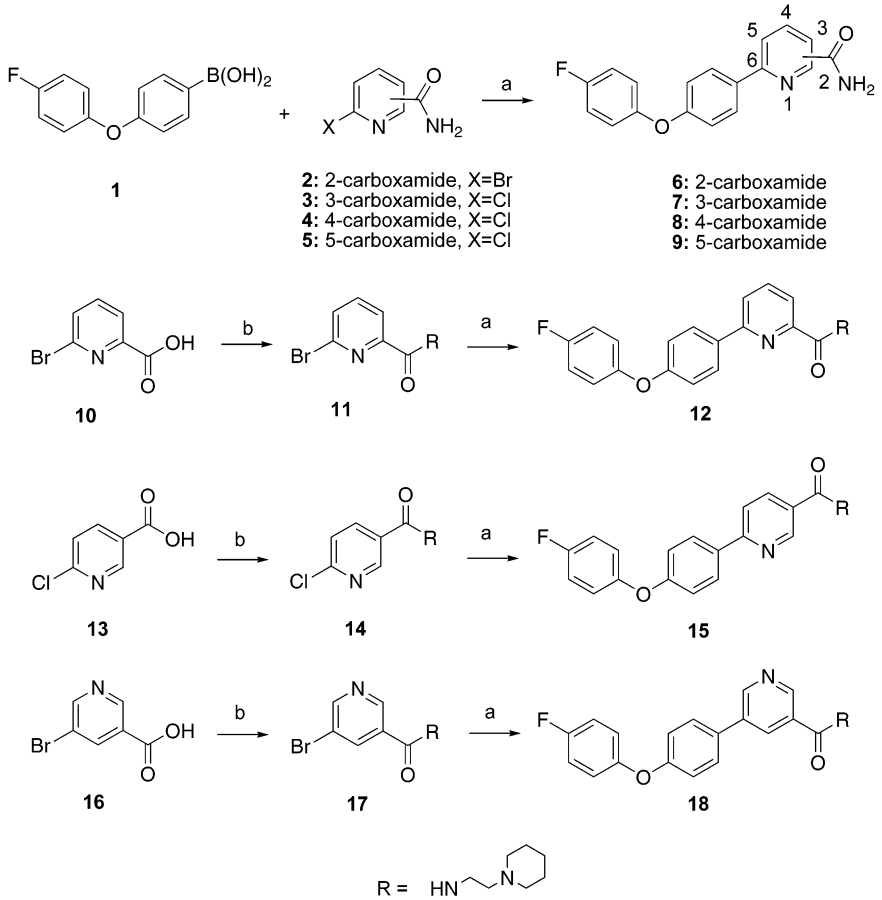



**Figure 3.** Analogue of NS-7.

**Scheme 2.** Synthesis of 6-(4-Fluorophenoxy)phenyl Pyridine Carboxamides[a]




[a] Reagents: (a) $Pd(PPh_3)_4$, boronic acid **1**, DME, $H_2O$ (**6**: 18%; **7**: 40%; **8**: 55%; **9**: 31%); (b) HOBT, DIC, DMF, 1-(2-aminoethyl)piperidine, $H_2O$ (**12**: 42% from **10**; **15**: 52% from **13**; **18**: 75% from **16**).

inhibition of native TTX-R and TTX-S sodium currents in acutely dissociated rat dorsal root ganglion (DRG) neurons[14] using a conventional whole-cell patch clamp technique. As discussed earlier, the first modification of the semicarbazone moiety in 4-(4-fluorophenoxy)-benzaldehyde semicarbazone involved the replacement of one nitrogen atom with a carbon atom and incorporation of the remaining moieties into a pyridine ring such as **6** (Figure 2).

Evaluation of compound **6**, the direct analogue of 4-(4-fluorophenoxy)benzaldehyde semicarbazone, led to the discovery of a potent sodium channel inhibitor (Table 1), with an apparent dissociation constant for the inactivated state of sodium channels ($K_i$) below 100 nM. Furthermore, its actions appear to be state-dependent, similar to 4-(4-fluorophenoxy)benzaldehyde semicarbazone as evidenced by its large $K_r/K_i$ ratio.

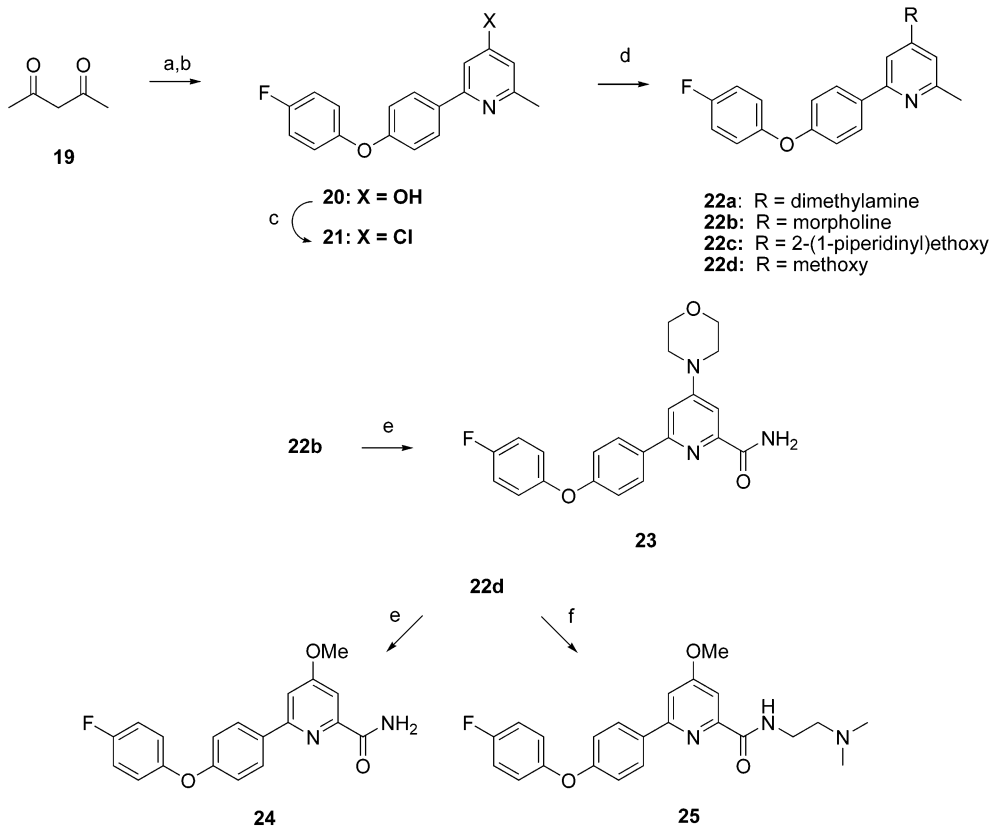
With **6** as a potent lead, we embarked on a systematic investigation of the SAR within this series. Compounds **7**−**9** were prepared by varying the point of attachment of the primary carboxamide to the pyridine ring. It was observed that when the amide was moved away from the 2-position, all analogues lost potency at the inactivated state of sodium channel, compound **9** showing this most dramatically.

On the basis of previous work,[15] we knew that amides substituted on nitrogen with a piperidinyl ethyl moiety showed increased potency toward the sodium channel. In addition, the incorporation of an additional basic center makes it possible to form a salt thereby potentially increasing water solubility. With such anticipation, compounds **12** and **15** were prepared (Scheme 2). When evaluated, **12** and **15** showed increased potency toward the sodium channel compared with their primary amide analogues (**6** and **7**, respectively). In addition, both **12** and **15** retained their favorable state dependence.

In compound **12**, the carboxamide and phenoxyphenyl substituents are in the same spatial orientation (meta-) as in compound **6**. While holding the position of these two substituents constant, we relocated the nitrogen in the pyridine ring, resulting in compound **18**. Both potency and state dependency of **18** are reduced, compared to **12** but not abolished. Thus, it would seem that as long as the relative orientation of the two substituents on the pyridine ring is maintained, the potency could be retained to a fair degree.

With the relative orientation of substituents on the pyridine ring established, we returned to the 2,6-relationship present in compounds **6** and **12** to assess the effect of additional substituents on the pyridine ring. 4-Substituted pyridines were investigated because of their ease of synthesis and the potential electronic effect of the substituent on the pyridine ring. Compounds **23**−**25** were prepared with amino and methoxy groups at the 4-position of the pyridine ring (Scheme 3). While the substituents are tolerated, there is a reduction in both potency and state dependency compared to **6**. When an additional basic center is attached to the amide

**Scheme 3.** Synthesis of 4-Substituted Pyridine Analogues[a]




[a] Reagents: (a) aniline, TsOH, toluene (100%); (b) LTMP, 4-(4-fluorophenoxy)benzonitrile, THF, −78 °C (60%); (c) $POCl_3$, $CH_2Cl_2$ (33% from **19**); (d) **22a**: NaH, dimethylamine, sealed tube, room temp, 48 h (10%); **22b**: NaH, morpholine, sealed tube, 135 °C, 2 h (100%); **22c**: NaH, 2-piperidinyl ethanol, DMF, 80 °C, 16 h (42%); **22d**: NaOMe, MeOH, sealed tube, 85 °C, 4 h (100%); (e) (i) $SeO_2$, pyridine, reflux, 3 days; (ii) thionyl chloride, MeOH, reflux, 12 h; (iii) 2 N $NH_3$ in MeOH, room temp, 12 h (**23**: 32%; **24**: 48%); (f) (i) $SeO_2$, pyridine, reflux, 3 days; (ii) thionyl chloride, MeOH, reflux, 12 h; (iii) excess *N*,*N*-dimethylethylenediamine, MeOH, room temp, 4 days (94%).

nitrogen, the state dependency is partially restored (compare **25** vs **24**).

Finally, the importance of the carboxamide was investigated in compounds **22a** and **22c**. Neither compound contains the amide moiety, yet they are potent and state-dependent sodium channel inhibitors, **22c** being the most state dependent. The fact that they are active at the sodium channel is not completely unexpected, especially for **22c**, in light of NS-7 (Figure 3).[12] However, the high degree of state dependency is surprising. NS-7 was reported to preferentially block sodium channels in the activated state rather than the inactivated state or the resting state, while **22c** blocks the channels of inactivated state preferentially.

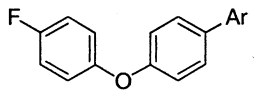
Within this series of compounds, we proceeded to select compounds for further in vivo evaluation in the rat Chung model of painful neuropathy. On the basis of results from a battery of screening assays including potency, pharmacokinetics, and pharmacodynamics, several compounds were evaluated in the Chung paradigm. At 3 and 10 mg/kg (oral administration), **23** reversed tactile allodynia in a dose-dependent manner (Figure 4). At 10 mg/kg the level of reversal was ca. 50%, comparable to the effect of carbamazepine at 100 mg/kg (oral administration). We further estimated the potential CNS side-effect by comparing the minimum effective dose (MED) in Chung model and minimum ataxic dose (MAD) in accelerated rotarod experiment. Compound **6**, which has a relatively large $K_r/K_i$ value of 252 (Table 1) and also dose dependently reverses tactile allodynia when administered orally, was selected for studies on this aspect. The corresponding values for **6** are $MED_{Chung} = 3$ mg/kg and MAD = 30 mg/kg, giving an estimated therapeutic index (TI) of 10. The corresponding values for carbamazepine are $MED_{Chung} = 100$ mg/kg and MAD = 100 mg/kg, giving an estimated TI of 1, i.e., efficacy in the Chung model was only seen at doses that produced ataxia. Clearly, compound **6** has an improved TI in rat compared to carbamazepine.

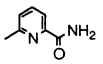
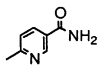
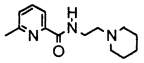
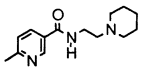
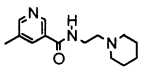
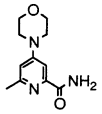
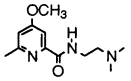
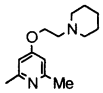
In summary, we have demonstrated that within the phenoxyphenyl pyridine series, compounds significantly more potent than lamotrigine or carbamazepine can be prepared, with improved state dependency. In addition, compounds **6** and **23** have shown oral efficacy in the rat Chung model. This demonstrates that state-dependent sodium channel inhibitors incorporating a pyridine scaffold have potential in the treatment of neuropathic pain.

## Experimental Section

**General Methods.** Unless otherwise indicated, reactions were run under an atmosphere of $N_2$. Solvents and reagents were purchased from commercial sources and used without further purification unless otherwise noted. Flash chromatography was routinely performed on silica gel. Yields for reactions are not typically optimized. Proton NMR spectra were recorded on a Bruker Avance 400 spectrometer and were referenced to TMS. LCMS was performed on an Agilent 1100 Series LC/MSD. HRMS were performed on a Bruker Apex II 4.7T FTMS. Analytical HPLC was carried out at room temperature with two diverse conditions. Robertson Microlit Labs,

**Table 1.** Apparent Dissociation Constants for Binding to Resting ($K_r$) and Inactivated ($K_i$) States of $rNa_v1.2$ Channels Stably Expressed in HEK-293 Cells and to Native $Na^+$ Channels in Rat DRG Neurons[a]




| | | HEK-293 cells | | | DRG | |
|---|---|---|---|---|---|---|
| Compd. | Ar | $K_r$, μM | $K_i$, μM | $K_r/K_i$ | TTX-S, μM | TTX-R, μM |
| **6** |  | 24.2 ± 7.8 | 0.096 ± 0.005 | 252 | 0.101 ± 0.015 | 0.27 ± 0.13 |
| **7** |  | d | 3.75 ± 0.38 | d | d | d |
| **8** |  | d | 2.64 ± 0.19 | d | d | d |
| **9** |  | 63.7 ± 16.7 | 13.4 ± 2.7 | 5 | d | d |
| **12** |  | 4.3 ± 1.1 | 0.028 ± 0.006 | 154 | d | 0.06 ± 0.009[b] |
| **15** |  | 107.3 ± 6.7 | 0.597 ± 0.125 | 180 | 1[c] | 1.56[c] |
| **18** |  | 10.5 ± 1.2 | 0.154 ± 0.034 | 68 | d | d |
| **23** |  | 11.6 ± 0.9 | 0.123 ± 0.039 | 94 | 0.06 ± 0.03 | 0.108 ± 0.015 |
| **24** |  | 87.7 ± 7.9 | 0.365 ± 0.033 | 24 | d | d |
| **25** |  | 23.0 ± 4.0 | 0.256 ± 0.099 | 90 | 0.18 ± 0.04 | 1.56 ± 0.28 |
| **22a** |  | 47.1 ±17.3 | 0.386 ± 0.052 | 122 | 0.53[c] | 0.34[c] |
| **22c** |  | 63.4 ± 13.6 | 0.175 ± 0.026 | 362 | 0.14 ± 0.05 | 0.08[c] |
| 4-(4-fluorophenoxy) benzaldehyde semicarbazone | | 34 ± 7[e] | 0.35 ± 0.02[e] | 100 | 0.25 ± 0.04[e] | 0.26 ± 0.14[e] |
| lamotrigine | | 1765 ± 252[e] | 29.2 ± 3.0 | 60 | 38.4 ± 4.8[e] | 103 ± 13[e] |
| carbamazepine | | 1320 ± 140[e] | 46.1 ± 4.9[e] | 29 | 28.0 ± 4.7 | 111 ± 23[e] |

[a] Three determinations unless otherwise noted. [b] Two determinations. [c] Single determination. [d] Not determined. [e] More than four determinations. The data are mean ± SEM.

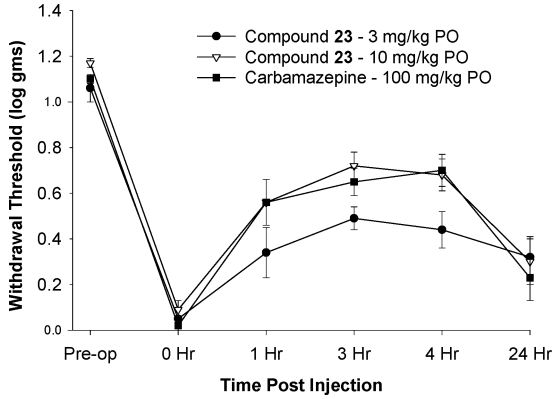



**Figure 4.** Reversal of tactile allodynia by compound **23** in the Chung model.

Madison, NJ, performed combustion analysis. 4-(4-Fluorophenoxy) benzene boronic acid was purchased from Magellan Laboratories, P.O Box 13341, Research Triangle Park, NC 27709. Melting points were obtained on Electrothermal IA9000 series digital melting point apparatus.

**6-Bromopyridine-2-carboxylic Acid Amide (2).** To a solution of 6-bromopicolinic acid (1 g, 5 mmol) in methanol (10 mL) was added slowly thionyl chloride (1.2 g, 10 mmol) at room temperature. The resulting mixture was refluxed for 8 h. The reaction mixture was then concentrated under reduced pressure to give pure methyl ester, which was treated with excess $NH_3$ in methanol (50 mL, 7 N, 350 mmol) for 12 h at room temperature. The solvent was removed under reduced pressure to give 955 mg **2** as white solid. mp 122−124 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.00 (s, 1H); 7.79 (d, $J$ = 7.2 Hz, 1H); 7.24 (t, $J$ = 8.4 Hz, 1H); 7.08 (m, 1H); 6.90 (d, $J$ = 8.4 Hz, 1H). MS ($ES^+$): 201($M^+$).

**6-[4-(4-Flurophenoxy)phenyl]pyridine-2-carboxylic Acid Amide (6).** To a solution of compound **2** (201 mg, 1.0 mmol) in 1,2-dimethoxyethane (10 mL) was added 4-(4-fluorophenoxy)phenyl boronic acid (278 mg, 1.2 mmol), followed by water (2 mL) and potassium carbonate (27.6 mg, 0.1 mmol). To this mixture was added $Pd(PPh_3)_4$ (23.1 mg, 0.02 mmol), and the reaction was heated at 85 °C for 16 h. The reaction was allowed to return to ambient temperature, and the phases were separated. The aqueous phase was extracted three times with ethyl acetate, and the combined organic phases were dried over sodium sulfate. The solution was filtered, concentrated, and then filtered through a bed of Florisil to give crude compound **6**. Purification was then carried out by flash chromatography (silica gel, 40% ethyl acetate/methylene chloride) to yield 56 mg of **6** as white solid (18%). mp 150−151 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.32 (d, $J$ = 9.0 Hz, 2H), 8.31 (bs, 1H), 8.12 (d, $J$ = 8.1 Hz, 1H), 8.03 (dd, $J$ = 8.1, 7.2 Hz, 1H), 7.94 (d, $J$ = 7.2 Hz, 1H), 7.69 (bs, 1H), 7.27 (t, $J$ = 9.0 Hz, 2H), 7.18−7.13 (m, 2H), 7.07 (d, $J$ = 9.0 Hz, 2H). MS ($ES^+$): 309 ($MH^+$). HRMS: calcd for $C_{18}H_{14}N_2O_2F$ ($MH^+$), 309.10338; found 309.10301. Anal. ($C_{18}H_{13}N_2O_2F$) C, H, N.

**6-[4-(4-Fluorophenoxy)phenyl]nicotinamide (7).** This compound was prepared as white solid in a manner similar to that described for **6** using **3** and 4-(4-fluorophenoxy)phenyl boronic acid (55%). mp 250−251 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 9.08 (d, $J$ = 2.0 Hz, 1H), 8.26 (dd, $J$ = 2.4, 8.4 Hz, 1H), 8.17 (m, 3H, including one amide NH), 8.03 (d, $J$ = 8.0 Hz, 1H), 7.60 (bs, 1H, amide NH), 7.28 (m, 2H), 7.17 (m, 2H), 7.08 (m, 2H). MS ($ES^+$): 309 ($MH^+$). Anal. ($C_{18}H_{13}N_2O_2F$) C, H, N.

**2-[4-(4-Fluorophenoxy)phenyl]isonicotinamide (8).** Compound **8** was prepared as white solid in a manner similar to that described for **6**. (55%). mp 172−173 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.81 (d, $J$ = 5.2 Hz, 1H), 8.10 (m, 1H), 8.03 (m, 2H), 7.51 (dd, $J$ = 1.6, 4.8 Hz, 1H), 7.10 (m, 6H), 6.31 (bs, 1H), 6.06 (bs, 1H). MS ($ES^+$): 309 ($MH^+$). HRMS: calcd for $C_{18}H_{13}N_2O_2F$, 308.09611; found, 308.09621. Anal. ($C_{18}H_{13}N_2O_2F$) C, H, N.

**2-[4-(4-Fluorophenoxy)phenyl]nicotinamide (9).** This compound was prepared as white solid in a manner similar to that described for **6** using **5** and 4-(4-fluorophenoxy)phenyl boronic acid (31%). mp 149−150 °C. $^1$H NMR (400 MHz, $CD_3OD$): $\delta$ 8.68 (d, $J$ = 4.9 Hz, 1H), 8.45 (d, $J$ = 4.9 Hz, 1H), 8.02−7.97 (m, 2H), 7.65 (d, $J$ = 8.8 Hz, 2H), 7.42−7.02 (m, 5H). MS ($ES^+$): 309 ($MH^+$). HRMS: calcd for $C_{18}H_{13}N_2O_2F$, 308.09611; found, 308.09597.

**6-Bromo-pyridine-2-carboxylic acid (2-piperidin-1-yl-ethyl)amide (11).** To a solution of 6-bromopicolinic acid (**10**, 5.0 g, 24.8 mmol) and 1-(2-aminoethyl)piperidine (3.3 g, 26.0 mmol) in DMF (100 mL) was added HOBT (3.4 g, 24.8 mmol) and DIC (3.1 g, 24.8 mmol). The reaction was allowed to stir 24 h at ambient temperature. The reaction was diluted with methylene chloride, and water was then added. The phases were separated, and the aqueous phase was extracted twice with methylene chloride. The combined organic phases were dried over sodium sulfate. The solution was filtered and then concentrated to give **11** as a pale-yellow oil. Purification by flash chromatography (silica gel, 40% ethyl acetate/methylene chloride) gave 7.3 g (94%) of **11**. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.23 (bs, 1H), 8.14 (d, $J$ = 7.6 Hz, 1H), 7.71 (t, $J$ = 7.6 Hz, 1H), 7.61 (d, $J$ = 7.6 Hz, 1H), 3.55 (m, 2H), 2.57 (t, $J$ = 6.4 Hz, 2H), 2.46 (bs, 4H), 1.62 (m, 4H), 1.46 (m, 2H). MS ($ES^+$): 313 ($MH^+$).

**6-[4-(4-Flurophenoxy)phenyl]pyridine-2-carboxylic acid (2-piperidin-1-yl-ethyl)amide (12).** This compound was prepared as white solid in a manner similar to that described for **6** using **11** and 4-(4-fluorophenoxy)phenyl boronic acid (45%). mp 216−217 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.80 (bs, 1H), 7.91−7.81 (m, 5H), 7.71−7.64 (m, 1H), 7.07−7.05 (m, 5H), 2.59 (t, $J$ = 6.3 Hz, 2H), 2.48 (bs, 2H), 1.67−1.61 (m, 4H), 1.48 (bs, 2H). MS ($ES^+$): 420 ($MH^+$). HRMS: calcd for $C_{25}H_{26}N_3O_2F$, 419.20090; found 419.20127. **12** was converted to an HCl salt for analysis. Anal. ($C_{25}H_{26}N_3O_2F$.HCl) C, H, N.

**6-Chloro-*N*-(2-piperidin-1-yl-ethyl) nicotinamide (14).** This compound was prepared and isolated as yellow solid in a manner similar to that described for **11** using **13** and 1-(2-aminoethyl)piperidine. mp 83−86 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.76 (d, $J$ = 2.0 Hz, 1H), 8.10 (dd, $J$ = 2.4, 8.3 Hz, 1H), 7.42 (d, $J$ = 8.3 Hz, 1H), 7.11 (bs, 1H), 3.52 (m, 2H), 2.56 (t, $J$ = 6.0 Hz, 2H), 2.44 (bs, 4H), 1.59 (m, 4H), 1.47 (m, 2H). MS ($ES^+$): 268.1 ($MH^+$).

**6-[4-(4-Fluorophenoxy)phenyl]-*N*-(2-piperidin-1-yl-ethyl)nicotinamide (15).** This compound was prepared as white solid in a manner similar to that described for **6** using **14** and 4-(4-fluorophenoxy)phenyl boronic acid (52% from **13**). mp 156−157 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 9.04 (s, 1H), 8.22 (d, $J$ = 8.3 Hz, 1H), 8.03 (d, $J$ = 8.8 Hz, 2H), 7.78 (d, $J$ = 8.3 Hz, 1H), 7.21 (bs, 1H), 7.11−7.04 (m, 6H), 3.58 (t, $J$ = 5.8 Hz, 2H), 2.61 (t, $J$ = 6.0 Hz, 2H), 2.48 (bs, 4H), 1.66−1.50 (m, 4H), 1.27 (bs, 2H). MS ($ES^+$): 420.1 ($MH^+$). HRMS: calcd for $C_{25}H_{26}N_3O_2F$, 419.20090; found, 419.20133. Anal, ($C_{25}H_{26}N_3O_2F$) H, N; C: calcd. 71.58; found 70.90.

**5-Bromo-*N*-(2-piperidin-1-yl-ethyl)nicotinamide (17).** This compound was prepared and isolated as white solid in a manner similar to that described for **11** using acid **16** and 1-(2-aminoethyl)piperidine. mp 97−99 °C. $^1$H NMR (400 MHz, $CD_3OD$): $\delta$ 8.96 (d, $J$ = 2.0 Hz, 1H), 8.82 (d, $J$ = 2.0 Hz, 1H), 8.45 (t, $J$ = 2.0 Hz, 1H), 3.58 (t, $J$ = 6.8 Hz, 2H), 2.63 (t, $J$ = 6.8 Hz, 2H), 2.56 (bs, 4H), 1.66 (m, 4H), 1.52 (m, 2H). MS ($ES^+$): 312 (M).

**5-[4-(4-Fluorophenoxy)phenyl]-*N*-(2-piperidin-1-yl-ethyl)nicotinamide (18).** This compound was prepared as yellow oil in a manner similar to that described for **8** using **17** and 4-(4-fluorophenoxy)phenyl boronic acid (75% from **16**). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.92 (d, $J$ = 2.1 Hz, 2H), 8.35 (t, $J$ = 2.2 Hz, 1H), 7.59 (d, $J$ = 8.6 Hz, 2H), 7.32 (bs, 1H), 7.11−7.03 (m, 6H), 3.58 (t, $J$ = 5.7 Hz, 2H), 2.60 (t, $J$ = 6.1 Hz, 2H), 2.47 (bs, 4H), 1.64−1.59 (m, 4H), 1.48 (bs, 2H). MS ($ES^+$): 420 ($MH^+$). HRMS: calcd for $C_{25}H_{26}N_3O_2F$, 419.20090; found, 419.20133.

**18** was converted to an HCl salt for analysis. Anal. ($C_{25}H_{26}N_3O_2F.HCl\cdot H_2O$) C, N; H: calcd, 6.35; found 5.64.

**2-[4-(4-Fluorophenoxy)phenyl]-6-methyl-1*H*-pyridine-4-one (20).** A solution of 2,4-pentanedione (**19**, 10 g, 100 mmol), aniline (11.2 g, 120 mmol), and a catalytic amount of *p*-toluenesulfonic acid monohydrate in toluene (100 mL) was refluxed for 12 h in a round-bottom flask equipped with an azeotropic apparatus and condenser. The solution was concentrated to dryness, and the enamine was used without purification (17.5 g, 100%). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.35 (t, $J$ = 5.69 Hz, 2H), 7.19 (t, $J$ = 6.4 Hz, 1H), 7.10 (d, $J$ = 7.5 Hz, 2H), 5.19 (s, 1H), 2.10 (s, 3H), 1.99 (s, 3H).

To a solution of 2,2,6,6-tetramethylpiperidine (7.21 g, 51 mmol) in THF (80 mL) at −78 °C was added dropwise 1.6 M *n*-BuLi (31 mL, 50 mmol) under an inert atmosphere. After the addition the reaction mixture was stirred for 30 min. To this solution was added dropwise a solution of the enamine (3 g, 17 mmol), prepared in the previous procedure, in THF (10 mL) at −78 °C. After addition, the reaction was stirred for 30 min. To the resulting dark red solution was added dropwise a solution of 4-(4-fluorophenoxyl)benzonitrile (2.7 g, 17 mmol) in THF (13 mL) at −78 °C. After addition the mixture was slowly warmed to −50 °C and stirred for 1 h. The reaction mixture was poured into a cold, saturated $NH_4Cl$ aqueous solution, and extracted twice with ethyl acetate. The organic phase was washed with brine and dried over magnesium sulfate. After filtration, the filtrate was concentrated to dryness to give 5 g of crude **20,** which contains the unreacted 4-(4-fluorophenoxyl)benzonitrile (40% based on integration from proton NMR). This crude **20** was used in the next step without purification.$^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.54 (d, $J$ = 3.8 Hz, 2H), 7.31 (m, 2H), 7.10−6.90 (m, 4H), 5.23 (s, 1H), 5.08 (s, 1H), 2.03 (s, 3H).

**4-Chloro-2-[4-(4-fluorophenoxy)phenyl]-6-methylpyridine (21).** To a flask containing $POCl_3$ (20 mL) heated to 120 °C using an oil bath was carefully added a mixture of crude compound **20** (5 g, 17 mmol) and DBU (2.6 mL, 17 mmol) in methylene chloride (20 mL). After addition, the reaction mixture was refluxed for 1 h. The resulting mixture was concentrated to dryness and diluted with ethyl acetate. To the solution was carefully added saturated aqueous sodium bicarbonate to pH 5−6. The organic phase was separated, and the aqueous was extracted with the same volume of ethyl acetate. The combined organics were then washed with brine, dried over magnesium sulfate, filtered, and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 5% ethyl acetate/hexane) to obtain 1.8 g (34%) of compound **21** as brown oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.93 (d, $J$ = 6.7 Hz, 2H), 7.48 (d, $J$ = 1.36 Hz, 1H), 7.09 (d, $J$ = 1.5 Hz, 1H), 7.00 (m, 6H), 2.59 (s, 3H). MS ($ES^+$): 314 ($MH^+$).

{**2-[4-(4-Fluorophenoxy)phenyl]-6-methyl-pyridine-4-yl**}**dimethylamine (22a).** In a three-neck round-bottom flask cooled to −78 °C, dimethylamine (20 mL) was condensed and then transferred to a sealed vessel containing compound **21** (50 mg, 0.16 mmol) at −78 °C. The sealed vessel was slowly allowed to warm to room temperature, and the solution was stirred for 48 h. The vessel was then cooled to −20 °C and opened. The remaining dimethylamine was evaporated at room temperature. The residue was purified by flash chromatography (silica gel, 5−10% methanol/methylene chloride) to give 5 mg (10%) of compound **22a** as brown oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.89 (d, $J$ = 6.7 Hz, 2H), 7.00 (m, 6H), 6.69 (d, $J$ = 2.3 Hz, 1H), 6.35 (d, $J$ = 2.3 Hz, 1H), 3.03 (s, 6H), 2.51 (s, 3H). MS ($ES^+$): 323 ($MH^+$). HRMS: calcd for $C_{20}H_{19}N_2OF$, 322.14814; found 322.14829. **22a** was converted to an HCl salt for analysis. Anal. ($C_{20}H_{19}N_2OF.HCl\cdot H_2O$) H, N; C: calcd, 63.74; found, 64.19.

**4-**{**2-[4-(4-Fluorophenoxy)phenyl]-6-methyl-pyridine-4-yl**}**morpholine (22b).** A mixture of compound **21** (2.6 g, 8.8 mmol) and NaH (60%, 704 mg, 17.6 mmol) in morpholine (8 mL) was heated in a sealed tube at 135 °C for 2 h using an oil bath. Methanol was carefully added to the cooled reaction mixture to quench the NaH. The resulting mixture was concentrated to dryness, and the residue was purified by flash chromatography (silica gel, 10% methanol/methylene chloride with 1% concentrated aqueous ammonium hydroxide) to obtain 3.2 g (100%) of **22b** as brown solid. mp 126−128 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.87 (d, $J$ = 8.7 Hz, 2H), 7.00 (m, 6H), 6.86 (d, $J$ = 2.2 Hz, 1H), 6.52 (d, $J$ = 2.2 Hz, 1H), 3.85 (t, $J$ = 4.9 Hz, 4H), 3.33 (t, $J$ = 4.9 Hz, 4H), 2.52 (s, 3H). MS ($ES^+$): 365 ($MH^+$). HRMS: calcd for $C_{22}H_{21}N_2O_2F$, 364.15871; found, 364.15890.

**2-[4-(4-Fluorophenoxy)phenyl]-6-methyl-4-[(2-piperidin-1-yl)ethoxy]pyridine (22c).** A solution of compound **21** (157 mg, 0.5 mmol), 2-(piperidinyl)ethanol (97 mg, 0.75 mmol), and NaH (60%, 40 mg, 1 mmol) in DMF (2.5 mL) was stirred at 80 °C for 16 h. After being partitioned between ethyl acetate and brine, the organic phase was dried over magnesium sulfate, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel, 10% methanol/ethyl acetate) to give 87 mg (42%) of **22c** as tan oil.$^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.92 (d, $J$ = 8.8 Hz, 2H), 7.03 (m, 7H), 6.63 (d, $J$ = 2.1 Hz, 1H), 4.19 (t, $J$ = 6.0 Hz, 2H), 2.81 (t, $J$ = 6.0 Hz, 2H), 2.57 (s, 3H), 2.51 (m, 4H), 1.61 (m, 4H), 1.42 (m, 2H). MS ($ES^+$): 407 ($MH^+$). HRMS: calcd for $C_{25}H_{27}N_2O_2F$, 406.20566; found, 406.20568. **22c** was converted to an HCl salt for analysis. Anal. ($C_{25}H_{27}N_2O_2F.2HCl\cdot H_2O$) H, N; C: calcd, 60.36; found, 60.89

**2-[4-(4-Fluorophenoxy)phenyl]-4-methoxy-6-methylpyridine (22d).** A sealed tube containing compound **21** (1.8 g, 4.8 mmol) in 10 mL of 25 wt % NaOMe in methanol was heated at 85 °C for 4 h. The reaction mixture was allowed to cool, concentrated to dryness, and diluted with ethyl acetate. The mixture was washed with saturated aqueous ammonium chloride, then brine. The organic phase was dried over magnesium sulfate, filtered, and concentrated to dryness to give 1.5 g (100%) of compound **22d** as white solid. mp 179−180 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.92 (d, $J$ = 6.8 Hz, 2H), 7.00 (m, 7H), 6.62 (d, $J$ = 2.1 Hz, 1H), 3.88 (s, 3H), 2.57 (s, 3H). MS ($ES^+$): 310 ($MH^+$).

**6-[4-(4-Fluorophenoxy)phenyl]-4-morpholin-4-yl-pyridine-2-carboxylic acid amide (23).** To a solution of compound **22b** (3.2 g, 8.7 mmol) in pyridine (90 mL) was added $SeO_2$ (2 g, 18 mmol), and the resulting solution was refluxed for 2 days. The cooled reaction mixture was concentrated to dryness and dissolved in methanol. It was then filtered through Celite and again concentrated to dryness. The residue was redissolved in methanol (100 mL), and to this solution of the crude acid was slowly added thionyl chloride (32 mL, 43.5 mmol). After addition, the resulting solution was refluxed for 12 h. The cooled reaction mixture was filtered and concentrated to dryness. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.95 (d, $J$ = 8.8 Hz, 2H), 7.55 (d, $J$ = 2.2 Hz, 1H), 7.15 (d, $J$ = 2.2 Hz, 1H), 7.04 (m, 6H), 4.12 (s, 3H), 3.89 (t, $J$ = 4.8 Hz, 4H), 3.44 (t, $J$ = 4.8 Hz, 4H). MS ($ES^+$): 408 (M).

To a solution of $NH_3$ (2 M, 50 mL) in methanol was added the crude methyl ester, and the resulting solution was stirred for 12 h at room temperature. The mixture was then concentrated to dryness, and the resulting solid was recrystallized from methanol to give 1.1 g (32% from **22b**) of **23** as white solid. mp 225−226 °C.$^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.05 (bs, 1H), 7.93 (d, $J$ = 8.8 Hz, 2H), 7.62 (d, $J$ = 2.5 Hz, 1H), 7.14 (d, $J$ = 2.5 Hz, 1H), 7.08 (m, 6H), 5.56 (bs, 1H), 4.15 (t, $J$ = 5.1 Hz, 4H), 3.47 (t, $J$ = 5.1 Hz, 4H). MS ($ES^+$): 394 ($MH^+$). HRMS: calcd for $C_{22}H_{20}N_3O_3F$, 393.14887; found, 393.14929. Anal. ($C_{22}H_{20}N_3O_3F\cdot H_2O$) H, N; C: calcd, 64.23, found, 64.73.

**6-[4-(4-Fluorophenoxy)phenyl]-4-methoxypyridine-2-carboxylic acid amide (24).** To a solution of 1.5 g (4.8 mmol) of compound **22d** in pyridine (36 mL) was added $SeO_2$ (2.1 g, 19 mmol), and the resulting solution was refluxed for 3 days. The cooled reaction mixture was concentrated to dryness and diluted with methanol. It was then filtered through Celite and concentrated to give 1.5 g (100%) of acid.$^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.92 (d, $J$ = 8.8 Hz, 2H), 7.69 (s, 1H), 7.38 (m, 3H), 7.07 (m, 4H), 3.97 (s, 3H). MS ($ES^+$): 321($MH^+$).

The residue was dissolved in methanol (50 mL), and to this solution of crude acid was carefully added thionyl chloride (7 mL, 9.6 mmol). After addition, the resulting solution was

refluxed for 12 h. The cooled reaction mixture was filtered and concentrated to dryness. The residue was then filtered through a plug of silica gel, eluting with 10% triethylamine in ethyl acetate. The filtrate was concentrated to dryness to yield 1.6 g (94%) of the methyl ester as brown solid. mp 86 °C. $^1$H NMR ($CDCl_3$): $\delta$ 7.98 (d, $J$ = 8.7 Hz, 2H), 7.61 (d, $J$ = 2.2 Hz, 1H), 7.33 (d, $J$ = 2.2 Hz, 1H), 7.00 (m, 6H), 4.05 (s, 3H), 4.00 (s, 3H). MS ($ES^+$): 354 ($MH^+$).

To a solution of $NH_3$ (2 M, 10 mL) in methanol was added crude methyl ester (140 mg, 0.39 mmol), and the resulting solution was stirred for 12 h. The mixture was then concentrated to dryness, and the resulting solid was recrystallized from methanol to give 67 mg (50%) of **24** as white solid. mp 202−203 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.31 (d, $J$ = 8.9 Hz, 2H), 8.27 (bs, 1H), 7.70 (bs, 1H), 7.61 (d, $J$ = 2.3 Hz, 1H), 7.47 (d, $J$ = 2.3 Hz, 1H), 7.26 (t, $J$ = 8.7 Hz, 2H), 7.13 (m, 2H), 7.03 (d, $J$ = 9.0 Hz, 2H), 3.94 (s, 3H). MS ($ES^+$): 339 ($MH^+$). HRMS: calcd for $C_{19}H_{15}N_2O_3F$, 338.10667; found, 338.10668. Anal. ($C_{19}H_{15}N_2O_3F\cdot H_2O$) C, N; H: calcd, 4.81, found, 4.00.

**6-[4-(4-Fluorophenoxy)phenyl]-4-methoxy-pyridine-2-carboxy acid (2-(dimethylamino)-ethyl)-amide (25).** Compound **25** was prepared as light brown oil in a manner similar to that described for **24** using **22d** and *N*,*N*-dimethylethylenediamine (94%). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.97 (bs, 1H), 8.10 (d, $J$ = 8.8 Hz, 2H), 7.61 (d, $J$ = 2.2 Hz, 1H), 7.32 (d, $J$ = 2.2 Hz, 1H), 7.05 (m, 6H), 4.00 (m, 1H), 3.96 (s, 3H), 3.78 (m, 1H), 3.63 (m, 1H), 3.45 (s, 3H), 3.27 (bs, 1H), 2.85 (s, 3H). MS ($ES^+$): 410 ($MH^+$). HRMS: calcd for $C_{23}H_{24}N_3O_3F$, 409.18017; found, 409.18035. **25** was converted to an HCl salt for analysis. Anal. ($C_{23}H_{24}N_3O_3F.2HCl\cdot H_2O$) C, H, N.

**In vitro pharmacology.** HEK-293 cell culture. The rat brain NaIIA-B2 cell line (hosted in HEK-293 cells) was established in house using standard techniques. It was found to expresses tetrodotoxin-sensitive (TTX-S) currents with an average $I_{Na}$ amplitude of ∼2.5 nA and with fast activation and inactivation properties characteristic of $Na^+$ channels observed in CHO cells expressing the rat brain IIa channel.[16] HEK-293 cells were cultured using standard techniques. For electrophysiology, cells were plated onto 35-mm Petri dishes (precoated with poly-D-lysine) at a density of ∼$10^4$ cells/dish on the day of reseeding from confluent cultures. HEK-293 cells were suitable for recordings for 3−4 days after plating.

**Drug application.** Drug solutions and intervening intervals of wash were applied through a linear array of flow pipes (Drummond Microcaps, 2-$\mu$L, 64-mm length). Drugs were dissolved in dimethyl sulfoxide (DMSO) to make 1−30 mM stock solutions. The stock solutions were diluted into external solution to generate final concentrations of 0.003−10 $\mu$M. The concentration of DMSO was 0.1%. At this level DMSO itself had only marginal inhibitory effects on the peak $Na^+$ current. For HEK-293 cells external solution contained (in mM): 150 NaCl, 5.4 KCl, 1.8 $CaCl_2$, 1 $MgCl_2$, 10 D-glucose, 5 HEPES; pH 7.4 (NaOH). The internal solution contained (in mM): 130 CsF, 20 NaCl, 1 $CaCl_2$, 2 $MgCl_2$, 10 EGTA, 10 HEPES, pH 7.4 (CsOH); osmolality was set at ∼10 mmol/kg lower than that for external solution.

**Experimental design and data analysis.** To quantify the affinity toward resting state cells were held at −110 mV and pulsed to 0 mV every 2 s to cause maximal $Na^+$ current. At such a negative voltage there was virtually no resting inactivation (≤1%, data not shown). Steady-state currents were measured after at least 1 min in control or drug-containing solutions. The magnitude of inhibition was measured at high drug concentration, usually 3 $\mu$M. From the fractional response (FR) at this concentration the estimate for the apparent dissociation constants for resting state, $K_r$, was obtained using the equation: $K_r$ = {FR/(1 − FR)} *[antagonist], where [antagonist] is concentration of antagonist.

To measure the affinity toward inactivated state a double-pulse protocol was used.[17] From a holding voltage of −110 mV cells were depolarized by a conditioning step to −20 mV for 3 s. This step caused complete inactivation of sodium channels and was long enough to ensure the steady-state for binding to inactivated channels even for the slowest compounds. This step was followed by a short (3 ms) hyperpolarizing gap back to −110 mV, which was sufficient to permit about 80% recovery from inactivation in control. Then a 5 ms test pulse to 0 mV was applied to measure the proportion of channels available for activation. In the presence of a drug only unbound channels have a chance to recover from inactivation at a normal pace since repriming from inactivation is significantly retarded by drug binding. Thus, the current caused by the test pulse reported the proportion of liganded (and blocked) channels. Reduction in the size of the current to test pulses in the presence of a compound was used to calculate the fractional response. For most compounds, a concentration was empirically chosen that caused about 50% inhibition. From the fractional response (FR) at this concentration the estimate for $K_i$ was obtained using the equation: $K_i$ = {FR/(1 − FR)} *[antagonist], where [antagonist] is concentration of antagonist. Data are presented as mean ± standard error.

**Acutely dissociated rat DRG neurons.** Acutely dissociated neurons were prepared from newborn Sprague Dawley rat pups by the technique described by Wilding and Huettner.[11] Liberated cells were plated on poly-D-lysine coated 35 mm plastic Petri dishes and were suitable for electrophysiological recordings for up to two weeks. Recordings were done with Axopatch 200A amplifier and analyzed with pClamp 6 software (Axon Instruments, Inc.). Tetrodotoxin (TTX), 0.4 $\mu$M, was used to dissect TTX-R component of the current. TTX-S currents were collected in a subset of neurons, which did not contain TTX-R component as justified by application of TTX. External solution was (in mM): 65 NaCl, 5 KCl, 50 choline chloride, 1.8 $CaCl_2$, 1 $MgCl_2$, 5 D-glucose, 5 HEPES, 5 HEPES $Na^+$ salt, 20 TEA chloride; pH 7.4 (NaOH). The internal solution contained (in mM): 130 CsF, 20 NaCl, 1 $CaCl_2$, 2 $MgCl_2$, 10 EGTA, 10 HEPES, pH 7.4 (CsOH). Osmolality was set ∼5 mmol/kg lower than that of the bathing solution. Protocol to measure fractional responses was essentially same as for HEK-293 cell culture with exception that depolarizing prepulse was 1 s long and the hyperpolarizing gap was set at 5 ms. Fractional responses were collected at least for three concentrations for each drug to get partial concentration−inhibition curves. Logistic fit to these curves returned $K_i$ values.

**In Vivo Pharmacology. Chung Model.** Male Sprague Dawley rats weighing between 150 and 200 g (Harlan Sprague−Dawley, Inc., San Diego) were anesthetized with halothane. The left branches of L5 and L6 spinal nerves were surgically exposed and tightly ligated with 6.0 silk sutures as previously described.[9] Rats were evaluated prior to surgery and 7 to 28 days post-surgery for the development of tactile allodynia. Manual measurements of tactile sensitivity were performed using Von Frey filaments (North Coast Medical), ranging from 3.64 to 5.46/0.6 to 26 g of pressure. Starting with the largest filament, filaments were applied to the plantar surface of the left hind paw with enough force to cause the filament to bend. This force was either maintained until the rat withdrew the limb, or for a maximum of 4 s. A positive or "allodynic" response was characterized by a sharp withdrawal of the hind limb that may be followed by flicking or licking of the paw. In the event of a positive response, a thinner filament was applied to the left hind paw as described. A negative response, as characterized by lack of reaction to the filament, resulted in cessation of testing. This cycle was repeated three times on each rat and values expressed as the log gram of force. The mean value of the three measurements was determined for each rat and the data expressed as the mean ± standard error (SEM) for each time point. Allodynic rats were defined as those animals with post-surgical baseline withdrawal thresholds below 0.30 log gram units. Rats were fasted for a minimum of 6 h prior to drug administration. A minimum 48-hour washout was allowed for each rat prior to subsequent experimental repetitions. Animals in the vehicle group were administered 1% DMSO, 10% TWEEN-80 PO. Drugs were administered orally at a volume of 10 mL/kg bodyweight.

Tactile allodynia measurements were recorded at 1, 2, 4, and 24 h postdrug administration.

**Acknowledgment.** We thank Dr. L. Zhou, Dr. F. Cheng, Ms. E. Dharmgrongartama for analytical support, and Mr. M. Suruki for technical assistance on the rotarod assay. We thank Dr. R. Woodward for fruitful discussions and help in the preparation of this manuscript.

**Supporting Information Available:** Proton NMR spectra, HRMS, LCMS spectra, and reverse-phase HPLC chromatograms of compounds in Table 1. This material is available free of charge via Internet at http://pubs.acs.org.

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JM040048D