Discovery and Biological Evaluation of 5-Aryl-2-furfuramides, Potent and Selective Blockers of the $Na_v1.8$ Sodium Channel with Efficacy in Models of Neuropathic and Inflammatory Pain

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$Na_v1.8$ (also known as PN3) is a tetrodotoxin-resistant (TTx-r) voltage-gated sodium channel (VGSC) that is highly expressed on small diameter sensory neurons and has been implicated in the pathophysiology of inflammatory and neuropathic pain. Recent studies using an $Na_v1.8$ antisense oligonucleotide in an animal model of chronic pain indicated that selective blockade of $Na_v1.8$ was analgesic and could provide effective analgesia with a reduction in the adverse events associated with nonselective VGSC blocking therapeutic agents. Herein, we describe the preparation and characterization of a series of 5-substituted 2-furfuramides, which are potent, voltage-dependent blockers (IC_{50} < 10 nM) of the human $Na_v1.8$ channel. Selected derivatives, such as **7** and **27**, also blocked TTx-r sodium currents in rat dorsal root ganglia (DRG) neurons with comparable potency and displayed >100-fold selectivity versus human sodium ($Na_v1.2$, $Na_v1.5$, $Na_v1.7$) and human ether-a-go-go (hERG) channels. Following systemic administration, compounds **7** and **27** dose-dependently reduced neuropathic and inflammatory pain in experimental rodent models.

Introduction

Voltage-gated sodium channels (VGSCs) are transmembrane proteins that open in response to changes in membrane potential to enable selective permeability for sodium ions.[1] These channels belong to a multigene family consisting of nine members, which can be distinguished pharmacologically on the basis of their sensitivity to blockade by natural toxins, particularly tetrodotoxin (TTx).[2,3] VGSCs contribute to the initiation and propagation of action potentials in excitable tissues such as nerve and muscle and participate in many physiological processes including locomotion, cognition, and nociception.[4–6]

Considerable data support the hypothesis that hyperexcitability and spontaneous action potential firing mediated by VGSCs in peripheral sensory neurons play a role in the pathophysiology of chronic pain.[7,8] Consistent with this hypothesis, nonselective blockade of sodium channels contributes to the analgesic activity of a number of clinically used agents, developed for other indications, such as mexiletine, lamotrigine, and carbamazepine (Figure 1). However, all of these drugs penetrate the CNS, possess off-target activities, and give rise to adverse events in the clinical setting.[9]

$Na_v1.8$ (also known as PN3) is a TTx-resistant (TTx-r) VGSC that is preferentially expressed on sensory neurons[10] and carries a major portion of the TTX-r current in peripheral nerves.[11] The highly localized distribution of $Na_v1.8$ in nociceptive small diameter neurons suggests this channel may be involved in the generation of action potentials in response to painful stimuli.[12] Altered levels of expression of $Na_v1.8$ in chronic pain states,[13] gene knockout data,[14–16] and analgesic effects of $Na_v1.8$-specific antisense oligodeoxynucleotides[17–19] provide compelling corroborative evidence supporting $Na_v1.8$ as an attractive target for analgesic drug discovery.[20,21]

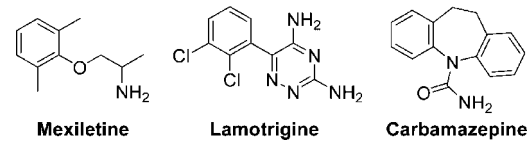

Figure 1. Clinically used sodium channel blockers.

The clinical utility of nonselective VGSC blockers may be a result of either a voltage-dependent mechanism of inhibition (preferential binding to the inactivated state of the channel), frequency-dependent (progressive channel block with repeated stimulation) biophysical properties, or the combination of both effects.[22,23] The available data indicate that the absence of subtype selectivity across the VGSC family may be principally responsible for the limited therapeutic indices associated with existing therapeutics.[12] Consequently, the clinically observed adverse effects of those agents might be mitigated by selectively targeting the $Na_v1.8$ subtype. Herein, we report the discovery of a series of subtype-selective small-molecule $Na_v1.8$ blockers and their characterization as novel analgesic agents.[24]

The furfuryl glycinamide derivative **1** (Figure 2) was identified as a hit from a focused screening strategy using an $Na_v1.8$ isotopic flux assay.[25,26] Whole cell voltage clamp electrophysiological characterization of this compound revealed modest potency in blocking half-maximally inactivated native rat TTX-r currents in dissociated dorsal root ganglia (DRG) neurons (estimated $IC_{50} = 10\ \mu M$) and recombinant human $Na_v1.8$ channels (estimated $IC_{50} \approx 0.9\ \mu M$). Furthermore, **1** showed similar inhibitory activity against other sodium channels (e.g., $hNa_v1.2$, $hNa_v1.5$) and significant activity in a human ether-a-go-go (hERG) flux assay ($IC_{50} = 0.8 \pm 0.1\ \mu M$).

A preliminary appraisal of **1** and available analogues led to an iterative truncation strategy whereby the structural determi-

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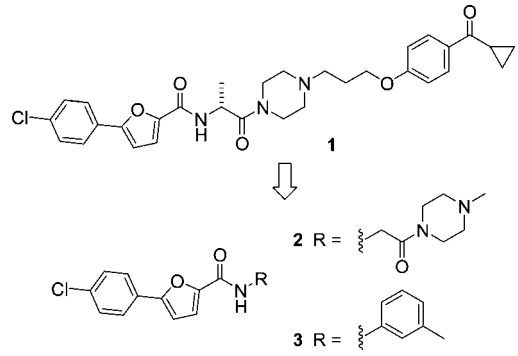
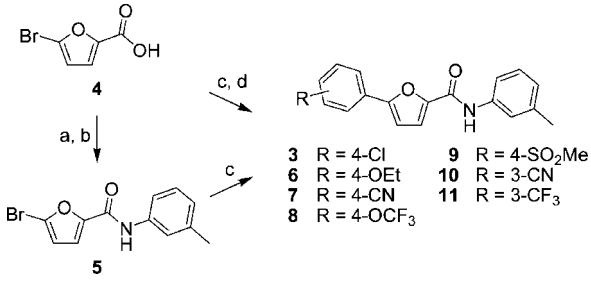


Figure 2. Furan glycinamide screening hit.

Scheme 1[a]



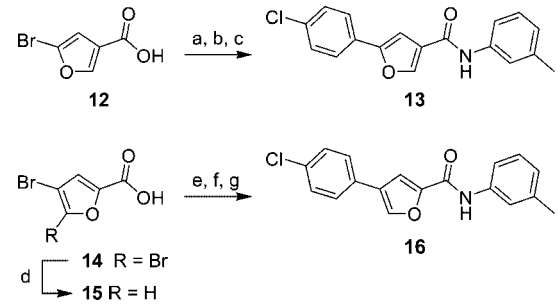
[a] Reagents: (a) $(COCl)_2$, cat. DMF, CH_2Cl_2, 23 °C; (b) *m*-toluidine, Et_3N, CH_2Cl_2, 23 °C; (c) arylboronic acid, $PdCl_2(PPh_3)_2$, aqueous Na_2CO_3, *i*-PrOH, reflux; (d) *m*-toluidine, BOP reagent, Et_3N, CH_2Cl_2, 23 °C.

nants conferring sodium channel activity and selectivity could be distilled from this relatively large (MW = 600), conformationally mobile starting point. Initial SAR studies revealed that the entire region comprising the cyclopropyl ketone, aryloxy, and alkylpiperazine moieties of **1** could be eliminated (**1** → **2**) without appreciable loss of $Na_v1.8$ activity. Similarly, the D-glycine residue linking the furfuroic acid and piperazine fragments could be excised if appropriate substitution was reintroduced in the form of an N-substituted furan carboxamide (**2** → **3**). On the other hand, deviation from sp^2-hybridizaton at the C-2 substituent on the furan core had a deleterious effect on activity. Likewise, removal of the C-5 aryl ring gave inactive compounds. Introduction of a basic nitrogen (ionizable at physiological pH) imparted favorable physicochemical properties albeit with erosion of selectivity versus sodium channel subtypes. These findings set the stage for a more detailed investigation of 5-aryl-2-furfuramide derivatives, the syntheses of which are detailed in Schemes 1–3.

Chemistry

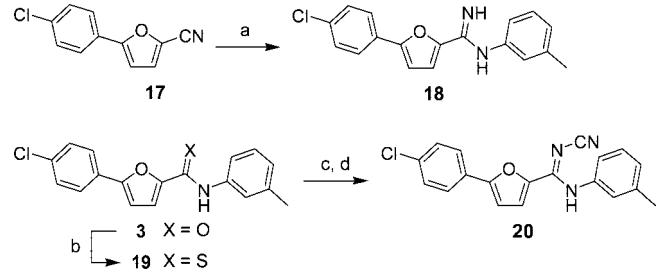
The influence of the furyl C-5 substituent on $Na_v1.8$ activity was evaluated via a series of 5-aryl derivatives (**3**, **6**−**11**) that were prepared (Scheme 1) from the commercially available 5-bromo-2-furfuroic acid (**4**). Reaction of the acid chloride **4** with *m*-toluidine and subsequent Suzuki coupling[27] provided a convenient route to the desired compounds. Alternatively, the sequence of carbon−carbon bond generation and amide formation could be reversed without a deleterious effect on overall yield. Coupling with BOP reagent[28] proved particularly suitable for the synthesis of certain amide derivatives. The regioisomeric 3,5- and 2,4-variants of **3** (**13** and **16**, respectively) were made by a similar series of transformations (Scheme 2) involving precursors **12** and **14**, respectively. In particular, access to **16**[29] was accomplished via the intermediacy of **15**, which was delivered in high yield by selective dehalogenation of 4,5-

Scheme 2[a]



[a] Reagents: (a) 4-chlorophenylboronic acid, $Pd(PPh_3)_4$, aqueous Na_2CO_3, DME, 23 °C; (b) $(COCl)_2$, cat. DMF, CH_2Cl_2, 23 °C; (c) *m*-toluidine, Et_3N, CH_2Cl_2, 23 °C, 51% for three steps; (d) Zn, aqueous NH_4OH, 23 °C, 98%; (e) 4-chlorophenylboronic acid, $PdCl_2(PPh_3)_2$, Na_2CO_3, *i*-PrOH, reflux; (f) $(COCl)_2$, cat. DMF, CH_2Cl_2, 23 °C; (g) *m*-toluidine, Et_3N, CH_2Cl_2, 23 °C, 54% for three steps.

Scheme 3[a]



[a] Reagents: (a) *m*-toluidine hydrochloride, $AlMe_3$, $PhCH_3$, 23 →110 °C, 67%; (b) Lawesson's reagent, $PhCH_3$, 110 °C, 99%; (c) MeI, CH_3CN, 23 °C; (d) $NCNH_2$, Et_3N, EtOH, 80 °C, 34% for two steps.

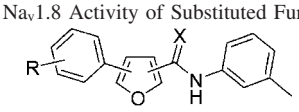
dibromo-2-furfuroic acid (**14**) with zinc metal.[30] The preparation of several isosteric replacements for the carbonyl residue in **3** is outlined in Scheme 3. Addition of 3-aminotoluene to 2-cyanofuran **17**[31] in the presence of trimethylaluminum provided amidine **18**, which could be conveniently isolated as the hydrochloride salt. Exposure of **3** to Lawesson's reagent[32] generated **19**, which was further elaborated to the corresponding cyanoamidine **20** by S-methylation and reaction with cyanamide.

Biological Evaluation

Compounds were evaluated for their ability to block the recombinant mouse $Na_v1.8$ sodium channel stably expressed in HEK293 cells using a modified version of an isotopic efflux assay.[25] Subsequently, the activity of a subset of potent blockers was confirmed by measuring their inhibition of TTx-r currents in dissociated rat DRG neurons and sodium currents in human $Na_v1.8$ expressing HEK293 cells using conventional voltage-clamp electrophysiology.[24] Selected analogues were also further examined for their selectivity versus other human sodium channel subtypes stably expressed in HEK293 cells. Since the biophysical properties vary among sodium channel subunits,[2,3] 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) or to a voltage that sets all channels in a resting state to allow a direct comparison of compound effects across channel subtypes (see Table 4 for details). Finally, compounds were tested against the hERG channel[33] and a series of other channels and receptors expressed in peripheral sensory neurons and, in some cases, against a broad (n = 70) receptor screening panel.[24]

On the basis of their pharmacokinetic profiles, compounds were further evaluated for analgesic efficacy using in vivo

Table 1. In Vitro $Na_v1.8$ Activity of Substituted Furan Derivatives[a]



compd	isomer	X	R	$Na_v1.8$ IC_{50} (μM)
3	2,5-	O	4-Cl	0.48 ± 0.32
6	2,5-	O	4-OEt	0.43 ± 0.07
7	2,5-	O	4-CN	0.48 ± 0.023
8	2,5-	O	4-OCF_3	0.29 ± 0.04
9	2,5-	O	4-SO_2Me	>30[b]
10	2,5-	O	3-CN	30 ± 9
11	2,5-	O	3-CF_3	7.5 ± 0.7
13	3,5-	O	4-Cl	20 ± 9
16	2,4-	O	4-Cl	5.3 ± 1.1
18	2,5-	NH	4-Cl	1.9 ± 0.1
20	2,5-	NCN	4-Cl	0.03 ± 0.01

[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 $Na_v1.8$ isotopic efflux assay as described in Experimental Section. Data shown with standard error (±SEM) represent the mean of two to five separate determinations. [b] An IC_{50} value could not be calculated because of low potency.

models of inflammatory and neuropathic pain.[34] These assays included the complete Freund's adjuvant (CFA) induced hyperalgesia model of chronic inflammatory pain, as well as the L5/L6 spinal nerve tight ligation (Chung) and sciatic nerve loose ligation (Bennett) models of neuropathic pain.[18,34,35]

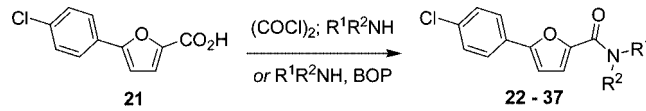
Results and Discussion

Our investigation of the furfuramides began by probing the requirements of the C-5 furan substituent (Table 1). It quickly became evident that full or partial saturation, deletion, or one-carbon homologation of the C-5 aryl ring resident in **3** led to a significant drop in $Na_v1.8$ blocking activity (data not shown). Our focus was thus directed to aromatic substitution at the 5-position of the furan. Within this selection of derivatives, substitution at the 4-position of the appended phenyl ring with relatively small (one to three atoms) substituents as in **3** and **6**−**8** proved optimal. Although functionalization at the 3-position of the aryl ring was tolerated (e.g., **10** and **11**), it generally led to a half-log or greater decrease in potency in the mouse $Na_v1.8$ flux assay (compare **7** versus **10**)., The corresponding ortho-substituted aryl subunits typically displayed very weak (IC_{50} > 30 μM, data not shown) inhibition of $Na_v1.8$ channels. The 3,5- and 2,4-regioisomers **13** and **16**, respectively, proved to be significantly less potent $Na_v1.8$ blockers than the 2,5-isomer **3**.

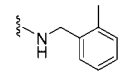
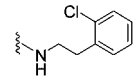
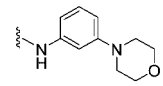
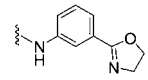
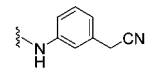
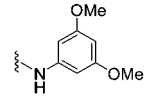
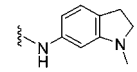
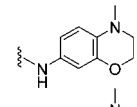
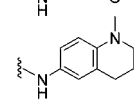
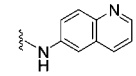
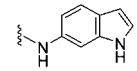
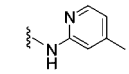
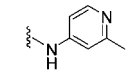
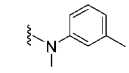
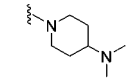
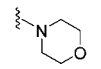
The limited aqueous solubility of these initial anilide derivatives (e.g., <0.1 μg/mL for **3**) was an impediment to definitively assessing their pharmacokinetic properties in vivo.[36] Subsequent exploration of structure–activity relationships was therefore driven by the need for changes that could improve physicochemical properties. Modification of the carboxamide linker was one approach pursued. Unsubstituted amidine **18** was less potent relative to **3** but offered the advantage of an ionizable group, which imparted enhanced water solubility (250 μg/mL as the hydrochloride salt). Furthermore, **18** possessed modest in vitro intrinsic clearance (220 μL min^{-1} mg^{-1}) and excellent oral bioavailability (F = 67% at 10 mg/kg) in rat. Conversely, increased potency was realized with the corresponding cyanoamidine **20**, wherein the amidine nitrogen is completely nonbasic. Analogues derived from replacement of either the amide carbonyl or nitrogen with a methylene unit or from inversion of the amide connectivity to the furan ring were inactive (IC_{50} > 30 μM) against $Na_v1.8$ channels.

With the establishment of the preferred relative orientation and substitution pattern of appendages on the furfuramide nucleus, an extensive survey of amide substitution was undertaken. In addition to defining the structural requirements for the pharmacophore, these efforts were focused on improving the aforementioned solubility limitations, as well as the rapid

Table 2. In Vitro $Na_v1.8$ Activity of Selected 5-(4-Chlorophenyl)furan Carboxamides[a]



21 22 - 37

Cmpd	—NR^1R^2	$Na_v1.8$ IC_{50}, μM
22		1.1 ± 0.3
23		1.9 ± 0.2
24		4.6 ± 0.01
25		2.5 ± 0.6
26		1.7 ± 0.1
27		0.85 ± 0.30
28		4.6 ± 0.2
29		0.97 ± 0.13
30		2.9 ± 0.2
31		10 ± 0.3
32		3.1 ± 0.6
33		0.96 ± 0.55
34		2.5 ± 1.1
35		3.4 ± 1.2
36		5.2 ± 0.1
37		>30[b]

[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 $Na_v1.8$ isotopic efflux assay as described in Experimental Section. Data shown with standard error (±SEM) represent the mean of two to five separate determinations. [b] An IC_{50} value could not be calculated because of low potency.

Table 3. Activity of Selected Furyl Carboxamides in Blocking Native TTx-r Currents in Rat Dorsal Root Ganglia and in HEK-293 Cells Expressing Human $Na_v1.8$[a]

	rat DRG TTx-r			hNa$_v$1.8		
		% inhib			% inhib	
compd	concn (μM)	$V_{1/2}$[b]	V_0[c]	concn (μM)	$V_{1/2}$[b]	V_0[c]
3	0.3	60 ± 6	18 ± 1	0.1	77 ± 1	67 ± 6
	0.1	37 ± 4	3 ± 2	0.03	68 ± 1	61 ± 1
7	0.3	74 ± 4	52 ± 2	0.03	51 ± 3	29 ± 2
	0.1	41 ± 5	38 ± 1	0.01	33 ± 2	14 ± 3
8	0.3	63 ± 2	30 ± 7	0.003	73 ± 1	33 ± 3
	0.1	40 ± 1	25 ± 5	0.001	40 ± 9	7 ± 3
18	1	60 ± 1	10 ± 3	1	75 ± 1	5 ± 2
	0.3	45 ± 3	2 ± 1	0.1	46 ± 4	1 ± 1
20	0.03	71 ± 6	45 ± 4	0.03	99 ± 2	94 ± 1
	0.003	51 ± 1	22 ± 3	0.001	76 ± 1	46 ± 2
27	0.3	71 ± 2	48 ± 1	0.01	59 ± 2	19 ± 2
	0.1	42 ± 1	14 ± 4	0.003	30 ± 4	5 ± 3
30	0.03	79 ± 1	28 ± 9	0.3	70 ± 3	66 ± 1
	0.003	44 ± 7	31 ± 3	0.03	56 ± 7	27 ± 3
33	10	88 ± 2	42 ± 6	3	81 ± 4	83 ± 2
	1	36 ± 1	9 ± 3	1	42 ± 6	58 ± 6

[a] Data shown with standard error (±SEM) represent the mean of two to six separate determinations. [b] Inactivated state protocol: the prepulse voltage at which 50% of channels are inactivated ($V_{1/2} = -40$ mV). [c] Resting state protocol: the prepulse voltage at which 100% of channels are available to be activated ($V_0 = -100$ mV).[24]

Table 4. Sodium Channel Selectivity of Selected Furylcarboxamide $Na_v1.8$ Blockers Measured at Half-Maximal Inactivation for Each Channel Subtype[a]

				% inhib				
compd	concn (μM)	% inhib hNa$_v$1.8[a]	concn (μM)	hNa$_v$1.2	hNa$_v$1.3	hNa$_v$1.5	hNa$_v$1.7	hERG IC_{50} (μM)[c]
3	0.1	77 ± 1	3	54 ± 4	61 ± 7	51 ± 6	41 ± 1	27 ± 3
	0.03	68 ± 1	1	33 ± 3	17 ± 5	ND[b]	ND[b]	
7	0.03	51 ± 3	10	57 ± 4	58 ± 7	74 ± 5	54 ± 3	5.8 ± 0.8
	0.01	33 ± 2	3	32 ± 10	47 ± 3	61 ± 7	26 ± 6	
8	0.003	73 ± 1	1	84 ± 4	ND[b]	87 ± 6	ND[b]	>30[d]
	0.001	40 ± 9	0.1	47 ± 1		52 ± 9		
18	1	75 ± 1	1	52 ± 1	36 ± 3	56 ± 3	ND[b]	2.1 ± 0.3
	0.1	46 ± 4						
20	0.03	99 ± 2	0.3	94 ± 2	24 ± 5	69 ± 5	70 ± 3	>30
	0.001	76 ± 1	0.03	91 ± 4	ND[b]	32 ± 3	ND[b]	
27	0.01	59 ± 2	10	53 ± 3	70 ± 4	49 ± 2	54 ± 4	>30
	0.003	30 ± 4	3	41 ± 5	52 ± 3	44 ± 2	42 ± 3	
30	0.3	70 ± 3	3	38 ± 6	37 ± 6	71 ± 1	44 ± 1	5.3 ± 0.9
	0.03	55 ± 5						
33	3	81 ± 4	1	12 ± 1	5 ± 5	24 ± 7	ND[b]	>30
	1	42 ± 6						

[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 prepulse voltage at which 50% of channels are inactivated). $V_{1/2} = -60$ mV for hNa$_v$1.2, hNa$_v$1.3, hNa$_v$1.7; $V_{1/2} = -90$ mV for hNa$_v$1.5.[24] [b] Not determined (compound was not tested). [c] IC_{50} values were determined by least-squares fitting of a logistic equation to data from full eight-point, half-log concentration–response curves. Data shown with standard error (±SEM) represent the mean of two to five separate determinations using a $Na_v1.8$ isotopic efflux assay as described in the Experimental Section. [d] An IC_{50} value could not be calculated because of low potency.

in vitro microsomal turnover generally observed with more lipophilic derirvatives (e.g., 850 μL min^{-1} mg^{-1} for **3**). As summarized in Table 2, relatively conservative alterations, such as one- or two-carbon elongation of the amide−aryl spacer (**22** and **23**, respectively), were tolerated but did not provide superior potency or microsomal stability. Placement of substituents at the 3-position (**24**-**27**) of the aryl amide, or at both the 3- and 4-positions as a fused heterocycle (**28**-**30**) or fused heteroaromatic (**30**, **31**), yielded active $Na_v1.8$ blockers with varying levels of potency. The inclusion of functionality bearing a heteroatom at these positions enhanced physicochemical properties, although weaker activity generally was noted with bicyclic systems, such as quinoline **31**. The activities of **33** and **34**, both pyridine analogues of **3**, were sensitive to regiochemistry, with **33** affording potency comparable to the most active disubstituted derivative (**27**). As evidenced with **35**, N-methylation of the amide residue resulted in an appreciable loss of $Na_v1.8$ activity relative to **3**. Saturated functional groups on the amide, including those bearing a heteroatom (e.g., **36**, **37**), were typically weaker $Na_v1.8$ blockers.

Active compounds, as assessed by preliminary $Na_v1.8$ flux data, were studied further using voltage-clamp electrophysiological recordings. As shown in Table 3 significant block of TTx-r currents in dissociated DRG neurons and in human $Na_v1.8$ expressing HEK293 cells was observed at both resting and half-maximal inactivated states; a consistent trend toward greater potency relative to the flux assay was noted. A number of these analogues (**8**, **20**, **27**) possessed estimated IC_{50} values in the single-digit nanomolar range. For comparison, mexiletine and lamotrigine produced <50% $Na_v1.8$ block at 30 μM under these assay conditions. In addition, the furfuramides generally exhibited greater potency following more depolarized prepulse potentials (−40 mV), possibly reflecting preferential affinity for the inactivated (−40 mV) versus resting (−100 mV) states of the $Na_v1.8$ channel. This voltage-dependent/state-dependent behavior is similar to that observed with other sodium channel blockers such as local anesthetics and other clinically used agents, although the absolute differences in potency between states are not as great.[12,37] A trend toward decreased potency was noted for blockade of native TTx-r currents in rat DRG

Table 5. In Vivo Activity[a] and Pharmacokinetic Profile[b] of $Na_v1.8$ Blockers **7** and **27**

	7	27
human $Na_v1.8$ IC_{50} (μM)[c]	0.079	0.008
native rat $Na_v1.8$ IC_{50} (μM)[c]	0.240	0.125
Chung ED_{50}, ip, mg/kg (% effect)	38 (86 ± 9)	47 (70 ± 12)
Bennett ED_{50}, ip, mg/kg (% effect)	>100 (21 ± 8)	85 (56 ± 10)
CFA ED_{50}, ip, mg/kg (% effect)	98 (55 ± 11)	41 (64 ± 6)
CL_{int} ((μL/min)/mg)[d]	260	140
F, po (%)	1 ± 0.3	13 ± 2
F, ip (%)	36 ± 4	26 ± 4
Clp (L/(h·kg))	2.4 ± 0.5	1.5 ± 0.2
$T_{1/2}$ (h)	1.9 ± 0.5	7.3 ± 1.2
C_{max}, ip (μg/mL)	0.75	0.35
V_{ss} (L/kg)	1.9 ± 0.5	6.4 ± 0.9
[brain]/[plasma]	0.35	1.1
plasma protein binding, rat (%)	98.3 ± 0.4	98.7 ± 0.4
Cerep (at 10 μM)[e]	BZD peripheral	BZD peripheral, CCK_A, D1, ML_1, 5-HT_{2A}

[a] Values shown with standard error (±SEM) represent the mean for experiments in rats, $n = 6$ per dose group. [b] Determined in rats ($n = 6$) following administration of a 5 mg/kg iv or 10 mg/kg ip dose. [c] Measured at $V_{1/2}$ (−40 mV). IC_{50} values were determined by least-squares fit of the Hill equation and were based on two to six independent determinations at four or more concentrations. [d] Intrinsic clearance based on incubation with rat microsomes (1 h, 37 °C). [e] Displayed >60% inhibition of control specific binding at indicated receptor.

neurons versus recombinant human $Na_v1.8$ channels. This apparent difference in activity most likely reflects a difference in native versus recombinant channels rather than a species difference between rat and human $Na_v1.8$ channels.[24] Nonetheless, it was still possible to identify highly potent analogues (e.g., **3**, **30**) in the native rat system.

The potent $Na_v1.8$ blockers identified in Table 3 were evaluated for their activity at other sodium channel subtypes and liability targets. Table 4 shows the activity of these compounds at $Na_v1.2$, 1.3, 1.5, and 1.7 (3 μM), as well as at the hERG channel (IC_{50}). The majority of compounds in Table 4 were approximately 100- to 1000-fold more potent in blocking $Na_v1.8$ compared to their activity at other sodium channels (e.g., **27**). For example, **3**, **7**, and **30** displayed $Na_v1.8$ selectivity comparable to **27** for all subtypes except $Na_v1.5$, where the potency versus $Na_v1.8$ was reduced to approximately 10- to 100-fold. Insertion of additional nitrogen atoms anywhere in the molecule was usually detrimental to sodium channel selectivity (e.g., **20**, **33**) and hERG selectivity (e.g., **7**, **30**) or both (e.g., **18**). In contrast, more lipophilic derivatives did not show any significant activity at the hERG channel. Compounds **7** and **27** were also tested against other channels and receptors expressed in peripheral sensory neurons including TRPV1, $P2X_{2/3}$, $Ca_v2.2$ calcium channels, and KCNQ2/3 potassium channels; neither had significant activity at these channels ($IC_{50} > 10$ μM). In addition, both were evaluated in a broad screening panel ($n = 70$) of cell-surface receptors, ion channels, and enzymes (CEREP, Poitiers, France) and showed no or weak ($IC_{50} > 2$ μM) activity (see Table 5).

The potency, selectivity, and pharmacokinetics (Table 5) of several 5-aryl-2-furfuramide analogues made them useful tools for evaluation of the analgesic effects of $Na_v1.8$ blockade. Intraperitoneal (ip) administration of either **7** or **27** resulted in dose-dependent attenuation of mechanical allodynia in the L5/L6 spinal nerve injury (Chung) model of neuropathic pain ($ED_{50} = 56$ and 47 mg/kg, respectively). These two analogues also dose-dependently reduced mechanical allodynia in the chronic constriction injury of the sciatic nerve (Bennett) model of neuropathic pain and thermal hyperalgesia in a CFA-induced inflammatory pain model. Both **7** and **27** penetrated the CNS; however, at doses up to 300 mg/kg (ip), **27** did not significantly impair either motor function or motor coordination and balance.[24]

Conclusion

We have identified a novel series of furan-based derivatives that are potent, selective blockers of the $Na_v1.8$ sodium channel. To our knowledge, this disclosure is the first demonstration of a small-molecule blocker of sodium channels showing both high potency and subtype selectivity among the sodium channel family.[38–40] SAR studies established the preferred C-5 aryl and amide substituents for $Na_v1.8$ activity in the more potent 2,5-furan regioisomers. This activity was confirmed with human $Na_v1.8$ channels and in isolated rat DRG neurons using electrophysiological recordings. In general, significant structural variation was not well tolerated on the C-5 phenyl group or in the 2-furfuramide region. Incorporation of certain heterocycles or amidine isosteres of the amide imparted a more favorable balance of $Na_v1.8$ and physiochemical properties, but typically the improvements came at the expense of subtype selectivity. The limited physicochemical and pharmacokinetic properties of many lead compounds complicated evaluation of their analgesic profiles in vivo. However, consistent with their in vitro profiles, the systemic administration of both **7** and **27** produced dose-dependent antinociceptive effects in three rodent pain models. In summary, these data demonstrate that acute and selective pharmacological blockade of $Na_v1.8$ sodium channels produces significant antinociception in animal models of neuropathic and inflammatory pain.

Experimental Section

General Procedures. Nuclear magnetic resonance spectra were obtained on a General Electric QE 300 or QZ 400 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 cm × 6 cm Kieselgel 60 F-254 plates precoated 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 mmHg. With the exception of amines, solvents and reagents were purchased from Aldrich Chemical Co. and were used without further purification unless otherwise specified. All amines were dried over molecular sieves (4 Å) for at least 24 h prior to use.

High-Throughput Mouse $Na_v1.8$ and hERG Isotopic Flux Assays. HEK293 cells stably expressing mouse $Na_v1.8$ Na channels or CHO cells stably expressing hERG K channels were loaded overnight with an appropriate radiotracer, followed by stimulation using variations on protocols previously described.[25,26] The radiotracer efflux was measured at a single time point that had been previously established to be on the linear portion of the efflux curve. Percentage inhibition of efflux was calculated as

$$\% \text{ inhibition} = 1 - \frac{\text{efflux(test compound)} - \text{efflux(ref blocker)}}{\text{efflux(control)} - \text{efflux(ref blocker)}} \times 100$$

Reference blockers for $Na_v1.8$ and hERG assays were tetracaine (30 μM) and terfenadine (30 μM), respectively. Concentration-

dependent activity was established via eight-point concentration–response curves, and assays were performed in duplicate.

Electrophysiology.[24,41] Rat Dorsal Root Ganglion Neurons.[42] Whole-cell patch clamp recordings were performed on dissociated rat small diameter DRG neurons (18–25 μm) from the L4 and L5 lumbar region at room temperature. For voltage clamp recordings, pipet solution contained (mM) the following: CsF 135, NaCl 5, CsCl 10, EGTA 5, HEPES 10, pH 7.2 (osmolarity, 285). The external solution contained the following (mM): NaCl 22, choline-Cl 110, $CaCl_2$ 1.8, $MgCl_2$ 0.8, HEPES 10, glucose 5, TTx 0.0005, $CdCl_2$ 0.1, pH 7.4 (osmolarity, 310).

Recombinant Human Sodium Channels. Human embryonic kidney (HEK-293) cells expressing recombinant sodium channels were grown in DMEM/high glucose Dulbecco's media, 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 5 M CsOH. Voltage offset was zeroed prior to seal formation. The external buffer consisted of the following (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 6 N NaOH. After establishment of a whole-cell recording, cellular capacitance was minimized using the analogue compensation available on the recording amplifier (Axopatch 200B). Series resistance was less than 5 MΩ and was compensated by >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.

Electrophysiological Recordings. Coverslips were mounted in a small flow-through chamber on the stage of an inverted microscope and were continuously perfused with bath external solution (see below). Cells were voltage-clamped via the whole cell configuration of the patch clamp with an Axopatch-200B amplifier (Molecular Devices/Axon Instruments, Foster City, CA) using standard techniques. Micropipettes were pulled from thin-walled borosilicate glass capillaries (TW-150F, World Precision Instruments, Saratoga, FL) with a Flaming Brown micropipette puller (P97, Sutter Instrument, Novato, CA) and polished on a microforge (Narishige, Tokyo) to obtain electrode resistances ranging from 1.0 to 2.5 MΩ. The pipet solution contained the following (in mM): 135 CsF, 5 NaCl, 10 HEPES, 10 CsCl, and 5 EGTA, pH 7.4 with CsOH (295 mOSM). Capacity transients were canceled, and series resistance was compensated (>80%) using the facilities of the amplifier. The bath solution contained the following (in mM): 110 choline-Cl, 22 NaCl, 5.4 KCl, 1.8 $CaCl_2$, 0.8 $MgCl_2$, 10 HEPES, and 5 glucose, plus 500 nM tetrodotoxin (TTx) and 50 μM $CdCl_2$, pH 7.4 with NaOH (300 mOSM). The pipet potential was zeroed before seal formation. Calculated liquid junction potentials were <5 mV and were not corrected. Whole cell currents were filtered at 5 kHz and acquired at 20 kHz using Clampex 8.2 software (Molecular Devices/Axon Instruments) and analyzed using Clampfit 8.2 (Molecular Devices/Axon Instruments). All experiments were performed at room temperature (21–25 °C). Compounds were dissolved in DMSO (10 mM) and added to extracellular solution (final DMSO concentration of <0.1%) immediately prior to use. Compounds were applied directly to the voltage-clamped cells at a flow rate of 1–2 mL/min via a custom-made perfusion manifold connected to an array of gravity-fed reservoirs. Sodium currents were evoked from a holding potential of −100 mV by a test pulse of 0 mV for 20 ms and pulsed every 15 s until stabilized. To measure drug effects, sodium currents were evoked with 20 ms steps to 0 mV following 8 s prepulses to either −100 or −40 mV. The prepulse was followed by a brief (20 ms) repolarization to −100 mV to relieve fast inactivation.

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 were 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 posthoc comparisons ($P < 0.05$) as previously described.[35] ED_{50} values were estimated using least-squares linear regression.

Spinal Nerve (L5/L6) Ligation Model of Neuropathic Pain. As previously described in detail by Kim and Chung,[43] 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, and the L5 and L6 spinal nerves were 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.

Sciatic Nerve Ligation Model of Neuropathic Pain. As previously described in detail by Bennett and Xie,[44] a 1.5 cm incision was made 0.5 cm below the pelvis in anesthetized rats, and the biceps femoris and the gluteous superficialis (right side) were separated. The sciatic nerve was exposed and isolated, and four loose ligatures (5–0 chromic catgut) with 1 mm spacing were placed around it. The rats were allowed to recover and then placed in a cage with soft bedding for 14 days before behavioral testing for mechanical allodynia as described above. Animals were also tested for mechanical allodynia using calibrated von Frey filaments (Stoelting, Wood Dale, IL). Briefly, rats were placed into individual Plexiglas containers and allowed to acclimate for 15–20 min before testing. Paw withdrawal threshold was determined by increasing and decreasing stimulus intensity and estimated using a Dixon nonparametric test. Only rats with threshold scores of ≤4.5 g were considered allodynic and utilized in compound testing experiments.

Complete Freund's Adjuvant (CFA) Induced Thermal Hyperalgesia. Unilateral inflammation was induced by injecting 150 μL of a 50% solution of complete Freund's adjuvant (CFA) (Sigma Chemical Co., St. Louis, MO) in physiological saline into the plantar surface of the right hind paw of the rat. CFA was injected 2 days before behavioral testing for thermal hyperalgesia.

Representative Procedure for Conversion of Carboxylic Acid Derivatives to Amides via Acid Chlorides (Method A). 5-Bromo-*N*-(3-methylphenyl)furan-2-carboxamide (4). 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 reaction mixture was stirred at ambient temperature for 2 h, and then solvent and excess oxalyl chloride were removed under reduced pressure to yield the intermediate acid chloride, which was used without further purification.

The crude acid chloride was redissolved in dichloromethane (10 mL), treated with *m*-toluidine (530 mg, 5.00 mmol) and triethylamine (1.50 mL, 11.0 mmol), and stirred at ambient temperature for 2 h. The mixture was diluted with additional dichloromethane (5 mL) and washed with 0.5 M HCl (10 mL) and brine (10 mL). The organic portion was dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (elution with 5% EtOAc in CH_2Cl_2), and the isolated product was crystallized from 25% EtOAc/hexanes to provide 1.15 g (4.12 mmol, 82%) of the desired product as off-white needles: mp 98–100 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.09 (s, 1H), 7.55 (s, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.36 (d, J = 3.4 Hz, 1H), 7.22 (t, J = 7.7 Hz, 1H), 6.93 (d, J = 7.4 Hz, 1H), 6.82 (s, 1H), 2.30 (s, 3H); MS (DCI/NH_3) m/z 280, 282 $(M + H)^+$. Anal. ($C_{12}H_{10}BrNO_2$) C, H, N.

Representative Procedure for Suzuki Reaction of Bromofurans and Arylboronic Acids (Method B). .5-(4-Chlorophenyl)-*N*-(3-methylphenyl)furan-2-carboxamide (3). To a suspension of **4** (375 mg, 1.34 mmol) in isopropanol (15 mL) and water (5 mL) was added 3-chlorophenylboronic acid (262 mg, 1.67 mmol). $PdCl_2(PPh_3)_2$ (29 mg, 0.039 mmol) and sodium carbonate (708 mg, 6.68 mmol) were added, the reaction vessel was equipped with a reflux condenser, and the mixture was heated at 80 °C for 5 h. The reaction mixture was diluted with EtOAc (30 mL) and additional water (10 mL) and was then partitioned. The organic portion was washed with 2 N HCl (5 mL) followed by brine (10 mL) and was then dried (Na_2SO_4), filtered, and concentrated in vacuo. The oily residue obtained was purified by flash chromatography on silica gel (elution with 25% EtOAc/hexanes) to provide 330 mg (1.06 mmol, 79%) of the desired product as a crystalline white solid: mp 139–140 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.11 (s, 1H), 8.01 (d, J = 8.8 Hz, 2H), 7.61–7.54 (m, 4H), 7.39 (d, J = 3.7 Hz, 1H), 7.29–7.22 (m, 1H), 7.23 (d, J = 3.7 Hz, 1H), 6.95 (d, J = 7.5 Hz, 1H), 2.32 (s, 3H); MS (DCI/NH_3) m/z 312 (M + H)$^+$. Anal. ($C_{18}H_{14}ClNO_2$) C, H, N.

5-(4-Ethoxyphenyl)-*N*-[(3-methyl)phenyl)]furan-2-carboxamide (6). 6 was prepared from 5-(4-ethoxyphenyl)furan-2-carboxylic acid[45] and *m*-toluidine according to method A: mp 128–130 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.02 (s, 1H), 7.9 (d, J = 8.8 Hz, 2H), 7.60–7.53 (m, 2H), 7.35 (d, J = 3.4 Hz, 1H), 7.24 (dd, J = 8.6, 7.6 Hz, 1H), 7.04 (d, J = 8.8 Hz, 1H), 7.01 (d, J = 3.7 Hz, 1H), 6.93 (d, J = 7.8 Hz, 1H), 4.1 (q, J = 7.1 Hz, 2H), 1.36 (t, J = 7.1 Hz, 3H), 2.32 (s, 3H); MS (ESI) m/z 322 (M + H)$^+$. Anal. ($C_{20}H_{19}NO_3 \cdot H_2O$) C, H, N.

Representative Procedure for Suzuki Reaction and Amide Formation Using Bromofuroic Acids (Method C). 5-(4-Cyanophenyl)-*N*-(3-methylphenyl)furan-2-carboxamide (7). To a suspension of 5-bromo-2-furoic acid (300 mg, 1.57 mmol) in 3:1 isopropanol−water (10 mL) was added 4-cyanophenylboronic acid (240 mg, 1.64 mmol) and sodium carbonate (306 mg, 2.88 mmol). Argon was bubbled through the stirred mixture for 2 min, and then $PdCl_2(PPh_3)_2$ (32 mg, 0.046 mmol) was added. The reaction vessel was equipped with a reflux condenser and heated at reflux for 3 h. The mixture was cooled to ambient temperature and filtered to remove solids. Isopropanol was removed under reduced pressure, and the resulting aqueous solution was adjusted to pH 2 with 6 N HCl and was then extracted with EtOAc (2 × 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered, concentrated, and filtered through a plug of silica gel (~2 g, 5% ethanol/EtOAc rinse) to provide 247 mg of the product 5-(4-cyanophenyl-)furan-2-carboxylic acid as a white solid, which was used without further purification. MS (DCI/NH_3) m/z 214 (M + H)$^+$.

The crude 5-(4-cyanophenyl)furan-2-carboxylic acid was dissolved in THF (9 mL) and treated sequentially with triethylamine (0.430 mL, 3.30 mmol), *m*-toluidine (210 mg, 2.02 mmol), and BOP reagent (667 mg, 1.50 mmol). The mixture was stirred at ambient temperature for 16 h and then transferred to a separatory funnel and washed with water (6 mL). The organic layer was then dried (Na_2SO_4), and the solvent was concentrated in vacuo. The residue was purified by flash chromatography on silica gel (elution with 30% EtOAc/hexanes) to provide 285 mg (0.942 mmol, 60%) of the desired product as a white crystalline solid: mp 134–135 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.19 (s, 1H), 8.18 (d, J = 8.5 Hz, 2H), 7.98 (d, J = 8.5 Hz, 2H), 7.61–7.54 (m, 2H), 7.43 (s, 2H) 7.26 (dd, J = 8.6, 7.6 Hz, 1H), 6.96 (d, J = 7.5 Hz, 1H), 2.33 (s, 3H); MS (ESI) m/z 302 (M + H)$^+$. Anal. ($C_{19}H_{14}N_2O_2$) C, H, N.

5-[(4-Trifluoromethoxy)phenyl]-*N*-(3-methylphenyl)furan-2-carboxamide (8). 8 was prepared from 5-bromo-2-furoic acid, (4-trifluoromethoxy)phenylboronic acid, and *m*-toluidine according to method C: mp 149–150 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.15 (s, 1H), 8.11 (d, J = 8.8 Hz, 2H), 7.63–7.57 (m, 2H), 7.50 (d, J = 8.1 Hz, 2H), 7.42 (d, J = 3.7 Hz, 1H), 7.29–7.22 (m, 1H), 7.23 (d, J = 3.7 Hz, 1H), 6.95 (d, J = 7.5 Hz, 1H), 2.33 (s, 3H); MS (DCI/NH_3) m/z 362 (M + H)$^+$. Anal. ($C_{19}H_{14}F_3NO_3$) C, H, N.

5-[(4-Methylsulfonyl)phenyl]-*N*-(3-methylphenyl)furan-2-carboxamide (9). 9 was prepared from **4** and (4-methylsulfonyl)phenylboronic acid according to method B: mp 149–152 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.23 (s, 1H), 8.42 (d, J = 8.6 Hz, 2H), 8.09 (d, J = 8.6 Hz, 2H), 7.65–7.59 (m, 2H), 7.41 (s, 2H), 7.26 (dd, J = 8.5, 7.5 Hz, 1H), 6.97 (d, J = 7.6 Hz, 1H), 3.42 (s, 3H), 2.33 (s, 3H); MS (DCI/NH_3) m/z 356 (M + H)$^+$. Anal. ($C_{19}H_{14}N_2O_2$) C, H, N.

5-(3-Cyanophenyl)-*N*-(3-methylphenyl)furan-2-carboxamide (10). 10 was prepared from **4** and 3-cyanophenylboronic acid according to method B: mp 142–143 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.15 (s, 1H), 8.30 (d, J = 7.8 Hz, 1H), 7.87 (d, J = 7.8 Hz, 1H), 7.71 (t, J = 8.5 Hz, 1H), 7.61–7.55 (m, 2H), 7.40 (d, J = 3.7 Hz, 1H), 7.38 (d, J = 3.7 Hz, 1H), 7.26 (t, J = 7.5 Hz, 1H), 6.97 (d, J = 6.4 Hz, 1H), 2.37 (s, 3H); MS (ESI) m/z 303 (M + H)$^+$. Anal. ($C_{19}H_{14}N_2O_2 \cdot 0.25H_2O$) C, H, N.

5-(3-Trifluoromethylphenyl)-*N*-(3-methylphenyl)furan-2-carboxamide (11). 11 was prepared from **4** and (3-trifluoromethyl)phenylboronic acid according to method B: mp 199–200 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.15 (s, 1H), 8.30 (m, 1H,) 8.28 (t, J = 4.4 Hz, 1H), 7.77–7.73 (m, 2H), 7.61–7.55 (m, 2H), 7.42 (d, J = 3.7 Hz, 1H), 7.38 (d, J = 3.7 Hz, 1H), 7.26 (t, J = 7.8 Hz, 1H), 6.97 (d, J = 6.5 Hz, 1H), 2.32 (s, 3H); MS (APCI) m/z 346 (M + H)$^+$. Anal. ($C_{19}H_{14}F_3NO_2$) C, H, N.

5-(4-Chlorophenyl)-*N*-(3-methylphenyl)furan-3-carboxamide (13). 5-Bromofuran-3-carboxylic acid (**12**)[29] (1.00 g, 5.20 mmol), 4-chlorophenylboronic acid (860 mg, 5.20 mmol), and tetrakis(triphenylphosphine)palladium(0) (300 mg, 0.260 mmol) were combined in DME (13 mL) and 2.0 M aqueous Na_2CO_3 (6.5 mL) and heated at 95 °C for 4 h. The reaction mixture was allowed to cool to ambient temperature and diluted with EtOAc (40 mL). The mixture was washed with 2.0 N HCl (2 × 25 mL), dried (Na_2SO_4), filtered through a pad of Celite, and evaporated under reduced pressure. The crude product was triturated from Et_2O to provide 688 mg of 5-(4-chlorophenyl)furan-3-carboxylic acid as a white powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.80 (s, 1H), 8.37 (d, J = 0.7 Hz, 1H), 7.78 (d, J = 8.8 Hz, 2H), 7.51 (d, J = 8.8 Hz, 2H), 7.28 (d, J = 0.9 Hz, 1H); MS (ESI−) m/z 221 (M − H)$^+$.

The crude carboxylic acid was then treated with *m*-toluidine according to method A to provide 823 mg (2.65 mmol, 51% for three steps) of the desired product, a white semicrystalline solid: mp 177–179 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.92 (s, 1H), 8.46 (d, J = 0.7 Hz, 1H), 7.77 (d, J = 8.8 Hz, 2H), 7.57–7.48 (m, 4H), 7.46 (d, J = 0.7 Hz, 1H), 7.29–7.19 (m, 1H), 6.92 (d, J = 7.8 Hz, 1H), 2.31 (s, 3H); MS (ESI) m/z 310 (M-H)$^+$. Anal. ($C_{18}H_{14}ClNO_2 \cdot 0.5H_2O$) C, H, N.

4-Bromofuran-2-carboxylic Acid (15).[30] 4,5-Dibromofuran-2-carboxylic acid (**12**) (5.50 g, 20.3 mmol) was suspended in water (63 mL) and NH_4OH (18 mL) with vigorous stirring at ambient temperature. Powdered zinc metal (1.30 g, 20.3 mmol) was added, and the mixture was allowed to stir at ambient temperature for 3 h. The reaction mixture was filtered through a pad of Celite and acidified (pH 2) with 2 N HCl. The filtrate was extracted with EtOAc (4 × 50 mL), dried (Na_2SO_4), and concentrated to dryness under reduced pressure to provide 3.80 g (19.9 mmol, 98%) of the desired product as a white powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.42 (br s, 1H), 8.17 (d, J = 1.0 Hz, 1H), 7.39 (d, J = 1.0 Hz, 1H); MS (ESI−) m/z 189 (M − H)$^+$.

4-(4-Chlorophenyl)-*N*-(3-methylphenyl)furan-2-carboxamide (16). To a suspension of 4-bromo-2-furoic acid (**15**) (900 mg, 4.71 mmol) in 3:1 isopropanol−water (30 mL) was added 4-chloroboronic acid (769 mg, 4.92 mmol) and sodium carbonate (918 mg, 8.64 mmol). Argon was bubbled through the stirred mixture for 3 min, and then $PdCl_2(PPh_3)_2$ (96 mg, 0.14 mmol) was added. The reaction vessel was equipped with a reflux condenser and heated at reflux for 4 h. The mixture was then cooled to ambient temperature and filtered to remove solids. Isopropanol was removed under reduced pressure, and the resulting aqueous solution was adjusted to pH 2 with 6 N HCl and was then extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered, concentrated, and filtered through a plug of silica gel (~5 g, 5% ethanol/EtOAc rinse) to provide 787 mg of the product 4-(4-

chlorophenyl)furan-2-carboxylic acid as a white solid, which was used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.41 (d, J = 1.0 Hz, 1H), 7.72 (d, J = 8.5 Hz, 2H), 7.65 (s, 1H), 7.46 (d, J = 8.5 Hz, 2H); MS (DCI/NH_3) m/z 240 $(M + NH_4)^+$.

The (4-chlorophenyl)furan-2-carboxylic acid obtained in the previous step was reacted with *m*-toluidine according to method A to yield 793 mg (2.54 mmol, 54% for three steps) of the desired product as a white solid: mp 147–148 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.16 (s, 1H), 8.53–8.48 (m, 1H), 7.82–7.78 (m, 1H), 7.74 (d, J = 8.8 Hz, 2H), 7.62–7.59 (m, 1H), 7.57 (d, J = 8.1 Hz, 1H), 7.51 (d, J = 8.5 Hz, 2H), 7.23 (t, J = 7.5 Hz, 1H), 6.95 (d, J = 7.5 Hz, 1H), 2.31 (s, 3H); MS (ESI) m/z 310 $(M - H)^+$. Anal. ($C_{18}H_{14}ClNO_2$) C, H, N.

5-(4-Chlorophenyl)-*N*-(3-methylphenyl)furan-2-carboxamidine Hydrochloride (18). *m*-Toluidine hydrochloride (300 mg, 2.09 mmol) was suspended in toluene (10 mL) at ambient temperature, and $AlMe_3$ (1.20 mL of a 2.0 M solution in toluene, 2.28 mmol) was added. The mixture was stirred at ambient temperature for 5 min. Then 5-(4-chlorophenyl)furan-2-carbonitrile (**17**)[46] (387 mg, 1.89 mmol) was added, and the mixture was heated at reflux for 1 h. The mixture was allowed to cool to ambient temperature, and saturated aqueous $NaHCO_3$ (75 mL) was added. The mixture was extracted with EtOAc (2 × 75 mL), and the combined extracts were dried (Na_2SO_4), filtered, and absorbed on silica gel. The mixture was chromatographed on silica gel (elution with EtOAc) and the purified product converted to the HCl salt with ethanolic HCl to provide the 440 mg (1.40 mmol, 67%) of the desired product as a white solid: mp >250 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.55 (s, 1H), 9.84 (s, 1H), 8.88 (s, 1H), 8.13 (d, J = 8.5 Hz, 2H), 8.00 (d, J = 3.7 H, 1H), 7.62 (d, J = 8.5 Hz, 2H), 7.49 (t, J = 8.0 Hz, 1H), 7.44 (d, J = 3.7 Hz, 1H), 7.34–7.25 (m, 3H), 2.40 (s, 3H); MS (ESI +) m/z 311 $(M - HCl + H)^+$. Anal. ($C_{18}H_{14}ClN_2O \cdot HCl \cdot 0.75H_2O$) C, H, N.

5-(4-Chlorophenyl)-*N*-(3-methylphenyl)furan-2-carbothioamide (19). Furfuramide **3** (1.79 g, 5.74 mmol) and Lawesson's reagent (1.28 g, 3.16 mmol) were suspended in toluene (75 mL) and heated at reflux. After 30 min, the reaction became homogeneous, and heating was continued for 4 h. The mixture was allowed to cool to ambient temperature and was absorbed on silica gel. Purification by silica gel chromatography (elution with 20% EtOAc/hexanes) provided 1.86 g (3.12 mmol, 99%) of the desired product as a pale-yellow powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.54 (s, 1H), 8.10 (d, J = 8.5 Hz, 2H), 7.57 (d, J = 8.5 Hz, 2H), 7.53–7.42 (m, 3H), 7.34 (t, J = 7.8 Hz, 1H), 7.23 (d, J = 3.7 Hz, 1H), 7.13 (d, J = 7.5 Hz, 1H), 2.36 (s, 3H); MS (ESI +) m/z 328 $(M + H)^+$.

(*E*)-5-(4-Chlorophenyl)-*N*-cyano-*N*′-(3-methylphenyl)furan-2-carboxamidine (20). Thioamide **19** (186 mg, 0.567 mmol) and iodomethane (299 mg, 2.10 mmol) were dissolved in acetonitrile (3 mL), and the mixture was stirred at ambient temperature for 16 h in a sealed vessel. The mixture was diluted with Et_2O (10 mL) and the product was collected by filtration and dried under vacuum to provide the thioimidate salt (184 mg) as a bright-yellow powder, which was used without further purification. MS (ESI+) m/z 342 $(M - HI + H)^+$.

The imidate from the previous step (100 mg, 0.392 mmol), cyanamide (17 mg, 0.392 mmol), and triethylamine (0.111 mL, 0.784 mmol) were combined in EtOH (4 mL) and heated at 80 °C in a sealed vessel for 16 h. The mixture was concentrated in vacuo and triturated with 50% EtOAc/hexanes to provide 65 mg (0.193 mmol, 34% for two steps) of the desired product as a white powder: mp 221–222 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.62 (s, 1H), 8.09 (d, J = 8.8 Hz, 2H), 7.88 (d, J = 4.1 Hz, 1H), 7.61 (d, J = 8.8 Hz, 2H), 7.45–7.38 (m, 3H), 7.33 (t, J = 8.0 Hz, 1H), 7.09 (d, J = 7.5 Hz, 1H), 2.35 (s, 3H); MS (ESI+) m/z 336 $(M + H)^+$. Anal. ($C_{19}H_{14}ClN_3O$) C, H, N.

General Procedure for the Synthesis of Compounds 22–37. Compounds **22**−**37** were prepared from commercially available 5-(4-chlorophenyl)furan-2-carboxylic acid (**21**) and commercially available amines unless indicated otherwise. Method A was used for the synthesis of **22**−**25**, **27**−**30**, and **35**−**37**; in the case of **28**, N-methylation was carried out subsequent to amine coupling to provide the final compound. For **31** and **33**–**34**, a modification of method A was employed using pyridine as the base and acetonitrile as the solvent. Compounds **26** and **32** were synthesized using the BOP coupling protocol (see method C).

5-(4-Chlorophenyl)-*N*-(2-methylbenzyl)furan-2-carboxamide (22). Mp 144–146 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.97 (t, 1H), 7.95 (d, J = 8.5 Hz, 2H), 7.53 (d, J = 8.5 Hz, 2H), 7.27–7.22 (m, 1H), 7.22 (d, J = 3.7 Hz, 1H), 7.19–7.10 (m, 4H), 4.47 (d, J = 5.8 Hz, 2H), 2.33 (s, 3H); MS (DCI/NH_3) m/z 326 $(M + H)^+$. Anal. ($C_{19}H_{16}ClNO_2$) C, H, N.

5-(4-Chlorophenyl)-*N*-[2-(2-chlorophenyl)ethyl]furan-2-carboxamide (23). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.74 (t, J = 5.9 Hz, 1H), 7.93 (d, J = 8.5 Hz, 2H), 7.55 (d, J = 8.8 Hz, 2H), 7.48 (d, J = 0.7 Hz, 1H), 7.45 (s, 1H), 7.29 (dd, J = 8.5, 7.5 Hz, 1H), 7.14 (s, 2H), 3.48 (q, J = 6.9 Hz, 2H), 3.18 (t, J = 7.3 Hz, 2H); MS (ESI APCI) m/z 361 $(M + H)^+$. Anal. ($C_{19}H_{15}Cl_2NO_2$) C, H, N.

5-(4-Chlorophenyl)-*N*-[(3-morpholin-4-yl)phenyl]furan-2-carboxamide Hydrochloride (24). 24 was prepared from **20** and 3-morpholin-4-yl-phenylamine (see Supporting Information). The product was converted to the HCl salt by treatment of the ethanolic solution with HCl in ether: mp 186–187 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.05 (s, 1H), 8.01 (d, J = 8.8 Hz, 2H), 7.57 (d, J = 8.5 Hz, 2H), 7.38 (d, J = 3.4 Hz, 1H), 7.35 (t, J = 2.0 Hz, 1H), 7.31–7.25 (m, 1H), 7.25–7.15 (m, 2H), 6.74 (ddd, J = 8.1, 2.4, 1.0 Hz, 1H), 3.81–3.71 (m, 4H), 3.16–3.05 (m, 4H); MS (DCI/NH_3) m/z 383 $(M + H)^+$. Anal. ($C_{21}H_{19}ClN_2O_3 \cdot HCl$) C, H, N.

5-(4-Chlorophenyl)-*N*-[3-(4,5-dihydrooxazol-2-yl)phenyl]furan-2-carboxamide Hydrochloride (25). 25 was prepared from **21** and [3-(4,5-dihydro-oxazol-2-yl)phenyl]amine.[31] The product was converted to the HCl salt by treatment of the ethanolic solution with HCl in ether: mp 225–227 °C (dec); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.34 (s, 1H), 8.81 (t, J = 1.7 Hz, 1H), 8.02 (d, J = 8.8 Hz, 2H), 8.00–7.97 (m, 1H), 7.62 (dt, J = 8.1, 1.2 Hz, 1H), 7.58 (d, J = 8.8 Hz, 2H), 7.47 (t, J = 8.0 Hz, 1H), 7.44 (d, J = 3.4 Hz, 1H), 7.24 (d, J = 3.7 Hz, 1H), 4.43 (t, J = 9.7 Hz, 2H), 3.98 (t, J = 9.5 Hz, 2H); MS (DCI/NH_3) m/z 367 $(M + H)^+$. Anal. ($C_{20}H_{15}ClN_2O_3 \cdot HCl \cdot 0.75H_2O$) C, H, N.

5-(4-Chlorophenyl)-*N*-[(3-cyanomethyl)phenyl]furan-2-carboxamide (26). Mp 161–162 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.29 (s, 1H), 8.01 (d, J = 8.8 Hz, 2H), 7.80 (s, 1H), 7.73 (d, J = 8.5 Hz, 1H), 7.60 (d, J = 8.8 Hz, 2H), 7.42 (d, J = 3.4 Hz, 1H), 7.37 (d, J = 8.1 Hz, 1H), 7.24 (d, J = 3.7 Hz, 1H), 7.10 (d, J = 8.5 Hz, 1H), 4.28 (s, 2H); MS (DCI/NH_3) m/z 354 $(M + NH_4)^+$. Anal. ($C_{19}H_{13}ClN_2O_2$) C, H, N.

5-(4-Chlorophenyl)-*N*-(3,5-dimethoxyphenyl)furan-2-carboxamide (27). Mp 138–139 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.10 (s, 1H), 7.98–8.03 (m, 2H), 7.55–7.60 (m, 2H), 7.40 (d, J = 3.7 Hz, 1H), 7.23 (d, J = 3.7 Hz, 1H), 7.05 (d, J = 2.4 Hz, 1H), 6.29 (t, J = 2.4 Hz, 1H), 3.75 (s, 6H); MS (DCI/NH_3) m/z 358 $(M + H)^+$. Anal. ($C_{19}H_{16}ClNO_4$) C, H, N.

5-(4-Chlorophenyl)-*N*-(1-methyl-2,3-dihydro-1*H*-indol-6-yl)-furan-2-carboxamide Hydrochloride (28). A solution of the 5-(4-chlorophenyl)-*N*-(2,3-dihydro-1*H*-indol-6-yl)furan carboxamide (100 mg, 0.200 mmol) (see Supporting Information) in methanol (5 mL) at ambient temperature was treated with a 35% aqueous solution of formaldehyde (0.100 mL, 1.20 mmol) followed by sodium cyanoborohydride (100 mg, 1.58 mmol). Acetic acid (0.10 mL) was added, and the mixture was stirred for 1 h. The mixture was concentrated, and the residue was purified by flash chromatography on silica gel (elution with 30% EtOAc/hexanes). The resulting material was treated with 2 N HCl in ethanol, which generated a white precipitate that was filtered and rinsed with diethyl ether to provide 54 mg (0.15 mmol, 77%) of the desired compound: mp 225–227 °C (dec); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.15 (s, 1H), 8.20 (d, J = 8.8 Hz, 2H), 7.57 (d, J = 8.8 Hz, 2H), 7.35 (d, J = 3.7 Hz, 1H), 7.22 (d, J = 3.7 Hz, 1H), 7.06–7.00 (m, 2H), 6.93–6.88 (m, 1H), 3.34–3.26 (m, 2H), 2.88–2.79 (m, 2H), 2.70 (s, 3H); MS (DCI/NH_3) m/z 353 $(M + H)^+$. Anal. ($C_{20}H_{17}ClN_2O_2 \cdot HCl$) C, H, N.

5-(4-Chlorophenyl)-*N*-(4-methyl-3,4-dihydro-2*H*-benzo[1,4]oxazin-7-yl)furan-2-carboxamide (29). 29 was prepared from **24** and 3,4-

dihydro-4-methyl-7-nitro-1,4-benzoxazine[47] using method A: mp 180–181 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.92 (s, 1H), 7.99 (d, J = 8.8 Hz, 2H), 7.20 (d, J = 3.4 Hz, 1H), 7.19–7.11 (m, 2H), 6.70 (d, J = 8.5 Hz, 1H), 4.27–4.21 (m, 2H), 3.24–3.15 (m, 2H), 2.81 (s, 3H); MS (DCI/NH_3) m/z 369 (M + H)$^+$. Anal. ($C_{20}H_{17}ClN_2O_3$) C, H, N.

5-(4-Chlorophenyl)-*N*-[(1-methyl-1,2,3,4-tetrahydroquinolin)-6-yl]furan-2-carboxamide Hydrochloride (30). 30 was prepared from **24** and [(1-methyl-1,2,3,4-tetrahydroquinolin)-6-yl]amine (see Supporting Information) using method A. The product was converted to the HCl salt by treatment of the ethanolic solution with HCl in ether: mp 232–233 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.95 (s, 1H), 8.00 (d, J = 8.8 Hz, 2H), 7.56 (d, J = 8.8 Hz, 2H), 7.42 (d, J = 8.1 Hz, 1H), 7.37–7.31 (m, 1H), 7.31 (d, J = 3.7 Hz, 1H), 7.20 (d, J = 3.7 Hz, 1H), 6.71 (s, 1H), 3.21 (t, J = 5.4 Hz, 2H), 2.87 (s, 3H), 2.73 (t, J = 6.3 Hz, 2H), 1.94 (quintet, J = 5.8 Hz, 2H); MS (DCI/NH_3) m/z 367 (M + H)$^+$. Anal. ($C_{21}H_{19}ClN_2O_2 \cdot$HCl) C, H, N.

5-(4-Chlorophenyl)-*N*-(quinolin-6-yl)furan-2-carboxamide (31). The product was converted to the HCl salt by treatment of the ethanolic solution with HCl in ether. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.50 (s, 1H), 8.86–8.81 (m, 1H), 8.50–8.43 (m, 1H), 8.35 (d, J = 6.4 Hz, 1H), 8.12–8.00 (m, 4H), 7.60 (d, J = 8.5 Hz, 2H), 7.57–7.51 (m, 1H), 7.47 (d, J = 3.7 Hz, 1H), 7.27 (d, J = 3.7 Hz, 1H); MS (DCI/NH_3) m/z 358 (M + H)$^+$. Anal. ($C_{20}H_{13}ClN_2O_2 \cdot$HCl$\cdot$1.1$H_2$O) C, H, N.

5-(4-Chlorophenyl)-*N*-(1*H*-indol-6-yl)furan-2-carboxamide (32). Mp 214–215 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.09 (s, 1H), 10.15 (s, 1H), 8.02 (d, J = 8.5 Hz, 2H), 8.01–7.98 (m, 1H), 7.57 (d, J = 8.5 Hz, 2H), 7.51 (d, J = 8.5 Hz, 1H), 7.39 (d, J = 3.7 Hz, 1H), 7.31 (t, J = 2.7 Hz, 1H), 7.27 (dd, J = 8.5, 1.7 Hz, 1H), 7.21 (d, J = 3.7 Hz, 1H), 6.40 (t, J = 2.4 Hz, 1H); MS (DCI/NH_3) m/z 337 (M + H)$^+$. Anal. ($C_{19}H_{13}ClN_2O_2$) C, H, N.

5-(4-Chlorophenyl)-*N*-[(5-methyl)pyridin-3-yl]furan-2-carboxamide (33). The product was converted to the HCl salt by treatment of the ethanolic solution with HCl in ether. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.98 (s, 1H), 8.28 (d, J = 5.1 Hz, 1H), 8.04 (d, J = 8.8 Hz, 2H), 8.01–7.98 (m, 1H), 7.59 (d, J = 3.7 Hz, 1H), 7.57 (d, J = 8.8 Hz, 2H), 7.25 (d, J = 3.7 Hz, 1H), 7.09 (dd, J = 5.4, 1.0 Hz, 1H), 2.39 (s, 3H); MS (DCI/NH_3) m/z 313 (M + H)$^+$. Anal. ($C_{17}H_{13}ClN_2O_2 \cdot$HCl) C, H, N.

5-(4-Chlorophenyl)-*N*-(2-methyl-pyridin-4-yl)furan-2-carboxamide Hydrochloride (34). 34 was prepared from **21** and (2-methyl-pyridin-4-yl)amine. The product was converted to HCl salt by treatment of the ethanolic solution with HCl in ether: mp >250 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.29 (s, 1H), 8.62 (d, J = 6.8 Hz, 1H), 8.17–8.08 (m, 2H), 8.01 (d, J = 8.5 Hz, 2H), 7.70 (d, J = 3.7 Hz, 1H), 7.61 (d, J = 8.5 Hz, 2H), 7.34 (d, J = 3.7 Hz, 1H), 2.67 (s, 3H); MS (DCI/NH_3) m/z 313 (M + H)$^+$. Anal. ($C_{17}H_{13}ClN_2O_2 \cdot$HCl) C, H, N.

5-(4-Chlorophenyl)-*N*-methyl-*N*-(3-methylphenyl)furan-2-carboxamide (35). Mp 104–106 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.16 (m, 4H), 7.09–7.02 (m, 2H), 6.55 (d, J = 3.4 Hz, 2H), 6.48 (d, J = 3.4 Hz, 2H), 3.44 (s, 3H), 2.38 (s, 3H); MS (DCI/NH_3) m/z 326 (M + H)$^+$. Anal. ($C_{19}H_{16}ClNO_2$) C, H, N.

[5-(4-Chlorophenyl)furan-2-yl]-[4-(dimethylamino)piperidin-1-yl]methanone (36). Mp 172–174 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 (d, J = 7.2 Hz, 2H), 7.55 (d, J = 7.3 Hz, 2H), 7.15 (d, J = 3.4 Hz, 1H), 7.08 (d, J = 3.3 Hz, 1H), 4.38 (br s, 2H), 4.33 (br s, 2H), 2.29–2.25 (m, 1H), 2.21 (br s, 6H), 1.87 (br s, 2H), 1.84 (br s, 2H); MS (ESI) m/z 333 (M + H)$^+$. Anal. ($C_{18}H_{21}ClN_2O_2$) C, H, N.

[5-(4-Chlorophenyl)furan-2-yl](morpholino)methanone (37). Mp 179–180 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.80 (d, J = 8.9 Hz, 2H), 7.53 (d, J = 8.8 Hz, 2H), 7.17 (d, J = 3.7 Hz, 1H), 7.14 (d, J = 3.7 Hz, 1H), 3.82–3.71 (m, 4H), 3.68–3.61 (m, 4H); MS (DCI/NH_3) m/z 292 (M + H)$^+$. Anal. ($C_{15}H_{14}ClNO_3$) C, H, N.

Supporting Information Available: Synthetic procedures and characterization data for precursors to **24**, **28**, and **30**; elemental analysis data for the reported compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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