Discovery of Potent, Orally Available Vanilloid Receptor-1 Antagonists. Structure−Activity Relationship of *N*-Aryl Cinnamides

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The vanilloid receptor-1 (TRPV1 or VR1) is a member of the transient receptor potential (TRP) family of ion channels and plays a role in regulating the function of sensory nerves. A growing body of evidence demonstrates the therapeutic potential of TRPV1 modulators, particularly in the management of pain. As a result of our screening efforts, we identified (*E*)-3-(4-*tert*-butylphenyl)-*N*-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)acrylamide (**1**), an antagonist that blocks the capsaicin-induced and pH-induced uptake of $^{45}Ca^{2+}$ in TRPV1-expressing Chinese hamster ovary cells with IC_{50} values of 17 ± 5 and 150 ± 80 nM, respectively. In this report, we describe the synthesis and structure−activity relationship of a series of *N*-aryl cinnamides, the most potent of which (**49a** and **49b**) exhibit good oral bioavailability in rats (F_{oral} = 39% and 17%, respectively).

Introduction

The vanilloid receptor-1 (TRPV1 or VR1[1]), a member of the transient receptor potential (TRP) family of ion channels, is a polymodal, nonselective cation channel that is highly expressed in sensory neurons.[2−4] TRPV1 is activated or sensitized by a variety of endogenous stimuli that are known to be generated as a result of tissue injury and inflammation. These endogenous activators include heat and low pH[5] and the products of lipid bilayer metabolism, such as anandamide[6] and lipoxygenase metabolites.[7] TRPV1 has been shown to be up-regulated during inflammation in research animals[8,9] and in humans.[10,11] Recent studies have demonstrated a reduction in thermal hyperalgesia in acute and subacute inflammatory pain models in mice lacking the TRPV1 gene.[12,13] These observations provide evidence for the role of TRPV1 in the perception of pain resulting from inflammation.

TRPV1 is also activated by exogenous stimuli such as the vanilloids capsaicin (the pungent component in chili peppers) and resiniferatoxin (RTX) (Figure 1). In humans, activation of TRPV1 by topical or intradermal exposure to capsaicin causes an intense burning pain, erythema, edema, thermal and mechanical hyperalgesia, and allodynia. Repeated exposure to large amounts of capsaicin results in insensitivity to further activation by this agent, presumably due to desensitization of the sensory nerves. Capsaicin is used in many over-the-counter topical preparations for the relief of muscle pain and both capsaicin and RTX have been used to treat the pain associated with diabetic neuropathy and arthritis.[2,4] The clinical uses of TRPV1 agonists such as capsaicin and RTX, however, are limited due to their agonist properties. At high doses, capsaicin causes gross neurotoxic effects.[3] In contrast, blockade of cell signaling with a TRPV1 antagonist should preclude the neurotoxicity associated with activation and subsequent desensitization of the nerve cell. This rationale has prompted the search for novel TRPV1 antagonists as potential therapeutics for pain.[14,15]

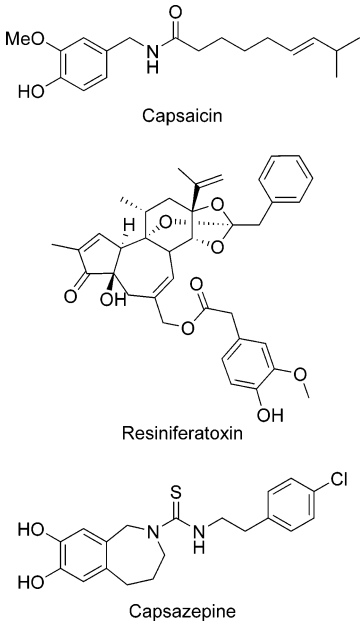

Figure 1.

Capsazepine (Figure 1), the first reported antagonist of TRPV1, was discovered in the course of a structure−activity relationship (SAR) investigation of capsaicin.[16] Capsazepine blocks the capsaicin-induced uptake of Ca^{2+} in neonatal rat dorsal root ganglia with a reported IC_{50} = 0.420 (±0.046) μM. In vivo, capsazepine demon-

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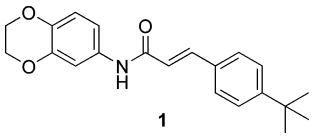


Figure 2.

strates species-dependent efficacies in various models of inflammatory hyperalgesia and chronic pain.[17−19] Interpretation of these results is complicated by the fact that, at efficacious doses, capsazepine blocks receptors other than TRPV1.[20,21] Moreover, capsazepine does not block acid- or heat-induced activation of TRPV1.

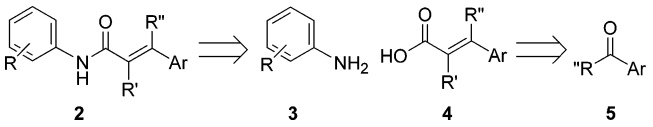
To better understand the pharmacology of TRPV1, we sought to identify novel potent TRPV1 antagonists that blocked multiple modes of activation of the ion channel. As a result of our screening efforts, we identified the potent TRPV1 antagonist (*E*)-3-(4-*tert*-butylphenyl)-*N*-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)acrylamide[22] (AMG 9810, compound **1**, Figure 2). [During the course of the study reported herein, a structurally similar TRPV1 antagonist, SB-366791, was disclosed by Davis and coworkers.[23,24]] Compound **1** blocks TRPV1 activation induced with capsaicin, acid (pH 5), heat (45 °C), and some of the proposed endogenous activators of TRPV1, such as anandamide, *N*-arachidonyl dopamine, and oleoyldopamine.[25,26] Schild analysis and electrophysiology experiments indicate that compound **1** is competitive with capsaicin and binds reversibly. Compound **1** is selective against a panel of over 80 other targets, including various voltage- and ligand-gated ion channels, G-protein-coupled receptors, and transporters. In a complete Freund's adjuvant-induced inflammatory injury model in rats, compound **1**, delivered intraperitoneally, brought about a reduction in both mechanical and thermal hyperalgesia. Compound **1**, however, suffers from high first-pass metabolism and poor oral absorption in rats. Therefore, we undertook an SAR investigation to identify analogs of **1** with improved pharmacokinetic properties.

In this report, we describe the synthesis and biological activity of a series of *N*-aryl cinnamides that modulate the function of TRPV1.[27] For the purposes of our study, we employed a rat−human chimera of the TRPV1 channel, recombinantly expressed in Chinese hamster ovary (CHO) cells. The rat−human chimera functioned equivalently to the human TRPV1 receptor but not the rat TRPV1 receptor. The ability of compounds to inhibit both the pH- and capsaicin-mediated influx of $^{45}Ca^{2+}$ was examined. Our investigation provided an understanding of the SAR of this class of compounds, resulting in the discovery of potent new TRPV1 antagonists (e.g., compounds **49a** and **49b**) with good oral bioavailability.

Chemistry

The cinnamides described in this report were prepared primarily by the method shown in the retrosynthetic sense in Scheme 1. Cinnamides **2** were prepared by direct coupling of the appropriately substituted aniline **3** to the cinnamic acid **4** using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC). Alternatively, the cinnamic acid **4** was converted to the cinnamoyl chloride with oxalyl chloride and then reacted with the aniline **3** to provide the cinnamide **2**. Cinnamic acids **4** were obtained from commercial sources or were prepared from the requisite aldehydes or ketones **5** via Horner−Emmons olefination with a phosphonate ester or by based-catalyzed Perkin reaction with an arylacetic acid.

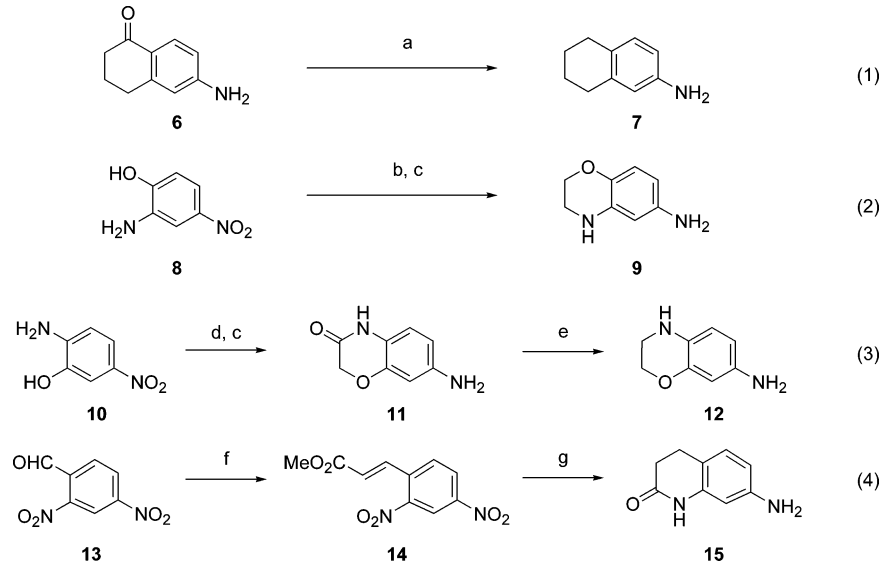
Scheme 1. Retrosynthesis of *N*-Aryl Cinnamides



The anilines used in the preparation of the cinnamides in Table 1 were either obtained from commercial sources, prepared by known methods, or were prepared as illustrated in Scheme 2. For example, reduction of 6-amino-1,2,3,4-tetrahydronaphthalen-1-one (**6**) with triethylsilane and trifluoroacetic acid provided 5,6,7,8-tetrahydronaphthylene-2-amine (**7**) (Scheme 2, eq 1). Oxazine **9** (Scheme 2, eq 2) was prepared by alkylation of 2-amino-4-nitrophenol (**8**) with 1,2-dibromoethane followed by reduction of the nitro group with hydrogen over palladium on carbon. Oxazinone **11** (Scheme 2, eq 3) was prepared by the reaction of 5-nitro-2-aminophenol (**10**) with chloroacetyl chloride under phase-transfer catalysis,[28] followed by reduction of the nitro group. Oxazinone **11** was reduced to oxazine **12** (Scheme 2, eq 3) with borane in tetrahydrofuran. Quinolinone **15** (Scheme 2, eq 4) was prepared in two steps starting from 2,4-dinitrobenzaldehyde (**13**). Wittig condensation of aldehyde **13** with methyl(triphenylphosphoranylidene)-acetate in refluxing benzene provided dinitrocinnamate **14**. Under hydrogenation conditions (60 psi H_2, 10% Pd on carbon) in ethanol and glacial acetic acid, both nitro groups of cinnamate **14** were reduced and cyclization occurred in situ to provide quinolinone **15**.

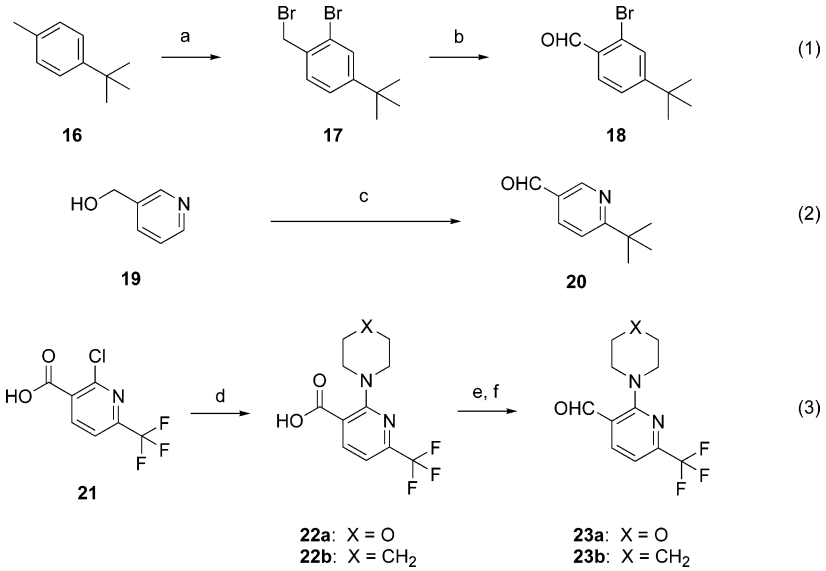
The aldehydes used in the preparation of the substituted phenyl and pyridyl cinnamides in Table 4, when not commercially available or readily prepared by known methods, were prepared according to the methods shown in Scheme 3. 2-Bromo-4-*tert*-butylbenzaldehyde[29] (**18**) (Scheme 3, eq 1) was prepared in two steps from 4-*tert*-butyltoluene (**16**). Following conditions reported by Ishii,[30] reaction of 4-*tert*-butyltoluene with sodium bromate and sodium bisulfite in water and acetonitrile provided 2-bromo-4-*tert*-butylbenzyl bromide (**17**) in a quantitative crude yield. Dibromide **17** was then oxidized to the aldehyde **18** according to the procedure described by Mallory.[29] The synthesis of 6-*tert*-butylpyridine-3-carbaldehyde (**20**) (Scheme 3, eq 2) by regioselective radical alkylation of pyridine-3-carbaldehyde with *tert*-butylmercury(II) chloride has been reported.[31] We circumvented the use of this highly toxic alkylmercury reagent by adopting conditions reported by Tada for the radical alkylation of nicotinamides.[32] Under Tada's conditions, treatment of pyridine-3-methanol (**19**) with silver nitrate, trimethylacetic acid, and ammonium persulfate resulted in regioselective alkylation of the pyridine ring with concurrent oxidation of the alcohol to provide the nicotinaldehyde **20** directly. The 2-amino-substituted nicotinaldehydes, **23a** and **23b** (Scheme 3, eq 3), were prepared starting with the nucleophilic addition of morpholine or piperidine to 2-chloro-6-trifluoromethylnicotinic acid (**21**) to provide the 2-amino-substituted nicotinic acids **22a** and **22b**. Reduction of the acids to the corresponding alcohols,

Scheme 2. Preparation of Anilines[a]



[a] (a) Et_3SiH, CF_3COOH; (b) 1,2-dibromoethane, K_2CO_3, DMF, 125 °C; (c) H_2, 10% Pd/C, MeOH; (d) chloroacetyl chloride, Et_3BnNCl, $NaHCO_3$, $CHCl_3$, 0−50 °C; (e) BH_3·THF; (f) $Ph_3P{=}CHCO_2Me$, benzene, reflux; (g) H_2 (60 psi), 10% Pd/C, AcOH, EtOH.

Scheme 3. Preparation of Aldehydes[a]

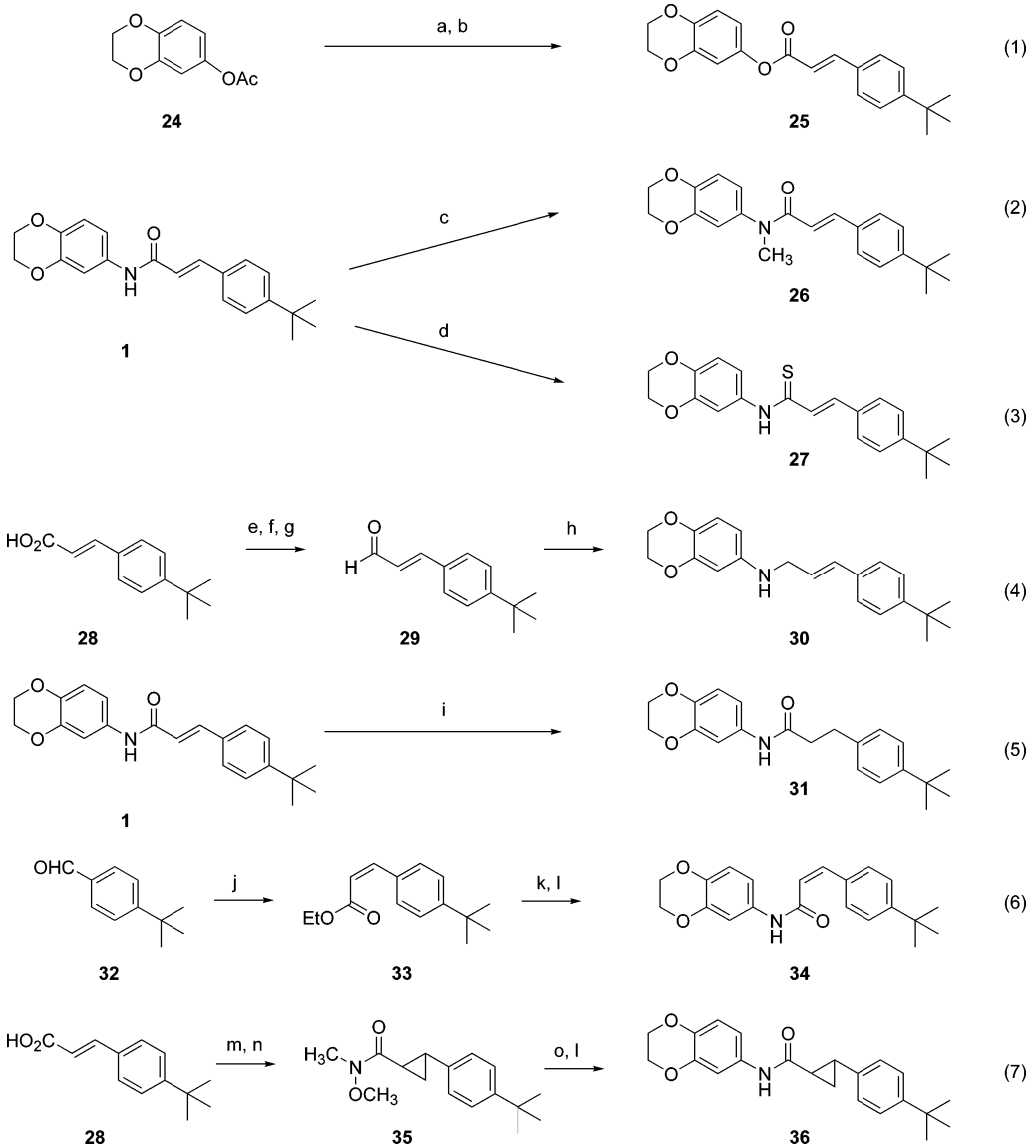


[a] (a) $NaBrO_3$, $NaHSO_3$, H_2O, CH_3CN; (b) 2-nitropropane, NaOEt, EtOH; (c) $(CH_3)_3CCO_2H$, $AgNO_3$, aq H_2SO_4, $(NH_4)_2S_2O_8$; (d) morpholine or piperidine, 25 °C; (e) LAH, THF; (f) oxalyl choride, DMSO, CH_2Cl_2; NEt_3.

followed by Swern oxidation, provided the desired nicotinaldehydes, **23a** and **23b**.

The analogs in Table 2 were prepared according to the methods shown in Scheme 4. Hydrolysis of 2,3-dihydro-1,4-benzodioxin-6-yl acetate[33] (**24**) provided the phenol, which was reacted with 4-*tert*-butylcinnamoyl chloride to yield the cinnamate ester **25** (Scheme 4, eq 1). Treatment of compound **1** with sodium hydride and iodomethane afforded the *N*-methylated analog **26** (Scheme 4, eq 2). Thioamide **27** (Scheme 4, eq 3) was prepared by heating compound **1** with Lawesson's reagent. The cinnamyl analog **30** (Scheme 4, eq 4) was prepared by reductive amination of 1,4-benzodioxan-6-amine with 4-*tert*-butyl-*trans*-cinnamaldehyde (**29**). The cinnamaldehyde was prepared from 4-*tert*-butyl-*trans*-cinnamic acid (**28**) by esterification with methanol, followed by diisobutylaluminum hydride reduction to the alcohol and oxidation with MnO_2. Hydrogenation of compound **1** under palladium catalysis provided the dihydrocinnamide analog **31** (Scheme 4, eq 5). The *cis*-cinnamate ethyl ester **33** (Scheme 4, eq 6) was prepared from 4-*tert*-butylbenzaldehyde (**32**) using the *cis*-selective modified Horner−Emmons reagent, ethyl diphenylphosphonoacetate.[34] Hydrolysis of **33** with lithium hydroxide, followed by EDC-mediated coupling to 1,4-benzodioxan-6-amine, provided the *cis*-cinnamide **34**. Direct cyclopropanation of compound **1** to the cyclopropane analog **36** (Scheme 4, eq 7) was unsuccessful, so a sequence described by Hollenberg and co-workers[35] utilizing the Weinreb amide was employed. Coupling of 4-*tert*-butyl-*trans*-cinnamic acid (**28**) with *N,O*-dimethylhydroxylamine provided the Weinreb amide, which was cyclopropanated to **35** with the ylide generated from trimethylsulfoxonium iodide and sodium hydride. Sa-

Scheme 4. Preparation of Analogs in Table 2[a]



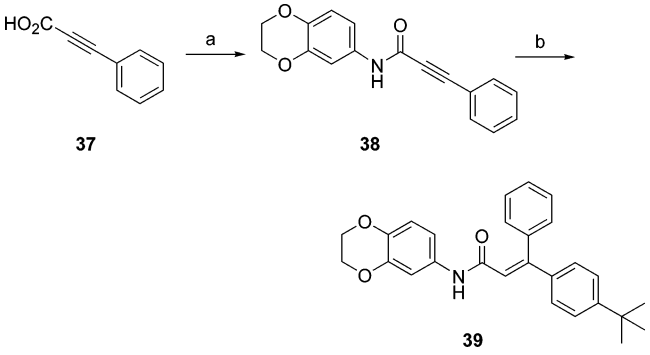
[a] (a) aq NaOH, MeOH; (b) 4-*tert*-butyl-*trans*-cinnamoyl chloride, pyridine, CH_2Cl_2; (c) NaH, MeI, THF; (d) Lawesson's reagent, toluene, 60 °C; (e) HCl/MeOH; (f) DIBAL-H, THF; (g) MnO_2, toluene; (h) 1,4-benzodioxan-6-amine, $NaBH(OAc)_3$, AcOH, DMF; (i) H_2, Pd/C, EtOH; (j) KHMDS, $(PhO)_2P(O)CH_2CO_2Et$, 18-crown-6, THF; (k) aq LiOH, THF, MeOH; (l) 1,4-benzodioxan-6-amine, EDC, DMF; (m) CH_3ONHCH_3·HCl, EDC, HOBT, *i*-Pr_2NEt, DMF; (n) DMSO, NaH, $(CH_3)_3S(O)I$; (o) *t*-BuOK, H_2O, Et_2O.

ponification of **35** according to Gassman's "anhydrous hydroxide" method[36] followed by EDC-mediated coupling to 1,4-benzodioxan-6-amine provided cyclopropanecarboxamide **36**.

The β-phenyl cinnamide analog **39** (Scheme 5) was prepared regio- and stereoselectively from the 3-phenylpropiolamide **38** utilizing a method reported by Hay and Mitchell.[37] Phenylpropiolic acid (**37**) was coupled to 1,4-benzodioxan-6-amine to give the phenylpropiolamide **38**, which was treated with 4-*tert*-butyliodobenzene in the presence of phosphine-free Pd(0) catalyst, diethylamine, and formic acid to provide exclusively the *E*-isomer **39**.

For the preparation of the remaining β-substituted 4-*tert*-butylcinnamide analogs in Table 3 (**45a**−**g**, **45i**), a more versatile synthetic method was developed (Scheme 6). First, the propargyl ester **41** was prepared by acylation of the lithium acetylide of 4-(*tert*-butyl)-phenylacetylene (**40**) with ethyl chloroformate. Reaction

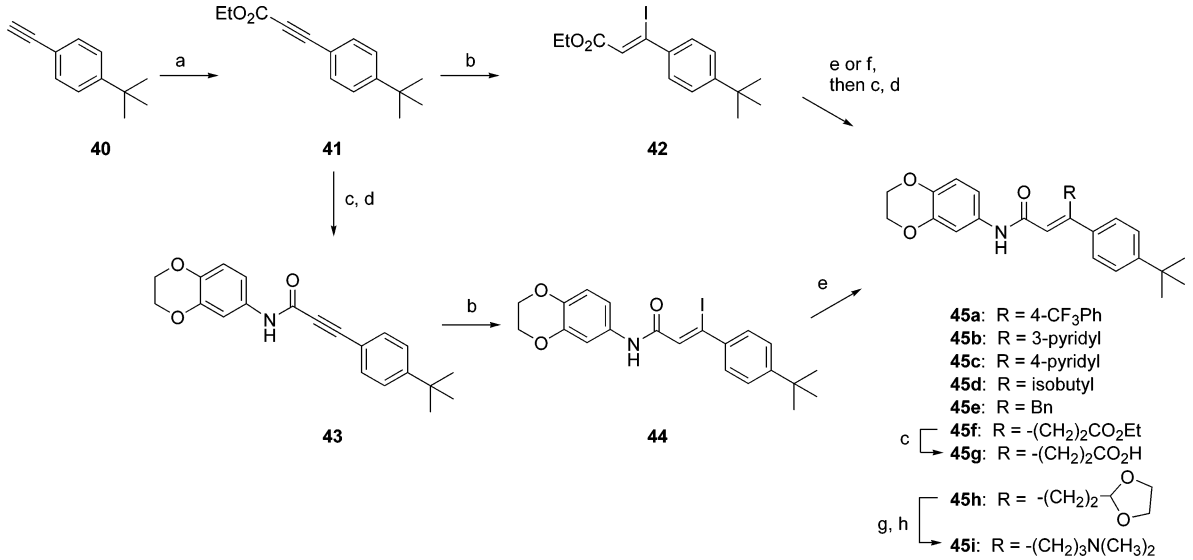
Scheme 5. Stereoselective Synthesis of Compound 39[a]



[a] (a) 1,4-benzodioxan-6-amine, EDC, DMF; (b) 4-*t*-BuPhI, $Pd(dba)_2$, Et_2NH, HCO_2H, EtOAc.

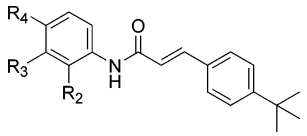
of **41** with sodium iodide in glacial acetic acid[38] provided exclusively the (*Z*)-iodocinnamic ester **42**. Propargyl ester **41** was also converted to propargyl amide **43**,

Scheme 6. Stereoselective Synthesis of Compounds **45a**−**i**.[a]



[a] (a) *n*-BuLi, $ClCO_2Et$, THF; (b) NaI, AcOH, 115 °C; (c) KOH, H_2O, 1,4-dioxane; (d) 1,4-benzodioxan-6-amine, EDC, DMF; (e) RZnBr, $(CH_3CN)_2PdCl_2$, DMF, THF; (f) $RB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, toluene, EtOH, 80 °C; (g) aq HCl, THF; (h) Me_2NH, $NaBH(OAc)_3$, AcOH, CH_2Cl_2.

Table 1. SAR: Variations on the Aniline



	R_2	R_3	R_4	IC_{50} (nM) capsaicin stimulus	IC_{50} (nM) pH stimulus	agonist activity EC_{50} (nM)
1	H	$-OCH_2CH_2O-$		17 ± 5	150 ± 80	
46a	H	H	H	330 ± 30	>4000	
46b	OCH_3	H	H	550 ± 40	>4000	
46c	H	OCH_3	H	21 ± 8	>4000	
46d	H	H	OCH_3	140 ± 90	>4000	
46e	H	OCH_3	OCH_3	170 ± 20	>4000	
46f	H	OH	OCH_3	30 ± 13	>4000	
46g	H	OCH_3	OH			440 ± 50
46h	H	$-OCH_2O-$		570 ± 90	>4000	
46i	H	$-CH_2CH_2CH_2CH_2-$		61 ± 15	960 ± 810	
46j	H	$-OCH_2CH_2NH-$		16 ± 6	57 ± 15	
46k	H	$-NHCH_2CH_2O-$		110 ± 60	>4000	
46l	H	$-OCH_2CONH-$		270 ± 100	>4000	
46m	H	$-NHCOCH_2O-$		6.5 ± 2.4	>4000	
46n	H	$-NHCOCH_2CH_2-$		2.5 ± 1.7	71 ± 61	
46o	H	$-NHCH_2CH_2CH_2-$		36 ± 15	160 ± 10	
46p	H	−N=CHCH=CH−		1.1 ± 0.2	2.02 ± 0.02	

which upon treatment with sodium iodide in glacial acetic acid provided the (*Z*)-iodocinnamide **44**. Both the (*Z*)-iodocinnamate **42** and the (*Z*)-iodocinnamide **44** were elaborated into the desired *β*-arylated or alkylated cinnamide analogs, with retention of double bond stereochemistry, via palladium-mediated coupling with arylboronic acids or organozinc reagents. The stereochemical assignment for all of the cinnamides listed in Table 3 was confirmed on the basis of 2D-NOESY NMR analysis.

Results and Discussion

Structure−Activity Relationships (SAR). The compounds were tested for their ability to block the capsaicin- or acid-induced (pH 5) uptake of $^{45}Ca^{2+}$ in CHO cells expressing a rat−human TRPV1 chimera. Functional activity is reported as IC_{50} ± SEM (nM) in Tables 1−5. The data for lead compound **1** are included in each table for comparison. All compounds were tested in a separate assay for agonist activity. All compounds reported herein behaved as antagonists, with the single exception of compound **46g**, in which case the agonist activity is reported as an EC_{50} ± SEM (nM). Results are the average of at least two independent experiments with three replicates at each concentration.

The effect on functional activity of alterations made to the aniline ring of compound **1** is summarized in Table 1. It was found that modifications to the aniline ring impacted the functional activity in the pH-mediated assay to a greater extent than in the capsaicin-mediated assay. For example, the unsubstituted aniline analog **46a** blocked capsaicin-induced uptake of $^{45}Ca^{2+}$ with an

IC_{50} of 330 nM, a 20-fold reduction in potency relative to **1**, while in the pH-mediated assay the IC_{50} for **46a** was greater than 4000 nM. The three isomeric methoxy-substituted analogs demonstrated antagonist activity in the capsaicin-mediated assay with potencies ranked in the order **46c** ($R_3 = OCH_3$) > **46d** ($R_4 = OCH_3$) > **46b** ($R_2 = OCH_3$). The IC_{50} values for all three of the isomeric methoxy-substituted analogs were greater than 4000 nM in the pH-mediated assay. The 3,4-dimethoxy analog **46e** was 10-fold less potent than **1** in the capsaicin-mediated assay and over 20-fold less potent than **1** in the pH-mediated assay. The 3-hydroxy-4-methoxy analog **46f** was roughly equipotent to **1** in the capsaicin-mediated assay ($IC_{50} = 30$ nM) but greater than 20-fold less active than **1** in the pH-mediated assay. In contrast, the isomeric 3-methoxy-4-hydroxy analog **46g** exhibited agonist activity ($EC_{50} = 440$ nM). This result is consistent with the agonist behavior observed for the 3-methoxy-4-hydroxyaniline analog of capsaicin.[39] It has previously been reported that subtle structural modifications to TRPV1 modulators can result in reversal of activity. For example, Lee and coworkers observed the reversal of activity from agonism to antagonism within a series of thioureas as a result of replacement of a phenolic hydroxyl with a methylsulfonylamino group.[40] It has also been shown that iodination of RTX [41] and capsaicin[42] converts these agonists into antagonists.

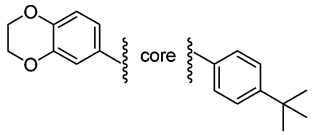
We substituted the benzodioxane in compound **1** with a series of fused bicyclic ring systems (**46h**−**p**). Truncation to the piperonyl analog (**46h**) was detrimental to activity in both assays, as was exchanging the benzodioxane oxygens with carbon (i.e. tetrahydronaphthyl, **46i**). Each of the oxygen atoms of the benzodioxane ring was replaced in turn with nitrogen, providing the isomeric benzooxazine analogs **46j** and **46k**. Benzooxazine **46j** (R_3−R_4 = $-OCH_2CH_2NH-$) was roughly equipotent to **1** in the capsaicin-mediated assay and more potent than **1** in the pH-mediated assay. A reduction in potency in both assays was observed for the isomeric benzooxazine **46k** (R_3−R_4 = $-NHCH_2CH_2O-$). In the capsaicin-mediated assay, benzooxazinone **46l** (R_3−R_4 = $-OCH_2CONH-$) was less potent than the isomeric benzooxazinone **46m** (R_3−R_4 = $-NHCOCH_2O-$). Benzooxazinone **46m** was more potent than **1** in the capsaicin-mediated assay, with an IC_{50} value of 6.5 nM; however, in the pH-mediated assay the IC_{50} for **46m** was greater than 4000 nM. Activity in the pH-mediated assay was improved when the oxygen at R_4 in **46m** was replaced with carbon, resulting in dihyroquinolinone **46n**. Compound **46n** demonstrated improved potency over **1**, with an IC_{50} value of 2.5 nM in the capsaicin-mediated assay and 71 nM in the pH-mediated assay. The corresponding dihydroquinoline analog **46o** was roughly equipotent to compound **1**. The 7-quinoline analog **46p** was the most potent antagonist in the series, with IC_{50} values of 1.1 and 2.02 nM in the capsaicin- and pH-mediated assays, respectively. In summary, these results show that, for the examples listed in Table 1, (1) a hydrogen-bond-accepting group at R_3 is favored; (2) a 6,6-fused bicyclic ring system is preferred, particularly to maintain potency in the pH-mediated assay; and (3) the 7-quinolinyl group affords the optimum potency in both assays.

The contributions made by the acrylamide core to the overall structure−activity profile are illustrated in Table 2. In general, these modifications to the core were detrimental to activity. For example, the cinnamate **25** was ca. 40-fold less potent than the cinnamide **1** in the capsaicin-mediated assay, and the *N*-methylated analog **26** was greater than 200-fold less active. The thioamide derivative **27** was over 10-fold less potent than **1** in the capsaicin-mediated assay, and the IC_{50} for the cinnamyl analog **30** was greater than 4000 nM in both assays. The dihydrocinnamide analog **31** was only moderately active, with an $IC_{50} = 150$ nM in the capsaicin-mediated assay and 660 nM in the pH-mediated assay. The *cis*-cinnamide **34** and the *trans*-cyclopropane analog **36** both exhibited very poor functional activity. Taken together these results indicate that the *trans*-cinnamide core provides the preferred geometry, as well as a favorable hydrogen-bonding interaction vis-à-vis the amide.

The effect on functional activity observed when substituents were appended to the acrylamide core is illustrated in Table 3. Aliphatic substituents appended to the α-position (R_α) were detrimental to activity, with potency decreasing as the size of the substituent increased [**47a** ($R_\alpha = CH_3$) > **47b** ($R_\alpha = CH_2CH_3$) > **47c** (R_α = Ph)]. In contrast, the addition of a methyl group to the β-position (R_β) resulted in only a slight reduction in potency (**47d**), while even larger groups such as phenyl (**39**), 4-trifluoromethylphenyl (**45a**), isobutyl (**45d**), and benzyl (**45e**) were well-tolerated. This trend did not extend to the bulky β-4-*tert*-butylphenyl analog (**47e**), however, which exhibited very low activity. The weakly basic β-3-pyridyl and β-4-pyridyl analogs (**45b** and **45c**, respectively) were not as potent as the corresponding β-phenyl analog (**39**). The addition of a flexible aliphatic ester (**45f**) was fairly well tolerated at R_β, but aliphatic groups with more polar termini such as carboxylic acid (**45g**) or amine (**45i**) were detrimental to activity. From these results we can conclude that the cinnamides bind in proximity to a lipophilic region on the ion channel. This lipophilic region can accommodate aliphatic and aromatic substituents at R_β but does not appear to tolerate polar or charged groups.

The functional activities for a series of substituted phenyl and pyridyl cinnamide derivatives are summarized in Table 4. Some general observations can be made from these data. For example, the presence of a substituent in the para-position (R_{para}) is strongly preferred; consequently, the IC_{50} values for the unsubstituted cinnamide **48a** were greater than 4000 nM in both assays. In addition, both the electronic character and relative size and shape of the para-substituent influence functional activity. When R_{para} was aliphatic, potency in the capsaicin-mediated assay improved with increasing size of the alkyl group, e.g. Me ≈ Et < *i*-Pr ≤ *t*-Bu (**48b** ≈ **48c** < **48d** ≤ **1**). Potency decreased when the para-substituent was bulkier than *tert*-butyl, e.g., isobutyl (**48e**), *n*-butyl (**48f**), or phenyl (**48g**). Overall, *tert*-butyl and isopropyl appeared to be optimal in terms of size and shape. The position of the alkyl group also affected activity such that the *m*-*tert*-butyl analog **48h** was 36-fold less potent than **1** in the capsaicin-mediated assay and greater than 20-fold less potent than **1** in the pH-mediated assay. In the case of the halogenated

Table 2. SAR: Variations to the Acrylamide Core



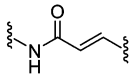
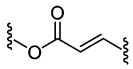
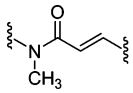
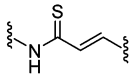
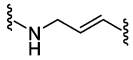
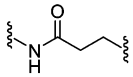
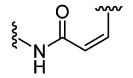
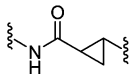
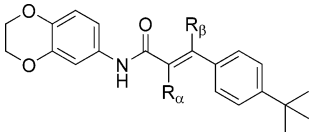
	core	capsaicin stimulus IC_{50} (nM)	pH stimulus IC_{50} (nM)
1		17 ± 5	150 ± 80
25		670 ± 50	3200 ± 600
26		>4000	>4000
27		280 ± 20	1400 ± 300
30		>4000	>4000
31		150 ± 30	660 ± 30
34		1200 ± 300	3200 ± 1900
36		1800 ± 200	>4000

Table 3. SAR: Substituents on the Acrylamide Core

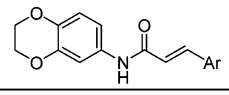


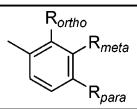
	R_α	R_β	IC_{50} (nM) capsaicin stimulus	IC_{50} (nM) pH stimulus
1	H	H	17 ± 5	150 ± 80
47a	CH_3	H	100 ± 40	600 ± 340
47b	CH_2CH_3	H	210 ± 20	800 ± 310
47c	Ph	H	>4000	>4000
47d	H	CH_3	39 ± 6	430 ± 280
39	H	Ph	20 ± 5	120 ± 60
45a	H	4-CF_3-phenyl	25 ± 3	180 ± 110
47e	H	4-t-Bu-phenyl	2700 ± 1300	>4000
45b	H	3-pyridyl	78 ± 12	510 ± 200
45c	H	4-pyridyl	44 ± 5	660 ± 250
45d	H	isobutyl	16 ± 1	94 ± 51
45e	H	benzyl	14 ± 3	110 ± 70
45f	H	$CH_2CH_2CO_2Et$	36 ± 8	290 ± 180
45g	H	$CH_2CH_2CO_2H$	>4000	>4000
45i	H	$(CH_2)_3N(CH_3)_2$	3900 ± 600	>4000

analogs, potency ranked in the order **48i** (R_{para} = Br) > **48j** (R_{para} = Cl) > **48k** (R_{para} = F). Electron-withdrawing groups such as NO_2 (**48l**) and CF_3 (**48m**) were better tolerated in the para-position than electron-donating groups such as OCH_3 (**48n**) and OH (**48o**). Of the electron-withdrawing groups, the trifluoromethyl group appeared to be a suitable replacement for the *tert*-butyl group. The effect of disubstitution of the phenyl ring was also investigated. The addition of a bromine atom to the ortho-position (R_{ortho}) in compound **1** (i.e., **48p**) led to a reduction in potency in both assays, while the addition of a carbethoxy group (**48q**) resulted in an improvement in potency in the pH-mediated assay. Hydrolysis of the ester in compound **48q** to the acid **48r**, however, resulted in a reduction in activity in both assays.

In addition, the effect of replacing the *tert*-butylphenyl ring with substituted pyridine was examined. The *tert*-butylpyridine analogs **48s** and **48t** were both significantly less potent than compound **1**, suggesting an unfavorable interaction with the pyridine nitrogen. Similarly, the trifluoromethylpyridine analog **48u** (IC_{50} = 870 nM, capsaicin-mediated assay) was significantly less potent than the corresponding trifluoromethylphenyl analog **48m** (IC_{50} = 46 nM, capsaicin-mediated assay). Introduction of a methyl group to the 2-position of the pyridine ring (i.e., **48v**) afforded a slight improvement in potency over compound **48u**. But adding larger groups, such as morpholine and piperidine, to the 2-position of the pyridine ring (**48w** and **48x**, respectively) provided analogs that were roughly equipotent to **1** in the capsaicin-mediated assay and more potent than **1** in the pH-mediated assay.

Table 4. SAR: Variations to the Cinnamide Aryl



	Ar = 			capsaicin stimulus	pH stimulus
	R_{ortho}	R_{meta}	R_{para}	IC_{50} (nM)	IC_{50} (nM)
1	H	H	*t*-Bu	17 ± 5	150 ± 80
48a	H	H	H	>4000	>4000
48b	H	H	CH_3	210 ± 60	1100 ± 260
48c	H	H	CH_2CH_3	170 ± 50	220 ± 20
48d	H	H	*i*-Pr	55 ± 18	82 ± 3
48e	H	H	*i*-Bu	360 ± 90	860 ± 160
48f	H	H	*n*-Bu	360 ± 10	2700 ± 300
48g	H	H	Ph	>4000	>4000
48h	H	*t*-Bu	H	620 ± 10	>4000
48i	H	H	Br	110 ± 30	370 ± 110
48j	H	H	Cl	250 ± 80	320 ± 50
48k	H	H	F	1000 ± 360	>4000
48l	H	H	NO_2	190 ± 10	440 ± 50
48m	H	H	CF_3	46 ± 18	100 ± 10
48n	H	H	OCH_3	1800 ± 360	>4000
48o	H	H	OH	>4000	>4000
48p	Br	H	*t*-Bu	60 ± 10	470 ± 330
48q	CO_2Et	H	*t*-Bu	15 ± 10	26 ± 1
48r	CO_2H	H	*t*-Bu	>4000	>4000

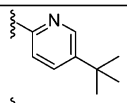
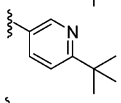
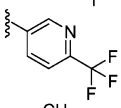
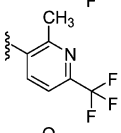
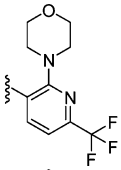
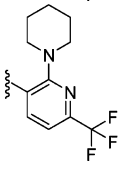
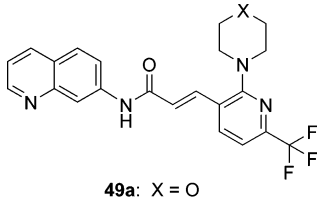
	Ar =	capsaicin stimulus	pH stimulus
		IC_{50} (nM)	IC_{50} (nM)
48s		500 ± 10	2900 ± 1000
48t		100 ± 40	2400 ± 1000
48u		870 ± 120	1290 ± 30
48v		360 ± 30	870 ± 500
48w		15 ± 6	40 ± 22
48x		27 ± 2	54 ± 3

Table 5. Inhibition of $^{45}Ca^{2+}$ Influx: Compounds **1**, **49a**, and **49b**



49a: X = O
49b: X = CH_2

	IC_{50} (nM)	
	capsaicin stimulus	pH stimulus
1	17 ± 5	150 ± 80
49a	1.9 ± 1.0	1.3 ± 0.3
49b	0.42 ± 0.18	1.00 ± 0.04

Table 6. Mean Pharmacokinetic Parameters Following Intravenous Dose in Sprague–Dawley Rats[a]

	dose[b] (mg/kg)	$AUC_{0-\infty}$ (ng h/mL)	CL (L/h/kg)	V_{ss} (mL/kg)	$t_{1/2}$ (h)
1	3	680	4.4	2100	1.1
49a	2	2300	0.9	1100	0.9
49b	2	2100	0.8	2800	2.9

[a] $n = 2$ animals per study. [b] Dosed as a solution in DMSO.

Table 7. Mean Pharmacokinetic Parameters Following Oral Dose[a] in Sprague–Dawley Rats[b]

	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0-\infty}$ (ng h/mL)	bioavailability, F (%)
1	25	0.5	24	3
49a	540	1.5	2600	39
49b[c]	320	2.0	2400	17

[a] Dosed at 5 mg/kg as a suspension in 5% Tween 80 in Oraplus. [b] $n = 2$ animals per study. [c] Data is the mean of four studies.

Optimum modifications to both aromatic rings were combined to provide compounds **49a** and **49b** (Table 5), the most potent cinnamides in the series. Compounds **49a** and **49b** were significantly more potent than compound **1** in both the capsaicin-mediated functional assay (IC_{50} = 1.9 and 0.42 nM, respectively) and the pH-mediated assay (IC_{50} = 1.3 and 1.0 nM, respectively).

Pharmacokinetic Profiles. Because of their in vitro potencies, we studied compounds **49a** and **49b** in more detail. The pharmacokinetic (PK) profiles with intravenous (iv) dosing in Sprague–Dawley rats for compounds **1**, **49a**, and **49b** are shown in Table 6. A high rate of clearance (CL) was observed for compound **1** (4.4 L/h/kg) following iv dosing. Metabolism studies of **1** in vitro indicated that the major metabolite resulted from oxidation of the *tert*-butyl group.[43] Compounds **49a** and **49b**, which lack the metabolically labile *tert*-butyl group, exhibited relatively low rates of clearance (0.9 and 0.8 L/h/kg, respectively). Although the rate of clearance for compound **49a** was lower than that for **1**, the volume of distribution was also lower (V_{ss} = 1100 mL/kg), consequently no improvement in half-life relative to **1** was observed. In contrast, compound **49b** demonstrated low clearance (0.8 L/h/kg), combined with a relatively high volume of distribution (2800 mL/kg), resulting in an overall increase in half-life to 2.9 h.

The results from PK studies in rats dosed orally (po) with suspensions of compounds **1**, **49a**, and **49b** are summarized in Table 7. While the oral bioavailability of compound **1** was negligible (F_{oral} = 3%), compounds **49a** and **49b** were relatively well-absorbed, with bioavailabilities of 39% and 17%, respectively. The maximum plasma concentration (C_{max}) following po dosage of compound **49a** was 540 ng/mL at 1.5 h, while that for **49b** was 320 ng/mL at 2 h, a significant improvement over compound **1** (C_{max} = 25 ng/mL at 0.5 h).

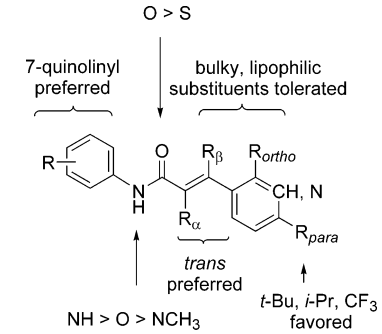


Figure 3. Summary of SAR.

Conclusions

As a result of our screening efforts, we identified the potent TRPV1 antagonist (*E*)-3-(4-*tert*-butylphenyl)-*N*-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)acrylamide (**1**). SAR investigation of compound **1** provided an understanding of the structural features that influence functional activity for this class of compounds (Figure 3). Replacement of the benzodioxan-7-yl group with the 7-quinolinyl group (i.e., **46p**) resulted in a significant improvement in functional activity. Alterations to the acrylamide core were detrimental to activity; consequently, the amide was preferred over the *N*-methyl amide, thioamide, or ester, and the *trans*-cinnamide was preferred over the dihydrocinnamide, *cis*-cinnamide, or cyclopropanated analog. Bulky lipophilic substituents were tolerated on the core at R_β and in the ortho-position (R_{ortho}) of the cinnamide, but not at R_α. With respect to potency, the optimum groups in the para-postion (R_{para}) of the phenyl ring of the cinnamide were *tert*-butyl, isopropyl, and trifluoromethyl. In addition, 2-morpholino-6-(trifluoromethyl)pyridin-3-yl and 2-(piperidin-1-yl)-6-(trifluoromethyl)-pyridin-3-yl were acceptable replacements for the 4-*tert*-butylphenyl group. As a result of this SAR investigation, we discovered novel potent cinnamides, **49a** and **49b**, that showed improved pharmocokinetic profiles over the lead compound. The in vivo efficacy of compounds in this series will be reported elsewhere.

Experimental Section

Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. (*E*)-3-(4-*tert*-Butylphenyl)-*N*-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)acrylamide (**1**), (*E*)-*N*-(benzo[*d*][1,3]dioxol-5-yl)-3-(4-*tert*-butylphenyl)acrylamide (**46h**), and (*E*)-*N*-(2,3-dihydrobenzo[*b*]-[1,4]dioxin-6-yl)-3-(4-isobutylphenyl)acrylamide (**48e**) were purchased from G & J Research, Devon, UK. (*E*)-3-(4-*tert*-Butylphenyl)-*N*-(2-methoxyphenyl)acrylamide (**46b**) was obtained from Polyphor LTD, Allschwil, Switzerland. Anhydrous solvents were obtained from Aldrich or EM Science and used directly. All reactions involving air- or moisture-sensitive reagents were performed under a nitrogen or argon atmosphere. All final compounds were purified to >95% purity as

determined by high-performance liquid chromatography (HPLC). Silica gel chromatography was performed using either glass columns packed with silica gel (200−400 mesh, Aldrich Chemical) or prepacked silica gel cartridges (Biotage). Melting points were determined on a Buchi-545 melting point apparatus and are uncorrected. NMR spectra were determined with a Bruker DRX 400 MHz spectrometer. Low-resolution mass spectral (MS) data were determined on a Perkin-Elmer-SCIEX API 165 mass spectrometer using ES ionization modes (positive or negative). Combustion analysis was performed by Atlantic Microlab, Inc., Norcross, GA, and were within 0.4% of calculated values unless otherwise noted.

(*E*)-2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl 3-(4-*tert*-butylphenyl)acrylate (25). A solution of 2,3-dihydro-1,4-benzodioxin-6-yl acetate[33] (1.4 g, 7.0 mmol) in MeOH (20 mL) was treated with 1 N NaOH (5 mL) and stirred at room temperature for 30 min. The reaction mixture was concentrated to ∼5 mL in vacuo and acidified to pH 1 with 1 N HCl. The mixture was extracted with EtOAc (3×). The combined extracts were washed with water and satd NaCl, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford the phenol (1.0 g, 95%) as a viscous brown oil. ^{1}H NMR ($CDCl_3$): δ 4.19−4.25 (m, 4 H), 4.73 (br s, 1 H), 6.33 (dd, J = 2.9, 8.7 Hz, 1 H), 6.39 (d, J = 2.9 Hz, 1 H), 6.72 (d, J = 8.7 Hz, 1 H). MS (ESI, pos. ion) *m/z*: 153 (M + 1).

A solution of 4-*tert*-butyl-*trans*-cinnamic acid (300 mg, 1.5 mmol) in anhydrous CH_2Cl_2 (10 mL) was magnetically stirred and treated with oxalyl chloride (0.88 mL, 1.8 mmol, 2.0 M in CH_2Cl_2) and DMF (5 μL). The reaction mixture was stirred at reflux for 30 min and then concentrated in vacuo, and the residue was dissolved in anhydrous CH_2Cl_2 (10 mL). A solution of the phenol from the previous step (220 mg, 1.4 mmol) in anhydrous CH_2Cl_2 (2 mL) was added, followed by pyridine (0.60 mL, 7.4 mmol). The reaction mixture was stirred at reflux for 30 min and concentrated in vacuo, and the residue was dissolved in EtOAc. The mixture was washed with 1 N HCl, satd $NaHCO_3$, water, and satd NaCl, dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by silica gel chromatography (9:1 hexane:EtOAc) provided the title compound (320 mg, 64%) as a white solid. Mp: 112−114 °C. ^{1}H NMR ($CDCl_3$): δ 1.34 (s, 9 H), 4.26 (s, 4 H), 6.57 (d, J = 16 Hz, 1 H), 6.65 (dd, J = 2.7, 8.7 Hz, 1 H), 6.72 (d, J = 2.6 Hz, 1 H), 6.87 (d, J = 8.7 Hz, 1 H), 7.44 (d, J = 8.4 Hz, 2 H), 7.52 (d, J = 8.3 Hz, 2 H), 7.83 (d, J = 16 Hz, 1 H). MS (ESI, pos. ion) *m/z*: 339 (M + 1). Anal. ($C_{21}H_{22}O_4$): C, H.

(*E*)-3-(4-*tert*-Butylphenyl)-*N*-(2,3-dihydrobenzo[*b*][1,4]-dioxin-6-yl)-*N*-methylacrylamide (26). A solution of compound **1** (250 mg, 0.74 mmol) in anhydrous THF (5 mL) was stirred under N_2 at room temperature and treated with NaH (33 mg, 0.82 mmol, 60% dispersion in mineral oil). The reaction mixture was stirred for 10 min and then treated with iodomethane (0.060 mL, 0.96 mmol). The reaction mixture was stirred at room temperature for 2 h, quenched with water, and extracted with EtOAc (2×). The organic extracts were combined and washed with water and satd NaCl, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by silica gel chromatography (45:45:10 CH_2Cl_2:hexane:EtOAc) provided the title compound (200 mg, 77%) as an amorphous white solid. ^{1}H NMR (DMSO-d_6): δ 1.24 (s, 9 H), 3.22 (s, 3 H), 4.28 (s, 4 H), 6.35 (br d, J = 14.7 Hz, 1 H), 6.76 (dd, J = 2.5, 8.5 Hz, 1 H), 6.88 (d, J = 2.5 Hz, 1 H), 6.92 (d, J = 8.5 Hz, 1 H), 7.31−7.38 (m, 4 H), 7.45 (d, J = 15.6 Hz, 1 H). MS (ESI, pos. ion) *m/z*: 352 (M + 1). Anal. ($C_{22}H_{25}NO_3$): C, H, N.

(*E*)-3-(4-*tert*-Butylphenyl)-*N*-(2,3-dihydrobenzo[*b*][1,4]-dioxin-6-yl)prop-2-enethioamide (27). Compound **1** (840 mg, 2.5 mmol) in toluene (10 mL) was treated with Lawesson's reagent (1.1 g, 2.7 mmol) and stirred in a 60 °C oil bath for 2 h. The reaction mixture was allowed to cool to room temperature and diluted with Et_2O (150 mL) and water (50 mL). The biphasic mixture was shaken and a solid precipitate formed which was removed by filtration and discarded. The Et_2O layer was separated and washed with water and satd NaCl, dried over $MgSO_4$, and concentrated in vacuo. Purification by silica gel chromatography (gradient, 10% to 30% EtOAc in hexane) provided a solid which was recrystallized from CH_2Cl_2/hexane to afford the title compound (190 mg, 22%) as bright orange crystals. Mp: 184.6−184.7 °C. ^{1}H NMR (DMSO-d_6): δ 1.30 (s, 9 H), 4.26 (s, 4 H), 6.89 (d, J = 8.7 Hz, 1 H), 7.24 (d, J = 15.4 Hz, 1 H), 7.28 (dd, J = 2.4, 9.0 Hz, 1 H), 7.47 (d, J = 8.3 Hz, 2 H), 7.57 (d, J = 8.3 Hz, 2 H), 7.70 (d, J = 2.2 Hz, 1 H), 7.75 (d, J = 15.2 Hz, 1 H), 11.50 (s, 1 H). MS (ESI, pos. ion) *m/z*: 354 (M + 1). Anal. ($C_{21}H_{23}NO_2S$): C, H, N, S.

***N*-(4-*tert*-Butylcinnamyl)-2,3-dihydrobenzo[*b*][1,4]-dioxin-6-amine (30).** A solution of 4-*tert*-butyl-*trans*-cinnamic acid (5.0 g, 25 mmol) in MeOH (100 mL) was purged with a stream of HCl gas at room temperature for 15 min. The reaction flask was then capped and the mixture stirred at 25 °C overnight. The solvent was removed in vacuo and the residue was partitioned between EtOAc and 5% aq K_2CO_3. The organic phase was washed with satd NaCl, dried over Na_2SO_4, filtered, and concentrated in vacuo to afford the ester as a clear oil (5.0 g, 94%). MS (ESI, pos. ion) *m/z*: 219 (M + 1).

A solution of the ester from the previous step (4.3 g, 20 mmol) in THF (120 mL), stirred at −78 °C under N_2, was treated with diisobutylaluminum hydride (40 mL, 60 mmol, 1.5 M in toluene) via syringe over 25 min. The reaction mixture was stirred at −78 °C for 3 h. The reaction was quenched by the careful addition of 10% aq NH_4Cl at 0 °C. The mixture was extracted with EtOAc and the organic phase was washed with satd NaCl (2×), dried over Na_2SO_4, filtered, and concentrated in vacuo to afford the alcohol (3.2 g, 85%). MS (ESI, pos. ion) *m/z*: 191 (M + 1).

A solution of the alcohol from the previous step (2.4 g, 13 mmol) in toluene (20 mL) was treated with MnO_2 (5.5 g, 63 mmol) and stirred at 25 °C for 2 h. The solids were removed by filtration, and the filtrate was concentrated in vacuo to afford compound **29** (2.2 g, 93%) as a yellow oil which was used without further purification. MS (ESI, pos. ion) *m/z*: 189 (M + 1).

A solution of compound **29** (1.1 g, 5.9 mmol) in DMF (20 mL) was treated with 1,4-benzodioxan-6-amine (890 mg, 5.9 mmol), glacial AcOH (0.5 mL), and $NaBH(OAc)_3$ (3.1 g, 15 mmol). The reaction mixture was magnetically stirred at 25 °C overnight. The reaction was quenched with water and extracted with EtOAc. The organic phase was washed with satd $NaHCO_3$ and water (2×), dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by silica gel chromatography (3:1 hexane:EtOAc) provided the title compound as an amorphous yellow solid. ^{1}H NMR (CD_3OD): δ 1.29 (s, 9 H), 3.77 (dd, J = 1.3, 5.9 Hz, 2 H), 4.11 (m, 2 H), 4.16 (m, 2 H), 6.22−6.25 (m, 2 H), 6.29 (t, J = 5.9 Hz, 1 H), 6.56 (d, J = 16.0 Hz, 1 H), 6.61 (d, J = 9.4 Hz, 1 H), 7.28 (d, J = 8.6 Hz, 2 H), 7.31 (d, J = 8.5 Hz, 2 H). MS (ESI, pos. ion) *m/z*: 324 (M + 1). Anal. ($C_{21}H_{25}NO_2$): C, H, N.

3-(4-*tert*-Butylphenyl)-*N*-(2,3-dihydrobenzo[*b*][1,4]-dioxin-6-yl)propanamide (31). Compound **1** (200 mg, 0.59 mmol) was dissolved in EtOH (25 mL), purged with N_2, treated with 10% Pd on carbon (50 mg), and then purged with H_2, and the suspension stirred at 25 °C, under 1 atm H_2, for 16 h. The suspension was purged with N_2, filtered through a pad of Celite, and concentrated in vacuo to provide a white foam. Purification by silica gel chromatography (45:45:10 hexane:CH_2Cl_2:EtOAc) provided the title compound (160 mg, 79%) as a clear glass. ^{1}H NMR (DMSO-d_6): δ 1.25 (s, 9 H), 2.54 (t, J = 7.5 Hz, 2 H), 2.84 (t, J = 7.5 Hz, 2 H), 4.18 (d, J = 9.5 Hz, 2 H), 4.20 (d, J = 9.6 Hz, 2 H), 6.75 (d, J = 8.7 Hz, 1 H), 6.93 (dd, J = 2.3, 8.7 Hz, 1 H), 7.15 (d, J = 8.1 Hz, 2 H), 7.22 (d, J = 2.3 Hz, 1 H), 7.29 (d, J = 8.2 Hz, 2 H), 9.73 (s, 1 H). MS (ESI, pos. ion) *m/z*: 340 (M + 1). Anal. ($C_{21}H_{25}NO_3$): C, H, N.

(*Z*)-3-(4-*tert*-Butylphenyl)-*N*-(2,3-dihydrobenzo[*b*][1,4]-dioxin-6-yl)acrylamide (34). Potassium bis(trimethylsilyl)-amide (6.1 mL, 3.1 mmol, 0.5 M in toluene) was added dropwise to a mixture of diphenylphosphonoacetic acid ethyl ester (0.98 g, 3.1 mmol) and 18-crown-6 (3.6 g, 13 mmol) in anhydrous THF (20 mL), with stirring, at −78 °C. The reaction mixture was stirred at −78 °C for 0.5 h and then treated dropwise with a solution of 4-*tert*-butylbenzaldehyde (0.42 mL,

2.5 mmol) in anhydrous THF (5 mL). The mixture was stirred at −78 °C for 1 h, quenched with satd NH_4Cl, warmed to 25 °C, diluted with water, and extracted with EtOAc (2×). The combined organic extracts were washed with satd NaCl, dried over $MgSO_4$, filtered, and concentrated in vacuo to provide compound **33** as a viscous brown oil which was used without purification. MS (ESI, pos. ion) *m/z*: 233 (M + 1).

A solution of crude compound **33** (0.83 g) in THF (5 mL) and MeOH (5 mL) was magnetically stirred in a round-bottomed flask at 25 °C and treated with 1 N LiOH (10 mL). The reaction mixture was stirred at 25 °C for 18 h, and then the organic solvents were removed in vacuo. The aqueous phase was washed with Et_2O, acidified with 10% aq citric acid, and extracted with EtOAc (3×). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo to provide the acid (0.50 g, 84% over two steps) as a white solid. ^{1}H NMR ($CDCl_3$): δ 1.33 (s, 9 H), 5.92 (d, J_{cis} = 12.8 Hz, 1 H), 7.03 (d, J_{cis} = 12.7 Hz, 1 H), 7.39 (d, J = 8.4 Hz, 2 H), 7.61 (d, J = 8.4 Hz, 2 H). MS (ESI, pos. ion) *m/z*: 205 (M + 1).

A solution of the acid from the previous step (0.46 g, 2.3 mmol), 1,4-benzodioxan-6-amine (0.38 g, 2.5 mmol), 1-hydroxybenzotriazole hydrate (0.34 g, 2.5 mmol), *N*,*N*-diisopropylethylamine (0.43 mL, 2.5 mmol), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.34 g, 2.5 mmol) in DMF (10 mL) was stirred for 16 h at 25 °C. The reaction mixture was diluted with EtOAc (100 mL) and washed with 5 N HCl, water, 5 N NaOH, and water. The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo to provide the title compound (0.41 g, 53%) as white crystals. Mp: 114−116 °C. ^{1}H NMR (DMSO-d_6): δ 1.27 (s, 9 H), 4.19−4.23 (m, 4 H), 6.09 (d, J_{cis} = 12.8 Hz, 1 H), 6.74 (d, J_{cis} = 12.8 Hz, 1 H), 6.78 (d, J = 8.7 Hz, 1 H), 7.29 (d, J = 2.4 Hz, 1 H), 7.36 (d, J = 8.5 Hz, 2 H), 7.59 (d, J = 8.4 Hz, 2 H), 10.03 (s, 1 H). MS (ESI, pos. ion) *m/z*: 338 (M + 1). Anal. ($C_{21}H_{23}NO_3$): C, H, N.

2-(4-*tert*-Butylphenyl)-*N*-(2,3-dihydrobenzo[*b*][1,4]-dioxin-6-yl)cyclopropanecarboxamide (36). To a round-bottomed flask was added 4-*tert*-butyl-*trans*-cinnamic acid (1.0 g, 5.1 mmol), *N*,*O*-dimethylhydroxylamine hydrochloride (0.54 g, 5.6 mmol), 1-hydroxybenzotriazole hydrate (0.75 g, 5.6 mmol), *N*,*N*′-diisopropylethylamine (2.7 mL, 16 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (1.1 g, 5.6 mmol), and anhydrous DMF (10 mL). The reaction mixture was stirred at 25 °C for 18 h, diluted with water, and extracted with EtOAc. The organic phase was washed with 1 M H_3PO_4 (3×), satd $NaHCO_3$ (3×), and satd NaCl, dried over Na_2SO_4, and concentrated in vacuo to provide the amide (1.1 g, 87%) as a viscous oil. ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 9 H), 3.31 (s, 3 H), 3.76 (s, 3 H), 7.01 (d, J = 15.8 Hz, 1 H), 7.41 (d, J = 8.3 Hz, 2 H), 7.52 (d, J = 8.3 Hz, 2 H), 7.73 (d, J = 15.8 Hz, 1 H). MS (ESI, pos. ion) *m/z*: 248 (M + 1).

Dimethyl sulfoxide (4.0 mL) was added dropwise with stirring at 25 °C to a mixture of NaH (0.11 g, 4.3 mmol, dry, 95%) and trimethylsulfoxonium iodide (0.94 g, 4.3 mmol). The reaction mixture was stirred at 25 °C for 0.5 h and a solution of the amide from the previous step (0.89 g, 3.6 mmol) in DMSO (4.0 mL) was added dropwise. The mixture was stirred at 25 °C for 18 h, poured into water, and extracted with Et_2O (2×). The combined organic extracts were washed with water and satd NaCl, dried over $MgSO_4$, filtered, and concentrated in vacuo to provide compound **35** (0.79 g, 84%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.24−1.33 (m, 2 H), 1.30 (s, 9 H), 1.60 (ddd, J_{trans} = 4.3 Hz, J_{trans} = 4.3 Hz, J_{cis} = 9.3 Hz, 1 H), 2.49 (ddd, J_{trans} = 4.3 Hz, J_{trans} = 6.3 Hz, J_{cis} = 9.8 Hz, 1 H), 3.24 (s, 3 H), 3.70 (s, 3 H), 7.08 (d, J = 8.3 Hz, 2 H), 7.31 (d, J = 8.3 Hz, 2 H). MS (ESI, pos. ion) *m/z*: 262 (M + 1).

A suspension of compound **35** (0.74 g, 2.8 mmol) and potassium *tert*-butoxide (2.0 g, 17 mmol) in Et_2O (10 mL) was treated with water (0.10 mL, 5.7 mmol) and stirred at 25 °C for 18 h. Crushed ice was added and the mixture was allowed to warm to room temperature and then washed with Et_2O. The aqueous phase was acidified with 1 N HCl at 0 °C. The resulting precipitate was collected by filtration, washed with water, and dried in vacuo to afford the acid (0.56 g, 91%) as a white solid. MS (ESI, pos. ion) *m/z*: 219 (M + 1).

Analogous to the first step, the carboxylic acid from the previous step and 1,4-benzodioxan-6-amine provided the title product (88%) as a white solid. Mp: 143−144 °C. ^{1}H NMR ($CDCl_3$) δ 1.25 (s, 9 H), 1.30 (ddd, J_{gem} = 4.1 Hz, J_{trans} = 6.3 Hz, J_{cis} = 8.2 Hz, 1 H), 1.43 (ddd, J_{gem} = 4.2 Hz, J_{trans} = 5.2 Hz, J_{cis} = 9.3 Hz, 1 H), 1.94 (ddd, J_{trans} = 4.2 Hz, J_{trans} = 5.3 Hz, J_{cis} = 8.4 Hz, 1 H), 2.28 (ddd, J_{trans} = 4.1 Hz, J_{trans} = 6.2 Hz, J_{cis} = 9.6 Hz, 1 H), 4.17−4.21 (m, 4 H), 6.76 (d, J = 8.7 Hz, 1 H), 6.95 (dd, J = 2.5, 8.7 Hz, 1 H), 7.08 (d, J = 8.4 Hz, 2 H), 7.23 (d, J = 2.4 Hz, 1 H), 7.30 (d, J = 8.4 Hz, 2 H), 10.03 (s, 1 H). MS (ESI, pos. ion) *m/z*: 352 (M + 1). Anal. ($C_{22}H_{25}NO_3$): C, H, N.

(*E*)-3-(4-*tert*-Butylphenyl)-*N*-(2,3-dihydrobenzo[*b*][1,4]-dioxin-6-yl)-3-phenylacrylamide (39). Analogous to the first step in the preparation of compound **36**, phenylpropiolic acid and 1,4-benzodioxan-6-amine provided compound **38** as a white solid. ^{1}H NMR ($CDCl_3$): δ 4.22 (s, 4 H), 6.80 (d, J = 8.6 Hz, 1 H), 6.98 (d, J = 8.5 Hz, 1 H), 7.22 (br s, 1 H), 7.28−7.46 (m, 4 H), 7.51 (d, J = 7.4 Hz, 1 H), 7.87 (br s, 1 H). MS (ESI, pos. ion) *m/z*: 280 (M + 1).

A solution of compound **38** (0.28 g, 1.0 mmol) and 1-*tert*-butyl-4-iodobenzene (0.18 mL, 1.0 mmol) in anhydrous EtOAc (50 mL) was treated with bis(dibenzylideneacetone)palladium-(0) (40 mg, 0.070 mmol), followed by Et_2NH (0.34 mL, 3.3 mmol) and 96% formic acid (0.10 mL, 2.6 mmol), with stirring under N_2 at room temperature. The mixture was stirred at reflux for 40 h, allowed to cool to room temperature and washed with 1 N HCl, 1 N NaOH, and satd NaCl. The organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography ($CHCl_3$) to provide the title compound (0.17 g, 40%) as an off-white solid. Mp: 139−140 °C. ^{1}H NMR ($CDCl_3$): δ 1.32 (s, 9 H), 4.20 (s, 4 H), 6.44 (dd, J = 2.3, 8.6 Hz, 1 H), 6.49 (s, 1 H), 6.60−6.70 (m, 2 H), 6.76 (d, J = 2.1 Hz, 1 H), 7.20−7.50 (m, 9 H). MS (ESI, pos. ion) *m/z*: 414 (M + 1). Anal. ($C_{27}H_{27}NO_3$): C, H, N.

Ethyl 3-(4-*tert*-Butylphenyl)propiolate (41). A solution of 4-*tert*-butylphenylacetylene (34 g, 0.21 mol) in anhydrous THF (220 mL) was stirred under N_2 at −78 °C and treated slowly with *n*-butyllithium (140 mL, 0.35 mol, 2.5 M in hexanes). After the addition was complete, the mixture was allowed to warm to 0 °C. The reaction mixture was stirred for 30 min at 0 °C, cooled to −78 °C, and treated with ethyl chloroformate (29 mL, 0.30 mol). After allowing to warm to 25 °C and stir overnight, the reaction was quenched with a 1:1 mixture of satd $NaHCO_3$ and satd NH_4Cl and extracted with Et_2O. The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo to afford a yellow oil. Purification by silica gel chromatography (gradient: 0.5%−3% EtOAc/hexane) provided the title compound (37 g, 75%) as a pale-yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.31−1.37 (m, 12 H), 4.29 (q, J = 7.1 Hz, 2 H), 7.39 (d, J = 8.4 Hz, 2 H), 7.53 (d, J = 8.4 Hz, 2 H). MS (ESI, pos. ion) *m/z*: 231 (M + 1).

(*Z*)-Ethyl 3-(4-*tert*-Butylphenyl)-3-iodoacrylate (42). To a round-bottomed flask equipped with a reflux condenser was added compound **41** (15 g, 65 mmol), sodium iodide (31 g, 210 mmol), and glacial AcOH (48 mL, 830 mmol). The reaction mixture was purged with N_2 and the flask immersed in a preheated 115 °C oil bath. The reaction mixture was stirred at 115 °C for 4 h and then allowed to cool to 25 °C and treated with water. The mixture was extracted with Et_2O and the organic phase was washed repeatedly with satd Na_2CO_3, until the evolution of CO_2 ceased. The organic phase was washed with 1 M $Na_2S_2O_3$ and satd NaCl, dried over Na_2SO_4, filtered, and concentrated in vacuo to provide the title compound (22 g, 94%) as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.32−1.37 (m, 12 H), 4.28 (q, J = 7.1 Hz, 2 H), 6.63 (s, 1 H), 7.37 (d, J = 8.5 Hz, 2 H), 7.48 (d, J = 8.5 Hz, 2 H). MS (ESI, pos. ion) *m/z*: 359 (M + 1).

3-(4-*tert*-Butylphenyl)-*N*-(2,3-dihydrobenzo[*b*][1,4]-dioxin-6-yl)propiolamide (43). A solution of compound **41** (10 g, 43 mmol) in 1,4-dioxane (50 mL) was treated with water (25 mL) and KOH (4.9 g, 87 mmol) and then stirred at reflux for 18 h. The mixture was allowed to cool to 25 °C, diluted

with water, and washed with hexane. The aqueous phase was acidified with 1 N HCl and extracted with CH_2Cl_2. The extract was washed with satd NaCl, dried over Na_2SO_4, filtered, and concentrated in vacuo to afford the acid (6.1 g, 70%) as a white solid. ^{1}H NMR ($CDCl_3$): δ 1.32 (s, 9 H), 7.42 (d, J = 8.4 Hz, 2 H), 7.56 (d, J = 8.4 Hz, 2 H). MS (ESI, pos. ion) *m/z*: 203 (M + 1).

Analogous to the first step in the preparation of compound **36**, the acid from the previous step and 1,4-benzodioxan-6-amine provided the title compound (53%) as a white solid. ^{1}H NMR ($CDCl_3$): δ 1.32 (s, 9 H), 4.27 (s, 4 H), 6.82 (d, J = 8.7 Hz, 1 H), 6.95 (dd, J = 2.5, 8.7 Hz, 1 H), 7.20 (d, J = 2.4 Hz, 1 H), 7.40 (m, 3 H), 7.51 (d, J = 8.4 Hz, 2 H). MS (ESI, pos. ion) *m/z*: 336 (M + 1).

(*Z*)-3-(4-*tert*-Butylphenyl)-*N*-(2,3-dihydrobenzo[*b*][1,4]-dioxin-6-yl)-3-iodoacrylamide (44). Following the procedure described for compound **42**, compound **43** was treated with sodium iodide in glacial AcOH to provide, after purification by silica gel chromatography (CH_2Cl_2), the title compound (80%) as a pale-yellow solid. ^{1}H NMR ($CDCl_3$): δ 1.33 (s, 9 H), 4.27 (s, 4 H), 6.68 (s, 1 H), 6.83 (d, J = 8.7 Hz, 1 H), 7.00−7.03 (m, 1 H), 7.33 (br s, 1 H), 7.37 (d, J = 8.4 Hz, 2 H), 7.47 (d, J = 8.4 Hz, 2 H). MS (ESI, pos. ion) *m/z*: 464 (M + 1).

(*Z*)-3-(4-*tert*-Butylphenyl)-*N*-(2,3-dihydrobenzo[*b*][1,4]-dioxin-6-yl)-3-(4-(trifluoromethyl)phenyl)acrylamide (45a). To a round-bottomed flask equipped with a reflux condenser was added compound **42** (0.75 g, 2.1 mmol), 4-trifluoromethylbenzeneboronic acid (0.60 g, 3.1 mmol), tetrakis-(triphenylphosphine)palladium(0) (0.24 g, 0.21 mmol), toluene (10 mL), EtOH (2 mL), and 2 M Na_2CO_3 (2 mL), under N_2. The reaction mixture was stirred at 80 °C overnight, allowed to cool to 25 °C, and diluted with EtOAc. The organic layer was separated, washed with water and satd NaCl, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by silica gel chromatography (gradient: 1.5% − 2% EtOAc/hexane) provided the product (0.76 g, 96%) as a white solid. ^{1}H NMR ($CDCl_3$): δ 1.11 (t, J = 7.1 Hz, 3 H), 1.31 (s, 9 H), 4.04 (q, J = 7.1 Hz, 2 H), 6.44 (s, 1 H), 7.20 (d, J = 8.5 Hz, 2 H), 7.32−7.36 (m, 4 H), 7.65 (d, J = 8.1 Hz, 2 H). MS (ESI, pos. ion) *m/z*: 377 (M + 1).

To a round-bottomed flask equipped with a reflux condenser was added the product from the previous step (0.74 g, 2.0 mmol), 1,4-dioxane (3 mL), KOH (0.66 g, 12 mmol), and water (1.5 mL). The reaction mixture was stirred at reflux overnight and then diluted with water and acidified with 1 N HCl. The mixture was extracted with CH_2Cl_2 (3×). The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo to provide the acid (0.68 g, 100%) as a white solid. ^{1}H NMR (DMSO-d_6): δ 1.26 (s, 9 H), 6.45 (s, 1 H), 7.19 (d, J = 8.5 Hz, 2 H), 7.36−7.41 (m, 4 H), 7.75 (d, J = 8.1 Hz, 2 H), 12.25 (s, 1 H). MS (ESI, pos. ion) *m/z*: 349 (M + 1).

Analogous to the first step in the preparation of compound **36**, the acid from the previous step and 1,4-benzodioxan-6-amine provided the title compound (96%) as a crystalline yellow solid. Mp: 150−151 °C. ^{1}H NMR ($CDCl_3$): δ 1.32 (s, 9 H), 4.20 (s, 4 H), 6.48 (s, 1 H), 6.57 (dd, J = 2.4, 8.7 Hz, 1 H), 6.72 (d, J = 8.7 Hz, 1 H), 6.80 (br s, 1 H), 6.94 (d, J = 2.1 Hz, 1 H), 7.19 (d, J = 8.3 Hz, 2 H), 7.36 (d, J = 8.3 Hz, 2 H), 7.44 (d, J = 7.9 Hz, 2 H), 7.68 (d, J = 8.1 Hz, 2 H). MS (ESI, pos. ion) *m/z*: 482 (M + 1). Anal. ($C_{28}H_{26}F_3NO_3$): C, H, N.

(*Z*)-3-(4-*tert*-Butylphenyl)-*N*-(2,3-dihydrobenzo[*b*][1,4]-dioxin-6-yl)-3-(pyridin-3-yl)acrylamide (45b). Following the procedure described for compound **45a**, pyridine-3-boronic acid, compound **42**, and 1,4-benzodioxan-6-amine provided the title compound as yellow crystals. Mp: 100−104 °C. ^{1}H NMR ($CDCl_3$): δ 1.32 (s, 9 H), 4.20 (s, 4 H), 6.48 (s, 1 H), 6.69−6.75 (m, 2 H), 6.88 (br s, 1 H), 6.98 (d, J = 1.9 Hz, 1 H), 7.21 (d, J = 8.3 Hz, 2 H), 7.33−7.38 (m, 3 H), 7.66 (d, J = 7.7 Hz, 1 H), 8.54 (br s, 1 H), 8.64 (d, J = 4.6 Hz, 1 H). MS (ESI, pos. ion) *m/z*: 415 (M + 1). Anal. ($C_{26}H_{26}N_2O_3$): C, H, N.

(*Z*)-3-(4-*tert*-Butylphenyl)-*N*-(2,3-dihydrobenzo[*b*][1,4]-dioxin-6-yl)-3-(pyridin-4-yl)acrylamide (45c). Following the procedure described for compound **45a**, pyridine-4-boronic acid, compound **42**, and 1,4-benzodioxan-6-amine provided the title compound as a yellow solid. Mp: 205−206 °C. ^{1}H NMR ($CDCl_3$): δ 1.32 (s, 9 H), 4.20 (s, 4 H), 6.49 (s, 1 H), 6.65 (dd, J = 2.3, 8.7 Hz, 1 H), 6.73 (d, J = 8.7 Hz, 2 H), 6.95 (s, 1 H), 6.97 (d, J = 2.2 Hz, 1 H), 7.18 (d, J = 8.3 Hz, 2 H), 7.24 (d, J = 5.6 Hz, 2 H), 7.36 (d, J = 8.4 Hz, 2 H), 8.66 (d, J = 5.5 Hz, 2 H). MS (ESI, pos. ion) *m/ z*: 415 (M + 1). Anal. Calcd for $C_{26}H_{26}N_2O_3$: C, 75.34; H, 6.32; N, 6.76. Found: C, 74.68; H, 6.29; N, 6.61.

(*E*)-3-(4-*tert*-Butylphenyl)-*N*-(2,3-dihydrobenzo[*b*][1,4]-dioxin-6-yl)-5-methylhex-2-enamide (45d). A solution of compound **42** (720 mg, 2.0 mmol) in anhydrous DMF (4 mL) was added dropwise to a solution of isobutylzinc bromide (12 mL, 6.0 mmol, 0.5 M solution in THF) with stirring under N_2 at 0 °C. The reaction mixture was treated with bis(acetonitrile)dichloropalladium(II) (78 mg, 0.30 mmol) in one portion and then stirred for 16 h at 25 °C. The reaction mixture was diluted with Et_2O and washed with 1 N HCl and satd NaCl. The organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo and the residue purified by silica gel chromatography (99:1 hexane:EtOAc) to provide the product (0.33 g, 57%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 0.87 (d, J = 6.5 Hz, 6 H), 1.25−1.35 (m, 12 H), 1.67 (sept, J = 6.8 Hz, 1 H), 3.07 (d, J = 7.3 Hz, 2 H), 4.19 (q, J = 7.1 Hz, 2 H), 6.05 (s, 1 H), 7.30−7.40 (m, 4 H). MS (ESI, pos. ion) *m/z*: 289 (M + 1).

To a round-bottomed flask equipped with a reflux condenser was added the product from the previous step (0.33 g, 1.1 mmol), 1,4-dioxane (2 mL), KOH (0.22 g, 4.0 mmol), and water (4 mL). The reaction mixture was stirred at reflux overnight and then diluted with water and acidified with 1 N HCl. The aqueous mixture was extracted with CH_2Cl_2 (3×). The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo to provide the acid (0.29 g, 99%) as a white solid. ^{1}H NMR ($CDCl_3$): δ 0.88 (d, J = 6.6 Hz, 6 H), 1.33 (s, 9 H), 1.68 (sept, J = 6.7 Hz, 1 H), 3.09 (d, J = 7.3 Hz, 2 H), 6.10 (s, 1 H), 7.30−7.40 (m, 4 H). MS (ESI, pos. ion) *m/z*: 261 (M + 1).

Analogous to the first step in the preparation of compound **36**, the acid from the previous step and 1,4-benzodioxan-6-amine provided the title compound (47%) as an off-white solid. Mp: 123.1−123.2 °C. ^{1}H NMR ($CDCl_3$): δ 0.89 (d, J = 6.6 Hz, 6 H), 1.33 (s, 9 H), 1.68 (sept, J = 6.7 Hz, 1 H), 3.11 (d, J = 7.3 Hz, 2 H), 4.25 (s, 4 H), 6.01 (s, 1 H), 6.81 (d, J = 8.6 Hz, 1 H), 6.98 (d, J = 8.7 Hz, 1 H), 7.06 (br s, 1 H), 7.18 (br s, 1 H), 7.34 (d, J = 8.4 Hz, 2 H), 7.38 (d, J = 8.4 Hz, 2 H). MS (ESI, pos. ion) *m/z*: 394 (M + 1). Anal. ($C_{25}H_{31}NO_3$): C, H, N.

(*E*)-3-(4-*tert*-Butylphenyl)-*N*-(2,3-dihydrobenzo[*b*][1,4]-dioxin-6-yl)-4-phenylbut-2-enamide (45e). Following the procedure described for compound **45d**, benzylzinc bromide, compound **42**, and 1,4-benzodioxan-6-amine provided the title product as off-white needles. Mp: 97−99 °C. ^{1}H NMR ($CDCl_3$): δ 1.29 (s, 9 H), 4.18 (s, 4 H), 4.48 (s, 2 H), 6.26 (s, 1 H), 6.78 (d, J = 8.6 Hz, 1 H), 6.85 (dd, J = 1.9, 8.7 Hz, 1 H), 7.10−7.28 (m, 7 H), 7.32 (d, J = 8.3 Hz, 2 H), 7.37 (d, J = 8.3 Hz, 2 H). MS (ESI, pos. ion) *m/z*: 428 (M + 1). Anal. ($C_{28}H_{29}NO_3$): C, H, N.

(*E*)-Ethyl 4-(4-*tert*-Butylphenyl)-6-(2,3-dihydrobenzo-[*b*][1,4]dioxin-6-ylamino)-6-oxohex-4-enoate (45f). Following the first step in the procedure described for compound **45d**, 3-ethoxy-3-oxopropylzinc bromide and compound **44** provided the title compound (40%) as a pale-yellow solid. Mp: 104−105 °C. ^{1}H NMR ($CDCl_3$): δ 1.12 (t, J = 7.1 Hz, 3 H), 1.25 (s, 9 H), 2.44 (t, J = 7.1 Hz, 2 H), 3.20 (t, J = 7.0 Hz, 2 H), 4.01 (q, J = 7.1 Hz, 2 H), 4.36 (s, 4 H), 6.0 (s, 1 H), 6.74 (d, J = 8.6 Hz, 1 H), 7.00 (dd, J = 2.0, 8.6 Hz, 1 H), 7.16−7.28 (m, 3 H), 7.30 (d, J = 8.2 Hz, 2 H), 8.47 (br s, 1 H). MS (ESI, pos. ion) *m/z*: 438 (M + 1). Anal. ($C_{26}H_{31}NO_5$): C, H, N.

(*E*)-4-(4-*tert*-Butylphenyl)-6-(2,3-dihydrobenzo[*b*][1,4]-dioxin-6-ylamino)-6-oxohex-4-enoic Acid (45g). A solution of compound **45f** (0.25 g, 0.57 mmol) in 1,4-dioxane (2 mL) was treated with 2 N KOH (0.70 mL, 2.5 mmol). The reaction mixture was stirred at room temperature overnight and then diluted with water and washed with EtOAc (4×). The alkaline water phase was acidified with 1 N HCl and extracted with CH_2Cl_2 (3×). The organic phase was dried over Na_2SO_4,

filtered, and concentrated in vacuo to provide a yellow foam. The foam was crystallized from EtOAc/hexane to afford the title product (0.13 g, 54%) as off-white flakes. Mp: 185.9−186.0 °C. ^{1}H NMR ($CDCl_3$): δ 1.26 (s, 9 H), 2.50 (t, J = 7.1 Hz, 2 H), 3.24 (t, J = 7.1 Hz, 2 H), 4.16 (s, 4 H), 6.03 (s, 1 H), 6.70 (d, J = 8.7 Hz, 1 H), 6.92 (dd, J = 2.2, 8.6 Hz, 1 H), 7.16 (d, J = 2.1 Hz, 1 H), 7.24 (d, J = 8.3 Hz, 2 H), 7.31 (d, J = 8.3 Hz, 2 H), 7.97 (br s, 1 H). MS (ESI, pos. ion) *m/z*: 410 (M + 1). Anal. ($C_{24}H_{27}NO_5$): C, H, N.

(*E*)-3-(4-*tert*-Butylphenyl)-*N*-(2,3-dihydrobenzo[*b*][1,4]-dioxin-6-yl)-5-(1,3-dioxolan-2-yl)pent-2-enamide (45h). Following the first step in the procedure described for compound **45d**, (1,3-dioxolan-2-ylethyl)zinc bromide and compound **44** provided the title compound (87%) as a white solid. Mp: 144−146 °C. ^{1}H NMR ($CDCl_3$): δ 1.33 (s, 9 H), 1.82−1.87 (m, 2 H), 3.19 (t, J = 7.7 Hz, 2 H), 3.82−3.90 (m, 2 H), 3.92−4.00 (m, 2 H), 4.24 (m, 4 H), 4.90 (t, J = 5.0 Hz, 1 H), 6.06 (s, 1 H), 6.80 (d, J = 8.7 Hz, 1 H), 7.01 (dd, J = 2.0, 8.6 Hz, 1 H), 7.22 (d, J = 2.0 Hz, 1 H), 7.37 (s, 4 H), 7.81 (br s, 1 H). MS (ESI, pos. ion) *m/z*: 438 (M + 1). Anal. ($C_{26}H_{31}NO_5$): C, H, N.

(*E*)-3-(4-*tert*-Butylphenyl)-*N*-(2,3-dihydrobenzo[*b*][1,4]-dioxin-6-yl)-6-(dimethylamino)hex-2-enamide Hydrochloride (45i). A solution of compound **45h** (0.65 g, 1.5 mmol) in THF (8 mL) was treated with 5 N HCl (16 mL). The reaction mixture was stirred at room temperature for 2 h and then basified with solid $NaHCO_3$ to pH 5−6. The mixture was extracted with CH_2Cl_2 (3×). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo to provide the aldehyde (0.57 g, 98%) as an off-white solid. ^{1}H NMR ($CDCl_3$): δ 1.33 (s, 9 H), 2.68 (t, J = 7.1 Hz, 2 H), 3.36 (t, J = 7.6 Hz, 2 H), 4.26 (s, 4 H), 6.06 (s, 1 H), 6.82 (d, J = 8.7 Hz, 1 H), 7.00−7.03 (m, 1 H), 7.24 (d, J = 2.4 Hz, 1 H), 7.32 (d, J = 8.4 Hz, 2 H), 7.39 (d, J = 8.4 Hz, 2 H), 7.89 (s, 1 H), 9.75 (s, 1 H). MS (ESI, pos. ion) *m/z*: 394 (M + 1).

A solution of the aldehyde from the previous step (50 mg, 0.13 mmol) in CH_2Cl_2 (1 mL) was treated with dimethylamine (0.13 mL, 0.26 mmol, 2.0 M in THF), followed by $NaBH(OAc)_3$ (42 mg, 0.19 mmol) and glacial AcOH (10 μL). The mixture was stirred at room temperature overnight, diluted with saturated $NaHCO_3$, and extracted with CH_2Cl_2 (3×). The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by silica gel chromatography (4% MeOH in CH_2Cl_2) provided the title compound (48 mg, 89%), which was treated with 1 N HCl in Et_2O and dried in vacuo to provide the hydrochloride salt as an amorphous pale-yellow solid. ^{1}H NMR ($CDCl_3$): δ 1.25 (s, 9 H), 1.91 (br s, 2 H), 2.64 (br s, 6 H), 3.01 (br s, 2 H), 3.11 (br s, 2 H), 4.21 (s, 4 H), 6.63 (s, 1 H), 6.74 (d, J = 8.4 Hz, 1 H), 7.16 (d, J = 7.8 Hz, 1 H), 7.27 (d, J = 8.4 Hz, 2 H), 7.35 (br d, 2 H), 7.44 (s, 1 H), 9.57 (s, 1 H), 11.49 (br s, 1 H). MS (ESI, pos. ion) *m/z*: 423 (M + 1). Anal. Calcd for $C_{26}H_{34}N_2O_3$·HCl: C, 68.03, H, 7.69, N, 6.10. Found: C, 65.43; H, 7.54; N, 6.14.

(*E*)-3-(4-*tert*-Butylphenyl)-*N*-phenylacrylamide (46a). To a 10 mL glass vial was added 4-*tert*-butyl-*trans*-cinnamic acid (200 mg, 0.98 mmol) followed by CH_2Cl_2 (5 mL), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (230 mg, 1.2 mmol), and aniline (0.098 mL, 100 mg, 1.1 mmol). The reaction mixture was stirred at 25 °C for 24 h and then diluted with EtOAc. The mixture was washed with 1 N NaOH, 1 N HCl, water, and satd NaCl, dried over $MgSO_4$, filtered, and concentrated in vacuo. Recrystallization of the crude product from hexane and CH_2Cl_2 provided the title compound (170 mg, 59%) as white crystals. Mp: 141−142 °C. ^{1}H NMR (DMSO-d_6): δ 1.30 (s, 9 H), 6.80 (d, J = 15.8 Hz, 1 H), 7.07 (m, 1 H), 7.32−7.36 (m, 2 H), 7.47 (d, J = 8.4 Hz, 2 H), 7.54−7.58 (m, 3 H), 7.69−7.71 (m, 2 H), 10.19 (s, 1 H). MS (ESI, pos. ion) *m/z*: 280 (M + 1). Anal. Calcd for $C_{19}H_{21}NO$: C, 81.68; H, 7.58; N, 5.01. Found: C, 81.15; H, 7.55; N, 5.05.

(*E*)-3-(4-*tert*-Butylphenyl)-*N*-(3-methoxyphenyl)acrylamide (46c). To a round-bottomed flask equipped with reflux condenser and drying tube was added 4-*tert*-butyl-*trans*-cinnamic acid (200 mg, 0.98 mmol) followed by CH_2Cl_2 (5 mL), oxalyl chloride (0.090 mL, 1.0 mmol), and DMF (1 μL). The reaction mixture was stirred at reflux for 30 min and then concentrated in vacuo. The residue was dissolved in acetone (2 mL) and added to a mixture of *m*-anisidine (150 mg, 1.2 mmol) and K_2CO_3 (200 mg, 1.4 mmol) in water (2 mL) and acetone (2 mL). The reaction mixture was stirred at 25 °C for 16 h, diluted with EtOAc, washed with 1 N HCl, 1 N NaOH, water, and satd NaCl, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the crude product by silica gel chromatography (4:1 hexane:EtOAc) provided the title compound (190 mg, 62%) as a clear glass. ^{1}H NMR (DMSO-d_6): δ 1.30 (s, 9 H), 3.74 (s, 3 H), 6.65 (m, 1 H), 6.78 (d, J = 15.7 Hz, 1 H), 7.20−7.26 (m, 2 H), 7.41 (m, 1 H), 7.47 (d, J = 8.4 Hz, 2 H), 7.55 (d, J = 15.6 Hz, 1 H), 7.55 (d, J = 8.4 Hz, 2 H), 10.18 (s, 1 H). MS (ESI, pos. ion) *m/z*: 310 (M + 1). Anal. ($C_{20}H_{23}NO_2$): C, H, N.

(*E*)-3-(4-*tert*-Butylphenyl)-*N*-(4-methoxyphenyl)acrylamide (46d). Following the procedure described for compound **46c**, *p*-anisidine and 4-*tert*-butyl-*trans*-cinnamic acid provided the title compound (61%) as yellow crystals. Mp: 174−175 °C. ^{1}H NMR (DMSO-d_6): δ 1.29 (s, 9 H), 3.73 (s, 3 H), 6.75 (d, J = 15.7 Hz, 1 H), 6.91 (m, 2 H), 7.46 (d, J = 8.5 Hz, 2 H), 7.52 (d, J = 15.6 Hz, 1 H), 7.54 (d, J = 8.4 Hz, 2 H), 7.61 (m, 2 H), 10.06 (s, 1 H). MS (ESI, pos. ion) *m/ z*: 310 (M + 1). Anal. ($C_{20}H_{23}NO_2$): C, H, N.

(*E*)-3-(4-*tert*-Butylphenyl)-*N*-(3,4-dimethoxyphenyl)-acrylamide (46e). Following the procedure described for compound **46c**, 4-*tert*-butyl-*trans*-cinnamic acid and 3,4-dimethoxyaniline provided the title compound (80%) as a yellow solid. Mp: 115−116 °C. ^{1}H NMR (DMSO-d_6): δ 1.29 (s, 9 H), 3.73 (s, 3 H), 3.74 (s, 3 H), 6.75 (d, J = 15.7 Hz, 1 H), 6.91 (d, J = 8.8 Hz, 1 H), 7.21 (dd, J = 2.3, 8.7 Hz, 1 H), 7.41 (d, J = 2.3 Hz, 1 H), 7.46 (d, J = 8.5 Hz, 2 H), 7.52 (d, J = 15.8 Hz, 1 H), 7.54 (d, J = 8.4 Hz, 2 H), 10.07 (s, 1 H). MS (ESI, pos. ion) *m/z*: 340 (M + 1). Anal. ($C_{21}H_{25}NO_3$): C, H, N.

(*E*)-3-(4-*tert*-Butylphenyl)-*N*-(3-hydroxy-4-methoxyphenyl)acrylamide (46f). Following the procedure described for compound **46c**, 5-amino-2-methoxyphenol and 4-*tert*-butyl-*trans*-cinnamic acid provided the title compound (52%) as white crystals. Mp: 173−174 °C.^{1}H NMR (DMSO-d_6): δ 1.30 (s, 9 H), 3.74 (s, 3 H), 6.75 (d, J = 15.6 Hz, 1 H), 6.86 (d, J = 9.0 Hz, 1 H), 7.06 (dd, J = 2.1, 8.7 Hz, 1 H), 7.28 (d, J = 2.1 Hz, 1 H), 7.46 (d, J = 8.3 Hz, 2 H), 7.50 (d, J = 16.1 Hz, 1 H), 7.53 (d, J = 8.5 Hz, 2 H), 9.08 (s, 1 H), 9.93 (s, 1 H). MS (ESI, pos. ion) *m/z*: 326 (M + 1). Anal. ($C_{20}H_{23}NO_3$): C, H, N.

(*E*)-3-(4-*tert*-Butylphenyl)-*N*-(4-hydroxy-3-methoxyphenyl)acrylamide (46g). To a round-bottomed flask was added 4-nitroguaiacol (500 mg, 3.0 mmol) and anhydrous EtOH (50 mL). The solution was stirred magnetically under N_2 and treated with 10% Pd on carbon (200 mg). The suspension was purged with H_2 and then stirred at 25 °C under 1 atm H_2 for 16 h. The suspension was purged with N_2, filtered through Celite, and concentrated in vacuo to provide a dark solid. The solid was washed with 1:1 CH_2Cl_2:hexane and dried in vacuo to provide the aniline (330 mg, 79%) as pale brown crystals. MS (ESI, pos. ion) *m/z*: 140 (M + 1).

Following the procedure described for compound **46c**, the aniline and 4-*tert*-butyl-*trans*-cinnamic acid provided the title compound (88%) as brown crystals. Mp: 203−204 °C. ^{1}H NMR (DMSO-d_6): δ 1.29 (s, 9 H), 3.75 (s, 3 H), 6.71 (d, J = 8.5 Hz, 1 H), 6.74 (d, J = 15.6 Hz, 1 H), 7.06 (dd, J = 2.3, 8.5 Hz, 1 H), 7.39 (d, J = 2.3 Hz, 1 H), 7.45−7.48 (m, 3 H), 7.53 (d, J = 8.3 Hz, 2 H), 8.78 (s, 1 H), 9.97 (s, 1 H). MS (ESI, pos. ion) *m/z*: 326 (M + 1). Anal. Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 72.70; H, 7.30; N, 4.23.

(*E*)-3-(4-*tert*-Butylphenyl)-*N*-(5,6,7,8-tetrahydronaphthalen-2-yl)acrylamide (46i). To a round-bottomed flask was added 6-amino-1,2,3,4-tetrahydronaphthalene-1-one (500 mg, 3.1 mmol), triethylsilane (2.5 mL, 16 mmol), and trifluoroacetic acid (5.0 mL, 66 mmol). The reaction mixture was stirred vigorously at 25 °C for 2 h. The solvents were removed in vacuo, and the residue was dissolved in EtOAc and extracted twice with 1 N HCl. The combined aqueous acidic extract was washed with EtOAc and then basified with 5 N NaOH, at 0 °C, to pH 10. The mixture was extracted with CH_2Cl_2 (3×),

and the combined organic extracts were washed with water and satd NaCl, dried over Na_2SO_4, filtered, and concentrated in vacuo to provide compound **7** (410 mg, 90%) as a brown oil. MS (ESI, pos. ion) *m/z*: 148 (M + 1).

Following the procedure described for compound **46a**, tetrahydronaphthylen-2-amine (**7**) and 4-*tert*-butyl-*trans*-cinnamic acid provided the title compound (55%) as white crystals. Mp: 198−199 °C. ^{1}H NMR (DMSO-d_6): δ 1.29 (s, 9 H), 1.72 (m, 4 H), 2.68 (m, 4 H), 6.77 (d, J = 15.7 Hz, 1 H), 6.99 (d, J = 8.3 Hz, 1 H), 7.38 (m, 1 H), 7.41 (m, 1 H), 7.46 (d, J = 8.5 Hz, 2 H), 7.51 (d, J = 15.5 Hz, 1 H), 7.54 (d, J = 8.4 Hz, 2 H), 10.02 (s, 1 H). MS (ESI, pos. ion) *m/z*: 334 (M + 1). Anal. ($C_{23}H_{27}NO$): C, H, N.

(*E*)-3-(4-*tert*-Butylphenyl)-*N*-(3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-7-yl)acrylamide (46j). Analogous to the method described by Huang and Chan,[28] a solution of chloroacetyl chloride (2.6 mL, 33 mmol) in $CHCl_3$ (5 mL) was added over a period of 30 min to a mixture of 5-nitro-2-aminophenol (4.6 g, 30 mmol), benzyltriethylammonium chloride (6.8 g, 30 mmol), and $NaHCO_3$ (13 g, 150 mmol) in $CHCl_3$ (100 mL) stirred at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and then at 50 °C for 16 h. The solvent was removed in vacuo, and the residue was treated with water to provide a suspension. The solid was collected by filtration, washed with water, and recrystallized from EtOH to provide the intermediate nitro compound (4.8 g, 83%). ^{1}H NMR (CD_3OD): δ 4.71 (s, 2 H), 7.05 (d, J = 8.7 Hz, 1 H), 7.83 (d, J = 2.3 Hz, 1 H), 7.92 (dd, J = 2.3, 8.7 Hz, 1 H). MS (ESI, neg. ion) *m/ z*: 193 (M−1).

A mixture of the nitro compound from the previous step (970 mg, 5.0 mmol) and 10% Pd on carbon (100 mg) in MeOH (20 mL) was stirred at room temperature under 1 atm H_2 for 2 h. The mixture was purged with N_2 and filtered through a pad of Celite. The filtrate was concentrated in vacuo to provide compound **11** (650 mg, 79%). MS (ESI, pos. ion) *m/z*: 165 (M + 1).

To a solution of borane−THF complex (2.5 mL, 2.5 mmol, 1.0 M in THF), stirred at 0 °C under N_2 in a round-bottomed flask equipped with a reflux condenser, was added compound **11** (160 mg, 1.0 mmol). The reaction mixture was stirred at reflux for 2 h and then treated with EtOH (0.5 mL) and reflux continued for an additional 1 h. The mixture was treated with concd HCl (0.5 mL) and reflux continued for 1 h. The solvent was removed in vacuo and the residue treated with 1 N NaOH and extracted with CH_2Cl_2 (3×). The combined organic extracts were washed with satd NaCl, dried over Na_2SO_4, filtered, and concentrated in vacuo to provide the crude aniline **12**. MS (ESI, pos. ion) *m/z*: 151 (M + 1).

Analogous to the procedure described for compound **46a**, the aniline **12** and 4-*tert*-butyl-*trans*-cinnamic acid provided the title compound (69% over two steps) as a pale-yellow solid. Mp: 186−188 °C. ^{1}H NMR (CD_3OD): δ 1.33 (s, 9 H), 3.42 (m, 2 H), 3.70 (br s, 1 H), 4.26 (t, J = 4.3 Hz, 2 H), 6.46 (d, J = 15.4 Hz, 1 H), 6.57 (d, J = 8.9 Hz, 1 H), 7.05 (s, 2 H), 7.12 (s, 1 H), 7.40 (d, J = 8.1 Hz, 1 H), 7.48 (d, J = 8.1 Hz, 2 H), 7.70 (d, J = 15.5 Hz, 1 H). MS (ESI, pos. ion) *m/z*: 337 (M + 1). Anal. Calcd for $C_{21}H_{24}N_2O_2$: C, 74.97; H, 7.19; N, 8.33. Found: C, 74.71; H, 7.76; N, 7.59.

(*E*)-3-(4-*tert*-Butylphenyl)-*N*-(3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-6-yl)acrylamide (46k). To a round-bottomed flask was added 2-amino-4-nitrophenol (1.0 g, 6.5 mmol), potassium carbonate (1.8 g, 13 mmol), DMF (5 mL), and 1,2-dibromoethane (0.59 mL, 6.9 mmol). The mixture was stirred in a 125 °C oil bath under N_2 for 2.5 h. After allowing to cool to 25 °C, the reaction mixture was diluted with EtOAc, washed with 1 N NaOH (3×), water, and satd NaCl, dried over Na_2SO_4, filtered, and concentrated to provide a dark oily residue [MS (ESI, pos. ion) *m/z*: 181 (M + 1)]. A solution of the residue in EtOH (100 mL) was purged with N_2, treated with 10% Pd on carbon (450 mg), purged with H_2, and stirred under 1 atm H_2 for 2 h. After purging with N_2, the suspension was filtered through Celite and the filtrate was concentrated in vacuo. Purification by silica gel chromatography (95:5 CH_2Cl_2:2 M NH_3 in EtOH) provided compound **9** (230 mg, 27% for two steps) as a viscous brown oil. ^{1}H NMR (DMSO-d_6): δ 3.17−3.19 (m, 2 H), 3.96 (m, 2 H), 4.32 (br s, 2 H), 5.44 (br s, 1 H), 5.71 (dd, J = 2.5, 8.3 Hz, 1 H), 5.82 (d, J = 2.6 Hz, 1 H), 6.30 (d, J = 8.3 Hz, 1 H). MS (ESI, pos. ion) *m/z*: 151 (M + 1).

Following the procedure described for compound **46c**, compound **9** and 4-*tert*-butyl-*trans*-cinnamic acid provided the title compound (35%) as an amorphous yellow solid. ^{1}H NMR (DMSO-d_6): δ 1.29 (s, 9 H), 3.25 (m, 2 H), 4.07 (m, 2 H), 5.89 (br s, 1 H), 6.57 (d, J = 8.6 Hz, 1 H), 6.71−6.73 (m, 1 H), 6.75 (d, J = 15.6 Hz, 1 H), 7.07 (m, 1 H), 7.44−7.53 (m, 5 H), 9.81 (s, 1 H). MS (ESI, pos. ion) *m/z*: 337 (M + 1). Anal. ($C_{21}H_{24}N_2O_2$): C, H, N.

(*E*)-3-(4-*tert*-Butylphenyl)-*N*-(3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-7-yl)acrylamide (46l). Analogous to the procedure described for compound **46a**, 4-*tert*-butyl-*trans*-cinnamic acid and compound **11** provided the title compound (58%) as a pale yellow solid. Mp: 226−227 °C. ^{1}H NMR (CD_3OD): δ 1.17 (s, 9 H), 4.38 (s, 2 H), 6.51 (d, J = 15.7 Hz, 1 H), 6.66 (d, J = 8.5 Hz, 1 H), 7.02 (dd, J = 2.3, 8.5 Hz, 1 H), 7.23 (d, J = 2.3 Hz, 1 H), 7.26 (d, J = 8.4 Hz, 2 H), 7.34 (d, J = 8.4 Hz, 2 H), 7.42 (d, J = 15.7 Hz, 1 H). MS (ESI, pos. ion) *m/z*: 351 (M + 1). Anal. Calcd for $C_{21}H_{22}N_2O_3$: C, 71.98; H, 6.33; N, 7.99. Found: C, 68.71; H, 6.48; N, 7.68.

(*E*)-3-(4-*tert*-Butylphenyl)-*N*-(3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-6-yl)acrylamide (46m). To a suspension of 6-nitro-2*H*,4*H*-benzo[*e*]1,4-oxazaperhydroin-3-one[28] (0.50 g, 2.6 mmol) and CuCl (0.77 g, 7.8 mmol) in anhydrous MeOH (25 mL), stirred at 25 °C in a round-bottomed flask, was added potassium borohydride (0.98 g, 18 mmol) in portions. The reaction mixture was stirred at 25 °C for 30 min, the solvent was removed in vacuo, and the residue was suspended in water and extracted with EtOAc (5×). The combined organic extracts were washed with satd NaCl, dried over Na_2SO_4, filtered, and concentrated in vacuo to provide the aniline (0.29 g, 67%) as a brown solid. MS (ESI, pos. ion) *m/z*: 165 (M + 1).

Analogous to the procedure described for compound **46a**, the aniline from the previous step and 4-*tert*-butyl-*trans*-cinnamic acid provided the title compound (32%) as a pale yellow solid. Mp: >280 °C. ^{1}H NMR (DMSO-d_6): δ 1.29 (s, 9 H), 4.53 (s, 2 H), 6.75 (d, J = 15.7 Hz, 1 H), 6.91 (d, J = 8.7 Hz, 1 H), 7.17 (dd, J = 2.4, 8.7 Hz, 1 H), 7.45−7.55 (m, 6 H), 10.14 (s, 1 H), 10.78 (s, 1 H). MS (ESI, pos. ion) *m/z*: 351 (M + 1). Anal. ($C_{21}H_{22}N_2O_3$): C, H, N.

(*E*)-3-(4-*tert*-Butylphenyl)-*N*-(2-oxo-1,2,3,4-tetrahydroquinolin-7-yl)acrylamide (46n). A mixture of 2,4-dinitrobenzaldehyde (10 g, 51 mmol) and methyl (triphenylphosphoranylidene)acetate (17 g, 51 mmol) in benzene (200 mL) was stirred at reflux, under N_2, for 3 h. The reaction mixture was allowed to cool to 25 °C and diluted with Et_2O. The mixture was washed with water (3×) and satd NaCl, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by silica gel chomatography (4:1 hexane:EtOAc) provided compound **14** (12 g, 88%) as a bright yellow solid. ^{1}H NMR (DMSO-d_6): δ 3.78 (s, 3 H), 6.81 (d, J = 15.9 Hz, 1 H), 7.97 (d, J = 15.9 Hz, 1 H), 8.21 (d, J = 8.7 Hz, 1 H), 8.55 (dd, J = 2.3, 8.4 Hz, 1 H), 8.79 (d, J = 2.3 Hz, 1 H).

A solution of compound **14** (10 g, 38 mmol) in EtOH (150 mL) and glacial AcOH (10 mL) was treated with 10% Pd on carbon (5.0 g, Aldrich) and hydrogenated on a Parr shaker apparatus at 25 °C, under 60 psi H_2, for 6 h. The reaction mixture was purged with N_2 and filtered through Celite, and the filter cake washed with EtOH (400 mL). The combined filtrate was concentrated in vacuo to provide compound **15** (5.8 g, 95%) as a yellow solid. ^{1}H NMR (DMSO-d_6): δ 2.35 (dd, J = 7.1, 7.8 Hz, 2 H), 2.66 (dd, J = 7.1, 7.8 Hz, 2 H), 4.95 (br s, 2 H), 6.09−6.13 (m, 2 H), 6.76 (d, J = 7.8 Hz, 1 H), 9.82 (s, 1 H). MS (ESI, pos. ion) *m/z*: 163 (M + 1).

Analogous to the procedure described for compound **46a**, 4-*tert*-butyl-*trans*-cinnamic acid and compound **15** provided the title compound (12%) as white crystals. Mp: 288−290 °C. ^{1}H NMR (DMSO-d_6): δ 1.30 (s, 9 H), 2.43 (t, J = 8.0 Hz, 2 H), 2.81 (t, J = 8.0 Hz, 2 H), 6.79 (d, J = 15.6 Hz, 1 H), 7.10 (d, J = 8.0 Hz, 1 H), 7.23 (dd, J = 2.0, 8.0 Hz, 1 H), 7.30 (d, J = 2.0 Hz, 1 H), 7.47 (d, J = 8.8 Hz, 2 H), 7.53 (d, J = 15.6 Hz, 1 H),

7.54 (d, J = 8.4 Hz, 2 H), 10.14 (s, 1 H), 10.16 (s, 1 H). MS (ESI, pos. ion) *m/z*: 349 (M + 1). Anal. ($C_{22}H_{24}N_2O_2$): C, H, N.

(*E*)-3-(4-*tert*-Butylphenyl)-*N*-(1,2,3,4-tetrahydroquinolin-7-yl)acrylamide (46o). Analogous to the procedure described for compound **46a**, 7-amino-1,2,3,4-tetrahydroquinoline[44] and 4-*tert*-butyl-*trans*-cinnamic acid provided the title compound (23%) as a yellow solid. Mp: 225−227 °C. ^{1}H NMR (DMSO-d_6): δ 1.29 (s, 9 H), 1.76 (m, 2 H), 2.60 (t, J = 6.2 Hz, 2 H), 3.14 (m, 2 H), 5.72 (s, 1 H), 6.69 (dd, J = 1.5 Hz, 6.8 Hz, 1 H), 6.74 (d, J = 6.8 Hz, 1 H), 6.77 (d, J = 15.5 Hz, 1 H), 6.90 (d, J = 1.3 Hz, 1 H), 7.45 (d, J = 8.4 Hz, 2 H), 7.48 (d, J = 15.5 Hz, 1 H), 7.52 (d, J = 8.4 Hz, 2 H), 9.79 (s, 1 H). MS (ESI, pos. ion) *m/z*: 335 (M + 1). Anal. Calcd for $C_{22}H_{26}N_2O$: C, 79.00; H, 7.84; N, 8.38. Found: C, 78.31; H, 7.88; N, 8.20.

(*E*)-3-(4-*tert*-Butylphenyl)-*N*-(quinolin-7-yl)acrylamide (46p). Analogous to the procedure described for compound **46a**, 7-aminoquinoline and 4-*tert*-butyl-*trans*-cinnamic acid provided the title compound (28%) as a white solid. Mp: 256−258 °C. ^{1}H NMR (DMSO-d_6): δ 1.31 (s, 9 H), 6.86 (d, J = 16 Hz, 1 H), 7.42 (dd, J = 4.4, 8.0 Hz, 1 H), 7.49 (d, J = 8.4 Hz, 2 H), 7.60 (d, J = 8.4 Hz, 2 H), 7.65 (d, J = 16 Hz, 1 H), 7.79 (dd, J = 2.0, 8.8 Hz, 1 H), 7.95 (d, J = 8.8 Hz, 1 H), 8.28 (d, J = 8.4 Hz, 1 H), 8.56 (d, J = 1.6 Hz, 1 H), 8.85 (dd, J = 1.6, 4.0 Hz, 1 H), 10.56 (s, 1 H). MS (ESI, pos. ion) *m/z*: 331 (M + 1). Anal. ($C_{22}H_{22}N_2O$): C, H, N.

(*E*)-3-(4-*tert*-Butylphenyl)-*N*-(2,3-dihydrobenzo[*b*][1,4]-dioxin-6-yl)-2-methylacrylamide (47a). Triethyl 2-phosphonopropionate (2.4 g, 10 mmol) was added dropwise to a suspension of NaH (0.44 g, 11 mmol, 60% dispersion in mineral oil) in anhydrous THF (18 mL) magnetically stirred at 0 °C. The reaction mixture was allowed to warm to 25 °C and then stirred at that temperature for 0.5 h. 4-*tert*-Butylbenzaldehyde (1.6 g, 10 mmol) was added, and the reaction mixture was stirred at 25 °C for 4 h and then heated at reflux for 1 h. The reaction mixture was allowed to cool to 25 °C and then quenched with water and extracted with Et_2O. The combined organic extract was washed with water, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude cinnamate was dissolved in 1,4-dioxane (2.5 mL), treated with water (7 mL) and KOH (1.1 g, 20 mmol), stirred, and heated at reflux for 18 h. The reaction mixture was allowed to cool to 25 °C, diluted with water, and washed with Et_2O. The aqueous phase was acidified with 1 N HCl and extracted with $CHCl_3$. The combined $CHCl_3$ extracts were washed with satd NaCl, dried over $MgSO_4$, filtered, and concentrated in vacuo to provide the acid (1.9 g, 87% over two steps) as a yellow solid. MS (ESI, pos. ion) *m/z*: 219 (M + 1).

Analogous to the first step in the preparation of compound **36**, the acid from the previous step and 1,4-benzodioxan-6-amine provided the title compound (65%) as an off-white solid. Mp: 157.5−157.6 °C. ^{1}H NMR ($CDCl_3$): δ 1.34 (s, 9 H), 2.21 (s, 3 H), 4.25 (s, 4 H), 6.82 (d, J = 8.7 Hz, 1 H), 6.98 (dd, J = 2.4, 8.7 Hz, 1 H), 7.24 (d, J = 8.3 Hz, 2 H), 7.30−7.50 (m, 5 H). MS (ESI, pos. ion) *m/z*: 352 (M + 1). Anal. ($C_{22}H_{25}NO_3$): C, H, N.

(*E*)-2-(4-*tert*-Butylbenzylidene)-*N*-(2,3-dihydrobenzo[*b*]-[1,4]dioxin-6-yl)butanamide (47b). Analogous to the procedure described for compound **47a**, triethyl 2-phosphonobutyrate, 4-*tert*-butylbenzaldehyde, and 1,4-benzodioxan-6-amine provided the title compound (34% over three steps) as a white solid. Mp: 133.6−134.2 °C. ^{1}H NMR ($CDCl_3$): δ 1.20 (t, J = 7.5 Hz, 3 H), 1.34 (s, 9 H), 2.65 (q, J = 7.5 Hz, 2 H), 4.25 (s, 4 H), 6.83 (d, J = 8.7 Hz, 1 H), 6.98 (dd, J = 2.4, 8.7 Hz, 1 H), 7.17 (s, 1 H), 7.20−7.45 (m, 6 H). MS (ESI, pos. ion) *m/z*: 366 (M + 1). Anal. ($C_{23}H_{27}NO_3$): C, H, N.

(*E*)-3-(4-*tert*-Butylphenyl)-*N*-(2,3-dihydrobenzo[*b*][1,4]-dioxin-6-yl)-2-phenylacrylamide (47c). A mixture of phenylacetic acid (2.7 g, 20 mmol), 4-*tert*-butylbenzaldehyde (2.2 g, 20 mmol), and triethylamine (2.8 mL, 20 mmol) in acetic anhydride (9.4 mL, 100 mmol) was heated at 100 °C with stirring under N_2 for 48 h. The reaction mixture was allowed to cool to 25 °C and then dissolved in hot benzene (100 mL). The benzene solution was allowed to cool to 25 °C and extracted with 10% aq NaOH (6×). The combined basic extracts were acidified with 5 N HCl and extracted with $CHCl_3$. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo to a solid residue. Recrystallization of the residue from EtOAc and hexane provided the acid as colorless needles. ^{1}H NMR ($CDCl_3$): δ 1.31 (s, 9 H), 6.93 (d, J = 8.4 Hz, 2 H), 7.12 (d, J = 8.4 Hz, 2 H), 7.15−7.37 (m, 5 H), 7.85 (s, 1 H). MS (ESI, pos. ion) *m/z*: 281 (M + 1).

Analogous to the first step in the preparation of compound **36**, the acid from the previous step and 1,4-benzodioxan-6-amine provided the title compound (45%) as a yellow solid. Mp: 134−137 °C. ^{1}H NMR ($CDCl_3$): δ 1.17 (s, 9 H), 4.15 (s, 4 H), 6.68 (d, J = 8.7 Hz, 1 H), 6.71 (dd, J = 2.4, 8.7 Hz, 1 H), 6.88 (d, J = 8.5 Hz, 2 H), 6.94 (br s, 1 H), 7.05 (d, J = 2.4 Hz, 1 H), 7.10 (d, J = 8.5 Hz, 2 H), 7.25−7.32 (m, 2 H), 7.38−7.50 (m, 3 H), 7.86 (s, 1 H). MS (ESI, pos. ion) *m/z*: 414 (M + 1). Anal. ($C_{27}H_{27}NO_3$): C, H, N.

(*E*)-3-(4-*tert*-Butylphenyl)-*N*-(2,3-dihydrobenzo[*b*][1,4]-dioxin-6-yl)but-2-enamide (47d). Triethyl phosphonoacetate (2.0 mL, 10 mmol) was added dropwise to a suspension of NaH (0.44 g, 11 mmol, 60% dispersion in mineral oil) in anhydrous THF (16 mL), stirred at 0 °C under N_2, in a round-bottomed flask equipped with a reflux condenser. The reaction mixture was allowed to warm to 25 °C and then stirred for 0.5 h. To the mixture was added 4′-*tert*-butylacetophenone (1.8 g, 10 mmol) in one portion and the reaction mixture was stirred at reflux for 48 h. After allowing the reaction mixture to cool to 25 °C, the reaction was quenched with water and extracted with Et_2O (4×). The combined organic extract was washed with water, dried over $MgSO_4$, filtered, and concentrated in vacuo to an oily residue. The residue was dissolved in 1,4-dioxane (2.5 mL), treated with water (7 mL) and KOH (1.1 g, 20 mmol), and then stirred at reflux for 18 h. The reaction mixture was allowed to cool to 25 °C, diluted with water, and washed with Et_2O. The aqueous phase was acidified with 1 N HCl and extracted with $CHCl_3$. The combined $CHCl_3$ extracts were washed with satd NaCl, dried over $MgSO_4$, filtered, and concentrated in vacuo to provide the acid (1.9 g, 87% over two steps) as a mixture of isomers. MS (ESI, pos. ion) *m/z*: 219 (M + 1).

Analogous to the first step in the preparation of compound **36**, the isomeric mixture of acids from the previous step and 1,4-benzodioxan-6-amine provided the title product as a mixture of isomers. The mixture was purified by silica gel chromatography (20% EtOAc in hexane) and then recrystallized from EtOAc to provide the title compound, a single isomer, as white crystals. Mp: 186.0−186.6 °C. ^{1}H NMR ($CDCl_3$): δ 1.33 (s, 9 H), 2.61 (s, 3 H), 4.25 (s, 4 H), 6.11 (s, 1 H), 6.81 (d, J = 8.6 Hz, 1 H), 6.96 (d, J = 8.3 Hz, 1 H), 7.09 (br s, 1 H), 7.21 (br s, 1 H), 7.35−7.45 (m, 4 H). MS (ESI, pos. ion) *m/z*: 352 (M + 1). Anal. Calcd for $C_{22}H_{25}NO_3$: C, 75.19; H, 7.17; N, 3.99. Found: C, 75.76; H, 7.44; N, 3.87.

3,3-Bis(4-*tert*-butylphenyl)-*N*-(2,3-dihydrobenzo[*b*][1,4]-dioxin-6-yl)acrylamide (47e). Following the procedure described for compound **47d**, triethyl phosphonoacetate, 4,4′-di-*tert*-butylbenzophenone, and 1,4-benzodioxan-6-amine provided the title compound (24% over three steps) as an off-white solid. Mp: 116−119 °C. ^{1}H NMR ($CDCl_3$): δ 1.32 (s, 9 H), 1.38 (s, 9 H), 4.18 (s, 4 H), 6.31 (dd, J = 2.4, 8.6 Hz, 1 H), 6.48 (s, 1 H), 6.63 (d, J = 8.7 Hz, 1 H), 6.64 (br s, 1 H), 6.72 (d, J = 2.3 Hz, 1 H), 7.27 (d, J = 10 Hz, 4 H), 7.36 (d, J = 8.4 Hz, 2 H), 7.50 (d, J = 8.1 Hz, 2 H). MS (ESI, pos. ion) *m/z*: 470 (M + 1). Anal. ($C_{31}H_{35}NO_3$): C, H, N.

***N*-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)cinnamamide (48a).** Following the procedure described for compound **46a**, *trans*-cinnamic acid and 1,4-benzodioxan-6-amine provided the title compound (64%) as tan crystals. Mp: 182−183 °C. ^{1}H NMR (DMSO-d_6): δ 4.22 (d, J = 9.3 Hz, 2 H), 4.23 (d, J = 9.5 Hz, 2 H), 6.78 (d, J = 15.8 Hz, 1 H), 6.82 (d, J = 8.7 Hz, 1 H), 7.06 (dd, J = 2.3, 8.7 Hz, 1 H), 7.38 (d, J = 2.2 Hz, 1 H), 7.41−7.47 (m, 3 H), 7.56 (d, J = 15.7 Hz, 1 H), 7.62 (m, 2 H), 10.06 (s, 1 H). MS (ESI, pos. ion) *m/z*: 282 (M + 1). Anal. ($C_{17}H_{15}NO_3$): C, H, N.

(*E*)-*N*-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-3-*p*-tolylacrylamide (48b). Following the procedure described for

compound **46a**, 4-methyl-*trans*-cinnamic acid and 1,4-benzodioxan-6-amine provided the title compound (54%) as pale-yellow crystals. Mp: 173−175 °C. ^{1}H NMR (DMSO-d_6): δ 2.32 (s, 3 H), 4.20 (d, J = 9.6 Hz, 2 H), 4.21 (d, J = 9.2 Hz, 2 H), 6.70 (d, J = 15.6 Hz, 1 H), 6.79 (d, J = 8.8 Hz, 1 H), 7.03 (dd, J = 2.4, 8.8 Hz, 1 H), 7.24 (d, J = 7.6 Hz, 2 H), 7.35 (d, J = 2.4 Hz, 1 H), 7.49 (d, J = 8.4 Hz, 2 H), 7.50 (d, J = 15.6 Hz, 1 H), 10.00 (s, 1 H). MS (ESI, pos. ion) *m/z*: 296 (M + 1). Anal. ($C_{18}H_{17}NO_3$): C, H, N.

(*E*)-*N*-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-3-(4-ethylphenyl)acrylamide (48c). Analogous to the procedure described for compound **47a**, triethyl phosphonoacetate, 4-ethylbenzaldehyde, and 1,4-benzodioxan-6-amine provided the title compound as pale-yellow crystals. Mp: 119−120 °C. ^{1}H NMR (DMSO-d_6): δ 1.02 (t, J = 7.6 Hz, 3 H), 2.62 (q, J = 7.6 Hz, 2 H), 4.20 (d, J = 9.2 Hz, 2 H), 4.21 (d, J = 9.2 Hz, 2 H), 6.71 (d, J = 15.6 Hz, 1 H), 6.79 (d, J = 8.8 Hz, 1 H), 7.04 (dd, J = 2.4, 8.8 Hz, 1 H), 7.27 (d, J = 8.0 Hz, 2 H), 7.36 (d, J = 2.0 Hz, 1 H), 7.50 (d, J = 15.2 Hz, 1 H), 7.51 (d, J = 8.4 Hz, 2 H), 10.00 (s, 1 H). MS (ESI, pos. ion) *m/z*: 310 (M + 1). Anal. ($C_{19}H_{19}NO_3$): C, H, N.

(*E*)-*N*-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-3-(4-isopropylphenyl)acrylamide (48d). Following the procedure described for compound **46a**, 4-isopropyl-*trans*-cinnamic acid and 1,4-benzodioxan-6-amine provided the title compound (43%) as white crystals. Mp: 165−166 °C. ^{1}H NMR (DMSO-d_6): δ 1.33 (d, J = 7.2 Hz, 6 H), 2.90 (sept, J = 6.8 Hz, 1 H), 4.20 (d, J = 9.2 Hz, 2 H), 4.21 (d, J = 9.6 Hz, 2 H), 6.71 (d, J = 15.6 Hz, 1 H), 6.79 (d, J = 8.8 Hz, 1 H), 7.04 (dd, J = 2.4, 8.4 Hz, 1 H), 7.30 (d, J = 8.0 Hz, 2 H), 7.36 (d, J = 2.4 Hz, 1 H), 7.50 (d, J = 16.0 Hz, 1 H), 7.52 (d, J = 8.0 Hz, 2 H), 10.01 (s, 1 H). MS (ESI, pos. ion) *m/z*: 324 (M + 1). Anal. ($C_{20}H_{21}NO_3$): C, H, N.

(*E*)-3-(4-Butylphenyl)-*N*-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)acrylamide (48f). Analogous to the procedure described for compound **47a**, triethyl phosphonoacetate, 4-*n*-butylbenzaldehyde, and 1,4-benzodioxan-6-amine provided the title compound as pale-yellow crystals. Mp: 120−121 °C. ^{1}H NMR (DMSO-d_6): δ 0.91 (t, J = 7.2 Hz, 3H), 1.27−1.36 (m, 2 H), 1.53−1.60 (m, 2 H), 2.61 (t, J = 7.6 Hz, 2 H), 4.20−4.23 (m, 4 H), 6.72 (d, J = 15.6 Hz, 1 H), 6.81 (d, J = 8.4 Hz, 1 H), 7.05 (dd, J = 2.4, 8.8 Hz, 1 H), 7.27 (d, J = 8.0 Hz, 2 H), 7.37 (d, J = 2.0 Hz, 1 H), 7.50−7.53 (m, 3 H), 10.02 (s, 1 H). MS (ESI, pos. ion) *m/z*: 338 (M + 1). Anal. ($C_{21}H_{23}NO_3$): C, H, N.

(*E*)-*N*-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-3-(4-biphenyl)acrylamide (48g). Following the procedure described for compound **46a**, 4-phenyl-*trans*-cinnamic acid and 1,4-benzodioxan-6-amine provided the title compound (13%) as pale-yellow needles. Mp: 204−205 °C. ^{1}H NMR (DMSO-d_6): δ 4.23 (d, J = 9.5 Hz, 2 H), 4.24 (d, J = 9.6 Hz, 2 H), 6.82 (d, J = 11.6 Hz, 1 H), 6.83 (d, J = 12.8 Hz, 1 H), 7.07 (dd, J = 2.3, 8.7 Hz, 1 H), 7.40 (m, 2 H), 7.5 (m, 2 H), 7.61 (d, J = 15.7 Hz, 1 H), 7.70−7.78 (m, 6 H), 10.08 (s, 1 H). MS (ESI, pos. ion) *m/z*: 358 (M + 1). Anal. Calcd for $C_{23}H_{19}NO_3$: C, 77.29; H, 5.36; N, 3.92. Found: C, 76.11; H, 5.40; N, 3.81.

(*E*)-3-(3-*tert*-Butylphenyl)-*N*-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)acrylamide (48h). Analogous to the procedure of Torii et al.,[45] to a round-bottomed flask was added 1-*tert*-butyl-3-methylbenzene (1.0 g, 6.8 mmol), ammonium cerium(IV) nitrate (18 g, 30 mmol), and 50% aq AcOH (150 mL). The reaction mixture was stirred at 90 °C for 1.5 h, allowed to cool to 25 °C, and extracted with 10% EtOAc in hexane. The organic extract was concentrated in vacuo to provide 3-*tert*-butylbenzaldehyde in a crude quantitative yield. ^{1}H NMR (DMSO-d_6): δ 1.32 (s, 9 H), 7.53 (t, J = 8 Hz, 1 H), 7.72 (d, J = 7.2 Hz, 1 H), 7.76 (d, J = 7.6 Hz, 1 H), 7.92 (s, 1 H), 10.01 (s, 1 H).

Analogous to the procedure described for compound **47a**, triethyl phosphonoacetate, 3-*tert*-butylbenzaldehyde, and 1,4-benzodioxan-6-amine provided the title compound as white crystals. Mp: 168−170 °C. ^{1}H NMR (DMSO-d_6): δ 1.30 (s, 9 H), 4.20 (d, J = 9.2 Hz, 2 H), 4.21 (d, J = 9.6 Hz, 2 H), 6.77 (d, J = 15.2 Hz, 1 H), 6.80 (d, J = 8.4 Hz, 1 H), 7.05 (dd, J = 2.4, 8.8 Hz, 1 H), 7.36−7.42 (m, 4 H), 7.55 (d, J = 15.6 Hz, 1 H), 7.63 (s, 1 H), 10.02 (s, 1 H). MS (ESI, pos. ion) *m/z*: 338 (M + 1). Anal. ($C_{21}H_{23}NO_3$): C, H, N.

(*E*)-3-(4-Bromophenyl)-*N*-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)acrylamide (48i). Following the procedure described for compound **46a**, 4-bromo-*trans*-cinnamic acid and 1,4-benzodioxan-6-amine provided the title compound (43%) as pale-yellow needles. Mp: 180−182 °C. ^{1}H NMR (DMSO-d_6): δ 4.21 (d, J = 9.0 Hz, 2 H), 4.22 (d, J = 9.3 Hz, 2 H), 6.78 (d, J = 14.2 Hz, 1 H), 6.81 (d, J = 8.6 Hz, 1 H), 7.04 (dd, J = 2.3, 8.7 Hz, 1 H), 7.36 (d, J = 2.2 Hz, 1 H), 7.52 (d, J = 15.8 Hz, 1 H), 7.56 (d, J = 8.5 Hz, 2 H), 7.64 (d, J = 8.4 Hz, 2 H), 10.07 (s, 1 H). MS (ESI, pos. ion) *m/z*: 360, 362 (M + 1, M + 3). Anal. ($C_{17}H_{14}BrNO_3$): C, H, N, Br.

(*E*)-3-(4-Chlorophenyl)-*N*-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)acrylamide (48j). Following the procedure described for compound **46a**, 4-chloro-*trans*-cinnamic acid and 1,4-benzodioxan-6-amine provided the title compound (37%) as pale-tan crystals. Mp: 187−188 °C. ^{1}H NMR (DMSO-d_6): δ 4.22 (d, J = 9.1 Hz, 2 H), 4.23 (d, J = 9.2 Hz, 2 H), 6.78 (d, J = 15.7 Hz, 1 H), 6.82 (d, J = 8.7 Hz, 1 H), 7.05 (dd, J = 2.3, 8.7 Hz, 1 H), 7.37 (d, J = 2.2 Hz, 1 H), 7.51 (d, J = 8.5 Hz, 2 H), 7.55 (d, J = 15.9 Hz, 1 H), 7.64 (d, J = 8.5 Hz, 2 H), 10.08 (s, 1 H). MS (ESI, pos. ion) *m/z*: 316 (M + 1). Anal. ($C_{17}H_{14}ClNO_3$): C, H, N, Cl.

(*E*)-*N*-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-3-(4-fluorophenyl)acrylamide (48k). Following the procedure described for compound **46a**, 4-fluoro-*trans*-cinnamic acid and 1,4-benzodioxan-6-amine provided the title compound (50%) as pale-tan crystals. Mp: 195−196 °C. ^{1}H NMR (DMSO-d_6): δ 4.22 (d, J = 9.3 Hz, 2 H), 4.23 (d, J = 9.3 Hz, 2 H), 6.72 (d, J = 15.7 Hz, 1 H), 6.81 (d, J = 8.7 Hz, 1 H), 7.05 (dd, J = 2.3, 8.7 Hz, 1 H), 7.29 (t, J = 8.8 Hz, 2 H), 7.37 (d, J = 2.2 Hz, 1 H), 7.56 (d, J = 15.7 Hz, 1 H), 7.68 (dd, J = 5.7, 8.5 Hz, 2 H), 10.05 (s, 1 H). MS (ESI, pos. ion) *m/z*: 300 (M + 1). Anal. ($C_{17}H_{14}FNO_3$): C, H, N, F.

(*E*)-*N*-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-3-(4-nitrophenyl)acrylamide (48l). Following the procedure described for compound **46a**, 4-nitro-*trans*-cinnamic acid and 1,4-benzodioxan-6-amine provided the title compound (30%) as bright-yellow crystals. Mp: 247−248 °C. ^{1}H NMR (DMSO-d_6): δ 4.23 (d, J = 8.7 Hz, 2 H), 4.24 (d, J = 9.0 Hz, 2 H), 6.83 (d, J = 8.7 Hz, 1 H), 6.96 (d, J = 15.8 Hz, 1 H), 7.07 (dd, J = 2.3, 8.7 Hz, 1 H), 7.39 (d, J = 2.3 Hz, 1 H), 7.67 (d, J = 15.7 Hz, 1 H), 7.88 (d, J = 8.7 Hz, 2 H), 8.30 (d, J = 8.7 Hz, 2 H), 10.22 (s, 1 H). MS (ESI, pos. ion) *m/z*: 327 (M + 1). Anal. ($C_{17}H_{14}N_2O_5$): C, H, N.

(*E*)-*N*-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-3-(4-(trifluoromethyl)phenyl)acrylamide (48m). Following the procedure described for compound **46a**, 4-trifluoromethyl-*trans*-cinnamic acid and 1,4-benzodioxan-6-amine provided the title compound (33%) as yellow needles. Mp: 200−201 °C. ^{1}H NMR (DMSO-d_6): δ 4.22 (d, J = 9.0 Hz, 2 H), 4.23 (d, J = 9.1 Hz, 2 H), 6.82 (d, J = 8.7 Hz, 1 H), 6.90 (d, J = 15.8 Hz, 1 H), 7.06 (dd, J = 2.3, 8.7 Hz, 1 H), 7.38 (d, J = 2.3 Hz, 1 H), 7.62 (d, J = 15.7 Hz, 1 H), 7.80 (d, J = 11.9 Hz, 2 H), 7.83 (d, J = 11.6 Hz, 2 H), 10.16 (s, 1 H). MS (ESI, pos. ion) *m/z*: 350 (M + 1). Anal. ($C_{18}H_{14}F_3NO_3$): C, H, N, F.

(*E*)-*N*-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-3-(4-methoxyphenyl)acrylamide (48n). Following the procedure described for compound **46a**, 4-methoxy-*trans*-cinnamic acid and 1,4-benzodioxan-6-amine provided the title compound (38%) as white crystals. Mp: 179−180 °C. ^{1}H NMR (DMSO-d_6): δ 3.80 (s, 3 H), 4.22 (d, J = 9.4 Hz, 2 H), 4.23 (d, J = 9.7 Hz, 2 H), 6.63 (d, J = 15.7 Hz, 1 H), 6.81 (d, J = 8.7 Hz, 1 H), 7.01 (d, J = 8.7 Hz, 2 H), 7.05 (dd, J = 2.2, 8.7 Hz, 1 H), 7.37 (d, J = 2.1 Hz, 1 H), 7.50 (d, J = 15.7 Hz, 1 H), 7.56 (d, J = 8.7 Hz, 2 H), 9.96 (s, 1 H). MS (ESI, pos. ion) *m/z*: 312 (M + 1). Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 68.60; H, 5.46; N, 4.41.

(*E*)-*N*-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-3-(4-hydroxyphenyl)acrylamide (48o). Following the procedure described for compound **46a**, 4-hydroxy-*trans*-cinnamic acid and 1,4-benzodioxan-6-amine provided the title compound (53%) as pale-tan crystals. Mp: 205−207 °C. ^{1}H NMR (DMSO-d_6): δ

4.20 (d, J = 9.6 Hz, 2 H), 4.21 (d, J = 9.6 Hz, 2 H), 6.54 (d, J = 15.7 Hz, 1 H), 6.78 (d, J = 8.4 Hz, 1 H), 6.80 (d, J = 8.1 Hz, 2 H), 7.03 (dd, J = 2.4, 8.8 Hz, 1 H), 7.35 (d, J = 2.3 Hz, 1 H), 7.43 (d, J = 8.8 Hz, 2 H), 7.44 (d, J = 15.2 Hz, 1 H), 9.90 (s, 1 H), 9.91 (s, 1 H). MS (ESI, pos. ion) *m/z*: 298 (M + 1). Anal. Calcd for $C_{17}H_{15}NO_4$: C, 68.68; H, 5.09; N, 4.71. Found: C, 68.22; H, 5.10; N, 4.60.

(*E*)-3-(2-Bromo-4-*tert*-butylphenyl)-*N*-(2,3-dihydrobenzo-[*b*][1,4]dioxin-6-yl)acrylamide (48p). To a solution of sodium bromate (22 g, 145 mmol) in water (75 mL), magnetically stirred in an Erlenmeyer flask at 25 °C, was added a solution of 4-*tert*-butyltoluene (5.0 mL, 29 mmol) in acetonitrile (60 mL). The biphasic mixture was vigorously stirred while a solution of sodium bisulfite (15 g, 145 mmol) in water (150 mL) was added dropwise, via addition funnel, over 20 min. The reaction mixture was stirred for 6 h and then extracted with Et_2O. The organic phase was washed with satd aq $Na_2S_2O_3$ (2×) and satd NaCl, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford compound **17** (9.0 g, 100%) as a pale orange oil. ^{1}H NMR ($CDCl_3$): δ 1.30 (s, 9 H), 7.31 (dd, J = 1.9, 8.0 Hz, 1 H), 7.38 (d, J = 8.1 Hz, 1 H), 7.57 (d, J = 1.9 Hz,1 H).

According to the method of Mallory,[29] a solution of sodium ethoxide (12 mL, 32 mmol, 21% in EtOH) in absolute EtOH (100 mL) was magnetically stirred under N_2 at 25 °C and treated with 2-nitropropane (2.9 mL, 32 mmol) followed by compound **17** (9.0 g, 29 mmol). The reaction mixture was stirred at 25 °C for 5 h and then concentrated in vacuo to an orange solid. The solid was partitioned between Et_2O and water. The layers were separated, and the organic phase was washed with water, 1 N NaOH (2×), and satd NaCl, dried over $MgSO_4$, filtered, and concentrated in vacuo to provide compound **18** (6.6 g, 94%) as an orange oil. ^{1}H NMR ($CDCl_3$): δ 1.32 (s, 9 H), 7.45 (ddd, J = 0.6, 1.7, 8.2 Hz, 1 H), 7.63 (d, J = 1.7 Hz, 1 H), 7.85 (d, J = 8.2 Hz, 1 H), 10.31 (s, 1 H).

To a suspension of NaH (1.2 g, 30 mmol, 60% dispersion in mineral oil) in anhydrous THF (50 mL), stirred at room temperature under N_2, was added neat triethyl phosphonoacetate (5.9 mL, 30 mmol) dropwise. The reaction mixture was stirred at room temperature for 0.5 h, and then a solution of compound **18** (6.5 g, 27 mmol) in anhydrous THF (50 mL) was added via cannula. The reaction mixture was stirred at reflux for 3 h and allowed to cool to room temperature. The mixture was diluted with water and extracted with EtOAc (3×). The organic extracts were combined and washed with water and satd NaCl, dried over $MgSO_4$, and concentrated in vacuo. Purification by silica gel chromatography (5% EtOAc/hexane) provided the cinnamate ester which was dissolved in MeOH (200 mL) and treated with 1 N NaOH (150 mL). The biphasic mixture was stirred at reflux for 3 h, concentrated in vacuo to ~200 mL, and diluted with water (100 mL). The solution was washed with EtOAc (2×) and acidified to pH 3 with concd HCl at 0 °C. The mixture was extracted with EtOAc (3×), and the organic extracts were combined, washed with water and satd NaCl, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford the acid (4.3 g, 56%) as a white solid. ^{1}H NMR ($CDCl_3$): δ 1.32 (s, 9 H), 6.39 (d, J = 15.9 Hz, 1 H), 7.36 (dd, J = 1.8, 8.3 Hz, 1 H), 7.59 (d, J = 8.3 Hz, 1 H), 7.62 (d, J = 1.9 Hz, 1 H), 8.16 (d, J = 15.9 Hz, 1 H). MS (ESI, pos. ion) *m/z*: 283, 285 (M + 1, M + 3).

The acid from the previous step (3.0 g, 11 mmol) was dissolved in anhydrous CH_2Cl_2 (100 mL) and treated with oxalyl chloride (5.8 mL, 12 mmol, 2.0 M in CH_2Cl_2) and anhydrous DMF (5 μL). The reaction mixture was stirred at reflux for 1.5 h and then concentrated in vacuo. The residue was dissolved in anhydrous CH_2Cl_2 (100 mL) and pyridine (5 mL), treated with 1,4-benzodioxan-6-amine (1.9 g, 13 mmol), and stirred for 4 h at 25 °C. The reaction mixture was concentrated in vacuo and the residue dissolved in EtOAc. The mixture was washed with 1 N HCl (2×), 1 N NaOH (2×), and satd NaCl, dried over $MgSO_4$, filtered, and concentrated in vacuo. Recrystallization of the crude product from CH_2Cl_2 and hexane provided the title compound (3.2 g, 73%) as off-white crystals. Mp: 206−210 °C. ^{1}H NMR (DMSO-d_6): δ 1.29 (s, 9 H), 4.22 (d, J = 9.3 Hz, 2 H), 4.23 (d, J = 9.3 Hz, 2 H), 6.75 (d, J = 15.6 Hz, 1 H), 6.82 (d, J = 8.7 Hz, 1 H), 7.05 (dd, J = 2.4, 8.7 Hz, 1 H), 7.37 (d, J = 2.4 Hz, 1 H), 7.51 (dd, J = 1.6, 8.3 Hz, 1 H), 7.66 (s, 1 H), 7.67 (d, J = 6.6 Hz, 1 H), 7.77 (d, J = 15.5 Hz, 1 H), 10.14 (s, 1 H). MS (ESI, pos. ion) *m/z*: 416, 418 (M + 1, M + 3). Anal. ($C_{21}H_{22}BrNO_3$): C, H, N, Br.

(*E*)-Ethyl 5-*tert*-Butyl-2-(3-(2,3-dihydrobenzo[*b*][1,4]-dioxin-6-ylamino)-3-oxoprop-1-enyl)benzoate (48q). Following conditions described by Ma et al.,[46] a solution of compound **48p** (200 mg, 0.48 mmol) in anhydrous EtOH (5 mL) and methyl sulfoxide (5 mL) was treated with triethylamine (0.067 mL, 0.48 mmol) and 1,3-bis(diphenylphosphino)-propane (50 mg, 0.12 mmol) under Ar. The mixture was purged with carbon monoxide, treated with palladium acetate (22 mg, 0.10 mmol), and stirred under a balloon of carbon monoxide in a 70 °C oil bath for 3 h. The reaction mixture was allowed to cool to 25 °C and partitioned between EtOAc and water. The organic phase was washed with water and satd NaCl, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by silica gel chromatography (step gradient: 4:1 hexane:EtOAc, followed by 3:1 hexane:EtOAc) provided a solid which was recrystallized from EtOAc and hexane to provide the title compound (140 mg, 71%) as white crystals. Mp: 155−157 °C. ^{1}H NMR (DMSO-d_6): δ 1.31 (s, 9 H), 1.34 (t, J = 7.1 Hz, 3 H), 4.21 (d, J = 9.3 Hz, 2 H), 4.23 (d, J = 9.4 Hz, 2 H), 4.34 (q, J = 7.1 Hz, 2 H), 6.65 (d, J = 15.6 Hz, 1 H), 6.81 (d, J = 8.7 Hz, 1 H), 7.05 (dd, J = 2.4, 8.7 Hz, 1 H), 7.37 (d, J = 2.4 Hz, 1 H), 7.67 (d, J = 8.3 Hz, 1 H), 7.71 (dd, J = 1.9, 8.4 Hz, 1 H), 7.82 (d, J = 1.9 Hz, 1 H), 8.09 (d, J = 15.6 Hz, 1 H), 10.07 (s, 1 H). MS (ESI, pos. ion) *m/z*: 410 (M + 1). Anal. Calcd for $C_{24}H_{27}NO_5$: C, 70.40; H, 6.65; N, 3.42. Found: C, 69.85; H, 6.56; N, 3.34.

(*E*)-5-*tert*-Butyl-2-(3-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-ylamino)-3-oxoprop-1-enyl)benzoic Acid (48r). Compound **48q** (100 mg, 0.24 mmol) was dissolved in MeOH (10 mL), treated with 1 N NaOH (50 mL), and stirred at room temperature for 48 h. The reaction mixture was concentrated in vacuo to ~50 mL and washed with EtOAc (2×). The aqueous phase was acidified to pH 2 with 1 N HCl at 0 °C and extracted with EtOAc (2×). The organic extract was washed with satd NaCl, dried over $MgSO_4$, filtered, and concentrated in vacuo to a solid. Recrystallization of the crude product from EtOAc and hexane provided the title compound (60 mg, 64%) as bright yellow crystals. Mp: 179−181 °C. ^{1}H NMR (DMSO-d_6): δ 1.31 (s, 9 H), 4.21 (d, J = 9.4 Hz, 2 H), 4.23 (d, J = 9.5 Hz, 2 H), 6.65 (d, J = 15.6 Hz, 1 H), 6.81 (d, J = 8.7 Hz, 1 H), 7.05 (dd, J = 2.3, 8.8 Hz, 1 H), 7.37 (d, J = 2.2 Hz, 1 H), 7.66 (m, 2 H), 7.85 (s, 1 H), 8.20 (d, J = 15.6 Hz, 1 H), 10.06 (s, 1 H), 13.23 (br s, 1 H). MS (ESI, pos. ion) *m/z*: 382 (M + 1). Anal. ($C_{22}H_{23}NO_5$): C, H, N.

(*E*)-3-(5-*tert*-Butylpyridin-2-yl)-*N*-(2,3-dihydrobenzo[*b*]-[1,4]dioxin-6-yl)acrylamide (48s). A solution of 5-*tert*-butylpyridine-2-carboxylic acid methyl ester[47] (0.37 g, 2.0 mmol) in anhydrous THF (20 mL) was treated dropwise with lithium aluminum hydride (3 mL, 3 mmol, 1.0 M in THF) with stirring under N_2 at 25 °C. The reaction mixture was stirred at 25 °C for 1 h and then quenched by the dropwise addition of water (1 mL), followed by 20% aq KOH (3 mL) and EtOAc (20 mL). The biphasic mixture was stirred vigorously for 1 h at 25 °C and then diluted with water (30 mL), and the phases separated. The aqueous phase was extracted with EtOAc (2×). The organic phases were combined and washed with 1 N NaOH (2×) and satd NaCl, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford the alcohol. MS (ESI, pos. ion) *m/z*: 166 (M + 1).

A solution of oxalyl chloride (1.5 mL, 3.0 mmol, 2.0 M in CH_2Cl_2) in anhydrous CH_2Cl_2 (20 mL) was magnetically stirred under N_2, in an oven-dried round-bottomed flask, at −60 °C. The solution was treated dropwise with methyl sulfoxide (0.3 mL, 5 mmol) and then stirred for 10 min. A solution of the alcohol from the previous step in anhydrous CH_2Cl_2 (2 mL) was added dropwise to the reaction mixture and stirred at −60 °C for 15 min. Triethylamine (1.0 mL, 7.0 mmol) was added, the cooling bath was removed, and the reaction mixture was allowed to warm to 25 °C and stirred at that temperature for 1 h. The mixture was washed with water and the aqueous

wash was extracted with Et_2O (2×). The combined organic phases were washed with water and satd NaCl, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by silica gel chromatography (9:1 hexane:EtOAc) provided the aldehyde (0.25 g, 77% over two steps) as a yellow oil. MS (ESI, pos. ion) *m/z*: 164 (M + 1).

Analogous to the procedure described for compound **47a**, triethyl phosphonoacetate, the aldehyde from the previous step, and 1,4-benzodioxan-6-amine provided the title compound as a pale-yellow amorphous solid. ^{1}H NMR (DMSO-d_6): δ 1.32 (s, 9 H), 4.20 (d, J = 9.2 Hz, 2 H), 4.21 (d, J = 9.6 Hz, 2 H), 6.80 (d, J = 8.8 Hz, 1 H), 7.06 (dd, J = 2.4, 8.8 Hz, 1 H), 7.20 (d, J = 15.2 Hz, 1 H), 7.37 (d, J = 2.4 Hz, 1 H), 7.51−7.55 (m, 2 H), 7.85 (dd, J = 2.8, 8.4 Hz, 1 H), 8.69 (d, J = 4.0 Hz, 1 H), 10.18 (s, 1 H). MS (ESI, pos. ion) *m/z*: 339 (M + 1). Anal. Calcd for $C_{20}H_{22}N_2O_3$: C, 70.99; H, 6.55; N, 8.28. Found: C, 70.35; H, 6.43; N, 8.15.

(*E*)-3-(6-*tert*-Butylpyridin-3-yl)-*N*-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)acrylamide (48t). Analogous to the method of Tada,[32] pyridine-3-methanol (2.2 g, 20 mmol), trimethylacetic acid (10 g, 100 mmol), silver nitrate (0.68 g, 4.0 mmol), and 10% aq H_2SO_4 (20 mL) were combined in a round-bottomed flask. The reaction mixture was magnetically stirred and treated with a solution of ammonium persulfate (9.1 g, 40 mmol) in water (40 mL). Evolution of gas was observed and the reaction mixture was stirred at 25 °C for 2 h. The pH of the reaction mixture was adjusted to pH 9 by the addition of aq NH_4OH and then the mixture was extracted with EtOAc. The organic extract was washed with water, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification of the crude product by silica gel chromatography (70:30 hexane: EtOAc) provided compound **20** (1.0 g, 31%). ^{1}H NMR ($CDCl_3$): δ 1.30 (s, 9 H), 7.45 (d, J = 8.3 Hz, 1 H), 8.03 (d, J = 8.3 Hz, 1 H), 8.94 (s, 1 H), 10.01 (s, 1 H). MS (ESI, pos. ion) *m/z*: 164 (M + 1).

Analogous to the procedure described for compound **47a**, triethyl phosphonoacetate, compound **20**, and 1,4-benzodioxan-6-amine provided the title compound as an amorphous off-white solid. ^{1}H NMR (DMSO-d_6): δ 1.32 (s, 9 H), 4.21 (d, J = 9.2 Hz, 2 H), 4.23 (d, J = 9.2 Hz, 2 H), 6.81 (d, J = 8.7 Hz, 1 H), 6.81 (d, J = 15.8 Hz, 1 H), 7.06 (dd, J = 2.4, 8.7 Hz, 1 H), 7.37 (d, J = 2.4 Hz, 1 H), 7.51 (d, J = 8.3 Hz, 1 H), 7.56 (d, J = 15.5 Hz, 1 H), 7.95 (dd, J = 2.3, 8.3 Hz, 1 H), 8.72 (d, J = 2.0 Hz, 1 H), 10.10 (s, 1 H). MS (ESI, pos. ion) *m/z*: 339 (M + 1). Anal. ($C_{20}H_{22}N_2O_3$): C, H, N.

(*E*)-*N*-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-3-(6-(trifluoromethyl)pyridin-3-yl)acrylamide (48u). Analogous to the procedure described for compound **47a**, triethyl phosphonoacetate, 6-(trifluoromethyl)pyridine-3-carboxaldehyde, and 1,4-benzodioxan-6-amine provided the title compound as a yellow amorphous solid. ^{1}H NMR (DMSO-d_6): δ 4.21 (d, J = 8.8 Hz, 2 H), 4.22 (d, J = 8.8 Hz, 2 H), 6.82 (d, J = 8.8 Hz, 1 H), 6.98 (d, J = 16 Hz, 1 H), 7.06 (dd, J = 2.4, 8.8 Hz, 1 H), 7.37 (d, J = 2.4 Hz, 1 H), 7.66 (d, J = 16 Hz, 1 H), 7.98 (d, J = 8.0 Hz, 1 H), 8.28 (d, J = 8.4 Hz, 1 H), 9.00 (s, 1 H), 10.22 (s, 1 H). (ESI, pos. ion) *m/z*: 351 (M + 1). Anal. Calcd for $C_{17}H_{13}F_3N_2O_3$: C: 58.29; H, 3.74; N, 8.00. Found: C, 56.69; H, 3.62; N, 7.82.

(*E*)-*N*-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-3-(2-methyl-6-(trifluoromethyl)pyridin-3-yl)acrylamide (48v). Analogous to the procedure described for compound **48s**, 2-methyl-6-(trifluoromethyl)pyridine-3-carboxylic acid, triethyl phosphonoacetate, and 1,4-benzodioxan-6-amine provided the title compound as yellow crystals. Mp: 186−187 °C. ^{1}H NMR (DMSO-d_6): δ 2.68 (s, 3 H), 4.23 (d, J = 8.8 Hz, 2 H), 4.24 (d, J = 9.2 Hz, 2 H), 6.84 (d, J = 8.8 Hz, 1 H), 6.84 (d, J = 15.2 Hz, 1 H), 7.07 (dd, J = 2.4, 8.4 Hz, 1 H), 7.39 (d, J = 2.4 Hz, 1 H), 7.74 (d, J = 15.6 Hz, 1 H), 7.83 (d, J = 8.0 Hz, 1 H), 8.18 (d, J = 8.0 Hz, 1 H), 10.22 (s, 1 H). MS (ESI, pos. ion) *m/z*: 365 (M + 1). Anal. ($C_{18}H_{15}F_3N_2O_3$): C, H, N.

Representative Procedure for the Synthesis of Compounds 48w, 48x, 49a, and 49b. (*E*)-*N*-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-3-(2-morpholino-6-(trifluoromethyl)pyridin-3-yl)acrylamide (48w). To a round-bottomed flask were added 2-chloro-6-trifluoromethylnicotinic acid (2.0 g, 8.9 mmol) and morpholine (5.0 g, 57 mmol). The reaction mixture was magnetically stirred at 25 °C for 48 h, diluted with 1 N HCl (100 mL), and extracted with EtOAc (100 mL). The aqueous phase was saturated with NaCl and extracted again with EtOAc (50 mL). The combined organic extracts were washed with 1 N HCl (50 mL) and satd NaCl (50 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to afford compound **22a** (2.1 g, 86%) as an off-white, waxy solid. ^{1}H NMR (DMSO-d_6): δ 3.40 (t, J = 4.5 Hz, 4 H), 3.66 (t, J = 4.5 Hz, 4 H), 7.18 (d, J = 7.6 Hz, 1 H), 8.00 (d, J = 7.6 Hz, 1 H). MS (ESI, pos. ion) *m/z*: 277 (M + 1).

A solution of compound **22a** (2.1 g, 7.6 mmol) in anhydrous THF (20 mL) was treated dropwise with lithium aluminum hydride (15 mL, 15 mmol, 1.0 M in THF) with stirring under N_2 at 25 °C. The reaction mixture was stirred at 25 °C for 1.5 h and then quenched by the dropwise addition of a 10% aq solution of potassium sodium tartrate. The biphasic mixture was diluted with EtOAc and stirred vigorously for 2 h at 25 °C. The mixture was diluted with water, the phases separated, and the aqueous phase was extracted with EtOAc (2×). The organic phases were combined and washed with 1 N NaOH (2×) and satd NaCl, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford the alcohol (1.7 g, 85%) as a viscous yellow oil. ^{1}H NMR (DMSO-d_6): δ 3.11 (dd, J = 4.4, 4.5 Hz, 4 H), 3.71 (dd, J = 4.4, 4.5 Hz, 4 H), 4.50 (d, J = 5.3 Hz, 2 H), 5.51 (d, J = 5.5 Hz, 1 H), 7.45 (d, J = 7.7 Hz, 1 H), 7.99 (d, J = 7.7 Hz, 1 H). MS (ESI, pos. ion) *m/z*: 263 (M + 1).

A solution of oxalyl chloride (3.6 mL, 7.2 mmol, 2.0 M in CH_2Cl_2) in anhydrous CH_2Cl_2 (20 mL) was magnetically stirred at −60 °C, under N_2, in an oven-dried round-bottomed flask. The solution was treated dropwise with methyl sulfoxide (1.1 mL, 15 mmol) and then stirred for 10 min. A solution of the alcohol from the previous step (1.7 g, 6.5 mmol) in anhydrous CH_2Cl_2 (20 mL) was added via cannula, and the reaction mixture stirred at −60 °C for 15 min. Triethylamine (4.5 mL, 32 mmol) was added, the cooling bath was removed, and the reaction mixture was allowed to warm to 25 °C and stirred at that temperature for 1 h. The mixture was washed with water and the aqueous wash was back-extracted with CH_2Cl_2 (2×). The combined organic extracts were washed with water and satd NaCl, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by silica gel chromatography (9:1 hexane: EtOAc) provided compound **23a** (1.2 g, 71%) as a viscous yellow oil. ^{1}H NMR (DMSO-d_6): δ 3.46 (t, J = 4.7 Hz, 4 H), 3.73 (t, J = 4.7 Hz, 4 H), 7.41 (d, J = 7.7 Hz, 1 H), 8.31 (d, J = 7.7 Hz, 1 H), 9.99 (s, 1 H). MS (ESI, pos. ion) *m/z*: 261 (M + 1).

Analogous to the procedure described for compound **47a**, triethyl phosphonoacetate, compound **23a**, and 1,4-benzodioxan-6 amine afforded the title product as pale tan crystals. Mp: 200−201 °C. ^{1}H NMR (DMSO-d_6): δ 3.23 (m, 4 H), 3.76 (m, 4 H), 4.22 (d, J = 8.7 Hz, 2 H), 4.23 (d, J = 9.0 Hz, 2 H), 6.82 (d, J = 8.8 Hz, 1 H), 6.85 (d, J = 16.0 Hz, 1 H), 7.07 (dd, J = 2.3, 8.8 Hz, 1 H), 7.36 (d, J = 2.2 Hz, 1 H), 7.50 (d, J = 8.0 Hz, 1 H), 7.53 (d, J = 16.1 Hz, 1 H), 8.06 (d, J = 7.8 Hz, 1 H), 10.17 (s, 1 H). MS (ESI, pos. ion) *m/z*: 436 (M + 1). Anal. ($C_{21}H_{20}F_3N_3O_4$): C, H, N, F.

(*E*)-*N*-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-3-(2-(piperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)acrylamide (48x) was generated as a yellow amorphous solid. ^{1}H NMR (DMSO-d_6): δ 1.60−1.65 (m, 6 H), 3.20 (m, 4 H), 4.20−4.22 (m, 4 H), 6.80 (d, J = 8.8 Hz, 1 H), 6.82 (d, J = 16.0 Hz, 1 H), 7.07 (dd, J = 2.4, 8.8 Hz, 1 H), 7.36 (d, J = 2.0 Hz, 1 H), 7.41 (d, J = 7.6 Hz, 1 H), 7.50 (d, J = 15.6 Hz, 1 H), 8.00 (d, J = 7.6 Hz, 1 H), 10.17 (s, 1 H). MS (ESI, pos. ion) *m/z*: 434 (M + 1). Anal. ($C_{22}H_{22}F_3N_3O_3$): C, H, N.

(*E*)-3-(2-Morpholino-6-(trifluoromethyl)pyridin-3-yl)-*N*-(quinolin-7-yl)acrylamide (49a) was generated as yellow crystals. Mp: 236−237 °C. ^{1}H NMR (DMSO-d_6): δ 3.26 (m, 4 H), 3.79 (m, 4 H), 6.98 (d, J = 15.7 Hz, 1 H), 7.43 (dd, J = 4.2, 8.2 Hz, 1 H), 7.52 (d, J = 7.8 Hz, 1 H), 7.64 (d, J = 15.7 Hz, 1 H), 7.81 (dd, J = 1.8, 8.9 Hz, 1 H), 7.96 (d, J = 8.9 Hz, 1 H), 8.11 (d, J = 7.8 Hz, 1 H), 8.29 (d, J = 8.1 Hz, 1 H), 8.55 (s, 1 H), 8.86 (dd, J = 1.6, 4.1 Hz, 1 H), 10.70 (s, 1 H). MS

(ESI, pos. ion) *m/z*: 429 (M + 1). Anal. ($C_{22}H_{19}F_3N_4O_2$): C, H, N, F.

(*E*)-3-(2-(Piperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)-*N*-(quinolin-7-yl)acrylamide (49b) was generated as a yellow amorphous solid. ^{1}H NMR (CD_3OD): δ 1.69−1.77 (m, 6 H), 3.30−3.33 (m, 4 H), 6.91 (d, J = 15.6 Hz, 1 H), 7.30 (d, J = 7.6 Hz, 1 H), 7.81−7.89 (m, 3 H), 8.04 (d, J = 7.6 Hz, 2 H), 8.23 (d, J = 8.8 Hz, 1 H), 8.91 (d, J = 8.4 Hz, 1 H), 9.01 (dd, J = 1.2, 5.2 Hz, 1 H), 9.04 (d, J = 1.6 Hz, 1 H). MS (ESI, pos. ion) *m/z*: 427 (M + 1). Anal. Calcd for $C_{23}H_{21}F_3N_4O$: C, 64.78; H, 4.96; N, 13.14. Found: C, 63.81; H, 5.15; N, 13.05.

Functional $^{45}Ca^{2+}$ Uptake Assays. Rat−human chimeric TRPV1-expressing CHO cells were routinely maintained in DMEM medium with 10% dialyzed fetal bovine serum, 1× nonessential amino acids, penicillin, streptomycin, and L-glutamine. Two days before the assays were run, the cells were seeded in Cytostar 96-well plates (Amersham) at a density of 20 000 cells per well. All of the $^{45}Ca^{2+}$ uptake assays had a final $^{45}Ca^{2+}$ concentration of 10 μCi/mL. For the capsaicin-mediated $^{45}Ca^{2+}$ uptake assay, the cells were preincubated with compound at room temperature for 2 min prior to the addition of $^{45}Ca^{2+}$ (ICN) and capsaicin (Sigma) in F12 medium, at a final capsaicin concentration of 500 nM, and then left for an additional 2 min prior to compound washout. For the pH-mediated $^{45}Ca^{2+}$ uptake assay, the cells were preincubated with compound at room temperature for 2 min prior to the addition of $^{45}Ca^{2+}$ in 30 mM HEPES/MES buffer (final assay pH 5) and then left for an additional 2 min prior to compound washout. For the measurement of agonist activity, the cells were incubated with compound in the presence of $^{45}Ca^{2+}$ in a 1:1 ratio of F12 medium to HBSS (Hanks buffered saline solution) supplemented with BSA (0.1 mg/mL) and 1 mM HEPES at pH 7.4 at room temperature for 2 min prior to compound washout. For compound washout, the assay plates were washed twice with phosphate-buffered saline containing BSA (0.1 mg/mL) using an ELX405 plate washer (Bio-Tek Instruments Inc.). Radioactivity remaining in the 96-well plates after washout was measured using a MicroBeta Jet (Perkin-Elmer). IC_{50} data was calculated using XLfit version 2.0.6 (ID Business Solutions Ltd).

Pharmacokinetic Studies. Male Sprague−Dawley rats (weight range 225−280 g) with surgically implanted femoral vein and jugular vein cannulae were obtained from Hilltop Lab Animals Inc. (Scottsdale, PA). Animals were fasted overnight and the following day compounds were administered either by oral gavage or by intravenous bolus injection. Oral formulations were prepared 24−48 h prior to dosing, while intravenous formulations were prepared on the day of dosing. Blood samples were collected over 8 h via jugular cannula into a heparinized tube. Following centrifugation, plasma samples were stored in a freezer to maintain −70 °C until analysis. Lithium-heparinized plasma samples (40 μL) were precipitated with acetonitrile containing an internal standard. The supernatant was analyzed by reverse phase (C-18) LC-MS/MS with atmospheric pressure chemical ionization (APCI) and a Sciex API3000 triple quadrupole mass detector operated in the multiple reaction monitoring (MRM) mode. Study sample concentrations were determined from a weighted ($1/x^2$) linear regression of peak area ratios (analyte peak area/IS peak area) versus the theoretical concentrations of the calibration standards. Pharmacokinetic parameters were calculated by non-compartmental methods using WinNonLin (Pharsight Corporation, Mountainview, CA).

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Supporting Information Available: Analysis data for the compounds synthesized. This material is available free of charge via the Internet at http://pubs.acs.org.

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